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(54) **2-ACYLAMINOTHIAZOLE DERIVATIVE OR SALT THEREOF**

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See application file for complete search history.

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(57) **ABSTRACT**

[Problem]

To provide a compound which is useful as an active ingredient for a pharmaceutical composition for preventing or treating urine storage dysfunction, voiding dysfunction, lower urinary tract dysfunction, and the like.

[Means for Solution]

The present inventors have found that a thiazole derivative substituted with pyrazinylcarbonylamino at the 2-position is an excellent muscarinic M_3 receptor-positive allosteric modulator and is expected as an agent for preventing or treating bladder/urinary tract diseases associated with bladder contractions via a muscarinic M_3 receptor, thereby completing the present invention. 2-Acylaminothiazole derivative or a salt thereof of the present invention is expected as an agent for preventing or treating bladder/urinary tract diseases associated with bladder contractions via a muscarinic M_3 receptor, for example voiding dysfunction such as underactive bladder.

23 Claims, No Drawings

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2-ACYLAMINOTHIAZOLE DERIVATIVE OR SALT THEREOF

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue; a claim printed with strikethrough indicates that the claim was canceled, disclaimed, or held invalid by a prior post-patent action or proceeding.

CROSS REFERENCE TO RELATED APPLICATION

This application is a National Stage entry under 35 USC 371 of PCT/JP2015/066321, filed on Jun. 5, 2015, and claims priority to Japanese Patent Application No. 2014-118046, filed on Jun. 6, 2014.

TECHNICAL FIELD

The present invention relates to a 2-acylaminothiazole derivative or a salt thereof which is useful as an active ingredient for a pharmaceutical composition, in particular, a pharmaceutical composition for treating bladder/urinary tract diseases related to bladder contractions via a muscarinic M_3 receptor.

BACKGROUND ART

The important roles of the lower urinary tract are urine storage and voiding, which are regulated by a coordinated action of the bladder and the urethra. That is, during urine storage, the bladder smooth muscle is relaxed and the urethral sphincter is contracted, whereby a state in which urethral resistance is high is maintained and urinary continence is maintained. On the other hand, during voiding, the bladder smooth muscle is contracted, the urethra smooth muscle is relaxed, and contraction of the external urethral sphincter is also inhibited. Examples of the lower urinary tract disorder include urine storage dysfunction such as overactive bladder, in which urine cannot be retained during urine storage, and voiding dysfunction, in which urine cannot be drained sufficiently during voiding due to an increase in the urethral resistance or a decrease in the bladder contractile force. These two disorders may develop simultaneously in some cases.

Voiding dysfunction is caused by a decrease in the bladder contractile force or an increase in urethral resistance during voiding, and causes difficulty in voiding, straining during voiding, a weak urine stream, extension of voiding time, an increase in residual urine, a decrease in voiding efficiency, or the like. The decrease in the bladder contractile force during voiding is referred to as underactive bladder, acontractile bladder, or the like. As a factor causing such a decrease in the bladder contractile force during voiding, for example, aging, diabetes mellitus, benign prostatic hyperplasia, neurological diseases such as Parkinson's disease and multiple sclerosis, spinal cord injury, neurological disorders by pelvic surgery, and the like have been known (Reviews in Urology, 15; pp. 11-22 (2013)).

As a mechanism to cause bladder contraction during voiding, involvement of muscarinic receptor stimulation has been known. That is, during urination, the pelvic nerve which is a parasympathetic nerve governing the bladder is excited to release acetylcholine from nerve terminals. The released acetylcholine binds to a muscarinic receptor present in the bladder smooth muscle to cause contraction of the bladder smooth muscle (Journal of Pharmacological Sciences, 112; pp. 121-127 (2010)). The muscarinic receptors are currently classified into five subtypes, M_1, M_2, M_3, M_4, and M_5, and it has been known that the subtypes involving the contraction in the bladder smooth muscle is mainly M_3 (Pharmacological Reviews, 50; pp. 279-290 (1998); The Journal of Neuroscience, 22; pp. 10627-10632 (2002)).

As a therapeutic drug for a decrease in bladder contractile force during voiding, bethanechol chloride which is a non-selective muscarinic receptor agonist and distigmine bromide which is a cholinesterase inhibitor have been known. However, it has been known that these drugs have cholinergic side effects such as diarrhea, abdominal pain, and perspiration. In addition, there may be cases where cholinergic crisis is occurred as a serious side effect, which require attention during use (Uhretid (registered trademark), tablet 5 mg, package insert, Torii Pharmaceutical Co., Ltd., and Besacholine (registered trademark) powder 5%, package insert, Eisai Co., Ltd.).

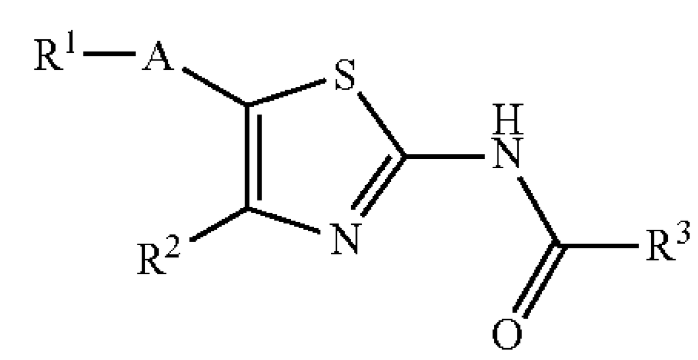
On the other hand, as a cause of an increase in urethral resistance, voiding dysfunction associated with benign prostatic hyperplasia has been well-known, which is characterized in that the urethra is partially occluded by nodular enlargement of the prostatic tissue. Currently, an adrenergic a, receptor antagonist has been used as a therapeutic drug for voiding dysfunction associated with benign prostatic hyperplasia (Pharmacology, 65; pp. 119-128 (2002)). On the other hand, the effectiveness of the adrenaline α, receptor antagonist for voiding dysfunction that is not associated with benign prostatic hyperplasia is unclear, as compared with the effectiveness against voiding dysfunction that is associated with benign prostatic hyperplasia (Journal of Pharmacological Sciences, 112; pp. 121-127 (2010)).

Furthermore, for voiding dysfunction caused by a decrease in bladder contractile force or an increase in urethral resistance, residual urine after voiding may be observed in some cases. The increased residual urine may cause a decrease in effective bladder capacity, and thus cause overactive bladder symptoms such as urinary frequency or severe symptoms such as hydronephrosis in some cases.

There has been a demand for a more effective therapeutic drug for such bladder/urethral diseases due to a decrease in the bladder contractile force or an increase in urethral resistance during voiding, or symptoms thereof (Reviews in Urology, 15; pp. 11-22 (2013)).

Patent Document 1 discloses that a compound represented by the following general formula (A) including a compound of the formula (A1) below, which is disclosed in Example 315, has a Ba/F3 cell proliferative activity through a human c-mycloproliferative leukemia virus type P (c-Mpl), and has thrombocyte increasing activity.

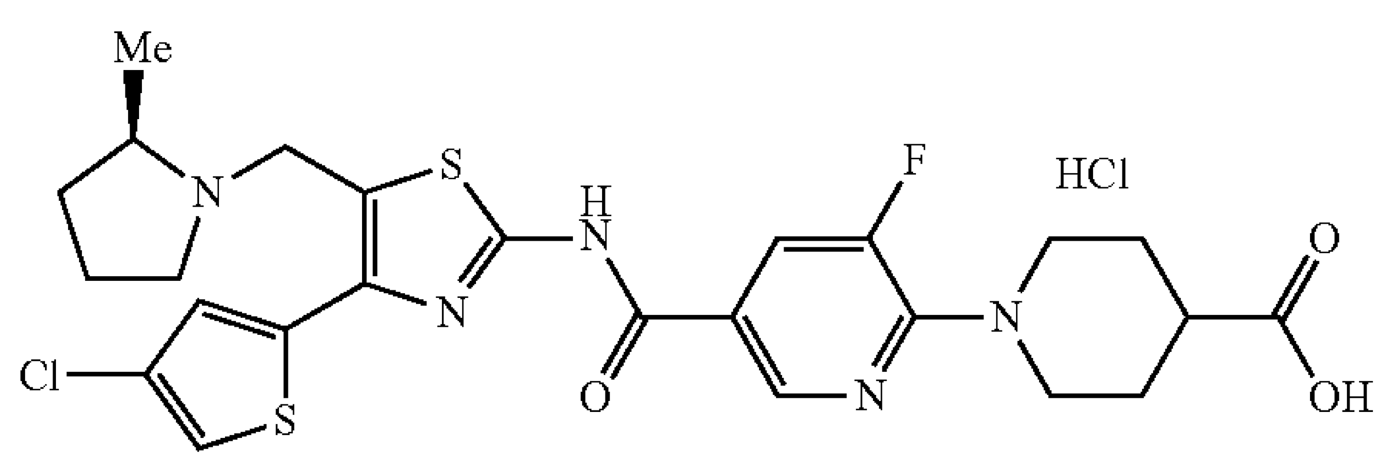
[Chem. 1]



(A)

-continued

(A1)

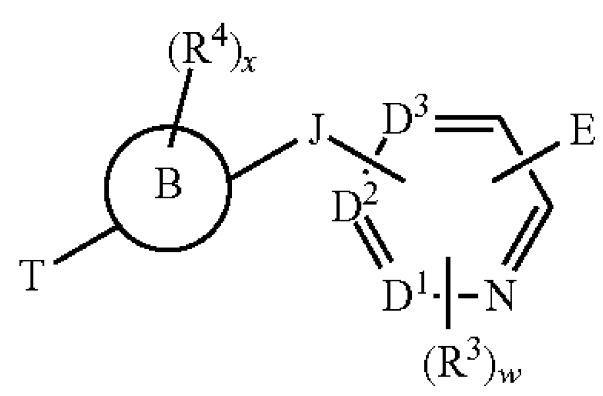


(in which R^3 represents an aromatic hetero ring which may be substituted, or the like. For the other symbols, refer to the patent publication).

Patent Document 2 discloses that a compound represented by the following general formula (B) has an AMPK pathway activating action.

[Chem. 2]

(B)

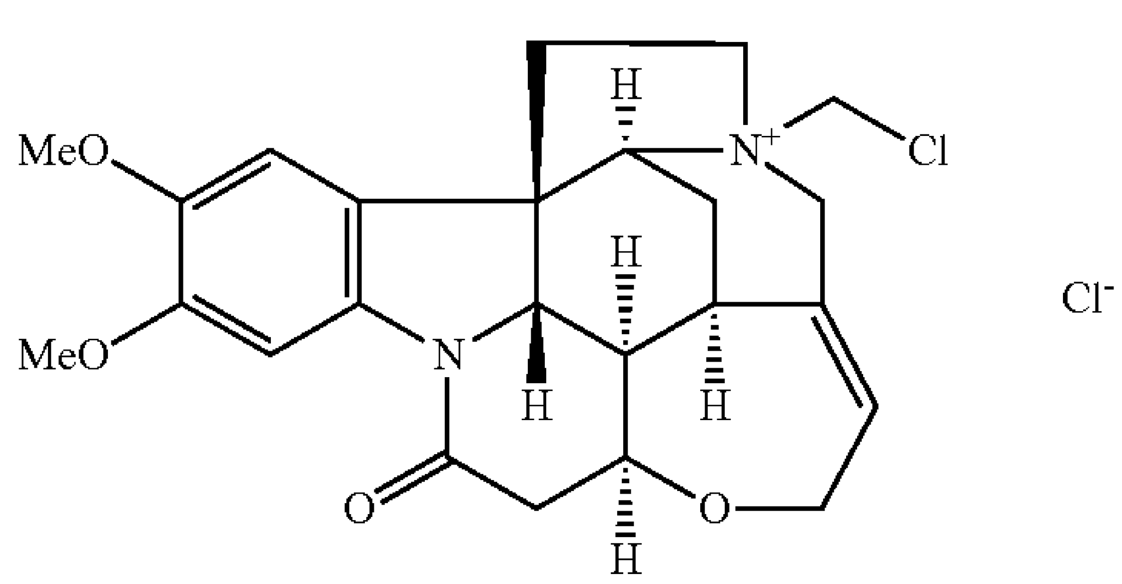


(in which Ring B represents a heteroarylene or the like, J represents —$NR^{13}C(O)$— or the like, D^1, D^2 and D^3 each represent N, CH, or the like, E represents —NR^1R^2 or the like, and R^1 and R^2 may be combined with an adjacent nitrogen atom to form a heterocycloalkyl which may be substituted. For the other symbols, refer to this publication).

Non-Patent Document 1 discloses that a compound represented by the following formula (C1) is an allosteric enhancer of a muscarinic M_3 receptor.

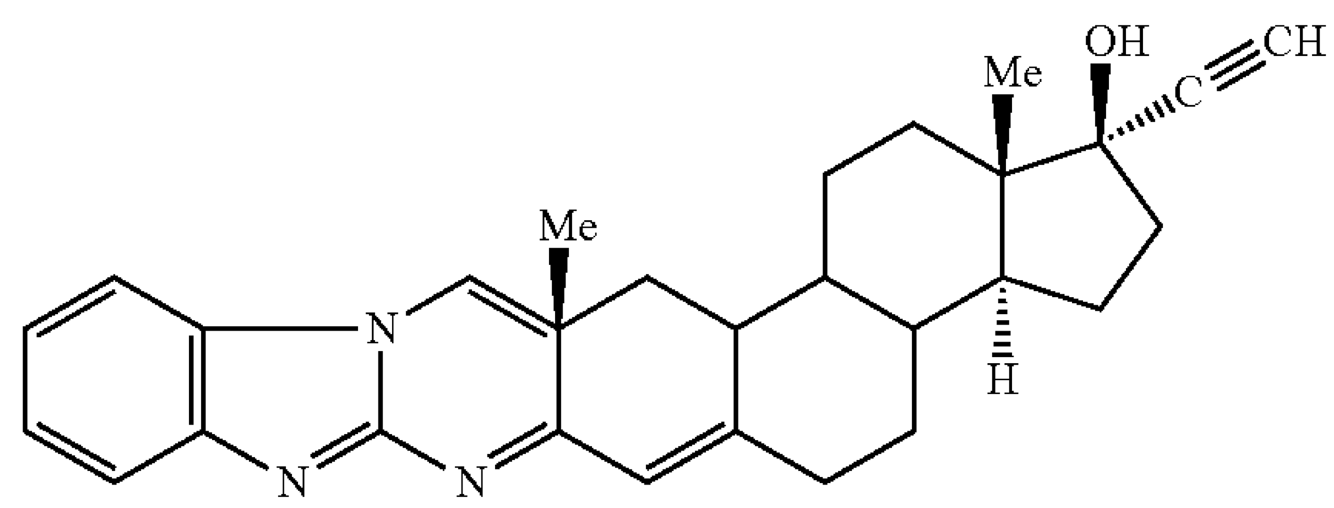
[Chem. 3]

(C1)



Non-Patent Document 2 discloses that WIN 62,577 represented by the following formula is a rat NK1 receptor antagonist and, at the same time, an allosteric enhancer of a muscarinic receptor.

[Chem. 4]



WIN 62,577

RELATED ART

Patent Document

[Patent Document 1] WO 2005/007651
[Patent Document 2] WO 2012/016217
[Non-Patent Document 1] Molecular Pharmacology, 55; pp 778-786 (1999)
[Non-Patent Document 2] Molecular Pharmacology, 62; pp 1492-1505 (2002)

DISCLOSURE OF INVENTION

Problems to be Solved by the Invention

The present invention provides a novel compound which is expected as an active ingredient for a pharmaceutical composition, in particular, for a pharmaceutical composition for preventing or treating bladder/urinary tract diseases associated with bladder contractions via a muscarinic M_3 receptor, which acts as a muscarinic M_3 receptor-positive allosteric modulator.

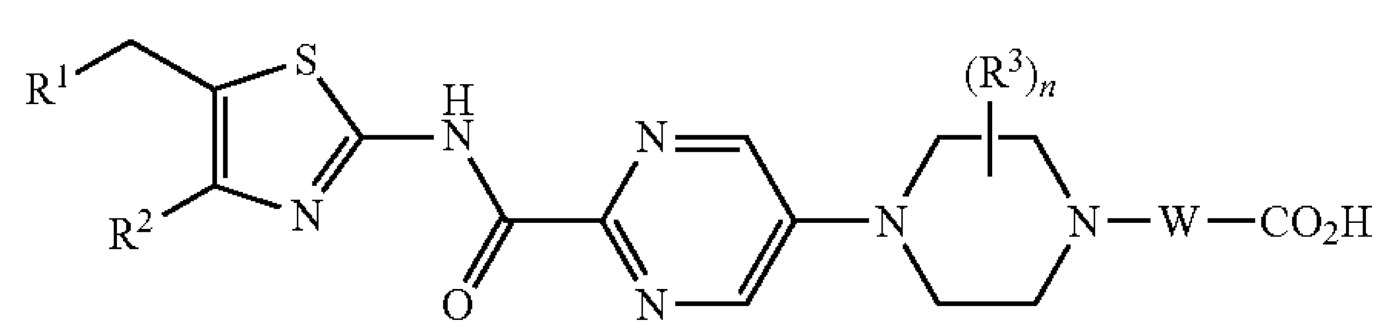
Means for Solving the Problems

The present inventors have found that a thiazole derivative substituted with pyrazinylcarbonylamino at the 2-position is an excellent muscarinic M_3 receptor-positive allosteric modulator and is expected as an agent for preventing or treating bladder/urinary tract diseases associated with bladder contractions via a muscarinic M_3 receptor, thereby completing the present invention.

That is, the present invention relates to a compound of the formula (I) or a salt thereof, and a pharmaceutical composition comprising a compound of the formula (I) or a salt thereof and an excipient.

[Chem. 5]

(I)



(wherein

R^1 is —N(—R^{11})(—R^{12}), or cyclic amino which may be substituted,

R^{11} is C_{1-6} alkyl,

R^{12} is C_{1-6} alkyl which may be substituted, or C_{3-8} cycloalkyl which may be substituted,

R^2 is aryl which may be substituted, monocyclic aromatic hetero ring which may be substituted, or bicyclic aromatic hetero ring which may be substituted,

R^3's are the same as or different from each other, and are each C_{1-6} alkyl,

W is C_{1-6} alkylene, and

n is an integer of 0 to 4).

Further, unless specifically described otherwise, when symbols in one formula in the present specification are also used in other formulae, same symbols denote same meanings.

Further, Patent Document 1 does not disclose a specific compound which is a compound of the formula (A) wherein R^3 is pyrazinyl, and neither discloses nor suggests an action on a muscarinic receptor or an action on bladder/urethral diseases.

Furthermore, Patent Document 2 does not disclose a specific compound which is a compound of the formula (B) wherein ring B is thiazole, and neither discloses nor suggests an action on a muscarinic receptor or an action on bladder/urethral diseases.

Further, the present invention relates to a pharmaceutical composition comprising the compound of the formula (I) or a salt thereof, and a pharmaceutically acceptable excipient. Furthermore, the present invention relates to a pharmaceutical composition for preventing or treating bladder/urinary tract diseases associated with bladder contractions via a muscarinic M_3 receptor, comprising the compound of the formula (I) or a salt thereof. Furthermore, the present invention relates to an agent for preventing or treating bladder/urinary tract diseases associated with bladder contractions via a muscarinic M_3 receptor, comprising the compound of the formula (I) or a salt thereof.

Moreover, the present invention relates to use of the compound of the formula (I) or a salt thereof for the manufacture of a pharmaceutical composition for preventing or treating bladder/urinary tract diseases related to bladder contractions via a muscarinic M_3 receptor, use of the compound of the formula (I) or a salt thereof for preventing or treating bladder/urinary tract diseases related to bladder contractions via a measuring M_3 receptor, the compound of the formula (I) or a salt thereof for preventing or treating bladder/urinary tract diseases related to bladder contractions via a muscarinic M_3 receptor, and a method for preventing or treating bladder/urinary tract diseases related to bladder contractions via a muscarinic M_3 receptor, comprising administering to a subject an effective amount of the compound of the formula (I) or a salt thereof. Further, the "subject" is a human or a non-human animal in need of the prevention or treatment, and in one embodiment, a human in need of the prevention or treatment.

Effects of the Invention

The compound of the formula (I) or a salt thereof is a muscarinic M_3 receptor-positive allosteric modulator, and can thus be used as an agent for preventing or treating bladder/urinary tract diseases associated with bladder contractions via a muscarinic M_3 receptor.

EMBODIMENTS FOR CARRYING OUT THE INVENTION

Hereinafter, the present invention will be described in detail.

In general, the positive allosteric modulator is a compound which binds to an allosteric site different from a ligand binding site, and has an effect of increasing the affinity of an agonist to a receptor by mainly causing a structural change in a receptor, and thus changing the signal level of agonistic activity. In the living body, the positive allosteric modulator does not exhibit an agonistic effect by itself, and increases the effect of an endogenous agonist. Examples of the advantages of positive allosteric modulator over the agonists include (1) avoiding the side effects since the positive allosteric modulator exhibits an enhancement in the endogenous agonist stimulation dependently, (2) having a possibility of obtaining high subtype selectively since the positive allosteric modulator binds to a site other than a ligand binding site, and (3) less probability of causing desensitization, which can be seen with the agonists (Pharmacological Reviews, 63; pp. 59-126 (2011)).

In the present specification, the muscarinic M_3 receptor-positive allosteric modulator means a compound which enhances an effect via the muscarinic M_3 receptor by an agonist stimulation-dependent or nerve stimulation-dependent manner. Accordingly, only during voiding, the effect on enhancing bladder contraction is expected and the muscarinic M_3 receptor-positive allosteric modulator is possibly useful as an agent for improving various symptoms associated with voiding dysfunction. Further, by such a specific action during voiding, it is expected that it is possible to avoid cholinergic side effects, known to be induced with bethanechol chloride and distigmine bromide. In addition, since the muscarinic M_3 receptor-positive allosteric modulator increases bladder contractile force during voiding, an effect in voiding dysfunction which is caused by an increase in urethral resistance can also be expected. A decrease in residual urine by such improvement of voiding dysfunction leads to an increase in the effective bladder capacity, and thus, it can be expected to improve urine storage functions as well as to avoid renal disorder. Thus, the muscarinic M_3 receptor-positive allosteric modulator is expected to be useful as an agent for preventing or treating bladder/urinary tract diseases related to bladder contractions via a muscarinic M_3 receptor. The present inventors have newly discovered a compound that acts as the modulator, thereby completing the present invention.

In the present specification, examples of the "bladder/urinary tract diseases associated with bladder contractions via a muscarinic M_3 receptor" include voiding dysfunction or urine storage dysfunction in underactive bladder, hypotonic bladder, acontractile bladder, detrustor underactivity, neurogenic bladder, urethra relaxation failure, detrustor-external urethral sphincter dyssynergia, overactive bladder, urinary frequency, nocturia, urinary incontinence, benign prostatic hyperplasia, interstitial cystitis, chronic prostatitis, urethral calculus, or the like, preferably, voiding dysfunction or urine storage dysfunction in underactivity bladder, hypotonic bladder, acontractile bladder, detrusor underactivity, and neurogenic bladder.

The "alkyl" is linear alkyl and branched alkyl. Accordingly, the "C_{1-6} alkyl" is linear or branched alkyl having 1 to 6 carbon atoms, and specific examples thereof include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, or n-hexyl; in one embodiment, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, or tert-butyl, each of which is C_{1-4} alkyl; in one embodiment, a group selected from the group consisting of methyl, ethyl, isopropyl, and isobutyl; and in one embodiment, a group selected from the group consisting of methyl and ethyl.

The "alkylene" is linear alkylene or branched alkylene. Accordingly, the "C_{1-6} alkylene" is linear or branched alkylene having 1 to 6 carbon atoms, and examples thereof include methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, propylene, methylmethylene, ethylethylene, 1,2-dimethylethylene, or 1,1,2,2-tetramethylethylene; in one embodiment, C_{1-3} alkylene; in one embodiment, methylene or ethylene; in one embodiment, methylene; and in another embodiment, ethylene.

The "halogeno-C_{1-6} alkyl" is C_{1-6} alkyl substituted with at least one halogen atom; in one embodiment, C_{1-6} alkyl substituted with 1 to 5 halogen atoms; in one embodiment, difluoromethyl or trifluoromethyl; and in one embodiment, trifluoromethyl.

The "cycloalkyl" is a saturated hydrocarbon cyclic group. Accordingly, the "C_{3-8} cycloalkyl" is a saturated hydrocarbon cyclic group having 3 to 8 ring members, and specific examples thereof include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl; in one embodiment, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, each of which is C_{3-6} cycloalkyl; and in one embodiment, cyclopropyl.

The "aryl" is a C_{6-14} monocyclic to tricyclic aromatic hydrocarbon cyclic group and includes a partially hydrogenated cyclic group thereof, and specific examples thereof include phenyl, naphthyl, tetrahydronaphthyl, indanyl, or indenyl; and in one embodiment, phenyl.

The "monocyclic aromatic hetero ring" is a monocyclic aromatic hetero ring group having 5 to 7 ring members, which has 1 to 4 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom, and a sulfur atom as a ring-constituting atom, and specific examples thereof include pyrrolyl, pyrazolyl, imidazolyl, triazolyl, furyl, thienyl, oxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, or azepanyl; in one embodiment, thienyl or pyridyl; and in one embodiment, thienyl.

The "bicyclic aromatic hetero ring" is a bicyclic aromatic hetero ring group in which the monocyclic aromatic hetero ring is fused with a benzene ring or monocyclic aromatic hetero ring and includes a partially hydrogenated ring group thereof, and specific examples thereof include indolyl, isoindolyl, indazolyl, benzotriazolyl, benzofuranyl, benzothienyl, benzooxazolyl, benzothiazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, furopyridyl, thienopyridyl, indolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, dihydroquinolyl, tetrahydroquinolyl, dihydroisoquinolyl, tetrahydroisoquinolyl, dihydrofuropyridyl, or dihydrothienopyridyl; and in one embodiment, benzothienyl.

The "saturated hetero ring" is a 3- to 8-membered saturated ring group, which has 1 to 4 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom, and a sulfur atom as a ring-constituting atom, and may be bridged with C_{1-6} alkylene, in which a sulfur atom as the ring-constituting atom may be oxidized. Specific examples thereof include azepanyl, diazepanyl, oxazepanyl, thiazepanyl, aziridinyl, azetidinyl, pyrrolidinyl, imidazolidinyl, piperidinyl, pyrazolidinyl, piperazinyl, azocanyl, thiomorpholinyl, thiazolindinyl, isothiazolindinyl, oxazolindinyl, morpholinyl, thiomorpholinyl, tetrahydrothiophenyl, oxathioranyl, oxiranyl, oxetanyl, dioxiranyl, tetrahydrofuranyl, tetrahydropyranyl, and 1,4-dioxanyl.

The "cyclic amino" is a 4- to 7-membered group having a bond at a ring-constituting nitrogen atom in the saturated hetero ring. Specific examples thereof include aziridin-1-yl, azetidin-1-yl, pyrrolidin-1-yl, piperidin-1-yl, azepan-1-yl, azocan-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperazin-1-yl, 1,4-diazepan-1-yl, 1,4-oxazepan-4-yl, or 1,4-thiazepan-4-yl; in one embodiment, pyrrolidin-1-yl, piperidin-1-yl, azetidin-1-yl, morpholin-4-yl, or piperazin-1-yl, and in one embodiment, pyrrolidin-1-yl or piperidin-1-yl.

The "halogen" means fluoro, chloro, bromo, or iodo; in one embodiment, fluoro, chloro, or bromo; in one embodiment, fluoro or chloro; in one embodiment, fluoro; and in another embodiment, chloro.

In the present specification, the expression "which may be substituted" means "which is not substituted" or "which is substituted with 1 to 5 substituents". Further, if it has a plurality of substituents, the substituents may be the same as or different from each other.

Examples of the acceptable substituent in the "cyclic amino which may be substituted", the "C_{3-8} cycloalkyl which may be substituted", the "aryl which may be substituted", the "monocyclic aromatic hetero ring which may be substituted", and the "bicyclic aromatic hetero ring which may be substituted" include substituents in the following Group G.

Group G

(a) C_{1-6} alkyl which may be substituted with at least one group selected from the group consisting of —OH, —O—(C_{1-6} alkyl), —CN, —SO_2—(C_{1-6} alkyl), and halogen,

(b) —OH,

(c) —O—(C_{1-6} alkyl which may be substituted with at least one group selected from the group consisting of —OH, —O—(C_{1-6} alkyl), —CN, —SO_2—(C_{1-6} alkyl), and halogen),

(d) C_{3-8} cycloalkyl,

(e) —O—(C_{3-8} cycloalkyl),

(f) halogen,

(g) —CN,

(h) —SO_2—(C_{1-6} alkyl),

(i) —CO_2—(C_{1-6} alkyl) and —COOH,

(j) —CO—N(C_{1-6} alkyl)$_2$, —CO—NH(C_{1-6} alkyl), and —$CONH_2$,

(k) —CO—(C_{1-6} alkyl),

(l) —SO_2—N(C_{1-6} alkyl)$_2$, —SO_2—NH(C_{1-6} alkyl), and —SO_2NH_2,

(m) —N(C_{1-6} alkyl)$_2$, —NH(C_{3-6} alkyl), and —NH_2,

(n) a saturated hetero ring, and

(o) —O-saturated hetero ring.

Examples of the substituent in the "cyclic amino which may be substituted" further include oxo (═O).

In addition, the preferable substituents in the "C_{1-6} alkyl which may be substituted" are the substituents described in (b) to (o) of Group G above.

Examples of the preferable substituents for the "cyclic amino which may be substituted" in R^1 include, in one embodiment, the substituents described in (a) to (c), (f), and (g) of Group G above; in one embodiment, C_{1-6} alkyl which may be substituted with at least one group selected from the group consisting of —OH, —O—(C_{1-6} alkyl), —CN, —SO_2—(C_{1-6} alkyl), and halogen; in one embodiment, a group selected from the group consisting of C_{1-6} alkyl and halogeno-C_{1-6} alkyl; and in one embodiment, a group selected from the group consisting of methyl and ethyl.

Examples of the preferable substituents for the "C_{1-6} alkyl which may be substituted" in R^{12} include, in one embodiment, the substituents described in (b) to (g), and (n) of Group G above; in one embodiment, a group selected from the group consisting of C_{3-8} cycloalkyl, —O—(C_{1-6} alkyl), —O—(C_{3-8} cycloalkyl), halogen, —CN, and cyclic amino; in one embodiment, a group selected from the group consisting of C_{3-8} cycloalkyl and —O—(C_{1-6} alkyl); and in one embodiment, a group selected from the group consisting of cyclopropyl and methoxy.

Examples of the preferable substituents for the "C_{3-8} cycloalkyl which may be substituted" in R^{13} include, in one embodiment, the substituents described in (a) to (c), (f), and (g) of Group G above; and in one embodiment, C_{1-6} alkyl which may be substituted with —O—(C_{1-6} alkyl).

Examples of the preferable substituents for the "aryl which may be substituted" in R^2 include, in one embodiment, the substituents described in (a) to (d), (f), (g), and (n) of Group G above; in one embodiment, a group selected from the group consisting of C_{1-6} alkyl, halogen-C_{1-6} alkyl, —O—(C_{1-6} alkyl), —O-(halogeno-C_{1-6} alkyl), halogen, C_{3-8} cycloalkyl, and —CN; in one embodiment, a group selected from the group consisting of halogeno-C_{1-6} alkyl and halogen; and in one embodiment, a group selected from the group consisting of trifluoromethyl and fluoro.

Examples of the preferable substituents for the "monocyclic aromatic hetero ring which may be substituted" and "bicyclic aromatic hetero ring which may be substituted" in R^2 include, in one embodiment, the substituents described in (a) to (d), (f), (g), and (n) of Group G above; in one embodiment, a group selected from the group consisting of C_{1-6} alkyl, halogeno-C_{1-6} alkyl, —O—(C_{1-6} alkyl), —O-(halogeno-C_{1-6} alkyl), halogen, C_{3-8} cycloalkyl, and —CN; in one embodiment, a group selected from the group consisting of C_{1-6} alkyl, halogeno-C_{1-6} alkyl, —O—(C_{1-6} alkyl), C_{3-8} cycloalkyl, and halogen; in one embodiment, a group selected from the group consisting of halogeno-C_{1-6} alkyl, —O—(C_{1-6} alkyl), and halogen; and in one embodiment, a group selected from the group consisting of trifluoromethyl, methoxy, and chloro.

One embodiment of the compound of the formula (I) or a salt thereof is shown below.

(1-1)

The compound of the formula (I) or a salt thereof, in which

R^1 is

i. cyclic amino which may be substituted with 1 to 5 substituents selected from the group consisting of Group G and oxo, or

ii. —N(—R^{11})(—R^{12}),

R^{11} is C_{1-6} alkyl, and

R^{12} is C_{1-6} alkyl which may be substituted with 1 to 5 substituents selected from the substituents described in (b) to (o) of Group G, or C_{3-8} cycloalkyl which may be substituted with 1 to 5 substituents selected from Group G.

(1-2)

The compound of the formula (I) or a salt thereof, in which

R^1 is

i. cyclic amino which may be substituted with 1 to 5 substituents selected from the group consisting of Group G and oxo, or

ii. —N(—R^{11})(—R^{12}),

R^{11} is C_{1-6} alkyl, and

R^{12} is C_{1-6} alkyl which may be substituted with 1 to 3 substituents selected from the substituents described in (b) to (g), and (n) of Group G.

(1-3)

The compounds of the formula (I) or a salt thereof, in which

R^1 is

i. pyrrolidin-1-yl or piperidin-1-yl, in which pyrrolidin-1-yl and piperidin-1-yl are each substituted with 1 to 2 substituents selected from the group consisting of C_{1-6} alkyl and halogen-C_{1-6} alkyl, or

ii. —N(—R^{11})(—R^{12}), in which

R^{11} is C_{1-6} alkyl, and

R^{12} is C_{1-6} alkyl which may be substituted with one group selected from the group consisting of C_{3-8} cycloalkyl and —O—(C_{1-6} alkyl).

(1-4)

The compound of the formula (I) or a salt thereof, in which R^1 is cyclic amino substituted with 1 to 2 groups selected from the group consisting of C_{1-6} alkyl and halogen-C_{1-6} alkyl.

(1-5)

The compound of the formula (I) or a salt thereof, in which R^1 is pyrrolidin-1-yl or piperidin-1-yl, in which pyrrolidin-1-yl and piperidin-1-yl may be substituted with 1 to 3 substituents selected from Group G.

(1-6)

The compound of the formula (I) or a salt thereof, in which R^1 is pyrrolidin-1-yl or piperidin-1-yl, in which pyrrolidin-1-yl and piperidin-1-yl are each substituted with 1 to 2 groups selected from the group consisting of C_{1-6} alkyl and halogeno-C_{1-6} alkyl.

(1-7)

The compound of the formula (I) or a salt thereof, in which R^1 is pyrrolidin-1-yl substituted with 1 to 2 groups selected from the group consisting of methyl and ethyl.

(1-8)

The compound of the formula (I) or a salt thereof, in which

R^1 is —N(—R^{11})(—R^{12}),

R^{11} is C_{1-6} alkyl, and

R^{12} is C_{1-6} alkyl which may be substituted with a group selected from the group consisting of C_{3-8} cycloalkyl and —O—(C_{1-6} alkyl),

(1-9)

The compound of the formula (I) or a salt thereof, in which

R^1 is —N(—R^{11})(—R^{12}),

R^{11} is methyl, ethyl, or isopropyl, and

R^{12} is methyl, ethyl, isopropyl, isobutyl, cyclopropylmethyl, or methoxyethyl.

(2-1)

The compound of the formula (I) or a salt thereof, in which

R^2 is

i. aryl which may be substituted with 1 to 5 substituents selected from Group G,

ii. monocyclic aromatic hetero ring which may be substituted with 1 to 5 substituents selected from Group G, or

iii. bicyclic aromatic hetero ring which may be substituted with 1 to 5 substituents selected from Group G.

(2-2)

The compound of the formula (I) or a salt thereof, in which

R^2 is

i. phenyl which may be substituted with 1 to 5 substituents selected from Group G,

ii. thienyl which may be substituted with 1 to 3 substituents selected from Group G

iii. pyridyl which may be substituted with 1 to 3 substituents selected from Group G, or

iv. benzothienyl which may be substituted with 1 to 5 substituents selected from Group G.

(2-3)

The compound of the formula (I) or a salt thereof, in which

R^2 is

i. phenyl which may be substituted with 1 to 3 groups selected from the group consisting of C_{1-6} alkyl, halogeno-C_{1-6} alkyl, —O—(C_{1-6} alkyl), —O-(halogeno-C_{1-6} alkyl), halogen, C_{3-8} cycloalkyl, and —CN,

ii. thienyl which may each be substituted with 1 to 3 groups selected from the group consisting of C_{1-6} alkyl, halogeno-C_{1-6} alkyl, —O—(C_{1-6} alkyl), C_{3-8} cycloalkyl, and halogen,

iii. pyridyl which may each be substituted with 1 to 3 groups selected from the group consisting of C_{1-6} alkyl, halogeno-C_{1-6} alkyl, —O—(C_{1-6} alkyl), C_{3-8} cycloalkyl, and halogen, or

iv. benzothienyl,

(2-4)

The compound of the formula (I) or a salt thereof, in which

R^2 is

i. phenyl di-substituted with trifluoromethyl and fluoro,

ii. thienyl mono-substituted with trifluoromethyl or chloro, or

iii. pyridyl di-substituted with trifluormethyl and methoxy.

(2-5)

The compound of the formula (I) or a salt thereof, in which R^2 is a monocyclic aromatic hetero ring which may be substituted with 1 to 3 groups selected from the group consisting of C_{1-6} alkyl, halogeno-C_{1-6} alkyl, —O—(C_{1-6} alkyl), C_{3-8} cycloalkyl, and halogen.

(2-6)

The compound of the formula (I) or a salt thereof, in which

R^2 is

i. thienyl which may be substituted with 1 to 3 groups selected from the group consisting of C_{1-6} alkyl, halogeno-C_{1-6} alkyl, —O—(C_{1-6} alkyl), C_{3-8} cycloalkyl, and halogen, or

ii. pyridyl which may be substituted with 1 to 3 groups selected from the group consisting of C_{1-6} alkyl, halogeno-C_{1-6} alkyl, —O—(C_{1-6} alkyl), C_{3-8} cycloalkyl, and halogen.

(2-7)

The compound of the formula (I) or a salt thereof, in which R^2 is thienyl which may be substituted with 1 to 3 groups selected from the group consisting of C_{1-6} alkyl, halogeno-C_{1-6} alkyl, C_{3-8} cycloalkyl, and halogen.

(2-8)

The compound of the formula (I) or a salt thereof, in which R^2 is thienyl which may be substituted with 1 or 2 substituents selected from the group consisting of halogeno-C_{1-6} alkyl and halogen.

(2-9)

The compound of the formula (I) or a salt thereof, in which R^2 is thienyl which may be substituted with 1 or 2 substituents selected from the group consisting of trifluoromethyl and chloro.

(2-10)

The compound of the formula (I) or a salt thereof, in which R^2 is thienyl mono-substituted with trifluoromethyl or chloro.

(2-11)

The compound of the formula (I) or a salt thereof, in which R^2 is pyridyl which may be substituted with 1 to 3 groups selected from the group consisting of halogeno-C_{1-6} alkyl and —O—(C_{1-6} alkyl),

(2-12)

The compound of the formula (I) or a salt thereof, in which R^2 is phenyl which may be substituted with 1 to 5 groups selected from the group consisting of C_{1-6} alkyl, halogen-C_{1-6} alkyl, —O—(C_{1-6} alkyl), —O-(halogeno-C_{1-6} alkyl), halogen, C_{3-8} cycloalkyl, and —CN.

(2-13)

The compound of the formula (I) or a salt thereof, in which R^2 is phenyl which may be substituted with 1 or 2 substituents selected from the group consisting of halogeno-C_{1-6} alkyl and halogen.

(2-14)

The compound of the formula (I) or a salt thereof, in which

R^2 is

i. thienyl which may be substituted with 1 or 2 substituents selected from the group consisting of halogeno-C_{1-6} alkyl and halogen, or

ii. phenyl which may be substituted with 1 or 2 substituents selected from the group consisting of halogeno-C_{1-6} alkyl and halogen.

(3-1)

The compound of the formula (I) or a salt thereof, in which R^3's are the same as or different from each other, and are each C_{1-6} alkyl.

(3-2)

The compound of the formula (I) or a salt thereof, in which R^3 is methyl.

(4-1)

The compound of the formula (I) or a salt thereof, in which W is C_{1-6} alkylene.

(4-2)

The compound of the formula (I) or a salt thereof, in which W is C_{1-3} alkylene.

(4-3)

The compound of the formula (I) or a salt thereof, in which W is methylene or ethylene.

(4-4)

The compound of the formula (I) or a salt thereof, in which W is methylene.

(4-5)

The compound of the formula (I) or a salt thereof, in which W is ethylene.

(5-1)

The compound of the formula (I) or a salt thereof, in which n is an integer of 0 to 4.

(5-2)

The compound of the formula (I) or a salt thereof, in which n is an integer of 0 to 2.

(5-3)

The compound of the formula (I) or a salt thereof, in which n is 0 or 1.

(6) The compound of the formula (I) or a salt thereof, which is a combination of any two or more of the groups, which are not inconsistent with each other, among some embodiments of each group described in (1-1) to (5-3) above. Examples thereof include the compounds or salts thereof shown below.

(6-1)

The compound of the formula (I) or a salt thereof, in which

R^1 is as described in (1-2) above,

R^2 is as described in (2-2) above,

R^3 is as described in (3-1) above,

W is as described in (4-1) above, and

n is as described in (5-1) above.

(6-2)

The compound or a salt thereof as described in (6-1) above, in which

R^1 is as described in (1-3) above,

R^2 is as described in (2-3) above,

W is as described in (4-2) above, and

n is as described in (5-3) above.

(6-3)

The compound or a salt thereof as described in (6-2) above, in which

R^2 is as described in (2-4) above, and

W is as described in (4-3) above.

(6-4)

The compound or a salt thereof as described in (6-2) above, in which

R^1 is as described in (1-6) above,

R^2 is as described in (2-14) above, and

W is as described in (4-3) above.

Examples of the specific compounds included in the present invention include the following compounds or salts thereof:

3-[(2S)-4-(5-{[4-(4-chlorothiophen-2-yl)-5-{[(2R)-2-methy)pyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl]carbamoyl}pyrazin-2-yl)-2-methylpiperazin-1-yl]propanoic acid,

3-[(3R)-4-{5-[(4-[3-fluoro-5-(trifluoromethyl)phenyl]-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl)carbamoyl]pyrazin-2-yl}-3-methylpiperazin-1-yl]propanoic acid,

[(3R)-4-{5-[(4-[3-fluoro-5-(trifluoromethyl)phenyl]-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl)carbamoyl]pyrazin-2-yl}-3-methylpiperazin-1-yl]acetic acid,

3-(4-{5-[(4-[3-fluoro-5-(trifluoromethyl)phenyl]-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl)carbamoyl]pyrazin-2-yl}piperazin-1-yl)propanoic acid,

3-[(2R)-4-(5-{[4-(4-chlorothiophen-2-yl)-5-{[(2R)-2-ethylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl]carbamoyl}pyrazin-2-yl)-2-methylpiperazin-1-yl]propanoic acid,

3-[(3R)-3-methyl-4-{5-[(5-{[(2R)-2-methylpyrrolidin-1-yl]methyl)}-4-[4-(trifluoromethyl)thiophen-2-yl]-1,3-thiazol-2-yl)carbamoyl]pyrazin-2-yl}piperazin-1-yl]propanoic acid,

3-(4-{5-[(5-{[(2R,5R)-2,5-dimethylpyrrolidin-1-yl]methyl}-4-[3-fluoro-5-(trifluoromethyl)phenyl]-1,3-thiazol-2-yl)carbamoyl]pyrazin-2-yl}piperazin-1-yl)propanoic acid, and

3-{(2R)-4-[5-({5-[(diethylamino)methyl]-4-[3-fluoro-5-(trifluoromethyl)phenyl]-1,3-thiazol-2-yl}carbamoyl)pyrazin-2-yl]-2-methylpiperazin-1-yl}propanoic acid.

In another embodiment, examples of the specific compounds included in the present invention include the following compounds or salts thereof:

3-[(3S)-4-(5-{[4-(4-chlorothiophen-2-yl)-5-{[(2R)-2-ethylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl]carbamoyl}pyrazin-2-yl)-3-methylpiperazin-1-yl]propanoic acid,

3-(4-{5-[(4-[6-methoxy-5-(trifluoromethyl)pyridin-3-yl]-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl)carbamoyl]pyrazin-2-yl}piperazin-1-yl)propanoic acid,

3-[4-(5-{[4-(4-chlorothiophen-2-yl)-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl]carbamoyl}pyrazin-2-yl)piperazin-1-yl]propanoic acid,

[(3R)-4-(5-{[4-(4-chlorothiophen-2-yl)-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl]carbamoyl}pyrazin-2-yl)-3-methylpiperazin-1-yl]acetic acid,

3-[4-(5-{[4-(4-chlorothiophen-2-yl)-5-{[(2R)-2-ethylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl]carbamoyl}pyrazin-2-yl)piperazin-1-yl]propanoic acid,

3-(4-{5-[(4-[3-fluoro-5-(trifluoromethyl)phenyl]-5-{[isobutyl(methyl)amino]methyl}-1,3-thiazol-2-yl)carbamoyl]pyrazin-2-yl}piperazin-1-yl)propanoic acid,

3-[(2R)-4-(5-{[4-(4-chlorothiophen-2-yl)-5-{[(cyclopropylmethyl)(methyl)amino]methyl}-1,3-thiazol-2-yl]carbamoyl}pyrazin-2-yl)-2-methylpiperazin-1-yl]propanoic acid,

3-(4-{5-[(5-{[(2R,5R)-2,5-dimethylpyrrolidin-1-yl]methyl}-4-[4-(trifluoromethyl)-thiophen-2-yl]-1,3-thiazol-2-yl)carbamoyl]pyrazin-2-yl}piperazin-1-yl)propanoic acid,

{(3R)-4-[5-({5-[(diethylamino)methyl]-4-[3-fluoro-5(trifluoromethyl)phenyl]-1,3-thiazol-2-yl}carbamoyl)pyrazin-2-yl]-3-methylpiperazin-1-yl}acetic acid, and

(4-{5-[(5-{[(2R,5R)-2,5-dimethylpyrrolidin-1-yl]methyl}-4-[3-fluoro-5-(trifluoromethyl)phenyl]-1,3-thiazol-2-yl)carbamoyl]pyrazin-2-yl}piperazin-1-yl)acetic acid.

With regard to the compound of the formula (I), tautomers or geometrical isomers thereof may exist, depending on the kinds of the substituents. In the present specification, the compound of the formula (I) may be described in only one form of isomers in some cases, but the present invention includes other isomers, isolated forms of the isomers, or a mixture thereof.

Furthermore, some of the compounds of the formula (I) may have asymmetric carbon atoms or asymmetries in some cases, and correspondingly, the optical isomers thereof can exist. The present invention includes the isolated form of the optical isomer of the compound of the formula (I) or a mixture thereof.

In addition, a pharmaceutically acceptable prodrug of the compound represented by the formula (I) is also included in the present invention. The pharmaceutically acceptable prodrug refers to a compound having a group which can be converted into an amino group, a hydroxyl group, a carboxyl group, or the like, by solvolysis or under a physiological condition. Examples of the groups forming the prodrug include those as described in Prog. Med., 5, 2157-2161 (1985) or "Pharmaceutically Research and Development" (Hirokawn Publishing Company, 1990), vol. 7, Drug Design, 163-198.

Moreover, the salt of the compound of the formula (I) is a pharmaceutically acceptable salt of the compound of the formula (I), and the compounds of the formula (I) may form an acid solution salt or a salt with a base, depending on the kinds of the substituents in some cases. Specifically, examples thereof include acid addition salts with inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, and phosphoric acid, and with organic acids such as formic acid, acetic acid, propanoic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, mandelic acid, tartaric acid, dibenzoyl tartaric acid, ditolyl tartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, aspartic acid, and glutamic acid, and salts with metal anions such as sodium, potassium, magnesium, calcium, and aluminum, and with organic bases such as methylamine, ethylamine, and ethanolamine, salts with various amino acids such as acetyl leucine, lysine, and omithine, or derivatives of amino acids, ammonium salts, and others.

In addition, the present invention also includes various hydrates or solvates, and crystal polymorph substances of the compound of the formula (I) and a salt thereof. In addition, the present invention also includes the compounds labeled with various radioactive or non-radioactive isotopes.

(Production Process)

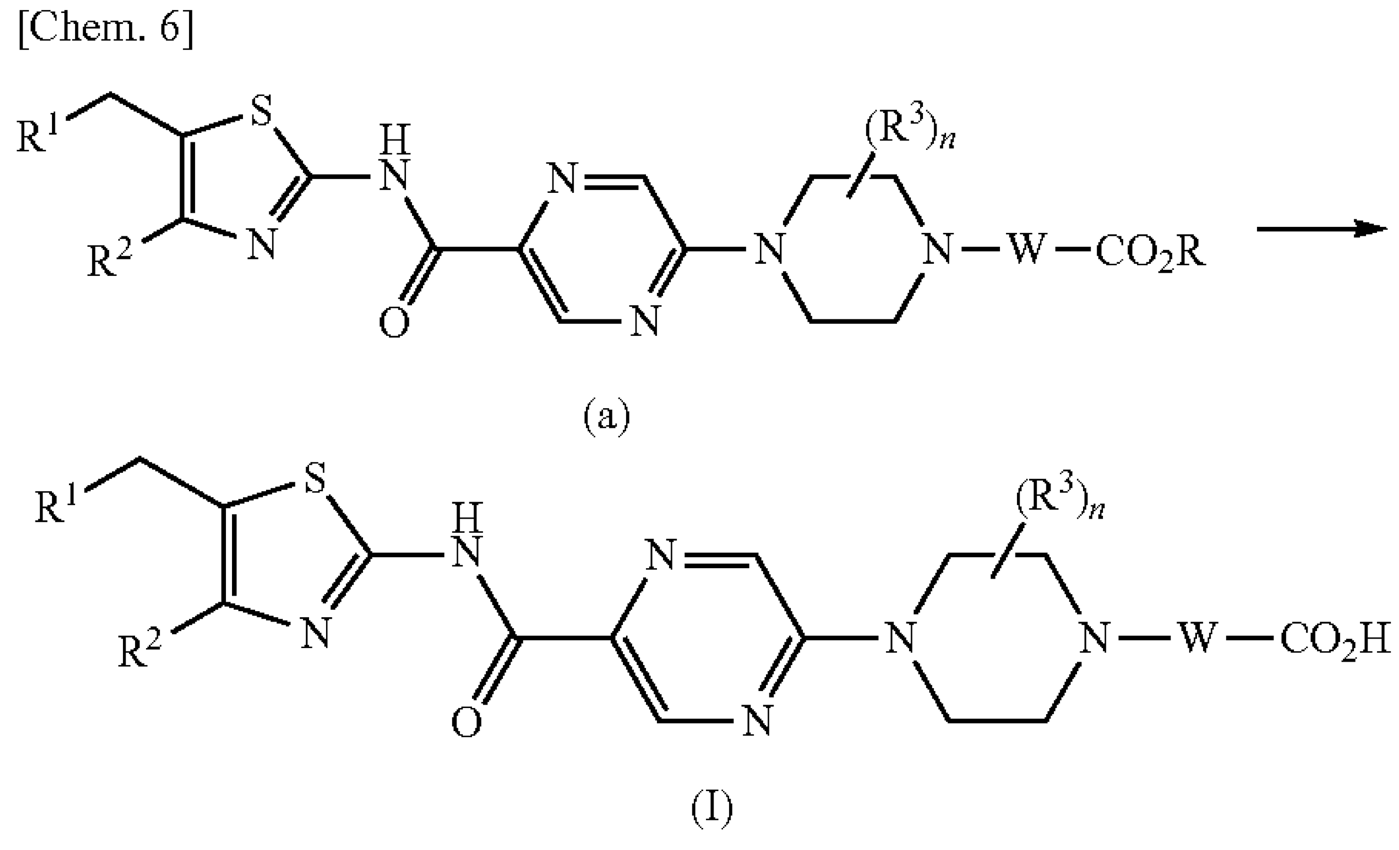
The compound of the formula (I) or a salt thereof can be prepared by applying various know synthetic methods, using the characteristics based on their basic structures or the kinds of the substituents. At this time, depending on the types of the functional groups, it is in some cases effective from the viewpoint of the preparation techniques to protect the functional group with an appropriate protective group (a group which is capable of being easily converted into the functional groups), during the steps from starting materials to intermediates. Examples of the protective group include the protective groups as described in "Greene's Protective Groups in Organic Synthesis (4th edition, 2006)", edited by P. G. M. Wuts and T. W. Greene, and the like, which may be appropriately selected and used depending on the reaction conditions. In these methods, a desired compound can be obtained by introducing the protective group to carry out the reaction, and then, if desired, removing the protective group.

In addition, the prodrug of the compound of the formula (I) can be prepared by introducing a specific group during the steps from starting materials to intermediates, in the same manner as for the above protective groups, or by further carrying out the reaction using the obtained compound of the formula (I). The reaction can be carried out by applying a method known to a person skilled in the art, such as common esterification, amidation, and dehydration.

Hereinbelow, typical preparation methods of the compound of the formula (I) and the compound of the formula (a) which is the starting compound will be described. Each of the production processes can also be carried out with reference to the documents appended to the description herein. Further, the preparation methods of the present invention are not limited to the examples as shown below.

(Production Process 1)

[Chem. 6]



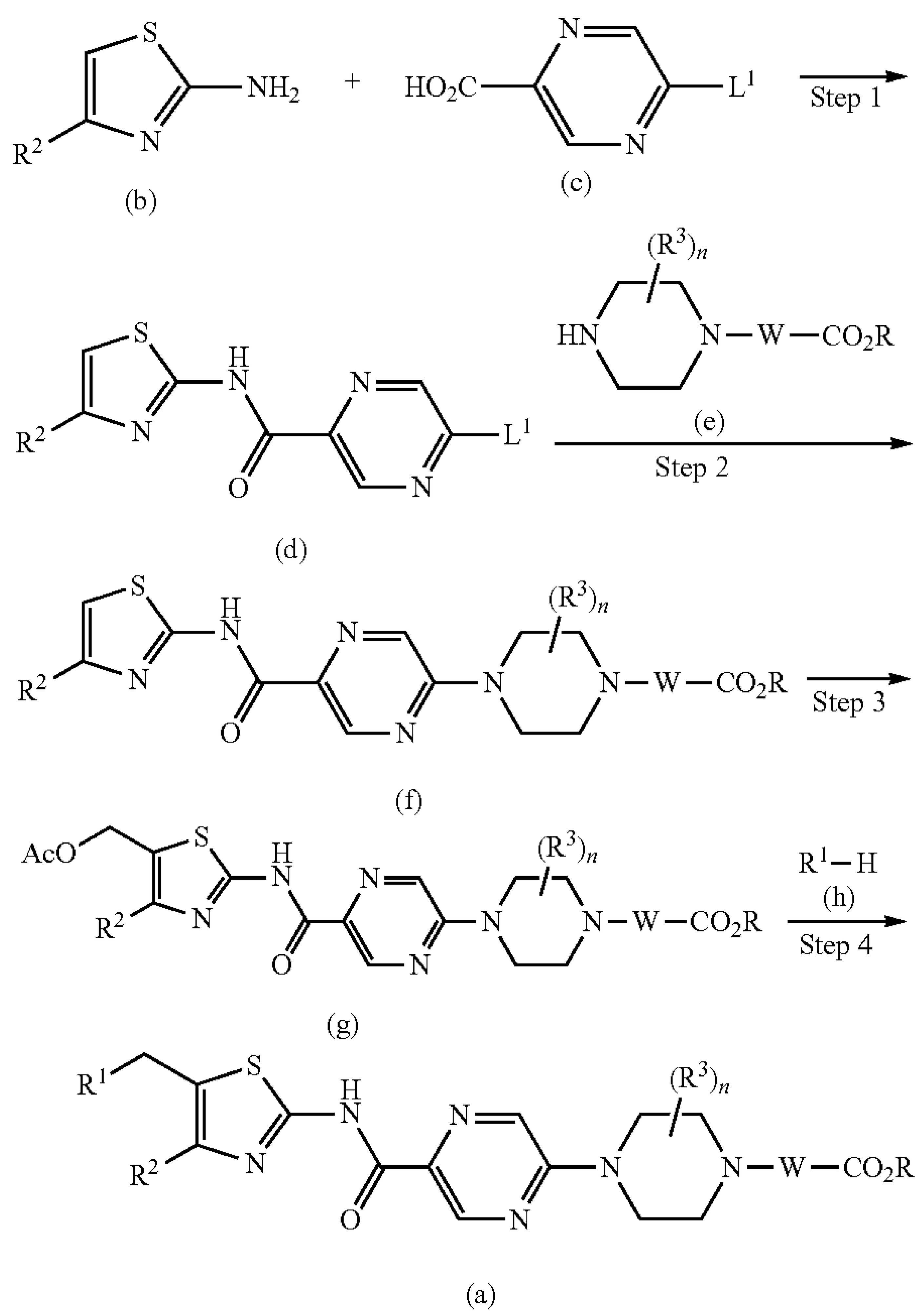
(in which, R represents C_{1-6} alkyl, which shall apply hereinafter).

This reaction is a method for producing a compound of the formula (I) which is a compound of the present invention, by deprotecting a compound of the formula (a).

This reaction is carried out using the compound of the formula (a) and a deprotecting reagent in equivalent amounts, or either thereof in an excess amount, by stirring the mixture under the temperature condition ranging from under cooling to heating to reflux, usually for 0.1 hours to 5 days, in a solvent which is insert to the reaction or without a solvent. Examples of the solvent used herein are not particularly limited, but include alcohols such as methanol, ethanol, n-propanol and the like, N,N-dimethylformamide, tetrahydrofuran, and the like. Further, there are some cases where a mixed solvent of the solvent and water is highly suitable for the reaction. Examples of the deprotecting reagent are not particularly limited, but include bases such as an aqueous sodium hydroxide solution, an aqueous potassium hydroxide solution and the like, and acids such as hydrochloric acid, trifluoroacetic acid and the like.

(Production Process 2)

[Chem. 7]



(in which, L^1 represents a leaving group, which shall apply hereinafter).

This production process is a method for producing the compound of the formula (a) which is a starting material of the compound of the formula (I). Here, examples of L^1 include chloro and the like.

(Step 1)

This step is a step of preparing a compound of the formula (d) by subjecting a compound of the formula (b) and a compound of the formula (c) to an amidation reaction.

The reaction is carried out using the formula (b) and the compound of the formula (c) in equivalent amounts, or either thereof in an excess amount, by stirring the mixture under the temperature condition ranging from under cooling to under heating, preferably at −20° C. to 60° C., usually for 0.1 hours to 5 days, in a solvent which is inert to the reaction, in the presence of a condensing agent. Examples of the solvent used herein are not particularly limited, but include aromatic hydrocarbons such as benzene, toluene, xylene and the like, halogenated hydrocarbons such as dichloromethane, 1,2-dichloroethane, chloroform and the like, ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, cyclopentylmethyl ether and the like, N,N-dimethylformamide, dimethylsulfoxide, ethyl acetate, acetonitrile, water, and a mixture thereof. Examples of the condensing reagent include 1-(3-dimethylamino propyl)-3-ethylcarbodiimide or a hydrochloride thereof, dicyclohexylcarbodiimide, 1,1'-carbonyldiimidazole, diphenylphosphoric azide, phosphorous oxychloride, N-[({[(1Z)-1-cyano-2-ethoxy-2-oxoethylidene]amino}oxy)morpholin-4-yl)methylene]-N-methylmethanaminium hexafluorophosphate (COMU), and the like, but are not limited thereto. It may be preferable in some cases for the reaction to use an additive (for example, 1-hydroxybenzotriazole), and it may be advantageous in some cases for the smooth progress of the reaction to carry out the reaction in the presence of an organic base such as triethylamine, N,N-diisopropylethylamine, N-methylmorpholine and the like, or an inorganic base such as potassium carbonate, sodium carbonate, potassium hydroxide and the like.

Furthermore, a method in which the carboxylic acid (c) is converted to a reactive derivative thereof, and then the reactive derivative is reacted with the amine (b) can also be used. Examples of the reactive derivative of the carboxylic acid include acid halides obtained by the reaction with a halogenating agent such as phosphorus oxychloride, thionyl chloride or the like, mixed acid anhydrides obtained by the reaction with isobutyl chloroformate or the like, and active esters obtained by condensation with 1-hydroxybenzotriazole or the like. The reaction of these reactive derivatives and the compound (b) can be carried out under the temperature condition ranging from under cooling to under heating, preferably at −20° C. to 60° C., in a solvent which is inert to the reaction, such as halogenated hydrocarbons, aromatic hydrocarbons, ethers and the like.

References

“Organic Functional Group Preparations” written by S. R. Sandler and W. Karo, 2nd edition, Vol. 1, Academic Press Inc., 1991

“Courses in Experimental Chemistry (5th edition)” edited by The Chemical Society of Japan, Vol. 16 (2005) (Maruzen).

(Step 2)

This step is a step of preparing a compound of the formula (f) by reacting a compound of the formula (d) with a compound of the formula (e).

This reaction is carried out using the formula (d) and the compound of the formula (e) in equivalent amounts, or either thereof in an excess amount, by stirring the mixture under the temperature condition ranging from under cooling to under heating to reflux, preferably at 0° C. to 80° C., usually for 0.1 hours to 5 days, in a solvent which is inert to the reaction or without a solvent. Examples of the solvent used herein are not particularly limited, but include aromatic hydrocarbons such as benzene, toluene, xylene and the like, ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like, halogenated hydrocarbons such as dichloromethane, 1,2-dichloroethane, chloroform and the like, N,N-dimethylformamide, N-methylpyrrolidone, dimethylsulfoxide, ethyl acetate, acetonitrile, and a mixture thereof. It may be advantageous in some cases for the smooth progress of the reaction to carry out the reaction in the presence of an organic base such as triethylamine, N,N-diisopropylethylamine, N-methylmorpholine and the like, or an organic base such as potassium carbonate, sodium carbonate, potassium hydroxide and the like.

References

“Organic Functional Group Preparations” written by S. R. Sandler and W. Karo, 2nd edition, Vol. 1, Academic Press Inc., 1991

“Courses in Experimental Chemistry (5th edition)” edited by The Chemical Society of Japan, Vol. 14 (2005) (Marazen).

(Step 3)

This step is a step of preparing a compound of the formula (g) by introducing an acetoxymethyl group into the 5-position of thiazole in the compound of the formula (f). The compound of the formula (f) is reacted with an aqueous formaldehyde solution or paraformaldehyde in the presence of an acetic acid solvent, which can be carried out under the temperature condition ranging from at room temperature to under heating to reflux. Further, the reaction can also be carried out by adding acetic acid into a solvent which is inert to the reaction, such as halogenated hydrocarbons, aromatic hydrocarbons, ethers and the like, instead of the acetic acid solvent. In addition, the reaction can also be carried out by further adding acetic anhydride.

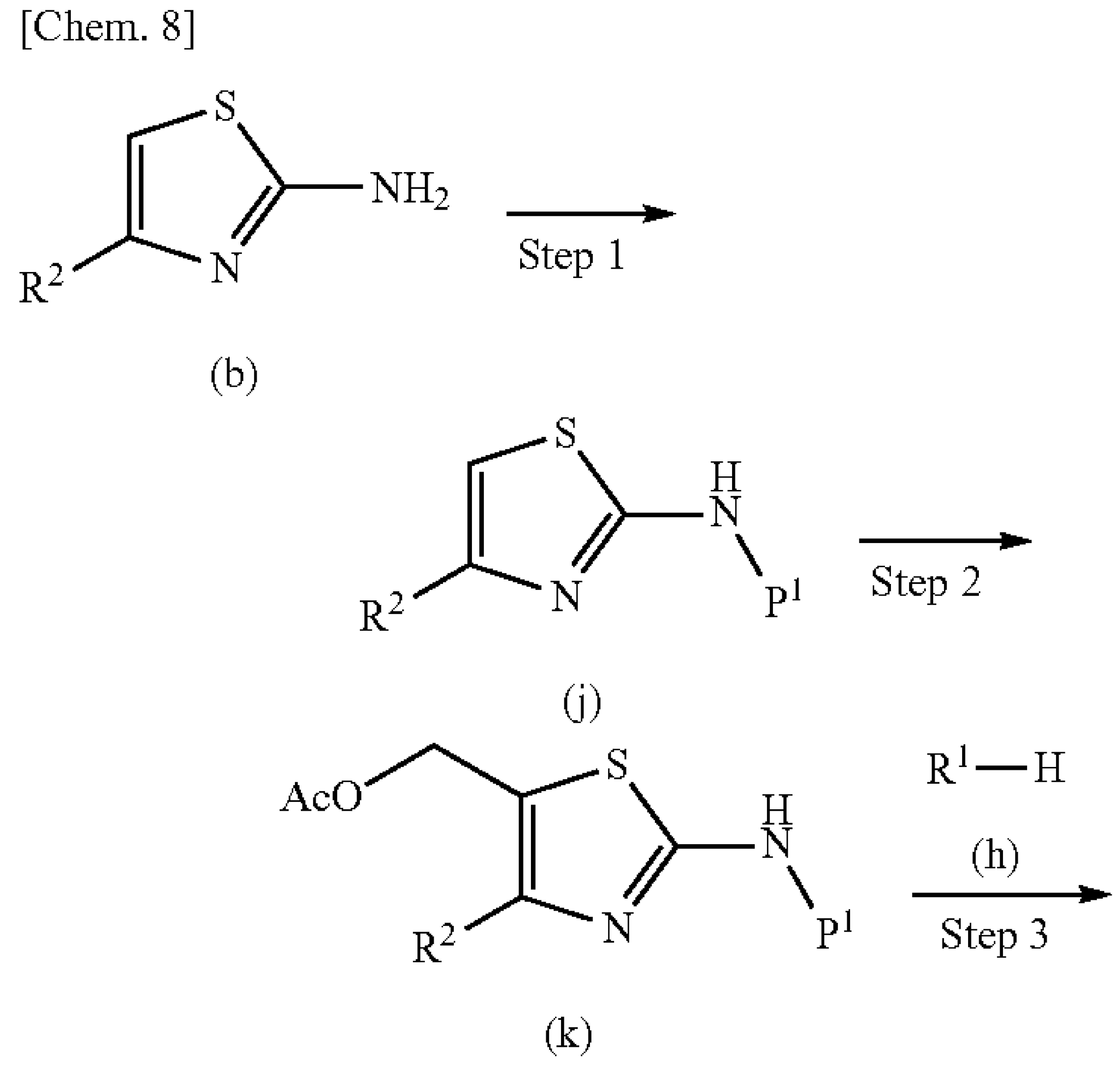
(Step 4)

This step is a step of preparing a compound of the formula (a) by reacting a compound of the formula (g) with a compound of the formula (h) under a basic condition. The present reaction can be carried out by reacting the compound of the formula (g) with the compound of the formula (h) in the presence of an organic base such as triethylamine and N,N-diisopropylethylamine, in an organic solvent which is inert to the reaction, such as halogenated hydrocarbons, aromatic hydrocarbons, ethers, esters, acetonitrile, N,N-dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone and the like. Further, the compound of the formula (h) may also used in an excess amount instead of the organic base. The reaction can be carried out under the temperature condition ranging from under cooling to at room temperature; from at room temperature to under heating; or from at room temperature to under refluxing.

In addition, the compound of the formula (a) can be directly obtained while not isolating the compound of the formula (g) by adding the compound of the formula (h) into the reaction mixture of Step 3.

(Production Process 3)

[Chem. 8]



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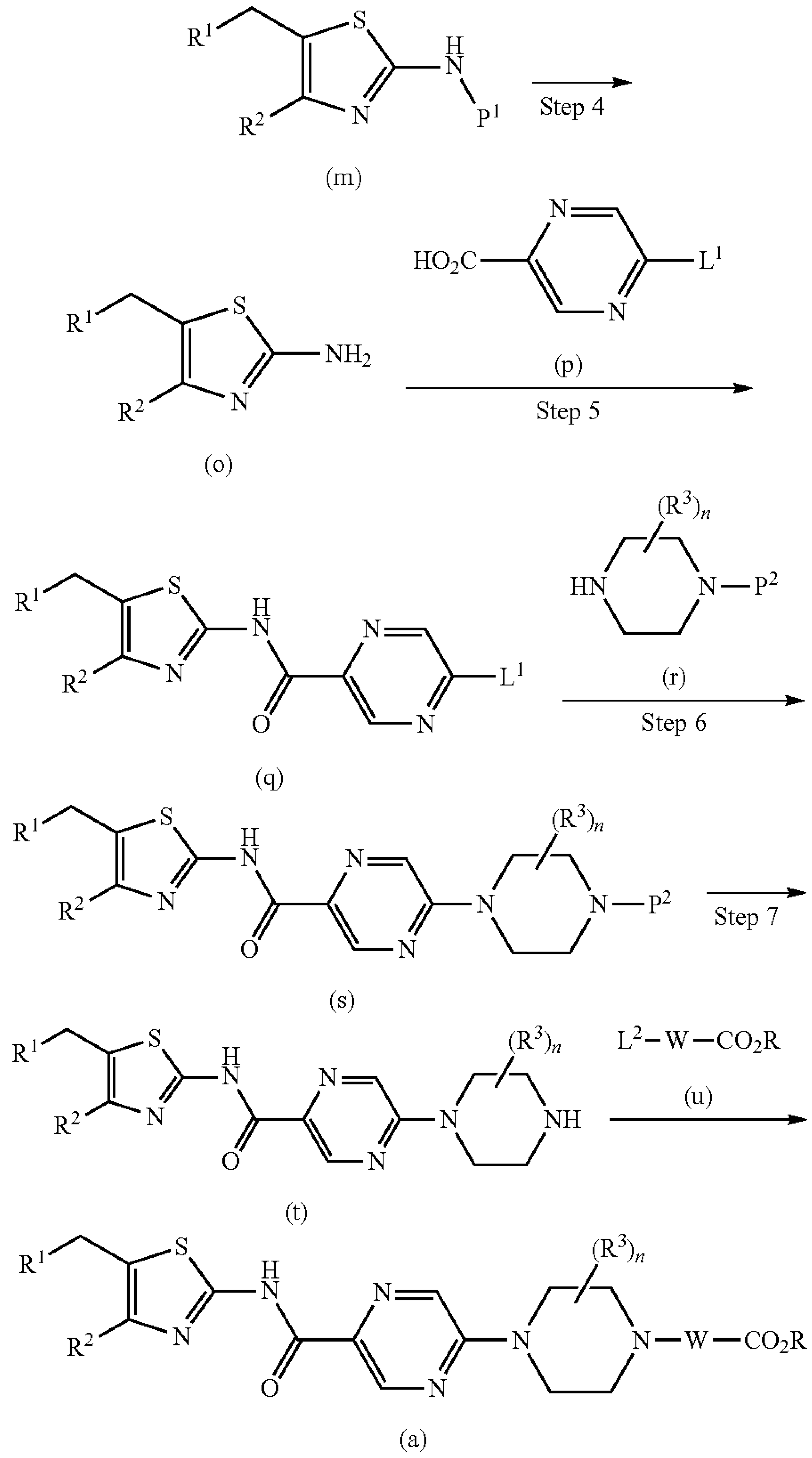

(in which P^1 and P^2 each represent a protective group, and L^2 represents a leaving group).

This production process is another preparation method for the compound of the formula (a), which is a starting material of the compound of the formula (I). Here, as the protective groups represented by P^1 and P^2, the groups of amino groups described in "Protective Groups in Organic Synthesis" written by Wuts and Greene, 4th edition, John Wiley & Sons Inc., 2006, and the like can be used. Examples of the P^1 include acetyl, trifluoroacetyl and the like, examples of P^2 include t-butoxycarbonyl and the like, and examples of L^2 include bromo and the like.

(Step 2)

This compound is a step of protecting the amino group of the compound (b). Here, the present reaction can be carried out with reference to "Protective Groups in Organic Synthesis" written by Wuts and Greene, 4th edition, John Wiley & Sons Inc., 2006.

(Step 2)

This step is a step of preparing a compound of the formula (k) by introducing an acetoxymethyl group into the 5-position of thiazole in a compound of the formula (j). The reaction conditions are the same as in Step 3 of Production Process 2.

(Step 3)

The step is a step of preparing a compound of the formula (m) by reacting a compound of the formula (h) and a compound of the formula (k) under a basic condition. The reaction conditions are the same as in Step 4 of Production Process 2.

(Step 4)

This step is a step of deprotecting a protective group P^1 of an amino group of the compound (m). Here, the present reaction can be carried out with reference to "Protective Groups in Organic Synthesis" written by Wuts and Greene, 4th edition, John Wiley & Sons Inc., 2006.

(Step 5)

This step is a step of obtaining a compound of the formula (q) by subjecting a compound of the formula (o) and a compound of the formula (p) to an amidation reaction. The reaction conditions are the same as in Step 1 of Production Process 2.

(Step 6)

This step is a step of preparing a compound of the formula (s) by reacting a compound of the formula (q) with a compound of the formula (r). The reaction conditions are the same as in Step 2 of Production Process 2.

(Step 7)

This step is a step of deprotecting a protective group P^2 of a compound of the formula (s).

This step can be carried out with reference to "Protective Groups in Organic Synthesis" written by Wuts and Greene, 4th edition, John Wiley & Sons Inc., 2006".

(Step 8)

This step is a step of obtaining the compound of the formula (a) by reacting a compound of the formula (t) and a compound of the formula (n). The present reaction is carried out using the compound (t) and the compound (u) in equivalent amounts, or either thereof in an excess amount, and stirring the mixture under the temperature condition ranging from under cooling to under heating to reflux, preferably at 0° C. to 100° C., usually for 0.1 hours to 5 days, in a solvent which is inert to the reaction, or without a solvent. Examples of the solvent used herein are not particularly limited, but include aromatic hydrocarbons such as benzene, toluene, xylene and the like, ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like, halogenated hydrocarbons such as dichloromethane, 1,2-dichloroethane, chloroform and the like, N,N-dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone, ethyl acetate, acetonitrile, and a mixture thereof. It may be advantageous in some cases for the smooth progress of the reaction to carry out the reaction in the presence of an organic base such as triethylamine, N,N-diisopropylethylamine, N-methylmorpholine and the like, or an inorganic base such as potassium carbonate, sodium carbonate, potassium hydroxide and the like.

References

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"Courses in Experimental Chemistry (5th edition)" edited by The Chemical Society of Japan, Vol. 14 (2005) (Maruzen).

The compound of the formula (I) is isolated and purified as its free compound, or a salt, a hydrate, a solvate, or crystal polymorph substance thereof. The salt of the compound of the formula (I) can also be prepared by a conventional method.

Isolation and purification are carried out by employing general chemical operations such as extraction, fractional crystallization, and various types of fractional chromatography.

Various isomers can be prepared by selecting appropriate starting compound, or separated by separation using differences in the physicochemical properties among the isomers. For example, the optical isomers can be obtained by means of general optical resolution methods of racemic compounds (for example, fractional crystallization introducing the compound into a diastereomer salt with an optically active base or acid; chromatography using a chiral column or the like; and others), or can also be prepared from appropriate optically active starting compound.

The pharmacological activity of the compound of the formula (I) was confirmed by the following test.

Test Example 1: Evaluation of Muscarinic M_3 Receptor Positive Allosteric Modulator Activity

a) Construction of Vector Expressing Human Muscarinic M_3 Receptor

A human muscarinic M_3 receptor gene (GenBank Accession No.: NM_00740.2) was introduced into an expression vector pcDNA3.1™ (Life Technologies).

b) Construction of Cells Stably Expressing Human Muscarinic M_3 Receptor

A vector expressing a human muscarinic M_3 receptor was introduced into a CHO—K1 cell (ATCC No.: CCL-61). The introduction was carried out according to the attached instructions, using a transfection reagent, Lipofectoamine (registered trademark) 2000 Reagent (Life Technologies). The cells were incubated in an alpha Modified Eagle Minimum Essential Medium (α-MEM) including 2 mM glutamine, 10% fetal bovine serum, and 2.0 mg/mL. Geneticin (registered trademark) (Life Technologies) for 4 weeks to acquire a drug-resistant clone.

c) Measurement of Intracellular Ca^{2+} Concentration

The cells obtained in b) above were suspended in an α-MEM including 2 mM glutamine, 10% fetal bovine serum, and 0.2 mg/mL. Geneticin (registered trademark) to the amount from 1.2 to 1.5×10^4 cells/well the day before the experiment, dispersed into a 384-well plate (Model No. 355962, BD Biosciences), and incubated overnight at 37° C. and 5% CO_2. The medium was replaced with a loading buffer (an assay buffer (Hank's balanced salt solution (HBSS), 1 g/L BSA, 20 mM HEPES (pH 7.5), and 2.5 mM probenecid), including 3.1 μM Fluo 4-AM (Dojindo Laboratories) and incubated for about 2 hours at room temperature. Thereafter, the cells were washed with a plate washer EL×405™ (BIO-TEK Instrument, Inc.) set with the assay buffer, and set in an intracellular Ca^{2+} concentration measuring system (FLIPR^{intra} (registered trademark), Molecular Device Co.). The test substances (final concentration of 1 μM or 10 μM) and carbachol (Sigma, final concentration of 0.0024 nM to 10 μM) which had each been dissolved in the assay buffer in advance were set in a FLIPR^{intra} (registered trademark). The test substances were added to the cells in the device and after about 5 minutes, carbachol was added to the cells. An increase rate of the intracellular Ca^{2+} concentration by carbachol was measured (excitement wavelength of 470 nm to 495 nm and a fluorescence wavelength of 515 nm to 575 nm).

For the muscarinic M_3 receptor-positive allosteric modulator activity, a shift toward a lower concentration side of a carbachol concentration-response curve by the test substance was used as an index. That is, a minimum value in the carbachol response was taken as 0%; a minimum value in the carbachol response was taken as 100% from the concentration-response curve of carbachol; the carbachol concentration exhibiting a 50% response was calculated as an EC_{50} value, using a Sigmoid-Emax model non-linear regression method, and thus, the muscarinic M_3 receptor-positive allosteric modulator activity was determined by dividing the EC_{50} value of carbachol in the absence of the test substance by the EC_{50} value of carbachol in the presence of the test substance. For example, when the EC_{50} value of the carbachol in the absence of the test substance was 0.1 μM and the EC_{50} value of carbachol in the presence of the test substance was 0.01 μM, the value of the muscarinic M_3 receptor-positive allosteric modulator activity becomes 10, showing that the test substance causes a 10-fold shift in the EC_{50} value toward to the low concentration side. In Tables below, the columns of 10 μM (-fold shift) show the values in a case where the test substance is added to a final concentration of 10 μM and the columns of 1 μM (-fold shift) show the values in a case where the test substance is added to a final concentration of 1 μM.

Test Example 2: Evaluation of Human c-Mpl-Introduced Ba/F3 Cell Proliferation Activity

The human c-Mpl-introduced Ba/F3 cell proliferation action was measured by the following method.

As a positive control, 1-(5-{[4-(4-chlorothiophen-2-yl)-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl]carbamoyl}-3-fluoropyridin-2-yl)piperidine-4 -carboxylic acid hydrochloride disclosed as Example 315 in Patent Document 1, represented by the formula (A1) above, was used. Further, it is known that the compound has a good human c-Mpl-introduced Ba/F3 cell proliferative activity as disclosed in Table 1 in Patent Document 1.

a) Construction of Vector Expressing Human c-Mpl Receptor

A human c-Mpl receptor gene (GenBank Accession No.: M90102.1) was transfected into an expression vector pEF-BOS (Nucleic Acids Research, 18; pp 4322 (1990)).

b) Concentration of Cell Stably Expressing Human c-Mpl Receptor

A vector expressing a human c-Mpl receptor was introduced into a Ba/F3 cell (RIKEN BRC: RCB0805). For the introduction, an electroporation method was used. pEF-BOS-c-mpl (10 μg), pSV2bsr (1 μg, Kaken Pharmaceutical Co., Ltd.) and 1×10^9 of Ba/F3 cells were put into cuvettes with a gap width of 0.4 cm and electroporated under a condition of 1.5 kV (25 μF) in a Gene Pulser (registered trademark) (BioRad). The cells were incubated in an RPMI-1640 medium supplemented with a 0.5% WEHI conditioned medium (BD Biosciences) and 10% fetal bovine serum for 3 days, and thereafter, and the cells were incubated for 30 days in an RPMI-1640 medium, to which 10 μg/mL blasticidin had been further added, thereby acquiring a drug-resistance clone.

c) Measurement of Cell Proliferative Activity

The cells obtained in b) above were dispersed into an RPMI-1640 medium supplemented with a 0.5% WEHI conditioned medium and 10% fetal bovine serum, and used. The day before the experiment, the test substances (final concentration of 100 mM to 10 μM) which has been dissolved in a medium for assay (an RPMI-1640 medium supplemented with 10% fetal bovine serum) were added to a 384-well plate (Model No. 781185, Greiner bio-one). The cells after the medium had been replaced with the medium for assay were dispensed to a 384-well plate to which the test substance had been added, to 1×10^4 cells/well, and incubated overnight at 37° C. and 5% CO_2. On the experiment day, a solution of a Cell counting kit (Dojindo Laboratories) was added to each well of the 384-well plate, and the cells were incubated for about 5 hours at 37° C., and 5% CO_2. Thereafter, the absorbance (an absorbance wavelength of 450 nm) of each well was measured using Safire^2 (registered trademark) (TECAN), and used as an index for the number of cells. Further, as a negative control, a well to which the test substances had not been added was prepared.

By taking the absorbance of the well to which the test substance had been not added as 0% and taking the absorbance in a case where the positive control had been added to a final concentration of 1 μM as 100%, a cell proliferation rate (%) was calculated from the absorbance of the well to which the test substance has been added. From the obtained results, the test substance concentration exhibiting 30% proliferation by a Sigmoid-Emax model non-linear regression method was calculated as an EC_{30} value.

Combinations of the muscarinic M_3 receptor-positive allosteric modulator activity (-fold shift) and the human c-Mpl-introduced Ba/F3 cell proliferative activity (EC_{30} value, nM) of some Example compounds of the present invention are shown in Tables 1 and 2. However, Ex represents Example Compound Nos. as described later (this shall apply hereinafter).

TABLE 1

	Test Example 1		Test Example 2
Ex	10 μM (-fold shift)	1 μM (-fold shift)	EC_{30} (nM)
3	253	101	780
4	200	25	>3000
10	87	21	>10000
11	226	33	>10000
12	178	33	>10000
13	326	43	>10000
15	159	31	>10000
17	109	15	>10000
21	149	25	>10000
27	330	31	>10000
28	108	36	5300
33	182	40	>10000
34	116	18	>10000
41	160	43	>10000
42	141	39	>10000
43	224	76	>10000
46	199	29	>10000
48	113	27	>10000
49	224	67	>10000
50	190	108	2300
51	287	102	2600
52	196	36	>10000
54	134	36	>10000
60	235	33	9700
61	229	35	1300
62	195	37	>10000
63	186	39	>10000
64	128	23	>10000
65	90	24	>10000
67	114	40	>10000
69	177	27	>10000

TABLE 2

	Test Example 1		Test Example 2
Ex	10 μM (-fold shift)	1 μM (-fold shift)	EC_{30} (nM)
71	151	28	>10000
72	152	31	>10000
79	171	60	>10000

TABLE 2-continued

	Test Example 1		Test Example 2
Ex	10 μM (-fold shift)	1 μM (-fold shift)	EC_{30} (nM)
81	94	89	1800
82	43	11	500
91	139	19	>10000
92	203	30	>10000
95	233	91	>10000
97	121	55	3000
100	229	82	2800
101	112	64	3200
103	307	202	2700
104	195	75	1700
106	270	41	>10000
107	318	73	>10000
108	169	56	>10000
109	191	30	>10000
111	627	203	5000
118	167	57	>10000
119	503	110	>10000
124	101	28	>10000
126	318	79	>10000
128	192	73	8000
129	148	67	>10000
130	151	95	>10000
132	41	15	>10000
133	164	30	>10000
135	204	25	>10000
140	158	28	>10000
141	159	45	>10000
142	160	52	4700
143	81	65	7800

In Test Example 1, a substantial number of the Example compounds which had been subjected to the present test shifted the EC_{50} values to almost 100-fold or more toward a lower concentration side when added at 10 μM, and shifted the EC_{50} values to almost 10-fold or more toward a lower concentration side when added at 1 μM. In addition, for some Example compounds of the present invention, from the viewpoint that the compounds alone do not change the intracellular Ca^{2+} concentration, it was found that these compounds have no muscarinic M_3 receptor agonistic activity.

Furthermore, in Test Example 2, it was found that a substantial number of the Example compounds which had been subjected to the present test have a weak human c-Mpl-introduced Ba/F3 cell proliferative activity or have none.

The compound of the present invention is used as an agent for preventing or treating bladder/urinary tract diseases associated with bladder concentrations via a muscarinic M_3 receptor, as a muscarinic M_3 receptor-positive allosteric modulator, and thus preferably has a weak or none increased platelet action based on c-Mpl-introduced Ba/F3 cell proliferative activity.

On the other hand, Table 1 of Patent Document 1 above discloses that the compound of Example 315 represented by the formula (A1) above has 3.2 nM of EC_{30} value of c-Mpl-introduced Ba/F3 cell proliferation action.

Test Example 3: Effect on Electrical Field Stimulation-Induced Contraction in Rat Isolated Bladder

As an effect on the nerve stimulation-dependent bladder contraction in in vitro, the effect of the Example compounds of the present invention in the electrical field stimulation-induced contraction of the rat isolated bladder was measured by the following method. That is, a bladder specimen having a width of about 2 mm and a length of about 10 mm in the longitudinal direction from the bladder isolated from a Sprague-Dawley (SD) female rat (Japan SLC, Inc.) was prepared. The prepared bladder specimen was suspended in an organ bath filled with 10 mL of a Krebs-Henseleite solution. The Krebs-Henseleite solution was aerated at 95% 02 and 5% CO_2, and kept at 37° C. After carrying out stabilization at an initial tension of 1 g, the contraction was caused twice with 60 nM KCl. After stabilization of the specimen with a Krebs-Henseleite solution, the concentration was caused by carrying out electrical field stimulation at 20 V with an electrical stimulation device (Nihon Kohden) (a stimulation frequency of 8 Hz, a pulse width of 0.3 msec, and a stimulation time of 10 seconds). By repeating the transmural electrical stimulation at an interval of 2 minutes, a voltage was adjusted to obtain a contraction height of approximately 50% of the contractile response at 20 V. After the contraction by electrical field stimulation had been stabilized, 10 μL of the test substances dissolved in 100% dimethyl sulfoxide in advance (final concentrations of 3 μM, 10 μM, and 30 μM) was added thereto. The test substances were cumulatively administered at the following concentrations after the low-concentration contractile response had been stabilized. The response was taken into a personal computer through a PowerLab (registered trademark) (AD Instruments, Inc.), and analyzed by LabChart (registered trademark) (AD Instruments, Inc.). When the area under the response (area under curve, AUC) in each contraction response was calculated and the value before treatment with the test substance was taken as 100%, the enhancement rate (% of pre) of the isolated bladder concentrations after treatment with the test substance was calculated.

The enhancement rates of the isolated bladder contractions by 10 μM of some Example compounds are shown in Table 3.

Furthermore, it was confirmed that all the Example compounds which have been subjected to the present test do not cause contraction in a state in which there is no electrical stimulation and the compounds alone do not show a bladder contraction action.

TABLE 3

Ex.	Enhancement rate (% of pre) of isolated bladder contractions
3	152
10	161
11	123
13	126
15	124
21	141
28	123
34	137
42	158
43	179
46	132
48	143
49	153
50	183
51	151
52	132
60	144
61	176
64	162
65	127
67	116
72	157
82	158

TABLE 3-continued

Ex.	Enhancement rate (% of pre) of isolated bladder contractions
95	150
109	183
119	154
124	132
133	151
135	139
140	161
141	121
142	196
143	140

From the above, it was confirmed that the Example compounds alone, which have been subjected to the present test, do not cause a contraction action in the isolated rate bladder, but have an action of enhancing electrical field stimulation-induced contraction.

Test Example 4: Effect on Pelvic Nerve Stimulation-Induced Elevation of Intravesical Pressure in Anesthetized Rats

The effect of the Example compounds of the present invention in the pelvic nerve electrical stimulation-induced elevation of intravesical pressure using rats as an action of nerve stimulation-dependent bladder contraction in vivo was measured by the following method. That is, SD female rats (Japan SLC, Inc.) were used and its lower abdomen was dissected at the midline under pentobarbital anesthesia (50 mg/kg ip). After ligating and cutting the ureter on both sides, a cannula (PE-5) for measuring the intravesical pressure was inserted into the bladder from the external urethral opening and fixed b a clip. After injecting about 200 μL of saline through the cannula that had been inserted into the bladder, the other side was connected to a pressure transducer to measure the intravesical pressure. Under a stereoscopic microscope observation, the pelvic nerve in the vicinity of the bladder was peeled and an electrode for nerve stimulation (unique Medical) was placed. The abdominal cavity was filled with mineral oil (MP BIOMEDICALS). After placing in a post-operative stabilization period, the pelvic nerve was subjected to electrical stimulation (stimulation voltage: 10 V, stimulation frequency: 8 Hz, pulse width: 0.3 msec, and stimulation time: 10 seconds) to elicit the elevation of intravesical pressure, using an electrical stimulator (Nihon Kohden). By repeating the electrical stimulation at an interval of 2 minutes while adjusting the voltage, the voltage was adjusted to elicit about 50% to 70% elevation of intravesical pressure elicited at 10 V. Thereafter, by repeating the electrical stimulation at an interval of 10 minutes, the increase in the intravesical pressure by electrical stimulation was stabilized three times or more, and the test substance (an administration amount of 3 mg/kg) was then administered from the catheter detained in the vein at a volume of 1 mL/kg, thus measuring an effect of the elevation of the intravesical pressure of the test substance for 1 hour. The test substance was dissolved in water supplemented with 10% dimethylsulfoxide and 10% Cremophor.

The response was applied to a personal computer through a PowerLab (registered trademark) and analyzed by LabChart (registered trademark). The AUC of each elevation of the intravesical pressure was calculated, the intravesical pressure elevation rate (% of pre) after the treatment with the test substance was calculated by taking an average value of the values measured three times before the treatment with the test substance as 100%, and the maximum effect during a period within one hour after administration of the compound was considered as the effect of the test substance.

The elevation rates (% of pre) of the intravesical pressure when some Example compounds were administered at 3 mg/kg are shown in Table 4.

TABLE 4

Ex.	Enhancement rate (% of pre) of isolated bladder contractions
3	251
10	145
11	132
13	132
15	142
21	155
28	184
34	134
42	149
43	125
46	126
48	121
49	172
50	207
51	223
52	129
60	130
61	129
64	135
65	128
67	126
72	155
82	138
95	239
109	180
119	173
124	143
133	150
135	168
140	148
141	175
142	199
143	172

In addition, it was confirmed that the Example compounds evaluated in the present test do not cause an elevation of the intravesical pressure in a state in which electrical stimulation is not given, and the compounds alone do not show elevation of the intravesical pressure.

From the above, it was confirmed that the Example compounds listed in Table 4 alone do not show elevation of the intravesical pressure but have an action of enhancing effect on the pelvic nerve electrical stimulation-induced elevation of intravesical pressure in the anesthetized rats.

As shown in the results of each of the tests above, it was confirmed that the compound of the formula (I) has a muscarinic M_3 receptor-positive allosteric modulator activity, and further, it enhances the bladder contraction in a nerve stimulation-dependent manner in in vitro, as well as enhances an elevation in the intravesical pressure in a nerve stimulation-dependent manner in in vitro. Accordingly, the compound of the formula (I) can be used to prevent or treat bladder/urinary tract diseases associated with bladder contractions via a muscarinic M_3 receptor, in particular, voiding dysfunction or urine storage dysfunction in the bladder/urethral diseases. The compound of the formula (I) can be used for preventing or treating, for example, voiding dysfunction or urine storage dysfunction in underactive bladder, hypotonic bladder, acontractile bladder, detrusor underactivity, neurogenic bladder, urethra relaxation failure, detrusor-external urethral sphincter dyssynergia, overactive bladder, urinary frequency, nocturia, urinary incontinence, benign prostatic hyperplasia, interstitial cystitis, chronic prostatitis, and urinary tract stones. In particular, the compound of the formula (I) can be used for preventing or treating voiding dysfunction or urine storage dysfunction in underactive bladder, hypotonic bladder, acontractile bladder, detrusor underactivity, and neurogenic bladder.

In addition, the compound of formula (I) can become a therapeutic drug that is more excellent in safety from the viewpoint that the compound alone does not show an agonistic effect on a muscarinic M_3 receptor, but shows an effect on enhancing the nerve stimulation-dependent bladder contraction, and accordingly, cholinergic side effects that have been reported in the existing drugs can be avoided.

A pharmaceutical composition including one or two or more kinds of the compound of the formula (I) as an active ingredient can be prepared using an excipient which is usually used in the art, that is, an excipient for a pharmaceutical preparation, a carrier for a pharmaceutical preparation, and the like, according to a method usually used.

Administration can be accomplished either by oral administration via tablets, pills, capsules, granules, powders, solutions, and the like, or parenteral administration via injections, such as intraarticular, intravenous, and intramuscular injections, suppositories, transdermal liquid preparations, ointments, transdermal patches, transmucosal liquid preparations, transmucosal patches, inhalers, and the like.

As a solid composition for oral administration, tablets, powders, granules, and the like are used. In such a solid composition, one kind or two or more kinds of the active ingredients are mixed with at least one inactive excipient. In a conventional method, the composition may contain inactive additives such as a lubricant, a disintegrating agent, a stabilizer, or a solubilization assisting agent. If necessary, tablets or pills may be coated with a sugar or with a film of a gastric or enteric coating substance.

The liquid composition for oral administration includes pharmaceutically acceptable emulsions, solutions, suspensions, syrups elixirs, or the like, and also includes generally used inert diluents, for example, purified water or ethanol. The liquid composition may also include auxiliary agents such as a solubilization assisting agent, a moisturizing agent, and a suspending agent, sweeteners, flavors, aromatics, and antiseptics, in addition to the inert diluent.

The injections for parenteral administration include sterile aqueous or non-aqueous solution preparations, suspensions, or emulsions. The aqueous solvent includes, for example, distilled water for injection and saline. Examples of the non-aqueous solvent include alcohols such as ethanol. Such a composition may further include a tonicity agent, an antiseptic, a moistening agent, an emulsifying agent, a dispersing agent, a stabilizing agent, or a solubilizing assisting agent. These are stabilized, for example, by filtration through a bacteria retaining filter, blending of a bactericide, or irradiation. In addition, these can also be used by preparing a sterile solid composition, and dissolving or suspending it in sterile water or a sterile solvent for injection prior to its use.

Examples of the agent for external use include ointments, hard plasters, creams, jellies, cataplasms, sprays, and lotions. The agent further contains generally used ointment bases, lotion bases, aqueous or non-aqueous liquid preparations, suspensions, emulsions, or the like.

As the transmucosal agents such as an inhaler and a transnasal agent, those in the form of a solid, liquid, or semi-solid state are used, and can be prepared in accordance with a method known in the related art. For example, a known excipient, and also a pH adjusting agent, an antiseptic, a surfactant, a lubricant, a stabilizing agent, a thickening agent, or the like may be appropriately added thereto. For the administration, an appropriate device for inhalation or blowing can be used. For example, a compound may be administered alone or as a powder of formulated mixture, or as a solution or suspension in combination with a pharmaceutically acceptable carrier, using a known device or sprayer such as a metered administration inhalation device. A dry powder inhaler or the like may be for single or multiple administration use, and a dry powder or a powder-containing capsule may be used. Alternatively, this may be in a form such as a pressurized aerosol spray that uses an appropriate propellant agent, for example, a suitable gas such as chlorofluoroalkanes, and carbon dioxide, or other forms.

Usually, in the case of oral administration, the daily dose is from about 0.001 mg/kg to 100 mg/kg, preferably from 0.1 mg/kg to 30 mg/kg, and more preferably from 0.1 mg/kg to 10 mg/kg, per body weight, administered in one portion or in 2 to 4 divided portions. In the case of intravenous administration, the daily dose is suitably administered from about 0.0001 mg/kg to 10 mg/kg per body weight, once a day or two or more times a day. In addition, a transmucosal agent is administered at a dose from about 0.001 mg/kg to 100 mg/kg per body weight, once or plural times a day. The dose is appropriately decided in response to the individual case by taking the symptoms, the age, and the gender, and the like into consideration.

Although there are differences depending on a route of administration, a dosage form, an administration site, and a type of the excipient or additive, a pharmaceutical composition of the present invention comprises 0.001% by weight to 100% by weight of, as an embodiment, 0.01% by weight to 50% by weight of, one or more of the compound of the formula (I) or a salt thereof which is the active ingredient.

The compound of the formula (I) may be used in combination with various agents for treating or preventing diseases on which the compound of the formula (I) is considered to show the effect. Such combined preparations may be administered simultaneously, or separately and continuously, or at a desired time interval. The preparations to be co-administered may be a blend, or may be prepared individually.

EXAMPLES

Hereinbelow, the production process for the compound of the formula (I) will be described in more detail with reference to Examples. Further, the present invention is not limited to the compounds described in the Examples below. Further, the production processes for the starting compounds will be described in Preparation Examples. In addition, the production processes for the compound of the formula (I) are not limited to the production processes of the specific Examples shown below, but the compound of the formula (I) can be prepared by a combination of these production processes or a method that is apparent to a person skilled in the art.

Further, in the present specification, nomenclature software such as ACDC/Name (registered trademark, Advanced Chemistry Development, Inc.) may be used for nomenclature of compounds in some cases.

The powder X-ray diffraction is measured using RINT-TTRII under the condition of a tube: Cu, a tube current: 300 mA, a tube voltage: 50 kV, a sampling width: 0.020°, a scanning speed: 4°/min, a wavelength: 1.54056 angstroms, and a measurement diffraction angle (2θ): 2.5° to 40°. Further, a device including data processing was handled in accordance with the method and procedure instructed in each device.

The values obtained from various spectra may cause some errors according to the direction of the crystal growth, particle sizes, measurement conditions, and the like in some cases. Accordingly, considering these errors, in the present specification, the description of diffraction angles (2θ (°)) in the powder X-ray diffraction patterns is measured value, but depending on the measuring conditions, these diffraction angles mean that error ranges which are usually acceptable may occur and means that they are approximate values. Usually, the error range of the diffraction angle (2θ (°)) in the powder X-ray diffraction is ±0.2°. However, for the powder X-ray diffraction patterns, in terms of the properties of data, crystal lattice spacing and general patterns are important in the certification of crystal identity, and the diffraction angle and the diffraction intensity may vary slightly depending on the direction of crystal growth, the particle size, and the measurement condition, and they should not be strictly construed.

Moreover, the following abbreviations may be used in Examples, Preparation Examples, and Tables below in some cases.

PEx: Preparation Example No., Ex: Example No., PSyn: Preparation Example No. prepared by the same method, Syn: Example No. prepared by the same method, Structure: Structural chemical formula (Me represents methyl, Et represents ethyl, Ac represents acetyl, nPr represnets n-propyl, iPr represents isopropyl, cPr represents cyclopropyl, iBu represents isobutyl, Boc represents tert-butoxycarbonyl, Ts represents 4-methylphenyl sulfonyl, COMU represents N-[({[(1Z)-1-cyano-2-ethoxy-2-oxoethylidene]amino}oxy)(morpholin-4-yl)methylene]-N-methylmethaminium hexafluorophosphate, WSCD.HCl represents N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide monohydrochloride, and ODS represents octadecylsilyl), Data: Physicochemical data, ESI+: m/z values in mass spectroscopy (Ionization method ESI, representing $[M+H]^+$ unless otherwise specified), ESI−: m/z values in mass spectroscopy (Ionization method ESI, representing $[M-H]^-$ unless otherwise specified), APCI/ESI+: APCI/ESI-MS (atmospheric pressure chemical ionization method APCI, representing $[M+H]^+$ unless otherwise specified; in which APCI/ESI means simultaneous measurement of APCI and ESI), EI: m/z values in mass spectroscopy (Ionization method EI, representing $[M]^+$ unless otherwise specified), CI: m/z values in mass spectroscopy (Ionization method CI, representing $[M+H]^+$ unless otherwise specified), NMR-DMSO-d: δ (ppm) of peaks in ^{1}H-NMR in DMSO-d_6, s: singlet (spectrum), d: doublet (spectrum), t: triplet (spectrum), br: broad line (spectrum) (e.g.: brs), m: multiplet (spectrum). Further, HCl in the structural formula indicates that the compound is a monohydrochloride; 2HCl indicates that the compound is a dihydrochloride: 3HCl indicates that the compound is a trihydrochloride, and 2 maleic acid indicates that the compound is a **[**dimalate**]** *dimaleate*.

In addition, for the sake of convenience, a concentration of mol/L is represented by M. For example, a 1 M aqueous sodium hydroxide solution means a 1 mol/L aqueous sodium hydroxide solution.

Preparation Example 1

A mixture of 4-[3-fluoro-5-(trifluoromethyl)phenyl]-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazolyl-2-amine (1.0 g), 5-chloropyrazine-2-carboxylic acid (685 mg), COMU (1.9 g), dioxane (10 mL), and N,N-diisopropylethylamine (1.5 mL) was stirred at room temperature for 1 hour. The reaction mixture was diluted with ethyl acetate, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain 5-chloro-N-(4-[3-fluoro-5-(trifluoromethyl)phenyl]-5-{([(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl)pyrazine-2-carboxamide (800 mg) as a solid.

Preparation Example 2

To a mixture of 5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-4-[4-(trifluoromethyl)thiophen-2-yl]-1,3-thiazol-2-amine (2.9 g) and dichloromethane (60 mL) were added 5-chloropyrazine-2-carboxylic acid (1.7 g), N,N-dimethyl-4-aminopyridine (340 mg), and WSCD.HCl (2.1 g), followed by stirring at 40° C. for 15 minutes. The reaction mixture was cooled to room temperature, diluted with chloroform, and washed with a saturated aqueous sodium hydrogen carbonate solution. The aqueous layer was extracted with chloroform/methanol and the organic layer was combined and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform-ethyl acetate) to obtain 5-chloro-N-(5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-4-[4-(trifluoromethyl)thiophen-2-yl]-1,3-thiazol-2-yl)pyrazine-2-carboxamide (2.4 g) as a solid.

Preparation Example 3

To a mixture of 5-chloropyrazine-2-carboxylic acid (30.5 g) and ethyl acetate (500 mL) were added thionyl chloride (55 mL) and N,N-dimethylformamide (0.57 mL), followed by stirring at 75° C. for 1.5 hours. The reaction mixture was concentrated under reduced pressure and toluene was added thereto, followed by carrying out a concentration operation.

A mixture of 4-(4-chlorothiophen-2-yl)-1,3-thiazol-2-amine (3.20 g) and cyclopentylmethyl ether (500 mL) was ice-cooled, and triethylamine (62 mL), and a mixture of the previously obtained compound and cyclopentyl ether (100 mL) were slowly added thereto. The reaction mixture was stirred at room temperature for 2-days. To the reaction mixture was added water, followed by extraction with ethyl acetate/tetrahydrofuran. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was mixed with diisopropyl ether and the solid was collected by filtration to obtain 5-chloro-N-[4-(4-chlorothiophen-2-yl)-1,3-thiazol-2-yl]pyrazine-2-carboxamide (46.6 g) as a solid.

Preparation Example 4

To a mixture of 6-methoxy-5-(trifluoromethyl)nicotinic acid (7.8 g) and dichloromethane (80 mL) were added N,O-dimethylhydroxylamine hydrochloride (4.3 g), WCSCD.HCl (9.5 g), and N,N-diisopropylethylamine (30 mL) under ice-cooling. The reaction mixture was stirred at room temperature for 17 hours. The reaction mixture was concentrated under reduced pressure, and to the residue were added ethyl acetate and water, followed by stirring for 30 minutes. The organic layer was separated, the aqueous layer was extracted with ethyl acetate, and the organic layer was combined, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain N,6-dimethoxy-N-methyl-5-(trifluoromethyl)nicotinamide (5.0 g) as an oil.

Preparation Example 5

A mixture of N-(4-[3-fluoro-5-(trifluoromethyl)phenyl]-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl) acetamide (1.4 g), ethanol (10 mL), and a 6 M aqueous sodium hydroxide solution (5 mL) was stirred at 120° C. for 15 minutes under microwave irradiation. To the reaction mixture was added water, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain 4-[3-fluoro-5-(trifluoromethyl)phenyl]-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-amine (1.0 g) as an oil.

Preparation Example 6

A mixture of N-(5-{[(2R,5R)-2,5-dimethylpyrrolidin-1-yl]methyl}-4-[3-fluoro-5-(trifluoromethyl)phenyl]-1,3-thiazol-2-yl)acetamide (916 mg) and 80% sulfuric acid (10 mL) was stirred at 100° C. for 1 hour. The reaction mixture was cooled to 5° C. and alkalified by the addition of a 5 M aqueous sodium hydroxide solution and a saturated aqueous sodium hydrogen carbonate solution. The mixture was extracted with chloroform, and the organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (hexane-ethyl acetate) to obtain 5-{[(2R,5R)-2,5-dimethylpyrrolidin-1-yl]methyl}-4-[3-fluoro-5-(trifluoromethyl)phenyl]-1,3-thiazol-2-amine (685 mg) as a solid.

Preparation Example 7

To a mixture of N-{5-[(diethylamino)methyl]-4-[3-fluoro-5-(trifluoromethyl)phenyl]-1,3-thiazol-2-yl}acetamide (392 mg) and ethanol (4 mL) was added a 6 M aqueous sodium hydroxide solution (2 mL), followed by heating to reflux for 5 hours. The reaction mixture was cooled to room temperature and water was added thereto, followed by extraction with chloroform. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (hexane-ethyl acetate) to obtain 5-[(diethylamino)methyl]-4-[3-fluoro-5-(trifluoromethyl)phenyl]-1,3-thiazol-2-amine (264 mg) as a solid.

Preparation Example 8

To a mixture of tert-butyl (3R)-4-[5-[(4-[3-fluoro-5-(trifluoromethyl)phenyl]-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl)carbamoyl]pyrazin-2-yl]-3-methylpiperzine-1-carboxylate (19.9 g) and methanol (60 mL) was added hydrogen chloride (4 M dioxane solution, 180 mL), followed by stirring at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure. To the residue was added ethyl acetate (250 mL), followed by stirring at room temperature for 30 minutes. The solid was collected by filtration to obtain N-(4-[3-fluoro-5-(trifluoromethyl)phenyl]-5-{[(2R)-2-methylpyrrolidin

-1-yl]methyl}-1,3-thiazol-2-yl)-5-[(2R)-2-methylpiperazin-1-yl]pyrazine-2-carboxamide trihydrochloride (20.1 g) as a solid.

Preparation 9

To a mixture of tert-butyl (3S)-4-(3-ethoxy-3-oxopropyl)-3-methylpiperazine-1-carboxylate (1.2 g) and ethanol (6 mL) was added hydrogen chloride (4 M ethyl acetate solution, 6 mL), followed by stirring at 80° C. for 1.5 hours. The reaction mixture was cooled to room temperature and stirred overnight. The solid was collected by filtration to obtain ethyl 3-[(2S)-2-methylpiperazin-1-yl]propanoate dihydrochloride (995 mg) as a solid.

Preparation Example 10

To a mixture of tert-butyl (2R)-2-ethylpyrrolidine-1-carboxylate (3.4 g) and dioxane (25 mL) was added hydrogen chloride (4 M dioxane solution, 25 mL), followed by stirring at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, and to the residue were added diethyl ether, followed by stirring. The solid was collected by filtration to obtain (2R)-2-ethylpyrrolidine hydrochloride (2.1 g) as a solid.

Preparation Example 11

A mixture of {2-acetamido-4-[3-fluoro-5-(trifluoromethyl)phenyl]-1,3-thiazol-5-yl}methyl acetate (500 mg), diethylamine (0.3 mL), N,N-diisopropylethylamine (0.7 mL), and N-methylpyrrolidone (5 mL) was stirred at 100° C. for 2 hours. To the reaction mixture was added ethyl acetate, followed by washing with water and saturated brine. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain N-{5-[(diethylamine)methyl]-4-[3-fluoro-5-(trifluoromethyl)phenyl]-1,3-thiazol-2-yl}acetamide (397 mg) as a solid.

Preparation Example 12

To a mixture of {2-acetamide-4-[3-chloro-5-(trifluoromethyl)phenyl]-1,3-thiazol-5-yl}methyl acetate (900 mg) and N,N-dimethylformamide (4 mL) were added (2R)-2-methylpyrrolidine (293 mg) and N,N-diisopropylethylamine (0.78 mL), followed by stirring at 110° C. for 30 minutes under microwave irradiation. To the reaction mixture was added water, followed by extraction with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (hexane-ethyl acetate) to obtain N-(4-[3-chloro-5-(trifluoromethyl)phenyl]-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl)acetamide (896 mg) as a solid.

Preparation Example 13

A mixture of N-[4-[3-fluoro-5-(trifluoromethyl)phenyl]-1,3-thiazol-2-yl]acetamide (6.0 g), acetic acid (30 mL), a 36% aqueous formaldehyde solution (7.5 mL), and acetic anhydride (9 mL) was stirred at 170° C. for 15 minutes under microwave irradiation. The reaction mixture was concentrated under reduced pressure, and to the residue was added ethyl acetate. The mixture was washed with a saturated aqueous sodium hydrogen carbonate solution, water, and saturated brine, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform-methanol) and the obtained solid was mixed with diisopropyl ether. The solid was collected by filtration to obtain {2-acetamido-4-[3-fluoro-5-(trifluoromethyl)phenyl]-1,3-thiazol-5-yl}methyl acetate (2.6 g) as a solid.

Preparation Example 14

A mixture of ethyl 3-[(2R)-4-(5-{[4-(4-chlorothiophen-2-yl)-1,3-thiazol-2-yl]carbamoyl}pyrazin-2-yl)-2-methylpiperazin-1-yl]propanoate (1.0 g), acetic acid (10 mL), a 37% aqueous formaldehyde solution (1.5 mL), and acetic anhydride (1.8 mL) was stirred at 80° C. for 7 hours. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. To the residue were added water and a saturated aqueous sodium hydrogen carbonate solution, followed by extraction with chloroform/isopropanol. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform-methanol).

The obtained compound and pyridine (10 mL) were mixed, and acetic anhydride (0.9 mL) was added thereto, followed by stirring at room temperature for 30 minutes. To the reaction mixture was added water, followed by extraction with ethyl acetate. The organic layer was washed with water and a saturated aqueous sodium hydrogen carbonate solution, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain ethyl 3-[(2R)-4-(5-{[5-(acetoxymethyl)-4-(4-chlorothiophen-2-yl)-1,3-thiazol-2-yl]carbamoyl}pyrazin-2-yl)-2-methylpiperazin-1-yl]propanoate (566 mg) as a solid.

Preparation Example 15

A mixture of N-{4-[4-methoxy-3-(trifluoromethyl)phenyl]-1,3-thiazol-2-yl}acetamide (3.0 g), 37% aqueous formaldehyde solution (7.2 mL), acetic anhydride (9 mL), and acetic acid (30 mL) was stirred at 100° C. for 5 hours. The reaction mixture was concentrated under reduced pressure, and to the residue was added diisopropyl ether. The solid was collected by filtration to obtain {2-acetamido-4-[4-methoxy-3-(trifluoromethyl)phenyl]-1,3-thiazol-5-yl}methyl acetate (2.0 g) as a solid.

Preparation Example 16

A mixture of N-{4-[3-fluoro-5-(trifluoromethyl)phenyl]-1,3-thiazol-2-yl}acetamide (2.8 g), acetic acid (20 mL), a 36% aqueous formaldehyde solution (3.6 mL), and acetic anhydride (4.4 mL) was stirred at 170° C. for 30 minutes under microwave irradiation. The reaction mixture was concentrated under reduced pressure, and then the obtained solid was washed with methanol and collected by filtration.

The obtained solid (1.8 g) was mixed with N-methylpyrrolidone (20 mL), (2R)-2-methylpyrrolidine (608 mg), and N,N-diisopropylethylamine (2.5 mL), followed by stirring at 100° C. for 30 minutes. The reaction was cooled to room temperature, and water was added thereto, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain N-(4-[3-fluoro-5-(trifluoromethyl)phenyl]-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl)acetamide (1.4 g) as a solid.

Preparation Example 17

N-[4-(4-Chlorothiophen-2-yl)-1,3-thiazol-2-yl]-2,2,2-trifluoroacetamide (5.0 mL), and a 36% aqueous formaldehyde solution (2.5 mL) were mixed, followed by stirring at 60° C. for 1 hour. The reaction mixture was concentrated under reduced pressure and diluted with ethyl acetate. The mixture was washed with a saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. A mixture of the obtained compound, ethanol (50 mL), and a 6 M aqueous sodium hydroxide solution (14 mL) was stirred at 90° C. for 2 hours. The reaction mixture was cooled to room temperature, and water was added thereto, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (hexane-ethyl acetate) to obtain 4-(4-chlorothiophen-2-yl)-5-{[(2R)-2-ethylpyrrolidin-1-yl]-methyl}-1,3-thiazol-2 -amine (2.7 g) as a solid.

Preparation Example 18

To a mixture of ethyl 3-[(2S)-4-(5-{[4-(4-chlorothiophen-2-yl)-1,3-thiazol-2-yl]carbamoyl}pyrazin-2-yl)-2-methylpiperazin-1-yl]propanoate (20 g) and acetic acid (200 mL) were added paraformaldehyde (3.5 g) and (2R)-2-methylpyrrolidine (6.6 g), followed by stirring at 75° C. for 3.5 hours. The reaction mixture was concentrated under reduced pressure. To the residue water added ethyl acetate (250 mL), toluene (125 mL), and water (200 mL), followed by neutralization by the addition of sodium carbonate. The organic layer was separated, the aqueous layer was extracted with ethyl acetate/toluene, the organic layers were dried over anhydrous sodium sulfate, and then amino silica gel (40 g) was added thereto. The mixture was stirred at room temperature for 30 minutes, the insoluble materials were separated by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (hexane-ethyl acetate) to obtain ethyl 3-[(2S)-4-(5-{[4-(4-chlorothiophen-2-yl)-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl]carbamoyl}pyrazin-2-yl)-2-methylpiperazin-1-yl]propanoate (19.5 g) as a solid.

Preparation Example 19

4-[3-Fluoro-5-(trifluoromethyl)phenyl]-1,3-thiazol-2-amine (2.8 g), pyridine (10 mL), and acetic acid anhydride (4 mL) were mixed, by stirring at 60° C. for 1 hour. The reaction mixture was cooled to room temperature, water was added thereto, and the generated solid was collected by filtration. The obtained solid was washed with methanol and the solid was collected by filtration to obtain N-{4-[3-fluoro-5-(trifluoromethyl)phenyl]-1,3-triazol-2-yl}acetamide (2.9 g) as a solid.

Preparation Example 20

A mixture of 4-(4-chlorothiophen-2-yl)-1,3-thiazol-2-amine (5.0 g), dichloromethane (100 mL), and triethylamine (5.0 mL) was stirred and ice-cooled, and trifluoroacetic anhydride (5 mL) was added thereto, followed by stirring a room temperature for 1 hour. The reaction mixture was diluted with chloroform, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate). The obtained solid was washed with hexane and the solid was collected by filtration to obtain N-[4-(4-chlorothiophen-2-yl)-1,3-thiazol-2-yl]-2,2,2-trifluoroacetamide (6.0 g) as a solid.

Preparation Example 21

A mixture of tert-butyl (3S)-4-{5-[(4-[3-fluoro-5(trifluoromethyl)phenyl]-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl)carbamoyl]pyrazin-2-yl}-3-methylpiperazine-1-carboxylate (410 mg), hydrogen chloride (4 M dioxane solution, 4 mL), and methanol (2 mL) was stirred at room temperature for 1 hour. To the reaction mixture was added ethyl acetate, followed by concentration under reduced pressure. A mixture of the obtained compound, N-methylpyrrolidone (6 mL), ethyl 3-bromopropanoate (0.4 mL), and potassium carbonate (683 mg) was stirred at 100° C. for 2 hours. The reaction mixture was cooled to room temperature and diluted with ethyl acetate. The mixture was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain ethyl 3-[(3S)-4-[5-[(4-[3-fluoro-5-(trifluoromethyl)phenyl]-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl]-1,3-thiazol-2-yl)carbamoyl]pyrazine-2-yl}-3-methylpiperazin-1-yl]propanoate 205 mg).

Preparation Example 22

A mixture of tert-butyl (3R)-4-(5-{[4-(4-chlorothiophen-2-yl)-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl]carbamoyl}pyrazin-2-yl)-3-methylpiperazine-1-carboxylate (271 mg), hydrogen chloride (4 M dioxane solution, 4 mL), and methanol (2 mL) was stirred at room temperature for 1 hour. To the reaction mixture was added ethyl acetate, followed by concentration under reduced pressure. A mixture of the residue, N,N-dimethylformamide (4 mL), ethyl bromoacetate (0.05 mL), and N,N-diisopropylethylamine (0.3 mL) was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) and purified by basic silica gel column chromatography (hexane-ethyl acetate) to obtain ethyl [(3R)-4-(5-{[4-(4-chlorothiophen-2-yl)-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl]carbamoyl}pyrazin-2-yl)-3-methylpiperazin-1-yl]acetate (1.54 mg) as a solid.

Preparation Example 23

A mixture of 1-[4-hydroxy-3-(trifluoromethyl)phenyl]ethanone (1 g), iodoethane (1.2 mL), cesium carbonate (1.9 g), and N,N-dimethylformamide (15 mL) was stirred at 60° C. for 3 hours. The reaction mixture was cooled to room temperature, and water was added thereto, followed by extraction with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain 1-[4-ethoxy-3-(trifluoromethyl)phenyl]ethanone (1.1 g) as a sold.

Preparation Example 24

To a mixture of 4-(4,5-dimethylthiophen-2-yl)-1,3-thiazol-2-amine (500 mg) and dichloromethane (10 mL) were added 5-chloropyrazine-2-carboxylic acid (530 mg), WSCD.HCl (730 mg), and N,N-dimethyl-4-aminopyridine (100 mg), followed by stirring at 40° C. for 30 minutes. The reaction mixture was cooled to room temperature, and ethyl acetate, water, and a saturated aqueous sodium hydrogen carbonate solution were added thereto. The insoluble materials were separated by filtration over Celite and the filtrate was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. To a mixture of the obtained compound and N-methylpyrrolidone (16 mL) were added ethyl 3-(piperazin-1-yl)propanoate dihydrochloride (1.0 g) and N,N-diisopropylethylamine (3 mL), followed by stirring at 80° C. for 2 hours. The reaction mixture was cooled to room temperature, and water and ethyl acetate were added thereto. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform-ethyl acetate). The obtained compound was washed with diisopropyl ether (4 mL) and hexane (20 mL), and the solid was collected by filtration to obtain ethyl 3-[4-(5-{[4-(4,5-dimethylthiophen-2-yl)-1,3-thiazol-2-yl]carbamoyl}pyrazin-2-yl)piperazin-1-yl]propanoate (95.4 mg) as a solid.

Preparation Example 25

To a mixture of N-(4-[3-fluoro-5-(trifluoromethyl)phenyl]-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl)-5-[(2R)-2-methylpiperazin-1-yl]pyrazine-2-carboxamide trihydrochloride (16.1 g) and N,N-dimethylformamide (400 mL) was added potassium carbonate (11.5 g), followed by stirring at room temperature for 5 minutes. To the reaction mixture was added ethyl bromoacetate (2.65 mL), followed by stirring at room temperature for 1 hour. To the reaction mixture was added ethyl bromoacetate (0.8 mL), followed by stirring at room temperature for 1.5 hours. The reaction mixture was poured into water, followed by extraction with ethyl acetate. The organic layer was washed with water and saturated brine, and anhydrous magnesium sulfate and activated carbon were added thereto. The insoluble materials were separated by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (hexane-ethyl acetate) to obtain ethyl [(3R)-4-{5-[(4-[3-fluoro-5-(trifluoromethyl)phenyl]-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl)carbamoyl]pyrazin-2-yl}-3-methylpiperazin-1-yl]acetate (11.0 g) as a solid.

Preparation Example 26

To a mixture of 1-[4-hydroxy-3-(trifluoromethyl)phenyl]ethane (1 g) and acetonitrile (10 mL) were added 1-bromopropane (0.9 mL), potassium carbonate (1.7 g), and tetrabutylammonium iodide (180 mg), followed by stirring at room temperature overnight. The insoluble materials were separated by filtration and the filtrate was concentrated under reduced pressure. The reside was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain 1-[4-propoxy-3-(trifluoromethyl)phenyl]ethanone (1.2 g) as an oil.

Preparation Example 27

To a mixture of copper iodide (I) (9.4 g) and diethyl ether (180 mL) was added dropwise methyllithium (about 1 M diethyl ether solution, 100 mL) at an internal temperature of 0° C. to 5° C. over 30 minutes, followed by stirring for 15 minutes. To the reaction mixture was added dropwise a solution of tert-butyl (2S)-2-({[(4-methylphenyl)sulfonyl]oxy}methyl)pyrrolidine-1-carboxylate (7.0 g) in dichloromethane (30 mL) at an internal temperature of 5° C. or lower over 20 minutes, followed by stirring at room temperature for 2.5 hours. To the reaction mixture was added dropwise a saturated aqueous ammonium chloride solution, followed by extraction with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain tert-butyl (2R)-2-ethylpyrrolidine-1-carboxylate (3.5 g) as an oil.

Preparation Example 28

A mixture of tert-butyl (2R)-2-methylpiperazine-1-carboxylate (3.0 g), N,N-dimethylformamide (30 mL), ethyl bromoacetate (2 mL), and potassium carbonate (5.0 g) was stirred at room temperature for 1 hour. To the reaction mixture was added ethyl acetate, followed by washing with water and saturated brine. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform-methanol) to obtain tert-butyl (2R)-4-(2-ethoxy-2-oxoethyl)-2-methylpiperazine-1-carboxylate (4.0 g) as an oil.

Preparation Example 29

To a mixture of 5-chloro-N-[4-(4-chlorothiophen-2-yl)-1,3-thiazol-2-yl]pyrazine-2-carboxamide (25.0 g) and N-methylpyrrolidone (50 mL) were added N,N-diisopropylethylamine (50 mL) and ethyl 3-[(2S)-methylpiperazin-1-yl]propanoate dihydrochloride (21.2 g), followed by stirring at 60° C. for 1.5 hours. The reaction mixture was cooled to room temperature, and ethyl acetate and water were added thereto, followed by extraction with ethyl acetate. The organic layer was washed with water and saturated brine, and anhydrous magnesium sulfate and activated carbon were added thereto. The insoluble materials were separate by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform-ethyl acetate). The obtained compound was mixed with diisopropyl ether (40 mL) and hexane (120 mL), followed by stirring at room temperature for 15 minutes. The solid was collected by filtration to obtain 3-[(2S)-4-(5-{[4-(4-chlorothiophen-2-yl)-1,3-thiazol-2-yl]carbamoyl}pyrazin-2-yl)-2-methylpiperazin-1-yl]propanoate (29.7 g) as a solid.

Preparation Example 30

To a mixture of 1-[3-fluoro-5-(trifluoromethyl)phenyl]ethanone (78 g) and tetrahyrofuran (625 mL) was added phenyltrimethylammonium tribromide (143 g), followed by stirring at room temperature for 1 hour. The insoluble materials were separated by filtration and the filtrate was concentrated under reduced pressure.

The obtained compound and ethanol (625 mL) were mixed, and thiourea (35 g) was added thereof, followed by stirring at 65° C. to 75° C. for 2 hours. The reaction mixture was ice-cooled, and water (625 mL) was added thereto. The the mixture was added a 1 M sodium hydroxide (600 mL), followed by stirring for 30 minutes. The solid was collected by filtration, and ethanol (30% aqueous, 600 mL) was added thereto and dissolved at 76° C. The obtained solution was cooled to room temperature and stirred overnight. The mixture was ice-cooled and stirred for 2 hours, and then the precipitated solid was collected by filtration to obtain 4-[3-fluoro-5-(trifluoromethyl)phenyl]-1,3-thiazol-2-amine (56.9 g) as a solid.

Preparation Example 31

To a mixture of 1-(4-bromothiophen-2-yl)ethanone (20 g) and N-methylpyrrolidone (400 mL) were added sodium trifluoroacetate (140 g) and copper iodide (I) (100 g), followed by stirring at 200° C. for 2.5 hours. The reaction mixture was cooled to room temperature, water and ethyl acetate were added thereto, and the insoluble materials were separated by filtration over Celite. The organic layer of the filtrate was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) and purified by basic silica gel column chromatography (hexane-ethyl acetate) to obtain 1-[4-(trifluoromethyl)thiophen-2-yl]ethanone (4.1 g) as an oil.

Preparation Example 32

To a mixture of N,6-dimethoxy-N-methyl-5-(trifluoromethyl)nicotinamide (3.7 g) and tetrahydrofuran (40 mL) was added methylmagnesium bromide (3 M tetrahydrofuran solution 7 mL) under ice-cooling, followed by stirring for 1 hour. To the reaction mixture was added a saturated aqueous ammonium chloride solution, followed by extraction with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain (1-[6-methoxy-5-(trifluoromethyl)pyridin-3-yl]ethanone (3.0 g) as an oil.

Preparation Example 33

A mixture of 1-(3,5-dichloro-4-hydroxyphenyl)ethanone (10.0 g), N,N-dimethylformamide (100 mL), potassium carbonate (8.1 g), and methyl iodide (6.1 mL) was stirred at room temperature overnight. To the reaction mixture was added water, followed by extraction with ethyl acetate. The organic layer was washed with 1 M hydrochloride acid and saturated brine, and dried over anhydrous magnesium sulfate. The mixture was filtered using a basic silica gel and the filtrate was concentrated under reduced pressure to obtain 1-(3,5-dichloro-4-methoxyphenyl)ethanone (7.6 g) as a solid.

Preparation Example 34

To a mixture of ethyl 6-methoxy-5-(trifluoromethyl)nicotinate (5.5 g) and ethanol (40 mL) were added a 3 M aqueous sodium hydroxide solution (40 mL), followed by stirring at 60° C. for 30 minutes. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. To the residue was added 1 M hydrochloric acid (120 mL) and the mixture was stirred for 1 hour. The precipitated solid was collected by filtration to obtain 6-methoxy-5-(trifluoromethyl)nicotinic acid (4.4 g) as a solid.

Preparation Example 35

A mixture of 5-bromo-2-methoxy-3-(trifluoromethyl)pyridine (7.8 g), palladium acetate (II) (170 mg), 1,1'-bis(diphenylphosphino)ferrence (840 mg), N,N-diisopropylethylamine (10 mL), ethanol (80 mL), and N,N-dimethylformamide (80 mL) was stirred at 90° C. for 19 hours under a carbon monoxide atmosphere. The reaction mixture was cooled to room temperature, and poured into water (500 mL) and ethyl acetate (500 mL), followed by stirring for 30 minutes. The organic layer was separated, washed with water and saturated brine, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain ethyl 6-methoxy-5-(trifluoromethyl)nicotinate (5.5 g) as a solid.

Preparation Example 36

2-Methoxy-3-(trifluoromethyl)pyridine (8 g), 1,3-dibromo-5,5-dimethylimidazolidine-2,4-dione (17 g), and trifluoroacetic acid (32 mL) were mixed, followed by stirring at room temperature for 22 hours. The reaction mixture was concentrated under reduced pressure, and to the residue was added diisopropyl ether. The precipitated solid was separated by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain 5-bromo-2-methoxy-3-(trifluoromethyl)pyridine (9.4 g) as an oil.

Preparation Example 37

To a mixture of 1-[4-hydroxy-3-(trifluoromethyl)phenyl]ethanone (1 g) and tetrahydrofuran (10 mL) were added 2-propanol (0.46 mL), a 40% diethylazodicarboxylate solution in toluene (2.3 mL) and triphenylphosphine (1.6 g), followed by stirring at room temperature overnight. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain 1-[4-isopropoxy-3-(trifluoromethyl)phenyl]ethanone (1.0 g) as an oil.

Preparation Example 38

A mixture of 1-[4-chloro-3-(trifluoromethyl)phenyl]ethanone (1.0 g), cyclopropylboronic acid (780 mg), dicyclohexyl (2',6'-dimethoxybiphenyl-2-yl)phosphine (185 mg), tripotassium phosphate (3.0 g), palladium acetate (II), (51 mg), toluene (10 mL), and water (1 mL was stirred at 100° C. for 3 hours under an argon atmosphere. The reaction mixture was cooled to room temperature, ethyl acetate and water were added thereto, and the insoluble materials were separated by filtration. The filtrate was extracted with ethyl acetate and the organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain 1-[4-cyclopropyl-3-(trifluoromethyl)phenyl]ethanone (10) as an oil.

Preparation Example 39

To a mixture of 1-(4-bromothiophen-2-yl)ethanone (9.4 g), toluene (200 mL) and water (100 mL) were added cyclopropylboronic acid (12.0 g), tetrakis(triphenylphosphine) palladium (0) (5.34 g), cesium carbonate (73.6 g), and tri-tert-butylphosphine (2.3 mL), followed by stirring at 80° C. for 3 hours. The reaction mixture was filtered over Celite, and to the filtrate were added water and diethyl ether. The organic layer was separated, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain 1-(4-cyclopropylthiophen-2-yl)ethanone (6.7 g) as an oil.

Preparation Example 40

A mixture of 3-bromo-5-(trifluoromethyl)benzoic acid (10.0 g), thionylchloride (40 mL), and N,N-dimethylformamide (1 droplet) was stirred at 80**2** C. for 2 hours. The reaction mixture was concentrated under reduced pressure, followed by carrying out a concentration operation with toluene twice and then drying under reduced pressure.

To a mixture of toluene (150 mL) and magnesium chloride (3.6 g) were added dimethyl malonate (5.1 mL) and triethylamine (12 mL), followed by stirring at room temperature for 1.5 hours. To the reaction mixture was first added dropwise a mixture of the obtained compound and toluene (50 mL) under stirring, followed by stirring at room temperature for 18 hours. To the reaction mixture was added 6 M hydrochloric acid (50 mL), and then water (300 mL) was added thereto, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was mixed with dimethylsulfoxide (50 mL) and water (5 mL), followed by stirring at 160° C. for 1 hour. The reaction mixture was cooled to room temperature, and water (300 mL) was added thereto, followed by extraction with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure to obtain 1-[3-bromo-5-(trifluoromethyl)phenyl]ethanone (10.0 g) as an oil.

Preparation Example 41

To a mixture of zinc powder (2.0 g), cobalt bromide (II) (600 mg), and acetonitrile (30 mL) was added trifluoroacetic acid (0.15 mL) under an argon atmosphere, followed by stirring at room temperature for 15 minutes. To the reaction mixture were added 5-bromo-1-fluoro-2-methoxy-3-(trifluoromethyl)benzene (5.0 g) and acetic anhydride (2.1 mL), followed by stirring at room temperature for 17 hours. To the reaction mixture was added 1 M hydrochloric acid (30 mL), followed by extraction with diethyl ether. The organic layer was washed with water and saturated with brine, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-diethyl ether) to obtain 1-[3-fluoro-4-methoxy-5-(trifluoromethyl)phenyl]ethanone (1.6 g) as an oil.

Preparation Example 42

To a mixture of 1-[4-hydroxy-3-(trifluoromethyl)phenyl]ethanone (3.0 g), N,N-dimethylformamide (36 mL), and water (3.6 mL) were added sodium chloro(difluoro)acetate (5.8 g) and cesium carbonate (7.2 g), followed by stirring at 100° C. for 3 hours. To the reaction mixture was added water, followed by extraction with ethyl acetate. The organic layer was washed with water and saturated brine, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate). To a mixture of the obtained compound (3.8 g) and tetrahydrofuran (50 mL) was added phenyltrimethylammonium tribromide (5.7 g), followed by stirring at room temperature for 45 minutes. The precipitated insoluble materials were separated by filtration and the filtrate was concentrated under reduced pressure. To a mixture of the residue and ethanol (50 mL) was added thiourea (1.5 g), followed by stirring at 80° C. for 2 hours. The reaction mixture was cooled to room temperature, and water (30 mL) and a 1 M aqueous sodium hydroxide solution (30 mL) were added thereto, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. To the residue was added diisopropyl ether and hexane, and the generated solid was collected by filtration to obtain 4-[4-(difluoromethoxy)-3-(trifluoromethyl)phenyl]-3-thiazol-2-amine (3.5 g) as a solid.

Preparation Example 43

To a mixture of 5-chloro-N-(4-[4-ethoxy-3-(trifluoromethyl)phenyl]-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl)pyrazine-2-carboxamide (407 mg) and N-methylpyrrolidone (6 mL) were added tert-butyl (3R)-3-methylpiperazine-1-carboxylate (400 mg) and N,N-diisopropylethylamine (0.7 mL), followed by stirring at 80° C. for 4 hours. The reaction mixture was cooled to room temperature, and water was added thereto, followed by extraction with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate).

A mixture of the obtained compound, hydrogen chloride (4 M dioxane solution, 6 mL), and methanol (2 mL) was stirred at room temperature for 4 hours. To the reaction mixture was added ethyl acetate (20 mL), and the solid was collected by filtration to obtain N-(4-[4-ethoxy-3-(trifluoromethyl)phenyl]-5{[(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl)-5-[(2R)-2-methylpiperazin-1-yl]pyrazine-2-carboxamide trihydrochloride (623 mg) as a solid.

Preparation Example 44

To a mixture of tert-butyl (2S)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (17 g), triethylamine (17.7 mL), 1-methyl-1H-imidazole (10.1 mL), and dichloromethane (255 mL) was added p-toluenesulfonyl chloride (17.7 g) under ice-cooling, followed by stirring at the same temperature for 1 hour. To the reaction mixture was added water, followed by extraction with dichloromethane. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain tert-butyl (2S)-2-({[(4-methylphenyl)sulfonyl]oxy}methyl)pyrrolidine-1-carboxylate (29.54 g) as an oil.

Preparation Example 45

A mixture of tert-butyl (3S)-3-methylpiperazine-1-carboxylate (5 g), ethyl acrylate (7.2 mL), and ethanol (15 mL) was heated and refluxed for 24 hours. The reaction mixture was concentrated under reduced pressure, and to the residue was added diethyl ether, followed by extraction with 1 M hydrochloric acid. The aqueous layer was alkalified to pH 8 by the addition of a 1 M aqueous sodium hydroxide solution and sodium hydrogen carbonate, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform-methanol) to obtain tert-butyl (3 S)-4-(3-ethoxy-3-oxopropyl)-3-methylpiperazine-1-carboxylate (7.5 g) as an oil.

Example 1

To a mixture of ethyl 3-[(2S)-4-(5-{[4-(4-chlorothiophen-2-yl)-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl]carbamoyl}pyrazin-2-yl)-2-methylpiperazin-1-yl] propanoate (10.2 g), tetrahydrofuran (50 mL), and ethanol (50 mL) was added a 1 M aqueous sodium hydroxide solution (50 mL), followed by stirring at 50° C. for 30 minutes. The reaction mixture was cooled to room temperature, and 1 M hydrochloric acid (50 mL) and water (100 mL) were added thereto, followed by extraction with chloroform. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform-methanol) to obtain a solid (6.0 g) of 3-[(2S)-4-(5{[4-(4-chlorothiophen-2-yl)-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl]carbamoyl}pyrazin-2-yl)-2-methylpiperazin-1-yl]propanoic acid.

To a mixture of the obtained solid and tetrahydrofuran (100 mL) was added hydrogen chloride (4 M dioxane solution, 12 mL), and the mixture was concentrated under reduced pressure. To the residue were added acetonitrile (200 mL) and water (12 mL), followed by stirring at 70° C. for 15 minutes, and then cooling at room temperature. To the mixture was added acetonitrile (100 mL), followed by stirring at room temperature for 1 hour. The solid was collected by filtration and dried to obtain 3-[(2S)-4-(5-{[4-(4-chlorothiophen-2-yl)-5-{[(2R)-2-methylpyrrolidin-1-yl] methyl}-1,3-thiazol-2-yl]carbamoyl}pyrazin-2-yl)-2-methylpiperazin-1-yl]propanoic acid dihydrochloride (6.7 g) as a solid.

Example 2

Under an argon gas flow, to a mixture of ethyl 3-(4-{5-[(4-[3-bromo-5-(trifluoromethyl)phenyl]-5-{[(2S)-2-isopropylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl)carbamoyl] pyrazin-2-yl}piperazin-1-yl)propanoate (660 mg), zinc powder (30 mg), biphenyl-2-yl(di-tert-butyl)phosphine (60 mg), and N,N-dimethylacetamide (13 mL) were added zinc cyanide (160 mg) and palladium trifluoroacetate (II) (30 mg), followed by stirring at 100° C. for 1 hour. The reaction mixture was cooled to room temperature, and ethyl acetate was added thereto. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate).

To a mixture of the obtained compound (401 mg), ethanol (5 mL), and tetrahydrofuran (5 mL) was added a 1 M aqueous sodium hydroxide solution (3 mL), followed by stirred at 50° C. for 30 minutes. The reaction mixture was concentrated under reduced pressure and the residue was purified by ODS column chromatography (acetonitrile-water). The obtained solid was mixed with hexane (20 mL) and diethyl ether (4 mL), and the solid was collected by filtration to obtain sodium 3-(4-{5-[(4-[3-cyano-5-(trifluoromethyl) phenyl]-5-{[(2S)-2-isopropylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl)carbamoyl]pyrazin-2-yl}piperazin-1-yl)propanoate (149 mg) as a solid.

Example 3

To a mixture of 5-chloro-N-(5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-4-[4-(trifluoromethyl)thiophen-2-yl]-1,3-thiazol-2-yl)pyrazine-2-carboxamide (300 mg) and N-methylpyrrolidone (6 mL) were added ethyl 3-[(3R)-3-methylpiperazin-1-yl]propanoate dihydrochloride (500 mg) and N,N-diisopropylethylamine (0.64 mL), followed by stirring at 90° C. for 2 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and washed with water and saturated brine. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (hexane-ethyl acetate).

To a mixture of the obtained compound, ethanol (6mL), and tetrahydrofuran (6 mL) was added a 1 M aqueous sodium hydroxide solution (3.5 mL), followed by stirring at 60° C. for 30 minutes. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by ODS column chromatography (acetonitrile—0.1% aqueous formic acid solution) to obtain a solid (204 mg). To a mixture of the obtained solid and ethyl acetate was added hydrogen chloride (4 M ethyl acetate solution, 0.25 mL). The reaction mixture was concentrated under reduced pressure to obtain 3-[(3R)-3-methyl-4-{5-[(5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-4-[4-(trifluoromethyl)thiophen-2-yl]-1,3-thiazol-2-yl)carbamoyl]pyrazin-2-yl}piperazin-1-yl]propanoic acid dihydrochloride (155 mg) as a solid.

Example 4

To a mixture of 5-chloro-N-(5-{[(2R)-2-methylpiperidin-1-yl]methyl}-4-[3-methyl-5-(trifluoromethyl)phenyl]-1,3-thiazol-2-yl)pyrazine-2-carboxamide (300 mg) and N-methylpyrrolidone (6 mL) were added ethyl 3-(piperazin-1-yl) propanoate dihydrochloride (250 mg) and N,N-diisopropylethylamine (0.7 mL), followed by stirring at 80° C. for 2 hours. The reaction mixture was cooled to room temperature, and water and ethyl acetate were added thereto. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate).

To a mixture of the obtained residue, ethanol (5 mL), and tetrahydrofuran (5 mL) was added a 1 M aqueous sodium hydroxide solution (3 mL), followed by stirring at 50° C. for 30 minutes. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by ODS column chromatography (acetonitrile-water) to obtain a solid (298 mg). The obtained solid was mixed with hexane (10 mL) and diethyl ether (2 mL), and the solid was collected by filtration to obtain sodium 3-(4-{5-[(5-{[(2R)-2-methylpiperidin-1-yl] methyl}-4-[3-methyl]-5-(trifluoromethyl)phenyl]-1,3-thiazol-2-yl)carbamoyl]pyrazine-2-yl}piperazin-1-yl)propanoate (284 mg) as a solid.

Example 5

A mixture of ethyl 3-[(2R)-4-(5-{[5-(acetoxymethyl)-4-(4-chlorothiophen-2-yl)-1,3-thiazol-2-yl]carbamoyl}pyrazin-2-yl)-2-methylpiperazin-1-yl]propanoate (200 mg), dimethylamine (2M tetrahydrofuran solution, 2 mL), and N-methylpyrrolidone (4 mL) was stirred at 80° C. for 3 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and washed with water and saturated brine. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (hexane-ethyl acetate) and purified by silica gel column chromatography (hexane-ethyl acetate). The obtained compound was mixed with ethanol (2 mL) and tetrahydrofuran (2 mL), and a 1 M aqueous sodium hydroxide solution (1 mL) was added thereto, followed by stirring at room temperature for 1 hour. To the reaction mixture was added 1 M hydrochloric acid (1 mL) and water, the mixture was extracted with chloroform/isopropanol, and the organic layer was washed with water and saturated brine. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. To a mixture of the obtained compound and ethyl acetate was added hydrogen chloride (4 M ethyl acetate solution, 1 mL). The reaction mixture was concentrated under reduced pressure, and to the residue was added ethyl acetate. The solid was collected by filtration to obtain 3-{(2R)-4-[5-({4-(4-chlorothiophen-2-yl)-5-[(dimethylamino)methyl]-1,3-thiazol-2-yl}carbamoyl)pyrazin-2-yl]-2-methylpiperazin-1-yl}propanoic acid dihydrochloride (33 mg) as a solid.

Example 6

A mixture of ethyl 3-[4-(5-{[4-(4,5-dimethylthiophen-2-yl)-1,3-thiazol-2-yl]carbamoyl}pyrazin-2-yl)piperazin-1-yl]propanoate (400 mg), (2R)-2-methylpyrrolidine (273 mg), a 36% aqueous formaldehyde solution (0.5 mL), and acetic acid (8 mL) was stirred at 60° C. for 1.5 hours. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. To the residue was added a saturated aqueous sodium hydrogen carbonate solution, followed by extraction with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (hexane-ethyl acetate).

To a mixture of the obtained compound (452 mg), ethanol (4 mL), and tetrahydrofuran (4 mL) was added a 1 M aqueous sodium hydroxide solution (4 mL), followed by stirring at 50° C. for 1 hour. The reaction mixture was cooled to room temperature, and 1 M hydrochloric acid (4 mL) and water were added thereto. The mixture was extracted from chloroform/isopropanol/tetrahydrofuran, and the organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. To a mixture of the obtained compound and tetrahydrofuran (20 mL) was added hydrogen chloride (4 M dioxane solution, 2 mL). The mixture was concentrated under reduced pressure, and to the residue was added diethyl ether (20 mL). The solid was collected by filtration to obtain 3-[4-(5-{[4-(4,5-dimethylthiophen-2-yl)-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl]carbamoyl}pyrazin-2-yl)piperazin-1-yl]propanoic acid trihydrochloride (440 mg) as a solid.

Example 7

To a mixture of N-(4-[4-ethoxy-3-(trifluoromethyl)phenyl]-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl)-5-[(2R)-2-methylpiperazin-1-yl]pyrazine-2-carboxamide trihydrochloride (300 mg) and N,N-dimethylformamide (5 mL) were added potassium carbonate (300 mg) and ethyl 3-bromopropanoate (0.25 mL), followed by stirring at 60° C. for 1.5 hours. Thereafter, to the reaction mixture were added potassium carbonate (300 mg) and ethyl 3-bromopropanoate (0.25 mL), followed by stirring at 60° C. for 1.5 hours. Again, to the reaction mixture were added potassium carbonate (300 mg) and ethyl 3-bromopropanoate (0.25 mL), followed by stirring at 60° C. for 1 hour. The reaction mixture was cooled to room temperature, and water was added thereto, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (hexane-ethyl acetate).

To a mixture of the obtained compound (151 mg), tetra hydrofuran (2 mL), and ethanol (2 mL) was added a 1 M aqueous sodium hydroxide solution (1 mL), followed by stirring at 50° C. for 30 minutes. The reaction mixture was cooled to room temperature, and 1 M hydrochloric acid (1 mL) and water (15 mL) were added thereto, followed by extracted with chloroform/isopropanol. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. To a mixture of the obtained compound and tetrahydrofuran (10 mL was added hydrogen chloride (4 M dioxane solution, 2 mL). The reaction mixture was concentrated under reduced pressure, and to the residue was added diethyl ether. The solid was collected by filtration to obtain 3-[(3R)-4-{5-[(4-[4-ethoxy-3-(trifluoromethyl)phenyl]-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl)carbamoyl]pyrazin-2-yl}-3-methylpiperazin-1-yl]propanoic acid trihydrochloride (142 mg) as a solid.

Example 8

To a mixture of N-(4-[4-ethoxy-3-(trifluoromethyl)phenyl]-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl)-5-[(2R)-2-methylpiperazin-1-yl]pyrazine-2-carboxamide trihydrochloride (381 mg) and N,N-dimethylformamide (8 mL) was added potassium carbonate (300 mg), followed by stirring at room temperature for 10 minutes. To the reaction mixture was added ethyl bromoacetate (0.09 mL), followed by stirring at room temperature for 1.5 hours. To the reaction mixture was added ethyl bromoacetate (0.09 mL), followed by stirring at room temperature for 30 minutes. To the reaction mixture was added water, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (hexane-ethyl acetate).

To a mixture of the obtained compound (211 mg), tetrahydrofuran (3 mL), and ethanol (3 mL) was added a 1 M aqueous sodium hydroxide solution (1.5 mL), followed by stirring at 50° C. for 30 minutes. The reaction mixture was cooled to room temperature, and 1 M hydrochloric acid (1.5 mL) and water (15 mL) were added thereto, followed by extraction with chloroform/isopropanol. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue was mixed with tetrahydrofuran (10 mL), and hydrogen chloride (4 M dioxane solution, 2 mL) was added thereto. The mixture was concentrated under reduced pressure, and to the residue was added diethyl ether. The solid was collected by filtration to obtain [(3R)-4-{5-[(4-[4-ethoxy-3-(trifluoromethyl)phenyl]-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl)carbamoyl]pyrazin-2-yl}-3-methylpiperazin-1-yl]acetic acid trihydrochloride (185 mg).

Example 9

To a mixture of 5-[(diethylamino)methyl]-4-[3-fluoro-5-(trifluoromethyl)phenyl]-1,3-thiazol-2-amine (820 mg), triethylamine (2 mL), and cyclopentylmethyl ether (16 mL) was added 5-chloropyrazine-2-carbonylchloride (590 mg), followed by stirring at room temperature for 20 hours. To the reaction mixture was added water (500 mL), followed by extraction with chloroform. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain a solid (1.0 g). To a mixture of the obtained compound (200 mg) and N-methylpyrrolidone (4 mL) were added ethyl 3-[(2R)-2-methylpiperazin-1-yl]propanoate dihydrochloride (168 mg) and N,N-diisopropylethylamine (0.5 mL), followed by stirring at 80° C. for 2 hours. The reaction mixture was cooled to room temperature, and water and ethyl acetate were added thereto. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The obtained compound was purified by silica gel column chromatography (hexane-ethyl acetate).

To a mixture of the obtained compound (249 mg), ethanol (4 mL), and tetrahydrofuran (4 mL) was added a 1 M aqueous sodium hydroxide solution (2 mL), followed by stirring at 50° C. for 30 minutes. The reaction mixture was cooled to room temperature, and 1 M hydrochloric acid (2 mL) and water (20 mL) were added thereto. The mixture was extracted with chloroform/isopropanol, and the organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue was mixed with tetrahydrofuran (10 mL), and hydrogen chloride (4 M dioxane solution, 2 mL) was added thereto. The mixture was concentrated under reduced pressure, and to the residue was added diethyl ether. The solid was collected by filtration to obtain 3-{(2R)-4-[5-({5-[(diethylamino)methyl]-4-[3-fluoro-5-trifluoromethyl)phenyl]-1,3-thiazol-2-yl}carbamoyl)pyrazine-2-yl]-2-methylpiperazin-1-yl}propanoic acid dihydrochloride (251 mg) as a solid.

Example 144

3-[(2S)-4-(5-{[4-(4-Chlorothiophen-2-yl)-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl]carbamoyl}pyrazin-2-yl)-2-methylpiperazin-1-yl]propanoic acid (500 mg) and maleic acid (148 mg) were dissolved in 2-butanone (0.5 mL) and dimethylsulfoxide (0.5 mL) under stirring at 60° C. To the solution was added 2-butanone (4.0 mL), followed by stirring at 60° C. for 30 minutes. Thereafter, the mixture was left to be slowly cooled to room temperature and stirred at room temperature for 16 hours. The precipitated solid was collected by filtration and dried under reduced pressure to obtain 3-[(2S)-4-(5-{[4-(4-chlorothiophen-2-yl)-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl]carbamoyl}pyrazin-2-yl)-2-methylpiperazin-1-yl]propanoic acid **[**dimalate**]** *dimaleate* (378 mg) as a white crystal.

The crystals obtained in the present Examples have peaks of powder X-ray diffraction at 2θ (°) 5.7, 6.6, 10.5, 12.0, 13.3, 15.8, 16.6, 17.3, 19.0, and 26.2.

The compounds of Preparation Examples and Examples shown in Tables below were produced in the same manner as the methods in Preparation Examples or Examples as described above.

TABLE 5

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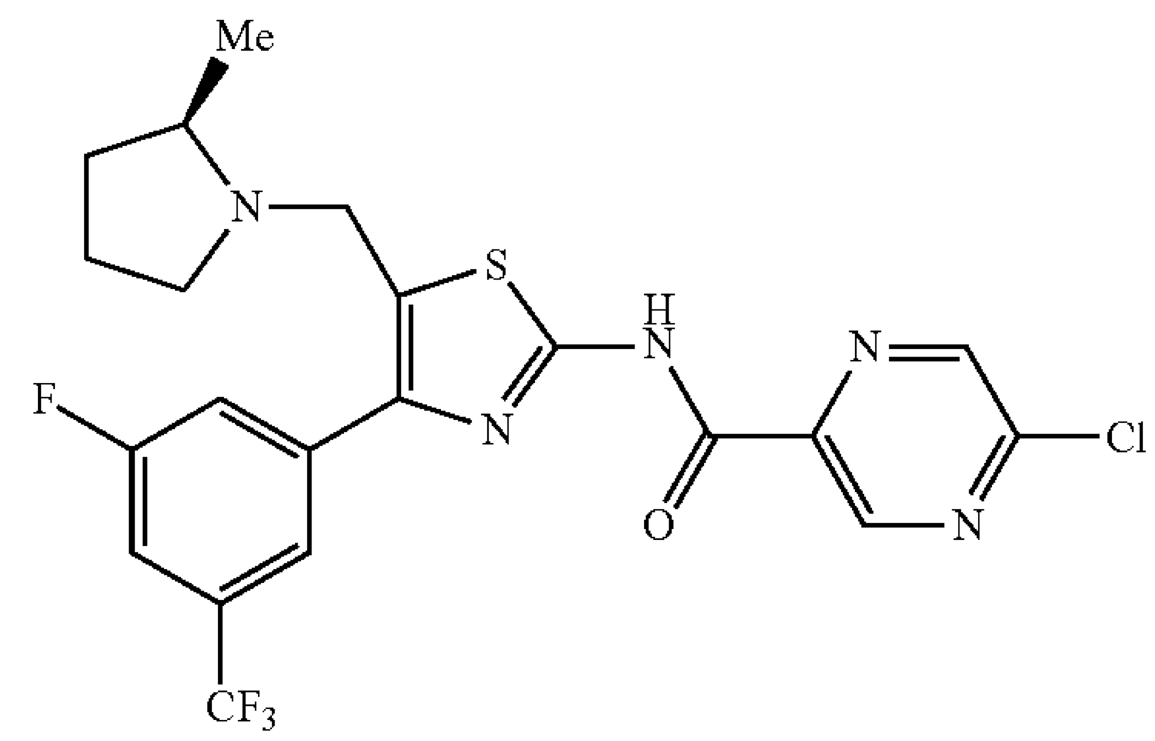
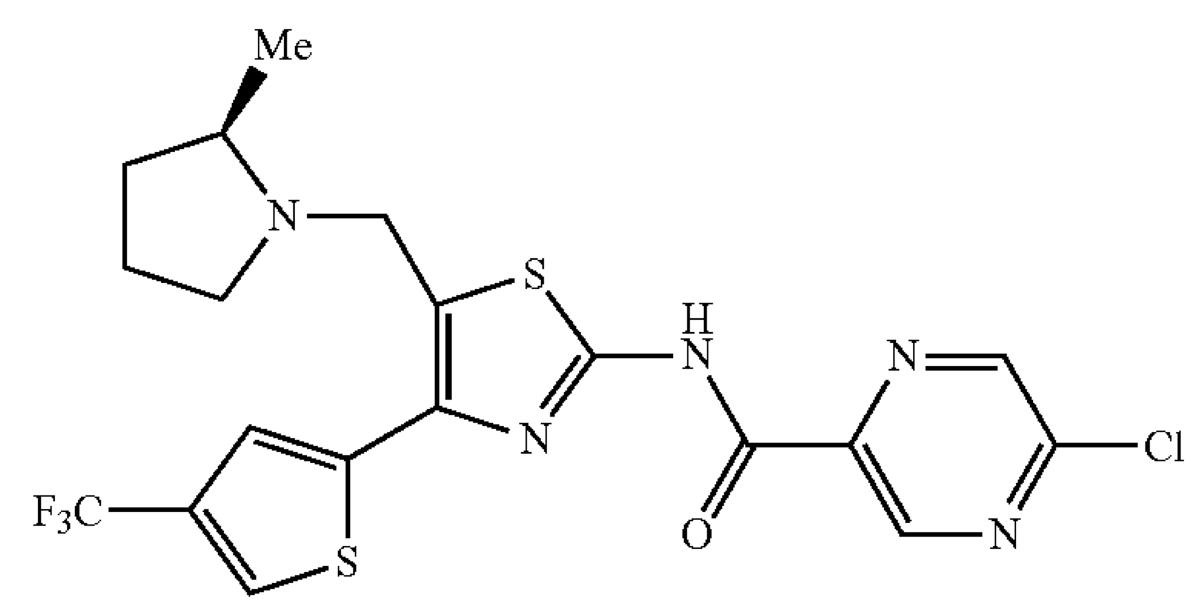
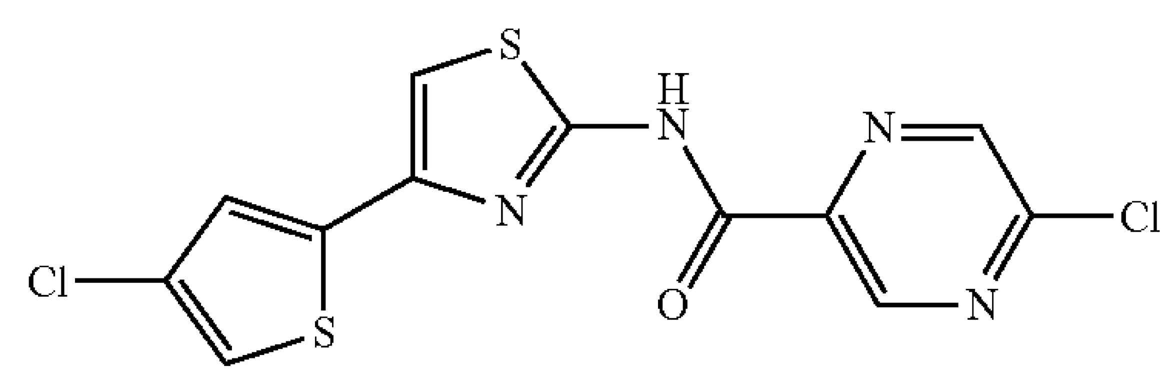
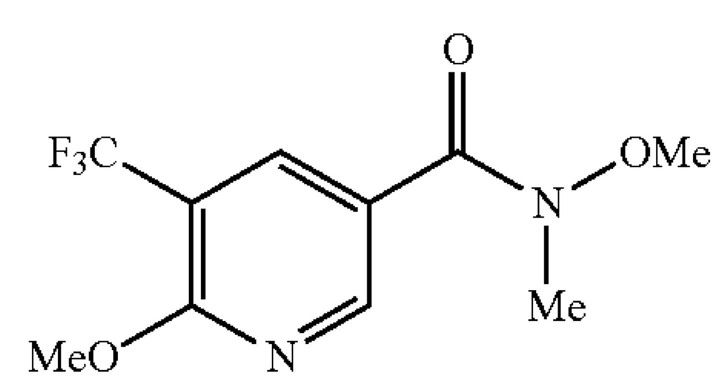
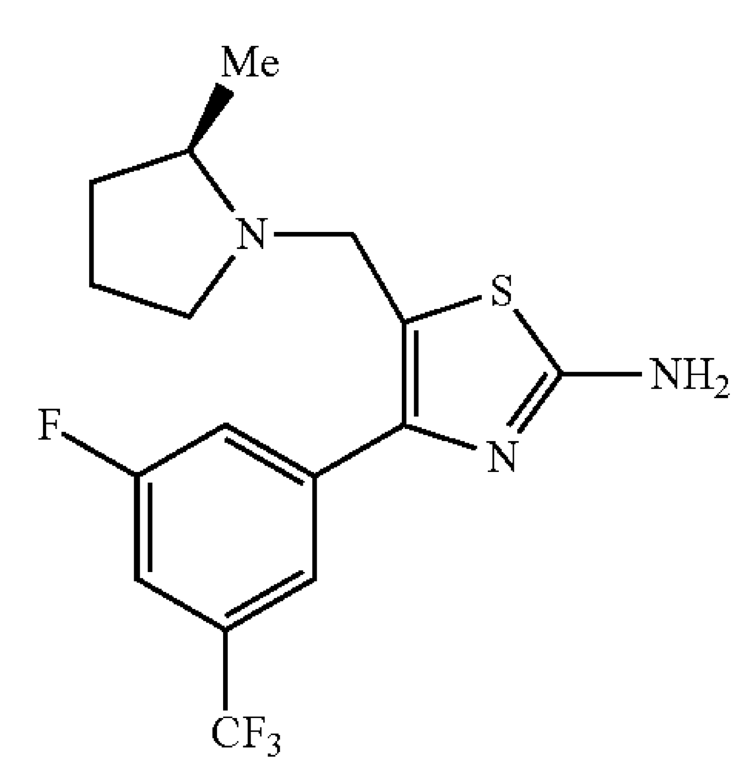
1	
2	
3	
4	
5	

TABLE 6

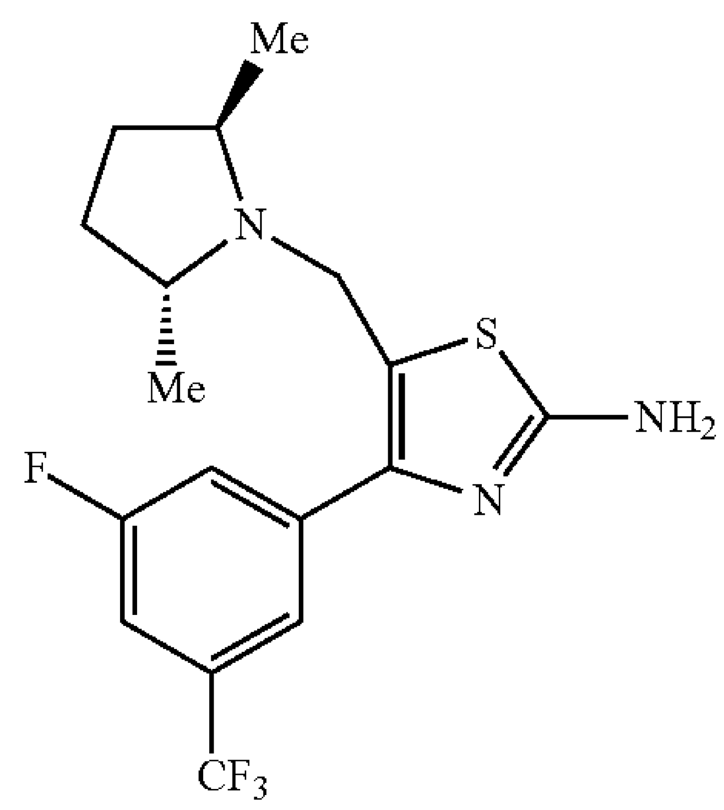
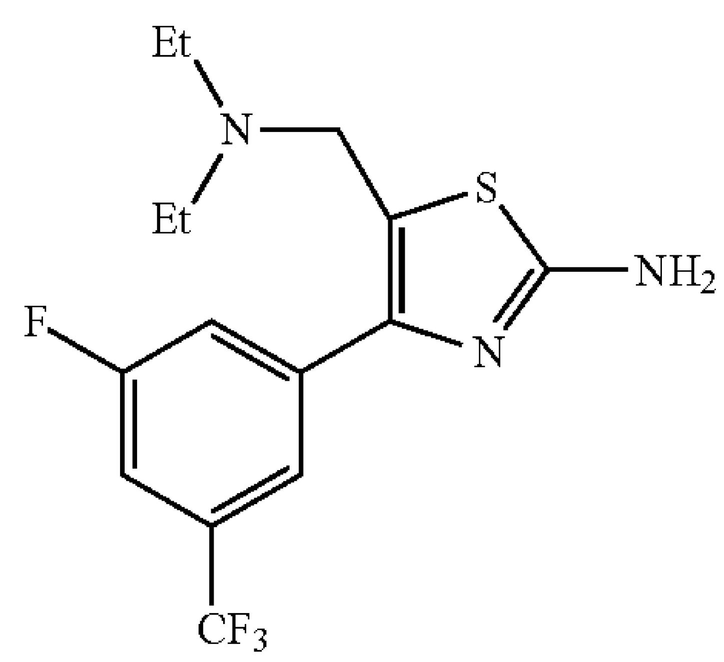
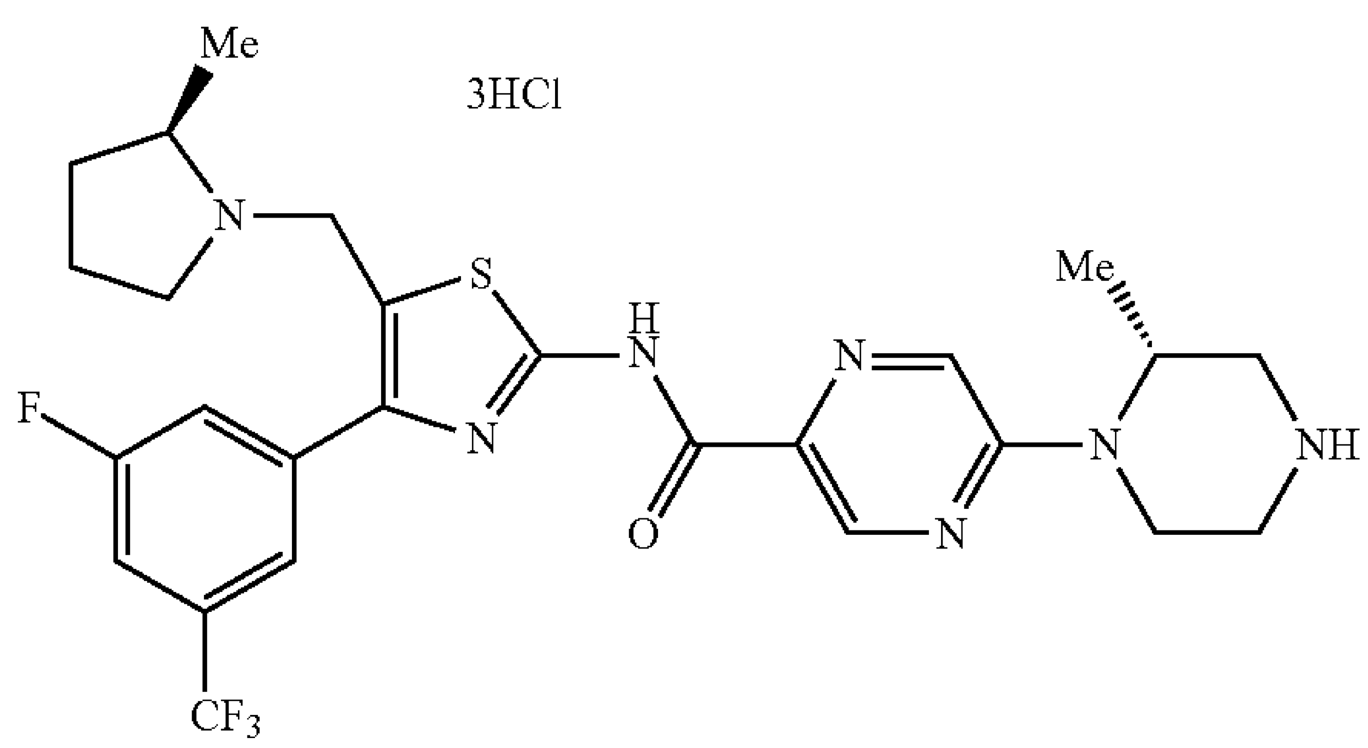
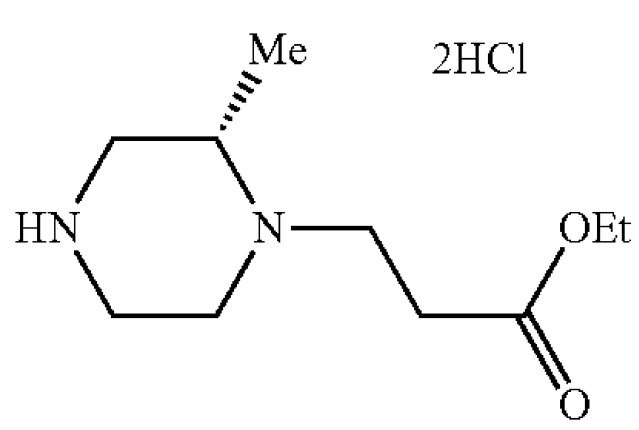
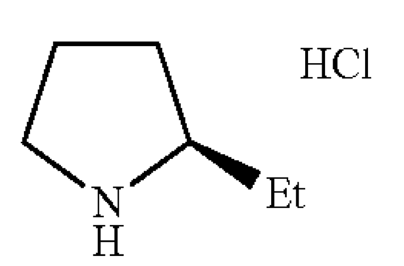
PEx	Structure
6	
7	
8	
9	
10	

TABLE 7

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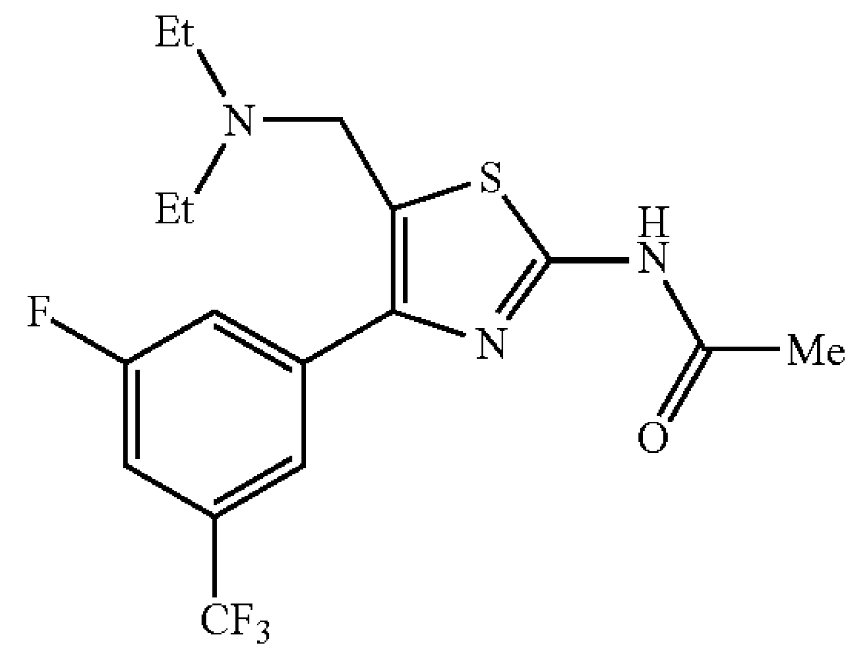
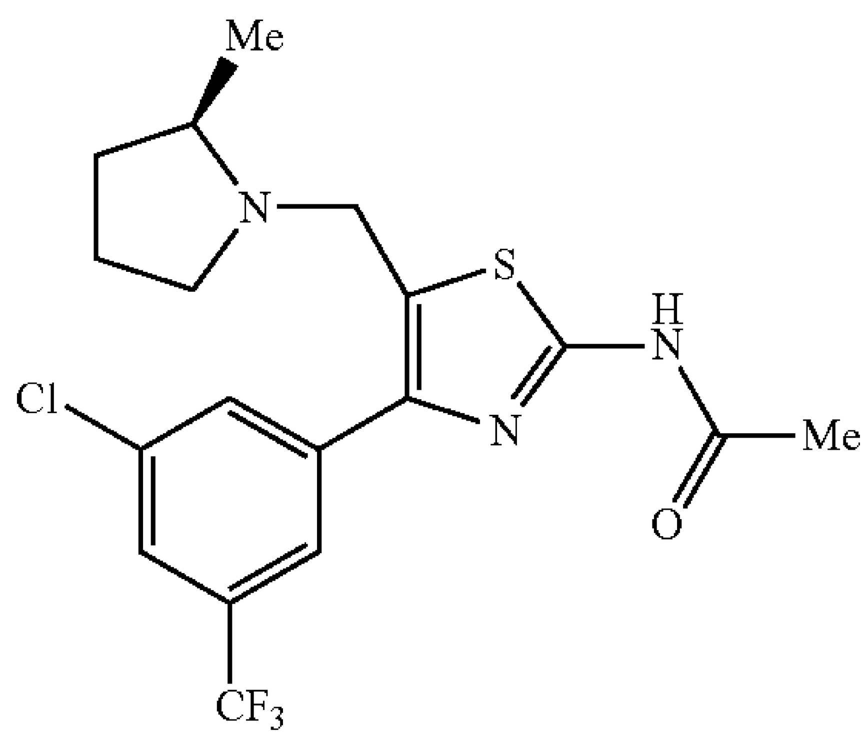
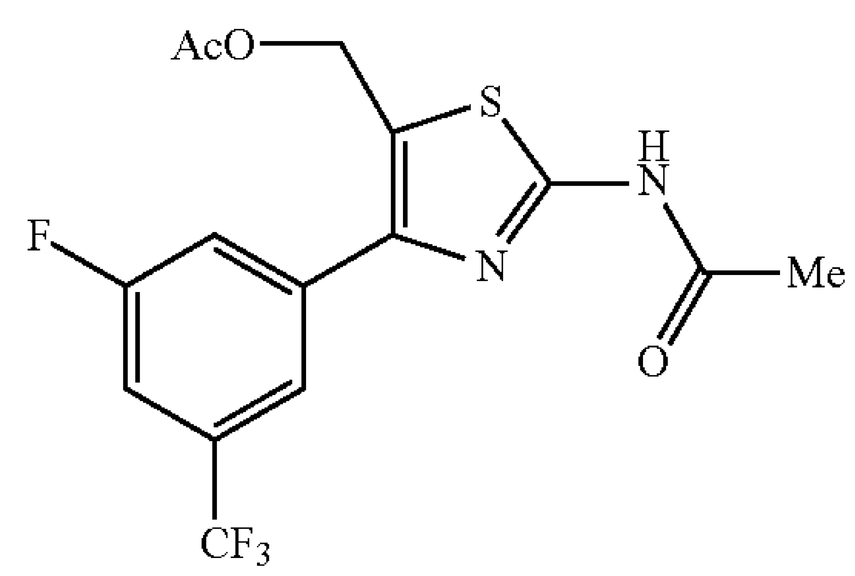
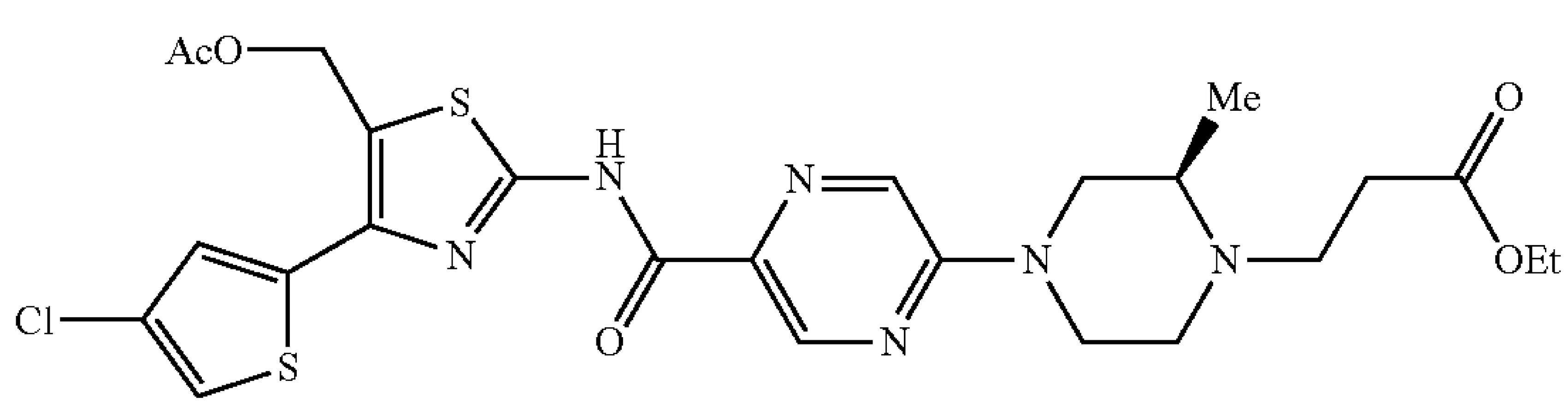
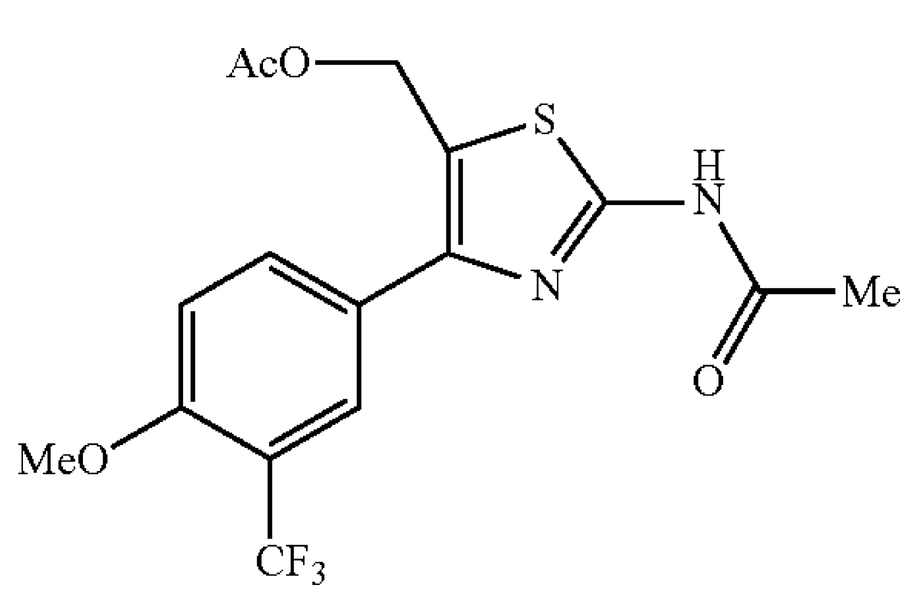
11	
12	
13	
14	
15	

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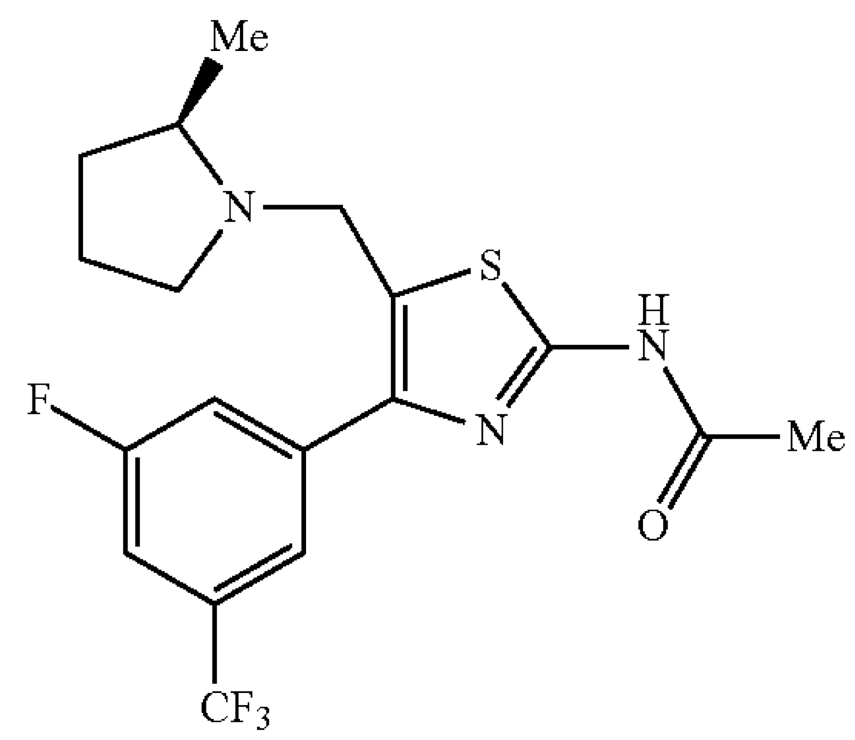
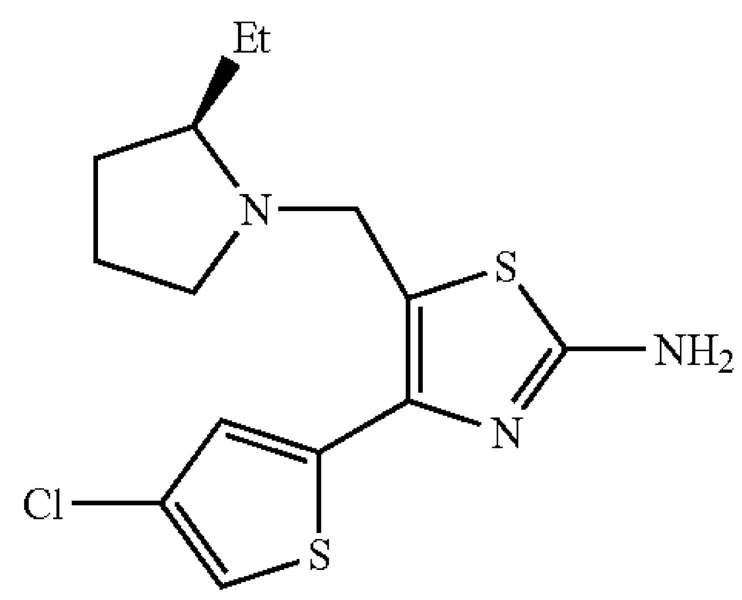
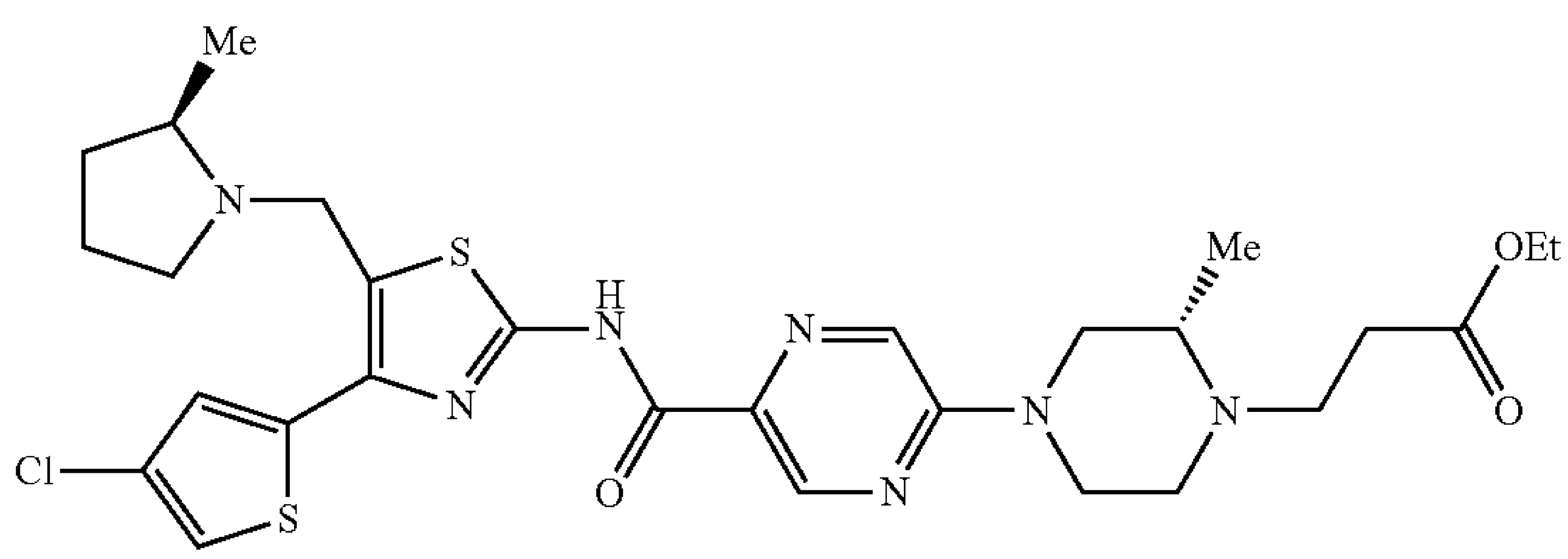
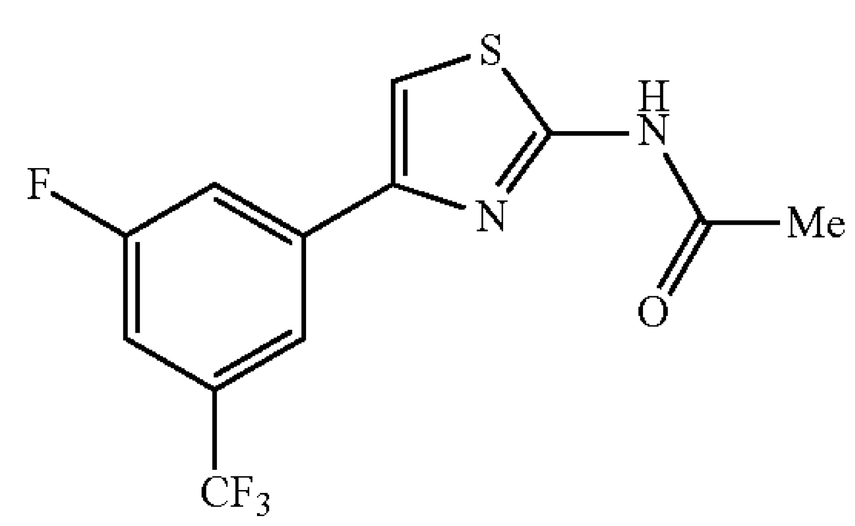
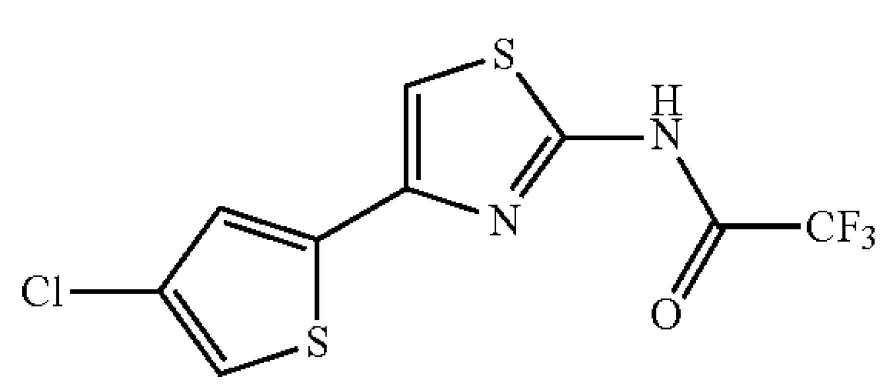
16	
17	
18	
19	
20	

TABLE 9

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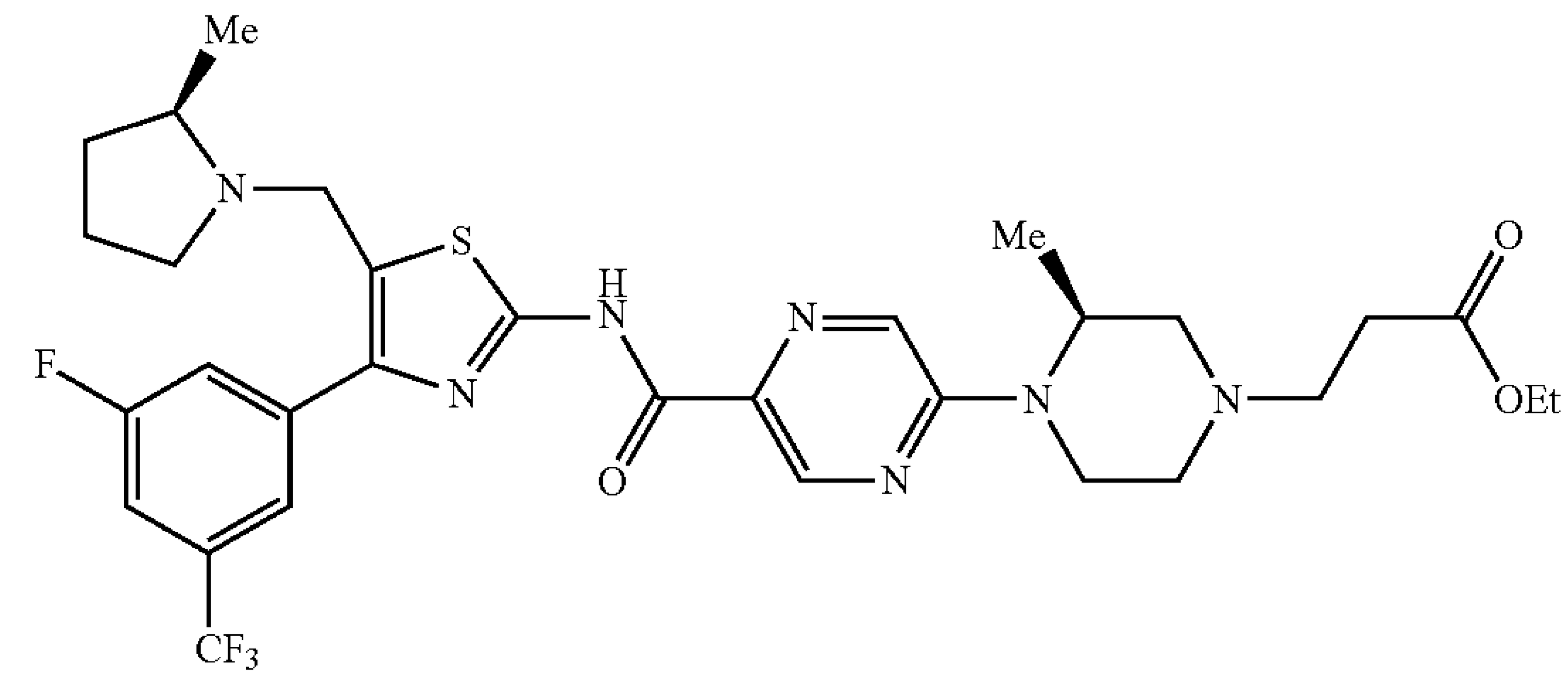
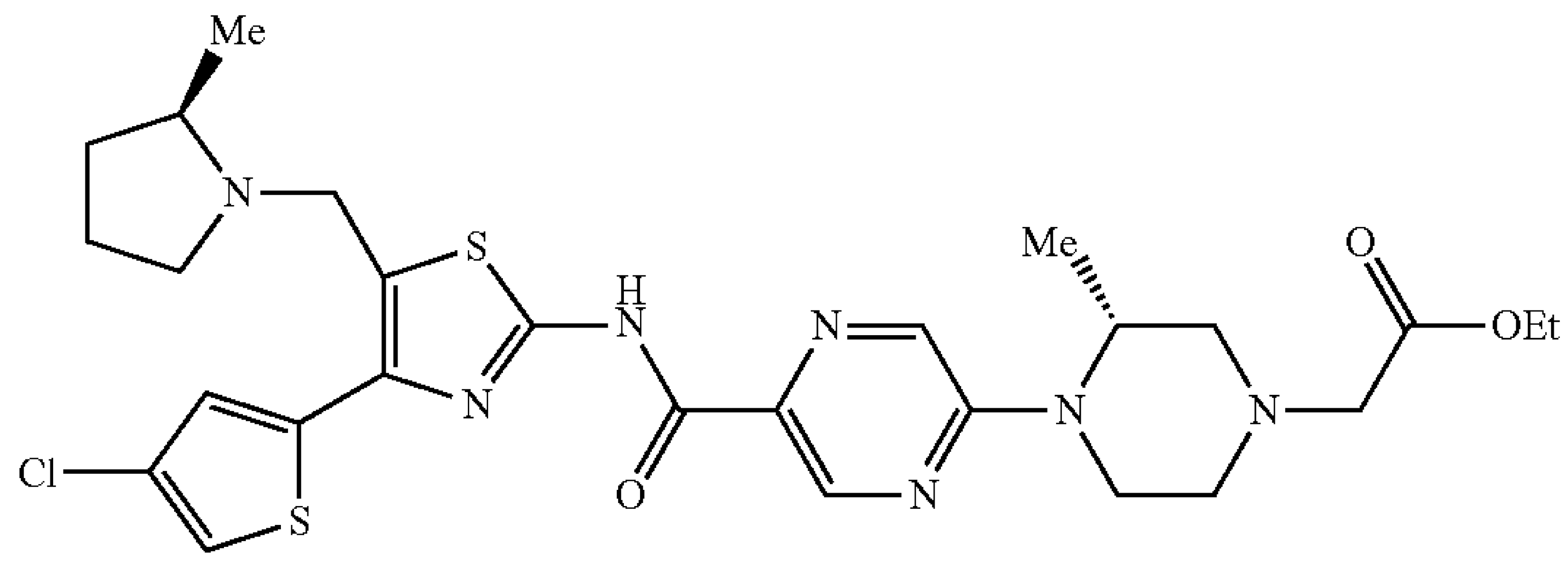
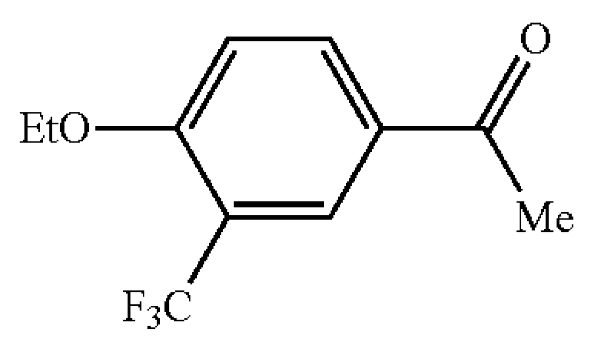
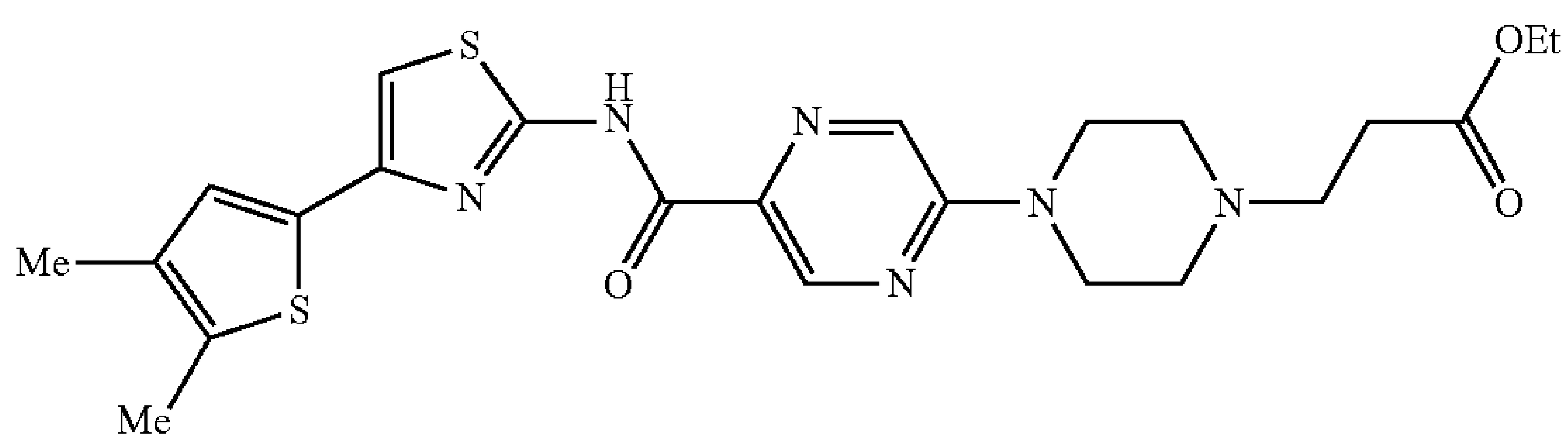
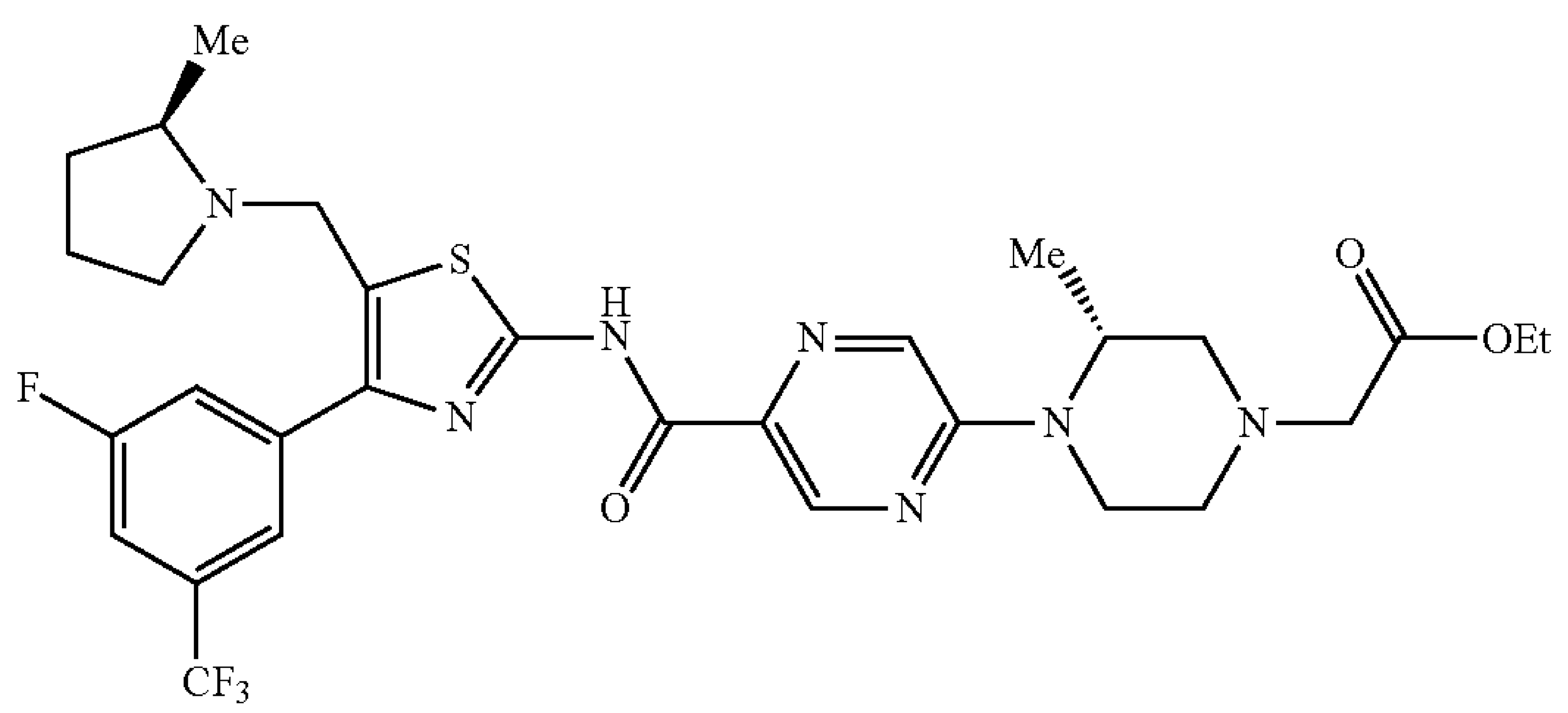
21	
22	
23	
24	
25	

TABLE 10

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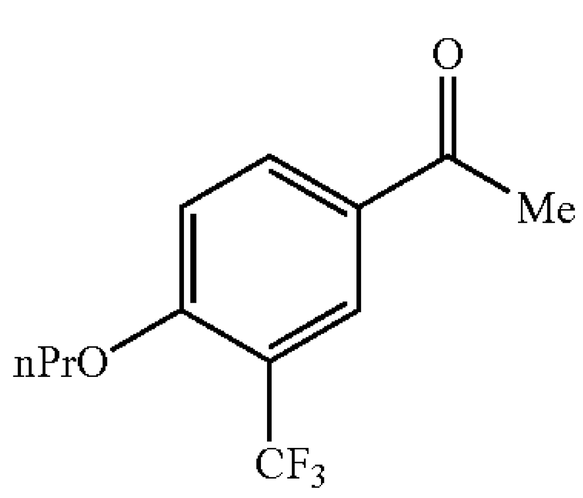
26	

TABLE 10-continued

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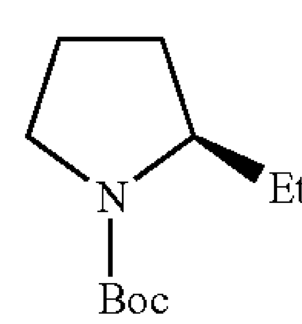
27	

TABLE 10-continued

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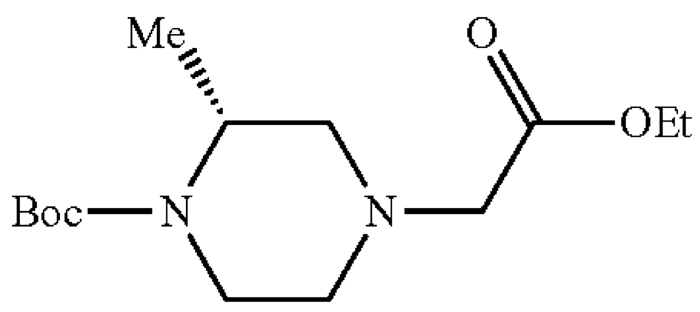
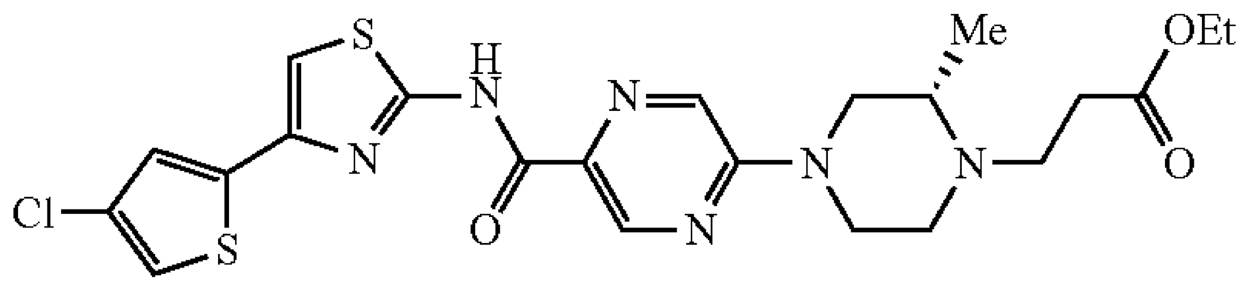
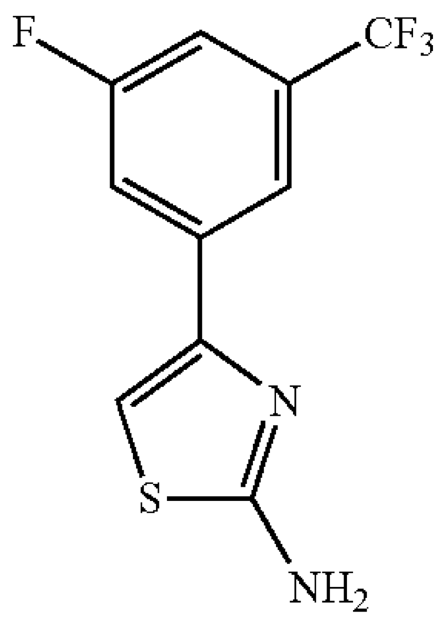
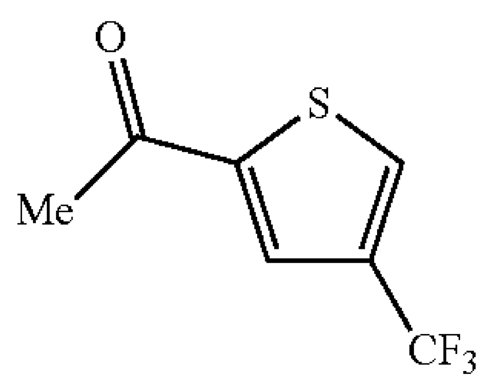
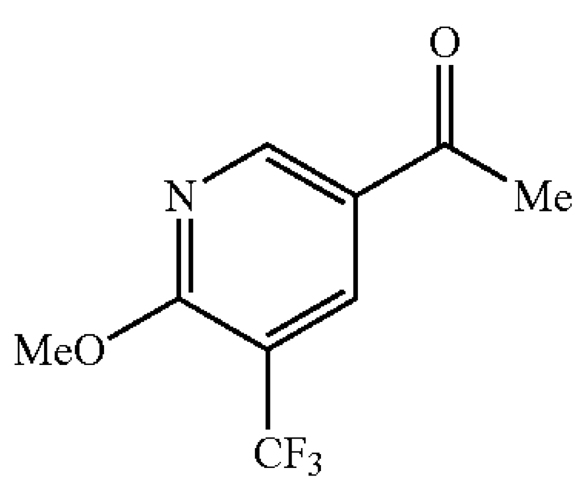
28	
29	
30	
31	
32	

TABLE 11

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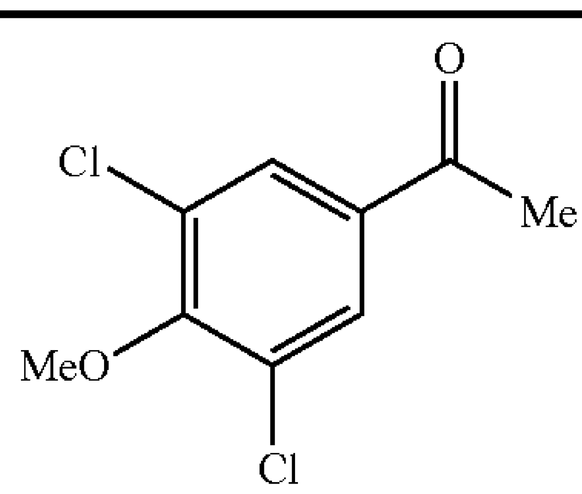
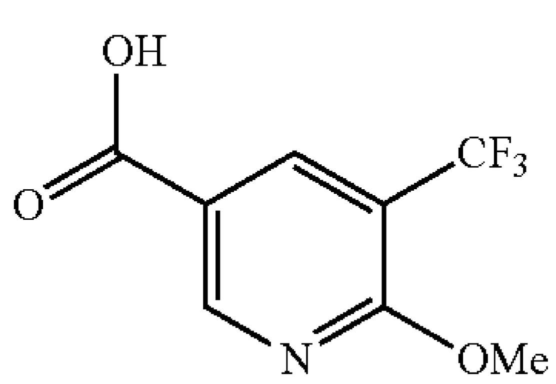
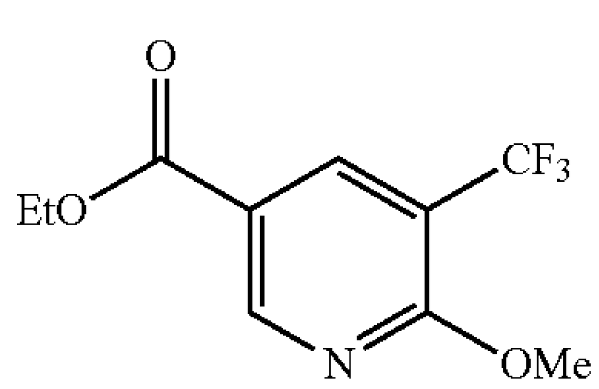
33	
34	
35	

TABLE 11-continued

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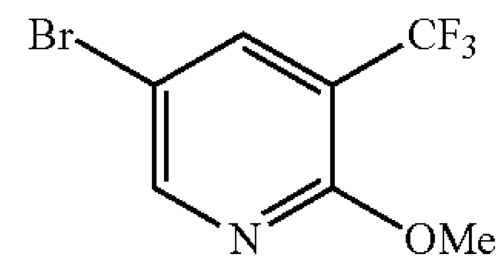
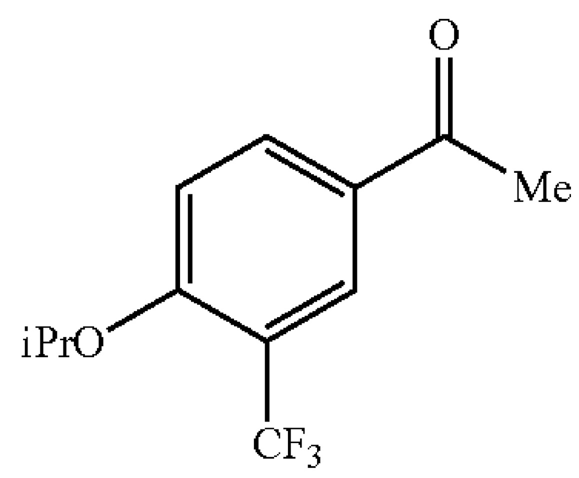
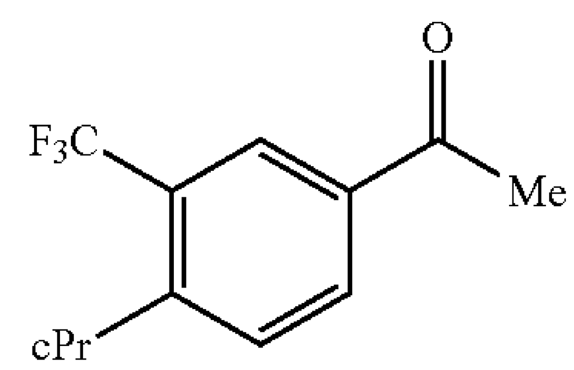
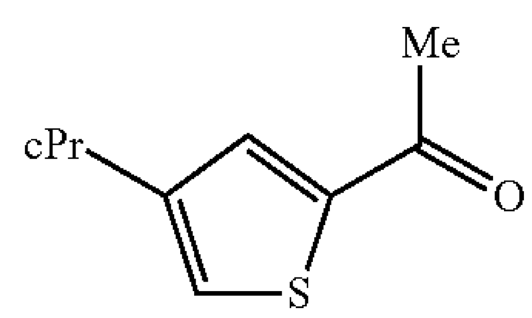
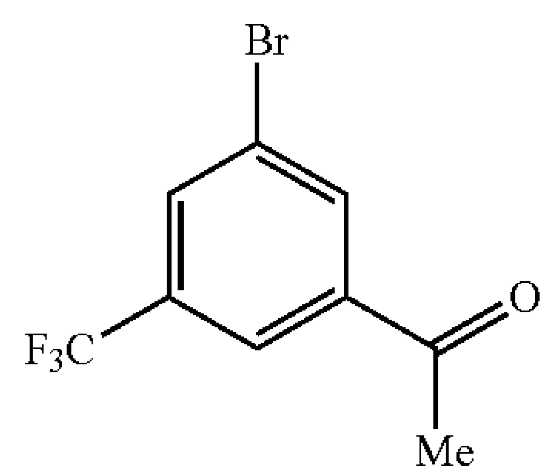
36	
37	
38	
39	
40	

TABLE 12

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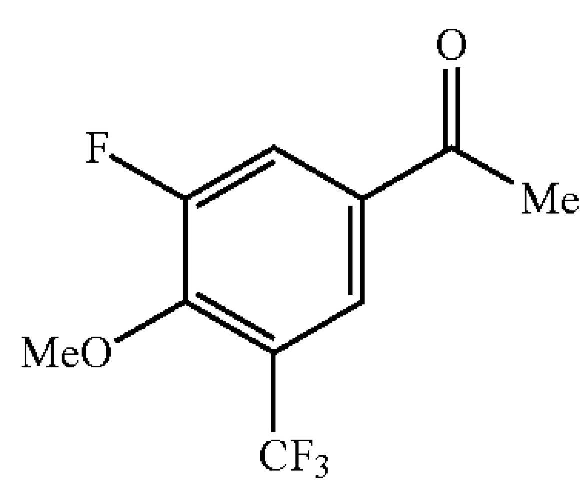
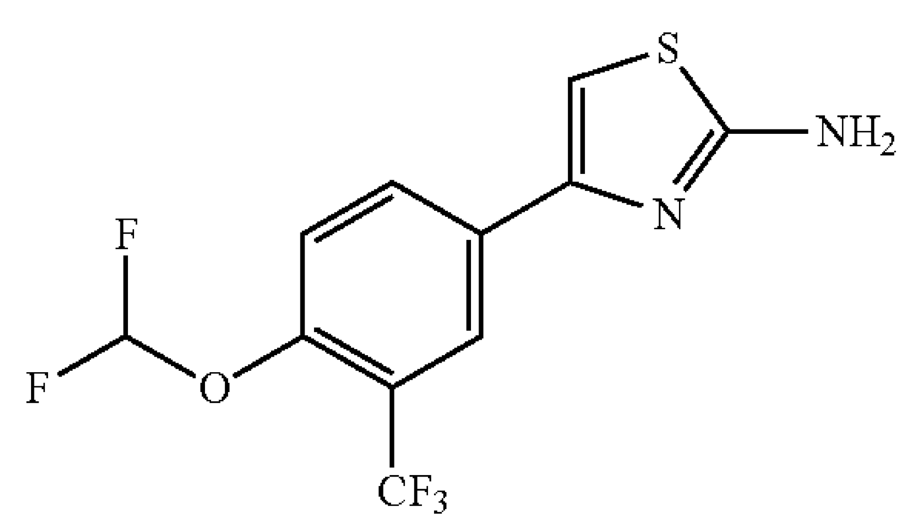
41	
42	

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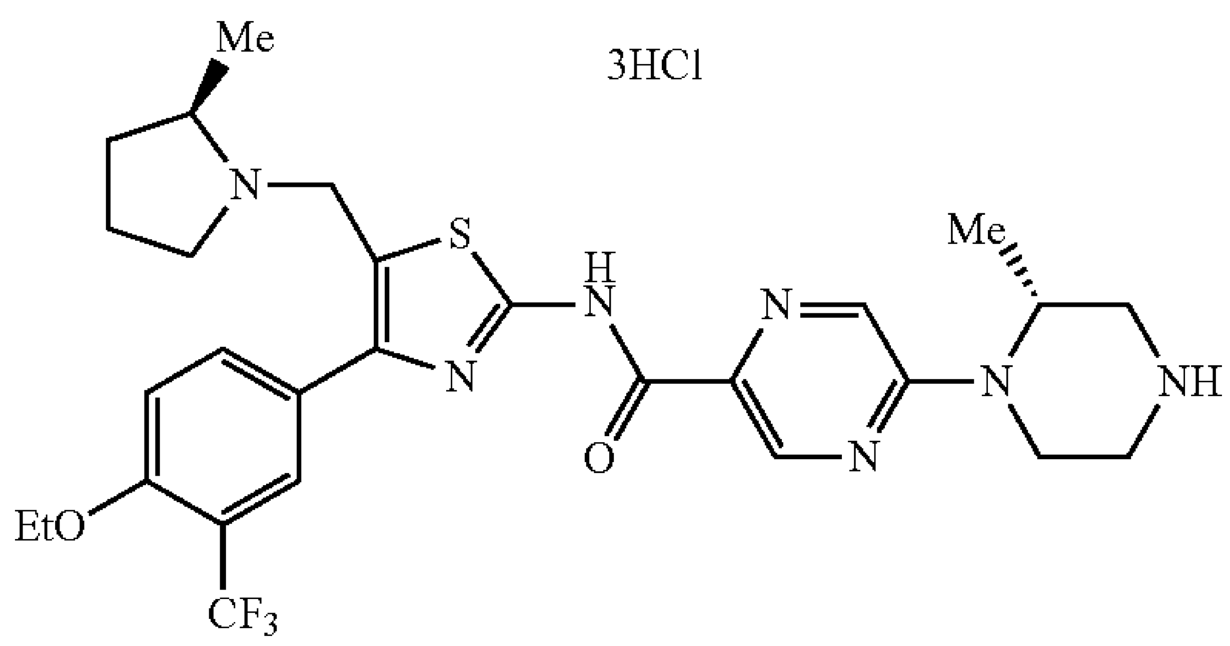
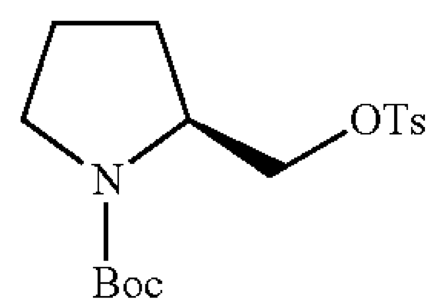
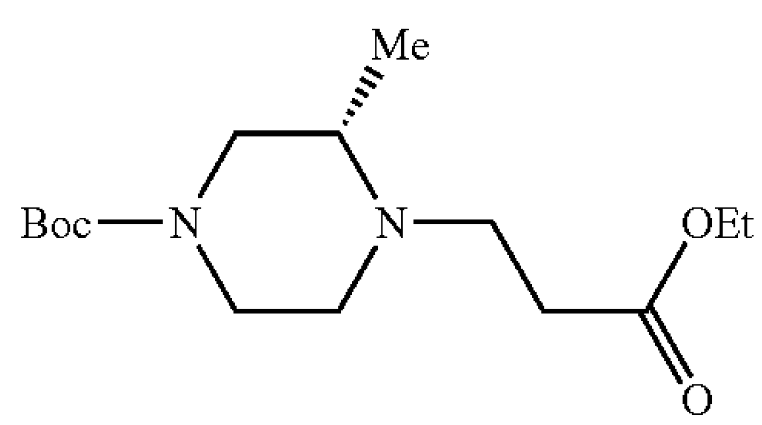
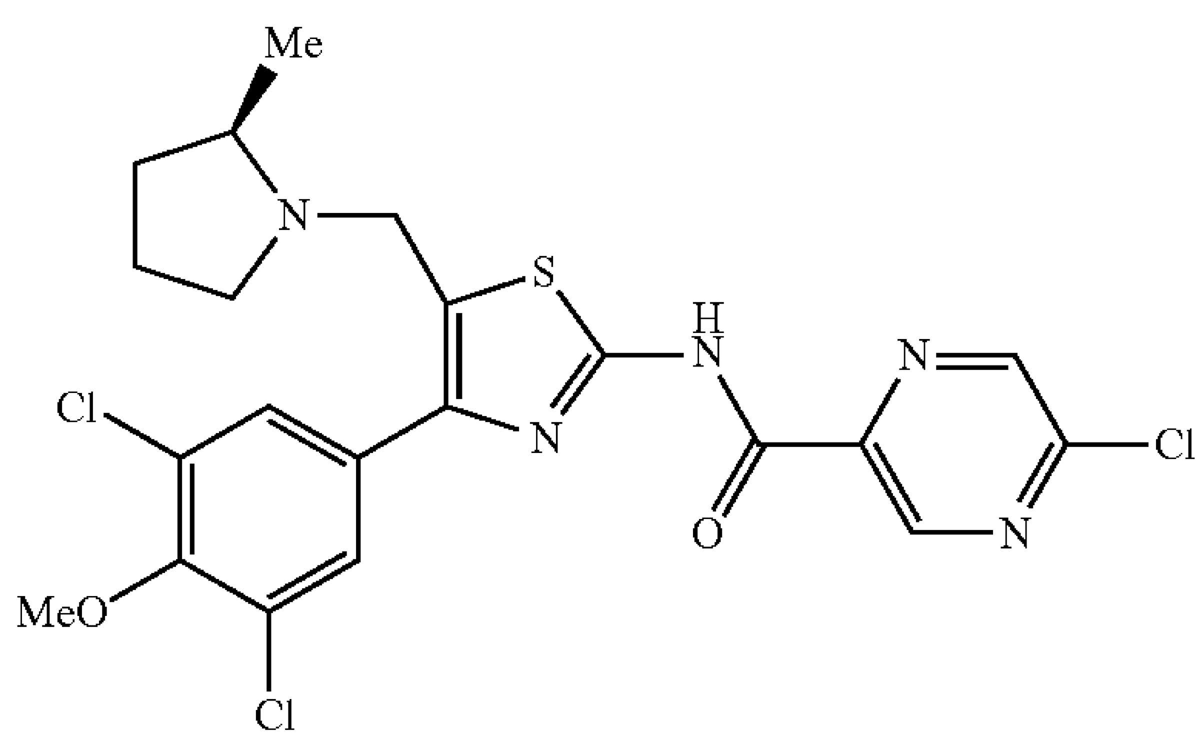
43	
44	
45	
46	

TABLE 13

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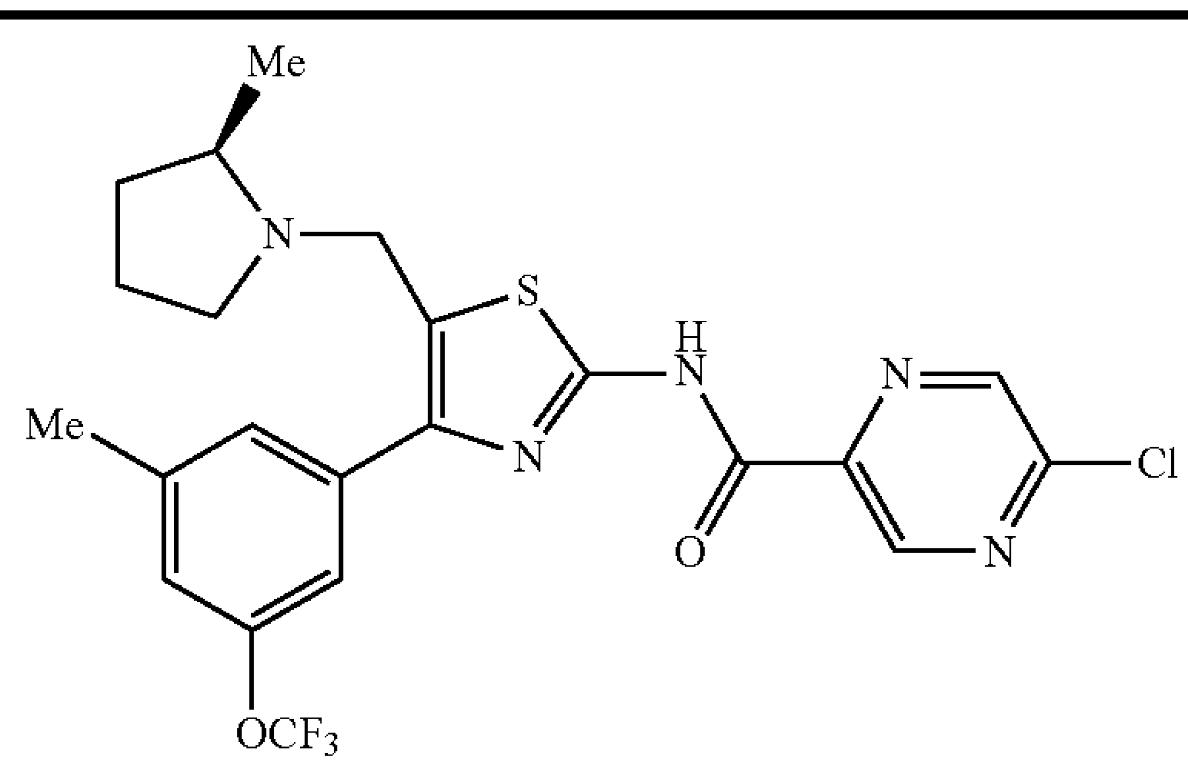
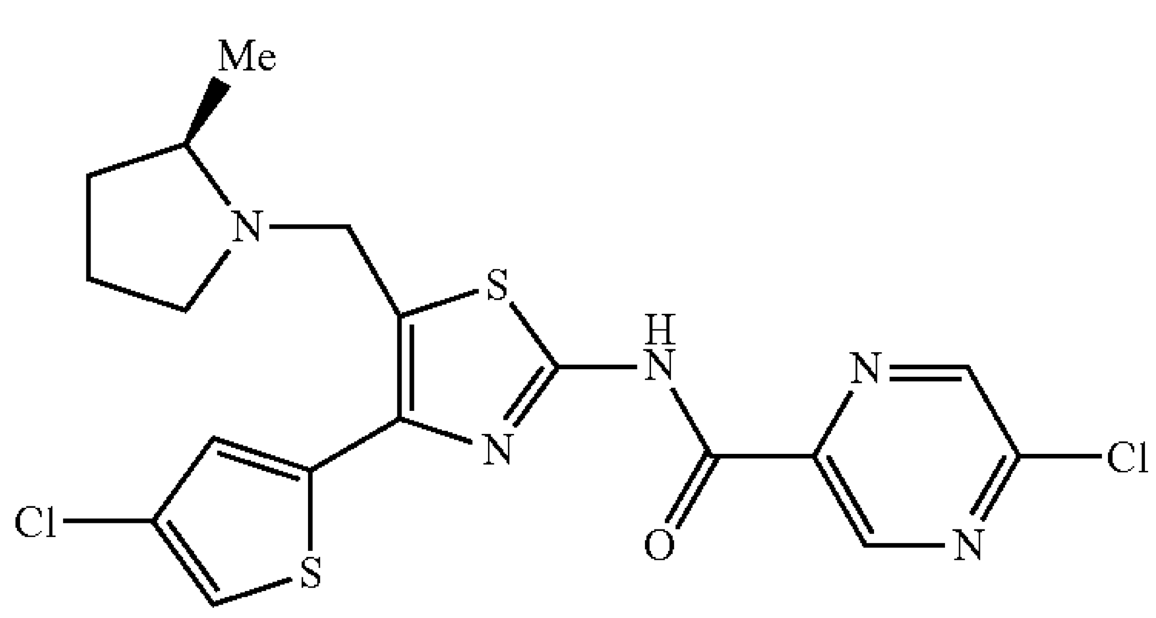
47	
48	

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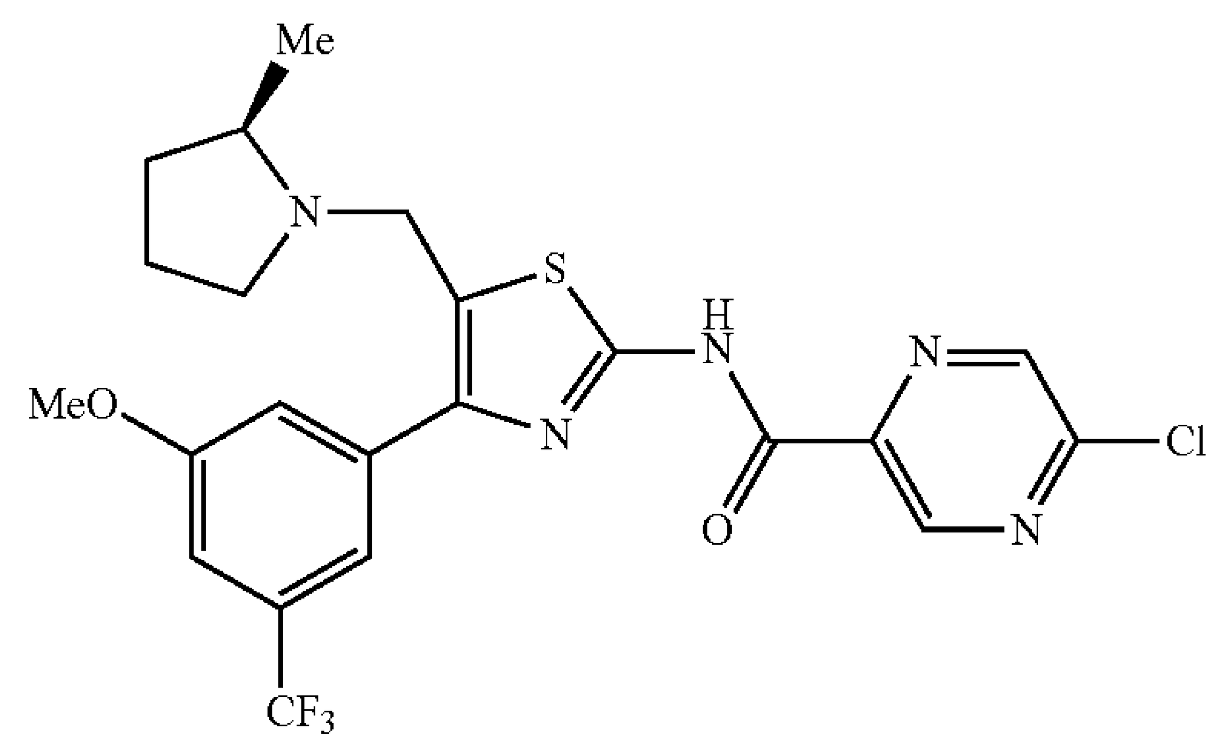
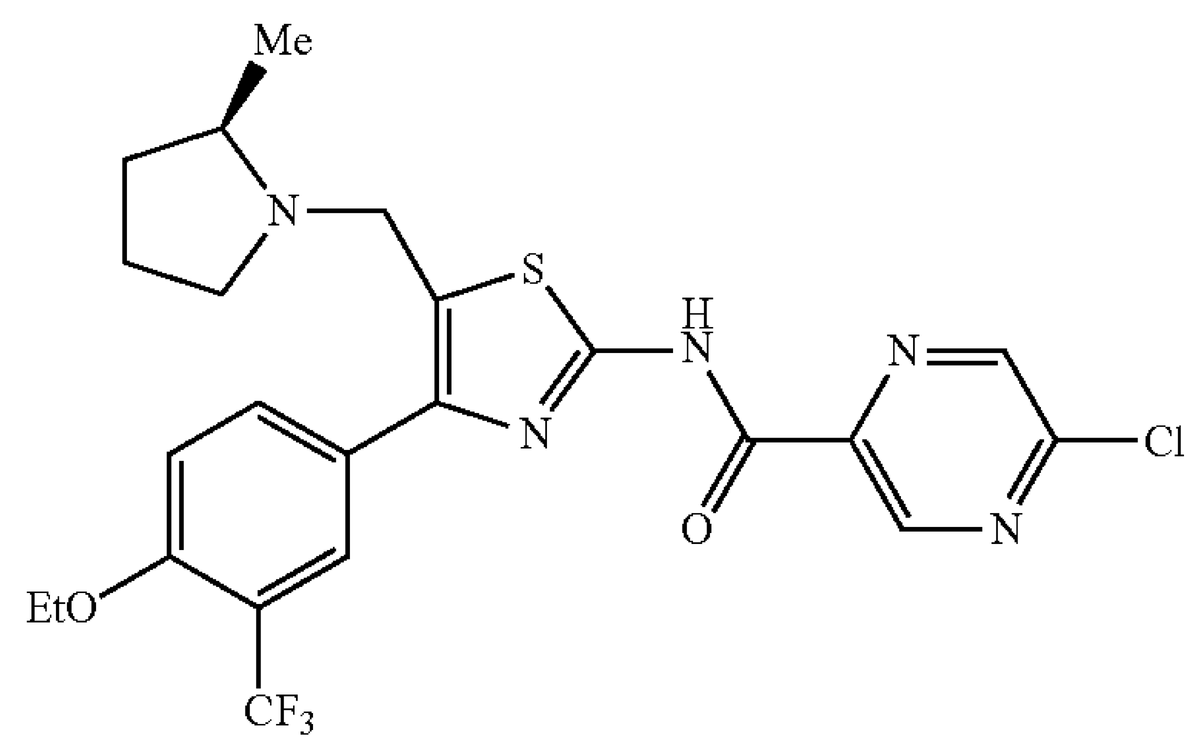
49	
50	

TABLE 14

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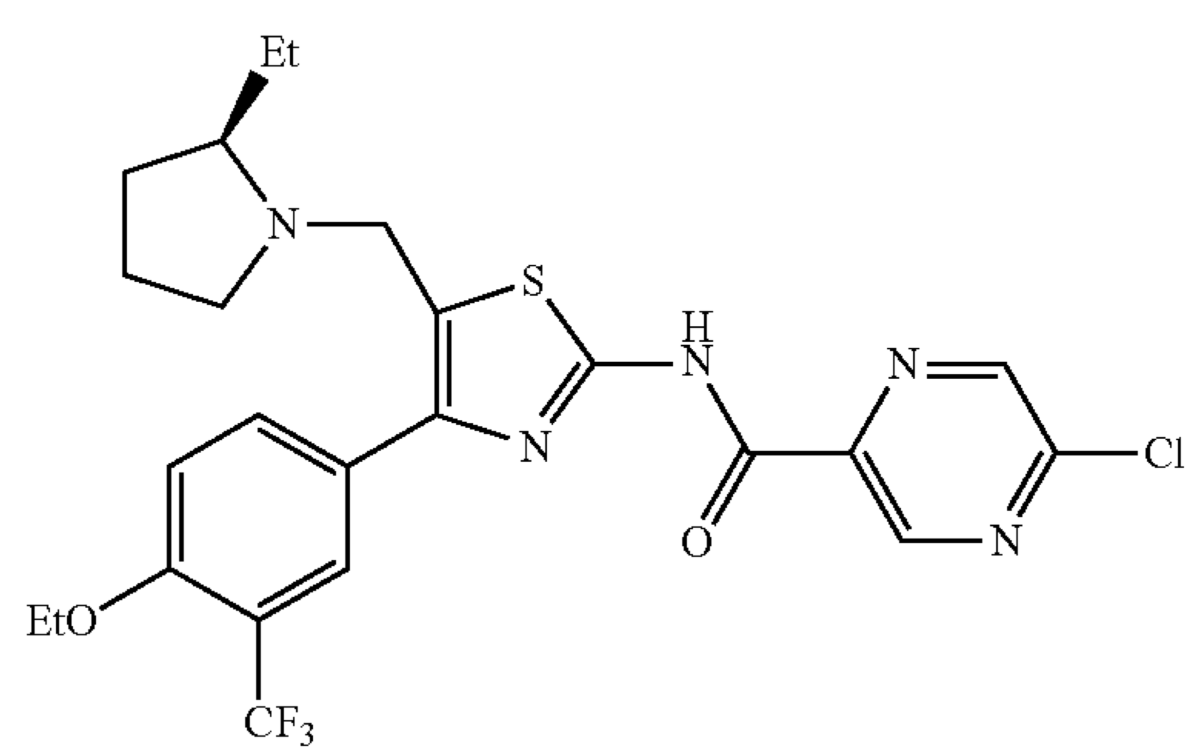
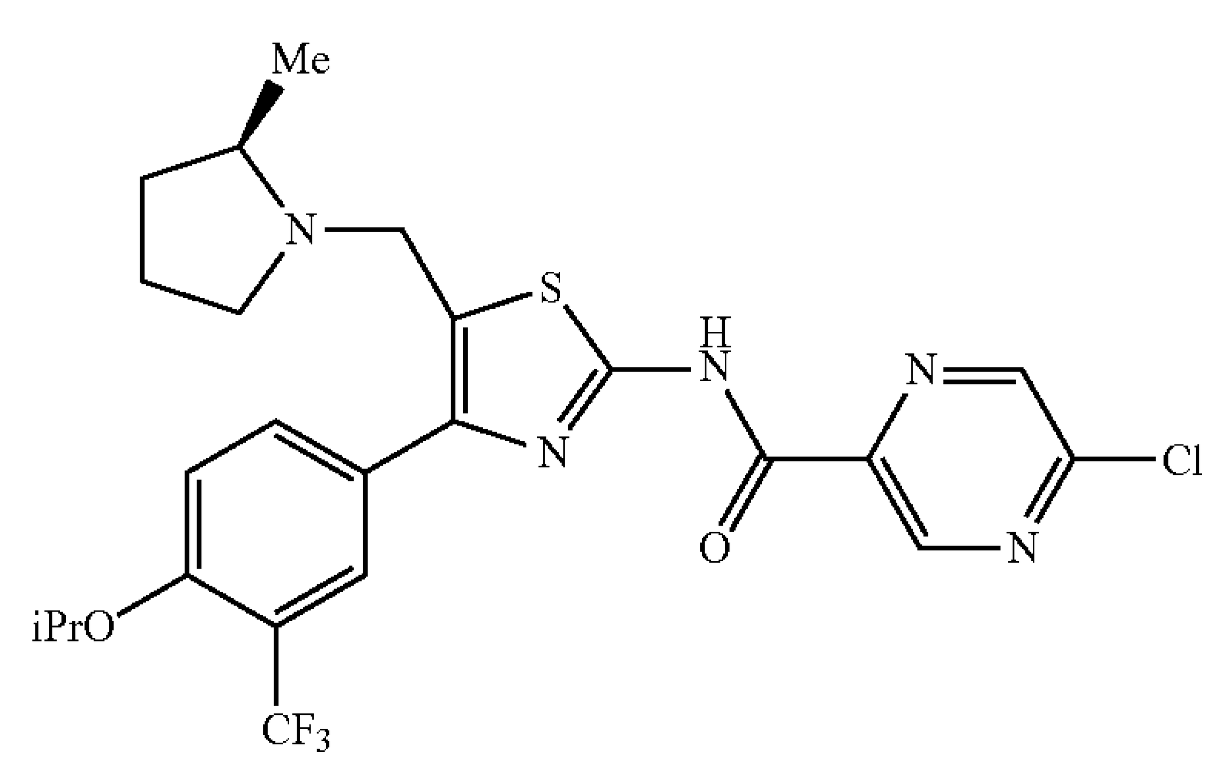
51	
52	

TABLE 14-continued

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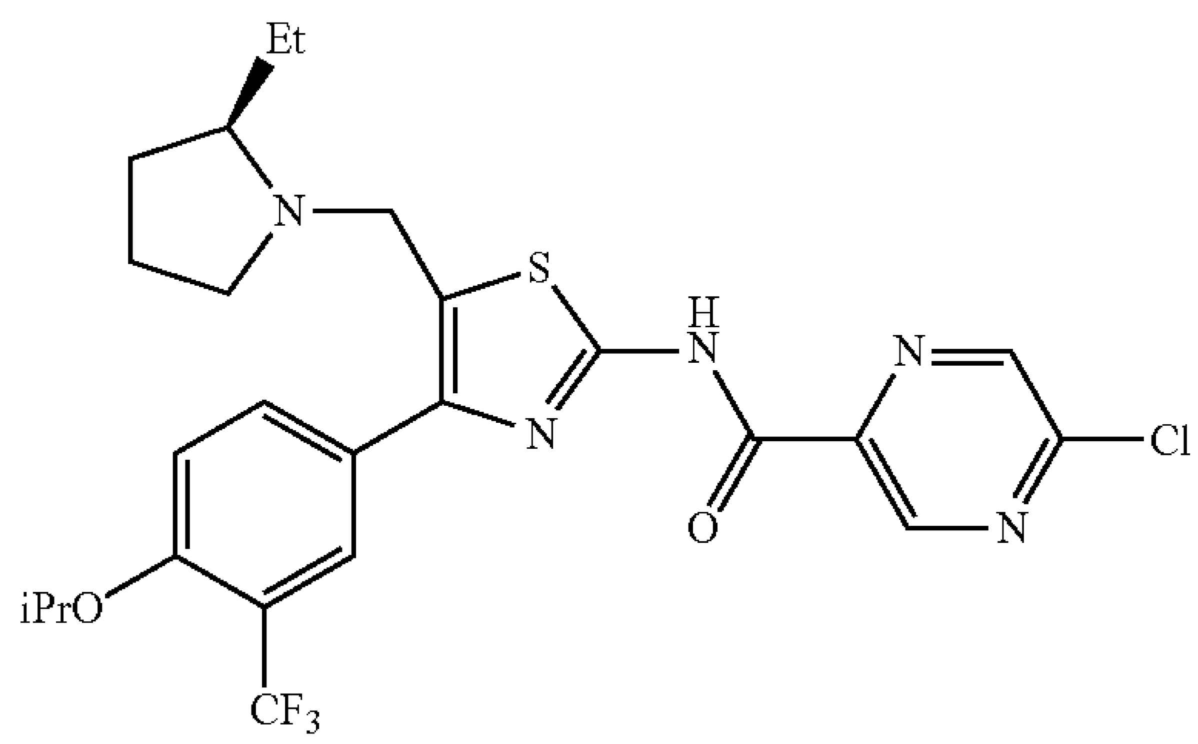
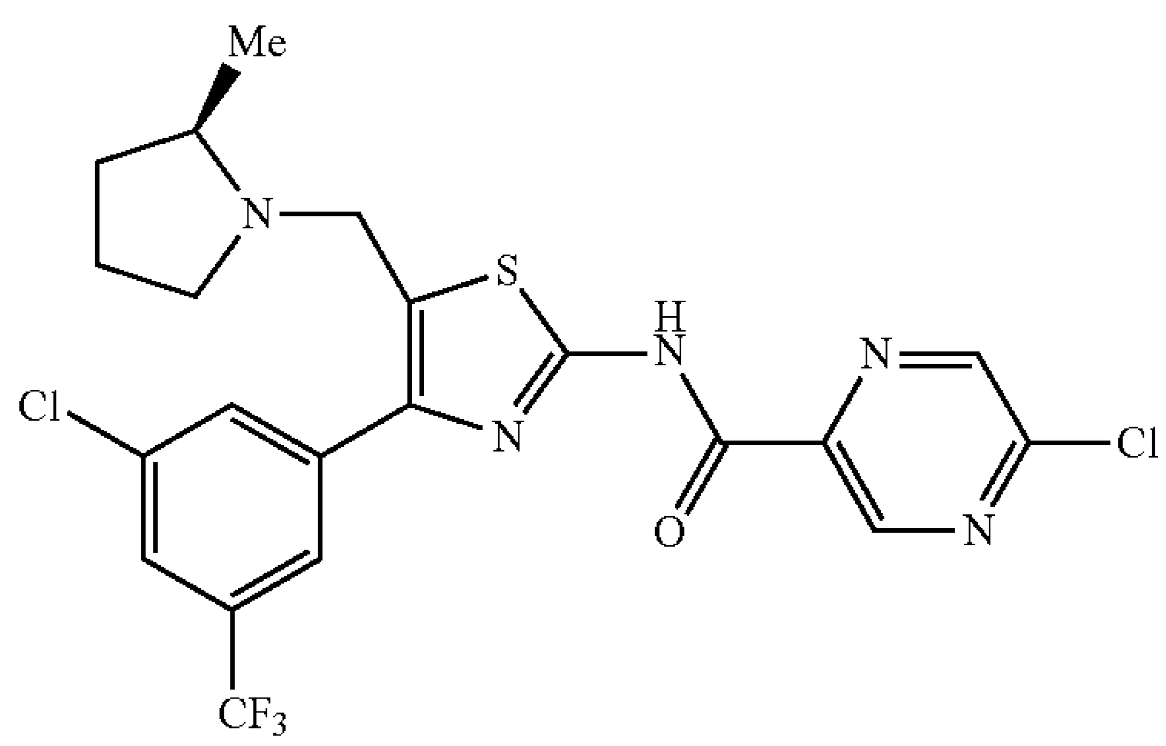
53	
54	

TABLE 15

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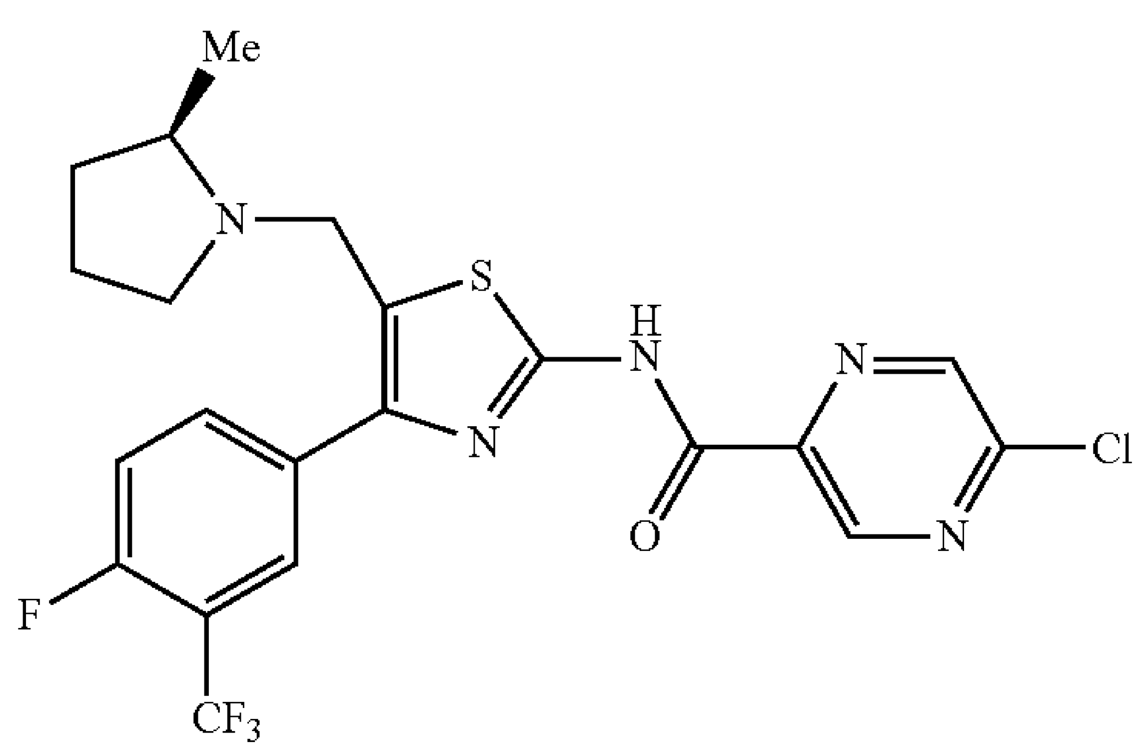
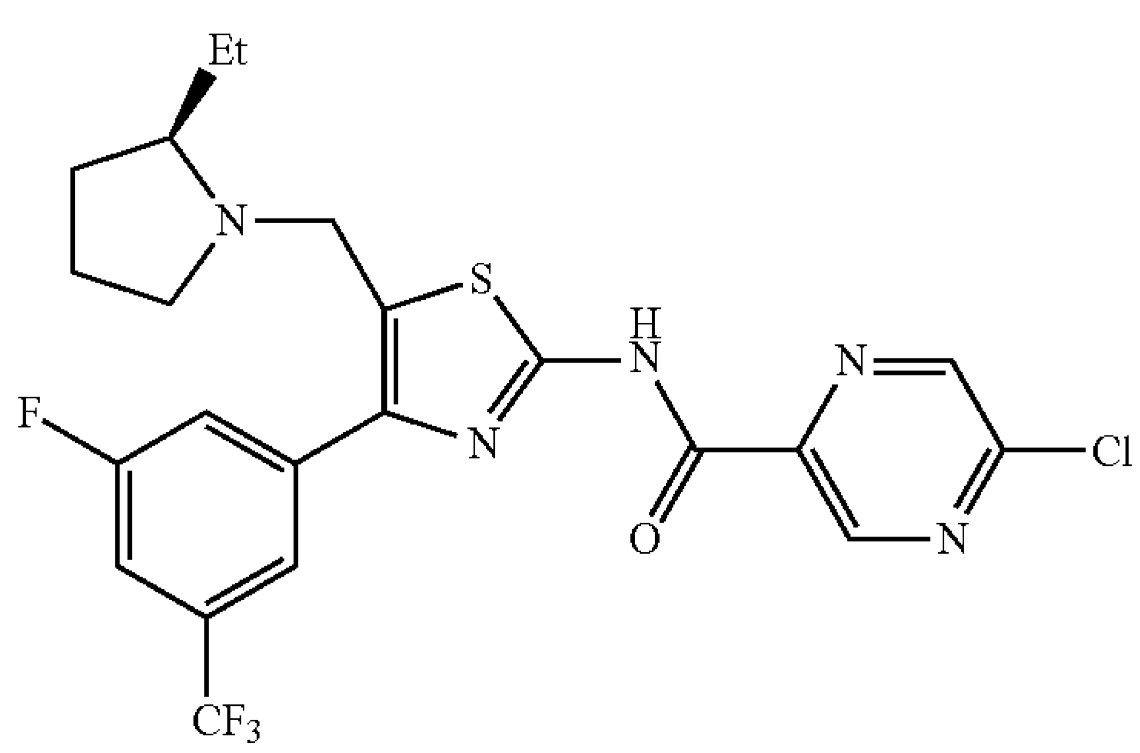
55	
56	

TABLE 15-continued

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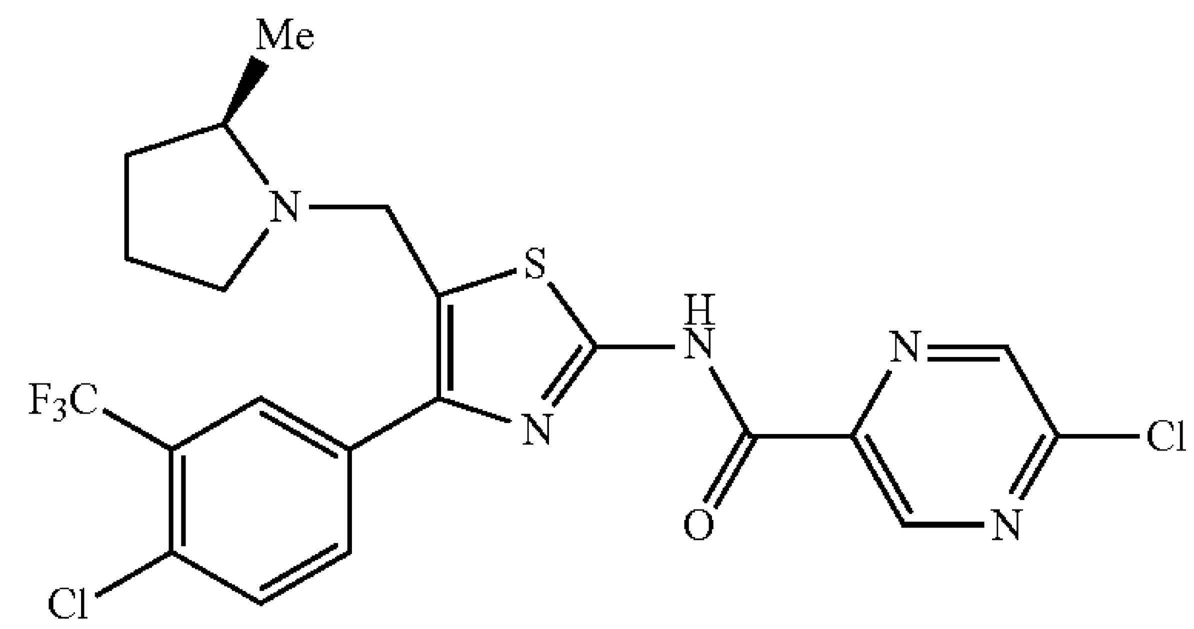
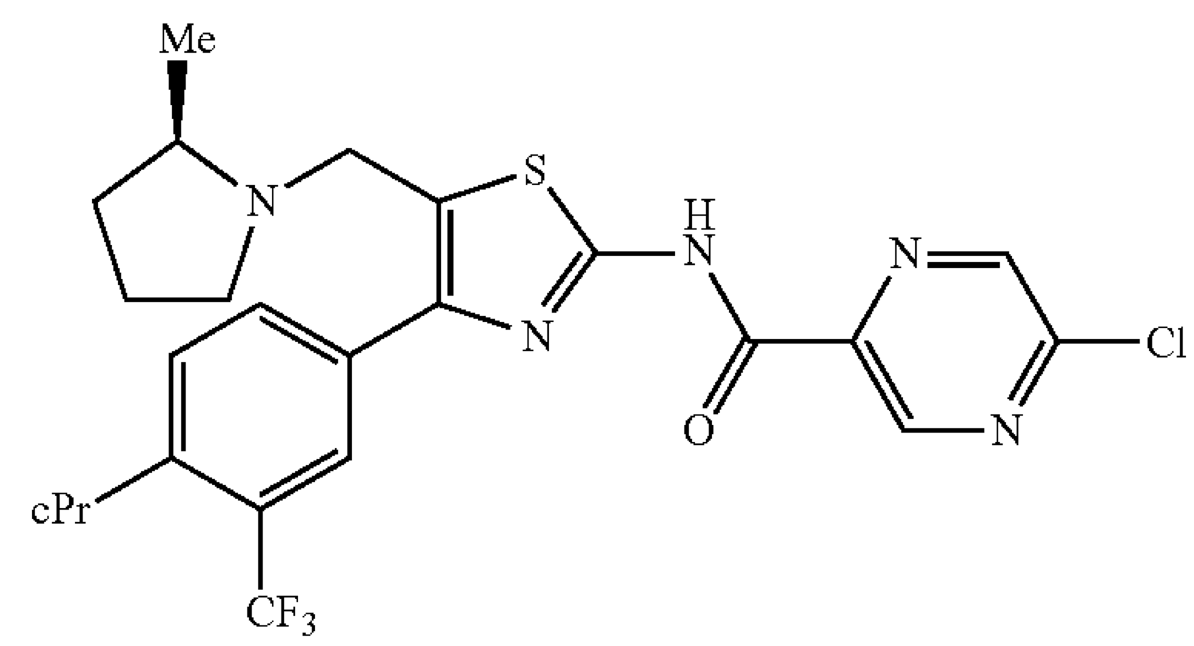
57	
58	

TABLE 16

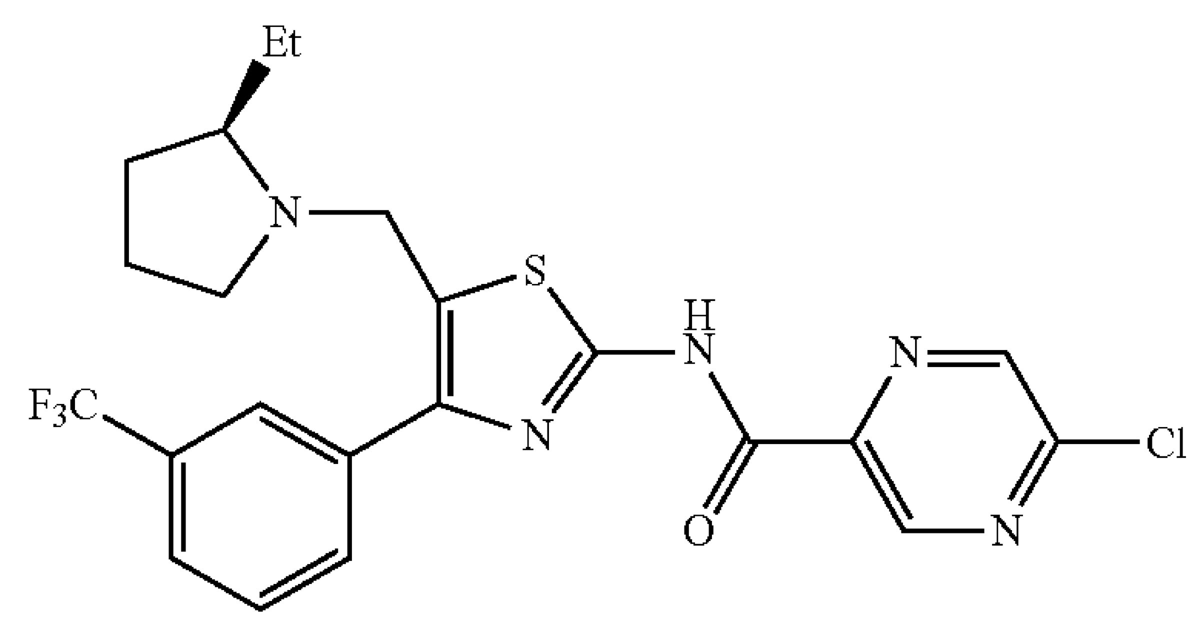
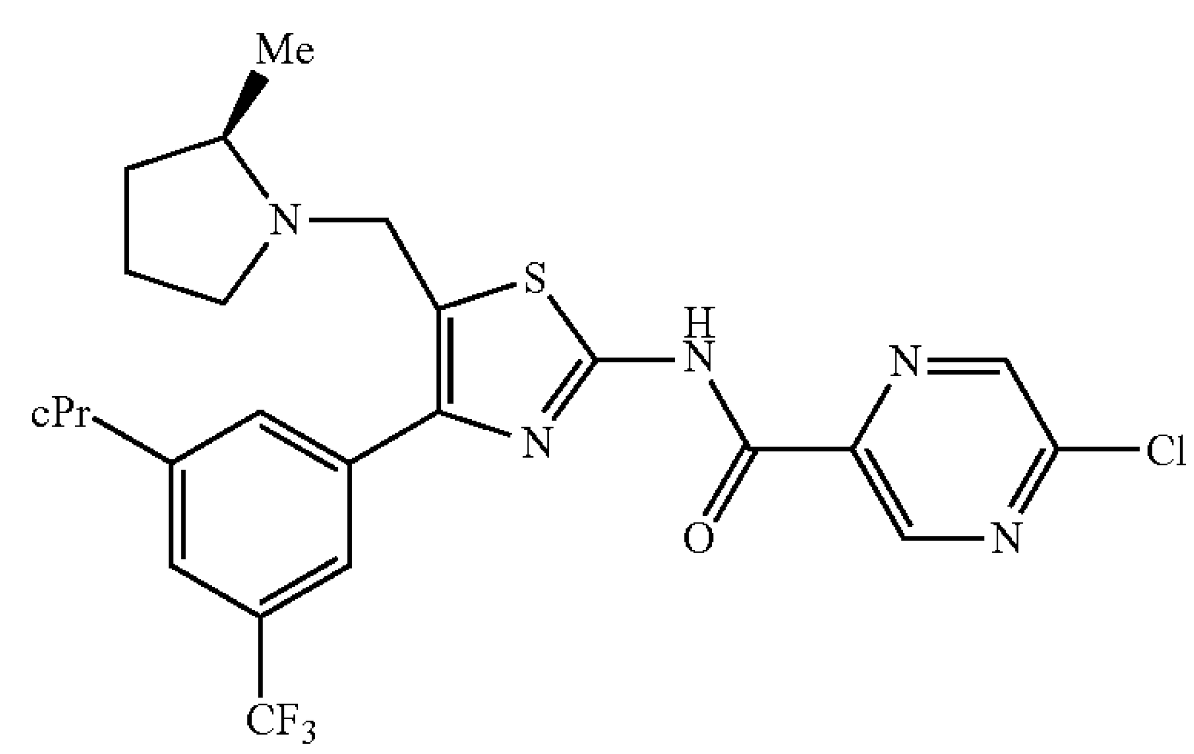
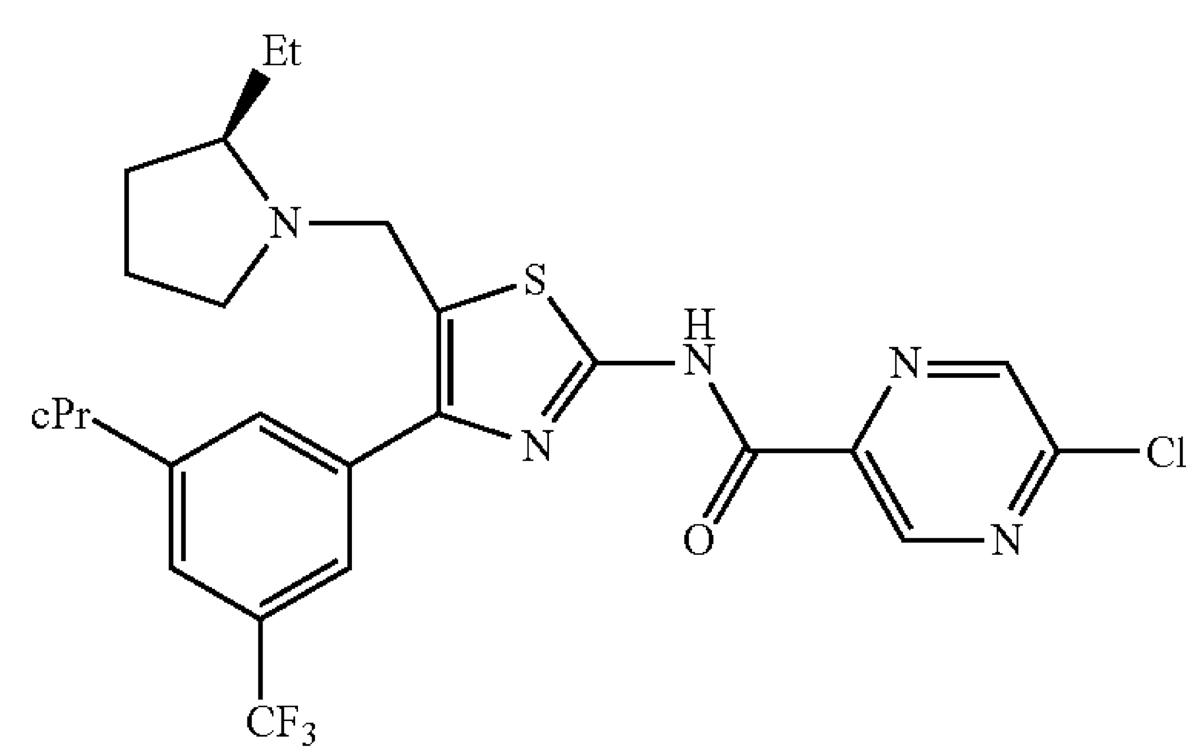
PEx	Structure
59	
60	
61	

TABLE 16-continued

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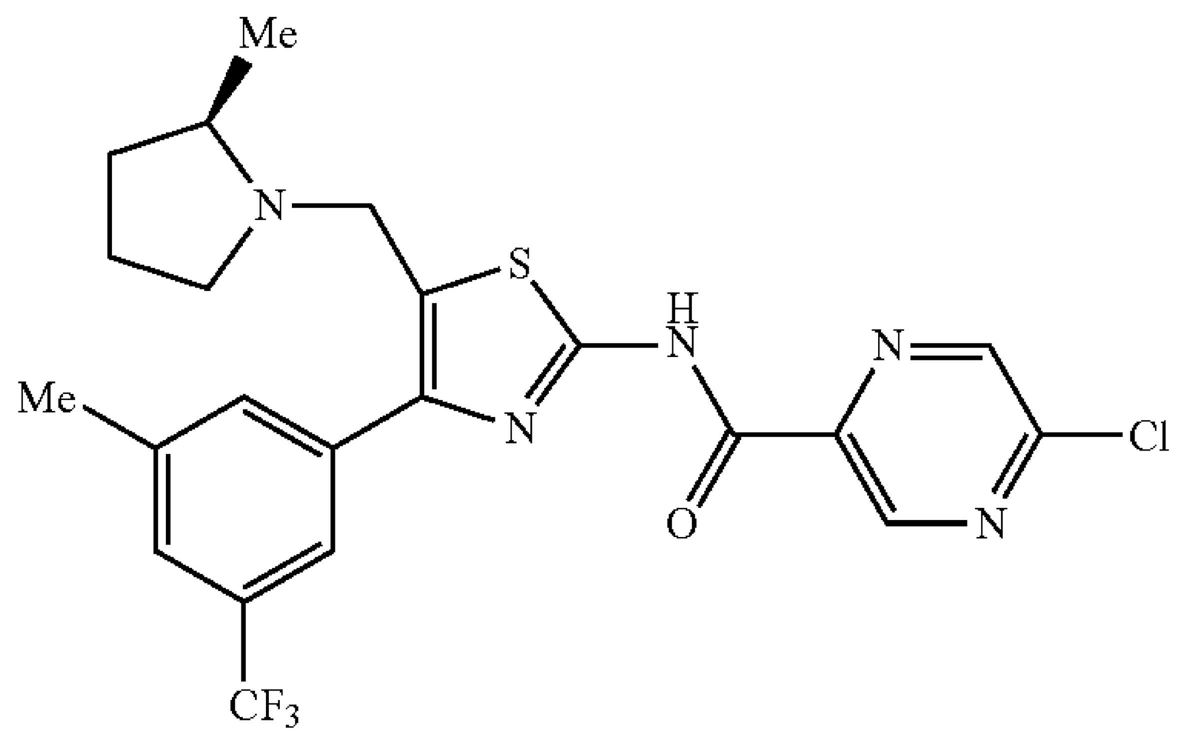
62	

TABLE 17

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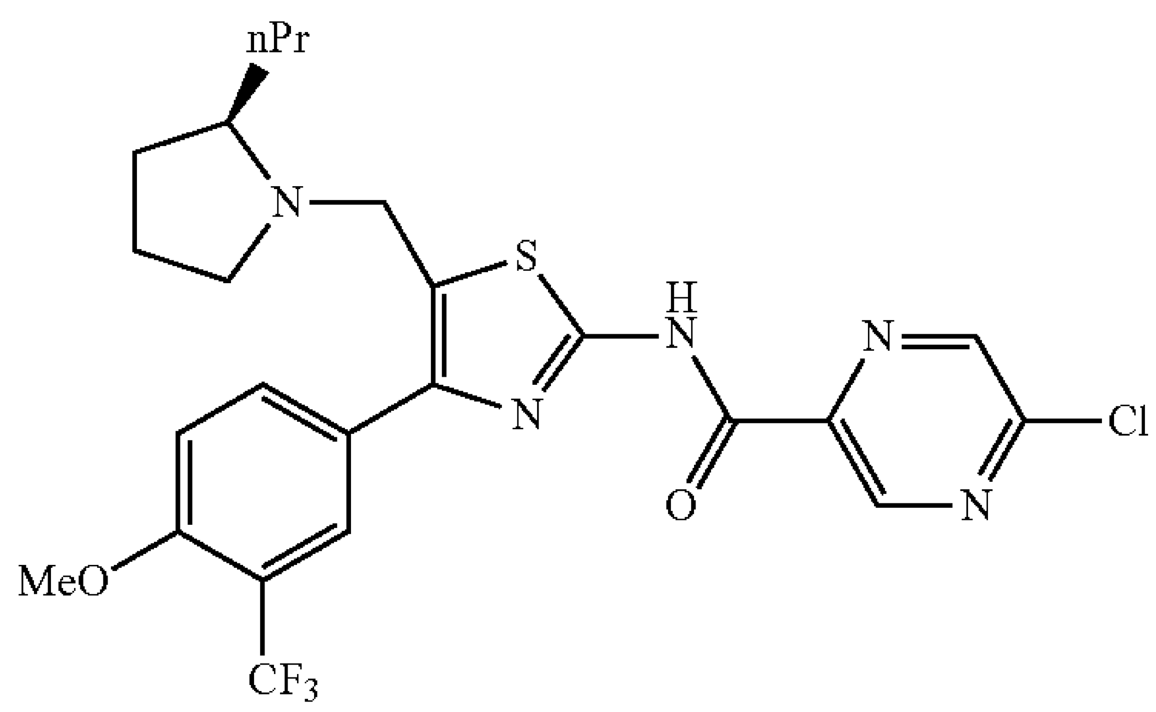
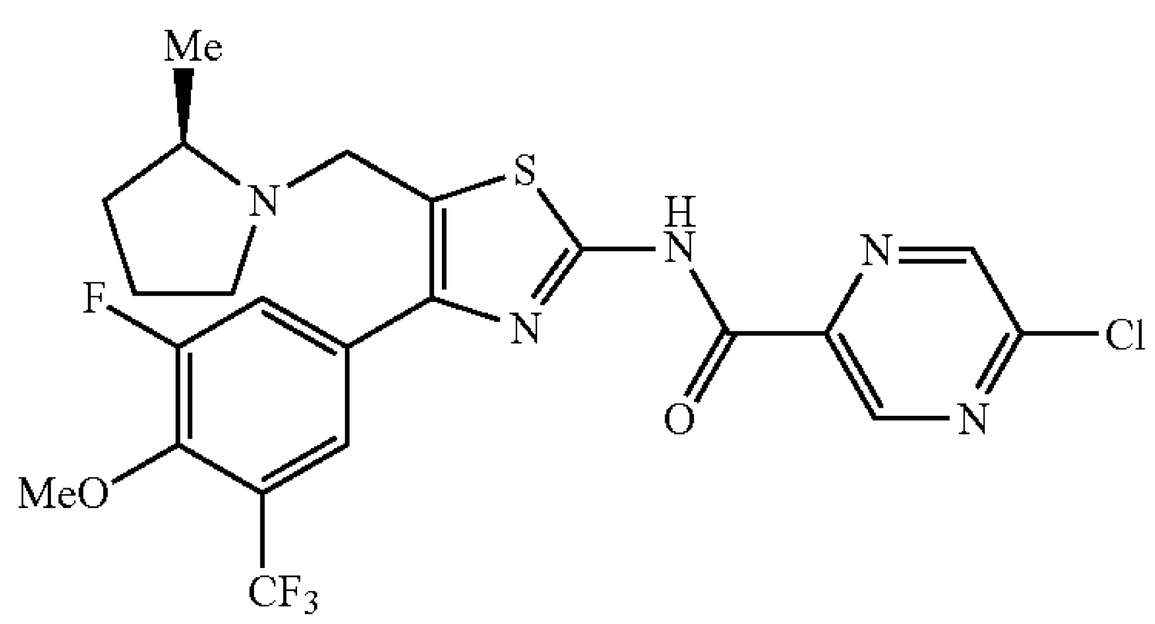
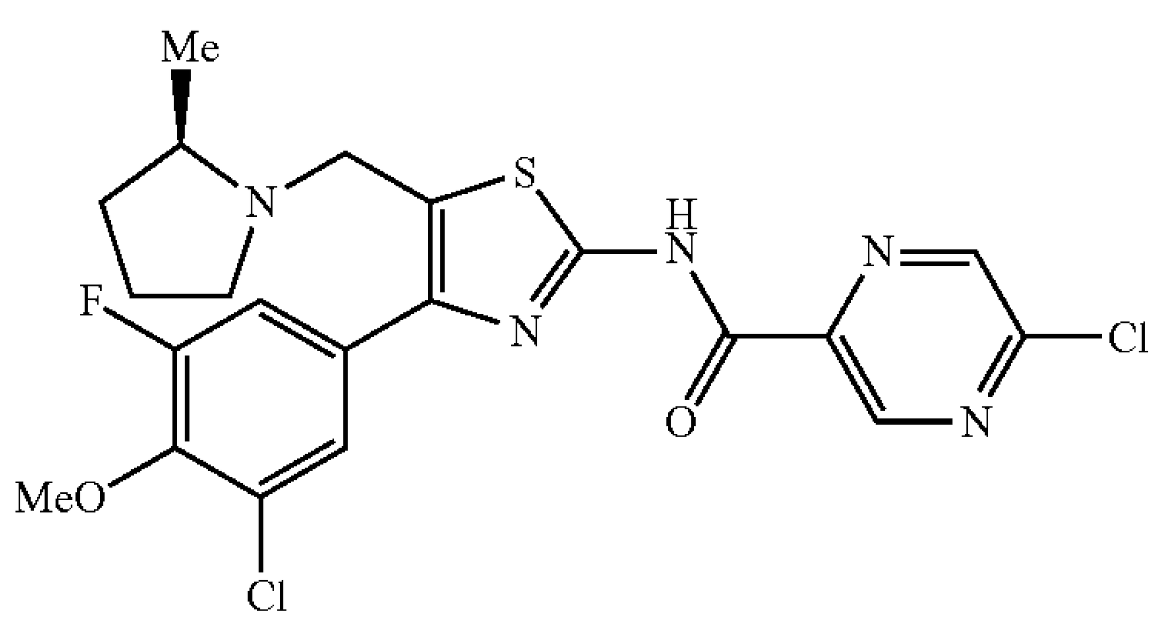
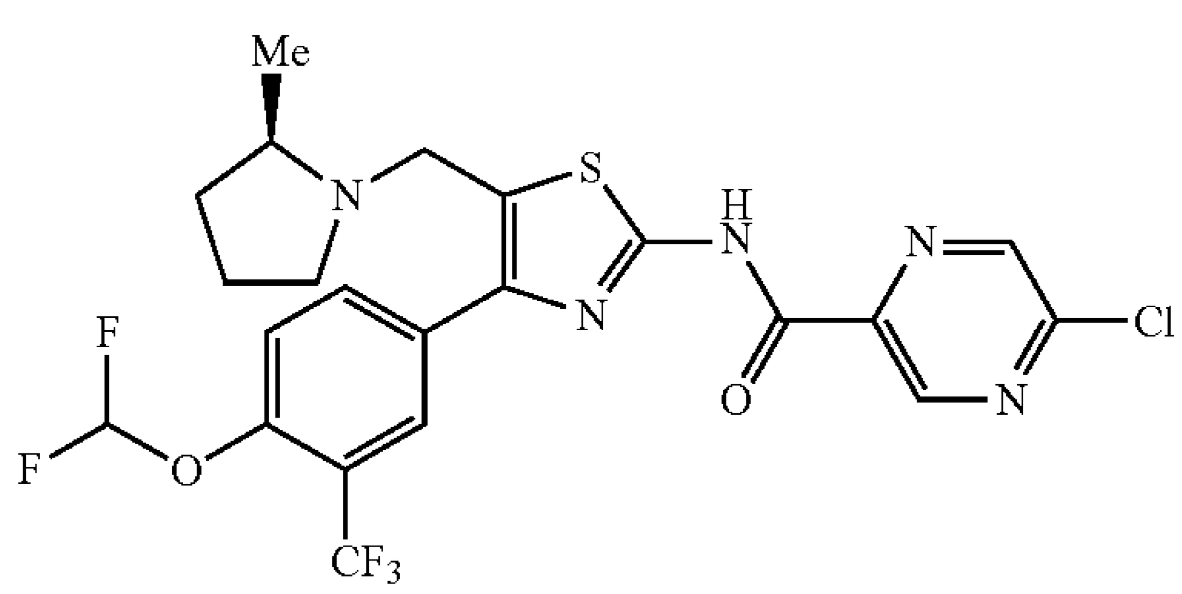
63	
64	
65	
66	

TABLE 18

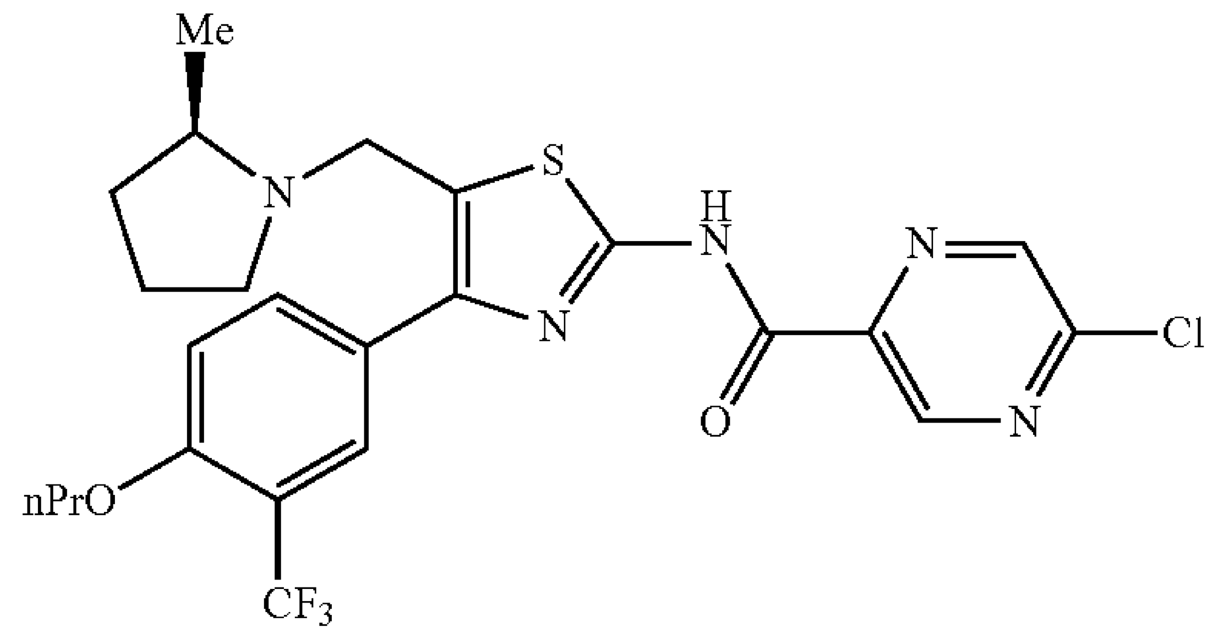
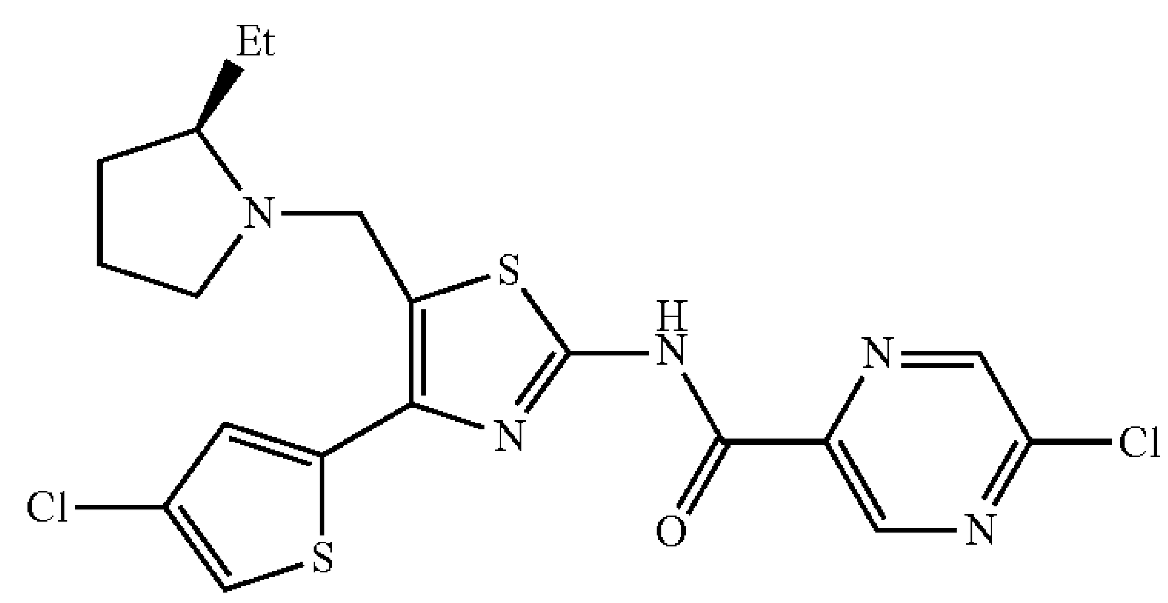
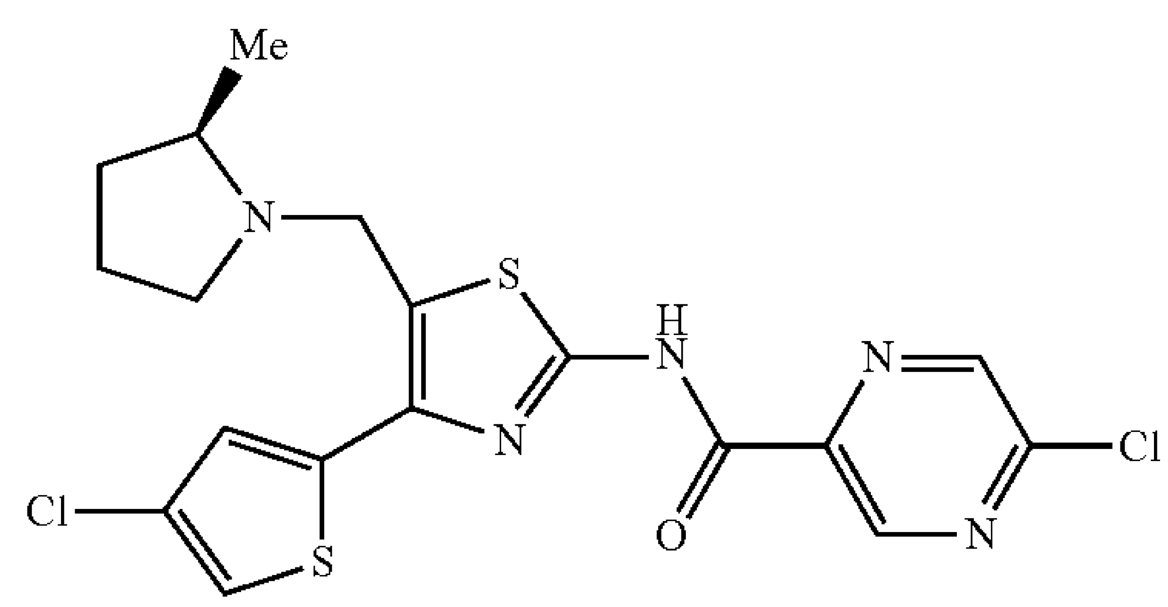
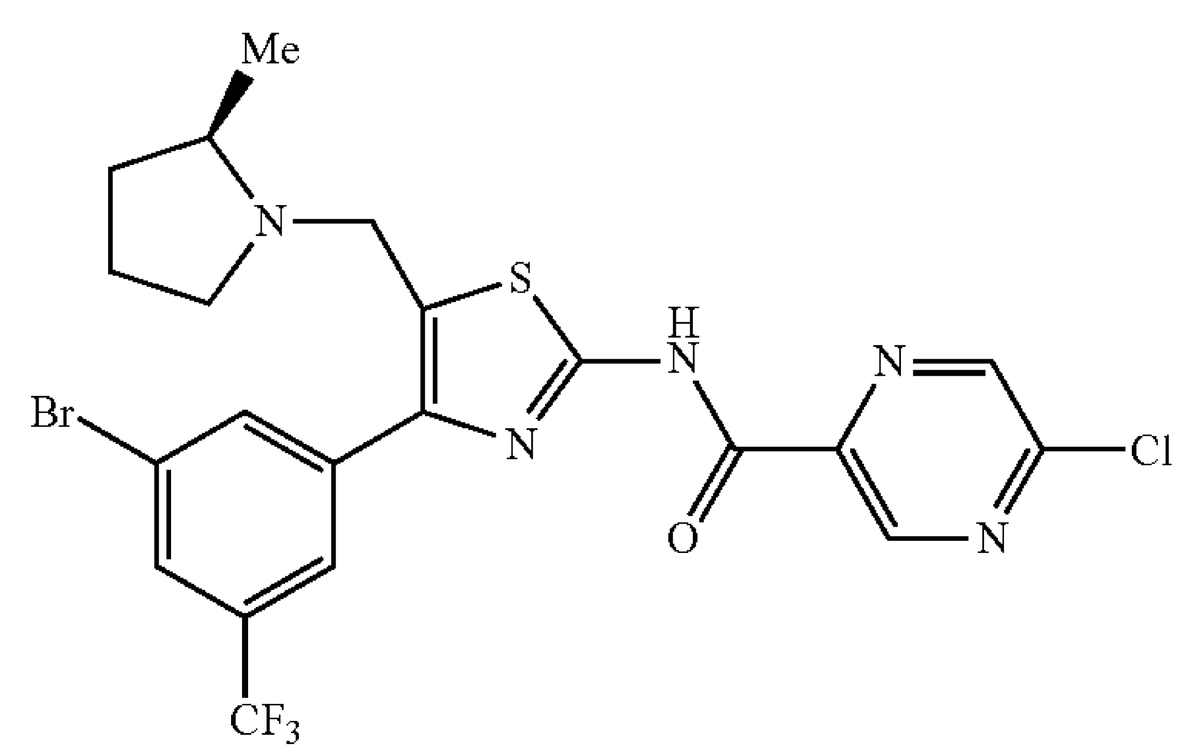
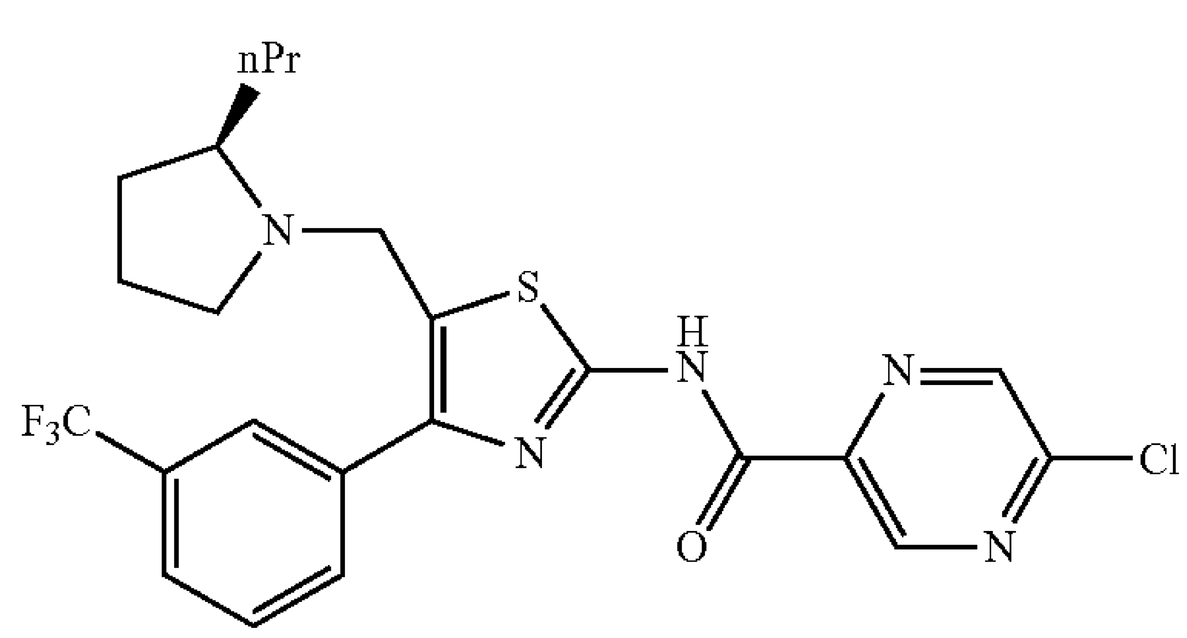
PEx	Structure
67	
68	
69	
70	
71	

TABLE 20

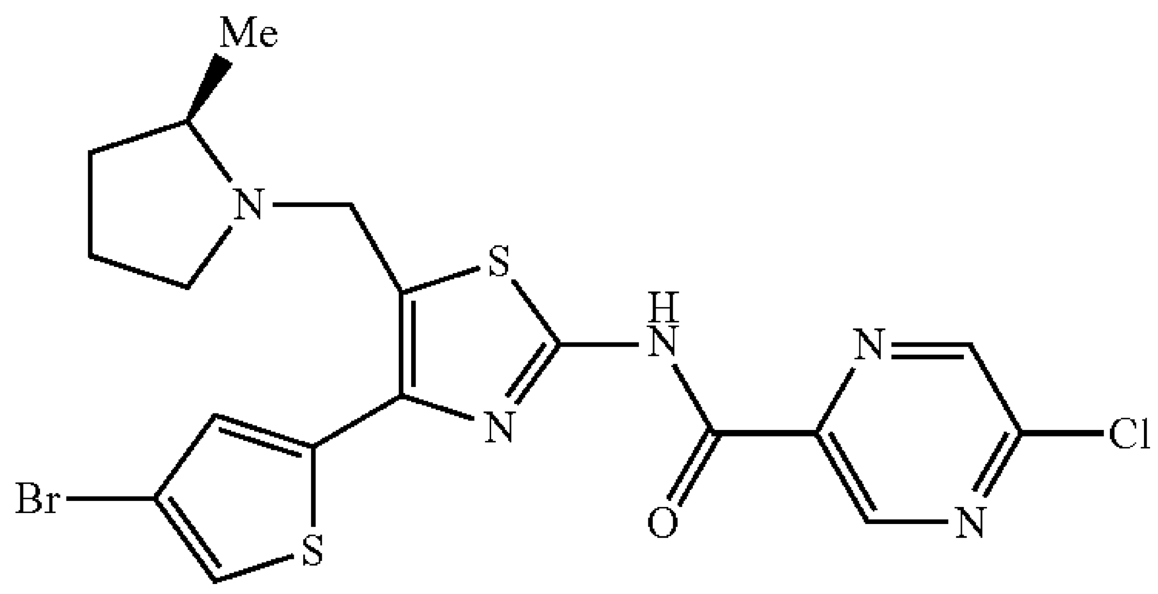
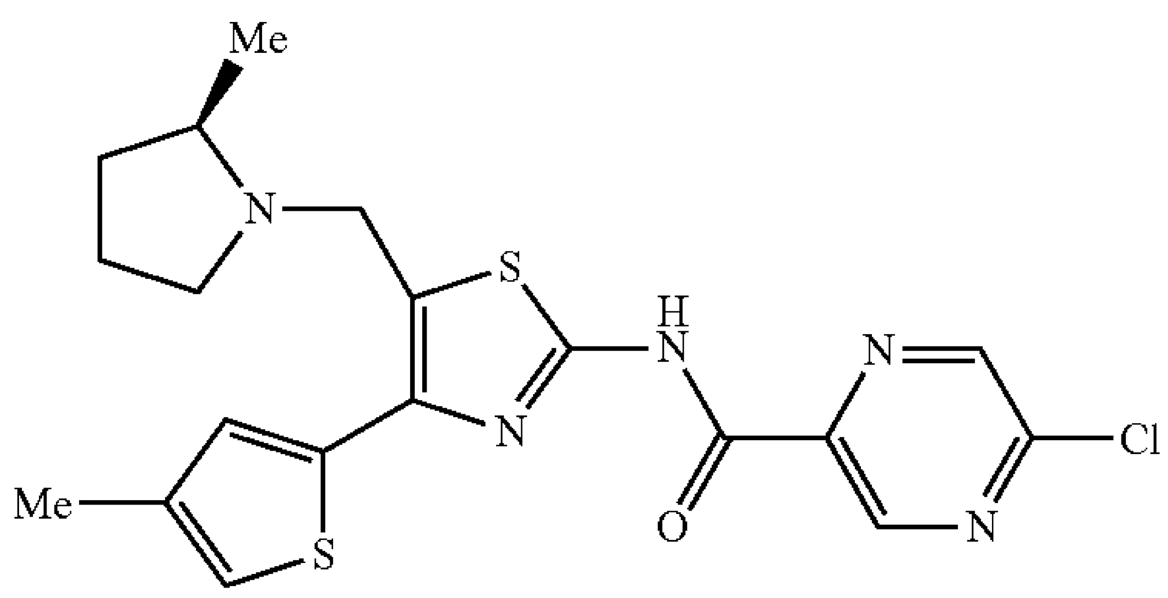
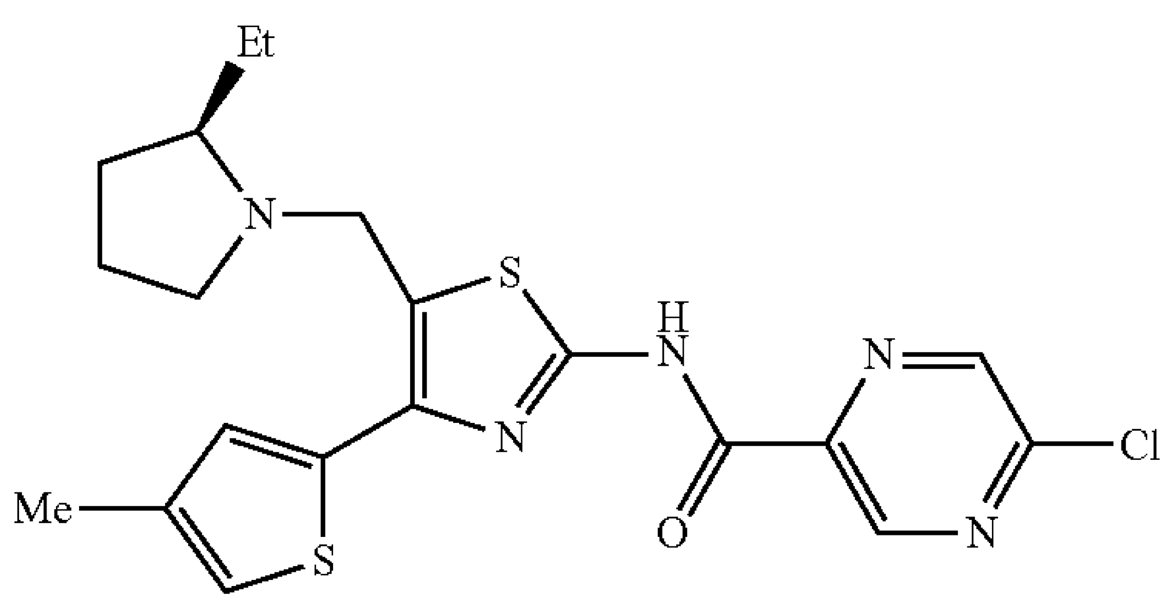
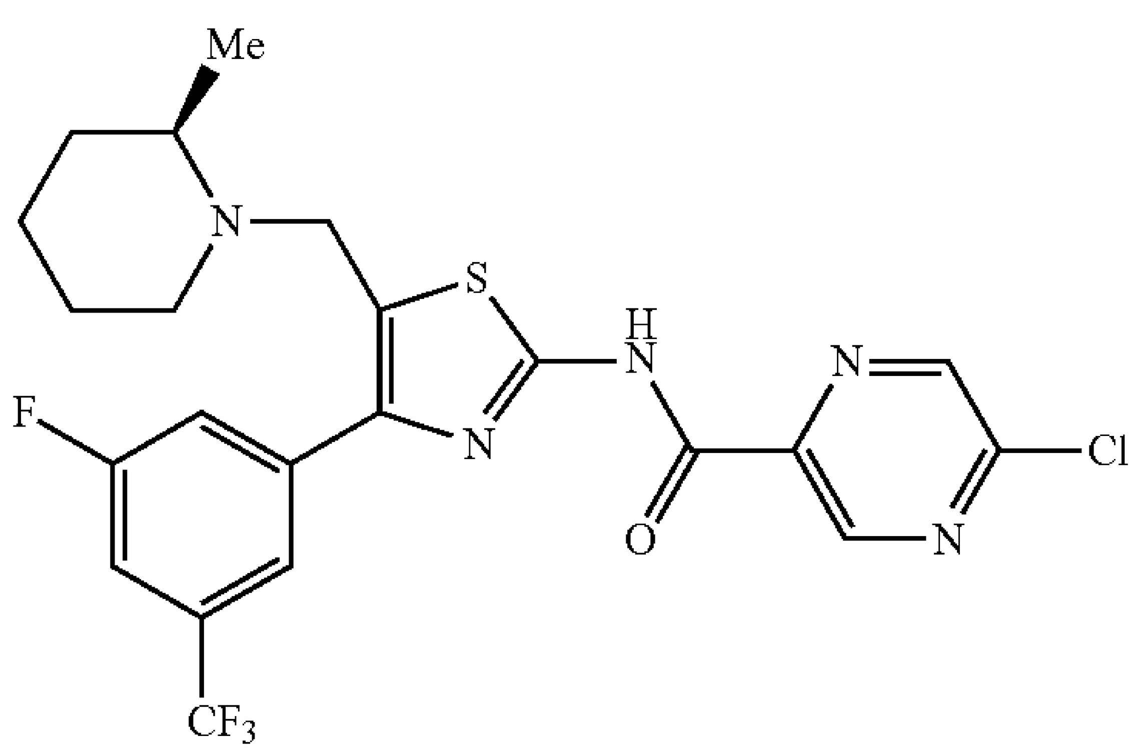
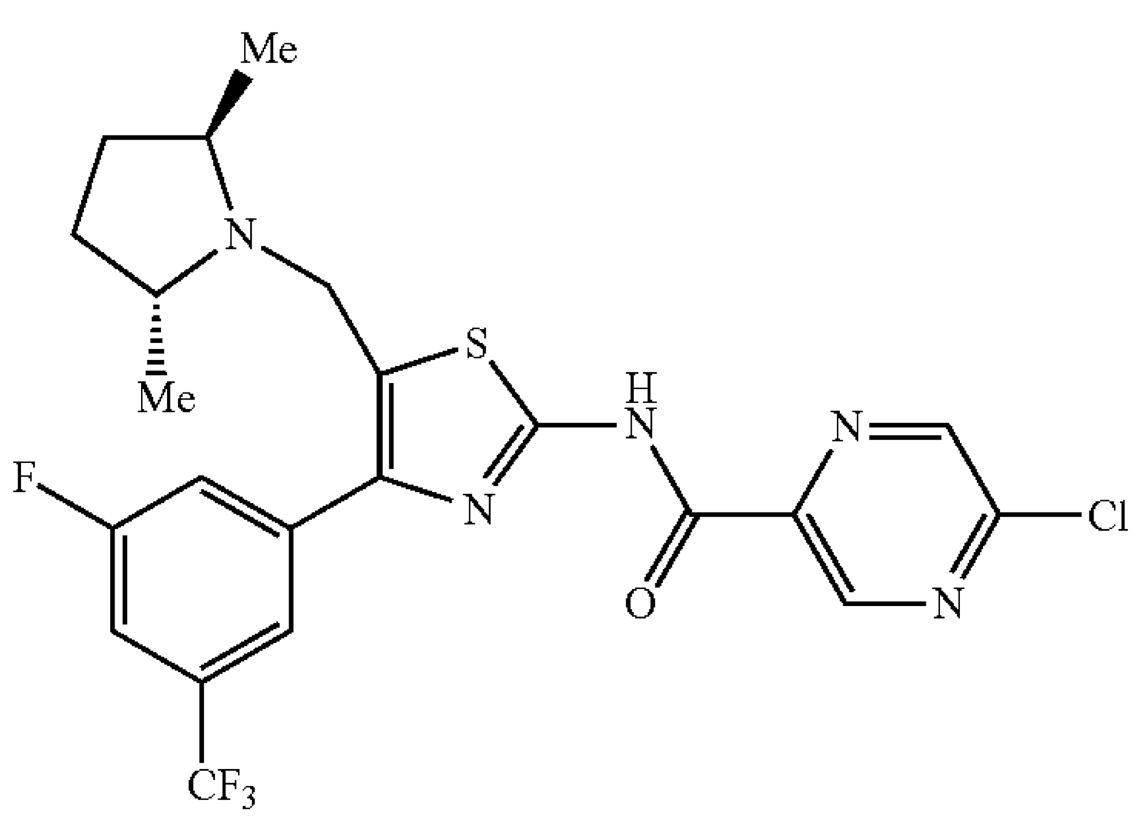
PEx	Structure
77	
78	
79	
80	
81	

TABLE 19

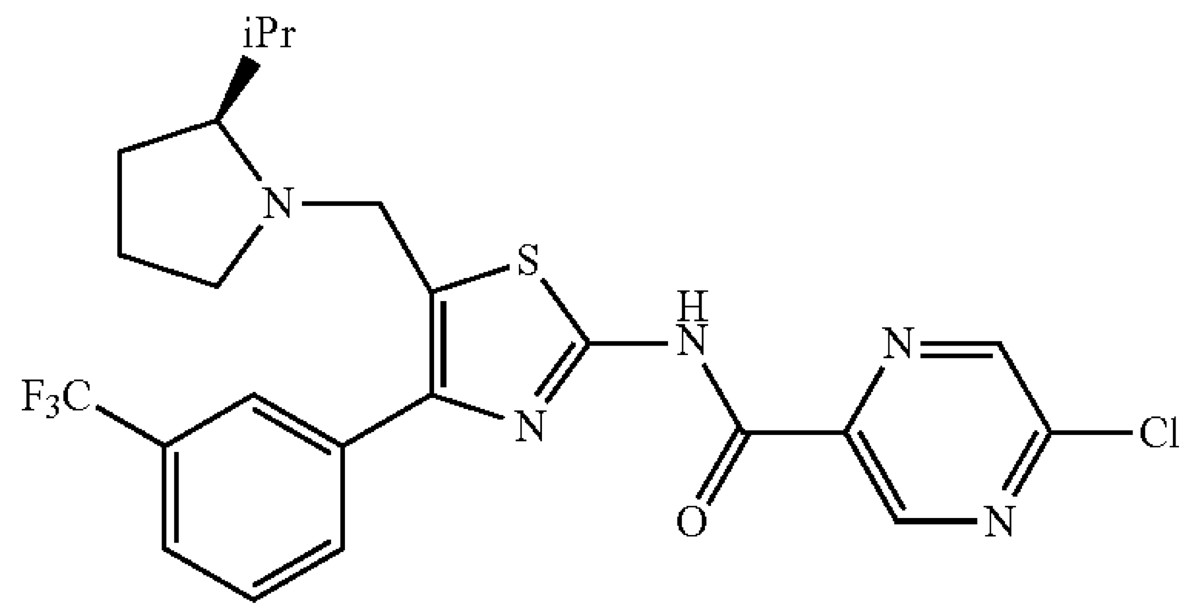
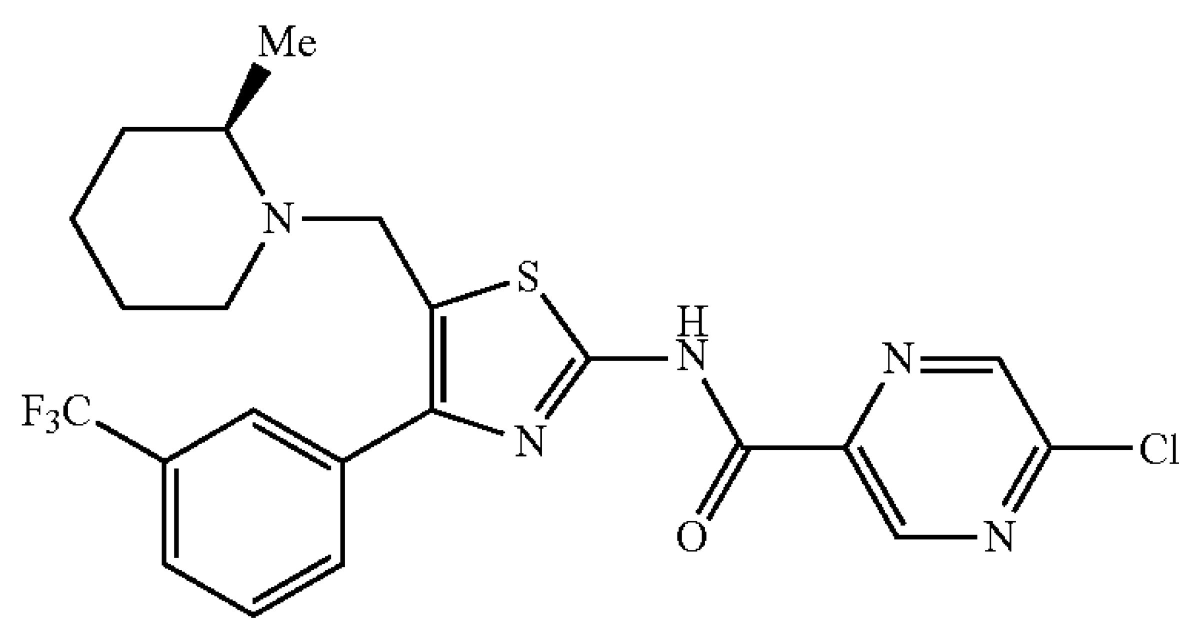
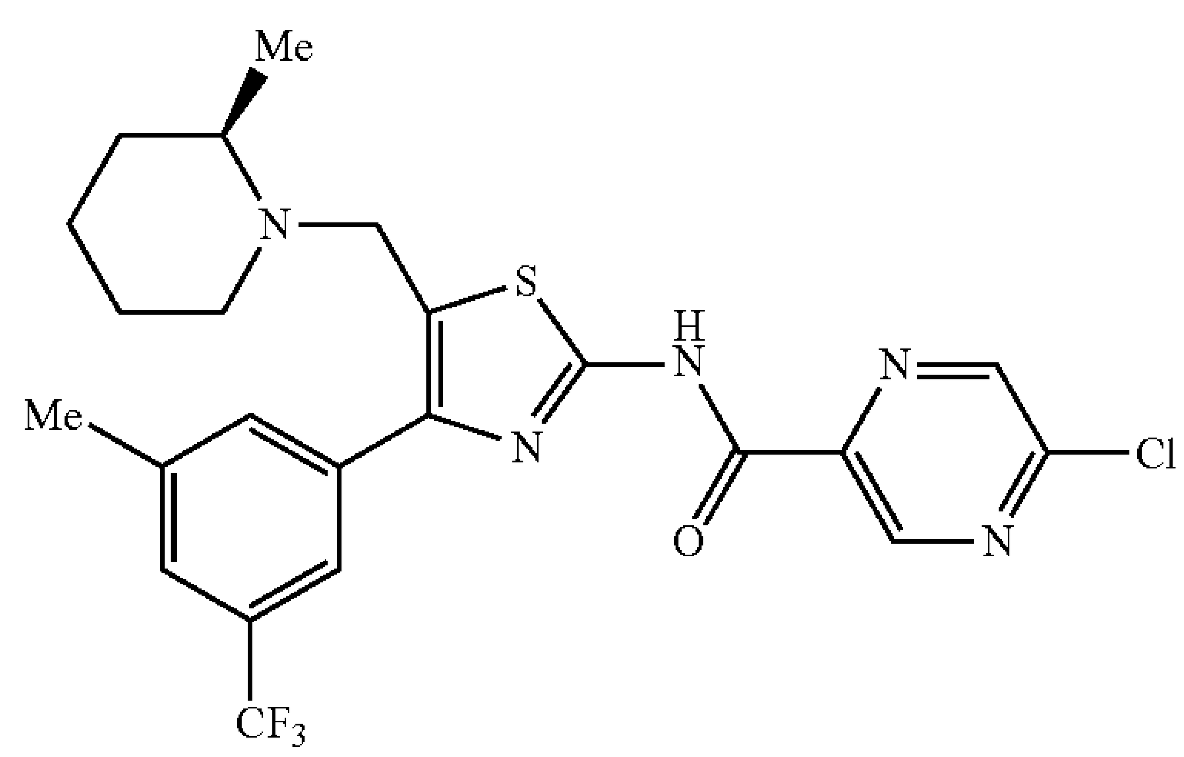
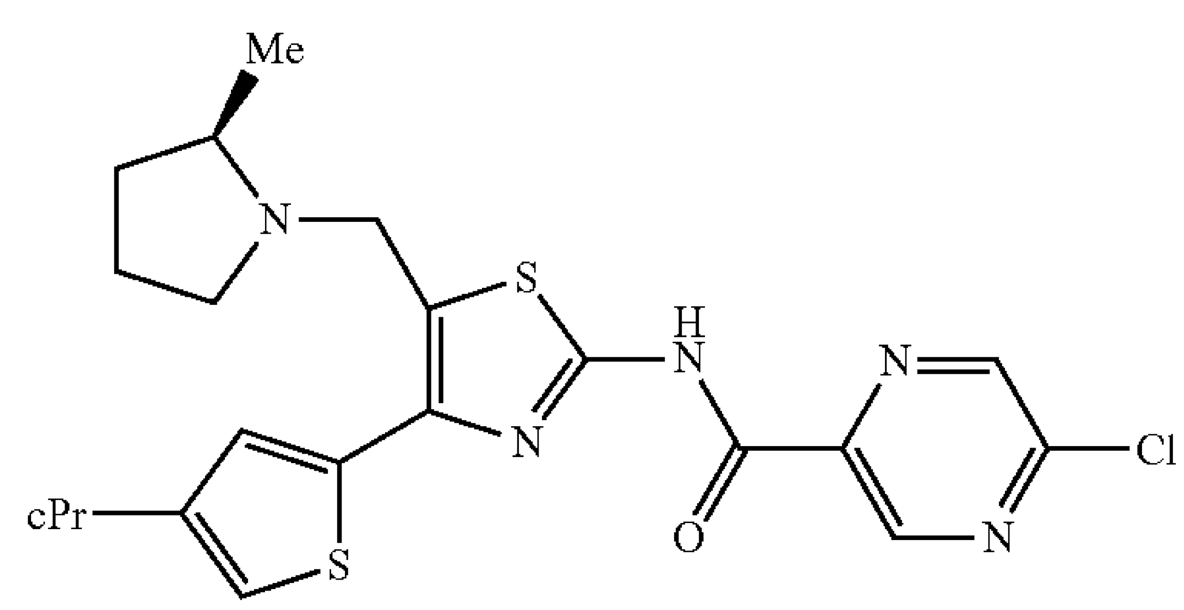
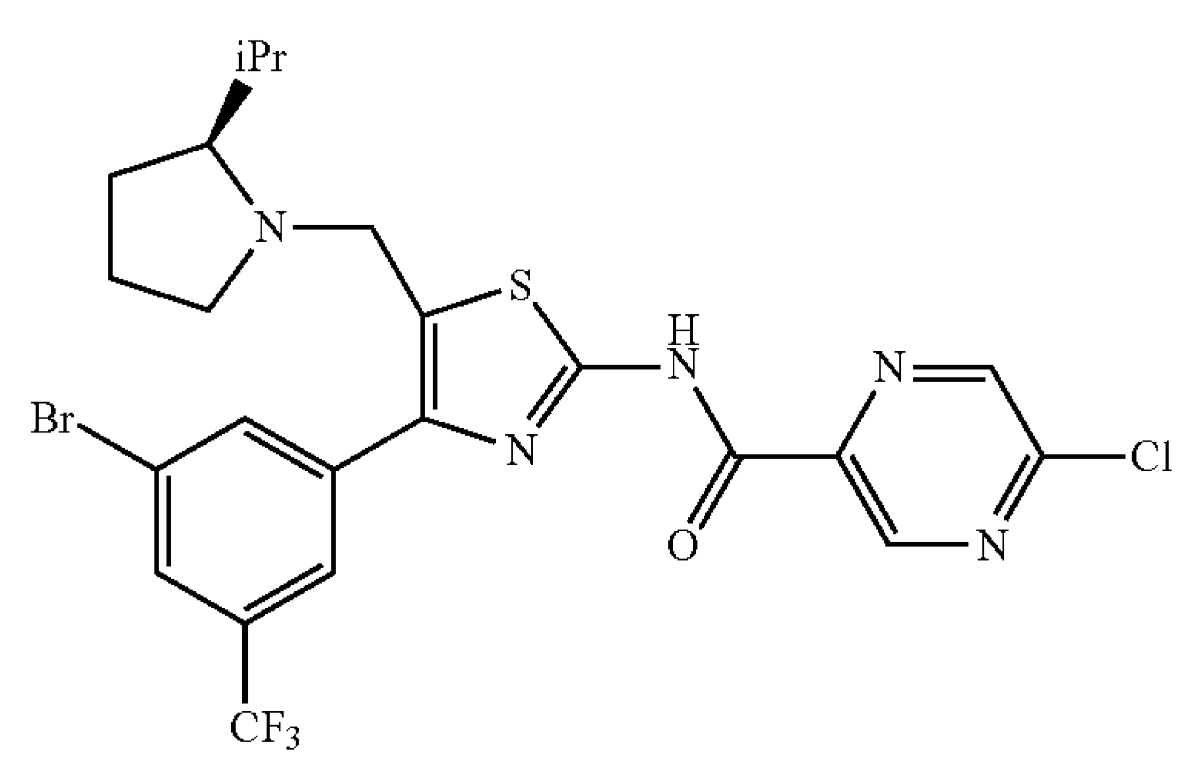
PEx	Structure
72	
73	
74	
75	
76	

TABLE 21

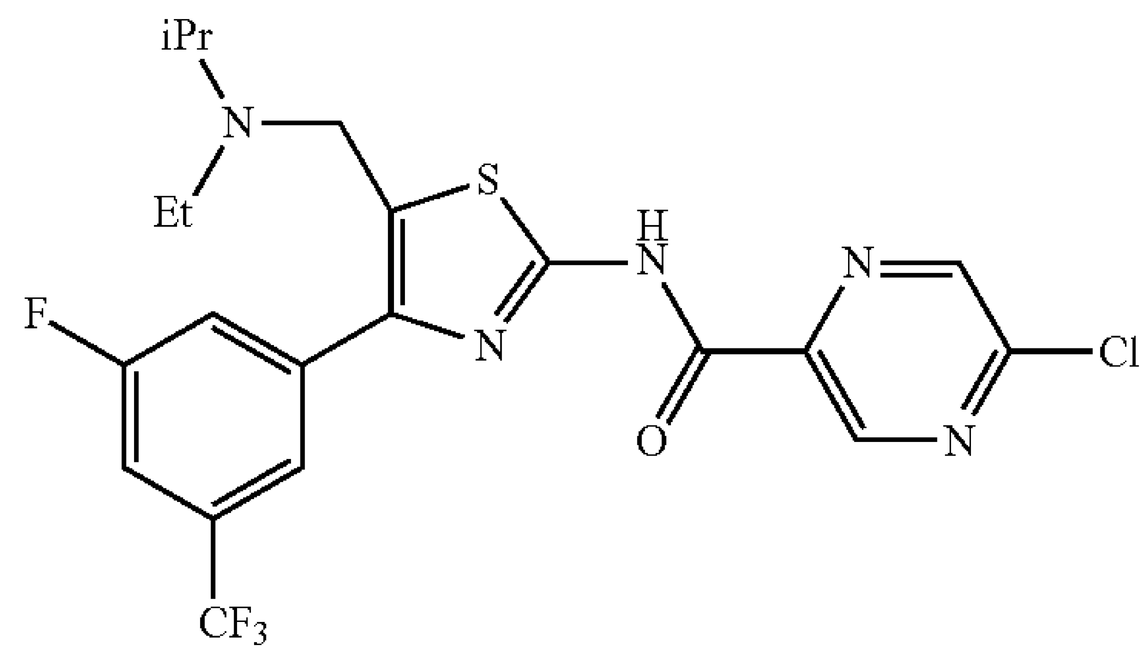
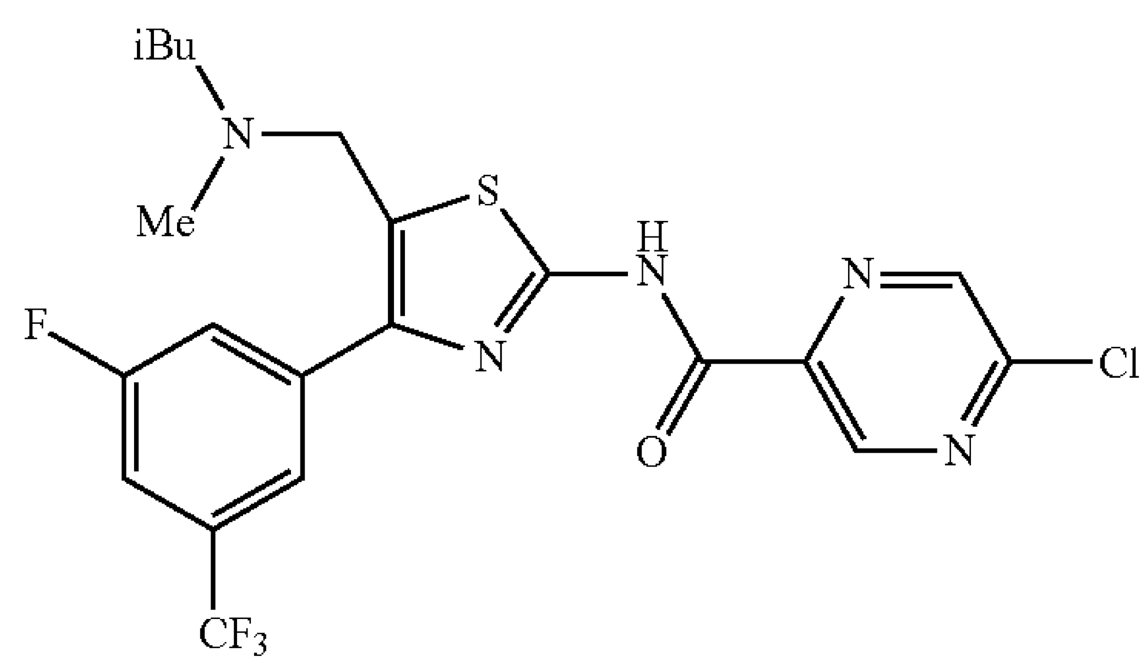
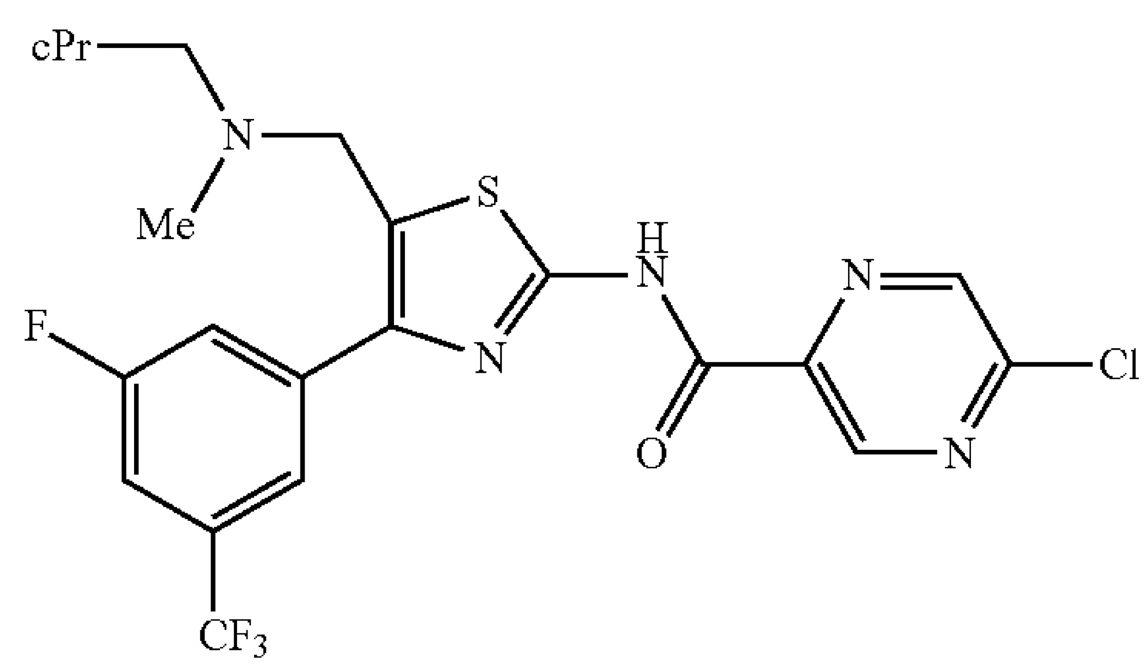
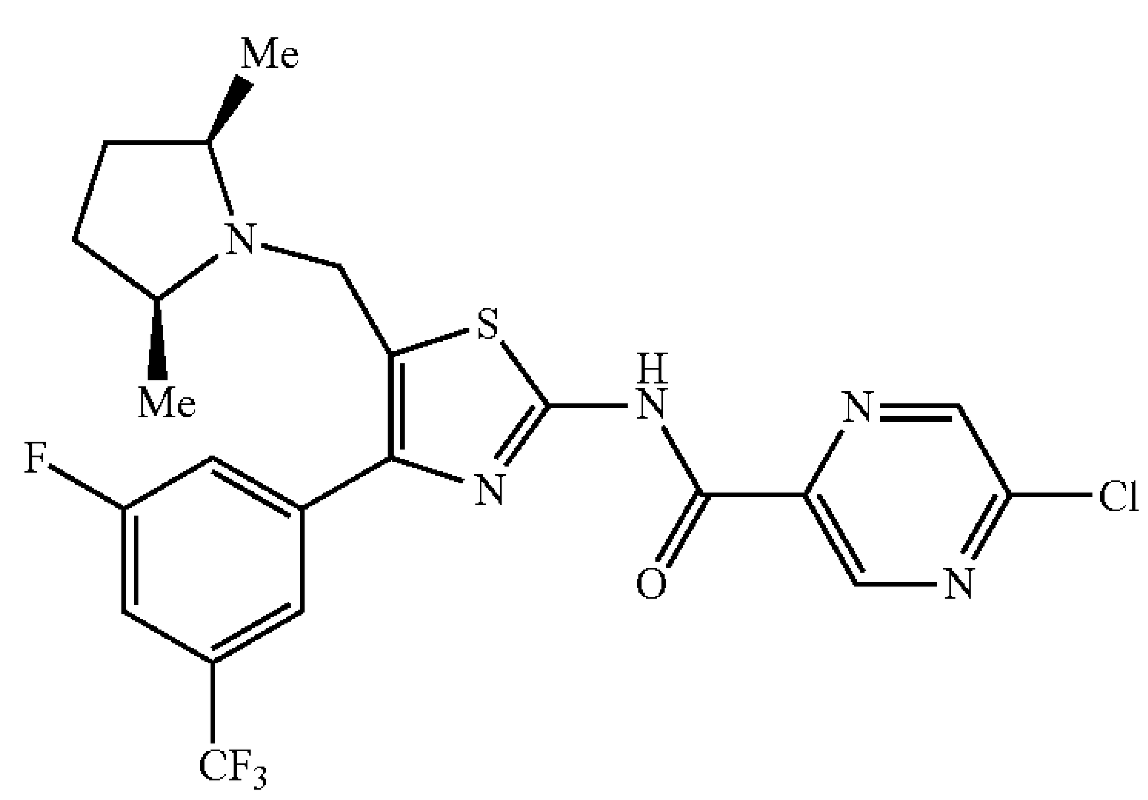
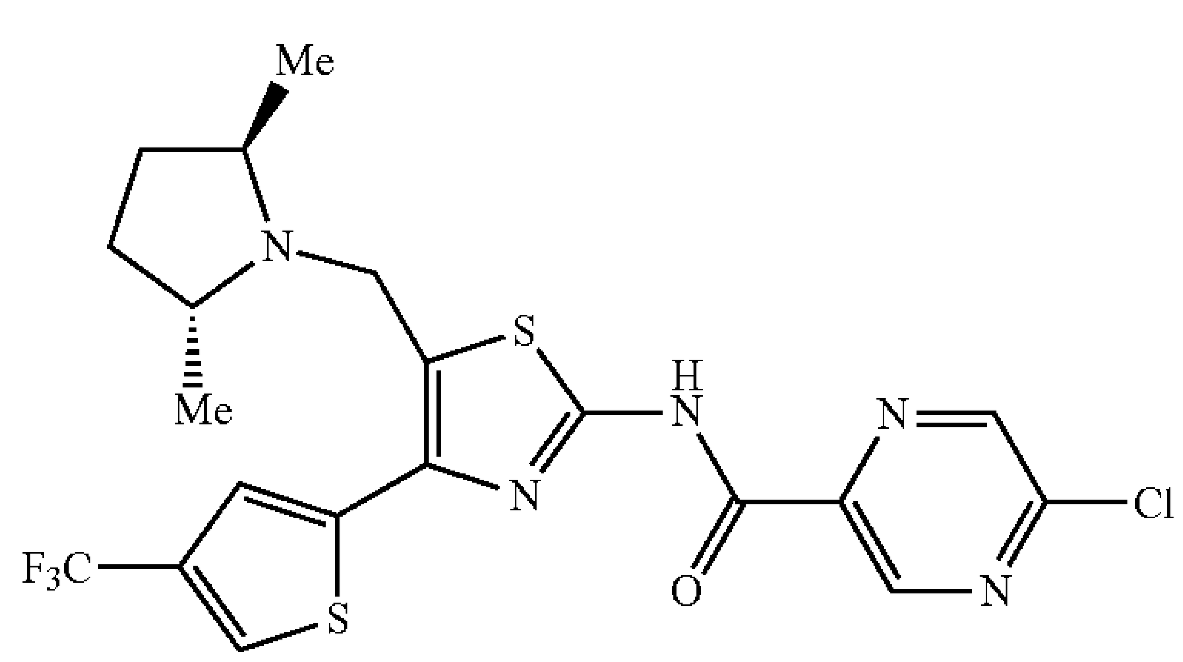
PEx	Structure
82	
83	
84	
85	
86	

TABLE 22

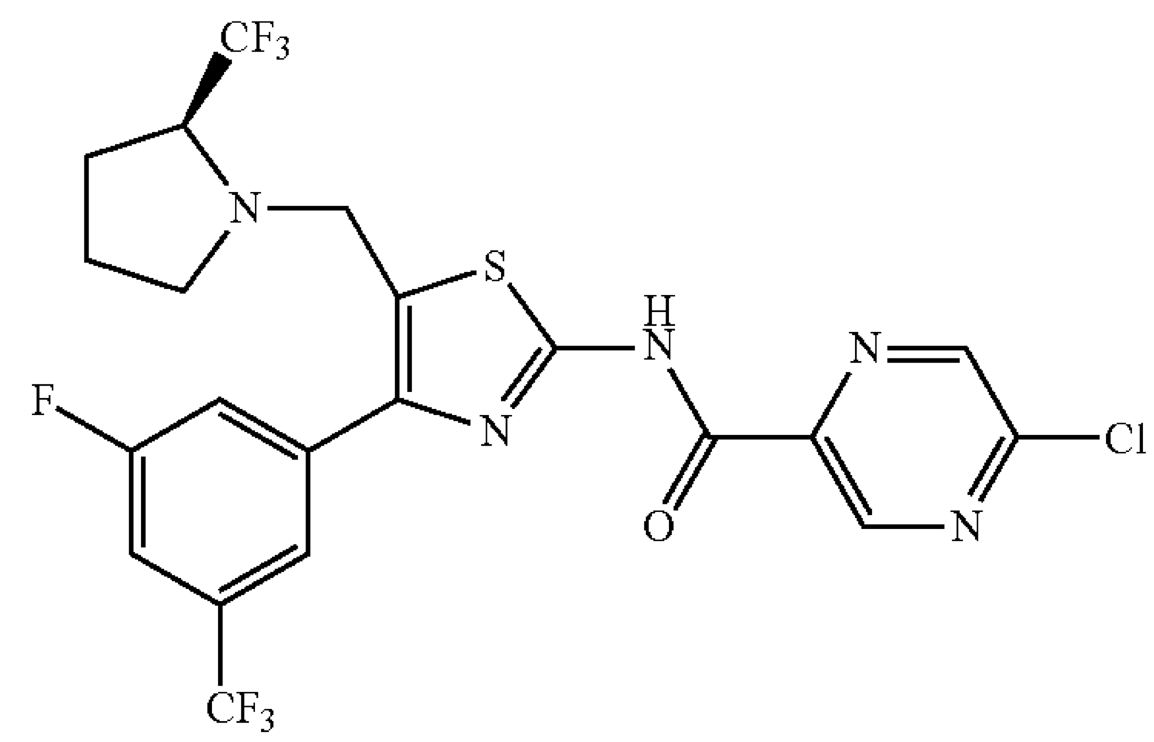
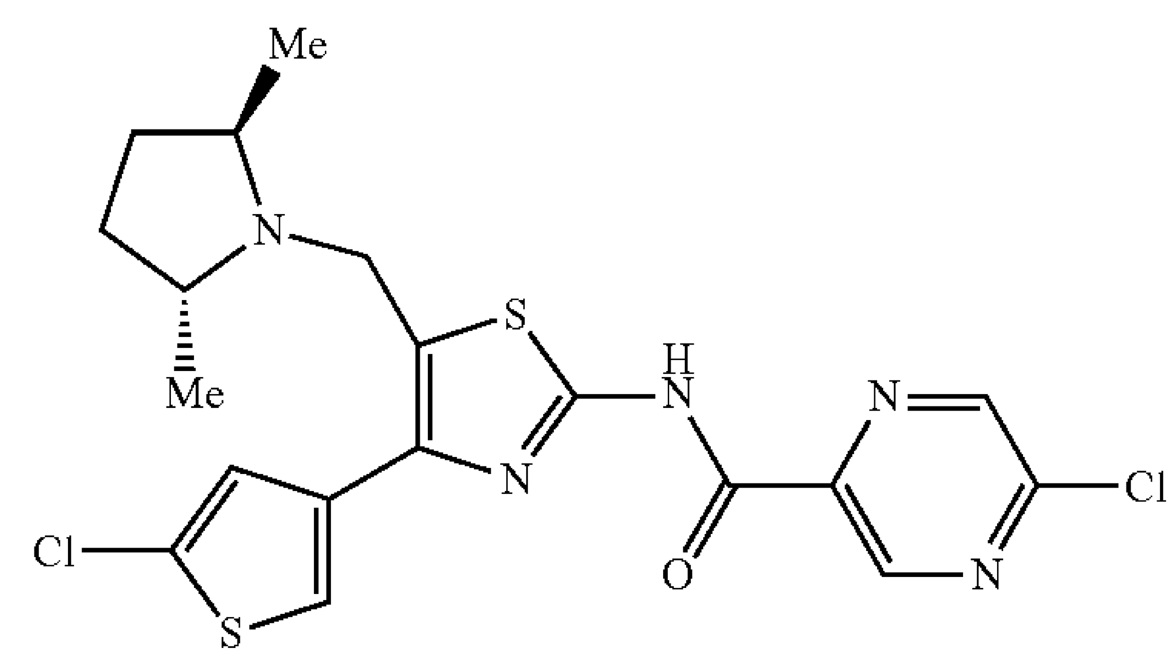
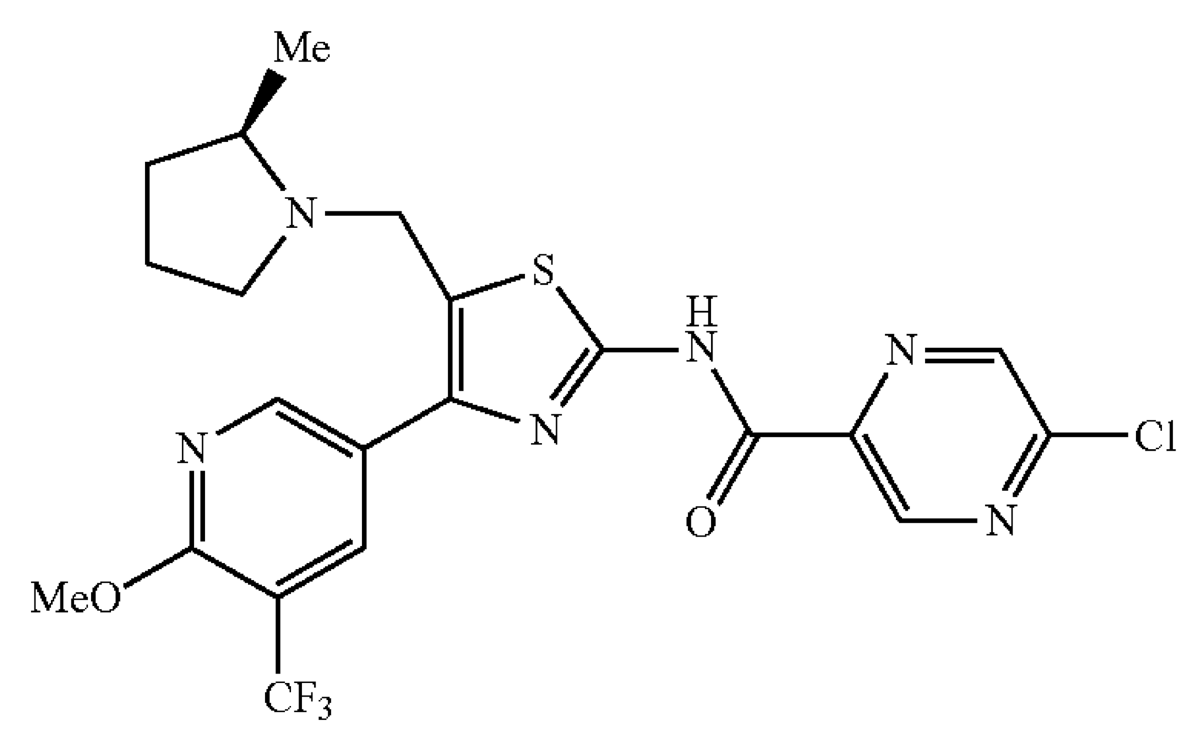
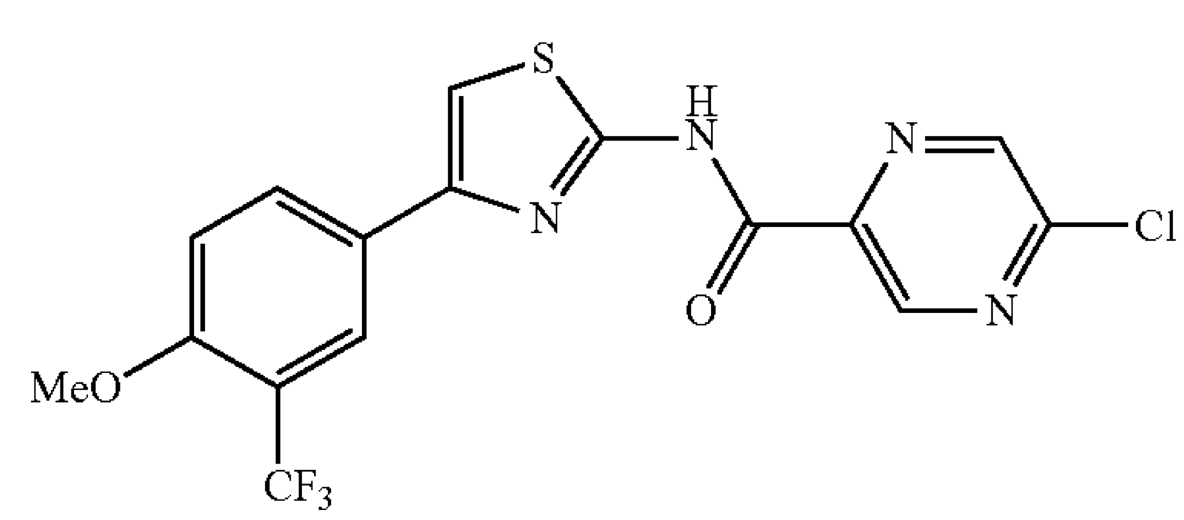
PEx	Structure
87	
88	
89	
90	

TABLE 23

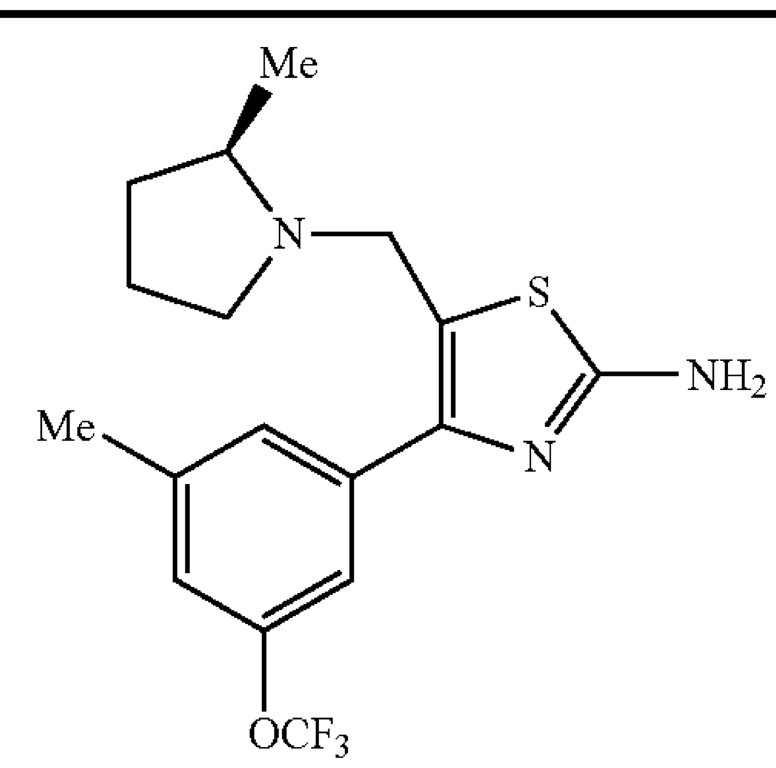
PEx	Structure
91	

TABLE 23-continued

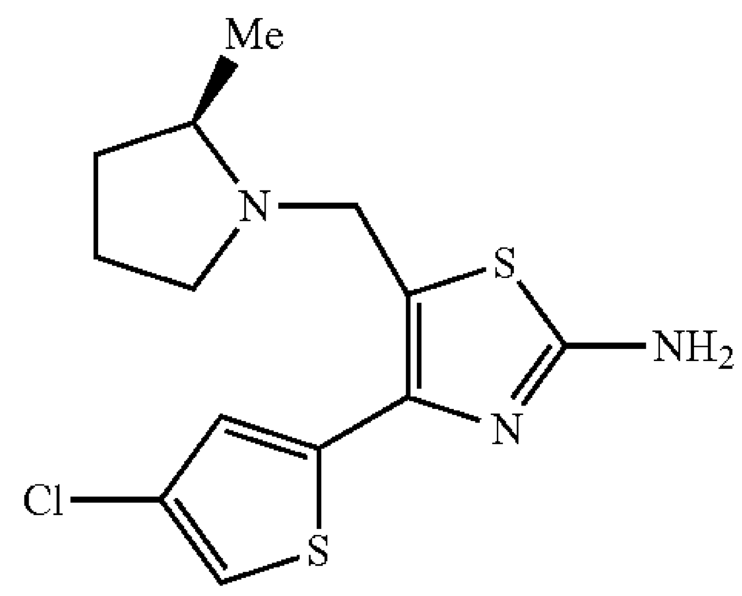
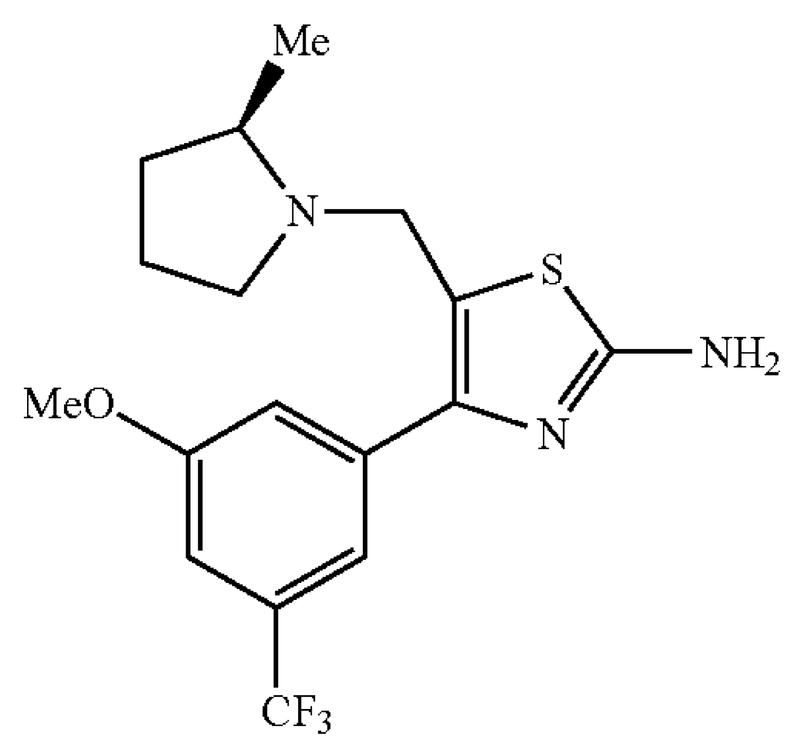
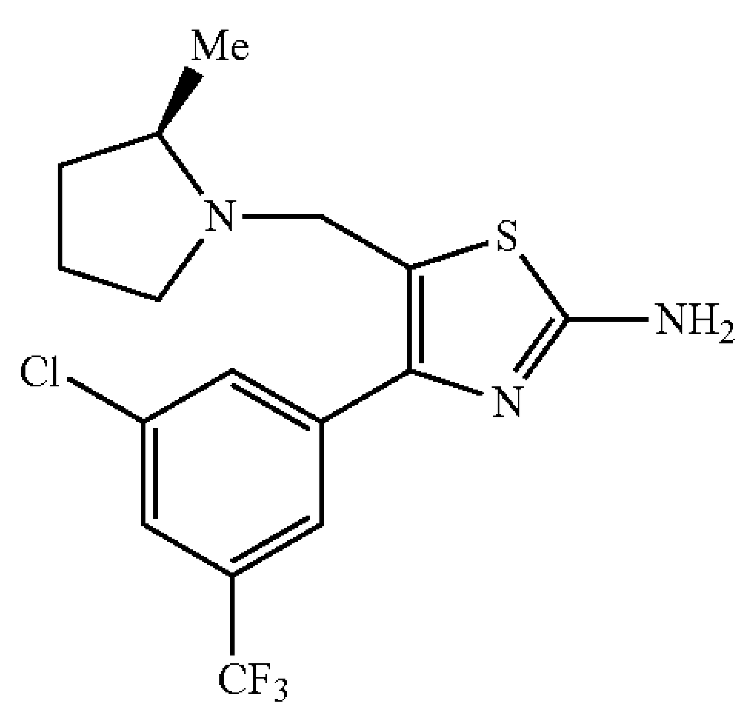
PEx	Structure
92	
93	
94	

TABLE 24

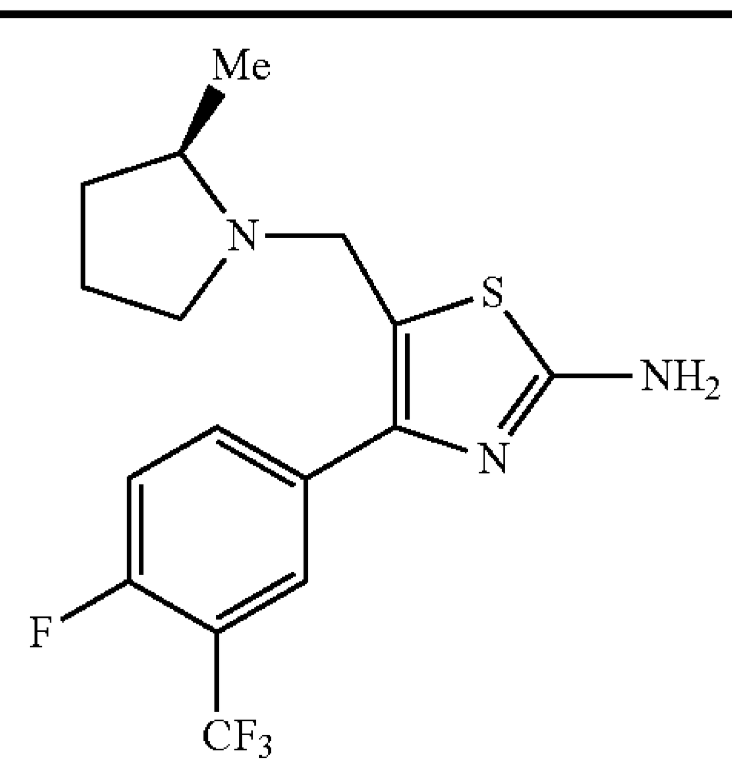
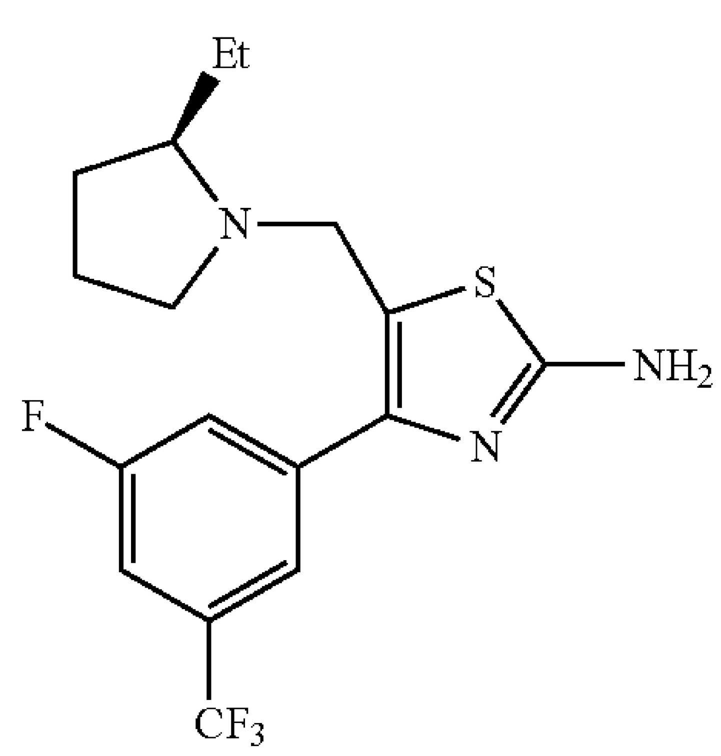
PEx	Structure
95	
96	

TABLE 24-continued

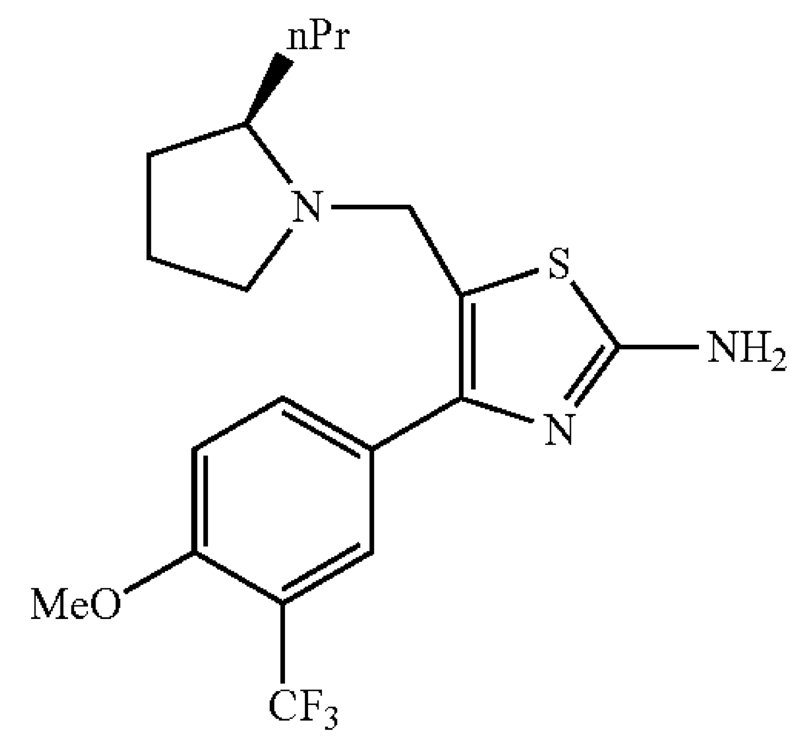
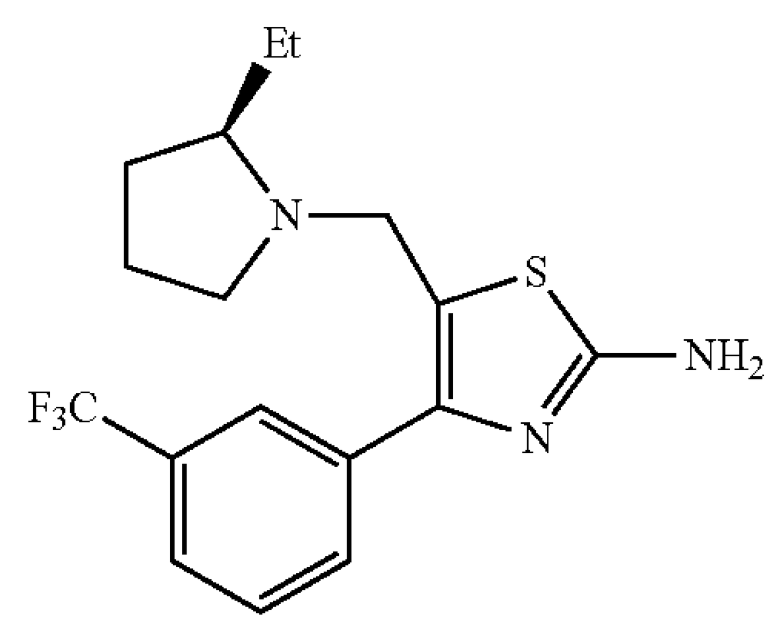
PEx	Structure
97	
98	

TABLE 25

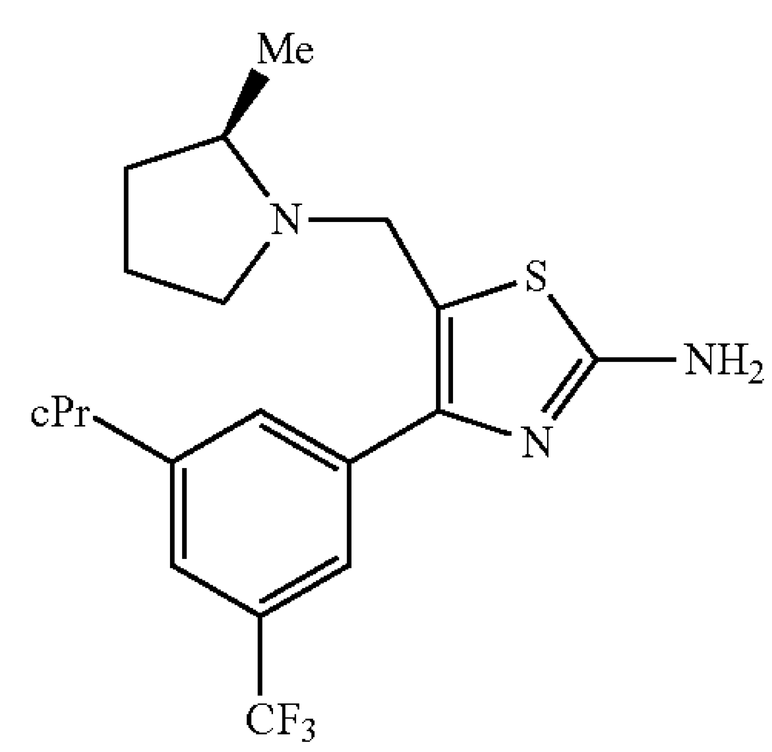
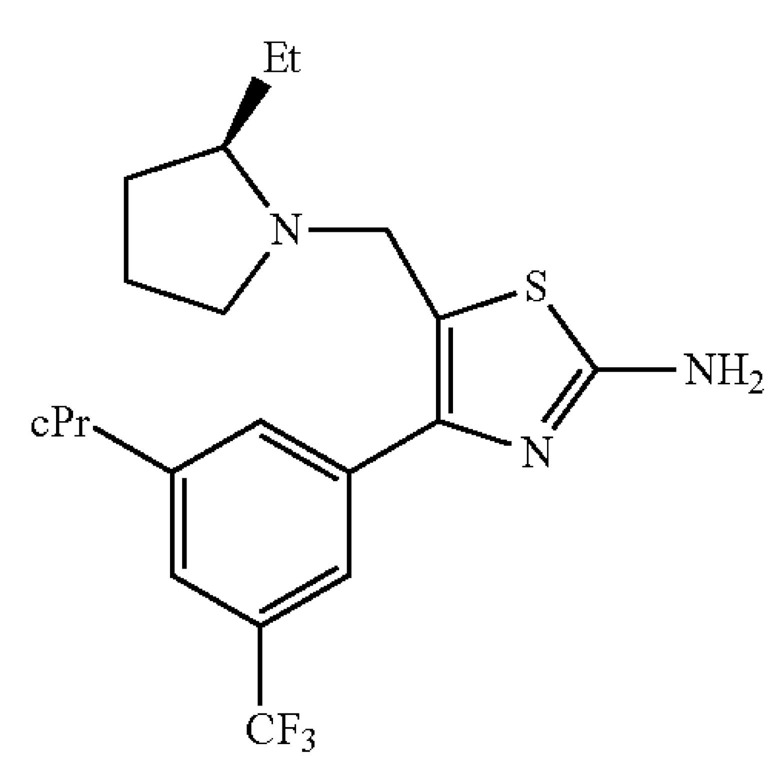
PEx	Structure
99	
100	

TABLE 25-continued

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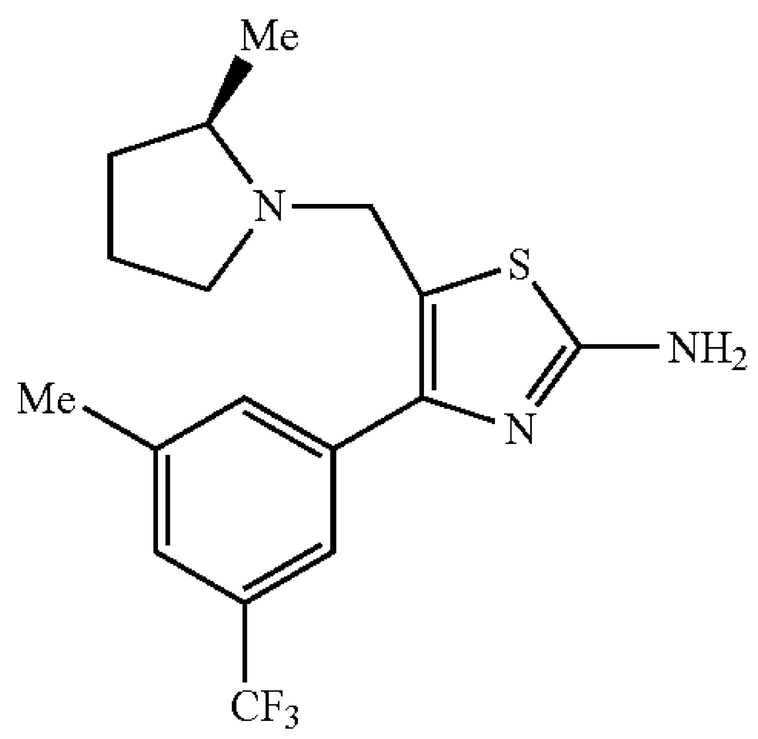
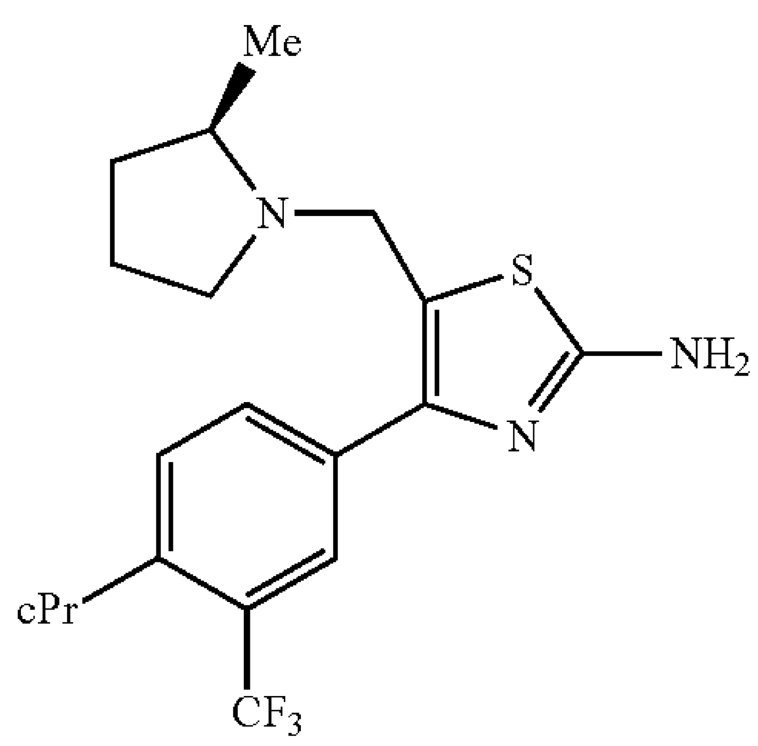
101	
102	

TABLE 26

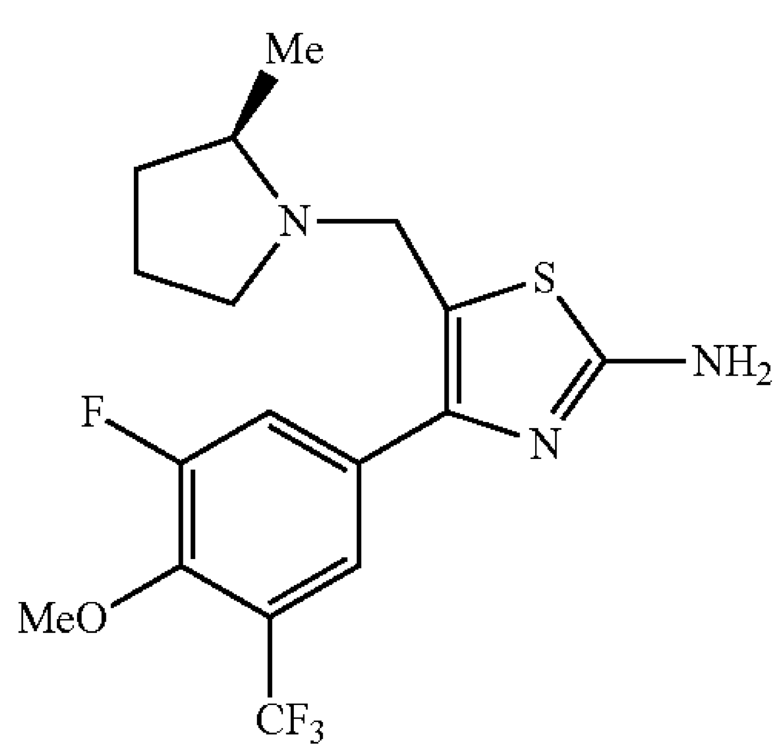
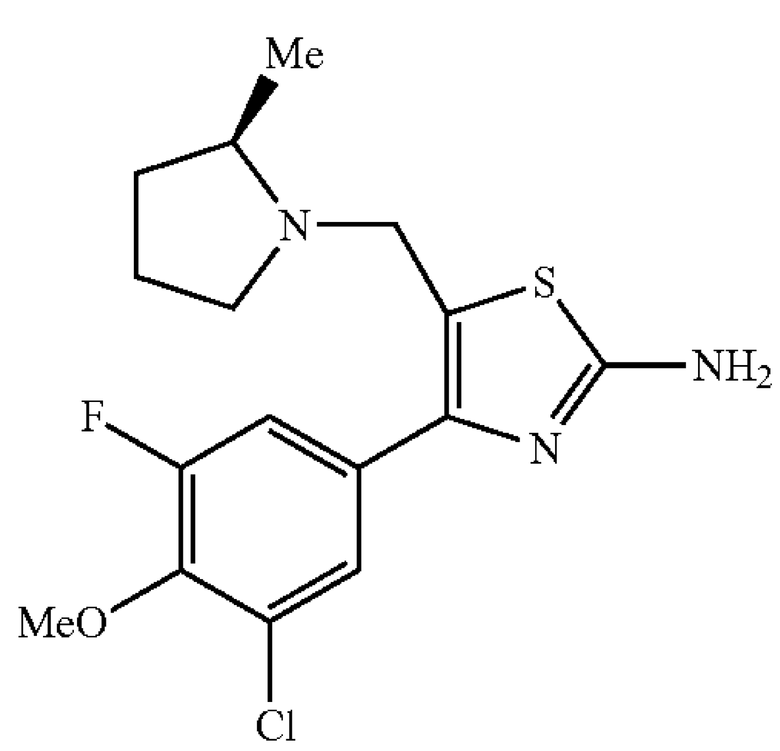
PEx	Structure
103	
104	

TABLE 26-continued

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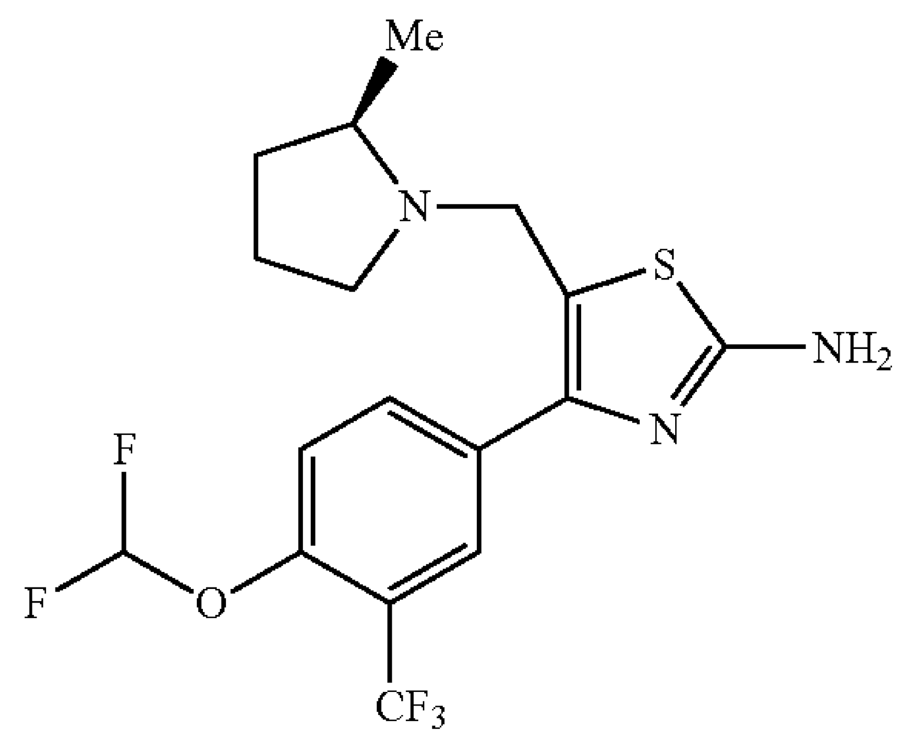
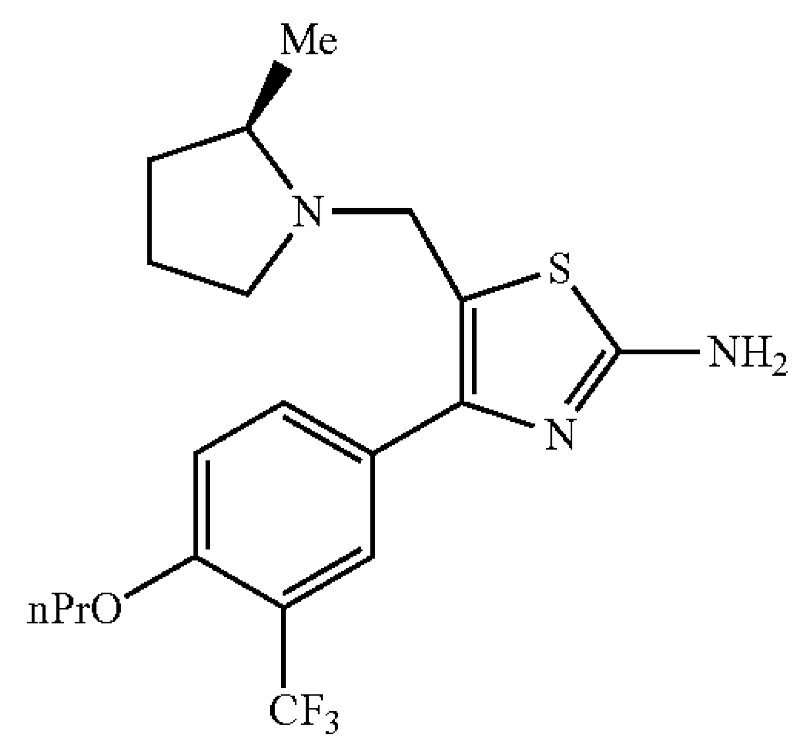
105	
106	

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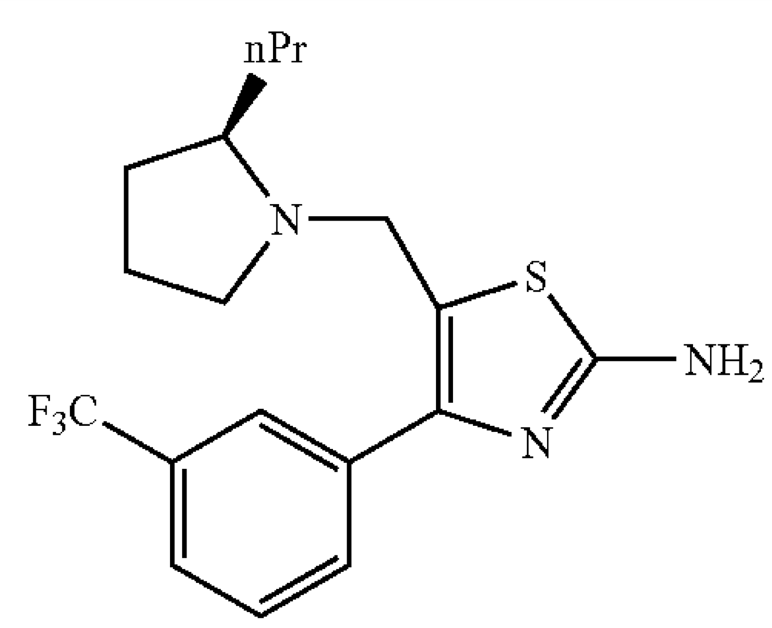
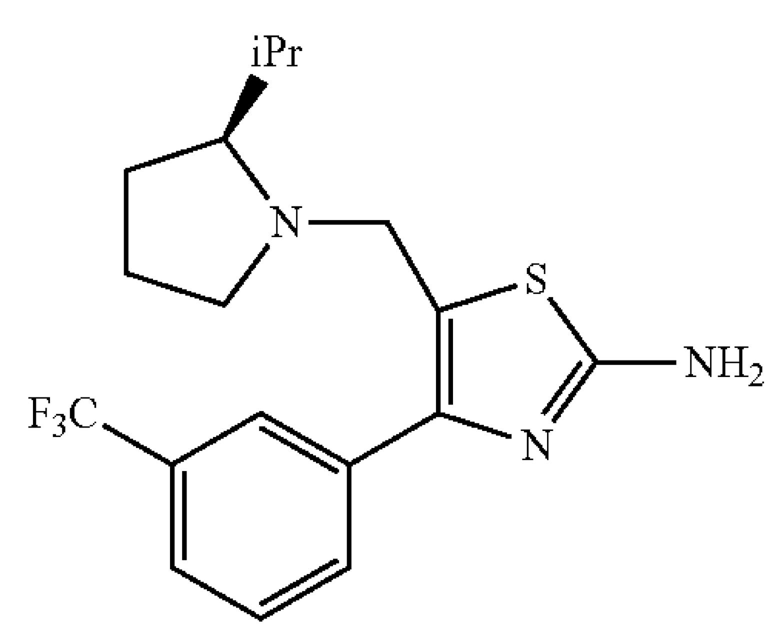
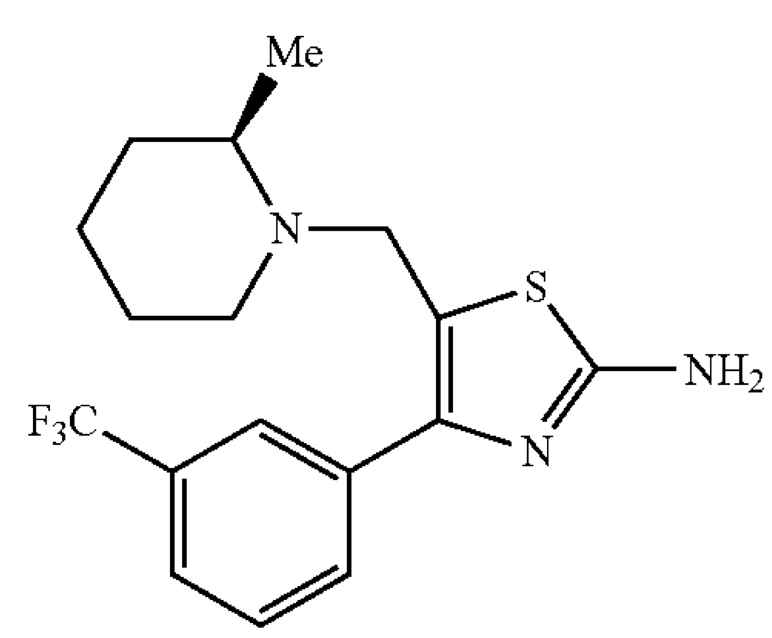
107	
108	
109	

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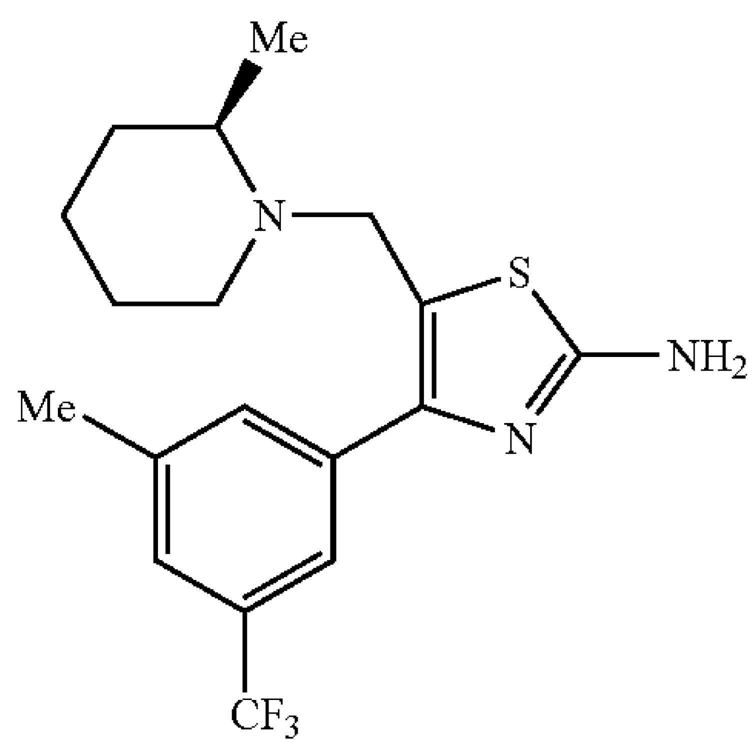
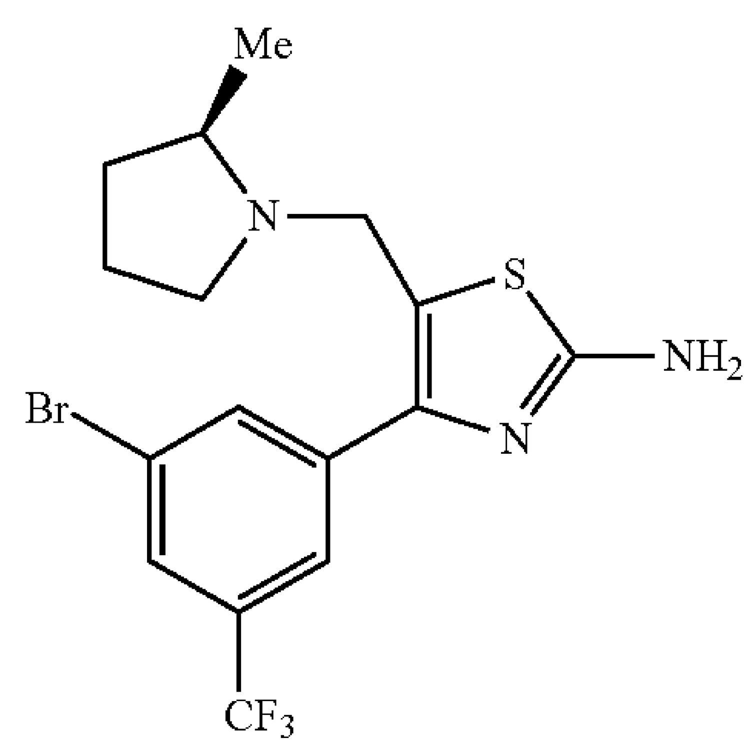
PEx	Structure
110	
111	

TABLE 28

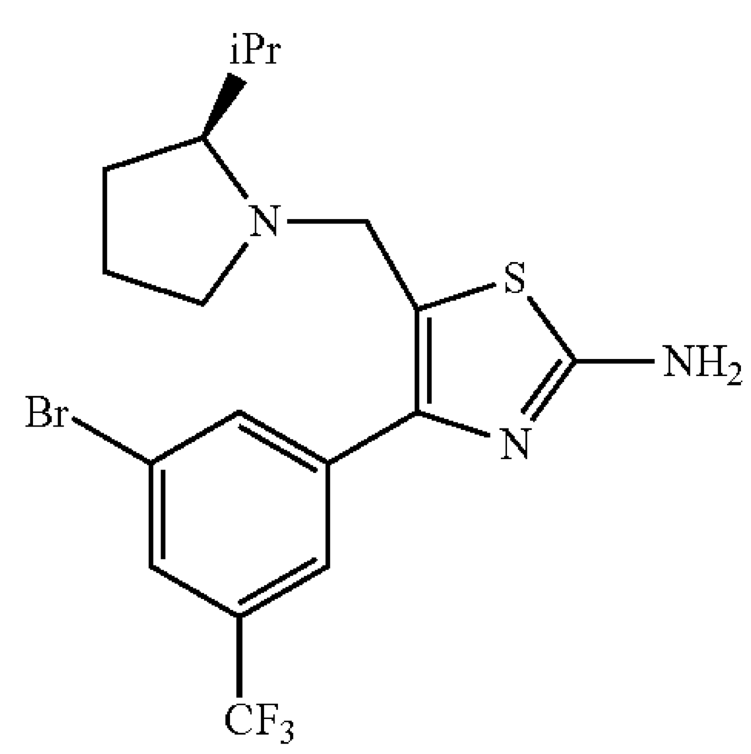
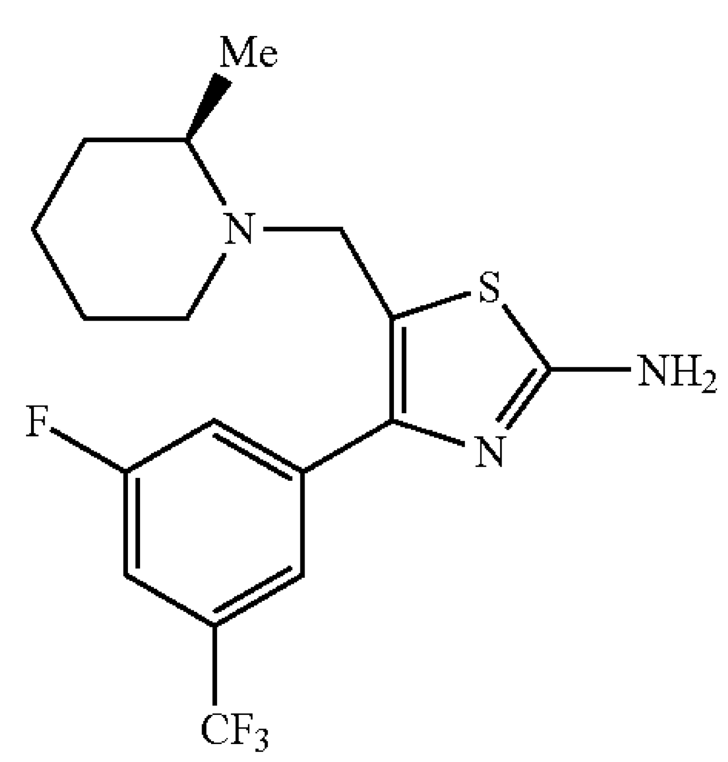
PEx	Structure
112	
113	

TABLE 28-continued

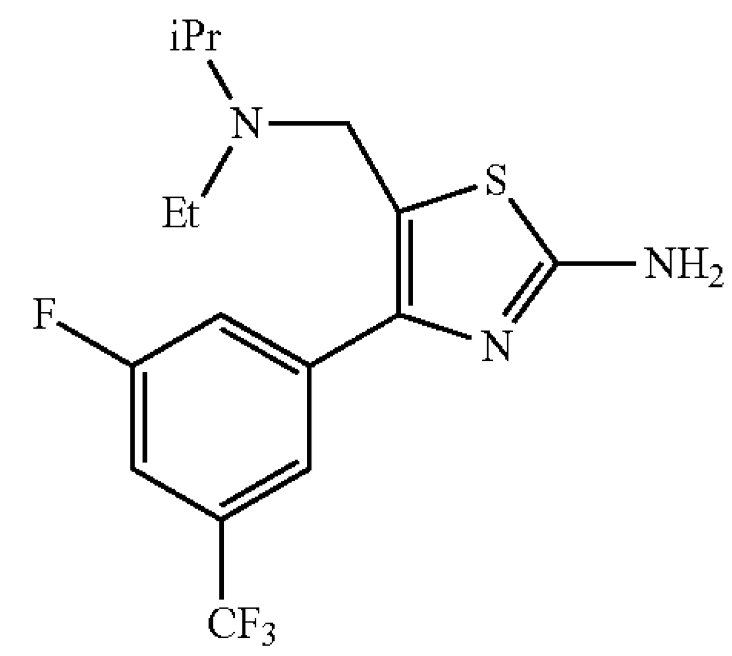
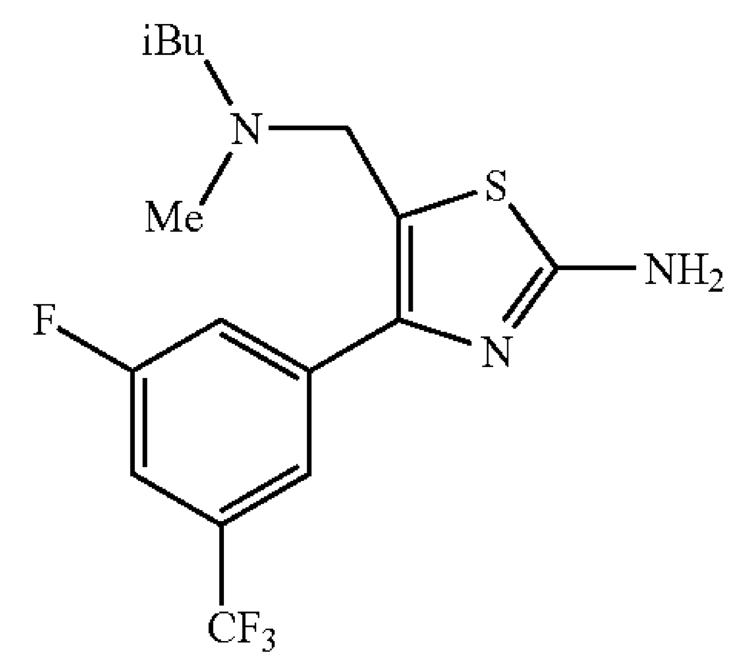
PEx	Structure
114	
115	

TABLE 29

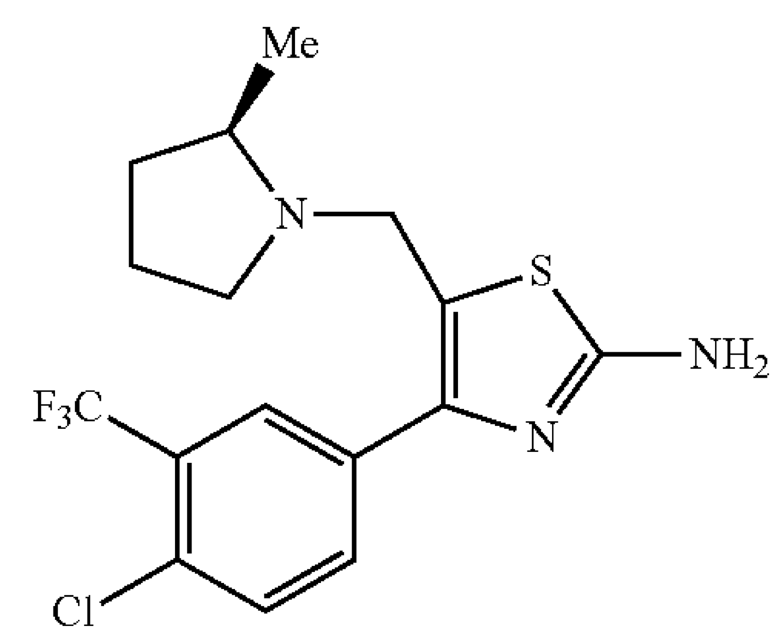
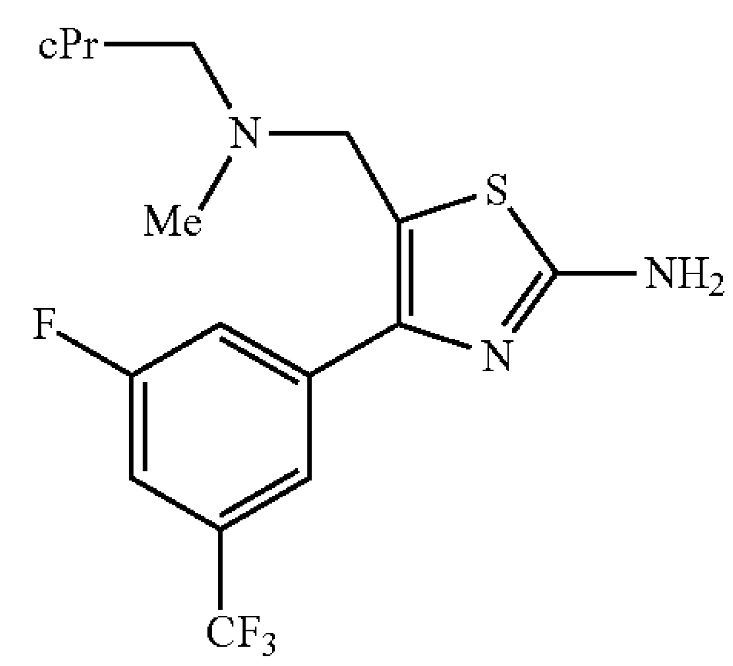
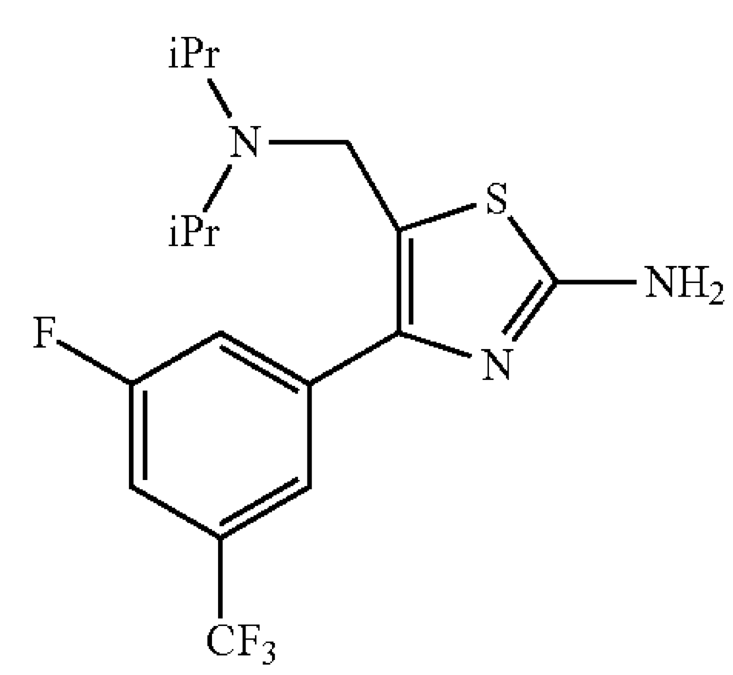
PEx	Structure
116	
117	
118	

TABLE 29-continued

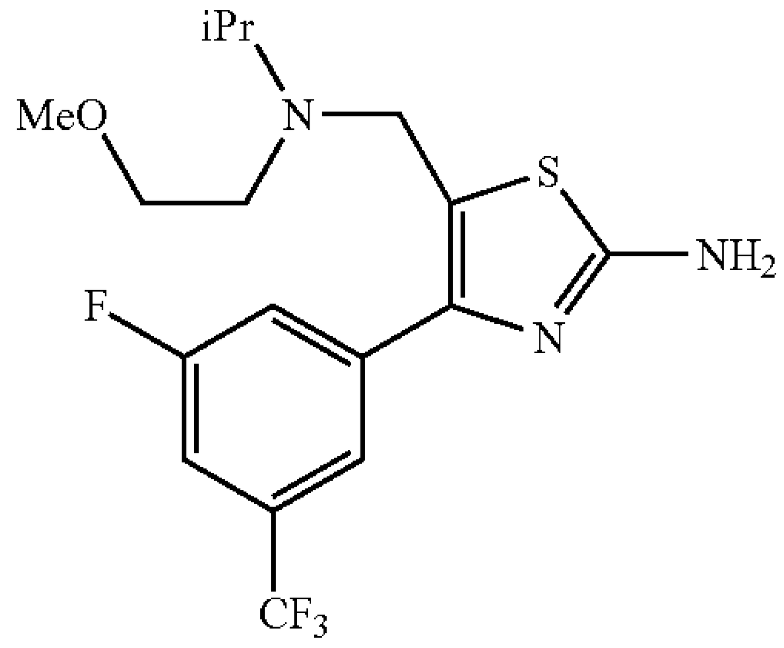
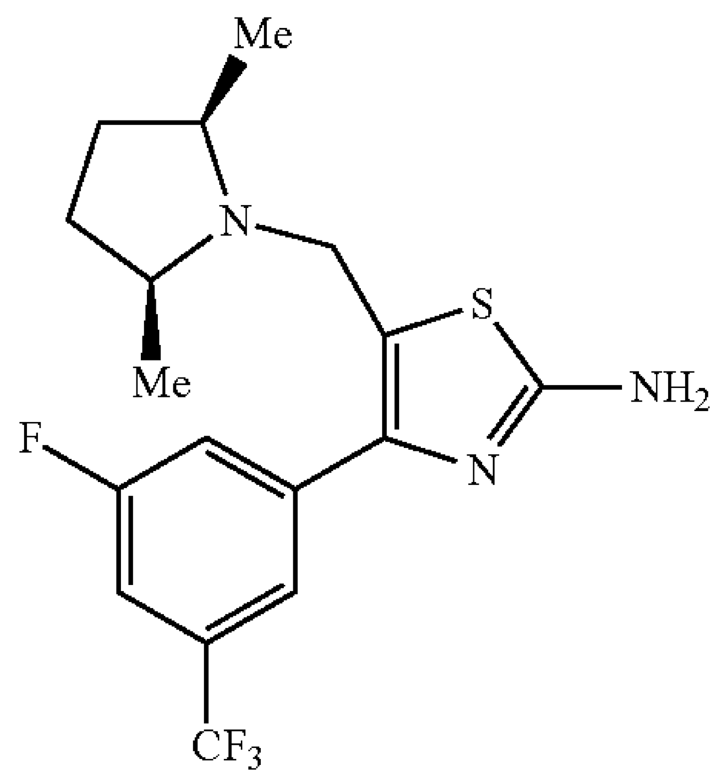
PEx	Structure
119	
120	

TABLE 30

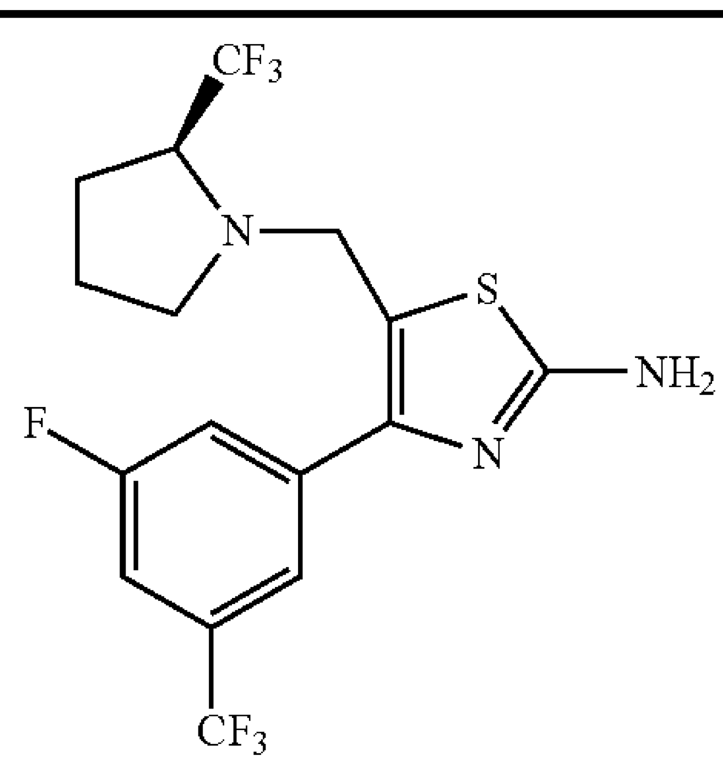
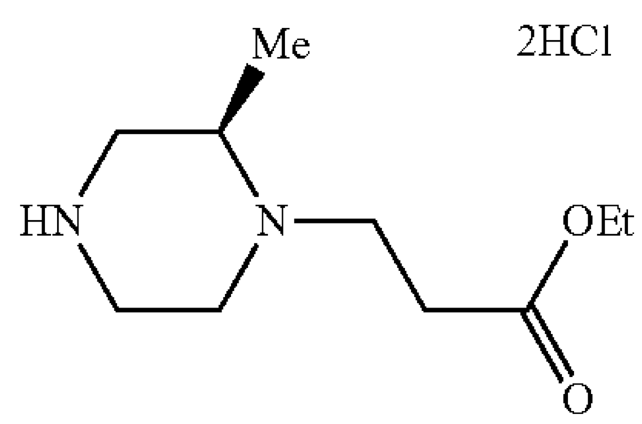
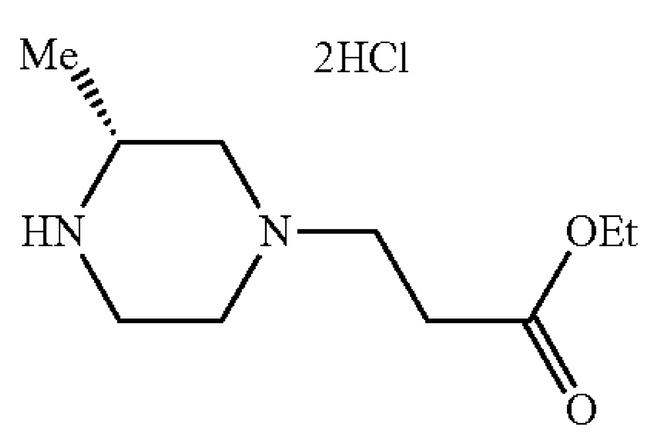
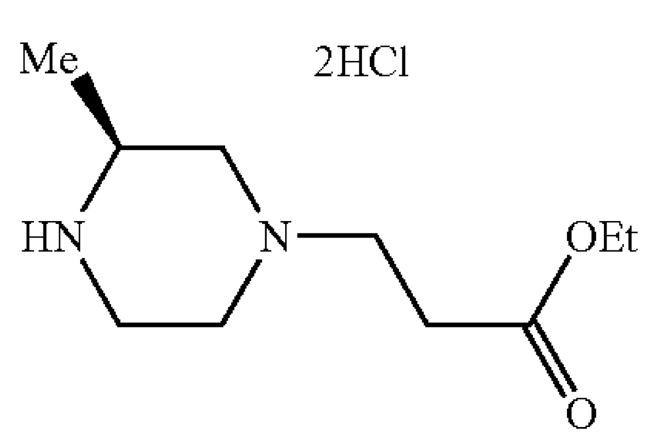
PEx	Structure
121	
122	 2HCl
123	 2HCl
124	 2HCl

TABLE 30-continued

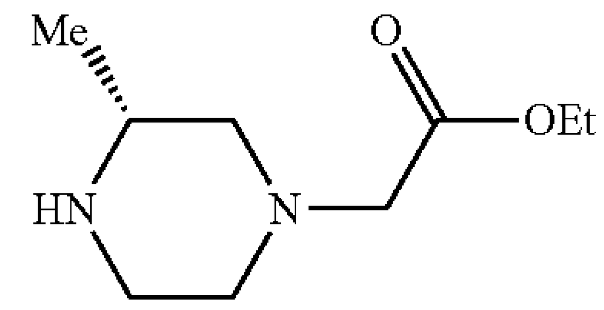
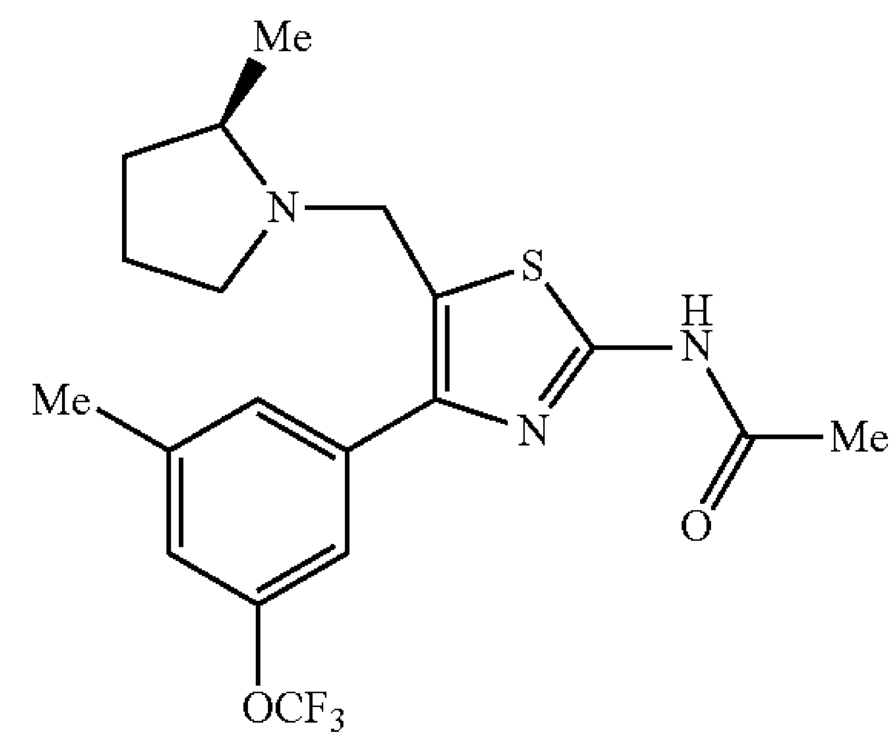
PEx	Structure
125	 2HCl
126	

TABLE 31

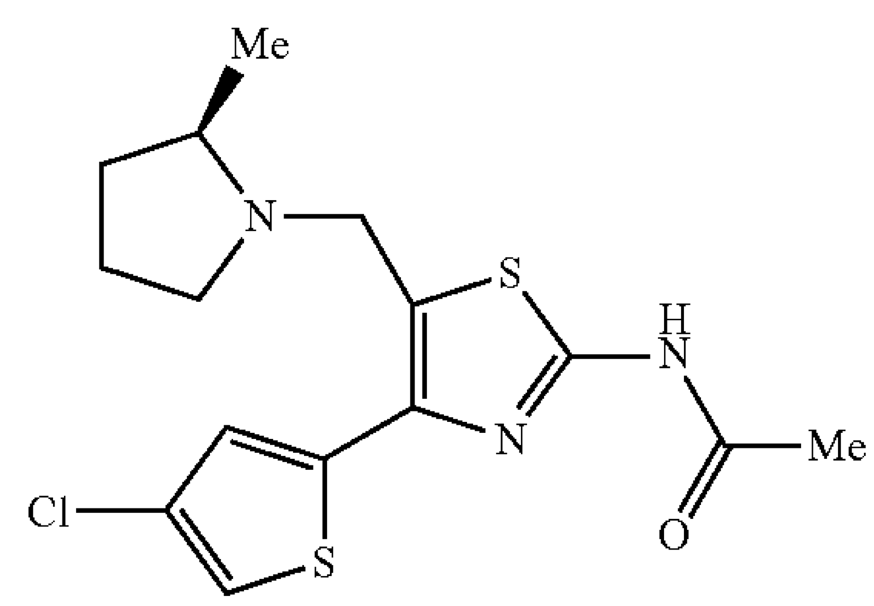
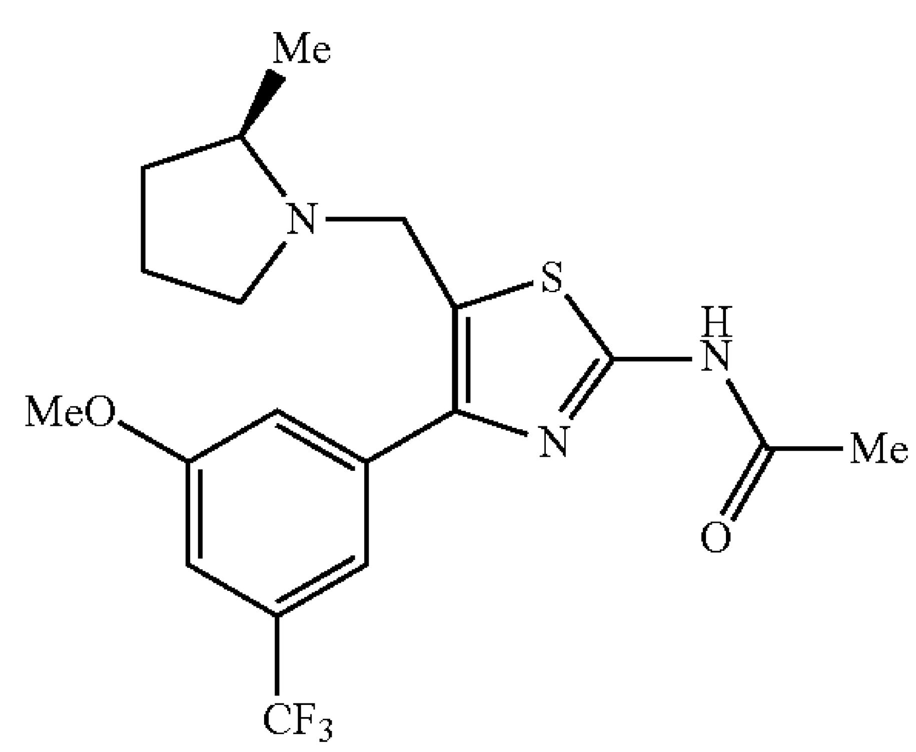
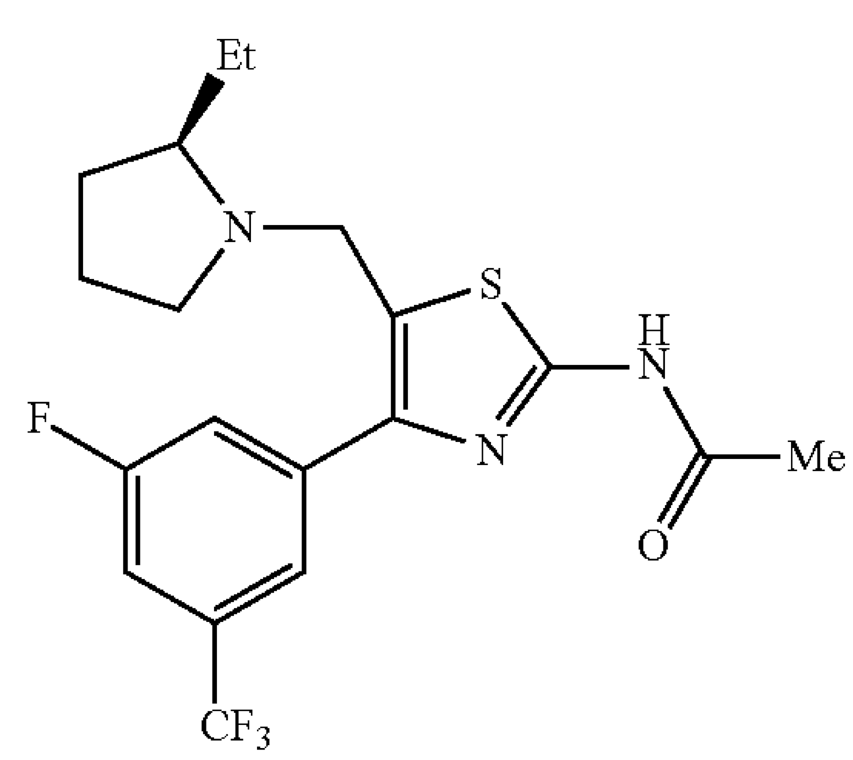
PEx	Structure
127	
128	
129	

TABLE 31-continued

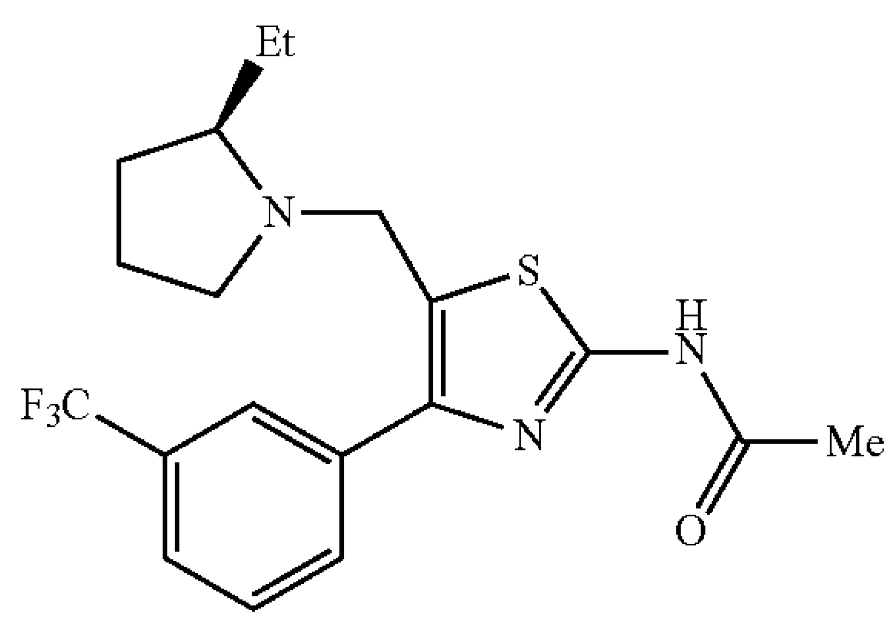
PEx	Structure
130	

TABLE 32

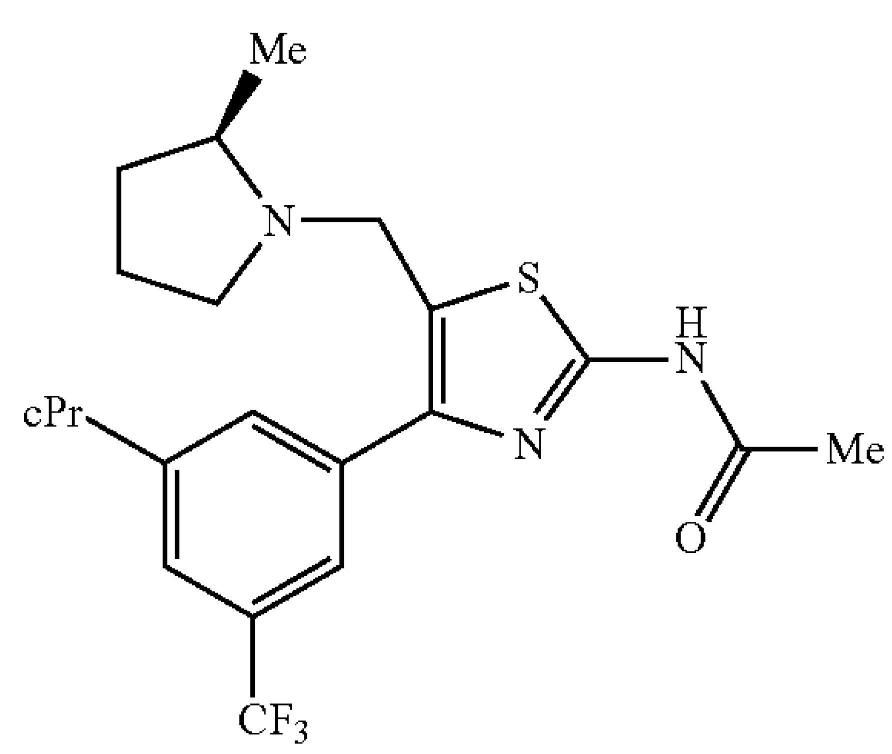
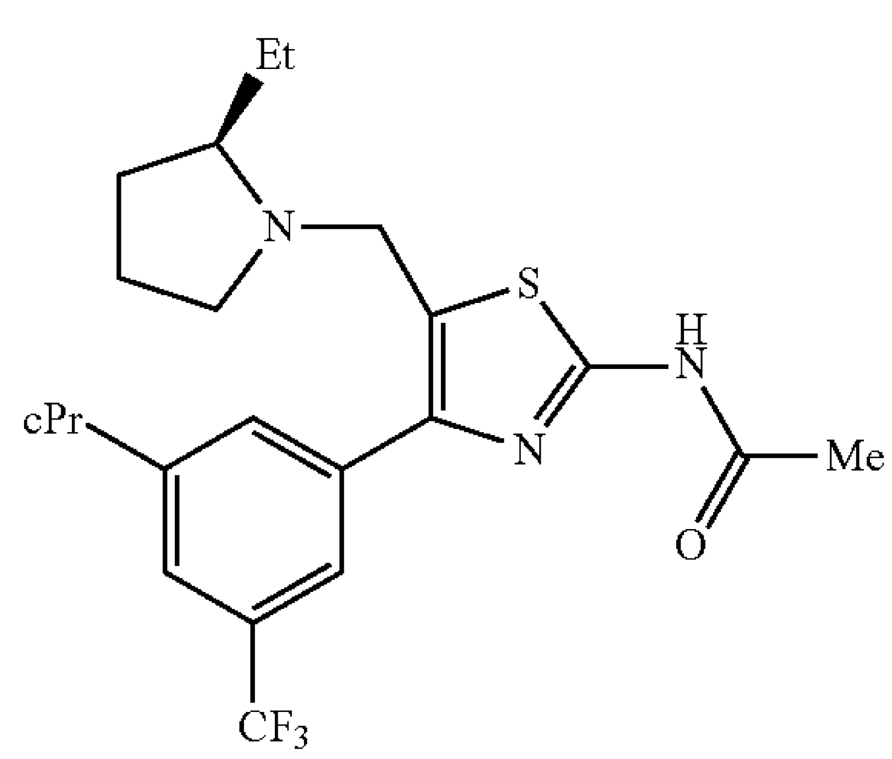
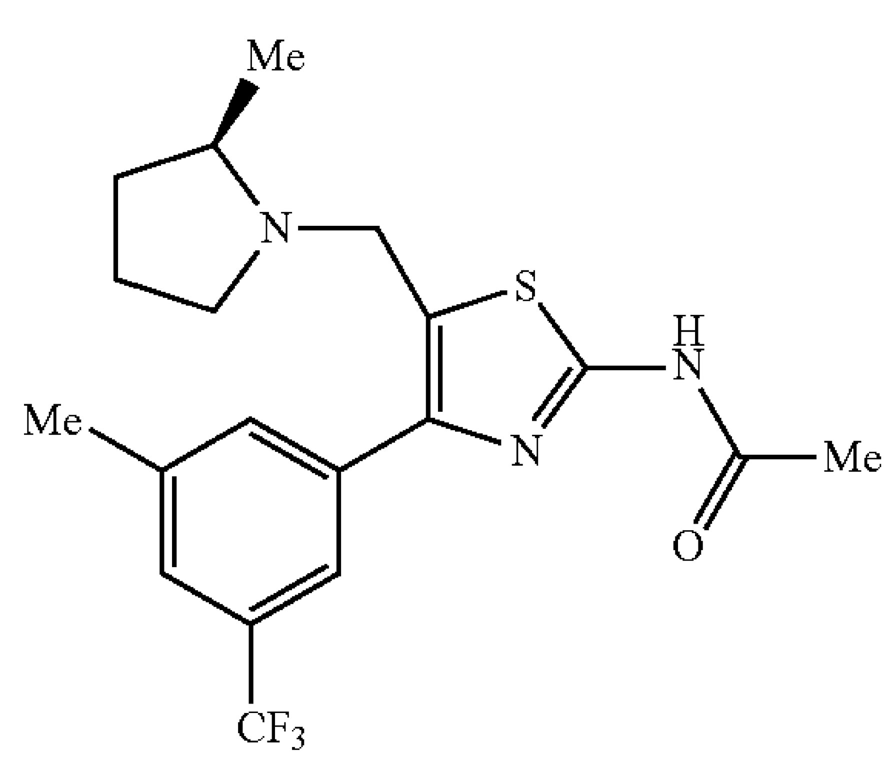
PEx	Structure
131	
132	
133	

TABLE 32-continued

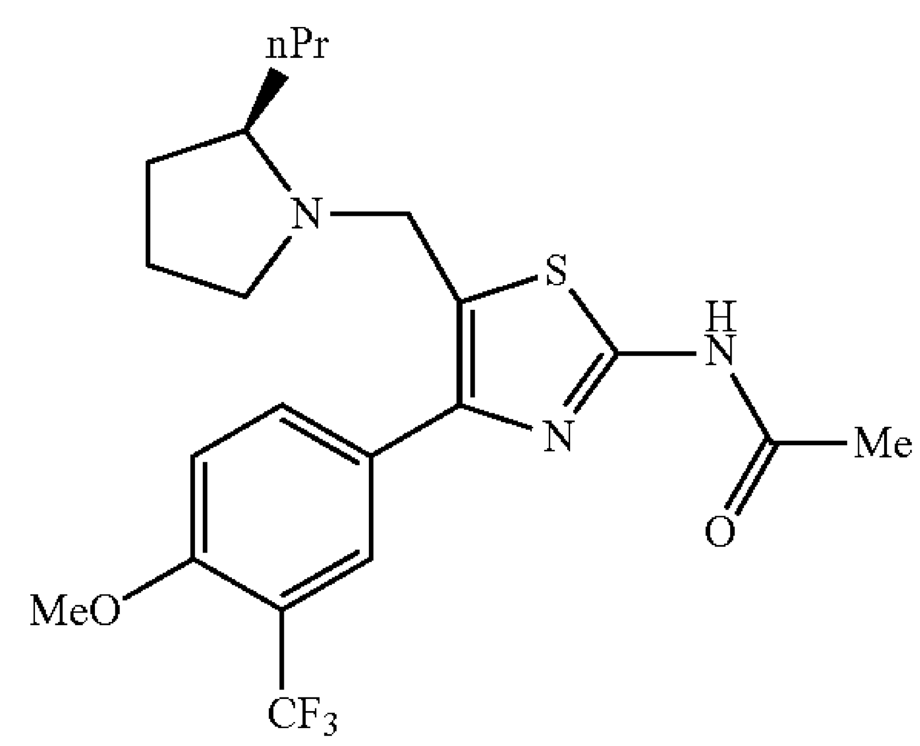
PEx	Structure
134	

TABLE 33

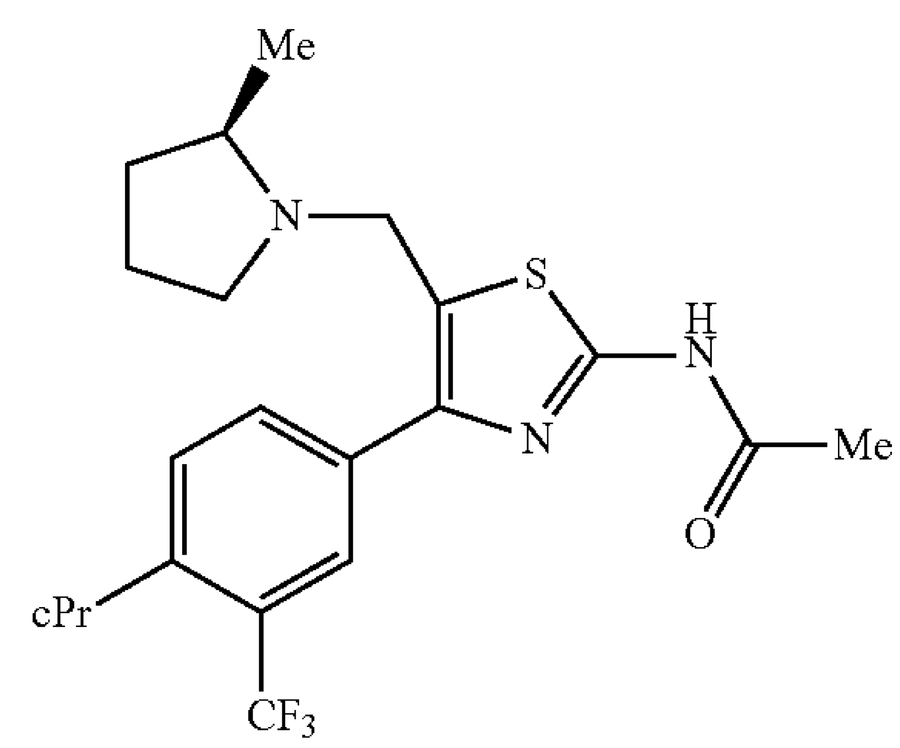
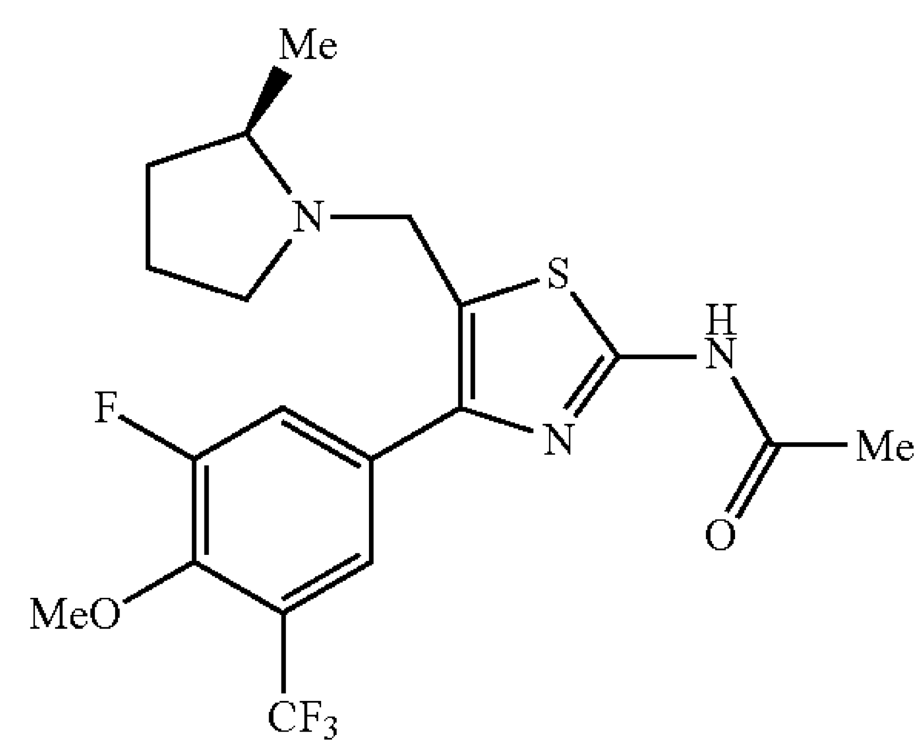
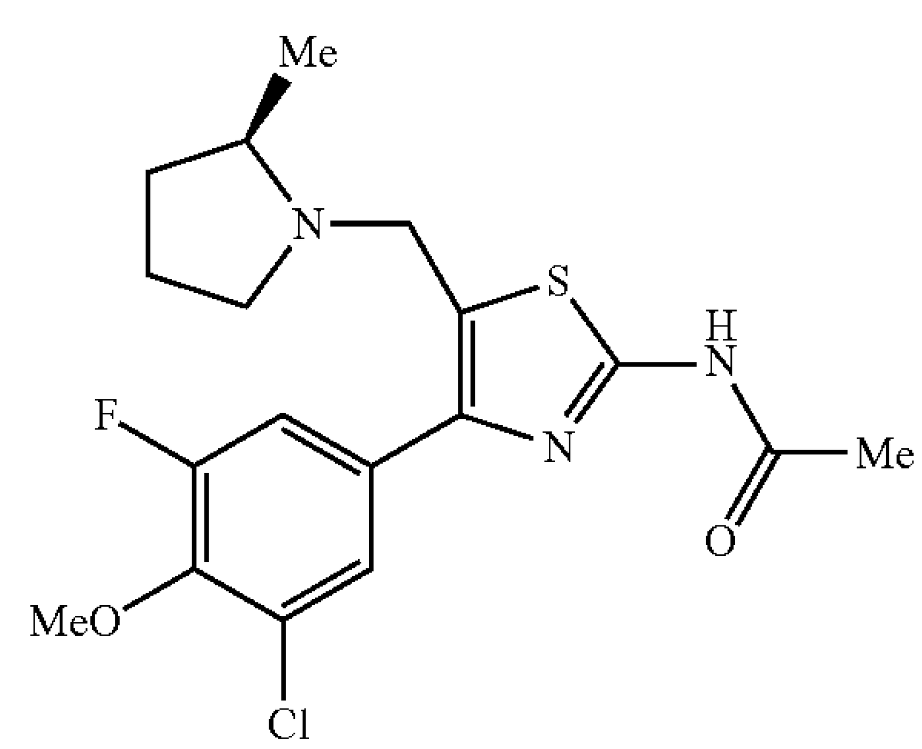
PEx	Structure
135	
136	
137	

TABLE 33-continued

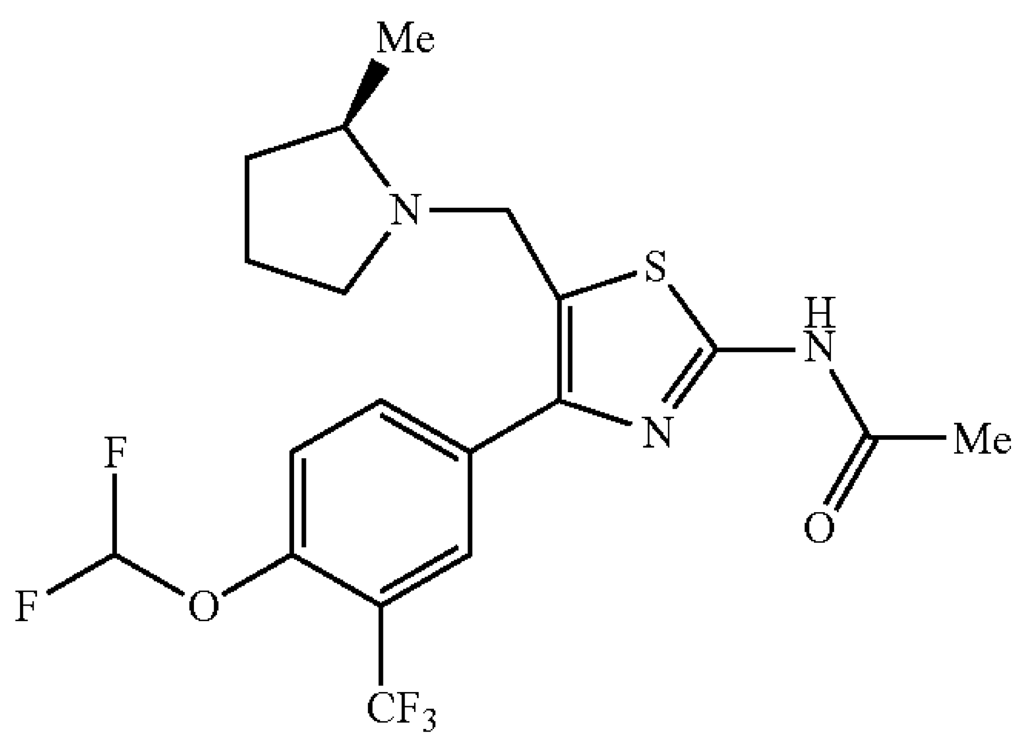
PEx	Structure
138	

TABLE 34

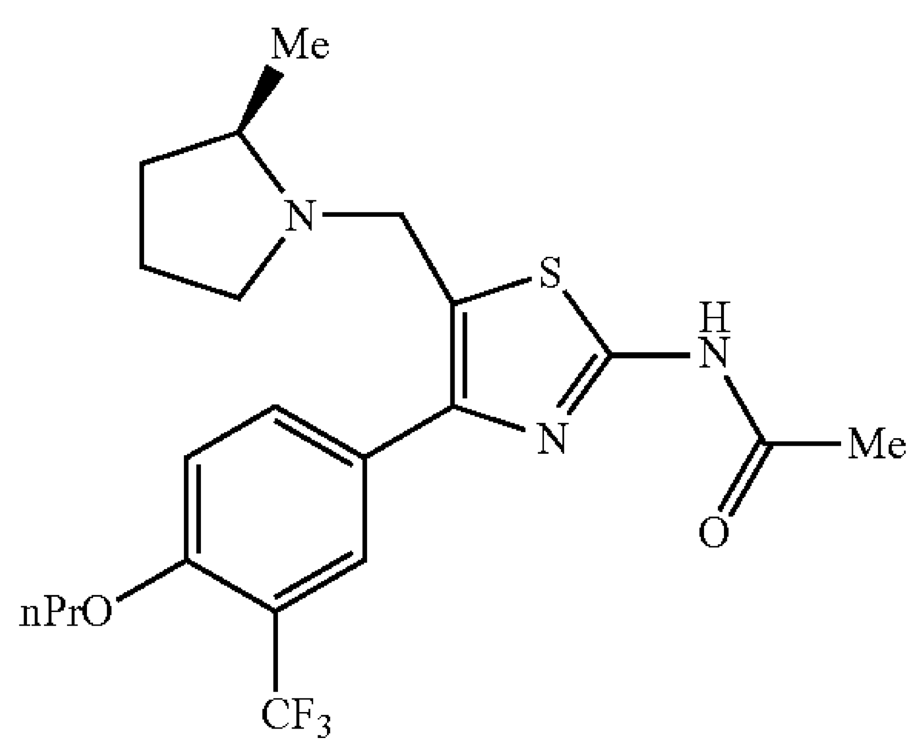
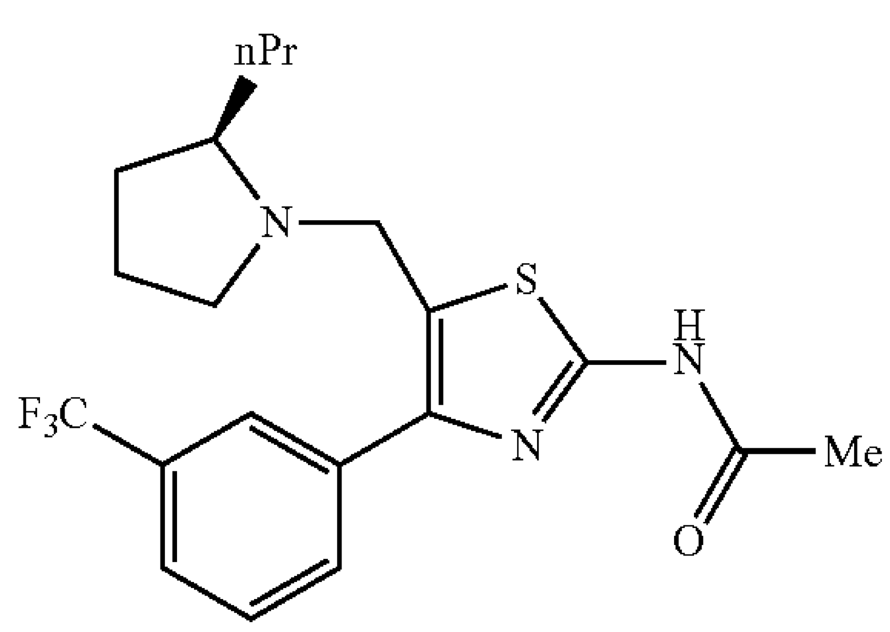
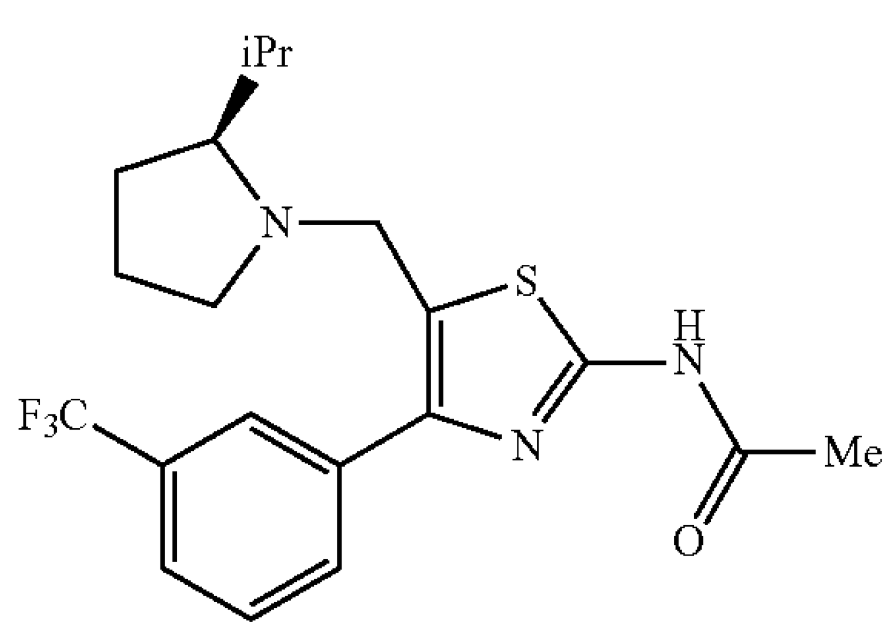
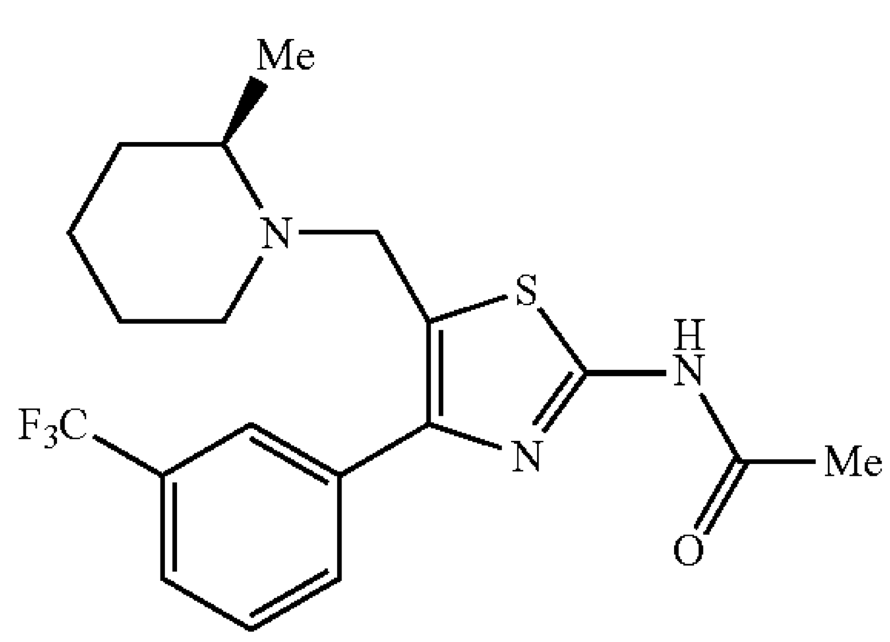
PEx	Structure
139	
140	
141	
142	

TABLE 34-continued

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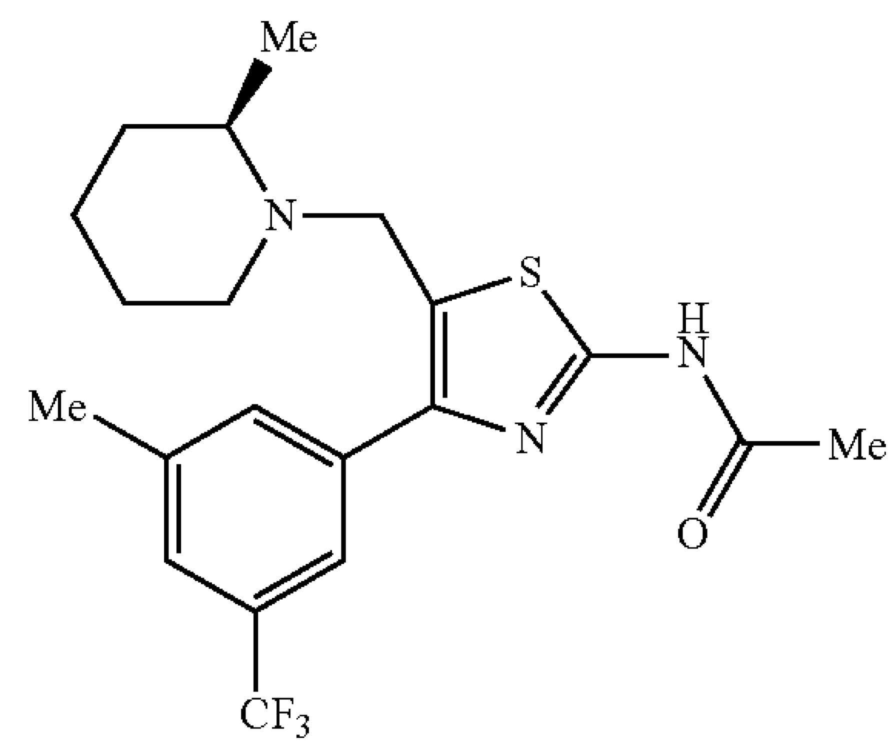
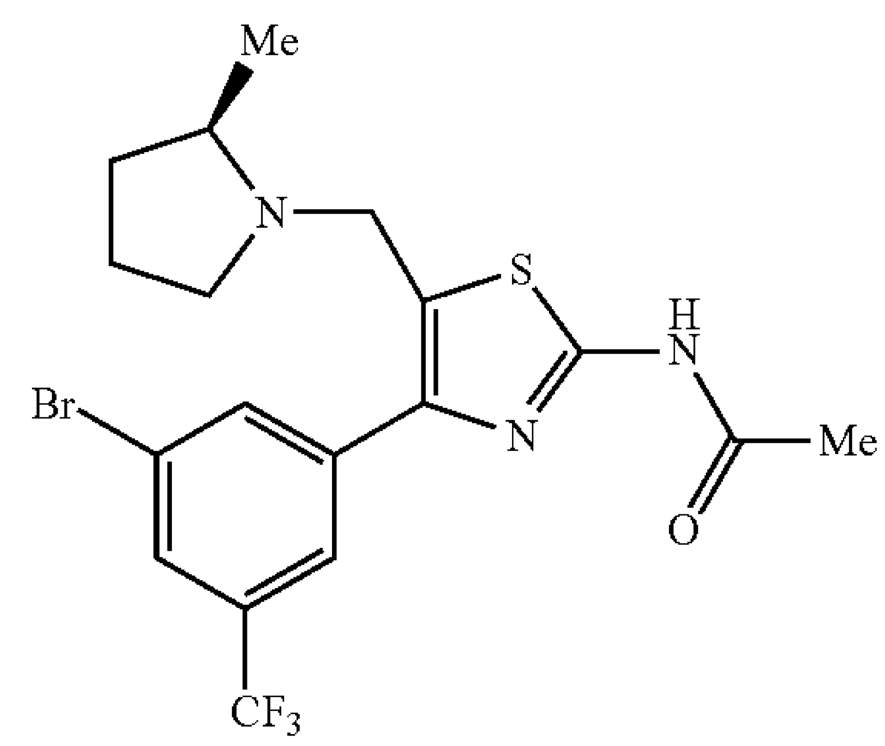
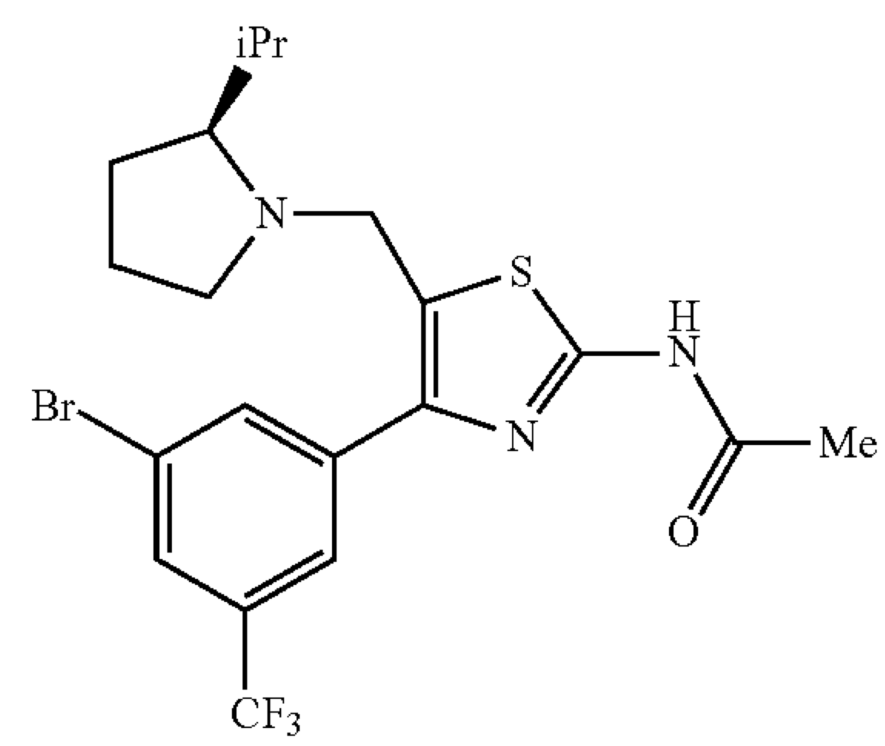
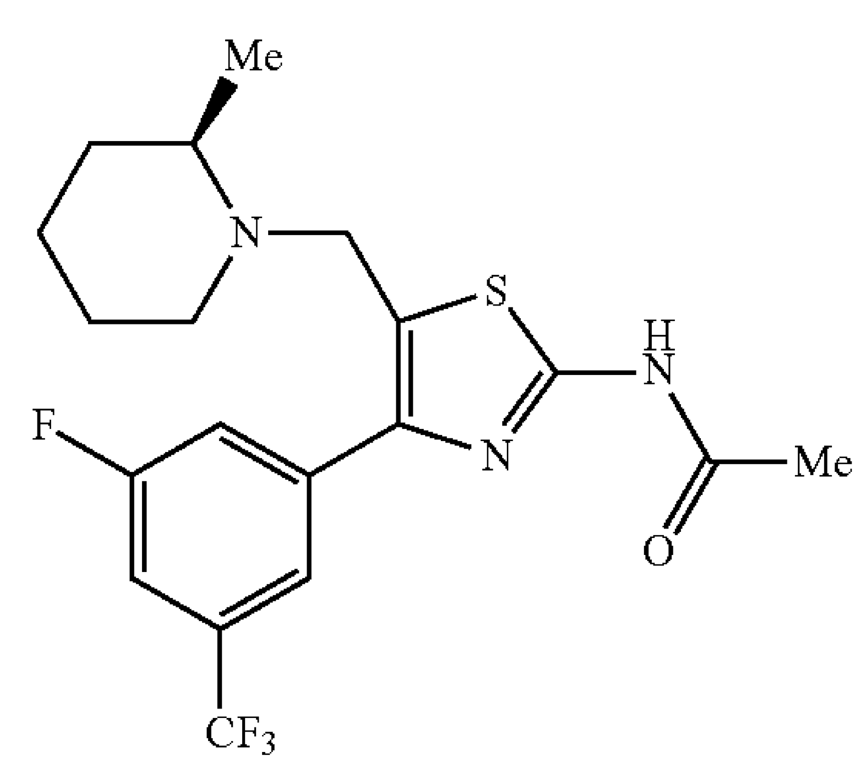
143	

TABLE 35

PEx	Structure
144	
145	
146	

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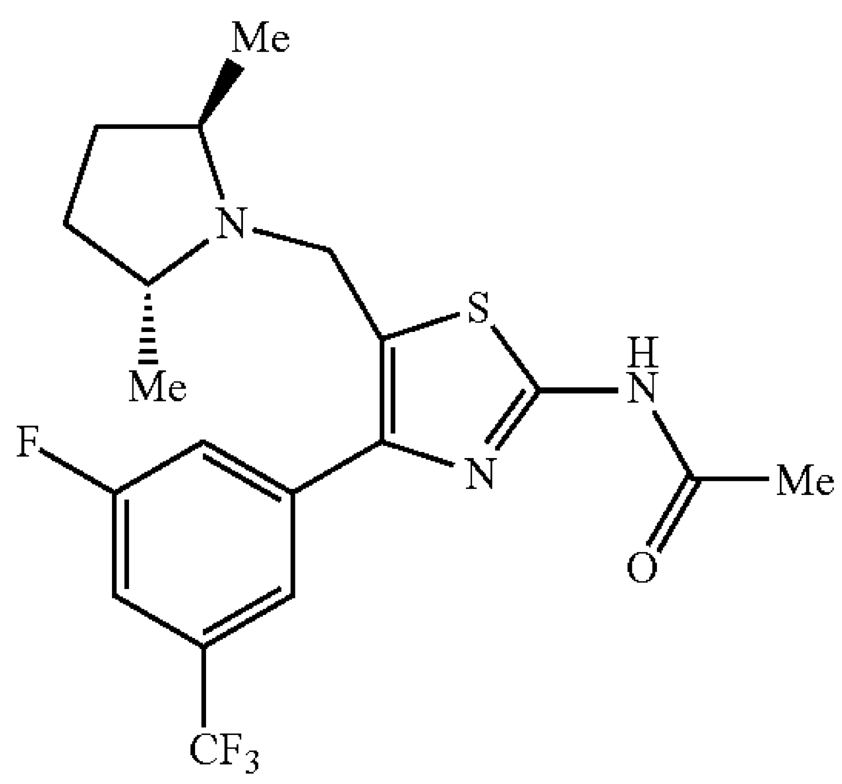


TABLE 36

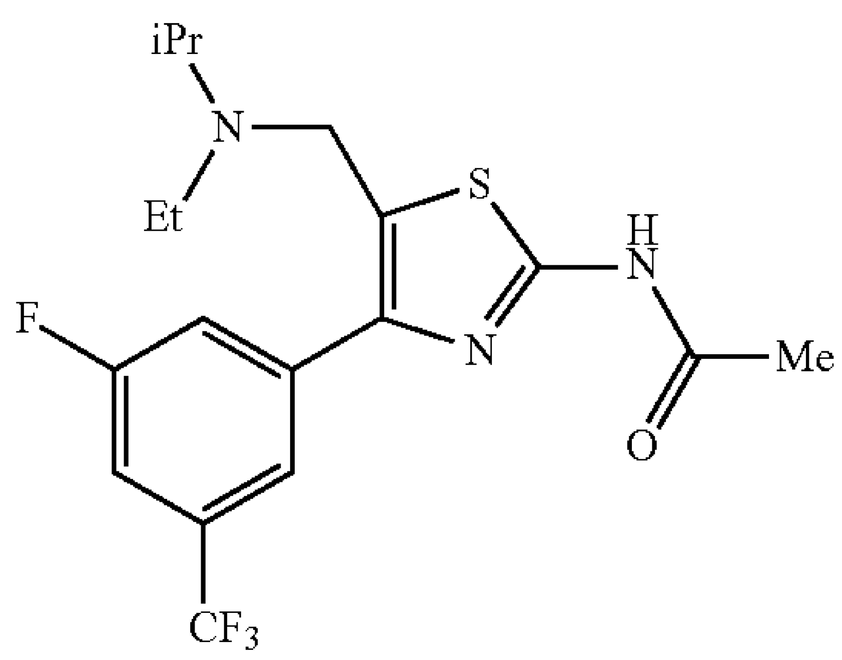
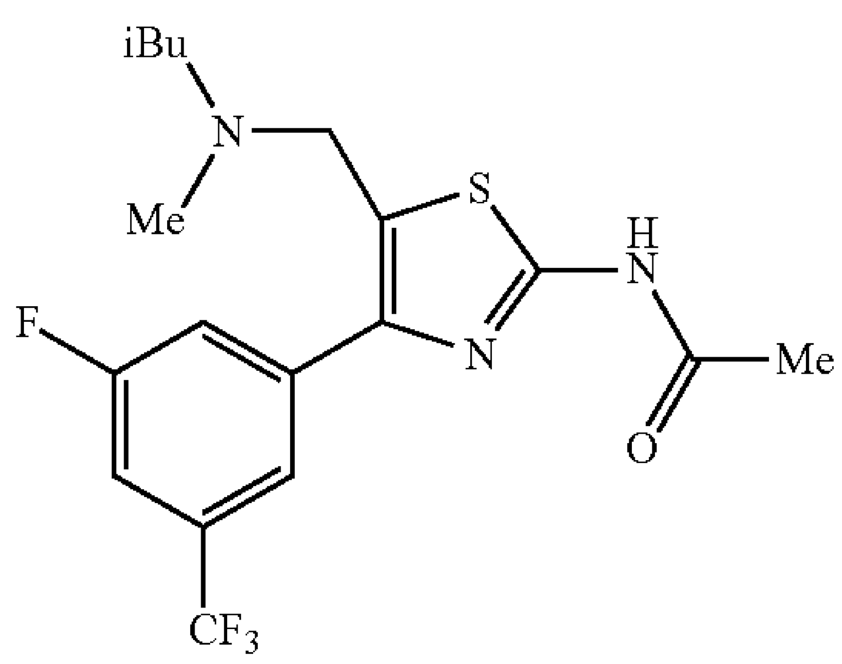
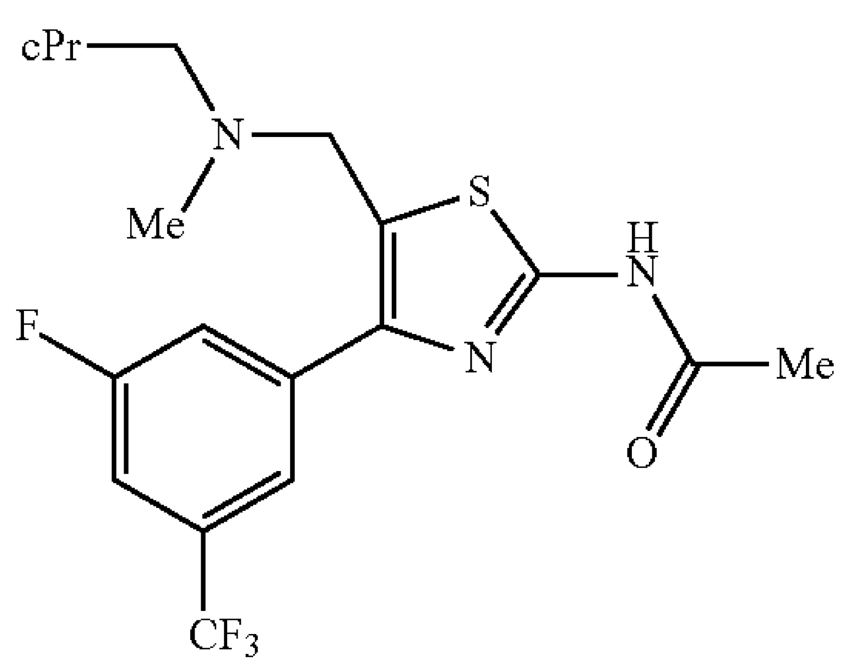
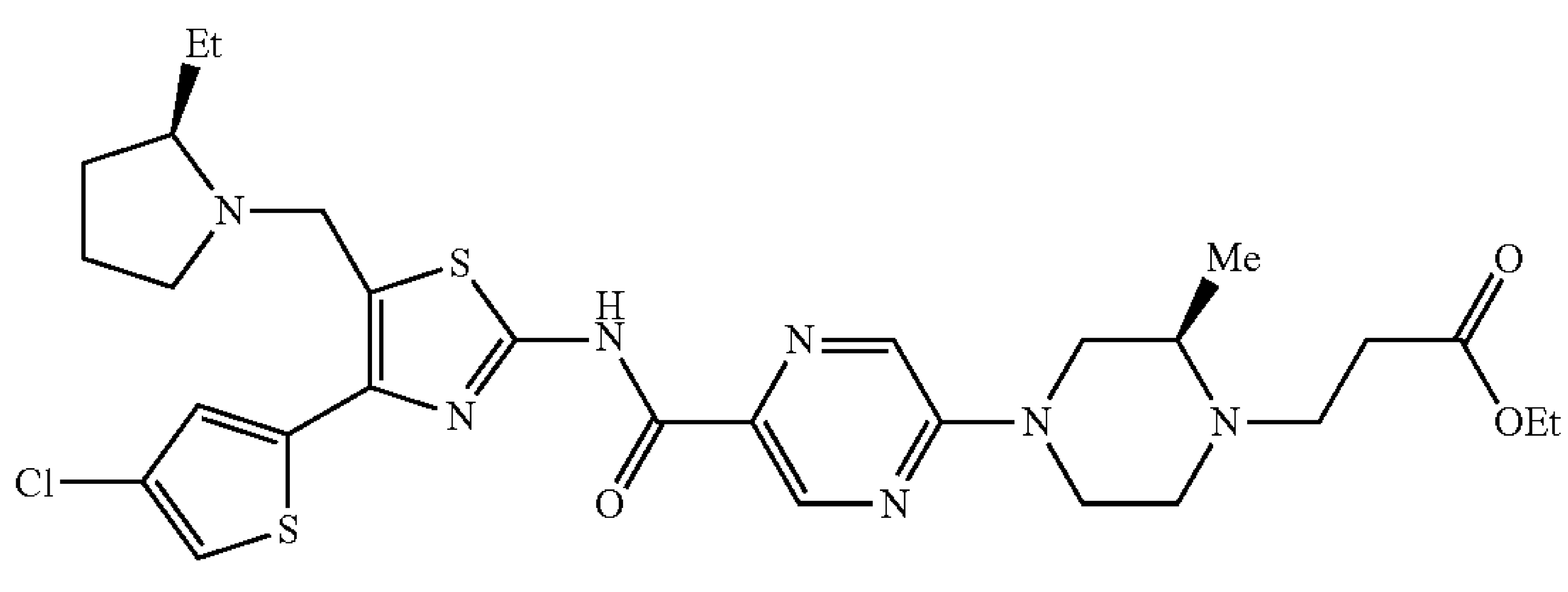
PEx	Structure
148	
149	
150	
151	

TABLE 36-continued

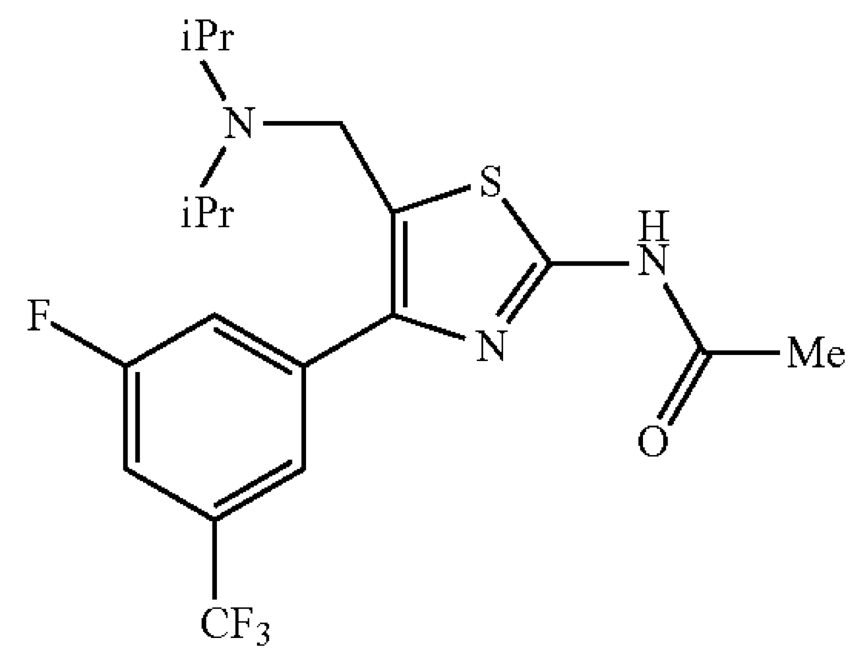
PEx	Structure
152	

TABLE 37

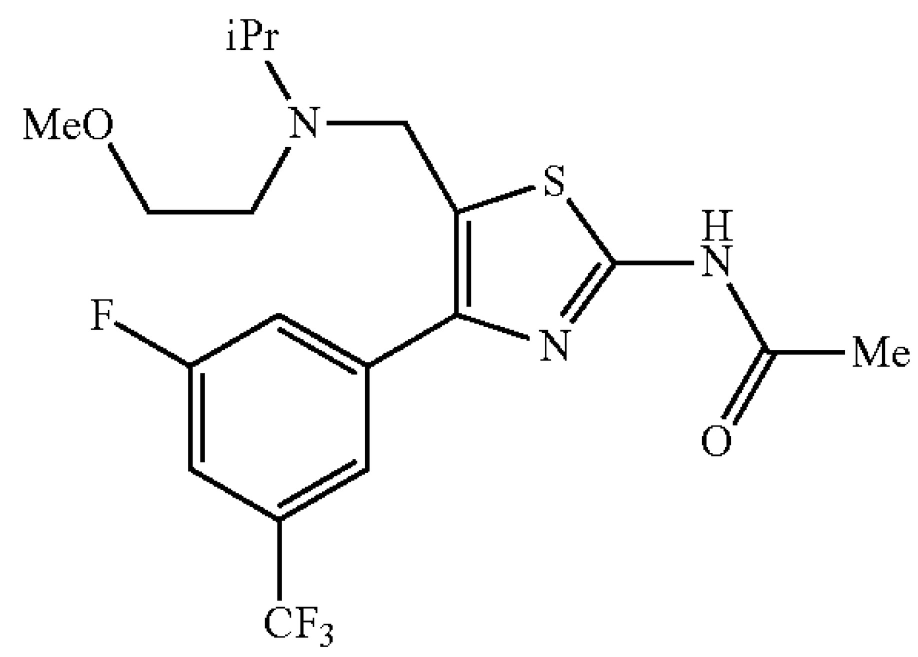
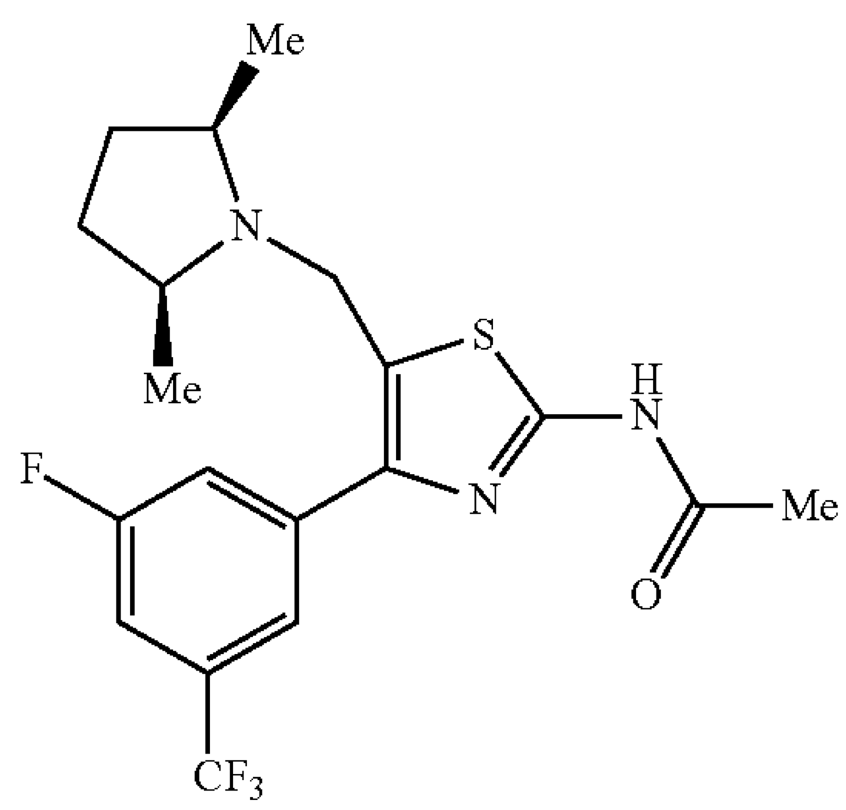
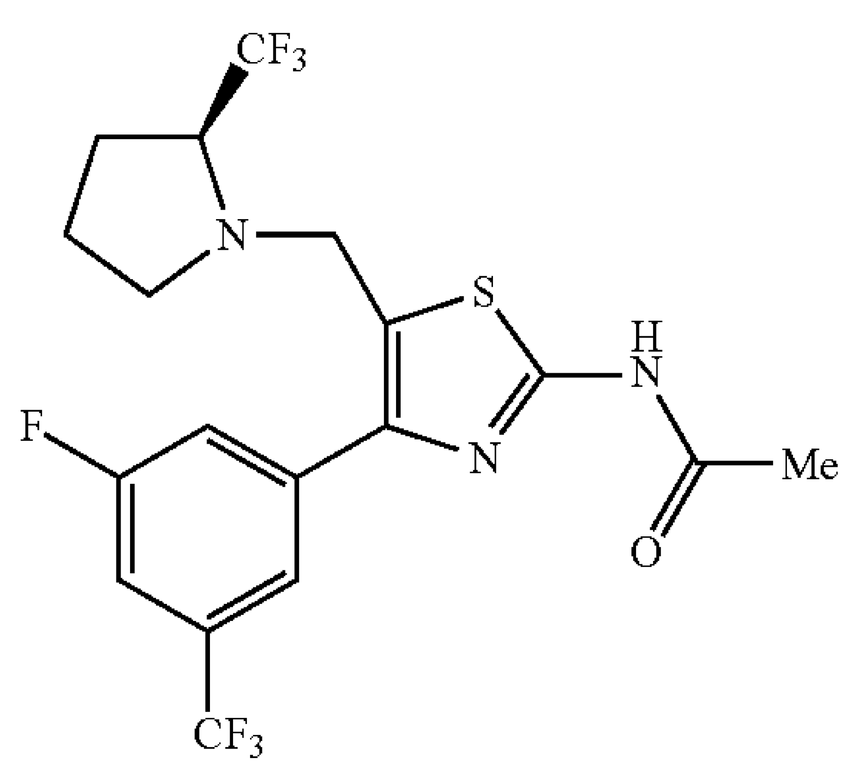
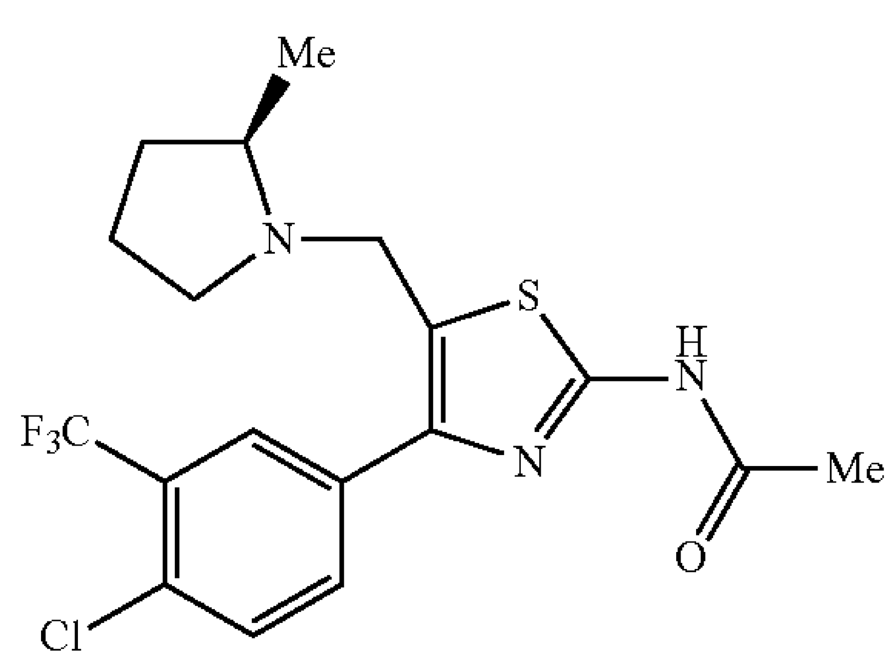
PEx	Structure
153	
154	
155	
156	

TABLE 37-continued

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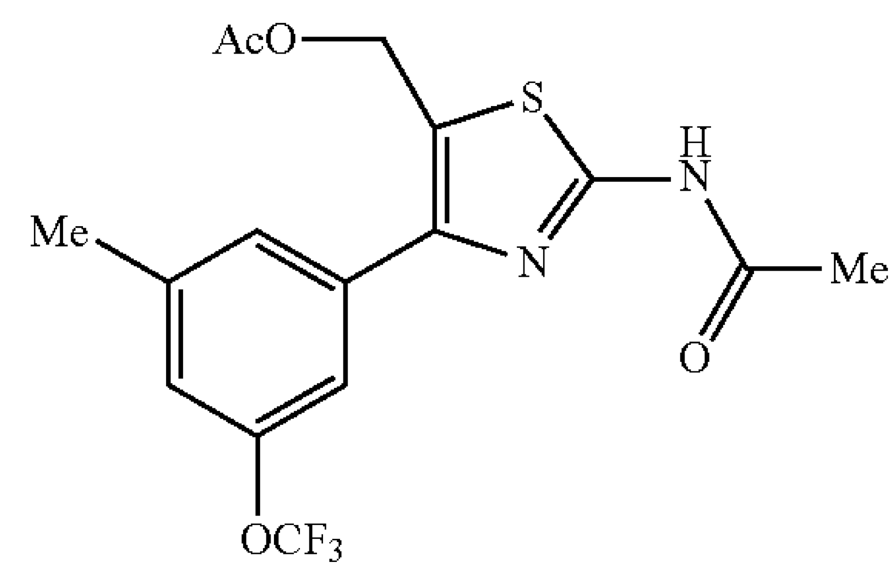
157	

TABLE 38

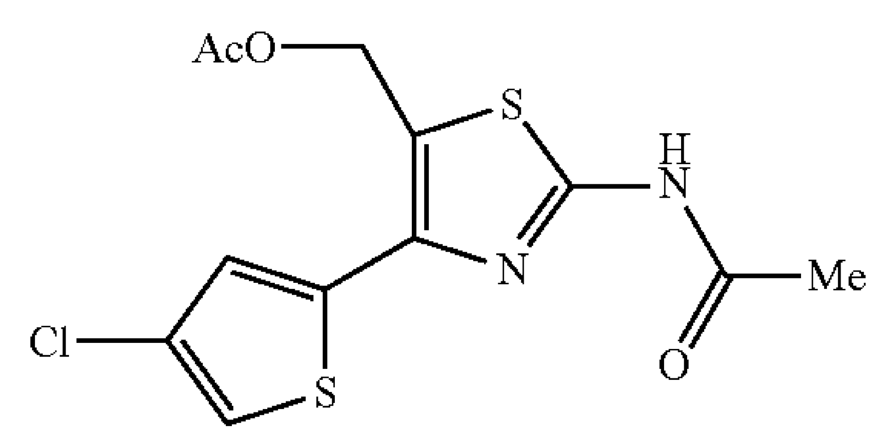
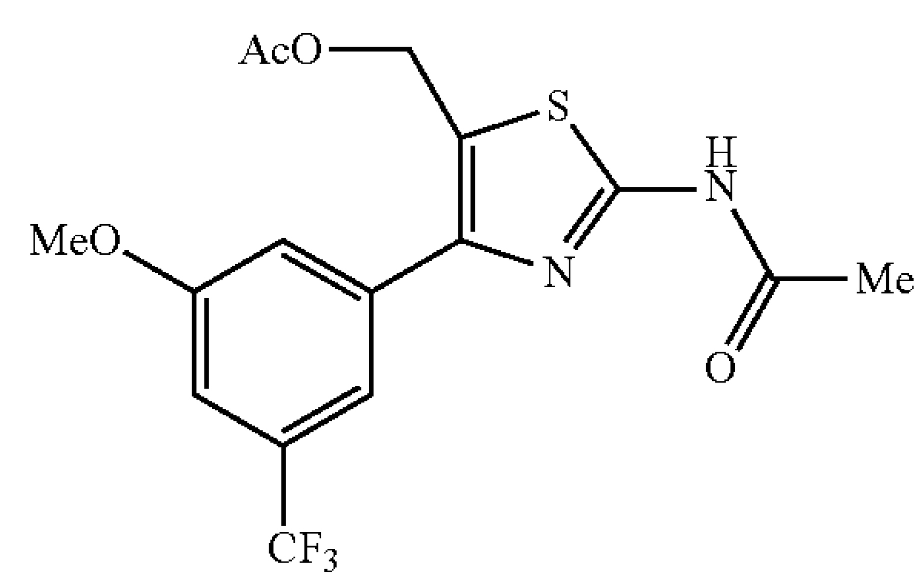
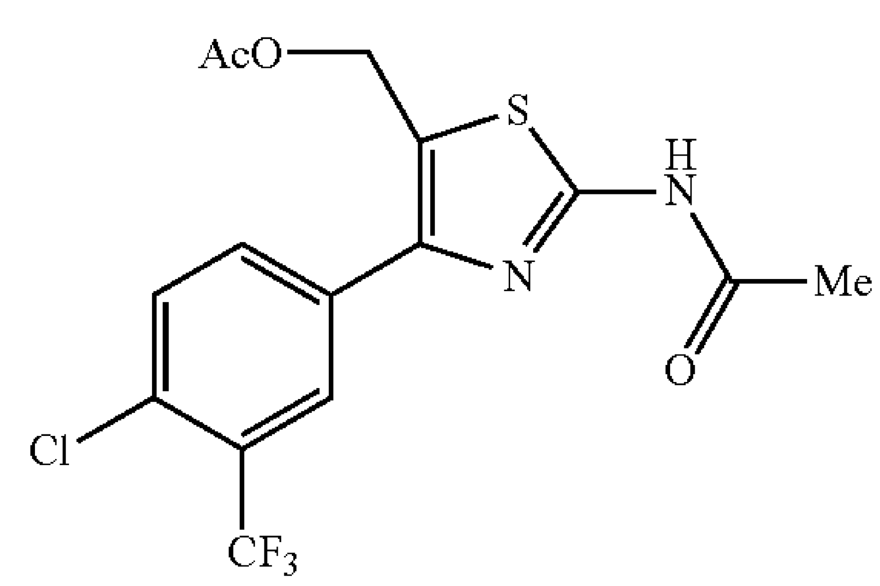
PEx	Structure
158	
159	
160	

TABLE 38-continued

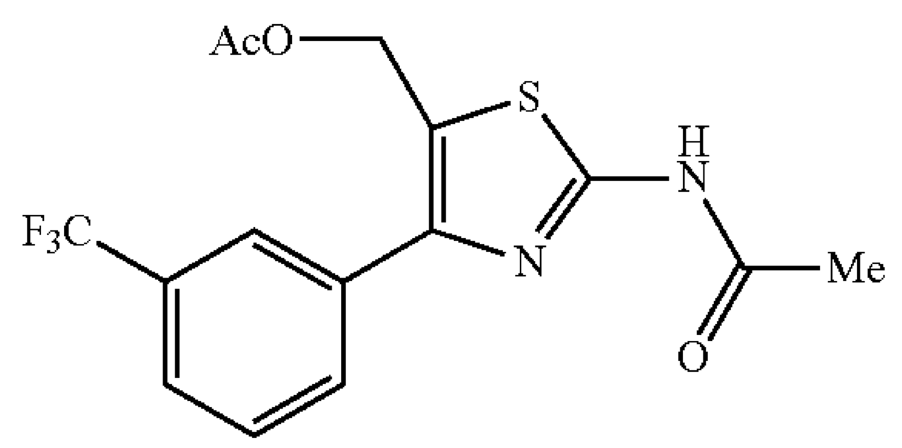
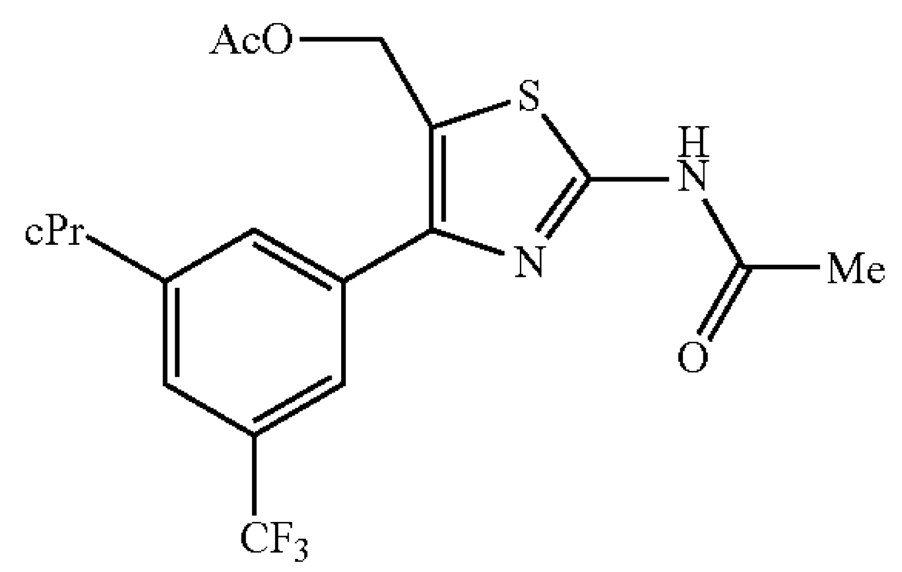
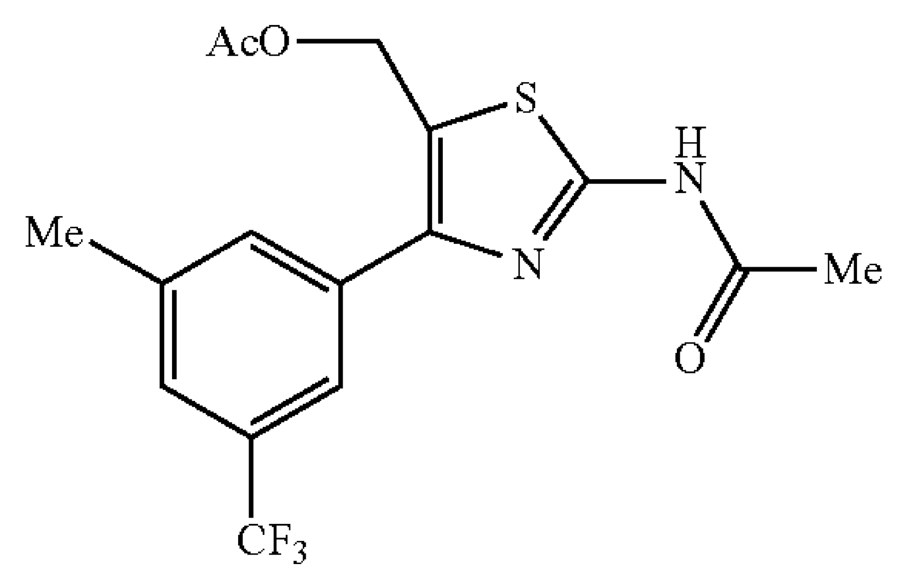
PEx	Structure
161	
162	
163	

TABLE 39

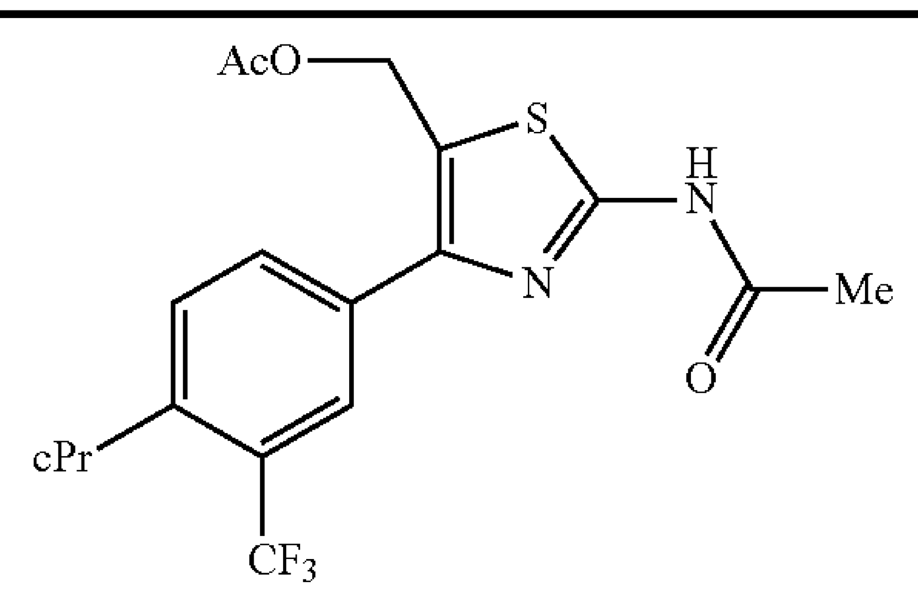
PEx	Structure
164	

TABLE 39-continued

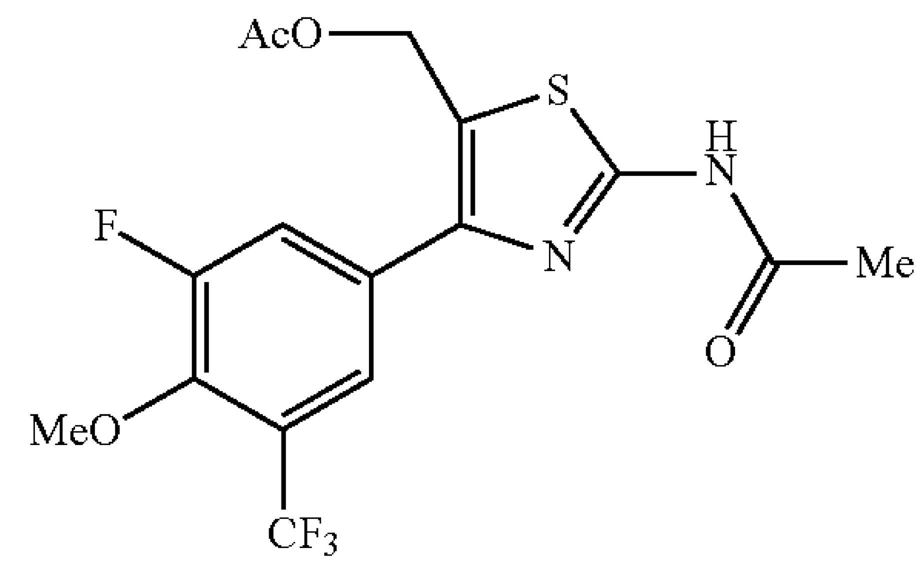
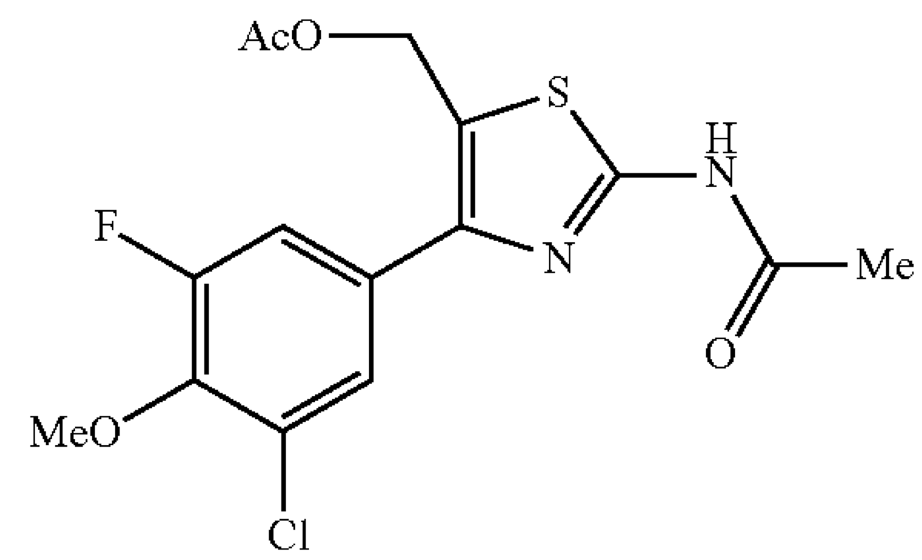
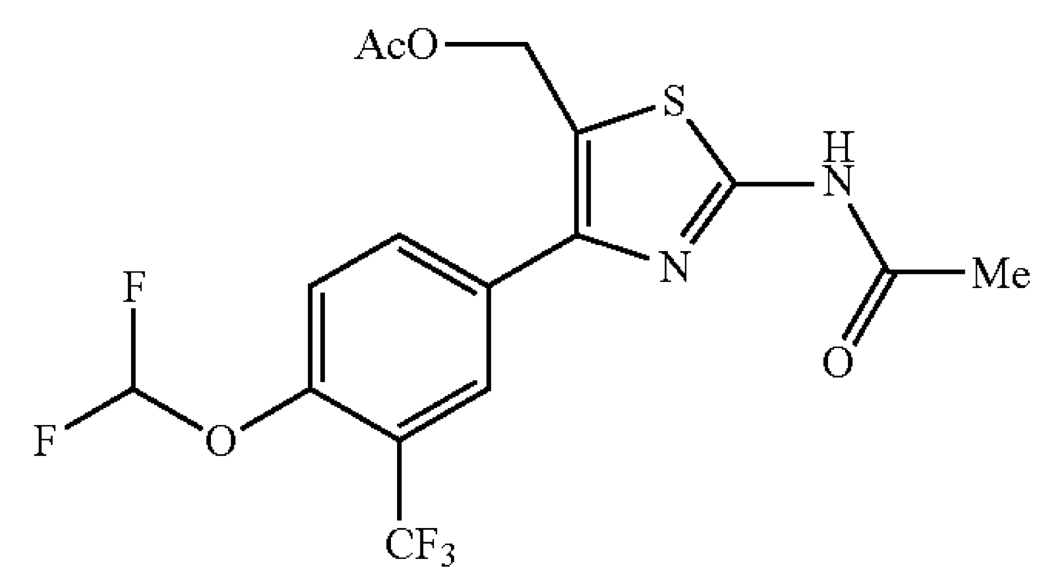
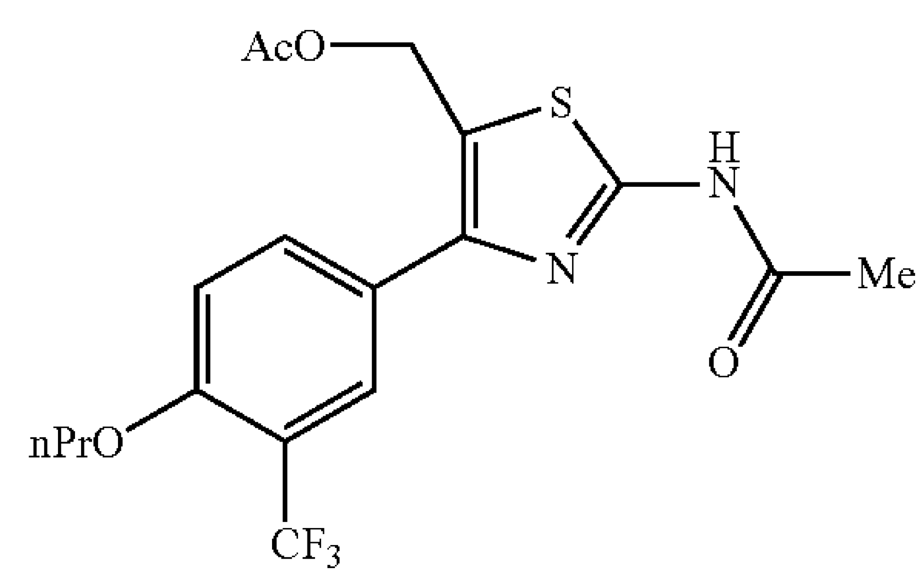
PEx	Structure
165	
166	
167	
168	

TABLE 40

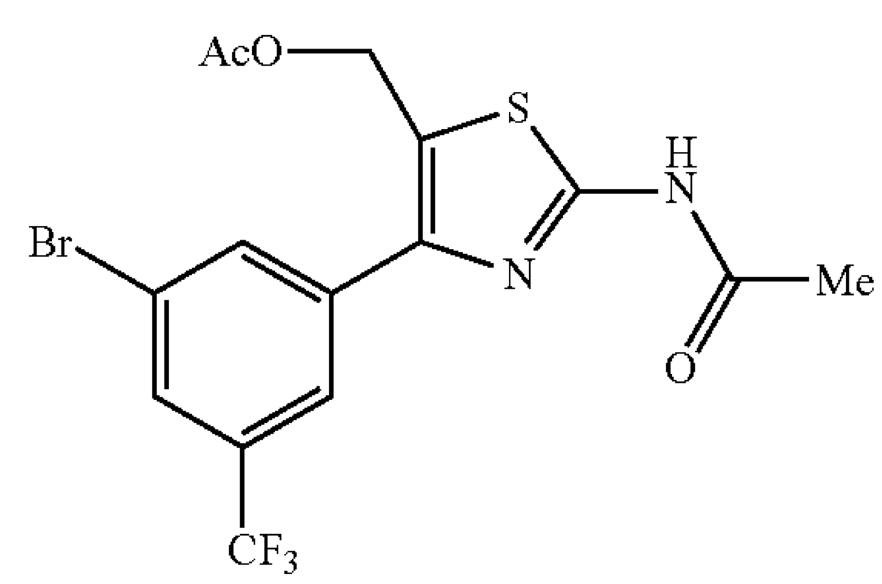
PEx	Structure
169	

TABLE 40-continued

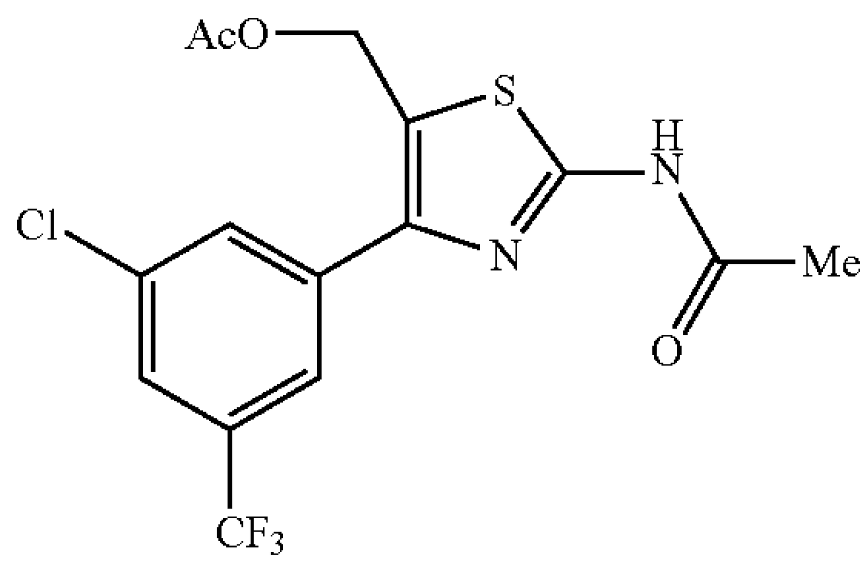
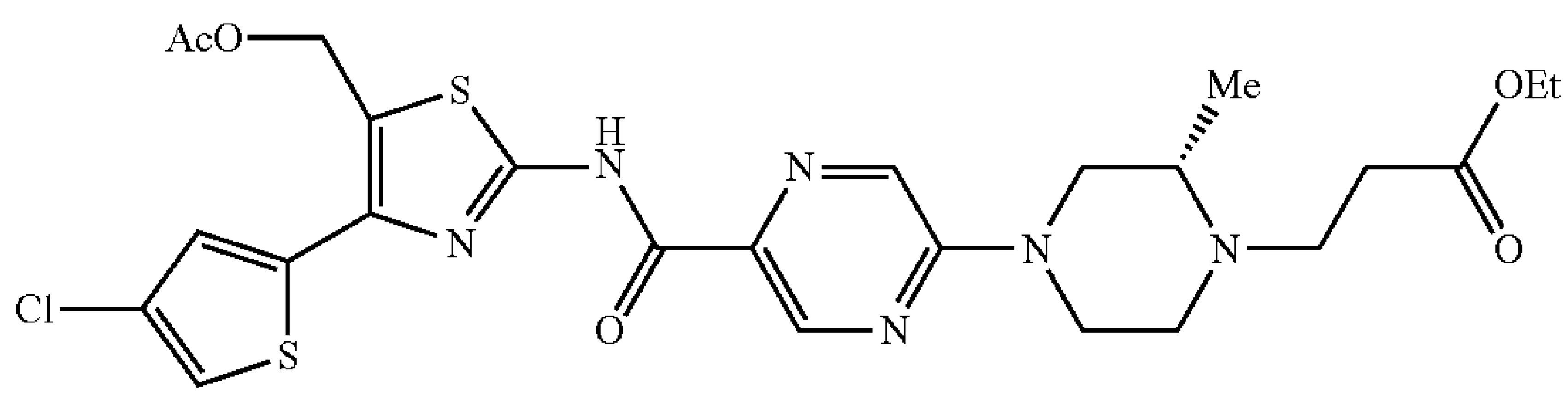
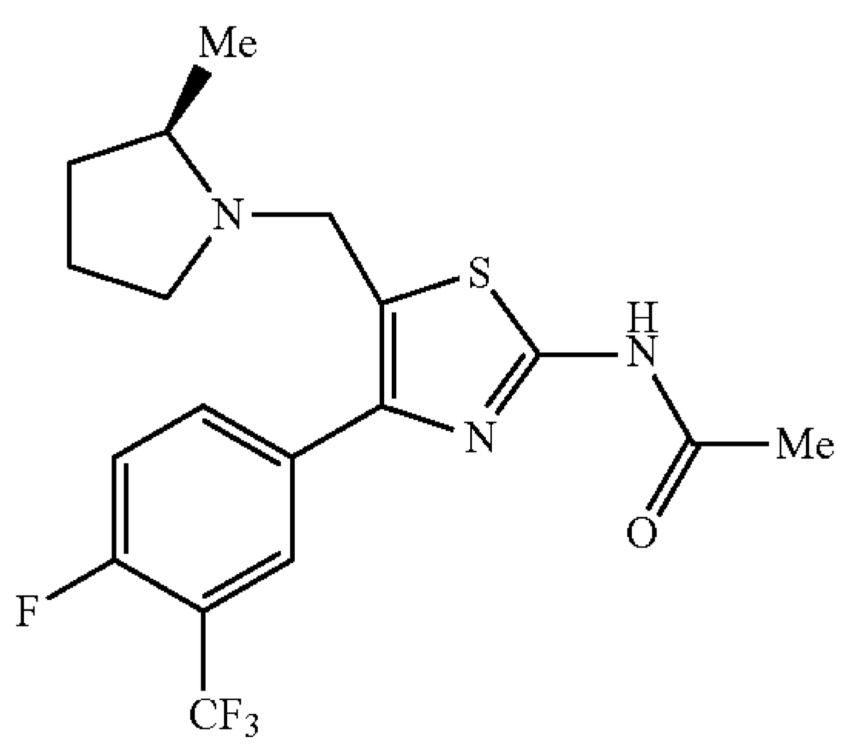
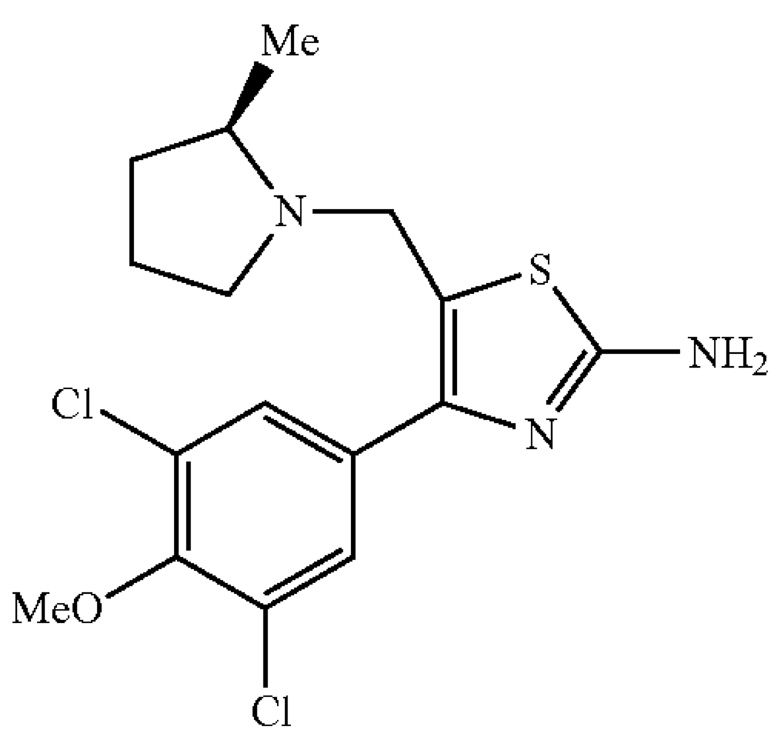
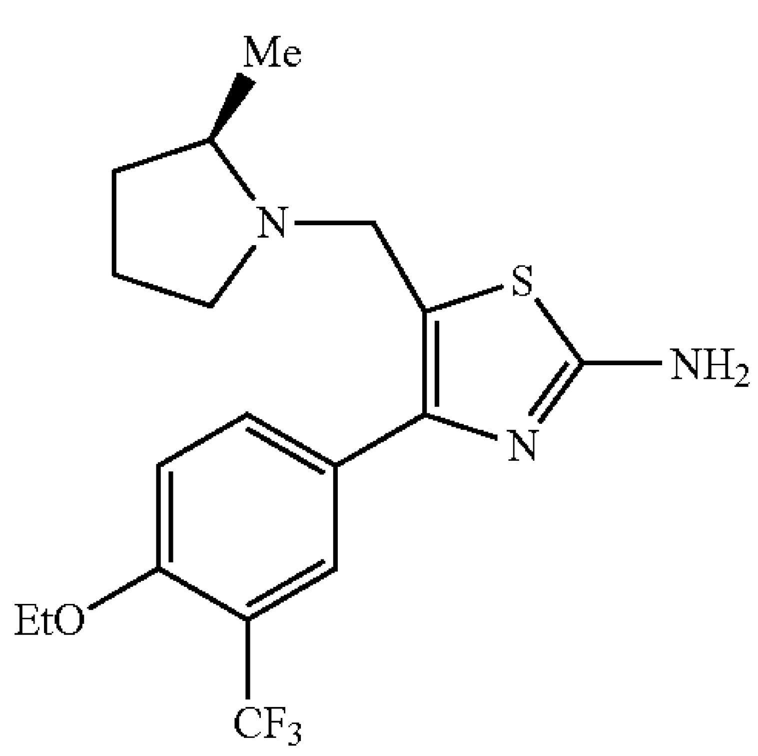
PEx	Structure
170	
171	
172	
173	

TABLE 41

PEx	Structure
174	

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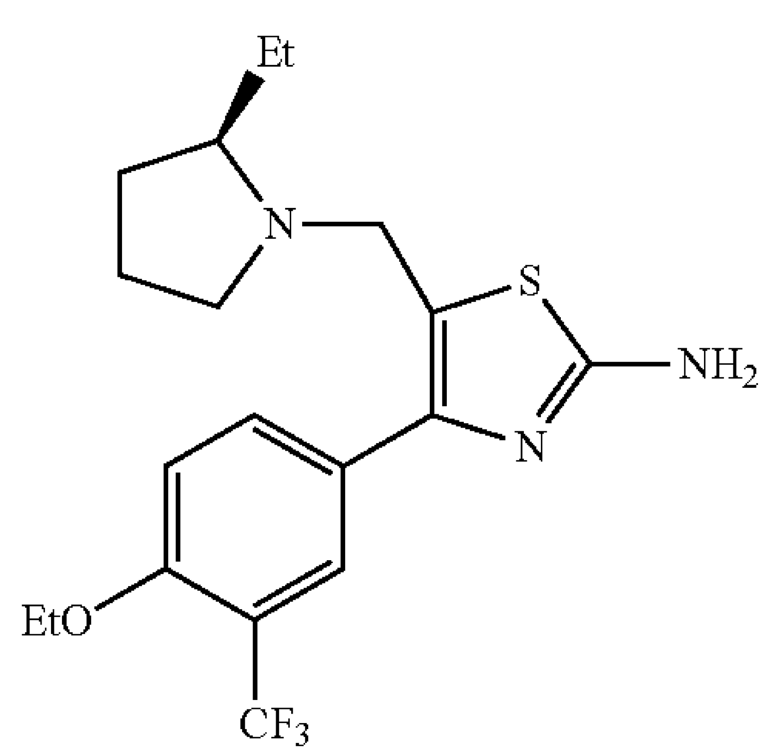
PEx	Structure
175	

TABLE 41-continued

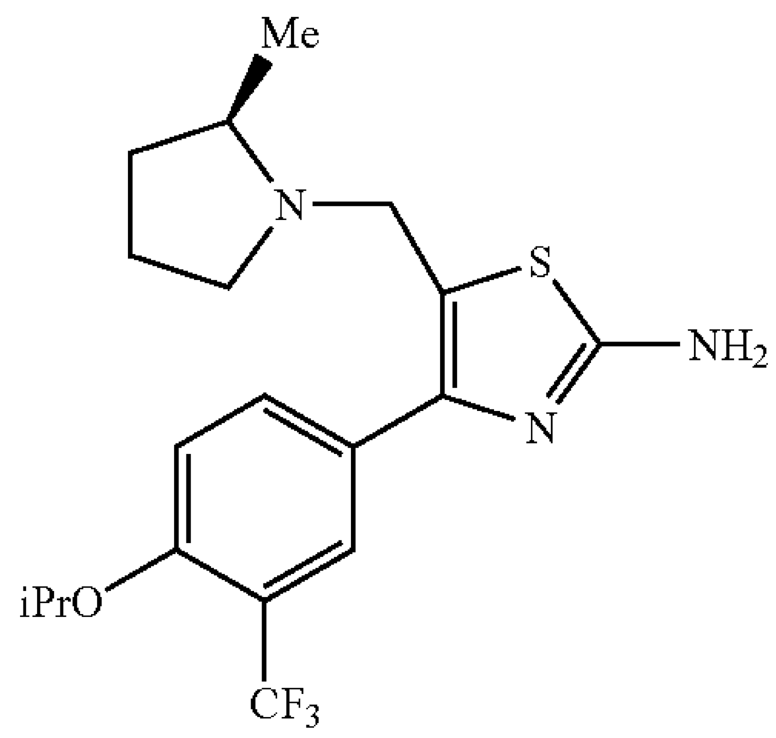
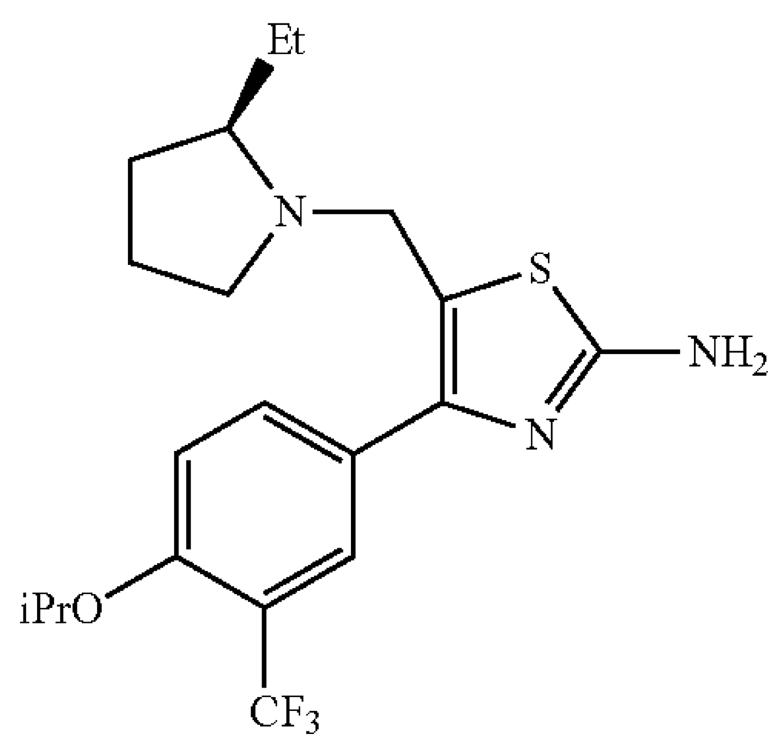
PEx	Structure
176	
177	

TABLE 42

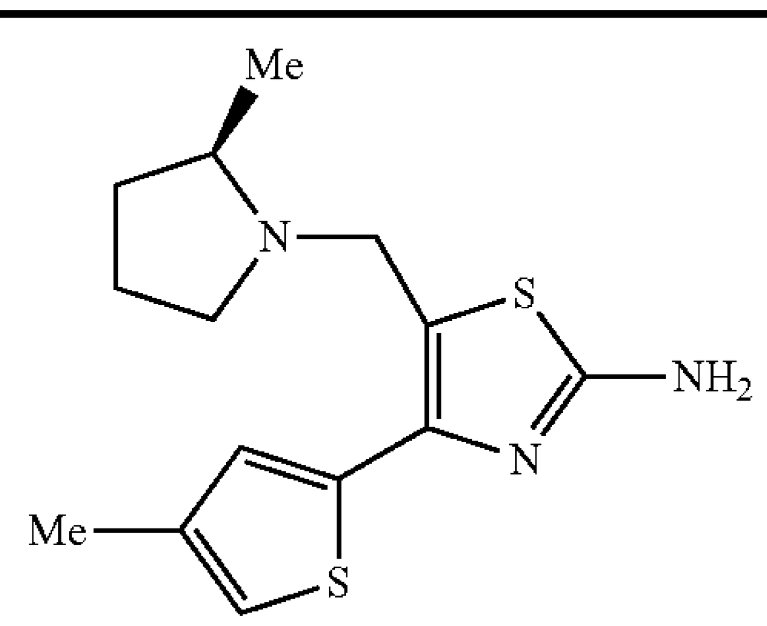
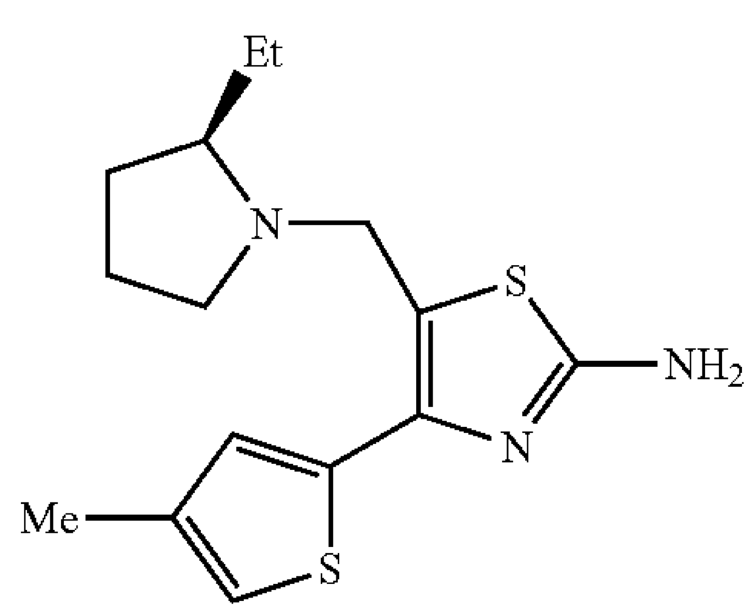
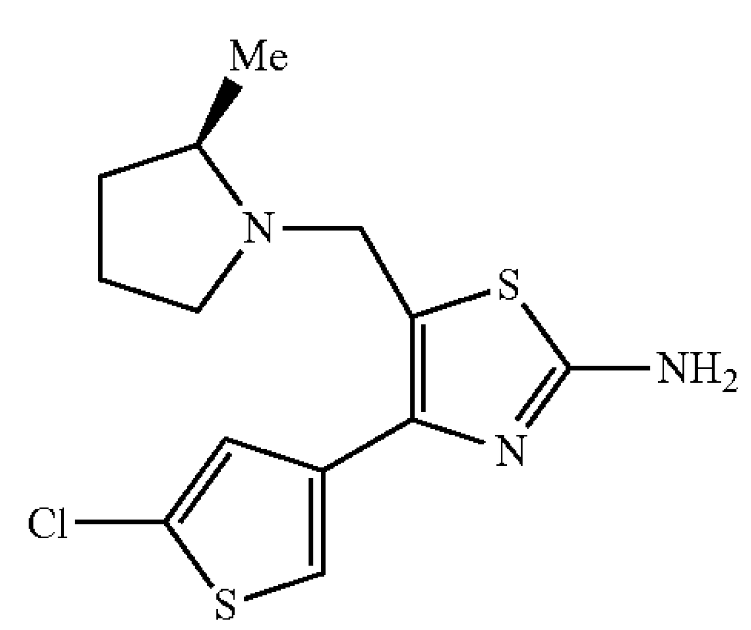
PEx	Structure
178	
179	
180	

TABLE 42-continued

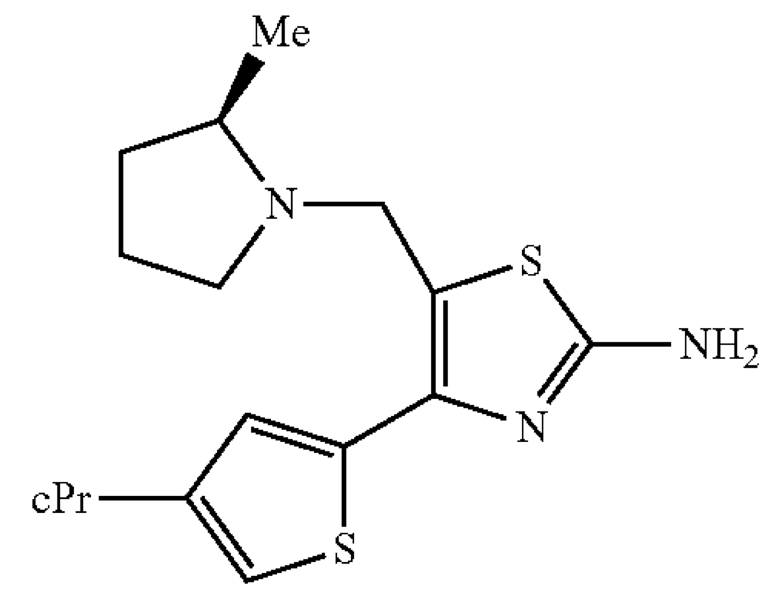
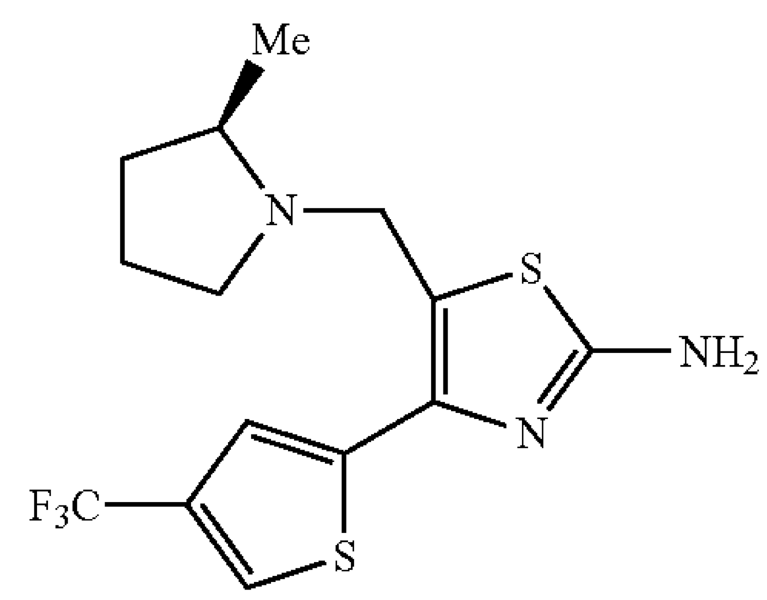
PEx	Structure
181	
182	

TABLE 43

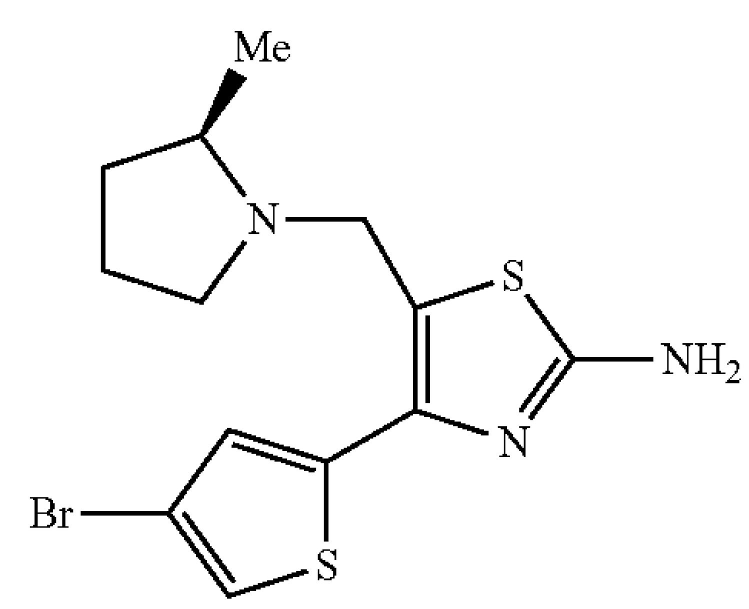
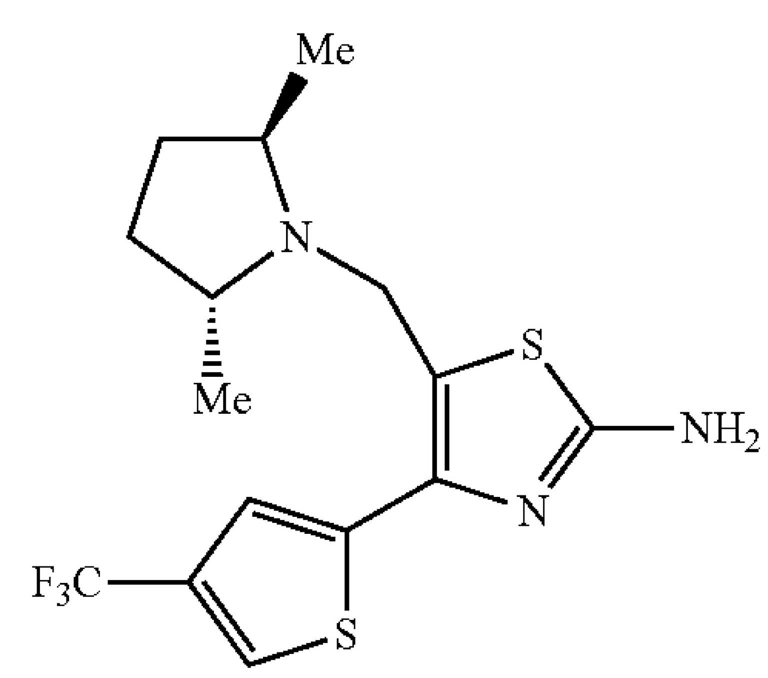
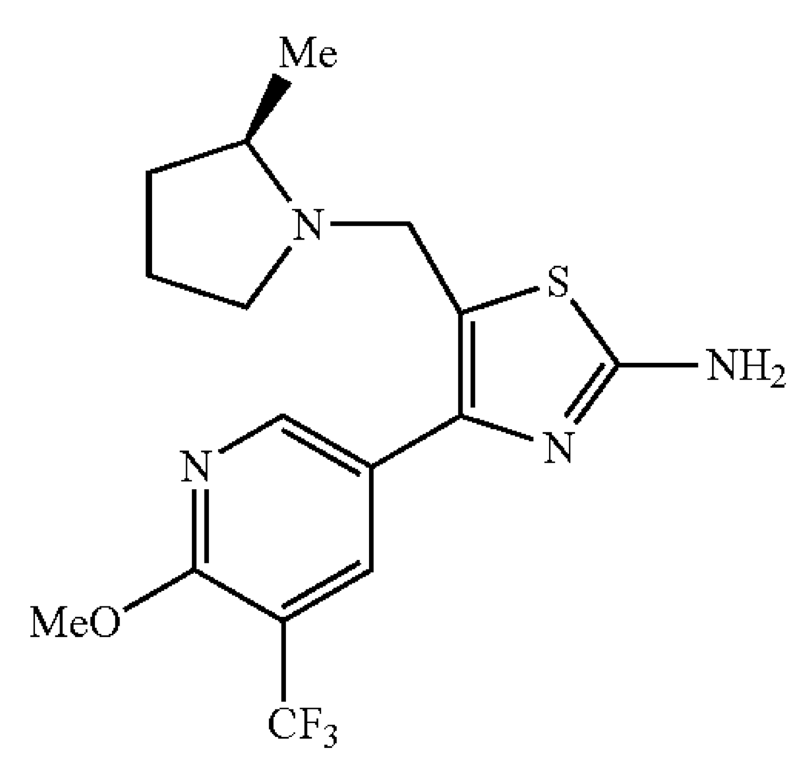
PEx	Structure
183	
184	
185	

TABLE 43-continued

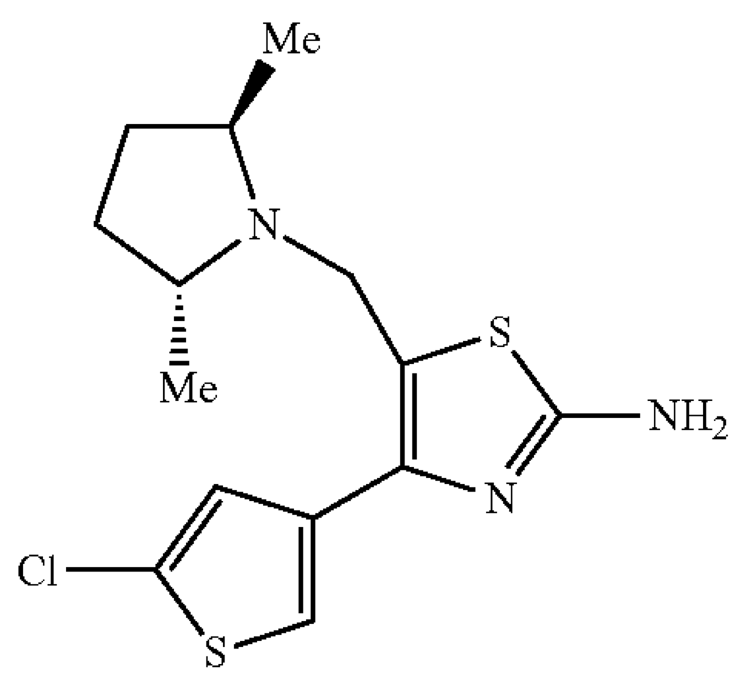
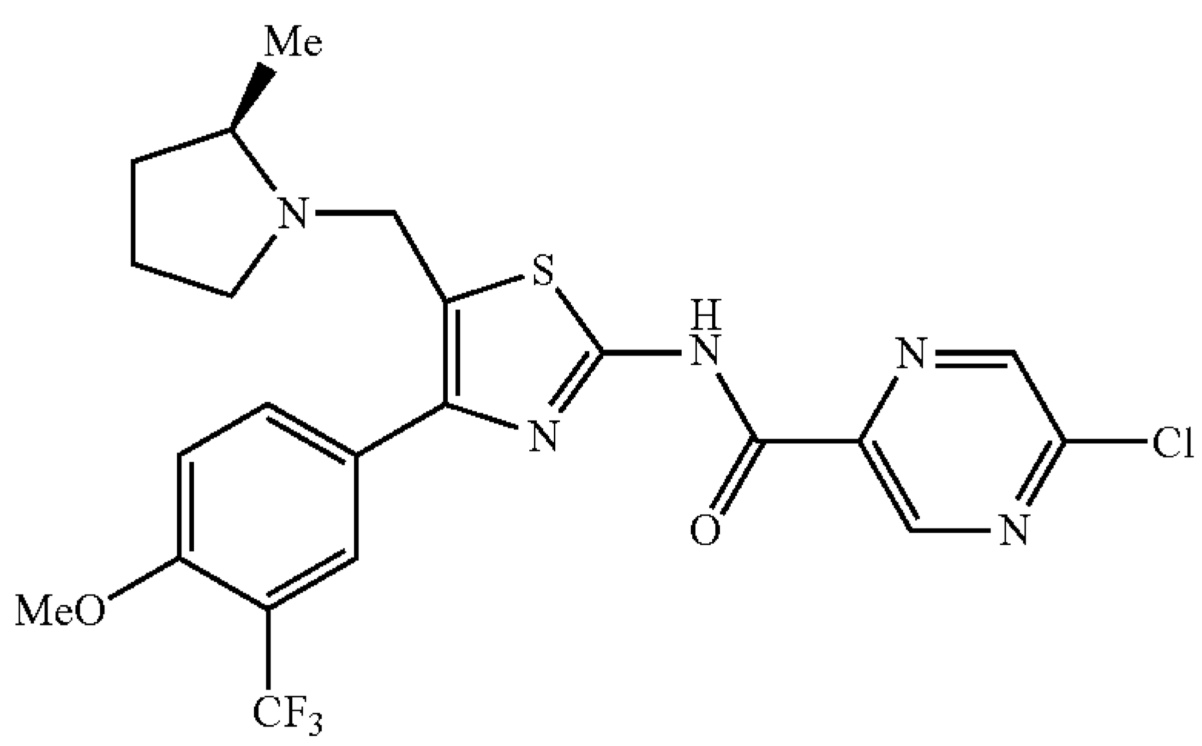
PEx	Structure
186	
187	

TABLE 44

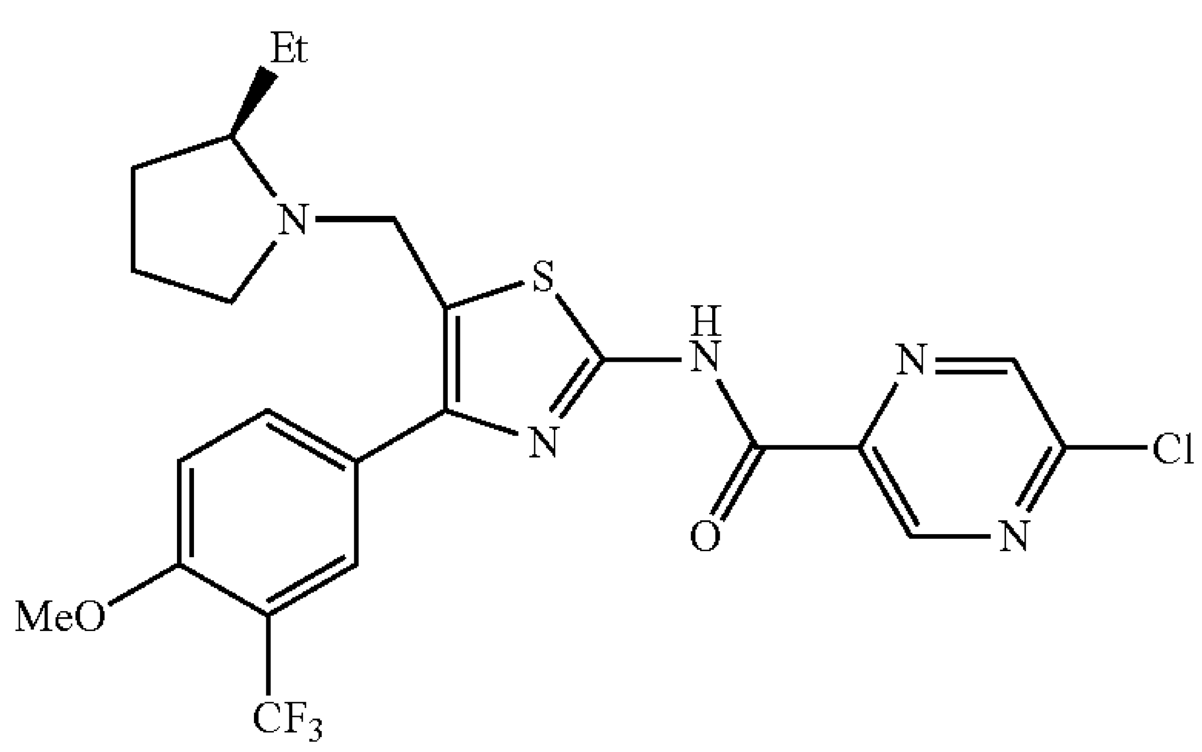
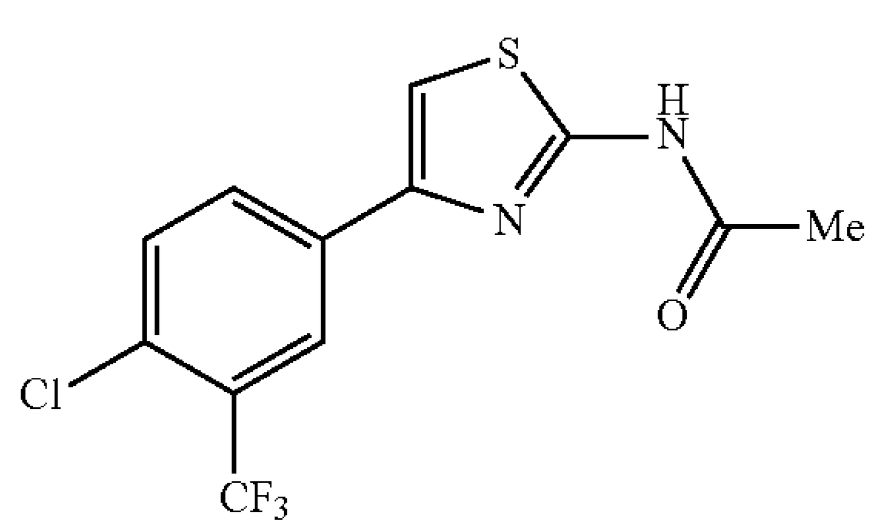
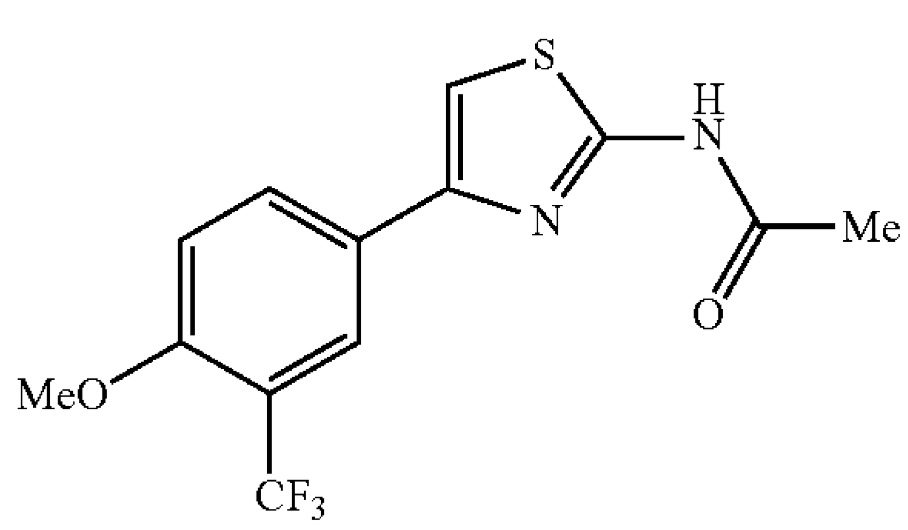
PEx	Structure
188	
189	
190	

TABLE 44-continued

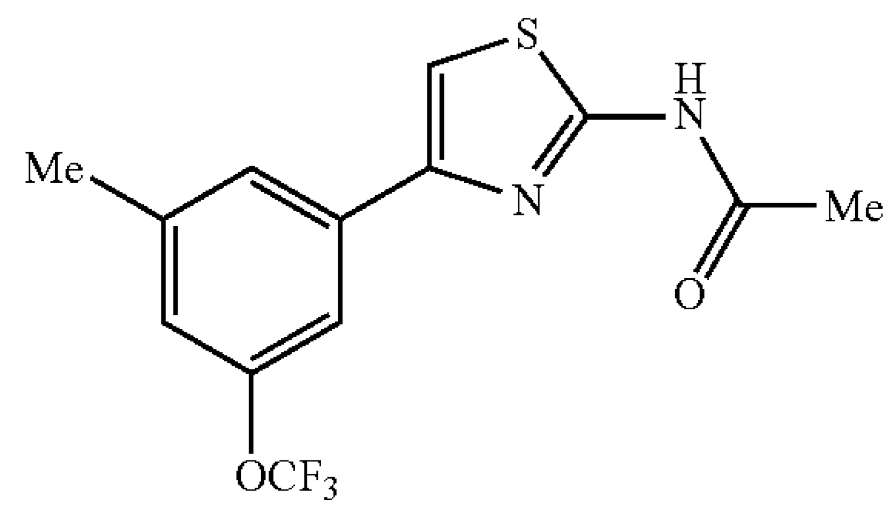
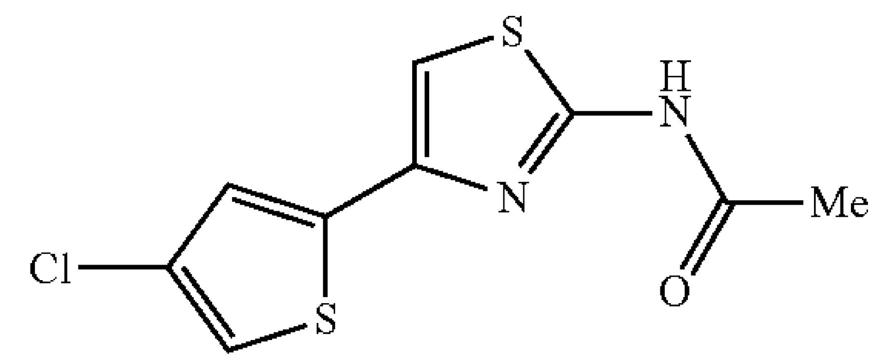
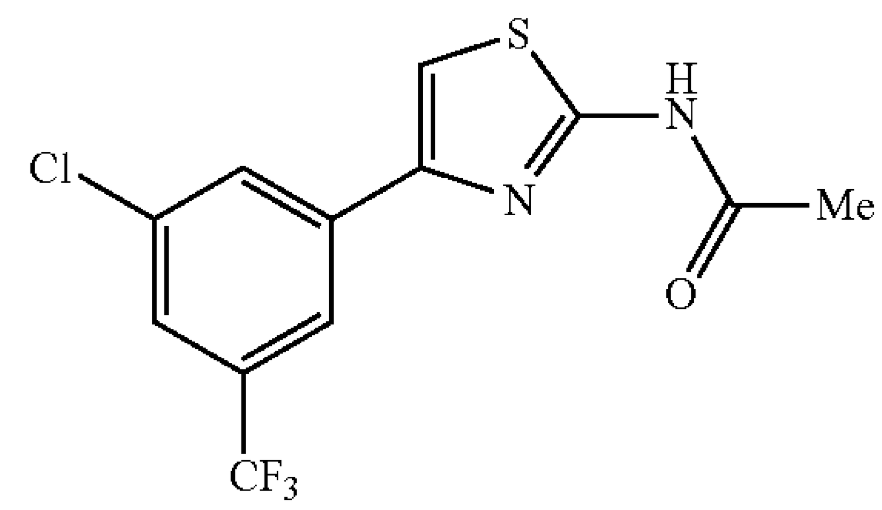
PEx	Structure
191	
192	
193	

TABLE 45

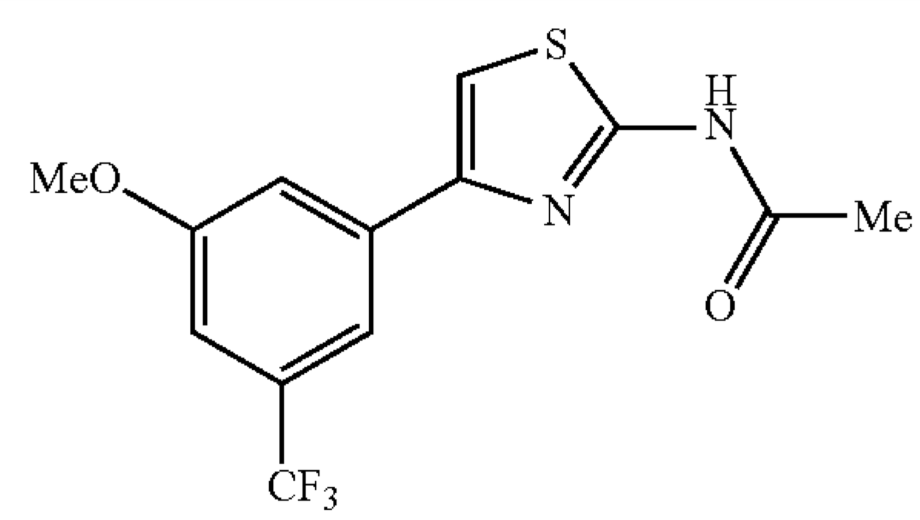
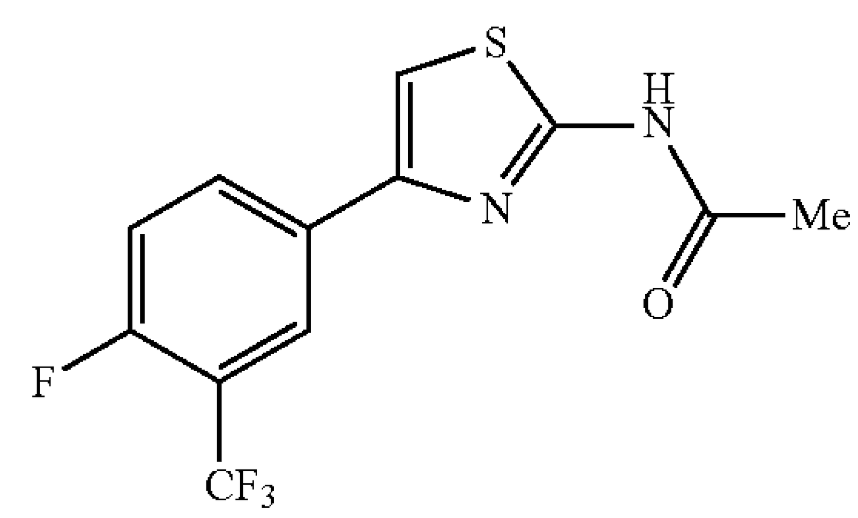
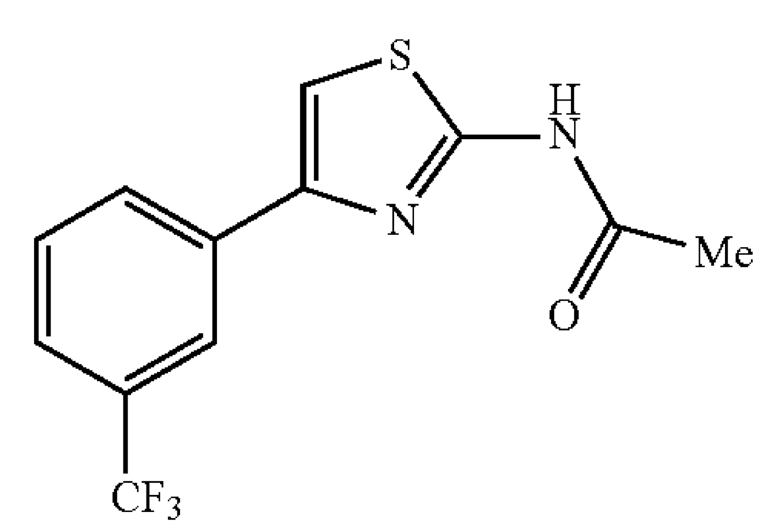
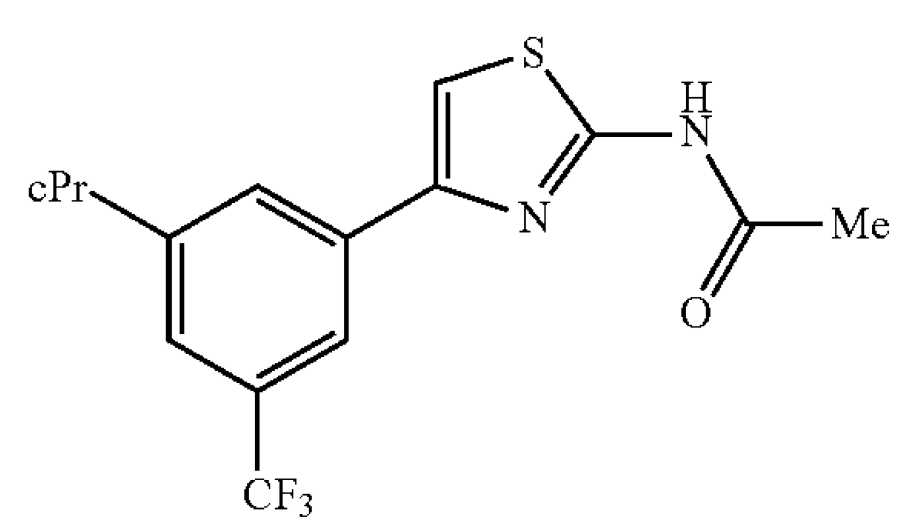
PEx	Structure
194	
195	
196	
197	

TABLE 45-continued

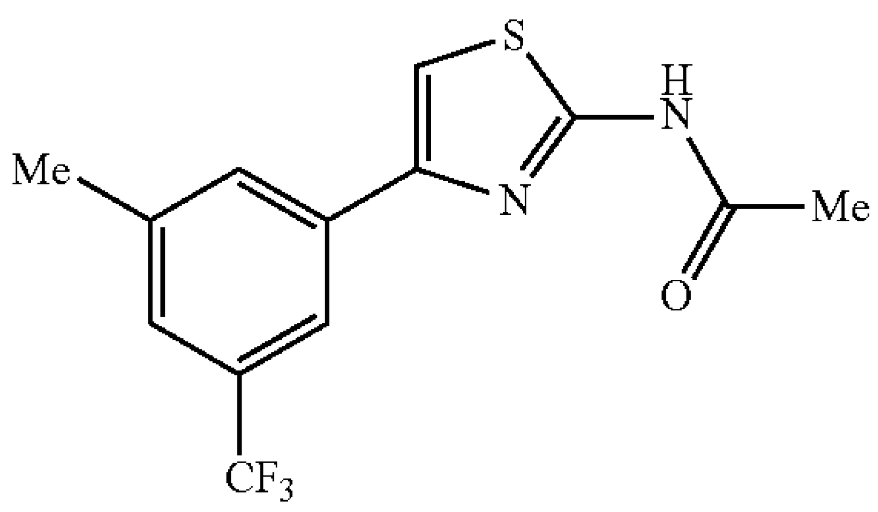
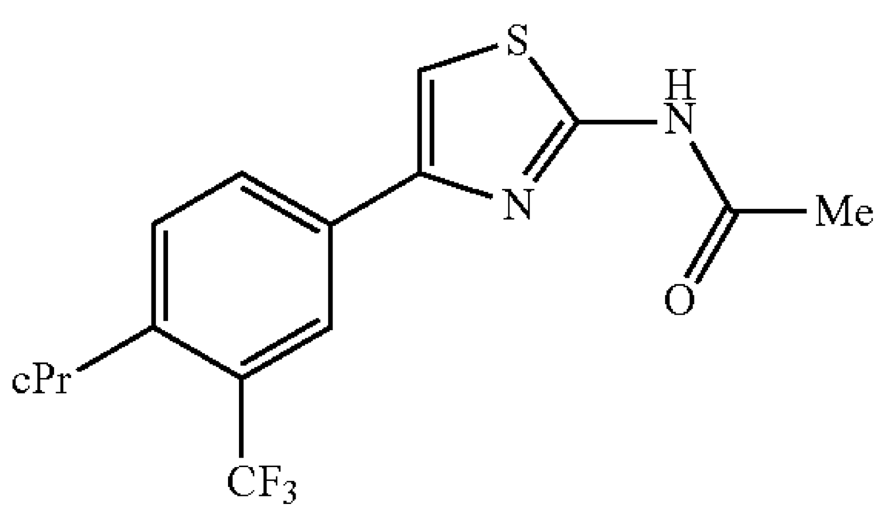
PEx	Structure
198	
199	

TABLE 46

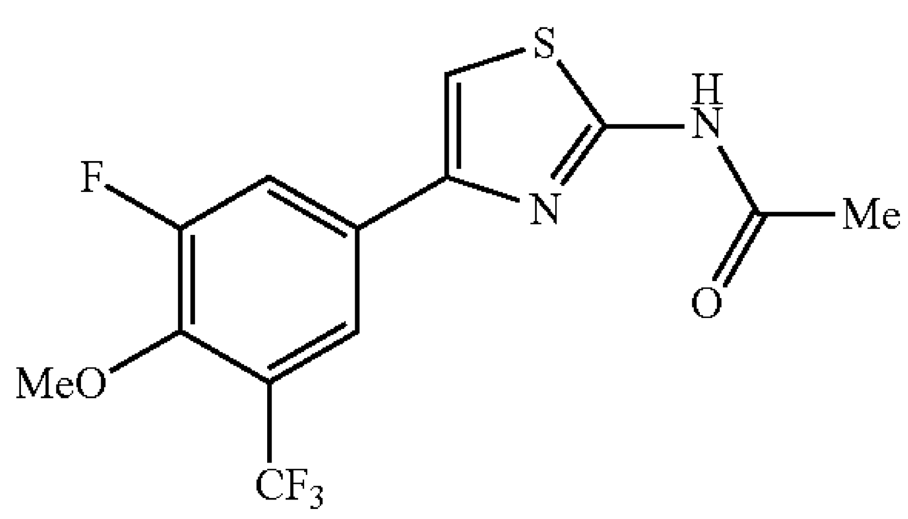
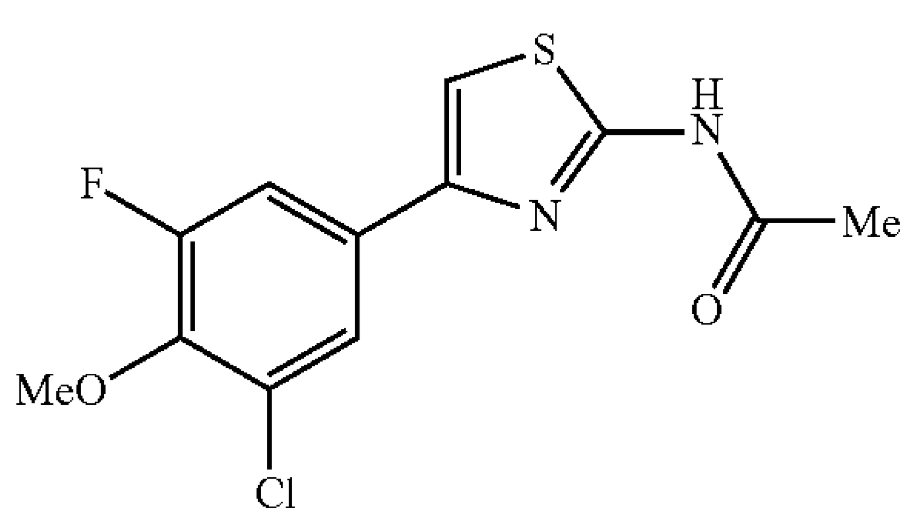
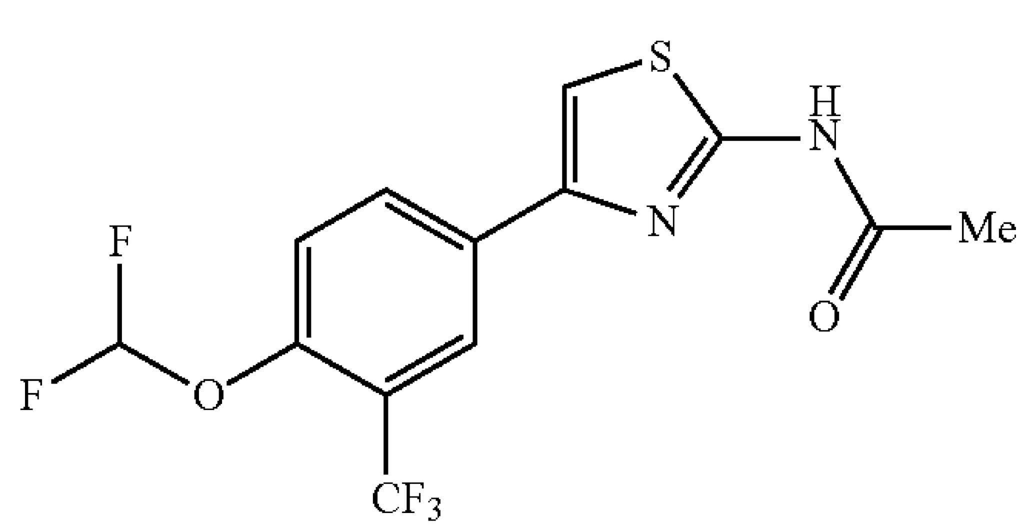
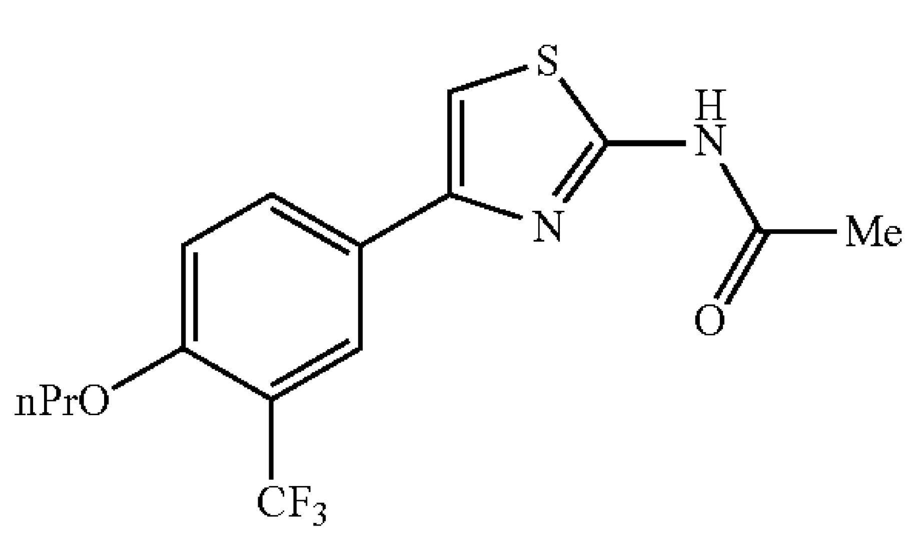
PEx	Structure
200	
201	
202	
203	

TABLE 46-continued

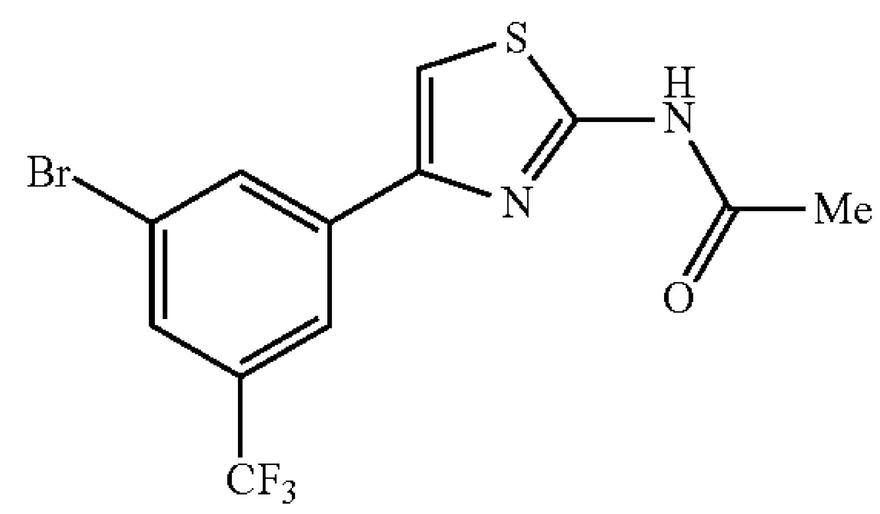
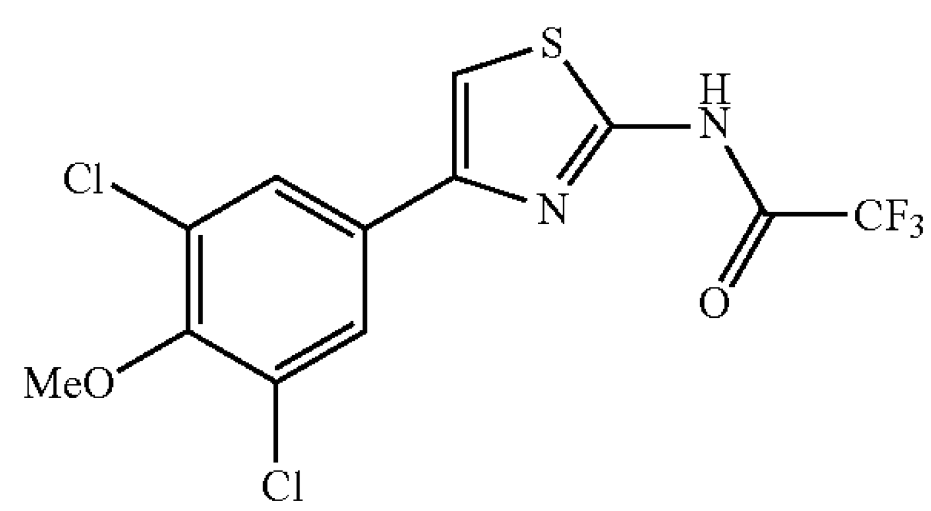
PEx	Structure
204	
205	

TABLE 47

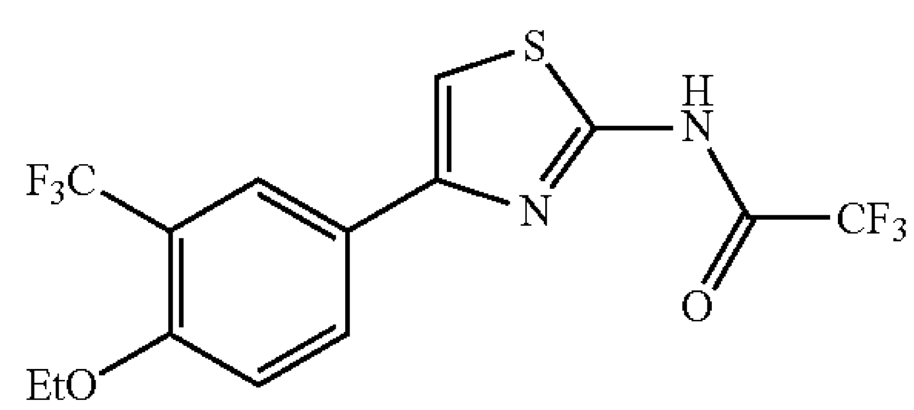
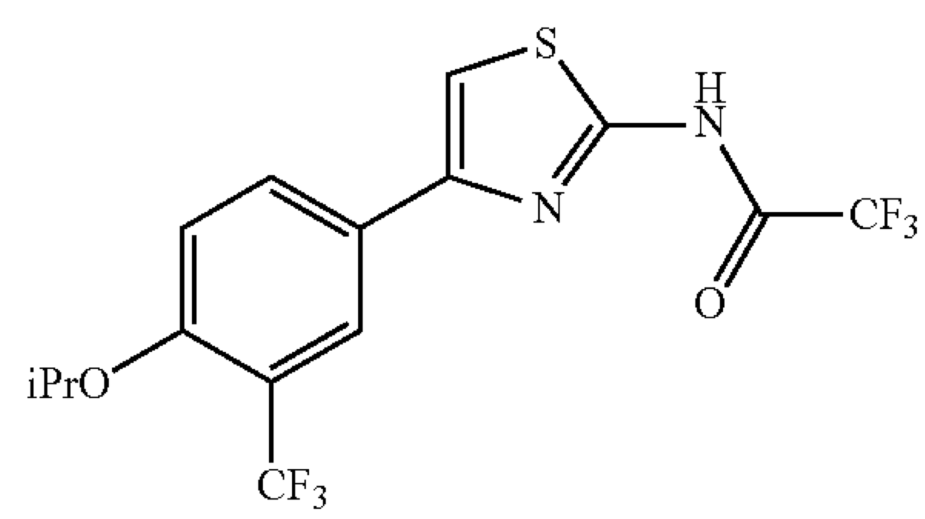
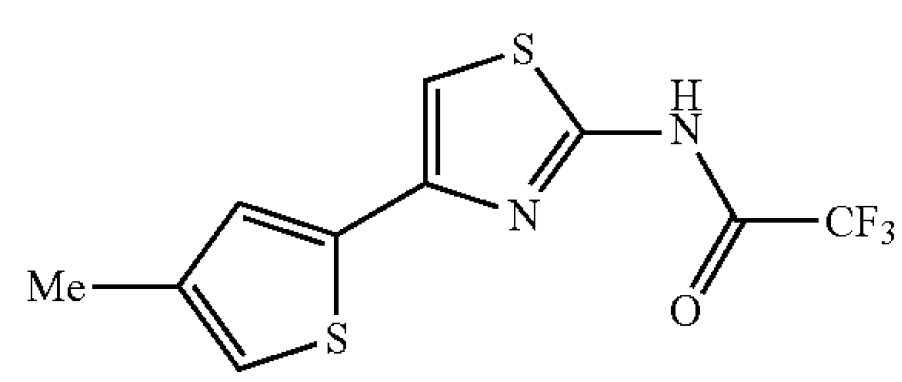
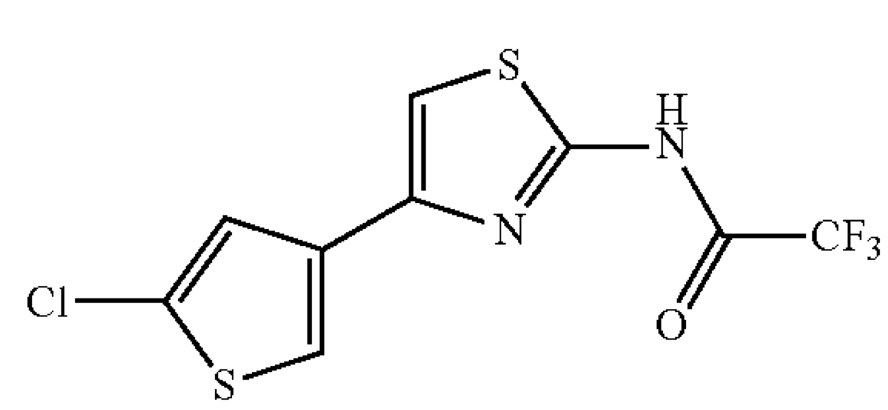
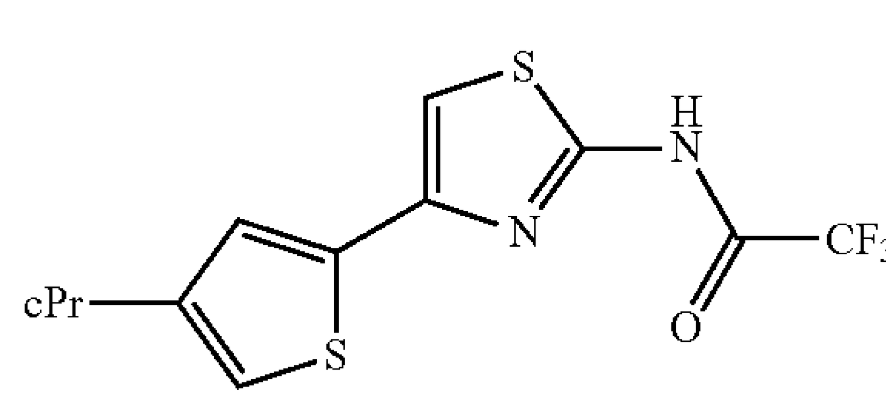
PEx	Structure
206	
207	
208	
209	
210	

TABLE 47-continued

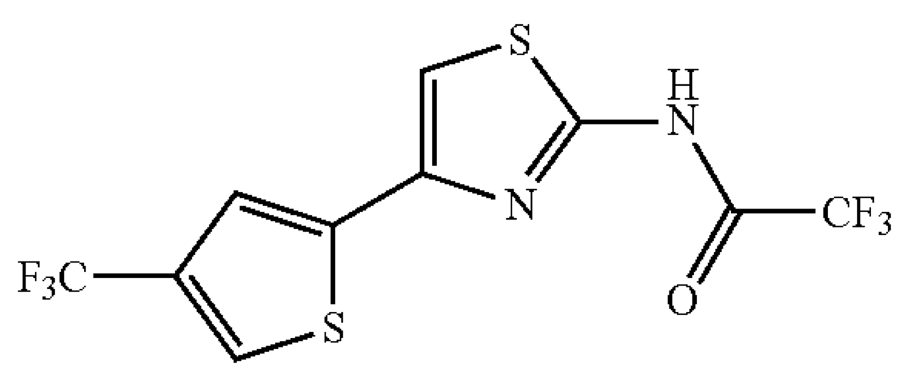
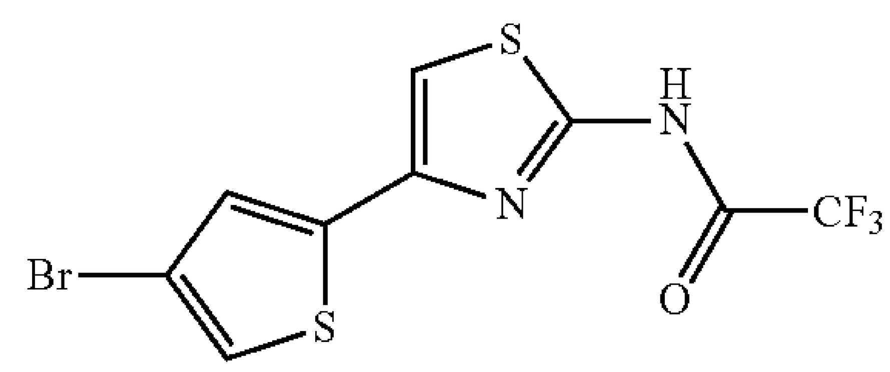
PEx	Structure
211	
212	

TABLE 48

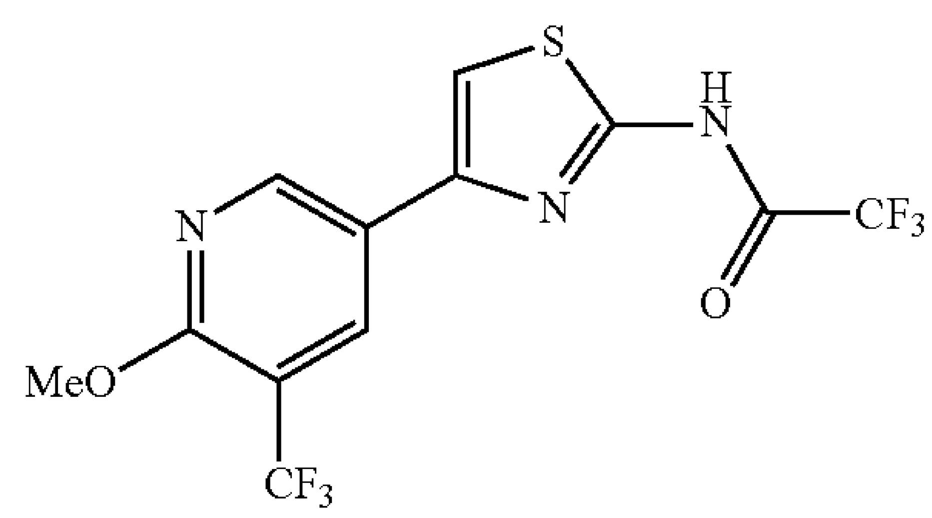
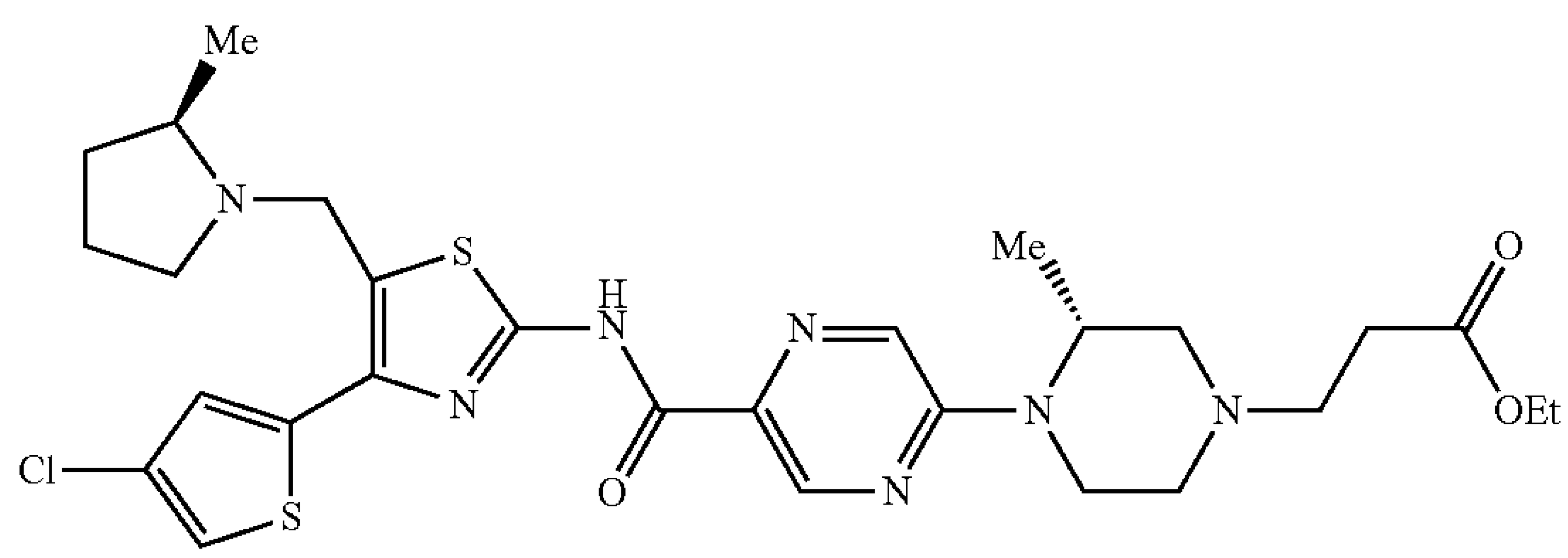
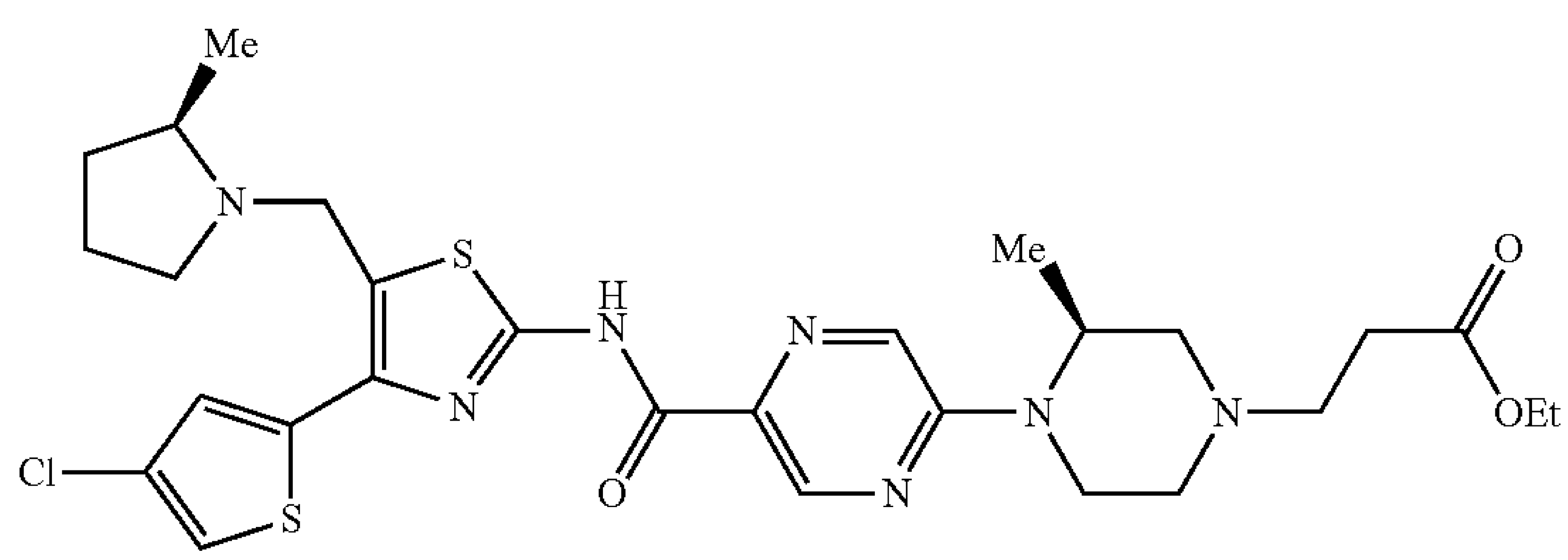
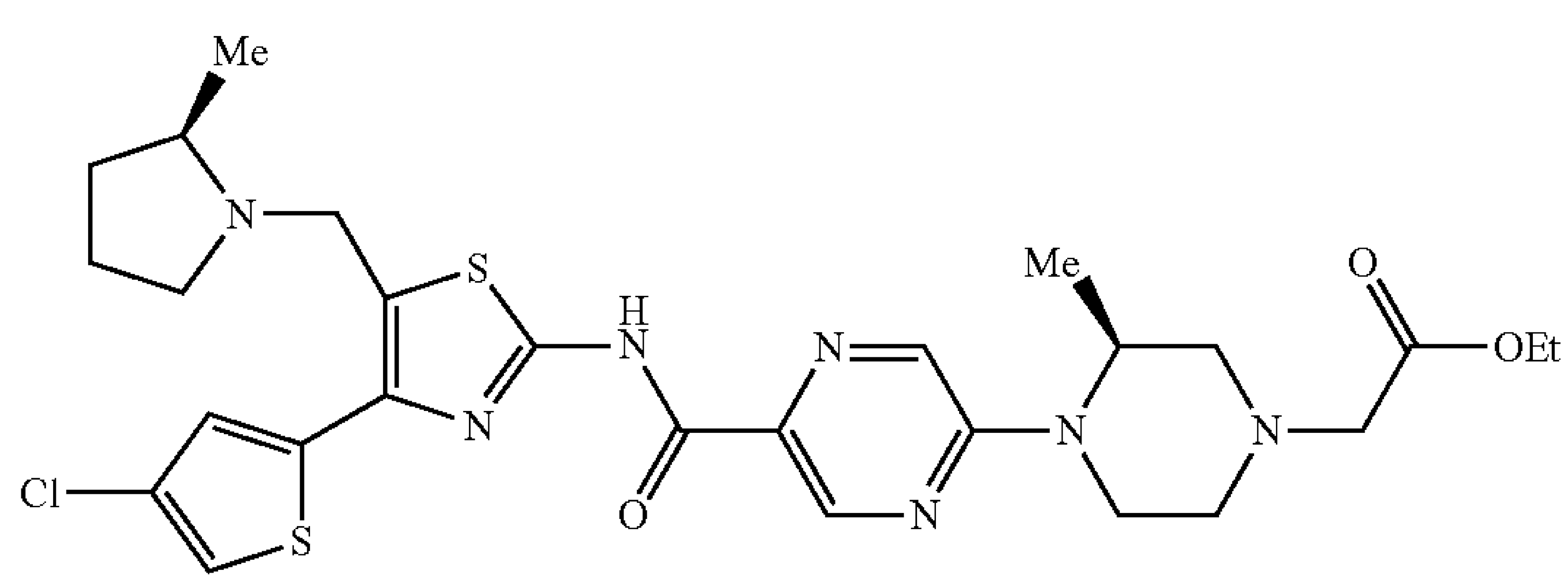
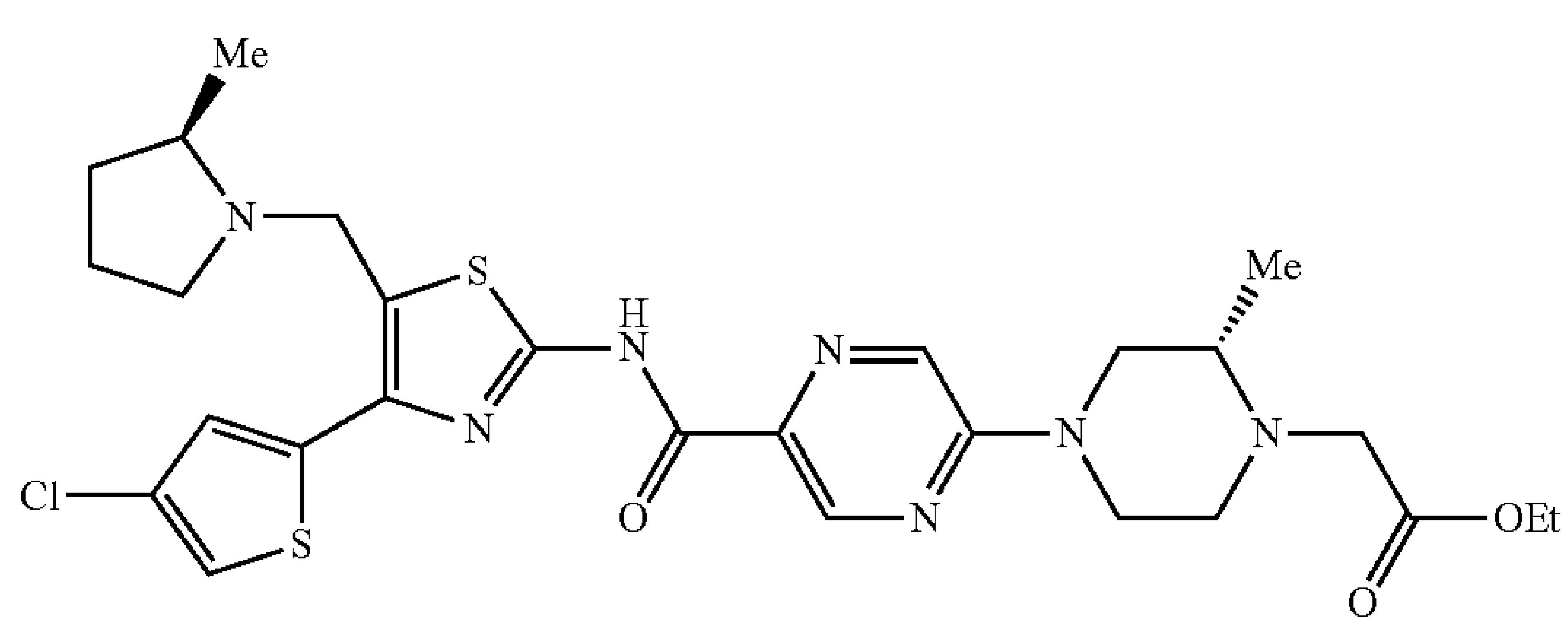
PEx	Structure
213	
214	
215	
216	
217	

TABLE 49

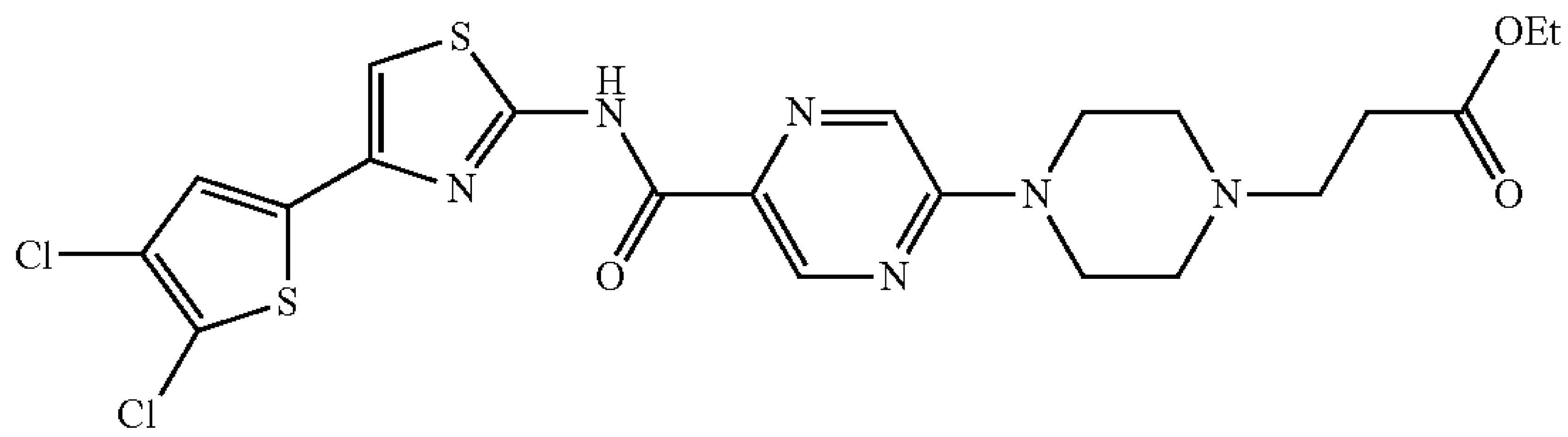
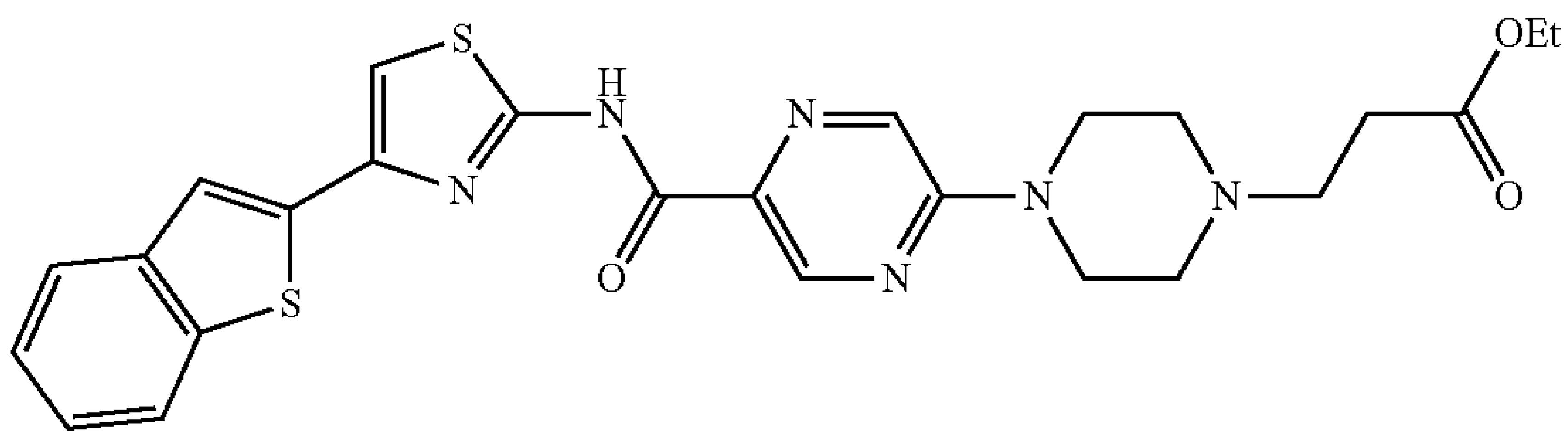
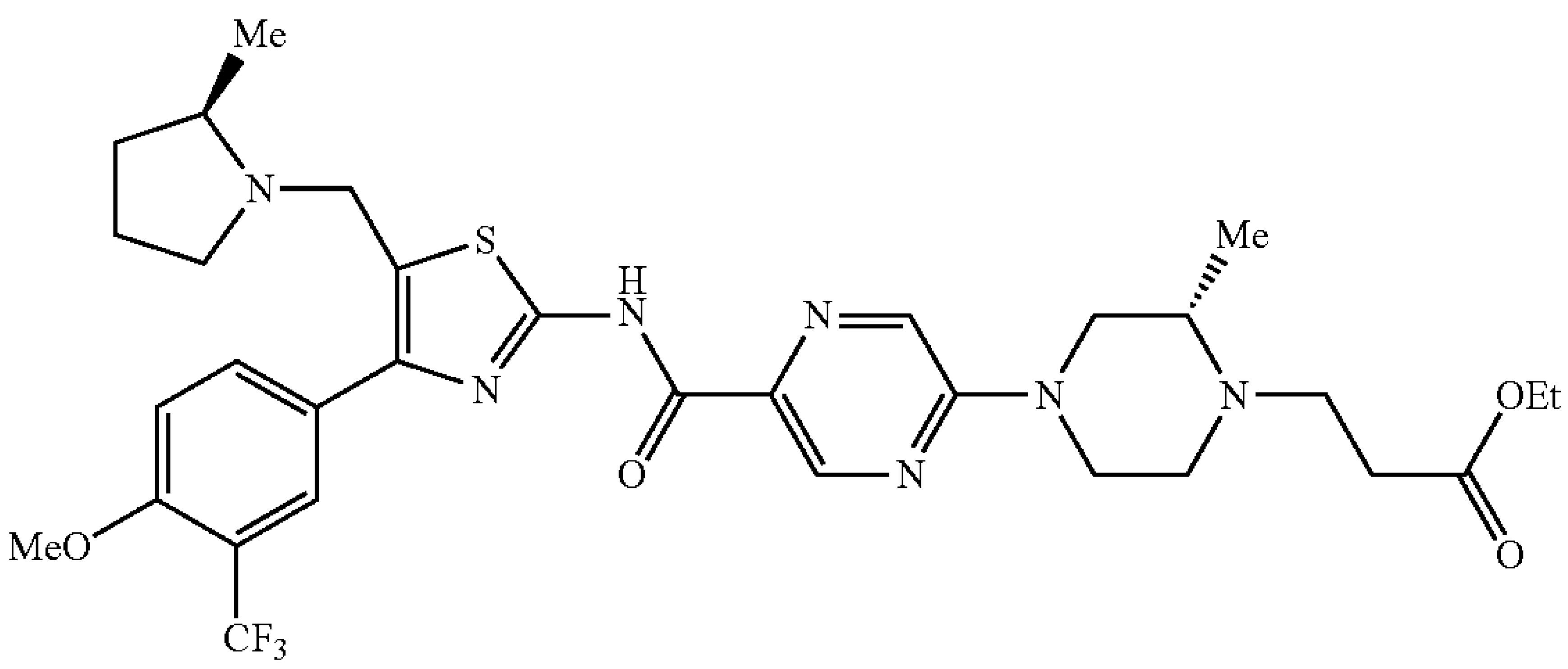
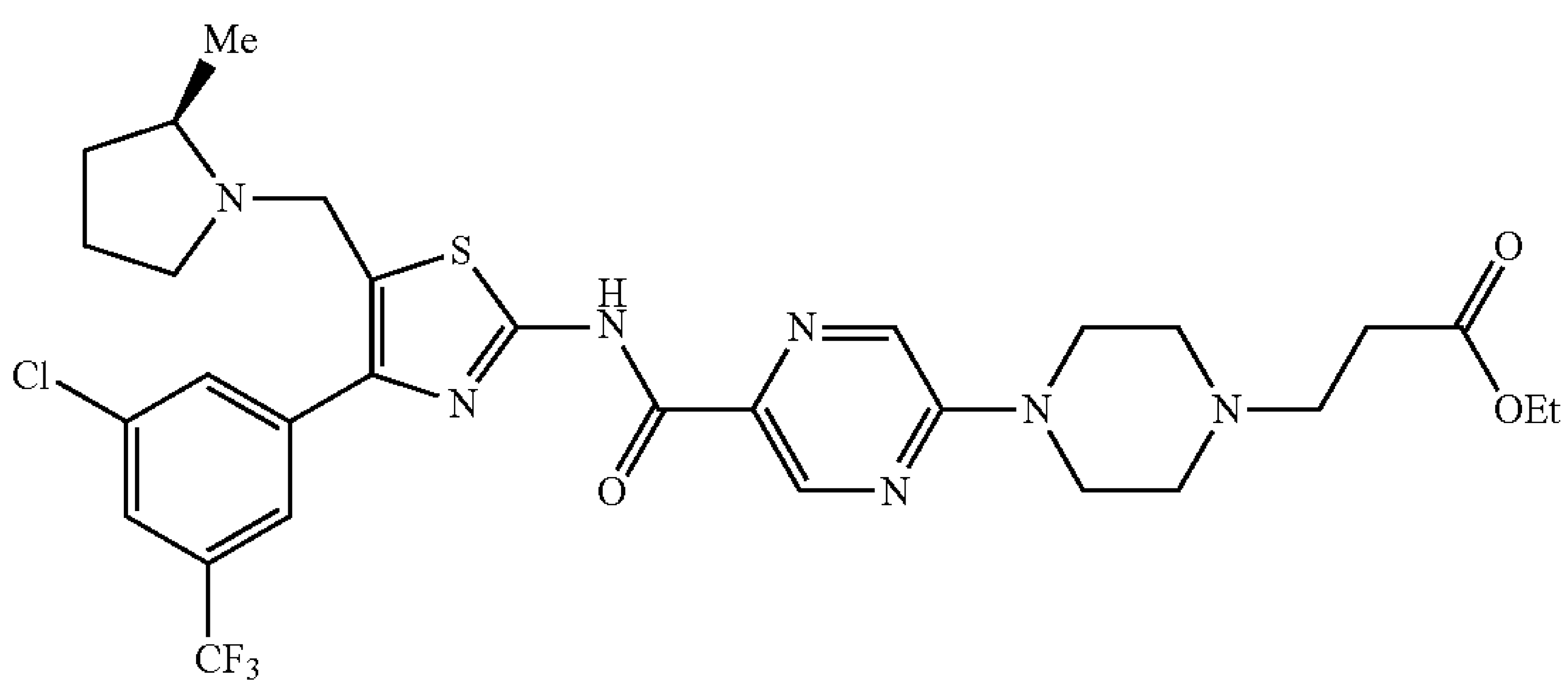
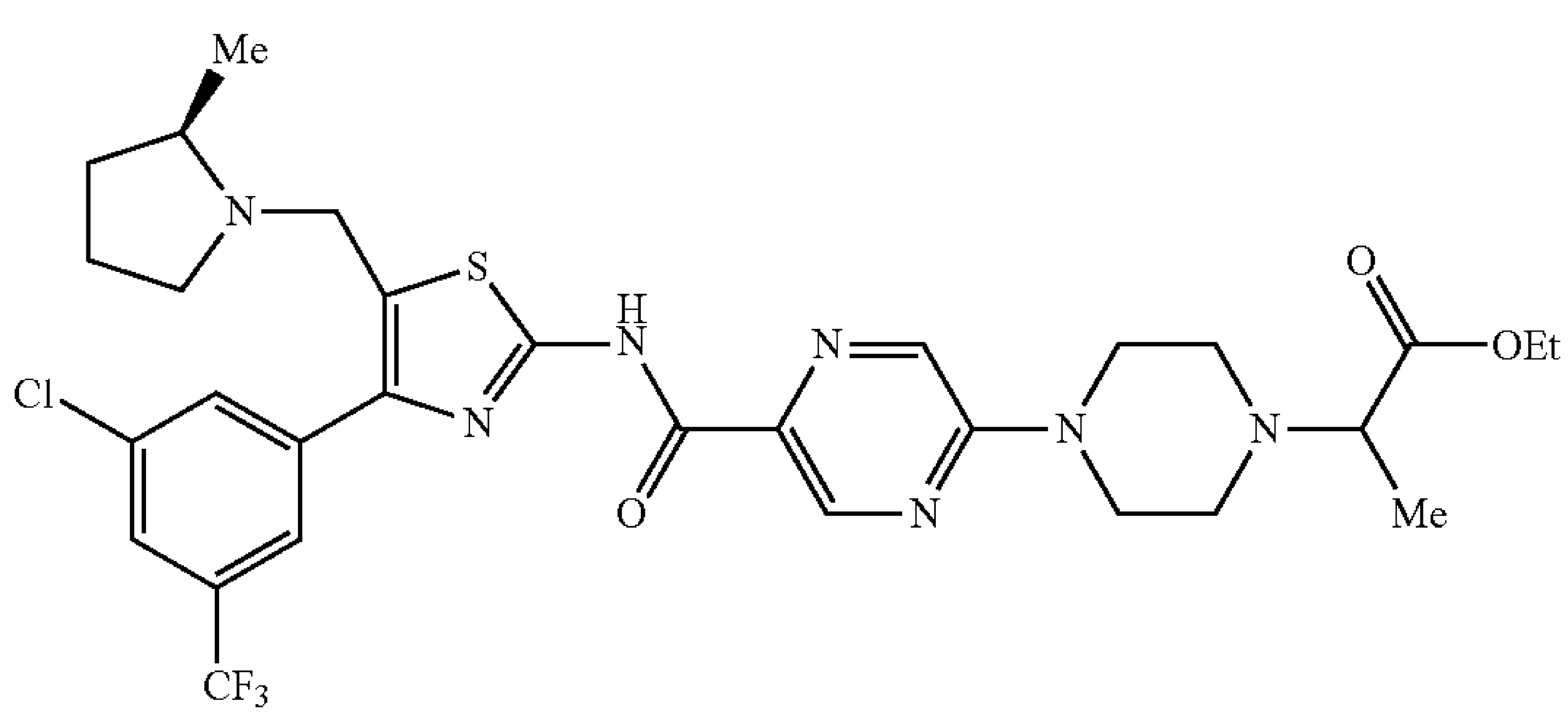
PEx	Structure
218	
219	
220	
221	
222	

TABLE 50

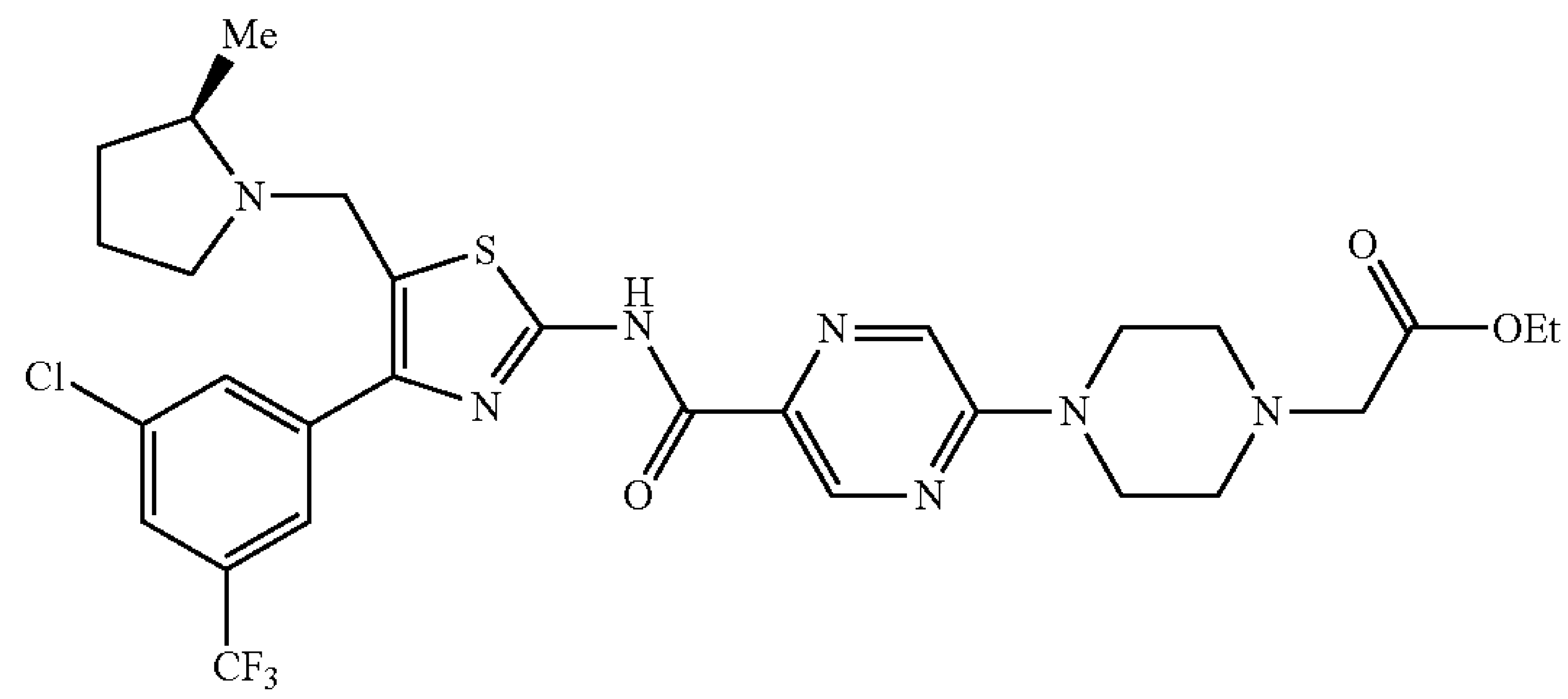
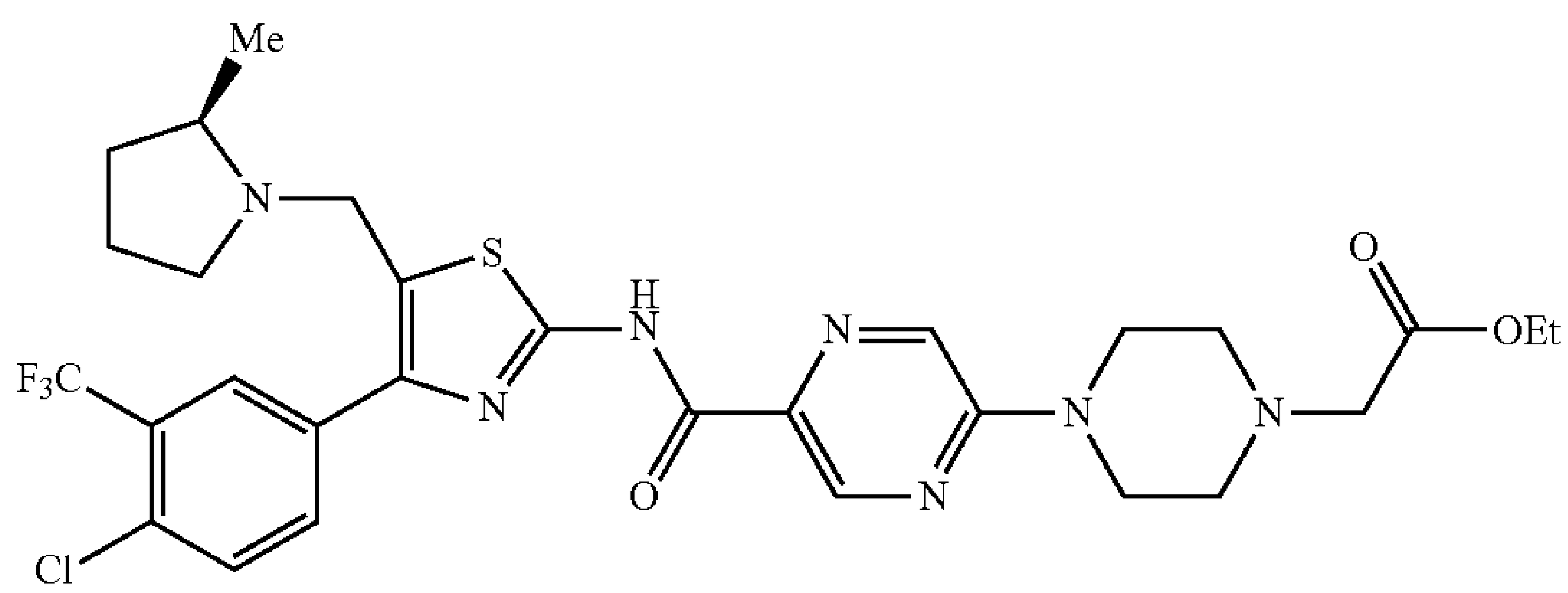
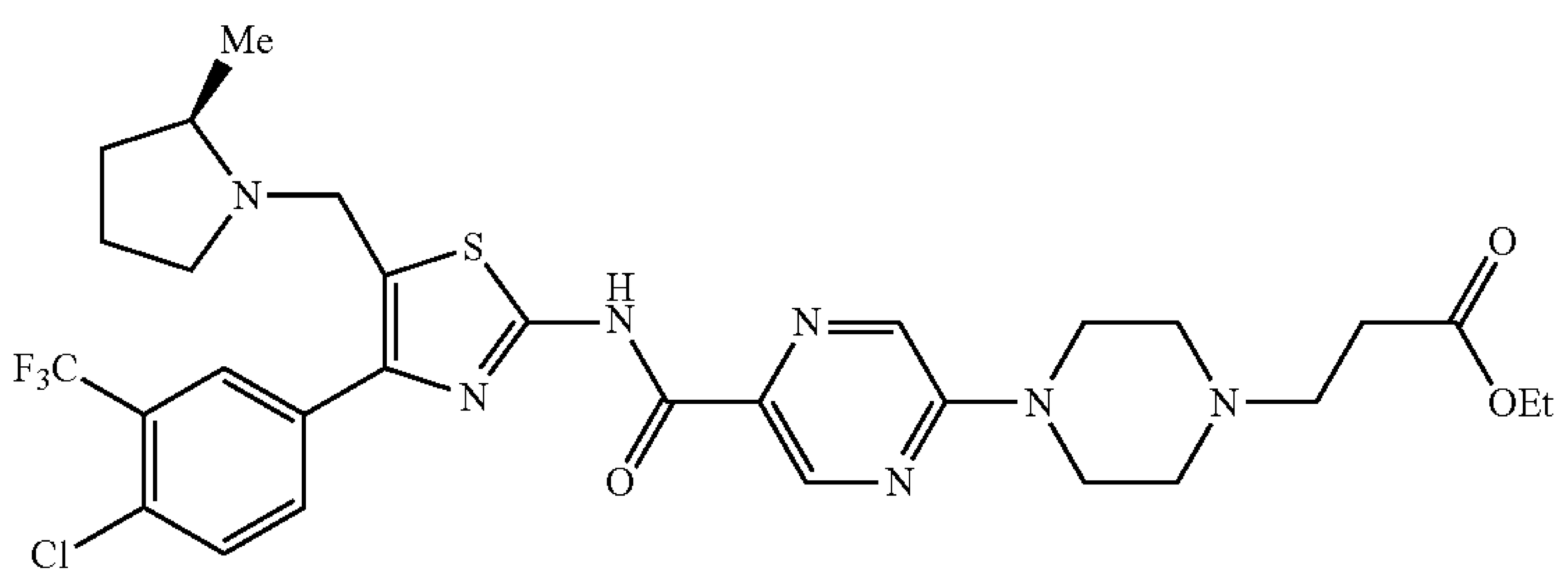
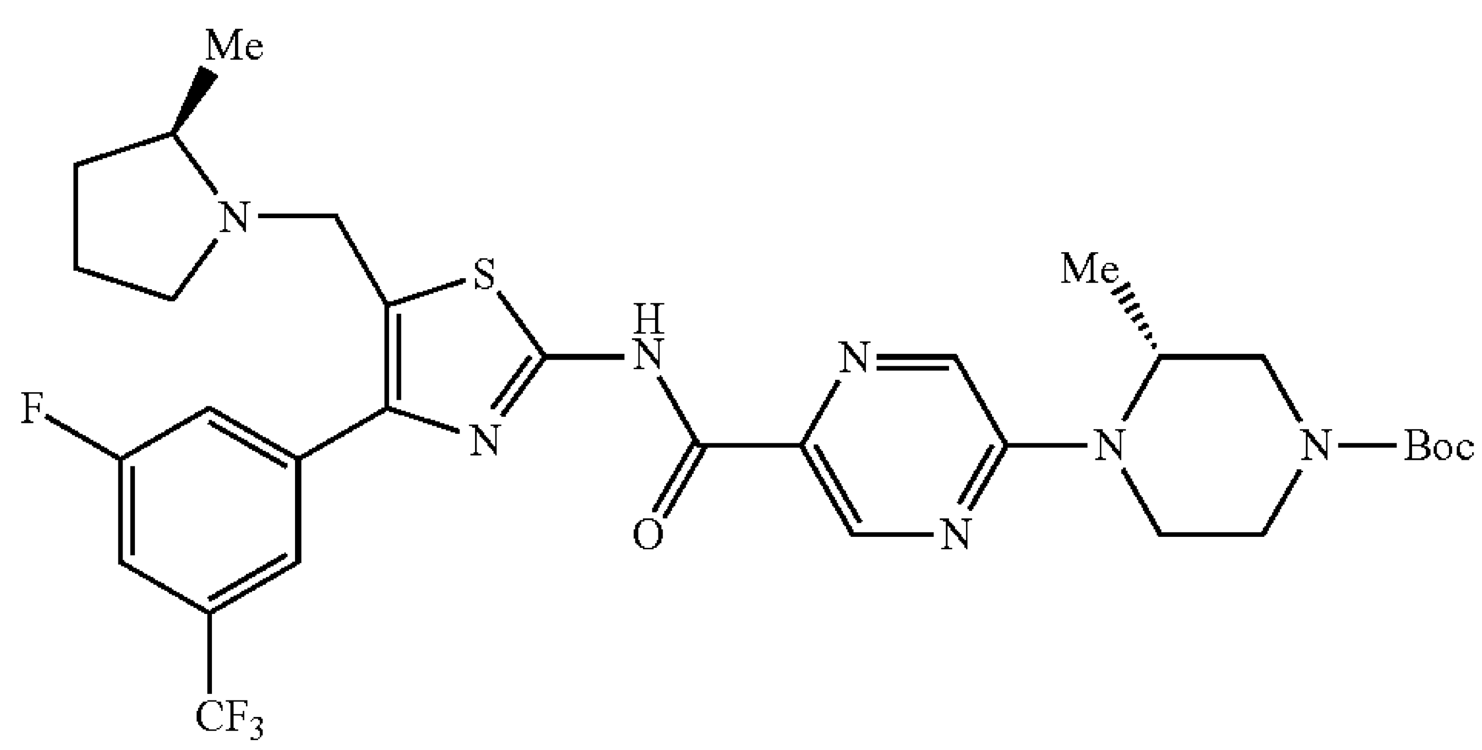
PEx	Structure
223	
224	
225	
226	

TABLE 51

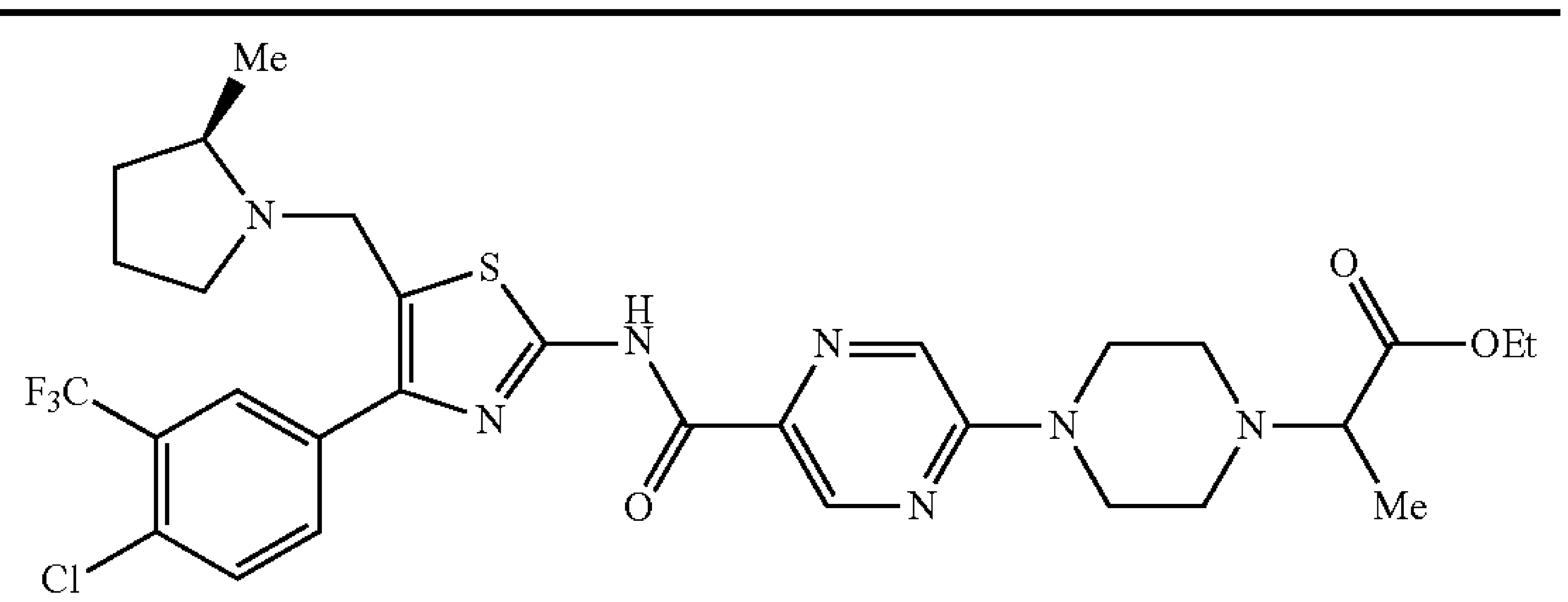
PEx	Structure
227	

TABLE 51-continued

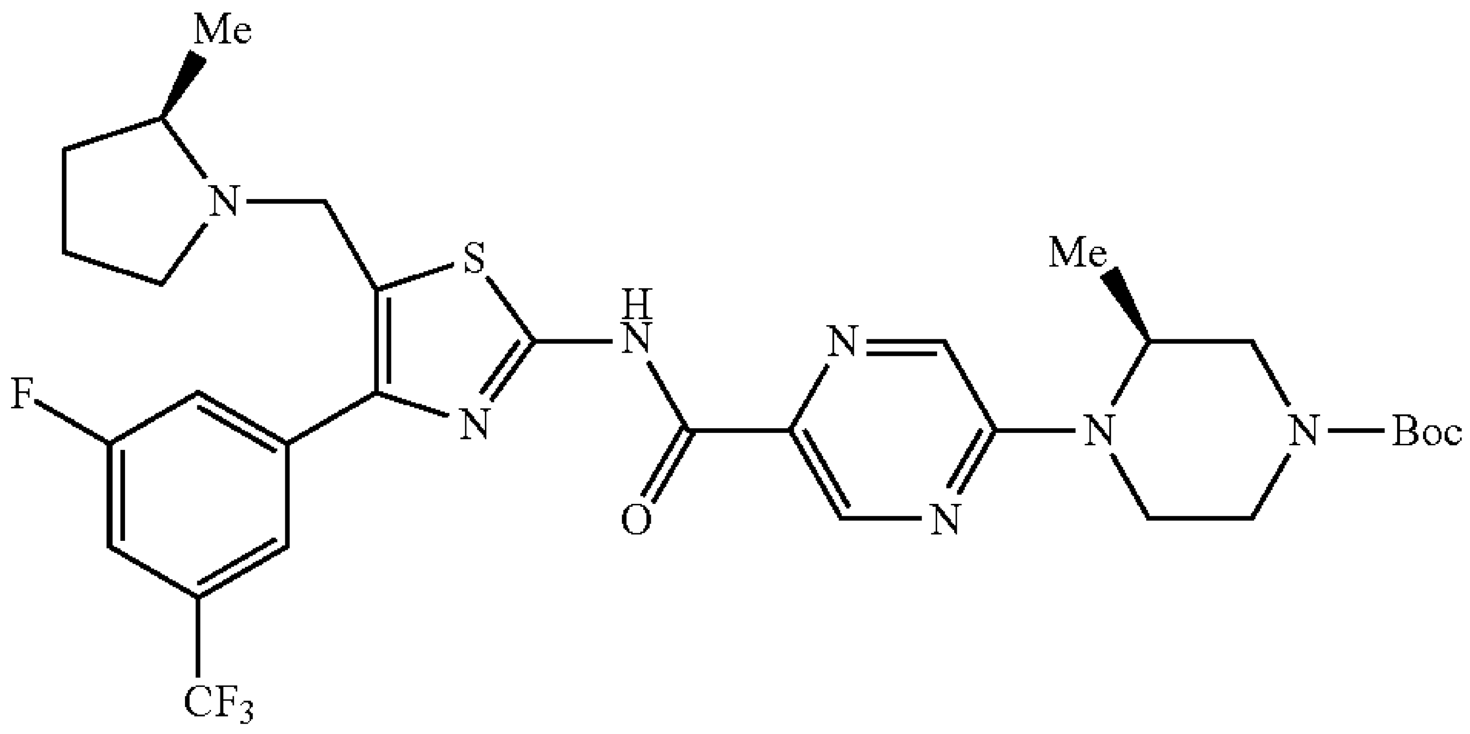
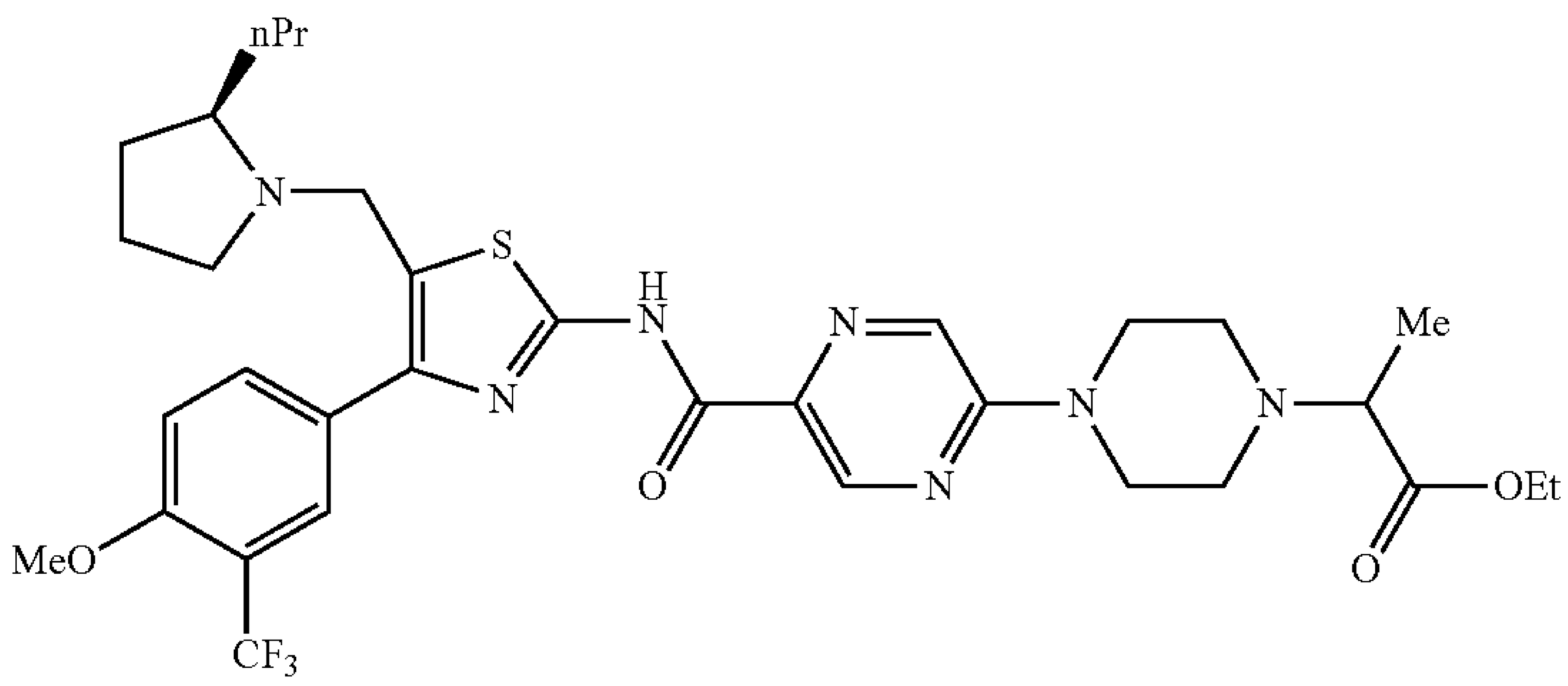
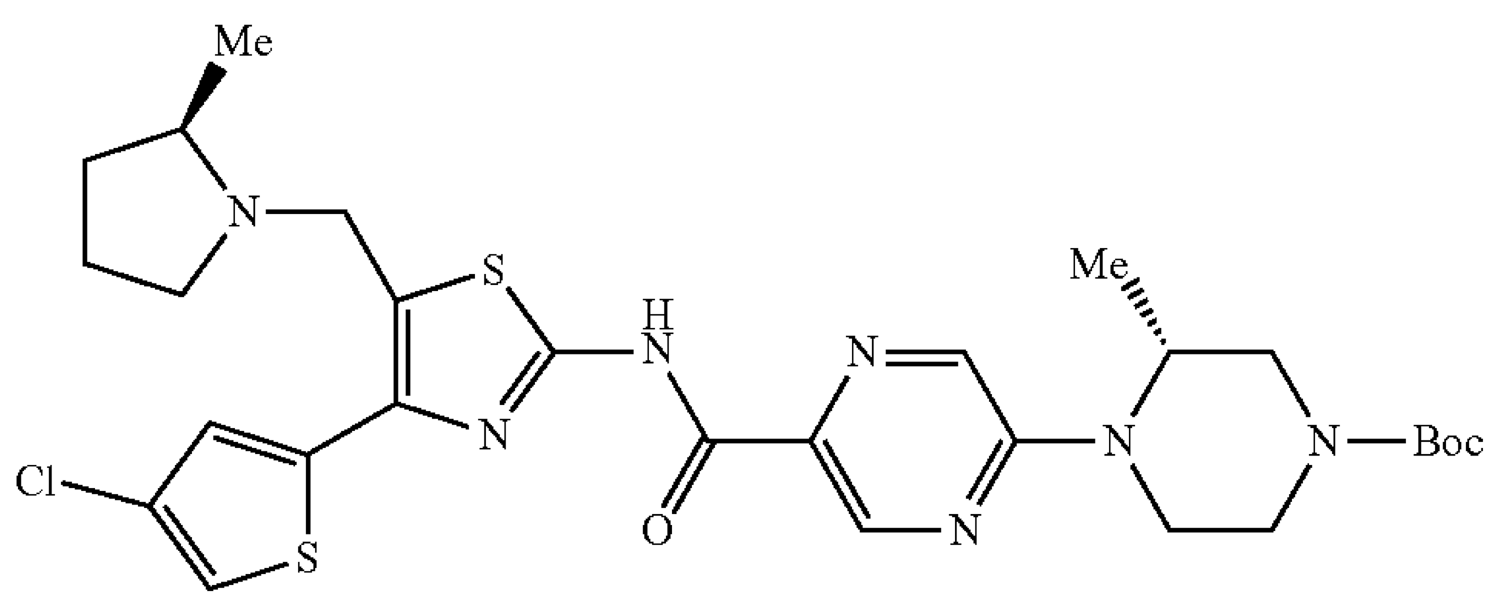
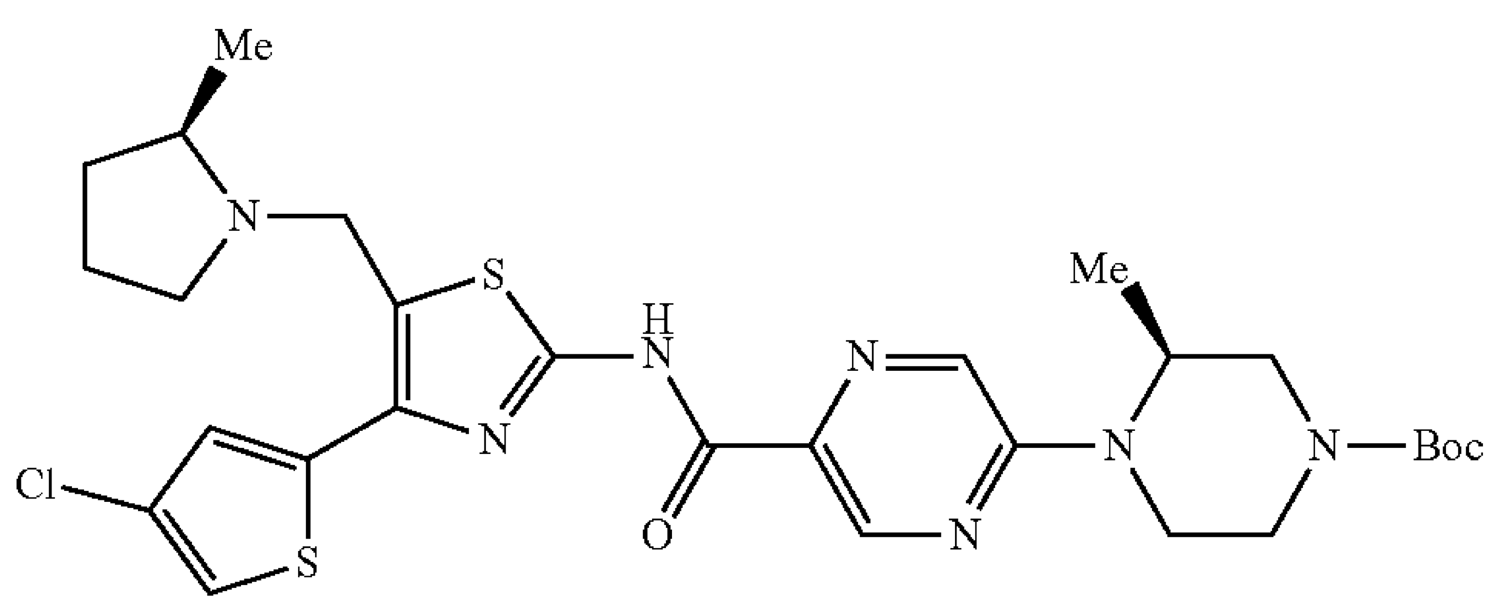
PEx	Structure
228	
229	
230	
231	

TABLE 52

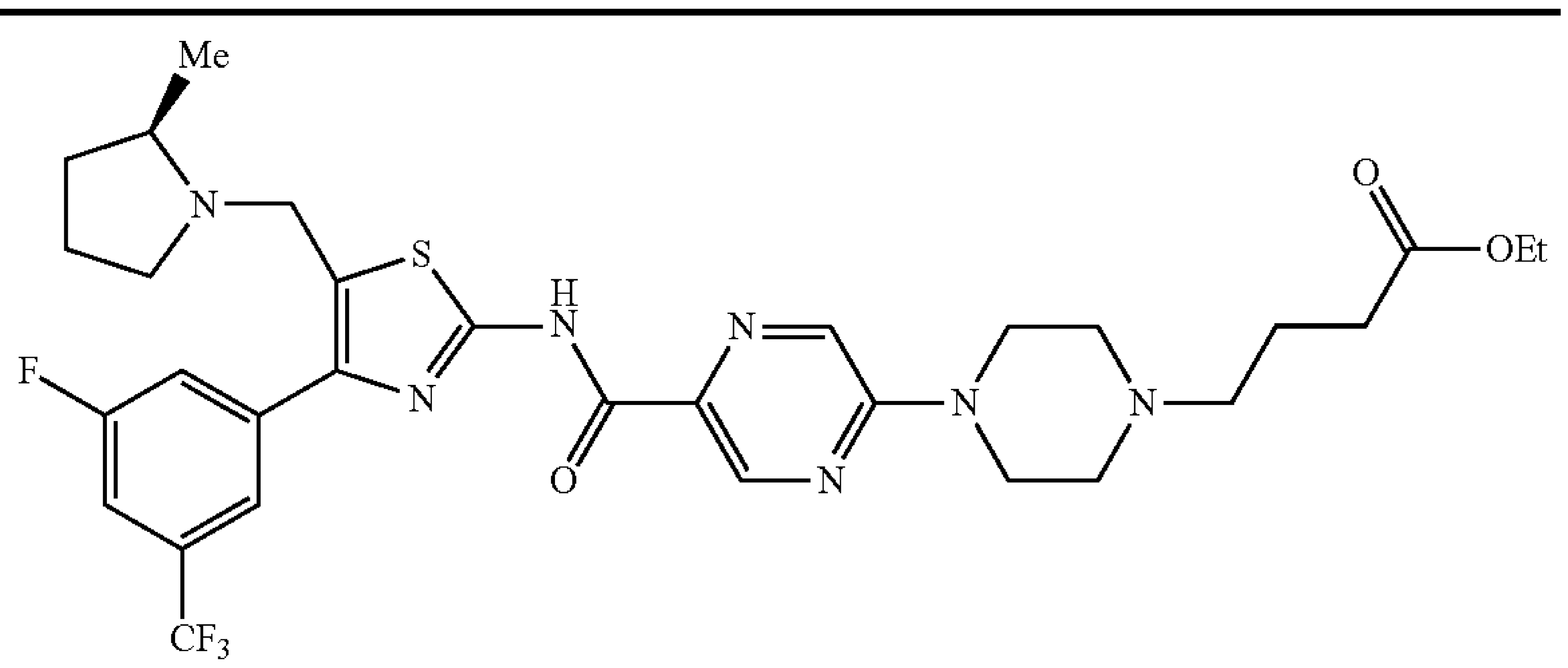
PEx	Structure
232	

TABLE 52-continued

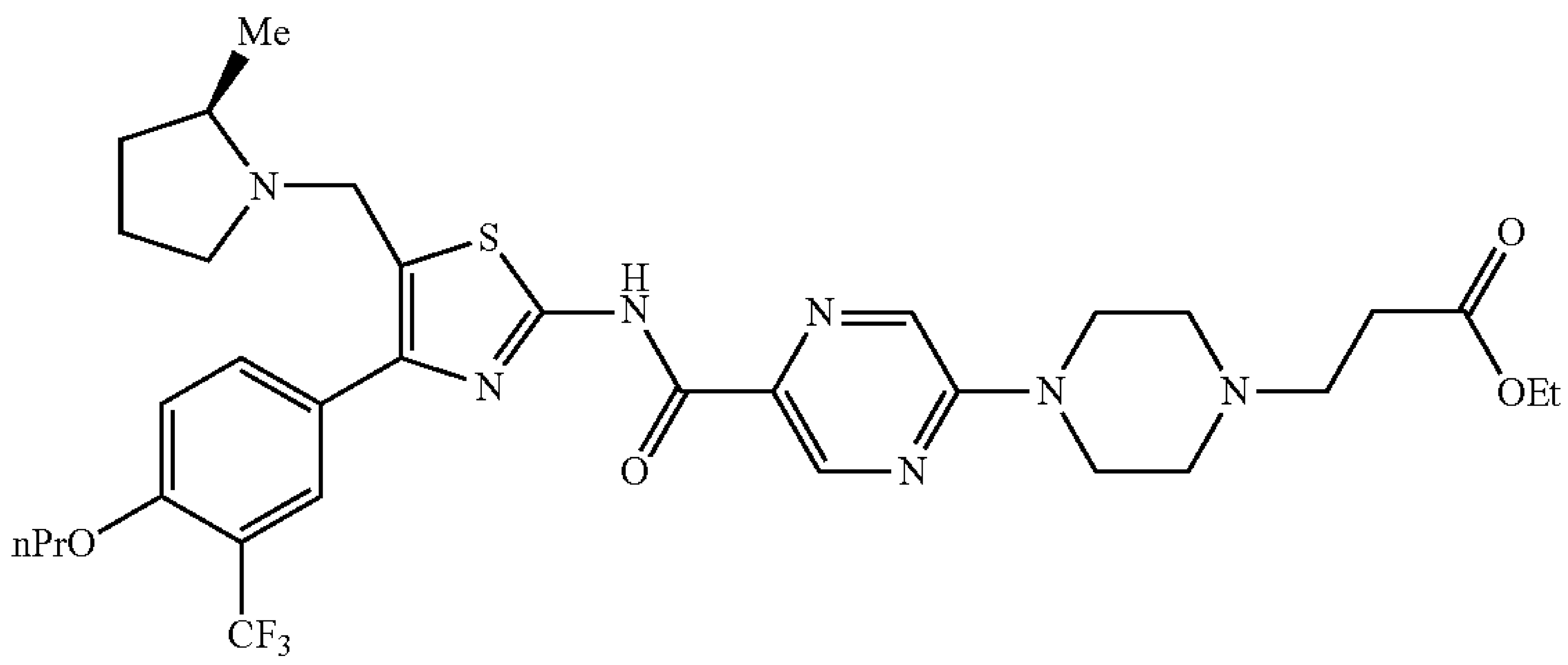
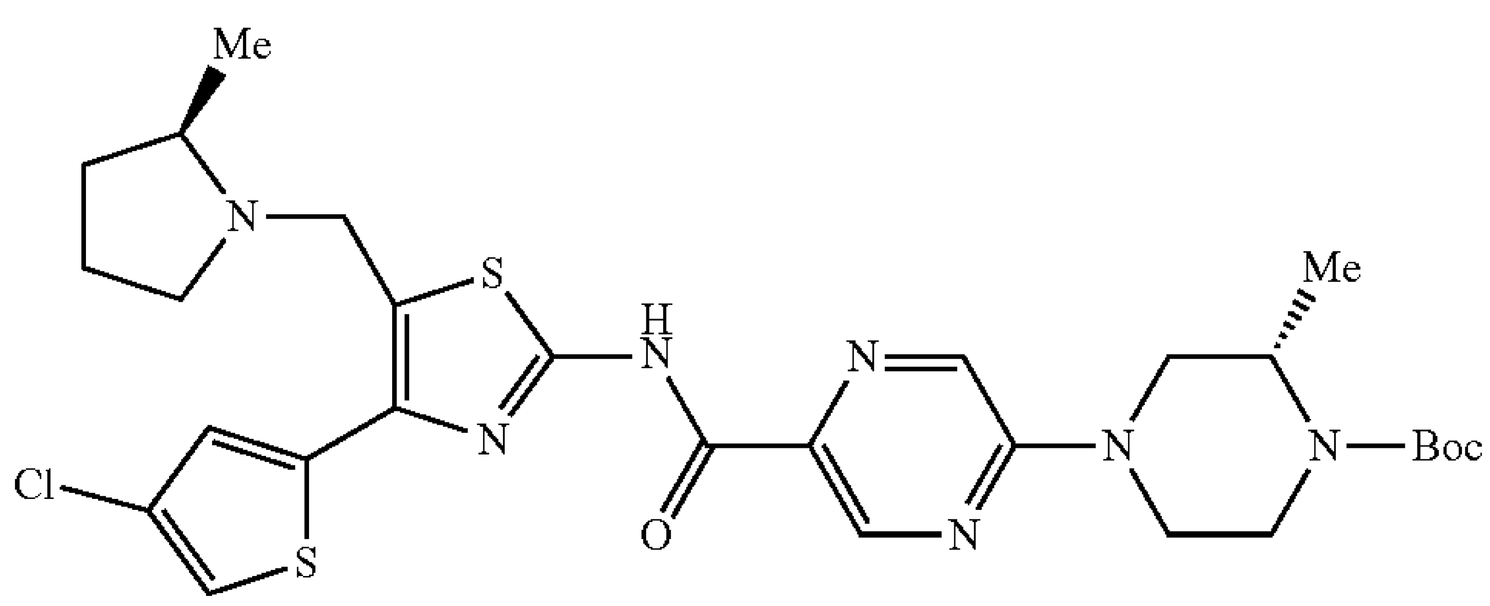
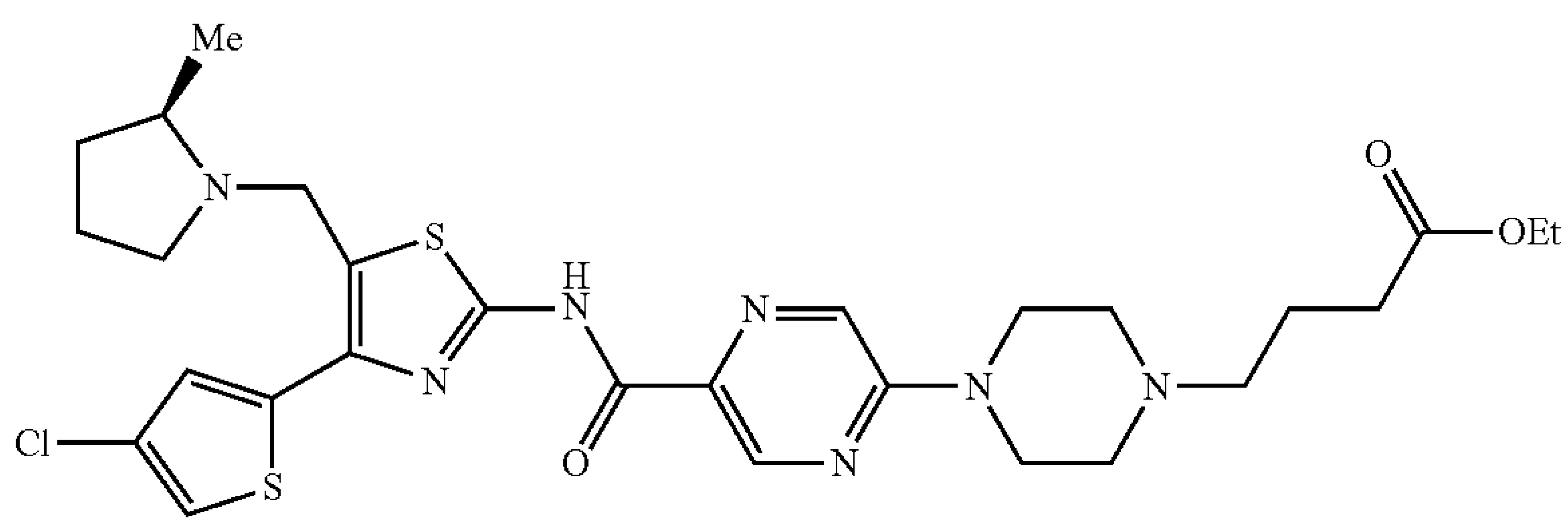
PEx	Structure
233	
234	
235	

TABLE 53

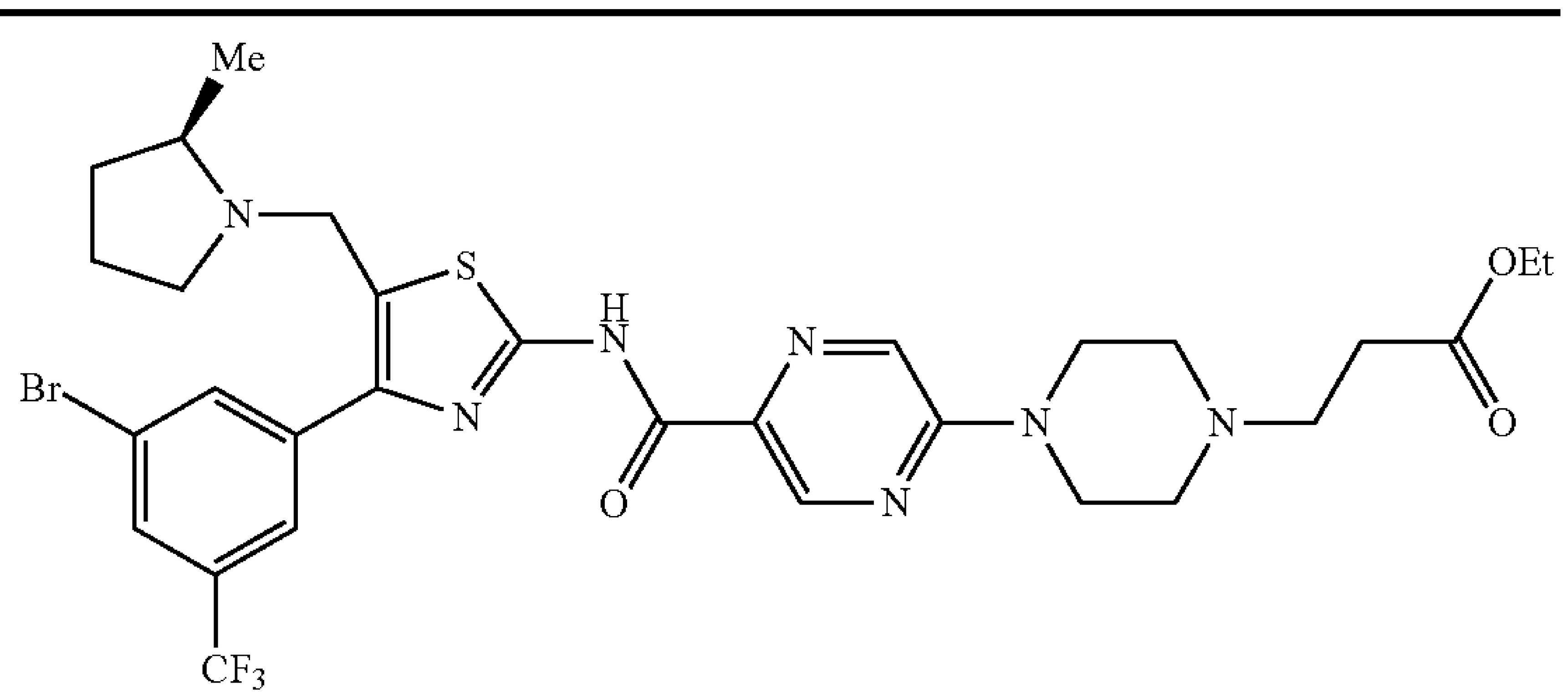
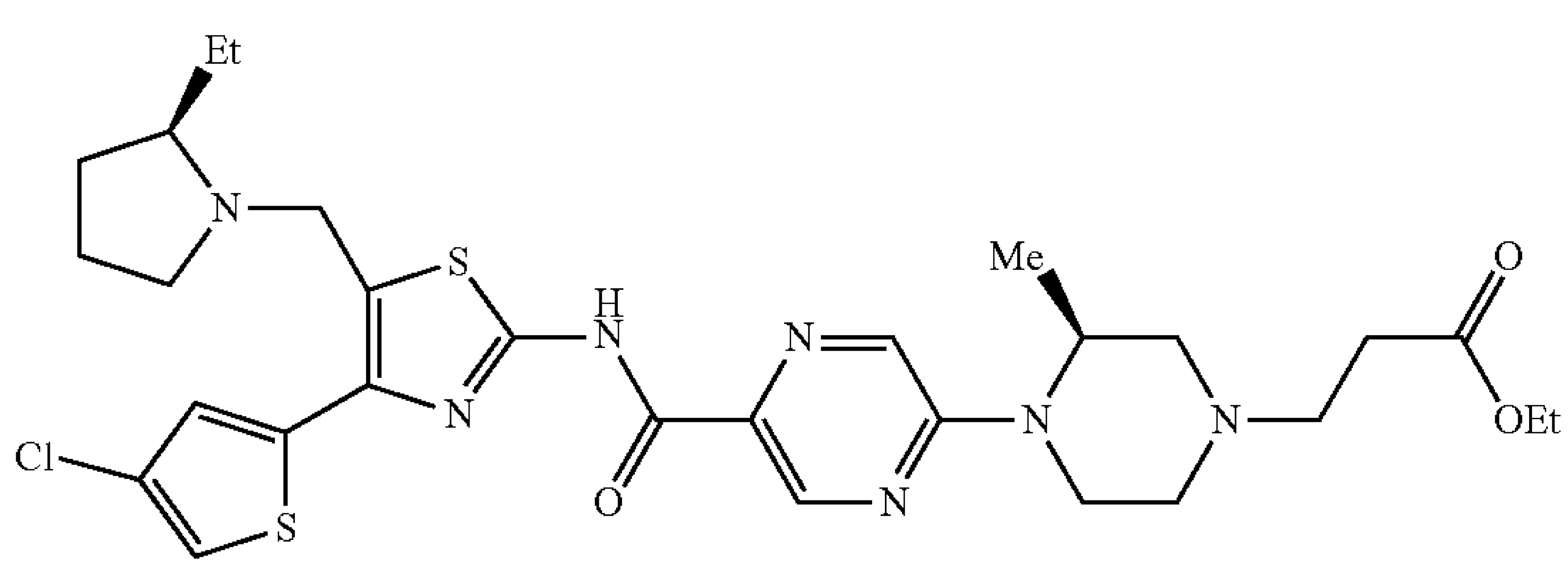
PEx	Structure
236	
237	

TABLE 53-continued

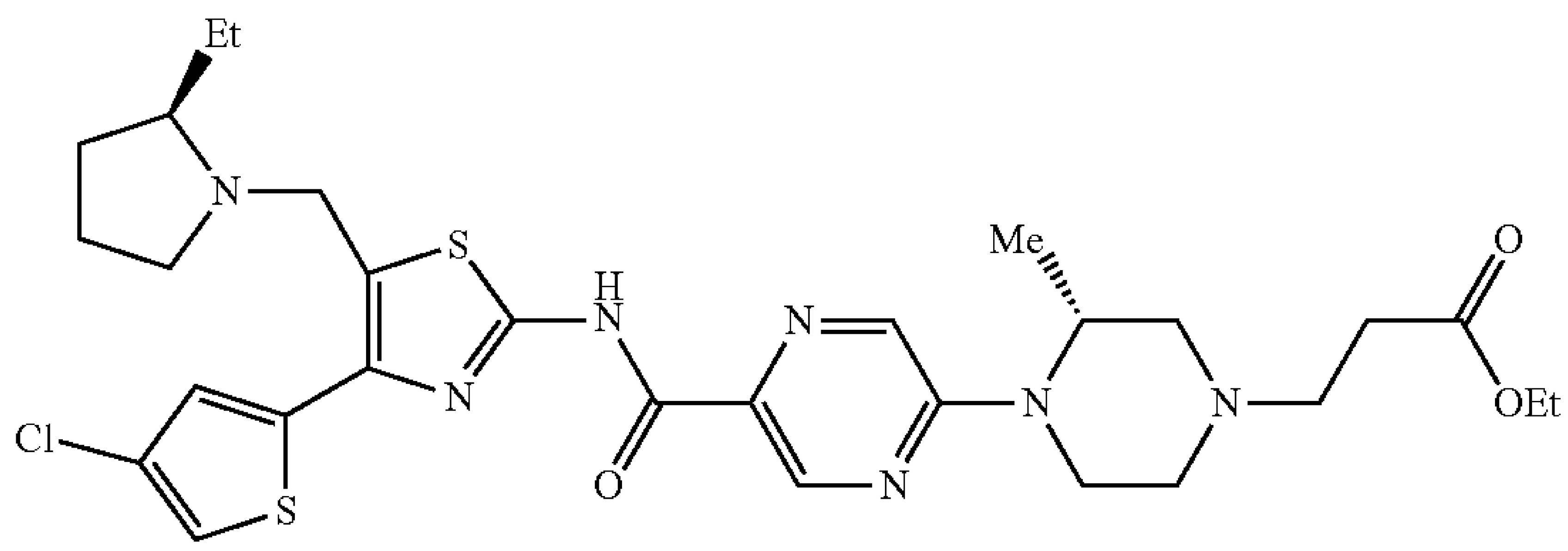
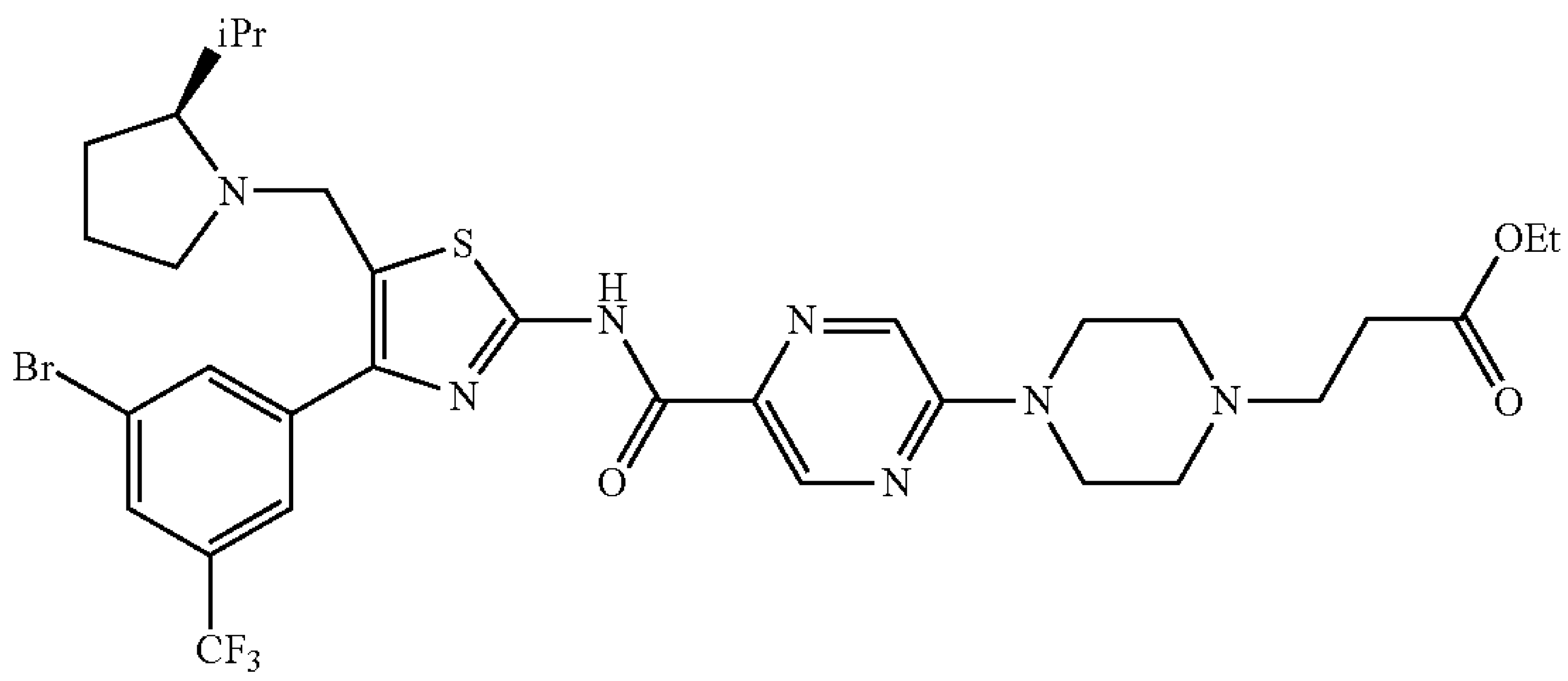
PEx	Structure
238	
239	

TABLE 54

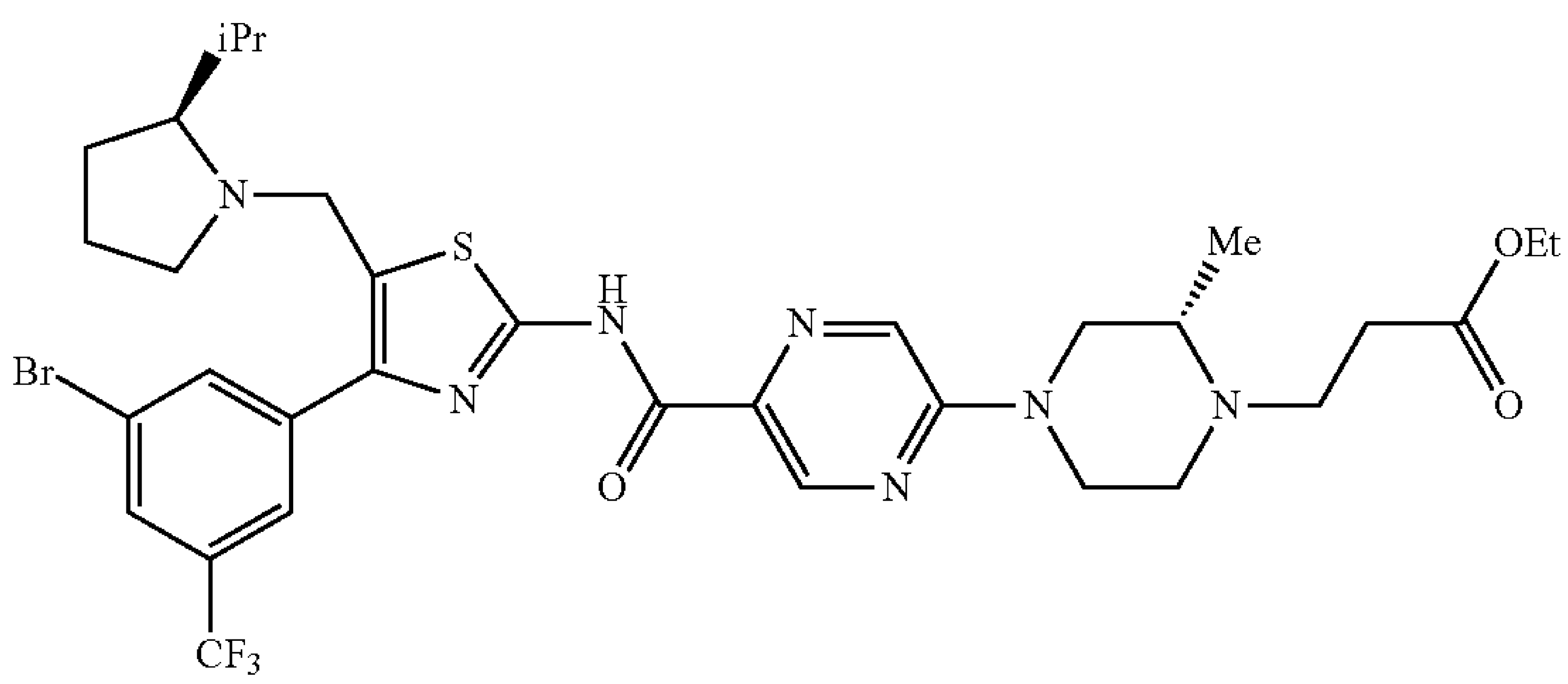
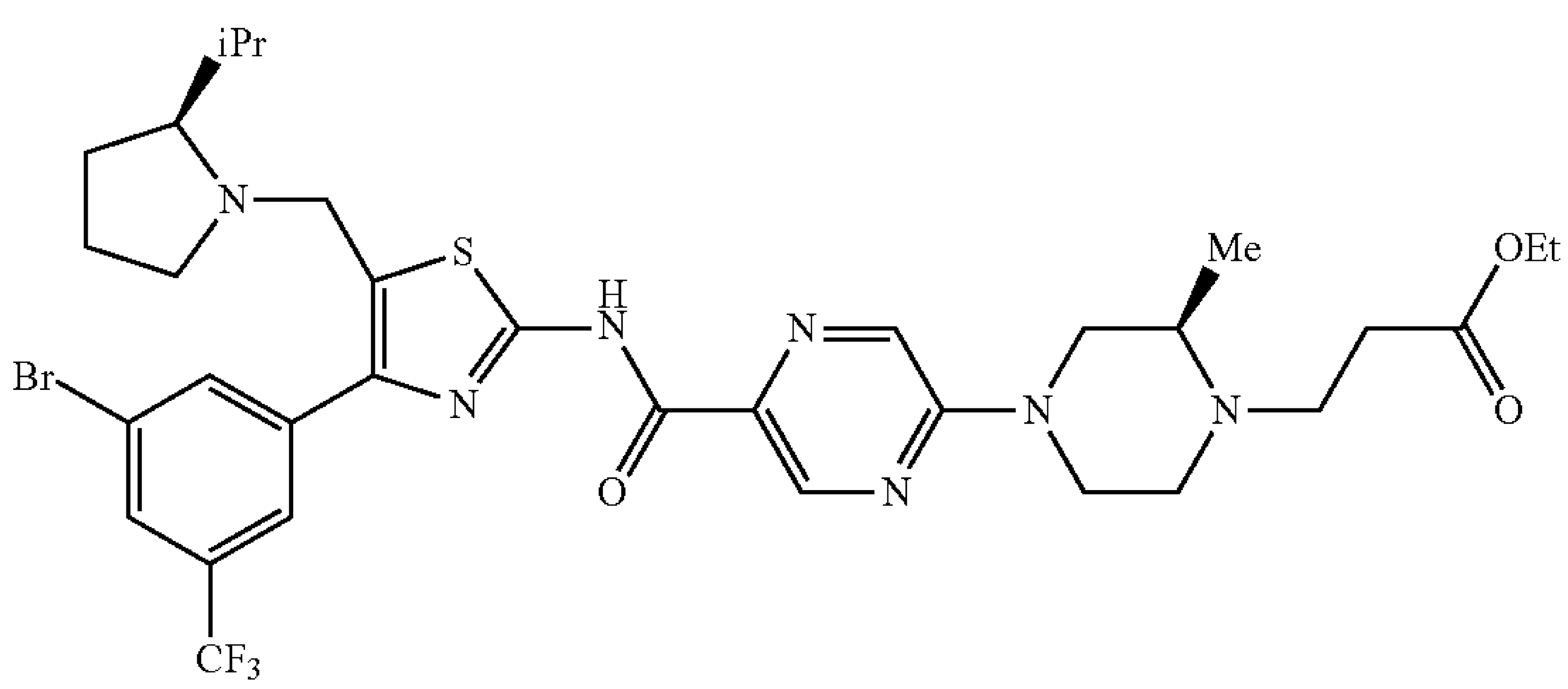
PEx	Structure
240	
241	

TABLE 54-continued

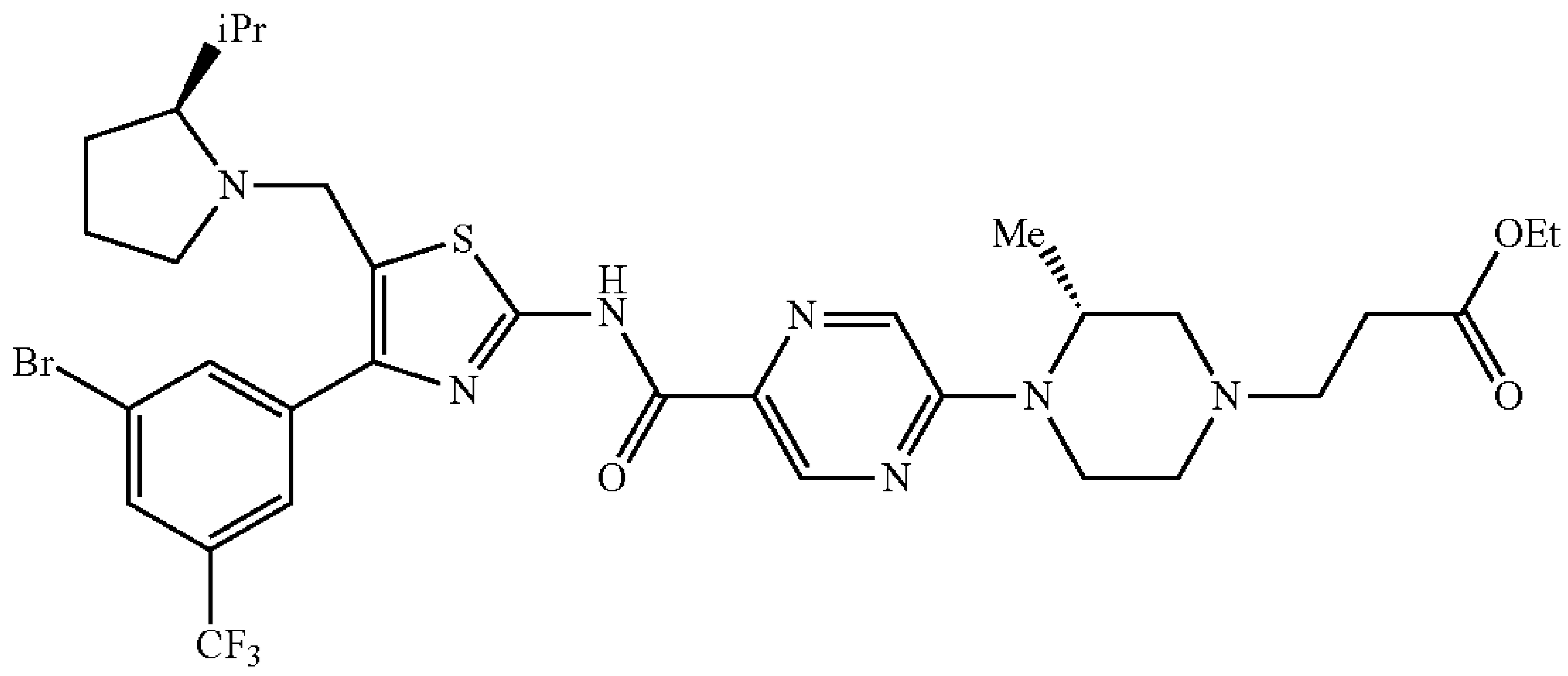
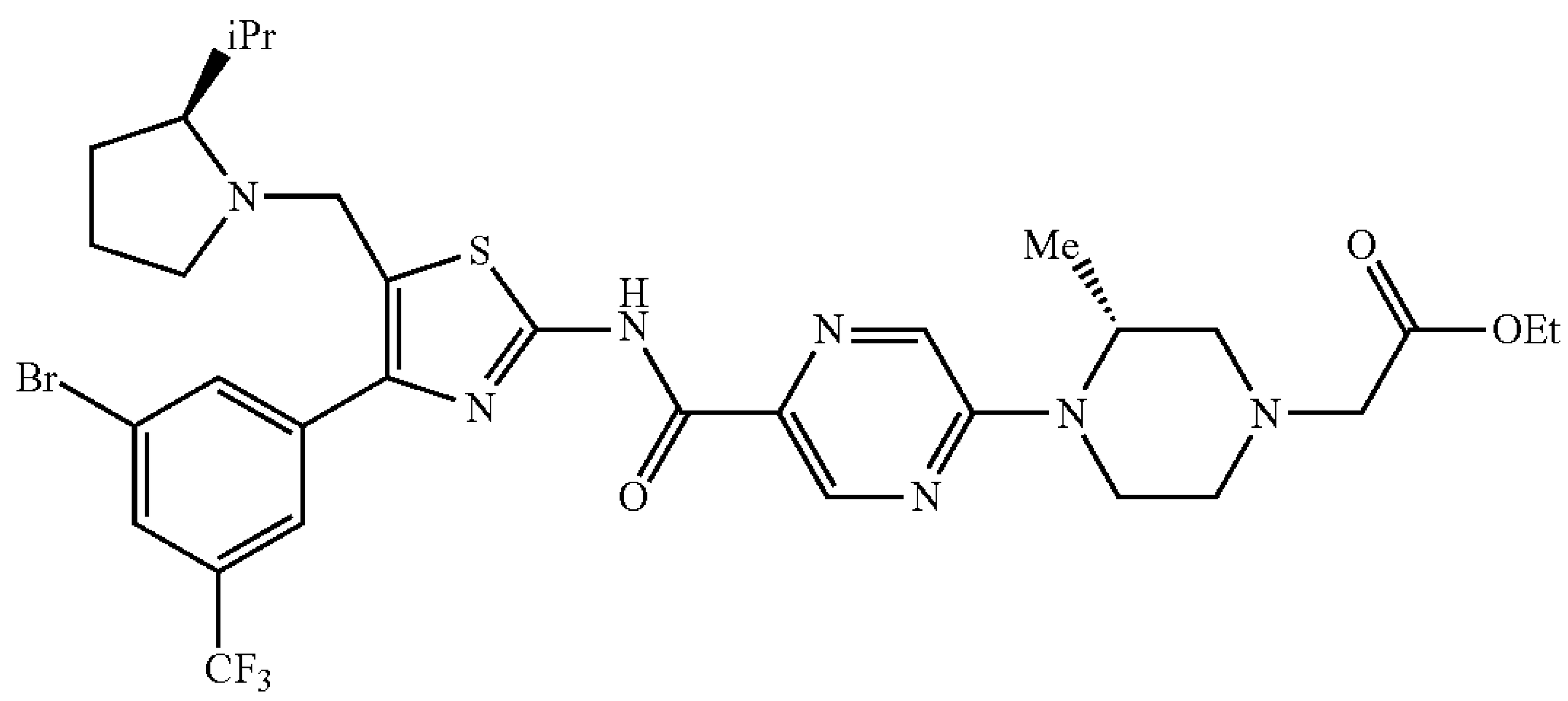
PEx	Structure
242	
243	

TABLE 55

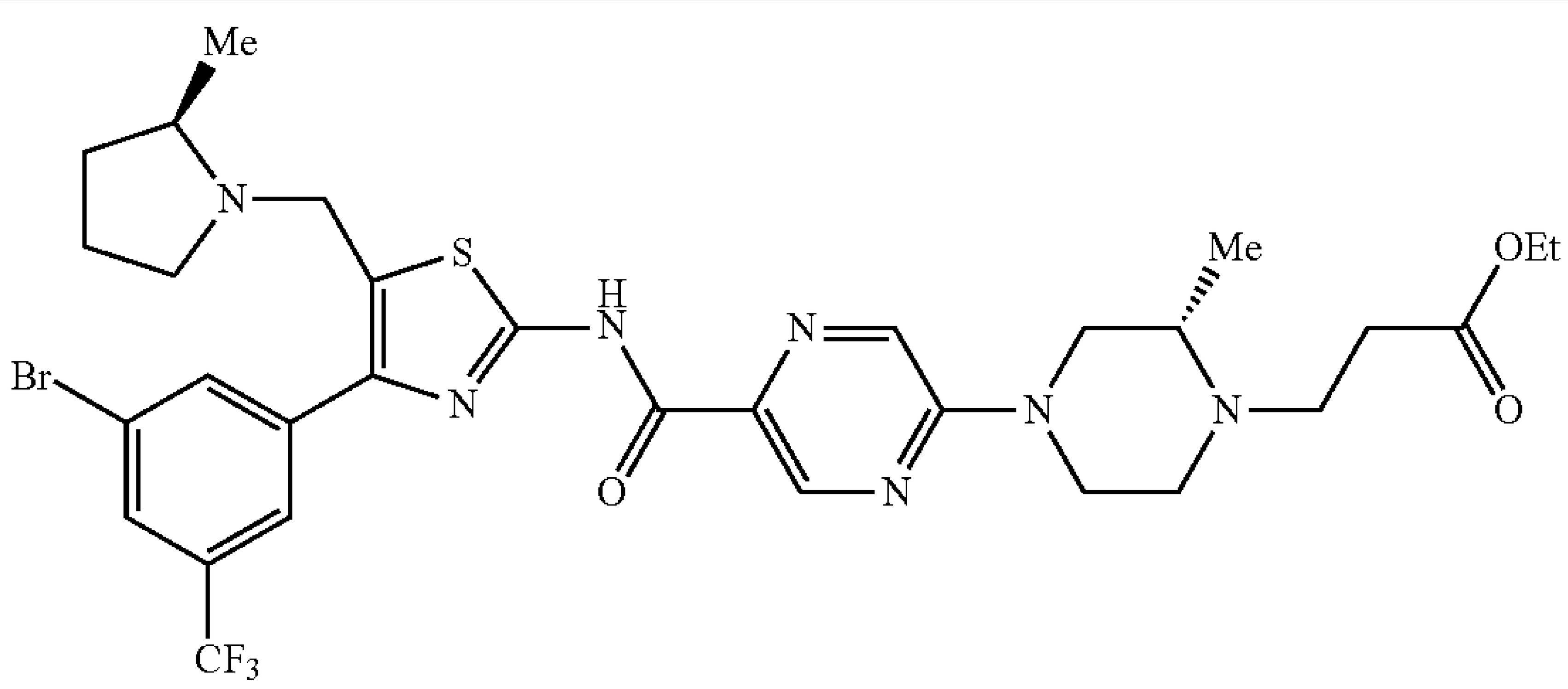
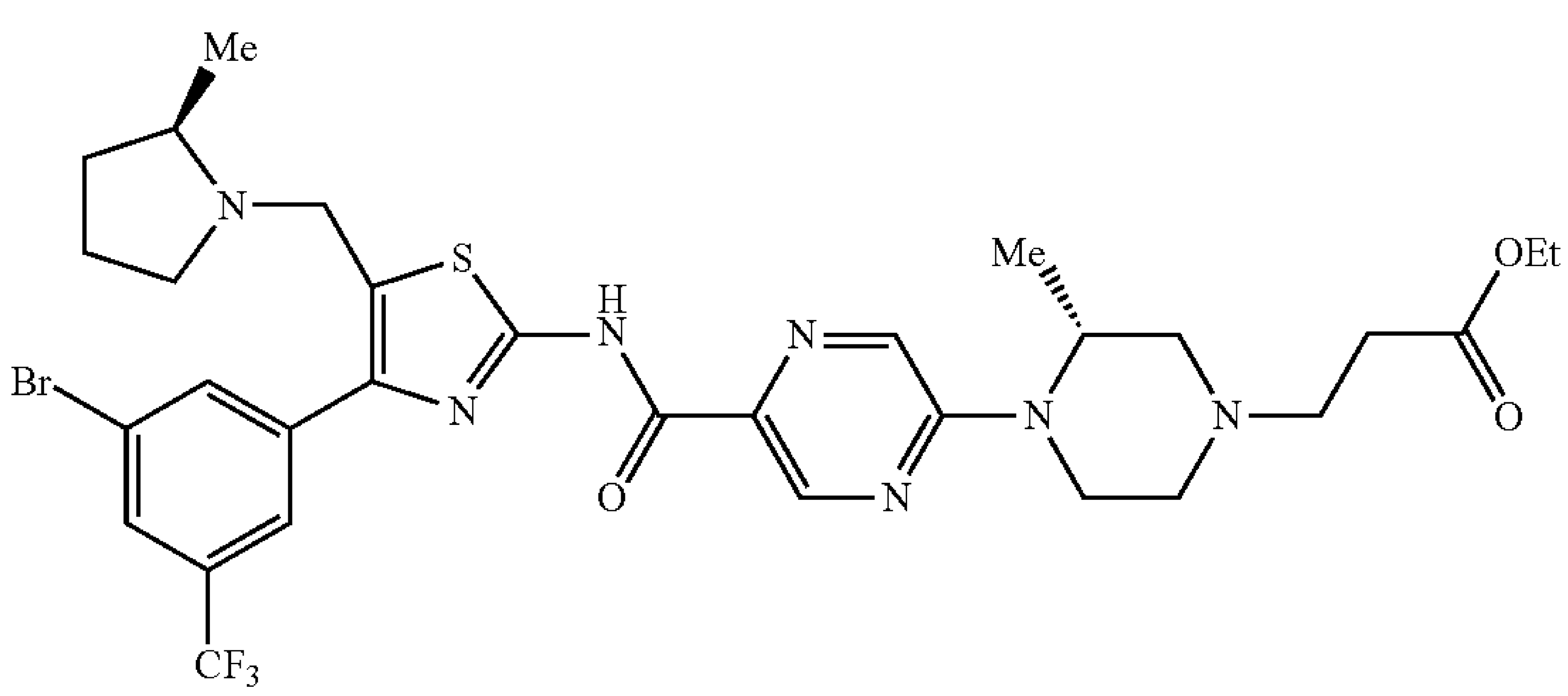
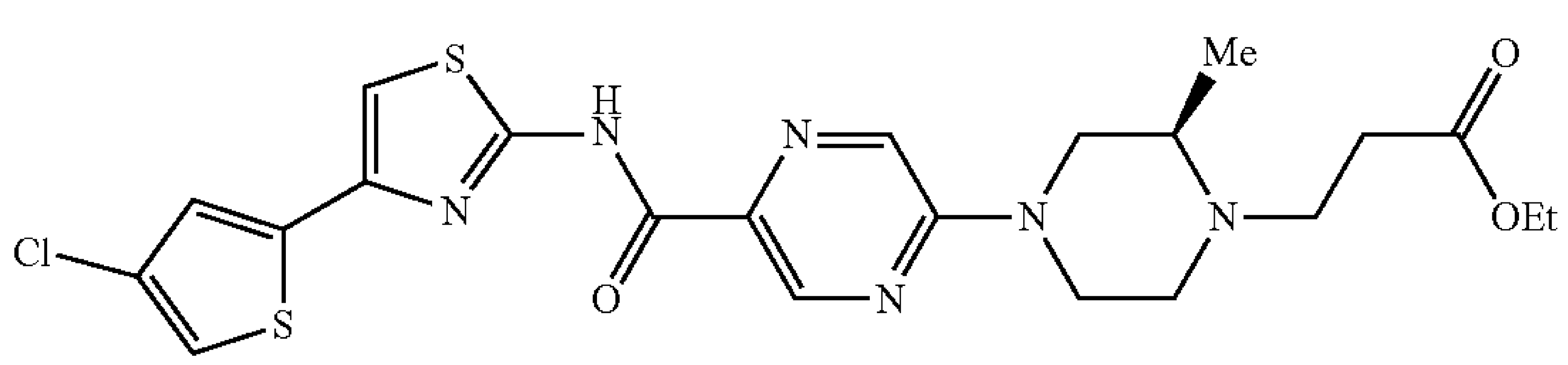
PEx	Structure
244	
245	
246	

TABLE 55-continued

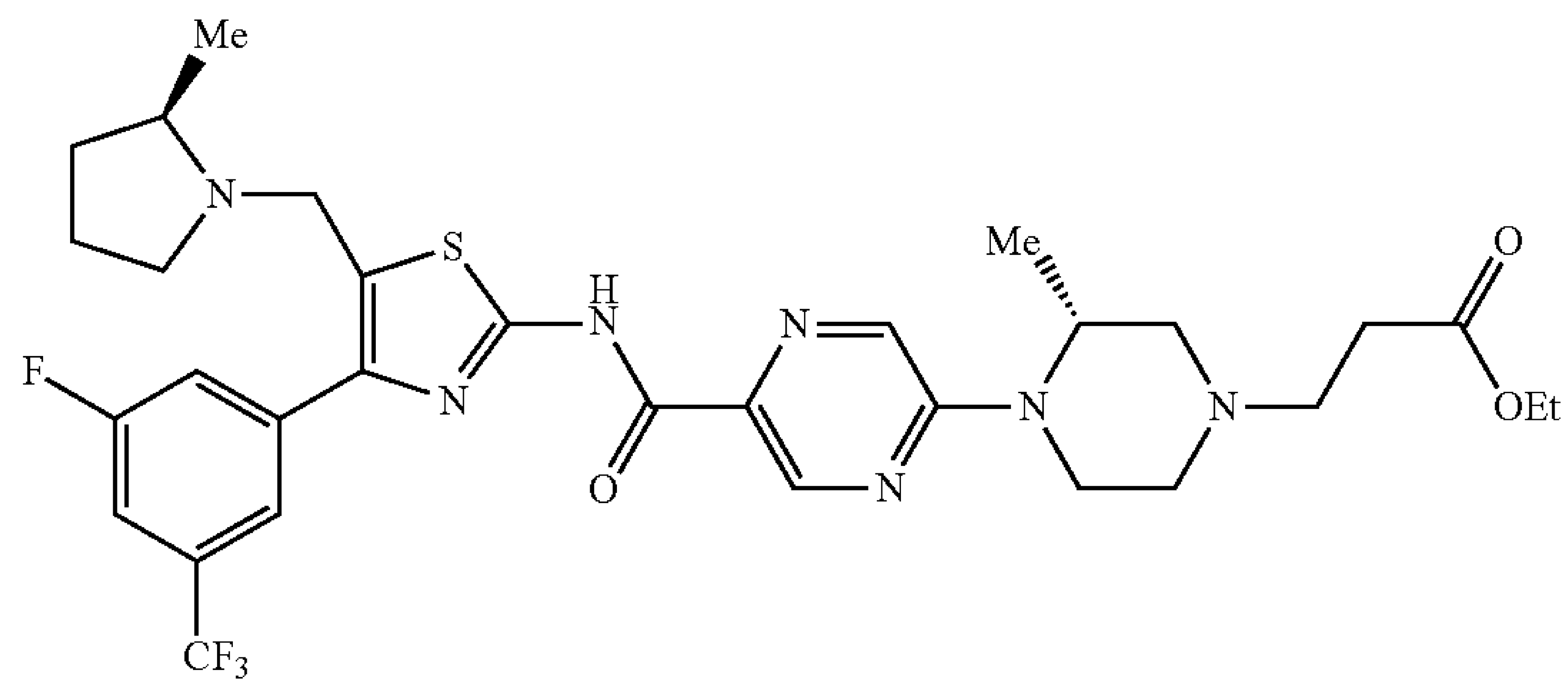
PEx	Structure
247	

TABLE 56

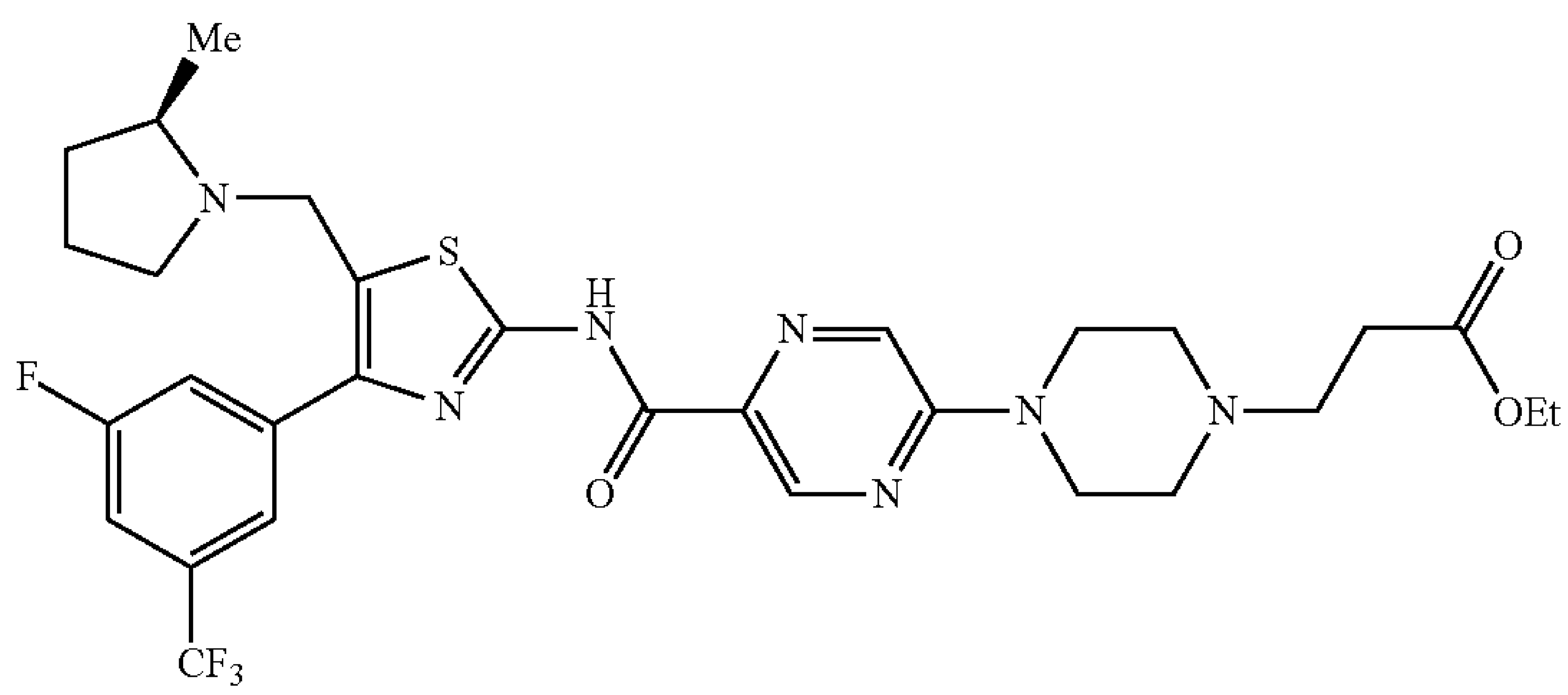
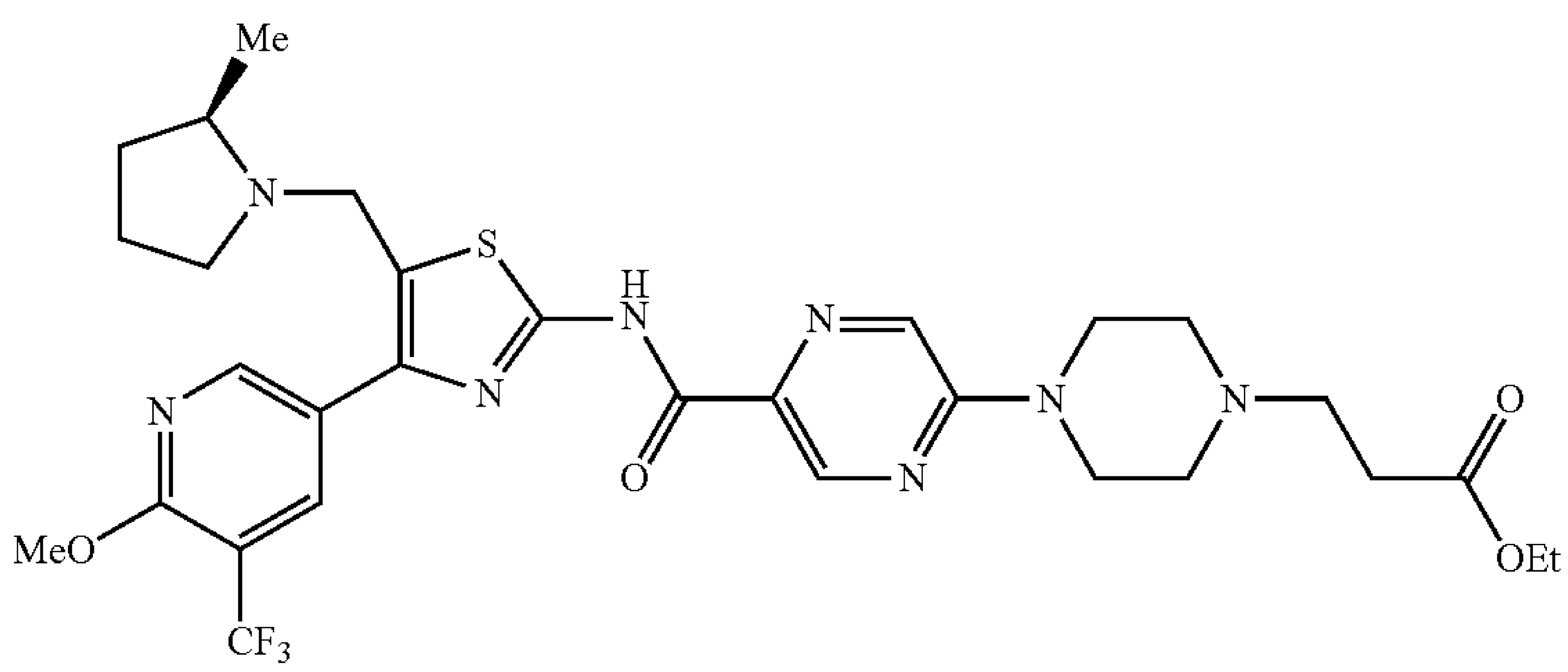
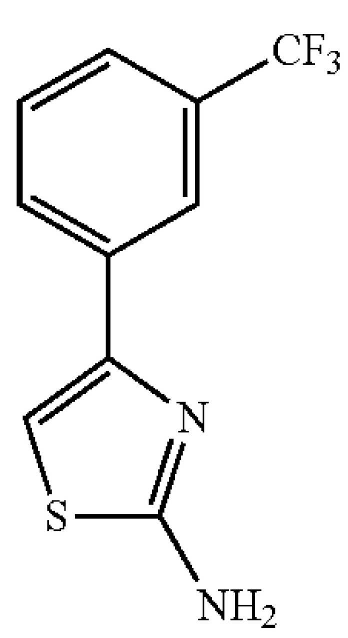
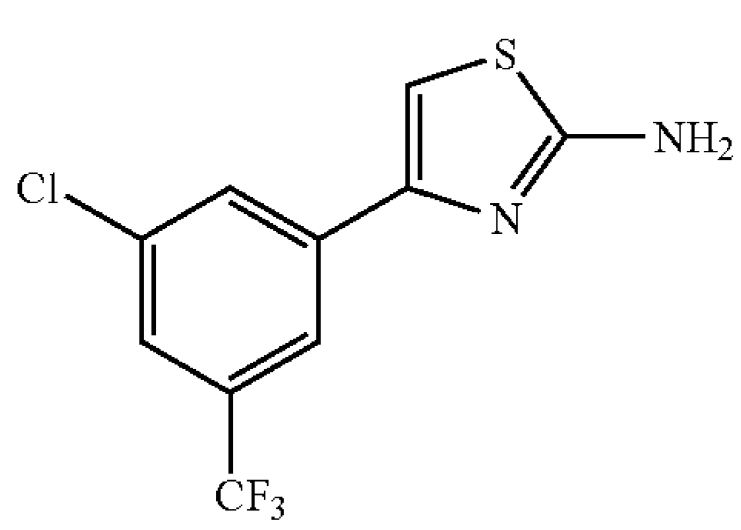
PEx	Structure
248	
249	
250	
251	

TABLE 57

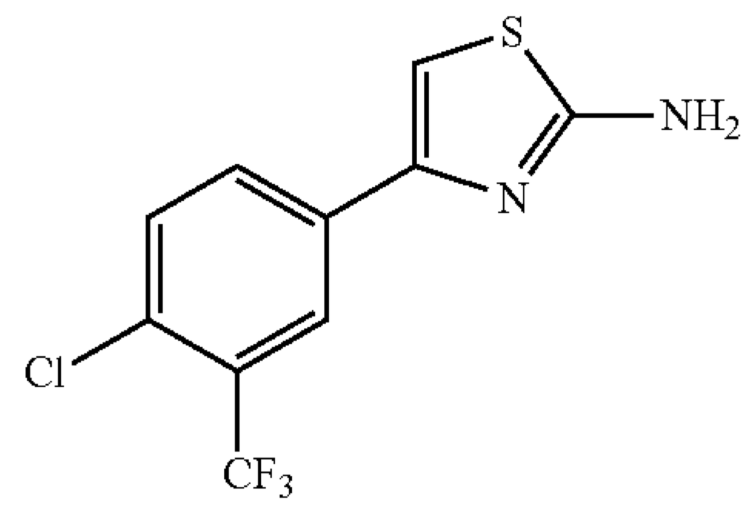
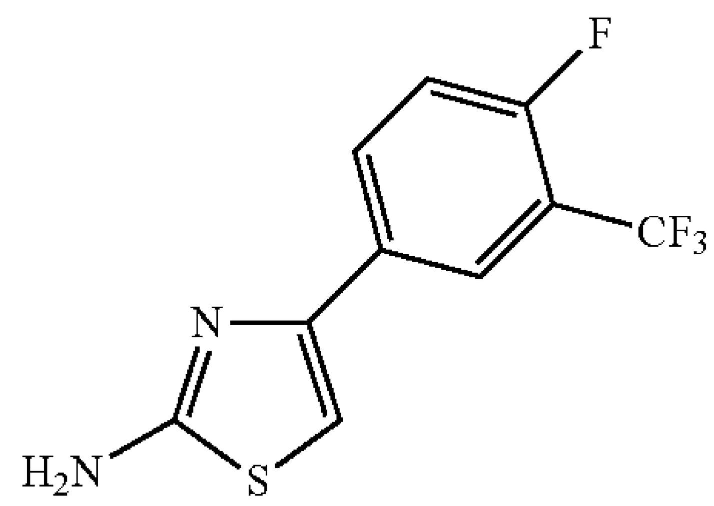
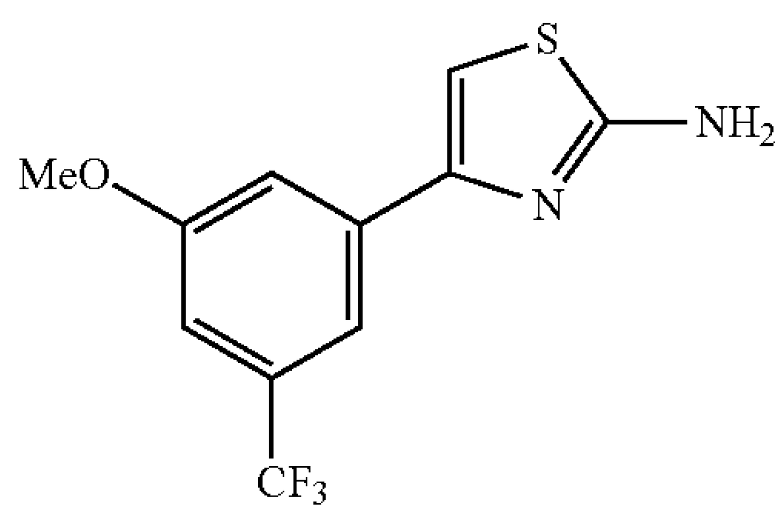
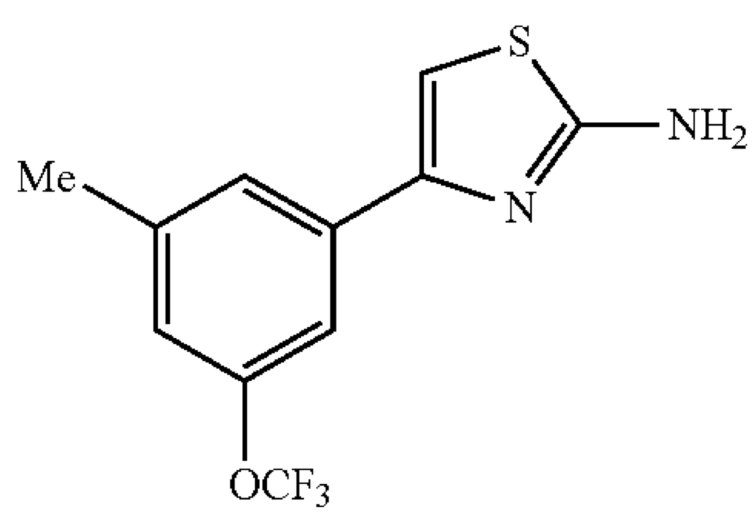
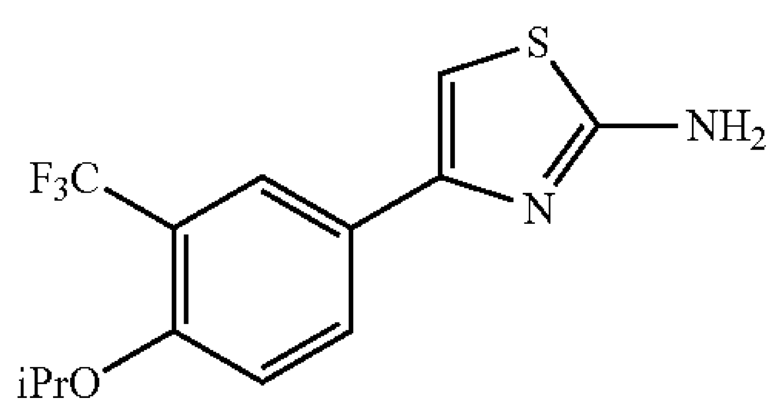
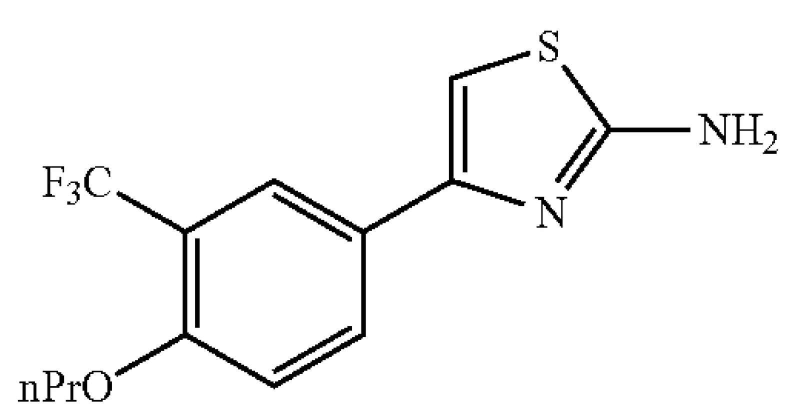
PEx	Structure
252	
253	
254	
255	
256	
257	

TABLE 58

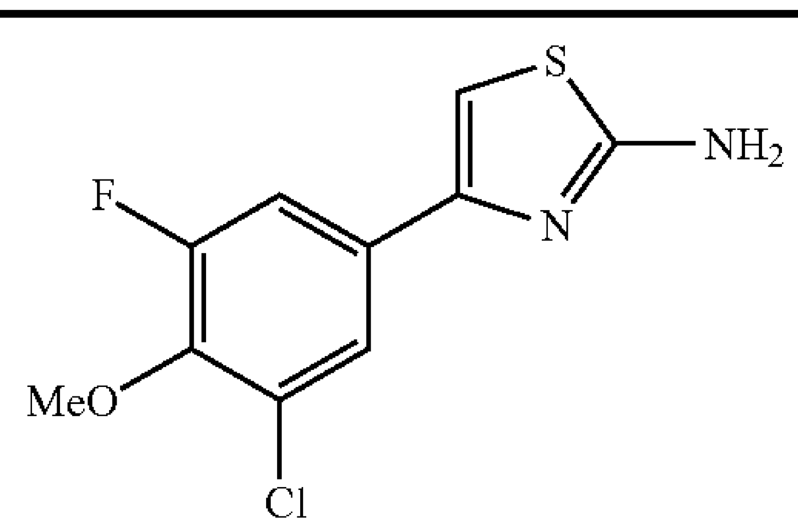
PEx	Structure
258	

TABLE 58-continued

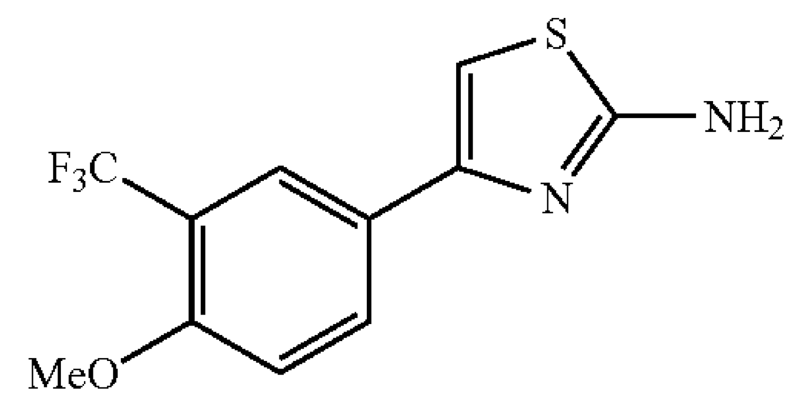
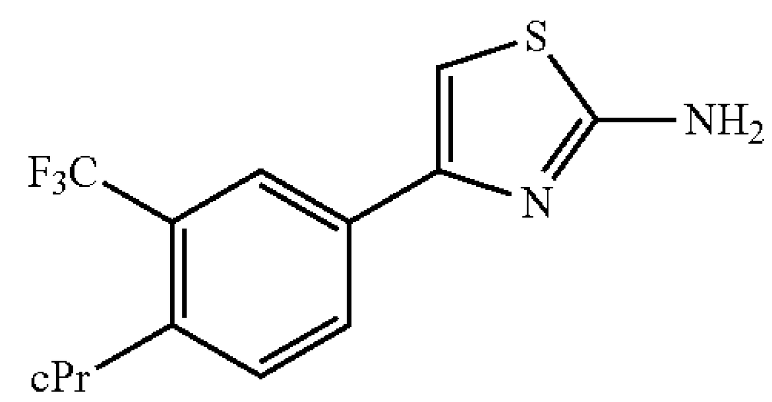
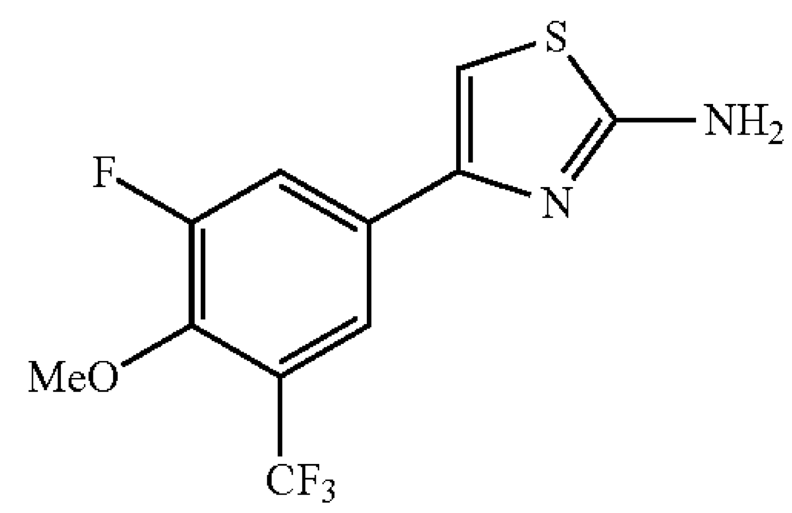
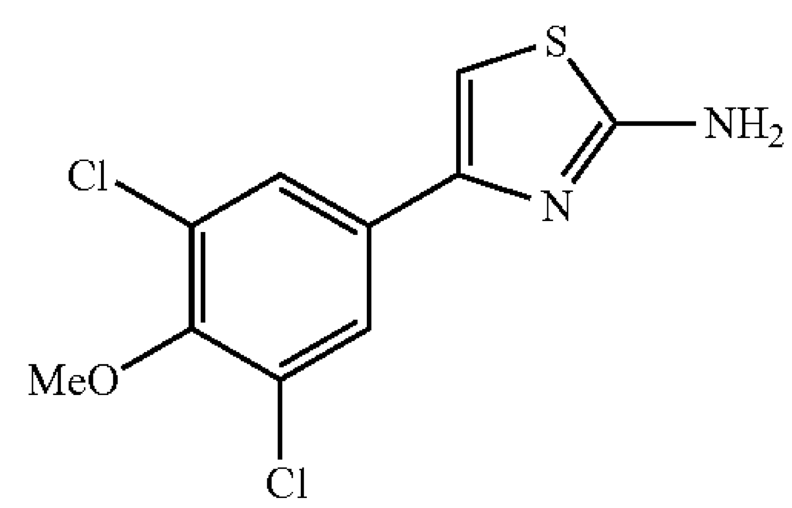
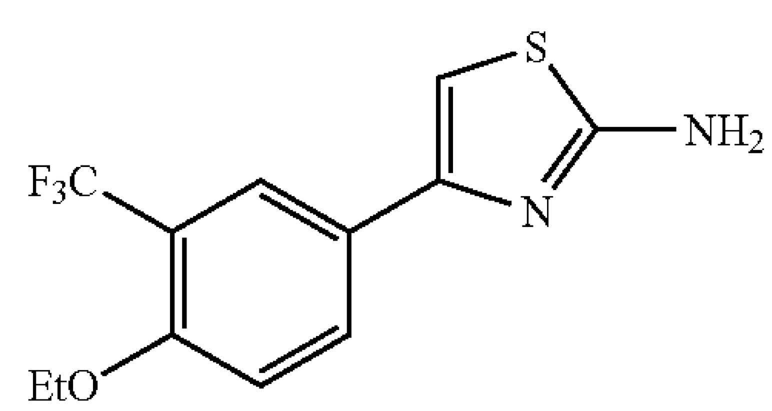
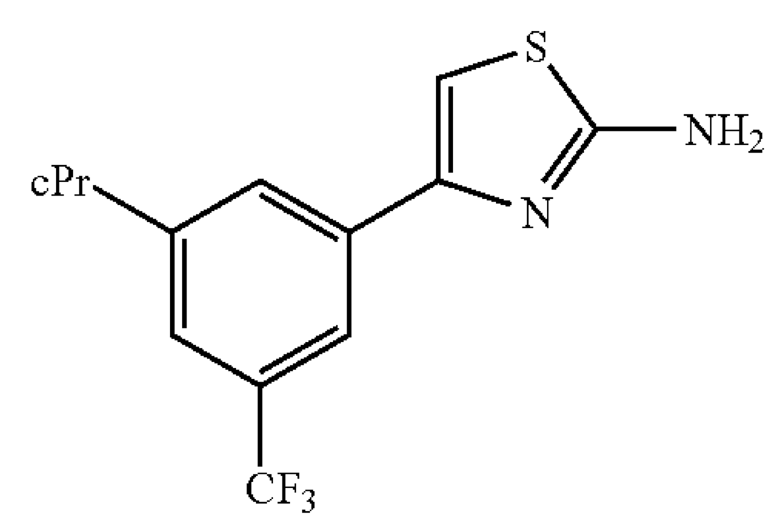
PEx	Structure
259	
260	
261	
262	
263	
264	

TABLE 59

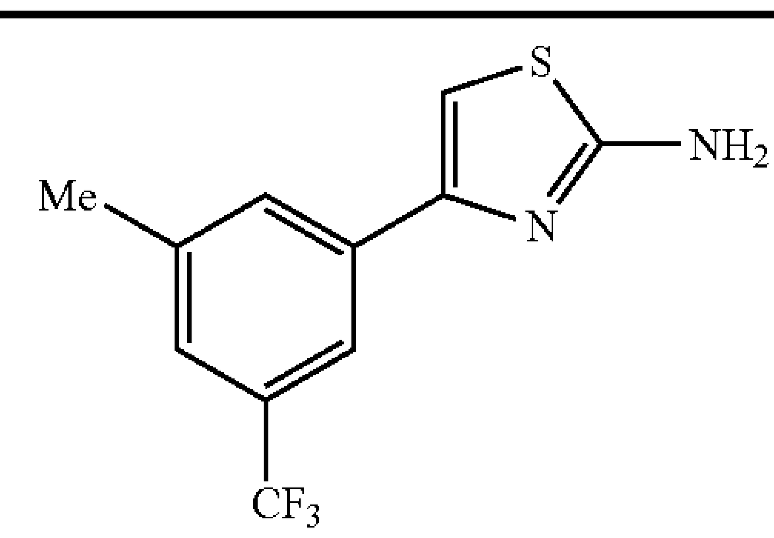
PEx	Structure
265	

TABLE 59-continued

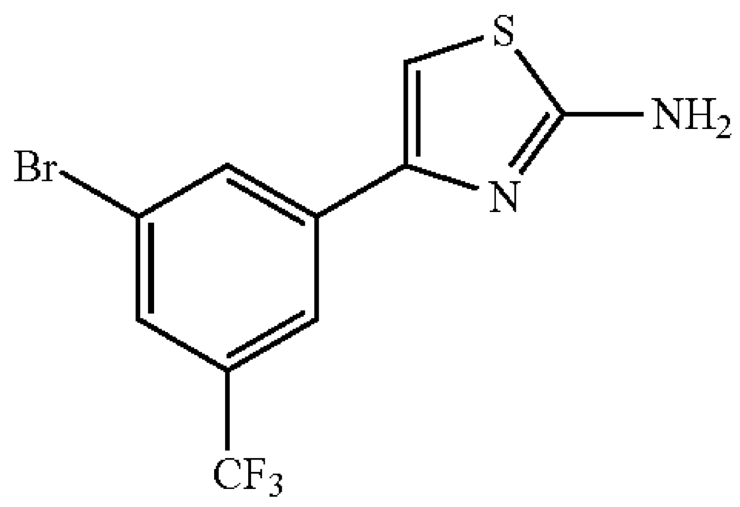
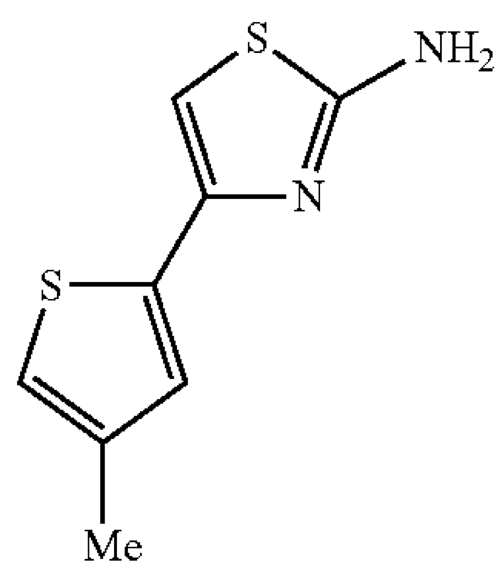
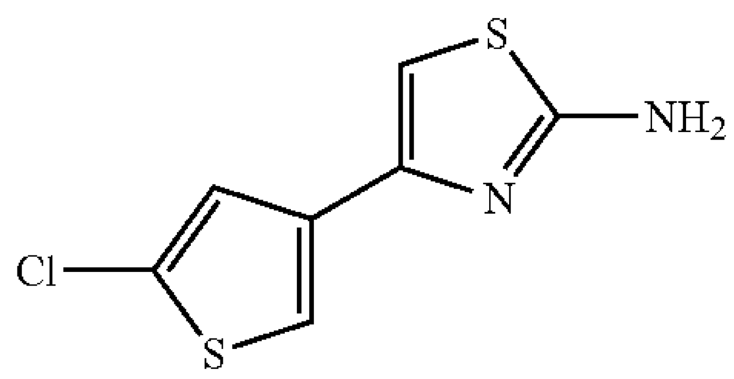
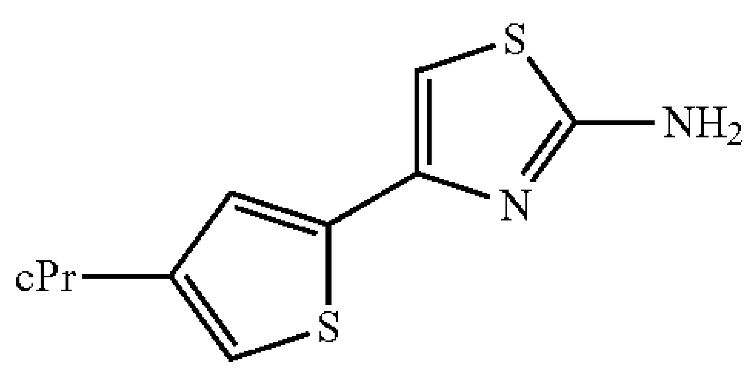
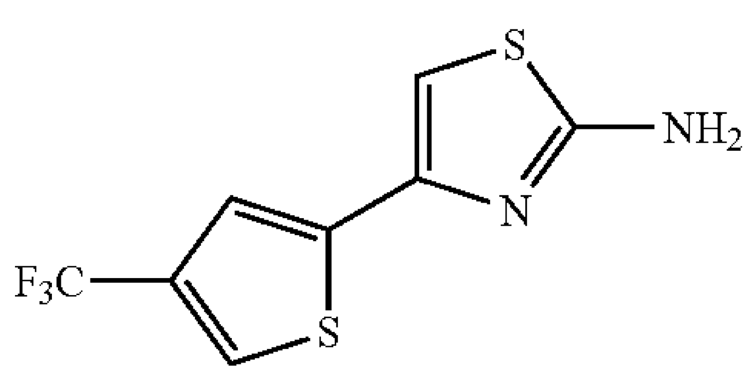
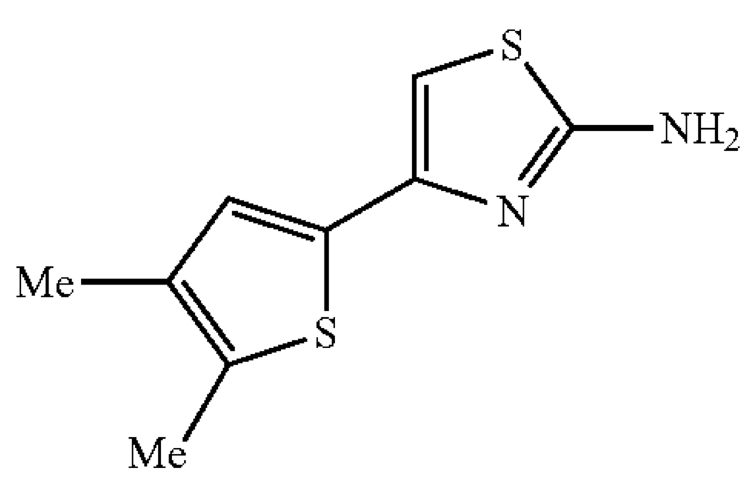
PEx	Structure
266	
267	
268	
269	
270	
271	

TABLE 60

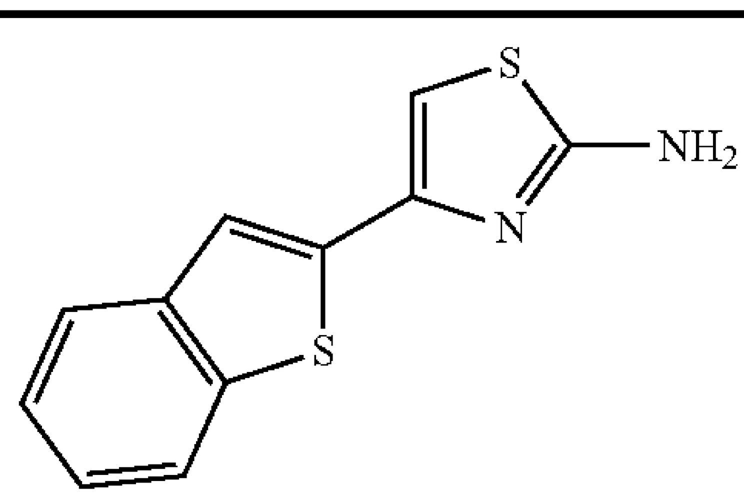
PEx	Structure
272	

TABLE 60-continued

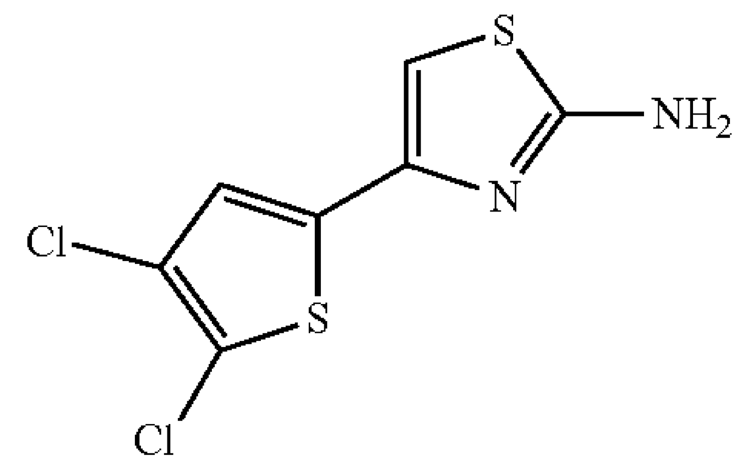
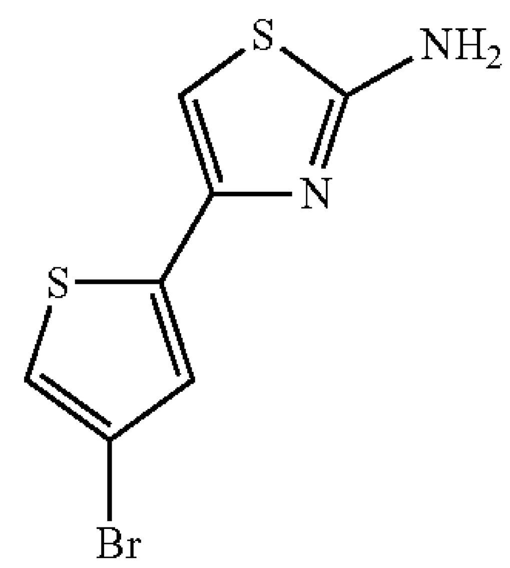
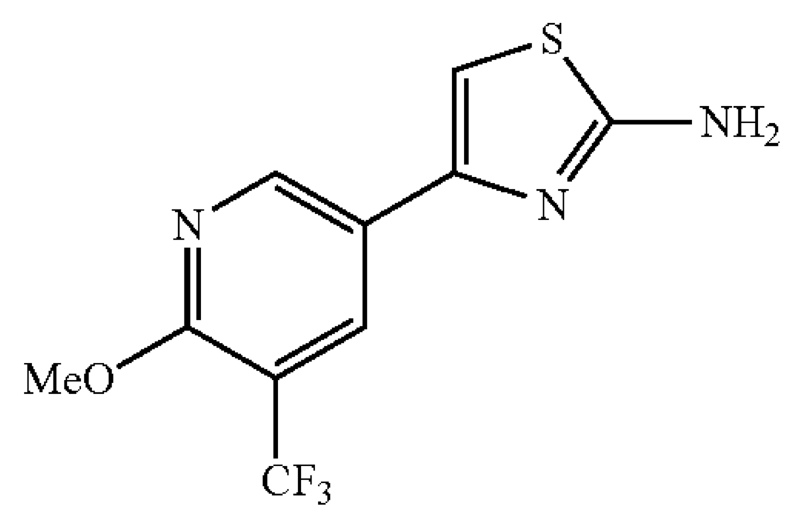
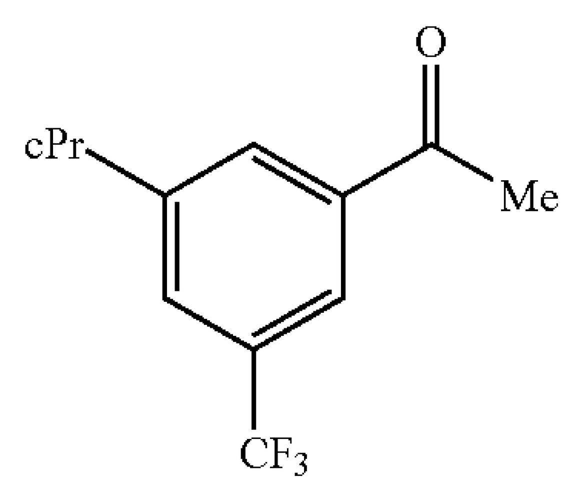
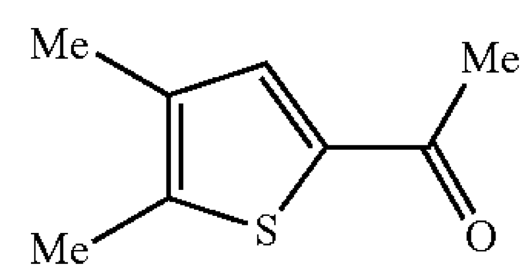
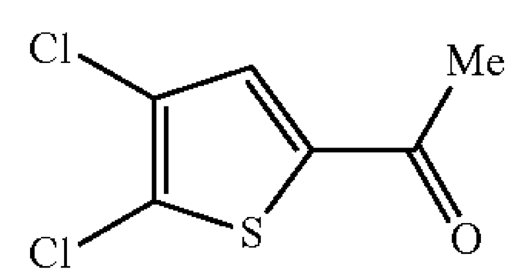
PEx	Structure
273	
274	
275	
276	
277	
278	

TABLE 61

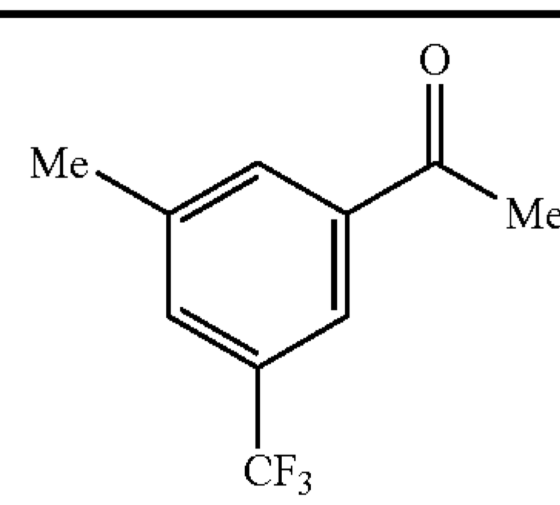
PEx	Structure
279	

TABLE 61-continued

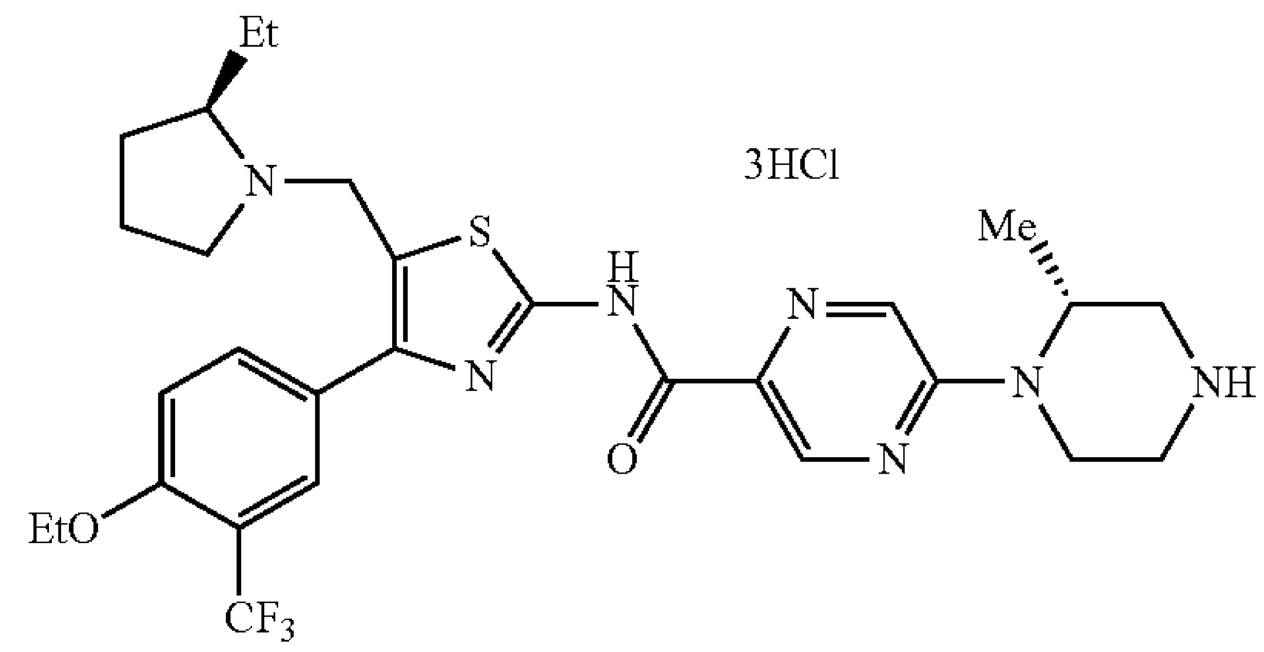
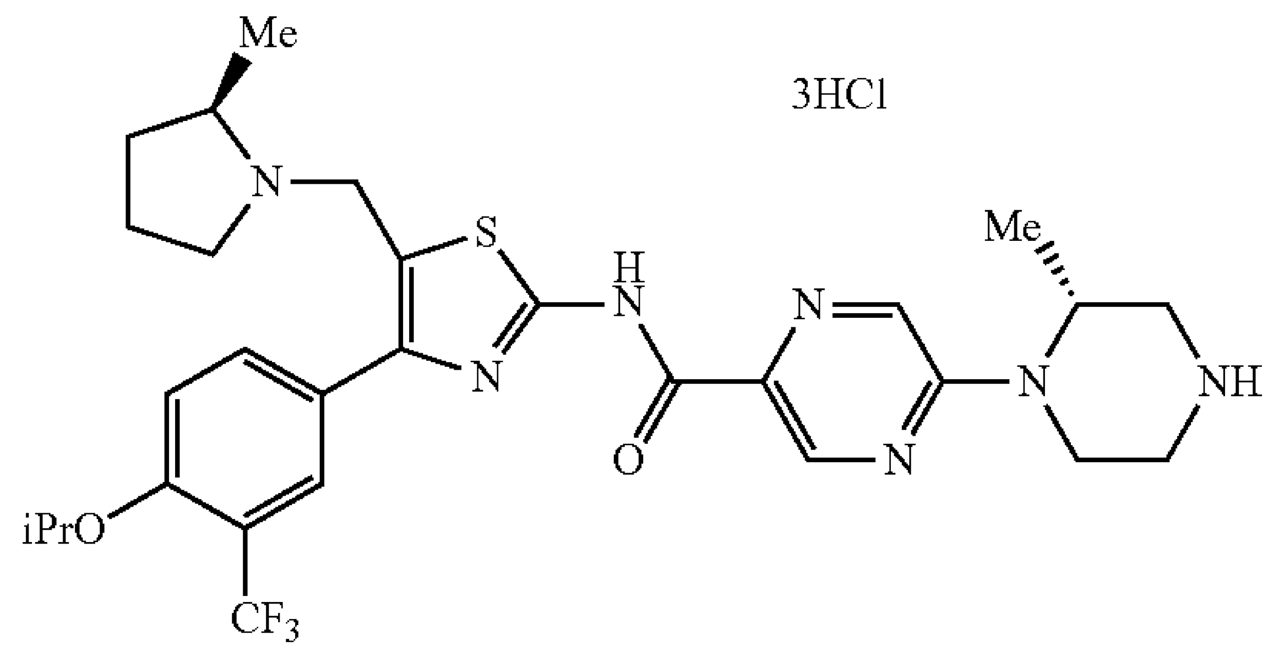
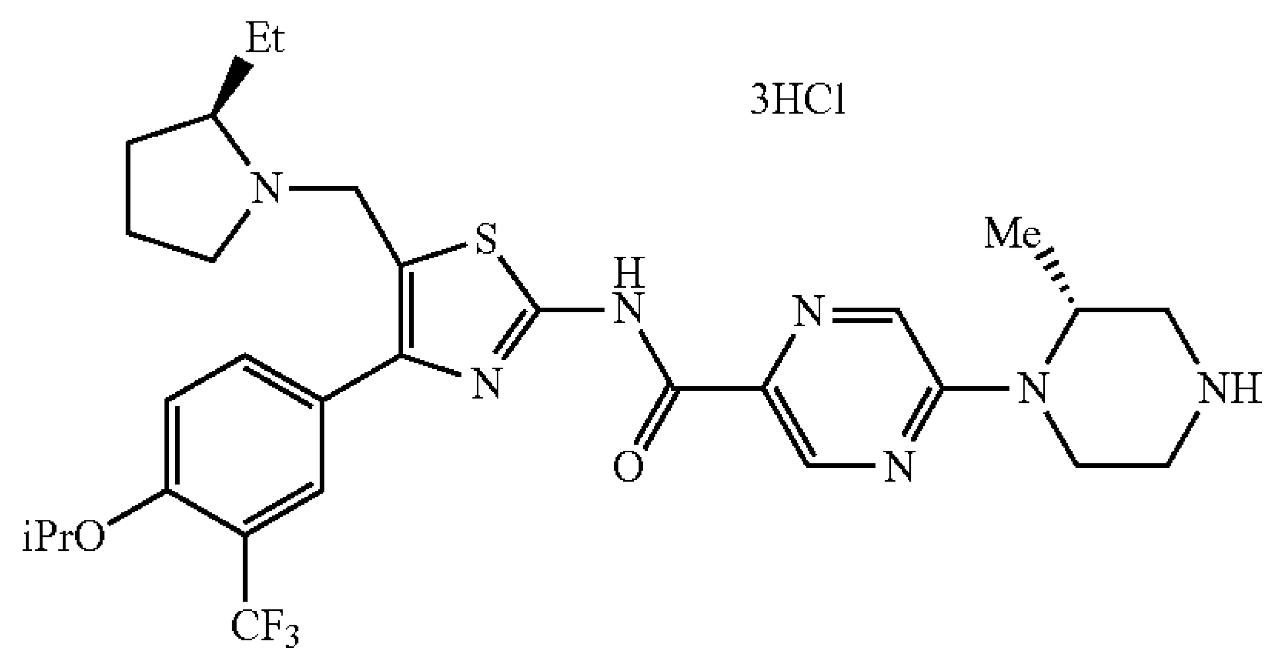
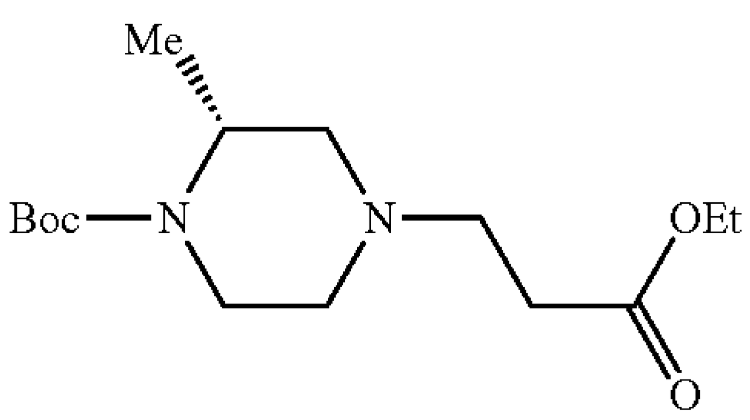
PEx	Structure
280	
281	
282	
283	

TABLE 62

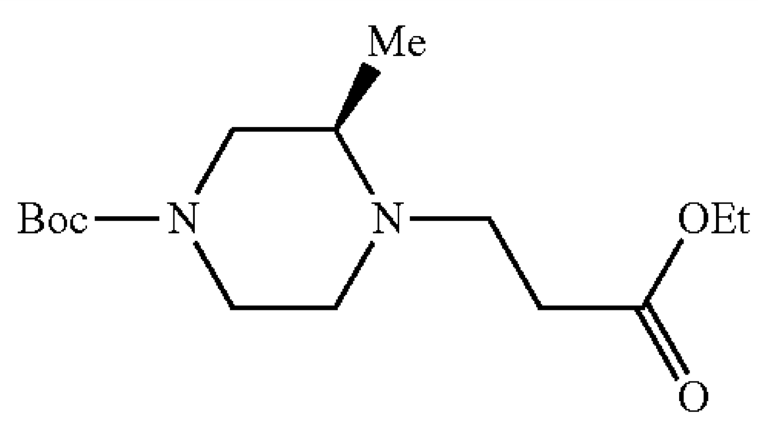
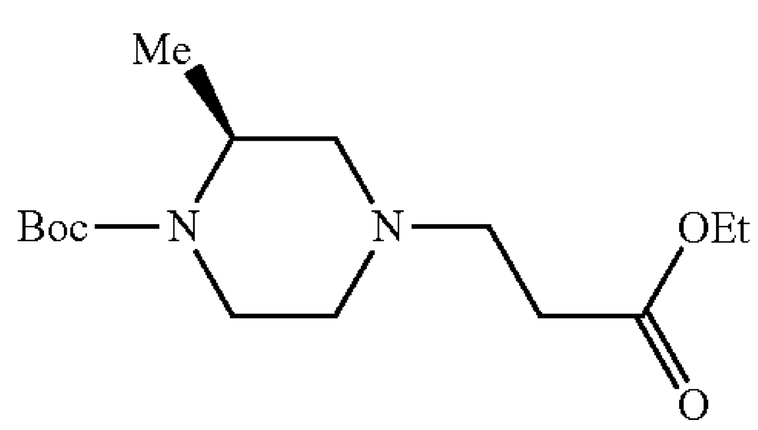
PEx	Structure
284	
285	

TABLE 63

PEx	PSyn	Data
1	PEx1	ESI+: 500, 502
2	PEx2	APCI/ESI+: 488
3	PEx3	NMR-DMSO-d6: 7.55 (1H, d, J = 1.5 Hz), 7.60 (1H, d, J = 1.5 Hz), 7.76 (1H, s), 8.98 (1H, d, J = 1.3 Hz), 9.15 (1H, d, J = 1.3 Hz), 12.68 (1H, brs)
4	PEx4	ESI+: 265
5	PEx5	ESI+: 360
6	PEx6	ESI+: 374
7	PEx7	ESI+: 348
8	PEx8	ESI+: 564
9	PEx9	ESI+: 201
10	PEx10	ESI+: 100
11	PEx11	ESI+: 390
12	PEx12	ESI+: 418, 420
13	PEx13	ESI+: 377
14	PEx14	ESI+: 593, 585
15	PEx15	ESI+: 389
16	PEx16	ESI+: 402
17	PEx17	ESI+: 328
18	PEx18	ESI+: 618
19	PEx19	ESI+: 305
20	PEx20	ESI+: 313, 315
21	PEx21	ESI+: 664
22	PEx22	ESI+: 604
23	PEx23	ESI+: 233
24	PEx24	ESI+: 501
25	PEx25	ESI+: 650
26	PEx26	ESI+: 247
27	PEx27	ESI+: 200
28	PEx28	ESI+: 287
29	PEx29	ESI+: 521, 523
30	PEx30	ESI+: 263
31	PEx31	CI+: 195
32	PEx32	ESI+: 220

TABLE 64

PEx	PSyn	Data
33	PEx33	ESI+: 219
34	PEx34	ESI+: 222
35	PEx35	ESI+: 250
36	PEx36	CI+: 256, 258
37	PEx37	ESI+: 247
38	PEx38	EI: 228
39	PEx39	APCI/ESI+: 167
40	PEx40	EI: 266, 268
41	PEx41	ESI+: 237
42	PEx42	ESI+: 311
43	PEx43	ESI+: 590
44	PEx44	ESI+: 378 [M + Na]+
45	PEx45	ESI+: 301
46	PEx1	ESI+: 512, 514
47	PEx1	ESI+: 512
48	PEx1	ESI+: 454
49	PEx1	ESI+: 512
50	PEx1	ESI+: 526, 528
51	PEx1	ESI+: 540, 542
52	PEx1	ESI+: 540, 542
53	PEx1	ESI+: 554, 556
54	PEx1	ESI+: 516, 518
55	PEx1	ESI+: 500
56	PEx1	ESI+: 514, 516
57	PEx1	ESI+: 516, 518
58	PEx1	ESI+: 522
59	PEx1	ESI+: 496, 498
60	PEx1	ESI+: 522, 524
61	PEx1	ESI+: 536, 538
62	PEx1	ESI+: 496, 498
63	PEx1	ESI+: 540, 542
64	PEx1	ESI+: 530
65	PEx1	ESI+: 496
66	PEx1	ESI+: 548

TABLE 65

PEx	PSyn	Data
67	PEx1	ESI+: 540
68	PEx2	ESI+: 468
69	PEx2	ESI+: 454, 456
70	PEx2	ESI+: 560, 562
71	PEx2	ESI+: 510, 512
72	PEx2	ESI+: 510, 512
73	PEx2	ESI+: 496, 498
74	PEx2	ESI+: 510, 512
75	PEx2	APCI/ESI+: 460
76	PEx2	ESI+: 588, 590
77	PEx2	APCI/ESI+: 498
78	PEx3	ESI+: 434, 436
79	PEx3	ESI+: 448, 450
80	PEx3	ESI+: 514, 516
81	PEx3	ESI+: 514, 516
82	PEx3	ESI+: 502, 504
83	PEx3	ESI+: 502, 504
84	PEx3	ESI+: 500, 502
85	PEx3	ESI+: 514, 516
86	PEx3	ESI+: 502, 504
87	PEx3	ESI+: 554, 556
88	PEx3	ESI+: 468, 470
89	PEx3	ESI+: 513, 515
90	PEx3	ESI+: 415, 417
91	PEx5	ESI+: 372
92	PEx5	ESI−: 312
93	PEx5	ESI+: 372
94	PEx5	ESI+: 376, 378
95	PEx5	ESI+: 360
96	PEx5	ESI+: 374
97	PEx5	ESI+: 400
98	PEx5	ESI+: 356
99	PEx5	ESI+: 382
100	PEx5	ESI+: 396

TABLE 66

PEx	PSyn	Data
101	PEx5	ESI+: 356
102	PEx5	ESI+: 382
103	PEx5	NMR-DMSO-d6: 1.11 (3H, d, J = 6 Hz), 1.30-1.41 (1H, m), 1.59-1.69 (2H, m), 1.87-1.98 (1H, m), 2.05-2.15 (1H, m), 2.35-2.45 (1H, m), 2.94-3.02 (1H, m), 3.18 (1H, d, J = 14 Hz), 3.97 (3H, d, J = 2 Hz), 3.98 (1H, d, J = 14 Hz), 6.98 (2H, brs), 7.87 (1H, brs), 8.02 (1H, dd, J = 13, 2 Hz)
104	PEx5	NMR-DMSO-d6: 1.14 (3H, d, J = 6 Hz), 1.30-1.42 (1H, m), 1.58-1.70 (2H, m), 1.87-1.98 (1H, m), 2.04-2.14 (1H, m), 2.34-2.44 (1H, m), 2.95-3.03 (1H, m), 3.14 (1H, d, J = 14 Hz), 3.91 (3H, d, J = 1 Hz), 3.98 (1H, d, J = 14 Hz), 6.93 (2H, brs), 7.63 (1H, dd, J = 13, 2 Hz), 7.72 (1H, t, J = 2 Hz)
105	PEx5	NMR-DMSO-d6: 1.08 (3H, d, J = 6 Hz), 1.29-1.41 (1H, m), 1.58-1.70 (2H, m), 1.86-1.97 (1H, m), 2.05-2.17 (1H, m), 2.34-2.45 (1H, m), 2.94-3.03 (1H, m), 3.22 (1H, d, J = 14 Hz), 3.96 (1H, d, J = 14 Hz), 6.96 (2H, brs), 7.42 (1H, t, J = 73 Hz), 7.48 (1H, d, J = 9 Hz), 8.04 (1H, dd, J = 9, 2 Hz), 8.14 (1H, d, J = 2 Hz)
106	PEx5	ESI+: 400
107	PEx5	ESI+: 370
108	PEx5	ESI+: 370
109	PEx5	ESI+: 356
110	PEx5	ESI+: 370
111	PEx5	ESI+: 420, 422
112	PEx5	ESI+: 448, 450
113	PEx6	ESI+: 374
114	PEx6	ESI+: 362
115	PEx6	ESI+: 362
116	PEx7	ESI+: 376, 378
117	PEx7	ESI+: 360
118	PEx7	ESI+: 376
119	PEx7	ESI+: 392
120	PEx7	ESI+: 374

TABLE 66-continued

PEx	PSyn	Data
121	PEx7	ESI+: 414
122	PEx9	ESI+: 201

TABLE 67

PEx	PSyn	Data
123	PEx9	ESI+: 201
124	PEx9	ESI+: 201
125	PEx9	ESI+: 187
126	PEx11	ESI+: 414
127	PEx11	ESI+: 356
128	PEx11	ESI+: 414
129	PEx11	ESI+: 416
130	PEx11	ESI+: 398
131	PEx11	ESI+: 424
132	PEx11	ESI+: 438
133	PEx11	ESI+: 398
134	PEx11	ESI+: 442
135	PEx11	ESI+: 424
136	PEx11	APCI/ESI+: 432
137	PEx11	APCI/ESI+: 398
138	PEx11	ESI+: 450
139	PEx11	ESI+: 442
140	PEx11	ESI+: 412
141	PEx11	ESI+: 412
142	PEx11	ESI+: 398
143	PEx11	ESI+: 412
144	PEx11	ESI+: 462, 464
145	PEx11	ESI+: 490, 492
146	PEx11	ESI+: 416
147	PEx11	ESI+: 416
148	PEx11	ESI+: 404
149	PEx11	ESI+: 404
150	PEx11	ESI+: 402
151	PEx18	ESI+: 632, 634
152	PEx11	ESI+: 418
153	PEx11	ESI+: 434
154	PEx11	ESI+: 416
155	PEx11	ESI+: 456
156	PEx12	ESI+: 418, 420

TABLE 68

PEx	PSyn	Data
157	PEx13	ESI+: 389
158	PEx13	ESI+: 331
159	PEx13	ESI+: 389
160	PEx13	ESI+: 393
161	PEx13	ESI+: 359
162	PEx13	ESI+: 399
163	PEx13	ESI+: 373
164	PEx13	ESI+: 399
165	PEx13	APCI/ESI+: 407
166	PEx13	APCI/ESI+: 373
167	PEx13	ESI+: 425
168	PEx13	ESI+: 417
169	PEx13	ESI+: 437, 439
170	PEx13	ESI+: 393, 395
171	PEx14	ESI+: 593, 595
172	PEx16	ESI+: 402
173	PEx17	ESI+: 372
174	PEx17	ESI+: 386
175	PEx17	ESI+: 400
176	PEx17	ESI+: 400
177	PEx17	ESI+: 414
178	PEx17	ESI+: 294
179	PEx17	ESI+: 308
180	PEx17	ESI+: 314
181	PEx17	APCI/ESI+: 320
182	PEx17	APCI/ESI+: 348
183	PEx17	APCI/ESI+: 358, 360

TABLE 68-continued

PEx	PSyn	Data
184	PEx17	ESI+: 362
185	PEx17	ESI+: 373
186	PEx17	ESI+: 328, 330
187	PEx18	ESI−: 510
188	PEx18	ESI+: 526
189	PEx19	ESI+: 321
190	PEx19	ESI+: 317

TABLE 69

PEx	PSyn	Data
191	PEx19	ESI+: 317
192	PEx19	ESI+: 259
193	PEx19	ESI+: 321
194	PEx19	ESI+: 317
195	PEx19	ESI+: 305
196	PEx19	ESI+: 287
197	PEx19	ESI+: 327
198	PEx19	ESI+: 301
199	PEx19	ESI+: 327
200	PEx19	ESI+: 335
201	PEx19	ESI+: 301
202	PEx19	ESI+: 353
203	PEx19	ESI+: 345
204	PEx19	ESI+: 365, 367
205	PEx20	NMR-DMSO-d6: 3.87 (3H, s), 8.01 (1H, s), 8.05 (2H, s)
206	PEx20	ESI+: 385
207	PEx20	ESI+: 399
208	PEx20	ESI+: 293
209	PEx20	ESI+: 313, 315
210	PEx20	APCI/ESI+: 319
211	PEx20	APCI/ESI+: 347
212	PEx20	APCI/ESI+: 357
213	PEx20	ESI+: 372
214	PEx21	NMR-DMSO-d6: 1.13-1.26 (9H, m), 1.34-1.45 (1H, m), 1.60-1.76 (2H, m), 1.90-2.12 (2H, m), 2.16-2.28 (2H, m), 2.45-2.70 (5H, m), 2.78-2.85 (1H, m), 2.92-2.99 (1H, m), 3.00-3.07 (1H, m), 3.10-3.22 (1H, m), 3.55-3.62 (1H, m), 4.01-4.14 (2H, m), 4.15-4.23 (1H, m), 4.26-4.35 (1H, m), 4.66-4.78 (1H, m), 7.45 (1H, d, J = 1.5 Hz), 7.58 (1H, d, J = 1.3 Hz), 8.32 (1H, d, J = 1.1 Hz), 8.75 (1H, d, J = 1.2 Hz), 11.57 (1H, s)
215	PEx21	ESI−: 616
216	PEx22	ESI+: 604
217	PEx22	ESI+: 604
218	PEx24	ESI+: 541, 543

TABLE 70

PEx	PSyn	Data
219	PEx24	ESI+: 523
220	PEx29	ESI+: 676
221	PEx29	ESI+: 666, 668
222	PEx29	ESI+: 666, 668
223	PEx29	ESI+: 652, 654
224	PEx29	ESI+: 652, 654
225	PEx29	ESI+: 666, 668
226	PEx29	ESI+: 664
227	PEx29	ESI+: 666, 668
228	PEx29	ESI+: 664
229	PEx29	ESI+: 690
230	PEx29	ESI+: 618, 620
231	PEx29	ESI+: 618
232	PEx29	ESI+: 664
233	PEx29	ESI+: 690
234	PEx29	ESI+: 618
235	PEx29	ESI+: 618
236	PEx29	ESI+: 710, 712
237	PEx29	ESI+: 632, 634
238	PEx29	ESI+: 632, 634
239	PEx29	ESI+: 738, 740

TABLE 70-continued

PEx	PSyn	Data
240	PEx29	ESI+: 752, 754
241	PEx29	ESI+: 752, 754
242	PEx29	ESI+: 752, 754
243	PEx29	ESI+: 738, 740
244	PEx29	ESI+: 724, 726
245	PEx29	ESI+: 724, 726
246	PEx29	ESI−: 519, 521
247	PEx29	ESI+: 664
248	PEx29	ESI+: 650
249	PEx29	ESI+: 663
250	PEx30	ESI+: 245
251	PEx30	ESI+: 279
252	PEx30	ESI+: 279, 281

TABLE 71

PEx	PSyn	Data
253	PEx30	ESI+: 263
254	PEx30	ESI+: 275
255	PEx30	ESI+: 275
256	PEx30	ESI+: 303
257	PEx30	ESI+: 303
258	PEx30	ESI+: 259, 261
259	PEx30	ESI+: 275
260	PEx30	ESI+: 285
261	PEx30	ESI+: 293
262	PEx30	ESI+: 275
263	PEx30	ESI+: 289
264	PEx30	ESI+: 285
265	PEx30	ESI+: 259
266	PEx30	ESI+: 323, 325
267	PEx30	ESI+: 197
268	PEx30	ESI+: 217, 219
269	PEx30	APCI/ESI+: 223
270	PEx30	APCI/ESI+: 251
271	PEx30	ESI+: 211
272	PEx30	ESI+: 233
273	PEx30	ESI+: 251, 253
274	PEx30	APCI/ESI+: 261, 263
275	PEx30	ESI+: 276
276	PEx38	EI: 228
277	PEx40	ESI+: 155
278	PEx40	EI: 194, 196
279	PEx41	EI: 202
280	PEx43	ESI+: 604
281	PEx43	ESI+: 604
282	PEx43	ESI+: 618
283	PEx45	ESI+: 301
284	PEx45	ESI+: 301
285	PEx45	ESI+: 301

TABLE 72

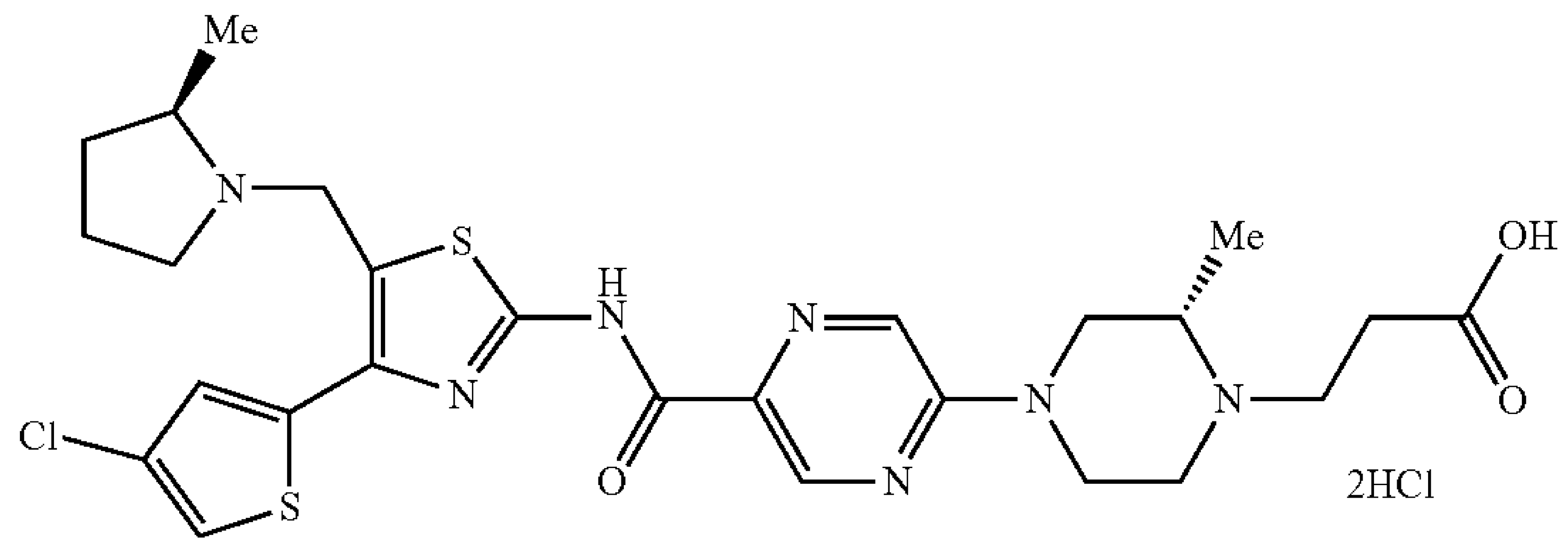
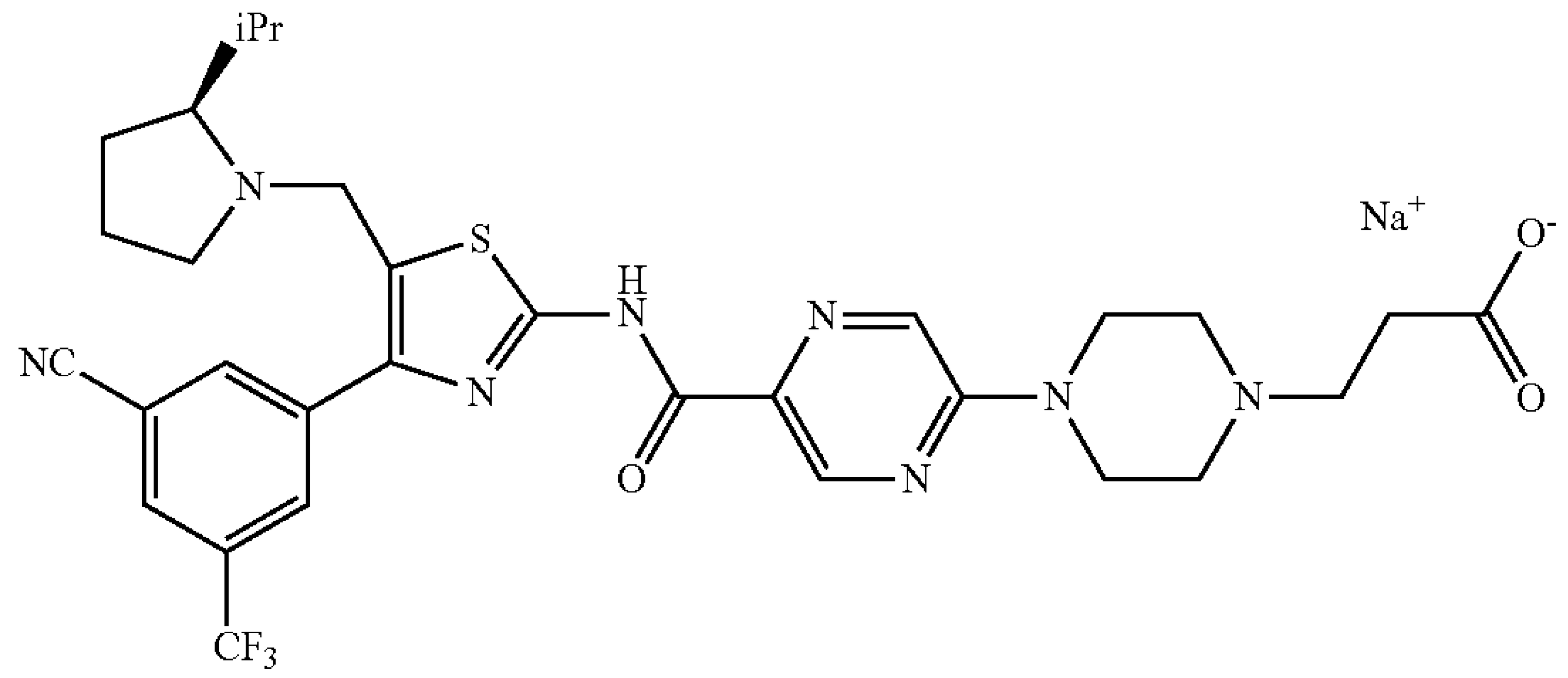
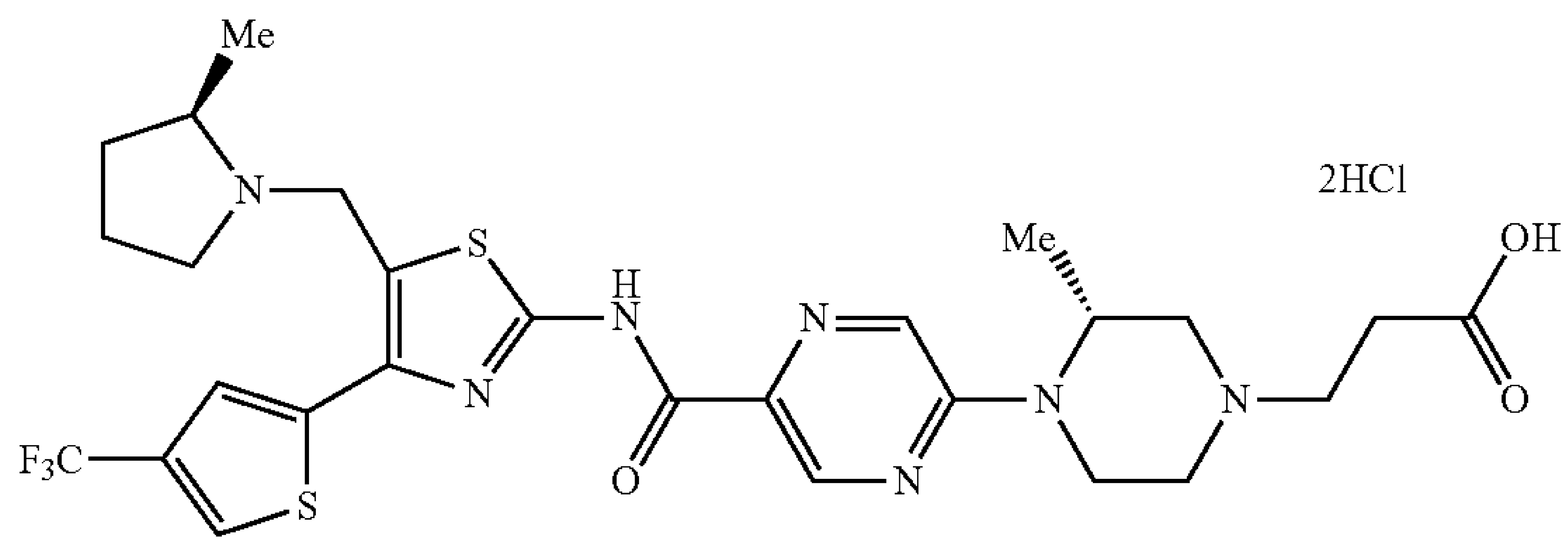
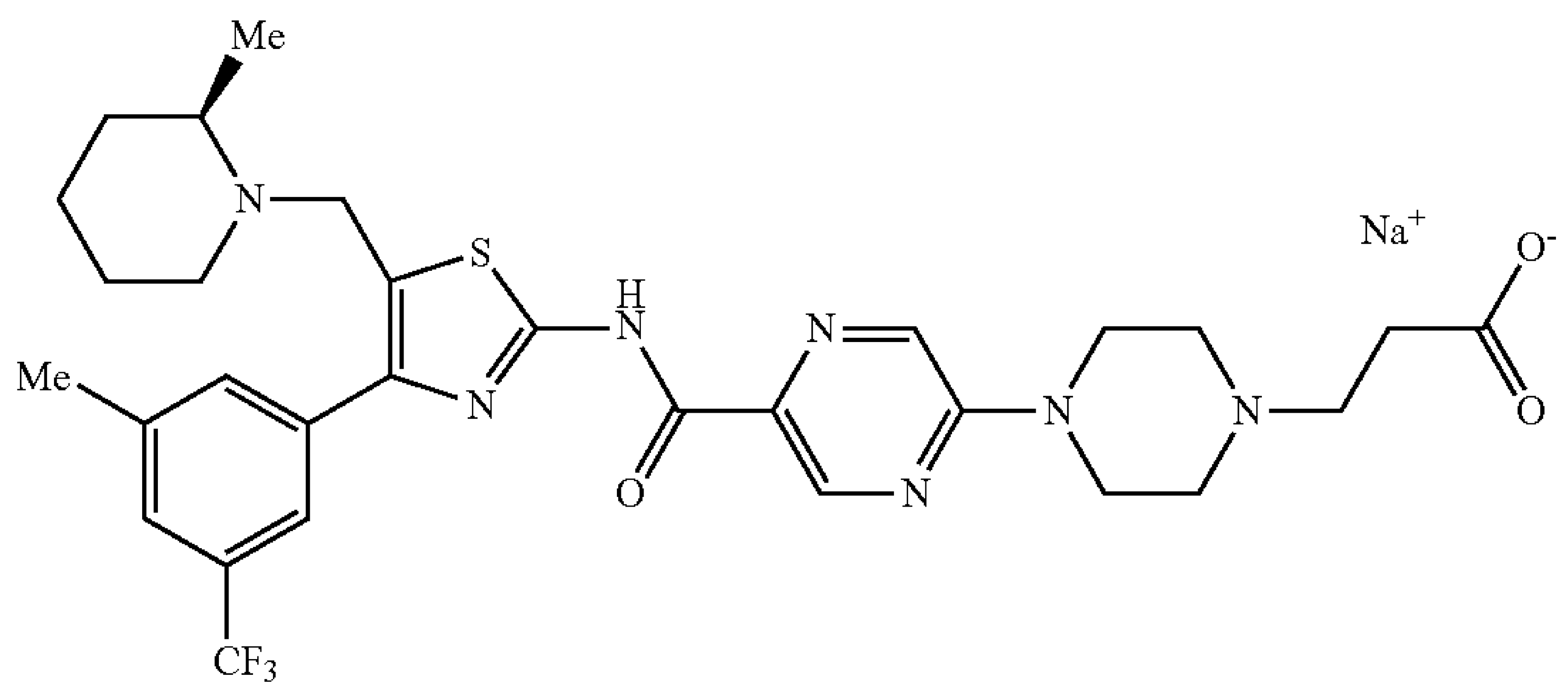
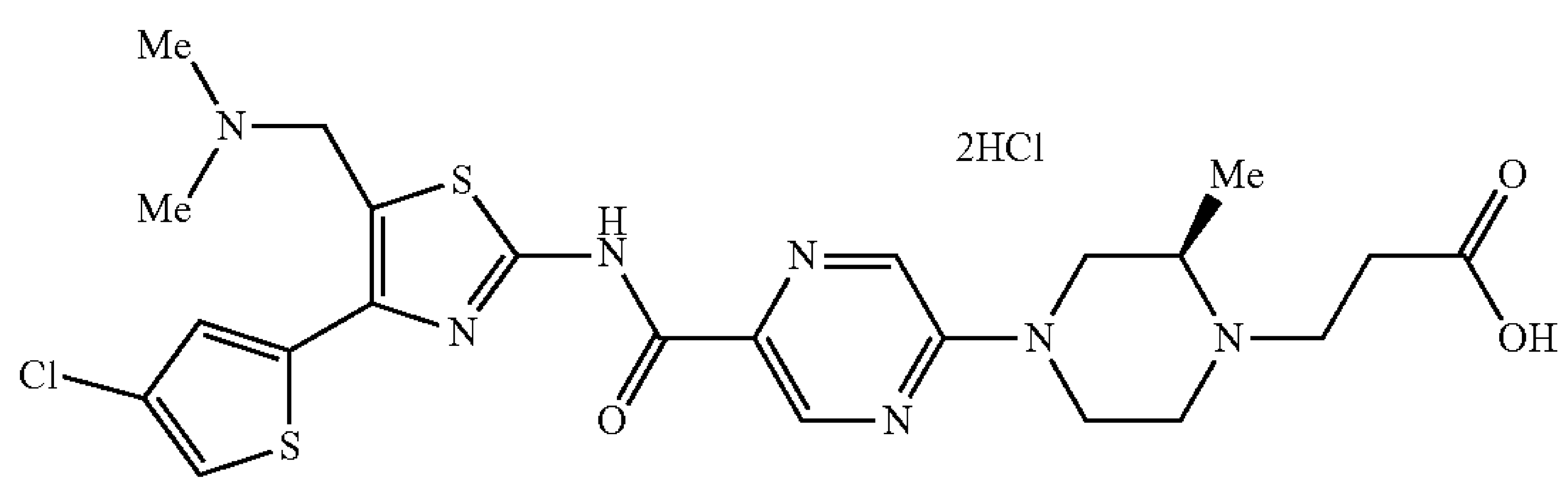
Ex	Structure
1	
2	
3	
4	
5	

TABLE 73

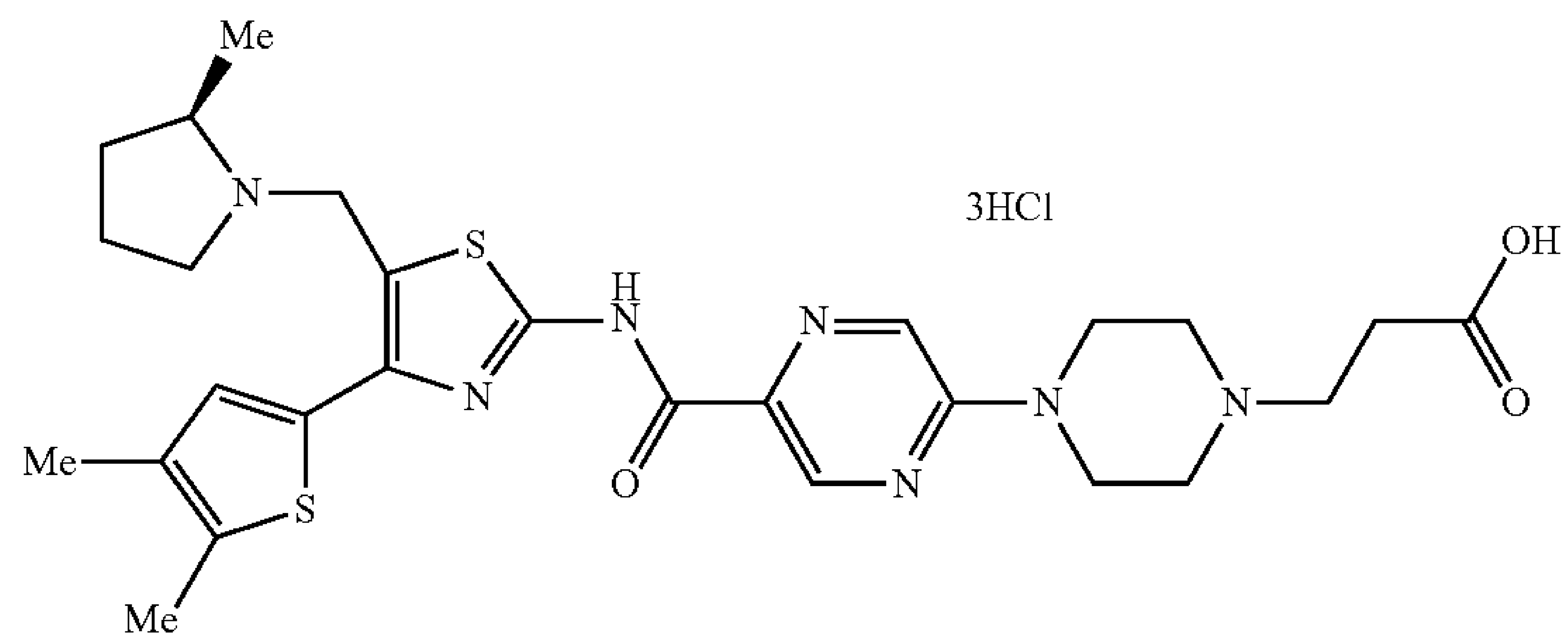
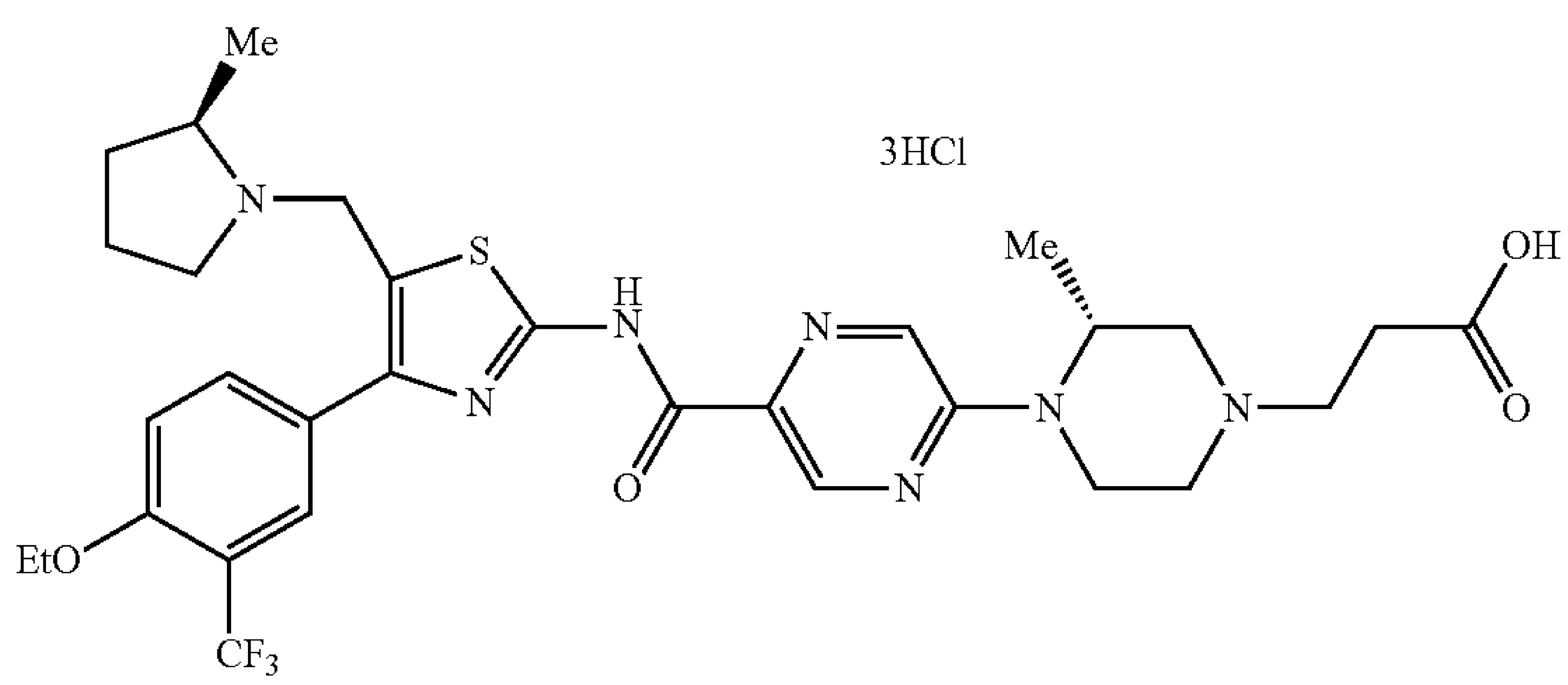
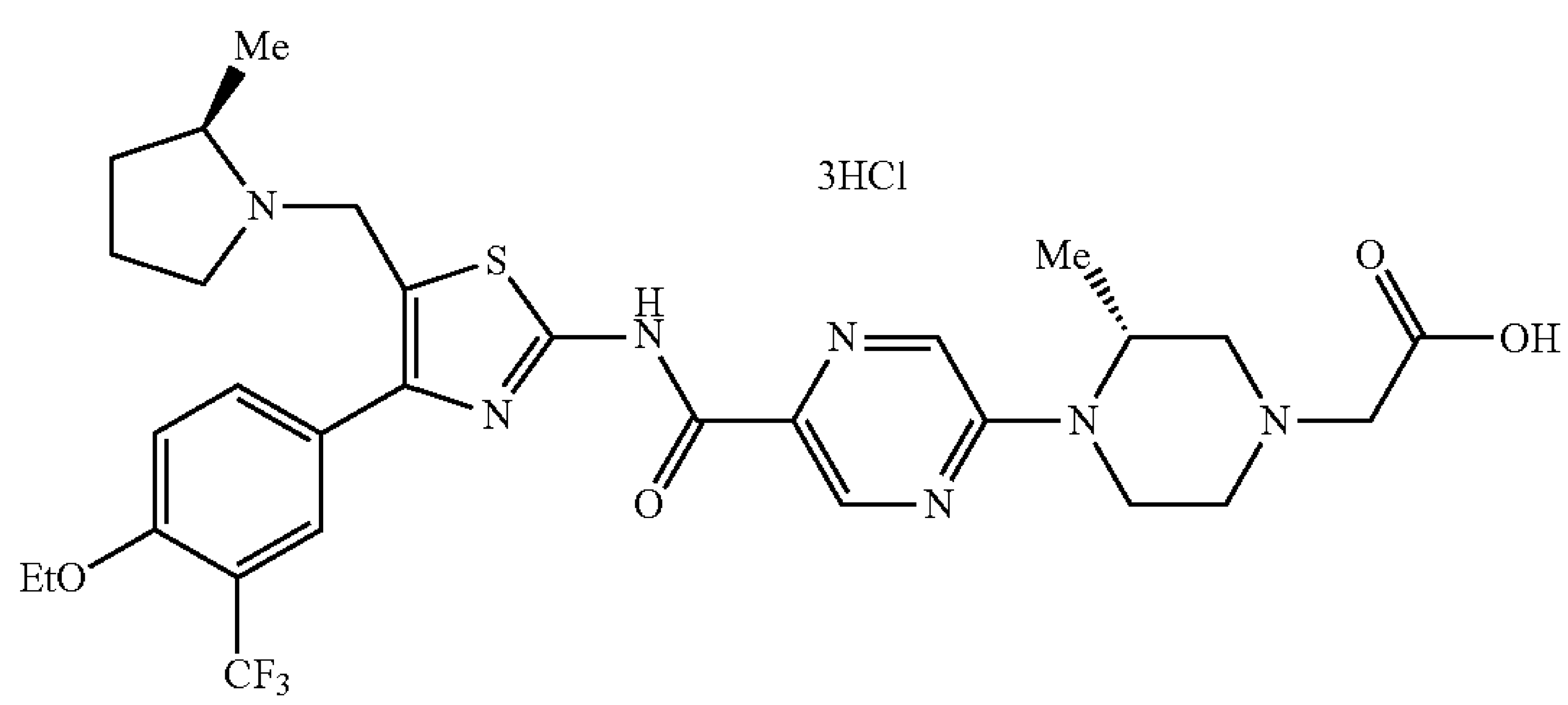
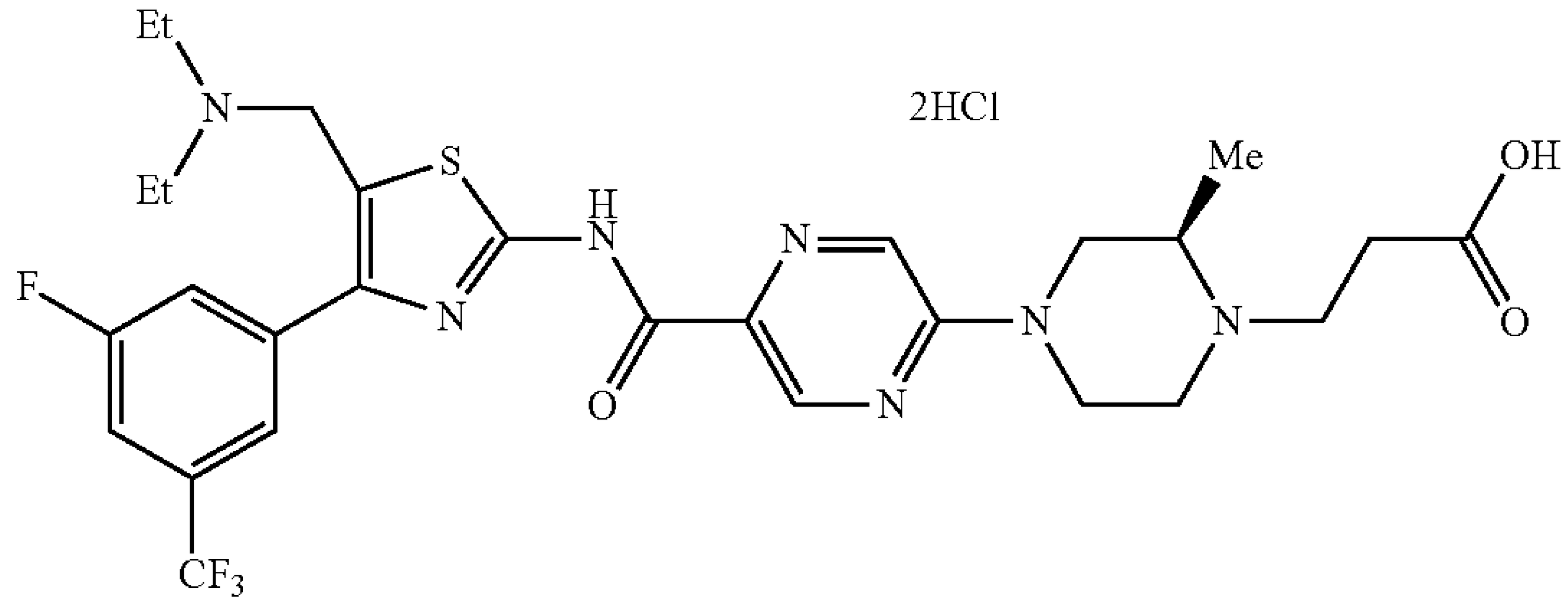
Ex	Structure
6	
7	
8	
9	

TABLE 74

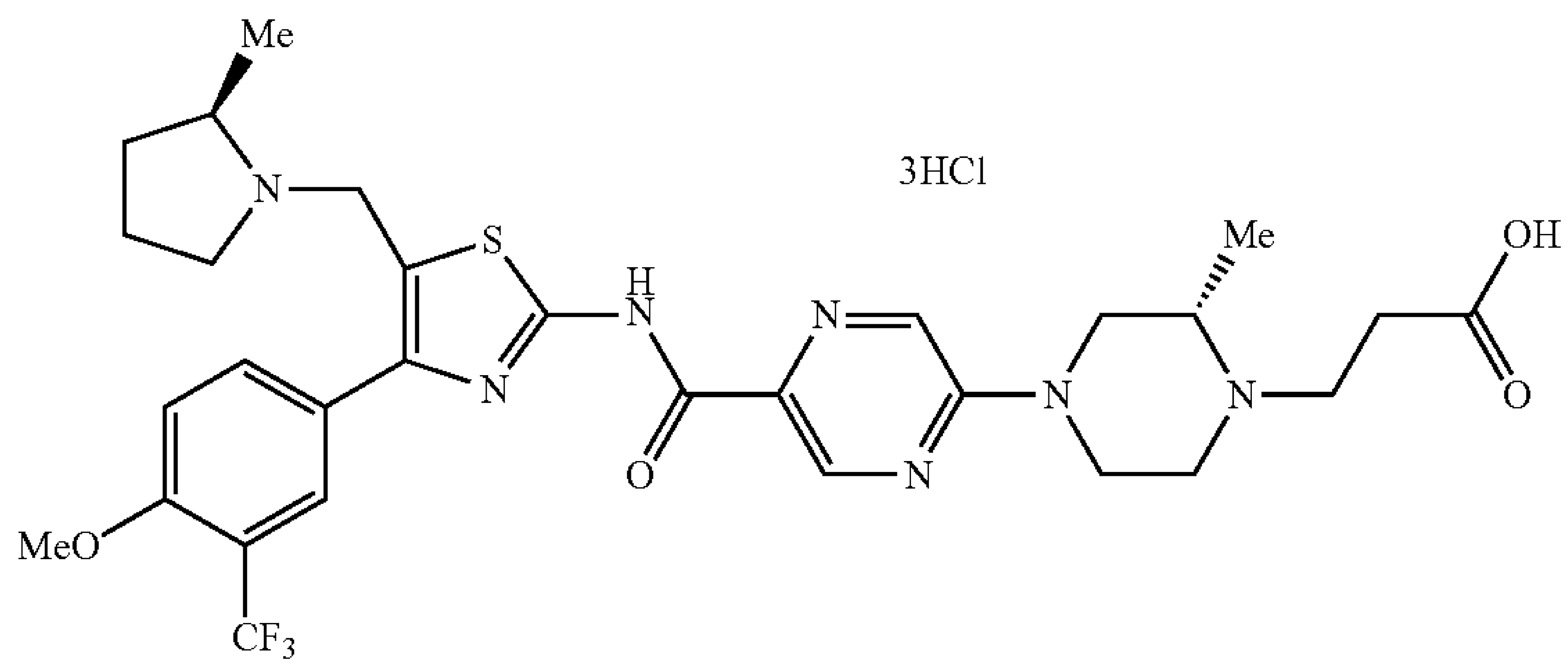
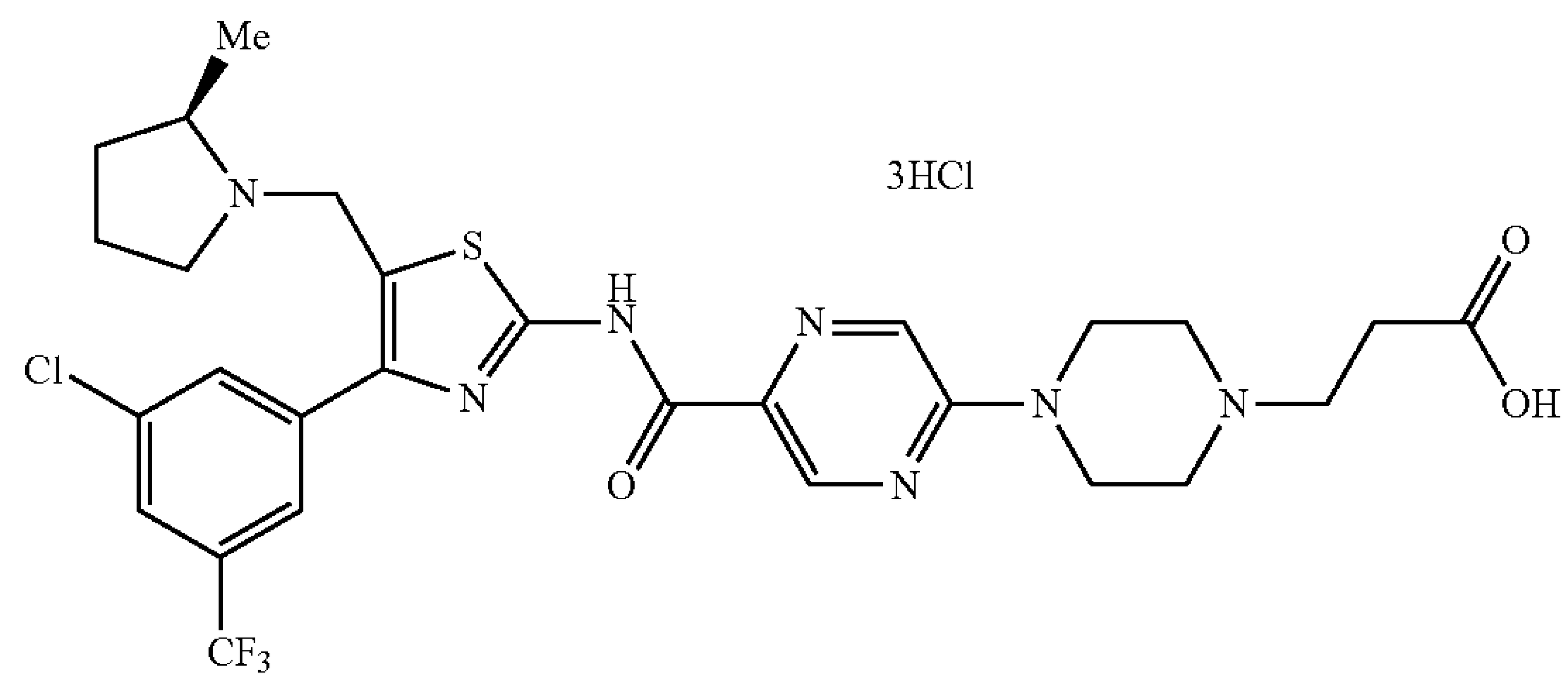
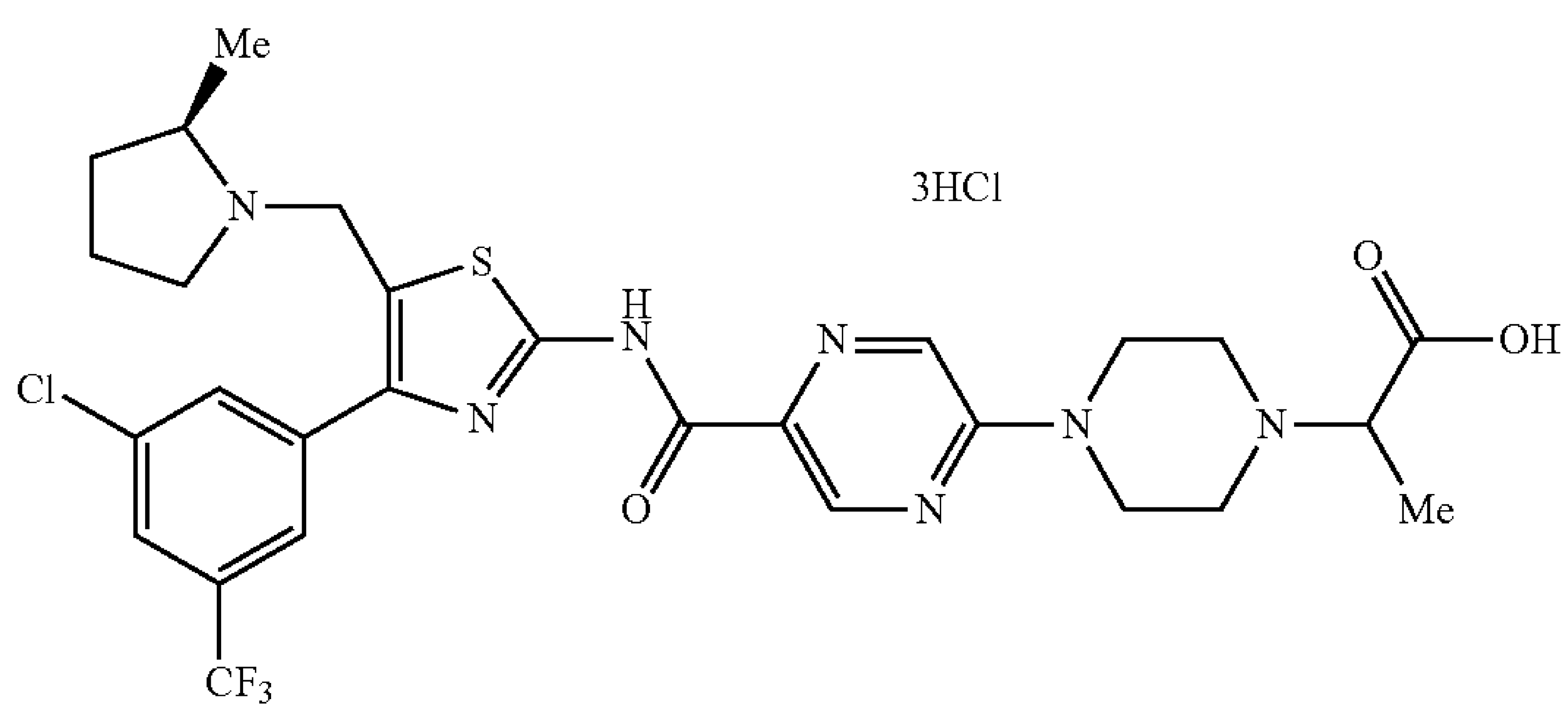
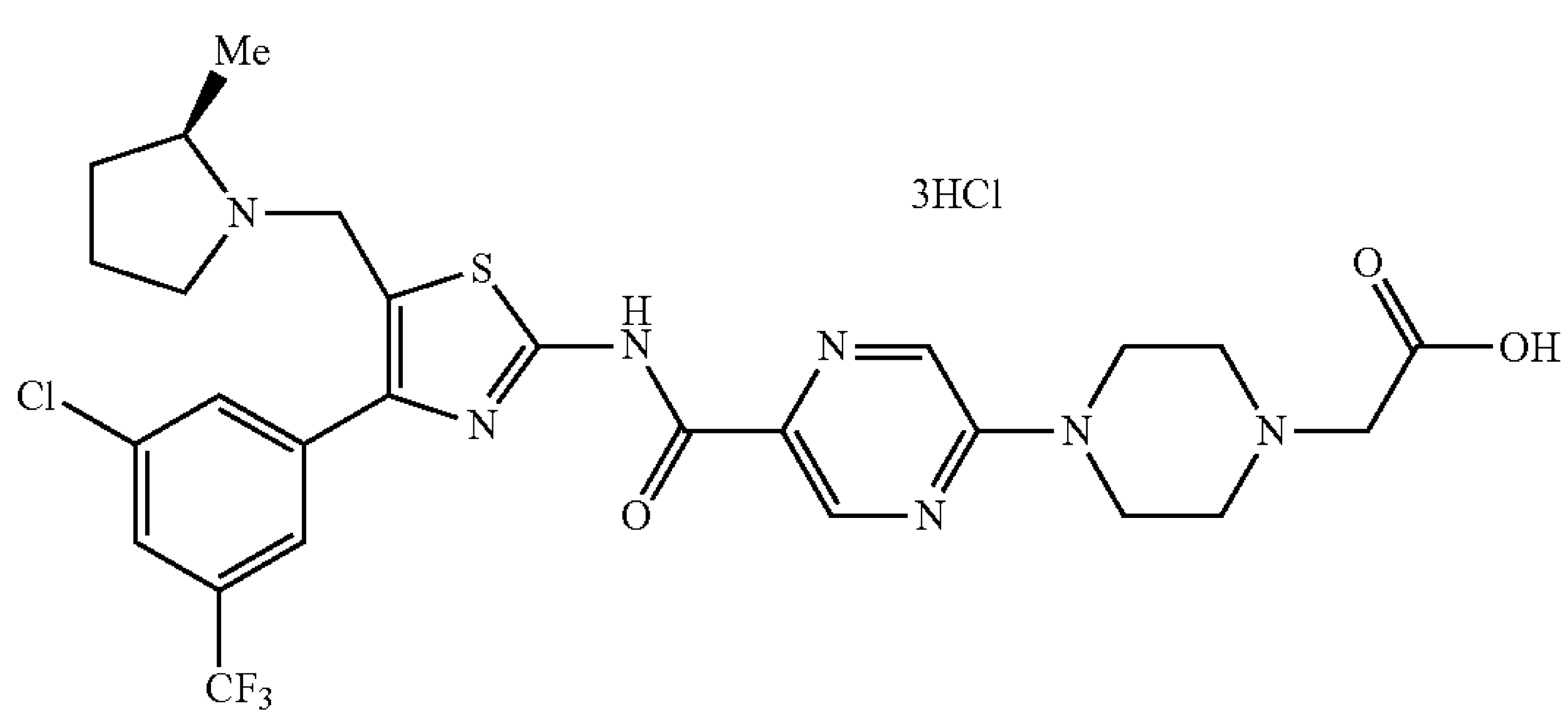
Ex	Structure
10	
11	
12	
13	

TABLE 75

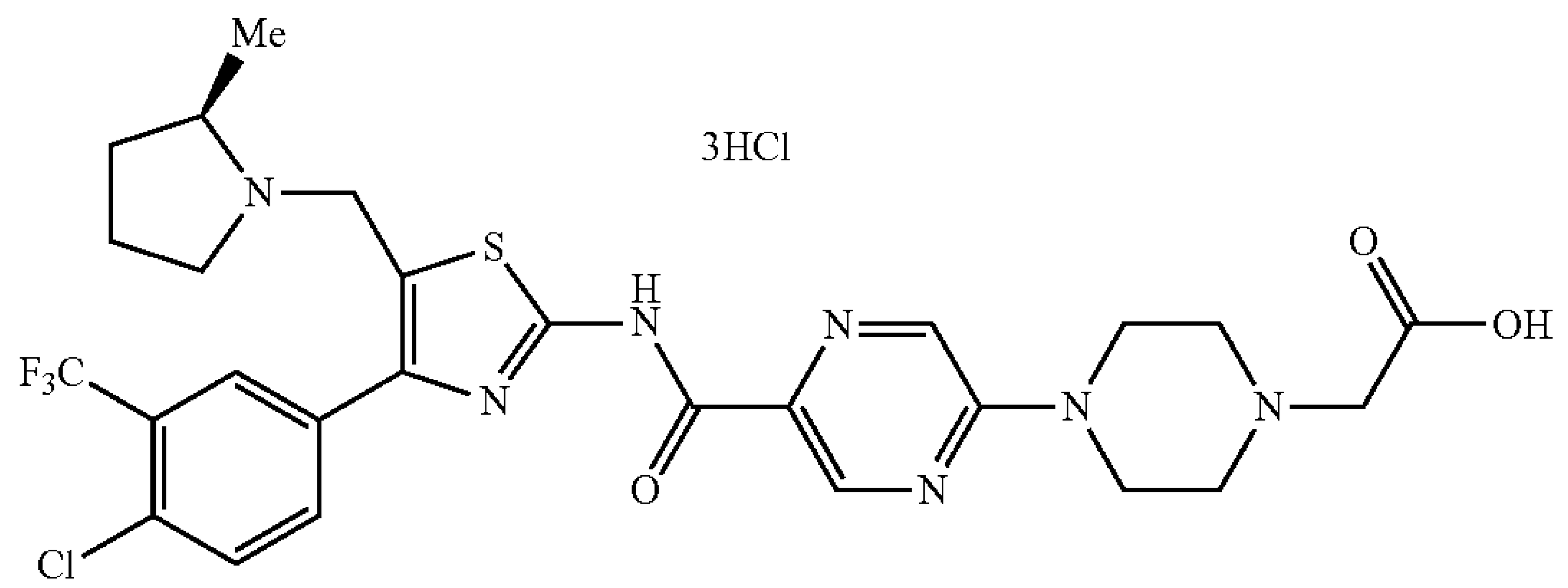
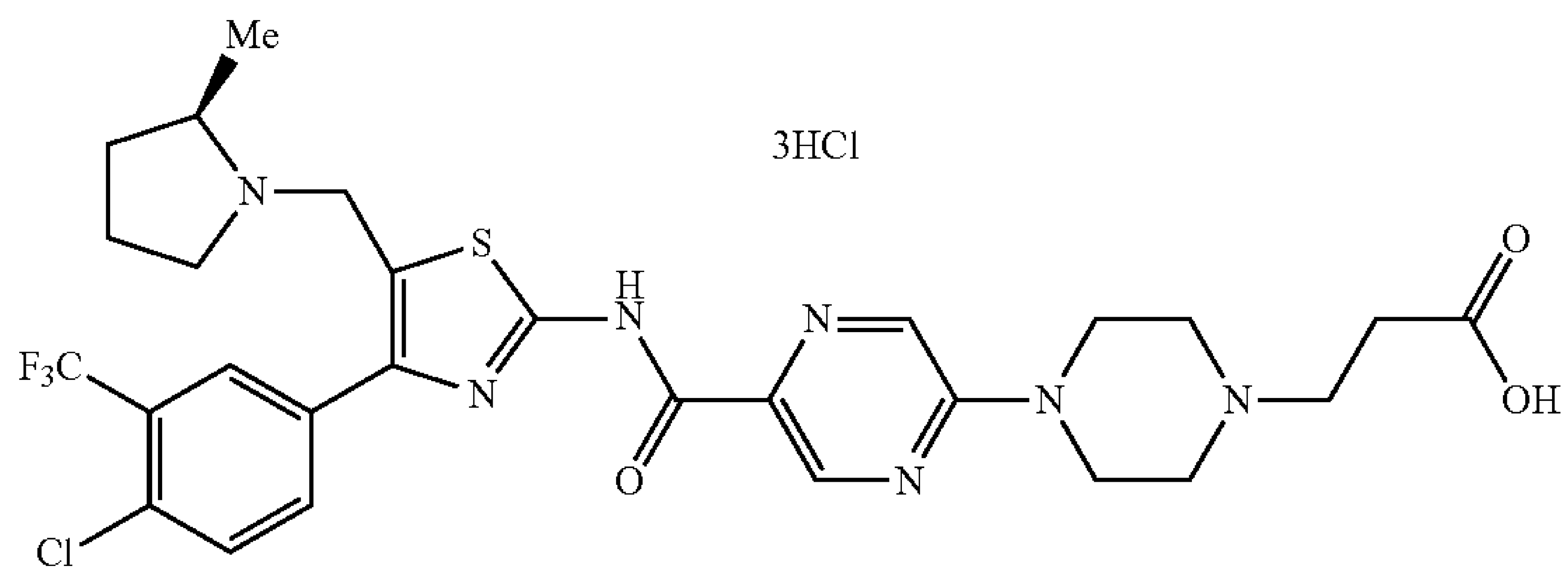
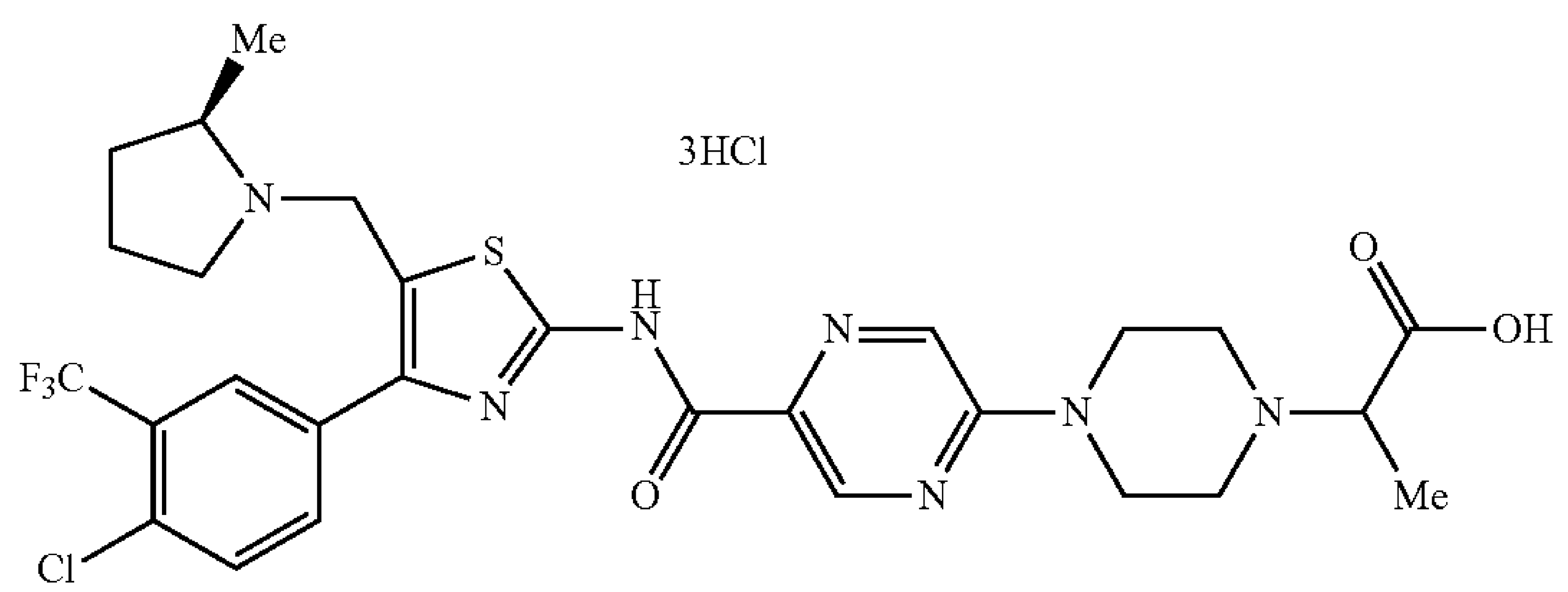
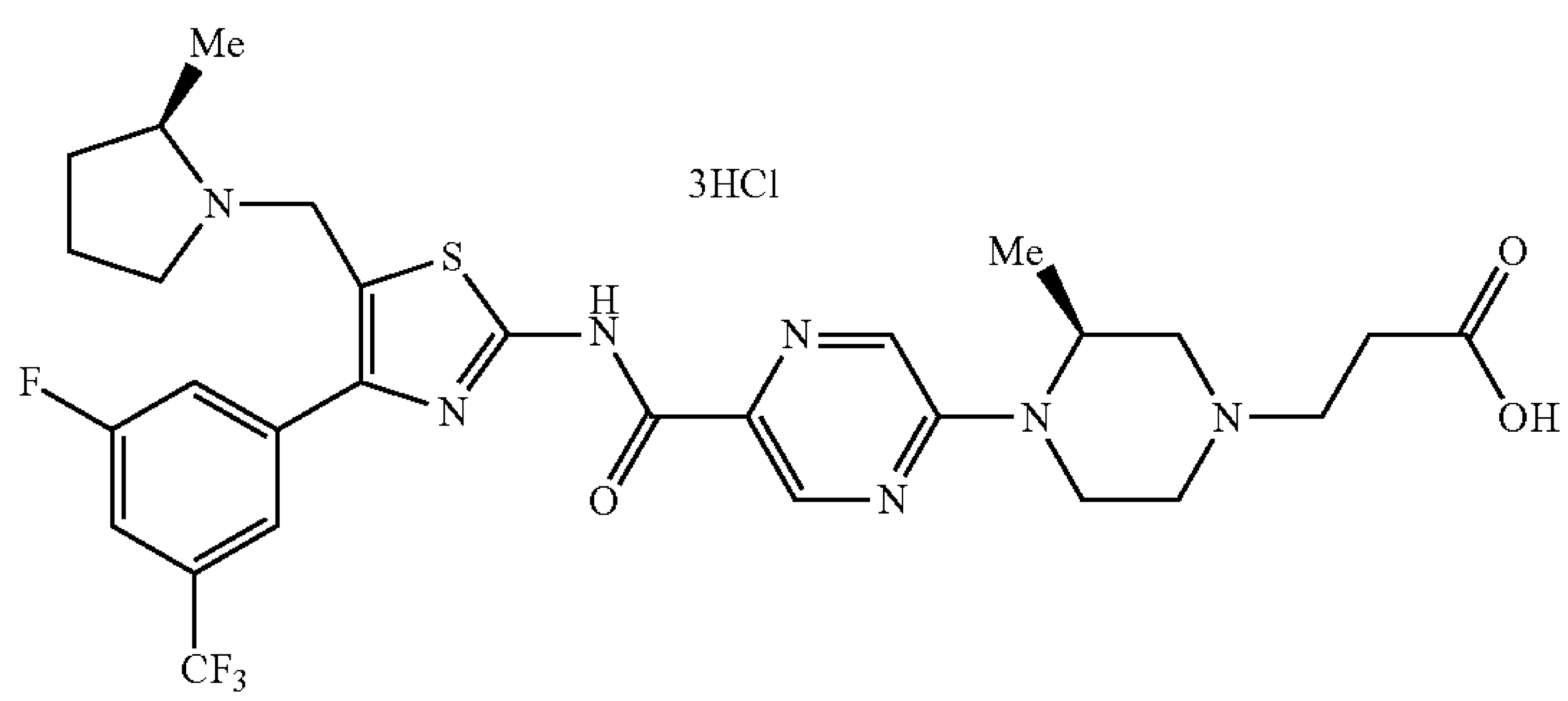
Ex	Structure
14	 3HCl
15	 3HCl
16	 3HCl
17	 3HCl

TABLE 76

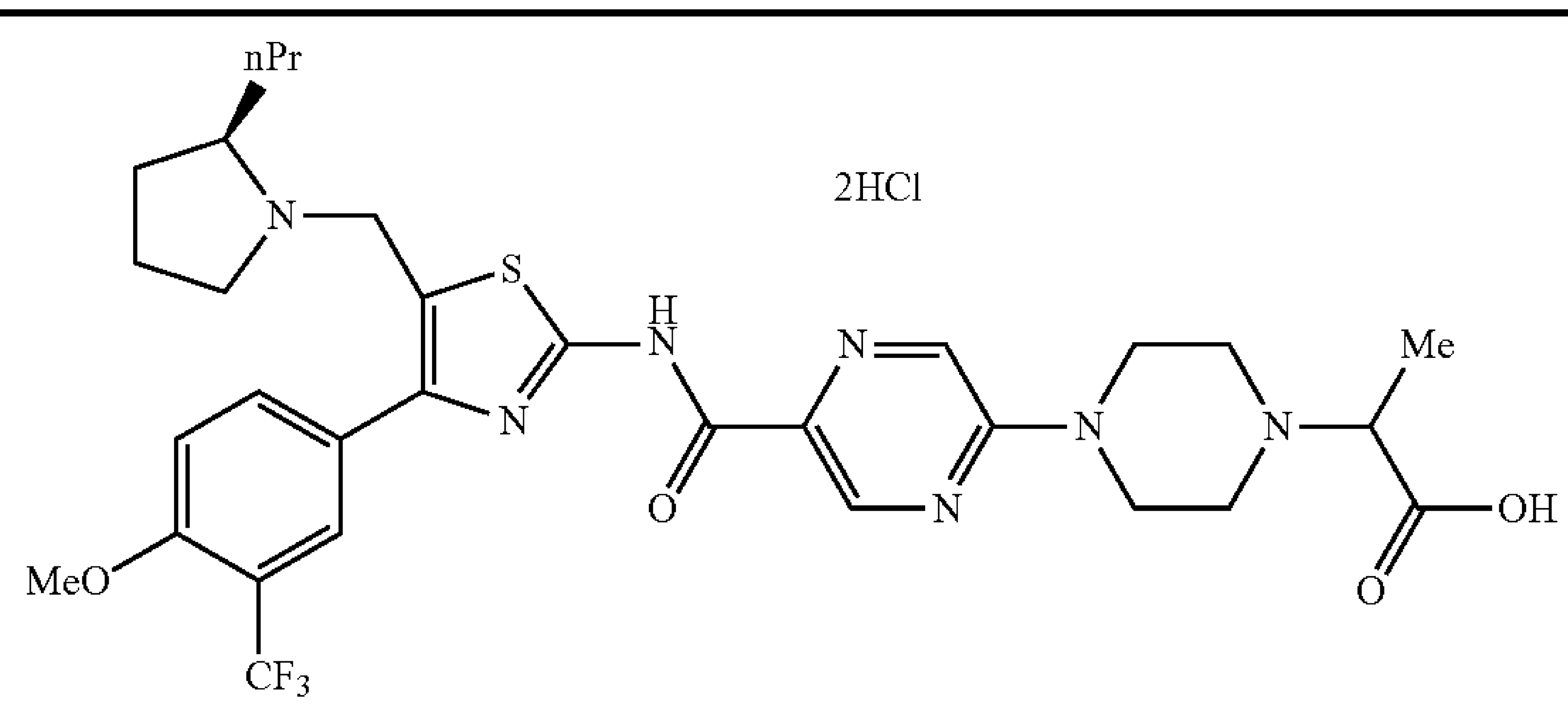
Ex	Structure
18	 2HCl

TABLE 76-continued

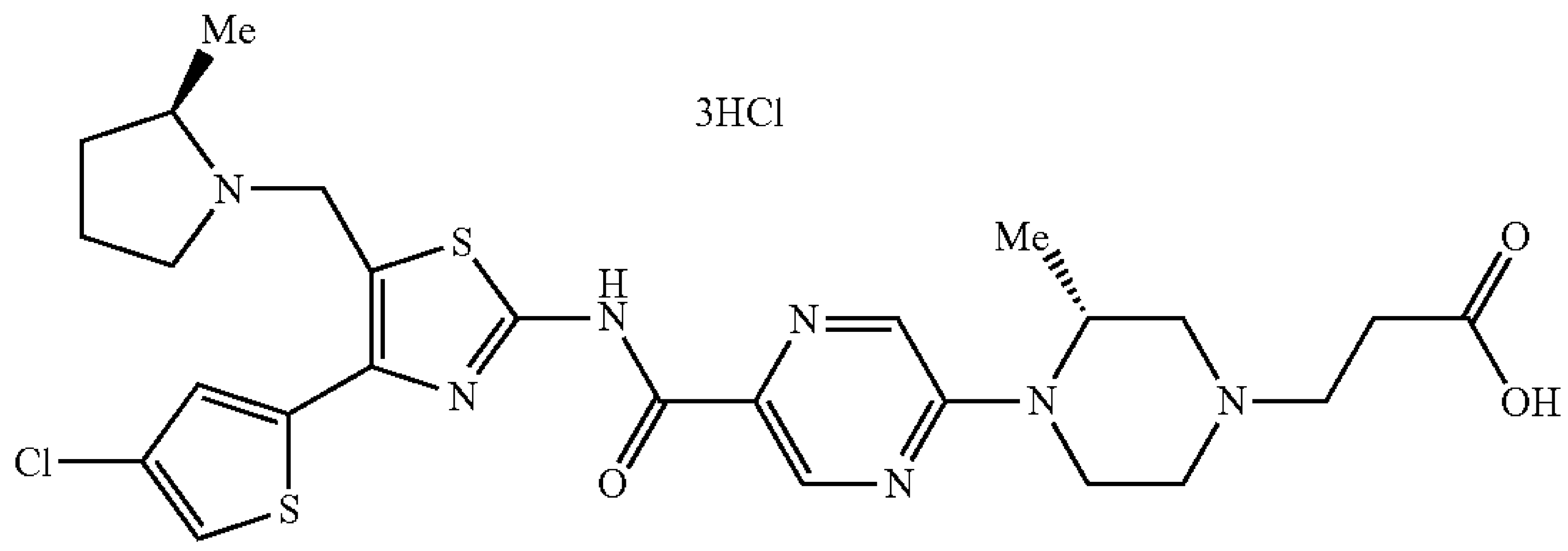
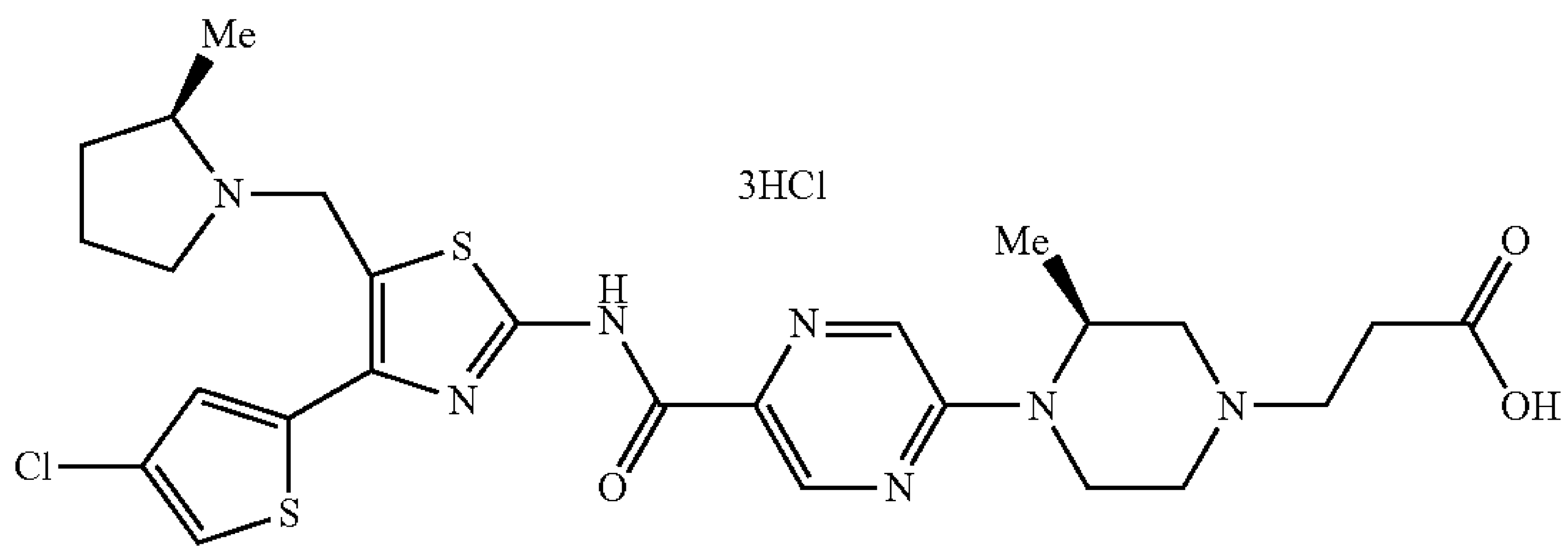
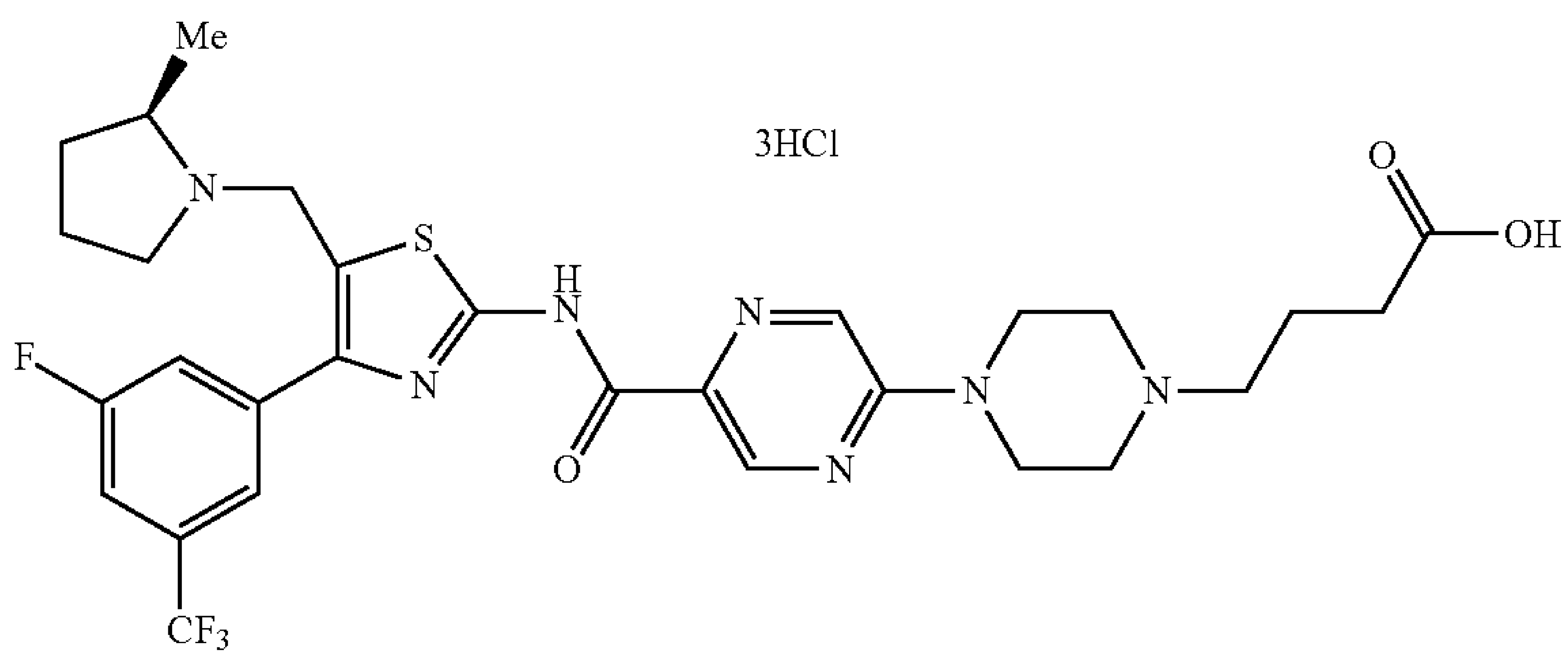
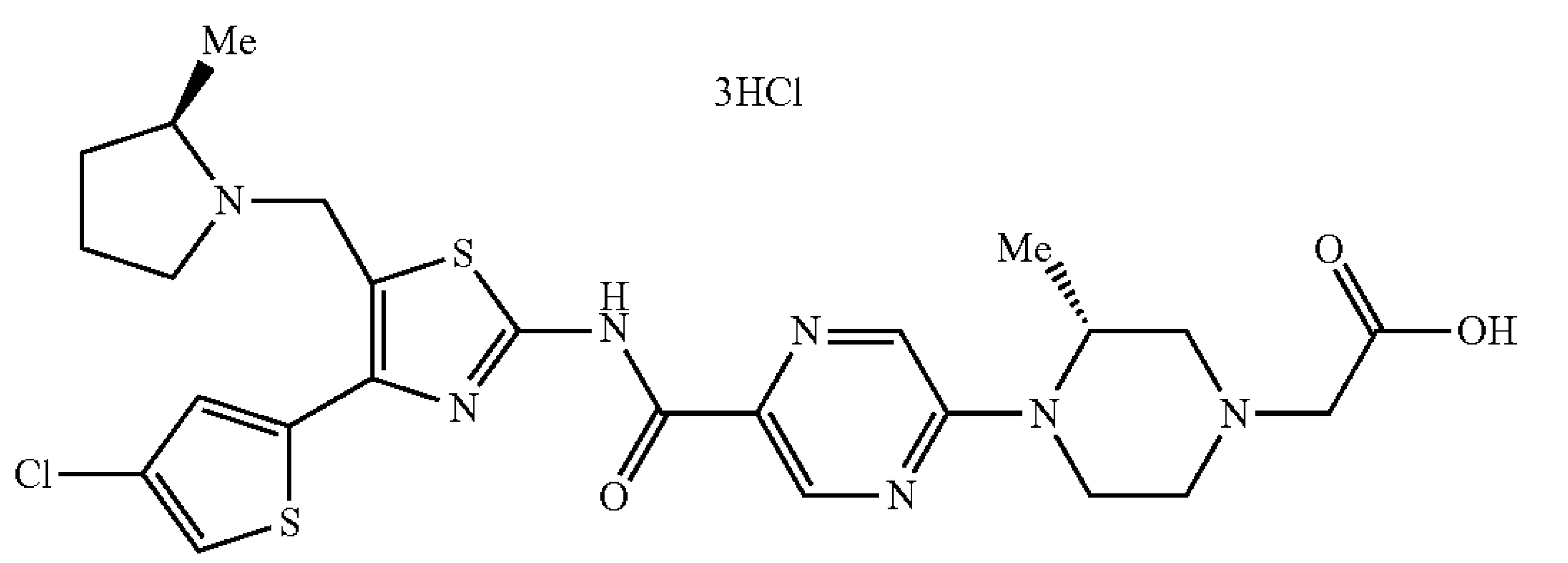
Ex	Structure
19	
20	
21	
22	

TABLE 77

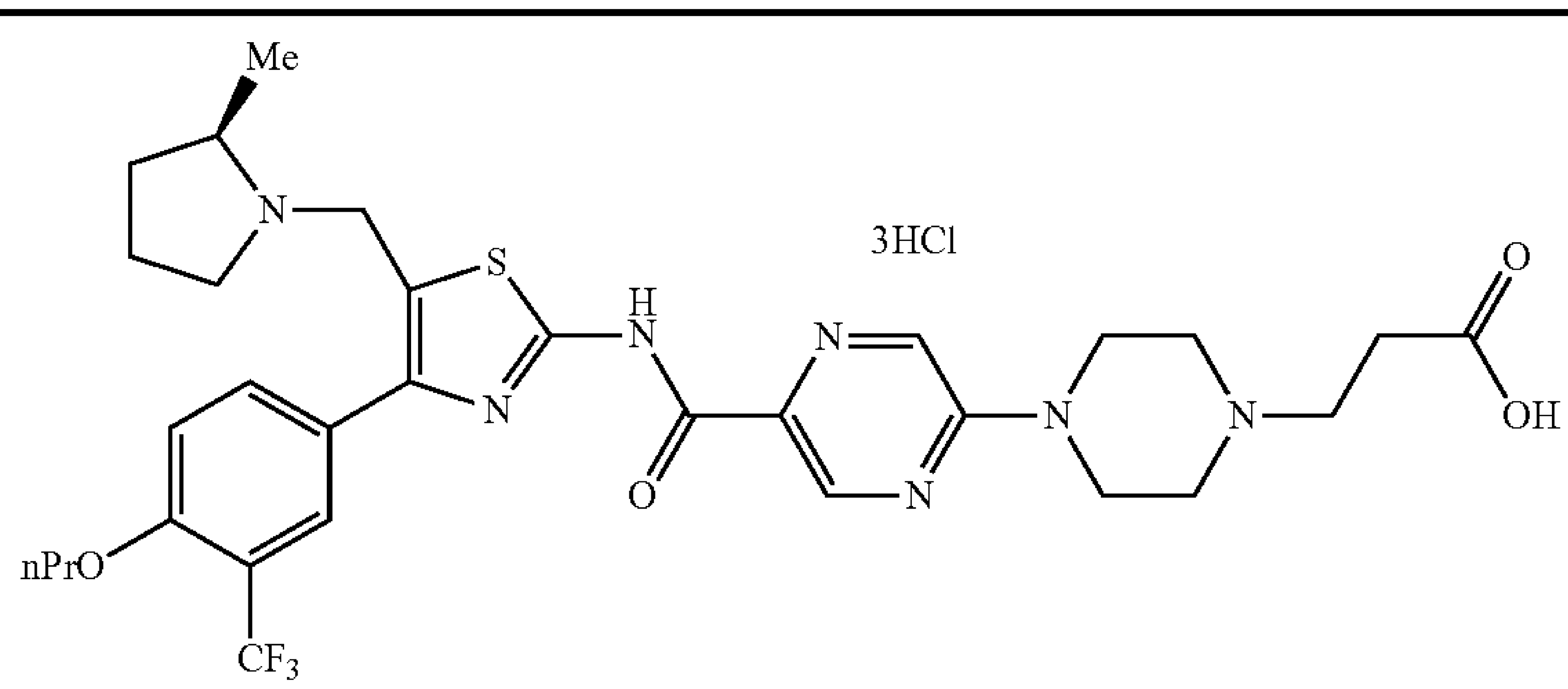
Ex	Structure
23	

TABLE 77-continued

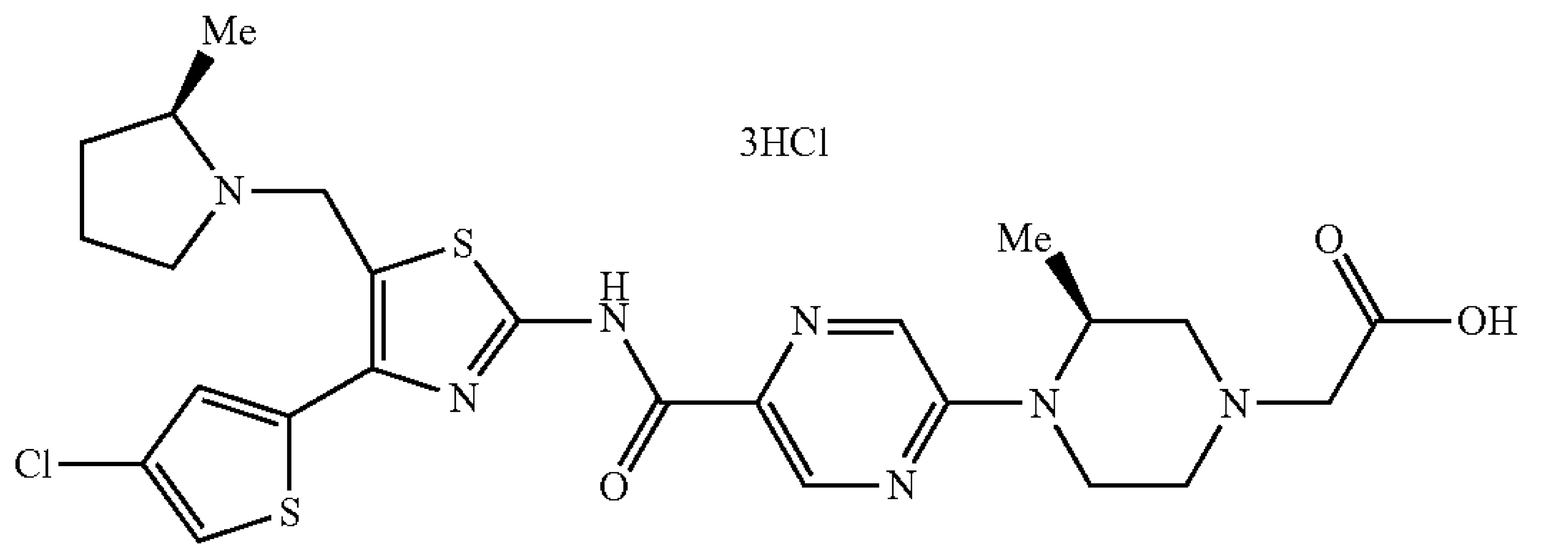
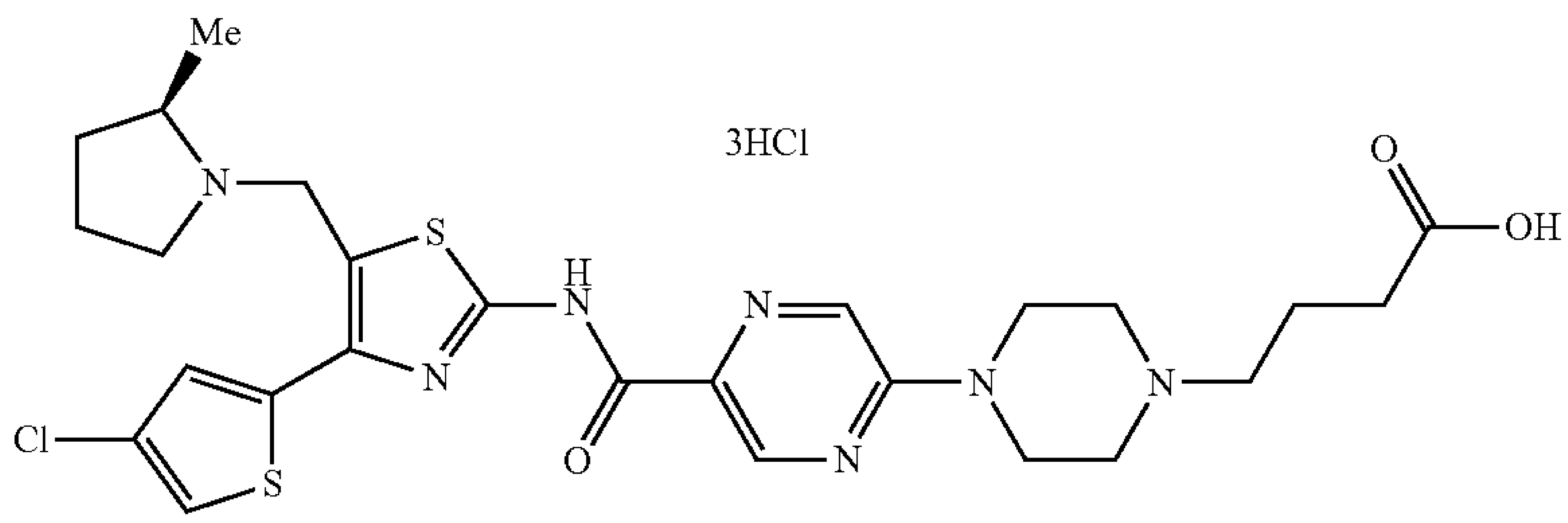
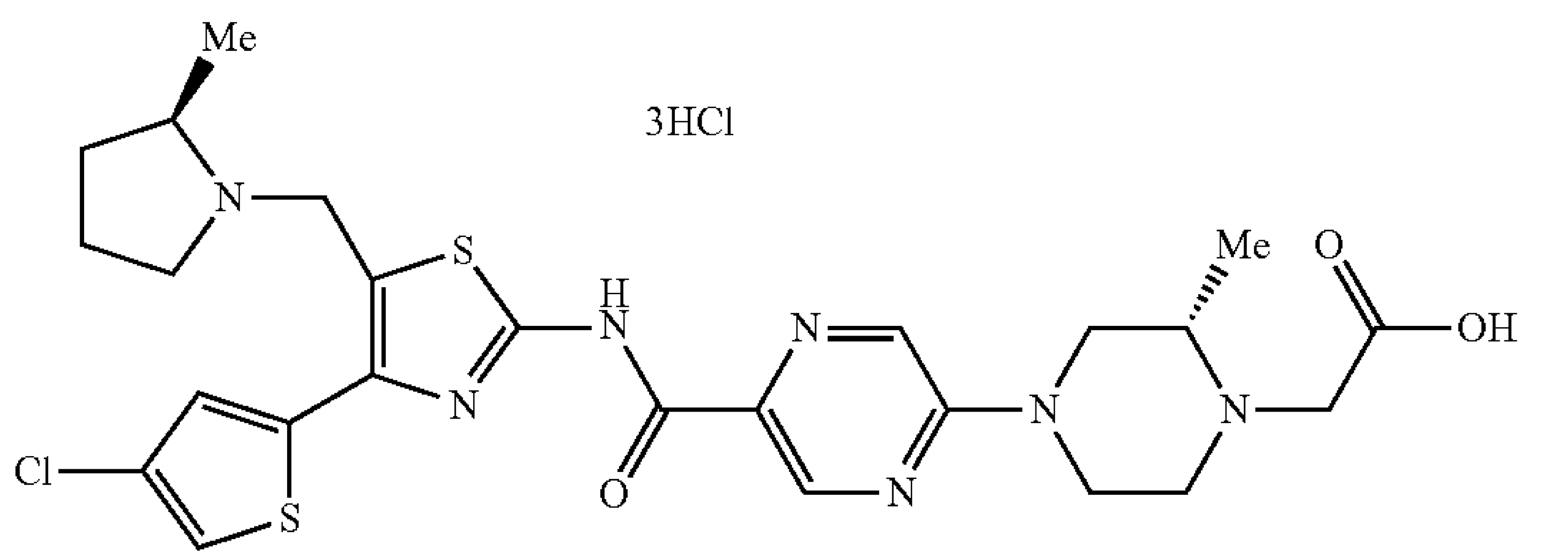
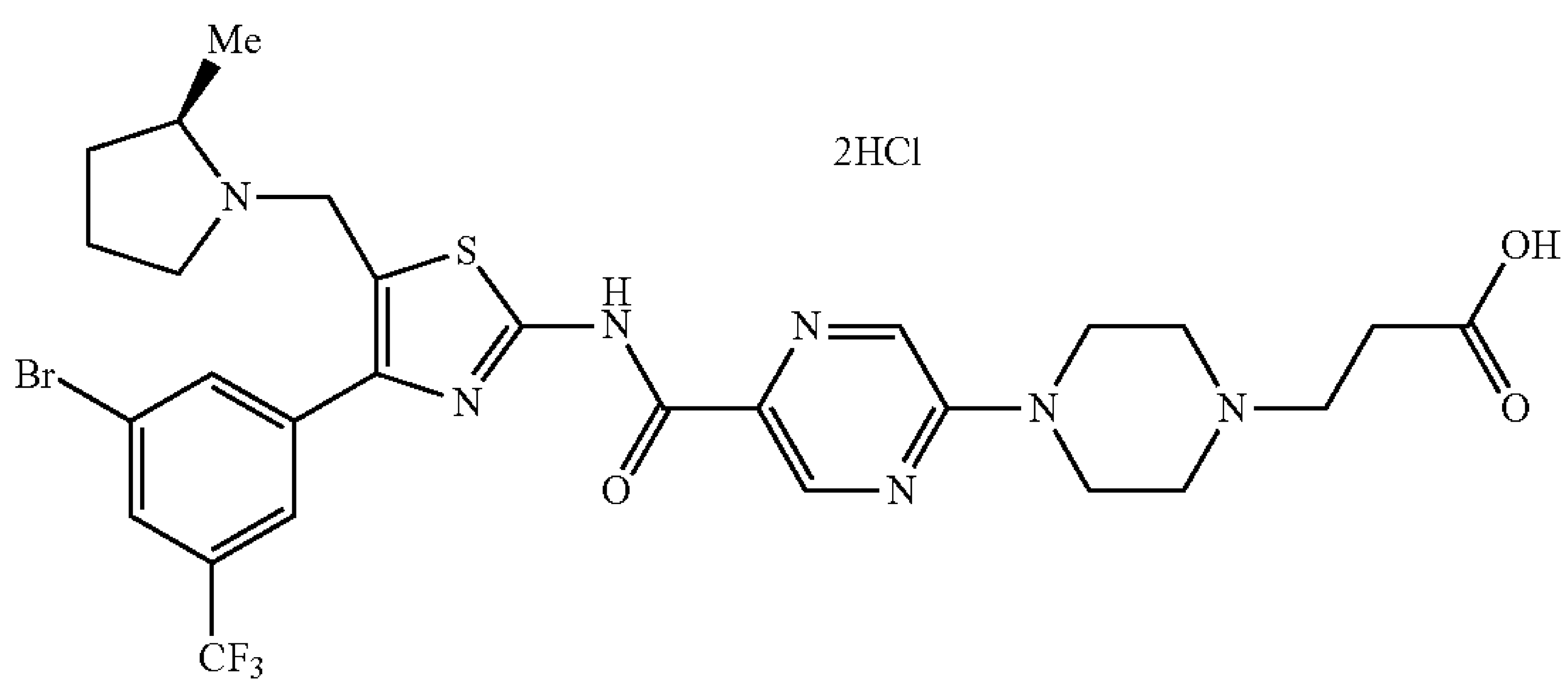
Ex	Structure
24	
25	
26	
27	

TABLE 78

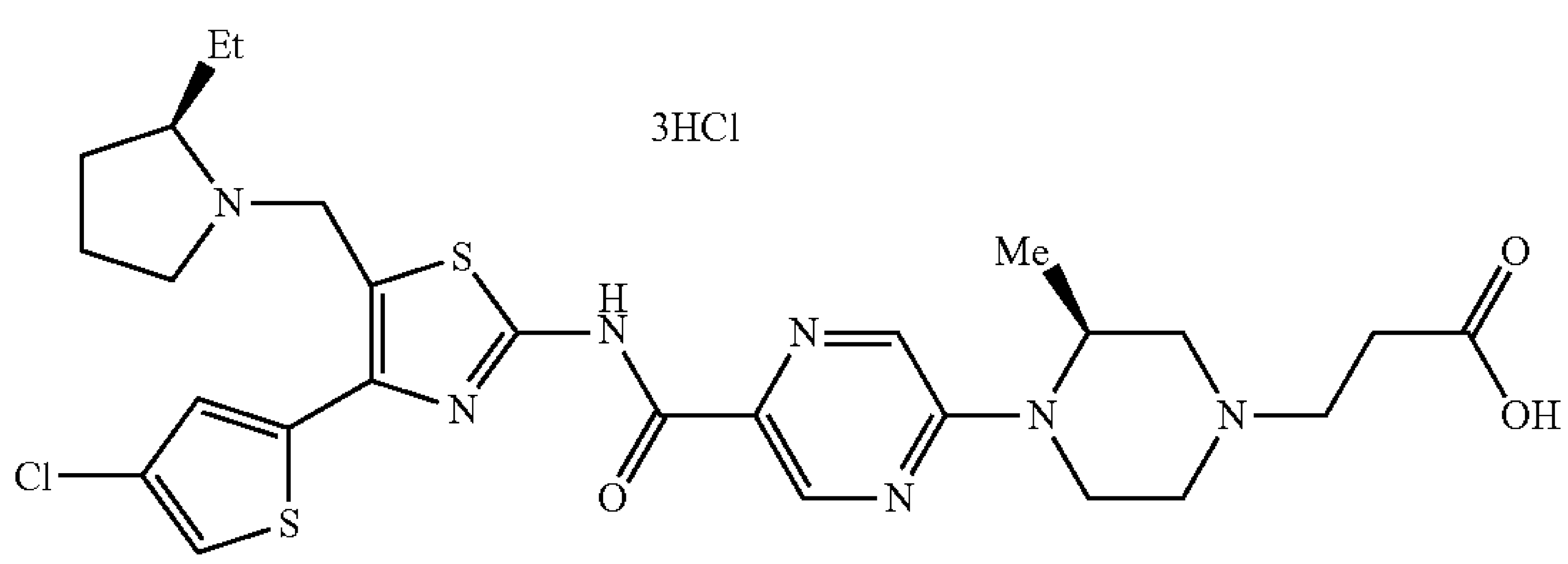
Ex	Structure
28	

TABLE 78-continued

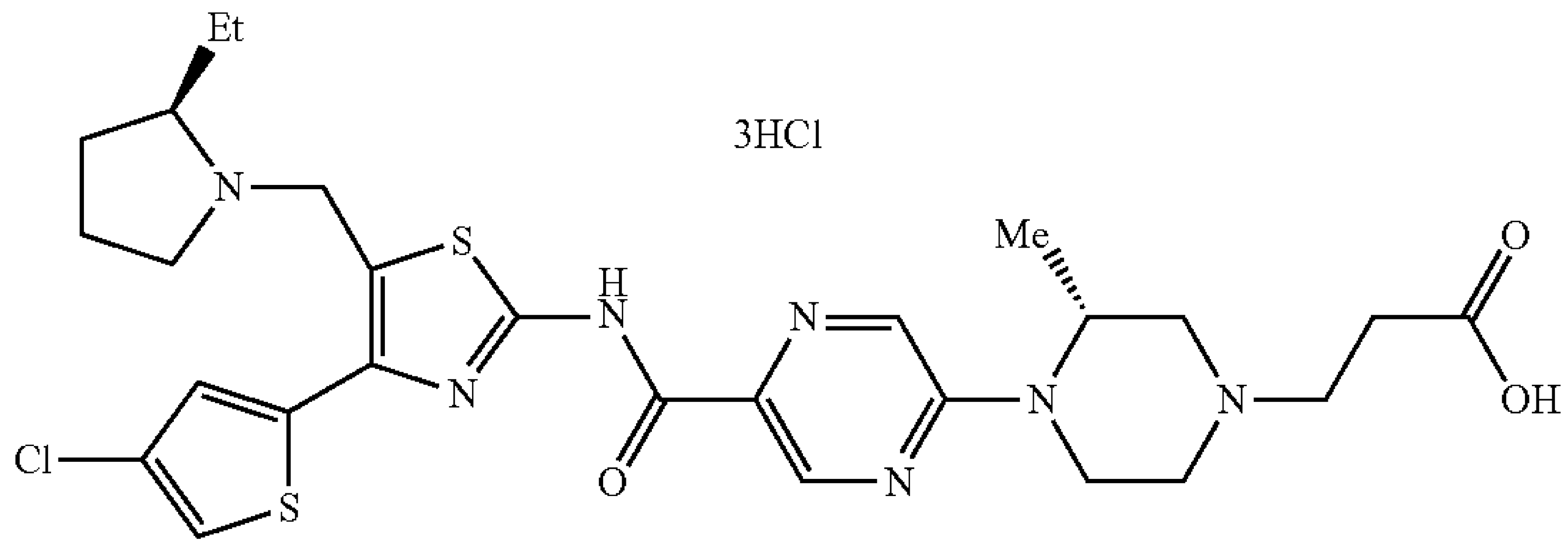
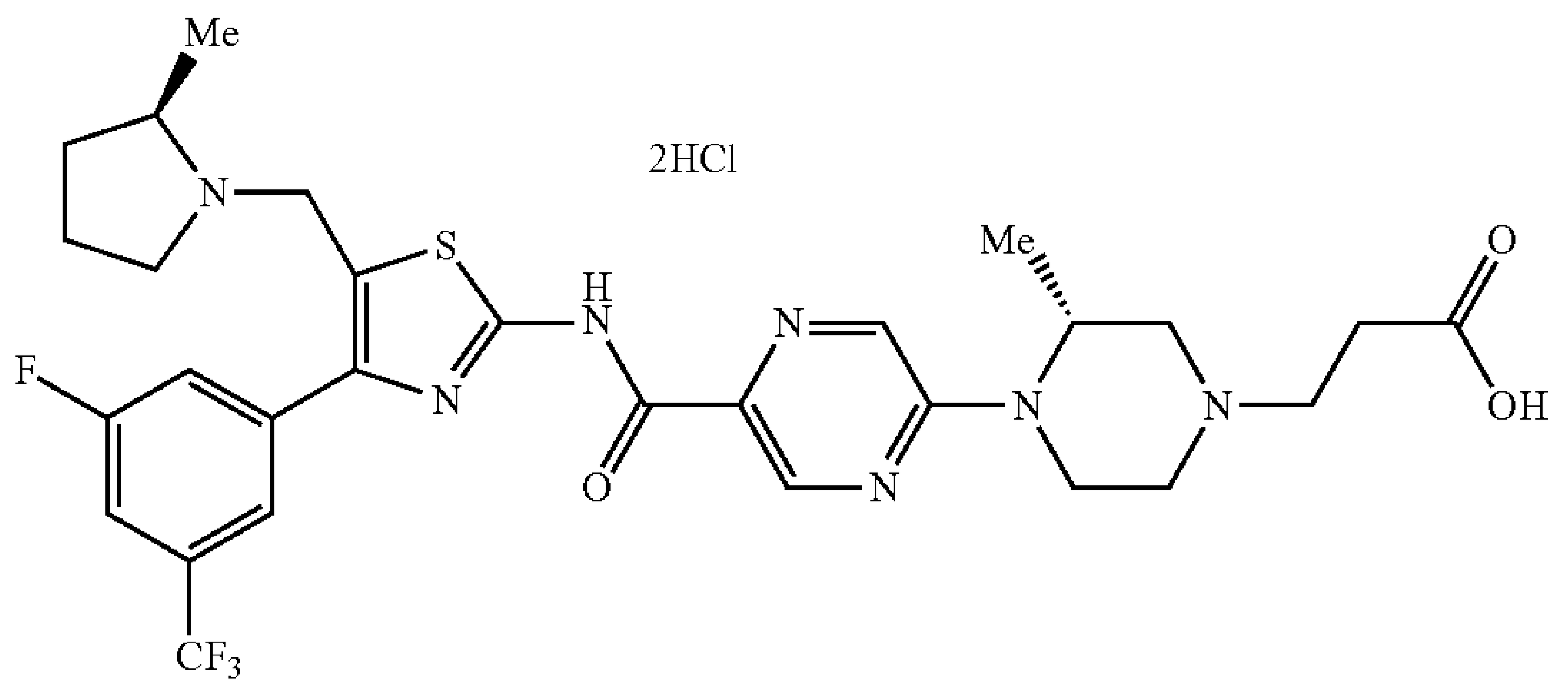
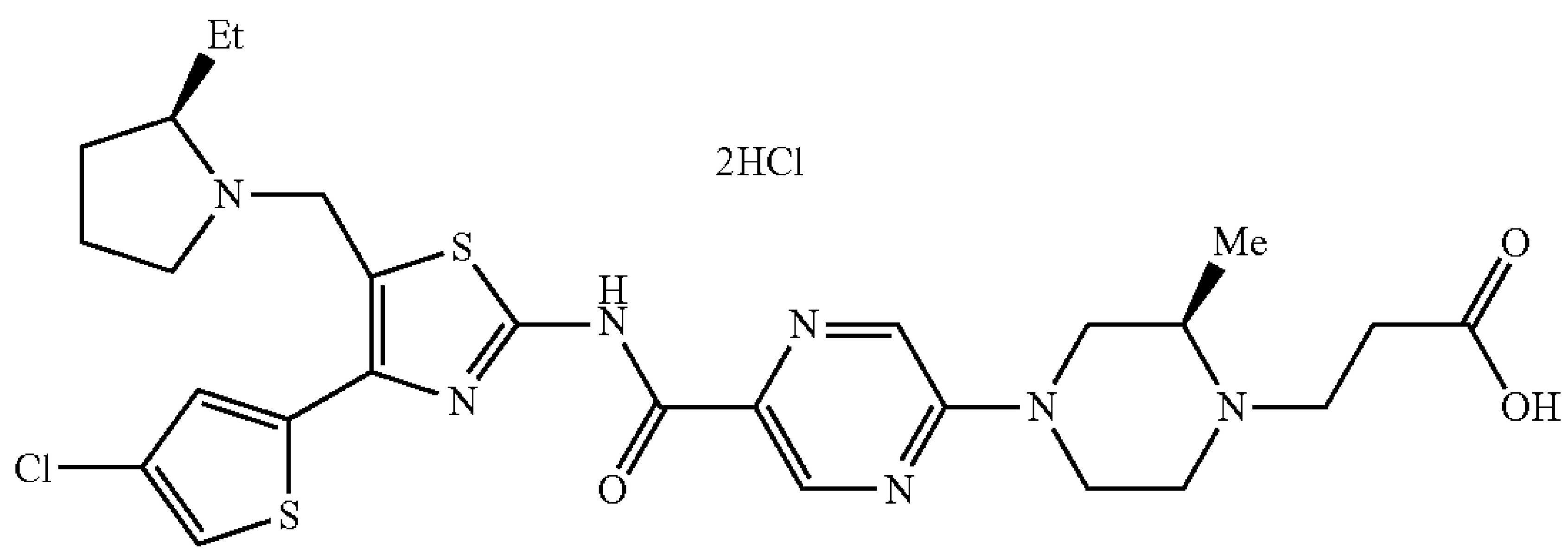
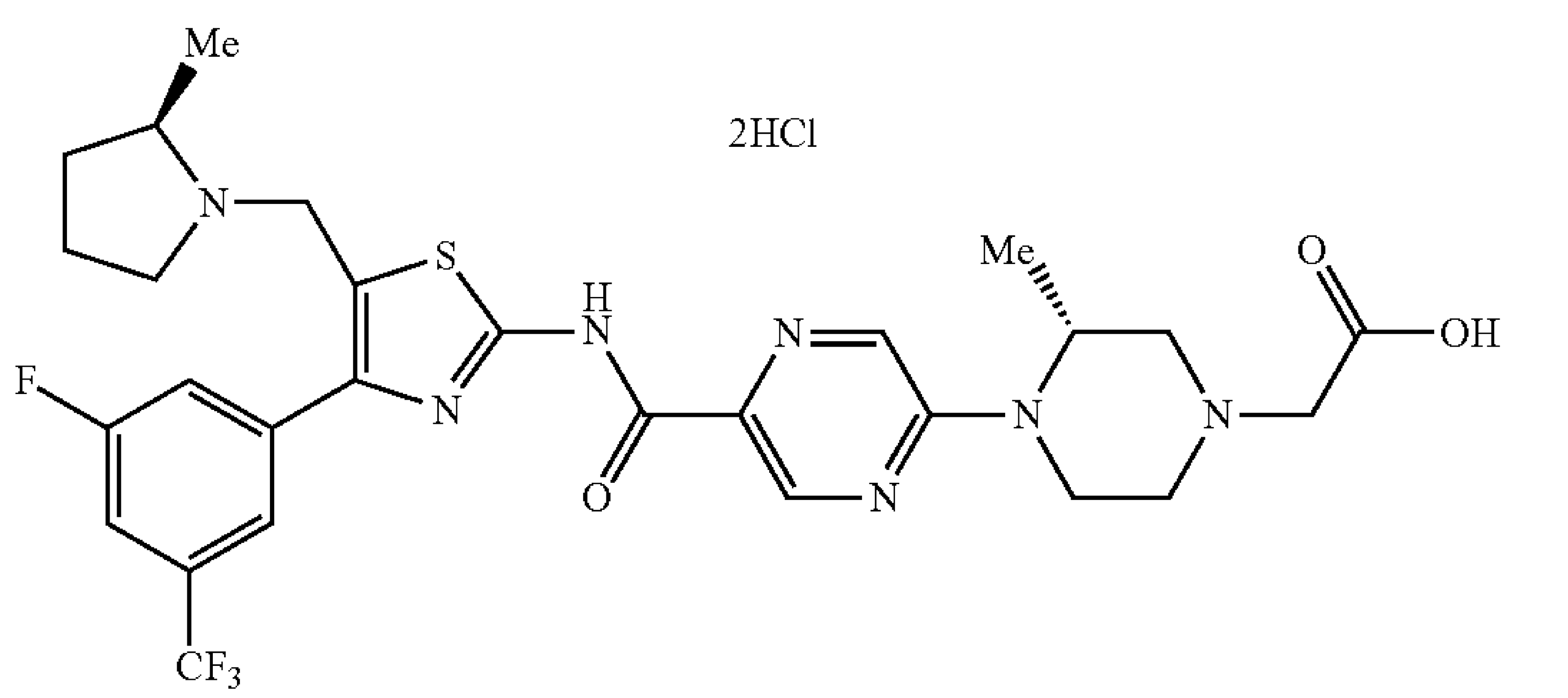
Ex	Structure
29	
30	
31	
32	

TABLE 79

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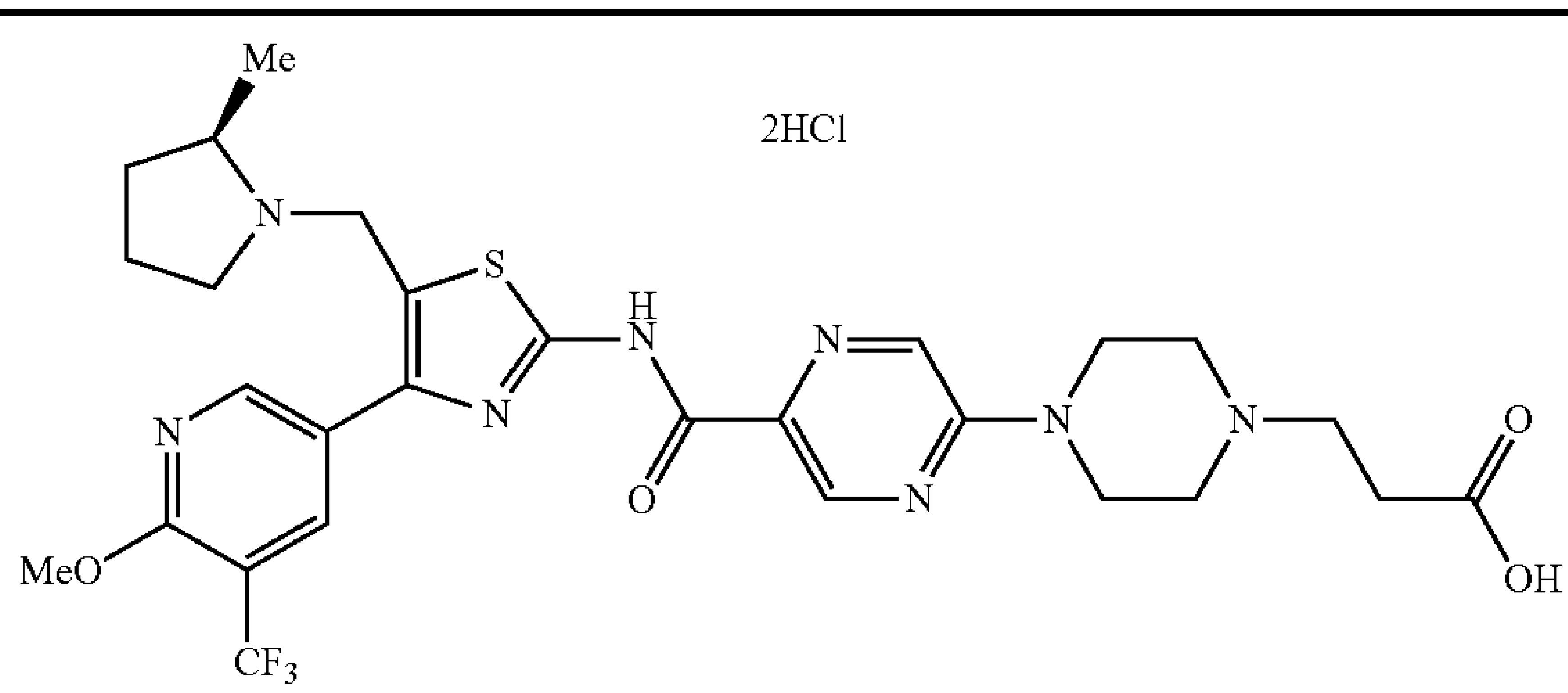
33	

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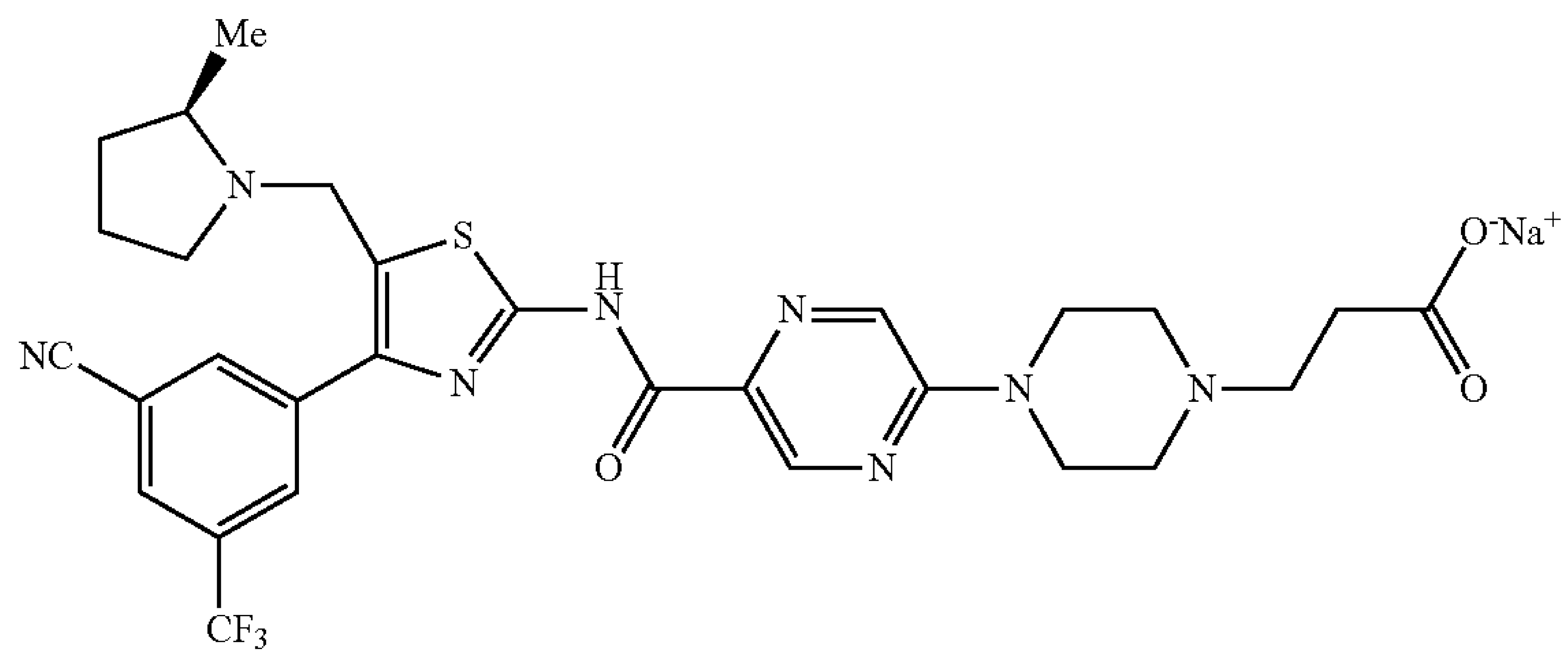
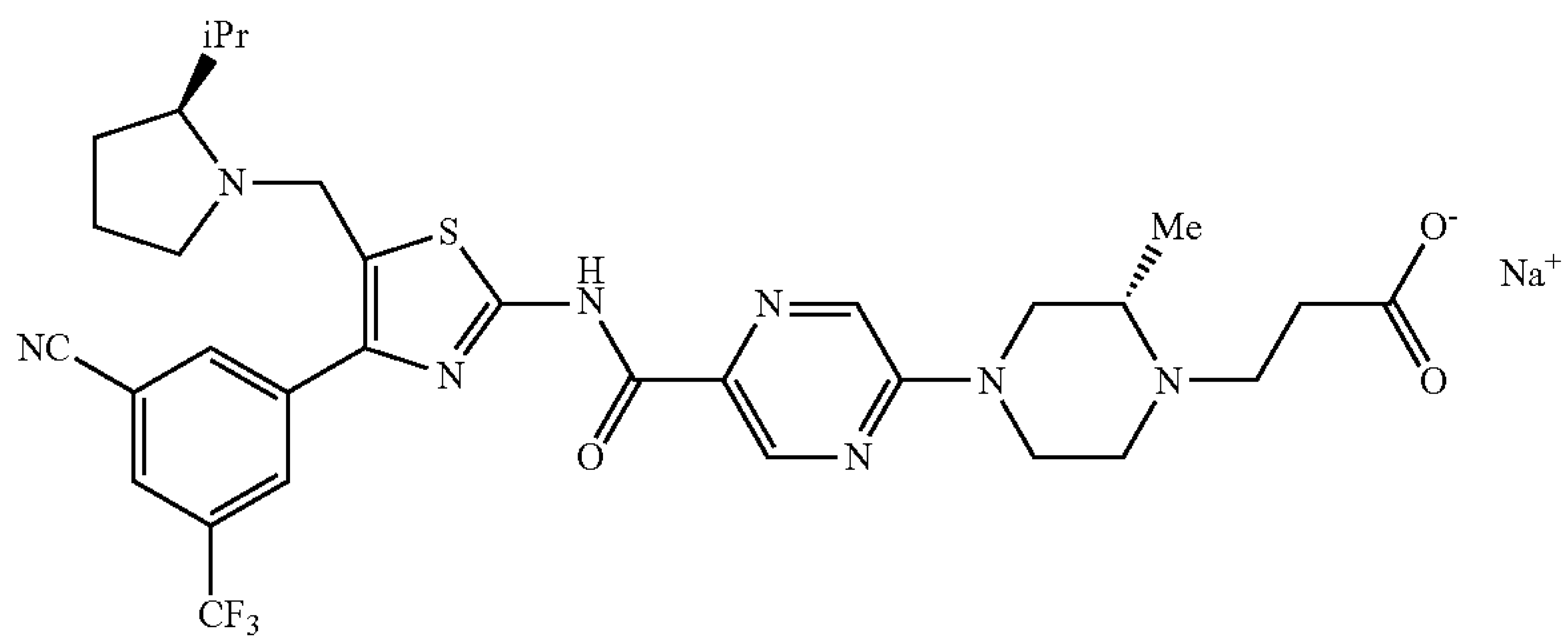
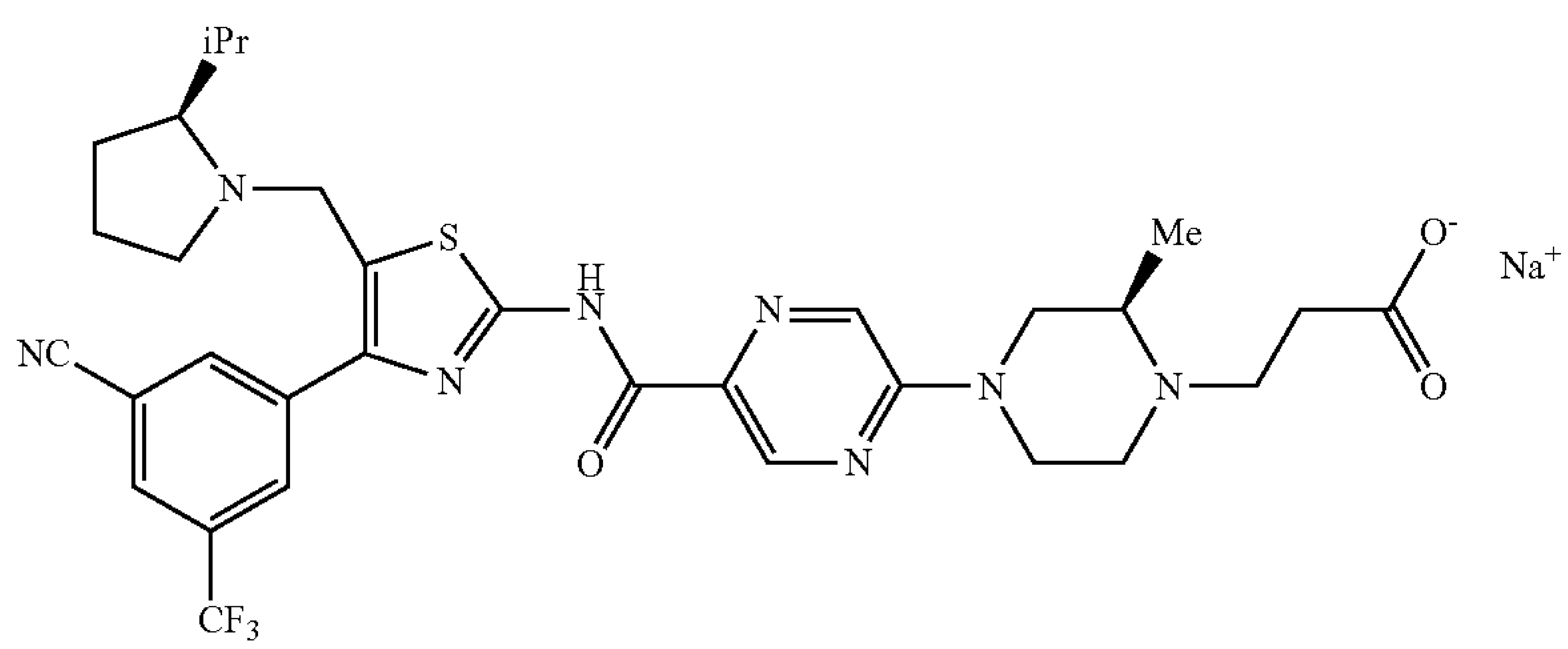
34	
35	
36	

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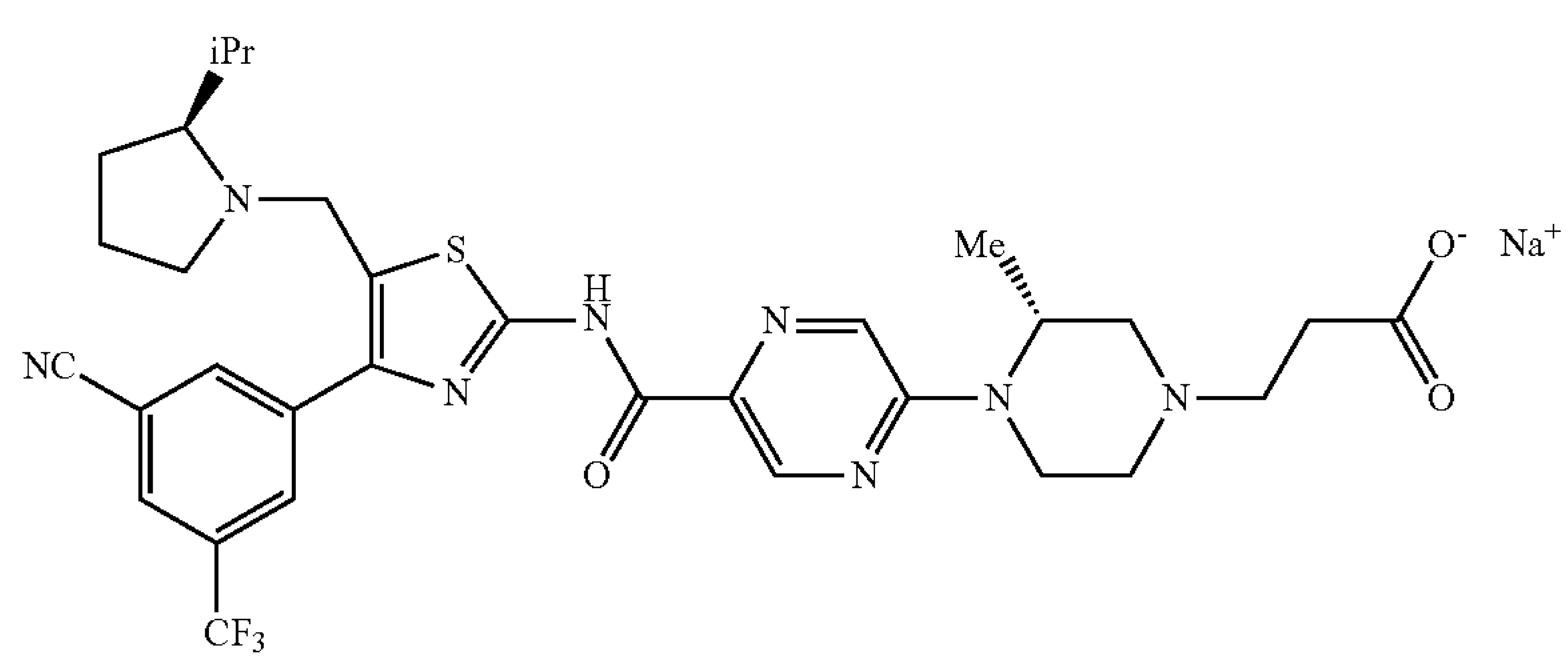
37	

TABLE 80-continued

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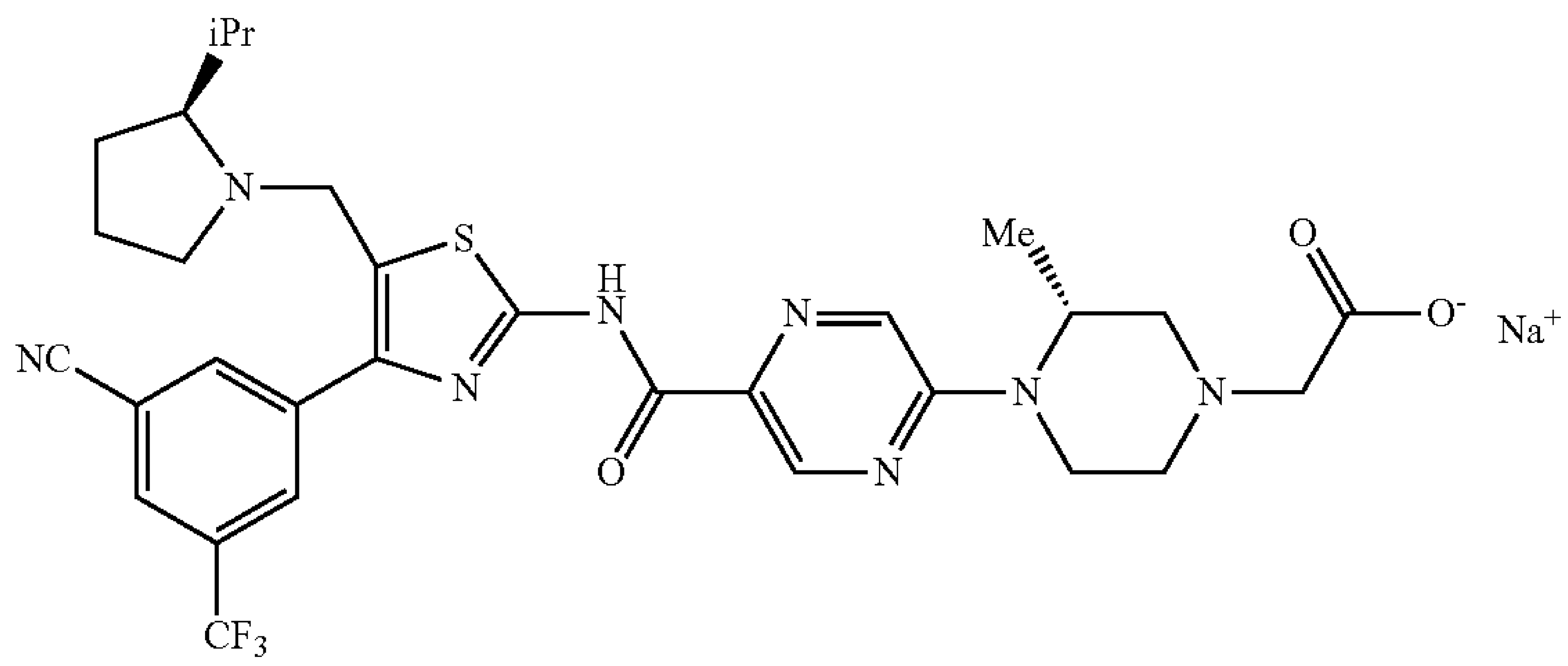
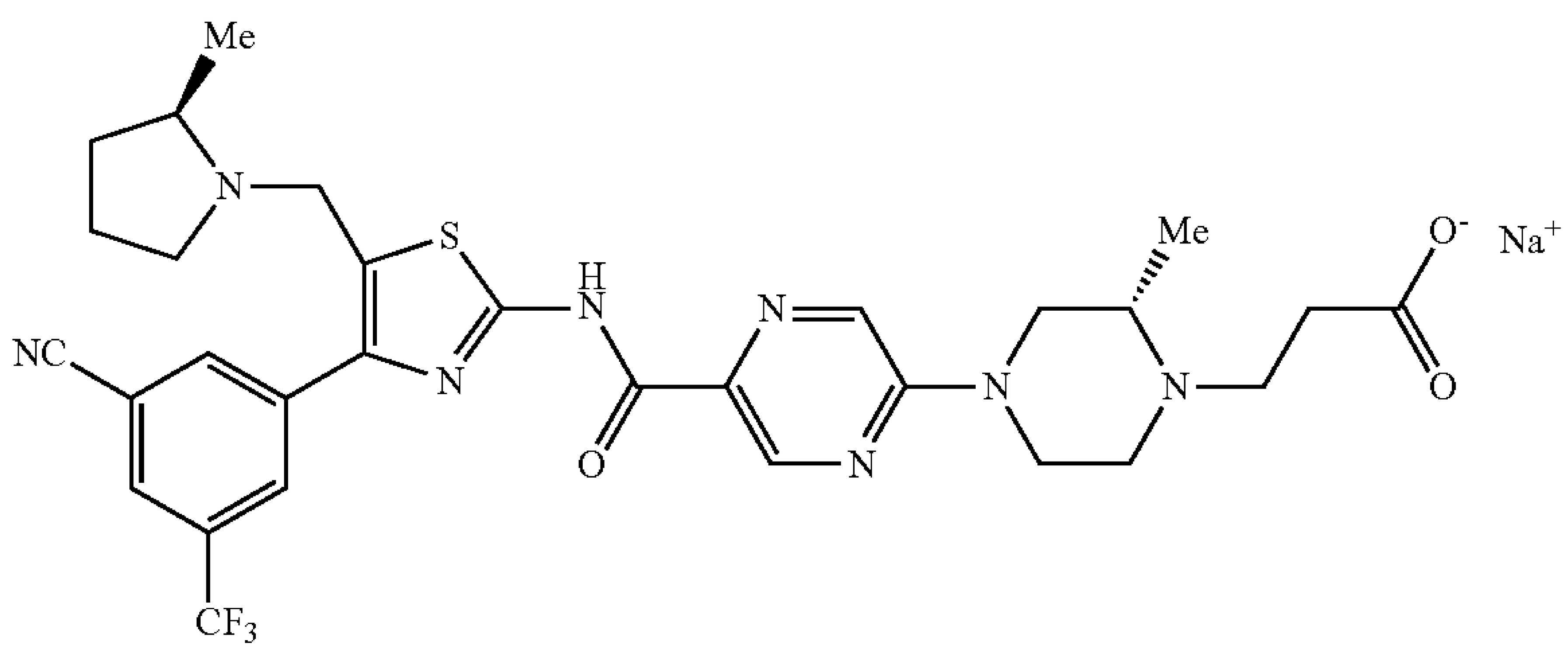
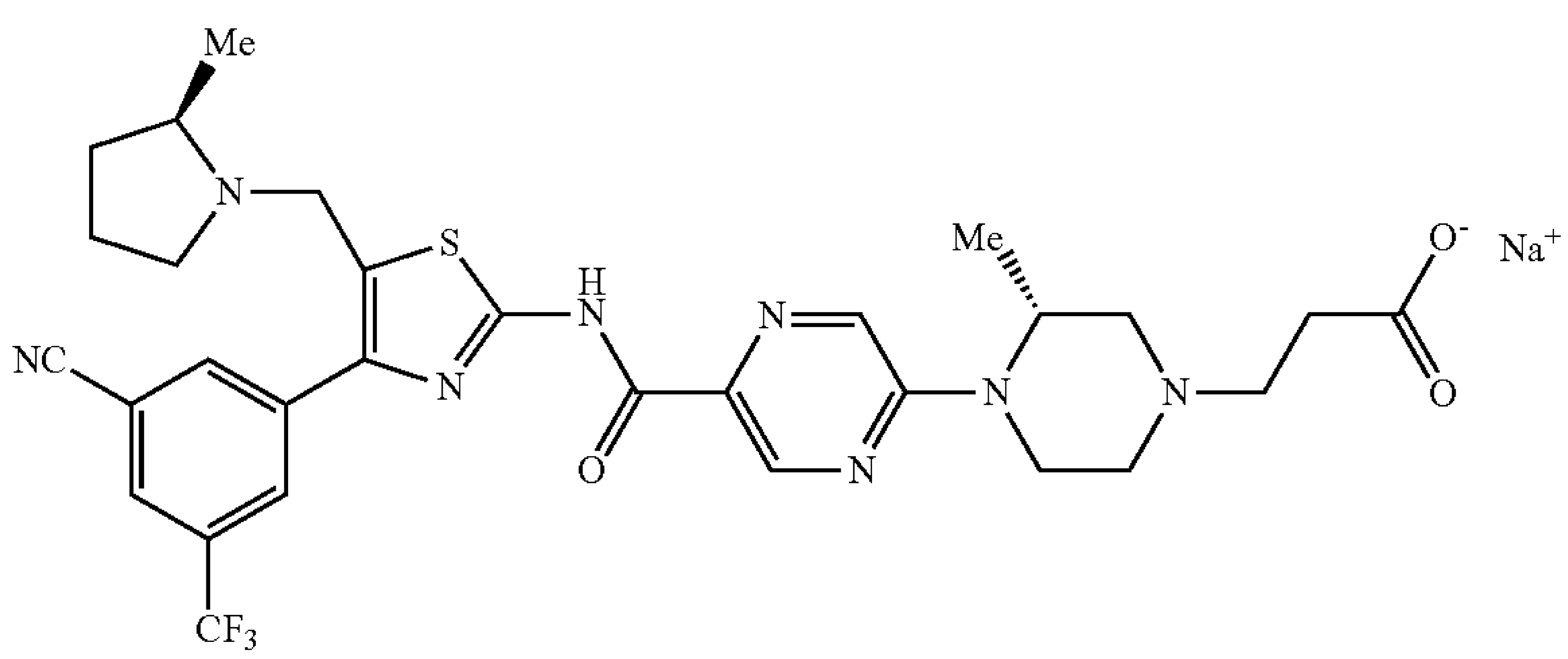
38	
39	
40	

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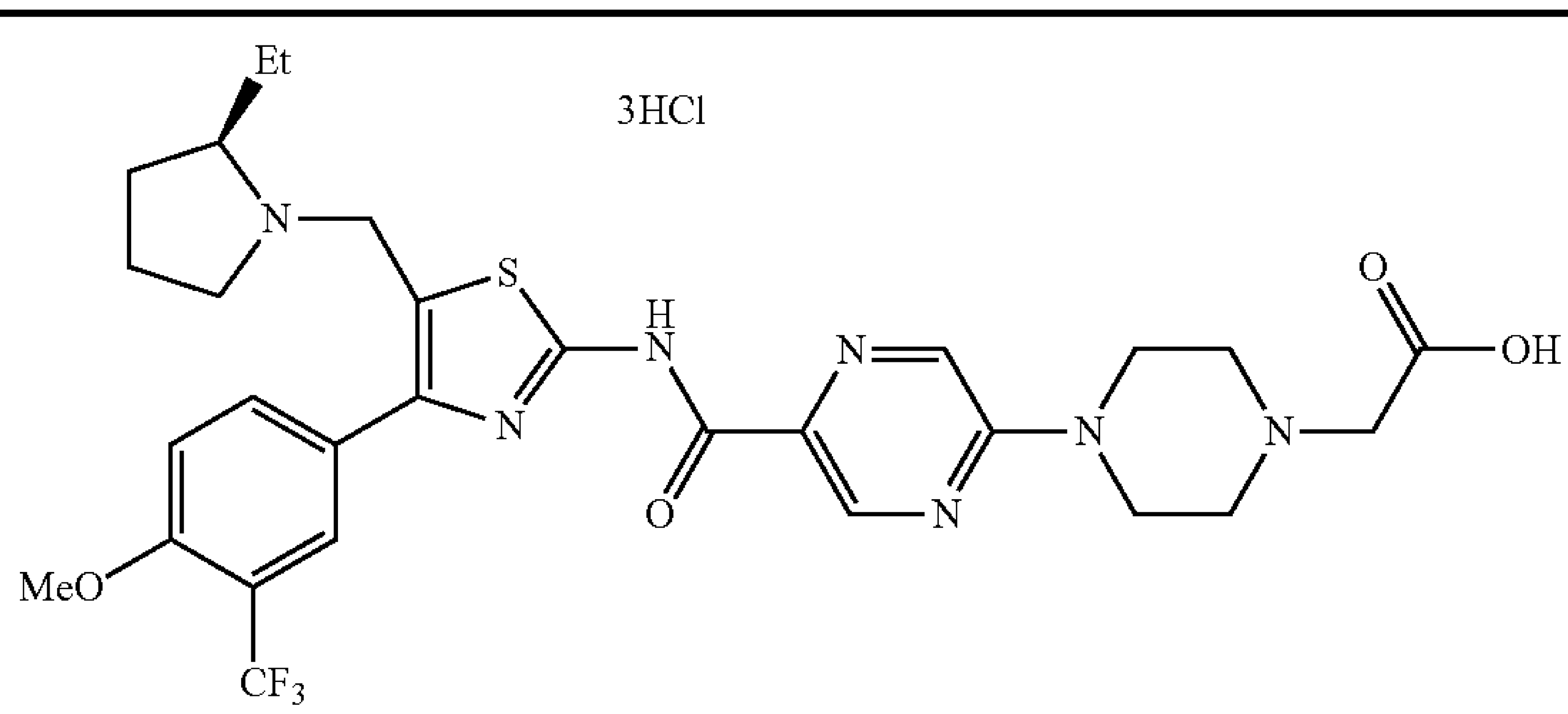
41	

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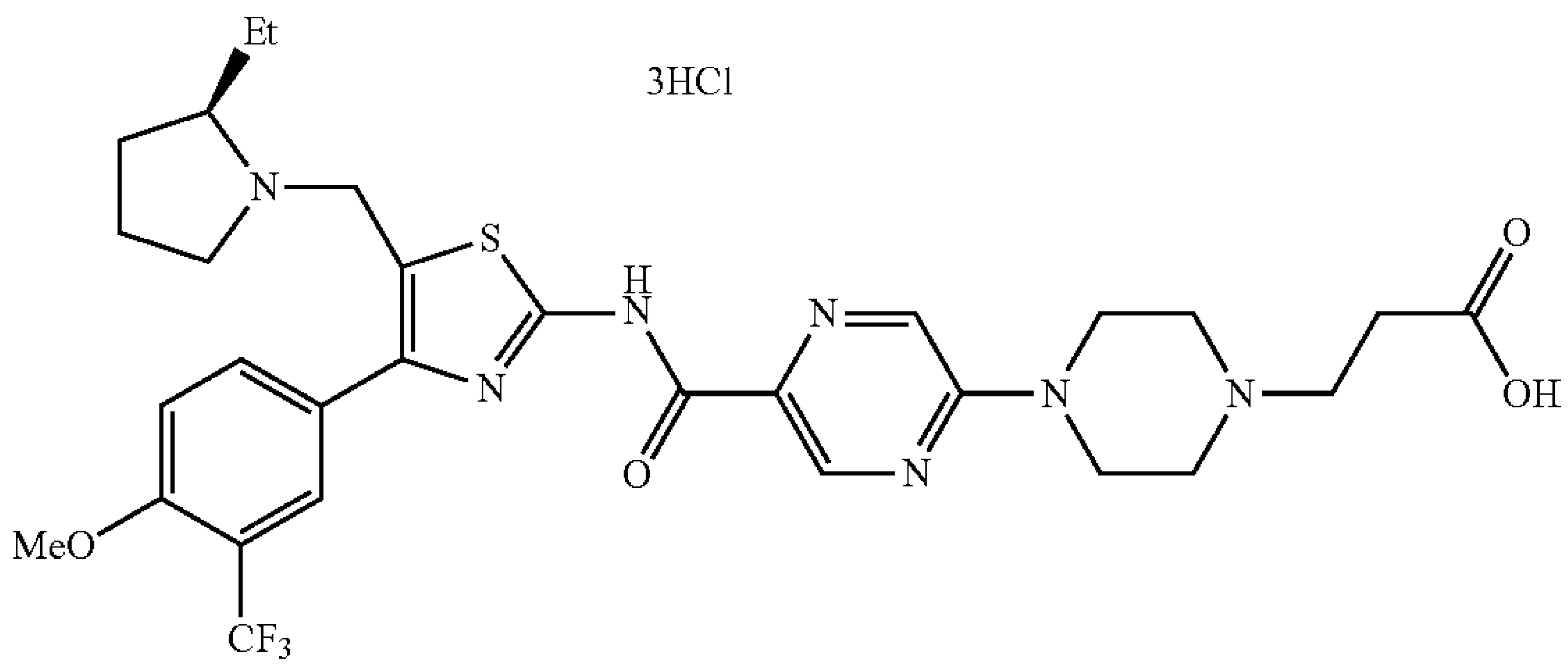
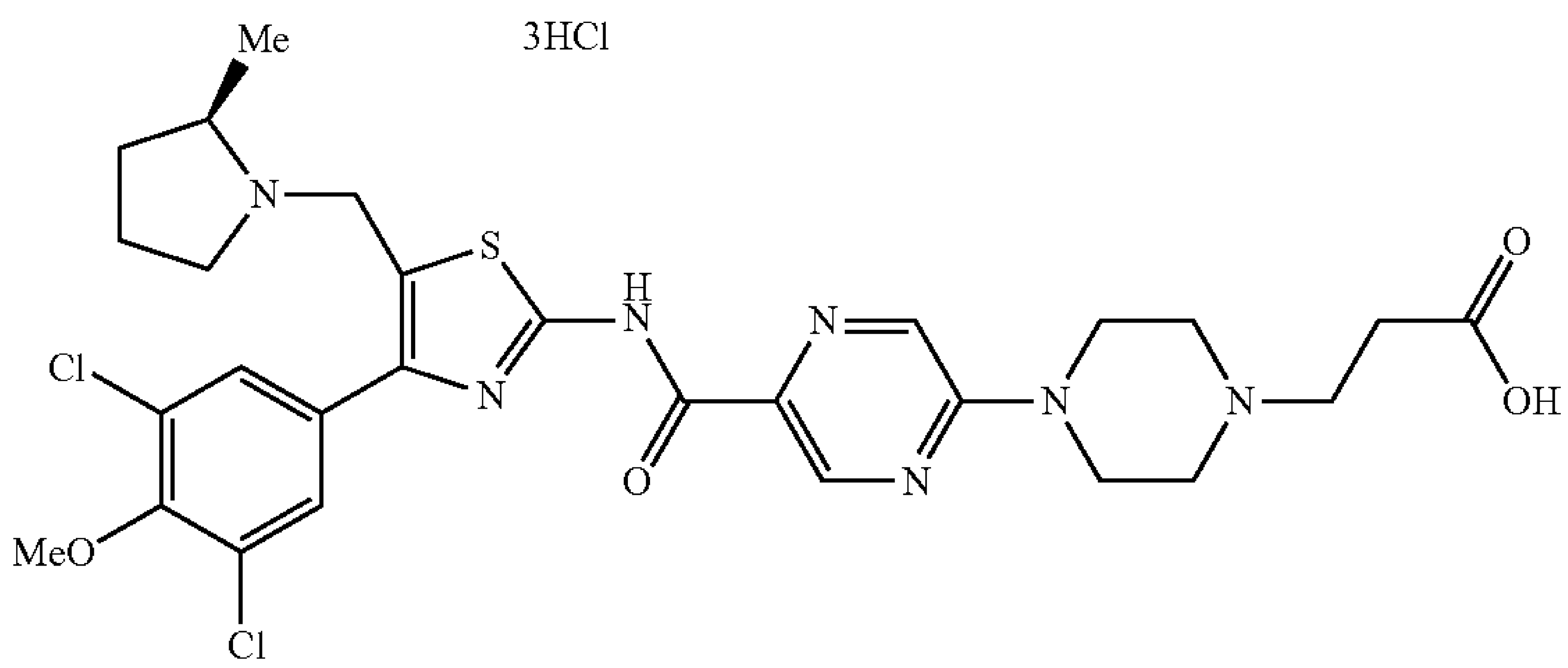
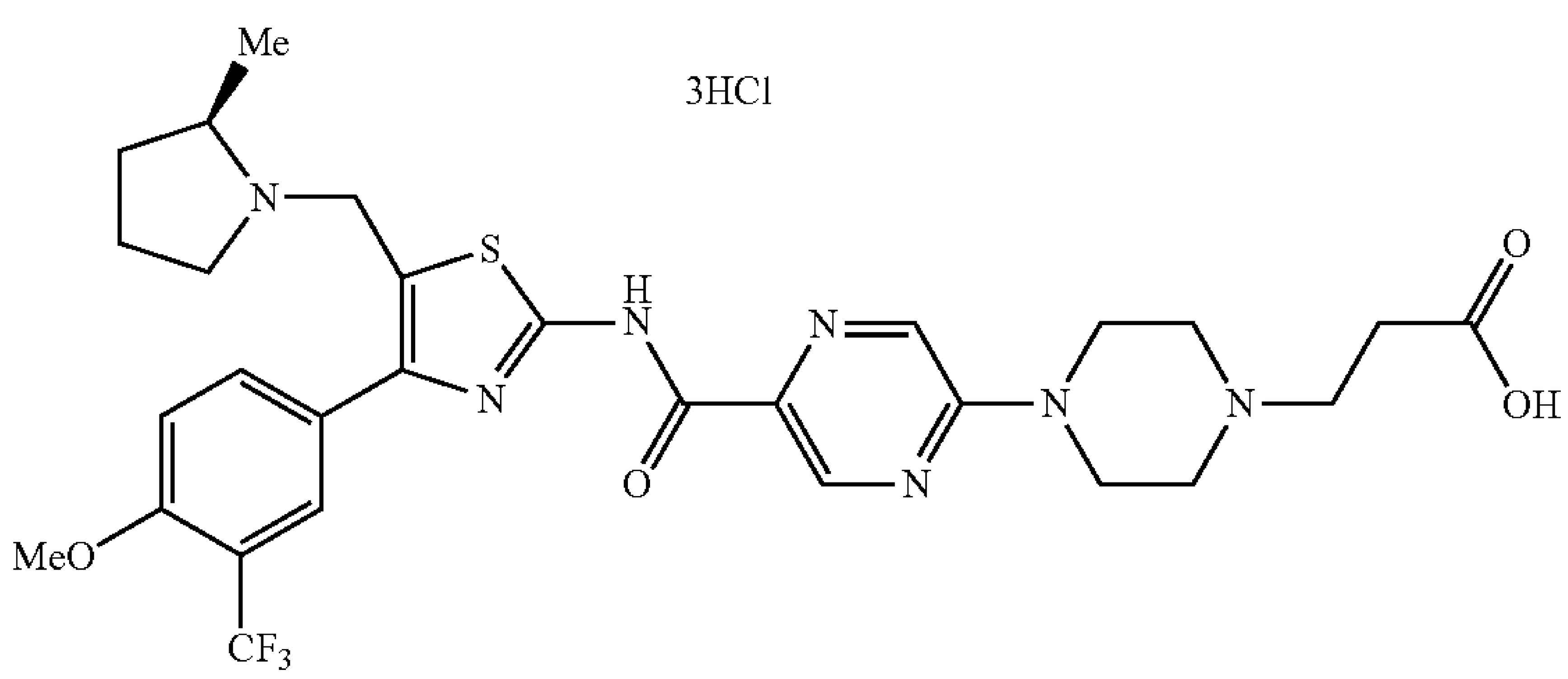
42	
43	
44	

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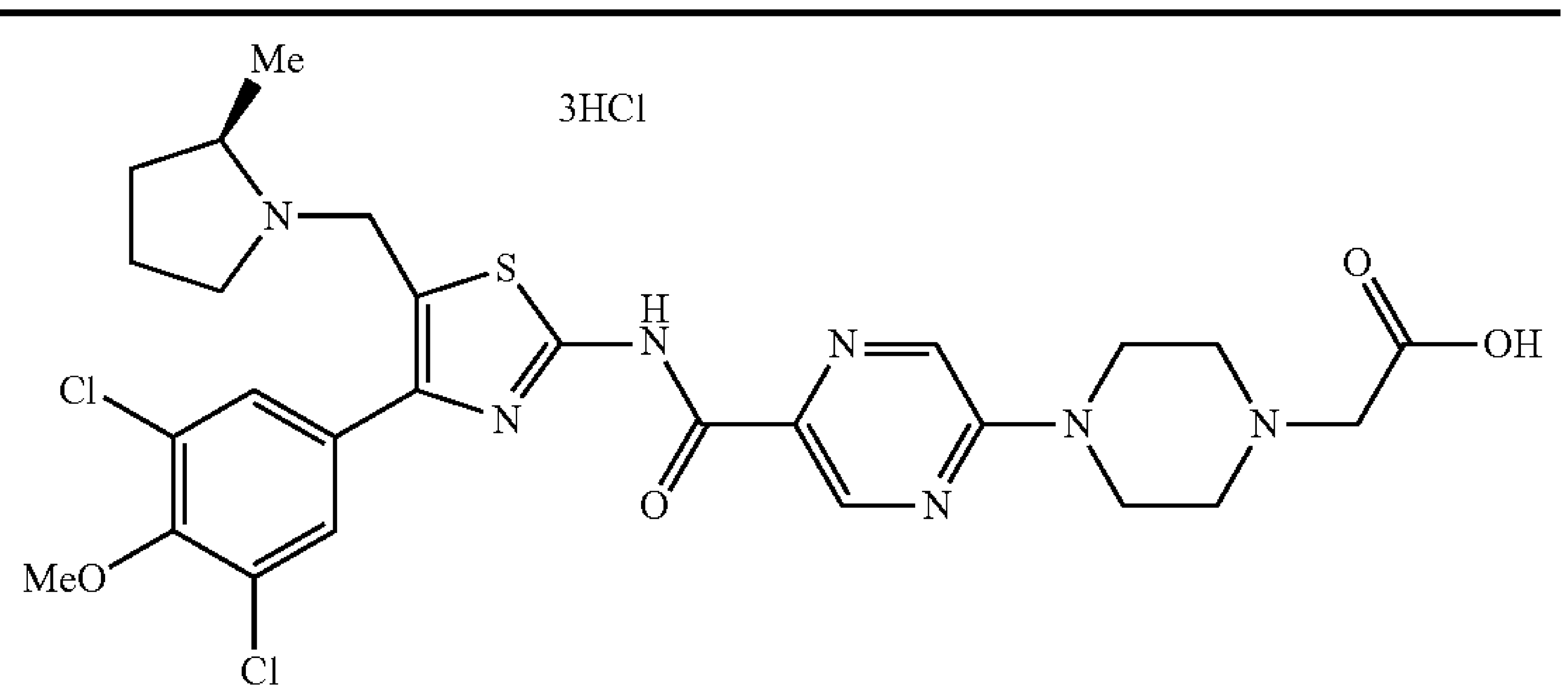
45	

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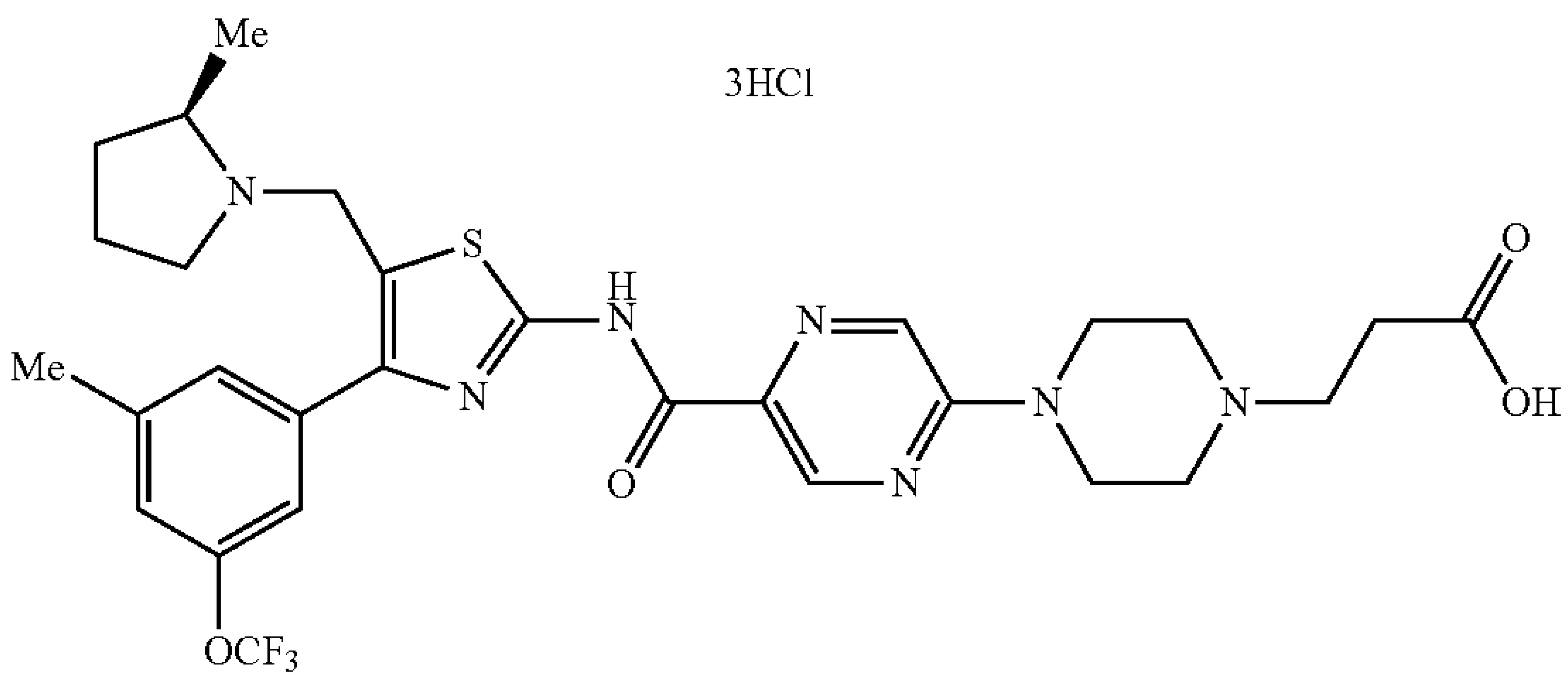
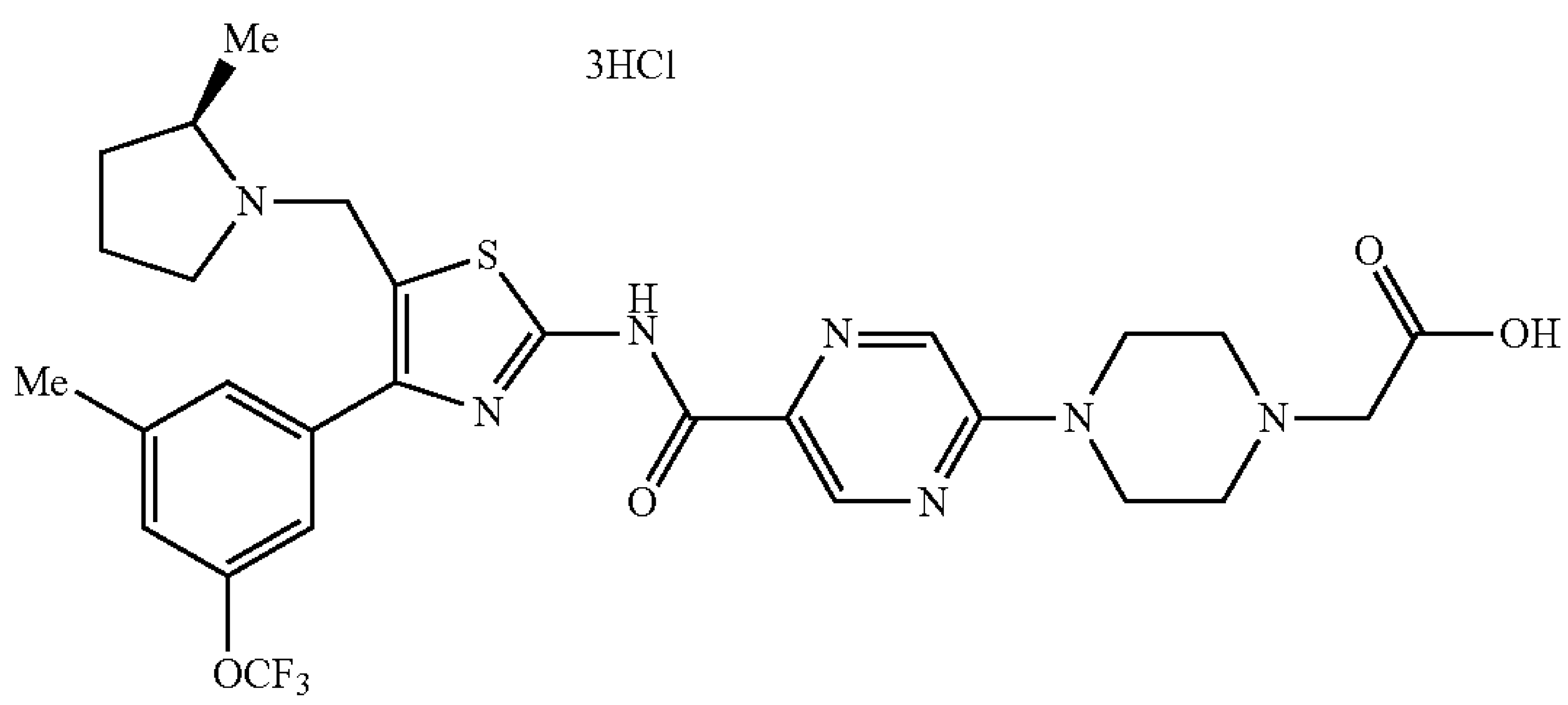
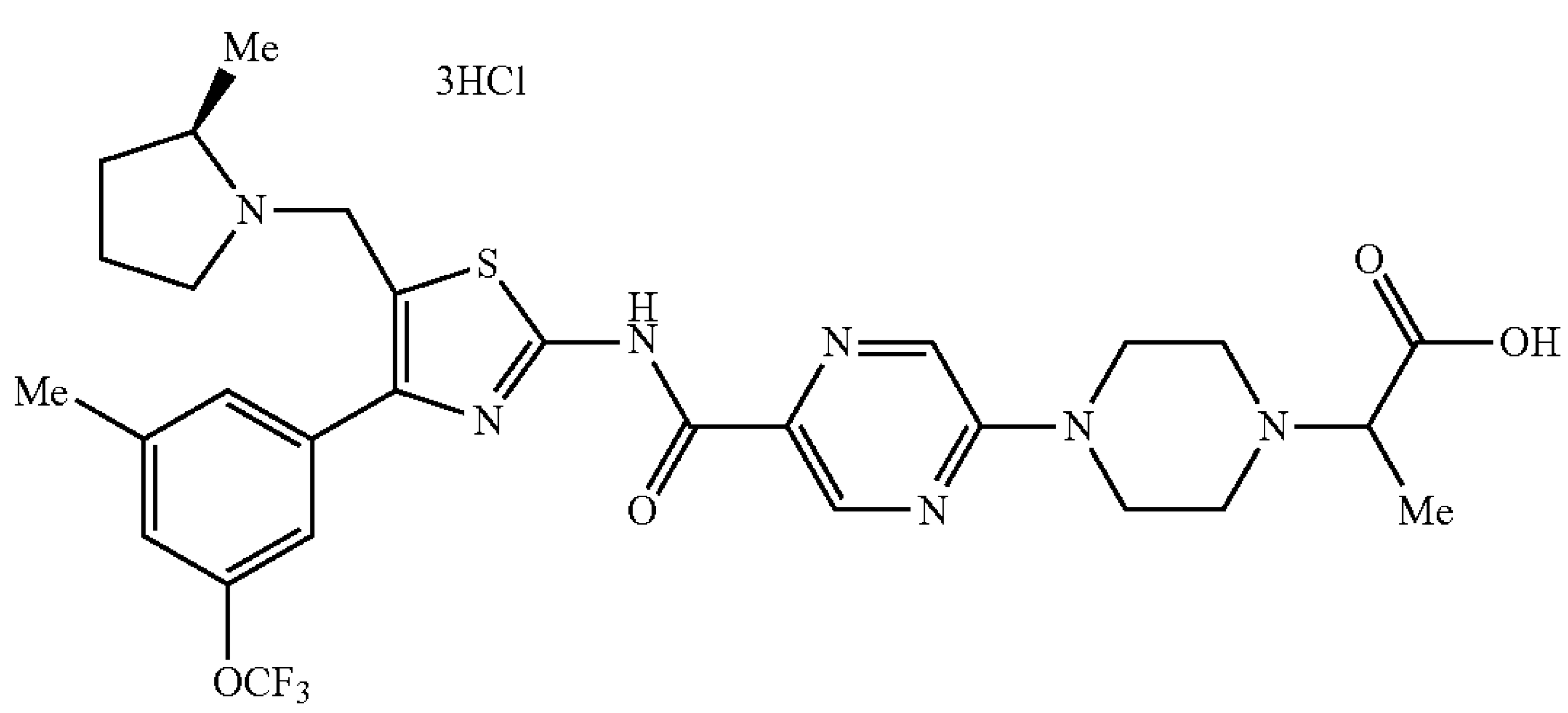
46	
47	
48	

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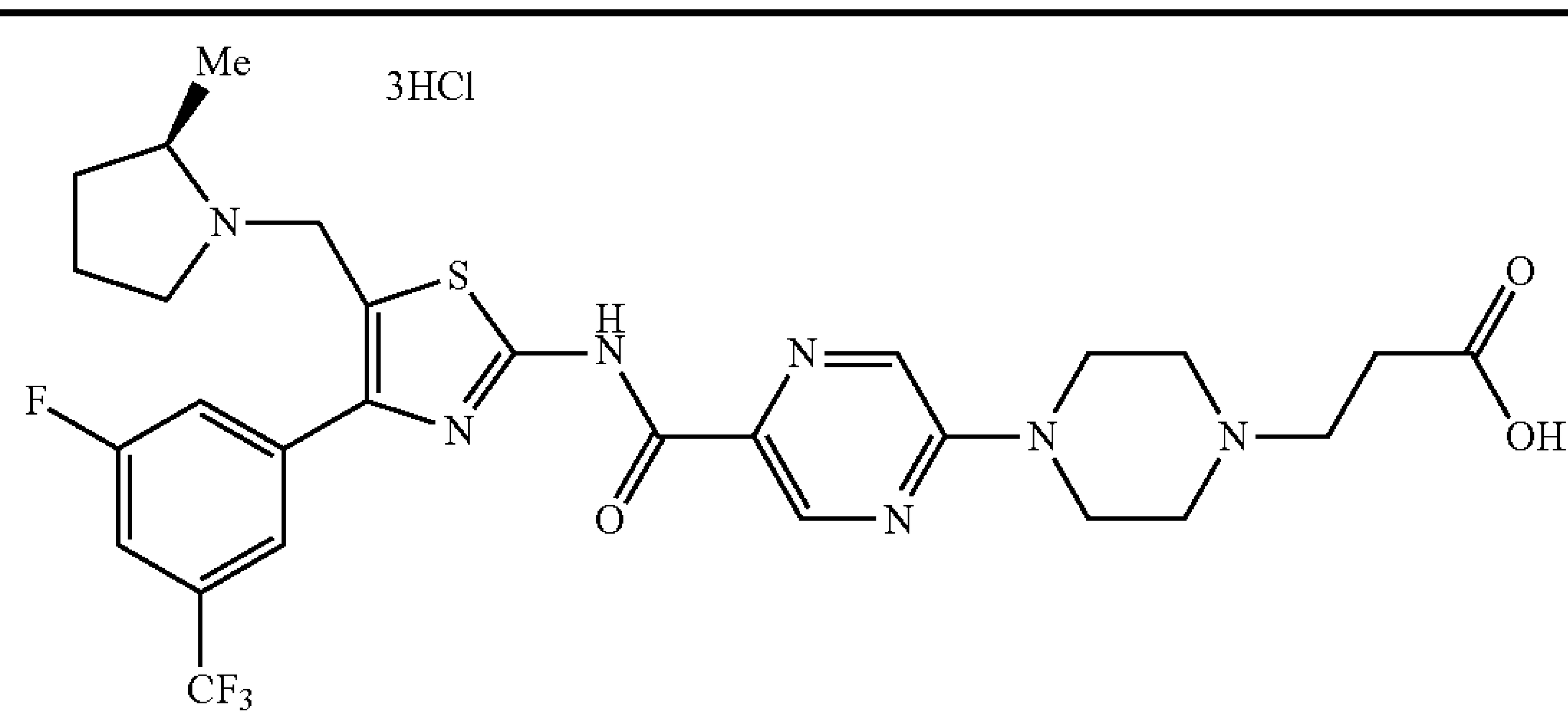
49	

TABLE 83-continued

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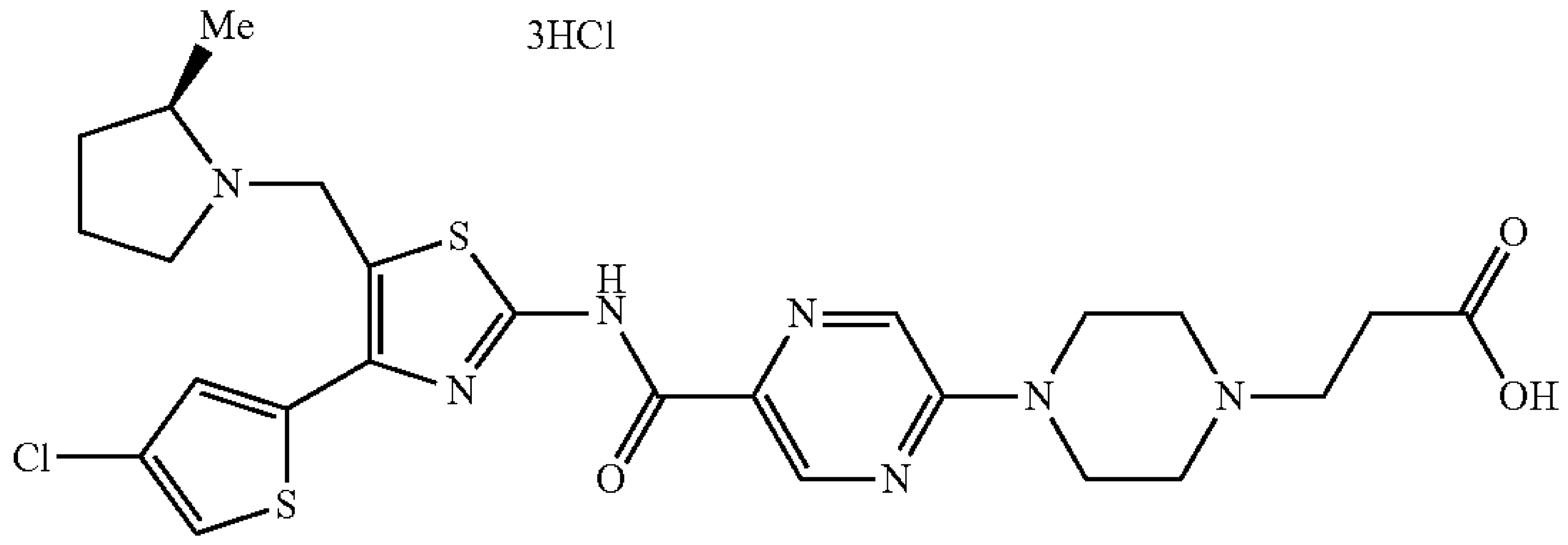
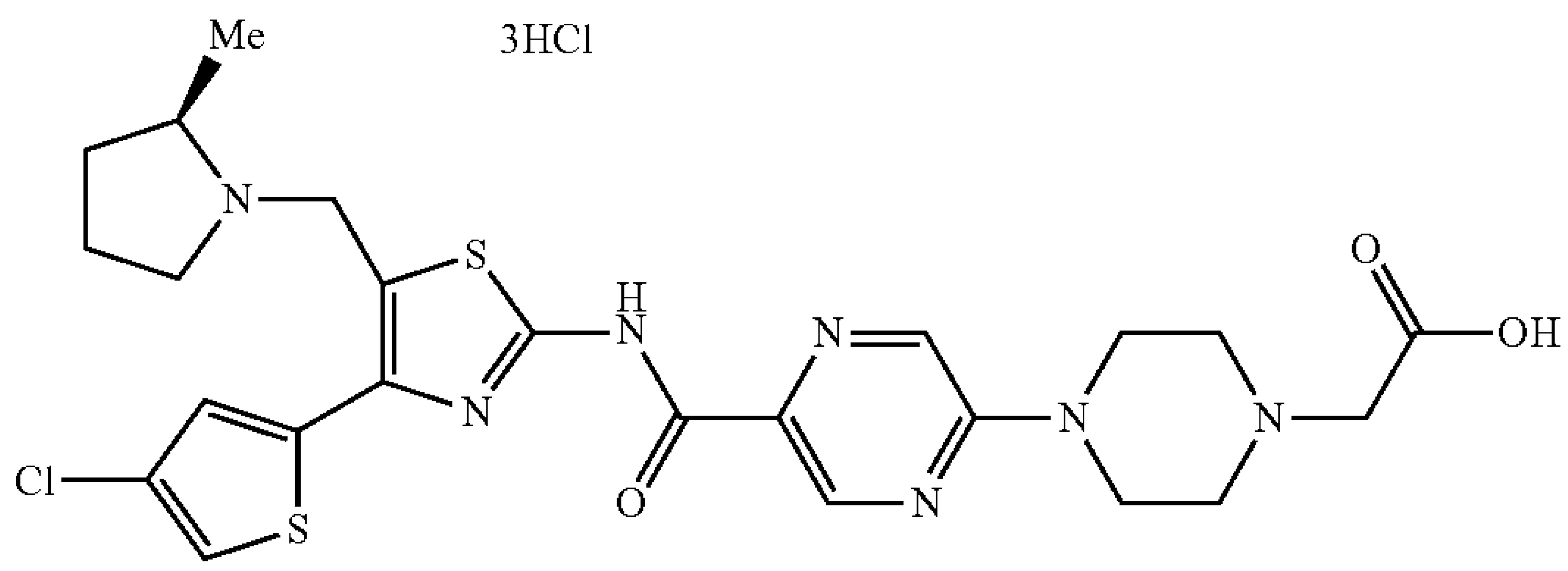
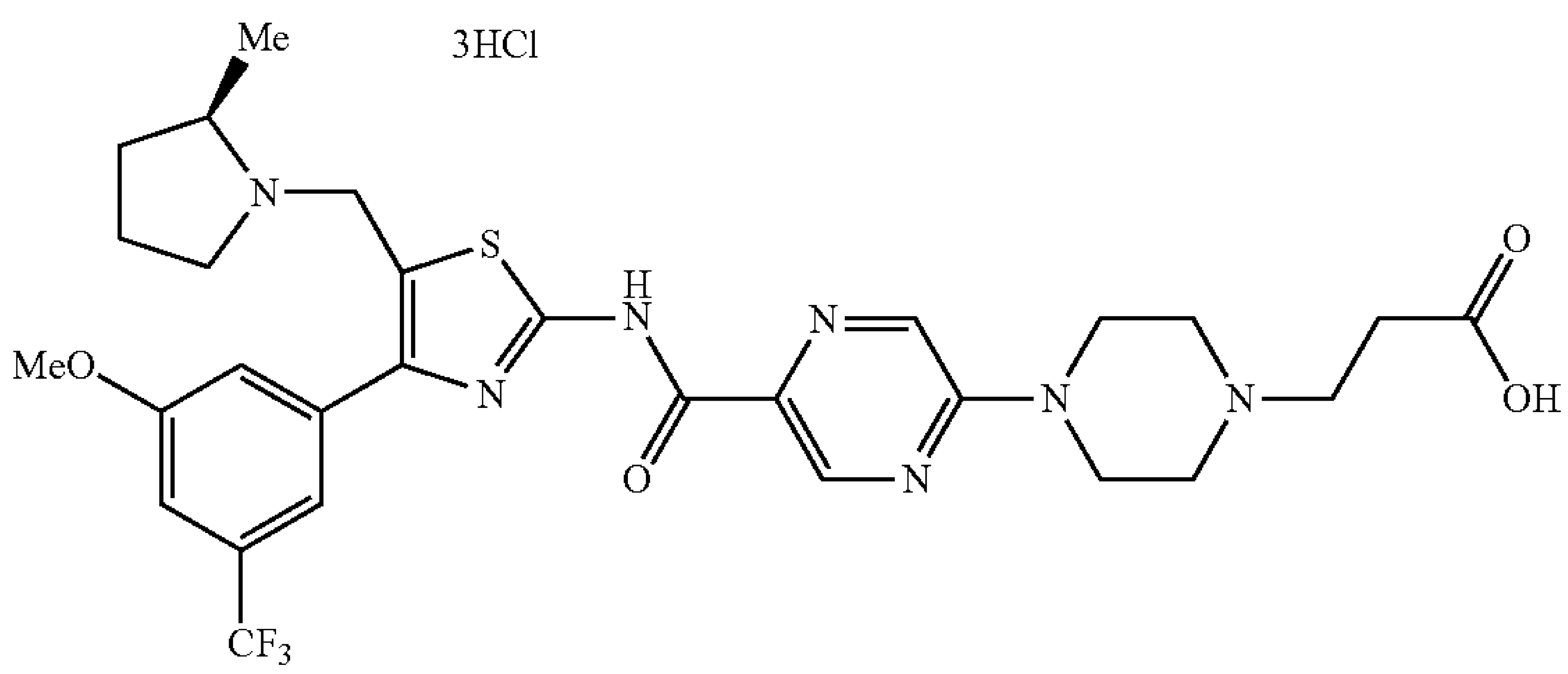
50	 3HCl
51	 3HCl
52	 3HCl

TABLE 84

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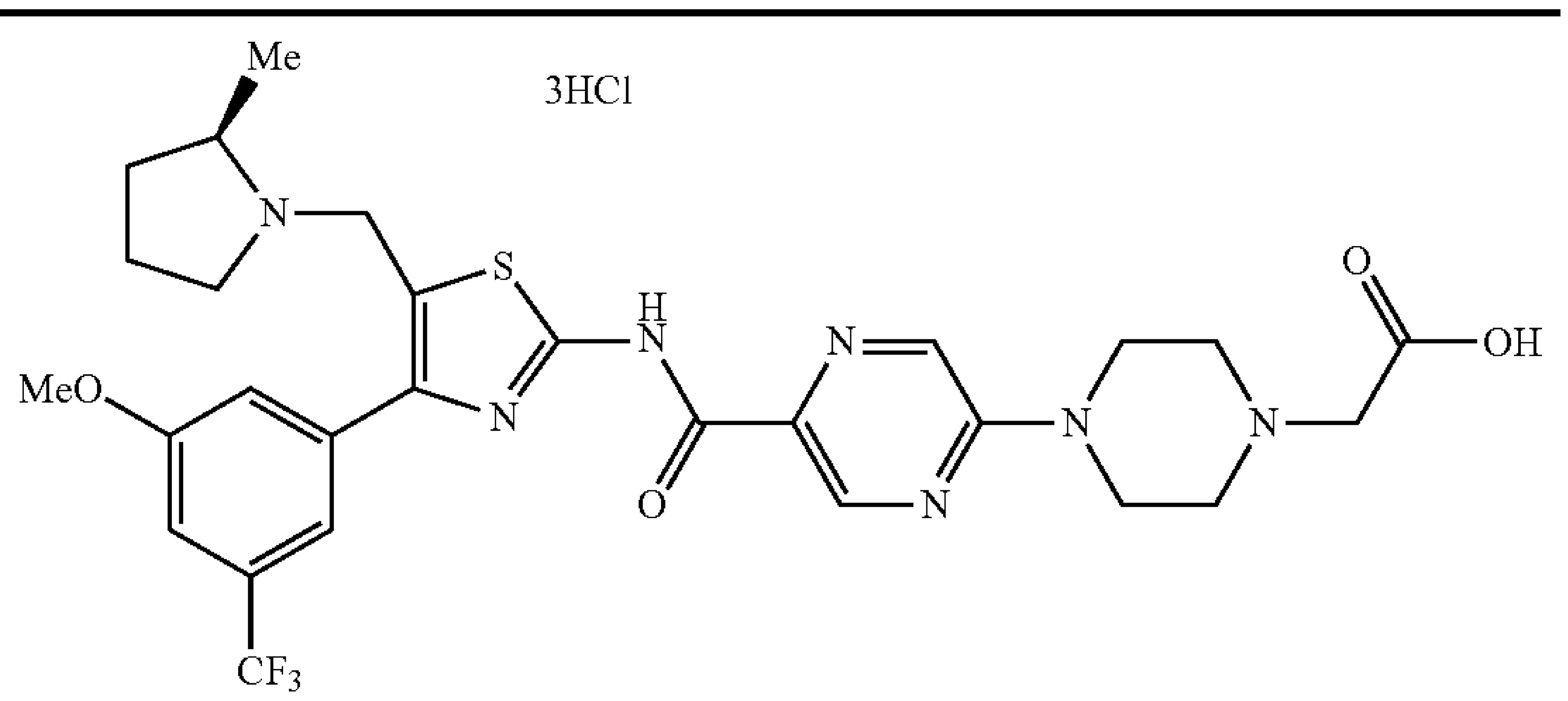
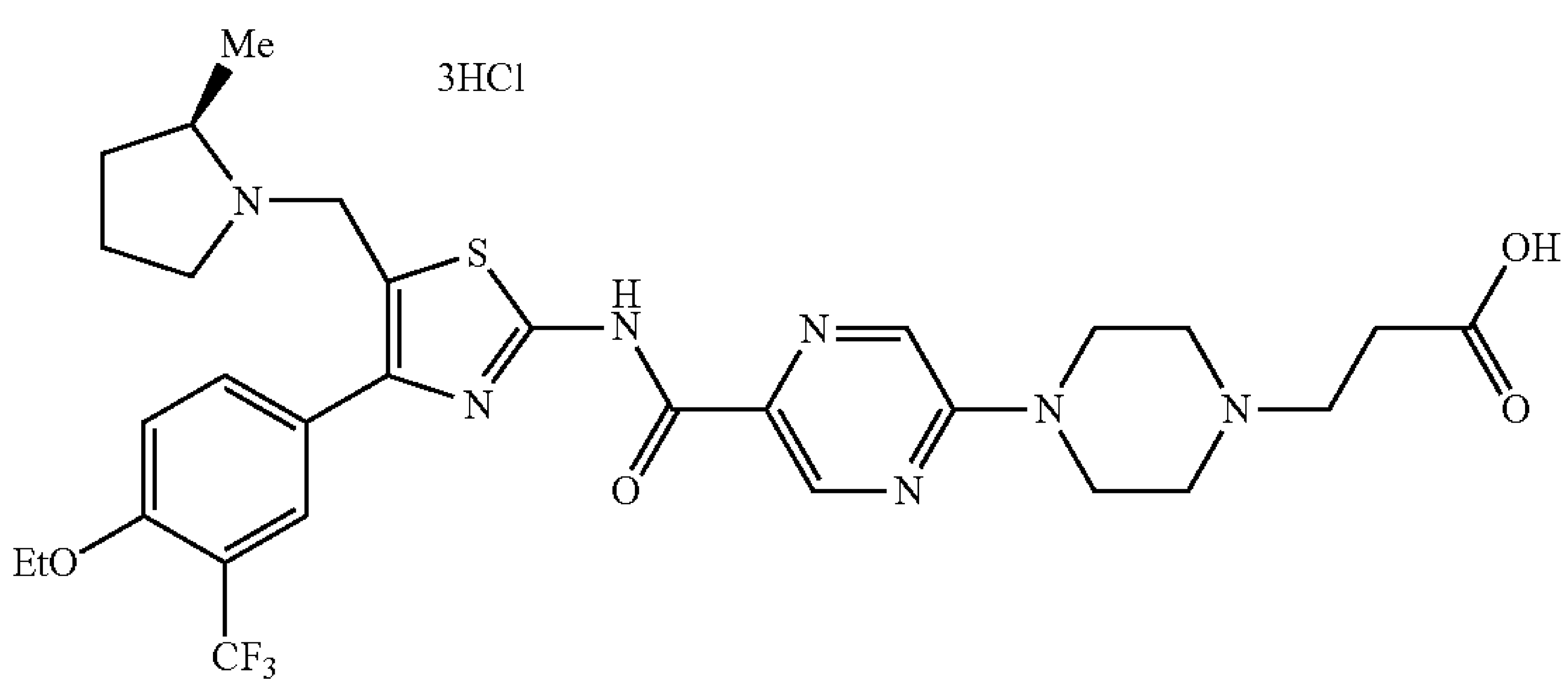
53	 3HCl
54	 3HCl

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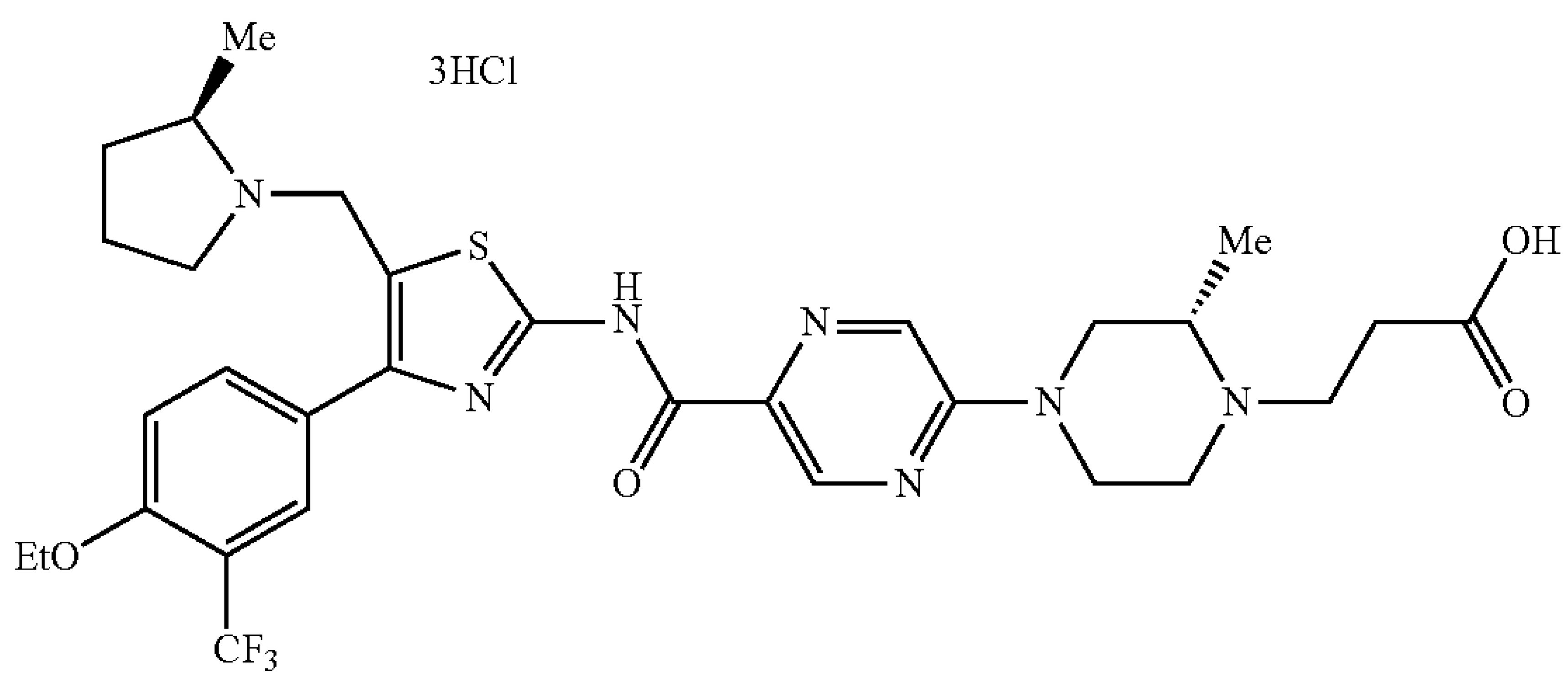
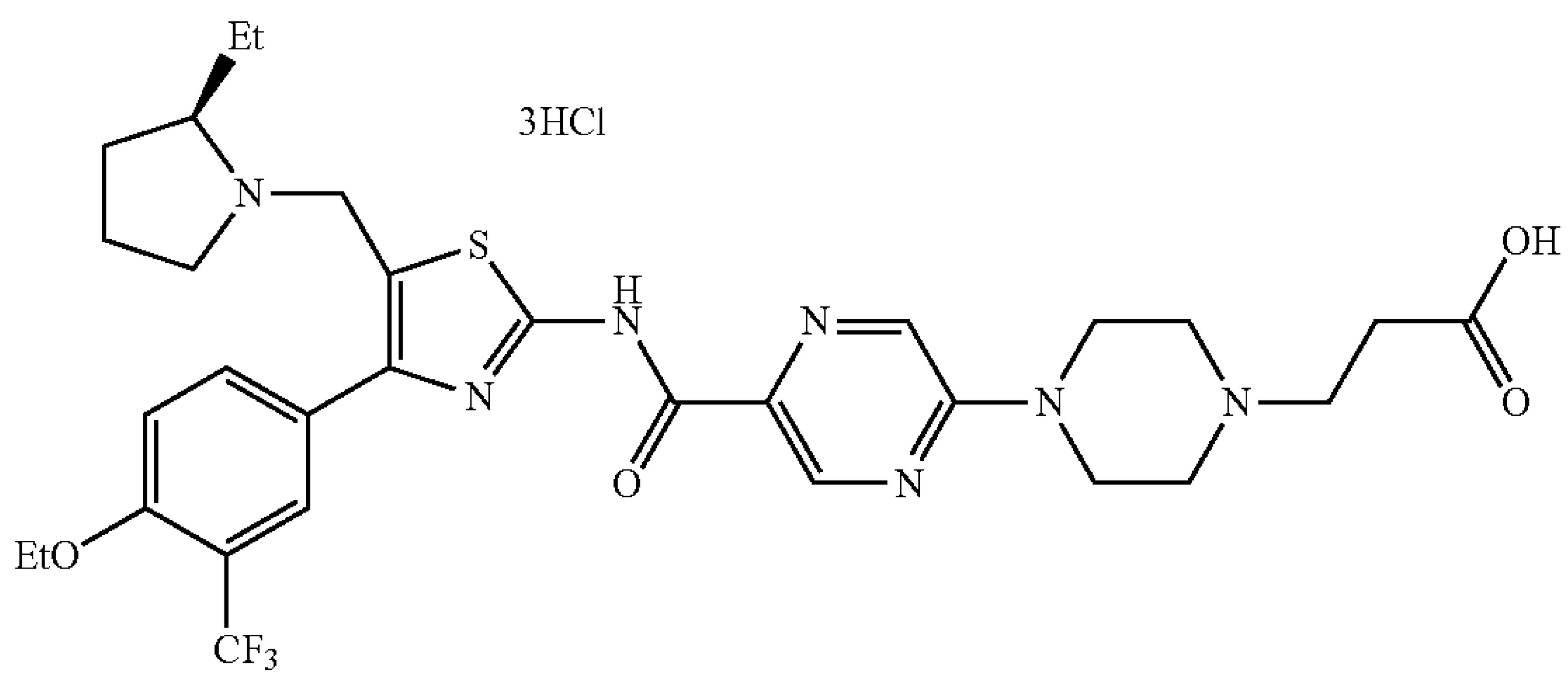
55	
56	

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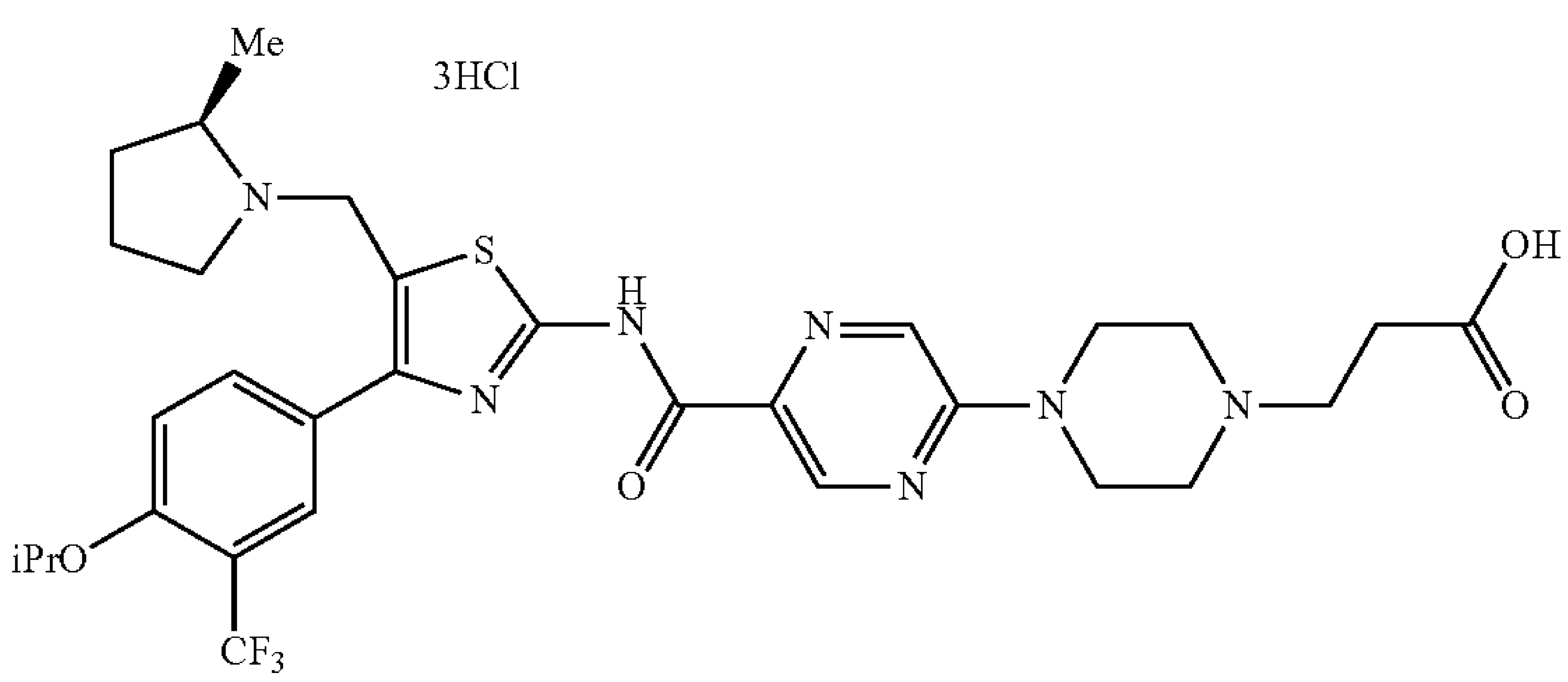
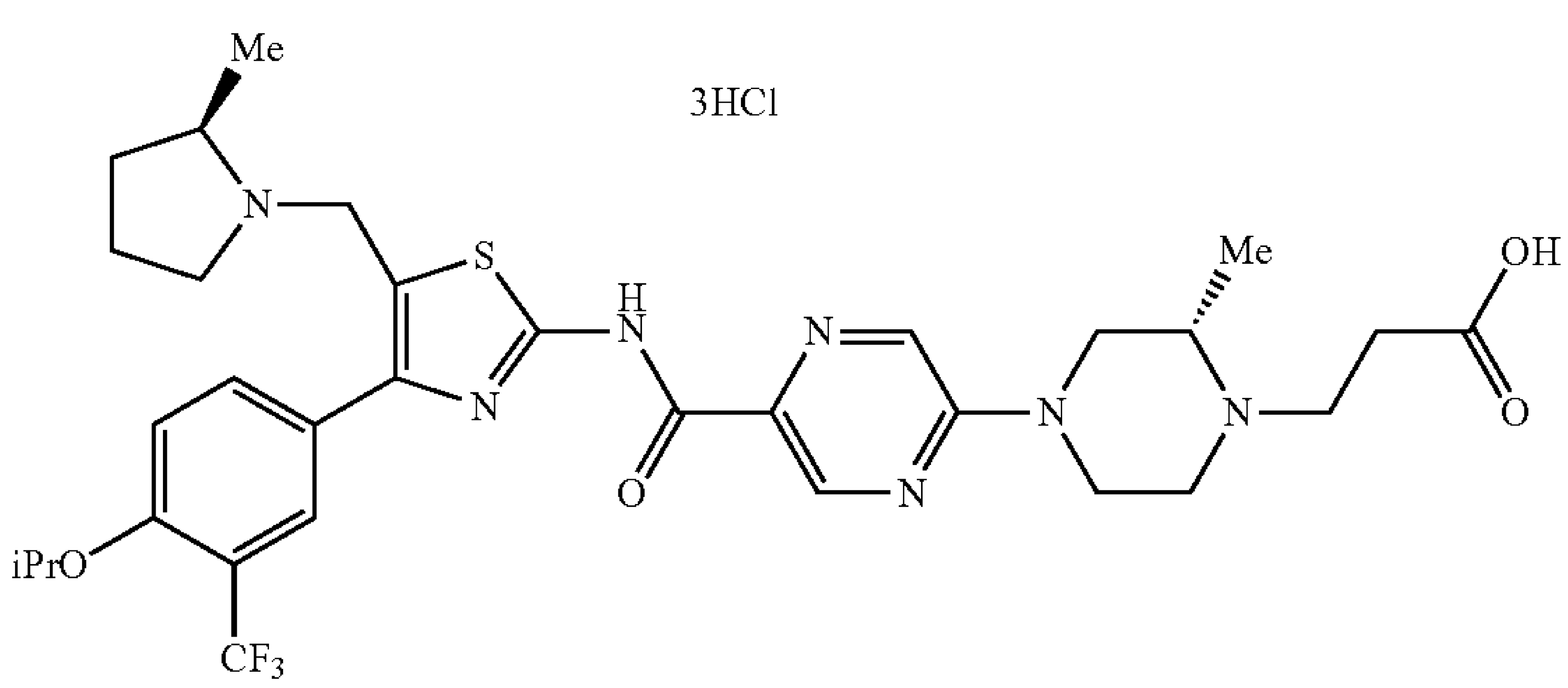
57	
58	

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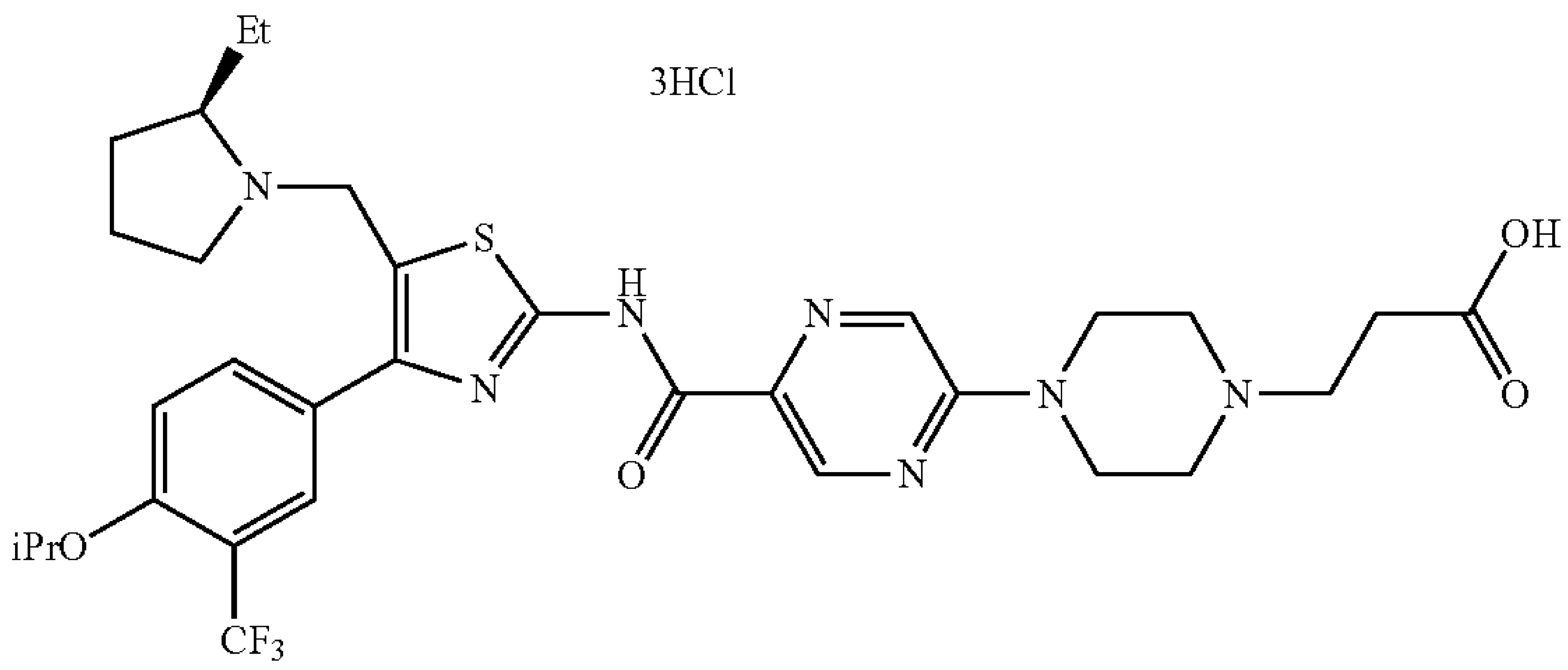
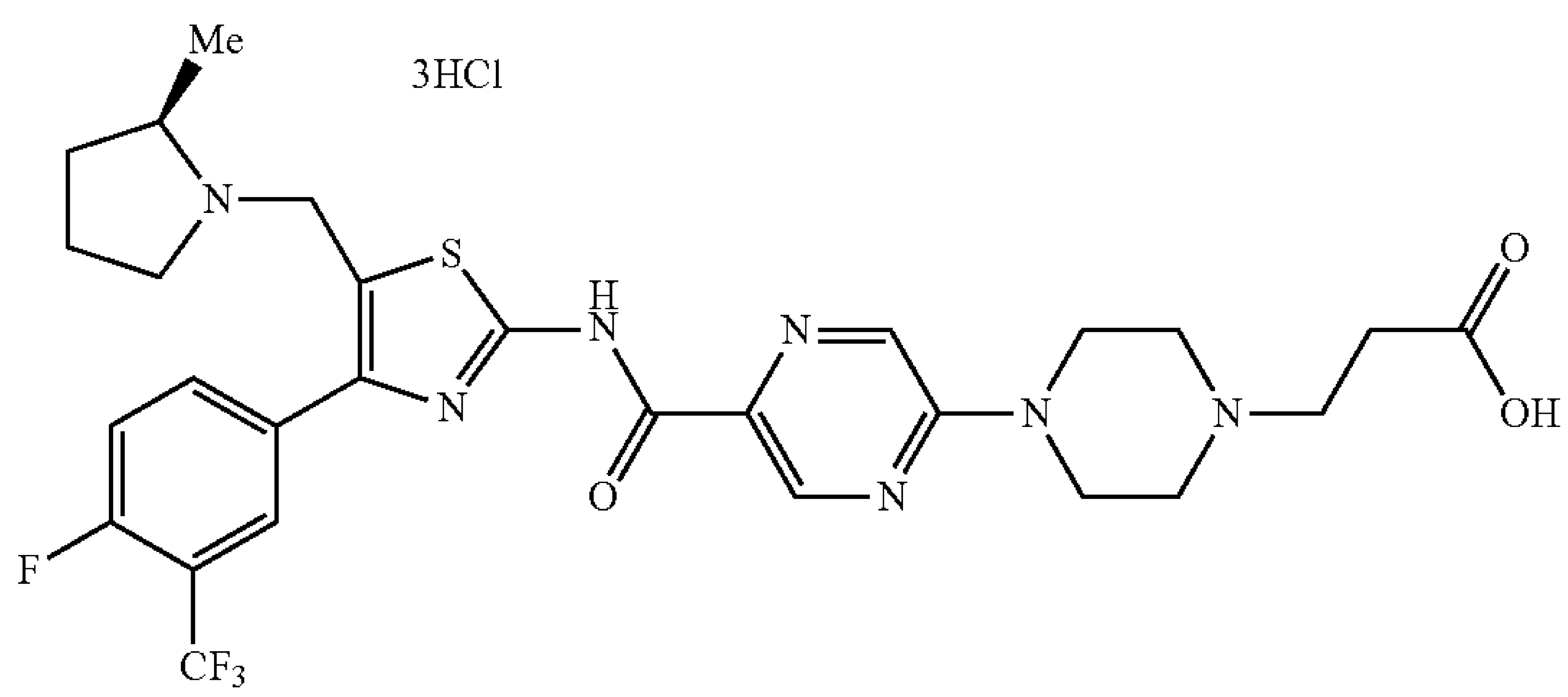
59	
60	

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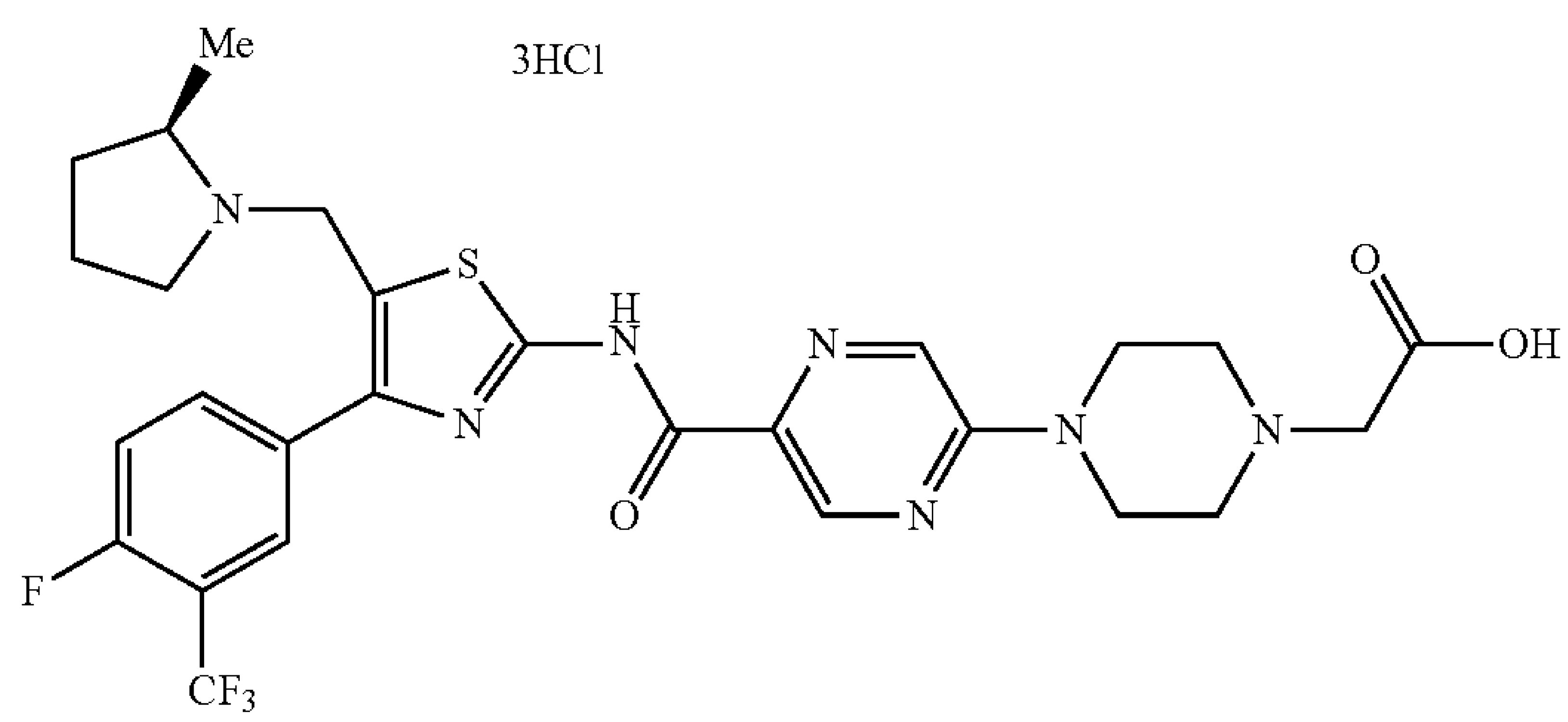
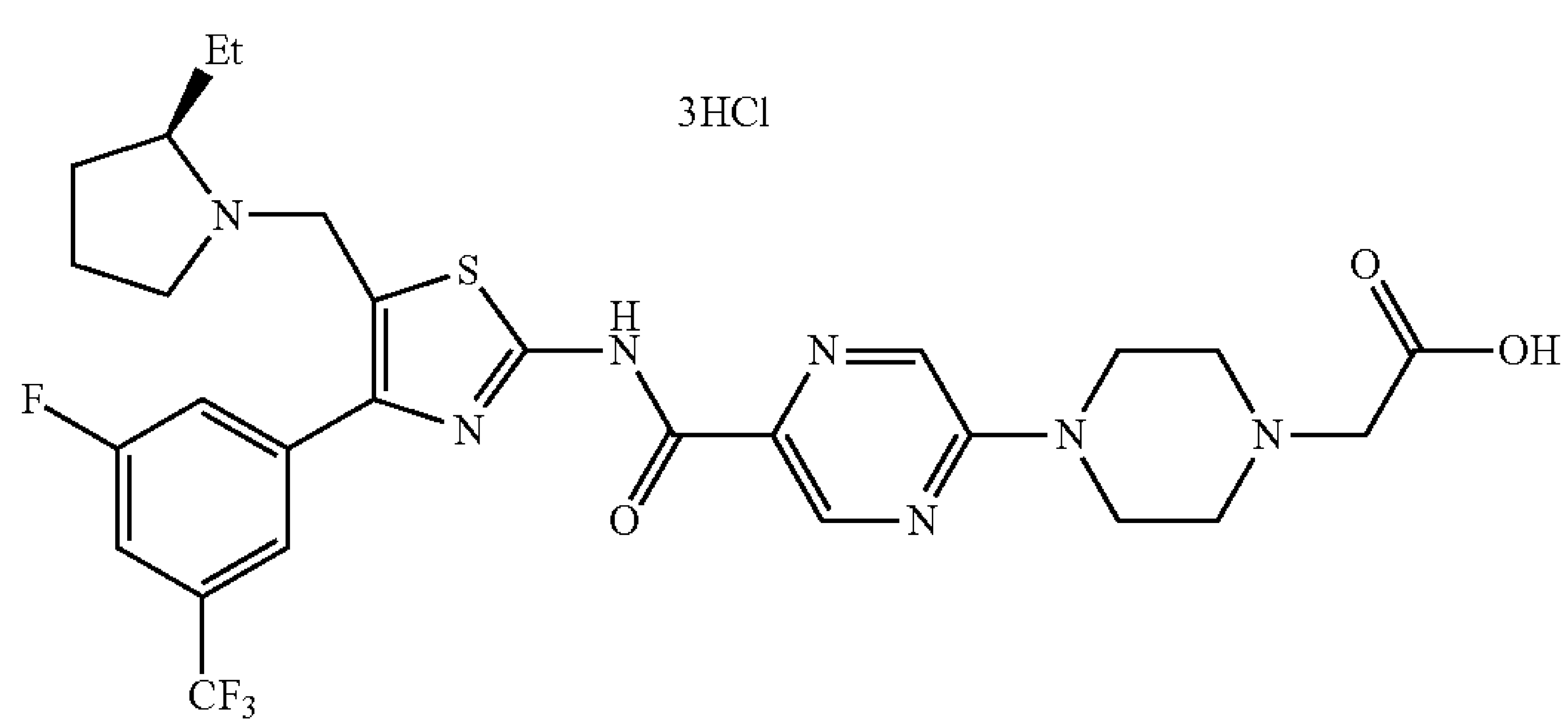
61	
62	

TABLE 86-continued

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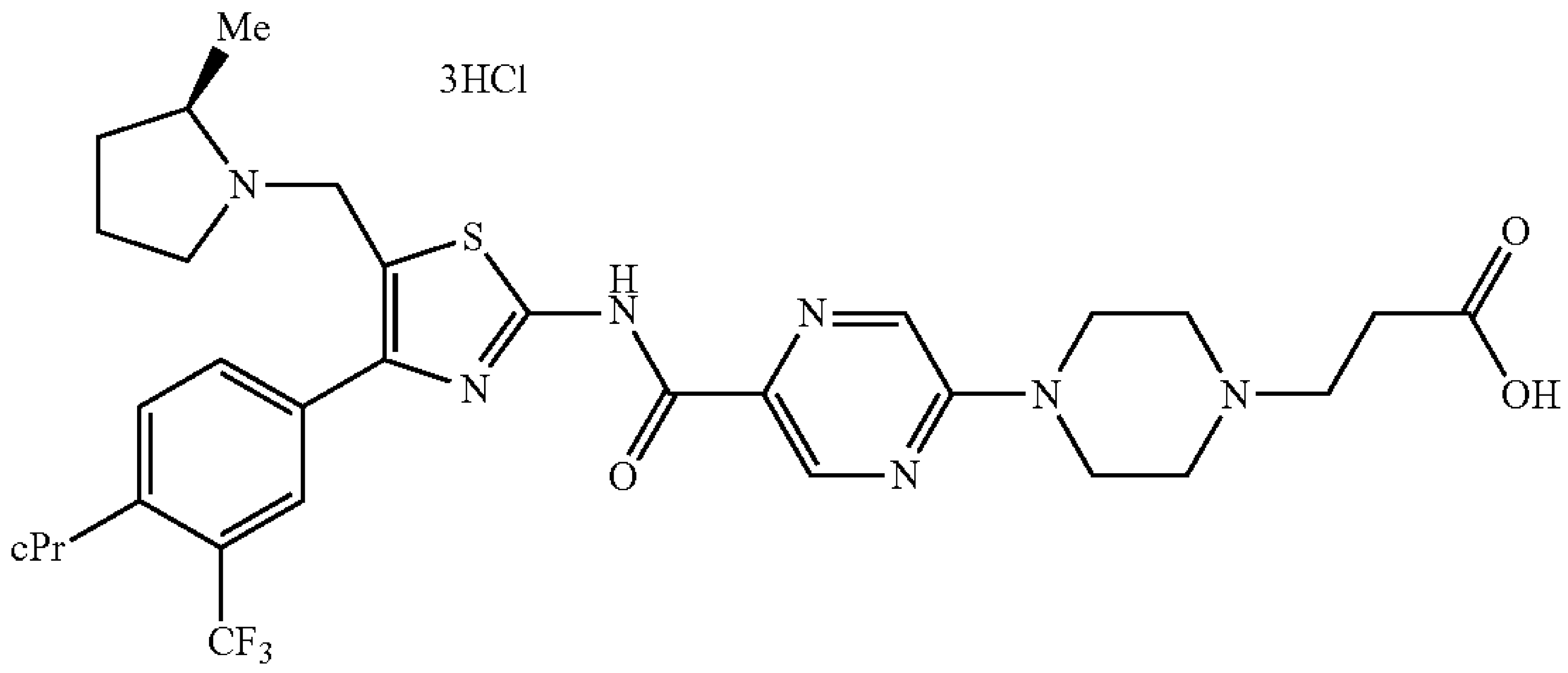
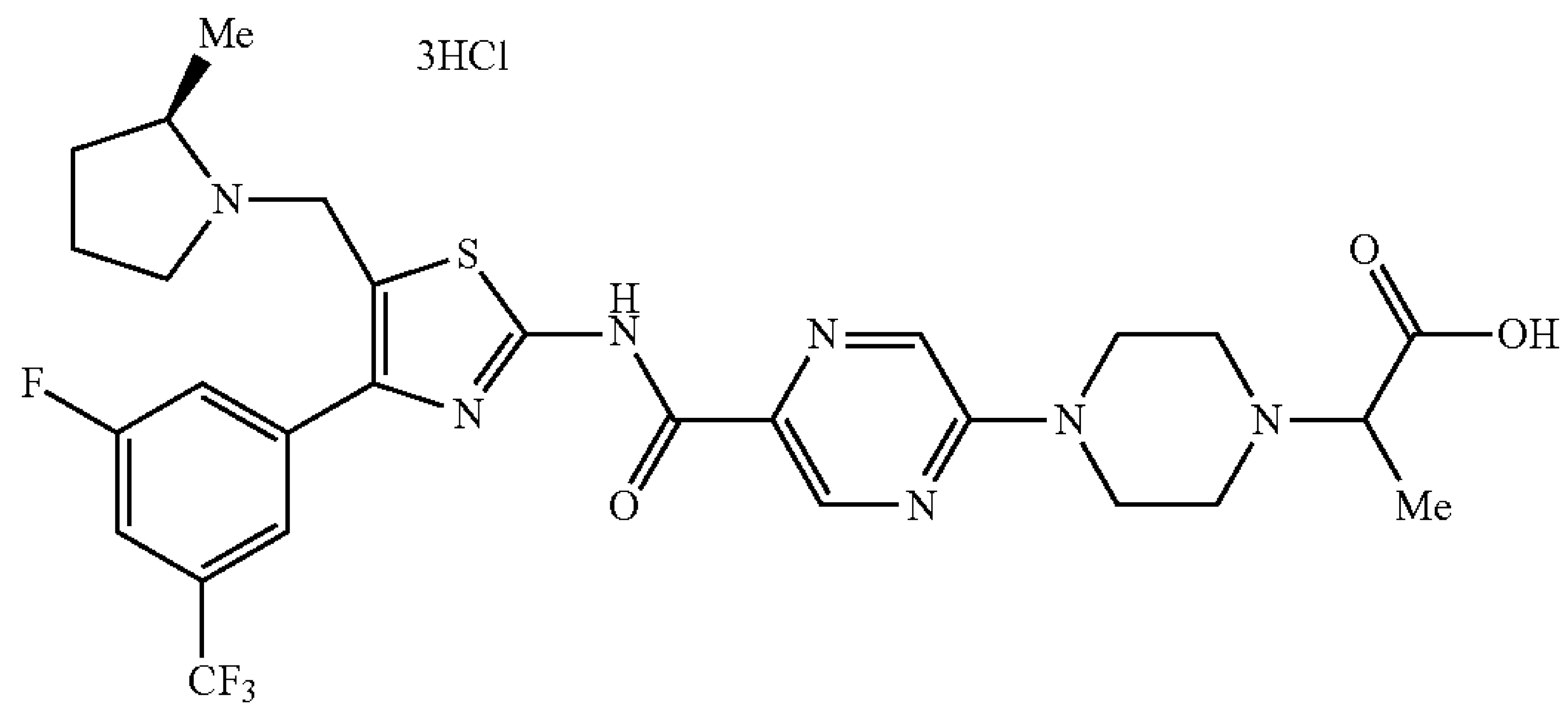
63	
64	

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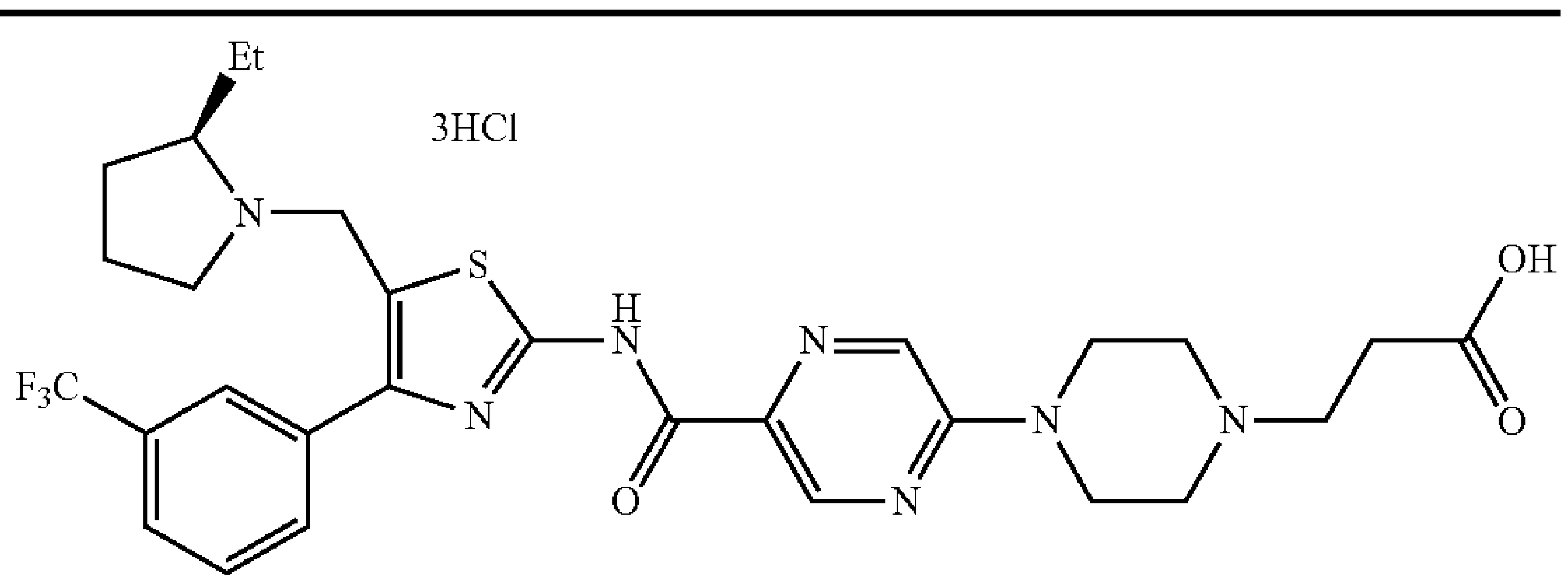
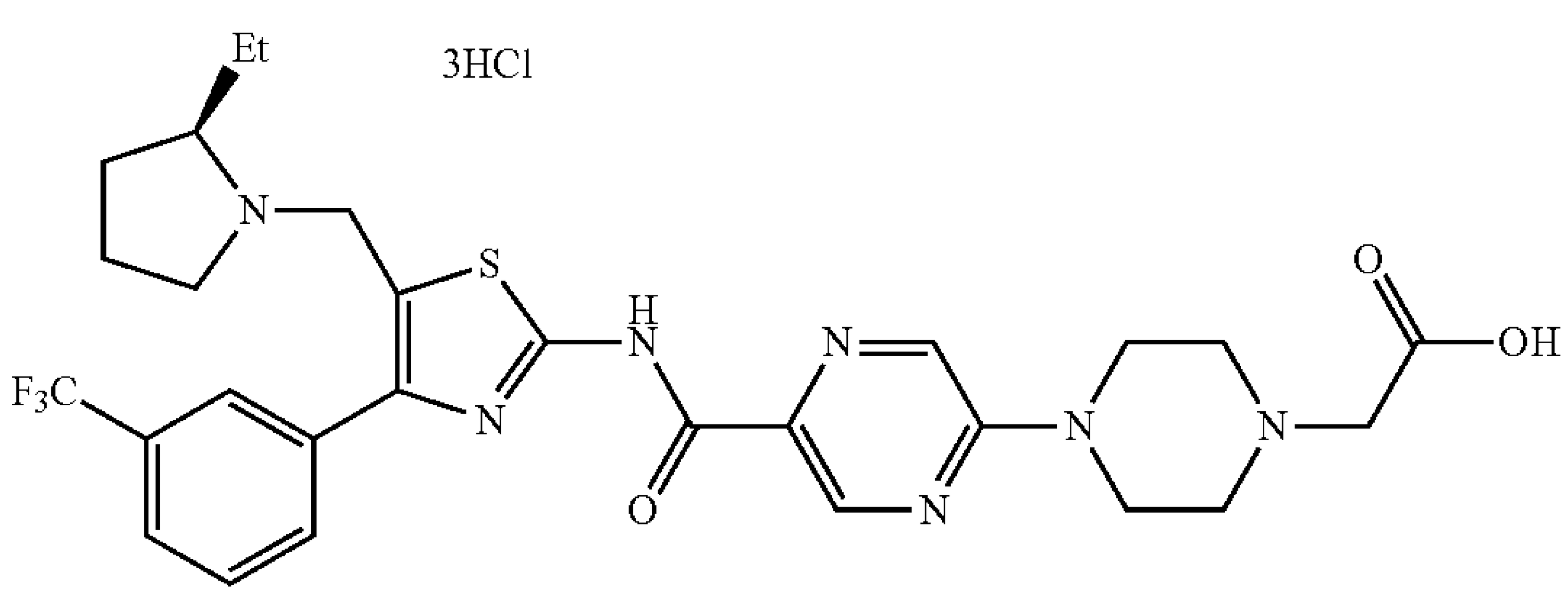
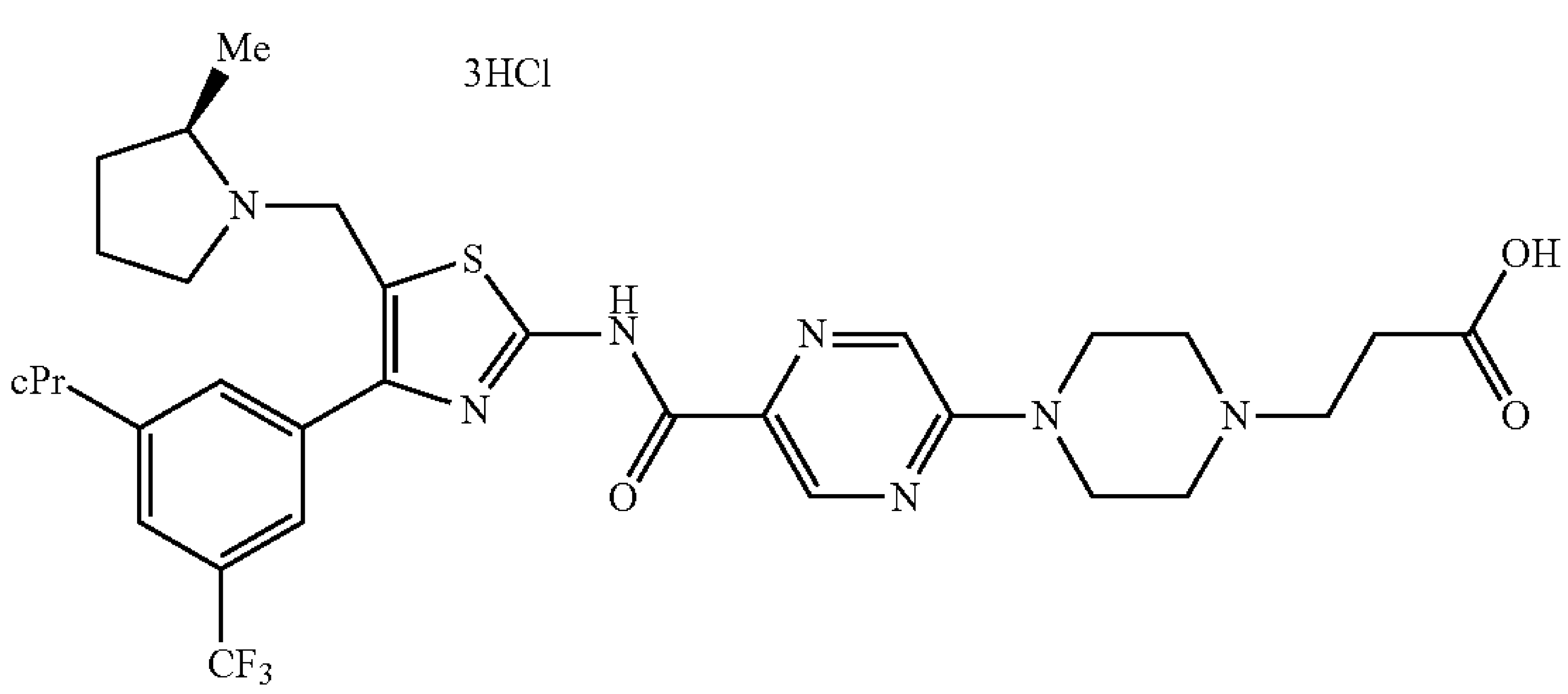
65	
66	
67	

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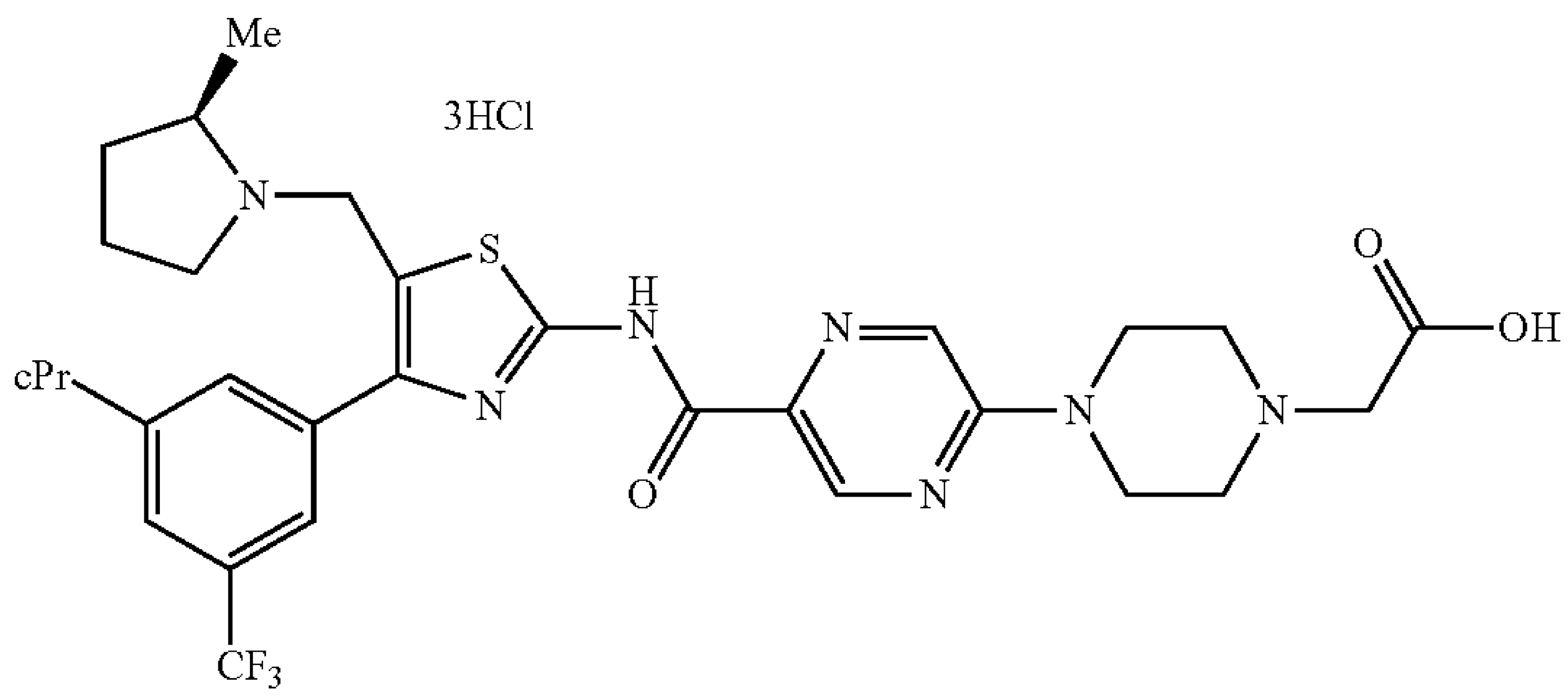
68	

TABLE 88

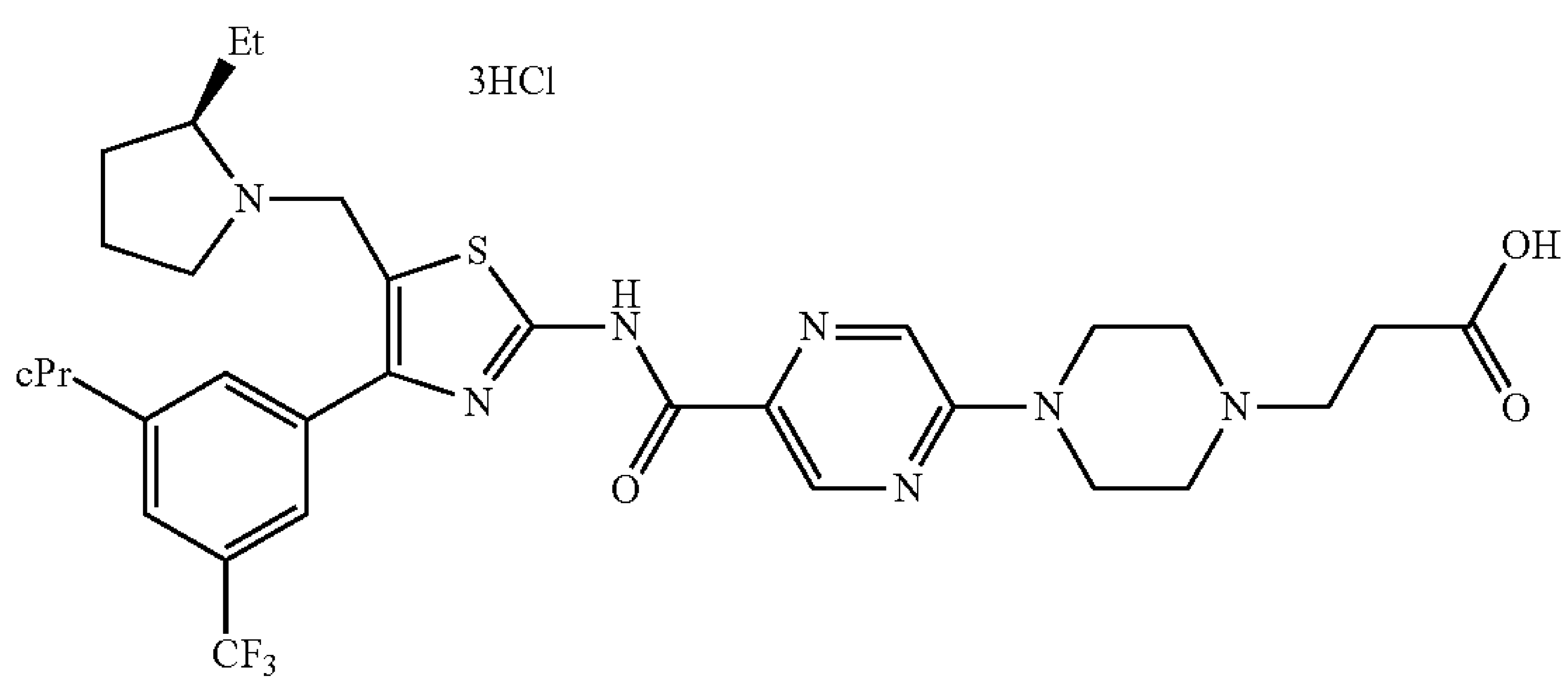
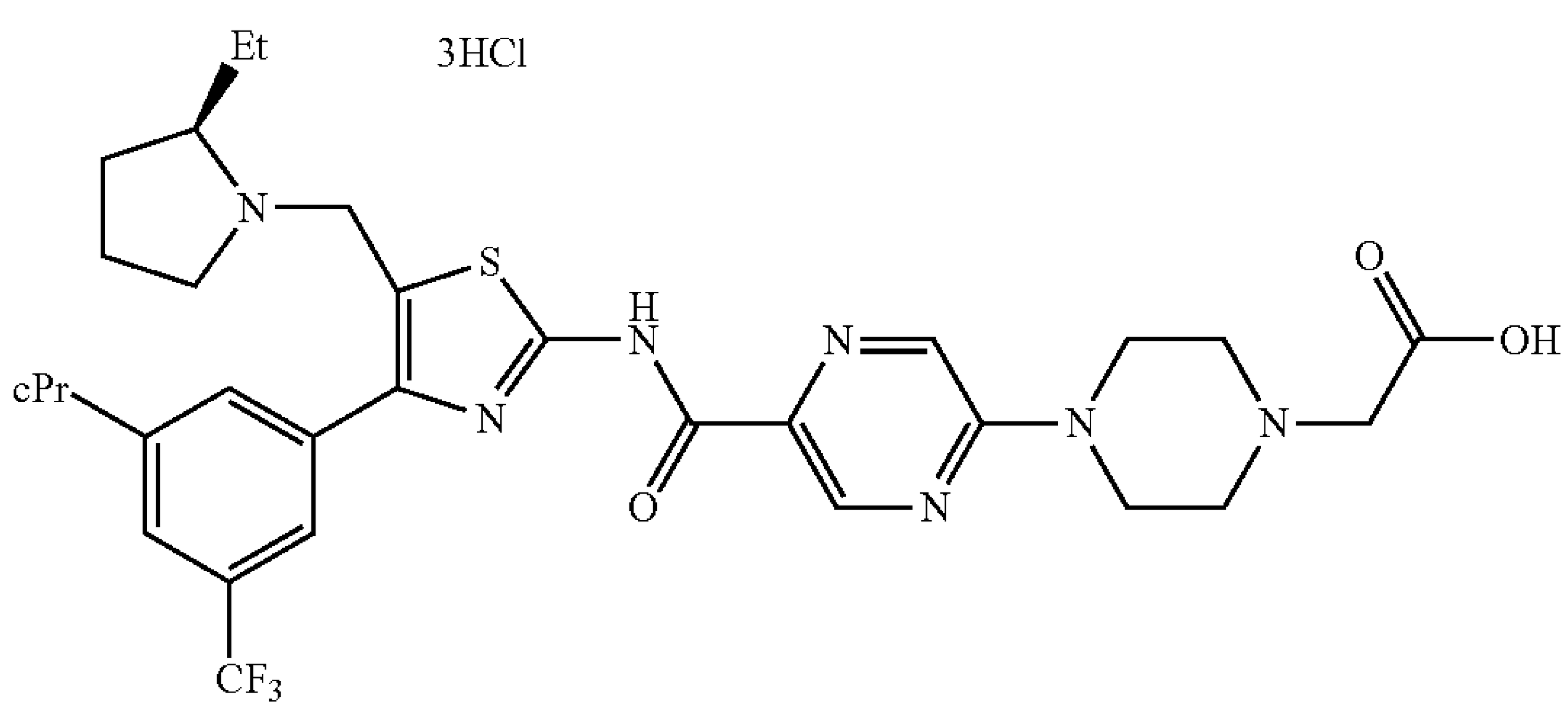
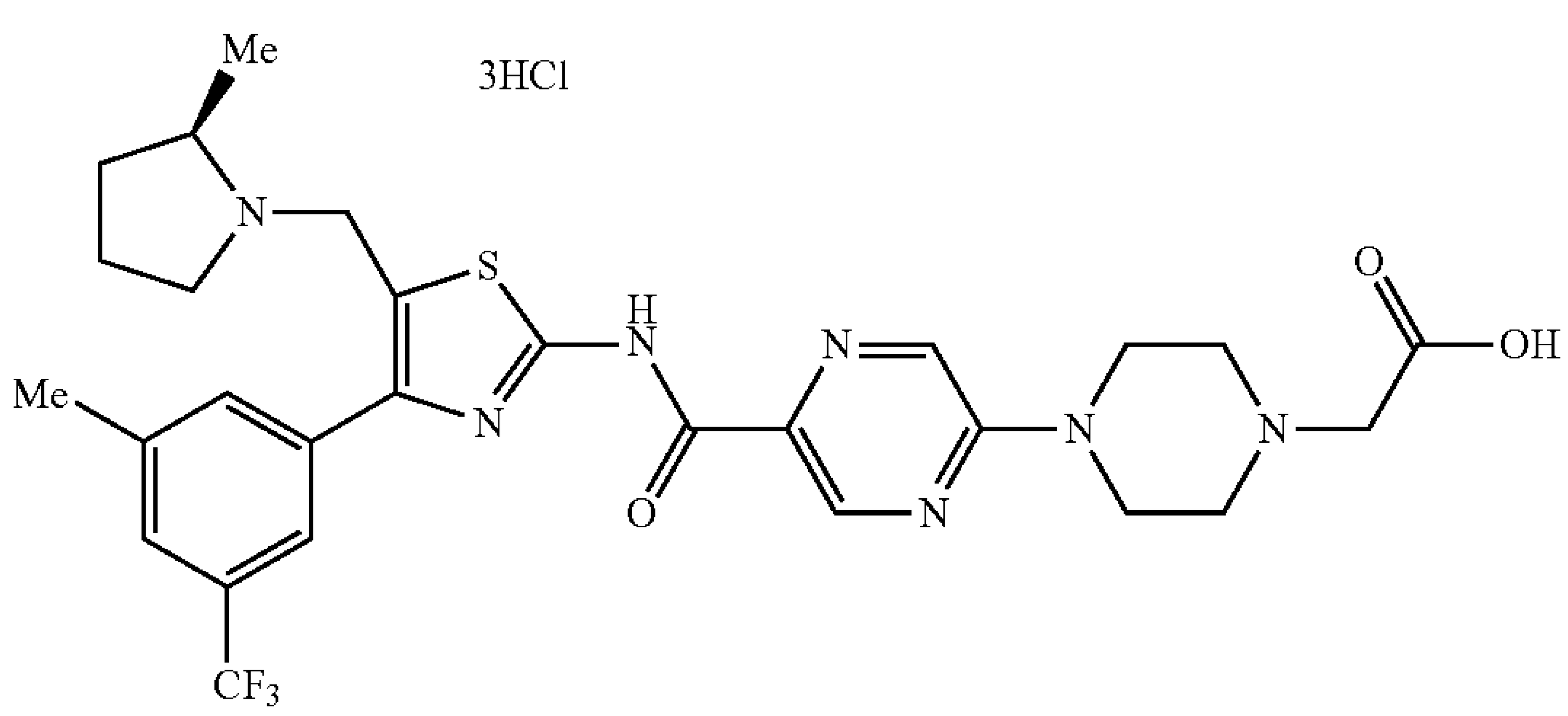
Ex	Structure
69	
70	
71	

TABLE 88-continued

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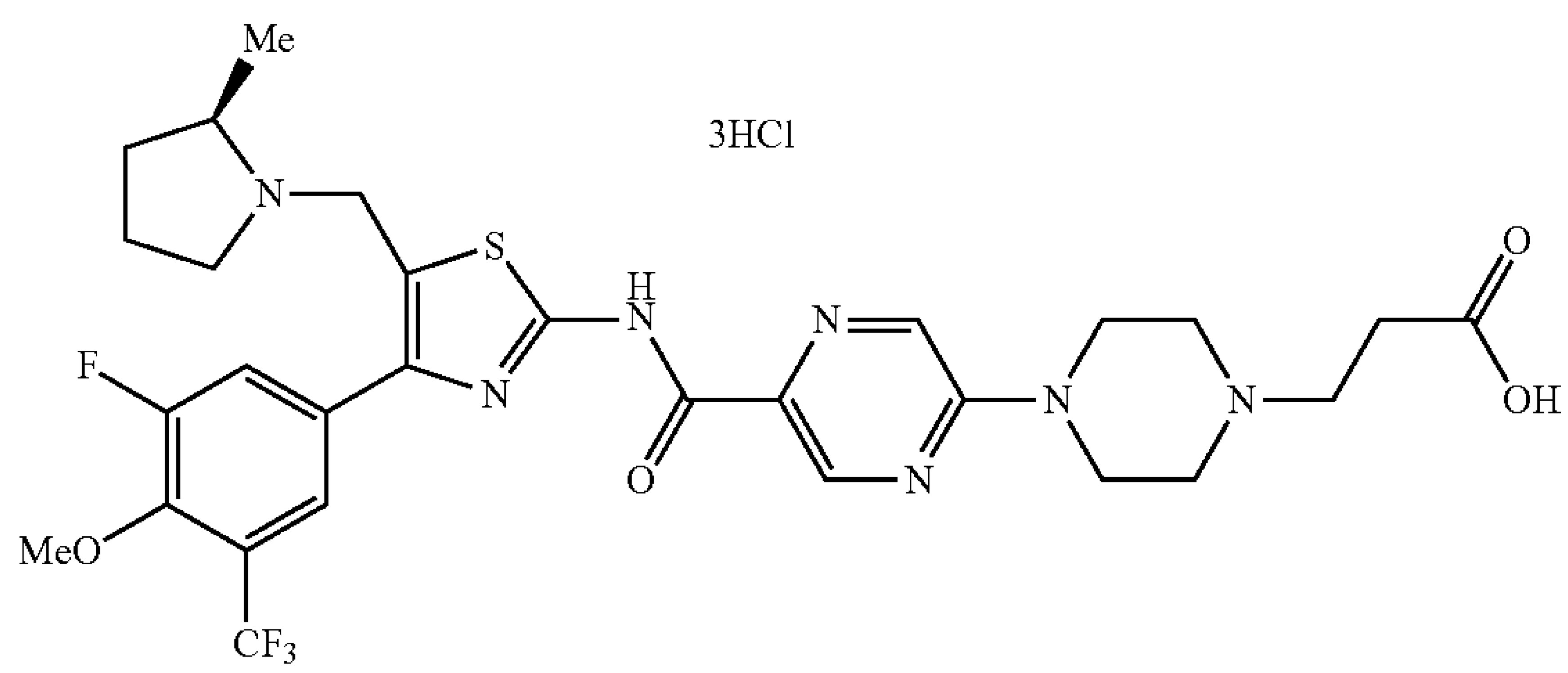
72	

TABLE 89

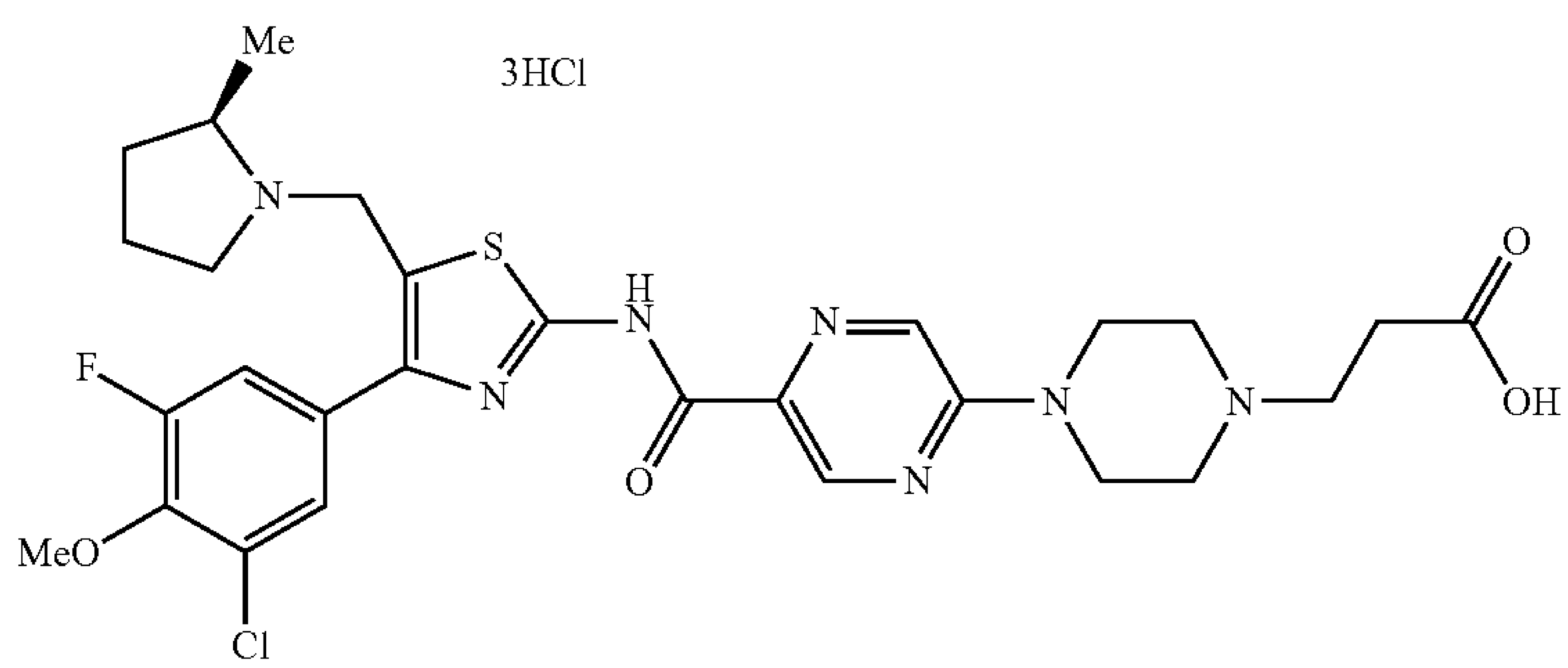
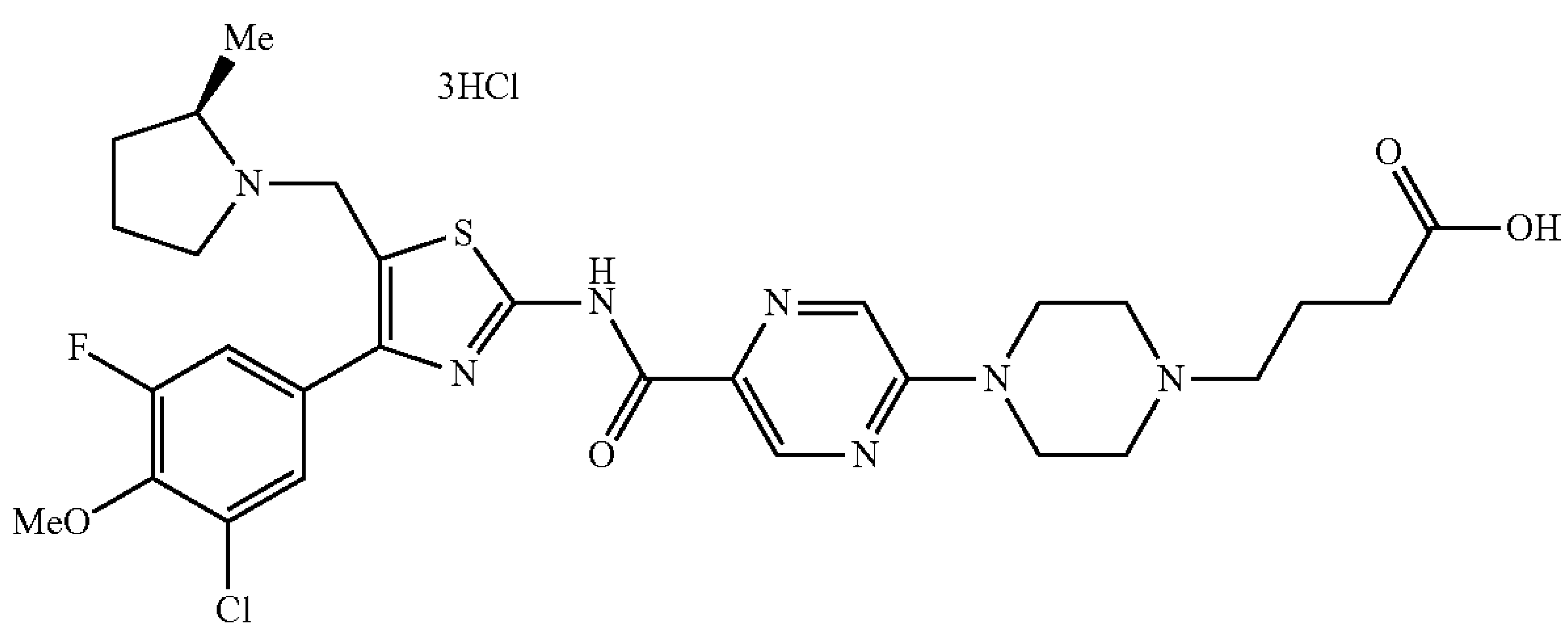
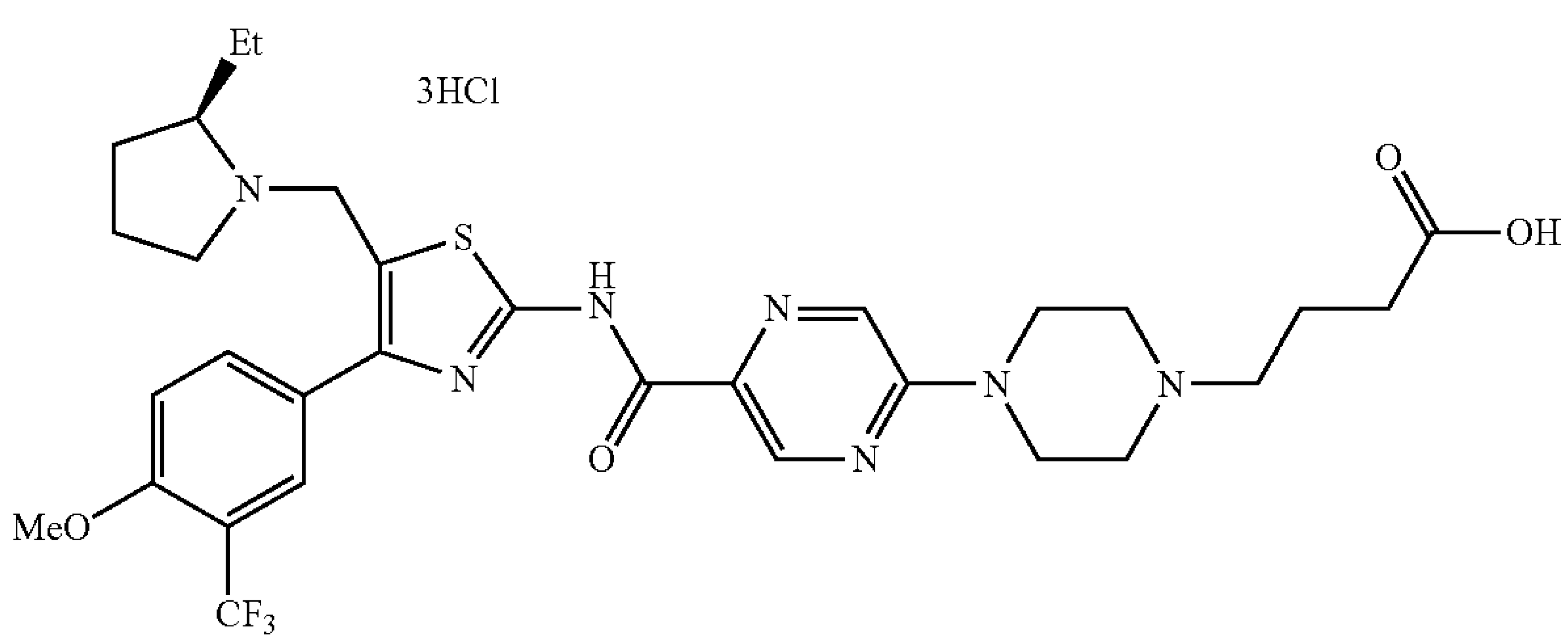
Ex	Structure
73	
74	
75	

TABLE 89-continued

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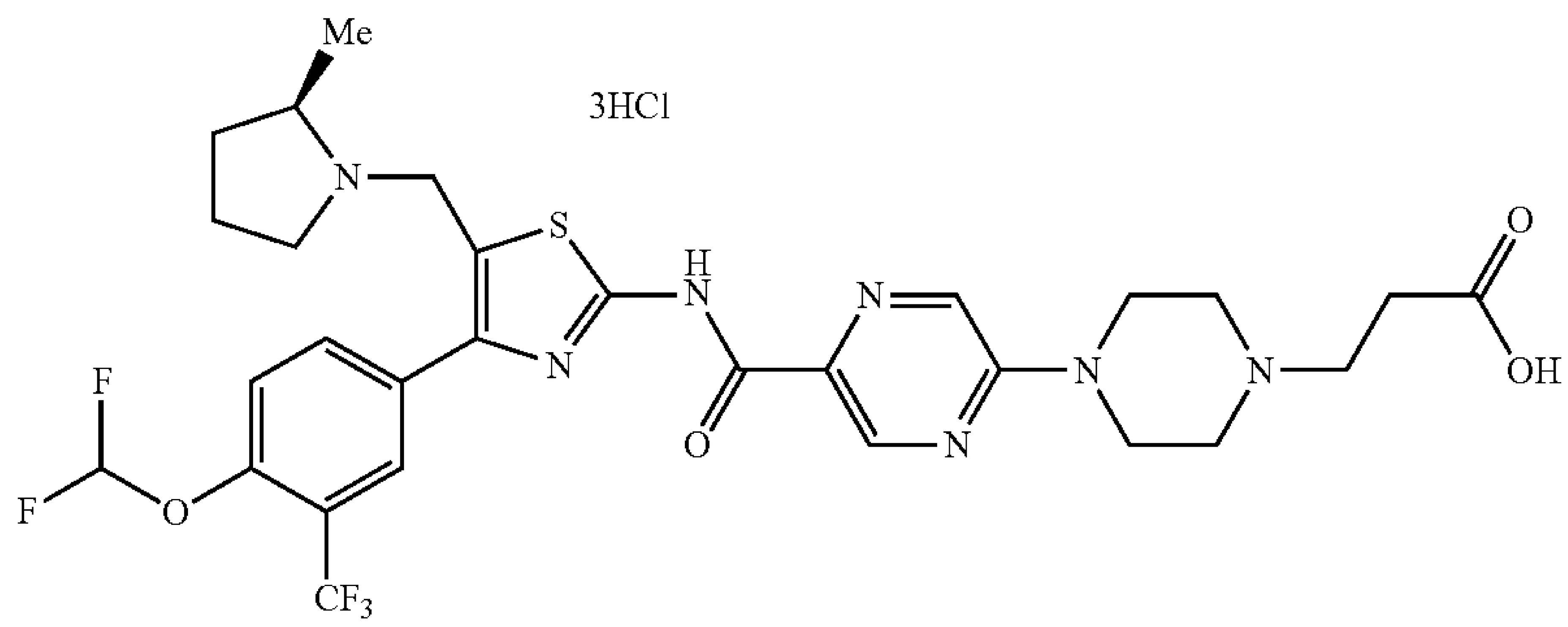
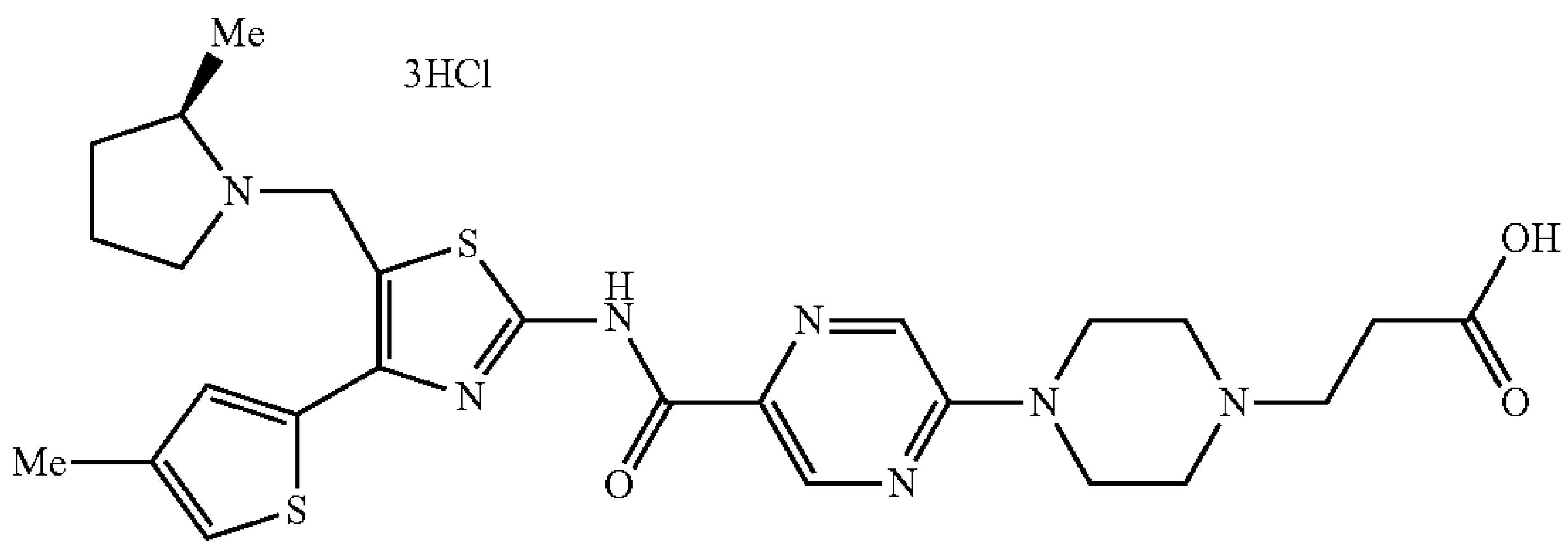
76	
77	

TABLE 90

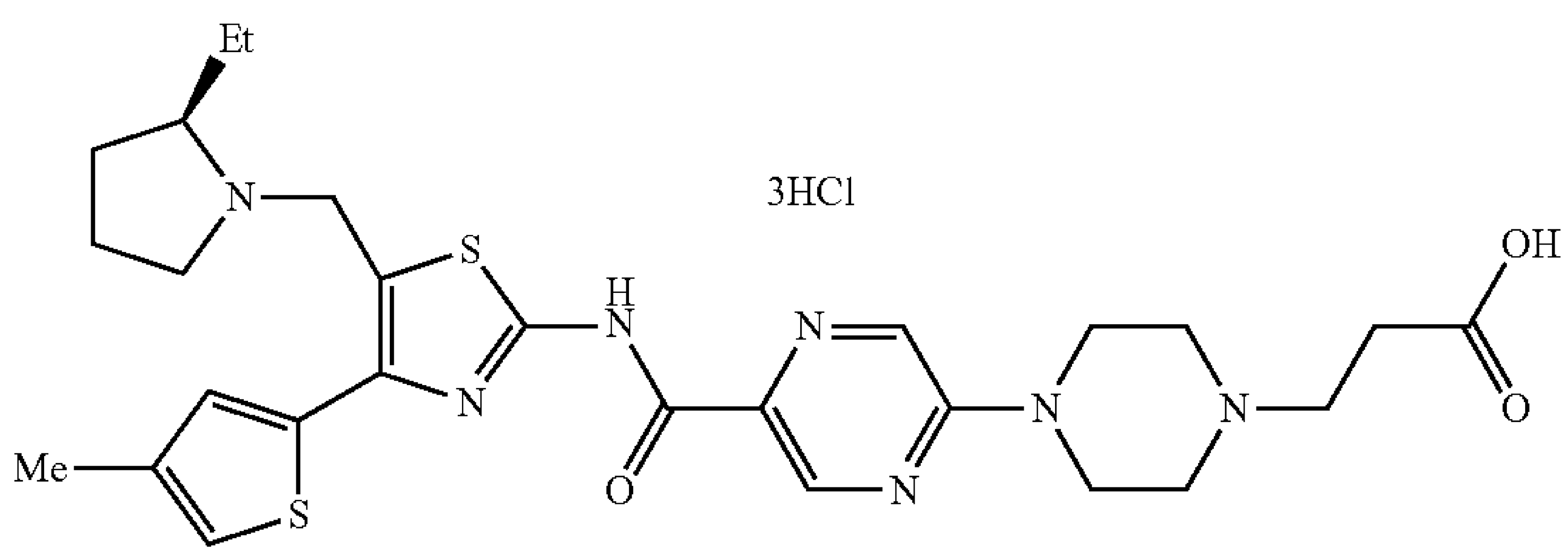
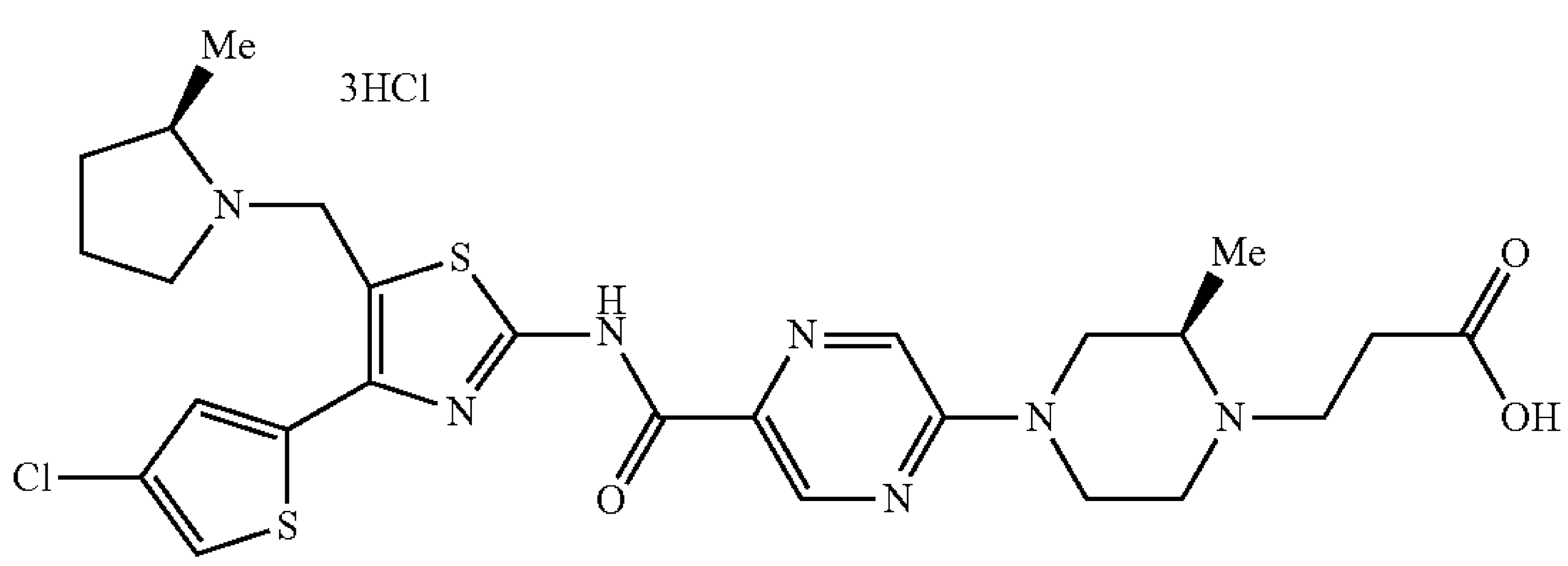
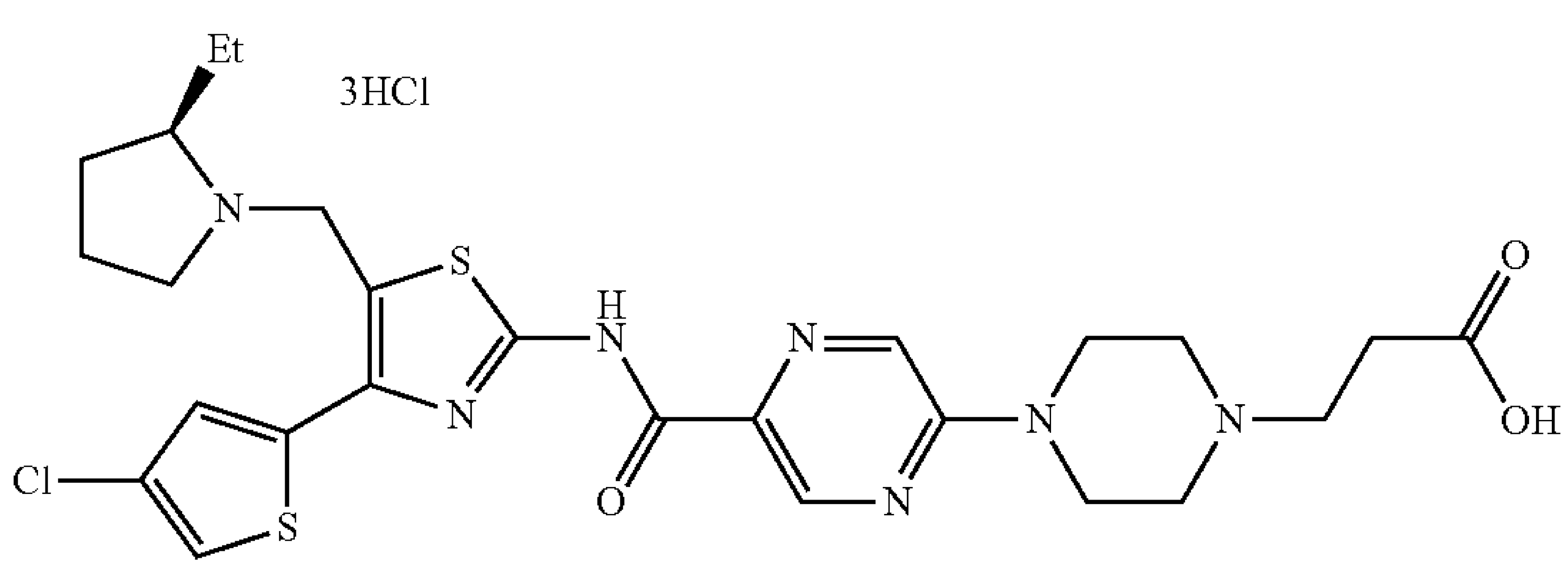
Ex	Structure
78	
79	
80	

TABLE 90-continued

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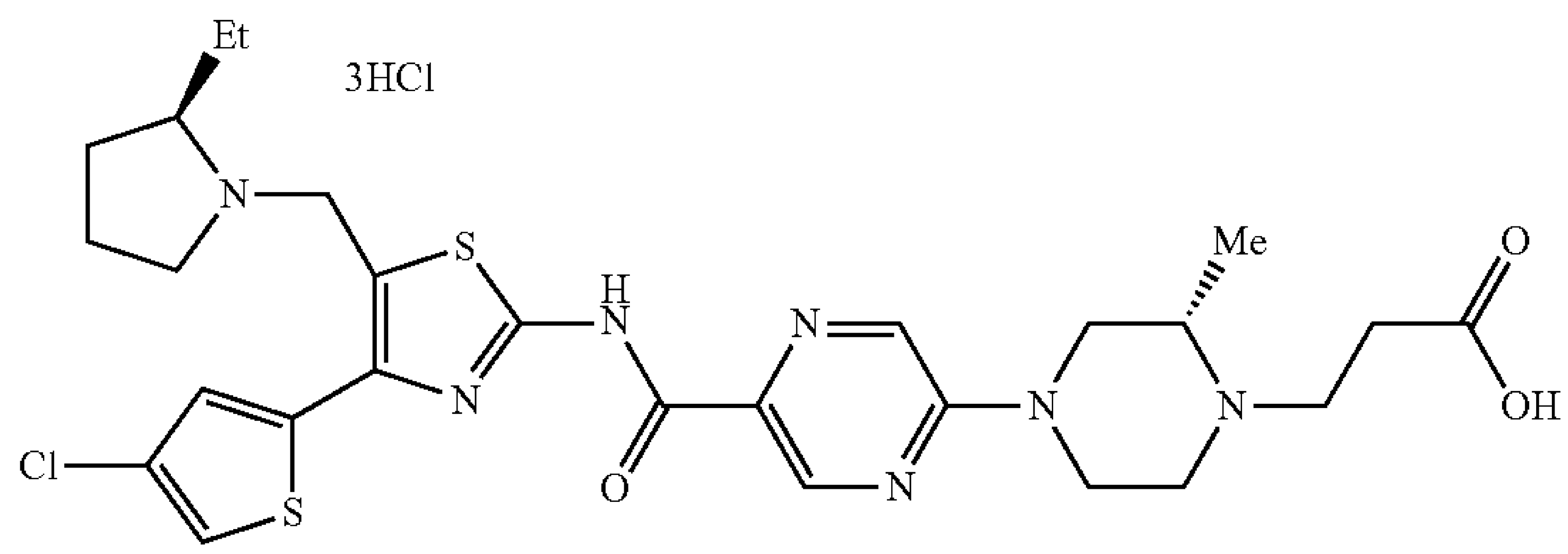
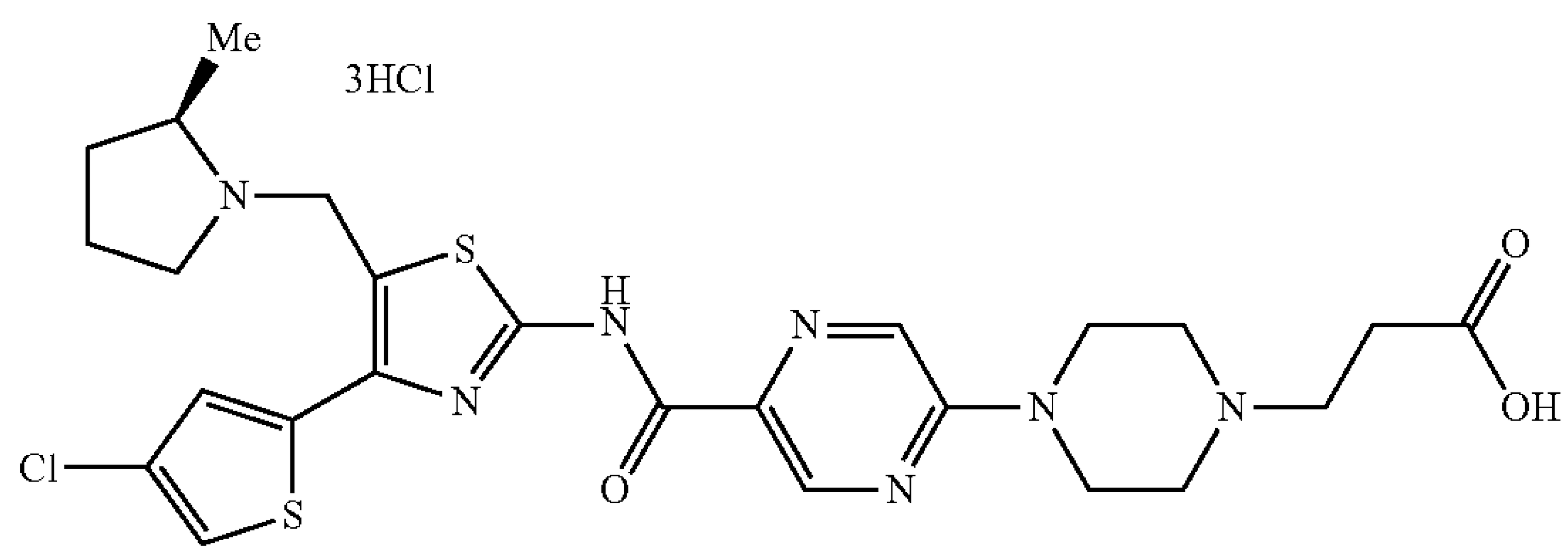
81	
82	

TABLE 91

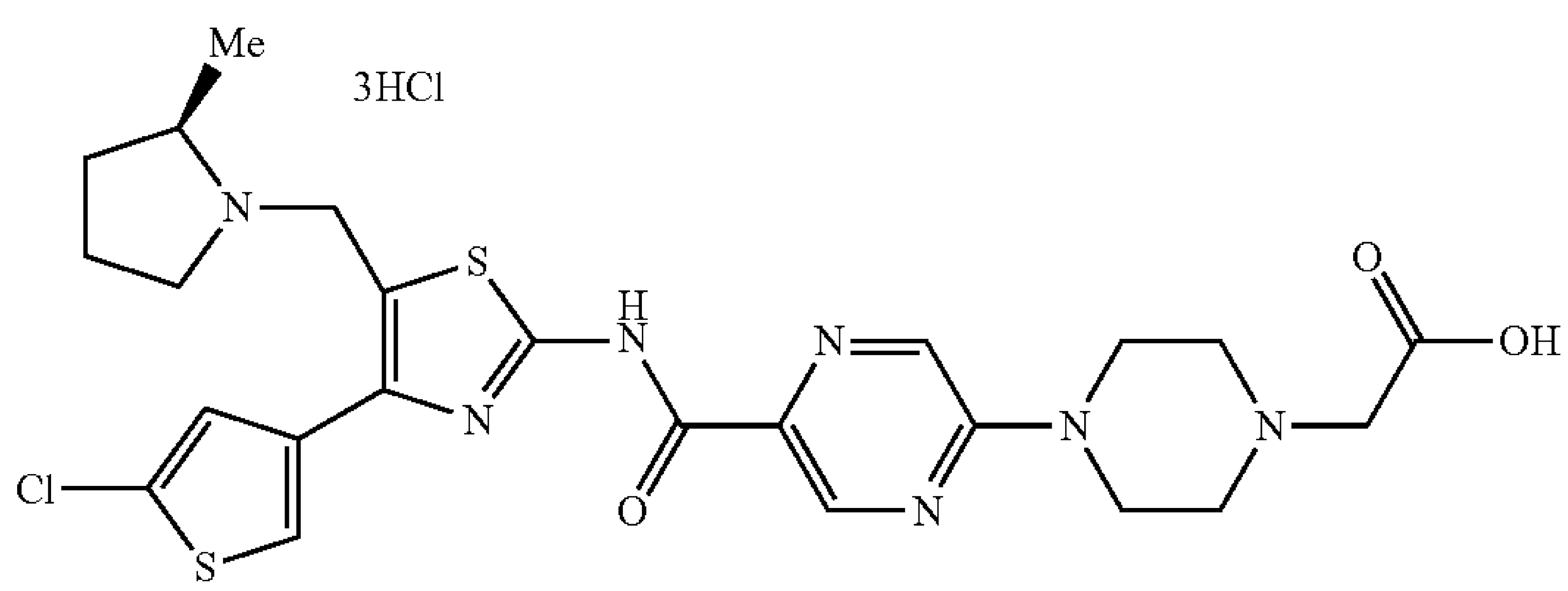
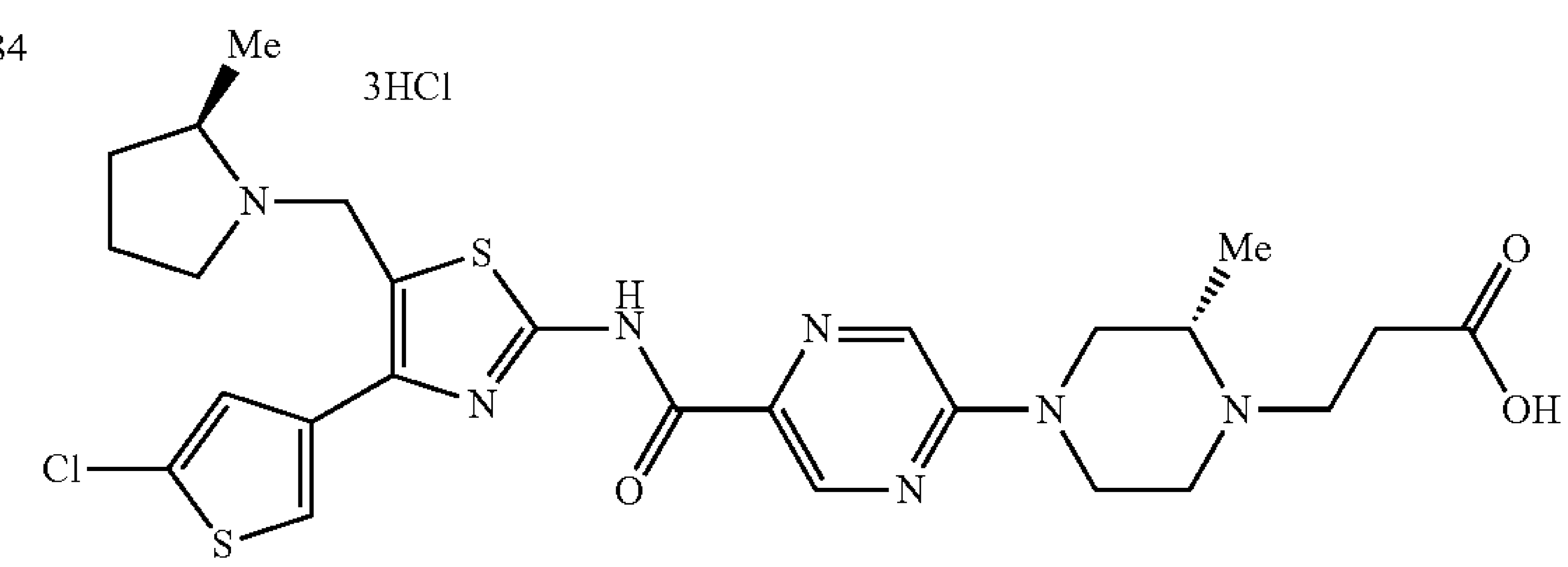
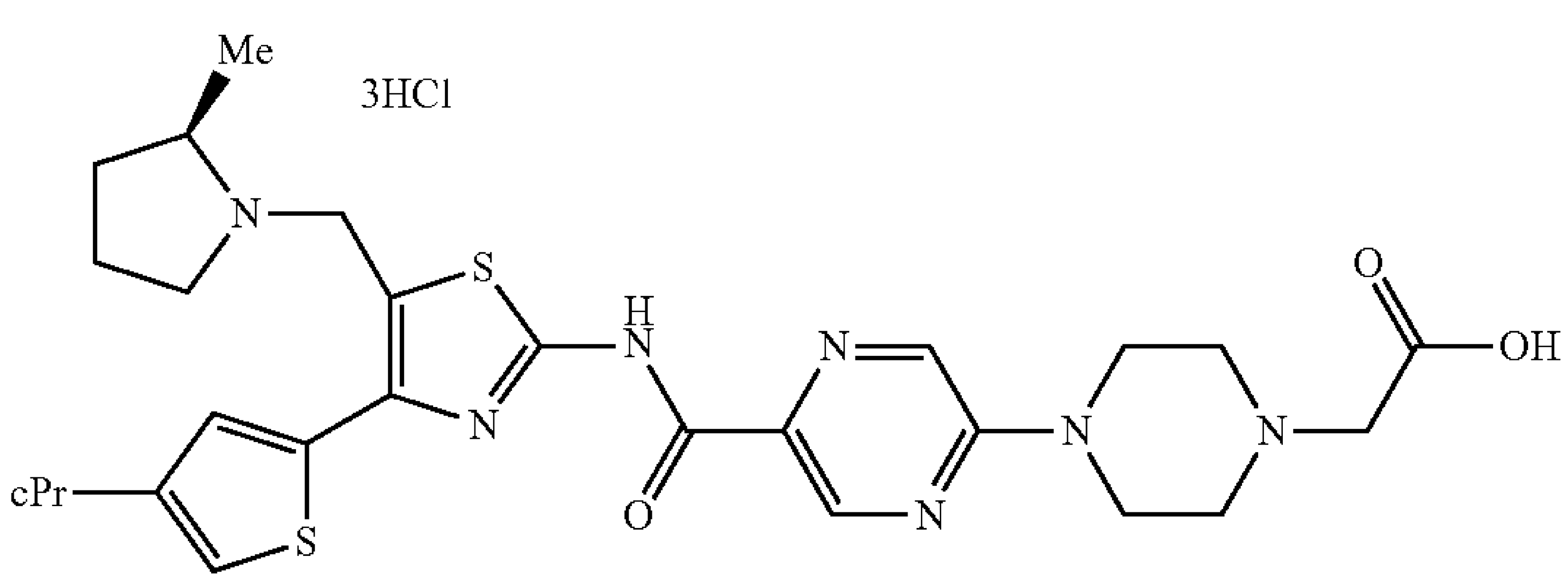
Ex	Structure
83	
84	
85	

TABLE 91-continued

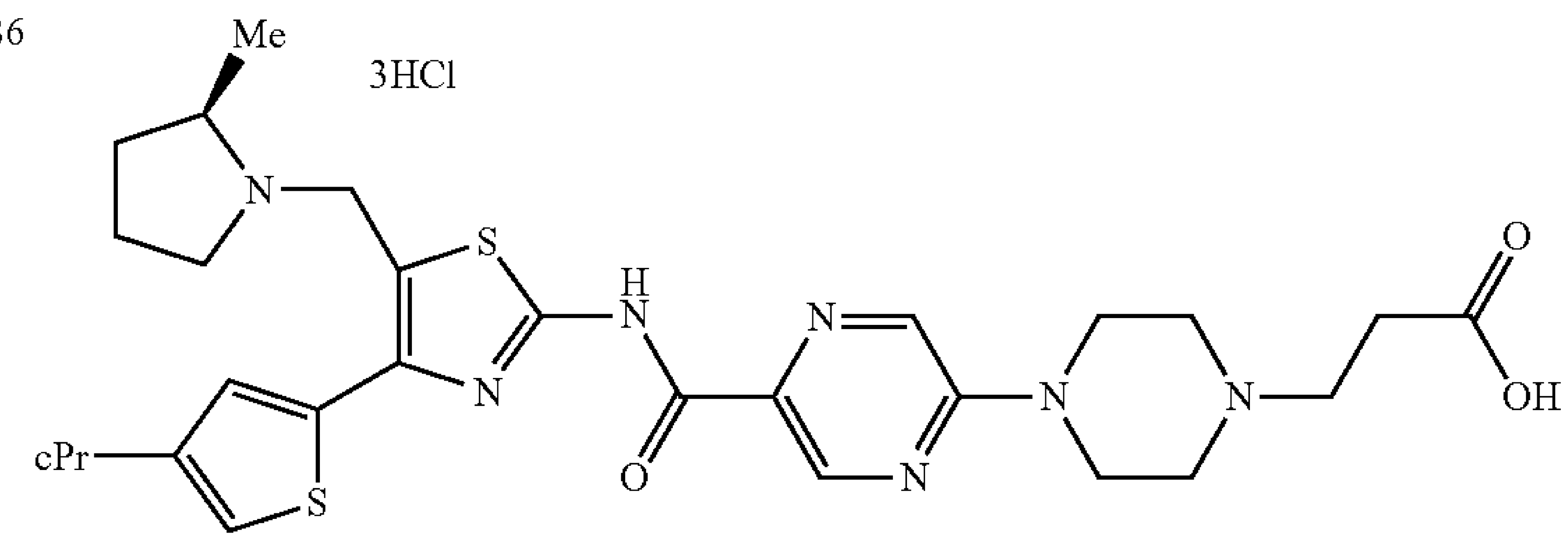
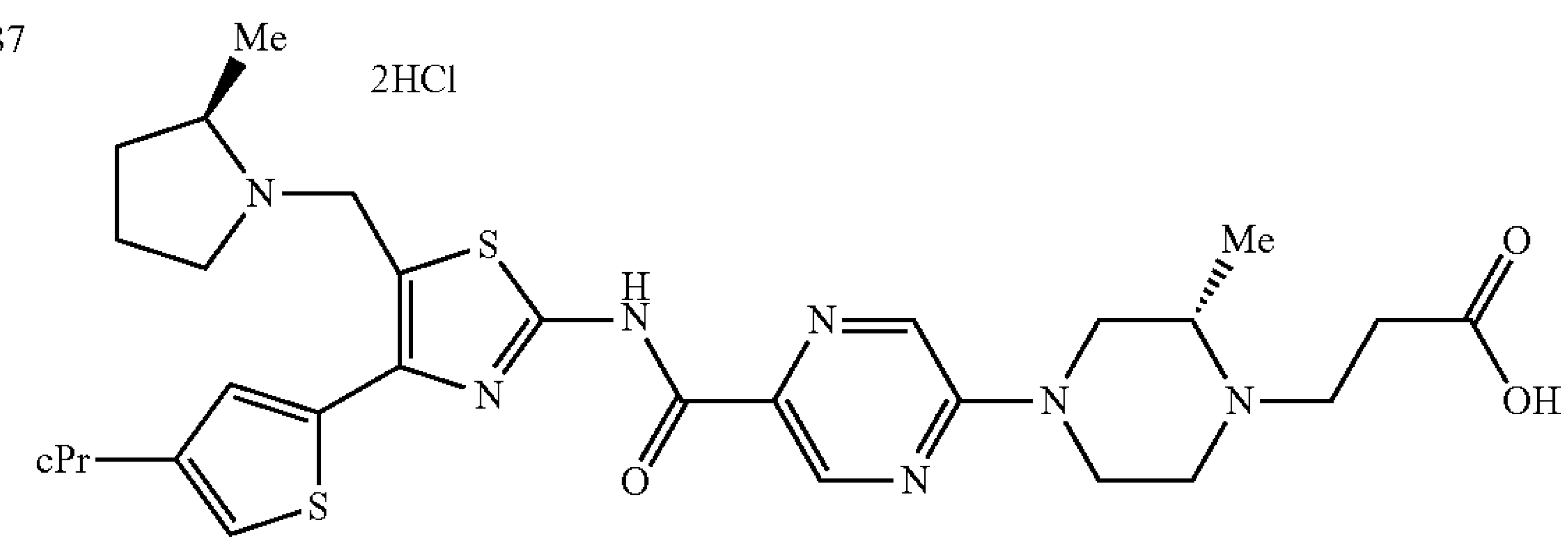
Ex	Structure
86	
87	

TABLE 92

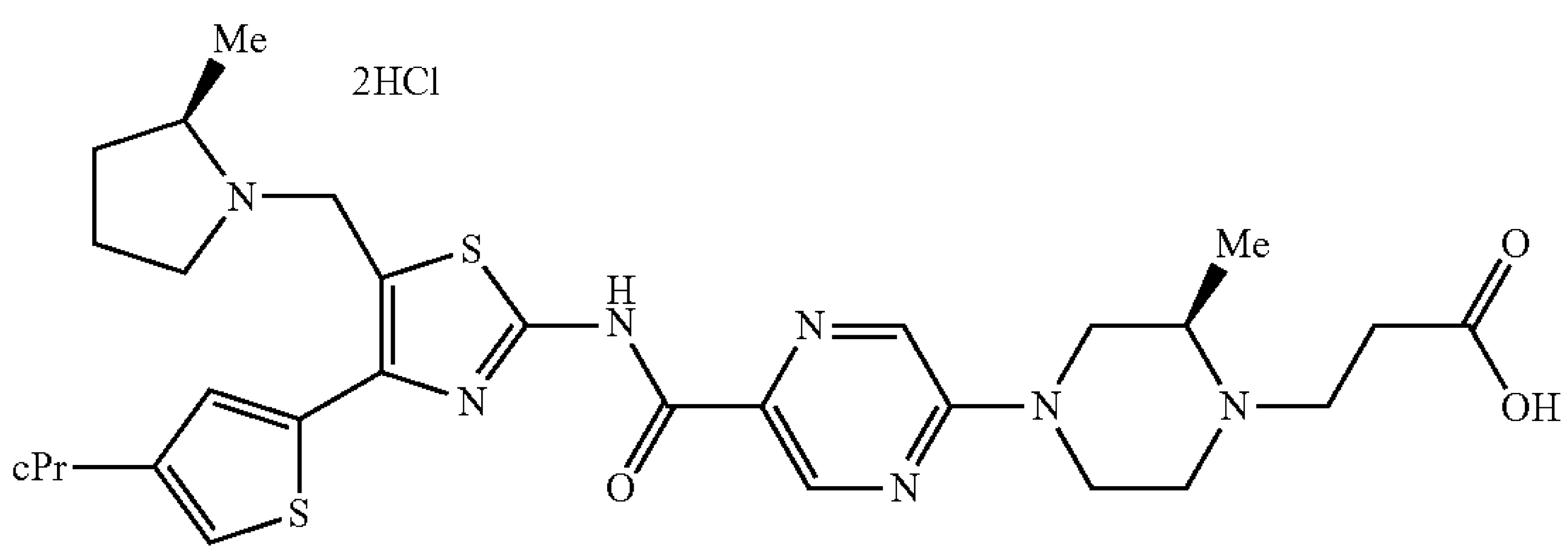
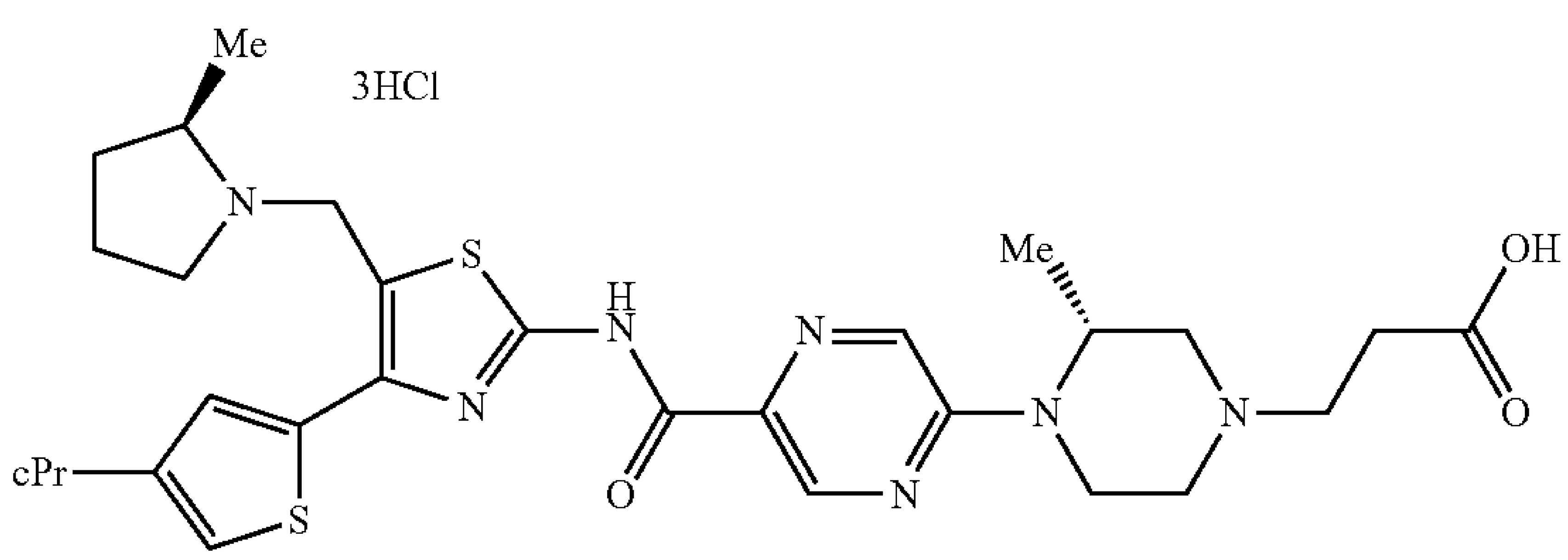
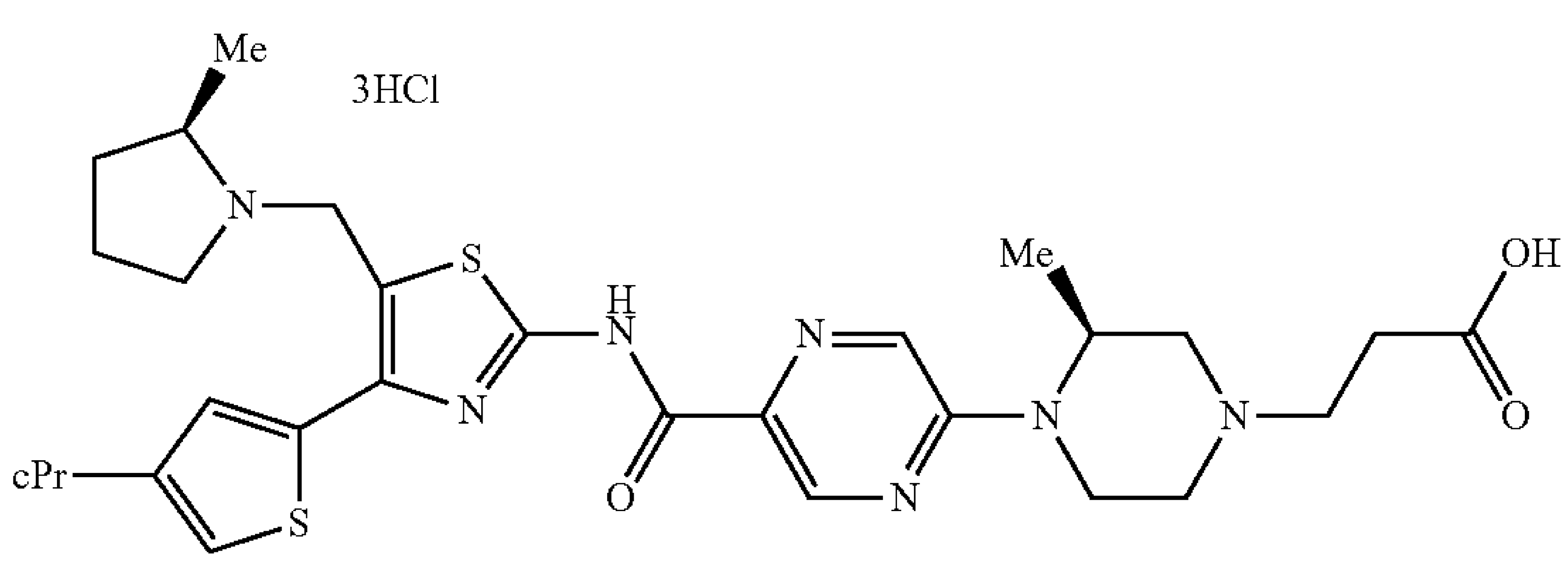
Ex	Structure
88	
89	
90	

TABLE 92-continued

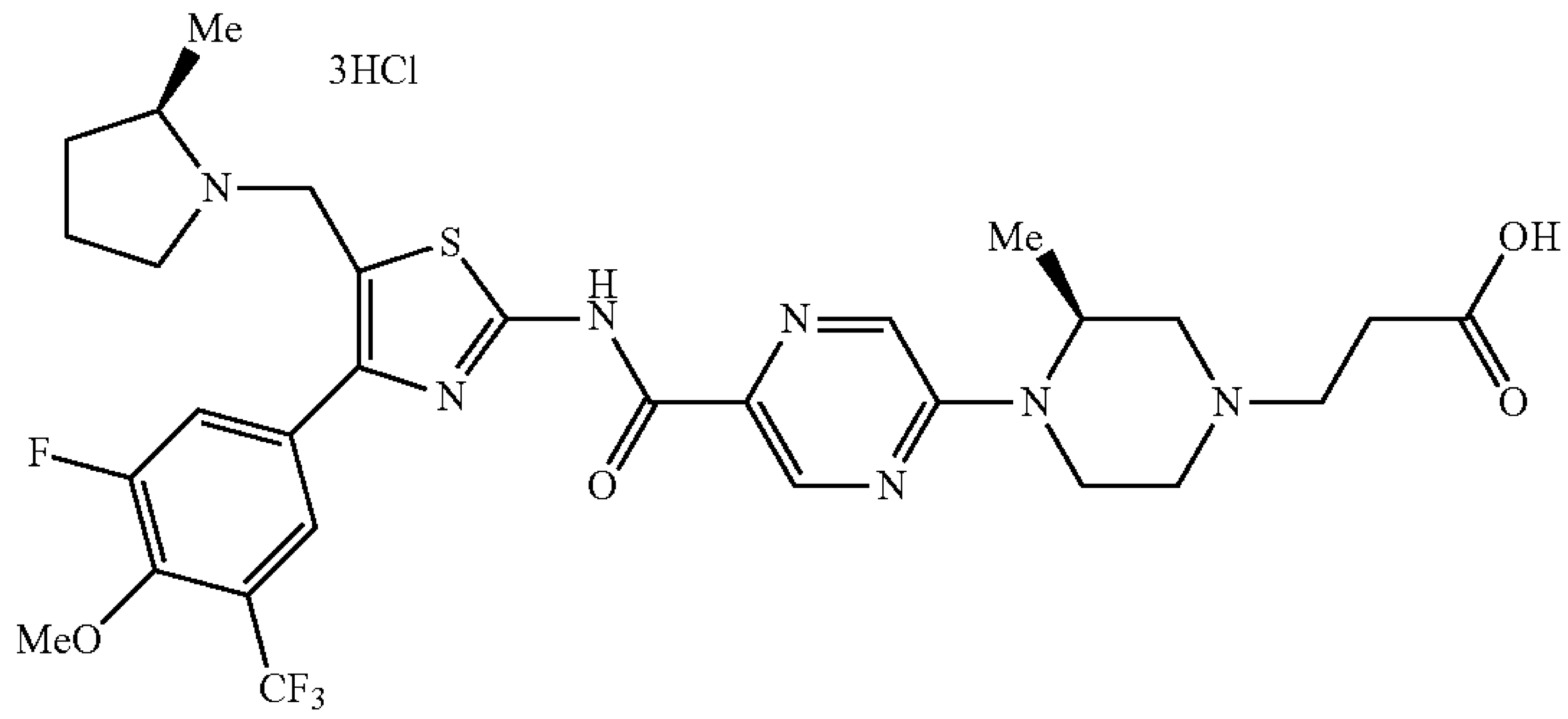
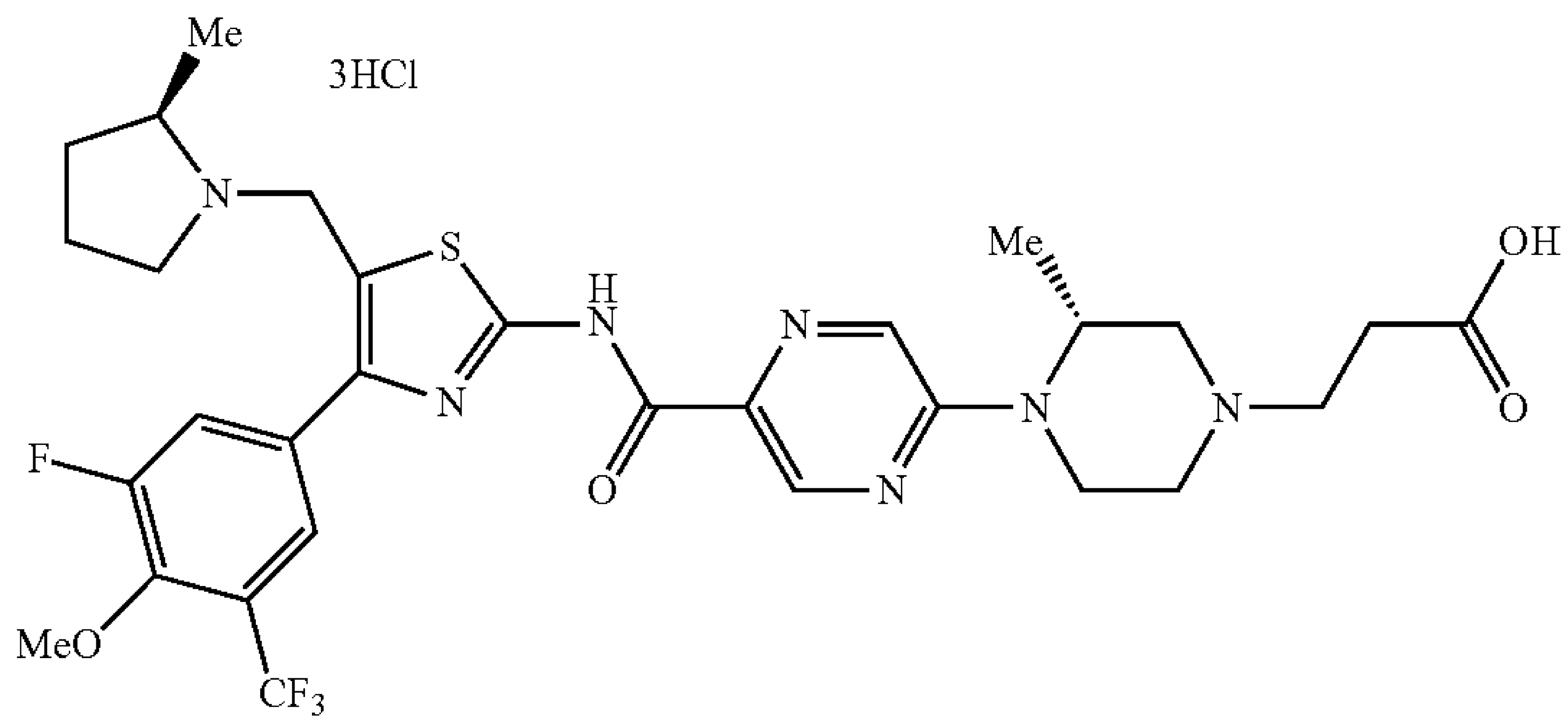
Ex	Structure
91	
92	

TABLE 93

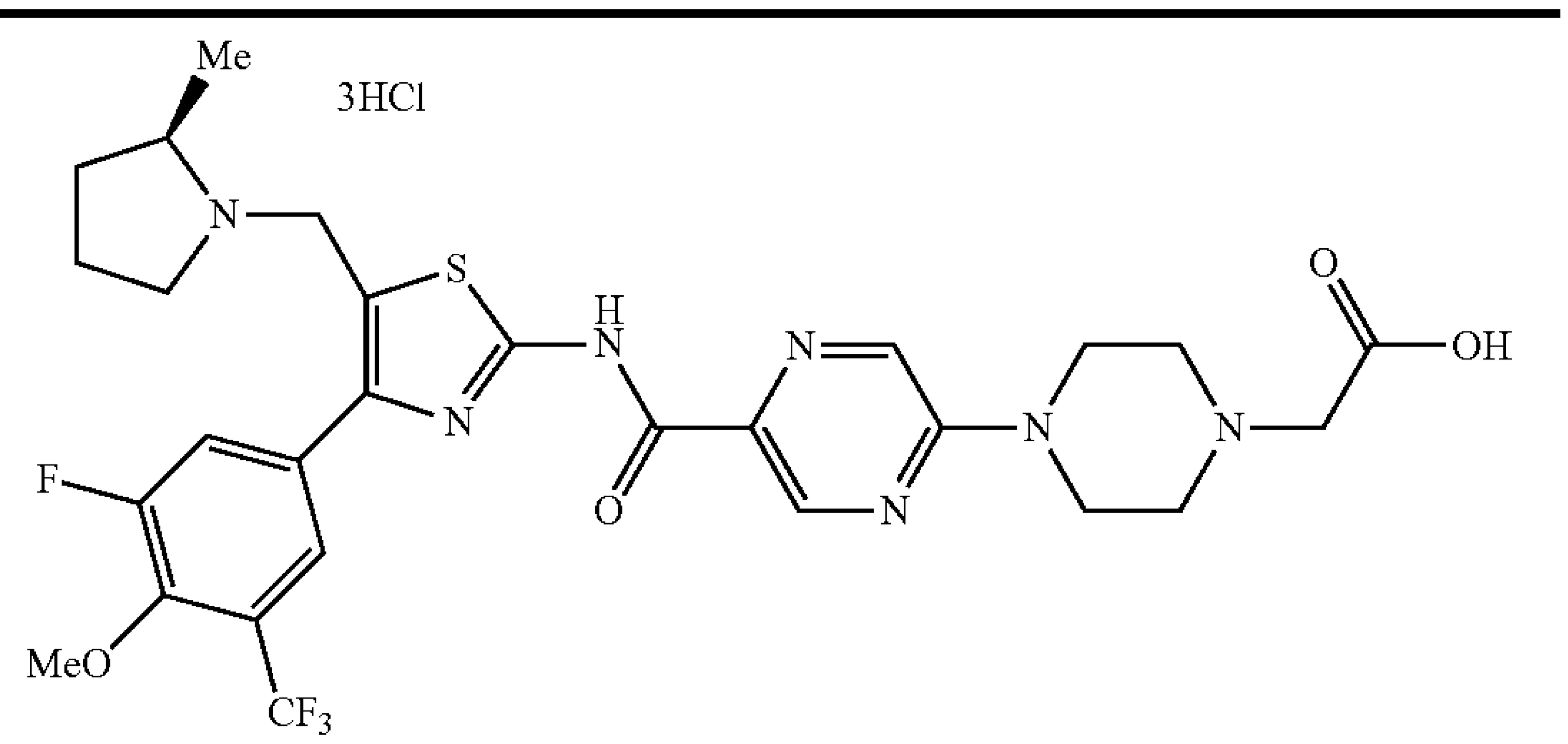
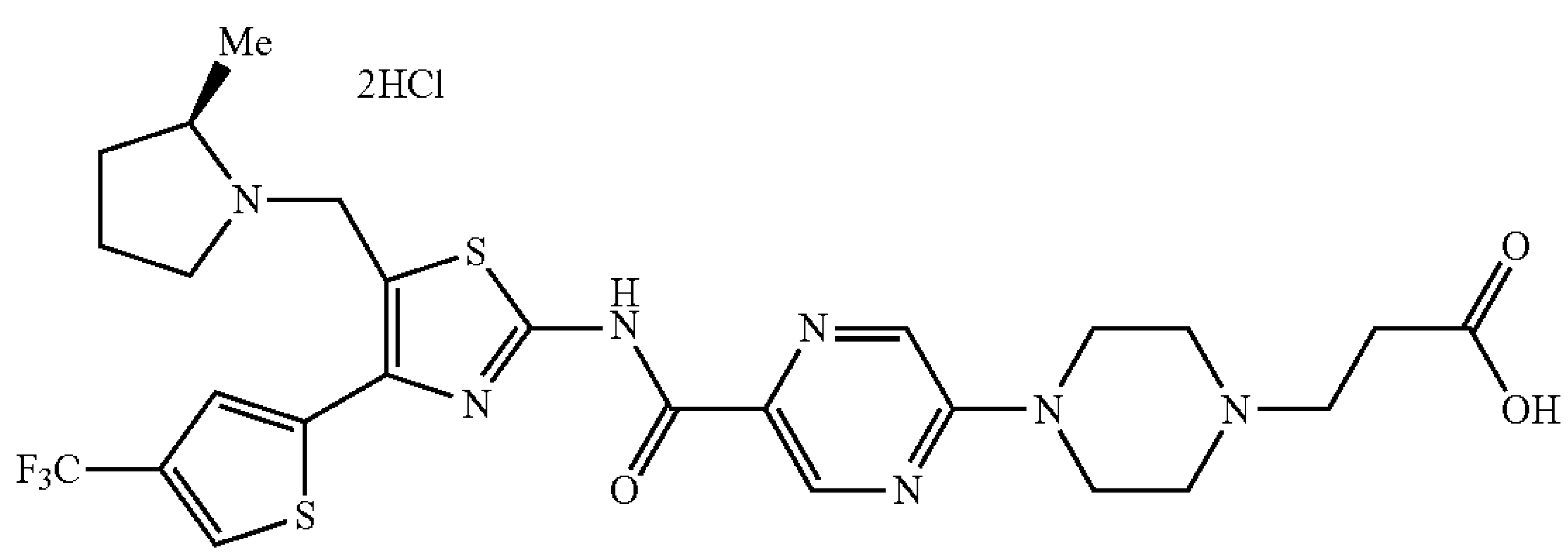
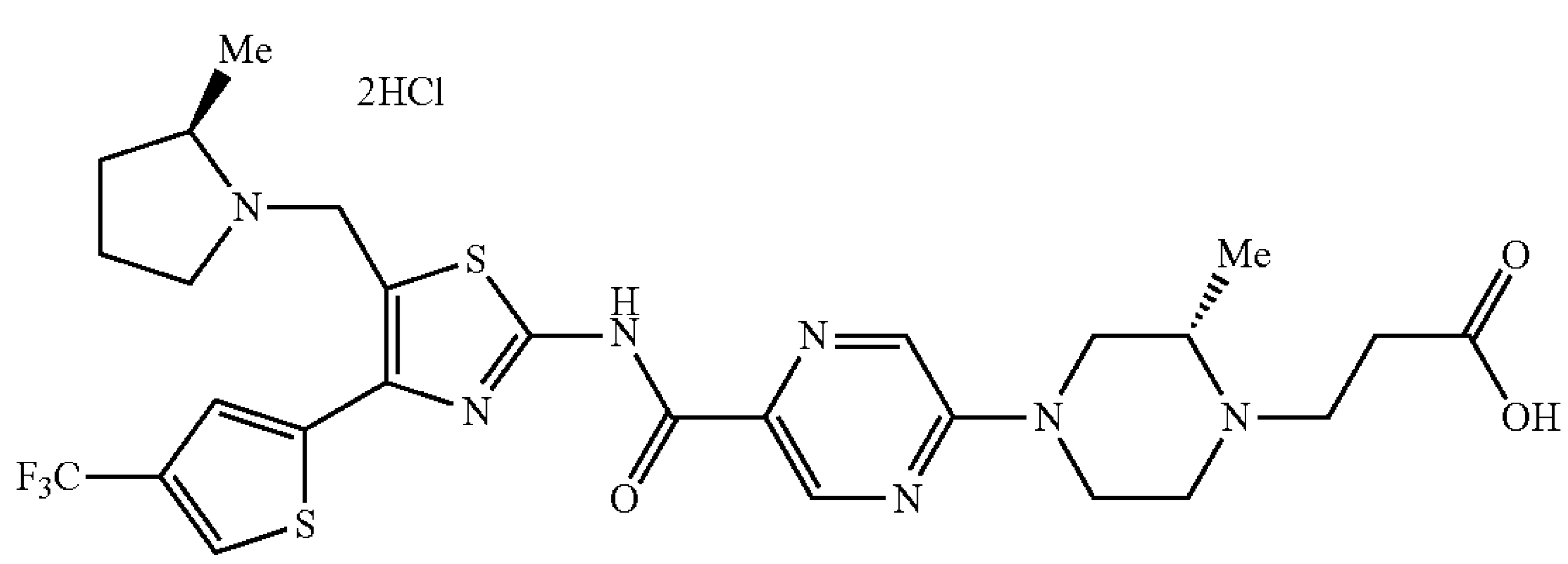
Ex	Structure
93	
94	
95	

TABLE 93-continued

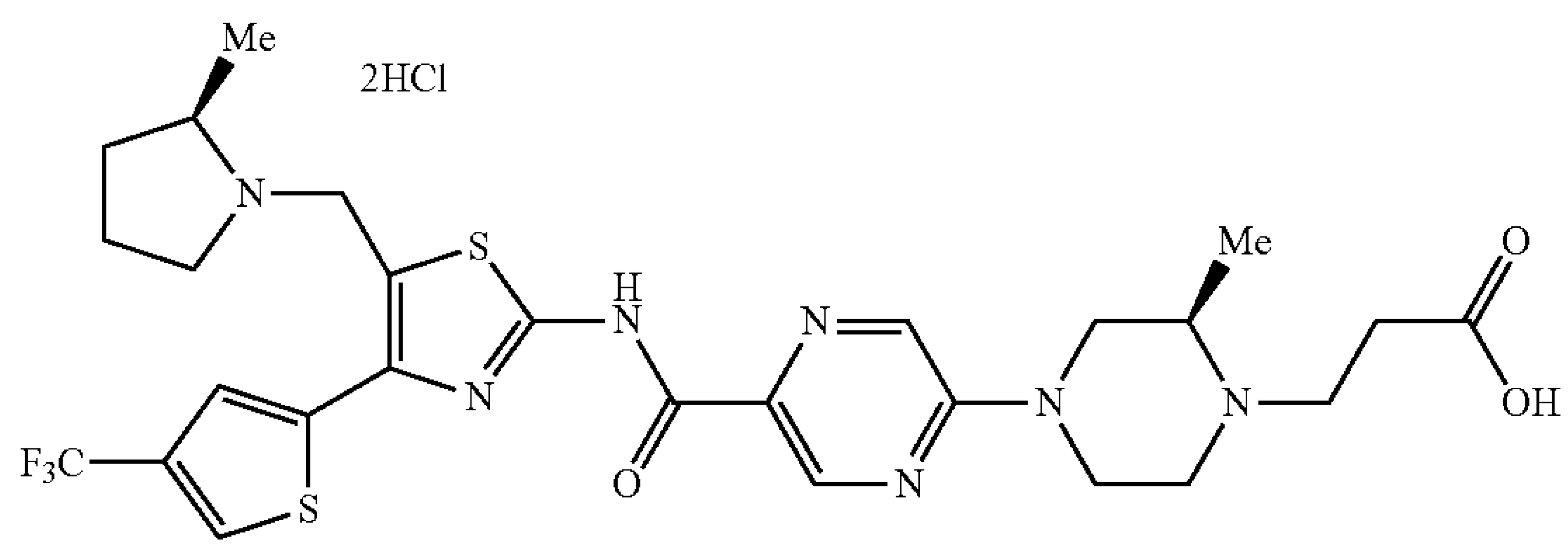
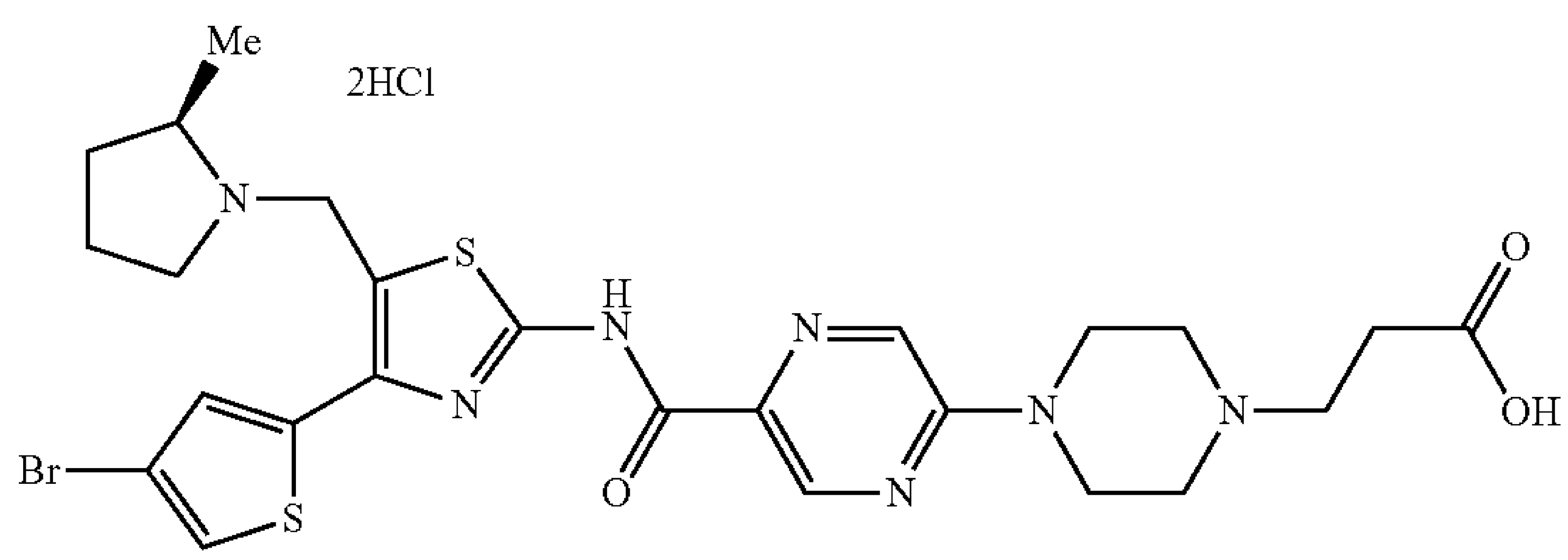
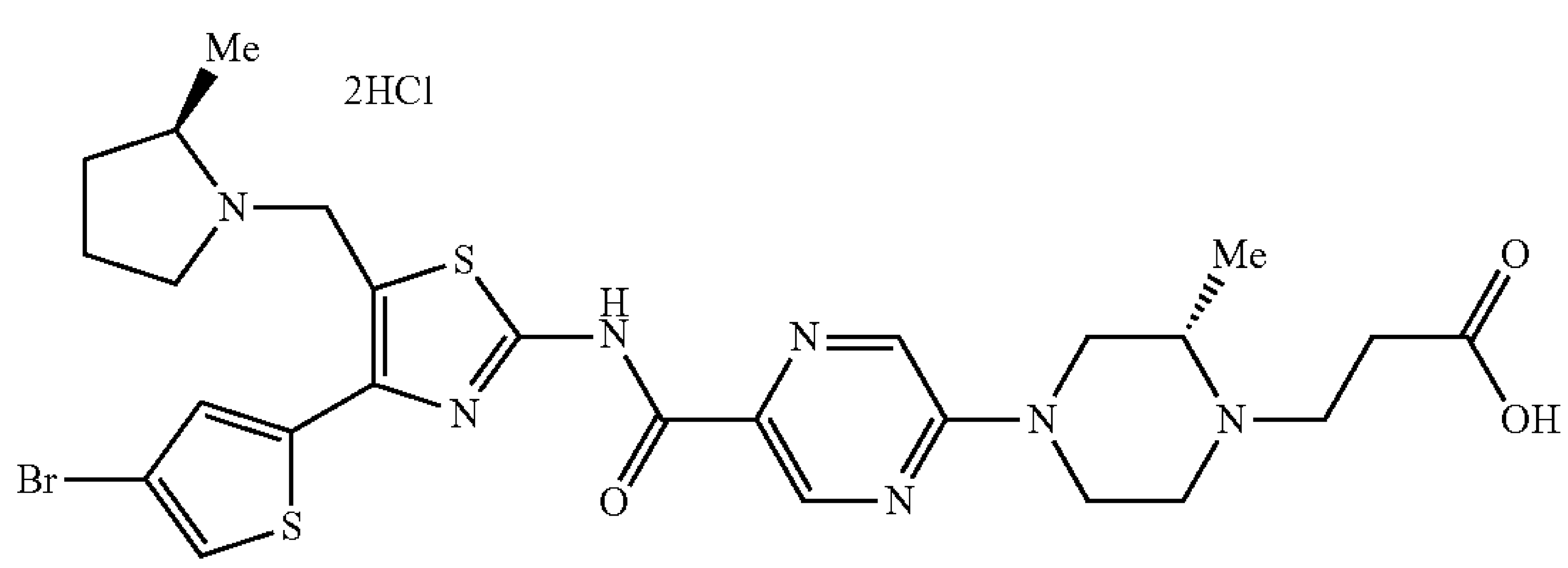
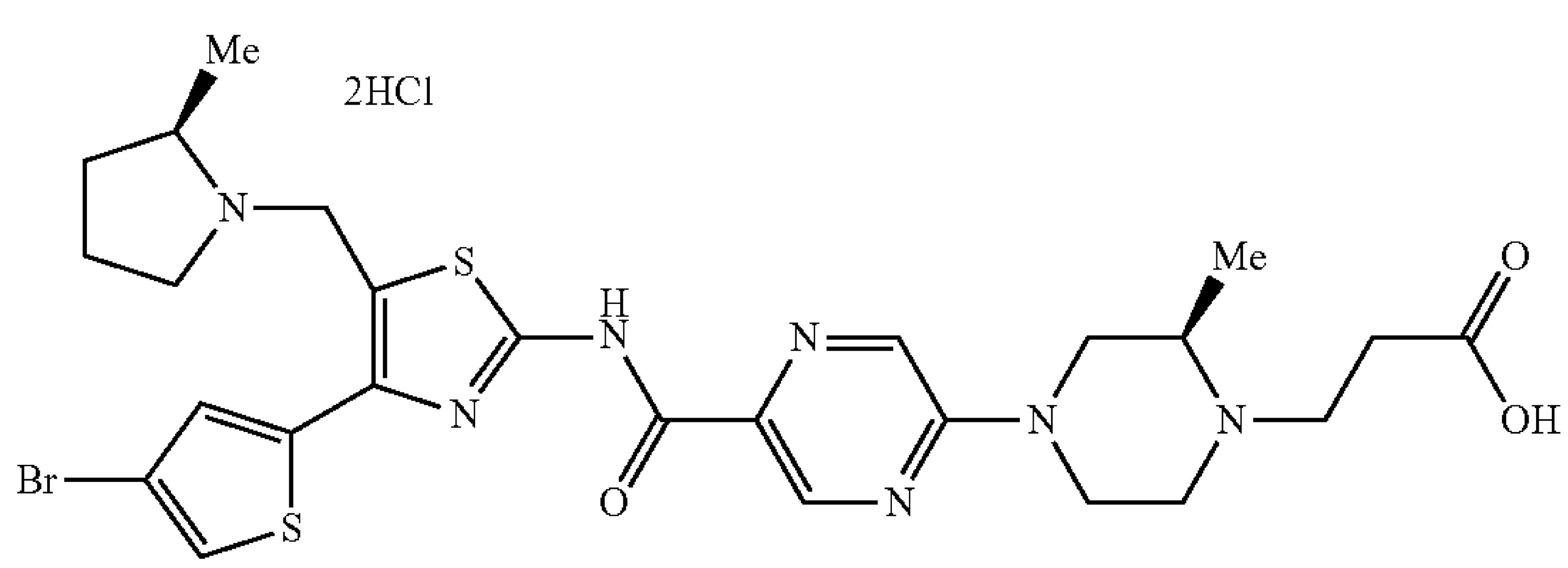
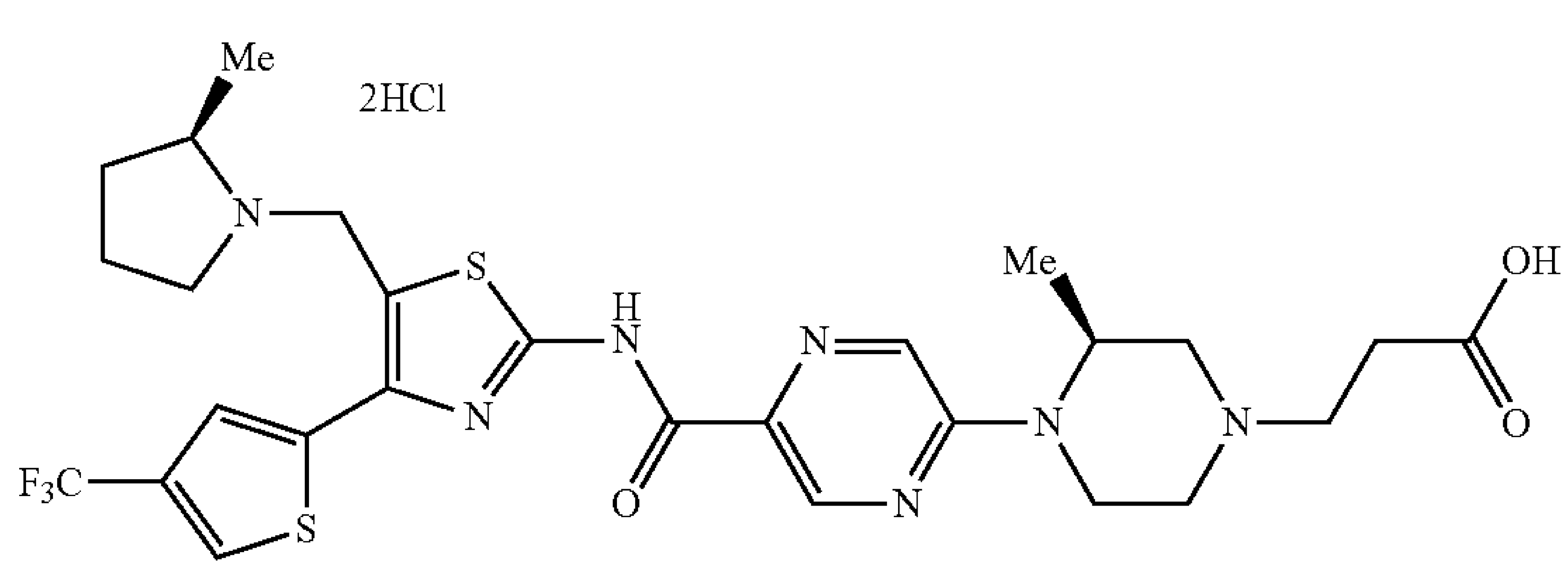
Ex	Structure
96	
97	

TABLE 94

Ex	Structure
98	
99	
100	

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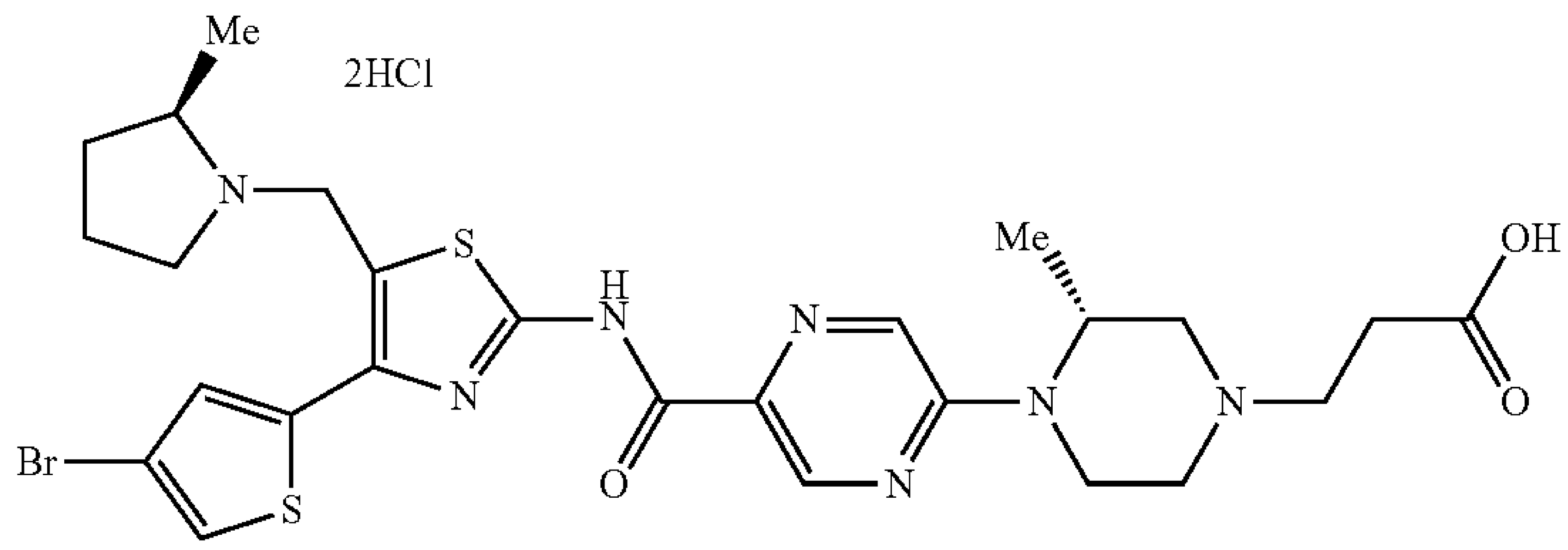
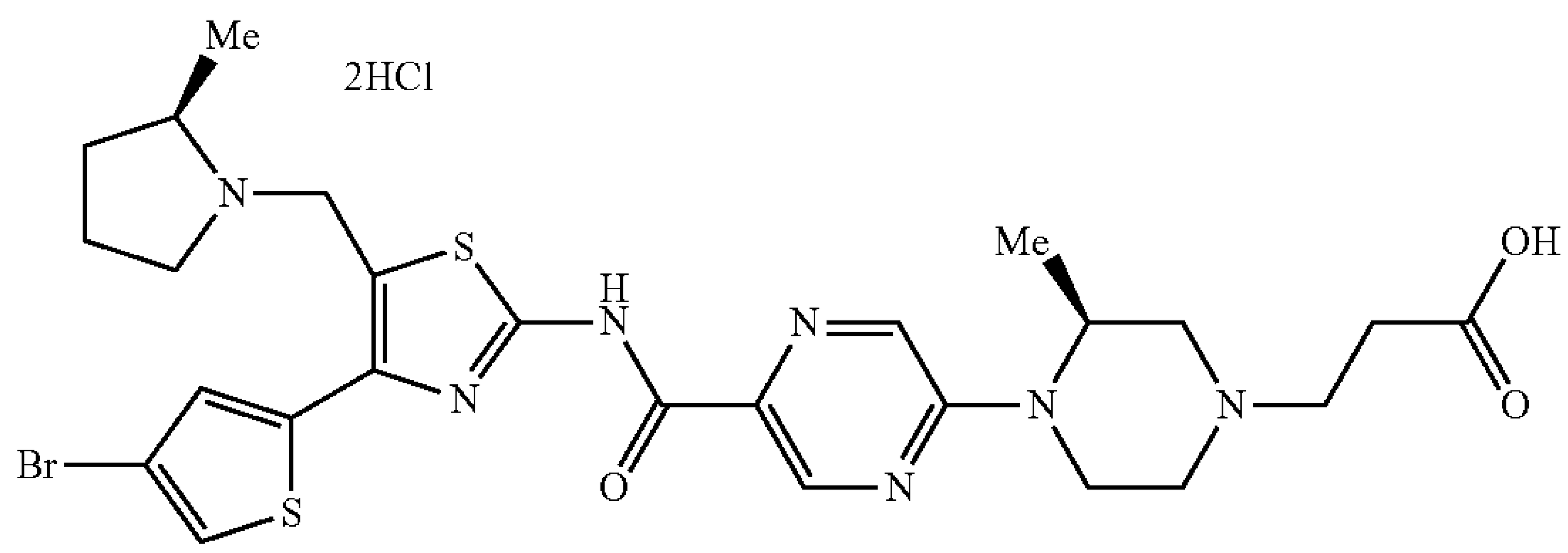
Ex	Structure
101	
102	

TABLE 95

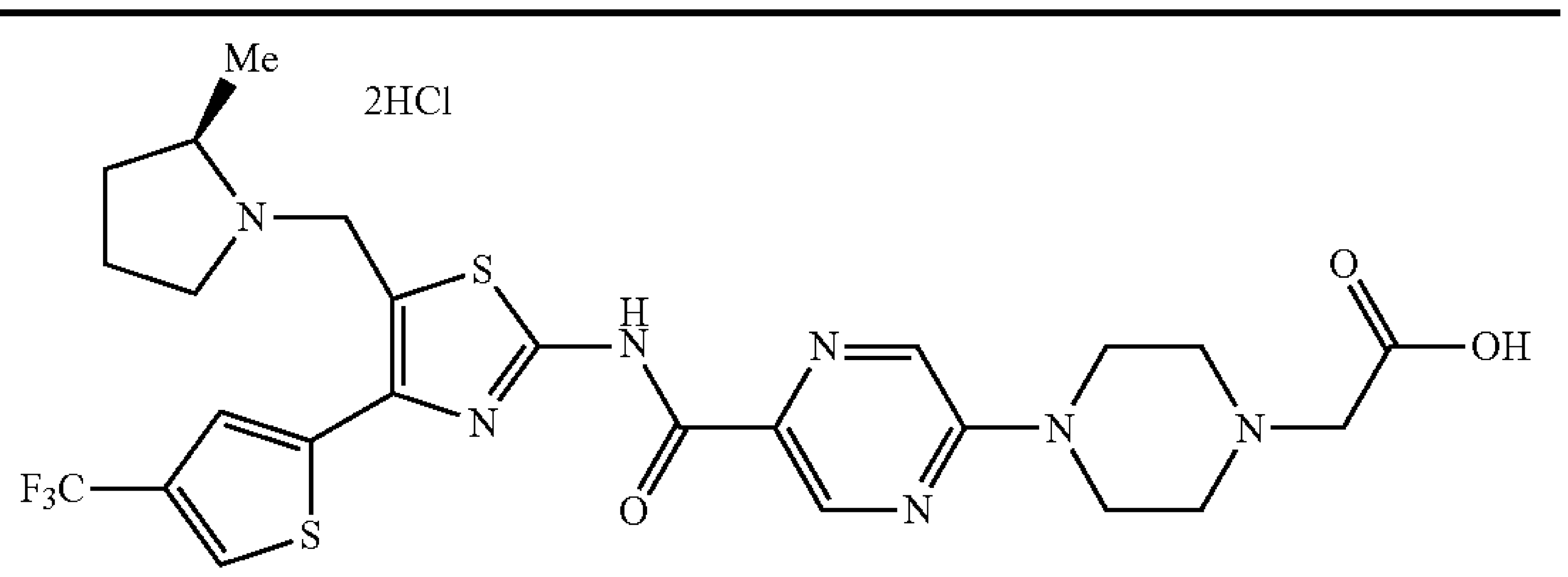
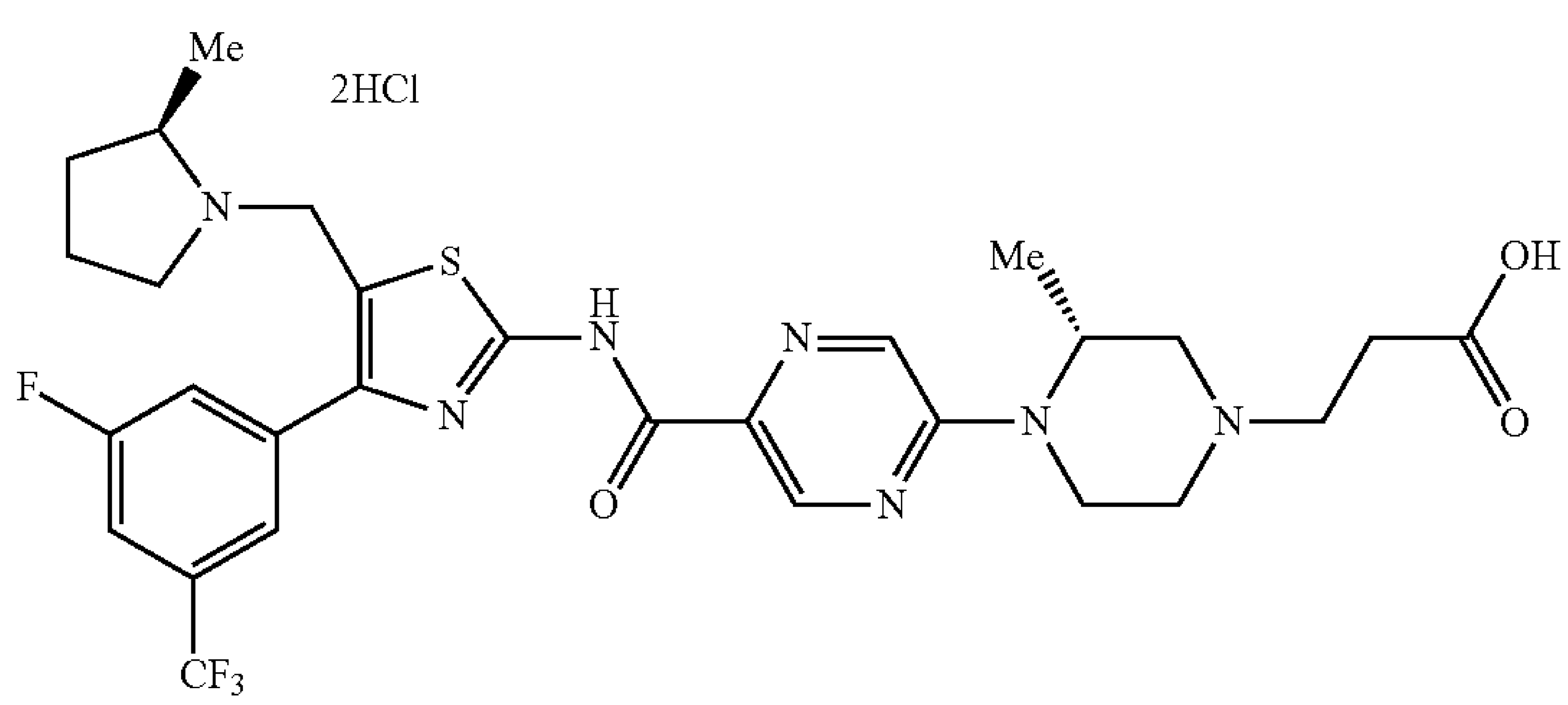
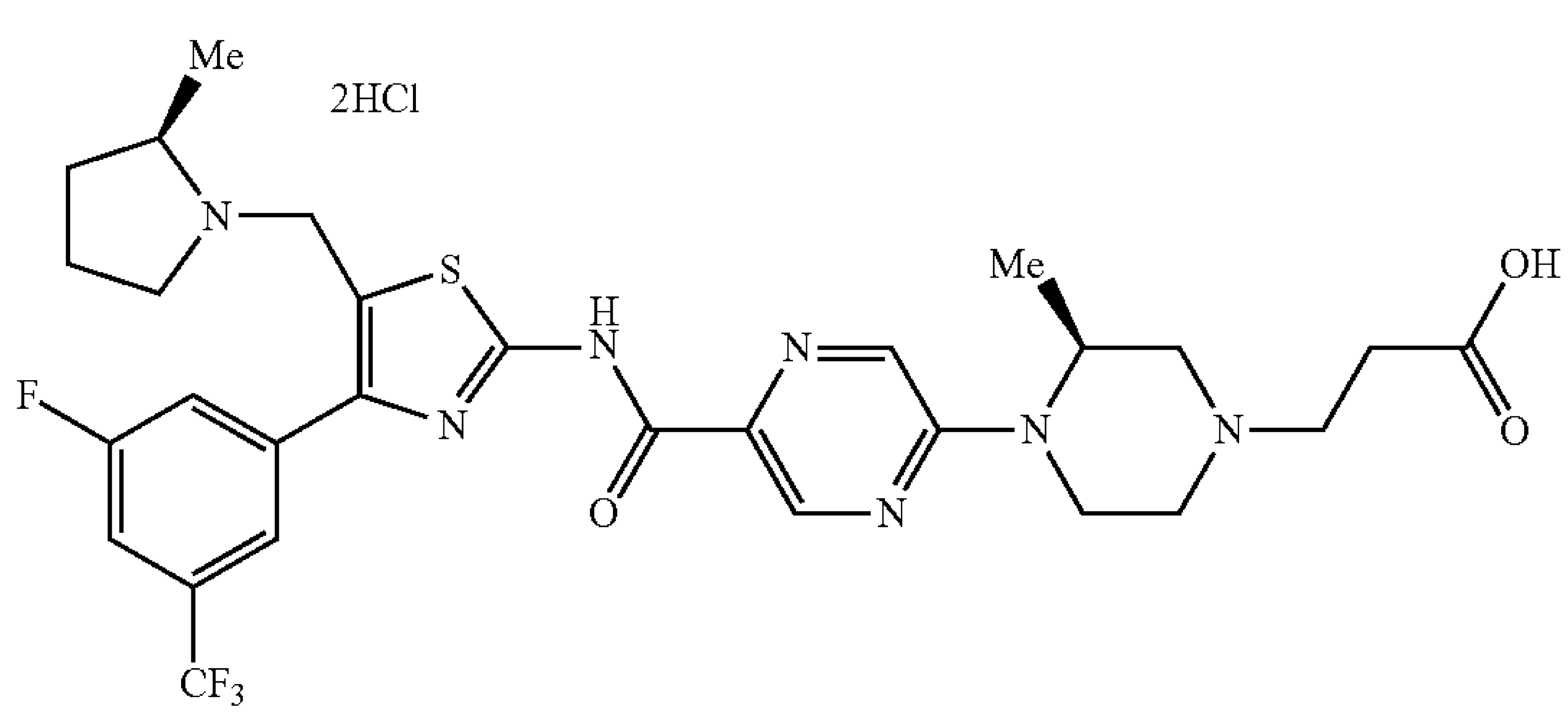
Ex	Structure
103	
104	
105	

TABLE 95-continued

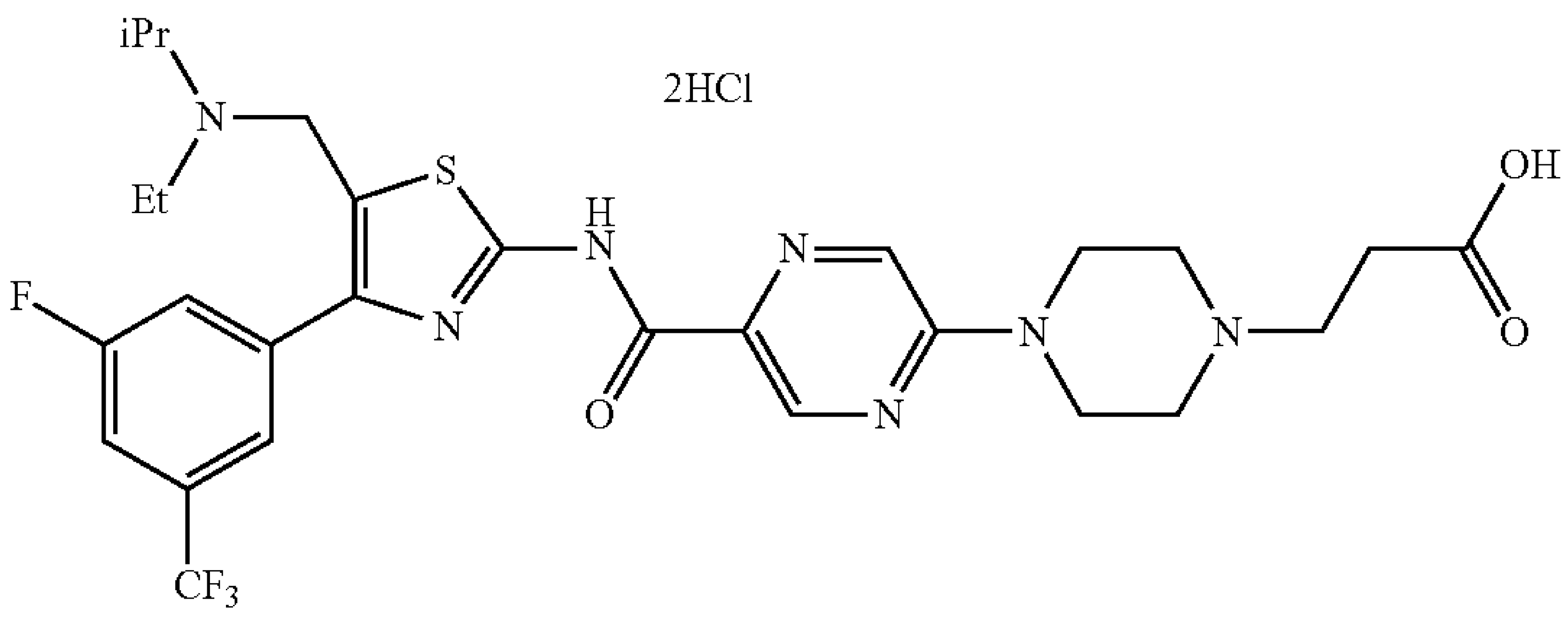
Ex	Structure
106	

TABLE 96

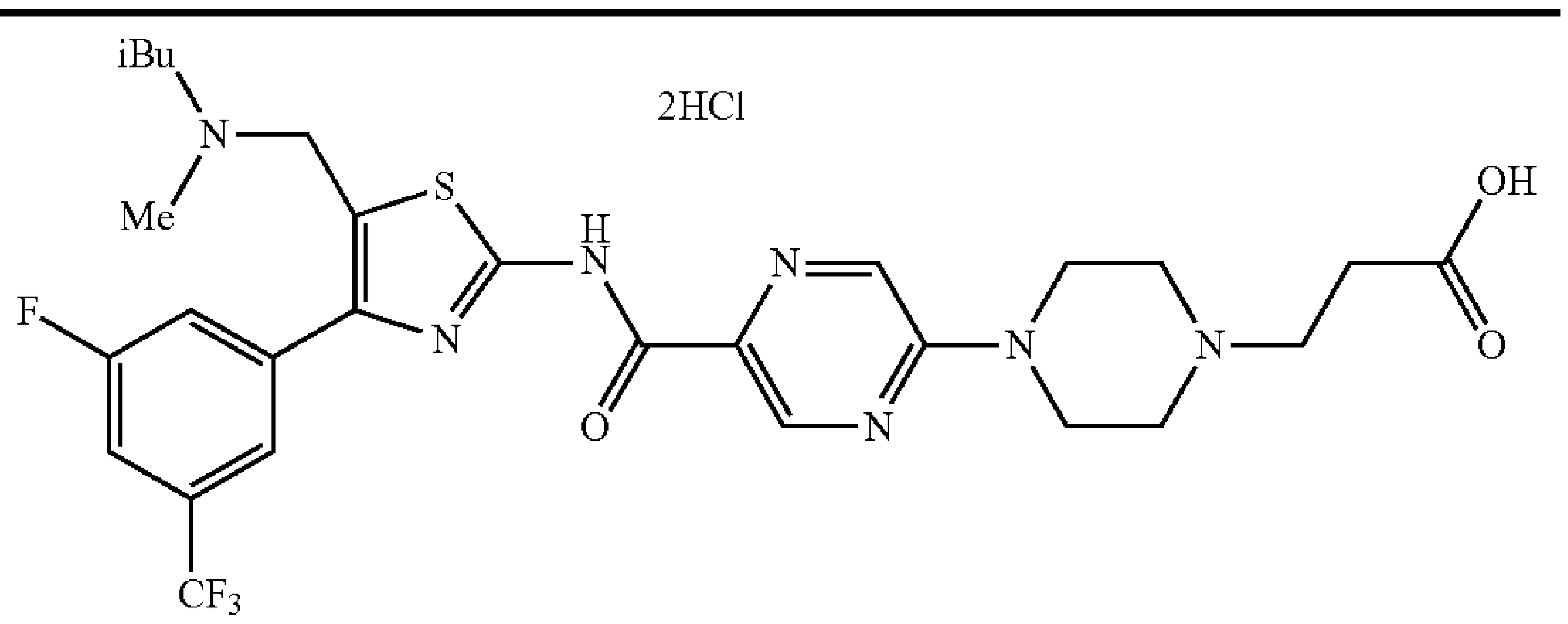
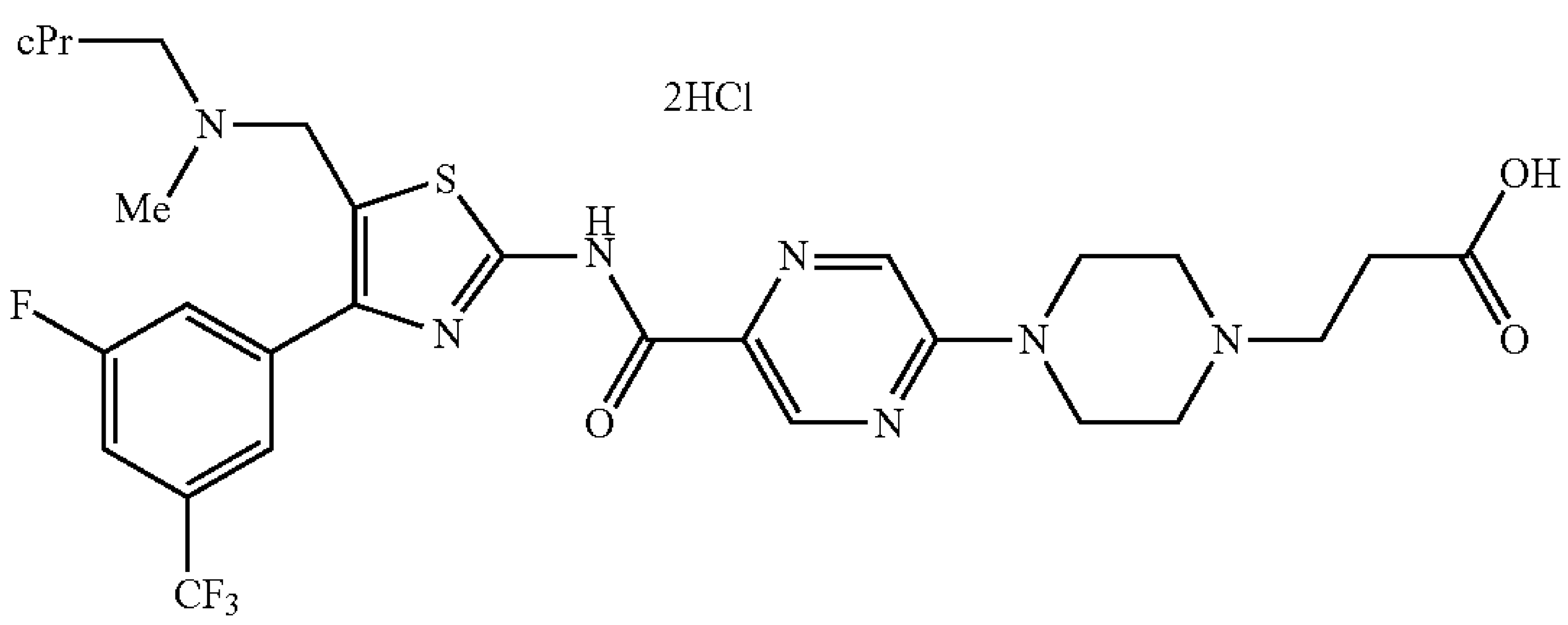
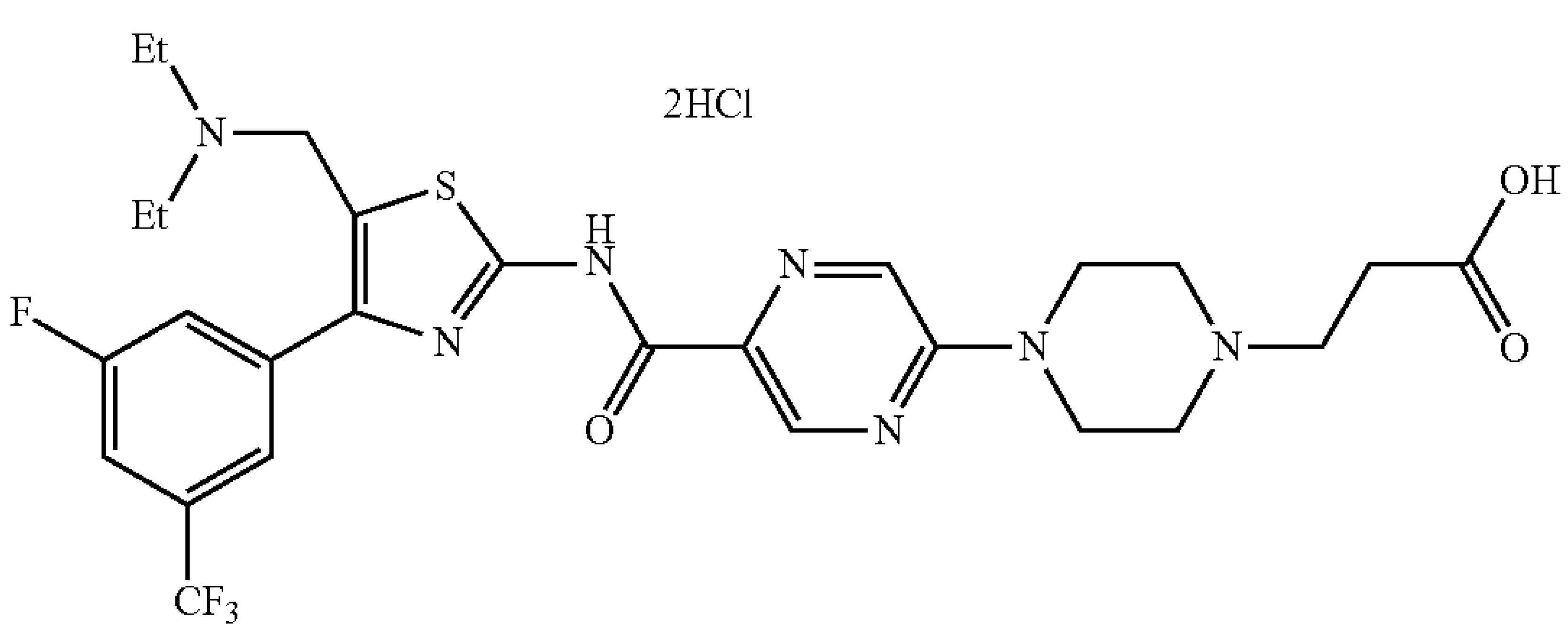
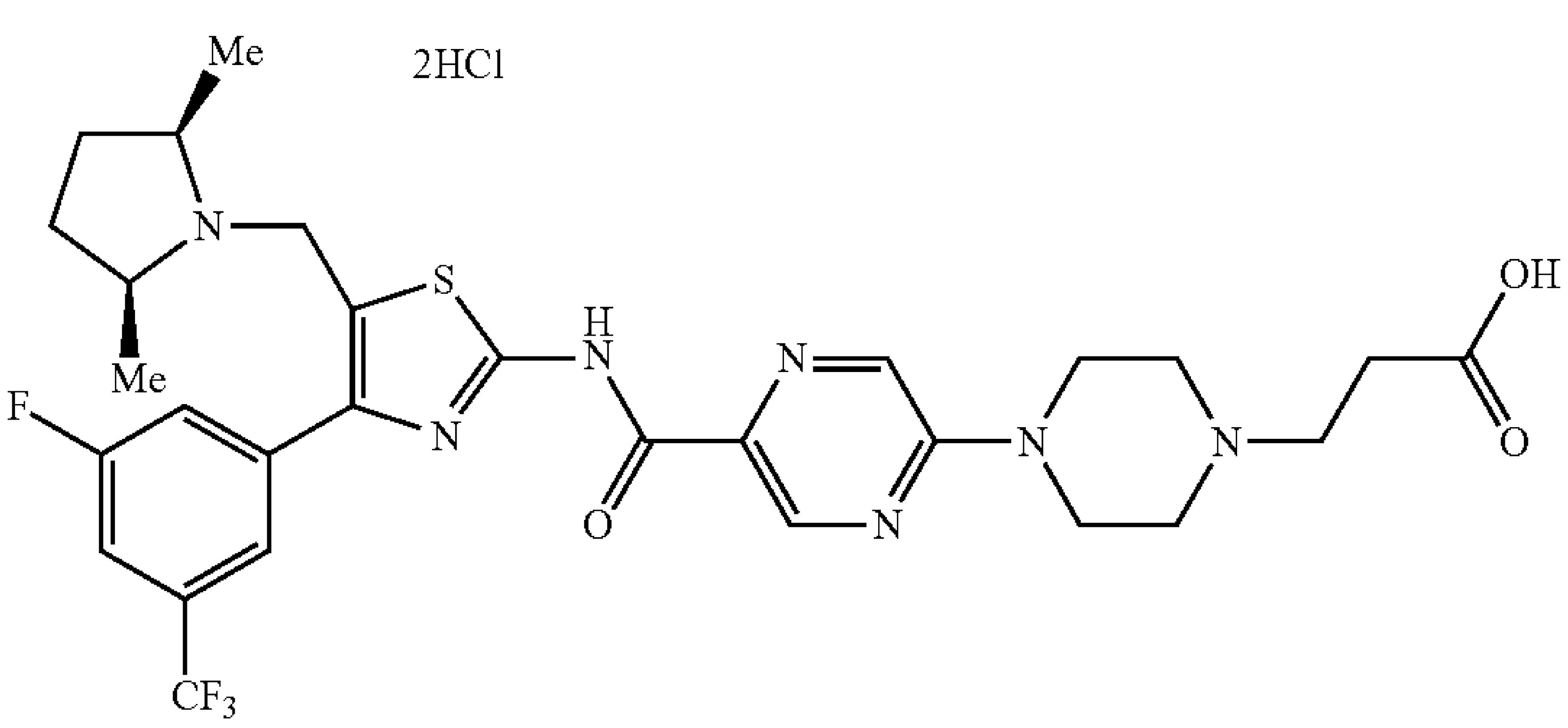
Ex	Structure
107	
108	
109	
110	

TABLE 96-continued

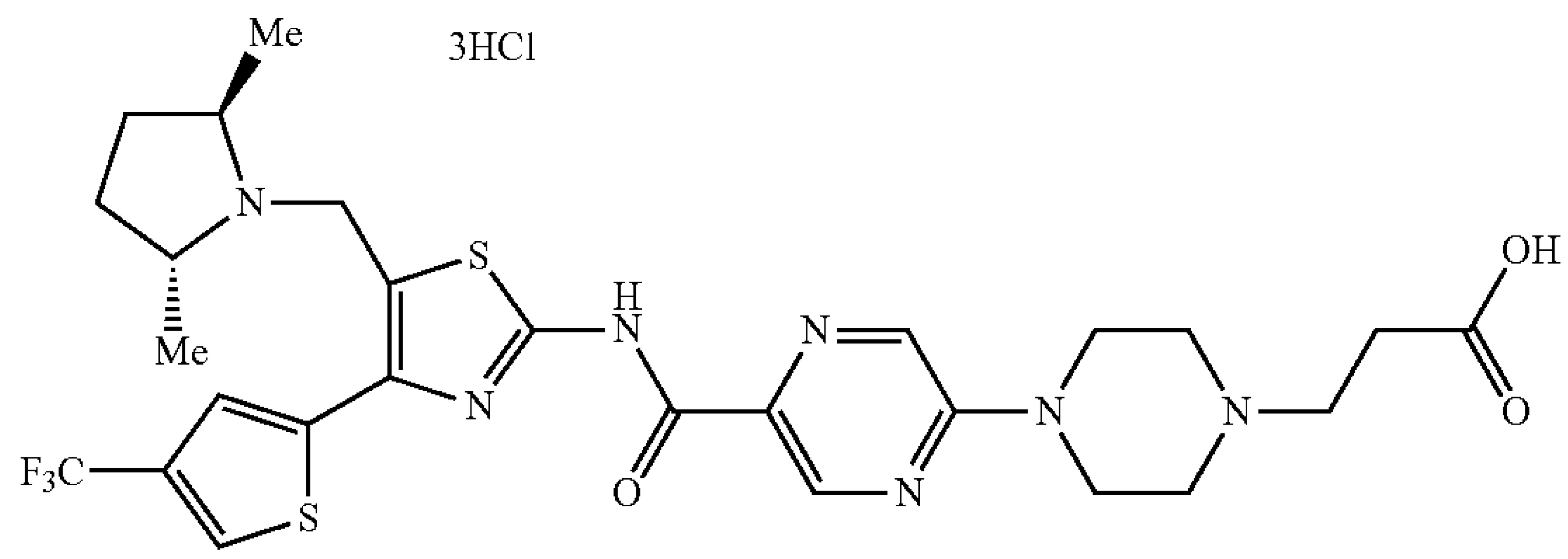
Ex	Structure
111	

TABLE 97

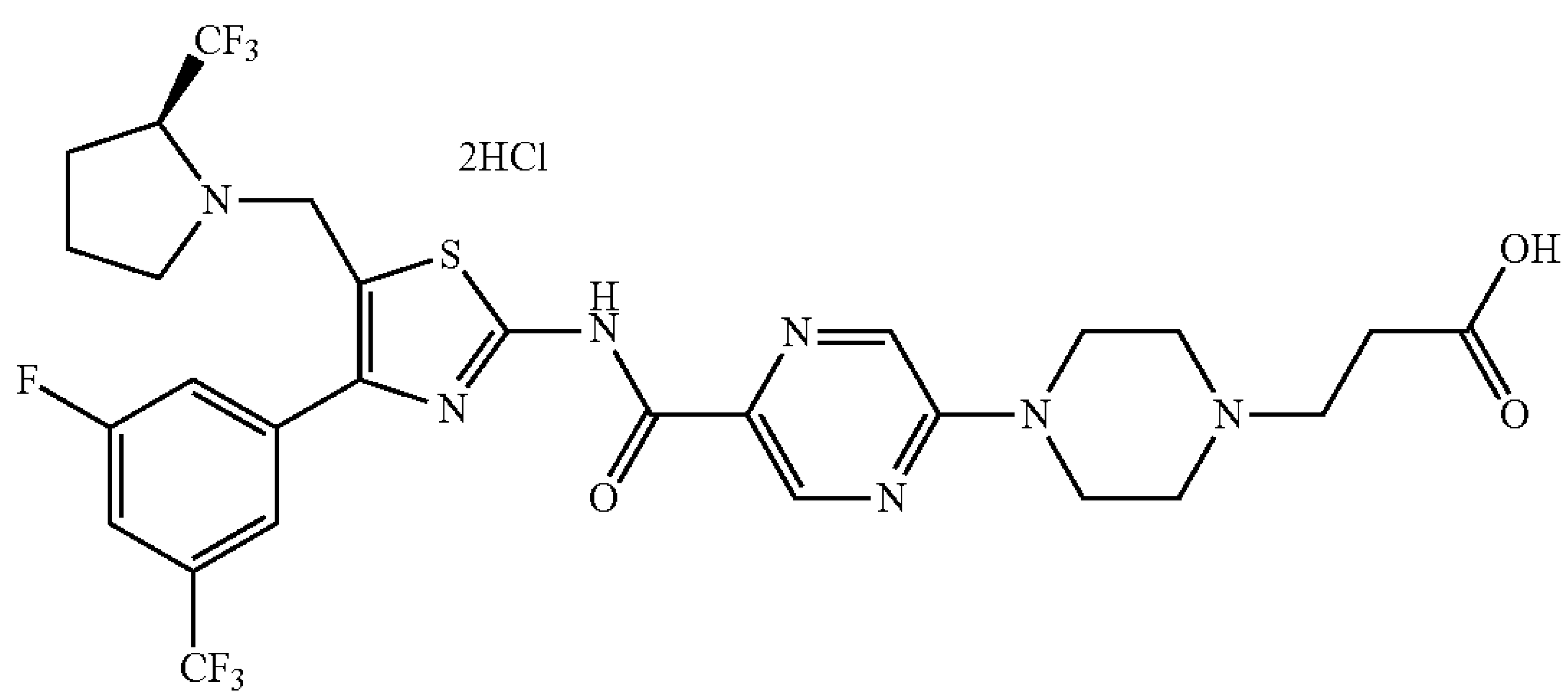
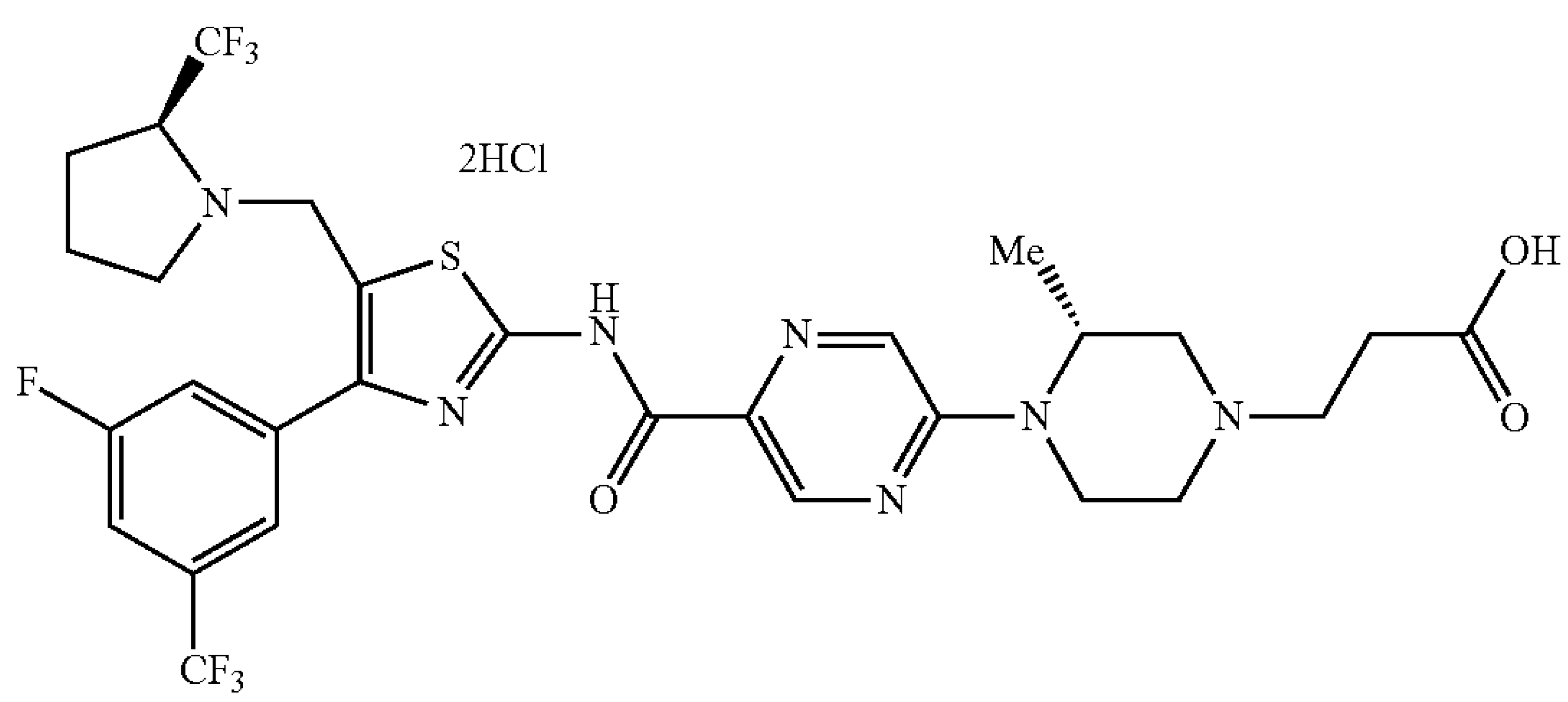
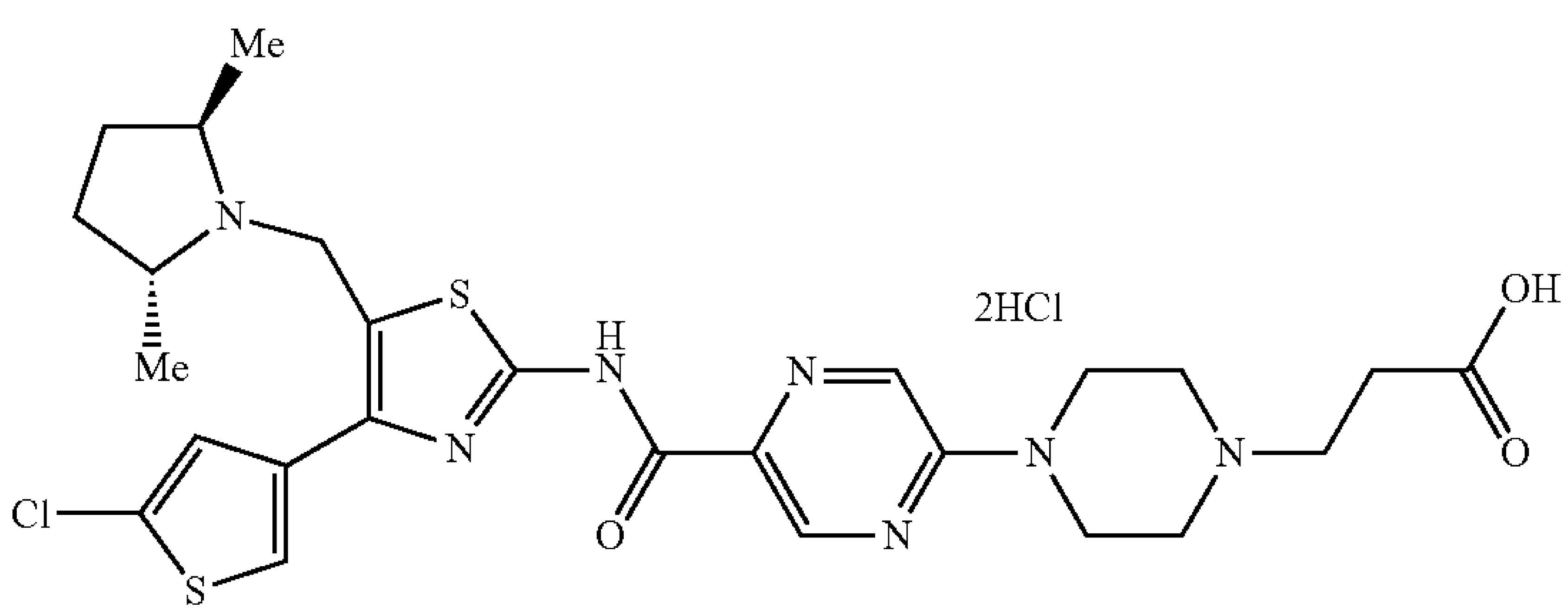
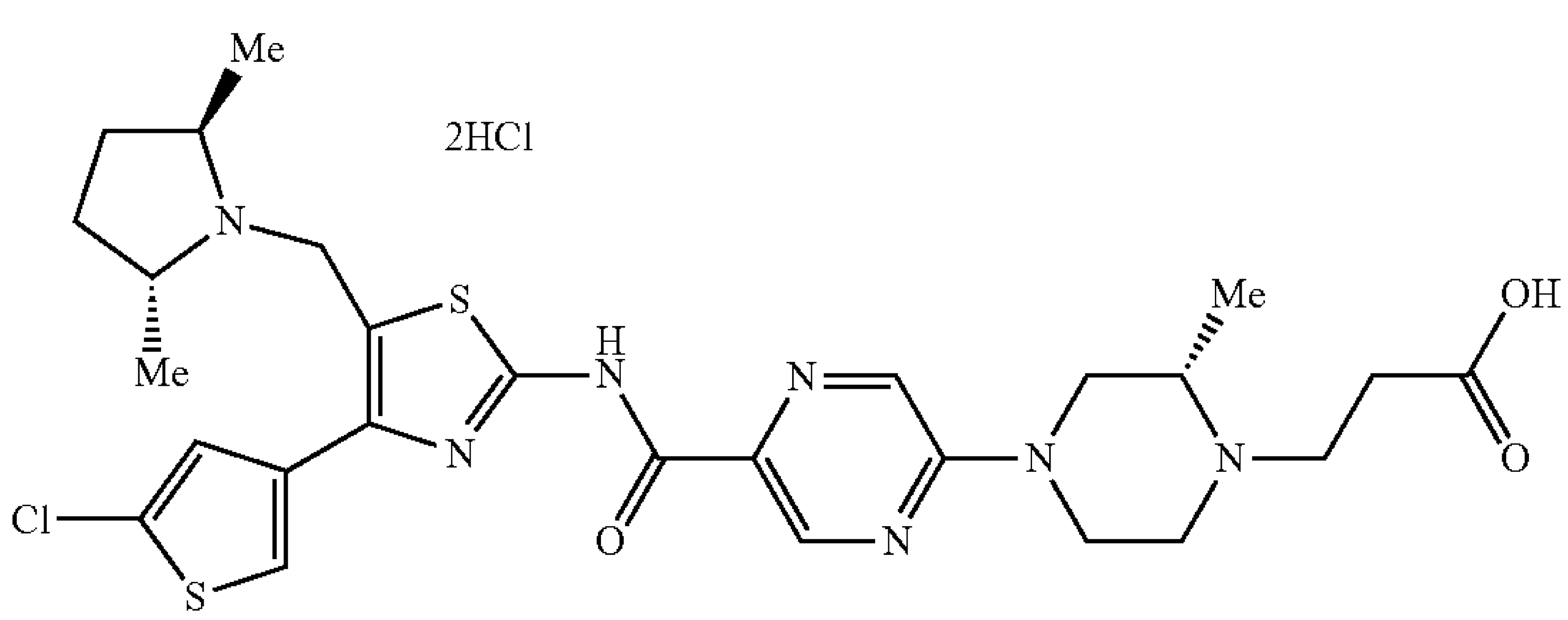
Ex	Structure
112	
113	
114	
115	

TABLE 98

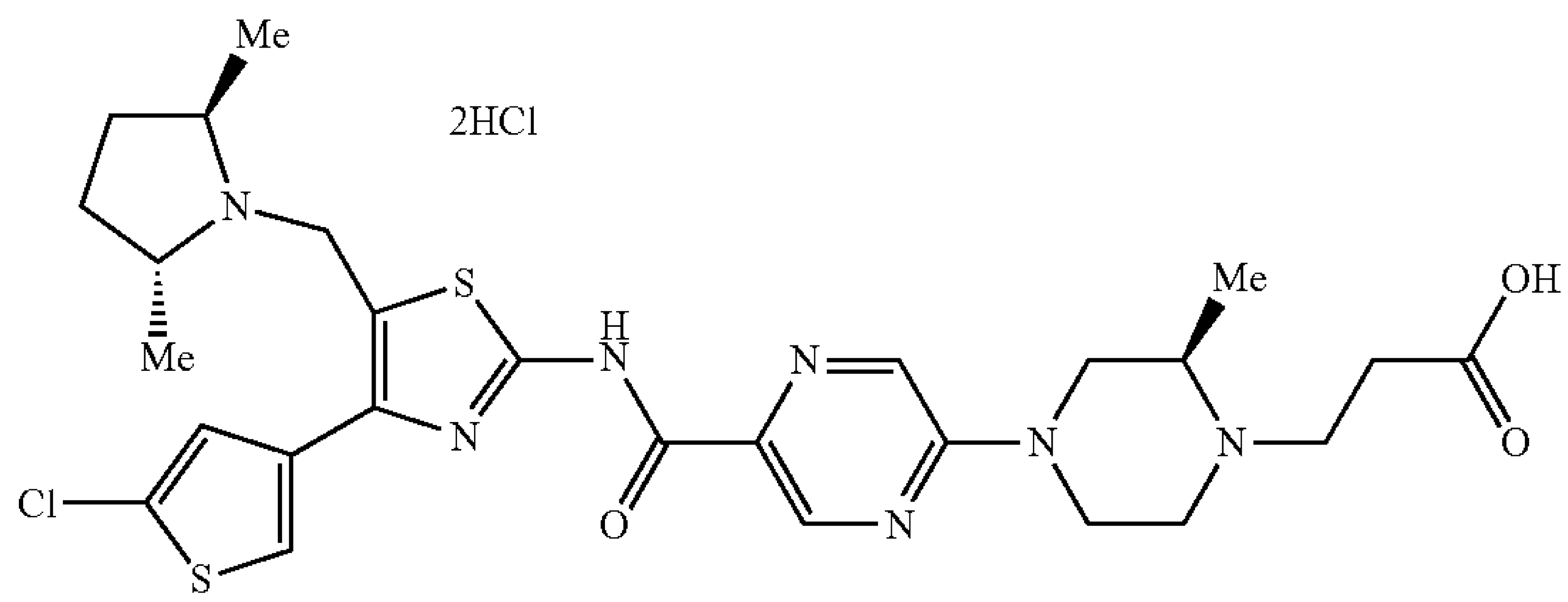
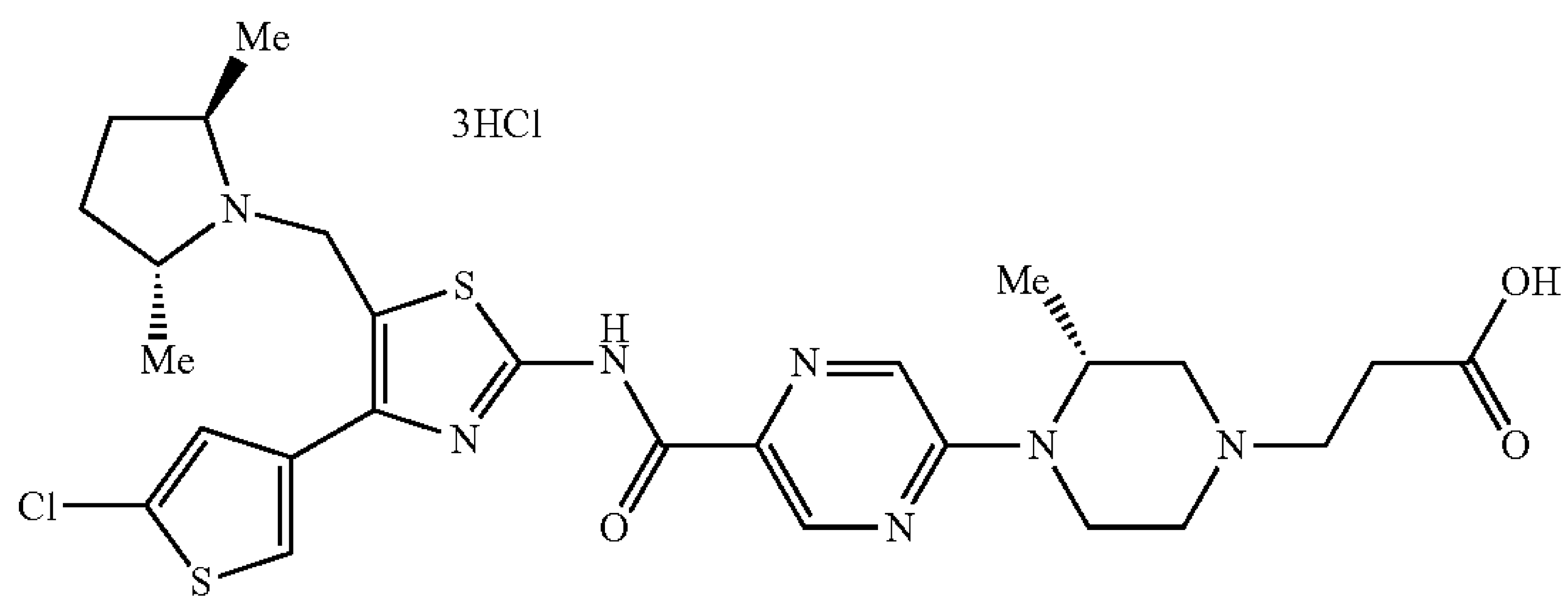
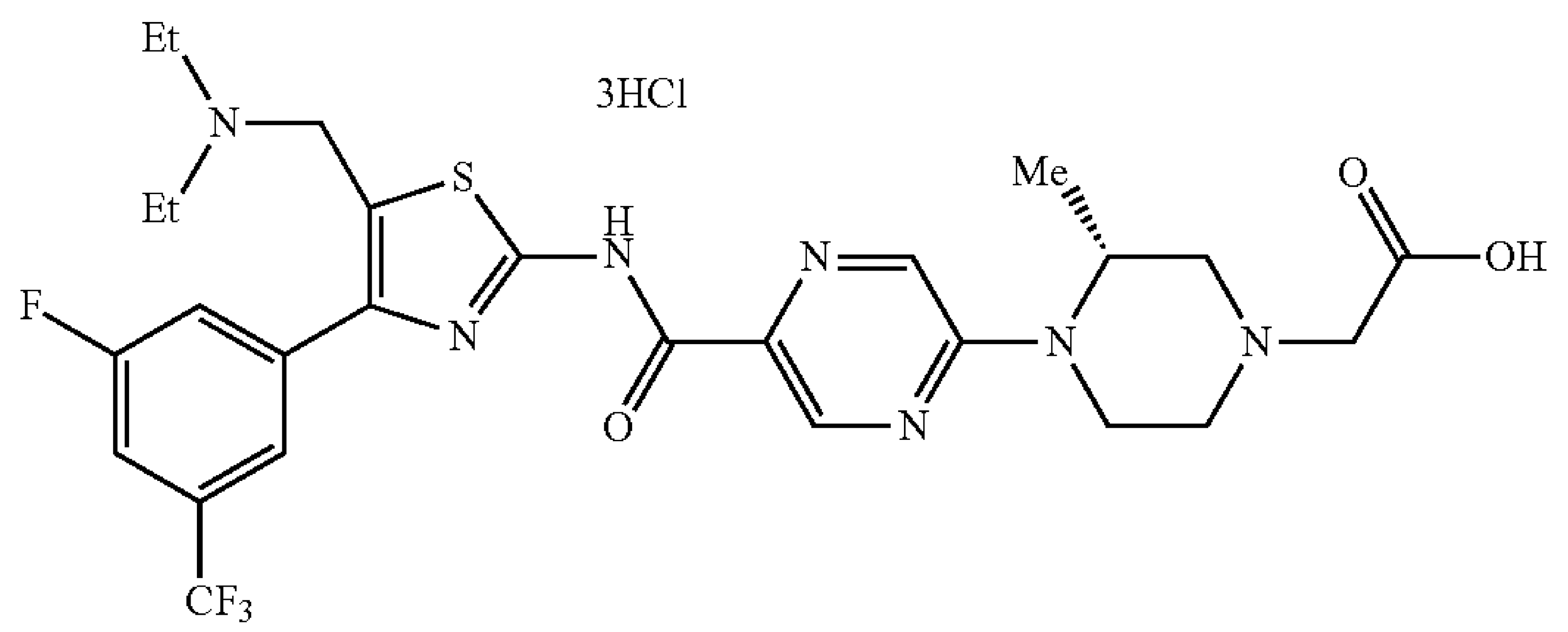
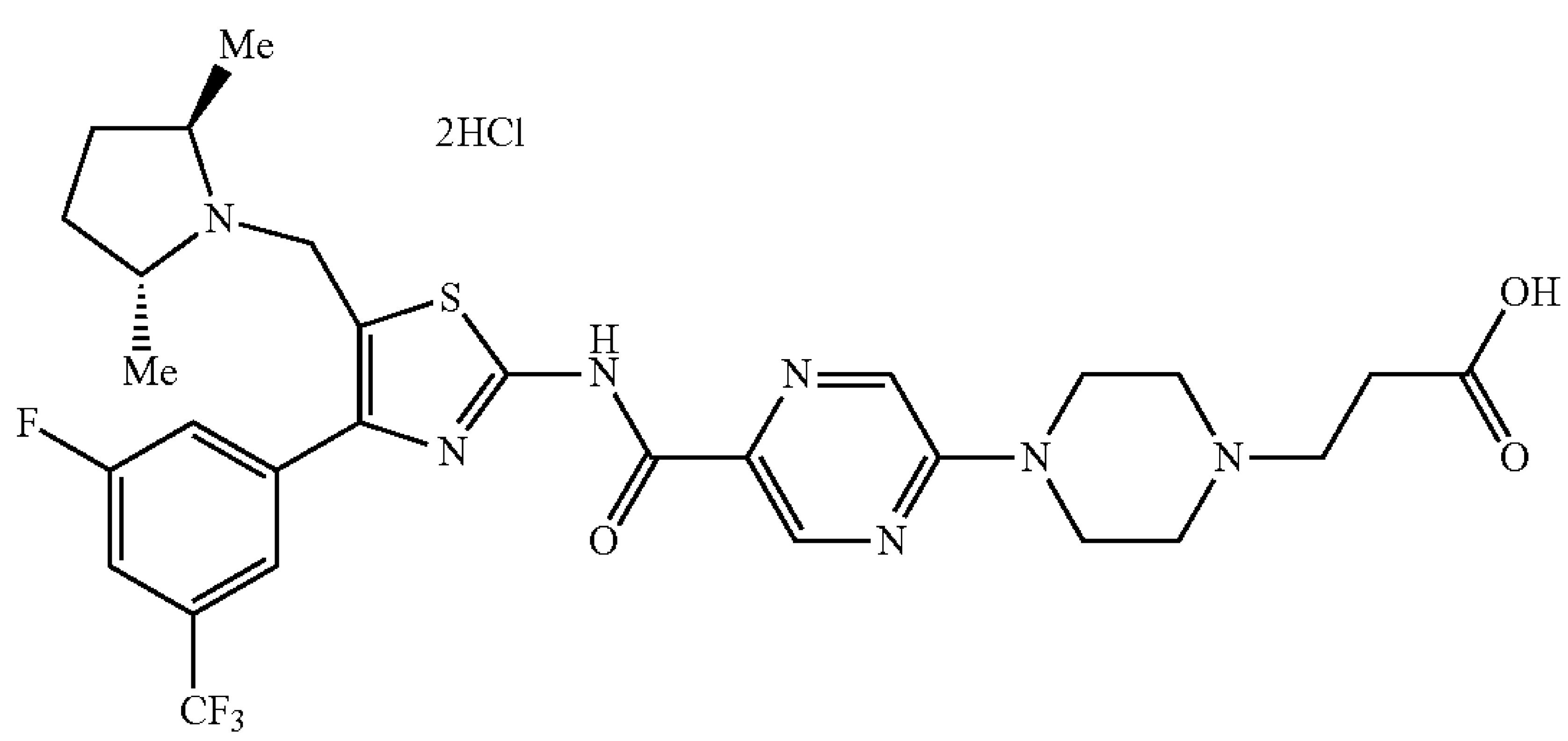
Ex	Structure
116	
117	
118	
119	

TABLE 99

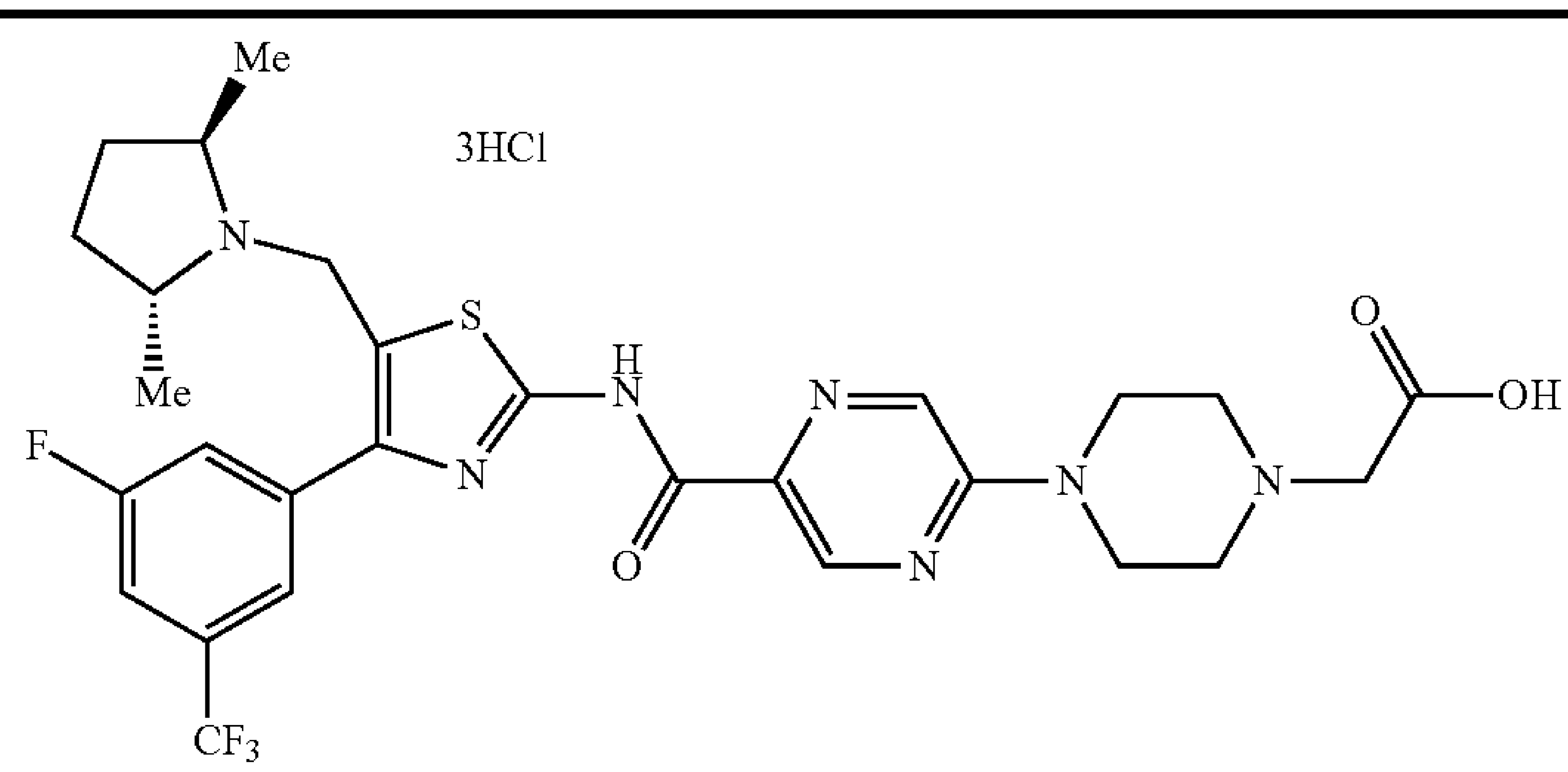
Ex	Structure
120	

TABLE 99-continued

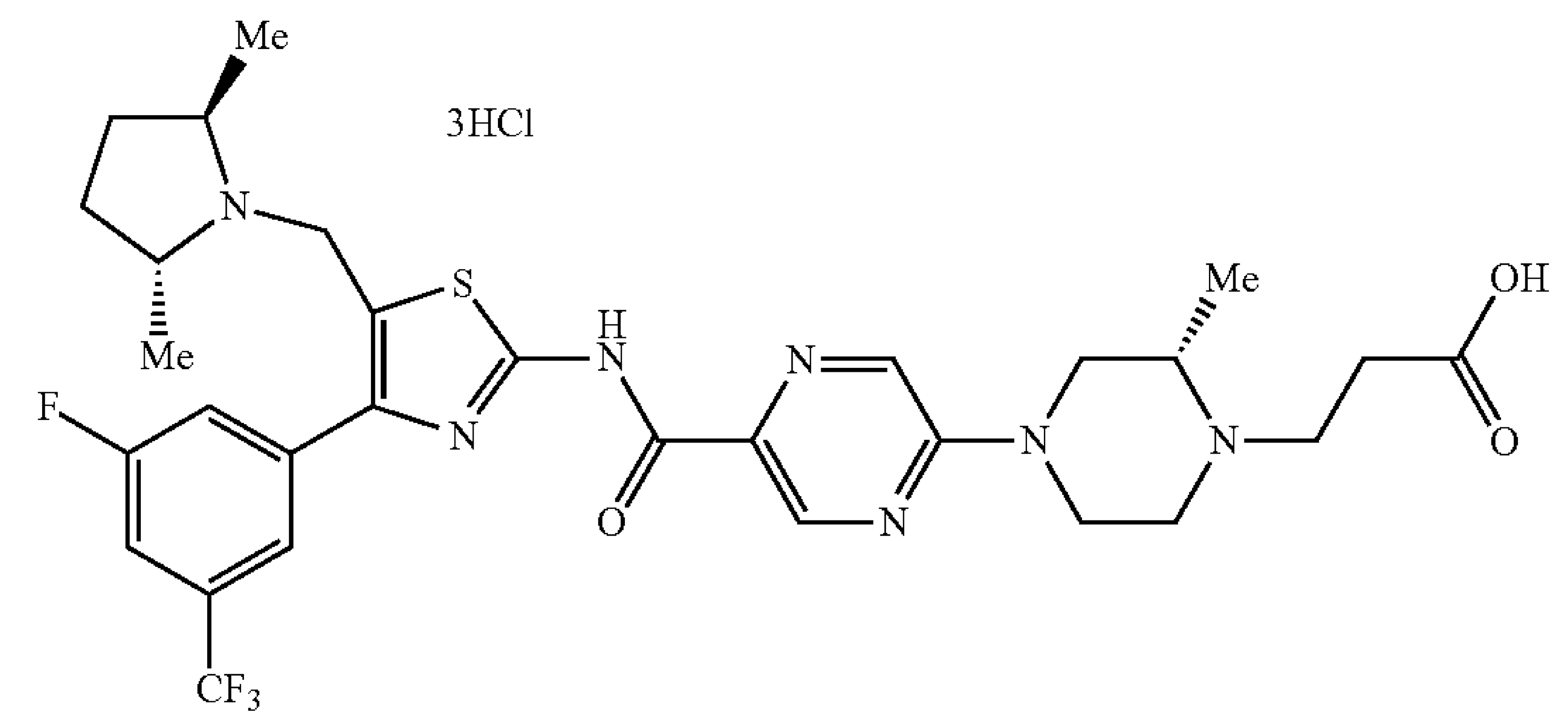
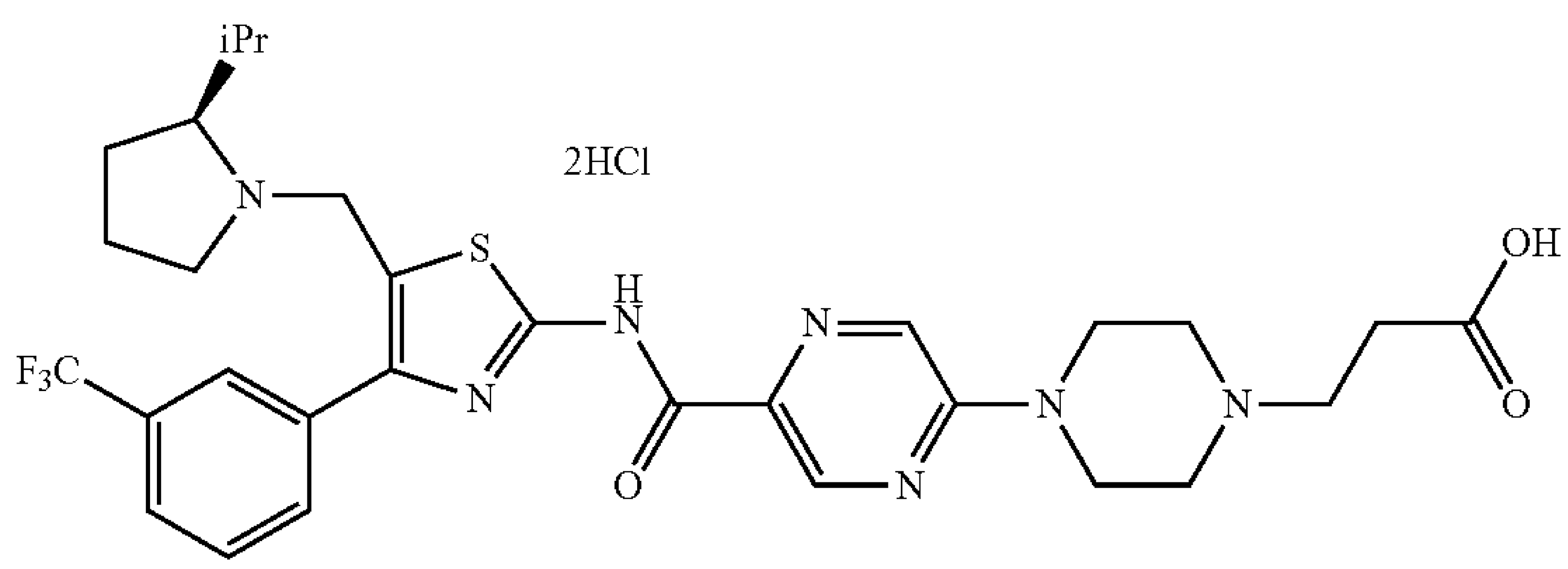
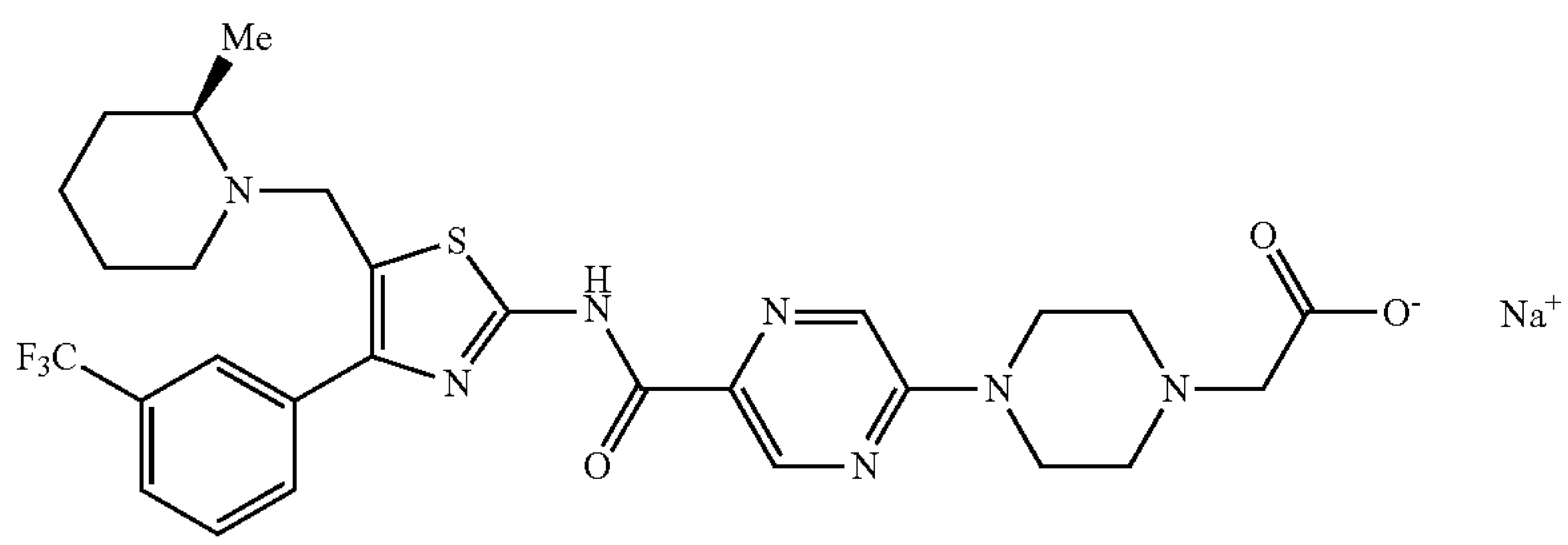
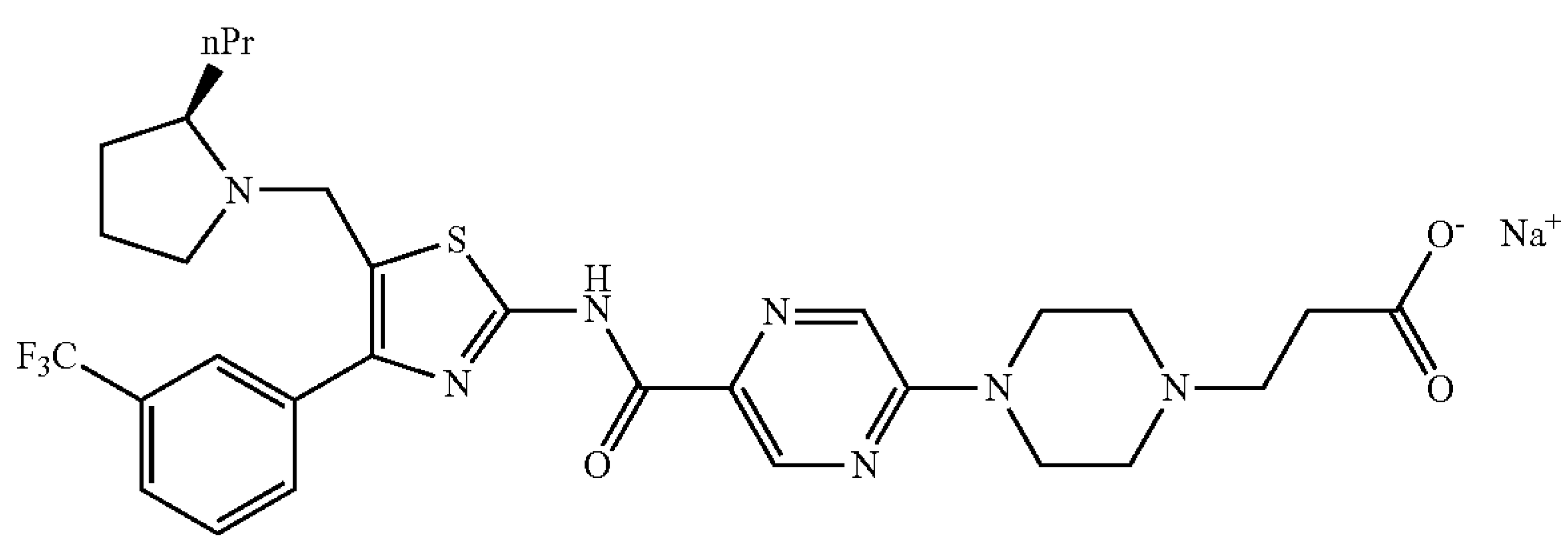
Ex	Structure
121	
122	
123	
124	

TABLE 100

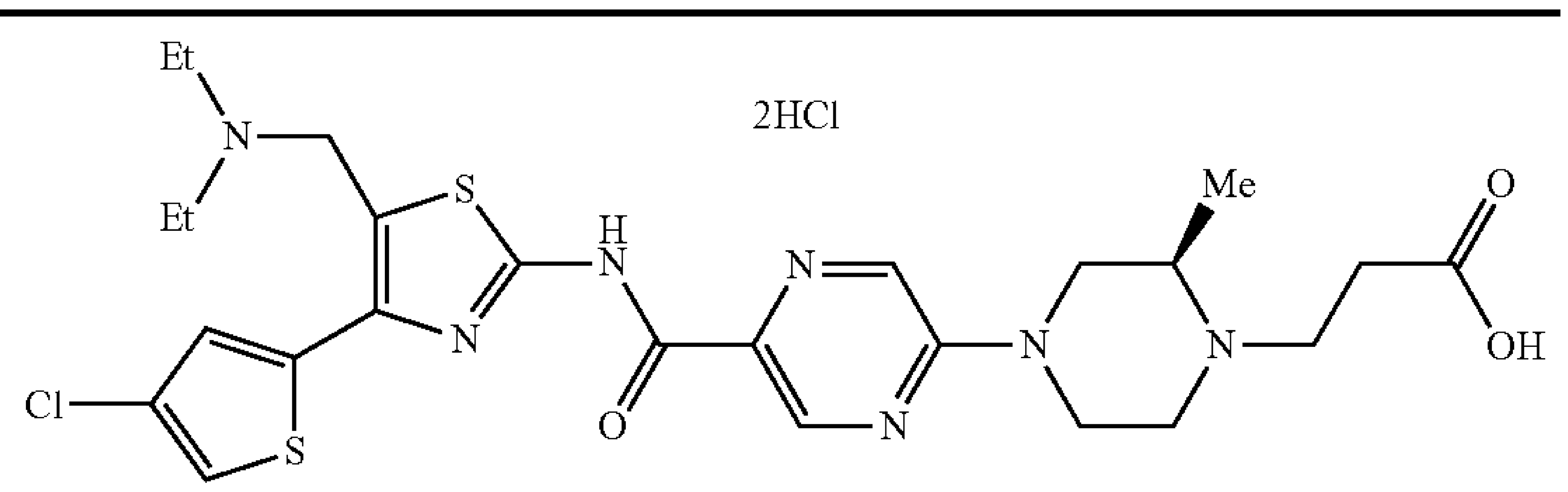
Ex	Structure
125	

TABLE 100-continued

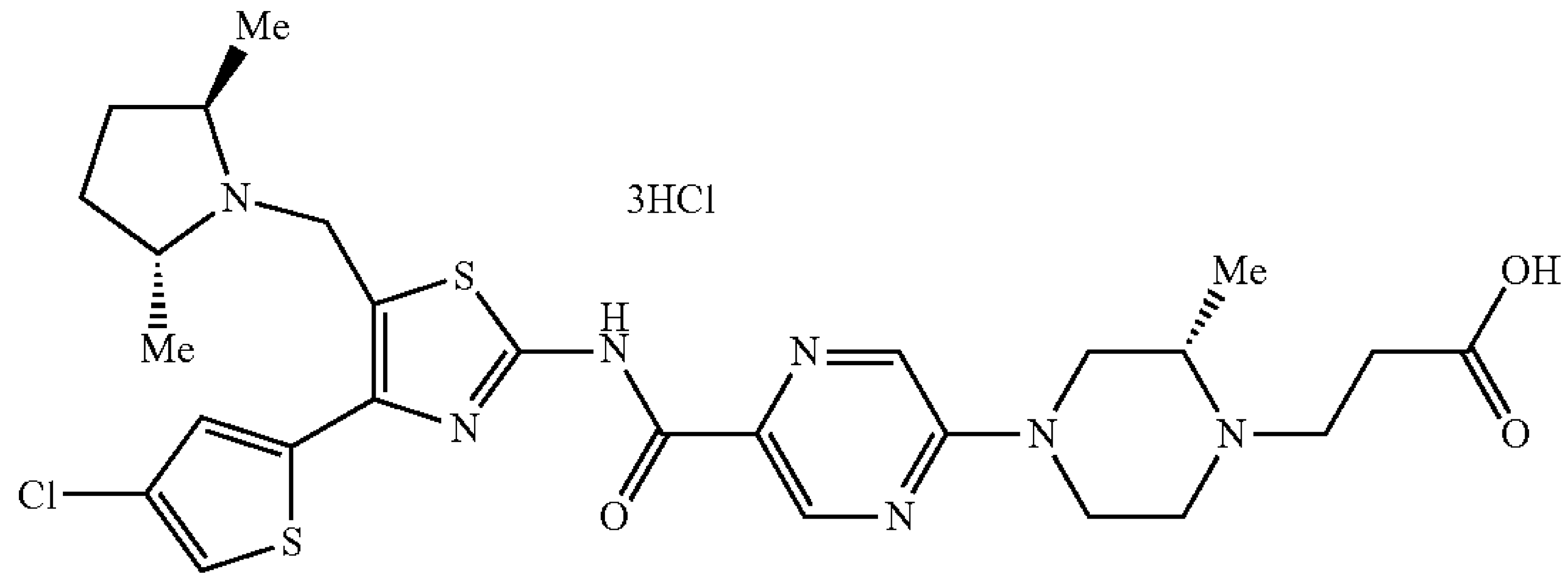
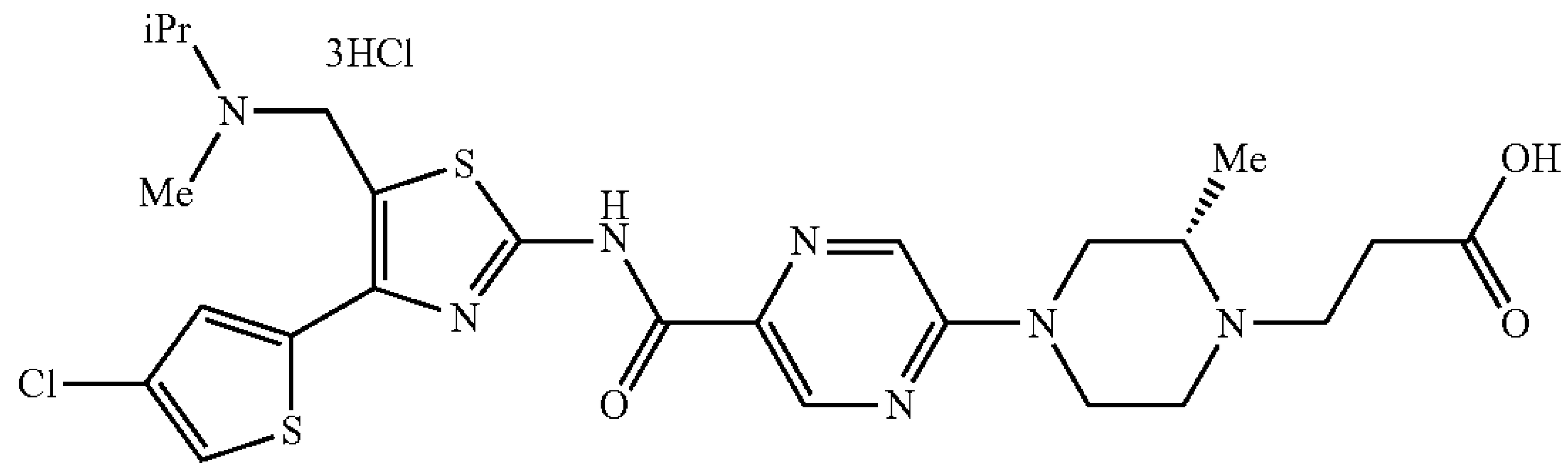
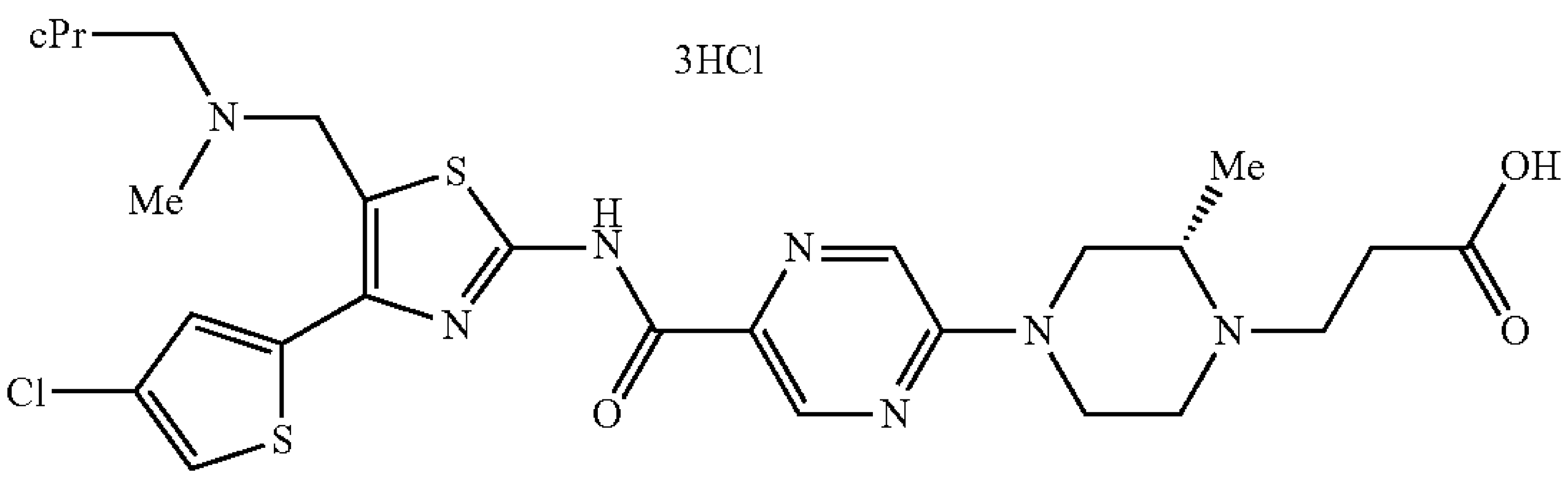
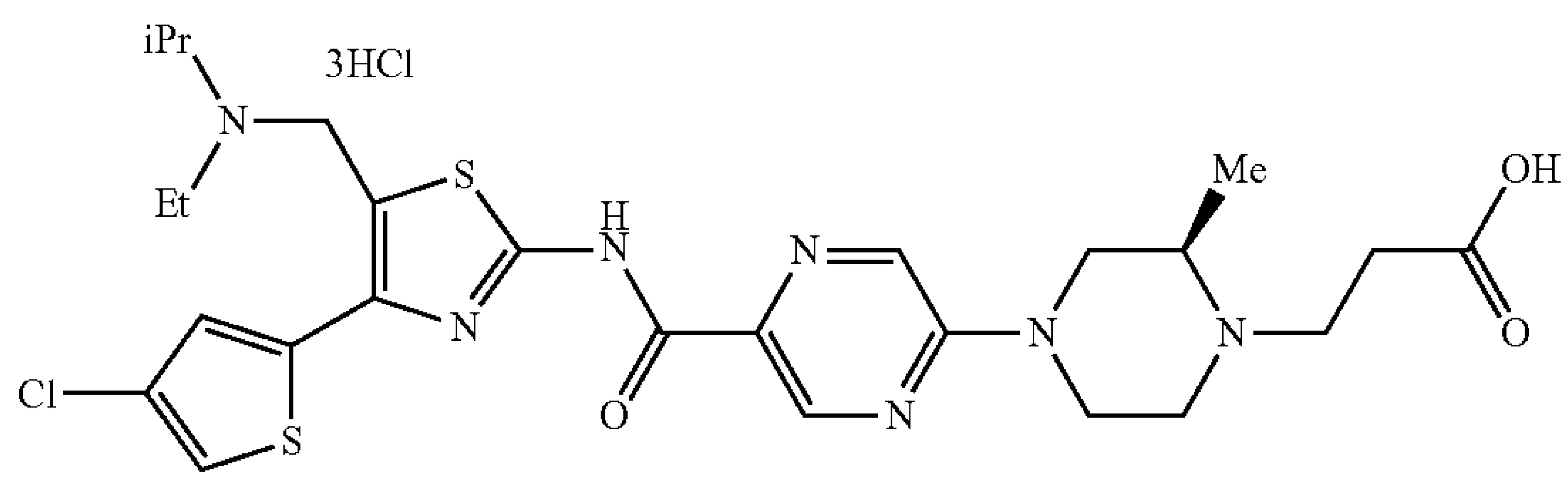
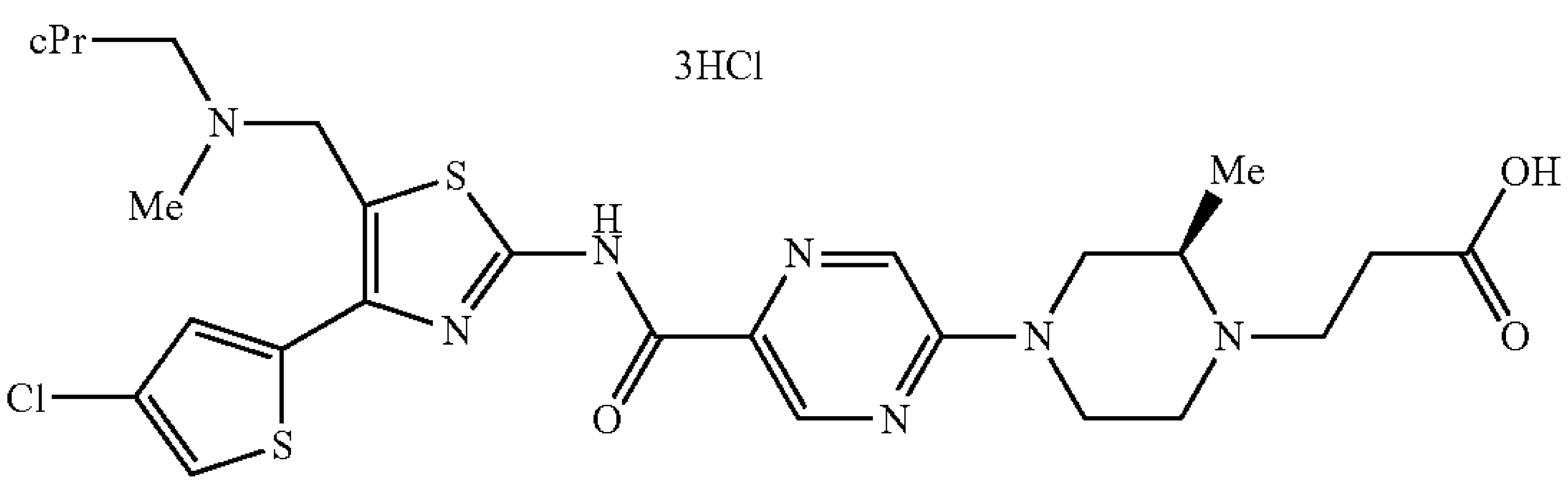
Ex	Structure
126	
127	
128	
129	
130	

TABLE 101

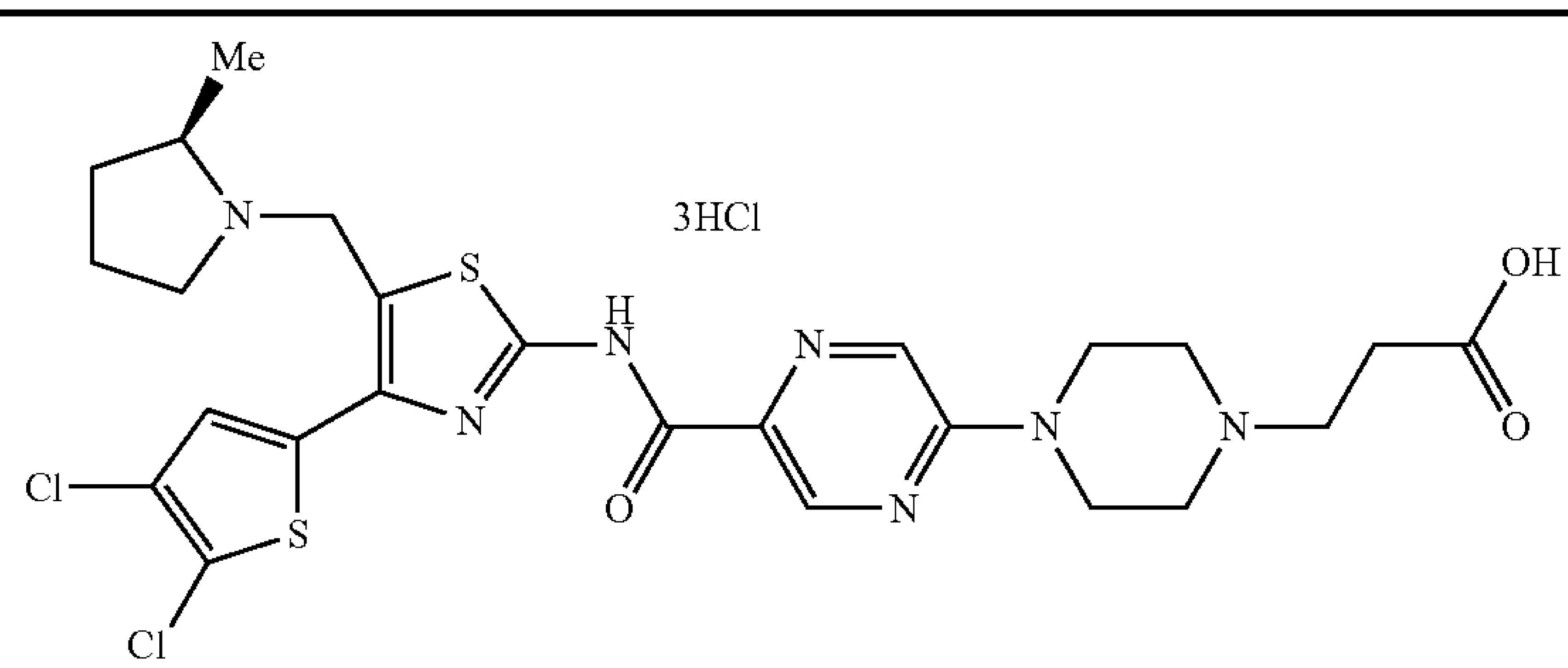
Ex	Structure
131	

TABLE 101-continued

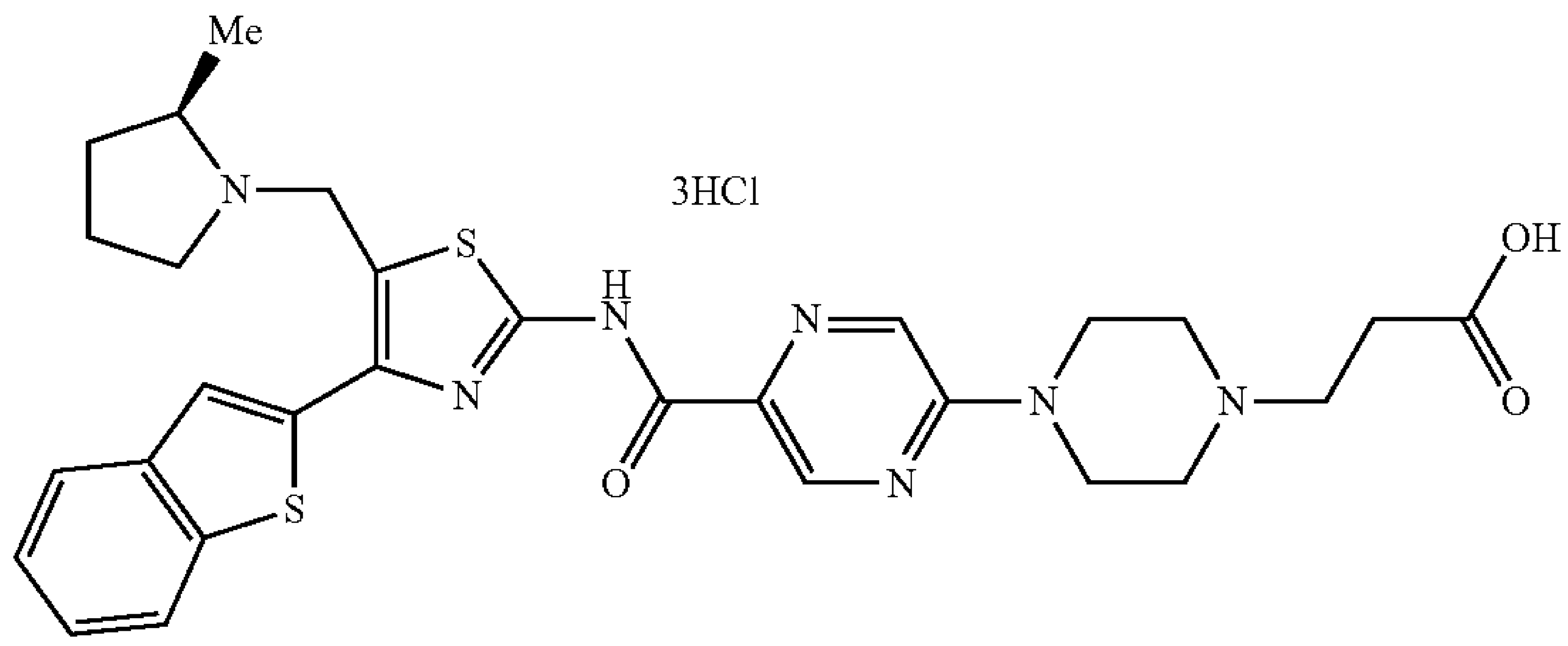
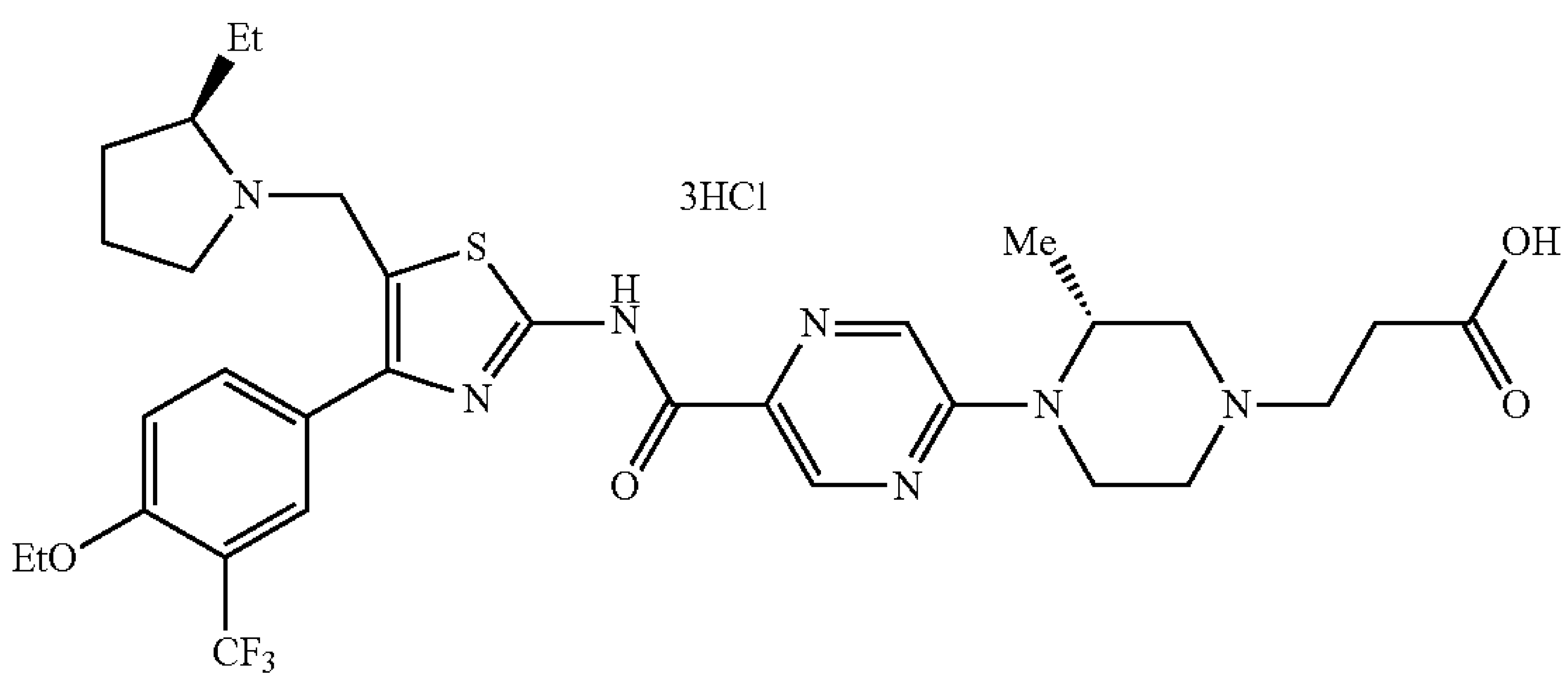
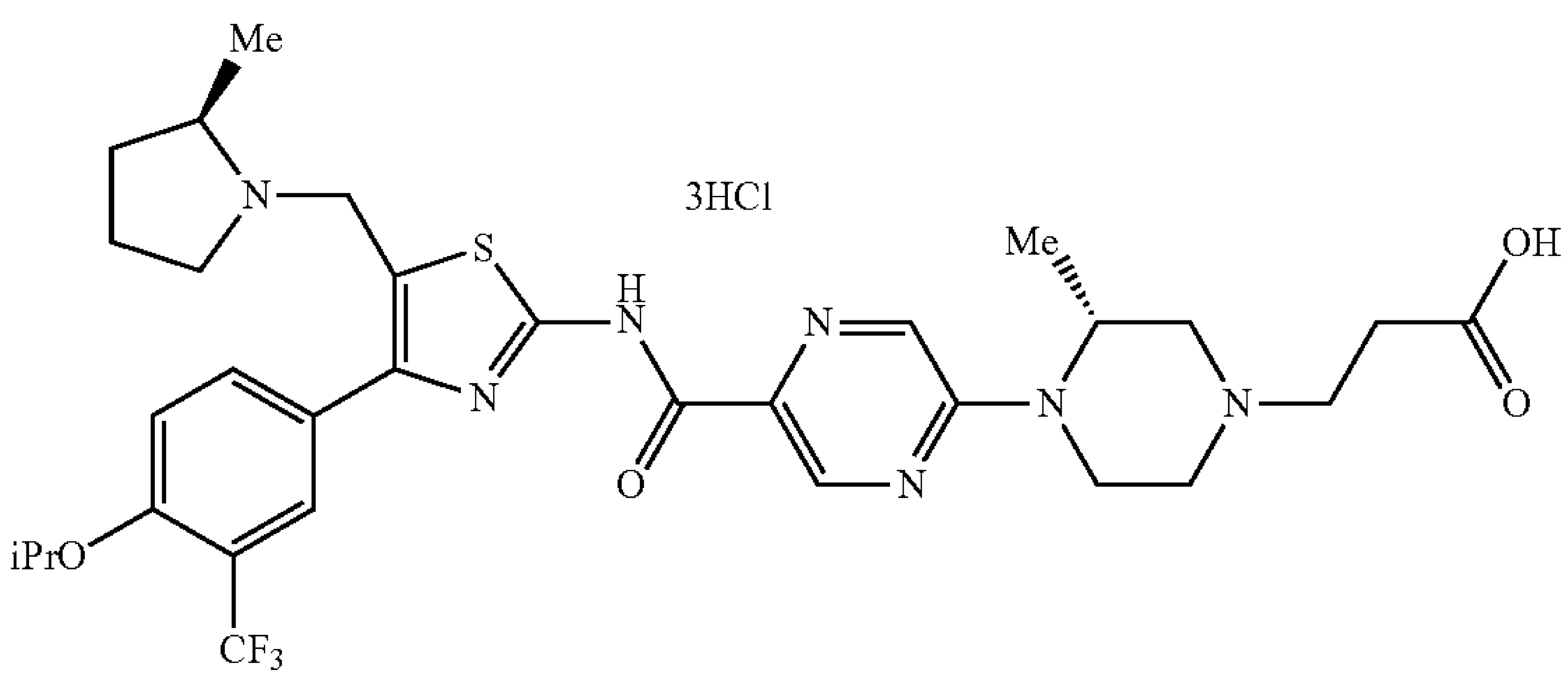
Ex	Structure
132	
133	
134	

TABLE 102

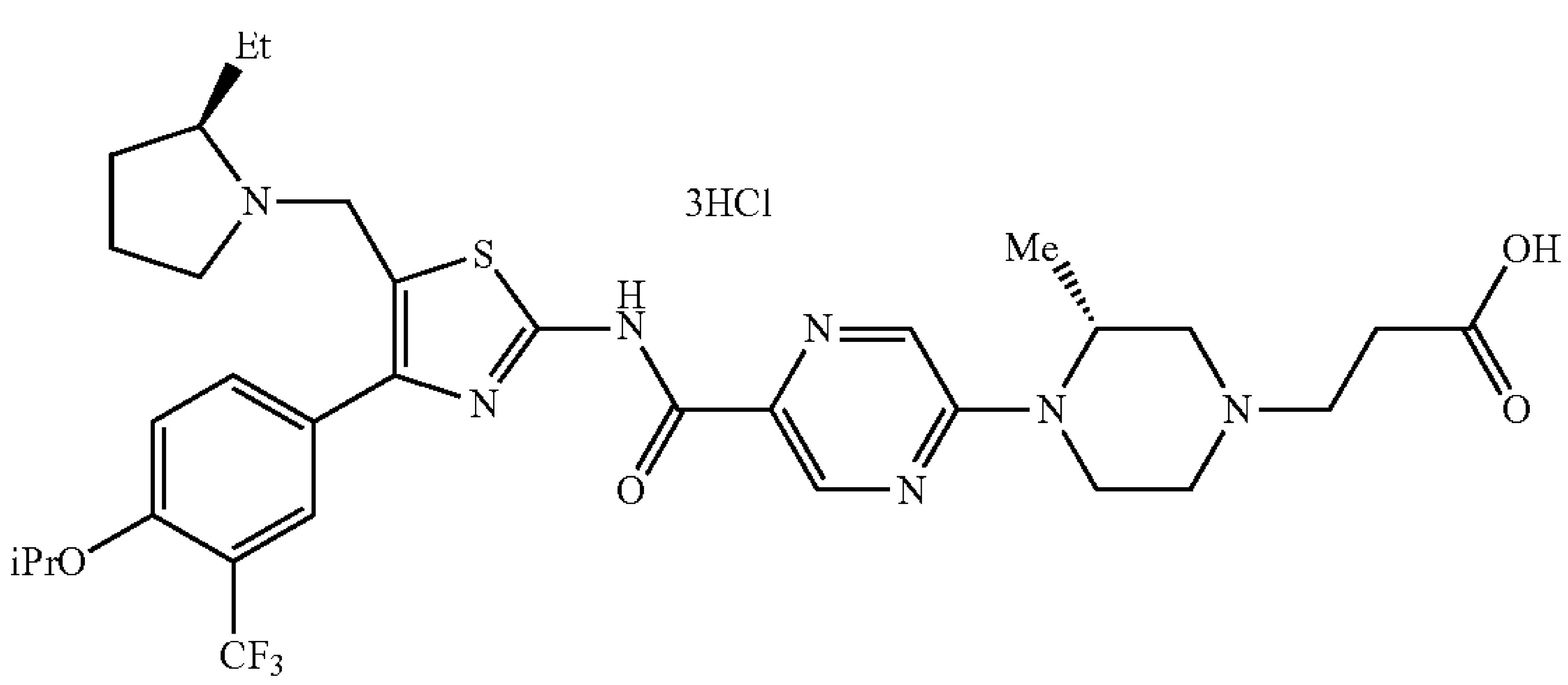
Ex	Structure
135	

TABLE 102-continued

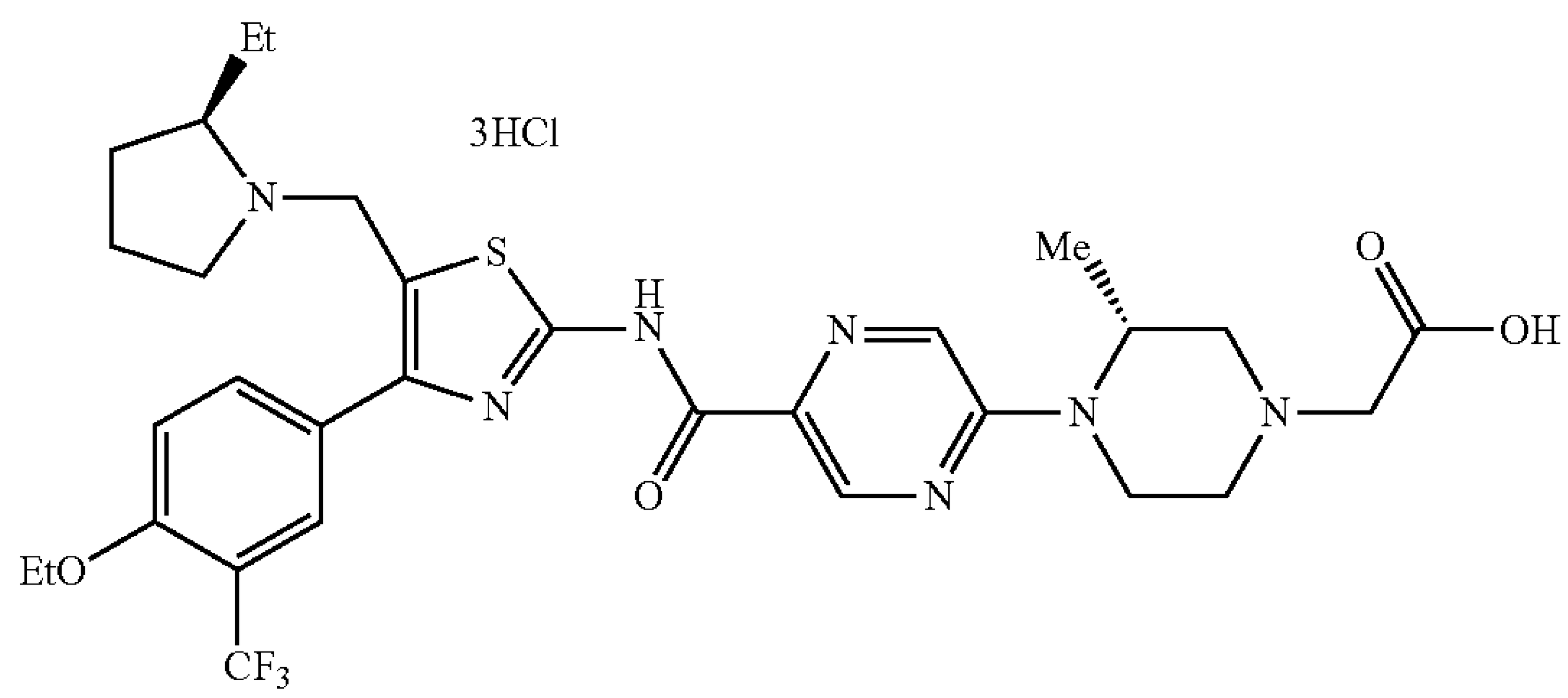
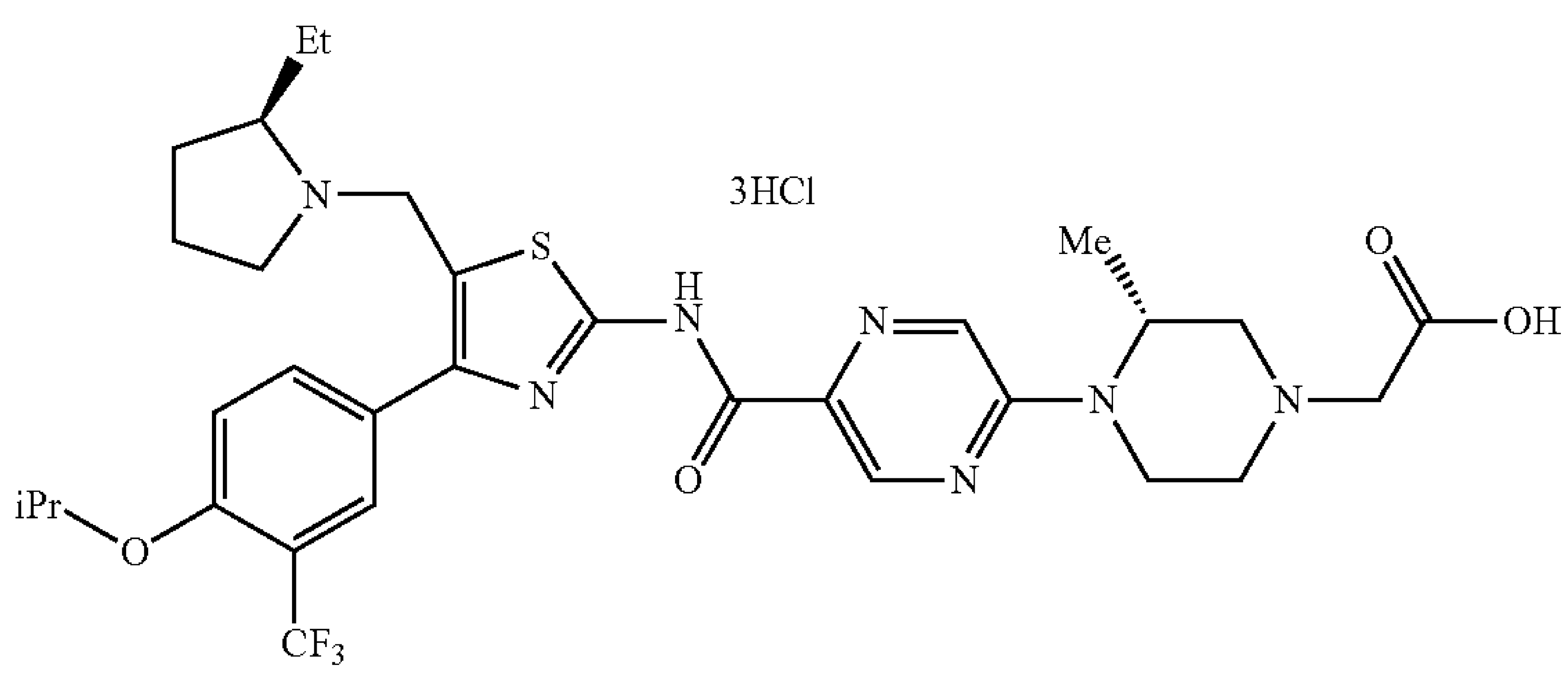
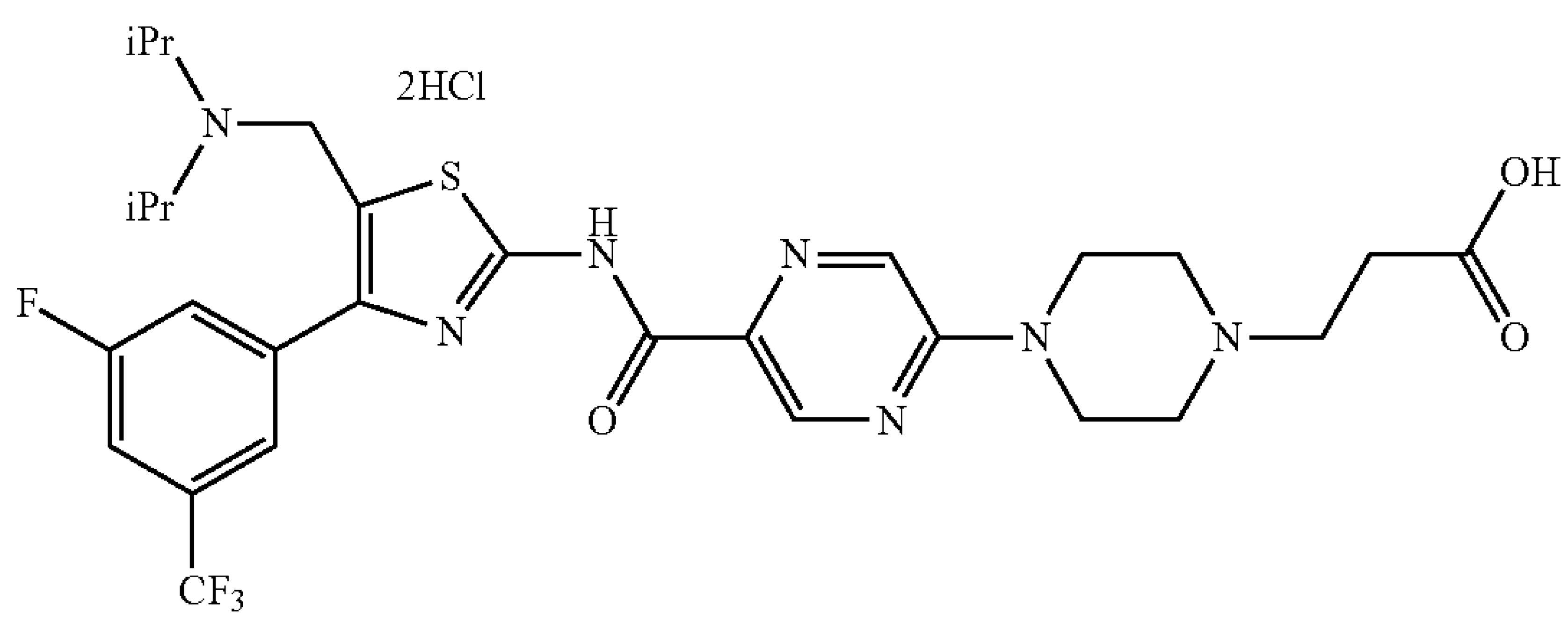
Ex	Structure
136	
137	
138	

TABLE 103

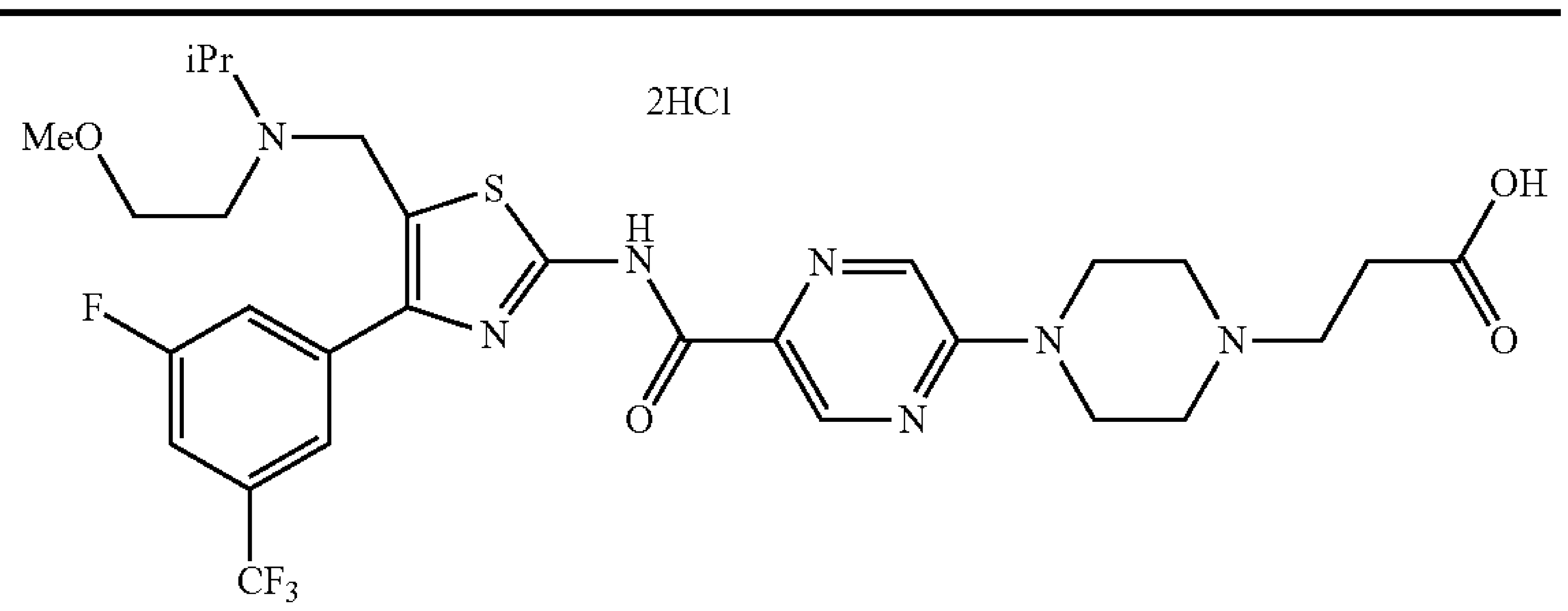
Ex	Structure
139	

TABLE 103-continued

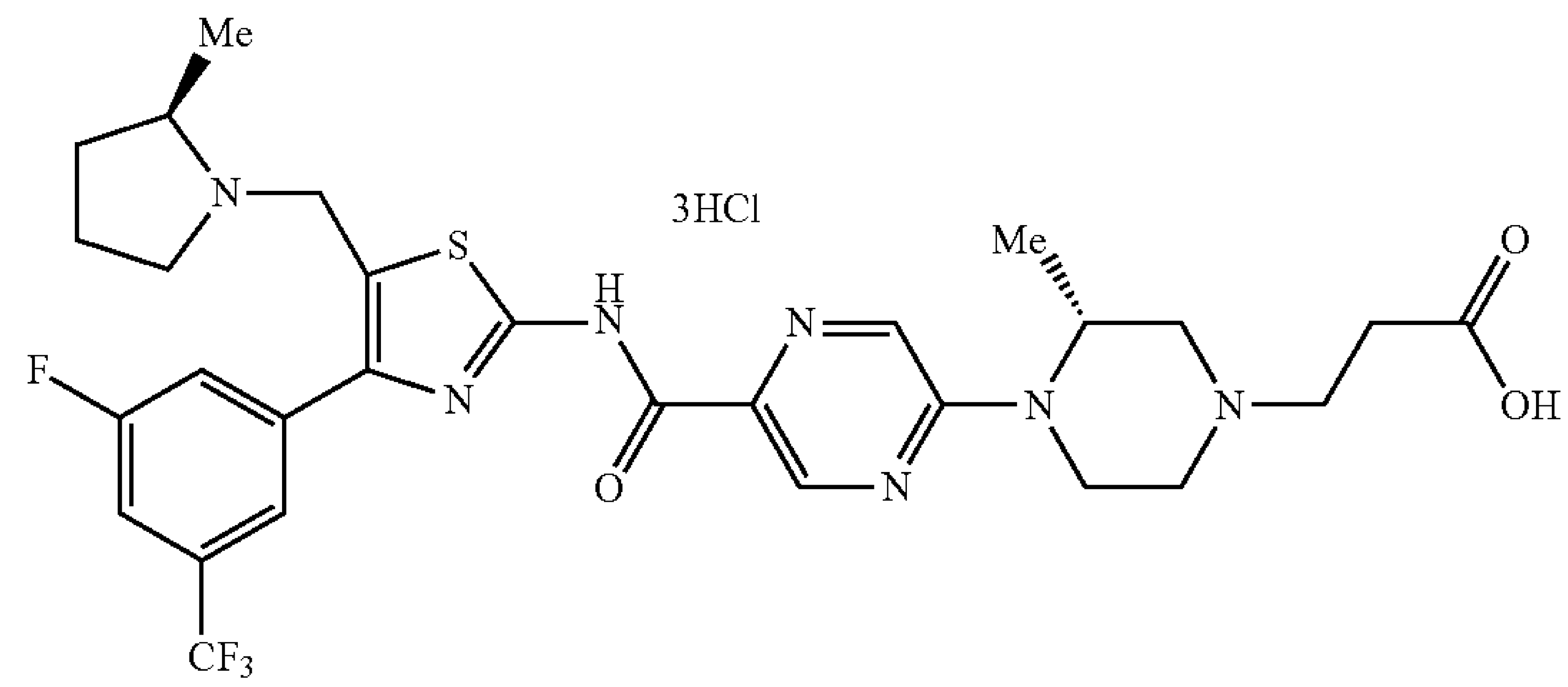
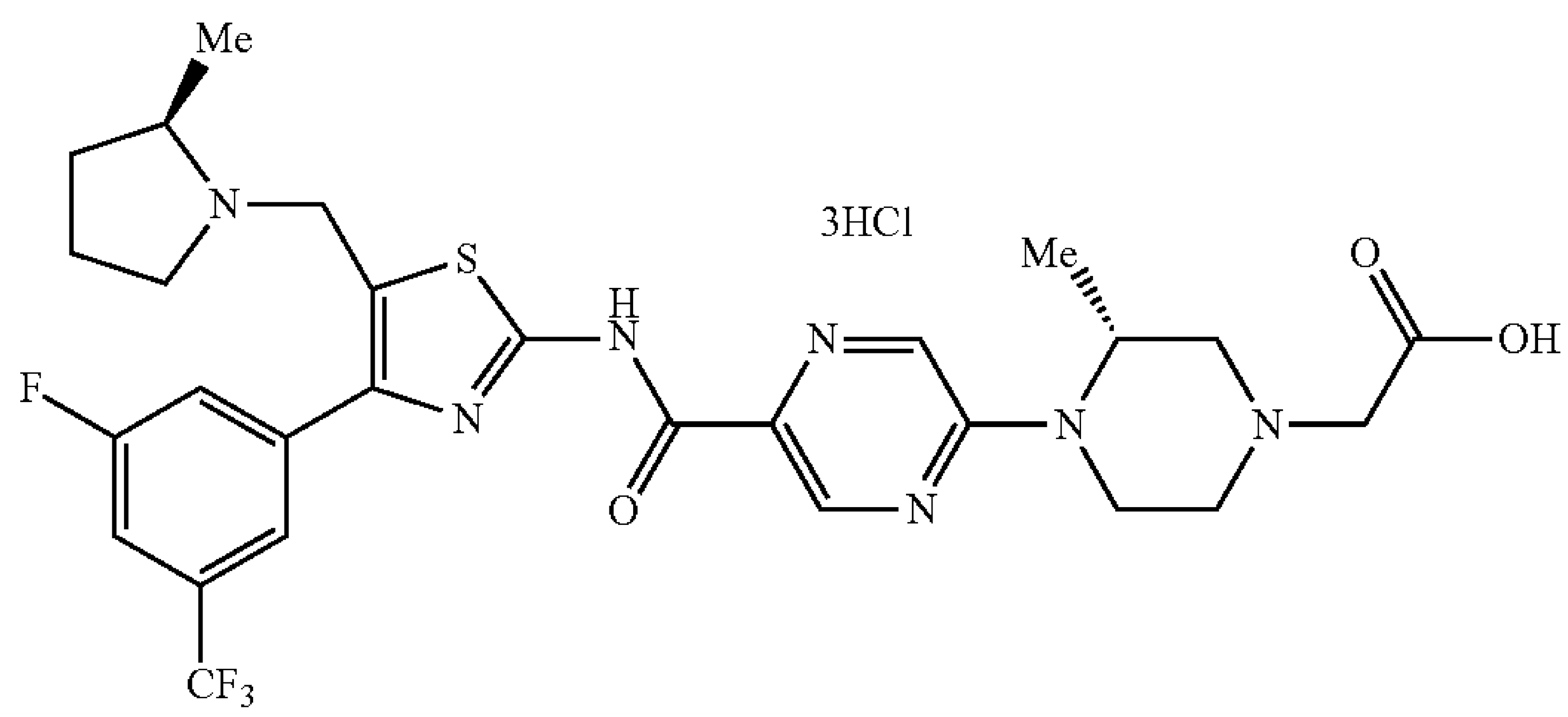
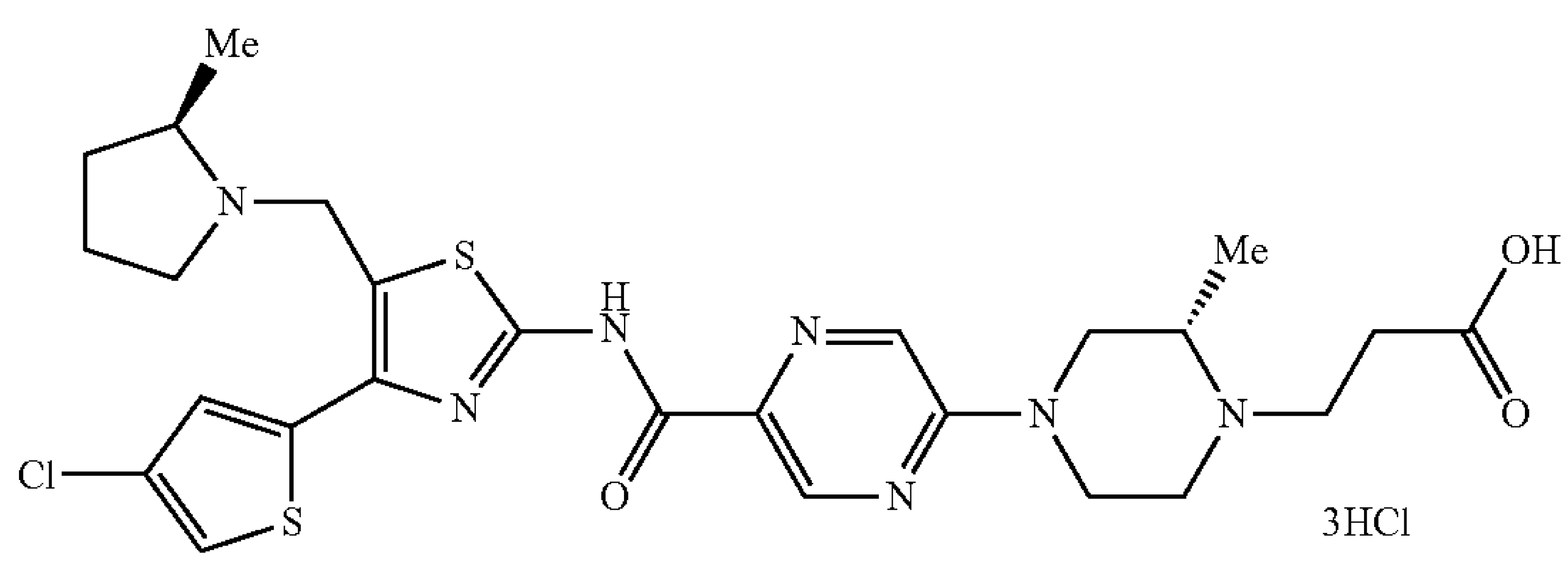
Ex	Structure
140	
141	
142	

TABLE 104

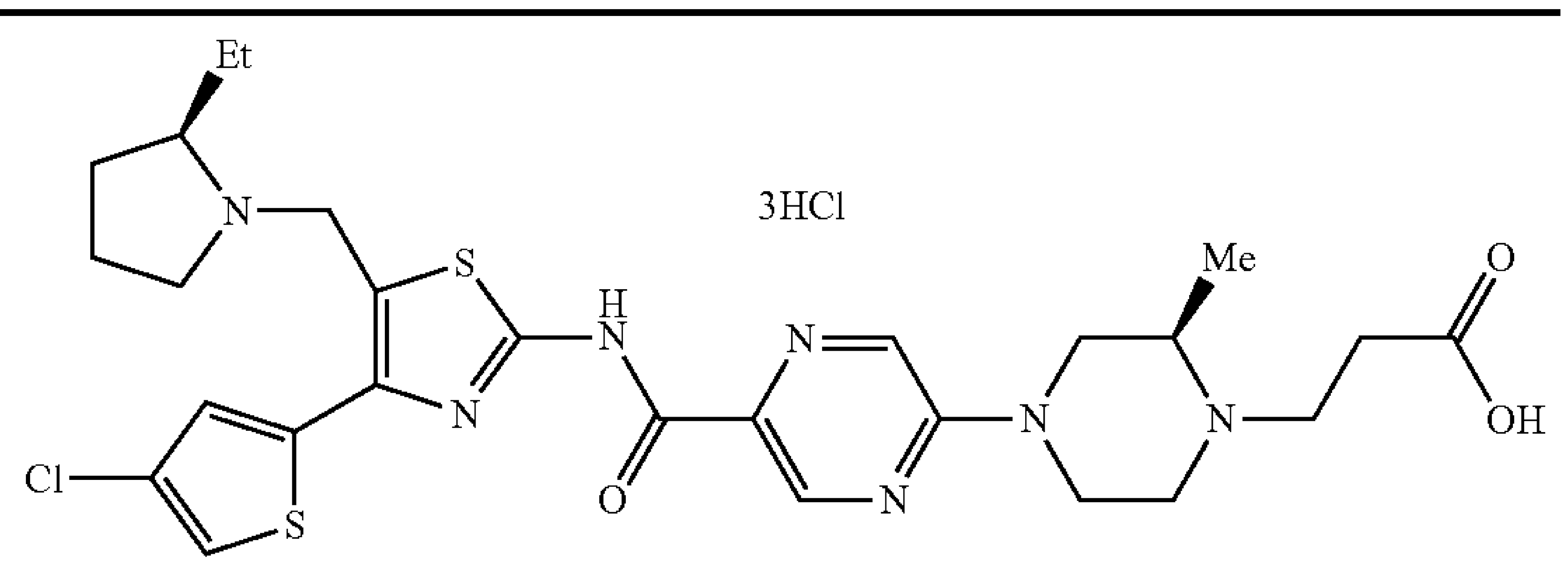
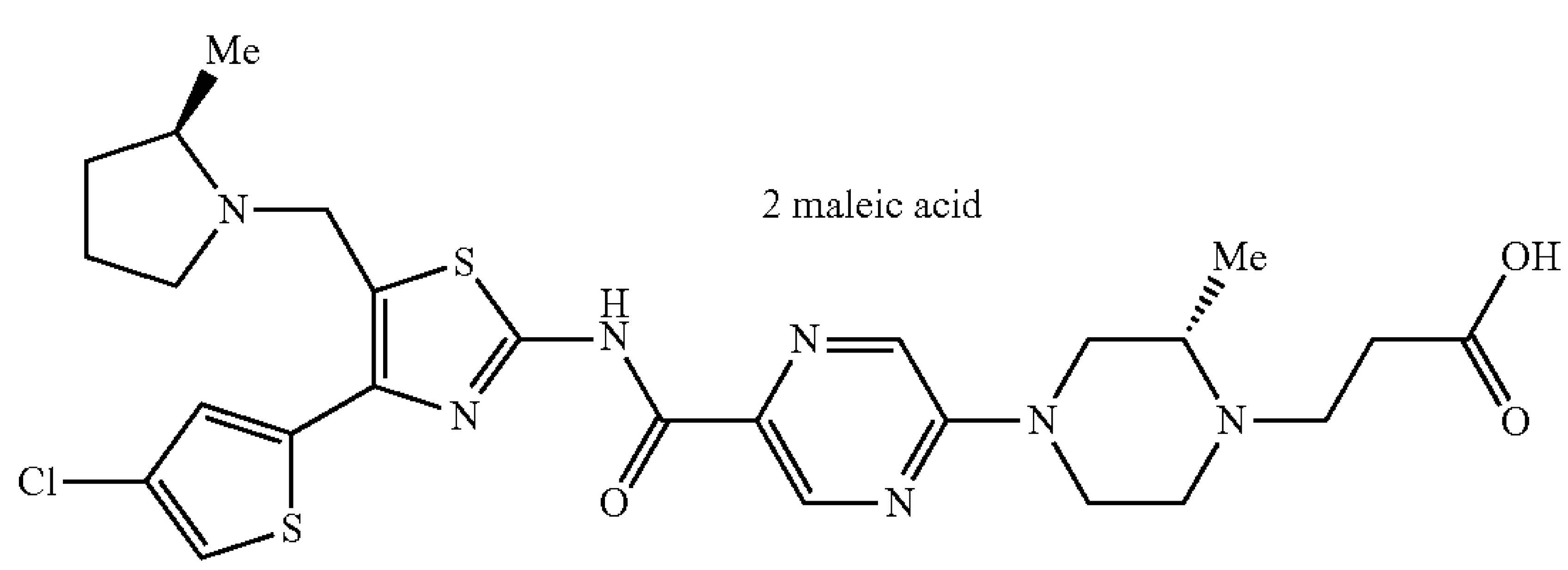
Ex	Structure
143	
144	

TABLE 105

Ex.	Syn.	Data
1	Ex1	ESI+: 592, 592 NMR-DMSO-d6: 1.20-1.52 (6H, m), 1.60-1.81 (1H, m), 1.85-2.03 (2H, m), 2.15-2.29 (1H, m), 2.77-300 (2H, m), 3.09-3.75 (9H, m), 3.75-4.77 (5H, m), 4.84-4.97 (1H, m), 7.65-7.71 (1H, m), 7.74 (1H, d, J = 1.3 Hz), 8.48-8.56 (1H, m), 8.79-8.85 (1H, m), 10.60-11.20 (1H, m), 11.45-11.84 (1H, m), 12.20-12.38 (1H, m)
2	Ex2	ESI+: 657
3	Ex3	ESI+: 624 NMR-DMSO-d6, 1.40-1.54 (6H, m), 1.61-1.75 (1H, m), 1.84-2.04 (2H, m), 2.16-2.28 (1H, m), 2.84-3.12 (3H, m), 3.16-3.30 (3H, m), 3.46-3.62 (6H, m), 4.55-4.72 (2H, m), 4.94 (1H, d, J = 15 Hz), 5.05 (1H, brs), 7.95 (1H, s), 8.40 (1H, t, J = 1 Hz), 8.47 (1H, s), 8.85 (1H, d, J = 1 Hz), 10.6 (1H, brs), 11.1 (1H, brs), 12.4 (1H, s), 12.7 (1H, brs)
4	Ex4	ESI+: 632
5	Ex5	ESI+: 548, 550 (M − H)−
6	Ex6	ESI+: 570
7	Ex7	ESI+: 662
8	Ex8	ESI+: 648
9	Ex9	ESI+: 624 NMR-DMSO-d6, 1.05-1.15 (6H, m), 1.20-1.52 (3H, m), 2.75-4.20 (14H, m), 4.40-4.80 (4H, m), 7.80-7.87 (1H, m), 7.88-7.96 (2H, m), 8.53 (1H, s), 8.84 (1H, s), 10.63 (1H, brs), 11.33-11.76 (1H, m), 12.30-12.42 (1H, m)
10	Ex1	ESI+: 648
11	Ex1	ESI+: 638, 640
12	Ex1	ESI+: 638, 640
13	Ex1	ESI+: 624
14	Ex1	ESI+: 624
15	Ex1	ESI+: 638
16	Ex1	ESI+: 638, 640
17	Ex1	ESI+: 636
18	Ex1	ESI+: 663
19	Ex1	ESI+: 590
20	Ex1	ESI+: 590, 592
21	Ex1	ESI+: 636

TABLE 106

Ex.	Syn.	Data
22	Ex1	ESI+: 576, 578 NMR-DMSO-d6; 1.34-1.50 (6H, m), 1.62-1.73 (1H, m), 1.84-2.02 (2H, m), 2.17-2.28 (1H, m), 2.92-4.27 (13H, m), 4.55-4.69 (2H, m), 4.87-4.96 (1H, m), 5.04 (1H, brs), 7.68 (1H, d, J = 1.4 Hz), 7.74 (1H, d, J = 1.4 Hz), 8.43 (1H, s), 8.84 (1H, d, J = 1.2 Hz), 10.57 (1H, brs), 12.32 (1H, s)
23	Ex1	ESI+: 662
24	Ex1	ESI+: 576, 578
25	Ex1	ESI+: 590
26	Ex1	ESI+: 576
27	Ex1	ESI+: 682, 684
28	Ex1	ESI+: 604 NMR-DMSO-d6; 0.89 (3H, t, J = 7.3 Hz), 1.47 (3H, d, J = 7.1 Hz), 1.60-1.74 (2H, m), 1.83-2.01 (3H, m), 2.16-2.26 (1H, m), 2.85-3.01 (14H, m), 4.58-4.77 (2H, m), 4.87-4.96 (1H, m), 5.02-5.11 (1H, m), 7.70 (1H, d, J = 1.3 Hz), 7.74 (1H, d, J = 1.3 Hz), 8.47 (1H, s), 8.84 (1H, d, J = 1.1 Hz), 10.59 (1H, brs), 11.11 (1H, brs), 12.32 (1H, s)
29	Ex1	ESI+: 604
28	Ex1	ESI+: 636 NMR-DMSO-d6; 1.36 (3H, t, J = 6.4 Hz), 1.44 (3H, d, J = 7.1 Hz), 1.59-1.69 (1H, m), 1.85-1.96 (2H, m), 2.14-2.22 (1H, m), 2.87-3.20 (4H, m), 3.20-3.74 (9H, m), 4.47-4.53 (1H, m), 4.61-4.69 (1H, m), 4.79-4.85 (1H, m), 5.03-5.10 (1H, m), 7.80-7.85 (1H, m), 7.91-7.96 (2H, m), 8.47 (1H, s), 8.86 (1H, d, J = 1.2 Hz), 10.48 (1H, brs), 10.76 (1H, brs) 12.34-12.38 (1H, m)

TABLE 106-continued

Ex.	Syn.	Data
31	Ex1	ESI+: 604 NMR-DMSO-d6; 0.89 (3H, t, J = 7.4 Hz), 1.18-1.52 (3H, m), 1.58-1.75 (2H, m), 1.81-2.02 (3H, m), 2.14-2.27 (1H, m), 2.78-2.95 (2H, m), 3.07-3.98 (10H, m), 4.37-4.78 (3H, m), 4.85-4.98 (1H, m), 7.69 (1H, s), 7.74 (1H, d, J = 1.2 Hz), 8.52 (1H, s), 8.80-8.84 (1H, m), 10.59 (1H, brs), 11.29-11.79 (1H, m), 12.32 (3H, s), 12.50-13.07 (1H, m)

TABLE 107

Ex.	Syn.	Data
32	Ex1	ESI+: 622 NMR-DMSO-d6; 1.14-1.51 (6H, m), 1.61-1.78 (1H, m), 1.83-2.00 (2H, m), 2.11-2.24 (1H, m), 3.00-4.30 (12H, m), 4.48 (1H, dd, J = 7.4, 14.8 Hz), 4.64 (1H, d, J = 14.0 Hz), 4.76 (1H, d, J = 14.5 Hz), 5.07 (1H, brs), 7.77-7.83 (1H, m), 7.90-8.04 (2H, m), 8.41-8.48 (1H, m), 8.85 (1H, d, J = 1.3 Hz), 11.05-11.60 (1H, m), 12.28-12.42 (1H, m)
33	Ex1	ESI+: 635 NMR-DMSO-d6; 1.36 (3H, d, J = 6.3 Hz), 1.59-1.69 (1H, m), 1.83-1.97 (2H, m), 2.13-2.22 (1H, m), 2.85-2.89 (2H, m), 3.03-3.78 (11H, m), 4.67 (3H, s), 4.39-4.87 (4H, m), 8.38-8.41 (1H, m), 8.49-8.52 (1H, m), 8.75-8.80 (1H, m), 8.84 (1H, d, J = 1.3 Hz), 10.50 (1H, brs), 10.76-11.73 (1H, m), 12.34 (1H, s), 12.40-12.90 (1H, br)
34	Ex2	ESI+: 629
35	Ex2	ESI+: 671
36	Ex2	ESI+: 671
37	Ex2	ESI+: 671
38	Ex2	ESI+: 657
39	Ex2	ESI+: 643
40	Ex2	ESI+: 643
41	Ex3	ESI+: 634
42	Ex3	ESI+: 646 [M − H]−
43	Ex3	ESI+: 634, 636
44	Ex3	ESI+: 634
45	Ex3	ESI+: 620, 622
46	Ex3	ESI+: 634
47	Ex3	ESI+: 620
48	Ex3	ESI+: 634
49	Ex3	ESI+: 622 NMR-DMSO-d6; 1.34-1.40 (3H, m), 1.58-1.76 (1H, m), 1.83-1.97 (2H, m), 2.11-2.23 (1H, m), 2.90 (2H, t, J = 7.6 Hz), 3.03-3.97 (13H, m), 4.42-4.56 (1H, m), 4.60-4.87 (3H, m), 7.79-7.85 (1H, m), 7.91-8.00 (2H, m), 8.51 (1H, d, J = 1.2 Hz), 8.85 (1H, d, J = 1.3 Hz), 10.75 (1H, brs), 11.05-11.45 (1H, m), 12.33-12.41 (1H, m)

TABLE 108

Ex.	Syn.	Data
50	Ex3	ESI+: 576, 578 NMR-DMSO-d6; 1.44 (3H, t, J = 6.5 Hz), 1.62-1.73 (1H, m), 1.84-2.02 (2H, m), 2.17-2.28 (1H, m), 2.90 (2H, t, J = 7.7 Hz), 3.08-3.23 (3H, m), 3.30-3.39 (2H, m), 3.42-4.07 (8H, m), 4.56-4.77 (3H, m), 4.88-4.96 (1H, m), 7.68 (1H, d, J = 1.4 Hz), 7.74 (1H, d, J = 1.4 Hz), 8.51 (1H, d, J = 1.2 Hz), 8.83 (1H, d, J = 1.2 Hz), 10.45-11.00 (1H, m)
51	Ex3	ESI+: 562
52	Ex9	ESI+: 634
53	Ex3	ESI+: 620
54	Ex3	ESI+: 648
55	Ex3	ESI+: 662
56	Ex3	ESI+: 662
57	Ex3	ESI+: 662
58	Ex3	ESI+: 676
59	Ex3	ESI+: 676
60	Ex3	ESI+: 622
61	Ex3	ESI+: 608
62	Ex3	ESI+: 622

TABLE 108-continued

Ex.	Syn.	Data
63	Ex3	ESI+: 644
64	Ex3	ESI+: 622
65	Ex3	ESI+: 618
66	Ex3	ESI+: 604
67	Ex3	ESI+: 664
68	Ex3	ESI+: 630
69	Ex3	ESI+: 658
70	Ex3	ESI+: 644
71	Ex3	ESI+: 604
72	Ex3	ESI+: 652
73	Ex3	ESI+: 618
74	Ex3	ESI+: 632, 634
75	Ex3	ESI+: 662
76	Ex3	ESI+: 670
77	Ex3	ESI+: 556
78	Ex3	ESI+: 570

TABLE 109

Ex.	Syn.	Data
79	Ex3	ESI+: 590
80	Ex3	ESI+: 590, 592 NMR-DMSO-d6; 0.89 (3H, t, J = 7.4 Hz), 1.58-1.72 (2H, m), 1.82-2.02 (3H, m), 2.16-2.27 (1H, m), 2.89 (2H, t, J = 7.6 Hz), 3.06-3.70 (13H, m), 4.60-4.78 (3H, m), 4.89-4.98 (1H, m), 7.69 (1H, d, J = 1.3 Hz), 7.74 (1H, d, J = 1.4 Hz), 8.51 (1H, d, J = 1.2 Hz), 8.84 (1H, d, J = 1.3 Hz), 10.43 (1H, brs), 11.30 (1H, brs), 12.35 (1H, s)
81	Ex3	ESI+: 604, 606
82	Ex9	ESI+: 576
83	Ex3	ESI+: 562
84	Ex3	ESI+: 590
85	Ex3	ESI+: 568
86	Ex3	ESI+: 582
87	Ex3	ESI+: 596
88	Ex3	ESI+: 596
89	Ex3	ESI+: 596
90	Ex3	ESI+: 596
91	Ex3	ESI+: 666
92	Ex3	ESI+: 666
93	Ex3	ESI+: 638
94	Ex3	ESI+: 610
95	Ex3	ESI+: 624
96	Ex3	ESI+: 624
97	Ex3	ESI+: 620, 622
98	Ex3	ESI+: 636, 638
99	Ex3	ESI+: 634, 636
100	Ex3	ESI+: 624
101	Ex3	ESI+: 634
102	Ex3	ESI+: 634
103	Ex3	ESI+: 596
104	Ex3	ESI+: 650
105	Ex3	ESI+: 650
106	Ex3	ESI+: 624

TABLE 110

Ex.	Syn.	Data
107	Ex3	ESI+: 624 NMR-DMSO-d6; 0.85 (3H, d, J = 6.6 Hz), 0.90 (3H, d, J = 6.5 Hz), 1.90-2.00 (1H, m), 2.60-2.71 (3H, m), 2.71-2.81 (2H, m), 2.91 (2H, t, J = 7.7 Hz), 3.05-3.25 (2H, m), 3.28-3.38 (2H, m), 3.49-3.67 (4H, m), 3.80-4.82 (5H, m), 7.82-7.90 (3H, m), 8.51 (1H, d, J = 1.2 Hz), 8.85 (1H , d, J = 1.3 Hz), 10.25 (1H, brs), 11.62 (1H, brs), 12.36 (1H, s)
108	Ex3	ESI+: 622
109	Ex9	ESI+: 610
110	Ex3	ESI+: 636
111	Ex3	ESI+: 624 NMR-DMSO-d6; 1.27 (3H, d, J = 6.8 Hz), 1.42 (3H, d, J = 6.5 Hz), 1.55-1.80 (2H, m), 2.12-2.34 (2H, m), 2.92 (2H, t,

TABLE 110-continued

Ex.	Syn.	Data
		J = 7.7 Hz), 3.05-3.25 (2H, m), 3.25-3.40 (2H, m), 3.48-3.79 (5H, m), 3.82-3.97 (1H, m), 4.51 (1H, dd, J = 7.2, 15.3 Hz), 4.59-4.83 (3H, m), 4.90-6.65 (2H, m), 7.96-7.99 (1H, m), 8.39-8.42 (1H, m), 8.49-8.53 (1H, m), 8.54 (1H, d, J = 1.3 Hz), 10.99 (1H, brs), 11.75 (1H, brs), 12.37-(1H, s)
112	Ex3	ESI+: 676
113	Ex3	ESI+: 690
114	Ex3	ESI+: 588, 590 [M − H]−
115	Ex3	ESI+: 602, 604 [M − H]−
116	Ex3	ESI+: 602, 604 [M − H]−
117	Ex3	ESI+: 602, 604 [M − H]−
118	Ex9	ESI+: 610 NMR-DMSO-d6; 1.06-1.14 (6H, m), 1.43 (3H, d, J = 6.8 Hz), 2.92-3.15 (4H, m), 3.16-3.45 (2H, m), 3.51-3.75 (4H, m), 3.80-4.84 (6H, m), 4.97-5.24 (1H, m), 7.80-7.86 (1H, m), 7.87-7.97 (2H, m), 8.42-8.48 (1H, m), 8.86 (1H, d, J = 1.2 Hz), 10.06-11.50 (2H, m), 12.37 (1H, s)
119	Ex3	ESI+: 636 NMR-DMSO-d6; 1.21 (3H, d, J = 6.8 Hz), 1.40 (3H, d, J = 6.5 Hz), 1.60-1.71 (2H, m), 2.17-2.30 (2H, m), 2.91 (2H, t, J = 7.7 Hz), 3.08-3.25 (2H, m), 3.29-3.37 (2H, m), 3.50-3.70 (4H, m), 3.87-3.98 (1H, m), 4.38 (1H, dd, J = 7.5, 15.3 Hz), 4.50-5.00 (5H, m), 7.79-7.85 (1H, m), 7.94-8.00 (2H, m), 8.51 (1H, d, J = 1.2 Hz), 8.85 (1H, d, J = 1.3 Hz), 11.08 (1H, m), 11.63 (1H, brs), 12.37 (1H, s)

TABLE 111

Ex.	Syn.	Data
120	Ex3	ESI+: 622 NMR-DMSO-d6; 1.22 (3H, d, J = 6.8 Hz), 1.41 (3H, d, J = 6.5 Hz), 1.57-1.75 (2H, m), 2.12-2.33 (2H, m), 3.11-4.03 (7H, m), 4.26 (2H, s), 4.25-5.21 (7H, m), 7.78-7.83 (1H, m), 7.95-8.03 (2H, m), 8.50 (1H, d, J = 1.2 Hz), 8.85 (1H, d, J = 1.3 Hz), 10.60-11.70 (2H, m), 12.38 (1H, s)
121	Ex3	ESI+: 650
122	Ex3	ESI+: 632
123	Ex4	ESI+: 604
124	Ex4	ESI+: 632
125	Ex5	ESI−: 576, 578 [M − H]−
126	Ex5	ESI−: 602, 604 [M − H]−
127	Ex5	ESI−: 576, 578 [M − H]−
128	Ex5	ESI−: 588, 590 [M − H]−
129	Ex5	ESI−: 576, 578 [M − H]−
130	Ex5	ESI−: 588, 590 [M − H]− NMR-DMSO-d6; 0.33-0.54 (2H, m), 0.60-0.72 (2H, m), 1.13-1.50 (4H, m), 2.75-2.81 (3H, m), 2.81-3.07 (3H, m), 3.11-3.74 (7H, m), 3.74-4.94 (7H, m), 7.68 (1H, d, J = 1.4 Hz), 7.74 (1H, d, J = 1.4 Hz), 8.47-8.57 (1H, m), 8.78-8.86 (1H, m), 10.58 (1H, brs), 11.33-11.77 (1H, m), 12.22-12.42 (1H, m)
131	Ex6	ESI+: 610, 612
132	Ex6	ESI+: 592
133	Ex7	ESI+: 676
134	Ex7	ESI+: 676
135	Ex7	ESI+: 690
136	Ex8	ESI+: 662
137	Ex8	ESI+: 676
138	Ex9	ESI+: 638
139	Ex9	ESI+: 654
140	Ex1	ESI+: 636 [M + H]+ NMR-DMSO-d6; 1.34-1.41 (3H, m), 1.47 (3H, d, J = 7.0 Hz), 1.60-1.74 (1H, m), 1.86-1.97 (2H, m), 2.11-2.23 (1H, m), 2.81-4.17 (15H, m), 4.43-4.54 (1H, m), 4.61-4.71 (1H, m), 4.75-4.84 (1H, m), 5.01-5.12 (1H, m), 7.79-7.84 (1H, m), 7.91-8.00 (2H, m), 8.45-8.49 (1H, m), 8.85 (1H, d, J = 1.2 Hz), 10.85 (1H, brs), 10.95-11.31 (1H, m), 12.30-12.41 (1H, m)

TABLE 112

Ex.	Syn.	Data
141	Ex1	ESI+: 622 [M + H]+ NMR-DMSO-d6; 1.34-1.47 (6H, m), 1.60-1.74 (1H, m), 1.86-1.97 (2H, m), 2.11-2.23 (1H, m), 3.10-4.29 (13H, m), 4.42-4.54 (1H, m), 4.57-4.72 (1H, m), 4.74-4.83 (1H, m), 5.09 (1H, brs), 7.78-7.85 (1H, m), 7.91-8.02 (2H, m), 8.45 (1H, s), 8.86 (1H, d, J = 1.3 Hz), 10.75-11.42 (1H, m), 12.32-12.41 (1H, m)
142	Ex3	ESI+: 590, 592 [M + H]+ NMR-DMSO-d6; 1.21-1.31 (1H, m), 1.35-1.49 (6H, m), 1.61-1.74 (1H, m), 1.84-2.02 (2H, m), 2.13-2.29 (1H, m), 2.79-2.98 (2H, m), 3.10-3.98 (10H, m), 4.40-4.77 (3H, m), 4.87-4.98 (1H, m), 7.67 (1H, d, J = 1.3 Hz), 7.74 (1H, d, J = 1.3 Hz), 8.52 (1H, s), 8.82 (1H, s), 10.39-10.97 (1H, m), 11.25-11.65 (1H, m), 12.25-12.42 (1H, m), 12.56-13.02 (1H, br)
143	Ex3	ESI+: 604, 606 [M + H]+ NMR-DMSO-d6; 0.89 (3H, t, J = 7.4 Hz), 1.22-1.30 (1H, m), 1.40-1.49 (2H, m), 1.59-1.73 (2H, m), 1.83-2.03 (3H, m), 2.14-2.27 (1H, m), 2.80-2.97 (2H, m), 3.10-3.95 (12H, m), 4.42-4.79 (3H, m), 4.88-4.97 (1H, m), 7.69 (1H, d, J = 1.3 Hz), 7.74 (1H, d, J = 1.3 Hz), 8.52 (1H, s), 8.83 (1H, s), 10.38-11.04 (1H, m), 11.20-11.24 (1H, m), 12.21-13.19 (2H, m)
144	Ex144	ESI+: 590, 592 [M + H]+ NMR-DMSO-d6; 1.13-1.45 (6H, m), 1.46-2.29 (4H, m), 2.53-2.70 (2H, m), 2.80-3.84 (14H, m), 4.00-5.18 (4H, m), 6.09 (4H, s), 7.57 (1H, s), 7.71 (1H, s), 8.47 (1H, s), 8.79 (1H, d, J = 1.2 Hz), 9.15-10.50 (1H, m), 11.70-12.50 (1H, m)

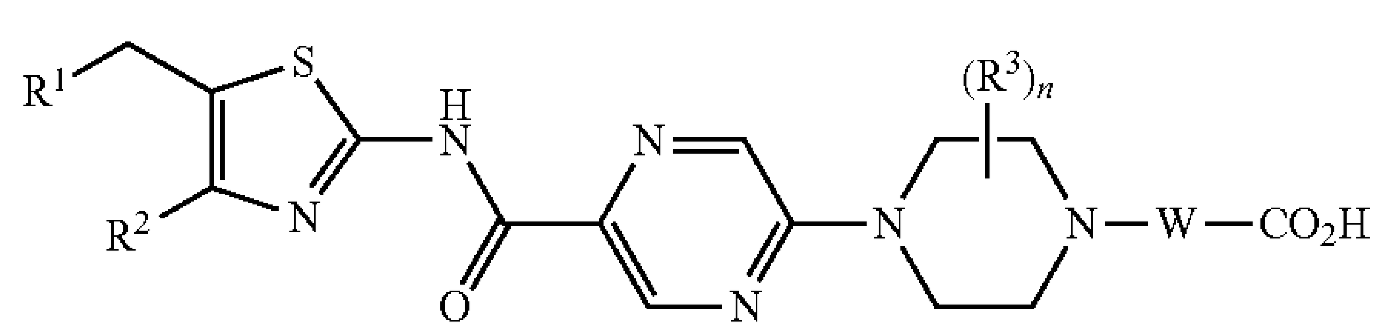
INDUSTRIAL APPLICABILITY

The compound of the formula (I) or a salt thereof is a muscarinic M_3 receptor-positive allosteric modulator, and can thus be used as an agent for preventing or treating bladder/urinary tract diseases associated wit bladder contractions via a muscarinic M_3 receptor.

The invention claimed is:

1. A compound of formula (I) or a salt thereof:

(I)



wherein

R^1 is **[**—N(—R^{12})(—R^{12})**]** *—N(—R^{11})(—R^{12})*, or optionally-substituted cyclic amino,

R^{11} is C_{1-6} alkyl,

R^{12} is optionally-substituted C_{1-6} alkyl, or optionally-substituted C_{3-8} cycloalkyl,

R^2 is optionally-substituted aryl, optionally-substituted monocyclic aromatic hetero ring, or optionally-substituted bicyclic aromatic hetero ring,

each R^3 if present is, independently, C_{1-6} alkyl,

W is C_{1-6} alkylene, and

n is an integer of 0 to 4.

2. The compound or salt thereof according to claim **1**, wherein

R^1 is cyclic amino optionally substituted with 1 to 5 of a substituent G and/or an oxo substituent, or R^3 is —N(—R^{11})(—R^{12}),

R^{11} is C_{1-6} alkyl

R^{12} is C_{1-6} alkyl optionally substituted with 1 to 3 substituents selected from the group consisting of

—OH,

O—C_{1-6} alkyl optionally substituted with at least one group selected from the group consisting of —OH, —O—(C_{1-6} alky), —CN, —SO_2—(C_{1-6} alkyl), and halogen,

C_{3-8} cycloalkyl,

O—(C_{3-8} cycloalkyl),

halogen,

—CN, and

a saturated hetero ring,

R^2 is phenyl optionally substituted with 1 to 5 substituents G, thienyl optionally substituted with 1 to 3 substituents G, pyridyl optionally substituted with 1 to 3 substituents G, or benzothienyl optionally substituted with 1 to 5 substituents G, and

each substituent G is a sustituent selected from the group consisting of:

C_{1-6} alkyl optionally substituted with at least one group selected from the group consisting of —OH, —O—(C_{1-6} alkyl), —CN, —SO_2—(C_{1-6} alkyl), and halogen,

—OH,

—O—C_{1-6} alkyl optionally substituted with at least one group selected from the group consisting of —OH, —O—(C_{1-6} alkyl), —CN, —SO_2—(C_{1-6} alkyl), and halogen,

C_{3-8} cycloalkyl,

—O—(C_{3-8} cycloalkyl),

halogen,

—CN,

—SO_2—(C_{1-6} alkyl),

—CO_2—(C_{1-6} alkyl),

—COOH,

—CO—N(C_{1-6} alkyl)$_2$,

—CO—NH(C_{1-6} alkyl),

—$CONH_2$,

—CO—(C_{1-6} alkyl),

—SO_2—N(C_{1-6} alkyl)$_2$,

—SO_2—NH(C_{1-6} alkyl),

—SO_2NH_2,

—N(C_{1-6} alkyl)$_2$,

—NH(C_{1-6} alkykl),

—NH_2,

a saturated hetero ring, and

—O-saturated hetero ring.

3. The compound or a salt thereof according to claim **2**, wherein

R^1 is pyrrolidin-1-yl or piperidin-1-yl, each substituted with 1 to 2 substituents selected from the group consisting of C_{1-6} alkyl and haogeno-C_{1-6} alkyl, or wherein R^1 is —N(—R^{11})(—R^{12}),

R^{11} is C_{1-6} alkyl, and

R^{12} is C_{1-6} alkyl optionally substituted with one group selected from the group consisting of C_{3-8} cycloalkyl and —O—(C_{1-6} alkyl),

R^2

phenyl optionally substituted with 1 to 3 groups selected from the group consisting of C_{1-6} alkyl, halogeno-C_{1-6} alkyl, —O—(C_{1-6} alkyl), —O-(halogeno-C_{1-6} alkyl), halogen, C_{3-8} cycloalkyl, and —CN;

thienyl optionally substituted with 1 to 3 groups selected from the group consisting of C_{1-6} alkyl, halogeno-C_{1-6} alkyl, —O—(C_{1-6} alkyl), C_{3-8} cycloalkyl, and halogen;

pyridyl optionally substituted with 1 to 3 groups selected from the group consisting of C_{1-6} alkyl, halogeno-C_{1-6} alkyl, —O—(C_{3-8} alkyl), C_{3-8} cycloalkyl, and halogen; or

benzothienyl,

W is C_{1-6} alkylene, and

n is 0 or 1.

4. The compound or a salt thereof according to claim **3**, wherein

R^2 is phenyl di-substituted with trifluoromethyl and fluoro, thienyl mono-substituted with trifluoromethyl or chloro, or pyridyl di-substituted with trifluoromethyl and methoxy, and

W is methylene or ethylene.

5. The compound or a salt thereof according to claim **3**, wherein

R^1 is pyrrolidin-1-yl or piperidin-1-yl, each substituted with 1 to 2 substituents selected from the group consisting of C_{1-6} alkyl and halogeno-C_{1-6} alkyl,

R^2 is thienyl optionally substituted with 1 or 2 substituents selected from the group consisting of halogeno-C_{1-6} alkyl and halogen, or wherein R^2 is phenyl optionally substituted with 1 or 2 substituents selected from the group consisting of halogeno-C_{1-6} alkyl and halogen, and

W is methylene or ethylene.

6. The compound or a salt thereof according to claim **1**, wherein the compound is a compound selected from the group consisting of:

3-[(2S)-4-(5-{[4-(4-chlorothiophen-2-yl)-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl]carbamoyl}pyrazin-2-yl)-2-methylpiperazin-1-yl]propanoic acid,

3-[(3R)-4-{5-[(4-[3-fluoro-5-(trifluoromethyl)phenyl]-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl)carbamoyl]pyrazin-2-yl}-3-methylpiperazin-1-yl]propanoic acid,

[(3R)-4-{5-[(4-[3-fluoro-5-(trifluoromethyl)phenyl]-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl)carbamoyl]pyrazin-2-yl}-3-methylpiperazin-1-yl]acetic acid,

3-(4-{5-[(4-[3-fluoro-5-(trifluoromethyl)phenyl]-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl)carbamoyl]pyrazin-2-yl}piperazin-1-yl)propanoic acid,

3-[(2R)-4-(5-{[4-(4-chlorothiophen-2-yl)-5-{[(2R)-2-ethylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl]carbamoyl}pyrazin-2-yl)-2-methylpiperazin-1-yl]propanoic acid,

3-[(3R)-3-methyl-4-{5-[(5-{[(2R)-2-methylpyrrolidin-1-yl]methyl)}-4-[4-(trifluoromethyl)thiophen-2-yl]-1,3-thiazol-2-yl)carbamoyl]pyrazin-2-yl}piperazin-1-yl]propanoic acid,

3-(4-{5-[(5-{[(2R,5R)-2,5-dimethylpyrrolidin-1-yl]methyl}-4-[3-fluoro-5-(trifluoromethyl)phenyl]-1,3-thiazol-2-yl)carbamoyl]pyrazin-2-yl}piperazin-1-yl)propanoic acid, and

3-{(2R)-4-[5-({5-[(diethylamino)methyl]-4-[3-fluoro-5-(trifluoromethyl)phenyl]-1,3-thiazol-2-yl}carbamoyl)pyrazin-2-yl]-2-methylpiperazin-1-yl}propanoic acid.

7. A pharmaceutical composition, comprising:

the compound or a salt thereof according to claim **1**; and a pharmaceutically acceptable excipient.

8. A method for treating a bladder/urinary tract disease associated with bladder contractions via a muscarinic M_3 receptor, the method comprising:

administering, to a subject in need thereof, an effective amount of the compound or a salt thereof according to claim **1**.

9. The method according to claim **8**, wherein the bladder/urinary tract disease associated with bladder contractions via a muscarinic M_3 receptor is voiding dysfunction or urine storage dysfunction in underactive bladder, hypotonic bladder, acontractile bladder, detrusor underactivity, or neurogenic bladder.

10. The compound or a salt thereof according to claim **6**, wherein the compound is 3-[(2S)-4-(5-{[4-(4-chlorothiophen-2-yl)-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl]carbamoyl}pyrazin-2-yl)-2-methylpiperazin-1-yl]propanoic acid.

11. The compound or a salt thereof according to claim **6**, wherein the compound is 3-[(3R)-4-{5-[(4-[3-fluoro-5-(trifluoromethyl)phenyl]-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl)carbamoyl]pyrazin-2-yl}-3-methylpiperazin-1-yl]propanoic acid.

12. The compound or a salt thereof according to claim **6**, wherein the compound is [(3R)-4-{5-[(4-[3-fluoro-5-(trifluoromethyl)phenyl]-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl)carbamoyl]pyrazin-2-yl}-3-methylpiperazin-1-yl]acetic acid.

13. The compound or a salt thereof according to claim **6**, wherein the compound is 3-(4-{5-[(4-[3-fluoro-5-(trifluoromethyl)phenyl]-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl)carbamoyl]pyrazin-2-yl}piperazin-1-yl)propanoic acid.

14. The compound or a salt thereof according to claim **6**, wherein the compound is 3-[(2R)-4-(5-{[4-(4-chlorothiophen-2-yl)-5-{[(2R)-2-ethylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl]carbamoyl}pyrazin-2-yl)-2-methylpiperazin-1-yl]propanoic acid.

15. The compound or a salt thereof according to claim **6**, wherein the compound is 3-[(3R)-3-methyl-4-{5-[(5-{[(2R)-2-methylpyrrolidin-1-yl]methyl]-4-[4-(trifluoromethyl)thiophen-2-yl]-1,3-thiazol-2-yl)carbamoyl]pyrazin-2-yl}piperazin-1-yl]propanoic acid.

16. The compound or a salt thereof according to claim **6**, wherein the compound is 3-(4-{5-[(5-([(2R,5R)-2,5-dimethylpyrrolidin-1-yl]methyl}-4-[3-fluoro-5-(trifluoromethyl)phenyl]-1,3-thiazol-2-yl)carbamoyl]pyrazin-2-yl}piperazin-1-yl)propanoic acid.

17. The compound or a salt thereof according to claim **6**, wherein the compound is 3-{(2R)-4-[5-([5-[(diethylamino)methyl]-4-[3-fluoro-5-(trifluoromethyl)phenyl]-1,3-thiazol-2-yl}carbamoyl)pyrazin-2-yl]-2-methylpiperazin-1-yl}propanoic acid.

18. The compound of claim 1 which is 3-[(2S)-4-(5-{[4-(4-chlorothiophen-2-yl)-5-{[(2R)-2-methylpyrrolidin-1-yl]methyl}-1,3-thiazol-2-yl]carbamoyl}pyrazin-2-yl)-2-methylpiperazin-1-yl]propanoic acid dimaleate.

19. A crystal polymorph of the compound of claim 18.

20. The crystal polymorph of claim 19 having peaks at 2θ (°) of 5.7, 6.6, 10.5, 12.0, 13.3, 15.8, 16.6, 17.3, 19.0, and 26.2 when measured by powder X-ray diffraction.

21. A pharmaceutical composition comprising the crystal polymorph of claim 20.

22. A method for treating bladder/urinary tract diseases associated with bladder contractions via a muscarinic M_3 receptor, comprising administering the composition of claim 21.

23. A method for treating bladder/urinary tract diseases associated with bladder contractions via a muscarinic M3 receptor voiding dysfunction or urine storage dysfunction in underactive bladder, hypotonic bladder, acontractile bladder, detrusor underactivity, or neurogenic bladder comprising administering the composition of claim 21.

* * * * *