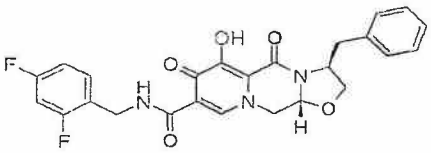
in example Z-2. 16 (60 mg, 0.13 mmol) and [(2*R*)-2-pyrrolidinylmethyl]amine (100 mg, 1.0 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (4a*S*,13a*R*)-*N*-[(4-fluorophenyl)methyl]-9,11-dioxo-10-[(phenylmethyl)oxy]-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide (60 mg, 91%). This material was hydrogenated in a second step as described in example Z-2 to give (4a*S*,13a*R*)-*N*-[(4-fluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide (21 mg, 42%) as a white solid. ^{1}H NMR (CDCl$_3$) δ 11.72 (m, 1 H), 1.37 (m, 1 H), 8.33 (s, 1 H), 7.29 (m, 2 H), 6.97 (m, 2 H), 4.57 (m, 2 H), 4.52 (m, 1 H), 4.24-4.19 (m, 2 H), 3.87-3.76 (m, 2 H), 3.14-3.07 (m, 2 H), 2.82 (m, 1 H), 2.11-1.89 (m, 3 H), 1.68 (m, 1 H); ES$^+$ MS: 413 (M+1).

Example Z-6:

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-3-(phenylmethyl)-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide.



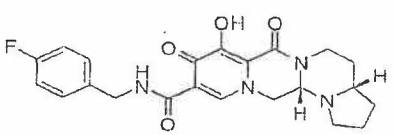
The title compound was made in two steps using a similar process to that described in example Z-2. 16a (37 mg, 0.08 mmol) and (2*S*)-2-amino-3-phenyl-1-propanol (35 mg, 0.24 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (3*S*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-5,7-dioxo-3-(phenylmethyl)-6-[(phenylmethy

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l)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (41 mg, 91%). This material was hydrogenated in a second step as described in example Z-2 to give (3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-3-(phenylmethyl)-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide. (25 mg, 75%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 11.47 (br, 1 H), 10.28 (m, 1 H), 8.35 (m, 1 H), 7.37-7.26 (m, 4 H), 7.18 (m, 2 H), 6.79 (m, 2 H), 5.03 (m, 1 H), 4.64-4.61 (m, 3 H), 4.40 (m, 1 H), 4.23 (apparent t, J = 7.2 Hz, 1 H), 3.96 (dd, J = 8.8, 6.4 Hz, 1 H), 3.88 (apparent t, J = 11.2 Hz, 1 H), 3.37 (dd, J = 13.6, 3.2 Hz, 1 H), 2.99 (dd, J = 13.2 8.8 Hz, 1 H); ES$^+$ MS: 482 (M+1).

Example Z-7:

(3a*S*,13a*S*)-*N*-[(4-Fluorophenyl)methyl]-8-hydroxy-7,9-dioxo-1,2,3,3a,4,5,7,9,13,13a-decahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrrolo[1,2-*d*]pyrimidine-10-carboxamide.

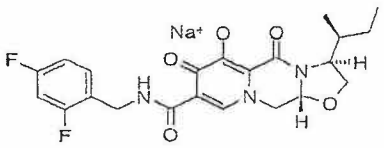


The title compound was made in two steps using a similar process to that described in example Z-2. 16 (84 mg, 0.13 mmol) and {2-[(2*S*)-2-Pyrrolidinyl]ethyl}amine (150 mg, 1.3 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (3a*S*,13a*S*)-*N*-[(4-fluorophenyl)methyl]-7,9-dioxo-8-[(phenylmethyl)oxy]-1,2,3,3a,4,5,7,9,13,13a-decahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrrolo[1,2-*d*]pyrimidine-10-carboxamide (86 mg, 90%). This material was hydrogenated in a second step as described in

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example Z-2 to give (3a*S*,13a*S*)-*N*-[(4-Fluorophenyl)methyl]-8-hydroxy-7,9-dioxo-1,2,3,3a,4,5,7,9,13,13a-decahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrrolo[1,2-*c*]pyrimidine-10-carboxamide. (63 mg, 88%) as a white solid. ^{1}H NMR ($CDCl_3/CD_3OD$) δ 10.45 (m, 1 H), 8.23 (s, 1 H), 7.35 (m, 2 H), 6.94 (t, *J* = 8.8 Hz, 2 H), 4.63 (m, 1 H), 4.58-4.48 (m, 2 H), 4.33 (dd, *J* = 13.6, 3.6 Hz, 1 H), 4.21 (m, 1 H), 4.11 (m, 1 H), 2.98 (m, 1 H), 2.85 (td, *J* = 13.2, 3.2 Hz, 1 H), 2.41 (m, 1 H), 2.29 (m, 1 H), 1.92 (m, 1 H), 1.83-1.75 (m, 3 H), 1.54-1.35 (m, 2 H); ES$^+$ MS: 427 (M+1).

Example Z-8: (3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[(1*S*)-1-methylpropyl]-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide sodium salt.



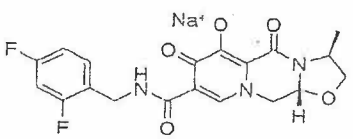
The title compound was made in two steps using a similar process to that described in example Z-1. 16a (417 mg, 0.89 mmol) and L-isoleucinol (259 mg, 2.21 mmol) were reacted in 1,2-dichloroethane (40 mL) with acetic acid to give (3*S*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-3-[(1*S*)-1-methylpropyl]-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (426 mg, 90%). This material was hydrogenated in a second step as described in example Z-1 to give

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(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[(1*S*)-1-methylpropyl]-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (376 mg, 99%) as a coarse white solid. ^{1}H NMR ($CDCl_3$) δ 11.48 (br, 1 H), 10.27 (br, 1 H), 8.32 (s, 1 H), 7.33 (m, 1 H), 6.79 (m, 2 H), 5.26 (dd, *J* = 9.6, 4.0 Hz, 1 H), 4.62 (m, 2 H), 4.42-4.35 (m, 2 H), 4.19 (dd, *J* = 8.8, 7.2 Hz, 1 H), 4.01 (dd, *J* = 8.8, 5.6 Hz, 1 H), 3.86 (dd, *J* = 12.0, 10.0 Hz, 1 H), 2.27 (m, 1 H), 1.40 (m, 1 H), 1.15 (m, 1 H), 0.97 (t, *J* = 7.2 hz, 3 H), 0.91 (d, *J* = 6.8 Hz, 3 H); ES$^+$ MS: 448 (M+1). This material (360 mg, 0.81 mmol) was treated with sodium hydroxide (0.81 mL, 1.0 M, 0.81 mmol) in ethanol (15 mL) as described in example Z-1 to provide its corresponding sodium salt (384 mg, 99%) as a white solid. ^{1}H NMR (DMSO-*d*$_6$) δ 10.82 (m, 1 H), 7.80 (m, 1 H), 7.33 (m, 1 H), 7.18 (m, 1 H), 7.00 (m, 1 H), 5.14 (m, 1 H), 4.47 (d, *J* = 5.6 Hz, 2 H), 4.31 (m, 1 H), 4.18 (m, 1 H), 3.96 (m, 1 H), 3.84 (m, 1 H), 3.71 (m, 1 H), 3.40 (m, 1 H), 1.88 (m, 1 H), 1.36 (m, 1 H), 1.04 (m, 1 H), 0.85 (t, *J* = 7.2 Hz, 3 H), 0.80 (d, *J* = 6.8 Hz, 3 H); ES$^+$ MS: 448 (M+1).

Example Z-9:

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide sodium salt.



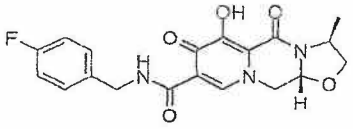
The title compound was made in two steps using a similar process to that described in example Z-1. 16a (510 mg, 1.08 mmol) and (2*S*)-2-amino-1-propanol (0.17 mL,

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2.17 mmol) were reacted in 1,2-dichloroethane (20 mL) with acetic acid to give (3*S*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-3-methyl-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (500 mg, 93%). This material was hydrogenated in a second step as described in example Z-1 to give 3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (386 mg, 94%) as a tinted white solid. ^{1}H NMR ($CDCl_3$) δ 11.46 (m, 1 H), 10.28 (m, 1 H), 8.32 (s, 1 H), 7.35 (m, 1 H), 6.80 (m, 2 H), 5.30 (dd, *J* = 10.0, 4.0 Hz, 1 H), 4.63 (m, 2 H), 4.48-4.37 (m, 3 H), 3.91 (dd, *J* = 12.0, 10.0 Hz, 1 H), 3.73 (m, 1 H), 1.48 (d, *J* = 6.0 Hz, 3 H); ES$^+$ MS: 406 (M+1). This material (385 mg, 0.95 mmol) was treated with sodium hydroxide (0.95 mL, 1.0 M, 0.95 mmol) in ethanol (15 mL) as described in example Z-1 to provide its corresponding sodium salt (381 mg, 94%) as a white solid. ^{1}H NMR (DMSO-*d*$_6$) δ 10.66 (m, 1 H), 7.93 (s, 1 H), 7.33 (m, 1 H), 7.20 (m, 1 H), 7.01 (m, 1 H), 5.19 (m, 1 H), 4.59 (m, 1 H), 4.48 (m, 2 H), 4.22 (m, 2 H), 3.75 (m, 1 H), 3.57 (m, 1 H), 1.24 (d, *J* = 5.6 Hz, 3 H).

Example Z-10:

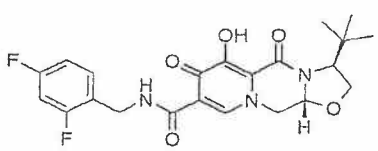
(3*S*,11a*R*)-*N*-[(4-Fluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide.



The title compound was made in two steps using a similar process to that described in example Z-2. 16 (100 mg, 0.22 mmol) and (2*S*)-2-amino-1-propanol (0.10 mL, 1.28 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (3*S*,11a*R*)-*N*-[(4-fluorophenyl)methyl]-3-methyl-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (100 mg, 95%). This material was hydrogenated in a second step as described in example Z-2 to give (3*S*,11a*R*)-*N*-[(4-Fluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (80 mg, 99%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 11.43 (br, 1 H), 10.28 (br, 1 H), 8.35 (s, 1 H), 7.28 (m, 2 H), 6.97 (m, 2 H), 5.29 (m, 1 H), 4.55-4.38 (m, 5 H), 3.89 (apparent t, *J* = 10.8 Hz, 1 H), 3.70 (m, 1 H), 1.45 (d, *J* = 5.6 Hz, 3 H); ES- MS: 386 (M-1).

Example Z-11:

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-3-(1,1-dimethylethyl)-6-hydroxy-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide



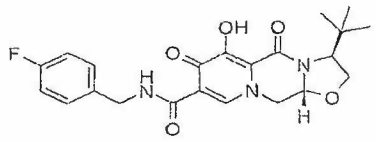
The title compound was made in two steps using a similar process to that described in example Z-2. 16a (41 mg, 0.09 mmol) and freebased L-*tert*-leucinol (59 mg, 0.50 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (3*S*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-3-(1,1-dimethylethyl)-5,7-dioxo-6-[(phenylm

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ethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (40 mg, 86%). This material was hydrogenated in a second step as described in example Z-2 to give (3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-3-(1,1-dimethylethyl)-6-hydroxy-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (33 mg, 99%) as a tinted white solid. ^{1}H NMR ($CDCl_3$) δ 10.29 (s, 1 H), 8.37 (s, 1 H), 7.34 (m, 1 H), 6.79 (m, 2 H), 5.43 (m, 1 H), 4.62 (m, 2 H), 4.36 (m, 2 H), 4.21 (m, 1 H), 3.99 (, 1 H), 3.81 (m, 1 H), 1.03 (s, 9 H); ES$^+$ MS: 448 (M+1).

Example Z-12:

(3*S*,11a*R*)-3-(1,1-Dimethylethyl)-*N*-[(4-fluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide.



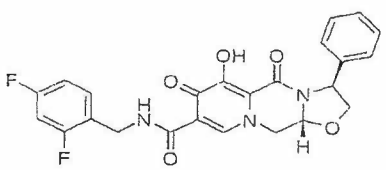
The title compound was made in two steps using a similar process to that described in example Z-2. 16 (41 mg, 0.09 mmol) and freebased L-*tert*-leucinol (59 mg, 0.50 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (3*S*,11a*R*)-3-(1,1-dimethylethyl)-*N*-[(4-fluorophenyl)methyl]-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (40 mg, 85%). This material was hydrogenated in a second step as described in example Z-2 to give (3*S*,11a*R*)-3-(1,1-Dimethylethyl)-*N*-[(4-fluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3,5,

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7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (32 mg, 97%) as a tinted white solid. ^{1}H NMR ($CDCl_3$) δ 11.15 (br, 1 H), 10.32 (s, 1 H), 8.38 (s, 1 H), 7.29 (m, 2 H), 6.98 (m, 2 H), 5.43 (m, 1 H), 4.58 (m, 2 H), 4.36 (m, 2 H), 4.21 (m, 1 H), 3.99 (, 1 H), 3.79 (m, 1 H), 1.02 (s, 9 H); ES$^+$ MS: 430 (M+1).

Example Z-13:

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-3-phenyl-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide.



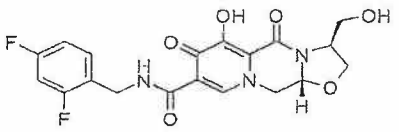
The title compound was made in two steps using a similar process to that described in example Z-2. 16a (33 mg, 0.07 mmol) and L-phenylglycinol (19 mg, 0.14 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (3*S*,11a*R*)-*N*-[(4-fluorophenyl)methyl]-5,7-dioxo-3-phenyl-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (37 mg, 95%). This material was hydrogenated in a second step as described in example Z-2 to give (3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-3-phenyl-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (33 mg, 99%) as a tinted white solid. ^{1}H NMR ($CDCl_3$) δ 11.23 (br, 1 H), 10.27 (s, 1 H), 8.39 (s, 1 H), 7.43-7.32 (m, 6 H), 6.80 (m, 2 H), 5.58 (d, J = 6.8 Hz, 1 H), 5.37 (apparent t, J = 6.8 Hz, 1 H), 4.67-4.62 (m, 3 H), 4.54 (d, J = 10.4 Hz, 1 H), 4.11 (m, 1 H), 4.01 (m, 1 H); ES$^+$

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MS: 468 (M+1).

Example Z-14:

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(hydroxymethyl)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide.

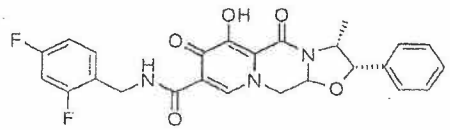


The title compound was made in two steps using a similar process to that described in example Z-2. 16a (50 mg, 0.10 mmol) and (2*R*)-2-amino-3-[(phenylmethyl)oxy]-1-propanol (0.1 mL) were reacted in dichloromethane (2 mL) with acetic acid to give (3*S*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-5,7-dioxo-6-[(phenylmethyl)oxy]-3-{[(phenylmethyl)oxy]methyl}-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (61 mg, 99%). This material was hydrogenated in a second step as described in example Z-2 to give (3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(hydroxymethyl)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (37 mg, 87%) as a tinted white solid. ^{1}H NMR ($CDCl_3/CD_3OD$) δ 8.23 (s, 1 H), 7.32 (m, 1 H), 6.79 (m, 2 H), 5.31 (d, *J* = 7.6 Hz, 1 H), 4.56 (s, 2 H), 4.42-4.36 (m, 3 H), 4.17-4.11 (m, 2 H), 3.85 (m, 1 H), 3.62 (d, *J* = 11.2 Hz, 1 H).

Example Z-15:

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(2*S*,3*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2-phenyl-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide.



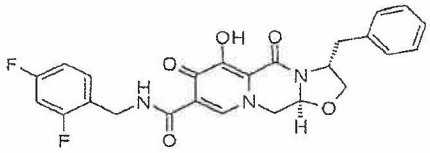
The title compound was made in two steps using a similar process to that described in example Z-2. 16a (25 mg, 0.05 mmol) and (1*S*,2*R*)-(+)-norephedrine (0.1 mL) were reacted in dichloromethane (2 mL) with acetic acid to give (2*S*,3*R*)-*N*-[(2,4-difluorophenyl)methyl]-3-methyl-5,7-dioxo-2-phenyl-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (30 mg, 99%). This material was hydrogenated in a second step as described in example Z-2 to give (2*S*,3*R*)-*N*-[(2,4-difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2-phenyl-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (25 mg, 91%) as a white solid. This material is a single diastereomer (>6:1 diastereomeric ratio but unconfirmed relative stereochemistry at the aminal center). ^{1}H NMR ($CDCl_3/CD_3OD$) δ 10.28 (m, 1 H), 8.38 (s, 1 H), 7.10-7.30 (m, 6 H), 6.78 (m, 2 H), 5.70 (d, J = 7.6 Hz, 1 H), 5.36 (d, J = 5.2 Hz, 1 H), 4.82 (m, 1 H), 4.61 (m, 2 H), 4.47 (d, J = 10.4 Hz, 1 H), 4.00 (apparent t, J = 10.4 Hz, 1 H), 0.94 (d, J = 6.4 Hz, 3 H); ES$^+$ MS: 482 (M+1).

Example Z-16:

(3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-3-(phenylmethyl)-2,3,5,

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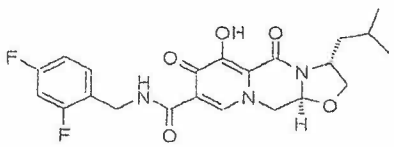
7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide



The title compound was made in two steps using a similar process to that described in example Z-2. 16a (34 mg, 0.07 mmol) and (2*R*)-2-amino-3-phenyl-1-propanol (D-phenylalaninol) (50 mg, 0.33 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (3*R*,11a*S*)-*N*-[(2,4-difluorophenyl)methyl]-5,7-dioxo-3-(phenylmethyl)-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (29 mg, 70%). This material was hydrogenated in a second step as described in example Z-2 to give (3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-3-(phenylmethyl)-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (24 mg, 98%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 11.46 (br, 1 H), 10.27 (m, 1 H), 8.33 (m, 1 H), 7.32-7.16 (m, 6 H), 6.78 (m, 2 H), 5.02 (m, 1 H), 4.61 (m, 3 H), 4.39 (m, 1 H), 4.22 (m, 1 H), 3.95 (m, 1 H), 3.87 (m, 1 H), 3.36 (m, 1 H), 2.97 (dd, J = 13.2 8.8 Hz, 1 H); ES$^+$ MS: 482 (M+1).

Example Z-17:

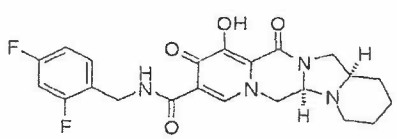
(3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(2-methylpropyl)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide.



The title compound was made in two steps using a similar process to that described in example Z-2. 16a (32 mg, 0.07 mmol) and (2*R*)-2-amino-4-methyl-1-pentanol (0.1 mL) were reacted in dichloromethane (2 mL) with acetic acid to give (3*R*,11a*S*)-*N*-[(2,4-difluorophenyl)methyl]-3-(2-methylpropyl)-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (43 mg, 99%). This material was hydrogenated in a second step as described in example Z-2 to give (3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(2-methylpropyl)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (32 mg, 90%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 11.47 (br, 1 H), 10.29 (m, 1 H), 8.35 (s, 1 H), 7.39 (m, 1 H), 6.80 (m, 2 H), 5.31 (m, 1 H), 4.62 (m, 2 H), 4.44 (m, 2 H), 4.37 (m, 1 H), 3.88 (m, 1 H), 3.84 (dd, *J* = 8.0, 5.6 Hz, 1 H), 2.04 (m, 1 H), 1.62 (m, 1 H), 1.41 (m, 1 H), 1.00 (d, *J* = 5.6 Hz, 3 H), 0.99 (d, *J* = 6.0 Hz, 3 H); ES$^+$ MS: 448 (M+1).

Example Z-18:

(5a*R*,14a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-11-hydroxy-10,12-dioxo-1,2,3,4,5a,6,10,12,14,14a-decahydropyrido[1,2-*a*]pyrido[1',2':3,4]imidazo[1,2-*d*]pyrazine-9-carboxamide.



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a) 1,1-Dimethylethyl (2*R*)-2-(aminocarbonyl)-1-piperidinecarboxylate. To a cold (0 °C) solution of (2*R*)-1-{[(1,1-dimethylethyl)oxy]carbonyl}-2-piperidinecarboxylic acid (1.0 g, 4.36 mmol) in THF (20 mL) was added triethylamine (0.60 mL, 4.36 mmol) followed by slow addition of methyl chloroformate (0.34 mL, 4.36 mmol). After a few minutes a suspension had formed. To this mixture was added concentrated NH_4OH (1.5 mL) and the solution was allowed to warm to rt as the bath warmed and stirred for a total of 4 h. The mixture was concentrated *in vacuo* and the residue was taken up in EtOAc. The organic layer was washed with citric acid, bicard and then brine, dried over Na_2SO_4. Filtration and concentration gave 1,1-dimethylethyl (2*R*)-2-(aminocarbonyl)-1-piperidinecarboxylate (1.0 g, 99%). ^1H NMR ($CDCl_3$) δ 6.03 (br, 1 H), 5.45 (br, 1 H), 4.77 (br, 1 H), 4.06 (br, 1 H), 2.82 (m, 1 H), 2.29 (m, 1 H), 1.67-1.43 (m, 13 H).

b) 1,1-Dimethylethyl (2*R*)-2-cyano-1-piperidinecarboxylate. To a cold (0 °C) solution of 1,1-dimethylethyl (2*R*)-2-(aminocarbonyl)-1-piperidinecarboxylate (269 mg, 1.17 mmol) in THF (10 mL) was added triethylamine (0.33 mL, 2.34 mmol) and then trifluoroacetic anhydride (0.17 mL, 1.17 mmol). The mixture was stirred at 0 °C for 1 h and concentrated *in vacuo*. The residue was taken up in EtOAc and washed successively with sodium bicarbonate, 0.5 *N* HCl and brine. The organics were dried over Na_2SO_4, filtered and concentrated to give 1,1-dimethylethyl (2*R*)-2-cyano-1-piperidinecarboxylate (255 mg, 99%) as a crystalline solid upon standing. ^1H NMR ($CDCl_3$) δ 5.23 (br, 1 H), 4.05 (br, 1 H), 2.93 (br, 1 H), 1.93-1.39 (m, 6 H), 1.46 (s, 9 H).

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c) 1,1-Dimethylethyl (2*R*)-2-(aminomethyl)-1-piperidinecarboxylate. An ammonia saturated ethanol solution of 1,1-dimethylethyl (2*R*)-2-cyano-1-piperidinecarboxylate (255 mg, 1.19 mmol) was reduced with Raney-Ni in a similar manner to that described in example Z-3 to give after filtration through a short plug of silica, 1,1-dimethylethyl (2*R*)-2-(aminomethyl)-1-piperidinecarboxylate (236 mg, 91%), as an oil. ^{1}H NMR ($CDCl_3/CD_3OD$) δ 4.15 (br, 1 H), 3.97 (m, 1 h), 2.96 (m, 1 H), 2.75-2.69 (m, 2 H), 2.23-2.08 (m, 3 H), 1.59-1.55 (m, 3 H), 1.43 (s, 9 H).

d) [(2*R*)-2-Piperidinylmethyl]amine bis HCl salt. A solution of 1,1-dimethylethyl (2*R*)-2-(aminomethyl)-1-piperidinecarboxylate (236 mg, 1.08 mmol) in THF (10 mL) was treated with 4 *N* HCl (3 mL) as described in example Z-3 to give the bis HCl salt of[(2*R*)-2-Piperidinylmethyl]amine. ^{1}H NMR (DMSO-*d6*) δ 9.67 (br, 1 H), 9.48 (br, 1 H), 8.48 (br, 2 H), 3.70 (br, 2 H), 3.20 (m, 1 H), 3.04 (m, 1 H), 2.86 (m, 1 H), 1.89-1.41 (m, 6 H).

e)

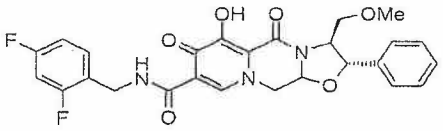
(5a*R*,14a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-11-hydroxy-10,12-dioxo-1,2,3,4,5a,6,10,12,14,14a-decahydropyrido[1,2-*a*]pyrido[1',2':3,4]imidazo[1,2-*d*]pyrazine-9-carboxamide. The title compound was made in two steps using a similar process to that described in example Z-2. 16a (50 mg, 0.11 mmol) and [(2*R*)-2-Piperidinylmethyl]amine (150 mg, 1.31 mmol) (free based using carbonate resin as described in example Z-3) were reacted in dichloromethane (2 mL) with acetic acid to give

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(5a*R*,14a*R*)-*N*-[(2,4-difluorophenyl)methyl]-10,12-dioxo-11-[(phenylmethyl)oxy]-1,2,3,4,5a,6,10,12,14,14a-decahydropyrido[1,2-*a*]pyrido[1',2':3,4]imidazo[1,2-*d*]pyrazine-9-carboxamide (50 mg, 88%). This material was hydrogenated in a second step as described in example Z-2 to give (5a*R*,14a*R*)-*N*-[(2,4-difluorophenyl)methyl]-11-hydroxy-10,12-dioxo-1,2,3,4,5a,6,10,12,14,14a-decahydropyrido[1,2-*a*]pyrido[1',2':3,4]imidazo[1,2-*d*]pyrazine-9-carboxamide (11 mg, 44%) as a white solid. ^{1}H NMR ($CD_3OD/CDCl_3$) δ 10.46 (m, 1 H), 8.32 (s, 1 H), 7.31 (m, 1 H), 6.80 (m, 2 H), 4.64-4.52 (m, 3 H), 4.14 (dd, *J* = 10.4, 2.8 Hz, 1 H), 3.91-3.82 (m, 2 H), 3.19 (apparent t, *J* = 10.8 Hz, 1 H), 3.08 (d, *J* = 10.4 Hz, 1 H), 2.50 (m, 1 H), 2.27 (m, 1 H), 1.99-1.30 m, 6 H); ES$^+$ MS: 445 (M+1).

Example Z-19:

(2*S*,3*S*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[(methyloxy)methyl]-5,7-dioxo-2-phenyl-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide



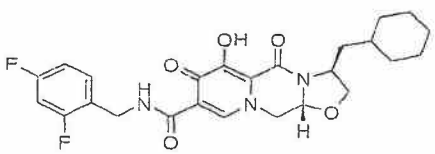
The title compound was made in two steps using a similar process to that described in example Z-2. 16a (36 mg, 0.07 mmol) and (2*R*)-2-amino-4-methyl-1-pentanol (0.1 mL) were reacted in dichloromethane (2 mL) with acetic acid to give (2*S*,3*S*)-*N*-[(2,4-difluorophenyl)methyl]-3-[(methyloxy)methyl]-5,7-dioxo-2-phenyl-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-c

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arboxamide. This material was hydrogenated in a second step as described in example Z-2 to give (2*S*,3*S*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[(methyloxy)methyl]-5,7-dioxo-2-phenyl-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (25 mg, 64% for 2 steps) as a white solid. This material is a single diastereomer (>6:1 diastereomeric ratio but unconfirmed relative stereochemistry at the aminal center). ^{1}H NMR ($CDCl_3$) δ 11.48 (br, 1 H), 10.30 (m, 1 H), 8.39 (s, 1 H), 7.39-7.24 (m, 6 H), 6.78 (m, 2 H), 5.46 (dd, *J* = 10.0, 3.6 Hz, 1 H), 5.33 (d, *J* = 7.2 Hz, 1 H), 4.63 (m, 2 H), 4.54 (dd, *J* = 12.4, 4.0 Hz, 1 H), 4.19 (m, 1 H), 4.12 (dd, *J* = 10.4, 3.2 Hz, 1 H), 4.06 (m, 1 H), 3.55 (dd, *J* = 10.4, 1.6 Hz, 1 H), 3.40 (s, 3 H); ES$^+$ MS: 512 (M+1).

Example Z-20:

(3*S*,11a*R*)-3-(Cyclohexylmethyl)-*N*-[(2,4-difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide.



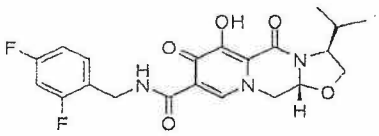
The title compound was made in two steps using a similar process to that described in example Z-2. 16a (36 mg, 0.08 mmol) and (2*S*)-2-amino-3-cyclohexyl-1-propanol (30 mg, 0.19 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (3*S*,11a*R*)-3-(cyclohexylmethyl)-*N*-[(2,4-difluorophenyl)methyl]-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (27 mg, 61%). This material was hydrogenated in a second step as described in

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example Z-2 to give (3*S*,11a*R*)-3-(cyclohexylmethyl)-*N*-[(2,4-difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (25 mg, 99%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 11.48 (br, 1 H), 10.28 (s, 1 H), 8.33 (s, 1 H), 7.33 (m, 1 H), 6.78 (m, 2 H), 5.29 (m, 1 H), 4.61 (m, 2 H), 4.47-4.33 (m, 3 H), 3.87-3.81 (m, 2 H), 2.05 (m, 1 H), 1.75-1.64 (m, 6 H), 1.39 (m, 1 H), 1.25-1.14 (m, 3 H), 1.02-0.97 (m, 2 H); ES$^+$ MS: 488 (M+1).

Example Z-21:

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(1-methylethyl)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide.



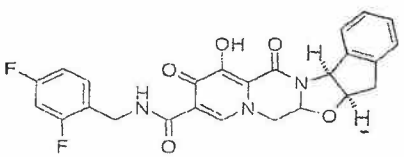
The title compound was made in two steps using a similar process to that described in example Z-1. 16a (42 mg, 0.09 mmol) and (2*S*)-2-amino-3-methyl-1-butanol (0.1 mL) were reacted in 1,2-dichloroethane (8 mL) with acetic acid to give (3*S*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-3-(1-methylethyl)-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (40 mg, 86%). This material was hydrogenated in a second step as described in example Z-1 to give (3*S*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-6-hydroxy-3-(1-methylethyl)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (34 mg,

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99%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 10.29 (br, 1 H), 8.36 (s, 1 H), 7.33 (m, 1 H), 6.79 (m, 2 H), 5.29 (d, J = 6.4 Hz, 1 H), 4.61 (m, 2 H), 4.44 (d, J = 9.6 Hz, 1 H), 4.34 (m, 1 H), 4.17 (m, 1 H), 4.02 (dd, J = 8.4, 5.2 Hz, 1 H), 3.86 (m, 1 H), 2.37 (m, 1 H), 0.97 (m, 6 H); ES$^+$ MS: 434 (M+1).

Example Z-22:

(5a*R*,14a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-5a,6a,7,11,13,14a-hexahydro-5*H*-indeno[1',2':4,5][1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-10-carboxamide.



The title compound was made in two steps using a similar process to that described in example Z-1. 16a (42 mg, 0.09 mmol) and (1*S*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-ol (100 mg, 0.67 mmol) were reacted in 1,2-dichloroethane (5 mL) with acetic acid to give (5a*R*,14a*S*)-*N*-[(2,4-difluorophenyl)methyl]-11,13-dioxo-12-[(phenylmethyl)oxy]-5a,6a,7,11,13,14a-hexahydro-5*H*-indeno[1',2':4,5][1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-10-carboxamide (55 mg, 99%). This material was hydrogenated in a second step as described in example Z-1 to give (5a*R*,14a*S*)-*N*-[(2,4-difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-5a,6a,7,11,13,14a-hexahydro-5*H*-indeno[1',2':4,5][1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-10-carboxamide (45 mg, 97%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 10.28 (m, 1 H), 8.33 (s, 1 H),

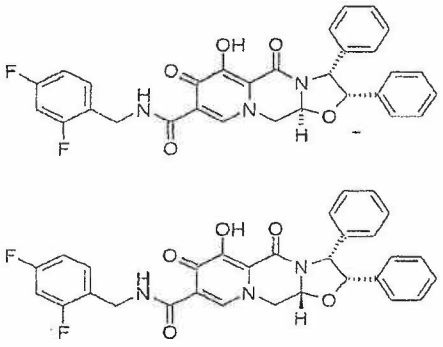
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7.69 (d, J = 7.2 Hz, 1 H), 7.34-7.19 (m, 4 H), 6.78 (m, 2 H), 5.96 (d, J = 6.0 Hz, 1 H), 5.32 (m, 1 H), 5.22 (m, 1 H), 4.60 (m, 2 H), 4.45 (d, J = 9.2 Hz, 1 H), 3.96 (apparent t, J = 10.8 Hz, 1 H), 3.40 (dd, J = 18.0, 6.8 Hz, 1 H), 3.24 (d, J = 17.6 Hz, 1 H);); ES+ MS: 480 (M+1).

Example Z-23 & Z-24:

(2*S*,3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3-diphenyl-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide &

(2*S*,3*R*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3-diphenyl-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide.



The title compounds were made in two steps using a similar process to that described in example Z-1. 16a (40 mg, 0.09 mmol) and (1*S*,2*R*)-2-amino-1,2-diphenylethanol (50 mg, 0.23 mmol) were reacted in 1,2-dichloroethane (5 mL) with acetic acid to give (2*S*,3*R*,11a*S*)-*N*-[(2,4-difluorophenyl)methyl]-5,7-dioxo-2,3-diphenyl-6-[(phenylmethyl)

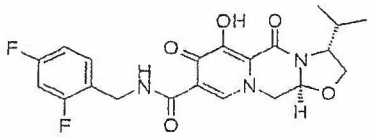
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oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (34 mg, 63%) and (2*S*,3*R*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-5,7-dioxo-2,3-diphenyl-6-[(phenylmethyl) oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (13 mg, 24%). These materials were hydrogenated in a second step as described in example Z-1 to give (2*S*,3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3-diphenyl-2,3,5,7, 11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (example Z-23, 29 mg, 99%) as a white solid and (2*S*,3*R*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3-diphenyl-2,3,5,7, 11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (example Z-24, 10 mg, 89%) as a white solid respectively. For example Z-23: ^{1}H NMR (DMSO-d_6) δ 10.29 (t, J = 5.6 Hz, 1 H), 8.55 (s, 1 H), 7.38 (m, 1 H), 7.22 (m, 1 H), 7.11-6.95 (m, 11 H), 6.16 (dd, J = 10.4, 3.6 Hz, 1 H), 5.71 (m, 2 H), 4.90 (m, 1 H), 4.54 (m, 2 H), 4.38 (t, J = 11.2 Hz, 1 H); ES$^+$ MS: 544 (M+1). For example Z-24: ^{1}H NMR ($CDCl_3$) δ 11.64 (br, 1 H), 10.30 (s, 1 H), 8.45 (s, 1 H), 7.34 (m, 1 H), 7.01-6.90 (m, 10 H), 6.80 (m, 2 H), 5.56 (m, 2 H), 5.42 (d, J = 6.4 Hz, 1 H), 4.73 (m, 1 H), 4.63 (m, 2 H), 4.49 (m, 1 H); ES$^+$ MS: 544 (M+1).

Example Z-25:

(3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(1-methylethyl)-5,7-dioxo-2,3,5, 7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide.

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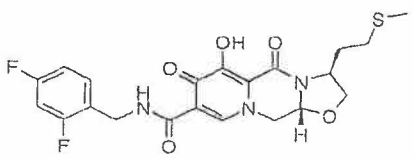


The title compound was made in two steps using a similar process to that described in example Z-1. 16a (40 mg, 0.09 mmol) and (2*R*)-2-amino-3-methyl-1-butanol (0.1 mL) were reacted in 1,2-dichloroethane (8 mL) with acetic acid to give (3*R*,11a*S*)-*N*-[(2,4-difluorophenyl)methyl]-3-(1-methylethyl)-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (41 mg, 92%). This material was hydrogenated in a second step as described in example Z-1 to give (3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(1-methylethyl)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (32 mg, 94%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 11.42 (br, 1 H), 10.27 (br, 1 H), 8.34 (s, 1 H), 7.31 (m, 1 H), 6.78 (m, 2 H), 5.28 (d, *J* = 6.0 Hz, 1 H), 4.60 (m, 2 H), 4.42 (m, 1 H), 4.33 (m, 1 H), 4.16 (m, 1 H), 4.01 (dd, *J* = 8.8, 5.2 Hz, 1 H), 3.85 (m, 1 H), 2.37 (m, 1 H), 0.97 (d, *J* = 6.8 Hz, 3 H), 0.95 (d, *J* = 6.4 Hz, 3 H); ES$^+$ MS: 434 (M+1).

Example Z-26

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[2-(methylthio)ethyl]-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide.

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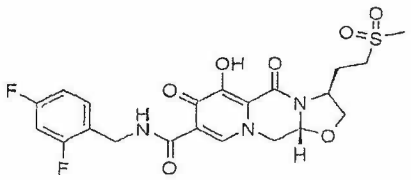


The title compound was made in two steps using a similar process to that described in example Z-1. 16a (43 mg, 0.09 mmol) and (2*S*)-2-amino-4-(methylthio)-1-butanol (0.1 mL) were reacted in 1,2-dichloroethane (5 mL) with acetic acid to give (3*S*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-3-[2-(methylthio)ethyl]-5,7-dioxo-6-[(phenyl methyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carbox amide (41 mg, 81%). This material (20 mg, 0.04 mmol) was treated with trifluoroacetic acid (1 mL) in dichloromethane (3 mL) at 0 °C to rt over 6 h. The mixture was concentrated *in vacuo* and subjected to reverse phase preparative HPLC purification to provide (3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[2-(methylthio)ethyl]-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (12 mg, 72%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 11.35 (br, 1 H), 10.25 (s, 1 H), 8.34 (s, 1 H), 7.33 (m, 1 H), 6.79 (m, 2 H), 5.32 (m, 1 H), 4.62-4.53 (m, 3 H), 4.43-4.39 (m, 2 H), 3.91-3.87 (m, 2 H), 2.68-2.53 (m, 2 H), 2.39 (m, 1 H), 2.12 (s, 3 H), 1.89 (m, 1 H); ES$^+$ MS: 466 (M+1).

Example Z-27

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[2-(methylsulfonyl)ethyl]-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide.

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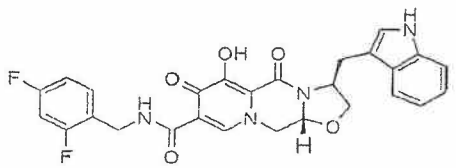


To a solution of (3*S*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-3-[2-(methylthio)ethyl]-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (20 mg, 0.04 mmol) in dichloromethane (5 mL) at 0 °C was added *m*-CPBA (20 mg, 70%, 0.082 mmol). The resultant solution was allowed to warm as the bath warmed and stirred a total of 3 h. The reaction was quenched by the addition of $Na_2S_2O_3$ (aq) and sodium bicarbonate. The layers were separated and the organic layer washed with brine. The aqueous layer was extracted with dichloromethane and the combined organics dried over Na_2SO_4. Filtration and concentration provided (3*S*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-3-[2-(methylsulfonyl)ethyl]-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (26 mg, 99%) as a white solid. This material was hydrogenated in a second step as described in example Z-1 to give (3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[2-(methylsulfonyl)ethyl]-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (22 mg, 99%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 11.00 (br, 1 H), 10.16 (s, 1 H), 8.33 (s, 1 H), 7.36 (m, 1 H), 6.81 (m, 2 H), 5.42 (m, 1 H), 4.62 (m, 3 H), 4.41 (m,2 H), 3.93 (m, 2 H), 3.31 (m, 2 H), 2.98 (s, 3 H), 2.40 (m, 1 H), 2.28 (m, 1 H); ES$^+$ MS: 498 (M+1).

Example Z-28:

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(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(1*H*-indol-3-ylmethyl)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide.



The title compound was made in two steps using a similar process to that described in example Z-1. 16a (43 mg, 0.09 mmol) and (2*S*)-2-amino-3-(1*H*-indol-3-yl)-1-propanol (100 mg, 0.52 mmol) were reacted in 1,2-dichloroethane (5 mL) with acetic acid to give (3*S*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-3-(1*H*-indol-3-ylmethyl)-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (36 mg, 64%). This material was hydrogenated in a second step as described in example Z-1 to give (3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(1*H*-indol-3-ylmethyl)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (29 mg, 95%) as a white solid. ^{1}H NMR ($CDCl_3/CD_3OD$) δ 10.34 (m, 1 H), 8.98 (br, 1 H), 8.24 (s, 1 H), 7.58 (d, J = 8.0 Hz, 1 H), 7.32 (m, 2 H), 7.15-7.01 (m, 3 H), 6.78 (m, 2 H), 4.94 (d, J = 6.8 Hz, 1 H), 4.71 (d, J = 5.6 Hz, 1 H), 4.59 (m, 2 H), 4.35 (d, J = 10.4 Hz, 1 H), 4.22 (m, 1 H), 3.99 (m, 1 H), 3.81 (m, 1 H), 3.40 (dd, J = 13.6, 11.6 Hz, 1 H), 3.18 (dd, J = 14.0, 8.4 Hz, 1 H); ES$^+$ MS: 521 (M+1).

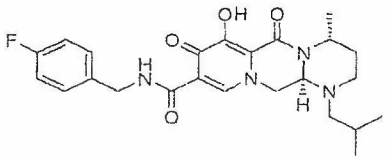
Example Z-29:

(4*R*,12a*R*)-*N*-[(4-fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(2-methylpropyl)-6,8-diox

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o-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamid

e.



a) (2*R*)-2-({[(1,1-Dimethylethyl)oxy]carbonyl}amino)propyl methanesulfonate. To a stirred solution of 1,1-dimethylethyl [(1*R*)-2-hydroxy-1-methylethyl]carbamate (5.00 g, 28.5 mmol) and triethylamine (5.92 mL, 42.9 mmol) in CH_2Cl_2 (30 mL) cooled to 0 °C and under a nitrogen atmosphere was added dropwise a solution of methanesulfonyl chloride (2.43 mL, 31.5 mmol) in CH_2Cl_2 (25 mL). Stirring was continued for 20 minutes at 0 °C, after which time the reaction was judged complete by TLC analysis (1:1 hexanes/EtOAc). The solution was poured into water and the layers were separated. The organic phase was washed with 0.1 N HCl and then with 5% $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated to give (2*R*)-2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)propyl methanesulfonate (7.08 g, 98%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (d, J = 6.8 Hz, 3H), 1.44 (s, 9H), 3.03 (s, 3H), 3.97 (m, 1H), 4.15 (dd, J = 4.2, 9.8 Hz, 1H), 4.21 (m, 1H), 4.61 (br s, 1H).

b) 1,1-Dimethylethyl [(1*R*)-2-cyano-1-methylethyl]carbamate. To a stirred solution of (2*R*)-2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)propyl methanesulfonate (7.08 g, 27.9 mmol) in DMSO (50 mL) was added NaCN (3.78 g, 84.0 mmol). The solution was stirred at 70 °C for 2 hours, over which time the formation of a precipitate was

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observed. After cooling at room temperature, water was added and the mixture was extracted with Et_2O. The ethereal layers were washed with a brine solution, dried over Na_2SO_4, filtered and concentrated to give 1,1-dimethylethyl [(1*R*)-2-cyano-1-methylethyl]carbamate (3.81 g, 73%) as a pale yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (d, J = 6.8 Hz, 3H), 1.42 (s, 9H), 2.51 (dd, J = 3.8, 16.6 Hz, 1H), 2.73 (m, 1H), 3.93 (m, 1H), 4.63 (br s, 1H).

c) 1,1-Dimethylethyl [(1*R*)-3-amino-1-methylpropyl]carbamate. A solution of 1,1-dimethylethyl [(1*R*)-2-cyano-1-methylethyl]carbamate (1.30 g, 7.1 mmol) in ethanol saturated with anhydrous ammonia was treated with Raney-Ni (1.5 mL of 50% aq. Suspension) and 55 psi of H_2 overnight. The mixture was filtered through Celite and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (80:19:1 CH_2Cl_2/MeOH/NH_4OH (37%) gradient elution) through a short plug of silica gel to give 1,1-dimethylethyl [(1*R*)-3-amino-1-methylpropyl]carbamate (1.37 g, 100%) as a clear oil that solidified. ^1H NMR (400 MHz, $CDCl_3$) δ 1.14 (d, J = 6.8 Hz, 3H), 1.43-1.62 (m, 13H), 2.76 (m, 2H), 3.77 (m, 1H), 4.57 (m, 1H).

d) 1,1-Dimethylethyl {(1*R*)-1-methyl-3-[(2-methylpropyl)amino]propyl}carbamate. 1,1-dimethylethyl [(1*R*)-3-amino-1-methylpropyl]carbamate (0.320 g, 1.70 mmol), isobutyraldehyde (150 µL, 1.62 mmol), and sodium triacetoxyborohydride (0.512 g, 2.42 mmol) were stirred in anhydrous dichloroethane (10 mL) at ambient temperature overnight. The reaction was quenched by the addition of saturated $NaHCO_3$ and

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then extracted with dichloromethane. The combined extracts were washed with water, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (80:19:1 CH_2Cl_2/MeOH/NH_4OH (37%) gradient elution) through a short plug of silica gel to afford 1,1-dimethylethyl {(1*R*)-1-methyl-3-[(2-methylpropyl)amino]propyl}carbamate (0.158 g, 40%) as a clear oil. ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, *J* = 6.4 Hz, 6H), 1.13 (d, *J* = 6.4 Hz, 3H), 1.42-1.51 (m, 11H), 1.67-1.75 (m, 2H), 2.33-2.42 (m, 2H), 2.58-2.72 (m, 2H), 3.72 (m, 1H), 5.20 (m, 1H).

e) [(3*R*)-3-Aminobutyl](2-methylpropyl)amine. An ice cold solution of 1,1-dimethylethyl {(1*R*)-1-methyl-3-[(2-methylpropyl)amino]propyl}carbamate (0.158 g, 0.65 mmol) in THF (8 mL) was treated with 4 *N* HCl (aq) (2 mL) and then stirred at room temperature for 2 h. The mixture was concentrated *in vacuo* to give [(3*R*)-3-aminobutyl](2-methylpropyl)amine dihydrochloride. The HCl salt was then dissolved in dichloromethane and a minimal amount of methanol and treated with solid supported carbonate resin (MP-Carbonate, Argonaut Technologies). After 30 minutes, the solution was filtered through a fritted tube and the solvents removed carefully *in vacuo* to give [(3*R*)-3-aminobutyl](2-methylpropyl)amine (65 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, *J* = 6.0 Hz, 6H), 1.06 (d, *J* = 5.6 Hz, 3H), 1.23-1.53 (m, 5H), 1.71-1.74 (m, 1H), 2.39 (m, 2H), 2.65 (m, 2H), 2.97 (m, 1H).

f)

(4*R*,12a*R*)-*N*-[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(2-methylpropyl)-6,8-dio

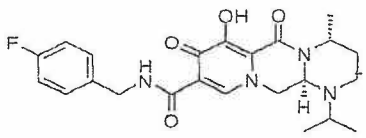
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xo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide. The title compound was made in two steps using a similar process to that described in example Z-2. 16 (40 mg, 0.09 mmol) and [(3*R*)-3-aminobutyl](2-methylpropyl)amine (65 mg, 0.45 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (4*R*,12a*R*)-*N*-[(4-fluorophenyl)methyl]-4-methyl-1-(2-methylpropyl)-6,8-dioxo-7-[(phenylmethyl)oxy]-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (29 mg, 60%). This material was hydrogenated in a second step as described in example Z-2 to give (4*R*,12a*R*)-*N*-[(4-fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (18 mg, 75%) as a tan solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77 (d, *J* = 6.4 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 3H), 1.32 (d, *J* = 7.2 Hz), 1.45-1.49 (m, 1H), 1.57-1.67 (m, 1H), 2.08-2.12 (m, 2H), 2.21-2.27 (m, 1H), 2.73-2.79 (m, 1H), 2.87-2.92 (m, 1H), 4.16-4.24 (m, 2H), 4.45 (s, 1H), 4.54-4.64 (m, 2H), 4.96-4.99 (m, 1H), 6.96-7.00 (m, 2H), 7.29-7.32 (m, 2H), 8.27 (s, 1H), 10.46 (s, 1H), 12.55 (s, 1H); ES$^+$ MS: 456 (M+1).

Example Z-30:

(4*R*,12a*R*)-*N*-[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(1-methylethyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide

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a) [(3*R*)-3-Aminobutyl](1-methylethyl)amine. The free diamine was prepared in a similar manner as described in example Z-29. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (d, J = 6.4 Hz, 6H), 1.06 (d, J = 6.4 Hz, 3H), 1.41-1.58 (m, 5H), 2.62-2.66 (m, 2H), 2.74-2.80 (m, 1H), 2.92-3.00 (m, 1H).

b)

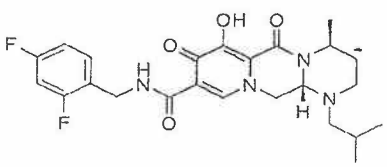
(4*R*,12a*R*)-*N*-[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(1-methylethyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide. The title compound was made in two steps using a similar process to that described in example Z-2. 16 (40 mg, 0.088 mmol) and [(3*R*)-3-aminobutyl](1-methylethyl)amine (78 mg, 0.60 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (4*R*,12a*R*)-*N*-[(4-fluorophenyl)methyl]-4-methyl-1-(1-methylethyl)-6,8-dioxo-7-[(phenylmethyl)oxy]-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (26 mg, 56%). This material was hydrogenated in a second step as described in example Z-2 to give (4*R*,12a*R*)-*N*-[(4-fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(1-methylethyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (21 mg, 90%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (d, J = 5.6 Hz, 3H), 1.06 (d, J = 6.0 Hz, 3H), 1.31 (d, J = 6.8 Hz, 3H), 1.57 (m, 1H), 1.98 (m, 1H),

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2.70-2.82 (m, 2H), 3.15 (m, 1H), 4.15-4.19 (m, 1H), 4.30 (m, 1H), 4.48 (s, 1H), 4.54-4.59 (m, 2H), 4.97 (m, 1H), 6.98 (m, 2H), 7.29-7.32 (m, 2H), 8.27 (s, 1H), 10.49 (s, 1H), 12.52 (s, 1H).

Example Z-31:

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide.



a) 1,1-Dimethylethyl [(1*S*)-2-cyano-1-methylethyl]carbamate. The nitrile was prepared in two steps using a modified procedure as described in example Z-29. To a stirred solution of (2*S*)-2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)propyl methanesulfonate (8.40 g, 33.2 mmol) in DMSO (50 mL) and KCN (6.51 g, 100.0 mmol) cooled to 0 °C was added 18-crown-6 (9.05 g, 34.3 mmol). The solution was allowed to warm to room temperature and then heated to 70 °C for 1 hour. After cooling at room temperature, water was added and the mixture was extracted with Et_2O. The ethereal layers were washed with a brine solution, dried over Na_2SO_4, filtered and concentrated to give 1,1-dimethylethyl [(1*S*)-2-cyano-1-methylethyl]carbamate (5.37 g, 88%) as a pale yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, J = 6.8 Hz, 3H), 1.44 (s, 9H), 2.52 (dd, J = 4.0, 16.4 Hz, 1H), 2.74 (m, 1H), 3.95 (m, 1H), 4.65 (br s, 1H).

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b) [(3*S*)-3-Aminobutyl](2-methylpropyl)amine dihydrochloride was prepared in a similar manner as described in example Z-29. ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$) δ 0.99 (m, 6H), 1.34 (m, 3H), 2.13-2.27 (m, 3H), 2.76 (m, 2H), 3.07 (m, 2H), 3.47 (m, 1H), 8.22 (m, 1 H), 8.83 (m, <1 H).

c)

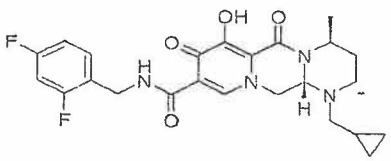
(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide. The title compound was made in two steps using a similar process to that described in example Z-2. 16a (80 mg, 0.17 mmol) and free based [(3*S*)-3-aminobutyl](2-methylpropyl)amine (107 mg, 0.74 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (4*S*,12a*S*)-*N*-[(2,4-difluorophenyl)methyl]-4-methyl-1-(2-methylpropyl)-6,8-dioxo-7-[(phenylmethyl)oxy]-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (76 mg, 76%) as a film. This material was hydrogenated in a second step as described in example Z-2 to give (4*S*,12a*S*)-*N*-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (39 mg, 80%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76 (d, *J* = 6.4 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 3H), 1.32 (d, *J* = 7.2 Hz, 3H), 1.45-1.50 (m, 1H), 1.60-1.69 (m, 1H), 2.03-2.12 (m, 2H), 2.21-2.27 (m, 1H), 2.73-2.79 (m, 1H), 2.87-2.93 (m, 1H), 4.16-4.25 (m, 2H), 4.45 (s, 1H), 4.57-4.68 (m, 2H), 4.96-5.01 (m, 1H), 6.75-6.82 (m, 2H),

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7.32-7.38 (m, 1H), 8.26 (s, 1H), 10.45 (s, 1H), 12.56 (s, 1H); ES+ MS: 475 (M+1).

Example Z-32:

(4*S*,12a*S*)-1-(Cyclopropylmethyl)-*N*-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide.



a) 1,1-Dimethylethyl {(1*S*)-3-[(cyclopropylmethyl)amino]-1-methylpropyl}carbamate. The protected diamine was prepared using a modified procedure as described in example Z-29. 1,1-dimethylethyl [(1*S*)-3-amino-1-methylpropyl]carbamate (0.293 g, 1.56 mmol), cyclopropane carboxaldehyde (96 µL, 1.30 mmol), and sodium triacetoxyborohydride (0.439 g, 2.07 mmol) were stirred in a 1:1 mixture of anhydrous dichloroethane and tetrahydrofuran (10 mL) at ambient temperature overnight. The reaction was quenched by the addition of saturated $NaHCO_3$ and then extracted with EtOAc. The combined extracts were washed with saturated $NaHCO_3$, then a solution of brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (80:19:1 CH_2Cl_2/MeOH/NH_4OH (37%) gradient elution) through a short plug of silica gel to afford 1,1-dimethylethyl {(1*S*)-3-[(cyclopropylmethyl)amino]-1-methylpropyl}carbamate (76 mg, 26%) as a clear oil. ^1H NMR (400 MHz, $CDCl_3$) δ 0.09-0.13 (m, 2H), 0.44-0.49 (m, 2H), 0.92-0.95 (m, 1H), 1.14 (d, J = 6.4 Hz, 3H), 1.43-1.70 (m, 12H), 2.38-2.50 (m, 2H), 2.62-2.73 (m, 2H),

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3.74 (m, 1H), 4.88 (m, 1H).

b) [(3*S*)-3-Aminobutyl](cyclopropylmethyl)amine dihydrochloride was prepared in a similar manner as described in example Z-29. ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$) δ 0.40 (m, 2H), 0.64 (m, 2H), 1.15 (m, 1H), 1.34 (m, 3H), 2.12-2.25 (m, 2H), 2.82 (m, 2H), 3.08 (m, 2H), 3.47 (m, 1H), 8.25 (br, < 1H), 9.04 (br, < 1H).

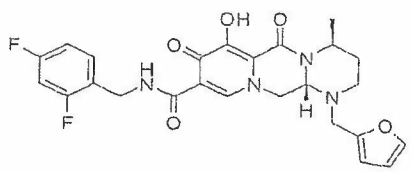
c) (4*S*,12a*S*)-1-(Cyclopropylmethyl)-*N*-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide. The title compound was made in two steps using a similar process to that described in example Z-2. 16a (50 mg, 0.106 mmol) and free based [(3*S*)-3-aminobutyl](cyclopropylmethyl)amine (44 mg, 0.31 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (4*S*,12a*S*)-1-(cyclopropylmethyl)-*N*-[(2,4-difluorophenyl)methyl]-4-methyl-6,8-dioxo-7-[(phenylmethyl)oxy]-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (50 mg, 83%) as a film. This material was hydrogenated in a second step as described in example Z-2 to give (4*S*,12a*S*)-1-(cyclopropylmethyl)-*N*-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (23 mg, 56%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.11 (m, 2H), 0.56-0.59 (m, 2H), 0.77 (m, 1H), 1.34 (d, J = 7.2 Hz, 3H), 1.46-1.50 (m, 1H), 2.04-2.13 (m, 1H), 2.30-2.34 (m, 1H), 2.46-2.51 (m, 1H), 2.90-2.96 (m, 1H), 3.16-3.19 (m, 1H),

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4.21-4.30 (m, 2H), 4.51 (s, 1H), 4.58-4.67 (m, 2H), 5.00-5.05 (m, 1H), 6.75-6.82 (m, 2H), 7.31-7.37 (m, 1H), 8.28 (s, 1H), 10.46 (s, 1H), 12.55 (br, 1H); ES+ MS: 473 (M+1).

Example Z-33:

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-1-(2-furanylmethyl)-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide.



a) [(3*S*)-3-Aminobutyl](2-furanylmethyl)amine dihydrochloride was prepared in a similar manner as described in example Z-32. ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$) δ 1.27 (d, J = 6.4 Hz, 3H), 1.96-2.05 (m, 1H), 2.14-2.19 (m, 1H), 3.00-3.04 (m, 2H), 3.38-3.39 (m, 1H), 4.11-4.18 (m, 2H), 6.34 (m, 1H), 6.59 (m, 1H), 7.40 (m, 1H), 8.18 (br, <1 H), 9.41 (br, < 1 H).

b)

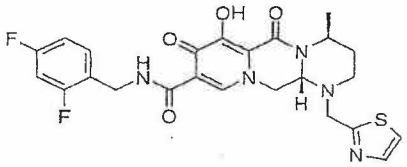
(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-1-(2-furanylmethyl)-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide. The title compound was made in two steps using a similar process to that described in example Z-2. 16a (36 mg, 0.076 mmol) and free based [(3*S*)-3-aminobutyl](2-furanylmethyl)amine (70 mg, 0.42 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give

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(4*S*,12a*S*)-*N*-[(2,4-difluorophenyl)methyl]-1-(2-furanylmethyl)-4-methyl-6,8-dioxo-7-[(phenylmethyl)oxy]-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (32 mg, 70%) as a film. This material was hydrogenated in a second step as described in example Z-2 to give (4*S*,12a*S*)-*N*-[(2,4-difluorophenyl)methyl]-1-(2-furanylmethyl)-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (20 mg, 76%), as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (d, *J* = 6.8 Hz, 3H), 1.45-1.49 (m, 1H), 2.04-2.13 (m, 1H), 2.77-2.82 (m, 1H), 2.94-3.01 (m, 1H), 3.65 (d, *J* = 15.6 Hz, 1H), 3.89 (d, *J* = 16.0 Hz, 1H), 4.27-4.31 (m, 1H), 4.39-4.41 (m, 1H), 4.49-4.53 (m, 1H), 4.58-4.66 (m, 1H), 4.98-5.03 (m, 1H), 6.24 (m, 1H), 6.36 (m, 1H), 6.75-6.82 (m, 2H), 7.31-7.39 (m, 1H), 7.40 (m, 1H), 8.26 (s, 1H), 10.47 (m, 1H), 12.50 (br, 1H); ES$^+$ MS: 499 (M+1).

Example Z-34:

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1-(1,3-thiazol-2-ylmethyl)-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide.



a) [(3*S*)-3-Aminobutyl](1,3-thiazol-2-ylmethyl)amine dihydrochloride was prepared in a similar manner as described in example Z-32. ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$) δ 1.28 (d, *J* = 6.4 Hz, 3H), 2.05 (m, 1H), 2.17 (m, 1H), 3.20 (m, 2H), 3.39 (m, 1H),

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4.51-4.58 (m, 2H), 7.52 (d, 1H), 7.82 (d, 1H).

b)

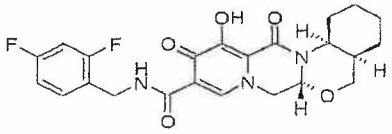
(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1-(1,3-thiazol-2-ylmethyl)-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide. The title compound was made in two steps using a similar process to that described in example Z-2. 16a (35 mg, 0.074 mmol) and free based [(3*S*)-3-aminobutyl](1,3-thiazol-2-ylmethyl)amine were reacted in dichloromethane (2 mL) with acetic acid to give (4*S*,12a*S*)-*N*-[(2,4-difluorophenyl)methyl]-4-methyl-6,8-dioxo-7-[(phenylmethyl)oxy]-1-(1,3-thiazol-2-ylmethyl)-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (36 mg, 80%) as a film. This material was debenzylated in a second step to in a manner similar to Z-26 to give (4*S*,12a*S*)-*N*-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1-(1,3-thiazol-2-ylmethyl)-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (18 mg, 60%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (d, *J* = 7.2 Hz. 3H), 1.49-1.53 (m, 1H), 2.12-2.18 (m, 1H), 2.93-2.96 (m, 1H), 3.07-3.13 (m, 1H), 3.99-4.03 (m, 1H), 4.13-4.17 (m, 1H), 4.24-4.27 (m, 1H), 4.57-4.61 (m, 3H), 5.03-5.06 (m, 1H), 6.75-6.82 (m, 2H), 7.26 (m, 1H), 7.31-7.37 (m, 2H), 7.76 (m, 1H), 7.94 (m, 1H), 10.40 (m, 1H), 12.48 (m, 1H); ES$^+$ MS: 516 (M+1).

Example Z-35:

racemic-(4a*R*,6a*R*,14a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-1,3,4,

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4a,5,6a,7,11,13,14a-decahydro-2*H*-pyrido[1',2':4,5]pyrazino[1,2-*a*][3,1]benzoxazine-10-carboxamide



a)

racemic-(4a*R*,6a*R*,14a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-11,13-dioxo-12-[(phenylmethyl)oxy]-1,3,4,4a,5,6a,7,11,13,14a-decahydro-2*H*-pyrido[1',2':4,5]pyrazino[1,2-*a*][3,1]benzoxazine-10-carboxamide. *racemic-cis*-2-Hydroxymethyl-1-cyclohexylamine hydrochloride (24 mg, 0.186 mmol) was dissolved in a dichloromethane solution containing a small amount of methanol (to dissolve) and excess MP-Carbonate (Argonaut Technologies) was added, the mixture was stirred for 30 minutes, and the MP-Carbonate was removed by filtration. The free amine solution was transferred to a microwave vessel containing 16a (29 mg, 0.0617 mmol). One drop of glacial acetic acid was added and the solution was heated for 10 minutes at 140 °C. The resultant solution was absorbed on celite and the material was purified by silica gel chromatography (0-12% methanol/dichloromethane gradient elution) to yield the desired product as a white solid (18 mg, 53%). ^{1}H NMR ($CDCl_3$) δ 10.40 (m, 1 H), 8.35 (s, 1 H), 7.60 (m, 2 H), 7.34-7.26 (m, 4 H), 6.80 (m, 2 H), 5.35-5.23 (m, 2 H), 5.13 (m, 1 H), 4.77 (m, 1 H), 4.70 (m, 2 H), 4.22 (dd, *J* = 13.2, 3.2 Hz, 1 H), 4.07 (dd, *J* = 13.2, 6.4, 1 H), 3.96 (m, 1 H), 3.76 (dd, *J* = 11.2, 4.4, 1 H), 2.22 (m, 1 H), 1.84 (m, 1 H), 1.74-1.40 (m, 6 H), 1.17 (m, 1 H); ES$^+$ MS: 550 (M +1).

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b)

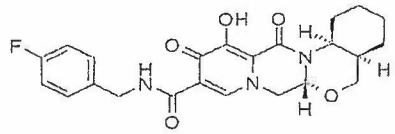
racemic-(4a*R*,6a*R*,14a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-1,3,4,4a,5,6a,7,11,13,14a-decahydro-2*H*-pyrido[1',2':4,5]pyrazino[1,2-*a*][3,1]benzoxazine-10-carboxamide.

racemic-(4a*R*,6a*R*,14a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-11,13-dioxo-12-[(phenylmethyl)oxy]-1,3,4,4a,5,6a,7,11,13,14a-decahydro-2*H*-pyrido[1',2':4,5]pyrazino[1,2-*a*][3,1]benzoxazine-10-carboxamide (13 mg, 0.0236 mmol) was dissolved in tetrahydrofuran and 10 w.t.% Pd/C (13 mg) was added. Hydrogen was passed through the solution several times and the mixture was stirred at 1 atm hydrogen for 18 hours until the reaction was determined complete by TLC (5% methanol/dichloromethane). The mixture was filtered through Celtite, eluting with methanol/chloroform and the filtrate was concentrated under reduced pressure and purified by HPLC to yield the title compound (7.3 mg, 73%) ^{1}H NMR (CDCl$_3$) δ 12.45 (m, 1 H), 10.38 (s, 1 H), 8.30 (s, 1 H), 7.32 (m, 1 H), 6.83-6.76 (m, 2 H), 5.23 (m, 1 H), 4.75 (m, 1 H), 4.63 (m, 2 H), 4.26 (m, 1 H), 4.12-4.01 (m, 2 H), 3.83 (m, 1 H), 2.30 (m, 1 H), 1.91 (m, 1 H), 1.80 (m, 1 H), 1.67-1.40 (m, 5 H), 1.20 (m, 1 H); ES$^+$ MS: 460 (M +1).

Example Z-36:

racemic-(4a*R*,6a*R*,14a*S*)-*N*-[(4-Fluorophenyl)methyl]-12-hydroxy-11,13-dioxo-1,3,4,4a,5,6a,7,11,13,14a-decahydro-2*H*-pyrido[1',2':4,5]pyrazino[1,2-*a*][3,1]benzoxazine-10-carboxamide.

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a)

racemic-(4aR,6aR,14aS)-N-[(4-Fluorophenyl)methyl]-11,13-dioxo-12-[(phenyl methyl)oxy]-1,3,4,4a,5,6a,7,11,13,14a-decahydro-2H-pyrido[1',2':4,5]pyrazino[1,2-a][3, 1]benzoxazine-10-carboxamide. In a manner similar to that described in example Z-35, from *racemic-cis*-2-Hydroxymethyl-1-cyclohexylamine hydrochloride (50 mg, 0.303 mmol) and 16 (45 mg, 0.0995 mmol) was prepared *racemic*-(4aR,6aR,14aS)-N-[(4-fluorophenyl)methyl]-11,13-dioxo-12-[(phenylmethyl)ox y]-1,3,4,4a,5,6a,7,11,13,14a-decahydro-2H-pyrido[1',2':4,5]pyrazino[1,2-a][3,1]benzoxa zine-10-carboxamide (48 mg, 91%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 10.42 (m, 1 H), 8.37 (s, 1 H), 7.59 (m, 2 H), 7.38-7.24 (m, 5 H), 6.98 (m, 2 H), 5.26-5.18 (m, 2 H), 5.07 (m, 1 H), 4.74 (m, 1 H), 4.62-4.51(m, 2 H), 4.20 (dd, J = 13.6, 4 Hz, 1 H), 4.04 (m, 1 H), 3.91 (m, 1 H), 3.71 (dd, J = 11.3, 4.8 Hz, 1 H), 2.18 (m, 1 H), 1.82 (m, 1 H), 1.78-1.63 (m, 2 H), 1.62-1.56 (m, 2 H), 1.48 (, 1 H), 1.38 (m, 1 H), 1.14 (m, 1 H); ES$^+$ MS: 532 (M +1).

b)

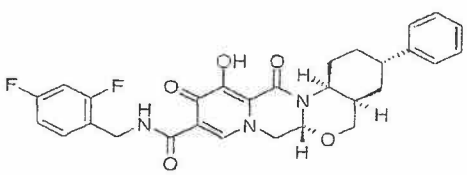
racemic-(4a*R*,6a*R*,14a*S*)-N-[(4-Fluorophenyl)methyl]-12-hydroxy-11,13-dioxo-1,3,4,4a, 5,6a,7,11,13,14a-decahydro-2H-pyrido[1',2':4,5]pyrazino[1,2-a][3,1]benzoxazine-10-car boxamide. In a manner similar to that described in example Z-37, from *racemic*-(4aR,6aR,14aS)-N-[(4-fluorophenyl)methyl]-11,13-dioxo-12-[(phenylmethyl)ox

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y]-1,3,4,4a,5,6a,7,11,13,14a-decahydro-2*H*-pyrido[1',2':4,5]pyrazino[1,2-a][3,1]benzoxazine-10-carboxamide (37 mg, 0.0696 mmol) and 10 w.t. % Pd/C (3 mg) was prepared the title compound (18 mg, 58%) as a white solid after purification by HPLC. ^{1}H NMR ($CDCl_3$) δ 12.47 (s, 1 H), 10.39 (m, 1 H), 8.32 (s, 1 H), 7.30 (m, 2 H), 6.98 (m, 2 H), 5.22 (m, 1 H), 4.74 (m, 1 H), 4.58 (m, 2 H), 4.28 (dd, J = 13.2, 4 Hz, 1 H), 4.12-3.98 (m, 2 H), 3.81 (dd, J = 11.6, 4.8 Hz, 1 H), 2.29 (m, 1 H), 1.91-1.19 (m, 8 H); ES$^+$ MS: 442 (M +1).

Example Z-37:

racemic-(3*S*,4a*R*,6a*R*,14a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-3-phenyl-1,3,4,4a,5,6a,7,11,13,14a-decahydro-2*H*-pyrido[1',2':4,5]pyrazino[1,2-*a*][3,1]benzoxazine-10-carboxamide.



a)

racemic-(3*S*,4a*R*,6a*R*,14a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-11,13-dioxo-3-phenyl-12-[(phenylmethyl)oxy]-1,3,4,4a,5,6a,7,11,13,14a-decahydro-2*H*-pyrido[1',2':4,5]pyrazino[1,2-*a*][3,1]benzoxazine-10-carboxamide. In a manner similar to that described in example Z-35, from *racemic*-[(1*R*,2*S*,5*S*)-2-amino-5-phenylcyclohexyl]methanol hydrochloride (32 mg, 0.160 mmol) and 16a (30 mg, 0.064 mmol) was prepared *racemic*-(3*S*,4a*R*,6a*R*,14a*S*)-*N*-[(2,4-difluorophenyl)methyl]-11,13-dioxo-3-phenyl-12-[(phenylmethyl)oxy]-1,3,4,4a,5,6a,7,11,13,14a-decahydro-2*H*-pyrido[1',2':4,5]pyrazino[1,

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2-*a*][3,1]benzoxazine-10-carboxamide (35 mg, 88%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 10.41 (m, 1 H), 8.38 (s, 1 H), 7.66 (m, 2 H), 7.40-7.26 (m, 6 H), 6.81 (m. 3 H), 5.32-5.25 (m, 2 H), 5.17 (m, 1 H), 4.89 (m, 1 H), 4.66-4.62 (m, 2 H), 4.26 (dd, *J* = 13.6, 4 Hz, 1 H), 4.13-4.04 (m, 2 H), 3.85 (dd, *J*=11.2, 4.4 Hz, 1 H), 2.56 (m, 1 H), 2.37 (m, 1 H), 2.03-1.64 (m, 6 H); ES$^+$ MS: 626 (M +1).

b)

racemic-(3*S*,4a*R*,6a*R*,14a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-3-phenyl-1,3,4,4a,5,6a,7,11,13,14a-decahydro-2*H*-pyrido[1',2':4,5]pyrazino[1,2-*a*][3,1]benzoxazine-10-carboxamide.

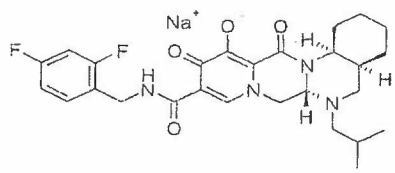
racemic-(3*S*,4a*R*,6a*R*,14a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-11,13-dioxo-3-phenyl-12-[(phenylmethyl)oxy]-1,3,4,4a,5,6a,7,11,13,14a-decahydro-2*H*-pyrido[1',2':4,5]pyrazino[1,2-*a*][3,1]benzoxazine-10-carboxamide (27 mg, 0.0432 mmol) was suspended in methanol, 10 w.t. % Pd/C (3 mg) was added and hydrogen was bubbled through the system several times until the reaction was determined complete by TLC (5% methanol/dichloromethane). The suspension was filtered through Celite eluting with methanol/chloroform and the filtrate was concentrated under reduced pressure and purified by HPLC to give the title compound (13 mg, 57%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 12.40 (br s, 1 H), 10.37 (m, 1 H), 8.32 (s, 1 H), 7.37-7.28 (m, 3 H), 7.24-7.15 (m, 4 H), 6.79 (m, 2 H), 5.78 (br s, 1 H), 4.85 (m, 1 H), 4.62 (m, 2 H), 4.29 (m, 1 H), 4.16-4.09 (m, 2 H), 3.92 (dd, *J* = 11.6, 4.8 Hz, 1 H), 2.58 (m, 1 H), 2.46 (m, 1 H), 2.07-1.64 (m, 7 H); ES$^+$ MS: 536 (M +1).

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Example Z-38:

Sodium

racemic-(4aS,6aS,14aS)-10-({[(2,4-difluorophenyl)methyl]amino}carbonyl)-6-(2-methylpropyl)-11,13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazolin-12-olate.



a) *racemic*-1,1-Dimethylethyl [(1S,2R)-2-(hydroxymethyl)cyclohexyl]carbamate. *racemic*-[(1*R*,2*S*,5*S*)-2-Amino-5-phenylcyclohexyl]methanol hydrochloride (800 mg, 4.82 mmol) was dissolved in MeOH (40 mL) and bis(1,1-dimethylethyl) dicarbonate (1.16 g, 5.30 mmol) and triethylamine (4 mL, 28.92 mmol) were added and the mixture was stirred 18 hours at ambient temperature. The solvents were removed under reduced pressure, ethyl acetate and aqueous saturated sodium bicarbonate were added and the product was extracted with ethyl acetate. The combined organics were dried over sodium sulfate and the solvents were removed under reduced pressure. Purification by silica gel chromatography (9:1 hexanes: ethyl acetate to ethyl acetate gradient elution) gave 1,1-dimethylethyl *racemic*-[(1S,2R)-2-(hydroxymethyl)cyclohexyl]carbamate (934 mg, 85%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 4.87 (m, 1H), 4.03-3.95 (m, 2 H), 3.26 (m, 1 H), 3.15 (m, 1 H), 1.73-1.48 (m, 5 H), 1.38 (s, 9 H). 1.27-1.15 (m, 3 H), 0.887 (m, 1 H).

b) *racemic*-1,1-Dimethylethyl [(1S,2R)-2-Formylcyclohexyl]carbamate. To a

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solution of dimethylsulfoxide (0.2 mL, 2.88 mmol) in dichloromethane (3 mL) at -78 °C was added oxalyl chloride (0.72 mL, 1.44 mmol) dropwise. The mixture was stirred 10 minutes and *racemic*-1,1-dimethylethyl [(1S,2R)-2-(hydroxymethyl)cyclohexyl]carbamate (220 mg, 0.961 mmol) in dichlormethane was added dropwise and stirred 10 minutes. Triethylamine (0.53 mL, 3.84 mmol) was added slowly and the reaction was stirred at -78 °C for one hour and allowed to warm to ambient temperature. Water was added and product was extracted with dichloromethane. The combined organics were washed with brine and dried over sodium sulfate. Removal of solvents under reduced pressure afforded *racemic*-1,1-dimethylethyl [(1S,2R)-2-formylcyclohexyl]carbamate (223 mg, quantitative) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 9.61 (s, 1 H), 5.19 (m, 1 H), 3.88 (m, 1 H), 2.61 (m, 1 H), 1.85 (m, 1 H), 1.63-1.49 (m, 4 H), 1.37-1.16 (m, 12 H).

c) *racemic*-1,1-dimethylethyl ((1S,2S)-2-{[(2-Methylpropyl)amino]methyl} cyclohexyl)carbamate. *racemic*-1,1-Dimethylethyl [(1S,2R)-2-formylcyclohexyl]carbamate (223 mg, 0.982 mmol) was dissolved in dichloroethane and 2-methylpropyl)amine (0.15 mL, 1.47 mmol) and sodium triacetoxyborohydride (290 mg, 1.37 mmol) were added and the reaction was stirred at ambient temperature for 18 hours. Aqueous sodium bicarbonate was added and the product was extracted with dichloromethane. The combined extracts were dried over sodium sulfate and the solvents were removed under reduced pressure. Purification by silica gel chromatography (dichloromethane to 1% ammonium hydroxide 19% methanol 80% dichloromethane gradient elution) afforded

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racemic-1,1-dimethylethyl ((1S,2S)-2-{[(2-methylpropyl)amino]methyl}cyclohexyl)carbamate (112 mg, 40%) as a clear colorless oil. ^{1}H NMR ($CDCl_3$) δ 6.06 (br s, 1 H), 3.76 (br s, 1 H), 2.63 (m, 1 H), 2.43-2.37 (m, 2 H), 2.25 (m, 1 H), 1.81 (m, 1 H), 1.71-1.59 (m, 3 H), 1.44-1.32 (m, 14 H), 1.27-1.19 (m, 2 H), 0.866 (m, 6 H).

d) *racemic*-(1S,2S)-2-{[(2-Methylpropyl)amino]methyl}cyclohexanamine hydrochloride.

In a manner similar to that describe in example Z-3, step e, from *racemic*-1,1-dimethylethyl ((1S,2S)-2-{[(2-methylpropyl)amino]methyl} cyclohexyl)carbamate (112 mg, 0.394 mmol) was prepared (1S,2S)-2-{[(2-methylpropyl)amino]methyl}cyclohexanamine hydrochloride (130 mg, > 100%) as a white solid. ^{1}H NMR (methanol-d_4/$CDCl_3$) δ 8.68-8.28 (m, 1 H), 3.62 (br s, 1 H), 3.26 (m, 1 H), 2.83-2.78 (m, 3 H), 2.54 (br s, 1 H), 2.12 (m, 1 H), 1.82-1.66 (m, 3 H), 1.53-1.39 (m, 5 H), 0.96 (m, 6 H), 0.766 (m, 1 H).

e)

racemic-(4aS,6aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-6-(2-methylpropyl)-11,13-dioxo-12-[(phenylmethyl)oxy]-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5] pyrazino[1,2-a]quinazoline-10-carboxamide. In a manner similar to that described in Z-35, from *racemic*-(1S,2S)-2-{[(2-methylpropyl)amino]methyl}cyclohexanamine hydrochloride (130 mg, 0.508 mmol) and 16a (55 mg, 0.117 mmol) was prepared

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racemic-(4aS,6aS,14aS)-N-[(2,4-difluorophenyl)methyl]-6-(2-methylpropyl)-11,13-dioxo-12-[(phenylmethyl)oxy]-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide (44 mg, 62%) with a 12: 1 d.r. ^{1}H NMR ($CDCl_3$) δ 10.46 (m, 1H), 8.33 (s, 1 H), 7.59 (m, 2 H), 7.37-7.24 (m, 4 H), 6.79 (m, 2 H), 5.30-5.23 (m, 2 H), 4.75-4.56 (m, 3 H), 4.23-4.09 (m, 3 H), 2.69-2.66 (m, 2 H), 2.21-1.98 (m, 3 H), 1.80 (m, 1 H), 1.71-1.33 (m, 6 H), 1.26-1.19 (m, 2 H), 0.810 (m, 3 H), 0.720 (m, 3 H); ES$^+$ MS: 605 (M +1).

f)

racemic-(4aS,6aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy-6-(2-methylpropyl)-11,13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide. In a manner similar to that described in example Z-37, from *racemic*-(4aS,6aS,14aS)-N-[(2,4-difluorophenyl)methyl]-6-(2-methylpropyl)-11,13-dioxo-12-[(phenylmethyl)oxy]-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide (39 mg, 0.064 mmol) and 10 w.t. % Pd/C (7 mg) was prepared *racemic*-(4aS,6aS,14aS)-N-[(2,4-difluorophenyl)methyl]-12-hydroxy-6-(2-methylpropyl)-11,13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide (36 mg, > 100%) as a tan solid. ^{1}H NMR ($CDCl_3$) δ 12.60 (br s, 1 H), 10.43 (br s, 1 H), 8.25 (s, 1 H), 7.35 (m, 1 H), 6.78 (m, 2 H), 4.77 (m, 1 H), 4.63 (m, 2 H), 4.49 (br s, 1 H), 4.30-4.13 (m, 2 H), 3.63-3.40 (m, 2 H), 2.88-2.71 (m, 2 H), 2.32-2.21 (m, 2 H), 2.05 (m, 1 H), 1.88-1.11 (m, 7 H), 0.830 (m, 3 H), 0.760 (m, 3

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H); AP+ MS: 515 (M +1).

g) Sodium *racemic*-(4aS,6aS,14aS)-10-({[(2,4-Difluorophenyl)methyl]amino}carbonyl)-6-(2-methylpropyl)-11,13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazolin-12-olate. In a manner similar to that described in example Z-1, from *racemic*-(4aS,6aS,14aS)-N-[(2,4-difluorophenyl)methyl]-12-hydroxy-6-(2-methylpropyl)-11,13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide (37 mg, 0.071 mmol) and 1 N sodium hydroxide (0.07 mL) the title compound was prepared as a yellow solid (26 mg, 68 %). ^{1}H NMR (DMSO-*d*$_6$) δ 10.73 (m, 1 H), 7.94 (s, 1 H), 7.32 (m, 1 H), 7.19 (m, 1 H), 7.00 (m, 1 H), 4.59-4.41 (m, 3 H), 4.28 (m, 2 H), 4.14 (br s, 1 H), 2.63-2.60 (m, 2 H), 1.98-1.61 (m, 5 H), 1.48-1.36 (m, 4 H), 0.997 (m, 3 H), 0.760 (m, 3 H), 0.660 (m, 2 H); AP+ MS: 515 (M +1 of free acid).

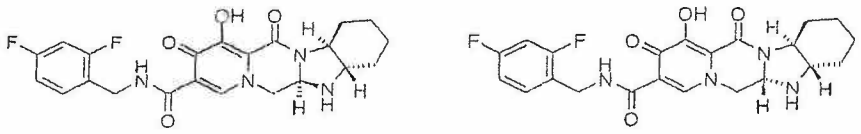
Example Z-39:

(6aR,7aS,11aS)-N-[(2,4-Difluorophenyl)methyl]-1-hydroxy-2,13-dioxo-2,6a,7,7a,8,9,10,11,11a,13-decahydro-6H-pyrido[1',2':4,5]pyrazino[1,2-a]benzimidazole-3-carboxamide

& Example Z-40:

(6aS,7aS,11aS)-N-[(2,4-Difluorophenyl)methyl]-1-hydroxy-2,13-dioxo-2,6a,7,7a,8,9,10,11,11a,13-decahydro-6H-pyrido[1',2':4,5]pyrazino[1,2-a]benzimidazole-3-carboxamide.

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a)

(6aR,7aS,11aS)-N-[(2,4-Difluorophenyl)methyl]-2,13-dioxo-1-[(phenylmethyl)oxy]-2,6a,7,7a,8,9,10,11,11a,13-decahydro-6H-pyrido [1',2':4,5] pyrazino[1,2-a] benzimidazole-3-carboxamide and (6aS,7aS,11aS)-N-[(2,4-difluorophenyl)methyl]-2,13-dioxo-1-[(phenylmethyl)oxy]-2,6a,7,7a,8,9,10,11,11a,13-decahydro-6H-pyrido[1',2':4,5]pyrazino[1,2-a]benzimidazole-3-carboxamide. In a manner similar to that described in example Z-2, from [(1S,2S)-2-aminocyclohexyl]amine (122 mg, 1.07 mmol) and 16a (200 mg, 0.426 mmol) was prepared (6aR,7aS,11aS)-N-[(2,4-difluorophenyl)methyl]-2,13-dioxo-1-[(phenylmethyl)oxy]-2,6a,7,7a,8,9,10,11,11a,13-decahydro-6H-pyrido [1',2':4,5] pyrazino[1,2-a] benzimidazole-3-carboxamide (58 mg) and (6aS,7aS,11aS)-N-[(2,4-difluorophenyl)methyl]-2,13-dioxo-1-[(phenylmethyl)oxy]-2,6a,7,7a,8,9,10,11,11a,13-decahydro-6H-pyrido[1',2':4,5]pyrazino[1,2-a]benzimidazole-3-carboxamide (10.6 mg) after separation of the diastereomers using silica gel chromatography (0-12% methanol/dichloromethane). (6aR,7aS,11aS)-N-[(2,4-difluorophenyl)methyl]-2,13-dioxo-1-[(phenylmethyl)oxy]-2,6a,7,7a,8,9,10,11,11a,13-decahydro-6H-pyrido [1',2':4,5] pyrazino[1,2-a] benzimidazole-3-carboxamide (major): ^{1}H NMR (CDCl$_3$) δ 10.40 (m, 1 H), 8.33 (s, 1 H), 7.57 (m, 2 H), 7.40-7.25 (m, 4 H), 6.81 (m, 2 H), 5.32 (d, J = 10 Hz, 1 H), 5.13 (d, J

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= 10 Hz, 1 H), 4.64-4.58 (m, 3 H), 4.21 (dd, J = 12.4, 3.2 Hz, 1 H), 3.79 (m, 1 H), 3.04 (m, 1 H), 2.73 (m, 1 H), 2.53 (m, 1 H), 2.01-1.79 (m, 4 H), 1.36-1.24 (m, 4 H); ES+ MS: 535 (M +1).

(6aS,7aS,11aS)-N-[(2,4-difluorophenyl)methyl]-2,13-dioxo-1-[(phenylmethyl)oxy]-2,6a,7,7a,8,9,10,11,11a,13-decahydro-6H-pyrido[1',2':4,5]pyrazino[1,2-a]benzimidazole-3-carboxamide (minor diastereomer): ^{1}H NMR ($CDCl_3$) δ 10.33 (m, 1 H), 8.28 (s, 1 H), 7.61 (m, 2 H), 7.39-7.28 (m, 3 H), 6.79 (m, 2 H), 5.29 (d, J = 9.6 Hz, 1 H), 5.05 (d, J = 9.6 Hz, 1 H), 4.84 (m, 1 H), 4.60 (m, 2 H), 3.90-3.84 (m, 2 H), 3.07 (m, 1 H), 2.75 (m, 1 H), 2.49 (m, 1 H), 2.07 (m, 1 H), 1.90-1.51 (m, 4 H), 1.33-1.19 (m, 4 H); MS data matches that of its diastereomer.

b) (For example Z-39).

(6aR,7aS,11aS)-N-[(2,4-Difluorophenyl)methyl]-1-hydroxy-2,13-dioxo-2,6a,7,7a,8,9,10,11,11a,13-decahydro-6H-pyrido[1',2':4,5]pyrazino[1,2-a]benzimidazole-3-carboxamide. In a manner similar to that described in example Z-37, from the minor diastereomer prepared in step a (6aS,7aS,11aS)-N-[(2,4-difluorophenyl)methyl]-2,13-dioxo-1-[(phenylmethyl)oxy]-2,6a,7,7a,8,9,10,11,11a,13-decahydro-6H-pyrido[1',2':4,5]pyrazino[1,2-a]benzimidazole-3-carboxamide (7 mg, 0.0131 mmol) and 10 w.t. % Pd/C (catalytic amount) was prepared (6aR,7aS,11aS)-N-[(2,4-difluorophenyl)methyl]-1-hydroxy-2,13-dioxo-2,6a,7,7a,8,9,10,11,11a,13-decahydro-6H-pyrido[1',2':4,5]pyrazino[1,2-a]benzimidazole-3-carboxamide (2.8 mg, 48%) after purification by HPLC. ^{1}H NMR ($CDCl_3$) δ 12.15 (br s, 1 H), 10.42 (br s, 1 H), 8.31 (s, 1 H), 7.36 (m, 1 H), 6.80 (m, 2 H), 5.01 (m, 1 H), 4.63 (m, 2

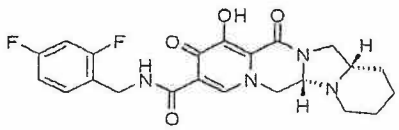
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H), 4.16 (m, 1 H), 3.96 (m, 1H), 3.06-2.93 (m, 2 H), 2.61 (m, 1 H), 2.18 (m, 1 H), 1.93 (m, 1 H), 1.60-1.13 (m, 4 H), 0.893-0.840 (m, 2 H); ES+ MS: 445 (M +1).

c) (For example Z-40). (6aS,7aS,11aS)-N-[(2,4-Difluorophenyl)methyl]-1-hydroxy-2,13-dioxo-2,6a,7,7a,8,9,10,11,11a,13-decahydro-6H-pyrido[1',2':4,5]pyrazino[1,2-a]benzimidazole-3-carboxamide. In a manner similar to that described in example Z-37, from the major diastereomer (30 mg, 0.0561 mmol) prepared in step a and 10 w.t. % Pd/C (catalytic amount), (6aS,7aS,11aS)-N-[(2,4-Difluorophenyl)methyl]-1-hydroxy-2,13-dioxo-2,6a,7,7a,8,9,10,11,11a,13-decahydro-6H-pyrido[1',2':4,5]pyrazino[1,2-a]benzimidazole-3-carboxamide was prepared as a white solid (15 mg, 60%) after purification by HPLC. ^{1}H NMR (methanol-d_4/$CDCl_3$) δ 10.41 (m, 1 H), 8.25 (s, 1 H), 7.30 (m, 1 H), 6.77 (m, 2 H), 4.77 (m, 1 H), 4.57 (m, 2 H), 4.45 (m, 1 H), 3.91 (m, 1 H), 3.12 (m, 1 H), 2.67 (m, 1 H), 2.12 (m, 1 H), 1.87-1.84 (m, 2 H), 1.47-1.33 (m, 4 H); ES+ MS: 445 (M +1).

Example Z-41:

(5aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-11-hydroxy-10,12-dioxo-1,2,3,4,5a,6,10,12,14,14a-decahydropyrido[1,2-a]pyrido[1',2':3,4]imidazo[1,2-d]pyrazine-9-carboxamide.



a) (5aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-10,12-dioxo-11-[(phenylmethyl)oxy]-1,2,3,4

,5a,6,10,12,14,14a-decahydropyrido[1,2-a]pyrido[1',2':3,4]imidazo[1,2-d]pyrazine-9-carboxamide. In a manner similar to that described in example Z-18, from 16a (50 mg, 0.108 mmol) and [(2S)-2-piperidinylmethyl]amine hydrochloride (50 mg, 0.269 mmol, made in a similar manner as described in example Z-18) was prepared (5aS,14aS)-N-[(2,4-difluorophenyl)methyl]-10,12-dioxo-11-[(phenylmethyl)oxy]-1,2,3,4,5a,6,10,12,14,14a-decahydropyrido[1,2-a]pyrido[1',2':3,4]imidazo[1,2-d]pyrazine-9-carboxamide (40 mg, 78 %). ^{1}H NMR ($CDCl_3$) δ 10.43 (m, 1 H), 8.38 (s, 1 H), 7.59 (m, 2 H), 7.59-7.25 (m, 4 H), 6.81 (m, 2 H), 5.38 (d, J = 10 Hz, 1 H), 5.19 (d, J = 10 Hz, 1 H), 4.65-4.62 (m, 2 H), 4.20 (dd, J = 12, 2.8 Hz, 1 H), 4.00 (dd, J = 12.4, 2.8 Hz, 1 H), 3.85 (m, 1 H), 3.74 (m, 1 H), 3.27 (m, 1 H), 2.99 (m, 1 H), 2.43 (m, 1 H), 2.24 (m, 1 H), 1.94-1.87 (m, 2 H), 1.77-1.58 (m, 2 H), 1.39-1.24 (m, 2 H); ES$^+$ MS: 535 (M +1).

b)

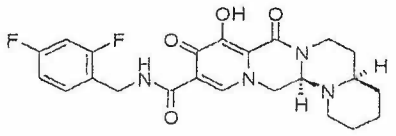
(5aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-11-hydroxy-10,12-dioxo-1,2,3,4,5a,6,10,12,14,14a-decahydropyrido[1,2-a]pyrido[1',2':3,4]imidazo[1,2-d]pyrazine-9-carboxamide. In a manner similar to that described in example Z-37, from (5aS,14aS)-N-[(2,4-difluorophenyl)methyl]-10,12-dioxo-11-[(phenylmethyl)oxy]-1,2,3,4,5a,6,10,12,14,14a-decahydropyrido[1,2-a]pyrido[1',2':3,4]imidazo[1,2-d]pyrazine-9-carboxamide (18 mg, 0.0337 mmol) and 10 w.t.% Pd/C (catalytic amount) was prepared the title compound as a white solid (13 mg, 87%) after purification by HPLC. ^{1}H NMR ($CDCl_3$) δ 11.71 (br s, 1 H), 10.36 (br s, 1 H), 8.31 (s, 1 H), 7.34 (m, 1 H), 6.78 (m, 2 H), 4.64-4.57 (m, 2 H), 4.28 (m, 1 H), 4.12 (m, 1 H), 3.92-3.89 (m, 2 H), 3.22 (m, 1 H), 3.04 (m, 1 H), 2.49 (m, 1 H), 2.28 (m, 1 H), 1.97-1.89 (m, 2 H), 1.78 (m, 1 H),

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1.66-1.60 (m, 2 H), 1.43-1.36 (m, 2 H); ES+ MS: 445 (M +1).

Example Z-42:

(4aR,14aR)-N-[(2,4-Difluorophenyl)methyl]-9-hydroxy-8,10-dioxo-2,8,4,4a,5,6,8,10,14,14a-decahydro-1H-pyrido[1,2-c]pyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-11-carboxamide.



a) Phenylmethyl (2R)-2-(hydroxymethyl)-1-piperidinecarboxylate. In a manner similar to that described in example Z-3a, from (2R)-1-{[(phenylmethyl)oxy]carbonyl}-2-piperidinecarboxylic acid (4.93 g, 18.75 mmol) was prepared phenylmethyl (2R)-2-(hydroxymethyl)-1-piperidinecarboxylate (2.24 g, 48%) as an oil that solidified upon standing to a white solid. ^{1}H NMR ($CDCl_3$) δ 7.36-7.26 (m, 5 H), 5.18-5.10 (m, 2 H), 4.37 (m, 1 H), 4.03 (m, 1 H), 3.84 (, m, 1 H), 3.63 (m, 1 H), 2.96 (br s, 1 H), 1.71-1.42 (m, 6 H).

b) Phenylmethyl (2R)-2-(cyanomethyl)-1-piperidinecarboxylate. In a manner similar to that described in example Z-3b, from phenylmethyl (2R)-2-(hydroxymethyl)-1-piperidinecarboxylate (1.09g, 4.38 mmol) was prepared phenylmethyl (2R)-2-({[(4-methylphenyl)sulfonyl]oxy}methyl)-1-piperidinecarboxylate (1.05g, 59% impure with uncharacterized byproduct) as a clear colorless oil after purification using silica gel chromatography (10-100% ethyl acetate-hexanes). It is

necessary to use this material in the next step as soon as possible or yields deteriorate dramatically. In a manner similar to that described in example Z-3c, from phenylmethyl (2R)-2-({[(4-methylphenyl)sulfonyl]oxy}methyl)-1-piperidinecarboxylate (1.05 g, 2.61 mmol) and sodium cyanide (383 mg, 7.82 mmol) was prepared phenylmethyl (2R)-2-(cyanomethyl)-1-piperidinecarboxylate (171 mg, 25 %) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.35-7.29 (m, 5 H), 5.13 (s, 2 H), 4.65 (m, 1 H), 4.10 (m, 1 H), 2.96 (m, 1 H), 2.60 (m, 2 H), 1.82-1.67 (m, 4 H), 1.54-1.39 (m, 2 H).

d) Phenylmethyl (2R)-2-(2-aminoethyl)-1-piperidinecarboxylate. In a manner similar to that described in example Z-3d, from phenylmethyl (2R)-2-(cyanomethyl)-1-piperidinecarboxylate (171 mg, 0.663 mmol) was prepared phenylmethyl (2R)-2-(2-aminoethyl)-1-piperidinecarboxylate (119 mg, 68%) as a clear colorless residue. ^{1}H NMR ($CDCl_3$) δ 7.32-7.25 (m, 5 H), 5.08 (m, 2 H), 4.39 (br s, 1 H), 4.01 (br s, 1 H), 2.78 (m, 1 H), 2.60-2.56 (m, 2 H), 1.95-1.86 (m, 3 H), 1.63-1.35 (m, 6 H).

e) {2-[(2R)-2-Piperidinyl]ethyl}amine. Phenylmethyl (2R)-2-(2-aminoethyl)-1-piperidinecarboxylate (119 mg, 0.454 mmol) was dissolved in methanol and 10 w.t.% Pd/C (120 mg) was added. Hydrogen was bubbled through the solution for 15 minutes and the reaction was stirred under 1 atm hydrogen for 18 hours until determined complete by TLC (1% ammonium hydroxide 19% methanol 80% dichloromethane). The suspension was filtered through Celite eluting with

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methanol and the filtrate was carefully concentrated under reduce pressure to yield a clear colorless liquid (58 mg, quantitative). ^{1}H NMR ($CDCl_3$) δ 2.99 (m, 1 H), 2.71-2.66 (m, 2 H), 2.57-2.48 (m, 2 H), 1.72 (m, 1 H), 1.61-1.52 (m, 2 H), 1.48-1.42 (m, 2 H), 1.35-1.25 (m, 2 H), 1.05 (m, 1 H).

f)

(4aR,14aR)-N-[(2,4-Difluorophenyl)methyl]-8,10-dioxo-9-[(phenylmethyl)oxy]-2,3,4,4a,5,6,8,10,14,14a-decahydro-1H-pyrido[1,2-c]pyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-11-carboxamide. In a manner similar to that described in example Z-35, from 16a (50 mg, 0.106 mmol) and {2-[(2R)-2-piperidinyl]ethyl}amine (58 mg, 0.454 mmol) was prepared (4aR,14aR)-N-[(2,4-difluorophenyl)methyl]-8,10-dioxo-9-[(phenylmethyl)oxy]-2,3,4,4a,5,6,8,10,14,14a-decahydro-1H-pyrido[1,2-c]pyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-11-carboxamide (47 mg, 81%). ^{1}H NMR ($CDCl_3$) δ 10.50 (br s, 1 H), 8.33 (s, 1 H), 7.60 (s, 2 H), 7.38-7.24 (m, 4 H), 6.80 (m, 2 H), 5.29-5.22 (m, 2 H), 4.66-4.56 (m, 3 H), 4.30 (m, 1 H), 4.19 (m, 1 H), 3.78 (br s, 1 H), 2.86-2.80 (m, 2 H), 2.18 (br s, 1 H), 1.94 (m, 1 H), 1.68-1.36 (m, 6 H), 1.23 (br s, 2 H); ES$^+$ MS: 549 (M +1).

g)

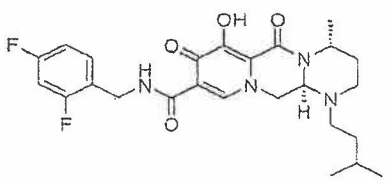
(4aR,14aR)-N-[(2,4-Difluorophenyl)methyl]-9-hydroxy-8,10-dioxo-2,3,4,4a,5,6,8,10,14,14a-decahydro-1H-pyrido[1,2-c]pyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-11-carboxamide. In a manner similar to that described in example Z-37, from (4aR,14aR)-N-[(2,4-difluorophenyl)methyl]-8,10-dioxo-9-[(phenylmethyl)oxy]-2,3,4,4a,

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5,6,8,10,14,14a-decahydro-1H-pyrido[1,2-c]pyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-1 1-carboxamide (47 mg, 0.0857 mmol) and a catalytic amount of 10 w.t.% Pd/C was prepared the title compound as a white solid (19 mg, 54%) after purification by HPLC. ^{1}H NMR ($CDCl_3$) δ 10.49 (m, 1 H), 8.29 (s, 1 H), 7.34 (m, 1 H), 6.79 (m, 2 H), 4.67-4.56 (m, 3 H), 4.41 (m, 1 H), 4.20 (m, 1 H), 3.93 (s, 1 H), 2.94-2.87 (m, 2 H), 2.28 (br s, 1 H), 2.01 (m, 1 H), 1.68-1.54 (m, 4 H), 1.44 (m, 1 H), 1.29-1.23 (m, 3 H), 0.850 (m, 1 H); ES$^+$ MS: 459 (M +1).

Example Z-43:

(4*R*,12a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(3-methylbutyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide.



a) [(3*R*)-3-Ainobutyl](3-methylbutyl)amine dihydrochloride was prepared in a similar manner as described in example Z-32. ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$) δ 0.87 (d, J = 5.2 Hz, 6H), 1.32 (m, 3H), 1.61 (m, 3H), 2.10-2.20 (m, 2H), 2.90-3.04 (m, 4H), 3.46 (m, 1H), 8.23 (br, < 1 H), 8.96 (br, < 1 H).

b)

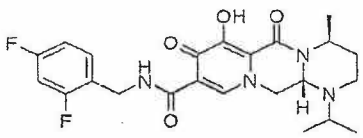
(4*R*,12a*R*)-*N*-[(2,4-Dfluorophenyl)methyl]-7-hydroxy-4-methyl-1-(3-methylbutyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxam

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ide. The title compound was made in two steps using a similar process to that described in example Z-2. 16a (40 mg, 0.085 mmol) and free [(3*R*)-3-aminobutyl](3-methylbutyl)amine (46 mg, 0.35 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (4*R*,12a*R*)-*N*-[(2,4-difluorophenyl)methyl]-4-methyl-1-(3-methylbutyl)-6,8-dioxo-7-[(phenylmethyl)oxy]-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (44 mg, 90%) as a film. This material was hydrogenated in a second step as described in example Z-2 to give (4*R*,12a*R*)-*N*-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(3-methylbutyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (11 mg, 30%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H), 1.24-1.36 (m, 5H), 1.47-1.53 (m, 2H), 2.02-2.11 (m, 1H), 2.36-2.43 (m, 1H), 2.54-2.61 (m, 1H), 2.77-2.92 (m, 2H), 4.16-4.26 (m, 2H), 4.44 (m, 1H), 4.62-4.64 (m, 2H), 4.95-5.02 (m, 1H), 6.75-6.81 (m, 2H), 7.31-7.37 (m, 1H), 8.27 (s, 1H), 10.43 (m, 1H), 12.54 (s, 1H); ES$^+$ MS: 489 (M+1).

Example Z-44:

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(1-methylethyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide.



a) [(3*S*)-3-Aminobutyl](1-methylethyl)amine dihydrochloride was prepared in a similar manner as described in example Z-29. ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$) δ 1.20-1.25 (m, 9H), 1.93-2.02 (m, 2H), 2.92 (m, 2H), 3.20-3.29 (m, 2H), 8.04 (br, < 1 H), 8.64 (br, < 1 H).

b)

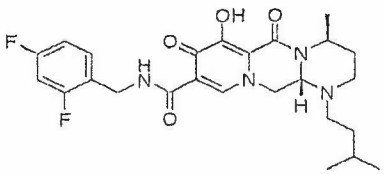
(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(1-methylethyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide. The title compound was made in two steps using a similar process to that described in example Z-2. 16a (60 mg, 0.13 mmol) and free based [(3*S*)-3-aminobutyl](1-methylethyl)amine (55 mg, 0.42 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (4*S*,12a*S*)-*N*-[(2,4-difluorophenyl)methyl]-4-methyl-1-(1-methylethyl)-6,8-dioxo-7-[(phenylmethyl)oxy]-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (40 mg, 57%) as a film. This material was hydrogenated in a second step as described in example Z-2 to give (4*S*,12a*S*)-*N*-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(1-methylethyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (17 mg, 50%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (d, *J* = 6.4 Hz, 3H), 1.07 (d, *J* = 6.4 Hz, 3H), 1.33 (d, *J* = 7.2 Hz, 3H), 1.55-1.58 (m, 1H), 1.94-2.03 (m, 1H), 2.70-2.77 (m, 1H), 2.81-2.86 (m, 1H), 3.11-3.18 (m, 1H), 4.17 (dd, *J* = 3.0, 13.8 Hz, 1H), 4.32 (dd, *J* = 3.2, 14.0 Hz, 1H), 4.48 (m, 1H), 4.59-4.69 (m, 2H), 4.97-5.00 (m, 1H), 6.77-6.83 (m, 2H), 7.33-7.39 (m, 1H), 8.28 (s, 1H), 10.50 (m, 1H), 12.55 (s, 1H);

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ES+ MS: 461 (M+1).

Example Z-45:

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(3-methylbutyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide.



a) [(3*S*)-3-Aminobutyl](3-methylbutyl)amine dihydrochloride was prepared in a similar manner as described in example Z-32. ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$) δ 0.86 (d, *J* = 5.6 Hz, 6H), 1.27 (d, *J* = 6.0 Hz, 3H), 1.58 (m, 3H), 2.03-2.14 (m, 2H), 2.87-2.99 (m, 4H), 3.38 (m, 1H), 8.15 (br, < 1 H), 8.87 (br, < 1 H).

b)

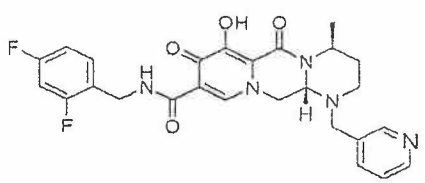
(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(3-methylbutyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide. The title compound was made in two steps using a similar process to that described in example Z-2. 16a (0.100 g, 0.21 mmol) and free based [(3*S*)-3-aminobutyl](3-methylbutyl)amine (0.104 g, 0.66 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (4*S*,12a*S*)-*N*-[(2,4-difluorophenyl)methyl]-4-methyl-1-(3-methylbutyl)-6,8-dioxo-7-[(phenylmethyl)oxy]-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine

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·9·carboxamide (88 mg, 72%) as a film. This material was hydrogenated in a second step as described in example Z·2 to give (4*S*,12a*S*)·*N*·[(2,4·difluorophenyl)methyl]·7·hydroxy·4·methyl·1·(3·methylbutyl)·6,8·dioxo·1,2,3,4,6,8,12,12a·octahydropyrido[1',2':4,5]pyrazino[1,2·*a*]pyrimidine·9·carboxamide (55 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (d, J = 6.4 Hz, 3H), 0.85·(d, J = 6.4 Hz, 3H), 1.24·1.37 (m, 5H), 1.45·1.53 (m, 2H), 2.02·2.11 (m, 1H), 2.37·2.44 (m, 1H), 2.56·2.63 (m, 1H), 2.80·2.92 (m, 2H), 4.22·4.29 (m, 2H), 4.45 (s, 1H), 4.62·4.68 (m, 2H), 4.97·5.00 (m, 1H), 6.75·6.82 (m, 2H), 7.31·7.37 (m, 1H), 8.37 (s, 1H), 10.48 (m, 1H), 12.53 (br, 1H); ES$^+$ MS: 489 (M+1).

Example Z·46:

(4*S*,12a*S*)·*N*·[(2,4·Difluorophenyl)methyl]·7·hydroxy·4·methyl·6,8·dioxo·1·(3·pyridinylmethyl)·1,2,3,4,6,8,12,12a·octahydropyrido[1',2':4,5]pyrazino[1,2·*a*]pyrimidine·9·carboxamide.



a) 1,1·Dimethylethyl {(1*S*)·1·methyl·3·[(3·pyridinylmethyl)amino]propyl}carbamate. The protected diamine was prepared using a modified procedure as described in example Z·32. A solution of 1,1·dimethylethyl [(1*S*)·3·amino·1·methylpropyl]carbamate (0.296 g, 1.6 mmol) and 3·pyridinecarboxaldehyde (120 µL, 1.3 mmol) in a 1:1 mixture of anhydrous dichloroethane and tetrahydrofuran (10 mL) was treated with acetic acid (374 µL, 6.6

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mmol) and stirred for 30 minutes. Sodium triacetoxyborohydride (0.444 g, 2.1 mmol) was added and the solution was stirred for 2 hours. The resultant was subjected to a workup and purification procedure as described in example Z-32 to give 1,1-dimethylethyl {(1*S*)-1-methyl-3-[(3-pyridinylmethyl)amino]propyl}carbamate (0.245 g, 66%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (d, J = 6.4 Hz, 3H), 1.42 (s, 9H), 1.46-1.54 (m, 1H), 1.68 (m, 1H), 2.61-2.75 (m, 2H), 3.73- 3.80 (m, 3H), 4.86 (m, 1H), 7.22-7.24 (m, 1H), 7.68 (d, J = 8.0 Hz, 1H), 8.48 (m, 1H), 8.53 (m, 1H).

b) [(3*S*)-3-Aminobutyl](3-pyridinylmethyl)amine dihydrochloride was prepared in a similar manner as described in example Z-29.

c)

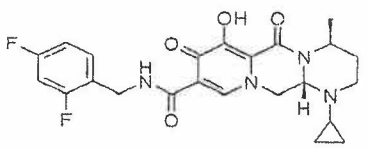
(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1-(3-pyridinyl methyl)-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carbo xamide. The title compound was made in two steps using a similar process to that described in example Z-2. 16a (60 mg, 0.13 mmol) and free based [(3*S*)-3-aminobutyl](3-pyridinylmethyl)amine (83 mg, 0.47 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (4*S*,12a*S*)-*N*-[(2,4-difluorophenyl)methyl]-4-methyl-6,8-dioxo-7-[(phenylmethyl)oxy]-1-(3-pyridinylmethyl)-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimi dine-9-carboxamide (72 mg, 95%) as a film. This material was hydrogenated in a second step as described in example Z-2 to give (4*S*,12a*S*)-*N*-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1-(3-pyridinyl

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methyl)-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (34 mg, 56%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (d, J = 6.8 Hz, 3H), 1.43-1.47 (m, 1H), 2.12 (m, 1H), 2.60-2.92 (m, 2H), 3.53 (d, J = 14.0 Hz, 1H). 3.82 (d, J = 14.4 Hz, 1H), 4.23-4.31 (m, 2H), 4.55-4.64 (m, 3H), 5.06-5.11 (m, 1H), 6.75-6.82 (m, 2H), 7.20-7.23 (m, 1H), 7.31-7.36 (m, 1H), 7.50 (m, 1H), 7.92 (s, 1H), 8.48 (s, 1H), 10.39 (m, 1H), 12.5 (br, 1H); ES$^+$ MS: 510 (M+1).

Example Z-47:

(4*S*,12a*S*)-1-Cyclopropyl-*N*-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide.



a) 1,1-Dimethylethyl [(1*S*)-1-methyl-3-oxopropyl]carbamate. To a stirred solution of 1,1-dimethylethyl [(1*S*)-2-cyano-1-methylethyl]carbamate (0.656 g, 3.56 mmol) in anhydrous ether cooled to -40 °C was added dropwise a 1.0 M solution of diisobutylaluminum hydride in hexanes (14.2 mL, 14.2 mmol) over 20 minutes. Stirring was continued at this temperature for an additional 20 minutes. The yellow solution was quenched with Rochelle's salt and the resultant stirred at room temperature for 1 hour. The solids were filtered off through celite and rinsed with EtOAc. The organics were washed with brine, concentrated, and flash chromatographed (10-100% EtOAc/hexanes) to give 1,1-dimethylethyl [(1*S*)-1-methyl-3-oxopropyl]carbamate (0.193 g, 30 %) as a clear oil. ^{1}H NMR (400

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MHz, $CDCl_3$) δ 1.22 (d, J = 6.8 Hz, 3H), 1.41 (s, 9H), 2.53-2.65 (m, 2H), 4.08-4.13 (m, 1H), 4.63 (m, 1H), 9.74-9.75 (m, 1H).

b) 1,1-Dimethylethyl [(1*S*)-3-(cyclopropylamino)-1-methylpropyl]carbamate. The protected diamine was prepared using a modified procedure as described in example Z-32. A solution of 1,1-dimethylethyl [(1*S*)-1-methyl-3-oxopropyl]carbamate (0.178 g, 0.95 mmol) and cyclopropylamine (197 µL, 2.85 mmol) in anhydrous dichloroethane (10 mL) was treated with acetic acid (272 µL, 4.8 mmol) and stirred for 30 minutes. Sodium triacetoxyborohydride (0.444 g, 2.1 mmol) was added and the solution was stirred for 20 hours. The resultant was subjected to a workup and purification procedure as described in example Z-32 to give 1,1-dimethylethyl [(1*S*)-3-(cyclopropylamino)-1-methylpropyl]carbamate (0.136 g, 63%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.32-0.42 (m, 4H), 1.12 (d, J = 6.8 Hz, 3H), 1.39-1.51 (m, 10H), 1.58-1.92 (m, 2H), 2.05-2.10 (m, 1H), 2.67-2.80 (m, 2H), 3.71 (m, 1H), 4.78 (m, 1H).

c) [(3*S*)-3-Aminobutyl]cyclopropylamine dihydrochloride was prepared in a similar manner as described in example Z-29. ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$) δ 0.70-0.75 (m, 2H), 0.90-0.94 (m, 2H), 1.18 (d, J = 6.8 Hz, 3H), 1.84-1.94 (m, 1H), 1.97-2.05 (m, 1H), 2.49-2.54 (m, 1H), 2.99-3.04 (m, 2H), 3.23-3.28 (m, 1H).

d)

(4*S*,12a*S*)-1-Cyclopropyl-*N*-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-

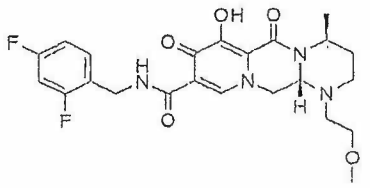
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1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide. The title compound was made in two steps using a similar process to that described in example Z-2. 16a (80 mg, 0.17 mmol) and free based [(3*S*)-3-aminobutyl]cyclopropylamine (75 mg, 0.59 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (4*S*,12a*S*)-1-cyclopropyl-*N*-[(2,4-difluorophenyl)methyl]-4-methyl-6,8-dioxo-7-[(phenylmethyl)oxy]-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (74 mg, 80%) as a film. This material was hydrogenated in a second step as described in example Z-2 to give (4*S*,12a*S*)-1-cyclopropyl-*N*-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (32 mg, 52%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.37-0.54 (m, 3H), 0.64-0.70 (m, 1H), 1.35 (d, *J* = 7.2 Hz, 3H), 1.45-1.49 (m, 1H), 1.76-1.80 (m, 1H), 2.03-2.12 (m, 1H), 2.86-2.93 (m, 1H), 2.99-3.04 (m, 1H), 4.30 (dd, *J* = 4.0, 13.6 Hz, 1H), 4.49-4.67 (m, 4H), 5.00-5.07 (m, 1H), 6.75-6.82 (m, 2H), 7.32-7.36 (m, 1H), 8.28 (s, 1H), 10.49 (m, 1H), 12.53 (s, 1H); ES$^+$ MS: 459 (M+1).

Example Z-48:

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-[2-(methyloxy)ethyl]-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide.

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a) [(3*S*)-3-Aminobutyl][2-(methyloxy)ethyl]amine dihydrochloride. The protected diamine, 1,1-dimethylethyl ((1*S*)-1-methyl-3-{[2-(methyloxy)ethyl]amino}propyl)carbamate was prepared in a similar manner as described in example Z-47. Subsequently, [(3*S*)-3-aminobutyl][2-(methyloxy)ethyl]amine dihydrochloride was prepared in a similar manner as described in example Z-29. ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$) δ 1.21 (d, J = 5.6 Hz, 3H), 1.93 (m, 1H), 2.04 (m, 1H), 2.98-3.05 (m, 4H), 3.22 (m, 2H), 3.26-3.31 (m, 4H), 8.06 (br, < 1 H), 8.81 (br, < 1 H).

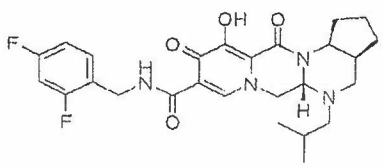
b) (4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-[2-(methyloxy)ethyl]-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide. The title compound was made in two steps using a similar process to that described in example Z-2. 16a (60 mg, 0.13 mmol) and free based [(3*S*)-3-aminobutyl][2-(methyloxy)ethyl]amine (68 mg, 0.37 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (4*S*,12a*S*)-*N*-[(2,4-difluorophenyl)methyl]-4-methyl-1-{2-(methyloxy)ethyl]-6,8-dioxo-7-[(phenylmethyl)oxy]-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (47 mg, 63%) as a film. This material was hydrogenated in a

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second step as described in example Z-2 to give (4*S*,12a*S*)-*N*-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-1-[2-(methyloxy)ethyl]-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (38 mg, 97%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (d, J = 7.2 Hz, 3H), 1.49 (m, 1H), 2.03-2.12 (m, 1H), 2.67-2.70 (m, 1H), 2.81-2.92 (m, 2H), 3.06-3.16 (m, 1H), 3.30-3.37 (m, 4H), 3.58-3.63 (m, 1H), 4.20 (dd, J = 3.4, 14.2 Hz, 1H), 4.50-4.59 (m, 1H), 4.62-4.65 (m, 3H), 5.00-5.03 (m, 1H), 6.75-6.81 (m, 2H), 7.31-7.37 (m, 1H), 8.27 (s, 1H), 10.46 (s, 1H), 12.54 (s, 1H); ES$^+$ MS: 477 (M+1).

Example Z-49:

racemic-(3aS,5aS,13aS)-N-[(2,4-Difluorophenyl)methyl]-11-hydroxy-5-(2-methylpropyl)-10,12-dioxo-2,3,3a,4,5,5a,6,10,12,13a-decahydro-1H-cyclopenta[e]pyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide.



a) *racemic*-(1S,2S)-2-{[(2-Methylpropyl)amino]methyl}cyclopentanamine hydrochloride.

In a manner similar to example Z-18a-c, from *racemic*-(1R,2S)-2-(([[(1,1-dimethylethyl)oxy]carbonyl}amino)cyclopentanecarboxylic acid (255 mg, 1.11 mmol) was prepared *racemic*-1,1-dimethylethyl [(1S,2S)-2-(aminomethyl)cyclopentyl]carbamate (153 mg, 64 % over 3 steps) as a white green residue. Reductive amination with isobutyraldehyde followed by deprotection

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as described in Z-38 steps c and d respectively, gave *racemic*-(1S,2S)-2-{[(2-methylpropyl)amino]methyl}cyclopentanamine hydrochloride (105 mg, 39% over 5 steps from amino acid). ^{1}H NMR (methanol-d_4/$CDCl_3$) 8.90 (br s, <1 H), 8.64 (br s, <1 H), 8.28 (m, 1 H), 3.97 (br s, 1 H), 3.37 (m, 1 H), 2.83-2.69 (m, 3 H), 2.18-1.69 (m, 7 H), 0.996 (m, 6 H).

b)

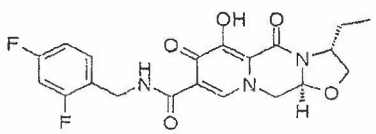
racemic-(3aS,5aS,13aS)-N-[(2,4-Difluorophenyl)methyl]-11-hydroxy-5-(2-methylpropyl)-10,12-dioxo-2,3,3a,4,5,5a,6,10,12,13a-decahydro-1H-cyclopenta[e]pyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide. In a manner similar to that described in example Z-35, from *racemic*-(1S,2S)-2-{[(2-methylpropyl)amino]methyl}cyclopentanamine hydrochloride 105 mg, 0.434 mmol) and 16a (56 mg, 0.119 mmol) was prepared *racemic*-(3aS,5aS,13aS)-N-[(2,4-difluorophenyl)methyl]-5-(2-methylpropyl)-10,12-dioxo-11-[(phenylmethyl)oxy]-2,3,3a,4,5,5a,6,10,12,13a-decahydro-1H-cyclopenta[e]pyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide (62 mg, 74%). This material was deprotected in a second step similar to the procedure described in example Z-37. Thus, from *racemic*-(3aS,5aS,13aS)-N-[(2,4-difluorophenyl)methyl]-5-(2-methylpropyl)-10,12-dioxo-11-[(phenylmethyl)oxy]-2,3,3a,4,5,5a,6,10,12,13a-decahydro-1H-cyclopenta[e]pyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide (48 mg, 0.081 mmol) and 10% Pd/C (catalytic amount), the title compound was prepared as a white solid after purification by HPLC (30 mg, 75%). ^{1}H NMR ($CDCl_3$) 12.59 (s, 1 H), 10.42 (s, 1 H), 828 (s, 1 H),

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7.34 (m, 1 H), 6.79 (m, 2 H), 4.83 (s, 1 H), 4.63-4.58 (m, 3 H), 4.29 (m, 1 H), 4.14 (m, 1 H), 2.91 (m, 1 H), 2.46-2.32 (m, 3 H), 2.15-2.09 (m, 2 H), 1.85-1.61 (m, 5 H), 1.39 (m, 1 H), 0.88 (m, 6 H); ES+ MS: 501 (M +1).

Example Z-50:

(3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-3-ethyl-6-hydroxy-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide.

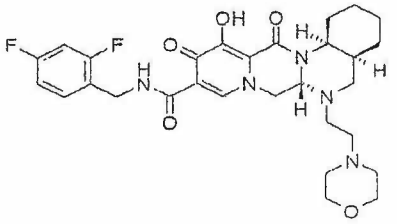


The title compound was made in two steps using a similar process to that described in example Z-2. 16a (40 mg, 0.09 mmol) and (2*R*)-2-amino-1-butanol (0.02 mL, 0.21 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (3*R*,11a*S*)-*N*-[(2,4-difluorophenyl)methyl]-3-ethyl-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (40 mg, 93%). This material was hydrogenated in a second step as described in example Z-2 to give (3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-3-ethyl-6-hydroxy-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (30 mg, 91%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 11.49 (br, 1 H), 10.28 (m, 1 H), 8.35 (s, 1 H), 7.34 (m, 1 H), 6.79 (m, 2), 5.30 (m, 1 H), 4.62 (m, 2 H), 4.45-4.32 (m, 3 H), 3.93-3.86 (m, 2 H), 2.11 (m, 1 H), 1.65 (m, 1 H), 0.98 (t, J = 7.6 Hz, 3 H); ES+ MS: 420 (M +1).

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Example Z-51:

racemic-(4aS,6aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy-6-[2-(4-morpholinyl)ethyl]-11,13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide.



a) *racemic*-1,1-Dimethylethyl [(1S,2R)-2-formylcyclohexyl]carbamate. An alternative procedure from the one given in example Z-38b follows: To a solution of Dess-Martin Periodane (564 mg, 1.33 mmol) in dichloromethane was added *racemic*-1,1-dimethylethyl [(1S,2R)-2-(hydroxymethyl)cyclohexyl]carbamate (305 mg, 1.33 mmol, see example Z-38a) dropwise as a solution in dichloromethane. The reaction was stirred 1 hour at ambient temperature until judged complete by TLC (1:1 hexanes: ethyl acetate $KMnO_4$ stain). The reaction was quenched with aqueous sodium bicarbonate and sodium thiosulfate solutions, extracted with dichloromethane, and the combined organics were dried over sodium sulfate. Silica gel chromatography (0-50% ethyl acetate/ hexanes gradient elution) gave *racemic*-1,1-dimethylethyl [(1S,2R)-2-formylcyclohexyl]carbamate (280, 93%). See example Z-38b for NMR data.

b) *racemic*-{[(1S,2S)-2-Aminocyclohexyl]methyl}[2-(4-morpholinyl)ethyl]amine

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hydrochloride. In a manner similar to that described in example Z-38c-d from *racemic*-1,1-dimethylethyl [(1S,2R)-2-formylcyclohexyl]carbamate (78 mg, 0.344 mmol, prepared using the procedure from example Z-38b) and [2-(4-morpholinyl)ethyl]amine (67 mg, 0.515 mmol) was prepared *racemic*-{[(1S,2S)-2-aminocyclohexyl]methyl}[2-(4-morpholinyl)ethyl]amine hydrochloride (95 mg, 78% over 2 steps) as a white solid. ^{1}H NMR (methanol-d_4/$CDCl_3$) 8.18 (br s, 1 H), 3.84-3.493 (m, 11 H), 3.19-3.119 (m, 5 H), 2.42 (m, 1 H), 2.11 (br s, 2 H), 1.87-1.17 (m, 10 H).

c)

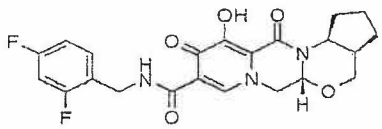
racemic-4aS,6aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy-6-[2-(4-morpholinyl)ethyl]-11,13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide. In a manner similar to that described in example Z-35, from *racemic*-{[(1S,2S)-2-aminocyclohexyl]methyl}[2-(4-morpholinyl)ethyl]amine hydrochloride (95 mg, 0.272 mmol) and 16a (45 mg, 0.0957 mmol) was prepared *racemic*-(4aS,6aS,14aS)-N-[(2,4-difluorophenyl)methyl]-6-[2-(4-morpholinyl)ethyl]-11,13-dioxo-12-[(phenylmethyl)oxy]-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide (27 mg, 43%). This material was deprotected in a second step similar to the procedure described in example Z-37. From *racemic*-(4aS,6aS,14aS)-N-[(2,4-difluorophenyl)methyl]-6-[2-(4-morpholinyl)ethyl]-11,13-dioxo-12-[(phenylmethyl)oxy]-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':

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4,5]pyrazino[1,2-a]quinazoline-10-carboxamide (27 mg, 0.0408 mmol) and 10% Pd/C (1 mg) the title compound was prepared as a white solid after purification by HPLC. ^{1}H NMR ($CDCl_3$) 12.30 (br s, <1 H), 10.41 (br s, 1 H), 8.29 (s, 1 H), 7.34 (m, 2 H), 6.78 (m, 2 H), 4.76 (m, 1 H), 4.62-4.54 (m, 3 H), 4.29 (m, 2 H), 3.65 (m, 4 H), 3.01 (m, 1 H), 2.76 (m, 2 H), 2.58-2.42 (m, 7 H), 2.21 (m, 1 H), 1.89-1.23 (m, 8 H); ES$^+$ MS: 572 (M +1).

Example Z-52:

racemic-(3aR,5aR,13aS)-N-[(2,4-Difluorophenyl)methyl]-11-hydroxy-10,12-dioxo-1,2,3,3a,4,5a,6,10,12,13a-decahydrocyclopenta[d]pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxamide.



a) *racemic*-1,1-Dimethylethyl [(1S,2R)-2-(hydroxymethyl)cyclopentyl]carbamate, *racemic*-(1R,2S)-2-({[(1,1-Dimethylethyl)oxy]carbonyl}amino)cyclopentanecarboxylic acid (22 mg, 0.096 mmol) was dissolved in tetrahydrofuran and placed in an ice-water bath. Triethylamine was added, followed by the slow addition of methyl chloroformate. The reaction was stirred ten minutes in the ice-bath and sodium borohydride was added. Methanol was then added slowly and stirring was continued for two hours while the ice-bath expired. 1 M Potassium hydrogen sulfate was added, the reaction was partially concentrated, and product was extracted with dichloromethane. The combined organics were washed with sodium bicarbonate, brine, and dried over sodium sulfate. Removal of solvents under reduced pressure

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afforded *racemic*-1,1-dimethylethyl [(1S,2R)-2-(hydroxymethyl)cyclopentyl]carbamate (25 mg, >100%). ^{1}H NMR ($CDCl_3$) 4.50 (br s, 1 H), 4.06 (m, 1 H), 3.54 (m, 1 H), 3.37 (m, 1 H), 2.09 (m, 1 H), 1.96 (m, 1 H), 1.64 (m, 3 H), 1.52 (m, 1 H), 1.43 (s, 9 H), 1.11 (m, 2 H).

b) *racemic*-[(1R,2S)-2-Aminocyclopentyl]methanol hydrochloride. In a manner similar to that described in example, from *racemic*-1,1-dimethylethyl [(1S,2R)-2-(hydroxymethyl)cyclopentyl]carbamate and 4 N HCl was prepared *racemic*-[(1R,2S)-2-aminocyclopentyl]methanol hydrochloride (20 mg, quantitative). ^{1}H NMR (methanol-d4-$CDCl_3$) 7.76 (br s, <1 H), 3.73 (m, 1 H), 3.61- 3.28 (m, 3 H), 2.27 (br s, 1 H), 2.01 (m, 2.01 (m, 1 H), 1.74-1.70 (m, 2 H), 1.56-1.42 (m, 2 H), 1.16 (br s, 1 H), 1.05 (br s, 1 H).

c)

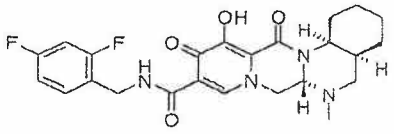
racemic-(3aR,13aS)-N-[(2,4-Difluorophenyl)methyl]-11-hydroxy-10,12-dioxo-1,2,3,3a,4,5a,6,10,12,13a-decahydrocyclopenta[d]pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxamide. In a manner similar to that described in example Z-35, from *racemic*-[(1R,2S)-2-aminocyclopentyl]methanol hydrochloride (20 mg, 0.132 mmol) and 16a (24 mg, 0.051 mmol) was prepared *racemic*-(3aR,13aS)-N-[(2,4-difluorophenyl)methyl]-10,12-dioxo-11-[(phenylmethyl)oxy]-1,2,3,3a,4,5a,6,10,12,13a-decahydrocyclopenta[d]pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxamide (7 mg, 26 %) as a white solid. This material was deprotected in a second step similar to the procedure described in example Z-37. Thus, from

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racemic-(3aR,13aS)-N-[(2,4-difluorophenyl)methyl]-10,12-dioxo-11-[(phenylmethyl)oxy]-1,2,3,3a,4,5a,6,10,12,13a-decahydrocyclopenta[d]pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxamide (7 mg, 0.012 mmol) and 10% Pd/C (1 mg), *racemic*-(3aR,13aS)-N-[(2,4-difluorophenyl)methyl]-11-hydroxy-10,12-dioxo-1,2,3,3a,4,5a,6,10,12,13a-decahydrocyclopenta[d]pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxamide (4 mg, 72%) white solid. ^{1}H NMR ($CDCl_3$) 12.20 (br s, 1 H), 10.37 (br s, 1 H), 8.31 (s, 1 H), 7.35 (m, 1 H), 6.80 (m, 2 H), 5.16 (m, 1 H), 4.77 (m, 1 H), 4.64 (m, 2 H), 4.28 (m, 1 H), 4.09 (m, 1 H), 3.97 (m, 1 H), 3.45 (m, 1 H), 2.49-2.20 (m, 2 H), 1.89-1.58 (m, 4 H), 0.936-0.840 (m, 1 H); ES$^+$ MS: 446 (M +1).

Example Z-53:

racemic-(4aS,6aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy-6-methyl-11,13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide.



a) *racemic*-{[(1S,2S)-2-Aminocyclohexyl]methyl}methylamine hydrochloride. In a manner similar to that described in example Z-38c-d from *racemic*-1,1-dimethylethyl [(1S,2R)-2-formylcyclohexyl]carbamate (0.410 mmol) and methyl amine (0.5 mL of a 2 M tetrahydrofuran solution) was prepared *racemic*-{[(1S,2S)-2-aminocyclohexyl]methyl}methylamine hydrochloride in two steps as a white solid (46 mg, 53% 2 steps). ^{1}H NMR (methanol-d_4/$CDCl_3$) 9.05 (br s,<1

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H), 8.72 (br s, < 1 H), 8.24 (br s, 1 H), 3.34 (m, 1 H), 3.29 (m, 1 H), 2.85 (br s, 1H), 2.66 (br s, 4 H), 2.38 (br s, 1 H), 2.07-1.83 (m, 2 H), 1.67-1.14 (m, 6 H).

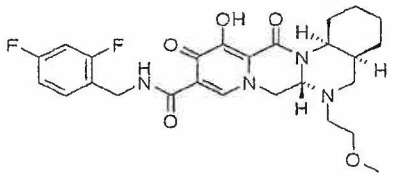
b)

racemic-(4aS,6aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy-6-methyl-11,13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide. In a manner similar to that described in example Z-35, from *racemic*-{[(1S,2S)-2-aminocyclohexyl]methyl}methylamine hydrochloride (46 mg, 0.215 mmol) and 16a (35 mg, 0.0744 mmol) was prepared *racemic*-(4aS,6aS,14aS)-N-[(2,4-difluorophenyl)methyl]-6-methyl-11,13-dioxo-12-[(phenylmethyl)oxy]-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide(17 mg, 41%) as a white solid. This material was deprotected in s second step similar to the procedure described in example Z-37. Thus, from *racemic*-(4aS,6aS,14aS)-N-[(2,4-difluorophenyl)methyl]-6-methyl-11,13-dioxo-12-[(phenylmethyl)oxy]-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide (17 mg, 0.0302 mmol) and 10% Pd/C (1 mg) was prepared the title compound as a white solid (9 mg, 64%). ^{1}H NMR ($CDCl_3$) 10.44 (m, 1 H), 8.29 (s, 1 H), 7.34 (m, 1 H), 6.79 (m, 2 H), 4.78 (m, 1 H), 4.62 (br s, 2 H), 4.29 (br s, 2 H), 3.41 (s, 1 H), 2.92 (m, 1 H), 2.66 (m, 1 H), 2.35-2.25 (m, 4 H), 1.90-1.74 (m, 2 H), 1.67-1.24 (m, 6 H); ES^+ MS: 473(M +1).

Example Z-54:

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racemic-(4aS,6aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy-6-[2-(methyloxy)ethyl]-11,13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide.



a) *racemic*-{[(1S,2S)-2-Aminocyclohexyl]methyl}[2-(methyloxy)ethyl]amine hydrochloride.

In a manner similar to that described in example Z-38c-d from *racemic*-1,1-dimethylethyl [(1S,2R)-2-formylcyclohexyl]carbamate (93 mg, 0.410 mmol) and [2-(methyloxy)ethyl]amine (0.05 mL, 0.615 mmol) was prepared in two steps *racemic*-{[(1S,2S)-2-aminocyclohexyl]methyl}[2-(methyloxy)ethyl]amine hydrochloride (63 mg, 60% 2 steps) as a white solid. ^{1}H NMR (methanol-d_4/$CDCl_3$) 9.02 (br s, <1 H), 8.78 (br s, <1, H), 8.29 (br s, 1 H), 3.69 (br s, 2 H), 3.46)s, 3 H), 3.36-3.18 (m, 4 H), 2.97 (br s, 1 H), 2.46 (br s, 1 H), 1.86-1.40 (m, 8 H).

b)

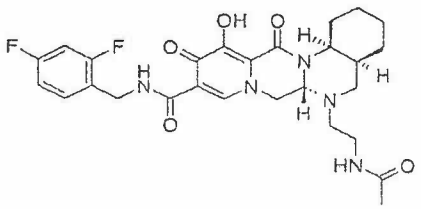
racemic-4aS,6aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy-6-[2-(methyloxy)ethyl]-11,13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide. In a manner similar to that described in example Z-35, from *racemic*-{[(1S,2S)-2-aminocyclohexyl]methyl}[2-(methyloxy)ethyl]amine hydrochloride (63mg, 0.244 mmol) and 16a (40 mg, 0.0851 mmol) was prepared

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racemic-(4aS,6aS,14aS)-N-[(2,4-difluorophenyl)methyl]-6-[2-(methyloxy)ethyl]-11,13-dioxo-12-[(phenylmethyl)oxy]-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide (44 mg, 81%) as a white solid. This material was deprotected in a second step similar to the procedure described in example Z-37. Thus, from *racemic*-(4aS,6aS,14aS)-N-[(2,4-difluorophenyl)methyl]-6-[2-(methyloxy)ethyl]-11,13-dioxo-12-[(phenylmethyl)oxy]-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide (44 mg, 0.0726mmol) and 10% Pd/C (1 mg) the title compound was prepared as a white solid (37 mg, quantitative). ^{1}H NMR ($CDCl_3$) 12.60 (br s, 1 H), 10.47 (m, 1 H), 8.28 (s, 1 H), 7.34 (m, 1 H), 6.79 (m, 2 H), 4.81 (m, 1 H), 4.64 (m 3 H), 4.51 (m, 1 H), 4.26 (m, 1 H), 3.63 (m, 1 H), 3.31 (s, 3 H), 3.19 (m, 1 H), 2.86 (m, 1 H), 2.67 (2m, 2 H), 2.21 (m, 1 H), 1.91-1.78 (m, 2 H), 1.671.62 (m, 4 H), 1.46-1.24 (m, 3 H); ES$^+$ MS: 517 (M +1).

Example Z-55:

racemic-(4aS,6aS,14aS)-6-[2-(Acetylamino)ethyl]-N-[(2,4-difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide.



a) *racemic*-N-[2-({[(1S,2S)-2-Aminocyclohexyl]methyl}amino)ethyl]acetamide

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hydrochloride. In a manner similar to that described in example Z-38c-d from *racemic*-1,1-dimethylethyl [(1S,2R)-2-formylcyclohexyl]carbamate (93 mg, 0.41 mmol) and N-(2-aminoethyl)acetamide (63 mg, 0.615 mmol), *racemic*-N-[2-({[(1S,2S)-2-aminocyclohexyl]methyl}amino)ethyl]acetamide hydrochloride was prepared in two steps as a white solid (82 mg), 71% 2 steps). ^{1}H NMR (methanol-d_4/CDCl$_3$) 8.86 (br s, 1 H), 8.29 (br s, 1 H), 3.62-3.51 (m, 3 H), 3.40-3.28 (m, 4 H), 3.22-2.93 (m, 3 H), 2.47 (m, 1 H), 2.08-2.06 (m, 4 H), 1.83-1.75 (m, 2 H), 1.56-1.44 (m, 3 H), 1.23 (m, 1 H).

b)

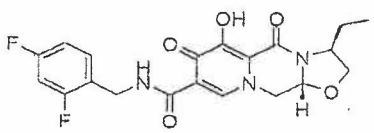
racemic-4aS,6aS,14aS)-6-[2-(Acetylamino)ethyl]-N-[(2,4-difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide. In a manner similar to that described in example Z-35, from *racemic*-N-[2-({[(1S,2S)-2-aminocyclohexyl]methyl}amino)ethyl]acetamide hydrochloride (82 mg, 0.349 mmol) and 16a (50 mg, 0.106 mmol) was prepared the title compound (24 mg, 36%). This material was deprotected in a second step similar to the procedure described in example Z-37. Thus, from *racemic*-(4aS,6aS,14aS)-6-[2-(acetylamino)ethyl]-N-[(2,4-difluorophenyl)methyl]-11,13-dioxo-12-[(phenylmethyl)oxy]-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide (24 mg, 0.0379 mmol) and 10% Pd/C (1 mg) was prepared the title compound as a white solid after purification by HPLC. ^{1}H NMR (CDCl$_3$) 12.59 (s, 1 H), 10.44 (s, 1 H), 8.35 (s, 1 H), 7.32 (m, 1 H), 6.79 (m, 2 H), 5.86

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(s, 1 H), 4.78 (m, 1 H), 4.61-4.50 (m, 3 H), 4.30 (m, 1 H), 3.35 (m, 1 H), 3.18 (m, 1 H), 2.96 (m, 1 H), 2.76 (m, 2 H), 2.48 (m, 1 H), 2.19 (m, 1 H), 1.89-1.23 (m, 12 H); ES+ MS: 544 (M +1).

Example Z-56:

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-3-ethyl-6-hydroxy-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide.

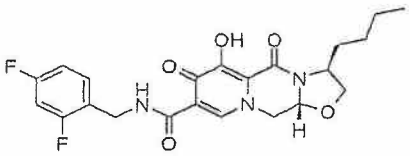


The title compound was made in two steps using a similar process to that described in example Z-2. 16a (40 mg, 0.09 mmol) and (2*S*)-2-amino-1-butanol (0.1 mL) were reacted in dichloromethane (2 mL) with acetic acid to give (3*S*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-3-ethyl-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (39 mg, 90%). This material was hydrogenated in a second step as described in example Z-2 to give (3*S*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-3-ethyl-6-hydroxy-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (37 mg, 99%) as a tinted white solid. ^{1}H NMR ($CDCl_3$) δ 11.47 (br, 1 H), 10.26 (m, 1 H), 8.35 (s, 1 H), 7.32 (m, 1 H), 6.77 (m, 2), 5.29 (m, 1 H), 4.60 (m, 2 H), 4.47-4.32 (m, 3 H), 3.93-3.85 (m, 2 H), 2.08 (m, 1 H), 1.68 (m, 1 H), 0.95 (t, J = 7.6 Hz, 3 H); ES+ MS: 420 (M +1).

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Example Z-57:

(3*S*,11a*R*)-3-Butyl-*N*-[(2,4-difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide.

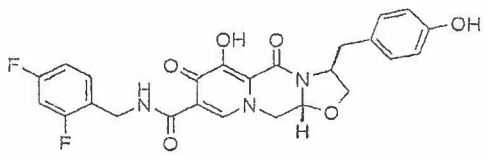


The title compound was made in two steps using a similar process to that described in example Z-2. 16a (40 mg, 0.09 mmol) and (2*S*)-2-amino-1-hexanol (100 mg) were reacted in dichloromethane (2 mL) with acetic acid to give (3*S*,11a*R*)-3-butyl-*N*-[(2,4-difluorophenyl)methyl]-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (43 mg, 94%). This material was hydrogenated in a second step as described in example Z-2 to give (3*S*,11a*R*)-3-butyl-*N*-[(2,4-difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (33 mg, 92%) as a tinted white solid. ^{1}H NMR ($CDCl_3$) δ 11.48 (br, 1 H), 10.27 (br, 1 H), 8.36 (br, 1 H), 7.31 (m, 1 H), 6.77 (m, 2), 5.28 (m, 1 H), 4.59-4.36 (m, 5 H), 3.88 (m, 2 H), 2.08 (m, 1 H), 1.58 (m, 1 H), 1.39-1.23 (m, 4 H), 0.90 (t, J = 6.8 Hz, 3 H); ES$^+$ MS: 448 (M+1).

Example Z-58:

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[(4-hydroxyphenyl)methyl]-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide

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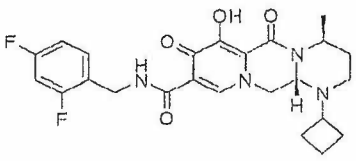


The title compound was made in two steps using a similar process to that described in example Z-2. 16a (40 mg, 0.09 mmol) and 4-[(2*S*)-2-amino-3-hydroxypropyl]phenol (43 mg, 0.21 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (3*S*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-3-[(4-hydroxyphenyl)methyl]-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (10 mg, 20%). This material was hydrogenated in a second step as described in example Z-2 and purified via preparative HPLC to give (3*S*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-6-hydroxy-3-[(4-hydroxyphenyl)methyl]-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (7 mg, 63%) as a white solid. ^{1}H NMR (CD_3OD) δ 10.43 (m, 1 H), 8.34 (s, 1 H), 7.33 (m, 1 H), 7.00 (d, J = 8.4 Hz, 2 H), 6.82 (m, 2 H), 6.71 (d, J = 8.4 Hz, 2 H), 5.05 (m, 1 H), 4.67-4.57 (m, 4 H), 4.21 (dd, J = 8.8, 7.2 Hz, 1 H), 3.94 (dd, J = 8.8, 6.4 Hz, 1 H), 3.21 (dd, J = 13.2, 3.2 Hz, 1 H), 2.90 (dd, J = 13.6, 8.8 Hz, 1 H); ES$^+$ MS: 498 (M+1).

Example Z-59:

(4S,12aS)-1-Cyclobutyl-N-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide.

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a) [(3*S*)-3-Aminobutyl]cyclobutylamine dihydrochloride was prepared in a similar manner as described in example Z-47. ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$) δ 1.23 (d, J = 6.4 Hz, 3H), 1.69-2.26 (m, 8H), 2.83 (m, 2H), 3.31-3.33 (m, 1H), 3.55 (m, 1H), 8.08 (br, <1H), 9.07 (br, <1H).

b)

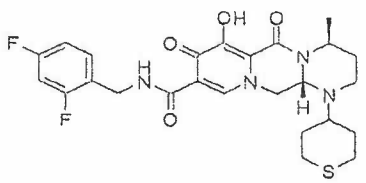
(4*S*,12a*S*)-1-Cyclobutyl-*N*-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide. The title compound was made in two steps using a similar process to that described in example Z-2. 16a (80 mg, 0.17 mmol) and free based [(3*S*)-3-aminobutyl]cyclobutylamine (96 mg, 0.68 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (4*S*,12a*S*)-1-cyclobutyl-*N*-[(2,4-difluorophenyl)methyl]-4-methyl-6,8-dioxo-7-[(phenylmethyl)oxy]-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (68 mg, 70%) as a film. This material was hydrogenated in a second step as described in example Z-2 to give (4*S*,12a*S*)-1-cyclobutyl-*N*-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (57 mg, 100%) as an off-white solid. ^{1}H NMR (400 MHz, CDCl3) δ 1.31 (d, J = 6.8 Hz, 3H), 1.46-1.70 (m, 4H), 1.91-2.12 (m, 4H), 2.52 (m, 1H), 2.90-2.93 (m, 1H), 3.06 (m,

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1H), 4.16-4.29 (m, 3H), 4.57-4.66 (m, 2H), 4.99-5.05 (m, 1H), 6.75-6.82 (m, 2H), 7.32-7.38 (m, 1H), 8.20 (s, 1H), 10.44 (s, 1H), 12.51 (s, 1H); ES+ MS: 473 (M+1).

Example Z-60:

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1-(tetrahydro-2*H*-thiopyran-4-yl)-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide.



a) [(3*S*)-3-Aminobutyl]tetrahydro-2*H*-thiopyran-4-ylamine dihydrochloride was prepared in a similar manner as described in example Z-47. ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$) δ 1.21 (d, J = 6.4 Hz , 3H), 1.65-1.75 (m, 2H), 1.90-2.10 (m, 2H), 2.35 (m, 2H), 2.56-2.61 (m, 4H), 2.92-2.98 (m, 3H), 3.27-3.31 (m, 1H), 8.05 (br, <1H), 8.90 (br, <1H).

b)

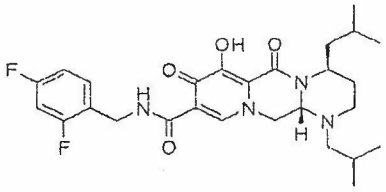
(4*S*,12a*S*)-*N*-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1-(tetrahydro-2*H*-thiopyran-4-yl)-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide. The title compound was made in two steps using a similar process to that described in example Z-2. 16a (80 mg, 0.17 mmol) and free based [(3S)-3-aminobutyl]tetrahydro-2H-thiopyran-4-ylamine (108 mg, 0.58 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give

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(4*S*,12a*S*)-*N*-[(2,4-difluorophenyl)methyl]-4-methyl-6,8-dioxo-7-[(phenylmethyl)oxy]-1-(tetrahydro-2*H*-thiopyran-4-yl)-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (56 mg, 54%) as a film. This material was debenzylated in a second step to in a manner similar to Z-26 to give (4*S*,12a*S*)-*N*-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1-(tetrahydro-2*H*-thiopyran-4-yl)-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (56 mg, >100%) as an off-white solid. ^{1}H NMR (400 MHz, CDCl3) δ 1.30 (d, *J* = 6.8 Hz , 3H), 1.54-1.58 (m, 1H), 1.72-1.82 (m, 3H), 1.97-2.11 (m, 2H), 2.60-2.76 (5H), 2.86 (m, 2H), 4.17-4.30 (m, 2H), 4.62-4.66 (m, 3H), 4.92-4.96 (m, 1H), 6.75-6.82 (m, 2H), 7.32-7.38 (m, 1H), 8.31 (s, 1H), 10.46 (s, 1H), 12.48 (s, 1H); ES$^+$ MS: 519 (M+1).

Example Z-61:

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-1,4-bis(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide.



a) [(3*S*)-3-Amino-5-methylhexyl](2-methylpropyl)amine dihydrochloride was prepared in a similar manner as described in example Z-32. ^{1}H NMR (400 MHz, CDCl$_3$/CD$_3$OD) δ 0.87 (d, *J* = 6.4 Hz ,6H), 0.97 (d, *J* = 6.8 Hz , 6H), 1.34-1.41 (m, 1H), 1.45-1.52 (m, 1H), 1.58-1.66 (m, 1H), 2.01-2.13 (m, 2H), 2.72-2.73 (m, 2H), 3.03-3.06

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(m, 2H), 3.29 (m, 2H), 8.07 (br, <1H), 8.71 (br, <1H).

b)

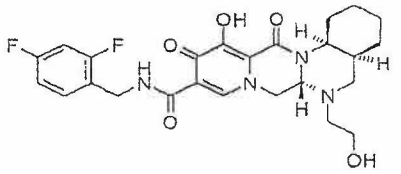
(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-1,4-bis(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide. The title compound was made in two steps using a similar process to that described in example Z-2. 16a (80 mg, 0.17 mmol) and free based [(3S)-3-amino-5-methylhexyl](2-methylpropyl)amine (117 mg, 0.63 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (4*S*,12a*S*)-*N*-[(2,4-difluorophenyl)methyl]-1,4-bis(2-methylpropyl)-6,8-dioxo-7-[(phenylmethyl)oxy]-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (68 mg, 66%) as a film. This material was hydrogenated in a second step as described in example Z-2 to give (4*S*,12a*S*)-*N*-[(2,4-difluorophenyl)methyl]-7-hydroxy-1,4-bis(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (56 mg, 97%) as an off-white solid. ^{1}H NMR (400 MHz, CDCl3) δ 0.74 (d, *J* = 6.4 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 3H), 0.97-1.00 (m, 6H), 1.37-1.83 (m, 5H), 2.03-2.12 (m, 2H), 2.21-2.28 (m, 1H), 2.77 (m, 1H), 2.90-2.93 (m, 1H), 4.19-4.40 (m, 3H), 4.59-4.70 (m, 2H), 4.96-4.97 (m, 1H), 6.77-6.83 (m, 2H), 7.33-7.39 (m, 1H), 8.28 (s, 1H), 10.47 (s, 1H), 12.59 (br, 1H); ES$^+$ MS: 517 (M+1).

Example Z-62:

racemic-(4aS,6aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy-6-(2-hydroxyethyl

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)-11,13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide.



a) *racemic*-2-({[(1S,2S)-2-Aminocyclohexyl]methyl}amino)ethanol hydrochloride. In a manner similar to that described in example Z-55a, from *racemic*-1,1-dimethylethyl [(1S,2R)-2-formylcyclohexyl]carbamate (112 mg, 0.497 mmol) and 2-aminoethanol (0.04 mLm 0.746 mmol) was prepared *racemic*-2-({[(1S,2S)-2-aminocyclohexyl]methyl}amino)ethanol bis-hydrochloride in two steps (102 mg, 84% over 2 steps). ^{1}H NMR (methanol-d_4/$CDCl_3$) 8.81-8.40 (m, < 2 H), 8.16 (br s, 1 H), 4.02-3.93 (m, 2 H), 3.80 (br s, 2 H), 3.53 (m, 1 H), 3.36-2.93 (m, 6 H), 2.41 (br s, 1 H), 2.05 (m, 1 H), 1.75-1.41 (m, 4 H).

b)

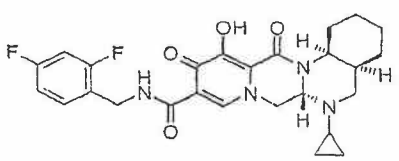
racemic-(4aS,6aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy-6-(2-hydroxyethyl)-11,13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide. In a manner similar to that described in example Z-35, from 16a (45 mg, 0.0957 mmol) and *racemic*-2-({[(1S,2S)-2-aminocyclohexyl]methyl}amino)ethanol hydrochloride (102 mg, 0.418 mmol) was prepared *racemic*-(4aS,6aS,14aS)-N-[(2,4-difluorophenyl)methyl]-6-(2-hydroxyethyl)-11,13-dioxo-12-[(phenylmethyl)oxy]-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyra

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zino[1,2-a]quinazoline-10-carboxamide (7 mg, 12 %) as a white solid after silica gel chromatography (1-12% methanol/dichloromethane gradient elution). This material was deprotected in a second step similar to the procedure described in example Z-37. Thus, from *racemic*-(4aS,6aS,14aS)-N-[(2,4-difluorophenyl)methyl]-6-(2-hydroxyethyl)-11,13-dioxo-12-[(phenylmethyl)oxy]-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide (7 mg, 0.0118 mmol) the title compound was prepared after purification by HPLC (3 mg, 50 %). ^{1}H NMR ($CDCl_3$) 12.57 (br s, 1 H), 10.45 (m, 1 H), 8.29 (s, 1 H), 7.34 (m, 1 H), 6.78 (m, 2 H), 4.80 (m, 1 H), 4.71 (s, 1 H), 4.62 (m, 2 H), 4.44 (m, 1 H), 4.33 (m, 1 H), 3.75 (m, 1 H), 3.62-3.20 (m, 3 H), 3.13 (m, 1 H), 2.74-2.71 (m, 2 H), 2.24 (m, 1 H), 1.90-1.37 (m, 12 H), 1.27-1.23 (m, 3 H)1.12 (m, 1 H); ES$^+$ MS: 503 (M +1).

Example Z-63:

racemic-(4aS,6aS,14aS)-6-Cyclopropyl-N-[(2,4-difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide.



a) *racemic*-(1S,2S)-2-[(Cyclopropylamino)methyl]cyclohexanamine hydrochloride. In a manner similar to that described in example Z-55a, from *racemic*-1,1-dimethylethyl [(1S,2R)-2-formylcyclohexyl]carbamate (11.2 mg, 0.497

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mmol) and cyclopropylamine (0.05 mL, 0.746 mmol) was prepared *racemic*-(1S,2S)-2-[(cyclopropylamino)methyl]cyclohexanamine bis hydrochloride salt in two steps (102 mg, 86% over 2 steps). This material was used without further purification. ^{1}H NMR (methanol-d_4/$CDCl_3$) 8.31 (br s, 1 H), 3.75 (br s, 1 H), 3.54 (m, 1 H), 2.96 (m, 1 H), 2.71 (m, 1 H), 2.27 (m, 1 H), 1.94 (m, 1 H), 1.76-1.15 (m, 8 H), 0.88-0.78 (m, 3 H).

b)

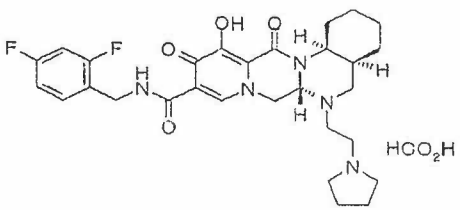
racemic-(4aS,6aS,14aS)-6-Cyclopropyl-N-[(2,4-difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide. In a manner similar to that described in example Z-35, from 16a (45 mg, 0.0957 mmol) and *racemic*-(1S,2S)-2-[(cyclopropylamino)methyl]cyclohexanamine hydrochloride (102 mg, 0.425 mmol) was prepared *racemic*-(4aS,6aS,14aS)-6-cyclopropyl-N-[(2,4-difluorophenyl)methyl]-11,13-dioxo-12-[(phenylmethyl)oxy]-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide as a white solid after silica gel chromatography (1-12% methanol/dichloromethane gradient elution). This material was deprotected in a second step similar to the procedure described in example Z-37. Thus, from *racemic*-(4aS,6aS,14aS)-6-cyclopropyl-N-[(2,4-difluorophenyl)methyl]-11,13-dioxo-12-[(phenylmethyl)oxy]-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide (56 mg, 0.0949 mmol) the title compound was prepared as a white solid (41 mg, 81%). ^{1}H NMR ($CDCl_3$) 12.10 (br s, < 1 H), 10.45

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(m, 1 H), 8.27 (s, 1 H), 7.33 (m, 1 H), 6.88 (m, 2 H), 4.77 (m, 1 H), 4.61-4.49 (m, 4 H), 4.33 (m, 1 H), 2.94 (m, 1 H), 2.79 (m, 1 H), 2.17 (m, 1 H), 1.86-0.86 (m, 10 H), 0.658 (m, 1 H), 0.499-0.32 (m, 2 H); ES+ MS: 499 (M +1).

Example Z-64:

racemic-(4aS,6aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-6-[2-(1-pyrrolidinyl)ethyl]-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide formic acid salt



a) *racemic*-(1S,2S)-2-({[2-(1-Pyrrolidinyl)ethyl]amino}methyl)cyclohexanamine hydrochloride. In a manner similar to that described in example Z-55a, from *racemic*-1,1-dimethylethyl [(1S,2R)-2-formylcyclohexyl]carbamate (112 mg, 0.497 mmol) and 2-(1-pyrrolidinyl)ethanamine (0.09 mL, 0.746 mmol) was prepared *racemic*-(1S,2S)-2-({[2-(1-pyrrolidinyl)ethyl]amino}methyl)cyclohexanamine (88 mg, 60% 2 steps) as the bis hydrochloride salt in two steps as a white solid. ^{1}H NMR (methanol-d_4/$CDCl_3$) 9.68 (br s, < 1 H), 9.24 (br s, < 1 H), 8.25 (br s, 1 H), 3.75-3.04 (m, 11 H), 2.37 (br s, 1 H), 2.06-1.20 (m, 12 H).

b)

racemic-(4aS,6aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy-11,13-dio

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xo-6-[2-(1-pyrrolidinyl)ethyl]-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide formic acid salt.

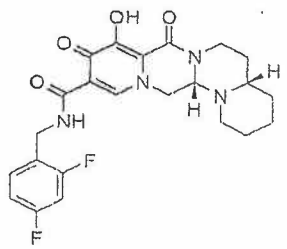
In a manner similar to that described in example Z-35, from 16a (30 mg, 0.0638 mmol) and *racemic*-(1S,2S)-2-({[2-(1-pyrrolidinyl)ethyl]amino}methyl)cyclohexanamine hydrochloride (88 mg, 0.296 mmol) was prepared *racemic*-(4aS,6aS,14aS)-N-[(2,4-difluorophenyl)methyl]-11,13-dioxo-12-[(phenylmethyl)oxy]-6-[2-(1-pyrrolidinyl)ethyl]-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide as a white solid (31 mg, 76%) after silica gel chromatography (1-12% methanol/dichloromethane gradient elution). This material was deprotected in a second step similar to the procedure described in example Z-37. Thus, from *racemic*-(4aS,6aS,14aS)-N-[(2,4-difluorophenyl)methyl]-11,13-dioxo-12-[(phenylmethyl)oxy]-6-[2-(1-pyrrolidinyl)ethyl]-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide (31 mg, 0.048 mmol) the title compound was prepared as a yellow solid after purification by HPLC (18 mg, 66%). ^{1}H NMR ($CDCl_3$) 10.39 (br s, 1 H), 8.56 (br s, 1 H), 8.39 (br s, 1 H), 7.34 (m, 1 H), 6.78 (m, 2 H), 4.76-4.40 (m, 6 H), 3.26-2.89 (m, 7 H), 2.73 (m, 1 H), 2.15 (m, 1 H), 2.02-1.18 (m, 14 H); ES$^+$ MS: 556 (M +1).

Example Z-65:

(4aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-9-hydroxy-8,10-dioxo-2,3,4,4a,5,6,8,10,14,14a-decahydro-1H-pyrido[1,2-c]pyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-11-carboxami

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de.



a) {2-[(2S)-2-Piperidinyl]ethyl}amine. This compound was prepared in a similar manner as its enantiomer described in example Z-42a.

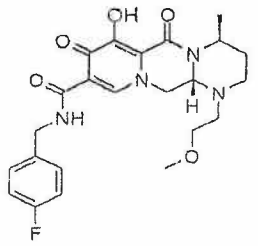
b)

(4aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-9-hydroxy-8,10-dioxo-2,3,4,4a,5,6,8,10,14,14a-decahydro-1H-pyrido[1,2-c]pyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-11-carboxamide. In a manner similar to that described in example Z-35, from {2-[(2S)-2-piperidinyl]ethyl}amine (28 mg, 0.218 mmol) and 16a (30 mg, 0.0638 mmol) was prepared (4aS,14aS)-N-[(2,4-difluorophenyl)methyl]-8,10-dioxo-9-[(phenylmethyl)oxy]-2,3,4,4a,5,6,8,10,14,14a-decahydro-1H-pyrido[1,2-c]pyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-11-carboxamide (29 mg, 82%). This material was deprotected in a second step similar to that described in example Z-37 to give the title compound as a white solid (26 mg, quantitative). ^{1}H NMR ($CDCl_3$) δ 12.44 (br s, 1 H), 10.48 (s, 1 H), 8.26 (s, 1 H), 7.35 (m, 1 H), 6.80 (m, 2 H), 4.68-4.57 (m, 2 H), 4.38 (m, 1 H), 4.20 (m, 1 H), 3.93 (s, 1H), 3.63-3.39 (m, 2 H), 2.91 (m, 2 H), 2.29 (br s, 1 H), 2.02 (m, 1 H), 1.69-1.45 (m, 4 H), 1.30-1.24 (m, 2 H), 1.12 (br s, 1 H); ES$^+$ MS: 459 (M+1).

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Example Z-66:

(4S,12aS)-N-[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-1-[2-(methyloxy)ethyl]-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide.



a) [(3S)-3-Aminobutyl][2-(methyloxy)ethyl]amine bis hydrochloride. In a manner similar to that described in example Z-47, from 1,1-dimethylethyl [(1S)-1-methyl-3-oxopropyl]carbamate (76 mg, 0.406 mmol) and 2-(methyloxy)ethyl]amine (0.05 mL, 0.609 mmol) was prepared [(3S)-3-aminobutyl][2-(methyloxy)ethyl]amine as the bis hydrochloride salt in two steps (19 mg, quantitative). ^{1}H NMR (methanol-d_4/$CDCl_3$) δ 9.02 (< 1 H), 8.24 (< 1 H), 3.68 (br s, 2 H), 3.49 (br s, 1 H), 3.34 (br s, 4 H), 3.15 (br s, 4 H), 2.26-2.11 (m, 2 H), 1.35 (br s, 3 H).

b)

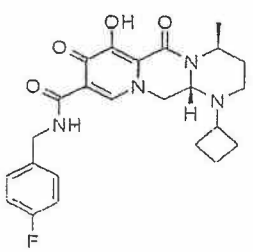
(4S,12aS)-N-[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-1-[2-(methyloxy)ethyl]-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide. In a manner similar to that described in example Z-35, from 16 (15

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mg, 0.034 mmol) and [(3S)-3-Aminobutyl][2-(methyloxy)ethyl]amine bis hydrochloride (19 mg, 0.087 mmol), (4S,12aS)-N-[(4-fluorophenyl)methyl]-4-methyl-1-[2-(methyloxy)ethyl]-6,8-dioxo-7-[(phenylmethyl)oxy]-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide was prepared as a white solid after silica gel chromatography (1-12% methanol/dichloromethane). This material was deprotected in a second step similar to that described in example Z-37 to give the title compound as a yellow solid (9 mg, 60 %, 2 steps). ^{1}H NMR ($CDCl_3$) δ 12.56 (s, 1 H), 10.51 (m, 1 H), 8.29 (s, 1 H), 7.32 (m, 2 H), 6.98 (m, 2 H), 5.03 (m, 1 H), 4.65-4.59 (m, 2 H), 4.53 (m, 1 H), 4.21 (m, 1 H), 3.61-3.40 (m, 2 H), 3.34-3.13 (m, 3 H), 3.08 (m, 1 H), 2.94-2.84 (m, 2 H), 2.68 (m, 1 H), 2.07 (m, 1 H), 1.50 (m, 1 H), 1.35 (d, J = 7.2 Hz, 3 H), 1.14 (m, 1 H); ES$^+$ MS: 459 (M+1).

Example Z-67:

(4S,12aS)-1-Cyclobutyl-N-[(4-fluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide.



a) [(3S)-3-Aminobutyl]cyclobutylamine bis-hydrochloride. In a manner similar to that described in example Z-47, from 1,1-dimethylethyl

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[(1S)-1-methyl-3-oxopropyl]carbamate (76 mg, 0.406 mmol) and cyclobutylamine (0.05 mL, 0.609 mmol) was prepared [(3S)-3-Aminobutyl]cyclobutylamine bis-hydrochloride in two steps (23 mg, 27%). ^{1}H NMR (methanol-d_4/$CDCl_3$) δ 8.86 (s, < 1 H), 7.97 (s, < 1 H), 3.46 (m, 1 H), 3.21 (m, 1 H), 2.74 (m, 2 H), 2.14-2.08 (m, 4 H), 1.94-1.62 (m, 5 H), 1.13 (d, J = 6 Hz, 1 H).

b)

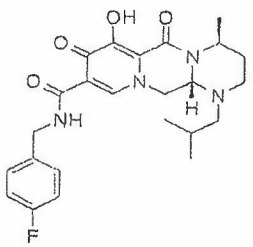
(4S,12aS)-1-Cyclobutyl-N-[(4-fluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide. In a similar manner to that described in example Z-35a, from 16 (18 mg, 0.39 mmol) and [(3S)-3-Aminobutyl]cyclobutylamine bis-hydrochloride (23 mg, 0.107 mmol),

(4S,12aS)-1-cyclobutyl-N-[(4-fluorophenyl)methyl]-4-methyl-6,8-dioxo-7-[(phenylmethyl)oxy]-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide was prepared as a white solid. This material was deprotected in a second step similar to that described in example Z-37 to give the title compound as a white solid after purification by HPLC (4.5 mg, 25 % 2 steps). ^{1}H NMR ($CDCl_3$) δ 12.54 (s, 1 H), 10.48 (s, 1 H), 8.20 (s, 1 H), 7.31 (m, 2 H), 6.98 (m, 2 H), 5.02 (m, 1 H), 4.61-4.57 (m, 2 H), 4.26-4.14 (m, 3 H), 3.05 (m, 1 H), 2.90 (m, 1 H), 2.49 (m, 1 H), 2.12 (m, 1 H), 2.05-1.87 (m, 3 H), 1.84-1.61 (m, 3 H), 1.46 (m, 1 H), 1.32 (m, 3 H); ES$^+$ MS: 455 (M+1).

Example Z-68:

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(4S,12aS)-N-[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide



a) [(3S)-3-Aminobutyl](2-methylpropyl)amine bis-hydrochloride. In a manner similar to that described in example Z-47, this compound was prepared from 1,1-dimethylethyl [(1S)-1-methyl-3-oxopropyl]carbamate (76 mg, 0.406 mmol) and (2-methylpropyl)amine (0.06 mL, 0.609 mmol) in two steps as the bis-hydrochloride salt (22 mg, 25 %). ^{1}H NMR (methanol-d_4/CDCl$_3$) δ 3.25 (br s, 1 H), 2.91 (br s, 2 H), 2.64 (m, 2 H), 2.02-1.93 (m, 3 H), 1.17 (m, 3 H), 0.88 (m, 6 H).

b)

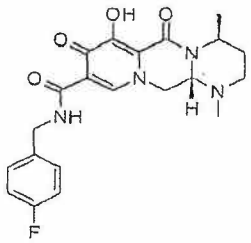
(4S,12aS)-N-[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide. In a similar manner to that described in example Z-35, from 16 (16 mg, 0.035 mmol) and [(3S)-3-Aminobutyl](2-methylpropyl)amine bis-hydrochloride (20 mg, 0.0925 mmol), (4S,12aS)-N-[(4-fluorophenyl)methyl]-4-methyl-1-(2-methylpropyl)-6,8-dioxo-7-[(phenylmethyl)oxy]-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-

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carboxamide was prepared as a white solid. This material was deprotected in a second step similar to that described in example Z-37 to give the title compound as a tan solid (13 mg, 68% 2 steps). ^{1}H NMR ($CDCl_3$) δ 12.57 (s, 1 H), 10.46 (s, 1 H), 8.27 (s, 1 H), 7.32 (m, 2 H), 6.99 (m, 2 H), 4.98 (m, 1 H), 4.63-4.54 (m, 2 H), 4.45 (m, 1 H),4.26-4.16 (m, 2 H), 2.91 (m, 1 H),-2.77-(m, 1 H), 2.24 (m, 1 H), 2.14-2.03 (m, 2 H), 1.63 (m, 1 H), 1.48 (m, 1 H), 1.33 (m, 3 H), 1.09 (m, 1 H), 0.850 (m, 3 H), 0.789 (m, 3 H); ES$^+$ MS: 457 (M+1).

Example Z-69:

(4S,12aS)-N-[(4-Fluorophenyl)methyl]-7-hydroxy-1,4-dimethyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide.



a) [(3S)-3-Aminobutyl]methylamine bis-hydrochloride. In a manner similar to that described in example Z-47, this compound was prepared from 1,1-dimethylethyl [(1S)-1-methyl-3-oxopropyl]carbamate (76 mg, 0.409 mmol) and excess methylamine (2 M in tetrhydrofuran) in two steps as the bis hydrochloride salt (17% 2 steps). ^{1}H NMR (methanol-d_4/$CDCl_3$) δ 3.16 (m, 1 H), 3.08 (s, 2 H), 2.83 (m, 2 H), 2.45 (s, 3 H), 1.88 (m, 1 H), 1.75 (m, 1 H), 1.09 (m, 3 H).

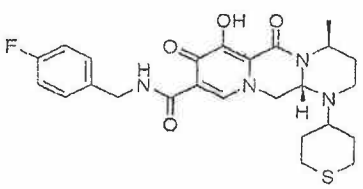
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b)

(4S,12aS)-N-[(4-Fluorophenyl)methyl]-7-hydroxy-1,4-dimethyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide. In a similar manner to that described in example Z-35, from 16 (18 mg, 0.0398 mmol) and [(3S)-3-aminobutyl]methylamine bis-hydrochloride (19 mg, 0.109 mmol, (4S,12aS)-N-[(4-fluorophenyl)methyl]-1,4-dimethyl-6,8-dioxo-7-[(phenylmethyl)oxy]-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide was prepared as a white solid. This material was deprotected in a second step similar to that described in example Z-37 to give the title compound as a tan solid (7 mg, 44% 2 steps). ^{1}H NMR ($CDCl_3$) δ 12.53 (s, 1 H), 10.47 (s, 1 H), 8.29 (s, 1 H), 7.32 (m, 2 H), 6.99 (m, 2 H), 5.04 (1 H), 4.60 (m, 2 H), 4.23 (s, 3 H), 2.83-2.80 (m, 2 H), 2.32 (s, 3 H), 2.13 (m, 1 H), 1.48 (m, 1 H), 1.34 (m, 3 H); ES$^+$ MS: 415 (M+1).

Example Z-70:

(4*S*,12a*S*)-*N*-[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1-(tetrahydro-2*H*-thiopyran-4-yl)-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide.

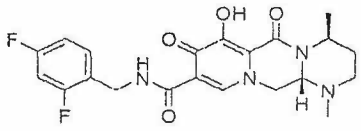


The title compound was made in two steps using a similar process to that described in example Z-2. 16 (25 mg, 0.055 mmol) and free based [(3*S*)-3-aminobutyl]tetrahydro-2*H*-thiopyran-4-ylamine (48 mg, 0.26 mmol) were

reacted in dichloromethane (2 mL) with acetic acid to give (4*S*,12a*S*)-*N*-[(4-fluorophenyl)methyl]-4-methyl-6,8-dioxo-7-[(phenylmethyl)oxy]-1-(tetrahydro-2*H*-thiopyran-4-yl)-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (16 mg, 49%) as a film. This material was debenzylated in a second step in a manner similar to Z-26 to give (4*S*,12a*S*)-*N*-[(4-fluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1-(tetrahydro-2*H*-thiopyran-4-yl)-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (8 mg, 59%) as an off-white solid. ^{1}H NMR (400 MHz, CDCl3) δ 1.30 (d, *J* = 7.2 Hz, 3H), 1.53-1.58 (m, 1H), 1.72-2.10 (m, 5H), 2.56-2.76 (m, 5H), 2.84-2.87 (m, 2H), 4.18 (dd, *J* = 2.8, 14.0 Hz, 1H), 4.26 (dd, *J* = 3.4, 14.2 Hz, 1H), 4.92-4.97 (m, 1H), 6.96-7.00 (m, 2H), 7.29-7.36 (m, 2H), 8.31 (s, 1H), 10.48 (m, 1H), 12.48 (br, 1H); ES$^+$ MS: 501 (M+1).

Example Z-71:

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-1,4-dimethyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide.



a) [(3*S*)-3-Aminobutyl]methylamine dihydrochloride was prepared in a similar manner as described in example Z-47. ^{1}H NMR (400 MHz, CDCl3) δ 1.18 (d, *J* = 6.8 Hz, 3H), 1.82-1.91 (m, 1H), 1.94-2.03 (m, 1H), 2.53 (s, 3H), 2.89-2.93 (m, 2H), 3.22-3.30 (m, 1H), 8.02 (br, <1H), 8.81 (br, <1H).

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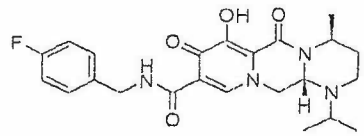
b)

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-1,4-dimethyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide. The title compound was made in two steps using a similar process to that described in example Z-2. 16a (40 mg, 0.085 mmol) and free based [(3*S*)-3-aminobutyl]methylamine (24 mg, 0.23 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (4*S*,12a*S*)-*N*-[(2,4-difluorophenyl)methyl]-1,4-dimethyl-6,8-dioxo-7-[(phenylmethyl)oxy]-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (39 mg, 89%) as a film. This material was hydrogenated in a second step as described in example Z-2 to give (4*S*,12a*S*)-*N*-[(2,4-difluorophenyl)methyl]-7-hydroxy-1,4-dimethyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (32 mg, 97%) as an off-white solid. ^{1}H NMR (400 MHz, CDCl3) δ 1.33 (d, J = 6.4 Hz, 3H), 1.46-1.50 (m, 1H), 2.12-2.14 (m, 1H), 2.32 (s, 3H), 2.83 (m, 2H), 4.24 (m, 3H), 4.62 (m, 2H), 5.02 (m, 1H), 6.77-6.79 (m, 2H), 7.33 (m, 1H), 8.30 (s, 1H), 10.43 (s, 1H), 12.50 (br, 1H); ES$^+$ MS: 433 (M+1).

Example Z-72:

(4*S*,12a*S*)-*N*-[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(1-methylethyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide.

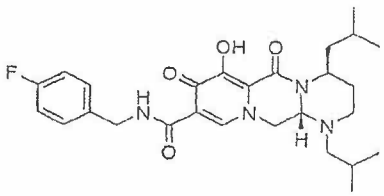
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The title compound was made in two steps using a similar process to that described in example Z-2. 16 (27 mg, 0.060 mmol) and free based [(3S)-3-aminobutyl](1-methylethyl)amine (67 mg, 0.51 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (4*S*,12a*S*)-*N*-[(4-fluorophenyl)methyl]-4-methyl-1-(1-methylethyl)-6,8-dioxo-7-[(phenylmethyl)oxy]-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (18 mg, 56%) as a film. This material was hydrogenated in a second step as described in example Z-2 to give (4*S*,12a*S*)-*N*-[(4-fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(1-methylethyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (15 mg, >100%) as an off-white solid. ^{1}H NMR (400 MHz, CDCl3) δ 1.02 (d, *J* = 6.4 Hz, 3H), 1.07 (d, *J* = 6.4 Hz, 3H), 1.32 (d, *J* = 6.8 Hz, 3H), 1.54-1.58 (m, 1H), 1.94-2.03 (m, 1H), 2.71-2.76 (m, 1H), 2.82-2.88 (m, 1H), 3.13-3.16 (m, 1H), 4.16-4.19 (m, 1H), 4.30-4.33 (m, 1H), 4.48 (m, 1H), 4.55-4.65 (m, 2H), 4.97-5.00 (m, 1H), 6.97-7.01 (m, 2H), 7.30-7.34 (m, 2H), 8.28 (s, 1H), 10.51 (m, 1H), 12.55 (s, 1H); ES$^+$ MS: 443 (M+1).

Example Z-73:

(4*S*,12a*S*)-*N*-[(4-Fluorophenyl)methyl]-7-hydroxy-1,4-bis(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide.



The title compound was made in two steps using a similar process to that described in example Z-2. 16 (25 mg, 0.055 mmol) and free based [(3S)-3-amino-5-methylhexyl](2-methylpropyl)amine (21 mg, 0.11 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (4*S*,12a*S*)-*N*-[(4-fluorophenyl)methyl]-1,4-bis(2-methylpropyl)-6,8-dioxo-7-[(phenylmethyl)oxy]-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (8 mg, 25%) as a film. This material was hydrogenated in a second step as described in example Z-2 to give (4*S*,12a*S*)-*N*-[(4-fluorophenyl)methyl]-7-hydroxy-1,4-bis(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (5 mg, 78%) as an off-white solid. ^{1}H NMR (400 MHz, CDCl3) δ 0.74 (d, *J* = 6.4 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 3H), 0.97-1.00 (m, 6H), 1.37-1.66 (m, 5H), 1.75-1.82 (m, 1H), 2.05-2.09 (m, 2H), 2.21-2.26 (m, 1H), 2.72-2.79 (m, 1H), 2.87-2.93 (m, 1H), 4.16-4.26 (m, 2H), 4.38 (m, 1H), 4.55-4.66 (m, 2H), 4.93-4.99 (m, 1H), 6.97-7.02 (m, 2H), 7.31-7.34 (m, 2H), 8.27 (s, 1H), 10.49 (m, 1H), 12.61 (s, 1H); ES$^+$ MS: 499 (M+1).

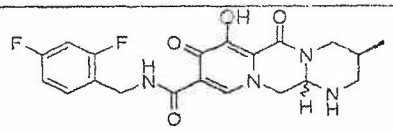
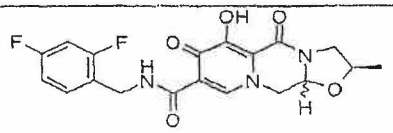
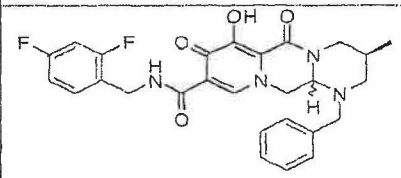
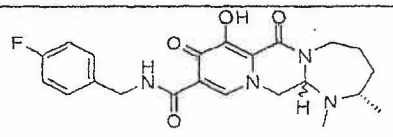
Example ZZ-1 to ZZ-24

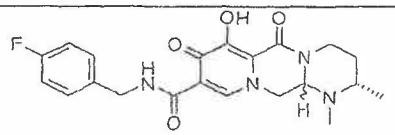
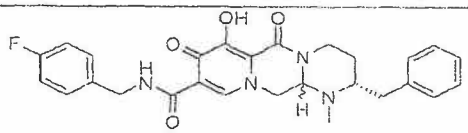
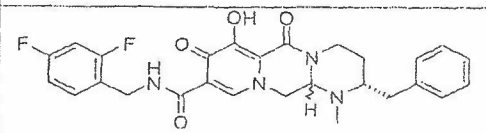
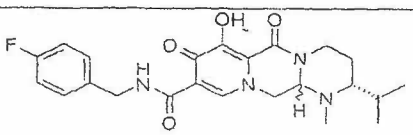
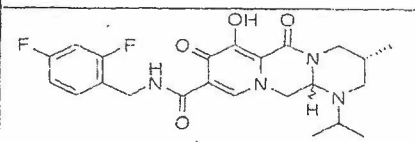
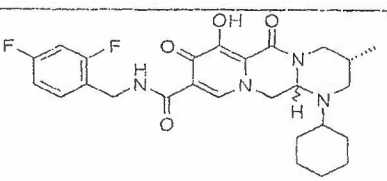
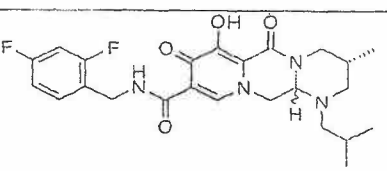
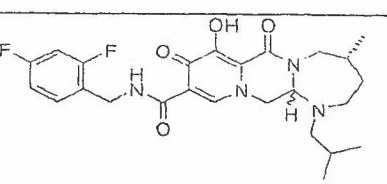
Examples in table below were isolated as a mixture of diastereomers ranging from 1:1 to >10:1 ratios of stereoisomers at the center indicated as undefined.

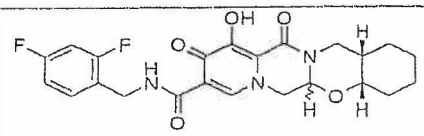
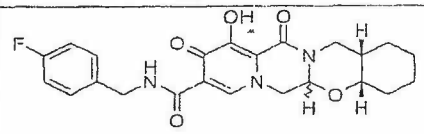
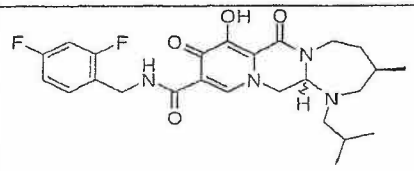
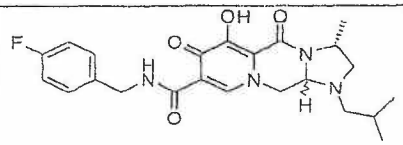
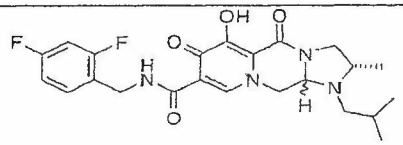
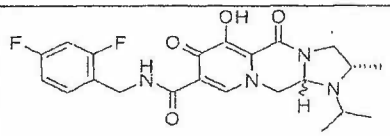
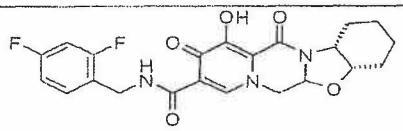
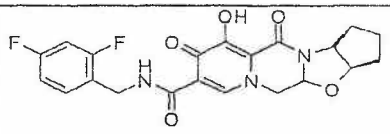
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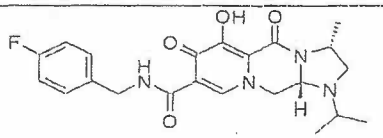
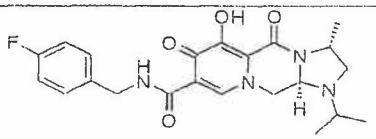
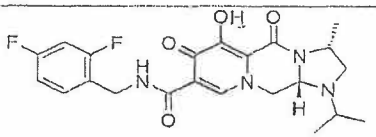
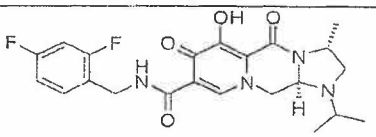
Characterization data reported herein consists of observed mass spectral signals for molecular ions (M+1) of the compounds using electrospray ionization methods in the positive mode using LC/MS techniques well known in the field. Reported retention times refer to observed UV peaks confirmed by NMR methods for the examples below using the following gradient on a phenomenex C18 reverse phase HPLC column (150 mmX4.6 mm 5 micron). Solvent A = water w/ 0.1% formic acid, solvent B = acetonitrile w/ 0.1% formic acid. Gradient = 10%B for 1 min, gradient from 10% to 90% B from 1 to 9 min, ramping to 100% B at 9.01 min and holding at 100% B for 2 min. In several cases the diastereomers were not separable by the standard HPLC conditions reported above and thus reported as a single retention time.

[Table A]

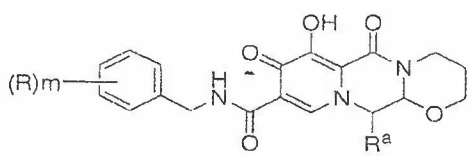
Example No.	Structure	Observed LC/MS or HPLC data
ZZ-1		ES+ MS: 419 (M +1)
ZZ-2		ES+ MS: 406 (M +1)
ZZ-3		ES+ MS: 509 (M +1)
ZZ-4		ES+ MS: 429 (M +1)

ZZ-5		ES+ MS: 415 (M +1)
ZZ-6		ES+ MS: 491 (M +1)
ZZ-7		ES+ MS: 509 (M +1)
ZZ-8		ES+ MS: 448 (M +1)
ZZ-9		ES+ MS: 461 (M +1)
ZZ-10		ES+ MS: 501 (M +1)
ZZ-11		ES+ MS: 475 (M +1)
ZZ-12		ES+ MS: 489 (M +1)

ZZ-13		ES+ MS: 460 (M +1)
ZZ-14		ES+ MS: 442 (M +1)
ZZ-15		ES+ MS: 489 (M +1)
ZZ-16		8.174 & 8.295 min.
ZZ-17		ES+ MS: 461 (M +1)
ZZ-18		ES+ MS: 447 (M +1)
ZZ-19		ES+ MS: 446 (M +1)
ZZ-20		ES+ MS: 432 (M +1)

ZZ-21		7.368 min
ZZ-22		7.150 min
ZZ-23		ES+ MS: 447 (M +1)
ZZ-24		ES+ MS: 447 (M +1)

The present invention further includes the following compounds.



(I-7)

[Table B]

No	(R) m	R^a
1	4 − F	$-CH_3$
2	4 − F	$-CH(CH_3)_2$
3	4 − F	$-CH_2CH_2OCH_3$
4	2, 4 − F	$-CH_3$
5	2, 4 − F	$-CH(CH_3)_2$
6	2, 4 − F	$-CH_2CH_2OCH_3$
7	2 − F, 3 − Cl	$-CH_3$
8	2 − F, 3 − Cl	$-CH(CH_3)_2$
9	2 − F, 3 − Cl	$-CH_2CH_2OCH_3$

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Experimental Example 1

The HIV integrase inhibitory activity was investigated based on the following assay method.

(1) Preparation of DNA solution

By the same method as that described in Experimental Example 1 of WO 2004/024693, a substrate DNA solution (2 pmol/μl) and a target DNA solution (5 pmol/μl) were prepared. After each target DNA solution was once boiled, a temperature was slowly lowered to anneal complementary chains, which was used. Each sequence of a substrate DNA and a target DNA is as described in the same Experimental Example.

(2) Measurement of inhibition rate (IC_{50} value)

Streptavidin (manufactured by Vector Laboratories) was dissolved in a 0.1M carbonate buffer solution (composition: 90 mM Na_2CO_3, 10 mM $NaHCO_3$) to a concentration of 40 μg/ml. Each 50 μl of this solution was added to a well of an immunoplate (manufactured by NUNC), this is allowed to stand at 4°C overnight to adsorb. Then, each well was washed with a phosphate buffer (composition: 13.7 mM NaCl, 0.27 mM KCl, 0.43 mM Na_2HPO_4, 0.14 mM KH_2PO_4) two times, and 300 μl of a phosphate buffer containing 1 % skim milk to block it for 30 minutes. Further, each well was washed with a phosphate buffer two times, 50 μl of a substrate DNA solution (2 pmol/μl) was added to adsorb at room temperature for 30 minutes while shaking, and this was washed with a phosphate buffer two times and, then, distilled water once.

Then, to each well prepared as described above were added 12 μl of a buffer (composition: 150 mM MOPS (pH7.2), 75 mM $MnCl_2$, 50 mM 2-mercaptoethanol, 25% glycerol, 500 μg/ml bovine serum albumin-fraction V), and 51 μl of a reaction solution prepared from 39 μl of distilled water. Then, 9 μl of an integrase solution (30 pmol) was added, and the mixture was mixed well. To a well as a negative control (NC) was added 9 μl of a diluting solution (composition: 20 mM MOPS (pH7.2), 400 mM potassium glutamete, 1 mM EDTA, 0.1% NP-40, 20% glycerol, 1 mM DTT, 4 M urea), and this was mixed well using a plate mixer.

After the plate was incubated at 30°C for 60 minutes, the reaction solution was discarded, followed by washing with 250 μl of a washing buffer (composition: 150 mM MOPS (pH7.2), 50 mM 2-mercaptoethanol, 25% glycerol, 500 μg/ml bovine serum albumin-fraction V) three times.

Then, to each well were added 12 μl of a buffer (composition: 150 mM MOPS

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(pH7.2), 75 mM $MgCl_2$, 50 mM 2-mercaptoethanol, 25% glycerol, 500 μg/ml bovine serum albumin-fraction V), and 53 μl of a reaction solution prepared from 41 μl of distilled water. Further, 6 μl of a solution of a test compound in DMSO was added to each well, and 6 μl of DMSO was added to a well as a positive control (PC), followed by mixing well using a plate mixer. After the plate was incubated at 30°C for 30 minutes, 1 μl of a target DNA (5 pmol/μl) was added, and this was mixed well using a plate mixer.

After each plate was incubated at 30°C for 10 minutes, the reaction solution was discarded, followed by washing with a phosphate buffer two times. Then, an anti-digoxigenin antibody labeled with alkaline phosphatase (sheep Fab fragment: manufactured by Boehringer) was diluted 2000-fold with an antibody diluting solution, 100 μl of the diluent was added to bind at 30°C for 1 hour, and this was washed successively with a phosphate buffer containing 0.05 % Tween20 two times, and a phosphate buffer once. Then, 150 μl of an alkaline phosphatase coloring buffer (composition: 10 mM paranitrophenyl phosphate (manufactured by Vector Laboratories), 5 mM $MgCl_2$, 100 mM NaCl, 100 mM Tris-HCl (pH 9.5)) was added to react at 30°C for 2 hours, 50 μl of a 1N NaOH solution was added to stop the reaction, an absorbance (OD405 nm) of each well was measured, and an inhibition rate (IC_{50}) was obtained according to the following calculation equation.

Inhibition rate (%) = 100[1-{(C abs.- NC abs.) / (PC abs.- NC abs.)}]

C abs.: absorbance of well of compound

NC abs.: absorbance of NC

PC abs.: absorbance of PC

Results are shown below.

[Table 1]

Example No.	Integrase inhibitory activity (IC50, ng/ml)
C-2	3.3
F-2	3.8
H-2	3.2

The present compound showed the strong integrase inhibitory activity against HIV.

Experimental Example 2

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A derivative of 293T cells expressing an attachment factor to improve adherence to plastic were used for the assay. A VSV-g pseudotyped HIV vector that expresses luciferase (herein referred to as PHIV) was produced by transfection of cells with the pGJ3-Luci vector plasmid (Jármy, G. et al., J. Medical Virology, 64:223-231, 2001) and pVSV-g (Clontech). Cells were mixed with the PHIV vector and then mixed with serially diluted compounds. After incubation at 37°C and 5% CO_2 for two days, the plates were read by using Steady Glo luciferase assay reagent (Promega) as recommended by the manufacturer. To assess non-HIV specific inhibition, a similar assay was performed, except that cell/PHIV vector mixture was replaced by cells which had been previously transduced and constitutively expressed luciferase.

[Table 2]

Example number	PHIV IC_{50} *=<10 nM, **=10-100 nM, ***>100 nM
Z-1	*
Z-2	*
Z-3	*
Z-4	*
Z-5	*
Z-6	*
Z-7	*
Z-8	**
Z-9	*
Z-10	*
Z-11	*
Z-12	*
Z-13	**
Z-14	**
Z-15	*
Z-16	*
Z-17	*
Z-18	*
Z-19	*
Z-20	**
Z-21	*
Z-22	*
Z-23	*

Z-24	*
Z-25	*
Z-26	*
Z-27	***
Z-28	*
Z-29	*
Z-30	*
Z-31	*
Z-32	*
Z-33	*
Z-34	*
Z-35	*
Z-36	*
Z-37	*
Z-38	**
Z-39	*
Z-40	*
Z-41	*
Z-42	*
Z-43	*
Z-44	*
Z-45	*
Z-46	*
Z-47	*
Z-48	*
Z-49	*
Z-50	*
Z-51	*
Z-52	*
Z-53	*
Z-54	*
Z-55	**
Z-59	*
Z-60	*

Formulation Example

A term "active ingredient" means the present compound, a tautomer thereof, a pharmaceutically acceptable thereof, or a solvate thereof.

(Formulation Example 1)

A hard gelatin capsule is prepared using the following ingredients:

	dose (mg/capsule)
Active ingredient	250
Starch (dried)	200
Magnesium stearate	10

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Total	460mg

(Formulation Example 2)

A tablet is prepared using the following ingredients:

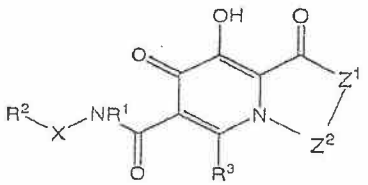
	dose (mg/tablet)
Active ingredient	250
Cellulose (microcrystalline)	400
Silicon dioxide (fumed)	10
Stearic acid	5
Total	665mg

Ingredients are mixed, and compressed to obtain tablets, each weighing 665 mg.

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[Name of Document] Scope of Claims

1. A compound of the formula:



(I)

(wherein,

Z^1 is NR^4;

R^4 is hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkyl lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted aryl, optionally substituted aryl lower alkyl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycle lower alkyl, optionally substituted heterocycleoxy, hydroxy, optionally substituted amino, optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue or lower alkyl substituted with optionally substituted phosphoric acid residue (the lower alkyl may be intervened by a heteroatom group selected from CO, O, S, SO, SO_2, NR^a (R^a is hydrogen or lower alkyl), ·N= and =N·)), O or CH_2;

Z^2 is optionally substituted lower alkylene or optionally substituted lower alkenylene, each may be intervened by a heteroatom group selected from O, S, SO, SO_2, NR^5 (R^5 is hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkyl lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted aryl, optionally substituted aryl lower alkyl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycle lower alkyl, optionally substituted heterocycleoxy, hydroxy or optionally substituted amino, optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue or lower alkyl substituted with optionally substituted phosphoric acid residue (the lower alkyl may be intervened by a heteroatom group selected from CO, O, S, SO, SO_2, NR^5 (R^5 is selected independently from the same substituent group as R^4), ·N= and =N·)), ·N= or

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=N-;

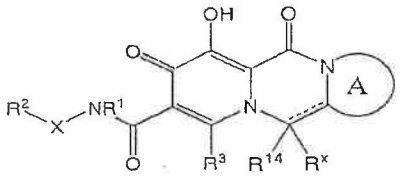
R^1 is hydrogen or lower alkyl;

X is a single bond, a heteroatom group selected from O, S, SO, SO_2 and NH, or lower alkylene or lower alkenylene each may be intervened by the heteroatom;

R^2 is optionally substituted aryl;

R^3 is hydrogen, halogen, hydroxy, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycleoxy or optionally substituted amino;

R^4 and Z^2 part taken together forms a ring, where the compound (I) is represented by the following formula (I-1), or (I-11):



(I-1)

(wherein,

A ring is optionally substituted heterocycle;

R^{14} and R^X are independently hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkyl lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryl lower alkyl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycle lower alkyl, optionally substituted heterocycleoxy, optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue or lower alkyl substituted with optionally substituted phosphoric acid residue (the lower alkyl may be intervened by a heteroatom group selected from O, S, SO, SO_2, NR^5 (R^5 is selected independently from the same substituent group as R^4), -N= and =N-), hydroxy, optionally substituted amino, optionally substituted lower alkyl carbonyl, optionally substituted cycloalkylcarbonyl, optionally substituted cycloalkyl lower alkyl carbonyl, optionally substituted lower alkoxy carbonyl, optionally substituted arylcarbonyl, optionally substituted aryl lower alkyl carbonyl, optionally substituted aryloxycarbonyl, optionally substituted heterocyclecarbonyl, optionally substituted

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heterocycle lower alkyl carbonyl, optionally substituted heterocycleoxy carbonyl or optionally substituted aminocarbonyl;

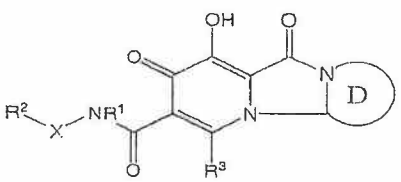
a broken line represents the presence or absence of a bond, provided that when the broken line represents the presence of a bond, R^X is not present;

R^1 is hydrogen or lower alkyl;

X is a single bond, a heteroatom group selected from O, S, SO, SO_2 and NH, or lower alkylene or lower alkenylene each may be intervened by the heteroatom group;

R^2 is optionally substituted aryl;

R^3 is hydrogen, halogen, hydroxy, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycleoxy or optionally substituted amino)



(I-11)

(wherein,

D ring is optionally substituted heterocycle;

R^1 is hydrogen or lower alkyl;

X is a single bond, a heteroatom group selected from O, S, SO, SO_2 and NH, or lower alkylene or lower alkenylene each may be intervened by the heteroatom group;

R^2 is optionally substituted aryl;

R^3 is hydrogen, halogen, hydroxy, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycleoxy or optionally substituted amino));

or a pharmaceutically acceptable salt, or solvate thereof.

2. A compound according to Claim 1, pharmaceutically acceptable salt, or solvate thereof, wherein R^1 is hydrogen.

3. A compound according to Claim 1, pharmaceutically acceptable salt, or solvate thereof, wherein X is lower alkylene; R^2 is phenyl or phenyl substituted with at least halogen.

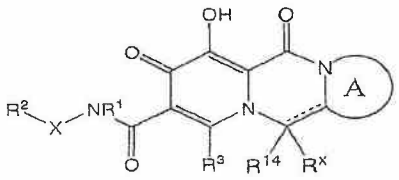
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4. A compound according to Claim 1, pharmaceutically acceptable salt, or solvate thereof, wherein R^3 is hydrogen, halogen, hydroxy, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy or optionally substituted amino.

5. A compound according to Claim 1, pharmaceutically acceptable salt, or solvate thereof, wherein R^3 is hydrogen.

6. A compound according to Claim 1, pharmaceutically acceptable salt, or solvate thereof, wherein R^1 is hydrogen or lower alkyl; X is lower alkylene; R^2 is phenyl or phenyl substituted with at least halogen; R^3 is hydrogen, halogen, hydroxy, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy or optionally substituted amino.

7. A compound of the formula:



(I-1)

(wherein,

A ring is optionally substituted heterocycle;

R^{14} and R^X are independently hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkyl lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryl lower alkyl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycle lower alkyl, optionally substituted heterocycleoxy, optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue or lower alkyl substituted with optionally substituted phosphoric acid residue (the lower alkyl may be intervened by a heteroatom group selected from O, S, SO, SO_2, NR^5 (R^5 is selected independently from the same substituent group as R^4), -N= and =N-), hydroxy, optionally substituted amino, optionally substituted lower alkyl carbonyl, optionally substituted cycloalkylcarbonyl, optionally substituted cycloalkyl lower alkyl carbonyl, optionally substituted lower alkoxy carbonyl, optionally substituted arylcarbonyl, optionally substituted aryl lower alkyl carbonyl, optionally substituted aryloxycarbonyl, optionally substituted heterocyclecarbonyl, optionally substituted

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heterocycle lower alkyl carbonyl, optionally substituted heterocycleoxy carbonyl or optionally substituted aminocarbonyl;

a broken line represents the presence or absence of a bond, provided that when the broken line represents the presence of a bond, R^X is not present;

R^1 is hydrogen or lower alkyl;

X is a single bond, a heteroatom group selected from O, S, SO, SO_2 and NH, or lower alkylene or lower alkenylene each may be intervened by the heteroatom group;

R^2 is optionally substituted aryl;

R^3 is hydrogen, halogen, hydroxy, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycleoxy or optionally substituted amino);

or a pharmaceutically acceptable salt, or solvate thereof

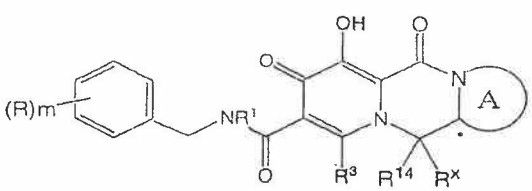
8. A compound according to Claim 7, pharmaceutically acceptable salt, or solvate thereof, wherein R^1 is hydrogen or lower alkyl; X is lower alkylene; R^2 is phenyl or phenyl substituted with at least halogen; R^3 is hydrogen, halogen, hydroxy, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy or optionally substituted amino.

9. A compound according to Claim 7, pharmaceutically acceptable salt, or solvate thereof, wherein a broken line represents the absence of a bond.

10. A compound according to Claim 7, pharmaceutically acceptable salt, or solvate thereof, wherein R^X is hydrogen; R^{14} is hydrogen or optionally substituted lower alkyl.

11. A compound according to Claim 7, pharmaceutically acceptable salt, or solvate thereof, wherein A ring is an optionally substituted and optionally condensed 5- to 7-membered heterocycle containing 1 to 2 hetero atom(s).

12. A compound of the formula:



(I-1-1)

(wherein,

A ring is an optionally substituted and optionally condensed 5- to 7- membered

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heterocycle containing 1 to 2 hetero atom(s);

the stereochemistry of an asymmetric carbon represented by * shows R- or S-configuration, or a mixture thereof;

R^{xd} and R^{x} are independently hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkyl lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryl lower alkyl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycle lower alkyl, optionally substituted heterocycleoxy, optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue or lower alkyl substituted with optionally substituted phosphoric acid residue (the lower alkyl may be intervened by a heteroatom group selected from O, S, SO, SO_2, NR^5 (R^5 is selected independently from the same substituent group as R^{xd}), -N= and =N-), hydroxy, optionally substituted amino, optionally substituted lower alkyl carbonyl, optionally substituted cycloalkylcarbonyl, optionally substituted cycloalkyl lower alkyl carbonyl, optionally substituted lower alkoxy carbonyl, optionally substituted arylcarbonyl, optionally substituted aryl lower alkyl carbonyl, optionally substituted aryloxycarbonyl, optionally substituted heterocyclecarbonyl, optionally substituted heterocycle lower alkyl carbonyl, optionally substituted heterocycleoxy carbonyl or optionally substituted aminocarbonyl;

R^3 is hydrogen, halogen, hydroxy, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycleoxy or optionally substituted amino), its pharmaceutically acceptable salt, or

R^1 is hydrogen or lower alkyl;

R is independently selected from halogen and Substituent group S1;

Substituent group S1(: optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue, or lower alkyl substituted with optionally substituted phosphoric acid residue (wherein the lower alkyl may be intervened with a heteroatom group(s) selected from CO, O, O, S, SO, SO_2, NR^a (R^a is hydrogen or lower alkyl), -N= and =N-), lower alkoxy lower alkyl, amino lower alkyl optionally

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substituted with mono- or di- lower alkyl, halogenated lower alkyl, lower alkoxy, carbamoyl optionally substituted with mono- or di- lower alkyl, optionally substituted lower alkyl sulfonyl amino, halogenated lower alkoxy, hydroxy lower alkyl)

m is an integer of 0 to 3);
or a pharmaceutically acceptable salt, or solvate thereof.

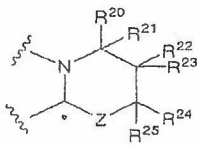
13. A compound according to Claim 12, pharmaceutically acceptable salt, or solvate thereof, wherein R^X and R^{14} are independently hydrogen or optionally substituted lower alkyl.

14. A compound according to Claim 12, pharmaceutically acceptable salt, or solvate thereof, wherein R^X and R^{14} are hydrogens.

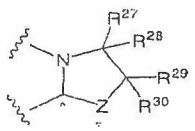
15. A compound according to Claim 12, pharmaceutically acceptable salt, or solvate thereof, wherein R^3 is hydrogen.

16. A compound according to Claim 12, pharmaceutically acceptable salt, or solvate thereof, wherein m is 0, or 1 to 3 and at least one of R is halogen.

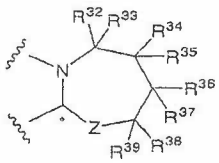
17. A compound according to Claim 7 or 12, pharmaceutically acceptable salt, or solvate thereof, wherein A ring is any one of the followings:



Z = O or NR^{26}
(A-1)



Z = O or NR^{31}
(A-2)



Z = O or NR^{40}
(A-3)

(wherein, R^{20} to R^{40} are each independently a group selected from Substituent group S2, or any two groups of R^{20} to R^{40}, which bonds to the same carbon atom, taken together with the carbon atom, may form an optionally substituted carbocyle or optionally substituted heterocycle, or each combination of (R^{20} and R^{22}), (R^{23} and R^{24}), (R^{25} and R^{26}), (R^{27} and R^{29}), (R^{30} and R^{31}), (R^{32} and R^{34}), (R^{35} and R^{36}), (R^{37} and R^{38}), and (R^{39}andR^{40}), taken together with the neighboring atom, may form an optionally substituted carbocyle or optionally substituted heterocycle.

Substituent group S2: hydrogen, optionally substituted lower alkyl, optionally

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substituted cycloalkyl, optionally substituted cycloalkyl lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryl lower alkyl, optionally substituted aryloxy, optionally substituted heterocycle, optionally substituted heterocycle lower alkyl, optionally substituted heterocycleoxy, hydroxy, optionally substituted amino, optionally substituted lower alkylcarbonyl, optionally substituted cycloalkylcarbonyl, optionally substituted cycloalkyl lower alkylcarbonyl, optionally substituted lower alkoxycarbonyl, optionally substituted arylcarbonyl, optionally substituted aryl lower alkylcarbonyl, optionally substituted aryl oxycarbonyl, optionally substituted heterocyclecarbonyl, optionally substituted heterocycle lower alkylcarbonyl, optionally substituted heterocycleoxycarbonyl, optionally substituted aminocarbonyl, optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue, or lower alkyl substituted with optionally substituted phosphoric acid residue (the lower alkyl may be intervened with a heteroatom group(s) selected from CO, O, S, SO, SO_2, NR^5 (R^5 is independently selected from the same Substituent group as R^4), -N= and =N-)

the stereochemistry of an asymmetric carbon represented by * shows R- or S- configuration, or a mixture thereof)

18. A compound according to Claim 17, pharmaceutically acceptable salt, or solvate thereof, wherein R^{20} to R^{40} are each independently hydrogen or substituted lower alkyl, or any two groups of R^{20} to R^{40}, which bonds to the same carbon atom, taken together with the carbon atom, may form an optionally substituted 3- to 7- membered carbocyle or optionally substituted 3- to 7- membered heterocycle, or each combination of (R^{20} and R^{22}), (R^{23} and R^{24}), (R^{25} and R^{26}), (R^{27} and R^{29}), (R^{30} and R^{31}), (R^{32} and R^{34}), (R^{35} and R^{36}), (R^{37} and R^{38}), and (R^{39}andR^{40}), taken together with the neighboring atom, may form an optionally substituted 5- to 7- membered carbocyle or optionally substituted 5- to 7- membered heterocycle.

19. A compound according to Claim 17, pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-1); one of R^{20} to R^{25} is optionally substituted lower alkyl and the others are hydrogens.

20. A compound according to Claim 17, pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-1); one of (R^{20} and R^{22}), (R^{23} and R^{24}), and (R^{25} and R^{26}), taken together with the neighboring atom, may form an

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optionally substituted 5- to 7- membered carbocyle or optionally substituted 5- to 7- membered heterocycle.

21. A compound according to Claim 17, pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-1); Z=NR^{26}, and R^{25} and R^{26} taken together with the neighboring atom may form an optionally substituted 5- to 7- membered heterocycle.

22. A compound according to Claim 17, pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-2); one of R^{27} to R^{30} is optionally substituted lower alkyl and the others are hydrogens.

23. A compound according to Claim 17, pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-2); one of ($R^{27}$and R^{29}) and (R^{30} and R^{31}), taken together with the neighboring atom, may form an optionally substituted 5- to 7- membered carbocyle or optionally substituted 5- to 7- membered heterocycle.

24. A compound according to Claim 17, pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-2); Z=NR^{31}, and R^{30} and R^{31} taken together with the neighboring atom may form an optionally substituted 5- to 7- membered heterocycle.

25. A compound according to Claim 17, pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-3); one of R^{32} to R^{39} is optionally substituted lower alkyl and the others are hydrogens.

26. A compound according to Claim 17, pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-3); one of (R^{32}andR^{34}),(R^{35}andR^{36}),(R^{37}andR^{38}),and(R^{39}andR^{40}), taken together with the neighboring atom, may form an optionally substituted 5- to 7- membered carbocyle or optionally substituted 5- to 7- membered heterocycle.

27. A compound according to Claim 17, pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-3); Z=NR^{40}, and R^{39} and R^{40} taken together with the neighboring atom may form an optionally substituted 5- to 7- membered heterocycle.

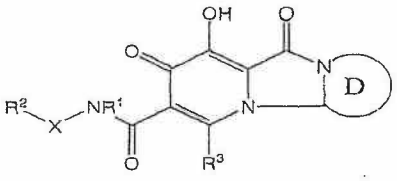
28. A compound according to Claim 12, pharmaceutically acceptable salt, or solvate thereof, wherein R^{x} is hydrogen; R^{14} is hydrogen or optionally substituted lower; R^{3} is hydrogen; m is 1 to 3 and at least one of Rs is halogen; A ring is a ring described in

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Claim 17.

29. A compound according to Claim 12, pharmaceutically acceptable salt, or solvate thereof, wherein R^X is hydrogen; R^{14} is hydrogen; R^3 is hydrogen; m is 0, or 1 to 3 and at least one of R is halogen; A ring is a ring described in Claim 17; R^{20} to R^{40} are each independently hydrogen or substituted lower alkyl, or any two groups of R^{20} to R^{40}, which bonds to the same carbon atom, taken together with the carbon atom, may form an optionally substituted 3- to 7- membered carbocyle or optionally substituted 3- to 7- membered heterocycle, or each combination of (R^{20} and R^{22}), (R^{23} and R^{24}), (R^{25} and R^{26}), (R^{27} and R^{29}), (R^{30} and R^{31}), (R^{32} and R^{34}), (R^{35} and R^{36}), (R^{37} and R^{38}), and (R^{39}andR^{40}), taken together with the neighboring carbon atom, may form an optionally substituted 5- to 7- membered carbocyle or optionally substituted 5- to 7- membered heterocycle.

30. A compound of the formula:



(I-11)

(wherein,

D ring is optionally substituted heterocycle;

R^1 is hydrogen or lower alkyl;

X is a single bond, a heteroatom group selected from O, S, SO, SO_2 and NH, or lower alkylene or lower alkenylene each may be intervened by the heteroatom group;

R^2 is optionally substituted aryl;

R^3 is hydrogen, halogen, hydroxy, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycleoxy or optionally substituted amino);

or a pharmaceutically acceptable salt, or solvate thereof

31. A compound selected from the group consisting of:

(3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

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(4a*R*,13a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide;

(3a*S*,13a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-8-hydroxy-7,9-dioxo-1,2,3,3a,4,5,7,9,13,13a-decahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrrolo[1,2-*c*]pyrimidine-10-carboxamide;

(4a*S*,13a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide;

(4a*S*,13a*R*)-*N*-[(4-Fluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-3-(phenylmethyl)-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3a*S*,13a*S*)-*N*-[(4-Fluorophenyl)methyl]-8-hydroxy-7,9-dioxo-1,2,3,3a,4,5,7,9,13,13a-decahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrrolo[1,2-*c*]pyrimidine-10-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[(1*S*)-1-methylpropyl]-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(4-Fluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-he

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xahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-3-(1,1-dimethylethyl)-6-hydroxy-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-3-(1,1-Dimethylethyl)-*N*-[(4-fluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-3-phenyl-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(hydroxymethyl)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(2*S*,3*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2-phenyl-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-3-(phenylmethyl)-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(2-methylpropyl)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(5a*R*,14a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-11-hydroxy-10,12-dioxo-1,2,3,4,5a,6,10,12,14,14a-decahydropyrido[1,2-*a*]pyrido[1',2':3,4]imidazo[1,2-*d*]pyrazine-9-carboxamide;

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(2*S*,3*S*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[(methyloxy)methyl]-5,7-dioxo-2-phenyl-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide

(3*S*,11a*R*)-3-(Cyclohexylmethyl)-*N*-[(2,4-difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(1-methylethyl)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(5a*R*,14a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-5a,6a,7,11,13,14a-hexahydro-5*H*-indeno[1',2':4,5][1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-10-carboxamide;

(2*S*,3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3-diphenyl-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(2*S*,3*R*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3-diphenyl-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(1-methylethyl)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[2-(methylthio)ethyl]-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

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(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[2-(methylsulfonyl)ethyl]-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(1*H*-indol-3-ylmethyl)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(4*R*,12a*R*)-*N*-[(4-fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*R*,12a*R*)-*N*-[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(1-methylethyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-1-(Cyclopropylmethyl)-*N*-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-1-(2-furanylmethyl)-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

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(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1-(1,3-thiazol-2-ylmethyl)-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4a*R*,6a*R*,14a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-1,3,4,4a,5,6a,7,11,13,14a-decahydro-2*H*-pyrido[1',2':4,5]pyrazino[1,2-*a*][3,1]benzoxazine-10-carboxamide;

(4a*R*,6a*R*,14a*S*)-*N*-[(4-Fluorophenyl)methyl]-12-hydroxy-11,13-dioxo-1,3,4,4a,5,6a,7,11,13,14a-decahydro-2*H*-pyrido[1',2':4,5]pyrazino[1,2-*a*][3,1]benzoxazine-10-carboxamide;

(3*S*,4a*R*,6a*R*,14a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-3-phenyl-1,3,4,4a,5,6a,7,11,13,14a-decahydro-2*H*-pyrido[1',2':4,5]pyrazino[1,2-*a*][3,1]benzoxazine-10-carboxamide;

(4aS,6aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy-6-(2-methylpropyl)-11,13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide;

(6aR,7aS,11aS)-N-[(2,4-Difluorophenyl)methyl]-1-hydroxy-2,13-dioxo-2,6a,7,7a,8,9,10,11,11a,13-decahydro-6H-pyrido[1',2':4,5]pyrazino[1,2-a]benzimidazole-3-carboxamide;

(6aS,7aS,11aS)-N-[(2,4-Difluorophenyl)methyl]-1-hydroxy-2,13-dioxo-2,6a,7,7a,8,9,10,11,11a,13-decahydro-6H-pyrido[1',2':4,5]pyrazino[1,2-a]benzimidazole-3-carboxamide;

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(5aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-11-hydroxy-10,12-dioxo-1,2,3,4,5a,6,10,12,14,14a-decahydropyrido[1,2-a]pyrido[1',2':3,4]imidazo[1,2-d]pyrazine-9-carboxamide;

(4aR,14aR)-N-[(2,4-Difluorophenyl)methyl]-9-hydroxy-8,10-dioxo-2,3,4,4a,5,6,8,10,14,14a-decahydro-1H-pyrido[1,2-c]pyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-11-carboxamide;

(4*R*,12a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(3-methylbutyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(1-methylethyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(3-methylbutyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1-(3-pyridinylmethyl)-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-1-Cyclopropyl-*N*-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-

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1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-[2-(methyloxy)ethyl]-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(3aS,5aS,13aS)-N-[(2,4-Difluorophenyl)methyl]-11-hydroxy-5-(2-methylpropyl)-10,12-dioxo-2,3,3a,4,5,5a,6,10,12,13a-decahydro-1H-cyclopenta[e]pyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide;

(3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-3-ethyl-6-hydroxy-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(4aS,6aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy-6-[2-(4-morpholinyl)ethyl]-11,13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide;

(3aR,5aR,13aS)-N-[(2,4-Difluorophenyl)methyl]-11-hydroxy-10,12-dioxo-1,2,3,3a,4,5a,6,10,12,13a-decahydrocyclopenta[d]pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxamide;

(4aS,6aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy-6-methyl-11,13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide;

(4aS,6aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy-6-[2-(methyloxy)ethyl]-11,

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13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide;

(4aS,6aS,14aS)-6-[2-(Acetylamino)ethyl]-N-[(2,4-difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-3-ethyl-6-hydroxy-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-3-Butyl-*N*-[(2,4-difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[(4-hydroxyphenyl)methyl]-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(4S,12aS)-1-Cyclobutyl-N-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1-(tetrahydro-2*H*-thiopyran-4-yl)-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-1,4-bis(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

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(4aS,6aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy-6-(2-hydroxyethyl)-11,13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide;

(4aS,6aS,14aS)-6-Cyclopropyl-N-[(2,4-difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide;

(4aS,6aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-6-[2-(1-pyrrolidinyl)ethyl]-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide;

(4aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-9-hydroxy-8,10-dioxo-2,3,4,4a,5,6,8,10,14,14a-decahydro-1H-pyrido[1,2-c]pyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-11-carboxamide;

(4S,12aS)-N-[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-1-[2-(methyloxy)ethyl]-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide;

(4S,12aS)-1-Cyclobutyl-N-[(4-fluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide;

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(4S,12aS)-N-[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide;

(4S,12aS)-N-[(4-Fluorophenyl)methyl]-7-hydroxy-1,4-dimethyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-*N*-[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1-(tetrahydro-2*H*-thiopyran-4-yl)-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-1,4-dimethyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-*N*-[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(1-methylethyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-*N*-[(4-Fluorophenyl)methyl]-7-hydroxy-1,4-bis(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

enantiomers thereof; diastereomers thereof; mixtures of enantiomers thereof; mixtures of diastereomers thereof; mixtures of enantiomers and diastereomers thereof; and pharmaceutically acceptable salts thereof.

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32. A compound selected from the group consisting of:

(4a*S*,13a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2'':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide;

(4a*S*,13a*R*)-*N*-[(4-Fluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2'':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[(1*S*)-1-methylpropyl]-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(4-Fluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2'':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-1-(Cyclopropylmethyl)-*N*-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2'':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4a*R*,6a*R*,14a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-1,3,4,4a,5,6a,7,11,13,14a-decahydro-2*H*-pyrido[1',2'':4,5]pyrazino[1,2-*a*][3,1]benzoxazine-10-carboxa

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mide;

(4a*R*,6a*R*,14a*S*)-*N*-[(4-Fluorophenyl)methyl]-12-hydroxy-11,13-dioxo-1,3,4,4a,5,6a,7,11,13,14a-decahydro-2*H*-pyrido[1',2':4,5]pyrazino[1,2-*a*][3,1]benzoxazine-10-carboxamide;

4S,9aR)-5-Hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4,-difluoro-benylamide;

4R,9aS)-5-Hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4,-difluoro-benylamide;

2R,9aS)-5-Hydroxy-2-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 4-fluoro-benylamide;

enantiomers thereof; diastereomers thereof; mixtures of enantiomers thereof; mixtures of diastereomers thereof; mixtures of enantiomers and diastereomers thereof; and pharmaceutically acceptable salts thereof.

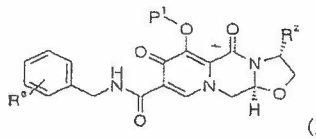
33. A compound according to claims 31 or 32 wherein the pharmaceutically acceptable salt is a sodium salt.

34. A pharmaceutical composition comprising a compound according to any one of Claims 1 to 33, or a pharmaceutically acceptable salt, or solvate thereof.

35. A pharmaceutical composition according to Claim 34, which is an anti-HIV agent.

36. A process for the preparation of a compound of formula (I-20a)

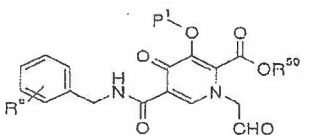
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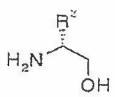
(I-20a)

wherein R^e is one or two halogen; R^z is C_{1-8}alkyl, C_{6-14}arylC_{1-8}alkyl, C_{6-14}aryl, or alkoxy; and P^1 is C_{6-14}arylC_{1-8}alkyl;

comprising condensing a compound of the formula

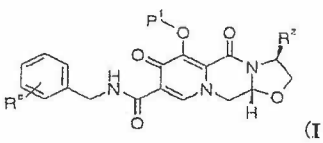


wherein R^e is one or two halogen; R^{60} is C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl;
with a compound of the formula



wherein R^z is C_{1-8}alkyl, C_{6-14}arylC_{1-8}alkyl, C_{6-14}aryl, or alkoxy;
to form a compound of formula (I-20a).

37. A process for the preparation of a compound of formula (I-20b)

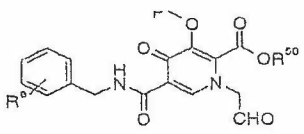


(I-20b)

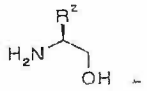
wherein R^e is one or two halogen; R^z is C_{1-8}alkyl, C_{6-14}arylC_{1-8}alkyl, C_{6-14}aryl, or alkoxy; and P^1 is C_{6-14}arylC_{1-8}alkyl;

comprising condensing a compound of the formula

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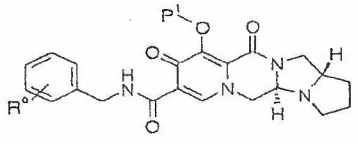


wherein R^e is one or two halogen; R^{50} is C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl; with a compound of the formula



wherein R^z is C_{1-8}alkyl, C_{6-14}arylC_{1-8}alkyl, C_{6-14}aryl, or alkoxy; to form a compound of formula (I-20b).

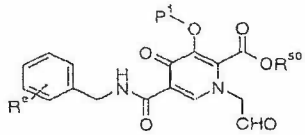
38. A process for the preparation of a compound of formula (I-21a)



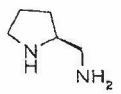
(I-21a)

wherein R^e is one or two halogen; and P^1 is C_{6-14}arylC_{1-8}alkyl;

comprising condensing a compound of the formula

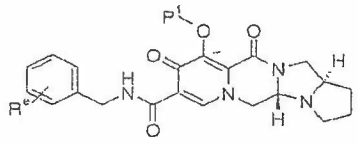


wherein R^e is one or two halogen; R^{50} is C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl; with a compound of the formula



to form a compound of formula (I-21a).

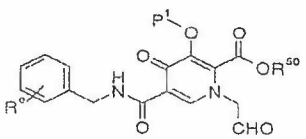
39. A process for the preparation of a compound of formula (I-21b)



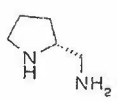
(I-21b)

wherein R^e is one or two halogen; and P^1 is C_{6-14}arylC_{1-8}alkyl;

comprising condensing a compound of the formula

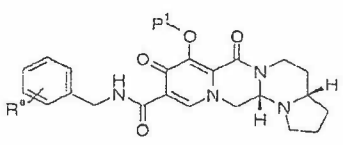


wherein R^e is one or two halogen; R^{50} is C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl; with a compound of the formula



to form a compound of formula (I-21b).

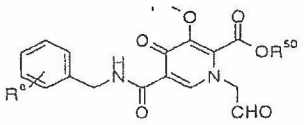
40. A process for the preparation of a compound of formula (I-22a)



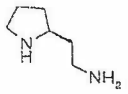
(I-22a)

wherein R^e is one or two halogen; and P^1 is C_{6-14}arylC_{1-8}alkyl;
comprising condensing a compound of the formula:

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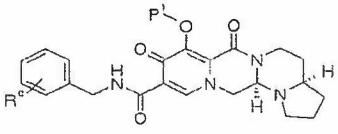


wherein R^a is one or two halogen; R^{50} is C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl; with a compound of the formula



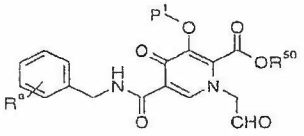
to form a compound of formula (I-22a).

41. A process for the preparation of a compound of formula (I-22b)

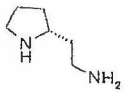


(I-22b)

wherein R^a is one or two halogen; and P^1 is C_{6-14}arylC_{1-8}alkyl; comprising condensing a compound of the formula



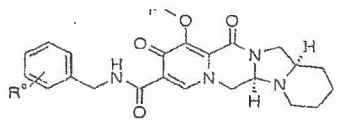
wherein R^a is one or two halogen; R^{50} is C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl; with a compound of the formula



to form a compound of formula (I-22b).

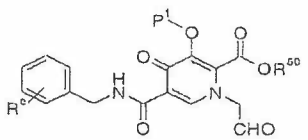
42. A process for the preparation of a compound of formula (I-23a)

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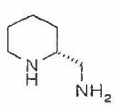


(I-23a)

wherein R^e is one or two halogen; and P^1 is $C_{6-14}arylC_{1-8}alkyl$; comprising condensing a compound of the formula

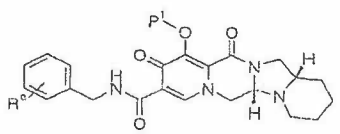


wherein R^e is one or two halogen; R^{50} is $C_{1-8}alkyl$; and P^1 is $C_{6-14}arylC_{1-8}alkyl$; with a compound of the formula



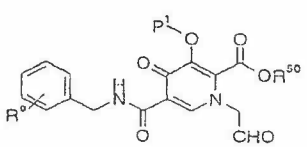
to form a compound of formula (I-23a).

43. A process for the preparation of a compound of formula (I-23b)



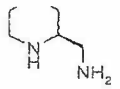
(I-23b)

wherein R^e is one or two halogen; and P^1 is $C_{6-14}arylC_{1-8}alkyl$; comprising condensing a compound of the formula



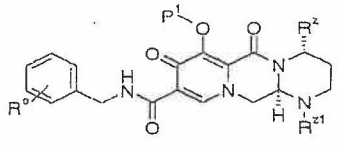
wherein R^e is one or two halogen; R^{50} is $C_{1-8}alkyl$; and P^1 is $C_{6-14}arylC_{1-8}alkyl$; with a compound of the formula -

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to form a compound of formula (I-23b).

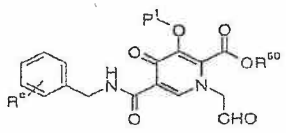
44. A process for the preparation of a compound of formula (I-24a)



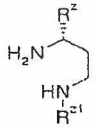
(I-24a)

wherein R^e is one or two halogen; R^{z1} is hydrogen, C_{3-6}cycloalkyl, heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-6}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl, or amino, wherein said amino may be optionally substituted with $-C(O)C_{1-8}$alkyl or C_{1-8}alkyl;
and P^1 is C_{6-14}arylC_{1-8}alkyl;

comprising condensing a compound of the formula



wherein R^e is one or two halogen; R^{50} is C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl;
with a compound of the formula

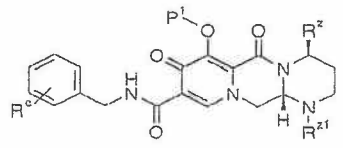


wherein R^z is C_{1-8}alkyl; R^{z1} is hydrogen, C_{3-6}cycloalkyl, , heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-6}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl, or amino, wherein said amino may be optionally substituted with $-C(O)C_{1-8}$alkyl or C_{1-8}alkyl;

to form a compound of the formula (I-24a).

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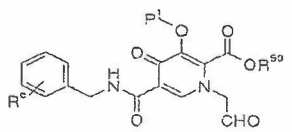
45. A process for the preparation of a compound of formula (I-24b)



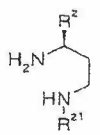
(I-24b)

wherein R^e is one or two halogen; R^{z1} is hydrogen, C_{3-6}cycloalkyl, heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-6}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl, or amino, wherein said amino may be optionally substituted with $-C(O)C_{1-8}$alkyl or C_{1-8}alkyl;
and P^1 is C_{6-14}arylC_{1-8}alkyl;

comprising condensing a compound of the formula

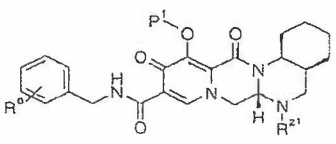


wherein R^e is one or two halogen; R^{50} is C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl;
with a compound of the formula



wherein R^z is C_{1-8}alkyl; R^{z1} is hydrogen, C_{3-6}cycloalkyl, heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-6}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl, or amino, wherein said amino may be optionally substituted with $-C(O)C_{1-8}$alkyl or C_{1-8}alkyl;
to form a compound of the formula (I-24b).

46. A process for the preparation of a racemic compound of formula (I-25)

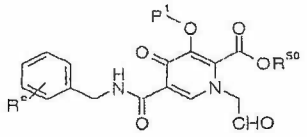


(I-25)

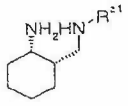
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wherein R^e is one or two halogen; R^{z1} is hydrogen, C_{3-6}cycloalkyl, heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-6}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl, or amino, wherein said amino may be optionally substituted with $-C(O)C_{1-8}$alkyl or C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl;

comprising condensing a compound of the formula



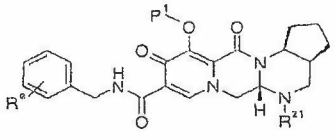
wherein R^e is one or two halogen; R^{50} is C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl; with a racemic compound of the formula



wherein R^{z1} is hydrogen, C_{3-6}cycloalkyl, heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-6}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl, or amino, wherein said amino may be optionally substituted with $-C(O)C_{1-8}$alkyl or C_{1-8}alkyl;

to form a racemic compound of the formula (I-25).

47. A process for the preparation of a racemic compound of formula (I-26)

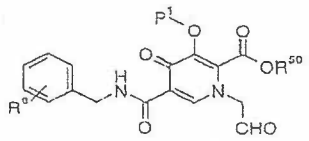


(I-26)

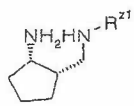
wherein R^e is one or two halogen; R^{z1} is hydrogen, C_{3-6}cycloalkyl, heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-6}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl, or amino, wherein said amino may be optionally substituted with $-C(O)C_{1-8}$alkyl or C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl;

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comprising condensing a compound of the formula

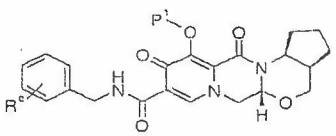


wherein R^e is one or two halogen; R^{50} is C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl; with a racemic compound of the formula



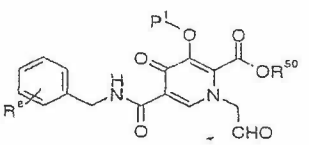
wherein R^{z1} is hydrogen, C_{3-6}cycloalkyl, heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-6}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl, or amino, wherein said amino may be optionally substituted with $-C(O)C_{1-8}$alkyl or C_{1-8}alkyl;
to form a racemic compound of formula (I-26).

48. A process for the preparation of a racemic compound of formula (I-27)



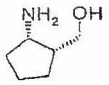
(I-27)

wherein R^e is halogen; and P^1 is C_{6-14}arylC_{1-8}alkyl;
comprising condensing a compound of the formula



wherein R^e is one or two halogen; R^{50} is C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl; with a racemic compound of the formula

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to form a racemic compound of formula (I-27).

49. A method of treatment of an HIV infection in a human comprising administering to said human an antiviral effective amount of a compound according to any of claims 1 to 33.

50. A compound as claimed in any of claims 1 to 33 for use in medical therapy.

51. Use of a compound as claimed in any of claims 1 to 33 in the manufacture of a medicament for the treatment or prophylaxis of an HIV infection.

52. A compound of formula (I-20a) described in Claim 36. formula (I-20b) described in Claim 37, formula (I-21a) described in Claim 38, formula (I-21b) described in Claim 39, formula (I-22a) described in Claim 40, formula (I-22b) described in Claim 41, formula (I-23a) described in Claim 42, formula (I-23b) described in Claim 43, formula (I-24a) described in Claim 44, formula (I-24b) described in Claim 45, formula (I-25) described in Claim 46, formula (I-26) described in Claim 47, or formula (I-27) described in Claim 48, or a pharmaceutically acceptable salt thereof.

53. A compound of formula (I-20a) described in Claim 36. formula (I-20b) described in Claim 37, formula (I-21a) described in Claim 38, formula (I-21b) described in Claim 39, formula (I-22a) described in Claim 40, formula (I-22b) described in Claim 41, formula (I-23a) described in Claim 42, formula (I-23b) described in Claim 43, formula (I-24a) described in Claim 44, formula (I-24b) described in Claim 45, formula (I-25) described in Claim 46, formula (I-26) described in Claim 47, or formula (I-27) described in Claim 48, or a pharmaceutically acceptable salt thereof, wherein each P^1 is hydrogen.

54. A pharmaceutical composition according to claim 34 wherein said composition comprises at least one additional therapeutic agent selected from reverse transcriptase inhibitors and protease inhibitors.

55. A method of treatment of an HIV infection in a human comprising administering to said human a composition comprising a compound according to any of claims 1 to

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33 and another therapeutic agent.

56. The method according to claim 55 wherein said therapeutic agent is selected from reverse transcriptase inhibitors and protease inhibitors.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US06/16604

A. CLASSIFICATION OF SUBJECT MATTER
IPC: **A01N 43/58**(2006.01),**43/60**(2006.01);**A61K 31/50**(2006.01),**31/495**(2006.01);**C07D 239/00**(2006.01),**241/36**(2006.01),**471/00**(2006.01),**487/00**(2006.01),**495/00**(2006.01),**497/00**(2006.01)

USPC: 514/250;544/247,250,251,343,346
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/250; 544/247, 250, 251, 343, 346

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN: structure search was conducted in file REGISTRY, answer set cross-referenced into file CAPLUS.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2005/0054645 (MIYAZAKI et al) 10 March 2005 (10.03.2005), page 105 compound #180, page 108 compound #196, page 111 compounds #213 and #214, 114 compound #234, page 116 compound #273, page 125 compound #372, page 126 compounds #377 and #378, page 127 compound #380 and page 135 compound #428.	1-6

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
21 August 2006 (21.08.2006)

Date of mailing of the international search report
18 SEP 2006

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
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Zachary C. Tucker
Telephone No. (571) 272-1600

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US06/16604

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 52 and 53
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Please See Continuation Sheet

3. ☒ Claims Nos.: 34,35,49-51 and 54-56
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US06/16504

Continuation of Box II Reason 2:
Claims 52 and 53 lack antecedent basis in the claims from which they depend. Claims 52 and 53 are drawn to compunds, while the claims from which they depend are drawn to methods. Thus, no meaningful search can be carried out for claims 52 and 53

Form PCT/ISA/210 (extra sheet) (April 2005)

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C07D 471/00 (2006.01) *A61K 31/495* (2006.01)
C07D 487/00 (2006.01) *A61P 31/18* (2006.01)
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(72) Inventors; and

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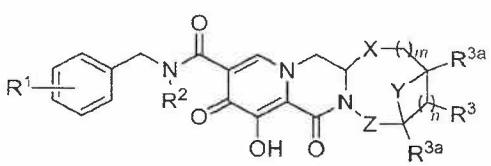
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

(54) Title: TETRACYCLIC HETEROCYCLE COMPOUNDS USEFUL AS HIV INTEGRASE INHIBITORS



(I)

(57) Abstract: The present invention relates to Tetracyclic Heterocycle Compounds of Formula (I) and pharmaceutically acceptable salts or prodrug thereof, wherein n, X, Y, Z, R^1, R^2, and R^3 are as defined herein. The present invention also relates to compositions comprising at least one Tetracyclic Heterocycle Compound, and methods of using the Tetracyclic Heterocycle Compounds for treating or preventing HIV infection in a subject.

WO 2015/039348 A1

TETRACYCLIC HETEROCYCLE COMPOUNDS USEFUL AS HIV INTEGRASE INHIBITORS

FIELD OF THE INVENTION

The present invention relates to Tetracyclic Heterocycle Compounds, compositions comprising at least one Tetracyclic Heterocycle Compound, and methods of using the Tetracyclic Heterocycle Compounds for treating or preventing HIV infection in a subject.

BACKGROUND OF THE INVENTION

A retrovirus designated human immunodeficiency virus (HIV), particularly the strains known as HIV type-1 (HIV-1) virus and type-2 (HIV-2) virus, is the etiological agent of the complex disease that includes progressive destruction of the immune system (acquired immune deficiency syndrome; AIDS) and degeneration of the central and peripheral nervous system. A common feature of retrovirus replication is the insertion by virally-encoded integrase of +proviral DNA into the host cell genome, a required step in HIV replication in human T-lymphoid and monocytoid cells. Integration is believed to be mediated by integrase in three steps: assembly of a stable nucleoprotein complex with viral DNA sequences; cleavage of two nucleotides from the 3' termini of the linear proviral DNA; covalent joining of the recessed 3' OH termini of the proviral DNA at a staggered cut made at the host target site. The fourth step in the process, repair synthesis of the resultant gap, may be accomplished by cellular enzymes.

Nucleotide sequencing of HIV shows the presence of a pol gene in one open reading frame [Ratner, L. et al., Nature, 313, 277(1985)]. Amino acid sequence homology provides evidence that the pol sequence encodes reverse transcriptase, integrase and an HIV protease [Toh, H. et al., EMBO J. 4, 1267 (1985); Power, M.D. et al., Science, 231, 1567 (1986); Pearl, L.H. et al., Nature, 329, 351 (1987)]. All three enzymes have been shown to be essential for the replication of HIV.

It is known that some antiviral compounds which act as inhibitors of HIV replication are effective agents in the treatment of AIDS and similar diseases, including reverse transcriptase inhibitors such as azidothymidine (AZT) and efavirenz and protease inhibitors such as indinavir and nelfinavir. The compounds of this invention are inhibitors of HIV integrase and inhibitors of HIV replication.

The following references are of interest as background:

International Publication Nos. WO 11/045330 and WO 11/121105 disclose macrocyclic compounds having HIV integrase inhibitory activity.

Kinzel et al., *Tet. Letters* 2007, 48(37): pp. 6552-6555 discloses the synthesis of tetrahydropyridopyrimidones as a scaffold for HIV-1 integrase inhibitors.

Ferrara et al., *Tet. Letters* 2007, 48(37), pp. 8379-8382 discloses the synthesis of a hexahydropyrimido[1,2-a]azepine-2-carboxamide derivative useful as an HIV integrase inhibitor.

Muraglia et al., *J. Med. Chem.* 2008, 51: 861-874 discloses the design and synthesis of bicyclic pyrimidinones as potent and orally bioavailable HIV-1 integrase inhibitors.

US2004/229909 discloses certain compounds having integrase inhibitory activity.

US 7232819 and US 2007/0083045 disclose certain 5,6-dihydroxypyrimidine-4-carboxamides as HIV integrase inhibitors.

US 7169780, US 7217713, and US 2007/0123524 disclose certain N-substituted 5-hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxamides as HIV integrase inhibitors.

US 7279487 discloses certain hydroxynaphthyridinone carboxamides that are useful as HIV integrase inhibitors.

US 7135467 and US 7037908 disclose certain pyrimidine carboxamides that are useful as HIV integrase inhibitors.

US 7211572 discloses certain nitrogenous condensed ring compounds that are HIV integrase inhibitors.

US 7414045 discloses certain tetrahydro-4H-pyrido[1,2-a]pyrimidine carboxamides, hexahydropyrimido[1,2-*a*]azepine carboxamides, and related compounds that are useful as HIV integrase inhibitors.

WO 2006/103399 discloses certain tetrahydro-4H-pyrimidooxazepine carboaxmides, tetrahydropyrazinopyrimidine carboxamides, hexahydropyrimidodiazepine carboxamides, and related compounds that are useful as HIV integrase inhibitors.

US 2007/0142635 discloses processes for preparing hexahydropyrimido[1,2-a]azepine-2-carboxylates and related compounds.

US 2007/0149556 discloses certain hydroxypyrimidinone derivatives having HIV integrase inhibitory activity.

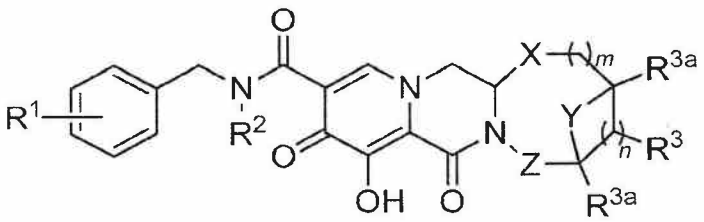
Various pyrimidinone compounds useful as HIV integrase inhibitors are also disclosed in US 7115601, US 7157447, US 7173022, US 7176196, US 7192948, US 7273859, and US 7419969.

US 2007/0111984 discloses a series of bicyclic pyrimidinone compounds useful as HIV integrase inhibitors.

US 2006/0276466, US 2007/0049606, US 2007/0111985, US 2007/0112190, US 2007/0281917, US 2008/0004265 each disclose a series of bicyclic pyrimidinone compounds useful as HIV integrase inhibitors.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides Compounds of Formula (I):



(I)

or a pharmaceutically acceptable salt or prodrug thereof,

wherein:

X is O, -CH(R^4)- or –N(R^5)-;

Y is O, -N(R^6)- or C_1-C_3 alkylene;

Z is a single bond or -C(R^7)-;

R^1 represents up to 5 optional phenyl group substituents, each independently selected from C_1-C_6 alkyl, -O-(C_1-C_6 alkyl) and halo;

R^2 is H;

R^3 is selected from H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -OR^6 and -N(R^6)$_2$;

each occurrence of R^{3a} is independently selected from H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -OR^6 and -N(R^6)$_2$;

R^4 is H or C_1-C_6 alkyl or –O-(C_1-C_6 alkyl);

R^5 is selected from H, C_1-C_6 alkyl and –C(O)R^8 and -SO_2R^8;

each occurrence of R^6 is independently H or C_1-C_6 alkyl;

R^7 is selected from H, C_1-C_6 alkyl and –O-(C_1-C_6 alkyl);

each occurrence of R^8 is C_1-C_6 alkyl or NR^6;

m is 0, 1 or 2; and

n is 1, 2 or 3, such that the sum of m+ n is 2 or 3.

The Compounds of Formula (I) (also referred to herein as the "Tetracyclic Heterocycle Compounds") and pharmaceutically acceptable salts or prodrugs thereof can be useful, for example, for inhibiting HIV viral replication or replicon activity, and for treating or preventing HIV infection in a subject. Without being bound by any specific theory, it is believed that the Tetracyclic Heterocycle Compounds inhibit HIV viral replication by inhibiting HIV Integrase.

Accordingly, the present invention provides methods for treating or preventing HIV infection in a subject, comprising administering to the subject an effective amount of at least one Tetracyclic Heterocycle Compound.

The details of the invention are set forth in the accompanying detailed description below.

Although any methods and materials similar to those described herein can be used in the practice or testing of the present invention, illustrative methods and materials are now described. Other embodiments, aspects and features of the present invention are either further described in or will be apparent from the ensuing description, examples and appended claims.

DETAILED DESCRIPTION OF THE INVENTION

The present invention includes Tetracyclic Heterocycle Compounds, compositions comprising at least one Tetracyclic Heterocycle Compound, and methods of using the Tetracyclic Heterocycle Compounds for treating or preventing HIV infection in a subject.

Definitions and Abbreviations

The terms used herein have their ordinary meaning and the meaning of such terms is independent at each occurrence thereof. That notwithstanding and except where stated otherwise, the following definitions apply throughout the specification and claims. Chemical names, common names, and chemical structures may be used interchangeably to describe the same structure. These definitions apply regardless of whether a term is used by itself or in combination with other terms, unless otherwise indicated. Hence, the definition of "alkyl" applies to "alkyl" as well as the "alkyl" portions of "hydroxyalkyl," "haloalkyl," "-O-alkyl," etc...

As used herein, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

A "subject" is a human or non-human mammal. In one embodiment, a subject is a human. In another embodiment, a subject is a primate. In another embodiment, a subject is a monkey. In another embodiment, a subject is a chimpanzee. In still another embodiment, a subject is a rhesus monkey.

The term "effective amount" as used herein, refers to an amount of Tetracyclic Heterocycle Compound and/or an additional therapeutic agent, or a composition thereof that is effective in producing the desired therapeutic, ameliorative, inhibitory or preventative effect when administered to a subject suffering from HIV infection or AIDS. In the combination

therapies of the present invention, an effective amount can refer to each individual agent or to the combination as a whole, wherein the amounts of all agents administered are together effective, but wherein the component agent of the combination may not be present individually in an effective amount.

The term "preventing," as used herein with respect to an HIV viral infection or AIDS, refers to reducing the likelihood or severity of HIV infection or AIDS.

The term "alkyl," as used herein, refers to an aliphatic hydrocarbon group having one of its hydrogen atoms replaced with a bond. An alkyl group may be straight or branched and contain from about 1 to about 20 carbon atoms. In one embodiment, an alkyl group contains from about 1 to about 12 carbon atoms. In different embodiments, an alkyl group contains from 1 to 6 carbon atoms (C_1-C_6 alkyl) or from about 1 to about 4 carbon atoms (C_1-C_4 alkyl). Non-limiting examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, neopentyl, isopentyl, n-hexyl, isohexyl and neohexyl. An alkyl group may be unsubstituted or substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkenyl, alkynyl, aryl, cycloalkyl, cyano, hydroxy, -O-alkyl, -O-aryl, -alkylene-O-alkyl, alkylthio, $-NH_2$, -NH(alkyl), $-N(alkyl)_2$, -NH(cycloalkyl), -O-C(O)-alkyl, -O-C(O)-aryl, -O-C(O)-cycloalkyl, -C(O)OH and –C(O)O-alkyl. In one embodiment, an alkyl group is linear. In another embodiment, an alkyl group is branched. Unless otherwise indicated, an alkyl group is unsubstituted.

The term "alkenyl," as used herein, refers to an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and having one of its hydrogen atoms replaced with a bond. An alkenyl group may be straight or branched and contain from about 2 to about 15 carbon atoms. In one embodiment, an alkenyl group contains from about 2 to about 12 carbon atoms. In another embodiment, an alkenyl group contains from about 2 to about 6 carbon atoms. Non-limiting examples of alkenyl groups include ethenyl, propenyl, n-butenyl, 3-methylbut-2-enyl, n-pentenyl, octenyl and decenyl. An alkenyl group may be unsubstituted or substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkenyl, alkynyl, aryl, cycloalkyl, cyano, hydroxy, -O-alkyl, -O-aryl, -alkylene-O-alkyl, alkylthio, $-NH_2$, -NH(alkyl), $-N(alkyl)_2$, -NH(cycloalkyl), -O-C(O)-alkyl, -O-C(O)-aryl, -O-C(O)-cycloalkyl, -C(O)OH and –C(O)O-alkyl. The term "C_2-C_6 alkenyl" refers to an alkenyl group having from 2 to 6 carbon atoms. Unless otherwise indicated, an alkenyl group is unsubstituted.

The term "alkynyl," as used herein, refers to an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and having one of its hydrogen atoms replaced with a bond. An alkynyl group may be straight or branched and contain from about 2 to about 15 carbon atoms. In one embodiment, an alkynyl group contains from about 2 to about 12 carbon atoms. In another embodiment, an alkynyl group contains from about 2 to about 6 carbon atoms. Non-limiting examples of alkynyl groups include ethynyl, propynyl, 2-butynyl and 3-methylbutynyl. An alkynyl group may be unsubstituted or substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkenyl, alkynyl, aryl, cycloalkyl, cyano, hydroxy, -O-alkyl, -O-aryl, -alkylene-O-alkyl, alkylthio, $-NH_2$, -NH(alkyl), $-N(alkyl)_2$, -NH(cycloalkyl), -O-C(O)-alkyl, -O-C(O)-aryl, -O-C(O)-cycloalkyl, -C(O)OH and –C(O)O-alkyl. The term "C_2-C_6 alkynyl" refers to an alkynyl group having from 2 to 6 carbon atoms. Unless otherwise indicated, an alkynyl group is unsubstituted.

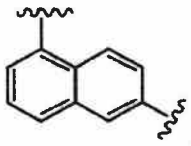
The term "alkylene," as used herein, refers to an alkyl group, as defined above, wherein one of the alkyl group's hydrogen atoms has been replaced with a bond. Non-limiting examples of alkylene groups include $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH(CH_3)CH_2CH_2-$, $-CH(CH_3)-$ and $-CH_2CH(CH_3)CH_2-$. In one embodiment, an alkylene group has from 1 to about 6 carbon atoms. In another embodiment, an alkylene group has from about 3 to about 5 carbon atoms. In another embodiment, an alkylene group is branched. In another embodiment, an alkylene group is linear. In one embodiment, an alkylene group is $-CH_2-$. The term "C_1-C_4 alkylene" refers to an alkylene group having from 1 to 4 carbon atoms. The term "C_2-C_4 alkylene" refers to an alkylene group having from 2 to 4 carbon atoms.

The term "alkenylene," as used herein, refers to an alkenyl group, as defined above, wherein one of the alkenyl group's hydrogen atoms has been replaced with a bond. Non-limiting examples of alkenylene groups include $-CH=CH-$, $-CH=CHCH_2-$, $-CH_2CH=CH-$, $-CH_2CH=CHCH_2-$, $-CH=CHCH_2CH_2-$, $-CH_2CH_2CH=CH-$ and $-CH(CH_3)CH=CH-$. In one embodiment, an alkenylene group has from 2 to about 6 carbon atoms. In another embodiment, an alkenylene group has from about 3 to about 5 carbon atoms. In another embodiment, an alkenylene group is branched. In another embodiment, an alkenylene group is linear. The term "C_2-C_6 alkylene" refers to an alkenylene group having from 2 to 6 carbon atoms. The term "C_3-C_5 alkenylene" refers to an alkenylene group having from 3 to 5 carbon atoms.

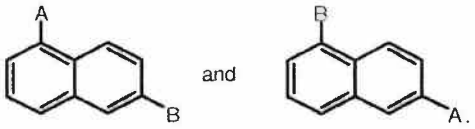
The term "aryl," as used herein, refers to an aromatic monocyclic or multicyclic ring system comprising from about 6 to about 14 carbon atoms. In one embodiment, an aryl group contains from about 6 to about 10 carbon atoms. An aryl group can be optionally

substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein below. In one embodiment, an aryl group can be optionally fused to a cycloalkyl or cycloalkanoyl group. Non-limiting examples of aryl groups include phenyl and naphthyl. In one embodiment, an aryl group is phenyl. Unless otherwise indicated, an aryl group is unsubstituted.

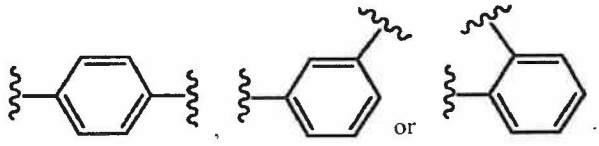
The term "arylene," as used herein, refers to a bivalent group derived from an aryl group, as defined above, by removal of a hydrogen atom from a ring carbon of an aryl group. An arylene group can be derived from a monocyclic or multicyclic ring system comprising from about 6 to about 14 carbon atoms. In one embodiment, an arylene group contains from about 6 to about 10 carbon atoms. In another embodiment, an arylene group is a naphthylene group. In another embodiment, an arylene group is a phenylene group. An arylene group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein below. An arylene group is divalent and either available bond on an arylene group can connect to either group flanking the arylene group. For example, the group "A-arylene-B," wherein the arylene group is:



is understood to represent both:

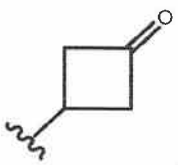


In one embodiment, an arylene group can be optionally fused to a cycloalkyl or cycloalkanoyl group. Non-limiting examples of arylene groups include phenylene and naphthalene. In one embodiment, an arylene group is unsubstituted. In another embodiment, an arylene group is:



Unless otherwise indicated, an arylene group is unsubstituted.

The term "cycloalkyl," as used herein, refers to a non-aromatic mono- or multicyclic ring system comprising from about 3 to about 10 ring carbon atoms. In one embodiment, a cycloalkyl contains from about 5 to about 10 ring carbon atoms. In another embodiment, a cycloalkyl contains from about 3 to about 7 ring atoms. In another embodiment, a cycloalkyl contains from about 5 to about 6 ring atoms. The term "cycloalkyl" also encompasses a cycloalkyl group, as defined above, which is fused to an aryl (*e.g.*, benzene) or heteroaryl ring. Non-limiting examples of monocyclic cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. Non-limiting examples of multicyclic cycloalkyls include 1-decalinyl, norbornyl and adamantyl. A cycloalkyl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein below. In one embodiment, a cycloalkyl group is unsubstituted. The term "3 to 7-membered cycloalkyl" refers to a cycloalkyl group having from 3 to 7 ring carbon atoms. Unless otherwise indicated, a cycloalkyl group is unsubstituted. A ring carbon atom of a cycloalkyl group may be functionalized as a carbonyl group. An illustrative example of such a cycloalkyl group (also referred to herein as a "cycloalkanoyl" group) includes, but is not limited to, cyclobutanoyl:



The term "halo," as used herein, means –F, -Cl, -Br or -I.

The term "haloalkyl," as used herein, refers to an alkyl group as defined above, wherein one or more of the alkyl group's hydrogen atoms has been replaced with a halogen. In one embodiment, a haloalkyl group has from 1 to 6 carbon atoms. In another embodiment, a haloalkyl group is substituted with from 1 to 3 F atoms. Non-limiting examples of haloalkyl groups include $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2Cl$ and $-CCl_3$. The term "C_1-C_6 haloalkyl" refers to a haloalkyl group having from 1 to 6 carbon atoms.

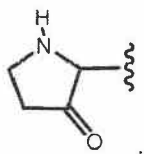
The term "hydroxyalkyl," as used herein, refers to an alkyl group as defined above, wherein one or more of the alkyl group's hydrogen atoms have been replaced with an –OH group. In one embodiment, a hydroxyalkyl group has from 1 to 6 carbon atoms. Non-limiting examples of hydroxyalkyl groups include $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$ and $-CH_2CH(OH)CH_3$. The term "C_1-C_6 hydroxyalkyl" refers to a hydroxyalkyl group having from 1 to 6 carbon atoms.

The term "heteroaryl," as used herein, refers to an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, wherein from 1 to 4 of the ring atoms is independently O, N or S and the remaining ring atoms are carbon atoms. In one embodiment, a heteroaryl group has 5 to 10 ring atoms. In another embodiment, a heteroaryl group is monocyclic and has 5 or 6 ring atoms. In another embodiment, a heteroaryl group is bicyclic. A heteroaryl group can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein below. A heteroaryl group is joined via a ring carbon atom, and any nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. The term "heteroaryl" also encompasses a heteroaryl group, as defined above, which is fused to a benzene ring. Non-limiting examples of heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridone (including N-substituted pyridones), isoxazolyl, isothiazolyl, oxazolyl, oxadiazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, oxindolyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, benzimidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like, and all isomeric forms thereof. The term "heteroaryl" also refers to partially saturated heteroaryl moieties such as, for example, tetrahydroisoquinolyl, tetrahydroquinolyl and the like. In one embodiment, a heteroaryl group is a 5-membered heteroaryl. In another embodiment, a heteroaryl group is a 6-membered monocyclic heteroaryl. In another embodiment, a heteroaryl group comprises a 5- to 6-membered monocyclic heteroaryl group fused to a benzene ring. Unless otherwise indicated, a heteroaryl group is unsubstituted.

The term "heterocycloalkyl," as used herein, refers to a non-aromatic saturated monocyclic or multicyclic ring system comprising 3 to about 11 ring atoms, wherein from 1 to 4 of the ring atoms are independently O, S, N or Si, and the remainder of the ring atoms are carbon atoms. A heterocycloalkyl group can be joined via a ring carbon, ring silicon atom or ring nitrogen atom. In one embodiment, a heterocycloalkyl group is monocyclic and has from about 3 to about 7 ring atoms. In another embodiment, a heterocycloalkyl group is monocyclic has from about 4 to about 7 ring atoms. In another embodiment, a heterocycloalkyl group is bicyclic and has from about 7 to about 11 ring atoms. In still another embodiment, a heterocycloalkyl group is monocyclic and has 5 or 6 ring atoms. In one embodiment, a heterocycloalkyl group is monocyclic. In another embodiment, a heterocycloalkyl group is bicyclic. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Any –NH group in a heterocycloalkyl

ring may exist protected such as, for example, as an -N(BOC), -N(Cbz), -N(Tos) group and the like; such protected heterocycloalkyl groups are considered part of this invention. The term "heterocycloalkyl" also encompasses a heterocycloalkyl group, as defined above, which is fused to an aryl (*e.g.*, benzene) or heteroaryl ring. A heterocycloalkyl group can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein below. The nitrogen or sulfur atom of the heterocycloalkyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of monocyclic heterocycloalkyl rings include oxetanyl, piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, delta-lactam, delta-lactone and the like, and all isomers thereof.

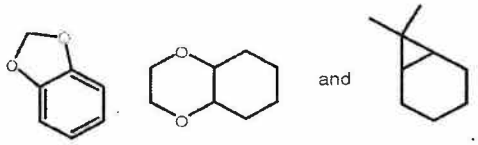
A ring carbon atom of a heterocycloalkyl group may be functionalized as a carbonyl group. An illustrative example of such a heterocycloalkyl group is:



In one embodiment, a heterocycloalkyl group is a 5-membered monocyclic heterocycloalkyl. In another embodiment, a heterocycloalkyl group is a 6-membered monocyclic heterocycloalkyl. The term "3 to 6-membered monocyclic heterocycloalkyl" refers to a monocyclic heterocycloalkyl group having from 3 to 6 ring atoms. The term "4 to 7-membered monocyclic heterocycloalkyl" refers to a monocyclic heterocycloalkyl group having from 4 to 7 ring atoms. The term "7 to 11-membered bicyclic heterocycloalkyl" refers to a bicyclic heterocycloalkyl group having from 7 to 11 ring atoms. Unless otherwise indicated, a heterocycloalkyl group is unsubstituted.

The term "ring system substituent," as used herein, refers to a substituent group attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different, each being independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, -alkylene-aryl, -arylene-alkyl, -alkylene-heteroaryl, -alkenylene-heteroaryl, -alkynylene-heteroaryl, -OH, hydroxyalkyl, haloalkyl, -O-alkyl, -O-haloalkyl, -alkylene-O-alkyl, -O-aryl, -O-alkylene-aryl, acyl, -C(O)-aryl, halo, $-NO_2$, -CN, $-SF_5$, -C(O)OH, -C(O)O-alkyl, -C(O)O-aryl, -C(O)O-alkylene-aryl, -S(O)-alkyl, $-S(O)_2$-alkyl, -S(O)-aryl, $-S(O)_2$-aryl, -S(O)-heteroaryl, $-S(O)_2$-heteroaryl, -S-alkyl, -S-aryl, -S-heteroaryl, -S-alkylene-aryl, -S-alkylene-heteroaryl, $-S(O)_2$-alkylene-aryl, $-S(O)_2$-alkylene-heteroaryl, $-Si(alkyl)_2$, $-Si(aryl)_2$, $-Si(heteroaryl)_2$, -

Si(alkyl)(aryl), -Si(alkyl)(cycloalkyl), - Si(alkyl)(heteroaryl), cycloalkyl, heterocycloalkyl, -O-C(O)-alkyl, -O-C(O)-aryl, -O-C(O)-cycloalkyl, -C(=N-CN)-NH_2, -C(=NH)-NH_2, -C(=NH)-NH(alkyl), -$N(Y_1)(Y_2)$, -alkylene-$N(Y_1)(Y_2)$, -$C(O)N(Y_1)(Y_2)$ and -$S(O)_2N(Y_1)(Y_2)$, wherein Y_1 and Y_2 can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl, and –alkylene-aryl. "Ring system substituent" may also mean a single moiety which simultaneously replaces two available hydrogens on two adjacent carbon atoms (one H on each carbon) on a ring system. Examples of such moiety are methylenedioxy, ethylenedioxy, -$C(CH_3)_2$- and the like which form moieties such as, for example:



The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound' or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "in substantially purified form," as used herein, refers to the physical state of a compound after the compound is isolated from a synthetic process (*e.g.*, from a reaction mixture), a natural source, or a combination thereof. The term "in substantially purified form," also refers to the physical state of a compound after the compound is obtained from a purification process or processes described herein or well-known to the skilled artisan (*e.g.*, chromatography, recrystallization and the like), in sufficient purity to be characterizable by standard analytical techniques described herein or well-known to the skilled artisan.

It should also be noted that any carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and tables herein is assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

When a functional group in a compound is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T. W. Greene *et al*, *Protective Groups in Organic Synthesis* (1991), Wiley, New York.

When any substituent or variable (*e.g.*, alkyl, R^1, R^7, etc.) occurs more than one time in any constituent or in Formula (I), its definition on each occurrence is independent of its definition at every other occurrence, unless otherwise indicated.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results from combination of the specified ingredients in the specified amounts.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design,* (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press. The term "prodrug" means a compound (*e.g.*, a drug precursor) that is transformed *in vivo* to provide a Tetracyclic Heterocycle Compound or a pharmaceutically acceptable salt of the compound. The transformation may occur by various mechanisms (*e.g.*, by metabolic or chemical processes), such as, for example, through hydrolysis in blood. For example, if a Tetracyclic Heterocycle Compound or a pharmaceutically acceptable salt, hydrate or solvate of the compound contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as, for example, (C_1-C_8)alkyl, (C_2-C_{12})alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C_1-C_2)alkylamino(C_2-C_3)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C_1-C_2)alkyl, N,N-di (C_1-C_2)alkylcarbamoyl-(C_1-C_2)alkyl and piperidino-, pyrrolidino- or morpholino(C_2-C_3)alkyl, and the like.

Similarly, if a Tetracyclic Heterocycle Compound contains an alcohol functional group, a prodrug can be formed by the replacement of one or more of the hydrogen atoms of the alcohol groups with a group such as, for example, (C_1-C_6)alkanoyloxymethyl, 1-$((C_1-C_6)$alkanoyloxy)ethyl, 1-methyl-1-$((C_1-C_6)$alkanoyloxy)ethyl, (C_1-C_6)alkoxycarbonyloxymethyl, N-(C_1-C_6)alkoxycarbonylaminomethyl, succinoyl, (C_1-C_6)alkanoyl, α-amino(C_1-C_4)alkyl, α-amino(C_1-C_4)alkylene-aryl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, or

glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).

If a Tetracyclic Heterocycle Compound incorporates an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as, for example, R-carbonyl-, RO-carbonyl-, NRR`-carbonyl- wherein R and R` are each independently (C_1-C_{10})alkyl, (C_3-C_7) cycloalkyl, benzyl, a natural α-aminoacyl, -C(OH)C(O)OY^1 wherein Y^1 is H, (C_1-C_6)alkyl or benzyl, -$C(OY^2)Y^3$ wherein Y^2 is (C_1-C_4) alkyl and Y^3 is (C_1-C_6)alkyl; carboxy (C_1-C_6)alkyl; amino(C_1-C_4)alkyl or mono-N- or di-N,N-(C_1-C_6)alkylaminoalkyl; -$C(Y^4)Y^5$ wherein Y^4 is H or methyl and Y^5 is mono-N- or di-N,N-(C_1-C_6)alkylamino morpholino; piperidin-1-yl or pyrrolidin-1-yl, and the like.

Pharmaceutically acceptable esters of the present compounds include the following groups: (1) carboxylic acid esters obtained by esterification of the hydroxy group of a hydroxyl compound, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (*e.g.*, methyl, ethyl, n-propyl, isopropyl, t-butyl, sec-butyl or n-butyl), alkoxyalkyl (*e.g.*, methoxymethyl), aralkyl (*e.g.*, benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (*e.g.*, phenyl optionally substituted with, for example, halogen, C_{1-4}alkyl, -O-(C_{1-4}alkyl) or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyl (for example, methanesulfonyl); (3) amino acid esters, including those corresponding to both natural and non-natural amino acids (*e.g.*, L-valyl or L-isoleucyl); (4) phosphonate esters and (5) mono-, di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a C_{1-20} alcohol or reactive derivative thereof, or by a 2,3-di (C_{6-24})acyl glycerol.

One or more compounds of the invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. "Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of solvates include ethanolates, methanolates, and the like. A "hydrate" is a solvate wherein the solvent molecule is water.

One or more compounds of the invention may optionally be converted to a solvate. Preparation of solvates is generally known. Thus, for example, M. Caira *et al*, *J. Pharmaceutical*

Sci., 93(3), 601-611 (2004) describe the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates, hemisolvates, hydrates and the like are described by E. C. van Tonder *et al*, *AAPS PharmSciTechours.* , 5(1), article 12 (2004); and A. L. Bingham *et al*, *Chem. Commun.*, 603-604 (2001). A typical, non-limiting, process involves dissolving the inventive compound in desired amounts of the desired solvent (organic or water or mixtures thereof) at a higher than room temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated by standard methods. Analytical techniques such as, for example IR spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

The Tetracyclic Heterocycle Compounds can form salts which are also within the scope of this invention. Reference to a Tetracyclic Heterocycle Compound herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a Tetracyclic Heterocycle Compound contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. In one embodiment, the salt is a pharmaceutically acceptable (*i.e.*, non-toxic, physiologically acceptable) salt. In another embodiment, the salt is other than a pharmaceutically acceptable salt. Salts of the Compounds of Formula (I) may be formed, for example, by reacting a Tetracyclic Heterocycle Compound with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use.* (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food &

Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamine, t-butyl amine, choline, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (*e.g.*, methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (*e.g.*, dimethyl, diethyl, and dibutyl sulfates), long chain halides (*e.g.*, decyl, lauryl, and stearyl chlorides, bromides and iodides), arylalkyl halides (*e.g.*, benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well-known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (*e.g.*, chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (*e.g.*, hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Sterochemically pure compounds may also be prepared by using chiral starting materials or by employing salt resolution techniques. Also, some of the Tetracyclic Heterocycle Compounds may be atropisomers (*e.g.*, substituted biaryls) and are considered as part of this invention. Enantiomers can also be directly separated using chiral chromatographic techniques.

It is also possible that the Tetracyclic Heterocycle Compounds may exist in different tautomeric forms, and all such forms are embraced within the scope of the invention. For example, all keto-enol and imine-enamine forms of the compounds are included in the invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates, hydrates, esters and prodrugs of the compounds as well as the salts, solvates and esters of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention. If a Tetracyclic

Heterocycle Compound incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention.

Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms "salt", "solvate", "ester", "prodrug" and the like, is intended to apply equally to the salt, solvate, ester and prodrug of enantiomers, stereoisomers, rotamers, tautomers, racemates or prodrugs of the inventive compounds.

In the Compounds of Formula (I), the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The present invention is meant to include all suitable isotopic variations of the compounds of generic Formula I. For example, different isotopic forms of hydrogen (H) include protium (^{1}H) and deuterium (^{2}H). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing *in vivo* half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. Isotopically-enriched Compounds of Formula (I) can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the Schemes and Examples herein using appropriate isotopically-enriched reagents and/or intermediates. In one embodiment, a Compound of Formula (I) has one or more of its hydrogen atoms replaced with deuterium.

The Tetracyclic Heterocycle Compounds are useful in human and veterinary medicine for treating or preventing HIV infection in a subject. In one embodiment, the Tetracyclic Heterocycle Compounds can be inhibitors of HIV viral replication. In a specific embodiment, the Tetracyclic Heterocycle Compounds are inhibitors of HIV-1. Accordingly, the Tetracyclic Heterocycle Compounds are useful for treating HIV infections and AIDS. In accordance with the invention, the Tetracyclic Heterocycle Compounds can be administered to a subject in need of treatment or prevention of HIV infection.

Accordingly, in one embodiment, the invention provides methods for treating HIV infection in a subject comprising administering to the subject an effective amount of at least one Tetracyclic Heterocycle Compound or a pharmaceutically acceptable salt thereof. In a specific embodiment, the present invention provides methods for treating AIDS in a subject

comprising administering to the subject an effective amount of at least one Tetracyclic Heterocycle Compound or a pharmaceutically acceptable salt thereof.

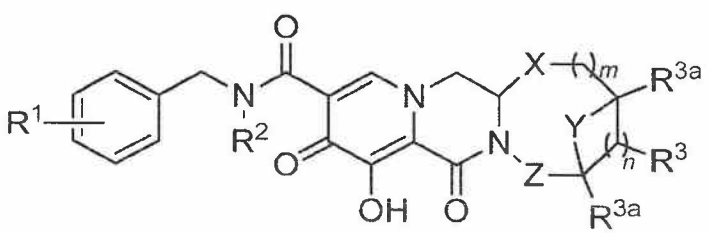
List of Abbreviations

	Anal.	=	analytical
	ACN	=	acetonitrile
	AcOH	=	acetic acid
	n-BuLi	=	*n*-butyl lithium
	BnBr	=	benzyl bromide
	br	=	broad
	calc.	=	calculated
	m-CPBA	=	3-chloroperoxybenzoic acid
	d	=	doublet
	DBU	=	1,8-diazabicycloundec-7-ene
	DCM	=	dichloromethane
	DEA	=	diethylamine
	DIPEA or DIEA	=	*N,N*-diisopropylethylamine
	DMF	=	dimethylformamide
	DMSO	=	dimethyl sulfoxide
	ESI	=	electrospray ionization
	Et_2O	=	diethylether
	Et_3N	=	triethylamine
	EtOAc	=	ethyl acetate
	EtOH	=	ethanol
	HCl	=	hydrochloric acid
	HPLC	=	high-pressure liquid chromatography
	IPA	=	*iso*-propyl alcohol
	IPAc	=	*iso*-propyl acetate
	KF	=	Karl-Fischer titration (to determine water content)
	KO*t*-Bu	=	potassium *tert*-butoxide
	LCMS	=	liquid chromatography-mass spectrometry
	LiHMDS	=	lithum hexamethyl silazane
	m	=	multiplet

	McCN	=	acetonitrile
	MeOH	=	methyl alcohol
	MPa	=	millipascal
	MS	=	mass spectroscopy
	MTBE	=	methyl *tert*-butyl ether
	$NaHCO_3$	=	sodium bicarbonate
	NBS	=	*N*-bromosuccinimide
	NHS	=	normal human serum
	NMP	=	*N*-methylpyrrolidine
	NMR	=	nuclear magnetic resonance spectroscopy
	Piv	=	pivalate, 2,2-dimethylpropanoyl
	Pd/C	=	palladium on carbon
	rt	=	room temperature
	s	=	singlet
	SFC	=	supercritical fluid chromatography
	SiO_2	=	silical gel
	t	=	triplet
	TFA	=	trifluoroacetic acid
	THF	=	tetrahydrofuran
	TLC	=	thin-layer chromatography
	$TMSN_3$	=	trimethylsilyl azide
	p-TsOH	=	*para*-toluene sulfonic acid
	wt%	=	percentage by weight

The Compounds of Formula (I)

The present invention provides Tetracyclic Heterocycle Compounds of Formula (I):



(I)

and pharmaceutically acceptable salts thereof, wherein m, n, X, Y, Z, R^1, R^2 and R^3 are defined above for the Compounds of Formula (I).

In one embodiment, X is O.

In another embodiment, X is $-CH_2-$.

In another embodiment, X is $-N(-C(O)CH_3)-$.

In one embodiment, Y is O.

In another embodiment, Y is $-N(R^6)-$.

In another embodiment, Y is C_1-C_3 alkylene.

In still another embodiment, Y is $-CH_2-$.

In one embodiment, Z is a single bond.

In another embodiment, Z is $-C(R^7)-$.

In one embodiment, R^1 represents 1 or 2 optional phenyl group substituents, each independently selected from C_1-C_6 alkyl, -O-(C_1-C_6 alkyl), halo.

In another embodiment, R^1 represents 1 or 2 optional phenyl group substituents, each independently selected from halo.

In another embodiment, R^1 represents an ortho F group and a para F group.

In one embodiment, R^3 is H.

In another embodiment, R^3 is C_1-C_6 alkyl.

In another embodiment, R^3 is methyl.

In one embodiment, each occurrence of R^{3a} is H.

In another embodiment, at least one occurrence of R^{3a} is C_1-C_6 alkyl.

In one embodiment, R^4 is H.

In another embodiment, R^4 is C_1-C_6 alkyl.

In one embodiment, R^5 is H.

In another embodiment, R^5 is C_1-C_6 alkyl.

In another embodiment, R^5 is $-C(O)R^8$.

In still another embodiment, R^5 is $-SO_2R^8$.

In one embodiment, each occurrence of R^6 is H or C_1-C_6 alkyl.

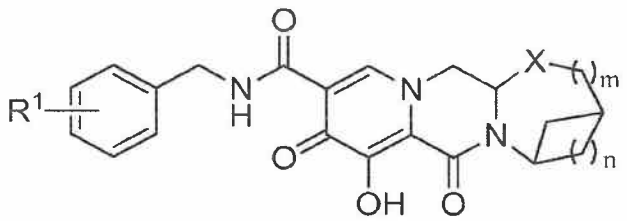
In another embodiment, at least one occurrence of R^6 is C_1-C_6 alkyl.

In one embodiment, R^7 is H.

In another embodiment, R^7 is C_1-C_6 alkyl.

In another embodiment, R^7 is $-O-(C_1$-C_6 alkyl).

In one embodiment, the compounds of formula (I) have the formula (Ia):



(Ia)

or a pharmaceutically acceptable salt or prodrug thereof,

wherein:

X is O or –N(-C(O)CH_3)-)-;

R^1 represents up to 2 optional phenyl group substituents, each independently selected from halo;

m is 0 or 1; and

n is 1, 2 or 3, such that the sum of m+n is 2 or 3.

In one embodiment, for the compounds of formulas (I) and (Ia), m is 0.

In another embodiment, for the compounds of formulas (I) and (Ia), m is 1.

In another embodiment, for the compounds of formulas (I) and (Ia), m is 2.

In one embodiment, for the compounds of formulas (I) and (Ia), n is 1.

In another embodiment, for the compounds of formulas (I) and (Ia), n is 2.

In another embodiment, for the compounds of formulas (I) and (Ia), n is 3.

In one embodiment, for the compounds of formulas (I) and (Ia), m is 0 and n is 2.

In another embodiment, for the compounds of formulas (I) and (Ia), m is 0 and n is 3.

In another embodiment, for the compounds of formulas (I) and (Ia), m is 1 and n is 1.

In one embodiment, variables m, n, X, Y, Z, R^1, R^2 and R^3 for the Compounds of Formula (I) are selected independently of each other.

In another embodiment, the Compounds of Formula (I) are in substantially purified form.

Other embodiments of the present invention include the following:

(a) A pharmaceutical composition comprising an effective amount of a Compound of Formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

(b) The pharmaceutical composition of (a), further comprising a second therapeutic agent selected from the group consisting of HIV antiviral agents, immunomodulators, and anti-infective agents.

(c) The pharmaceutical composition of (b), wherein the HIV antiviral agent is an antiviral selected from the group consisting of HIV protease inhibitors, HIV integrase inhibitors, nucleoside reverse transcriptase inhibitors, CCR5 co-receptor antagonists and non-nucleoside reverse-transcriptase inhibitors.

(d) A pharmaceutical combination that is (i) a Compound of Formula (I) and (ii) a second therapeutic agent selected from the group consisting of HIV antiviral agents, immunomodulators, and anti-infective agents; wherein the Compound of Formula (I) and the second therapeutic agent are each employed in an amount that renders the combination effective for inhibiting HIV replication, or for treating HIV infection and/or reducing the likelihood or severity of symptoms of HIV infection.

(e) The combination of (d), wherein the HIV antiviral agent is an antiviral selected from the group consisting of HIV protease inhibitors, HIV integrase inhibitors, nucleoside reverse transcriptase inhibitors, CCR5 co-receptor antagonists and non-nucleoside reverse-transcriptase inhibitors.

(f) A method of inhibiting HIV replication in a subject in need thereof which comprises administering to the subject an effective amount of a Compound of Formula (I).

(g) A method of treating HIV infection and/or reducing the likelihood or severity of symptoms of HIV infection in a subject in need thereof which comprises administering to the subject an effective amount of a Compound of Formula (I).

(h) The method of (g), wherein the Compound of Formula (I) is administered in combination with an effective amount of at least one second therapeutic agent selected from the group consisting of HIV antiviral agents, immunomodulators, and anti-infective agents.

(i) The method of (h), wherein the HIV antiviral agent is an antiviral selected from the group consisting of HIV protease inhibitors, HIV integrase inhibitors, nucleoside reverse transcriptase inhibitors, CCR5 co-receptor antagonists and non-nucleoside reverse-transcriptase inhibitors.

(j) A method of inhibiting HIV replication in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b) or (c) or the combination of (d) or (e).

(k) A method of treating HIV infection and/or reducing the likelihood or severity of symptoms of HIV infection in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b) or (c) or the combination of (d) or (e).

The present invention also includes a compound of the present invention for use (i) in, (ii) as a medicament for, or (iii) in the preparation of a medicament for: (a) medicine, (b) inhibiting HIV replication or (c) treating HIV infection and/or reducing the likelihood or severity of symptoms of HIV infection. In these uses, the compounds of the present invention can optionally be employed in combination with one or more second therapeutic agents selected from HIV antiviral agents, anti-infective agents, and immunomodulators.

Additional embodiments of the invention include the pharmaceutical compositions, combinations and methods set forth in (a)-(k) above and the uses set forth in the preceding paragraph, wherein the compound of the present invention employed therein is a compound of one of the embodiments, aspects, classes, sub-classes, or features of the compounds described above. In all of these embodiments, the compound may optionally be used in the form of a pharmaceutically acceptable salt or hydrate as appropriate. It is understood that references to compounds would include the compound in its present form as well as in different forms, such as polymorphs, solvates and hydrates, as applicable.

It is further to be understood that the embodiments of compositions and methods provided as (a) through (k) above are understood to include all embodiments of the compounds, including such embodiments as result from combinations of embodiments.

The Compounds of Formula (I) may be referred to herein by chemical structure and/or by chemical name. In the instance that both the structure and the name of a Compound of Formula (I) are provided and a discrepancy is found to exist between the chemical structure and the corresponding chemical name, it is understood that the chemical structure will predominate.

Non-limiting examples of the Compounds of Formula (I) include compounds 1-10 as set forth below, and pharmaceutically acceptable salts thereof.

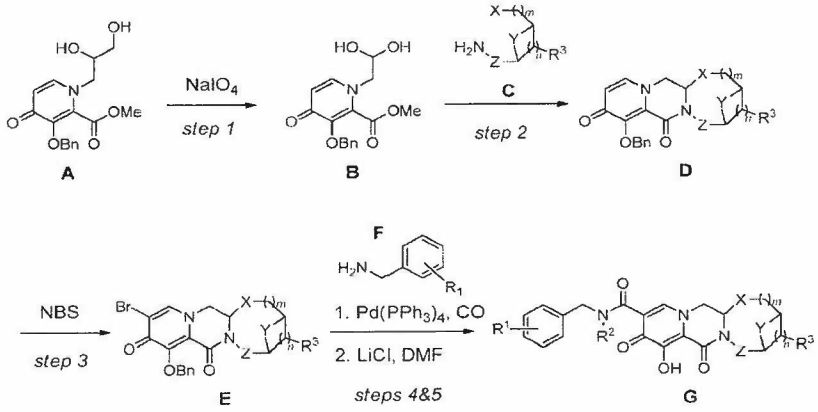
Methods For Making the Compounds of Formula (I)

The Compounds of Formula (I) may be prepared from known or readily prepared starting materials, following methods known to one skilled in the art of organic synthesis.

Methods useful for making the Compounds of Formula (I) are set forth in the Examples below and generalized in Scheme 1 below. Alternative synthetic pathways and analogous structures will be apparent to those skilled in the art of organic synthesis.

Scheme 1 describes a method for making the compounds of formula (I), which corresponds to the bridged tetracyclic 4-pyridinone compounds of Formula (I).

Scheme 1



A compound of formula A is oxidized to a dihydropyridinone of formula B then condensed with amines of type C to provide bridged dihydropyridinone compounds of formula D. Bromination followed by carbonylation with amines of formula F and deprotection of the benzyl protecting group provides the product G.

EXAMPLES

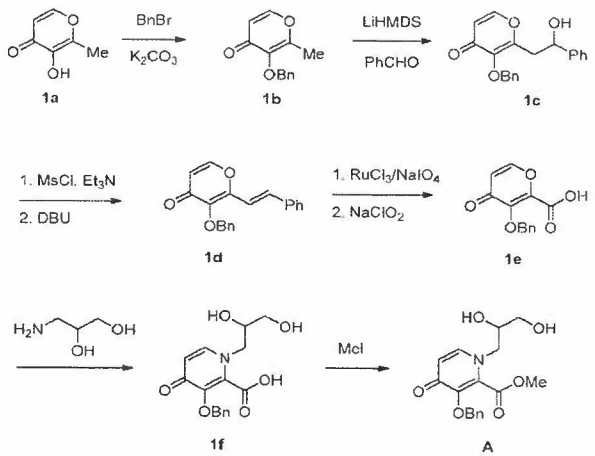
General Methods

The compounds described herein can be prepared according to the procedures of the following schemes and examples, using appropriate materials and are further exemplified by the following specific examples. The compounds illustrated in the examples are not, however, to be construed as forming the only genus that is considered as the invention. The examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds. All temperatures are degrees Celsius unless otherwise noted. Mass spectra (MS) were measured by electrospray ion-mass spectroscopy (ESI). ^{1}H NMR spectra were recorded at 400-500 MHz. Compounds

described herein were synthesized as a racemic mixture unless otherwise stated in the experimental procedures.

Example 1

Preparation of Intermediate Compound A



Step A – Synthesis of Intermediate Compound 1b

To a 20L 4-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 3-hydroxy-2-methyl-4H-pyran-4-one 1a (2 kg, 15.87 mol, 1.00 equiv), MeCN (10 L), potassium carbonate (2.63 kg, 19.01 mol, 1.20 equiv), BnBr (2.85 kg, 16.67 mol, 1.05 equiv). The resulting solution was heated to reflux overnight. The solid was filtered. The filtrate was concentrated *in vacuo*. This resulted in 3.5 kg (crude) of 3-(benzyloxy)-2-methyl-4H-pyran-4-one 1b as brown oil which was used directly.

Step B – Synthesis of Intermediate Compound 1c

Into a 20-L 4-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 3-(benzyloxy)-2-methyl-4H-pyran-4-one 1b (930 g, 4.30 mol, 1.00 equiv), THF (4.75 L). This was followed by the addition of LiHMDS (5 L, 1 N in THF, 1.20 equiv) dropwise with stirring at -60°C. The resulting solution was stirred for 3 h at -60°C. To this was added benzaldehyde (450 g, 4.25mol, 1.20 equiv) dropwise with stirring at -60°C. The resulting solution was allowed to react, with stirring, for an additional 2 h at -60°C. The reaction was then quenched by the addition of 1.2 L of conc. hydrogen chloride dropwise at -20°C. The resulting solution was diluted with 10 L/5 L of EtOAc/H_2O. The aqueous phase was

extracted with 2x5 L of EtOAc and the organic layers combined,dried and concentrated *in vacuo*. The solid was washed with Et_2O (3x2 L). This resulted in 3-(benzyloxy)-2-(2-hydroxy-2-phenylethyl)-4H-pyran-4-one (907 g, 65% yield) 1c, as yellow crystals.

Step C – Synthesis of Intermediate Compound 1d

Into a 20-L 4-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 3-(benzyloxy)-2-(2-hydroxy-2-phenylethyl)-4H-pyran-4-one 1c (900 g, 2.79 mol, 1.00 equiv), dichloromethane (4.5 L), TEA (423.8 g, 4.19 mol, 1.50 equiv). This was followed by the addition of MsCl (419.0 g, 3.66mol, 1.31 equiv) dropwise with stirring at -30°C. The resulting solution was stirred for 2 h at -30°C. To this was added DBU (1.698 kg, 11.15mol, 4.00 equiv) dropwise with stirring at 0°C. The resulting solution was stirred for an additional 20 min at 0°C. The pH of the solution was adjusted to 5 with hydrogen chloride (conc.). The combined organic layer was washed with 3x3 L of Na_2SO_3, dried over anhydrous sodium sulfate and concentrated *in vacuo*. This resulted in 3-(benzyloxy)-2-[(E)-2-phenylethenyl]-4H-pyran-4-one (740 g, 87% yield) 1d as a yellow solid.

Step D – Synthesis of Intermediate Compound 1e

Into a 20-L 4-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 3-(benzyloxy)-2-[(*E*)-2-phenylethenyl]-4H-pyran-4-one 1d (950 g, 3.12 mol, 1.00 equiv), MeCN (3 L), EtOAc (3 L), water (3 L). To this was added $RuCl_3$ (13 g, 62.67 mmol, 0.02 equiv) at 15°C. This was followed by the addition of $NaIO_4$ (2.673 kg, 12.50 mol, 4.00 equiv) in portions at 15°C in 2 hrs. To this was added sodium chlorite (847.87 g, 9.37 mol, 3.00 equiv) in portions at 20°C. The resulting solution was stirred for 2 h at 20°C. The solid was filtered out and washed with 3x2 L of THF. The combined filtrate was diluted with 5 L of Na_2SO_3 (0.7 N). The pH of the solution was adjusted to 11 with sodium hydroxide (1 mol/L). The resulting solution was extracted with 2x5 L of EtOAc. The pH of the combined aqueous layer was adjusted to 3 with hydrogen chloride (12mol/L). The resulting solution was extracted with 2x5 L of EtOAc. The combined organic layer was dried then concentrated *in vacuo*. The resulting solid was washed with 4x1 L of ether. This resulted in 3-(benzyloxy)-4-oxo-4H-pyran-2-carboxylic acid (397 g ,52% yield) 1e as a white solid.

Step E – Synthesis of Intermediate Compound 1f

Into a 2-L 4-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 3-(benzyloxy)-4-oxo-4H-pyran-2-carboxylic acid 1e (200 g,

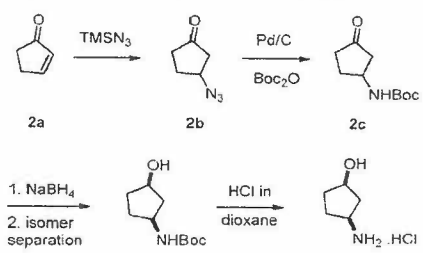
812.30 mmol, 1.00 equiv), ethanol (800 mL), 3-aminopropane-1,2-diol (222 g, 2.44 mol, 3.00 equiv). The resulting solution was heated to reflux overnight. The resulting solution was diluted with 200 mL of water. The resulting mixture was concentrated *in vacuo* to remove EtOH. The resulting solution was extracted with 2x200 mL of EtOAc and the aqueous layers combined. The pH value of the solution was adjusted to 3 with hydrogen chloride (conc.). The solids were collected by filtration and washed with water (2x100 mL), dried in an oven *in vacuo*. This resulted in 3-(benzyloxy)-1-(2,3-dihydroxypropyl)-4-oxo-1,4-dihydropyridine-2-carboxylic acid (200 g,77% yield) 1f as a white solid.

Step E – Synthesis of Intermediate Compound A

Into a 2-L 4-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen. This was followed by the addition of 3-(benzyloxy)-1-(2,3-dihydroxypropyl)-4-oxo-1,4-dihydropyridine-2-carboxylic acid 1f (200 g, 626.35 mmol, 1.00 equiv), NMP (1000 mL), sodium bicarbonate (158 g, 1.88 mol, 3.00 equiv), CH_3I (133.5 g, 940.54 mmol, 1.50 equiv). The resulting solution was stirred overnight at room temperature. The reaction mixture was cooled to 0 °C with a water/ice bath. The resulting solution was diluted with a solution of NaCl (73 g) in 500 mL of H_2O. Then the pH value of the solution was adjusted to 4 with hydrogen chloride (conc.). The reaction mixture was then stirred for another 2 hours. The solids were collected by filtration, washed with water (2x100 mL) and then dried in an oven *in vacuo*. This resulted in methyl 3-(benzyloxy)-1-(2,3-dihydroxypropyl)-4-oxo-1,4-dihydropyridine-2-carboxylate (117.6 g, 55% yield) A as a white solid.

Example 2

Preparation of Intermediate Compound 2e



Step A – Synthesis of Intermediate Compound 2b

To a stirred solution of $TMSN_3$ (167.0 g, 1.41 mol) in DCM (3.0 L) was added AcOH (84 g, 1.41 mol) and the resulting solution was stirred at room temperature for 30 min. A solution of cyclopent-2-enone 2a (100 g, 1.21 mol) in DCM (200 mL) was added and then cooled to 0 °C. Et_3N (370 mL, 2.78 mol) was added for 30 min at the same temperature. The resulting reaction mixture was warmed to room temperature and stirred overnight. The reaction progress was monitored by TLC [40 % EtOAc in petroleum ether, using $KMNO_4$ solution to visualize the spot]. R_f values of starting material and product are 0.1 and 0.4 respectively. After completion of the reaction (TLC), the reaction mixture was diluted with water and extracted into DCM (2 x 500 mL) and washed with $NaHCO_3$ solution. The organic layer was concentrated *in vacuo* to provide the crude compound 2b (220 g). This was used as such in the next step without further purification.

Step B – Synthesis of Intermediate Compound 2c

To a slurry of Pd/C (10 g) in ethanol (450 mL) was added solution of compound 2b (220 g, 1.76 mol) and Boc anhydride (200 mL, 0.88 mol). The resulting reaction mixture was hydrogenated in a Parr shaker at room temperature for 5 h at 30 psi. The reaction progress was monitored by TLC [60 % EtOAc in petroleum ether, using $KMnO_4$ to visualize the spot]. R_f values of the starting material and product are 0.4 and 0.6 respectively. After completion of reaction (TLC), the reaction mixture was filtered through a Celite bed and the filtrate was concentrated *in vacuo* to get the crude compound 2c (180.0 g). The crude compound 2c was adsorbed on 400 g of 100-200 silica gel, which was loaded over a pre-packed column with silica gel [120 mm x 75 cm width and height of column, loaded with 2.4 kg of 100-200 silica gel]. Elution started with 10 % EtOAc/ petroleum ether and finished with 30 % EtOAc/ petroleum ether. All the pure fractions were collected, concentrated *in vacuo* to provide compound 2c (110 g, 31% yield) as a liquid.

Step C – Synthesis of Intermediate Compound 2d

To a stirred solution of compound 2c (110 g, 0.55 mol) in methanol (700 mL) was added $NaBH_4$ (20.79 g, 0.55 mol) portion wise at 0 °C and stirred for 5 h. The reaction progress was monitored by TLC [60 % EtOAc in petroleum ether, using $KMnO_4$ to visualize the spot]. R_f values of starting material and product are 0.6 and 0.3 respectively. After completion of reaction (TLC), methanol was concentrated *in vacuo* and diluted with water, then extracted with EtOAc (2 x 1.0 L). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to get a crude mixture of cis & trans isomers (65 g). The crude mixture was adsorbed on

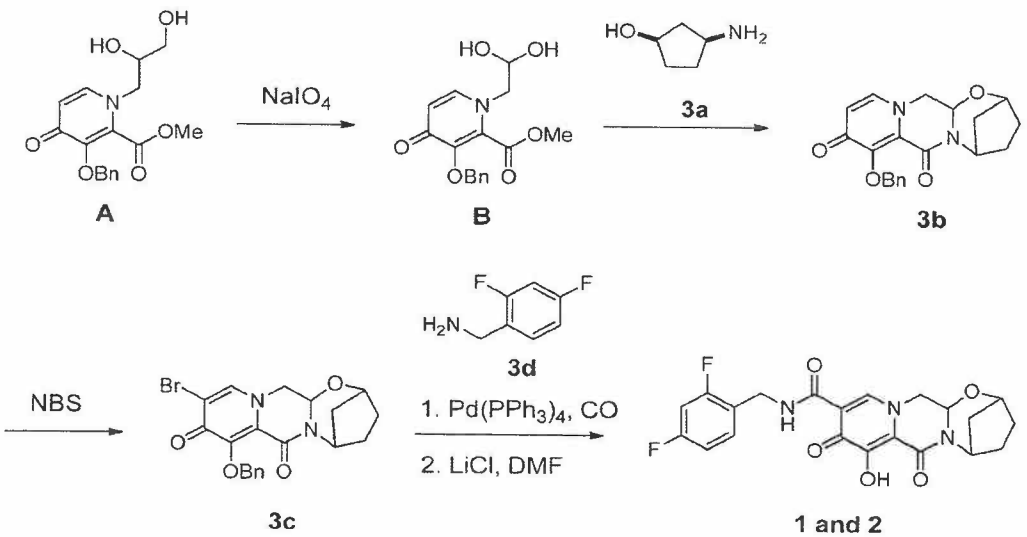
200 g of 100-200 silica gel, which was loaded over a pre-packed column with silica gel [100 mm x 60 cm width and height of column, loaded with 1.2 kg of 100-200 silica gel]. Elution started with 30 % EtOAc/ petroleum ether and finished with 40 % EtOAc/ petroleum ether. All the pure fractions were collected, concentrated *in vacuo* to provide the compound 2d (47 g, 45% yield) as a colorless gum liquid.

Step D – Synthesis of Intermediate Compound 2e

To a stirred solution of compound 2e (47 g, 0.23 mol) in Dioxane (400 mL) was added 2M Dioxane in HCl (150 mL) at 0 °C and stirred for 5 h. The reaction progress was monitored by TLC [100 % EtOAc, using $KMnO_4$ to visualize the spot]. R_f values of the starting material and product are 0.6 and 0.1 respectively. After completion of reaction (TLC), dioxane was concentrated *in vacuo* to get the crude compound 2e (36 g). The crude mixture was washed with acetonitrile to provide the title compound 2e (31 g, 96 % yield) as an off white solid. IR (KBr, cm^{-1}): 3431, 2969, 1626 and 1024. ^1H NMR (400 MHz, DMSO-d_6) δ: 8.0 (s, 3 H), 4.97 (d, 1 H, J = 3.6 Hz), 4.12 (t, 1 H, J = 4.4 Hz), 3.43 (t, 1 H, J = 6 Hz), 2.12-2.0 (m, 1 H), 1.98-1.85 (m, 1 H), 1.80-1.60 (m, 3 H), 1.60-1.50 (m, 1 H). ^{13}C NMR (100.57 MHz, DMSO-d_6) δ: 70.5, 49.7, 33.2, 28.3. M+1 = 102.2

Example 3

Preparation of Compounds 1 and 2



Step A - Synthesis of Intermediate B

To a solution of compound A (0.4 g, 1.2 mmol) in acetonitrile/water (1:1 - 4 mL/4 mL) was added acetic acid (7.21 mg, 0.12 mmol) and sodium periodate (0.308 g, 1.44 mmol) at room temperature. The mixture was then stirred for 2 h at the same temperature, LCMS showed the reaction was complete. Aqueous sodium thiosulfate (10%, 1.2 mL) was added and the mixture was cooled to 5-10°C, concentrated and filtered by washing with water to provide compound B (0.23 g, 61% yield) as a white solid. ^{1}H-NMR: (400 MHz, DMSO-d_6) δ 7.61 (d, *J* = 7.6Hz, 1H), 7.39~7.34 (m, 5H), 6.37~6.28 (m, 3H), 5.09 (s, 2H), 4.94~4.89 (m, 1H), 3.80 (s, 3H), 3.74 (d, *J* = 5.6 Hz, 2H). M+1: 319.9.

Step B - Synthesis of Compound 3b

To a solution of compound 3a (HCl salt) in MeOH was added saturated $NaHCO_3$ (1 equiv) solution and the resuoting reaction was stirred for 10 minutes, then concentrated *in vacuo*. To the residue was added MeOH, then filtered (repeated twice to remove salts), the filtrate was concentrated *in vacuo* for cyclization.

Compound B (800 mg, 2.51 mmol) was taken up in MeOH (20 mL) and heated until complete dissolution. The solution was then concentrated *in vacuo*, and toluene (20 mL) was added stirred for 5 minutes and concentrated *in vacuo*. To the mixture, toluene (35 mL), acetic acid (0.8 mL, 2.51 mmol), and amino alcohol 3a (free base, 537 mg, 4.51 mmol) were added and the mixture was heated and stirred at 90°C for 2 h. The mixture was concentrated *in vacuo* washed with saturated aqueous $NaHCO_3$ (20 mL) and extracted with DCM (15 mL x 3). The organic layers were concentrated *in vacuo* and the residue was purified using column chromatography (SiO_2, DCM: MeOH = 50:1 to 30:1) to provide compound 3b (300 mg, 34% yield) as a light yellow solid. ^{1}H-NMR: (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.2Hz, 2H), 7.35~7.27 (m, 3H), 7.13 (d, *J* = 7.2 Hz, 1H), 6.46 (d, *J* = 7.2 Hz, 1H), 5.41 (d, *J* = 10.0 Hz, 1H), 5.35~5.34 (m, 1H), 5.25~5.19 (m, 2H), 4.59 (s, 1H), 3.90~3.84 (m, 2H), 2.04~1.97 (m, 4H), 1.77~1.75 (m, 1H), 1.56~1.51 (m, 1H). M+1: 352.9.

Step C - Synthesis of Compound 3c

To a solution of compound 3b (37 mg, 0.11 mmol) in NMP (2 mL) was added NBS (20.6 mg, 0.12 mmol) at room temperature. The reaction mixture was stirred for 2 h, then H_2O (3 mL) was added, and then extracted with DCM (6 mL). The organic layers were washed with H_2O (2 mL) concentrated *in vacuo* and purified using prep-TLC (DCM: MeOH = 15: 1) to provide compound 3c (45 mg, quantitative) as a white solid. ^{1}H-NMR: (400 MHz, $CDCl_3$) δ

7.66 (d, J = 6.8 Hz, 2H), 7.60 (s,1H), 7.36~7.28 (m, 3H), 5.40 (d, J = 10.0 Hz, 1H), 5.33~5.26 (m, 1H), 5.24~5.23 (m, 1H), 5.18 (d, J = 10.0 Hz, 1H), 4.60 (s, 1H), 4.01~3.89 (m, 2H), 2.05~2.01 (m, 4H), 1.77~1.72 (m, 1H), 1.56~1.52 (m, 1H). M+1: 430.8.

Steps D&E - Synthesis of Compound 1&2

To a solution of compound 3c (300 mg, 0.7 mmol) in DMSO (2 mL) was added benzyl amine 3d (1 g, 7.0 mmol), Et_3N (0.61 mL, 3.5 mmol) and $Pd(PPh_3)_4$ (80.6 mg, 0.07 mmol) at room temperature under CO atmosphere. The mixture was then heated to 90°C and stirred for 15 h. Reaction progresss was followed by LC-MS. Then H_2O (20 mL) was added, extracted with EtOAc (15 mL x 4), and the organic layers were washed with H_2O (10 x 2 mL). The mixture was concentrated *in vacuo* and purified using column chromatography (SiO_2, DCM: MeOH = 100:1 to 20:1) to provide the racemic mixture (130 mg, 34% yield) as a white solid, which was resolved and deprotected using the procedures below. ^{1}H-NMR: (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.61 (d, J = 7.2 Hz, 2H), 7.35~7.30 (m, 3H), 6.79~6.74 (m, 3H), 5.35~5.33 (m, 2H), 5.26~5.23 (m, 1H), 5.20~5.17 (m, 1H), 4.81 (s, 2H), 4.62 (s, 2H), 4.13~4.11 (m, 1H), 4.00~3.97 (m, 1H), 2.06~1.99 (m, 4H), 1.79~1.76 (m, 1H), 1.55~1.54 (m, 1H). M+1: 522.0.

Separated by chiral SFC (SFC condition: Column: Chiralpak AD 250 × 30mm I.D., 20μm, Mobile phase: Supercritical CO_2/A (0.1%) $NH_3 \cdot H_2O$ = 45/55 at 80 mL/min, A= EtOH+ACN (2:1), Column Temp: 38°C, Nozzle Pressure: 100 Bar, Nozzle Temp: 60°C, Evaporator Temp: 20°C, Trimmer Temp: 25°C, Wavelength: 220 nm) to provide Peak 1 (50 mg) & Peak 2 (50 mg).

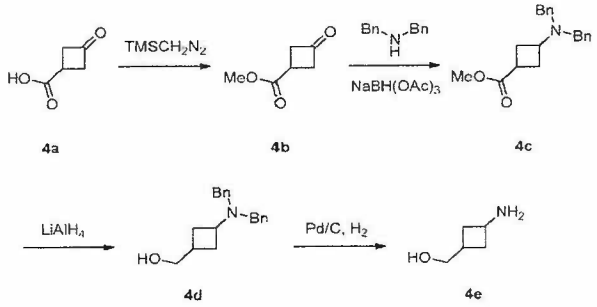
To a solution of compound from peak 1 (50 mg, 0.096 mmol) in DMF (2 mL) was added LiCl (120.9 mg, 2.88 mmol) at room temperature under N_2 atmosphere, then the mixture was stirred at 95°C for 2 h, LCMS showed the reaction was completed. The mixture was purified using prep-HPLC to provide compound 1 (30 mg, 73% yield) as a white solid. ^{1}H-NMR: (400 MHz, DMSO-d_6) δ 12.47 (s, 1H), 10.37 (t, J = 6.0Hz, 1H), 8.46 (s, 1H), 7.39~7.37 (m, 1H), 7.27~7.22 (m, 1H), 7.09~7.06 (m, 1H), 5.46~5.43 (m, 1H), 5.09 (s, 1H), 4.69 (d, J = 8.8Hz, 1H), 4.60 (s, 1H), 4.53 (t, J = 6.0Hz, 2H), 4.06~4.02 (m, 1H), 1.94 (s, 4H), 1.83 (d, J = 12.0Hz, 1H), 1.59~1.56 (m, 1H). M+1= 431.9.

To a solution of compound from peak 2 (50 mg, 0.096 mmol) in DMF (2 mL) was added LiCl (120.9 mg, 2.88 mmol) at room temperature under N_2 atmosphere, then the

mixture was stirred at 95 °C for 2 h, LCMS showed the reaction was completed. The mixture was purified using prep-HPLC to provide compound 2 (31 mg, 75% yield) as a white solid. ^{1}H-NMR: (400 MHz, DMSO-d_6) δ 12.47 (s, 1H), 10.37 (t, J = 6.0Hz, 1H), 8.46 (s, 1H), 7.39~7.37 (m, 1H), 7.27~7.22 (m, 1H), 7.09~7.06 (m, 1H), 5.46~5.43 (m, 1H), 5.09 (s, 1H), 4.69 (d, J = 8.8Hz, 1H), 4.60 (s, 1H), 4.53 (t, J = 6.0Hz, 2H), 4.06~4.02 (m, 1H), 1.94 (s, 4H), 1.83 (d, J = 12.0Hz, 1H), 1.59~1.56 (m, 1H). M+1= 431.9.

Example 4

Preparation of Intermediate Compound 4e



Step A – Synthesis of Intermediate Compound 4b

To a solution of compound 4a (4.0 g, 35.1 mmol) in DCM (50 ml) and MeOH (5 mL) was added $TMSCH_2N_2$ (30 mL, 60.0 mmol) at 0 °C. The solution was allowed to stir at 0°C for 1.5 h. The solvent was evaporated *in vacuo* to provide the compound 4b (4.4 g, 98% yield) as an oil.

Step B – Synthesis of Intermediate Compound 4c

To a solution of compound 4b (4.4 g, 34.3 mmol) and dibenzylamine (8.13 g, 41.2 mmol) in AcOH (5 mL)/THF (50 mL) at room temperature was added $NaBH(OAc)_3$ (17.5 g, 82 mmol) and allowed to stir at room temperature overnight. The mixture was concentrated *in vacuo* and diluted with H_2O (100 mL), the pH was adjusted to 8 with aqueous $NaHCO_3$, and then extracted with EtOAc (80 mL x 3). The combined organic layers were concentrated *in vacuo* and the residue was purified using column chromatography (petroleum ether: EtOAc 100:1 to 30:1) to provide compound 4c (7.35 g, 69% yield) as a colorless oil.

Step C – Synthesis of Intermediate Compound 4d

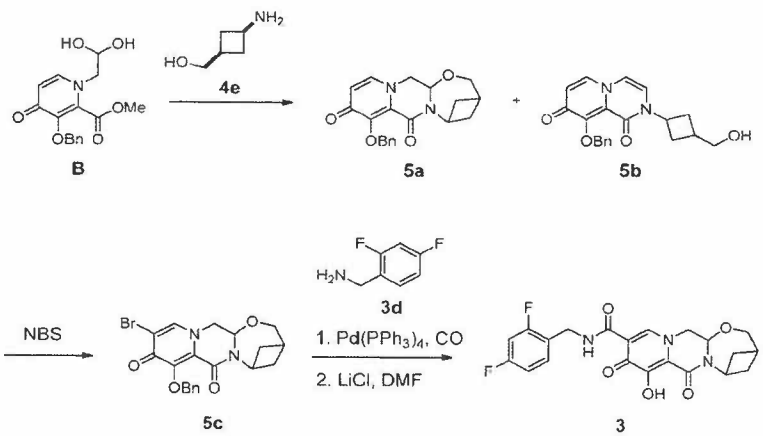
To a solution of compound 4c (7.35 g, 24.88 mmol) in THF (40 mL) at 0°C was added to a solution of $LiAlH_4$ (1.03 g, 27.4 mmol) in THF (40 mL) dropwise. The mixture solution was allowed to stir at 0°C for 2.5 h then mixture was quenched with H_2O (1 mL), 15%NaOH (1 mL) and H_2O (3 mL), then dried over $MgSO_4$. The solution was filtered and concentrated *in vacuo* to provide compound 4d (6.0 g, 86% yield) as an oil.

Step D – Synthesis of Intermediate Compound 4e

A mixture of compound 4d (4.69 g, 16.67 mmol) and 10% Pd/C (1.77 g , 1.67 mmol) in AcOH (2.0 mL)/EtOH (40 mL) was allowed to stir at room temperature under H_2 (50 psi) for 16 h. The mixture was filtered through Celite eluting with excess 1:1 MeOH/DCM, and the filtrate was concentrated *in vacuo*. The resulting residue was dissolved in 45 mL MeOH. 1 mL AcOH was added to the solution, and it was loaded onto a pre-packed cation exchane column. The column was washed with 250 mL MeOH. Product was eluted off the column with 250 mL 2 N NH_3 in MeOH. The filtrate was concentrated *in vacuo* to provide compound 4e (1.39 g, 82% yield) as a clear oil, and a ~5:1 mixture of cis/trans isomers. Data reported are for the major cis isomer. ^1H NMR: (500 MHz, CD_3OD) δ 3.45-3.40 (m, 2H), 3.28-3.20(m, 1H), 2.38-2.24 (m, 2H), 2.18-2.00 (m, 1H), 1.57-1.41 (m, 2H).

Example 5

Preparation of Compound 3



Step A - Synthesis of Compound 5a

Compound B (1000 mg, 3.13 mmol) was suspended in MeOH (5 mL) and heated at 65 °C for 15 mins, to complete dissolution. The solution was then concentrated *in vacuo* and THF (31 mL) was added. With stirring, acetic acid (1.03 mL mL, 17.2 mmol), and aminoalcohol 4e (950 mg, 9.40 mmol) were added, and the reaction mixture was heated and stirred at 70 °C for 5 h, until LCMS analysis indicated complete consumption of starting material. LCMS showed a ratio 5a: 5b ~1:1. The mixture was concentrated *in vacuo* and the residue was purified directly by gradient elution on SiO_2 (2% to 8% MeOH/DCM over 35 mins) to provide 5a (370 mg, 34% yield) as a tan gum. ^{1}H-NMR: (400 MHz, CD_3OD) δ 7.77 (d, J = 7.2 Hz, 1H), 7.51-7.49 (m, 2H), 7.34-7.29 (m, 3H), 6.58 (d, J = 7.2 Hz, 1H), 5.56-5.55 (m, 1H), 5.16 (s, 2H), 4.48-4.45 (m, 1H), 4.35-4.26 (m, 1H), 3.94 (s, 2H), 3.68-3.66 (m, 1H), 2.82-2.78 (m, 1H), 2.67-2.52 (m, 2H), 2.09-2.02 (m, 1H), 1.86-1.81 (m, 1H). M+1: 352.9.

Step B - Synthesis of Compound 5c

To a solution of compound 5a (50 mg, 0.142 mmol) in DCM (1.5 mL) was added NBS (30.3 mg, 0.170 mmol) at room temperature. The mixture was stirred for 45 mins, concentrated *in vacuo*, and purified directly by reverse phase chromatogrpahy (SunFire™ Prep C18 OBD™ 5um 30 x 150 mm column; 5 to 95% CH_3CN/water with 0.1% TFA modifier over 18 minutes). Product was extracted out of the combined aquoues fraction with 2x 25 mL DCM. The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford compound 5c (56 mg, 92% yield) as a white solid. ^{1}H-NMR: (400 MHz, CD_3OD) δ 8.29 (s, 1H), 7.53-7.51 (m, 2H), 7.34-7.30 (m, 3H), 5.59-5.56 (m, 1H), 5.18 (s, 2H), 4.93-4.92 (m, 1H), 4.48-4.47 (m, 1H), 4.34-4.33 (m, 1H), 3.94 (s, 2H), 2.84-2.78 (m, 1H), 2.70-2.66 (m, 2H), 2.07-2.04 (m, 1H), 1.87-1.84 (m, 1H). M+1: 430.8.

Steps C&D - Synthesis of Compound 3

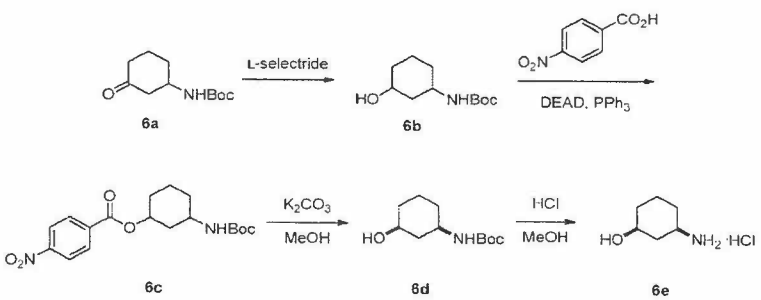
To a solution of compound 5c (56 mg, 0.130 mmol) in DMSO (4.3 mL) was added benzyl amine 3d (74.3 mg, 0.519 mmol), DIEA (0.113 mL, 0.649 mmol) and $Pd(PPh_3)_4$ (60 mg, 0.052 mmol) at room temperature. The resulting suspension was degassed under N_2 for 5 mins, evacuated, and back-filled with $CO_{(g)}$ three times. The mixture was then heated to 105 °C and stirred under a balloon of $CO_{(g)}$ for 1 h. The reaction mixture was cooled to room temperature, filtered, and purified directly by reverse phase chromatogrpahy (SunFire™ Prep C18 OBD™ 5um 30 x 150 mm column; 5 to 95% CH_3CN/water with 0.1% TFA modifier over 18 minutes). Product was extracted out of the combined aquoues fraction with 2x 25 mL DCM.

The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the penultimate intermediate (38 mg, 56% yield) as a tan solid.

A solution of the intermediate product above (15 mg, 0.029 mmol) in MeOH (1 mL) was degassed with N_2 for 2 min, and then charged with 10% Pd/C (6.12 mg, 0.0058 mmol). The resulting suspension was evacuated, and back-filled with H_2 (gas) three times. The mixture was then stirred at room temperature for 2 h. The reaction mixture was filtered, and then purified directly by reverse phase chromatogrpahy (SunFire™ Prep C18 OBD™ 5um 30 x 150 mm column; 5 to 95% CH_3CN/water with 0.1% TFA modifier over 18 minutes). Product was isolated by lyophilization to afford compound 3 (7.5 mg, 60% yield) as an off-white solid. ^{1}HNMR: (400 MHz, DMSO-d_6) δ 12.49 (s, 1H), 10.37 (s, 1H), 8.55 (s, 1H), 7.40-7.39 (m, 1H), 7.27-7.22 (m, 1H), 7.07-7.05 (m, 1H), 5.78 (s, 1H), 4.82-4.81 (m,1H), 4.58-4.55 (m, 4H), 3.90-3.87 (m, 2H), 2.59-2.52 (m, 3H), 2.10-2.06 (m, 1H), 1.72-1.67 (m, 1H), M+1 = 432.0

Example 6

Preparation of Intermediate Compound 6e



6a 6b 6c 6d 6e

Step A – Synthesis of Intermediate Compound 6b

To a solution of compound 6a (5.0 g, 23.44 mmol) in THF (50 ml) was added L-Selectride (35.2 mL, 35.2 mmol) at -78°C. The mixture was stirred at -78°C for 2 h. TLC showed the reaction was complete and the reaction was quenched with 10% aqueous NaOH (20 mL). After concentration, the residue was diluted with EtOAc (200 mL), washed with brine (200 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified using column chromatography (SiO_2, Petroleum ether: EtOAc = 10:1 to 1:1) to provide compound 6b (4.1 g, 81% yield) as a white solid.

Step B – Synthesis of Intermediate Compound 6c

To a solution of compound 6b (4.1 mg, 19.04 mmol), 4-nitrobenzoic acid (3.82 g, 22.85 mmol), and PPh_3 (9.9g, 38.1 mmol) in THF (60 ml) was added DEAD (6.03 mL, 38.1 mmol) at 0°C. The reaction mixture was then stirred at 25°C for 16 h, quenched with water (100 mL) and extracted with EtOAc (100 mL x 3). The combined organic phase was washed with water (100 mL x 2), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified using column chromatography (SiO2, Petroleum ether: EtOAc = 10: 1 to 5: 1) to provide compound 6c (1.3 g, 81% yield) as a white solid.

Step C – Synthesis of Intermediate Compound 6d

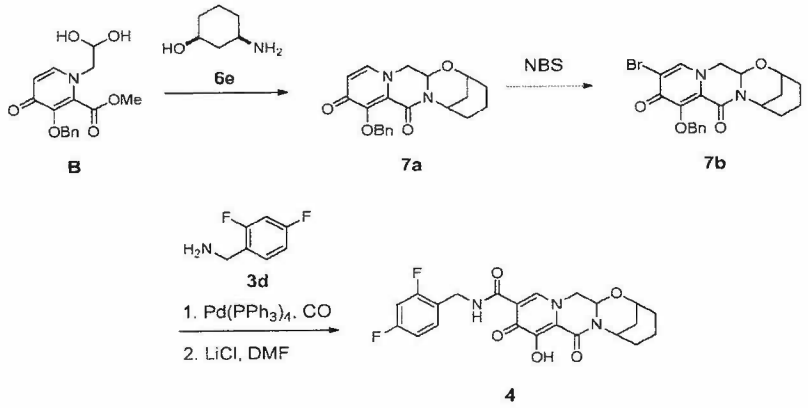
To a solution of compound 6c (1.3 g, 3.57 mmol) in MeOH (40 mL) was added K_2CO_3 (1.97 g, 14.27 mmol). The mixture was stirred at room temperature for 16 h. After concentration, the residue was diluted with EtOAc (50 mL), washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo* to provide compound 6d (700 mg, 91% yield) as a white solid.

Step D – Synthesis of Intermediate Compound 6e

A mixture of compound 6d (700 mg, 3.25 mmol) and 4M HCl/MeOH (10 mL) was stirred at room temperature for 1 h and concentrated *in vacuo* to provide compound 6e (350 mg, 93% yield) as a brown oil. ^{1}HNMR: (400 MHz, DMSO-d_6) δ 3.57~3.51 (m, 1H), 3.06~2.99 (m, 1H), 2.12 (d, J = 15.6 Hz, 1H), 1.85-1.75 (m, 3H), 1.30~1.14 (m, 4H). M+1=116.

Example 7

Preparation of Compound 4



Step A - Synthesis of Compound 7a

Compound B (200 mg, 0.626 mmol) was taken up in MeOH (5 mL) and heated until complete dissolution. The solution was then concentrated *in vacuo*, toluene (20 mL) was then added and the solution was stirred for 5 minutes and concentrated *in vacuo*. To the mixture, toluene (20 mL), acetic acid (263 mg, 4.38 mmol), and amino alcohol 6e (free base, 537 mg, 4.51 mmol) were added, and the mixture was heated and stirred at 90°C for 1.5 h. The mixture was concentrated *in vacuo* and the residue was purified using prep-TLC separation to provide compound 7a (50 mg, 22% yield) as a solid.

Step B - Synthesis of Compound 7b

To a solution of compound 7a (50 mg, 0.136 mmol) in DCM (3 mL) was added NBS (48.6 mg, 0.273 mmol) at room temperature. The mixture was stirred for 2 h, then concentrated *in vacuo* and purified using prep-TLC (DCM: MeOH = 15: 1) to provide compound 7b (20 mg, 74% yield) as a yellow oil.

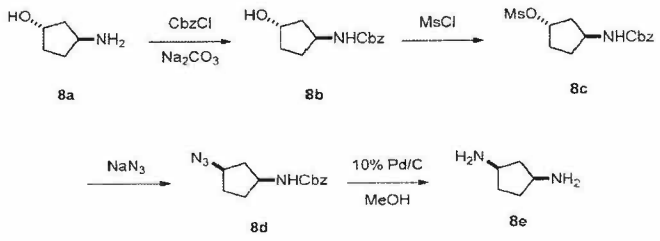
Steps C&D - Synthesis of Compound 4

To a solution of compound 7b (30 mg, 0.067 mmol) in DMSO (3 mL) was added benzyl amine 3d (33.2 mg, 0.232 mmol), DIEA (0.04 mL, 0.232 mmol) and $Pd(PPh_3)_4$ (11 mg, 9.30 mmol) at room temperature under CO atmosphere. The mixture was then heated to 90°C and stirred for 15h. Reaction progresss was followed by LC-MS. Then H_2O (20 mL) was added, the mixture was extracted with EtOAc (15 mL x 4), and the organic layers were washed with H_2O (10 x 2 mL). The mixture was concentrated *in vacuo* and the residue was purified using prep-TLC separation to provide the intermediate (10 mg, 28% yield) as a solid, which was deprotected using the procedure below.

To a solution of the intermediate (10 mg, 0.019 mmol) in DMF (0.5 mL) was added LiCl (24 mg, 0.56 mmol) at room temperature under N_2 atmosphere, then the mixture was stirred at 90°C for 2 h, LCMS showed the reaction was completed, the mixture was purified using prep-HPLC to provide compound 4 (5 mg, 60% yield) as a pink solid. ^{1}HNMR: (400 MHz, DMSO-d_6) δ 10.38 (s, 1H), 8.31 (s, 1H), 7.39~7.33 (m, 1H), 6.83~6.78 (m, 2H), 5.52 (s, 1H), 4.64~4.50 (m, 4H), 4.25~4.12 (m, 1H), 4.05~3.95 (m, 1H), 2.46 (d, J = 14 Hz, 1H), 2.15 (d, J = 14.8Hz, 1H), 1.89~1.81 (m, 3H), 1.55~1.43 (m, 3H). M+1=446.

Example 8

Preparation of Intermediate Compound 8e



Step A – Synthesis of Intermediate Compound 8b

To a solution of compound 8a (140 mg, 1.39 mmol) in DCM (2 mL) : H_2O (2 mL) was added Na_2CO_3 (294 mg, 2.77 mmol). The mixture was stirred at room temperature for 5 min then added CbzCl (237 mg, 1.39 mmol). The reaction mixture was stirred at room temperature for 1.5 h. After concentration, the residue was diluted with H_2O (20 mL), extracted with DCM (20 mL x 3), dried over Na_2SO_4, and concentrated *in vacuo* to provide compound 8b (260 mg, 77% yield) as a brown solid.

Step B – Synthesis of Intermediate Compound 8c

To a solution of compound 8b (260 mg, 1.07 mmol) in DCM (4 mL) was added Et_3N (0.3 mL, 2.14 mmol). The mixture was stirred at 0°C for 5 min then added MsCl (0.17 mL, 2.14 mmol). The mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with H_2O (20 mL), extracted with DCM (20 mL x 3), dried over Na_2SO_4, and concentrated *in vacuo* to provide a crude mixture of compound 8c (400 mg) as a brown solid.

Step C – Synthesis of Intermediate Compound 8d

To a solution of compound 8c (400 mg, 1.28 mmol) in DMF (5 mL) was added NaN_3 (166 mg, 2.56 mmol). The mixture was stirred at 60°C for 2 h. The reaction mixture was quenched with water (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic phase was washed with water (30 mL x 2), dried over Na_2SO_4 and concentrated *in vacuo* to provide compound 8d (300 mg, 90% yield) as a brown oil.

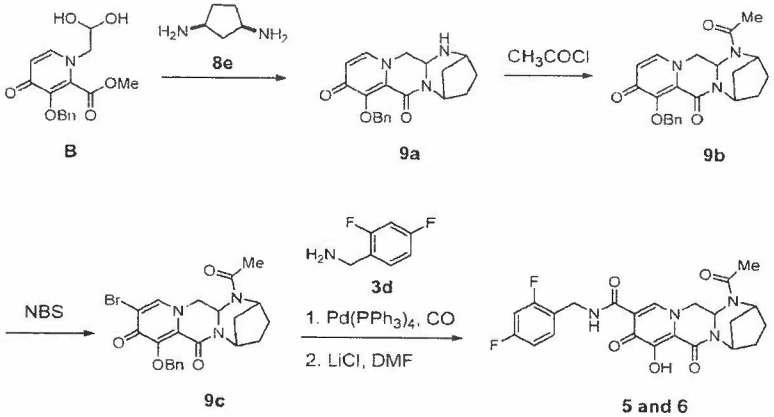
Step D – Synthesis of Intermediate Compound 8e

A mixture of compound 8d (300 mg, 1.15 mmol) and 10% Pd/C (30 mg) in MeOH (15 mL) was stirred at 30°C under H_2 balloon for 16 h. The reaction mixture was filtered and filtrate was concentrated *in vacuo* to provide compound 8e (140 mg, 93% yield) as a

colorless oil. ^{1}H-NMR: (400 MHz, MeOH-d_4) 3.33~3.28 (m, 2H), 2.27~2.23 (m, 1H), 1.94~1.89 (m, 2H), 1.56~1.53 (m, 2H), 1.20~1.17 (m, 1H). M+1: 101.

Example 9

Preparation of Compounds 5 and 6



Step A - Synthesis of Compound 9a

Compound B (80 mg, 0.25 mmol) was taken up in MeOH (2 mL) and heated until complete dissolution. The solution was then concentrated *in vacuo*, toluene (2 mL) was added and the mixture was stirred for 5 minutes and concentrated *in vacuo*. To the mixture, toluene (2 mL), acetic acid (0.08 mL), and diamine 8e (30 mg, 0.3 mmol) were added and the mixture was heated and stirred at 90°C for 1.5 h. The mixture was concentrated *in vacuo* and the residue was purified using prep-TLC separation to provide compound 9a (50 mg, 57% yield) as a brown solid.

Step B - Synthesis of Compound 9b

To a solution of compound 9a (35 mg, 0.100 mmol) in DCM (1 mL) was added Et_3N (0.028 mL, 0.199 mmol). The mixture was stirred at room temperature for 5 min, then added acetyl chloride (10.16 mg, 0.129 mmol). The mixture was stirred at room temperature for 2 h. The reaction was quenched with H_2O (1 mL), the residue was diluted with DCM (20 mL), washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo* to provide compound 9b (50 mg, 77% yield) as yellow oil.

Step C - Synthesis of Compound 9c

To a solution of compound 9b (30 mg, 0.076 mmol) in DCM (1 mL) was added NBS (20.36 mg, 0.114 mmol). The mixture was stirred at room temperature for 2 h. The residue was purified using prep-TLC (DCM: MeOH = 10: 1) to provide compound 9c (25 mg, 69% yield) as yellow oil.

Steps D&E - Synthesis of Compounds 5 and 6

To a solution of compound 9c (20 mg, 0.042 mmol) in DMSO (3 mL) was added DIEA (0.037mL, 0.212 mmol), (2, 4-difluorophenyl) methanamine (60.6 mg, 0.423 mmol) and $Pd(Ph_3P)_4$ (9.79 mg, 8.47 μmol) at room temperature under CO atmosphere, then the mixture was stirred at 90 °C for 15 h. The reaction was quenched with H_2O (10 mL), extracted with EtOAc (10 mL x4) and the organic layers were concentrated *in vacuo*. The residue was purified using prep-TLC (DCM:MeOH = 10:1) to provide the intermediate (6 mg, 25% yield) as a colorless oil, which was resolved and then deprotected using the procedures below.

Separated by chiral SFC (SFC condition: Column: Chiralpak OJ 250 × 30mm I.D., 20μm, Mobile phase: Supercritical CO_2/A (0.1%) at 80 mL/min, A= EtOH+ $NH_3 \cdot H_2O$ (1:1), Column Temp: 38°C, Nozzle Pressure: 100 Bar, Nozzle Temp: 60°C, Evaporator Temp: 20°C, Trimmer Temp: 25°C, Wavelength: 220 nm) to provide Peak 1 (18 mg) & Peak 2 (15 mg).

To a solution of the intermediate from peak 1 (6 mg, 0.010 mmol) in DMF (0.5 mL) was added LiCl (14 mg, 0.32 mmol) at room temperature under N_2 atmosphere. The mixture was stirred at 90°C for 2 h, LCMS showed the reaction was completed, the mixture was purified using prep-HPLC to provide compound 5 as a pink solid. ^{1}H-NMR: (400 MHz, MeOH-d_4) δ 8.44 (s, 1H), 7.45 (s, 1H), 7.00~6.82 (m, 2H), 5.60 (m, 1H), 5.33 (m, 1H), 5.06~5.00 (m, 1H), 4.73~4.66 (m, 2H), 4.11~4.00 (m, 1H), 2.30 (s, 3H), 2.17~2.09 (m, 2H), 2.00~1.97 (m, 1H), 1.87~1.63 (m, 4H). M+1: 473. A similar deprotection procedure was used starting with peak 2 to provide compound 6 ^{1}H-NMR: (400 MHz, MeOH-d_4) δ 8.44 (s, 1H), 7.45 (s, 1H), 7.00~6.82 (m, 2H), 5.60 (m, 1H), 5.33 (m, 1H), 5.06~5.00 (m, 1H), 4.73~4.66 (m, 2H), 4.11~4.00 (m, 1H), 2.30 (s, 3H), 2.17~2.09 (m, 2H), 2.00~1.97 (m, 1H), 1.87~1.63 (m, 4H). M+1: 473.

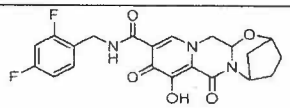
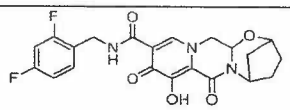
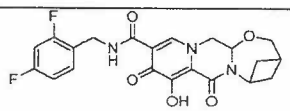
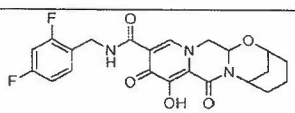
Example 10

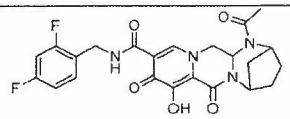
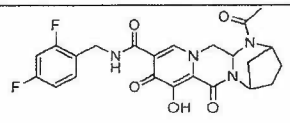
Assay for inhibition of HIV replication

This assay is a kinetic assay that employs a reporter cell line (MT4-gag-GFP) to quantify the number of new cells infected in each round of replication.

MT4-GFP cells (250,000 cells/ml) were bulk-infected with HIV-1 (NL4-3 strain) at low multiplicity of infection (MOI) in RPMI + 10% FBS for 24 hours. Cells were then washed once in RPMI + 10% FBS and resuspended in RPMI + 0% or 10% or 100% normal human serum (NHS). Test compounds were serial-diluted in DMSO on ECHO. The infected MT4-GFP cells were added to a 384-well poly-D-lysine coated black plate with clear bottom in which the diluted test compounds were placed. The cells were seeded at 8,000 cells per well and the final DMSO concentration was 0.4%. The infected cells (Green GFP cells) were quantified at both 24 and 48 hours post incubation using Acumen eX3. Viral reproductive ratio (R_0) was determined using the number of infected cells at 48 hours divided by the number of infected cells at 24 hours. Percent viral growth inhibition was calculated by $[1-(R-R_{tripledrug})/(R_{DMSO}-R_{tripledrug})]*100$. Compound potency IP or IC_{50} was determined by a 4-parameter dose response curve analysis.

Illustrative compounds of the present invention were tested using this assay protocol and results are presented in the Table below.

No.	Structure	WILD TYPE CELL ASSAY IP (0% NHS)	WILD TYPE CELL ASSAY IP (100% NHS)
1	 single enantiomer A	2 nM	209 nM
2	 single enantiomer B	2 nM	466 nM
3	 racemic	2 nM	86 nM
4	 racemic	4 nM	88 nM

5	 single enantiomer A	2 nM	43 nM
6	 single enantiomer B	2 nM	37 nM

Treatment or Prevention of HIV Infection

The Tetracyclic Heterocycle Compounds are useful in the inhibition of HIV, the inhibition of HIV integrase, the treatment of HIV infection and/or reduction of the likelihood or severity of symptoms of HIV infection and the inhibition of HIV viral replication and/or HIV viral production in a cell-based system. For example, the Tetracyclic Heterocycle Compounds are useful in treating infection by HIV after suspected past exposure to HIV by such means as blood transfusion, exchange of body fluids, bites, accidental needle stick, or exposure to subject blood during surgery or other medical procedures.

Accordingly, in one embodiment, the invention provides methods for treating HIV infection in a subject, the methods comprising administering to the subject an effective amount of at least one Tetracyclic Heterocycle Compound or a pharmaceutically acceptable salt or prodrug thereof. In a specific embodiment, the amount administered is effective to treat or prevent infection by HIV in the subject. In another specific embodiment, the amount administered is effective to inhibit HIV viral replication and/or viral production in the subject. In one embodiment, the HIV infection has progressed to AIDS.

The Tetracyclic Heterocycle Compounds are also useful in the preparation and execution of screening assays for antiviral compounds. For example the Tetracyclic Heterocycle Compounds are useful for identifying resistant HIV cell lines harboring mutations, which are excellent screening tools for more powerful antiviral compounds. Furthermore, the Tetracyclic Heterocycle Compounds are useful in establishing or determining the binding site of other antivirals to the HIV Integrase.

The compositions and combinations of the present invention can be useful for treating a subject suffering from infection related to any HIV genotype.

Combination Therapy

In another embodiment, the present methods for treating or preventing HIV infection can further comprise the administration of one or more additional therapeutic agents which are not Tetracyclic Heterocycle Compounds.

In one embodiment, the additional therapeutic agent is an antiviral agent.

In another embodiment, the additional therapeutic agent is an immunomodulatory agent, such as an immunosuppressive agent.

Accordingly, in one embodiment, the present invention provides methods for treating a viral infection in a subject, the method comprising administering to the subject: (i) at least one Tetracyclic Heterocycle Compound (which may include two or more different Tetracyclic Heterocycle Compounds), or a pharmaceutically acceptable salt or prodrug thereof, and (ii) at least one additional therapeutic agent that is other than a Tetracyclic Heterocycle Compound, wherein the amounts administered are together effective to treat or prevent a viral infection.

When administering a combination therapy of the invention to a subject, therapeutic agents in the combination, or a pharmaceutical composition or compositions comprising therapeutic agents, may be administered in any order such as, for example, sequentially, concurrently, together, simultaneously and the like. The amounts of the various actives in such combination therapy may be different amounts (different dosage amounts) or same amounts (same dosage amounts). Thus, for non-limiting illustration purposes, a Tetracyclic Heterocycle Compound and an additional therapeutic agent may be present in fixed amounts (dosage amounts) in a single dosage unit (*e.g.*, a capsule, a tablet and the like).

In one embodiment, at least one Tetracyclic Heterocycle Compound is administered during a time when the additional therapeutic agent(s) exert their prophylactic or therapeutic effect, or *vice versa*.

In another embodiment, at least one Tetracyclic Heterocycle Compound and the additional therapeutic agent(s) are administered in doses commonly employed when such agents are used as monotherapy for treating a viral infection.

In another embodiment, at least one Tetracyclic Heterocycle Compound and the additional therapeutic agent(s) are administered in doses lower than the doses commonly employed when such agents are used as monotherapy for treating a viral infection.

In still another embodiment, at least one Tetracyclic Heterocycle Compound and the additional therapeutic agent(s) act synergistically and are administered in doses lower than the doses commonly employed when such agents are used as monotherapy for treating a viral infection.

In one embodiment, at least one Tetracyclic Heterocycle Compound and the additional therapeutic agent(s) are present in the same composition. In one embodiment, this composition is suitable for oral administration. In another embodiment, this composition is suitable for intravenous administration. In another embodiment, this composition is suitable for subcutaneous administration. In still another embodiment, this composition is suitable for parenteral administration.

Viral infections and virus-related disorders that can be treated or prevented using the combination therapy methods of the present invention include, but are not limited to, those listed above.

In one embodiment, the viral infection is HIV infection.

In another embodiment, the viral infection is AIDS.

The at least one Tetracyclic Heterocycle Compound and the additional therapeutic agent(s) can act additively or synergistically. A synergistic combination may allow the use of lower dosages of one or more agents and/or less frequent administration of one or more agents of a combination therapy. A lower dosage or less frequent administration of one or more agents may lower toxicity of therapy without reducing the efficacy of therapy.

In one embodiment, the administration of at least one Tetracyclic Heterocycle Compound and the additional therapeutic agent(s) may inhibit the resistance of a viral infection to these agents.

As noted above, the present invention is also directed to use of a compound of Formula I with one or more anti-HIV agents. An "anti-HIV agent" is any agent which is directly or indirectly effective in the inhibition of HIV reverse transcriptase or another enzyme required for HIV replication or infection, the treatment or prophylaxis of HIV infection, and/or the treatment, prophylaxis or delay in the onset or progression of AIDS. It is understood that an anti-HIV agent is effective in treating, preventing, or delaying the onset or progression of HIV infection or AIDS and/or diseases or conditions arising therefrom or associated therewith. For example, the compounds of this invention may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in combination with effective amounts of one or more anti-HIV agents selected from HIV antiviral agents, immunomodulators, antiinfectives, or vaccines useful for treating HIV infection or AIDS. Suitable HIV antivirals for use in combination with the compounds of the present invention include, for example, those listed in Table A as follows:

Table A

Name	Type
abacavir, ABC, Ziagen®	nRTI
abacavir +lamivudine, Epzicom®	nRTI
abacavir + lamivudine + zidovudine, Trizivir®	nRTI
amprenavir, Agenerase®	PI
atazanavir, Reyataz®	PI
AZT, zidovudine, azidothymidine, Retrovir®	nRTI
darunavir, Prezista®	PI
ddC, zalcitabine, dideoxycytidine, Hivid®	nRTI
ddI, didanosine, dideoxyinosine, Videx®	nRTI
ddI (enteric coated), Videx EC®	nRTI
delavirdine, DLV, Rescriptor®	nnRTI
efavirenz, EFV, Sustiva®, Stocrin®	nnRTI
efavirenz + emtricitabine + tenofovir DF, Atripla®	nnRTI + nRTI
emtricitabine, FTC, Emtriva®	nRTI
emtricitabine + tenofovir DF, Truvada®	nRTI
emvirine, Coactinon®	nnRTI
enfuvirtide, Fuzeon®	FI
enteric coated didanosine, Videx EC®	nRTI
etravirine, TMC-125	nnRTI
fosamprenavir calcium, Lexiva®	PI
indinavir, Crixivan®	PI
lamivudine, 3TC, Epivir®	nRTI
lamivudine + zidovudine, Combivir®	nRTI
lopinavir	PI
lopinavir + ritonavir, Kaletra®	PI
maraviroc, Selzentry®	EI
nelfinavir, Viracept®	PI
nevirapine, NVP, Viramune®	nnRTI

rilpivirine, TMC-278	nnRTI
ritonavir, Norvir®	PI
saquinavir, Invirase®, Fortovase®	PI
stavudine, d4T,didehydrodeoxythymidine, Zerit®	nRTI
tenofovir DF (DF = disoproxil fumarate), TDF, Viread®	nRTI
tipranavir, Aptivus®	PI

EI = entry inhibitor; FI = fusion inhibitor; PI = protease inhibitor; nRTI = nucleoside reverse transcriptase inhibitor; nnRTI = non-nucleoside reverse transcriptase inhibitor. Some of the drugs listed in the table are used in a salt form; e.g., abacavir sulfate, indinavir sulfate, atazanavir sulfate, nelfinavir mesylate.

In one embodiment, one or more anti-HIV drugs are selected from, lamivudine, abacavir, ritonavir, darunavir, atazanavir, emtricitabine, tenofovir, rilpivirine and lopinavir.

In another embodiment, the compound of formula (I) is used in combination with lamivudine.

In still another embodiment, the compound of formula (I) is used in combination atazanavir.

In another embodiment, the compound of formula (I) is used in combination with darunavir.

In another embodiment, the compound of formula (I) is used in combination with rilpivirine.

In one embodiment, the compound of formula (I) is used in combination with lamivudine and abacavir.

In another embodiment, the compound of formula (I) is used in combination with darunavir.

In another embodiment, the compound of formula (I) is used in combination with emtricitabine and tenofovir.

In still another embodiment, the compound of formula (I) is used in combination atazanavir.

In another embodiment, the compound of formula (I) is used in combination with ritonavir and lopinavir.

In another embodiment, the compound of formula (I) is used in combination with lamivudine.

In one embodiment, the compound of formula (I) is used in combination with abacavir and lamivudine.

In another embodiment, the compound of formula (I) is used in combination with lopinavir and ritonavir.

In one embodiment, the present invention provides pharmaceutical compositions comprising (i) a compound of formula (I) or a pharmaceutically acceptable salt or prodrug thereof; (ii) a pharmaceutically acceptable carrier; and (iii) one or more additional anti-HIV agents selected from lamivudine, abacavir, ritonavir and lopinavir, or a pharmaceutically acceptable salt or prodrug thereof, wherein the amounts present of components (i) and (iii) are together effective for the treatment or prophylaxis of infection by HIV or for the treatment, prophylaxis, or delay in the onset or progression of AIDS in the subject in need thereof.

In another embodiment, the present invention provides a method for the treatment or prophylaxis of infection by HIV or for the treatment, prophylaxis, or delay in the onset or progression of AIDS in a subject in need thereof, which comprises administering to the subject (i) a compound of formula (I) or a pharmaceutically acceptable salt or prodrug thereof and (ii) one or more additional anti-HIV agents selected from lamivudine, abacavir, ritonavir and lopinavir, or a pharmaceutically acceptable salt or prodrug thereof, wherein the amounts administered of components (i) and (ii) are together effective for the treatment or prophylaxis of infection by HIV or for the treatment, prophylaxis, or delay in the onset or progression of AIDS in the subject in need thereof.

It is understood that the scope of combinations of the compounds of this invention with anti-HIV agents is not limited to the HIV antivirals listed in Table A, but includes in principle any combination with any pharmaceutical composition useful for the treatment or prophylaxis of AIDS. The HIV antiviral agents and other agents will typically be employed in these combinations in their conventional dosage ranges and regimens as reported in the art, including, for example, the dosages described in the Physicians' Desk Reference, Thomson PDR, Thomson PDR, 57th edition (2003), the 58th edition (2004), the 59th edition (2005), and the like. The dosage ranges for a compound of the invention in these combinations are the same as those set forth above.

The doses and dosage regimen of the other agents used in the combination therapies of the present invention for the treatment or prevention of HIV infection can be

determined by the attending clinician, taking into consideration the approved doses and dosage regimen in the package insert; the age, sex and general health of the subject; and the type and severity of the viral infection or related disease or disorder. When administered in combination, the Tetracyclic Heterocycle Compound(s) and the other agent(s) can be administered simultaneously (*i.e.*, in the same composition or in separate compositions one right after the other) or sequentially. This is particularly useful when the components of the combination are given on different dosing schedules, *e.g.*, one component is administered once daily and another component is administered every six hours, or when the preferred pharmaceutical compositions are different, *e.g.*, one is a tablet and one is a capsule. A kit comprising the separate dosage forms is therefore advantageous.

Compositions and Administration

When administered to a subject, the Tetracyclic Heterocycle Compounds can be administered as a component of a composition that comprises a pharmaceutically acceptable carrier or vehicle. The present invention provides pharmaceutical compositions comprising an effective amount of at least one Tetracyclic Heterocycle Compound and a pharmaceutically acceptable carrier. In the pharmaceutical compositions and methods of the present invention, the active ingredients will typically be administered in admixture with suitable carrier materials suitably selected with respect to the intended form of administration, *i.e.*, oral tablets, capsules (either solid-filled, semi-solid filled or liquid filled), powders for constitution, oral gels, elixirs, dispersible granules, syrups, suspensions, and the like, and consistent with conventional pharmaceutical practices. For example, for oral administration in the form of tablets or capsules, the active drug component may be combined with any oral non-toxic pharmaceutically acceptable inert carrier, such as lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, talc, mannitol, ethyl alcohol (liquid forms) and the like. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. Powders and tablets may be comprised of from about 0.5 to about 95 percent inventive composition. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

Moreover, when desired or needed, suitable binders, lubricants, disintegrating agents and coloring agents may also be incorporated in the mixture. Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes. Among the lubricants there may be mentioned for use in these dosage forms, boric acid, sodium benzoate, sodium

acetate, sodium chloride, and the like. Disintegrants include starch, methylcellulose, guar gum, and the like. Sweetening and flavoring agents and preservatives may also be included where appropriate.

Liquid form preparations include solutions, suspensions and emulsions and may include water or water-propylene glycol solutions for parenteral injection.

Liquid form preparations may also include solutions for intranasal administration.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Additionally, the compositions of the present invention may be formulated in sustained release form to provide the rate controlled release of any one or more of the components or active ingredients to optimize therapeutic effects, *i.e.*, antiviral activity and the like. Suitable dosage forms for sustained release include layered tablets containing layers of varying disintegration rates or controlled release polymeric matrices impregnated with the active components and shaped in tablet form or capsules containing such impregnated or encapsulated porous polymeric matrices.

In one embodiment, the one or more Tetracyclic Heterocycle Compounds are administered orally.

In another embodiment, the one or more Tetracyclic Heterocycle Compounds are administered intravenously.

In one embodiment, a pharmaceutical preparation comprising at least one Tetracyclic Heterocycle Compound is in unit dosage form. In such form, the preparation is subdivided into unit doses containing effective amounts of the active components.

Compositions can be prepared according to conventional mixing, granulating or coating methods, respectively, and the present compositions can contain, in one embodiment, from about 0.1% to about 99% of the Tetracyclic Heterocycle Compound(s) by weight or volume. In various embodiments, the present compositions can contain, in one embodiment, from about 1% to about 70% or from about 5% to about 60% of the Tetracyclic Heterocycle Compound(s) by weight or volume.

The compounds of Formula I can be administered orally in a dosage range of 0.001 to 1000 mg/kg of mammal (e.g., human) body weight per day in a single dose or in divided doses. One preferred dosage range is 0.01 to 500 mg/kg body weight per day orally in a single dose or in divided doses. Another preferred dosage range is 0.1 to 100 mg/kg body weight per day orally in single or divided doses. For oral administration, the compositions can be provided in the form of tablets or capsules containing 1.0 to 500 milligrams of the active ingredient, particularly 1, 5, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the subject to be treated. The specific dose level and frequency of dosage for any particular subject may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

For convenience, the total daily dosage may be divided and administered in portions during the day if desired. In one embodiment, the daily dosage is administered in one portion. In another embodiment, the total daily dosage is administered in two divided doses over a 24 hour period. In another embodiment, the total daily dosage is administered in three divided doses over a 24 hour period. In still another embodiment, the total daily dosage is administered in four divided doses over a 24 hour period.

The amount and frequency of administration of the Tetracyclic Heterocycle Compounds will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the subject as well as severity of the symptoms being treated. The compositions of the invention can further comprise one or more additional therapeutic agents, selected from those listed above herein.

Kits

In one aspect, the present invention provides a kit comprising a therapeutically effective amount of at least one Tetracyclic Heterocycle Compound, or a pharmaceutically acceptable salt or prodrug of said compound and a pharmaceutically acceptable carrier, vehicle or diluent.

In another aspect the present invention provides a kit comprising an amount of at least one Tetracyclic Heterocycle Compound, or a pharmaceutically acceptable salt or prodrug of said compound and an amount of at least one additional therapeutic agent listed above, wherein the amounts of the two or more active ingredients result in a desired therapeutic effect. In one

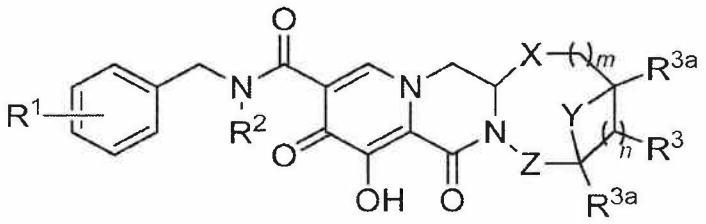
embodiment, the one or more Tetracyclic Heterocycle Compounds and the one or more additional therapeutic agents are provided in the same container. In one embodiment, the one or more Tetracyclic Heterocycle Compounds and the one or more additional therapeutic agents are provided in separate containers.

The present invention is not to be limited by the specific embodiments disclosed in the examples that are intended as illustrations of a few aspects of the invention and any embodiments that are functionally equivalent are within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art and are intended to fall within the scope of the appended claims.

A number of references have been cited herein, the entire disclosures of which are incorporated herein by reference.

CLAIMS

1. A compound having the formula:



(I)

or a pharmaceutically acceptable salt or prodrug thereof,

wherein:

X is O, -CH(R^4)- or –N(R^5)-;

Y is O, -N(R^6)- or C_1-C_3 alkylene;

Z is a single bond or -C(R^7)-;

R^1 represents up to 5 optional phenyl group substituents, each independently selected from C_1-C_6 alkyl, -O-(C_1-C_6 alkyl) and halo;

R^2 is H;

R^3 is selected from H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -OR^6 and -N(R^6)$_2$;

each occurrence of R^{3a} is independently selected from H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -OR^6 and -N(R^6)$_2$;

R^4 is H or C_1-C_6 alkyl or –O-(C_1-C_6 alkyl);

R^5 is selected from H, C_1-C_6 alkyl and –C(O)R^8 and -SO_2R^8;

each occurrence of R^6 is independently H or C_1-C_6 alkyl;

R^7 is selected from H, C_1-C_6 alkyl and –O-(C_1-C_6 alkyl);

each occurrence of R^8 is C_1-C_6 alkyl or NR^6;

m is 0, 1 or 2; and

n is 1, 2 or 3, such that the sum of m+ n is 2 or 3.

2. The compound of claim 1, wherein X is O or –N(-C(O)CH_3)-.

3. The compound of claim 1 or 2, wherein Y is CH_2.

4. The compound of any of claims 1-3, wherein Z is a single bond.

5. The compound of claim 4, wherein X is O and Y is CH_2.

6. The compound of any of claims 1-5, wherein R^1 represents 1 or 2 halo groups.

7. The compound of claim 6, wherein R^1 represents an ortho F group and a para F group.

8. The compound of any of claims 1-7, wherein R^3 is H and each of occurrence R^{3a} is H.

9. The compound of any of claims 1-8, wherein R^4, when present, is H.

10. The compound of any of claims 1-9, wherein n is 1.

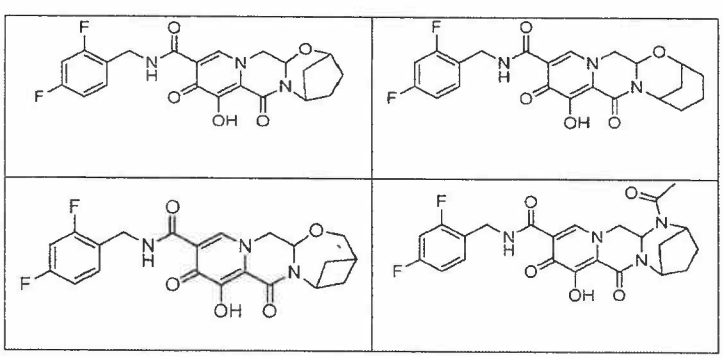
11. The compound of any of claims 1-9, wherein n is 2.

12. The compound of any of claims 1-9, wherein n is 3.

13. The compound of any of claims 1-11, wherein m is 0.

14. The compound of any of claims 1-11, wherein m is 1.

15. A compound having the structure:



or a pharmaceutically acceptable salt or prodrug thereof.

16. A pharmaceutical composition comprising an effective amount of a compound according to any one of claims 1 to 15, or a pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically acceptable carrier.

17. The pharmaceutical composition of claim 16, further comprising one or more additional therapeutic agents selected from, lamivudine, abacavir, ritonavir, darunavir, atazanavir, emtricitabine, tenofovir, rilpivirine and lopinavir.

18. A method for the inhibition of HIV integrase in a subject in need thereof which comprises administering to the subject an effective amount of the compound according to any one of claims 1 to 15, or a pharmaceutically acceptable salt or prodrug thereof.

19. A method for the treatment of infection by HIV or for the treatment, prophylaxis, or delay in the onset or progression of AIDS in a subject in need thereof, which comprises administering to the subject an effective amount of the compound according to any one of claims 1 to 15, or a pharmaceutically acceptable salt or prodrug thereof.

20. The method of claim 19, further comprising administering to the subject one or more additional therapeutic agents selected from, abacavir, lamivudine, ritonavir and lopinavir, wherein the amounts administered of the compound of any one of claims 1-15 and the one or more additional therapeutic agents, are together effective to treat infection by HIV or to treat, prevent or delay the onset or progression of AIDS.

21. A compound according to any one of claims 1 to 15, or a pharmaceutically acceptable salt or prodrug thereof, for use in the inhibition of HIV integrase, for the treatment or prophylaxis of infection by HIV, or for the treatment, prophylaxis, or delay in the onset or progression of AIDS in a subject in need thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2013/083998

A. CLASSIFICATION OF SUBJECT MATTER

C07D 239/00(2006.01)i; C07D 241/36(2006.01)i; C07D 471/00(2006.01)i; C07D 487/00(2006.01)i; C07D 495/00(2006.01)i; C07D 497/00(2006.01)i; A61K 31/50(2006.01)i; A61K 31/495(2006.01)i; A61P 31/18(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D; A61K; A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, EPODOC, CNPAT(CN), CNKI(CN), Chinese Pharmaceutical Abstract (CN), CHEMICAL ABSTRACTS(US), EMBASE, STN: HIV, AIDS, pyridinone, pyridone, amido, amino, formyl, phenyl, piperidyl, structure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006116764A1 (SMITHKLINE BEECHAM CORPORATION ET AL.) 02 November 2006 (2006-11-02) see description page 2 paragraph 0004, page 78 lines 5-13, 20-31, pages 237-239 table A example ZZ-4, ZZ-12, ZZ-13, ZZ-15, claims 49-51, 54-56.	1-21

☐ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 June 2014	**01 July 2014**
Name and mailing address of the ISA/ **STATE INTELLECTUAL PROPERTY OFFICE OF THE P.R.CHINA(ISA/CN)** **6,Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088 China**	Authorized officer **XIU,Wen**
Facsimile No. **(86-10)62019451**	Telephone No. **(86-10)62411205**

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2013/083998

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: **18-20**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] The claims relate to a method for the inhibition of HIV integrase in a subject in need thereof or a method for the treatment of infection by HIV or for the treatment, prophylaxis, or delay in the onset or progression of AIDS in a subject in need thereof (PCT R39.1(iv)), but the search has been carried out and based on the reasonably anticipant subjects, i.e. the use of a compound according to any one of claims 1 to 15, or a pharmaceutically acceptable salt or prodrug thereof, in manufacture of medicaments for the inhibition of HIV integrase in a subject in need thereof or for the treatment of infection by HIV or for the treatment, prophylaxis, or delay in the onset or progression of AIDS in a subject in need thereof.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2013/083998

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
WO 2006116764A1	02 November 2006	NO 20075165A	22 November 2007
		EP 1874117A1	09 January 2008
		AU 2006239177A1	02 November 2006
		US 2008161271A1	03 July 2008
		ZA 200708970A	30 July 2008
		CN 101212903A	02 July 2008
		CN 101212903B	24 July 2013
		KR 20080009733A	29 January 2008
		CA 2606282A1	02 November 2006
		IN 200703865E	18 July 2008
		JP 2008540343A	20 November 2008
		TW 200800988A	01 January 2008
		MX 07013351A	01 January 2008
		JP 2009079058A	16 April 2009
		JP 4295353B	15 July 2009
		ZA 200803423A	26 August 2009
		US 2009318421A1	24 December 2009
		NZ 562339A	28 January 2011
		US 8129385B2	06 March 2012
		BR 0610030A2	11 October 2011
		AU 2006239177B8	16 February 2012
		AU 2006239177B2	20 October 2011
		US 2012115875A1	10 May 2012
		EP 2465580A1	20 June 2012
		MX 302718B	27 August 2012
		EP 2527007A1	28 November 2012
		US 8410103B2	02 April 2013
		HK 1172282A0	19 April 2013
		US 2013172559A1	04 July 2013
		EP 1874117B1	28 August 2013
		HK 1178473A0	13 September 2013
		MX 312216B	12 August 2013
		VN 34404A	25 July 2013
		EP 2465580B1	18 December 2013
		KR 20130133061A	05 December 2013
		SG 136604A1	28 December 2007
		IN 201300485E	28 June 2013

Form PCT/ISA/210 (patent family annex) (July 2009)

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

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WIPO | PCT

(10) International Publication Number
WO 2014/100323 A1

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C07D 498/14 (2006.01) *C07D 471/22* (2006.01)
C07D 471/04 (2006.01) *C07D 487/04* (2006.01)
C07D 471/14 (2006.01)

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PCT/US2013/076367

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19 December 2013 (19.12.2013)

(25) Filing Language: English

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(30) Priority Data:
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61/788,397 15 March 2013 (15.03.2013) US
61/845,803 12 July 2013 (12.07.2013) US

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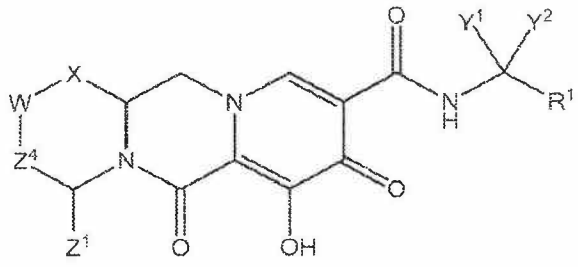
(74) Agents: **WAGNER, Emily, W.** et al.; Cooley LLP, 1299 Pennsylvania Avenue, NW, Suite 700, Washington, DC 20004 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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Published:
— *with international search report (Art. 21(3))*

(54) Title: POLYCYCLIC-CARBAMOYLPYRIDONE COMPOUNDS AND THEIR PHARMACEUTICAL USE



(I)

(57) Abstract: Compounds for use in the treatment of human immunodeficiency virus (HIV) infection are disclosed. The compounds have the following Formula (I): including stereoisomers and pharmaceutically acceptable salts thereof, wherein R_1, X, W, Y_1, Y_2, Z_1 and Z_4 are as defined herein. Methods associated with preparation and use of such compounds, as well as pharmaceutical compositions comprising such compounds, are also disclosed.

WO 2014/100323 A1

POLYCYCLIC-CARBAMOYLPYRIDONE COMPOUNDS AND THEIR PHARMACEUTICAL USE

CROSS-REFERENCE TO RELATED APPLICATIONS

This patent application claims the benefit under 35 U.S.C. §119(e) of U.S. Provisional Patent Application No. 61/745,375, filed December 21, 2012, U.S. Provisional Patent Application No. 61/788,397, filed March 15, 2013, and U.S. Provisional Patent Application No. 61/845,803, filed July 12, 2013. The foregoing applications are incorporated herein by reference in their entireties.

BACKGROUND

Field

Compounds, compositions, and methods for the treatment of human immunodeficiency virus (HIV) infection are disclosed. In particular, novel polycyclic carbamoylpyridone compounds and methods for their preparation and use as therapeutic or prophylactic agents are disclosed.

Description of the Related Art

Human immunodeficiency virus infection and related diseases are a major public health problem worldwide. Human immunodeficiency virus type 1 (HIV-1) encodes three enzymes which are required for viral replication: reverse transcriptase, protease, and integrase. Although drugs targeting reverse transcriptase and protease are in wide use and have shown effectiveness, particularly when employed in combination, toxicity and development of resistant strains have limited their usefulness (Palella, et al. *N. Engl. J Med.* (1998) 338:853–860; Richman, D. D. *Nature* (2001) 410:995–1001).

Pregnane X receptor (PXR) is a nuclear receptor that is one of the key regulators of enzymes involved in metabolism and elimination of small molecules from the body. Activation of PXR is known to up-regulate or induce the production of metabolic enzymes such as cytochrome P450 3A4 (CYP3A4) as well as enzymes involved in transport such as OATP2 in the liver and intestine (*Endocrine Reviews*

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(2002) 23(5):687–702). When one drug causes the up-regulation of these and other enzymes by activation of PXR, this can reduce the absorption and/or exposure of a co-administered drug that is susceptible to the up-regulated enzymes. To minimize the risk of this type of drug-drug interaction, it is desirable to minimize PXR activation. Further, it is known that PXR is activated by many different classes of molecules (*Endocrine Reviews* (2002) 23(5):687–702). Thus for drugs that will be co-administered with other drugs. it is important to test for and minimize PXR activation.

Transporters have been identified as playing a role in the pharmacokinetic, safety and efficacy profile or drugs, and certain drug-drug interactions are mediated by transporters. See, Giacomini KM, *et al.* ""Membrane transporters in drug development," *Nat.Rev Drug Discov.* 9: 215-236, 2010; Zhang L., *et al.* "Transporter-Mediated Drug-Drug Interactions," *Clin. Pharm. Ther.* 89(4):481-484 (2011). -One tranporter, the organic cation transporter 2 (OCT2; SLC22A2), is a member of the solute carrier (SLC) super-family of transporters and is primarily localized on the basolateral membrane of the renal proximal tubule. OCT2, in concert with apical expressed multidrug and toxin extrusion (MATE) transporters 1 and 2-K, is believed to form the major cationic secretion pathway in the kidney and has been shown to transport endogenous compounds including creatinine and xenobiotics including metformin. Inhibition of OCT2 can thus lead to increased levels of serum creatinine and the potential for increased levels of other OCT2 substrates. It is important as well to test and reduce OCT2 inhibition of drugs.

A goal of antiretroviral therapy is to achieve viral suppression in the HIV infected patient. Treatment guidelines published by the United States Department of Health and Human Services provide that achievement of viral suppression requires the use of combination therapies, i.e., several drugs from at least two or more drug classes. (Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Section accessed March 14, 2013.) In addition, decisions regarding the treatment of HIV infected patients are complicated when the patient requires treatment for other medical conditions (Id. at E-12). Because the standard of care requires the use of multiple different drugs to

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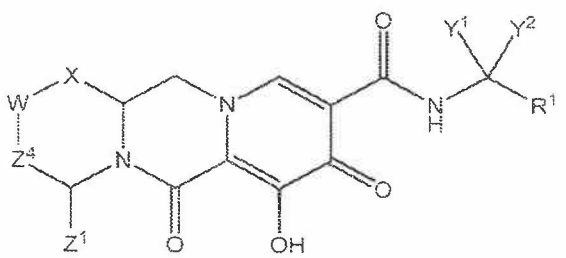
suppress HIV, as well as to treat other conditions the patient may be experiencing, the potential for drug interaction is a criterion for selection of a drug regimen. As such, there is a need for antiretroviral therapies having a decreased potential for drug interactions.

Accordingly, there is a need for new agents that inhibit the replication of HIV and that minimize PXR activation when co-administered with other drugs.

BRIEF SUMMARY

The present invention is directed to novel polycyclic carbamoylpyridone compounds, having antiviral activity, including stereoisomers and pharmaceutically acceptable salts thereof, and the use of such compounds in the treatment of HIV infections. The compounds of the invention may be used to inhibit the activity of HIV integrase and may be used to reduce HIV replication.

In one embodiment of the present invention, compounds having the following Formula (I) are provided:



(I)

or a stereoisomer or pharmaceutically acceptable salt thereof,

wherein:

X is -O- or -NZ^3- or -CHZ^3-;

W is -CHZ^2-;

Z^1, Z^2 and Z^3 are each, independently, hydrogen or C_{1-3}alkyl, or wherein Z^1 and Z^2 or Z^1 and Z^3, taken together, form -L- wherein L is -$C(R^a)_2$-, -$C(R^a)_2C(R^a)_2$-, -$C(R^a)_2C(R^a)_2C(R^a)_2$-, or -$C(R^a)_2C(R^a)_2C(R^a)_2C(R^a)_2$-, wherein at least one of Z^1 and Z^2 or Z^1 and Z^3, taken together, form -L-;

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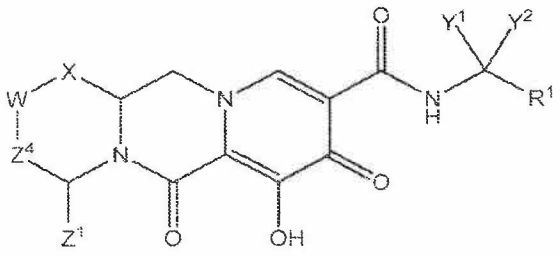
Z^4 is a bond, $-CH_2-$, or $-CH_2CH_2-$;

Y^1 and Y^2 are each, independently, hydrogen, C_{1-3}alkyl or C_{1-3}haloalkyl;

R^1 is phenyl substituted with one to three halogens; and

each R^a is, independently, hydrogen, halo, hydroxyl or C_{1-4}alkyl.

In another embodiment of the present invention, compounds having the following Formula (I) are provided:



(I)

or a stereoisomer or pharmaceutically acceptable salt thereof,

wherein:

X is -O- or $-NZ^3-$ or $-CHZ^3-$;

W is -O- or $-NZ^2-$ or $-CHZ^2-$;

Z^1, Z^2 and Z^3 are each, independently, hydrogen or C_{1-3}alkyl, or wherein Z^1 and Z^2 or Z^1 and Z^3, taken together, form -L- wherein L is $-C(R^a)_2-$, $-C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2C(R^a)_2C(R^a)_2-$, $-C(R^a)_2OC(R^a)_2-$, $-C(R^a)_2NR^aC(R^a)_2-$, $-C(R^a)_2SC(R^a)_2-$, $-C(R^a)_2S(O)C(R^a)_2-$, $-C(R^a)_2SO_2C(R^a)_2-$, $-C(R^a)_2OC(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2OC(R^a)_2-$, $-C(R^a)_2NR^aC(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2NR^aC(R^a)_2-$, $-C(R^a)_2SC(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2SC(R^a)_2-$, $-C(R^a)_2S(O)C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2S(O)C(R^a)_2-$, $-C(R^a)_2SO_2C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2SO_2C(R^a)_2-$, $-C(R^a)_2SO_2NR^aC(R^a)_2-$ or $-C(R^a)_2NR^aSO_2C(R^a)_2-$;

Z^4 is a bond or $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2OCH_2-$, $-CH_2NR^aCH_2-$, $-CH_2SCH_2-$,$-CH_2S(O)CH_2-$ or $-CH_2SO_2CH_2-$;

Y^1 and Y^2 are each, independently, hydrogen, C_{1-3}alkyl or C_{1-3}haloalkyl, or Y^1 and Y^2, together with the carbon atom to which they are attached, form a carbocyclic ring having from 3 to 6 ring atoms or a heterocyclic ring having from 3 to 6

ring atoms, wherein the carbocyclic or heterocyclic ring is optionally substituted with one or more R^a;

R^1 is optionally substituted aryl or optionally substituted heteroaryl; and

each R^a is, independently, hydrogen, halo, hydroxyl or C_{1-4}alkyl, or wherein two R^a groups, together with the carbon atom to which they are attached, form =O, and

wherein at least one of: (i) Z^1 and Z^2 or Z^1 and Z^3, taken together, form -L-; or (ii) Y^1 and Y^2, together with the carbon atom to which they are attached, form a carbocyclic ring having from 3 to 6 ring atoms or a heterocyclic ring having from 3 to 6 ring atoms.

In another embodiment, a pharmaceutical composition is provided comprising a compound having Formula (I), or a stereoisomer or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

The invention also provides the use of a pharmaceutical composition as described hereinabove for the treatment of an HIV infection in a human being having or at risk of having the infection.

In another embodiment, a method of using a compound having Formula (I) in therapy is provided. In particular, a method of treating the proliferation of the HIV virus, treating AIDS, or delaying the onset of AIDS or ARC symptoms in a mammal (e.g., a human) is provided, comprising administering to the mammal a compound having Formula (I), or a stereoisomer or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

In another embodiment, use of a compound of Formula (I) as described herein, or a pharmaceutically acceptable salt thereof, for the treatment of an HIV infection in a human being having or at risk of having the infection is disclosed.

In another embodiment, the use of a compound of Formula (I) as described herein, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of an HIV infection in a human being having or at risk of having the infection is disclosed.

In another embodiment, an article of manufacture comprising a composition effective to treat an HIV infection; and packaging material comprising a label which indicates that the composition can be used to treat infection by HIV is

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disclosed. Exemplary compositions comprise a compound of Formula (I) according to this invention or a pharmaceutically acceptable salt thereof.

In still another embodiment, a method of inhibiting the replication of HIV is disclosed. The method comprises exposing the virus to an effective amount of the compound of Formula (I), or a salt thereof, under conditions where replication of HIV is inhibited.

In another embodiment, the use of a compound of Formula (I) to inhibit the activity of the HIV integrase enzyme is disclosed.

In another embodiment, the use of a compound of Formula (I), or a salt thereof, to inhibit the replication of HIV is disclosed.

Other embodiments, objects, features and advantages will be set forth in the detailed description of the embodiments that follows, and in part will be apparent from the description, or may be learned by practice, of the claimed invention. These objects and advantages will be realized and attained by the processes and compositions particularly pointed out in the written description and claims hereof. The foregoing Summary has been made with the understanding that it is to be considered as a brief and general synopsis of some of the embodiments disclosed herein, is provided solely for the benefit and convenience of the reader, and is not intended to limit in any manner the scope, or range of equivalents, to which the appended claims are lawfully entitled.

DETAILED DESCRIPTION

In the following description, certain specific details are set forth in order to provide a thorough understanding of various embodiments of the invention. However, one skilled in the art will understand that the invention may be practiced without these details. The description below of several embodiments is made with the understanding that the present disclosure is to be considered as an exemplification of the claimed subject matter, and is not intended to limit the appended claims to the specific embodiments illustrated. The headings used throughout this disclosure are provided for convenience only and are not to be construed to limit the claims in any way. Embodiments illustrated under any heading may be combined with embodiments illustrated under any other heading.

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Definitions

Unless the context requires otherwise, throughout the present specification and claims, the word "comprise" and variations thereof, such as, "comprises" and "comprising" are to be construed in an open, inclusive sense, that is as "including, but not limited to".

Reference throughout this specification to "one embodiment" or "an embodiment" means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment of the present invention. Thus, the appearances of the phrases "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily all referring to the same embodiment. Furthermore, the particular features, structures, or characteristics may be combined in any suitable manner in one or more embodiments.

Unless the context requires otherwise, reference throughout this specification to "a compound of Formula (I)" or "compounds of Formula (I)" refers to all embodiments of Formula (I), including, for example, compounds of Formulas (II-A), (II-B), (II-C), (III-A), (III-B), (III-C), (III-D), (III-E), (III-F), (III-G), (III-H), (IV-AA), (IV-AB), (IV-AC), (IV-AD), (IV-AE), (IV-AF), (IV-AG), (IV-AH), (IV-BA), (IV-BB), (IV-BC), (IV-BD), (IV-BE), (IV-BF), (IV-BG), and (IV-BH), as well as the specific compounds disclosed herein.

"Amino" refers to the $-NH_2$ radical.

"Cyano" refers to the -CN radical.

"Hydroxy" or "hydroxyl" refers to the -OH radical.

"Imino" refers to the =NH substituent.

"Nitro" refers to the $-NO_2$ radical.

"Oxo" refers to the =O substituent.

"Thioxo" refers to the =S substituent.

"Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, which is saturated or unsaturated (*i.e.*, contains one or more double and/or triple bonds), having from one to twelve carbon atoms (C_1-C_{12} alkyl), preferably one to eight carbon atoms (C_1-C_8 alkyl) or one to six carbon atoms (C_1-C_6 alkyl), and which is attached to the rest of the molecule by a single bond. *e.g.*, methyl, ethyl, *n*-propyl, 1-methylethyl (*iso*-propyl), *n*-butyl, *n*-pentyl,

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1,1-dimethylethyl (*t*-butyl), 3-methylhexyl, 2-methylhexyl, ethenyl, prop-1-enyl, but-1-enyl, pent-1-enyl, penta-1,4-dienyl, ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like. Unless stated otherwise specifically in the specification, an alkyl group may be optionally substituted.

"Alkylene" or "alkylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, which is saturated or unsaturated (*i.e.*, contains one or more double and/or triple bonds), and having from one to twelve carbon atoms, e.g., methylene, ethylene, propylene, *n*-butylene, ethenylene, propenylene, *n*-butenylene, propynylene, *n*-butynylene, and the like. The alkylene chain is attached to the rest of the molecule through a single or double bond and to the radical group through a single or double bond. The points of attachment of the alkylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain. Unless stated otherwise specifically in the specification, an alkylene chain may be optionally substituted.

"Alkoxy" refers to a radical of the formula $-OR_A$ where R_A is an alkyl radical as defined above containing one to twelve carbon atoms. Unless stated otherwise specifically in the specification, an alkoxy group may be optionally substituted.

"Alkylamino" refers to a radical of the formula $-NHR_A$ or $-NR_AR_A$ where each R_A is, independently, an alkyl radical as defined above containing one to twelve carbon atoms. Unless stated otherwise specifically in the specification, an alkylamino group may be optionally substituted.

Thioalkyl" refers to a radical of the formula $-SR_A$ where R_A is an alkyl radical as defined above containing one to twelve carbon atoms. Unless stated otherwise specifically in the specification, a thioalkyl group may be optionally substituted.

"Aryl" refers to a monocylic hydrocarbon ring system radical comprising hydrogen and 6 to 18 carbon atoms. Aryl radicals include, but are not limited to, aryl radicals derived from benzene. Unless stated otherwise specifically in the specification, the term "aryl" or the prefix "ar-" (such as in "aralkyl") is meant to include aryl radicals that are optionally substituted.

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"Aralkyl" refers to a radical of the formula $-R_B-R_C$ where R_B is an alkylene chain as defined above and R_C is one or more aryl radicals as defined above, for example, benzyl. Unless stated otherwise specifically in the specification, an aralkyl group may be optionally substituted.

"Cycloalkyl" or "carbocyclic ring" refers to a stable non-aromatic monocyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, having from three to fifteen carbon atoms, preferably having from three to ten carbon atoms, and which is saturated or unsaturated and attached to the rest of the molecule by a single bond. Monocyclic radicals include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Unless otherwise stated specifically in the specification, a cycloalkyl group may be optionally substituted.

"Cycloalkylalkyl" refers to a radical of the formula $-R_BR_D$ where R_B is an alkylene chain as defined above and R_D is a cycloalkyl radical as defined above. Unless stated otherwise specifically in the specification, a cycloalkylalkyl group may be optionally substituted.

"Halo" or "halogen" refers to bromo, chloro, fluoro or iodo.

"Haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, trifluoromethyl, difluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like. Unless stated otherwise specifically in the specification, a haloalkyl group may be optionally substituted.

"Heterocyclyl" or "heterocyclic ring" refers to a stable 3- to 18-membered non-aromatic ring radical which consists of two to twelve carbon atoms and from one to six heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. In the embodiments disclosed herein, the heterocyclyl radical is a monocyclic ring system; and the heterocyclyl radical may be partially or fully saturated. Examples of such heterocyclyl radicals include, but are not limited to, dioxolanyl, thienyl, [1,3]dithianyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl,

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1-oxo-thiomorpholinyl, and 1,1-dioxo-thiomorpholinyl. Unless stated otherwise specifically in the specification, a heterocyclyl group may be optionally substituted.

"*N*-heterocyclyl" refers to a heterocyclyl radical as defined above containing at least one nitrogen and where the point of attachment of the heterocyclyl radical to the rest of the molecule is through a nitrogen atom in the heterocyclyl radical. Unless stated otherwise specifically in the specification, an *N*-heterocyclyl group may be optionally substituted.

"Heterocyclylalkyl" refers to a radical of the formula $-R_BR_E$ where R_B is an alkylene chain as defined above and R_E is a heterocyclyl radical as defined above, and if the heterocyclyl is a nitrogen-containing heterocyclyl, the heterocyclyl may be attached to the alkyl radical at the nitrogen atom. Unless stated otherwise specifically in the specification, a heterocyclylalkyl group may be optionally substituted.

"Heteroaryl" refers to a 5- to 14-membered monocyclic ring system radical comprising hydrogen atoms, one to thirteen carbon atoms, one to six heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. Examples include, but are not limited to, azepinyl, furanyl, furanonyl, isothiazolyl, imidazolyl, isoxazolyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, thiophenyl, and thienyl. Unless stated otherwise specifically in the specification, a heteroaryl group may be optionally substituted.

"*N*-heteroaryl" refers to a heteroaryl radical as defined above containing at least one nitrogen and where the point of attachment of the heteroaryl radical to the rest of the molecule is through a nitrogen atom in the heteroaryl radical. Unless stated otherwise specifically in the specification, an *N*-heteroaryl group may be optionally substituted.

"Heteroarylalkyl" refers to a radical of the formula $-R_BR_F$ where R_B is an alkylene chain as defined above and R_F is a heteroaryl radical as defined above. Unless stated otherwise specifically in the specification, a heteroarylalkyl group may be optionally substituted.The term "substituted" used herein means any of the above groups (*i.e.*, alkyl, alkylene, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclyl, *N*-heterocyclyl, heterocyclylalkyl, heteroaryl,

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N-heteroaryl and/or heteroarylalkyl) wherein at least one hydrogen atom is replaced by a bond to a non-hydrogen atoms such as, but not limited to: a halogen atom such as F, Cl, Br, and I; an oxygen atom in groups such as hydroxyl groups, alkoxy groups, and ester groups; a sulfur atom in groups such as thiol groups, thioalkyl groups, sulfone groups, sulfonyl groups, and sulfoxide groups; a nitrogen atom in groups such as amines, amides, alkylamines, dialkylamines, arylamines, alkylarylamines, diarylamines, N-oxides, imides, and enamines; a silicon atom in groups such as trialkylsilyl groups, dialkylarylsilyl groups, alkyldiarylsilyl groups, and triarylsilyl groups; and other heteroatoms in various other groups. "Substituted" also means any of the above groups in which one or more hydrogen atoms are replaced by a higher-order bond (e.g., a double- or triple-bond) to a heteroatom such as oxygen in oxo, carbonyl, carboxyl, and ester groups; and nitrogen in groups such as imines, oximes, hydrazones, and nitriles. For example, "substituted" includes any of the above groups in which one or more hydrogen atoms are replaced with $-NR_GR_H$, $-NR_GC(=O)R_H$, $-NR_GC(=O)NR_GR_H$, $-NR_GC(=O)OR_H$, $-NR_GC(=NR_G)NR_GR_H$, $-NR_GSO_2R_H$, $-OC(=O)NR_GR_H$, $-OR_G$, $-SR_G$, $-SOR_G$, $-SO_2R_G$, $-OSO_2R_G$, $-SO_2OR_G$, $-NSO_2R_G$, and $-SO_2NR_GR_H$. "Substituted also means any of the above groups in which one or more hydrogen atoms are replaced with $-C(=O)R_G$, $-C(=O)OR_G$, $-C(=O)NR_GR_H$, $-CH_2SO_2R_G$, $-CH_2SO_2NR_GR_H$. In the foregoing, R_G and R_H are the same or different and independently hydrogen, alkyl, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclyl, *N*-heterocyclyl, heterocyclylalkyl, heteroaryl, *N*-heteroaryl and/or heteroarylalkyl. "Substituted" further means any of the above groups in which one or more hydrogen atoms are replaced by a bond to an amino, cyano, hydroxyl, imino, nitro, oxo, thioxo, halo, alkyl, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclyl, *N*-heterocyclyl, heterocyclylalkyl, heteroaryl, *N*-heteroaryl and/or heteroarylalkyl group. In addition, each of the foregoing substituents may also be optionally substituted with one or more of the above substituents.

The term "protecting group," as used herein, refers to a labile chemical moiety which is known in the art to protect reactive groups including without limitation, hydroxyl and amino groups, against undesired reactions during synthetic procedures. Hydroxyl and amino groups protected with a protecting group are referred to herein as

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"protected hydroxyl groups" and "protected amino groups", respectively. Protecting groups are typically used selectively and/or orthogonally to protect sites during reactions at other reactive sites and can then be removed to leave the unprotected group as is or available for further reactions. Protecting groups as known in the art are described generally in Greene and Wuts, Protective Groups in Organic Synthesis, 3rd edition, John Wiley & Sons, New York (1999). Generally, groups are protected or present as a precursor that will be inert to reactions that modify other areas of the parent molecule for conversion into their final groups at an appropriate time. Further representative protecting or precursor groups are discussed in Agrawal, et al., Protocols for Oligonucleotide Conjugates, Eds, Humana Press; New Jersey, 1994; Vol. 26 pp. 1–72. Examples of "hydroxyl protecting groups" include, but are not limited to, t-butyl, t-butoxymethyl, methoxymethyl, tetrahydropyranyl, 1-ethoxyethyl, 1-(2-chloroethoxy)ethyl, 2-trimethylsilylethyl, p-chlorophenyl, 2,4-dinitrophenyl, benzyl, 2,6-dichlorobenzyl, diphenylmethyl, p-nitrobenzyl, triphenylmethyl, trimethylsilyl, triethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl (TBDPS), triphenylsilyl, benzoylformate, acetate, chloroacetate, trichloroacetate, trifluoroacetate, pivaloate, benzoate, p-phenylbenzoate, 9-fluorenylmethyl carbonate, mesylate and tosylate. Examples of "amino protecting groups" include, but are not limited to, carbamate-protecting groups, such as 2-trimethylsilylethoxycarbonyl (Teoc), 1-methyl-1-(4-biphenylyl)ethoxycarbonyl (Bpoc), t-butoxycarbonyl (BOC), allyloxycarbonyl (Alloc), 9-fluorenylmethyloxycarbonyl (Fmoc), and benzyloxycarbonyl (Cbz); amide protecting groups, such as formyl, acetyl, trihaloacetyl, benzoyl, and nitrophenylacetyl; sulfonamide-protecting groups, such as 2-nitrobenzenesulfonyl; and imine and cyclic imide protecting groups, such as phthalimido and dithiasuccinoyl.

The invention disclosed herein is also meant to encompass all pharmaceutically acceptable compounds of Formula (I) being isotopically-labeled by having one or more atoms replaced by an atom having a different atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, and ^{125}I, respectively. These radiolabeled compounds could be useful to help determine or measure the effectiveness of the compounds, by characterizing, for

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example, the site or mode of action, or binding affinity to pharmacologically important site of action. Certain isotopically-labeled compounds of Formula (I), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.* ^{3}H, and carbon-14, *i.e.* ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with heavier isotopes such as deuterium, *i.e.* ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, *in vivo* half-life may increase or dosage requirements may be reduced. Thus, heavier isotopes may be preferred in some circumstances.

Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Isotopically-labeled compounds of Formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the Examples as set out below using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

The invention disclosed herein is also meant to encompass the *in vivo* metabolic products of the disclosed compounds. Such products may result from, for example, the oxidation, reduction, hydrolysis, amidation, esterification, and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the invention includes compounds produced by a process comprising administering a compound of this invention to a mammal for a period of time sufficient to yield a metabolic product thereof. Such products are typically identified by administering a radiolabeled compound of the invention in a detectable dose to an animal, such as rat, mouse, guinea pig, monkey, or to human, allowing sufficient time for metabolism to occur, and isolating its conversion products from the urine, blood or other biological samples.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

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"Mammal" includes humans and both domestic animals such as laboratory animals and household pets (e.g., cats, dogs, swine, cattle, sheep, goats, horses, rabbits), and non-domestic animals such as wildlife and the like.

"Optional" or "optionally" means that the subsequently described event of circumstances may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" means that the aryl radical may or may not be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution.

"Pharmaceutically acceptable carrier, diluent or excipient" includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier which has been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

"Pharmaceutically acceptable salt" refers to a salt of a compound that is pharmaceutically acceptable and that possesses (or can be converted to a form that possesses) the desired pharmacological activity of the parent compound. Examples of "pharmaceutically acceptable salts" of the compounds disclosed herein include salts derived from an appropriate base, such as an alkali metal (for example, sodium), an alkaline earth metal (for example, magnesium), ammonium and NX_4^+ (wherein X is C_1–C_4 alkyl). Pharmaceutically acceptable salts of a nitrogen atom or an amino group include for example salts of organic carboxylic acids such as acetic, benzoic, camphorsulfonic, citric, glucoheptonic, gluconic, lactic, fumaric, tartaric, maleic, malonic, malic, mandelic, isethionic, lactobionic, succinic, 2-napththalenesulfonic, oleic, palmitic, propionic, stearic, and trimethylacetic acids; organic sulfonic acids, such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids; and inorganic acids, such as hydrochloric, hydrobromic, sulfuric, nitric, phosphoric and sulfamic acids. Pharmaceutically acceptable salts of a compound of a hydroxy group include the anion of said compound in combination with a suitable cation such as Na^+ and NX_4^+ (wherein X is independently selected from H or a C_1–C_4 alkyl group). Pharmaceutically acceptable salts also include salts formed when an acidic proton

present in the parent compound is replaced by either a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as diethanolamine, triethanolamine, N-methylglucamine and the like. Also included in this definition are ammonium and substituted or quaternized ammonium salts. Representative non-limiting lists of pharmaceutically acceptable salts can be found in S.M. Berge et al., J. Pharma Sci., 66(1), 1-19 (1977), and Remington: The Science and Practice of Pharmacy, R. Hendrickson, ed., 21st edition, Lippincott, Williams & Wilkins, Philadelphia, PA, (2005), at p. 732, Table 38-5, both of which are hereby incorporated by reference herein.

For therapeutic use, salts of active ingredients of the compounds disclosed herein will typically be pharmaceutically acceptable, *i.e.* they will be salts derived from a physiologically acceptable acid or base. However, salts of acids or bases which are not pharmaceutically acceptable may also find use, for example, in the preparation or purification of a compound of Formula (I) or another compound of the invention. All salts, whether or not derived from a physiologically acceptable acid or base, are within the scope of the present invention.

Metal salts typically are prepared by reacting the metal hydroxide with a compound of this invention. Examples of metal salts which are prepared in this way are salts containing Li^+, Na^+, and K^+. A less soluble metal salt can be precipitated from the solution of a more soluble salt by addition of the suitable metal compound.

In addition, salts may be formed from acid addition of certain organic and inorganic acids, *e.g.*, HCl, HBr, H_2SO_4, H_3PO_4 or organic sulfonic acids, to basic centers, typically amines. Finally, it is to be understood that the compositions herein comprise compounds disclosed herein in their un-ionized, as well as zwitterionic form, and combinations with stoichiometric amounts of water as in hydrates.

Often crystallizations produce a solvate of the compound of the invention. As used herein, the term "solvate" refers to an aggregate that comprises one or more molecules of a compound of the invention with one or more molecules of solvent. The solvent may be water, in which case the solvate may be a hydrate. Alternatively, the solvent may be an organic solvent. Thus, the compounds of the present invention may exist as a hydrate, including a monohydrate, dihydrate, hemihydrate, sesquihydrate, trihydrate, tetrahydrate and the like, as well as the

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corresponding solvated forms. The compound of the invention may be true solvates, while in other cases, the compound of the invention may merely retain adventitious water or be a mixture of water plus some adventitious solvent.

A "pharmaceutical composition" refers to a formulation of a compound of the invention and a medium generally accepted in the art for the delivery of the biologically active compound to mammals, e.g., humans. Such a medium includes all pharmaceutically acceptable carriers, diluents or excipients therefor.

"Effective amount" or "therapeutically effective amount" refers to an amount of a compound according to the invention, which when administered to a patient in need thereof, is sufficient to effect treatment for disease-states, conditions, or disorders for which the compounds have utility. Such an amount would be sufficient to elicit the biological or medical response of a tissue system, or patient that is sought by a researcher or clinician. The amount of a compound according to the invention which constitutes a therapeutically effective amount will vary depending on such factors as the compound and its biological activity, the composition used for administration, the time of administration, the route of administration, the rate of excretion of the compound, the duration of the treatment, the type of disease-state or disorder being treated and its severity, drugs used in combination with or coincidentally with the compounds of the invention, and the age, body weight, general health, sex and diet of the patient. Such a therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to their own knowledge, the state of the art, and this disclosure.

The term "treatment" as used herein is intended to mean the administration of a compound or composition according to the present invention to alleviate or eliminate symptoms of HIV infection and/or to reduce viral load in a patient. The term "treatment" also encompasses the administration of a compound or composition according to the present invention post-exposure of the individual to the virus but before the appearance of symptoms of the disease, and/or prior to the detection of the virus in the blood, to prevent the appearance of symptoms of the disease and/or to prevent the virus from reaching detectible levels in the blood, and the administration of a compound or composition according to the present invention to prevent perinatal transmission of HIV from mother to baby, by administration to the mother before giving birth and to the child within the first days of life.

The term "antiviral agent" as used herein is intended to mean an agent (compound or biological) that is effective to inhibit the formation and/or replication of a virus in a human being, including but not limited to agents that interfere with either host or viral mechanisms necessary for the formation and/or replication of a virus in a human being.

The term "inhibitor of HIV replication" as used herein is intended to mean an agent capable of reducing or eliminating the ability of HIV to replicate in a host cell, whether *in vitro*, *ex vivo* or *in vivo*.

The compounds of the invention, or their pharmaceutically acceptable salts may contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)- or, as (D)- or (L)- for amino acids. The present invention is meant to include all such possible isomers, as well as their racemic and optically pure forms. Optically active (+) and (-), (*R*)- and (*S*)-, or (D)- and (L)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, for example, chromatography and fractional crystallization. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC). When the compounds described herein contain olefinic double bonds or other centres of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included.

A "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures, which are not interchangeable. The present invention contemplates various stereoisomers and mixtures thereof and includes "enantiomers", which refers to two stereoisomers whose molecules are nonsuperimposeable mirror images of one another.

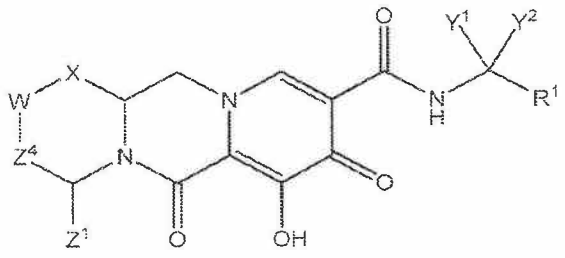
A "tautomer" refers to a proton shift from one atom of a molecule to another atom of the same molecule. The present invention includes tautomers of any said compounds.

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A "prodrug" refers to a compound that is chemically designed to efficiently liberate the parent drug after overcoming biological barriers to oral delivery. In certain embodiments, the present invention includes prodrugs of the compounds of Formula (I).

Compounds

As noted above, in one embodiment of the present invention, compounds having antiviral activity are provided, the compounds having the following Formula (I):



(I)

or a stereoisomer or pharmaceutically acceptable salt thereof,

wherein:

X is -O- or -NZ^3- or -CHZ^3-;

W is -CHZ^2-;

Z^1, Z^2 and Z^3 are each, independently, hydrogen or C_{1-3}alkyl, or wherein Z^1 and Z^2 or Z^1 and Z^3, taken together, form -L- wherein L is -$C(R^a)_2$-, -$C(R^a)_2C(R^a)_2$-, -$C(R^a)_2C(R^a)_2C(R^a)_2$-, or -$C(R^a)_2C(R^a)_2C(R^a)_2C(R^a)_2$-, wherein at least one of Z^1 and Z^2 or Z^1 and Z^3, taken together, form -L-;

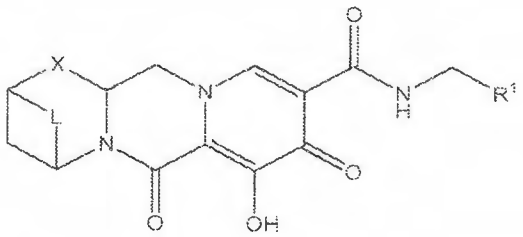
Z^4 is a bond, -CH_2-, or -CH_2CH_2-;

Y^1 and Y^2 are each, independently, hydrogen, C_{1-3}alkyl or C_{1-3}haloalkyl;

R^1 is phenyl substituted with one to three halogens; and

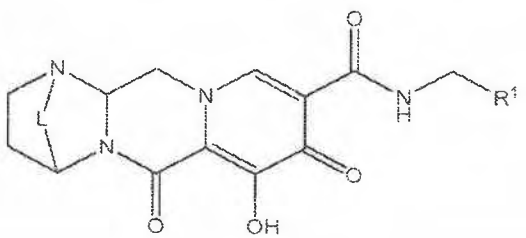
each R^a is, independently, hydrogen, halo, hydroxyl or C_{1-4}alkyl.

In another embodiment, compounds are provided having the following Formula (II-A):



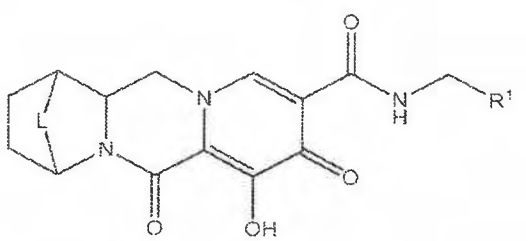
(II-A)

In another embodiment, compounds are provided having the following Formula (II-B):



(II-B)

In another embodiment, compounds are provided having the following Formula (II-C):



(II-C)

In another embodiment, L is $-C(R^a)_2-$. In a further embodiment, L is $-C(R^a)_2C(R^a)_2-$. In still a further embodiment. L is $-C(R^a)_2C(R^a)_2C(R^a)_2-$. In still a

further embodiment, each R^a is hydrogen. In still a further embodiment, one R^a is methyl and each remaining R^a is hydrogen. In still a further embodiment, one R^a is halogen and each remaining R^a is hydrogen. In still a further embodiment, two R^a are halogen and each remaining R^a is hydrogen. In still a further embodiment, one R^a is halogen and each remaining R^a is hydrogen.

In another embodiment, X is -O-. In another embodiment, X is $-NZ^3-$. In another embodiment, X is -NH-. 16. In another embodiment, X is $-CHZ^3-$ and Z^1 and Z^3, taken together, form -L-. In a further embodiment, Z^2 is hydrogen. In another embodiment, X is $-CH_2-$.

In another embodiment, Z^4 is a bond or $-CH_2-$. In another embodiment, Z^4 is $-CH_2-$. In another embodiment, Z^4 is a bond.

In another embodiment, Y^1 and Y^2 are each independently hydrogen, methyl or trifluoromethyl.

In another embodiment, R^1 is substituted with one halogen. In a further embodiment, R^1 is 4-fluorophenyl or 2-fluorophenyl.

In another embodiment, R^1 is substituted with two halogens. In a further embodiment, R^1 is 2,4-difluorophenyl, 2,3-difluorophenyl, 2,6-difluorophenyl, 3-fluoro-4-chlorophenyl, 3,4-difluorophenyl, 2-fluoro-4-chlorophenyl, or 3,5-difluorophenyl. In still a further embodiment, R^1 is 2,4-difluorophenyl.

In another embodiment, R^1 is substituted with three halogens. In a further embodiment, R^1 is 2,4,6-trifluorophenyl or 2,3,4-trifluorophenyl. In still a further embodiment, R^1 is 2,4,6-trifluorophenyl.

In one embodiment, a pharmaceutical composition is provided comprising a compound of any one of the Formulas (I), (II-A), (II-B), or (II-C), as noted above, or a stereoisomer or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

Another embodiment is provided comprising a method of treating an HIV infection in a human having or at risk of having the infection by administering to the human a therapeutically effective amount of a compound of any one of the Formulas (I), (II-A), (II-B), or (II-C), as noted above, or a pharmaceutical composition thereof. Another embodiment is provided comprising a method of treating or preventing an HIV infection in a human having or at risk of having the infection by

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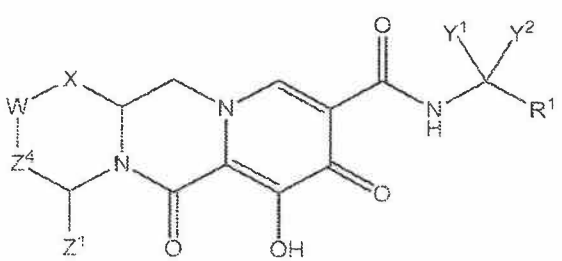
administering to the human a therapeutically effective amount of a compound of any one of the Formulas (I), (II-A), (II-B), or (II-C), as noted above, or a pharmaceutical composition thereof.

In another embodiment, the use of a compound of any one of the Formulas (I), (II-A), (II-B), or (II-C), as noted above, or a pharmaceutical composition thereof, for the treatment of an HIV infection in a human having or at risk of having the infection is provided. In another embodiment, the use of a compound of any one of the Formulas (I), (II-A), (II-B), or (II-C), as noted above, or a pharmaceutical composition thereof, for the treatment or prevention of an HIV infection in a human having or at risk of having the infection is provided.

In another embodiment, the use in medical therapy of a compound of any one of the Formulas (I), (II-A), (II-B), or (II-C), as noted above, or a pharmaceutical composition thereof, is provided.

In another embodiment, the use of a compound of any one of the Formulas (I), (II-A), (II-B), or (II-C), as noted above, or a pharmaceutical composition thereof, for use in the therapeutic treatment of an HIV infection is provided. In another embodiment, the use of a compound of any one of the Formulas (I), (II-A), (II-B), or (II-C), as noted above, or a pharmaceutical composition thereof, for use in the prophylactic or therapeutic treatment of an HIV infection is provided.

As further noted above, in another embodiment of the present invention, compounds having antiviral activity are provided, the compounds having the following Formula (I):



(I)

or a stereoisomer or pharmaceutically acceptable salt thereof,

wherein:

X is -O- or -NZ^3- or -CHZ^3-;

W is -O- or -NZ^2- or -CHZ^2-;

Z^1, Z^2 and Z^3 are each, independently, hydrogen, C_{1-3}alkyl or C_{1-3}haloalkyl, or wherein Z^1 and Z^2 or Z^1 and Z^3, taken together, form -L- wherein L is -$C(R^a)_2$-, -$C(R^a)_2C(R^a)_2$-, -$C(R^a)_2C(R^a)_2C(R^a)_2$-, -$C(R^a)_2C(R^a)_2C(R^a)_2C(R^a)_2$-, -$C(R^a)_2OC(R^a)_2$-, -$C(R^a)_2NR^aC(R^a)_2$-, -$C(R^a)_2SC(R^a)_2$-, -$C(R^a)_2S(O)C(R^a)_2$-, -$C(R^a)_2SO_2C(R^a)_2$-, -$C(R^a)_2OC(R^a)_2C(R^a)_2$-, -$C(R^a)_2C(R^a)_2OC(R^a)_2$-, -$C(R^a)_2NR^aC(R^a)_2C(R^a)_2$-, -$C(R^a)_2C(R^a)_2NR^aC(R^a)_2$-, -$C(R^a)_2SC(R^a)_2C(R^a)_2$-, -$C(R^a)_2C(R^a)_2SC(R^a)_2$-, -$C(R^a)_2S(O)C(R^a)_2C(R^a)_2$-, -$C(R^a)_2C(R^a)_2S(O)C(R^a)_2$-, -$C(R^a)_2SO_2C(R^a)_2C(R^a)_2$-, -$C(R^a)_2C(R^a)_2SO_2C(R^a)_2$-, -$C(R^a)_2SO_2NR^aC(R^a)_2$- or -$C(R^a)_2NR^aSO_2C(R^a)_2$-;

Z^4 is a bond or -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -CH_2OCH_2-, -$CH_2NR^aCH_2$-, -CH_2SCH_2-, -$CH_2S(O)CH_2$- or -$CH_2SO_2CH_2$-;

Y^1 and Y^2 are each, independently, hydrogen or C_{1-3}alkyl, or Y^1 and Y^2, together with the carbon atom to which they are attached, form a carbocyclic ring having from 3 to 6 ring atoms or a heterocyclic ring having from 3 to 6 ring atoms, wherein the carbocyclic or heterocyclic ring is optionally substituted with one or more R^a;

R^1 is optionally substituted aryl or optionally substituted heteroaryl; and

each R^a is, independently, hydrogen, halo, hydroxyl or C_{1-4}alkyl, or wherein two R^a groups, together with the carbon atom to which they are attached, form =O, and

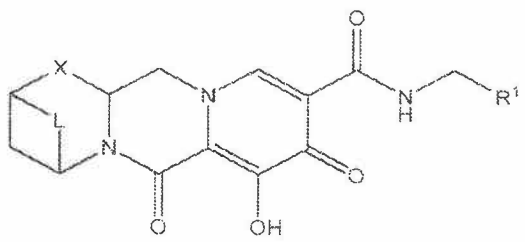
wherein at least one of: (i) Z^1 and Z^2 or Z^1 and Z^3, taken together, form -L-; or (ii) Y^1 and Y^2, together with the carbon atom to which they are attached, form a carbocyclic ring having from 3 to 6 ring atoms or a heterocyclic ring having from 3 to 6 ring atoms.

In another embodiment, W is -CHZ^2-.

In another embodiment, Z^1 and Z^2 or Z^1 and Z^3, taken together, form -L-.

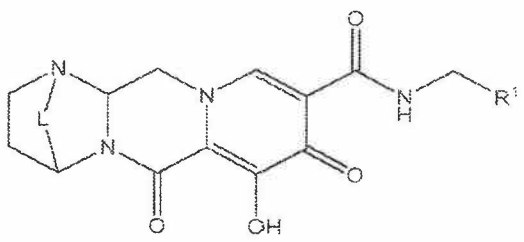
In another embodiment, compounds are provided having one of the following Formulas (II-A), (II-B), or (II-C):

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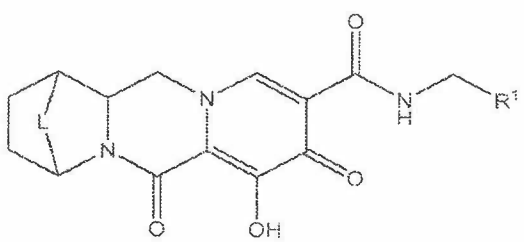
;

(II-A)



; or

(II-B)



,

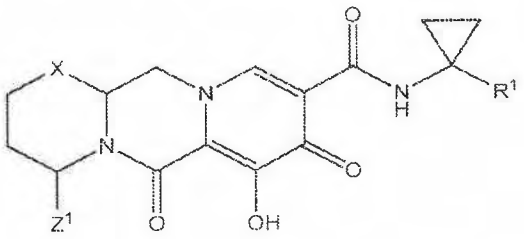
(II-C)

wherein L is $-C(R^a)_2-$, $-C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2C(R^a)_2C(R^a)_2-$, $-C(R^a)_2OC(R^a)_2-$, $-C(R^a)_2NR^aC(R^a)_2-$, $-C(R^a)_2SC(R^a)_2-$, $-C(R^a)_2S(O)C(R^a)_2-$, $-C(R^a)_2SO_2C(R^a)_2-$, $-C(R^a)_2OC(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2OC(R^a)_2-$, $-C(R^a)_2NR^aC(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2NR^aC(R^a)_2-$, $-C(R^a)_2SC(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2SC(R^a)_2-$, $-C(R^a)_2S(O)C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2S(O)C(R^a)_2-$, $-C(R^a)_2SO_2C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2SO_2C(R^a)_2-$, $-C(R^a)_2SO_2NR^aC(R^a)_2-$ or $-C(R^a)_2NR^aSO_2C(R^a)_2-$.

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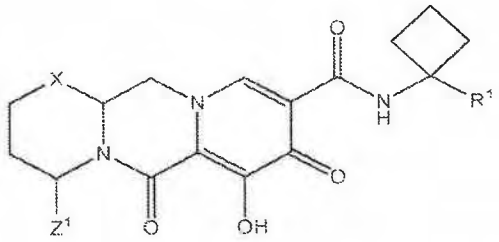
In another embodiment, Y^1 and Y^2, together with the carbon atom to which they are attached, form a carbocyclic ring having from 3 to 6 ring atoms or a heterocyclic ring having from 3 to 6 ring atoms.

In another embodiment, compounds are provided having one of the following Formulas (III-A), (III-B), (III-C) or (III-D):



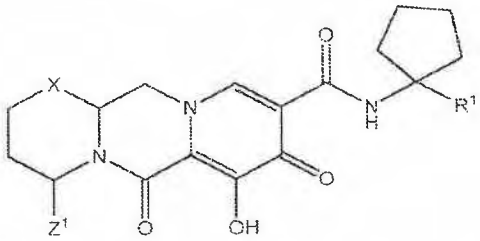
;

(III-A)



;

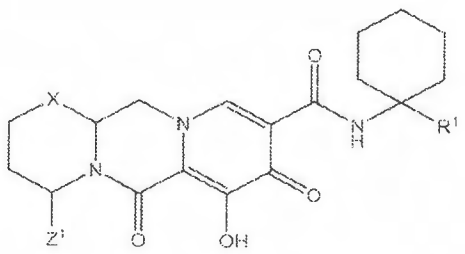
(III-B)



; or

(III-C)

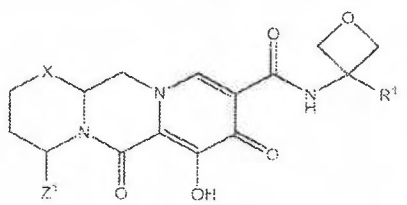
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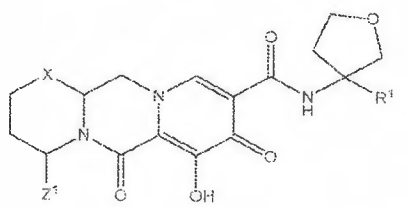
(III-D)

wherein Z^1 and Z^3 are each, independently, hydrogen or C_{1-3}alkyl.

In another embodiment, compounds are provided having one of the following Formulas (III-E), (III-F), (III-G) or (III-H):

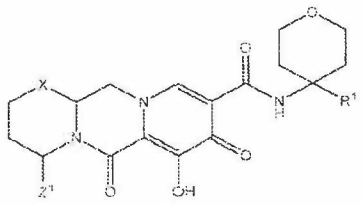


(III-E)



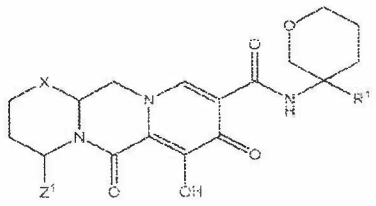
(III-F)

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; or

(III-G)

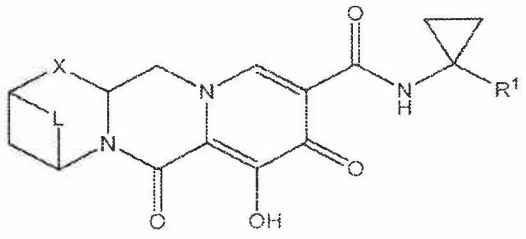


(III-H)

wherein Z^1 and Z^2 are each, independently, hydrogen or C_{1-3}alkyl.

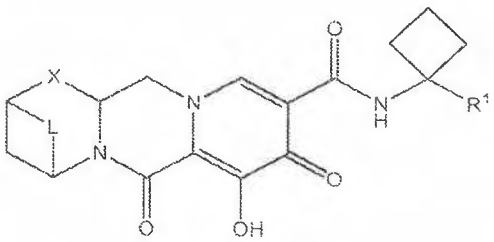
In another embodiment, both (i) Z^1 and Z^2 or Z^1 and Z^3, taken together, form -*L*-, and (ii) Y^1 and Y^2, together with the carbon atom to which they are attached, form a carbocyclic ring having from 3 to 6 ring atoms or a heterocyclic ring having from 3 to 6 ring atoms.

In another embodiment, compounds are provided having one of the following Formulas (IV-AA), (IV-AB), (IV-AC), (IV-AD), (IV-AE), (IV-AF), (IV-AG) or (IV-AH):

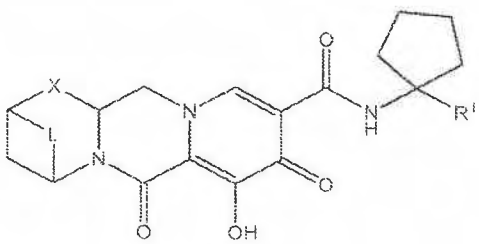


;

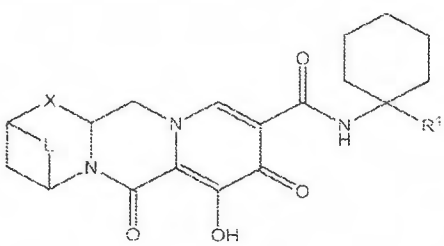
(IV-AA)



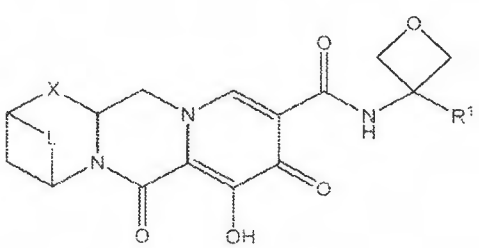
(IV-AB)



(IV-AC)

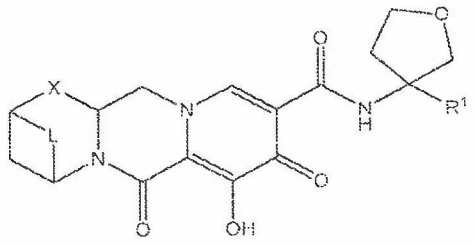


(IV-AD)

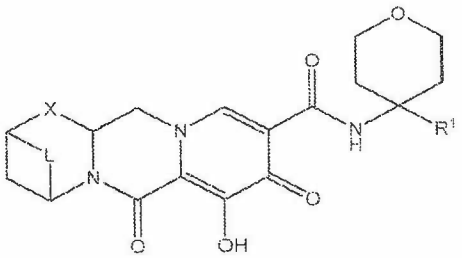


(IV-AE)

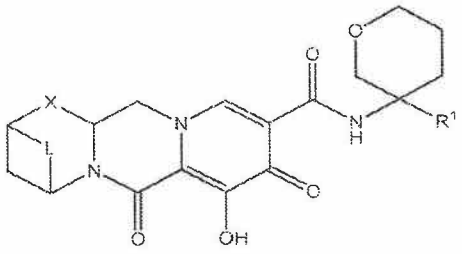
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(IV-AF)



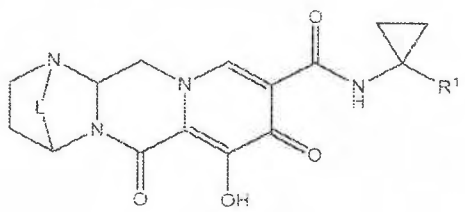
(IV-AG)



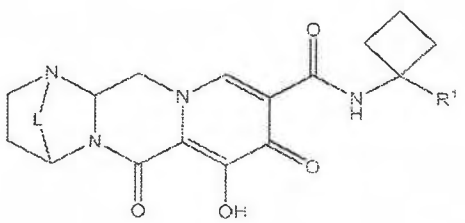
(IV-AH)

wherein L is $-C(R^a)_2-$, $-C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2C(R^a)_2C(R^a)_2-$, $-C(R^a)_2OC(R^a)_2-$, $-C(R^a)_2NR^aC(R^a)_2-$, $-C(R^a)_2SC(R^a)_2-$, $-C(R^a)_2S(O)C(R^a)_2-$, $-C(R^a)_2SO_2C(R^a)_2-$, $-C(R^a)_2OC(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2OC(R^a)_2-$, $-C(R^a)_2NR^aC(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2NR^aC(R^a)_2-$, $-C(R^a)_2SC(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2SC(R^a)_2-$, $-C(R^a)_2S(O)C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2S(O)C(R^a)_2-$, $-C(R^a)_2SO_2C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2SO_2C(R^a)_2-$, $-C(R^a)_2SO_2NR^aC(R^a)_2-$ or $-C(R^a)_2NR^aSO_2C(R^a)_2-$.

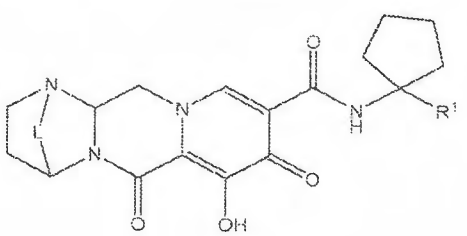
In another embodiment, compounds are provided having one of the following Formulas (IV-BA), (IV-BB), (IV-BC), (IV-BD), (IV-BE), (IV-BF), (IV-BG) or (IV-BH):



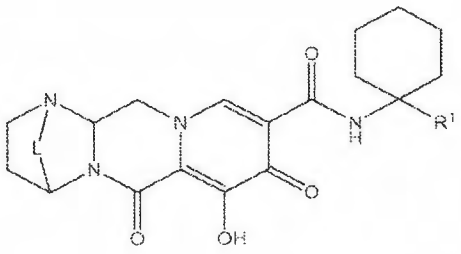
(IV-BA);



(IV-BB);

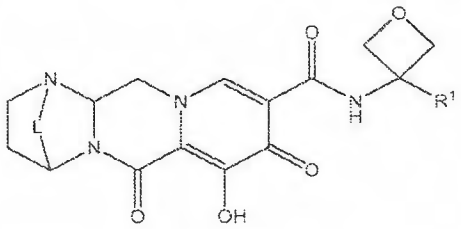


(IV-BC);



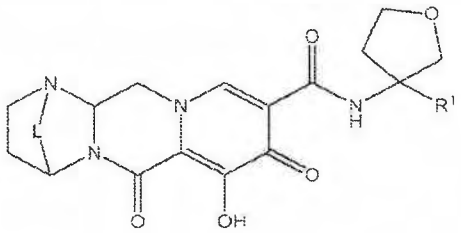
;

(IV-BD)



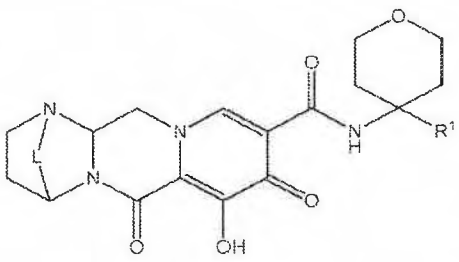
;

(IV-BE)



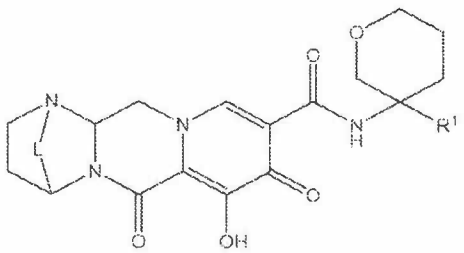
;

(IV-BF)



; or

(IV-BG)



(IV-BH)

wherein L is $-C(R^a)_2-$, $-C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2C(R^a)_2C(R^a)_2-$, $-C(R^a)_2OC(R^a)_2-$, $-C(R^a)_2NR^aC(R^a)_2-$, $-C(R^a)_2SC(R^a)_2-$, $-C(R^a)_2S(O)C(R^a)_2-$, $-C(R^a)_2SO_2C(R^a)_2-$, $-C(R^a)_2OC(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2OC(R^a)_2-$, $-C(R^a)_2NR^aC(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2NR^aC(R^a)_2-$, $-C(R^a)_2SC(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2SC(R^a)_2-$, $-C(R^a)_2S(O)C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2S(O)C(R^a)_2-$, $-C(R^a)_2SO_2C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2SO_2C(R^a)_2-$, $-C(R^a)_2SO_2NR^aC(R^a)_2-$ or $-C(R^a)_2NR^aSO_2C(R^a)_2-$.

In another embodiment, L is $-C(R^a)_2-$, $-C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2C(R^a)_2-$, or $-C(R^a)_2C(R^a)_2C(R^a)_2C(R^a)_2-$. In a further embodiment, L is $-C(R^a)_2-$. In still a further embodiment, L is $-C(R^a)_2C(R^a)_2-$. In still a further embodiment, L is $-C(R^a)_2C(R^a)_2C(R^a)_2-$. In still a further embodiment, each R^a is hydrogen. In still a further embodiment, one R^a is methyl and each remaining R^a is hydrogen. In still a further embodiment, one R^a is halogen and each remaining R^a is hydrogen. In still a further embodiment, two R^a are halogen and each remaining R^a is hydrogen. In still a further embodiment, one R^a is halogen and each remaining R^a is hydrogen.

In another embodiment, L is $-C(R^a)_2OC(R^a)_2-$, $-C(R^a)_2NR^aC(R^a)_2-$, $-C(R^a)_2SC(R^a)_2-$, $-C(R^a)_2S(O)C(R^a)_2-$, or $-C(R^a)_2SO_2C(R^a)_2-$. In a further embodiment, L is $-C(R^a)_2OC(R^a)_2-$. In still a further embodiment, each R^a is hydrogen. In still a further embodiment, one R^a is methyl and each remaining R^a is hydrogen. In still a further embodiment, one R^a is halogen and each remaining R^a is hydrogen. In still a further embodiment, two R^a are halogen and each remaining R^a is hydrogen. In still a further embodiment, one R^a is halogen and each remaining R^a is hydrogen.

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In another embodiment, X is -O-. In a further embodiment, Z^2 is hydrogen. In another embodiment, X is $-NZ^3-$. In another embodiment, X is -NH-. In another embodiment, X is $-CHZ^3-$. In another embodiment, X is $-CH_2-$.

In another embodiment, Z^4 is a bond or $-CH_2-$. In another embodiment, Z^4 is $-CH_2-$. In another embodiment, Z^4 is a bond.

In another embodiment, Y^1 and Y^2 are each independently hydrogen, methyl or trifluoromethyl.

In another embodiment, R^1 is substituted with one halogen. In a further embodiment, R^1 is 4-fluorophenyl or 2-fluorophenyl.

In another embodiment, R^1 is phenyl. In another embodiment, R^1 is pyridinyl.

In another embodiment, R^1 is substituted with at least one halogen.

In another embodiment, R^1 is substituted with one halogen. In a further embodiment, R^1 is 4-fluorophenyl or 2-fluorophenyl.

In another embodiment, R^1 is substituted with two halogens. In a further embodiment, R^1 is 2,4-difluorophenyl, 2,3-difluorophenyl, 2,6-difluorophenyl, 3-fluoro-4-chlorophenyl, 3,4-difluorophenyl, 2-fluoro-4-chlorophenyl, or 3,5-difluorophenyl. In still a further embodiment, R^1 is 2,4-difluorophenyl.

In another embodiment, R^1 is substituted with three halogens. In a further embodiment, R^1 is 2,4,6-trifluorophenyl or 2,3,4-trifluorophenyl. In still a further embodiment, R^1 is 2,4,6-trifluorophenyl.

In another embodiment, R^1 is 3-trifluoromethyl-4-fluorophenyl or 2-cyclopropoxy-4-fluorophenyl.

In one embodiment, a pharmaceutical composition is provided comprising a compound of any one of Formulas (I), (II-A), (II-B), (II-C), (III-A), (III-B), (III-C), (III-D), (III-E), (III-F), (III-G), (III-H), (IV-AA), (IV-AB), (IV-AC), (IV-AD), (IV-AE), (IV-AF), (IV-AG), (IV-AH), (IV-BA), (IV-BB), (IV-BC), (IV-BD), (IV-BE), (IV-BF), (IV-BG), and (IV-BH), as noted above, or a stereoisomer or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

Another embodiment is provided comprising a method of treating an HIV infection in a human having or at risk of having the infection by administering to

the human a therapeutically effective amount of a compound of any one of Formulas (I), (II-A), (II-B), (II-C), (III-A), (III-B), (III-C), (III-D), (III-E), (III-F), (III-G), (III-H), (IV-AA), (IV-AB), (IV-AC), (IV-AD), (IV-AE), (IV-AF), (IV-AG), (IV-AH), (IV-BA), (IV-BB), (IV-BC), (IV-BD), (IV-BE), (IV-BF), (IV-BG), and (IV-BH), as noted above, or a pharmaceutical composition thereof. Another embodiment is provided comprising a method of treating or preventing an HIV infection in a human having or at risk of having the infection by administering to the human a therapeutically effective amount of a compound of any one of Formulas (I), (II-A), (II-B), (II-C), (III-A), (III-B), (III-C), (III-D), (III-E), (III-F), (III-G), (III-H), (IV-AA), (IV-AB), (IV-AC), (IV-AD), (IV-AE), (IV-AF), (IV-AG), (IV-AH), (IV-BA), (IV-BB), (IV-BC), (IV-BD), (IV-BE), (IV-BF), (IV-BG), and (IV-BH), as noted above, or a pharmaceutical composition thereof.

In another embodiment, the use of a compound of any one of Formulas (I), (II-A), (II-B), (II-C), (III-A), (III-B), (III-C), (III-D), (III-E), (III-F), (III-G), (III-H), (IV-AA), (IV-AB), (IV-AC), (IV-AD), (IV-AE), (IV-AF), (IV-AG), (IV-AH), (IV-BA), (IV-BB), (IV-BC), (IV-BD), (IV-BE), (IV-BF), (IV-BG), and (IV-BH), as noted above, or a pharmaceutical composition thereof for the treatment of an HIV infection in a human having or at risk of having the infection. In another embodiment, the use of a compound of any one of Formulas (I), (II-A), (II-B), (II-C), (III-A), (III-B), (III-C), (III-D), (III-E), (III-F), (III-G), (III-H), (IV-AA), (IV-AB), (IV-AC), (IV-AD), (IV-AE), (IV-AF), (IV-AG), (IV-AH), (IV-BA), (IV-BB), (IV-BC), (IV-BD), (IV-BE), (IV-BF), (IV-BG), and (IV-BH), as noted above, or a pharmaceutical composition thereof for the treatment or prevention of an HIV infection in a human having or at risk of having the infection.

In another embodiment, the use in medical therapy of a compound of any one of the Formulas (I), (II-A), (II-B), (II-C), (III-A), (III-B), (III-C), (III-D), (III-E), (III-F), (III-G), (III-H), (IV-AA), (IV-AB), (IV-AC), (IV-AD), (IV-AE), (IV-AF), (IV-AG), (IV-AH), (IV-BA), (IV-BB), (IV-BC), (IV-BD), (IV-BE), (IV-BF), (IV-BG), and (IV-BH), as noted above, or a pharmaceutical composition thereof, is provided.

In another embodiment, the use of a compound of any one of the Formulas (I), (II-A), (II-B), (II-C), (III-A), (III-B), (III-C), (III-D), (III-E), (III-F),

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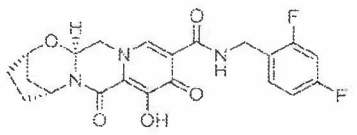
(III-G), (III-H), (IV-AA), (IV-AB), (IV-AC), (IV-AD), (IV-AE), (IV-AF), (IV-AG), (IV-AH), (IV-BA), (IV-BB), (IV-BC), (IV-BD), (IV-BE), (IV-BF), (IV-BG), and (IV-BH), as noted above, or a pharmaceutical composition thereof, for use in the therapeutic treatment of an HIV infection is provided. In another embodiment, the use of a compound of any one of the Formulas (I), (II-A), (II-B), (II-C), (III-A), (III-B), (III-C), (III-D), (III-E), (III-F), (III-G), (III-H), (IV-AA), (IV-AB), (IV-AC), (IV-AD), (IV-AE), (IV-AF), (IV-AG), (IV-AH), (IV-BA), (IV-BB), (IV-BC), (IV-BD), (IV-BE), (IV-BF), (IV-BG), and (IV-BH), as noted above, or a pharmaceutical composition thereof, for use in the prophylactic or therapeutic treatment of an HIV infection is provided.

It is understood that any embodiment of the compounds of Formulas (I), (II-A), (II-B), (II-C), (III-A), (III-B), (III-C), (III-D), (III-E), (III-F), (III-G), (III-H), (IV-AA), (IV-AB), (IV-AC), (IV-AD), (IV-AE), (IV-AF), (IV-AG), (IV-AH), (IV-BA), (IV-BB), (IV-BC), (IV-BD), (IV-BE), (IV-BF), (IV-BG), and (IV-BH), as set forth above, and any specific substituent set forth herein for a R^1, R^a, X, W, Y^1, Y^2, L, Z^1, Z^2, Z^3, or Z^4 group in the compounds of Formulas (I), (II-A), (II-B), (II-C), (III-A), (III-B), (III-C), (III-D), (III-E), (III-F), (III-G), (III-H), (IV-AA), (IV-AB), (IV-AC), (IV-AD), (IV-AE), (IV-AF), (IV-AG), (IV-AH), (IV-BA), (IV-BB), (IV-BC), (IV-BD), (IV-BE), (IV-BF), (IV-BG), and (IV-BH), as set forth above, may be independently combined with other embodiments and/or substituents of compounds of Formulas (I), (II-A), (II-B), (II-C), (III-A), (III-B), (III-C), (III-D), (III-E), (III-F), (III-G), (III-H), (IV-AA), (IV-AB), (IV-AC), (IV-AD), (IV-AE), (IV-AF), (IV-AG), (IV-AH), (IV-BA), (IV-BB), (IV-BC), (IV-BD), (IV-BE), (IV-BF), (IV-BG), and (IV-BH), to form embodiments of the inventions not specifically set forth above. In addition, in the event that a list of substituents is listed for any particular R^1, R^a, X, W, Y^1, Y^2, L, Z^1, Z^2, Z^3, or Z^4 in a particular embodiment and/or claim, it is understood that each individual substituent may be deleted from the particular embodment and/or claim and that the remaining list of substituents will be considered to be within the scope of the invention.

As one of skill in the art will appreciate, compounds of Formulas (I), (II-A), (II-B), (II-C), (IV-AA), (IV-AB), (IV-AC), (IV-AD), (IV-AE), (IV-AF), (IV-AG), (IV-AH), (IV-BA), (IV-BB), (IV-BC), (IV-BD), (IV-BE), (IV-BF), (IV-BG),

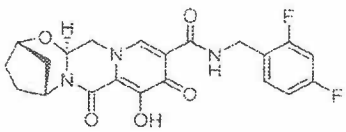
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and (IV-BH), wherein Z^1 and Z^2 or Z^1 and Z^3, taken together, form -L- may be shown in several different ways. For example, the Compound 3 of Example 3 may be shown as:



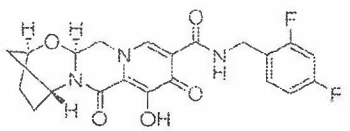
3

,



3

or



3

Pharmaceutical Compositions

For the purposes of administration, in certain embodiments, the compounds described herein are administered as a raw chemical or are formulated as pharmaceutical compositions. Pharmaceutical compositions disclosed herein include a compound of Formula (I) and one or more of: a pharmaceutically acceptable carrier, diluent or excipient. The compound of Formula (I) is present in the composition in an amount which is effective to treat a particular disease or condition of interest. The activity of compounds of Formula (I) can be determined by one skilled in the art, for example, as described in the Examples below. Appropriate concentrations and dosages can be readily determined by one skilled in the art. In certain embodiments, a compound of Formula (I) is present in the pharmaceutical composition in an amount from about 25 mg to about 500 mg. In certain embodiments, a compound of Formula (I) is present in the pharmaceutical composition in an amount of about 100 mg to about 300 mg. In certain embodiments, a compound of Formula (I) is present in the pharmaceutical composition in an amount of about 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg or about 500 mg.

Administration of the compounds of the invention, or their pharmaceutically acceptable salts, in pure form or in an appropriate pharmaceutical

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composition, is carried out via any of the accepted modes of administration of agents for serving similar utilities. The pharmaceutical compositions of the invention are prepared by combining a compound of the invention with an appropriate pharmaceutically acceptable carrier, diluent or excipient, and in specific embodiments are formulated into preparations in solid, semi-solid, liquid or gaseous forms, such as tablets, capsules, powders, granules, ointments, solutions, suppositories, injections, inhalants, gels, microspheres, and aerosols. Exemplary routes of administering such pharmaceutical compositions include, without limitation, oral, topical, transdermal, inhalation, parenteral, sublingual, buccal, rectal, vaginal, and intranasal. Pharmaceutical compositions of the invention are formulated so as to allow the active ingredients contained therein to be bioavailable upon administration of the composition to a patient. Compositions that will be administered to a subject or patient take the form of one or more dosage units, where for example, a tablet may be a single dosage unit, and a container of a compound of the invention in aerosol form may hold a plurality of dosage units. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see *Remington: The Science and Practice of Pharmacy*, 20th Edition (Philadelphia College of Pharmacy and Science, 2000). The composition to be administered will, in any event, contain a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, for treatment of a disease or condition of interest in accordance with the teachings described herein.

The pharmaceutical compositions disclosed herein are prepared by methodologies well known in the pharmaceutical art. For example, in certain embodiments, a pharmaceutical composition intended to be administered by injection is prepared by combining a compound of the invention with sterile, distilled water so as to form a solution. In some embodiments, a surfactant is added to facilitate the formation of a homogeneous solution or suspension. Surfactants are compounds that non-covalently interact with the compound of the invention so as to facilitate dissolution or homogeneous suspension of the compound in the aqueous delivery system.

The compounds of the invention, or their pharmaceutically acceptable salts, are administered in a therapeutically effective amount, which will vary depending

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upon a variety of factors including the activity of the specific compound employed; the metabolic stability and length of action of the compound; the age, body weight, general health, sex, and diet of the patient; the mode and time of administration; the rate of excretion; the drug combination; the severity of the particular disorder or condition; and the subject undergoing therapy.

Combination Therapy

In one embodiment, a method for treating or preventing an HIV infection in a human having or at risk of having the infection is provided, comprising administering to the human a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents.

In one embodiment, pharmaceutical compositions comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with one or more additional therapeutic agents, and a pharmaceutically acceptable carrier, diluent or excipient are provided.

In one embodiment, combination pharmaceutical agents comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with one or more additional therapeutic agents are provided.

In the above embodiments, the additional therapeutic agent may be an anti-HIV agent. For example, in some embodiments, the additional therapeutic agent is selected from the group consisting of HIV protease inhibitors, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, entry inhibitors (e.g., CCR5 inhibitors, gp41 inhibitors (i.e., fusion inhibitors) and CD4 attachment inhibitors), CXCR4 inhibitors, gp120 inhibitors, G6PD and NADH-oxidase inhibitors, compounds that target the HIV capsid ("capsid inhibitors"; e.g., capsid polymerization inhibitors or capsid disrupting compounds such as those disclosed in WO 2013/006738 (Gilead Sciences), US 2013/0165489 (University of Pennsylvania), and WO 2013/006792 (Pharma Resources), pharmacokinetic enhancers, and other drugs for treating HIV, and

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combinations thereof. In further embodiments, the additional therapeutic agent is selected from one or more of:

(1) HIV protease inhibitors selected from the group consisting of amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir, nelfinavir, saquinavir, tipranavir, brecanavir, darunavir, TMC-126, TMC-114, mozenavir (DMP-450), JE-2147 (AG1776), L-756423, RO0334649, KNI-272, DPC-681, DPC-684, GW640385X, DG17, PPL-100, DG35, and AG 1859;

(2) HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase selected from the group consisting of capravirine, emivirine, delaviridine, efavirenz, nevirapine, (+) calanolide A, etravirine, GW5634, DPC-083, DPC-961, DPC-963, MIV-150, TMC-120, rilpivirene, BILR 355 BS, VRX 840773, lersivirine (UK-453061), RDEA806, KM023 and MK-1439;

(3) HIV nucleoside inhibitors of reverse transcriptase selected from the group consisting of zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, MIV-210, ℓ-FTC, D-d4FC, emtricitabine, phosphazide, fozivudine tidoxil, apricitibine (AVX754), KP-1461, GS-9131 (Gilead Sciences) and fosalvudine tidoxil (formerly HDP 99.0003);

(4) HIV nucleotide inhibitors of reverse transcriptase selected from the group consisting of tenofovir, tenofovir disoproxil fumarate, tenofovir alafenamide fumarate (Gilead Sciences), GS-7340 (Gilead Sciences), GS-9148 (Gilead Sciences), adefovir, adefovir dipivoxil, CMX-001 (Chimerix) or CMX-157 (Chimerix);

(5) HIV integrase inhibitors selected from the group consisting of curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic acid phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin, derivatives of quercetin, S-1360, AR-177, L-870812, and L-870810, raltegravir, BMS-538158, GSK364735C, BMS-707035, MK-2048, BA 011, elvitegravir, dolutegravir and GSK-744;

(6) HIV non-catalytic site, or allosteric, integrase inhibitors (NCINI) including, but not limited to, BI-224436, CX0516, CX05045, CX14442, compounds disclosed in WO 2009/062285 (Boehringer Ingelheim), WO 2010/130034 (Boehringer

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Ingelheim), WO 2013/159064 (Gilead Sciences), WO 2012/145728 (Gilead Sciences), WO 2012/003497 (Gilead Sciences), WO 2012/003498 (Gilead Sciences) each of which is incorporated by references in its entirety herein;

(7) gp41 inhibitors selected from the group consisting of enfuvirtide, sifuvirtide, albuvirtide, FB006M, and TRI-1144;

(8) the CXCR4 inhibitor AMD-070;

(9) the entry inhibitor SP01A;

(10) the gp120 inhibitor BMS-488043;

(11) the G6PD and NADH-oxidase inhibitor immunitin;

(12) CCR5 inhibitors selected from the group consisting of aplaviroc, vicriviroc, maraviroc, cenicriviroc, PRO-140, INCB15050, PF-232798 (Pfizer), and CCR5mAb004;

(13) CD4 attachment inhibitors selected from the group consisting of ibalizumab (TMB-355) and BMS-068 (BMS-663068);

(14) pharmacokinetic enhancers selected from the group consisting of cobicistat and SPI-452; and

(15) other drugs for treating HIV selected from the group consisting of BAS-100, SPI-452, REP 9, SP-01A, TNX-355, DES6, ODN-93, ODN-112, VGV-1, PA-457 (bevirimat), HRG214, VGX-410, KD-247, AMZ 0026, CYT 99007A-221 HIV, DEBIO-025, BAY 50-4798, MDX010 (ipilimumab), PBS 119, ALG 889, and PA-1050040 (PA-040),

and combinations thereof

In certain embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with two, three, four or more additional therapeutic agents. In certain embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with two additional therapeutic agents. In other embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with three additional therapeutic agents. In further embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with four additional therapeutic agents. The two, three four or more additional therapeutic agents can be different therapeutic agents selected from the same class of therapeutic agents, or they can be selected from different classes of

therapeutic agents. In a specific embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with an HIV nucleotide inhibitor of reverse transcriptase and an HIV non-nucleoside inhibitor of reverse transcriptase. In another specific embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with an HIV nucleotide inhibitor of reverse transcriptase, and an HIV protease inhibiting compound. In a further embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with an HIV nucleotide inhibitor of reverse transcriptase, an HIV non-nucleoside inhibitor of reverse transcriptase, and an HIV protease inhibiting compound. In an additional embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with an HIV nucleotide inhibitor of reverse transcriptase, an HIV non-nucleoside inhibitor of reverse transcriptase, and a pharmacokinetic enhancer.

In certain embodiments, when a compound disclosed herein is combined with one or more additional therapeutic agents as described above, the components of the composition are administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations.

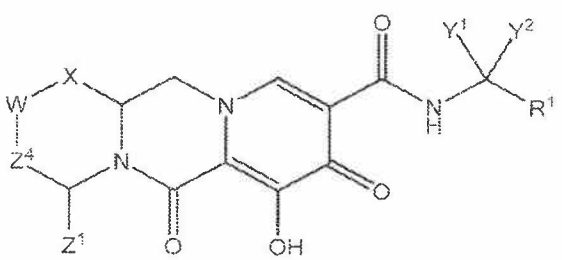
In certain embdoiments, a compound disclosed herein is combined with one or more additional therapeutic agents in a unitary dosage form for simultaneous administration to a patient, for example as a solid dosage form for oral administration.

In certain embodiments, a compound disclosed herein is administered with one or more additional therapeutic agents. Co-administration of a compound disclosed herein with one or more additional therapeutic agents generally refers to simultaneous or sequential administration of a compound disclosed herein and one or more additional therapeutic agents, such that therapeutically effective amounts of the compound disclosed herein and one or more additional therapeutic agents are both present in the body of the patient.

Co-administration includes administration of unit dosages of the compounds disclosed herein before or after administration of unit dosages of one or more additional therapeutic agents, for example, administration of the compound disclosed herein within seconds, minutes, or hours of the administration of one or more additional therapeutic agents. For example, in some embodiments, a unit dose of a

compound disclosed herein is administered first, followed within seconds or minutes by administration of a unit dose of one or more additional therapeutic agents. Alternatively, in other embodiments, a unit dose of one or more additional therapeutic agents is administered first, followed by administration of a unit dose of a compound disclosed herein within seconds or minutes. In some embodiments, a unit dose of a compound disclosed herein is administered first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of one or more additional therapeutic agents. In other embodiments, a unit dose of one or more additional therapeutic agents is administered first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of a compound disclosed herein.

The following Examples illustrate various methods of making compounds of this invention, *i.e.*, compound of Formula (I):



(I)

wherein R^1, X, W, Y^1, Y^2, Z^1, Z^2, or Z^4 are as defined above. It is understood that one skilled in the art may be able to make these compounds by similar methods or by combining other methods known to one skilled in the art. It is also understood that one skilled in the art would be able to make, in a similar manner as described below, other compounds of Formula (I) not specifically illustrated below by using the appropriate starting components and modifying the parameters of the synthesis as needed. In general, starting components may be obtained from sources such as Sigma Aldrich, Lancaster Synthesis, Inc., Maybridge, Matrix Scientific, TCI, and Fluorochem USA, etc. or synthesized according to sources known to those skilled in the art (see, for example, Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 5th

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edition (Wiley, December 2000)) or prepared as described herein.

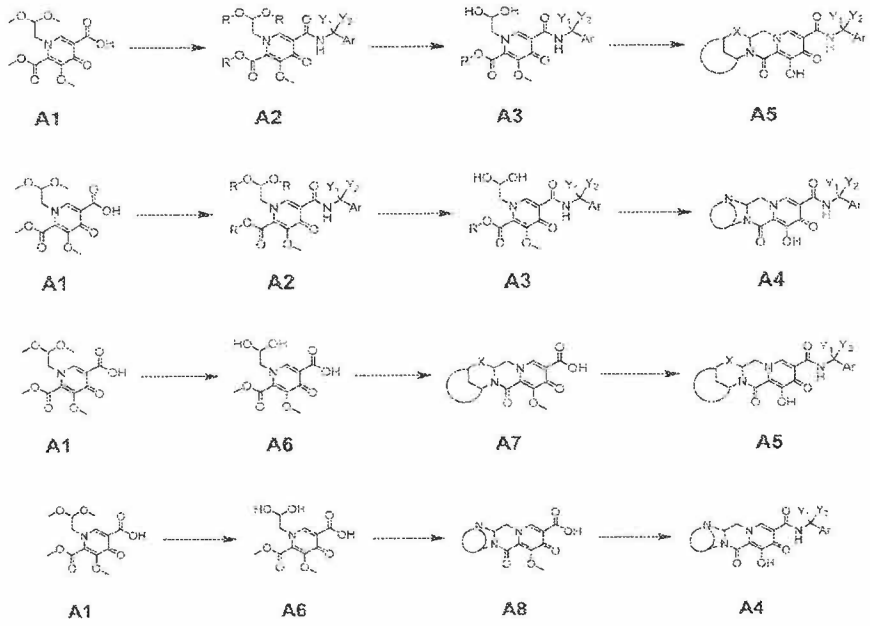
The following examples are provided for purposes of illustration, not limitation.

EXAMPLES

General Synthetic Schemes

Schemes 1–3 are provided as further embodiments of the invention and illustrate general methods which were used to prepare compounds having Formula (I) and which can be used to prepare additional compound having Formula (I).

Scheme 1

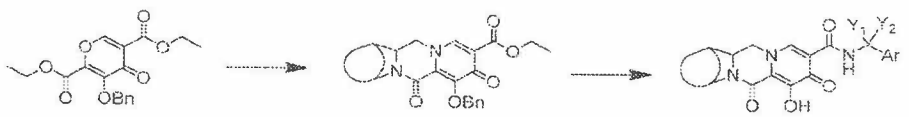


A1 can be converted to amide **A2** with an appropriate amine and a coupling reagent such as HATU or EDCI. **A2** can be converted to **A3** with a strong acid such as methanesulfonic acid. **A3** can be converted to either **A5** or **A4** by heating with

an appropriate cyclic diamine or cyclic aminoalcohol followed by methyl deprotection with a reagent such as magnesium bromide.

Alternatively, **A1** can be converted to **A6** by treatment with a strong acid such as methanesulfonic acid. **A6** can be condensed with an appropriate cyclic diamine or cyclic aminoalcohol followed by methyl deprotection with a reagent such as magnesium bromide to form either **A7** or **A8** respectively. **A7** or **A8** can be converted into amides **A5** and **A4** by treatment with an appropriate amine and a coupling reagent such as HATU or EDCI followed by methyl deprotection with a reagent such as magnesium bromide.

Scheme 2



B1 **B2** **B3**

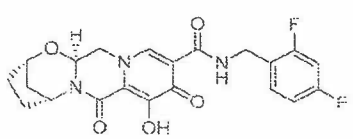
B1 (as described in WO2012/018065) is condensed with diamine under reflux condition to give **B2**. **B2** is hydrolyzed and coupled with an amine by an amide-forming method to afford product **B3** upon removal of a benzyl protecting group.

REPRESENTATIVE COMPOUNDS

Example 1

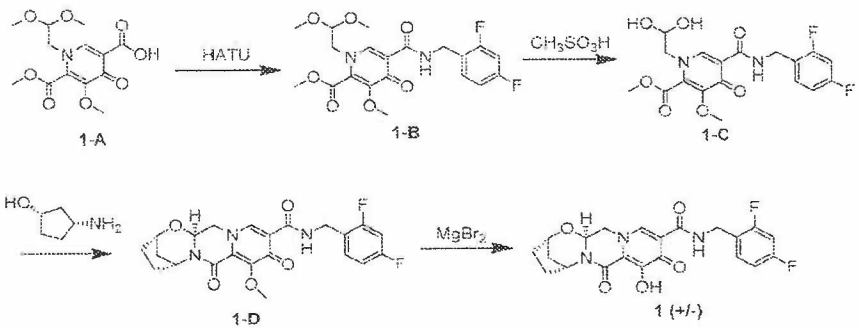
Preparation of Compound **1**

N-(2,4-difluorobenzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



1 (+/-)

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Step 1

1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (**1-A**, 0.300 g, 0.95 mmol), prepared as described in WO2011/119566 A1, was evaporated once from dry toluene, suspended in acetonitrile (4 mL) and treated with N,N-diisopropylethylamine (DIPEA) (0.329 mL, 1.90 mmol), 2,4-difluorobenzylamine (0.125 mL, 1.05 mmol) and HATU (0.433 g, 1.14 mmol). The reaction mixture was stirred for 10 minutes and concentrated. The residue was purified by flash chromatography on silica gel (10 to 60% ethyl acetate:dichloromethane) to afford the compound methyl 5-(2,4-difluorobenzylcarbamoyl)-1-(2,2-dimethoxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate, **1-B**. **^{1}H-NMR** (400 MHz, DMSO-d6) δ 10.28 (t, J = 6.0 Hz, 1H), 8.46 (s, 1H), 7.42 (dd, J = 15.4, 8.6 Hz, 1H), 7.24 (m, 1H), 7.06 (m, 1H), 4.52 (m, 3H), 4.22 (d, J = 4.4 Hz, 2H), 3.92 (s, 3H), 3.80 (s, 3H),3.29 (d, 6H). **LCMS-ESI$^+$** (m/z): $[M+H]^+$ calculated for $C_{20}H_{23}F_2N_2O_7$: 441.15; found: 441.2.

Step 2

Methyl 5-(2,4-difluorobenzylcarbamoyl)-1-(2,2-dimethoxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate (**1-B**, 0.106 g, 0.24 mmol) in acetonitrile (0.9 mL) and acetic acid (0.1 mL) was treated with methanesulfonic acid (0.005 mL, 0.072 mmol), sealed with a yellow cap, and heated to 70 °C. After 16 hours, the mixture was cooled to afford a crude solution of methyl 5-(2,4-difluorobenzylcarbamoyl)-1-(2,2-dihydroxyethyl)-3-methoxy-4-oxo-1,4-

dihydropyridine-2-carboxylate, **1-C**. **LCMS-ESI**$^+$ (*m/z*): [M+H]$^+$ calculated for $C_{18}H_{19}F_2N_2O_7$: 413.12; found: 413.1.

Steps 3 and 4

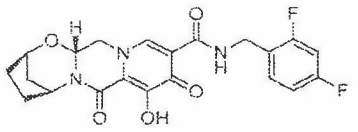
Methyl 5-(2,4-difluorobenzylcarbamoyl)-1-(2,2-dihydroxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate (**1-C**, 0.65 mL of the crude mixture from the previous step, 0.17 mmol) was treated with acetonitrile (0.65 mL) and *cis*-3-aminocyclpentanol (0.06 mL). The reaction mixture was sealed and heated to 90 °C. After 30 minutes, the reaction mixture was cooled and magnesium bromide (0.063 g, 0.34 mmol) was added. The mixture was resealed and heated to 50 °C. After 10 minutes, the reaction mixture was partitioned between dichloromethane and hydrochloric acid (0.2 M aq). The organic layer was removed and the aqueous layer extracted again with dichlormethane. The combined organic layers were dried over sodium sulfate, filtered and concentrated. Prep-HPLC purification (30-70% acetonitrile:water, 0.1% TFA) afforded Compound **1** as a racemic mixture. ^{1}**H-NMR** (400 MHz, DMSO-d6) δ 12.45 (br s, 1H), 10.35 (t, J = 5.8 Hz, 1H), 8.45 (s, 1H), 7.37 (dd, J = 15.4, 8.6 Hz, 1H), 7.23 (dt, J = 2.5, 9.9 Hz, 1H), 7.05 (dt, J = 2.2, 8.7 Hz, 1H), 5.43 (dd, J = 9.6, 4.0 Hz, 1H), 5.09 (br s, 1H), 4.68 (dd, J = 13.2, 4.0 Hz, 1H), 4.59 (br s, 1H), 4.53 (m, 2H), 4.02 (dd, J = 12.6, 9.4 Hz), 1.93 (br s, 4H), 1.83 (d, J = 12.0 Hz), 1.57 (dt, J = 12.2, 3.2 Hz). **LCMS-ESI**$^+$ (*m/z*): [M+H]$^+$ calculated for $C_{21}H_{20}F_2N_3O_5$: 432.14; found: 432.2.

Examples 2 and 3

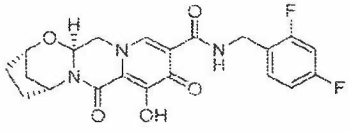
Preparation of Compounds **2** and **3**

(2R,5S,13aR)-N-(2,4-difluorobenzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (**2**) and (2S,5R,13aS)-N-(2,4-difluorobenzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (**3**)

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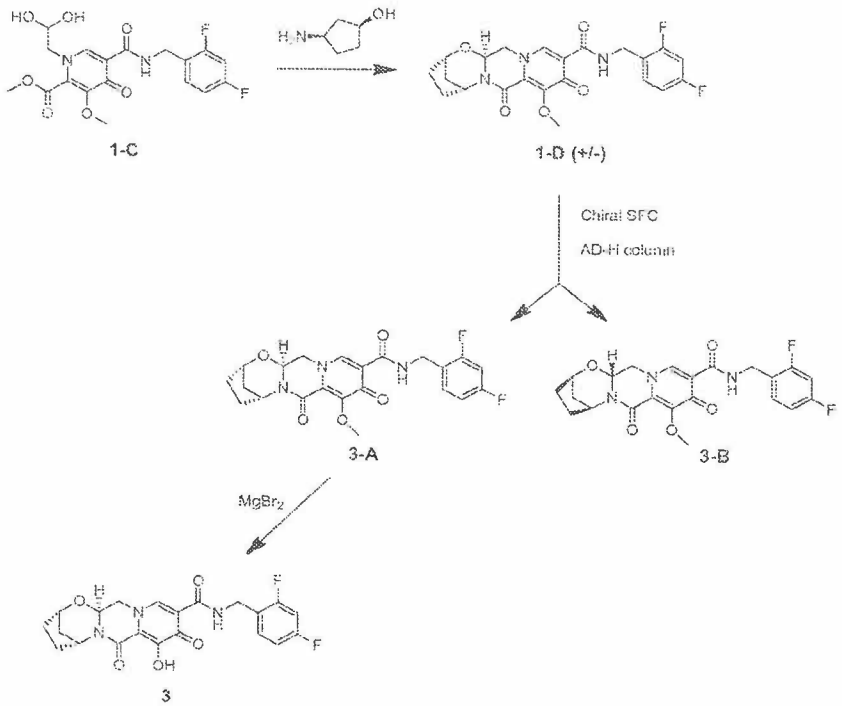
2



3

Compound **1** (16 mg) was separated by chiral HPLC using Chiralpak AS-H with 100% ethanol as eluent to afford Compounds **2** and **3** in enantiomerically enriched form. For Compound **2**: **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}F_2N_3O_5$: 432.14; found: 432.2, **Chiral HPLC** retention time = 4.50 minutes (Chiralpak AS-H, 150 x 4.6 mm, 1 mL/min EtOH). For Compound **3**: **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}F_2N_3O_5$: 432.14; found: 432.2, **Chiral HPLC** retention time = 6.84 minutes (Chiralpak AS-H, 150 x 4.6 mm, 1 mL/min EtOH). **^{1}H-NMR** (400 MHz, DMSO-d6) δ 12.45 (br s, 1H), 10.35 (t, *J* = 5.8 Hz, 1H), 8.44 (s, 1H), 7.37 (dd, *J* = 15.2, 8.4 Hz, 1H), 7.23 (m, 1H), 7.05 (dt, *J* = 1.8 Hz, 8.7 Hz, 1H), 5.44 (dd, *J* = 9.6, 4.0 Hz), 5.09 (br s, 1H), 4.68 (dd, *J* = 12.8, 4.0 Hz, 1H), 4.59 (br s, 1H), 4.53 (m, 2H), 4.02 (dd, *J* = 12.6, 9.4 Hz, 1H), 1.93 (br s, 4H), 1.83 (d, *J* = 12.4 Hz, 1H), 1.57 (m, 1H).

Alternatively, Compound **3** was prepared as follows:



Methyl 5-(2,4-difluorobenzylcarbamoyl)-1-(2,2-dihydroxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate (**1-C**, 1.2 mmol in 5 mL of 9:1 acetonitrile:acetic acid containing 0.026 mL methanesulfonic acid) was treated with acetonitrile (5.0 mL) and *cis*-3-aminocyclpentanol (0.24 g, 2.4 mmol). The reaction mixture was sealed and heated to 90 °C. After 30 minutes, the reaction mixture was cooled, treated with potassium carbonate (0.332 g, 2.4 mmol), sealed and reheated to 90 °C. After 15 minutes, the mixture was cooled and partitioned between dichlormethane and hydrochloric acid (0.2 M aqueous). The organic layer was removed and the aqueous solution was extracted again with dichioromethane. The combined organic layers were dried over sodium sulfate (anhydrous), filtered and concentrated. The residue was purified by flash chromatography (0-8% ethanol (containing 11% saturated aqueous ammonium hydroxide) in dichioromethane) to afford Intermediate **1-D**. **LCMS-ESI**$^+$ (*m/z*): [M+H]$^+$ calculated for $C_{22}H_{22}F_2N_3O_5$: 446.15; found: 446.2

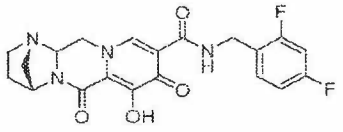
Intermediate **1-D** (270 mg) was separated by chiral SFC on a 50 mm Chiralpak AD-H column using 50% (1:1 methanol:acetonitrile) in supercritical carbon dioxide as eluent to afford Intermediates **3-A** (first eluting peak) and **3-B** (second eluting peak) in enantioenriched form. For **3-A: LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{22}F_2N_3O_5$: 446.15; found: 446.2. For **3-B**: **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{22}F_2N_3O_5$: 446.15; found: 446.2.

Intermediate **3-A** (0.110 g, 0.247 mmol) in acetonitrile (5 mL) was treated portion wise with magnesium bromide (0.091 g, 0.494 mmol), sealed and heated to 50 °C. After 10 minutes the mixture was cooled and partitioned between dichloromethane and hydrochloric acid (0.2 M aqueous). The organic layer was separated and the aqueous extracted again with dichloromethane. The combined organic layers were dried over sodium sulfate, filtered and concentrated. Preparative HPLC purification (30-70% acetonitrile:water, 0.1% TFA) afforded Compound **3** in enantioenriched form. **Chiral HPLC** retention time = 6.51 minutes (Chiralpak AS-H, 150 x 4.6 mm, 1 mL/min EtOH). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}F_2N_3O_5$: 432.14; found: 432.2. **^{1}H-NMR** (400 MHz, DMSO-d6) δ 12.45 (br s, 1H), 10.35 (t, *J* = 5.8 Hz, 1H), 8.44 (s, 1H), 7.37 (dd, *J* = 15.2, 8.4 Hz, 1H), 7.23 (m, 1H), 7.05 (dt, *J* = 1.8 Hz, 8.7 Hz, 1H), 5.44 (dd, *J* = 9.6, 4.0 Hz), 5.09 (br s, 1H), 4.68 (dd, *J* = 12.8, 4.0 Hz, 1H), 4.59 (br s, 1H), 4.53 (m, 2H), 4.02 (dd, *J* = 12.6, 9.4 Hz, 1H), 1.93 (br s, 4H), 1.83 (d, *J* = 12.4 Hz, 1H), 1.57 (m, 1H).

Example 4

Preparation of Compound 4

(1S,4R)-N-(2,4-difluorobenzyl)-7-hydroxy-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-1,4-methanopyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide



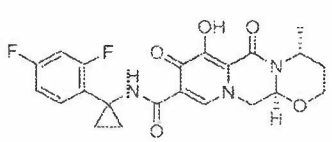
4

Methyl 5-(2,4-difluorobenzylcarbamoyl)-1-(2,2-dihydroxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate (1-C, 0.12 mmol in 0.53 mL of 9:1 acetonitrile:acetic acid containing 0.002 mL methanesulfonic acid) was treated with acetonitrile then (R)-pyrrolidin-3-amine (0.032 mL, 0.36 mmol). The reaction mixture was capped and heated to 90 °C for 5.5 hours. After cooling, the mixture was partitioned between dichloromethane and sodium bicarbonate (1M aqueous). The organic layer was separated and the aqueous was extracted again with ethyl acetate. The combined organic layers were dried over sodium sulfate (anhydrous), filtered and concentrated. The residue was dissolved in acetonitrile (1 mL), treated with magnesium bromide (0.022 g, 0.12 mmol), capped and heated to 50 °C for 10 minutes. After cooling the mixture was partitioned between dichloromethane and ammonium chloride (sat). The organic layer was separated and the aqueous was extracted again with dichloromethane. The aqueous layer was adjusted to pH = 1 with HCl (aq) and extracted again with dichloromethane. The aqueous solution was adjusted to pH = 3 with NaOH (aq) and extracted again with dichloromethane. The combined organic layers were dried over sodium sulfate, filtered, and concentrated. Preparative HPLC purification (10-55% acetonitrile:water, 0.1% TFA) afforded Compound 4. **^{1}H-NMR** (400 MHz, CD_3OD-d4) δ 8.42 (s, 1H), 7.42, (q, J = 7.7 Hz, 1H), 6.99 – 6.90 (m, 2H), 5.07 (br s, 1H), 4.73 (br d, J = 10.8 Hz, 1H), 4.62 (s, 2H), 4.51 (br d, J = 12.8 Hz, 1H), 4.07 (t, J = 11.8 Hz, 1H), 3.4- 3.0 (m, 3H), 2.76 (br d, J = 8.8 Hz, 1H), 2.15-2.0 (m, 1H), 1.9-1.8 (m, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{20}H_{19}F_2N_4O_4$: 417.14; found: 417.2.

Example 5

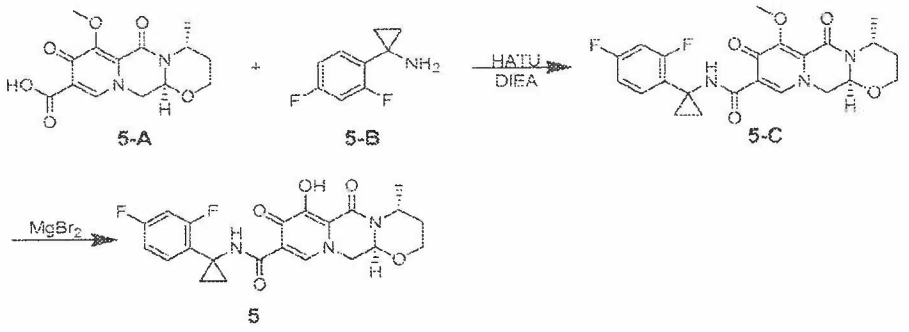
Preparation of Compound 5

(4R,12aS)-N-(1-(2,4-difluorophenyl)cyclopropyl)-7-hydroxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-[1,3]oxazino[3,2-d]pyrido[1,2-a]pyrazine-9-carboxamide



5

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Step 1

(4R,12aS)-7-methoxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-[1,3]oxazino[3,2-d]pyrido[1,2-a]pyrazine-9-carboxylic acid (Intermediate **5-A**) was prepared in an analogous manner to (3S,11aR)-6-methoxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydrooxazolo[3,2-d]pyrido[1,2-a]pyrazine-8-carboxylic acid as described in WO2011/119566, substituting (R)-3-aminobutan-1-ol for (S)-2-aminopropan-1-ol. WO2011/119566 is incorporated herein by reference in its entirety. A suspension of Intermediate **5-A** (24.8 mg, 0.080 mmol), 1-(2,4-difluorophenyl)cyclopropanamine HCl salt (**5-B**, 21.9 mg, 0.107 mmol), and HATU (48 mg, 0.126 mmol) in CH_2Cl_2 (2 mL) was stirred at ambient temperature as N,N-diisopropylethylamine (DIPEA) (0.1 mL, 0.574 mmol) was added. After 30 minutes, the reaction mixture was diluted with ethyl acetate before washing with 10% aqueous citric acid solution (x1) and saturated aqueous $NaHCO_3$ solution (x1). After the aqueous fractions were extracted with ethyl acetate (x1), the organic fractions were combined, dried ($MgSO_4$), and concentrated. The residue was purified by combiflash (12 g column) using hexanes, ethyl acetate, and 20% methanol in ethyl acetate to obtain (4R,12aS)-N-(1-(2,4-difluorophenyl)cyclopropyl)-7-methoxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-[1,3]oxazino[3,2-d]pyrido[1,2-a]pyrazine-9-carboxamide, Intermediate **5-C**. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{23}H_{24}F_2N_3O_5$: 460.17; found 460.2.

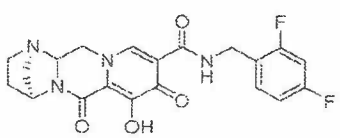
Step 2

A suspension of Intermediate **5-C** (39 mg, 0.080 mmol) and magnesium bromide (42 mg, 0.2282 mmol) in acetonitrile (2 mL) was stirred at 50 °C. After 1 hour, the reaction mixture was stirred at 0 °C bath when 1 N HCl (2 mL) was added. After the resulting mixture was diluted with water (~20 mL), the product was extracted with dichloromethane (x3) and the combined extracts were dried ($MgSO_4$) and concentrated. The residue was purified by preparative HPLC to obtain (4R,12aS)-N-(1-(2,4-difluorophenyl)cyclopropyl)-7-hydroxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-[1,3]oxazino[3,2-d]pyrido[1,2-a]pyrazine-9-carboxamide, compound **5**, as TFA salt. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.72 (br s, 1H), 8.37 (s, 1H), 7.57 (d, J = 7.9 Hz, 1H), 6.71-6.81 (m, 2H), 5.23 (dd, J = 5.6 and 4.4 Hz, 1H), 4.98 (br quint, J = ~6.5 Hz, 1H), 4.26 (dd, J = 13.6 and 4.4 Hz, 1H), 4.12 (dd, J = 13.6 and 5.6 Hz, 1H), 4.00-4.06 (m, 2H), 2.16-2.25 (m, 1H), 1.55 (br dd, J = 13.8 and 1.8 Hz, 1H), 1.40 (d, J = 6.8 Hz, 3H), 1.22-1.31 (m, 4H). **^{19}F NMR** (376.1 MHz, $CDCl_3$) δ -76.38 (s, 3F), -111.69 ~ -111.645 (m, 2F). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{22}F_2N_3O_5$: 446.15; found: 446.2.

Example 6

Preparation of Compound 6

(1R,4S)-N-(2,4-difluorobenzyl)-7-hydroxy-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-1,4-methanopyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide



6

Methyl 5-(2,4-difluorobenzylcarbamoyl)-1-(2,2-dihydroxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate (**1-C**, 0.100 g, 0.243 mmol), (S)-pyrrolidin-3-amine (0.043 mL, 0.485 mmol) and potassium carbonate (0.067 g, 0.485 mmol) were suspended in acetonitrile (1.9 mL) and acetic acid (0.1 mL) and heated to 90 °C for 1.5 hours. After cooling, the mixture was treated with magnesium bromide

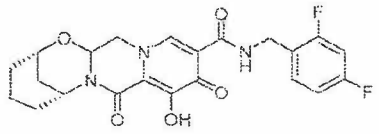
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(0.090 g) and heated to 50 °C for 30 minutes. After cooling, the mixture partitioned between dichloromethane and 0.2 M HCl. The organic layer was separated and the aqueous was extracted again with dichloromethane. The combined organic layers were dried over sodium sulfate (anhydrous), filtered and concentrated. Preparative HPLC purification (25-50% acetonitrile:water, 0.1% TFA) afforded Compound **6**. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 10.33 (t, J = 6.0 Hz, 1H), 8.44 (s, 1H), 7.48 – 7.32 (m, 1H), 7.31 – 7.15 (m, 1H), 7.14 – 6.97 (m, 1H), 4.86 (d, J = 2.9 Hz, 1H), 4.62 – 4.54 (m, 1H), 4.52 (d, J = 5.9 Hz, 1H), 4.01 (d, J = 13.0 Hz, 1H), 2.99 – 2.76 (m, 3H), 1.96 – 1.81 (m, 1H), 1.71 – 1.53 (m, 1H). **LCMS-ESI$^+$** (m/z): $[M+H]^+$ calculated for $C_{20}H_{19}F_2N_4O_4$: 417.14; found: 417.2.

Example 7

Preparation of Compound 7

(2S,6R)-N-(2,4-difluorobenzyl)-9-hydroxy-8,10-dioxo-3,4,5,6,8,10,14,14a-octahydro-2H-2,6-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazocine-11-carboxamide



7

Methyl 5-(2,4-difluorobenzylcarbamoyl)-1-(2,2-dihydroxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate (**1-C**, 0.050 g, 0.121 mmol), (1S,3R)-3-aminocyclohexanol (0.028 g, 0.243 mmol) and potassium carbonate (0.034 g, 0.243 mmol) were suspended in acetonitrile (0.95 mL) and heated to 90 °C for 0.5 hour. After cooling, acetic acid (0.050 mL) was added and the mixture was reheated to 90 °C for 2h. After cooling the mixture was treated with magnesium bromide (0.044 g) and heated to 50 °C for 1 hour. After cooling, a second portion of magnesium bromide (0.044 g) was added and the mixture was reheated to 50 °C for 15 minutes. After cooling, the mixture partitioned between dichloromethane and 0.2 M HCl. The organic layer was separated and the aqueous was extracted again with dichloromethane. The combined organic layers were dried over sodium sulfate (anhydrous), filtered and

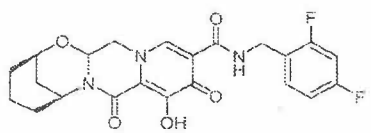
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concentrated. Preparative HPLC purification (40-80% acetonitrile:water, 0.1% TFA) afforded Compound 7. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.40 (s, 1H), 10.36 (t, J = 6.1 Hz, 1H), 8.45 (s, 1H), 7.48 – 7.29 (m, 1H), 7.31 – 7.13 (m, 1H), 7.13 – 6.97 (m, 1H), 5.56 (dd, J = 10.0, 4.1 Hz, 1H), 4.70 (dd, J = 12.7, 4.1 Hz, 1H), 4.52 (d, J = 5.5 Hz, 2H), 4.40 – 4.29 (m, 2H), 4.06 (dd, J = 12.5, 10.2 Hz, 1H), 2.46 – 2.36 (m, 1H), 1.98 – 1.63 (m, 4H), 1.57 – 1.30 (m, 3H). **LCMS-ESI$^+$** (*m/z*): [M+H]$^+$ calculated for $C_{22}H_{22}F_2N_3O_5$: 446.15; found: 446.2.

Example 8

Preparation of Compound **8**

(2R,6S)-N-(2,4-difluorobenzyl)-9-hydroxy-8,10-dioxo-3,4,5,6,8,10,14,14a-octahydro-2H-2,6-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazocine-11-carboxamide



8

Compound **8** was prepared in a similar manner to compound 7 using (1R,3S)-3-aminocyclohexanol in place of (1S,3R)-3-aminocyclohexanol. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.40 (s, 1H), 10.36 (t, J = 6.1 Hz, 1H), 8.45 (s, 1H), 7.48 – 7.30 (m, 1H), 7.23 (td, J = 10.6, 2.7 Hz, 1H), 7.05 (td, J = 8.3, 2.3 Hz, 1H), 5.56 (dd, J = 10.1, 4.1 Hz, 1H), 4.70 (dd, J = 12.8, 3.9 Hz, 1H), 4.52 (d, J = 5.6 Hz, 2H), 4.39 – 4.27 (m, 2H), 4.06 (dd, J = 12.6, 10.0 Hz, 1H), 2.47 – 2.35 (m, 1H), 2.00 – 1.64 (m, 4H), 1.58 – 1.30 (m, 3H). **LCMS-ESI$^+$** (*m/z*): [M+H]$^+$ calculated for $C_{22}H_{22}F_2N_3O_5$: 446.15; found: 446.2.

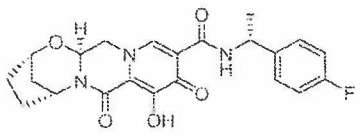
Examples 9 and 10

Preparation of Compounds **9** and **10**

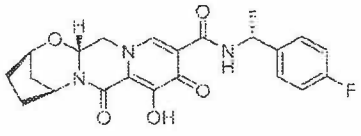
(2S,5R,13aS)-N-((R)-1-(4-fluorophenyl)ethyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide **9** and (2R,5S,13aR)-N-((R)-1-(4-fluorophenyl)ethyl)-8-hydroxy-7,9-dioxo-

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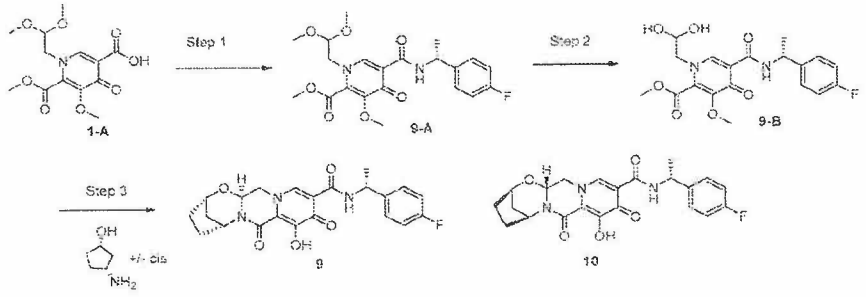
2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide **10**



9



10



Step 1

1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (**1-A**, 0.500 g, 1.59 mmol), was suspended in acetonitrile (6 mL) and treated with N,N-diisopropylethylamine (DIPEA) (0.550 mL, 3.17 mmol), (R)-1-(4-fluorophenyl)ethanamine (0.242 mg, 1.74 mmol) and HATU (0.661 g, 1.74 mmol). The reaction mixture was stirred for 2 hours and partitioned between ethyl acetate and water. The organic layer was separated and washed with HCl (10% aq), sodium bicarbonate (1M aq), dried over sodium sulfate, filtered and concentrated to afford crude (R)-methyl 1-(2,2-dimethoxyethyl)-5-(1-(4-fluorophenyl)ethylcarbamoyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate which was used without purification in the next step: **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{26}FN_2O_7$: 437.17; found: 437.1.

Step 2

(R)-methyl 1-(2,2-dimethoxyethyl)-5-(1-(4-fluorophenyl)ethylcarbamoyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate

was suspended in acetonitrile (5.7 mL) and acetic acid (0.6 mL) and treated with methane sulfonic acid (0.031 mL, 0.477 mmol). The mixture was capped and heated to 75 °C. After 7h, the mixture was cooled and used without purification in the next step: **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{19}H_{22}FN_2O_7$: 409.14; found: 409.0.

Step 3

(R)-methyl 1-(2,2-dihydroxyethyl)-5-(1-(4-fluorophenyl)ethylcarbamoyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate (3.6 mL of the crude mixture from Step 2, 0.8 mmol) was diluted with acetonitrile (3.6 mL) and treated with *cis*-3-aminocyclpentanol, HCl salt (0.219 g, 1.6 mmol) and potassium carbonate (0.276 g, 2.0 mmol). The mixture was capped and heated to 90 °C. After 20 minutes, the reaction mixture was cooled and partitioned between dichloromethane and HCl (0.2 M aq). The layers were separated and the aqueous layer was extracted again with dichloromethane. The combined organic layers were treated with a small amount of acetonitrile, dried over sodium sulfate, filtered and concentrated.

The residue was suspended in acetonitrile (4 mL) and treated with magnesium bromide (0.177 g). The mixture was capped and heated to 50 °C. After 10 minutes, the reaction mixture was cooled and partitioned between dichloromethane and HCl (0.2 M aq). The layers were separated and the aqueous layer was extracted again with dichlormethane. The combined organic layers were dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel (0-8% ethanol:DCM) to afford a diastereomeric mixture of desired **9** and **10**.

The mixture was separated by chiral HPLC using Chiralpak AD-H with 100% ethanol as eluent to afford Compounds **9** and **10** in enantiomerically enriched form:

For Compound **9**: **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{23}FN_3O_5$: 428.16; found: 428.1. **Chiral HPLC** retention time = 10.177 minutes (Chiralpak AD-H, 150 x 4.6 mm, 1 mL/min EtOH). **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.45 (s, 1H), 10.45 (d, J = 7.7 Hz, 1H), 8.40 (s, 1H), 7.37 (dd, J = 8.6, 5.6 Hz, 2H), 7.15 (t, J = 8.9 Hz, 2H), 5.44 (dd, J = 9.5, 4.2 Hz, 1H), 5.17 – 5.04 (m, 2H), 4.73 – 4.62

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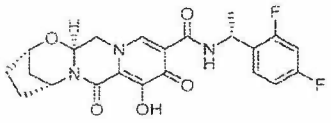
(m, 1H), 4.59 (s, 1H), 4.00 (dd, J = 12.7, 9.5 Hz, 1H), 1.93 (s, 4H), 1.83 (d, J = 11.8 Hz, 1H), 1.56 (dt, J = 12.1, 3.4 Hz, 1H), 1.44 (d, J = 6.9 Hz, 3H).

For Compound **10**: **LCMS-ESI**$^+$ (m/z): $[M+H]^+$ calculated for $C_{22}H_{23}FN_3O_5$: 428.16; found: 428.1. **Chiral HPLC** retention time = 14.061 minutes (Chiralpak AD-H, 150 x 4.6 mm, 1 mL/min EtOH). **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.44 (s, 1H), 10.46 (d, J = 7.8 Hz, 1H), 8.41 (s, 1H), 7.37 (dd, J = 8.6, 5.6 Hz, 2H), 7.15 (t, J = 8.9 Hz, 2H), 5.42 (dd, J = 9.6, 4.1 Hz, 1H), 5.18 – 5.02 (m, 2H), 4.67 (dd, J = 12.8, 4.2 Hz, 1H), 4.59 (s, 1H), 4.02 (dd, J = 12.7, 9.6 Hz, 1H), 1.93 (s, 4H), 1.83 (d, J = 12.0 Hz, 1H), 1.57 (dt, J = 13.0, 3.5 Hz, 1H), 1.44 (d, J = 6.9 Hz, 3H).

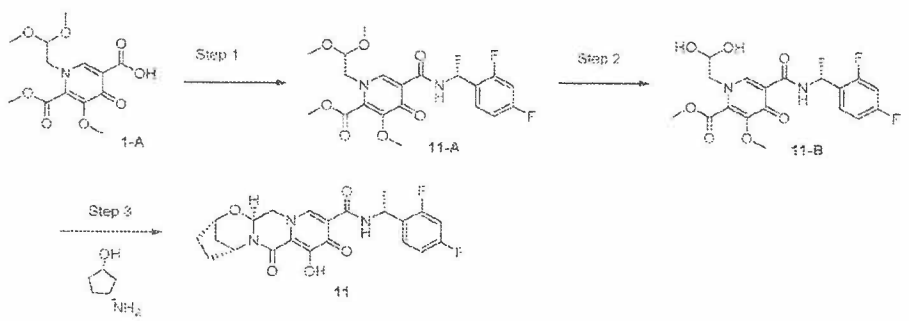
Example 11

Preparation of Compound **11**

(2S,5R,13aS)-N-((R)-1-(2,4-difluorophenyl)ethyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



11



Step 1

1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (**1-A**, 0.315 g, 1.00 mmol), was suspended in acetonitrile (4 mL) and treated with N,N-diisopropylethylamine (DIPEA) (0.348 mL, 2.00 mmol), (R)-1-(2,4-difluorophenyl)ethanamine HCl salt (0.213 mg, 1.10 mmol) and HATU (0.418 g, 1.10 mmol). The reaction mixture was stirred for 1 hour and partitioned between dichloromethane and HCl (10% aq). The organic layer was separated and washed sodium bicarbonate (1M aq), dried over sodium sulfate, filtered and concentrated to afford crude (R)-methyl 5-(1-(2,4-difluorophenyl)ethylcarbamoyl)-1-(2,2-dimethoxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate which was used without purification in the next step. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{25}F_2N_2O_7$: 455.16; found: 455.1.

Step 2

(R)-methyl 5-(1-(2,4-difluorophenyl)ethylcarbamoyl)-1-(2,2-dimethoxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate was suspended in acetonitrile (3.6 mL) and acetic acid (0.4 mL) and treated with methane sulfonic acid (0.020 mL). The mixture was capped and heated to 75 °C. After 16 hours, the crude mixture was cooled and used without purification in the next step. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{19}H_{21}F_2N_2O_5$: 427.13; found: 427.1.

Step 3

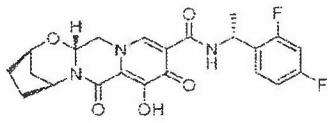
(R)-methyl 5-(1-(2,4-difluorophenyl)ethylcarbamoyl)-1-(2,2-dihydroxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate (half of the crude

mixture from Step 2, approx 0.5 mmol) was diluted with acetonitrile (2.5 mL) and treated with (1S,3R)-3-aminocyclopentanol (0.110 g, 1.09 mmol) and potassium carbonate (0.069 g, 0.50 mmol). The mixture was capped and heated to 90 °C. After 15 minutes, the reaction mixture was cooled and magnesium bromide (0.184 g) was added. The reaction mixture was heated to 50 °C. After 10 minutes, the mixture was cooled and treated with an additional portion of magnesium bromide (0.184 g). The reaction mixture was reheated to 50 °C and stirred for 10 minutes. After cooling, the mixture was partitioned between dichloromethane and HCl (0.2 M aq). The layers were separated and the aqueous layer was extracted again with dichloromethane. The combined organic layers were dried over sodium sulfate, filtered and concentrated. Preparative HPLC purification (30-60% acetonitrile:water, 0.1% TFA) afforded desired Compound **11**. **LCMS-ESI**$^+$ (*m/z*): [M+H]$^+$ calculated for $C_{22}H_{22}F_2N_3O_5$: 446.15; found: 446.1. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.46 (s, 1H), 10.53 (d, J = 7.5 Hz, 1H), 8.38 (s, 1H), 7.39 (q, J = 8.5 Hz, 1H), 7.29 – 7.12 (m, 1H), 7.13 – 6.93 (m, 1H), 5.44 (dd, J = 9.8, 4.2 Hz, 1H), 5.28 (p, J = 7.3, 6.8 Hz, 1H), 5.09 (s, 1H), 4.66 (dd, J = 13.2, 4.3 Hz, 1H), 4.59 (s, 1H), 3.99 (dd, J = 13.1, 9.6 Hz, 1H), 1.93 (s, 4H), 1.83 (d, J = 12.4 Hz, 1H), 1.56 (dt, J = 12.5, 2.9 Hz, 1H), 1.45 (d, J = 6.9 Hz, 3H).

Example 12

Preparation of Compound **12**

(2R,5S,13aR)-N-((R)-1-(2,4-difluorophenyl)ethyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



12

Compound **12** was prepared in a similar manner to compound **11** using (1R,3S)-3-aminocyclopentanol in place of (1S,3R)-3-aminocyclopentanol. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.43 (s, 1H), 10.52 (d, J = 8.2 Hz, 1H), 8.38 (s, 1H), 7.39 (q,

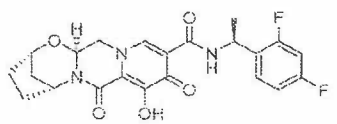
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J = 8.4 Hz, 1H), 7.28 – 7.12 (m, 1H), 7.11 – 6.97 (m, 1H), 5.41 (dd, J = 10.0, 4.0 Hz, 1H), 5.35 – 5.20 (m, 1H), 5.08 (s, 1H), 4.65 (dd, J = 13.1, 3.8 Hz, 1H), 4.58 (s, 1H), 4.01 (dd, J = 12.8, 9.5 Hz, 1H), 1.92 (s, 4H), 1.83 (d, J = 11.5 Hz, 1H), 1.61 – 1.51 (m, 1H), 1.44 (d, J = 6.9 Hz, 3H). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{22}F_2N_3O_5$: 446.15; found: 446.1.

Example 13

Preparation of Compound **13**

(2S,5R,13aS)-N-((S)-1-(2,4-difluorophenyl)ethyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



13

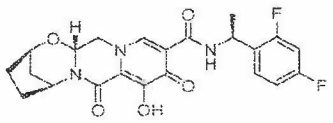
Compound **13** was prepared in a similar manner to compound **11** using (S)-1-(2,4-difluorophenyl)ethanamine in place of (R)-1-(2,4-difluorophenyl)ethanamine, and using only a single portion of magnesium bromide (0.184 g). **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.44 (s, 1H), 10.53 (d, J = 7.8 Hz, 1H), 8.39 (s, 1H), 7.39 (q, J = 8.5 Hz, 1H), 7.32 – 7.14 (m, 1H), 7.05 (t, J = 9.1 Hz, 1H), 5.42 (dd, J = 9.5, 4.2 Hz, 1H), 5.29 (p, J = 6.9 Hz, 1H), 5.09 (s, 1H), 4.65 (dd, J = 12.9, 4.3 Hz, 1H), 4.59 (s, 1H), 4.02 (dd, J = 12.6, 9.8 Hz, 1H), 1.92 (s, 4H), 1.83 (d, J = 12.1 Hz, 1H), 1.61 – 1.52 (m, 1H), 1.44 (d, J = 6.9 Hz, 3H). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{22}F_2N_3O_5$: 446.15; found: 446.2.

Example 14

Preparation of Compound **14**

(2R,5S,13aR)-N-((S)-1-(2,4-difluorophenyl)ethyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide

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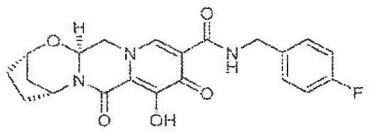
14

Compound **14** was prepared in a similar manner to compound **11** using (S)-1-(2,4-difluorophenyl)ethanamine in place of (R)-1-(2,4-difluorophenyl)ethanamine and using (1R,3S)-3-aminocyclopentanol in place of (1S,3R)-3-aminocyclopentanol. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.46 (s, 1H), 10.53 (d, J = 7.6 Hz, 1H), 8.38 (s, 1H), 7.39 (q, J = 8.6 Hz, 1H), 7.28 – 7.14 (m, 1H), 7.05 (t, J = 8.5 Hz, 1H), 5.44 (dd, J = 9.8, 3.8 Hz, 1H), 5.28 (p, J = 8.0 Hz, 1H), 5.09 (s, 1H), 4.66 (dd, J = 12.9, 4.0 Hz, 1H), 4.59 (s, 1H), 3.99 (dd, J = 12.5, 9.6 Hz, 1H), 1.93 (s, 4H), 1.83 (d, J = 12.6 Hz, 1H), 1.56 (dt, J = 13.0, 3.3 Hz, 1H), 1.45 (d, J = 6.9 Hz, 3H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{23}H_{22}F_2N_2O_5$: 446.15; found: 446.1.

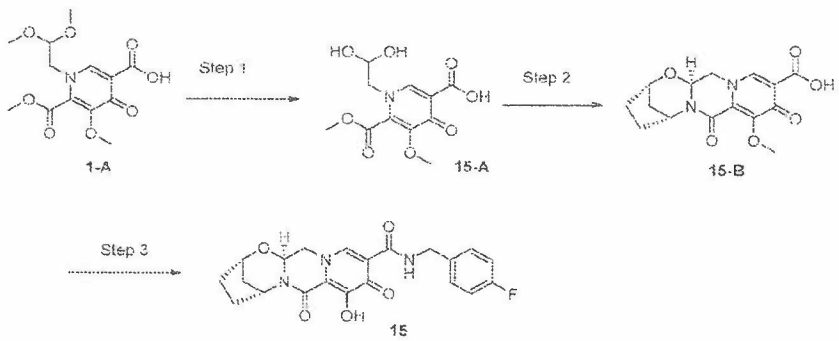
Example 15

Preparation of Compound **15**

(2S,5R,13aS)-N-(4-fluorobenzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



15



Step 1

1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (**1-A**, 3.15 g, 10.0 mmol), suspended in acetonitrile (36 mL) and acetic acid (4 mL) was treated with methane sulfonic acid (0.195 mL). The mixture heated to 75 °C. After 7 hours, the crude mixture was cooled and stored in a -10°C for three days. The crude mixture was reheated to 75 °C for 2 hours, cooled used without purification in the next step. **LCMS-ESI**$^+$ (*m/z*): [M+H]$^+$ calculated for $C_{19}H_{21}F_2N_2O_7$: 288.07; found: 288.1.

Step 2

Crude 1-(2,2-dihydroxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (16.8 mL of crude mixture from Step 1, approx 4 mmol) was combined with (1S,3R)-3-aminocyclopentanol (0.809 g, 8 mmol), diluted with acetonitrile (16.8 mL), and treated with potassium carbonate (0.553 g, 4 mmol). The reaction mixture was heated to 85 °C, stirred for 15 minutes, cooled to ambient temperature and stirred an additional 16 hours. HCl (50 mL, 0.2M aq) was added and the clear yellow solution was extracted three times with dichloromethane. The combined organics were dried over sodium sulfate, filtered and concentrated to a yellow solid. This crude material was precipitated from dichloromethane/hexanes to afford desired intermediate **15-B** as a light beige powder. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 8.72 (s, 1H), 5.42 (dd, J = 9.6, 4.1 Hz, 1H), 5.09 (s, 1H), 4.72 (dd, J = 13.0, 3.7 Hz, 1H), 4.57 (s, 1H), 4.09 (dd, J = 12.5, 9.6 Hz, 1H), 3.83 (s, 3H), 1.92 (s, 3H), 1.78

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(m, 2H), 1.62 – 1.47 (m, 1H). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{15}H_{17}N_2O_6$: 321.11; found: 321.2.

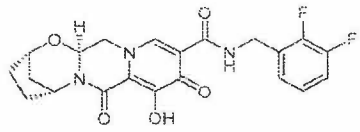
Step 3

Intermediate **15-B** (0.040 g, 0.125 mmol) and (4-fluorophenyl)methanamine (0.017 g, 0.137 mmol) were suspended in acetonitrile (1 mL) and treated with N,N-diisopropylethylamine (DIPEA) (0.033 mL, 0.187 mmol) and HATU (0.052 g, 0.137 mmol). After stirring for 30 minutes, the reaction mixture was treated with magnesium bromide (0.046 g, 0.25 mmol) and heated to 50 °C. After 10 minutes, the reaction mixture was cooled and treated with HCl (2 mL, 10% aq). After a few minutes, the precipitate was filtered and washed with HCl (10% aq) and water. Preparative HPLC purification of the precipitate (20-65% acetonitrile:water, 0.1% TFA) afforded desired Compound **15**. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.44 (s, 1H), 10.36 (t, J = 6.0 Hz, 1H), 8.46 (s, 1H), 7.37 – 7.28 (m, 2H), 7.19 – 7.09 (m, 2H), 5.43 (dd, J = 9.6, 4.0 Hz, 1H), 5.08 (s, 1H), 4.68 (dd, J = 12.8, 4.1 Hz, 1H), 4.59 (s, 1H), 4.58 – 4.42 (m, 3H), 4.02 (dd, J = 12.7, 9.6 Hz, 1H), 1.92 (s, 5H), 1.83 (d, J = 12.2 Hz, 1H), 1.56 (dt, J = 12.0, 3.4 Hz, 1H). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{21}FN_3O_5$: 414.15; found: 414.2.

Example 16

Preparation of Compound **16**

(2S,5R,13aS)-N-(2,3-difluorobenzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



16

Compound **16** was prepared in a similar manner to compound **15** using (2,3-difluorophenyl)methanamine in place of (4-fluorophenyl)methanamine. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.46 (s, 1H), 10.41 (t, J = 6.1 Hz, 1H), 8.45 (s, 1H), 7.43 –

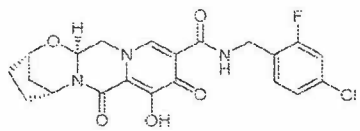
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7.25 (m, 1H), 7.25 – 7.05 (m, 2H), 5.44 (dd, J = 9.5, 3.9 Hz, 1H), 5.09 (s, 1H), 4.68 (dd, J = 12.8, 4.0 Hz, 1H), 4.65 – 4.53 (m, 3H), 4.02 (dd, J = 12.7, 9.8 Hz, 1H), 3.56 (s, 1H), 1.93 (s, 4H), 1.83 (d, J = 11.9 Hz, 1H), 1.57 (dt, J = 11.5, 3.0 Hz, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}F_2N_3O_5$: 432.14; found: 432.2.

Example 17

Preparation of Compound **17**

(2S,5R,13aS)-N-(4-chloro-2-fluorobenzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



17

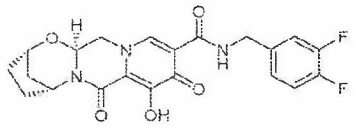
Compound **17** was prepared in a similar manner to compound **15** using (4-chloro-2-fluorophenyl)methanamine in place of (4-fluorophenyl)methanamine. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.46 (s, 1H), 10.45 – 10.29 (m, 1H), 8.44 (s, 1H), 7.42 (dd, J = 10.0, 2.0 Hz, 1H), 7.33 (t, J = 8.1 Hz, 1H), 7.26 (dd, J = 8.4, 1.8 Hz, 1H), 5.50 – 5.38 (m, 1H), 5.09 (s, 1H), 4.68 (dd, J = 13.0, 4.0 Hz, 1H), 4.59 (s, 1H), 4.54 (m, 2H), 4.02 (dd, J = 12.8, 9.7 Hz, 1H), 1.93 (s, 4H), 1.83 (d, J = 12.0 Hz, 1H), 1.57 (dt, J = 11.9, 3.4 Hz, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}ClFN_3O_5$: 448.11; found: 448.2.

Example 18

Preparation of Compound **18**

(2S,5R,13aS)-N-(3,4-difluorobenzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide

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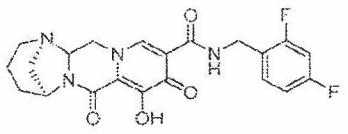
18

Compound **18** was prepared in a similar manner to compound **15** using (3,4-difluorophenyl)methanamine in place of (4-fluorophenyl)methanamine. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.46 (s, 1H), 10.51 – 10.27 (m, 1H), 8.46 (s, 1H), 7.50 – 7.23 (m, 2H), 7.23 – 7.03 (m, 1H), 5.44 (dd, J = 9.5, 3.6 Hz, 1H), 5.09 (s, 1H), 4.75 – 4.63 (m, 1H), 4.60 (s, 1H), 4.57 – 4.44 (m, 2H), 4.02 (dd, J = 12.6, 9.8 Hz, 1H), 1.93 (s, 4H), 1.83 (d, J = 12.0 Hz, 1H), 1.57 (dt, J = 12.0, 3.4 Hz, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}F_2N_3O_5$: 432.14; found: 432.2.

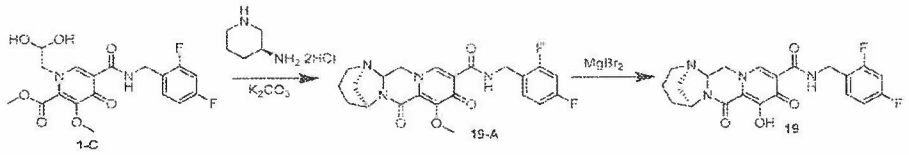
Example 19

Preparation of Compound **19**

(1R,5S)-N-(2,4-difluorobenzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-1,5-methanopyrido[1',2':4,5]pyrazino[1,2-a][1,3]diazepine-10-carboxamide



19



Steps 1 and 2

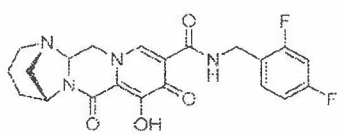
Methyl 5-(2,4-difluorobenzylcarbamoyl)-1-(2,2-dihydroxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate (**1-C**, 97.5 mg, 0.236 mmol) was treated with acetonitrile (1.9 mL), acetic acid (0.1 mL), potassium carbonate (145 mg,

1.05 mmol), and (S)-piperidin-3-amine dihydrochloride (82 mg, 0.472 mmol). The reaction mixture was sealed and heated to 90 °C. After 60 minutes, the reaction mixture was cooled partitioned between brine and dichloromethane. The aqueous phase was thrice extracted into dichloromethane and the combined organic phases were combined, dried over MgSO4, filtered, concentrated. The crude product was dissolved into acetonitrile (2 mL) and magnesium bromide (89.1 mg, 0.48 mmol) was added. The mixture was resealed and heated to 50 °C. After 90 minutes, the reaction mixture was quenched with ~5 mL of 0.2M HCl(aq), the pH adjusted to ~10, diluted with brine, and thrice extracted into DCM. HPLC purification (Acetonitrile:water, 0.1% TFA) afforded Compound **19**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 10.43 (t, J = 5.9 Hz, 1H), 8.43 (s, 1H), 7.39 – 7.30 (m, 1H), 6.81 (q, J = 8.1 Hz, 2H), 4.89 (dd, J = 11.6, 3.8 Hz, 1H), 4.69 (s, 1H), 4.64 (d, J = 5.8 Hz, 2H), 4.26 (dd, J = 12.6, 3.8 Hz, 1H), 3.91 (t, J = 12.1 Hz, 1H), 3.20 – 3.10 (m, 2H), 3.06 (s, 2H), 2.14 – 2.02 (m, 1H), 1.96 – 1.81 (m, 2H), 1.81 – 1.70 (m, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}F_2N_4O_4$: 431.15; found: 431.2.

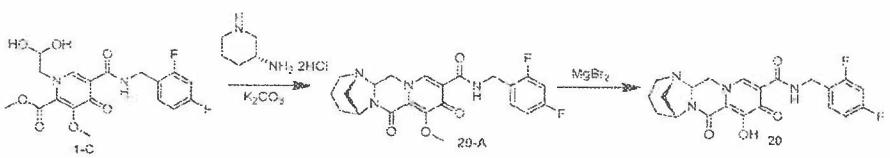
Example 20

Preparation of Compound **20**

(1S,5R)-N-(2,4-difluorobenzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-1,5-methanopyrido[1',2':4,5]pyrazino[1,2-a][1,3]diazepine-10-carboxamide



20



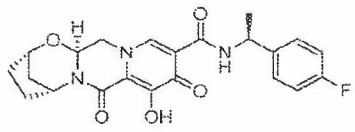
Steps 1 and 2

Methyl 5-(2,4-difluorobenzylcarbamoyl)-1-(2,2-dihydroxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate (**1-C**, 103.3 mg, 0.25 mmol) was treated with acetonitrile (1.9 mL), acetic acid (0.1 mL), potassium carbonate (159.8 mg, 1.16 mmol), and (R)-piperidin-3-amine dihydrochloride (90 mg, 0.52 mmol). The reaction mixture was sealed and heated to 90 °C. After 40 minutes, the reaction mixture was cooled partitioned between brine and dichloromethane. The aqueous phase was thrice extracted into dichloromethane and the combined organic phases were combined, dried over $MgSO_4$, filtered, concentrated. The crude product was dissolved into acetonitrile (2 mL) and magnesium bromide (96.5 mg, 0.52 mmol) was added. The mixture was resealed and heated to 50 °C. After 80 minutes, the reaction mixture was quenched with ~5 mL of 0.2M HCl (aq), the pH adjusted to ~10, diluted with brine, and thrice extracted into DCM. HPLC purification (Acetonitrile:water, 0.1% TFA) afforded Compound **20**. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 10.35 (t, J = 6.0 Hz, 1H), 8.48 (s, 1H), 7.45 – 7.33 (m, 1H), 7.29 – 7.18 (m, 1H), 7.05 (td, J = 8.5, 2.4 Hz, 1H), 5.06 (dd, J = 11.4, 3.5 Hz, 1H), 4.56 – 4.47 (m, 3H), 4.44 (s, 1H), 4.05 (t, J = 11.8 Hz, 1H), 3.07 – 2.89 (m, 4H), 1.85 – 1.73 (m, 3H), 1.54 – 1.46 (m, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}F_2N_4O_4$: 431.15; found: 431.2.

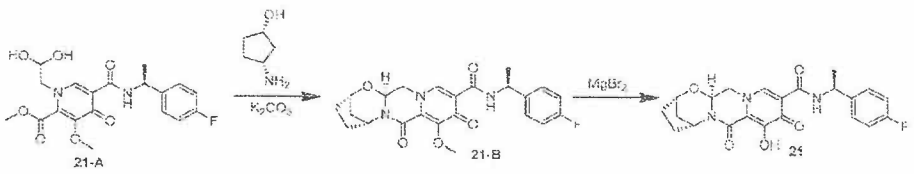
Example 21

Preparation of Compound **21**

(2S,5R,13aS)-N-((S)-1-(4-fluorophenyl)ethyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



21



Steps 1 and 2

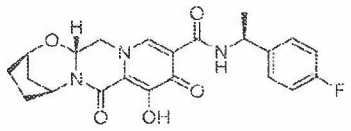
(S)-Methyl 1-(2,2-dihydroxyethyl)-5-(1-(4-fluorophenyl)ethylcarbamoyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate (**21-A**, 1 mL, 0.23 M solution in 19:1 acetonitrile:acetic acid, prepared as per (R)-methyl 1-(2,2-dihydroxyethyl)-5-(1-(4-fluorophenyl)ethylcarbamoyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate **9-A** from Example 9 using (S)-1-(4-fluorophenyl)ethanamine in place of (R)-1-(4-fluorophenyl)ethanamine) was treated with (1S,3R)-3-aminocyclopentanol (62 mg, 0.61 mmol) and potassium carbonate (34 mg, 0.25 mmol). The reaction mixture was sealed and heated to 90 °C. After 60 minutes, the reaction mixture was cooled partitioned between brine and dichloromethane. The aqueous phase was thrice extracted into dichloromethane and the combined organic phases were combined, dried over $MgSO_4$, filtered, and concentrated. The crude product was dissolved into acetonitrile (2 mL) and magnesium bromide (74 mg, 0.4 mmol) was added. The mixture was rescaled and heated to 50 °C. After 100 minutes, the reaction mixture was quenched with 0.2M HCl (aq), diluted with brine, and thrice extracted into DCM. HPLC purification (acetonitrile:water, 0.1% TFA) afforded Compound **21**. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.42 (br s, 1H), 10.45 (d, J = 7.9 Hz, 1H), 8.40 (s, 1H), 7.36 (dd, J = 8.6, 5.5 Hz, 2H), 7.14 (t, J = 8.9 Hz, 2H), 5.42 (dd, J = 9.6, 4.2 Hz, 1H), 5.15 – 5.04 (m, 2H), 4.72 – 4.55 (m, 2H), 4.02 (dd, J = 12.7, 9.7 Hz, 1H), 1.97 – 1.89 (m, 4H), 1.82 (d, J = 12.2 Hz, 1H), 1.56 (dt, J = 11.9, 3.3 Hz, 1H), 1.43 (d, J = 6.9 Hz, 3H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{22}FN_3O_5$: 428.16; found: 428.1.

Example 22

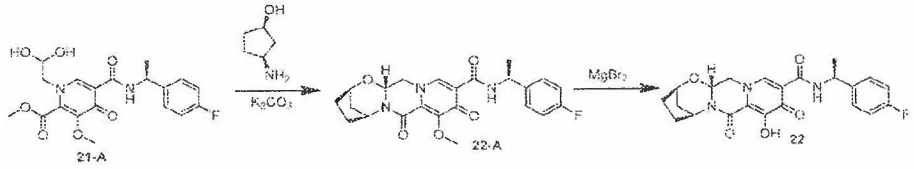
Preparation of Compound 22

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(2R,5S,13aR)-N-((S)-1-(4-fluorophenyl)ethyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



22



21-A 22-A 22

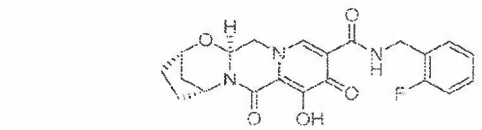
Steps 1 and 2

(S)-methyl 1-(2,2-dihydroxyethyl)-5-(1-(4-fluorophenyl)ethylcarbamoyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate (**21-A**, 1 mL, 0.23 M solution in 19:1 acetonitrile:acetic acid) was treated with (1R,3S)-3-aminocyclopentanol (52 mg, 0.51 mmol) and potassium carbonate (31 mg, 0.22 mmol). The reaction mixture was sealed and heated to 90 °C. After 60 minutes, the reaction mixture was cooled partitioned between brine and dichloromethane. The aqueous phase was thrice extracted into dichloromethane and the combined organic phases were combined, dried over $MgSO_4$, filtered, and concentrated. The crude product was dissolved into acetonitrile (2 mL) and magnesium bromide (91 mg, 0.49 mmol) was added. The mixture was resealed and heated to 50 °C. After 100 minutes, the reaction mixture was quenched with 0.2M HCl(aq), diluted with brine, and thrice extracted into DCM. HPLC purification (acetonitrile:water, 0.1% TFA) afforded Compound **22**. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.44 (br s, 1H), 10.45 (d, J = 7.7 Hz, 1H), 8.39 (s, 1H), 7.36 (dd, J = 8.5, 5.6 Hz, 2H), 7.14 (t, J = 8.9 Hz, 2H), 5.43 (dd, J = 9.6, 4.0 Hz, 1H), 5.15 – 5.06 (m, 2H), 4.66 (dd, J = 12.8, 3.9 Hz, 1H), 4.58 (s, 1H), 3.99 (dd, J = 12.6, 9.5 Hz, 1H), 1.93 (s, 4H), 1.82 (d, J = 12.0 Hz, 1H), 1.56 (dt, J = 12.0, 3.0 Hz, 1H), 1.44 (d, J = 6.9 Hz, 3H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{22}FN_3O_5$: 428.16; found: 428.1.

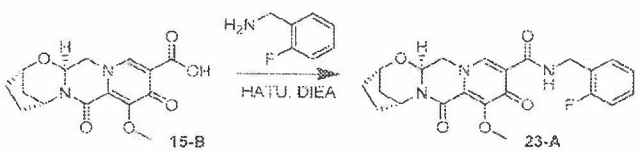
Example 23

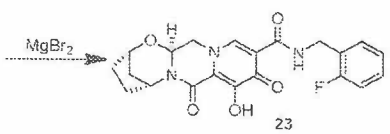
Preparation of Compound 23

(2S,5R,13aS)-N-(2-fluorobenzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



23





Steps 1 and 2

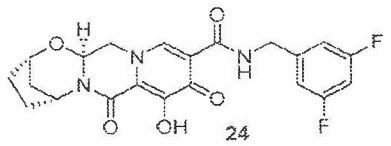
15-B (41 mg, 0.13 mmol) was treated with acetonitrile (1 mL), (2-fluorophenyl)methanamine (17 mg, 0.14 mmol), HATU (67 mg, 0.18 mmol), and N,N-diisopropylethylamine (DIPEA) (24 mg, 0.19 mmol). The reaction mixture was stirred at room temperature for one hour and magnesium bromide (47 mg, 0.26 mmol) was added. The mixture was sealed and heated to 50 °C. After 60 minutes, the reaction mixture was quenched with 0.2M HCl (aq), diluted with brine, and thrice extracted into DCM. HPLC purification (Acetonitrile:water, 0.1% TFA) afforded Compound **23**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 10.42 (s, 1H), 8.34 (s, 1H), 7.36 (t, J = 7.9 Hz, 1H), 7.24 – 7.17 (m, 1H), 7.12 – 6.97 (m, 2H), 5.40 – 5.32 (m, 1H), 5.29 (t, J = 3.5 Hz, 1H), 4.67 (s, 3H), 4.28 – 4.20 (m, 1H), 4.06 – 3.95 (m, 1H), 2.20 – 1.96 (m, 4H), 1.95 – 1.84 (m, 1H), 1.59 (dt, J = 12.4, 3.3 Hz, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}FN_3O_5$: 414.15; found: 414.2.

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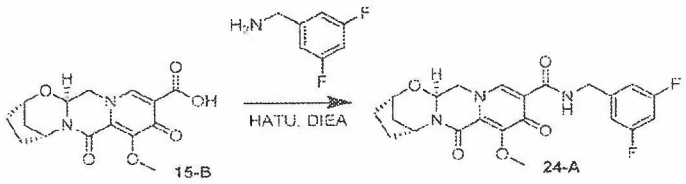
Example 24

Preparation of Compound **24**

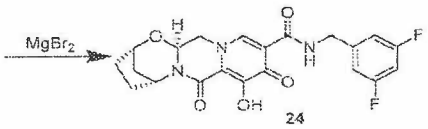
(2S,5R,13aS)-N-(3,5-difluorobenzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



24



15-B **24-A**



24

Steps 1 and 2

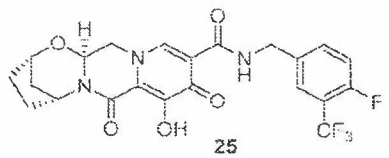
15-B (44 mg, 0.14 mmol) was treated with acetonitrile (1 mL), (3,5-difluorophenyl)methanamine (32 mg, 0.23 mmol), HATU (54 mg, 0.14 mmol), and N,N-diisopropylethylamine (37 mg, 0.29 mmol). The reaction mixture was stirred at room temperature for one hour and magnesium bromide (57 mg, 0.31 mmol) was added. The mixture was sealed and heated to 50 °C. After 60 minutes, the reaction mixture was quenched with 0.2M HCl (aq), diluted with brine, and thrice extracted into DCM. HPLC purification (Acetonitrile:water, 0.1% TFA) afforded Compound **24.** **^{1}H-NMR** (400 MHz, Chloroform-d) δ 10.39 (s, 1H), 8.42 (s, 1H), 6.82 (d, J = 7.9 Hz, 2H), 6.65 (t, J = 8.8 Hz, 1H), 5.38 (d, J = 7.7 Hz, 1H), 5.28 (s, 1H), 4.78 – 4.41 (m, 3H), 4.32 (d, J = 12.1 Hz, 1H), 4.02 (t, J = 10.9 Hz, 1H), 2.30 – 1.97 (m, 4H), 1.97 – 1.81 (m,

1H), 1.59 (d, J = 12.3 Hz, 1H). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{19}F_4N_3O_5$: 432.14; found: 432.2.

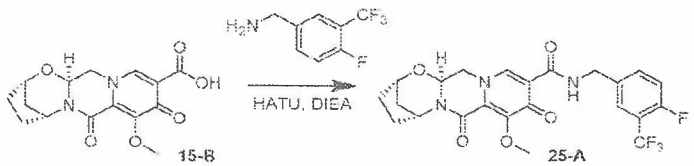
Example 25

Preparation of Compound **25**

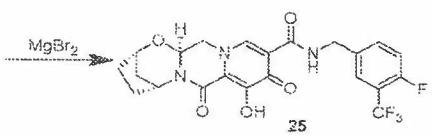
(2S,5R,13aS)-N-(4-fluoro-3-(trifluoromethyl)benzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



25



15-B **25-A**



25

Steps 1 and 2

15-B (43 mg, 0.13 mmol) was treated with acetonitrile (1 mL), (4-fluoro-3-(trifluoromethyl)phenyl)methanamine (29 mg, 0.15 mmol), HATU (62 mg, 0.16 mmol), and N,N-diisopropylethylamine (26 mg, 0.20 mmol). The reaction mixture was stirred at room temperature for one hour and magnesium bromide (62 mg, 0.34 mmol) was added. The mixture was sealed and heated to 50 °C. After 60 minutes, the reaction mixture was quenched with 0.2M HCl(aq), diluted with brine, and thrice extracted into DCM. HPLC purification (Acetonitrile:water, 0.1% TFA) afforded Compound **25**. ^{1}**H-**

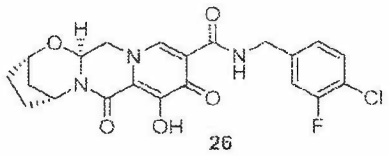
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NMR (400 MHz, Chloroform-d) δ 10.44 (s, 1H), 8.29 (s, 1H), 7.56 – 7.38 (m, 2H), 7.06 (t, J = 9.2 Hz, 1H), 5.30 (dd, J = 9.3, 3.5 Hz, 1H), 5.21 (s, 1H), 4.65 – 4.45 (m, 3H), 4.21 (dd, J = 12.8, 3.4 Hz, 1H), 3.95 (dd, J = 12.4, 9.7 Hz, 1H), 2.11 – 1.89 (m, 4H), 1.89 – 1.74 (m, 1H), 1.53 (dt, J = 12.4, 3.2 Hz, 1H). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{19}F_2N_3O_5$: 482.14; found: 482.2.

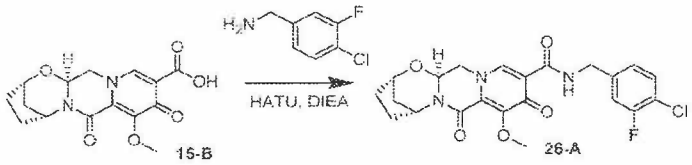
Example 26

Preparation of Compound **26**

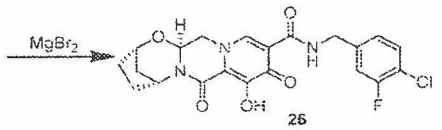
(2S,5R,13aS)-N-(4-chloro-3-fluorobenzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



26



15-B **26-A**



26

Steps 1 and 2

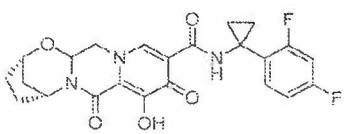
15-B (41 mg, 0.13 mmol) was treated with acetonitrile (1 mL), (4-chloro-3-fluorophenyl)methanamine (40 mg, 0.25 mmol), HATU (60 mg, 0.16 mmol), and N,N-diisopropylethylamine (28 mg, 0.22 mmol). The reaction mixture was stirred at room temperature for one hour and magnesium bromide (48 mg, 0.26 mmol) was added. The mixture was sealed and heated to 50 °C. After 60 minutes, the reaction mixture was quenched with 0.2M HCl (aq), diluted with brine, and thrice extracted into

DCM. HPLC purification (Acetonitrile:water, 0.1% TFA) afforded Compound **26**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 10.41 (s, 1H), 8.30 (s, 1H), 7.24 (t, J = 6.1 Hz, 1H), 7.13 – 6.90 (m, 2H), 5.30 (dd, J = 9.1, 3.2 Hz, 1H), 5.22 (s, 1H), 4.61 (s, 1H), 4.51 (s, 2H), 4.20 (d, J = 9.4 Hz, 1H), 3.95 (d, J = 12.0 Hz, 1H), 2.11 – 1.90 (m, 4H), 1.90 – 1.76 (m, 1H), 1.53 (d, J = 12.2 Hz, 1H). **LCMS-ESI$^+$** (*m/z*): [M+H]$^+$ calculated for $C_{21}H_{19}ClFN_3O_5$: 448.11; found: 448.2.

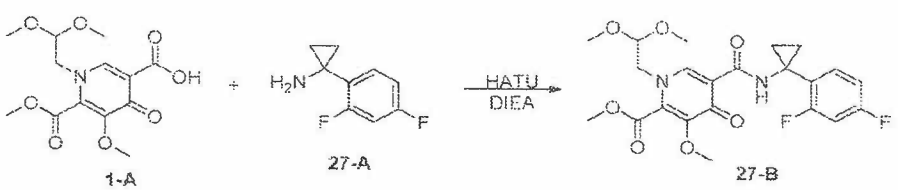
Example 27

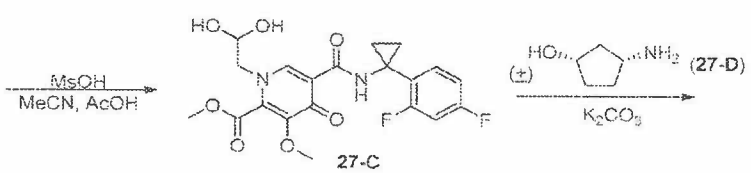
Preparation of Compound 27

(2S,5R)-N-(1-(2,4-difluorophenyl)cyclopropyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



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Step 1

A suspension of the compound **1-A** (1.004 g, 3.19 mmol), the amine **27-A** (688 mg, 3.35 mmol), and HATU (1.453 g 3.82 mmol) in CH_2Cl_2 (20 mL) was stirred in 0 °C bath as N,N-diisopropylethylamine (DIPEA) (2 mL, 11.48 mmol) was added. After 1 hour at 0 °C, the reaction mixture was concentrated to a syrup, diluted with ethyl acetate, and washed with water (x 2). After the aqueous fractions were extracted with ethyl acetate (x 1), the organic fractions were combined, dried (Na_2SO_4), and concentrated. The residue was purified by CombiFlash (120 g column) using hexanes- ethyl acetate as eluents. The major peak was combined and concentrated to afford 1.082 g (73%) of the product **27-B**. After the minor peak was combined and concentrated, the concentrated residue was dissolved in CH_2Cl_2 and some insoluble materials were filtered. The filtrate was concentrated to get 361 mg (24%) of the additional product **27-B**. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{25}F_2N_2O_7$: 467.16; found: 467.1.

Step 2 and 3

Compound **27-B** (81 mg, 0.174 mmol) was dissolved in a mixture (1 mL) of acetonitrile (22 mL), AcOH (2 mL), and methanesulfonic acid (0.14 mL, 2.16 mmol) at room temperature and the resulting solution was stirred at 65 °C for 20 hours.

After the resulting solution was cooled to room temperature, the aminoalcohol **27-D** (50 mg, racemic, 0.363 mmol), K_2CO_3 (50 mg, 0.362 mmol), and acetonitrile (2 mL) were added to the solution. The resulting mixture was stirred at 65 °C bath for 1 hour. After the reaction mixture was cooled to room temperature, it was acidified with 1 N HCl (~2 mL), diluted with water (~8 mL), and extracted with CH_2Cl_2 (x 3). Combined extracts were dried (Na_2SO_4), concentrated, and purified by CombiFlash to obtain 67 mg (82%) of compound **27-E**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.53 (s, 1H), 8.25 (s, 1H), 7.60 (td, *J* = 8.5, 6.5 Hz, 1H), 6.85 – 6.57 (m, 2H), 5.33 (br, 1H), 5.26 (dd, *J* = 9.6, 3.9 Hz, 1H), 4.60 (t, *J* = 3.0 Hz, 1H), 4.18 – 4.06 (m, 1H), 4.01 (s, 3H), 3.92 (dd, *J* = 12.7, 9.6 Hz, 1H) , 2.11 – 1.91 (m, 4H), 1.88 – 1.71 (m, 1H), 1.60 – 1.49 (m, 1H), 1.31 – 1.10 (m, 4H). **^{19}F-NMR** (376.1 MHz, $CDCl_3$) δ -111.80 (q, *J* =

8.8 Hz, 1F), -112.05 (p, J = 7.9 Hz, 1F). **LCMS-ESI$^+$** (*m/z*): [M+H]$^+$ calculated for $C_{24}H_{24}F_2N_3O_5$: 472.17; found: 472.1.

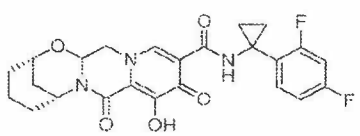
Step 4

A mixture of compound **27-E** (67 mg, 0.142 mmol) and $MgBr_2$ (66 mg, 0.358 mmol) in MeCN (3 mL) was stirred at 50 °C for 30 minutes and cooled to 0 °C before treating with 1 N HCl (3 mL). After the mixture was diluted with water (~30 mL), the product was extracted with CH_2Cl_2 (x 3), and the combined extracts were dried (Na_2SO_4) and concentrated. The product was purified by preparative HPLC and freeze-dried to obtain product **27** as a 1:1 mixture with trifluoroacetic acid. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.70 (s, 1H), 8.35 (s, 1H), 7.57 (q, J = 8.2 Hz, 1H), 6.91 – 6.56 (m, 2H), 5.31 (dt, J = 14.3, 4.0 Hz, 2H), 4.68 (s, 1H), 4.22 (dd, J = 13.2, 3.9 Hz, 1H), 3.99 (dd, J = 12.8, 9.3 Hz, 1H), 2.28 – 1.96 (m, 5H), 1.88 (ddt, J = 12.1, 8.6, 3.7 Hz, 1H), 1.71 – 1.49 (m, 1H), 1.38 – 1.11 (m, 4H). **^{19}F-NMR** (376.1 MHz, $CDCl_3$) δ -76.37 (s, 3F), -111.6 ~ -111.75 (m, 2F). **LCMS-ESI$^+$** (*m/z*): [M+H] calculated for $C_{23}H_{22}F_2N_3O_5$: 458.15; found: 458.1.

Example 28

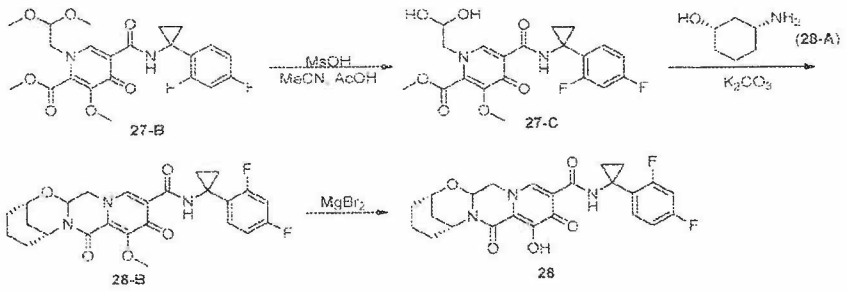
Preparation of Compound **28**

(2S,6R)-N-(1-(2,4-difluorophenyl)cyclopropyl)-9-hydroxy-8,10-dioxo-3,4,5,6,8,10,14,14a-octahydro-2H-2,6-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazocine-11-carboxamide



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Step 1 and 2

Compound **27-B** (87 mg, 0.187 mmol) was dissolved in a mixture (2 mL) of acetonitrile (22 mL), AcOH (2 mL), and methanesulfonic acid (0.14 mL, 2.16 mmol) at room temperature and the resulting solution was stirred at 65 °C for 20 hours.

After the resulting solution was cooled to room temperature, the aminoalcohol **28-A** (44 mg, racemic, 0.382 mmol) and acetonitrile (2 mL) were added to the solution. After the resulting mixture was stirred at 65 °C bath for 30 minutes, K_2CO_3 (41 mg, 0.297 mmol) was added and the mixture was stirred at 65 °C for 21 hours. The reaction mixture was cooled to room temperature, it was acidified with 1 N HCl (~2 mL), diluted with water (~8 mL), and extracted with CH_2Cl_2 (x 3). Combined extracts were dried (Na_2SO_4), concentrated, and purified by preparative HPLC and the fraction containing the product was freeze-dried. After the residue was dissolved in ethyl acetate, the solution was washed with saturated $NaHCO_3$ (x 1), dried (Na_2SO_4), and concentrated to obtain 18 mg (20%) of compound **28-B** as a 1:1 mixture with trifluoroacetic acid. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.54 (s, 1H), 8.26 (s, 1H), 7.63 (td, J = 8.6, 6.6 Hz, 1H), 6.76 (dddd, J = 21.9, 11.2, 8.7, 2.3 Hz, 2H), 5.39 (dd, J = 9.6, 3.7 Hz, 1H), 4.53 – 4.36 (m, 2H), 4.09 (dd, J = 12.8, 3.7 Hz, 1H), 4.03 (s, 3H), 3.99 (dd, J = 12.7, 9.7 Hz, 1H), 2.41 – 2.20 (m, 2H), 1.84 (dtd, J = 19.7, 9.3, 8.8, 4.4 Hz, 2H), 1.74 (dd, J = 14.6, 2.5 Hz, 1H), 1.62 – 1.35 (m, 2H), 1.34 – 1.14 (m, 5H). **^{19}F-NMR** (376.1 MHz, $CDCl_3$) δ -111.75 (q, J = 8.9 Hz, 1F), -112.01 (p, J = 7.9 Hz, 1F). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{25}H_{26}F_2N_3O_5$: 486.18; found: 486.2.

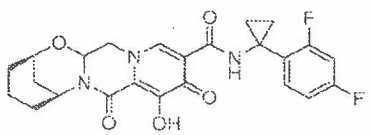
Step 3

Compound **28-B** (18 mg, 0.037 mmol) was treated with $MgBr_2$ as described in step4 in the synthesis of compound **27-E** to obtain compound **28**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.66 (s, 1H), 8.29 (s, 1H), 7.59 (td, *J* = 8.5, 6.6 Hz, 1H), 6.89 – 6.60 (m, 2H), 5.51 (dd, *J* = 9.9, 4.0 Hz, 1H), 4.55 (s, 1H), 4.48 (t, *J* = 4.2 Hz, 1H), 4.21 (dd, *J* = 12.9, 4.1 Hz, 1H), 3.99 (dd, *J* = 12.8, 9.8 Hz, 1H), 2.56 – 2.35 (m, 1H), 2.14 (dd, *J* = 16.1, 5.9 Hz, 1H), 1.96 – 1.74 (m, 3H), 1.66 – 1.37 (m, 3H), 1.28 (d, *J* = 4.4 Hz, 2H), 1.26 – 1.19 (m, 2H). **^{19}F-NMR** (376.1 MHz, $CDCl_3$) δ -76.41 (s, 3F, -111.79 (m, 2F). **LCMS-ESI$^+$** (*m/z*): [M+H]$^+$ calculated for $C_{24}H_{23}F_2N_3O_5$: 472.17; found: 472.1.

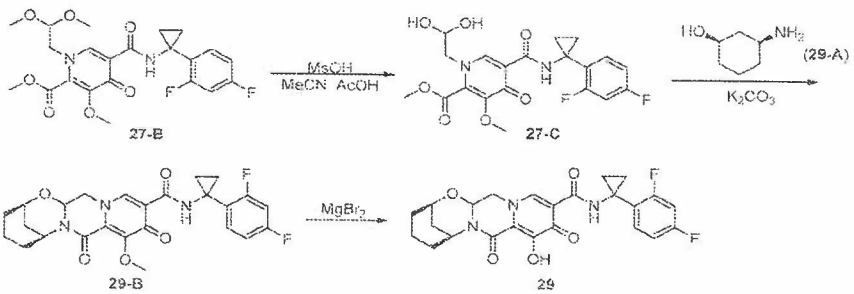
Example 29

Preparation of Compound **29**

(2R,6S)-N-(1-(2,4-difluorophenyl)cyclopropyl)-9-hydroxy-8,10-dioxo-3,4,5,6,8,10,14,14a-octahydro-2H-2,6-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazocine-11-carboxamide



29



Step 1 and 2

Compound **29-B** (13 mg, 14%) was prepared from compound **27-B** (87 mg, 0.187 mmol) and the aminoalcohol **29-A** (45 mg, 0.391 mmol) in a manner similar

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to that described in step 1 of the synthesis of compound **28-B**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.54 (s, 1H), 8.26 (s, 1H), 7.63 (td, *J* = 8.6, 6.6 Hz, 1H), 6.76 (dddd, *J* = 21.9, 11.2, 8.7, 2.3 Hz, 2H), 5.39 (dd, *J* = 9.6, 3.7 Hz, 1H), 4.53 – 4.36 (m, 2H), 4.09 (dd, *J* = 12.8, 3.7 Hz, 1H), 4.03 (s, 3H), 3.99 (dd, *J* = 12.7, 9.7 Hz, 1H), 2.41 – 2.20 (m, 2H), 1.84 (ddd, *J* = 19.7, 9.3, 8.8, 4.4 Hz, 2H), 1.74 (dd, *J* = 14.6, 2.5 Hz, 1H), 1.62 – 1.35 (m, 2H), 1.34 – 1.14 (m, 5H). **^{19}F-NMR** (376.1 MHz, $CDCl_3$) δ -111.75 (q, *J* = 8.9 Hz, 1F), -112.01 (p, *J* = 7.9 Hz, 1F). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{25}H_{26}F_2N_3O_5$: 486.18; found: 486.2.

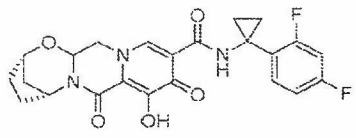
Step 3

Compound **29** was prepared from compound **29-B** in a manner similar to that described in step 2 of the synthesis of compound **16**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.66 (s, 1H), 8.29 (s, 1H), 7.59 (td, *J* = 8.5, 6.6 Hz, 1H), 6.89 – 6.60 (m, 2H), 5.51 (dd, *J* = 9.9, 4.0 Hz, 1H), 4.55 (s, 1H), 4.48 (t, *J* = 4.2 Hz, 1H), 4.21 (dd, *J* = 12.9, 4.1 Hz, 1H), 3.99 (dd, *J* = 12.8, 9.8 Hz, 1H), 2.56 – 2.35 (m, 1H), 2.14 (dd, *J* = 16.1, 5.9 Hz, 1H), 1.96 – 1.74 (m, 3H), 1.66 – 1.37 (m, 3H), 1.28 (d, *J* = 4.4 Hz, 2H), 1.26 – 1.19 (m, 2H). **^{19}F-NMR** (376.1 MHz, $CDCl_3$) δ -76.41 (s, 3F, -111.79 (m, 2F). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{24}H_{23}F_2N_3O_5$: 472.17; found: 472.1.

Example 30

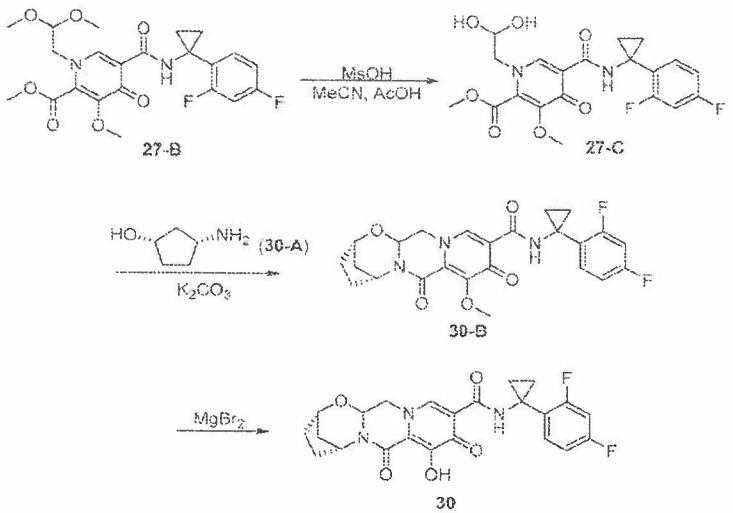
Preparation of Compound **30**

(2S,5R,13aS)-N-(1-(2,4-difluorophenyl)cyclopropyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



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Step 1 and 2

Compound **27-B** (150 mg, 0.322 mmol) was dissolved in acetonitrile (2 mL), AcOH (0.2 mL), and methanesulfonic acid (0.007 mL, 0.108 mmol) at room temperature and the resulting solution was stirred at 65 °C for 20 hours. After the resulting solution was cooled to room temperature, the aminoalcohol **30-A** (72.1 mg, chiral, 0.713 mmol), K_2CO_3 (89.4 mg, 0.647 mmol), and acetonitrile (2 mL) were added to the solution. The resulting mixture was stirred at 65 °C bath for 0.5 hour. After the reaction mixture was cooled to room temperature, it was acidified with 1 N HCl (~3 mL), diluted with water (~12 mL), and extracted with CH_2Cl_2 (x 3). Combined extracts were dried (Na_2SO_4), concentrated, and purified by CombiFlash to obtain 128 mg (84%) of compound **30-B**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.52 (s, 1H), 8.24 (s, 1H), 7.61 (td, J = 8.6, 6.6 Hz, 1H), 6.85 - 6.65 (m, 2H), 5.33 (t, J = 4.1 Hz, 1H), 5.25 (dd, J = 9.5, 3.9 Hz, 1H), 4.61 (d, J = 3.4 Hz, 1H), 4.18 - 4.08 (m, 1H), 4.02 (s, 3H), 3.99 - 3.87 (m, 1H), 2.12 - 1.91 (m, 4H), 1.85 - 1.69 (m, 1H), 1.55 (ddd, J = 12.3, 4.1, 2.8 Hz, 1H), 1.31 - 1.14 (m, 4H). **^{19}F-NMR** (376.1 MHz, $CDCl_3$) δ -111.79 (q, J = 8.8 Hz, 1F), -112.05 (p, J = 7.9 Hz, 1F). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{24}H_{24}F_2N_3O_5$: 472.17; found: 472.2.

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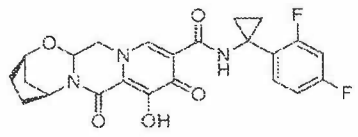
Step 3

A mixture of compound **30-B** (128 mg, 0.272 mmol) and $MgBr_2$ (130 mg, 0.706 mmol) in MeCN (5 mL) was stirred at 50 °C for 30 minutes and cooled to 0 °C before treating with 1 N HCl (4 mL). After the mixture was diluted with water, the product was extracted with CH_2Cl_2 (x 3), and the combined extracts were dried (Na_2SO_4) and concentrated. The product was purified by CombiFlash to obtain product **30**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 12.27 (s, 1H), 10.52 (s, 1H), 8.16 (s, 1H), 7.61 (td, J = 8.6, 6.6 Hz, 1H), 6.96 – 6.54 (m, 2H), 5.36 – 5.23 (m, 2H), 4.66 (t, J = 3.1 Hz, 1H), 4.18 – 4.06 (m, 1H), 3.94 (dd, J = 12.8, 9.4 Hz, 1H), 2.20 – 1.95 (m, 4H), 1.89 (td, J = 11.4, 9.8, 6.7 Hz, 1H), 1.70 – 1.54 (m, 1H), 1.32 – 1.15 (m, 4H). **^{19}F-NMR** (376.1 MHz, $CDCl_3$) δ -111.87 (q, J = 8.9 Hz, 1F), -112.21 (p, J = 7.9 Hz, 1F). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{23}H_{22}F_2N_3O_5$: 458.15; found: 458.2.

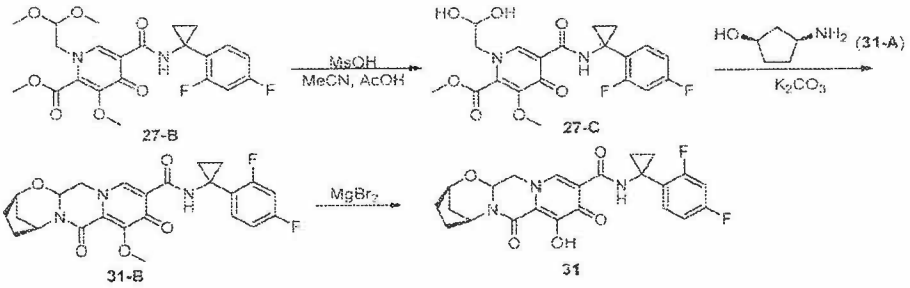
Example 31

Preparation of Compound **31**

(2R,5S)-N-(1-(2,4-difluorophenyl)cyclopropyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



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Step 1 and 2

Compound **31-B** (123 mg, 81%) was prepared from compound **27-B** (150 mg, 0. 322 mmol) and the aminoalcohol **31-A** (70.3 mg, 0.695 mmol) in a manner similar to that described in step 1 and 2 of the synthesis of compound **30-B**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.52 (s, 1H), 8.24 (s, 1H), 7.62 (td, *J* = 8.6, 6.6 Hz, 1H), 6.91 - 6.63 (m, 2H), 5.33 (t, *J* = 4.1 Hz, 1H), 5.25 (dd, *J* = 9.5, 3.9 Hz, 1H), 4.61 (d, *J* = 3.4 Hz, 1H), 4.14 - 4.07 (m, 1H), 4.03 (s, 3H), 3.93 (dd, *J* = 12.7, 9.5 Hz, 1H), 2.12 - 1.91 (m, 4H), 1.85 - 1.69 (m, 1H), 1.55 (ddd, *J* = 12.3, 4.1, 2.8 Hz, 1H), 1.31 - 1.14 (m, 4H). **^{19}F-NMR** (376.1 MHz, $CDCl_3$) δ -111.79 (q, *J* = 9.2, 8.7 Hz, 1F), -112.03 (h, *J* = 8.1, 7.5 Hz, 1F). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{24}H_{24}F_2N_3O_5$: 472.17; found: 472.1.

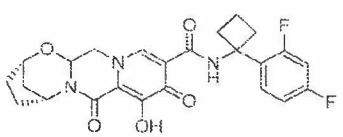
Step 3

Compound **31** was prepared from compound **31-B** in a manner similar to that described in step 3 of the synthesis of compound **30**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 12.26 (s, 1H), 10.49 (s, 1H), 8.13 (s, 1H), 7.58 (td, *J* = 8.6, 6.5 Hz, 1H), 6.90 - 6.56 (m, 2H), 5.32 (dd, *J* = 9.4, 4.1 Hz, 1H), 5.27 - 5.22 (m, 1H), 4.64 (t, *J* = 3.1 Hz, 1H), 4.11 (dd, *J* = 12.8, 4.0 Hz, 1H), 4.01 - 3.79 (m, 1H), 2.28 - 1.95 (m, 4H), 1.95 - 1.80 (m, 1H), 1.71 (m, 1H), 1.56 (m, 1H), 1.42 - 1.08 (m, 4H). **^{19}F-NMR** (376.1 MHz, $CDCl_3$) δ -111.95 (q, *J* = 8.9 Hz, 1F), -112.22 (p, *J* = 7.9 Hz, 1F). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{23}H_{22}F_2N_3O_5$: 458.15; found: 458.1.

Example 32

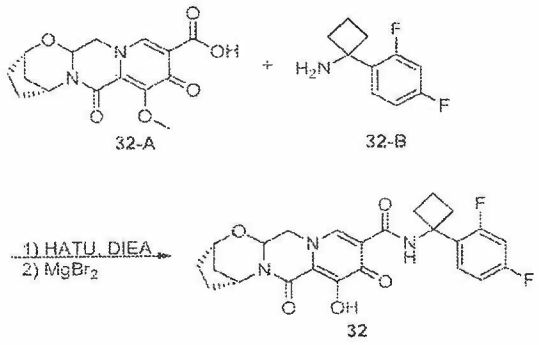
Preparation of Compound 32

(2S,5R)-N-(1-(2,4-difluorophenyl)cyclobutyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



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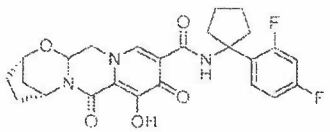
A solution of compound **32-A** (22.2 mg, 0.069 mmol), compound **32-B** (18.7 mg, 0.102 mmol), and HATU (43 mg, 0.113 mmol) in CH_2Cl_2 (2 mL) was stirred at room temperature as N,N-diisopropylethylamine (DIPEA) (0.075 mL, 0.431 mmol) was added. After 30 minutes, the reaction mixture was diluted with ethyl acetate and washed with water (x 2). After the aqueous fractions were extracted with EA (x 1), the organic fractions were combined, dried, concentrated, and dried in vacuum.

A mixture of the above crude product and $MgBr_2$ (35 mg, 0.190 mmol) in MeCN (2 mL) was stirred at 50 °C bath for 1 hour and cooled to 0 °C before being treated with 1 N HCl (~ 1 mL). The resulting solution was diluted with water, and extracted with CH_2Cl_2 (x 3). The combined extracts were dried (Na_2SO_4), and concentrated. The product was purified by preparative HPLC and freeze-dried to obtain compound **32**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.87 (s, 1H), ~9.3 (br, 1H), 8.35 (s, 1H), 7.50 (td, *J* = 8.7, 6.3 Hz, 1H), 6.89 - 6.78 (m, 1H), 6.72 (ddd, *J* = 11.2, 8.9, 2.6 Hz, 1H), 5.48 - 5.12 (m, 2H), 4.72 - 4.60 (m, 1H), 4.22 (dd, *J* = 13.0, 4.1 Hz, 1H), 3.98 (dd, *J* = 12.9, 9.4 Hz, 1H), 2.68 (m, 4H), 2.33 - 1.98 (m, 6H), 1.90 (m, 2H), 1.60 (ddd, *J* = 12.4, 4.1, 2.7 Hz, 1H). **^{19}F-NMR** (376.1 MHz, CD_3CN) δ -76.39 (s, 3F), -110.50 (q, *J* = 9.2 Hz, 1F), -112.65 (p, *J* = 7.8 Hz, 1F). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{24}H_{24}F_2N_3O_5$: 472.17; found: 472.0.

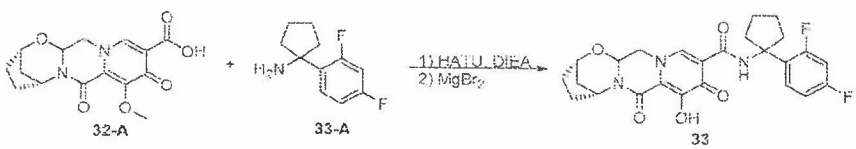
Example 33

Preparation of Compound **33**

(2S,5R)-N-(1-(2,4-difluorophenyl)cyclopentyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



33



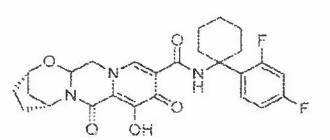
32-A 33-A 33

Compound **33** was obtained from compound **32-A** and compound **33-A** as described in the synthesis of compound **32**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.70 (s, 1H), ~9.5 (br, 1H), 8.41 (s, 1H), 7.43 (td, *J* = 8.9, 6.4 Hz, 1H), 6.85 - 6.76 (m, 1H), 6.72 (ddd, *J* = 11.5, 8.8, 2.6 Hz, 1H), 5.48 - 5.18 (m, 2H), 4.68 (t, *J* = 3.2 Hz, 1H), 4.26 (dd, *J* = 13.0, 4.1 Hz, 1H), 4.00 (dd, *J* = 13.0, 9.4 Hz, 1H), 2.72 - 2.45 (m, 2H), 2.22 - 1.96 (m, 6H), 1.96 - 1.75 (m, 5H), 1.60 (ddd, *J* = 12.5, 4.1, 2.7 Hz, 1H). **^{19}F-NMR** (376.1 MHz, CD_3CN) δ -76.41 (s, 3F), -107.86 (q, J = 9.4 Hz, 1F), -113.13 (p, J = 8.0 Hz, 1F). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{25}H_{26}F_2N_3O_5$: 486.18; found: 485.9.

Example 34

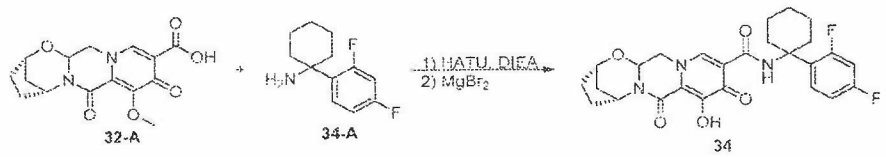
Preparation of Compound **34**

(2S,5R)-N-(1-(2,4-difluorophenyl)cyclohexyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



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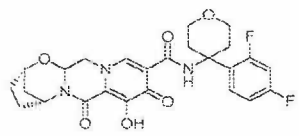
32-A 34-A 34

Compound **34** was obtained from compound **32-A** and compound **34-A** as described in the synthesis of compound **32**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.83 (s, 1H), ~9.6 (br, 1H), 8.44 (s, 1H), 7.37 (td, *J* = 9.0, 6.4 Hz, 1H), 6.97 - 6.76 (m, 1H), 6.69 (ddd, *J* = 11.9, 8.8, 2.7 Hz, 1H), 5.48 - 5.18 (m, 2H), 4.68 (t, *J* = 3.0 Hz, 1H), 4.28 (dd, *J* = 13.1, 4.1 Hz, 1H), 4.03 (dd, *J* = 13.0, 9.4 Hz, 1H), 2.60 (d, *J* = 13.1 Hz, 2H), 2.29 - 1.96 (m, 4H), 1.95 - 1.77 (m, 4H), 1.77 - 1.65 (m, 4H), 1.61 (ddd, *J* = 12.5, 4.1, 2.7 Hz, 1H), 1.30 (br, 1H). **^{19}F-NMR** (376.1 MHz, CD_3CN) δ -76.41 (s, 3F), -107.86 (q, *J* = 9.4 Hz, 1F), -113.13 (p, *J* = 8.0 Hz, 1F). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{24}H_{28}F_2N_3O_5$: 500.20; found: 500.0.

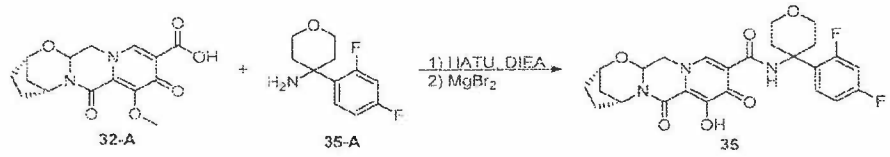
Example 35

Preparation of Compound **35**

(2S,5R)-N-(4-(2,4-difluorophenyl)tetrahydro-2H-pyran-4-yl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



35



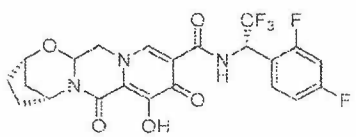
32-A 35-A 35

Compound **35** was obtained from compound **32-A** and compound **35-A** as described in the synthesis of compound **32**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.95 (s, 1H), 8.33 (s, 1H), ~7.6 (br, 1H), 7.38 (td, *J* = 9.0, 6.3 Hz, 1H), 6.85 (td, *J* = 8.4, 2.6 Hz, 1H), 6.73 (ddd, *J* = 11.7, 8.6, 2.6 Hz, 1H), 5.32 (dt, *J* = 14.4, 4.0 Hz, 2H), 4.68 (t, *J* = 3.1 Hz, 1H), 4.24 (dd, *J* = 13.0, 3.9 Hz, 1H), 4.11 - 3.81 (m, 5H), 2.60 (d, *J* = 13.7 Hz, 2H), 2.33 - 2.17 (m, 2H), 2.18 - 1.97 (m, 4H), 1.87 (m, 1H), 1.61 (dt, *J* = 12.5, 3.3 Hz, 1H). **^{19}F-NMR** (376.1 MHz, CD_3CN) δ -76.40 (s, 3F), -108.78 (q, *J* = 10.3, 9.8 Hz, 1F), -112.63 (p, *J* = 8.0 Hz, 1F). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{25}H_{26}F_5N_3O_6$: 502.18; found: 502.0.

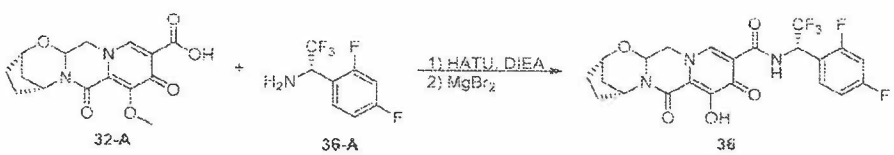
Example 36

Preparation of Compound **36**

(2S,5R)-N-((S)-1-(2,4-difluorophenyl)-2,2,2-trifluoroethyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



36



32-A **36-A** **36**

Compound **36** was obtained from compound **32-A** and compound **36-A** as described in the synthesis of compound **32**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 11.31 (d, *J* = 9.4 Hz, 1H), 8.41 (s, 1H), 7.65 - 7.44 (m, 1H), 6.95 (ddd, *J* = 9.6, 5.6, 2.0 Hz, 1H), 6.92 - 6.79 (m, 1H), 6.15 (h, *J* = 7.4 Hz, 1H), ~6 (br, 1H), 5.41 (dd, *J* = 9.5, 4.0 Hz, 1H), 5.31 (t, *J* = 4.0 Hz, 1H), 4.70 (s, 1H), 4.34 (dd, *J* = 12.8, 3.9 Hz, 1H), 4.05 (dd, *J* = 12.9, 9.4 Hz, 1H), 2.26 - 1.99 (m, 4H), 1.99 - 1.87 (m, 1H), 1.62 (dt, *J* = 12.6, 3.4 Hz,

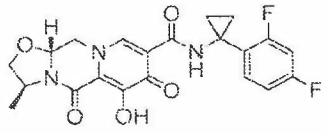
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1H). **^{19}F-NMR** (376.1 MHz, $CDCl_3$) δ -75.23 (t, *J* = 6.9 Hz, 3F), -76.33 (s, 3F), -108.31 (m, 1F), -112.30 (p, *J* = 8.0 Hz, 1F). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{19}F_5N_3O_5$: 500.12; found: 500.1.

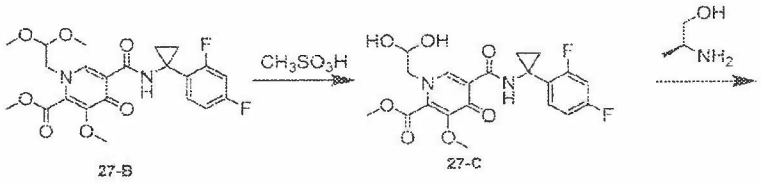
Example 37

Preparation of Compound 37

(3S,11aR)-N-(1-(2,4-difluorophenyl)cyclopropyl)-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydrooxazolo[3,2-a]pyrido[1,2-d]pyrazine-8-carboxamide



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Step 1

Methyl 5-(1-(2,4-difluorophenyl)cyclopropylcarbamoyl)-1-(2,2-dimethoxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate (**27-B**, 0.150 g, 0.32 mmol) in acetonitrile (1.5 mL) and acetic acid (0.2 mL) was treated with methanesulfonic acid (0.05 mL), sealed with a yellow cap, and heated to 70 °C. After 16 hours, the mixture was cooled to afford a crude solution of methyl 5-(1-(2,4-difluorophenyl)cyclopropylcarbamoyl)-1-(2,2-dihydroxyethyl)-3-methoxy-4-oxo-1,4-

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dihydropyridine-2-carboxylate **27-C**. **LCMS-ESI**$^+$ (*m/z*): [M+H]$^+$ calculated for $C_{18}H_{16}F_2N_2O_7$: 439; found: 439.

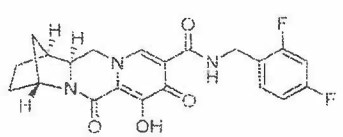
Steps 2 and 3

Methyl 5-(1-(2,4-difluorophenyl)cyclopropylcarbamoyl)-1-(2,2-dihydroxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate (**27-C**, 0.32 mmol, the crude mixture from the previous step) was dissolved in acetonitrile (1.5 mL) and acetic acid (0.2 mL). (S)-2-aminopropan-1-ol (0.048 g, 0.64 mmol) and K_2CO_3 (0.088 g, 0.64 mmol) were added to the reaction mixture. The reaction mixture was sealed and heated to 70 °C. After 3 hours, the reaction mixture was cooled and magnesium bromide (0.081 g, 0.44 mmol) was added. The mixture was resealed and heated to 50 °C. After 10 minutes, the reaction mixture was cooled to 0 °C and 1 N hydrochloric acid (0.5 mL) was added in. Then the reaction mixture was diluted with MeOH (2 mL). After filtration, the crude was purified by Prep-HPLC (30-70% acetonitrile:water, 0.1% TFA) to afford Compound **37** as a TFA salt. **^{1}H-NMR** (400 MHz, Methanol-d_4) δ 8.31 (s, 1H), 7.62 (td, J = 9.2, 8.7, 6.5 Hz, 1H), 7.02 – 6.78 (m, 2H), 5.53 – 5.20 (m, 1H), 4.68 (dd, J = 12.3, 4.2 Hz, 1H), 4.40 (dq, J = 19.1, 6.7 Hz, 2H), 3.98 (dd, J = 12.2, 10.0 Hz, 1H), 3.71 (dd, J = 8.3, 6.3 Hz, 1H), 1.41 (d, J = 6.1 Hz, 3H), 1.22 (s, 4H). **^{19}F-NMR** (376 MHz, Methanol-d_4) δ -113.66 – -113.95 (m, 1F), -113.94 – -114.29 (m, 1F). **LCMS-ESI**$^+$ (*m/z*): [M+H]$^+$ calculated for $C_{21}H_{20}F_2N_3O_5$: 432.; found: 432.

Example 38

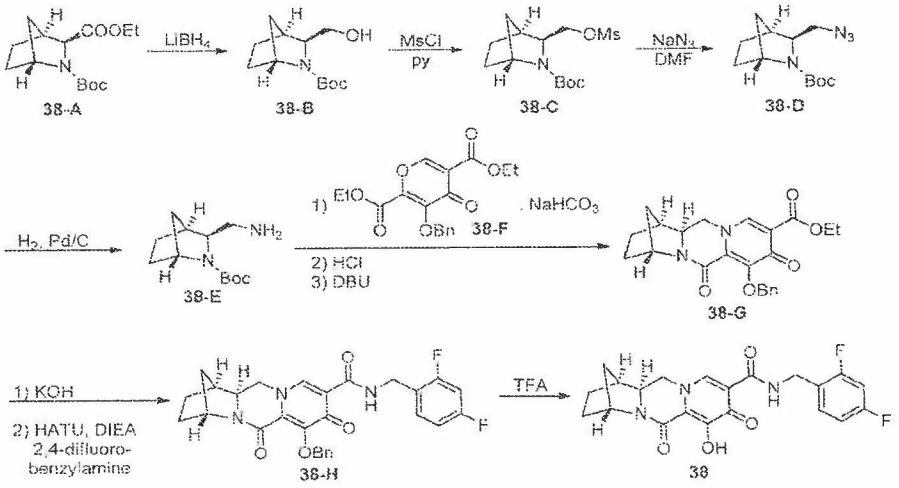
Preparation of Compound **38**

(1S,4R,12aR)-N-(2,4-difluorobenzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



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Step 1

A solution of compound **38-A** (1562 mg, 5.799 mmol) (see Example 41b in WO 97/05139) in THF (10 mL) was stirred at -78 °C as 2.0 M $LiBH_4$ in THF (3.2 mL) was added and the resulting mixture was stirred at room temperature. After 3 hours, additional 2.0 M $LiBH_4$ in THF (3.2 mL) was added and the solution was stirred at room temperature for 17.5 hours. After the reaction mixture was diluted with ethyl acetate and added water slowly, two phases were separated, and the separated aqueous fraction was extracted with ethyl acetate (x 1). Two organic fractions were washed with water (x 1), combined, dried (Na_2SO_4), and concentrated. The residue was purified by CombiFlash (40 g column) using hexanes - ethyl acetate as eluents to afford compound **38-B**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 4.11 (s, 1H), 3.65 - 3.52 (m, 2H), 3.45 (m, 1H), 2.32 (d, J = 4.1 Hz, 1H), 2.20 (s, 1H), 1.75 - 1.64 (m, 2H), 1.61 (m, 2H), 1.49 – 1.41 (m, 1H), 1.47 (s, 9H), 1.28 - 1.23 (d, J = 10 Hz, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{12}H_{22}NO_3$: 228.16; found: 227.7.

Step 2

A solution of compound **38-B** (589 mg, 2.591 mmol) and NEt_3 (0.47 mL, 3.369 mmol) in CH_2Cl_2 (6 mL) was stirred at 0 °C as MsCl (0.22 mL, 2.842 mmol) was added. After 1 hour at room temperature, the mixture was diluted with ethyl acetate

and washed with water (x 2). The aqueous fractions were extracted with ethyl acetate (x 1), and the organic fractions were combined, dried (Na_2SO_4), and concentrated. The residue was purified by Combi Flash (40 g column) using hexanes - ethyl acetate as eluents to afford compound **38-C**. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 4.39 – 4.28 (m, 1H), 4.16 (s, 0.4H), 4.06 (s, 0.6H), 3.98 (dd, *J* = 10.0, 8.7 Hz, 0.6H), 3.86 (t, *J* = 9.6 Hz, 0.4H), 3.51 (dd, *J* = 9.3, 3.7 Hz, 0.6H), 3.43 (dd, *J* = 9.3, 3.6 Hz, 0.4H), 3.02 (s, 3H), 2.59 (m, 1H), 1.82 – 1.58 (m, 4H), 1.51 – 1.44 (m, 9H), 1.41 (d, *J* = 14.8 Hz, 1H), 1.31 (s, 0.6H), 1.29 (s, 0.4H).

Step 3

To a solution of compound **38-C** (769 mg, 2.518 mmol,) in DMF (5 mL) was added sodium azide (819 mg, 12.6 mmol). The reaction mixture was stirred at 50 °C for 15 hours, at 80 °C for 5 hours, and at 100 °C for 19 hours. The reaction mixture was diluted with 5% LiCl solution and the product was extracted with ethyl acetate (x 2). After the organic fractions were washed with water (x 1), the two organic fractions were combined, dried (Na_2SO_4), and concentrated. The residue was purified by CombiFlash (40 g column) using hexanes - ethyl acetate as eluents to afford compound **38-D**. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 4.16 (s, 0.4H), 4.06 (s, 0.6H), 3.61 (dd, *J* = 12.2, 3.6 Hz, 0.6H), 3.51 (dd, *J* = 12.1, 3.2 Hz, 0.4H), 3.38 (dd, *J* = 9.4, 3.4 Hz, 0.6H), 3.26 (dd, *J* = 9.8, 3.3 Hz, 0.4H), 3.06 (dd, *J* = 12.2, 9.4 Hz, 0.6H), 3.01 – 2.92 (m, 0.4H), 2.48 (d, *J* = 5.2 Hz, 1H), 1.82 – 1.57 (m, 4H), 1.46 (d, *J* = 3.0 Hz, 9H), 1.42 (m, 1H), 1.28 (m, 0.6H), 1.27 – 1.23 (m, 0.4H).

Step 4

To a solution of compound **38-D** (507 mg, 2.009 mmol,) in ethyl acetate (10 mL) and EtOH (10 mL) was added 10% Pd/C (52 mg). The reaction mixture was stirred under H_2 atmosphere for 1.5 hours. The mixture was filtered through celite and the filtrate was concentrated to afford crude compound **38-E**. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{12}H_{23}N_2O_2$: 227.18; found: 226.8.

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Step 5

The mixture of crude compound **38-E** (206 mg, 0.910 mmol), compound **38-F** (330 mg, 0.953 mmol), and $NaHCO_3$ (154 mg, 1.833 mmol) in water (3 mL) and EtOH (3 mL) was stirred at room temperature for 20 hours. After the reaction mixture was diluted with water and extracted with ethyl acetate (x 2), the extracts were washed with water (x 1), combined, dried (Na_2SO_4), and concentrated to afford the crude pyridine product.

The crude residue (388 mg) was dissolved in CH_2Cl_2 (4 mL) and 4 N HCl in dioxane (4 mL). After 1.5 hours, additional 4 N HCl in dioxane (4 mL) was added and stirred for 1 hour at room temperature. The mixture was concentrated to dryness, coevaporated with toluene (x 1) and dried in vacuum for 30 minutes.

The crude residue and 1,8-diazabicycloundec-7-ene (DBU) (1.06 mL, 7.088 mmol) in toluene (10 mL) was stirred at 110 °C bath. After 30 minutes, the mixture was concentrated and the residue was purified by CombiFlash (40 g column) using ethyl acetate - 20% MeOH/ethyl acetate as eluents to obtain compound **38-G**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 8.03 (s, 1H), 7.68 - 7.58 (m, 2H), 7.36 - 7.27 (m, 3H), 5.53 (d, J = 9.9 Hz, 1H), 5.11 (d, J = 9.9 Hz, 1H), 4.93 (s, 1H), 4.43 - 4.30 (m, 2H), 3.89 (dd, J = 12.2, 3.3 Hz, 1H), 3.73 (t, J = 12.0 Hz, 1H), 3.59 (dd, J = 11.9, 3.3 Hz, 1H), 2.53 (d, J = 2.8 Hz, 1H), 1.87 - 1.67 (m, 4H), 1.55 (d, J = 10.0 Hz, 1H), 1.51 - 1.45 (m, 1H), 1.38 (t, J = 7.1 Hz, 3H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{25}H_{25}N_2O_5$: 409.18; found: 409.2.

Step 6

The mixture of compound **38-G** (232 mg, 0.568 mmol) in THF (3 mL) and MeOH (3 mL) was stirred at room temperature as 1 N KOH (3 mL) was added. After 1 hour, the reaction mixture was neutralized with 1 N HCl (~3.1 mL), concentrated, and the residue was concentrated with toluene (x 3). After the residue was dried in vacuum for 30 minutes, a suspension of the crude residue, 2,4-difluorobenzylamine (86 mg, 0.601 mmol), and HATU (266 mg, 0.700 mmol) were in CH_2Cl_2 (4 mL) and DMF (4 mL) was stirred at 0 °C as N,N-diisopropylethylamine (DIPEA) (0.7 mL, 4.019 mmol) was added. After 45 minutes, additional 2,4-difluorobenzylamine (86 mg, 0.559 mmol), HATU (266 mg, 0.700 mmol), and N,N-

diisopropylethylamine (DIPEA) (0.7 mL, 4.019 mmol) were added at room temperature. After 1.25 hours, the mixture was concentrated to remove most of CH_2Cl_2, diluted with ethyl acetate, and washed with 5% LiCl (x 2). After the aqueous fractions were extracted with ethyl acetate (x 1), the organic fractions were combined, dried (Na2SO4), and concentrated. The residue was purified by Combiflash (40 g column) using ethyl acetate -20%MeOH/ethyl acetate as eluents to afford compound **38-H**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 10.48 (t, J = 6.0 Hz, 1H), 8.33 (s, 1H), 7.62 - 7.51 (m, 2H), 7.40 - 7.27 (m, 4H), 6.87 - 6.75 (m, 2H), 5.39 (d, J = 10.0 Hz, 1H), 5.15 (d, J = 10.0 Hz, 1H), 4.92 (s, 1H), 4.68 - 4.53 (m, 2H), 3.97 (dd, J = 12.5, 3.4 Hz, 1H), 3.77 (t, J = 12.2 Hz, 1H), 3.55 (dd, J = 12.1, 3.3 Hz, 1H), 2.53 (d, J = 3.1 Hz, 1H), 1.88 - 1.62 (m, 4H), 1.59 - 1.42 (m, 2H). **^{19}F-NMR** (376 MHz, Chloroform-d) δ -112.17 (q, J = 7.6 Hz, 1F), -114.79 (q, J = 8.6 Hz, 1F). **LCMS-ESI$^+$** *(m/z)*: $[M+H]^+$ calculated for C28H26F2N3O4: 506.19; found: 506.2.

Step 7

Compound **38-H** (240 mg, 0.475 mmol) was dissolved in TFA (3 mL) at room temperature for 30 minutes, and the solution was concentrated. The residue was purified by CombiFlash (40 g column) using CH_2Cl_2-20% MeOH in CH_2Cl_2 as eluents. After the collected product fractions were concentrated, the residue was triturated in MeCN (~2 mL) at 0 °C for 15 minutes, and the solids were filtered and washed with MeCN. The collected solids were dried in vacuum to afford compound **38**.

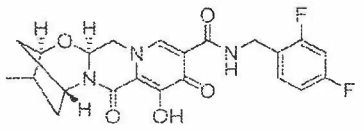
The filtrate was concentrated, and the residue was dissolved in MeCN (~1 mL) and water (~1 mL) by heating. The solution was slowly cooled to room temperature and then in ice bath for 15 minutes. The solids were filtered and washed with MeCN, and dried in vacuum to afford additional compound **38**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 11.68 (s, 1H), 10.42 (s, 1H), 8.27 (s, 1H), 7.41 - 7.31 (m, 1H), 6.86 - 6.73 (m, 2H), 4.90 (d, J = 2.5 Hz, 1H), 4.71 - 4.53 (m, 2H), 4.07 (d, J = 10.6 Hz, 1H), 3.90 - 3.67 (m, 2H), 2.68 (s, 1H), 2.01 (s, 1H), 1.97 - 1.80 (m, 3H), 1.80 - 1.62 (m, 2H). **^{19}F-NMR** (376 MHz, Chloroform-d) δ -112.28 (m, 1F), -114.74 (m, 1F). **LCMS-ESI$^+$** *(m/z)*: $[M+H]^+$ calculated for $C_{21}H_{19}F_2N_3O_4$: 416.14; found: 416.3.

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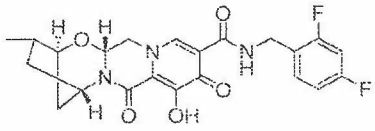
Examples 39 and 40

Preparation of Compounds **39** and **40**

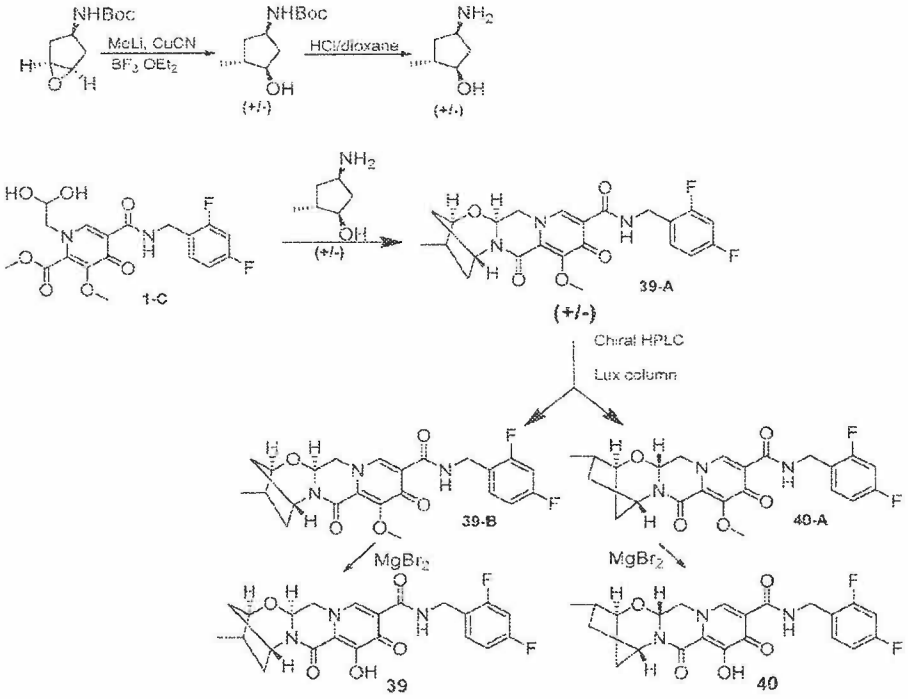
(2R,3S,5R,13aS)-N-(2,4-difluorobenzyl)-8-hydroxy-3-methyl-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide **39** and (2S,3R,5S,13aR)-N-(2,4-difluorobenzyl)-8-hydroxy-3-methyl-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide **40**



39



40



Step 1

Cuprous cyanide (290 mg, 3.27 mmol) was suspended in 3.3 mL THF and cooled to -78 °C. A 1.6M solution of MeLi (4.1 mL, 6.56 mmol) in diethyl ether was added dropwise, the reaction solution was allowed to warm to room temperature over the course of 2 hours, and recooled to -78 °C. Tert-butyl (1R,3R,5S)-6-oxabicyclo[3.1.0]hexan-3-ylcarbamate (330 mg, 1.66 mmol) was added dropwise in 3.3 mL THF, followed by boron trifluoride diethyl etherate (0.25 mL, 1.99 mmol), allowed to warm to -30 °C over 30 minutes, and stirred between -35 °C and -25 °C for one hour. The reaction solution was then warmed to room temperature and quenched with a mixture of saturated NH_3(aq)/NH_4(aq), extracted to EtOAc, washed with brine, dried over MgSO4, filtered, concentrated, and purified by SGC (0-10% EtOH/DCM) to afford racemic tert-butyl (1S,3S,4S)-3-hydroxy-4-methylcyclopentylcarbamate. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 5.16 (s, 1H), 3.98 (s, 1H), 3.74 (q, *J* = 4.3 Hz, 1H), 3.65 (q, *J* = 7.0 Hz, 1H), 2.23 (dt, *J* = 14.0, 7.0 Hz, 1H), 1.98 (dt, *J* = 13.3, 7.0 Hz, 1H), 1.89 – 1.79 (m, 1H), 1.58 – 1.44 (m, 1H), 1.38 (s, 9H), 1.18 (t, *J* = 7.0 Hz, 1H), 0.91 (d, *J* = 7.0 Hz, 3H).

Step 2

3 mL HCl/dioxane (4M, 12 mmol) was added to a solution of racemic tert-butyl (1S,3S,4S)-3-hydroxy-4-methylcyclopentylcarbamate (182 mg, 0.85 mmol) in 3 mL dioxane. The reaction mixture was stirred at room temperature for 2 hours, concentrated and twice chased with toluene to afford racemic (1S,2S,4S)-4-amino-2-methylcyclopentanol.

Step 3

Methyl 5-(2,4-difluorobenzylcarbamoyl)-1-(2,2-dihydroxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate (**1-C**, 310 mg, 0.75 mmol), racemic (1S,2S,4S)-4-amino-2-methylcyclopentanol (115 mg, 0.76 mmol), and potassium carbonate (232 mg, 1.68 mmol) were taken up in 3.8 mL acetonitrile/0.2 mL acetic acid and stirred at 90 °C for 2 hours, after which the reaction mixture was partitioned between DCM and brine, the aqueous phase extracted to DCM, combined organic

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phases dried over $MgSO_4$, filtered, concentrated, and purified by SGC (0-10% EtOH/DCM) to afford intermediate **39-A**.

Step 4

Intermediate **39-A** (190 mg) was separated by chiral Prep-HPLC on a Lux Cellulose-2 column using 9:1 ACN:MeOH as eluent to afford Intermediates **39-B** (first eluting peak) and **40-A** (second eluting peak) in enantioenriched form. For intermediate **39-B**: (absolute stereochemistry confirmed by XRay crystallography), **Chiral HPLC** retention time = 3.98 minutes (Lux Cellulose-2 IC, 150 x 4.6 mm, 2 mL/min 9:1 ACN:MeOH). For intermediate **40-A**: (absolute stereochemistry confirmed by XRay crystallography), **Chiral HPLC** retention time = 6.35 minutes (Lux Cellulose-2 IC, 150 x 4.6 mm, 2 mL/min 9:1 ACN:MeOH).

Step 5a

Magnesium bromide (68 mg, 0.37 mmol) was added to a solution of intermediate **39-B** (83 mg, 0.18 mmol) in 2 mL acetonitrile. The reaction mixture was stirred at 50 °C for 1 hour, acidified with 10% aqueous HCl, partitioned between the aqueous and dichloromethane, and the aqueous phase extracted to dichloromethane. The combined organic phases were dried over MgSO4, filtered, concentrated, and purified by silica gel chromatography (0-10% EtOH/DCM) to afford compound **39**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 12.32 (s, 1H), 10.36 (s, 1H), 8.29 (s, 1H), 7.44 – 7.33 (m, 1H), 6.88 – 6.76 (m, 2H), 5.37 (dd, J = 9.5, 4.1 Hz, 1H), 5.28 (t, J = 5.3 Hz, 1H), 4.63 (d, J = 5.9 Hz, 2H), 4.23 (d, J = 23.0 Hz, 2H), 3.99 (dd, J = 12.7, 9.5 Hz, 1H), 3.72 (q, J = 7.0 Hz, 1H), 2.51 (dq, J = 13.7, 6.8, 6.1 Hz, 1H), 2.15 (ddd, J = 14.7, 8.3, 2.3 Hz, 1H), 1.94 (d, J = 12.7 Hz, 1H), 1.77 (ddd, J = 12.7, 4.0, 2.9 Hz, 1H), 1.61 (dt, J = 14.6, 5.2 Hz, 2H), 1.24 (t, J = 7.0 Hz, 1H), 1.09 (d, J = 7.2 Hz, 3H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{22}F_2N_3O_5$: 446.15; found: 446.2.

Step 5b

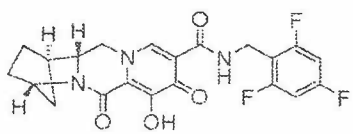
Magnesium bromide (59 mg, 0.32 mmol) was added to a solution of intermediate **40-A** (70 mg, 0.15 mmol) in 2 mL acetonitrile. The reaction mixture was stirred at 50 °C for 1 hour, acidified with 10% aqueous HCl, partitioned between the

aqueous and dichloromethane, and the aqueous phase extracted to dichloromethane. The combined organic phases were dried over $MgSO_4$, filtered, concentrated, and purified by silica gel chromatography (0-10% EtOH/DCM) to afford compound **40**. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 12.32 (s, 1H), 10.36 (s, 1H), 8.29 (s, 1H), 7.44 – 7.33 (m, 1H), 6.88 – 6.76 (m, 2H), 5.37 (dd, *J* = 9.5, 4.1 Hz, 1H), 5.28 (t, *J* = 5.3 Hz, 1H), 4.63 (d, *J* = 5.9 Hz, 2H), 4.23 (d, *J* = 23.0 Hz, 2H), 3.99 (dd, *J* = 12.7, 9.5 Hz, 1H), 3.72 (q, *J* = 7.0 Hz, 1H), 2.51 (dq, *J* = 13.7, 6.8, 6.1 Hz, 1H), 2.15 (ddd, *J* = 14.7, 8.3, 2.3 Hz, 1H), 1.94 (d, *J* = 12.7 Hz, 1H), 1.77 (ddd, *J* = 12.7, 4.0, 2.9 Hz, 1H), 1.61 (dt, *J* = 14.6, 5.2 Hz, 2H), 1.24 (t, *J* = 7.0 Hz, 1H), 1.09 (d, *J* = 7.2 Hz, 3H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{22}F_2N_3O_5$: 446.15; found: 446.2.

Example 41

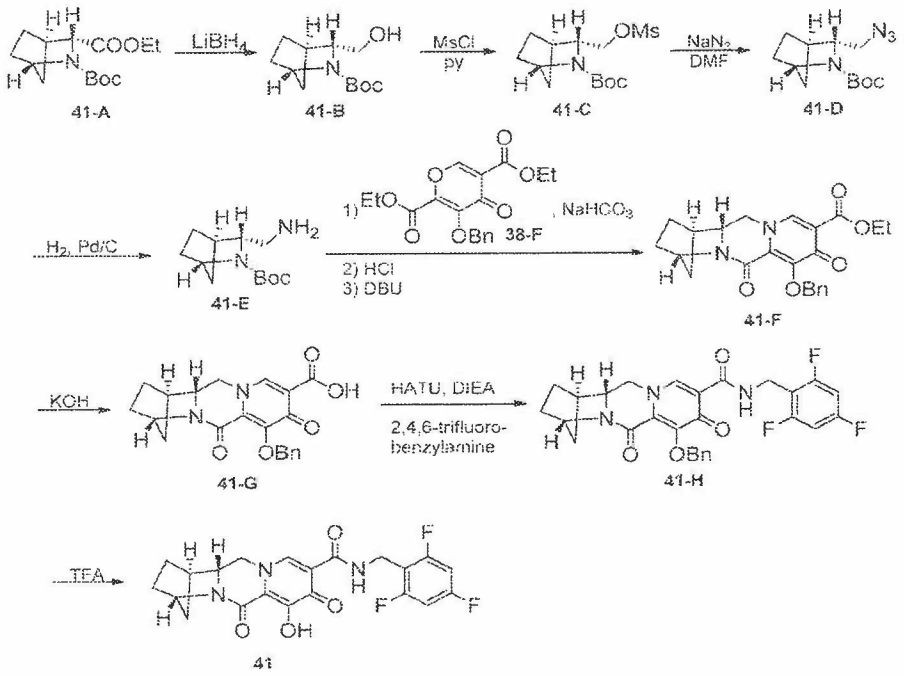
Preparation of Compound **41**

(1R,4S,12aR)-7-hydroxy-6,8-dioxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



41

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Step 1

A solution of the **41-A** (2020 mg, 7.463 mmol) (prepared by the same method as **38-A**) in THF (14 mL) was stirred at 0 °C as 2.0 M $LiBH_4$ in THF (7.5 mL, 15 mmol) was added. After the resulting mixture was stirred at rt for 21 h, it was cooled at 0 °C and diluted with EA before water was added slowly to quench. After two phases were separated, the aqueous fraction was extracted with EA (x 1) and the two organic fractions were washed with water (x 1), combined, dried (Na_2SO_4), and concentrated. The residue was purified by CombiFlash (120 g column) using hexanes - EA as eluents to get **41-B**. **LCMS-ESI**$^+$ (*m/z*): $[M-C_4H_8+H]^+$ calculated for $C_8H_{14}NO_3$: 172.10; found: 171.95.

Step 2

A 100-mL round bottom flask was charged with reactant **41-B** (1.6 g, 7.05 mmol) and triethylamine (0.94 g, 9.3 mmol) in DCM (20 mL). Methanesulfonyl

chloride (0.91 g, 8.0 mmol) was added to the reaction mixture. Then the reaction mixture was stirred at room temperature for 3 hours. The mixture was diluted with EA (100 mL) and washed with water (2x). The aqueous fractions were extracted with EA (1x), and the organic fractions were combined, dried (Na2SO4), and concentrated. The residue was purified by Combi Flash (120 g column, cartridge used) using hexanes - EA as eluents to afford **41-C**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{18}H_{19}F_2N_2O_7$: 306; found: 306.

Step 3

A 100-mL round bottom flask was charged with reactant **41-C** (2.1 g, 6.9 mmol) and sodium azide (2.3 g, 34.5 mmol) in DMF (10 mL). Then the reaction mixture was stirred at 100 °C for overnight. The mixture was diluted with EA (100 mL) and washed with water (2x). The aqueous fractions were extracted with EA (1x), and the organic fractions were combined, dried (Na_2SO_4), and concentrated. The residue was purified by Combi Flash (120 g column, cartridge used) using hexanes - EA as eluents to afford **41-D**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{18}H_{19}F_2N_2O_7$: 253; found: 253.

Step 4

To a solution (purged with N_2) of reactant **41-D** (1.3 g) in EA (20 mL) and EtOH (20 mL) was added Pd/C (130 mg). The mixture was stirred under H_2 for 3 hours. The mixture was filtered through celite and the filtrate was concentrated to afford compound **41-E**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{18}H_{19}F_2N_2O_7$: 227; found: 227.

Step 5

A 100-mL round bottom flask was charged with reactant **41-E** (1.05 g, 4.62 mmol) and reactant **38-F** (1.6 g, 4.62 mmol) in Ethanol (20 mL). Sodium bicarbonate (0.77 g, 9.2 mmol) in water (20 mL) was added to the reaction mixture. Then the reaction mixture was stirred at room temperature overnight. The mixture was diluted with EA (100 mL) and washed with water (2x). The aqueous fractions were extracted with EA (1x), and the organic fractions were combined, dried (Na2SO4), and

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concentrated. The crude product (2.4 g) was used for next step without further purification. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{18}H_{19}F_2N_2O_7$: 556; found: 556.

A 100-mL round bottom flask was charged with the crude product from the previous reaction in 4 N HCl /dioxane (24.7 mL). Then the reaction mixture was stirred at room temperature for 1 hour. After concentration, the intermediate (2.1 g) and DBU (3.27 g, 21.5 mmol) in toluene (30 mL) was heated to 110 °C with stirring for 1 hour. After concentration, the residue was purified by CombiFlash (120 g column) using hexanes - ethyl acetate as eluents to afford **41-F**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{18}H_{19}F_2N_2O_7$: 409; found: 409.

Step 6

A 100-mL round bottom flask was charged with reactant **41-F** (0.5 g, 1.22 mmol) in THF (5 mL) and MeOH (5 mL). 1 N KOH (3.7 mL) was added to the reaction mixture. Then the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was acidified by adding 1 N HCl (3.7 mL), concentrated to remove most of organic solvents, and extracted with EtOAc (2 X). The organic layers were combined, dried (Na_2SO_4), and concentrated to afford compound **41-G**.

Step 7

A 100-mL round bottom flask was charged with reactant **41-G** (0.14 g, 0.37 mmol), (2,4,6-trifluorophenyl)methanamine (0.12 g, 0.73 mmol), N,N-diisopropylethylamine (DIPEA) (0.24 g, 1.84 mmol) and HATU (0.28 g, 0.74 mmol) were dissolved in DCM (5 mL). The reaction mixture was stirred at room temperature for 2 hours. The mixture was diluted with EA (100 mL) and washed with saturated $NaHCO_3$ (2x), saturated NH_4Cl (2x) and dried over Na_2SO_4. After concentration, the crude was purified by column chromatography on silica gel with hexane-EtOAc to afford compound **41-H**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{18}H_{19}F_2N_2O_7$: 524.5; found: 524.5.

Step 8

A 50-mL round bottom flask was charged with reactant **41-H** (0.13 g, 0.25 mmol) in TFA (2 mL). The reaction mixture was stirred at room temperature for

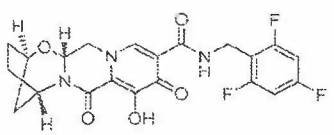
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30 minutes. After concentration, the crude was purified by column chromatography on silica gel with EtOAc-MeOH to afford compound **41**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 11.61 (s, 1H), 10.70 - 10.01 (m, 1H), 8.26 (s, 1H), 6.65 (t, J = 8.1 Hz, 2H), 4.88 (s, 1H), 4.65 (dd, J = 6.1, 2.4 Hz, 2H), 4.07 (d, J = 10.9 Hz, 1H), 3.93 - 3.58 (m, 2H), 2.67 (d, J = 3.1 Hz, 1H), 2.08 - 1.41 (m, 7H). **^{19}F-NMR** (376 MHz, Chloroform-d) δ -109.22 (d, J = 11.6 Hz, 1F), -111.04 - -112.79 (m, 2F). **LCMS-ESI$^+$** (*m/z*): [M+H] calculated for $C_{21}H_{20}F_2N_3O_5$: 434.; found: 434.

Example 42

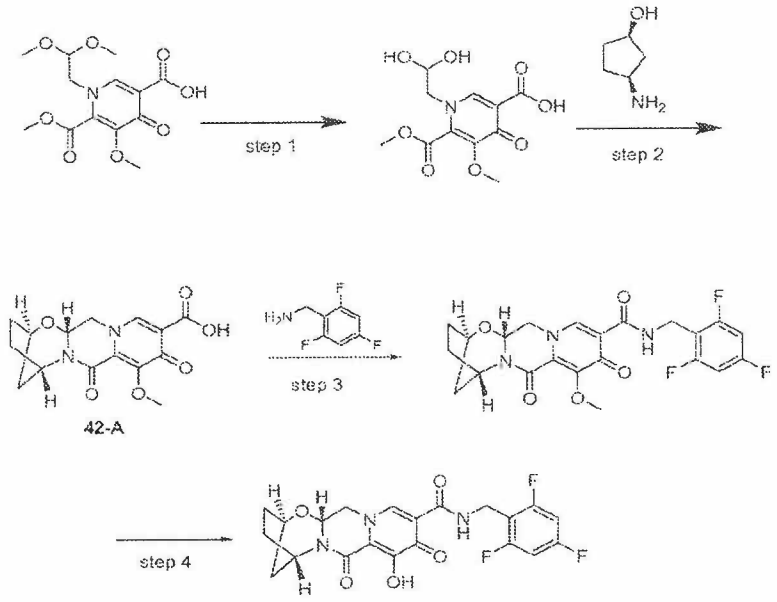
Preparation of Compound **42**

(2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



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Step 1

1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (3.15 g, 10 mmol) in acetonitrile (36 mL) and acetic acid (4 mL) was treated with methanesulfonic acid (0.195 mL, 3 mmol) and placed in a 75 deg C bath. The reaction mixture was stirred for 7 h, cooled and stored at -10 °C for 3 days and reheated to 75 °C for an additional 2 h. This material was cooled and carried on crude to the next step.

Step 2

Crude reaction mixture from step 1 (20 mL, 4.9 mmol) was transferred to a flask containing (1R,3S)-3-aminocyclopentanol (0.809 g, 8 mmol). The mixture was diluted with acetonitrile (16.8 mL), treated with potassium carbonate (0.553 g, 4 mmol) and heated to 85 °C. After 2 h, the reaction mixture was cooled to ambient temperature and stirred overnight. 0.2M HCl (50 mL) was added, and the clear yellow solution was extracted with dichloromethane (2x150 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated to 1.49 g of a light

orange solid. Recrystallization from dichloromethane:hexanes afforded the desired intermediate **42A**: **LCMS-ESI**$^+$ (*m/z*): [M+H]$^+$ calculated for $C_{15}H_{17}N_2O_6$: 321.11; found: 321.3.

Step 3

Intermediate **42-A** (0.225 g, 0.702 mmol) and (2,4,6-trifluorophenyl)methanamine (0.125 g, 0.773 mmol) were suspended in acetonitrile (4 mL) and treated with N,N-diisopropylethylamine (DIPEA) (0.183 mmol, 1.05 mmol). To this suspension was added (dimethylamino)-*N*,*N*-dimethyl(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yloxy)methaniminium hexafluorophosphate (HATU, 0.294 g, 0.774 mmol). After 1.5 hours, the crude reaction mixture was taken on to the next step. **LCMS-ESI**$^+$ (*m/z*): [M+H]$^+$ calculated for $C_{22}H_{21}F_3N_3O_5$: 464.14; found: 464.2.

Step 4

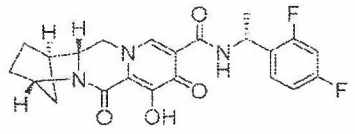
To the crude reaction mixture of the previous step was added $MgBr_2$ (0.258 g, 1.40 mmol). The reaction mixture was stirred at 50 °C for 10 minutes, acidified with 10% aqueous HCl, and extract twice with dichloromethane. The combined organic phases were dried over $MgSO_4$, filtered, concentrated, and purified by silica gel chromatography (EtOH/dichloromethane) followed by HPLC (ACN/H_2O with 0.1% TFA modifier) to afford compound **42**: ^{1}**H-NMR** (400 MHz, DMSO-d_6) δ 12.43 (s, 1H), 10.34 (t, *J* = 5.7 Hz, 1H), 8.42 (s, 1H), 7.19 (t, *J* = 8.7 Hz, 2H), 5.43 (dd, *J* = 9.5, 4.1 Hz, 1H), 5.08 (s, 1H), 4.66 (dd, *J* = 12.9, 4.0 Hz, 1H), 4.59 (s, 1H), 4.56 – 4.45 (m, 2H), 4.01 (dd, *J* = 12.7, 9.7 Hz, 1H), 1.93 (s, 4H), 1.83 (d, *J* = 12.0 Hz, 1H), 1.56 (dt, *J* = 12.0, 3.4 Hz, 1H). **LCMS-ESI**$^+$ (*m/z*): [M+H]$^+$ calculated for $C_{21}H_{19}F_3N_3O_5$: 450.13; found: 450.2.

Example 43

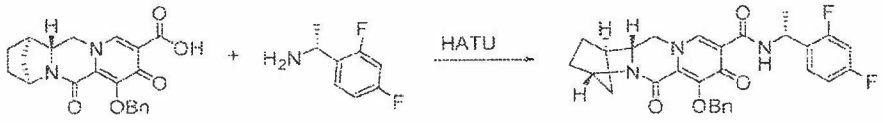
Preparation of Compound **43**

(12aR)-N-((R)-1-(2,4-difluorophenyl)ethyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide

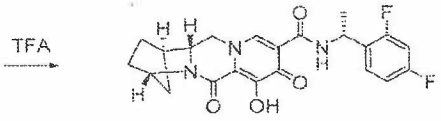
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43



41-G 43-A



43

Step 1

A 100-mL round bottom flask was charged with reactant **41-G** (0.14 g, 0.37 mmol), (R)-1-(2,4-difluorophenyl)ethanamine (0.12 g, 0.74 mmol), *N,N*-diisopropylethylamine (0.24 g, 1.84 mmol) and HATU (0.28 g, 0.74 mmol) and were dissolved in DCM (5 mL). The reaction mixture was stirred at room temperature for 2 hours. The mixture was diluted with EA (100 mL) and washed with saturated $NaHCO_3$ (2x), saturated NH_4Cl (2x) and dried over Na_2SO_4. After concentration, the crude was purified by column chromatography on silica gel with hexane-EtOAc to afford compound **43-A**. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{18}H_{19}F_2N_2O_7$: 520; found: 520.

Steps 2

A 50-mL round bottom flask was charged with reactant **43-A** (0.14 g, 0.27 mmol) in TFA (2 mL). The reaction mixture was stirred at room temperature for 30 minutes. After concentration, the crude was purified by column chromatography on silica gel with EtOAc-MeOH to afford compound **43**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 11.65 (s, 1H), 10.57 (s, 1H), 8.22 (s, 1H), 7.31 (m, 1H), 6.99 - 6.62 (m, 2H), 5.64 - 5.32 (m, 1H), 4.90 (d, J = 2.7 Hz, 1H), 4.04 (d, J = 11.5 Hz, 1H), 3.93 - 3.63

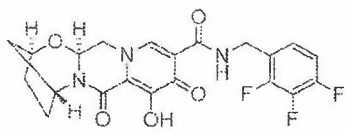
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(m, 2H), 2.67 (s, 1H), 2.08 - 1.40 (m, 9H). **^{19}F-NMR** (376 MHz, Chloroform-d) δ -113.09 (m, 1F), -115.01 (m, 1F). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}F_2N_3O_5$: 430.; found: 430.

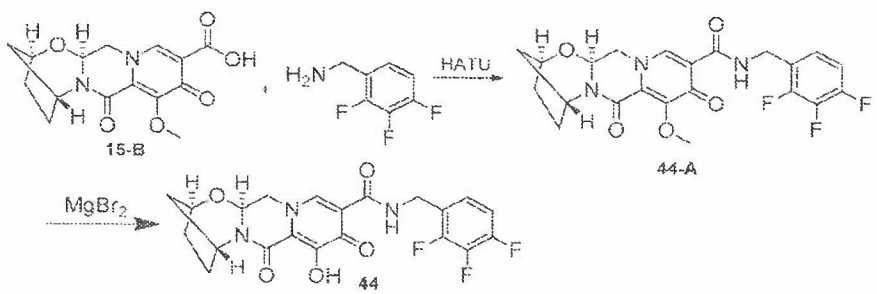
Example 44

Preparation of Compound **44**

(13aS)-8-hydroxy-7,9-dioxo-N-(2,3,4-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



44



15-B **44-A** **44**

Step 1

Compound **15-B** (40 mg, 0.12 mmol) was taken up in 1 mL acetonitrile and treated with 2,3,4-trifluorobenzylamine (29 mg, 0.18 mmol), HATU (53 mg, 0.14 mmol), N,N-diisopropylethylamine (DIPEA) (20 mg, 0.16 mmol), and stirred at room temperature for 2 hours, after which LCMS analysis revealed complete consumption of compound **15-B** and formation of intermediate **44-A**. The reaction mixture was carried onto the next step.

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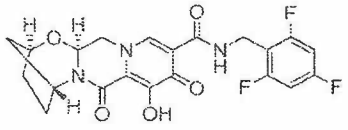
Step 2

To the crude reaction solution of the previous step was added $MgBr_2$ (63 mg, 0.34 mmol). The reaction mixture was stirred at 50 °C for one hour, acidified with 10% aqueous HCl, partitioned between the aqueous and dichloromethane, and the aqueous phase extracted to dichloromethane. The combined organic phases were dried over $MgSO_4$, filtered, concentrated, and purified by HPLC (ACN/H_2O with 0.1% TFA modifier) to compound **44**. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.45 (s, 1H), 10.38 (t, J = 6.0 Hz, 1H), 8.43 (s, 1H), 7.27 (q, J = 9.2 Hz, 1H), 7.16 (q, J = 8.5 Hz, 1H), 5.42 (dd, J = 9.5, 4.0 Hz, 1H), 5.08 (s, 1H), 4.76 – 4.47 (m, 4H), 4.01 (dd, J = 12.8, 9.7 Hz, 1H), 1.92 (s, 4H), 1.82 (d, J = 12.1 Hz, 1H), 1.55 (dt, J = 12.2, 2.9 Hz, 1H). **LCMS-ESI$^+$** (*m/z*): [M+H]$^+$ calculated for $C_{21}H_{19}F_3N_3O_5$: 450.13; found: 450.2.

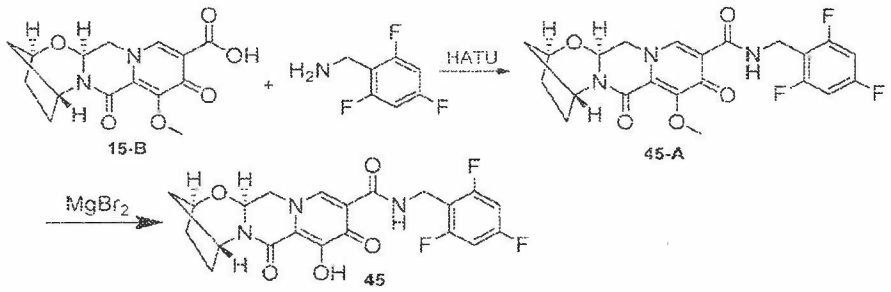
Example 45

Preparation of Compound **45**

(13aS)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



45



Step 1

Compound **15-B** (38 mg, 0.12 mmol) was taken up in 1 mL acetonitrile and treated with 2,4,6-trifluorobenzylamine (34 mg, 0.21 mmol), HATU (50 mg, 0.13 mmol), N,N-diisopropylethylamine (DIPEA) (23 mg, 0.18 mmol), and stirred at room temperature for 2 hours, after which LCMS analysis revealed complete consumption of compound **15-B** and formation of intermediate **45-A**. The reaction mixture was carried onto the next step.

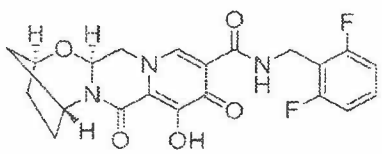
Step 2

To the crude reaction solution of the previous step was added $MgBr_2$ (55 mg, 0.30 mmol). The reaction mixture was stirred at 50 °C for one hour, acidified with 10% aqueous HCl, partitioned between the aqueous and dichloromethane, and the aqueous phase extracted with dichloromethane. The combined organic phases were dried over $MgSO_4$, filtered, concentrated, and purified by HPLC (ACN/H_2O with 0.1% TFA modifier) to afford compound **45**. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.37 (s, 1H), 10.37 – 10.25 (m, 1H), 8.37 (s, 1H), 7.14 (t, J = 8.7 Hz, 2H), 5.37 (dd, J = 9.5, 4.0 Hz, 1H), 5.02 (s, 1H), 4.66 – 4.40 (m, 4H), 3.95 (dd, J = 12.8, 9.6 Hz, 1H), 1.87 (s, 4H), 1.77 (d, J = 11.9 Hz, 1H), 1.50 (dt, J = 11.8, 3.2 Hz, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{19}F_3N_3O_5$: 450.13; found: 450.2.

Example 46

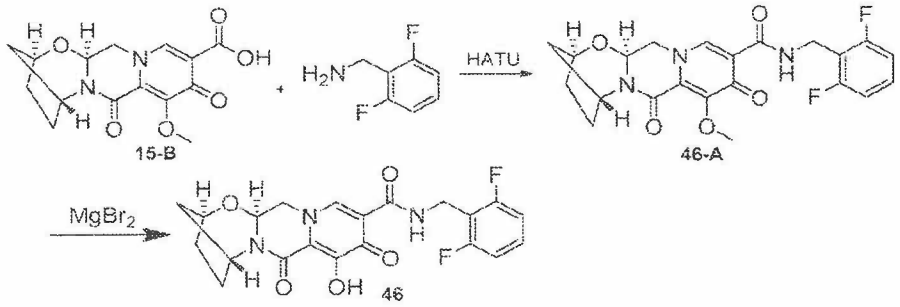
Preparation of Compound **46**

(13aS)-N-(2,6-difluorobenzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



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Step 1

Compound **15-B** (38 mg, 0.12 mmol) was taken up in 1 mL acetonitrile and treated with 2,6-difluorobenzylamine (19 mg, 0.14 mmol), HATU (56 mg, 0.15 mmol), N,N-diisopropylethylamine (DIPEA) (20 mg, 0.15 mmol), and stirred at room temperature for 90 minutes, after which LCMS analysis revealed complete consumption of compound **A** and formation of intermediate **46-A**. The reaction mixture was carried onto the next step.

Step 2

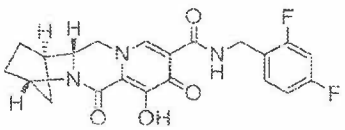
To the crude reaction solution of the previous step was added $MgBr_2$ (50 mg, 0.27 mmol). The reaction mixture was stirred at 50 °C for one hour, acidified with 10% aqueous HCl, partitioned between the aqueous and dichloromethane, and the aqueous phase extracted with dichloromethane. The combined organic phases were dried over $MgSO_4$, filtered, concentrated, and purified by HPLC (ACN/H_2O with 0.1% TFA modifier) to afford compound **46**. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.37 (s, 1H), 10.33 – 10.26 (m, 1H), 8.37 (s, 1H), 7.39 – 7.29 (m, 1H), 7.05 (t, J = 7.9 Hz, 2H), 5.37 (dd, J = 9.5, 4.1 Hz, 1H), 5.02 (s, 1H), 4.66 – 4.45 (m, 4H), 3.95 (dd, J = 12.7, 9.6 Hz, 1H), 1.87 (s, 4H), 1.77 (d, J = 12.0 Hz, 1H), 1.50 (dt, J = 12.2, 3.5 Hz, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}F_2N_3O_5$: 432.14; found: 432.2.

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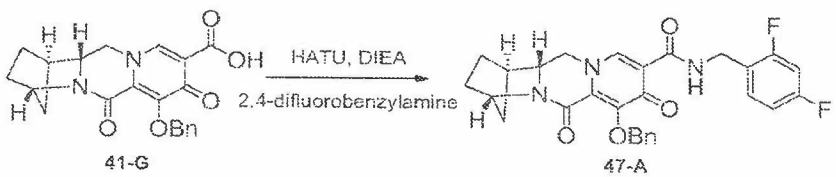
Example 47

Preparation of Compound 47

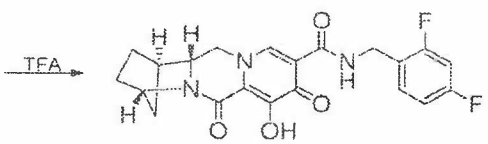
(1R,4S,12aR)-N-(2,4-difluorobenzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



47



41-G 47-A



47

Step 1

The crude acid **41-G** (0.45 g, 1.18 mmol), 2,4-difluobenzylamine (0.35 g, 2.44 mmol), N,N-diisopropylethylamine (DIPEA) (0.79 g, 6.11 mmol) and HATU (0.93 g, 2.44 mmol) were dissolved in DCM (10 mL). The reaction mixture was stirred at room temperature for 2 hours. The mixture was diluted with EA (100 mL) and washed with saturated $NaHCO_3$ (2x), saturated NH_4Cl (2x) and dried over Na_2SO_4. After concentration, the crude was purified by column chromatography on silica gel with hexane-EtOAc to afford compound **47-A**. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{18}H_{19}F_2N_2O_7$: 506; found: 506.

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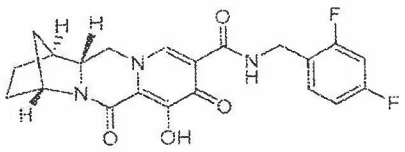
Step 2

A 50-mL round bottom flask was charged with reactant **47-A** (0.5 g, 0.99 mmol) in TFA (6 mL). The reaction mixture was stirred at room temperature for 30 minutes. After concentration, the crude was purified by column chromatography on silica gel with EtOAc-MeOH to afford compound **47**. **^{1}H NMR** (400 MHz, Chloroform-d) δ 11.70 (s, 1H), 10.44 (s, 1H), 8.29 (s, 1H), 7.60 - 7.29 (m, 1H), 6.95 - 6.58 (m, 2H), 4.10 (s, 1H), 4.02 - 3.54 (m, 3H), 2.68 (d, J = 3.1 Hz, 1H), 2.00 - 1.40 (m, 8H). **^{19}F NMR** (376 MHz, Chloroform-d) δ -112.31 (d, J = 8.0 Hz, 1F), -114.77 (d, J = 8.4 Hz, 1F). **LCMS-ESI$^+$** (*m/z*): [M+H]$^+$ calculated for $C_{21}H_{20}F_2N_3O_5$: 416.; found: 416.

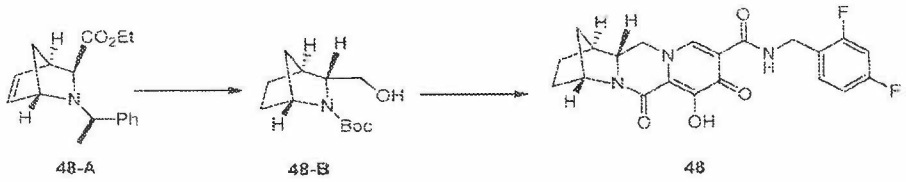
Example 48

Preparation of Compound **48**

(1S,4R,12aS)-N-(2,4-difluorobenzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



48



48-A **48-B** **48**

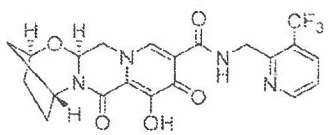
48-B was prepared analogously to **55-H** in Example 55, substituting **48-A** for **55-A**. Compound **48** was prepared as described for compound **38** in Example 38, substituting **48-B** for **38-B** to afford compound **48**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 11.79 (s, 1H), 10.44 (m, 1H), 8.33 (s, 1H), 7.42 – 7.31 (m, 1H), 6.86 – 6.74 (m,

2H), 4.74 (s, 1H), 4.63 (d, J = 5.8 Hz, 2H), 4.19 (m, 1H), 4.07 – 4.03 (m, 2H), 2.83 (s, 1H), 1.92 – 1.68 (m, 6H). ^{19}F NMR (376 MHz, Chloroform-d) δ -112.3 (m, 1F), -114.8 (m, 1F). **LCMS-ESI**$^+$ (*m/z*): [M+H]$^+$ calculated for $C_{21}H_{20}F_3N_5O_4$: 416.14.; found: 416.07.

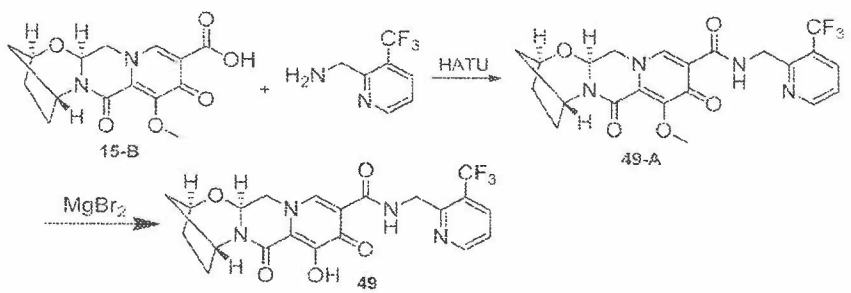
Example 49

Preparation of Compound **49**

(2S,5R,13aS)-8-hydroxy-7,9-dioxo-N-((3-(trifluoromethyl)pyridin-2-yl)methyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



49



Step 1

Compound **15-B** (44 mg, 0.14 mmol) was taken up in 1 mL acetonitrile and treated with (3-(trifluoromethyl)pyridin-2-yl)methanamine (38 mg, 0.18 mmol, HCl salt), HATU (69 mg, 0.18 mmol), N,N-diisopropylethylamine (DIPEA) (0.07 mL, 0.40 mmol), and stirred at room temperature for 1 hour, after which LCMS analysis revealed complete consumption of compound **15-B** and formation of intermediate **49-A**. The reaction mixture was carried onto the next step.

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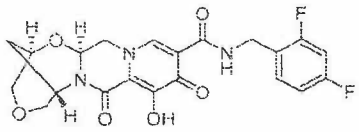
Step 2

To the crude reaction solution of the previous step was added $MgBr_2$ (51 mg, 0.28 mmol). The reaction mixture was stirred at 50 °C for 90 minutes, acidified with 10% aqueous HCl, partitioned between the aqueous and dichloromethane, and the aqueous phase extracted with dichloromethane. The combined organic phases were dried over $MgSO_4$, filtered, concentrated, and triturated by methanol followed by diethyl ether to afford compound **49**. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.42 (s, 1H), 10.80 – 10.70 (m, 1H), 8.83 (d, J = 5.0 Hz, 1H), 8.44 (s, 1H), 8.19 (d, J = 8.6 Hz, 1H), 7.56 (dd, J = 7.7, 5.2 Hz, 1H), 5.43 (dd, J = 9.5, 4.0 Hz, 1H), 5.08 (s, 1H), 4.86 – 4.80 (m, 2H), 4.67 (dd, J = 12.9, 4.0 Hz, 1H), 4.59 (s, 1H), 4.02 (dd, J = 12.6, 9.8 Hz, 1H), 1.93 (s, 4H), 1.82 (d, J = 12.1 Hz, 1H), 1.60 – 1.52 (m, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}F_3N_4O_5$: 465.14; found: 465.2.

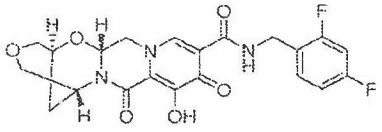
Examples 50 and 51

Preparation of Compounds **50** and **51**

N-(2,4-difluorobenzyl)-9-hydroxy-8,10-dioxo-2,3,5,6,8,10,14,14a-octahydro-2,6-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,6,3]dioxazocine-11-carboxamide **50** and **51**

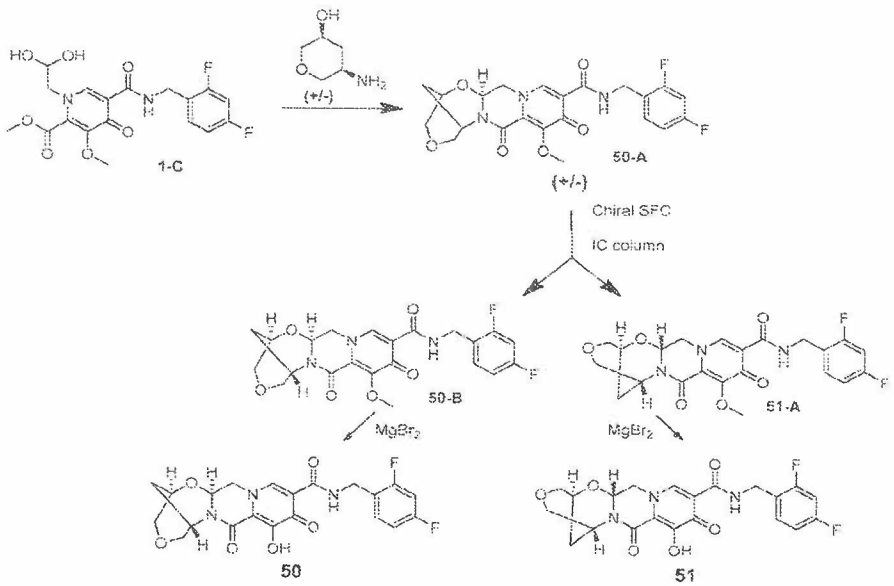


50



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Step 1

Methyl 5-(2,4-difluorobenzylcarbamoyl)-1-(2,2-dihydroxyethyl)-3-methoxy-4-oxo-1,4-dihydropyridine-2-carboxylate (**1-C**, 392 mg, 0.95 mmol) (Example 87), racemic *cis*-5-aminotetrahydro-2H-pyran-3-ol (WO 2012/145569 Bennett, B. L. et al, filed April 20, 2012) (112 mg, 0.95 mmol), and potassium carbonate (134 mg, 0.97 mmol) were taken up in 3.8 mL acetonitrile/0.2 mL acetic acid and stirred at 90 °C for 90 minutes, after which the reaction mixture was partitioned between DCM and brine, the aqueous phase extracted with DCM, combined organic phases dried over $MgSO_4$, filtered, concentrated, and purified by SGC (0-10% EtOH/DCM) to afford intermediate **50-A**.

Step 2

Intermediate **50-A** (40 mg) was separated by chiral SFC on a Chiralpak IC column using 10% DMF in supercritical carbon dioxide as eluent to afford Intermediates **50-B** (first eluting peak) and **51-A** (second eluting peak) in enantioenriched form. For intermediate **50-B**: (absolute stereochemistry unknown), **Chiral HPLC** retention time = 11.48 minutes (Chiralpak IC, 150 x 4.6 mm, 1 mL/min

MeOH). For intermediate **51-A**: (absolute stereochemistry unknown), **Chiral HPLC** retention time = 14.35 minutes (Chiralpak IC, 150 x 4.6 mm, 1 mL/min MeOH).

Step 3a

Magnesium bromide (12 mg, 0.06 mmol) was added to a solution of intermediate **50-B** (10.5 mg, 0.02 mmol, absolute stereochemistry unknown) in 1 mL acetonitrile. The reaction mixture was stirred at 50 °C for 1 hour, acidified with 10% aqueous HCl, partitioned between the aqueous and dichloromethane, and the aqueous phase extracted with dichloromethane. The combined organic phases were dried over $MgSO_4$, filtered, concentrated, and purified by HPLC (ACN/H_2O with 0.1% TFA modifier) to afford compound **50**. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 10.47 (t, *J* = 5.8 Hz, 1H), 8.42 (s, 1H), 7.35 (q, *J* = 8.6, 8.2 Hz, 1H), 6.81 (q, *J* = 8.7, 8.0 Hz, 2H), 6.41 (dd, *J* = 10.0, 3.6 Hz, 1H), 4.79 (s, 1H), 4.65 (s, 2H), 4.36 – 4.26 (m, 2H), 4.20 – 4.08 (m, 2H), 3.98 (dd, *J* = 12.4, 10.2 Hz, 1H), 3.88 (t, *J* = 11.8 Hz, 2H), 2.27 (dt, *J* = 13.3, 3.1 Hz, 1H), 2.15 – 2.06 (m, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}F_2N_3O_6$: 448.40; found: 448.2.

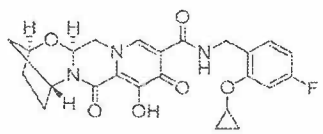
Step 3b

Magnesium bromide (13 mg, 0.07 mmol) was added to a solution of intermediate **51-A** (13.2 mg, 0.03 mmol, absolute stereochemistry unknown) in 1 mL acetonitrile. The reaction mixture was stirred at 50 °C for 1 hour, acidified with 10% aqueous HCl, partitioned between the aqueous and dichloromethane, and the aqueous phase extracted with dichloromethane. The combined organic phases were dried over $MgSO_4$, filtered, concentrated, and purified by HPLC (ACN/H_2O with 0.1% TFA modifier) to afford compound **51**. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 10.47 (t, *J* = 5.8 Hz, 1H), 8.42 (s, 1H), 7.35 (q, *J* = 8.6, 8.2 Hz, 1H), 6.81 (q, *J* = 8.7, 8.0 Hz, 2H), 6.41 (dd, *J* = 10.0, 3.6 Hz, 1H), 4.79 (s, 1H), 4.65 (s, 2H), 4.36 – 4.26 (m, 2H), 4.20 – 4.08 (m, 2H), 3.98 (dd, *J* = 12.4, 10.2 Hz, 1H), 3.88 (t, *J* = 11.8 Hz, 2H), 2.27 (dt, *J* = 13.3, 3.1 Hz, 1H), 2.15 – 2.06 (m, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}F_2N_3O_6$: 448.40; found: 448.2.

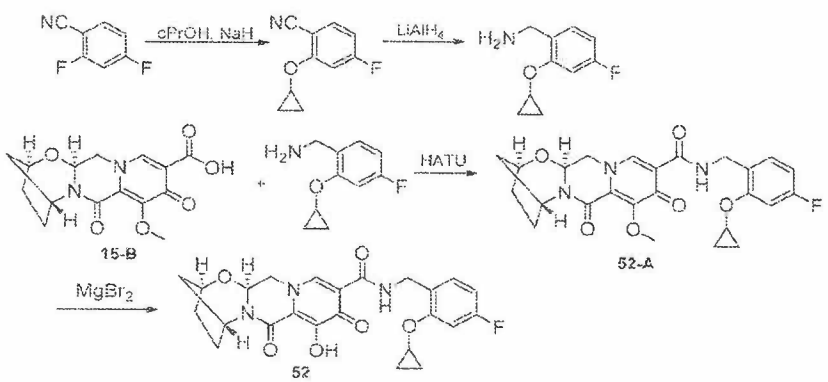
Example 52

Preparation of Compound 52

(2S,5R,13aS)-N-(2-cyclopropoxy-4-fluorobenzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



52



Step 1

A solution cyclopropanol (1.9 g, 29 mmol) in 20 mL dioxane was added dropwise to a 0 °C solution of Sodium hydride (60% dispersion in mineral oil, 1.04 g, 26 mmol) in 80 mL dioxane. The reaction mixture was allowed to warm to room temperature, 2,4-difluorobenzonitrile (3.48 g, 25 mmol) was added portionwise, and reaction temperature raised to 95 °C. The reaction solution was cooled to room temperature after stirring for 18 hours, diluted with ethyl acetate, washed twice with water and twice with brine, dried over $MgSO_4$, filtered, and concentrated onto silica gel. Purification by silica gel chromatography (0-10% EtOAc/hexanes) afforded 2-cyclopropoxy-4-fluorobenzonitrile. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 7.52 (dd, *J* =

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8.6, 6.2 Hz, 1H), 7.05 (dd, J = 10.5, 2.3 Hz, 1H), 6.73 (td, J = 8.2, 2.3 Hz, 1H), 3.87 – 3.76 (m, 1H), 0.87 (m, 4H).

Step 2

To a 0 °C suspension of lithium aluminum hydride in THF (1M, 15 mL, 15 mmol) was added 2-cyclopropoxy-4-fluorobenzonitrile in 14 mL diethyl ether dropwise. The reaction solution was stirred for 3 hours, gradually warming to room temperature, at which point it was recooled to 0 °C, an additional 8 mL lithium aluminum hydride in THF (1M, 8 mmol) added, and stirred for an additional 90 minutes. The reaction was quenched by sequential addition of 0.9 mL water, 0.9 mL 15% $NaOH_{(aq)}$, and 2.7 mL water. The reaction was filtered through celite with diethyl ether rinses, dried over $MgSO_4$, and concentrated to afford 2-cyclopropoxy-4-fluorobenzylamine of sufficient purity to carry on as crude. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 7.17 – 7.08 (m, 1H), 6.96 (dd, J = 10.9, 2.4 Hz, 1H), 6.61 (td, J = 8.3, 2.5 Hz, 1H), 3.78 – 3.66 (m, 3H), 0.89 – 0.72 (m, 4H).

Step 3

Compound **15-B** (46 mg, 0.14 mmol) was taken up in 1 mL acetonitrile and treated with 2-cyclopropoxy-4-fluorobenzylamine (32 mg, 0.18 mmol), HATU (62 mg, 0.16 mmol), N,N-diisopropylethylamine (DIPEA) (0.04 mL, 0.22 mmol), and stirred at room temperature for 2 hours, after which LCMS analysis revealed complete consumption of compound **15-B** and formation of intermediate **52-A**. The reaction mixture was carried onto the next step.

Step 4

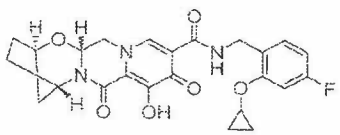
To the crude reaction solution of the previous step was added $MgBr_2$ (56 mg, 0.30 mmol). The reaction mixture was stirred at 50 °C for 90 minutes, acidified with 10% aqueous HCl, partitioned between the aqueous and dichloromethane, and the aqueous phase extracted with dichloromethane. The combined organic phases were dried over $MgSO_4$, filtered, concentrated, and purified by HPLC (ACN/H_2O with 0.1% TFA modifier) to afford compound **52**. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.44 (s, 1H), 10.21 (t, J = 5.8 Hz, 1H), 8.41 (s, 1H), 7.22 – 7.15 (m, 1H), 7.12 (dd, J = 11.2, 2.5

Hz, 1H), 6.72 (td, J = 8.5, 2.5 Hz, 1H), 5.42 (dd, J = 9.6, 4.1 Hz, 1H), 5.07 (s, 1H), 4.66 (dd, J = 12.8, 4.1 Hz, 1H), 4.58 (s, 1H), 4.34 (dd, J = 5.6, 2.4 Hz, 2H), 4.04 – 3.91 (m, 2H), 1.92 (s, 4H), 1.82 (d, J = 11.9 Hz, 1H), 1.55 (dt, J = 12.4, 3.5 Hz, 1H), 0.80 (q, J = 6.3, 5.7 Hz, 2H), 0.72 (q, J = 6.0, 4.9 Hz, 2H). **LCMS-ESI**$^+$ (m/z): $[M+H]^+$ calculated for $C_{24}H_{25}FN_3O_6$: 470.17; found: 470.1.

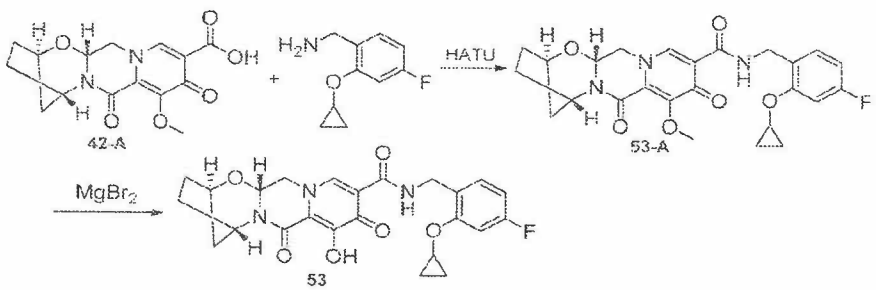
Example 53

Preparation of Compound **53**

(2R,5S,13aR)-N-(2-cyclopropoxy-4-fluorobenzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



53



Step 1

Compound **42-A** (46 mg, 0.14 mmol) was taken up in 1 mL acetonitrile and treated with 2-cyclopropoxy-4-fluorobenzylamine (33 mg, 0.18 mmol), HATU (61 mg, 0.16 mmol), N,N-diisopropylethylamine (DIPEA) (0.04 mL, 0.24 mmol), and stirred at room temperature for 2 hours, after which LCMS analysis revealed complete consumption of compound **42-A** and formation of intermediate **53-A**. The reaction mixture was carried onto the next step.

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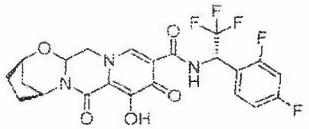
Step 2

To the crude reaction solution of the previous step was added $MgBr_2$ (55 mg, 0.30 mmol). The reaction mixture was stirred at 50 °C for 90 minutes, acidified with 10% aqueous HCl, partitioned between the aqueous and dichloromethane, and the aqueous phase extracted with dichloromethane. The combined organic phases were dried over $MgSO_4$, filtered, concentrated, and purified by HPLC (ACN/H_2O with 0.1% TFA modifier) to afford compound **53**. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 12.44 (s, 1H), 10.21 (t, J = 5.8 Hz, 1H), 8.41 (s, 1H), 7.22 – 7.15 (m, 1H), 7.12 (dd, J = 11.2, 2.5 Hz, 1H), 6.72 (td, J = 8.5, 2.5 Hz, 1H), 5.42 (dd, J = 9.6, 4.1 Hz, 1H), 5.07 (s, 1H), 4.66 (dd, J = 12.8, 4.1 Hz, 1H), 4.58 (s, 1H), 4.34 (dd, J = 5.6, 2.4 Hz, 2H), 4.04 – 3.91 (m, 2H), 1.92 (s, 4H), 1.82 (d, J = 11.9 Hz, 1H), 1.55 (dt, J = 12.4, 3.5 Hz, 1H), 0.80 (q, J = 6.3, 5.7 Hz, 2H), 0.72 (q, J = 6.0, 4.9 Hz, 2H). **LCMS-ESI$^+$** (m/z): [M+H]$^+$ calculated for $C_{24}H_{25}FN_4O_6$: 470.17; found: 470.1.

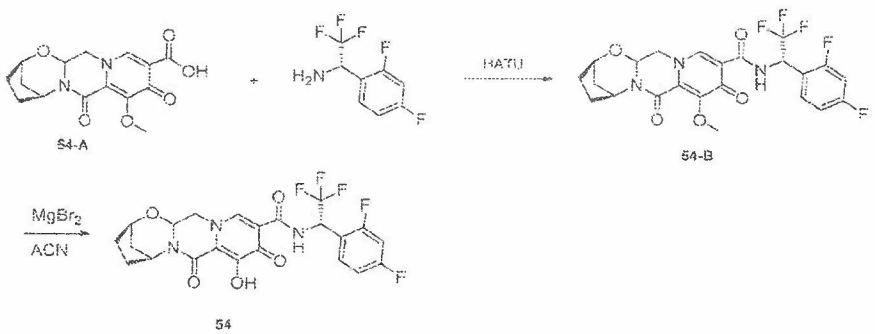
Example 54

Preparation of Compound **54**

(2R,5S)-N-((S)-1-(2,4-difluorophenyl)-2,2,2-trifluoroethyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



54



Step 1

A 50-mL round bottom flask was charged with reactant **54-A** (0.02 g, 0.06 mmol), (S)-1-(2,4-difluorophenyl)-2,2,2-trifluoroethanamine (0.019 g, 0.09 mmol), N,N-diisopropylethylamine (DIPEA) (0.048 g, 0.38 mmol) and HATU (0.036 g, 0.09 mmol) in DCM (2 ml). The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated down, re-dissolved in EtOAc (50 mL), washed with saturated $NaHCO_3$ (2x), saturated NH_4Cl and dried over Na_2SO_4. After concentration, the crude was purified by column chromatography on silica gel with hexane-EtOAc to obtain **54-B**. **LCMS-ESI**$^+$ (*m/z*): [M+H] calculated for $C_{18}H_{16}F_5N_2O_7$: 514; found: 514.

Step 2

A 50-mL round bottom flask was charged with reactant **54-B** (0.03 g, 0.058 mmol) and magnesium bromide (0.03 g, 0.15mmol) in acetonitrile (2 mL). The reaction mixture was heated to 50 °C. After 10 minutes, the reaction mixture was cooled to 0 °C and 1 N hydrochloric acid (0.5 mL) was added in. Then the reaction mixture was diluted with MeOH (2 mL). After filtration, the crude was purified by Pre-HPLC purification (30-70% acetonitrile:water, 0.1% TFA) afforded compound **54** as TFA salt. ^{1}**H-NMR** (400 MHz, Chloroform-d) δ 11.28 (d, J = 9.4 Hz, 1H), 8.39 (s, 1H), 7.54 (q, J = 7.8 Hz, 1H), 7.12 - 6.76 (m, 2H), 6.40 - 5.98 (m, 1H), 5.57 - 5.18 (m, 2H), 4.68 (s, 1H), 4.29 (dd, J = 13.1, 4.0 Hz, 1H), 4.05 (dd, J = 12.9, 9.3 Hz, 1H), 2.39 - 1.94 (m, 4H), 1.86 (t, J = 10.5 Hz, 1H), 1.60 (dt, J = 12.6, 3.4 Hz, 1H). ^{19}**F-NMR** (376 MHz, Chloroform-d) δ -75.30 (t, J = 6.8 Hz, 3 F), -108.33 (dd, J = 8.6, 6.3 Hz, 1F), -111.56 - -

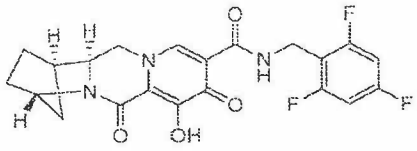
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113.23 (m, 1 F). **LCMS-ESI**$^+$ (m/z): $[M+H]^+$ calculated for $C_{21}H_{20}F_2N_3O_5$: 500.; found: 500.

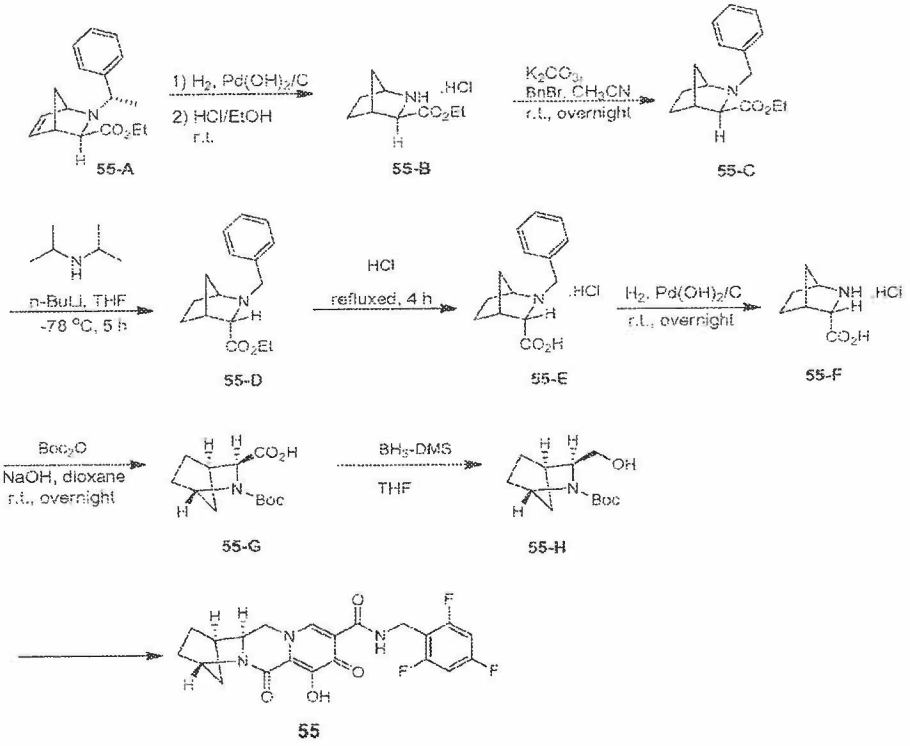
Example 55

Preparation of Compound **55**

(1R,4S,12aS)-7-hydroxy-6,8-dioxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



55



Step 1

A mixture of compound **55-A** (40.60 g, 150 mmol) and $Pd(OH)_2/C$ (12 g) in EtOH (400 mL) under an atmosphere of H_2 was stirred at room temperature overnight. The reaction mixture was filtered and treated with HCl/EtOH (400 ml). The mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated to give compound **55-B**, which was used in next step without purification. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_9H_{10}NO$: 170.1.; found: 170.2.

Step 2

To a solution of compound **55-B** (92.25 g, 0.45 mol) and K_2CO_3 (186.30 g, 1.35 mol) in CH_3CN (1 L) was added benzyl bromide (76.50 g, 0.45 mol) at 0 °C. The mixture was stirred at room temperature overnight. The reaction mixture was filtered, concentrated and the residue was purified by chromatography on silica gel to give compound **55-C**.

Step 3

To a mixture of diisopropylamine (50 g, 0.50 mol) in THF (400 mL) was added n-BuLi (200 mL, 0.50 mol) at -78 °C at N_2 atmosphere. After 0.5 h, the reaction mixture was warmed to 20 °C and stirred for 0.5 h. The mixture was cooled to -78 °C and added a solution of compound **55-C** (64.75 g, 0.25 mol) in THF (600 mL) under N_2 atmosphere. The mixture was stirred for 4 h and quenched with saturated NH_4Cl solution. The mixture was extracted with EtOAc and the organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel to give compound **55-D**.

Step 4

A mixture of compound **55-D** (129.50 g 0.50 mol) in 4N HCl (1.30 L) was refluxed for 4 h. the mixture was concentrated. The residue was purified by HPLC to give compound **55-E**.

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Step 5

To a mixture of compound **55-E** (47 g, 176 mmol) and $Pd(OH)_2/C$ (9 g) in EtOH (400 mL) under an atmosphere of H_2 was stirred at room temperature overnight. The reaction mixture was concentrated to give compound **55-F**, which was used in next step without purification. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 4.22 (s, 1H), 4.06 (s, 1H), 2.98-2.95 (d, J = 11.2 Hz, 1H), 1.96-1.93 (d, J = 11.2 Hz, 1H), 1.86-1.82 (m, 2H), 1.76-1.74 (d, J = 9.2 Hz, 2H), 1.49 (s, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_7H_{12}NO_2$: 142.1.; found: 142.1.

Step 6

To a mixture of compound **55-F** (29.20 g, 165 mmol) and 2N NaOH solution (330 mL, 0.66 mol) in dioxane (120 mL) was added Boc_2O (39.60 g, 181 mmol) at 0 °C. The reaction mixture was stirred at room temperature overnight. The mixture was adjusted with 3N HCl to pH=5~6 and extracted with DCM. The organic layer was dried over Na_2SO_4, filtered and concentrated to give **55-G**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 4.40 (s, 1H), 4.26 (s, 1H), 2.89 (s, 1H), 1.76-1.74 (s, 1H), 1.69-1.59 (m, 4H), 1.50 (s, 1H), 1.47 (s, 9H). **LCMS-ESI$^+$** (*m/z*): $[M+Na]^+$ calculated for $C_{12}H_{19}NNaO_4$: 264.1.; found: 264.1.

Step 7

To a mixture of compound **55-G** (500 mg, 2.07 mmol) in THF (10 mL) chilled to 0 °C was added BH_3-DMS THF complex (2N in THF, 8.23 mmol, 4.1 mL) slowly. Gas evolution occured. Internal temperature was monitored to ensure no major exotherm. Reaction was allowed to warm to r.t. overnight. Some starting material remained by LC/MS, additional 2 mL BH_3-DMS THF complex was added and the mixture was stirred for additional 3 hr then cooled reaction to 0 °C and slowly quenched with methanol (gas evolution occurs). Internal temperature monitored to ensure exotherm below 25 °C. The mixture was concentrated then purified by silica gel chromotography (20-40% EtOAc/Hexanes) to afford **55-H**.

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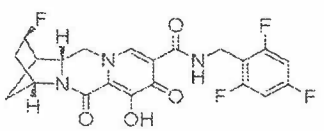
Step 8

Compound **55** was prepared as described for Example 41, substituting **55-H** for **41-B** to afford compound **55**. **^{1}H-NMR** (400 MHz, DMSO-d6) δ 11.81 (s, 1H), 10.40 (t, J = 5.8 Hz, 1H), 8.39 (s, 1H), 7.19 (t, J = 8.6 Hz, 2H), 4.59 – 4.48 (m, 4H), 4.16 (t, J = 12.2 Hz, 1H), 4.03 (d, J = 12.2 Hz, 1H), 2.69 (s, 1H), 1.75 (d, J = 10.1 Hz, 1H), 1.69 – 1.55 (m, 5H). ^{19}F NMR (376 MHz, DMSO-d6) δ -109.3 (m, 1F), -112.5 (m, 1F). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{19}F_3N_3O_4$: 434.13.; found: 434.32.

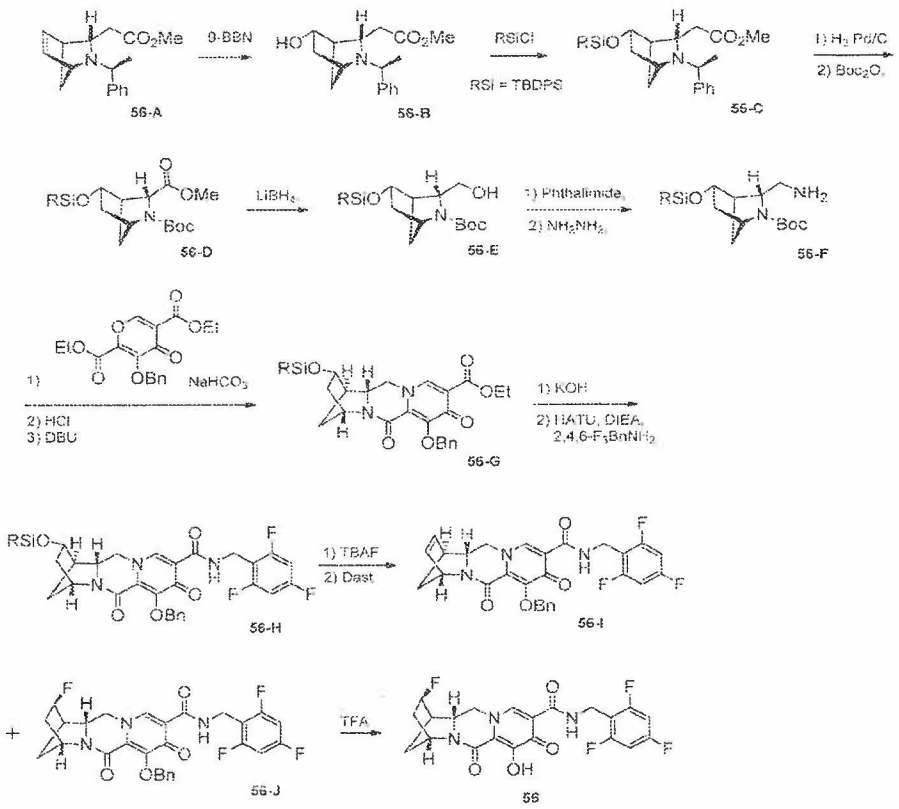
Example 56

Preparation of Compound **56**

(1R,2S,4R,12aR)-2-fluoro-7-hydroxy-6,8-dioxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



56



Step 1

A solution of **56-A** (5 g, 19.43 mmol) in tetrahydrofuran (65 ml) was cooled in an ice bath as 0.5 M 9-borabicyclo[3.3.1]nonane (48.58 ml) was added dropwise. The reaction mixture was warmed up to room temperature. After 18 hours, the reaction was cooled to 0 °C and a mixture of 2M sodium hydroxide (34 ml) and hydrogen peroxide (9.34 ml, 97.15 mmol) was added dropwise. After 2 hours at 0 °C, the reaction was warmed up to room temperature and stirred for 1 hour. The mixture was diluted with EtOAc and washed with water. The aqueous fractions were extracted with EtOAc, and the organic fractions combined were dried (Na_2SO_4) and concentrated. The residue was purified by silica column chromatography (50-70% EtOAc/hexanes) to afford **56-B** (3.05 g, 57%). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{16}H_{21}NO_3$: 275.34; found: 276.122.

Step 2

To a solution of **56-B** (1.45 g, 5.27 mmol) in N,N-dimethylformamide (12 ml) was added tert-butylchlorodiphenylsilane (1.51 ml, 5.79 mmol) and imidazole (1.08 g, 15.8 mmol). After 18 hours, the mixture was diluted with water, extracted into EtOAc (2x), the organic fractions were combined, dried (Na_2SO_4), and concentrated. The residue was purified by silica column chromatography (10-20% EtOAc/hexanes) to afford **56-C** (2.6 g, 96.1%). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{32}H_{39}NO_3Si$: 513.74; found: 514.625.

Step 3

To a solution of **56-C** (3.27 g, 6.36 mmol) in EtOH (26 mL) and acetic acid (3 mL) was added 10% PdOH/C (0.52 g, 3.7 mmol) and the suspension was shaken in a Parr apparatus at 50 atm for 20 hours. After filtering through Celite, the cake was washed with EtOH, the filtrate was concentrated under vacuum. The residue was dissolved in ethanol (26 ml) and acetic acid (3 ml, 52.4 mmol), treated with 10% PdOH/C (0.52 g, 3.7 mmol) and shaken in a Parr apparatus at 50 atm for 20 hours. Filtered through Celite, the cake was washed with EtOH, the filtrate was concentrated under vacuum to dryness to afford the crude deprotected product (2.07g, 79.4 %). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{24}H_{33}NO_3Si$: 409.59; found: 410.485.

To the crude residue (2 g, 4.88 mmol) and di-tert-butyl dicarbonate 97% (2.14 g, 9.79 mmol) in THF (20 ml) was added N,N-diisopropylethylamine (DIPEA) (2.14 ml, 12.27 mmol). After 20 h, the reaction mixture was diluted with water, extracted into EtOAC (2x) and the two organic fractions were washed with water, combined, dried (Na_2SO_4), and concentrated. The residue was purified by silica column chromatography (10-20% EtOAc/Hexanes) to afford **56-D** (2.13 g, 86.14%). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{30}H_{41}NO_5Si$: 523.74; found: 523.922.

Step 4

A solution of **56-D** (2.07 g, 4.06 mmol) in THF (20 ml) was stirred in an ice bath as 2.0 M $LiBH_4$ in THF (4.07 ml) was added and the resulting mixture was stirred at room temperature for 18 h. After, the reaction mixture was diluted with ethyl

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acetate and treated slowly with water. The two phases were separated, and the aqueous fraction was extracted again with ethyl acetate. The two organic fractions were washed with water, combined, dried (Na_2SO_4), and concentrated. The residue was purified by silica column chromatography (20-40% EOAc/hexanes) to afford **56-E** (1.59 g, 81.3%). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{25}H_{39}NO_4Si$: 481.7; found: 482.337.

Step 5

A mixture of **56-E** (1.58 g, 3.28 mmol), phthalimide (0.79 g, 5.38 mmol) and triphenylphosphine (1.93 g, 7.37 mmol) in THF (90 ml) was cooled in an ice bath. Diisopropyl azodicarboxylate, 95% (1.46 ml, 7.42 mmol) was added. The mixture was then warmed up to room temperature and stirred for 20 h. After, the reaction mixture was concentrated and the residue dissolved in ether, cooled in an ice bath and stirred for 1.5 h. The solids were filtered off and the filtrate was concentrated. The residue was purified by silica column chromatography (10-30% EtOAc/hexanes) to afford the protected amino compound (1.86 g, 92.8%).

A solution of the protected amino compound **56-F** (1.85 g, 3.03 mmol) and hydrazine hydrate (0.6 ml, 12.39 mmol) in ethanol (19 ml) was stirred at 70 °C for 2 h. The reaction mixture was cooled in an ice bath, ether (10 ml) was added and the mixture was stirred for 30 min. The solid formed was filtered off and the filtrate was concentrated under vacuum to dryness.

Step 6

A mixture of crude amino compound **56-F** (991 mg, 2.06 mmol), compound **38-F** (Example 38) (714 mg, 2.06 mmol) and $NaHCO_3$ (347 mg, 4.12 mmol) in water (15 mL) and EtOH (15 mL) was stirred for 20 h. The reaction mixture was concentrated under vacuum and the residue was partitioned between water and EtOAc. The aqueous layer was re-extracted with EtOAc and the combined organic layers were dried (Na_2SO_4) and concentrated. The residue (1.5 g) was dissolved in CH_2Cl_2 (5 mL) and 4N HCl in dioxane (18.6 mL) was added. After 1.5 hours the mixture was concentrated to dryness, co-evaporated with toluene and dried in vacuo.

The crude residue (1.38 g) and DBU (1.4 ml, 9.38 mmol) in toluene (25 ml) was stirred at 110 °C. After 35 minutes the mixture was concentrated and the

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residue was purified by silica column chromatography (5-15% MeOH/EtOAc) to afford **56-G** (450 mg, 72.3%). **LCMS-ESI$^+$** (*m/z*): [M+H]$^+$ calculated for $C_{39}H_{42}N_2O_6Si$: 662.85; found: 663.766.

Step 7

The mixture of **56-G** (890 mg, 1.34 mmol) in MeOH (14 ml) and THF (14 ml) was stirred at room temperature as 1M KOH (7.09 ml) was added. After 30 min the reaction mixture was neutralized with 1N HCl, extracted into EtOAc (2x) and the combined organic extracts were dried (Na_2SO_4) and concentrated.

A suspension of the crude residue (850 mg), 2,4,6-trifluorobenzylamine (248 mg, 1.54 mmol) and HATU (662 mg, 1.74 mmol) in dichloromethane (5 ml) was stirred at room temperature as N,N-diisopropylethylamine (DIPEA) (1.63 ml, 9.37 mmol) was added. After 1 h, additional 2,4,6-difluorobenzylamine (32 mg, 0.2 mmol), HATU (153 mg, 0.4 mmol) and N,N-diisopropylethylamine (DIPEA) (0.12 ml, 0.67 mmol) were added. After 30 minutes the mixture was diluted with water, extracted into EtOAc (3x) the combined organic phases were dried (Na_2SO_4), concentrated and the residue was purified by silica column chromatography (50-75% EtOAc/hexanes) to afford **56-H** (919 mg, 88.23%). **LCMS-ESI$^+$** (*m/z*): [M+H]$^+$ calculated for $C_{44}H_{42}F_3N_3O_5Si$: 777.9; found: 778.409.

Step 8

A solution of **56-H** (915 mg, 1.18 mmol) in THF (5 ml) was stirred in an ice bath as 1.0 M tetrabutylammonium fluoride in THF (1.18 ml) was added dropwise. The resulting mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under vacuum and the residue was diluted with EtOAc, washed with water, dried (Na_2SO_4), concentrated and the residue was purified by silica column chromatography (50-75% EtOAc/hexanes then 5% MeOH/EtOAc). The resulting material (248 mg, 0.46 mmol) was dissolved in dichloromethane (2 ml) cooled to -78°C as diethylaminosulfur trifluoride (0.07 mL, 0.55 mmol) was added dropwise and the reaction was warmed to room temperature and stirred for 1 h. The reaction was cooled in an ice bath and quenched with saturated $NaHCO_3$, two phases were separated, and the separated aqueous fraction was extracted with CH_2Cl_2. The two organic fractions

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were combined dried (Na_2SO_4), and concentrated. The residue was purified by silica column chromatography (1% MeOH/EtOAc) to afford **56-J** (75 mg) (**LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{28}H_{23}F_4N_3O_4$: 541.49; found: 542.320) and **56-I** (30 mg) (**LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{28}H_{22}F_3N_3O_4$: 521.49; found: 522.05).

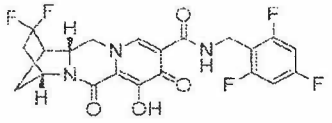
Step 9

Compound **56-J** (75 mg, 139 mmol) was dissolved in TFA (1 mL), stirred at room temperature for 10 minutes, and the solution was concentrated. The residue was purified by reverse phase HPLC (Gemini, 15 to 43% ACN/H_2O + 0.1% TFA) to afford compound **56**. **^{1}H-NMR** (400 MHz, DMSO-d6) δ 10.67 (s, 1H), 7.80 (s, 1H), 7.17 (t, J = 8.6 Hz, 2H), 5.45 – 5.18 (m, 1H), 4.70 – 4.39 (m, 3H), 4.23 (d, J = 11.5 Hz, 1H), 4.11 – 3.85 (m, 2H), 2.85 (dd, J = 4.2, 2.0 Hz, 1H), 2.34 – 2.13 (m, 1H), 1.81 (s, 1H), 1.55 – 1.33 (m, 2H). **^{19}F-NMR** (376 MHz, DMSO-d_6) δ -74.20 (m), -106.95 – -116.45 (m), -190.65 – -194.54 (m).

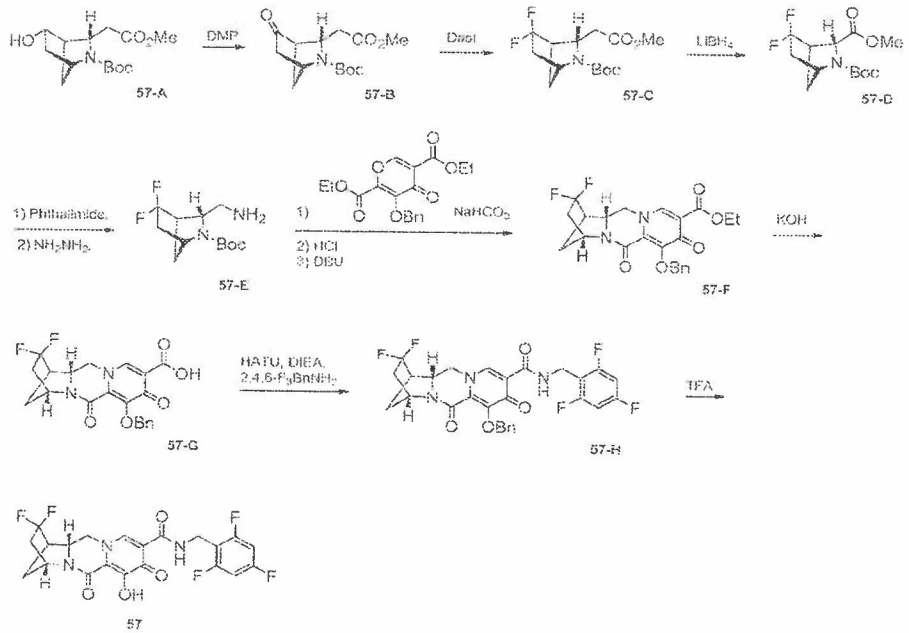
Example 57

Preparation of Compound **57**

(1R,4R,12aR)-2,2-difluoro-7-hydroxy-6,8-dioxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



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Step 1

A solution of **57-A** (1.45 g, 5.34 mmol) in dichloromethane (30 ml) was cooled in an ice bath as Dess Martin periodinane (4.53 g, 10.69 mmol) was added in portions and the reaction was stirred at room temperature for 18 h. The reaction was quenched by addition of water, the precipitate was filtered off and a saturated solution of $Na_2S_2O_3$ was added. The mixture was stirred until the biphasic solution turned then saturated $NaHCO_3$ was added and the aqueous layer extracted with CH_2Cl_2. The combined organic fractions were dried (Na_2SO_4) and concentrated. The residue was purified by silica column chromatography (30-50% EtOAc/Hexanes) to afford 57-B (1.13 g, 78.2 %). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{13}H_{19}NO_5$: 269.29; found: 269.722.

Step 2

A solution of **57-B** (0.5 g, 1.86 mmol) in dichloromethane (10 ml) was cooled to -78°C as diethylaminosulfur trifluoride (0.52 mL, 3.91 mmol) was added dropwise and the reaction was warmed to room temperature and stirred for 18 h. The

reaction was cooled in an ice bath and quenched with saturated $NaHCO_3$, two phases were separated, and the separated aqueous fraction was extracted with CH_2Cl_2. The two organic fractions were combined, dried (Na_2SO_4) and concentrated. The residue was purified by silica column chromatography (20-50% EtOAc/hexanes) to afford **57-C** (518 mg, 95.39%). **^{1}H-NMR** (400 MHz, Chloroform-d) δ 4.43 (s, 1H), 4.36 – 4.27 (m, 1H), 4.22 (s, 1H), 3.75 (s, 3H), 2.95 (t, J = 8.1 Hz, 1H), 2.30 – 1.98 (m, 2H), 1.85 – 1.71 (m, 1H), 1.44 (m, 9H).

Step 3

A solution of **57-C** (935 mg, 3.21 mmol) in THF (10 ml) was stirred in an ice bath as 2.0 M LiBH4 in THF (3.22 ml) was added and the resulting mixture was stirred at room temperature for 18 h. After, the reaction mixture was diluted with ethyl acetate and water was added slowly. The two phases were separated, and the separated aqueous fraction was extracted with ethyl acetate. The two organic fractions were washed with water, combined, dried (Na_2SO_4), and concentrated. The residue was purified by silica column chromatography (20-40% EtOAc/hexanes) to afford **57-D** (724 mg, 85.67%). **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 4.30 – 3.48 (m, 5H), 2.75 – 2.56 (m, 1H), 2.24 – 1.90 (m, 3H), 1.86 – 1.65 (m, 1H), 1.47 (s, 9H).

Step 4

A mixture of **57-D** (720 mg, 2.74 mmol), phthalimide (402 mg, 2.73 mmol) and triphenylphosphine (1.61 g, 6.15 mmol) in THF (45 ml) was cooled in an ice bath. Diisopropyl azodicarboxylate, 95% (1.22 ml, 6.19 mmol), was added. The mixture was then warmed up to room temperature and stirred for 20 h. After, the reaction mixture was concentrated and the residue dissolved in ether, cooled in an ice bath and stirred for 1.5 h. After the solids were filtered off, the filtrate was concentrated. The residue was purified by silica column chromatography (40-60% EtOAc/hexanes) to afford the phthalimide adduct (1.07 g, 99.7%). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{20}H_{22}F_2N_2O_4$: 392.4; found: 393.204

A solution of the phthalimide adduct (1.07 g, 2.73 mmol) and hydrazine hydrate (0.54 mL, 11.15 mmol) in ethanol (10 ml) was stirred at 70 °C for 2 hours. The reaction mixture was cooled in an ice bath and ether (10 ml) was added. The mixture

was stirred for 30 min. The solid formed was filtered off and the filtrate was concentrated under vacuum to dryness to afford crude **57-E**.

Step 5

A mixture of crude **57-E** (709 mg, 2.7 mmol) compound **38-F** (Example 38) (936 mg, 2.7 mmol) and $NaHCO_3$ (454 mg, 5.41 mmol) in water (15 mL) and EtOH (15 mL) was stirred for 20 h. The reaction mixture was concentrated under vacuum and the residue was partitioned between water and EtOAc. The aqueous layer was re-extracted with EtOAc and the combined organic layers were dried (Na_2SO_4) and concentrated. The residue (1.5 g) was dissolved in CH_2Cl_2 (7 mL) and 4N HCl in dioxane (26.9 mL) was added. After 1.5 hours the mixture was concentrated to dryness, co-evaporated with toluene and dried in vacuum. The crude residue (1.3 g) and DBU (2 ml, 13.4 mmol) in toluene (25 ml) was stirred at 110 °C. After 35 minutes the mixture was concentrated and the residue was purified by silica column chromatography (5-15% MeOH/EtOAc) to afford **57-F** (426 mg, 36.17%). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{23}H_{22}F_2N_2O_5$: 444.43; found: 445.280.

Step 6

The mixture of compound **57-F** (426 mg, 0.96 mmol) in MeOH (7 ml) and THF (7 ml) was stirred at room temperature as 1M KOH (5.06 ml) was added. After 30 minutes the reaction mixture was neutralized with 1N HCl, extracted into EtOAc (2x) and the combined organic extracts were dried (Na_2SO_4) and concentrated to crude **57-G**.

Step 7

A suspension of the crude residue **57-G** (189 mg), 2,4,6-trifluorobenzylamine (95 mg, 0.59 mmol) and HATU (276 mg, 0.73 mmol) in dichloromethane (3 ml) was stirred at room temperature as N,N-diisopropylethylamine (DIPEA) (0.59 ml, 3.4 mmol) was added. After 1 h he mixture was diluted with water, extracted into EtOAc (3x). The combined organic phases were dried (Na_2SO_4) and concentrated to **57-H**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{28}H_{22}F_5N_3O_4$: 559.48; found: 560.24.

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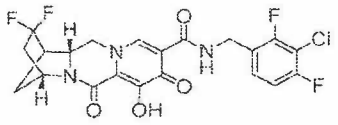
Step 8

Compound **57-H** (150 mg, 0.27 mmol) was dissolved in TFA (2 mL), stirred at room temperature for 10 min, and the solution was concentrated. The residue was purified by reverse phase HPLC (Gemini, 15 to 60% ACN/H_2O + 0.1% TFA), to afford compound **57** (85 mg, 67.5%). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{16}F_5N_3O_4$: 469.36; found: 470.229. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 10.41 (t, *J* = 5.6 Hz, 1H), 8.20 (s, 1H), 7.12 (t, *J* = 8.7 Hz, 2H), 4.79 (s, 1H), 4.48 (m, 3H), 4.10 (m, 2H), 3.02 (d, *J* = 5.7 Hz, 1H), 2.33 (m, 1H), 2.22 – 1.97 (m, 2H), 1.85 (d, *J* = 11.0 Hz, 1H), 1.21 (s, 1H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -69.88 , -71.77 , -74.09 , -88.33 (dd, *J* = 222.6, 23.8 Hz), -109.15 – -109.60 (m), -110.04 , -112.44 (t, *J* = 7.6 Hz).

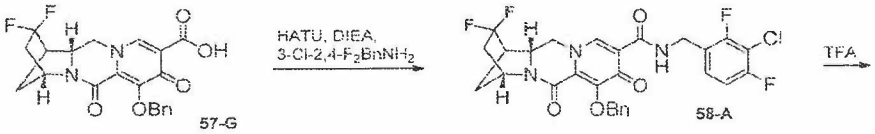
Example 58

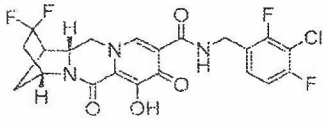
Preparation of Compound **58**

(1R,4R,12aR)-N-(3-chloro-2,4-difluorobenzyl)-2,2-difluoro-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



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Step 1

A suspension of the crude residue **57-G** (120 mg), 3-chloro,2,4-difluorobenzylamine (67 mg, 0.38 mmol) and HATU (175 mg, 0.46 mmol) in dichloromethane (3 ml) was stirred at room temperature as N,N-diisopropylethylamine (DiPEA) (0.38 ml, 0.28 mmol) was added. After 1 h the mixture was diluted with water, extracted into EtOAc (3x) the combined organic phases were dried (Na_2SO_4) and concentrated to yield **58-A**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{25}H_{22}ClF_4N_3O_4$: 575.94; found: 576.394.

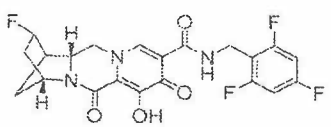
Step 2

Compound **58-A** (166 mg) was dissolved in TFA (2 mL), stirred at room temperature for 10 min, and the solution was concentrated. The residue was purified by reverse phase HPLC (Gemini, 15 to 70% ACN/H_2O + 0.1% TFA), to afford compound **57** (60 mg, 42.8%). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{16}ClF_4N_3O_4$: 485.82; found: 486.135. **^{1}H-NMR** (400 MHz, DMSO-d6) δ 10.77 (t, J = 6.0 Hz, 1H), 7.77 (s, 1H), 7.28 (m, 2H), 4.77 (s, 1H), 4.64 – 4.40 (m, 2H), 4.27 (d, J = 9.1 Hz, 1H), 3.93 (m, 2H), 2.95 (d, J = 5.8 Hz, 1H), 2.51 (s, 1H), 2.42 – 2.17 (m, 1H), 2.14 – 1.89 (m, 2H), 1.77 (m, 1H). **^{19}F-NMR** (376 MHz, DMSO-d_6) δ -87.63 , -88.23 , -108.67 , -109.27 , -116.42 (t, *J* = 7.0 Hz), -118.48 (d, *J* = 7.8 Hz).

Example 59

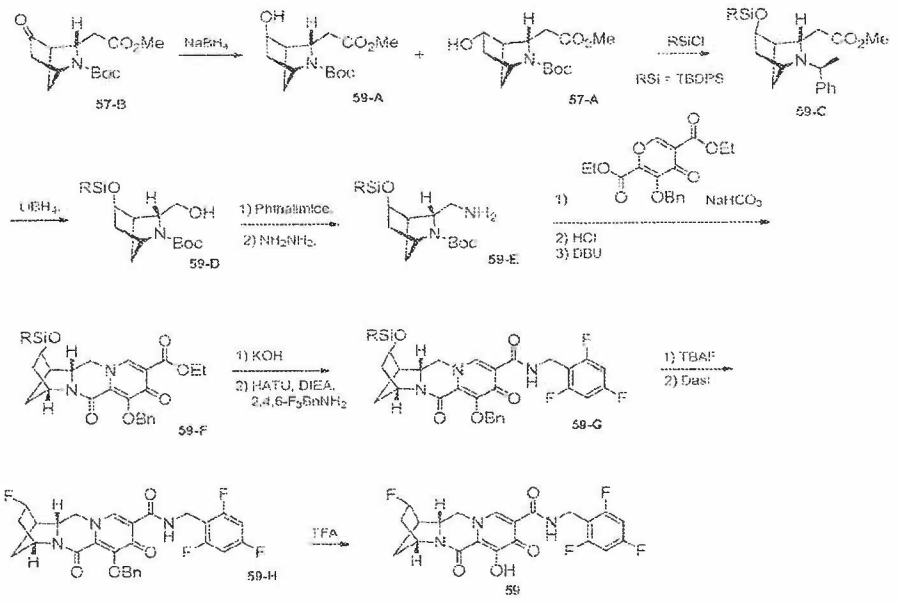
Preparation of Compound **59**

(1R,2R,4R,12aR)-2-fluoro-7-hydroxy-6,8-dioxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



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Step 1

A solution of **57-B** (1.9 g, 7.06 mmol) in methanol (35 mL) was stirred at 0 °C as sodium borohydride (667 mg, 17.64 mmol) was added portionwise and the resulting mixture was stirred at room temperature for 30 min. The reaction mixture was cooled in an ice bath, quenched by addition of water and concentrated. The residue was partitioned between water and EtOAc. The aqueous layer was re-extracted with EtOAc and the combined organic layers were dried (Na_2SO_4) and concentrated The residue was purified by silica column chromatography (30-60% EtOAc/hexanes) to afford **59-A** (1.49 g). **^{1}H-NMR** (400 MHz, chloroform-*d*) δ 4.57 (s, 1H), 4.52 – 4.42 (m, 2H), 4.28 (s, 1H), 4.14 (s, 1H), 3.72 (d, J = 2.1 Hz, 3H), 2.74 (s, 1H), 2.08 – 1.87 (m, 2H), 1.43 (d, J = 23.1 Hz, 10H) and **57-A** (96 mg): **^{1}H-NMR** (400 MHz, chloroform-*d*) δ 4.65 – 4.40 (m, 2H), 4.34 – 4.02 (m, 1H), 3.73 (d, J = 2.3 Hz, 3H), 2.74 (t, J = 5.3 Hz, 1H), 2.12 – 1.55 (m, 3H), 1.52 – 1.18 (m, 11H).

Step 2

To a solution of **59-A** (686 mg, 2.53 mmol) in N,N-dimethylformamide

(5 ml) was added tert-butylchlorodiphenylsilane (0.723 mL, 2.78 mmol) and imidazole (516 mg, 7.56 mmol). After 18 h, the mixture was diluted with water, extracted into EtOAc (2x), and the organic fractions were combined, dried (Na_2SO_4), and concentrated. The residue was purified by silica column chromatography (10-20% EtOAc/hexanes) to afford **59-C**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{29}H_{39}NO_5Si$: 509.71: found: 510.793.

Step 3

A solution of **59-C** (1.23 g, 2.41 mmol) in THF (13 ml) was stirred in an ice bath as 2.0 M $LiBH_4$ in THF (2.42mL, 4.84 mmol)) was added and the resulting mixture was stirred at room temperature for 18 h. After the reaction mixture was diluted with ethyl acetate water was added slowly, two phases were separated, and the separated aqueous fraction was extracted with ethyl acetate. The two organic fractions were washed with water, combined, dried (Na_2SO_4), and concentrated. The residue was purified by silica column chromatography (20-40% EtOAc/hexanes) to afford **59-D**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{28}H_{39}NO_4Si$: 481.7; found: 482.741.

Step 4

A mixture of **59-D** (963 mg, 2.0 mmol), phthalimide (482 mg, 3.28 mmol) and triphenylphosphine (1.18 g, 4.49 mmol) in THF (50 ml) was cooled in an ice bath. Diisopropyl azodicarboxylate, 95% (0.89 mL, 4.52 mmol) was added. The mixture was then warmed up to room temperature and stirred for 20 h. After, the reaction mixture was concentrated and the residue dissolved in ether, cooled in an ice bath and stirred for 1.5 h. After, the solids were filtered off and the filtrate was concentrated. The residue was purified by silica column chromatography (10-30% EtOAc/hexanes) to afford the phthalimide adduct. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{36}H_{43}N_2O_5Si$: 610.81; found: 611.935.

A solution of the phthalimide adduct (1.2 g, 1.97 mmol) and hydrazine hydrate (0.4 ml, 8.03 mmol) in ethanol (12 ml) was stirred at 70 °C for 2h. The reaction mixture was cooled in an ice bath and ether (10 ml) was added, the mixture was stirred for 30 min. The solid formed was filtered off and the filtrate was concentrated under vacuum to dryness to afford **59-E**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for

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$C_{28}H_{40}N_2O_3Si$: 480.71; found: 481.356.

Step 5

A mixture of crude **59-E** (770 mg, 1.60 mmol), compound **38-F** (Example 38) (555 mg, 1.60 mmol) and $NaHCO_3$ (269 mg, 3.20 mmol) in water (12 mL) and EtOH (12 mL) was stirred for 20 h. The reaction mixture was concentrated under vacuum and the residue was partitioned between water and EtOAc. The aqueous layer was re-extracted with EtOAc and the combined organic layers were dried (Na_2SO_4) and concentrated.

The residue (1.29 g) was dissolved in CH_2Cl_2 (4 mL) and 4N HCl in dioxane (15.6 mL) was added. After 1.5 hours the mixture was concentrated to dryness, co-evaporated with toluene and dried in vacuum. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{41}H_{48}N_2O_7Si$: 708.91; found: 709.782.

The crude residue (1.09 mg) and DBU (1.17 ml, 7.8 mmol) in toluene (20 ml) was stirred at 110 °C. After 35 min the mixture was concentrated and the residue was purified by silica column chromatography (5-15% MeOH/EtOAc) to afford **59-F**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{39}H_{42}N_2O_6Si$: 662.85; found: 663.677.

Step 6

A mixture of **59-F** (680 mg, 1.03 mmol) in MeOH (10 ml) and THF (10 ml) was stirred at room temperature as 1M KOH (5.42 ml) was added. After 30 min the reaction mixture was neutralized with 1N HCl, extracted into EtOAc (2x) and the combined organic extracts were dried (Na_2SO_4) and concentrated. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{37}H_{38}N_2O_6Si$: 634.79; found: 635.466.

A suspension of the crude residue (650 mg), 2,4,6-trifluorobenzylamine (214 mg, 1.33 mmol) and HATU (623 mg, 1.64 mmol) in dichloromethane (6 ml) was stirred at room temperature as N,N-diisopropylethylamine (DIPEA) (1.34 ml, 7.68 mmol) was added. After 2 h, the mixture was diluted with water, extracted into EtOAc (3x) nad the combined organic phases were dried (Na_2SO_4), concentrated and the residue was purified by silica column chromatography (50-75% EtOAc/hexanes) to afford **59-G**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{44}H_{42}F_3N_3O_5Si$: 777.9; found:

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778.566.

Step 7

A solution of **59-G** (648 mg, 0.83 mmol) in THF (10 ml) was stirred in an ice bath as 1.0 M tetrabutylammonium fluoride in THF (0.83 ml) was added dropwise and the resulting mixture was stirred at room temperature for 30 min. Additional 1.0 M tetrabutylammonium fluoride in THF (0.1 ml) was added dropwise. After 30 minutes, the reaction mixture was concentrated under vacuum and the residue was diluted with EtOAc, washed with water, dried (Na_2SO_4), concentrated and the residue was purified by silica column chromatography (5% MeOH/EtOAc). A solution of the residue (290 mg, 0.54 mmol) in dichloromethane (3 ml)was cooled to -78°C as diethylaminosulfur trifluoride (0.09 mL, 0.65 mmol) was added dropwise and the reaction was warmed to room temperature and stirred for 2.5 h. The reaction was cooled in an ice bath, quenched with saturated $NaHCO_3$, two phases were separated, and the separated aqueous fraction was extracted with CH_2Cl_2. The two organic fractions were combined, dried (Na_2SO_4), and concentrated. The residue was purified by silica column chromatography (1% MeOH/EtOAc) to afford **59-H**. **LCMS-ESI**$^+$ (*m/z*): [M+H]$^+$ calculated for $C_{28}H_{23}F4N_3O_4$: 541.49; found: 542.320.

Step 8

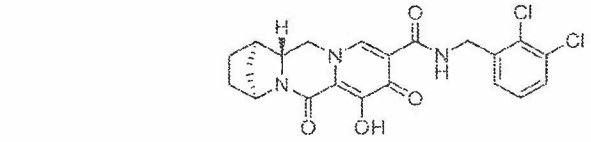
Compound **59-H** (103 mg, 0.19 mmol) was dissolved in TFA (1.4 mL) at room temperature for 15 min, and the solution was concentrated. The residue was suspended in DMF, filtered off, and the precipitated product was washed with water, dried under vacuum to afford compound **59**. **LCMS-ESI**$^+$ (*m/z*): [M+H]$^+$ calculated for $C_{21}H_{17}F_4N_3O_4$: 451.37, found: 452.226. **^{1}H-NMR** (400 MHz, DMSO-d6) δ 11.53 (s, 1H), 10.35 (t, J = 5.8 Hz, 1H), 8.34 (s, 1H), 7.18 (t, J = 8.6 Hz, 2H), 5.15 – 4.88 (m, 1H), 4.73 (d, J = 3.3 Hz, 1H), 4.49 (m, 3H), 4.04 (t, J = 12.4 Hz, 1H), 3.65 (dd, J = 12.4, 3.7 Hz, 1H), 2.95 – 2.76 (m, 1H), 2.26 – 2.03 (m, 1H), 1.96 – 1.64 (m, 3H). **^{19}F-NMR** (376 MHz, DMSO-d_6) δ -73.93 , -74.74 (d, *J* = 28.8 Hz), -109.31 (m), -112.51 (m), -165.65 (m).

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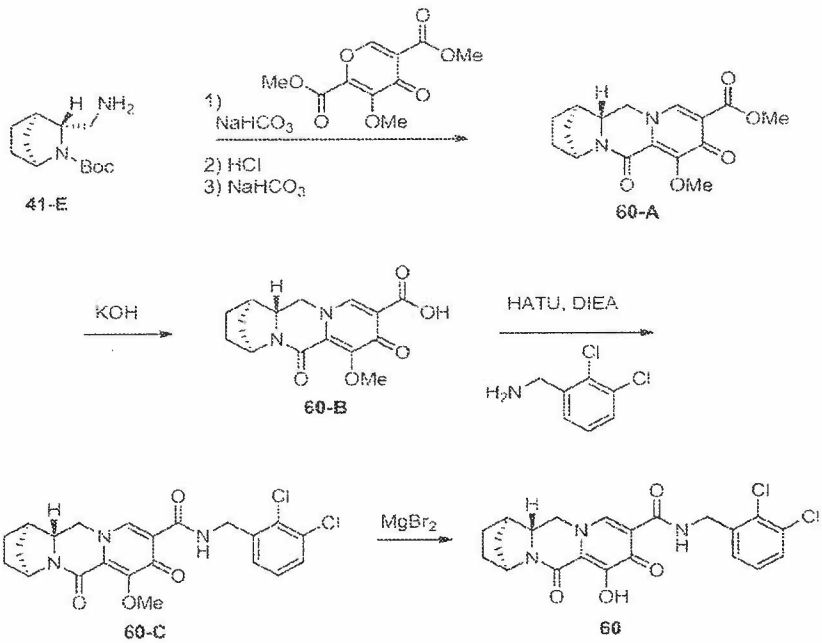
Example 60

Preparation of Compound **60**

(1R,4S,12aR)-N-(2,3-dichlorobenzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



60



Step 1

To a solution of dimethyl 3-methoxy-4-oxo-4H-pyran-2,5-dicarboxylate (5.5 g, 23 mmol) in MeOH (100 mL) was added **41-E** (Example 41) (5 g, 22 mmol) and sodium bicarbonate (3.6 g, 43 mmol). The solution was stirred at room temperature for 1.5 h. 4M HCl (in dioxane, 55 mL, 221 mmol) was added and the solution was heated

to 50 °C for 2h. The reaction was cooled to room temperature and concentrated *in vacuo*. The resulting oil was dissolved in sodium bicarbonate and washed with EtOAc. The aqueous layers were then extracted with CH_2Cl_2 (4x). The combined CH_2Cl_2 extractions were dried over Na_2SO_4 and concentrated to provide **60-A**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{16}H_{19}N_2O_5$: 319.13; found: 319.20.

Step 2

To a suspension of **60-A** (3.7 g, 11.6 mmol) in MeOH (12 mL) and THF (23 mL) was added aqueous KOH (2M, 15.7 mL, 31.4 mmol). The resulting solution was stirred at room temperature for 10 min. Volatiles were removed *in vacuo*, and the resulting aqueous layer was acidified with 1N HCl. The resulting white solid was filtered, washed with water, and dried *in vacuo* to provide **60-B**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 8.36 (s, 1H), 5.01 (d, J = 2.7 Hz, 1H), 4.12 (s, 4H), 3.90 (t, J = 12.2 Hz, 1H), 3.78 (dd, J = 12.1, 3.1 Hz, 1H), 2.69 (s, 1H), 1.95 - 1.71 (m, 4H), 1.70 - 1.54 (m, 2H). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{15}H_{17}N_2O_5$: 305.11; found: 305.15.

Step 3

To a solution of **60-B** (0.10 g, 0.33 mmol) in CH_2Cl_2 (3.5 mL) was added (2,3-dichlorophenyl)methanamine (0.12 g, 0.70 mmol), HATU (0.25 g, 0.66 mmol), and N,N-diisopropylethylamine (DIPEA) (0.29 mL, 1.64 mmol). The resulting solution was stirred at room temperature until judged complete by LC/MS. The reaction mixture was diluted with CH_2Cl_2 and washed with 1N HCl. The aqueous layer was back-extracted with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was dissolved in hot DMF and allowed to precipitate upon cooling. Filtration provided **60-C**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{22}Cl_2N_3O_4$: 462.10; found: 462.14.

Step 4

To a slurry of **60-C** (0.11 g, 0.24 mmol), in acetonitrile (4.5 mL), was added magnesium bromide (0.089 g, 0.48 mmol). The reaction mixture was heated to 45 °C for 2.5 h and then cooled to room temperature. The slurry was diluted with

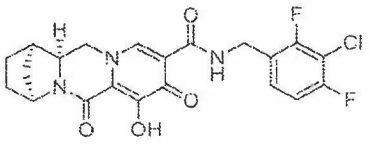
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CH_2Cl_2 and washed with 1N HCl and brine. The aqueous layers were back-extracted with CH_2Cl_2 (2x) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude solid was triturated with methanol and filtered to provide **60**. **^{1}H-NMR** (400 MHz, DMSO-d6) δ 11.72 (s, 1H), 10.50 (t, 1H), 8.34 (s, 1H), 7.55 (dd, 1H), 7.40 – 7.24 (m, 2H), 4.67 (s, 1H), 4.61 (d, 2H), 4.45 (dd, 1H), 3.95 (t, 1H), 3.84 – 3.73 (m, 1H), 1.86 – 1.67 (m, 3H), 1.66 – 1.40 (m, 4H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}Cl_2N_3O_4$: 448.08; found: 448.18.

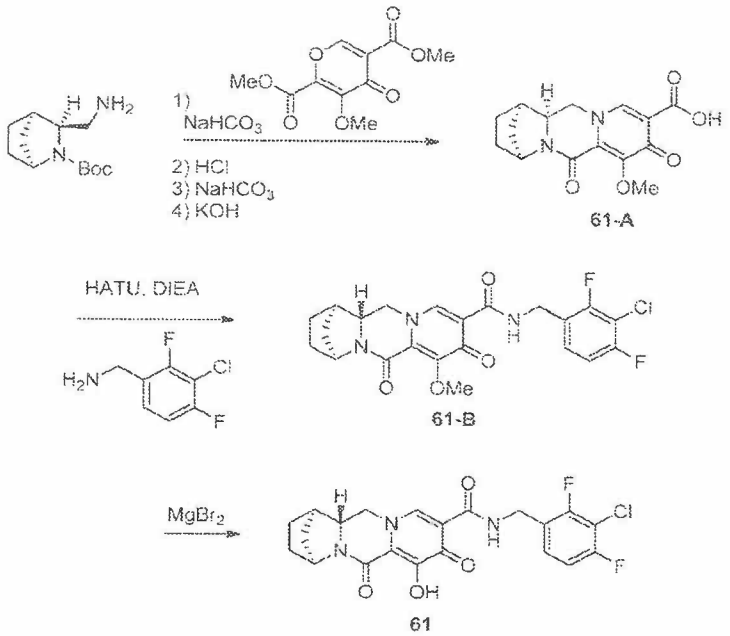
Example 61

Preparation of Compound **61**

(1R,4S,12aS)-N-(3-chloro-2,4-difluorobenzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



61



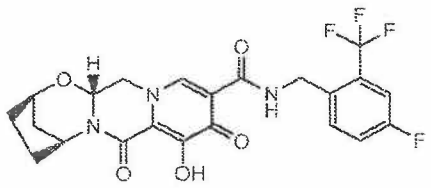
61 was prepared analogously to Example **60**, substituting (1S,3S,4R)-tert-butyl 3-(aminomethyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate (prepared in Example **55**) for **41-E**, and (3-chloro-2,4-difluorophenyl)methanamine for (2,3-dichlorophenyl)methanamine. ^{1}**H-NMR** (400 MHz, DMSO-d6) δ 11.85 (s, 1H), 10.45 (t, 1H), 8.40 (s, 1H), 7.37 (td, 1H), 7.27 (td, 1H), 4.63 - 4.46 (m, 4H), 4.17 (t, 1H), 4.04 (dt, 1H), 1.76 (d, 1H), 1.73 - 1.54 (m, 5H). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{19}ClF_2N_3O_4$: 450.10; found: 450.15.

Example 62

Preparation of Compound **62**

'(2R,5S,13aR)-N-(4-fluoro-2-(trifluoromethyl)benzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide

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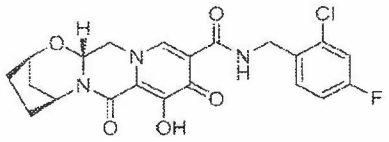
62

Compound **62** was prepared in a similar manner to compound **42** using (4-fluoro-2-(trifluoromethyl)phenyl)methanamine in place of (2,4,6-trifuloropheny1phenyl)methanamine. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 10.50 (s, 1H), 8.38 (s, 1H), 7.57 (dd, 1H), 7.36 (dd, 1H), 7.19 (td, 1H), 5.40 - 5.28 (m, 2H), 4.79 (t, 2H), 4.69 (s, 1H), 4.25 (dd, 1H), 4.03 (dd, 1H), 2.17 - 1.98 (m, 4H), 1.96 - 1.84 (m, 1H), 1.61 (dt, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{20}F_4N_3O_5$: 482.13; found: 482.145.

Example 63

Preparation of Compound **63**

(2R,5S,13aR)-N-(2-chloro-4-fluorobenzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



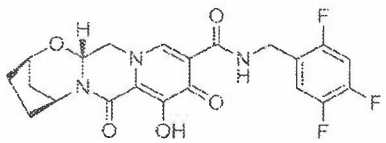
63

Compound **63** was prepared in a similar manner to compound **42** using (2-chloro-4-fluorophenyl)methanamine in place of (2,4,6-trifuloropheny1phenyl)methanamine. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 10.48 (s, 1H), 8.45 (s, 1H), 7.39 (dd, 1H), 7.12 (dd, 1H), 6.93 (td, 1H), 5.37 (d, 1H), 5.31 (t, 1H), 4.68 (s, 3H), 4.29 (d, 1H), 4.04 (t, 1H), 2.21 - 2.01 (m, 4H), 1.97 - 1.82 (m, 1H), 1.67 - 1.56 (m, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}ClFN_3O_5$: 448.10; found: 448.143.

Example 64

Preparation of Compound **64**

(2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,5-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



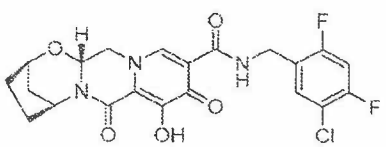
64

Compound **64** was prepared in a similar manner to compound **42** using (2,4,5-trifluorophenyl)methanamine in place of (2,4,6-trifuloropbenylphenyl)methanamine. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 10.42 (s, 1H), 8.42 (s, 1H), 7.19 (ddd, 1H), 6.91 (td, 1H), 5.38 (dd, 1H), 5.31 (t, 1H), 4.69 (s, 1H), 4.61 (d, 2H), 4.29 (dd, 1H), 4.05 (dd, 1H), 2.18 - 2.02 (m, 4H), 1.96 - 1.84 (m, 1H), 1.66 - 1.56 (m, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{19}F_3N_3O_5$: 450.12; found: 450.119.

Example 65

Preparation of Compound **65**

(2R,5S,13aR)-N-(5-chloro-2,4-difluorobenzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



65

Compound **65** was prepared in a similar manner to compound 42 using (5-chloro-2,4-difluorophenyl)methanamine in place of (2,4,6-trifuloropbenylphenyl)methanamine. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 10.47 (t,

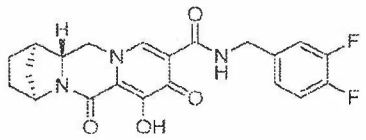
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1H), 8.41 (s, 1H), 7.40 (dd, 1H), 6.90 (t, 1H), 5.37 (dd, 1H), 5.31 (t, 1H), 4.69 (s, 1H), 4.62 (d, 2H), 4.28 (d, 1H), 4.04 (dd, 1H), 2.17 - 2.02 (m, 4H), 1.94 - 1.86 (m, 1H), 1.61 (dt, 1H). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{19}ClF_2N_3O_5$: 466.09; found: 466.107.

Example 66

Preparation of Compound **66**

(1R,4S,12aR)-N-(3,4-difluorobenzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



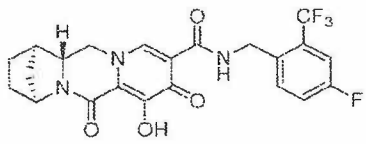
66

Compound **66** was prepared in a similar manner to compound **60** using (3,4-difluorophenyl)methanamine in place of (2,3-dichlorophenyl)methanamine. ^{1}**H-NMR** (400 MHz, Chloroform-*d*) δ 10.59 (s, 1H), 7.24 – 7.16 (m, 2H), 7.14 – 7.04 (m, 2H), 4.91 (s, 1H), 4.58 (d, 3H), 3.94 – 3.82 (m, 1H), 3.79 (d, 1H), 1.99 – 1.81 (m, 4H), 1.76 (d, 1H), 1.70 – 1.60 (m, 3H). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}F_2N_3O_5$: 416.13; found: 416.415.

Example 67

Preparation of Compound **67**

(1R,4S,12aR)-N-(4-fluoro-2-(trifluoromethyl)benzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



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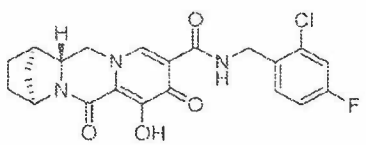
67

Compound **67** was prepared in a similar manner to compound **60** using (4-fluoro-2-(trifluoromethyl)phenyl)methanamine in place of (2,3-dichlorophenyl)methanamine. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 11.72 (s, 1H), 10.55 (s, 1H), 8.29 (s, 1H), 7.61 (s, 1H), 7.36 (dd, 1H), 7.18 (td, 1H), 4.91 (s, 1H), 4.80 (d, 3H), 4.11 (s, 1H), 1.99 – 1.80 (m, 4H), 1.76 (d, 1H), 1.71 – 1.47 (m, 3H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{20}F_4N_3O_4$: 466.13; found: 466.297.

Example 68

Preparation of Compound **68**

(1R,4S,12aR)-N-(2-chloro-4-fluorobenzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



68

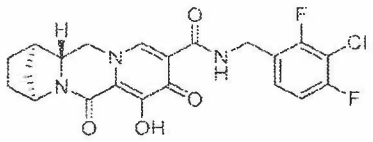
Compound **68** was prepared in a similar manner to compound **60** using (2-chloro-4-fluorophenyl)methanamine in place of (2,3-dichlorophenyl)methanamine. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 11.68 (s, 1H), 10.52 (s, 1H), 8.27 (s, 1H), 7.44 – 7.37 (m, 1H), 7.11 (dd, 1H), 6.93 (td, 1H), 4.90 (s, 1H), 4.68 (d, 2H), 4.16 – 4.01 (m, 1H), 3.88 – 3.70 (m, 2H), 2.00 – 1.79 (m, 4H), 1.75 (d, 1H), 1.70 – 1.57 (m, 2H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{20}ClFN_3O_4$: 432.10; found: 432.214.

Example 69

Preparation of Compound **69**

(1R,4S,12aR)-N-(3-chloro-2,4-difluorobenzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide

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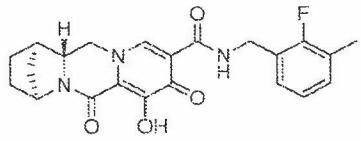
69

Compound **69** was prepared in a similar manner to compound **60** using (3-chloro-2,4-difluorophenyl)methanamine in place of (2,3-dichlorophenyl)methanamine. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 11.71 (s, 1H), 10.48 (s, 1H), 8.26 (s, 1H), 7.27 (s, 1H), 6.92 (td, 1H), 4.90 (s, 1H), 4.66 (d, 2H), 4.08 (s, 1H), 3.91 – 3.69 (m, 2H), 2.01 – 1.79 (m, 3H), 1.75 (d, 1H), 1.71 – 1.44 (m, 2H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{19}ClF_2N_3O_4$: 450.10; found: 450.27.

Example 70

Preparation of Compound **70**

(1R,4S,12aR)-N-(2-fluoro-3-methylbenzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



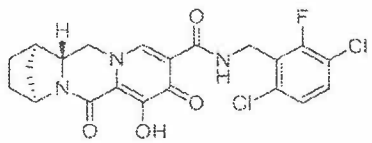
70

Compound **70** was prepared in a similar manner to compound **60** using (2-fluoro-3-methylphenyl)methanamine in place of (2,3-dichlorophenyl)methanamine. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 11.62 (s, 1H), 10.39 (s, 1H), 8.30 (s, 1H), 7.19 (t, 1H), 7.07 (t, 1H), 6.96 (t, 1H), 4.89 (d, 1H), 4.67 (d, 2H), 4.08 (s, 1H), 3.88 - 3.67 (m, 2H), 2.26 (d, 3H), 1.97 - 1.79 (m, 3H), 1.78 - 1.39 (m, 3H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{23}FN_3O_4$: 412.16; found: 412.26.

Example 71

Preparation of Compound 71

(1R,4S,12aR)-N-(3,6-dichloro-2-fluorobenzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



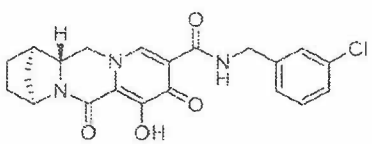
71

Compound **71** was prepared in a similar manner to compound **60** using (3,6-dichloro-2-fluorophenyl)methanamine in place of (2,3-dichlorophenyl)methanamine. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 11.62 (s, 1H), 10.47 (t, 1H), 8.29 (s, 1H), 7.13 (dd, 1H), 4.88 (s, 1H), 4.85 - 4.73 (m, 2H), 4.09 (d, 1H), 3.88 - 3.68 (m, 2H), 1.99 - 1.53 (m, 8H). **LCMS-ESI$^-$** (*m/z*): $[M+H]^-$ calculated for $C_{21}H_{19}Cl_2FN_3O_4$: 466.07; found: 466.257.

Example 72

Preparation of Compound 72

(1R,4S,12aR)-N-(3-chlorobenzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



72

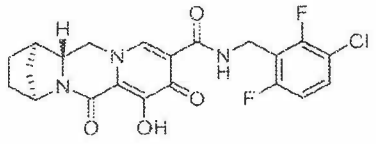
Compound **72** was prepared in a similar manner to compound **60** using (3-chlorophenyl)methanamine in place of (2,3-dichlorophenyl)methanamine. **^{1}H-NMR** (400 MHz, DMSO-d6) δ 11.75 (s, 1H), 10.44 (t, 1H), 8.38 (s, 1H), 7.42 - 7.22 (m, 4H), 4.68 (s, 1H), 4.54 (d, 2H), 4.48 (dd, 1H), 3.97 (t, 1H), 3.81 (dd, 1H), 2.58 (s, 1H), 1.87 -

1.69 (m, 3H), 1.68 - 1.51 (m, 2H), 1.46 (d, 1H). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{21}ClN_3O_4$: 414.11; found: 414.21.

Example 73

Preparation of Compound **73**

(1R,4S,12aR)-N-(3-chloro-2,6-difluorobenzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



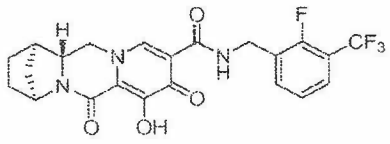
73

Compound **73** was prepared in a similar manner to compound **60** using (3-chloro-2,6-difluorophenyl)methanamine in place of (2,3-dichlorophenyl)methanamine. ^{1}**H-NMR** (400 MHz, DMSO-d6) δ 11.71 (s, 1H), 10.46 (t, 1H), 8.34 (s, 1H), 7.60 (td, 1H), 7.19 (td, 1H), 4.67 (s, 1H), 4.62 (d, 2H), 4.44 (dd, 1H), 3.95 (t, 1H), 3.78 (dd, 1H), 2.57 (s, 1H), 1.86 - 1.68 (m, 3H), 1.67 - 1.49 (m, 2H), 1.45 (d, 1H). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{19}ClF_2N_3O_4$: 450.10; found: 450.16.

Example 74

Preparation of Compound **74**

(1R,4S,12aR)-N-(2-fluoro-3-(trifluoromethyl)benzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



74

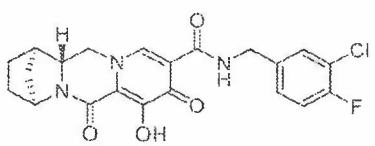
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Compound 74 was prepared in a similar manner to compound **60** using (2-fluoro-3-(trifluoromethyl)phenyl)methanamine in place of (2,3-dichlorophenyl)methanamine. **^{1}H-NMR** (400 MHz, DMSO-d6) δ 11.76 (s, 1H), 10.48 (t, 1H), 8.36 (s, 1H), 7.68 (q, 2H), 7.38 (t, 1H), 4.68 (s, 1H), 4.65 (d, 2H), 4.47 (dd, 1H), 3.96 (t, 1H), 3.80 (dd, 1H), 2.57 (s, 1H), 1.88 - 1.69 (m, 3H), 1.67 - 1.50 (m, 2H), 1.45 (d, 1H). **LCMS-ESI$^+$** (*m/z*): [M+H]$^+$ calculated for $C_{22}H_{20}F_4N_3O_4$: 466.13; found: 466.142.

Example 75

Preparation of Compound **75**

(1R,4S,12aR)-N-(3-chloro-4-fluorobenzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



75

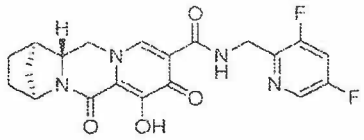
Compound **75** was prepared in a similar manner to compound **60** using (3-chloro-4-fluorophenyl)methanamine in place of (2,3-dichlorophenyl)methanamine. **^{1}H-NMR** (400 MHz, DMSO-d6) δ 11.75 (s, 1H), 10.43 (t, 1H), 8.38 (s, 1H), 7.51 (dd, 1H), 7.42 - 7.28 (m, 2H), 4.68 (s, 1H), 4.51 (d, 2H), 4.47 (dd, 1H), 3.97 (t, 1H), 3.80 (dd, 1H), 2.58 (s, 1H), 1.86 - 1.68 (m, 3H), 1.68 - 1.52 (m, 2H), 1.46 (d, 1H). **LCMS-ESI$^+$** (*m/z*): [M+H]$^+$ calculated for: $C_{21}H_{20}ClFN_3O_4$: 432.10; found: 432.159.

Example 76

Preparation of Compound **76**

(1R,4S,12aR)-N-((3,5-difluoropyridin-2-yl)methyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide

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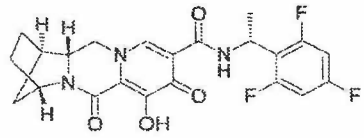
76

Compound **76** was prepared in a similar manner to compound **60** using (3,5-difluoropyridin-2-yl)methanamine in place of (2,3-dichlorophenyl)methanamine. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 10.80 (s, 1H), 8.81 (s, 1H), 8.33 (d, 1H), 7.20 (td, 1H), 4.90 (s, 1H), 4.82 (s, 2H), 4.28 (d, 1H), 3.92 – 3.75 (m, 2H), 3.48 (s, 2H), 1.98 – 1.80 (m, 3H), 1.77 (d, 1H), 1.71 – 1.58 (m, 2H). **LCMS-ESI$^+$** (*m/z*): [M+H]$^+$ calculated for $C_{20}H_{19}F_2N_4O_4$: 417.13; found: 417.189.

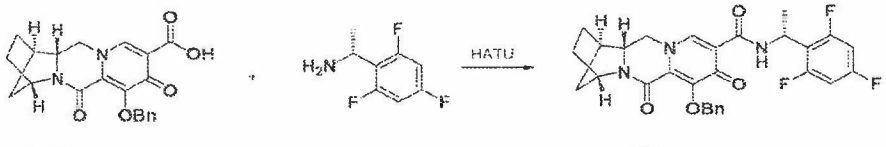
Example 77

Preparation of Compound 77

(1R,4S,12aR)-7-hydroxy-6,8-dioxo-N-((R)-1-(2,4,6-trifluorophenyl)ethyl)-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide

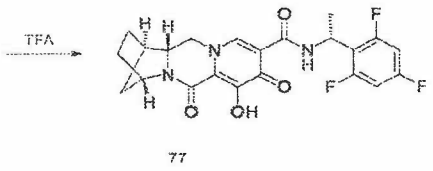


77



77-A

77-B



77

Step 1

A 50-mL round bottom flask was charged with 77-A (0.15 g, 0.39 mmol), (*R*)-1-(2,4,6-trifluorophenyl)ethanamine (0.14 g, 0.78 mmol), N,N-diisopropylethylamine (DIPEA) (0.25 g, 1.97 mmol) and HATU (0.29 g, 0.79 mmol) in DCM (10 ml). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated down, re-dissolved in EtOAc (50 mL), washed with saturated $NaHCO_3$ (2x), saturated NH_4Cl and dried over Na_2SO_4. After concentration, the crude was purified by column chromatography on silica gel with hexane-EtOAc to obtain 77-B as a white solid. **LCMS-ESI**$^+$ (*m/z*): [M+H]$^+$ found: 538.

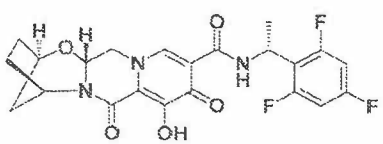
Step 2

A 50-mL round bottom flask was charged with 77-B (0.20 g, 0.37 mmol) in TFA (2 mL). The reaction mixture was stirred at room temperature for 30 min. The solution was concentrated and the residue was purified by flash chromatography using EtOAc-20% MeOH in EtOAc as eluents to afford compound 77. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 10.67 (d, J = 8.2 Hz, 1H), 8.22 (s, 1H), 6.61 (t, J = 8.4 Hz, 2H), 5.60 (dd, J = 8.1, 6.9 Hz, 1H), 4.85 (s, 1H), 3.82 (t, J = 12.2 Hz, 1H), 3.71 (dd, J = 12.4, 3.4 Hz, 1H), 2.75 - 2.55 (m, 3H), 1.97 - 1.57 (m, 9H). **^{19}F-NMR** (376 MHz, Chloroform-d) δ -109.65 - -111.29 (m), -111.76 - -113.09 (m). **LCMS-ESI**$^+$ (*m/z*): [M+H]$^+$ found: 448.

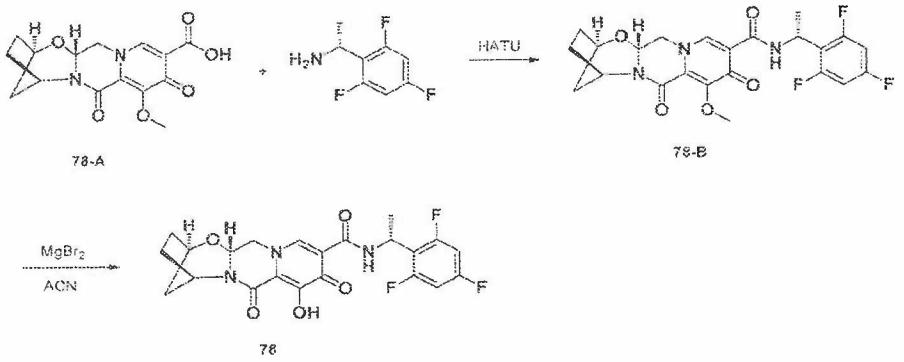
Example 78

Preparation of Compound 78

(2R,13aR)-8-hydroxy-7,9-dioxo-N-((R)-1-(2,4,6-trifluorophenyl)ethyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



78



78-A 78-B 78

Step 1

A 50-mL round bottom flask was charged with **78-A** (0.30 g, 0.94 mmol), (R)-1-(2,4,6-trifluorophenyl) ethanamine (0.39 g, 1.87 mmol), N,N-diisopropylethylamine (DIPEA) (0.61 g, 4.87 mmol) and HATU (0.71 g, 1.87 mmol) in DCM (10 ml). The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated down, re-dissolved in EtOAc (50 mL), washed with saturated $NaHCO_3$ (2x), saturated NH_4Cl and dried over Na_2SO_4. After concentration, the crude was purified by column chromatography on silica gel with hexane-EtOAc to obtain **78-B** as a white solid. **LCMS-ESI$^+$** (*m/z*): [M+H] ; found: 478.

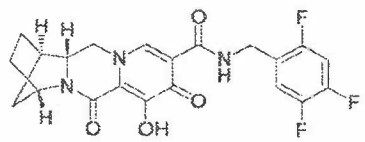
Step 2

A 50-mL round bottom flask was charged with **78-B** (0.4 g, 0.84 mmol) and magnesium bromide (0.4 g, 2.2 mmol) in acetonitrile (5 mL). The reaction mixture was heated to 50 °C. After 10 minutes, the reaction mixture was cooled to 0 ^{0}C and 1 N hydrochloric acid (4 mL) was added in. More water (~ 5 mL) was added and the solid was filtrated and washed with water and dried to afford afford compound **78**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 12.30 (s, 1H), 10.59 (d, J = 8.3 Hz, 1H), 8.21 (s, 1H), 6.60 (t, J = 8.4 Hz, 2H), 5.59 (t, J = 7.4 Hz, 1H), 5.37 (dd, J = 9.4, 4.1 Hz, 1H), 5.31 - 5.09 (m, 1H), 4.64 (t, J = 3.0 Hz, 1H), 4.20 (dd, J = 12.9, 4.1 Hz, 2H), 3.96 (dd, J = 12.8, 9.4 Hz, 2H), 2.21 - 1.85 (m, 4H), 1.71 - 1.43 (m, 3H). **^{19}F-NMR** (376 MHz, Chloroform-d) δ -110.37 (tt, J = 8.7, 6.1 Hz), -112.19 (t, J = 7.2 Hz). **LCMS-ESI$^+$** (*m/z*): [M+H]$^+$ found: 464.

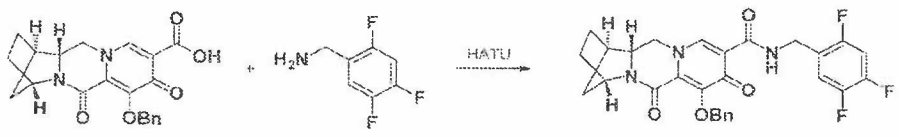
Example 79

Preparation of Compound 79

(1R,4S,12aR)-7-hydroxy-6,8-dioxo-N-(2,4,5-trifluorobenzyl)-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide

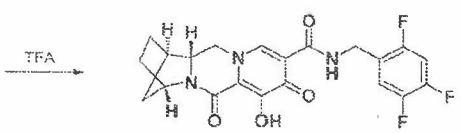


79



79-A

79-B



79

Step 1

A 50-mL round bottom flask was charged with **79-A** (0.12 g, 0.32 mmol), (2,4,5-trifluorophenyl)methanamine (0.10 g, 0.63 mmol), N,N-diisopropylethylamine (DIPEA) (0.20 g, 1.58 mmol) and HATU (0.24 g, 0.63 mmol) in DCM (10 ml). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated down, re-dissolved in EtOAc (50 mL), washed with saturated $NaHCO_3$ (2x), saturated NH_4Cl and dried over Na_2SO_4. After concentration, the crude was purified by column chromatography on silica gel with hexane-EtOAc to obtain **79-B** as a white solid. **LCMS-ESI**$^+$ (*m/z*): [M+H]$^+$; found: 524.

Step 2

A 50-mL round bottom flask was charged with **79-B** (0.15 g, 0.29 mmol)

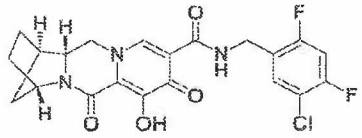
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in TFA (2 mL). The reaction mixture was stirred at room temperature for 30 min. The solution was concentrated and the residue was purified by flash chromatography using EtOAc-20% MeOH in EtOAc as eluents to afford compound **79**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 11.70 (s, 1H), 10.65 - 10.18 (m, 1H), 8.27 (s, 1H), 7.26 (m, 1H), 6.90 (td, J = 9.7, 6.4 Hz, 1H), 4.89 (s, 1H), 4.60 (d, J = 6.0 Hz, 2H), 4.09 (dd, J = 11.4, 2.6 Hz, 1H), 3.96 - 3.66 (m, 2H), 2.68 (s, 1H), 2.15 - 1.43 (m, 6H). **^{19}F-NMR** (376 MHz, Chloroform-d) δ 120.53 - -120.85 (m), -134.68 - -136.79 (m), -142.26 - -144.11 (m). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ found: 434.

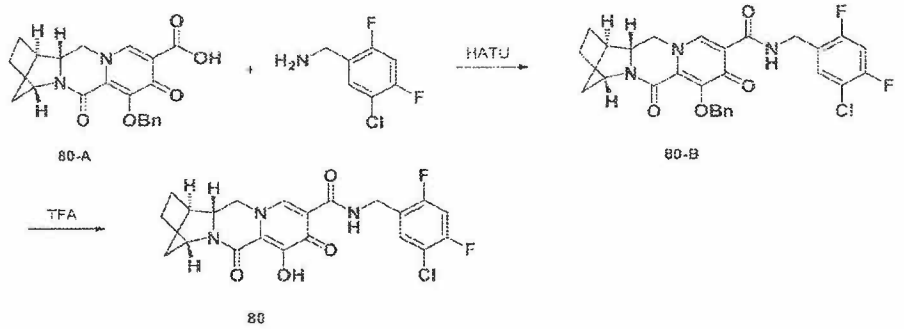
Example 80

Preparation of Compound **80**

(1R,4S,12aR)-N-(5-chloro-2,4-difluorobenzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



80



80-A **80-B** **80**

Step 1

A 50-mL round bottom flask was charged with **80-A** (0.12 g, 0.32 mmol), (5-chloro-2,4-difluorophenyl)methanamine (0.11 g, 0.63 mmol), N,N-diisopropylethylamine (DIPEA) (0.20 g, 1.58 mmol) and HATU (0.24 g, 0.63 mmol) in DCM (10 ml). The reaction mixture was stirred at room temperature for 1 h. The

reaction mixture was concentrated down, re-dissolved in EtOAc (50 mL), washed with saturated $NaHCO_3$ (2x), saturated NH_4Cl and dried over Na_2SO_4. After concentration, the crude was purified by column chromatography on silica gel with hexane-EtOAc to obtain **80-B** as a white solid. **LCMS-ESI**$^+$ (*m/z*): [M+H]$^+$; found: 541.

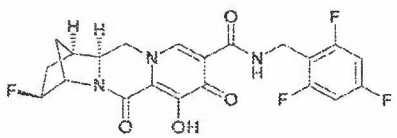
Step 2

A 50-mL round bottom flask was charged with **80-B** (0.14 g, 0.26 mmol) in TFA (2 mL). The reaction mixture was stirred at room temperature for 30 minutes. The solution was concentrated and the residue was purified by flash chromatography using EtOAc-20% MeOH in EtOAc as eluents to afford compound **80**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 10.46 (s, 1H), 8.27 (s, 1H), 7.40 (t, J = 7.8 Hz, 1H), 6.89 (t, J = 9.1 Hz, 1H), 4.90 (s, 1H), 4.78 - 4.48 (m, 2H), 4.08 (dd, J = 11.3, 2.5 Hz, 1H), 3.95 - 3.63 (m, 2H), 2.68 (s, 1H), 2.22 - 1.51 (m, 7H). **^{19}F-NMR** (376 MHz, Chloroform-d) δ -113.37 (q, J = 8.1 Hz), -116.37 (q, J = 8.0 Hz). **LCMS-ESI**$^+$ (*m/z*): [M+H]$^+$ found: 451.

Example 81

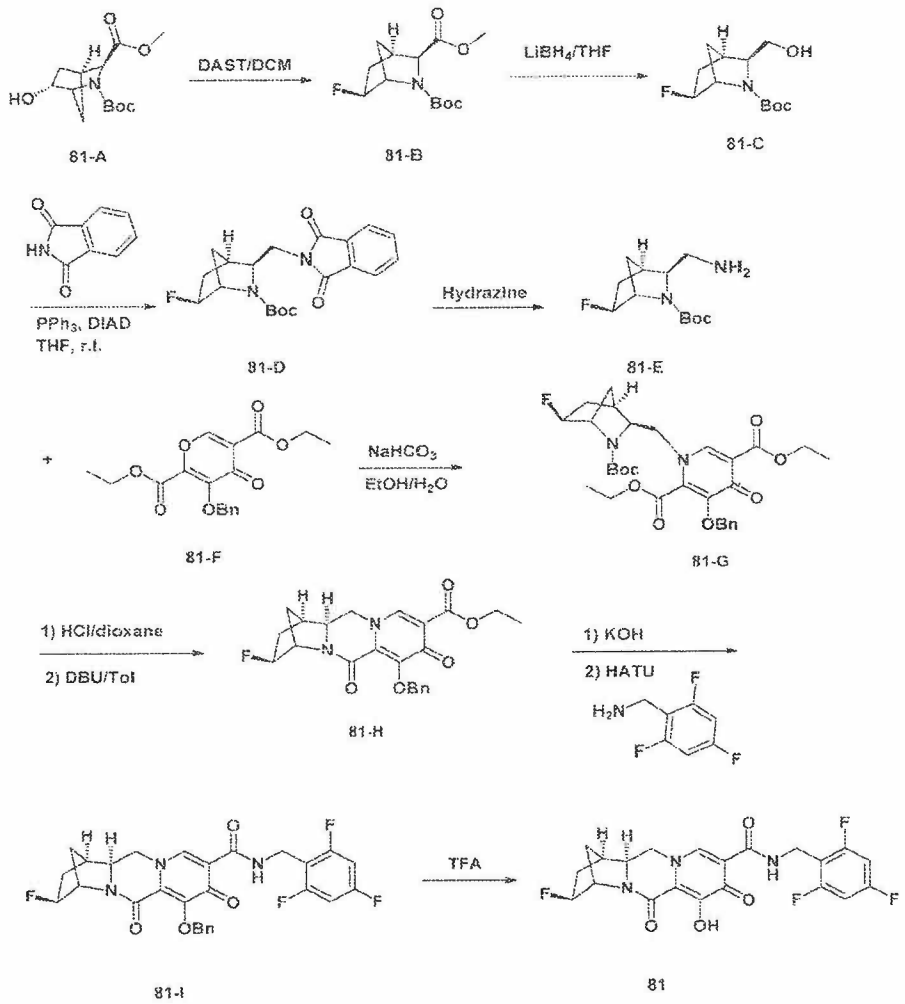
Preparation of Compound **81**

(1R,3S,4S,12aS)-3-fluoro-7-hydroxy-6,8-dioxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



81

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Step 1

A 100-mL round bottom flask was charged with **81-A** (1.0 g, 3.7 mmol) in DCM (10 mL). The reaction mixture was cooled to 0 ^{0}C. Diethylaminosulfur trifluoride (DAST) (0.58 mL, 4.1 mmol) was slowly added in. Then the reaction mixture was stirred at room temperature for one hour. The mixture was cooled back to 0 ^{0}C. Saturated $NaHCO_3$ (5 mL) was added dropwise to quench the reaction. Then the reaction mixture was diluted with EtOAc (100 mL), washed with sat. $NaHCO_3$, brine,

and dried over Na_2SO_4. After concentration, the residue was purified by flash chromatography using hexanes - EtOAc as eluents to afford **81-B**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 274.

Step 2

A 100-mL round bottom flask was charged with **81-B** (0.8 g, 3.0 mmol) in THF (10 mL). The reaction mixture was stirred at -78 ^{0}C. 2.0 M $LiBH_4$ in THF (3.2 mL, 6.4 mmol) was slowly added in. Then the reaction mixture was warmed up and stirred at room temperature for 3 hours. Then the reaction mixture was diluted with EtOAc (100 mL) and treated slowly with water (H_2 evolution). After the two phases were separated, the aqueous fraction was extracted with EtOAc and the two organic fractions were combined, washed with water, and dried over Na_2SO_4. After concentration, the residue was purified by flash chromatography using hexanes - EtOAc as eluents to afford **81-C**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 246.

Step 3

A 100-mL round bottom flask was charged with **81-C** (0.57 g, 2.3 mmol), triphenylphosphine (1.3 g, 5.1 mmol) and phthalimide (0.55 g, 3.7 mmol) in THF (15 mL). Then the reaction mixture was cooled to 0 ^{0}C with stirring. Diisopropyl azodicarboxylate (DIAD) (1.0 mL, 5.1 mmol) was slowly added to the reaction mixture. The reaction mixture was stirred at room temperature for overnight. After concentration, the residue was purified by flash chromatography using hexanes - EtOAc as eluents to afford **81-D**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 375.

Step 4

To a solution of **81-D** (0.8 g, 2.1 mmol) EtOH (40 mL) was added hydrazine monohydrate (0.6 mL). The reaction mixture was heated to 70 ^{0}C with stirring for 3 hours. After filtration to remove the solid, the filtrate was concentrated to afford **81-E**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 245.

Step 5

A 100-mL round bottom flask was charged with **81-E** (0.49 g, 2.0 mmol)

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and **81-F** (0.7 g, 2.0 mmol) in ethanol (7 mL). Sodium bicarbonate (0.34 g, 4.0 mmol) in water (7 mL) was added to the reaction mixture. Then the reaction mixture was stirred at room temperature for overnight. The mixture was diluted with EtOAc (50 mL) and washed with water (2 x). The aqueous fractions were extracted with EtOAc (1 x), and the organic fractions were combined, dried (Na_2SO_4), and concentrated. The crude **81-G** was used for next step without further purification. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 573.

Step 6

A 100-mL round bottom flask was charged with **81-G** (1.1 g, 1.9 mmol) in 4 N HCl /dioxane (11 mL). Then the reaction mixture was stirred at room temperature for 1 hour. After concentration, 1.0 g intermediate was obtained. The intermediate and DBU (1.3 g, 8.8 mmol) were dissolved in toluene (10 mL). The reaction mixture was heated to 110 ^{0}C with stirring for 1 hour. After concentration, the residue was purified by flash chromatography using hexanes - EtOAc as eluents to afford **81-H**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 413.

Step 7

A 100-mL round bottom flask was charged with **81-H** (0.56 g, 1.4 mmol) in THF (5 mL) and MeOH (5 mL). 1 N KOH (4 mL) was added to the reaction mixture. Then the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was acidified by adding 1 N HCl (4 mL). After concentration, the residue was co-evaporated with toluene (3 x). Half of the crude acid, 2,4,6-trifluobenzylamine (0.2 g, 1.3 mmol), N,N-diisopropylethylamine (DIPEA) (0.41 g, 3.1 mmol) and HATU (0.48 g, 1.25 mmol) were dissolved in DMF (10 mL). The reaction mixture was stirred at room temperature for 2 hours. The mixture was diluted with EtOAc (100 mL) and washed with saturated $NaHCO_3$ (2x), saturated NH_4Cl (2x) and dried over Na_2SO_4. After concentration, the crude was purified by column chromatography on silica gel with hexane-EtOAc to afford **81-I**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 542.

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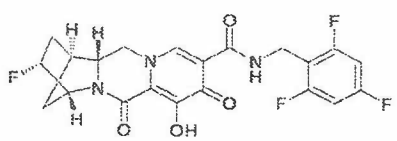
Step 8

A 50-mL round bottom flask was charged with **81-I** (0.31 g, 0.58 mmol) in TFA (3 mL). The reaction mixture was stirred at room temperature for 30 minutes. After concentration, the crude was purified by column chromatography on silica gel with EtOAc-MeOH to afford compound **81**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 10.29 (s, 1H), 8.31 (s, 1H), 6.65 (dd, J = 8.7, 7.5 Hz, 2H), 5.05 - 4.75 (m, 2H), 4.65 (d, J = 5.6 Hz, 2H), 4.11 (d, J = 12.2 Hz, 1H), 3.83 (t, J = 12.3 Hz, 1H), 3.56 (dd, J = 12.3, 3.3 Hz, 1H), 2.77 (s, 1H), 2.25 - 1.97 (m, 2H), 1.95 (d, J = 11.0 Hz, 2H), 1.77 (d, J = 11.2 Hz, 1H). **^{19}F-NMR** (376 MHz, Chloroform-d) δ -108.98 (t, J = 8.2 Hz), -112.03 (t, J = 7.2 Hz), -168.00. **LCMS-ESI$^+$** (*m/z*): found: 452.

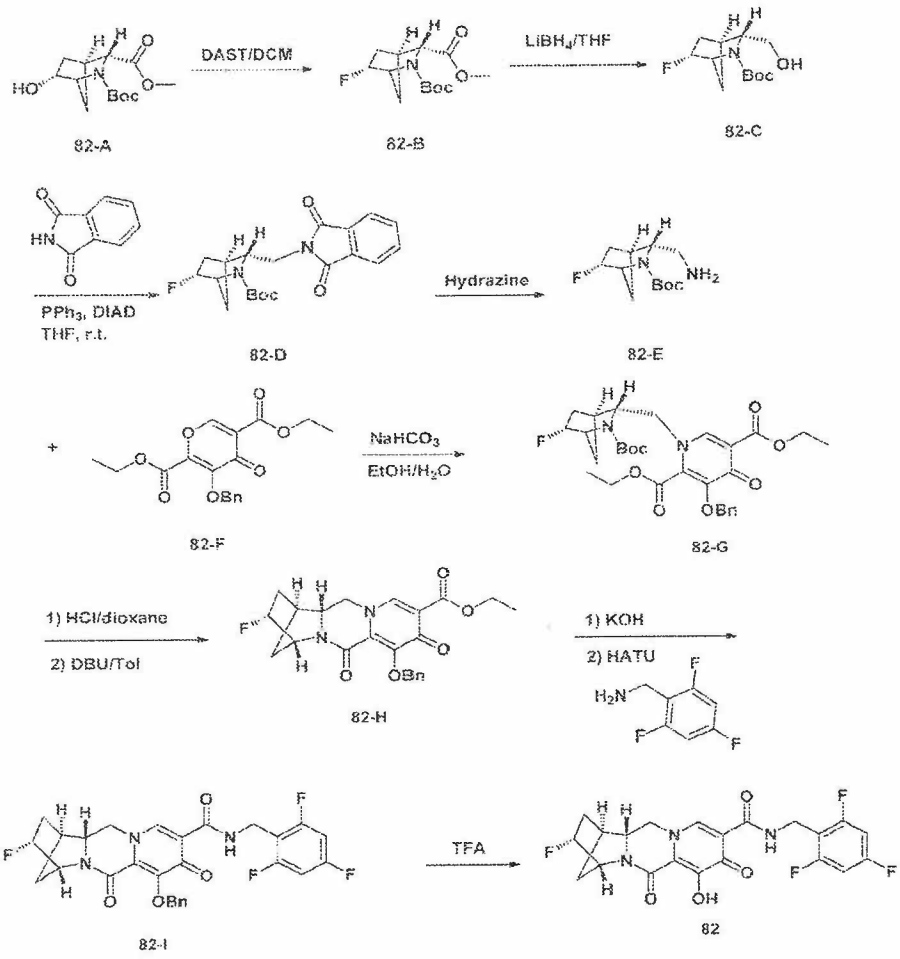
Example 82

Preparation of Compound **82**

(1S,3R,4R,12aR)-3-fluoro-7-hydroxy-6,8-dioxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



82



Step 1

A 100-mL round bottom flask was charged with **82-A** (0.6 g, 2.1 mmol) in DCM (6 mL). The reaction mixture was cooled to 0 ^{0}C. DAST (0.35 mL, 3.0 mmol) was slowly added in. Then the reaction mixture was stirred at room temperature for one hour. The mixture was cooled back to 0 ^{0}C. Saturated $NaHCO_3$ (5 mL) was added drop wise to quench the reaction. Then the reaction mixture was diluted with EtOAc (100 mL), washed with sat. $NaHCO_3$, brine, and dried over Na_2SO_4. After concentration, the residue was purified by flash chromatography using hexanes - EtOAc as eluents to

afford **82-B**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 274.

Step 2

A 100-mL round bottom flask was charged with **82-B** (0.4 g, 1.5 mmol) in THF (10 mL). The reaction mixture was stirred at -78 ^{0}C. 2.0 M $LiBH_4$ in THF (1.6 mL, 3.2 mmol) was slowly added in. Then the reaction mixture was warmed up and stirred at room temperature for 3 hours. Then the reaction mixture was diluted with EtOAc (100 mL) and added water slowly (H_2 evolution). After the two phases were separated, the aqueous fraction was extracted with EtOAc and the two organic fractions were combined, washed with water and dried over Na_2SO_4. After concentration, the residue was purified by flash chromatography using hexanes - EtOAc as eluents to afford **82-C**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 246.

Step 3

A 100-mL round bottom flask was charged with **82-C** (0.25 g, 1.0 mmol), triphenylphosphine (0.59 g, 2.2 mmol) and phthalimide (0.24 g, 1.6 mmol) in THF (10 mL). Then the reaction mixture was cooled to 0 ^{0}C with stirring. DIAD (0.44 mL, 2.2 mmol) was slowly added to the reaction mixture. The reaction mixture was stirred at room temperature for overnight. After concentration, the residue was purified by flash chromatography using hexanes - EtOAc as eluents to afford **82-D**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 375.

Step 4

To a solution of **82-D** (0.35 g, 0.9 mmol) EtOH (20 mL) was added hydrazine monohydrate (0.3 mL). The reaction mixture was heated to 70 ^{0}C with stirring for 3 hours. After filtration to remove the solid, the filtrate was concentrated to afford **82-E**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 245.

Step 5

A 100-mL round bottom flask was charged with **82-E** (0.21 g, 0.87 mmol) and **82-F** (0.3 g, 0.87 mmol) in ethanol (7 mL). Sodium bicarbonate (0.15 g, 1.7 mmol) in water (7 mL) was added to the reaction mixture. Then the reaction mixture

was stirred at room temperature for overnight. The mixture was diluted with EtOAc (50 mL) and washed with water (2 x). The aqueous fractions were extracted with EtOAc, and the organic fractions were combined, dried (Na_2SO_4), and concentrated. The crude **82-G** was used for next step without further purification. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 573.

Step 6

A 100-mL round bottom flask was charged with **82-G** (0.49 g, 0.86 mmol) in 4 N HCl /dioxane (5 mL). Then the reaction mixture was stirred at room temperature for 1 hour. After concentration, 0.4 g intermediate was obtained. The intermediate and DBU (0.6 g, 4.0 mmol) were dissolved in toluene (10 mL). The reaction mixture was heated to 110 ^{0}C with stirring for 1 hour. After concentration, the residue was purified by flash chromatography using hexanes - EtOAc as eluents to afford **82-H**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 413.

Step 7

A 100-mL round bottom flask was charged with **82-H** (0.2 g, 0.49 mmol) in THF (5 mL) and MeOH (5 mL). 1 N KOH (1.5 mL) was added to the reaction mixture. Then the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was acidified by adding 1 N HCl (1.5 mL). After concentration, the residue was co-evaporated with toluene (3 x). The crude acid, 2,4,6-trifluobenzylamine (0.15 g, 0.95 mmol), N,N-diisopropylethylamine (DIPEA) (0.31 g, 2.4 mmol) and HATU (0.36 g, 0.95 mmol) were dissolved in DCM (10 mL). The reaction mixture was stirred at room temperature for 2 hours. The mixture was diluted with EtOAc (100 mL) and washed with saturated $NaHCO_3$ (2x), saturated NH_4Cl (2x) and dried over Na_2SO_4. After concentration, the crude was purified by column chromatography on silica gel with hexane-EtOAc to afford **82-I**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 542.

Step 8

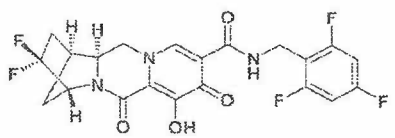
A 50-mL round bottom flask was charged with **82-I** (0.22 g, 0.41 mmol) in TFA (3 mL). The reaction mixture was stirred at room temperature for 30 minutes. After concentration, the crude was purified by column chromatography on silica gel

with EtOAc-MeOH to afford compound **82**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 10.25 (s, 1H), 8.28 (s, 1H), 6.65 (s, 2H), 5.15 - 4.77 (m, 2H), 4.65 (s, 2H), 4.32 - 3.41 (m, 2H), 2.78 (s, 1H), 1.86 (dd, J = 144.8, 72.3 Hz, 6H). **^{19}F-NMR** (376 MHz, Chloroform-d) δ -108.98 (t, J = 8.2 Hz), -112.03 (t, J = 7.2 Hz), -168.00. **LCMS-ESI$^+$** (*m/z*): found: 452.

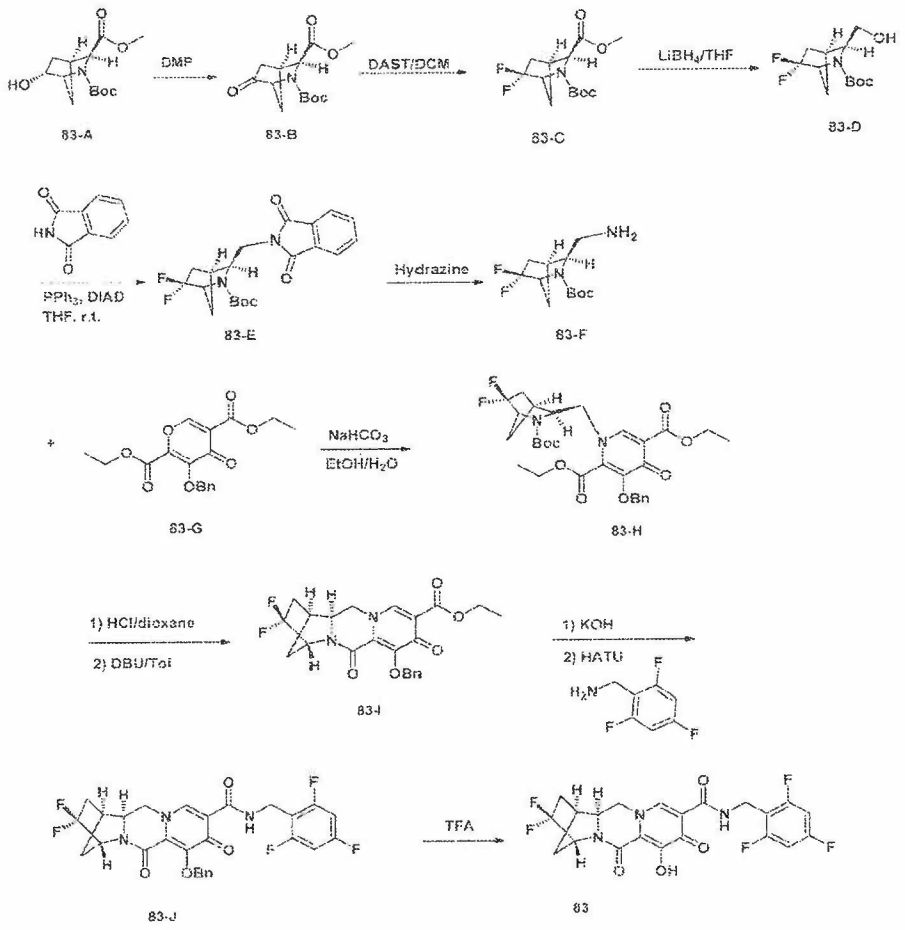
Example 83

Preparation of Compound **83**

(1S,4R,12aS)-3,3-difluoro-7-hydroxy-6,8-dioxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



83



Step 1

A 100-mL round bottom flask was charged with **83-A** (1.0 g, 3.7 mmol) in DCM (20 mL). The reaction mixture was cooled to 0 °C. Dess-Martin periodinane (1.8 g, 4.2 mmol) was slowly added in. Then the reaction mixture was stirred at room temperature for 3 hours. After concentration, the residue was purified by flash chromatography using hexanes - EtOAc as eluents to afford **83-B**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 270.

Step 2

A 100-mL round bottom flask was charged with **83-B** (0.85 g, 3.2 mmol) in DCM (15 mL). The reaction mixture was cooled to 0 ^{0}C. DAST (1.5 mL, 11.3 mmol) was slowly added in. Then the reaction mixture was stirred at room temperature overnight. The mixture was cooled back to 0 ^{0}C. Saturated $NaHCO_3$ (5 mL) was added dropwise to quench the reaction. Then the reaction mixture was diluted with EtOAc (100 mL), washed with sat. $NaHCO_3$, brine, and dried over Na_2SO_4. After concentration, the residue was purified by flash chromatography using hexanes - EtOAc as eluents to afford **83-C**. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ found: 292.

Step 3

A 100-mL round bottom flask was charged with **83-C** (0.44 g, 1.5 mmol) in THF (6 mL). The reaction mixture was stirred at -78 ^{0}C. 2.0 M $LiBH_4$ in THF (1.6 mL, 3.2 mmol) was slowly added in. Then the reaction mixture was warmed up and stirred at room temperature for 3 hours. Then the reaction mixture was diluted with EtOAc (100 mL) and added water slowly (H_2 evolution). After the two phases were separated, the aqueous fraction was extracted with EtOAc and the two organic fractions were combined, washed with water, and dried over Na_2SO_4. After concentration, the residue was purified by flash chromatography using hexanes - EtOAc as eluents to afford **83-D**. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ found: 264.

Step 4

A 100-mL round bottom flask was charged with **83-D** (0.17 g, 0.65 mmol), triphenylphosphine (0.37 g, 1.4 mmol) and phthalimide (0.15 g, 1.0 mmol) in THF (10 mL). Then the reaction mixture was cooled to 0 ^{0}C with stirring. DIAD (0.28 mL, 1.4 mmol) was slowly added to the reaction mixture. The reaction mixture was stirred at room temperature for overnight. After concentration, the residue was purified by flash chromatography using hexanes - EtOAc as eluents to afford **83-E**. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ found: 393.

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Step 5

To a solution of **83-E** (0.25 g, 0.64 mmol) EtOH (20 mL) was added hydrazine monohydrate (0.3 mL). The reaction mixture was heated to 70 ^{0}C with stirring for 3 hours. After filtration to remove the solid, the filtrate was concentrated to afford **83-F**. **LCMS-ESI**$^{+}$ (*m/z*): $[M+H]^{+}$ found: 263.

Step 6

A 100-mL round bottom flask was charged with **83-F** (0.18 g, 0.69 mmol) and **83-G** (0.324g, 0.69 mmol) in ethanol (7 mL). Sodium bicarbonate (0.12 g, 1.4 mmol) in water (7 mL) was added to the reaction mixture. Then the reaction mixture was stirred at room temperature overnight. The mixture was diluted with EtOAc (50 mL) and washed with water. The aqueous fractions were extracted with EtOAc, and the organic fractions were combined, dried (Na_2SO_4), and concentrated. The crude **83-H** was used for next step without further purification. **LCMS-ESI**$^{+}$ (*m/z*): $[M+H]^{+}$ found: 591.

Step 7

A 100-mL round bottom flask was charged with **83-H** (0.4 g, 0.68 mmol) in 4 N HCl /dioxane (3.8 mL). Then the reaction mixture was stirred at room temperature for 1 hour. After concentration, 0.35 g intermediate was obtained. The intermediate and DBU (0.51 g, 3.3 mmol) were dissolved in toluene (10 mL). The reaction mixture was heated to 110 ^{0}C with stirring for 1 hour. After concentration, the residue was purified by flash chromatography using hexanes - EtOAc as eluents to afford **83-I**. **LCMS-ESI**$^{+}$ (*m/z*): $[M+H]^{+}$ found: 431.

Step 8

A 100-mL round bottom flask was charged with **83-I** (0.2 g, 0.47 mmol) in THF (5 mL) and MeOH (5 mL). 1 N KOH (1.4 mL) was added to the reaction mixture. Then the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was acidified by adding 1 N HCl (1.4 mL). After concentration, the residue was co-evaporated with toluene (3 x). The crude acid, 2,4,6-trifluobenzylamine (0.14 g, 0.91 mmol), N,N-diisopropylethylamine (DIPEA) (0.29 g, 2.2 mmol) and

HATU (0.35 g, 0.91 mmol) were dissolved in DCM (10 mL). The reaction mixture was stirred at room temperature for 2 hours. The mixture was diluted with EtOAc (100 mL) and washed with saturated $NaHCO_3$ (2x), saturated NH_4Cl (2x) and dried over Na_2SO_4. After concentration, the crude was purified by column chromatography on silica gel with hexane-EtOAc to afford **83-J**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 560.

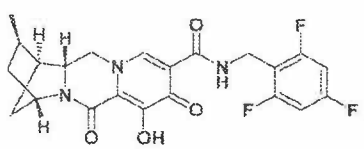
Step 9

A 50-mL rbf was charged with **83-J** (0.18 g, 0.32 mmol) in TFA (3 mL). The reaction mixture was stirred at room temperature for 30 minutes. After concentration, the crude was purified by column chromatography on silica gel with EtOAc-MeOH to afford compound **83** as a white solid. ^{1}**H-NMR** (400 MHz, Chloroform-d) δ 10.29 (d, J = 6.1 Hz, 1H), 8.34 (s, 1H), 6.65 (dd, J = 8.7, 7.5 Hz, 2H), 4.83 (s, 1H), 4.72 - 4.58 (m, 2H), 4.36 - 4.10 (m, 2H), 4.05 (t, J = 11.5 Hz, 1H), 2.97 (d, J = 4.4 Hz, 1H), 2.49 - 2.08 (m, 3H), 2.12 - 1.94 (m, 2H). ^{19}**F-NMR** (376 MHz, Chloroform-d) δ - 92.32 (ddd, J = 225.6, 22.5, 9.1 Hz), -107.64 - -109.54 (m), -112.05 (t, J = 7.0 Hz), -114.67 (d, J = 226.7 Hz). **LCMS-ESI**$^+$ (*m/z*): found: 470.

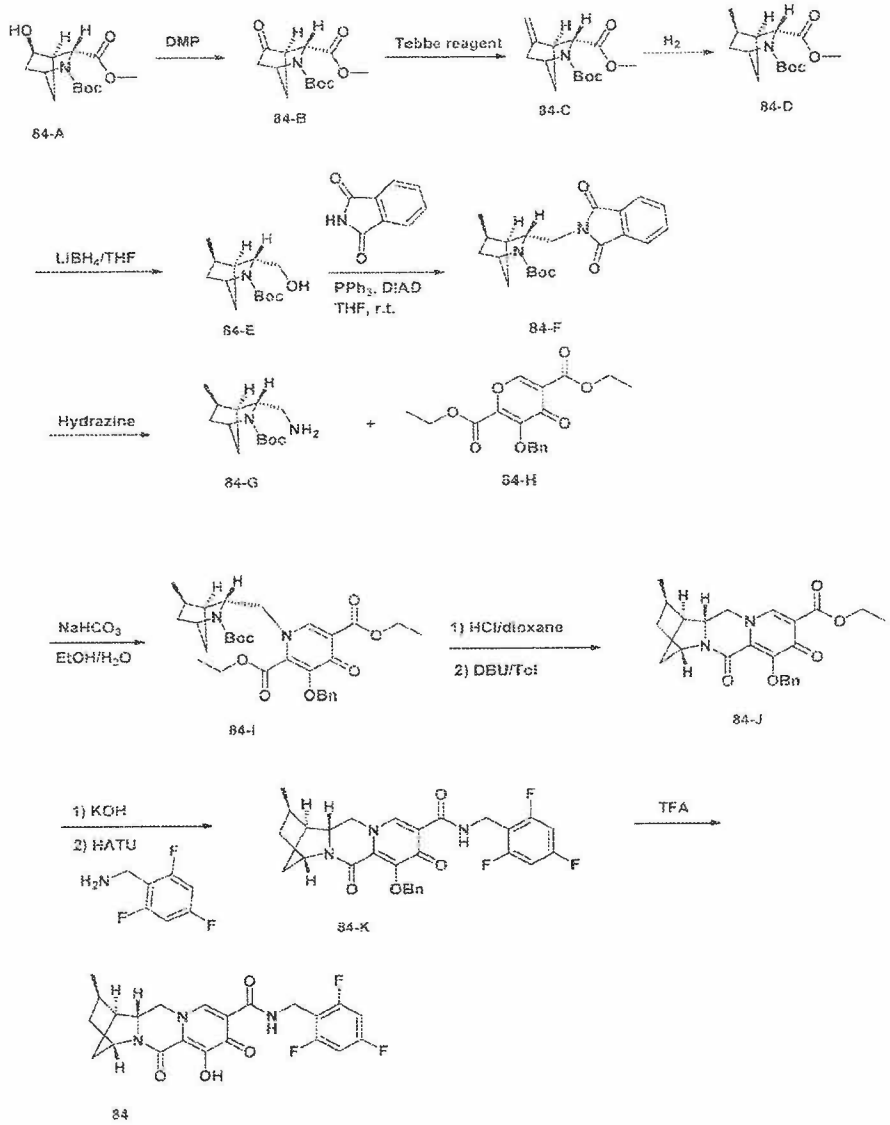
Example 84

Preparation of Compound **84**

(1S,2R,4S,12aR)-7-hydroxy-2-methyl-6,8-dioxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



84



Step 1

A 100-mL round bottom flask was charged with **84-A** (1.6 g, 5.9 mmol) in DCM (20 mL). The reaction mixture was cooled to 0 °C. Dess-Martin periodinane (4.9 g, 11.7 mmol) was slowly added in. Then the reaction mixture was stirred at room

temperature for 3 hours. After concentration, the residue was purified by flash chromatography using hexanes - EtOAc as eluents to afford **84-B**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 270.

Step 2

A 100-mL round bottom flask was charged with **84-B** (1.3 g, 4.8 mmol) in THF (30 mL). The reaction mixture was cooled to 0 ^{0}C. Tebbe reagent (0.5 M in toluene, 19.4 mL, 9.7 mmol) was slowly added in. Then the reaction mixture was stirred at room temperature for 2 hours. The mixture was cooled back to 0 ^{0}C. Saturated $NaHCO_3$ (5 mL) was added drop wise to quench the reaction. The reaction mixture was stirred at room temperature for another 15 minutes and filtered through celite. The filtered cake was washed with DCM (2 x). The combined filtrates were concentrated in vacuum and the residue was purified by flash chromatography using hexanes - EtOAc as eluents to afford **84-C**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 268.

Step 3

To a solution (purged with N_2) of **84-C** (0.9 g, 3.4 mmol) in EtOH (20 mL) was added Pd/C (0.18 g). The mixture was stirred under H_2 for 3 hours. The mixture was filtered through celite and the filtrate was concentrated to afford **84-D**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 270.

Step 4

A 100-mL round bottom flask was charged with **84-D** (0.9 g, 3.3 mmol) in THF (6 mL). The reaction mixture was stirred at -78 ^{0}C. 2.0 M $LiBH_4$ in THF (13.2 mL, 26.4 mmol) was slowly added in. Then the reaction mixture was warmed up and stirred at room temperature for 3 hours. Then the reaction mixture was diluted with EtOAc (100 mL) and added water slowly (H_2 evolution). After the two phases were separated, the aqueous fraction was extracted with EtOAc and the two organic fractions were combined, washed with water, and dried over Na_2SO_4. After concentration, the residue was purified by flash chromatography using hexanes - EtOAc as eluents to afford **84-E**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 242.

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Step 5

A 100-mL round bottom flask was charged with **84-E** (0.4 g, 1.66 mmol), triphenylphosphine (0.96 g, 3.6 mmol) and phthalimide (0.39 g, 2.7 mmol) in THF (15 mL). Then the reaction mixture was cooled to 0 ^{0}C with stirring. DIAD (0.7 mL, 3.6 mmol) was slowly added to the reaction mixture. The reaction mixture was stirred at room temperature for overnight. After concentration, the residue was purified by flash chromatography using hexanes - EtOAc as eluents to afford **84-F**. **LCMS-ESI**$^{+}$ (*m/z*): $[M+H]^{+}$ found: 371.

Step 6

To a solution of **84-F** (0.55 g, 1.5 mmol) EtOH (20 mL) was added hydrazine monohydrate (0.3 mL). The reaction mixture was heated to 70 ^{0}C with stirring for 3 hours. After filtration to remove the solid, the filtrate was concentrated to afford **84-G**. **LCMS-ESI**$^{+}$ (*m/z*): $[M+H]^{+}$ found: 241.

Step 7

A 100-mL round bottom flask was charged with **84-G** (0.35 g, 1.4 mmol) and **84-H** (0.5g, 1.4 mmol) in ethanol (10 mL). Sodium bicarbonate (0.24 g, 2.8 mmol) in water (10 mL) was added to the reaction mixture. Then the reaction mixture was stirred at room temperature for overnight. The mixture was diluted with EtOAc (50 mL) and washed with water (2 x). The aqueous fractions were extracted with EtOAc, and the organic fractions were combined, dried (Na_2SO_4), and concentrated. The crude **84-I** was used for next step without further purification. **LCMS-ESI**$^{+}$ (*m/z*): $[M+H]^{+}$ found: 583.

Step 8

A 100-mL rbf was charged with **84-I** (0.84 g, 1.4 mmol) in 4 N HCl /dioxane (8.2 mL). Then the reaction mixture was stirred at room temperature for 1 hour. After concentration, 0.74 g intermediate was obtained. The intermediate and DBU (1.1 g, 7.2 mmol) were dissolved in toluene (10 mL). The reaction mixture was heated to 110 ^{0}C with stirring for 1 hour. After concentration, the residue was purified by flash

chromatography using hexanes - EtOAc as eluents to afford **84-J**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 409.

Step 9

A 100-mL round bottom flask was charged with **84-J** (0.4 g, 0.98 mmol) in THF (5 mL) and MeOH (5 mL). 1 N KOH (3.0 mL) was added to the reaction mixture. Then the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was acidified by adding 1 N HCl (3.0 mL). After concentration, the residue was co-evaporated with toluene (3 x). The crude acid, 2,4,6-trifluobenzylamine (0.32 g, 1.96 mmol), N,N-diisopropylethylamine (DiPEA) (0.63 g, 4.9 mmol) and HATU (0.74 g, 1.9 mmol) were dissolved in DCM (10 mL). The reaction mixture was stirred at room temperature for 2 hours. The mixture was diluted with EtOAc (100 mL) and washed with saturated $NaHCO_3$ (2x), saturated NH_4Cl (2x) and dried over Na_2SO_4. After concentration, the crude was purified by column chromatography on silica gel with hexane-EtOAc to afford **84-K**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 538.

Step 10

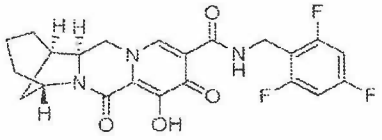
A 50-mL round bottom flask was charged with **84-K** (0.5 g, 0.93 mmol) in TFA (6 mL). The reaction mixture was stirred at room temperature for 30 minutes. After concentration, the crude was purified by column chromatography on silica gel with EtOAc-MeOH to afford compound **84**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 10.37 (s, 1H), 8.28 (s, 1H), 6.65 (t, J = 8.1 Hz, 2H), 4.80 (s, 1H), 4.77 - 4.52 (m, 3H), 4.08 (d, J = 13.1 Hz, 1H), 3.88 (d, J = 12.3 Hz, 1H), 2.47 (d, J = 3.2 Hz, 1H), 2.35 (s, 1H), 2.16 (ddd, J = 14.3, 11.2, 3.6 Hz, 1H), 1.93 - 1.57 (m, 3H), 1.29 - 1.19 (m, 1H), 1.17 (d, J = 7.0 Hz, 3H). **^{19}F-NMR** (376 MHz, Chloroform-d) δ -109.24 , -111.98. **LCMS-ESI**$^+$ (*m/z*): found: 448.

Example 85

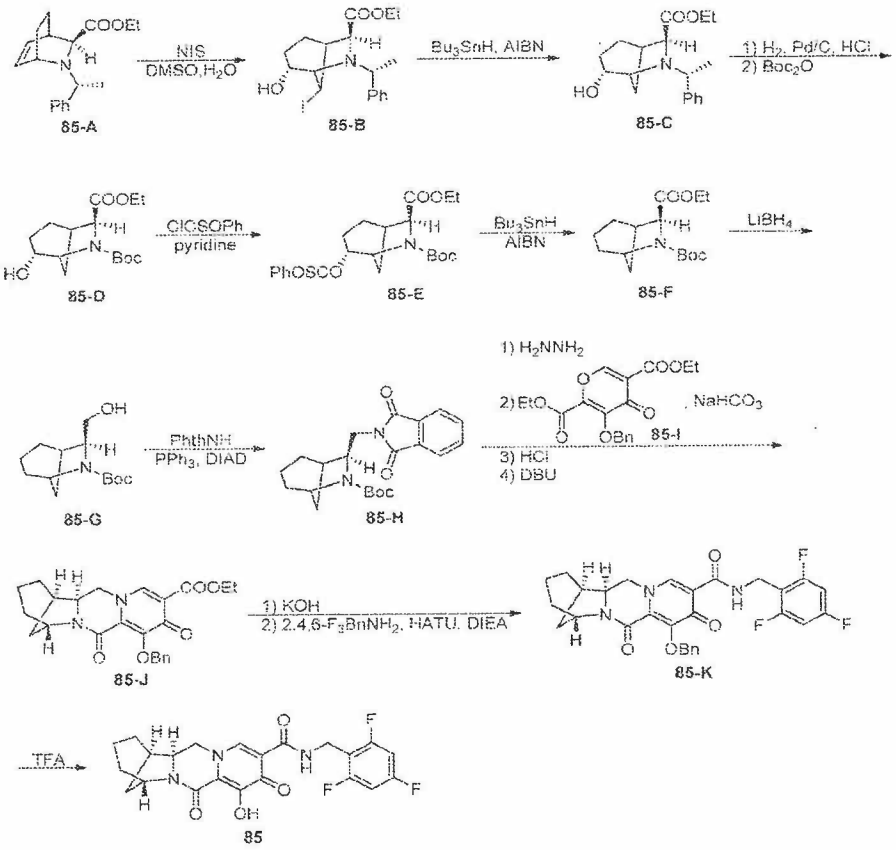
Preparation of Compound **85**

(6aS,7R,11S)-1-hydroxy-2,13-dioxo-N-(2,4,6-trifluorobenzyl)-6,6a,7,8,9,10,11,13-octahydro-2H-7,11-methanopyrido[1',2':4,5]pyrazino[1,2-a]azepine-3-carboxamide

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85



Step 1

A solution of **85-A** (1100 mg, 3.855 mmol) in DMSO (6 mL) and water (0.75 mL) was stirred at room temperature as N-iodosuccinmide (885 mg, 3.934 mmol) was added. After 2 h, additional N-iodosuccinmide (88 mg, 0.391 mmol) was added and the resulting mixture was stirred at room temperature for 1.5 h. The dark brown reaction mixture was diluted with EtOAc, and washed with a mixture of 10 % aq.

$Na_2S_2O_3$ solution and aq. $NaHCO_3$ solution (~1:4 mixture) and then with water (with some brine). After the aqueous fractions were extracted with EtOAc, the organic fractions were combined, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography using hexanes - EtOAc as eluents to obtain **85-B**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.51 - 7.44 (m, 2H), 7.33 - 7.17 (m, 3H), 4.22 - 4.05 (m, 2H), 4.02 - 3.86 (m, 2H), 3.77 (d, J = 5.3 Hz, 1H), 3.54 - 3.44 (m, 1H), 3.27 (t, J = 4.5 Hz, 1H), 2.75 - 2.66 (m, 1H), 2.30 (dddd, J = 14.8, 13.1, 7.2, 5.8 Hz, 1H), 2.14 (dddd, J = 14.8, 13.0, 6.1, 2.1 Hz, 1H), 1.97 (d, J = 8.9 Hz, 1H), 1.58 - 1.46 (m, 1H), 1.45 - 1.34 (m, 4H), 1.24 (t, J = 7.1 Hz, 3H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{15}H_{25}INO_3$: 430.1; found: 430.0.

Step 2

A solution of **85-B** (993 mg, 2.313 mmol), AIBN (305 mg, 1.857 mmol), and tributyltin hydride (1392 mg, 4.799 mmol) in toluene (15 mL) was stirred at 100 °C. After 2 h, the reaction mixture was cooled to room temperature, diluted with EtOAc, and washed with water and brine. After the aqueous fractions were extracted with EtOAc, the organic fractions were combined, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography using hexanes - EtOAc as eluents to obtain **85-C**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.57 - 7.49 (m, 2H), 7.32 - 7.23 (m, 2H), 7.23 - 7.15 (m, 1H), 4.24 - 4.02 (m, 2H), 3.97 (q, J = 6.7 Hz, 1H), 3.83 (d, J = 5.1 Hz, 1H), 3.48 (t, J = 4.6 Hz, 1H), 3.19 - 3.04 (m, 1H), 2.58 (p, J = 4.0 Hz, 1H), 2.30 (dddd, J = 14.7, 13.1, 7.0, 4.5 Hz, 1H), 1.98 (d, J = 11.2 Hz, 1H), 1.64 (tdd, J = 13.3, 6.2, 2.6 Hz, 1H), 1.49 - 1.33 (m, 3H), 1.37 (d, J = 6.7 Hz, 3H), 1.32 - 1.26 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{15}H_{26}NO_3$: 304.2; found: 304.1.

Step 3

A mixture of **85-C** (725 mg, 2.39 mmol) and 20% $Pd(OH)_2/C$ (351 mg) in EtOH (25 mL) and 4 N HCl in dioxane (0.9 mL) was stirred under H_2 atmosphere. After 2 h, the reaction mixture was filtered, and the filtrate was concentrated. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{10}H_{18}NO_3$: 200.13; found: 200.1. After the residue was co-evaporated with toluene (x 2), the residue and Boc_2O (720 mg, 3.299 mmol) in

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THF (15 mL) was stirred at room temperature as N,N-diisopropylethylamine (DIPEA) (1.2 mL, 6.889 mmol) was added. After 1 h, the reaction mixture was diluted with water and extracted with EtOAc (x 2). After the organic extracts were washed with water, the combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash using hexanes - EtOAc as eluents to obtain **85-D** which appears to be a mixture of rotamers. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 4.42 - 3.97 (m, 5H), 2.62 (d, J = 5.6 Hz, 1H), 2.45 - 2.26 (m, 1H), 2.25 - 2.15 (m, 1H), 1.80 (td, J = 13.7, 6.7 Hz, 1H), 1.66 (dd, J = 12.3, 6.6 Hz, 2H), 1.55 - 1.70 (m, 2H), 1.47 (s, 2H), 1.42 (s, 7H), 1.28 (dt, J = 9.5, 7.1 Hz, 3H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{15}H_{26}NO_5$: 300.2; found: 299.7.

Step 4

To a solution of **85-D** (568 mg, 1.897 mmol) and pyridine (0.25 mL, 3.091 mmol) in THF (5 mL) was added phenyl chlorothionoformate (0.3 mL, 2.169 mmol) at 0 °C, which produced insoluble material quickly. After ~30 min at 0 °C, additional pyridine (0.3 mL, 3.709 mmol) and phenyl chlorothionoformate (0.3 mL, 2.169 mmol) were added. After 1.5 h at 0 °C and 1 h at room temperature, the mixture was concentrated, and the residue was dissolved in EtOAc and water. After separation of two layers, the organic fraction was washed with ~0.1 N HCl, saturated aqueous $NaHCO_3$, and brine . After the aqueous fractions were extracted with EtOAc, the combined organic fractions were dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography using EtOAc/hexanes as eluents to afford **85-E**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.47 - 7.37 (m, 2H), 7.30 (t, J = 6.9 Hz, 1H), 7.11 (dd, J = 8.0, 4.0 Hz, 2H), 5.54 (dt, J = 9.0, 4.9 Hz, 1H), 4.50 (dt, J = 9.8, 5.3 Hz, 1H), 4.35 (dd, J = 21.4, 5.0 Hz, 1H), 4.30 - 4.14 (m, 2H), 2.71 (s, 1H), 2.54 (s, 1H), 2.14 - 2.00 (m, 1H), 1.82 (m, 3H), 1.54 (m, 1H), 1.48 (s, 4.5H), 1.45 (s, 4.5H), 1.30 (dt, J = 9.4, 7.1 Hz, 3H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{30}NO_6S$: 436.2; found: 435.8.

Step 5

A mixture of **85-E** (602 mg, 1.382 mmol), AIBN (182 mg, 1.108 mmol), and tributyltin hydride (608 mg, 2.096 mmol) in toluene (8 mL) was stirred at 100 °C. After 1 h, the reaction mixture was concentrated and the residue was dissolved in

EtOAc before washing with water and brine. After the aqueous fractions were extracted with EtOAc, the combined organic fractions were dried (Na_2SO_4) and concentrated. The residue was purified with flash chromatography using EtOAc/hexanes as eluents to give **85-F** which appears to be a mixture of rotamers. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 4.37 - 4.06 (m, 4H), 2.69 - 2.53 (m, 1H), 2.11 (m, 1H), 1.97 (m,0.65H), 1.93 - 1.80 (m, 1.35H), 1.54 (s, 5H), 1.46 (s, 3.15H), 1.42 (s, 5.85H), 1.27 (m, 3H). **LCMS-ESI$^+$** (*m/z*): $[M-C_4H_8+H]^+$ calculated for $C_{11}H_{18}NO_4$: 228.1; found: 227.9.

Step 6

85-F (420 mg) was repurified and the purified **85-F** in THF (3 mL) was stirred at 0 °C as 2.0 M $LiBH_4$ in THF (1.5 mL) was added. After 5 min, the mixture was stirred at room temperature for 17 h and additional 2.0 M $LiBH_4$ in THF (1.5 mL) was added at room temperature. After 23 h at room temperature, additional 2.0 M $LiBH_4$ in THF (3 mL) was added and the resulting mixture was stirred for ~72 h. After the reaction mixture was stirred at 0 °C as water was slowly added and further diluted with water, the product was extracted with EtOAc (x 2). The extracts were washed with water, combined, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography using hexane - EtOAc as eluents to give **85-G**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 4.12 (t, J = 5.3 Hz, 1H), 3.99 (dd, J = 12.0, 7.9 Hz, 1H), 3.85 (dd, J = 8.0, 4.7 Hz, 1H), 3.73 (dd, J = 11.9, 1.4 Hz, 1H), 2.28 (d, J = 4.6 Hz, 1H), 1.90 - 1.73 (m, 2H), 1.68 - 1.45 (m, 6H), 1.47 (s, 9H), 1.43 - 1.33 (m, 1H). **LCMS-ESI$^+$** (*m/z*): $[M-C_4H_8+H]^+$ calculated for $C_9H_{16}NO_3$: 186.1; found: 186.0.

Step 7

A solution of **85-G** (198 mg, 0.820 mmol), phthalimide (200 mg, 1.359 mmol), and PPh_3 (488 mg, 1.861 mmol) in THF (10 mL) was stirred at 0 °C bath as DIAD (0.36 mL, 1.828 mmol) was added. After 30 min at 0 °C, the mixture was stirred at room temperature for 17 h. The reaction mixture was concentrated and the residue was purified by flash chromatography using hexane-EtOAc as eluents to **85-H** which appears to be a mixture of rotamers. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.82 (dd, J = 5.4, 3.1 Hz, 2H), 7.69 (dd, J = 5.4, 3.1 Hz, 2H), 4.46 (s, 1H), 4.19 (m, 2H), 3.95 (s, 1H),

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2.31 - 2.14 (m, 1H), 2.05 (d, J = 16.5 Hz, 1H), 1.84 (m, 2H), 1.79 - 1.70 (m, 1H), 1.66 (m, 1H), 1.61 - 1.30 (m, 12H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{27}N_2O_4$: 371.2; found: 370.8.

Step 8

To a solution of **85-H** (270 mg, 0.729 mmol) in EtOH (12 mL) was added hydrazine hydrate (0.145 mL, 3.083 mmol) at room temperature and the resulting solution was stirred at 70 °C. After 1.5 h, the mixture was cooled to 0 °C and diluted with ether (30 mL) before stirring for 1 h at 0 °C. The mixture was filtered and the filtrate was concentrated. The residue was dissolved in CH_2Cl_2 and filtered to remove some insoluble material. The resulting filtrate was concentrated. The residue, combined with **85-I** (257 mg, 0.742 mmol), and $NaHCO_3$ (131 mg, 1.559 mmol) in water (3 mL) and EtOH (3 mL) was stirred at room temperature. After 1 h, the mixture was diluted with water and extracted with EtOAc (x 2). After the extracts were washed with water, the organic extracts were combined, dried (Na_2SO_4), and concentrated. To a solution of the residue in CH_2Cl_2 (2 mL) was added 4 N HCl in dioxane (6 mL). After 1.5 h at room temperature, the solution was concentrated and co-evaporated with toluene. A mixture of the residue and DBU (0.6 mL, 4.012 mmol) in toluene (5 mL) was stirred at 100 °C bath. After 1 h, additional DBU (0.3 mL, 2.006 mmol) was added and the mixture was stirred another 1 h at 100 °C. After the mixture was concentrated, the residue was purified by flash chromatography using EtOAc - 20% MeOH/EtOAc as eluents to give **85-J**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.71 - 7.62 (m, 2H), 7.36 - 7.29 (m, 2H), 7.29 - 7.23 (m, 1H), 5.44 (d, J = 9.8 Hz, 1H), 5.10 (d, J = 9.8 Hz, 1H), 4.44 - 4.28 (m, 3H), 4.23 (t, J = 13.0 Hz, 1H), 3.99 (ddt, J = 10.2, 6.3, 3.6 Hz, 2H), 2.44 - 2.36 (m, 1H), 2.29 (dt, J = 11.6, 5.3 Hz, 1H), 1.84 (dt, J = 10.8, 5.3 Hz, 2H), 1.77 - 1.61 (m, 3H), 1.57 (d, J = 11.7 Hz, 1H), 1.48 (ddd, J = 20.9, 12.3, 5.5 Hz, 1H), 1.38 (t, J = 7.1 Hz, 3H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{24}H_{27}N_2O_5$: 423.2; found: 423.3.

Step 9

A mixture of **85-J** (214 mg, 0.507 mmol) in THF (4 mL) and MeOH (4 mL) was stirred at room temperature as 1 N KOH (1.1 mL) was added. After 30 min,

the reaction mixture was concentrated to ~1 mL, acidified with 1 N HCl (~1.2 mL), and diluted with brine before extraction with CH_2Cl_2 (20 mL x 2). The combined extracts were dried (Na_2SO_4) and concentrated to obtain the crude acid. **LCMS-ESI$^+$** (*m/z*): [M+H]$^+$ calculated for $C_{22}H_{23}N_2O_5$: 395.2; found: 395.3.

A mixture of the crude acid (199 mg, 0.505 mmol), 2,4,6-trifluorobenzyl amine (130 mg, 0.807 mmol), and HATU (304 mg, 0.800 mmol) in CH_2Cl_2 (6 mL) was stirred at room temperature as N,N-diisopropylethylamine (DIPEA) (0.62 mL, 3.559 mmol) was added. After 30 min, the reaction mixture was concentrated and the residue was dissolved in EtOAc, washed with saturated aqueous NH_4Cl (x 2), saturated aqueous $NaHCO_3$ (x 2), and brine. After the aqueous fractions were extracted with EtOAc, two organic fractions were combined, dried (Na_2SO_4) and concentrated. The residue was purified by flash using EtOAc-20%MeOH/EA as eluents to obtain **85-K**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.40 (t, J = 5.7 Hz, 1H), 8.42 (s, 1H), 7.68 - 7.54 (m, 2H), 7.33 (ddd, J = 7.7, 6.3, 1.5 Hz, 2H), 7.30 - 7.26 (m, 1H), 6.74 - 6.60 (m, 2H), 5.37 (d, J = 10.0 Hz, 1H), 5.17 (d, J = 10.0 Hz, 1H), 4.76 - 4.57 (m, 2H), 4.46 (dd, J = 6.0, 4.3 Hz, 1H), 4.34 (t, J = 12.4 Hz, 1H), 4.07 (dd, J = 12.4, 3.6 Hz, 1H), 3.91 (dt, J = 12.4, 3.9 Hz, 1H), 2.52 - 2.44 (m, 1H), 2.32 (dd, J = 11.8, 6.2 Hz, 1H), 1.92 (dt, J = 10.7, 5.4 Hz, 1H), 1.83 - 1.70 (m, 3H), 1.67 (d, J = 11.7 Hz, 1H), 1.52 (dddt, J = 25.5, 17.0, 11.8, 5.3 Hz, 2H). **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -109.15 (dq, J = 15.0, 7.5, 7.1 Hz, 1F), -111.85 (t, J = 6.8 Hz, 2F). **LCMS-ESI$^+$** (*m/z*): [M+H]$^+$ calculated for $C_{29}H_{22}F_5N_3O_4$: 538.2; found: 538.3.

Step 10

85-K (187 mg, 0.348 mmol) was dissolved in trifluoroacetic acid (3 mL) at room temperature and stirred at room temperature. After 1 h, the solution was concentrated and the residue was dissolved in CH_2Cl_2. After the solution was washed with 0.1 N HCl, the aqueous fraction was extracted with CH_2Cl_2 (x 2). The organic fractions were combined, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography using CH_2Cl_2-20% MeOH in CH_2Cl_2 as eluents to obtain 150 mg (96%) of compound **85**. Compound **85** was further purified by recrystallization from methanol (10 mL) to give compound **85**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 12.09 (s, 1H), 10.39 (t, J = 5.7 Hz, 1H), 8.36 (s, 1H), 6.74 - 6.48 (m, 2H), 4.64 (d, J = 5.7 Hz,

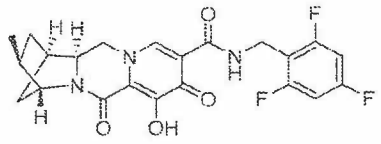
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2H), 4.59 (dd, J = 6.1, 4.4 Hz, 1H), 4.36 - 4.18 (m, 2H), 4.12 (dt, J = 12.4, 4.1 Hz, 1H), 2.68 - 2.47 (m, 1H), 2.25 - 2.10 (m, 1H), 2.10 - 1.98 (m, 1H), 1.98 - 1.66 (m, 4H), 1.66 - 1.48 (m, 2H). **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -109.23 (ddd, J = 15.1, 8.6, 6.0 Hz, 1F), -112.02 (t, J = 6.9 Hz, 2F). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{21}F_3N_3O_4$: 448.2; found: 448.3.

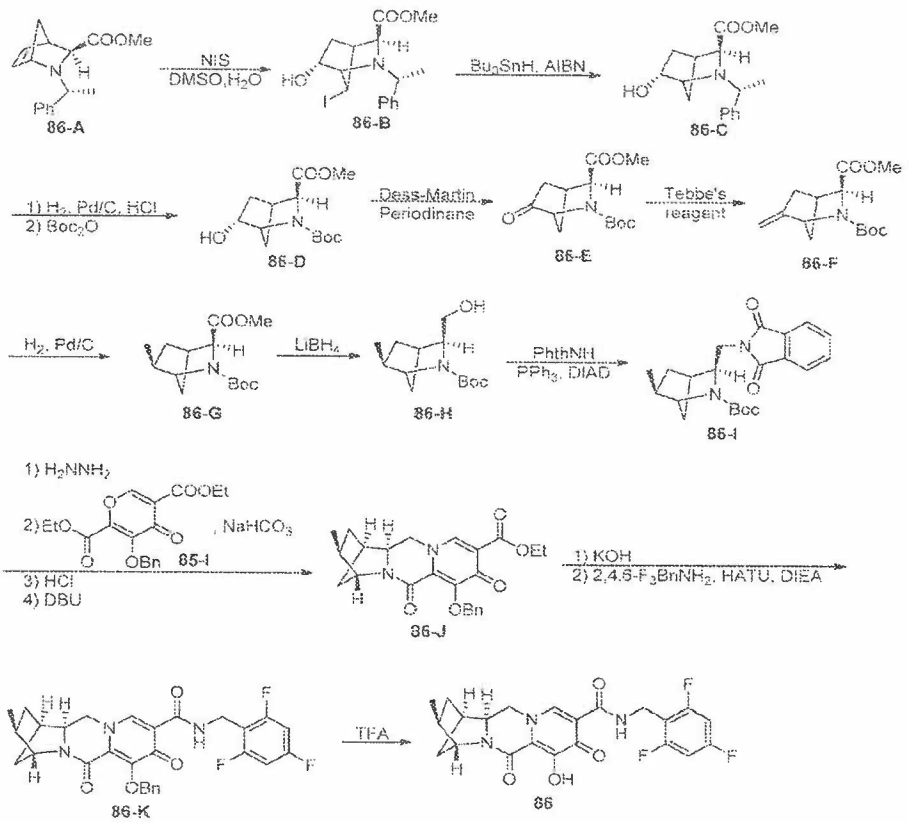
Example 86

Preparation of Compound **86**

(1R,3S,4R,12aS)-7-hydroxy-3-methyl-6,8-dioxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



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Step 1

A solution of **86-A** (10.160 g, 39.48 mmol) in DMSO (52 mL) and water (6.5 mL) was stirred at room temperature as N-iodosuccinmide (8.888 g, 39.50 mmol) was added. After 30 min, the dark brown reaction mixture was diluted with EtOAc, and washed with saturated aqueous $NaHCO_3$ solution, 10 % aqueous $Na_2S_2O_3$ solution],and brine. After the aqueous fractions were extracted with EtOAc, the organic fractions were combined, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography using hexanes - EtOAc as eluents to obtain **86-B** as a white solid. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.33 - 7.19 (m, 5H), 4.25 - 4.12 (m, 1H), 3.79 (q, J = 1.6 Hz, 1H), 3.72 (q, J = 6.5 Hz, 1H), 3.51 (s, 1H), 3.47 (s, 3H), 3.31 (dd, J = 3.9, 1.6 Hz, 1H), 2.76 - 2.69 (m, 1H), 2.13 (ddd, J = 14.3, 7.8, 1.7 Hz, 1H), 2.08 - 1.97 (m, 1H), 1.91

(dtd, J = 14.1, 4.0, 1.5 Hz, 1H), 1.42 (d, J = 6.5 Hz, 3H). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{16}H_{21}INO_3$: 402.1; found: 402.0.

Step 2

A solution of **86-B** (12.468 g, 31.07 mmol), azobisisobutyronitrile (AIBN) (4.082 g, 24.86 mmol), and tributyltin hydride (18.047 g, 62.22 mmol) in toluene (150 mL) was stirred at 100 °C. After 30 min, the reaction mixture was cooled to room temperature, diluted with EtOAc, and washed with water and brine. After the aqueous fractions were extracted with EtOAc, the organic fractions were combined, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography twice using hexanes - EtOAc as eluents to obtain **86-C**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.39 - 7.31 (m, 2H), 7.31 - 7.24 (m, 2H), 7.24 - 7.17 (m, 1H), 4.11 (s, 1H), 3.72 (s, 1H), 3.49 (s, 3H), 3.33 (d, J = 3.4 Hz, 1H), 3.27 (d, J = 6.4 Hz, 1H), 2.65 - 2.51 (m, 1H), 1.92 (ddd, J = 13.6, 6.8, 2.4 Hz, 1H), 1.69 - 1.50 (m, 2H), 1.47 (d, J = 10.1 Hz, 1H), 1.41 (d, J = 6.6 Hz, 3H), 1.21 - 1.07 (m, 1H). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{16}H_{22}NO_3$: 276.2; found: 276.1.

Step 3

A mixture of **86-C** (4.187 g, 15.21 mmol) and 20% $Pd(OH)_2/C$ (1.022 g) in EtOH (100 mL) and 4 N HCl in dioxane (5.7 mL) was stirred under H_2 atmosphere. After 1.5 h, the reaction mixture was filtered, and the filtrate was concentrated. After the residue was co evaporated with toluene, the residue was used for the next step. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_8H_{14}NO_3$: 172.1; found: 172.1.

After the residue was co-evaporated with toluene, the residue and Boc_2O (5.712 g, 26.17 mmol) in THF (45 mL) was stirred at room temperature as N,N-diisopropylethylamine (DIPEA) (8 mL, 45.93 mmol) was added. After 30 min, the reaction mixture was diluted with water and extracted with EtOAc (x 2). After the organic extracts were washed with water, the combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography using hexanes - EtOAc as eluents to obtain **86-D**. ^{1}H NMR spectrum suggests a mixture of rotamers. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 4.20 (d, J = 7.6 Hz, 1H), 4.19 - 4.10 (m, 2H), 4.08 (d, J = 3.5 Hz, 1H), 3.72 (s, 3H), 2.74 (d, J = 5.6 Hz, 1H), 1.97 (ddd, J = 13.6, 6.9,

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2.8 Hz, 1H), 1.88 - 1.78 (m, 1H), 1.79 - 1.50 (m, 1H), 1.46 (s, 3H), 1.38 (s, 6H), 1.31 (d, J = 13.3 Hz, 1H). **LCMS-ESI**$^+$ (*m/z*): [M+H]$^+$ calculated for $C_{13}H_{22}NO_5$: 272.2; found: 271.6.

Step 4

A solution of **86-D** (1659 mg, 6.115 mmol) in CH_2Cl_2 (35 mL) was stirred at 0 °C bath as Dess-Martin periodinane (5.183 g, 12.22 mmol) was added in portions. After 5 min, the mixture was stirred at room temperature. After 2 h, the reaction mixture was cooled in an ice bath, quenched with water, and filtered. The filtrate was washed with saturated $NaHCO_3$, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography using hexanes - EtOAc as eluents to give **86-E**. ^{1}H NMR spectrum suggests two rotamers. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 4.43 (d, J = 3.8 Hz, 0.5H), 4.39 (s, 1H), 4.26 (s, 0.5H), 3.75 (s, 3H), 3.10 (s, 1H), 2.24 (d, J = 4.5 Hz, 0.5H), 2.19 (d, J = 4.4 Hz, 0.5H), 2.12 (d, J = 4.4 Hz, 0.5H), 2.07 (d, J = 4.2 Hz, 0.5H), 2.01 (dd, J = 4.5, 2.2 Hz, 0.5H), 1.98 (dt, J = 4.3, 1.9 Hz, 0.5H), 1.80 (s, 0.5H), 1.77 (s, 0.5H), 1.46 (s, 4.5H), 1.40 (d, J = 2.8 Hz, 4.5H). **LCMS-ESI**$^+$ (*m/z*): [M-C_4H_8+H]$^+$ calculated for $C_9H_{12}NO_5$: 214.1; found: 213.8.

Step 5

A solution of **86-E** (528 mg, 1.961mmol) in THF (12 mL) was stirred at 0 °C as 0.5 M solution of Tebbe reagent in toluene (7.9 mL, 3.95 mmol) was added dropwise. After addition, the brown solution was allowed to warm to room temperature slowly and was stirred at room temperature for 2.5 h. The reaction mixture was stirred at 0 °C bath as the reaction was quenched carefully by the addition of saturated aqueous $NaHCO_3$ solution. After the mixture was diluted with CH_2Cl_2 and stirred at room temperature for 15 minutes, the resulting mixture was filtered through celite pad and the filter cake was washed with CH_2Cl_2. After the two fractions in the filtrate were separated, the aq. fraction was extracted with CH_2Cl_2, and the organic fractions were combined, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography using hexanes - EtOAc as eluents to give **86-F**. ^{1}H NMR spectrum suggests two rotamers. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 5.13 (s, 0.6H), 5.04 (s, 0.4H), 4.82 - 4.71 (m, 1H), 4.55 (s, 0.6H), 4.43 (s, 0.4H), 4.29 (d, J = 3.7 Hz, 0.4H), 4.24 (d, J

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= 3.7 Hz, 0.6H), 3.71 (s, 3H), 2.84 (s, 1H), 2.14 (m, 2H), 1.75 (s, 0.6H), 1.74 - 1.70 (s, 0.4H), 1.55 (m, 1H), 1.45 (s, 3.6H), 1.37 (s, 5.4H). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{14}H_{22}NO_4$: 268.2; found: 267.6.

Step 6

A mixture of **86-F** (333 mg, 1.246 mmol) and 20% $Pd(OH)_2/C$ (53 mg) in EtOH (5 mL) was stirred under H_2 atmosphere. After 30 min, the mixture was filtered and the filtrate was concentrated to give **86-G**. ^{1}H NMR spectrum suggests two rotamers. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 4.20 (m, 1H), 4.08 (m, 1H), 3.71 (two s, 3H), 2.68 (m, 1H), 2.06 (m, 1H), 1.80 - 1.63 (m, 2H), 1.63 - 1.51 (m, 1H), 1.44 (s, 4H), 1.38 (s, 5H), 1.13 (m, 3H), 0.92 (m, 1H). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{14}H_{24}NO_4$: 270.2; found: 269.7.

Step 7

A solution of **86-G** (336 mg, 1.482 mmol) in THF (5 mL) was stirred at 0 °C as 2.0 M $LiBH_4$ in THF (1.5 mL) was added. After 5 min, the mixture was stirred at room temperature. After 2 h, additional 2.0 M $LiBH_4$ in THF (1.5 mL) was added. After 21 h at room temperature, additional 2.0 M $LiBH_4$ in THF (3 mL) was added. After 3 h at room temperature, the solution was heated at 35 °C for 18 h. The reaction mixture was cooled to 0 °C and quenched carefully with water. After the mixture was extracted with EtOAc (x 2), the two organic fractions were washed with water, combined, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography using hexanes - EtOAc to give **86-H**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 4.95 - 4.09 (br, 1H), 4.05 (s, 1H), 3.82 (dd, J = 11.5, 7.7 Hz, 1H), 3.76 - 3.69 (m, 1H), 3.66 (d, J = 11.5 Hz, 1H), 2.45 (d, J = 4.1 Hz, 1H), 2.03 (dqdd, J = 11.4, 7.0, 4.5, 2.6 Hz, 1H), 1.77 - 1.57 (m, 2H), 1.48 (dd, J = 10.1, 1.8 Hz, 1H), 1.45 (s, 9H), 1.00 (d, J = 6.9 Hz, 3H), 0.93 (ddd, J = 13.2, 4.7, 2.6 Hz, 1H). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{13}H_{24}NO_3$: 242.2; found: 241.7.

Step 8

A solution of **86-H** (218 mg, 0.903 mmol), phthalimide (218 mg, 1.482 mmol), and PPh_3 (535 mg, 2.040 mmol) in THF (10 mL) was stirred at 0 °C bath as

DIAD (0.40 mL, 2.032 mmol) was added. After 10 min at 0 °C, the mixture was stirred at room temperature for 19 h. The reaction mixture was concentrated and the residue was purified by flash chromatography using hexane-EtOAc as eluents to give **86-I**. ^{1}H NMR suggests two rotamers. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.82 (dt, J = 7.3, 3.6 Hz, 2H), 7.70 (d, J = 5.3 Hz, 2H), 4.53 - 4.26 (m, 1H), 4.26 - 3.89 (m, 2H), 3.89 - 3.65 (m, 1H), 2.28 (m, 1H), 2.04 (m, 1H), 1.82 - 1.65 (m, 2H), 1.66 - 1.43 (m, 7H), 1.38 (s, 4H), 1.19 - 1.01 (m, 3H). **LCMS-ESI$^+$** (*m/z*): [M +H]$^+$ calculated for $C_{21}H_{27}N_2O_4$: 371.2; found: 370.8.

Step 9

To a solution of **86-I** (319 mg, 0.861 mmol) in EtOH (12 mL) was added hydrazine hydrate (0.17 mL, 3.494 mmol) at room temperature and the resulting solution was stirred at 70 °C bath. After 1.5 h, the mixture was cooled to 0 °C and diluted with ether (25 mL) before stirring for 1 h at 0 °C. The mixture was filtered and the filtrate was concentrated. The residue was dissolved in CH_2Cl_2 and filtered to remove some insoluble material. The resulting filtrate was concentrated to give crude amine. **LCMS-ESI$^+$** (*m/z*): [M +H]$^+$ calculated for $C_{13}H_{25}N_2O_2$: 241.2; found: 240.9.

After the crude amine was co-evaporated with toluene, a mixture of the crude amine, **85-I** (300 mg, 0.866 mmol), and $NaHCO_3$ (150 mg, 1.845 mmol) in water (3 mL) and EtOH (3 mL) was stirred at room temperature. After 2 h, the mixture was diluted with water and extracted with EtOAc (x 2). After the extracts were washed with water, the organic extracts were combined, dried (Na_2SO_4), and concentrated. To a solution of the residue in CH_2Cl_2 (2 mL) was added 4 N HCl in dioxane (6 mL). After 1.5 h at room temperature, the solution was concentrated and co-evaporated with toluene. A mixture of the residue and DBU (0.65 mL, 4.347 mmol) in toluene (6 mL) was stirred at 100 °C. After 1 h, additional DBU (0.65 mL, 4.347 mmol) was added and the mixture was stirred at 100 °C. Additional DBU (0.65 mL, 4.347 mmol) was added after 1 h and the mixture was stirred another 2.5 h at 100 °C. The mixture was diluted with CH_2Cl_2 and washed with water containing 3 mL of 1 N HCl. The organic fraction was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography using EtOAc-20% MeOH/EtOAc as eluents to give **86-J**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.70 - 7.62 (m, 2H), 7.37 - 7.27 (m, 3H), 5.48 (d, J =

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9.9 Hz, 1H), 5.16 (d, J = 9.9 Hz, 1H), 4.53 (s, 1H), 4.38 (m, 2H), 4.11 (m, 1H), 3.97 (dd, J = 12.2, 3.0 Hz, 1H), 3.88 (dt, J = 12.2, 3.0 Hz, 1H), 2.63 (d, J = 4.2 Hz, 1H), 2.28 (qd, J = 7.2, 3.1 Hz, 1H), 2.00 - 1.88 (m, 1H), 1.80 - 1.56 (m, 2H), 1.39 (t, J = 7.1 Hz, 3H), 1.07 (d, J = 6.9 Hz, 3H), 1.04 (dd, J = 5.0, 2.5 Hz, 1H). **LCMS-ESI**$^+$ (*m/z*): [M +H]$^+$ calculated for $C_{24}H_{27}N_3O_5$: 423.2; found: 423.2.

Step 10

A mixture of **86-J** (83 mg, 0.196 mmol) in THF (2 mL) and EtOH (2 mL) was stirred at room temperature as 1 N KOH (0.4 mL) was added. After 30 min, the reaction mixture was diluted with water and washed with CH_2Cl_2. After the aqueous fraction was acidified with 1 N HCl 0.45 mL), the product was extracted with CH_2Cl_2 (x 2). The combined extracts were dried (Na_2SO_4) and concentrated to obtain the crude acid. **LCMS-ESI**$^+$ (*m/z*): [M +H]$^+$ calculated for $C_{27}H_{23}N_3O_5$: 395.2; found: 395.2.

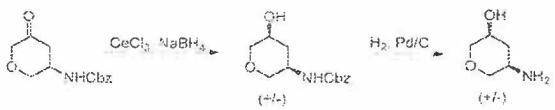
A mixture of the crude acid (69 mg, 0.175 mmol), 2,4,6-trifluorobenzyl amine (42 mg, 0.261 mmol), and HATU (106 mg, 0.279 mmol) in CH_2Cl_2 (3 mL) was stirred at room temperature as N,N-diisopropylethylamine (DIPEA) (0.25 mL, 1.435 mmol) was added. After 30 min, the reaction mixture was concentrated and the residue was dissolved in EtOAc, washed with saturated aqueous NH_4Cl (x 2), saturated aqueous $NaHCO_3$ (x 2), and brine. After the aqueous fractions were extracted with EtOAc, two organic fractions were combined, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography using EtOAc-20%MeOH/EtOAc as eluents to obtain **86-K**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.40 (t, J = 5.7 Hz, 1H), 8.40 (s, 1H), 7.66 - 7.51 (m, 2H), 7.36 - 7.29 (m, 2H), 7.29 - 7.23 (m, 1H), 6.71 - 6.61 (m, 2H), 5.36 (d, J = 10.0 Hz, 1H), 5.18 (d, J = 10.0 Hz, 1H), 4.73 - 4.58 (m, 2H), 4.53 (s, 1H), 4.22 - 4.11 (m, 1H), 4.03 (dd, J = 12.4, 3.1 Hz, 1H), 3.81 (dt, J = 12.3, 3.1 Hz, 1H), 2.68 - 2.59 (m, 1H), 2.29 (dddd, J = 11.4, 7.1, 4.7, 2.4 Hz, 1H), 1.94 (ddd, J = 13.5, 11.2, 4.6 Hz, 1H), 1.88 - 1.67 (m, 2H), 1.06 (d, J = 7.0 Hz, 3H), 1.03-1.09 (m, 1H). **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -109.14 (ddd, J = 15.2, 8.7, 6.2 Hz, 1F), -111.86 (t, J = 7.0 Hz, 2F). **LCMS-ESI**$^+$ (*m/z*): [M +H]$^+$ calculated for $C_{20}H_{17}F_3N_3O_4$: 538.2; found: 538.1.

Step 11

86-K (61 mg, 0.113 mmol) was dissolved in trifluoroacetic acid (2 mL) and stirred at room temperature. After 1 h, the solution was concentrated and the residue was dissolved in CH_2Cl_2. After the solution was washed with 0.1 N HCl, the aqueous fraction was extracted with CH_2Cl_2 (x 2). The organic fractions were combined, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography using CH_2Cl_2-20% MeOH in CH_2Cl_2 as eluents to obtain compound **86**. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 12.02 (s, 1H), 10.40 (t, J = 5.7 Hz, 1H), 8.35 (s, 1H), 6.63 (t, J = 8.1 Hz, 2H), 4.62 (d, J = 5.7 Hz, 2H), 4.59 (s, 1H), 4.22 (dd, J = 12.2, 3.5 Hz, 1H), 4.13 (t, J = 11.9 Hz, 1H), 4.05 (dt, J = 12.0, 3.1 Hz, 1H), 2.77 - 2.70 (m, 1H), 2.31 m, 1H), 2.09 - 1.93 (m, 1H), 1.93 - 1.81 (m, 2H), 1.10 (ddd, J = 13.9, 5.0, 2.1 Hz, 1H), 1.02 (d, J = 6.9 Hz, 3H). **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -109.22 (ddd, J = 15.1, 8.7, 6.1 Hz, 1F), -112.05 (t, J = 6.9 Hz, 2F). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{21}F_3N_3O_4$: 448.2; found: 448.3.

Example 87

Preparation of *cis*-5-aminotetrahydro-2H-pyran-3-ol



Step 1

A solution of benzyl (5-oxotetrahydro-2H-pyran-3-yl)carbamate (740 mg, 3.0 mmol) and cerium(III) chloride heptahydrate (1.12 g, 3.0 mmol) in 20 mL methanol was cooled to 0 °C and sodium borohydride (120 mg, 3.2 mmol) was then added portionwise. The reaction mixture was allowed to stir at 0 °C for 45 minutes and then quenched by slow addition of 1 mL acetone followed by 3 hours stirring at room temperature. The reaction mixture was partitioned between water and dichloromethane and the aqueous phase extracted into dichloromethane followed by 2-butanol. The combined organic phases were dried over magnesium sulfate, filtered, concentrated, and the residue purified by flash chromatography (0-100% EtOAc/hexanes) to afford the desired *cis*-benzyl ((3R,5S)-5-hydroxytetrahydro-2H-pyran-3-yl)carbamate. **^{1}H-**

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NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.26 (m, 5H), 6.06 (br s, 1H), 5.07 (s, 2H), 3.86 – 3.70 (m, 2H), 3.69 – 3.47 (m, 4H), 2.00 – 1.89 (m, 1H), 1.76 (d, *J* = 13.5 Hz, 1H). The undesired *trans*-isomer was also isolated.

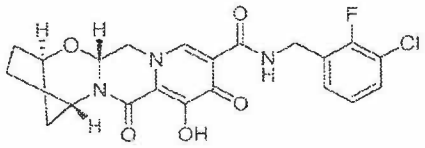
Step 2

To a solution of *cis*-benzyl ((3R,5S)-5-hydroxytetrahydro-2H-pyran-3-yl)carbamate (290 mg, 1.16 mmol) in 5 mL 1:1 DCM:EtOH was added 10wt% Pd/C (255 mg). This mixture was stirred under balloon pressure hydrogen for 18 hours and palladium removed by filtration thru celite with ethanol rinse. Upon concentration of filtrate, the *cis*-5-aminotetrahydro-2H-pyran-3-ol was afforded and carried on as crude.

Example 88

Preparation of Compound **88**

'(2R,5S,13aR)-N-(3-chloro-2-fluorobenzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



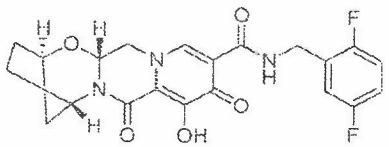
88

Compound **88** was prepared in a similar manner to compound **15** using (3-chloro-2-fluorophenyl)methanamine in place of (4-fluorophenyl)methanamine. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 10.43 (br s, 1H), 8.34 (br s, 1H), 7.32 – 7.24 (m, 2H), 7.02 (t, *J* = 7.9 Hz, 1H), 5.36 (d, *J* = 9.4 Hz, 1H), 5.30 (s, 2H), 4.70 (d, *J* = 6.0 Hz, 3H), 4.24 (d, *J* = 12.0 Hz, 1H), 4.00 (dd, *J* = 12.7, 9.5 Hz, 1H), 2.18 – 1.96 (m, 4H), 1.96 – 1.83 (m, 1H), 1.60 (dt, *J* = 12.4, 3.1 Hz, 1H). **LCMS-ESI$^+$** (*m/z*): [M+H]$^+$ calculated for $C_{21}H_{19}ClFN_3O_5$: 448.11; found: 448.2.

Example 89

Preparation of Compound **89**

(2R,5S,13aR)-N-(2,5-difluorobenzyl)-8-hydroxy-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide



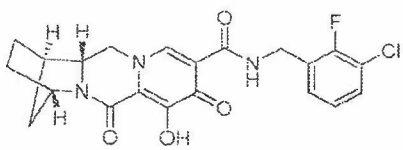
89

Compound **89** was prepared in a similar manner to compound **15** using (2,5-difluorophenyl)methanamine in place of (4-fluorophenyl)methanamine. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 10.32 (t, *J* = 5.8 Hz, 1H), 8.31 (br s, 1H), 7.15 – 6.89 (m, 2H), 6.86 (d, *J* = 8.5 Hz, 1H), 5.40 (d, *J* = 9.3 Hz, 1H), 5.24 (s, 1H), 4.67 – 4.51 (m, 3H), 4.35 – 4.28 (m, 1H), 3.99 – 3.90 (m, 1H), 2.16 – 1.85 (m, 5H), 1.60 – 1.50 (m, 1H). **LCMS-ESI$^+$** (*m/z*): [M+H]$^+$ calculated for $C_{21}H_{19}F_2N_3O_5$: 432.14; found: 432.2.

Example 90

Preparation of Compound **90**

(1R,4S,12aR)-N-(3-chloro-2-fluorobenzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



90

Compound **90** was prepared in a similar manner to compound **41** using (3-chloro-2-fluorophenyl)methanamine in place of (2,4,6-trifluorophenyl)methanamine. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 9.22 (s, 1H), 8.79 (s, 1H), 7.39 – 7.28 (m, 2H), 7.06 (t, *J* = 8.0 Hz, 1H), 4.89 (s, 1H), 4.70 – 4.56 (m, 3H), 4.06 – 3.83 (m, 2H), 3.04 –

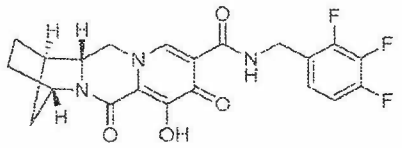
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2.88 (m, 1H), 2.77 (s, 1H), 1.97 – 1.58 (m, 6H). **LCMS-ESI**$^+$ (*m/z*): [M+H]$^+$ calculated for $C_{21}H_{19}ClFN_3O_4$: 432.11; found: 432.2.

Example 91

Preparation of Compound **91**

(1R,4S,12aR)-7-hydroxy-6,8-dioxo-N-(2,3,4-trifluorobenzyl)-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



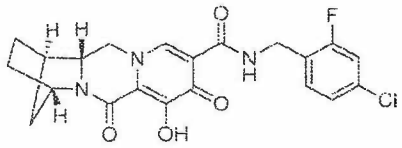
91

Compound **91** was prepared in a similar manner to compound **41** using (2,3,4-trifluorophenyl)methanamine in place of (2,4,6-trifluorophenyl)methanamine. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 10.25 (s, 1H), 8.45 (s, 1H), 7.10 (d, *J* = 5.1 Hz, 1H), 6.90 (d, *J* = 8.7 Hz, 1H), 4.89 (s, 1H), 4.63 (s, 2H), 4.22 (d, *J* = 11.6 Hz, 1H), 3.93 – 3.73 (m, 2H), 2.71 (s, 1H), 1.97 – 1.57 (m, 6H). **LCMS-ESI**$^+$ (*m/z*): [M+H]$^+$ calculated for $C_{21}H_{18}F_3N_3O_4$: 434.13; found: 434.2.

Example 92

Preparation of Compound **92**

(1R,4S,12aR)-N-(4-chloro-2-fluorobenzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



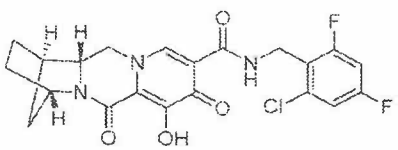
92

Compound **92** was prepared in a similar manner to compound **41** using (4-chloro-2-fluorophenyl)methanamine in place of (2,4,6-trifluorophenyl)methanamine. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 10.28 (s, 1H), 8.41 (s, 1H), 7.29 (s, 1H), 7.11 – 6.95 (m, 2H), 4.85 (s, 1H), 4.57 (s, 2H), 4.22 (d, *J* = 10.2 Hz, 1H), 3.81 (q, *J* = 13.9, 13.1 Hz, 2H), 2.68 (s, 1H), 1.99 – 1.50 (m, 6H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{19}ClFN_3O_4$: 432.11; found: 432.2.

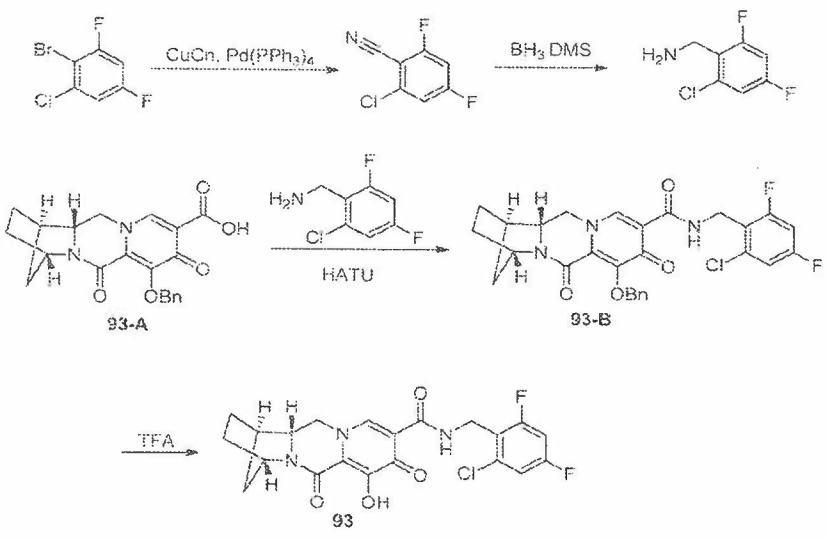
Example 93

Preparation of Compound **93**

(1R,4S,12aR)-N-(2-chloro-4,6-difluorobenzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



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Step 1

A 5 mL microwave vial was charged with 2-bromo-1-chloro-3,5-difluorobenzene (540 mg, 2.4 mmol), cuprous cyanide (436 mg, 4.87 mmol), tetrakis(triphenylphosphine)palladium (63 mg, 0.05 mmol), sealed, and evacuated/backfilled with nitrogen. To this was added 5 mL degassed DMF. The sealed vessel was heated at 110 °C for 18 hours, diluted with ethyl acetate, and washed sequentially with twice 9:1 NH_4OH:$NH_4Cl_{(aq)}$, twice 5% $LiCl_{(aq)}$, and brine. The organic phase was then dried over magnesium sulfate, filtered, and concentrated. The crude residue was purified by flash chromatography (100% hexanes) to afford 2-chloro-4,6-difluorobenzonitrile. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 7.13 (dt, *J* = 8.0, 1.9 Hz, 1H), 6.93 (td, *J* = 8.5, 2.3 Hz, 1H).

Step 2

To a solution of 2-chloro-4,6-difluorobenzonitrile (210 mg, 1.2 mmol) in 2.4 mL THF was added a 2M solution of borane-DMS in THF (0.6 mL). This reaction mixture was allowed to stir at refluxing temperature for 18 hours resulting in a loss of all solvent. The residue was re-dissolved in 3 mL THF, cooled to 0 °C, a 6M solution of $HCl_{(aq)}$ was carefully added, and the mixture returned to reflux for 30 minutes. The reaction mixture was once again cooled to 0 °C and treated with 4M $NaOH_{(aq)}$. The aqueous phase was extracted with DCM, combined organic phases dried over magnesium sulfate, filtered, and concentrated. The crude residue was purified by flash chromatography (0-10% MeOH/DCM) to afford (2-chloro-4,6-difluorophenyl)methanamine. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 6.95 (dt, *J* = 8.3, 2.1 Hz, 1H), 6.76 (td, *J* = 9.4, 2.5 Hz, 1H), 3.94 (d, *J* = 1.9 Hz, 2H).

Steps 3 and 4

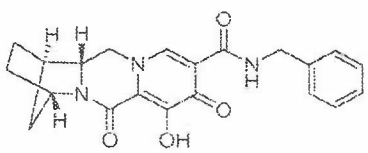
A solution of **93-A** (74 mg, 0.11 mmol), (2-chloro-4,6-difluorophenyl)methanamine (48.5 mg, 0.27 mmol), HATU (100 mg, 0.26 mmol), and N,N-diisopropylethylamine (0.1 mL, 0.57 mmol) in 1 mL dichloromethane was stirred at room temperature for one hour at which point complete disappearance of **93-A** and formation of **93-B** was observed by LCMS. TFA (0.65 M) was added and the mixture

was stirred at room temperature for one hour, at which point 1 mL DMF was added. The reaction mixture and then concentrated and purified by preparative HPLC (ACN/H_2O + 0.1% TFA) to afford compound **93**. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 10.41 (t, J = 5.7 Hz, 1H), 8.33 (s, 1H), 7.41 – 7.26 (m, 2H), 4.72 – 4.57 (m, 3H), 4.43 (dd, J = 12.5, 3.6 Hz, 1H), 3.94 (t, J = 12.4 Hz, 2H), 3.77 (dd, J = 12.4, 3.6 Hz, 3H), 1.87 – 1.67 (m, 3H), 1.67 – 1.45 (m, 2H), 1.43 (d, J = 10.4 Hz, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{18}ClF_2N_3O_4$: 450.10; found: 450.2.

Example 94

Preparation of Compound **94**

(1R,4S,12aR)-N-benzyl-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



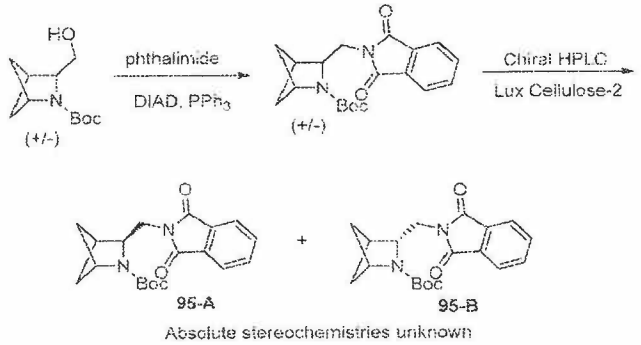
94

Compound **94** was prepared in a similar manner to compound **41** using phenylmethanamine in place of (2,4,6-trifluorophenyl)methanamine. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 10.37 (s, 1H), 8.26 (s, 1H), 7.37 – 7.19 (m, 5H), 4.55 (d, J = 4.8 Hz, 1H), 4.34 (d, J = 5.7 Hz, 1H), 4.23 (d, J = 9.8 Hz, 1H), 4.09 (d, J = 28.2 Hz, 1H), 3.78 (d, J = 10.9 Hz, 1H), 3.64 (d, J = 13.2 Hz, 1H), 3.14 – 3.01 (m, 1H), 1.91 – 1.49 (m, 4H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{21}N_3O_4$: 380.16; found: 380.2.

Example 95

Preparation of chiral tert-butyl 3-((1,3-dioxoisoindolin-2-yl)methyl)-2-azabicyclo[2.1.1]hexane-2-carboxylates **95-A** and **95-B**

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Step 1

To a 0 °C solution of racemic tert-butyl 3-(hydroxymethyl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (285 mg, 1.34 mmol), triphenylphosphine (425 mg, 1.62 mmol), and phthalimide (240 mg, 1.62 mmol) in 9 mL THF was added dropwise a solution of diisopropyl azodicarboxylate (0.35 mL, 1.8 mmol) in 1 ml THF. The reaction mixture was warmed to room temperature, stirred for 90 minutes, concentrated onto silica, and purified by flash chromatography (0-25% EtOAc/hexanes) to afford tert-butyl 3-((1,3-dioxoisoindolin-2-yl)methyl)-2-azabicyclo[2.1.1]hexane-2-carboxylate as a racemic mixture. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{19}H_{23}N_2O_4$: 343.2; found: 342.8.

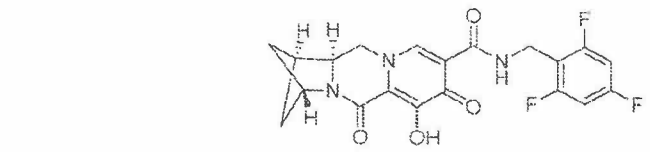
Step 2

Racemic tert-butyl 3-((1,3-dioxoisoindolin-2-yl)methyl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (655 mg, 1.91 mmol) was separated by chiral HPLC on a Lux Cellulose-2 column using an acetronitrile eluent to afford chiral **95-A** (first eluting peak) and **95-B** (second eluting peak) in enantioenriched form. For **95-A**: 144 mg, 98%ee (absolute stereochemistry unknown). For **95-B**: 242 mg, 49%ee (absolute stereochemistry unknown).

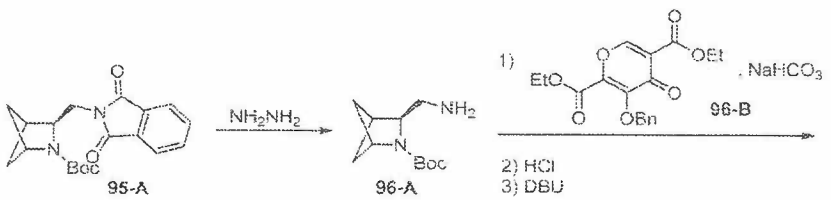
Example 96

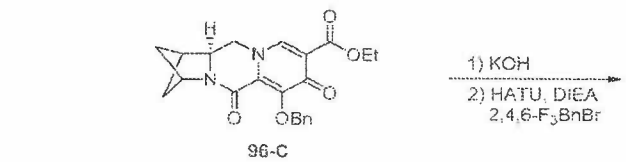
Preparation of Compound **96**

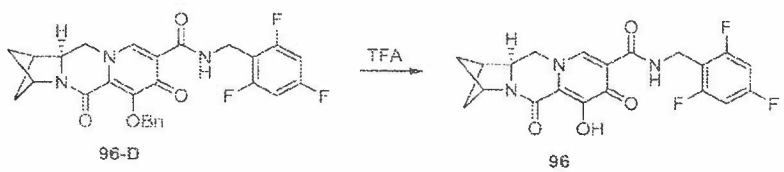
(1R,3R,11aS)-6-hydroxy-5,7-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,5,7,11,11a-hexahydro-1H-1,3-methanopyrido[1,2-a]pyrrolo[1,2-d]pyrazine-8-carboxamide



96







(Absolute stereochemistries unknown)

Step 1

To a solution of intermediate **95-A** (141 mg, 0.41 mmol, 98% ee, unknown absolute stereochemistry) in 9 mL ethanol was added hydrazine hydrate (0.5 mL, 10.3 mmol) and stirred at 70 °C for 18 hours to afford **96-A** of unknown absolute stereochemistry. Solids were removed by filtration and the filtrate concentrated and carried on as crude.

Step 2

A mixture of crude **96-A** (0.41 mmol assumed), **96-B** (430 mg, 1.25 mmol), and sodium bicarbonate (69 mg, 0.82 mmol) in 2 mL water and 2 mL ethanol were stirred at room temperature for 18 hours, after which the reaction mixture was diluted with water and thrice extracted to ethyl acetate. The combined organic phases were dried over magnesium sulfate, filtered, concentrated. The crude residue (222 mg) was dissolved in 1.5 mL DCM and 4 N HCl in dioxane (4 mL) was added and stirred for 90 minutes at room temperature. The mixture was concentrated to dryness and coevaporated with toluene. The crude residue and DBU (0.3 mL, 2.0 mmol) in 6 mL methanol was stirred at 50 °C for 90 minutes. The reaction mixture was then concentrated onto silica gel and purified by flash chromatography (0-10% MeOH/DCM) to afford **96-C**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{22}N_2O_5$: 395.16; found: 395.2.

Step 3

A mixture of **96-C** (112 mg, 0.28 mmol), 1M aqueous potassium hydroxide (1 mL), 4 mL methanol, and 4 mL THF was stirred at room temperature for 3 hours, at which point the mixture was diluted with dichloromethane, acidified by addition of 1M aqueous hydrogen chloride, and the organic phase extracted to dichloromethane. The combined organics were dried, filtered, and concentrated from toluene. After drying under vacuum, the residue was suspended in 1.5 mL DCM and trifluorobenzylamine (62 mg, 0.38 mmol), HATU (220 mg, 0.58 mmol), and N,N-diisopropylethylamine (DIPEA) (0.15 mL, 0.86 mmol) were added. This reaction mixture was stirred at room temperature for 2 hours to afford **96-D** which was carried forward as crude.

Step 4

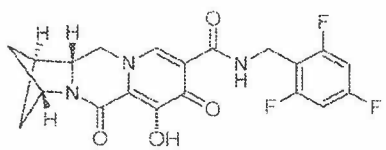
Trifluoroacetic acid (1.7 mL, 22.2 mmol) was added to the crude reaction solution containing **96-D** from the prior step and the reaction mixture allowed to stir at room temperature for 90 minutes. 1 mL of DMF was then added, the reaction mixture concentrated down to ~1 mL, filtered, and purified by preparative HPLC

(ACN/water + 0.1% TFA) to afford compound **96** (unknown absolute stereochemistry). **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 10.45 – 10.35 (m, 1H), 8.39 (s, 1H), 7.23 – 7.09 (m, 2H), 4.67 (dd, J = 12.6, 4.8 Hz, 2H), 4.53 (d, J = 5.5 Hz, 2H), 4.20 (dd, J = 11.9, 3.8 Hz, 1H), 4.05 – 3.95 (m, 1H), 2.96 – 2.88 (m, 1H), 2.16 (d, J = 7.0 Hz, 1H), 1.97 (d, J = 7.0 Hz, 1H), 1.68 – 1.60 (m, 1H), 1.53 – 1.45 (m, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{20}H_{16}F_3N_3O_4$: 420.12; found: 420.2.

Example 97

Preparation of Compound **97**

(1S,3S,11aR)-6-hydroxy-5,7-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,5,7,11,11a-hexahydro-1H-1,3-methanopyrido[1,2-a]pyrrolo[1,2-d]pyrazine-8-carboxamide



(Absolute stereochemistry unknown)

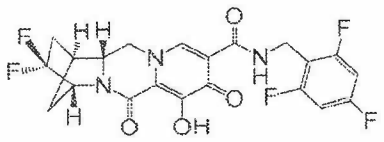
97

Compound **97** (49% ee, unknown absolute stereochemistry) was prepared in a similar manner to compound **96** using intermediate **95-B** (49% ee, unknown absolute stereochemistry) in place of enantiomerically opposite intermediate **95-A**. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 10.39 (t, J = 5.7 Hz, 1H), 8.42 (s, 1H), 7.25 – 7.13 (m, 2H), 4.73 – 4.66 (m, 2H), 4.54 (d, J = 5.7 Hz, 2H), 4.20 (dd, J = 12.3, 3.9 Hz, 1H), 4.01 (t, J = 12.4 Hz, 1H), 2.93 (dd, J = 6.7, 3.4 Hz, 1H), 2.19 – 2.14 (m, 1H), 1.97 (d, J = 8.3 Hz, 1H), 1.65 (dd, J = 10.4, 7.9 Hz, 1H), 1.49 (dd, J = 10.5, 7.7 Hz, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{20}H_{16}F_3N_3O_4$: 420.12; found: 420.2.

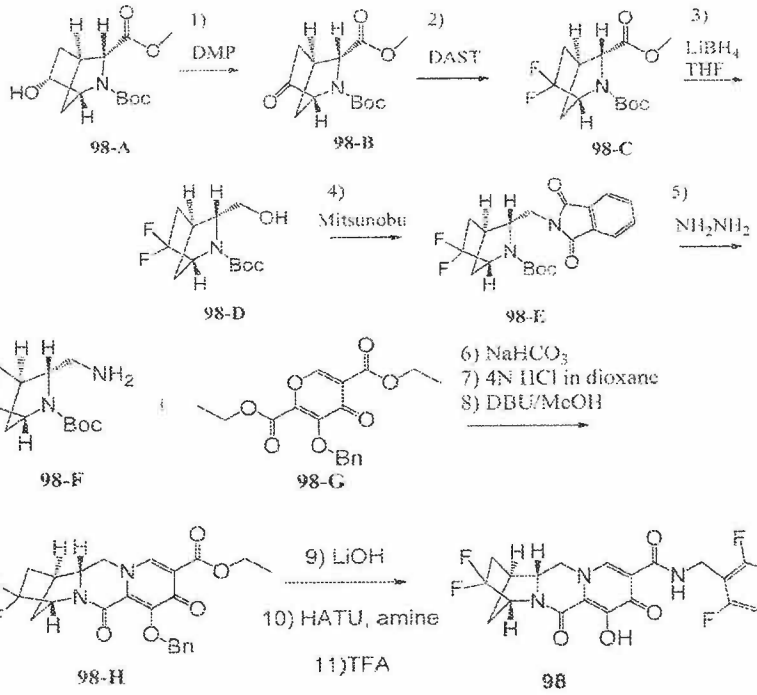
Example 98

Preparation of Compound **98**

(1S,4R,12aR)-3,3-difluoro-7-hydroxy-6,8-dioxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



98



Step 1

98-A (0.5g, 1.87mmol) was dissolved in DCM (20 mL) and cooled to 0 °C under Nitrogen. Dess-Martin Periodinane (1.59 g, 3.74 mmol) was added slowly. The mixture was stirred for 2 h at room temperature, quenched with $Na_2S_2O_3$/$NaHCO_3$ (7:1) aqueous saturated solution (160 mL) and stirred vigorously until two layers were separated. The crude product was twice extracted with DCM. The combined organic layers was dried over sodium sulfate and concentrated. The crude product was purified by flash chromatography on silica gel with 0-20%MeOH/DCM to afford **98-B**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 4.34 - 4.05 (m, 1H), 3.97 - 3.75 (m, 1H), 3.69 (s,

3H), 2.89 (dd, J = 4.4, 2.1 Hz, 1H), 2.30 - 1.97 (m, 3H), 1.56 (d, J = 11.3 Hz, 1H), 1.35 (s, 9H). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{13}H_{19}NO_5$: 269.13; found: 270.78.

Step 2

A solution of **98-B** (504 mg, 1.87mmol) in DCM (15 mL) was stirred at 0 °C. DAST (1ml) was added drop wise to the reaction mixture. After overnight stirring at room temperature, the reaction mixture was cooled back to 0 °C. Saturated $NaHCO_3$ (10 mL) was added slowly. The mixture was extracted with twice with DCM and dried over Na_2SO_4. After concentrating, the residue was purified by flash chromatography 0-50% EtOAc/hexanes to give **98-C**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 4.45 - 4.18 (m, 1H), 3.85 (m, 1H), 3.72 (d, J = 1.5 Hz, 3H), 2.72 (ddd, J = 5.1, 3.2, 1.6 Hz, 1H), 2.27 - 1.52 (m, 4H), 1.41 (d, J = 21.9 Hz, 9H). **^{19}F-NMR** (376 MHz, Chloroform-d) δ -91.72 - -93.99 (m), -113.65 - -115.98 (m). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{13}H_{19}F_2NO_4$: 291.13; found: 291.55.

Step 3

98-C (476 mg, 1.634mmol) in THF (20 mL) was stirred at 0 °C as 2.0 M $LiBH_4$ in THF (2.4 mL, 4.8mmol) was added. The mixture was warmed to room temperature and stirred for 4 h. The reaction mixture was quenched with ice and diluted with EtOAc and saturated NH_4Cl (some H_2 evolution). After the two phases were separated, the organic fraction was washed with brine, dried (Na_2SO_4), and concentrated. The crude product of **98-D** was used as is for the next step. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{12}H_{19}F_2NO_3$: 263.13; found: 164.10.

Step 4

98-D (1.634mmol), phthalimide (0.36 g, 2.4 5mmol), and PPh_3 (0.855 g, 3.26mmol) in THF (10 mL) was stirred at 0 °C bath as DIAD (0.642 mL, 3.26mmol) was added. After addition, the mixture was stirred at 0 °C for 30 min and then at room temperature for 16 h. It was diluted with EtOAc, and saturated NH_4Cl. After stirring for 5 min, a solid was filtered off and the two phases were separated. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by flash chromatography with 0-50%EA/Hex as eluents to give **98-E**. **^{1}H-**

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NMR suggests a mixture of two rotamers. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 7.89 - 7.80 (m, 2H), 7.78 - 7.66 (m, 2H), 5.02 (ddt, J = 16.6, 12.5, 6.3 Hz, 1H), 4.24 (d, J = 71.8 Hz, 1H), 4.10 - 3.92 (m, 1H), 3.83 - 3.51 (m, 2H), 2.46 (s, 1H), 2.21 - 1.98 (m, 2H), 1.87 - 1.62 (m, 2H),1.31 (d, J = 8.5 Hz, 9H); **^{19}F-NMR** (376 MHz, Chloroform-d) δ -91.22 - -93.58 (m), -113.20 - -115.45 (m). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{20}H_{22}F_2N_2O_4$: 392.15; found: 393.3.

Step 5

To a solution of **98-E** (696 mg, 1.774mmol) in EtOH (10mL) was added hydrazine hydrate (1mL) at room temperature and the resulting solution was stirred at room temperature for 2 h. The mixture was diluted with ethyl ether (30 mL) and stirred at 0 °C for 60 min before filtration. The filtrate was concentrated and the residue was dissolved in CH_2Cl_2 and filtered. The filtrate was concentrated and purified by flash chromatography on silica gel with 0-20% MeOH (0.2% TEA) /DCM to give **98-F**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 4.91 (p, J = 6.2 Hz, 1H), 4.29 - 3.97 (m, 1H), 3.36 - 2.93 (m, 2H), 2.49 (qt, J = 8.8, 5.2 Hz, 2H), 2.08 (dddd, J = 25.5, 14.0, 7.1, 4.9 Hz, 1H), 1.89 - 1.49 (m, 4H), 1.41 and 1.21 (d, J = 6.2 Hz, 9H). **^{19}F-NMR** (376 MHz, Chloroform-d) δ -91.63 - -93.16 (m), -113.11 - -115.08 (m). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{12}H_{20}F_2N_2O_2$: 262.15; found: 262.8.

Step 6, 7 and 8

The mixture of **98-G** (375.8 mg, 1.55 mmol), **98-E** (370 mg, 1.41 mmol), and $NaHCO_3$ (261 mg, 3.10 mmol) in water (5 mL) and EtOH (5 mL) was stirred at room temperature for 2 h. The mixture was diluted with brine and extracted with EtOAc (x 2). The extracts were combined, dried (Na_2SO_4), concentrated, and dried in vacuo to afford crude **A**. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ 591.59. Crude **A** (1.38mmol) in CH_2Cl_2 (5 mL) was added 4 N HCl in dioxane (5 mL). After 2 h at room temperature, mixture was concentrated to dryness. It was co-evaporated with toluene once and dried in vacuo to afford crude **B**. **B** (1.38mmol + 0.442mmol) and DBU (3 mL, 11mmol) in anhydrous MeOH (15 mL) were stirred at 50 °C bath for 40 min. The mixture was concentrated. The residue was purified by flash chromatography (80 g

column) using 0 - 20% MeOH/DCM as eluents to give **98-H**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{23}H_{22}F_2N_2O_5$: 444.15; found: 445.36 (90%), 431.18 (10%).

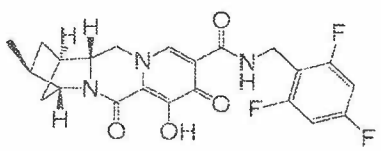
Steps 9.10 and 11

The remaining steps were performed using procedures similar to Example **41** to afford desired compound **98**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 10.29 (d, J = 6.1 Hz, 1H), 8.34 (s, 1H), 6.65 (dd, J = 8.7, 7.5 Hz, 2H), 4.83 (s, 1H), 4.72 - 4.58 (m, 2H), 4.36 - 4.10 (m, 2H), 4.05 (t, J = 11.5 Hz, 1H), 2.97 (d, J = 4.4 Hz, 1H), 2.49 - 2.08 (m, 3H), 2.12 - 1.94 (m, 1H). **^{19}F-NMR** (376 MHz, Chloroform-d) δ -92.08 - -93.57 (m, 1F), -108.92 (ddd, J = 15.1, 8.8, 6.3 Hz, 1F), -109.30 - -110.65 (m, 1F), -112.16 (p, J = 7.3 Hz, 2F). **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{16}F_5N_3O_4$: 469.11; found: 470.23.

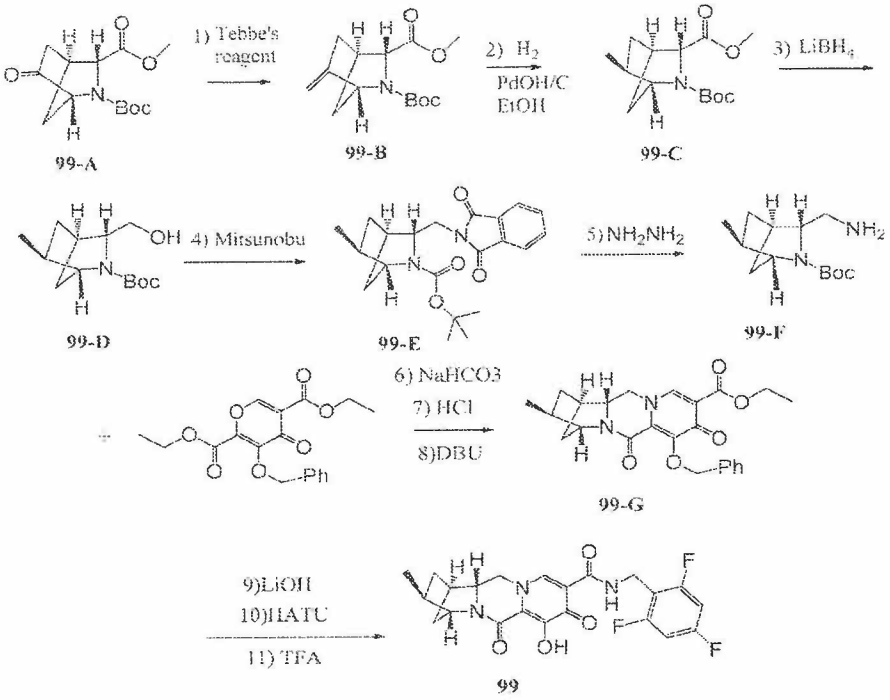
Example 99

Preparation of Compound **99**

(1R,3S,4R,12aR)-7-hydroxy-3-methyl-6,8-dioxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



99



Step 1

To a stirred solution of **99-A** (1 g, 3.71 mmol) in THF (20 mL) was added dropwise a solution of the Tebbe reagent (0.5 M in toluene, 14.85mL, 7.42 mmol) at 0 °C. After addition, the brown solution was allowed to warm to room temperature slowly and was stirred at room temperature for 2 h. The reaction was quenched carefully by the addition of saturated $NaHCO_3$ solution at 0 °C, and the mixture was stirred at room temperature for 15 minutes. The mixture was filtered through celite, and the filter cake was washed with ether and DCM (1:1) twice. After separated layers, the organics were combined and concentrated in vacuo, and the residue was purified by column chromatography on silica gel column with 0-50% EtOAc/hexanes to afford **99-B**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 5.06 (dt, J = 48.6, 2.6 Hz, 1H), 4.73 (d, J = 7.0 Hz, 1H), 4.42 (d, J = 61.8 Hz, 1H), 3.81 (d, J = 48.2 Hz, 1H), 3.73 (d, J = 1.6 Hz, 3H), 2.74 (dd, J = 9.4, 4.4 Hz, 1H), 2.38 (ddt, J = 13.5, 4.5, 2.5 Hz, 1H), 2.18 - 2.06 (m, 1H), 1.99 (dt, J = 10.2, 2.4 Hz, 1H), 1.58 (s, 1H), 1.42 (d, J

= 25.5 Hz, 9H). **LCMS-ESI$^+$** (*m/z*): [M+H] calculated for $C_{14}H_{21}NO_4$: 267.15; found: 267.65.

Step 2

A mixture of **99-B** (675 mg, 2.506 mmol) and 20% $Pd(OH)_2/C$ (500 mg) in EtOH (50 mL) was stirred under H_2 atmosphere. The mixture was filtered through Celite and the filtrate was concentrated to give **99-C**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 4.23 - 3.99 (m, 1H), 3.77 - 3.64 (m, 4H), 2.55 (d, J = 4.8 Hz, 1H), 2.14 - 1.86 (m, 3H), 1.42 (d, J = 24.2 Hz, 9H), 0.96 (d, J = 6.6 Hz, 3H), 0.85 (ddd, J = 12.5, 4.8, 2.4 Hz, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{14}H_{23}NO_4$: 269.16; found: 269.69.

Step 3

99-C (670 mg, 2.488 mmol) in THF (20 mL) was stirred at 0 °C as 2.0 M $LiBH_4$ in THF (3.7mL, 7.46 mmol) was added. The mixture was warmed to room temperature and stirred for 4h. The reaction mixture was quenched with ice and diluted with EtOAc and saturated NH_4Cl (some H_2 evolution). After two phases were separated, the organic fraction was washed with brine, dried (Na_2SO_4), and concentrated. The crude alcohol **99-D** was used as is for the next step. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{13}H_{23}NO_3$: 241.17; found: 241.76.

Steps 4 and 5

Steps 4 and 5 were performed using procedures similar to those in Example **41** to afford **99-F**. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{13}H_{24}N_2O_2$: 240.18; found: 241.2.

Step 6, 7 and 8

Steps 6, 7 and 8 were performed using procedures similar to that of Example **41** to give **99-G**. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{24}H_{36}N_2O_5$: 422.18; found: 423.21.

Step 9, 10 and 11

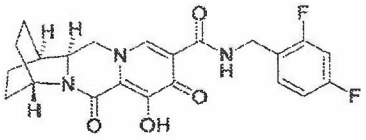
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The remaining steps were performed using procedures similar to Example **41** to afford compound **99**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 11.71 (s, 1H), 10.36 (t, J = 5.7 Hz, 1H), 8.28 (s, 1H), 6.63 (t, J = 8.1 Hz, 2H), 4.63 (t, J = 5.4 Hz, 3H), 4.12 (dd, J = 12.3, 3.5 Hz, 1H), 3.83 (t, J = 12.3 Hz, 1H), 3.67 (dd, J = 12.3, 3.4 Hz, 1H), 2.64 - 2.52 (m, 1H), 2.30 (ddq, J = 10.5, 7.2, 3.6 Hz, 1H), 2.13 (td, J = 12.1, 4.4 Hz, 1H), 1.82 - 1.63 (m, 2H), 1.24 (d, J = 3.3 Hz, 1H), 1.04 (d, J = 6.9 Hz, 4H), 0.90 - 0.79 (m, 1H). **^{19}F-NMR** (376 MHz, Chloroform-d) δ -109.20 (ddd, J = 15.0, 8.8, 6.2 Hz), -112.03 (t, J = 7.0 Hz). **LCMS-ESI$^+$** (*m/z*): [M+H]$^+$ calculated for $C_{22}H_{20}F_3N_3O_4$: 447.14; found: 448.32.

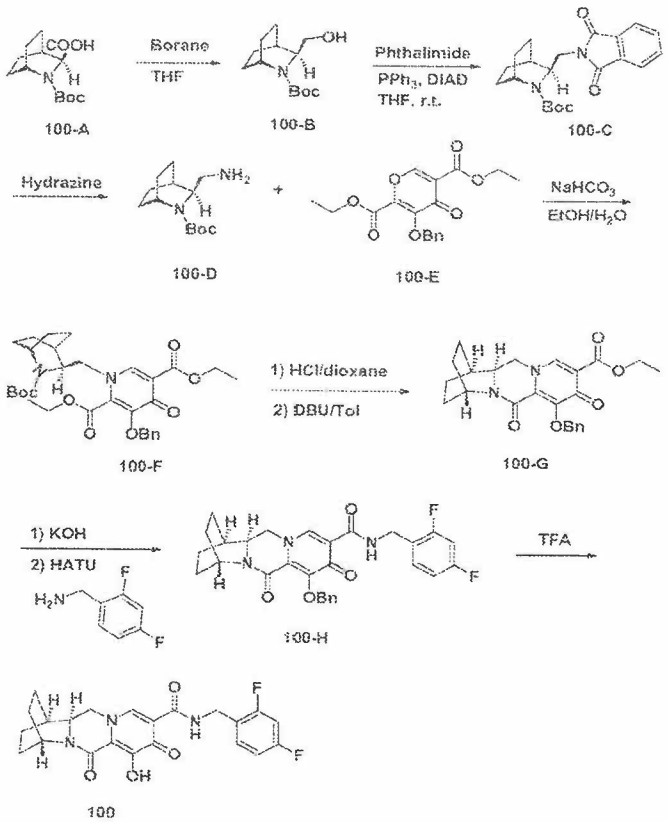
Example 100

Preparation of Compound **100**

(1R,4R,12aS)-N-(2,4-difluorobenzyl)-7-hydroxy-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydro-1,4-ethanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



100



Step 1

A 100-mL rbf was charged with **100-A** (2.0 g, 7.8 mmol) in THF (20 mL). The reaction mixture was cooled to 0 ^{0}C. Borane dimethyl sulfide (2 N in THF, 17.6 mL) was slowly added in. Then the reaction mixture was stirred at room temperature for overnight. The reaction mixture was cooled back to 0 ^{0}C. Methanol (8 mL) was added drop wise to quench the reaction. After concentration, the residue was purified by Combi Flash (40 g column, cartridge used) using hexanes - EA as eluents to afford **100-B**. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ found: 242.

Step 2

A 100-mL rbf was charged with **100-B** (1.8 g, 7.4 mmol),

triphenylphosphine (4.3 g, 16.2 mmol) and phthalimide (1.8 g, 12.2 mmol) in THF (30 mL). Then the reaction mixture was cooled to 0 ^{0}C with stirring. DIAD (3.2 mL, 16.2 mmol) was slowly added to the reaction mixture. The reaction mixture was stirred at room temperature for overnight. After concentration, the residue was purified by Combi Flash (80 g column, cartridge used) using hexanes - EA as eluents to afford **100-C**. **LCMS-ESI**$^{+}$ (*m/z*): $[M+H]^{+}$ found: 371.

Step 3

To a solution of **100-C** (2.5 g, 6.8 mmol) in EtOH (50 mL) was added hydrazine monohydrate (1.7 mL). The reaction mixture was heated to 70 ^{0}C with stirring for 3 hours. After filtration to remove the solid, the filtrate was concentrated to afford **100-D**. **LCMS-ESI**$^{+}$ (*m/z*): $[M+H]^{+}$ found: 241.

Step 4

A 100-mL rbf was charged with **100-D** (1.6 g, 6.7 mmol) and **100-E** (2.3 g, 6.7 mmol) in ethanol (30 mL). Sodium bicarbonate (1.2 g, 1.4 mmol) in water (30 mL) was added to the reaction mixture. Then the reaction mixture was stirred at room temperature for overnight. The mixture was diluted with EA (200 mL) and washed with water (2 x). The aqueous fractions were extracted with EA (1 x), and the organic fractions were combined, dried (Na_2SO_4), and concentrated. The crude **100-F** was used for next step without further purification. **LCMS-ESI**$^{+}$ (*m/z*): $[M+H]^{+}$ found: 569.

Step 5

A 100-mL rbf was charged with **100-F** (3.7 g, 6.5 mmol) in 4 N HCl /dioxane (38 mL). Then the reaction mixture was stirred at room temperature for 1 hour. After concentration, 3.2 g intermediate was obtained. The intermediate and DBU (5.1 g, 33.8 mmol) were dissolved in toluene (100 mL). The reaction mixture was heated to 110^{0}C with stirring for 1 hour. After concentration, the residue was purified by Combi Flash (80 g column, cartridge used) using hexanes - EA as eluents to afford **100-G**. **LCMS-ESI**$^{+}$ (*m/z*): $[M+H]^{+}$ found: 423.

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Step 6

A 100-mL rbf was charged with **100-G** (2.0 g, 4.7 mmol) in THF (20 mL) and MeOH (20 mL). 1 N KOH (18.9 mL) was added to the reaction mixture. Then the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was acidified by adding 1 N HCl (18.9 mL). After concentration, the residue was co-evaporated with toluene (3 x). The crude acid (0.28 g, 0.72 mmol), 2, 4-difluobenzylamine (0.2 g, 1.44 mmol), N,N-diisopropylethylamine (DIPEA) (0.47 g, 3.6 mmol) and HATU (0.55 g, 1.44 mmol) were dissolved in DCM (20 mL). The reaction mixture was stirred at room temperature for 2 hours. The mixture was diluted with EA (100 mL) and washed with saturated $NaHCO_3$ (2x), saturated NH_4Cl (2x) and dried over Na_2SO_4. After concentration, the crude was purified by column chromatography on silica gel with hexane-EtOAc to afford **100-H**. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ found: 520.

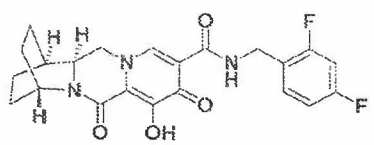
Step 7

A 50-mL rbf was charged with **100-H** (0.36 g, 0.69 mmol) in TFA (5 mL). The reaction mixture was stirred at room temperature for 30 minutes. After concentration, the crude was purified by column chromatography on silica gel with EtOAc-MeOH to afford compound **100**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 12.25 (m, 1H), 10.47 (t, J = 5.9 Hz, 1H), 8.30 (s, 1H), 7.58 - 7.29 (m, 1H), 6.98 - 6.50 (m, 2H), 4.62 (dd, J = 14.8, 4.9 Hz, 3H), 4.22 (t, J = 12.2 Hz, 1H), 4.14 - 4.07 (m, 1H), 3.96 (dd, J = 12.2, 3.1 Hz, 1H), 2.26 - 1.44 (m, 9H). **^{19}F-NMR** (376 MHz, Chloroform-d) δ -112.38 (t, J = 7.7 Hz), -114.78 (q, J = 8.5 Hz). **LCMS-ESI$^+$** (*m/z*): found: 430.

Example 101

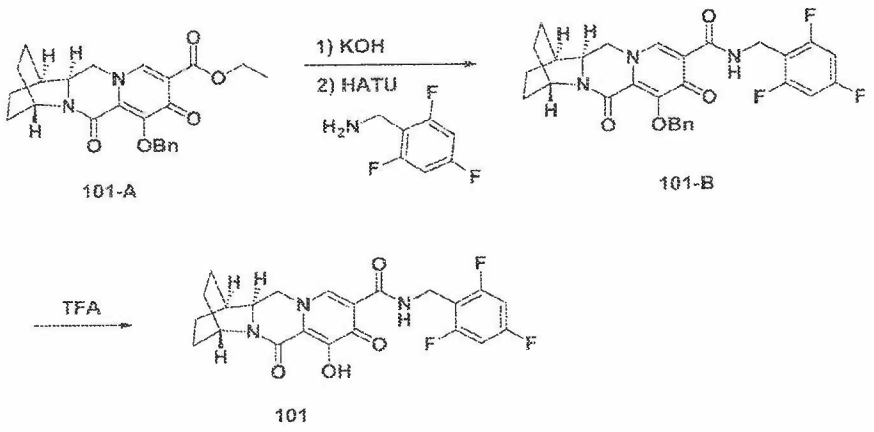
Preparation of Compound **101**

(1R,4R,12aS)-7-hydroxy-6,8-dioxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4,6,8,12,12a-octahydro-1,4-ethanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



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101



Step 1

A 100-mL rbf was charged with **101-A** (0.3 g, 0.72 mmol) in THF (2 mL) and MeOH (2 mL). 1 N KOH (2.1 mL) was added to the reaction mixture. Then the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was acidified by adding 1 N HCl (2.1 mL). After concentration, the residue was co-evaporated with toluene (3 x). The crude acid (0.72 mmol), 2, 4, 6-trifluobenzylamine (0.23 g, 1.44 mmol), N,N-diisopropylethylamine (DIPEA) (0.47 g, 3.6 mmol) and HATU (0.55 g, 1.44 mmol) were dissolved in DCM (20 mL). The reaction mixture was stirred at room temperature for 2 hours. The mixture was diluted with EA (100 mL) and washed with saturated $NaHCO_3$ (2x), saturated NH_4Cl (2x) and dried over Na_2SO_4. After concentration, the crude was purified by column chromatography on silica gel with hexane-EtOAc to afford **101-B**. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ found: 538.

Step 2

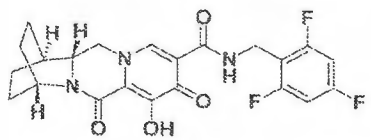
A 50-mL rbf was charged with **101-B** (0.36 g, 0.67 mmol) in TFA (5 mL). The reaction mixture was stirred at room temperature for 30 minutes. After concentration, the crude was purified by column chromatography on silica gel with EtOAc-MeOH to afford compound **101**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 12.11 (s, 1H), 10.40 (t, J = 5.8 Hz, 1H), 8.28 (s, 1H), 6.91 - 6.39 (m, 2H), 4.62 (ddd, J = 25.0,

6.5, 2.8 Hz, 3H), 4.21 (t, J = 12.2 Hz, 1H), 4.09 (dd, J = 12.5, 3.0 Hz, 1H), 3.93 (dd, J = 12.2, 3.1 Hz, 1H), 2.35 - 1.39 (m, 9H). **^{19}F NMR** (376 MHz, Chloroform-d) δ -112.38 (t, J = 7.7 Hz), -114.78 (q, J = 8.5 Hz). **LCMS-ESI$^+$** (*m/z*): found: 448.

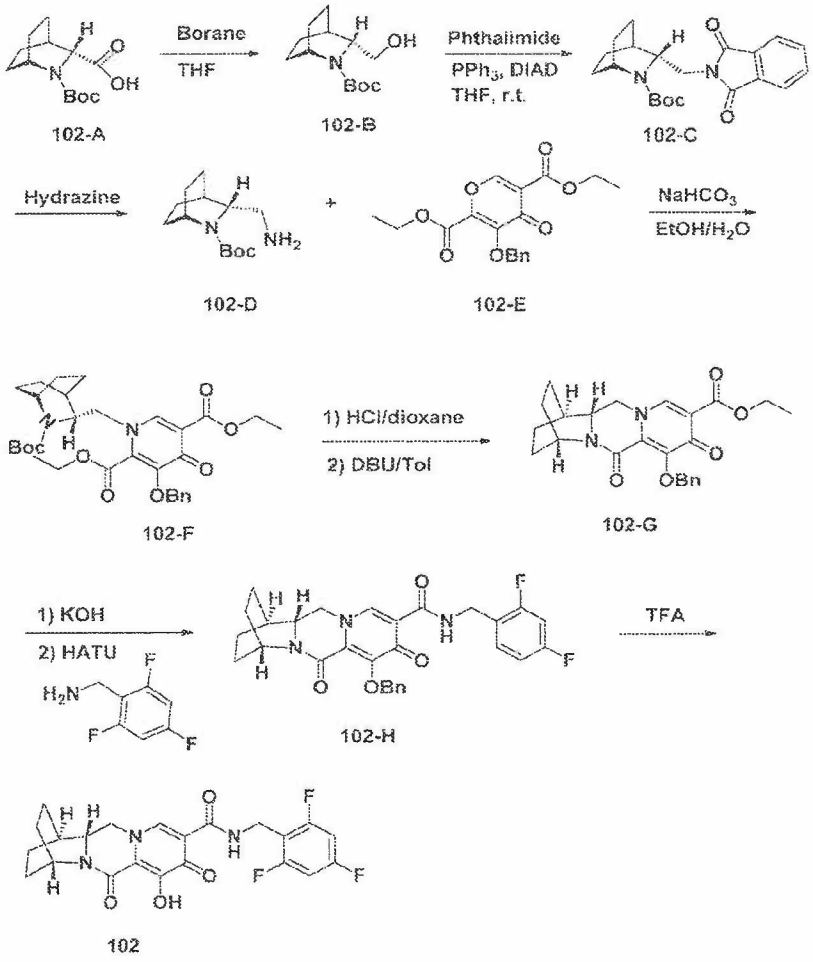
Example 102

Preparation of Compound **102**

(1S,4S,12aR)-7-hydroxy-6,8-dioxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4,6,8,12,12a-octahydro-1,4-ethanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



102



Step 1

A 100-mL rbf was charged with **102-A** (2.0 g, 7.8 mmol) in THF (20 mL). The reaction mixture was cooled to 0 °C. Borane dimethyl sulfide (2 N in THF, 17.6 mL) was slowly added in. Then the reaction mixture was stirred at room temperature for overnight. The reaction mixture was cooled back to 0 °C. Methanol (8 mL) was added drop wise to quench the reaction. After concentration, the residue was purified by Combi Flash (40 g column, cartridge used) using hexanes - EA as eluents to afford **102-B**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 242.

Step 2

A 100-mL rbf was charged with **102-B** (1.8 g, 7.4 mmol), triphenylphosphine (4.3 g, 16.2 mmol) and phthalimide (1.8 g, 12.2 mmol) in THF (30 mL). Then the reaction mixture was cooled to 0 ^{0}C with stirring. DIAD (3.2 mL, 16.2 mmol) was slowly added to the reaction mixture. The reaction mixture was stirred at room temperature for overnight. After concentration, the residue was purified by Combi Flash (80 g column, cartridge used) using hexanes - EA as eluents to afford **102-C**. **LCMS-ESI**$^{+}$ (*m/z*): [M+H] found: 371.

Step 3

To a solution of **102-C** (2.5 g, 6.8 mmol) in EtOH (50 mL) was added hydrazine monohydrate (1.7 mL). The reaction mixture was heated to 70 ^{0}C with stirring for 3 hours. After filtration to remove the solid, the filtrate was concentrated to afford **102-D**. **LCMS-ESI**$^{+}$ (*m/z*): $[M+H]^{+}$ found: 241.

Step 4

A 100-mL rbf was charged with **102-D** (1.6 g, 6.7 mmol) and **102-E** (2.3 g, 6.7 mmol) in ethanol (30 mL). Sodium bicarbonate (1.2 g, 1.4 mmol) in water (30 mL) was added to the reaction mixture. Then the reaction mixture was stirred at room temperature for overnight. The mixture was diluted with EA (200 mL) and washed with water (2 x). The aqueous fractions were extracted with EA (1 x), and the organic fractions were combined, dried (Na_2SO_4), and concentrated. The crude **102-F** was used for next step without further purification. **LCMS-ESI**$^{+}$ (*m/z*): $[M+H]^{+}$ found: 569.

Step 5

A 100-mL rbf was charged with **102-F** (3.7 g, 6.5 mmol) in 4 N HCl /dioxane (38 mL). Then the reaction mixture was stirred at room temperature for 1 hour. After concentration, 3.2 g intermediate was obtained. The intermediate and DBU (5.1 g, 33.8 mmol) were dissolved in toluene (100 mL). The reaction mixture was heated to 110^{0}C with stirring for 1 hour. After concentration, the residue was purified by Combi Flash (80 g column, cartridge used) using hexanes - EA as eluents to afford **102-G**.

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LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ found: 423.

Step 6

A 100-mL rbf was charged with **102-G** (0.3 g, 0.72 mmol) in THF (2 mL) and MeOH (2 mL). 1 N KOH (2.1 mL) was added to the reaction mixture. Then the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was acidified by adding 1 N HCl (2.1 mL). After concentration, the residue was co-evaporated with toluene (3x). The crude acid (0.72 mmol), 2, 4, 6-trifluobenzylamine (0.23 g, 1.44 mmol), N,N-diisopropylethylamine (DIPEA) (0.47 g, 3.6 mmol) and HATU (0.55 g, 1.44 mmol) were dissolved in DCM (20 mL). The reaction mixture was stirred at room temperature for 2 hours. The mixture was diluted with EA (100 mL) and washed with saturated $NaHCO_3$ (2x), saturated NH_4Cl (2x) and dried over Na_2SO_4. After concentration, the crude was purified by column chromatography on silica gel with hexane-EtOAc to afford **102-H**. **LCMS-ESI**$^+$ (*m/z*): $[M+H]^+$ found: 538.

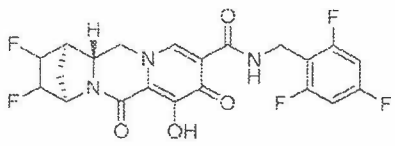
Step 7

A 50-mL rbf was charged with **102-H** (0.36 g, 0.67 mmol) in TFA (5 mL). The reaction mixture was stirred at room temperature for 30 minutes. After concentration, the crude was purified by column chromatography on silica gel with EtOAc-MeOH to afford compound **102**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 12.13 (s, 1H), 10.40 (t, J = 5.8 Hz, 1H), 8.28 (s, 1H), 6.64 (t, J = 8.1 Hz, 2H), 4.89 - 4.41 (m, 3H), 4.22 (t, J = 12.2 Hz, 1H), 4.09 (dd, J = 12.3, 3.1 Hz, 1H), 3.95 (dd, J = 12.1, 4.1 Hz, 1H), 2.45 - 1.60 (m, 9H). **^{19}F-NMR** (376 MHz, Chloroform-d) δ - 109.26 (ddd, J = 15.1, 8.8, 6.3 Hz), -111.99 (t, J = 6.9 Hz). **LCMS-ESI**$^+$ (*m/z*): found: 448.

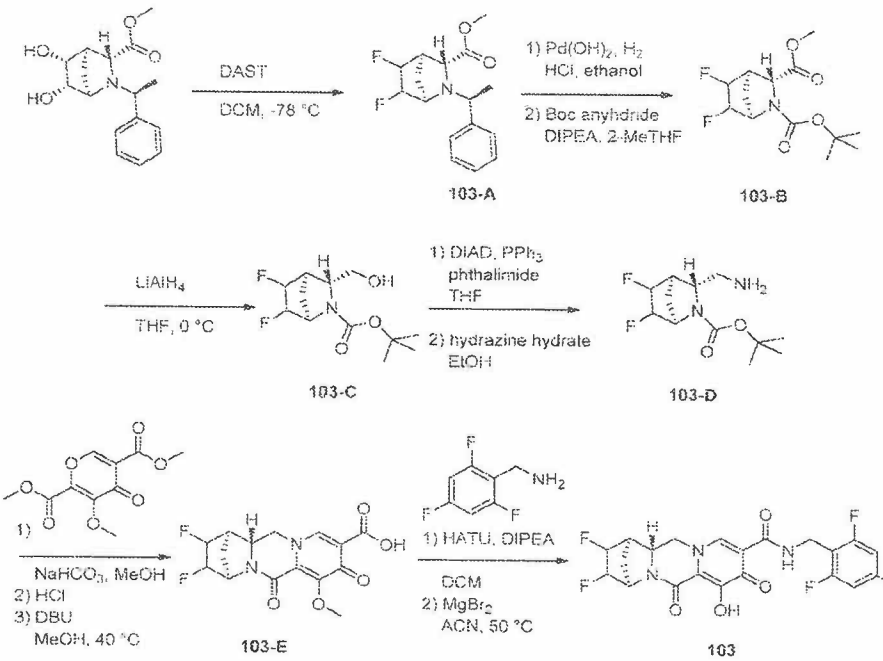
Example 103

Preparation of Compound **103**

(1R,4R,12aR)-2,3-difluoro-7-hydroxy-6,8-dioxo-N-(2,4,6-trifluorobenzyl)-1,2,3,4,6,8,12,12a-octahydro-1,4-methanodipyrido[1,2-a:1',2'-d]pyrazine-9-carboxamide



103



103-A 103-B 103-C 103-D 103-E 103

Step 1

A solution of (1R,3R,4R,5R,6S)-methyl 5,6-dihydroxy-2-((S)-1-phenylethyl)-2-azabicyclo[2.2.1]heptane-3-carboxylate (2.0g, 6.9mmol) in DCM (27mL) was cooled to -78 °C in a dry ice/acetone bath. To this solution was added DAST (2.18 ml, 16.48 mmol) via plastic tipped pipette. The solution was stirred at -78 °C for 30 minutes after which time it was removed from the bath, let warm slowly to room temperature, and stirred at room temperature for one hour. The reaction was quenched by slow addition of the reaction mixture to a stirring solution of saturated sodium bicarbonate (150mL) via plastic tipped pipette. The layers were separated and

the aqueous layer was back-extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The crude product was purified by silica gel chromatography (7-28% ethyl acetate/hexane) to provide **103-A**. **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 7.43 – 7.16 (m, 5H), 5.01 – 4.60 (m, 2H), 3.85 (q, *J* = 7.1, 6.6 Hz, 1H), 3.55 (s, 2H), 3.53 – 3.42 (m, 2H), 2.76 (dq, *J* = 5.1, 2.0 Hz, 1H), 2.19 – 2.07 (m, 1H), 2.03 – 1.88 (m, 1H), 1.39 (d, *J* = 6.7 Hz, 3H).

Steps 2 and 3

To a solution of **103-A** (0.96 g, 3.24 mmol) in Ethanol (36.01 ml) and 1.25M HCl-ethanol (4.09 ml) was added 20% PdOH/C (1.14 g, 1.62 mmol) the suspension was stirred under an atmosphere of hydrogen for 22 hours. After filtering through Celite, the cake was washed with EtOH, the filtrate was concentrated under vacuum to dryness to afford the crude deprotected product which was assumed to be 3.24mmol for next step. **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_8H_{12}F_2NO_2$: 192.08; found: 192.110.

To the crude residue (0.62 g, 3.24 mmol) and Di-tert-butyl dicarbonate (1.06 g, 4.86 mmol) in 2-Methyltetrahydrofuran (32.43 ml) was added N,N-diisopropylethylamine (0.56 ml, 0 mol). Upon completion, the reaction mixture was diluted with water, extracted into EtOAC (2x) and the organic fractions were washed with water, combined, dried (Na_2SO_4), and concentrated. The residue was purified by silica column chromatography (0-55% EtOAc/Hexanes) to afford **103-B**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 5.12 - 5.01 (m, 1H), 4.92 (s, 1H), 4.49 (s, 1H), 4.14 (d, J = 14.7 Hz, 1H), 3.75 (s, 3H), 2.91 (s, 1H), 2.24 - 1.98 (m, 2H), 1.47 (s, 5H), 1.38 (s, 5H). LCMS-ESI$^+$ (*m/z*): $[M+H]^+$ calculated for $C_{13}H_{20}F_2NO_4$: 292.13; found: 291.75.

Step 4

A solution of **103-B** (0.68 g, 2.33 mmol) in THF (15 ml) was stirred in an ice bath as 1.0 M $LiBH_4$ in THF (4.65 ml) was added and the resulting mixture was stirred at 0 °C for 30 minutes at which time it was shown to be complete by TLC. The reaction mixture was carefully treated with water (0.3 mL), then with NaOH (~15%, 3.5M, 0.3 mL), then finally with additional water (0.9 mL). The mixture was stirred at

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room temperature for 15 minutes, and the ppt that formed was filtered, washed with diethyl ether and the supernate was concentrated to afford **103-C**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 4.83 (s, 1H), 4.56 (d, J = 10.5 Hz, 1H), 4.37 (s, 1H), 3.78 - 3.47 (m, 3H), 2.76 (s, 1H), 2.36 - 2.18 (m, 1H), 2.17 - 1.98 (m, 1H), 1.55 (s, 1H), 1.48 (s, 9H).

Steps 5 and 6

A mixture of **103-C** (0.59 g, 2.25 mmol), phthalimide (0.53 g, 3.6 mmol) and triphenylphosphine (1.3 g, 4.95 mmol) in THF (11 ml) was cooled in an ice bath. Diisopropyl Azodicarboxylate (0.97 ml, 4.95 mmol) was added. The mixture was then warmed up to room temperature and stirred for 14h and then concentrated in vacuo. The residue was dissolved in ether, stirred for 1 h, then the solids were filtered off and the filtrate was concentrated. The residue was purified by silica column chromatography (10-31-91% EtOAc/hexanes) to afford the protected amino compound (assumed 2.25mmol of product). **LCMS-ESI$^+$** (*m/z*): [M+H]$^+$ calculated for $C_{20}H_{23}F_2N_2O_4$: 393.15; found: 392.77.

A solution of the protected amino compound (0.88 g, 2.25 mmol) and hydrazine hydrate (0.46 ml, 9.52 mmol) in ethanol (22 ml) was stirred at 60 °C for 2 h. The reaction mixture was cooled in an ice bath, ether (10 ml) was added and the mixture was stirred for 30 min. The solid formed was filtered off and the filtrate was concentrated under vacuum to dryness to give **103-D**. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 5.17 - 4.61 (m, 2H), 4.37 (s, 1H), 3.80 (s, 1H), 3.11 - 2.77 (m, 1H), 2.01 (s, 2H), 1.87 (s, 1H), 1.83 (d, J = 7.4 Hz, 1H), 1.46 (s, 9H), 1.30 (d, J = 6.4 Hz, 1H), 1.27 (d, J = 6.3 Hz, 3H). **LCMS-ESI$^+$** (*m/z*): [M+H]$^+$ calculated for $C_{12}H_{20}F_2N_2O_2$: 263.15; found: 262.86.

Steps 7, 8 and 9

Compound **103** was prepared in a similar manner to compound **60** using **103-D** in place of **41-E** and using (2,4,6-trifluorophenyl)methanamine in place of (2,3-dichlorophenyl)methanamine. A single diastereomer resulted. The stereochemistry of the fluorines is unknown. **^{1}H-NMR** (400 MHz, Chloroform-d) δ 8.08 (s, 1H), 6.46 - 6.27 (m, 2H), 4.95 (d, J = 53.5 Hz, 1H), 4.65 (d, J = 54.9 Hz, 1H), 4.45 (s, 1H), 4.33 (d,

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J = 5.6 Hz, 2H), 3.84 (t, J = 3.6 Hz, 2H), 2.75 (s, 1H), 2.28 (p, J = 1.9 Hz, 2H), 2.20 (s, 1H), 1.91 (dd, J = 33.3, 15.2 Hz, 1H), 0.95 (s, 1H). **LCMS-ESI$^+$** (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{17}F_5N_3O_4$: 470.11; found: .470.13.

ANTIVIRAL ASSAY

Example 104

Antiviral Assays in MT4 Cells

For the antiviral assay utilizing MT4 cells, 0.4 µL of 189X test concentration of 3-fold serially diluted compound in DMSO was added to 40 µL of cell growth medium (RPMI 1640, 10% FBS, 1% penicilline/Streptomycine, 1% L-Glutamine, 1% HEPES) in each well of 384-well assay plates (10 concentrations) in quidruplicate.

1 mL aliquots of 2×10^6 MT4 cells are pre-infected for 1 and 3 hours respectively at 37 °C with 25 µL (MT4) or of either cell growth medium (mock-infected) or a fresh 1:250 dilution of an HIV-IIIb concentrated ABI stock (0.004 m.o.i. for MT4 cells). Infected and uninfected cells are diluted in cell growth medium and 35 µL of 2000 (for MT4) cells is added to each well of the assay plates.

Assay plates were then incubated in a 37 °C incubator. After 5 days of incubation, 25 µL of 2X concentrated CellTiter-Glo™ Reagent (catalog # G7573, Promega Biosciences, Inc., Madison, WI) was added to each well of the assay plate. Cell lysis was carried out by incubating at room temperature for 2–3 minutes, and then chemiluminescence was read using the Envision reader (PerkinElmer).

Compounds of the present invention demonstrate antiviral activity in this assay as depicted in Table 1 below. Accordingly, the compounds of the invention may be useful for treating the proliferation of the HIV virus, treating AIDS, or delaying the onset of AIDS or ARC symptoms.

Table 1

Compound Number	nM in MT-4	
	EC_{50}	CC_{50}

Compound Number	nM in MT-4	
	EC_{50}	CC_{50}
1	2.6	5819
2	2.2	3111
3	2.0	38446
4	14.8	45769
5	8.1	10452
6	5.3	53192
7	3.5	15610
8	2.5	13948
9	5.1	13451
10	6.1	3670
11	4.9	10274
12	5.9	3337
13	46.0	12666
14	65.5	4939
15	2.2	16268
16	1.5	13633
17	5.9	6613
18	4.1	10263
19	2.8	38690
20	3.3	27990
21	38.3	13010
22	64.3	4433
23	2.3	13444
24	6.1	12074
25	26.2	5233
26	10.3	8836
27	4.4	8751
28	15.6	18687

Compound Number	nM in MT-4	
	EC_{50}	CC_{50}
29	13.9	9446
30	4.0	6828
31	9.0	4525
32	14.0	4684
33	43.5	3971
34	422.1	3585
35	157.0	15546
36	7.6	11424
37	10.2	19486
38	1.7	10223
39	3.6	12174
40	2.4	9560
41	2.1	15675
42	2.5	3544
43	6.9	10321
44	2.3	9869
45	2.4	15765
46	2.6	19295
47	1.9	11301
48	2.7	13967
49	33.3	52219
50/51 (racemic mixture)	1.9	37173
52	15.0	12943
53	14.3	3347
54	15.6	3236
55	1.5	11100
56	3.1	17238

Compound Number	nM in MT-4	
	EC_{50}	CC_{50}
57	2.3	11751
58	1.5	7694
59	3.1	22200
60	2.1	3308
61	1.8	25881
62	9.2	3492
63	2.5	3164
64	3.5	3332
65	2.4	2508
66	9.4	11848
67	10.7	2981
68	2.7	4175
69	1.9	4767
70	5.1	8413
71	2.6	4660
72	4.3	6255
73	1.8	9194
74	29.3	4340
75	2.8	5292
76	17.8	34581
77	5.6	10145
78	5.6	3198
79	3.4	12092
80	4.6	5045
81	1.9	12298
82	2.9	30434
83	1.9	27501
84	2.9	9727

Compound Number	nM in MT-4	
	EC_{50}	CC_{50}
85	2.0	10378
86	2.3	22405
88	2.9	3230
89	8.4	4629
90	5.7	8086
91	5.0	7183
92	18.6	4553
93	2.2	6158
94	11.5	51173
96	2.6	26586
97	2.1	17341
98	2.4	17947
99	2.0	8475
100	2.2	11580
101	2.1	11585
102	2.3	12042
103	10.3	35127

Example 105

Human PXR Activation Assay

Luciferase Reporter Gene Assay. A stably transformed tumor cell line (DPX2) was plated on 96-well microtiter plates. DPX2 cells harbor the human PXR gene (NR1I2) and a luciferase reporter gene linked to two promoters identified in the human CYP3A4 gene, namely XREM and PXRE. The cells were treated with six concentrations of each compound (0.15 ~ 50 μM) and incubated for 24 hours. The number of viable cells was determined and the reporter gene activity was assessed. Positive control: Rifampicin at 6 concentrations (0.1 ~ 20 μM). $\%E_{max}$ relative to the maximum fold induction by 10 or 20 μM RIF was calculated for test compounds

according to the following equation which adjusts for the DMSO background: $\%E_{max}$ = (Fold induction – 1)/(Maximum fold induction by RIF – 1) x 100%.

Table 2

Compound Number	$\%E_{max}$ at 15 μM
2	4.5
3	7.5
4	3
5	32
6	0
7	6
8	7
9	7
10	19
15	20
16	17
17	7
18	4
19	2
20	2
23	45
28	6
29	3
32	14
33	17
36	3
37	2
38	7
39	6

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Compound Number	$\%E_{max}$ at 15 μM
40	0
41	11.5
42	21
43	18
44	4
45	19
46	34
47	11
48	5
54	2
55	24
56	3
57	3
58	1
59	4
60	3
61	1
63	13
64	8
66	0
67	0
68	6
69	5
70	10
71	3
72	4
73	7
75	0

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Compound Number	$\%E_{max}$ at 15 μM
77	11
79	0
80	2
81	1
82	1
83	1
84	21
85	77
86	30
88	27
89	5
90	11
91	3
92	3
93	9
96	11
97	9
98	0
99	17
100	45
102	123
103	0

Example 106

OCT2 Inhibition Assay

The dose dependent inhibition of OCT2 mediated uptake of a model substrate ^{14}C-Tetraethylammonium (TEA) by test compounds was studied in wild-type and OCT2-transfected MDCKII cells at 7 concentrations from 0.014 μM to 10 μM.

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MDCKII cells were maintained in minimal essential medium (MEM) with 1% Pen/Strep, 10% fetal bovine serum, and 0.25 mg/mL hygromycin B in an incubator set at 37 °C, 90% humidity and 5% CO_2. 24 hours prior to assay, media containing 5 mM sodium butyrate were added to MDCKII cells in flasks, and cells were grown to 80-90% confluence. On assay day, cells were trypsinized and resuspended in Krebs-Henseleit Buffer (KHB), pH 7.4 at 5 x 10^6 million cells/mL. Cells were preincubated for 15 min in assay plate before addition of test compound or substrate.

Test compounds were serially diluted in DMSO and then spiked (2 µL) into in 0.4 mL KHB buffer containing wild-type or OCT2-transfected cells and incubated for 10 minutes. Assay was initiated with the addition of 0.1 mL of 100 µM ^{14}C-TEA in KHB buffer (20 µM final concentration after mixing). The concentration of TEA is based on the K_m. After 10 minutes of incubation, the assay mixture was quenched with addition of 0.5 mL of ice-cold 1X PBS buffer. Samples were then centrifuged at 1000 rpm for 5 min and supernatants were removed. Wash steps were repeated four times with ice-cold PBS. Finally, the cell pellets were lysed with 0.2N NaOH and let sit at room temperature for at least 30 min to ensure complete lysis. Samples were then counted on liquid scintillation counter and dpm counts were used to perform the following calculations. The % inhibition was calculated as follows: % inhibition = [1- { $[OCT2]_i$ - $[WT]_{ni}$ } / {$[OCT2]_{ni}$-$[WT]_{ni}$}]*100 where, $[OCT2]_i$ represents the dpm count in the presence of test compound for either OCT2 cells, $[OCT2]_{ni}$ represents the dpm count in the absence of test compound for OCT2 cells and $[WT]_{ni}$ represents the dpm count in the absence of test compound for wild type cells, respectively.

Table 3

Compound Number	IC_{50} (nM)
2	240
3	250
5	2230
11	10000

Compound Number	IC_{50} (nM)
13	610
36	10000
39	358
40	204
41	2823
42	487
45	137
47	6200
48	4909
55	476
63	42
64	94
77	3830
82	10000
83	10000
96	1357
98	3726
99	1506
100	450

The data in Tables 1, 2 and 3 represent an average over time of each assays for each compound. For certain compounds, multiple assays have been conducted over the life of the project. Thus, the data reported in Tables 1, 2 and 3 include the data reported in the priority documents, as well as data from assays run in the intervening period.

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Example 107

Pharmacokinetic Analysis Following Oral or Intravenous Administration to Beagle Dogs

Pharmacokinetic analysis was performed on various test compounds following intravenous or oral administration to beagle dogs.

For pharmacokinetic analysis of intravenously administered compounds, the test compounds were formulated in 5% Ethanol, 55% PEG 300, and 40% water at 0.1 mg/mL for IV infusion. For pharmacokinetic analysis of orally administered compounds, the test compounds were formulated as an aqueous suspension in 0.1% Tween 20, 0.5% HPMC LV100 in Di Water at 1 mg/kg.

Each dosing group consisted of 3 male, non-naïve purebred beagle dogs. At dosing, the animals weighed between 10 to 13 kg. The animals were fasted overnight prior to dose administration and up to 4 hr after dosing. For studies of intravenous administration, the test article was administered to the animals by intravenous infusion over 30 min. The rate of infusion was adjusted according to the body weight of each animal to deliver a dose of 0.5 mg/kg. For studies of oral administration, the test article was administered according to the body weight of each animal to deliver a dose of 1 mg/kg.

For pharmacokinetic analysis of intravenously administered compounds, serial venous blood samples (approximately 1 mL each) were taken from each animal at 0, 0.250, 0.483, 0.583, 0.750, 1.00, 1.50, 2.00, 4.00, 8.00, 12.0, and 24.0 hours after dosing. The blood samples were collected into Vacutainer™ tubes containing EDTA-K2 as the anti-coagulant and were immediately placed on wet ice pending centrifugation for plasma. An LC/MS/MS method was used to measure the concentration of the test compound in plasma. An aliquot of 100 µL of each plasma sample was added to a clean 96 well plate, and 400 µL of cold acetonitrile/internal standard solution (ACN)/(ISTD) was added. After protein precipitation, an aliquot of 110 µL of the supernatant was transferred to a clean 96-well plate and diluted with 300 µL of water. An aliquot of 25 µL of the above solution was injected into a TSQ Quantum Ultra LC/MS/MS system utilizing a Hypersil Gold C_{18} HPLC column (50 X 3.0 mm, 5 µm; Thermo-Hypersil Part # 25105-053030). An Agilent 1200 series binary

pump (P/N G1312A Bin Pump) was used for elution and separation, and an HTS Pal autosampler (LEAP Technologies, Carrboro, NC) was used for sample injection. A TSQ Quantum Ultra triple quadrupole mass spectrometer was utilized in selective reaction monitoring mode (Thermo Finnigan, San Jose, CA). Liquid chromatography was performed using two mobile phases: mobile phase A contained 1% acetonitrile in 2.5 mM ammonium formate aqueous solution with pH of 3.0, and mobile phase B contained 90% acetonitrile in 10 mM ammonium formate with pH of 4.6. Non-compartmental pharmacokinetic analysis was performed on the plasma concentration-time data. The resulting data are shown in the first three columns of Table 4. In Table 4, **CL** refers to clearance, which characterizes the rate at which drug is removed from plasma. The lower the clearance of a drug is, the longer the elimination half-life is in the body. V_{ss} refers to the steady state volume of distribution and indicates how well a drug is distributed into the tissues. The larger the V_{ss} is, the longer the elimination half-life is in the body. **MRT** refers to mean residence time, which is a measure of the average time molecules exist in the body.

For pharmacokinetic analysis of orally administered compounds, serial venous blood samples (approximately 0.3 mL each) were taken from each animal at time points of 0, 0.25, 0.50, 1.0, 2.0, 4.0, 6.0, 8.0, 12.0 and 24.0 hours after dosing. Blood samples were collected, prepared and analyzed in a similar way to the intravenous studies described above. Non-compartmental pharmacokinetic analysis was performed on the plasma concentration-time data. The resulting data are shown in the last three columns of Table 4. In Table 4, F (%) refers to oral bioavailability. C_{max} refers to the peak plasma concentration of the compound after administration. AUC refers to area under the curve and is a measure of total plasma exposure of the indicated compound.

Table 4

Compound #	CL (L/h/kg)	V_{ss} (L/kg)	MRT (h)	F (%) aqueous suspension	C_{max} (μM) aqueous suspension	AUC (μM*h) aqueous suspension

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98	0.047	0.16	3.3	n/a	n/a	n/a
83	0.161	0.38	2.4	n/a	n/a	n/a
55	0.058	0.24	4.2	n/a	n/a	n/a
77	0.300	0.64	2.2	n/a	n/a	n/a
41	0.015	0.11	7.5	10.7	2.4	16.3
42	0.020	0.15	7.1	28.0	4.5	28.6
47	0.014	0.10	7.4	12.6	2.8	20.4
8	0.498	0.87	1.8	n/a	n/a	n/a
7	0.510	1.20	2.3	n/a	n/a	n/a
3	0.047	0.23	4.9	18.7	1.2	9.2
2	0.030	0.20	6.5	40.7	7.8	66.1

All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification are incorporated herein by reference, in their entirety to the extent not inconsistent with the present description.

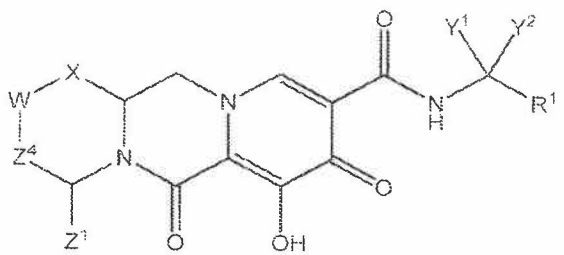
From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

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CLAIMS

What is claimed is:

1. A compound having the following Formula (I):



(I)

or a stereoisomer or pharmaceutically acceptable salt thereof,

wherein:

X is -O- or -NZ^3- or -CHZ^3-;

W is -CHZ^2-;

Z^1, Z^2 and Z^3 are each, independently, hydrogen or C_{1-3}alkyl, or wherein Z^1 and Z^2 or Z^1 and Z^3, taken together, form -L- wherein L is -$C(R^a)_2$-, -$C(R^a)_2C(R^a)_2$-, -$C(R^a)_2C(R^a)_2C(R^a)_2$-, or -$C(R^a)_2C(R^a)_2C(R^a)_2C(R^a)_2$-, wherein at least one of Z^1 and Z^2 or Z^1 and Z^3, taken together, form -L-;

Z^4 is a bond, -CH_2-, or -CH_2CH_2-;

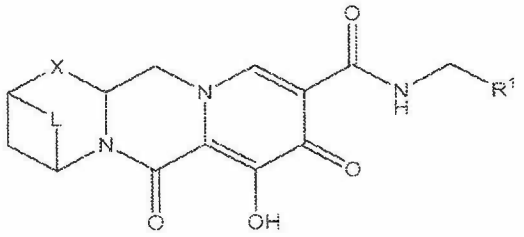
Y^1 and Y^2 are each, independently, hydrogen, C_{1-3}alkyl or C_{1-3}haloalkyl;

R^1 is phenyl substituted with one to three halogens; and

each R^a is, independently, hydrogen, halo, hydroxyl or C_{1-4}alkyl.

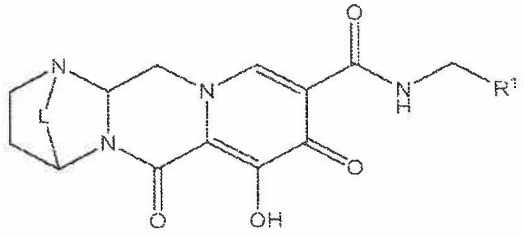
2. A compound of claim 1 having the following Formula (II-A):

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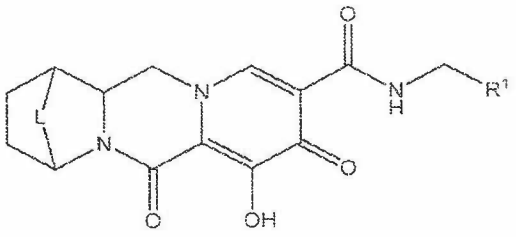
(II-A)

3. A compound of claim 1 having the following Formula (II-B):



(II-B)

4. A compound of claim 1 having the following Formula (II-C):



(II-C)

5. A compound of any one of claims 1–4 wherein L is $-C(R^a)_2-$.

6. A compound of any one of claims 1–4 wherein L is $-C(R^a)_2C(R^a)_2-$.

7. A compound of any one of claims 1–4 wherein L is $-C(R^a)_2C(R^a)_2C(R^a)_2-$.

8. A compound of any one of claims 1–7 wherein each R^a is hydrogen.

9. A compound of any one of claims 1–7 wherein one R^a is methyl and each remaining R^a is hydrogen.

10. A compound of any one of claims 1-7 wherein at least one R^a is halogen and each remaining R^a is hydrogen.

11. A compound of any one of claims 1-7 wherein two R^a are halogen and each remaining R^a is hydrogen.

12. A compound of any one of claims 1-7 wherein one R^a is halogen and each remaining R^a is hydrogen.

13. A compound of any one of claims 1–2 or 5–12 wherein X is -O-.

14. A compound of any one of claims 1–2 or 5–12 wherein X is $-NZ^3-$.

15. A compound of any one of claims 1–2 or 5–12 wherein X is -NH-.

16. A compound of any one of claims 1–2 or 5–12 wherein X is $-CHZ^3-$ and Z^1 and Z^3, taken together, form -L-.

17. A compound of claim 16 wherein Z^2 is hydrogen.

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18. A compound of any one of claims 1–2 or 5–12 wherein X is $-CH_2-$.

19. A compound of any one of claims 1 or 5-18 wherein Z^4 is a bond or $-CH_2-$.

20. A compound of any one of claims 1 or 5-18 wherein Z^4 is $-CH_2-$.

21. A compound of any one of claims 1 or 5-18 wherein Z^4 is a bond.

22. A compound of any one of claims 1 or 5-21 wherein Y^1 and Y^2 are each independently hydrogen, methyl or trifluoromethyl.

23. A compound of any one of claims 1–22 wherein R^1 is substituted with one halogen.

24. A compound of claim 23 wherein R^1 is 4-fluorophenyl or 2-fluorophenyl.

25. A compound of any one of claims 1–22 wherein R^1 is substituted with two halogens.

26. A compound of claim 25 wherein R^1 is 2,4-difluorophenyl, 2,3-difluorophenyl, 2,6-difluorophenyl, 3-fluoro-4-chlorophenyl, 3,4-difluorophenyl, 2-fluoro-4-chlorophenyl, or 3,5-difluorophenyl.

27. A compound of claim 26 wherein R^1 is 2,4-difluorophenyl.

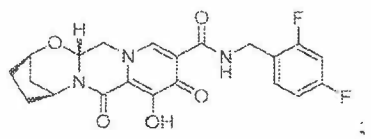
28. A compound of any one of claims 1–22 wherein R^1 is substituted with three halogens.

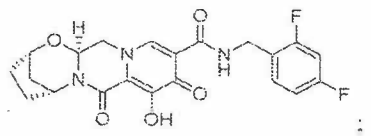
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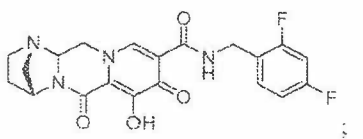
29. A compound of claim 28 wherein R^1 is 2,4,6-trifluorophenyl or 2,3,4-trifluorophenyl.

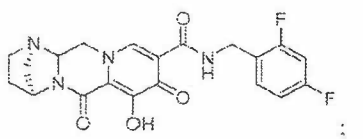
30. A compound of claim 29 wherein R^1 is 2,4,6-trifluorophenyl.

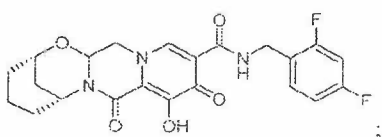
31. A compound of claim 1 selected from:

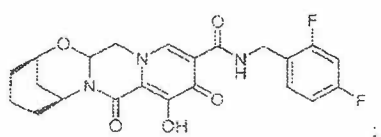

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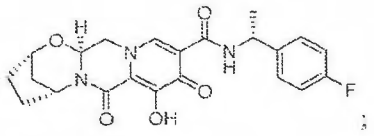

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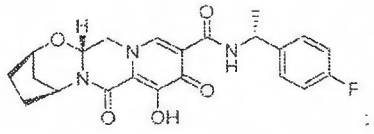

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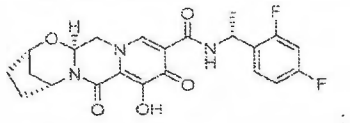

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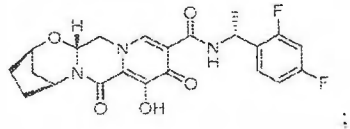

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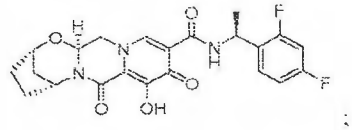
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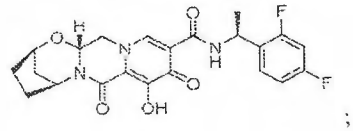

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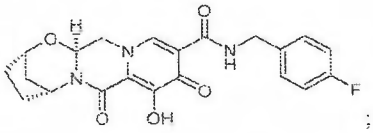

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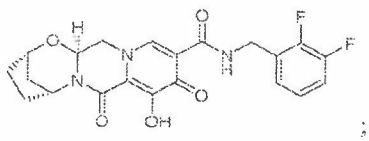

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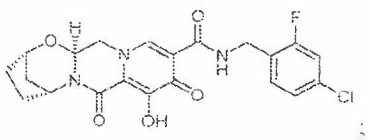

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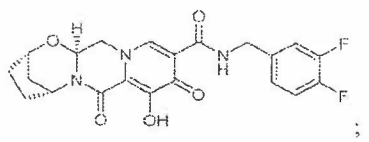

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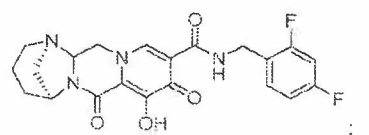

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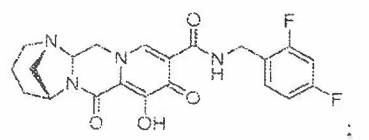

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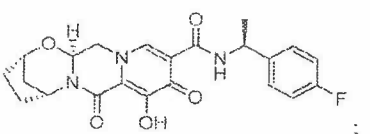

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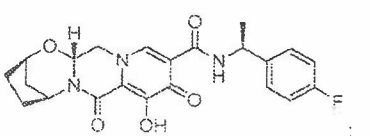

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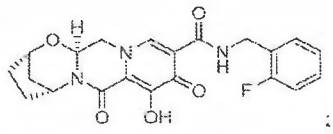

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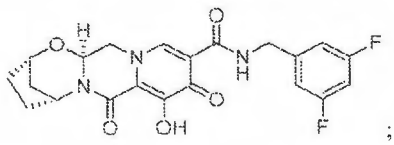

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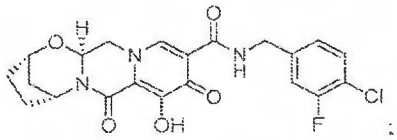

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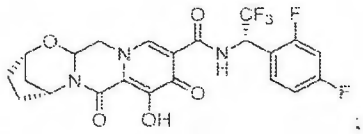

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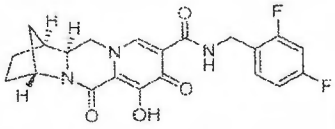

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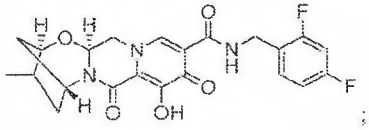


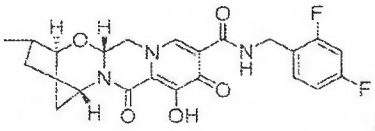


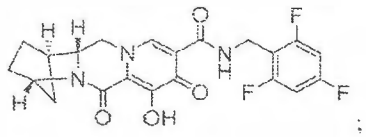


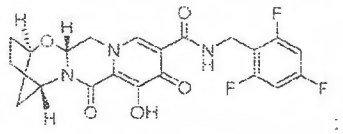


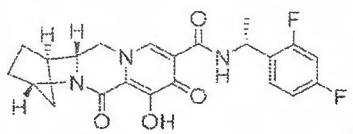


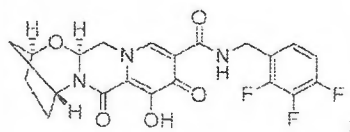


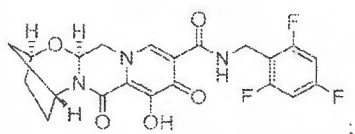


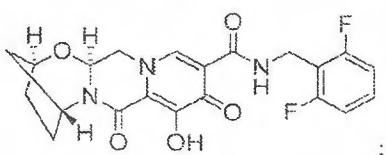

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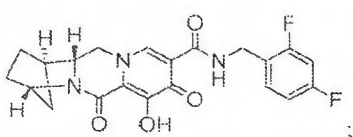

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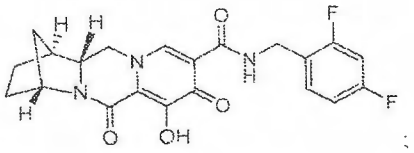

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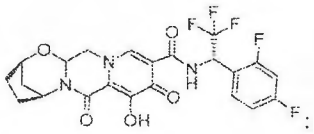

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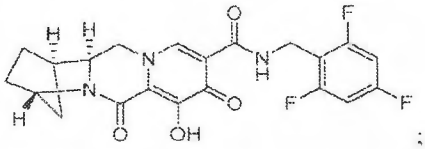

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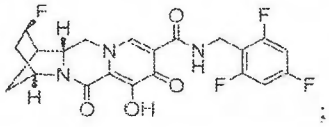

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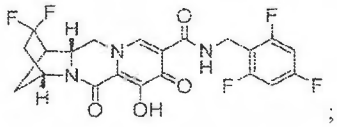

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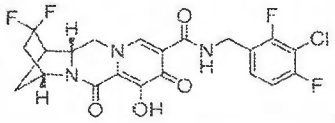

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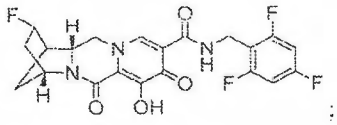

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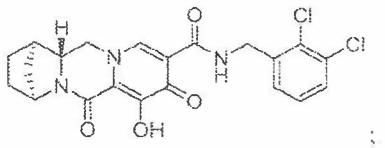

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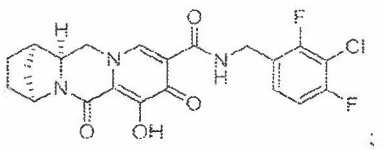

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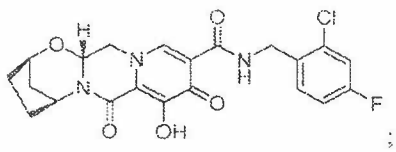

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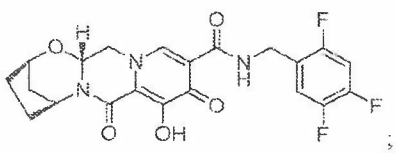

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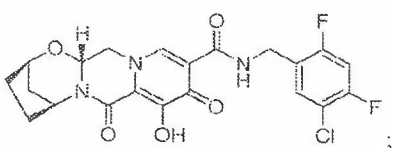

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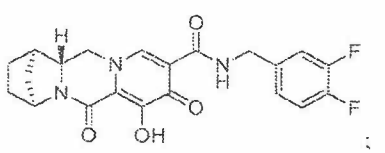


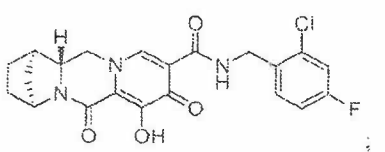


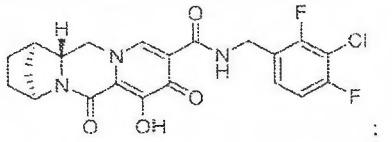


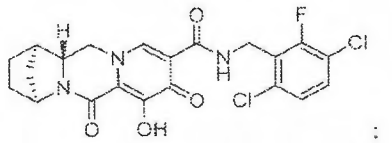


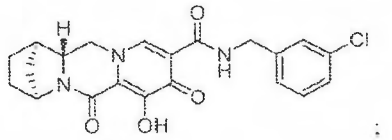


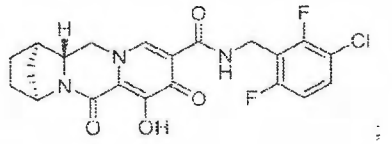


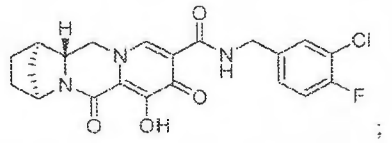


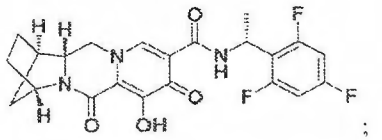

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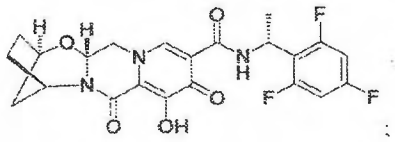

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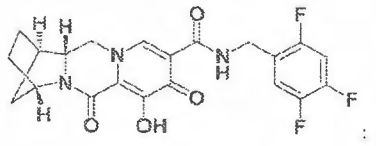

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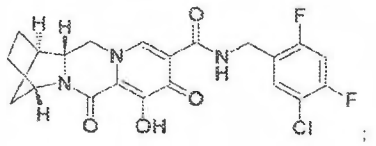

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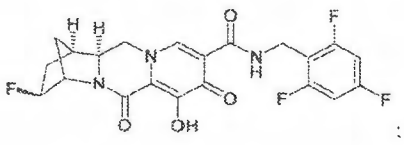

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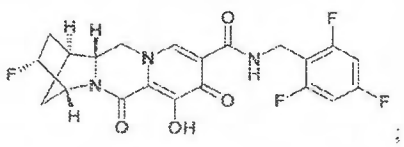

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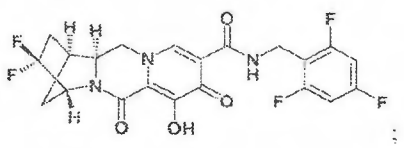

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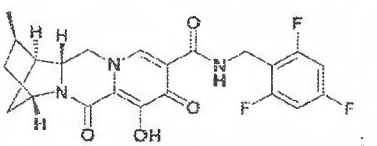


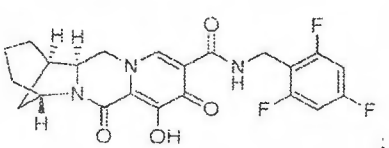


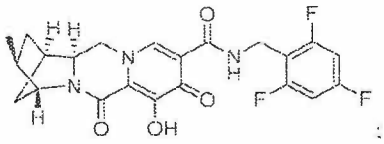


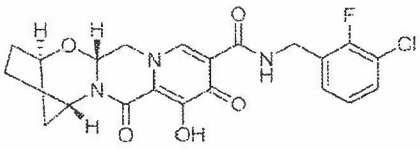


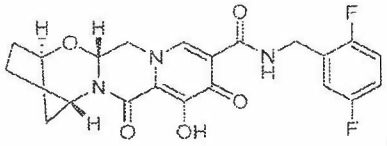


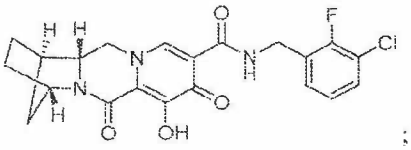


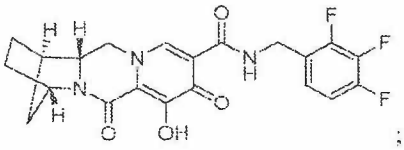


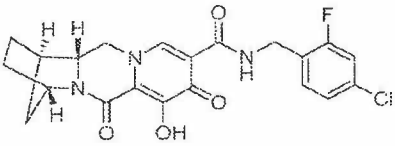


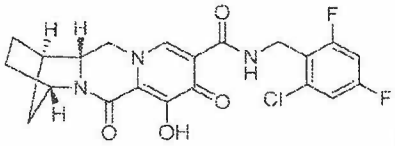


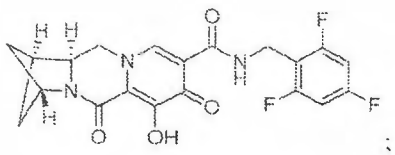


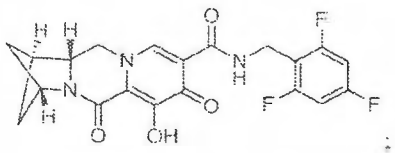


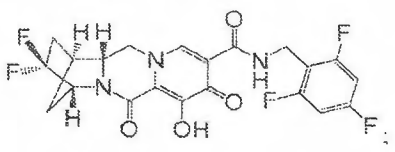


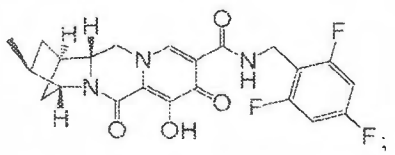


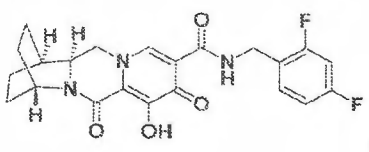


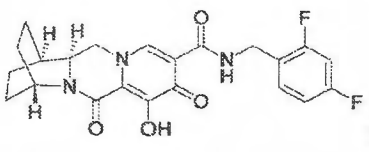

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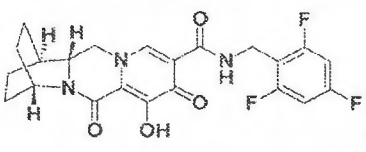

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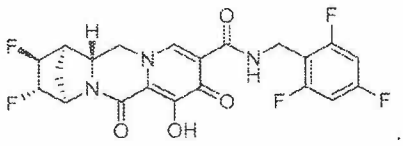

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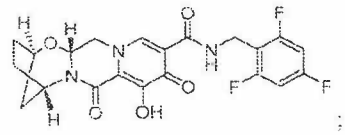

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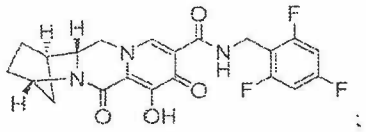

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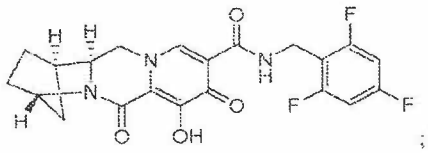
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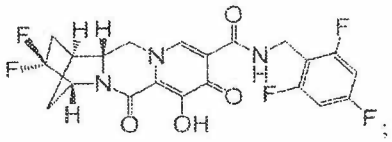


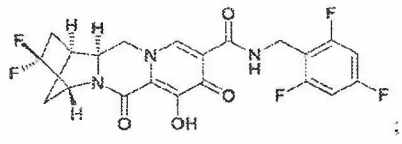
32. A compound of claim 1 selected from:

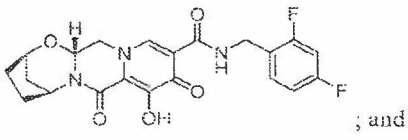

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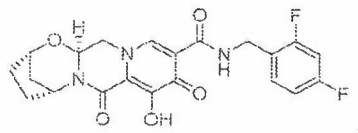

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; and



33. A pharmaceutical composition comprising a compound of any one of claims 1–32, or a stereoisomer or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

34. A pharmaceutical composition of claim 33 further comprising one or more additional therapeutic agents.

35. A pharmaceutical composition of claim 34 wherein the one or more one additional therapeutic agents is an anti-HIV agent.

36. A pharmaceutical composition of claim 35 wherein the one or more additional therapeutic agents is selected from the group consisting of HIV protease inhibitors, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, and combinations thereof.

37. A method of treating an HIV infection in a human having or at risk of having the infection by administering to the human a therapeutically effective amount of a compound of any one of claims 1–32 or a pharmaceutical composition of claim 33.

38. A method of claim 37 further comprising administering to the human a therapeutically effective amount of one or more additional therapeutic agents.

39. A method of claim 38 wherein the one or more additional therapeutic agents is an anti-HIV agent.

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40. A method of claim 39 wherein the one or more additional therapeutic agents is selected from the group consisting of HIV protease inhibitors, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, and combinations thereof.

41. Use of a compound of any one of claims 1-32 or a pharmaceutical composition of claim 33 for the treatment of an HIV infection in a human having or at risk of having the infection.

42. A use of claim 41 further comprising administering to the human a therapeutically effective amount of one or more additional therapeutic agents.

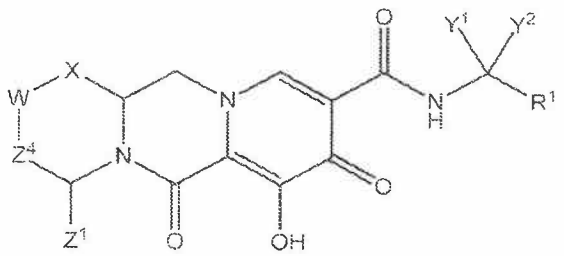
43. A use of claim 42 wherein the one or more additional therapeutic agents is an anti-HIV agent.

44. A use of claim 43 wherein the one or more additional therapeutic agents is selected from the group consisting of HIV protease inhibitors, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, and combinations thereof.

45. A compound as described in any one of claims 1–32, or a pharmaceutically acceptable salt thereof for use in medical therapy.

46. A compound as described in any one of claims 1–32, or a pharmaceutically acceptable salt thereof, for use in the therapeutic treatment of an HIV infection.

47. A compound having the following Formula (I):



(I)

or a stereoisomer or pharmaceutically acceptable salt thereof,

wherein:

X is -O- or -NZ^3- or -CHZ^3-;

W is -O- or -NZ^2- or -CHZ^2-;

Z^1, Z^2 and Z^3 are each, independently, hydrogen or C_{1-3}alkyl, or wherein Z^1 and Z^2 or Z^1 and Z^3, taken together, form -L- wherein L is -$C(R^a)_2$-, -$C(R^a)_2C(R^a)_2$-, -$C(R^a)_2C(R^a)_2C(R^a)_2$-, -$C(R^a)_2C(R^a)_2C(R^a)_2C(R^a)_2$-, -$C(R^a)_2OC(R^a)_2$-, -$C(R^a)_2NR^aC(R^a)_2$-, -$C(R^a)_2SC(R^a)_2$-, -$C(R^a)_2S(O)C(R^a)_2$-, -$C(R^a)_2SO_2C(R^a)_2$-, -$C(R^a)_2OC(R^a)_2C(R^a)_2$-, -$C(R^a)_2C(R^a)_2OC(R^a)_2$-, -$C(R^a)_2NR^aC(R^a)_2C(R^a)_2$-, -$C(R^a)_2C(R^a)_2NR^aC(R^a)_2$-, -$C(R^a)_2SC(R^a)_2C(R^a)_2$-, -$C(R^a)_2C(R^a)_2SC(R^a)_2$-, -$C(R^a)_2S(O)C(R^a)_2C(R^a)_2$-, -$C(R^a)_2C(R^a)_2S(O)C(R^a)_2$-, -$C(R^a)_2SO_2C(R^a)_2C(R^a)_2$-, -$C(R^a)_2C(R^a)_2SO_2C(R^a)_2$-, -$C(R^a)_2SO_2NR^aC(R^a)_2$- or -$C(R^a)_2NR^aSO_2C(R^a)_2$-;

Z^4 is a bond or -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -CH_2OCH_2-, -$CH_2NR^aCH_2$-, -CH_2SCH_2-,-$CH_2S(O)CH_2$- or -$CH_2SO_2CH_2$-;

Y^1 and Y^2 are each, independently, hydrogen, C_{1-3}alkyl or C_{1-3}haloalkyl, or Y^1 and Y^2, together with the carbon atom to which they are attached, form a carbocyclic ring having from 3 to 6 ring atoms or a heterocyclic ring having from 3 to 6 ring atoms, wherein the carbocyclic or heterocyclic ring is optionally substituted with one or more R^a;

R^1 is optionally substituted aryl or optionally substituted heteroaryl; and

each R^a is, independently, hydrogen, halo, hydroxyl or C_{1-4}alkyl, or wherein two R^a groups, together with the carbon atom to which they are attached, form C=O, and

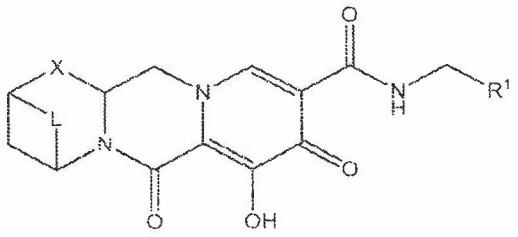
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wherein at least one of: (i) Z^1 and Z^2 or Z^1 and Z^3, taken together, form -L-; or (ii) Y^1 and Y^2, together with the carbon atom to which they are attached, form a carbocyclic ring having from 3 to 6 ring atoms or a heterocyclic ring having from 3 to 6 ring atoms.

48. A compound of claim 47 wherein W is $-CHZ^2-$

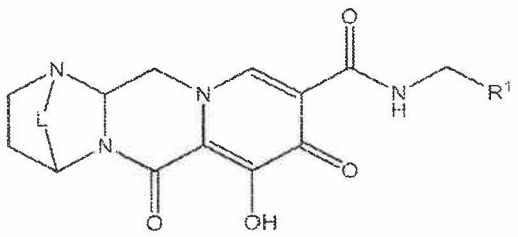
49. A compound of claim 47 or 48 wherein Z^1 and Z^2 or Z^1 and Z^3, taken together, form -L-.

50. A compound of claim 49 having one of the following Formulas (II-A), (II-B), or (II-C):



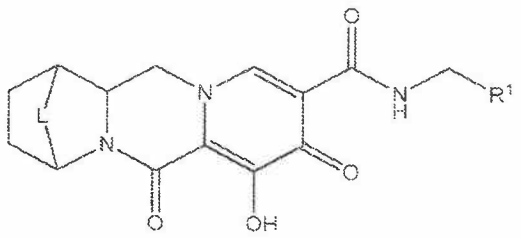
;

(II-A)



; or

(II-B)

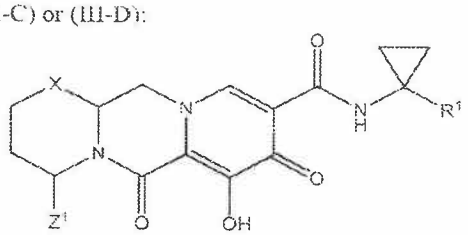


(II-C)

wherein L is $-C(R^a)_2-$, $-C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2C(R^a)_2C(R^a)_2-$, $-C(R^a)_2OC(R^a)_2-$, $-C(R^a)_2NR^aC(R^a)_2-$, $-C(R^a)_2SC(R^a)_2-$, $-C(R^a)_2S(O)C(R^a)_2-$, $-C(R^a)_2SO_2C(R^a)_2-$, $-C(R^a)_2OC(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2OC(R^a)_2-$, $-C(R^a)_2NR^aC(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2NR^aC(R^a)_2-$, $-C(R^a)_2SC(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2SC(R^a)_2-$, $-C(R^a)_2S(O)C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2S(O)C(R^a)_2-$, $-C(R^a)_2SO_2C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2SO_2C(R^a)_2-$, $-C(R^a)_2SO_2NR^aC(R^a)_2-$ or $-C(R^a)_2NR^aSO_2C(R^a)_2-$.

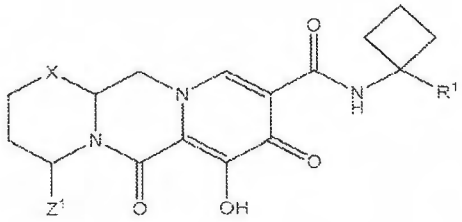
51. A compound of claim 47 or 48 wherein Y^1 and Y^2, together with the carbon atom to which they are attached, form a carbocyclic ring having from 3 to 6 ring atoms or a heterocyclic ring having from 3 to 6 ring atoms.

52. A compound of claim 51 having one of the following Formulas (III-A), (III-B), (III-C) or (III-D):



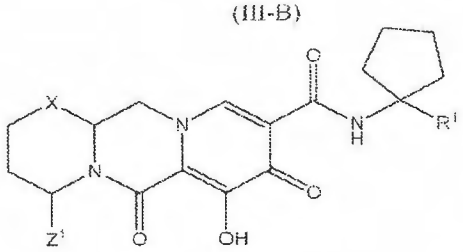
(III-A)

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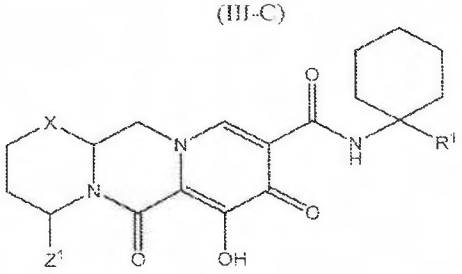
;

(III-B)



; or

(III-C)

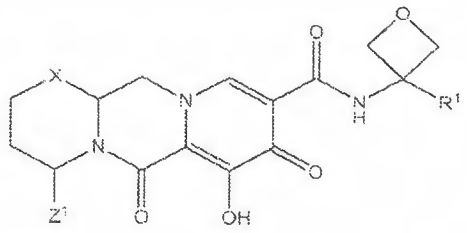


,

(III-D)

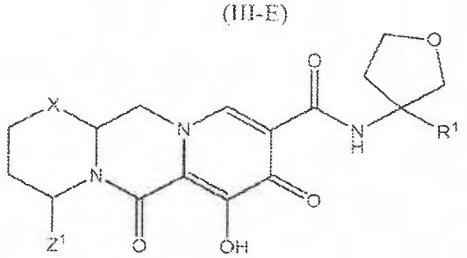
wherein Z^1 and Z^3 are each, independently, hydrogen or C_{1-3}alkyl.

53. A compound of claim 51 having one of the following Formulas (III-E), (III-F), (III-G) or (III-H):



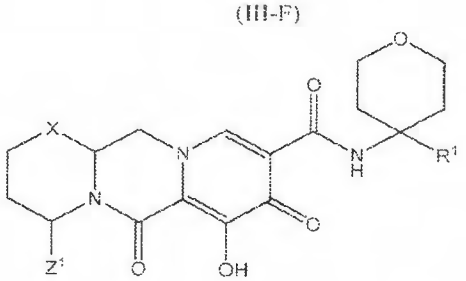
;

(III-E)



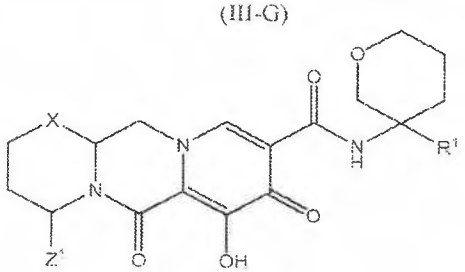
;

(III-F)



; or

(III-G)



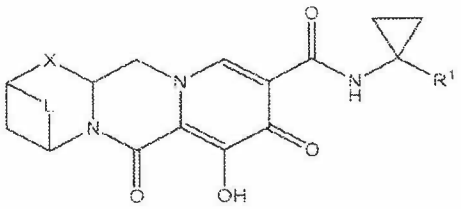
,

(III-H)

wherein Z^1 and Z^2 are each, independently, hydrogen or C_{1-3}alkyl.

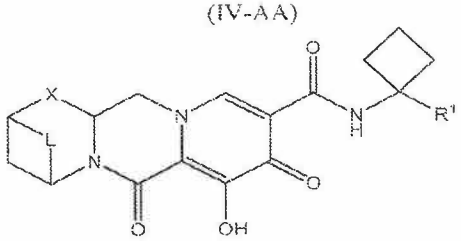
54. A compound of claim 47 or 48 wherein both (i) Z^1 and Z^2 or Z^1 and Z^3, taken together, form -L-, and (ii) Y^1 and Y^2, together with the carbon atom to which they are attached, form a carbocyclic ring having from 3 to 6 ring atoms or a heterocyclic ring having from 3 to 6 ring atoms.

55. A compound of claim 54 having one of the following Formulas (IV-AA), (IV-AB), (IV-AC), (IV-AD), (IV-AE), (IV-AF), (IV-AG) or (IV-AH):



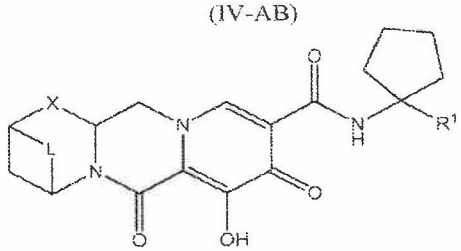
;

(IV-AA)



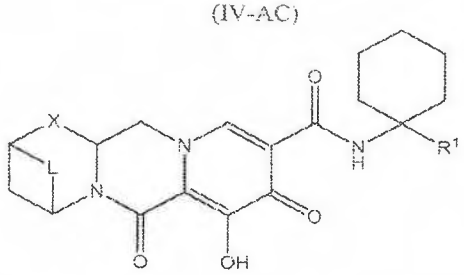
;

(IV-AB)

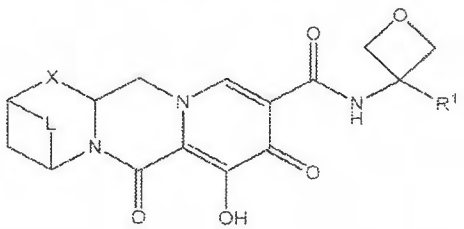


;

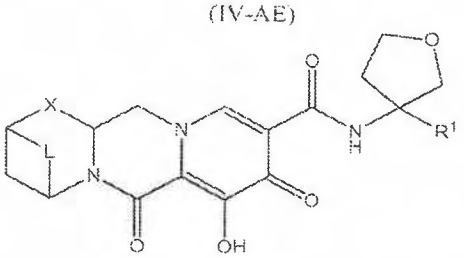
(IV-AC)



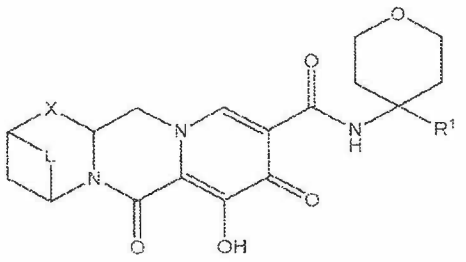
(IV-AD)



(IV-AE)

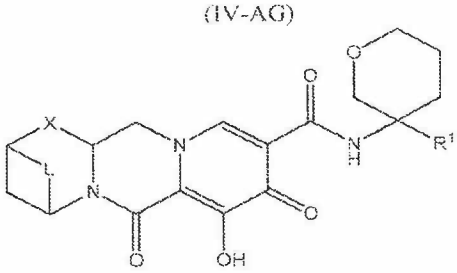


(IV-AF)



; or

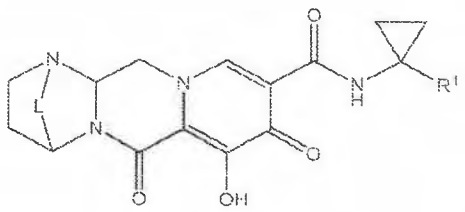
(IV-AG)



(IV-AH)

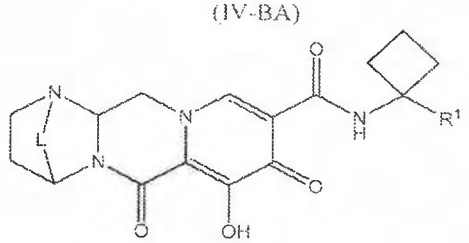
wherein L is $-C(R^a)_2-$, $-C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2C(R^a)_2C(R^a)_2-$, $-C(R^a)_2OC(R^a)_2-$, $-C(R^a)_2NR^aC(R^a)_2-$, $-C(R^a)_2SC(R^a)_2-$, $-C(R^a)_2S(O)C(R^a)_2-$, $-C(R^a)_2SO_2C(R^a)_2-$, $-C(R^a)_2OC(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2OC(R^a)_2-$, $-C(R^a)_2NR^aC(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2NR^aC(R^a)_2-$, $-C(R^a)_2SC(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2SC(R^a)_2-$, $-C(R^a)_2S(O)C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2S(O)C(R^a)_2-$, $-C(R^a)_2SO_2C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2SO_2C(R^a)_2-$, $-C(R^a)_2SO_2NR^aC(R^a)_2-$ or $-C(R^a)_2NR^aSO_2C(R^a)_2-$.

56. A compound of claim 54 having one of the following Formulas (IV-BA), (IV-BB), (IV-BC), (IV-BD), (IV-BE), (IV-BF), (IV-BG) or (IV-BH):



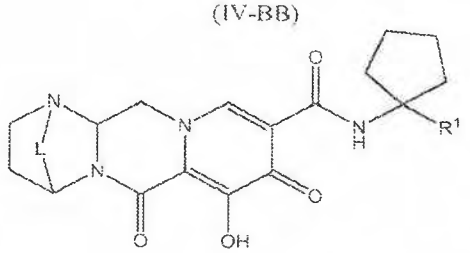
;

(IV-BA)



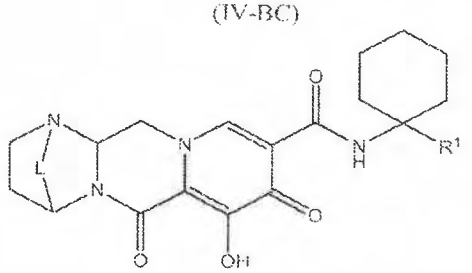
;

(IV-BB)



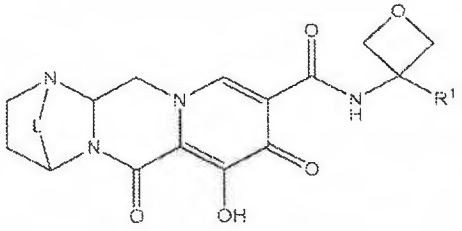
;

(IV-BC)



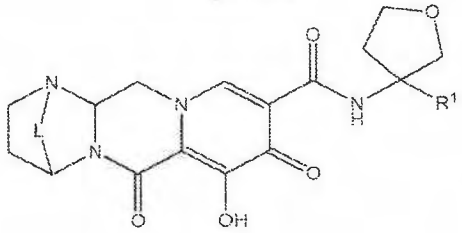
;

(IV-BD)



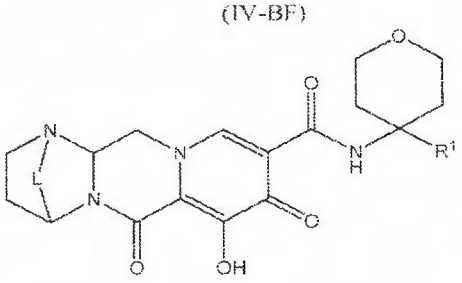
;

(IV-BE)



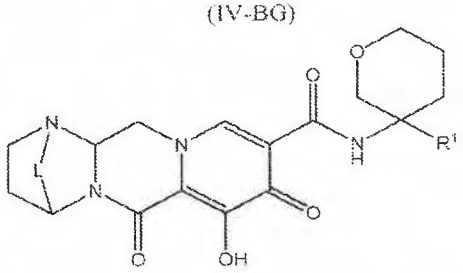
;

(IV-BF)



; or

(IV-BG)



;

(IV-BH)

wherein L is $-C(R^a)_2-$, $-C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2C(R^a)_2C(R^a)_2-$, $-C(R^a)_2OC(R^a)_2-$, $-C(R^a)_2NR^aC(R^a)_2-$, $-C(R^a)_2SC(R^a)_2-$, $-C(R^a)_2S(O)C(R^a)_2-$, $-C(R^a)_2SO_2C(R^a)_2-$, $-C(R^a)_2OC(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2OC(R^a)_2-$, $-C(R^a)_2NR^aC(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2NR^aC(R^a)_2-$, $-C(R^a)_2SC(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2SC(R^a)_2-$, $-C(R^a)_2S(O)C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2S(O)C(R^a)_2-$, $-C(R^a)_2SO_2C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2SO_2C(R^a)_2-$, $-C(R^a)_2SO_2NR^aC(R^a)_2-$ or $-C(R^a)_2NR^aSO_2C(R^a)_2-$.

57. A compound of any one of claims 47-50 or 54-56 wherein L is $-C(R^a)_2-$, $-C(R^a)_2C(R^a)_2-$, $-C(R^a)_2C(R^a)_2C(R^a)_2-$, or $-C(R^a)_2C(R^a)_2C(R^a)_2C(R^a)_2-$.

58. A compound of claim 57 wherein L is $-C(R^a)_2-$.

59. A compound of claim 57 wherein L is $-C(R^a)_2C(R^a)_2-$.

60. A compound of claim 57 wherein L is $-C(R^a)_2C(R^a)_2C(R^a)_2-$.

61. A compound of any one of claims 47-50 or 54-60 wherein each R^a is hydrogen.

62. A compound of any one of claims 47-50 or 54-60 wherein one R^a is methyl and each remaining R^a is hydrogen.

63. A compound of any one of claims 47-50 or 54-60 wherein at least one R^a is halogen and each remaining R^a is hydrogen.

64. A compound of any one of claims 47-50 or 54-60 wherein two R^a are halogen and each remaining R^a is hydrogen.

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65. A compound of any one of claims 47-50 or 54-60 wherein one R^a is halogen and each remaining R^a is hydrogen.

66. A compound of any one of claims 47-50 or 54-56 wherein L is $-C(R^a)_2OC(R^a)_2-$, $-C(R^a)_2NR^aC(R^a)_2-$, $-C(R^a)_2SC(R^a)_2-$, $-C(R^a)_2S(O)C(R^a)_2-$, or $-C(R^a)_2SO_2C(R^a)_2-$.

67. A compound of any one of claims 47-50 or 54-56 wherein L is $-C(R^a)_2OC(R^a)_2-$.

68. A compound of claim 66 or 67 wherein each R^a is hydrogen.

69. A compound of claim 66 or 67 wherein one R^a is methyl and each remaining R^a is hydrogen.

70. A compound of claim 66 or 67 wherein at least one R^a is halogen and each remaining R^a is hydrogen.

71. A compound of claim 66 or 67 wherein two R^a are halogen and each remaining R^a is hydrogen.

72. A compound of claim 66 or 67 wherein one R^a is halogen and each remaining R^a is hydrogen.

73. A compound of any one of claims 47–55 or 57–72 wherein X is -O-.

74. A compound of claim 73 wherein Z^2 is hydrogen.

75. A compound of any one of claims 47–72 wherein X is $-NZ^2-$.

76. A compound of any one of claims 47-72 wherein X is -NH-.

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77. A compound of any one of claims 47-55 or 57-72 wherein X is -CHZ^3-

78. A compound of any one of claims 47–55 or 57–72 wherein X is -CH_2-.

79. A compound of any one of claims 47-49, 51, 54 or 57-78 wherein Z^3 is a bond or -CH_2-.

80. A compound of any one of claims 47-49, 51, 54 or 57-78 wherein Z^4 is -CH_2-.

81. A compound of any one of claims 47-49, 51, 54 or 57-78 wherein Z^4 is a bond.

82. A compound of any one of claims 47-49 or 57-81 wherein Y^1 and Y^2 are each independently hydrogen, methyl or trifluoromethyl.

83. A compound of any one of claims 47-82 wherein R^1 is phenyl.

84. A compound of any one of claims 47-82 wherein R^1 is pyridinyl.

85. A compound of any one of claims 47-84 wherein R^1 is substituted with at least one halogen.

86. A compound of any one of claims 47-84 wherein R^1 is substituted with one halogen.

87. A compound of claim 86 wherein R^1 is 4-fluorophenyl or 2-fluorophenyl.

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88. A compound of any one of claims 47-84 wherein R^1 is substituted with two halogens.

89. A compound of claim 88 wherein R^1 is 2,4-difluorophenyl, 2,3-difluorophenyl, 2,6-difluorophenyl, 3-fluoro-4-chlorophenyl, 3,4-difluorophenyl, 2-fluoro-4-chlorophenyl, or 3,5-difluorophenyl.

90. A compound of claim 89 wherein R^1 is 2,4-difluorophenyl.

91. A compound of any one of claims 47-84 wherein R^1 is substituted with three halogens.

92. A compound of claim 91 wherein R^1 is 2,4,6-trifluorophenyl or 2,3,4-trifluorophenyl.

93. A compound of claim 92 wherein R^1 is 2,4,6-trifluorophenyl.

94. A compound of claim 85 wherein R^1 is 3-trifluoromethyl-4-fluorophenyl or 2-cyclopropoxy-4-fluorophenyl.

95. A pharmaceutical composition comprising a compound of any one of claims 47-94, or a stereoisomer or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

96. A pharmaceutical composition of claim 95 further comprising one or more additional therapeutic agents.

97. A pharmaceutical composition of claim 96 wherein the one or more one additional therapeutic agents is an anti-HIV agent.

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98. A pharmaceutical composition of claim 97 wherein the one or more additional therapeutic agents is selected from the group consisting of HIV protease inhibitors, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, and combinations thereof.

99. A method of treating an HIV infection in a human having or at risk of having the infection by administering to the human a therapeutically effective amount of a compound of any one of claims 47-94 or a pharmaceutical composition of claim 95.

100. A method of claim 99 further comprising administering to the human a therapeutically effective amount of one or more additional therapeutic agents.

101. A method of claim 100 wherein the one or more additional therapeutic agents is an anti-HIV agent.

102. A method of claim 101 wherein the one or more additional therapeutic agents is selected from the group consisting of HIV protease inhibitors, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, and other drugs for treating HIV, and combinations thereof.

103. Use of a compound of any one of claims 47-94 or a pharmaceutical composition of claim 95 for the treatment of an HIV infection in a human having or at risk of having the infection.

104. A use of claim 103 further comprising administering to the human a therapeutically effective amount of one or more additional therapeutic agents.

105. A use of claim 104 wherein the one or more additional therapeutic agents is an anti-HIV agent.

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106. A use of claim 105 wherein the one or more additional therapeutic agents is selected from the group consisting of HIV protease inhibitors, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, and other drugs for treating HIV, and combinations thereof.

107. A compound as described in any one of claims 47-94, or a pharmaceutically acceptable salt thereof for use in medical therapy.

108. A compound as described in any one of claims 47-94, or a pharmaceutically acceptable salt thereof, for use in the therapeutic treatment of an HIV infection.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/076367

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D498/14 C07D471/04 C07D471/14 C07D471/22 C07D487/04
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/116764 A1 (SHIONOGI & CO [JP]; JOHNS BRIAN ALVIN [US]; KAWASUJI TAKASHI [JP]; TAI) 2 November 2006 (2006-11-02) page 8, line 4 to page 9, line 23;; page 12, lines 4-8; page 48, line 4 - page 50, line 12; page 72, line 3, "Preferred compounds...." - page 75, line 7; page 239, ZZ-19 and ZZ-20; Experimental Examples, e.g. page 243, Table 2; claims	1-108
A	EP 2 412 709 A1 (SHIONOGI & CO [JP]) 1 February 2012 (2012-02-01) [0008]; [0269]; claims	1-108

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 March 2014	12/03/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Sen, Alina

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2013/076367

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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19 June 2015 (19.06.2015)

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(30) Priority Data:
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62/017,183 25 June 2014 (25.06.2014) US

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(74) Agents: **EDWARDS, Mary, J.** et al.; Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, CA 94404 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

[Continued on next page]

(54) Title: CRYSTALLINE FORMS OF (2R,5S,13AR)-8-HYDROXY-7,9-DIOXO-N-(2,4,6-TRIFLUOROBENZYL)-2,3,4,5,7,9,13,13A-OCTAHYDRO-2,5-METHANOPYRIDO [1',2':4,5] PYRAZINO [2,1-B] [1,3] OXAZEPINE-10-CARBOXAMIDE

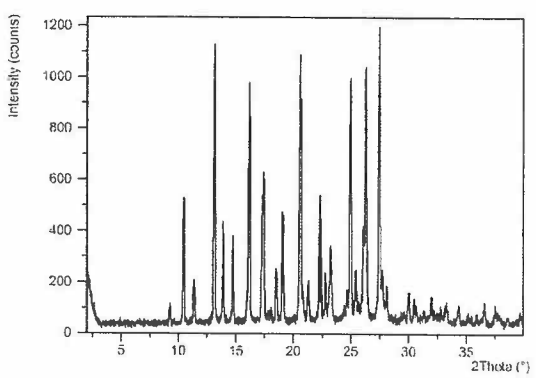


Figure 1

(57) Abstract: The present invention relates to crystalline forms and co-crystals of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, the pharmaceutical formulations, and the therapeutic uses thereof. The present invention also relates to novel crystalline forms of sodium (2 R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I.

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CRYSTALLINE FORMS OF (2R,5S,13AR)-8-HYDROXY-7,9-DIOXO-N-(2,4,6-TRIFLUOROBENZYL)-2,3,4,5,7,9,13,13A-OCTAHYDRO-2,5-METHANOPYRIDO[1',2':4,5]PYRAZINO[2,1-B][1,3]OXAZEPINE-10-CARBOXAMIDE

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to and the benefit under 35 U.S.C. 119(e) of U.S. Provisional Patent Application Serial Nos. 62/015,238, filed June 20, 2014 and 62/017,183, filed June 25, 2014, the disclosures of which are hereby incorporated by reference in their entirety.

FIELD

[0002] The present invention relates to novel crystalline forms and co-crystals of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, the pharmaceutical formulations, and the therapeutic uses thereof.

BACKGROUND

[0003] Human immunodeficiency virus infection and related diseases are a major public health problem worldwide. Human immunodeficiency virus type 1 (HIV-1) encodes three enzymes which are required for viral replication: reverse transcriptase, protease, and integrase. Although drugs targeting reverse transcriptase and protease are in wide use and have shown effectiveness, particularly when employed in combination, toxicity and development of resistant strains have limited their usefulness (Palella, et al. *N. Engl. J Med.* (1998) 338:853–860; Richman, D. D. *Nature* (2001) 410:995–1001).

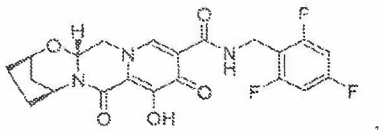
[0004] A goal of antiretroviral therapy is to achieve viral suppression in the HIV infected patient. Treatment guidelines published by the United States Department of Health and Human Services provide that achievement of viral suppression requires the use of combination therapies, i.e., several drugs from at least two or more drug classes. In addition, decisions regarding the treatment of HIV infected patients are complicated when the patient requires treatment for other medical conditions. Because the standard of care requires the use

of multiple different drugs to suppress HIV, as well as to treat other conditions the patient may be experiencing, the potential for drug interaction is a criterion for selection of a drug regimen. As such, there is a need for antiretroviral therapies having a decreased potential for drug interactions.

[0005] As discussed in co-pending application United States Serial No. 14/133,855, filed December 19, 2013 entitled "POLYCYCLIC-CARBAMOYLPYRIDONE COMPOUNDS AND THEIR PHARMACEUTICAL USE", (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide demonstrates anti-viral activity. As discussed in co-pending application PCT Serial No. US2013/076367, filed December 19, 2013 entitled "POLYCYCLIC-CARBAMOYLPYRIDONE COMPOUNDS AND THEIR PHARMACEUTICAL USE", (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide demonstrates anti-viral activity.

[0006] (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, (Formula I), has the following structure:

(I)



[0007] It is desired to have physically stable forms of the compound that are suitable for the therapeutic use and the manufacturing process.

SUMMARY

[0008] In one aspect, the present invention is directed to novel forms of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide.

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[0009] In one embodiment, the present invention is directed to (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form I.

[0010] In a further embodiment, the present invention is directed to (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form II.

[0011] In a still further embodiment, the present invention is directed to (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form III.

[0012] In a yet further embodiment, the present invention is directed to (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form IV.

[0013] In a yet further embodiment, the present invention is directed to (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form V.

[0014] In a yet further embodiment, the present invention is directed to (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form VI.

[0015] In a yet further embodiment, the present invention is directed to (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form VII.

[0016] In a yet further embodiment, the present invention is directed to (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form VIII.

[0017] In a certain embodiment, the present invention is directed to a fumaric acid co-crystal of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide.

[0018] In another embodiment, the present invention is directed to a citric acid co-crystal

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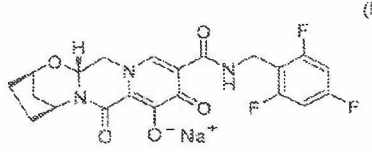
of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide.

[0019] In yet another embodiment, the present invention is directed to an oxalic acid co-crystal of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide.

[0020] In particular embodiments, the present invention is directed to crystalline forms and co-crystals of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide.

[0021] In a further aspect, the present invention is directed to novel forms of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, having the following structure (Formula II):

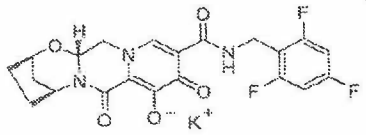
(II)



[0022] In a still further embodiment, the present invention is directed to sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I.

[0023] In yet a further aspect, the present invention is directed to novel forms of potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, having the following structure (Formula III):

(III)



[0024] In yet another embodiment, the present invention is directed to potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I.

[0025] In yet another embodiment, the present invention is directed to potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form II.

[0026] In yet another embodiment, the present invention is directed to potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form III.

[0027] In a still other embodiment, the present invention is directed to hydrated potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate.

[0028] In still another embodiment, the present invention is directed to methods of treating or prophylactically preventing an HIV infection by administering a compound (*e.g.* Formulas (I), (II), and/or (III)) provided herein.

[0029] In still another embodiment, the present invention is directed to a compound (*e.g.* Formulas (I), (II), and/or (III)) provided herein for use in methods of treating or prophylactically preventing an HIV infection.

[0030] In still another embodiment, the present invention is directed to the use of a compound (*e.g.* Formulas (I), (II), and/or (III)) provided herein in the manufacture of a medicament for treating or prophylactically preventing HIV infection.

DESCRIPTION OF THE FIGURES

[0031] **Figure 1:** XRPD pattern for (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form I.

[0032] **Figure 2:** XRPD pattern for (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form II.

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[0033] **Figure 3:** XRPD pattern for (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form III.

[0034] **Figure 4:** XRPD pattern for (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form IV.

[0035] **Figure 5:** XRPD pattern for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I.

[0036] **Figure 6:** Actual and calculated XRPD pattern for (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide oxalic acid co-crystal Form I.

[0037] **Figure 7:** DSC for (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form I.

[0038] **Figure 8:** DSC for (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form III.

[0039] **Figure 9:** DSC for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I.

[0040] **Figure 10:** TGA for (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form I.

[0041] **Figure 11:** TGA for (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form III.

[0042] **Figure 12:** TGA for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I.

[0043] **Figure 13:** DVS for (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form I.

[0044] **Figure 14:** DVS for (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form III.

[0045] **Figure 15:** DVS for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I.

[0046] **Figure 16:** Calculated and Experimental XRPD pattern for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I.

DETAILED DESCRIPTION

[0047] In the following description, certain specific details are set forth in order to provide a thorough understanding of various embodiments of the invention. However, one skilled in the art will understand that the invention may be practiced without these details. The description below of several embodiments is made with the understanding that the present disclosure is to be considered as an exemplification of the claimed subject matter, and is not intended to limit the appended claims to the specific embodiments illustrated. The headings used throughout this disclosure are provided for convenience only and are not to be construed to limit the claims in any way. Embodiments illustrated under any heading may be combined with embodiments illustrated under any other heading.

Definitions

[0048] Unless the context requires otherwise, throughout the present specification and claims, the word "comprise" and variations thereof, such as, "comprises" and "comprising"

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are to be construed in an open, inclusive sense, that is as "including, but not limited to".

[0049] Reference throughout this specification to "one embodiment" or "an embodiment" means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment of the present invention. Thus, the appearances of the phrases "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily all referring to the same embodiment. Furthermore, the particular features, structures, or characteristics may be combined in any suitable manner in one or more embodiments.

[0050] Embodiments that reference throughout this specification to "a compound" or "*e.g.* Formulas (I), (II), and/or (III)" includes the polymorphic, salt, co-crystal, and solvate forms of the formulas and/or compounds disclosed herein. Thus, the appearances or the phrases "a compound" or "*e.g.* Formulas (I), (II), and/or (III)" includes Forms I-VIII of Formula I, Form I of Formula II, Forms I-II of Formula III, and/or the fumaric acid, citric acid, and oxalic acid co-crystals as described herein.

[0051] The invention disclosed herein is also meant to encompass all pharmaceutically acceptable compounds of Formulas (I), (II), and (III) being isotopically-labeled by having one or more atoms replaced by an atom having a different atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, and ^{125}I, respectively. These radiolabeled compounds could be useful to help determine or measure the effectiveness of the compounds, by characterizing, for example, the site or mode of action, or binding affinity to pharmacologically important site of action. Certain isotopically-labeled compounds of Formulas (I), (II) and (III), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.* ^{3}H, and carbon-14, *i.e.* ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

[0052] Substitution with heavier isotopes such as deuterium, *i.e.* ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability. For example, *in vivo* half-life may increase or dosage requirements may be reduced. Thus, heavier isotopes may be preferred in some circumstances.

[0053] Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Isotopically-labeled compounds of Formulas (I), (II), (III) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the Examples as set out below using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

[0054] "Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

[0055] "Optional" or "optionally" means that the subsequently described event or circumstances may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" means that the aryl radical may or may not be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution.

[0056] "Pharmaceutically acceptable carrier, diluent or excipient" includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier which has been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

[0057] A "pharmaceutical composition" refers to a formulation of a compound of the invention and a medium generally accepted in the art for the delivery of the biologically active compound to mammals, *e.g.*, humans. Such a medium includes all pharmaceutically acceptable carriers, diluents or excipients therefor.

[0058] "Effective amount" or "therapeutically effective amount" refers to an amount of a compound according to the invention, which when administered to a patient in need thereof, is sufficient to effect treatment for disease-states, conditions, or disorders for which the compounds have utility. Such an amount would be sufficient to elicit the biological or medical response of a tissue system, or patient that is sought by a researcher or clinician. The amount of a compound according to the invention which constitutes a therapeutically effective amount will vary depending on such factors as the compound and its biological activity, the composition used for administration, the time of administration, the route of

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administration, the rate of excretion of the compound, the duration of the treatment, the type of disease-state or disorder being treated and its severity, drugs used in combination with or coincidentally with the compounds of the invention, and the age, body weight, general health, sex and diet of the patient. Such a therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to their own knowledge, the state of the art, and this disclosure.

[0059] In certain embodiments, the term "treatment" is intended to mean the administration of a compound or composition according to the present invention to alleviate or eliminate symptoms of HIV infection and/or to reduce viral load in a patient. The term "treatment" also encompasses the administration of a compound or composition according to the present invention post-exposure of the individual to the virus but before the appearance of symptoms of the disease, and/or prior to the detection of the virus in the blood, to prevent the appearance of symptoms of the disease and/or to prevent the virus from reaching detectible levels in the blood, and the administration of a compound or composition according to the present invention to prevent perinatal transmission of HIV from mother to baby, by administration to the mother before giving birth and to the child within the first days of life. In certain embodiments, the term "treatment" as used herein is intended to mean the administration of a compound or composition according to the present invention to alleviate or eliminate symptoms of HIV infection and/or to reduce viral load in a patient. In certain embodiments, the term "treatment" as used herein is further or alternatively intended to mean the administration of a compound or composition according to the present invention to maintain a reduced viral load in a patient. The term "treatment" also encompasses the administration of a compound or composition according to the present invention post-exposure of the individual to the virus but before the appearance of symptoms of the disease; and/or prior to the detection of the virus in the blood, to prevent the appearance of symptoms of the disease and/or to prevent the virus from reaching detectible levels in the blood, and the administration of a compound or composition according to the present invention to prevent perinatal transmission of HIV from mother to baby, by administration to the mother before giving birth and to the child within the first days of life. In certain embodiments, the term "treatment" as used herein is further or alternatively intended to mean the administration of a compound or composition according to the present invention post-exposure of the individual to the virus as a subsequent or additional therapy to a first-line therapy (e.g., for maintenance of low viral load).

[0060] "Prevention" or "preventing" means any treatment of a disease or condition that causes the clinical symptoms of the disease or condition not to develop. The term "prevention" also encompasses the administration of a compound or composition according to the present invention pre-exposure of the individual to the virus (*e.g.*, pre-exposure prophylaxis), to prevent the appearance of symptoms of the disease and/or to prevent the virus from reaching detectible levels in the blood.

[0061] The terms "Subject" or "patient" refer to an animal, such as a mammal (including a human), that has been or will be the object of treatment, observation or experiment. The methods described herein may be useful in human therapy and/or veterinary applications. In some embodiments, the subject is a mammal (or the patient). In some embodiments the subject (or the patient) is human, domestic animals (e.g., dogs and cats), farm animals (e.g., cattle, horses, sheep, goats and pigs), and/or laboratory animals (e.g., mice, rats, hamsters, guinea pigs, pigs, rabbits, dogs, and monkeys). In one embodiment, the subject (or the patient) is a human. "Human (or patient) in need thereof" refers to a human who may have or is suspect to have diseases or conditions that would benefit from certain treatment; for example, being treated with the compounds disclosed herein according to the present application.

[0062] The term "antiviral agent" as used herein is intended to mean an agent (compound or biological) that is effective to inhibit the formation and/or replication of a virus in a human being, including but not limited to agents that interfere with either host or viral mechanisms necessary for the formation and/or replication of a virus in a human being.

[0063] The term "inhibitor of HIV replication" as used herein is intended to mean an agent capable of reducing or eliminating the ability of HIV to replicate in a host cell, whether *in vitro, ex vivo* or *in vivo*.

[0064] A "tautomer" refers to a proton shift from one atom of a molecule to another atom of the same molecule. The present invention includes tautomers of any said compounds.

[0065] Reference to "about" a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. For example, description referring to "about X" includes description of "X". Also, the singular forms "a" and "the" include plural references unless the context clearly dictates otherwise. Thus, e.g., reference to "the compound" includes a plurality of such compounds and reference to "the assay"

includes reference to one or more assays and equivalents thereof known to those skilled in the art.

[0066] "Pharmaceutically acceptable" or "physiologically acceptable" refer to compounds, salts, compositions, dosage forms and other materials which are useful in preparing a pharmaceutical composition that is suitable for veterinary or human pharmaceutical use.

[0067] "Unit dosage forms" are physically discrete units suitable as unitary dosages for subjects (e.g., human subjects and other mammals), each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier.

Crystalline Forms

Formula I

[0068] It is desirable to develop a crystalline form of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide that may be useful in the synthesis of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide. A form of a (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide may be an intermediate to the synthesis of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide. A polymorphic form or polymorph or cocrystal may have properties such as bioavailability and stability at certain conditions that may be suitable for medical or pharmaceutical uses.

[0069] A crystalline form of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide may provide the advantage of bioavailability and stability, suitable for use as an active ingredient in a pharmaceutical composition. Variations in the crystal structure of a pharmaceutical drug substance or active ingredient may affect the

dissolution rate (which may affect bioavailability, *etc.*), manufacturability (*e.g.*, ease of handling, ability to consistently prepare doses of known strength) and stability (*e.g.*, thermal stability, shelf life, etc.) of a pharmaceutical drug product or active ingredient. Such variations may affect the preparation or formulation of pharmaceutical compositions in different dosage or delivery forms, such as solid oral dosage form including tablets and capsules. Compared to other forms such as non-crystalline or amorphous forms, crystalline forms may provide desired or suitable hygroscopicity, particle size controls, dissolution rate, solubility, purity, physical and chemical stability, manufacturability, yield, and/or process control. Thus, crystalline forms of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide may provide advantages such as: improving the manufacturing process of an active agent or the stability or storability of a drug product form of the compound or an active ingredient, and/or having suitable bioavailability and/or stability as an active agent.

[0070] The use of certain solvents has been found to produce different polymorphic forms of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, including any one or more of polymorphic Forms I, II, III, IV, V, VI, VII, and VIII, which may exhibit one or more favorable characteristics described above. The processes for the preparation of the polymorphs described herein, and characterization of these polymorphs are described in greater detail below.

[0071] The compound name provided above is named using ChemBioDraw Ultra and one skilled in the art understands that the compound structure may be named or identified using other commonly recognized nomenclature systems and symbols. By way of example, the compound may be named or identified with common names, systematic or non-systematic names. The nomenclature systems and symbols that are commonly recognized in the art of chemistry including but not limited to Chemical Abstract Service (CAS) and International Union of Pure and Applied Chemistry (IUPAC). Accordingly, the compound structure provided above may also be named or identified as (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide under IUPAC and 2,5-Methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide,

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2,3,4,5,7,9,13,13a-octahydro-8-hydroxy-7,9-dioxo-N-[(2,4,6-trifluorophenyl)methyl]-, (2R,5S,13aR)- under CAS; CAS Registry Number 1611493-60-7.

[0072] In particular embodiments, crystalline forms and co-crystals of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide are disclosed.

Formula I, Form I

[0073] In one embodiment, provided is polymorphic Form I of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, wherein the polymorph exhibits an X-ray powder diffraction (XRPD) pattern substantially as shown in FIG. 1. Polymorphic Form I may exhibit a differential scanning calorimetry (DSC) thermogram substantially as shown in FIG. 7. Polymorphic Form I may exhibit a thermographic analysis (TGA) graph substantially as shown in FIG. 10. Polymorphic Form I may exhibit dynamic vapour sorption (DVS) graphs substantially as shown in FIG. 13.

[0074] The term "substantially as shown in" when referring, for example, to an XRPD pattern, a DSC thermogram, or a TGA graph includes a pattern, thermogram or graph that is not necessarily identical to those depicted herein, but that falls within the limits of experimental error or deviations when considered by one of ordinary skill in the art.

[0075] Polymorphic Form I may have a unit cell as determined by crystal X-ray crystallography of the following dimensions: a = 11.4498 (4) Å; b = 8.4767 (3) Å; c = 19.9163 (8) Å; α = 90 °; β = 106.286 (2) °; and γ = 90 °.

[0076] In some embodiments of polymorphic Form I, at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, or all of the following (a)-(k) apply: (a) polymorphic Form I has an XRPD pattern substantially as shown in FIG. 1; (b) polymorphic Form I has a DSC thermogram substantially as shown in FIG. 7; (c) polymorphic Form I has a TGA graph substantially as shown in FIG. 10; (d) polymorphic Form I has DVS graphs substantially as shown in FIG. 13; (e) polymorphic Form I has a unit cell, as determined by crystal X-ray crystallography, of the following dimensions: a = 11.4498 (4) Å; b = 8.4767 (3) Å; c = 19.9163 (8) Å; α = 90 °; β = 106.286 (2) °; and γ = 90 °; (f) polymorphic Form I has an endothermic event onset; (g)

polymorphic Form I has a monoclinic crystal system; (h) polymorphic Form I has a P2(1) space group; (i) polymorphic Form I has a volume of 1855.44(12) $Å^3$; (j) polymorphic Form I has a Z value of 4; and (k) polymorphic Form I has a density of 1.609 g/cm^3.

[0077] In some embodiments, polymorphic Form I has at least one, at least two, at least three, or all of the following properties:

(a) an XRPD pattern substantially as shown in FIG. 1;

(b) a DSC thermogram substantially as shown in FIG. 7;

(c) DVS graphs substantially as shown in FIG. 13; and

(d) a unit cell, as determined by crystal X-ray crystallography, of the following dimensions: a = 11.4498 (4) Å; b = 8.4767 (3) Å; c = 19.9163 (8) Å; α = 90 °; β = 106.286 (2) °; and γ = 90 °.

[0078] In some embodiments, polymorphic Form I has an XRPD pattern displaying at least two, at least three, at least four, at least five, or at least six of the degree 2θ-reflections with the greatest intensity as the XRPD pattern substantially as shown in FIG. 1.

[0079] In certain embodiments, polymorphic Form I has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 27.4, 13.1, and 17.4. In one embodiment, polymorphic Form I has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 27.4, 13.1, and 17.4 and one or more of the degree 2θ-reflections (+/- 0.2 degrees 2θ) at 10.5, 20.6, and 25.0. In one embodiment, polymorphic Form I has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 27.4, 13.1, and 17.4 and one of the degree 2θ-reflections (+/- 0.2 degrees 2θ) at 10.5, 20.6, and 25.0. In one embodiment, polymorphic Form I has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 27.4, 13.1, and 17.4 and two of the degree 2θ-reflections (+/- 0.2 degrees 2θ) at 10.5, 20.6, and 25.0. In one embodiment, polymorphic Form I has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 27.4, 13.1, and 17.4 and three of the degree 2θ-reflections (+/- 0.2 degrees 2θ) at 10.5, 20.6, and 25.0. In one embodiment, polymorphic Form I has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 27.4,

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13.1, 17.4, 10.5, 20.6, and 25.0. In one embodiment, polymorphic Form I has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 27.4, 13.1, 17.4, 10.5, 20.6, 25.0 , 16.2, and 22.3. In one embodiment, polymorphic Form I has an XRPD pattern comprising any three degree 2θ-reflections (+/- 0.2 degrees 2θ) selected from the group consisting of 27.4, 13.1, 17.4, 10.5, 20.6, 25.0, 16.2, 22.3, 13.9, 11.4, and 9.3.

Formula 1, Form II

[0080] In one embodiment, provided is polymorphic Form II of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, wherein the polymorph exhibits an X-ray powder diffraction (XRPD) pattern substantially as shown in FIG. 2.

[0081] Polymorphic Form II may have a unit cell as determined by crystal X-ray crystallography of the following dimensions: a = 8.5226 (7) Å; b = 26.934 (2) Å; c = 8.6861 (8) Å; α = 90 °; β = 101.862 (2) °; and γ = 90 °.

[0082] In some embodiments of polymorphic Form II, at least one, at least two, at least three, at least four, at least five, at least six, or all of the following (a)-(g) apply: (a) polymorphic Form II has an XRPD pattern substantially as shown in FIG. 2; (b) polymorphic Form II has a unit cell, as determined by crystal X-ray crystallography, of the following dimensions: a = 8.5226 (7) Å; b = 26.934 (2) Å; c = 8.6861 (8) Å; α = 90 °; β = 101.862 (2) °; and γ = 90 °; (c) polymorphic Form II has a monoclinic crystal system; (d) polymorphic Form II has a P2(1) space group; (e) polymorphic Form II has a volume of 1951.3(3) $Å^3$; (f) polymorphic Form II has a Z value of 4; and (g) polymorphic Form II has a density of 1.537 Mg/m^3.

[0083] In some embodiments, polymorphic Form II has at least one, or all of the following properties:

(a) an XRPD pattern substantially as shown in FIG. 2;

(b) a unit cell, as determined by crystal X-ray crystallography, of the following dimensions: a = 8.5226 (7) Å; b = 26.934 (2) Å; c = 8.6861 (8) Å; α = 90 °; β = 101.862 (2) °; and γ = 90 °.

[0084] In some embodiments, polymorphic Form II has an XRPD pattern displaying at least two, at least three, at least four, at least five, or at least six of the degree 2θ-reflections with the greatest intensity as the XRPD pattern substantially as shown in FIG. 2.

[0085] In certain embodiments, polymorphic Form II has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 6.6, 21.4, and 10.6. In one embodiment, polymorphic Form II has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 6.6, 21.4, and 10.6 and one or more of the degree 2θ-reflections (+/- 0.2 degrees 2θ) at 12.5, 16.2, and 14.3. In one embodiment, polymorphic Form II has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 6.6, 21.4, and 10.6 and one of the degree 2θ-reflections (+/- 0.2 degrees 2θ) at 12.5, 16.2, and 14.3. In one embodiment, polymorphic Form II has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 6.6, 21.4, and 10.6 and two of the degree 2θ-reflections (+/- 0.2 degrees 2θ) at 12.5, 16.2, and 14.3. In one embodiment, polymorphic Form II has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 6.6, 21.4, and 10.6 and three of the degree 2θ-reflections (+/- 0.2 degrees 2θ) at 12.5, 16.2, and 14.3. In one embodiment, polymorphic Form II has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 6.6, 21.4, 10.6, 12.5, 16.2, and 14.3. In one embodiment, polymorphic Form II has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 6.6, 21.4, 10.6, 12.5, 16.2, 14.3, 25.6, and 23.5. In one embodiment, polymorphic Form II has an XRPD pattern comprising any three degree 2θ-reflections (+/- 0.2 degrees 2θ) selected from the group consisting of 6.6, 21.4, 10.6, 12.5, 16.2, 14.3, 25.6, and 23.5.

Formula I, Form III

[0086] In one embodiment, provided is polymorphic Form III of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, wherein the polymorph exhibits an X-ray powder diffraction (XRPD) pattern substantially as shown in FIG. 3. Polymorphic Form III may exhibit a differential scanning calorimetry (DSC)

thermogram substantially as shown in FIG. 8. Polymorphic Form III may exhibit a thermographic analysis (TGA) graph substantially as shown in FIG. 11. Polymorphic Form III may exhibit dynamic vapour sorption (DVS) graphs substantially as shown in FIG. 14.

[0087] Polymorphic Form III may have a unit cell as determined by crystal X-ray crystallography of the following dimensions: a = 18.002 (2) Å; b = 10.9514 (12) Å; c = 20.687 (2) Å; α = 90 °; β = 107.770 (4) °; and γ = 90 °.

[0088] In some embodiments of polymorphic Form III, at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, or all of the following (a)-(k) apply: (a) polymorphic Form III has an XRPD pattern substantially as shown in FIG. 3; (b) polymorphic Form III has a DSC thermogram substantially as shown in FIG. 8; (c) polymorphic Form III has a TGA graph substantially as shown in FIG. 11; (d) polymorphic Form III has DVS graphs substantially as shown in FIG. 14; (e) polymorphic Form III has a unit cell, as determined by crystal X-ray crystallography, of the following dimensions: a = 18.002 (2) Å; b = 10.9514 (12) Å; c = 20.687 (2) Å; α = 90 °; β = 107.770 (4) °; and γ = 90 °; (f) polymorphic Form I has an endothermic event onset (g) polymorphic Form III has a monoclinic crystal system; (h) polymorphic Form III has a P2(1) space group; (i) polymorphic Form III has a volume of 3884.0(8) $Å^3$; (j) polymorphic Form III has a Z value of 8; and (k) polymorphic Form III has a density of 1.537 g/cm^3.

[0089] In some embodiments, polymorphic Form III has at least one, at least two, at least three, or all of the following properties:

(a) an XRPD pattern substantially as shown in FIG. 3;

(b) a DSC thermogram substantially as shown in FIG. 8;

(c) DVS graphs substantially as shown in FIG. 14; and

(d) a unit cell, as determined by crystal X-ray crystallography, of the following dimensions a = 18.002 (2) Å; b = 10.9514 (12) Å; c = 20.687 (2) Å; α = 90 °; β = 107.770 (4) °; and γ = 90 °.

[0090] In some embodiments, polymorphic Form III has an XRPD pattern displaying at

least two, at least three, at least four, at least five, or at least six of the degree 2θ-reflections with the greatest intensity as the XRPD pattern substantially as shown in FIG. 3.

[0091] In certain embodiments, polymorphic Form III has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 20.0, 18.5, and 9.6. In one embodiment, polymorphic Form III has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 20.0, 18.5, and 9.6 and one or more of the degree 2θ-reflections (+/- 0.2 degrees 2θ) at 22.5, 14.0, and 25.0. In one embodiment, polymorphic Form III has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 20.0, 18.5, and 9.6 and one of the degree 2θ-reflections (+/- 0.2 degrees 2θ) at 22.5, 14.0, and 25.0. In one embodiment, polymorphic Form III has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 20.0, 18.5, and 9.6 and two of the degree 2θ-reflections (+/- 0.2 degrees 2θ) at 22.5, 14.0, and 25.0. In one embodiment, polymorphic Form III has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 20.0, 18.5, and 9.6 and three of the degree 2θ-reflections (+/- 0.2 degrees 2θ) at 22.5, 14.0, and 25.0. In one embodiment, polymorphic Form III has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 20.0, 18.5, 9.6, 22.5, 14.0, and 25.0. In one embodiment, polymorphic Form III has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 20.0, 18.5, 9.6, 22.5, 14.0, 25.0, 12.1, and 27.0. In one embodiment, polymorphic Form III has an XRPD pattern comprising any three degree 2θ-reflections (+/- 0.2 degrees 2θ) selected from the group consisting of 20.0, 18.5, 9.6, 22.5, 14.0, 25.0, 12.1, 27.0, 16.2, and 29.0.

Formula I, Form IV

[0092] In one embodiment, provided is polymorphic Form IV of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, wherein the polymorph exhibits an X-ray powder diffraction (XRPD) pattern substantially as shown in FIG. 4.

[0093] Polymorphic Form IV may have a unit cell as determined by crystal X-ray crystallography of the following dimensions: a = 29.948 (2) Å; b = 16.5172 (9) Å; c = 13.2051 (8) Å; α = 90 °; β = 108.972 (4) °; and γ = 90 °.

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[0094] In some embodiments of polymorphic Form IV, at least one, at least two, at least three, at least four, at least five, at least six, or all of the following (a)-(g) apply: (a) polymorphic Form IV has an XRPD pattern substantially as shown in FIG. 4; (b) polymorphic Form IV has a unit cell, as determined by crystal X-ray crystallography, of the following dimensions: a = 29.948 (2) Å; b = 16.5172 (9) Å; c = 13.2051 (8) Å; α = 90 °; β = 108.972 (4) °; and γ = 90 °; (c) polymorphic Form IV has a monoclinic crystal system; (d) polymorphic Form IV has a C2 space group; (e) polymorphic Form IV has a volume of 6177.3(7) $Å^3$; (f) polymorphic Form IV has a Z value of 12; and (g) polymorphic Form IV has a density of 1.484 Mg/m^3.

[0095] In some embodiments, polymorphic Form IV has at least one, or all of the following properties:

(a) an XRPD pattern substantially as shown in FIG. 4;

(b) a unit cell, as determined by crystal X-ray crystallography, of the following dimensions: a = 29.948 (2) Å; b = 16.5172 (9) Å; c = 13.2051 (8) Å; α = 90 °; β = 108.972 (4) °; and γ = 90 °.

[0096] In some embodiments, polymorphic Form IV has an XRPD pattern displaying at least two, at least three, at least four, at least five, or at least six of the degree 2θ-reflections with the greatest intensity as the XRPD pattern substantially as shown in FIG. 4.

[0097] In certain embodiments, polymorphic Form IV has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 16.3, 6.2, and 8.6. In one embodiment, polymorphic Form IV has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 16.3, 6.2, and 8.6 and one or more of the degree 2θ-reflections (+/- 0.2 degrees 2θ) at 22.7, 22.3, and 25.8. In one embodiment, polymorphic Form IV has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 16.3, 6.2, and 8.6 and one of the degree 2θ-reflections (+/- 0.2 degrees 2θ) at 22.7, 22.3, and 25.8. In one embodiment, polymorphic Form IV has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 16.3, 6.2, and 8.6 and two of the degree 2θ-reflections (+/- 0.2 degrees 2θ) at 22.7, 22.3, and 25.8. In one embodiment, polymorphic Form IV has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 16.3, 6.2, and 8.6 and three of the degree 2θ-

reflections (+/- 0.2 degrees 2θ) at 22.7, 22.3, and 25.8. In one embodiment, polymorphic Form IV has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 16.3, 6.2, 8.6, 22.7, 22.3, and 25.8. In one embodiment, polymorphic Form IV has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 16.3, 6.2, 8.6, 22.7, 22.3, 25.8, 20.0, and 18.7. In one embodiment, polymorphic Form IV has an XRPD pattern comprising any three degree 2θ-reflections (+/- 0.2 degrees 2θ) selected from the group consisting of 16.3, 6.2, 8.6, 22.7, 22.3, 25.8 20.0, 18.7, 27.7, and 13.2.

Formula I, Form V

[0098] In one embodiment, provided is polymorphic Form V of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide.

[0099] Polymorphic Form V may have a unit cell as determined by crystal X-ray crystallography of the following dimensions: a = 8.4993 (6) Å; b = 8.7290 (8) Å; c = 13.8619 (13) Å; α = 99.278 (5) °; β = 101.427 (4) °; and γ = 100.494 (4) °.

[0100] In some embodiments of polymorphic Form V, at least one, at least two, at least three, at least four, at least five, or all of the following (a)-(f) apply: (a) polymorphic Form V has a unit cell, as determined by crystal X-ray crystallography, of the following dimensions: a = 8.4993 (6) Å; b = 8.7290 (8) Å; c = 13.8619 (13) Å; α = 99.278 (5) °; β = 101.427 (4) °; and γ = 100.494 (4) °; (b) polymorphic Form V has a triclinic crystal system; (c) polymorphic Form V has a P2(1) space group; (d) polymorphic Form V has a volume of 970.18(14) $Å^3$; (e) polymorphic Form V has a Z value of 2; and (f) polymorphic Form V has a density of 1.573 Mg/m^3.

[0101] In some embodiments, polymorphic Form V has the following properties:

[0102] a unit cell, as determined by crystal X-ray crystallography, of the following dimensions: a = 8.4993 (6) Å; b = 8.7290 (8) Å; c = 13.8619 (13) Å; α = 99.278 (5) °; β = 101.427 (4) °; and γ = 100.494 (4) °.

Formula I, Form VI

[0103] In one aspect, provided is polymorphic Form VI of a (2R,5S,13aR)-8-hydroxy-

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7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide.

[0104] Polymorphic Form VI may have a unit cell as determined by crystal X-ray crystallography of the following dimensions: a = 19.5163 (5) Å; b = 6.4593 (2) Å; c = 16.6066 (5) Å; α = 90 °; β = 103.5680 (13) °; and γ = 90 °.

[0105] In some embodiments of polymorphic Form VI, at least one, at least two, at least three, at least four, at least five, or all of the following (a)-(f) apply: (a) polymorphic Form VI has a unit cell, as determined by crystal X-ray crystallography, of the following dimensions: a = 19.5163 (5) Å; b = 6.4593 (2) Å; c = 16.6066 (5) Å; α = 90 °; β = 103.5680 (13) °; and γ = 90 °; (b) polymorphic Form VI has a monoclinic crystal system; (c) polymorphic Form V has a P2(1) space group; (d) polymorphic Form VI has a volume of 2035.03(10) $Å^3$; (e) polymorphic Form V has a Z value of 4; and (f) polymorphic Form V has a density of 1.545 Mg/m^3.

[0106] In some embodiments, polymorphic Form VI has the following properties:

(a) a unit cell, as determined by crystal X-ray crystallography, of the following dimensions: a = 19.5163 (5) Å; b = 6.4593 (2) Å; c = 16.6066 (5) Å; α = 90 °; β = 103.5680 (13) °; and γ = 90 °.

Formula 1, Form VII

[0107] In one embodiment, provided is polymorphic Form VII of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide.

[0108] Polymorphic Form VII may have a unit cell as determined by crystal X-ray crystallography of the following dimensions: a = 30.785 (12) Å; b = 16.685 (6) Å; c = 25.956 (10) Å; α = 90 °; β = 108.189 (10) °; and γ = 90 °.

[0109] In some embodiments of polymorphic Form VII, at least one, at least two, at least three, at least four, at least five, or all of the following (a)-(f) apply: (a) polymorphic Form VII has a unit cell, as determined by crystal X-ray crystallography, of the following dimensions: a = 30.785 (12) Å; b = 16.685 (6) Å; c = 25.956 (10) Å; α = 90 °; β = 108.189

(10) °; and γ = 90 °; (b) polymorphic Form VII has a monoclinic crystal system; (c) polymorphic Form VII has a P2(1) space group; (d) polymorphic Form VI has a volume of 12666(8) $Å^3$; (e) polymorphic Form VII has a Z value of 24; and (f) polymorphic Form VII has a density of 1.468 Mg/m^3.

[0110] In some embodiments, polymorphic Form VI has the following properties:

(a) a unit cell, as determined by crystal X-ray crystallography, of the following dimensions: a = 30.785 (12) Å; b = 16.685 (6) Å; c = 25.956 (10) Å; α = 90 °; β = 108.189 (10) °; and γ = 90 °.

Formula I, Form VIII

[0111] In one embodiment, provided is polymorphic Form VIII of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide.

[0112] Polymorphic Form VIII may have a unit cell as determined by crystal X-ray crystallography of the following dimensions: a = 10.3242 (18) Å; b = 10.7826 (17) Å; c = 17.848 (3) Å; α = 90 °; β = 105.578 (8) °; and γ = 90 °.

[0113] In some embodiments of polymorphic Form VIII, at least one, at least two, at least three, at least four, at least five, or all of the following (a)-(f) apply: (a) polymorphic Form VIII has a unit cell, as determined by crystal X-ray crystallography, of the following dimensions: a = 10.3242 (18) Å; b = 10.7826 (17) Å; c = 17.848 (3) Å; α = 90 °; β = 105.578 (8) °; and γ = 90 °; (b) polymorphic Form VIII has a monoclinic crystal system; (c) polymorphic Form VIII has a C2 space group; (d) polymorphic Form VIII has a volume of 1913.9(6) $Å^3$; (e) polymorphic Form VIII has a Z value of 4; and (f) polymorphic Form VIII has a density of 1.560 Mg/m^3.

[0114] In some embodiments, polymorphic Form VIII has the following properties:

(a) a unit cell, as determined by crystal X-ray crystallography, of the following dimensions: a = 10.3242 (18) Å; b = 10.7826 (17) Å; c = 17.848 (3) Å; α = 90 °; β = 105.578 (8) °; and γ = 90 °.

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Formula II

[0115] It is desirable to develop a crystalline form of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate that may be useful in the synthesis of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate. A form of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate may be an intermediate to the synthesis of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate. A form of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate may be the final product in the synthesis of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate. A polymorphic form or polymorph or cocrystal may have properties such as bioavailability and stability at certain conditions that may be suitable for medical or pharmaceutical uses.

[0116] A crystalline form of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate may provide the advantage of bioavailability and stability, suitable for use as an active ingredient in a pharmaceutical composition. In certain embodiments, a crystalline form sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate provides an advantage of improved bioavailability (Table 3) and/or stability (Table 4). Variations in the crystal structure of a pharmaceutical drug substance or active ingredient may affect the dissolution rate (which may affect bioavailability, *etc.*), manufacturability (*e.g.*, ease of handling, ability to consistently prepare doses of known strength) and stability (*e.g.*, thermal stability, shelf life, etc.) of a pharmaceutical drug product or active ingredient. Such variations may affect the preparation or formulation of pharmaceutical compositions in different dosage or delivery forms, such as solid oral dosage form including tablets and capsules. Compared to other

forms such as non-crystalline or amorphous forms, crystalline forms may provide desired or suitable hygroscopicity, particle size controls, dissolution rate, solubility, purity, physical and chemical stability, manufacturability, yield, and/or process control. Thus, crystalline forms of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate may provide advantages such as: improving the manufacturing process of an active agent or the stability or storability of a drug product form of the compound or an active ingredient, and/or having suitable bioavailability and/or stability as an active agent.

[0117] The use of certain solvents has been found to produce different polymorphic forms of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, including polymorphic Form I, which may exhibit one or more favorable characteristics described above. In certain embodiments, Form I of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate provides an advantage of improved bioavailability (Table 3) and/or stability (Table 4). The processes for the preparation of the polymorphs described herein and characterization of these polymorphs are described in greater detail below.

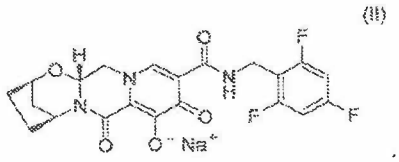
[0118] The compound name provided above is named using ChemBioDraw Ultra and one skilled in the art understands that the compound structure may be named or identified using other commonly recognized nomenclature systems and symbols. By way of example, the compound may be named or identified with common names, systematic or non-systematic names. The nomenclature systems and symbols that are commonly recognized in the art of chemistry including but not limited to Chemical Abstract Service (CAS) and International Union of Pure and Applied Chemistry (IUPAC). Accordingly, the compound structure provided above may be named or identified as sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate under IUPAC.

[0119] In particular embodiments, crystalline forms of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate are disclosed.

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Formula II, Form I

[0120] In a certain embodiment, novel forms of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, having the following structure (Formula II) are disclosed:



(II)

[0121] In a further embodiment, crystalline forms of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate are disclosed.

[0122] In a certain embodiment, sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I is disclosed.

[0123] In one embodiment, provided is polymorphic Form I of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, wherein the polymorph exhibits an X-ray powder diffraction (XRPD) pattern substantially as shown in FIG. 5 and/or FIG. 16. Polymorphic sodium Form I may exhibit a differential scanning calorimetry (DSC) thermogram substantially as shown in FIG. 9. Polymorphic sodium Form I may exhibit a thermographic analysis (TGA) graph substantially as shown in FIG. 12. Polymorphic sodium Form I may exhibit dynamic vapour sorption (DVS) graphs substantially as shown in FIG. 15.

[0124] The term "substantially as shown in" when referring, for example, to an XRPD pattern, a DSC thermogram, or a TGA graph includes a pattern, thermogram or graph that is not necessarily identical to those depicted herein, but that falls within the limits of experimental error or deviations when considered by one of ordinary skill in the art.

[0125] Polymorphic sodium Form I may have a unit cell as determined by crystal X-ray crystallography of the following dimensions: a = 8.9561 (10) Å; b = 13.9202 (14) Å; c = 31.115 (3) Å; α = 90 °; β = 90 °; and γ = 90 °.

[0126] In some embodiments of polymorphic sodium Form I, at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or all of the following (a)-(j) apply: (a) polymorphic Form I has an XRPD pattern substantially as shown in FIG. 5 and/or FIG. 16; (b) polymorphic sodium Form I has a DSC thermogram substantially as shown in FIG. 9; (c) polymorphic sodium Form I has a TGA graph substantially as shown in FIG. 12; (d) polymorphic sodium Form I has DVS graphs substantially as shown in FIG. 15; (e) polymorphic sodium Form I has a unit cell, as determined by crystal X-ray crystallography, of the following dimensions: a = 8.9561 (10) Å; b = 13.9202 (14) Å; c = 31.115 (3) Å; α = 90 °; β = 90 °; and γ = 90 °; (f) polymorphic sodium Form I has an orthorhombic crystal system; (g) polymorphic sodium Form I has a P212121 space group; (h) polymorphic sodium Form I has a volume of 3879.2 $Å^3$; (i) polymorphic Form I has a Z value of 4; and (j) polymorphic Form I has a density of 1.614 Mg/m^3.

[0127] In some embodiments, polymorphic sodium Form I has at least one, at least two, at least three, at least four, or all of the following properties:

(a) an XRPD pattern substantially as shown in FIG. 5 and/or FIG. 16;

(b) a DSC thermogram substantially as shown in FIG. 9;

(c) TGA graphs substantially as shown in FIG. 12;

(d) DVS graphs substantially as shown in FIG. 15; and

(e) a unit cell, as determined by crystal X-ray crystallography, of the following dimensions a = 8.9561 (10) Å; b = 13.9202 (14) Å; c = 31.115 (3) Å; α = 90 °; β = 90 °; and γ = 90 °;

[0128] In some embodiments, polymorphic sodium Form I has an XRPD pattern displaying at least two, at least three, at least four, at least five, or at least six of the degree

2θ-reflections with the greatest intensity as the XRPD pattern substantially as shown in FIG. 1 and/or FIG. 8.

[0129] In certain embodiments, polymorphic sodium Form I has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 5.5, 16.1, and 23.3. In one embodiment, polymorphic sodium Form I has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 5.5, 16.1, and 23.3 and one or more of the degree 2θ-reflections (+/- 0.2 degrees 2θ) at 22.1, 28.5, and 22.5. In one embodiment, polymorphic sodium Form I has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 5.5, 16.1, and 23.3 and one of the degree 2θ-reflections (+/- 0.2 degrees 2θ) at 22.1, 28.5, and 22.5. In one embodiment, polymorphic sodium Form I has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 5.5, 16.1, and 23.3 and two of the degree 2θ-reflections (+/- 0.2 degrees 2θ) at 22.1, 28.5, and 22.5. In one embodiment, polymorphic sodium Form I has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 5.5, 16.1, and 23.3 and three of the degree 2θ-reflections (+/- 0.2 degrees 2θ) at 22.1, 28.5, and 22.5. In one embodiment, polymorphic sodium Form I has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 5.5, 16.1, 23.3, 22.1, 28.5, and 22.5. In one embodiment, polymorphic sodium Form I has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 5.5, 16.1, 23.3, 22.1, 28.5, 22.5, 19.5, and 26.6. In one embodiment, polymorphic sodium Form I has an XRPD pattern comprising any three degree 2θ-reflections (+/- 0.2 degrees 2θ) selected from the group consisting of 5.5, 16.1, 23.3, 22.1, 28.5, 22.5, 19.5, 26.6, and 17.9.

Formula III

[0130] It is desirable to develop a crystalline form of potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate that may be useful in the synthesis of potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate. A form of a potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate may be an intermediate to the synthesis of potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-

methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate. A polymorphic form or polymorph or cocrystal may have properties such as bioavailability and stability at certain conditions that may be suitable for medical or pharmaceutical uses.

[0131] A crystalline form of potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate may provide the advantage of bioavailability and stability, suitable for use as an active ingredient in a pharmaceutical composition. Variations in the crystal structure of a pharmaceutical drug substance or active ingredient may affect the dissolution rate (which may affect bioavailability, *etc.*), manufacturability (*e.g.*, ease of handling, ability to consistently prepare doses of known strength) and stability (*e.g.*, thermal stability, shelf life, etc.) of a pharmaceutical drug product or active ingredient. Such variations may affect the preparation or formulation of pharmaceutical compositions in different dosage or delivery forms, such as solid oral dosage form including tablets and capsules. Compared to other forms such as non-crystalline or amorphous forms, crystalline forms may provide desired or suitable hygroscopicity, particle size controls, dissolution rate, solubility, purity, physical and chemical stability, manufacturability, yield, and/or process control. Thus, crystalline forms of potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate may provide advantages such as: improving the manufacturing process of an active agent or the stability or storability of a drug product form of the compound or an active ingredient, and/or having suitable bioavailability and/or stability as an active agent.

[0132] The use of certain solvents has been found to produce different polymorphic forms of potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, including any one or more of polymorphic Forms I, II, and III which may exhibit one or more favorable characteristics described above. The processes for the preparation of the polymorphs described herein, and characterization of these polymorphs are described in greater detail below.

[0133] The compound name provided above is named using ChemBioDraw Ultra and one skilled in the art understands that the compound structure may be named or identified using other commonly recognized nomenclature systems and symbols. By way of example,

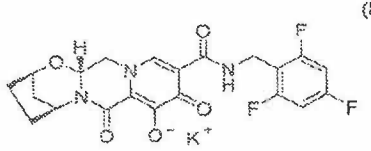
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the compound may be named or identified with common names, systematic or non-systematic names. The nomenclature systems and symbols that are commonly recognized in the art of chemistry including but not limited to Chemical Abstract Service (CAS) and International Union of Pure and Applied Chemistry (IUPAC). Accordingly, the compound structure provided above may be named or identified as potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate under IUPAC.

[0134] In particular embodiments, crystalline forms and co-crystals of potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate are disclosed.

[0135] In yet a further embodiment, novel forms of potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, having the following structure (Formula III) are disclosed.

(III)



[0136] In yet another embodiment, potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I is disclosed.

[0137] In yet another embodiment, potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form II is disclosed.

[0138] In yet another embodiment, potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form III is disclosed.

[0139] In a still other embodiment, hydrated potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-

methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate is disclosed.

Formula III, Form I

[0140] In one aspect, provided is polymorphic Form I of potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate.

[0141] Polymorphic potassium Form I may have a unit cell as determined by crystal X-ray crystallography of the following dimensions: a = 32.0409 (11) Å; b = 10.2935 (4) Å; c = 15.4691 (7) Å; α = 90 °; β = 90 °; and γ = 90 °.

[0142] In some embodiments of polymorphic potassium Form I, at least one, at least two, at least three, at least four, at least five, or all of the following (a)-(f) apply: (a) polymorphic potassium Form I has a unit cell, as determined by crystal X-ray crystallography, of the following dimensions: a = 32.0409 (11) Å; b = 10.2935 (4) Å; c = 15.4691 (7) Å; α = 90 °; β = 90 °; and γ = 90 °; (b) potassium Form I has an orthorhombic crystal system; (c) polymorphic potassium Form I has a P 21 21 2 space group; (d) polymorphic potassium Form I has a volume of 5101.9(4) $Å^3$; (e) polymorphic potassium Form I has a Z value of 8; and (f) potassium Form I has a density of 1.498 Mg/m^3.

[0143] In some embodiments, polymorphic potassium Form I has the following properties:

(a) a unit cell, as determined by crystal X-ray crystallography, of the following dimensions a = 32.0409 (11) Å; b = 10.2935 (4) Å; c = 15.4691 (7) Å; α = 90 °; β = 90 °; and γ = 90 °.

Formula III, Form II (Dimer)

[0144] In one aspect, provided is polymorphic Form II of potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate.

[0145] Polymorphic potassium Form II may have a unit cell as determined by crystal X-ray crystallography of the following dimensions: a = 32.0285 (17) Å; b = 10.3029 (7) Å; c =

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15.5363 (10) Å; α = 90 °; β = 90 °; and γ = 90 °.

[0146] In some embodiments of potassium Form II, at least one, at least two, at least three, at least four, at least five, or all of the following (a)-(f) apply: (a) polymorphic potassium Form II has a unit cell, as determined by crystal X-ray crystallography, of the following dimensions: a = 32.0285 (17) Å; b = 10.3029 (7) Å; c = 15.5363 (10) Å; α = 90 °; β = 90 °; and γ = 90 °; (b) polymorphic potassium Form II has an orthorhombic crystal system; (c) polymorphic potassium Form II has a P 21 21 2 space group; (d) polymorphic potassium Form II has a volume of 5126.8(6) $Å^3$; (e) polymorphic potassium Form II has a Z value of 4; and (f) polymorphic potassium Form II has a density of 1.336 Mg/m^3.

[0147] In some embodiments, polymorphic potassium Form II has the following properties:

(a) a unit cell, as determined by crystal X-ray crystallography, of the following dimensions a = 32.0285 (17) Å; b = 10.3029 (7) Å; c = 15.5363 (10) Å; α = 90 °; β = 90 °; and γ = 90 °.

Formula III, Form III

[0148] In one aspect, provided is polymorphic Form III of potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate.

[0149] Polymorphic potassium Form III may have a unit cell as determined by crystal X-ray crystallography of the following dimensions: a = 8.8412 (3) Å; b = 10.8837 (4) Å; c = 13.9107 (5) Å; α = 71.3620 (1) °; β = 76.343 (2) °; and γ = 82.943 (2) °.

[0150] In some embodiments of polymorphic potassium Form III, at least one, at least two, at least three, at least four, at least five, or all of the following (a)-(f) apply: (a) polymorphic potassium Form III has a unit cell, as determined by crystal X-ray crystallography, of the following dimensions: a = 8.8412 (3) Å; b = 10.8837 (4) Å; c = 13.9107 (5) Å; α = 71.3620 (1) °; β = 76.343 (2) °; and γ = 82.943 (2) °; (b) potassium Form III has a triclinic crystal system; (c) polymorphic potassium Form III has a P1 space group; (d) polymorphic potassium Form III has a volume of 1230.86 (8) $Å^3$; (e) polymorphic potassium Form III has a Z value of 2; and (f) potassium Form III has a density of 1.483

Mg/m^3.

[0151] In some embodiments, polymorphic potassium Form III has the following properties:

1. a unit cell, as determined by crystal X-ray crystallography, of the following dimensions a = 8.8412 (3) Å; b = 10.8837 (4) Å; c = 13.9107 (5) Å; α = 71.3620 (1) °; β = 76.343 (2) °; and γ = 82.943 (2) °

Co-Crystals

Formula I Citric Acid Co-Crystal

[0152] In another embodiment, a citric acid co-crystal of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide is disclosed.

[0153] In one embodiment, provided is Formula I citric acid co-crystal of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide.

[0154] Formula I citric acid co-crystal may have a unit cell as determined by crystal X-ray crystallography of the following dimensions: a = 7.4315 (6) Å; b = 15.5755 (13) Å; c = 15.6856 (13) Å; α = 88.784 (2) °; β = 77.029 (2) °; and γ = 76.832 (2) °.

[0155] In some embodiments of Formula I citric acid co-crystal, at least one, at least two, at least three, at least four, at least five, or all of the following (a)-(g) apply: (a) Formula I citric acid co-crystal has a unit cell, as determined by crystal X-ray crystallography, of the following dimensions: a = 7.4315 (6) Å; b = 15.5755 (13) Å; c = 15.6856 (13) Å; α = 88.784 (2) °; β = 77.029 (2) °; and γ = 76.832 (2) °; (b) Formula I citric acid co-crystal has a triclinic crystal system; (c) Formula I citric acid co-crystal has a P1 space group; (d) Formula I citric acid co-crystal has a volume of 1721.9(2) $Å^3$; (e) Formula I citric acid co-crystal has a Z value of 2; and (f) Formula I citric acid co-crystal has a density of 1.608 Mg/m^3.

[0156] In some embodiments, Formula I citric acid co-crystal has all of the following

properties:

(a) a unit cell, as determined by crystal X-ray crystallography, of the following dimensions a = 7.4315 (6) Å; b = 15.5755 (13) Å; c = 15.6856 (13) Å; α = 88.784 (2) °; β = 77.029 (2) °; and γ = 76.832 (2) °.

Formula I Fumaric Acid Co-Crystal

[0157] In a certain embodiment, a fumaric acid co-crystal of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide is disclosed.

[0158] In one aspect, provided is Formula I fumaric acid co-crystal of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide.

[0159] Formula I fumaric acid co-crystal may have a unit cell as determined by crystal X-ray crystallography of the following dimensions: a = 26.767 (5) Å; b = 8.2313 (14) Å; c = 24.089 (4) Å; α = 90 °; β = 99.283 (4) °; and γ = 90 °.

[0160] In some embodiments of Formula I fumaric acid co-crystal, at least one, at least two, at least three, at least four, at least five, or all of the following (a)-(f) apply: (a) Formula I fumaric acid co-crystal has a unit cell, as determined by crystal X-ray crystallography, of the following dimensions: a = 26.767 (5) Å; b = 8.2313 (14) Å; c = 24.089 (4) Å; α = 90 °; β = 99.283 (4) °; and γ = 90 °; (b) Formula I fumaric acid co-crystal has a monoclinic crystal system; (c) Formula I fumaric acid co-crystal has a C2 space group; (d) Formula I fumaric acid co-crystal has a volume of 5237.9(16) $Å^3$; (e) Formula I fumaric acid co-crystal has a Z value of 8; and (f) Formula I fumaric acid co-crystal has a density of 1.503 Mg/m^3.

[0161] In some embodiments, Formula I fumaric acid co-crystal has all of the following properties:

(a) a unit cell, as determined by crystal X-ray crystallography, of the following dimensions a = 26.767 (5) Å; b = 8.2313 (14) Å; c = 24.089 (4) Å; α = 90 °; β = 99.283 (4) °; and γ = 90 °.

Formula I Oxalic Acid Co-Crystal

[0162] In yet another embodiment, a oxalic acid co-crystal of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide is disclosed.

[0163] In one embodiment, provided is Formula I oxalic acid co-crystal of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide.

[0164] Formula I oxalic acid co-crystal may have a unit cell as determined by crystal X-ray crystallography of the following dimensions: a = 7.8562 (3) Å; b = 14.5031 (5) Å; c = 19.9756 (7) Å; α = 90 °; β = 101.291 (2) °; and γ = 90 °.

[0165] In some embodiments of Formula I oxalic acid co-crystal, at least one, at least two, at least three, at least four, at least five, or all of the following (a)-(f) apply: (a) Formula I oxalic acid co-crystal has a unit cell, as determined by crystal X-ray crystallography, of the following dimensions: a = 7.8562 (3) Å; b = 14.5031 (5) Å; c = 19.9756 (7) Å; α = 90 °; β = 101.291 (2) °; and γ = 90 °; (b) Formula I oxalic acid co-crystal has a monoclinic crystal system; (c) Formula I oxalic acid co-crystal has a P2(1) space group; (d) Formula I oxalic acid co-crystal has a volume of 2231.95(14) $Å^3$; (e) Formula I oxalic acid co-crystal has a Z value of 4; and (f) Formula I oxalic acid co-crystal has a density of 1.604 g/cm^3.

[0166] In some embodiments, Formula I oxalic acid co-crystal has the following properties:

(a) a unit cell, as determined by crystal X-ray crystallography, of the following dimensions a = 7.8562 (3) Å; b = 14.5031 (5) Å; c = 19.9756 (7) Å; α = 90 °; β = 101.291 (2) °; and γ = 90 °.

[0167] In certain embodiments, Formula I oxalic acid co-crystal has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 19.1, 14.5, and 9.1. In one embodiment, Formula I oxalic acid co-crystal has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 19.1, 14.5, and 9.1 and one or more of the degree 2θ-reflections (+/- 0.2 degrees 2θ) at 7.6, 26.5, and 17.1. In one embodiment, Formula I oxalic

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acid co-crystal has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 19.1, 14.5, and 9.1 and one of the degree 2θ-reflections (+/- 0.2 degrees 2θ) at 7.6, 26.5, and 17.1. In one embodiment, Formula I oxalic acid co-crystal has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 19.1, 14.5, and 9.1 and two of the degree 2θ-reflections (+/- 0.2 degrees 2θ) at 7.6, 26.5, and 17.1. In one embodiment, Formula I oxalic acid co-crystal has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 19.1, 14.5, and 9.1 and three of the degree 2θ-reflections (+/- 0.2 degrees 2θ) at 7.6, 26.5, and 17.1. In one embodiment, Formula I oxalic acid co-crystal has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 19.1, 14.5, 9.1, 7.6, 26.5, and 17.1. In one embodiment, Formula I oxalic acid co-crystal has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 19.1, 14.5, 9.1, 7.6, 26.5, 17.1, 21.8, and 39.4. In one embodiment, polymorphic Formula I oxalic acid co-crystal has an XRPD pattern comprising any three degree 2θ-reflections (+/- 0.2 degrees 2θ) selected from the group consisting of 19.1, 14.5, 9.1, 7.6, 26.5, 17.1, 21.8, 39.4, 29.7, and 11.6.

Pharmaceutical Compositions

[0168] For the purposes of administration, in certain embodiments, the compounds described herein are administered as a raw chemical or are formulated as pharmaceutical compositions. Pharmaceutical compositions of the present invention comprise a compound of Formulas (I), (II) or (III), including forms and co-crystals thereof, and a pharmaceutically acceptable carrier, diluent or excipient. The compound of Formulas (I), (II), or (III) is present in the composition in an amount which is effective to treat a particular disease or condition of interest. The activity of compounds of Formulas (I), (II), and (III) can be determined by one skilled in the art, for example, as described in co-pending application U.S. Serial No. 14/133,855, filed December 19, 2013 entitled "POLYCYCLIC-CARBAMOYLPYRIDONE COMPOUNDS AND THEIR PHARMACEUTICAL USE". The activity of compounds of Formulas (I), (II), and (III) can also be determined by one skilled on the art, for example, as described in co-pending PCT Serial No. US2013/076367, filed December 19, 2013 entitled, "POLYCYCLIC-CARBAMOYLPYRIDONE COMPOUNDS AND THEIR PHARMACEUTICAL USE." Appropriate concentrations and dosages can be readily determined by one skilled in the art. In certain embodiments, a compound of Formulas (I), (II), and/or (III) is present in the pharmaceutical composition in an amount from about 25 mg

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to about 500 mg. In certain embodiments, a compound of Formulas (I), (II), and/or (III) is present in the pharmaceutical composition in an amount of about 100 mg to about 300 mg. In certain embodiments, a compound of Formulas (I), (II), and/or (III) is present in the pharmaceutical composition in an amount of about 5 mg to about 100 mg. In certain embodiments, a compound of Formulas (I), (II), and/or (III) is present in the pharmaceutical composition in an amount of about 25 mg to about 100 mg. In certain embodiments, a compound of Formulas (I), (II), and/or (III) is present in the pharmaceutical composition in an amount of about 50 mg to about 100 mg. In certain embodiments, a compound of Formula (I), (II), and/or (III) is present in the pharmaceutical composition in an amount of about 5 mg, 25 mg, 50 mg, 75, mg, 100 mg, 200 mg, 300 mg, 400 mg or about 500 mg.

Formula I

[0169] Provided are also compositions comprising at least one, at least two, at least three, at least four, at least five, at least six, at least seven, or all of polymorphs (*e.g.*, any one or more of Formula I polymorphic Forms I, II, III, IV, V, VI, VII, and VIII) as described herein. In a particular embodiment, a composition comprising one of Formula I polymorphic Forms I, II, III, IV, V, VI, VII, and VIII described herein is provided. In a particular embodiment, a composition comprising two of Formula I polymorphic Forms I, II, III, IV, V, VI, VII, and VIII described herein is provided. In a particular embodiment, a composition comprising three of Formula I polymorphic Forms I, II, III, IV, V, VI, VII, and VIII described herein is provided. In a particular embodiment, a composition comprising four of Formula I polymorphic Forms I, II, III, IV, V, VI, VII, and VIII described herein is provided. In a particular embodiment, a composition comprising five of Formula I polymorphic Forms I, II, III, IV, V, VI, VII, and VIII described herein is provided. In a particular embodiment, a composition comprising six of Formula I polymorphic Forms I, II, III, IV, V, VI, VII, and VIII described herein is provided. In a particular embodiment, a composition comprising seven of Formula I polymorphic Forms I, II, III, IV, V, VI, VII, and VIII described herein is provided. In a particular embodiment, a composition comprising eight of Formula I polymorphic Forms I, II, III, IV, V, VI, VII, and VIII described herein is provided. In other embodiments, the compositions described herein may comprise substantially pure polymorphic forms, or may be substantially free of other polymorphs and/or impurities.

[0170] In some embodiments, the composition comprises a polymorphic form of

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(2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide. In certain embodiments are provided compositions comprising a polymorphic form as described herein, wherein the (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide within the composition is substantially pure (*i.e.*, substantially pure Form I, Form II, Form III, Form IV, Form V, Form VI or Form VII or Form VIII). In particular embodiments of compositions comprising a polymorphic form of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide present in the composition is one of the polymorphic forms disclosed herein. In certain embodiments, the composition includes at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% of one of the polymorphic forms of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide.

[0171] In other embodiments of compositions comprising a polymorphic form disclosed herein, less than about 50%, less than about 40%, less than about 30%, less than about 20%, less than about 10%, less than about 5%, less than about 4%, less than about 3%, less than about 2% or less than about 1% of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide present in the composition are other polymorphs of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide and/or impurities.

[0172] In yet other embodiments of compositions comprising the polymorphic forms disclosed herein, impurities make up less than about 5%, less than about 4%, less than about

3%, less than about 2% or less than about 1% of the total mass relative to the mass of the polymorphic forms present. Impurities may, for example, include by-products from synthesizing (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, contaminants, degradation products, other polymorphic forms, amorphous form, water, and solvents. In certain embodiments, impurities include by-products from the process of synthesizing (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide. In certain embodiments, impurities include contaminants from the process of synthesizing (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide. In certain embodiments, impurities include degradation products of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide. In certain embodiments, impurities include other polymorphic forms of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide. In certain embodiments, impurities include water or solvent. In certain embodiments of compositions comprising a polymorphic form disclosed herein, impurities are selected from the group consisting of by-products from synthesizing (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, contaminants, degradation products, other polymorphic forms, water, solvents and combinations thereof.

[0173] In yet other embodiments, the composition comprising a polymorphic form disclosed herein has less than about 5%, less than about 4%, less than about 3%, less than about 2%, or less than about 1% by weight of amorphous or non-crystalline (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide.

Formula II

[0174] Provided are also compositions comprising at least one polymorph (*e.g.*, any one or more of Formula II polymorphic Forms I) as described herein. In a particular

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embodiment, a composition comprising Formula II polymorphic Form I, described herein is provided. In other embodiments, the compositions described herein may comprise substantially pure polymorphic forms, or may be substantially free of other polymorphs and/or impurities.

[0175] In some embodiments, the composition comprises a polymorphic form of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate. In certain embodiments are provided compositions comprising a polymorphic form as described herein, wherein the sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate within the composition is substantially pure (*i.e.*, substantially pure Form I). In particular embodiments of compositions comprising a polymorphic form of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate present in the composition is Formula II, Form I, disclosed herein. In certain embodiments, the composition includes at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% of Form I of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate.

[0176] In other embodiments of compositions comprising a polymorphic form disclosed herein, less than about 50%, less than about 40%, less than about 30%, less than about 20%, less than about 10%, less than about 5%, less than about 4%, less than about 3%, less than about 2% or less than about 1% of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate present in the composition are other polymorphs of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-

olate and/or impurities.

[0177] In yet other embodiments of compositions comprising the polymorphic forms disclosed herein, impurities make up less than about 5%, less than about 4%, less than about 3%, less than about 2% or less than about 1% of the total mass relative to the mass of the polymorphic forms present. Impurities may, for example, include by-products from synthesizing sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, contaminants, degradation products, other polymorphic forms, amorphous form, water, and solvents. In certain embodiments, impurities include by-products from the process of synthesizing sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate. In certain embodiments, impurities include contaminants from the process of synthesizing sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate. In certain embodiments, impurities include degradation products of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate. In certain embodiments, impurities include other polymorphic forms of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate. In certain embodiments, impurities include water or solvent. In certain embodiments of compositions comprising a polymorphic form disclosed herein, impurities are selected from the group consisting of by-products from synthesizing sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, contaminants, degradation products, other polymorphic forms, water, solvents and combinations thereof.

[0178] In yet other embodiments, the composition comprising Formula II, Form I disclosed herein has less than about 5%, less than about 4%, less than about 3%, less than about 2%, or less than about 1% by weight of amorphous or non-crystalline sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate.

[0179] In some embodiments, the term "substantially pure" or "substantially free" with

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