

SPHINGOSINE-1-PHOSPHATE RECEPTOR MODULATORS FOR TREATMENT OF CARDIOPULMONARY DISORDERS

CROSS-REFERENCE TO RELATED APPLICATION

5 This application claims the priority of U.S. provisional application serial number 62/056,946, filed Sept. 29, 2014, the disclosure of which is incorporated by reference herein in its entirety.

STATEMENT OF GOVERNMENT SUPPORT

10 This invention was made with government support under MH084512, awarded by the National Institutes of Health. The government has certain rights in the invention.

BACKGROUND

15 Antagonism of the subtype 3 of the sphingosine-1-phosphate receptors (S1PRs) is proposed to have therapeutic utility in asthma, chronic obstructive pulmonary diseases, as well as additional therapeutic utilities based upon receptor expression and the effects of pharmacological antagonism of gene deletion. Five high affinity G-protein coupled receptors for sphingosine 1-phosphate (S1P) are identified (1) and the crystal structure of S1PR₁ has been solved (2). This cluster of receptors is medically important because the non-selective S1PR agonist fingolimod is
20 an effective oral therapy for the treatment of relapsing-remitting multiple sclerosis by altering lymphocyte function. Various S1P receptor subtypes that differ in spatial distribution, coupling and function can singly or in combination, play complex roles in embryonic formation of the arterial media, blood pressure regulation and cardiac function. FTY720 (fingolimod) in man is associated with significant sinus bradycardia, heart block and a prolongation of QTc interval (3,
25 4). Atropine reversal of the sinus bradycardia (5) and the demonstration of sinus bradycardia with S1PR₁-selective agonists in man (6) as well as rodents (7) suggested that sino-atrial (SA) node effects and those events resulting from alterations in ventricular conduction are distinctly regulated. Mice deficient in S1PR₃ are resistant to a variety of pharmacological effects produced by agonists of S1PR₃ including pulmonary and cardiac fibrosis (8-10), cardiac arrhythmias (11)
30 as well as being resistant to complex pathologies such as cytokine storm and sepsis syndrome.

Sepsis syndrome, a consequence of infection and characterized by a state of uncontrolled systemic inflammation, kills approximately 200,000 people per year in the US (12, 13).

According to global estimates, the incidence of sepsis is believed to range from 140-240 cases per 100,000, with fatality rates as high as 30%. If associated with circulatory collapse and end-organ failures, fatality rates remain in 50-80% range (14, 15). The 1979-2000 epidemiologic sepsis study estimated a 17 billion annual cost of sepsis care in the US (16), a value that is likely to be higher today due to the increased cost of healthcare. Although early intervention and modern supportive care practices in sepsis have slightly increased in overall sepsis survival rates, to 37 to 30% (17-21), there is still an obvious unmet medical need that requires development of new therapeutic strategies to combat this healthcare burden.

Despite measures to alter pathogen burden, and intensive supportive care, sepsis syndrome has high morbidity, mortality and a significant cost burden, reflecting imbalance between pro-inflammatory cytokines and elements of inflammation essential for host protection (22). Recent work defining the signature for key elements regulating systemic inflammation, has defined new, chemically tractable targets for therapeutic intervention that are genetically validated in animal models. Our recent work has demonstrated that blunting not abolishing host responses and cytokine storm provides important protection from immunopathology while sparing antiviral immune responses (23-25). In bacterial infections we have now demonstrated by both genetic deletion of receptor (26), as well as with the use of early selective, neutral antagonists, that S1P signaling via S1PR₃ on dendritic cells (DC) exacerbates systemic inflammation and lethality in stringent models of sepsis, i.e. both LPS-induced inflammation and in cecal ligation puncture (CLP) models.

Sepsis syndrome is a significant unmet medical need, as no effective treatment options exist beyond antimicrobial therapies and supportive intensive care. Behind this medical challenge lie multiple, complex pathological endpoints that coalesce in final common pathways of end-organ failure, and prospective identification of patient subsets is a work in progress. None-the-less, the importance of the unmet medical need, coupled with new mechanistic insights into shared critical pathways, offers new opportunities for mechanism-based interventions. Characteristic pathological symptoms of severe sepsis include profound inflammation, dysregulated coagulation, tissue microvascular edema, cardiovascular collapse, renal dysfunction and ultimately death. An additional long-term consequence is pulmonary fibrosis. These

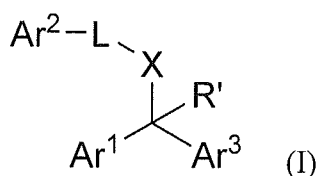
symptoms result primarily from the hyper-activation of the host's immune system reacting to the pathogen's invasion (27, 28). Understanding the factor(s) regulating the onset and progression of the host's immune overactivation is relevant for designing novel effective therapies for sepsis. Multiple lines of evidence support crucial roles for S1PRs in the control of immune cell trafficking and cardiovascular functions in physiology and disease (29, 30). S1P, a circulating bioactive lysophospholipid derived from the ceramide pathway (Fig. 1), binds to and activates five closely related G-protein coupled receptors, referred to as S1PR₁₋₅. Interestingly, human diseases with an active inflammatory component, such as multiple sclerosis (MS), coronary atherosclerosis, and lupus, have elevated plasma or local S1P levels (31-34). In the case of sepsis, there is even plasma elevation of a major S1P carrier lipoprotein, Apoprotein M, in disease subjects, and is now a risk factor for poor prognosis (35, 36). Thus it is likely that S1P signaling tone is consequently altered in septicemia. Since discontinuation of Xigris (37), an intended target of the endothelial components of sepsis, and since immunosuppressive corticosteroidal therapy can be controversial due to adrenal insufficiency occurring in sepsis (38, 39), there is a limited arsenal to combat sepsis. Inhibiting, with a systemic selective small molecule antagonist, S1PR₃ on DCs, on vascular smooth muscle, coronary artery smooth muscle and bronchial smooth muscle can contribute to improving the therapeutic outcome in multiple clinical syndromes characterized by bronchoconstriction, pulmonary fibrosis, coronary artery constriction, cytokine amplification by dendritic cells, as well as the generation of disseminated intravascular coagulopathy, based upon data showing that S1PR₃ signaling contributes to pro-inflammatory signals, fibrosis and and to poor sepsis outcome.

Previous findings indicated that S1PR₃ deficient DCs (taken from S1PR₃ knockouts), significantly enhanced the survival of mice administered with a 90% lethal dose (LD90) of LPS or in mice following the Cecal Ligation Puncture (CLP) model of polymicrobial sepsis (26). Most importantly, the study pointed out that treatment with AUY954, a selective S1P₁ agonist that sequesters B- and T-lymphocytes from the blood (40), and is useful for dampening inflammation in animal models of localized inflammation (41), did not infer any protection in the same study. Another report using similar transfer methods has just shown that S1PR₃-deficiency in DCs significantly blunted pro-inflammatory mediators in renal ischemia/reperfusion studies and lowered kidney immunopathology in mice (42). Interesting, the authors further implicated IL-4 signaling as a downstream mediator of the S1PR₃ deficiency benefits in renal

ischemia/reperfusion. Furthermore, siRNA knockdown of S1PR₃ in bone marrow derived DCs (BMDC) greatly reduced transwell DC migration, and migration to the mesenteric lymph node (43), suggesting that S1PR₃ is directly involved in DC migration. Overall, the available evidence strongly suggests that down-modulating S1PR₃ DC signaling, as proposed with a systemic S1PR₃ antagonist, may open a new therapeutic opportunity in sepsis syndrome. These data strongly suggest that an S1PR₃ antagonist may be valuable during the early management period of sepsis care, characterized as the critical therapeutic window with potential for boosting survival (44) (45).

SUMMARY

The invention provides, in various embodiments, a compound of formula (I)



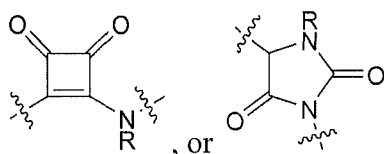
wherein each of Ar¹, Ar², and Ar³ is independently selected (C6-C10)aryl ring system or a (5- to 10-membered) heteroaryl ring system, wherein any aryl or heteroaryl ring system of Ar¹, Ar², or Ar³ is optionally fused with a cycloalkyl or a heterocyclyl ring; wherein any aryl or heteroaryl of Ar¹, Ar², or Ar³ is each optionally independently mono- or multi-substituted with up to three substituents selected from the group consisting of (C1-C4)alkyl, (C2-C4)alkenyl, halo, halo(C1-C4)alkyl, OH, monohydroxy(C1-C4)alkyl, dihydroxy(C2-C4)alkyl, monohydroxy(C1-C4)alkoxy, dihydroxy(C2-C4)alkoxy, (C1-C4)alkoxy, (C2-C6)acyl, (C1-C6)alkoxycarbonyl(CH₂)₀₋₂, carboxy(CH₂)₀₋₂, oxo, cyano, NR₂(CH₂)₀₋₂, NR₂C(=O)(CH₂)₀₋₂, NR₂C(=O)(CH₂)₀₋₂O(CH₂)₀₋₂, (C1-C4)C(=O)N(R), (C1-C4)OC(=O)N(R), C=NOR, (C3-C10)cycloalkyl, (5- to 10-membered)heterocyclyl, (C6-C10)aryl, and (5- to 10-membered) heteroaryl; wherein any cycloalkyl, heterocyclyl, aryl or heteroaryl substituent of Ar¹, Ar², or Ar³ is itself optionally substituted with up to three secondary substituents selected from the group consisting of (C1-C4)alkyl, (C2-C4)alkenyl, halo, halo(C1-C4)alkyl, OH, monohydroxy(C1-C4)alkyl, dihydroxy(C2-C4)alkyl, monohydroxy(C1-C4)alkoxy, dihydroxy(C2-C4)alkoxy, (C1-C4)alkoxy, (C2-C6)acyl, (C1-C6)alkoxycarbonyl(CH₂)₀₋₂, carboxy(CH₂)₀₋₂, oxo, cyano, NR₂(CH₂)₀₋₂, NR₂C(=O)(CH₂)₀₋₂, NR₂C(=O)(CH₂)₀₋₂O(CH₂)₀₋₂, (C1-C4)C(=O)N(R), (C1-C4)OC(=O)N(R), and C=NOR;

each R is independently H, (C1-C4)alkyl, hydroxy(C2-C4)alkyl, cyano, or ((C1-C4)alkyl-O)₁₋₂(C1-C4)alkyl, or two R groups together with an atom to which they are both joined can form a ring;

each R' is independently H, (C1-C4)alkyl, hydroxy(C2-C4)alkyl, (CH₂)₀₋₂C(=O)O(C1-C4)alkyl, or (C3-C6)cycloalkyl;

X is a bond, (CH₂)₁₋₂, (CH₂)₀₋₂N(R)(CH₂)₀₋₂, (CH₂)₀₋₂O(CH₂)₀₋₂, (CH₂)₀₋₂N(R)C(=O)(CH₂)₀₋₂, (CH₂)₀₋₂C(=O)N(R)(CH₂)₀₋₂, (CH₂)₀₋₂N(R)C(=O)O(CH₂)₀₋₂, or (CH₂)₀₋₂OC(=O)N(R)(CH₂)₀₋₂;

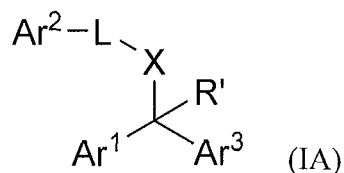
L is a bond, NR, C(=O), SO₂, C(=NR), C(=O)CR₂, C(=O)CH(N(R)C(=O)(C1-C4)alkyl), C(=O)CH(N(R)C(=O)O(C1-C4)alkyl), C(=O)CH(NR₂), C(=O)CR(halo), or is



wherein wavy lines indicate points of bonding,

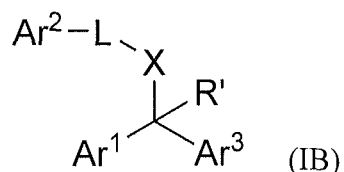
or a pharmaceutically acceptable salt thereof.

For example, the compound can be of formula (IA)



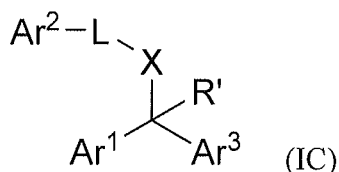
wherein each of Ar¹, Ar², and Ar³ is independently selected aryl; X, L, R, and R' are as defined herein.

For example, the compound can be of formula (IB)



wherein Ar¹ and Ar² are independently selected aryl and Ar³ is heteroaryl; X, L, R, and R' are as defined herein.

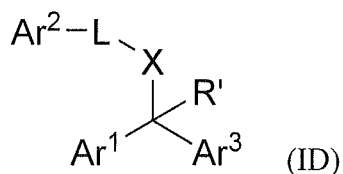
For example, the compound can be of formula (IC)



wherein

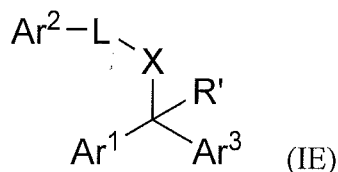
Ar¹ is aryl, Ar² and Ar³ are independently selected heteroaryl; X, L, R, and R' are as defined herein.

5 For example, the compound can be of formula (ID)



wherein Ar¹ and Ar³ are independently selected aryl, and Ar² is heteroaryl; X, L, R, and R' are as defined herein.

For example, the compound can be of formula (IE)



wherein Ar¹ and Ar³ are independently selected heteroaryl, and Ar² is aryl; X, L, R, and R' are as defined herein.

In various embodiments, the invention provides a pharmaceutical composition comprising a compound of the invention and a pharmaceutically acceptable excipient.

15 The invention further provides, in various embodiments, a method of treatment of a cardiopulmonary disease in a patient afflicted therewith, comprising administering an effective amount of a compound of the invention. For instance, the disease can be asthma or a chronic obstructive pulmonary disease; or, the disease can comprises sepsis; or, wherein the disease is coronary atherosclerosis. In various embodiments, the invention provides a method of treatment
 20 wherein the disease comprises a clinical syndrome characterized by bronchoconstriction, pulmonary fibrosis, coronary artery constriction, cytokine amplification by dendritic cells, or the generation of disseminated intravascular coagulopathy. More specifically, the invention provides a method of treatment of a disease in a patient afflicted therewith wherein the disease

comprises inflammation by influenza infection, or wherein the disease is cardiovascular disease, hypertension (including malignant hypertension), angina, myocardial infarction, cardiac arrhythmias, congestive heart failure, coronary heart disease, atherosclerosis, angina pectoris, dysrhythmias, cardiomyopathy (including hypertrophic cardiomyopathy), heart failure, cardiac arrest, bronchitis, asthma, chronic obstructive pulmonary disease, cystic fibrosis, croup, emphysema, pleurisy, pulmonary fibrosis, pneumonia, pulmonary embolus, pulmonary hypertension, mesothelioma, ventricular conduction abnormalities, complete heart block, adult respiratory distress syndrome, sepsis syndrome, idiopathic pulmonary fibrosis, scleroderma, systemic sclerosis, retroperitoneal fibrosis, prevention of keloid formation, or cirrhosis.

Accordingly, the invention provides, in various embodiments, a medical use comprising use of a compound of the invention, such as in a pharmaceutical composition, for treatment of any of the above-enumerated medical conditions.

DETAILED DESCRIPTION

Definitions

As used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise.

The term "about" as used herein, when referring to a numerical value or range, allows for a degree of variability in the value or range, for example, within 10%, or within 5% of a stated value or of a stated limit of a range.

The term "disease" or "disorder" or "malcondition" are used interchangeably, and are used to refer to diseases or conditions wherein a sphingosine-1-phosphate receptor plays a role in the biochemical mechanisms involved in the disease or malcondition or symptom(s) thereof such that a therapeutically beneficial effect can be achieved by acting on sphingosine-1-phosphate receptor, e.g. with an effective amount or concentration of a synthetic ligand of the invention. "Acting on" a sphingosine-1-phosphate receptor, or "modulating" a sphingosine-1-phosphate receptor, can include binding to the sphingosine-1-phosphate receptor and/or inhibiting the bioactivity of the sphingosine-1-phosphate receptor and/or allosterically regulating the bioactivity of the sphingosine-1-phosphate receptor *in vivo*.

The expression "effective amount", when used to describe therapy to an individual suffering from a disorder, refers to the quantity or concentration of a compound of the invention

that is effective to inhibit or otherwise act on a sphingosine-1-phosphate receptor in the individual's tissues wherein the sphingosine-1-phosphate receptor involved in the disorder, wherein such inhibition or other action occurs to an extent sufficient to produce a beneficial therapeutic effect.

5 “Treating” or “treatment” within the meaning herein refers to an alleviation of symptoms associated with a disorder or disease, or inhibition of further progression or worsening of those symptoms, or prevention or prophylaxis of the disease or disorder, or curing the disease or disorder. Similarly, as used herein, an “effective amount” or a “therapeutically effective amount” of a compound of the invention refers to an amount of the compound that alleviates, in
10 whole or in part, symptoms associated with the disorder or condition, or halts or slows further progression or worsening of those symptoms, or prevents, or provides prophylaxis for, the disorder or condition. In particular, a “therapeutically effective amount” refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result. A therapeutically effective amount is also one in which any toxic or detrimental effects of
15 compounds of the invention are outweighed by the therapeutically beneficial effects.

It is to be further understood that where descriptions of various embodiments use the term “comprising,” those skilled in the art would understand that in some specific instances, an embodiment can be alternatively described using language “consisting essentially of” or “consisting of.”

20 By “chemically feasible” is meant a bonding arrangement or a compound where the generally understood rules of organic structure are not violated; for example a structure within a definition of a claim that would contain in certain situations, e.g., a pentavalent carbon atom that would not exist in nature would be understood to not be within the claim. The structures disclosed herein, in all of their embodiments are intended to include only “chemically feasible”
25 structures, and any recited structures that are not chemically feasible, for example in a structure shown with variable atoms or groups, are not intended to be disclosed or claimed herein.

When a substituent is specified to be an atom or atoms of specified identity, “or a bond”, a configuration is referred to when the substituent is “a bond” that the groups that are immediately adjacent to the specified substituent are directly connected to each other in a
30 chemically feasible bonding configuration.

All single enantiomer, diastereomeric, and racemic forms of a structure are intended, unless a particular stereochemistry or isomeric form is specifically indicated. In several instances though an individual stereoisomer is described among specifically claimed compounds, the stereochemical designation does not imply that alternate isomeric forms are less preferred, undesired, or not claimed. Compounds used in the present invention can include enriched or resolved optical isomers at any or all asymmetric atoms as are apparent from the depictions, at any degree of enrichment. Both racemic and diastereomeric mixtures, as well as the individual optical isomers can be isolated or synthesized so as to be substantially free of their enantiomeric or diastereomeric partners, and these are all within the scope of the invention.

As used herein, the terms "stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent. Only stable compounds are contemplated herein.

When a group is recited, wherein the group can be present in more than a single orientation within a structure resulting in more than single molecular structure, e.g., a carboxamide group $C(=O)NR$, it is understood that the group can be present in any possible orientation, e.g., $X-C(=O)N(R)-Y$ or $X-N(R)C(=O)-Y$, unless the context clearly limits the orientation of the group within the molecular structure.

Substituted ring groups such as substituted cycloalkyl, aryl, heterocyclyl and heteroaryl groups also include rings and fused ring systems in which a bond to a hydrogen atom is replaced with a bond to a carbon atom, or to a substituent group as defined above. Therefore, substituted cycloalkyl, aryl, heterocyclyl and heteroaryl groups can also be substituted with alkyl, alkenyl, and alkynyl groups, or with the substituent groups listed above or other substituent groups known to persons of ordinary skill in the art.

By a "ring system" as the term is used herein is meant a moiety comprising one, two, three or more rings, which can be substituted with non-ring groups or with other ring systems, or both, which can be fully saturated, partially unsaturated, fully unsaturated, or aromatic, and when the ring system includes more than a single ring, the rings can be fused, bridging, or spirocyclic.

Ring systems can be mono- or independently multi-substituted with substituents as are described above. By "spirocyclic" is meant the class of structures wherein two rings are fused at a single tetrahedral carbon atom, as is well known in the art.

As to any of the groups described herein, which contain one or more substituents, it is understood, of course, that such groups do not contain any substitution or substitution patterns which are sterically impractical and/or synthetically non-feasible. In addition, the compounds of this disclosed subject matter include all stereochemical isomers arising from the substitution of these compounds.

When a number of carbon atoms in a group, e.g., an alkyl, alkenyl, alkynyl, cycloalkyl, aryl, etc., is specified as a range, each individual integral number representing the number of carbon atoms is intended. For example, recitation of a (C₁-C₄)alkyl group indicates that the alkyl group can be any of methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, or tert-butyl. It is understood that a specification of a number of carbon atoms must be an integer.

When a number of atoms in a ring is specified, e.g., a 3- to 9-membered cycloalkyl or heterocyclyl ring, the cycloalkyl or heterocyclyl ring can include any of 3, 4, 5, 6, 7, 8, or 9 atoms. A cycloalkyl ring is carbocyclic; a heterocyclyl ring can include atoms of any element in addition to carbon capable of forming two or more bonds, e.g., nitrogen, oxygen, sulfur, and the like. The number of atoms in a ring is understood to necessarily be an integer.

Alkyl groups include straight chain and branched carbon-based groups having from 1 to about 20 carbon atoms, and typically from 1 to 12 carbons or, in some embodiments, from 1 to 8 carbon atoms. Examples of straight chain alkyl groups include those with from 1 to 8 carbon atoms such as methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, and n-octyl groups. Examples of branched alkyl groups include, but are not limited to, isopropyl, iso-butyl, sec-butyl, t-butyl, neopentyl, isopentyl, and 2,2-dimethylpropyl groups. As used herein, the term "alkyl" encompasses n-alkyl, isoalkyl, and anteisoalkyl groups as well as other branched chain forms of alkyl. Representative substituted alkyl groups can be substituted one or more times with any of the substituent groups listed above, for example, amino, hydroxy, cyano, carboxy, nitro, thio, alkoxy, and halogen groups. Exemplary alkyl groups include, but are not limited to, straight or branched hydrocarbons of 1-6, 1-4, or 1-3 carbon atoms, referred to herein as C₁₋₆alkyl, C₁₋₄alkyl, and C₁₋₃alkyl, respectively. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, 2-methyl-1-butyl, 3-methyl-2-butyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, etc.

Cycloalkyl groups are groups containing one or more carbocyclic ring including, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl groups. In some embodiments, the cycloalkyl group can have 3 to about 8-12 ring members, whereas in other embodiments the number of ring carbon atoms range from 3 to 4, 5, 6, or 7. Cycloalkyl groups further include polycyclic cycloalkyl groups such as, but not limited to, norbornyl, adamantyl, bornyl, camphenyl, isocamphenyl, and carenyl groups, and fused rings such as, but not limited to, decalanyl, and the like. Cycloalkyl groups also include rings that are substituted with straight or branched chain alkyl groups as defined above.

Alkenyl groups include straight and branched chain and cyclic alkyl groups as defined above, except that at least one double bond exists between two carbon atoms. Thus, alkenyl groups have from 2 to about 20 carbon atoms, and typically from 2 to 12 carbons or, in some embodiments, from 2 to 8 carbon atoms. Examples include, but are not limited to vinyl, $-\text{CH}=\text{CH}(\text{CH}_3)$, $-\text{CH}=\text{C}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)=\text{CH}_2$, $-\text{C}(\text{CH}_3)=\text{CH}(\text{CH}_3)$, $-\text{C}(\text{CH}_2\text{CH}_3)=\text{CH}_2$, cyclohexenyl, cyclopentenyl, cyclohexadienyl, butadienyl, pentadienyl, and hexadienyl among others. Exemplary alkenyl groups include, but are not limited to, a straight or branched group of 2-6 or 3-4 carbon atoms, referred to herein as C_{2-6} alkenyl, and C_{3-4} alkenyl, respectively. Exemplary alkenyl groups include, but are not limited to, vinyl, allyl, butenyl, pentenyl, etc.

Aryl groups are cyclic aromatic hydrocarbons that do not contain heteroatoms in the ring. An aromatic compound, as is well-known in the art, is a multiply-unsaturated cyclic system that contains $4n+2$ π electrons where n is an integer. Thus aryl groups include, but are not limited to, phenyl, azulenyl, heptalenyl, biphenyl, indacenyl, fluorenyl, phenanthrenyl, triphenylenyl, pyrenyl, naphthacenyl, chrysenyl, biphenylenyl, anthracenyl, and naphthyl groups. In some embodiments, aryl groups contain about 6 to about 14 carbons in the ring portions of the groups. Aryl groups can be unsubstituted or substituted, as defined above. Representative substituted aryl groups can be mono-substituted or substituted more than once, such as, but not limited to, 2-, 3-, 4-, 5-, or 6-substituted phenyl or 2-8 substituted naphthyl groups, which can be substituted with carbon or non-carbon groups such as those listed above.

Aralkyl, also termed arylalkyl, groups are alkyl groups as defined above in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to an aryl group as defined above. Representative aralkyl groups include benzyl and phenylethyl groups and fused (cycloalkylaryl)alkyl groups such as 4-ethyl-indanyl. Aralkenyl group are alkenyl groups as

defined above in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to an aryl group as defined above.

Heterocyclyl groups or the term "heterocyclyl" includes aromatic and non-aromatic ring compounds containing 3 or more ring members, of which one or more ring atom is a heteroatom such as, but not limited to, N, O, and S. Thus a heterocyclyl can be a cycloheteroalkyl, or a heteroaryl, or if polycyclic, any combination thereof. In some embodiments, heterocyclyl groups include 3 to about 20 ring members, whereas other such groups have 3 to about 15 ring members. A heterocyclyl group designated as a C₂-heterocyclyl can be a 5-ring with two carbon atoms and three heteroatoms, a 6-ring with two carbon atoms and four heteroatoms and so forth. Likewise a C₄-heterocyclyl can be a 5-ring with one heteroatom, a 6-ring with two heteroatoms, and so forth. The number of carbon atoms plus the number of heteroatoms sums up to equal the total number of ring atoms. Ring sizes can also be expressed by the total number of atoms in the ring, e.g., a 3- to 10-membered heterocyclyl group, counting both carbon and non-carbon ring atoms. A heterocyclyl ring can also include one or more double bonds. A heteroaryl ring is an embodiment of a heterocyclyl group. The term "heterocyclyl group" includes fused ring species including those comprising fused aromatic and non-aromatic groups. For example, a dioxolanyl ring and a benzodioxolanyl ring system (methylenedioxyphenyl ring system) are both heterocyclyl groups within the meaning herein. The term also includes polycyclic, e.g., bicyclo- and tricyclo- ring systems containing one or more heteroatom such as, but not limited to, quinuclidyl.

Heterocyclyl groups can be unsubstituted, or can be substituted as discussed above. Heterocyclyl groups include, but are not limited to, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridinyl, thiophenyl, benzothiophenyl, benzofuranyl, dihydrobenzofuranyl, indolyl, dihydroindolyl, azaindolyl, indazolyl, benzimidazolyl, azabenzimidazolyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, imidazopyridinyl, isoxazolopyridinyl, thianaphthalenyl, purinyl, xanthinyl, adeninyl, guaninyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, quinoxalinyl, and quinazolinyl groups. Representative substituted heterocyclyl groups can be mono-substituted or substituted more than once, such as, but not limited to, piperidinyl or quinolinyl groups, which are 2-, 3-, 4-, 5-, or 6-substituted, or disubstituted with groups such as those listed above.

Heteroaryl groups are aromatic ring compounds containing 5 or more ring members, of which, one or more is a heteroatom such as, but not limited to, N, O, and S; for instance,

heteroaryl rings can have 5 to about 8-12 ring members. A heteroaryl group is a variety of a heterocyclyl group that possesses an aromatic electronic structure, which is a multiply-unsaturated cyclic system that contains $4n+2$ π electrons wherein n is an integer. A heteroaryl group designated as a C_2 -heteroaryl can be a 5-ring (i.e., a 5-membered ring) with two carbon atoms and three heteroatoms, a 6-ring (i.e., a 6-membered ring) with two carbon atoms and four heteroatoms and so forth. Likewise a C_4 -heteroaryl can be a 5-ring with one heteroatom, a 6-ring with two heteroatoms, and so forth. The number of carbon atoms plus the number of heteroatoms sums up to equal the total number of ring atoms. Heteroaryl groups include, but are not limited to, groups such as pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, thiophenyl, benzothiophenyl, benzofuranyl, indolyl, azaindolyl, indazolyl, benzimidazolyl, azabenzimidazolyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, imidazopyridinyl, isoxazolopyridinyl, thianaphthalenyl, purinyl, xanthinyl, adeninyl, guaninyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, quinoxalinyl, and quinazolinyl groups. Heteroaryl groups can be unsubstituted, or can be substituted with substituent groups as is discussed above. Representative substituted heteroaryl groups can be substituted one or more times with independently selected groups such as those listed above.

Additional examples of aryl and heteroaryl groups include but are not limited to phenyl, biphenyl, indenyl, naphthyl (1-naphthyl, 2-naphthyl), N-hydroxytetrazolyl, N-hydroxytriazolyl, N-hydroxyimidazolyl, anthracenyl (1-anthracenyl, 2-anthracenyl, 3-anthracenyl), thiophenyl (2-thienyl, 3-thienyl), furyl (2-furyl, 3-furyl), indolyl, oxadiazolyl, isoxazolyl, quinazolinyl, fluorenyl, xanthenyl, isoindanyl, benzhydryl, acridinyl, thiazolyl, pyrrolyl (2-pyrrolyl), pyrazolyl (3-pyrazolyl), imidazolyl (1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), triazolyl (1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, 1,2,3-triazol-4-yl, 1,2,4-triazol-3-yl), oxazolyl (2-oxazolyl, 4-oxazolyl, 5-oxazolyl), thiazolyl (2-thiazolyl, 4-thiazolyl, 5-thiazolyl), pyridyl (2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl (2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl), pyrazinyl, pyridazinyl (3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl), quinolyl (2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, 8-quinolyl), isoquinolyl (1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, 6-isoquinolyl, 7-isoquinolyl, 8-isoquinolyl), benzo[b]furanyl (2-benzo[b]furanyl, 3-benzo[b]furanyl, 4-benzo[b]furanyl, 5-benzo[b]furanyl, 6-benzo[b]furanyl, 7-benzo[b]furanyl), 2,3-dihydro-benzo[b]furanyl (2-(2,3-dihydro-benzo[b]furanyl), 3-(2,3-dihydro-benzo[b]furanyl), 4-(2,3-dihydro-benzo[b]furanyl),

5- (2,3-dihydro-benzo[b]furanyl), 6- (2,3-dihydro-benzo[b]furanyl), 7- (2,3-dihydro-benzo[b]furanyl), benzo[b]thiophenyl (2-benzo[b]thiophenyl, 3-benzo[b]thiophenyl, 4-benzo[b]thiophenyl, 5-benzo[b]thiophenyl, 6-benzo[b]thiophenyl, 7-benzo[b]thiophenyl), 2,3-dihydro-benzo[b]thiophenyl, (2- (2,3-dihydro-benzo[b]thiophenyl), 3- (2,3-dihydro-benzo[b]thiophenyl), 4- (2,3-dihydro-benzo[b]thiophenyl), 5- (2,3-dihydro-benzo[b]thiophenyl), 6- (2,3-dihydro-benzo[b]thiophenyl), 7- (2,3-dihydro-benzo[b]thiophenyl), indolyl (1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl, 7-indolyl), indazole (1-indazolyl, 3-indazolyl, 4-indazolyl, 5-indazolyl, 6-indazolyl, 7-indazolyl), benzimidazolyl (1-benzimidazolyl, 2-benzimidazolyl, 4-benzimidazolyl, 5-benzimidazolyl, 6-benzimidazolyl, 7-benzimidazolyl, 8-benzimidazolyl), benzoxazolyl (1-benzoxazolyl, 2-benzoxazolyl), benzothiazolyl (1-benzothiazolyl, 2-benzothiazolyl, 4-benzothiazolyl, 5-benzothiazolyl, 6-benzothiazolyl, 7-benzothiazolyl), carbazolyl (1-carbazolyl, 2-carbazolyl, 3-carbazolyl, 4-carbazolyl), 5H-dibenz[b,f]azepine (5H-dibenz[b,f]azepin-1-yl, 5H-dibenz[b,f]azepine-2-yl, 5H-dibenz[b,f]azepine-3-yl, 5H-dibenz[b,f]azepine-4-yl, 5H-dibenz[b,f]azepine-5-yl), 10,11-dihydro-5H-dibenz[b,f]azepine (10,11-dihydro-5H-dibenz[b,f]azepine-1-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-2-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-3-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-4-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-5-yl), and the like.

Any heterocyclyl or heteroaryl comprising nitrogen can be an N-oxide or N-metho salt or other N-quaternarized salt thereof; when a cationic N-quaternarized salt is present, it is understood that an anionic counterion is present for charge balance. Any heterocyclyl or heteroaryl comprising sulfur can be an sulfoxide or sulfone or an S-metho salt or other S-alkylated salt thereof; when a cationic S-alkylated salt is present, it is understood that an anionic counterion is present for charge balance.

The term "alkoxy" or "alkoxyl" refers to an oxygen atom connected to an alkyl group, including a cycloalkyl group, as are defined above. Examples of linear alkoxy groups include but are not limited to methoxy, ethoxy, n-propoxy, n-butoxy, n-pentyloxy, n-hexyloxy, and the like. Examples of branched alkoxy include but are not limited to isopropoxy, sec-butoxy, tert-butoxy, isopentyloxy, isohexyloxy, and the like. Exemplary alkoxy groups include, but are not limited to, alkoxy groups of 1-6 or 2-6 carbon atoms, referred to herein as C₁₋₆alkoxy, and C₂.

alkoxy, respectively. Exemplary alkoxy groups include, but are not limited to methoxy, ethoxy, isopropoxy, etc.

An alkoxy group can include one to about 12-20 carbon atoms bonded to the oxygen atom, and can further include double or triple bonds, and can also include heteroatoms. For example, an allyloxy group is an alkoxy group within the meaning herein. A methoxyethoxy group is also an alkoxy group within the meaning herein, as is a methylenedioxy group in a context where two adjacent atoms of a structures are substituted therewith.

The terms "halo" or "halogen" or "halide" by themselves or as part of another substituent mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom, preferably, fluorine, chlorine, or bromine.

A "haloalkyl" group includes mono-halo alkyl groups, poly-halo alkyl groups wherein all halo atoms can be the same or different, and per-halo alkyl groups, wherein all hydrogen atoms are replaced by the same or differing halogen atoms, such as fluorine and/or chlorine atoms. Examples of haloalkyl include trifluoromethyl, 1,1-dichloroethyl, 1,2-dichloroethyl, 1,3-dibromo-3,3-difluoropropyl, perfluorobutyl, and the like.

An "acyl" group as the term is used herein refers to a group containing a carbonyl moiety wherein the group is bonded via the carbonyl carbon atom. The carbonyl carbon atom is also bonded to another carbon atom, which can be part of an alkyl, aryl, aralkyl cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl group or the like. In the special case wherein the carbonyl carbon atom is bonded to a hydrogen atom, the group is a "formyl" group, also an example of an acyl group as the term is defined herein. An acyl group can include 0 to about 12-20 additional carbon atoms bonded to the carbonyl group. An acyl group can include double or triple bonds within the meaning herein. An acryloyl group is an example of a double bond-containing acyl group. An acyl group can also include heteroatoms within the meaning here. A nicotinoyl group (pyridyl-3-carbonyl) group is an example of an acyl group within the meaning herein. Other examples include acetyl, benzoyl, phenylacetyl, pyridylacetyl, cinnamoyl, and acryloyl groups and the like. When the group containing the carbon atom that is bonded to the carbonyl carbon atom contains a halogen, the group is termed a "haloacyl" group. An example is a trifluoroacetyl group.

The term "amine" includes primary, secondary, and tertiary amines having, e.g., the formula $N(\text{group})_3$ wherein each group can independently be H or non-H, such as alkyl, aryl, and

the like. Amines include but are not limited to $R-NH_2$, wherein R is a carbon-based moiety, for example, alkylamines, arylamines, alkylarylamines; R_2NH wherein each R is independently selected carbon-based moiety, such as dialkylamines, diarylamines, aralkylamines, heterocyclamines and the like; and R_3N wherein each R is independently selected carbon-based moiety, such as trialkylamines, dialkylarylamines, alkylarylamines, triarylamines, and the like. The term "amine" as used herein also includes positively charged (cationic) forms such as amine salts and quaternarized amines.

An "amino" group is a substituent group of the form $-NH_2$, $-NHR$, $-NR_2$, or $-NR_3^+$, wherein each R is an independently selected carbon-based group, and protonated forms of each, except for $-NR_3^+$, which cannot be protonated. Accordingly, any compound substituted with an amino group can be viewed as an amine. An "amino group" within the meaning herein can be a primary, secondary, tertiary or quaternary amino group. An "alkylamino" group includes a monoalkylamino, dialkylamino, and trialkylamino (trialkylammonium) group.

An "ammonium" ion includes the unsubstituted ammonium ion NH_4^+ , but unless otherwise specified, it also includes any protonated or quaternarized forms of amines. Thus, trimethylammonium hydrochloride and tetramethylammonium chloride are both ammonium ions, and amines, within the meaning herein.

The term "amide" (or "amido") includes C- and N-amide groups, i.e., $-C(O)NR_2$, and $-NRC(O)R$ groups, respectively. Amide groups therefore include but are not limited to primary carboxamide groups ($-C(O)NH_2$) and formamide groups ($-NHC(O)H$). A "carboxamido" group is a group of the formula $C(O)NR_2$, wherein R can be H, alkyl, aryl, etc.

Standard abbreviations for chemical groups such as are well known in the art are used; e.g., Me = methyl, Et = ethyl, i-Pr = isopropyl, Bu = butyl, t-Bu = tert-butyl, Ph = phenyl, Bn = benzyl, Ac = acetyl, Bz = benzoyl, and the like.

A "salt" as is well known in the art includes an organic compound such as a carboxylic acid, a sulfonic acid, or an amine, in ionic form, in combination with a counterion. For example, acids in their anionic form can form salts with cations such as metal cations, for example sodium, potassium, and the like; with ammonium salts such as NH_4^+ or the cations of various amines, including tetraalkyl ammonium salts such as tetramethylammonium, or other cations such as trimethylsulfonium, and the like. A "pharmaceutically acceptable" or "pharmacologically acceptable" salt is a salt formed from an ion that has been approved for human consumption and

is generally non-toxic, such as a chloride salt or a sodium salt. A "zwitterion" is an internal salt such as can be formed in a molecule that has at least two ionizable groups, one forming an anion and the other a cation, which serve to balance each other. For example, amino acids such as glycine can exist in a zwitterionic form. A "zwitterion" is a salt within the meaning herein. The compounds of the present invention may take the form of salts. The term "salts" embraces addition salts of free acids or free bases which are compounds of the invention. Salts can be "pharmaceutically-acceptable salts." The term "pharmaceutically-acceptable salt" refers to salts which possess toxicity profiles within a range that affords utility in pharmaceutical applications. Pharmaceutically unacceptable salts may nonetheless possess properties such as high crystallinity, which have utility in the practice of the present invention, such as for example utility in process of synthesis, purification or formulation of compounds of the invention.

"Pharmaceutically or pharmacologically acceptable" include molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, or a human, as appropriate. For human administration, preparations should meet sterility, pyrogenicity, and general safety and purity standards as required by FDA Office of Biologics standards.

Suitable pharmaceutically-acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid. Examples of inorganic acids include hydrochloric, hydrobromic, hydriodic, nitric, carbonic, sulfuric, and phosphoric acids. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which include formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, trifluoromethanesulfonic, 2-hydroxyethanesulfonic, p-toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, stearic, alginic, β -hydroxybutyric, salicylic, galactaric and galacturonic acid. Examples of pharmaceutically unacceptable acid addition salts include, for example, perchlorates and tetrafluoroborates.

If a value of a variable that is necessarily an integer, e.g., the number of carbon atoms in an alkyl group or the number of substituents on a ring, is described as a range, e.g., 0-4, what is meant is that the value can be any integer between 0 and 4 inclusive, i.e., 0, 1, 2, 3, or 4.

In various embodiments, the compound or set of compounds, such as are used in the inventive methods, can be any one of any of the combinations and/or sub-combinations of the above-listed embodiments.

5 In various embodiments, a compound as shown in any of the Examples, or among the exemplary compounds, is provided. Provisos may apply to any of the disclosed categories or embodiments wherein any one or more of the other above disclosed embodiments or species may be excluded from such categories or embodiments.

10 The compounds described herein can be prepared in a number of ways based on the teachings contained herein and synthetic procedures known in the art. In the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, can be chosen to be the conditions standard for that reaction, unless otherwise indicated. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule should be compatible with the reagents
15 and reactions proposed. Substituents not compatible with the reaction conditions will be apparent to one skilled in the art, and alternate methods are therefore indicated. The starting materials for the examples are either commercially available or are readily prepared by standard methods from known materials. All commercially available chemicals were obtained from Aldrich, Alfa Aesare, Wako, Acros, Fisher, Fluka, Maybridge or the like and were used without
20 further purification, except where noted. Dry solvents are obtained, for example, by passing these through activated alumina columns.

The present invention further embraces isolated compounds of the invention. The expression "isolated compound" refers to a preparation of a compound of the invention, or a mixture of compounds the invention, wherein the isolated compound has been separated from the
25 reagents used, and/or byproducts formed, in the synthesis of the compound or compounds. "Isolated" does not mean that the preparation is technically pure (homogeneous), but it is sufficiently pure to compound in a form in which it can be used therapeutically. Preferably an "isolated compound" refers to a preparation of a compound of the invention or a mixture of compounds of the invention, which contains the named compound or mixture of compounds of
30 the invention in an amount of at least 10 percent by weight of the total weight. Preferably the preparation contains the named compound or mixture of compounds in an amount of at least 50

percent by weight of the total weight; more preferably at least 80 percent by weight of the total weight; and most preferably at least 90 percent, at least 95 percent or at least 98 percent by weight of the total weight of the preparation.

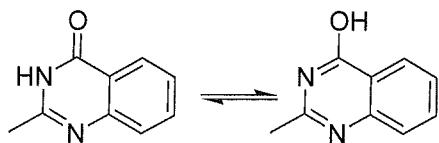
The compounds of the invention and intermediates may be isolated from their reaction mixtures and purified by standard techniques such as filtration, liquid-liquid extraction, solid phase extraction, distillation, recrystallization or chromatography, including flash column chromatography, or HPLC.

Tautomerism

Within the present invention it is to be understood that a compound of the formula (I) or a salt thereof may exhibit the phenomenon of tautomerism whereby two chemical compounds that are capable of facile interconversion by exchanging a hydrogen atom between two atoms, to either of which it forms a covalent bond. Since the tautomeric compounds exist in mobile equilibrium with each other they may be regarded as different isomeric forms of the same compound. It is to be understood that the formulae drawings within this specification can represent only one of the possible tautomeric forms. However, it is also to be understood that the invention encompasses any tautomeric form, and is not to be limited merely to any one tautomeric form utilized within the formulae drawings. The formulae drawings within this specification can represent only one of the possible tautomeric forms and it is to be understood that the specification encompasses all possible tautomeric forms of the compounds drawn not just those forms which it has been convenient to show graphically herein. For example, tautomerism may be exhibited by a pyrazolyl group bonded as indicated by the wavy line. While both substituents would be termed a 4-pyrazolyl group, it is evident that a different nitrogen atom bears the hydrogen atom in each structure.



Such tautomerism can also occur with substituted pyrazoles such as 3-methyl, 5-methyl, or 3,5-dimethylpyrazoles, and the like. Another example of tautomerism is amido-imido (lactam-lactim when cyclic) tautomerism, such as is seen in heterocyclic compounds bearing a ring oxygen atom adjacent to a ring nitrogen atom. For example, the equilibrium:



is an example of tautomerism. Accordingly, a structure depicted herein as one tautomer is intended to also include the other tautomer.

Optical Isomerism

It will be understood that when compounds of the present invention contain one or more chiral centers, the compounds may exist in, and may be isolated as single and substantially pure enantiomeric or diastereomeric forms or as racemic mixtures. The present invention therefore includes any possible enantiomers, diastereomers, racemates or mixtures thereof of the compounds of the invention.

The compounds of the invention, or compounds used in practicing methods of the invention, may contain one or more chiral centers and, therefore, exist as stereoisomers. The term “stereoisomers” when used herein consist of all enantiomers or diastereomers. These compounds may be designated by the symbols “(+),” “(-),” “R” or “S,” depending on the configuration of substituents around the stereogenic carbon atom, but the skilled artisan will recognize that a structure may denote a chiral center implicitly. The present invention encompasses various stereoisomers of these compounds and mixtures thereof. Mixtures of enantiomers or diastereomers may be designated “(±)” in nomenclature, but the skilled artisan will recognize that a structure may denote a chiral center implicitly.

The compounds of the disclosure may contain one or more double bonds and, therefore, exist as geometric isomers resulting from the arrangement of substituents around a carbon-carbon double bond. The symbol $\text{—}\text{—}\text{—}\text{—}$ denotes a bond that may be a single, double or triple bond as described herein. Substituents around a carbon-carbon double bond are designated as being in the “Z” or “E” configuration wherein the terms “Z” and “E” are used in accordance with IUPAC standards. Unless otherwise specified, structures depicting double bonds encompass both the “E” and “Z” isomers. Substituents around a carbon-carbon double bond alternatively can be referred to as “cis” or “trans,” where “cis” represents substituents on the same side of the double bond and “trans” represents substituents on opposite sides of the double bond.

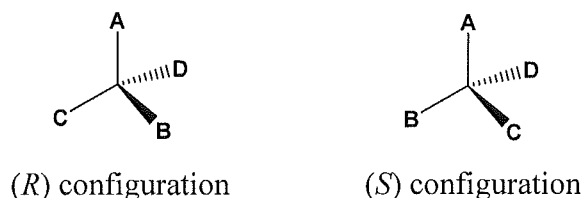
Compounds of the invention, or compounds used in practicing methods of the invention, may contain a carbocyclic or heterocyclic ring and therefore, exist as geometric isomers resulting from the arrangement of substituents around the ring. The arrangement of substituents around a

carbocyclic or heterocyclic ring are designated as being in the “Z” or “E” configuration wherein the terms “Z” and “E” are used in accordance with IUPAC standards. Unless otherwise specified, structures depicting carbocyclic or heterocyclic rings encompass both “Z” and “E” isomers. Substituents around a carbocyclic or heterocyclic rings may also be referred to as “cis” or “trans”, where the term “cis” represents substituents on the same side of the plane of the ring and the term “trans” represents substituents on opposite sides of the plane of the ring. Mixtures of compounds wherein the substituents are disposed on both the same and opposite sides of plane of the ring are designated “cis/trans.”

Individual enantiomers and diastereomers of contemplated compounds can be prepared synthetically from commercially available starting materials that contain asymmetric or stereogenic centers, or by preparation of racemic mixtures followed by resolution methods well known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary, (2) salt formation employing an optically active resolving agent, (3) direct separation of the mixture of optical enantiomers on chiral liquid chromatographic columns or (4) kinetic resolution using stereoselective chemical or enzymatic reagents. Racemic mixtures can also be resolved into their component enantiomers by well known methods, such as chiral-phase liquid chromatography or crystallizing the compound in a chiral solvent. Stereoselective syntheses, a chemical or enzymatic reaction in which a single reactant forms an unequal mixture of stereoisomers during the creation of a new stereocenter or during the transformation of a pre-existing one, are well known in the art. Stereoselective syntheses encompass both enantio- and diastereoselective transformations, and may involve the use of chiral auxiliaries. For examples, see Carreira and Kvaerno, *Classics in Stereoselective Synthesis*, Wiley-VCH: Weinheim, 2009.

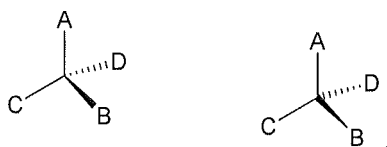
The isomers resulting from the presence of a chiral center comprise a pair of non-superimposable isomers that are called “enantiomers.” Single enantiomers of a pure compound are optically active, *i.e.*, they are capable of rotating the plane of plane polarized light. Single enantiomers are designated according to the *Cahn-Ingold-Prelog* system. The priority of substituents is ranked based on atomic weights, a higher atomic weight, as determined by the systematic procedure, having a higher priority ranking. Once the priority ranking of the four groups is determined, the molecule is oriented so that the lowest ranking group is pointed away

from the viewer. Then, if the descending rank order of the other groups proceeds clockwise, the molecule is designated as having an (*R*) absolute configuration, and if the descending rank of the other groups proceeds counterclockwise, the molecule is designated as having an (*S*) absolute configuration. In the example in the Scheme below, the *Cahn-Ingold-Prelog* ranking is $A > B > C > D$. The lowest ranking atom, D is oriented away from the viewer. The solid wedge indicates that the atom bonded thereby projects toward the viewer out of the plane of the paper, and a dashed wedge indicates that the atom bonded thereby projects away from the viewer out of the plane of the paper, i.e., the plane “of the paper” being defined by atoms A, C, and the chiral carbon atom for the (*R*) configuration shown below.



A carbon atom bearing the A-D atoms as shown above is known as a “chiral” carbon atom, and the position of such a carbon atom in a molecule is termed a “chiral center.” Compounds of the invention may contain more than one chiral center, and the configuration at each chiral center is described in the same fashion.

There are various conventions for depicting chiral structures using solid and dashed wedges. For example, for the (*R*) configuration shown above, the following two depictions are equivalent:



The present invention is meant to encompass diastereomers as well as their racemic and resolved, diastereomerically and enantiomerically pure forms and salts thereof. Diastereomeric pairs may be resolved by known separation techniques including normal and reverse phase chromatography, and crystallization.

“Isolated optical isomer” or “isolated enantiomer” means a compound which has been substantially purified from the corresponding optical isomer(s) of the same formula. Preferably, the isolated isomer is at least about 80%, more preferably at least 90% enantiomerically pure, even more preferably at least 98% enantiomerically pure, most preferably at least about 99%

enantiomerically pure, by weight. By “enantiomeric purity” is meant the percent of the predominant enantiomer in an enantiomeric mixture of optical isomers of a compound. A pure single enantiomer has an enantiomeric purity of 100%.

Isolated optical isomers may be purified from racemic mixtures by well-known chiral separation techniques. According to one such method, a racemic mixture of a compound of the invention, or a chiral intermediate thereof, is separated into 99% wt.% pure optical isomers by HPLC using a suitable chiral column, such as a member of the series of DAICEL[®] CHIRALPAK[®] family of columns (Daicel Chemical Industries, Ltd., Tokyo, Japan). The column is operated according to the manufacturer’s instructions.

Another well-known method of obtaining separate and substantially pure optical isomers is classic resolution, whereby a chiral racemic compound containing an ionized functional group, such as a protonated amine or carboxylate group, forms diastereomeric salts with an oppositely ionized chiral nonracemic additive. The resultant diastereomeric salt forms can then be separated by standard physical means, such as differential solubility, and then the chiral nonracemic additive may be either removed or exchanged with an alternate counter ion by standard chemical means, or alternatively the diastereomeric salt form may be retained as a salt to be used as a therapeutic agent or as a precursor to a therapeutic agent.

Another aspect of an embodiment of the invention provides compositions of the compounds of the invention, alone or in combination with another medicament. As set forth herein, compounds of the invention include stereoisomers, tautomers, solvates, prodrugs, pharmaceutically acceptable salts and mixtures thereof. Compositions containing a compound of the invention can be prepared by conventional techniques, e.g. as described in Remington: *The Science and Practice of Pharmacy*, 19th Ed., 1995, or later versions thereof, incorporated by reference herein. The compositions can appear in conventional forms, for example capsules, tablets, aerosols, solutions, suspensions or topical applications.

The compounds of the invention can be administered to a mammal, especially a human in need of such treatment, prevention, elimination, alleviation or amelioration of a malcondition. Such mammals include also animals, both domestic animals, e.g. household pets, farm animals, and non-domestic animals such as wildlife.

The compounds of the invention are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from about 0.05 to about 5000 mg, preferably from about

1 to about 2000 mg, and more preferably between about 2 and about 2000 mg per day can be used. A typical dosage is about 10 mg to about 1000 mg per day. In choosing a regimen for patients it can frequently be necessary to begin with a higher dosage and when the condition is under control to reduce the dosage. The exact dosage will depend upon the activity of the compound, mode of administration, on the therapy desired, form in which administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge.

Generally, the compounds of the invention are dispensed in unit dosage form including from about 0.05 mg to about 1000 mg of active ingredient together with a pharmaceutically acceptable carrier per unit dosage.

Usually, dosage forms suitable for oral, nasal, pulmonal or transdermal administration include from about 125 µg to about 1250 mg, preferably from about 250 µg to about 500 mg, and more preferably from about 2.5 mg to about 250 mg, of the compounds admixed with a pharmaceutically acceptable carrier or diluent.

Dosage forms can be administered daily, or more than once a day, such as twice or thrice daily. Alternatively dosage forms can be administered less frequently than daily, such as every other day, or weekly, if found to be advisable by a prescribing physician.

Evaluations

It is within ordinary skill to evaluate any compound disclosed and claimed herein for effectiveness in inhibition of a sphingosine-1-phosphate receptor and in the various cellular assays using the procedures described above or found in the scientific literature. Accordingly, the person of ordinary skill can prepare and evaluate any of the claimed compounds without undue experimentation.

Any compound found to be an effective inhibitor of the sphingosine-1-phosphate receptor can likewise be tested in animal models and in human clinical studies using the skill and experience of the investigator to guide the selection of dosages and treatment regimens.

In various embodiments, the compound is any of those shown in Tables 1, 2, or 3, below. Such compounds can be prepared by synthetic methods disclosed herein in combination with the knowledge of a person of ordinary skill in the art of organic synthesis, including the use of appropriately selected precursors, intermediates, reagents, and reaction mechanisms.

While the invention has been described and exemplified in sufficient detail for those skilled in this art to make and use it, various alternatives, modifications, and improvements will be apparent to those skilled in the art without departing from the spirit and scope of the claims.

All patents and publications referred to herein are incorporated by reference herein to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference in its entirety.

The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the appended claims.

Description

Although published tool compounds provide for a valuable proof-of-concept, sphingolipid analogs that are amino-phosphate esters, in general do not have the necessary kinetics and stability for optimal usefulness. Our recent publications have documented key aspects separating the S1PR₁ from S1PR₃ binding pockets, (7, 46). Although the systemic “immunosuppressive” actions of S1PR₁ modulators would be theoretically useful to dampen inflammation in localized environments, eg inflammation of the CNS in EAE or lung inflammation by influenza infection (25, 47), S1PR₁ agonists would likely pose risks in sepsis because of bradycardia (6, 7) and their potential to increase lung microvascular permeability (48) (49). Thus, dampening systemic inflammation in sepsis with selective S1PR₃ antagonist devoid of S1P₁ affinity is desired.

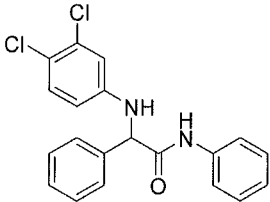
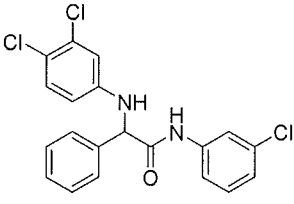
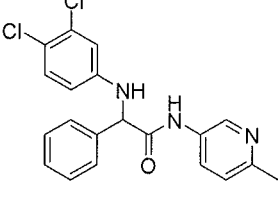
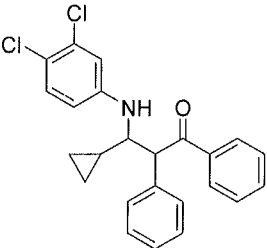
Recently, (Jo et al, 2012 and references therein) we described a model of S1PR₃ based upon our published X-ray structure of the very similar S1PR₁ subtype (2). Using a combination of site-directed mutagenesis, ligand competition binding, functional assays, and molecular modeling, we demonstrated that the endogenous pan-S1P receptor agonist, S1P binds to the orthosteric site as expected (50), that the novel S1PR₃ selective agonist CYM-5541 binds to an

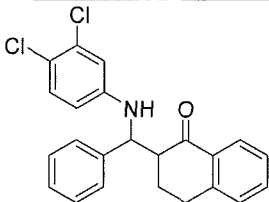
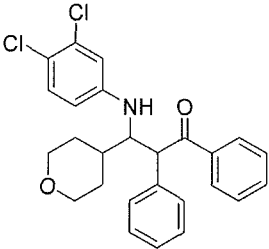
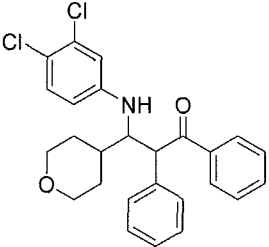
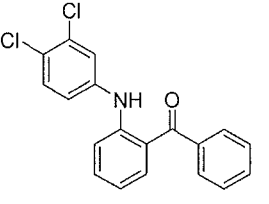
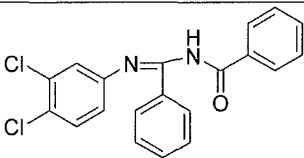
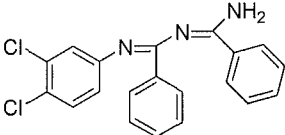
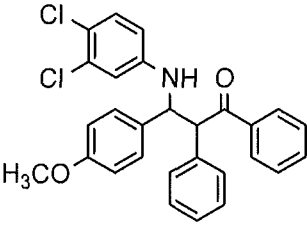
allosteric site and is therefore an allosteric agonist and that the S1PR₃ selective antagonist, SPM-242 competes for binding to both the orthosteric and allosteric sites and is said to be “bitopic”.

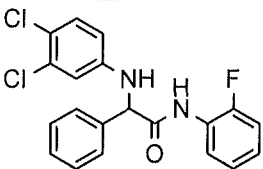
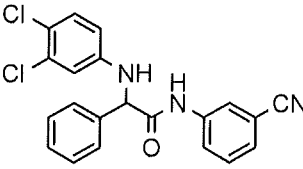
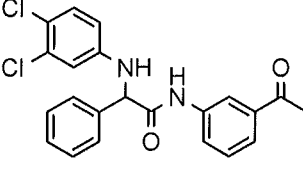
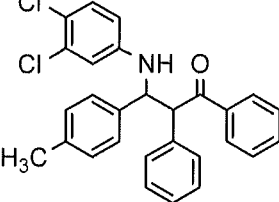
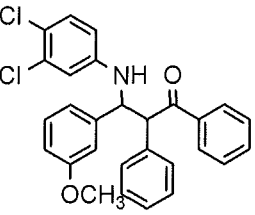
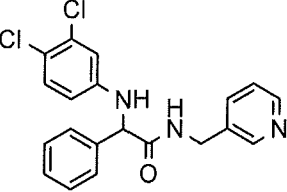
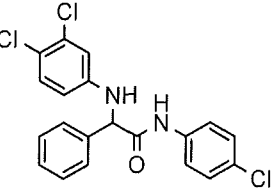
The S1PR₃ selectivity of SPM-242 and CYM-5541, was concluded to come from binding to the less conserved, (non-orthosteric) regions of the S1P receptor family. In our quest for a drug-like

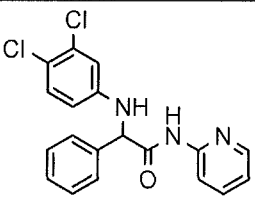
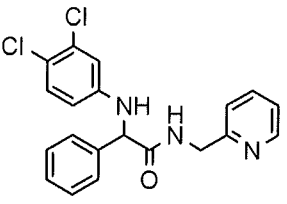
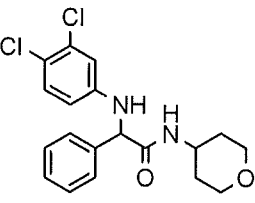
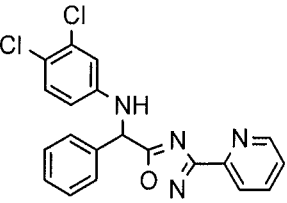
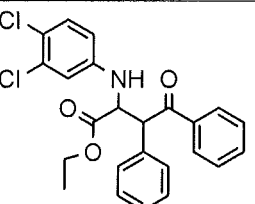
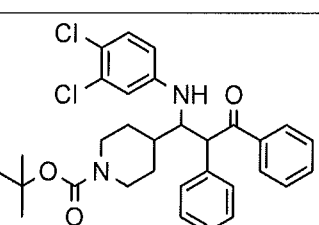
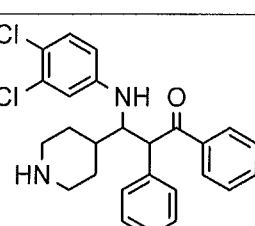
- 5 S1PR₃ antagonist, we chose to use the allosteric agonist CYM-5541 as our starting point. We hypothesize that by attaching other “drug-friendly” functional groups (-OH, -NR₂, etc) onto the relatively low molecular weight CYM-5541 scaffold, we should be able to pick up accessory binding groups on the receptor such as hydrogen bonding to the peptide backbone or nearby side-chains such as Asn-95, Ser-99, Gln-281, Glu-115 and Arg-114, resulting is a new bitopic
- 10 ligand with enhanced solubility characteristics.

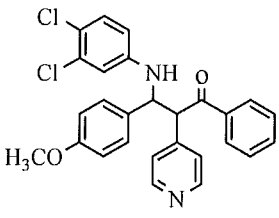
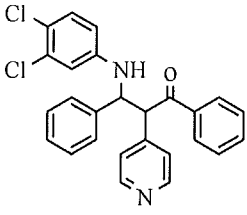
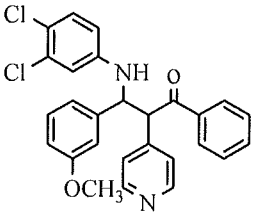
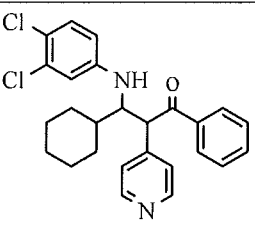
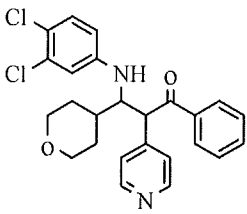
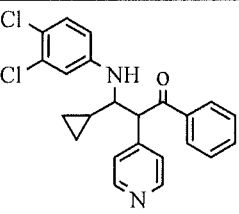
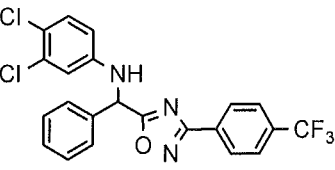
Table 1: Specific Compounds of the Invention

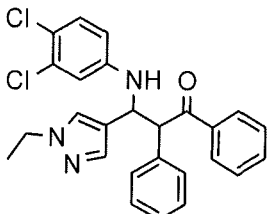
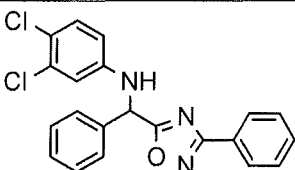
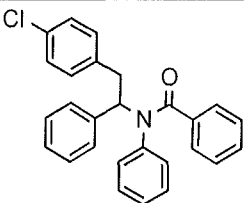
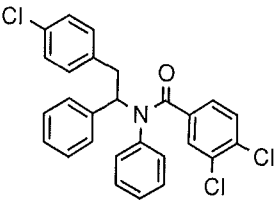
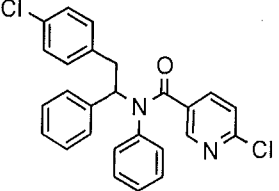
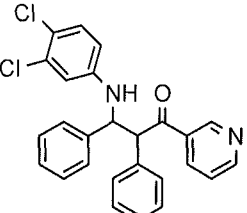
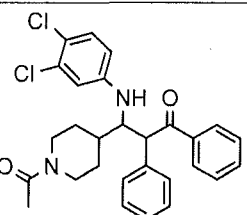
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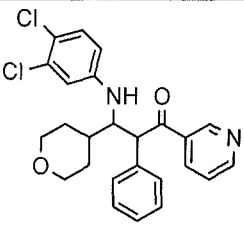
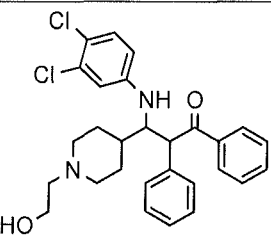
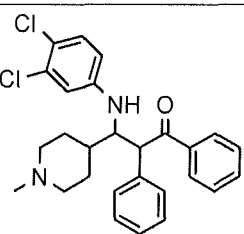
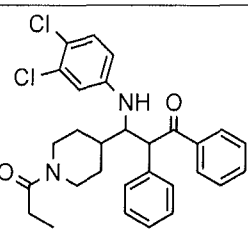
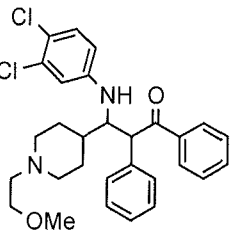
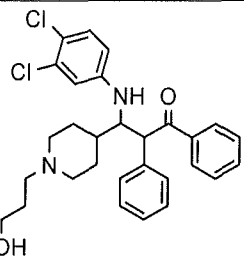
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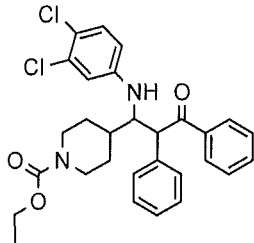
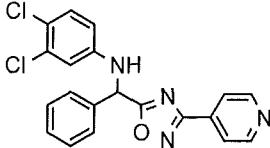
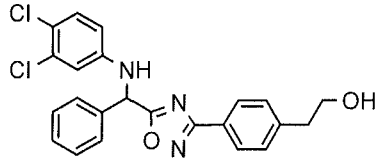
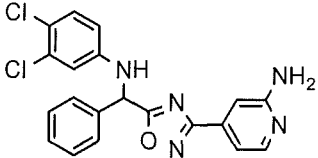
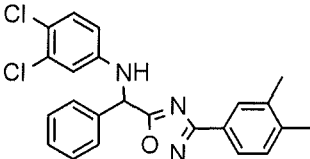
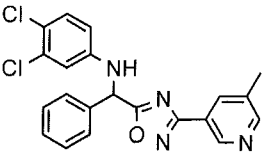
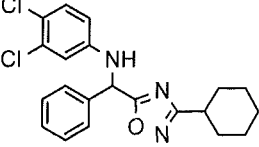
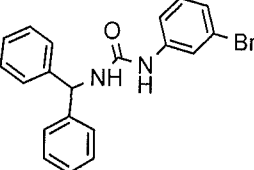
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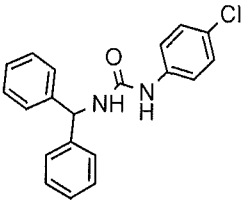
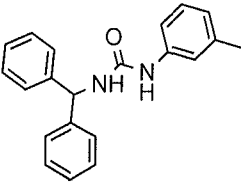
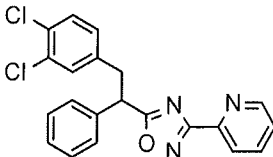
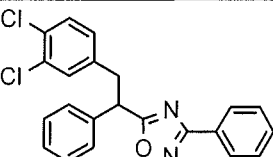
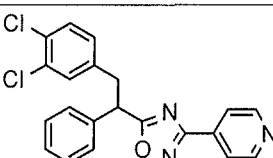
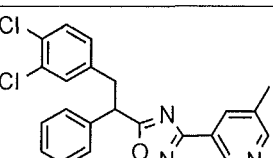
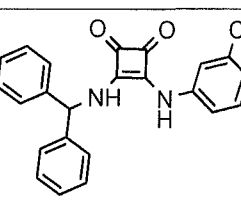
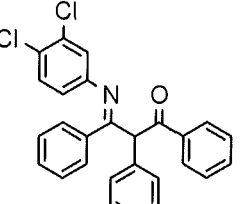
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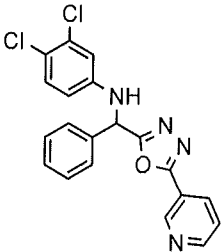
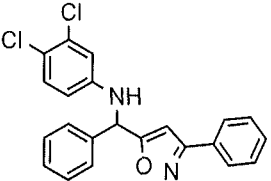
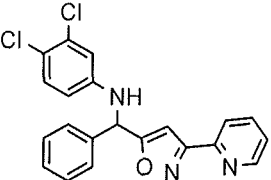
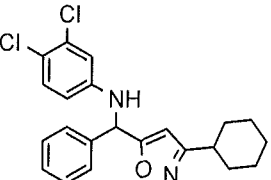
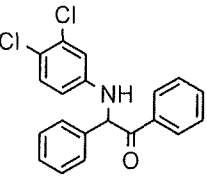
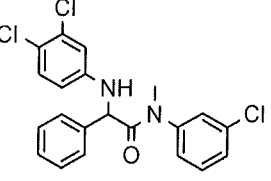
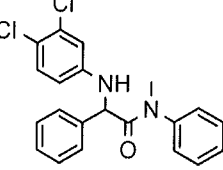
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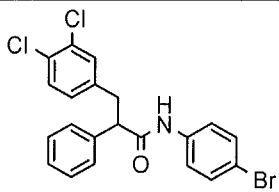
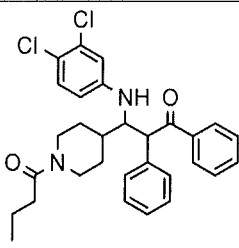
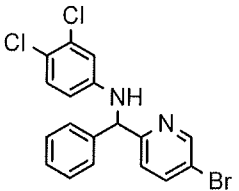
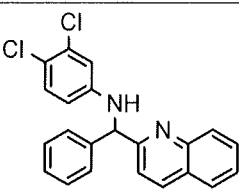
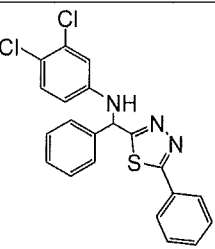
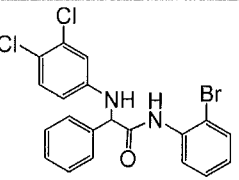
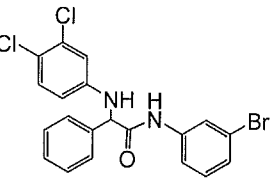
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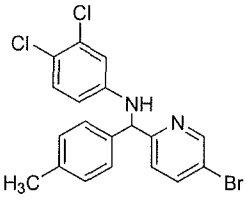
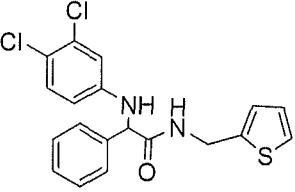
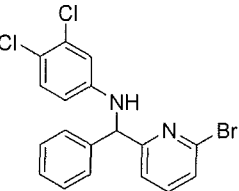
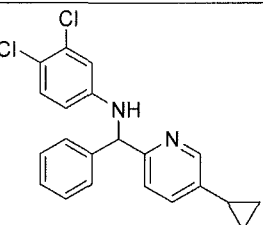
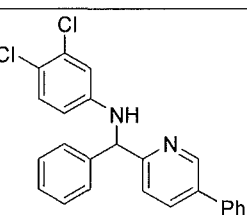
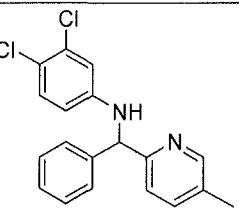
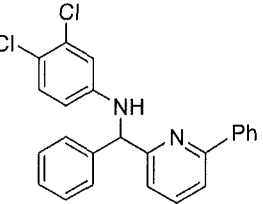
CYM 52213 not I	
CYM 52214 not I	
CYM 52215 not I	
CYM 52216 not I	
CYM 52217 not I	
CYM 52218 not I	

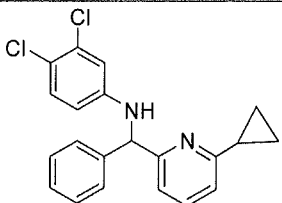
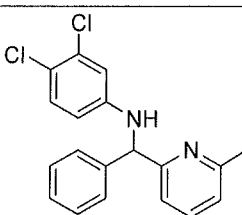
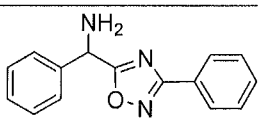
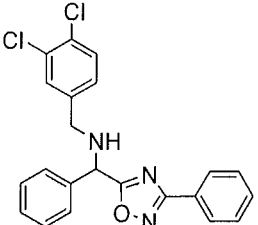
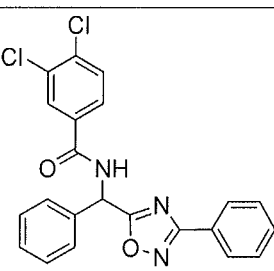
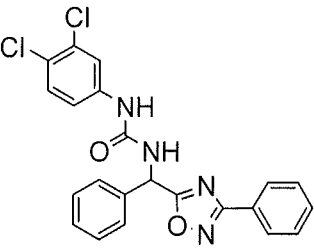
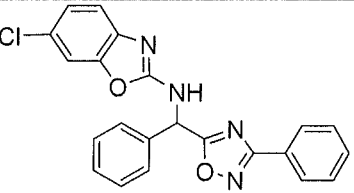
CYM 52219 not I	
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CYM 52247 IB	
CYM 52248 IB	
CYM 52249 IB	
CYM 52250 IB	
CYM 52251 IB	
CYM 52252 IA	

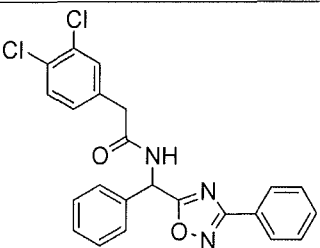
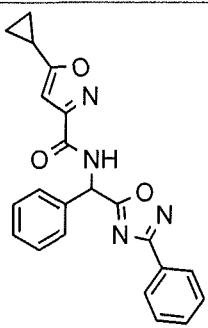
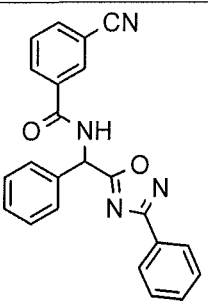
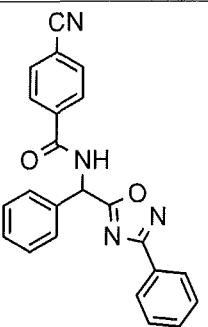
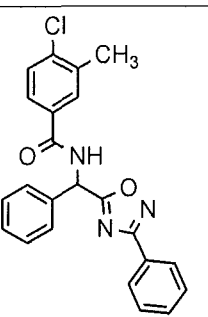
CYM 52253 IA	
CYM 52254 IA	
CYM 52255 IB	
CYM 52256 IB	
CYM 52257 IB	
CYM 52258 IB	
CYM 52259 60 IA	
CYM 52260 not I	

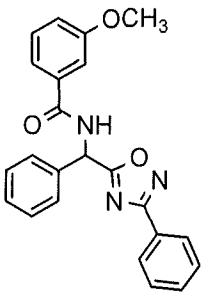
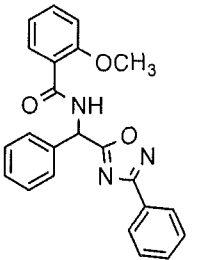
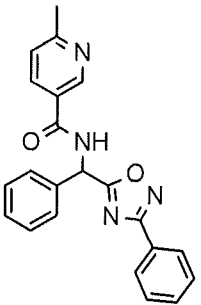
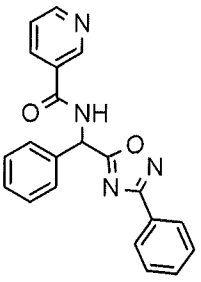
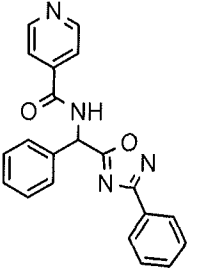
CYM 52264 IB	
CYM 52266 IB	
CYM 52267 IB	
CYM 52268 IB	
CYM 52269 not I	
CYM 52270 not I	
CYM 52271 not I	

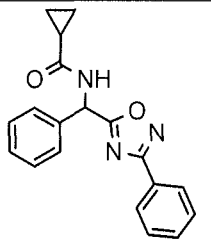
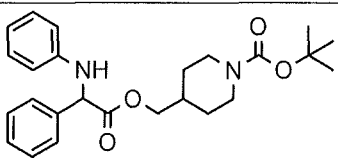
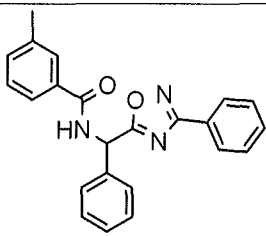
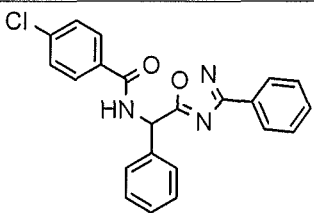
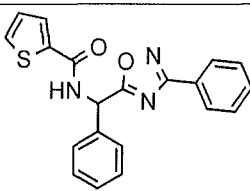
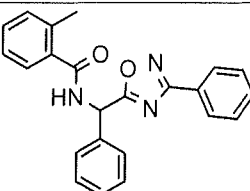
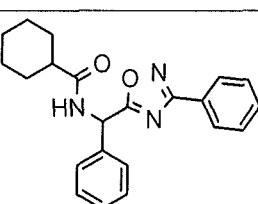
CYM 52272 not I	 <chem>Clc1cc(Cl)ccc1CC(=O)Nc2ccc(Br)cc2</chem>
CYM 52273 not I	 <chem>Clc1cc(Cl)ccc1CC(=O)N[C@@H](c2ccccc2)C(=O)OCC</chem>
CYM 52274 IB	 <chem>Clc1cc(Cl)ccc1CC(=O)Nc2ccncc2Br</chem>
CYM 52276 IB	 <chem>Clc1cc(Cl)ccc1CC(=O)Nc2cnc3ccccc3n2</chem>
CYM 52289 IB	 <chem>Clc1cc(Cl)ccc1CC(=O)Nc2nn[nS]c2c3ccccc3</chem>
CYM 52290 not I	 <chem>Clc1cc(Cl)ccc1CC(=O)NNC(=O)Nc2ccc(Br)cc2</chem>
CYM 52291 not I	 <chem>Clc1cc(Cl)ccc1CC(=O)NNC(=O)Nc2ccc(Br)cc2</chem>

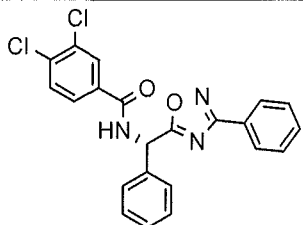
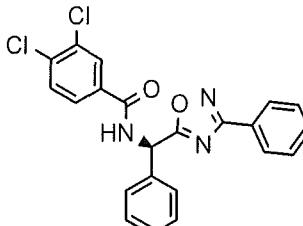
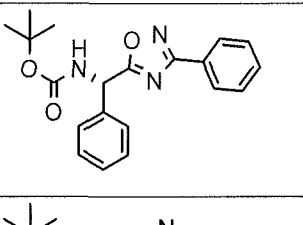
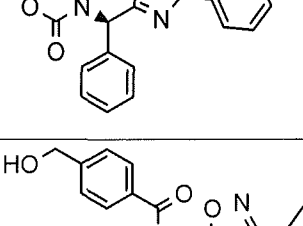
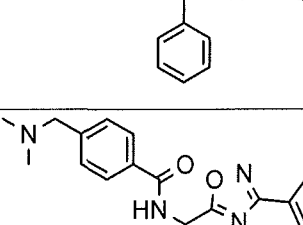
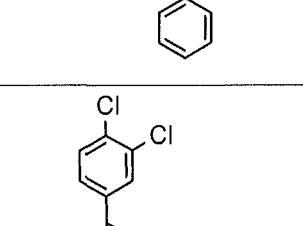
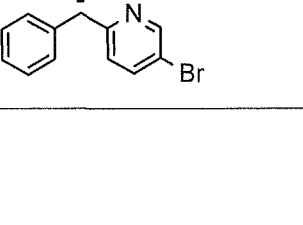
CYM 52294 IB	
CYM 52295 not I	
CYM 52296 IB	
CYM 52297 IB	
CYM 52298 IB	
CYM 52299 IB	
CYM 52300 IB	

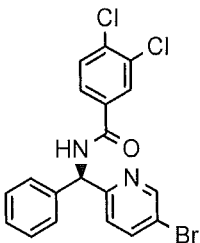
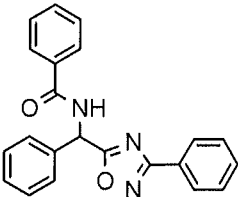
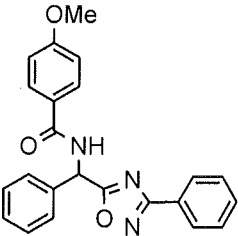
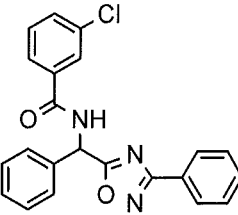
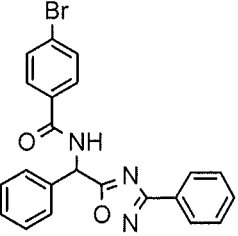
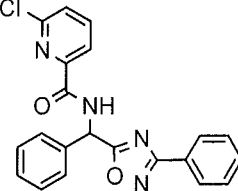
CYM 52301 IB	
CYM 52302 IB	
CYM 52303 not I	
CYM 52304 IB	
CYM 52305 IB	
CYM 52306 IB	
CYM 52307 IC	

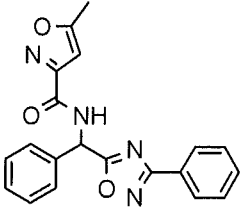
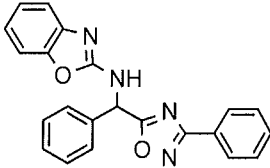
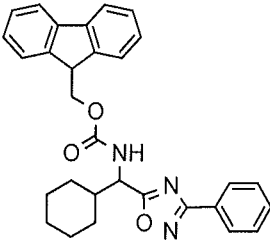
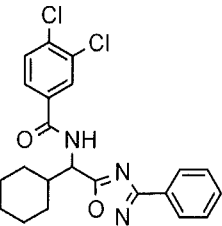
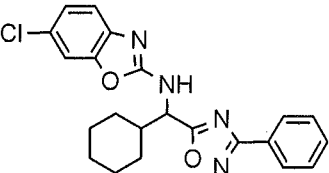
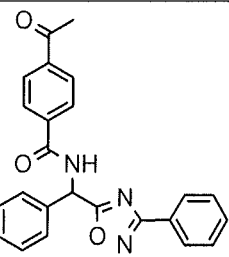
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CYM 52309 IC	
CYM 52310 IB	
CYM 52311 IB	
CYM 52312 IB	

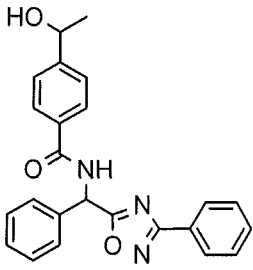
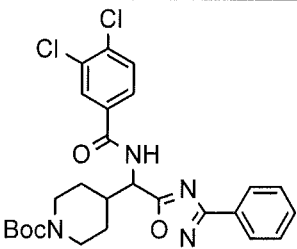
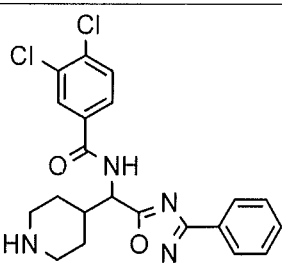
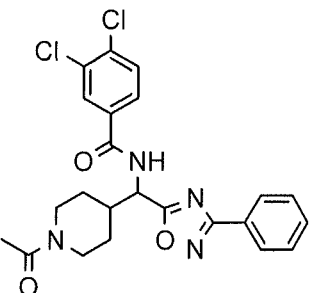
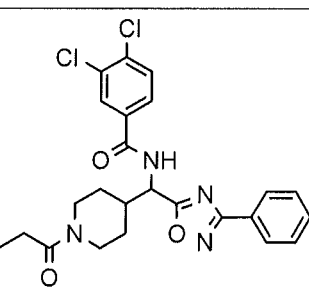
CYM 52313 IB	
CYM 52314 IB	
CYM 52315 IC	
CYM 52316 IC	
CYM 52317 IC	

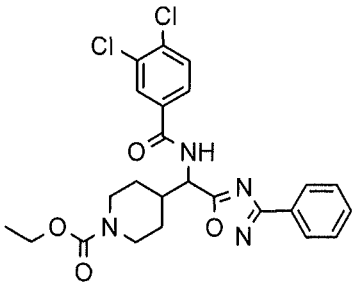
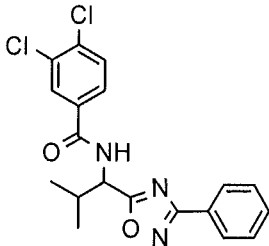
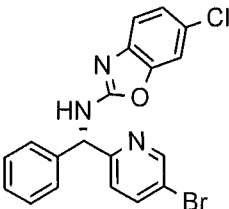
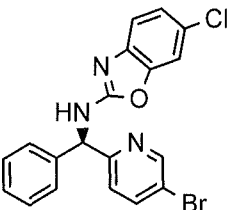
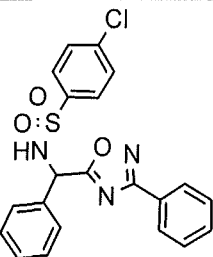
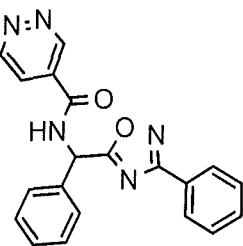
CYM 52318 not I	
CYM 52319 not I	
CYM 52320 IB	
CYM 52321 IB	
CYM 52322 IC	
CYM 52323 IB	
CYM 52324 not I	

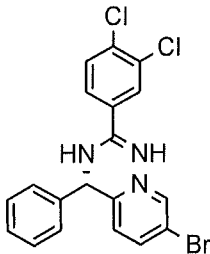
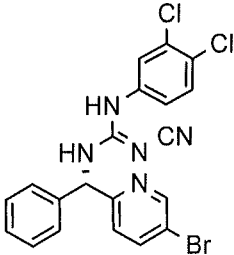
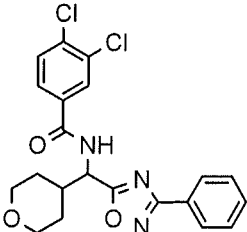
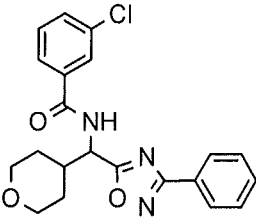
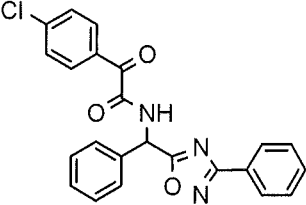
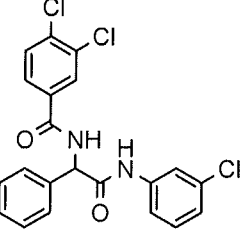
CYM 52325 IB	
CYM 52326 IB	
CYM 52327 not I	
CYM 52328 not I	
CYM 52329 IB	
CYM 52330 IB	
CYM 52331 IB	

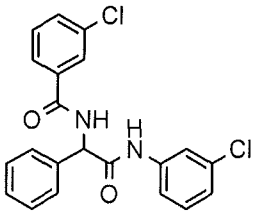
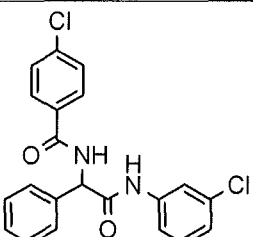
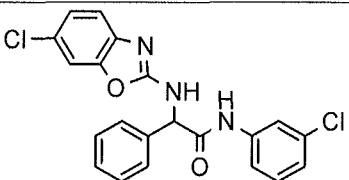
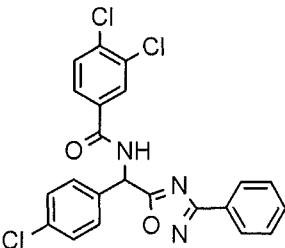
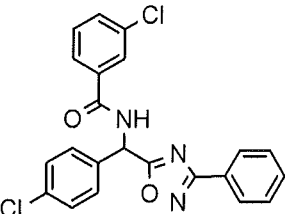
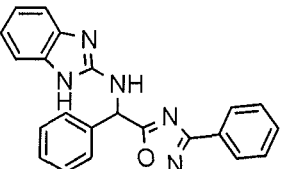
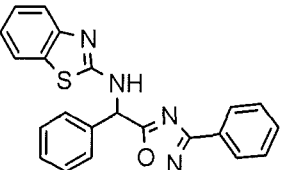
CYM 52332 IB	
CYM 52333 IB	
CYM 52334 IB	
CYM 52335 IB	
CYM 52336 IB	
CYM 52337 IC	

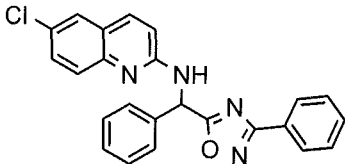
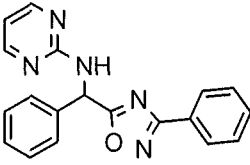
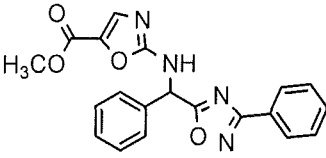
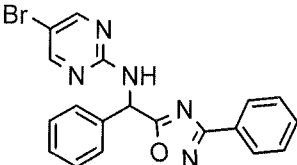
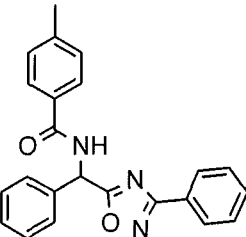
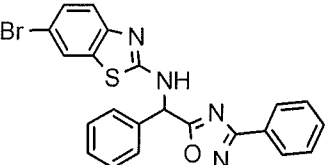
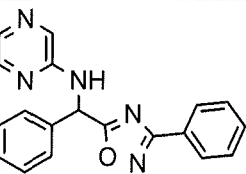
CYM 52338 IC	
CYM 52339 IC	
CYM 52340 not I	
CYM 52341 not I	
CYM 52342 not I	
CYM 52343 IB	

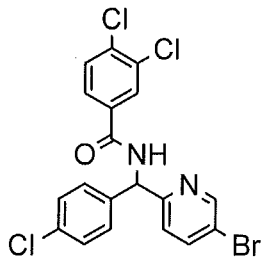
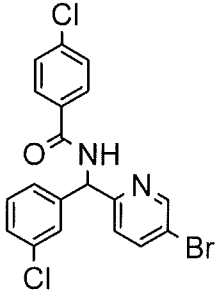
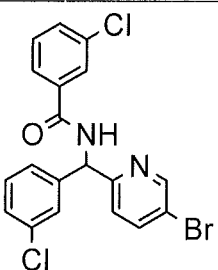
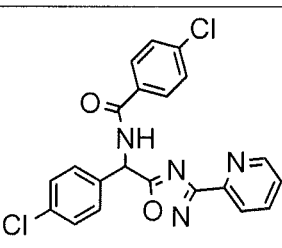
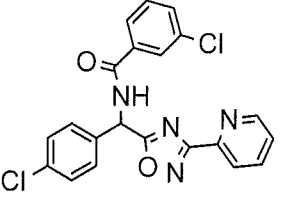
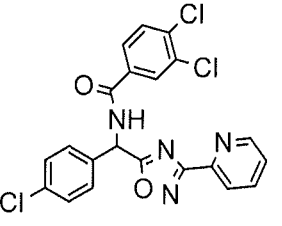
CYM 52344 IB	 <chem>CC1=CC=C(C=C1C(=O)NC(C2=CC=CC=C2)C(=O)N3C=NN=C3c4ccccc4)C5=CC=C(C=C5)O</chem>
CYM 52345 not I	 <chem>CC1(C)CC(C1)C(=O)N2C=CC(=C(C=C2)Cl)C(=O)NC(C3=CC=CC=C3)C(=O)N4C=NN=C4c5ccccc5C6CCN(CC6)C(=O)OC7C(C)C(C)C7</chem>
CYM 52346 not I	 <chem>CC1=CC=C(C=C1C(=O)NC(C2=CC=CC=C2)C(=O)N3C=NN=C3c4ccccc4)C5CCNCC5C6=CC=C(C=C6)Cl</chem>
CYM 52347 not I not I	 <chem>CC1(C)CC(C1)C(=O)N2C=CC(=C(C=C2)Cl)C(=O)NC(C3=CC=CC=C3)C(=O)N4C=NN=C4c5ccccc5C6CCN(CC6)C(=O)OC7C(C)C(C)C7</chem>
CYM 52348 not I	 <chem>CC1(C)CC(C1)C(=O)N2C=CC(=C(C=C2)Cl)C(=O)NC(C3=CC=CC=C3)C(=O)N4C=NN=C4c5ccccc5C6CCN(CC6)C(=O)OC7C(C)C(C)C7</chem>

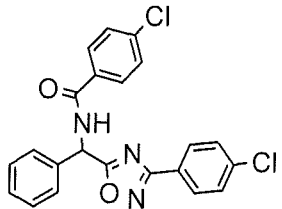
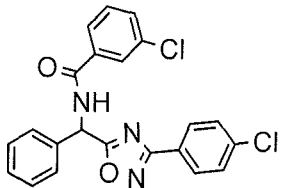
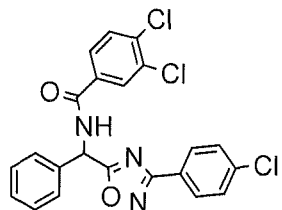
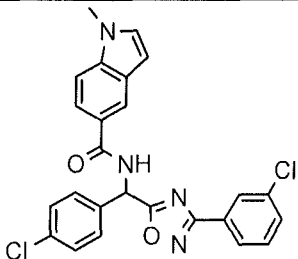
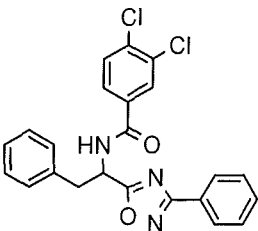
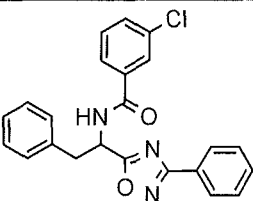
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CYM 52350 not I	
CYM 52351 IC	
CYM 52352 IC	
CYM 52353 IB	
CYM 52354 IC	

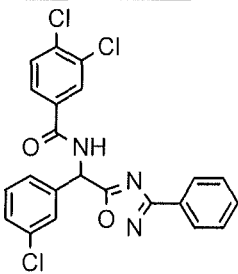
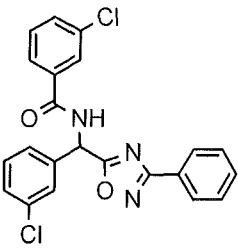
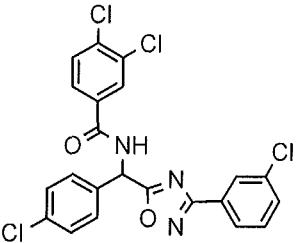
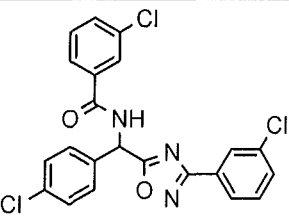
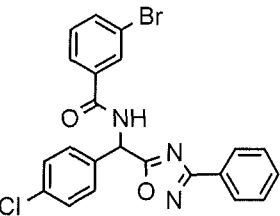
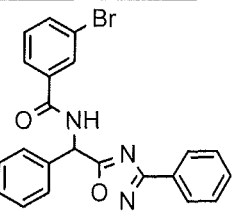
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CYM 52358 not I	
CYM 52359 IB	
CYM 52360 not I	

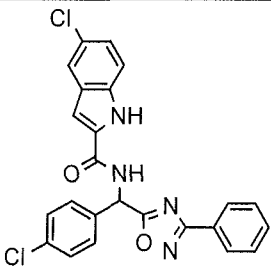
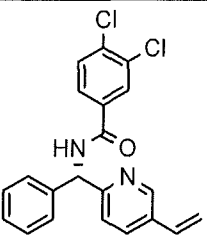
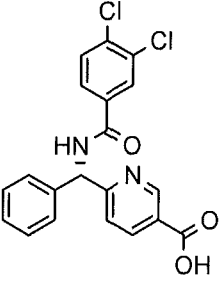
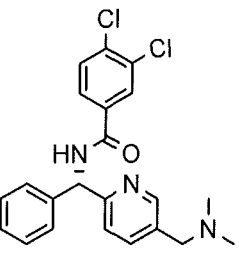
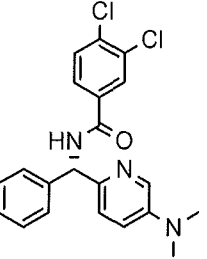
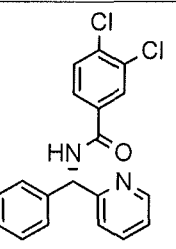
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CYM 52364 IB	
CYM 52365 IB	
CYM 52366 IC	
CYM 52367 IC	

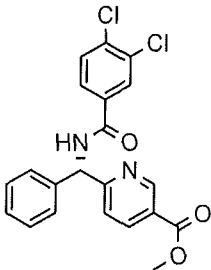
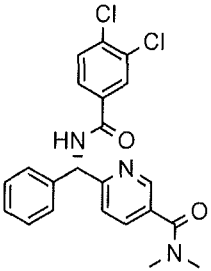
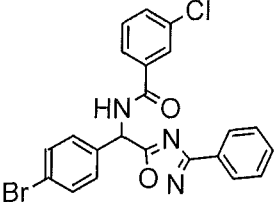
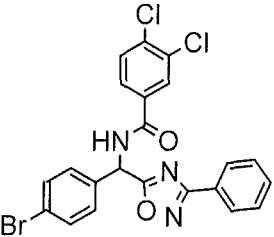
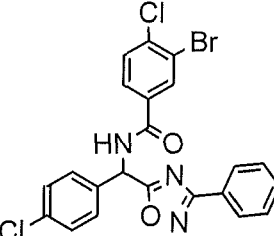
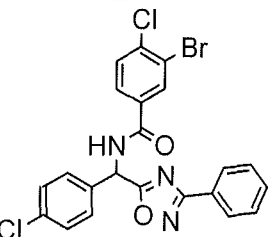
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CYM 52369 IC	
CYM 52370 IC	
CYM 52371 IC	
CYM 52372 IB	
CYM 52373 IC	
CYM 52374 IC	

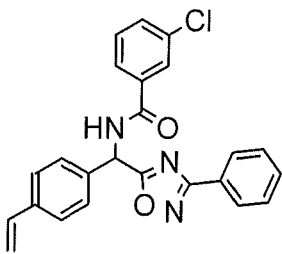
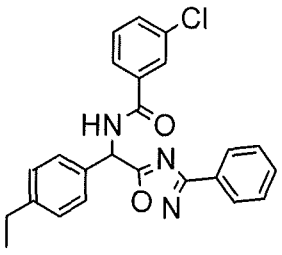
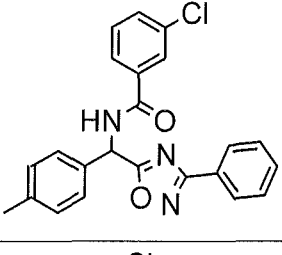
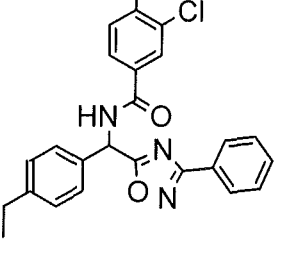
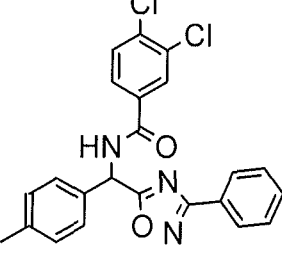
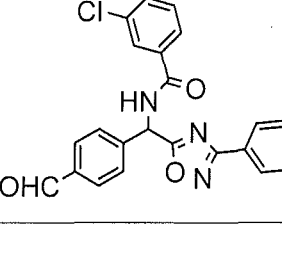
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CYM 52376 IB	 <chem>c1ccc(cc1)C(=O)N[C@H](c2ccc(Cl)cc2)c3ccncc3Br</chem>
CYM 52377 IB	 <chem>Clc1ccc(cc1)C(=O)N[C@H](c2ccc(Cl)cc2)c3ccncc3Br</chem>
CYM 52378 IB	 <chem>Clc1ccc(cc1)C(=O)N[C@H](c2ccc(Cl)cc2)C(=O)N1C=NC(=N1)c2ccncc2</chem>
CYM 52379 IB	 <chem>Clc1ccc(cc1)C(=O)N[C@H](c2ccc(Cl)cc2)C(=O)N1C=NC(=N1)c2ccncc2</chem>
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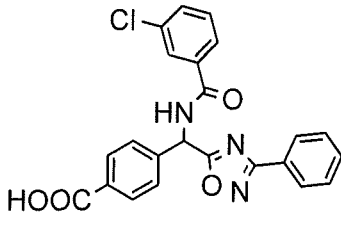
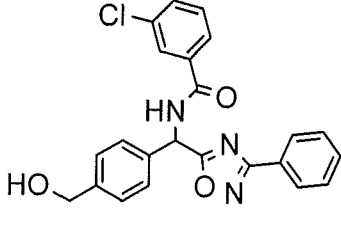
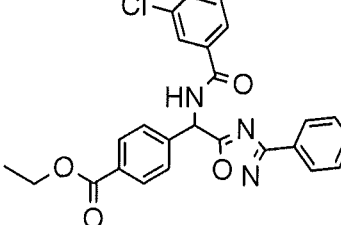
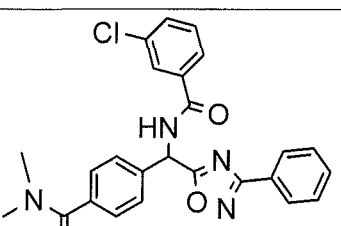
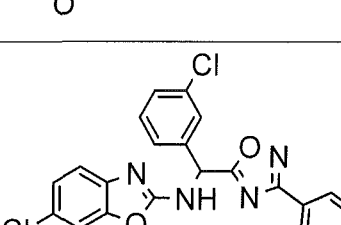
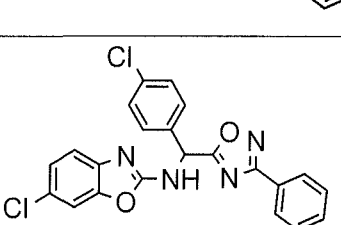
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CYM 52382 IB	
CYM 52383 IB	
CYM 52384 IC	
CYM 52385 not I	
CYM 52386 not I	

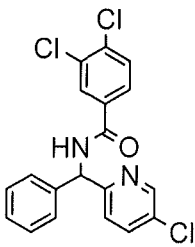
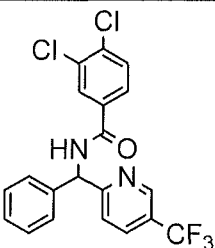
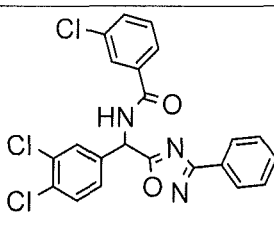
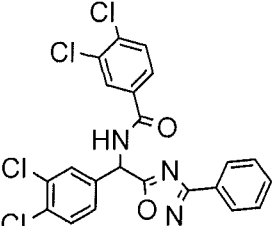
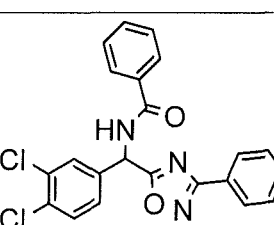
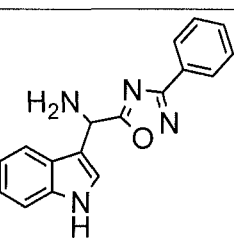
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CYM 52392 IB	

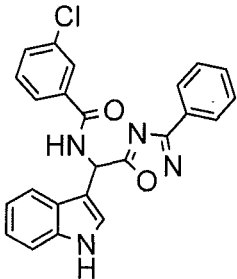
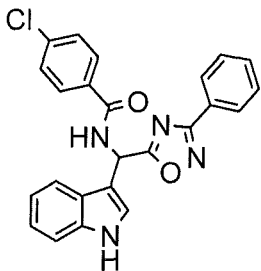
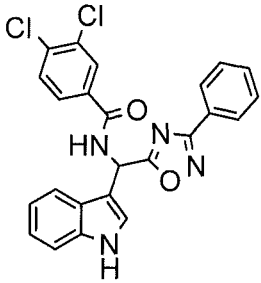
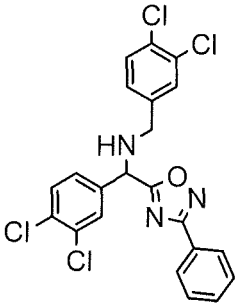
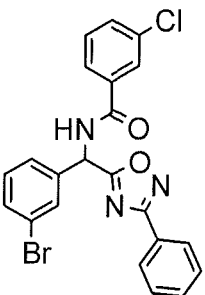
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CYM 52394 IB	
CYM 52395 IB	
CYM 52396 IB	
CYM 52397 IB	
CYM 52398 IB	

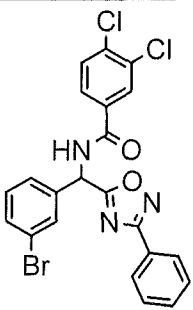
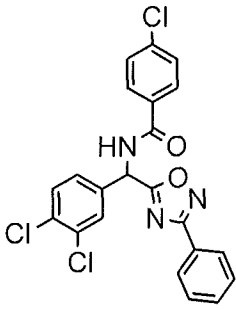
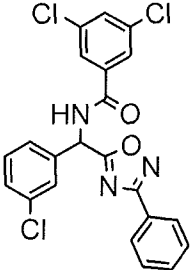
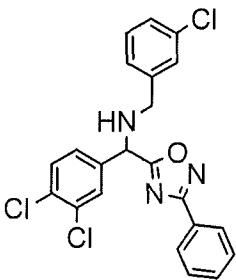
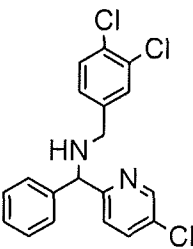
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CYM 52401 IB	
CYM 52402 IB	
CYM 52403 IB	
CYM 52404 IB	

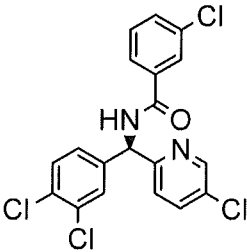
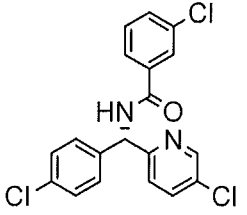
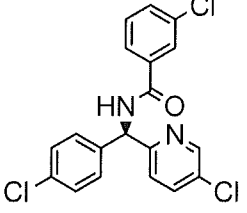
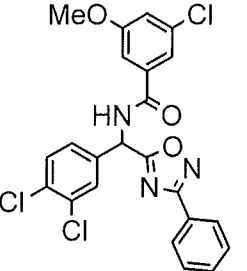
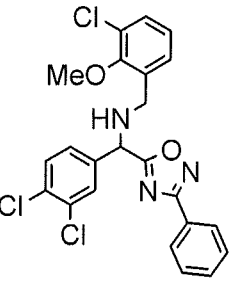
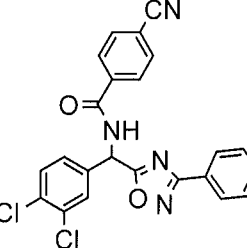
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CYM 52409 IB	
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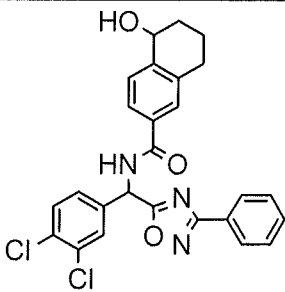
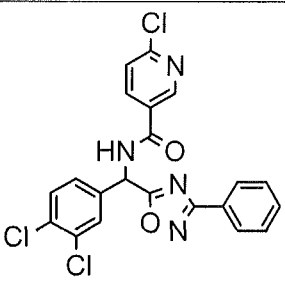
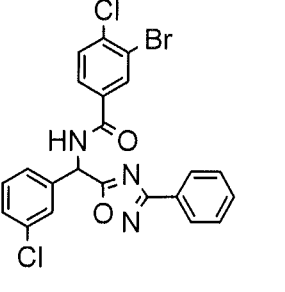
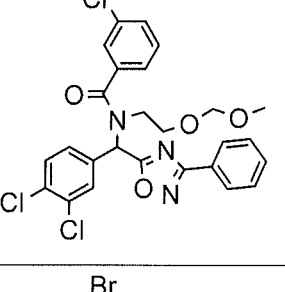
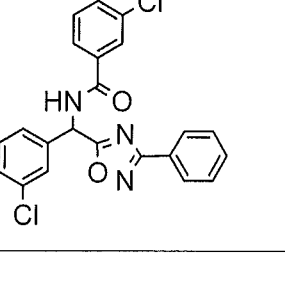
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CYM 52420 IB	
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CYM 52422 not I	

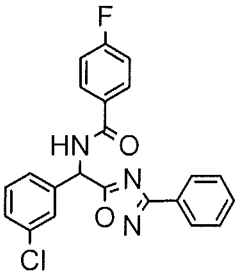
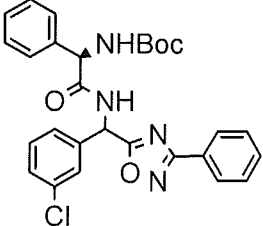
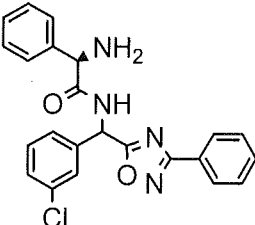
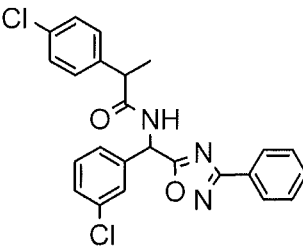
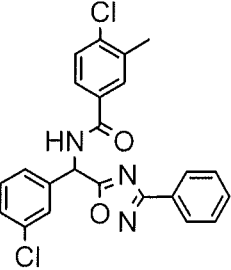
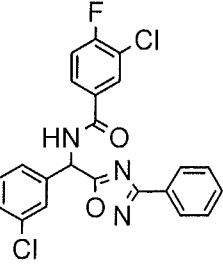
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CYM 52427 IB	

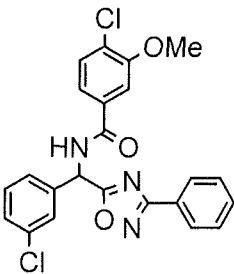
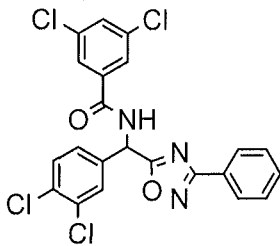
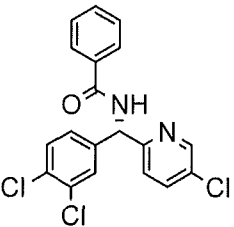
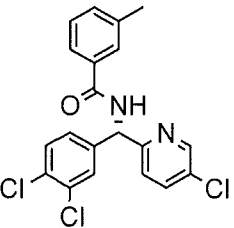
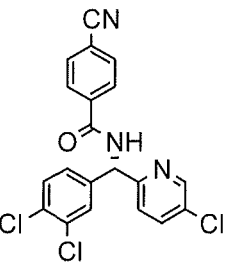
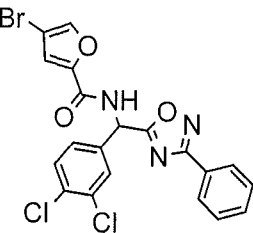
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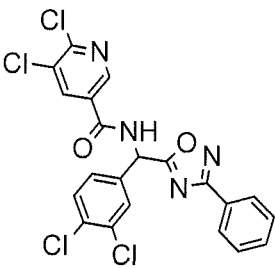
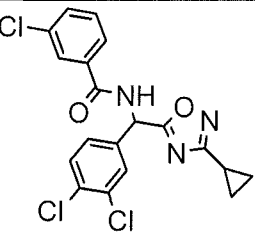
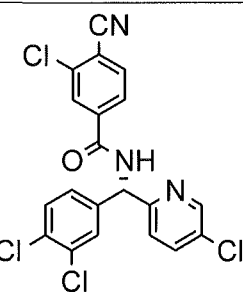
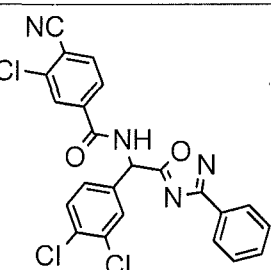
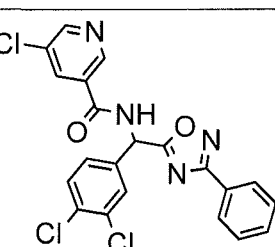
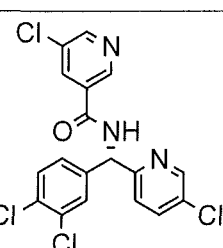
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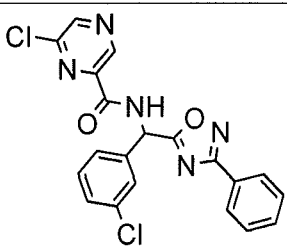
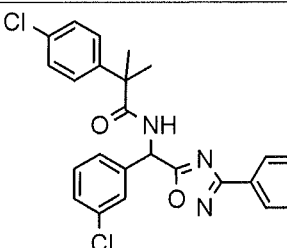
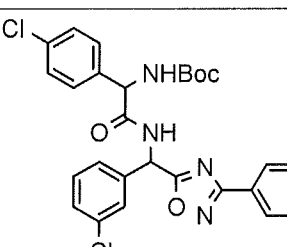
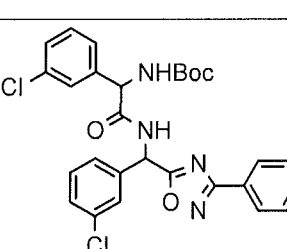
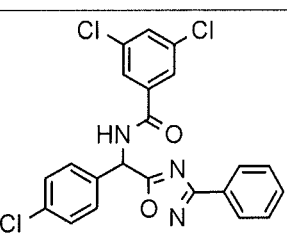
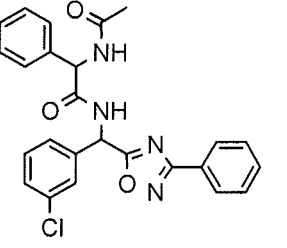
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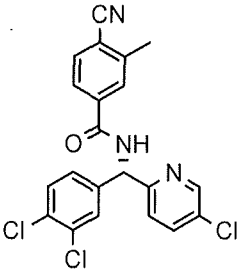
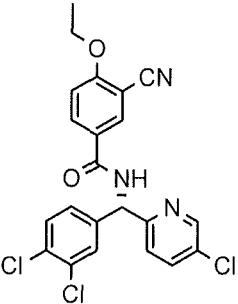
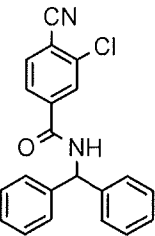
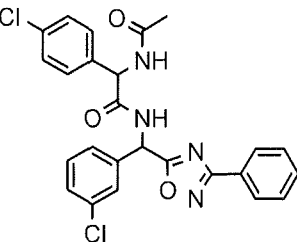
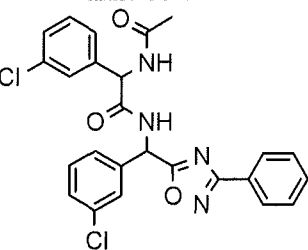
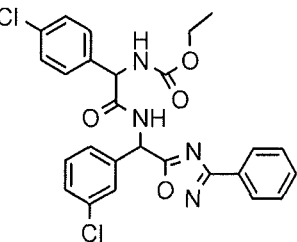
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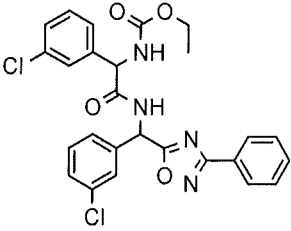
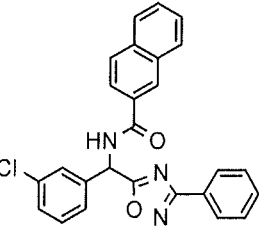
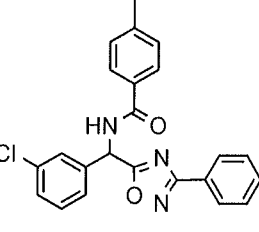
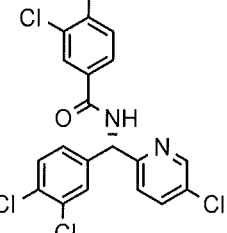
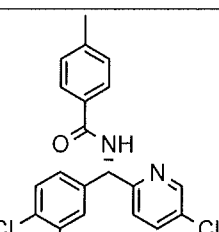
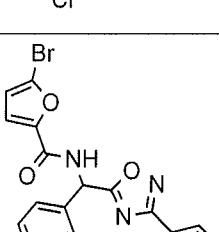
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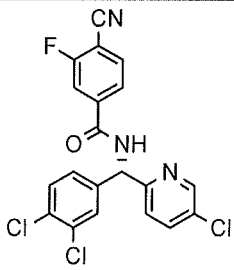
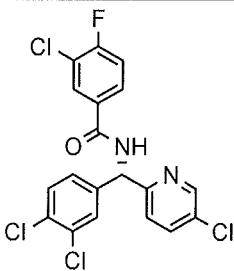
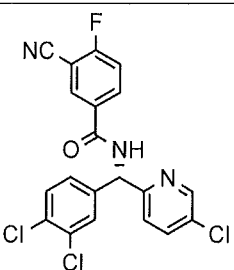
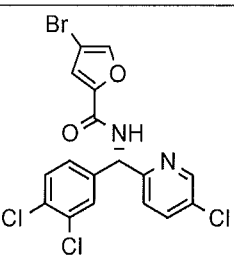
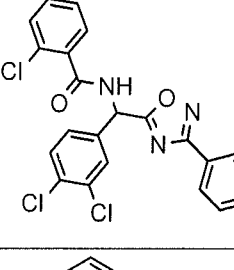
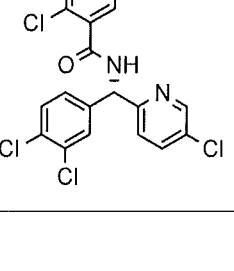
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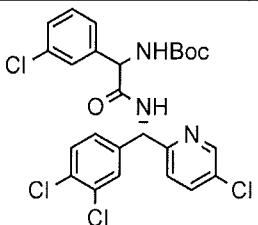
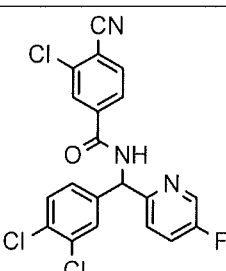
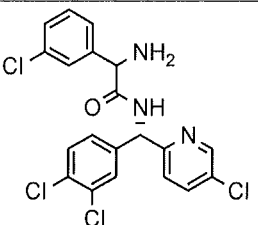
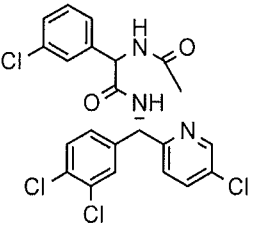
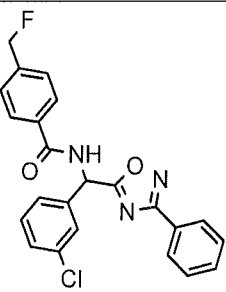
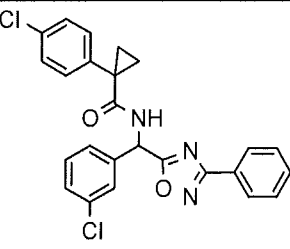
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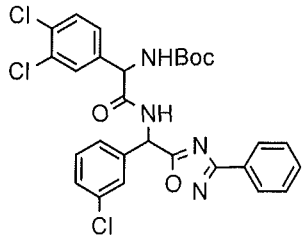
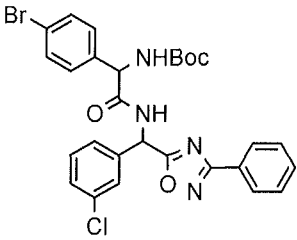
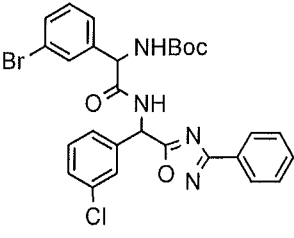
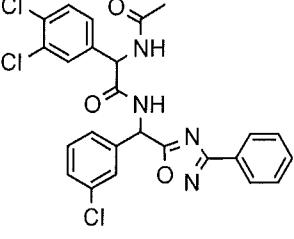
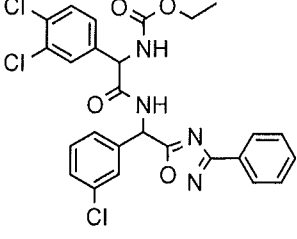
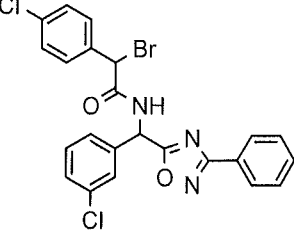
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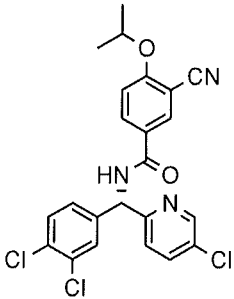
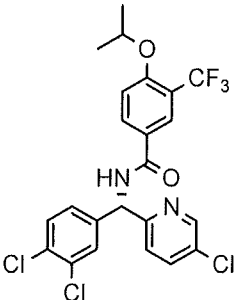
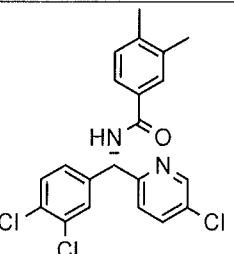
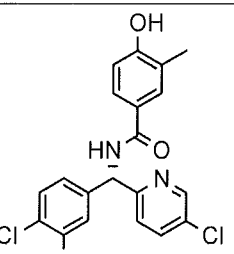
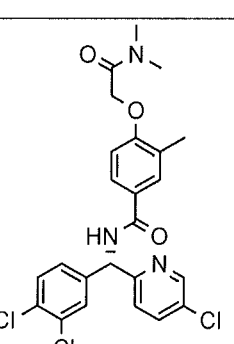
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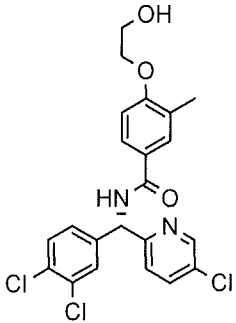
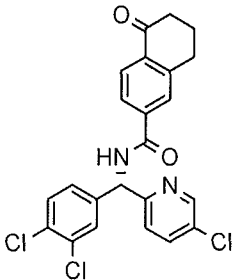
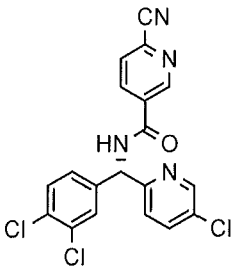
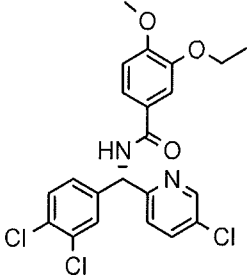
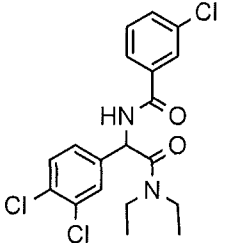
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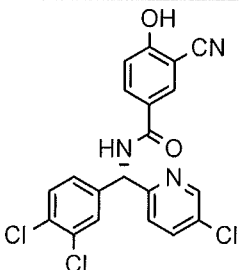
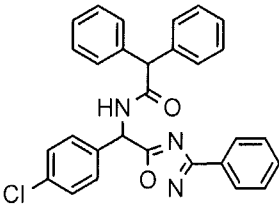
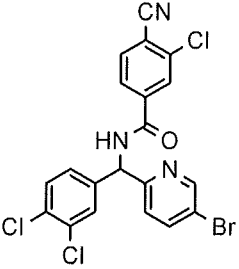
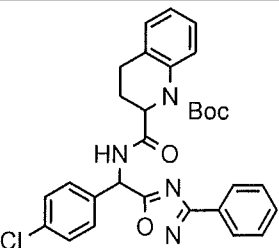
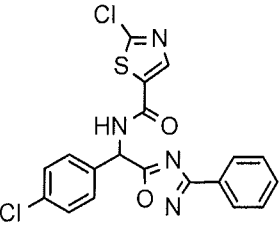
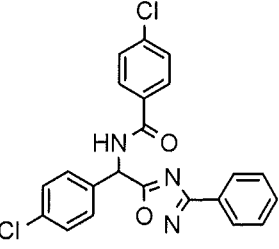
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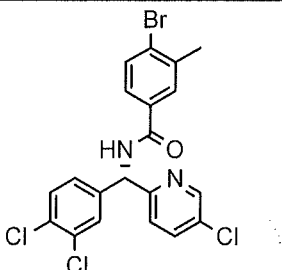
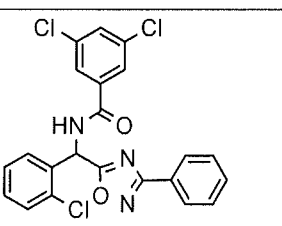
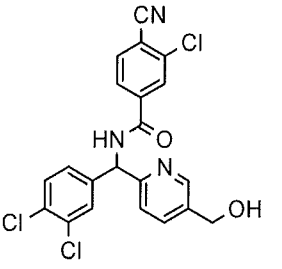
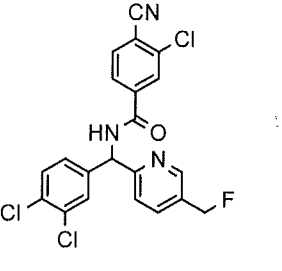
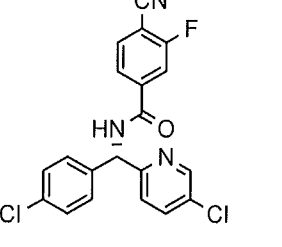
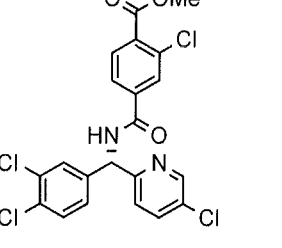
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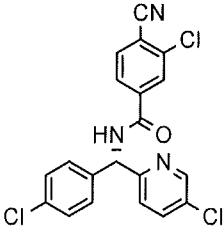
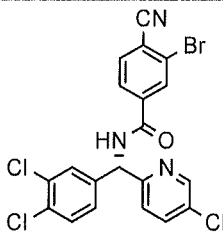
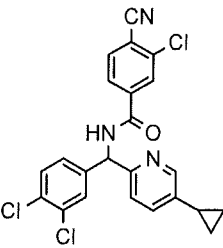
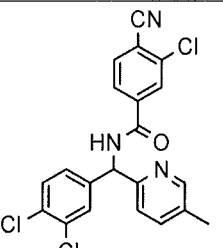
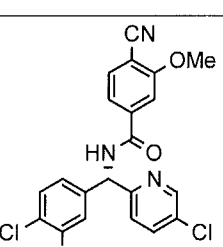
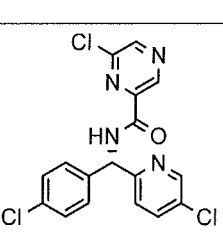
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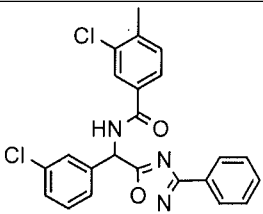
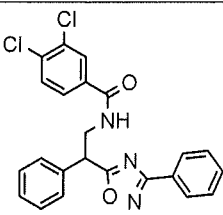
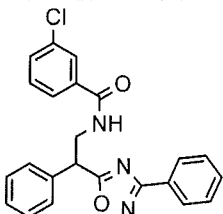
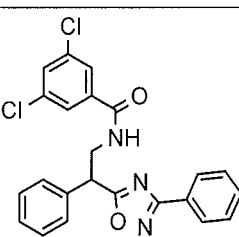
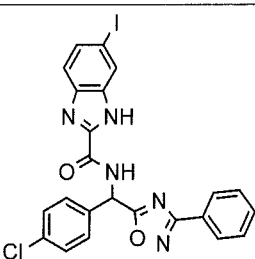
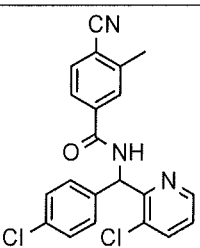
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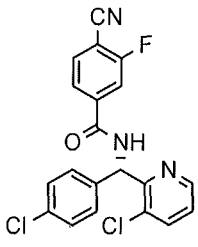
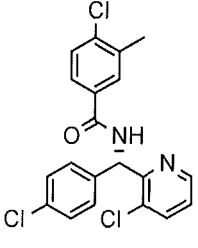
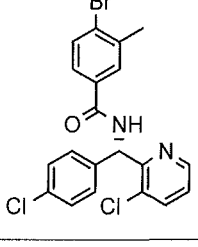
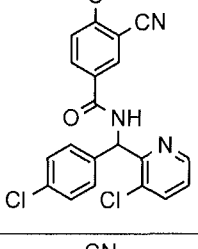
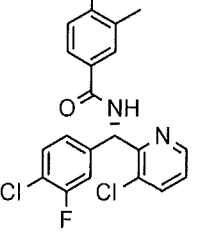
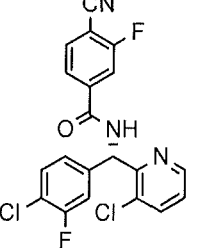
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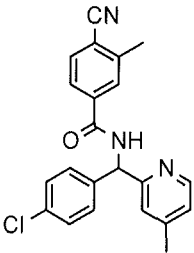
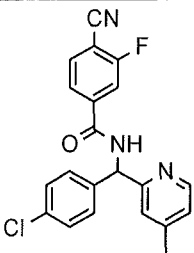
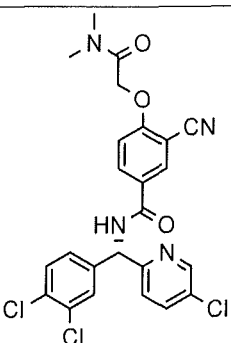
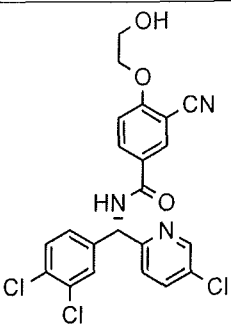
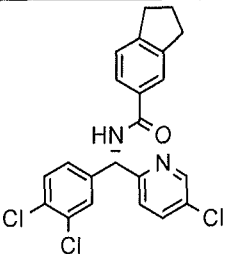
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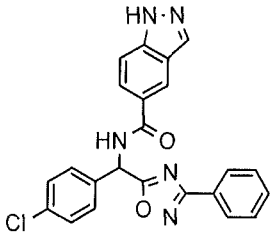
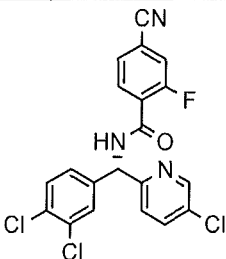
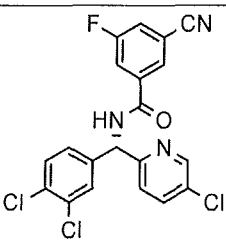
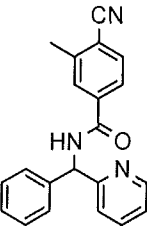
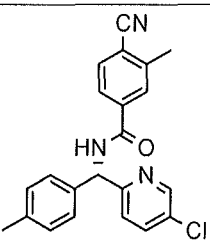
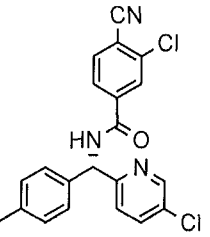
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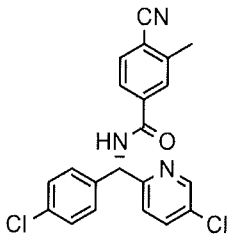
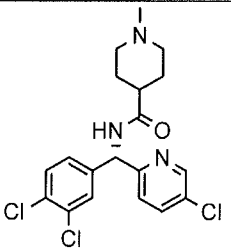
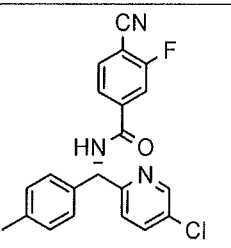
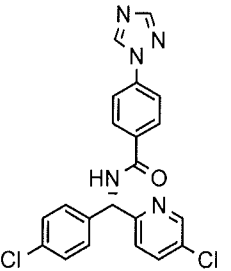
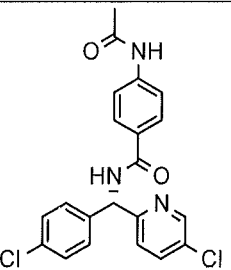
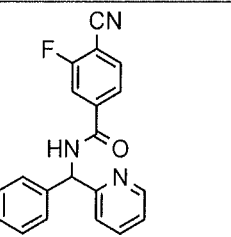
CYM52526 IB	 <chem>Clc1cc(CNC(=O)c2ccc(Cl)cc2)ccn1</chem>
CYM52527 IB	 <chem>Clc1cc(CNC(=O)c2ccc(Br)cc2)ccn1</chem>
CYM52528 IB	 <chem>Clc1cc(CNC(=O)c2ccc(Cl)cc2)cc(C1CC1)n1</chem>
CYM52529 IB	 <chem>Clc1cc(CNC(=O)c2ccc(Cl)cc2)cc(C)n1</chem>
CYM52530 IB	 <chem>Clc1cc(CNC(=O)c2ccc(OC)cc2)ccn1</chem>
CYM52531 IC	 <chem>Clc1cc(CNC(=O)c2ccc(Cl)cc2)cc(C3=NC=NC(Cl)=N3)n1</chem>

CYM52532 IB	
CYM 52533 IB	
CYM 52534 IB	
CYM 52535 IB	
CYM 52536 IC	
CYM 52542 IB	

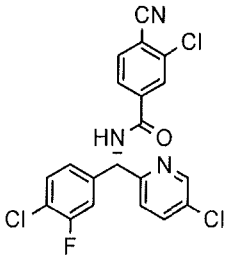
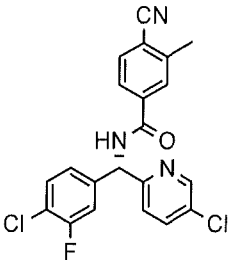
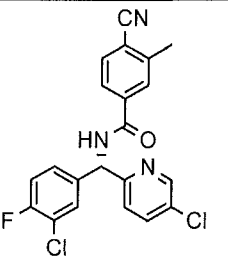
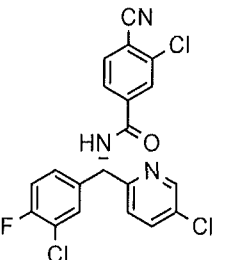
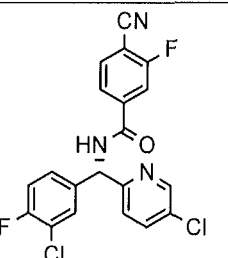
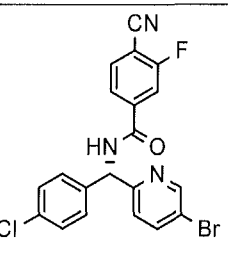
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CYM 52545 IB	
CYM 52546 IB	
CYM 52547 IB	
CYM 52548 IB	

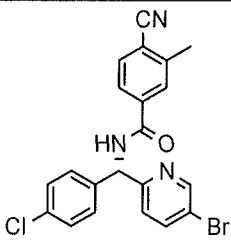
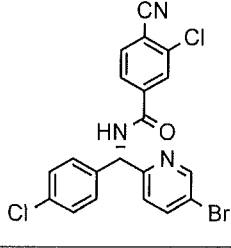
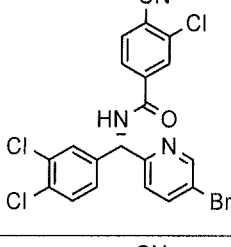
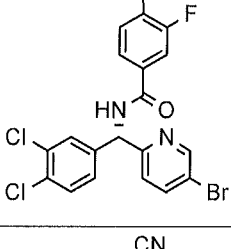
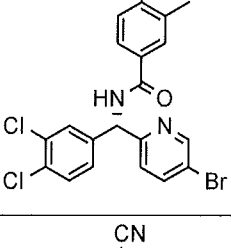
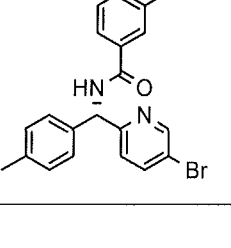
CYM 52549 IB	
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CYM 52551 IB	
CYM 52552 IB	
CYM 52553 IB	

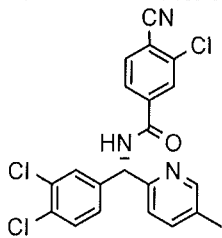
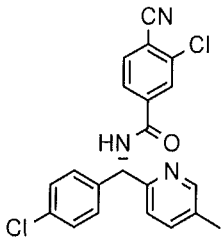
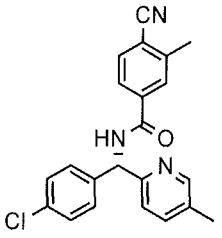
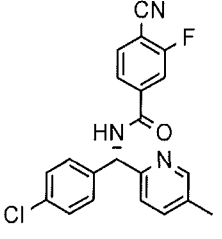
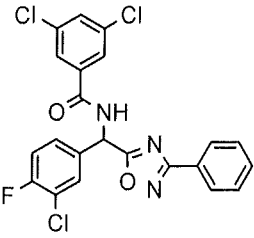
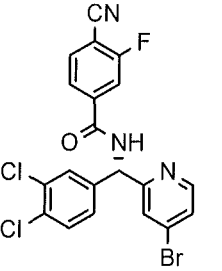
CYM 52554 IC	
CYM 52555 IB	
CYM 52556 IB	
CYM 52557 IB	
CYM 52558 IB	
CYM 52559 IB	

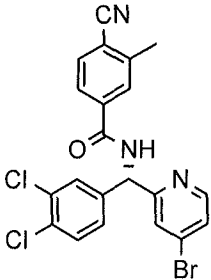
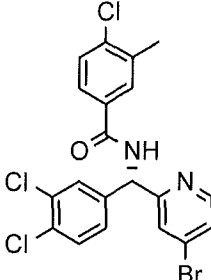
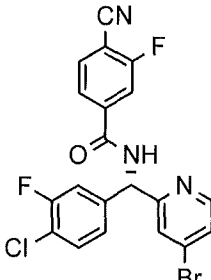
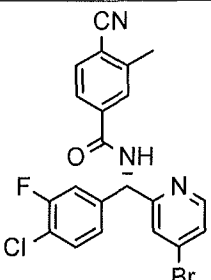
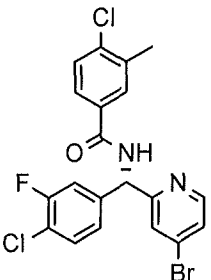
CYM 52560 IB	
CYM 52561 not I	
CYM 52562 IB	
CYM 52563 IB	
CYM 52564 IB	
CYM 52565 IB	

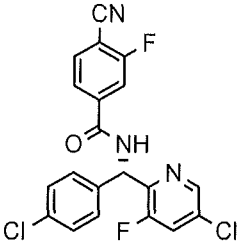
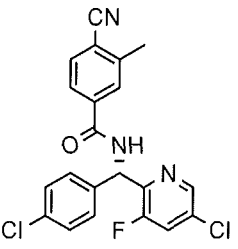
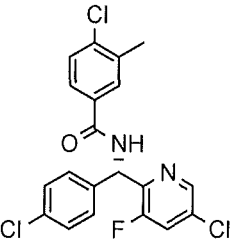
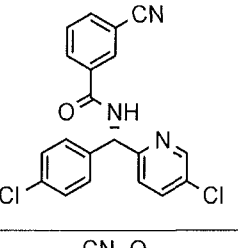
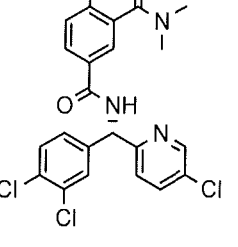
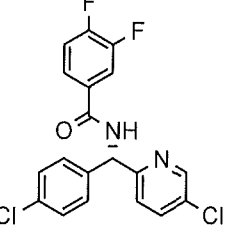
CYM 52566 IB	 <chem>CCOCC(=O)Nc1ccc(C#N)cc1NCc2ccc(Cl)cc2c3cc(Cl)ccn3</chem>
CYM 52567 IB	 <chem>CC(C)CN(=O)c1ccc(C#N)cc1NCc2ccc(Cl)cc2c3cc(Cl)ccn3</chem>
CYM 52568 IC	 <chem>C#NCC1=CC=C(C#N)S1NC(=O)Nc2ccc(Cl)cc2c3cc(Cl)ccn3</chem>
CYM 52569 IB	 <chem>Clc1ccc(cc1)C(=O)Nc2cc(Cl)c(Cl)cc2NCc3ccc(Cl)cc3c4cc(Cl)ccn4</chem>
CYM 52570 IB	 <chem>Clc1ccc(cc1)C(=O)Nc2ccccc2NCc3ccc(Cl)cc3c4cc(Cl)ccn4</chem>
CYM 52571 IB	 <chem>Fc1cc(C#N)ccc1NC(=O)Nc2ccc(Cl)cc2c3cc(Cl)ccn3Cc4cc(Cl)cc(F)c4</chem>

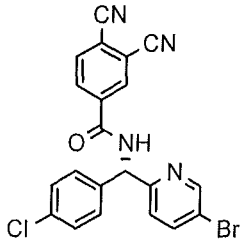
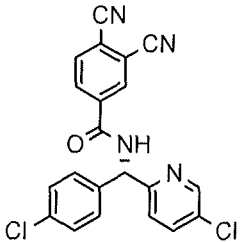
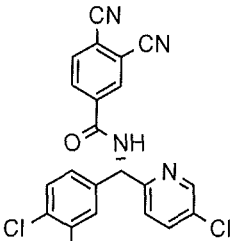
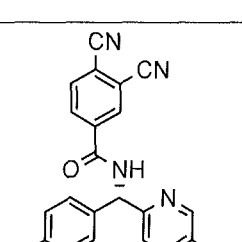
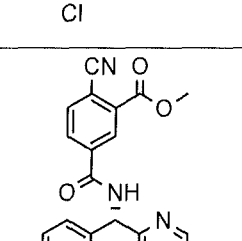
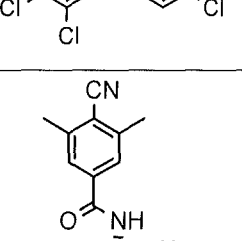
CYM 52572 IB	
CYM 52573 IB	
CYM 52574 IB	
CYM 52575 IB	
CYM 52576 IB	
CYM 52577 IB	

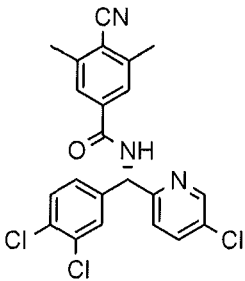
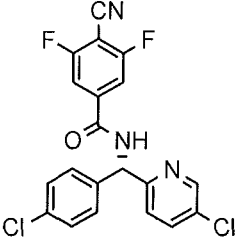
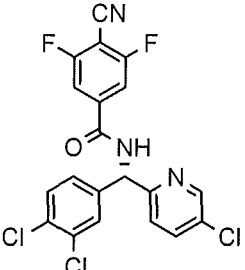
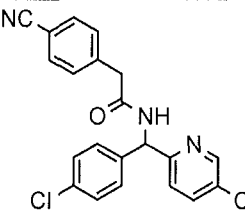
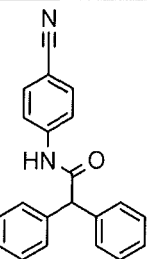
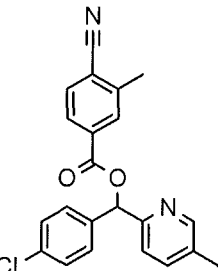
CYM 52578 IB	 <chem>Cc1cc(C#N)ccc1C(=O)Nc1cc(Br)nc(Cc2ccc(Cl)cc2)n1</chem>
CYM 52579 IB	 <chem>Cc1cc(C#N)c(Cl)cc1C(=O)Nc1cc(Br)nc(Cc2ccc(Cl)cc2)n1</chem>
CYM 52580 IB	 <chem>Cc1cc(C#N)c(Cl)c(Cl)c1C(=O)Nc1cc(Br)nc(Cc2ccc(Cl)cc2)n1</chem>
CYM 52581 IB	 <chem>Fc1cc(C#N)c(Cl)c(Cl)c1C(=O)Nc1cc(Br)nc(Cc2ccc(Cl)cc2)n1</chem>
CYM 52582 IB	 <chem>Cc1cc(C#N)c(Cl)c(Cl)c1C(=O)Nc1cc(Br)nc(Cc2cc(Cl)c(Cl)cc2)n1</chem>
CYM 52583 IB	 <chem>Cc1cc(C#N)ccc1C(=O)Nc1cc(Br)nc(Cc2cccc(C)c2)n1</chem>

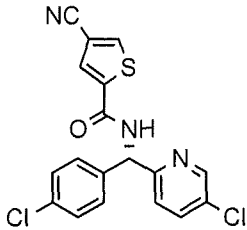
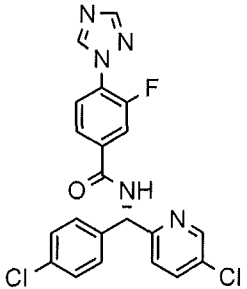
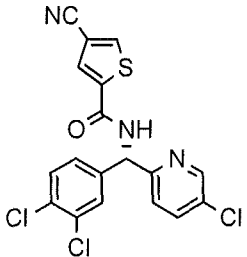
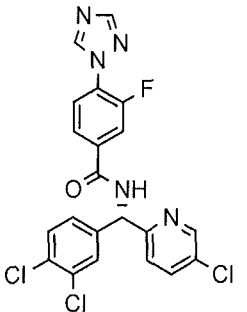
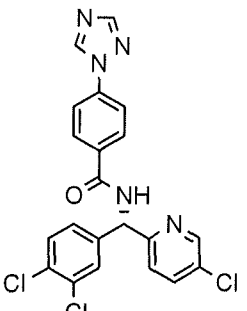
CYM 52584 IB	
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CYM 52586 IB	
CYM 52587 IB	
CYM 52588 IB	
CYM 52589 IB	

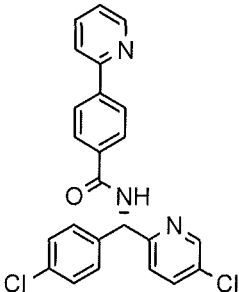
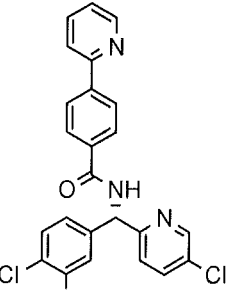
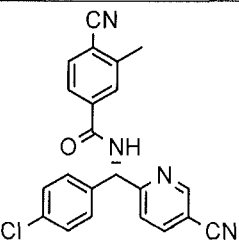
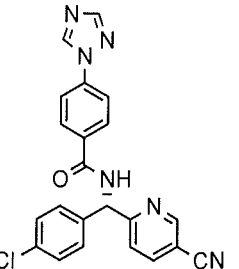
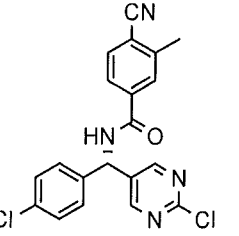
CYM 52590 IB	
CYM 52591 IB	
CYM 52592 IB	
CYM 52593 IB	
CYM 52594 IB	

CYM 52595 IB	 <chem>N#Cc1cc(F)cc(C(=O)Nc2ccc(Cl)cc2Cc3cc(Cl)nc(F)c3)c1</chem>
CYM 52596 IB	 <chem>Cc1cc(C#N)cc(C(=O)Nc2ccc(Cl)cc2Cc3cc(Cl)nc(F)c3)c1</chem>
CYM 52597 IB	 <chem>Cc1cc(Cl)cc(C(=O)Nc2ccc(Cl)cc2Cc3cc(Cl)nc(F)c3)c1</chem>
CYM 52598 IB	 <chem>N#Cc1ccc(C(=O)Nc2ccc(Cl)cc2Cc3cc(Cl)nc(F)c3)cc1</chem>
CYM 52599 IB	 <chem>CN(C)C(=O)c1cc(C#N)cc(C(=O)Nc2ccc(Cl)cc2Cc3cc(Cl)nc(F)c3)c1</chem>
CYM 52600 IB	 <chem>Fc1cc(F)cc(C(=O)Nc2ccc(Cl)cc2Cc3cc(Cl)nc(F)c3)c1</chem>

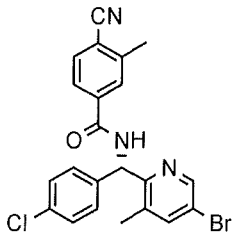
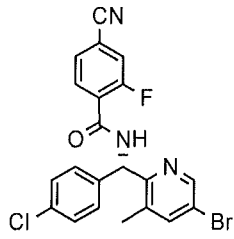
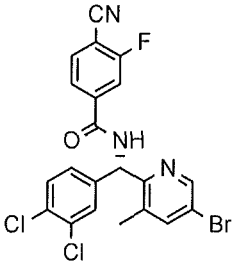
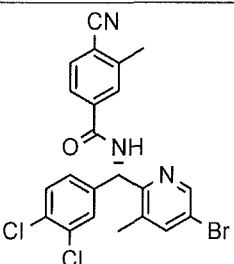
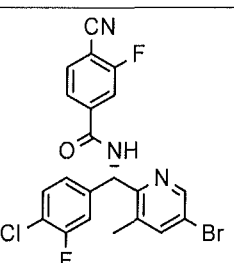
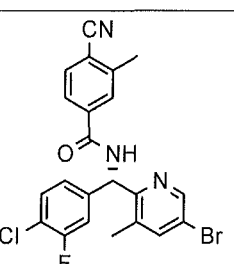
CYM 52601 IB	 <chem>N#Cc1cc(C#N)ccc1C(=O)N[C@H](Cc1ccc(Cl)cc1)Cc1ccncc1Br</chem>
CYM 52602 IB	 <chem>N#Cc1cc(C#N)ccc1C(=O)N[C@H](Cc1ccc(Cl)cc1)Cc1cc(Cl)ncn1</chem>
CYM 52603 IB	 <chem>N#Cc1cc(C#N)ccc1C(=O)N[C@H](Cc1cc(Cl)c(Cl)cc1)Cc1cc(Cl)ncn1</chem>
CYM 52604 IB	 <chem>N#Cc1cc(C#N)ccc1C(=O)N[C@H](Cc1cc(Cl)c(Cl)cc1)Cc1ccncc1Br</chem>
CYM 52605 IB	 <chem>COC(=O)c1cc(C#N)ccc1C(=O)N[C@H](Cc1cc(Cl)c(Cl)cc1)Cc1cc(Cl)ncn1</chem>
CYM 52606 IB	 <chem>Cc1cc(C#N)c(C)cc1C(=O)N[C@H](Cc1ccc(Cl)cc1)Cc1cc(Cl)ncn1</chem>

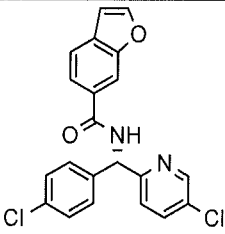
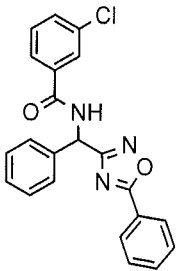
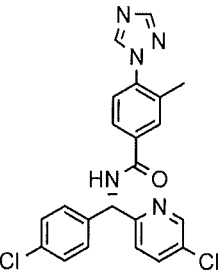
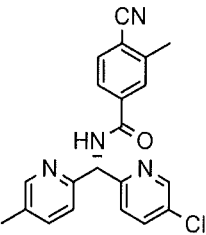
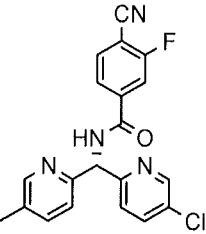
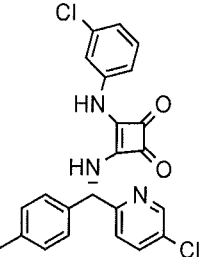
CYM 52607 IB	
CYM 52608 IB	
CYM 52609 IB	
CYM 52610 IB	
CYM 52611 IA	
CYM 52612 IB	

CYM 52613 IC	
CYM 52614 IB	
CYM 52615 IC	
CYM 52616 IB	
CYM 52617 IB	

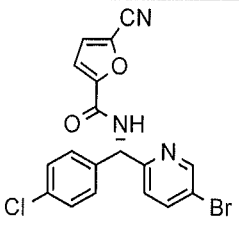
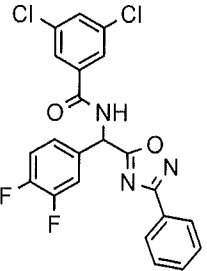
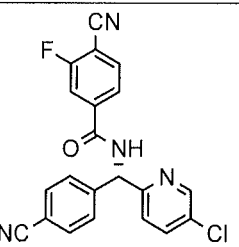
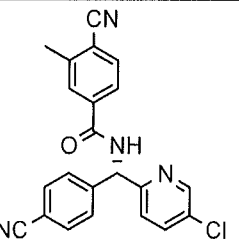
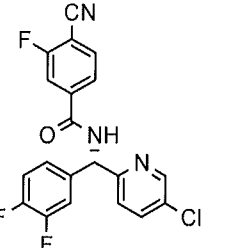
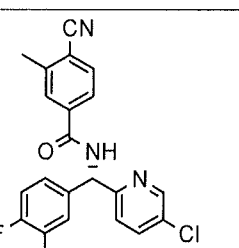
CYM 52618 IB	 <chem>Clc1cc(Cc2cc(C(=O)Nc3ccc(cc3c4cccnc4)cc5cccnc52)ccc(Cl)c1)c3ccncc3Cl</chem>
CYM 52619 IB	 <chem>Clc1cc(Cc2cc(C(=O)Nc3ccc(cc3c4cccnc4)cc5cccnc52)cc(Cl)c(Cl)c1)c3ccncc3Cl</chem>
CYM 52620 IB	 <chem>Cc1cc(C(=O)Nc2cc(Cc3cc(C#N)ccn3)ccc(Cl)c2)ccc(C#N)c1</chem>
CYM 52621 IB	 <chem>C#Nc1cc(Cc2cc(C(=O)Nc3ccc(cc3c4cnn[n4])cc5cccnc52)ccc(Cl)c1)c3ccncc3Cl</chem>
CYM 52622 IB	 <chem>Cc1cc(C(=O)Nc2cc(Cc3cc(C#N)nn3)ccc(Cl)c2)ccc(C#N)c1</chem>

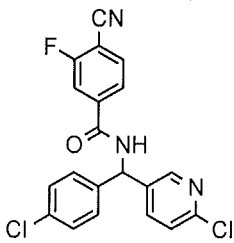
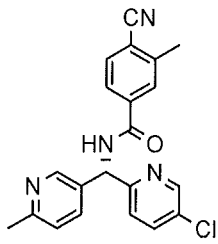
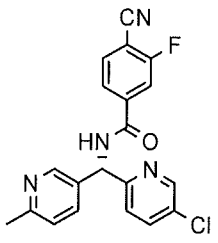
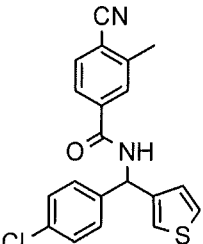
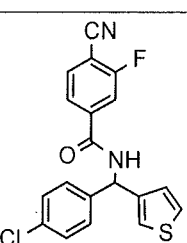
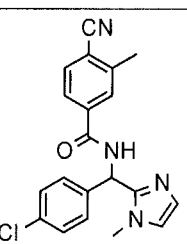
CYM 52623 IB	 <chem>Nc(=O)c1cc(C#N)c(F)cc1Cc2ccc(Cl)cc2</chem>
CYM 52624 IB	 <chem>Nc(=O)c1cc(C#N)c(F)cc1Cc2ccc(Cl)cc2</chem>
CYM 52625 IA	 <chem>Cc1cc(C#N)cc(NC(=O)c2ccc(Cl)cc2)cc1</chem>
CYM 52626 IA	 <chem>Nc(=O)c1cc(C#N)c(F)cc1Cc2ccc(Cl)cc2</chem>
CYM 52627 IB	 <chem>Nc(=O)c1cc(C#N)c(F)cc1Cc2ccc(Cl)cc2</chem>
CYM 52628 IB	 <chem>Nc(=O)c1cc(C#N)c(F)cc1Cc2ccc(Cl)cc2</chem>

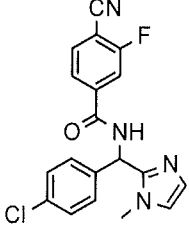
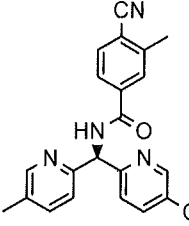
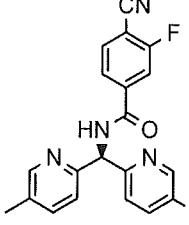
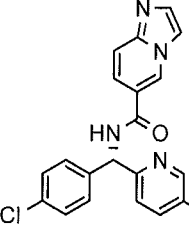
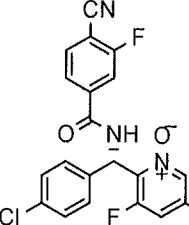
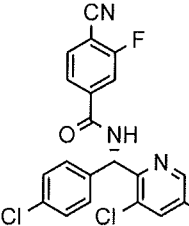
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CYM 52631 IB	
CYM 52632 IB	
CYM 52633 IB	
CYM 52634 IB	

CYM 52635 IC	
CYM 52636 IB	
CYM 52637 IB	
CYM 52638 IE	
CYM 52639 IE	
CYM 52640 IB	

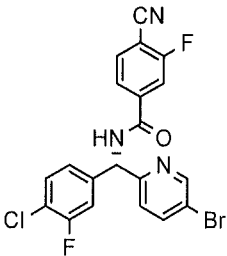
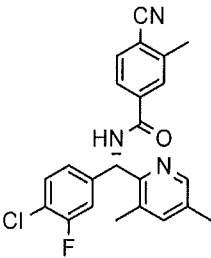
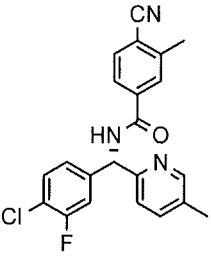
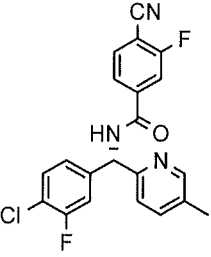
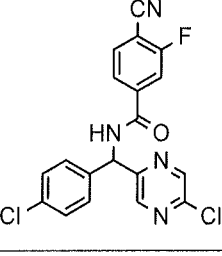
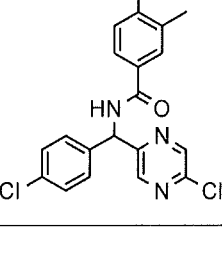
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CYM 52642 ID	 <chem>Clc1ccc(cc1)[C@H](c1ccc(Cl)cc1)C(=O)Nc2ccncc2</chem>
CYM 52643 IB	 <chem>Clc1cc(Cl)ccc1C(=O)N[C@H](c1ccc(Cl)cc1)C2=NN=C(N2)c3ccccc3</chem>
CYM 52644 IC	 <chem>Clc1cc(Cl)ccc1C(=O)N[C@H](c1ccncc1Cl)C2=C(C=COC2=N)O</chem>
CYM 52645 IC	 <chem>Clc1ccc(cc1)[C@H](c1ccncc1Br)C(=O)Nc2cc(C=C(O)N)oc2</chem>
CYM 52646 IC	 <chem>Clc1cc(Cl)ccc1C(=O)N[C@H](c1ccncc1Cl)C2=C(C=C(C#N)O2)</chem>

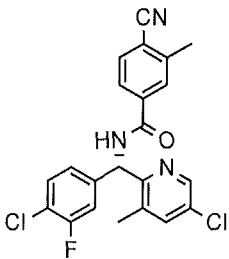
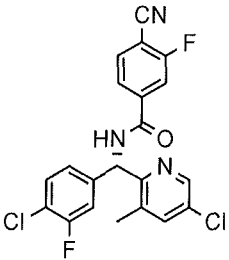
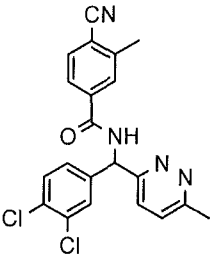
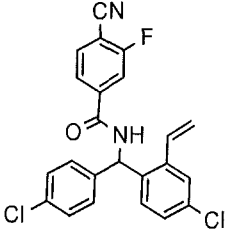
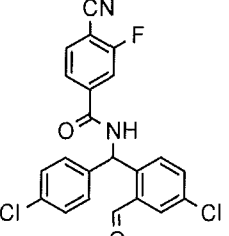
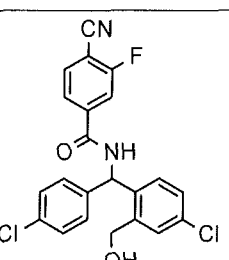
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CYM 52649 IB	
CYM 52650 IB	
CYM 52651 IB	
CYM 52652 IB	

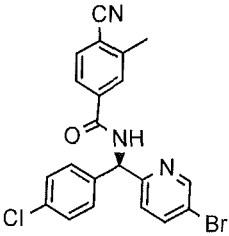
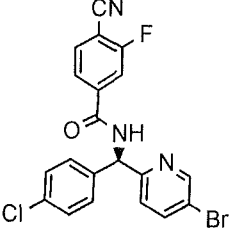
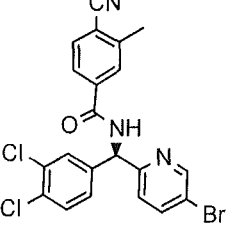
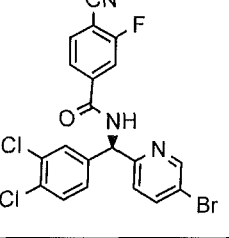
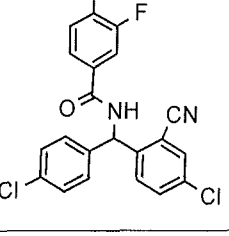
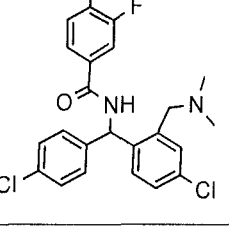
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CYM 52656 IB	
CYM 52657 IB	
CYM 52658 IB	

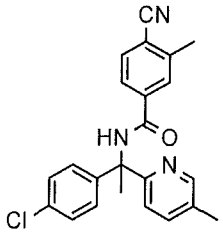
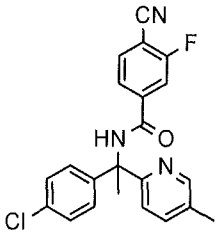
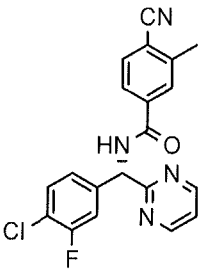
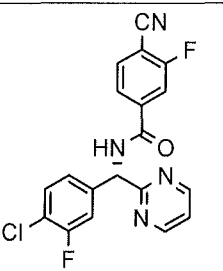
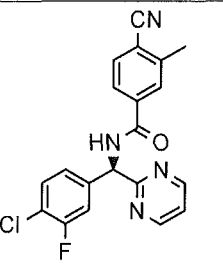
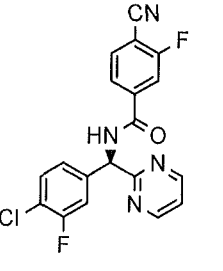
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CYM 52662 IE	
CYM 52663 IB	
CYM 52664 IB	

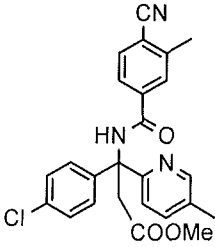
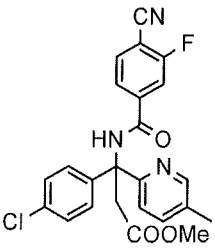
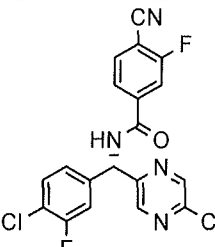
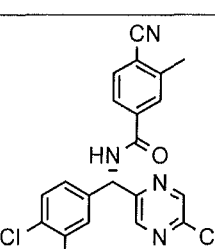
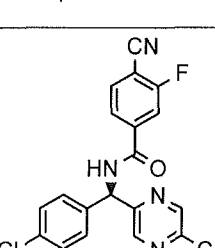
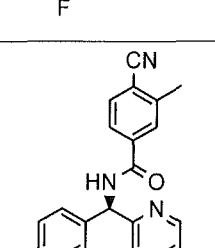
CYM 52665 IB	Chemical structure of compound CYM 52665: A 4-cyano-3-fluorophenyl group is connected via an amide bond to a 1-((4-chlorophenyl)(2-chloro-5-chloropyridin-3-yl)methyl)pyrrolidine-2-carboxamide moiety.
CYM 52666 IB	Chemical structure of compound CYM 52666: A 4-cyano-3-methylphenyl group is connected via an amide bond to a 1-((4-chlorophenyl)(2-chloro-5-chloropyridin-3-yl)methyl)pyrrolidine-2-carboxamide moiety.
CYM 52667 IB	Chemical structure of compound CYM 52667: A 4-cyano-3-fluorophenyl group is connected via a sulfonamide bond to a 1-((4-chlorophenyl)(2-bromo-5-methylpyridin-3-yl)methyl)pyrrolidine-2-carboxamide moiety.
CYM 52668 IA	Chemical structure of compound CYM 52668: A 4-cyano-3-fluorophenyl group is connected via an amide bond to a 1-((4-chlorophenyl)(2-chloro-5-fluoropyridin-3-yl)methyl)pyrrolidine-2-carboxamide moiety.
CYM 52669 IA	Chemical structure of compound CYM 52669: A 4-cyano-3-methylphenyl group is connected via an amide bond to a 1-((4-chlorophenyl)(2-chloro-5-fluoropyridin-3-yl)methyl)pyrrolidine-2-carboxamide moiety.
CYM 52670 IB	Chemical structure of compound CYM 52670: A 4-cyano-3-methylphenyl group is connected via an amide bond to a 1-((4-chloro-3-fluorophenyl)(2-bromo-5-methylpyridin-3-yl)methyl)pyrrolidine-2-carboxamide moiety.

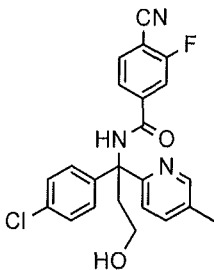
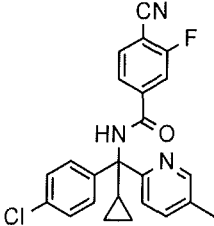
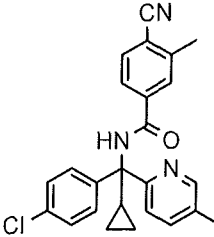
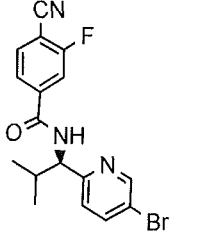
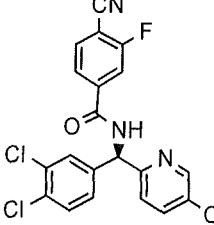
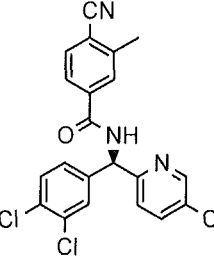
CYM 52671 IB	 <chem>Clc1cc(ccc1F)C(NC(=O)c2ccc(C#N)c(F)c2)c3ccncc3Br</chem>
CYM 52672 IB	 <chem>Clc1cc(ccc1F)C(NC(=O)c2ccc(C#N)c(C)c2)c3ccncc3C</chem>
CYM 52673 IB	 <chem>Clc1cc(ccc1F)C(NC(=O)c2ccc(C#N)c(C)c2)c3ccncc3C</chem>
CYM 52674 IB	 <chem>Clc1cc(ccc1F)C(NC(=O)c2ccc(C#N)c(F)c2)c3ccncc3C</chem>
CYM 52675 IB	 <chem>Clc1cc(ccc1)C(NC(=O)c2ccc(C#N)c(F)c2)c3ccncc3Cl</chem>
CYM 52676 IB	 <chem>Clc1cc(ccc1)C(NC(=O)c2ccc(C#N)c(C)c2)c3ccncc3Cl</chem>

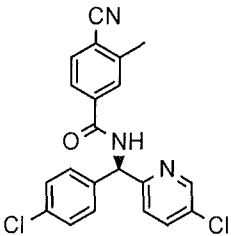
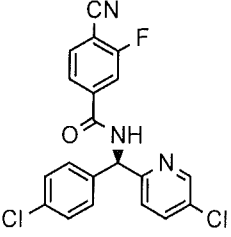
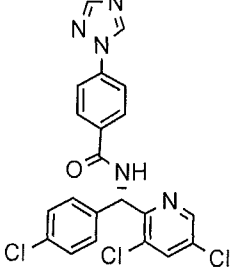
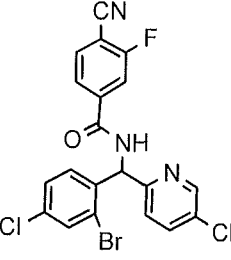
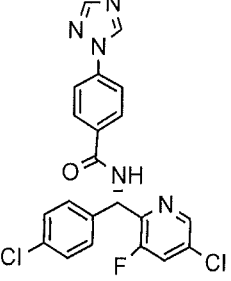
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CYM 52682 IA	

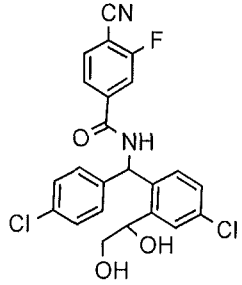
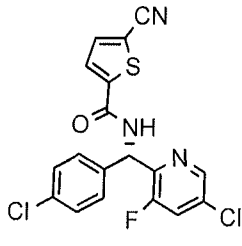
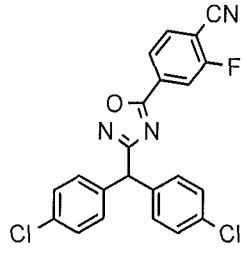
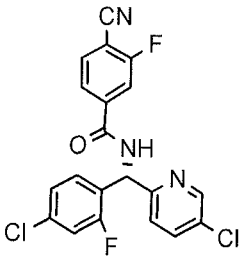
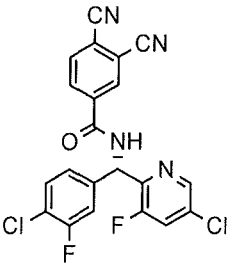
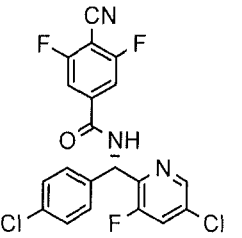
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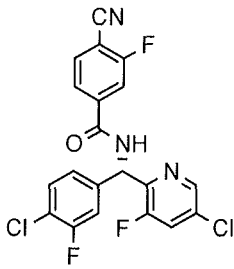
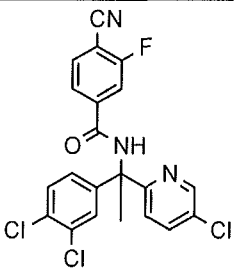
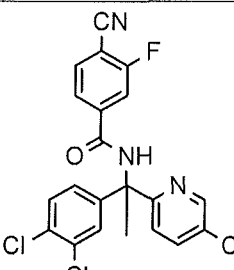
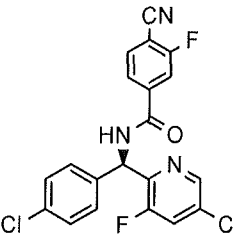
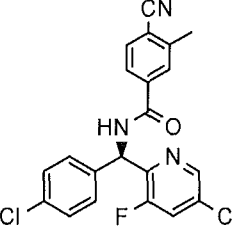
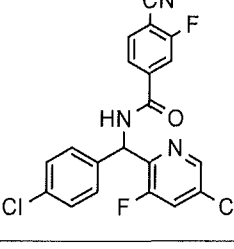
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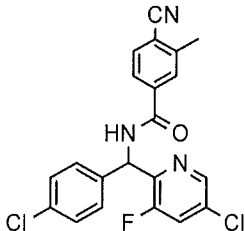
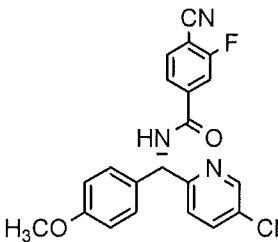
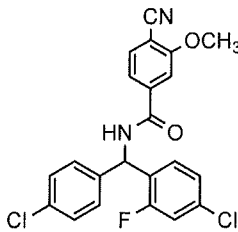
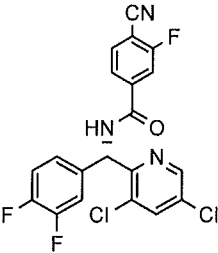
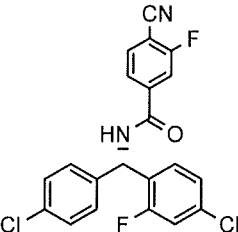
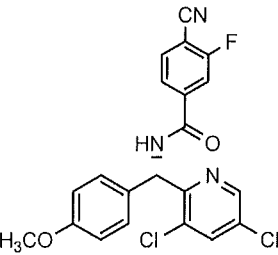
CYM 52695 IB	 <chem>COC(=O)C1=CC=CC=C1N=C(C)C=C(C1C(C2=CC(=CC=C2)C(=O)NC3=CC(=CC=C3)C#N)C4=CC=C(C)C#N4)C5=CC=C(C)C#N5</chem>
CYM 52696 IB	 <chem>COC(=O)C1=CC=CC=C1N=C(C)C=C(C1C(C2=CC(=CC=C2)C(=O)NC3=CC(=CC=C3)C(F)=CC#N)C4=CC=C(C)C#N4)C5=CC=C(C)C#N5</chem>
CYM 52697 IB	 <chem>COC(=O)C1=CC=CC=C1N=C(C)C=C(C1C(C2=CC(=CC=C2)C(=O)NC3=CC(=CC=C3)C(F)=CC#N)C4=CC=C(C)C#N4)C5=CC=C(C)C#N5</chem>
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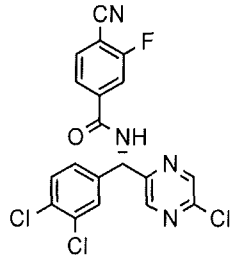
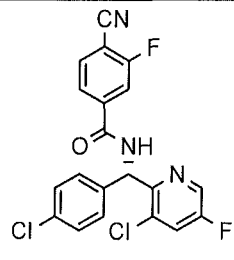
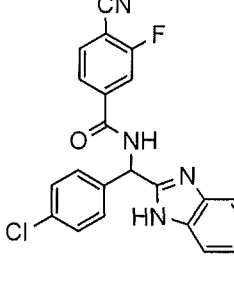
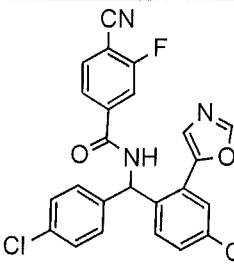
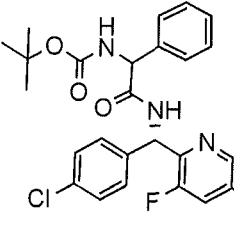
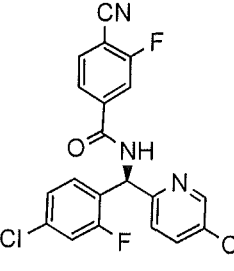
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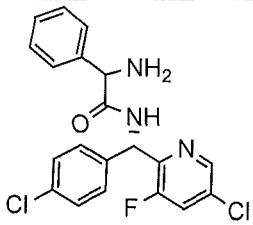
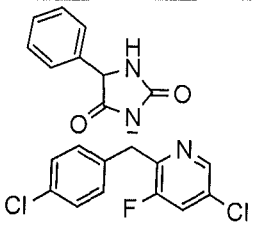
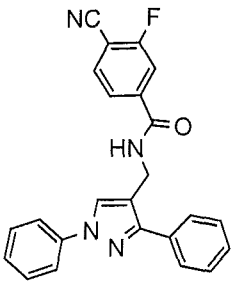
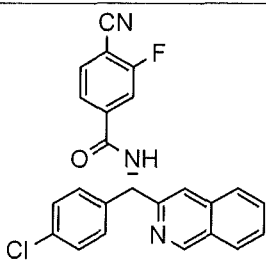
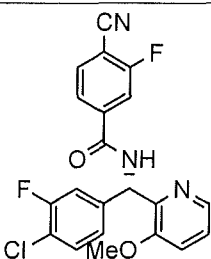
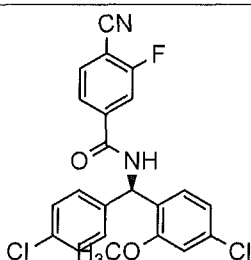
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CYM-52709 IB	 <chem>c1cc(Cl)cn1[C@H](C(=O)Nc1ccc(cc1N2N=NN=C2)c3ccc(Cl)cc3)c4ccc(Cl)cc4</chem>
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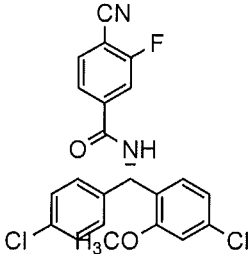
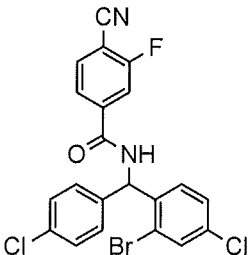
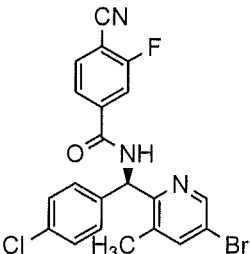
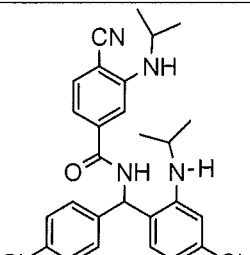
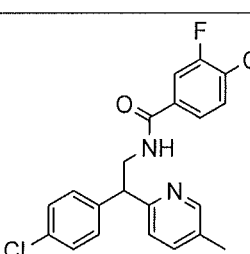
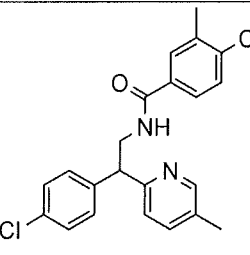
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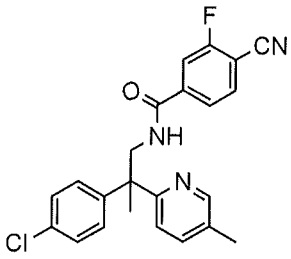
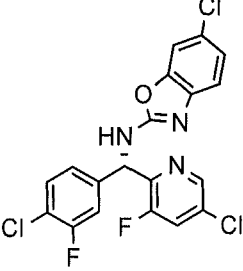
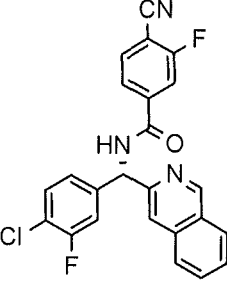
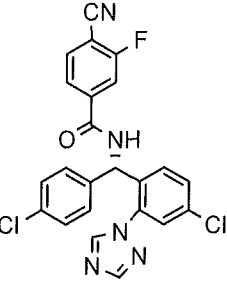
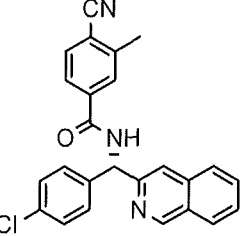
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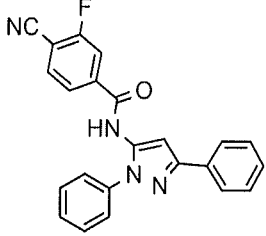
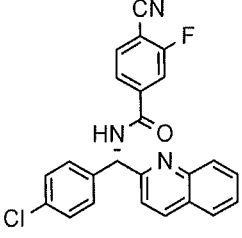
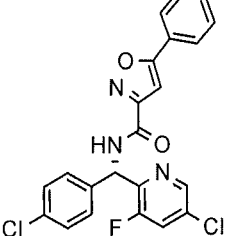
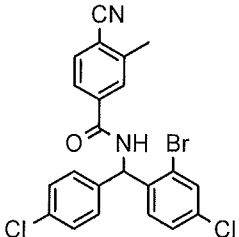
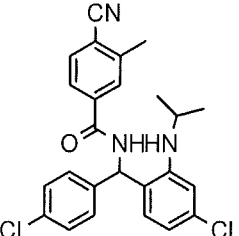
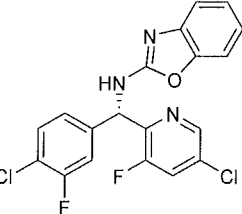
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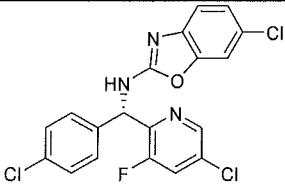
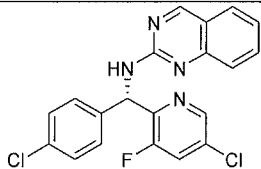
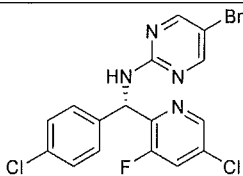
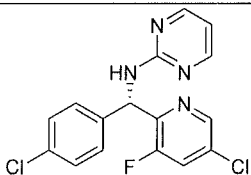
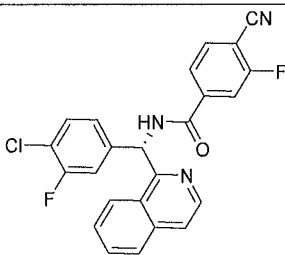
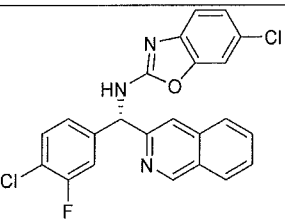
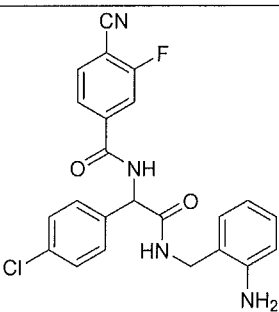
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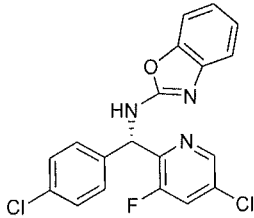
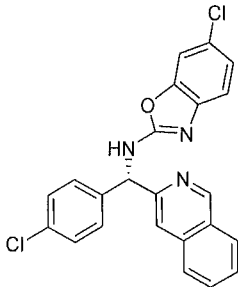
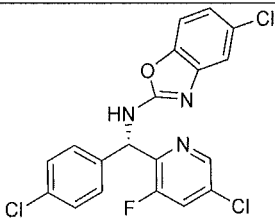
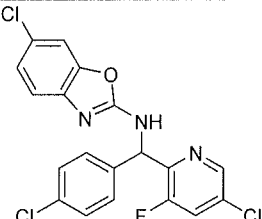
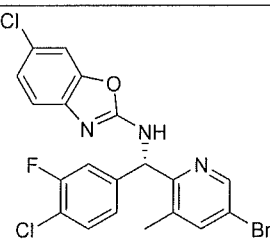
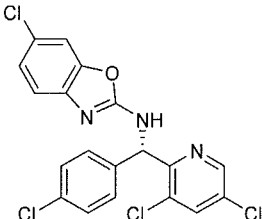
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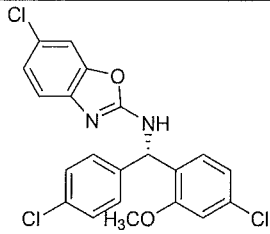
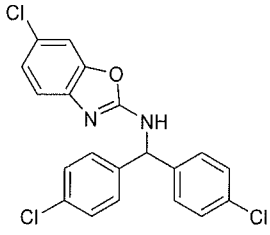
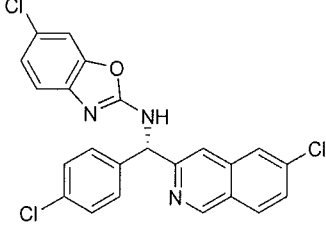
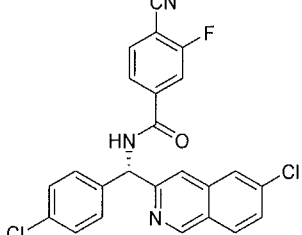
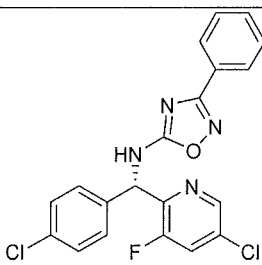
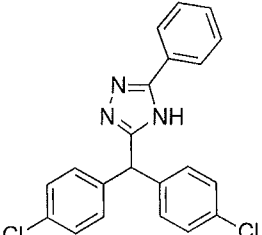
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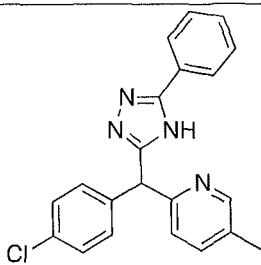
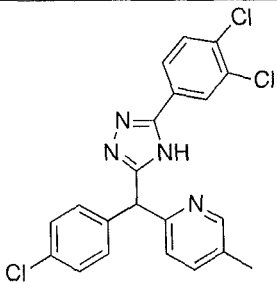
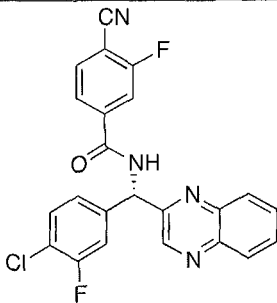
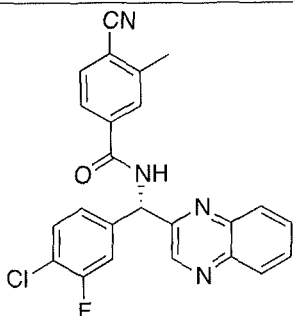
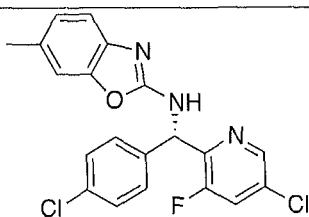
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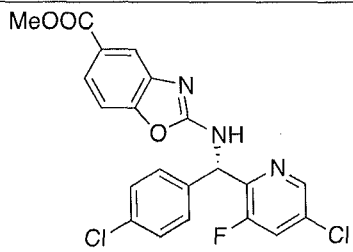
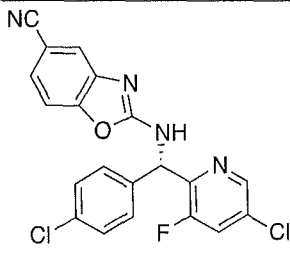
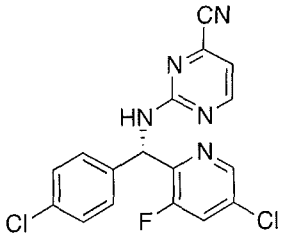
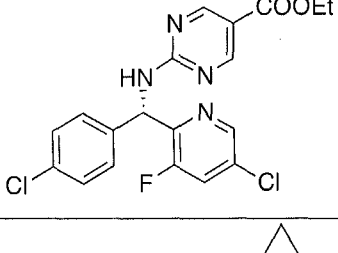
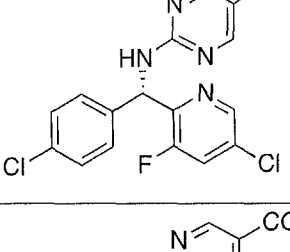
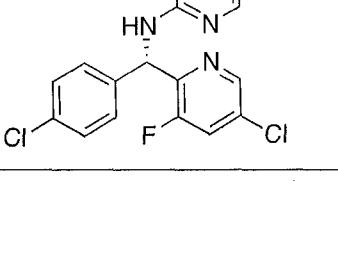
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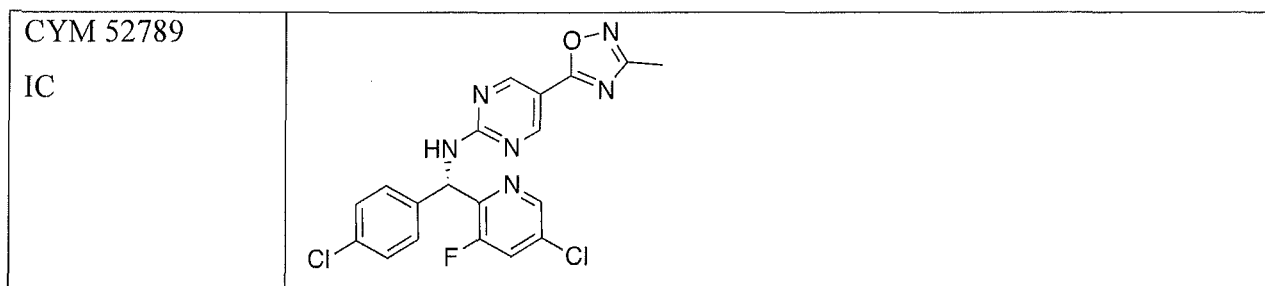
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CYM 52765 not I	

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CYM 52767 IC	
CYM 52768 IC	
CYM 52769 IC	
CYM 52770 IC	
CYM 52771 IC	

CYM 52772 ID	
CYM 52773 ID	
CYM 52774 IC	
CYM 52775 IB	
CYM 52776 IC	
CYM 52777 ID	

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CYM 52781 IB	
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CYM 52786 IC	
CYM 52787 IC	
CYM 52788 IC	



Boc = t-butoxycarbonyl

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Examples

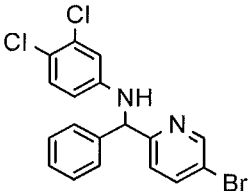
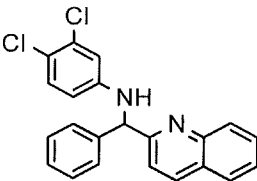
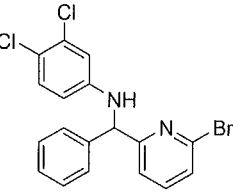
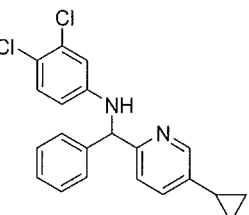
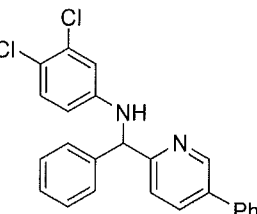
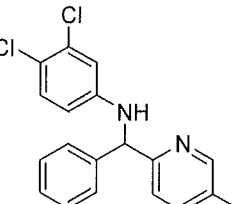
Compounds are presented that selectively modify the action(s) of Sphingosine-1-Phosphate Receptors (S1P-R's) and therefore have potential for the treatment(s) of diseases or disorders of the cardiovascular and/or pulmonary systems. These diseases/disorders include but are not limited to:

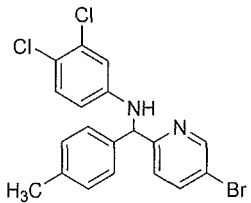
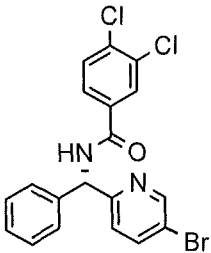
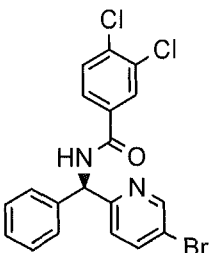
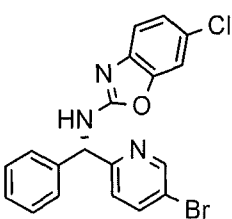
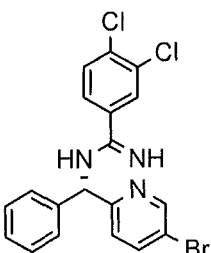
Cardiovascular disease, hypertension (including malignant hypertension), angina, myocardial infarction, cardiac arrhythmias, congestive heart failure, Coronary heart disease, atherosclerosis, angina pectoris, dysrhythmias, cardiomyopathy (including hypertrophic cardiomyopathy), heart failure, cardiac arrest, bronchitis, asthma, chronic obstructive pulmonary disease, cystic fibrosis, croup, emphysema, pleurisy, pulmonary fibrosis, pneumonia, pulmonary embolus, pulmonary hypertension, mesothelioma, Ventricular Conduction abnormalities, Complete Heart Block Adult Respiratory Distress Syndrome and Sepsis Syndrome, Idiopathic Pulmonary fibrosis, scleroderma, systemic sclerosis, retroperitoneal fibrosis, prevention of keloid formation, cirrhosis.

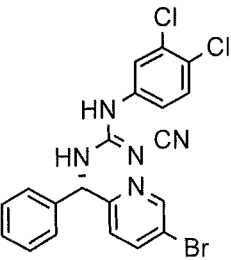
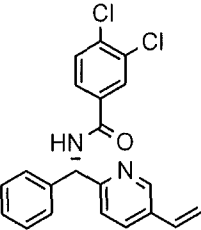
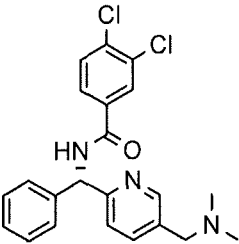
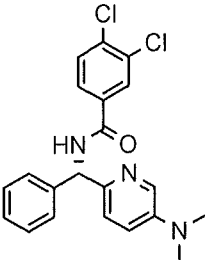
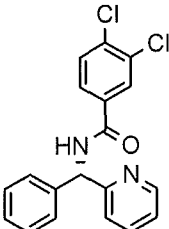
Compounds of the invention below have been shown to demonstrate activity as antagonist/agonist of one or more of the known sphingosine-1-phosphate receptors with IC₅₀/EC₅₀ values lower than 10 micromolar. Representative examples are given in Tables 2 and 3, below.

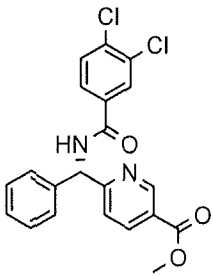
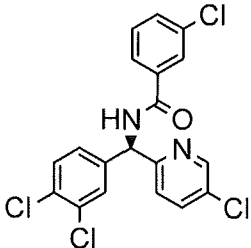
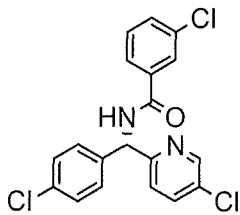
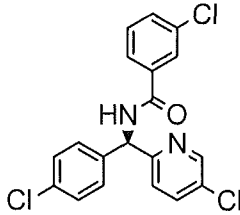
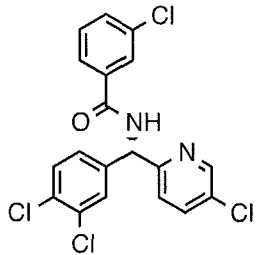
Table 2

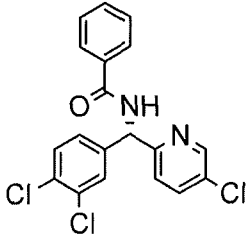
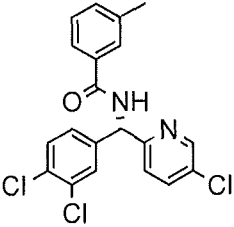
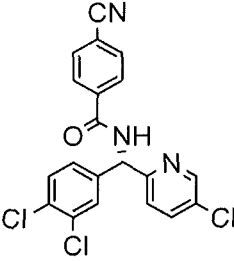
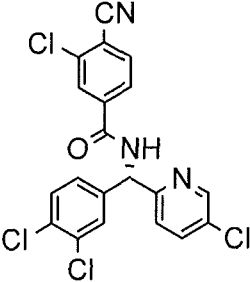
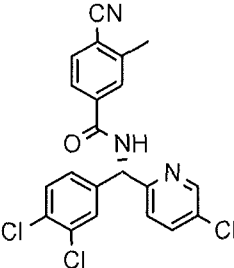
CYM	Structure	S1P1	S1P2	S1P3AA	S1P4AA	S1P5AA
Generic formula		AA IC ₅₀	AA IC ₅₀ μM	IC ₅₀ μM	IC ₅₀ μM	IC ₅₀ μM

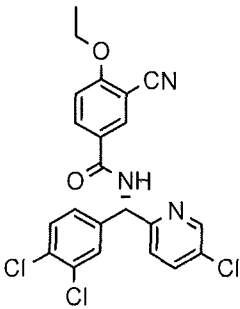
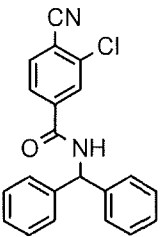
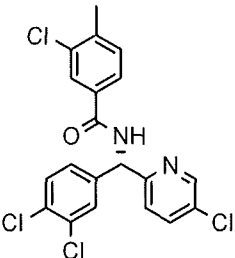
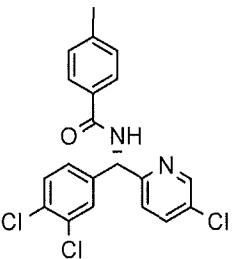
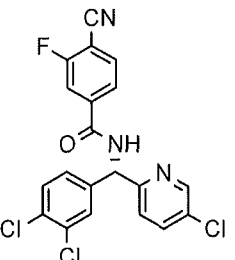
		μM				
52274		-	-	0.772	44.0	-
IB						
52276		-	-	17.2	>50	-
IB						
52296		-	39.7	10.3	35.4	-
IB						
52297		-	>50	1.9	>50	-
IB						
52298		-	>50	>50	>50	-
IB						
52299		-	29.7	2.2	39.1	-
IB						

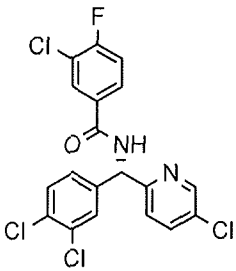
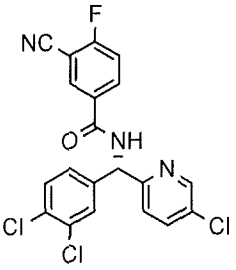
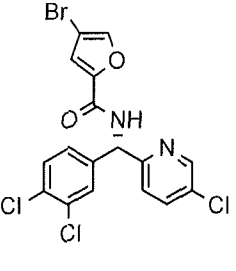
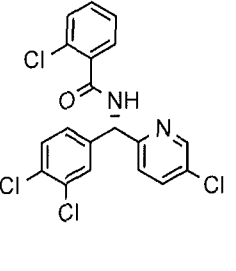
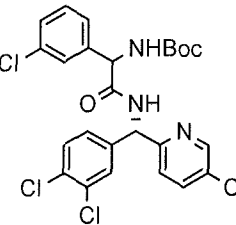
52294		-	>50	1.6	5.7	-
IB						
52331		-	14.7	0.667	21.3	-
IB						
52332		-	15.9	1.5	17.9	-
IB						
52351		-	>50	4.2	>50	-
IC						
52355		-	>50	26	>50	-
IB						

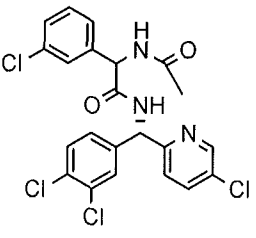
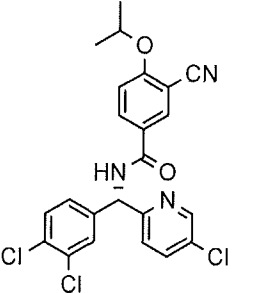
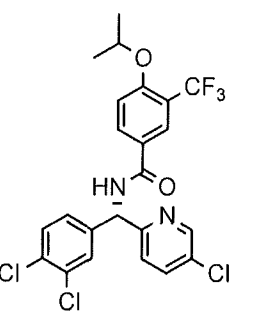
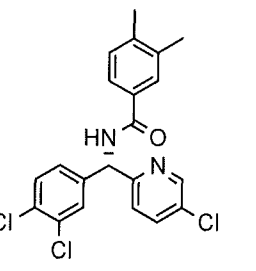
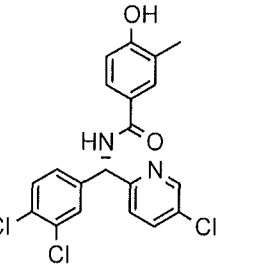
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IB					
52394	-	1.0	0.246	0.873	-
IB					
52396	-	44.3	30.8	>50	-
IB					
52397	-	30.8	8.8	21.6	-
IB					
52398	-	21.7	3.1	12.7	-
IB					

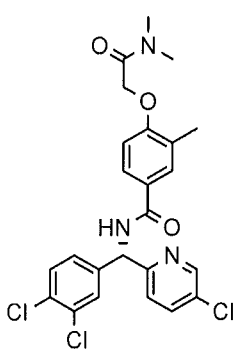
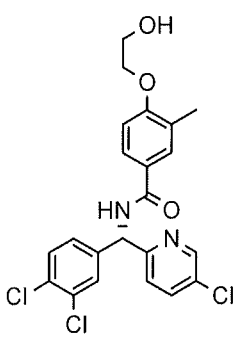
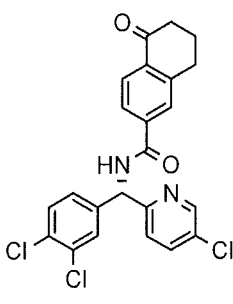
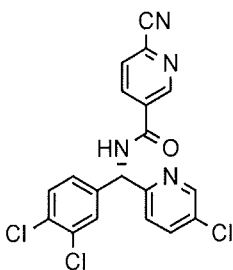
52399		-	>50	8.4	28.2	-
IB						
52433		-	>50	0.649	15.1	-
IB						
52434		-	29.4	0.317	9.9	-
IB						
52435		-	32.2	1.6	8.2	-
IB						
52442		-	>50	0.07	9.3	-
IB						

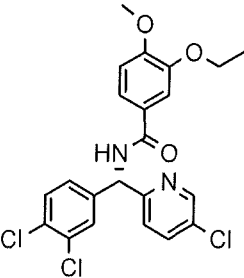
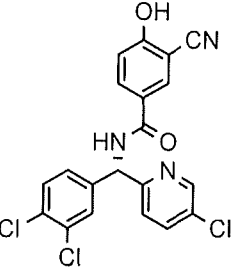
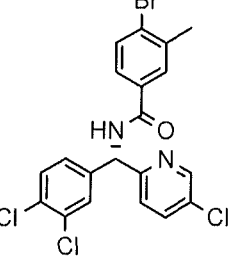
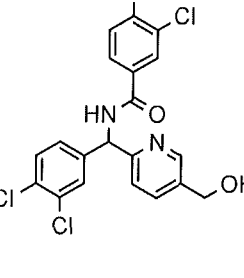
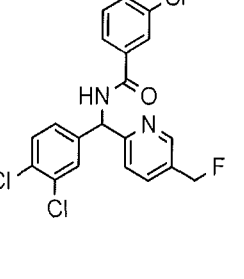
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IB						
52459		-	24.6	0.236	8.2	
IB						
52460		-	>50	0.09	8.8	-
IB						
52464		-	>50	0.022	8.3	-
IB						
52474		0.227	>50	0.014	>50	-
IB						

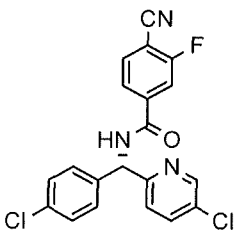
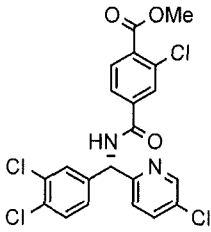
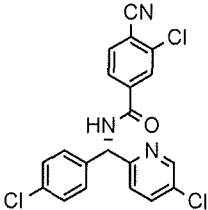
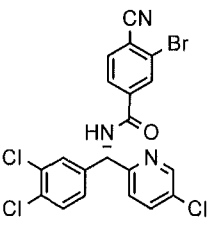
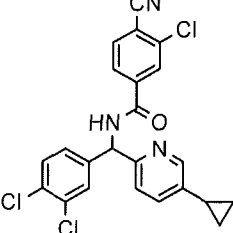
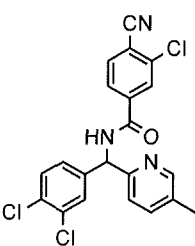
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IB						
52476		>28	>50	0.906	>50	-
IA						
52483		0.91	>50	0.097	6.5	-
IB						
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IB						
52486		1.3	>50	0.028	>50	-
IB						

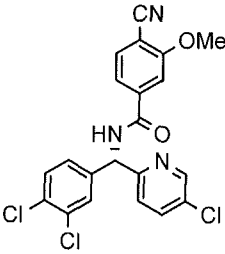
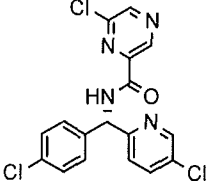
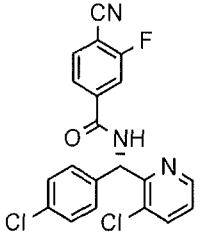
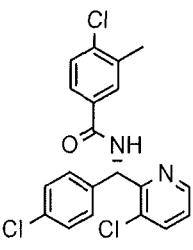
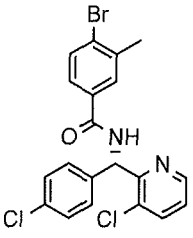
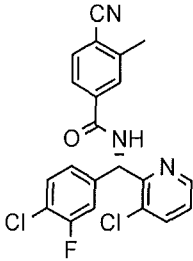
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52491	IB		>28	>50	3.9	30.6	-
52492	IB		>28	>50	5.1	>50	-

52495		>28	15.6	9.8	>50	-
IB						
52504		2.8	-	0.152	-	-
IB						
52505		>50	-	0.576	-	-
IB						
52506		1.5	-	0.172	-	-
IB						
52507		2.2	-	0.112	-	-
IB						

52508		>50	-	0.796	-	-
IB						
52509		>50	-	2.5	-	-
IB						
52510		0.899	-	0.213	-	-
IB						
52511		6.4	-	0.308	-	-
IC						

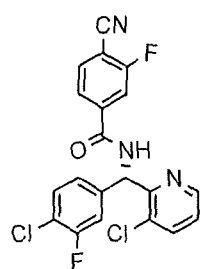
52512		25.5	-	4.1	-	-
IB						
52514		>50	-	29.6	-	-
IB						
52520		0.22	>50	0.035	16.2	-
IB						
52522		3.6	-	0.39	-	-
IB						
52523		7.3	-	0.168	-	-
IB						

52524		>50	-	0.065	-	-
IB						
52525		2.0	-	0.076	-	-
IB						
52526		1.8	6.7	0.027	>50	-
IB						
52527		0.204	-	0.032	-	-
IB						
52528		1.4	-	0.063	-	-
IB						
52529		1.4	44.9	0.041	18.8	-
IB						

52530		0.333	-	0.040	-	-
IB						
52531		>50	-	2.7	-	-
IC						
52543		17.6	-	0.405	-	-
IB						
52544		>28	-	9.1	-	-
IB						
52545		3.5	-	0.792	-	-
IB						
52547		1.9	-	0.249	-	-
IB						

52548

IB



3.2

-

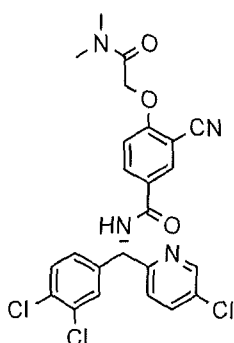
0.13

-

-

52551

IB



>28

-

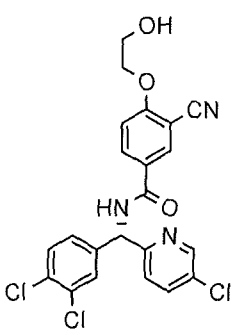
0.964

-

-

52552

IB



10.2

-

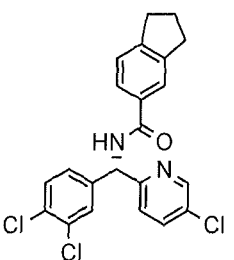
1.0

-

-

52553

IB



0.574

-

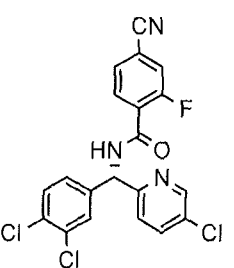
0.147

-

-

52555

IB



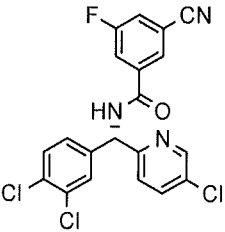
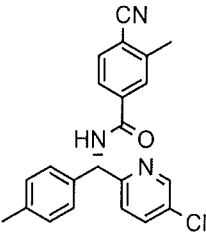
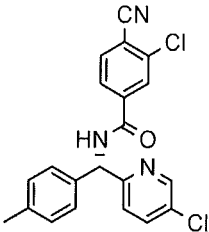
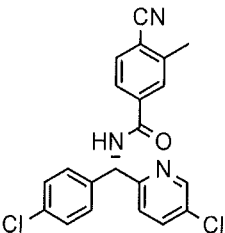
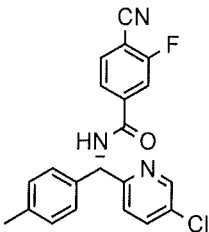
7.1

>50

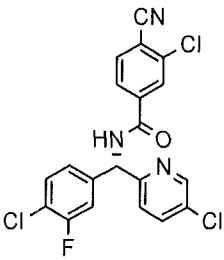
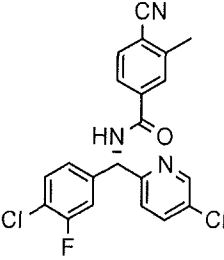
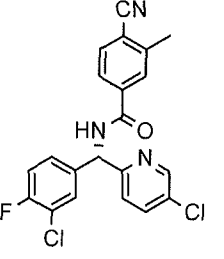
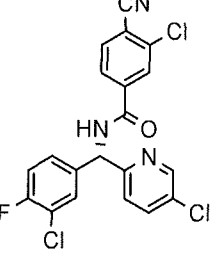
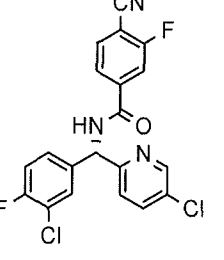
0.057

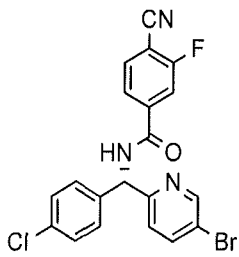
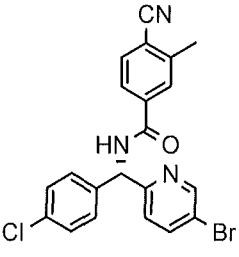
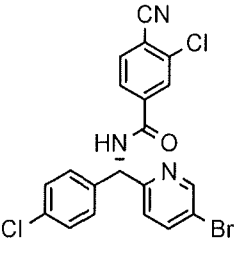
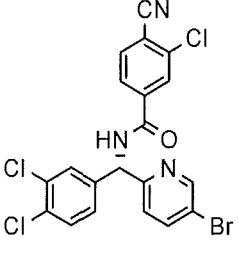
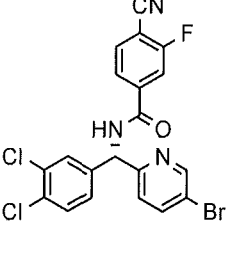
8.5

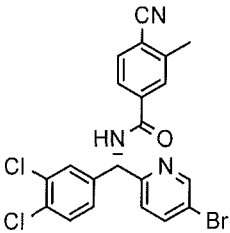
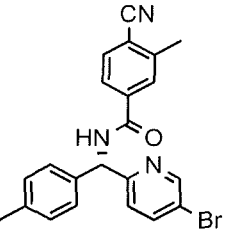
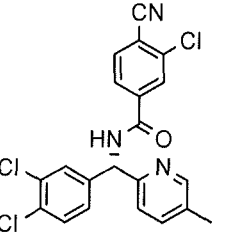
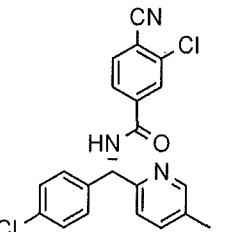
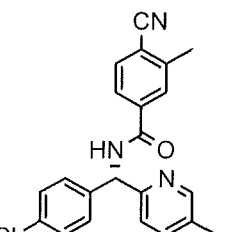
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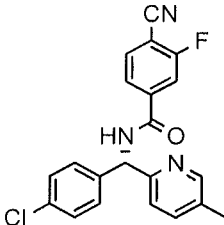
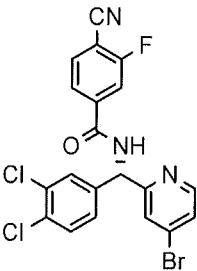
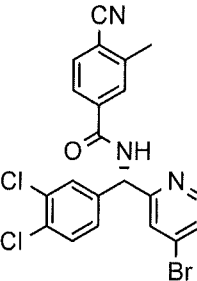
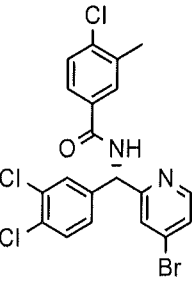
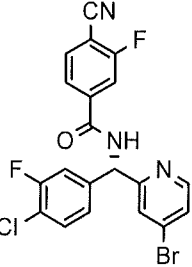
52556		0.285	-	0.061	-	-
IB						
52558		1.4	-	0.057	-	-
IB						
52559		0.604	44.7	0.016	14.8	-
IB						
52560		2.3	19.9	0.038	22.1	-
IB						
52562		5.3	>50	0.042	20.9	-
IB						

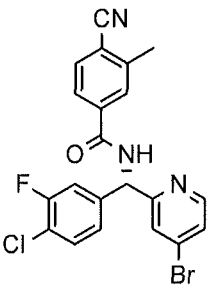
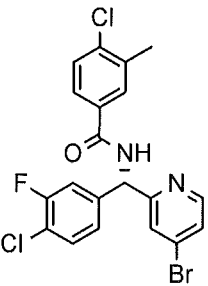
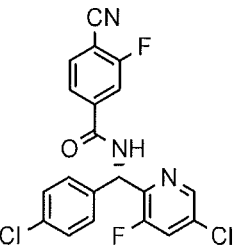
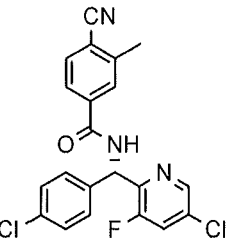
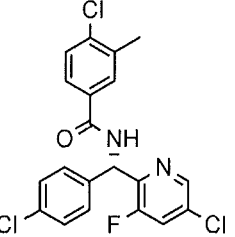
52563		17.2	-	0.114	-	-
IB						
52564		>28	-	3.7	-	-
IB						
52566		>28	-	10.3		
IB						
52568		6.3	14.1	0.052	10.3	-
IC						
52571		4.4	>50	0.29	25.4	-
IB						

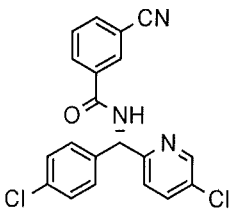
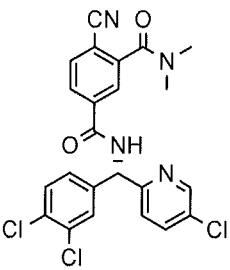
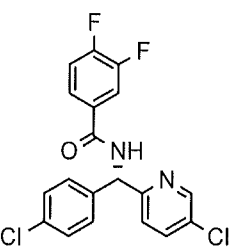
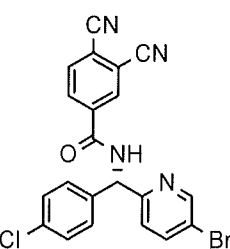
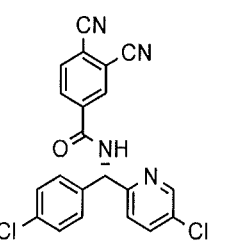
52572		0.81	18.9	0.013	34.4	-
IB						
52573		1.1	40.0	0.032	28.8	-
IB						
52574		2.1	-	0.092	-	-
IB						
52575		1.5	24.3	0.034	21.4	-
IB						
52576		7.8	-	0.077	-	-
IB						

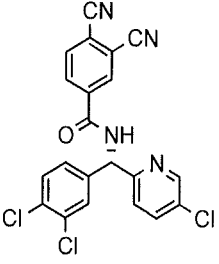
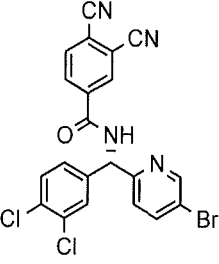
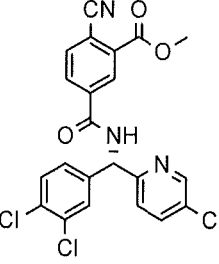
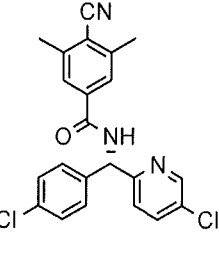
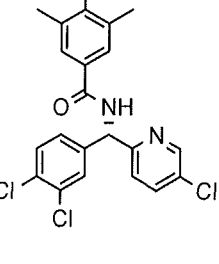
52577		>28	>50	0.026	>50	-
IB						
52578		1.7	32.6	0.029	13.6	-
IB						
52579		1.1	44.8	0.016	>50	-
IB						
52580		0.141	>50	0.007	24.8	-
IB						
52581		0.566	>50	0.009	14.1	-
IB						

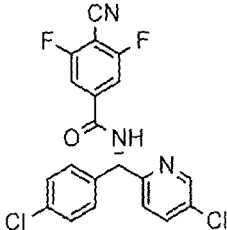
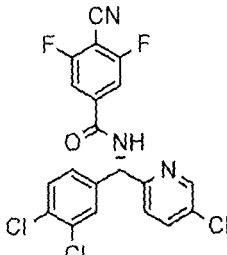
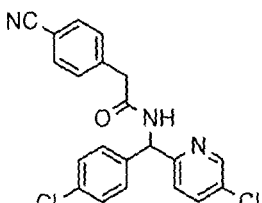
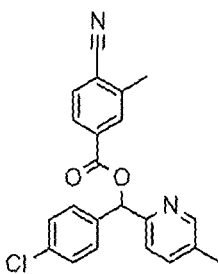
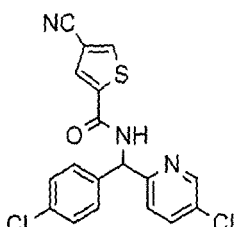
52582		0.308	>50	0.018	27.6	-
IB						
52583		1.1	>50	0.032	23.1	-
IB						
52584		0.505	>50	0.02	38.9	-
IB						
52585		17.9	-	0.21	-	-
IB						
52586		10	-	0.154	-	-
IB						

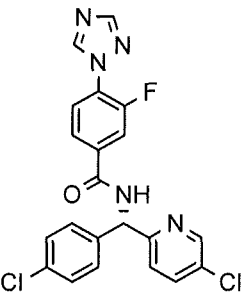
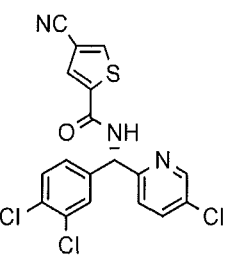
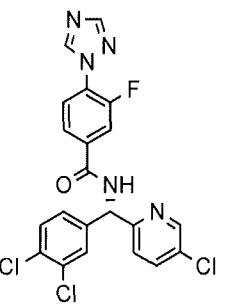
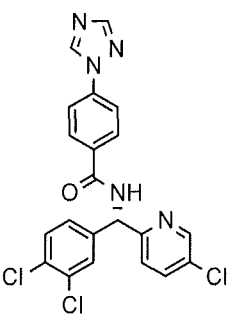
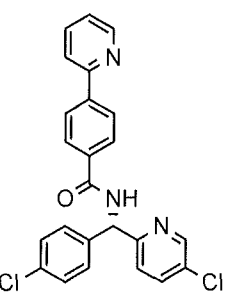
52587		19	-	0.135	-	-
IB						
52589		31.8	-	1.1	-	-
IB						
52590		2.1	-	1.0	-	-
IB						
52591		1.4	-	1.5	-	-
IB						
52592		10.6	-	0.863	-	-
IB						

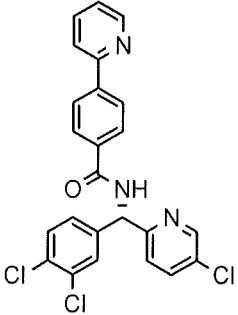
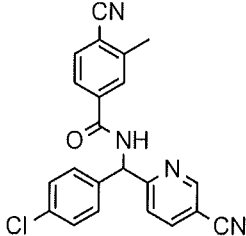
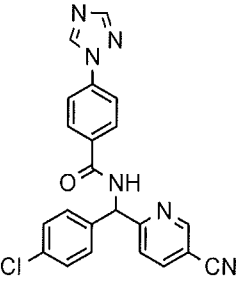
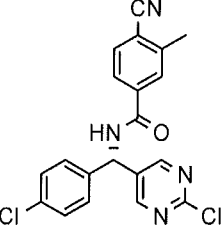
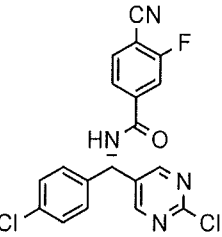
52593		9.3	-	1.8	-	-
IB						
52594		2.5	-	1.3	-	-
IB						
52595		2.7	44.8	0.012	16.5	-
IB						
52596		0.878	12.5	0.012	>50	-
IB						
52597		0.332	43.2	0.026	>50	-
IB						

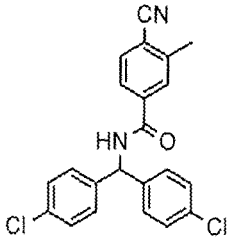
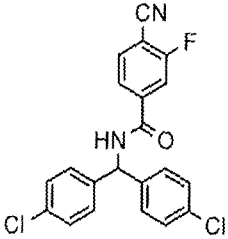
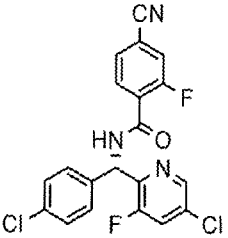
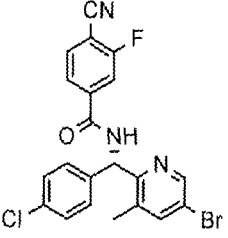
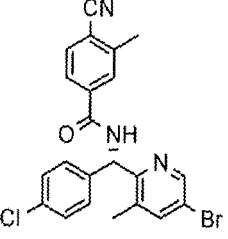
52598		5.1	-	0.350	-	-
IB						
52599		23.3	-	3.5	-	-
IB						
52600		6.4	-	0.396	-	-
IB						
52601		1.4	13.5	0.03	26.8	-
IB						
52602		3.2	-	0.073	-	-
IB						

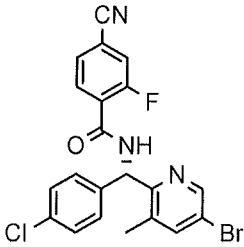
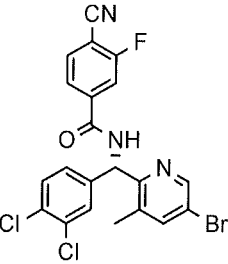
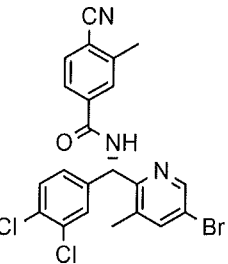
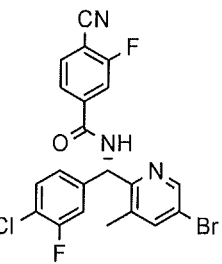
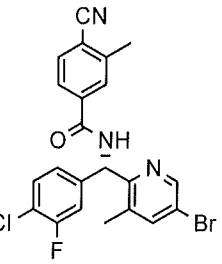
52603		0.389	-	0.048	-	-
IB						
52604		0.099	35.4	0.010	23.5	-
IB						
52605		0.4	-	0.228	-	-
IB						
52606		>28	12.0	0.157	>50	-
IB						
52607		0.452	12.0	0.021	>50	-
IB						

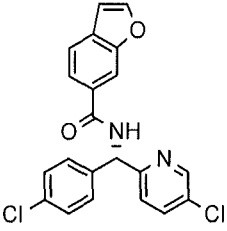
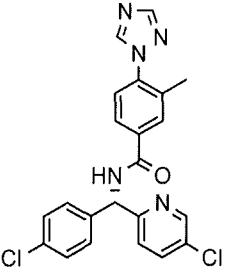
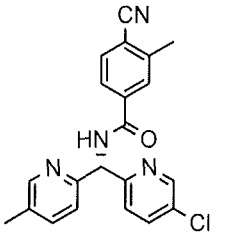
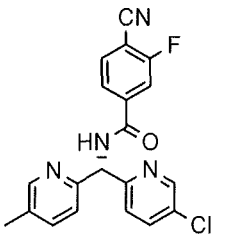
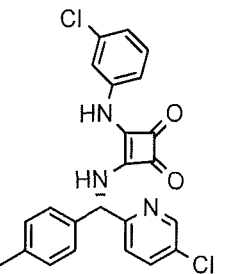
52608		>28	-	0.253	-	-
IB						
52609		>28	19.6	0.042	16.1	-
IB						
52610		5	-	0.647	-	-
IB						
52612		>28	-	0.456	-	-
IB						
52613		10.4	-	0.257	-	-
IC						

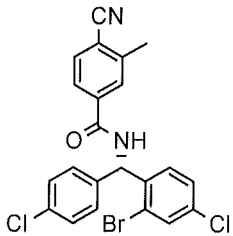
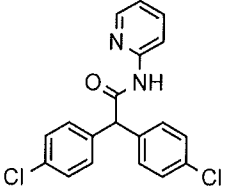
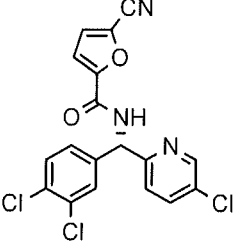
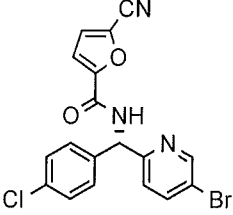
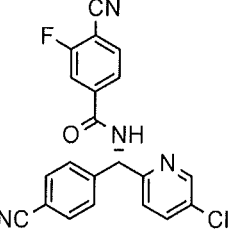
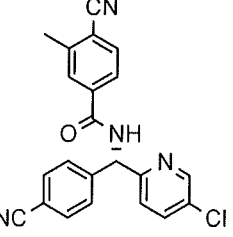
52614		>28	-	0.581	-	-
IB						
52615		1.4	-	0.098	-	-
IC						
52616		4.1	-	0.15	-	-
IB						
52617		4.1	17.3	0.031	11.7	-
IB						
52618		>28	-	3.2	-	-
IB						

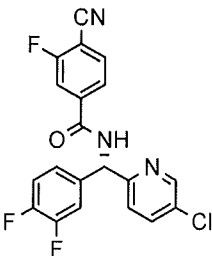
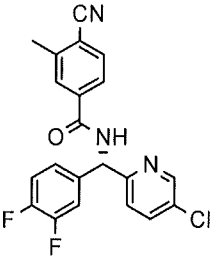
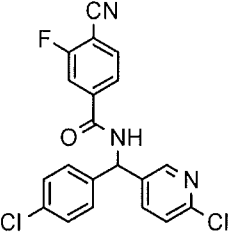
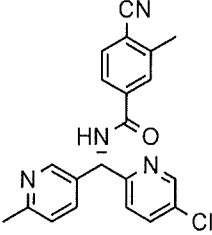
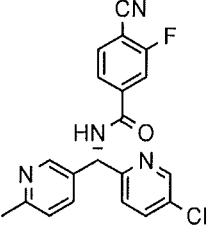
52619		7	-	0.551	-	-
IB						
52620		>28	-	1.7	-	-
IB						
52621		>28	-	19.2	-	-
IB						
52622		>28	-	7.6	-	-
IB						
52624		>28	-	9.2	-	-
IB						

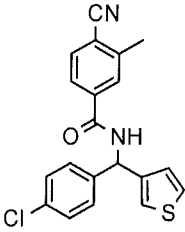
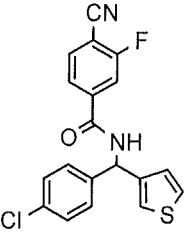
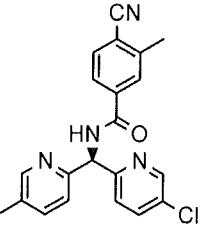
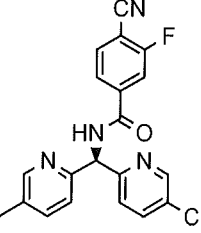
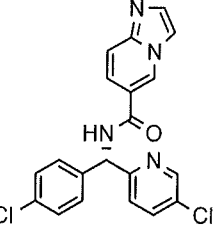
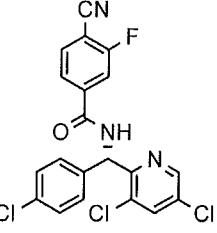
52625		>28	-	0.248	-	-
IA						
52626		>28	-	0.113	-	-
IA						
52627		>28	>50	0.104	>50	-
IB						
52628		4	-	0.036	-	-
IB						
52629		1.1	-	0.042	-	-
IB						

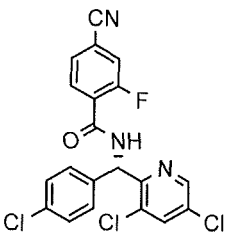
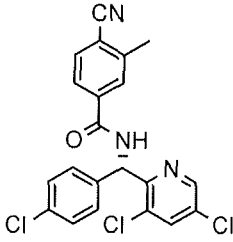
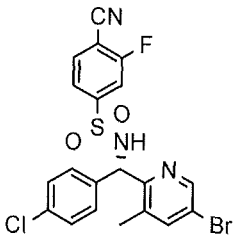
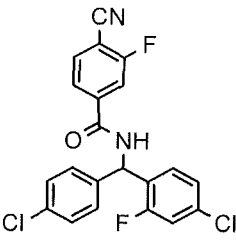
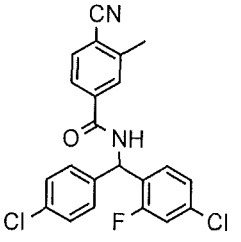
52630		>28	-	0.416	-	-
IB						
52631		1.6	-	0.042	-	-
IB						
52632		0.177	-	0.02	-	-
IB						
52633		1.6	-	0.026	-	-
IB						
52634		0.133	-	0.018	-	-
IB						

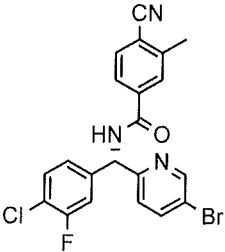
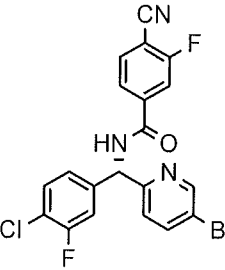
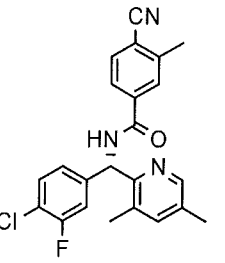
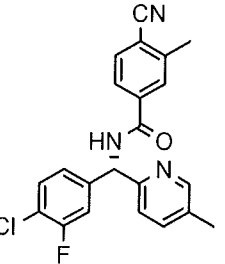
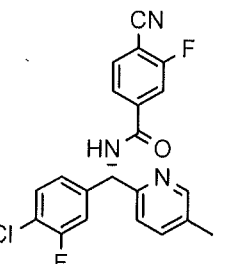
52635		8.1	-	0.122	-	-
IC						
52637		>28	-	32.3	-	-
IB						
52638		>28	-	0.645	-	-
IB						
52639		>28	-	0.4	-	-
IB						
52640		>28	-	1.7	-	-
IB						

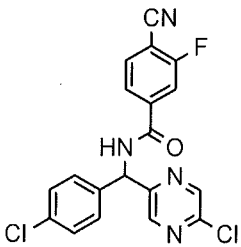
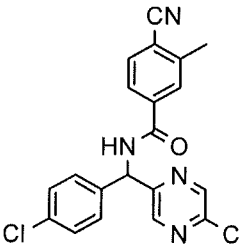
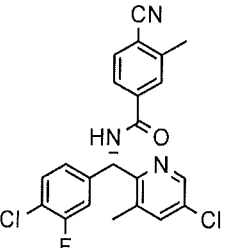
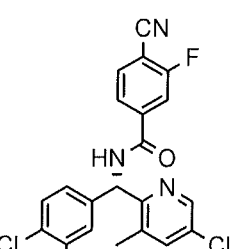
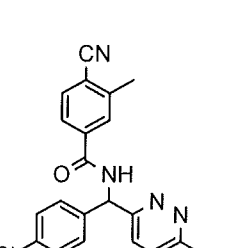
52641 IA		>28	-	0.113	-	-
52642 ID		11.1	-	1.7	-	-
52646 IC		2.5	-	0.329	-	-
52647 IC		9.5	-	0.629	-	-
52649 IB		>28	-	0.95	-	-
52650 IB		>28	-	0.834	-	-

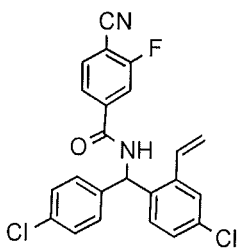
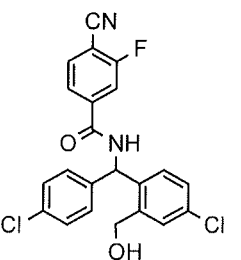
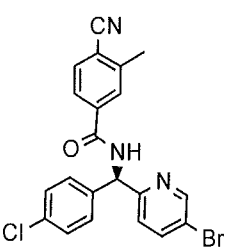
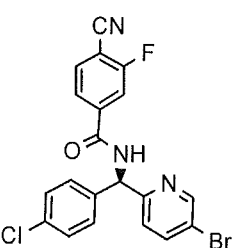
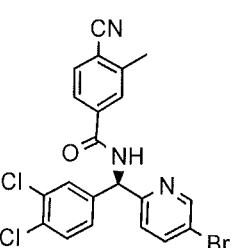
52651		>28	-	0.096	-	-
IB						
52652		3.7	-	0.137	-	-
IB						
52653		>28	-	1.6	-	-
IB						
52654		>28	-	2	-	-
IE						
52655		>28	-	2.3	-	-
IE						

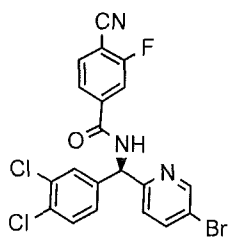
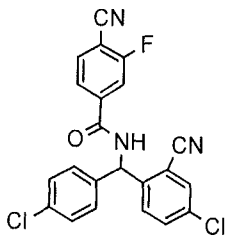
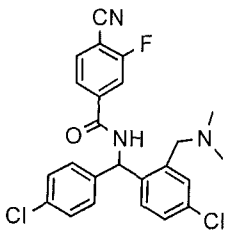
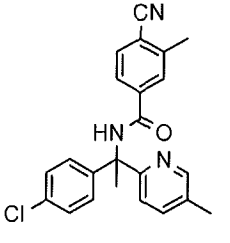
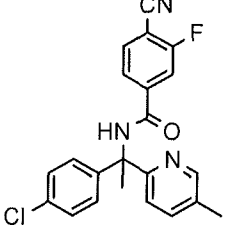
52656		4.0	-	1.2	-	-
IB						
52657		4.5	-	0.439	-	-
IB						
52660		>28	-	0.442	-	-
IE						
52661		>28	-	0.345	-	-
IE						
52662		>28	-	1.1	-	-
IC						
52664		1.4	-	0.013	-	-
IB						

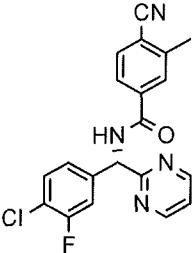
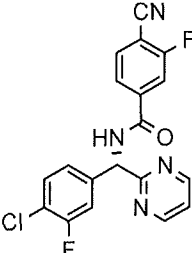
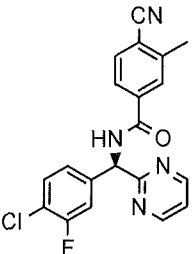
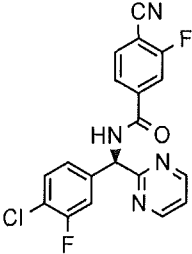
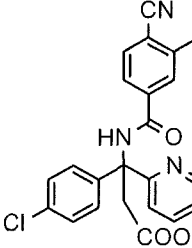
52665		>28	-	0.121	-	-
IB						
52666		0.528	-	0.028	-	-
IB						
52667		6.6	-	16.3	-	-
IB						
52668		>28	-	0.679	-	-
IA						
52669		27.5	-	2.8	-	-
IA						

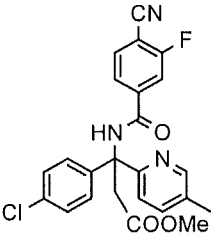
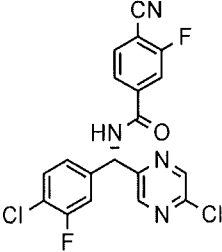
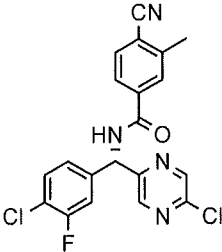
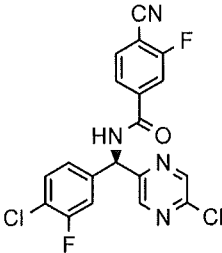
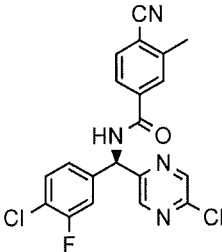
52670		0.452	-	0.011	-	-
IB						
52671		1.8	-	0.011	-	-
IB						
52672		1.4	-	0.051	-	-
IB						
52673		3.3	-	0.076	-	-
IB						
52674		6.4	-	0.027	-	-
IB						

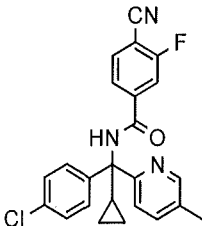
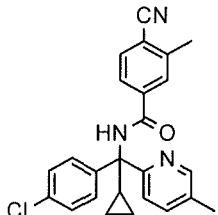
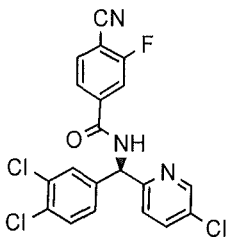
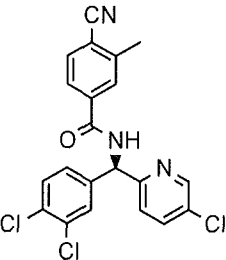
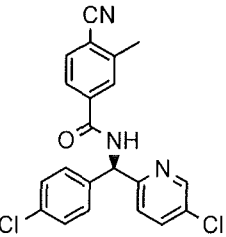
52675		>28	-	0.214	-	-
IB						
62676		12.0	-	0.301	-	-
IB						
52677		0.621	-	0.033	-	-
IB						
52678		1.5	-	0.023	-	-
IB						
52679		>28	-	3.1	-	-
IB						

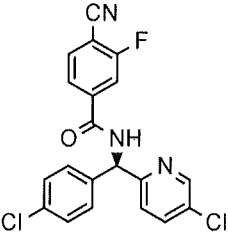
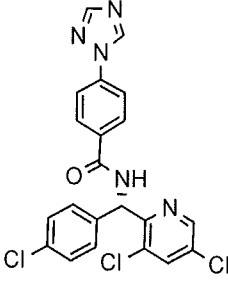
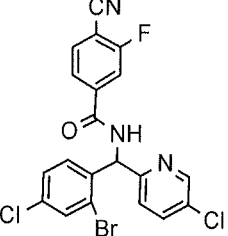
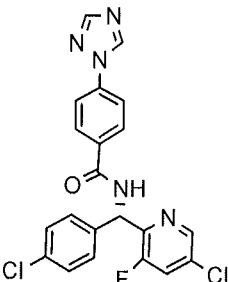
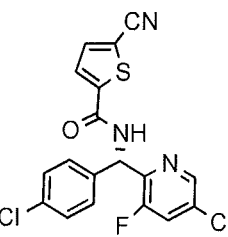
52680		>28	-	0.037	-	-
IA						
52682		>28	-	0.672	-	-
IA						
52683		18.4	-	0.124	-	-
IB						
52684		>28	-	0.075	-	-
IB						
52685		3.3	-	0.056	-	-
IB						

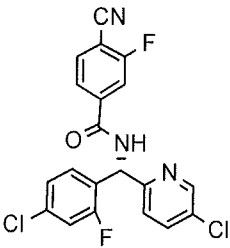
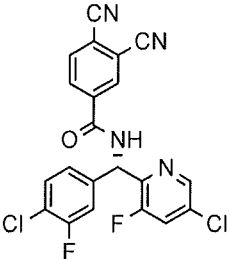
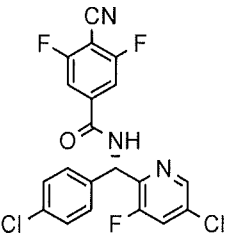
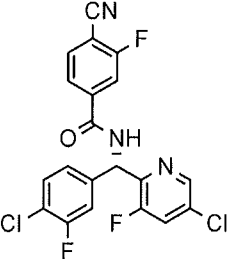
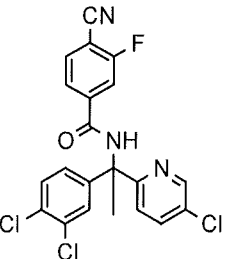
52686		6.6	-	0.047	-	-
IB						
52687		22.4	-	0.426	-	-
IA						
52688		>28	-	3.3	-	-
IA						
52689		10.2	-	0.392	-	-
IB						
52690		>28	-	0.492	-	-
IB						

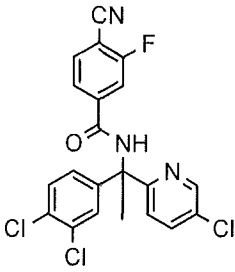
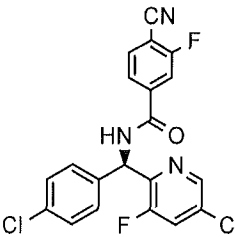
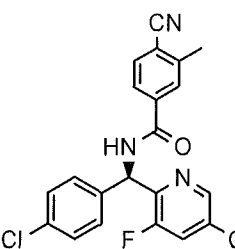
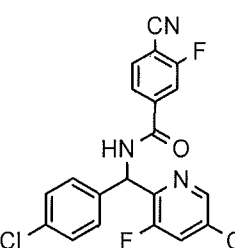
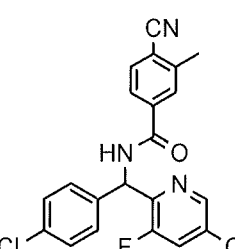
52691		>28	-	6.8	-	-
IB						
52692		>28	-	7.3	-	-
IB						
52693		>28	-	2.1	-	-
IB						
52694		>28	-	1.4	-	-
IB						
52695		>28	-	2.1	-	-
IB						

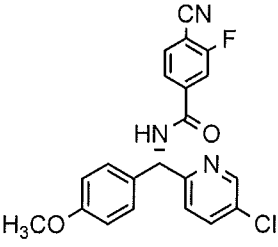
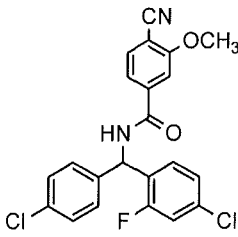
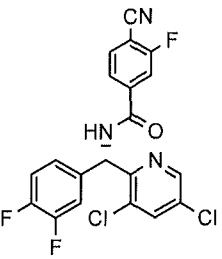
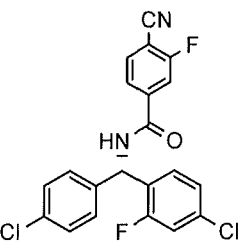
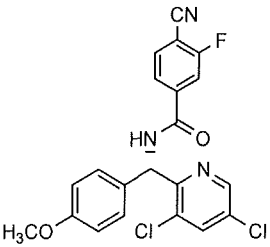
52696		>28	-	2.2	-	-
IB						
52697		>28	-	0.049	-	-
IB						
52698		4	-	0.063	-	-
IB						
52699		>28	-	0.447	-	-
IB						
52700		>28	-	0.627	-	-
IB						

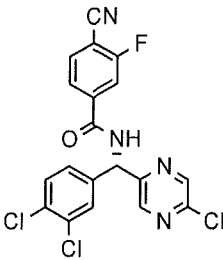
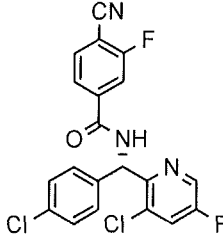
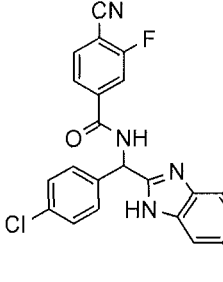
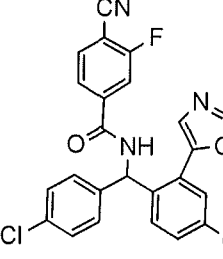
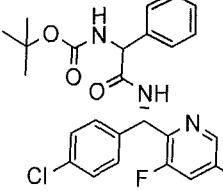
52702		>28	-	0.542	-	-
IB						
52703		>28	-	0.641	-	-
IB						
52705		4.7	-	0.048	-	-
IB						
52706		4.5	-	0.153	-	-
IB						
52707		26.2	-	0.511	-	-
IB						

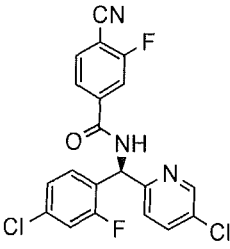
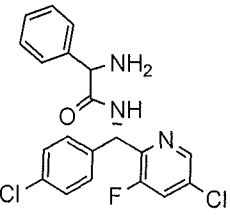
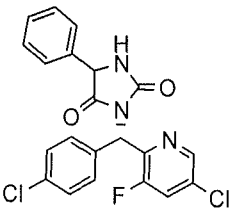
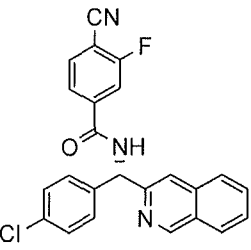
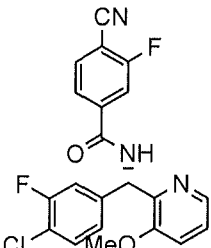
52708		>28	-	0.527	-	-
IB						
52709		3.7	-	0.035	-	-
IB						
52710		16.1	-	5.3	-	-
IB						
52711		5.3	-	0.04	-	-
IB						
52713		0.923	-	0.014	-	-
IC						

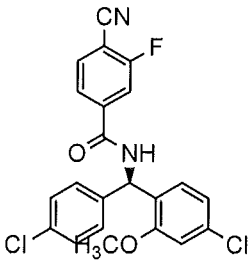
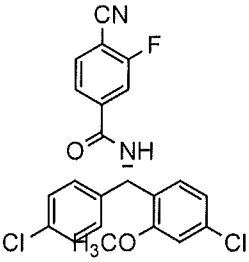
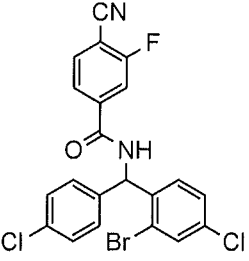
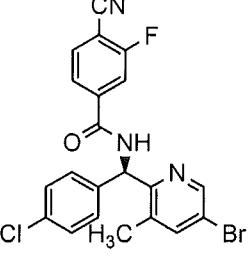
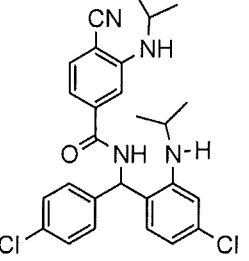
52715 IB		>28	-	1.6	-	-
52716 IB		0.21	-	0.018	-	-
52717 IB		12.7	-	0.096	-	-
52718 IB		0.86	-	0.006	-	-
5271IB	 isomer 1	>28	-	11.9	-	-

52720		5.1	-	0.211	-	-
IB	isomer 2					
52721		10	-	0.068	-	-
IB						
52722		2.6	-	0.057	-	-
IB						
52723		3.1	-	0.021	-	-
IB						
52724		1.3	-	0.033	-	-
IB						

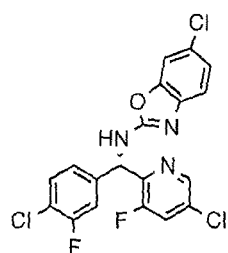
52725		>28	-	1.0	-	-
IB						
52726		22.3	-	2.0	-	-
IA						
52727		3.6	-	0.057	-	-
IB						
52728		>28	-	0.304	-	-
IA						
52729		27.4	-	0.151	-	-
IB						

52730 IB		9.5	-	0.039	-	-
52731 IB		22.1	-	0.231	-	-
52732 IB		0.886	-	1.1	-	-
52733 IA		>28	-	3.1	-	-
52734 IB		>28	-	1.5	-	-

52735		>28	-	20.4	-	-
IB						
52736		14.2	-	3.5	-	-
IB						
52737		13.5	-	12.1	-	-
IB						
52739		18.5	-	0.079	-	-
IB						
52740		10.1	-	0.927	-	-
IB						

52741		>28	-	0.396	-	-
IA						
52742		>28	-	0.342	-	-
IA						
52743		>28	-	0.33	-	-
IA						
52744		>28	-	0.349	-	-
IB						
52745		>28	-	2.2	-	-
IA						

52749



0.199

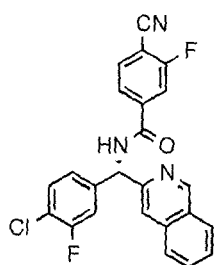
-

0.019

-

-

52750



4.3

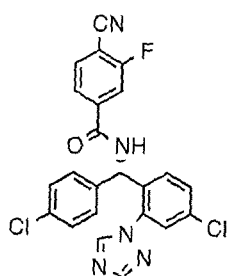
-

0.046

-

-

52751



>28

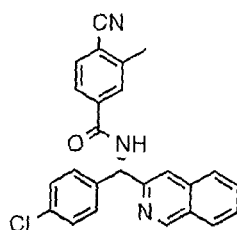
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4.4

-

-

52752



7.8

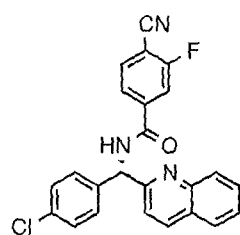
-

0.164

-

-

52754



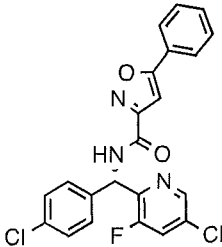
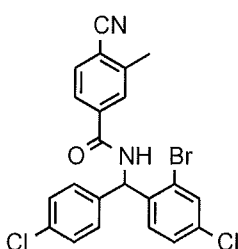
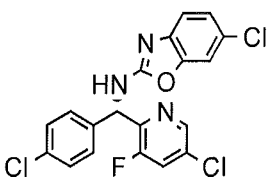
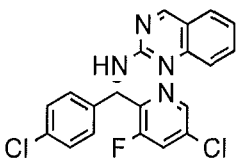
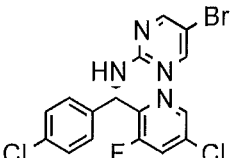
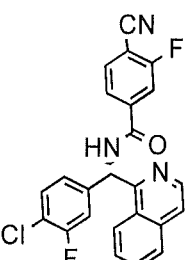
6.0

-

0.189

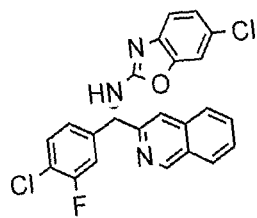
-

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52755		3.9	-	2.7	-	-
52756		>28	-	0.489	-	-
52759		0.352	-	0.027	-	-
52760		>28	-	0.439	-	-
52761		1.5	-	0.133	-	-
52763		3.0	-	0.682	-	-

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52764



4.3

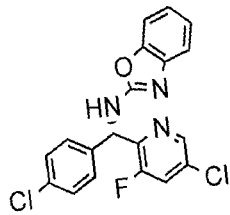
-

0.251

-

-

52766



1.6

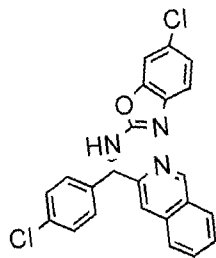
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0.112

-

-

52767



15.4

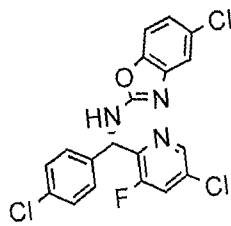
-

0.445

-

-

52768



1.2

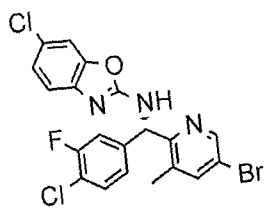
-

0.088

-

-

52770



0.636

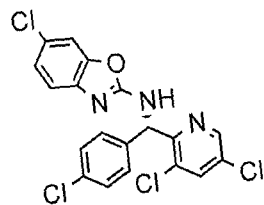
-

0.040

-

-

52771



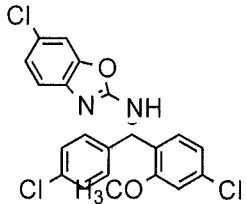
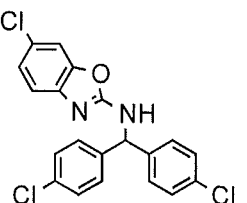
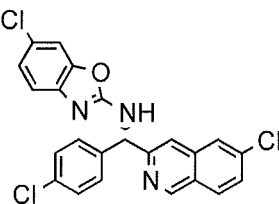
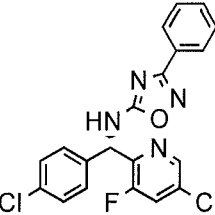
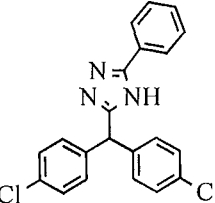
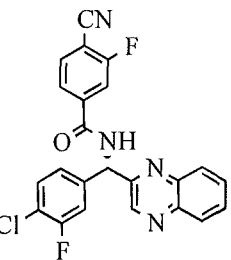
0.268

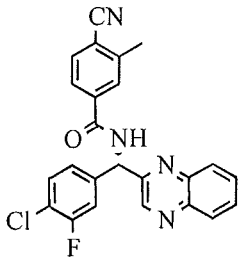
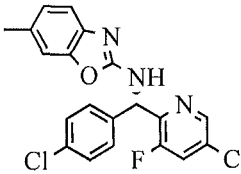
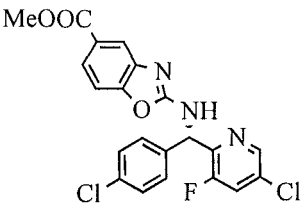
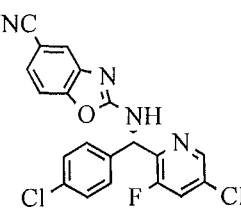
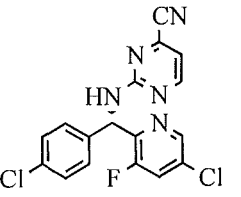
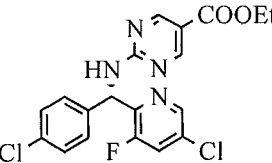
-

0.036

-

-

52772		>28	-	1.2	-	-
52773		>28	-	0.485	-	-
52774		>28	-	1.1	-	-
52776		0.858	-	3.5	-	-
52777		3.2	-	3.2	-	-
52780		5.6	-	0.091	-	-

52781		0.939	-	0.105	-	-
52782		1.5	-	0.105	-	-
52783		0.537	-	0.048	-	-
52784		0.088	-	0.030	-	-
52785		9.2	-	2.4	-	-
52786		5.8	-	0.540	-	-

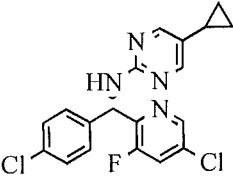
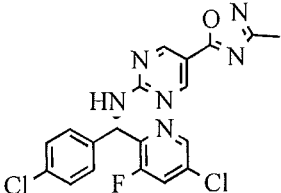
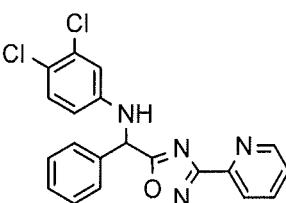
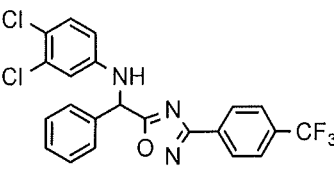
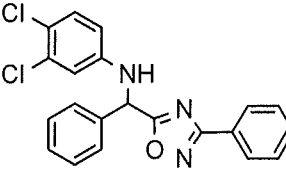
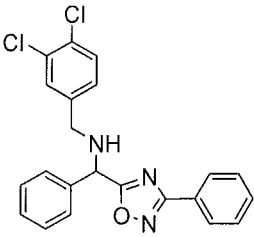
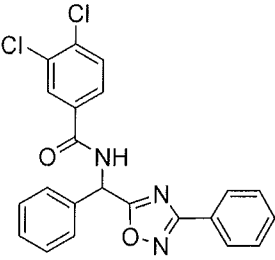
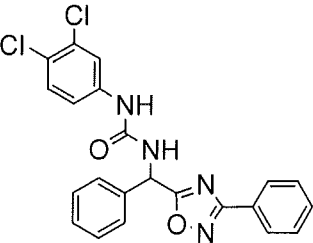
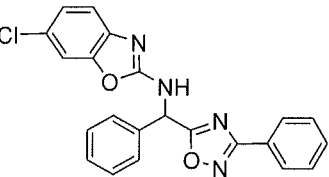
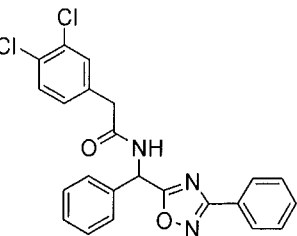
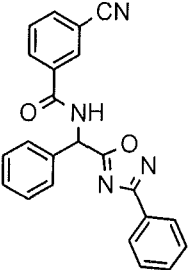
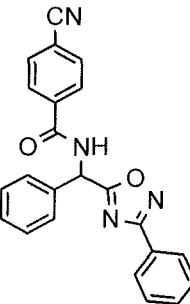
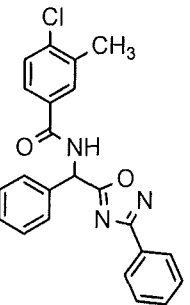
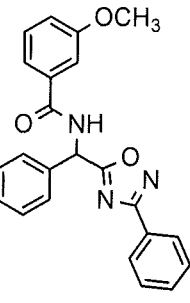
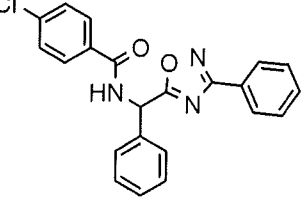
52787		14.3	-	0.438	-	-
52789		3.8	-	0.451	-	-

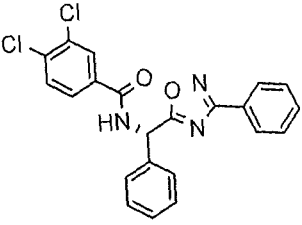
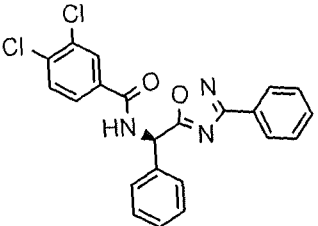
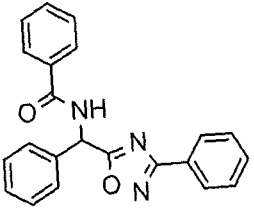
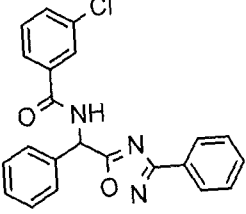
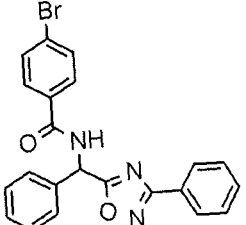
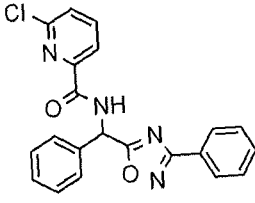
Table 3:

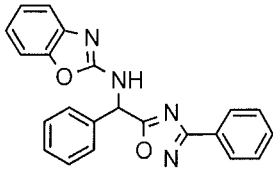
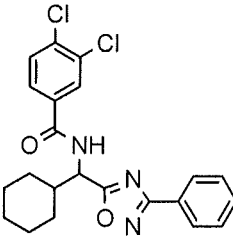
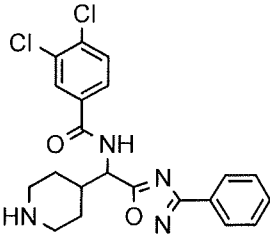
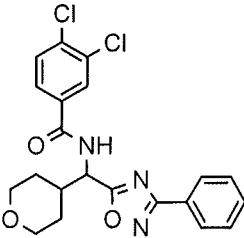
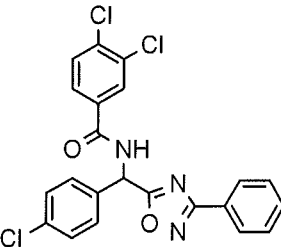
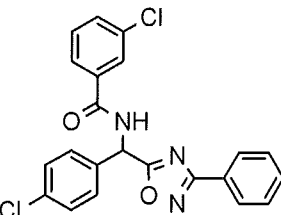
CYM	Structure	S1P1 AA IC ₅₀ μM	S1P2 AA IC ₅₀ μM	S1P3AA IC ₅₀ μM	S1P4AA IC ₅₀ μM	S1P5AA IC ₅₀ μM
Generic formula						
52167 IB		-	-	0.7	5.2	-
52205 IB		-	-	4.3	34	-
52207 IB		-	-	1.3	30.4	-

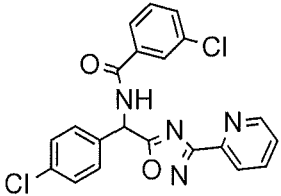
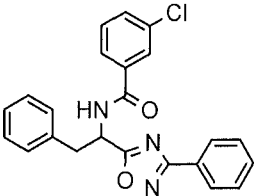
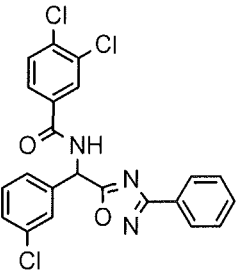
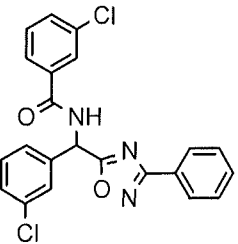
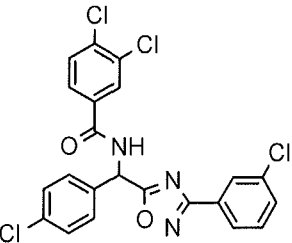
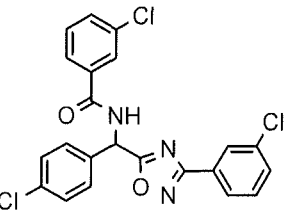
52304		7.9	>50	1.2	7.8	21.8
IB						
52305		1.6	>50	0.521	>50	>50
IB						
52306		0.881	2.8	0.586	2.6	5.1
IB						
52307		-	>50	0.899	>50	-
IC						
52308		>50	>50	3.9	>50	>50
IB						

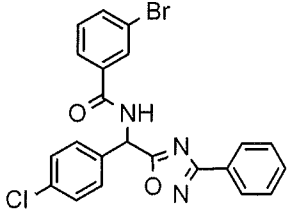
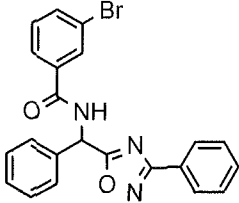
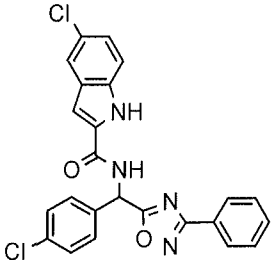
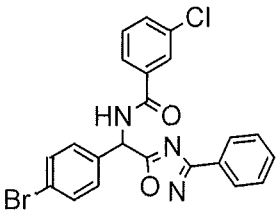
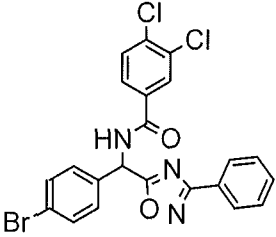
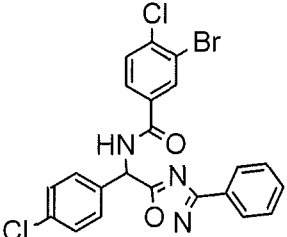
52310		-	>50	3.5	>50	-
IB						
52311		-	>50	2.3	30.2	-
IB						
52312		-	>50	3.1	>50	-
IB						
52313		-	>50	2.2	>50	-
IB						
52321		-	>50	2.4	39.7	>50
IB						

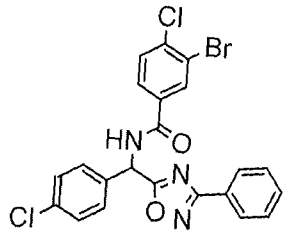
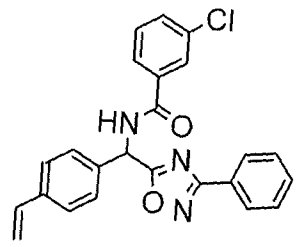
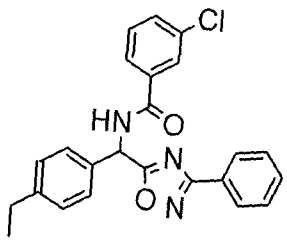
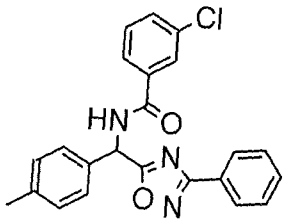
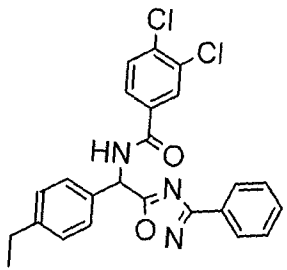
WO 2016/053855

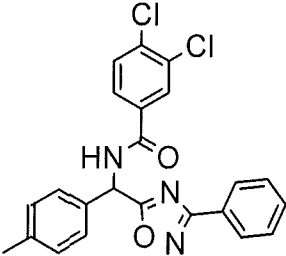
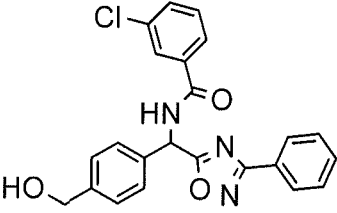
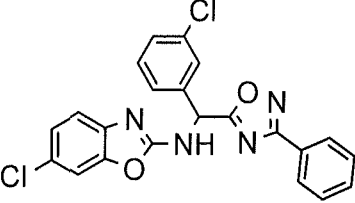
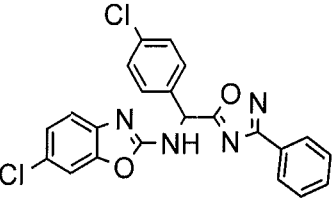
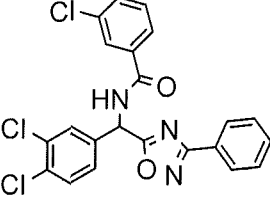
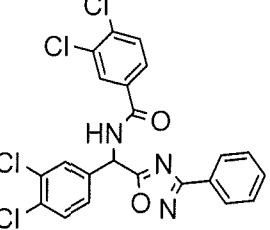
52325	IB		-	>50	2.8	>50	-
52326	IB		-	>50	3.4	>50	-
52333	IB		-	>50	3.8	>50	-
52335	IB		1.6	>50	0.415	>50	>50
52336	IB		-	>50	1.7	>50	-
52337	IC		7.3	>50	2.8	>50	25.1

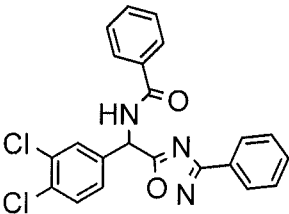
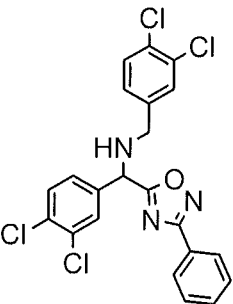
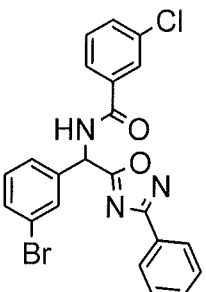
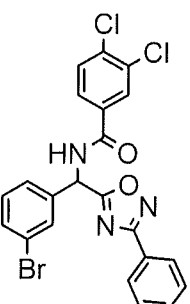
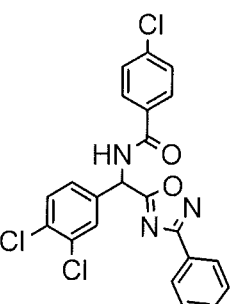
52339		-	23.4	1.2	5.9	-
IC						
52341		1.8	>50	3.3	>50	>50
IB						
52346		-	5.2	5.7	5.1	-
IB						
52357		2.1	>50	2.8	12.9	>50
IB						
52364		17.5	>50	0.368	>50	>50
IB						
52365		>50	>50	0.214	14.3	>50
IB						

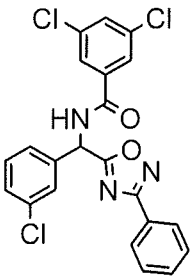
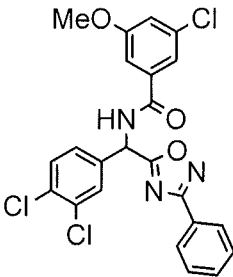
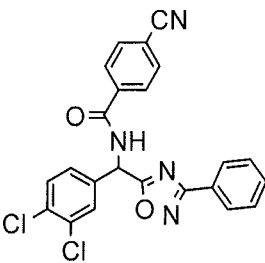
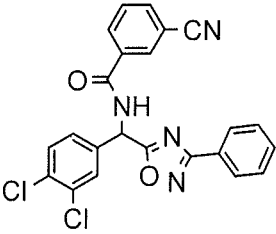
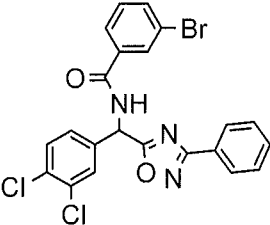
52379		>50	>50	2.9	>50	>50
IB						
52386		>50	43.7	5.7	21.6	12.4
IB						
52387		0.392	>50	0.229	>50	>50
IB						
52388		0.456	>50	0.104	5.2	5.1
IB						
52389		-	>50	5.3	>50	-
IB						
52390		>50	>50	1.1	>50	>50
IB						

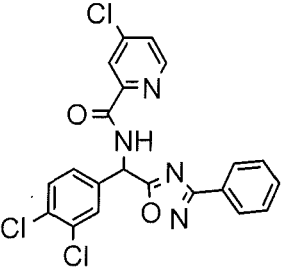
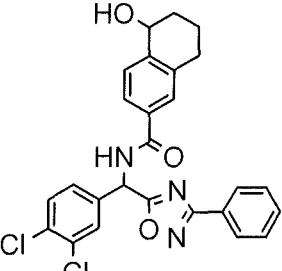
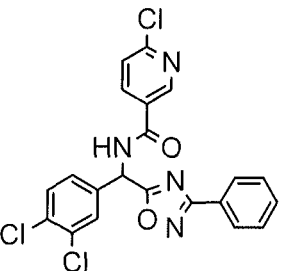
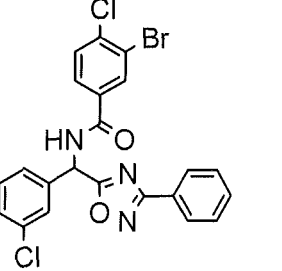
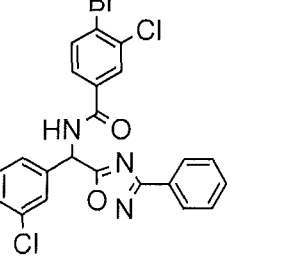
52391		9.5	>50	0.278	30.5	16.1
IB						
52392		0.564	>50	0.108	>50	>50
IB						
52393		-	>50	6.4	>50	-
IC						
52401		-	>50	0.226	21.2	-
IB						
52402		>50	>50	0.214	>50	>50
IB						
52403		10.1	>50	0.39	>50	>50
IB						

52404						
IB		-	>50	0.376	37.9	-
52405						
IB		-	>50	2.0	>50	-
52406						
IB		>50	>50	0.406	>50	>50
52407						
IB		4.0	>50	0.219	>50	39.4
52408						
IB		-	>50	0.898	>50	-

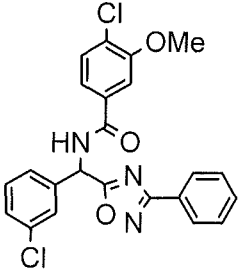
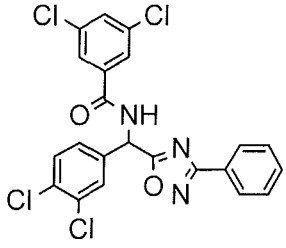
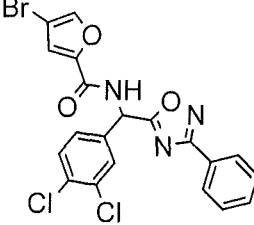
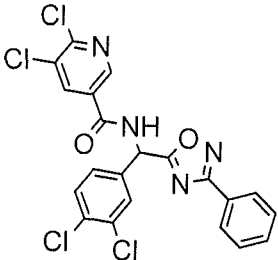
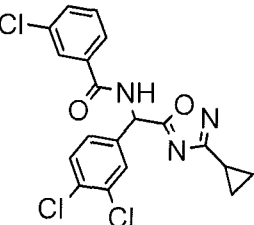
52409		-	>50	0.381	>50	-
IB						
52412		-	>50	3.7	24.2	-
IB						
52415		-	>50	0.556	25.4	-
IC						
52416		-	>50	0.411	22.2	-
IC						
52419		0.823	>50	0.053	34.6	20
IB						
52420		0.426	>50	0.066	>50	>50
IB						

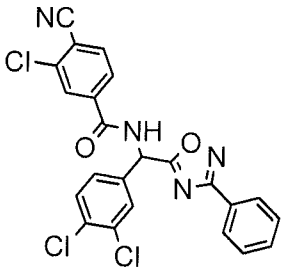
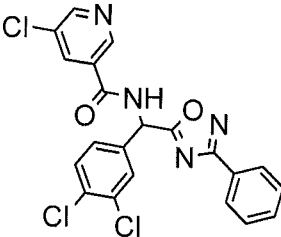
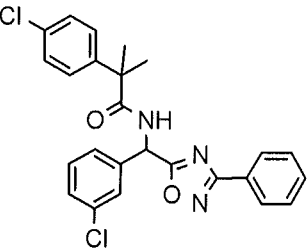
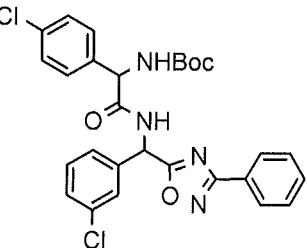
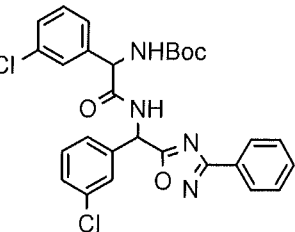
52421		2.7	>50	0.211	>50	>50
IB						
52426		-	>50	2.15	>50	-
IB						
52427		-	>50	0.111	17.5	-
IB						
52428		-	>50	0.198	23.3	-
IB						
52429		1.2	>50	0.076	38.5	16.2
IB						

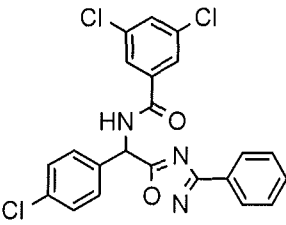
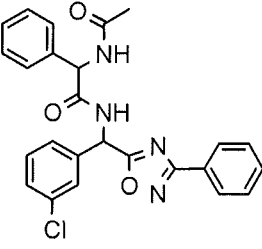
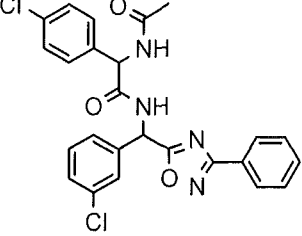
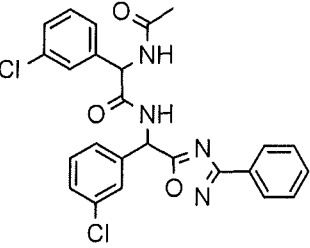
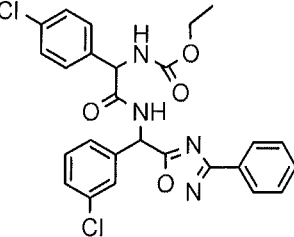
52430		0.112	>50	0.033	>50	>50
IB						
52436		-	>50	0.264	>50	-
IB						
52438		9.6	>50	0.32	3.1	17.1
IB						
52439		-	>50	0.584	44.8	-
IB						
52440		-	>20	0.086	>50	-
IB						

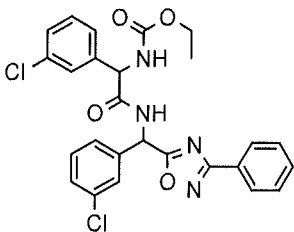
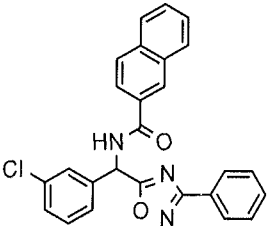
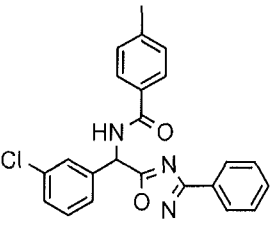
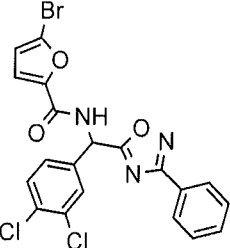
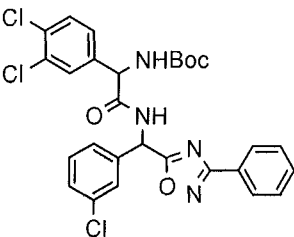
52441		-	>30	2.5	20.3	-
IB						
52445		-	>50	1.5	17.1	-
IB						
52446		-	22.7	0.370	9.2	-
IC						
52447		-	>50	0.26	>50	-
IB						
52449		-	>50	0.219	16.3	-
IB						

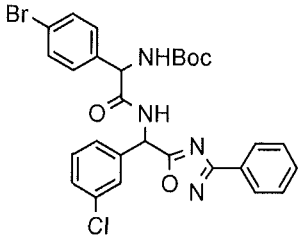
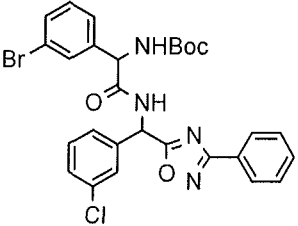
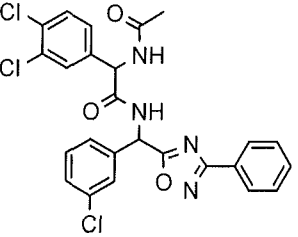
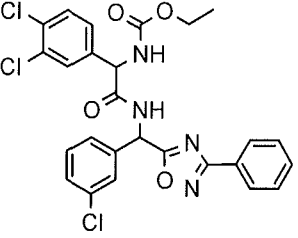
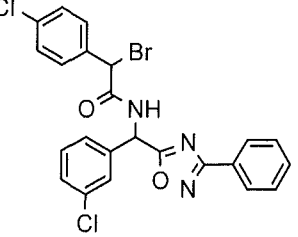
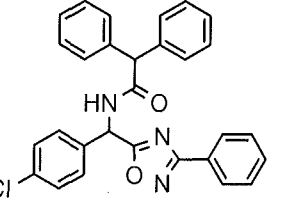
52450		-	>50	0.184	19.2	-
IB						
52451		-	8.7	0.475	>50	-
IB						
52453		-	10.9	0.215	6.7	-
IB						
52454		-	>50	0.24	>50	-
IB						
52455		-	>50	0.091	12.4	-
IB						

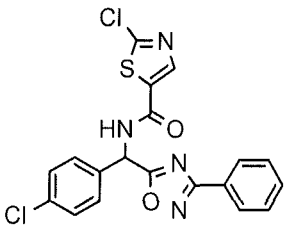
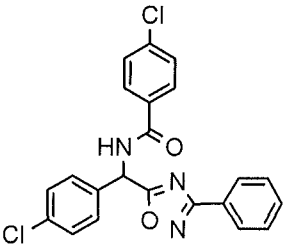
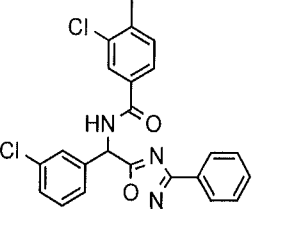
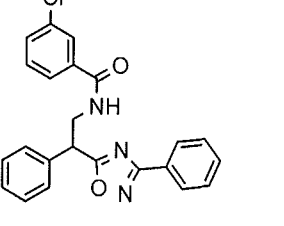
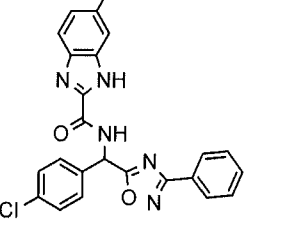
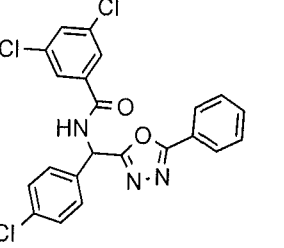
52456		-	>50	0.201	38.4	-
IB						
52457		-	>50	0.06	>50	-
IB						
52461		-	>50	0.045	19.9	-
IC						
52462		-	35	6.6	42.3	29.5
IC						
52463		-	43.1	0.341	15.5	-
IB						

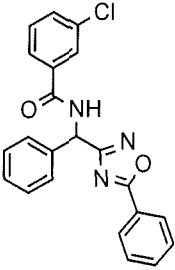
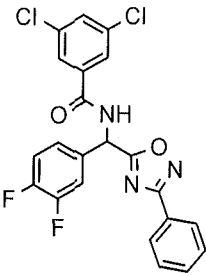
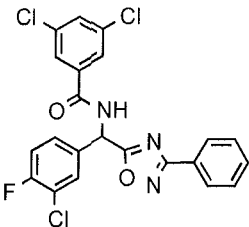
52465 IB		-	44.5	0.175	8.6	-
52466 IC		-	>50	1.1	28.7	-
52469 IB		6.2	10.5	1.4	15.7	-
52470 IB		20.1	>50	0.382	>50	-
52471 IB		0.475	31.1	0.214	>50	-

52472		>28	>50	0.113	>50	-
IB						
52473		>28	>50	1.7	>50	-
IB						
52477		>28	>50	3.2	>50	-
IB						
52478		17.9	>50	1.1	>50	-
IB						
52479		1.2	>50	0.31	>50	-
IB						

52480		0.39	>50	0.147	>50	-
IB						
52481		1.5	>50	0.425	>50	-
IB						
52482		3.5	>50	0.319	>50	-
IB						
52485		3.5	>50	0.984	>50	-
IC						
52498		34.3	-	0.166	-	-
IB						

52499		40.5	-	0.429	-	-
IB						
52500		0.959	-	0.095	-	-
IB						
52501		22.2	-	0.839	-	-
IB						
52502		1.4	-	0.109	-	-
IB						
52503		0.527	-	0.147	-	-
IB						
52515		>50	-	0.685	-	-
IB						

52518	IC		9.8	-	1.5	-	-
52519	IB		>50	-	0.194	-	-
52532	IB		2.0	-	0.405	-	-
52534	IB		8.4	-	2.2	-	-
52536	IC		>50	-	4.9	-	-
52569	IB		>28	-	2.2	-	-

52636		1.9	-	0.098	-	-
IB						
52648		0.401	-	0.046	-	-
IB						
52588		0.392	-	0.047	-	-
IB						

Boc = t-butoxycarbonyl

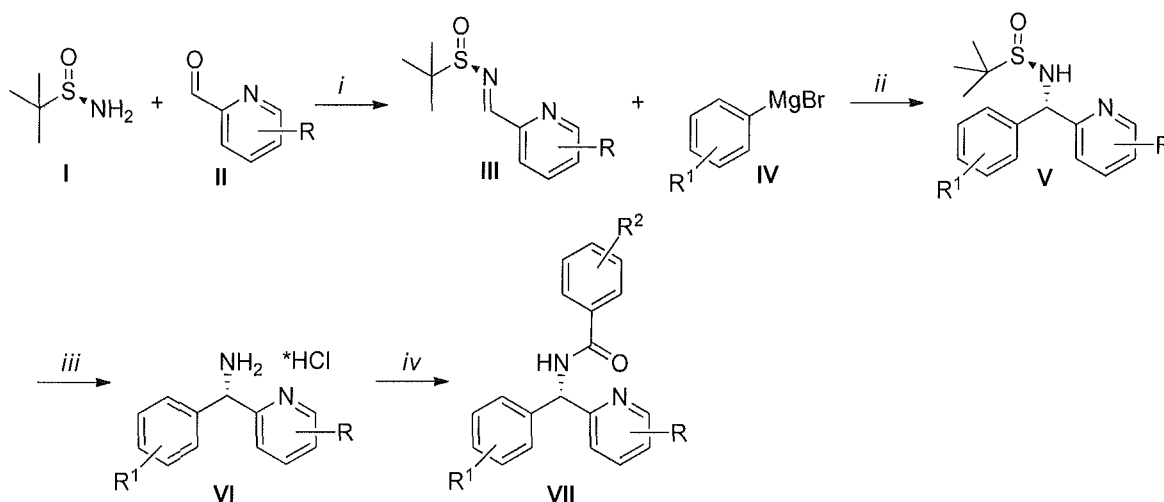
Ph = phenyl

Rac = racemate; all compounds as shown include all stereoisomers unless otherwise indicated.

Isomer 1, isomer 2; indicates separated stereoisomers of a structure, but absolute configuration

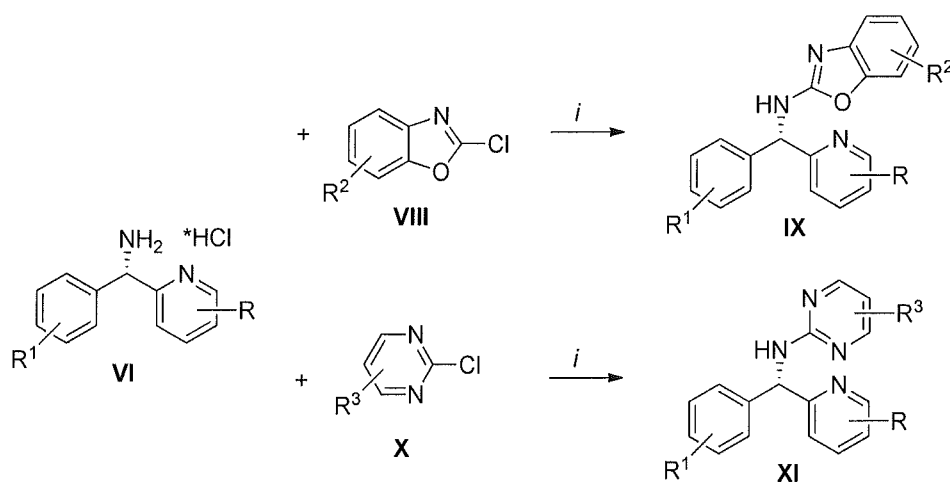
5 unstated.

General synthetic schemes:



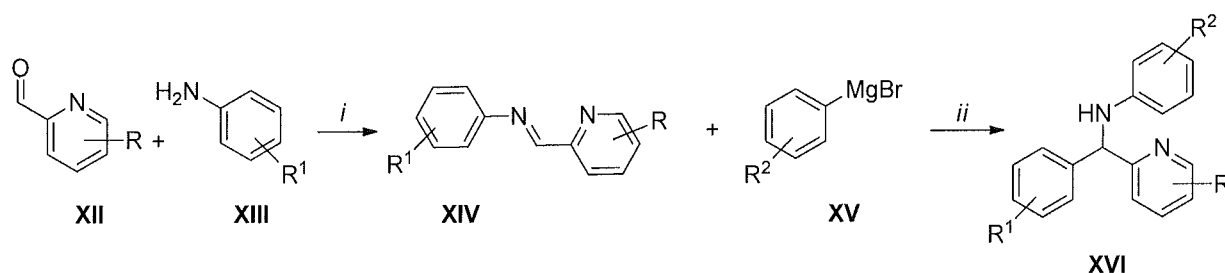
Reagents and conditions: *i*) **I** (1.2 equiv.), **II** (1 equiv.), Ti(OEt)₄, 70°C, 30 min; *ii*) **III** (1 equiv.), **IV** (3 equiv.), -78°C, 2h; *iii*) HCl (2 equiv.), MeOH, rt, 30 min; *iv*) **VI** (1 equiv.), carboxylic acid derivative (1.2 equiv.), EDCI (1.2 equiv.), HOBT (1.2 equiv.), DIPEA (1.2 equiv.), CH₂Cl₂, rt, 2h.

A mixture of **I**, **II** and Ti(OEt)₄ in a sealed tube was heated at 70°C for 30min. The mixture was dissolved in EtOAc and washed with brine. The organic phase was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The product **III** was used without further purification. To a solution of **III** in THF at -78°C was slowly added aryl magnesium bromide **IV** and the reaction was stirred for 2h. The mixture was quenched with a saturated solution of ammonium chloride and the product extracted with EtOAc. The organic phase was dried over anhydrous Na₂SO₄ and concentrated in vacuo, followed by the purification of product **V** by column chromatography (CC) using hexanes/EtOAc. To a solution of **V** in MeOH was added a 4M solution of HCl in dioxane and the reaction was stirred for 30 min at room temperature (rt). The mixture was concentrated under reduced pressure and the product **VI** used without further purification. A solution of **VI**, the appropriated carboxylic acid, EDCI, HOBT and DIPEA in dichloromethane was stirred at rt for 2h. The mixture was concentrated under reduced pressure and the product **VII** purified by HPLC.



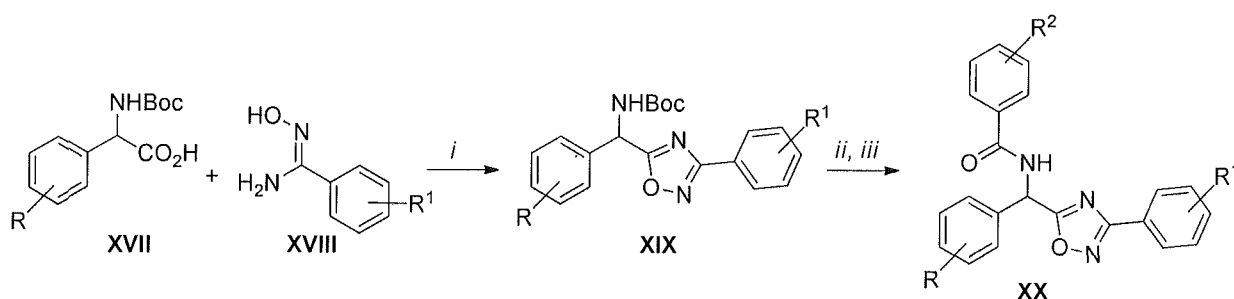
Reagents and conditions: *i*) **VI** (1 equiv.), **VIII** (1.1 equiv.) or **X** (1.1 equiv.), DIPEA (2 equiv.), EtOH, MW, 130°C, 30 min.

A mixture of the appropriate aryl chloride (**VIII** or **X**), **VI** and DIPEA in EtOH was heated with microwave irradiation at 130°C for 30 minutes to afford the corresponding products (**IX** or **XI**) that were purified by HPLC.



Reagents and conditions: *i*) **XII** (1 equiv.), **XIII** (1 equiv.), HCO₂H (cat.), EtOH, 60°C, overnight; *ii*) **XIV** (1 equiv.), **XV** (1 equiv.), THF, 0°C to rt, overnight

A mixture of **XII**, **XIII** and catalytic amount of formic acid in EtOH was heated at 60°C overnight. The crude was concentrated and purified by CC using hexanes/EtOAc. To a solution of **XIV** in THF at 0°C was added dropwise a solution of **XV** in Et₂O; the reaction mixture was stirred overnight at rt. The mixture was quenched with a saturated solution of ammonium chloride and the product extracted with EtOAc. The organic phase was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The product **XVI** was purified by CC using hexanes/EtOAc or HPLC.

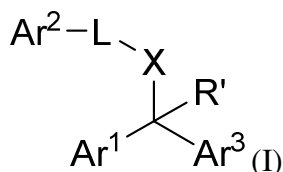


Reagents and conditions: *i*) **XVII** (1 equiv.), **XVIII** (1.2 equiv.), EDCI (1.2 equiv.), HOBt (1.2 equiv.), dioxane, MW, 110°C, 30 min; *ii*) **XIX** (1 equiv.), TFA (20 equiv.), CH₂Cl₂, rt, 20 min; *iii*) carboxylic acid derivative (1.2 equiv.), EDCI (1.2 equiv.), HOBt (1.2 equiv.), DIPEA (1.2 equiv.), CH₂Cl₂, rt, 2h.

In a microwave vial a stirring solution of **XVII** in dioxane was treated with HOBt and EDCI at rt. The reaction was stirred for 10 minutes followed by the addition of **XVIII**. The reaction was stirred for additional 30 minutes at rt, then heated to 110°C under microwave irradiation for 30 minutes. To the reaction was added brine and the product was extracted with EtOAc (3X). The organic phase was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The product **XIX** was purified by CC using hexanes/EtOAc. A solution of **XIX** in dichloromethane was stirred with TFA at rt for 20 minutes. The mixture was concentrated under reduced pressure and the product used without further purification. A solution of the TFA salt, the appropriate carboxylic acid, EDCI, HOBt and DIPEA in dichloromethane was stirred at rt for 2h. The mixture was concentrated under reduced pressure and the product **XX** purified by HPLC.

CLAIMS

1. Use of a compound of formula (I) for the manufacture of a medicament for treating a chronic obstructive pulmonary disease, sepsis, coronary atherosclerosis, bronchoconstriction, pulmonary fibrosis, coronary artery constriction, cytokine amplification by dendritic cells, or the generation of disseminated intravascular coagulopathy, inflammation by influenza infection, cardiovascular disease, hypertension (including malignant hypertension), angina, myocardial infarction, cardiac arrhythmias, congestive heart failure, coronary heart disease, atherosclerosis, angina pectoris, dysrhythmias, cardiomyopathy (including hypertrophic cardiomyopathy), heart failure, cardiac arrest, bronchitis, cystic fibrosis, croup, emphysema, pleurisy, pulmonary fibrosis, pneumonia, pulmonary embolus, pulmonary hypertension, mesothelioma, ventricular conduction abnormalities, complete heart block, adult respiratory distress syndrome, sepsis syndrome, idiopathic pulmonary fibrosis, or systemic sclerosis in a patient, wherein the compound of formula (I) is



wherein

Ar^1 is a phenyl optionally substituted with up to three substituents selected from the group consisting of (C₁-C₄)alkyl, halo, halo(C₁-C₄)alkyl, OH, and (C₁-C₄)alkoxy;

Ar^2 is phenyl or pyridyl, wherein Ar^2 is optionally substituted with up to three substituents selected from the group consisting of halo, cyano, (C₁-C₄)alkoxy, (C₁-C₆)alkoxycarbonyl(CH₂)₀₋₂, halo(C₁-C₄)alkyl, OH, monohydroxy(C₁-C₄)alkyl, NR₂C(=O)(CH₂)₀₋₂O(CH₂)₀₋₂, NR₂C(=O)(CH₂)₀₋₂, (C₁-C₄)C(=O)N(R), (5- to 10-membered)heterocyclyl, (5- to 10-membered) heteroaryl; and

Ar^3 is pyridyl optionally substituted with up to three substituents selected from the group consisting of (C₁-C₄)alkyl, (C₂-C₄)alkenyl, halo, halo(C₁-C₄)alkyl, OH, (C₁-C₄)alkoxy, (C₁-C₆)alkoxycarbonyl(CH₂)₀₋₂, carboxy(CH₂)₀₋₂, monohydroxy(C₁-C₄)alkyl, NR₂(CH₂)₀₋₂, and (C₃-C₁₀)cycloalkyl;

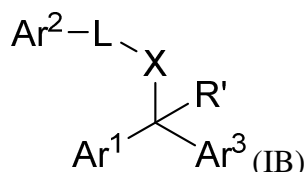
each R is independently H or (C₁-C₄)alkyl;

R' is H;

X is N(R); and

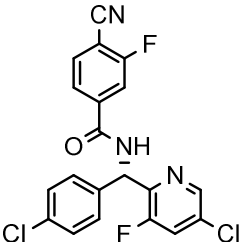
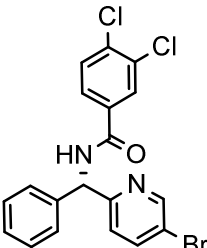
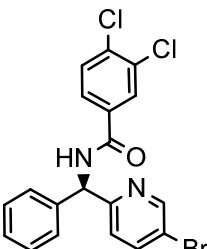
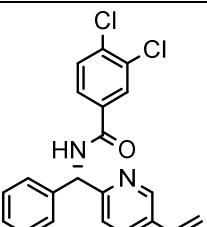
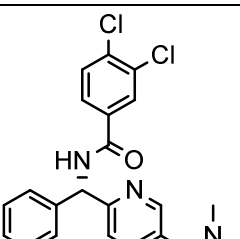
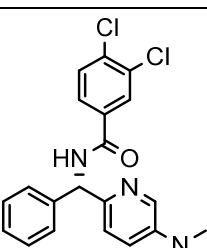
L is C(=O).

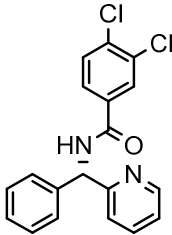
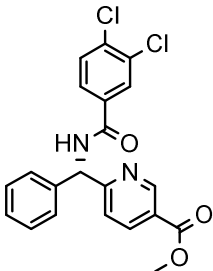
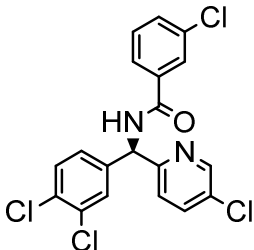
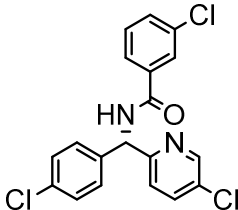
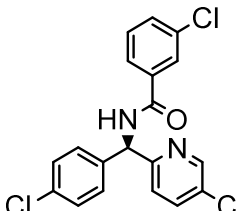
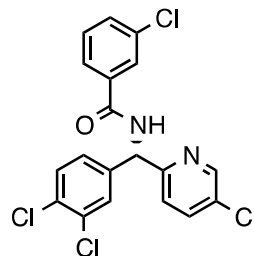
2. The use of claim 1, wherein the compound of formula (I) is a compound of formula (IB)

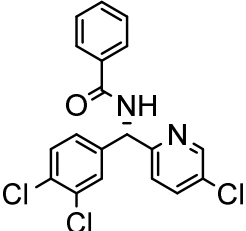
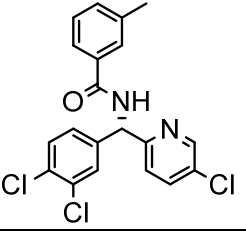
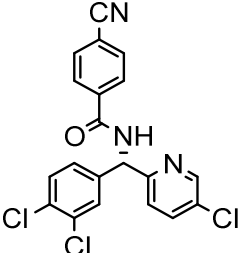
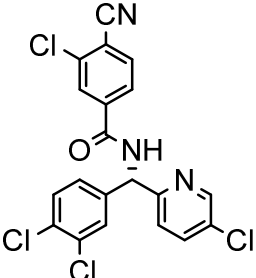
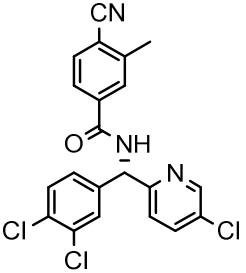
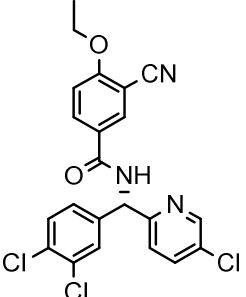


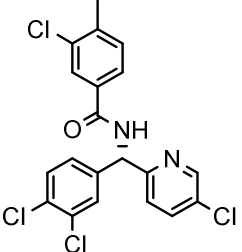
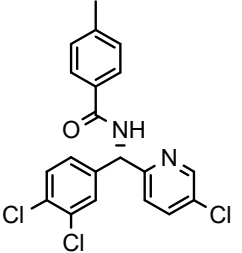
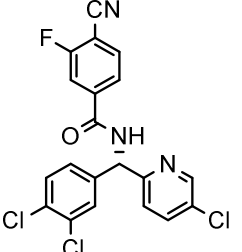
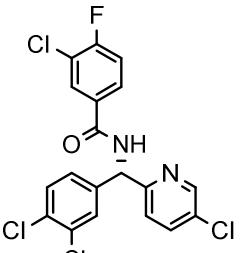
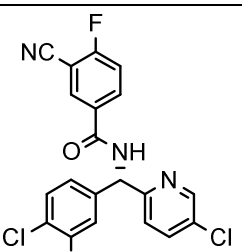
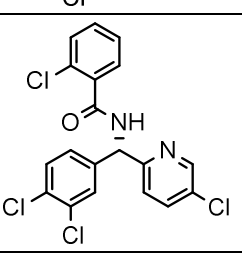
wherein Ar¹ and Ar² are phenyl.

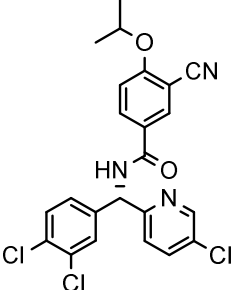
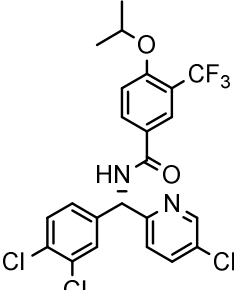
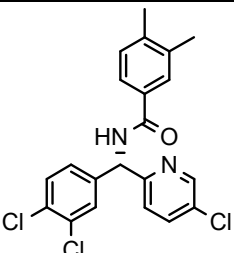
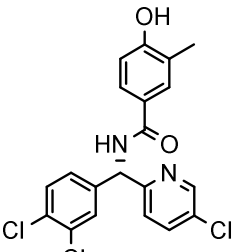
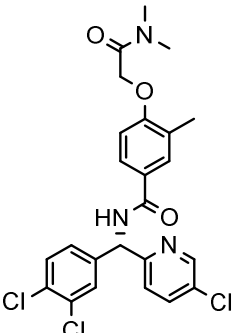
3. The use of claim 1, wherein the compound is selected from the following table:

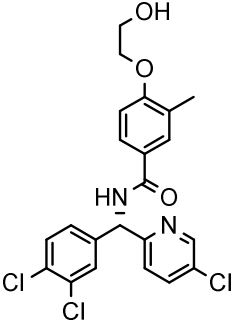
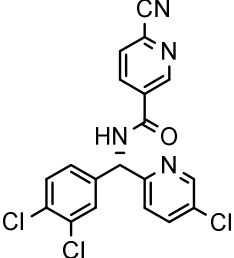
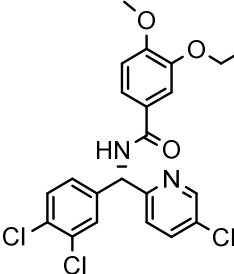
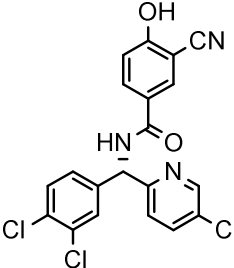
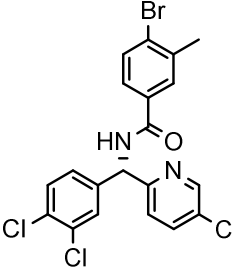
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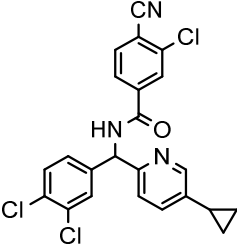
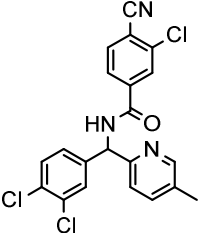
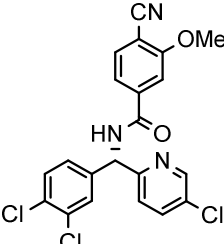
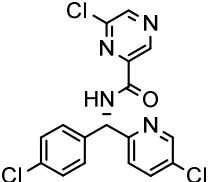
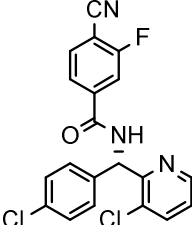
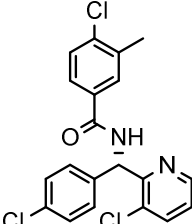
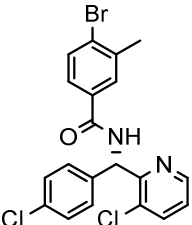
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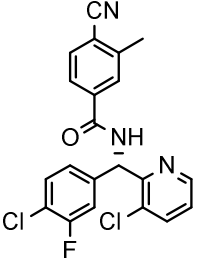
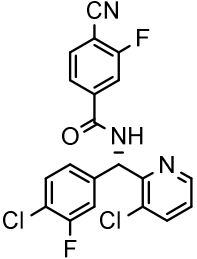
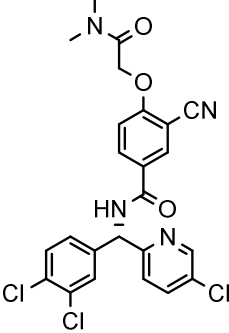
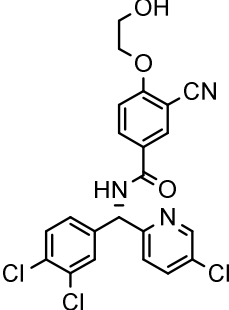
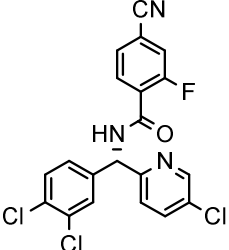
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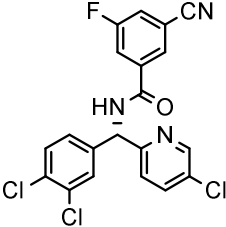
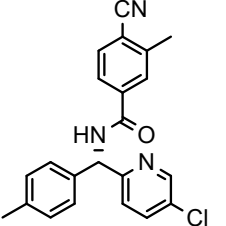
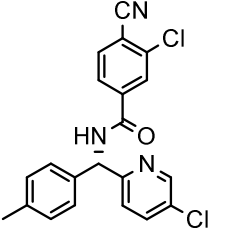
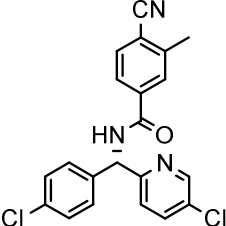
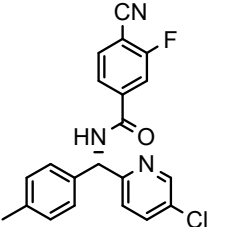
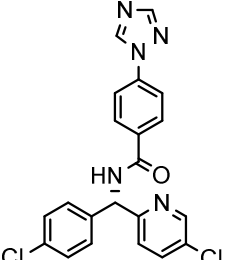
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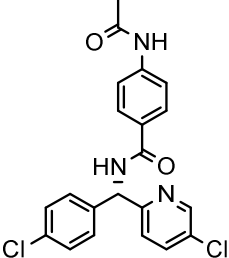
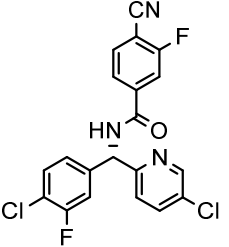
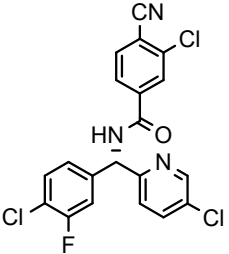
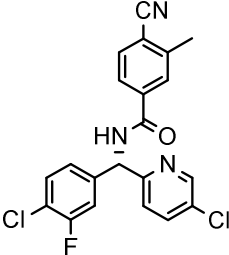
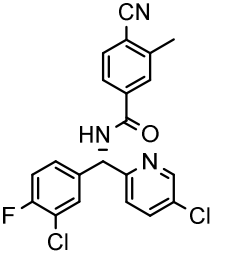
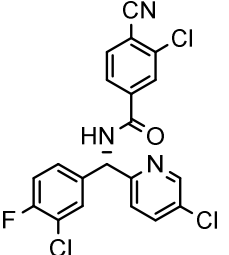
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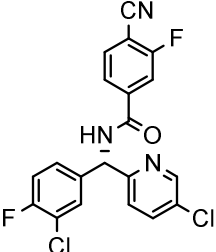
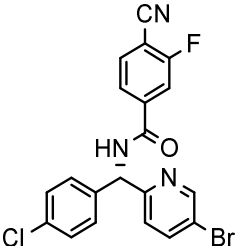
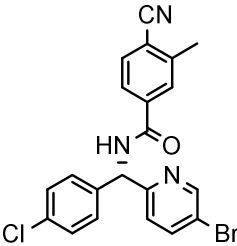
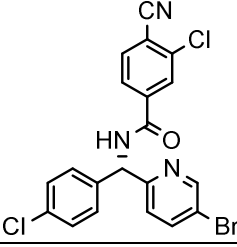
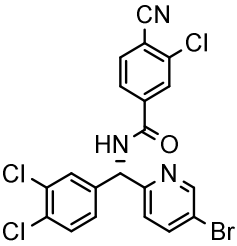
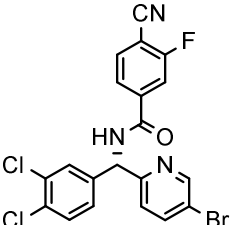
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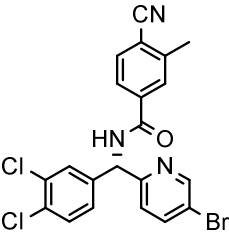
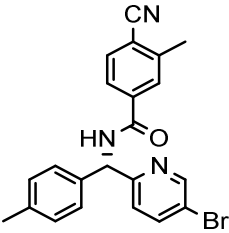
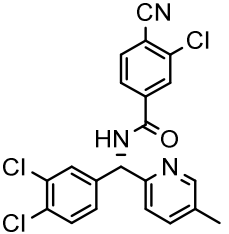
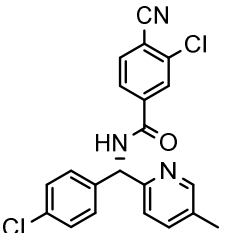
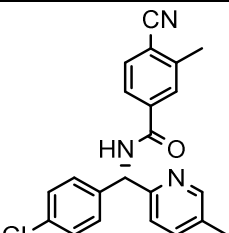
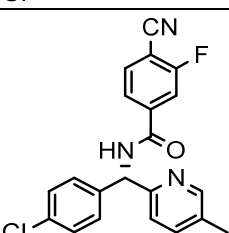
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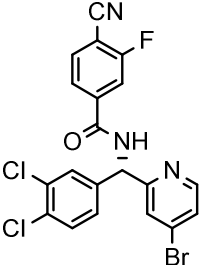
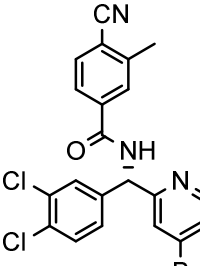
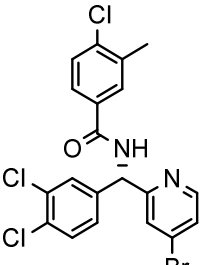
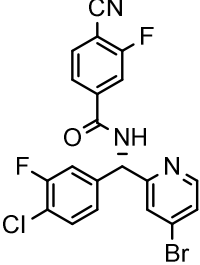
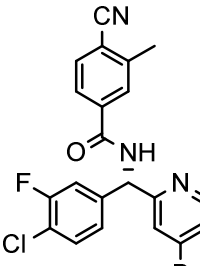
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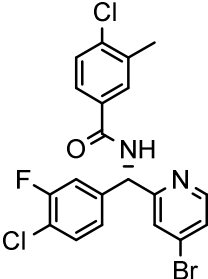
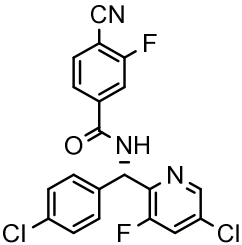
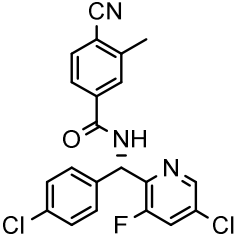
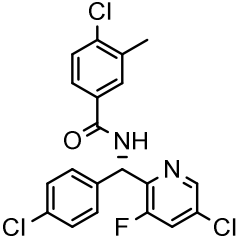
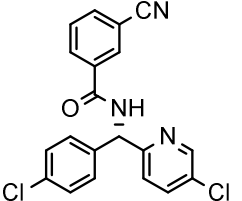
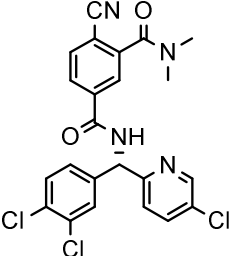
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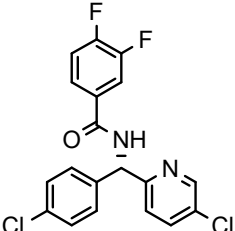
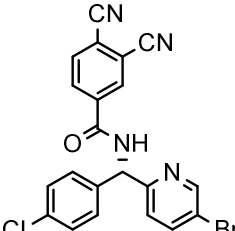
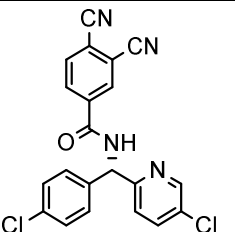
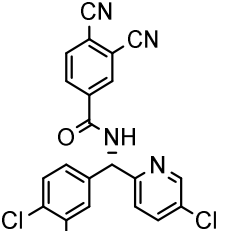
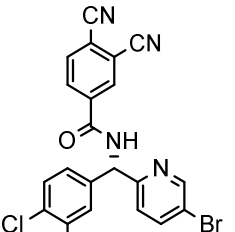
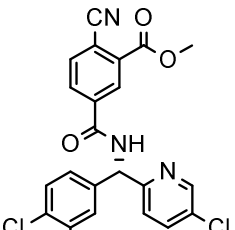
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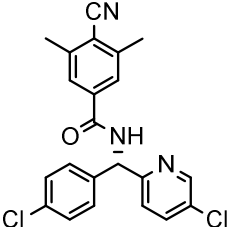
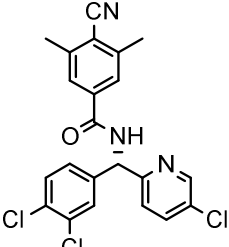
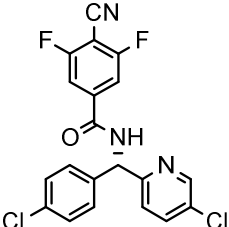
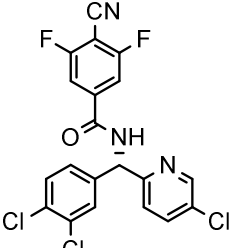
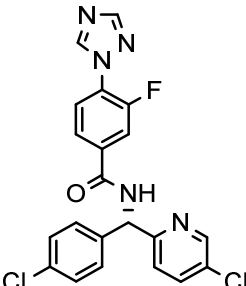
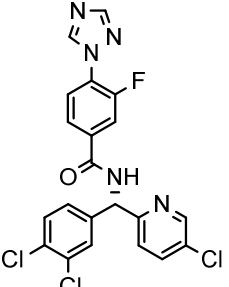
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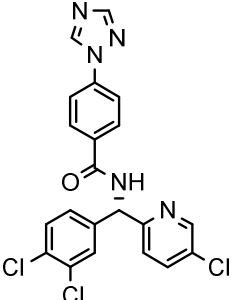
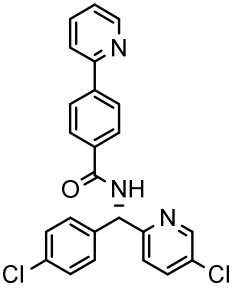
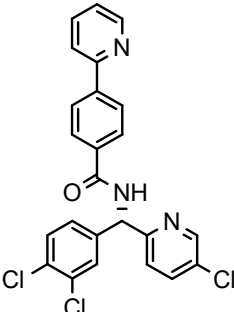
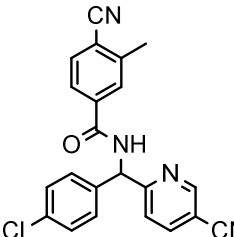
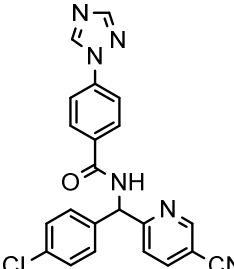
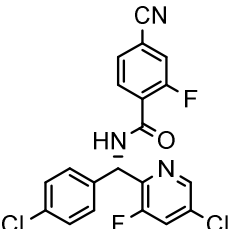
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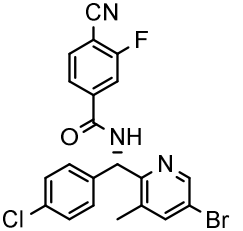
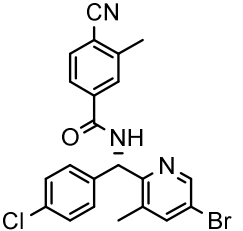
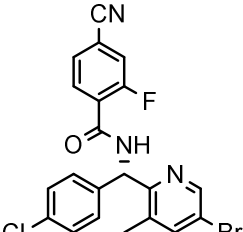
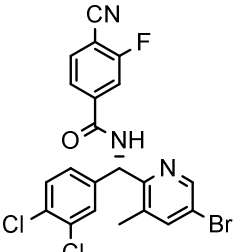
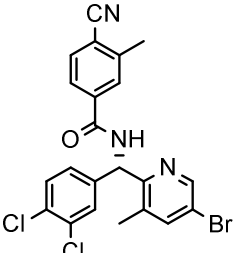
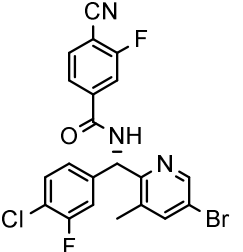
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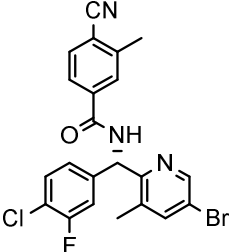
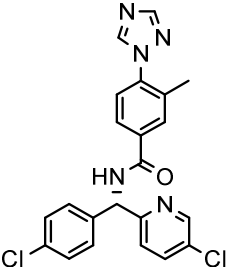
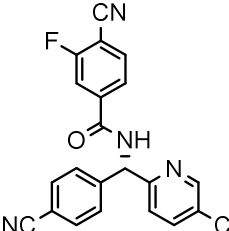
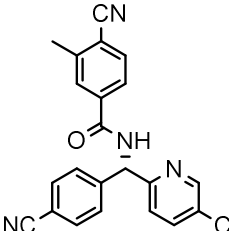
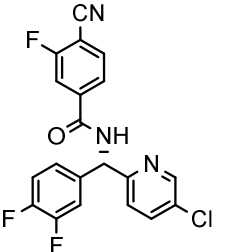
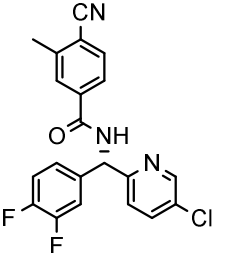
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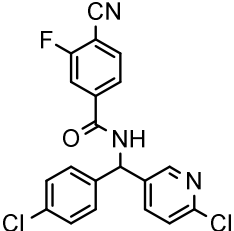
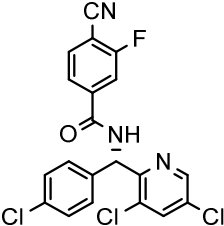
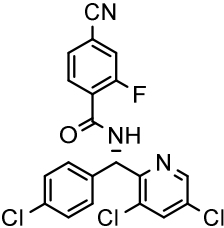
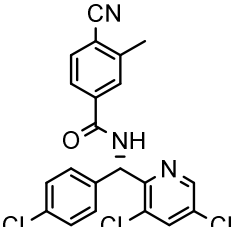
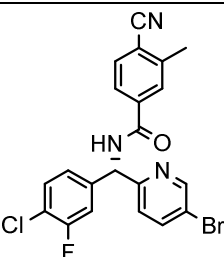
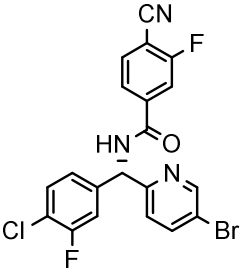
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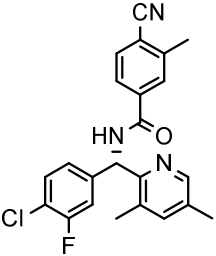
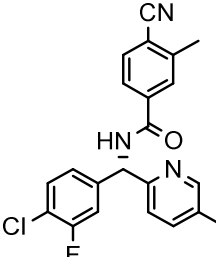
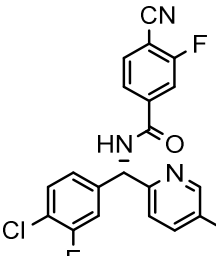
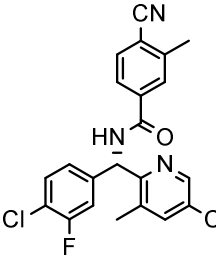
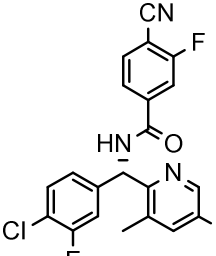
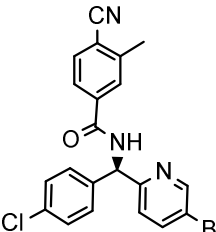
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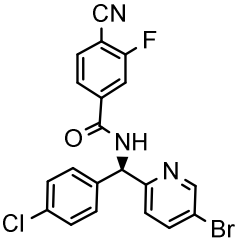
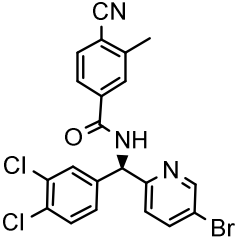
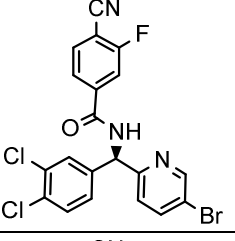
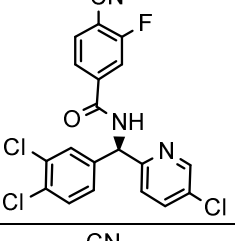
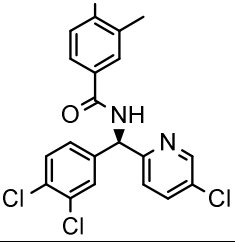
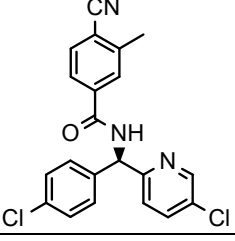
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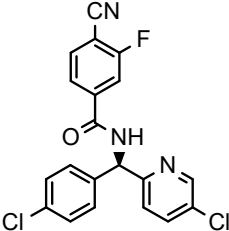
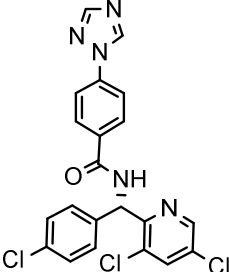
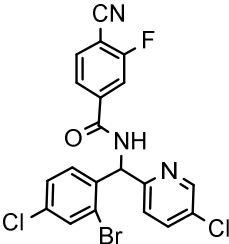
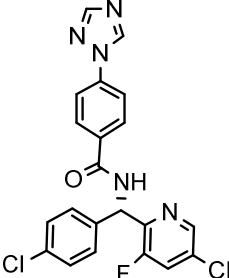
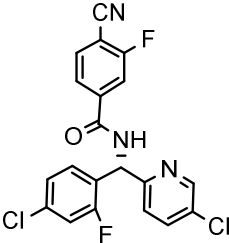
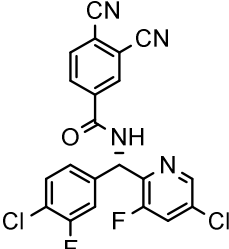
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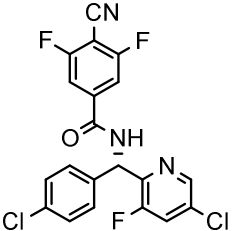
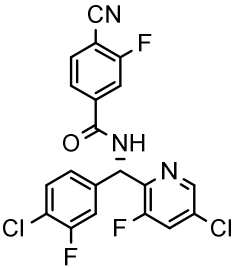
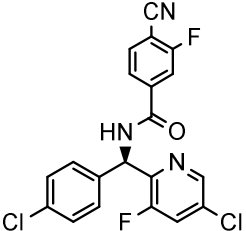
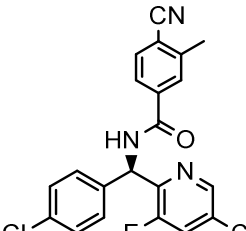
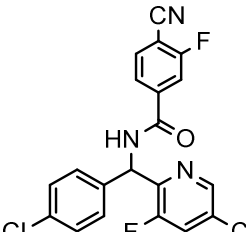
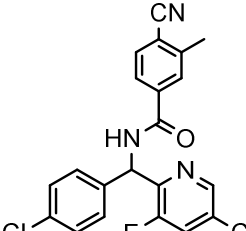
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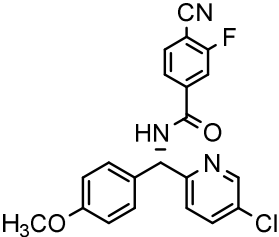
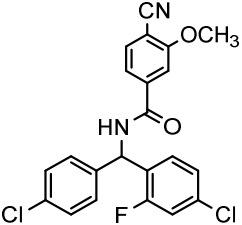
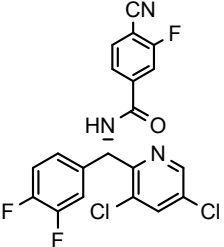
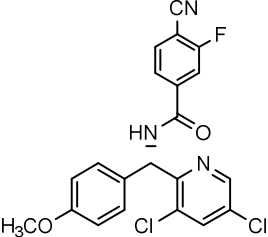
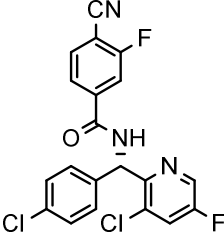
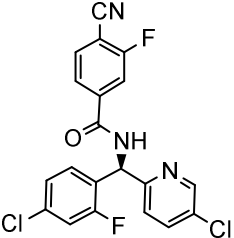
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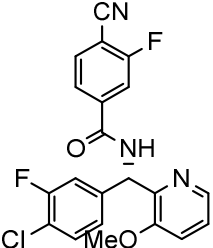
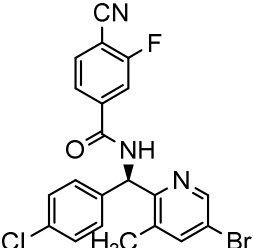
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4. The use of claim 1, wherein the disease is a chronic obstructive pulmonary disease.
5. The use of claim 1, wherein the disease comprises sepsis.
6. The use of claim 1, wherein the disease is coronary atherosclerosis.
7. The use of claim 1, wherein the disease comprises a clinical syndrome characterized by bronchoconstriction, pulmonary fibrosis, coronary artery constriction, cytokine amplification by dendritic cells, or the generation of disseminated intravascular coagulopathy.
8. The use of claim 1, wherein the disease comprises inflammation by influenza infection.
9. The use of claim 1, wherein the disease is cardiovascular disease, hypertension (including malignant hypertension), angina, myocardial infarction, cardiac arrhythmias, congestive heart failure, coronary heart disease, atherosclerosis, angina pectoris, dysrhythmias, cardiomyopathy (including hypertrophic cardiomyopathy), heart failure, cardiac arrest, bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, croup, emphysema, pleurisy, pulmonary fibrosis, pneumonia, pulmonary embolus, pulmonary hypertension, mesothelioma, ventricular conduction abnormalities, complete heart block, adult respiratory distress syndrome, sepsis syndrome, idiopathic pulmonary fibrosis, or systemic sclerosis.