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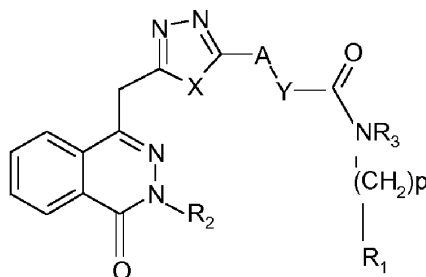
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[Continued on next page]

(54) **Title:** NOVEL IL-2/IL-15 RECEPTOR ANTAGONIST COMPOUNDS AND USES THEREOF FOR THE TREATMENT OF AUTOIMMUNE AND INFLAMMATORY DISEASES OR GRAFT REJECTION



(I)

(57) **Abstract:** Novel IL-2/IL-15 Receptor antagonist compounds and uses thereof for the treatment of autoimmune and inflammatory diseases or graft rejection Novel IL-2/IL-15 Receptor antagonist compounds and uses thereof for the treatment of autoimmune and inflammatory diseases or graft rejection. The invention relates to a compound of general formula (1) wherein X represents O, S or NR₄, wherein R₄ is alkyl; A is selected from S, SO, SO₂, NH and O; Y represents (CR₅R₆)_n or (CR₅R₆O)_n, wherein R₅ and R₆ identical or different are H or alkyl and n represents an integer from 1 to 15; R₁ represents a 5 to 10 membered aromatic or non-aromatic mono- or bicyclic, 1 optionally bridged ring, R₂ is C₁-C₄ alkyl; R₃ is H or alkyl; p is 0 or 1; or a pharmaceutically acceptable salt thereof. The compounds of the invention are inhibitors of the interactions of IL-2/15 to IL-2/15Rβ and hence useful in the treatment of an autoimmune or an inflammatory diseases and graft rejection.



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Novel IL-2/IL-15 Receptor antagonist compounds and uses thereof for the treatment of autoimmune and inflammatory diseases or graft rejection

5 FIELD OF THE INVENTION:

The present invention relates to novel compounds that are inhibitors of the interactions of IL-2/15 to IL-2/15R β as well as their uses, in particular for the treatment of autoimmune and inflammatory diseases and graft rejection.

10 BACKGROUND OF THE INVENTION:

There remain considerable unmet medical needs for inflammatory and autoimmune diseases such as rheumatoid arthritis, psoriasis and intestinal inflammatory diseases. Cytokine targeting is now established as a feasible method for treating such chronic inflammatory diseases and this is best exemplified by the blockade of tumor necrosis factor (TNF) α in
15 rheumatoid arthritis (RA), psoriasis and Crohn's diseases (Feldmann M and Maini RN, Nat Med 2003, 9:1245-1250). Interleukin(IL)-15, a 14-15 kDa cytokine belonging to the IL-2 cytokine family, has been simultaneously identified by two research groups as a T activating factor (Grabstein KH et al., Science 1994, 264: 965-968; Burton ID et al., Proc Nat Acad Sci USA 1994, 91, 4935-4939) and is involved in the differentiation and proliferation of NK and
20 T cells. High levels of IL-15 expression have been associated to the pathogenesis of autoimmune and inflammatory diseases like in Crohn's disease (Kirman I et al., Am J Gastroenterol 1996, 91: 1789-1794), psoriasis (Rückert R et al., J Immunol 2000, 165: 2240-2250), leukemias (Yamada Y et al., Leukemia and Lymphoma 1999,35:37-45), RA (McInnes IB and Liew FY, Immunology Today 1998, 19:75-79) and graft rejection (Pavlakakis M et al.,
25 Transplantation 1996, 62:543-545; Manfro RC et al., Transplant Proc 1997, 29: 1077-1078). In support of this view, several IL-15- or IL-15 receptor (IL-15R)-directed monoclonal antibodies and fusion proteins have been effective in ameliorating RA in animal models (Ruchatz H et al., J Immunol 1998, 160: 5654-5660; Ferrari-Lacraz S et al., J Immunol 2004, 173: 5818-5826; Wang D et al., Mol Immunol 2010, 47: 1535-1543). Moreover, the targeting
30 by siRNA of the IL-15R β chain which is also shared by IL-2 receptor was shown to be effective in reducing disease severity in adjuvant-induced arthritis rats (Zhang T et al., PLoS One 2013, 8:e78619), highlighting the interest of IL-2/15R β as a therapeutic target for the treatment of RA.

Thus, autoimmune and inflammatory diseases continue to be important pathologies in need of safe and efficacious treatments. To date no small molecule IL-2/15 antagonists have been reported. It would be desirable to develop orally available new chemical entities that are inhibitors of the interaction of IL-2/15 to IL-2/15R β .

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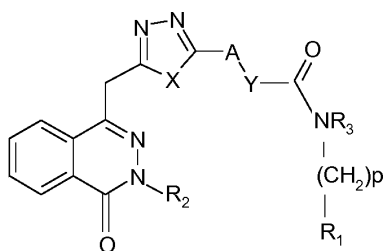
SUMMARY OF THE INVENTION:

The present invention relates to novel compounds inhibiting the interaction of IL-2/15 to IL-2/15R β and uses thereof, in particular for the treatment of autoimmune diseases and inflammatory diseases and graft rejection.

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DETAILED DESCRIPTION OF THE INVENTION:

The invention relates to compounds of general formula (1):



15

wherein

X represents O, S or NR₄, wherein R₄ is alkyl;

A is selected from S, SO, SO₂, NH and O;

20

Y represents (CR₅R₆)_n or (CR₅R₆O)_n, wherein R₅ and R₆ identical or different are H or alkyl and n represents an integer from 1 to 15;

R₁ represents a 5 to 10 membered aromatic or non-aromatic mono- or bicyclic, optionally bridged ring, optionally interrupted by one or two heteroatoms or heterogroups selected from O, S and NH and optionally substituted with one to four substituents selected from halo, hydroxy, alkyl, alkyloxy, amino, alkyl amino, dialkylamino, nitro, trifluoromethyl, aryl, alkyl-aryl, acyl, or aryloxy and azide;

25

R₂ is C₁-C₄ alkyl;

R₃ is H or alkyl;

p is 0 or 1;

or a pharmaceutically acceptable salt thereof.

In the general formula (1),

- Alkyl denotes a straight-chain or a branched group containing 1 to 6 carbon atoms. This also applies if the groups carry substituents or occur as substituents of other radicals, for example in O-alkyl radicals, S-alkyl radicals etc. Examples of suitable alkyl radicals are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, hexyl, etc.
 - Aryl denotes an aromatic carbon ring comprising from 6 to 10 carbon atoms,
 - Cycloalkyl denotes a cyclic alkyl group comprises 3 to 10 carbon atoms and include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl,
 - Halo denotes a halogen atom selected from the group consisting of fluoro, chloro, bromo and iodo;
 - R₁ may be a saturated or unsaturated aromatic or non aromatic mono- or bicyclic optionally bridged structure, consisting of carbon atoms. Preferred carbocyclic saturated groups are cyclohexyl and adamantyl. Preferred aromatic carbocyclic groups are phenyl and naphthyl.
- R₁ may further be a heterocyclic structure as defined above, e.g. furyl, tetrahydrofuryl, thienyl, tetrahydrothienyl, pyrrolyl, pyridinyl, pyrrolidinyl, piperidyl, pyrimidyl, pyrazinyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl or pyranyl.
- Acyl groups are groups of formula COR' where R' is as defined previously for alkyl or aryl.

Preferred groups of compounds are those wherein one or several of the following features are present:

- X represents NR₄, wherein R₄ is C₁-C₄ alkyl, preferably methyl;
- A represents S;
- Y represents (CH₂)_n with n ranging from 5 to 10 ;
- R₂ is methyl ;
- R₃ is H ;
- p is 0 and R₁ is phenyl, optionally substituted with 1 to 3 substituents selected from chloro, bromo, fluoro, hydroxyl and methoxy in the ortho or para position; or
- p is 0 and R₁ is naphthyl, optionally substituted with 1-3 substituents selected from chloro, bromo, fluoro, hydroxyl and methoxy in the ortho or para position; or
- p is 0 and R₁ is adamantyl, optionally substituted with 1-3 substituents selected from chloro, bromo, fluoro, hydroxyl and methoxy in the ortho or para position; or

- p is 1 and R₁ is furyl, preferably 2-furyl, optionally substituted with 1-3 substituents selected from chloro, bromo, fluoro, hydroxyl and methoxy

Preferred R₁ groups are the following: 2,4- dichlorophenyl, 2,4- difluorophenyl, 2,4-
5 dibromophenyl, 2,4- dihydroxyphenyl, 2-hydroxyphenyl, 2-chlorophenyl, 2-hydroxy-4-
methoxyphenyl and 4-azidophenyl.

Most preferred compounds are the following:

- N-(2,4-dichlorophenyl)-2-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-
yl)methyl)-4H-1,2,4-triazol-3-yl)sulfonyl)acetamide;
- 10 2-methyl-4-((4-methyl-5-(methylthio)-4H-1,2,4-triazol-3-yl)methyl)phthalazin-1(2H)-
one;
- N-(adamantan-1-yl)-2-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-
yl)methyl)-4H-1,2,4-triazol-3-yl)thio)acetamide;
- 2-methyl-4-((4-methyl-5-(methylsulfinyl)-4H-1,2,4-triazol-3-yl)methyl)phthalazin-
15 1(2H)-one;
- 2-methyl-4-((4-methyl-5-(methylsulfonyl)-4H-1,2,4-triazol-3-yl)methyl)phthalazin-
1(2H)-one;
- N-(2,4-dichlorophenyl)-2-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-
yl)methyl)-4H-1,2,4-triazol-3-yl)thio)acetamide;
- 20 N-(2,4-dichlorophenyl)-4-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-
yl)methyl)-4H-1,2,4-triazol-3-yl)thio)butanamide;
- N-(2,4-dichlorophenyl)-6-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-
yl)methyl)-4H-1,2,4-triazol-3-yl)thio)hexanamide;
- N-(2,4-dichlorophenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-
25 yl)methyl)-4H-1,2,4-triazol-3-yl)thio)octanamide;
- N-(2,4-dibromophenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-
yl)methyl)-4H-1,2,4-triazol-3-yl)thio)octanamide;
- N-(2,4-difluorophenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-
yl)methyl)-4H-1,2,4-triazol-3-yl)thio)octanamide;
- 30 N-(2,4-dihydroxyphenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-
yl)methyl)-4H-1,2,4-triazol-3-yl)thio)octanamide;

- N-(2-hydroxyphenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)octanamide;
- N-(2-hydroxy-4-methoxyphenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)octanamide;
- 5 N-(4-azidophenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)octanamide;
- N-(adamantan-1-yl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)octanamide;
- N-(2-Chloro-4-methylphenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)octanamide;
- 10 Ethyl 3-(8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)octanamido)benzoate;
- N-(2,4-dichlorophenyl)-11-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)undecanamide;
- 15 N-(2-chlorophenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)undecanamide;
- N-(3-chlorophenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)undecanamide;
- N-(4-chlorophenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)undecanamide;
- 20 N-(2-chlorophenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)undecanamide;
- 11-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)-N-(naphthalen-1-yl)undecanamide;
- 25 N-(furan-2-ylmethyl)-11-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)undecanamide;
- 4-((5-(decylthio)-4-methyl-4H-1,2,4-triazol-3-yl)methyl)-2-methylphthalazin-1(2H)-one;
- N-(2,4-dichlorophenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)oxy)octanamide;
- 30 N-(adamantan-1-yl)-2-(((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)methyl)benzamide;
- N-(adamantan-1-yl)-4-(((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)methyl)benzamide;

Methyl 2-(((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)methyl)benzoate;

N-(2,4-dichlorophenyl)-4-(((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)methyl)benzamide;

5 N-(2,4-dichlorophenyl)-11-(((4-methyl-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)undecanamide;

N-(2,4-dichlorophenyl)-11-(((5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-1,3,4-oxadiazol-2-yl)thio)undecanamide;

10 N-(2,4-dichlorophenyl)-11-(((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)undecanamide;

N-(2,4-dichlorophenyl)-11-(((5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-1,3,4-oxadiazol-2-yl)thio)undecanamide;

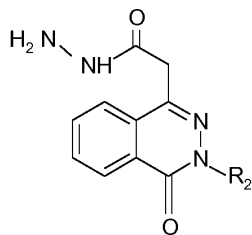
N-(2,4-dichlorophenyl)-7-(((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)heptanamide (compound C5).

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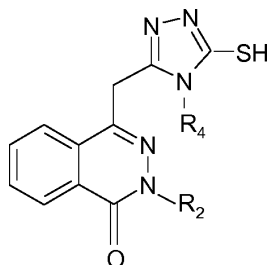
Compounds of formula (1) may be prepared using conventional procedures such as by the following illustrative methods in which the various substituents are as previously defined for the compounds of the formula (1) unless otherwise stated.

20 In particular, compounds of general formula (1) wherein A represents S, may be obtained by a method comprising the following steps:

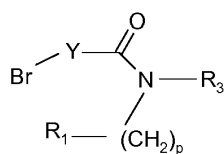
- Reacting a compound of formula (2)



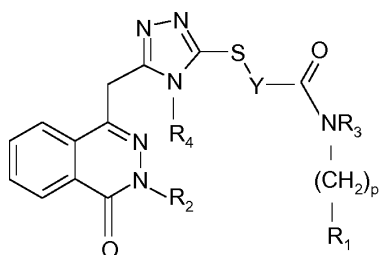
25 (i) either with $R_3\text{NCS}$ in the presence of a base in an appropriate solvent and under appropriate conditions in order to obtain a compound of general formula (4)



- 5 (ii) reacting the compound of general formula (4) with a compound of formula (5)

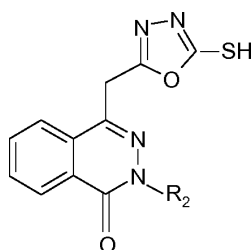


under appropriate conditions in order to obtain a compound of general formula (6)



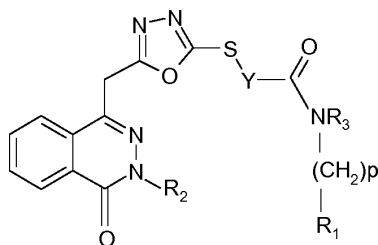
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- (iii) or with CS₂ in the presence of a strong base in an appropriate solvent under appropriate conditions in order to obtain a compound of general formula (7)



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- (iv) reacting the compound of general formula (7) with a compound of general formula (5) as defined above under appropriate conditions in order to obtain a compound of general formula (8):



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The following reaction conditions are preferably carried out for the steps above:

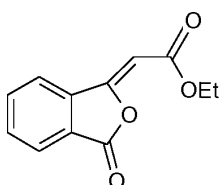
- (i) : 2eq R₃NCS; 3 eq Et₃N/ EtOH/5 h
 (ii) : 3eq K₂CO₃/DMF/24h/RT
 (iii) : 2eq KOH/CS₂/reflux/18 h
 (iv) : 3eq K₂CO₃/DMF/24h/RT

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The compound of general formula (2) as defined above may be obtained by a method comprising the following steps:

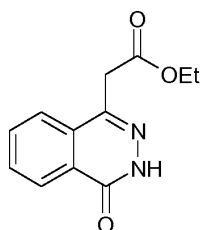
- (v) Reacting phthalic anhydride with ethyl (triphenylphosphoranylidene)acetate under appropriate conditions so as to obtain a compound of formula (9):

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- (vi) Reacting the compound obtained thereby with NH₂NH₂ under appropriate conditions so as to obtain a compound of formula (10)

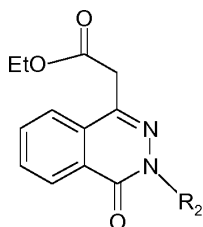


(vii) reacting the compound (10) with a compound of general formula(11)



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wherein X is halogen, preferably iodine under appropriate conditions so as to obtain a compound of general formula (12)



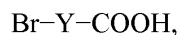
10 (viii) Reacting the compound (12) with NH_2-NH_2 under appropriate conditions so as to obtain the compound of formula (2) above.

The following reaction conditions are preferably carried out for the steps above:

- 15 (v) : 1.1 eq ethyl (triphenylphosphoranylidene)acetate /toluene/3h/rt/15min reflux
 (vi) : 1eq NH_2NH_2 /THF/30min/rt
 (vii) : 5eq R_2X ;3eq K_2CO_3 /DMF
 (viii) : 4eq NH_2NH_2 ;H₂O/EtOH/2h/reflux

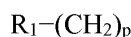
The compound of formula (5) may be obtained by the following steps

20 (ix) reacting a compound of general formula(13):



with $COCl_2$ so as to obtain the corresponding acid halide, and

25 (x) reacting the acid halide with a compound of formula general formula (14) :



5 in the presence of a base under appropriate conditions so as to obtain the compound of formula (5) which is then purified.

The following reaction conditions are preferably carried out for the steps above:

(ix) : 1.2eq COCl₂/DMFcat/DCM/24h/20-25°C

(x) : Et₃N/THF/1h/20-25°C

10 The abbreviations above have the general meaning in the art.

Hereinafter all references to compounds of formula (1) include references to salts, solvates and complexes thereof and to solvates and complexes of salts thereof.

Pharmaceutically acceptable salts of the compounds of formula (1) include the acid addition salts thereof. Suitable acid addition salts are formed from acids, which form non-toxic salts. Examples include the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, malcate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, 20 palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, saccharate, stearate, succinate, tartrate, tosylate and trifluoroacetate and xinafoate salts. et le sel de Tris ?

For a review on suitable salts, see "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

Pharmaceutically acceptable salts of compounds of formula (1) may be prepared by one or 25 more of three methods:

- (i) by reacting the compound of formula (1) with the desired acid or base; and
- (ii) by converting one salt of the compound of formula (1) to another by reaction with an appropriate acid or base or by means of a suitable ion exchange column.

The reactions are typically carried out in solution. The resulting salt may precipitate out 30 and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionization in the resulting salt may vary from completely ionized to almost non-ionized.

The compounds of the invention may exist in both unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising the compound of the

invention and a stoichiometric amount of one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

Included within the scope of the invention are complexes such as clathrates, drug-host inclusion complexes wherein, in contrast to the aforementioned solvates, the drug and host are present in stoichiometric or non-stoichiometric amounts. Also included are complexes of the drug containing two or more organic and/or inorganic components, which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be ionised, partially ionized, or non-ionized. For a review of such complexes, see J Pharm Sci, 64 (8), 1269-1288 by Halebian (August 1975).

The compounds of the invention include compounds of formula (1) as hereinbefore defined, including all polymorphs and crystal habits thereof, prodrugs and isomers thereof whenever relevant.

So-called 'pro-drugs' of the compounds of formula (1) are also within the scope of the invention. Thus certain derivatives of compounds of formula (1) which may have little or no pharmacological activity themselves can, when administered into or onto the body, be converted into compounds of formula (1) having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as 'prodrugs'. Further information on the use of prodrugs may be found in 'Pro-drugs as Novel Delivery Systems, Vol. 14, ACS Symposium Series (T. Higuchi and W. Stella) and 'Bioreversible Carriers in Drug Design', Pergamon Press, 1987 (ed. E. B Roche, American Pharmaceutical Association).

Prodrugs in accordance with the invention can, for example, be produced by replacing appropriate functionalities present in the compounds of formula (1) with certain moieties known to those skilled in the art as 'pro-moieties' as described, for example, in "Design of Prodrugs" by H. Bundgaard (Elsevier, 1985).

Some examples of prodrugs in accordance with the invention include amides thereof, for example, a compound wherein, as the case may be the hydrogen of the amino functionality of the compound of formula (1) is/are replaced by (C1-C10)alkanoyl.

Further examples of replacement groups in accordance with the foregoing examples and examples of other prodrug types may be found in the aforementioned references.

Moreover, certain compounds of formula (1) may themselves act as prodrugs of other compounds of formula (1).

Also included within the scope of the invention are metabolites of compounds of formula (1), that is, compounds formed in vivo upon administration of the drug, such as a primary amino derivatives thereof or phenol derivative thereof, or carboxylic acid derivative

Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, e.g. D₂O.

The compounds of formula (1), their pharmaceutically acceptable salts and/or derived forms, are valuable pharmaceutically active IL-15 antagonists.

5 The pharmacological activity of the compounds may be assessed using the following methods:

- SPR (assessment of K_d (μM)):

10 The SPR experiments are performed at 25°C with a BIAcore 3000 biosensor (GE Healthcare, Chalfont St Giles, UK). Recombinant IL-15 or RLI (an IL-15 superagonist, Mortier E et al., J Biol Chem 2006, 281: 1612-1619) are covalently linked to CM5 sensor chips using the amine coupling method in accordance with the manufacturer's instructions, and the binding of compounds at 100μM or in increasing concentrations is monitored. Analysis of sensorgrams is performed using BIAeval 4.1 software.

- In vitro HTRF (% of inhibition):

15 HTRF assays are performed using the donor, Lumi4®-Tb-NHS cryptate (Tb) conjugated to CF1 (a mouse anti-human IL-2Rβ mAb), and the acceptor, D2 conjugated to Streptavidin (Streptavidin-D2) (HTRF® Dye labeling kits, Cisbio). The donor excitation at 320 nm leads to energy emission at 620 nm that induces in close proximity (d<10 nm) the acceptor excitation and emission at 665 nm. The assays are carried out in a white 384 well
20 Small Volume™ HiBase Polystyrene Microplate (Greiner) at room temperature. After a 30min-pre-incubation period of biotinylated human IL-15 (Fluorokine®, R&D Systems) with compounds, recombinant human IL-2Rβ (R&D Systems) is added for a 30min-supplemental incubation time. Finally, the donor CF1-Tb and the acceptor Streptavidin-D2 are added to the mixture and incubated for 30min. Final concentrations are 100μM for
25 compounds and 20nM for biotinylated IL-15, IL-2Rβ, CF1-Tb and Streptavidin-D2 in PBS, 0.1% BSA 1% DMSO. The results are read in a Mithras reader (Berthold) at excitation 320nm and emission 620nm and 665nm. The HTRF signals are calculated as normalized fluorescence transfer value (ΔF): the fluorescence value at 665 nm (F_{665nm}) of the sample is divided by the fluorescence value at 620 nm of the sample. The resulting
30 value is subtracted by the background and divided by the background (see equation below).

$$\Delta F = \frac{(F_{665nmSample}/F_{620nmSample}) - (F_{665nmcontrol}/F_{620nmcontrol})}{(F_{665nmcontrol}/F_{620nmcontrol})}$$

- Inhibition of RLI-induced 32Dβ cell proliferation (assessment of IC₅₀(μM)) :

32D β cells are cultured in RPMI-1640 medium containing 10% heat-inactivated fetal calf serum and 2mM glutamine, supplemented with 0.4ng/ml murine IL-3, 10 μ M 2-mercaptoethanol and 250 μ g/ml geneticin. The proliferation response of 32D β cells to RLI is assessed by Alamar blue reduction assay (AbDSerotec). Cells are starved in the culture medium without cytokine during 4h. They are plated at 1x10⁴ cells in 100 μ l and cultured in the medium supplemented with 100pM RLI, previously preincubated for 30min with increasing concentrations of compounds. Alamar blue (10 μ M) is added to each well and the fluorescence was measured at excitation 560nm and emission 590nm using Fluoroskan Ascent FL reader (Thermo Electro Corporation) after a 6h-incubation period at 37°C.

10 The compounds of the invention are suitable for the therapy and prophylaxis of autoimmune diseases and inflammatory diseases.

Accordingly, the invention also relates to a pharmaceutical composition comprising a compound of the invention and a pharmaceutically acceptable carrier or excipient.

"Pharmaceutically" or "pharmaceutically acceptable" refer to molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to a mammal, especially a human, as appropriate. A pharmaceutically acceptable carrier or excipient refers to a non-toxic solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type.

20 The compounds of the invention may also be combined with sustained-release matrices, such as biodegradable polymers, to form therapeutic compositions.

The pharmaceutical compositions of the invention are useful for the prevention or treatment of an autoimmune or inflammatory disease.

In addition to the compounds of the invention, the pharmaceutical composition may further comprise an additional active ingredient for the treatment of the same disease as the compound of the invention or a different disease.

25 The composition of the invention preferably comprises a combination of a compound of the invention and an additional active ingredient for the treatment of an autoimmune or an inflammatory disease and a pharmaceutically acceptable carrier.

The active ingredients are for administered simultaneous or sequential administration.

30 The compounds of the invention may be administered by any suitable route.

Thus, a compound of the invention may be formulated as a pharmaceutical composition for oral, buccal, intranasal, parenteral (e. g. intravenous, intramuscular or subcutaneous), topical, or rectal administration or in a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical composition may take the form of, for example, a tablet or capsule prepared by conventional means with a pharmaceutically acceptable excipient such as a binding agent (e. g., pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); filler (e. g., lactose, microcrystalline cellulose or calcium phosphate); lubricant (e. g., magnesium stearate, talc or silica);
5 disintegrant (e. g., potato starch or sodium starch glycolate); or wetting agent (e. g., sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of a, for example, solution, syrup or suspension, or they may be presented as a dry product for constitution with water or other
10 suitable vehicle before use.

Such liquid preparations may be prepared by conventional means with a pharmaceutically acceptable additive such as a suspending agent (e. g., sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agent (e. g., lecithin or acacia); non-aqueous vehicle (e. g., almond oil, oily esters or ethyl alcohol); and preservative (e. g., methyl
15 or propyl p-hydroxybenzoates or sorbic acid).

For buccal administration, the composition may take the form of tablets or lozenges formulated in conventional manner. A compound of the present invention may also be formulated for sustained delivery according to methods well known to those of ordinary skill in the art.

20 Examples of such formulations can be found in United States Patents 3,538, 214, 4,060, 598,4, 173,626, 3,119, 742, and 3,492, 397, which are herein incorporated by reference in their entirety.

A compound of the invention may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations
25 for injection may be presented in unit dosage form, e.g., in ampules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain a formulating agent such as a suspending, stabilizing and/or dispersing agent. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e. g. ,
30 sterile pyrogen-free water, before use parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

The present invention further relates to a method of suppressing the immune response in a subject by administering a dose of an antagonist of the invention, and thereby modulating IL-15 dependent immune responses.

This method may be used to treat a subject who is suffering from an autoimmune disease, including but not limited to the following: (1) a rheumatic disease such as rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, scleroderma, mixed connective tissue disease, dermatomyositis, polymyositis, Reiter's syndrome or Behcet's disease (2) type II diabetes (3) an autoimmune disease of the thyroid, such as Hashimoto's thyroiditis or Graves' Disease (4) an autoimmune disease of the central nervous system, such as multiple sclerosis, myasthenia gravis, or encephalomyelitis (5) a variety of pemphigus, such as pemphigus vulgaris, pemphigus vegetans, pemphigus foliaceus, Senechal-Usher syndrome, or Brazilian pemphigus, (6) psoriasis, and (7) inflammatory bowel disease (e.g., ulcerative colitis or Crohn's Disease).

The compounds of the invention may also be useful in the treatment of acquired immune deficiency syndrome (AIDS).

Another credible use for a compound of the invention includes the treatment of late phase HTLV (human T-cell lymphotropic virus) I-induced adult T-cell leukemia-lymphoma, See Burton et al., Proc. Natl. Acad. Sci., 91:4935 (1994).

Similarly, the method may be used to treat a subject who has received a transplant of biological materials, such as an organ, tissue, or cell transplant. For example, a compound of the invention may be particularly suitable, in promoting graft survival (allograft or xenograft) and in treating subjects with graft versus host disease.

Typically, a compound of the invention is administered in a therapeutically effective amount. By "therapeutically effective amount" is meant a sufficient amount of the antagonist of the invention to treat and/or to prevent the disease at a reasonable benefit/risk ratio applicable to any medical treatment. It will be understood that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular subject will depend upon a variety of factors including the disease being treated and the severity of the disease; activity of the specific compound employed; the specific composition employed, the age, body weight, general health, sex and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific polypeptide employed; and like factors well known in the

medical arts. For example, it is well known within the skill of the art to start doses of the compound at levels lower than those required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved. However, the daily dosage of the products may be varied over a wide range from 0.01 to 1,000 mg per adult per day.

5 Preferably, the compositions contain 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100, 250 and 500 mg of the active ingredient for the symptomatic adjustment of the dosage to the subject to be treated. A medicament typically contains from about 0.01 mg to about 500 mg of the active ingredient, preferably from 1 mg to about 100 mg of the active ingredient. An effective amount of the drug is ordinarily supplied at a dosage level from 0.0002 mg/kg to

10 about 20 mg/kg of body weight per day, especially from about 0.001 mg/kg to 7 mg/kg of body weight per day. These dosages are based on an average human subject having a weight of about 65 kg to 70 kg. The physician will readily be able to determine doses for subjects whose weight falls outside this range, such as infants and the elderly.

For the avoidance of doubt, references herein to "treatment" include references to

15 curative, palliative and prophylactic treatment.

The subject may be a human patient or an animal, preferably a mammal.

The invention will be further illustrated by the attached figure, representing the inhibitory effect of representative compounds of the invention *versus* their concentration, and the examples. However, these examples and figure should not be interpreted in any way as

20 limiting the scope of the present invention.

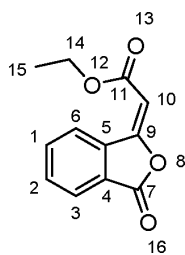
The following examples illustrate the preparation of the compounds of the formula (1) and their pharmacological properties

Preparation of ethyl [(E)-3-oxo-1,3-dihydroisobenzofuran-1-ylidene]acetate :

25 C. Niebel, and al, Eur. J. Org. Chem., 2008, 3691-3697

Ethyl (triphenylphosphoranylidene)acetate (9.305 g, 26.8 mmol, 1.1 eq) is added portionwise for 10 minutes to a suspension of phthalic anhydride (3.705 g, 24.5 mmol, 1 eq) in toluene (150 mL). Once completion of the addition, the stirring is maintained for 3 hours at 20°C then the mixture is refluxed for 1 hour until formation of a dark red solution. The

30 mixture is concentrated in vacuum at 40°C. The residue is dissolved in dichloromethane and then adsorbed on silica to finally be eluted on silice with dichloromethane. The pure product is obtained after concentration of the organic fractions. Only the E isomer is isolated.

Chemical Formula: $C_{12}H_{10}O_4$

Molecular Weight: 218.21

Yield : 88 %

Rf : 0.9 (DCM)

¹H NMR (400 MHz in $CDCl_3$) : δ (ppm) 9.01 (dt, 3J = 8 Hz, 4J = 0.9 Hz, 1H, H-6) ; 7.93 (ddd, 3J = 7.7 Hz, 4J = 1.2 Hz, 1H, H-3) ; 7.78 (ddd, 3J = 8.6 Hz, 3J = 7.4 Hz, 4J = 1.2, 1H H-1) ; 7.67 (ddd, 1H, 3J = 7.4 Hz, 3J = 7.4 Hz, 4J = 0.9 Hz, H-2) ; 6.10 (s, 1H, H-10) ; 4.27 (q, 2H, H-14) ; 1.34 (t, 3H, H-15).

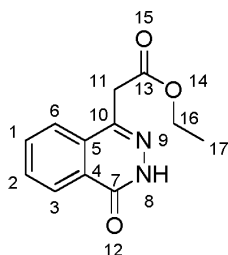
¹³C NMR (100 MHz in $CDCl_3$) : δ (ppm) 165.7 (C-7) ; 165.6 (C-11) ; 157.9 (C-9) ; 136.2 (C-5) ; 135.3 (C-1) ; 132.5 (C-2) ; 128.3 (C-6) ; 126.6 (C-4) ; 125.4 (C-3) ; 102.5 (C-10) ; 61.0 (C-14) ; 14.3 (C-15).

HRMS-MALDI : calcd for $C_{12}H_{11}O_4$ [M+H]⁺ : 219.0652, found : 219.0644.

Mp : 71.1°C (cyclohexane)

Preparation of ethyl 2-(3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)acetate :

To a solution of [(E)-3-oxo-1,3-dihydroisobenzofuran-1-ylidene]acetate (4.34 g, 20 mmol, 1 eq) in THF (80 mL), is added a 1 M solution of hydrazine in THF. The mixture is then heated to reflux for 15 minutes. The mixture was finally concentrated to obtain a white solid. The product is recrystallized in toluene.

Chemical Formula: $C_{12}H_{12}N_2O_3$

Molecular Weight: 232.24

Yield : 99 %, white solid

Rf : 0.26 (PE/EtOAc, 6/4)

¹H NMR (400 MHz in $CDCl_3$) : δ (ppm) 11.3 (s, 1H, H-8) ; 8.49 (dd, 3J = 7.7 Hz, 4J = 1.2 Hz, 1H, H-3) ; 7.83 (ddd, 3J = 8.2 Hz, 3J = 7.5 Hz, 4J = 1.4 Hz, 1H, H-1) ; 7.78 (ddd, 3J = 8.3 Hz, 3J = 7.4 Hz, 4J = 1.3, 1H, H-2) ; 7.73 (dd, 1H, 3J = 8.3 Hz, 4J = 0.7 Hz, H-6) ; 4.18 (q, 3J = 7.2 Hz, 2H, H-16) ; 3.98 (s, 2H, H-11) ; 1.22 (t, 3J = 7.2 Hz, 3H, H-17).

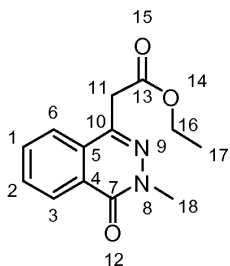
¹³C NMR (100 MHz in CDCl₃) : δ (ppm) 169.7 (C-13) ; 160.9 (C-7) ; 141.8 (C-10) ; 133.8 (C-1) ; 131.7 (C-2) ; 130.0 (C-5) ; 128.2 (C-4) ; 127.2 (C-3) ; 124.8 (C-6) ; 61.6 (C-16) ; 39.1 (C-11) ; 14.2 (C-17).

HRMS-MALDI : calcd for C₁₂H₁₃N₂O₃ [M+H]⁺ : 233.0921, found : 233.0931.

5 Mp : 180.3°C (toluene)

Procedure for N-alkylation of ethyl 2-(3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)acetate :

To a suspension of dry K₂CO₃ (7.77 g, 55.5 mmol, 3 eq) in DMF (80 mL) is added
10 phthalazinone (4.23 g, 18.5 mmol, 1 eq). Methyl iodide is then added (11 mL, 175 mmol, 9.5 eq). Once completion of the addition, stirring is maintained for 3 hours at 20°C then the mixture is quenched with a saturated solution of NH₄Cl (200 mL). The product is extracted with AcOEt. The organic layers are washed with water then brine, drying over MgSO₄ and concentrated in vacuo to give a solid residue which is purified by column chromatography
15 on silica gel (eluent : PE/AcOEt ; 8/2).



Chemical Formula: C₁₃H₁₄N₂O₃
Molecular Weight: 246.27

Yield : 95 %, white solid

R_f : 0.26 (PE/Ethyl Acetate, 8/2)

20 ¹H NMR (400 MHz in CDCl₃) : δ (ppm) 8.47 (m, 1H, H-6) ; 7.82-7.68 (m, 3H, H-3, H-2, H-1) ; 4.20 (q, 3J = 7.2, 2H, H-11) ; 3.96 (s, 2H, H-11) ; 3.84 (s, 3H, H-18) ; 1.24 (t, 3H, 3J = 7.2, H-17).

¹³C NMR (100 MHz in CDCl₃) : δ (ppm) 169.9 (C-13) ; 159.7 (C-7) ; 140.4 (C-10) ; 133.1 (C-1) ; 131.1 (C-2) ; 129.6 (C-5) ; 128.0 (C-4) ; 127.3 (C-3) ; 124.6 (C-6) ; 61.6 (C-16) ; 39.5 (C-18) ; 39.1 (C-11) ; 14.3 (C-17).

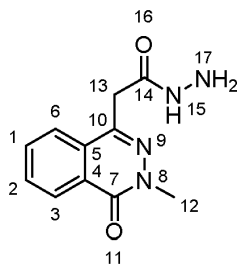
25 HRMS-MALDI : calcd for C₁₃H₁₅N₂O₃ [M+H]⁺ : 247.1077, found : 247.1086.

Mp : 86.3 °C (toluene)

Procedure for the preparation of hydrazide 2-(3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)acetohydrazide:

To a 1M solution of 2-(3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)acetate (1.56 g, 6.3 mmol, 1 eq), in EtOH (6 mL), is added hydrazine monohydrate (2 mL, 39.6 mmol, 6.3 eq).

- 5 The solution is heated at reflux during 6 h and the resulting suspension is cooled to 20°C and filtered. The resulting white powder is washed with Et₂O and is directly used in the next step without further purification.



Chemical Formula: C₁₁H₁₂N₄O₂

Molecular Weight: 232.24

Yield : 95 %, white powder

- 10 R_f : 0.35 (DCM/MeOH , 95/5)

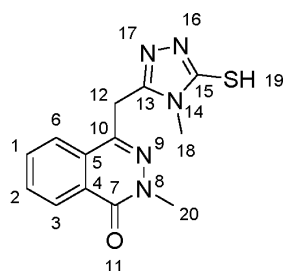
¹H NMR (400 MHz in DMSO) : δ (ppm) 9,36 (bs, 1H) ; 8,28 (m, 1H) ; 7,96-7.81 (m, 3H) ; 4.2 (bs, 2H) ; 3,77 (s, 2H) ; 3,70 (s, 3H).

HRMS-MALDI : calcd for C₁₁H₁₃N₄O₂ [M+H]⁺ : 233.1033, found : 233.1035

- 15 **Procedure for the preparation of 4-((5-mercapto-4-methyl-4H-1,2,4-triazol-3-yl)methyl)-2-methylphthalazin-1(2H)-one.**

U. Salgın-Gökşen, and al, Bioorg & Med Chem, 15 (17), 2007, 5738–5751

- 20 To a suspension of 2-(3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)acetohydrazide (2.76 g, 11.9 mmol, 1 eq) in EtOH (28 mL) is added methylisothiocyanate (4.54 g, 62 mmol, 5 eq) and the reaction mixture is heated to reflux under vigorous stirring during 8 h. The resulting suspension is cooled to 20°C and filtered. The white powder obtained is then washed with Et₂O and can be directly used in the next step without further purification.



Chemical Formula: $C_{13}H_{13}N_5OS$

Molecular Weight: 287.34

Yield : 99 % white powder

Rf: 0.23 (DCM/MeOH, 98/2)

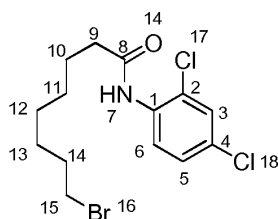
- 5 ^1H NMR (400 MHz in DMSO) : δ (ppm) : 13.56 (bs, 1H, H-19) ; 8.30 (m, 1H, H-3) ; 7.97-7.84 (m, 3H, H-6, H-1, H-2) ; 4.51 (s, 2H, H-12) ; 3.67 (s, 3H, H-20) ; 3.49 (s, 3H, H-18).
 ^{13}C NMR (100 MHz in DMSO) : δ (ppm) : 166.9 (C-15) ; 158.4 (C-7) ; 149.6 (C-13) ; 140.3 (C-10) ; 133.2 (C-1) ; 131.9 (C-2) ; 128.7 (C-5) ; 127.1 (C-4) ; 126.0 (C-3) ; 125.6 (C-6) ; 39.0 (C-20) ; 30.2 (C-18) ; 28.3 (C-12).
 10 HRMS-ESI : calcd for $C_{13}H_{14}N_5OS$ [M+H]⁺ : 288.09136, found 288.09189

General procedure 1 : Preparation of bromoalkylamides (B. Z. Lu and al, Organic Letters, 2006, 8(16), 3573-3575)

- The bromoacid reagent (1 eq) is dissolved in anhydrous DCM and oxalyl chloride (1.2 eq) is added at 25 °C. A catalytic amount of DMF is then added. The mixture is stirred vigorously
 15 under argon atmosphere for 1 h. The mixture is then stirred for another 24 h. Bromoacid complete conversion is determined by the ^1H NMR in deuterated benzene after concentration in vacuum. The mixture is then concentrated to dryness and the residual acyl chloride is taken up in anhydrous THF. The amine reagent (1.2 eq) is then added followed by triethylamine (5 eq). After completion of the reaction, water was added and the aqueous phase is extracted
 20 with Et₂O. The organic phase is dried, dried over MgSO₄ and concentrated under vacuum. The amide product is then purified by column chromatography on silica gel.

Example 1 : Preparation of 8-bromo-N-(2,4-dichlorophenyl)octanamide

- 25 The title compound was obtained starting from 2,4-dichloroaniline (5 mmol, 0.8 g), 8-bromooctanoyl chloride (6 mmol, 1 mL) and triethylamine (5 mmol, 3.6 mL) following procedure 1.



Chemical Formula: $C_{14}H_{18}BrCl_2NO$

Molecular Weight: 367,11

Yield : 85 %

Rf : 0.61 (PE/Et₂O, 7/3)

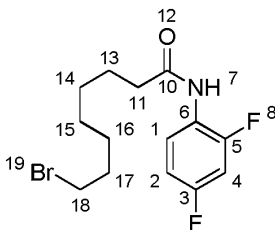
¹H NMR (300 MHz in CDCl₃) : δ (ppm) : 8.31 (d, 3J = 8.9 Hz, 1H, H-6) ; 7.56 (bs, 1H, H-7) ; 7.35 (d, 4J = 2.4 Hz, 1H, H-3) ; 7.23 (dd, 3J = 8.9 Hz, 4J = 2.4 Hz, 1H, H-5) ; 3.39 (t, 3J = 6.8 Hz, 2H, H-15) ; 2.41 (t, 3J = 7.4 Hz, 2H, H-9) ; 1.84 (m, 2H, H-14) ; 1.73 (m, 2H, H-10) ; 1.51-1.29 (m, 6H, H-13, H-12, H-11).

¹³C NMR (75 MHz in CDCl₃) : δ (ppm) : 171.3 (C-8) ; 133.5 (C-1) ; 129.0 (CIV) ; 128.7 (C-3) ; 127.9 (C-5) ; 123.1 (CIV) ; 122.4 (C-6) ; 37.9 (C-9) ; 33.9 (C-15) ; 32.8 (C-14) ; 29.0-28.6-28.0 (C-13, C-12, C-11) ; 25.4 (C10).

LRMS-Cl : [M+H]⁺ : 366.1, 368.1, 370.1 ; [M+NH₄]⁺ : 383.0, 385.0, 387.1

Example 2 : Preparation of 8-bromo-N-(2,4-difluorophenyl)octanamide

The title compound was obtained starting from 2,4-difluoroaniline (5 mmol, 0.49 mL), 8-bromooctanoyl chloride (6 mmol, 1 mL) and triethylamine (5 mmol, 3.6 mL) following general procedure 1.



Chemical Formula: $C_{14}H_{18}BrF_2NO$

Molecular Weight: 334,20

Yield : 45 %

Rf : 0.50 (DCM)

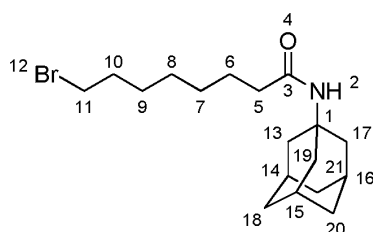
NMR ¹H (300 MHz) : δ (ppm) 8.19 (m, 1H, H-4) ; 7.35 (bs, 1H, H-7) ; 6.83 (m, 2H, H-1, H-2) ; 3.39 (t, 3J = 6.8 Hz, 2H, H-18) ; 2.38 (t, 3J = 7.4 Hz, 2H, H-11) ; 1.84 (m, 2H, H-17) ; 1.71 (m, 2H, H-13) ; 1.49-1.27 (m, 6H, H-14, H-15, H-16).

13C NMR (75 MHz in CDCl₃) : δ (ppm) 171.3 (C-10) ; 158.6 (dd, 1JC-F = 245.9 Hz, 3JC-F = 11.5 Hz, C-FIV) ; 152.6 (dd, 1JC-F = 245.8 Hz, 3JC-F = 11.6 Hz, C-FIV) ; 123.2 (d, 3JC-F = 8.3 Hz, C-1), 122.7 (d, 2JC-F = 8.5 Hz, C-6) ; 111.2 (d, 2JC-F 20.4 Hz, C-2) ; 103.6 (dd, 2JC-F = 25.2 Hz, 2JC-F = 25.2 Hz, C-4) ; 37.6 (C-11) ; 34.0 (C-18) ; 32.8 (C-17) ; 29.0-28.6-
5 28.0 (C-16, C-15, C-14) ; 25.4 (C-13).

LRMS-Cl : [M+H]⁺ : 334.1, 336.1

Example 3: Preparation of 8-bromo-N-(adamant-1-yl)octanamide

The title compound was obtained starting from adamantanamine (5 mmol, 0.75 g), 8-bromooctanoyl chloride (6 mmol, 1 mL) and triethylamine (5 mmol, 3.6 mL) following
10 procedure 1.



Chemical Formula: C₁₈H₃₀BrNO

Molecular Weight: 356,34

Yield : The crude product obtained was directly used in the next step without further purification.

15 R_f : 0.30 (PE/DCM, 9/1)

¹H NMR (300 MHz in CDCl₃) : δ (ppm) 5.10 (bs, 1H, H-2) ; 3.39 (t, 3J = 7.8 Hz, 2H, H-11) ; 2.41 (t, 3J = 7.3 Hz, 2H, H-5) ; 1.95 (m, 6H, H-13, H-19, H-17) ; 1.81 (m, 2H) ; 1.70-1.50 (m, 9H) ; 1.50-1.20 (m, 8H).

LRMS-Cl : [M+H]⁺ : 356.1, 358.1

20

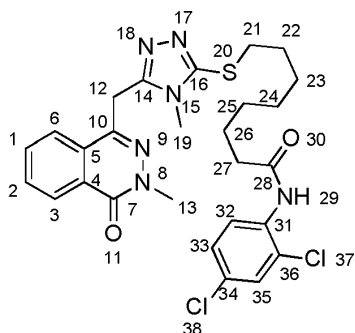
General procedure 2 : S-alkylation of 4-((5-mercapto-4-methyl-4H-1,2,4-triazol-3-yl)methyl)-2-methylphthalazin-1(2H)-one with bromoalkylamide

To a suspension of dry K₂CO₃ (3 eq) in DMF is added 4-((5-mercapto-4-methyl-4H-1,2,4-triazol-3-yl)methyl)-2-methylphthalazin-1(2H)-one (1 eq). Bromoalkylamides are then
25 added (1.2 to 3 eq). The stirring is maintained for 18 to 24 h at 20°C then the mixture is quenched with a saturated solution of NH₄Cl (150 mL). The product is extracted with AcOEt and the organic layers are washed with water then brine. After drying over MgSO₄, the

organic layer is concentrated in vacuum and the solid residue is purified by chromatography on silica gel (eluent: 98/2, DCM/MeOH).

Example 4: Preparation of N-(2,4-dichlorophenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)octanamide

The title compound was obtained starting from 4-((5-mercapto-4-methyl-4H-1,2,4-triazol-3-yl)methyl)-2-methylphthalazin-1(2H)-one (1 mmol, 0.29 g), 8-bromo-N-(2,4-dichlorophenyl)octanamide (3 mmol, 1.09 g) and K₂CO₃ (3 mmol, 0.42g) in 5 mL of DMF following procedure 2.



Chemical Formula: C₂₇H₃₀Cl₂N₆O₂S

Molecular Weight: 573.54

10

Yield : 74 %

R_f : 0.20 (DCM/MeOH, 98/2)

¹H NMR (400 MHz in CDCl₃) : δ (ppm) 8.43 (m, 1H, H-3) ; 8.31 (d, 3J = 9.0 Hz, 1H, H-32) ; 8.22 (m, 1H, H-6) ; 7.80 (m, 1H, H-1) ; 7.75 (m, 1H, H-2) ; 7.60 (bs, 1H, H-29) ; 7.35 (d, 4J = 2.4 Hz, 1H, H-35) ; 7.23 (dd, 3J = 9.0 Hz, 4J = 2.4 Hz, 1H, H-33) ; 4.47 (s, 2H, H-12) ; 3.79 (s, 3H, H-13) ; 3.54 (s, 3H, H-19) ; 3.18 (t, 3J = 7.3 Hz, 2H, H-21) ; 2.40 (t, 3J = 7.5 Hz, 2H, H-27) ; 1.73 (m, 4H, H-26, H-22) ; 1.48 – 1.29 (m, 6H, H-25, H-24, H-23).

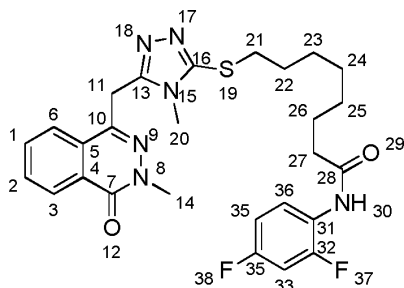
¹³C NMR (100 MHz in CDCl₃) : δ (ppm) 171.5 (C-28) ; 159.6 (C-7) ; 152.1 (C-16) ; 152.0 (C-14) ; 140.9 (C-10) ; 133.6 (C-31) ; 133.4 (C-1) ; 132.0 (C-2) ; 129.1 (C-5) ; 129.1 (C-36 or C-34) ; 128.8 (C-35) ; 128.1 (C-4) ; 128.0 (C-33) ; 127.2 (C-3) ; 125.4 (C-6) ; 123.3 (C-36 or C-34) ; 122.6 (C-32) ; 39.5 (C-13) ; 38.1 (C-27) ; 33.0 (C-21) ; 30.7 (C-19) ; 30.2 (C-12) ; 29.6 (C-22) ; 29.2 – 28.15 (C-23, C-24, C-25) ; 25.4 (C-26).

HRMS-MALDI : calcd for C₂₇H₃₀Cl₂N₆O₂S [M+H]⁺ : 573.1601, found 573.1583

25

Example 5: Preparation of N-(2,4-difluorophenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)octanamide

The title compound was obtained starting from 4-((5-mercapto-4-methyl-4H-1,2,4-triazol-3-yl)methyl)-2-methylphthalazin-1(2H)-one (1 mmol, 0.29 g), 8-bromo-N-(2,4-difluoro)octanamide (2 mmol, 0.26 g) and K₂CO₃ (3 mmol, 0.42g) in 5 mL of DMF following procedure 2.



Chemical Formula: C₂₇H₃₀F₂N₆O₂S
Molecular Weight: 540.63

5

Yield : 15 %

R_f : 0.23 (DCM/MeOH, 98/2)

¹H NMR (400 MHz in CDCl₃) : δ (ppm) 8.41 (m, 1H, H-3) ; 8.16 (m, 2H, H-33, H6) ; 7.77 (m, 1H, H-1) ; 7.74 (m, 1H, H-2) ; 6.82 (m, 2H, H-36, H-35) ; 4.46 (s, 2H, H-11) ; 3.77 (s, 3H, H-14) ; 3.54 (s, 3H, H-20) ; 3.15 (t, 3J = 7.03 Hz, 2H, H-21) ; 2.26 (t, 3J = 7.73 Hz, 2H, H-24) ; 1.68 (m, 4H, H-25, H-22) ; 1.45-1.25 (m, 6H, H-26, H-24, H-23).

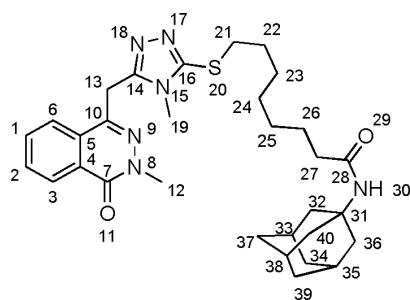
¹³C NMR (100 MHz in CDCl₃) : δ (ppm) 171.7 (C-28) ; 159.6 (C-7) ; 152.1 (C-16) ; 152.0 (C-13) ; 140.9 (C-11) ; 133.5 (C-1) ; 132.0 (C-2) ; 129.0 (C-5) ; 127.9 (C-4) ; 127.1 (C-3) ; 125.2 (C-6) ; 123.4, 111.4, 111.1, 103.9, 103.6, 103.3 (carbon of N-2,4-difluorophenyl) ; 39.5 (C-14) ; 37.2 (C-27) ; 33.5 (C-21) ; 30.7 (C-20) ; 30.0 (C-11) ; 29.4 (C-22) ; 29.2-27.7 (C-25, C-24, C-23) ; 25.3 (C-26).

HRMS-MALDI : calcd for C₂₇H₃₀F₂N₆O₂S [M+H]⁺ : 541.2192, found 541.2196

Example 6: Preparation of N-(adamantan-1-yl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)octanamide.

20

The title compound was obtained starting from 4-((5-mercapto-4-methyl-4H-1,2,4-triazol-3-yl)methyl)-2-methylphthalazin-1(2H)-one (1 mmol, 0.29 g), 8-bromo-N-(adamantan-1-yl)octanamide (3 mmol, 1.06 g) and K₂CO₃ (3 mmol, 0.42g) in 5 mL of DMF following procedure 2

Chemical Formula: C₃₁H₄₂N₆O₂S

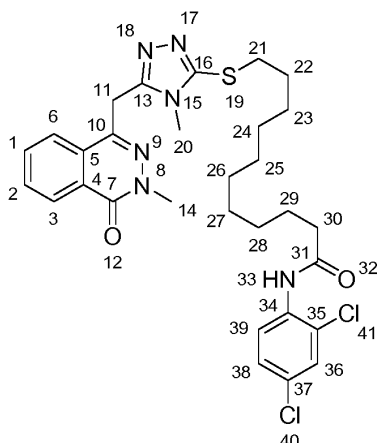
Molecular Weight: 562,77

Yield : 75 %

Rf: 0.31 (DCM/MeOH, 98/2)

- 5 ¹H NMR (400 MHz in CDCl₃) : δ (ppm) 8.37 (m, 1H, H-3) ; 8.18 (m, 1H, H-6) ; 7.76 (m, 1H, H-2) ; 7.71 (m, 1H, H-1) ; 5.26 (bs, 1H, H-30) ; 4.44 (s, 2H, H-13) ; 3.75 (s, 3H, H-12) ; 3.51 (s, 3H, H-19) ; 3.12 (m, 2H, H-21) ; 2.00 (m, 2H, H-27) ; 1.98 (3H, H-38, H-35, H-33) ; 1.94 (m, 6H, H-40, H-36, H-32) ; 1.65 (m, 2H, H-22) ; 1.61 (m, 6H, H-39, H-37, H-34) ; 1.51 (m, 2H, H-26) ; 1.42-1.13 (m, 6H, H-25, H-24, H-23).
- 10 ¹³C NMR (100 MHz in CDCl₃) : δ (ppm) 172.4 (C-28) ; 159.5 (C-7) ; 151.9 (C-16) ; 151.8 (C-14) ; 140.8 (C-10) ; 133.3 (C-1) ; 131.9 (C-2) ; 129.1 (C-5) ; 127.8 (C-4) ; 127.0 (C-3) ; 125.3 (C-6) ; 51.7 (C-31) ; 41.7 (C-40, C-36, C-32) ; 39.8 (C-12) ; 37.6 (C-27) ; 36.4 (C-39, C-37, C-34) ; 33.0 (C-21) ; 30.6 (C-19) ; 30.2 (C-13) ; 30.3-27.6 (C-25, C-24, C-23) ; 29.4 (C-38, C-35, C-33) ; 29.3 (C-22) ; 25.7 (C-26).
- 15 HRMS-MALDI : calcd for C₃₁H₄₂N₆O₂S [M+H]⁺ : 563.3163, found 563.3163

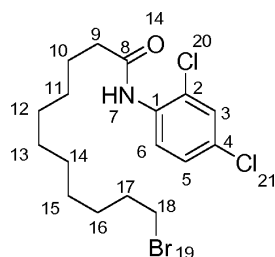
Example 7: Preparation of N-(2,4-dichlorophenyl)-11-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)undecanamide



Chemical Formula: $C_{30}H_{36}Cl_2N_6O_2S$
Molecular Weight: 615,6

Preparation of 11-bromo-N-(2,4-dichlorophenyl)undecanamide

The title compound was obtained starting from 2,4-dichloroaniline (5 mmol, 0.8 g), 11-bromoundecanoyl chloride (6 mmol, 1 mL) and triethylamine (5 mmol, 3.6 mL) following
5 general procedure 1.



Chemical Formula: $C_{17}H_{24}BrCl_2NO$
Molecular Weight: 409.19

Yield : 77 %

Rf : 0.50 (PE/Et₂O, 6/4)

¹H NMR (300 MHz in CDCl₃) : □ (ppm) 8.33 (d, 3J = 8.8 Hz, 1H, H-6) ; 7.56 (bs, 1H, H-7) ;
10 7.35 (d, 4J = 2.4 Hz, 1H, H-3) ; 7.21 (dd, 3J = 8.8 Hz, 4J = 2.4 Hz, 1H, H-5) ; 3.39 (t, 3J = 6.9 Hz, 2H, H-18) ; 2.41 (t, 3J = 7.4 Hz, 2H, H-9) ; 1.83 (m, 2H, H-17) ; 1.71 (m, 2H, H-10) ; 1.48-1.19 (m, 12H, H-16, H-15, H-14, H-13, H-12, H-11).

¹³C NMR (75 MHz in CDCl₃) : □ (ppm) : 171.4 (C-8) ; 133.5 (C-1) ; 128.9 (C-4) ; 128.7 (C-3) ; 127.9 (C-5) ; 123.1 (C-2) ; 122.4 (C-6) ; 37.9 (C-9) ; 34.1 (C-18) ; 32.9 (C-17) ; 30.2-27.6
15 (C-16, C-15, C-14, C-13, C-12, C-11) ; 25.5 (C-10).

LRMS-Cl : [M+H]⁺ : 407.1, 409.1, 411.1

Preparation of the title compound

The title compound was obtained starting from 4-((5-mercapto-4-methyl-4*H*-1,2,4-triazol-3-yl)methyl)-2-methylphthalazin-1(2*H*)-one (1 mmol, 0.29 g), 11-bromo-*N*-(2,4-dichlorophenyl)undecanamide (3 mmol, 1.21 g) and K₂CO₃ (3 mmol, 0.42g) in 5 mL of DMF following general procedure 2.

5

Yield : 65%

R_f : 0.33 (DCM/MeOH, 8/2)

¹H NMR (400 MHz in CDCl₃): □ (ppm) 8.42 (d, 3J = 7.5 Hz, 1H, H-3) ; 8.32 (d, 3J = 8.8 Hz, 1H, H-39) ; 8.21 (d, 3J = 7.9 Hz 1H, H-6) ; 7.79 (ddd, 3J = 8.2 Hz, 3J = 7.4 Hz, 4J = 1.5, 1H, H-1) ; 7.74 (ddd, 3J = 8.2 Hz, 3J = 7.8 Hz, 4J = 1.2, 1H, H-2) ; 7.60 (bs, 1H, H-33) ; 7.35 (d, 4J = 2.4 Hz, 1H, H-36) ; 7.22 (dd, 3J = 8.9 Hz, 4J = 2.4 Hz, 1H, H-38) ; 4.46 (s, 2H, H-11) ; 3.79 (s, 3H, H-14) ; 3.53 (s, 3H, H-20) ; 3.17 (t, 3J = 7.4 Hz, 2H, H-21) ; 2.41 (t, 3J = 7.3 Hz, 2H, H-30) ; 1.70 (m, 4H, H-23, H-22) ; 1.4-1.18 (m, 12H, H-28, H-27, H-26, H-25, H-24, H23).

¹³C NMR (100 MHz in CDCl₃) : □ (ppm) 171.5 (C-31) ; 159.5 (C-7) ; 152.1 (C-16) ; 152.0 (C-13) ; 140.9 (C-10) ; 133.6 (C-34) ; 133.4 (C-1) ; 131.9 (C-2) ; 129.1 (CIV) ; 129.0 (C-5) ; 128.8 (C-36) ; 128.0 (C-4) ; 127.9 (C-38) ; 127.2 (C-3) ; 125.4 (C-6) ; 123.3 (CIV) ; 122.5 (C-39) ; 39.5 (C-14) ; 37.9 (C-30) ; 33.2 (C-21) ; 30.7 (C-20) ; 30.2 (C-11) ; 29.6 (C-22) ; 29.6-28.6 (C-23, C-24, C-25, C-26, C-27, C-28) ; 25.54 (C-29).

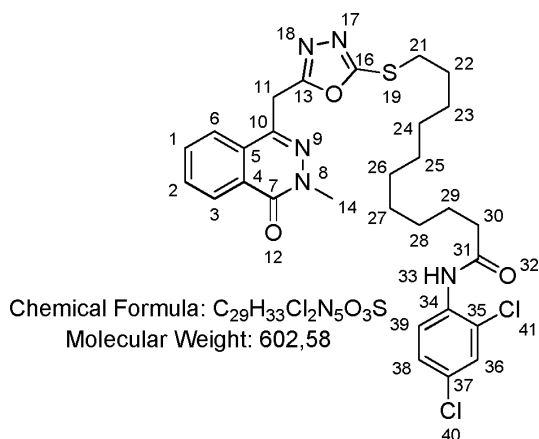
HRMS-MALDI : calcd for C₃₀H₃₇N₆O₂S [M+H]⁺ : 615.2070, found 615.2076

Example 8 : N-(2,4-dichlorophenyl)-11-((5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-1,3,4-oxadiazol-2-yl)thio)undecanamide (D4)

To a suspension of 2-(3-4-oxo-3,4-dihydrophthalazin-1-yl) acetyohydrazide (0.23 g, 1 mmol 1 eq) in CS₂ (10 mL) is added KOH (0.23 g, 5 mmol, 5 eq) and the reaction mixture is heated to reflux vigorously stirring during 3 h. The resulting suspension cooled to 10°C was filtered. The precipitate was taken up in boiling EtOH and after cooling the white powder was filtered and 4-((5-mercapto-1,3,4-oxadiazol-2-yl)methyl)-2-methylphthalazin-1(2*H*)-one was obtained in 65%. It was directly used in the next step without further purification.

¹H NMR (300 MHz in DMSO) : δ (ppm) : 8.29 (m, 1H, Har) ; 8.00-7.90 (m, 3H, Har) ; 4.55 (s, 2H, CH₂) ; 3.99 (s, 3H, Me).

The title compound was then obtained starting from 4-((5-mercapto-4-methyl-4*H*-1,2,4-triazol-3-yl)methyl)-2-methylphthalazin-1(2*H*)-one (1 mmol, 0.29 g), 11-bromo-*N*-(2,4-dichlorophenyl)undecanamide (3 mmol, 1.21 g) and K₂CO₃ (3 mmol, 0.42g) in 5 mL of DMF following procedure 2.



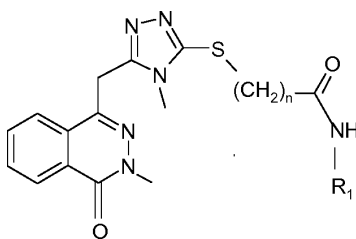
Yield : 45%

¹H NMR (300 MHz in CDCl₃): □ (ppm) 8.47 (d, 3J = 6.7 Hz, 1H, H-3) ; 8.35 (d, 3J = 8.9 Hz, 1H, H-6) ; 7.85-7.65 (m, 3H, Har) ; 7.58 (bs, 1H, NH) ; 7.36 (d, 4J = 2.4 Hz, 1H, H-36) ; 7.24 (dd, 3J = 8.9 Hz, 4J = 2.4 Hz, 1H, H-38) ; 4.50 (s, 2H, H-11) ; 3.83 (s, 3H, H-14) ; 3.19 (t, 3J = 7.4 Hz, 2H, H-21) ; 2.42 (t, 3J = 7.3 Hz, 2H, H-30) ; 1.72 (m, 4H, H-29, H-22) ; 1.4-1.18 (m, 12H, H-28, H-27, H-26, H-25, H-24, H23).

¹³C NMR (75 MHz in CDCl₃) : □ (ppm) 171.32 (CO) ; 163.92 (CO) ; 160.52 (CIV) ; 159.44 (CIV) ; 139.08 (CIV) ; 133.37 (CIV) ; 133.24 (CHar) ; 131.78 (CHar) ; 128.8 (CIV) ; 128.61 (CHar) ; 127.87 (CHar) ; 127.31 (CHar) ; 124.22 (CHar) ; 122.97 (CIV) ; 122.27 (CHar) ; 39.44 (N-CH₃) ; 37.88 (CH₂CONH) ; 32.41 (CH₂S) ; 29.85 (CH₂) ; 29.25-28.49 (6x CH₂) ; 25.37 (CH₂CH₂CONH).

15 **Example 9: Pharmacological activities of the compounds of the invention:**

IC₅₀ are measured by means of the Inhibition of RLI-induced 32Dβ cell proliferation test described above.



Name	R1	n	IC ₅₀ (μM) () nb of determinations
C1	dichloro-phenyl	1	10.77 + 1.97 (6)
C5	dichloro-phenyl	6	1.18 + 0.13 (4)
G2	dichloro-phenyl	7	2.45 + 0.76 (15)
E1	dichloro-phenyl	10	3.81 + 0.40 (12)
A4	adamantyle	7	1.44 + 0.20 (12)

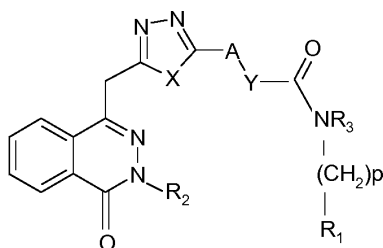
In addition, compound D4 (wherein X =O) has the following IC₅₀ (μM): **8.73 ± 0.63**

REFERENCES:

- 5 Throughout this application, various references describe the state of the art to which this invention pertains. The disclosures of these references are hereby incorporated by reference into the present disclosure.

CLAIMS :

1. A compound of general formula (1)



5 wherein

X represents O, S or NR₄, wherein R₄ is alkyl;

A is selected from S, SO, SO₂, NH and O;

Y represents - (CR₅R₆)_n or (CR₅R₆O)_n, wherein R₅ and R₆ identical or different are H or alkyl and n represents an integer from 1 to 15;

10 R₁ represents a 5 to 10 membered aromatic or non-aromatic mono- or bicyclic, optionally bridged ring, optionally interrupted by one or two heteroatoms or heterogroups selected from O, S and NH and optionally substituted with one to four substituents selected from halo, hydroxy, alkyl, alkyloxy, amino, alkyl amino, dialkylamino, nitro, trifluoromethyl, aryl, alkyl-aryl, acyl, or aryloxy and azide;

15 R₂ is C₁-C₄ alkyl;

R₃ is H or alkyl;

p is 0 or 1;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein

20 - X represents NR₄, wherein R₄ is C₁-C₄ alkyl, preferably methyl and/or

- A represents S, and/or

- Y represents (CH₂)_n with n ranging from 5 to 10, and/or

- R₂ is methyl, and/or

- R₃ is H.

3. A compound according to anyone of the preceding claims wherein p is 0 and R₁ is phenyl, optionally substituted with 1-3 substituents selected from chloro, bromo, fluoro, hydroxyl and methoxy in the ortho or para position with respect to the NH-group.
- 5 4. A compound according to claim 1 or 2, wherein p is 0 and R₁ is selected from 2,4-dichlorophenyl, 2,4-difluorophenyl, 2,4-dibromophenyl, 2,4-dihydroxyphenyl, 2-hydroxyphenyl, 2-chlorophenyl, 2-hydroxy-4-methoxyphenyl and phenylazide
- 10 5. A compound according to claim 1 or 2, wherein p is 0 and R₁ is naphthyl, optionally substituted with 1-3 substituents selected from chloro, bromo, fluoro, hydroxyl and methoxy.
6. A compound according to claim 1 or 2, wherein p is 0 and R₁ is adamantyl, optionally substituted with 1-3 substituents selected from chloro, bromo, fluoro, hydroxyl and methoxy.
- 15 7. A compound according to claim 1 or 2, wherein p is 1 and R₁ is furyl, preferably 2-furyl, optionally substituted with 1-3 substituents selected from chloro, bromo, fluoro, hydroxyl and methoxy.
8. A compound according to claim 1 selected from:
- 20 N-(2, 4-dichlorophenyl)-2-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)sulfonyl)acetamide,
2-methyl-4-((4-methyl-5-(methylthio)-4H-1,2,4-triazol-3-yl)methyl)phthalazin-1(2H)-one,
N-(adamantan-1-yl)-2-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)acetamide,
2-methyl-4-((4-methyl-5-(methylsulfinyl)-4H-1,2,4-triazol-3-yl)methyl)phthalazin-1(2H)-one,
25 2-methyl-4-((4-methyl-5-(methylsulfonyl)-4H-1,2,4-triazol-3-yl)methyl)phthalazin-1(2H)-one,
N-(2,4-dichlorophenyl)-2-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)acetamide,

- N-(2,4-dichlorophenyl)-4-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)butanamide,
- N-(2,4-dichlorophenyl)-6-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)hexanamide,
- 5 N-(2,4-dichlorophenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)octanamide,
- N-(2,4-dibromophenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)octanamide,
- N-(2,4-difluorophenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)octanamide,
- 10 N-(2,4-dihydroxyphenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)octanamide,
- N-(2-hydroxyphenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)octanamide,
- 15 N-(2-hydroxy-4-methoxyphenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)octanamide,
- N-(4-azidophenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)octanamide,
- N-(adamantan-1-yl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)octanamide,
- 20 N-(2-Chloro-4-methylphenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)octanamide,
- Ethyl 3-(8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)octanamido)benzoate,
- 25 N-(2,4-dichlorophenyl)-11-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)undecanamide,
- N-(2-chlorophenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)undecanamide,
- N-(3-chlorophenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)undecanamide,
- 30 N-(4-chlorophenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)undecanamide,

- N-(2-chlorophenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)undecanamide,
 11-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)-N-(naphthalen-1-yl)undecanamide,
 5 N-(furan-2-ylmethyl)-11-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)undecanamide,
 4-((5-(decylthio)-4-methyl-4H-1,2,4-triazol-3-yl)methyl)-2-methylphthalazin-1(2H)-one,
 N-(2,4-dichlorophenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)oxy)octanamide,
 10 N-(adamantan-1-yl)-2-(((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)methyl)benzamide,
 N-(adamantan-1-yl)-4-(((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)methyl)benzamide,
 15 Methyl 2-(((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)methyl)benzoate,
 N-(2,4-dichlorophenyl)-4-(((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)methyl)benzamide,
 N-(2,4-dichlorophenyl)-11-((4-methyl-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)undecanamide, and
 20 N-(2,4-dichlorophenyl)-11-((5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-1,3,4-oxadiazol-2-yl)thio)undecanamide;
 N-(2,4-dichlorophenyl)-11-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)undecanamide;
 25 N-(2,4-dichlorophenyl)-11-((5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-1,3,4-oxadiazol-2-yl)thio)undecanamide;
 N-(2,4-dichlorophenyl)-7-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)heptanamide.
9. A compound according to anyone of the preceding claims for use in the treatment of
 30 an autoimmune, an inflammatory disease or a graft rejection.
10. A compound as defined in claim 9, wherein the inflammatory disease is an inflammatory bowel disease.

11. A compound as defined in claim 10, wherein the inflammatory disease is rheumatoid arthritis.
12. A pharmaceutical composition comprising a compound of anyone of claims 1 to 11 and a pharmaceutically acceptable carrier.
- 5 13. A pharmaceutical composition comprising a combination of a compound of anyone of claims 1 to 11 and an additional active ingredient for the treatment of an autoimmune or an inflammatory disease and a pharmaceutically acceptable carrier.
14. A pharmaceutical composition according to claim 13, wherein the active ingredients are administered simultaneously or sequentially.
- 10 15. A method for the treatment of an autoimmune or an inflammatory disease comprising the step of administering a therapeutically effective amount of a composition of anyone of claims 12 to 14 to an animal or human in need thereof.

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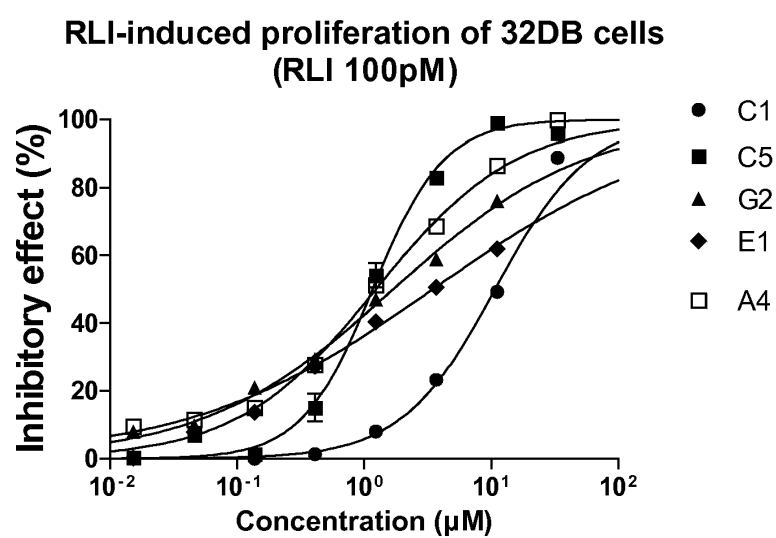


Figure 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/062167

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D403/12
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, BIOSIS, CHEM ABS Data, COMPENDEX, EMBASE, INSPEC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 5 May 2006 (2006-05-05), XP002732825, retrieved from STN Database accession no. 883097-78-7 compound with RN 883097-78-7 -----	1-7
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 30 April 2006 (2006-04-30), XP002732826, retrieved from STN Database accession no. 882292-53-7 compound with RN 882292-53-7 ----- -/-	1-7

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

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"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

8 July 2015

Date of mailing of the international search report

17/07/2015

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2015/062167

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GREENIDGE P A ET AL: "Pharmacophores incorporating numerous excluded volumes defined by X-ray crystallographic structure in three-dimensional database searching: application to the thyroid hormone receptor", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 41, no. 14, 1 January 1998 (1998-01-01), pages 2503-2512, XP002212204, ISSN: 0022-2623, DOI: 10.1021/JM9708691 page 2510; figure 4; compounds 5, 6 -----	1-15
X	WO 95/03053 A1 (FUJISAWA PHARMACEUTICAL CO [JP]; SAKAI FUMIHIKO [JP]; YAMAMOTO NOBUCHI) 2 February 1995 (1995-02-02) compound 15 -----	1-15
X	ABDEL-FATTAH, B.; AL-ASHMAWI, M. I.; EL-FEKY, S.; RODER, E.: "Synthesis of certain phthalazine derivatives of 1,3,4-oxadiazoles and s-triazolothiadiazines of possible antimicrobial activities AU - Abdel-Fattah, B.", EGYPTIAN JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 29, no. 1-4, 2 January 1988 (1988-01-02), pages 259-268, XP009181366, ISSN: 0301-5068 page 263; table 1; compounds 18, 19 -----	1-7

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2015/062167

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9503053	A1	02-02-1995	
		AU 7195594 A	20-02-1995
		JP H09506068 A	17-06-1997
		WO 9503053 A1	02-02-1995

Form PCT/ISA/210 (patent family annex) (April 2005)