

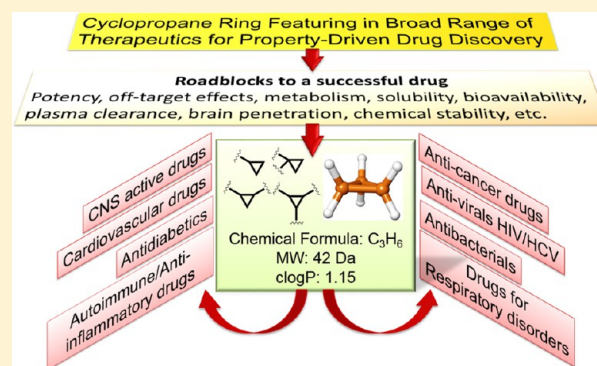
The “Cyclopropyl Fragment” is a Versatile Player that Frequently Appears in Preclinical/Clinical Drug Molecules

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S Supporting Information

ABSTRACT: Recently, there has been an increasing use of the cyclopropyl ring in drug development to transition drug candidates from the preclinical to clinical stage. Important features of the cyclopropane ring are, the (1) coplanarity of the three carbon atoms, (2) relatively shorter (1.51 Å) C–C bonds, (3) enhanced π -character of C–C bonds, and (4) C–H bonds are shorter and stronger than those in alkanes. The present review will focus on the contributions that a cyclopropyl ring makes to the properties of drugs containing it. Consequently, the cyclopropyl ring addresses multiple roadblocks that can occur during drug discovery such as (a) enhancing potency, (b) reducing off-target effects, (c) increasing metabolic stability, (d) increasing brain permeability, (e) decreasing plasma clearance, (f) contributing to an entropically more favorable binding to the receptor, (g) conformational restriction of peptides/peptidomimetics to prevent proteolytic hydrolysis, and (h) altering drug pK_a to reduce its P-glycoprotein efflux ratio.



HISTORICAL SYNOPSIS OF THE CYCLOPROPANE RING

The cyclopropane ring was first synthesized in 1882.¹ It is a colorless, flammable, sweet-smelling gas, with anesthetic properties.² The cyclopropyl skeleton, present in pyrethrins (e.g., compound 1/*trans*-chrysanthemic acid) from pyrethrum flowers, contributes to the insecticidal properties of these compounds.³ (Figure 1) 1-Aminocyclopropane carboxylic acid (compound 2),

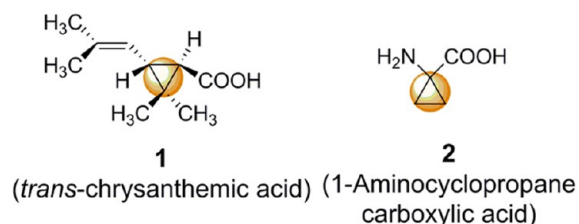


Figure 1. Structures of compounds 1 (*trans*-chrysanthemic acid) and 2 (1-aminocyclopropane carboxylic acid).

of wide occurrence in green plants, serves as a precursor for the plant hormone ethylene.⁴ (Figure 1)

The introduction of the cyclopropyl ring into the structure of pharmacologically active compounds, dating back to the 1960s, is exemplified by two major classes of drugs: phenylcyclopropylamine-based, monoamine oxidase (MAO) inhibitors, and opioid antagonists such as naltrexone.⁵ These two classes of drugs paved the way for the use of the cyclopropyl scaffold in drug research to

achieve specific therapeutic goals. From the 1960s to the present, the cyclopropyl ring has appeared frequently in the U.S. FDA approved drugs and it is likely to continue to play a significant role in the development of new drugs to meet specific therapeutic goals.

The frequent appearance of the cyclopropyl ring system in drug molecules has led to advances in elegant synthetic methods⁶ for the preparation of highly strained cyclopropane building blocks. As a result, the medicinal chemistry community has been able to incorporate this ring system into small, pharmacologically active drug molecules. Because synthetic methods for the preparation of cyclopropane building blocks have been extensively reviewed elsewhere,⁷ they will not be discussed in this review.

PHYSICOCHEMICAL PROPERTIES OF THE CYCLOPROPANE RING

The cyclopropane ring is exceptional among various carbocycles in both its properties and reactivity because of its uncommon bonding and characteristic ring strain (27.5 kcal/mol).⁸ Its chemical reactivity is quite similar to that of an olefinic double bond. In essence, both groups interact with neighboring π -electron systems and π -electron centers.⁹ The C–C single bond in cyclopropane resembles a C=C double bond.¹⁰ The C–C bonds in the cyclopropane ring have more p character, whereas its C–H bonds have more s character.¹¹ The C–H bonds

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in the cyclopropane ring are shorter and stronger (106 kcal/mol) compared to the C–H bonds in ethane (101 kcal/mol).¹² On the basis of this observation, one can expect to achieve a metabolically stable derivative upon replacement of the methyl group with a cyclopropane ring. This latter property occurs as proton abstraction from a cyclopropane ring would be more difficult than from a methyl group, which is required for oxidative metabolism to proceed. Because the three carbons of the cyclopropane ring are in the same plane, the C–H bonds are forced to remain eclipsed,¹⁰ making the less lipophilic cyclopropane ring an excellent surrogate for a hydrophobic phenyl ring. Moreover, existence of a bond angle of 60° between the sp³ hybridized carbon atoms in the cyclopropane ring represents a significant shift from the 109° angle observed for sp³ hybridized orbitals in aliphatic chains. This bond angle difference creates an enormous amount of angular strain in the cyclopropane ring.¹⁰ Additional strain in the cyclopropane ring comes from the torsional strain, a consequence of the coplanar arrangement of the C atoms that forces the C–H bonds into an eclipsed conformation.¹⁰ The cyclopropane ring serves as a π electron donor.¹⁰ The cyclopropyl synthon, carrying an isocyanate group, can be conveniently transformed into cyclopropyl urea analogues that are kinase inhibitors. The cyclopropane scaffold may also contribute toward disruption of overall planarity due to increased sp³ character and three-dimensionality favoring noncoplanarity, less crystal packing, low melting point, and higher aqueous solubility.¹³

■ INFLUENCE OF THE CYCLOPROPANE RING ON PHARMACOLOGICAL ACTIVITY

This perspective is focused on the frequently occurring cyclopropyl ring system in the form of a substituent, a fused cyclopropane ring, a spirocyclopropane ring, and a 1,2-disubstituted/1,2,3-trisubstituted cyclopropane chiral scaffold that contributed toward numerous drug properties, including increases in potency, receptor subtype selectivity, bioavailability, half-life, microsomal stability, brain permeability, adaptation to mutable binding site of target proteins, aqueous solubility, and entropically favorable binding, and decreases in lipophilicity, metabolic liability, off-target pharmacology, and entropic penalty upon binding factors that increases the likelihood of a drug molecule to be therapeutically useful. Some notable pharmaceutical properties that are influenced by the cyclopropane ring include intrinsic lipophilicity, metabolic stability, alteration of the pK_a, and binding to target proteins among others. The lipophilicity of a compound can be reduced by replacing the isopropyl (clogP ~ 1.5) and phenyl (clogP ~ 2.0) groups with the less lipophilic and isosteric cyclopropyl (clogP ~ 1.2) group.^{14–16} Similarly, increased metabolic stability is achievable through (a) replacing the *N*-ethyl group, which is susceptible to CYP450-mediated oxidation, with the metabolically stable *N*-cyclopropyl moiety,^{17,18} (b) the spirocyclopropanation at the α -C of the glycine amide bond to prevent amide hydrolysis,¹⁹ and (c) the replacement of the metabolically labile benzylic carbon atom with the spirocyclopropane.²⁰ Furthermore, locking the *E/Z*-isomerizable noncyclic alkene bond into a cyclopropane ring can lead to geometrically stable isomers for in vivo studies.^{21,22} The cyclopropane ring can be used to eliminate a reactive Michael acceptor (α,β -unsaturated carbonyl functionality) group in the form of a fused cyclopropyl carbonyl group.²³ The pK_a of the benzyl amine moiety in drug molecules can also be altered by the spirocyclopropyl substitution at the benzylic carbon to modulate central nervous system (CNS) permeability.²⁴ A 1,2-disubstituted/1,2,3-trisubstituted cyclopropane ring could

serve as a chiral scaffold to project pendant substituents into favorable binding sites of the target proteins.^{25,26} Geminal-dimethyl/geminal-difluoride and methylene groups have been replaced with a bioisosteric spirocyclopropyl ring in medicinal chemistry research.²⁷ Conformational restriction by inclusion of a cyclopropane ring can facilitate bioactive conformation.²⁸

It is striking to find that eight of the 200 best selling drugs approved by the U.S. FDA contain a cyclopropyl ring.²⁹ Further analysis of the top 100 ring systems appearing in the 2012 FDA *Orange Book* drug database indicated the cyclopropane ring system had a frequency value of 28 and a rank order of 10.³⁰ As of May 2016, there were at least 46 launched drugs containing the cyclopropane ring, which are rather close to that of fluorine-containing FDA approved drugs (DrugBank v4.5 database search).³¹ At present, there are about 65 unique cyclopropane-containing compounds that are in various stages of clinical trials and about 55 that are in preclinical stages (based on DrugBank v4.5 database search³¹ and examples described in this article). Some of the therapeutic areas where the cyclopropane ring has played a crucial role includes but not limited to cancer, AIDS, HCV infections, bacterial infections, hyperlipidemia, diabetes, CNS disorders, asthma, inflammation, cardiovascular diseases, bone disorders, and cystic fibrosis. Collectively, it is clearly evident that the cyclopropane ring system has a positive impact on the biological actions of drugs approved by the FDA for a wide range of human diseases. Consequently, the number of cyclopropyl-containing drugs will continue to rise. These facts point toward the firm establishment of the sp³-hybridized three-carbon ring system in modern drug discovery research. This perspective will discuss the role of the cyclopropane moiety as a determinant of the therapeutic activity of drugs already approved by the U.S. FDA or currently undergoing preclinical/clinical evaluation.

Though this perspective primarily highlights a direct/sole contribution of the cyclopropyl ring toward influencing target potency, target specificity, physicochemical, and pharmacokinetic (PK) properties, caution should be exercised as there are a few examples where the role of a cyclopropyl ring is amalgamated with additional molecular modifications. It is a daunting task to express, in detail, how the cyclopropane ring has contributed toward the evolution of clinical drug candidates; therefore, I have directed the reader to the original references for further information.

■ PRECLINICAL/CLINICAL/APPROVED DRUG CANDIDATES FOR CANCER THERAPY

Kinase Inhibitors. *MEK Kinase Inhibitor 4 (Trametinib/Mekinist)*. Compound 4 (trametinib/GSK1120212), as a dimethyl sulfoxide solvate (JTP-74057),¹⁵ is a selective allosteric inhibitor of mitogen/extracellular signal-regulated kinases (MEK1 and MEK2) approved by the U.S. FDA to treat metastatic melanoma in adult patients carrying BRAF Val600Glu or Val600Lys mutations. MEK has been reported to be involved in the pathology of various malignant tumors.³² Abe and co-workers¹⁵ started their discovery chemistry with compound 3 that contained three aromatic rings on the pyridopyrimidine scaffold that presented an unattractive starting point for further optimization due to significant hydrophobicity. (Figure 2) Therefore, these investigators reduced the hydrophobicity of 3 by replacing the hydrophobic phenyl ring at *N*-3 with the bioisosteric, relatively polar cyclopropyl ring and by making other key modifications that involved replacement of *para*-chloroaniline with the frequently occurring MEK kinase inhibitory

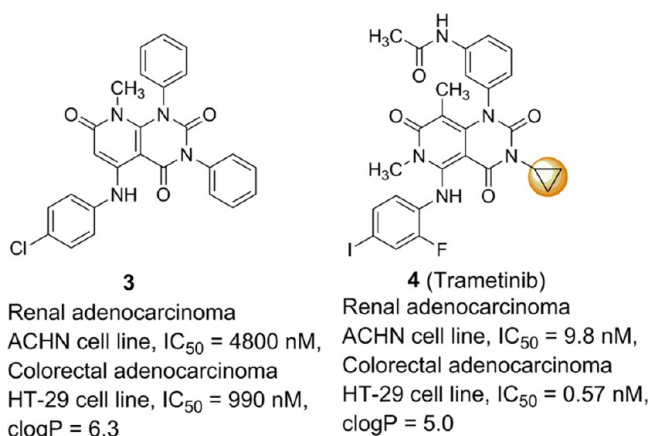


Figure 2. Structures and in vitro potency of compounds 3 and 4 (trametinib).

2-fluoro-4-iodoaniline pharmacophore (*para*-iodine consistently forms electrostatic interactions with the backbone atoms of Val127)³³ and a polarity-enhancing acetamide substitution on N1-phenyl ring. This work eventually yielded compound 4, which exhibited significantly reduced hydrophobicity and improved cellular potency by ~490- and ~1700-fold, respectively, against the renal adenocarcinoma ACHN cell line and the colorectal adenocarcinoma HT-29 cell line as shown in Figure 2.¹⁵

Tyrosine Kinase Inhibitor 5 (Lenvatinib/Lenvima). Compound 5 (lenvatinib/E7080)³⁴ is an orally active multikinase inhibitor that targets vascular endothelial growth factor receptors (VEGFR1–3), fibroblast growth factor receptors (FGFR1–4), platelet derived growth factor receptor α (PDGFR α), Kit, and rearranged during transfection (RET) kinases. It was approved by the U.S. FDA in 2015 to treat patients with differentiated thyroid cancer.³⁴ Chemically, compound 5 has a cyclopropyl urea moiety with a hinge-binding 4,6,7-trisubstituted quinoline ring (Figure 3). Analysis of kinetic interactions of 5 with

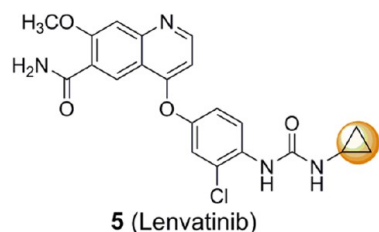


Figure 3. Structure of compound 5 (lenvatinib).

VEGFR2 indicated that 5 had a fast association rate constant and a slow dissociation rate constant, thereby increasing the amount of time it is bound to VEGFR2.³⁵ X-ray cocrystal studies have shown that compound 5 binds to VEGFR2 in a DFG-in conformation, a situation that was facilitated by the presence of a small cyclopropane substituent. The cyclopropyl ring is usually occupied by the larger phenyl ring of other receptor tyrosine kinase inhibitors that bind in the DFG out conformations. Apart from the ATP-binding active site interactions, compound 5 interacts with the side chain of residue Phe1047 in the neighboring (allosteric site) region through a CH– π interaction with the cyclopropyl ring, eventually leading to a potentially long residence time in complex with VEGFR2.³⁵

Plk1 Inhibitor 6 (Volasertib). Polo-like kinase 1 (Plk1), a serine/threonine protein kinase, plays an important role in

multiple stages of mitosis and serves as a prime therapeutic target for the development of antineoplastic drugs.³⁶ An early compound 6 (BI 6727) (Plk1, IC_{50} = 0.87 nM), discovered through the high-throughput screening of a small molecule library and subsequent lead optimization efforts, is an example of a dihydropteridinone compound, known to demonstrate a high potency and inhibitory selectivity toward Plk1³⁷ (Figure 4).

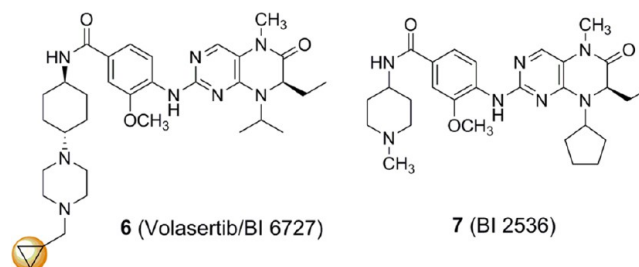


Figure 4. Structures of compounds 6 and 7.

On the basis of the X-ray cocrystal structure of Plk1–compound 6,³⁷ it is apparent that the benzamide substituent (cyclopropylmethyl-piperazinyl-cyclohexyl) is solvent-exposed and it has contributed toward improved PK properties of this compound. A structurally related analogue, compound 7 (BI 2536),³⁸ lacked the cyclopropylmethyl-piperazinyl moiety and showed a poor PK profile compared to the PK profile of compound 6, thereby substantiating the role of the cyclopropylmethyl-piperazinyl moiety in influencing the PK profile. It may be noted that the cyclopropylmethyl substituted piperazine ring serves as a solubilizing basic side chain that is solvent-exposed.

Polo-like Kinase 4 (Plk4) Inhibitor 10. This type of serine/threonine kinase is a conserved upstream regulator of centriole duplication that produces centrosome amplification, genome instability, and tumor development.³⁹ Work by Sampson and co-workers²¹ on the lead compound 8⁴⁰ showed significant Plk4 potency and intraperitoneal antitumor efficacy (Figure 5). However, this molecule had suboptimal PK properties (Figure 5). These investigators realized that the configurational instability of 8 was due to the presence of an alkene moiety, which permits the potential isomerization of pharmacologically active *E*-isomer into a mixture with a less active *Z*-isomer in vivo. By replacing the alkene bond with a bioisosteric cyclopropane ring, these authors not only achieved configurational stability in this series but also improved aqueous solubility due to the increased sp^3 character (three-dimensionality). These efforts led to the synthesis of 9, a molecule with enzyme- and cell-based activity comparable to that of 8 but with an excellent PK profile (Figure 5). Additional structure–activity relationship (SAR) studies on 9 resulted in the discovery of the orally bioavailable molecule, 10.²¹

Multiple Tyrosine Kinase Inhibitors 12 (Cabozantinib/Cometriq), 13 (Foretinib), 14 (Altiratinib), and 15 (Golvatinib). Compound 12 (cabozantinib) was approved by the U.S. FDA in 2012 for the treatment of medullary thyroid cancer. It is an inhibitor of multiple tyrosine kinase receptors as shown in Figure 6.⁴¹ The replacement of a chemically unstable acyl thiourea linker in compound 11 with a novel cyclopropyl-1,1-dicarboxamide linker led to the discovery of many clinically important compounds, including compound 12, with the ability to inhibit different types of kinases. For example, compound 13 (foretinib/XL-880), a structurally related analogue of cabozantinib, exhibiting a morpholinyl propoxy group in place of the 7-methoxy group, inhibited multiple kinases.⁴² Similarly, compound 14

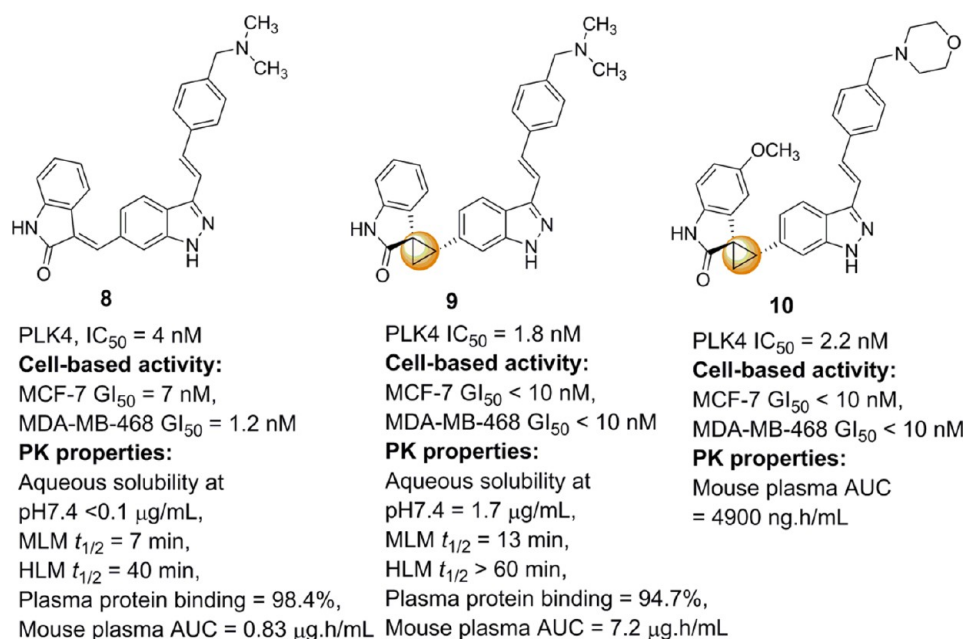


Figure 5. Structures, in vitro potency, and PK properties of Plk4 inhibitory compounds 8–10.

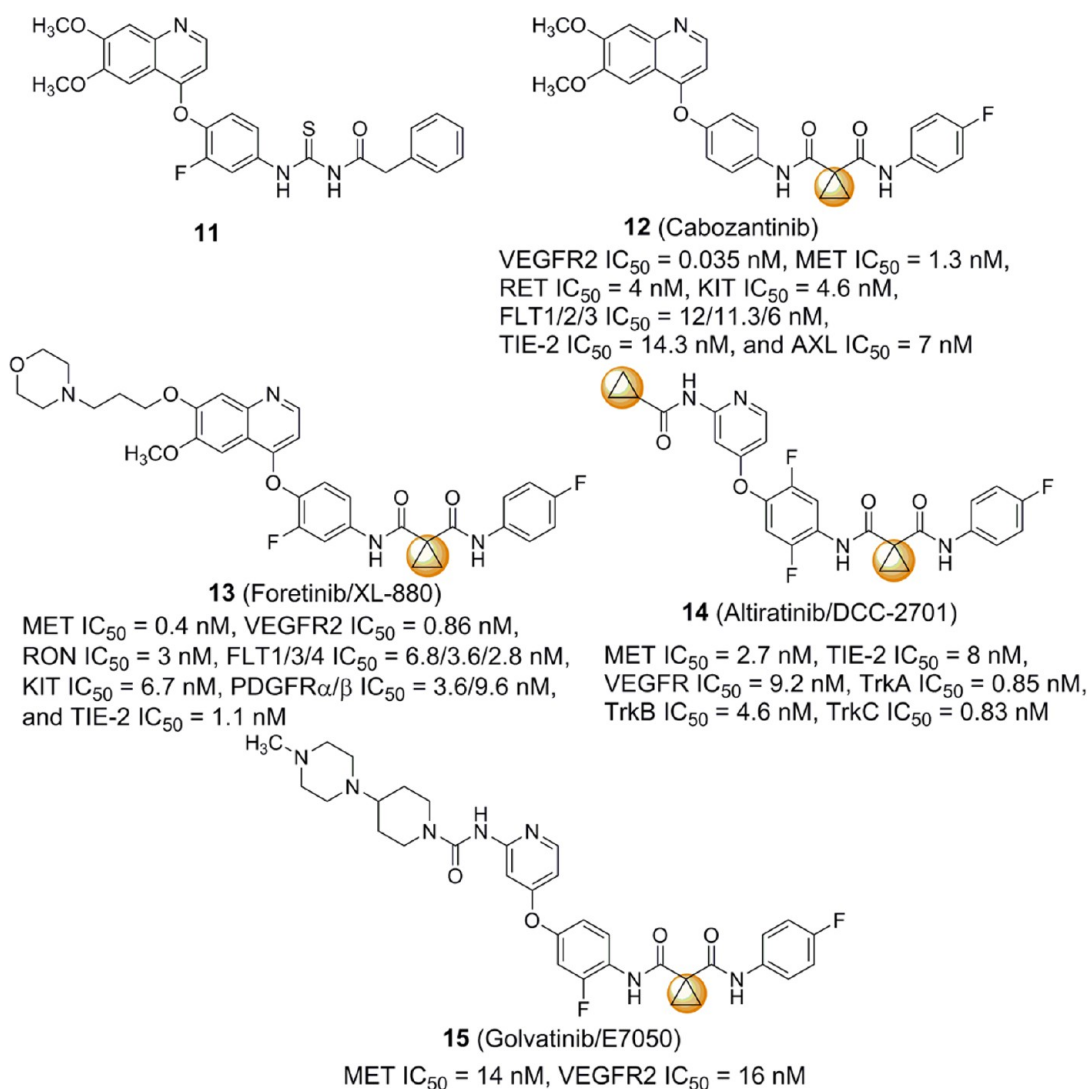


Figure 6. Structures and in vitro potency of tyrosine kinase inhibitors 11–15.

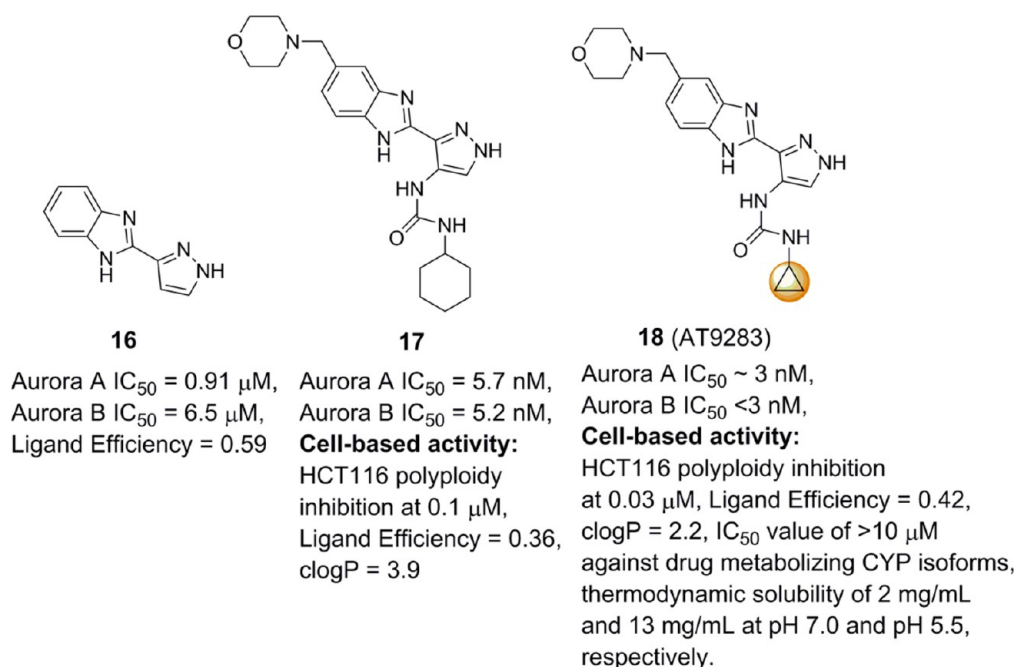


Figure 7. Structures, in vitro potency, and physicochemical properties of Aurora kinase inhibitors 16–18.

(altiratinib/DCC-2701) demonstrated balanced inhibition of c-Met/hepatocyte growth factor receptor (HGFR), VEGFR2, Tie 2 receptor tyrosine kinase (TIE2), and tropomyosin receptor kinase (Trk) with promising oral antiangiogenic and antineoplastic efficacy.⁴³ Compound 14 is currently undergoing phase I clinical trials (NCT02228811). In contrast, compound 15 (golitinib/E7050) inhibits only MET and VEGFR2, with nanomolar IC_{50} values as shown in Figure 6.⁴⁴ The spirocyclopropyl substitution at the methylene unit of the malonamides in 12–15 primarily contributed toward PK properties.

Aurora Kinase Inhibitor 18. This compound has been found to inhibit not only Aurora A and Aurora B kinases but also other oncogenic kinases like Janus kinase 2 (JAK2) and Abelson tyrosine kinase (Abl) (Thr315Ile mutant). The discovery of compound 18 (AT9283) by Howard and co-workers⁴⁵ began with the ligand-efficient pyrazolyl benzimidazole fragment hit 16 (Figure 7). This led to the identification of a cyclohexyl urea analogue 17, which had acceptable affinity toward Aurora A and a 10-fold increased affinity for Aurora B compared to an early phenyl urea lead. However, analogue 17 was very lipophilic. To reduce the lipophilicity of 17, the large lipophilic cyclohexyl urea moiety was replaced with a smaller and less lipophilic cyclopropyl urea moiety. This structural modification resulted in the discovery of a cyclopropyl urea-containing clinical candidate 18 that demonstrated significantly improved enzymatic- and cell-based potencies, clogP value, and aqueous solubility as shown in Figure 7.⁴⁵ Crystal structure studies (PDB ID 2w1g) indicated that 18 has a folded bioactive conformation enforced by intramolecular hydrophobic interactions between the cyclopropyl group and the core benzimidazole ring.⁴⁵ Because 18 does not utilize the Thr315 gatekeeper residue for its binding, it can bind to the imatinib-resistant Thr315Ile mutant Abl kinase.⁴⁵ On the basis of the above properties, 18 is currently undergoing clinical trials for the treatment of cancer (NCT00443976).

Additional examples of clinically valuable cyclopropane-containing kinase inhibitory anticancer compounds including P21 activated kinase inhibitor, Pim kinase inhibitor, lucitanib, and XL228 are given in the Supporting Information.

Non-Kinase Inhibitory Drug Candidates. Poly(ADP-ribose)polymerase (PARP) Inhibitor 20 (Olaparib/Lynparza). Compound 20 (olaparib/AZD2281/KU0059436),⁴⁶ a phthalazinone derivative with potent PARP-inhibitory activity, was introduced in 2014 as Lynparza for the treatment of germline breast cancer susceptibility gene (BRCA) mutated advanced ovarian cancers⁴⁷ (Figure 8). The cyclopropyl moiety in 20 yielded the highest oral absorption (mouse plasma concentration 1 h after oral dosing of 0.59 vs 0.3 μ g/mL for its precursor ethyl amide analogue, 19).⁴⁶ Furthermore, a cyclopropyl amide analogue 20 showed a significantly higher oral exposure (100% bioavailability in rats) compared to an ethyl amide analogue (40% bioavailability in rats).⁴⁶

Lysine Specific Demethylase 1 Inhibitor 21. Compound 21 (GSK2879552) is an orally active mechanism-based covalent inhibitor of the flavin-dependent lysine (K) specific demethylase 1 (LSD1), also referred to as KDM1A, with a potential application as an antineoplastic drug.⁴⁸ Because of the considerable similarity between the active sites of flavin-dependent LSD1 and MAO enzymes, Johnson and co-workers⁴⁹ began their mechanism-based LSD1 inhibitor discovery efforts with the clinically approved MAO inhibitor, tranlycypromine (compound 95, see CNS Active Drugs section). Specifically, the 4-carboxybenzylpiperidinemethyl moiety was added onto the amine group of tranlycypromine to obtain a highly selective compound 21 as shown in Figure 9. As stated for tranlycypromine (see CNS Active Drugs section), presence of a chiral cyclopropane linker moiety facilitated the projection of the phenyl and the amino groups in a desirable *trans*-geometry. Compound 21 is currently undergoing clinical trials for the treatment of refractory small cell lung carcinoma (NCT02034123) and acute myeloid leukemia (NCT02177812).

P-Glycoprotein (P-gp) Inhibitor 23 (Zosuquidar). P-gp is a target for the treatment of certain types of multidrug resistance (MDR) cancer resulting from the overexpression of P-gp.⁵⁰ Compound 22 (MS-073), a dibenzosuberylpiperazine derivative, was developed by Sato and co-workers⁵¹ to cope with cancers showing MDR (Figure 10). However, compound 22 had

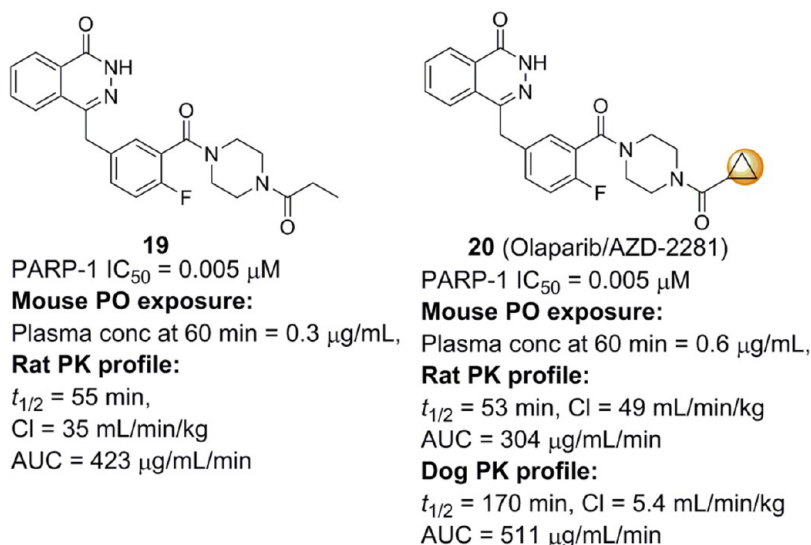


Figure 8. Structures, in vitro potency, and PK properties of PARP inhibitors **19** and **20**.

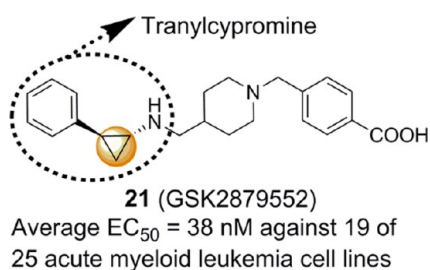


Figure 9. Structure and in vitro potency of LSD1 inhibitor **21**.

inadequate oral bioavailability owing to the unstable nature of the *N*-dibenzosuberyl moiety under acidic conditions (*t*_{1/2} at pH 2/37 °C ~ 15 min). Subsequently, Pfister and co-workers⁵² undertook the structural modification of compound **22** in an effort to improve the pharmacological activity of the parent compound. One of the modifications, a fusion of the cyclopropyl ring at the ethylene bridge of the dibenzosuberone, led to either similar or improved activity compared to compound **22**. A geminal difluoro substitution on the cyclopropane ring yielded the highly acid-stable, phase III clinical candidate, compound **23**/zosuquidar/RS 33295/LY-335979 (*t*_{1/2} at pH 2/37 °C > 72 h compared to hydrogen substituted counterpart, *t*_{1/2} ~ 3 h) as shown in Figure 10.⁵² However, further development of **23** was discontinued due to toxicity and insufficient inhibition of P-gp.

Interested readers are directed to the Supporting Information for additional examples of cyclopropane-containing nonkinase inhibitory anticancer compounds including histone deacetylase inhibitors, bromodomain inhibitors, heat shock protein 90 inhibitor, and LSD1 inhibitors.

■ PRECLINICAL/CLINICAL/APPROVED DRUG CANDIDATES FOR INFECTIOUS DISEASES

Anti-HCV Drug Candidates: Hepatitis C Virus (HCV) NS3/4A Protease Inhibitors. Compound **25** (Boceprevir/Victrelis). Compound **25** (boceprevir/SCH 503034)⁵³ is a direct-acting hepatitis C virus (HCV) NS3/4A protease inhibitor as shown in Figure 11. HCV NS3/4A protease is critical to the replication of HCV. Therefore, it serves as a prime target for anti-HCV drug development. Venkatraman and co-workers⁵³ used an inhibitor design strategy that was entirely based on information

gathered from substrate-HCV NS3/4A protease active site complex interactions. This strategy resulted in the synthesis of long peptidic compounds that spanned the entire substrate-binding site (P1–P6 and P1'–P5'). Early efforts were directed to designing small peptidomimetic/nonpeptidic compounds with enhanced potencies in both HCV NS3 protease enzymatic- and HCV replicon-based assays. To this end, the high molecular weight (1265 Da) undecapeptide ketoamide inhibitor (compound **24**), with a slow and tight two stage binding mechanism, served as a starting lead (Figure 11). Subsequently, this lead compound was subjected to a series of stepwise truncations at both ends. This was followed with optimization of enzymatic and replicon potencies and PK-enhancing P1 and P2 moieties, P3 capping, and a reversible warhead α -ketoamide Ser139-covalent trap, which resulted in the discovery of compound **25** as shown in Figure 11.⁵³ One of the key synthetic modifications leading to this compound was the introduction of the *gem*-dimethylcyclopropylproline moiety at the P2 position as a surrogate of leucine, which was at that time proved to be the most optimal P2 moiety. Overall, the improved potency of compound **25** results from a favorable interaction of the *gem*-dimethylcyclopropylproline P2 moiety with the methyl side chain of Ala156 (PDB ID 3LOX).⁵³

Compound 29 (Telaprevir/Incivek). Compound **29** received approval from the U.S. FDA in 2011 for the treatment of chronic genotype 1 HCV infected patients. Chemically, it is a tetrapeptide featuring a reversible α -ketoamide serving as a covalent trap for Ser139 at the active site of HCV protease. Initial work by Perni and co-workers⁵⁴ culminated in the design and synthesis of uncharged tetrapeptide with micromolar inhibitory action on the HCV protease. These efforts led to the sequential discovery of compounds **26** and **27**, with **27** providing a 4-fold increase in inhibition of HCV NS3/4A protease (Figure 12). Subsequently, Perni and co-workers⁵⁵ developed compound **28** by replacing the nondrug-like aldehyde functionality in **27** with drug-like α -ketoamide featuring an S1'-binding cyclopropane P1' moiety, which had improved enzyme- and replicon-based potencies over **27**. Two papers^{56,57} described the synthesis of compound **29**, a bicycloproline P2 bearing compound as shown in Figure 12. The increased enzyme- and cell-based potencies of **28** and **29** compared to **27** is a result of two molecular modifications: the P2/P2* moiety and the acyl cyclopropyl carboxamide P1' moiety.

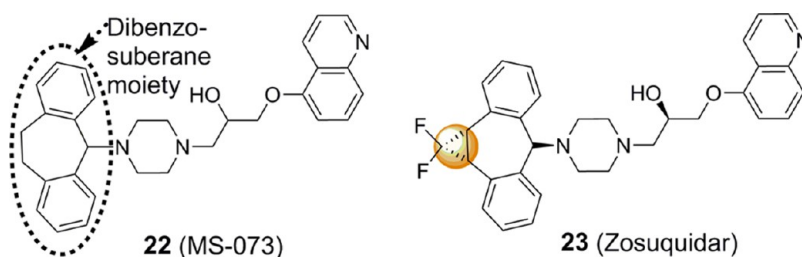


Figure 10. Structures of P-gp inhibitors 22 and 23.

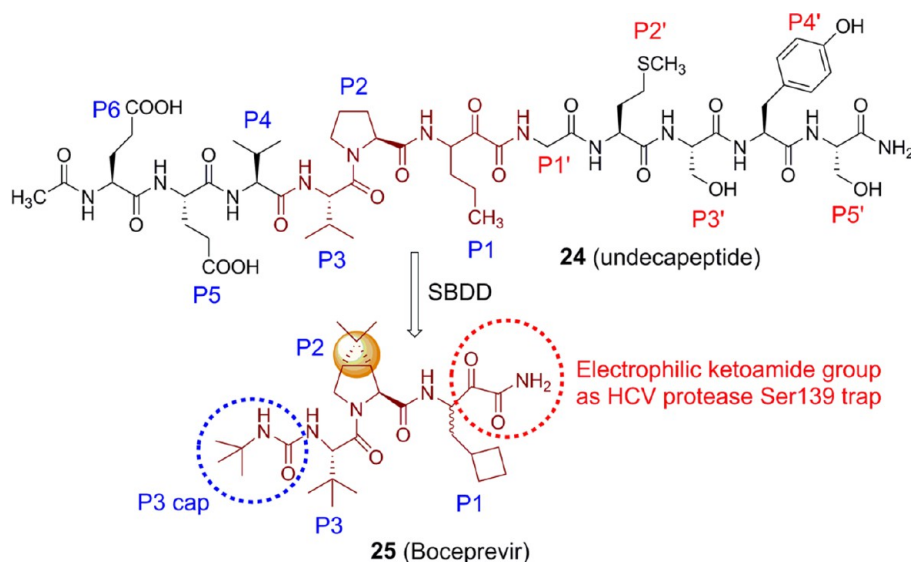


Figure 11. Structures of HCV NS3/4A protease inhibitors 24 and 25.

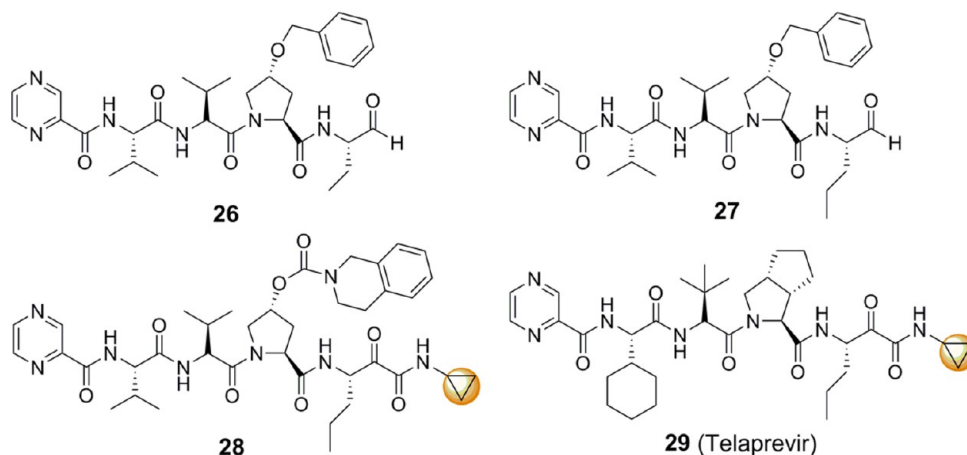


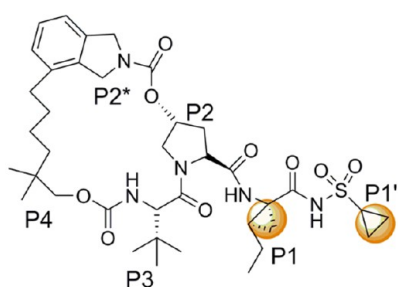
Figure 12. Structures of HCV NS3/4A protease inhibitors 26–29.

Compound 30 (Vaniprevir). McCauley and co-workers⁵⁸ used a lead optimization program that was comprised of: (1) macrocyclization between the P2 and P4 moieties, (2) variations of the linker between P2 and P4, (3) addition of novel heterocycles at P2 moiety, and (4) a P1 side chain exploration. The aforementioned modifications resulted in the discovery of compound 30 (vaniprevir/MK-7009),⁵⁸ a P2–P4 macrocyclic HCV genotype 1 and 2 NS3/4A protease inhibitor, which had an excellent liver exposure and desirable PK profile (Figure 13). The rationale for the inclusion of the ethylcyclopropyl P1 moiety and the acylcyclopropylsulfonamide P1' moiety in the structure of 30 was to increase enzymatic and HCV replicon-based potencies

and to improve PK profile.⁵⁸ A similar rationale was used for the synthesis of other related HCV NS3/4A protease inhibitors.

Compound 33 (Grazoprevir). Compound 33 (grazoprevir/MK-5172) is a second-generation HCV NS3/4A protease inhibitor with substantial potency against HCV genotypes 1 and 3 and A156 mutant variants.⁵⁹ To develop compounds with enhanced potency against broad genotypes and mutant variants of the HCV NS3/4A protease, as well as desirable cellular activity and liver exposure upon oral dosing, Harper and co-workers⁵⁹ used a P2–P4 linker and P2 moiety optimization approach. The potency of the lead compound 31 (Figure 14) against A156 mutant variants and various genotypes, although difficult to

achieve, was realized by the insertion of a fused cyclopropyl ring at C1 and C2 of the macrocyclic linker, leading to **32** as shown in Figure 14.⁵⁹ The excellent liver exposure of **32** was considered a favorable property due to the liver being the predominant organ where HCV replication occurs.⁶⁰ The rationale for the 4–10-fold increase in the potency of **32** against Ala156 mutant enzymes compared to **31** was based on molecular modeling studies. In general, if the compounds binding affinity is not dependent upon a highly mutable residue, then one can hypothesize the retention of the wild-type enzyme binding affinity against mutant variants, e.g., Ala156 of HCV NS3/4A protease in this case. The presence of a cyclopropyl steric constraint in **32** will move the macrocycle away from the Ala156 residue compared to compound **31** to create an additional space for the binding of **32** to drug-resistant A156 mutants such as Ala156Thr or Ala156Val. The increased potency of **32** was proposed to result from the entropically more favorable binding by a fused-cyclopropyl constrained analogue.⁵⁹



30 (MK-7009/Vaniprevir)

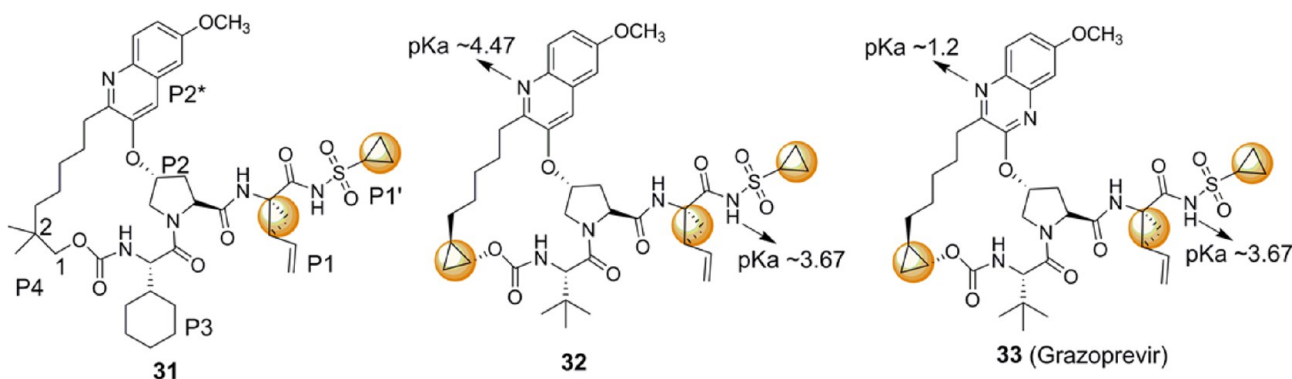
GT-1b K_i = 0.05 nM, GT-2a K_i = 0.9 nM,
 replicon GT-1b 10% FBS IC_{50} = 3 nM,
 replicon GT-1b 50% normal human
 serum IC_{50} = 19 nM,
 replicon GT-2a 10% FBS IC_{50} = 9 nM

Figure 13. Structure and in vitro potency of HCV NS3/4A protease inhibitor **30**.

In an aqueous milieu, the solubility of the potassium salt of compound **32** is 9.7 mg/mL, but it quickly drops to <0.009 mg/mL when it disproportionates to the significantly less soluble crystalline zwitterionic form. The formation of this zwitterionic form is driven by the basic P2 quinoline ring nitrogen (calculated pK_a of 4.47) and acidic sulfonimide NH group (calculated pK_a of 3.67). This limitation to the aqueous solubility of compound **32** was addressed by insertion of an alternative P2 heterocycle (quinoxaline) that had a less basic characteristic ($pK_a \sim 1.2$) and lower likelihood to generate the less soluble zwitterion. These efforts led to the discovery of clinical candidate compound **33**, with an optimal PK and pharmacodynamic profile as shown in Figure 14.⁵⁹

The regularly featured cyclopropyl sulfonimide and the ethyl/vinyl cyclopropyl moieties at the P1' and P1 positions, respectively, intended to bind to the shallow S1' and S1 pockets, present in the core structures of many HCV NS3/4A protease inhibitors, has been rationalized in other examples, such as compound **36** (see below).

Compound 36. Compound **36** (BMS-605339) is a Boc-protected tripeptidic HCV NS3/4A protease inhibitor, whose structure is comprised of a novel isoquinoline ring on the P2 moiety and an acyl cyclopropylsulfonamide as P1' group.⁶¹ Scola and co-workers⁶¹ began their search for potent HCV NS3/4A protease inhibitors based on early leads typified by the tripeptidic carboxylic acid **34** shown in Figure 15. Guided by molecular modeling analysis, this group wanted to exploit the S1' shallow pocket by introducing the bioisosteric replacement of the carboxyl group with an alkyl acylsulfonamide that fulfills the hydrogen bonding capacity of the original group while establishing new van der Waals interactions between the alkyl and the S1' site residues. This concept resulted in the development of the next acyl cyclopropylsulfonamide, lead compound **35**, with significantly greater enzymatic and replicon potencies than compound **34**. (Figure 15) Seeking improvement of the aqueous solubility and PK profile, these investigators focused on optimizing P2* heterocycles by replacing the 7-methoxy-2-phenylquinoline ring with a 6-methoxyisoquinoline ring, thus



HCV NS3/4A PR GT-1b K_i = 0.02 nM,
 GT-3a K_i = 1.9 nM,
 GT-1b R155K K_i = 0.16 nM,
 GT-1b A156T K_i = 12 nM,
 GT-1b A156V K_i = 64 nM,
 GT-1b replicon (50% NHS) = 28 nM,
 rat liver at 4 h = 9.8 μ M

HCV NS3/4A PR GT-1b K_i = 0.02 nM,
 GT-3a K_i = 0.31 nM,
 GT-1b R155K K_i = 0.02 nM,
 GT-1b A156T K_i = 2.9 nM,
 GT-1b A156V K_i = 5.7 nM,
 GT-1b D168V K_i = 0.05 nM,
 GT-1b replicon (50% NHS) = 13 nM,
 rat liver at 4 h = 20 μ M

HCV NS3/4A PR GT-1b K_i = 0.02 nM,
 GT-3a K_i = 0.7 nM,
 GT-1b R155K K_i = 0.07 nM,
 GT-1b A156T K_i = 5.3 nM,
 GT-1b A156V K_i = 12 nM,
 GT-1b D168V K_i = 0.14 nM,
 GT-1b replicon (50% NHS) = 7.4 nM,
 rat liver at 4 h = 23 μ M
rat PK profile: CI = 28 mL/min/kg, $t_{1/2}$ = 1.4 h

Figure 14. Structures and in vitro potency of HCV NS3/4A protease inhibitors **31**–**33**.

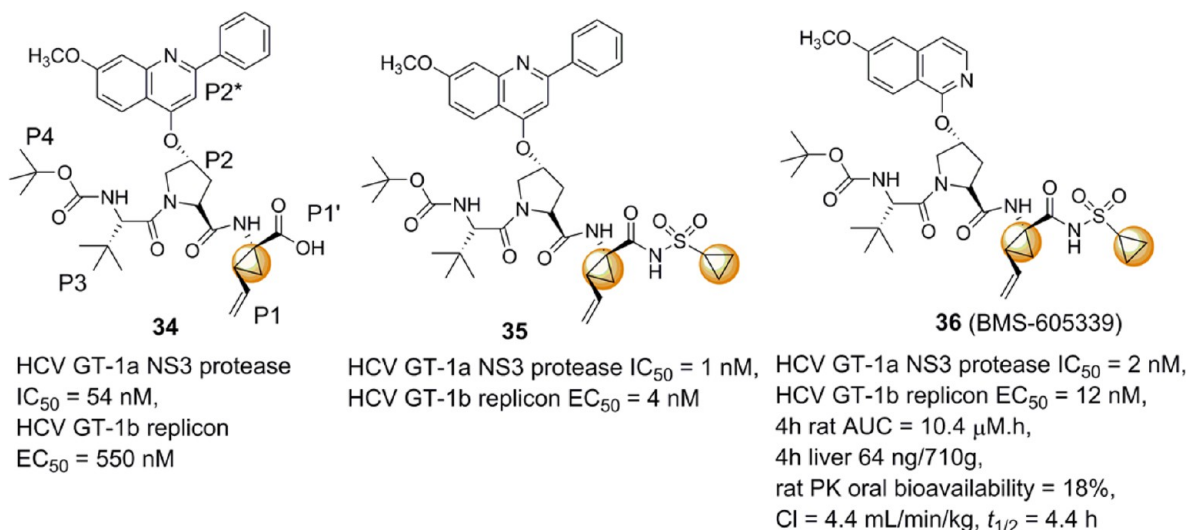


Figure 15. Structure, in vitro potency, and PK properties of HCV NS3/4A protease inhibitor 34–36.

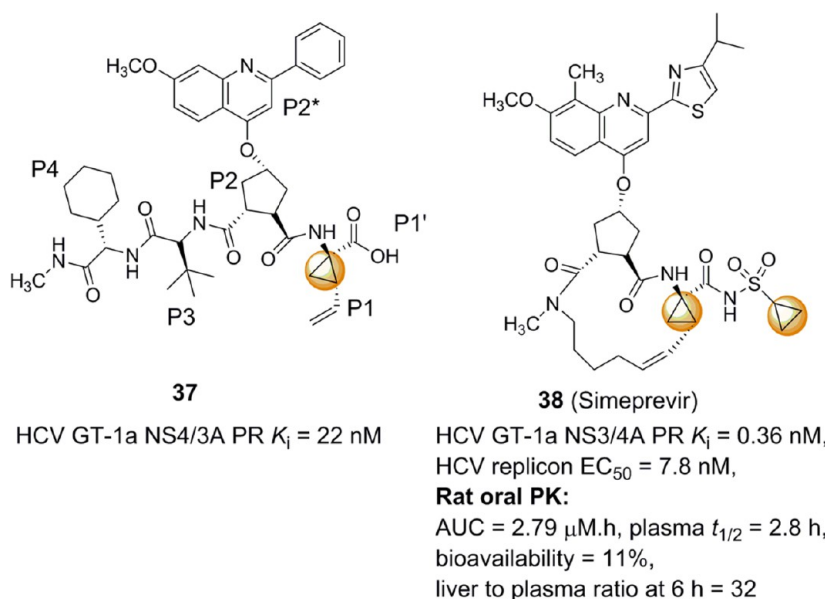


Figure 16. Structures, in vitro potency, and PK properties of HCV NS3/4A protease inhibitors 37 and 38.

obtaining the orally bioavailable clinical candidate 36 (Figure 15), with excellent in vivo efficacy in GT-1 infected patients. A cocrystal structure of 36 with HCV NS3/4A protease (PDB ID 4NWK) showed optimal van der Waals interactions between the cyclopropyl P1' moiety and the hydrophobic residues of the shallow S1' pocket.⁶¹

Compound 38 (Simeprevir/Olysio). Compound 38 (TMC435/simeprevir) was developed by Rosenquist and co-workers,⁶² starting from the P2 cyclopentanedecarbonyl, serving as a mimic of the P2 proline moiety in compound 37 as shown in Figure 16. Compound 37 was developed into 38 through four structural modifications: (a) potency- and PK-enhancing replacement of the carboxylic acid with a bioisosteric S1' binding acyl cyclopropylsulfonamide, (b) truncation of the peptide backbone, (c) macrocyclization of truncated peptides, and (d) optimization of the P2* quinoline moiety. As shown in Figure 16, compound 38 has an optimal pharmacodynamic and PK profile.⁶² The function of the vinylcyclopropyl P1 moiety and the

cyclopropyl sulfonamide as the P1' moiety is the same as previously explained.

HCV NS5A Inhibitor 40 (Ledipasvir/Harvoni in Combination with Sofosbuvir). Link and co-workers⁶³ sought to identify inhibitory compounds targeted to the HCV nonstructural protein 5A (NS5A) with a high potency and an extended half-life to reduce the emergence of viral resistance. Such inhibitors could be combined with direct acting antiviral drugs with complementary mechanisms of actions to obtain a significant, sustained virologic response in HCV infected patients. These investigators initiated SAR studies on a series of symmetric bis-benzimidazole and unsymmetric imidazole/benzimidazole scaffolds that ultimately yielded several HCV NS5A inhibitors. Among these, an unsymmetric series was found to be advantageous with respect to potency and PK optimization. As shown in Figure 17, the precursor compound 39 proved to be a very potent HCV NS5A inhibitor. The protein-adjusted EC_{50} of 39 against HCV genotype 1a was 784 pM , reflecting a protein-binding shift of 14-fold (Figure 17). The final optimization of 39

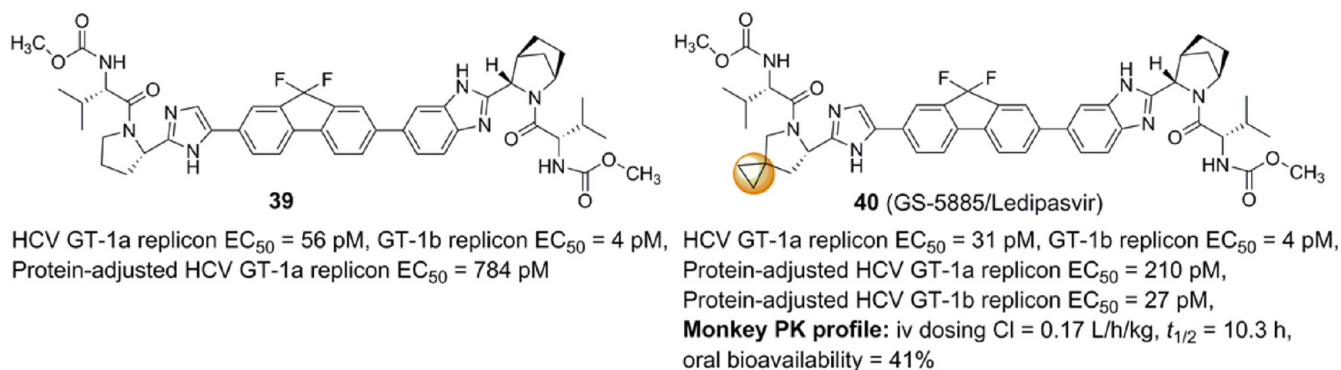


Figure 17. Structures, in vitro potency, and PK properties of HCV NS5A inhibitors **39** and **40**.

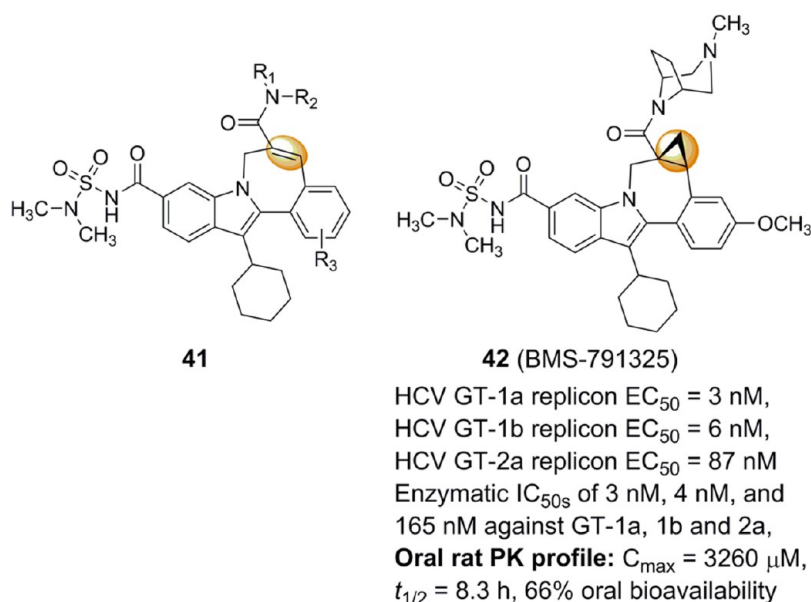


Figure 18. Structures, in vitro potency, and PK properties of HCV NS5B inhibitors **41** and **42**.

involved the insertion of a spiro-cyclopropylpyrrolidine ring in place of the pyrrolidine ring to produce the most potent HCV NS5A inhibitor, compound **40** (ledipasvir/GS-5885), as shown in Figure 17.⁶³ The protein adjusted EC_{50} values of compound **40** for GT-1a and GT-1b were 210 and 27 pM, respectively, corresponding to a protein-binding shift of only 6.7-fold as opposed to 14-fold obtained with its precursor compound **39**.⁶³ Thus, the presence of a spiro-cyclopropyl substituent at the 4-position of the pyrrolidine ring has been found to contribute not only to enhancing potency and improving protein-adjusted EC_{50} values but also to a notable PK profile in monkeys (Figure 17) and in healthy volunteers.⁶³

HCV NS5B Non-Nucleoside Inhibitor 42. The HCV non-structural protein 5B (NS5B), a 66 kDa RNA-dependent RNA polymerase (RdRp), serves as an attractive anti-HCV target because of its key role in the replication of HCV RNA genome and humans lack its functional equivalent.⁶⁴ It is a cyclopropyl-fused indolobenzazepine class of HCV NS5B polymerase inhibitor targeted to the allosteric thumb domain I. To gain complementary mechanism of action, this compound has the potential to be used in combination with direct acting antiviral drugs. Gentles and co-workers²³ began their drug discovery efforts with a general lead structure represented by compound **41** as shown in Figure 18. The transition of the novel lead indolobenzazepine structure **41** into **42** (BMS-791325)²³ started

with introducing a cyclopropyl moiety at the olefinic double bond of the tetracyclic indolobenzazepine core structure. This strategy has led to meet the following anticipated goals: (a) introducing a conformational rigidity within the tetracyclic ring system, (b) establishing productive molecular interactions between the cyclopropyl group and the residues from the thumb domain I of HCV NS5B polymerase,⁶⁵ and (c) eliminating a potentially reactive Michael acceptor (α,β -unsaturated carbonyl) functionality.²³ In general, the potency of the cyclopropyl analogues was greater than that of the olefin counterparts, presumably because of the interaction of the cyclopropyl ring hydrogens with the carbonyl oxygen backbone of Leu492 (PDB ID 4NLD).²³ These investigations eventually led to discovery of the clinical candidate, compound **42**, as shown in Figure 18. It is currently in phase III clinical trials in combination with daclatasvir (HCV NS5A inhibitor) and asunaprevir (HCV NS3/4A protease inhibitor) (NCT02170727).

Additional examples of cyclopropane-containing HCV NS3/4A protease inhibitors (MK-1220, asunaprevir, danoprevir, narlaprevir, vedoprevir, neceprevir, paritaprevir, and sovalprevir) are described in the Supporting Information.

Anti-Respiratory Syncytial Virus Clinical Candidate. Respiratory Syncytial Virus (RSV) Fusion Inhibitor 45. Compound **45** (BMS-433771)¹⁴ is a RSV fusion inhibitor. Yu and co-workers¹⁴ began optimization of compound **43** that had

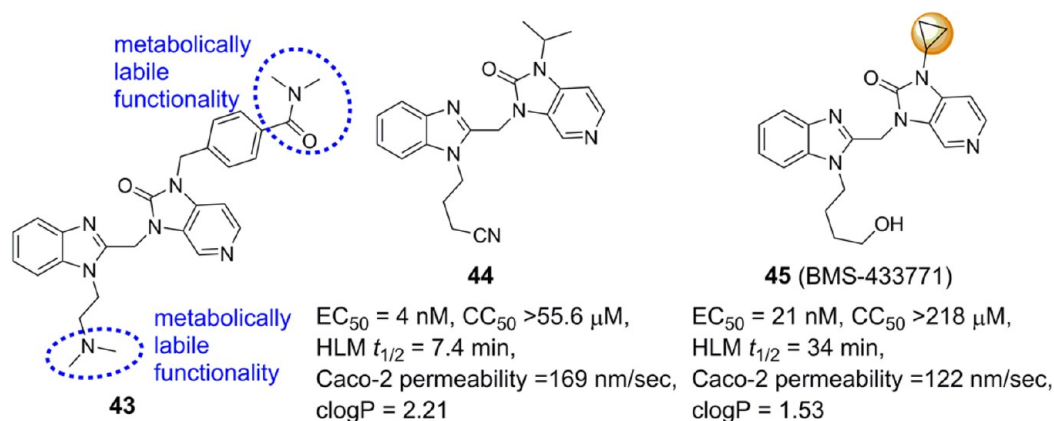


Figure 19. Structures, in vitro potency, and physicochemical properties of RSV fusion inhibitors 43–45.

oral anti-RSV activity in RSV-infected mice. However, **43** undergoes significant *N*-demethylation at its dimethylamine and dimethylamide functionalities as shown in Figure 19.⁶⁶ To address this metabolic liability of **43**, these investigators replaced the dimethylamino ethyl substituent at *N*₁ of the benzimidazole ring with the butyronitrile moiety and the bulky substituent at benzimidazolone ring with a small substituent (e.g., isopropyl) to yield compound **44**, having excellent antiviral potency and Caco-2 permeability as shown in Figure 19.¹⁴ However, compound **44** had a poor human liver microsome (HLM) stability. This drawback was remediated by replacing the isopropyl substituent with an isosteric cyclopropyl ring, which is less lipophilic (hydrophobic substituent constant π for cyclopropyl is 1.2)⁶⁷ than the isopropyl group (π = 1.53).⁶⁸ Through polarity-enhancing molecular modifications (i.e., isopropyl to cyclopropyl and butyronitrile to hydroxybutyl), it was possible to develop candidate **45** as shown in Figure 19. Compound **45** showed excellent plasma exposure in rats, mice, dogs, and monkeys, a dose-dependent reduction in RSV titers in the lungs of infected animal models, did not produce genotoxicity in the Ames mutation assay, and an IC_{50s} > 26.5 μM against major drug metabolizing CYP450 isoforms.¹⁴

Anti-HIV Clinical Candidate Drugs. HIV-1 RT Inhibitor 47 (Nevirapine/Viramune). Compound **47** (nevirapine), approved as a drug in 1996, is a first-generation non-nucleoside HIV-1 reverse transcriptase inhibitor (NNRTI) used for the treatment of HIV infected patients.⁶⁹ HIV-1 RT is a well established target for the development of inhibitors for the treatment of HIV infections. The precursor of compound **47**, the *N*-11 ethyl analogue **46**, demonstrated potential metabolic liability due to oxidative *N*-deethylation metabolism. To overcome this problem, the *N*-11 ethyl group on the tricyclic bispyridodiazepinone core was replaced with the cyclopropyl moiety to yield the metabolically more stable compound **47** as shown in Figure 20.¹⁸

HIV-1 RT Inhibitor 48 (Efavirenz/Sustiva). Compound **48** (DMP-266/efavirenz),⁷⁰ approved in 1998, is a second-generation NNRTI used for the treatment of HIV infected patients (Figure 21). The favorable contacts between the smaller, less polarizable cyclopropyl ethynyl moiety in **48**, in contrast to bulky methyl substituted aromatic pyridine ring in **47**, and the mutable HIV-1 RT allosteric binding site aromatic side chains of Tyr181 and Tyr188 are very limited.^{70,71} As a result, these interaction patterns with the target enzyme allow compound **48** to adapt to Tyr181Cys and Tyr188Cys of the mutant HIV-1 RT much better than compound **47**.^{70,71}

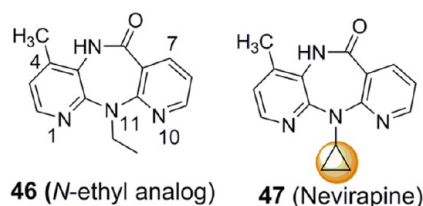


Figure 20. Structures of HIV-1 RT inhibitors **46** and **47**.

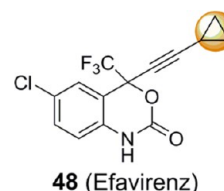


Figure 21. Structure of HIV-1 RT inhibitor **48**.

HIV-1 RT Inhibitor 50 (Abacavir/Ziagen). Abacavir (compound **50**), approved by the U.S. FDA in 1998, is a synthetic carbocyclic nucleobase prodrug of carbovir (compound **49**) that upon oral administration undergoes unique intracellular metabolic activation to a potent HIV-1 RT inhibitor, carbovir triphosphate.⁷² Compound **49** has shown excellent in vitro anti-HIV activity; however, it had low oral bioavailability in rats and monkeys and a limited CNS penetration.⁷² Among the various C-6 amino substituents that were investigated to increase the oral bioavailability and CNS penetration of **49**, the cyclopropyl amino derivative yielded compound **50**, with significant oral bioavailability, as well as CNS penetration as shown in Figure 22.⁷²

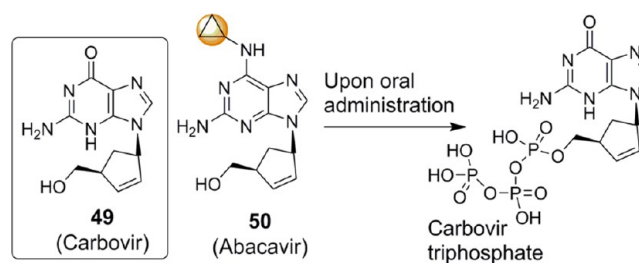


Figure 22. Structures of HIV-1 RT inhibitors **49** and **50**.

A cyclopropane-containing clinical HIV-1 RT inhibitor (MIV-150) is described in Supporting Information.

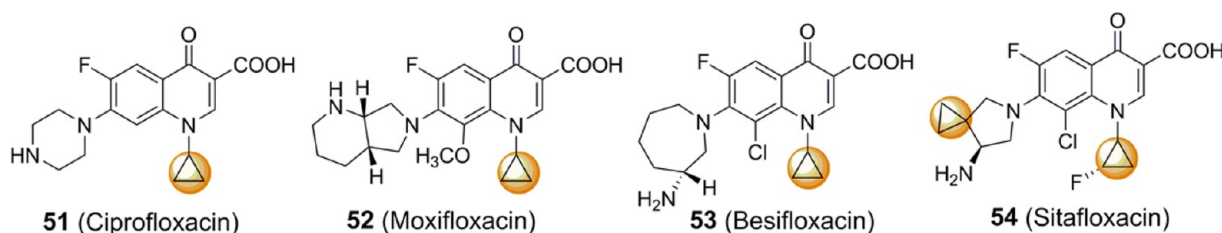


Figure 23. Structures of quinolone antibacterial drugs 51–54.

Antibacterial Clinical Drug Candidates. *Quinolone Antibacterials 51–54.* The quinolone antibacterials have become an important class of chemotherapeutic drugs since the introduction of nalidixic acid as an antibacterial drug in the 1960s.⁷³ However, nalidixic acid and structurally related analogues lack activity against Gram-positive bacteria, a feature that limits their therapeutic effectiveness.⁷⁴ Extensive SAR studies have led to the introduction of a fluoro group at position 6, a piperazine ring at position 7, and more importantly, a cyclopropyl substituent at position 1 of the quinolone core.^{75,76} These modifications eventually resulted in more than a dozen 1-cyclopropyl-containing fluoroquinolone antibacterial drugs. Representative of these are compound 51/ciprofloxacin (Ciloxan, Cipro), compound 52/moxifloxacin (Vigamox, Avelox, Moxeza), compound 53/besifloxacin (Besivance), and compound 54/sitafloxacin (Gracevit) as shown in Figure 23. The cyclopropyl ring contributed toward increased antibacterial potency and a wider antibacterial spectrum including both Gram-negative and Gram-positive bacterial infections. Moreover, the cyclopropyl ring in these quinolone antibacterials may contribute to drug binding to the binary complex of bacterial DNA gyrase/topoisomerase enzyme–DNA complex and produced an optimized PK profile.

DHP-I Inhibitor 55 (Cilastatin). This cysteine derivative (compound 55/MK0791) is a high affinity reversible inhibitor of the renal enzyme dehydropeptidase-I (DHP-I) as shown in Figure 24.⁷⁷ DHP-I is responsible for the hydrolytic degradation

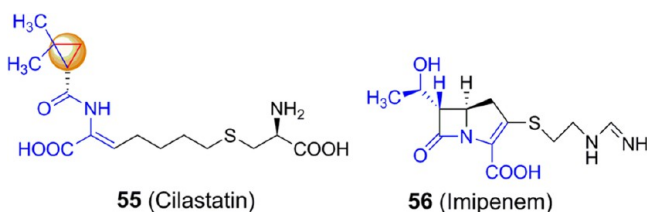


Figure 24. Structures of compounds 55 and 56.

of the β -lactam ring present in the antibacterial drug 56 (imipenem).⁷⁸ Thus, compound 55, when combined with 56 (marketed as Primaxin), increases compound 56's in vivo stability and prolongs antibacterial action by preventing the metabolism of 56 to inactive compounds.⁷⁹

Compound 56 is rapidly metabolized in the kidney by the enzyme DHP-I, which decreases the urinary levels of the drug below the minimum inhibitory concentration of certain bacteria that cause urinary tract infections.⁸⁰ Birnbaum and co-workers⁷⁷ addressed this problem by designing peptide compounds carrying a dehydro (olefinic) bond to mimic the double bond present in the five membered ring of 56, with the aim of developing a competitive inhibitor of DHP-I that could be used in combination with 56 to decrease its metabolism and thus to prolong its antibacterial action. These efforts led to discovery of the cyclopropyl-containing compound 55, which, except for the

dehydro bond and the carboxyl and the amino groups both directly attached to the dehydro bond, is dissimilar from 56. The coordination of the *N*-terminal amino group with Zn1 is important for the hydrolysis of peptide substrates. Similarly, the hydroxyl group of 56 coordinates with Zn1 and undergoes hydrolysis. Because compound 55 contains a cyclopropyl moiety instead of an amino of dipeptide substrates and a hydroxyl group as in 56, it does not coordinate with Zn1 and, thus, can inhibit enzyme activity.⁸¹

On the basis of X-ray crystallographic data⁸² and on computational modeling,⁸¹ it was concluded that repulsion exists between the cyclopropyl ring and Zn1 at the active site of DHP-I. Moreover, the cyclopropyl moiety entered into hydrophobic interaction with the side chain of Tyr68, thus preventing departure of the leaving group from the transition state.⁸² As stated earlier, repulsion causes the carbonyl group of 55 to move slightly away and, thus, to be shielded from nucleophilic attack. Overall, the above observations explain why compound 55 is a DHP-I inhibitor and not a substrate.⁸³

■ RESPIRATORY SYSTEM PRECLINICAL/CLINICAL DRUG CANDIDATES

Phosphodiesterase 4 (PDE4) Inhibitor 57 (Roflumilast/Daliresp). Compound 57, introduced in the U.S. market in 2011, and its pharmacologically active *N*-oxide metabolite, are potent and selective PDE4 inhibitors (PDE4B IC₅₀ = 0.84 nM) as shown in Figure 25.⁸⁴ Compound 57 is indicated for the

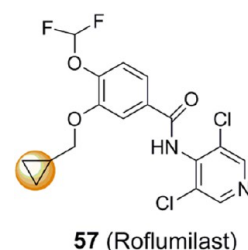


Figure 25. Structure of phosphodiesterase 4 inhibitor 57.

treatment of chronic obstructive pulmonary disease (COPD).⁸⁵ The cyclopropylmethyl moiety of this drug forms hydrophobic interactions within the large hydrophobic Q2 pocket formed by Met411, Phe414, Met431, and Phe446 residues of PDE4B (PDB ID 1XMU).⁸⁴

Leukotriene D₄ (LTD₄) Antagonist 59 (Montelukast/Singulair). This drug (compound 59/MK-476)⁸⁶ is approved by the U.S. FDA for the treatment of asthma and allergic rhinitis. The montelukast precursor compound 58 (MK-679/Venzair), a LTD₄ antagonist (LTD₄ IC₅₀ = 3.1 nM), produced severe liver abnormalities in patients due to induction of peroxisomal enzyme activity (mice 400 mg/kg per oral peroxisomal enzyme induction/PEI = 65%), an effect that prompted its withdrawal

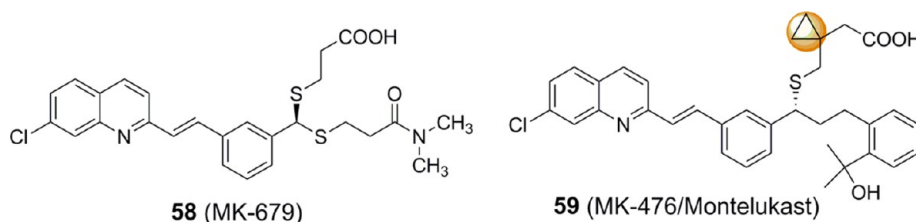


Figure 26. Structures of LTD₄ antagonists **58** and **59**.

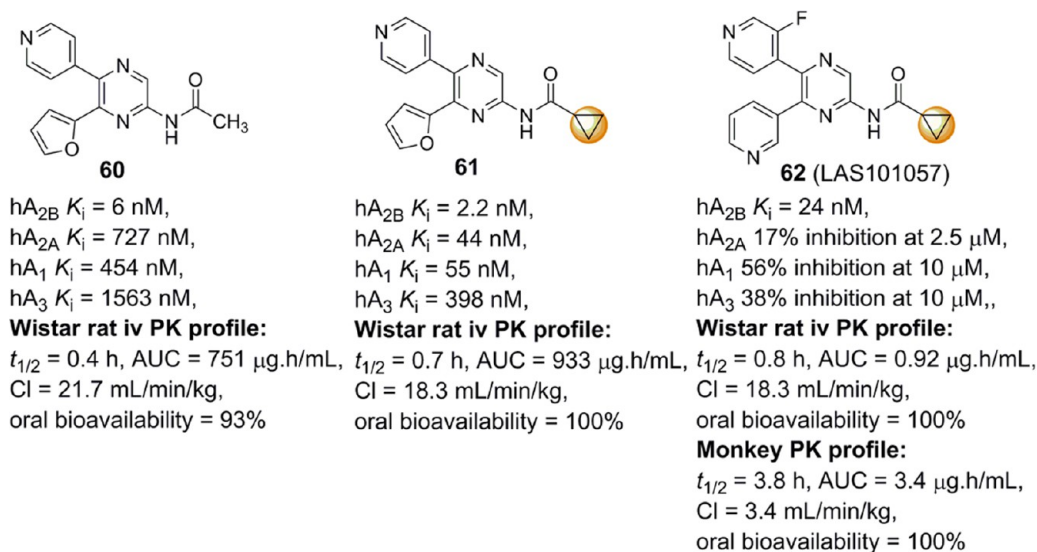


Figure 27. Structures, in vitro potency, and PK properties of adenosine A_{2B} antagonists **60**–**62**.

from the market as shown in Figure 26.⁸⁶ To attenuate liver toxicity, Labele and colleagues⁸⁶ first replaced one of the thioacetal groups in **58** with an arylalkyl group and this resulted in enhanced potency. However, most of the **58**-induced peroxisomal enzyme activity was eliminated by introducing geminal substituents, specifically a spirocyclopropyl fragment, on the β -carbon of the thiopropionic acid side chain. Taking cues from the observation that peroxisomes recognize and β -oxidize fatty acids, the unsubstituted β -position, as in **58**, was thought to be the cause for significant PEI activity. Consequently, the PEI activity of **58** was successfully eliminated by attaching the spirocyclopropyl ring to the β -carbon.⁸⁶ These aforementioned changes led to the clinically validated thiomethyl cyclopropyl acetic acid side chain analogue **59** (LTD₄ IC₅₀ = 0.5 nM, PEI = 16%) as shown in Figure 26.⁸⁶

Adenosine A_{2B} Receptor Antagonist 62. The adenosine A_{2B} receptor, a G-protein coupled receptor, has been shown to mediate the release of inflammatory mediators from mast cells and airways epithelial cells, which plays a role in the pathophysiology of asthma.⁸⁷ Eastwood and co-workers⁸⁸ have conducted SAR studies on a promising diaryl substituted pyrazine amide lead **60** as shown in Figure 27, with the intention of developing orally active compound for the treatment of asthma. Although **60** showed an excellent bioavailability as well as an acceptable plasma exposure, it had a very short intravenous half-life (Figure 27). The replacement of the methyl amide of **60** with a cyclopropyl amide yielded compound **61**, with significantly improved potency and PK profile (Figure 27). Because the cyclopropyl amide analogue **61** had a better overall therapeutic feature than other alkyl and aryl amides, this ring structure was kept constant and the two pendant aryl rings were modified.

Implementation of these changes led to the discovery of a potent, selective, and orally efficacious clinical candidate, compound **62** (LAS101057),⁸⁸ which, in addition, was devoid of metabolically labile and potentially toxicophoric furan ring⁸⁹ as shown in Figure 27.

I κ B Kinase 2 (IKK2) Inhibitor 64. The IKK complex is comprised of two catalytic subunits, IKK1 and IKK2, and a regulatory subunit, nuclear factor- κ B (NF- κ B) essential modulator (NEMO).⁹⁰ It is hypothesized that IKK2 catalyzes the phosphorylation of I κ B in the cytoplasm, decreasing its association with NF- κ B and allowing for the nuclear translocation of NF- κ B to regulate gene transcription.⁹¹ The dysfunction of the NF- κ B signaling pathway has been proposed to be involved in the pathophysiology of rheumatoid arthritis, COPD, and asthma.⁹² Because IKK1-deficient mice showed skeletal and skin abnormalities,⁹² selective IKK2 inhibitors could be used to treat rheumatoid arthritis, COPD, and asthma. Liddle and co-workers⁹³ sought to develop selective IKK2 inhibitors for the treatment of various inflammatory disorders. Their program began with the potent and selective IKK2 inhibitor **63** shown in Figure 28. The activity of compound **63** in a whole blood cellular assay (inhibition of lipopolysaccharide (LPS) stimulated TNF α in human whole blood) was decreased by $\sim$ 100-fold compared to IKK2 enzymatic inhibitory activity. Subsequently, compound **63** optimization was initiated to increase whole blood activity and enhance the PK profile in preclinical studies without compromising potency and selectivity toward IKK2. Among the various noncyclic and cyclic aliphatic substituents introduced at the 2-position of the 7-azaindole core structure, the cyclopropyl substituent (compound **64**) turned out to be superior in terms of potency, selectivity, activity in whole blood, and favorable

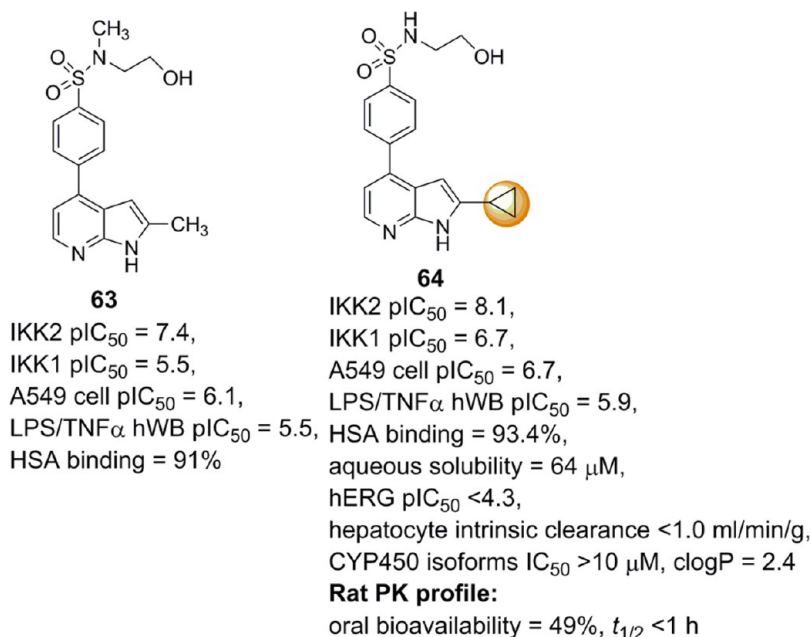


Figure 28. Structures, in vitro potency, and PK properties of IKK inhibitors 63 and 64.

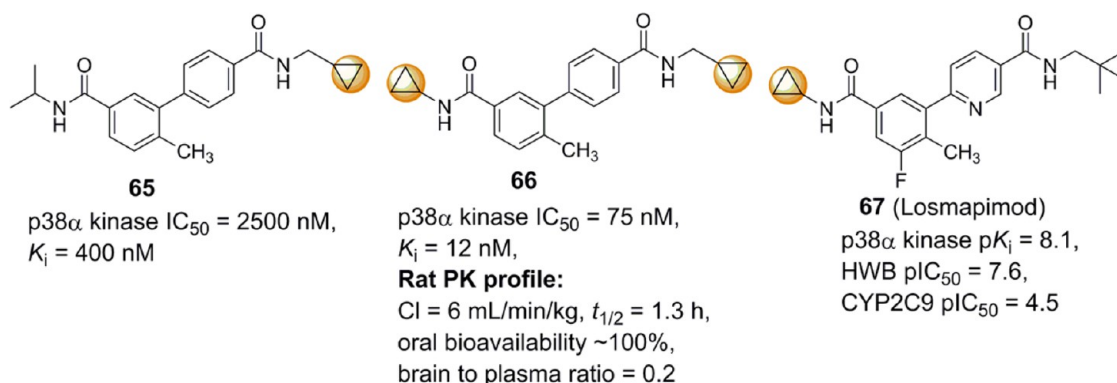


Figure 29. Structures, in vitro potency, and PK properties of p38 α MAP kinase inhibitors 65–67.

in vivo clearance and oral bioavailability in the rat as shown in Figure 28.⁹³

p38 α MAP Kinase Inhibitor 67 (Losmapimod). Compound 67 is currently undergoing clinical trials for the treatment of COPD (NCT01218126) and acute coronary syndrome (NCT02145468). p38 α MAP kinase, a serine/threonine kinase, has been implicated in the production of inflammatory cytokines such as TNF α and IL-1 β , thus making this kinase an attractive target for developing effective antirheumatic drugs.⁹⁴ Angell et al.⁹⁵ began p38 α MAP kinase inhibitor discovery chemistry with a biphenylbenzamide scaffold. These SAR investigations led to the isopropyl analogue 65 (Figure 29). The replacement of the isopropyl group with a cyclopropyl moiety yielded compound 66 (Figure 29). X-ray cocrystal studies (PDB ID 3IPH) revealed a perfect fit of the cyclopropyl ring within the precise lipophilic pocket lined by Leu74 and Phe169. These findings also revealed the strict steric requirements of this pocket in the enzyme.⁹⁵ Because compound 66 is endowed with an excellent PK profile in rats, further investigations on it are warranted (Figure 29). It should be noted that compound 66 had a low brain to plasma ratio, thus decreasing the likelihood of 66 producing CNS toxicity.⁹⁵ On the knowledge that the cyclopropylamine moiety fits perfectly within the lipophilic pocket of p38 α kinase,

Aston and co-workers⁹⁶ kept this moiety while performing structural modifications on the rest of the structure of 66. The goal was to improve the inhibition of TNF α production in human whole blood and decrease the inhibition of drug metabolizing CYP450 2C9 enzyme. To reach this goal, these investigators modified the biphenyl scaffold and replaced the cyclopropylmethyl substituent with a *tert*-butylmethyl group, leading to the discovery of the clinical candidate 67 as shown in Figure 29.⁹⁶ The replacement of the phenyl and cyclopropyl rings in 66 with pyridine-3-yl and *tert*-butylmethyl groups, respectively, was necessary to improve human whole blood activity and decrease CYP2C9 inhibition. The replacement of the cyclopropylmethyl group on biaryl carboxamide moiety in 66 with a *tert*-butylmethyl group led to a final candidate 67.

Interleukin-2 Inducible T-Cell Kinase (ITK) Inhibitor 70. The ITK has been shown to play a role in T-cell development, differentiation, and effector functions.⁹⁷ Many studies have demonstrated that ITK is essential for the control of T helper 2 (Th2) responses and pathological conditions such as lung inflammation, eosinophil infiltration, and mucous production.⁹⁸ Consequently, ITK is a therapeutic target for the development of drugs to treat allergic asthma and inflammatory disorders.

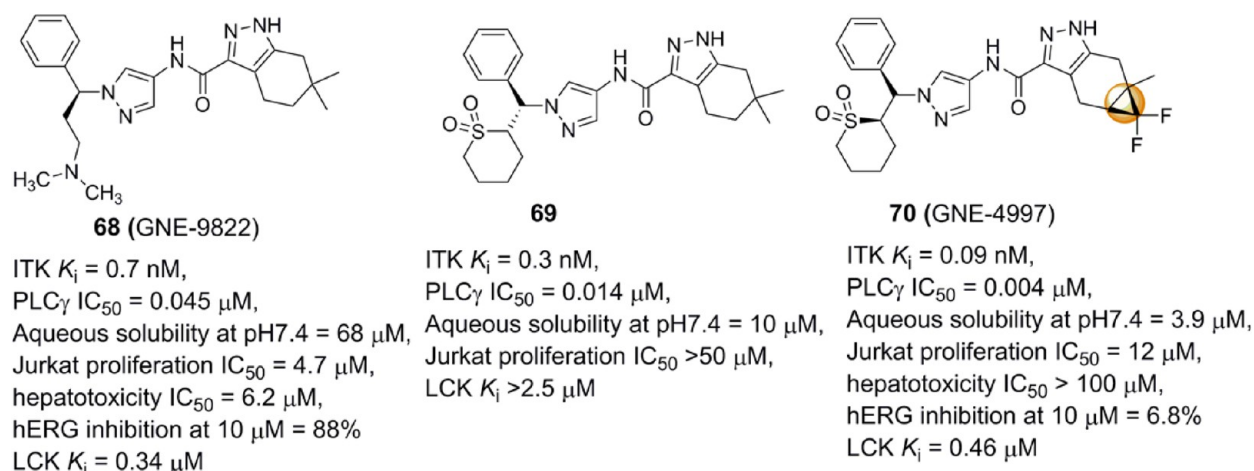


Figure 30. Structures, in vitro potency, and physicochemical properties of ITK inhibitors 68–70.

Burch and co-workers⁹⁹ previously disclosed a tetrahydroindazole scaffold **68** (GNE-9822), with potent and selective inhibition of ITK activity (Figure 30). Further profiling of **68** revealed its off-target binding and cytotoxicity toward hepatocytes and Jurkat cells. Furthermore, **68** significantly inhibited the human ether-a-go-go-related gene (hERG) encoded potassium channel.¹⁰⁰ These liabilities made this compound unsuitable for the treatment of asthma. Therefore, Burch and colleagues¹⁰⁰ decided to optimize **68** to minimize adverse effects. Their results indicated that reducing the basicity of tetrahydroindazole compounds ($pK_a < 7.5$) was associated with reduced cytotoxicity. Consequently, they replaced the basic dimethylaminoethyl side chain on benzylic carbon with the cyclic sulfone, yielding compound **69**, with an excellent inhibition of ITK enzyme activity, phospholipase C- γ (PLC- γ) phosphorylation in Jurkat cells, and a desirable reduction in cytotoxicity to Jurkat cells as shown in Figure 30. Subsequently, these investigators focused on increasing the ITK inhibitory potency. Ultimately, they optimized **69** to increase the interactions between **69** and the lipophilic pocket present in the vicinity of Phe435 of ITK active site. This was done by replacing the geminal dimethyl substituent with a difluorocyclopropyl methyl group, leading to the identification of compound **70** (GNE-4997), with drug-like properties as shown in Figure 30.¹⁰⁰ The X-ray cocrystal structure of **70** with ITK (PDB ID 4rfm) revealed efficient space filling of the lipophilic pocket present in close proximity to a gatekeeper residue Phe435 by a difluoromethylene moiety of cyclopropane ring. This may explain the enhanced potency of **70**.¹⁰⁰

Histamine H₄ Receptor (H₄R) Antagonist 72. The H₄R, an aminergic G-protein coupled receptor, is expressed on immune cells and has been shown to be a contributing factor for diseases whose pathophysiology is linked to inflammation such as asthma, allergic rhinitis, pain, irritable bowel disease, and cancer. Consequently, the H₄R antagonist may be useful in treating the above-mentioned diseases.¹⁰¹ Mowbray and co-workers¹⁰² recently disclosed the discovery of compound **72** (ZPL-3893787/PF-3893787). One of the early lead structures was the trisubstituted pyrimidine compound **71** that showed selective H₄R antagonist potency. In addition, this compound had drug-like physicochemical properties including aqueous solubility, permeability, and oral bioavailability as shown in Figure 31. However, it was predicted to exhibit a high clearance and extended half-life from rat and dog PK studies. Nonetheless,

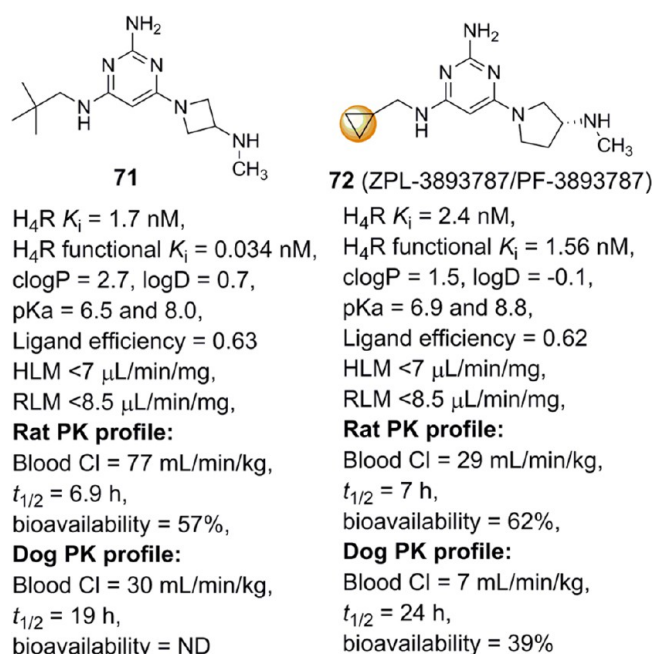


Figure 31. Structures, in vitro potency, and PK properties of histamine H₄ receptor antagonists **71** and **72**.

compound **71** served as an excellent tool compound for further optimization and detailed preclinical investigations. These efforts eventually resulted in discovery of a clinical compound, **72**, as shown in Figure 31. Compound **72** had a significantly lower rate of clearance compared to **71** in both rat and dog.¹⁰² This was reasoned based on a one log unit lower log D of **72** compared to that of **71**. However, compound **72** was still predicted to exhibit a long human half-life of 40 h. Compound **72** is currently undergoing phase II clinical trials for the treatment of atopic dermatitis (NCT02424253).

The replacement of the *tert*-butylmethyl group in **71** with a cyclopropylmethyl group gave **72**, with an improved PK profile. In contrast, replacement of the cyclopropylmethyl group in **66** with the *tert*-butylmethyl group yielded a final drug candidate **67**. Therefore, there are no firm rules and that the same exchange of groups in different molecules does not give the same results.

Cyclopropane-containing lumacaftor useful in the treatment of cystic fibrosis is described in Supporting Information.

■ ANTI-INFLAMMATORY PRECLINICAL/CLINICAL DRUG CANDIDATES

Lymphocyte-Specific Protein Tyrosine Kinase (Lck) Inhibitor 74.

Lck belong to the Src family of tyrosine kinases.¹⁰³ It is primarily expressed in T cells, where it facilitates T cell proliferation and production of interleukin 2.¹⁰⁴ Therefore, a compound that can potently and selectively inhibit Lck will also inhibit T cell activation and, as a result, be of potential use in the treatment of acute and chronic T cell-mediated autoimmune and inflammatory disorders.¹⁰⁵ Wityak and colleagues¹⁶ began SAR optimization of 2-amino-5-carboxamidothiazoles as novel Lck inhibitors. These SAR studies led to the identification of the phenyl carboxamide analogue 73 (hLck IC₅₀ = 0.89 μM), which was further modified to obtain the cyclopropane carboxamide analogue 74 (hLck IC₅₀ = 0.035 μM) (Figure 32). These

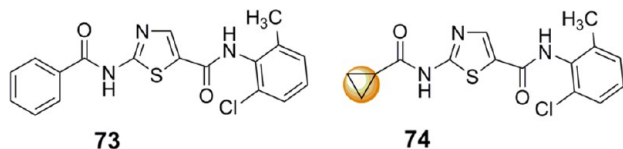


Figure 32. Structures of Lck inhibitors 73 and 74.

compounds are clear demonstration of the remarkable influence that a less lipophilic cyclopropyl moiety can have as a successful surrogate for the phenyl substituent. Compound 74 also showed excellent selectivity when subjected to in vitro screening against a panel of potential kinase targets.¹⁶ Whether a cyclopropyl ring has contributed toward excellent selectivity profile remains to be evaluated.

Bruton's Tyrosine Kinase (BTK) Inhibitor 78. Pharmacological inhibition of BTK, a downstream kinase of SYK kinase, is an excellent strategy to develop drugs to treat rheumatoid arthritis due to its key role in activating B cells.¹⁰⁶ Consequently, Lou and co-workers¹⁰⁷ began their small molecule BTK inhibitor discovery efforts with the initial lead 75 (BTK IC₅₀ = 10 nM). (Figure 33) Compound 75 showed suboptimal efficacy when tested in human whole blood (HWB) assays (HWB IC₅₀ for CD69 inhibition >1 μM) and had a high molecular weight and lipophilicity.¹⁰⁷ To surmount these problems, these investigators conducted further SAR studies involving three molecular modifications: (a) truncation of the imidazopyrazine ring to a monocyclic pyridone, (b) constraining of the carboxamide into a dihydroisoquinoline ring, and (c) replacing the hydrophobic *tert*-butyl group with a dimethylamino group that yielded 76 (BTK IC₅₀ = 7 nM and HWB IC₅₀ = 100 nM).¹⁰⁷ However, the poor aqueous

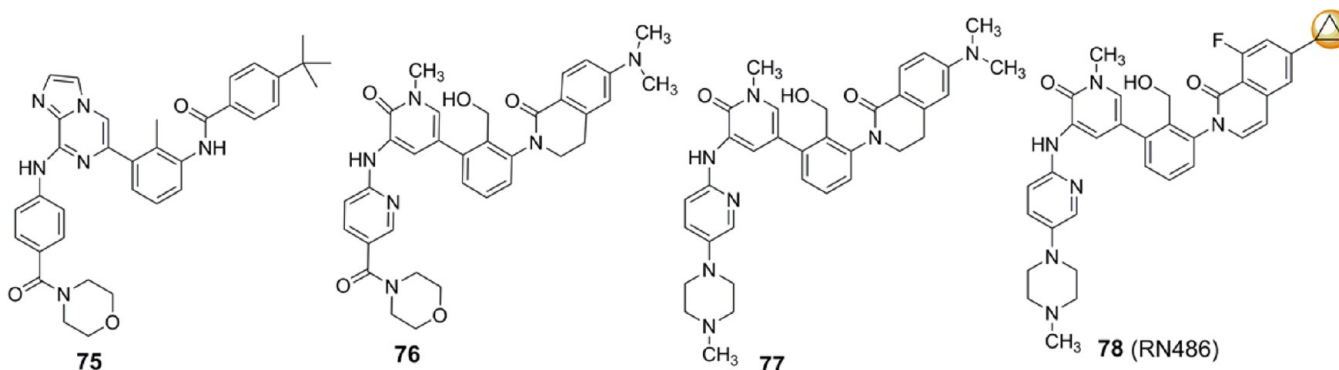


Figure 33. Structures of BTK inhibitors 75–78.

solubility of 76 prompted these authors to replace the morpholine carbonyl functionality with a water-solubilizing *N*-methylpiperazine moiety to yield compound 77, which not only exhibited improved aqueous solubility but also a greater potency in HWB assays. Subsequent structural alterations, such as substitution of the fluoro and cyclopropyl groups on the isoquinoline ring and introduction of unsaturation in isoquinoline ring, yielded compound 78/RN486 (BTK K_d = 0.3 nM and HWB IC₅₀ = 17 nM) as shown in Figure 33.¹⁰⁷ Furthermore, unlike 77, compound 78, bearing a cyclopropyl moiety instead of *N,N*-dimethylamino group, is expected to obviate the formation of hepatotoxic primary aniline metabolites upon didemethylation by CYP450 oxidizing enzymes.¹⁰⁷

Uric Acid Transporter 1 (URAT1) Inhibitor 80 (Lesinurad/Zurampic). By selectively inhibiting URAT1, a transporter in kidney cells that mediates the renal reabsorption of urate, compound 80 (lesinurad/RDEA-594) is a uricosuric drug with potential to treat gout.¹⁰⁸ Compound 80 was serendipitously discovered that the major amide hydrolysis metabolite of a discontinued NNRTI, compound 79 (RDEA-806), unexpectedly lowered the uric acid levels in HIV patients as shown in Figure 34.¹⁰⁹

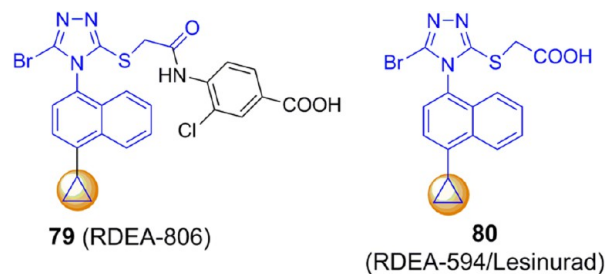


Figure 34. Structures of URAT1 inhibitors 79 and 80.

p38α MAP Kinase Inhibitor 83. Liu and co-workers¹¹⁰ sought to develop potent p38α MAP kinase inhibitors for the treatment of rheumatoid arthritis. They began SAR studies with a potent lead compound 81, which had a high in vivo clearance and lower plasma exposures as shown in Figure 35. These aforementioned undesired properties resulted from the hydrolytic degradation of *N*-methoxybenzamide into a major, inactive acid metabolite. Subsequently, they replaced the *N*-methoxy group with various alkyl groups, leading to significantly less potent compounds. They hypothesized that replacing the methoxy group with an electron withdrawing group would render the benzamide NH a strong hydrogen bond donor and higher potency. This NH forms a key hydrogen bond with the Glu71 of p38α. Among the alkyl groups tried, the cyclopropyl

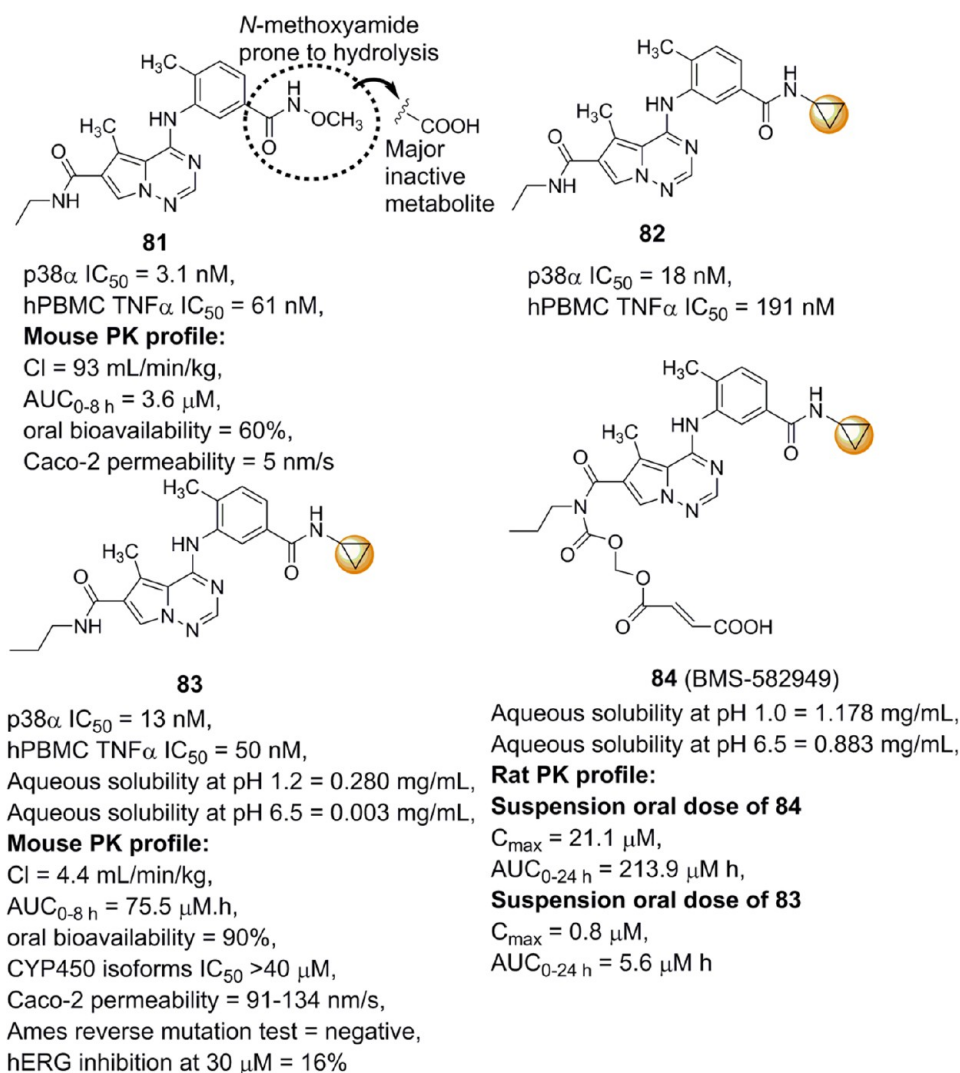


Figure 35. Structures, in vitro potency, and PK properties of p38 α MAP kinase inhibitors **81**–**84**.

substituent (e.g., compound **82**) demonstrated p38 α MAP kinase inhibition that was comparable to that of lead compound **81**. This could be a result of the sp² character of the cyclopropyl carbons. They also anticipated an improved PK profile as a result of insertion of the cyclopropyl moiety at the benzamide. Furthermore, SAR exploration at the other carboxamide group ultimately yielded clinical candidate, **83**, which had excellent enzyme potency and significant activity against LPS-induced TNF α production in human peripheral blood mononuclear cells (hPBMC). Compound **83** inhibited LPS-induced TNF α production in vivo more efficaciously than **81**. Although **83** is four times less potent than **81** against p38 α , it showed higher in vivo efficacy in both acute and chronic disease models.¹¹⁰ This was shown through the improved PK properties of **83** compared to **81** (Figure 35). Compound **83** has been investigated in phase II clinical trials for the treatment of severe plaque psoriasis (NCT00399906), atherosclerosis (NCT00570752), and rheumatoid arthritis (NCT00605735).

Compound **83** had a pH-dependent solubility of 0.280 and 0.003 mg/mL at pH 1.2 and 6.5, respectively. Consequently, it was considered to be of limited use for the treatment of rheumatoid arthritis as rheumatoid arthritis patients are usually prescribed with the drugs that increase stomach pH.¹¹¹ To address the above problem, Liu and co-workers¹¹² decided

to develop a prodrug of compound **83** that is chemically stable between pH 1 and pH 7 and totally biotransformed into active metabolite **83** without releasing toxic byproducts. Ultimately, prodrug **84** (BMS-582949), as shown in Figure 35, was developed and upon oral dosing to rats as a suspension showed a superior PK profile compared to the corresponding suspension dose of **83**.¹¹²

Retinoic Acid Receptor-Related Orphan Receptor Gamma (ROR γ) Inhibitor **87.** ROR γ is a nuclear receptor that regulates the production of IL-17 and the differentiation of pro-inflammatory T helper 17 cells that play an important role in the pathogenesis of autoimmune diseases such as psoriasis and rheumatoid arthritis.¹¹³ Therefore, ROR γ serves as a therapeutic target to develop treatments for immunological diseases. Toward this objective, Hirata and co-workers¹¹⁴ began optimization of HTS-derived 1,2,5-trisubstituted 1,3,4-triazole hit compound that resulted in **85**. However, **85** suffered from poor metabolic stability as shown in Figure 36. The replacement of the ethyl group with a cyclopropyl moiety led to **86** with comparable ROR γ inhibition but with significantly improved metabolic stability. Because cyclopropyl analogue **86** was more stable in human liver microsomal preparations, this moiety was kept in subsequent optimization schemes that ultimately resulted in the discovery of **87**, which had submicromolar ROR γ inhibition

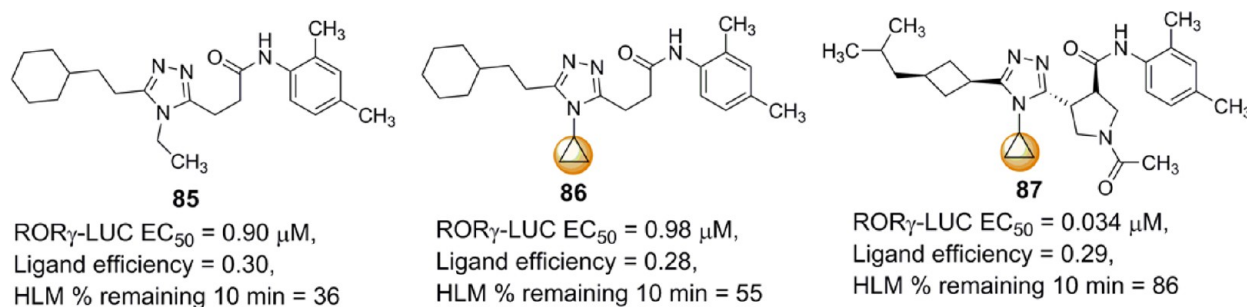


Figure 36. Structures, in vitro potency, and liver microsomal stability data of $ROR\gamma$ inhibitors 85–87.

and excellent stability in human liver microsomal preparations (Figure 36).

■ CNS ACTIVE PRECLINICAL/CLINICAL DRUG CANDIDATES

Compounds 88 (Milnacipran/Savella) and 89 (Levomilnacipran/Fetzima). Compound 88 (Z-Milnacipran), previously known as midalcipran, was discovered in 1987 by Bonnaud and co-workers.¹¹⁵ Compound 88, approved by the FDA in 2009, is a mixture of enantiomers, (1*R*,2*S*) and (1*S*,2*R*), whereas compound 89 (levomilnacipran), approved by the FDA in 2013 to treat major depressive disorders, is a pure enantiomer (1*S*,2*R*-milnacipran) as shown in Figure 37. Compound 89

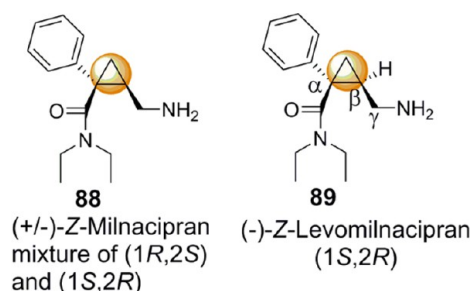


Figure 37. Structures of serotonin and norepinephrine reuptake inhibitors 88 and 89.

produced a 50- and 13-fold greater inhibition of norepinephrine and serotonin reuptake, respectively, than that of the racemic 88.¹¹⁶ It is likely that compounds 88 and 89 produce their antidepressant action by competitively inhibiting serotonin and norepinephrine reuptake in the CNS. The cyclopropyl ring conformationally restricts the pendant tertiary carboxamide and primary γ -amine groups in a Z-geometry.¹¹⁵ These geometric constraints produced by the cyclopropane ring, as well as the presence of an unsubstituted phenyl ring at the α -position of the carboxamide group and *trans* to the γ -amine (mimic of a typical *trans*-like arrangement of an aryl/heteroaryl ethylamine neurotransmitters: norepinephrine and serotonin), collectively form a pharmacophore framework.

Compounds 91 (Naltrexone/Vivitrol) and 92 (Nalmefene/Revex). Compound 91 (naltrexone) binds with high affinity to μ -opioid (K_i = 0.11 nM) and κ -opioid (K_i = 0.19 nM) receptors and with lower affinity to δ -opioid receptor (K_i = 60 nM).¹¹⁷ Compound 92 (nalmefene) is an opioid receptor antagonist (μ -opioid receptor K_i = 0.24 nM, κ -opioid receptor K_i = 0.083 nM, and δ -opioid receptor K_i = 16 nM).¹¹⁸ The cyclopropylmethyl substituent at the N-17 of the pentacyclic scaffold in 91 and 92 mimics the allyl “message” group present in compound 90

(naltrexone) and is thought to optimally fit in a narrow hydrophobic antagonist cleft in the μ -opioid receptor as shown in Figure 38.¹¹⁹ The cyclopropylmethyl-substituted opioid receptor antagonists 91 and 92 have improved potency compared to the allyl substituted compound 90. The enhanced potency of compounds 91 and 92, both more lipophilic than compound 90, could be a result of their extensive CNS distribution. Moreover, the relatively bulky antagonist-directing cyclopropylmethyl group¹²⁰ contributed to their antagonism of the opioid receptors. Not unexpectedly, the *N*-dealkylated metabolites usually act as an opioid receptor agonists.

Compound 93 (Buprenorphine/Buprenex/Subuxone/Subutex). Compound 93 is a highly lipophilic compound with a long duration of action (Figure 39). It is a partial μ -opioid receptor agonist (monkey brain μ -opioid receptor apparent K_i = 0.08 nM) and a weak κ - (monkey brain κ -opioid receptor apparent K_i = 0.44 nM) and δ -opioid receptor (monkey brain δ -opioid receptor apparent K_i = 0.82 nM)¹²¹ antagonist approved by the U.S. FDA for the treatment of pain and opioid addiction. As previously explained, the antagonist profile of compound 93 is derived from the presence of the antagonist-directing cyclopropylmethyl group at N-17, apart from a hydrophobic and hydrogen bond-forming functionality at C-7.

Compound 94 (Samidorphan). Compound 94 as shown in Figure 40 was discovered in 2005 by Wentland and co-workers.¹¹⁷ It was designed based on naltrexone as a template. It acts as a μ -opioid receptor (K_i = 0.052 nM) antagonist. As previously stated, an antagonist-directing cyclopropylmethyl substituent at the N-17 confers μ -opioid receptor antagonist property to this drug. In combination with buprenorphine, it is currently undergoing FDA fast track clinical trial for the treatment of major depressive disorder.¹²²

Compound 95 (Tranylcypromine/(±)-*trans*-2-phenylcyclopropan-1-amine/Parnate). This drug is a cyclopropyl analogue of amphetamine synthesized by Burger and co-workers in 1948.¹²³ Subsequently, Tedeschi et al.,¹²⁴ have shown that it is a potent MAO inhibitor in vivo (Figure 41). The presence of the cyclopropyl moiety makes it a more stable compound than its ethylene analogue. The cyclopropyl moiety also offers a fixed stereochemistry that is resistant to spontaneous and bidirectional *cis*- to *trans*-isomer interconversions. Furthermore, it provides a rigid chiral backbone for achieving the desired three-dimensional placement of its pendant phenyl and amine groups to mimic the bioactive conformation of the endogenous phenylethylamine pharmacophore substrates of MAO. Compound 95 forms a covalent adduct at the C-4a position of the cofactor flavin-MAO-B enzyme complex through opening of the strained cyclopropyl ring and either simultaneous or subsequent release of ammonia¹²⁵ (Figure 41).

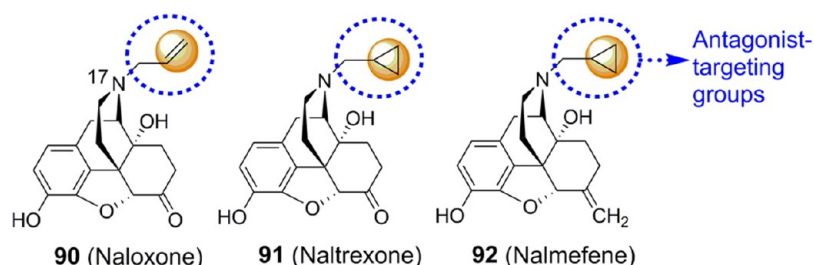


Figure 38. Structures of opioid antagonists 90–92.

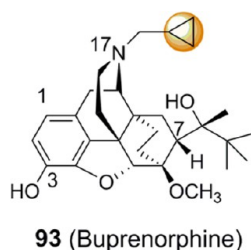


Figure 39. Structure of opioid receptor partial agonist 93.

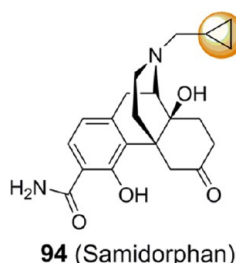


Figure 40. Structure of opioid receptor antagonist 94.

Compound 97 (Tasimelteon/Hetlioz). Because compound 96 (melatonin), an endogenous ligand, regulates sleep and the circadian rhythms by activating melatonin 1 and 2 receptors (MT_1 and MT_2), MT -receptors are an attractive area of research for development of drugs to treat insomnia.¹²⁶ Compound 97 (tasimelteon/VEC-162), a potent MT_1/MT_2 agonist, is approved by the U.S. FDA for the treatment of non-24-h sleep–wake disorder.¹²⁷ When compared to 96, the structure of 97 shows two differences, a 5-methoxy group constrained onto C-4 to form an indole isosteric dihydrobenzofuran nucleus and a conformationally constrained chiral *trans*-geometrical cyclopropyl linker located between the aromatic ring and the side chain carboxamide functional group as shown in Figure 42. On the basis of pharmacophore modeling and constrained analogue synthetic approaches,¹²⁸ it was hypothesized that the chiral *trans*-geometrical cyclopropane ring linker facilitates the specific orientation of the pendant pharmacophoric

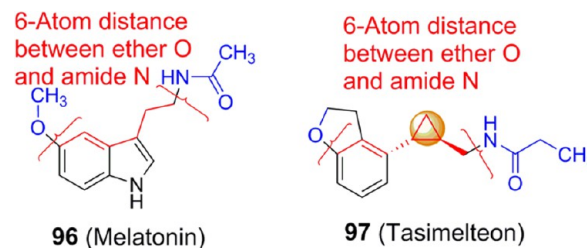


Figure 42. Structures of melatonin receptor agonists 96 and 97.

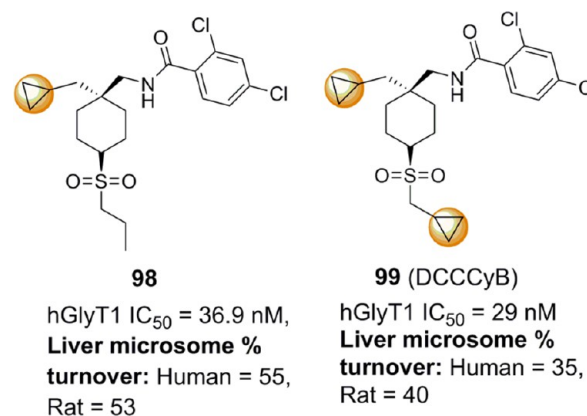


Figure 43. Structures, in vitro potency, and liver microsomal stability data of GlyT1 inhibitors 98 and 99.

groups of 97 (the 5-methoxy and the carboxamide highlighted in blue; the six-atom distance between the ether oxygen and the carboxamide *N* is highlighted in red) for effective binding to the MT -receptors.

Glycine Uptake Transporter 1 (GlyT1) Inhibitor 99. It has been postulated that the dysfunction of the *N*-methyl-D-aspartate (NMDA) receptor may play a critical role in the pathophysiology of schizophrenia.¹²⁹ It has been proposed that the levels of glycine, a coagonist whose presence is an absolute requirement for NMDA activation, are below saturation at synapses that are tonically maintained by GlyT1, a Na^+/Cl^- -dependent type 1

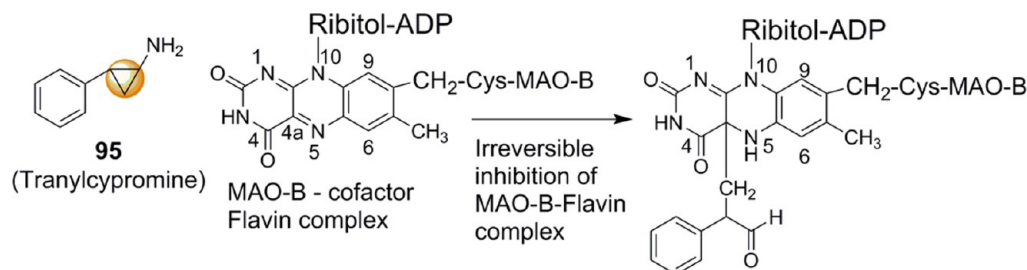


Figure 41. Structure and mechanism of action of MAO inhibitor 95.

glycine uptake transporter.¹³⁰ Therefore, GlyT1 inhibitors would be predicted to control synaptic glycine concentrations and to potentiate NMDA receptor function in vivo to ameliorate the negative symptoms of schizophrenia.¹³¹ Blackaby and co-workers¹³² initiated their human GlyT1 inhibitor development efforts around the cyclohexane sulfone analogue **98** as shown in Figure 43. Subsequent replacement of the *n*-propyl sulfonyl moiety with a cyclopropylmethyl sulfonyl moiety yielded **99** (DCCyB),¹³² with a marginal increase in potency. However, this molecular modification significantly improved human and rat liver microsomal turnover compared to **98** as shown in Figure 43.¹³² Compound **99** has a good PK profile in animal models. Furthermore, it is not a substrate of P-gp and thus achieves a high brain to plasma ratio of 2.3 and is efficacious in various rodent models.¹³²

Neurokinin-3 (NK-3) Antagonists 102 and 103. The NK-3 receptor, a G-protein coupled receptor, activated by neurokinin B (NKB), is expressed in the brain regions such as cortical regions and basal ganglia structures of the mammalian CNS. It has been hypothesized that the antagonism of NK-3 receptors may be useful in treating certain psychiatric diseases.¹³³ Smith and co-workers¹⁷ began SAR studies with a previously disclosed NK-3 antagonist, **100** (SB-222200), that also showed CNS activity.¹³⁴ However, in vivo data obtained with **100** revealed formation of significant levels of the circulating racemic ketone metabolite **101**, which had a low CNS permeability (Figure 44). These investigators wanted to develop a novel quinoline series of NK-3 antagonists with increased metabolic stability and CNS NK-3 receptor occupancy. Many analogues of **100** were prepared containing the ethyl group at the chiral center. However, similar to **100**, all of these analogues underwent oxidative metabolism at the ethyl group. Consequently, Smith and co-workers¹⁷ replaced the ethyl group with a cyclopropyl ring, with simultaneous substitution of the fluoro group on C-2 phenyl ring, leading to the identification of **102** (GSK172981), as shown in Figure 44. It may be noted that it is the ethyl to cyclopropyl exchange that contributed toward enhanced metabolic stability and not the other two molecular modifications such as methyl to amino and *meta*-fluoro substitutions.¹⁷ Many of the compounds reported by Smith and colleagues¹⁷ had a clogP of >6, including **102**. It is well-known that such a high clogP can increase the risk of attrition in later stages of drug development and therefore these investigators aimed to reduce the lipophilicity. To achieve this goal, they introduced a novel *tert*-sulfonamide substituent at the 3-position of the quinoline ring, yielding **103** (GSK256471),¹⁷ as

shown in Figure 44. Furthermore, **102** and **103** had a significantly higher cortical NK-3 receptor occupancy than the starting lead compounds. Both **102** and **103** were efficacious in various in vitro, ex vivo, and in vivo models, suggesting that they may have utility for the treatment of schizophrenia.¹³⁵

BACE1 Inhibitor 105. β -Site amyloid precursor protein (APP)-cleaving enzyme 1 (BACE1), a membrane-bound aspartyl protease, catalyzes the production of amyloid β ($A\beta$) neuropeptides.¹³⁶ Because the formation of $A\beta$ aggregates is a pathophysiologic hallmark of Alzheimer's disease, BACE1 may serve as a prime target for the development of disease-modifying treatments for Alzheimer's disease. To identify BACE1 inhibitors with reduced lipophilicity and improved brain penetration, Lerchner and colleagues²⁴ began discovery chemistry work using a macrocyclic BACE1 inhibitory lead compounds. This work led to the identification of improved lead compound **104**, belonging to macrocyclic ethanolamine series, which demonstrated excellent selectivity and potency against BACE1 as shown in Figure 45. However, it had a poor permeability and a high efflux ratio (ER) in the MDR1-MDCK cell line. Furthermore, it was apparent that the increased basicity of the ethanolamine moiety was associated with an increased ER by P-gp and, hence, a low permeability. To circumvent these problems, Lerchner and co-workers²⁴ used a pK_a lowering strategy around the ethanolamine group of lead **104**. The introduction of the spirocyclopropane moiety at the benzylic carbon adjacent to the ethanolamine group yielded **105** ($pK_a = 7.3$), a compound with improved passive permeability, lower ER values, and retention of potency against BACE1 as shown in Figure 45. The reduced ER value for compound **105** increased the concentration in the brain ($C_b = 0.32 \mu M$), resulting in a 72% reduction in the brain levels of $A\beta_{40}$ compared to the precursor benzylamine analogue **104** ($C_b = 0.04 \mu M$; $A\beta_{40} = 7\%$). The loss of selectivity of the cyclopropyl analogue over closely related aspartyl proteases resulted in termination of further progress with this series.²⁴ It is interesting to note that the cyclopropyl ring has played a role in achieving selectivity in many of the examples described previously; however, a spirocyclopropyl substitution at the benzylic position in **105** led to the loss of selectivity. The reason for the loss of selectivity of **105** is not known at this time. Therefore, one design strategy does not work for all cases and is context dependent.

BACE1 Inhibitor 109. Cumming and co-workers¹³⁷ began a discovery program for small molecule BACE1 inhibitors that would penetrate the CNS and reduce CNS-derived $A\beta_{40}$ levels.

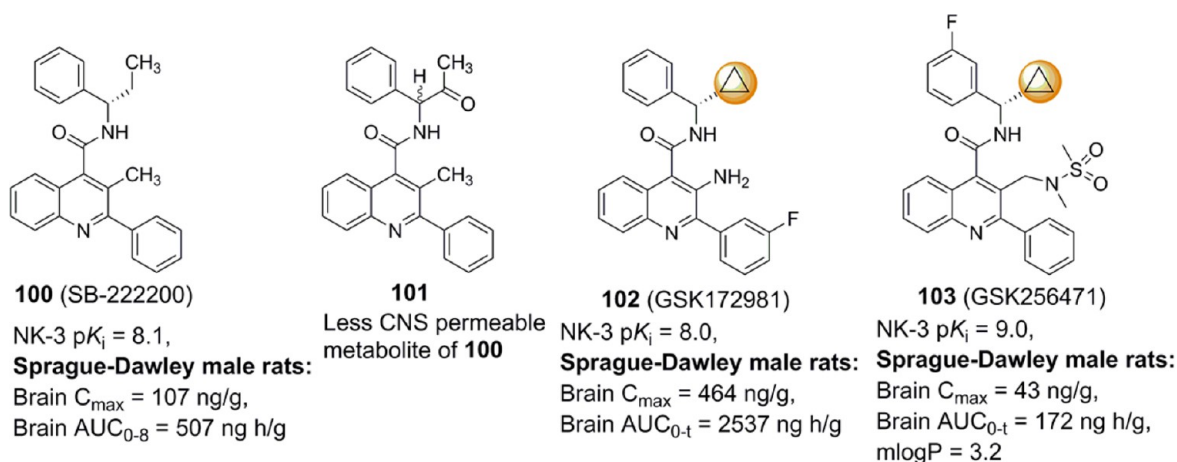


Figure 44. Structures, in vitro potency, and PK profile of NK-3 inhibitors **100**–**103**.

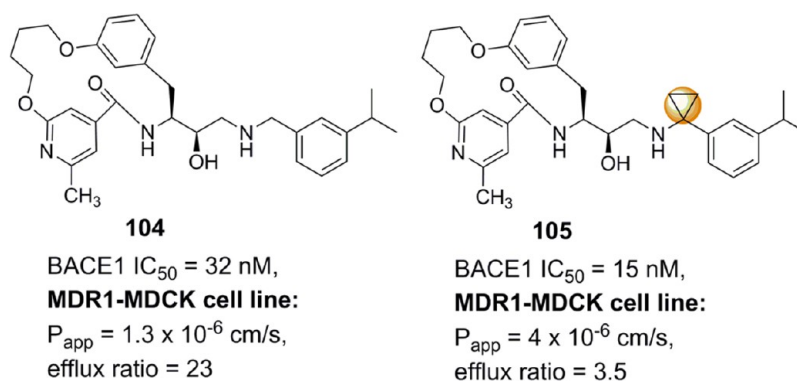


Figure 45. Structures, in vitro potency, and permeability data of BACE1 inhibitors **104** and **105**.

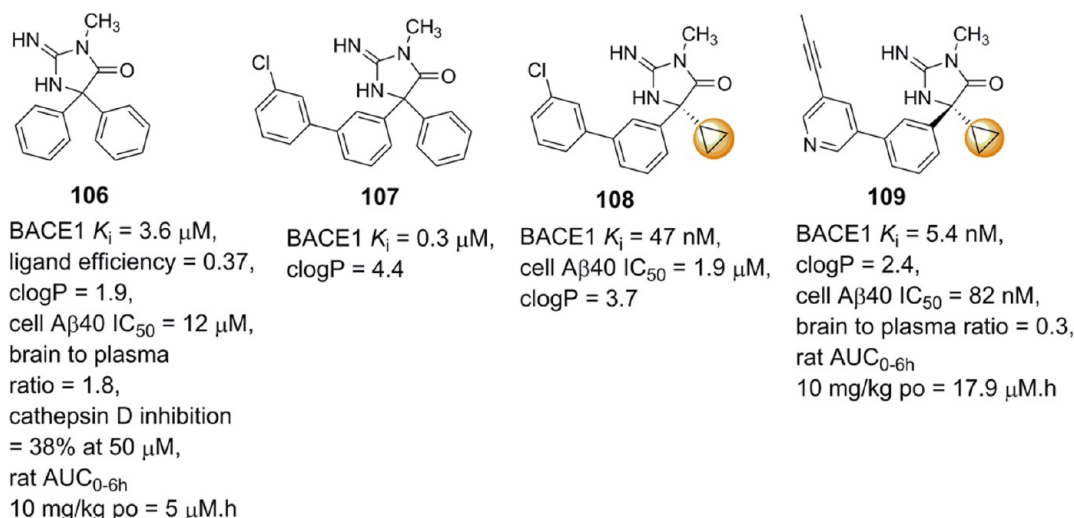


Figure 46. Structures, in vitro potency, and PK properties of BACE1 inhibitors **106**–**109**.

They started with the low micromolar, 5,5-diphenyl-2-iminohydantoin BACE1 inhibitor **106** (Figure 46). Although **106** was less potent than early lead compounds, it was endowed with excellent ligand efficiency, PK properties, and selectivity toward BACE1 over related aspartyl proteases such as cathepsin D. Therefore, **106** served as an excellent lead compound, particularly because its X-ray cocrystal structure was known, allowing structure-based optimization. The replacement of one of the phenyl rings with a 3-substituted biaryl ring system consistently provided compounds that significantly inhibited BACE1, e.g., compound **107** (Figure 46). Next, the influence of the modification of the second phenyl ring was examined. Subsequently, a replacement of the phenyl ring with an isosteric cyclopropyl ring yielded compound **108**, with a high affinity for BACE1 (Figure 46). Finally, a biaryl ring system optimization was used with the intention of improving the BACE1 affinity while decreasing the gap between the BACE1 K_i and cell A β 40 IC_{50} s. Eventually, the replacement of the distal chlorophenyl ring with the 3-propynylpyridyl moiety resulted in the discovery of **109** as shown in Figure 46, demonstrating a high oral efficacy, selectivity, and brain penetration.¹³⁷

γ -Secretase Inhibitor 111. γ -Secretase is an evolving therapeutic target for the development of drugs to treat Alzheimer's disease because it catalyzes the formation of A β peptides that are involved in the pathophysiology of this disease.¹³⁸ Josien et al.¹³⁹ began their medicinal chemistry efforts with the 3,5-disubstituted morpholine lead compound **110**. This compound showed a

minimal shift between cell and membrane A β 40 IC_{50} values and, most importantly, an improved CYP3A4 profile compared to their early hit compounds containing a piperidine core (Figure 47). Among the three molecular modifications (i.e., cyclopropyl substituent at the 5-position, a spiro-cyclopropyl ring at the 3-position flanked methylene, and the bridged piperazine ring at a carbamate functionality), the cyclopropyl rings consistently provided compounds with excellent metabolic stability and in vivo oral activity.¹³⁹ A representative of the optimized series is compound **111** (Figure 47) that dose-dependently decreased A β 40 levels in plasma as well as brain and had a 13-fold greater IC_{50} of 194 nM against Notch processing in whole cells compared to cell A β 40 IC_{50} value.¹³⁹ The inhibition of Notch processing in whole cells had been linked to adverse effects.¹⁴⁰

$\alpha 4\beta 2$ Selective Nicotinic Acetyl Choline Receptor (nAChR) Partial Agonist 116. The $\alpha 4\beta 2$ nAChR serves as a therapeutic target for drugs to treat depression, attention deficit hyperactivity disorder (ADHD), and neuropathic pain.¹⁴¹ Because binding of ligands to the ganglionic $\alpha 3\beta 4^*$ -nAChR is thought to be associated with adverse effects, such as nausea and emesis,¹⁴² Zhang and colleagues¹⁴³ developed highly selective, fast acting partial agonists for the $\alpha 4\beta 2$ -nAChR. They began their efforts with lead compound **112** (sazetidine-A) that showed very potent $\alpha 4\beta 2$ -nAChR partial agonist activity, with significant selectivity over $\alpha 3\beta 4^*$ -nAChR,¹⁴⁴ and had in vivo antidepressant and anxiolytic efficacy in rodent models.¹⁴⁵ However, **112** generated concerns about its metabolic liability due to its

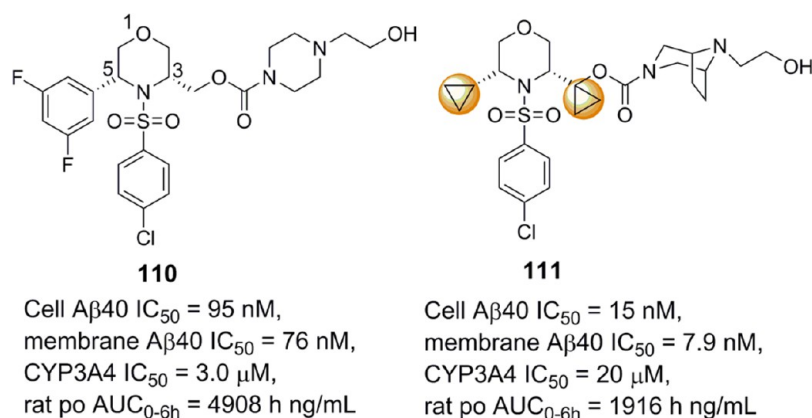


Figure 47. Structures, in vitro potency, and PK properties of gamma secretase inhibitors **110** and **111**.

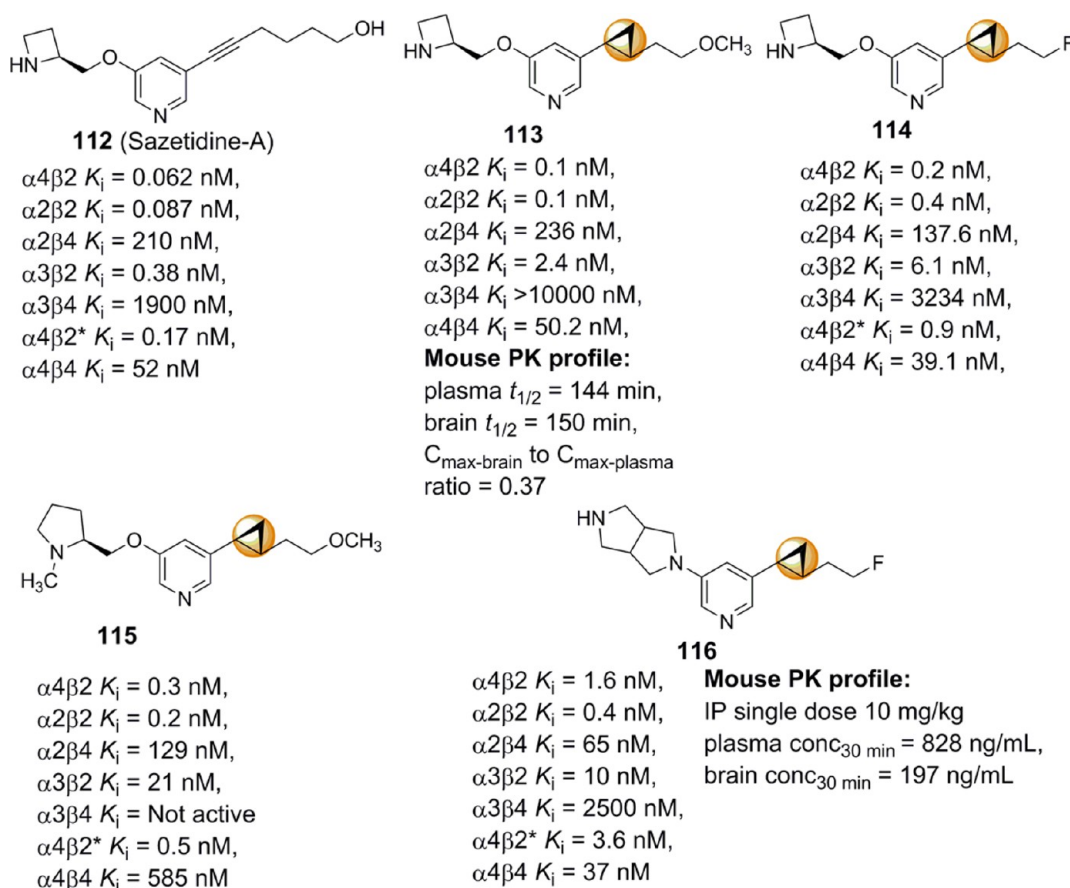


Figure 48. Structures and in vitro potency of α 4 β 2 nAChR partial agonists **112**–**116**.

acetylene group. Therefore, Zhang and co-workers¹⁴³ replaced the acetylene group with a small and constrained cyclopropane ring. It was anticipated that the cyclopropane ring will not only act as a spacer to place the pendant side chain moiety in the right position to interact with the receptor but will also interact with the receptor residues. Subsequently, a highly selective compound **113**, with subtype selective (1*S*,2*R*)-stereochemistry at the cyclopropane ring, was identified as shown in Figure 48. In vivo mouse PK studies revealed a promising profile for compound **113** as shown in Figure 48. When subjected to CYP isoform inhibition profiling, compound **113** only caused a 25% inhibition of major drug metabolizing CYP enzymes (CYP1A, CYP2C9, CYP2C19, CYP2D6, and CYP3A) at 10 μ M. Because compound **113** only

produced a 13.7% inhibition of hERG potassium channel at 10 μ M concentration, it is less likely to cause hERG-related cardiovascular toxicity.¹⁴³ Further optimization of **113** by Zhang and co-workers¹⁴⁶ using X-ray and homology structural information resulted in identification of fluorinated compound **114**, which showed improved metabolic stability compared to compound **113** (Figure 48). Further systematic SAR around the azetidine and cyclopropane substituted side chains in the core pyridine ring led to discovery of compound **115** that featured a stable *N*-methylpyrrolidine ring in place of azetidine. Compound **115** had: (1) excellent human/mouse liver microsomal stability, (2) no more than 30% inhibition of CYP1A, CYP2C9, CYP2C19, and CYP3A isoforms at 10 μ M, (3) a 31% binding to

human plasma, (4) an excellent Caco-2 cell permeability, (5) no efflux by P-gp, (6) a negative Ames genotoxicity test at 100 μ M concentration, and (7) a hERG potassium channel inhibition by 23% at a concentration of 10 μ M.¹⁴⁶

The (1*S*,2*R*)-cyclopropane side chain at the 5-position of the pyridine scaffold is critical for achieving exceptional α 4 β 2-nAChR subtype selectivity. Consequently, Onajole and co-workers¹⁴⁷ inserted a (1*S*,2*R*)-configured cyclopropane side chain at the 5-position of their *N*-pyridyldiazabicyclo[3.3.0]octane motif, a move that eventually led to the discovery of compound **116**, showing a 1600-fold selectivity for α 4 β 2 over α 3 β 4-nAChR as shown in Figure 48. In vivo mouse PK studies revealed an acceptable brain to plasma ratio (0.24 at 30 min and 1.75 at 120 min) of compound **116**. The binding of compound **116** to mouse plasma and brain tissue amounted to 27% and 73%, respectively.¹⁴⁷

Bradykinin B1 Receptor Antagonist 120. Because the bradykinin B1 receptor has been shown to play a role in chronic inflammation and pain, there is a great interest in developing compounds that could antagonize this receptor.¹⁴⁸ Although earlier peptidic¹⁴⁹ and nonpeptidic¹⁵⁰ antagonistic compounds supported the bradykinin B1 receptor as a therapeutic target, these compounds lacked the physicochemical and PK profile to make them effective by the oral route. Feng et al.,¹⁵¹ reported SAR studies on the diaminopyridine scaffold **117** as a bradykinin B1 receptor antagonist (Figure 49). However, further developments along these lines were hampered by the realization that this scaffold formed reactive metabolites.¹⁵² To overcome this metabolic liability, Wood and co-workers¹⁵³ discovered that the problematic diaminopyridine scaffold could be efficiently replaced with a cyclopropylamino acid moiety. This design concept yielded biphenyl cyclopropane carboxamide compound **118**, with an improved PK profile, although potency was decreased (Figure 49). It was reasoned that the favorable PK profile of compound **118** could be a combined effect of the stability of unnatural α -amino acids toward

proteolytic enzymes, in concert with the absence of the metabolically reactive diaminopyridine scaffold.¹⁵³ Although compound **118** had reasonable affinity toward B1 receptor, it did not have optimal PK properties and had only moderate CNS receptor occupancy. Moreover, compound **118**-related structures were found to be substrates of P-gp, thereby compromising their CNS penetration.¹⁵⁴ Therefore, the same research group¹⁵⁵ conducted further SAR optimization around the biphenyl and trifluoropropionamide regions of **118** to improve the shortcomings associated with early compounds. These studies led to compound **119** as shown in Figure 49. Compound **119** had a promising PK profile in the dog and rhesus monkey, as shown in Figure 49. Because compound **119** demonstrated moderate CNS receptor occupancy in a transgenic mouse model, further SAR optimization efforts were undertaken.¹⁵⁵ These SAR studies identified several promising leads, notably compound **120**, which showed excellent potency and promising PK profile in dog and rhesus monkey as shown in Figure 49.¹⁵⁵

Orexin Receptor Antagonist 121. Pharmacological blockade of both orexin receptor 1 and 2 (OX1R/OX2R) has been

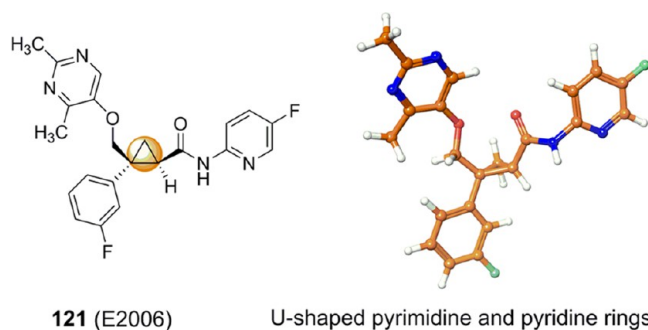


Figure 50. 2D Structure (left panel) and 3D model (right panel) of orexin receptor antagonist **121**.

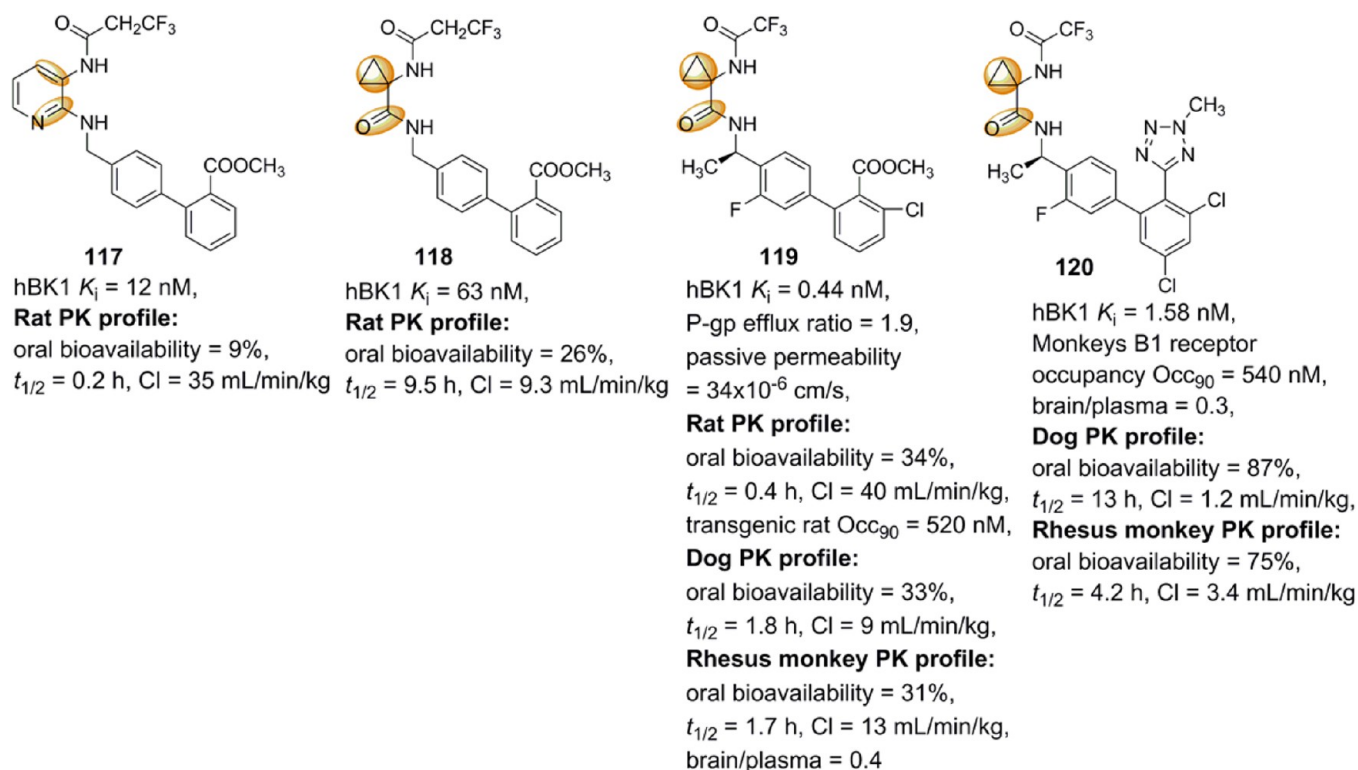


Figure 49. Structures, in vitro potency, and PK properties of bradykinin B1 receptor antagonist **117–120**.

intensely pursued for the development of drugs to treat insomnia.¹⁵⁶ Suvorexant,¹⁵⁷ a dual orexin receptor antagonist, was approved by the U.S. FDA in 2014 for the treatment of insomnia. Suvorexant adopts a horseshoe-shaped (U-shape) conformation in the binding pocket of the human OX2R.¹⁵⁸ Yoshida and colleagues,²⁵ using extensive SAR studies, discovered a cyclopropane carboxamide derivative typified by the most advanced compound **121** (E2006) as a dual OX1R/OX2R receptor antagonist as shown in Figure 50. Similar to the U-shaped conformation of OX2R-bound suvorexant,¹⁵⁸ molecular simulation studies on isolated **121** showed a U-shaped, low energy state conformation. The cyclopropyl moiety provides a chiral spacer that produces the above-mentioned bioactive U-shaped (*cis*) conformation of the pendant 5-pyrimidine and 2-pyridine rings as shown in Figure 50.²⁵

Histamine H₃ Receptor (H₃R) Antagonist 123 (Bavisant). It is a potent antagonist of the H₃R, which has been implicated in the promotion of wakefulness. As a result, antagonists of this type of receptor may be useful in the treatment of daytime sleepiness, narcolepsy, and ADHD.¹⁵⁹ Letavic et al.,¹⁶⁰ began medicinal chemistry work to synthesize H₃ receptor antagonists with piperazinecarboxyl benzylamine as a lead scaffold. Several analogues were prepared and tested by these authors in histamine H₃ receptor binding affinity assays, resulting in the identification of clinically relevant compound **122** as shown in Figure 51. However, **122** produced prolonged insomnia due to a longer half-life. To eliminate this problem, Letavic et al.,¹⁶⁰ replaced the isopropyl moiety present on the terminal piperazine nitrogen

with the cyclopropyl moiety to yield compound **123** (bavisant/JNJ-31001074) as shown in Figure 51. These results support the concept that fine-tuning of the PK profile of a compound is possible by altering its physicochemical properties. Specifically, introduction of a cyclopropyl ring reduced the pK_a of the piperazine ring compared to the isopropyl substitution, thereby increasing plasma clearance and reducing half-life.¹⁶⁰ It may be noted that, unlike other examples (compounds **40**, **61**, **72**, and **130**) where a cyclopropyl ring led to increased half-life, in the case of **123** the cyclopropyl ring produced decreased half-life. Therefore, PK properties can be modulated with a cyclopropyl group; however, it is context dependent and one strategy does not work in all cases.

PDE4 Inhibitor 127. Among the 11 phosphodiesterases (PDEs) so far known, cAMP-specific PDE4 is of great interest due to its role in controlling the intracellular levels of cAMP.¹⁶¹ Therefore, inhibitors of PDE4 will increase cAMP level, promoting the late phase, long-term potentiation cascade, thereby increasing the likelihood of enhancing cognition.¹⁶² Gallant et al.,¹⁶³ sought to develop brain-penetrating PDE4 inhibitors endowed with a significantly high plasma protein shift (low human whole blood potency) and high oral bioavailability and rapid GI absorption. These properties are postulated to enhance the therapeutic index and decrease gastrointestinal-related adverse side effects. To meet this goal, these authors selected compound **124** as the starting point (Figure 52). In this compound, the *N*-cyclopropyl amide functionality at the 3-position of the naphthyridinone scaffold was found to be optimal based on preliminary SAR work.¹⁶⁴ The first SAR task involved optimization of the aliphatic carboxylic acid chain at the biphenyl moiety. Among the several groups tested, the cyclopropane carboxylic acid moiety in **125** was the best as it had low potency in the HWB assay and an improved oral bioavailability compared to **124** as shown in Figure 52.¹⁶³ While keeping the biphenyl functionality of **125** constant, these investigators revisited optimization of the cyclopropyl amide moiety and obtained **126**, a compound with a suboptimal profile (Figure 52). Overall, it can be concluded that the cyclopropyl groups at the naphthyridinone and the biphenyl scaffolds are critical for the pharmacological profile of these PDE4 inhibitors. Final optimization involved elucidation of the bioactive stereochemical configuration of the chiral cyclopropane carboxylic acid center and substitution of the fluorine at the biphenyl scaffold. These molecular modifications

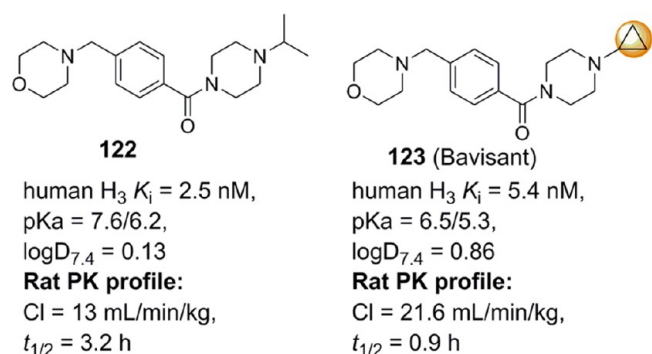


Figure 51. Structures, in vitro potency, and PK properties of histamine H₃ receptor antagonists **122** and **123**.

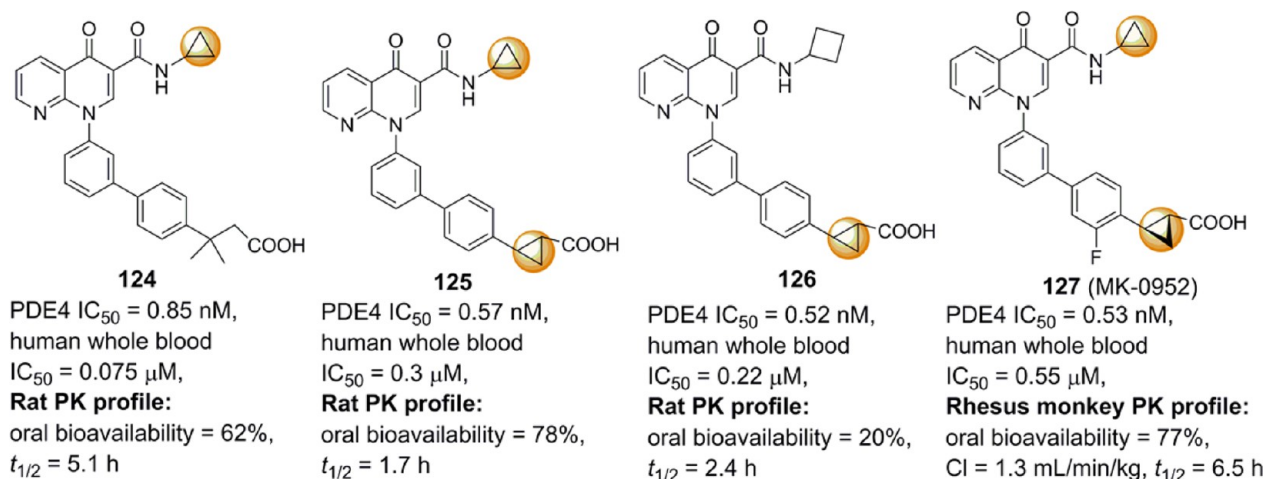


Figure 52. Structures, in vitro potency, and PK properties of PDE4 inhibitors **124**–**127**.

eventually led to the discovery of the clinical candidate **127** (*R,R*)-MK-0952 as shown in Figure S2.¹⁶³

Triple Reuptake Inhibitor 128. The simultaneous inhibition of the serotonin reuptake transporter (SERT), norepinephrine reuptake transporter (NET), and dopamine reuptake transporter (DAT) has potential for the treatment of depression.¹⁶⁵ Micheli and colleagues¹⁶⁶ conducted developmental work on antidepressants based on a triple reuptake inhibitor pharmacophore model typified by the presence of a positive charge center, three hydrophobic groups, one aromatic ring, and a hydrogen bond acceptor group. Their goal was to develop new compounds with an inhibitory rank of SERT ≥ NET > DAT. This led to discovery of a clinical compound **128** (GSK1360707F), with a (1*S*, 6*R*) configuration at the cyclopropane ring, which showed a balanced inhibition of the three transporters (hSERT pK_i = 9.2, hNET pK_i = 8.1, and hDAT pK_i = 8.0)¹⁶⁶ (Figure S3).

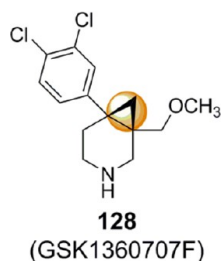


Figure S3. Structure of a triple reuptake inhibitor **128**.

A chiral fused cyclopropane ring across the C3–C4 bond in the piperidine ring allowed the projection of the 3,4-dichlorophenyl and the methoxymethyl substituents of **128** into respective hydrophobic regions of the triple reuptake pharmacophore model.¹⁶⁶

Additional examples of cyclopropane-containing CNS active compounds including corticotrophin releasing factor 1 antagonist, amitifadine, etomidate prodrug, and ciplralisant are described in the Supporting Information.

CARDIOVASCULAR PRECLINICAL/CLINICAL DRUG CANDIDATES

β_1 -Adrenoceptor Blocker 130 (Betaxolol). Manoury and co-workers¹⁶⁷ sought to develop antihypertensive β -blockers that (a) would be more potent than available β -blockers, (b) showed increased β_1 adrenoceptor selectivity, and (c) possessed a desirable PK profile, including excellent oral absorption, low first pass metabolism, and a plasma half-life >12 h that will permit once-a-day dosing. Because compound **129** (metoprolol) was known to be a cardioselective β_1 -adrenoceptor blocker, it was considered to be a good starting point for SAR studies. It should be noted that compound **129** has a short duration of action and a significant first-pass inactivation (through *O*-demethylation of the methoxyethyl side chain followed by oxidation to an acid metabolite)¹⁶⁸ and, consequently, to poor oral bioavailability.

Manoury and co-workers¹⁶⁷ hypothesized that the metabolically labile methoxyethyl substituent in **129** could be replaced with a metabolically stable bulky substituent such as the cyclopropylmethoxyethyl group (Figure S4). In fact, this modification of compound **129** [β_1 antagonist activity in rat atria model ($pA_2 \beta_1$) = 7.64] led to the discovery of compound **130**/betaxolol ($pA_2 \beta_1$ = 8.53), which showed a significantly improved β_1 -antagonist activity. Furthermore, the metabolism of compound **130** was 6-fold lower than that of **129**. The half-life of compound **130** in humans has ranged from 16 to 22 h compared to 3 to 6 h for **129**.¹⁶⁷

P2Y₁₂ Receptor Antagonist 133 (Ticagrelor/Brilinta). Compound **133** (ticagrelor), approved by the U.S. FDA in 2011, is the first reversible P2Y₁₂ receptor antagonist with antiplatelet activity and it has a conformationally constrained chiral cyclopropane bridge.¹⁶⁹ Unlike the thienopyridine compounds **134** (clopidogrel) and **135** (prasugrel), it is not a prodrug and, therefore, it does not require preliminary metabolism to a pharmacologically active form.¹⁷⁰ Moreover, in comparison to the irreversible P2Y₁₂ receptor antagonists **134** and **135**, it acts in a reversible manner. Chemically, it is a cyclopentyl triazolopyrimidine isosteric analogue of adenosine that is known to allosterically bind to the P2Y₁₂ receptor in an area dissimilar to the ADP-binding site.¹⁷¹ This allosteric binding mechanism is thought to lock the P2Y₁₂ receptor in its inactive conformational state, consequently inhibiting ADP signaling and P2Y₁₂ receptor conformational flexibility.¹⁶⁹ On the knowledge that ATP is an endogenous P2Y₁₂ receptor antagonist, Springthorpe and colleagues¹⁷² sought to develop novel drug-like nonphosphate ATP analogues. To meet this goal, they synthesized and tested ~6000 compounds that ultimately yielded the nonacidic lead compound **131** as shown in Figure S5. Furthermore, these investigators replaced the butylamine group at position 7 of the triazolopyrimidine core of **131** with the lipophilic *trans*-2-phenylcyclopropylamine, resulting in compound **132**, with a 100-fold increase in affinity toward the P2Y₁₂ receptor and a good metabolic stability (Figure S5). Eventually, compound **133** was obtained by exchanging the hydroxymethyl group for a hydroxyethoxy group and a 3,4-difluoro substitution at the phenyl ring as shown in Figure S5.¹⁷²

P2Y₁₂ Receptor Antagonist 135 (Prasugrel/Effient). This third-generation thienopyridine compound **135** (prasugrel) is an irreversible P2Y₁₂ receptor antagonist that was approved by the U.S. FDA in 2009 as an antiplatelet drug. It blocks P2Y₁₂-mediated platelet activation and aggregation. In an effort to circumvent the inactivation of compound **134** (clopidogrel) through hydrolysis of methyl ester group to an inactive carboxylic acid metabolite,¹⁷³ structural modifications were initiated, the most prominent being the conversion of the hydrolytically unstable methyl ester group to a stable cyclopropyl carbonyl group to yield compound **135** as shown in Figure S6. Unlike compound **134**, compound **135** is metabolically transformed to a single active metabolite as shown in Figure S6.¹⁷⁴

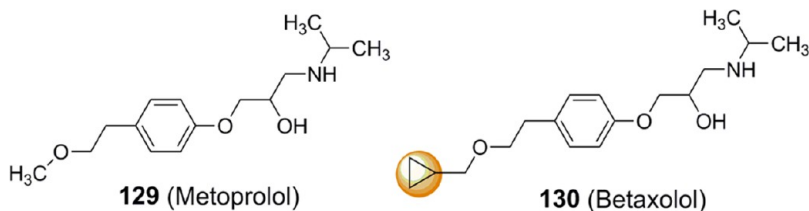


Figure S4. Structures of β blockers **129** and **130**.

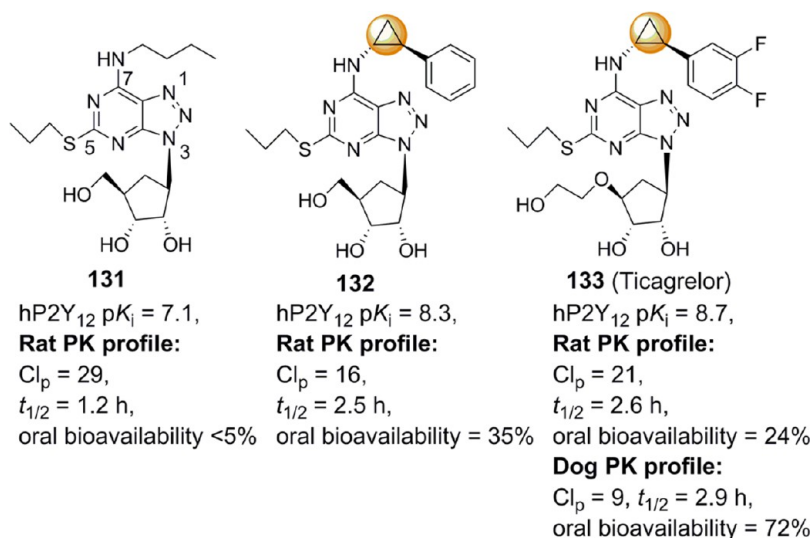


Figure 55. Structures, in vitro potency, and PK properties of P2Y₁₂ receptor antagonists 131–133.

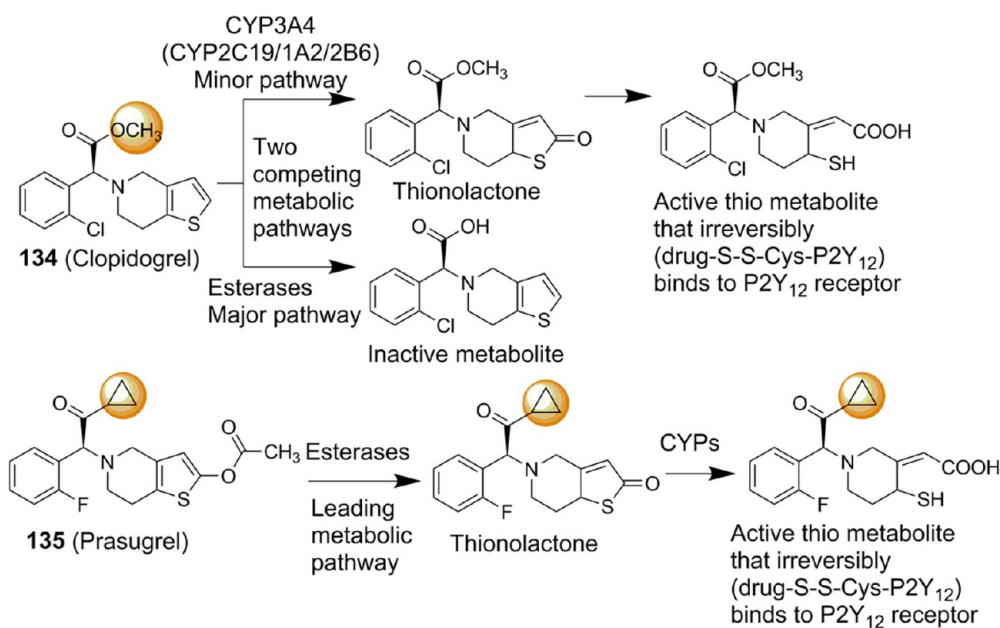


Figure 56. Structures and metabolism of P2Y₁₂ receptor antagonists 134 and 135.

Factor Xa (FXa) Inhibitor 137. FXa is a key enzyme of the coagulation cascade, and its inhibition significantly decreases the incidence of arterial and venous thrombosis.¹⁷⁵ Qiao et al.¹⁷⁶ sought to optimize the in vitro and in vivo potencies of their previously reported lead compound 136 (FXa K_i = 0.3 nM) that is typified by an *ortho*-dimethylaminomethyl substituted biphenyl P4 moiety as shown in Figure S7.¹⁷⁷ On the basis of the X-ray crystal structure and molecular modeling studies with lead compound 136, it became apparent that the two phenyl rings of the biphenyl ring system are noncoplanar with a perpendicular arrangement of the basic *ortho*-substituent, an optimal pharmacophore for binding to the S4 subsite of FXa.^{176,178} Subsequently, Qiao et al.¹⁷⁶ replaced the terminal phenyl ring with a cyclopropane ring and added a pyrrolidinylmethyl moiety, a cyclic mimic of the dimethylamino methyl moiety, to the α -position of the cyclopropane ring. They hypothesized that the perpendicular conformation of a basic α -substituent on the phenylcyclopropane would mimic the bioactive conformation of the *ortho*-substituted biphenyl P4 moiety. It should be noted that

among two possible conformations of the phenylcyclopropane ring (i.e., the perpendicular conformation and the bisected conformation), it was envisioned that the phenylcyclopropane with the α -substituent would preferentially adopt a perpendicular conformation,¹⁷⁹ thereby mimicking the bioactive conformation of the P4 moiety. The choice of the cyclopropyl ring over other cycloalkyl rings was dictated by its smaller size and greater metabolic stability. These efforts eventually led to discovery of novel compound 137 as a potent inhibitor of FXa (K_i = 0.021 nM) (Figure S7). The X-ray crystal structure of the most potent FXa inhibitor bound to human FXa indicated the existence of a perpendicular conformation of the phenylcyclopropyl P4 moiety within the S4 subsite of enzyme. These structural studies also showed extensive hydrophobic contacts between the cyclopropyl ring and the S4 subsite residues Tyr99, Phe174, and Trp215. These investigators stated that the exceptional potency of compound 137 could have resulted from the combined influence of (a) a favorable hydrophobic and polar interactions of pyrrolidinyl moiety, respectively, with the edges of

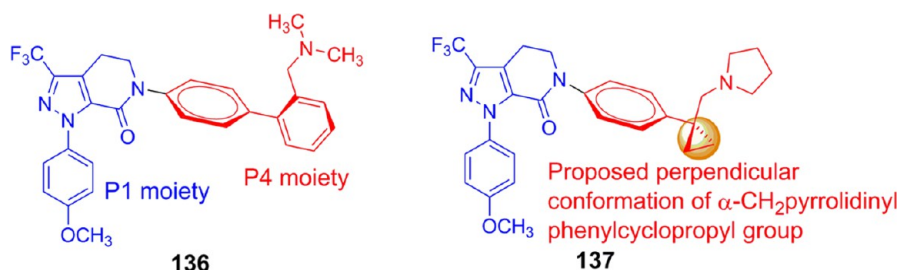


Figure 57. Structures of FXa inhibitors 136 and 137.

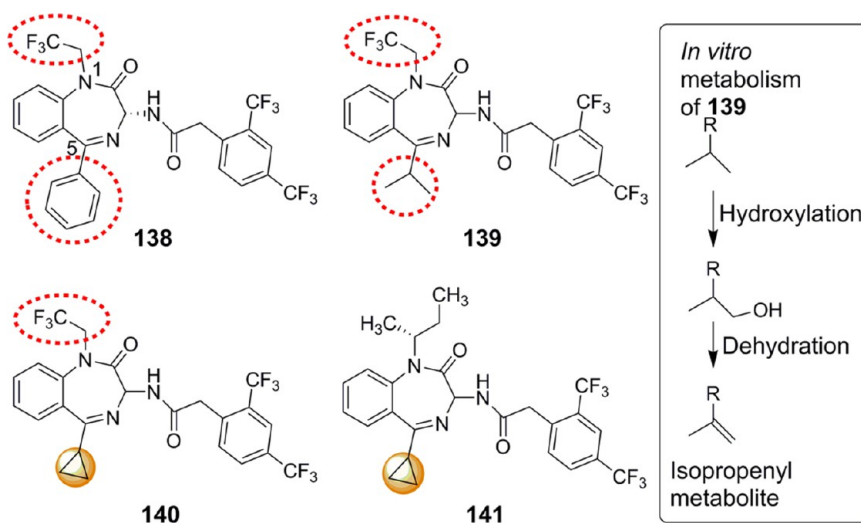


Figure 58. Structures (left panel) and metabolism (right panel) of the Iks inhibitors 138–141. Stereochemistry at the C3-chiral center in 139–141 is not determined.

Phe174 and Tyr99 and backbone of Glu97 and Thr98, and (b) a preferred perpendicular conformation of the phenylcyclopropyl that direct the bulky α -substituent orthogonal to the plane of the phenyl ring.¹⁷⁶

Slowly Activating Cardiac Delayed Rectifier Potassium Current (I_{ks}) Inhibitor 141. The selective and potent pharmacological inhibition of the I_{ks} over its rapid counterpart, I_{kr}, is a potential therapeutic approach for treating ventricular arrhythmias.¹⁸⁰ To develop class III antiarrhythmic drugs with significantly enhanced I_{ks} inhibition, Butcher et al.¹⁸¹ began their quest from the 1,5-disubstituted-1,4-benzodiazepin-2-one analogue 138 (I_{ks} IC₅₀ = 6 nM, and I_{kr} IC₅₀ = 6000 nM), a selective, potent, and orally active I_{ks} inhibitor, as shown in Figure 58.¹⁸² These investigators observed that substitution of the phenyl ring at position 5 of 138 with an isopropyl group yielded compound 139 (I_{ks} IC₅₀ = 6 nM and I_{kr} IC₅₀ > 1000 nM) without loss of I_{ks} inhibitory potency. However, the isopropyl analogue 139 underwent rapid and extensive in vitro deactivating metabolism, yielding first a hydroxylated 5-isopropenyl metabolite which, upon dehydration, turned into the 5-isopropenyl metabolite as shown in Figure 58.¹⁸¹ To circumvent the metabolic liability of 139, the 5-isopropyl group was replaced with the metabolically stable 5-cyclopropyl moiety to obtain compound 140 (I_{ks} IC₅₀ = 1.5 nM, and I_{kr} IC₅₀ > 1000 nM) (Figure 58). These changes introduced metabolic stability because incubation of the cyclopropyl and the isopropyl analogues with human microsomes for 60 min, resulted in respective metabolism of ~15% and ~70% and also raised the I_{ks} inhibitory potency by 4-fold compared to compounds 138 and 139.¹⁸¹ Compound 141, a class III antiarrhythmic and highly selective I_{ks} inhibitor, was synthesized by keeping the

cyclopropyl ring at the 5-position and replacing the trifluoroethyl substituent at position 1 with the chiral *sec*-butyl (*R*-stereochemistry) group (I_{ks} IC₅₀ = 0.08 nM, and I_{kr} IC₅₀ > 1000 nM) as shown in Figure 58.¹⁸¹

Soluble Epoxide Hydrolase (sEH) Inhibitor 144. sEH is a cytosolic enzyme that catalyzes the breakdown of physiologically important epoxy-eicosa-trienoic acids into inactive hydrophilic dihydro-eicosa-trienoic acids.¹⁸³ The epoxy-eicosa-trienoic acids are physiologically important for functions such as vasodilation, antimigratory actions on vascular smooth muscle cells, and analgesic and anti-inflammatory action. Therefore, the development of sEH inhibitors has been an active field of research for the treatment of cardiovascular diseases, inflammation, and neuropathic pain.¹⁸⁴

Takai and co-workers¹⁸⁵ sought to optimize their previously disclosed sEH inhibitory lead 142, for which X-ray cocrystal structure with sEH is known (PDB ID 4X6Y) (Figure 59). This cocrystal structure indicated that the phenoxypiperidine and the cyclopropylphenyl moieties occupied A and B pockets within the active site of sEH, respectively. Interestingly, these investigators noted the vacant C pocket around the C3-position of the cyclopropane ring. This information prompted them to branch out the third position of the cyclopropane ring with a phenyl substituent, yielding compound 143 (Figure 59). The cocrystal structure of 143 and sEH (PDB ID 4X6X) showed binding interactions similar to the lead 142, with an additional binding of the phenyl ring to the C pocket. To expand the molecular space, these investigators initiated further optimization around the phenoxy-piperidine region, leading to the discovery of the most potent sEH inhibitor, 144, known so far¹⁸⁵ (Figure 59).

Unoccupied pocket C on sEH active site

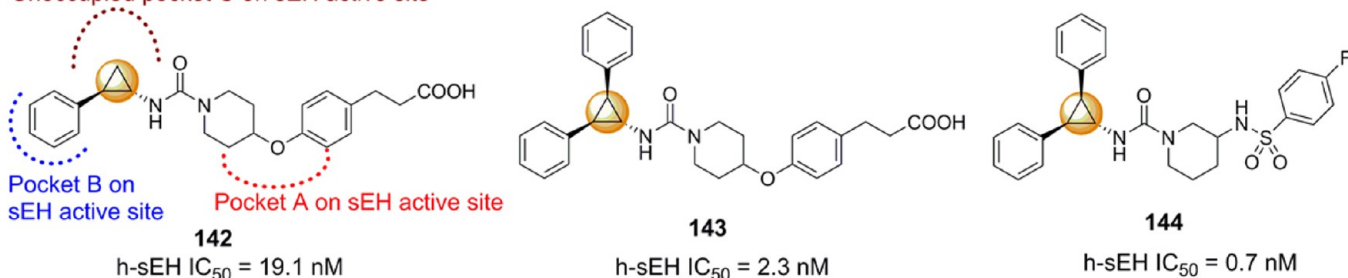


Figure 59. Structures of sEH inhibitors 142–144.

Additional examples of cyclopropane-containing cardiovascular drugs, including saprisartan (GR138950), remikiren (Ro 42-5892), ciprokiren (Ro 44-9375), zoniporide (CP-597396), and BMS-795311, are provided in [Supporting Information](#).

■ PRECLINICAL/CLINICAL DRUG CANDIDATES FOR METABOLIC DISORDERS

HMG-CoA Reductase Inhibitor 146 (Pitavastatin/Livalo). Compound 146 (pitavastatin/NK-104)¹⁸⁶ is a highly potent 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitor approved by the U.S. FDA in 2009 for treating patients with high serum cholesterol levels (Figure 60). It was

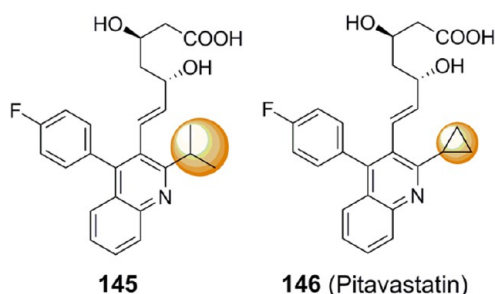


Figure 60. Structures of HMG-CoA inhibitors 145 and 146.

discovered by Suzuki and colleagues,¹⁸⁶ who were searching for synthetic statins with a greater potency than currently used statins such as pravastatin, simvastatin, atorvastatin, and lovastatin. During the course of a SAR optimization program, they identified compound 145, having heptenoate as the basic structure, a quinoline ring at its core, and 4-fluorophenyl and isopropyl moieties as pendant groups and showing an IC_{50} of 19 nM for HMG-CoA reductase.¹⁸⁶ The replacement of the isopropyl group in 145 with the metabolically stable cyclopropyl moiety led to the discovery of 146, an approximately 5-fold more potent compound (IC_{50} = 4.1 nM). An additional advantage of introducing the cyclopropyl group was to curtail CYP3A4-mediated metabolism, thus allowing for increased bioavailability and longer duration of action of pitavastatin relative to other statins and previous analogues.

The cyclopropane-containing farnesoid X receptor agonist (LY2562175) is described in the [Supporting Information](#).

■ PRECLINICAL/CLINICAL DRUG CANDIDATES FOR THE ENDOCRINE SYSTEM

Dipeptidylpeptidase-IV (DPP-IV) Inhibitor 147 (Saxagliptin/Onglyza). Compound 147 (Saxagliptin/BMS-477118),¹⁸⁷ a highly selective and competitive inhibitor of DPP-IV, was approved by the U.S. FDA in 2009 for the

management of type 2 diabetes. One of the problems with earlier DPP-IV inhibitory cyanopyrrolidine structural analogues was their short duration of action and chemical instability as shown in Figure 61 (right panel).¹⁸⁸ Notably, the conversion of the DPP-IV binding *trans*-rotamer to the *cis*-rotamer, where the proximal nucleophilic amino group attacks the cyano group, leading to the intramolecular cyclized imidate intermediate and formation of the piperazine-2,5-dione, which are inactive against DPP-IV¹⁸⁹ (Figure 61). It was proposed that the locking of the cyanopyrrolidine into a stable *trans*-rotameric conformation would enhance favorable, directed binding within the active site of DPP-IV and preclude the inactivating intramolecular cyclization reaction.¹⁸⁹ To substantiate this hypothesis, Magnin and co-workers¹⁸⁹ introduced the *cis*-4,5-methano (fused cyclopropyl ring) across the C4 and C5 of the cyanopyrrolidine P1 moiety, and in a separate communication,¹⁸⁷ Augeri and co-workers introduced the sterically demanding adamantyl P2 moiety on the N-terminus, leading to the discovery of compound 147 (Figure 61, left panel). Both the steric bulk at P2 and the sterically constrained cyclopropane fused pyrrolidine P1 moiety cooperatively contributed toward enhancing the *trans*-rotameric conformational stability and in vitro potency of 147. The X-ray cocrystal structure of 147 and DPP-IV revealed an efficient filling of the hydrophobic S1 pocket of DPP-IV by the cyclopropane-fused pyrrolidine P1 moiety.¹⁹⁰ Furthermore, it was also speculated that the cyclopropyl moiety in 147 displaces active site water molecules required for hydrolysis, thereby preventing 147 from undergoing hydrolysis. Thus, compound 147 is an inhibitor, not a substrate of DPP-IV. Compound 147 has excellent PK/PD features, such as a novel slow tight-binding kinetic inhibition¹⁹¹ of hDPP-IV K_i = 0.6 nM, 87% ex vivo inhibition of plasma DPP-IV, a slow rate of microsomal turnover, no CYP3A4 inhibition up to 100 μ M, and rat oral bioavailability of 75%, and a $t_{1/2}$ = 2.1 h.¹⁸⁷

Diacylglycerol Acyltransferase 2 (DGAT2) Inhibitor

149. Compound 149 (PF-06424439) was the first orally bioavailable advanced preclinical candidate that inhibits DGAT2.²⁰ Because DGAT2 represents a therapeutic target for the treatment of metabolic disorders such as hyperlipidemia and hyperglycemia, Futatsugi and co-workers²⁰ sought to identify highly potent, selective, and orally bioavailable DGAT2 inhibitors. One of their early lead DGAT2 inhibitory compounds, 148, had high potency, appreciable selectivity over other acyltransferases, and ligand lipophilic efficiency as shown in Figure 62. Unfortunately, compound 148 showed a high metabolic turnover in HLM, a high clearance through N-glucuronidation, and undesirable off-target activities against adenosine A_{2A} , muscarinic M_1 , histamine H_1 , adrenergic α_{1A} , and phosphodiesterase 1B, 5A, 6A, and 11 receptors. The higher HLM turnover of 148 could be a result of increased lipophilicity and the presence of a metabolically unstable pyrrolidine ring.²⁰

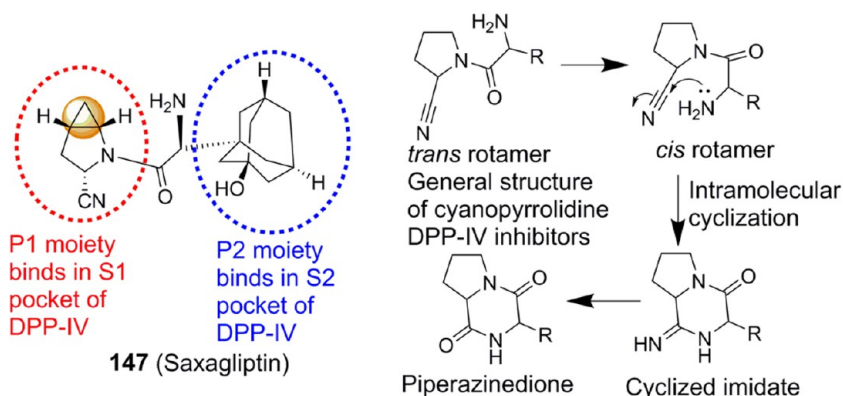


Figure 61. Structure of DPP-IV inhibitor **147** (left panel) and mechanism of acid catalyzed inactivation of noncyclopropane analogues of compound **147** (right panel).

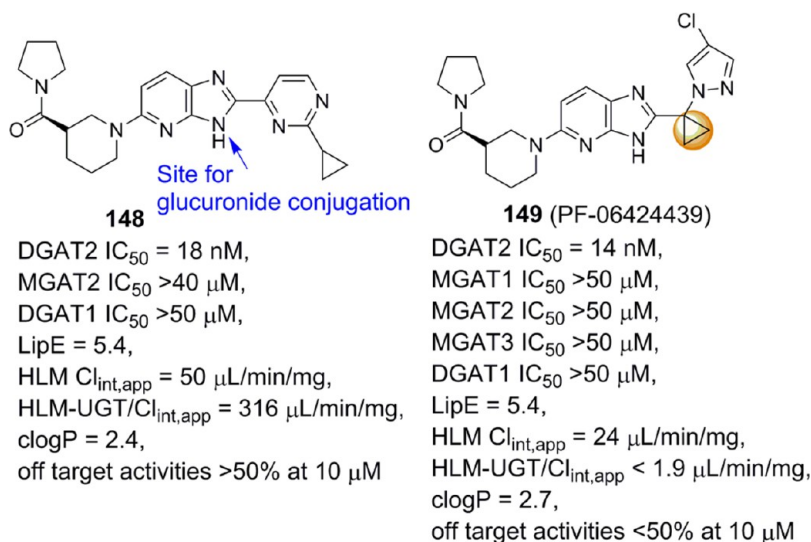


Figure 62. Structures, in vitro potency, and microsomal stability data of DGAT2 inhibitors **148** and **149**.

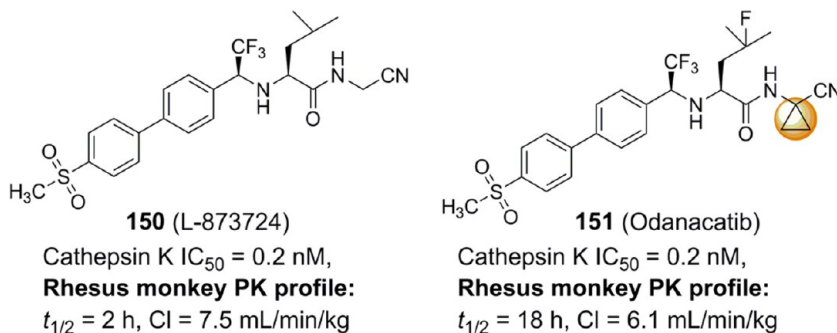


Figure 63. Structures, in vitro potency, and PK properties of cathepsin K inhibitors **150** and **151**.

Follow up studies on compound **148** indicated that it underwent phase II metabolism via *N*-glucuronidation of the imidazopyridine ring –NH group. To circumvent off-target pharmacology and the *N*-glucuronidation associated with compound **148**, Futatsugi et al.²⁰ carried out two elegant molecular modifications. The first involved the introduction of an sp^3 -hybridized carbon spacer between the imidazopyridine ring and the eastern heteroaryl ring, with the intention of increasing the three-dimensionality of the core structure to mitigate off-target effects. The second molecular modification involved the addition of steric bulkiness at the sp^3 -hybridized

carbon spacer in the form of a spiro-cyclopropyl moiety to decrease the likelihood of *N*-glucuronidation. The spiro-cyclopropyl moiety in **149** significantly improved HLM turnover, in addition to producing desirable properties such as a moderate increase in lipophilicity and a nonchiral spacer as shown in Figure 62.²⁰

Lysosomal Cysteine Protease (Cathepsin K) Inhibitor 151 (Odanacatib). Compound **151** (odanacatib/MK-0822) is a potent and selective inhibitor of lysosomal cysteine protease (cathepsin K)¹⁹ (Figure 63). Because cathepsin K serves as a molecular target for treating osteoporosis, Gauthier et al.¹⁹ began

their discovery chemistry work with a highly potent and selective cathepsin K inhibitory lead compound **150** (L-873724). Although **150** had an excellent activity against cathepsin K, with >800-fold selectivity over other cathepsin isoforms, it was unsuitable for further development due to significant metabolic liability as shown in Figure 63.¹⁹² One of the two metabolites resulted from the hydrolysis of the amide bond. To increase the stability of an amide bond toward hydrolysis, the spiro-cyclopropyl moiety was inserted at the C α -atom of the P1 aminonitrile group. This molecular modification, in conjunction with the introduction of the 4-fluoroleucine as a P2 moiety, yielded a metabolically stable compound **151** and preserved the inhibitory activity and selectivity toward cathepsin K as shown in Figure 63.¹⁹

Compound 154 (Drospirenone). Compound **152** (spironolactone), a steroidal aldosterone antagonist, is used as an antidiuretic drug and for the treatment of heart failure. It produces adverse hormonal effects such as gynecomastia, impotence, and menstrual irregularity.¹⁹³ To develop steroid derivatives devoid of these adverse effects, Weichert and co-workers¹⁹⁴ synthesized several hundred steroid-like compounds. These studies led to the cyclopropane fused derivative **153** (spirorenone), which was 5-fold more potent than **152** as an aldosterone antagonist and produced fewer hormonal side effects (Figure 64). Compound **154** (drospirenone), a 1,2-dihydrospirorenone, is an orally active metabolite of **153** formed by the Δ^1 -hydrase enzyme (Figure 64). Compound **154** has progestin activity, as well as antiandrogen and antimineralocorticoid actions.¹⁹⁵ It has been developed as a contraceptive. The potent activity of **154** was thought to be a result of C-1 saturation of the A ring and two cyclopropane rings fused to rings B and D across the 6,7 and 15,16 bonds. An enhanced in vivo activity of **153** and **154** compared to **152** is possibly due to inhibition of metabolic

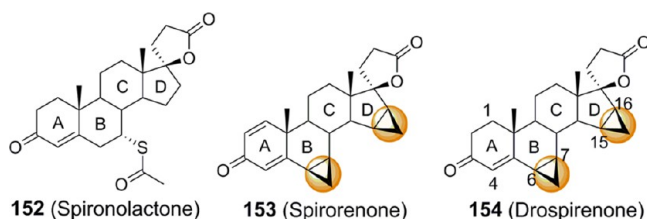


Figure 64. Structures of steroids 152–154.

inactivation at the cyclopropane ring fused positions of the steroid nucleus.¹⁹⁶

Additional examples of cyclopropane-containing endocrine drugs (TGR5 agonist and calcipotriol) are given in Supporting Information.

MISCELLANEOUS PRECLINICAL/CLINICAL DRUG CANDIDATES

Human Ghrelin (GRLN) Receptor Agonist 157 (Ulimorelin). Compound **157** (ulimorelin/TZP-101)¹⁹⁷ is a human GRLN receptor agonist that is currently undergoing phase III clinical trials for the treatment of postoperative ileus. Hoveyda and co-workers¹⁹⁷ transformed the high-throughput screening derived macrocyclic lead GRLN agonist **155** (nor-valine/*n*-propyl at AA1 position) into a clinical candidate **157** (Figure 65). In the SAR optimization study, these investigators¹⁹⁷ retained the cyclopropyl group at AA1 as it is smaller in size and provides conformational restriction compared to the *sec*-butyl-containing Ile analogue **156** (Figure 65). In addition, these aforementioned changes provided a greater metabolic stability compared to the noncyclic alkyl counterparts.¹⁹⁸ The cyclopropyl AA1 side chain in **157** turned out to be an important structural element for an improved PK profile in the rat compared to Ile analogue **156** as shown in Figure 65.¹⁹⁷ The cyclopropyl ring is less lipophilic and electron-donating based on Hansch π and Hammett σ values compared to other cyclic alkyl groups. It was also noted that the electron-donating effect of the cyclopropyl moiety increased the basicity of the secondary amine at the AA1 position (pK_a of 7.17 ± 0.04 for ulimorelin **157** versus pK_a of 6.45 ± 0.08 for analogous *n*-propyl side chain at AA1 position), producing stronger intramolecular hydrogen bonding between the positively charged amine at AA1 and the phenoxy oxygen at the tether group.¹⁹⁷ The cyclopropyl AA1 side chain was also postulated to shield this hydrogen bond from surrounding water molecules. An intramolecular hydrogen bond, supported by the cyclopropyl side chain, augmented the conformational rigidity of **157**. Compound **157**, being less lipophilic, had improved aqueous solubility at ca. pH 5 (1–8 mg/mL range), as opposed to 0.1 to 0.5 mg/mL observed for related compounds, where the cyclopropyl group was replaced with norvaline or Ile.¹⁹⁷

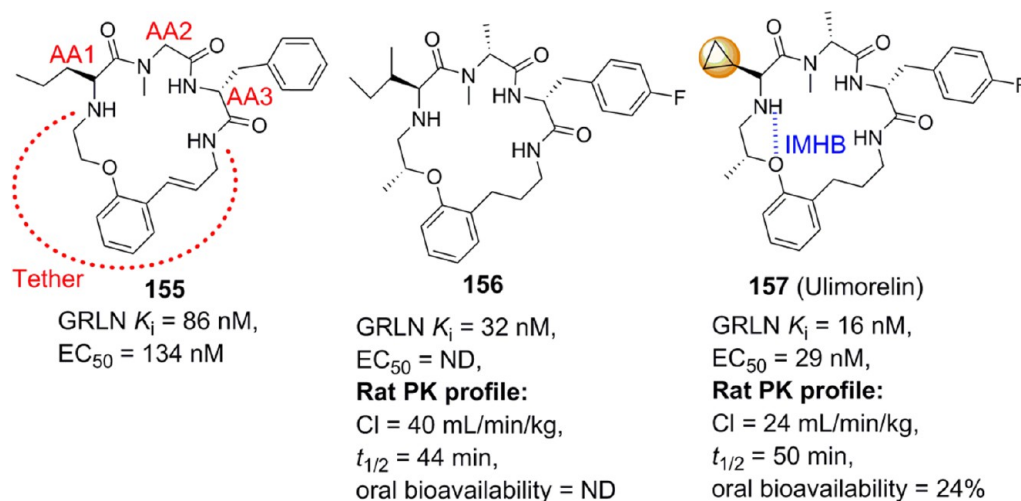


Figure 65. Structures, in vitro potency, and PK properties of ghrelin receptor agonists 155–157.

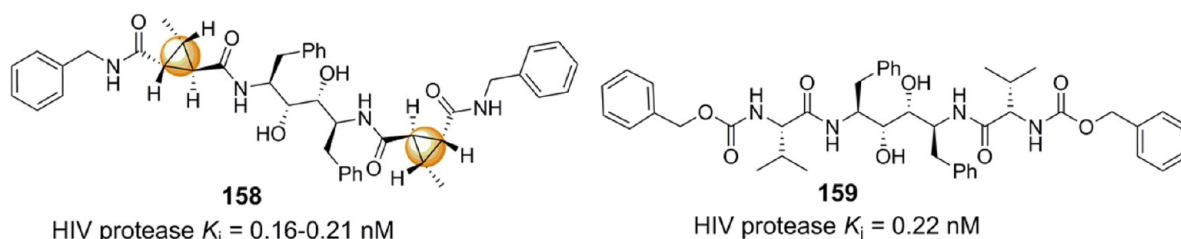


Figure 66. Structures and in vitro potency of peptidomimetic HIV protease inhibitors **158** and **159**.

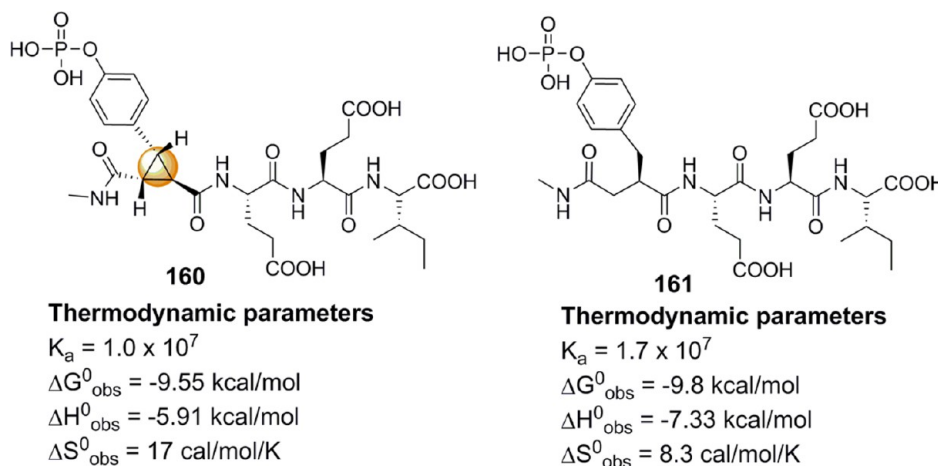


Figure 67. Structures, binding affinity, and thermodynamic properties of peptidomimetic Src SH2 domain inhibitors **160** and **161**.

THE ROLE OF CYCLOPROPANE RING IN CONFORMATIONALLY RESTRICTED PEPTIDOMIMETICS

The concept of preorganizing or locking of flexible biologically active compounds into their bioactive conformation has been widely used in medicinal chemistry research, particularly for the design of aspartyl protease inhibitors. This concept was based on the hypothesis that bioactive conformational locking would increase affinity through a decreased loss of conformational entropy upon binding to the active site of the target protein. Two representative examples are given below to illustrate the concept of ligand preorganization by comparing a flexible and constrained ligand pairs. Martin and co-workers¹⁹⁹ demonstrated that the 1,2,3-trisubstituted cyclopropane scaffold-derived peptidomimetics can efficiently stabilize the extended bioactive conformation of a peptidic compound as shown in Figure 66. They reported a marginal increase in affinity of constrained peptidomimetic analogue **158** when compared to the affinity of flexible peptide compound **159** toward HIV-1 protease. Furthermore, computational alignment studies of cyclopropanyl (rigid) and vanilyl (flexible) analogues revealed near-identical localization of the methyl groups of rigid analogues and the γ -methyl groups of flexible analogues. This has supported the observed comparable HIV-1 protease inhibitory potency as shown in Figure 66.¹⁹⁹

As explained above, preorganizing/locking a ligand into a bioactive conformation will lead to entropically favorable binding. Davidson and co-workers²⁰⁰ designed, synthesized, and thermodynamically characterized a novel cyclopropanated phosphotyrosyl peptidomimetics as Src SH2 domain binding inhibitors as shown in Figure 67. As expected, compound **160** bound to Src SH2 domain with a significant entropic advantage compared to the flexible compound **161**. This has strengthened

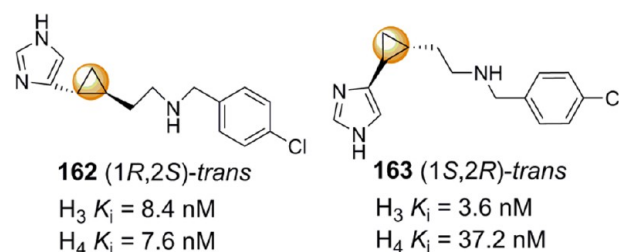


Figure 68. Structures and in vitro potency of H_3/H_4 receptor antagonists **162** and **163**.

the concept of conformational restriction by 1,2,3-trisubstituted cyclopropane ring leads to entropically favorable binding. However, conformationally rigid analogue **160** exhibited less favorable binding enthalpy. Comparable binding affinities of **160** and **161** to the Src SH2 domain is a result of favorable entropy change which is being compensated for by an unfavorable enthalpy change. Therefore, it is important to consider the enthalpic component during conformational restriction of the peptidic ligands.²⁰⁰

THE ROLE OF A CYCLOPROPANE RING IN PROBING THE RECEPTOR TOPOLOGY AND DEVELOPMENT OF RECEPTOR ANTAGONISTS

Watanabe and colleagues²⁰¹ utilized a stereochemical diversity oriented conformational restriction approach to develop potent histamine H_3 and H_4 receptor antagonists. The pendant pharmacophore groups, the imidazole ring, and the hydrophobic 4-chlorobenzyl moiety are projected in various three-dimensional arrangements due to the chiral *cis*- and *trans*-cyclopropane central spacer scaffold. The (1*R*,2*S*)-*trans*-cyclopropane isomer **162** had comparable antagonism of H_3 and H_4 receptors, whereas the (1*S*,2*R*)-*trans*-cyclopropane isomer **163** was a highly selective

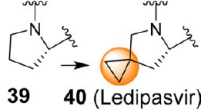
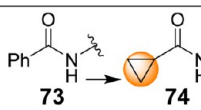
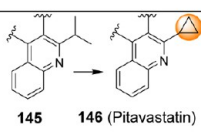
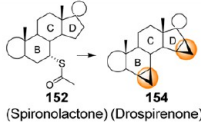
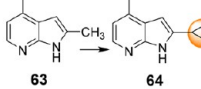
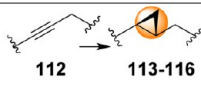
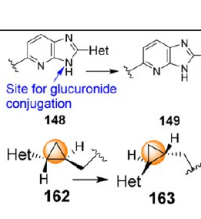
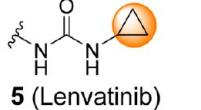
antagonist for H₃ receptor as shown in Figure 68.²⁰¹ Therefore, one can achieve receptor subtype potency and selectivity by modifying the molecular configuration at the cyclopropane spacer scaffold. Similarly, the cyclopropane ring has been successfully utilized for the development of antagonists/molecular probes for the understanding of receptors, including

excitatory amino acid receptors²⁰² and nicotinic/muscarinic acetylcholine receptors.²⁰³

SUMMARY

The centrally located cyclopropane ring can impose significant steric constraints on the conformation of an entire molecule (e.g.,

Table 1. Summary of the Contributions of a Cyclopropyl Ring towards the PK/PD/Physicochemical Properties of Selected Compounds Described in This Article

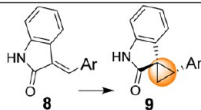
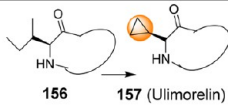
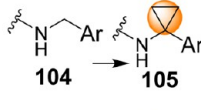
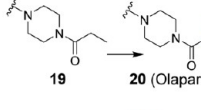
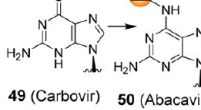
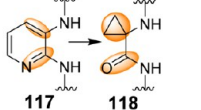
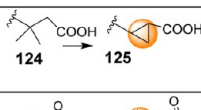
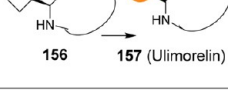
PK/PD/physicochemical properties	Contribution	Compound/drug example, mechanism of action and disease area		
		Compound/drug example	Mechanism of action	Therapeutic area
Potency	Increased	 39 40 (Ledipasvir)	HCV NS5A inhibitor	HCV
		 65 66	p38α MAP kinase inhibitor	Rheumatoid arthritis
		 73 74	Lck inhibitor	Autoimmune and Inflammatory diseases
		 145 146 (Pitavastatin)	HMG-CoA reductase inhibitor	Hyperlipidemia
		 152 (Spironolactone) 154 (Drospirenone)	Anti-androgen and anti-mineralocorticoid	Contraceptive
Selectivity	Increased	 63 64	IKK2 inhibitor	Rheumatoid arthritis, COPD, asthma
		 112 113-116	α4β2 nAChR partial agonist	Depression, ADHD and neuropathic pain
		 148 149 162 163	DGAT2 inhibitor H ₃ receptor antagonist	Hyperlipidemia and diabetes Narcolepsy
Long residence at receptor binding site	Targets DFG in conformation and exploit allosteric binding pocket occupancy	 5 (Lenvatinib)	Multi-kinase inhibitor	Thyroid cancer

milnacipran, tranilcypromine, tasimelteon, ticagrelor, cabozantinib, and montelukast), whereas the terminally located cyclopropane ring is expected to impose only limited steric rigidity (e.g., betaxolol, telaprevir, olaparib, abacavir, and lenvatinib). The centrally located chiral cyclopropane ring, through its considerable rigidity, helps to position pendant pharmacophore groups in complementary binding pockets of the target protein. Furthermore, the molecular configuration provided by the centrally located cyclopropane ring can enhance noncoplanarity, target specificity, mitigate off target activity, reduce crystal packing, and increase aqueous solubility. The cyclopropane ring has also been widely used as a convenient

biological probe to understand molecular mechanisms, receptor topology, and receptor subtype selectivity, which can promote the design of new chemical entities.

This perspective highlights the role played by the versatile cyclopropyl ring as exemplified by FDA approved drugs and preclinical/clinical candidates and summarized in Table 1. The author anticipates that this perspective will inspire scientists involved in drug discovery to exploit the cyclopropane ring either as a substituent, as a chiral bridge, and as a spiro or fused ring in solving multiple challenges that occur during the course of drug discovery program and including target specificity, therapeutic potency, ligand

Table 1. continued

PK/PD/physicochemical properties	Contribution	Compound/drug example, mechanism of action and disease area		
		Compound/drug example	Mechanism of action	Therapeutic area
Aqueous solubility	Increased		Plk4 inhibitor	Cancer
			Ghrelin receptor agonist	Postoperative ileus
P-gp efflux	Decreased		BACE1 inhibitor	Alzheimer's disease
			$\alpha 4\beta 2$ nAChR partial agonist	Depression, ADHD and neuropathic pain
Plasma protein binding	Decreased		$\alpha 4\beta 2$ nAChR partial agonist	Depression, ADHD and neuropathic pain
Oral bioavailability	Increased		PARP-1 inhibitor	BRCA-deficient tumors
			HIV-1 RT inhibitor	HIV/AIDS
			Bradykinin B1 receptor antagonist	Pain
			PDE4 inhibitor	Cognition
			Ghrelin receptor agonist	Postoperative ileus

efficiency, ligand lipophilic efficiency, aqueous solubility, pK_a , $\log P$, tuning of phase I oxidative/hydrolytic drug metabolism, sterically

limiting the phase II glucuronide conjugation, cell permeability, oral bioavailability, plasma clearance, biological half-life, chemical

Table 1. continued

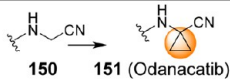
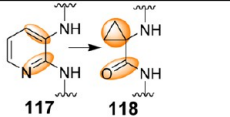
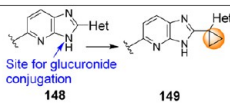
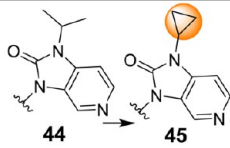
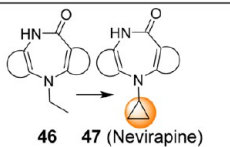
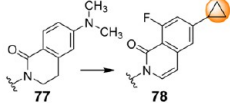
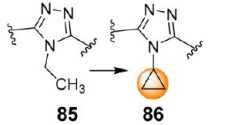
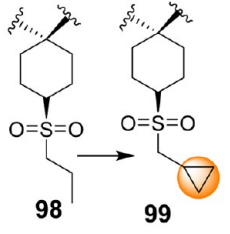
PK/PD/physicochemical properties	Contribution	Compound/drug example, mechanism of action and disease area		
		Compound/drug example	Mechanism of action	Therapeutic area
Plasma clearance	Decreased	 150 → 151 (Odanacatib)	Cathepsin inhibitor	K Osteoporosis
		 117 → 118	Bradykinin B1 receptor antagonist	B1 Pain
		 148 → 149 Site for glucuronide conjugation	DGAT2 inhibitor	Hyperlipidemia and diabetes
		 156 → 157 (Ulimorelin)	Ghrelin receptor agonist	Postoperative ileus
Metabolic stability	Increased	 44 → 45	RSV fusion inhibitor	Infection
		 46 → 47 (Nevirapine)	HIV-1 inhibitor	RT HIV/AIDS
		 77 → 78	BTK inhibitor	Rheumatoid arthritis
		 85 → 86	ROR γ inhibitor	Psoriasis and rheumatoid arthritis
		 98 → 99	GlyT1 inhibitor	Schizophrenia
		 129 (Metoprolol) → 130 (Betaxolol)	Adrenergic blocker	β Hypertension

Table 1. continued

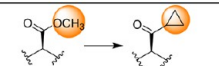
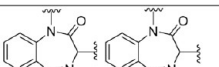
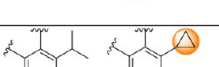
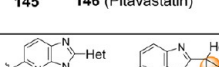
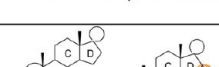
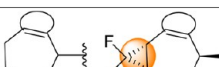
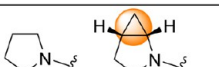
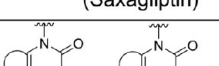
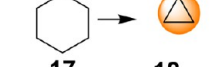
PK/PD/physicochemical properties	Contribution	Compound/drug example, mechanism of action and disease area		
		Compound/ drug example	Mechanism of action	Therapeutic area
		 134 (Clopidogrel) 135 (Prasugrel)	P2Y ₁₂ receptor antagonist	Coronary artery disease
		 139 140	Iks inhibitor	Arrhythmia
		 145 146 (Pitavastatin)	HMG-CoA reductase inhibitor	Hyperlipidemia
		 148 149 Site for glucuronide conjugation	DGAT2 inhibitor	Hyperlipidemia and diabetes
		 150 151 (Odanacatib)	Cathepsin K inhibitor	Osteoporosis
		 152 (Spironolactone) 154 (Drospirenone)	Anti-androgen and anti-mineralocorticoid	Contraceptive
Chemical stability	Increased	 22 23 (Zosuquidar)	P-gp inhibitor	Cancer
		 147 (Saxagliptin)	DPP-IV inhibitor	Diabetes
Lipophilicity	Decreased	 3 4 (Trametinib)	MEK1/MEK2 inhibitor	Melanoma
		 17 18	Aurora kinase inhibitor	Solid tumors and lymphoma
		 73 74	Lck inhibitor	Autoimmune and Inflammatory diseases

Table 1. continued

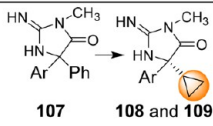
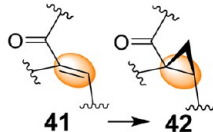
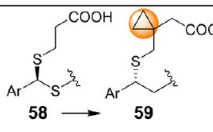
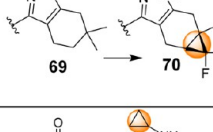
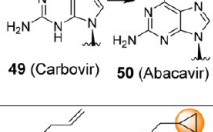
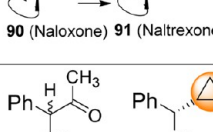
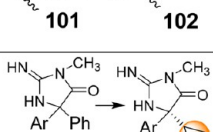
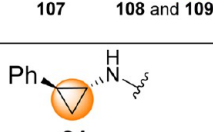
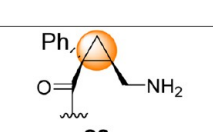
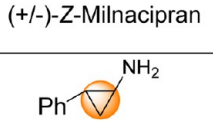
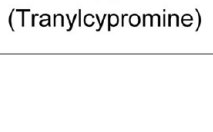
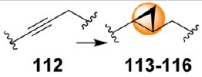
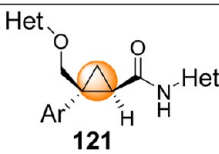
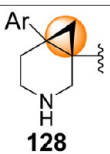
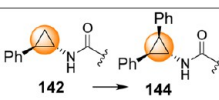
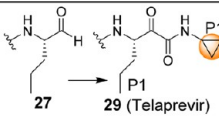
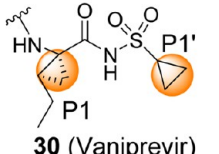
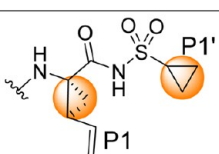
PK/PD/physicochemical properties	Contribution	Compound/drug example, mechanism of action and disease area		
		Compound/ drug example	Mechanism of action	Therapeutic area
		 107 108 and 109	BACE1 inhibitor	Alzheimer's disease
Toxicity	Decreased	 41 42	HCV NS5B polymerase inhibitor	HCV
		 58 59	LTD ₄ antagonist	Asthma
		 69 70	ITK inhibitor	Allergic asthma and inflammatory conditions
CNS exposure	Increased	 49 (Carbovir) 50 (Abacavir)	HIV-1 RT inhibitor	HIV/AIDS
		 90 (Naloxone) 91 (Naltrexone)	μ- and κ-opioid receptor antagonist	Opioid addiction
		 101 102	NK-3 inhibitor	Schizophrenia
		 107 108 and 109	BACE1 inhibitor	Alzheimer's disease
Binding pocket exploitation	Chiral scaffold that projected pharmacophore groups in desired binding pockets through the conformational restriction	 21	LSD1 inhibitor	Small cell lung carcinoma and acute myeloid leukemia
		 88 (+/-)-Z-Milnacipran	5-HT and NE reuptake inhibitor	Depression
		 95 (Tranylcypromine)	MAO-B inhibitor	Depression

Table 1. continued

PK/PD/physicochemical properties	Contribution	Compound/drug example, mechanism of action and disease area		
		Compound/ drug example	Mechanism of action	Therapeutic area
		 97 (Tasimelteon)	MT ₁ and MT ₂ agonists	Insomnia
		 112 → 113-116	α 4 β 2 nAChR partial agonist	Depression, ADHD and neuropathic pain
		 121	OX1R and OX2R antagonist	Insomnia
		 128	SERT, NET and DAT inhibitor	Depression
		 142 → 144	Soluble epoxide hydrolase inhibitor	Cardiovascular, inflammation, neuropathic pain
	To exploit a shallow S1'-binding site of the HCV NS3/4A protease	 27 → 29 (Telaprevir)	HCV NS3/4A protease inhibitor	HCV
		 30 (Vaniprevir)	HCV NS3/4A protease inhibitor	HCV
		 33 (Grazoprevir)	HCV NS3/4A protease inhibitor	HCV

stability, liver microsomal stability, eliminating isomerizable non-cyclic C=C bond through cyclopropanation, removal of Michael acceptor through cyclopropanation, and in the case of CNS active drugs, tuning of brain penetration, P-gp efflux ratio, and CNS receptor occupancy (Table 1).

■ ASSOCIATED CONTENT

📄 Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.jmedchem.6b00472](https://doi.org/10.1021/acs.jmedchem.6b00472).

Additional examples of clinically relevant cyclopropane-containing compounds ([PDF](#))

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Notes

The author declares no competing financial interest.

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ABBREVIATIONS USED

A_{2A} and A_{2B}, adenosine receptor types 2A and 2B; Abl, abelson tyrosine kinase; A β , amyloid β peptide; nAChR, nicotinic acetylcholine receptor; ADHD, attention deficit hyperactivity disorder; AUC, area under the curve; BACE-1, β -site amyloid precursor protein (APP)-cleaving enzyme-1; BRCA, breast cancer susceptibility gene; BTK, Bruton's tyrosine kinase; C_b, concentration in the brain; Cl, clearance; Clp, plasma clearance; DAT, dopamine reuptake transporter; DGAT, diacylglycerol acyltransferase; DHP-I, dehydropeptidase-I; DPP-IV, dipeptidylpeptidase-IV; FGFR 1 and 2, fibroblast growth factor receptor 1 and 2; FXa, factor Xa; GlyT1, human glycine uptake transporter 1; GRLN, ghrelin; hERG, human ether-a-go-go-related gene encoded potassium channel; HGFR, hepatocyte growth factor receptor; HLM, human liver microsomes; HMG-CoA, 3-hydroxy-3-methyl-glutaryl-CoA; hPBMc, human peripheral blood mononuclear cells; H₄R, histamine H₄ receptor; HWB, human whole blood; IKK, I κ B kinase; ITK, interleukin-2 inducible T-cell kinase; JAK2, janus kinase 2; K_a, association constant; KDM, lysine (K) demethylase; LipE, lipophilic efficiency; LSD1, lysine-specific demethylase 1; LTD₄, leukotriene D₄; MAO, monoamine oxidase; MAP, mitogen activated protein; MDR, multidrug resistance; MEK 1 and 2, mitogen/extracellular signal-regulated kinase 1 and 2; MGAT, monoacylglycerol acyltransferase; MLM, mouse liver microsomes; MT, melatonin receptor; NEMO, nuclear factor- κ B essential modulator; NET, norepinephrine reuptake transporter; NF- κ B, nuclear factor- κ light-chain-enhancer of B cells; NK-3, neurokinin-3; NKB, neurokinin B; NMDA, N-methyl-D-aspartate; NNRTI, non-nucleoside reverse transcriptase inhibitor; OX1R/OX2R, orexin receptor 1 and 2; P_{app}, passive permeability; PARP, poly(ADP-ribose)polymerase; PDE4, phosphodiesterase 4; PDGFR, platelet derived growth factor receptor; PEI, peroxisomal enzyme induction; P-gp, P-glycoprotein; PLC- γ , phospholipase C- γ ; Plk1 and 4, polo-like kinase 1 and 4; RET, rearranged during transfection; RLM, rat liver microsomes; ROR γ , retinoic acid receptor-related orphan receptor gamma; RSV, respiratory syncytial virus; sEH, soluble epoxide hydrolase; SERT, serotonin reuptake transporter; Th2, T helper 2; TIE2, Tie 2 receptor tyrosine kinase; TNF α , tumor necrosis factor α ; Trk, tropomyosin receptor kinase; URAT1, uric acid transporter

1; VEGFR 1, 2, and 3, vascular endothelial growth factor receptor 1, 2, and 3

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