



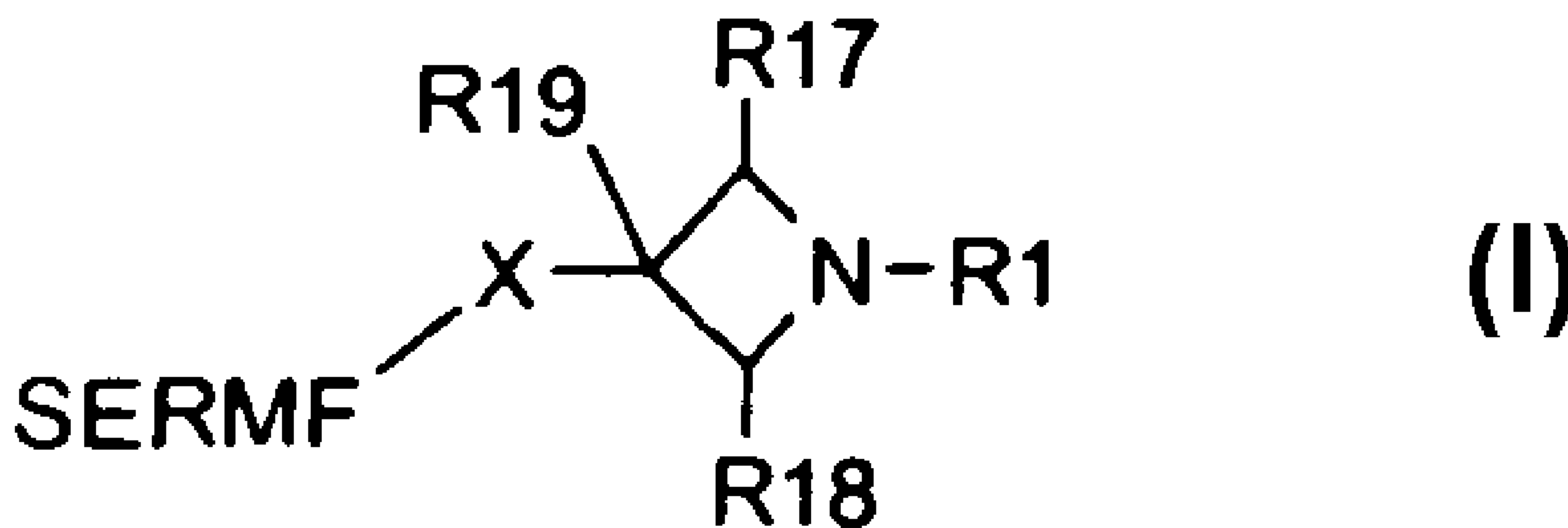
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(54) Titre : DERIVES D'AZETIDINE N-SUBSTITUES
(54) Title: N-SUBSTITUTED AZETIDINE DERIVATIVES



(57) Abrégé/Abstract:

The present invention relates to novel N-substituted azetidine derivatives < of the formula (I); wherein SERMF is a Selective Estrogen Receptor Modulator fragment; X is no atom, O, S, CH₂, carbonyl, N-R₅; R₁ is H, (C₁-8)alkyl, (C₃-8)cycloalkyl, (C₃-6)heterocycloalkyl, (C₂-6)alkenyl, (C₂-6)alkynyl, (C₁-4)alkylcarbonyl, (C₁-4)alkoxy(C₂-4)alkyl, (C₃-6)cycloalkyl(C₁-3)-alkyl, (C₃-6)heterocycloalkyl(C₁-3)alkyl, each independently optionally substituted with one or more halogen, nitrile, hydroxyl or (C₁-2)alkyl; R₅ is H, (C₁-3)alkyl, optionally substituted with one or more fluorine; R₁₇, R₁₈ and R₁₉ are independently of each other H, fluorine, nitrile or (C₁-3)-alkyl, optionally substituted with one or more fluorine; or a prodrug, isotopically-labelled derivative or pharmaceutically acceptable salt thereof, > to pharmaceutical compositions comprising these compounds and to their use in therapy, in particular to their use for the prevention or treatment of ovulatory dysfunction, uterine cancer, endometrium cancer, ovarian cancer, endometriosis, osteoporosis, prostate cancer, benign prostatic hypertrophy, and breast cancer, in particular ER-positive breast cancer, more in particular ER- positive, hormone treatment-resistant breast cancer. Said N-substituted azetidine derivatives have estrogen receptor alpha (ERα) antagonistic and - in certain embodiments - selective estrogen receptor downregulating (SERD) activity in ER-positive breast cancer cells.



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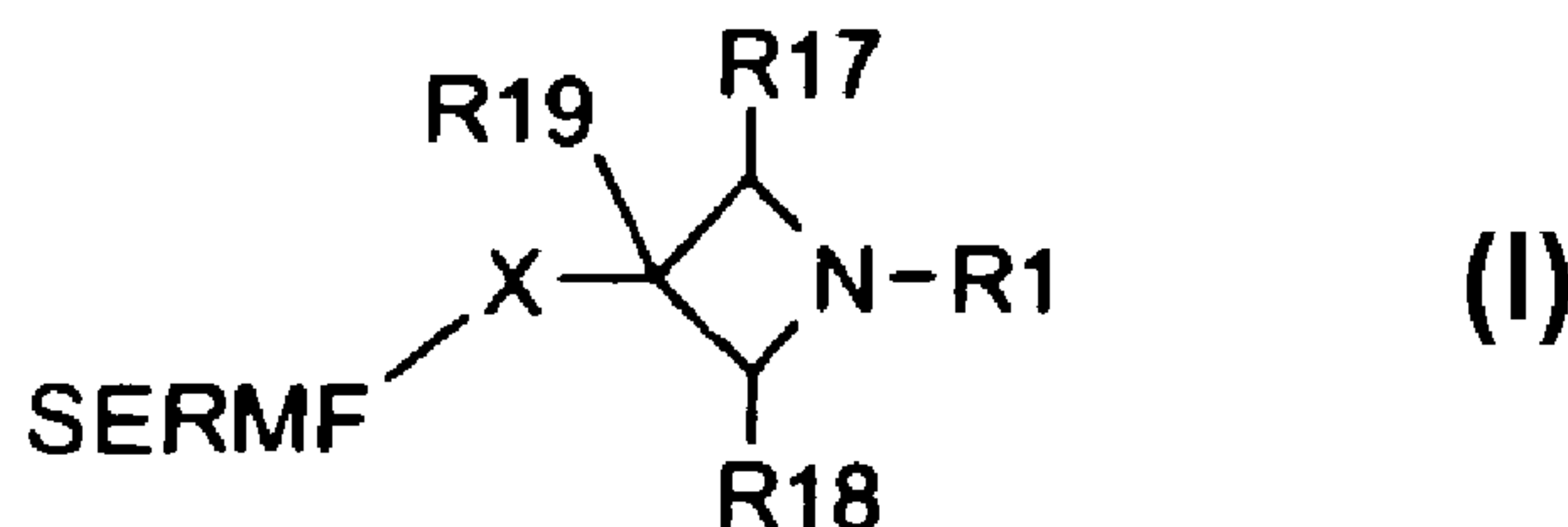
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(54) Title: N-SUBSTITUTED AZETIDINE DERIVATIVES



(57) **Abstract:** The present invention relates to novel N-substituted azetidine derivatives < of the formula (I); wherein SERMF is a Selective Estrogen Receptor Modulator fragment; X is no atom, O, S, CH₂, carbonyl, N-R₅; R₁ is H, (C₁-8)alkyl, (C₃-8)cycloalkyl, (C₃-6)heterocycloalkyl, (C₂-6)alkenyl, (C₂-6)alkynyl, (C₁-4)alkylcarbonyl, (C₁-4)alkoxy(C₂-4)alkyl, (C₃-6)cycloalkyl(C₁-3)-alkyl, (C₃-6)heterocycloalkyl(C₁-3)alkyl, each independently optionally substituted with one or more halogen, nitrile, hydroxyl or (C₁-2)alkyl; R₅ is H, (C₁-3)alkyl, optionally substituted with one or more fluorine; R₁₇, R₁₈ and R₁₉ are independently of each other H, fluorine, nitrile or (C₁-3)-alkyl, optionally substituted with one or more fluorine; or a prodrug, isotopically-labelled derivative or pharmaceutically acceptable salt thereof, > to pharmaceutical compositions comprising these compounds and to their use in therapy, in particular to their use for the prevention or treatment of ovulatory dysfunction, uterine cancer, endometrium cancer, ovarian cancer, endometriosis, osteoporosis, prostate cancer, benign prostatic hypertrophy, and breast cancer, in particular ER-positive breast cancer, more in particular ER-positive, hormone treatment-resistant breast cancer. Said N-substituted azetidine derivatives have estrogen receptor alpha (ERα) antagonistic and - in certain embodiments - selective estrogen receptor downregulating (SERD) activity in ER-positive breast cancer cells.

N-SUBSTITUTED AZETIDINE DERIVATIVES

The present invention relates to a new series of N-substituted azetidine
5 derivatives, i.e. a series of Selective Estrogen Receptor Modulator (SERM)
fragments derivatized with an N-substituted azetidine group, to pharmaceutical
compositions comprising these compounds, and to their use in therapy, in
particular to their use for the prevention or treatment of ovulatory dysfunction,
uterine cancer, endometrium cancer, ovarian cancer, endometriosis, osteoporosis,
10 prostate cancer, benign prostatic hypertrophy, and breast cancer, in particular
estrogen receptor (ER)-positive breast cancer, more in particular ER-positive
hormone treatment-resistant breast cancer. In one embodiment, the new
compounds contain an N-substituted azetidine moiety, attached via an ether
linkage to SERM-derived chemical scaffolds which are estrogen receptor alpha
15 antagonists.

The estrogen receptor (ER) is a ligand-activated transcription factor that belongs
to the nuclear hormone receptor superfamily. Estrogens play an important role in
the regulation of a number of physiological processes, both in females and males.
20 In humans, two different ER subtypes are known: ER α and ER β , each with a
distinct tissue distribution and with different biological roles. ER α has high
presence in endometrium, breast cancer cells, ovarian stroma cells, and in the
hypothalamus. The expression of the ER β protein has been documented in
kidney, brain, bone, heart, lungs, intestinal mucosa, prostate, bladder, ovary,
25 testis, and endothelial cells. For a review see: J.W. Ullrich and C.P. Miller, *Expert
Opin. Ther. Patents*, 16 (2006) 559-572.

Well-known examples of SERMs are tamoxifen and raloxifene. Tamoxifen, for
example, behaves like an estrogen in bone and endometrium, whereas it behaves
30 like an anti-estrogen in breast tissue. SERMs are furthermore characterized by two
common structural features: a phenolic hydroxyl group (or a bioisostere thereof)
and a side chain containing a basic amine. At the time of administration *in vivo*, the
hydroxyl group of a SERM may not yet be present; it may be formed *in vivo* by de-

masking of a prodrug (for example by demethylation of a phenolic methoxy group or by hydrolysis of a phenolic ester group) or by metabolic introduction (for example the metabolic conversion of tamoxifen into 4-hydroxy-tamoxifen, an active metabolite of tamoxifen). Examples of side chains containing a basic amine
5 are 2-(dimethylamino)ethoxy (like in tamoxifen), 2-(1-piperidinyl)ethoxy (like in raloxifene), and 2-(1-pyrrolidinyl)ethoxy (like in lasofoxifene). Upon binding of a SERM to the estrogen receptor, the basic amine in the side chain forms an interaction with amino acid residue Asp351 (in ER α) or Asp303 (in ER β) resulting in a conformational change of the receptor. For reviews on SERMs see: C.P.
10 Miller, *Current Pharmaceutical Design* 8 (2002) 2089-2111; V.C Jordan, *J. Med. Chem.* 46 (2003) 883-908, and J.H. Pickar *et al.*; *Maturitas* 67 (2010) 129-138.

Breast cancer is the predominant neoplastic disease in women. ER α is a major driver of breast cancer progression. Multiple existing treatment approaches aim to
15 reduce estrogen levels or block its binding to ER α thereby minimizing tumor progression or even inducing tumor regression in ER-positive breast cancer. Tamoxifen is a first generation SERM used for first-line treatment of ER-positive breast cancer (see V.C. Jordan, *Nature Reviews Drug Discovery*, 2 (2003) 205-213). Efficacy in breast cancer treatment is seriously compromised by intrinsic or
20 newly developed resistance to anti-hormonal therapy such as treatment with tamoxifen or aromatase inhibitors. Such resistance can exist or develop as a result of ER phosphorylation or regulation of key components in hormone receptor and/or growth factor signal transduction pathways (see V.C. Jordan and B.W. O'Malley, *J. Clin. Oncol.* 25 (2007) 5815-5824; V.C. Jordan, *J. Nat. Cancer Inst.*, 98 (2006)
25 657-659; S.J. Cleator *et al.*, *Clinical Breast Cancer* 9 (2009) S6-S17).

Tamoxifen resistance is driven by the residual agonist activity of tamoxifen and its 4-OH metabolites. Second generation SERMs such as toremifene, droloxifene, idoxifene, arzoxifene, and raloxifene have failed to improve upon the efficacy of
30 tamoxifen in the treatment of ER-positive breast cancer and/or demonstrated cross-resistance with each other (V. Deshmane *et al.*, *J. Clin. Oncol.* 25 (2007) 4967-4973); J.H. Pickar *et al.*, *Maturitas* 67 (2010) 129-138).

Fulvestrant, a steroidal C7-substituted 17 β -estradiol derivative and a pure ER antagonist without the partial agonist activity which is so typical for the SERMs, is the only marketed SERD (Selective Estrogen Receptor Downregulator) efficacious in second-line treatment of breast cancer. Besides antagonizing ERs, fulvestrant
5 also effectively downregulates ER α protein levels in cells. This SERD activity inhibits ER α -driven proliferation and tumor growth (in contrast to tamoxifen which upregulates ER α). Fulvestrant, when administered *i.m.* once a month at 250 mg is equally effective to tamoxifen in treatment of ER-positive advanced breast cancer (A. Howell *et al.*, *J. Clin. Oncol.* 22 (2004) 1605-1613). In second-line treatment of
10 ER-positive tamoxifen-resistant breast cancer, fulvestrant, when administered *i.m.* once a month at 250 mg, is equally effective to aromatase inhibitors, despite relatively poor bioavailability and/or target exposure which limits its clinical efficacy (Robertson *et al.*, *San Antonio Breast Cancer Symposium*, 2009; Linden *et al.*, *San Antonio breast Cancer Symposium*, 2007).

15

Other known SERDs are ICI 164,384, i.e. a structural analogue of fulvestrant, GW5638, i.e. a structural analogue of tamoxifen, and GW7604, i.e. a structural analogue of 4-hydroxy-tamoxifen. For a review on SERDs see: M. Fan *et al.*, *Breast Cancer Res. Treat.* 103 (2007) 37-44.

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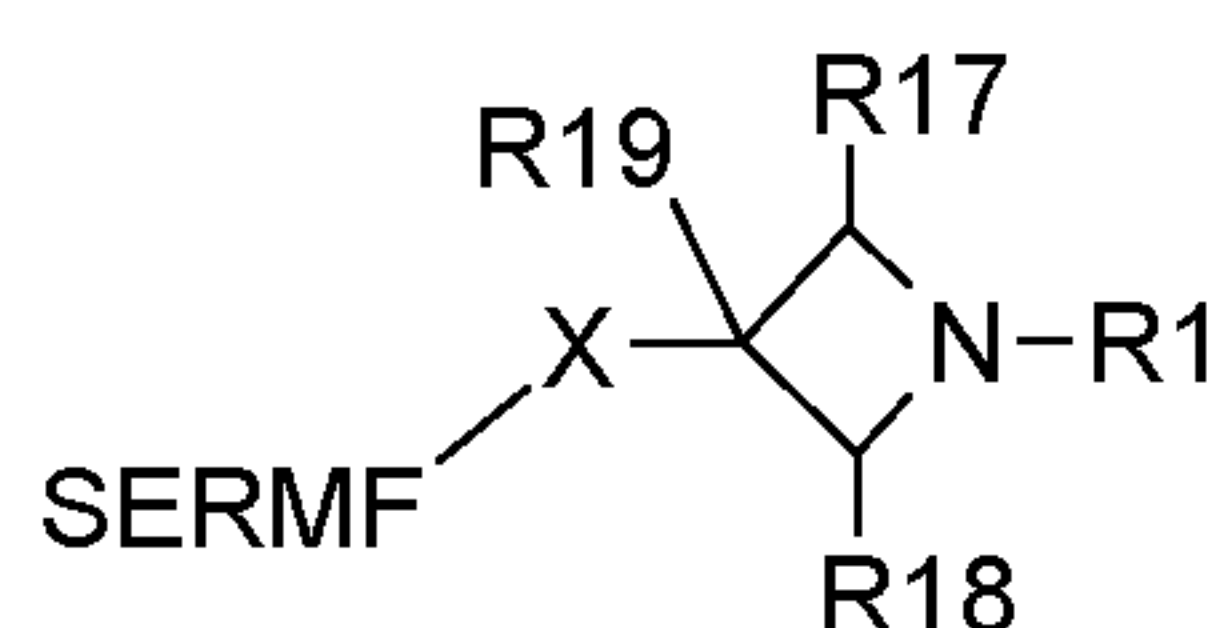
Merck has reported a series of 2,3-dihydrobenzo[b][1,4]-oxathiine derivatives, in which a modified (i.e. a bis-methylated pyrrolidinyloxy) basic amine side chain all at once behaved as a SERD instead of as a SERM. However, when said modified basic amine side chain was placed on other SERM-derived chemical
25 scaffolds, such as the benzothiophene of raloxifene, the tetrahydronaphthalene of lasofoxifene and the indole of bazedoxifene, these modified compounds did not behave as SERDs. See page 561 of J.W. Ullrich and C.P. Miller, *Expert Opin. Ther. Patents*, 16 (2006) 559-572, and references 18 and 101-103 cited therein.

30 Hence, there is a need for new, potent ER α antagonists, which would preferably have ER downregulating activity (in breast cancer cells), do not stimulate proliferation in ER-positive, hormone treatment-resistant breast cancer cells, be

orally administrable, and be useful in the treatment of *inter alia* ER-positive, hormone treatment-resistant breast cancer.

Apart from the treatment of breast cancer, SERMs have also been used in the treatment of a number of other disorders and/or diseases. The treatment of ovulatory dysfunction by tamoxifen and clomiphene citrate, which induce ovulation, is described by A. Steiner *et al.* in *Human Reproduction* 20 (2005) 1511-1515; and by J.H. Pickar *et al.* in *Maturitas* 67 (2010) 129-138. J.H. Pickar *et al.* in *Maturitas* 67 (2010) 129-138 also describe the treatment of uterine cancer, endometrium cancer, osteoporosis, prostate cancer, and benign prostatic hypertrophy using SERMs. S.J. Ellem and G.P. Risbridger in *Nature Reviews Cancer* 7 (2007) 621-627 also describe the treatment of prostate cancer and benign prostatic hyperplasia (or hypertrophy). The treatment of ovarian cancer is described by G.M. Clinton and W. Hua in *Crit. Rev. Oncol. Hematol.* 25 (1997) 1-9. S. E. Bulun in *N. Engl. J. Med.* 360 (2009) 268-279 reviews the role of estrogen and estrogen receptor signaling in endometriosis.

The present invention provides a series of N-substituted azetidine derivatives of the following Formula 1



Formula 1

wherein

SERMF is a Selective Estrogen Receptor Modulator fragment;

X is no atom, O, S, CH₂, carbonyl, N-R5;

R1 is H, (C1-8)alkyl, (C3-8)cycloalkyl, (C3-6)heterocycloalkyl, (C2-6)alkenyl, (C2-6)alkynyl, (C1-4)alkylcarbonyl, (C1-4)alkoxy(C2-4)alkyl, (C3-6)cycloalkyl(C1-3)-alkyl, (C3-6)heterocycloalkyl(C1-3)alkyl, each independently optionally substituted with one or more halogen, nitrile, hydroxyl or (C1-2)alkyl;

R5 is H, (C1-3)alkyl, optionally substituted with one or more fluorine;

R17, R18 and R19 are independently of each other H, fluorine, nitrile or (C1-3)-alkyl, optionally substituted with one or more fluorine;
or a prodrug, isotopically-labelled derivative or pharmaceutically acceptable salt thereof.

5

The N-substituted azetidine derivatives of the present invention are generally derived from the corresponding SERMs in which a SERM fragment (abbreviated as SERMF), e.g. the substituted benzothiophene of raloxifene, the substituted tetrahydronaphthalene of lasofoxifene, the substituted indole of bazedoxifene, the
10 substituted *trans*-1,2-diphenylbut-1-ene of tamoxifen etc., instead of being connected to a basic amine side chain, i.e. the piperidinyloxy moiety of raloxifene, the pyrrolidinyloxy moiety of lasofoxifene, the homopiperidinyloxy moiety of bazedoxifene or the dimethylaminoethoxy moiety of tamoxifen etc., is now connected to an N-substituted azetidine-X moiety, in
15 particular an N-substituted azetidyl-3-oxy moiety. For a review on a whole variety of suitable SERM fragments, see J.W. Ullrich and C.P. Miller, in *Expert Opin. Ther. Patents*, 16 (2006) 559-572.

The term (C1-8)alkyl means a linear or branched alkyl chain having 1-8 carbon
20 atoms, for example methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, and n-octyl.

The term (C1-6)alkyl means a linear or branched alkyl chain having 1-6 carbon
atoms, for example methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl,
25 tert-butyl, n-pentyl and n-hexyl.

The term (C1-4)alkyl means a linear or branched alkyl chain having 1-4 carbon
atoms, being methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-
butyl.

30

The term (C1-3)alkyl means a linear or branched alkyl chain having 1-3 carbon
atoms, being methyl, ethyl, n-propyl and isopropyl.

The term (C1-2)alkyl means a alkyl chain having 1-2 carbon atoms, being methyl and ethyl.

The term (C3-8)cycloalkyl means a cycloalkyl group having 3-8 carbon atoms, such as cyclopropyl, ethylcyclopropyl, cyclobutyl, methylcyclobutyl, cyclopentyl, cyclohexyl and bicyclo[2.2.1]heptyl.

The term (C3-6)cycloalkyl means a cycloalkyl group having 3-6 carbon atoms, such as cyclopropyl, ethylcyclopropyl, cyclobutyl, methylcyclobutyl, cyclopentyl, cyclohexyl and bicyclo[1.1.1]pentyl.

The term (C3-6)heterocycloalkyl means a heterocycloalkyl group having 3-6 carbon atoms and 1-2 heteroatoms selected from N, O and/or S, which is attached via carbon atom. Examples are oxetanyl, methyloxetanyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidiny, tetrahydrothiopyranyl and oxazepanyl.

The term (C2-6)alkenyl means a branched or unbranched alkenyl group having 2-6 carbon atoms, such as ethenyl, 2-propen-1-yl, 2-butenyl and n-pentenyl.

The term (C2-6)alkynyl means a branched or unbranched alkynyl group having 2-6 carbon atoms, such as ethynyl, 2-propyn-1-yl, 2-butylnyl and n-pentylnyl.

The term (C1-4)alkylcarbonyl means an alkylcarbonyl group, the alkyl group of which is a branched or unbranched alkyl group having 1-4 carbon atoms, as defined hereinabove, connected via a carbonyl group.

The term (C1-6)alkoxy means alkyloxy group, the alkyl group of which is a branched or unbranched alkyl group having 1-6 carbon atoms, as defined hereinabove, connected via the oxygen atom. Examples are methoxy, ethoxy, propoxy, isopropoxy and hexyloxy.

The term (C1-3)alkoxy means alkyloxy group, the alkyl group of which is a branched or unbranched alkyl group having 1-3 carbon atoms, as defined herein-

above, connected via the oxygen atom. Examples being methoxy, ethoxy, propoxy and isopropoxy.

The term (C1-3)alkylthio means alkylthio group, the alkyl group of which is a
5 branched or unbranched alkyl group having 1-3 carbon atoms, connected via the sulfur atom, being methylsulfanyl, ethylsulfanyl, propylsulfanyl and isopropylsulfanyl.

The term (C1-4)alkoxy(C2-4)alkyl as used herein means an alkyl group having 2-4
10 carbon atoms, to which an alkoxy group is attached, connected via the oxygen atom, with the alkoxy group having 1-4 carbon atoms. Examples are 2-methoxyethyl, 3-methoxypropyl, propoxymethyl and 2-ethoxyethyl.

The term (C1-2)alkoxy(C2-4)alkyl as used herein means an alkyl group having 2-4
15 carbon atoms, to which an alkoxy group is attached, connected via the oxygen atom, with the alkoxy group having 1-2 carbon atoms. Examples are 2-methoxyethyl, 3-methoxypropyl and 2-ethoxyethyl.

The term (C3-6)cycloalkyl(C1-3)alkyl as used herein means an alkyl group having
20 1-3 carbon atoms, to which a cycloalkyl substituent is attached having 3-6 carbon atoms. Examples are cyclopropylmethyl, cyclobutylethyl and methylcyclobutylmethyl.

The term (C3-6)heterocycloalkyl(C1-3)alkyl as used herein means an alkyl group
25 having 1-3 carbon atoms, to which a (C3-6)heterocycloalkyl substituent is attached with the same meaning as previously defined. Examples are oxetanylmethyl, tetrahydrofuranylmethyl, tetrahydropyranylethyl and N-methylazetidinylmethyl.

30 The term halogen means fluorine, chlorine, bromine and iodine, in particular fluorine and chlorine, more in particular fluorine.

Depending on the nature of the scaffold or the substituents on the structures in Formula 1 or in other Formulae described hereinbelow, the compounds of this invention can exist as a racemic mixture of enantiomers, containing substantially equal amounts of the two enantiomers, as mixtures of enantiomers in any 5 proportions or as the pure enantiomers. The present invention includes the aforementioned mixtures and racemic mixtures within its scope and each of the individual (+) and (-) enantiomers substantially free of the other enantiomer, *i.e.* an enantiomer associated with less than 5%, preferably less than 2%, in particular less than 1% of the other enantiomer.

10

Depending on the nature of the scaffold or the substituents on the structures in Formulae 1 or in other Formulae described hereinbelow, the compounds of this invention can exist as a mixture of diastereomers. The present invention includes the aforementioned mixture of diastereomers within its scope and each of the 15 individual diastereomers substantially free of another diastereomer, *i.e.* a diastereomer associated with more than 95%, preferably more than 98%, in particular more than 99% diastereomeric excess.

A prodrug is defined as being a compound which is converted in the body of a 20 recipient to a compound as defined by Formula 1 or by other Formulae described hereinbelow. Notably, a phenolic hydroxyl group at the A-ring of the skeleton of Formula 1 can for example be substituted by an alkyl, alkenyl, acyl, aroyl, alkoxy-carbonyl, alkylsulfonyl, arylsulfonyl, alkylsulfamate, arylsulfamate, phosphate group or glycosyl group, whereby the carbon chain length is not considered to be 25 sharply delimited, while aroyl and aryl generally will comprise a phenyl, pyridinyl or pyrimidinyl, which groups can have substitutions customary in the art, such as alkyl, hydroxy, halogen, nitro, cyano, and (mono-, or dialkyl)amino groups. The carbon chain length is selected depending on the desired properties of the prodrugs, whereby the longer chained prodrugs with for example lauryl or caproyl 30 chains generally are more suitable for sustained release and depot preparations. It is known that such substituents spontaneously hydrolyze or are enzymatically hydrolyzed to the free hydroxyl substituents on the skeleton of the compound. Such prodrugs will have biological activity comparable to the compounds to which

they are converted in the body of the recipients. The active compound to which a prodrug is converted is called the parent compound. The onset of action and duration of action as well as the distribution in the body of a prodrug may differ from such properties of the parent compound. Also the resulting plasma
5 concentration of the parent compound after administration of the prodrug may differ from the resulting plasma concentration after direct administration of the parent compound. For other types of prodrugs it should be realized that the hydroxyl group(s) in compounds according to Formula 1 can be placed in position by the metabolic system of the recipient. The hydroxyl group(s) contribute(s)
10 significantly to the affinity for the estrogen receptor. Thus, compounds as defined by Formula 1, but lacking phenolic hydroxyl group(s) in the SERMF moiety are also made available as compounds according to this invention, and which compounds are referred to as prodrugs.

15 In one embodiment of the present invention, a phenolic hydroxyl group attached to the SERMF fragment of Formula 1 or of other Formulae described hereinbelow, is substituted with a (C1-8)alkyl or a (C1-18)acyl group, e.g. methyl, ethyl, tert.-butyl, n-octyl, acyl, octanoyl, dodecanoyl and octadecanoyl. In another embodiment, the hydroxyl group is substituted with a (C1-C4)alkyl or a (C1-C8)acyl group, e.g.
20 methyl, ethyl, tert.-butyl, acyl and octanoyl.

Prodrugs of N-substituted azetidine derivatives of Formula 1 or of other Formulae described hereinbelow, may be prepared to increase their aqueous solubility in order to facilitate pharmaceutical formulation and/or to improve bioavailability
25 following various routes of administration (e.g. intestinal absorption after oral administration). Such solubilizing prodrugs are well known to those of skill in the art. Representative examples of this approach can be found in V.J. Stella and W.N.-A. Kwame, *Advanced Drug Delivery Reviews*, 59 (2007) 677-694.

30 The present invention also embraces isotopically-labelled derivatives of any of the compounds according to Formula 1 or to other Formulae described hereinbelow, which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from

the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the present invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine and iodine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , ^{36}Cl and ^{123}I ,
5 respectively.

Certain isotopically-labelled derivatives of the compounds of Formula 1 (e.g. those labelled with ^3H and ^{14}C) or of other Formulae described hereinbelow, are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e. ^3H) and
10 carbon-14 (i.e. ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Certain isotopically-labelled compounds of Formula 1 or of other Formulae described hereinbelow, can be useful for medical imaging purposes. E.g., those labelled with positron-emitting isotopes like ^{11}C or ^{18}F can be useful for application in Positron Emission Tomography (PET) and those labelled with
15 gamma ray emitting isotopes like ^{123}I can be useful for application in Single Photon Emission Computed Tomography (SPECT). Further, substitution with heavier isotopes such as deuterium (i.e. ^2H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g. increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances.
20 Isotopically-labelled compounds of Formula 1 or of other Formulae described hereinbelow, in particular those containing isotopes with longer half lives ($T_{1/2} > 1$ day), can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples hereinbelow, by substituting an appropriate isotopically-labelled reagent for a non-isotopically labelled reagent.

25

Pharmaceutically acceptable salts are well known in the art. They may be obtained during the final isolation and purification of the compounds of the present invention, or separately by reacting the free base function with an organic acid such as for example ascorbic acid, citric acid, tartaric acid, lactic acid, maleic acid
30 or suitable mineral acids such as hydrochloric acid, phosphoric acid, or sulfuric acid, or with malonic acid, fumaric acid, glycolic acid, succinic acid, propionic acid, acetic acid, methanesulfonic acid, and the like. Alternatively, the acid function of any of the compounds of the present invention can be reacted with an organic or a

mineral base, like sodium hydroxide, potassium hydroxide or lithium hydroxide to give a pharmaceutically acceptable salt.

The N-substituted azetidine derivatives of the present invention are ER α antagonists. In certain embodiments, the compounds of the present invention are specifically useful for treating ER-positive breast cancer i.e. demonstrate very low efficacy in stimulating proliferation of ER-positive, tamoxifen-resistant breast cancer cells, are capable of inducing ER downregulation in ER-positive breast cancer cells, are orally bioavailable and can be dosed to a level sufficient to achieve good bioavailability and/or target exposure and optimal efficacy.

In the context of the present invention with SERM (Selective Estrogen Receptor Modulator) is meant a synthetic compound that binds to ER α and exerts estrogenic or anti-estrogenic activities in a tissue- or cell-specific manner. Typically, SERMs are compounds that in an *in vitro* bioassay with recombinant Chinese Hamster Ovary (CHO) cells stably co-transfected with the human estrogen receptor α (hER α), the rat oxytocin promoter (RO) and the luciferase reporter gene (LUC) as described in Example 11 hereinbelow, inhibit 17 β -estradiol-induced transactivation with a pIC₅₀ >6 and a minimum antagonistic efficacy of 0.80 relative to the anti-estrogen ICI 164,384 and, using the same bioassay, demonstrate a maximal agonistic efficacy of 0.20.

Also, SERMs are capable of stimulating proliferation in ER-positive, tamoxifen-resistant MCF-7H breast cancer cells as described in Example 12 hereinbelow, with a pEC₅₀ >7 and an efficacy >0.10.

25

In the context of the present invention with SERD (Selective Estrogen Receptor Downregulator) is meant a synthetic compound that binds to the ER α , is capable of destabilizing or downregulating ER α and primarily exerts anti-estrogenic activities in tissues or cells. Typically, SERDs are compounds that in an *in vitro* bioassay with recombinant CHO cells stably co-transfected with hER α , the rat oxytocin promoter (RO) and the luciferase reporter gene (LUC) as described in Example 11 hereinbelow, inhibit 17 β -estradiol-induced transactivation with a pIC₅₀ >6 and a minimum antagonistic efficacy of 0.80, and, using the same bioassay,

demonstrate a maximal agonistic efficacy of 0.20. Also, SERDs generally do not stimulate proliferation in ER-positive, tamoxifen-resistant MCF-7H breast cancer cells as described in Example 12 hereinbelow, and will therefore show an efficacy equal to or <0.10 . Additionally, SERDs show a minimum of 20% downregulation of ER α in a bioassay in T47D cells as described in Example 13 hereinbelow.

In one embodiment, the invention relates to compounds of Formula 1 wherein X is O, S or NR⁵. In another embodiment, X is O or S. In yet another embodiment, X is O.

10

In another embodiment, the invention relates to compounds of Formula 1 wherein R¹⁷, R¹⁸ and R¹⁹ are H, fluorine or (C₁₋₃)alkyl. In another embodiment, R¹⁷, R¹⁸ and R¹⁹ are H, fluorine or methyl. In yet another embodiment, R¹⁷, R¹⁸ and R¹⁹ are H.

15

In one embodiment, the invention relates to compounds of Formula 1 wherein R¹ is (C₁₋₄)alkyl, (C₃₋₆)cycloalkyl, (C₃₋₆)heterocycloalkyl, (C₂₋₆)alkenyl, (C₁₋₂)alkoxy(C₂₋₄)alkyl, (C₃₋₆)cycloalkyl(C₁₋₃)alkyl, (C₃₋₆)heterocycloalkyl(C₁₋₃)alkyl, each independently optionally substituted with one or more fluorine.

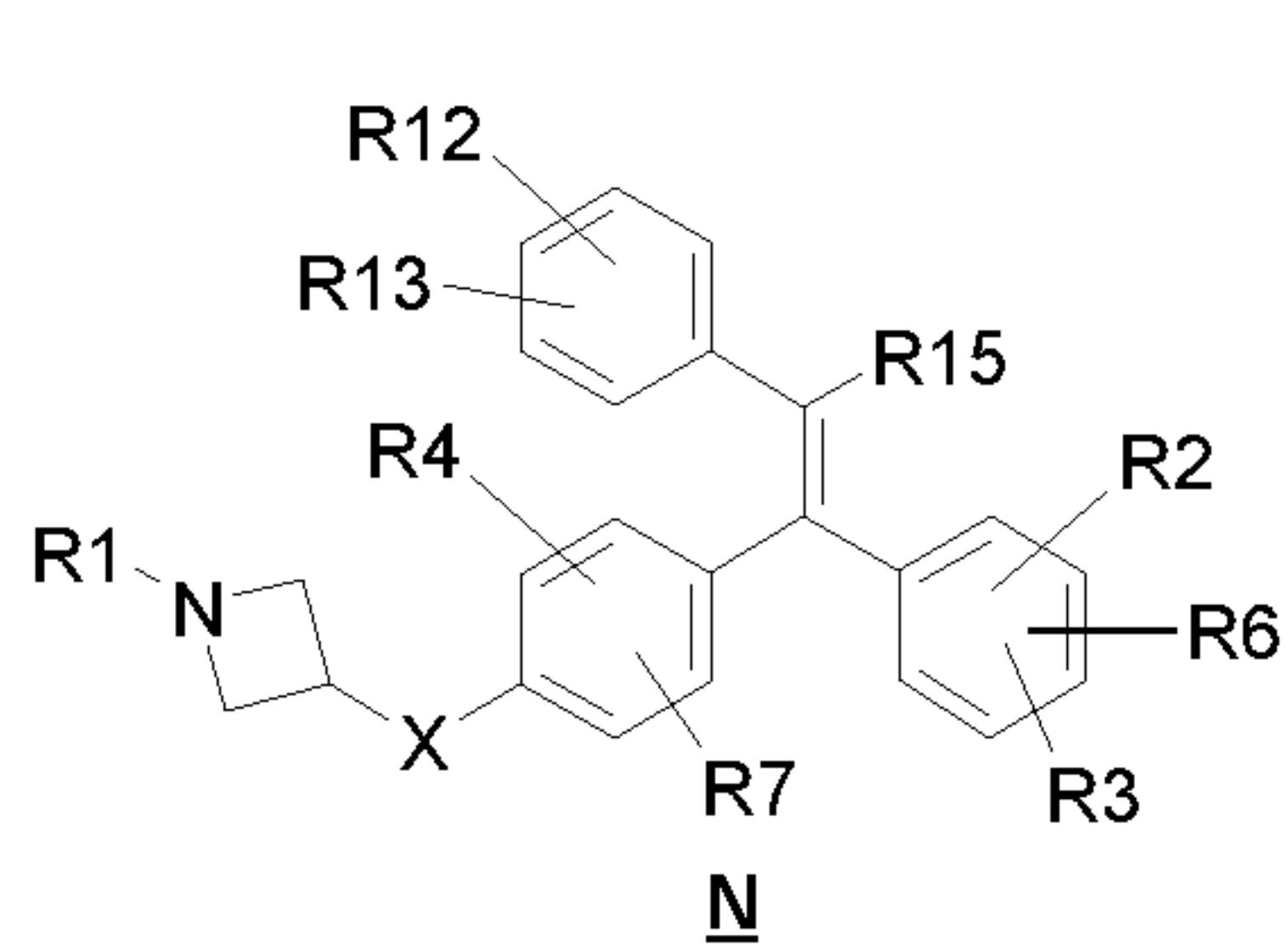
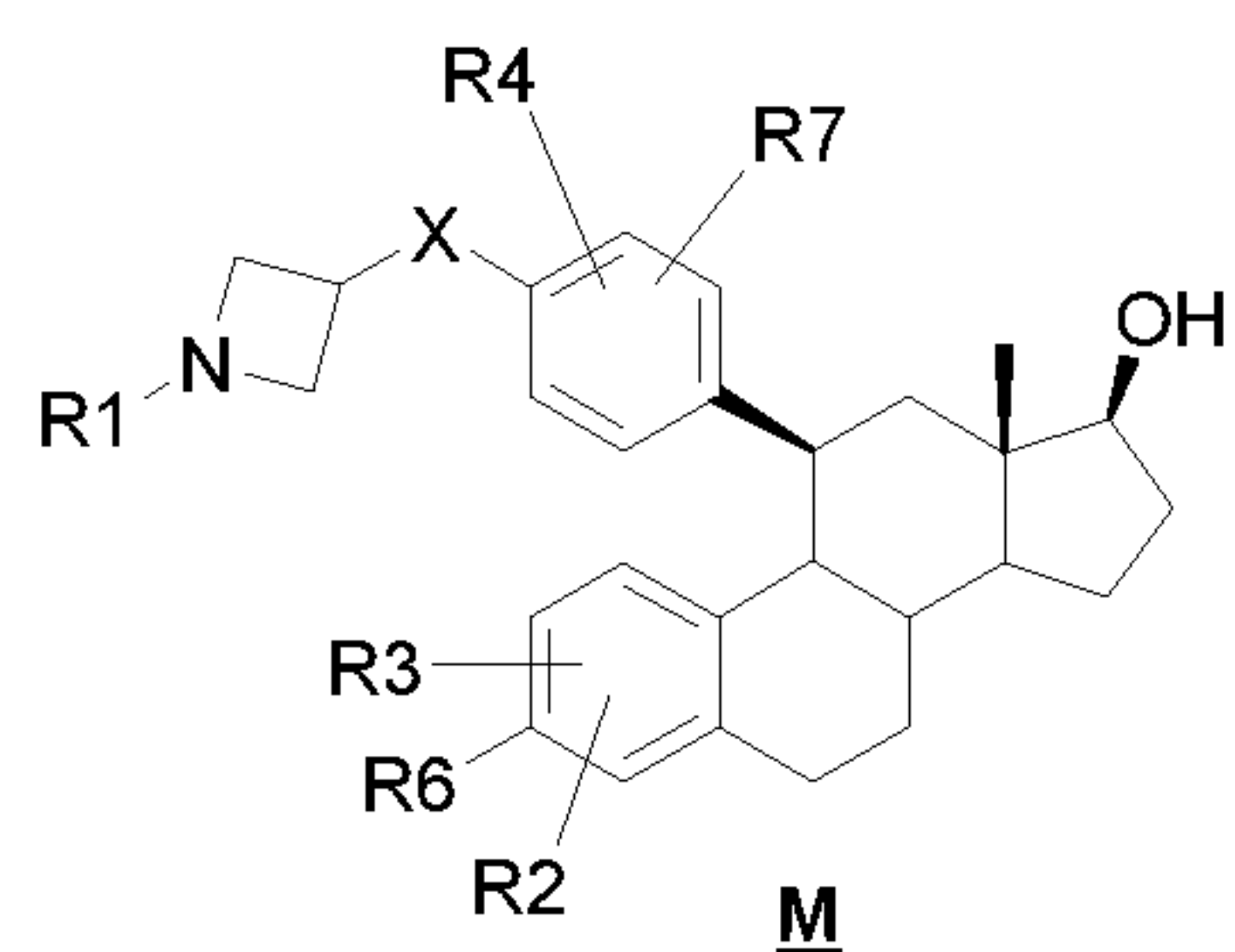
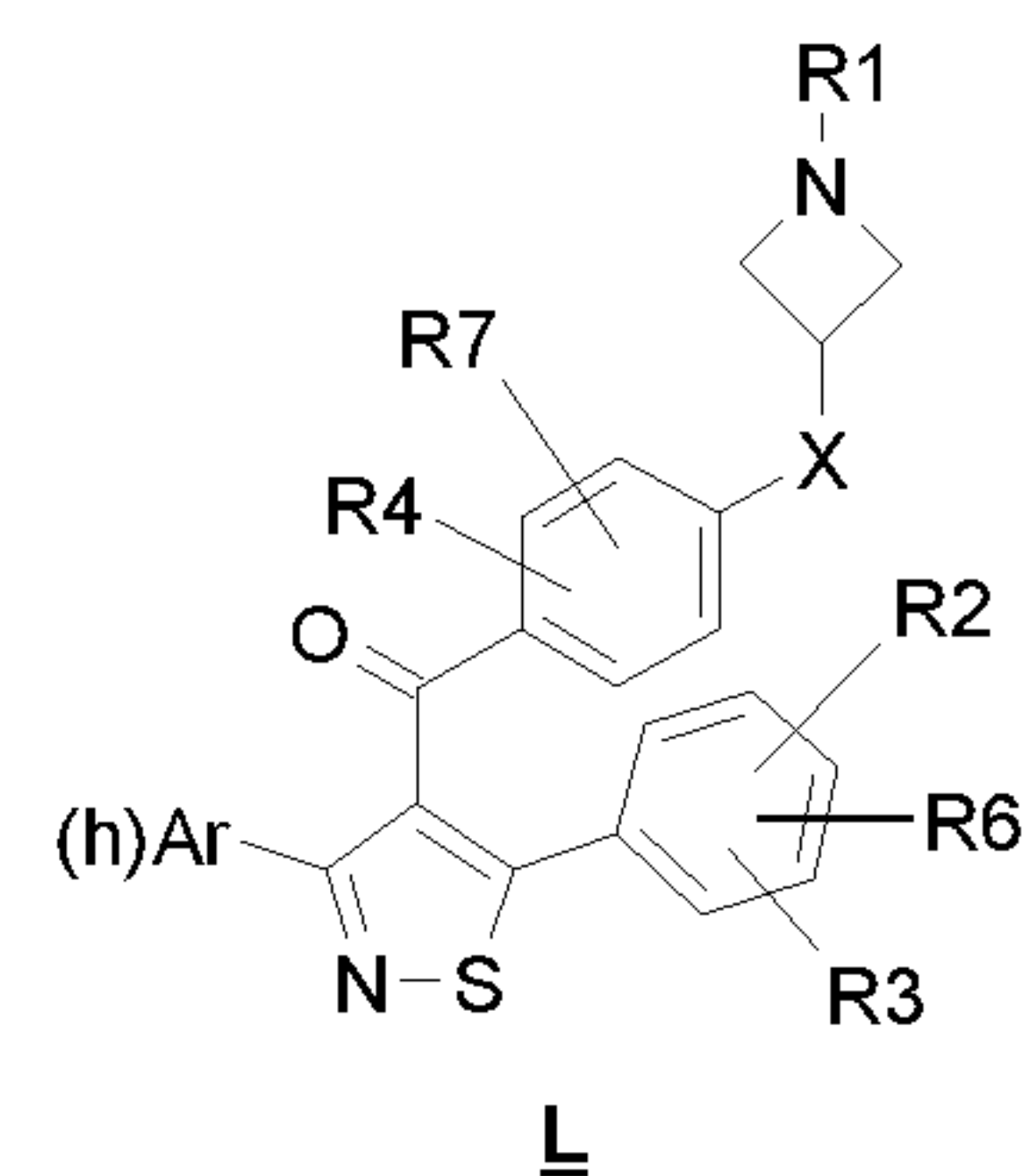
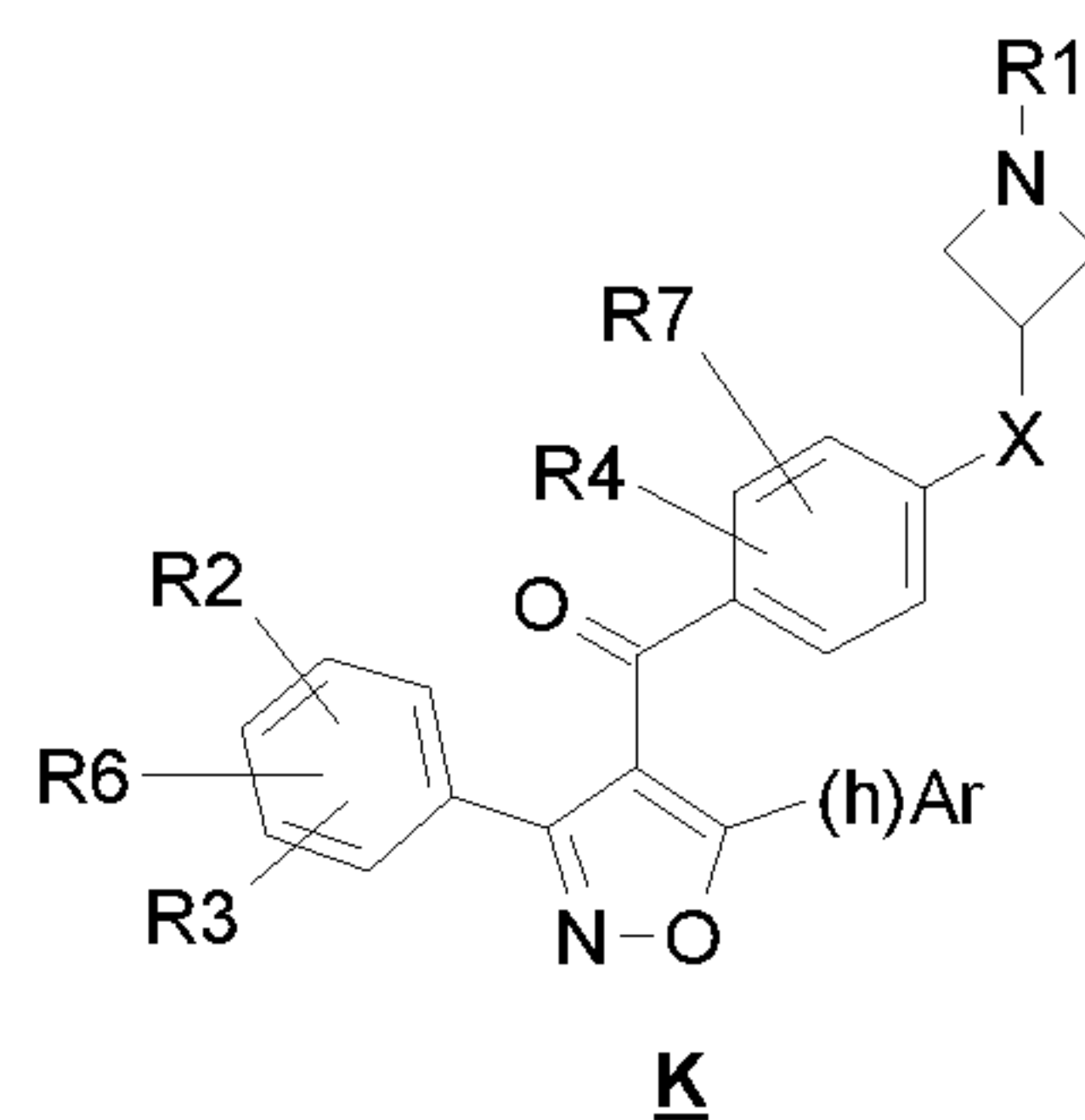
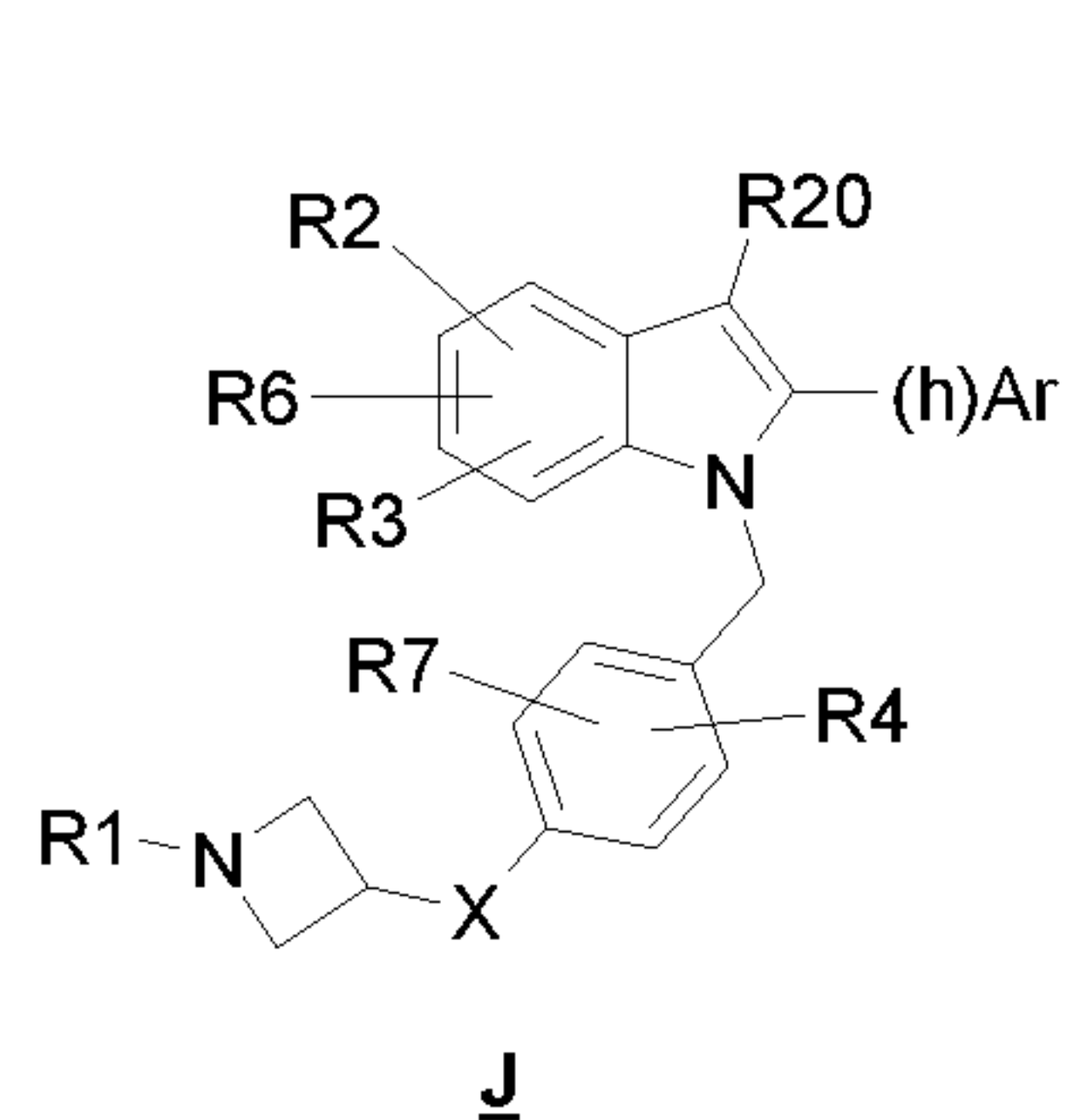
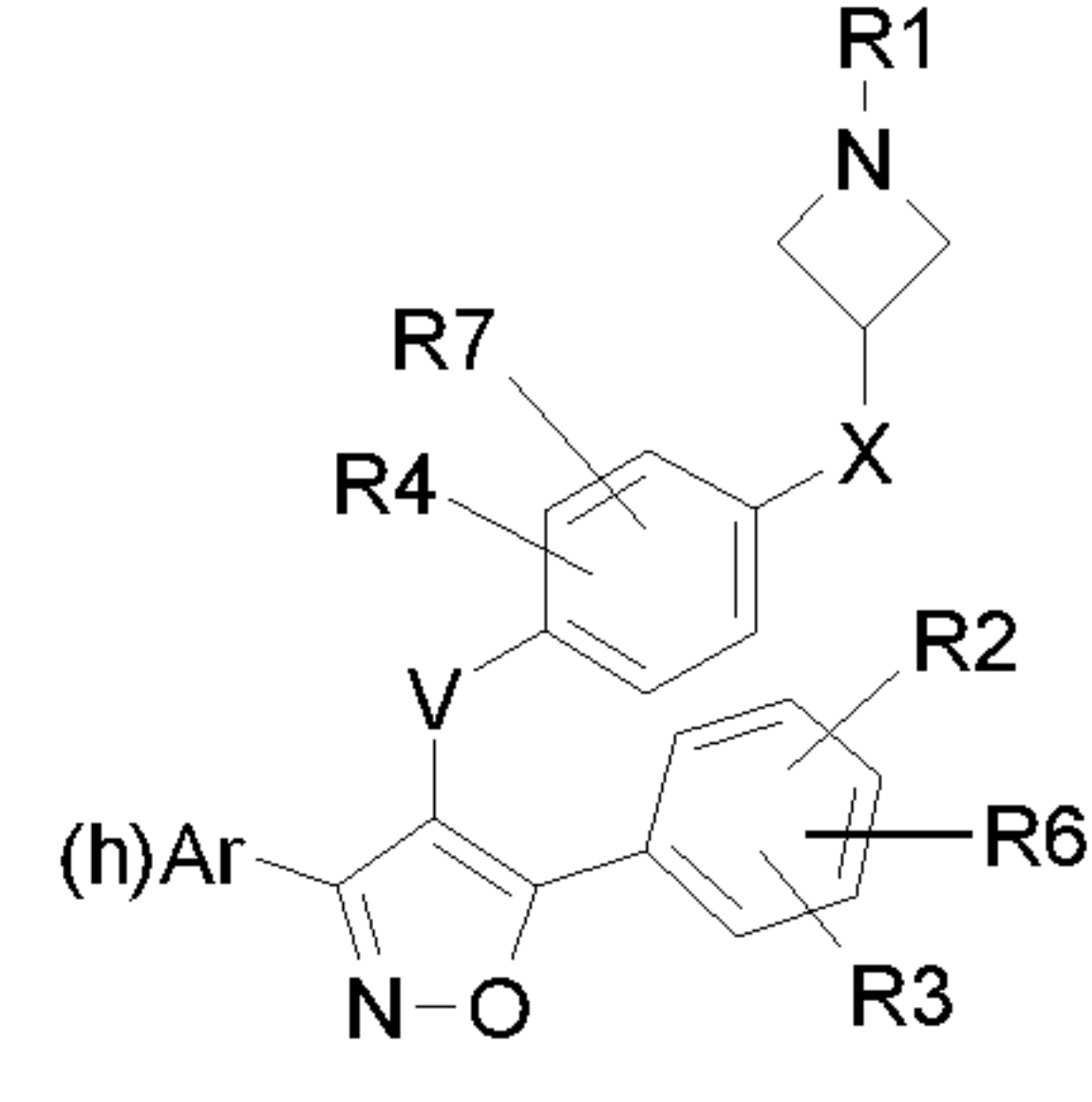
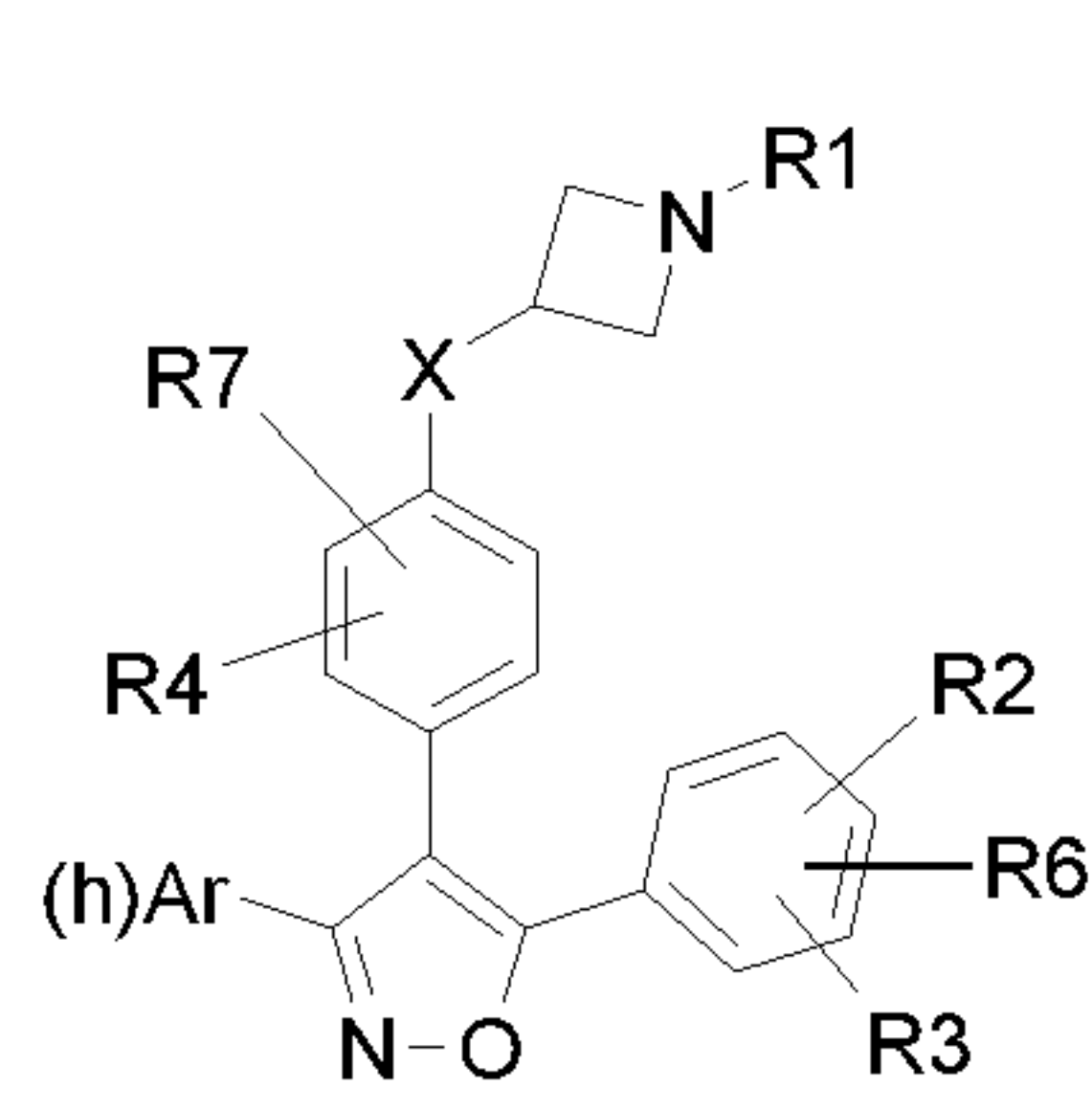
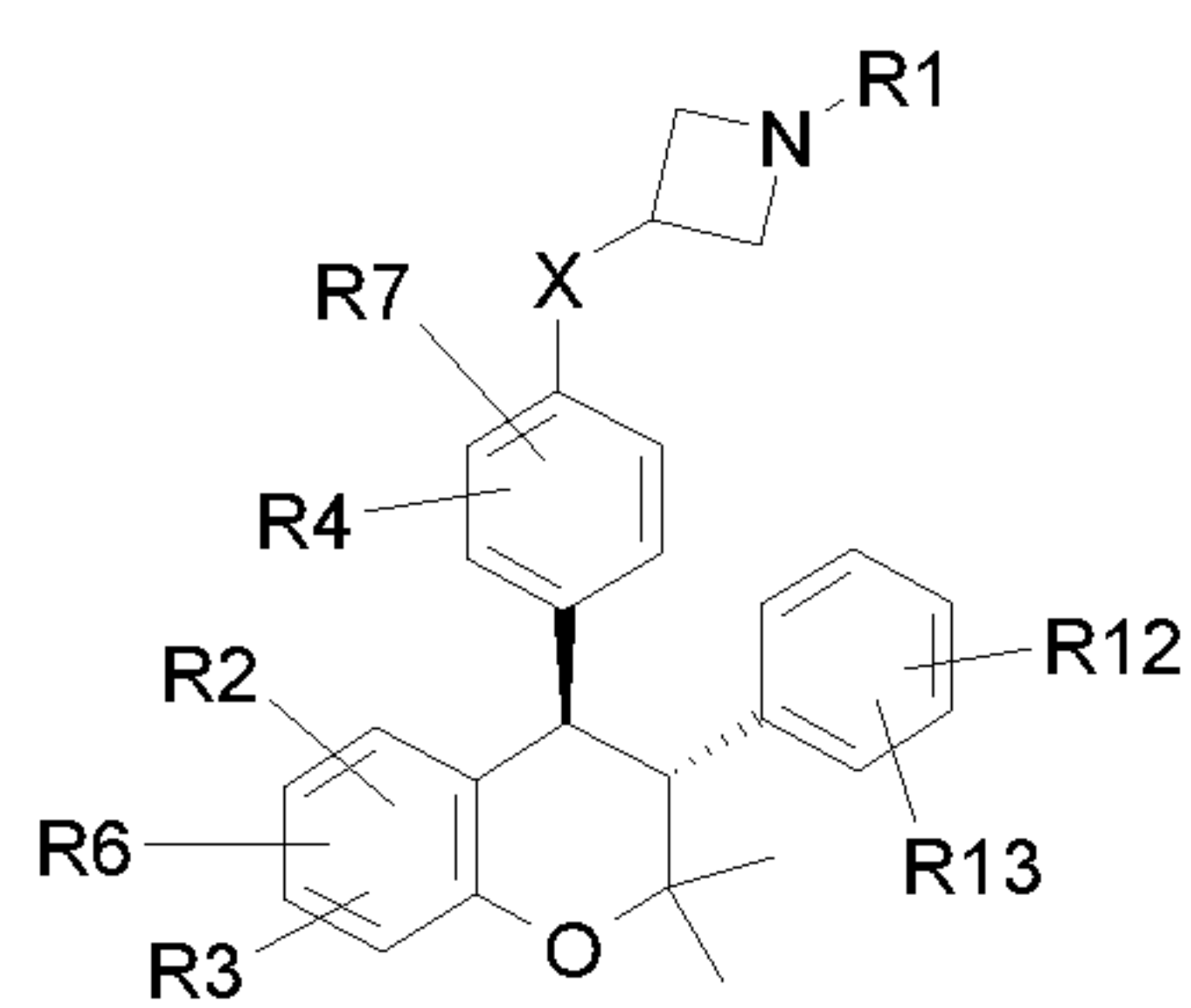
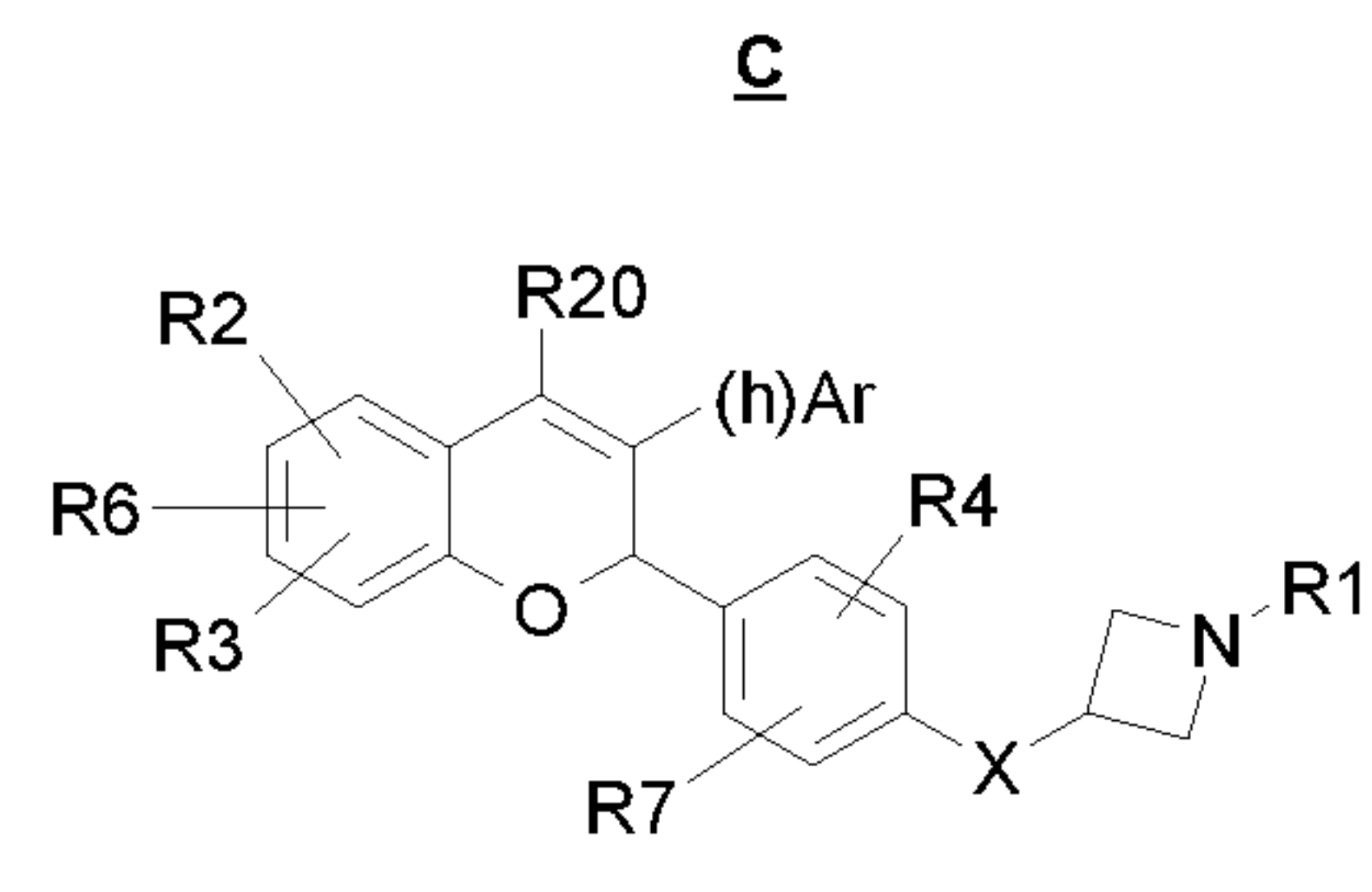
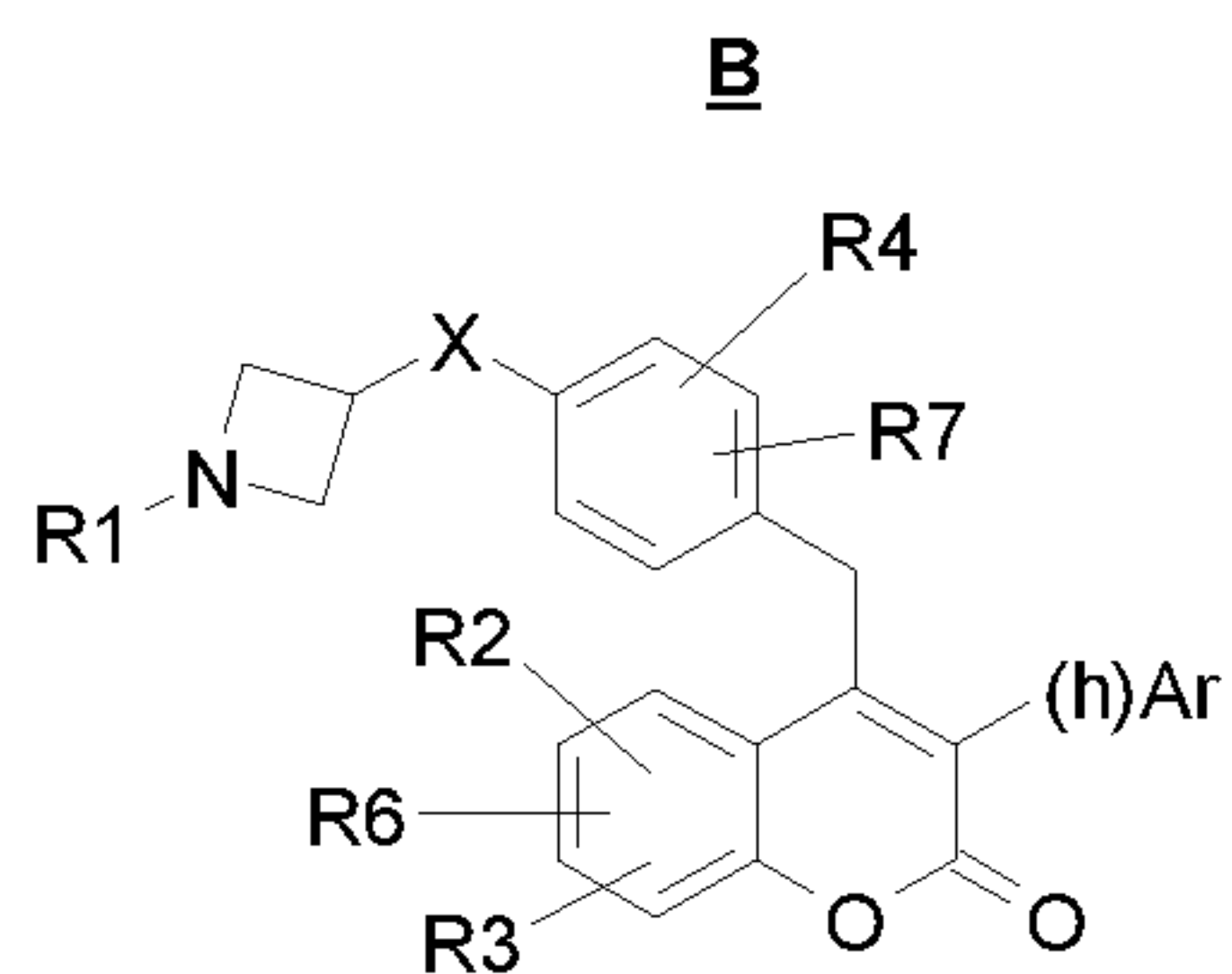
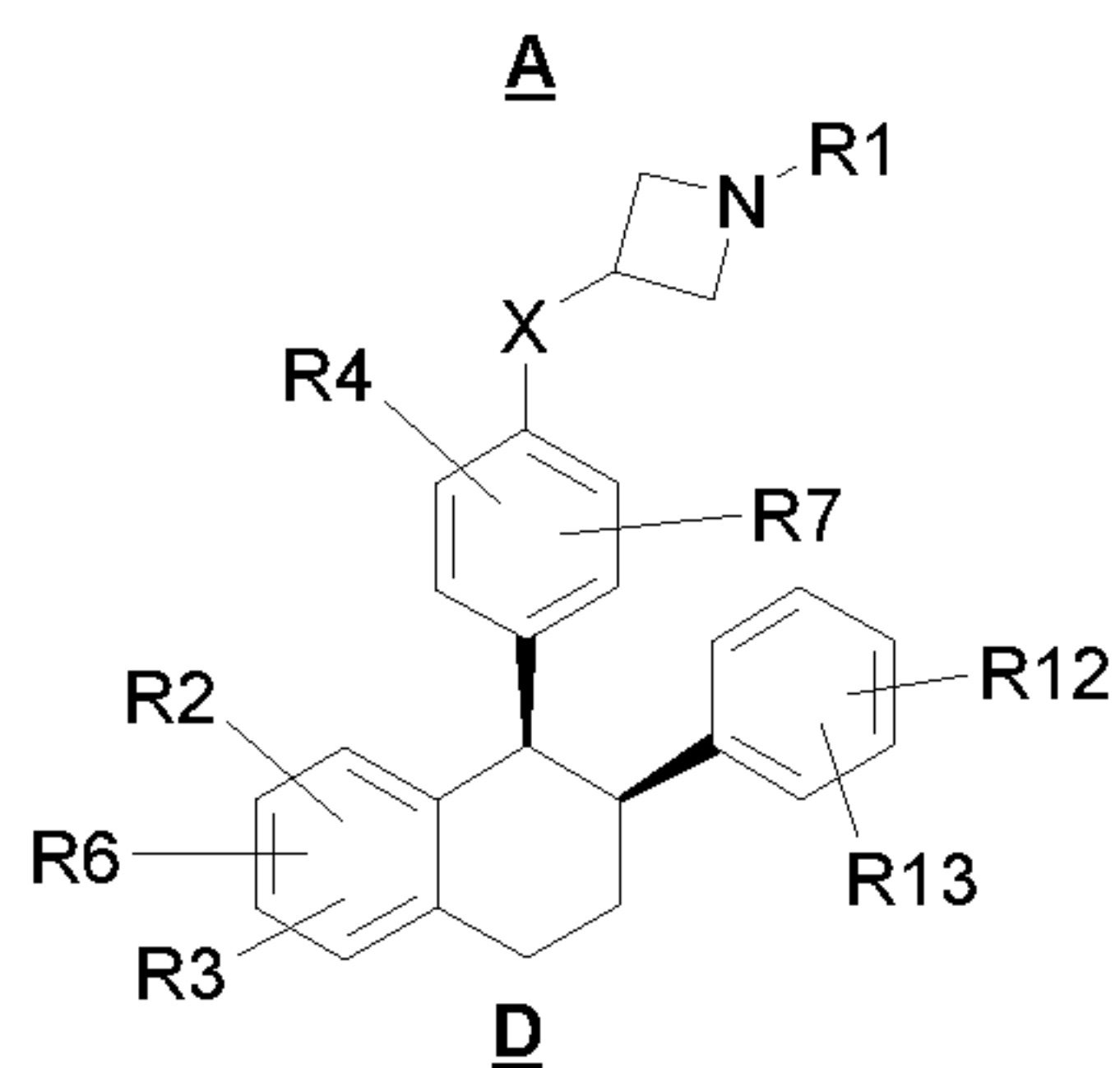
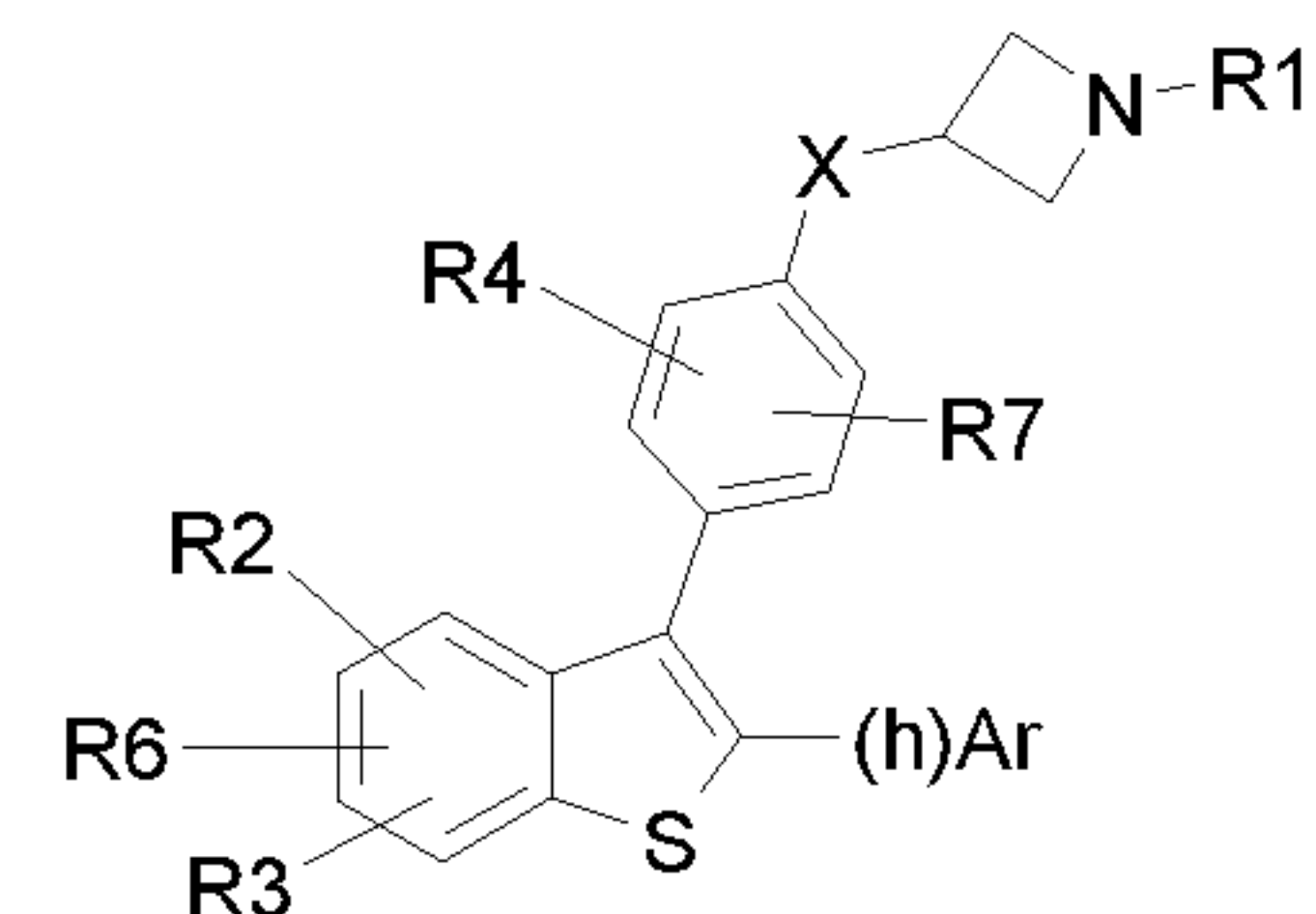
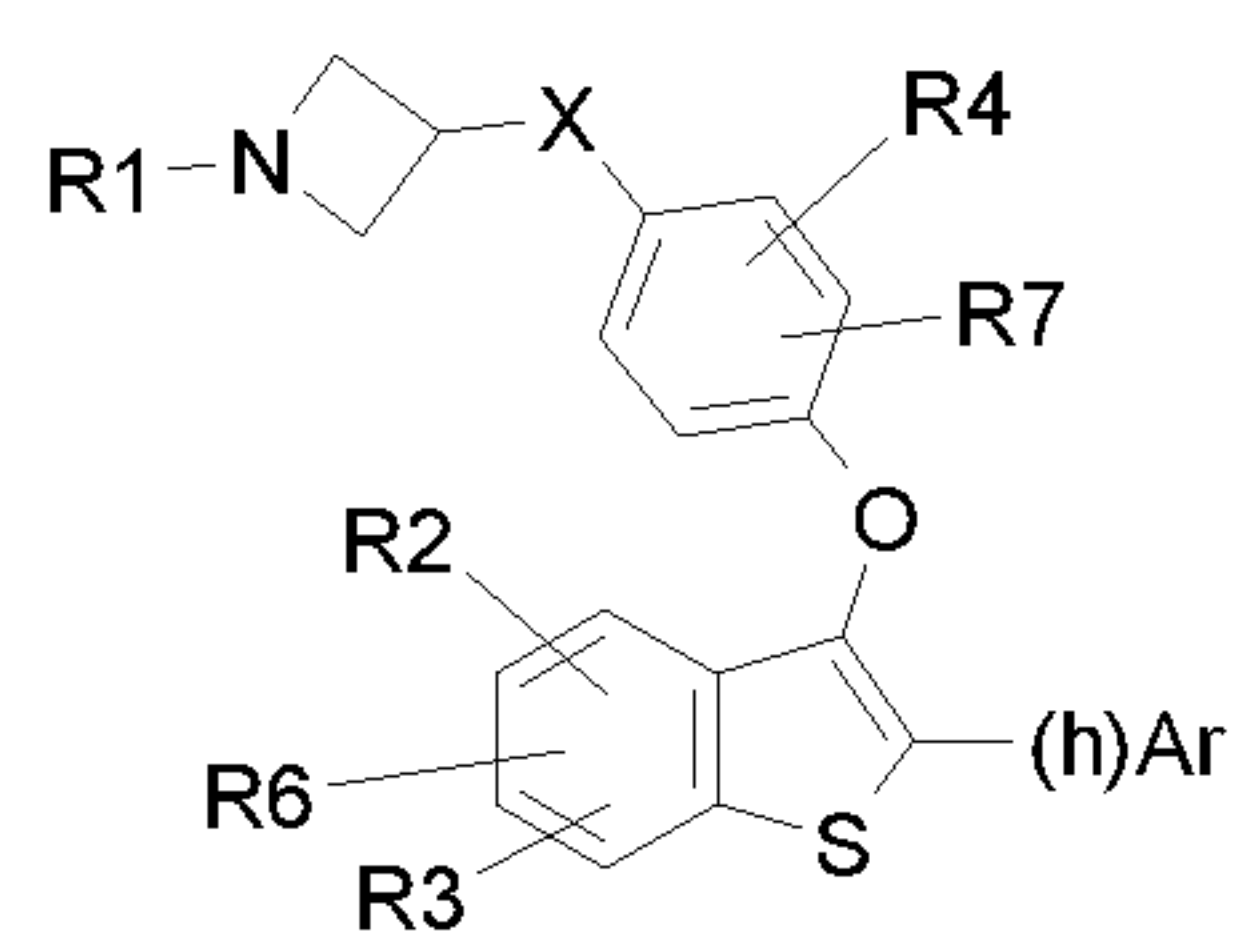
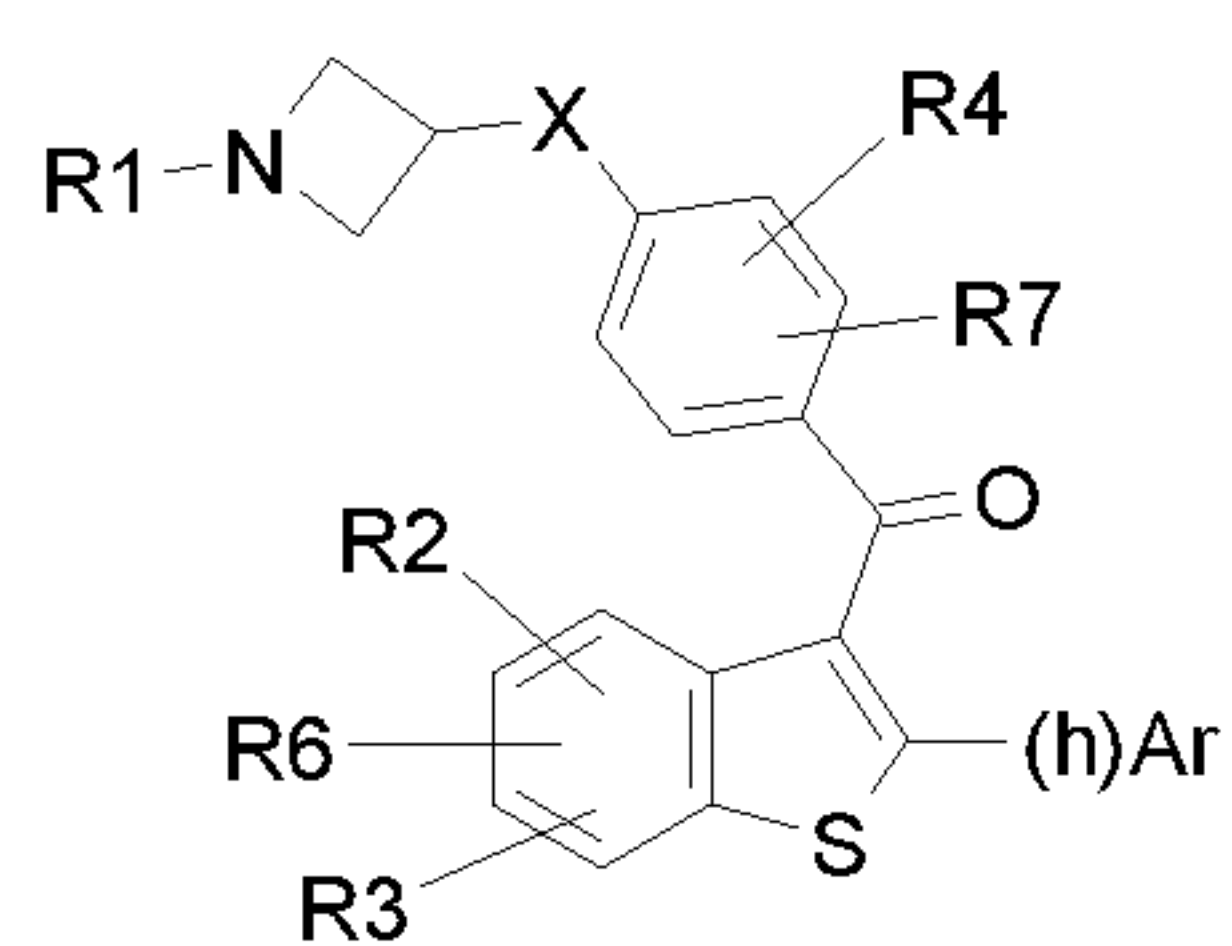
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In another embodiment, R¹ is (C₁₋₄)alkyl, (C₃₋₆)cycloalkyl, (C₃₋₆)heterocycloalkyl, (C₂₋₆)alkenyl, (C₁₋₂)alkoxy(C₂₋₄)alkyl, (C₃₋₆)cycloalkyl(C₁₋₃)alkyl, each independently optionally substituted with one or more fluorine.

25 In another embodiment of the present invention, R¹ is methyl, ethyl, n-propyl, isobutyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclopropylmethyl, cyclobutylmethyl, (3-tetrahydrofuranyl)methyl, 3-methoxypropyl, 3,3,3-trifluoropropyl, 3-fluoropropyl or 2-propenyl.

30 In one embodiment of the present invention, the N-substituted azetidine derivative is selected from the group consisting of compounds according to any one of Formulae 3A to 3BF

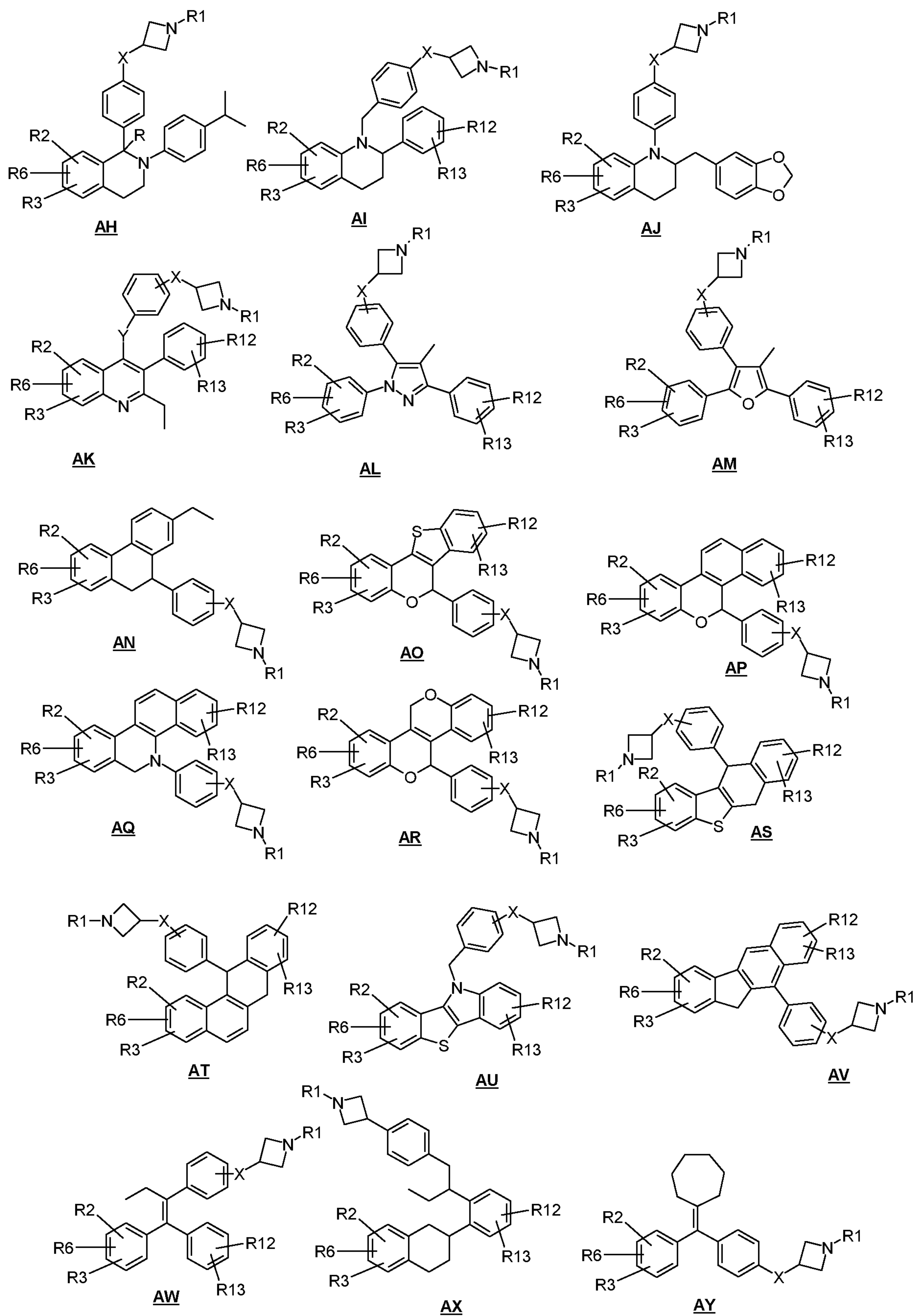
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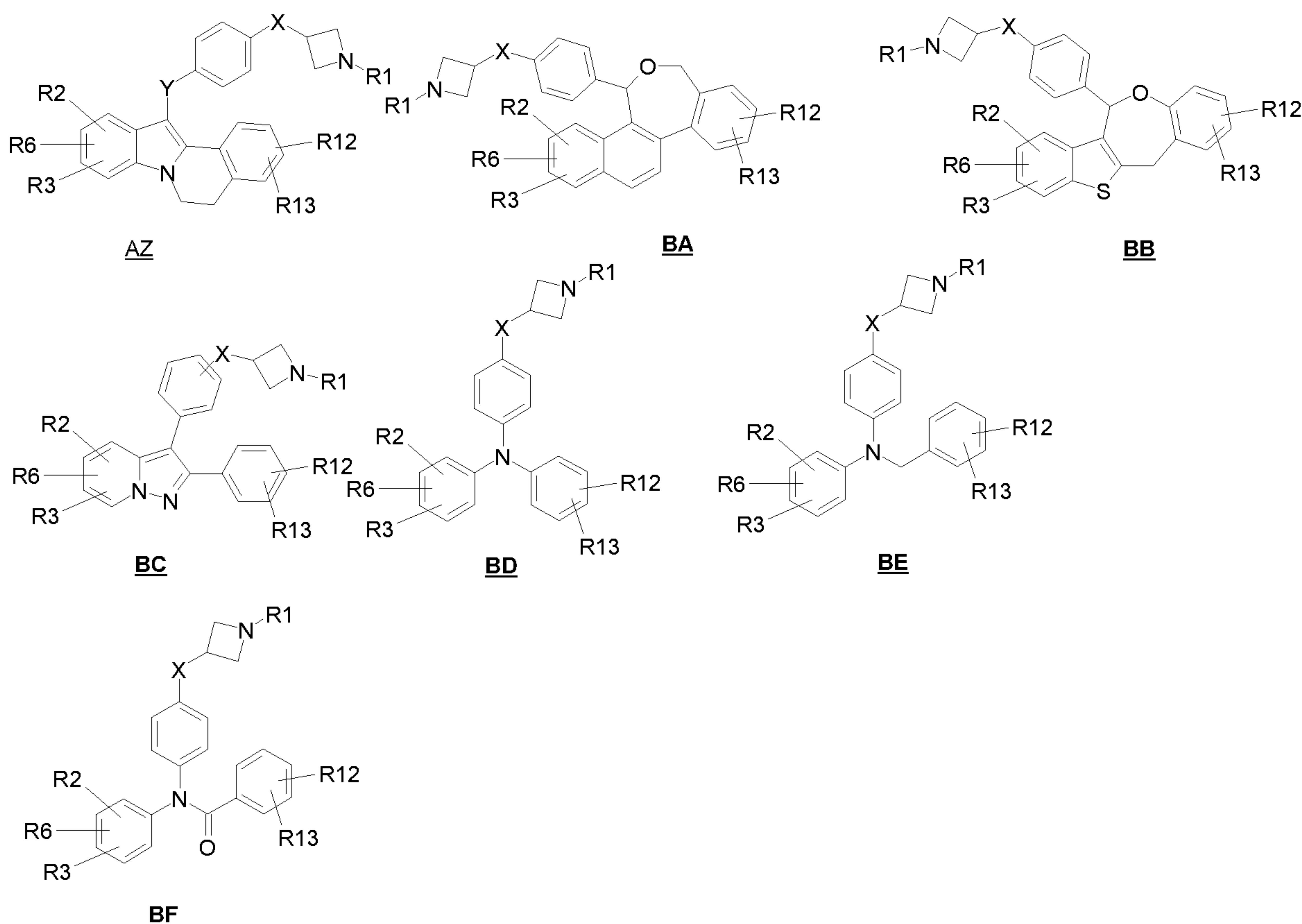


Formulae 3

AG

15





Formulae 3

wherein

- 5 R₁ is (C1-8)alkyl, (C3-8)cycloalkyl, (C3-6)heterocycloalkyl, (C2-6)alkenyl, (C2-6)-alkynyl, (C1-4)alkylcarbonyl, (C1-4)alkoxy(C2-4)alkyl, (C3-6)cycloalkyl(C1-3)alkyl, (C3-6)heterocycloalkyl(C1-3)alkyl, each independently optionally substituted with one or more halogen, nitrile, hydroxyl or (C1-2)alkyl;
X is no atom, O, S, CH₂, carbonyl, N-R₅;
- 10 (h)Ar is a (hetero)aromatic ring, optionally substituted with R₁₂ and R₁₃;
R₂ and R₃ are independently of each other H, fluorine, chlorine, (C1-3)alkyl, (C1-3)alkoxy, (C1-3)alkylthio, CF₃ or nitrile;
R₄ and R₇ are independently of each other H, fluorine, chlorine, (C1-2)alkyl, CF₃ or nitrile;
- 15 R₁₂ is H, fluorine, chlorine, (C1-2)alkyl, (C1-2)alkoxy, nitrile or hydroxyl;
R₁₃ is H, fluorine, chlorine, (C1-3)alkyl, (C1-3)alkoxy, (C1-3)alkylthio, CF₃ or nitrile;
R₆ is H, hydroxyl, amine or (C1-6)alkoxy;

R6 and R2 may be linked to form a (hetero)aromatic ring which is optionally substituted with fluorine, chlorine or (C1-3)alkyl;

R5 is H, (C1-3)alkyl, optionally substituted with one or more fluorine;

V is O, S, CH₂, CHOH, CH(C1-3)alkoxy, C=CH₂, carbonyl, N-R16;

5 R15 is H, halogen, nitro, nitrile or (C1-6)alkyl, optionally substituted with one or more halogen;

R16 is H, (C1-4)alkyl, (C1-4)alkenyl, optionally substituted with one or more halogen;

R20 is (C1-3)alkyl, optionally substituted with one or more fluorine.

10

In another embodiment of the present invention, the N-substituted azetidine derivative is selected from the group consisting of compounds according to any one of Formulae 4A to 4N and 4Z, shown hereinbelow,

15 wherein

R1 is (C1-8)alkyl, (C3-8)cycloalkyl, (C3-6)heterocycloalkyl, (C2-6)alkenyl, (C2-6)-alkynyl, (C1-4)alkylcarbonyl, (C1-4)alkoxy(C2-4)alkyl, (C3-6)cycloalkyl(C1-3)alkyl, (C3-6)heterocycloalkyl(C1-3)alkyl, each independently optionally substituted with one or more halogen, nitrile, hydroxyl or (C1-2)alkyl;

20 X is no atom, O, S, CH₂, carbonyl, N-R5;

(h)Ar is a (hetero)aromatic ring, optionally substituted with R12 and R13;

R2 and R3 are independently of each other H, fluorine, chlorine, (C1-3)alkyl, (C1-3)alkoxy, (C1-3)alkylthio, CF₃ or nitrile;

25 R4 and R7 are independently of each other H, fluorine, chlorine, (C1-2)alkyl, CF₃ or nitrile;

R12 is H, fluorine, chlorine, (C1-2)alkyl, (C1-2)alkoxy, nitrile or hydroxyl;

R13 is H, fluorine, chlorine, (C1-3)alkyl, (C1-3)alkoxy, (C1-3)alkylthio, CF₃ or nitrile;

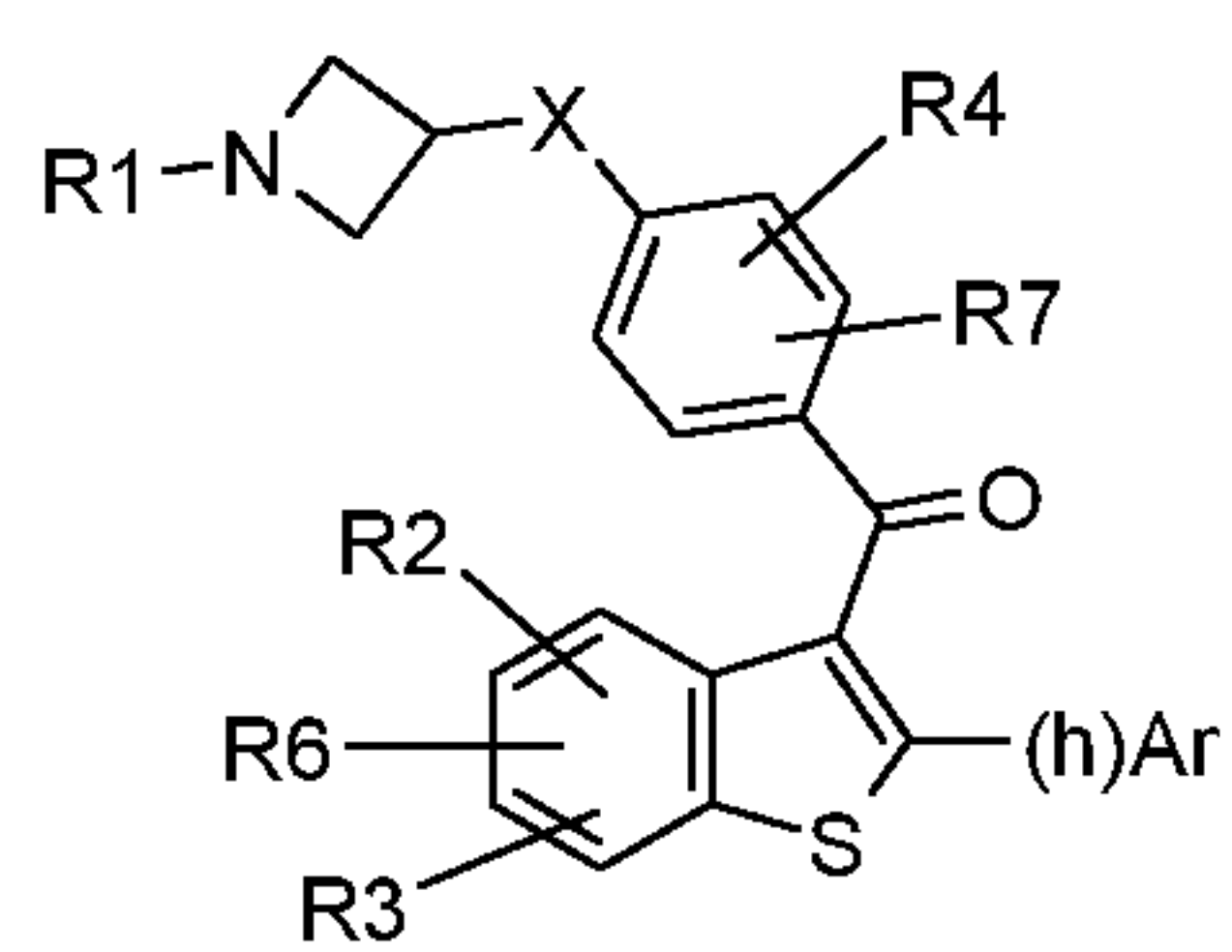
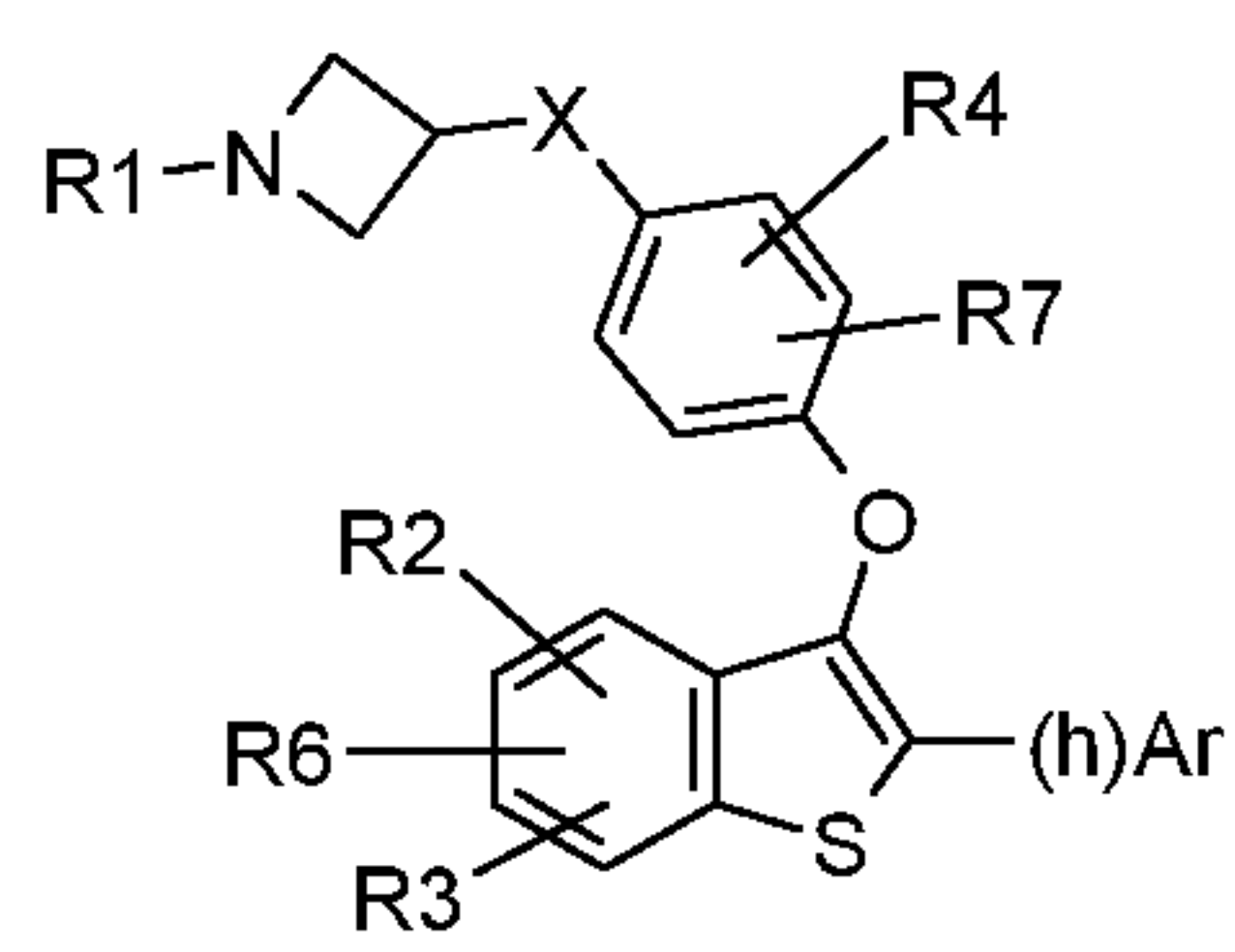
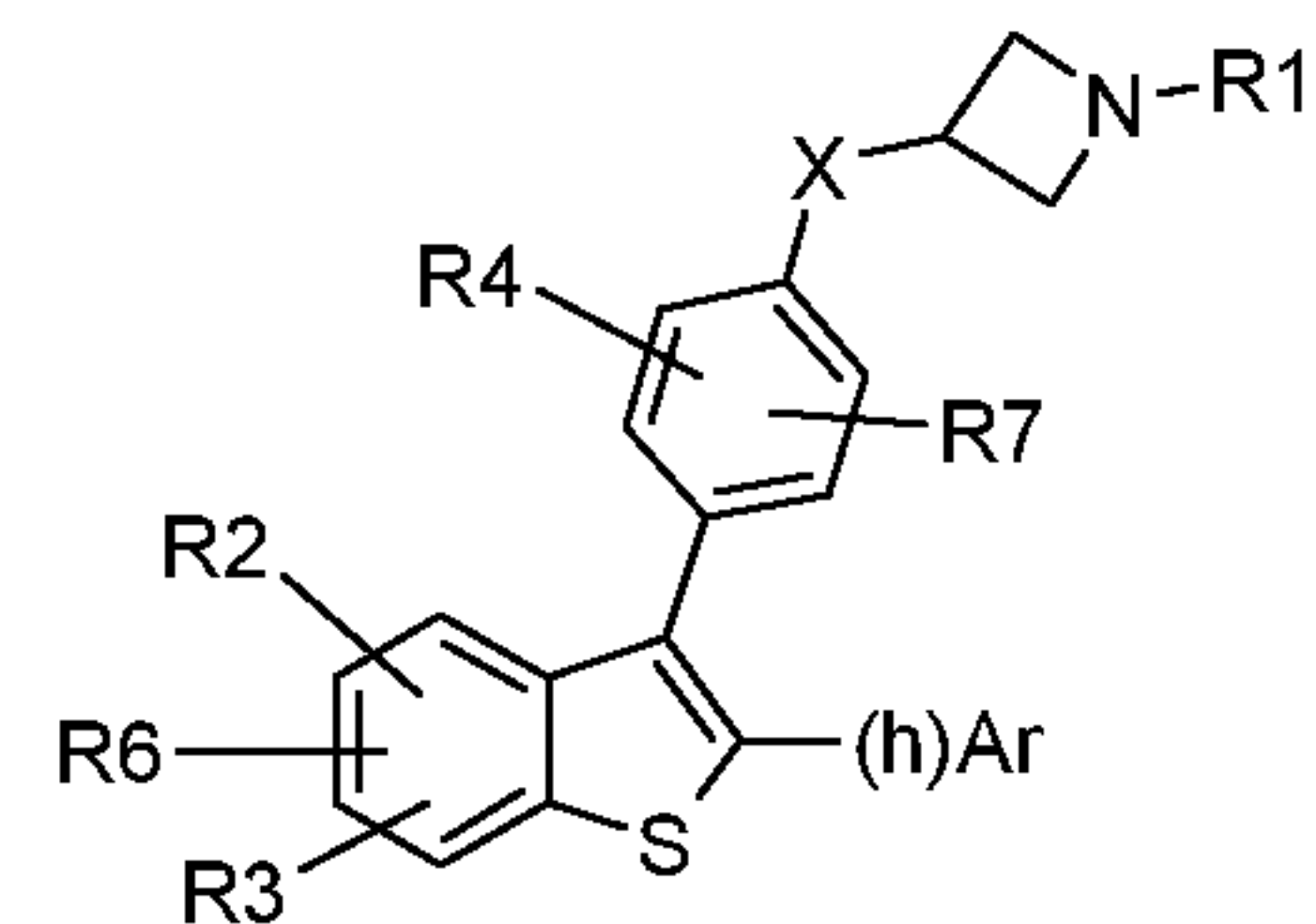
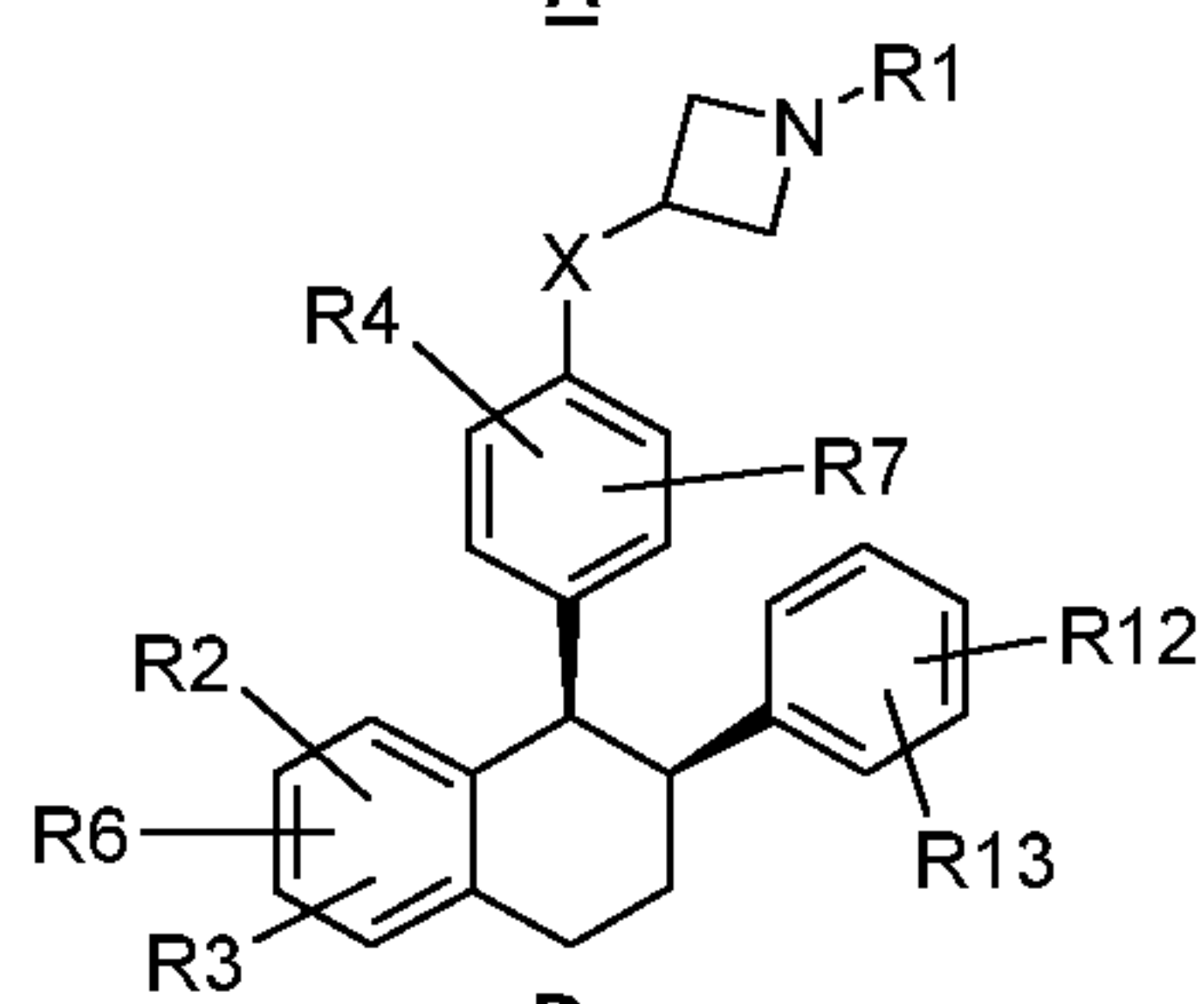
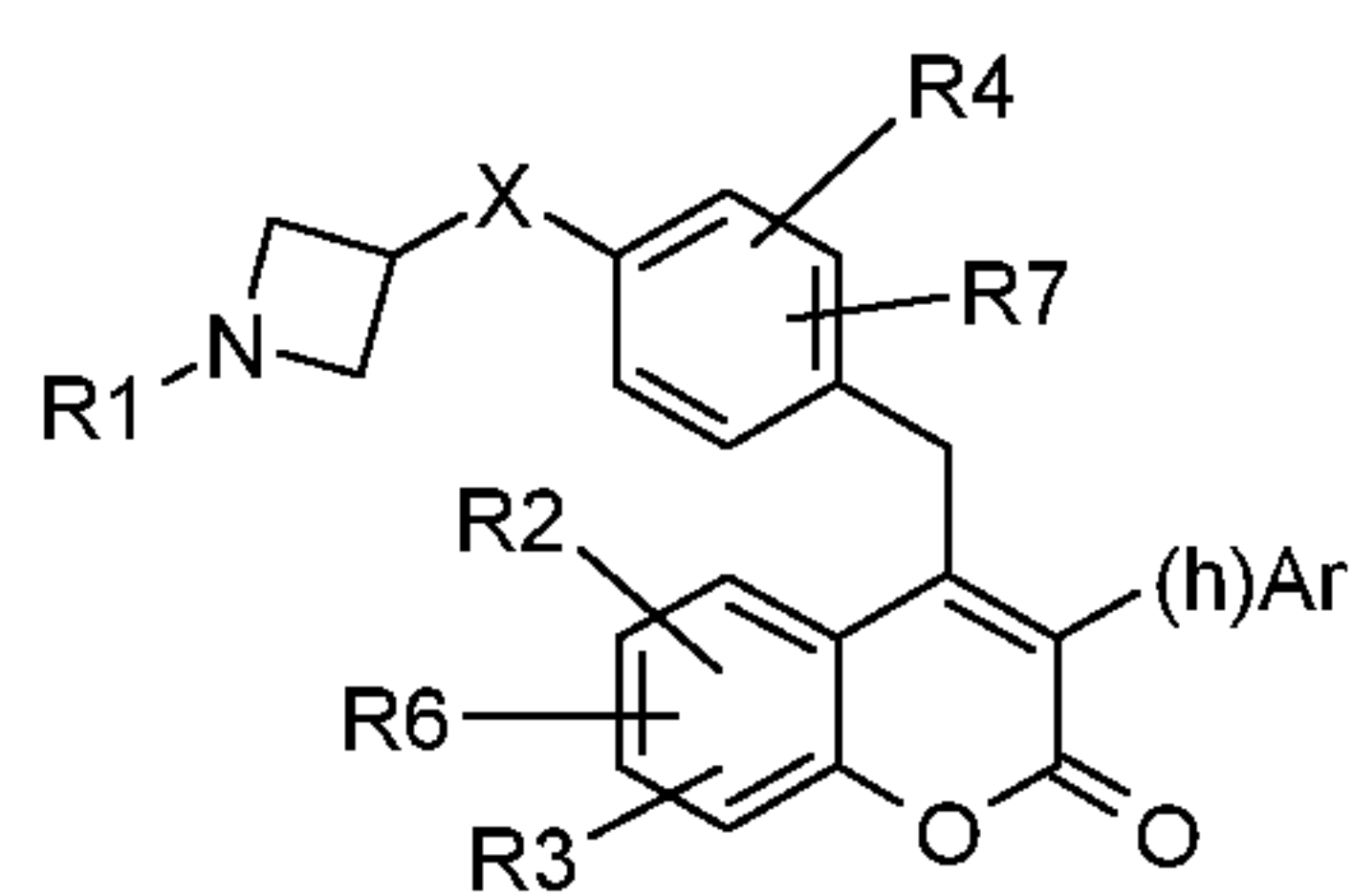
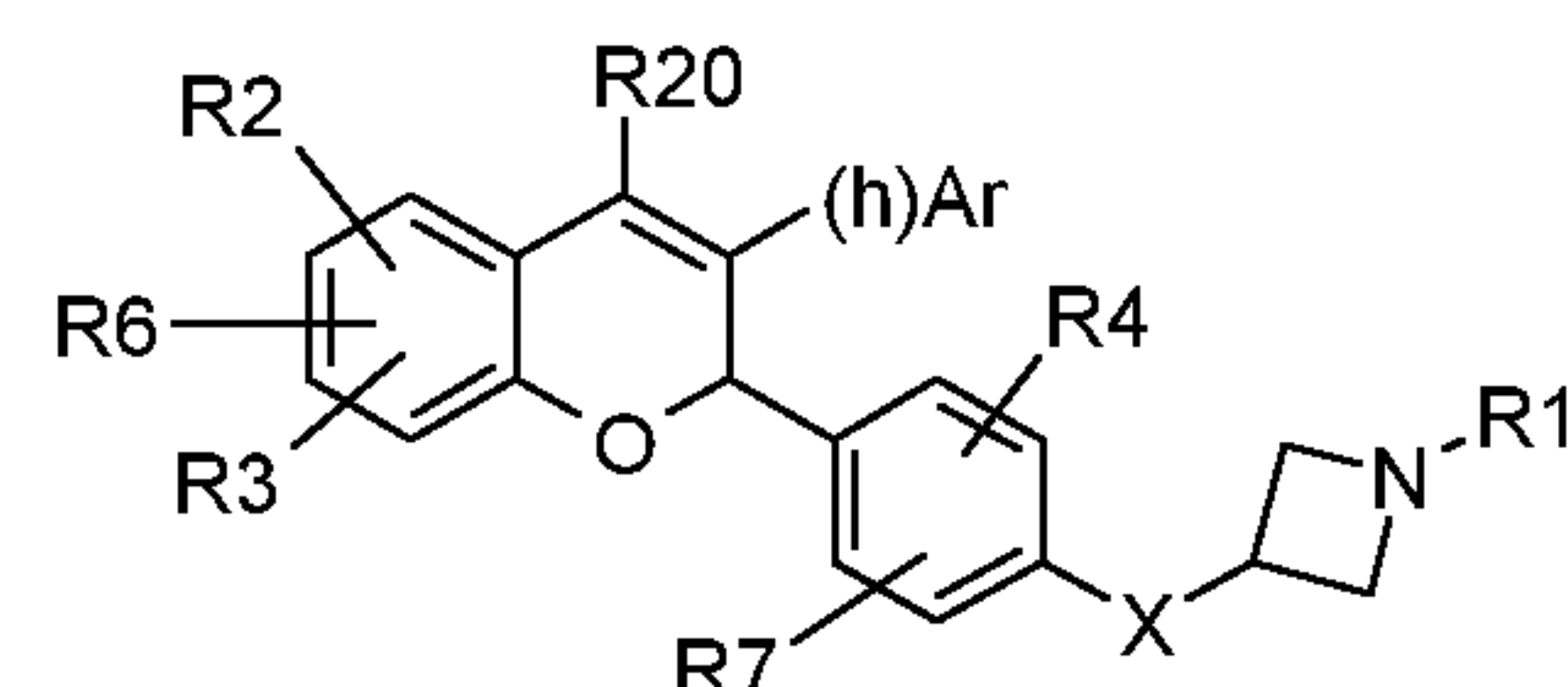
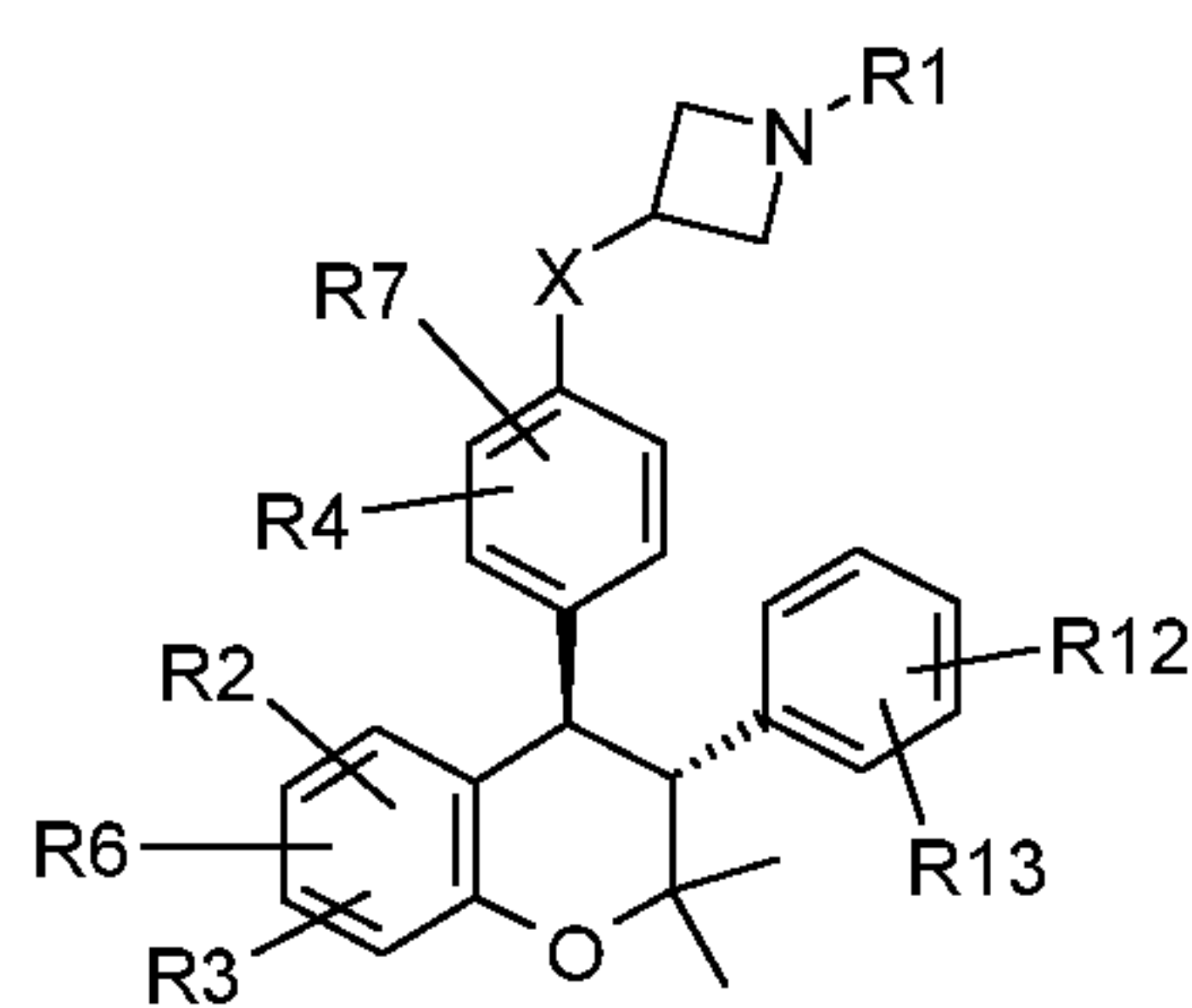
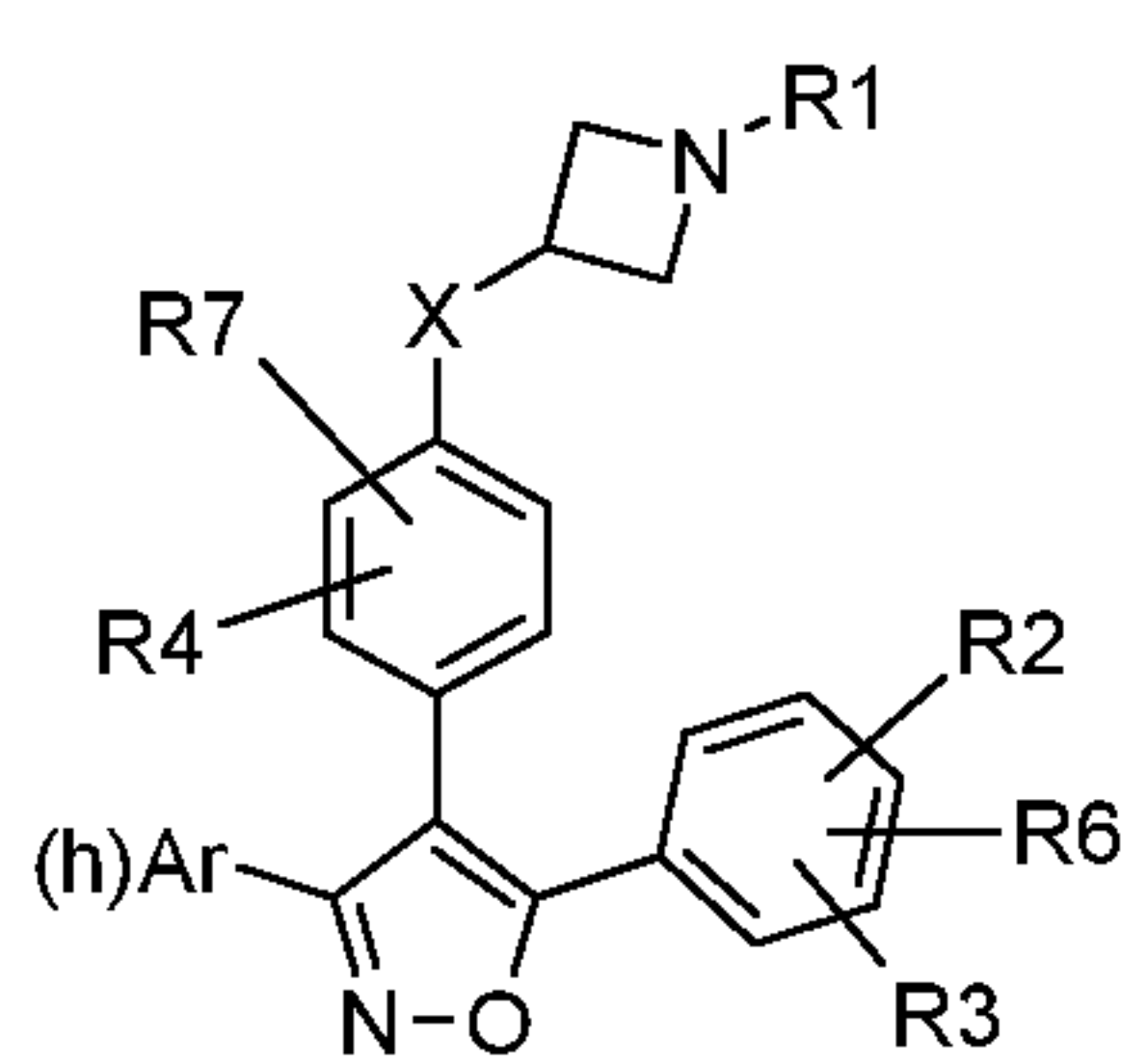
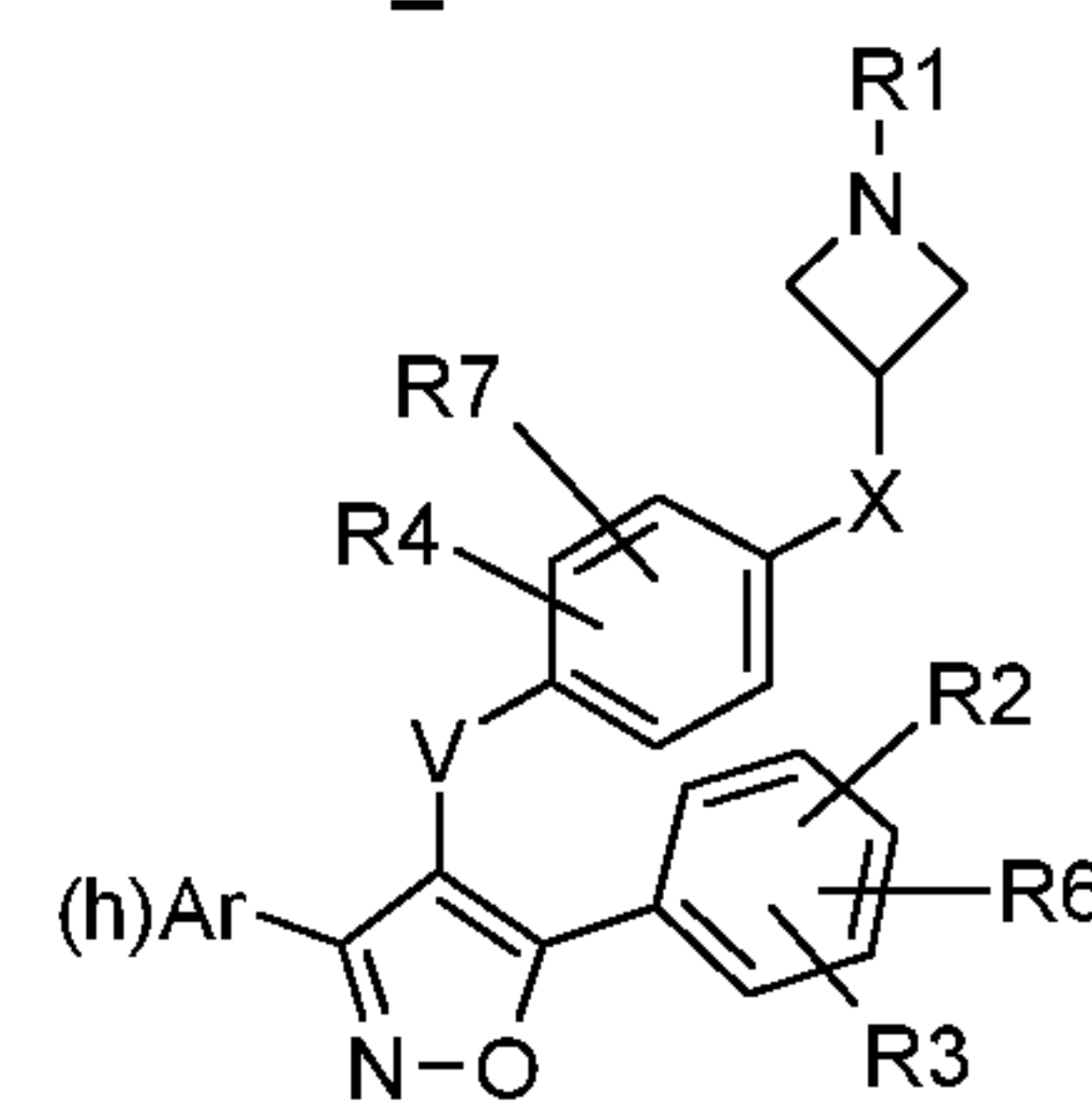
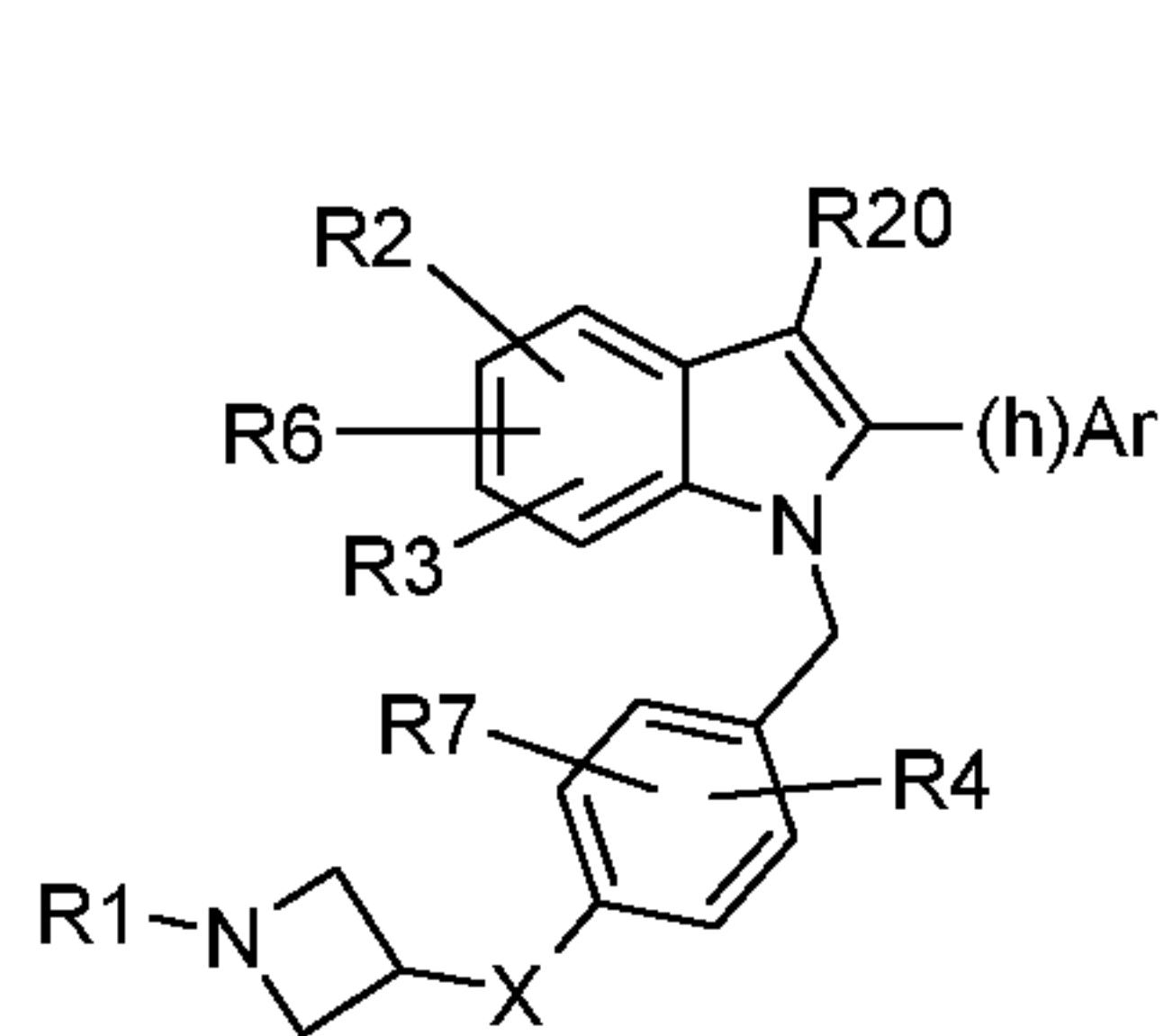
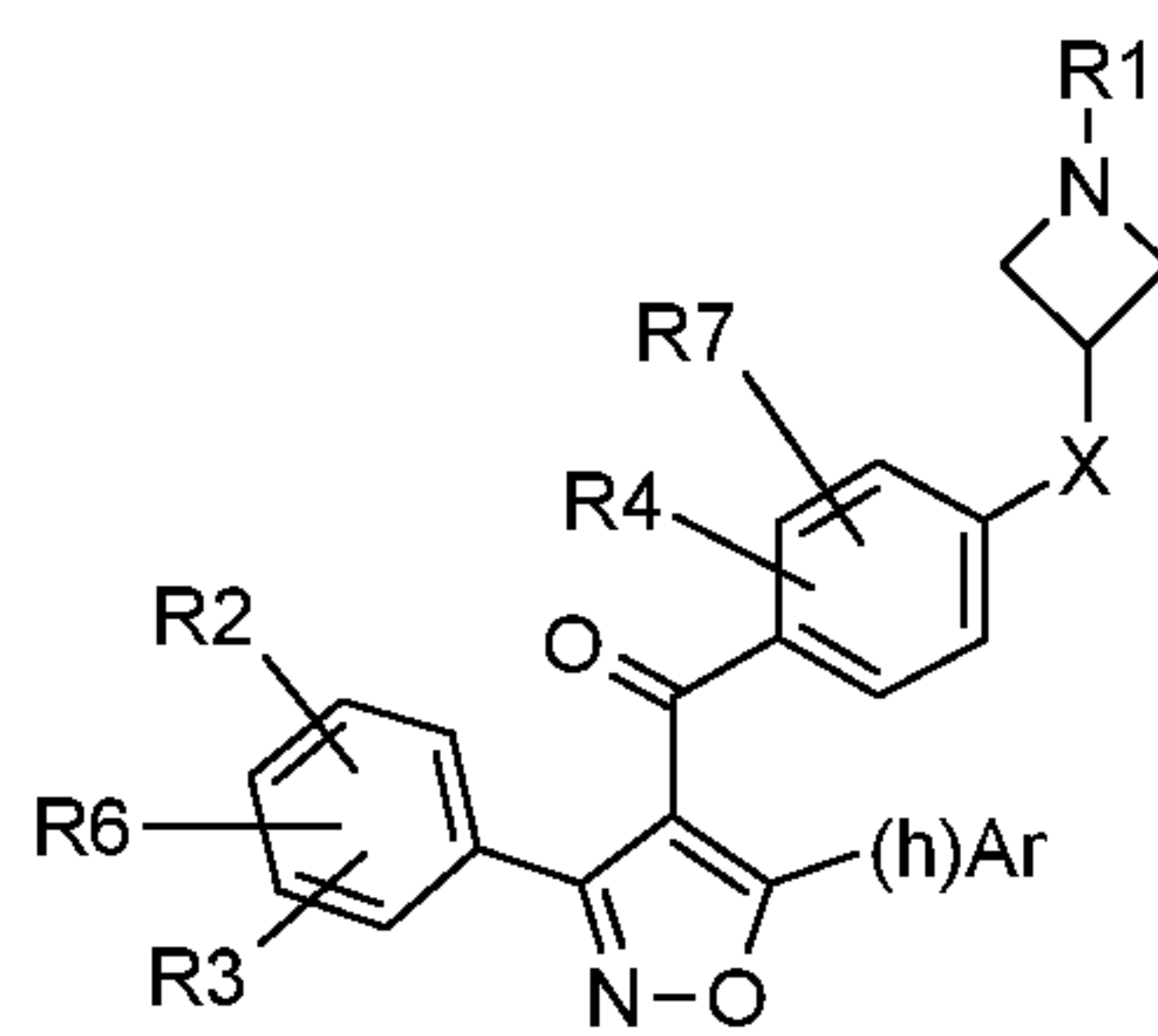
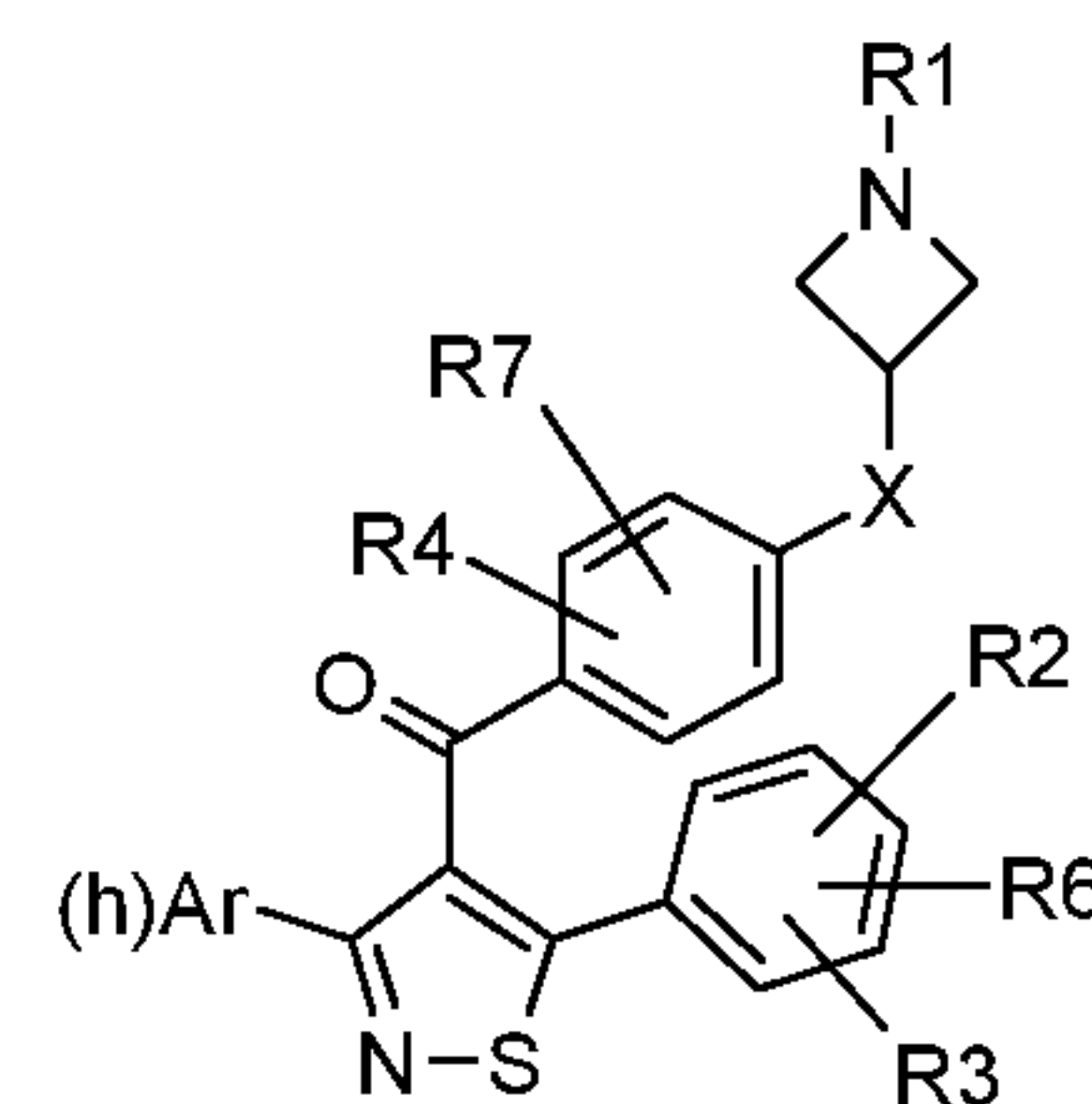
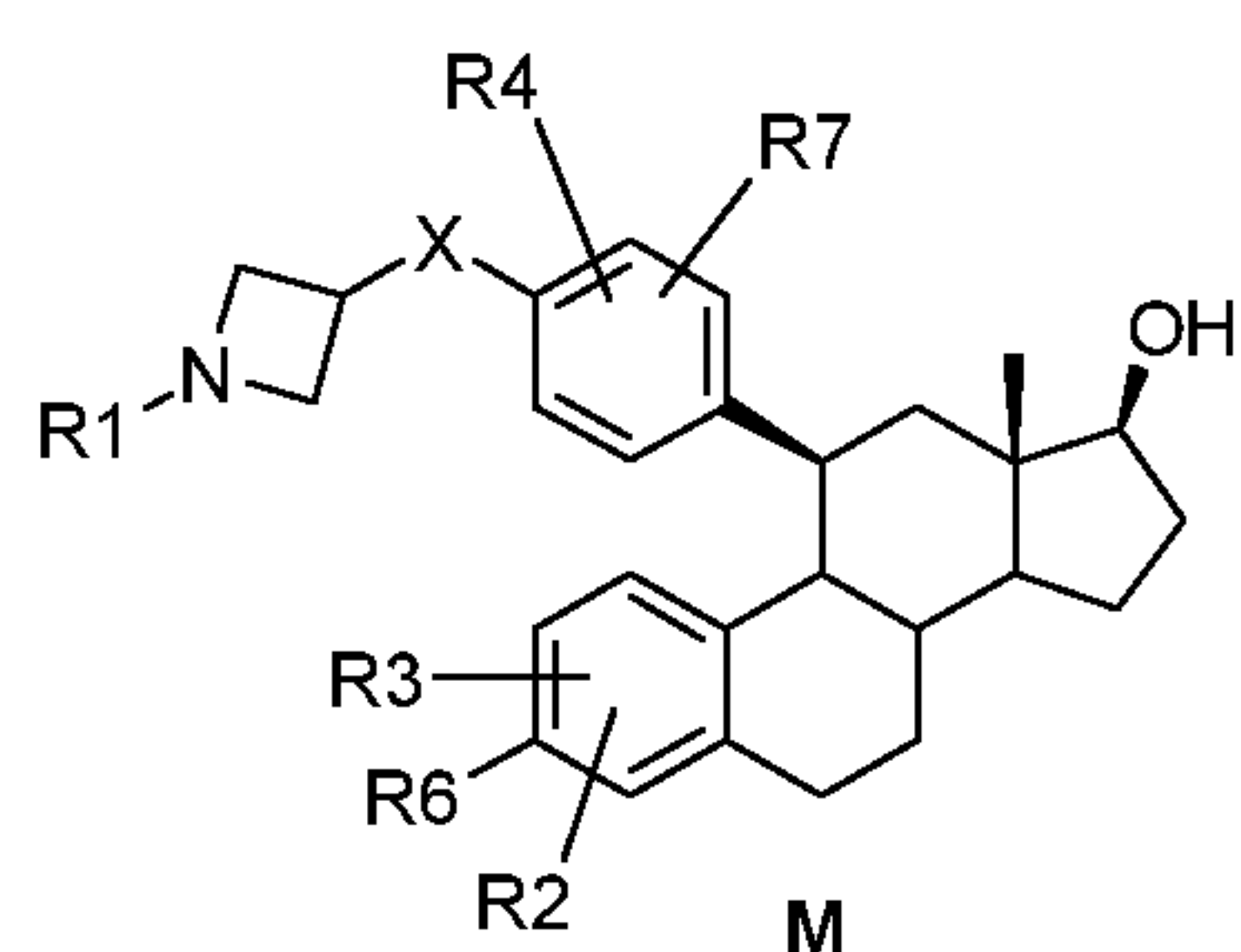
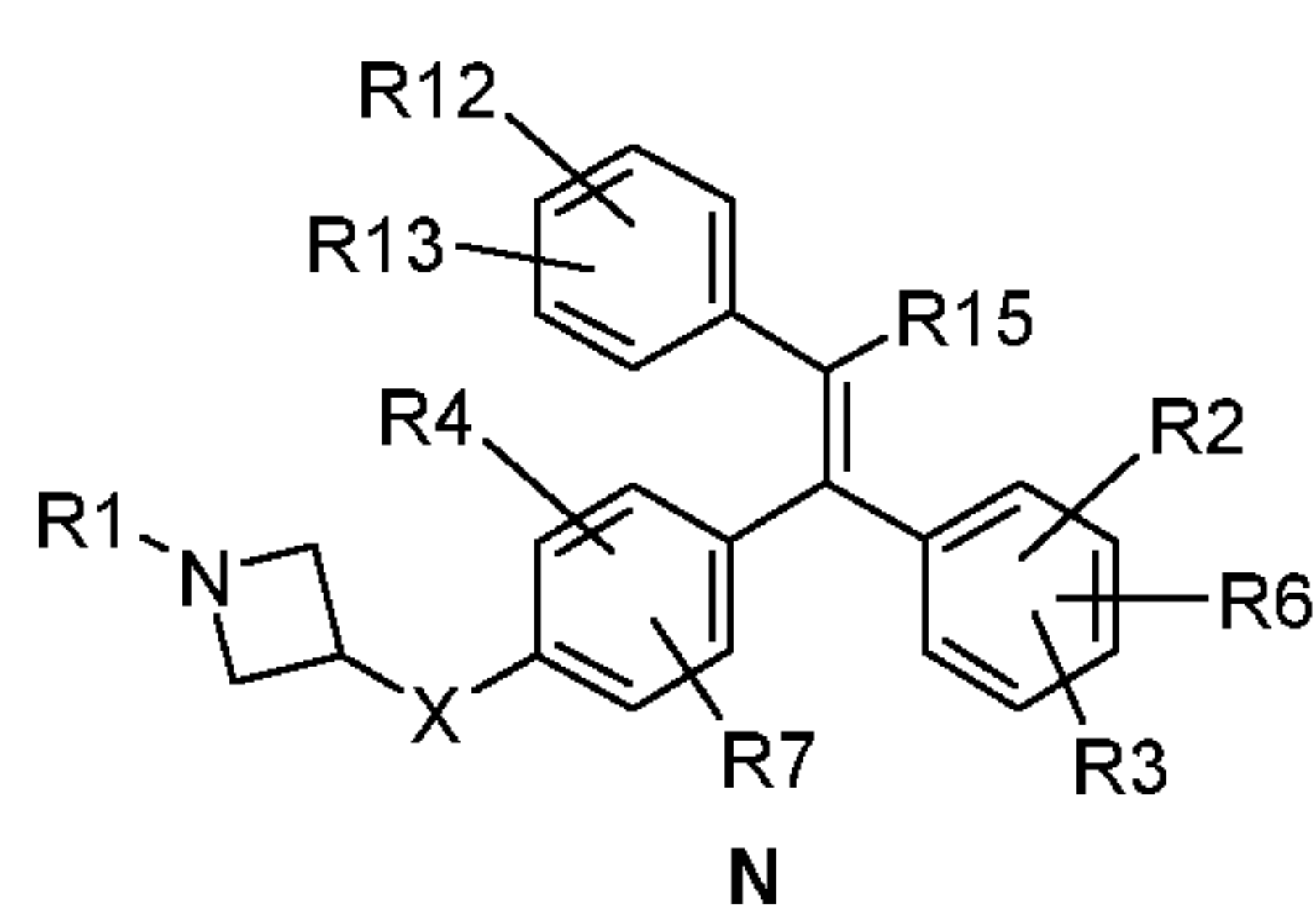
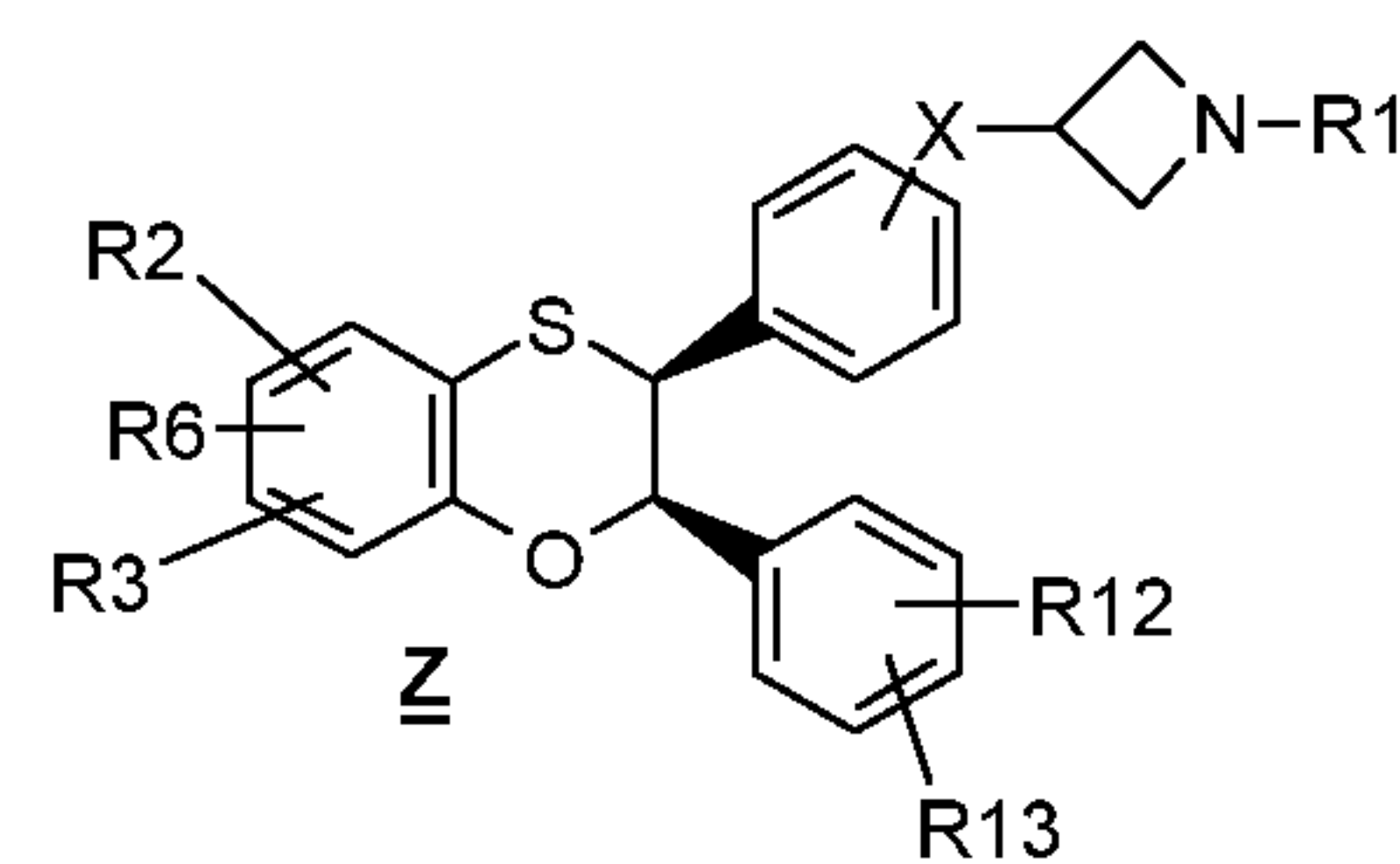
R6 is H, hydroxyl, amine or (C1-6)alkoxy;

30 R6 and R2 may be linked to form a (hetero)aromatic ring which is optionally substituted with fluorine, chlorine or (C1-3)alkyl;

R5 is H, (C1-3)alkyl, optionally substituted with one or more fluorine;

V is O, S, CH₂, CHOH, CH(C1-3)alkoxy, C=CH₂, carbonyl, N-R16;

18

ABCDEFGHIJKLMNO

Formulae 4

R15 is H, halogen, nitro, nitrile or (C1-6)alkyl, optionally substituted with one or more halogen;

R16 is H, (C1-4)alkyl, (C1-4)alkenyl, optionally substituted with one or more halogen;

5 R20 is (C1-3)alkyl, optionally substituted with one or more fluorine.

The term (h)Ar or (hetero)aromatic ring means an aromatic or heteroaromatic ring system, the aromatic skeleton of which containing five to ten atoms of which zero to four atoms other than carbon, selected from oxygen, nitrogen or sulfur.

10 Examples are phenyl, naphthyl, pyridyl, thienyl, furanyl, thiazolyl, oxazolyl, pyrrolyl, thiadiazolyl, tetrazolyl, benzopyrrolyl and benzopyrrazolyl.

The term CH(C1-3)alkoxy means a methylene linker that is substituted with an alkoxy group containing 1-3 carbon atoms, being methoxymethylene, ethoxy-

15 methylene and propyloxymethylene.

In one embodiment, the present invention relates to compounds of Formulae 3 or 4 wherein R1 is (C1-4)alkyl, (C3-6)cycloalkyl, (C3-6)heterocycloalkyl, (C2-6)-alkenyl, (C1-2)alkoxy(C2-4)alkyl, (C3-6)cycloalkyl(C1-3)alkyl, (C3-6)heterocyclo-
20 alkyl(C1-3)alkyl, each independently optionally substituted with one or more fluorine.

In another embodiment, R1 is (C1-4)alkyl, (C3-6)cycloalkyl, (C3-6)heterocycloalkyl, (C2-6)alkenyl, (C1-2)alkoxy(C2-4)alkyl, (C3-6)cycloalkyl(C1-3)alkyl, each
25 independently optionally substituted with one or more fluorine.

In another embodiment of the present invention, R1 is methyl, ethyl, n-propyl, isobutyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclopropylmethyl, cyclobutylmethyl, (3-tetrahydrofuranyl)methyl, 3-methoxypropyl, 3,3,3-trifluoropropyl, 3-fluoropropyl or
30 2-propenyl.

In one embodiment, the present invention relates to compounds of Formulae 3 or 4 wherein X is O, S or N-R5. In another embodiment, X is O or S. In yet another embodiment, X is O.

- 5 In another embodiment, the invention relates to compounds of Formulae 3 or 4 wherein R2 and R3 are independently of each other H, fluorine, chlorine, (C1-2)-alkyl, CF₃ or nitrile. In yet another embodiment, R2 and R3 are independently of each other H, fluorine, chlorine or (C1-2)alkyl.
- 10 In another embodiment, the invention relates to compounds of Formulae 3 or 4 wherein R4 and R7 are independently of each other H, fluorine, chlorine or (C1-2)-alkyl. In yet another embodiment, R4 and R7 are independently of each other H or fluorine.
- 15 In another embodiment, the invention relates to compounds of Formulae 3 or 4 wherein R5 is H or methyl.

In another embodiment, the invention relates to compounds of Formulae 3 or 4 wherein R6 is H, hydroxyl or (C1-2)alkoxy or wherein R6 is, together with R2, part
20 of a (hetero)aromatic ring. In yet another embodiment, R6 is H, hydroxyl or (C1-2)-alkoxy.

In another embodiment, the invention relates to compounds of Formulae 3 or 4 wherein R12 is H, fluorine, chlorine, (C1-2)alkyl, nitrile or hydroxyl.

25

In another embodiment, the invention relates to compounds of Formulae 3 or 4 wherein R13 is H, fluorine, chlorine, (C1-2)alkyl, (C1-2)alkoxy, CF₃ or nitrile. In yet another embodiment, R13 is H, fluorine, chlorine or (C1-2)alkyl.

- 30 In another embodiment, the invention relates to compounds of Formulae 3 or 4 wherein R15 is H, chlorine, nitrile or (C1-4)alkyl, optionally substituted with one or more halogen. In yet another embodiment, R15 is H, chlorine or (C1-3)alkyl, optionally substituted with one or more fluorine or chlorine.

In another embodiment, the invention relates to compounds of Formulae 4 wherein V is O, CH₂, CHOH, CH(C1-2)alkoxy, C=CH₂ or carbonyl.

- 5 In another embodiment, the invention relates to compounds of Formulae 4 wherein R16 is H, (C1-3)alkyl, optionally substituted with one or more halogen. In yet another embodiment, R16 is H or methyl.

In one embodiment, the present invention relates to compounds of Formulae 4
10 wherein R20 is methyl or CF₃.

In yet another embodiment of the present invention, the N-substituted azetidine derivative is selected from the group consisting of compounds according to any one of Formulae 5A to 5T, shown hereinbelow,

15

wherein

R1 is (C1-8)alkyl, (C3-8)cycloalkyl, (C3-6)heterocycloalkyl, (C2-6)alkenyl, (C2-6)-alkynyl, (C1-4)alkylcarbonyl, (C1-4)alkoxy(C2-4)alkyl, (C3-6)cycloalkyl(C1-3)alkyl, (C3-6)heterocycloalkyl(C1-3)alkyl, each independently optionally substituted with
20 one or more halogen, nitrile, hydroxyl or (C1-2)alkyl;

(h)Ar is a (hetero)aromatic ring, optionally substituted with R12 and R13;

R2 and R3 are independently of each other H, fluorine, chlorine, (C1-3)alkyl, (C1-3)alkoxy, (C1-3)alkylthio, CF₃ or nitrile;

R4 and R7 are independently of each other H, fluorine, chlorine, (C1-2)alkyl, CF₃
25 or nitrile;

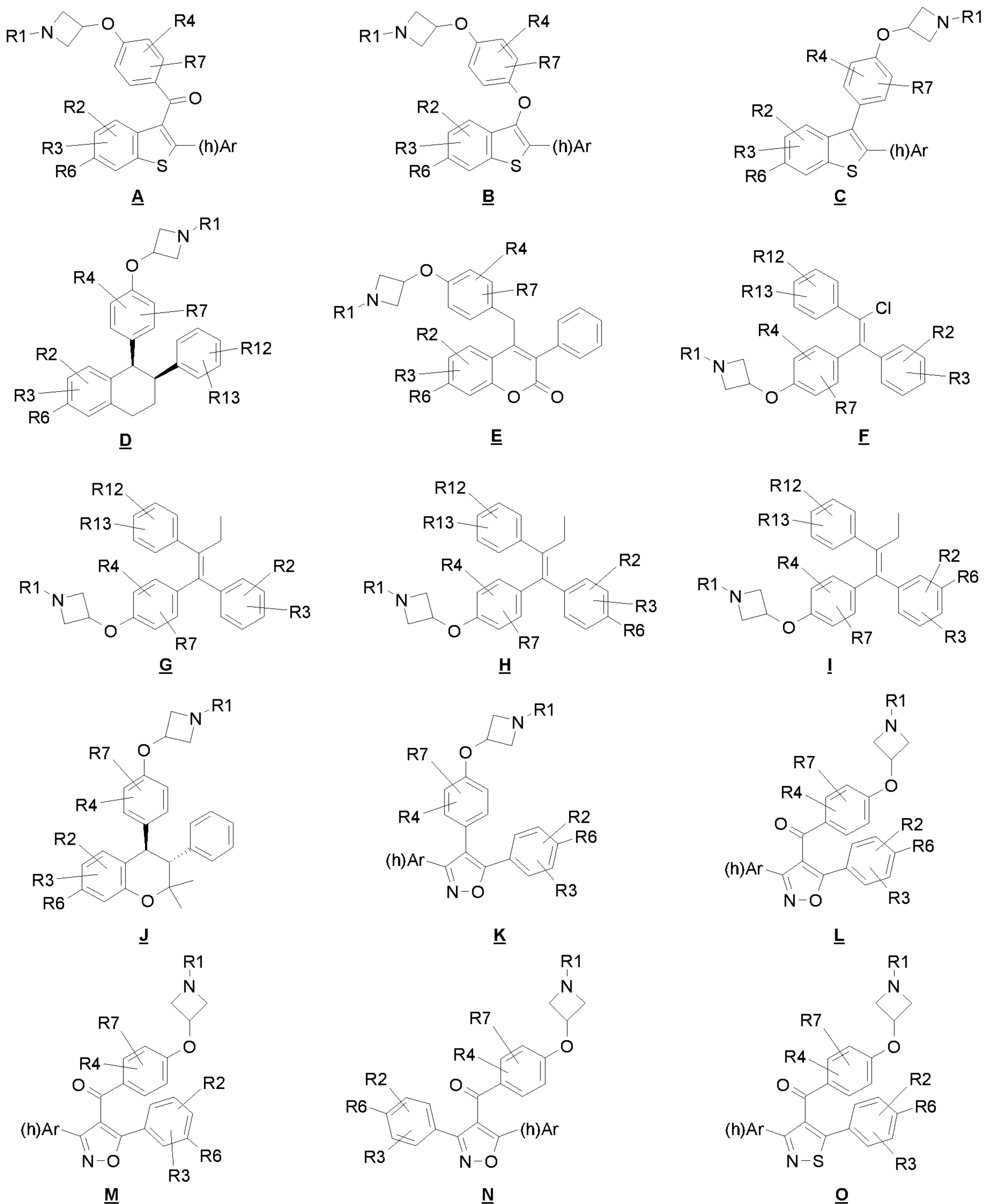
R12 is H, fluorine, chlorine, (C1-2)alkyl, (C1-2)alkoxy, nitrile or hydroxyl;

R13 is H, fluorine, chlorine, (C1-3)alkyl, (C1-3)alkoxy, (C1-3)alkylthio, CF₃ or nitrile;

R6 is H, hydroxyl, amine or (C1-6)alkoxy;

30 R6 and R2 may be linked to form a (hetero)aromatic ring which is optionally substituted with fluorine, chlorine or (C1-3)alkyl.

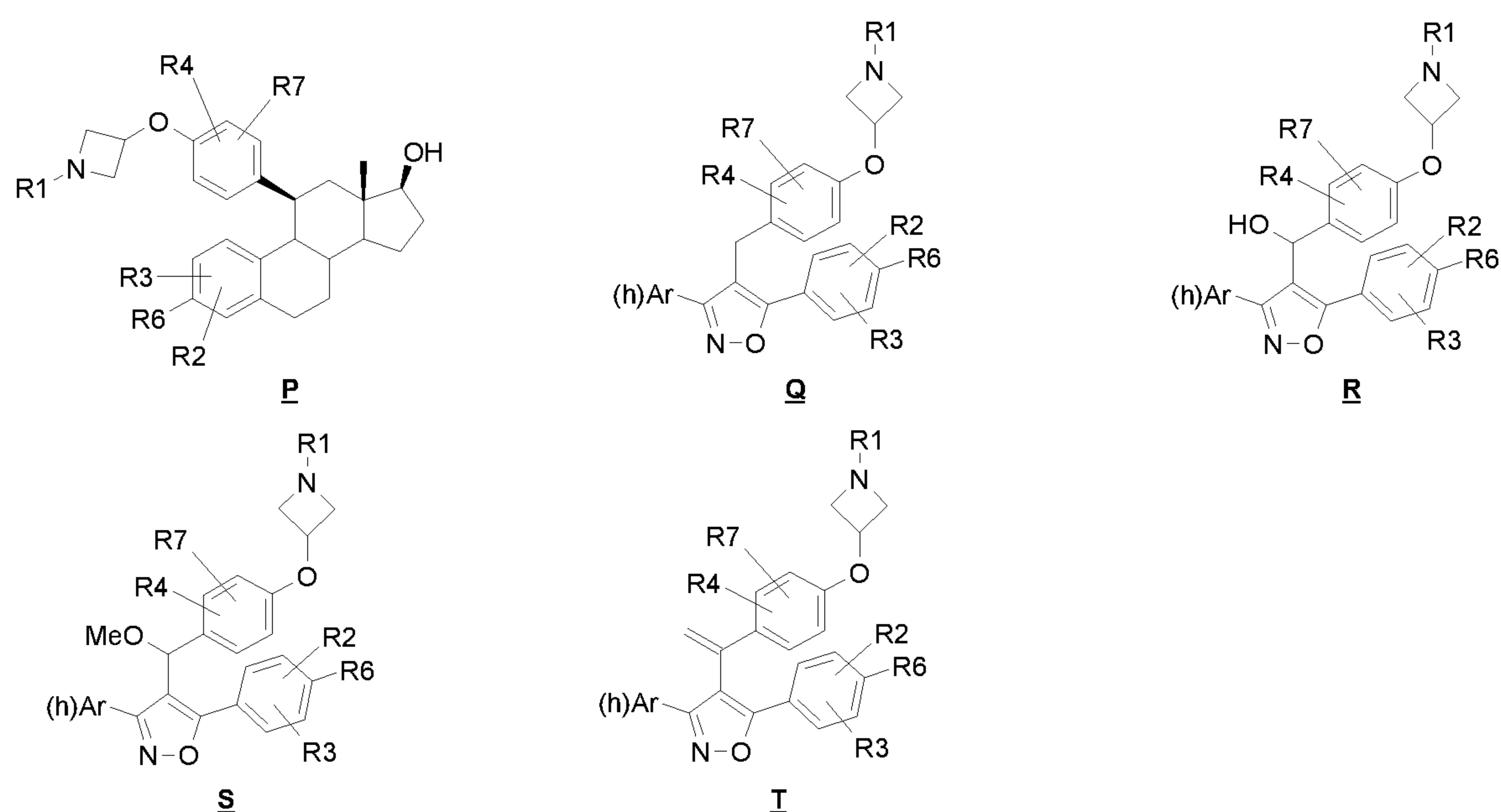
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Formulae 5

- 5 In one embodiment the present invention relates to compounds of Formulae 5 wherein R1 is (C1-4)alkyl, (C3-6)cycloalkyl, (C3-6)heterocycloalkyl, (C2-6)alkenyl, (C1-2)alkoxy(C2-4)alkyl, (C3-6)cycloalkyl(C1-3)alkyl, (C3-6)heterocycloalkyl(C1-3)alkyl, each independently optionally substituted with one or more fluorine.

23



Formulae 5

- 5 In another embodiment, R1 is methyl, ethyl, n-propyl, iso-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclopropylmethyl, cyclobutylmethyl, (3-tetrahydrofuranyl)-methyl, 3-methoxypropyl, 3,3,3-trifluoropropyl, 3-fluoropropyl or 2-propenyl.

In another embodiment, the invention relates to compounds of Formulae 5 wherein
 10 R2 and R3 are independently of each other H, fluorine, chlorine, (C1-2)alkyl, CF₃ or nitrile. In yet another embodiment, R2 and R3 are independently of each other H, fluorine, chlorine or (C1-2)alkyl.

In another embodiment, the invention relates to compounds of Formulae 5 wherein
 15 R4 and R7 are independently of each other H, fluorine, chlorine or (C1-2)alkyl. In yet another embodiment, R4 and R7 are independently of each other H or fluorine.

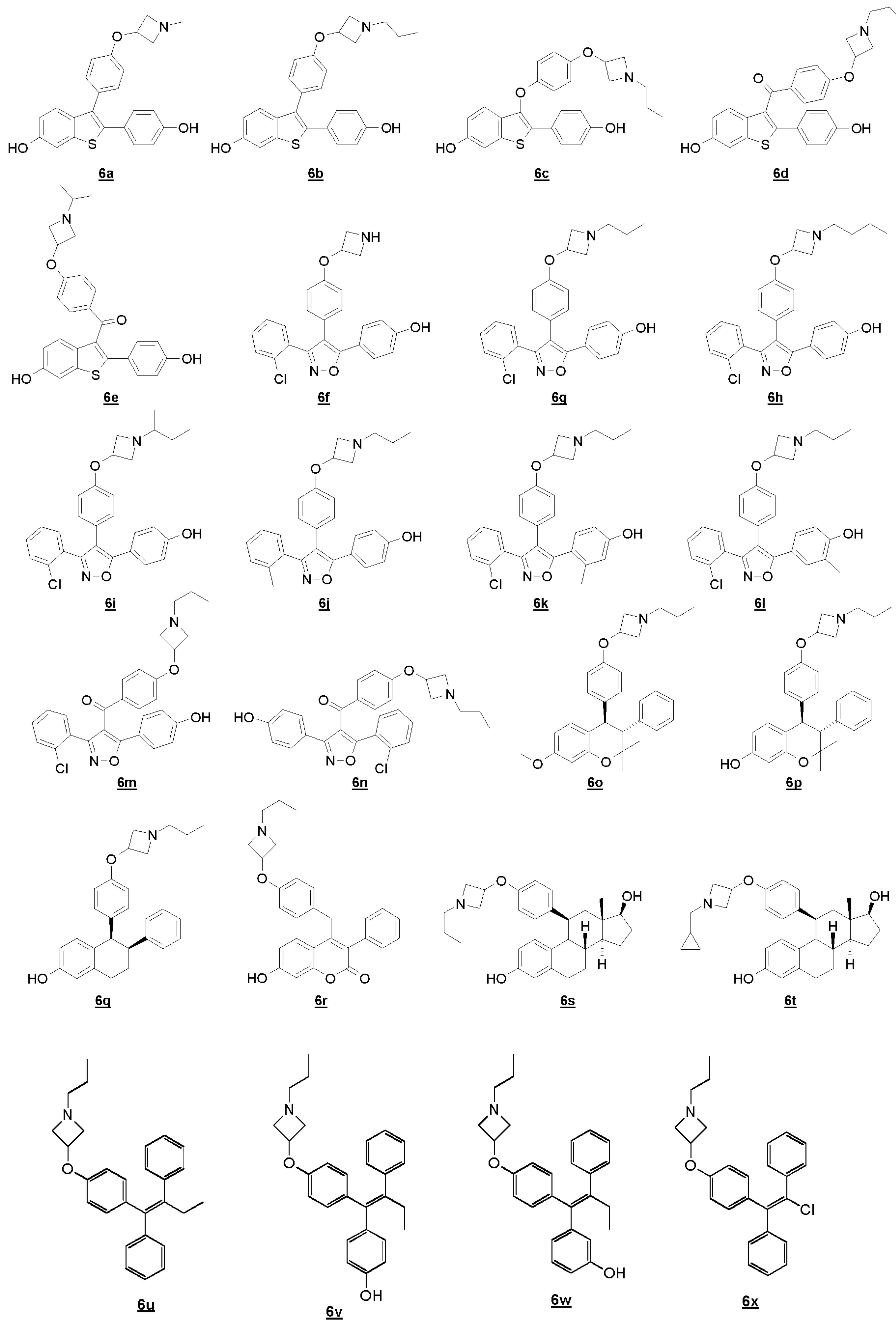
In another embodiment, the invention relates to compounds of Formulae 5 wherein
 R6 is H, hydroxyl or (C1-2)alkoxy or wherein R6 is, together with R2, part of a
 20 (hetero)aromatic ring. In yet another embodiment, R6 is H, hydroxyl or (C1-2)-alkoxy.

In another embodiment, the invention relates to compounds of Formulae 5 wherein R12 is H, fluorine, chlorine, (C1-2)alkyl, nitrile or hydroxyl.

In another embodiment, the invention relates to compounds of Formulae 5 wherein
5 R13 is H, fluorine, chlorine, (C1-2)alkyl, (C1-2)alkoxy, CF₃ or nitrile. In yet another embodiment, R13 is H, fluorine, chlorine or (C1-2)alkyl.

In one embodiment of the present invention, the N-substituted azetidine derivative is selected from the group consisting of compounds according to any one of
10 Formulae 6a-6x, shown hereinbelow.

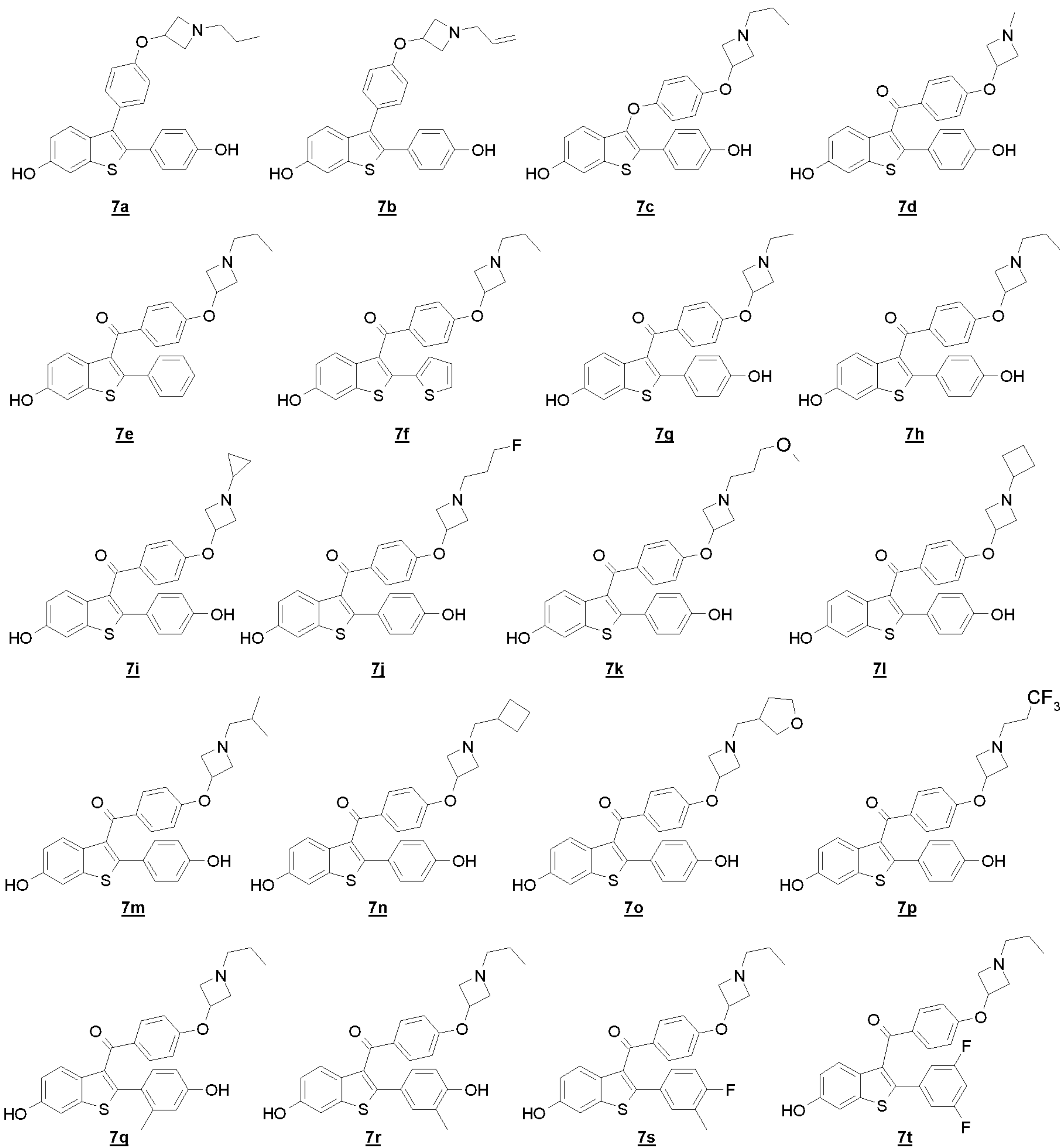
The N-substituted azetidine derivatives of Formulae 6 are ER α antagonists with pIC₅₀ >7 as defined hereinabove (see also Table 3 hereinbelow).



Formulae 6

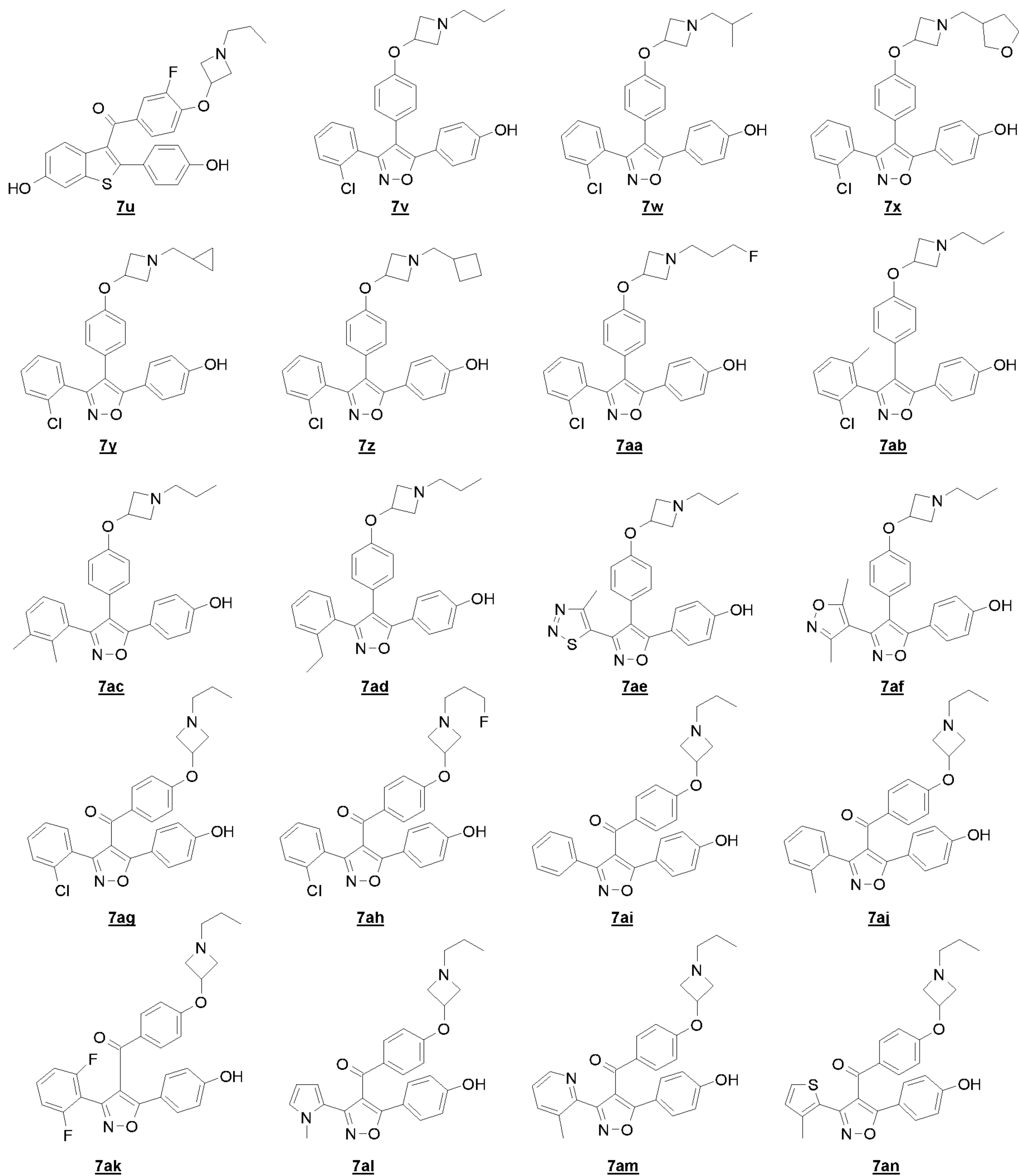
In another embodiment of the present invention, the N-substituted azetidine derivative is selected from the group consisting of compounds according to any one of Formulae 7a-7bj

5



Formulae 7

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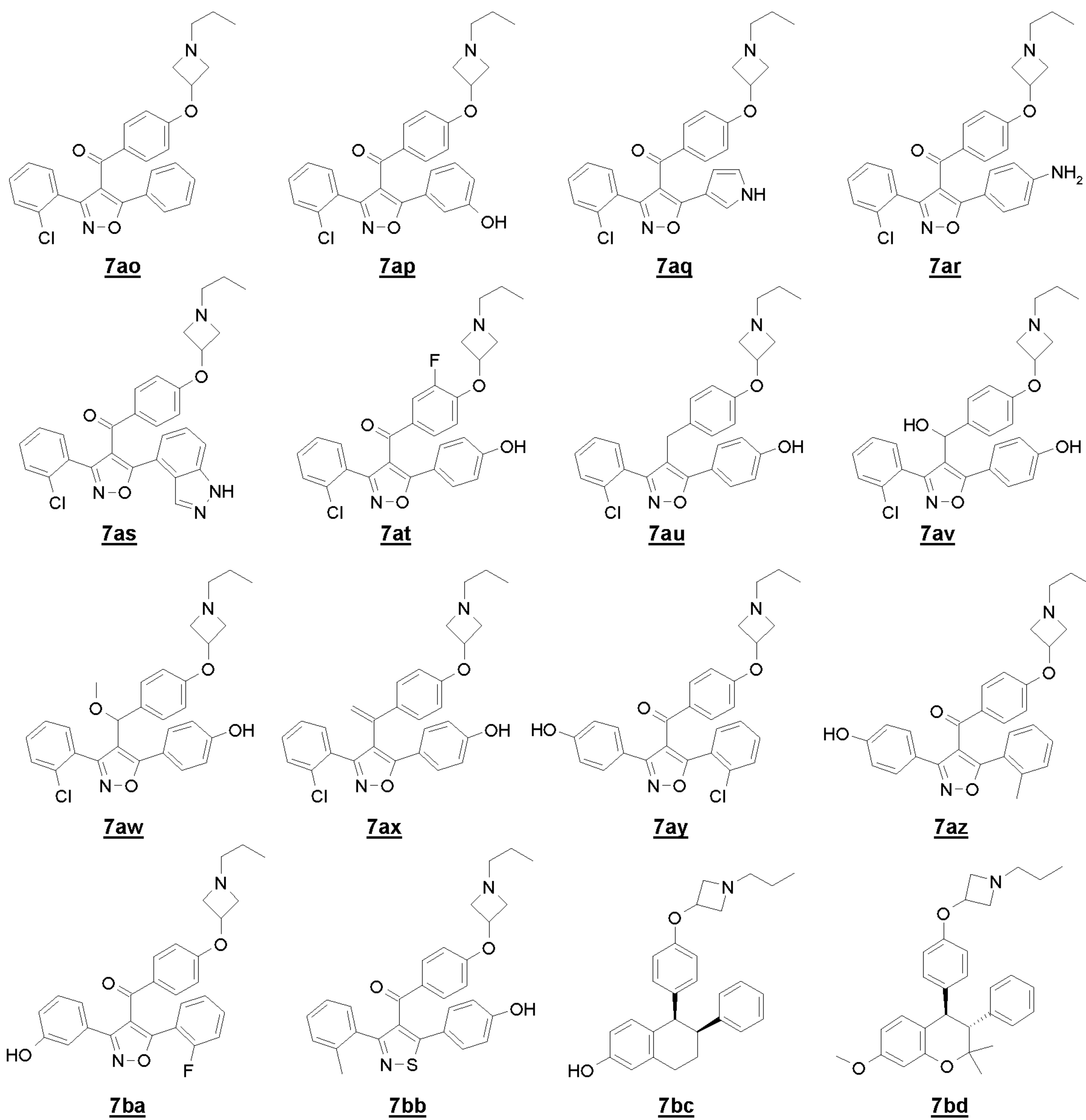


Formulae 7

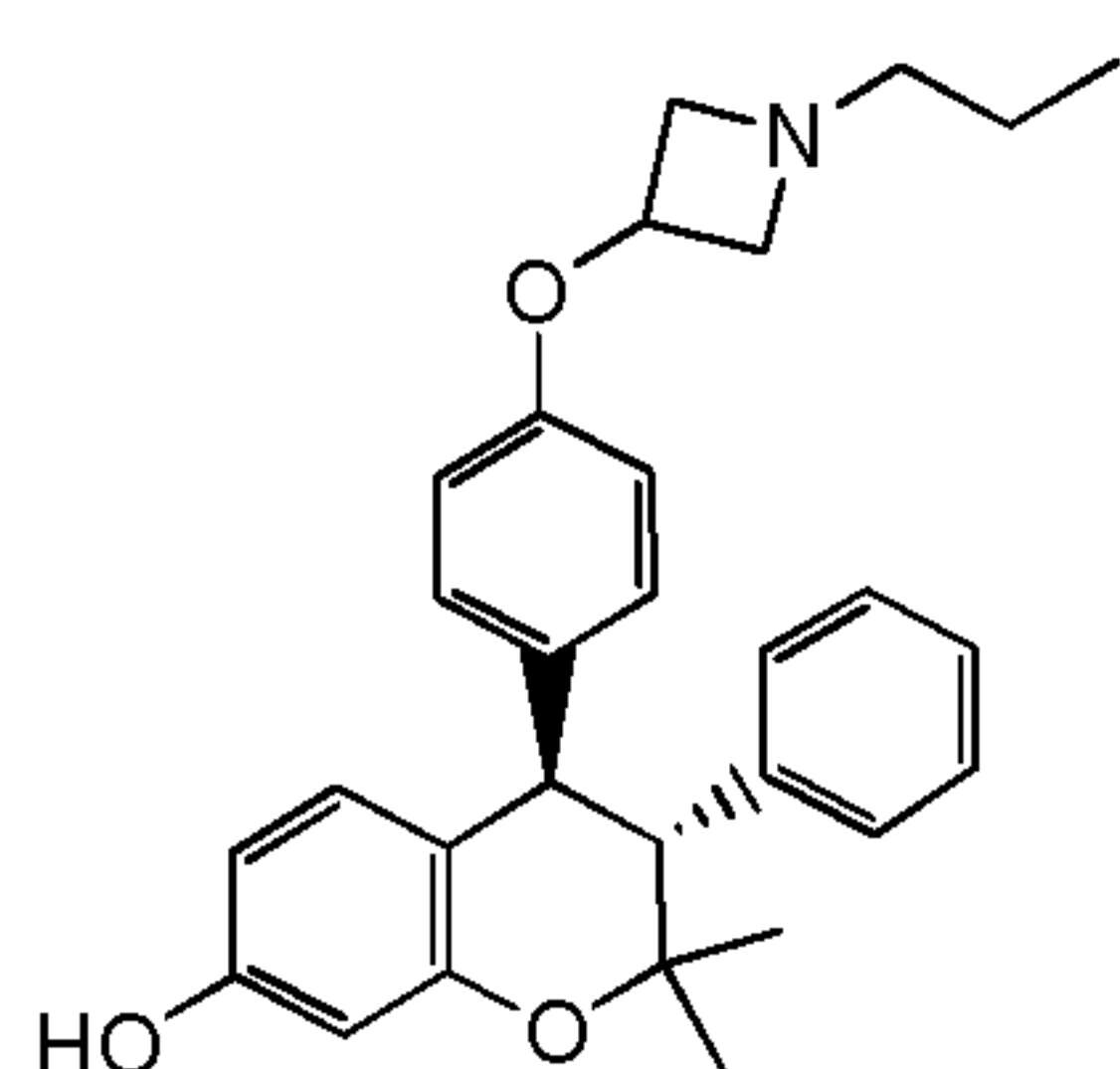
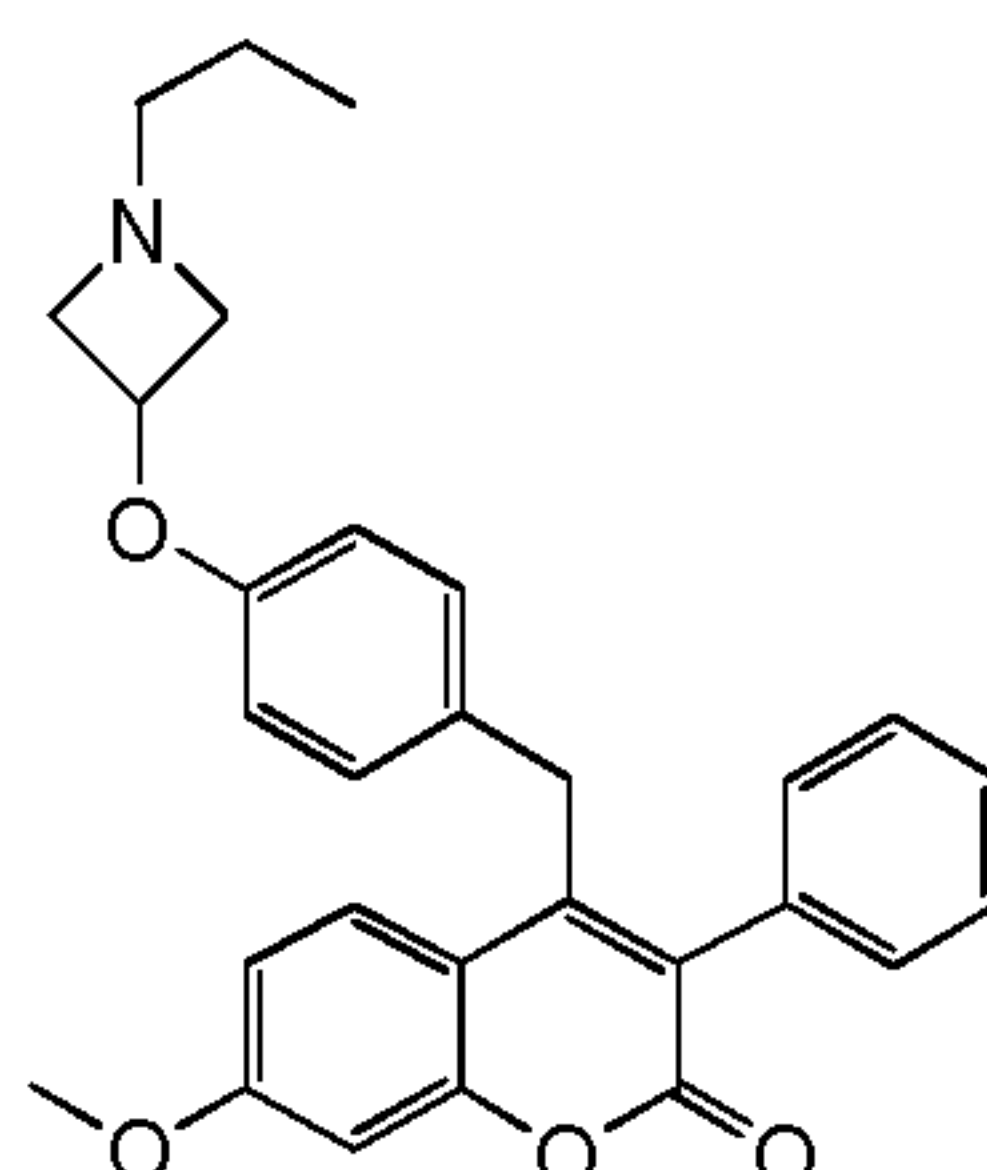
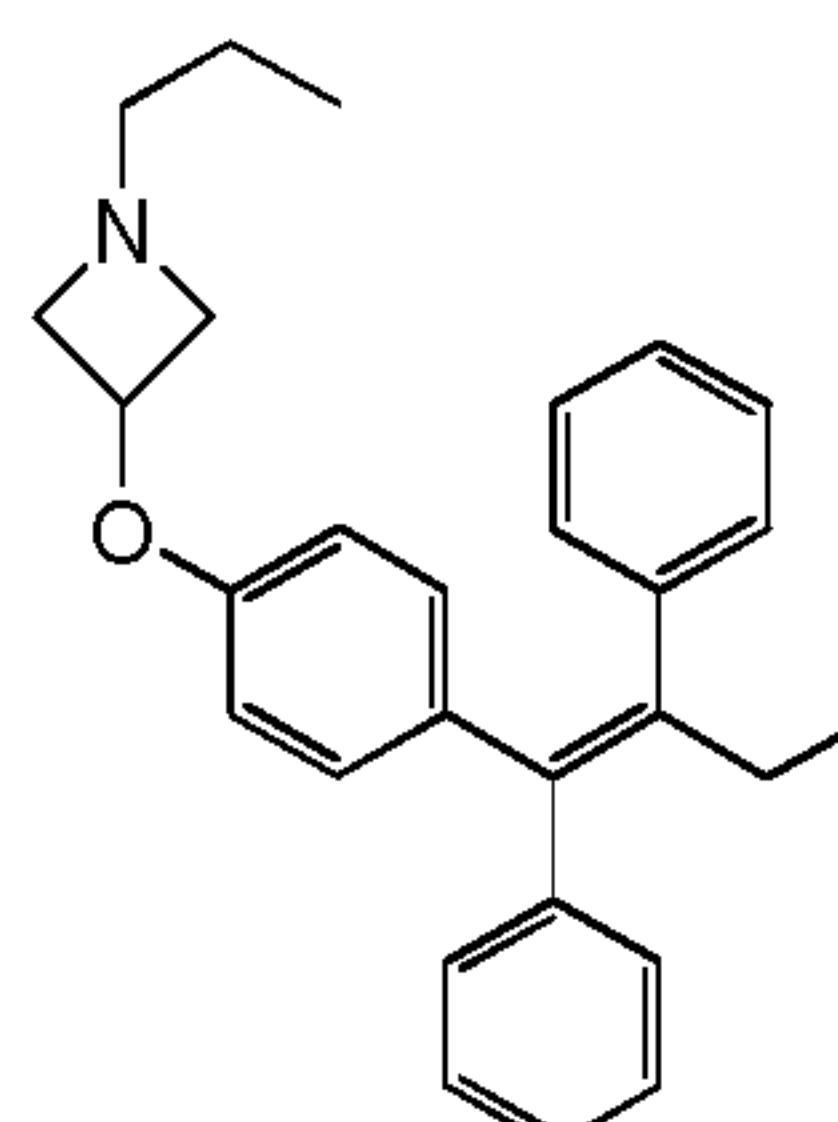
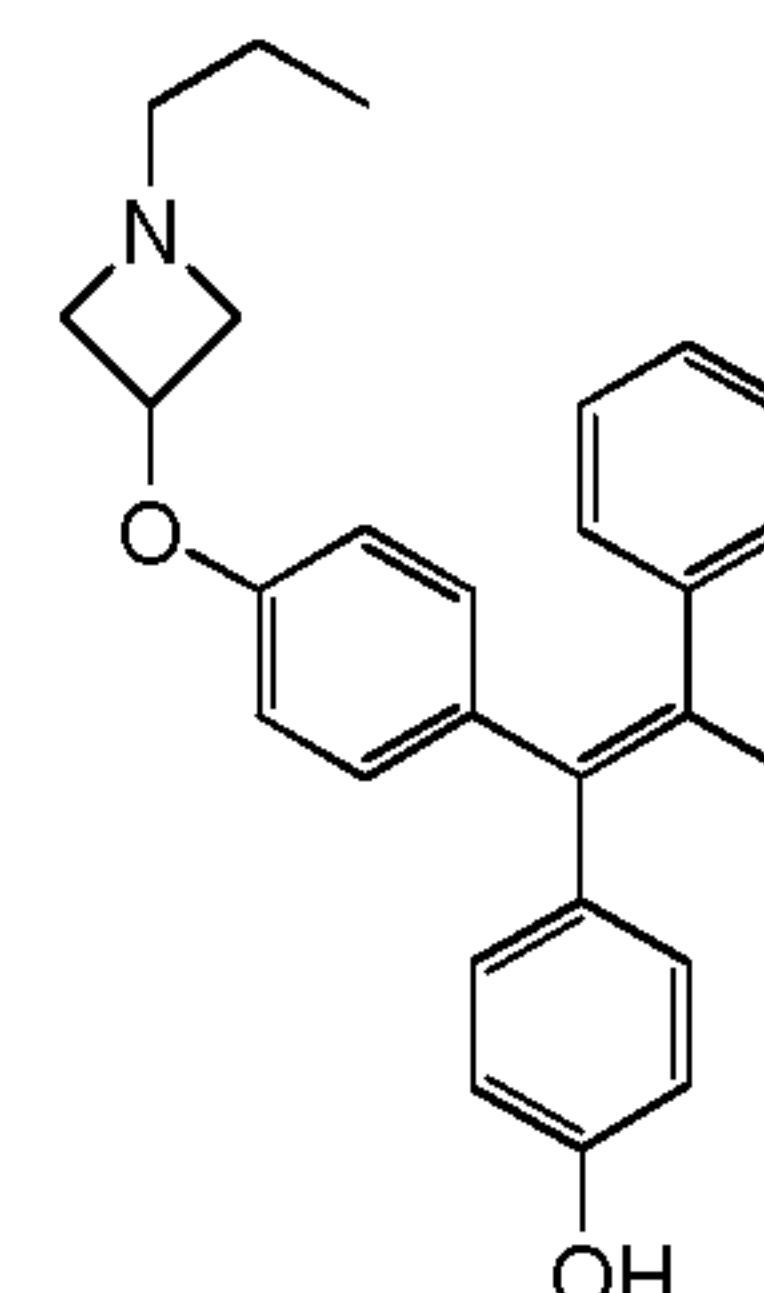
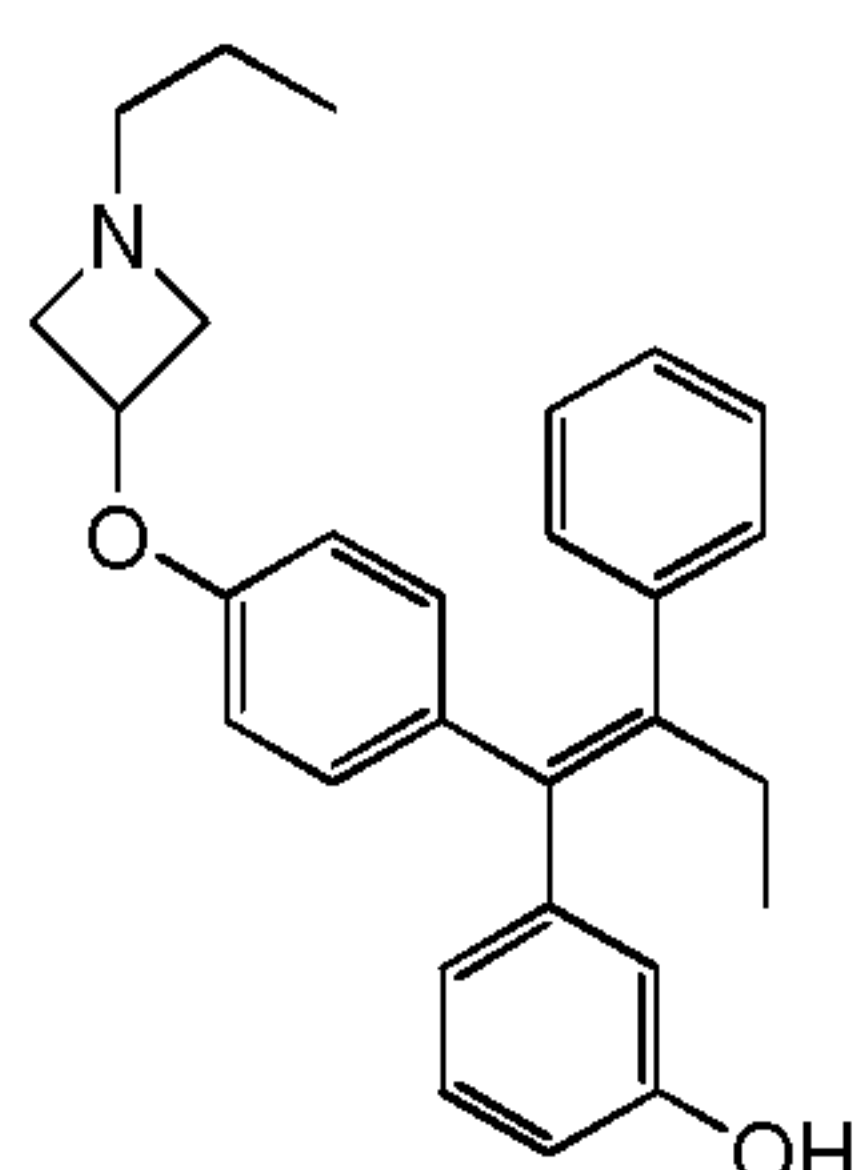
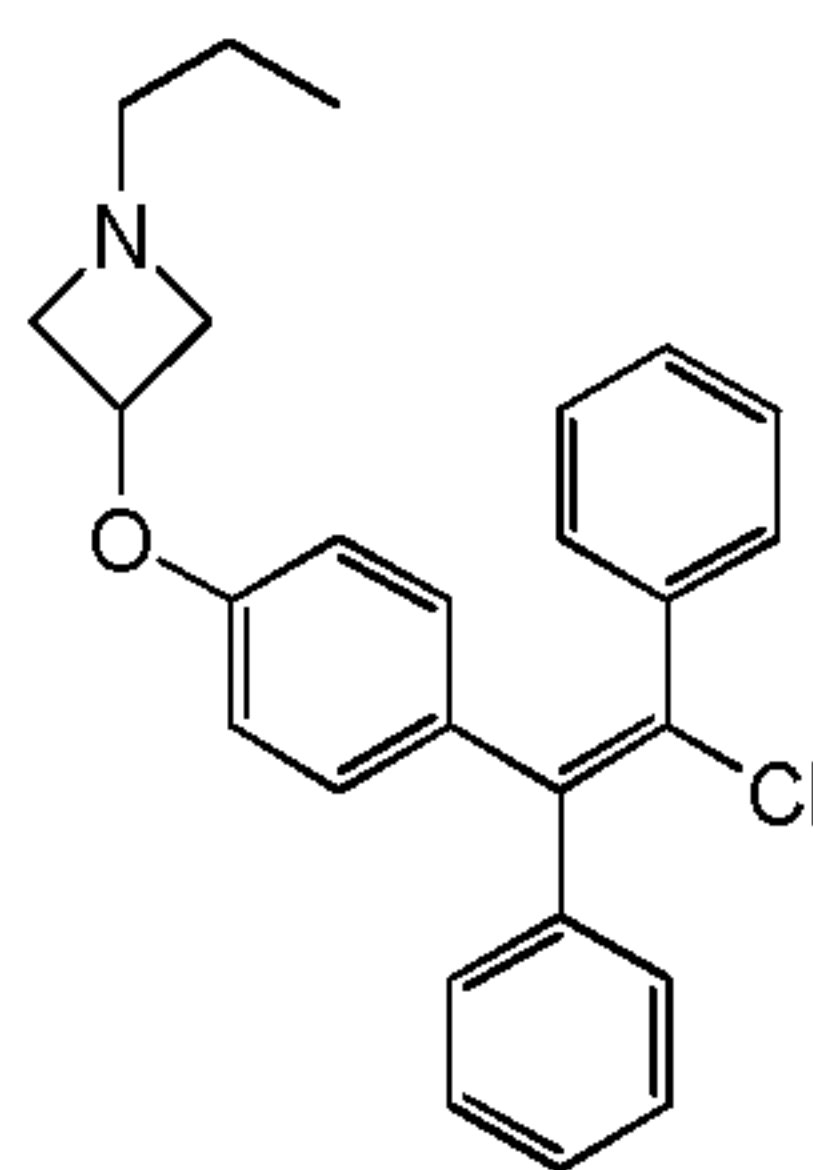
5

Besides being ER α antagonists with pIC₅₀ >7, the N-substituted azetidine derivatives of Formulae 7 are SERDs, showing a minimum of 20% downregulation of ER α in T47D cells, as defined hereinabove (see also Table 4 hereinbelow). In some embodiments, the N-substituted azetidines of the present invention show a

relative shift towards estrogen receptor downregulation, when compared to the corresponding compounds having a classical SERM basic amine side chain (see footnotes (c) and (d) in Table 4 hereinbelow).



Formulae 7

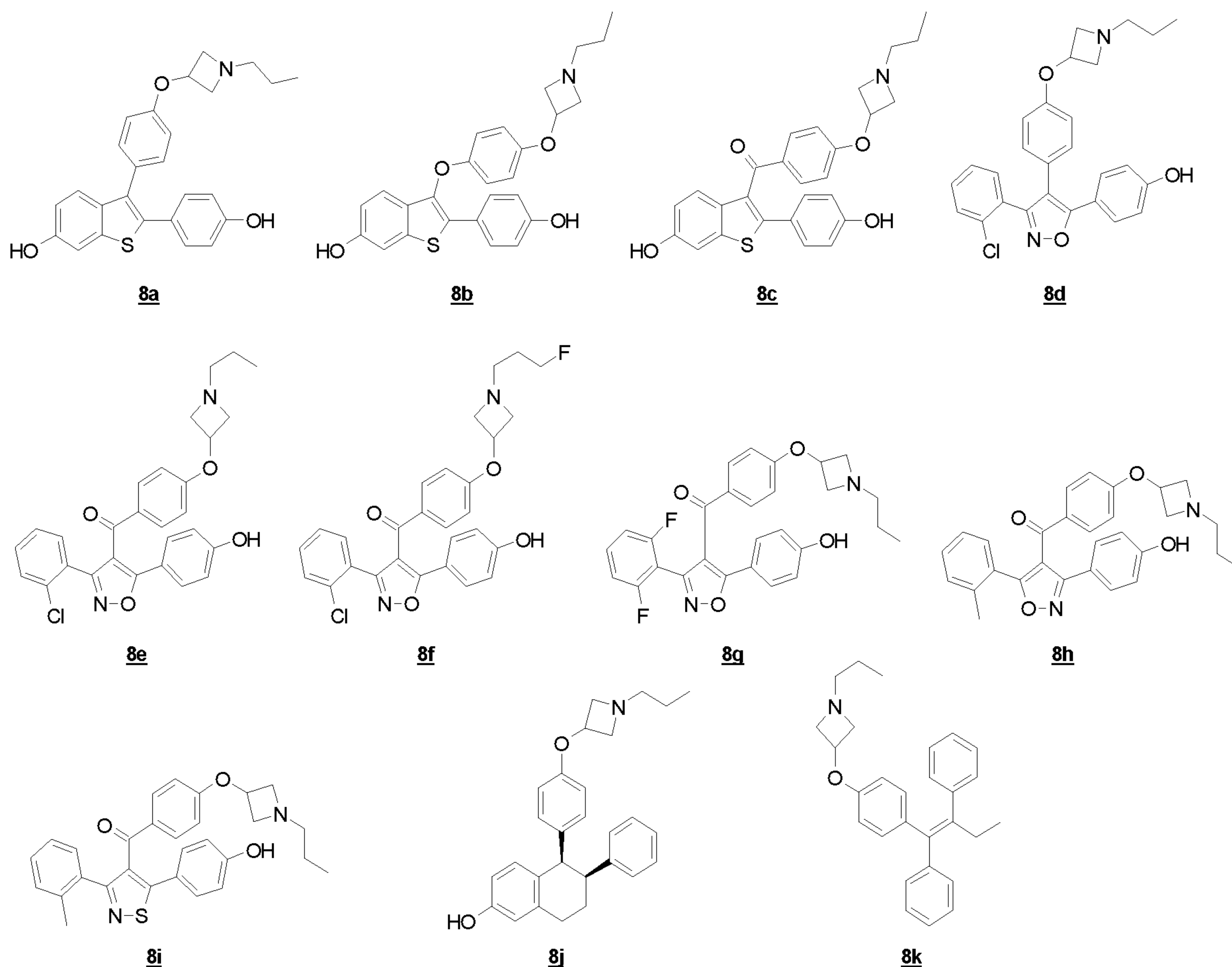
**7be****7bf****7bg****7bh****7bi****7bj**

Formulae 7

In yet another embodiment of the present invention, the N-substituted azetidine
5 derivative is selected from the group consisting of compounds according to any
one of Formulae 8a-8k, shown hereinbelow.

The N-substituted azetidine derivatives of Formulae 8 are ER α antagonists with
pIC₅₀ >7, are SERDs showing a minimum of 20% downregulation of ER α in T47D
10 cells, and do not (efficacy equal to or <0.10) stimulate proliferation in ER-positive,
tamoxifen-resistant MCF-7H breast cancer cells, as defined hereinabove (see also
Table 5 hereinbelow).

30



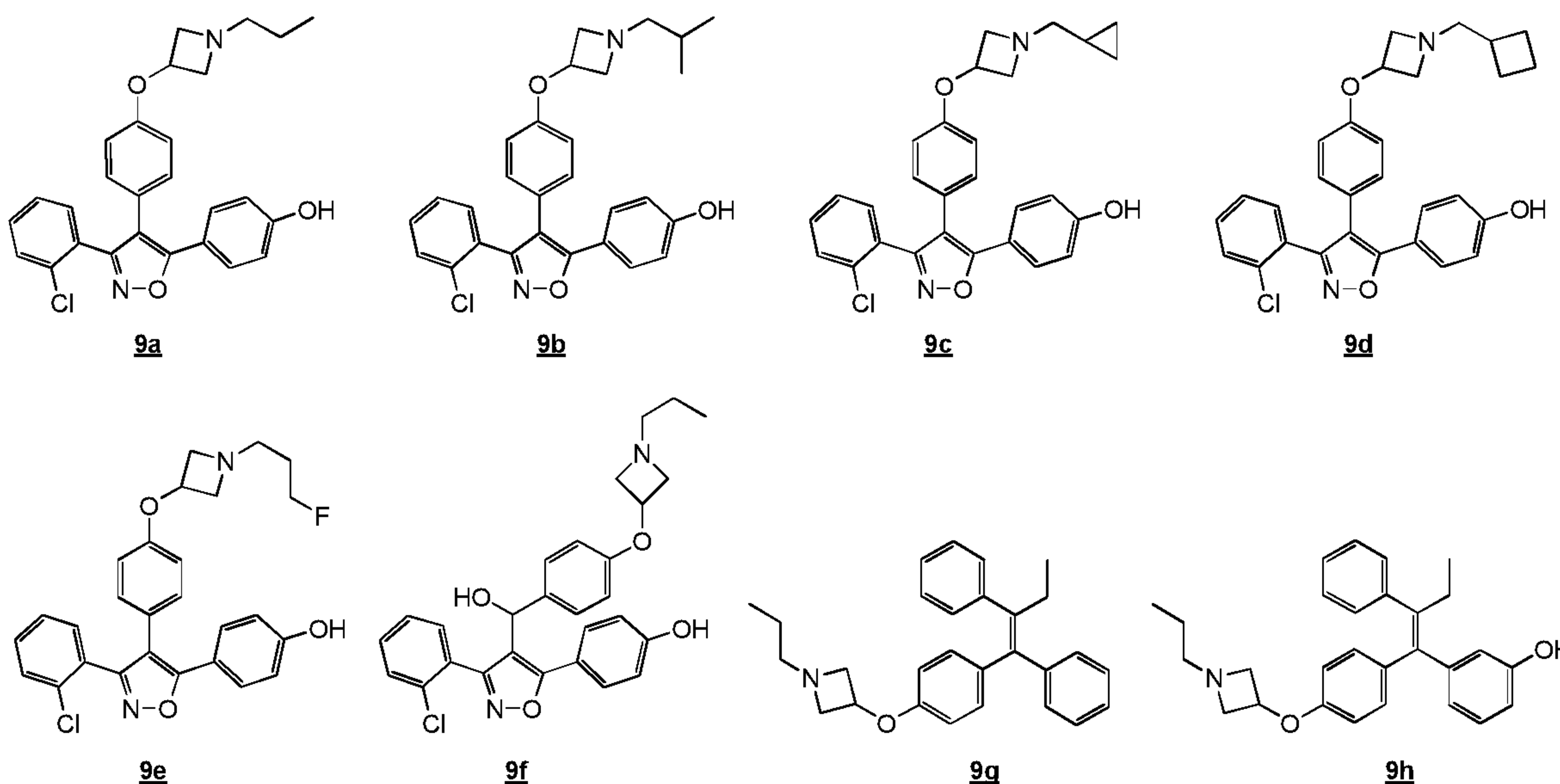
Formulae 8

5 In yet another embodiment of the present invention, the N-substituted azetidine derivative is selected from the group consisting of compounds according to any one of Formulae 9a-9h, shown hereinbelow.

The N-substituted azetidine derivatives of Formulae 9 are ER α antagonists with
 10 pIC₅₀ >7, are SERDs showing a minimum of 20% downregulation of ER α in T47D cells, do not (efficacy equal to or <0.10) stimulate proliferation in ER-positive, tamoxifen-resistant MCF-7H breast cancer cells, and are also orally bioavailable in the rat (see also Table 6 hereinbelow).

15 In the context of the present invention with "orally bioavailable" is meant that compounds, when dosed orally to a rat show oral exposure as determined by quantification of compound plasma levels in that rat. Typically, compounds are

dosed orally at 20 $\mu\text{mol/kg}$, as described in Example 14 hereinbelow. Oral exposure is determined by measuring plasma levels over the time range of 0-6 h after dosing and is expressed by AUC(0-6h). Compounds are considered orally bioavailable with an AUC(0-6h) $>0.3 \mu\text{M.h}$, and preferably with an AUC(0-6h) >1 5 $\mu\text{M.h}$.



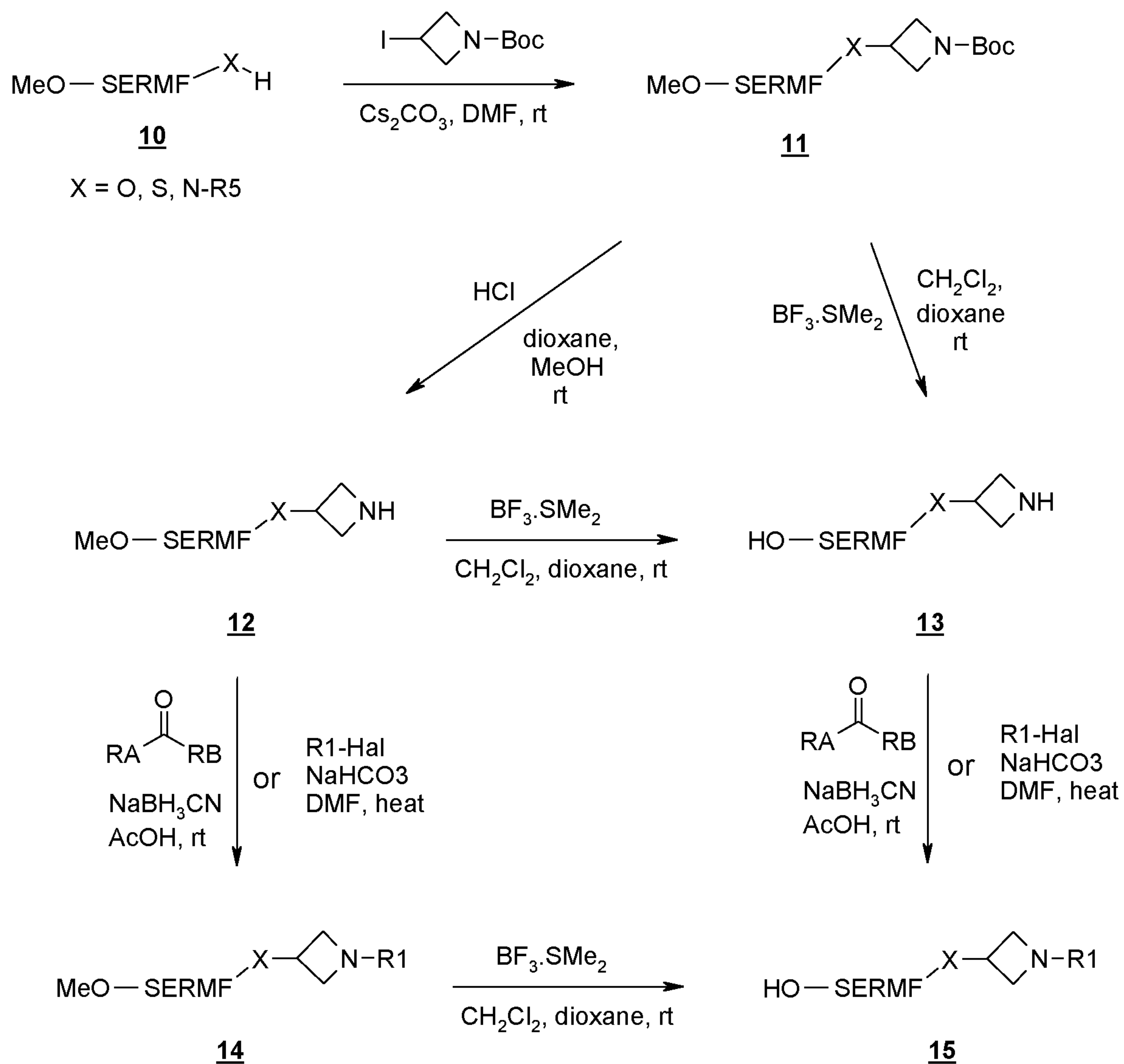
Formulae 9

10 The compounds of the present invention can be produced by various methods known in the art of organic chemistry. The general synthetic procedures used to prepare the compounds described in the examples below are depicted in the following reaction schemes. Variations to these schemes can easily be made by one skilled in the art. In the following schemes, PG refers to any suitable
15 protecting group and the R groups are as defined in the Formulae depicted above; where needed a functional group can be capped with a suitable protecting group during the synthesis.

A SERM typically contains a phenolic hydroxyl group. During the synthetic
20 sequences described below, this phenolic hydroxyl group, when present in intermediates, generally needs to be protected. In Schemes 1-4, a methoxy group is used as an example of a protected phenolic hydroxyl group. These groups are

indicated in the reaction schemes shown hereinbelow as MeO- and HO- attached to a SERMF fragment.

Scheme 1. Preparation of N-substituted azetidine derivatives

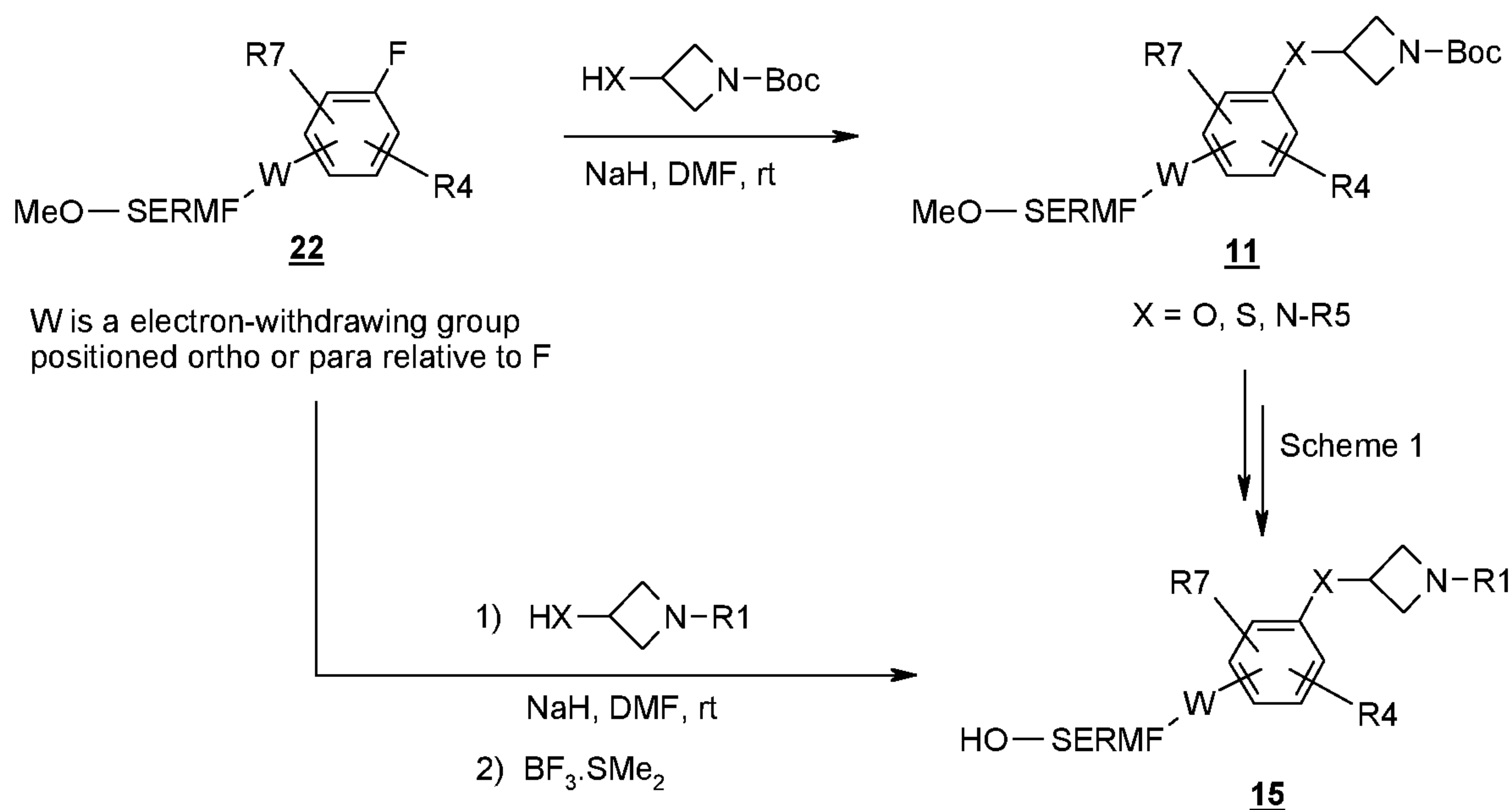


5

Starting from scaffold 10, containing a hydroxyl (X is O), thiol (X is S) or amine (X is N-R5) group on one side of the fragment SERMF, and on the other side a phenolic methoxy group, the X-H group is substituted by *tert*-butyl 3-iodoazetidine-1-carboxylate in dimethylformamide (DMF) as solvent and a suitable base, like cesium carbonate, to give the N-Boc azetidine compound 11. Deprotection of the azetidine nitrogen by removal of the Boc group, under acidic conditions, for

example by treatment with hydrochloric acid in methanol and 1,4-dioxane as co-solvent, gives azetidine compound 12. The phenolic methoxy group of compound 12 can be converted to a phenol group by reaction with borontrifluoride dimethylsulfide complex in methylene chloride to give compound 13. The azetidine
5 nitrogen of compounds 12 and 13 can be substituted by R1, for example by reaction with a suitable halide R1-Hal (Hal is Cl, Br or I) in the presence of NaHCO₃ as a base in dimethylformamide (DMF) as solvent in a sealed tube at elevated temperature under microwave irradiation to give compounds 14 and 15, respectively. Alternatively, R1 groups may be introduced by other commonly
10 known methods in the art of organic chemistry, like reductive amination, in which R1 is introduced by reaction of unprotected azetidine 12 or 13 with an appropriate aldehyde or ketone (R_A(C=O)R_B in which R_A and R_B, together with the carbon atom of the carbonyl moiety, form R1) under reductive conditions, for example in the presence of sodium cyanoborohydride in a suitable solvent, like methanol or
15 acetic acid, to give compounds 14 and 15, respectively.

An alternative route to introduce an N-substituted azetidine-X moiety onto a SERMF fragment is outlined in Scheme 2. In case the SERMF fragment contains a fluorophenyl group with an electron withdrawing group W *ortho* or *para* relative
20 to the fluorine, like compound 22, then direct substitution on the fluorine is possible to arrive at compound 11 by an aromatic substitution reaction. The required electron withdrawing substituent can be one or both of the substituents R4 or R7 or can be the linker W connecting the fluorophenyl group to the SERMF fragment. An example of such an electron withdrawing group W is a carbonyl group.
25 Compound 22 can be converted to compound 15 according to Scheme 1, but can also directly be converted to compound 15 by reaction with an azetidine moiety to which R1 is already attached as shown in the lower part of Scheme 2.

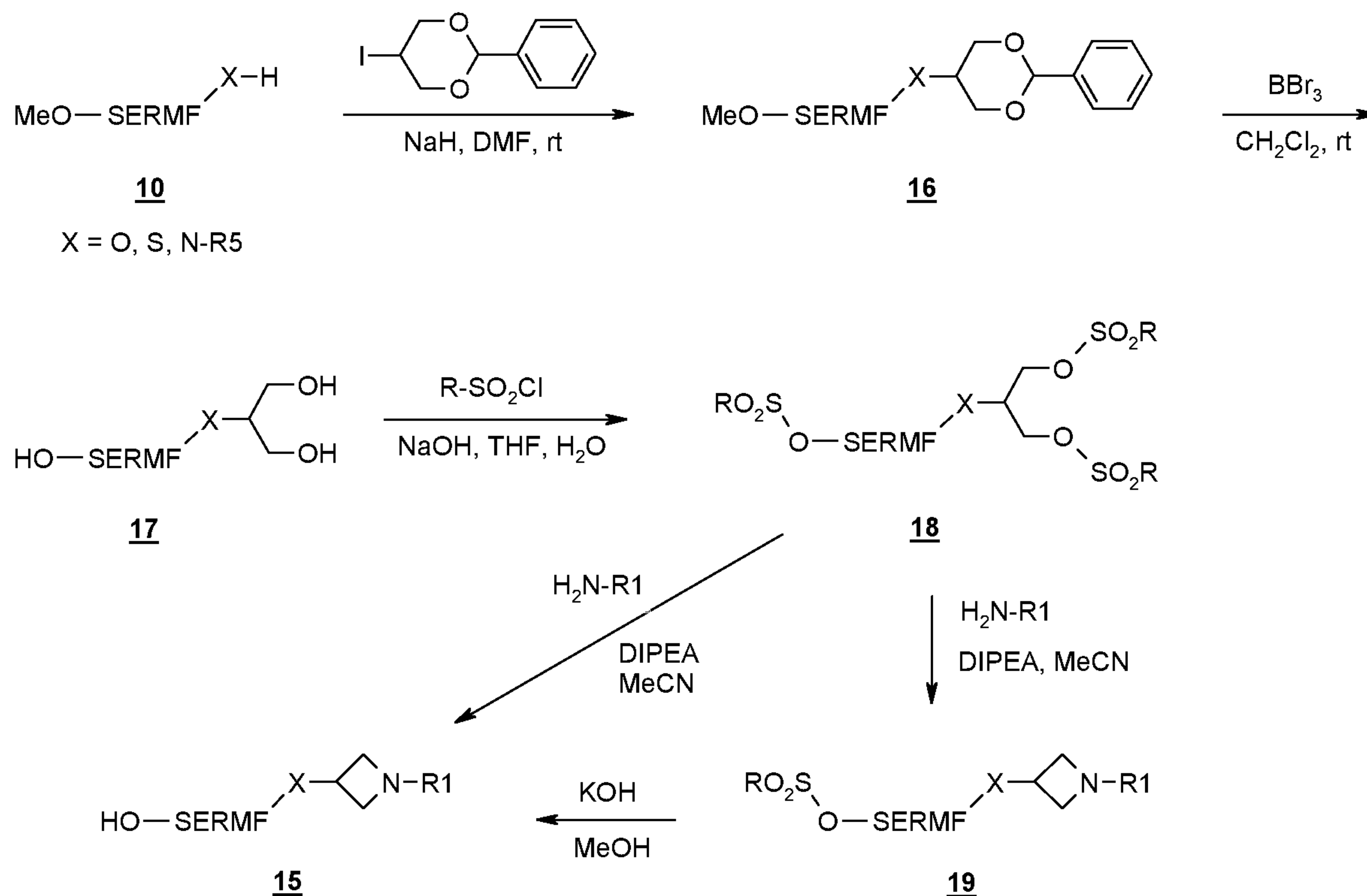
Scheme 2. Synthesis of compound 11 by aromatic substitution

5

An alternative way to prepare N-substituted azetidine compounds 15 is outlined in Scheme 3. In this approach, compound 10 is substituted by 5-iodo-2-phenyl-1,3-dioxane under basic conditions, for example with sodium hydride in dimethylformamide (DMF), to give compound 16. Simultaneous deprotection of the 2-phenyl-1,3-dioxane moiety and the phenolic methoxy group on the SERMF fragment with boron tribromide in methylene chloride gives compound 17. The hydroxyl groups in compound 17 can be converted to sulfonates by reaction with a suitable sulfonyl chloride (for example tosyl chloride or mesyl chloride) under basic conditions, like sodium hydroxide in a tetrahydrofuran/water mixture, to give compound 18. The 1,3-bis-sulfonate moiety in compound 18 can be converted to an N-substituted azetidine by reaction with amine $\text{H}_2\text{N-R}^1$ under basic conditions, for example with *N,N*-diisopropylethylamine in acetonitrile, resulting in the formation of compound 19. The sulfonate group attached to the phenolic hydroxyl group in compound 18 will not react under the conditions used for the conversion of compound 18 to compound 19 and will therefore still be present in compound 19. In the case of a tosyl group, it may be removed by reaction with potassium hydroxide in methanol, to give compound 15. In case the sulfonate group in

compound 18 is a mesyl group, then compound 18 can be converted directly into compound 15 when the mesylate group attached to the phenolic hydroxyl group is deprotected during work-up/purification to give phenolic compound 15.

5 Scheme 3. Preparation of substituted azetidine derivatives through sulfonates

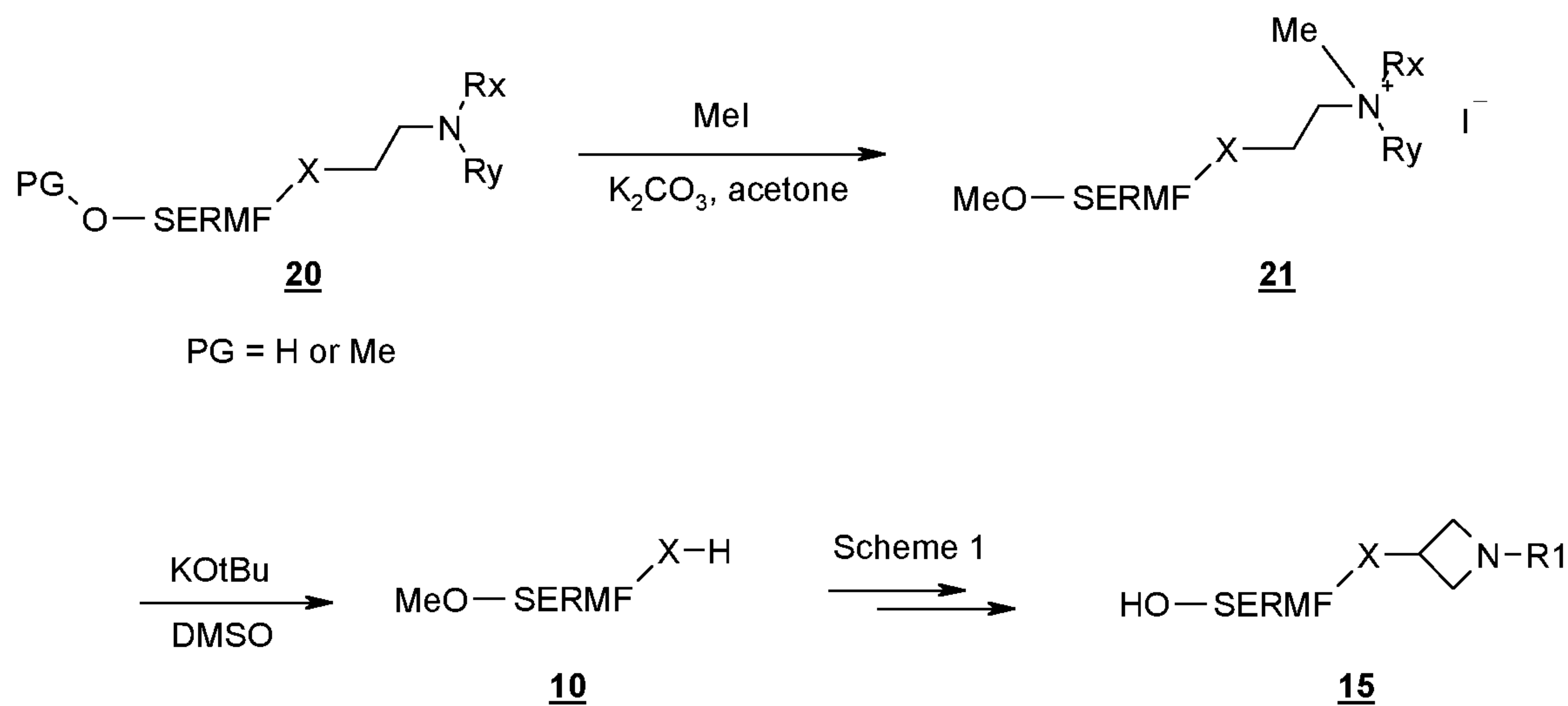


In those cases where the final product is an R1-substituted azetidine-X analogue of a SERM compound 20, the starting material 10 may be prepared starting from compound 20 containing a typical basic amine side chain of the general formula $\text{XCH}_2\text{CH}_2\text{NR}_x\text{R}_y$ attached to the SERMF fragment, as outlined in Scheme 4.

In the first step, the amine group in compound 20 is converted to the ammonium salt by reaction with iodomethane in the presence of potassium carbonate as base in acetone as solvent, to give compound 21. Simultaneously, an unprotected phenolic hydroxyl group on the SERMF fragment of compound 20 (*i.e.* when PG = H) will be converted to a methoxy group. The ethylammonium side chain of 21 can be removed by a Hofmann elimination reaction, under basic conditions, for example by the use of potassium *tert.*-butoxide in dimethylsulfoxide (DMSO) as

solvent, to give compound 10. Compound 10 can then be converted into compound 15 according to Scheme 1.

Scheme 4. Removal of basic amine side chain of a SERM

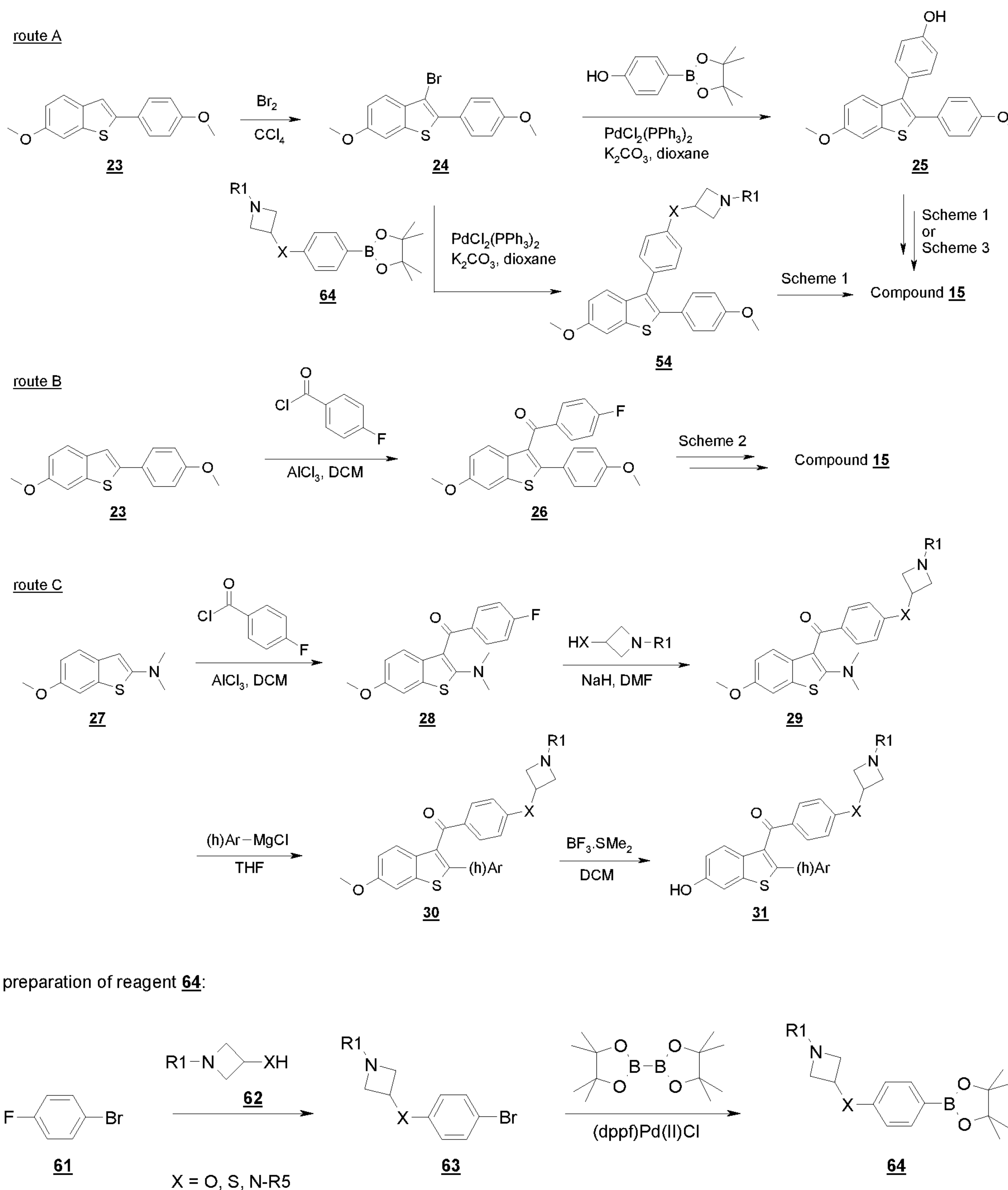


The required starting materials 10 and 22 in Schemes 1-4 can be prepared according to methods described in the literature.

10 In Scheme 5, synthetic routes are given for the preparation of a benzothiophene analogue of compound 10 (*i.e.* compound 25) and a benzothiophene analogue of compound 22 (*i.e.* compound 26). Such compounds can be further converted to final compounds according to Schemes 1-3. Compound 24 can also directly be converted to final compound 54 by reaction with a boronate that already contains

15 the N-substituted azetidine moiety. Introduction of heteroaryl groups on the 2-position of a benzothiophene scaffold can be accomplished according to route C in Scheme 5. The benzothiophene compounds in Scheme 5 can be substituted with R groups as defined in any one of the relevant Formulae 4 and 5, shown hereinabove.

Scheme 5. Synthesis of benzothiophene compounds



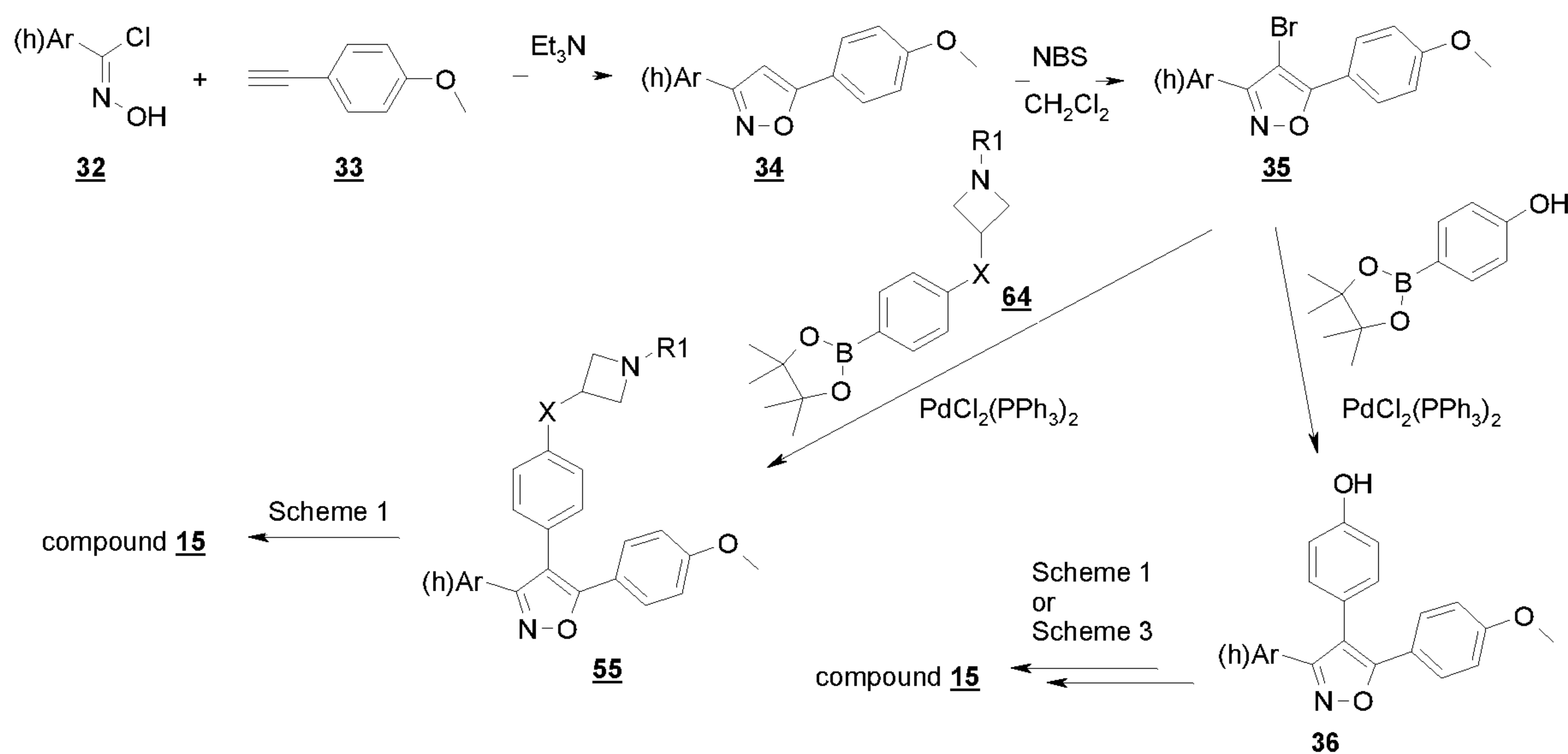
In Scheme 6, synthetic routes are given for the preparation of an isoxazole analogue of compound **10** (i.e. compound **36**) and an isoxazole analogue of compound **22** (i.e. compounds **44** and **47**). Such compounds can be further converted to final compounds according to Schemes 1-3. Compounds like **35** and

41 can also directly be converted to final compound 55 by reaction with a boronate that already contains the N-substituted azetidine moiety. The isoxazole compounds in Scheme 6 can be substituted with R groups as defined in any one of the relevant Formulae 4 and 5, shown hereinabove.

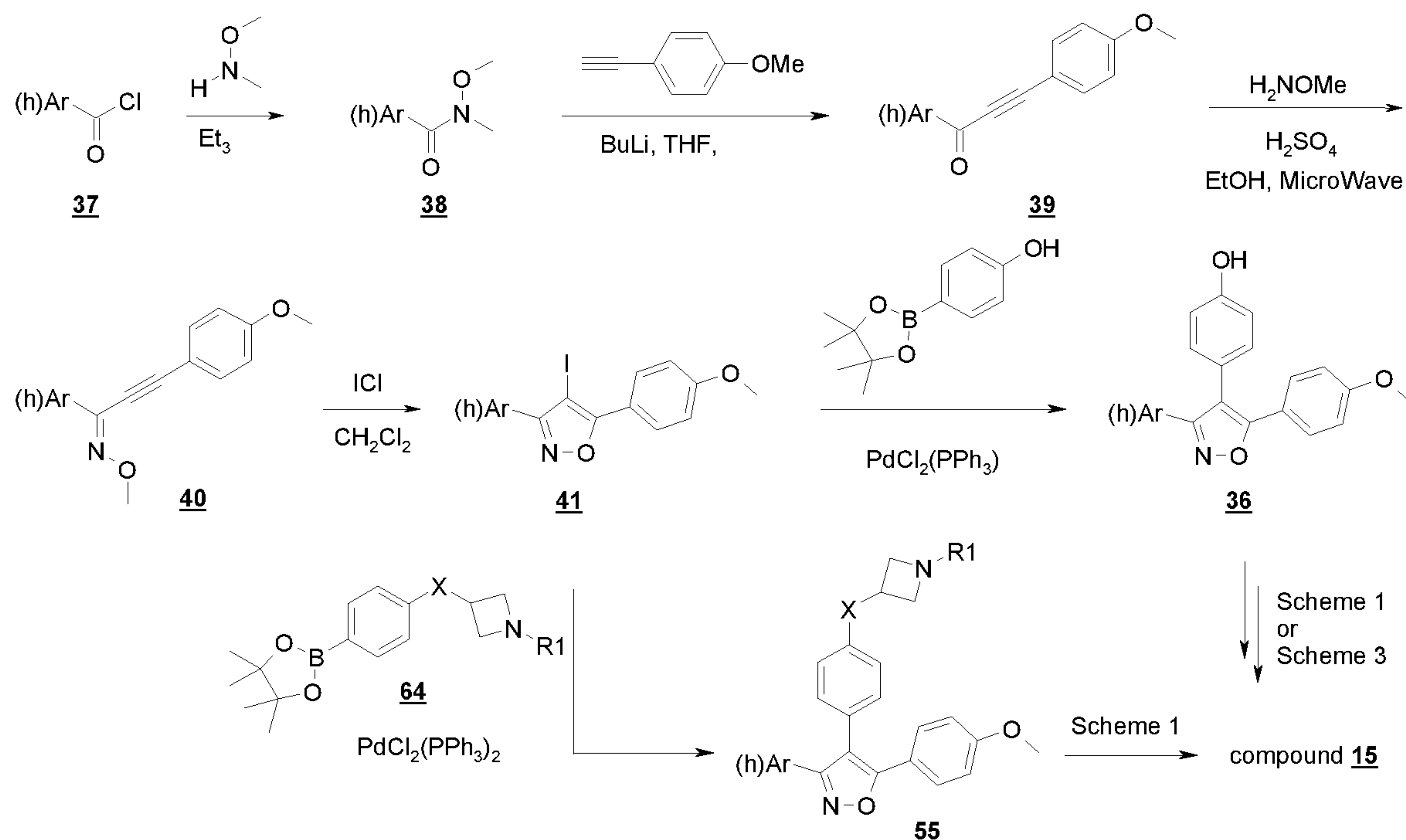
5

Scheme 6. Synthesis of isoxazole compounds

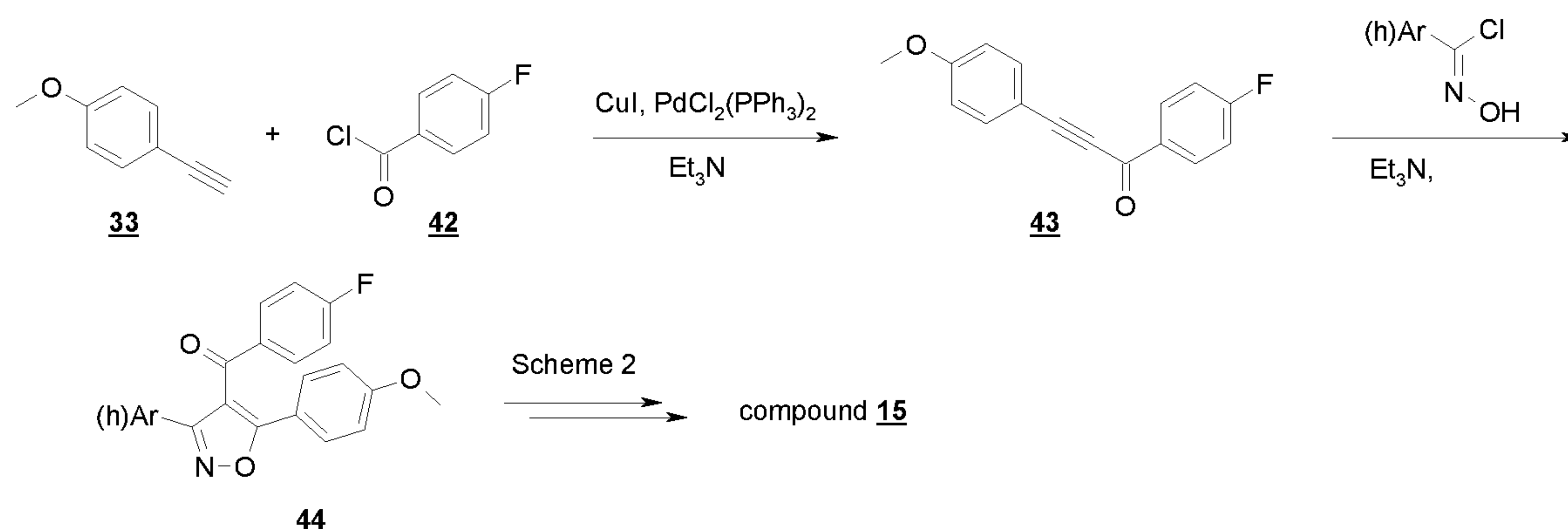
route A



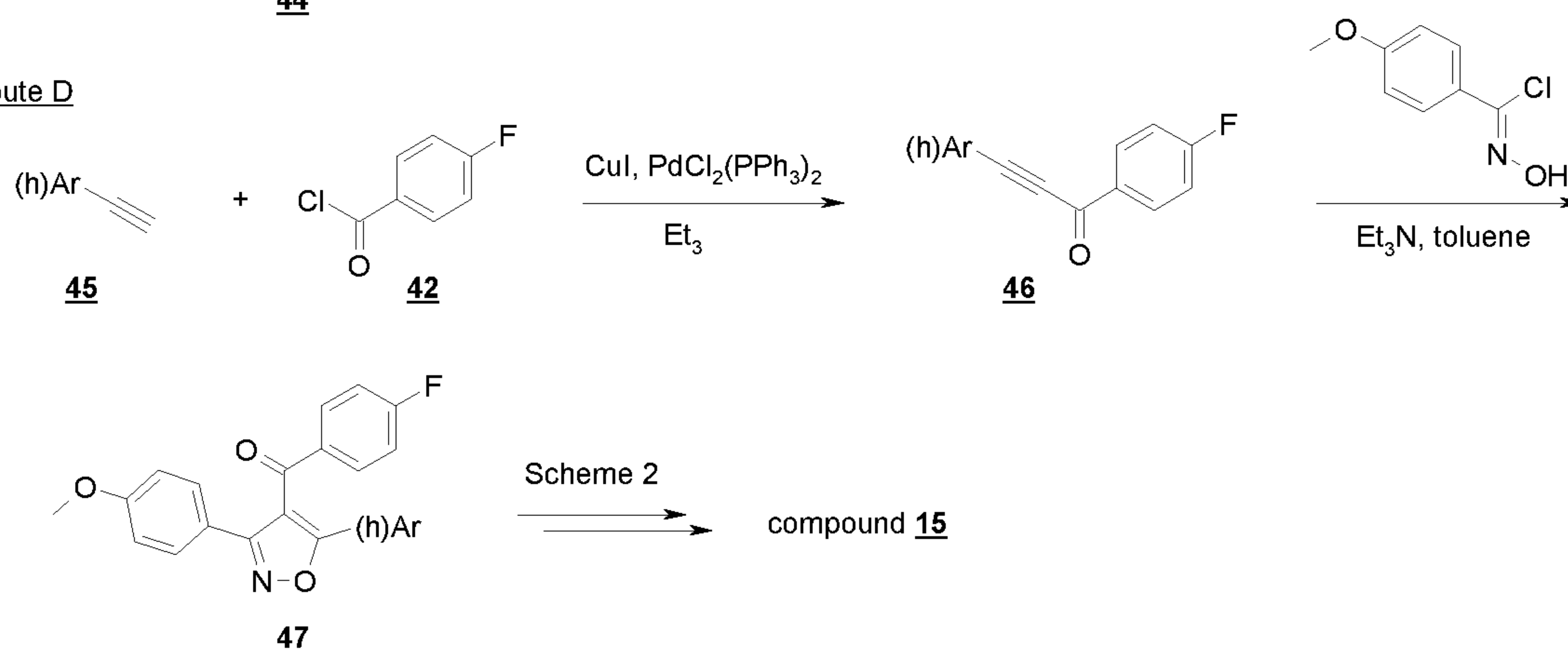
route B



route C



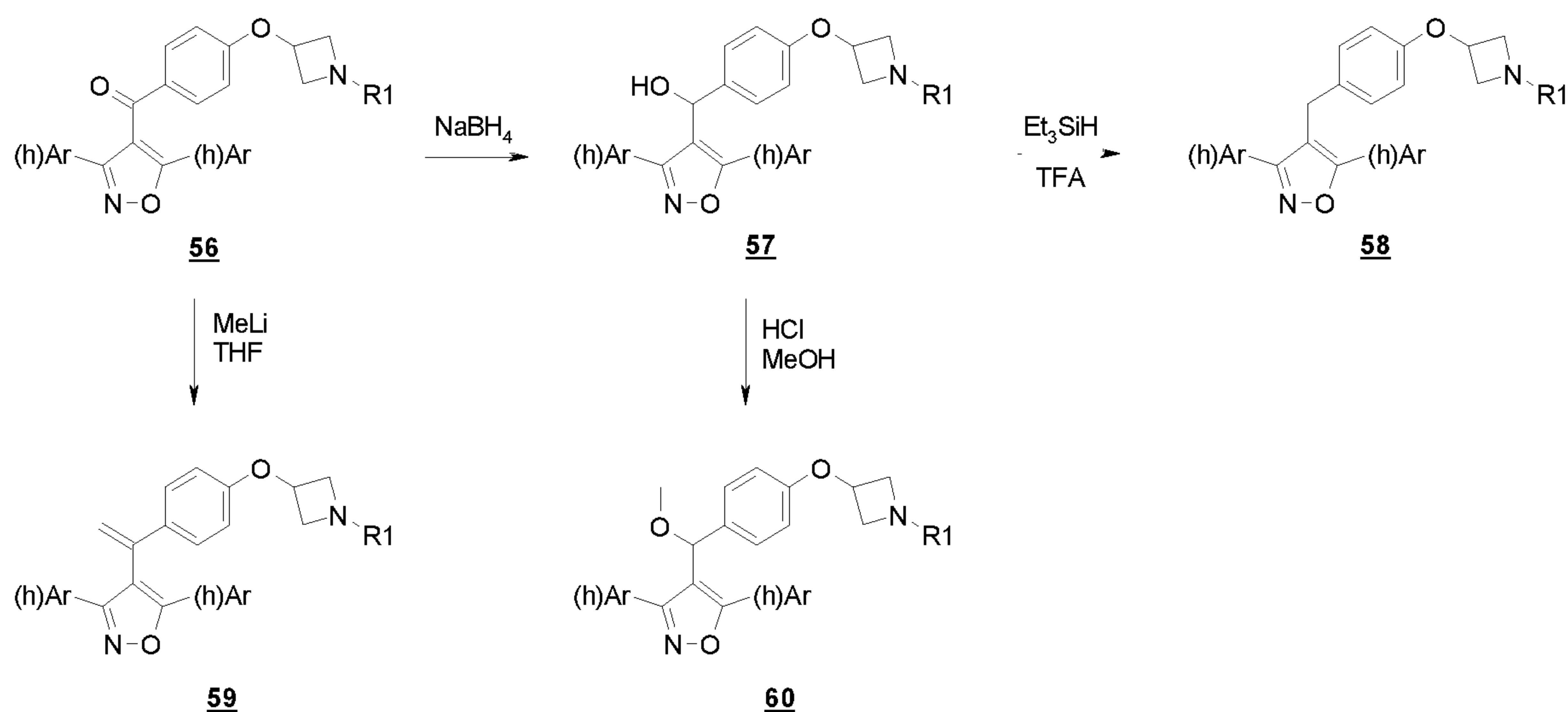
route D



5 Analogues with different linker moieties V, as indicated in Formula 4, can be prepared as exemplified in Scheme 7. For example, isoxazole **56**, which has a carbonyl group as linker V, can be converted to a hydroxymethylene linker analogue by reduction with sodium borohydride to give compound **57**, which can be further reduced to a methylene linker analogue by reduction with triethylsilane and trifluoro acetic acid (TFA) to give compound **58**. Compound **56** can also be converted to a linker with V being C=CH₂, by reaction with methyllithium, to give compound **59**. A compound with linker V being CH(OMe) can be obtained by stirring compound **57** in a methanolic HCl solution to give compound **60**.

40

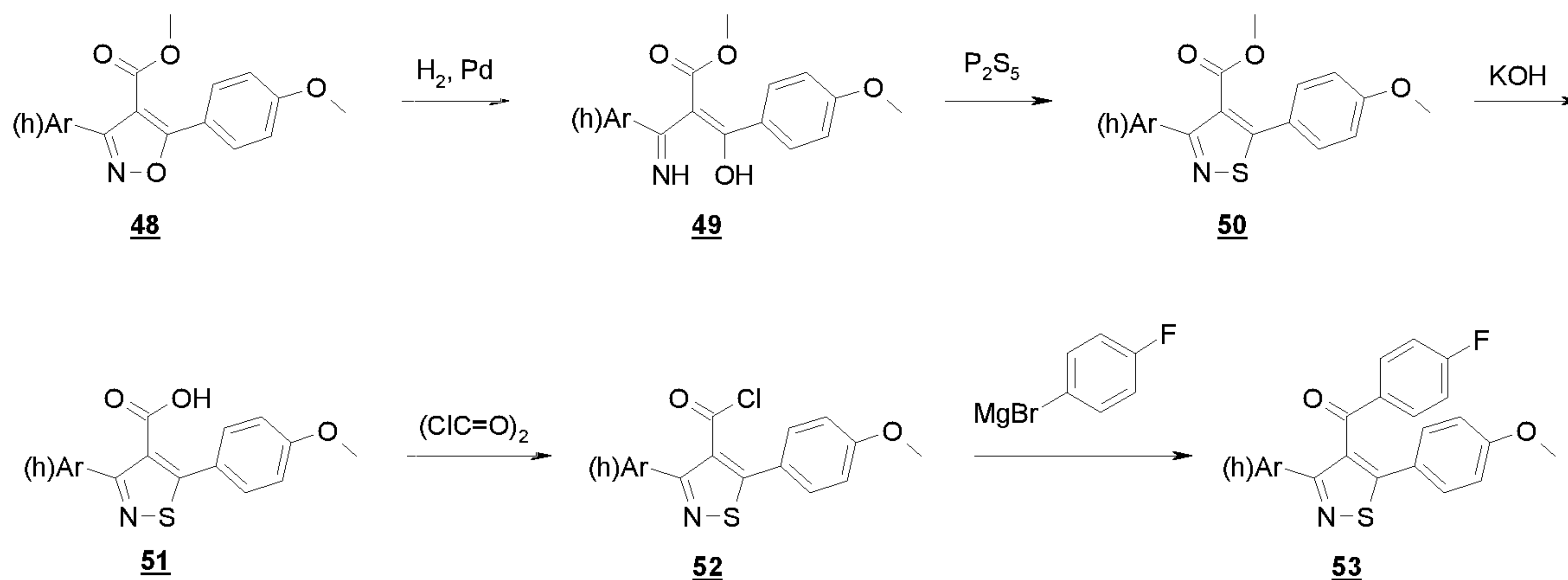
Scheme 7. Modification of carbonyl linker



5

Isothiazoles can be prepared from isoxazoles according to the synthetic sequence shown in Scheme 8. Reductive ring-opening of isoxazole 48 gives compound 49, which can be ring-closed with phosphorus pentasulfide to give isothiazole 50. Subsequent saponification and reaction with oxalyl chloride gives acid chloride 52, which can be converted with a Grignard reagent to compound 53. Such compounds can be further converted to final compounds according to Schemes 1-3. The isothiazole compound in Scheme 8 can be substituted with R groups as defined in any one of the Formulae 4 and 5, shown hereinabove.

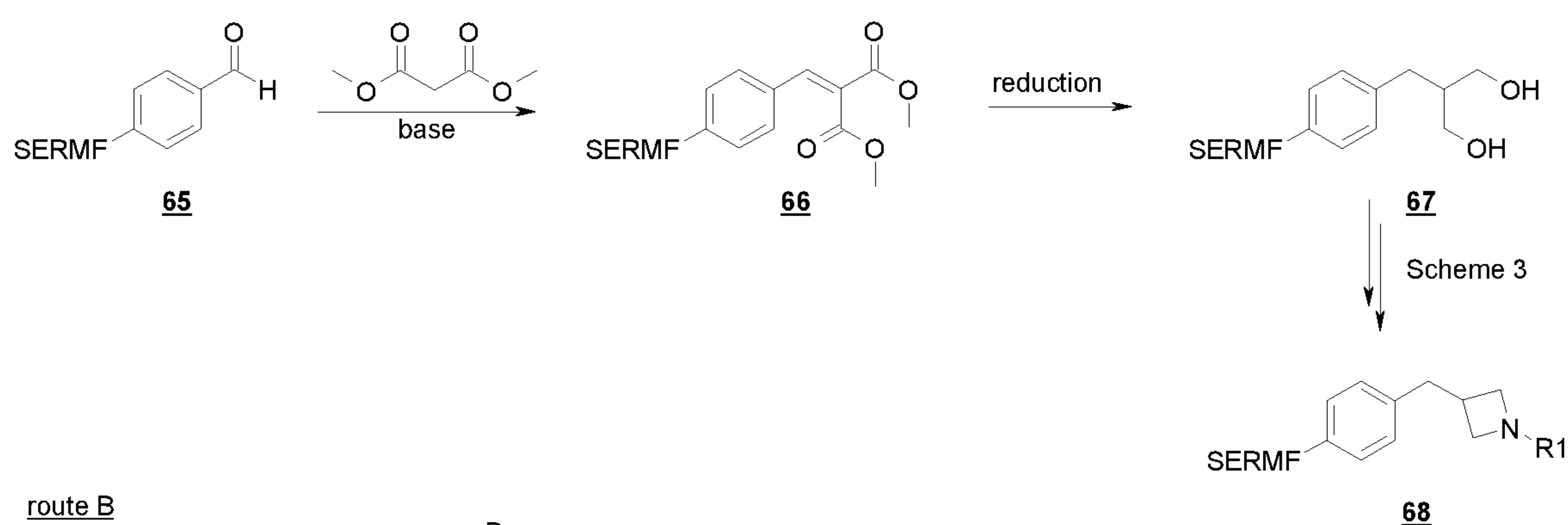
15 Scheme 8. Conversion of isoxazole to isothiazole



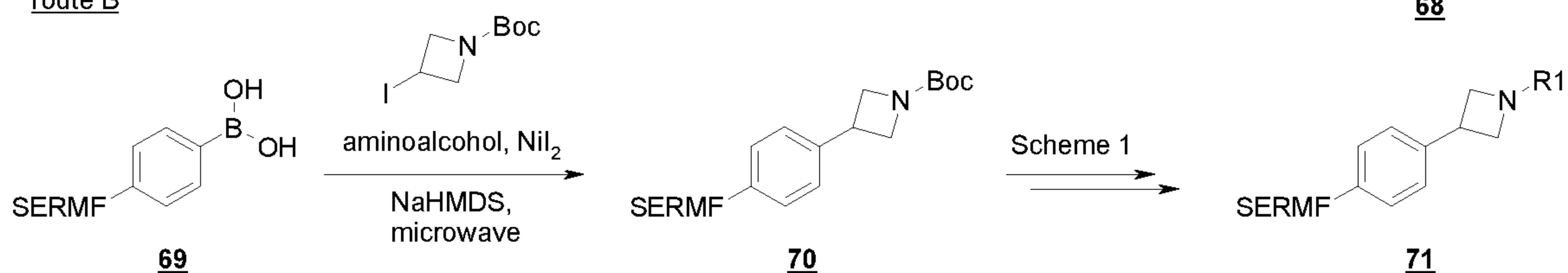
Compounds of Formula 1 in which the group X is CH₂ can be synthesized starting from compound 65, as outlined in Scheme 9, route A. Conversion of compound 65 to compound 66 by a Knoevenagel condensation, followed by reduction of the double bond gives compound 67, which can be converted to compound 68 according to Scheme 3.

Scheme 9. Synthesis of compounds of Formula 1 in which X is CH₂, carbonyl or a direct bond

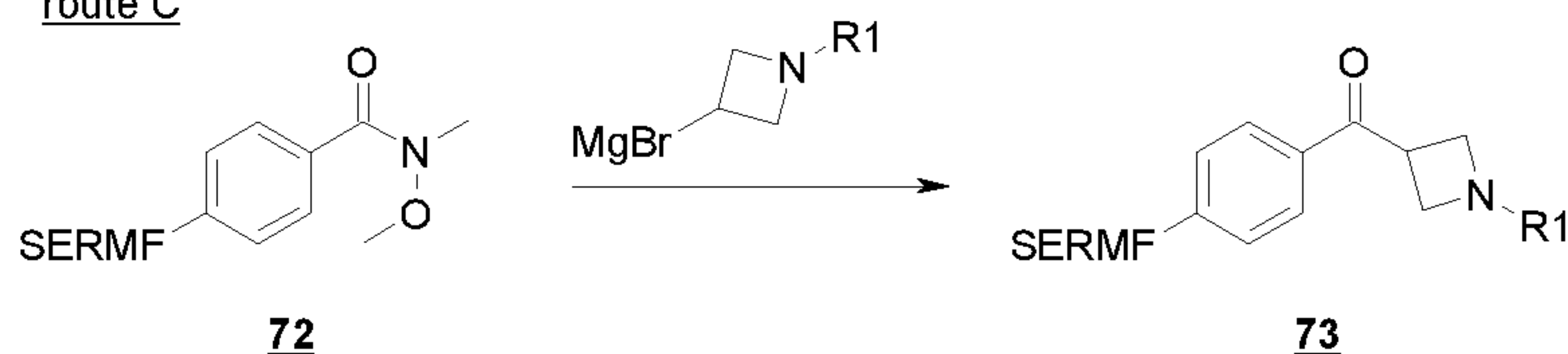
route A



route B



route C



10

Compounds of Formula 1 in which the group X is a direct bond can be synthesized starting from compound 69, as outlined in Scheme 9, route B. Compound 69 can be converted to compound 70 by a Suzuki reaction. Compound 70 can be converted to compound 71 according to Scheme 1.

15

Compounds of Formula 1 in which the group X is carbonyl can be synthesized starting from compound 72, as outlined in Scheme 9, route C. Weinreb amide 72 can be converted to compound 73 by a Grignard reaction.

- 5 The enantiomers of chiral compounds may be separated in a conventional way by chiral HPLC or chiral supercritical fluid carbondioxide (SFC) HPLC, using an appropriate chiral HPLC column, for example a Chiralpak AD, OD or AS column, to give single enantiomers associated with less than 5%, preferably less than 2%, in particular less than 1% of the other enantiomer.
- 10 Ester prodrugs can be made of the parent compounds by esterification of free hydroxyl groups, for example by reaction with an appropriate acid anhydride in pyridine.
- 15 In a further aspect, the N-substituted azetidine derivatives of the present invention and their prodrugs, isotopically-labelled derivatives or pharmaceutically acceptable salts thereof, i.e. in accordance with any one of the Formulae described hereinabove, are useful in therapy. As such the N-substituted azetidine derivatives of the present invention are useful for the prevention or treatment of
- 20 ovulatory dysfunction, uterine cancer, endometrium cancer, ovarian cancer, endometriosis, osteoporosis, prostate cancer, benign prostatic hypertrophy, and breast cancer, in particular ER-positive, hormone treatment-resistant breast cancer.
- 25 The present invention further includes a method for the treatment of a mammal, including a human and an animal, suffering from or liable to suffer from any of the aforementioned diseases or disorders, which comprises administering a therapeutically effective amount of an N-substituted azetidine derivative according to the present invention or a prodrug, isotopically-labelled derivative or
- 30 pharmaceutically acceptable salt thereof to a mammal in need thereof. By effective amount or therapeutically effective amount is meant an amount of compound or a composition of the present invention effective in inhibiting the above-noted

diseases and thus producing the desired therapeutic, ameliorative, inhibitory or preventative effect.

The present invention also relates to a method of preventing or treating ovulatory
5 dysfunction, uterine cancer, endometrium cancer, ovarian cancer, endometriosis, osteoporosis, prostate cancer, benign prostatic hypertrophy, and breast cancer, in particular ER-positive, hormone treatment-resistant breast cancer, comprising administering therapeutically effective amounts of an N-substituted azetidine derivative in accordance with the present invention to a mammal in need thereof.

10

In another aspect, the present invention relates to the use of an N-substituted azetidine derivative, in accordance with any one of the Formulae described hereinabove, in combination with an agent, or a therapy, that reduces circulating levels of estrogens in premenopausal women suffering from endometriosis.
15 Examples of such agents or therapies being treatment with progestagens, selective progesterone receptor modulators (SPRMs), gonadotropin releasing hormone receptor (GnRH-R) agonists or antagonists, or combined estrogen-progestagen preparations - also known as contraceptives.

20 In a still further aspect, the present invention relates to a pharmaceutical composition comprising an N-substituted azetidine derivative in accordance with the present invention in admixture with a pharmaceutically acceptable excipient. With a pharmaceutically acceptable excipient is meant one or more pharmaceutically acceptable excipients.

25

The present invention also relates to a method of preventing or treating ovulatory dysfunction, uterine cancer, endometrium cancer, ovarian cancer, endometriosis, osteoporosis, prostate cancer, benign prostatic hypertrophy, and breast cancer, in particular ER-positive, hormone treatment-resistant breast cancer, comprising
30 administering therapeutically effective amounts of a pharmaceutical composition comprising an N-substituted azetidine derivative in admixture with a pharmaceutically acceptable excipient in accordance with the present invention to a mammal in need thereof.

In a preferred embodiment, the present invention relates to the use of an N-substituted azetidine derivative in accordance with any one of Formulae 6, 7, 8 or 9 for the prevention or treatment of ovulatory dysfunction, uterine cancer, endometrium cancer, ovarian cancer, endometriosis, osteoporosis, prostate cancer, benign prostatic hypertrophy, and breast cancer, in particular ER-positive, hormone treatment-resistant breast cancer. Relevant biological activity data of the compounds according to any one of Formulae 6, 7, 8 or 9 can be found in Tables 3, 4, 5 and 6, respectively, as depicted hereinbelow.

10

In another preferred embodiment, the present invention relates to the use of an N-substituted azetidine derivative in accordance with any one of Formulae 6, 7, 8 or 9 for the treatment of ER-positive, tamoxifen-resistant breast cancer.

15 The amount of N-substituted azetidine derivative in accordance with the present invention, also referred to herein as the active ingredient, which is required to achieve a therapeutic effect will, of course, vary with the particular compound, the route of administration, the age and condition of the recipient and the particular disorder or disease being treated.

20

The exact dose and regimen of administration of the active ingredient, or a pharmaceutical composition thereof, may vary with the particular compound, the route of administration, and the age and condition of the individual subject to whom the medicament is to be administered.

25

In general, parenteral administration requires lower dosages than other methods of administration which are more dependent upon absorption. However, a suitable dosage for humans may be 0.0001-10 mg per kilogram body weight, more in particular 0.01-10 mg per kilogram body weight. The desired dose may be presented as one dose or as multiple subdoses administered at appropriate intervals throughout the day or as doses to be administered at appropriate daily intervals. It may also be administered once-a-week or once-a-month. The dosage

30

as well as the regimen of administration may differ between a female and a male recipient.

Whilst it is possible for the active ingredient to be administered alone, it is
5 preferable to present it as a pharmaceutical composition. The present invention
therefore also provides a pharmaceutical composition comprising an N-substituted
azetidine derivative according to the present invention in admixture with one or
more pharmaceutically acceptable excipients, such as the ones described in
Gennaro *et al.*, Remington: *The Science and Practice of Pharmacy*, 20th Edition,
10 Lippincott, Williams and Wilkins, 2000; see especially part 5: pharmaceutical
manufacturing. Suitable excipients are described e.g., in the Handbook of
Pharmaceutical Excipients, 2nd Edition; Editors A. Wade and P.J. Weller, American
Pharmaceutical Association, Washington, The Pharmaceutical Press, London,
1994. Compositions include those suitable for oral, nasal, pulmonary, topical
15 (including buccal, sublingual and transdermal), parenteral (including
subcutaneous, intravenous and intramuscular) or rectal administration.

The mixtures of an N-substituted azetidine derivative according to the present
invention and one or more pharmaceutically acceptable excipients may be
20 compressed into solid dosage units, such as tablets, or be processed into
capsules or suppositories. By means of pharmaceutically suitable liquids the
compounds can also be applied as an injection preparation in the form of a
solution, suspension, emulsion, or as a spray, e.g., a nasal or buccal spray. For
making dosage units e.g., tablets, the use of conventional additives such as fillers,
25 colorants, polymeric binders and the like is contemplated. In general, any
pharmaceutically acceptable additive can be used. The compounds of the
invention are also suitable for use in an implant, a patch, a gel or any other
preparation for immediate and/or sustained release.

30 Suitable fillers with which the pharmaceutical compositions can be prepared and
administered include lactose, starch, cellulose and derivatives thereof, and the
like, or mixtures thereof used in suitable amounts. For parenteral administration,
aqueous suspensions, isotonic saline solutions and sterile injectable solutions may

be used, containing pharmaceutically acceptable dispersing agents and/or wetting agents, such as propylene glycol or butylene glycol.

The present invention further includes a pharmaceutical composition, as
5 hereinbefore described, in combination with packaging material suitable for said composition, said packaging material including instructions for the use of the composition as described hereinbefore.

The present invention is illustrated in the following examples.

10

EXAMPLES

In the following examples, the numbering of compounds follows the numbering of compounds shown in the Schemes of the description above. Analytical data on the
15 compounds of Formulae 6, 7, 8 and 9 synthesized can be found in Tables 3, 4, 5 and 6, respectively hereinbelow.

General Procedure A (Synthesis according to Scheme 1)

20 **Step 1** - Coupling with 1-Boc-3-iodo-azetidine

A suspension of compound 10 and cesium carbonate (4 equivalents) in dimethylformamide (DMF) was stirred for 5 minutes at room temperature under N₂ atm. Then 1-Boc-3-iodo-azetidine (2 equivalents) was added. This reaction mixture was stirred overnight at room temperature. The reaction mixture was
25 poured into water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na₂SO₄) and evaporated to dryness to afford the crude compound, which was purified by column chromatography (EtOAc/Heptane) to give the desired Boc azetidine 11.

30 **Step 2** - Acidic cleavage of Boc group

To a solution of Boc azetidine 11 in methanol, 15 equivalents of hydrogen chloride (4 N in dioxane) was added. The reaction mixture was stirred for 3h at room temperature. According to LCMS desired product was formed. The reaction

mixture was diluted with methanol and was concentrated. The resulting residue was used in the next step without purification or was triturated with diethyl ether and subsequently filtered over a medium fritted glass funnel, rinsed with diethyl ether, and collected to give compound 12 as a white solid.

5

Step 3 - Reductive amination of azetidine

To a mixture of compound 12, aldehyde R1-CHO (2 equivalents) and sodium cyanoborohydride (2 equivalents) in methanol and molsieves (3Å), acetic acid (1 equivalent) was added. This reaction mixture was stirred overnight at room temperature under N₂ atm. The reaction mixture was diluted with methanol, filtered and then flushed over a SCX-2 column with methanol to get rid of the impurities. Then the desired product was eluted with 0.7 N ammonia/methanol solution to give compound 14.

15 **Step 4 - Demethylation of methoxy (and cleavage of Boc, if present)**

To a solution of compound 14 in dichloromethane (DCM) borontrifluoride-methyl sulfide complex (20 equivalents) was added. This reaction mixture was stirred overnight at room temperature under N₂ atm. The reaction mixture was quenched with methanol and stirred at room temperature for 30 min. The mixture was further diluted with methanol, filtered and loaded onto a SCX-2 column. The SCX-2 column was flushed with methanol to get rid of the impurities and was then eluted with 0.7 N ammonia solution to obtain the desired product. The crude product was concentrated and purified by prep. HPLC (acetonitrile/water). The product-containing fractions were freeze-dried to afford compound 15 as a white solid.

25

General Procedure B (Synthesis according to Scheme 2)

To a suspension of 1-Boc-3-(hydroxy)azetidine (0.5 mmol) and cesium carbonate (1.5 mmol) in dimethylformamide (4 ml) was added compound 22 (0.25 mmol). The mixture was stirred under a nitrogen atmosphere at room temperature for 16 h. Then water was added and the mixture was extracted with ethyl acetate (2x). The combined organic layers were washed with brine (1x), dried (Na₂SO₄) and

30

concentrated. The crude product was purified by prep. HPLC (acetonitrile/water) to give compound 11 in good purity.

Under a nitrogen atmosphere, at room temperature, sodium hydride (70 mmol; 5 washed with heptane) was suspended in dimethylformamide (120 ml). Then 1-propylazetidin-3-ol hydrochloride (19.9 mmol) was added slowly and the resulting mixture was stirred at room temperature for 15 min. Then, compound 22 (PG=H or Me) (11.7 mmol) was added and the mixture was stirred at room temperature for 16 h. Water was added and the mixture was extracted with ethyl acetate (4x). The 10 combined organic layers were washed with brine (1x), dried (Na_2SO_4) and concentrated. The crude product was purified by prep. HPLC (acetonitrile/water). The product-containing fractions were freeze-dried from acetonitrile/2N HCl to afford the target compound as HCl salt as a white solid in good purity.

15 Compound 14 (PG=Me) can be converted to compound 15 (PG=H) according to General Procedure A, Step 4.

General Procedure C (Synthesis according to Scheme 3)

20 Step 1

To a stirring solution of 2-phenyl-1,3-dioxan-5-ol (60 mmol) in dimethylformamide (145 ml), at room temperature and under a nitrogen atmosphere, was added sodium hydride (159 mmol) and the mixture was stirred for 20 min. To this mixture a solution of compound 10 (26 mmol) in dimethylformamide (105 ml) was added. 25 The resulting mixture was stirred at room temperature for 16 h. The reaction was quenched with saturated aqueous ammonium chloride solution and the mixture was extracted with ethyl acetate (4x). The combined organic layers were washed with water (1x) and brine (1x), dried (Na_2SO_4) and concentrated to give compound 16, which was used as such in the next step.

30

Step 2

Under a nitrogen atmosphere, compound 16 (29 mmol) was dissolved in methylene chloride (700 ml). The mixture was cooled to 0°C and boron tribromide

(147 mmol) was added. The reaction mixture was stirred at 0°C for 90 min and was then poured into ice/water. The resulting mixture was extracted with ethyl acetate (2x). The combined organic layers were washed with brine (1x), dried (Na₂SO₄) and concentrated. The crude product was purified by column chromatography over silica to give compound 17 in good purity.

Step 3

Under a nitrogen atmosphere at 0°C compound 17 (18 mmol) and triethylamine (151 mmol) were dissolved in ethyl acetate (250 ml), methanesulphonyl chloride (149 mmol) was added and the resulting mixture was stirred for 16 h. Then, ethyl acetate was added and the mixture was washed with water. The organic layer was dried (Na₂SO₄) and concentrated to give compound 18, which was used as such in the next step.

Step 4

A solution of compound 18 (SO₂R=mesyl) (0.21 mmol) and amine R1-NH₂ (5 equivalents) in acetonitrile (6 ml) was stirred at 100°C in a sealed tube for 16 h. The reaction mixture was concentrated and was purified by prep. HPLC (acetonitrile/water). To the product-containing fractions 4N HCl was added and the mixture was freeze-dried to afford compound 15 as a white solid in good purity.

Step 5

A solution of compound 18 (SO₂R=tosyl) (0.20 mmol) and amine R1-NH₂ (5 equivalents) in acetonitrile (6 ml) was stirred at 100°C in a sealed tube for 16 h. The reaction mixture was concentrated and was purified by prep. HPLC (acetonitrile/water). To the product-containing fractions 4N HCl was added and the mixture was freeze-dried to afford compound 19 as a white solid in good purity.

Step 6

To a solution of compound 19 (0.04 mmol) in methanol (3 ml) was added potassium hydroxide (200 mg). The mixture was stirred at 80°C in a sealed tube for 2 h and was then cooled to room temperature and loaded onto an SCX-2 column (10 g column material). The column was washed with methanol and then

the product was eluted with 0.7M ammonia in methanol. The crude product was further purified by prep. HPLC (acetonitrile/water). The product-containing fractions were mixed with 4N HCl and the mixture was freeze-dried to afford compound 15 as a white solid in good purity.

5

General Procedure D (Synthesis according to Scheme 4)**Step 1** - Converting the amine group to the ammonium salt

A yellow suspension of compound 20, iodomethane (8 equivalents), and
10 potassium carbonate (8 equivalents) in acetone was stirred at room temperature for 16 h. The reaction mixture was diluted with methanol and was concentrated. The resulting crude product was either used directly in the next step without purification or was triturated with diethyl ether, filtered through a medium fritted glass funnel, rinsed with diethyl ether, giving the desired ammonium salt 21 after
15 collection as a yellow solid in quantitative yield.

Step 2 - Cleavage of ethylammonium side chain

A solution of compound 21 and potassium tert-butoxide (5 equivalents) in DMSO was stirred for 3h at room temperature. The reaction mixture was diluted with
20 water and HCl was added until pH=1. The mixture was stirred for another 15 min and was then extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried (Na₂SO₄) and evaporated to dryness to afford the crude compound, which was purified by column chromatography (EtOAc/Heptane) to give the desired phenol 10 in excellent yield.

25

Compound 10 can be converted to compound 15 according to General Procedure A.

General Procedure E (Syntheses according to Scheme 5)

30 Compound 24 can be prepared as described in literature (A.D. Palkowitz *et al.*, *J. Med. Chem.* 40 (1997) 1407-1416).

A solution of compound 24 (1.0 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (2.0 mmol), $K_3PO_4 \cdot 7H_2O$ (3.0 mmol) and $PdCl_2(PPh_3)_2$ (0.05 mmol) in dioxane (10 ml) was stirred under N_2 atmosphere at 90°C for 16 h. The reaction mixture was then cooled to room temperature. Water was added and the mixture
5 was extracted with ethylacetate (3x). The combined organic layers were washed with brine (1x), dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography to give compound 25 in good purity.

Synthesis of pinacolboronate 64

10 Step 1

Under a nitrogen atmosphere, sodium hydride (30 mmol) was added to anhydrous dimethylformamide (10 ml) and then compound 62 (15 mmol) was added. The mixture was stirred at room temperature for 30 min. Then a solution of 4-bromo-fluorobenzene (18 mmol) in dimethylformamide (5 ml) was added dropwise. The
15 mixture was stirred at 60°C for 16 h. Then, ethyl acetate was added and the mixture was poured into water. The organic phase was separated and washed with water (3x) and brine (1x), dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography over silica (methylene chloride/-methanol) to afford compound 63 in good purity.

20

Step 2

Under a nitrogen atmosphere, compound 63 (10 mmol), bis(pinacolato)diboron (15 mmol) and potassium acetate (10 mmol) were dissolved in dioxane (30 ml). Then 1,1'-bis(diphenylphosphino)ferrocene palladium(II) chloride (0.5 mmol) was added
25 and the mixture was stirred at 80°C for 16 h. The reaction mixture was poured into water and was extracted with ethyl acetate (2x). The organic layers were dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography over silica (methylene chloride/methanol) to afford compound 64 in good purity.

30

A solution of compound 24 (1.0 mmol), compound 64 (2.0 mmol), $K_3PO_4 \cdot 7H_2O$ (3.0 mmol) and $PdCl_2(PPh_3)_2$ (0.05 mmol) in dioxane (10 ml) was stirred under N_2 atmosphere at 90°C for 16 h. The reaction mixture was then cooled to room

temperature. Water was added and the mixture was extracted with ethylacetate (3x). The combined organic layers were washed with brine (1x), dried (Na₂SO₄) and concentrated. The crude product was purified by column chromatography to give compound 54 in good purity.

5

Compounds 25 and 54 can be converted to compound 15 according to General Procedure A.

Compound 26 can be prepared according to the method described by C. Yang *et al.*, *Bioorg. Med. Chem. Lett.* 15 (2005) 1505-1507. Compound 26 can be converted to compound 15 according to General Procedure A.

The syntheses in Scheme 5, route C were performed analogously to the methods described by D.A. Bradley *et al.* in *Tetrahedron Letters* 40 (1999) 5155-5159.

15

General Procedure F (Synthesis according to Scheme 6, route A)

Step 1

(E/Z)-2-chlorobenzaldehyde oxime

To a cooled (5°C) solution of 2-chlorobenzaldehyde (40.1 ml, 356 mmol) in ethanol (100 ml) was added an aqueous solution of hydroxylamine (27.2 g; 391 mmol) in water (100 ml), followed by addition of 5N sodium hydroxide (73.6 ml). The mixture was stirred at 5°C for 90 min. The mixture was then acidified with 6N HCl until pH6 was reached and was extracted with tert.butylmethylether (3x). The combined organic layers were dried (Na₂SO₄) and concentrated to give the target compound as a white solid (55 g; 99% yield; HPLC purity 97%). The product was used as such in the next step.

Step 2

(E/Z)-2-chloro-N-hydroxybenzimidoyl chloride (an example of compound 32)

To a cooled (10°C) solution of (E/Z)-2-chlorobenzaldehyde oxime (4.0 g, 25.7 mmol) in DMF (12 ml) was added N-chlorosuccinimide (3.43 g, 25.7 mmol) in portions. After the addition was complete, water (50 ml) was added and the

reaction mixture was extracted 3x with THF. The combined organic layers were washed with water (1x), dried (Na_2SO_4) and concentrated to give the target compound as a yellow oil (4.98 g, HPLC purity 74%, quant.). The crude product was used as such in the next step.

5

Step 3

3-(2-Chlorophenyl)-5-(4-methoxyphenyl)isoxazole (an example of compound 34)

To a cooled (0°C) solution of (E/Z)-2-chloro-N-hydroxybenzimidoyl chloride (0.50 g, 1.71 mmol) and 1-eth-1-ynyl-4-methoxybenzene (0.271 g, 2.05 mmol) in THF (7 ml) was added triethylamine (0.238 ml, 1.71 mmol). The mixture was stirred at room temperature for 16 h and was then filtered. The filtrate was concentrated and was recrystallized from ethanol to give the target compound as a white solid (0.33 g, HPLC purity: 99%; 68% yield).

15

Step 4

4-Bromo-3-(2-chlorophenyl)-5-(4-methoxyphenyl)isoxazole (an example of compound 35)

To a solution of 3-(2-chlorophenyl)-5-(4-methoxyphenyl)isoxazole (285 mg, 0.997 mmol) in DCM (3 ml) was added at room temperature N-bromosuccinimide (231 mg, 1.297 mmol) in portions, followed by p-toluenesulfonic acid (9.5 mg, 0.05 mmol). The mixture was stirred at room temperature for 17 h. The mixture was then washed with sat. aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution (2x), sat. aqueous NaHCO_3 solution (1x) and water (2x). The organic phase was dried (Na_2SO_4) and concentrated. The crude product was purified by prep. HPLC to give the target compound as a white solid (264 mg, HPLC purity 99%; yield: 73%).

25

Step 5

4-(3-(2-chlorophenyl)-5-(4-methoxyphenyl)isoxazol-4-yl)phenol (an example of compound 36)

30

A solution of 4-bromo-3-(2-chlorophenyl)-5-(4-methoxyphenyl)isoxazole (1.26 g, 3.46 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (1.52 g, 6.92 mmol), $\text{K}_3\text{PO}_4 \cdot 7\text{H}_2\text{O}$ (3.51 g, 10.38 mmol) and $\text{PdCl}_2(\text{PPh}_3)_2$ in dioxane (20 ml)

was stirred under N₂ atmosphere at 90°C for 16 h. The reaction mixture was then cooled to room temperature. Water was added and the mixture was extracted with ethyl acetate (3x). The combined organic layers were washed with brine (1x), dried (Na₂SO₄) and concentrated. The crude product was purified by column chromatography to give the target compound as a white solid (910 mg, yield: 70%).

Step 6 (is General Procedure A, Step 1)

tert-butyl 3-(4-(3-(2-chlorophenyl)-5-(4-methoxyphenyl)isoxazol-4-yl)-phenoxy)-azetidine-1-carboxylate

To a solution of 4-(3-(2-chlorophenyl)-5-(4-methoxyphenyl)isoxazol-4-yl)phenol (740 mg, 1.959 mmol) and 1-Boc-3-iodo-azetidine (832 mg, 2.94 mmol) in DMF (20 ml) was added cesium carbonate (2.55 g, 7.83 mmol). The mixture was stirred at room temperature for 16 h. Then, ethyl acetate was added and the mixture was washed with water. The organic layer was dried (Na₂SO₄) and concentrated. The crude product was purified by column chromatography to give the target compound as a white solid (700 mg; yield: 67%).

¹H-NMR (400 MHz, CDCl₃): δ 4.83 (m, 1H, azetidine 3-H).

Step 7 (is General Procedure A, Step 4)

4-(4-(4-(azetidin-3-yloxy)phenyl)-3-(2-chlorophenyl)isoxazol-5-yl)phenol
(compound 6f)

To a solution of tert-butyl 3-(4-(3-(2-chlorophenyl)-5-(4-methoxyphenyl)isoxazol-4-yl)phenoxy)-azetidine-1-carboxylate (533 mg, 1.00 mmol) in methylene chloride (20 ml) under N₂ atmosphere was added boron trifluoride-methyl sulfide complex (2.10 ml, 20.0 mmol) at room temperature. The reaction mixture was stirred for 16 h. Then water was added and the mixture was extracted with ethyl acetate (3x). The combined organic layers were dried (Na₂SO₄) and concentrated. The crude product was dissolved in methanol and was purified over a SCX column (impurities washed with methanol; product eluted with 0.7N NH₃ in methanol to give the target compound (387 mg; yield: 92%).

Step 8 (is General Procedure A, Step 3)

4-(4-(4-(N-propylazetidin-3-yloxy)phenyl)-3-(2-chlorophenyl)isoxazol-5-yl)-phenol (compound 6g = 7v = 8d = 9a)

To a solution of 4-(4-(4-(azetidin-3-yloxy)phenyl)-3-(2-chlorophenyl)isoxazol-5-yl)-phenol (630 mg, 1.504 mmol) and propionaldehyde (219 μ l, 3.01 mmol) in 5 methanol (50 ml) was added acetic acid (86 μ l, 1.50 mmol) and sodium cyanoborohydride (189 mg, 3.01 mmol). The mixture was stirred at room temperature for 16 h and was then filtered and loaded onto a SCX column. The impurities were rinsed from the column by methanol and the product was eluted with 0.7N NH₃ in methanol. The obtained crude product was further purified by prep. HPLC (10 to 10 60% acetonitrile/water/3% TFA). To the product-containing fractions 2N HCl was added and the mixture was freeze dried to give the target compound as HCl salt as a white solid (174 mg, yield: 23%).

¹H-NMR (400 MHz, DMSO-D₆): δ 0.88 (t, 3H), 1.51 (m, 2H), 3.14 (t, br, 2H), 4.10 (m, br, 1H), 4.18 (m, br, 1H), 4.39 (m, br, 1H), 4.62 (m, br, 1H), 4.97 and 5.09 (2x 15 m, br, 1H, azetidine H-3), 6.81 and 7.10 (2x d, AB system, 4H), 7.37-7.53 (m, 8H), 10.14 (s, br, 1H, OH), 10.54 and 10.68 (2x s, br, 1H; HCl).

A solution of compound 35 (1.0 mmol), compound 64 (2.0 mmol), K₃PO₄·7H₂O (3.0 mmol) and PdCl₂(PPh₃)₂ (0.05 mmol) in dioxane (10 ml) was stirred under N₂ 20 atmosphere at 90°C for 16 h. The reaction mixture was then cooled to room temperature. Water was added and the mixture was extracted with ethyl acetate (3x). The combined organic layers were washed with brine (1x), dried (Na₂SO₄) and concentrated. The crude product was purified by column chromatography to give compound 55 in good purity.

25

Compound 55 can be converted to compound 15 according to General Procedure A.

General Procedure G (Synthesis according to Scheme 6, route B)

30

Step 1

Under a nitrogen atmosphere 1-ethynyl-4-methoxybenzene (12 mmol) was dissolved in tetrahydrofuran (30 ml). The solution was cooled to -78°C and n-butyl-

lithium (1.6M in hexanes; 13 mmol) was added. The mixture was stirred at -40°C and then a solution of compound 38 (11 mmol) in tetrahydrofuran (10 ml) was added. The mixture was stirred at room temperature for 1 h. Then water (50 ml) was added and the mixture was extracted with ethyl acetate (2x). The combined 5 organic layers were dried (Na₂SO₄) and concentrated. The crude compound was triturated with diisopropylethylether (10 ml) to give compound 39 in good purity.

Step 2

Methoxylamine hydrochloride (45 mmol) was added at room temperature to a 10 solution of sodium hydroxide (54 mmol) in ethanol (50 ml). The resulting suspension was stirred at room temperature for 1 h. Then Na₂SO₄ was added and the mixture was filtered. The filtrate was added dropwise to a cooled (0°C) solution of sulfuric acid (4 ml) and compound 39 (9 mmol) in ethanol (5 ml) to give a very exothermic reaction. The mixture was stirred at 80°C for 30 min. Then, water (100 15 ml) was added and the mixture was extracted with ethyl acetate (2x). The combined organic layers were dried (Na₂SO₄) and concentrated. The crude product contained both E and Z-isomer. Purification by prep. HPLC (acetonitrile/-water) afforded the desired Z-isomer of compound 40 in good purity.

20 Step 3

To a cooled (0°C) solution of compound 40 (1.4 mmol) in methylene chloride (10 ml) was added iodine monochloride (2.1 mmol). The mixture was stirred at 0°C for 1 h. Then, NaS₂O₃ and water were added and the mixture was extracted with methylene chloride (2x). The combined organic layers were dried (Na₂SO₄) and 25 concentrated. The crude product was triturated from diisopropylethylether to afford compound 41 in good purity.

Compound 41 can be converted to compound 15 in several steps analogous to the conversion of compound 35 to compound 15 (according to General Procedure F, 30 Step 5 and onwards).

General Procedure H (Synthesis according to Scheme 6, route C)

Step 1

Under a nitrogen atmosphere, to a solution of 4-fluorobenzoyl chloride (119 mmol) in triethylamine (660 ml) was added bis(triphenylphosphine)palladium(II) chloride (0.79 mmol) and copper(I) iodide (95 mmol). The mixture was stirred at room temperature for 30 min. Then, 1-ethynyl-4-methoxybenzene (79 mmol) was added to give an exothermic reaction. The mixture was stirred at room temperature for 16 h. The saturated aqueous NH_4Cl solution was added and the mixture was extracted with ethyl acetate (3x). The combined organic layers were dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography over silica (heptane/ethyl acetate 9:1) to give compound 43 in good purity.

Step 2

Under a nitrogen atmosphere, to a solution of compound 43 (30 mmol) in toluene (100 ml) was added, at room temperature, (E)-2-chloro-N-hydroxybenzimidoyl chloride (38 mmol) and triethylamine (33 mmol). The mixture was stirred at 60°C for 16 h. Then, water was added and the mixture was extracted with ethyl acetate (3x). The combined organic layers were dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography over silica to give compound 44 in good purity.

Compound 44 can be converted to compound 15 in several steps according to General Procedure B.

25 General Procedure I (Synthesis according to Scheme 6, route D)**Step 1**

Compound 46 was prepared according to General procedure H, Step 1.

30 Step 2

Compound 47 was prepared according to General procedure H, Step 2.

Compound 47 can be converted to compound 15 in several steps according to General Procedure B.

2-(4-hydroxyphenyl)-3-(4-(1-methylazetidin-3-yloxy)phenyl)benzo[b]thiophen-6-ol 2,2,2-trifluoroacetate (compound 6a)

Synthesis according to General procedure C (Scheme 3)

2-(4-hydroxyphenyl)-3-(4-(1-propylazetidin-3-yloxy)phenyl)benzo[b]thiophen-6-ol 2,2,2-trifluoroacetate (compound 6b = 7a = 8a)

10 Synthesis according to General procedure A (Scheme 1)

2-(4-hydroxyphenyl)-3-(4-(1-propylazetidin-3-yloxy)phenoxy)benzo[b]thiophen-6-ol 2,2,2-trifluoroacetate (compound 6c = 7c = 8b)

Synthesis according to General procedure A (Scheme 1)

15 The title compound was obtained as white solid after freeze drying (106mg; 62% yield).

¹H-NMR (400 MHz, DMSO) 0.87 (t, 3H), 1.48 (m, 2H), 3.12 (m, 2H), 4.10 (br m, 2H), 4.50 (br m, 2H), 4.95 (br m, 1H), 6.80 (m, 5H), 6.90 (d, 2H), 7.10 (d, 1H), 7.28 (d, 1H), 7.50 (d, 2H), 9.79 (s, 1H), 9.82 (s, 1H).

20

(6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)(4-(1-propylazetidin-3-yloxy)phenyl)methanone 2,2,2-trifluoroacetate (compound 6d = 7h = 8c)

Synthesis according to General procedure A (Scheme 1)

25 **(6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)(4-(1-isopropylazetidin-3-yloxy)phenyl)methanone hydrochloride** (compound 6e)

Synthesis according to General procedure A (Scheme 1)

30 **4-(4-(4-(1-butylazetidin-3-yloxy)phenyl)-3-(2-chlorophenyl)isoxazol-5-yl)-phenol hydrochloride** (compound 6h)

Synthesis according to General Procedure F (Scheme 6, route A)

4-(4-(4-(1-sec-butylazetidin-3-yloxy)phenyl)-3-(2-chlorophenyl)isoxazol-5-yl)-phenol hydrochloride (compound 6j)

Synthesis according to General procedure A (Scheme 1)

5 **4-(4-(4-(1-propylazetidin-3-yloxy)phenyl)-3-o-tolylisoxazol-5-yl)phenol 2,2,2-trifluoroacetate** (compound 6j)

Synthesis according to General procedure F (Scheme 6, route A)

10 **4-(3-(2-chlorophenyl)-4-(4-(1-propylazetidin-3-yloxy)phenyl)isoxazol-5-yl)-3-methylphenol 2,2,2-trifluoroacetate** (compound 6k)

Synthesis according to General procedure F (Scheme 6, route A)

15 **4-(3-(2-chlorophenyl)-4-(4-(1-propylazetidin-3-yloxy)phenyl)isoxazol-5-yl)-2-methylphenol 2,2,2-trifluoroacetate** (compound 6l)

Synthesis according to General procedure F (Scheme 6, route A)

(3-(2-chlorophenyl)-5-(4-hydroxyphenyl)isoxazol-4-yl)(4-(1-propylazetidin-3-yloxy)phenyl)methanone hydrochloride (compound 6m = 7ag = 8e)

Synthesis according to General procedure B (Scheme 2)

20

(5-(2-chlorophenyl)-3-(4-hydroxyphenyl)isoxazol-4-yl)(4-(1-propylazetidin-3-yloxy)phenyl)methanone (compound 6n = 7ay)

Synthesis according to General procedure B (Scheme 2)

25 **3-(4-((3S,4S)-7-methoxy-2,2-dimethyl-3-phenylchroman-4-yl)phenoxy)-1-propylazetidine 2,2,2-trifluoroacetate** (compound 6o = 7bd)

Synthesis according to General procedure A (Scheme 1)

Product was obtained as white solid after freeze drying (67.2 mg; 53% yield).

¹H-NMR (400 MHz, DMSO) 0.85 (t, 3H), 1.18 (s, 3H), 1.28 (s, 3H), 1.48 (m, 2H),
30 3.12 (t, 2H), 3.30 (d, 1H), 3.69 (s, 3H), 4.10 (br m, 2H), 4.49 (d, 1H), 4.60 (br m, 2H), 4.91 (br m, 1H), 6.32 (dd, 1H), 6.39 (m, 2H), 6.61 (br d, 1H), 7.05 (d, 2H), 7.12 (m, 1H), 7.20 (m, 2H), 7.31 (br m, 2H).

(3S,4S)-2,2-dimethyl-3-phenyl-4-(4-(1-propylazetidin-3-yloxy)phenyl)chroman-7-ol 2,2,2-trifluoroacetate (compound 6p = 7be)

Synthesis according to General procedure A (Scheme 1)

Product was obtained as white solid after freeze drying (32.5 mg; 49% yield).

5 ¹H-NMR (400 MHz, DMSO) 0.85 (t, 3H), 1.15 (s, 3H), 1.25 (s, 3H), 1.47 (m, 2H), 3.12 (t, 2H), 3.28 (d, 1H), 4.10 (br m, 2H), 4.49 (d, 1H), 4.60 (br m, 2H), 4.92 (br m, 1H), 6.17 (dd, 1H), 6.19 (d, 1H), 6.29 (d, 1H), 6.61 (d, 2H), 7.02 (d, 2H), 7.12 (m, 1H), 7.19 (m, 2H), 7.30 (br m, 2H), 9.21 (s, 1H).

10 **(5R,6S)-6-phenyl-5-(4-(1-propylazetidin-3-yloxy)phenyl)-5,6,7,8-tetrahydronaphthalen-2-ol hydrochloride** (compound 6q = 7bc = 8j)

Synthesis according to General procedure A (Scheme 1)

7-hydroxy-3-phenyl-4-(4-(1-propylazetidin-3-yloxy)benzyl)-2H-chromen-2-one

15 **2,2,2-trifluoroacetate** (compound 6r)

Synthesis according to General procedure A (Scheme 1)

The title compound was obtained as white solid after freeze drying (55 mg; yield 60%).

20 ¹H-NMR (400 MHz, CDCl₃) 1.00 (t, 3H), 1.69 (m, 2H), 3.11 (t, 2H), 3.75 (br m, 2H), 3.99 (s, 2H), 4.80 (br m, 2H), 5.12 (br m, 1H), 6.62 (d, 2H), 6.75 (d, 1H), 6.82 (d, 1H), 6.98 (d, 2H), 7.23 (d, 2H), 7.31 (d, 1H), 7.38 (m, 3H).

(8S,11S,13S, 14S,17S)-13-methyl-11-(4-(1-propylazetidin-3-yloxy)phenyl)-7,8,9,10,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene-3,17-

25 **diol** (compound 6s)

Synthesis according to General procedure A (Scheme 1)

(8S,11S,13S, 14S,17S)-11-(4-(1-(cyclopropylmethyl)azetidin-3-yloxy)phenyl)-13-methyl-7,8,9,10,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phen-

30 **anthrene-3,17-diol** (compound 6t)

Synthesis according to General procedure A (Scheme 1)

3-(4-(1,2-diphenylbut-1-enyl)phenoxy)-1-propylazetidine 2,2,2-trifluoroacetate

(compound 6u = 7bg = 8k = 9g)

Synthesis according to General procedure A (Scheme 1)

The title compound was obtained as colorless oil (126 mg; 46% yield).

¹H-NMR (400 MHz, DMSO) 0.80-0.94 (m, 12H), 1.50 (m, 4H), 2.40 (m, 4H),
5 3.12, 3.19 2x (br t, 2H), 4.00-4.30 (br m, 4H), 4.30-4.75 (br m, 4H), 4.82-5.17 2x (br
m, 2H), 6.55 (br m, 2H), 6.75-6.93 (m, 6H), 6.95-7.07 (m, 3H), 7.07-7.25 (m, 14H),
7.30 (m, 1H), 7.40 (m, 2H).

(E/Z)-4-(2-phenyl-1-(4-(1-propylazetidin-3-yloxy)phenyl)but-1-enyl)phenol 2,-
10 **2,2-trifluoroacetate** (compound 6v = 7bh)

Synthesis according to General procedure A (Scheme 1)

The title compound was obtained as white solid after freeze drying (117 mg; 58%
yield).

¹H-NMR (400 MHz, DMSO) 0.87 4x (t, 3H), 1.48 2x (m, 2H), 2.40 2x (m, 2H), 3.13
15 2x (t, 2H), 4.10 2x (br m, 2H), 4.50 2x (br m, 2H), 4.90, 5.09 2x (br m, 1H), 6.40 (d,
2H), 6.53 (d, 2H), 6.60 (d, 2H), 6.77 (d, 4H), 6.88 (d, 2H), 6.98 (d, 2H), 7.07-7.21
(m, 12H), 9.21 (s, 1H), 9.46 (s, 1H).

(E/Z)-3-(2-phenyl-1-(4-(1-propylazetidin-3-yloxy)phenyl)but-1-enyl)phenol
20 (compound 6w = 7bi = 9h)

Synthesis according to General procedure A (Scheme 1)

The title compound was obtained as white solid after freeze drying (107 mg; 64%
yield).

¹H-NMR (400 MHz, DMSO) 0.85 4x (t, 3H), 1.45 2x (m, 2H), 2.38 2x (m, 2H), 3.15
25 2x (t, 2H), 4.15 2x (br m, 2H), 4.60 2x (br m, 2H), 5.01 2x (br m, 1H), 6.25 (m, 2H),
6.39 (d, 1H), 6.55 (m, 3H), 6.62 (d, 1H), 6.69 (d, 1H), 6.80 (m, 3H), 6.89 (br d, 2H),
7.08-7.22 (m, 13H), 9.09 (s, 1H), 9.42 (s, 1H).

(E/Z)-3-(4-(2-chloro-1,2-diphenylvinyl)phenoxy)-1-propylazetidine 2,2,2-tri-
30 **fluoroacetate** (compound 6x = 7bj)

Synthesis according to General procedure A (Scheme 1)

The title compound was obtained as white solid after freeze drying (60 mg; 46%
yield).

¹H-NMR (400 MHz, DMSO) 0.88 2x (t, 3H), 1.45 2x (m, 2H), 3.15 2x (t, 2H), 4.15 2x (br m, 2H), 4.60 2x (br m, 2H), 5.01 2x (br m, 1H), 6.65 (d, 2H), 6.90 (d, 4H), 6.96 (m, 2H), 7.15 (m, 4H), 7.20-7.38 (m, 14H), 7.42 (m, 2H).

5 **3-(4-(1-allylazetidin-3-yloxy)phenyl)-2-(4-hydroxyphenyl)benzo[b]thiophen-6-ol 2,2,2-trifluoroacetate** (compound 7b)

Synthesis according to General procedure C (Scheme 3)

10 **(6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)(4-(1-methylazetidin-3-yloxy)phenyl)methanone hydrochloride** (compound 7d)

Synthesis according to General procedure A (Scheme 1)

(6-hydroxy-2-phenylbenzo[b]thiophen-3-yl)(4-(1-propylazetidin-3-yloxy)-phenyl)methanone hydrochloride (compound 7e)

15 Synthesis according to General Procedure E (Scheme 5, route C)

(6-hydroxy-2-(thiophen-2-yl)benzo[b]thiophen-3-yl)(4-(1-propylazetidin-3-yloxy)phenyl)methanone hydrochloride (compound 7f)

Synthesis according to General Procedure E (Scheme 5, route C)

20

(4-(1-ethylazetidin-3-yloxy)phenyl)(6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)methanone 2,2,2-trifluoroacetate (compound 7g)

Synthesis according to General Procedure E (Scheme 5, route C)

25 **(4-(1-cyclopropylazetidin-3-yloxy)phenyl)(6-hydroxy-2-(4-hydroxyphenyl)-benzo[b]thiophen-3-yl)methanone 2,2,2-trifluoroacetate** (compound 7i)

Synthesis according to General procedure C (Scheme 3)

30 **(4-(1-(3-fluoropropyl)azetidin-3-yloxy)phenyl)(6-hydroxy-2-(4-hydroxy-phenyl)benzo[b]thiophen-3-yl)methanone 2,2,2-trifluoroacetate** (compound 7j)

Synthesis according to General procedure A (Scheme 1)

(6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)(4-(1-(3-methoxy-propyl)azetidin-3-yloxy)phenyl)methanone 2,2,2-trifluoroacetate (compound 7k)

Synthesis according to General procedure C (Scheme 3)

5

(4-(1-cyclobutylazetidin-3-yloxy)phenyl)(6-hydroxy-2-(4-hydroxyphenyl)-benzo[b]thiophen-3-yl)methanone hydrochloride (compound 7l)

Synthesis according to General procedure A (Scheme 1)

10 **(6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)(4-(1-isobutylazetidin-3-yloxy)phenyl)methanone hydrochloride** (compound 7m)

Synthesis according to General procedure C (Scheme 3)

15 **(4-(1-(cyclobutylmethyl)azetidin-3-yloxy)phenyl)(6-hydroxy-2-(4-hydroxy-phenyl)benzo[b]thiophen-3-yl)methanone hydrochloride** (compound 7n)

Synthesis according to General procedure C (Scheme 3)

20 **(6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)(4-(1-((tetrahydrofuran-3-yl)methyl)azetidin-3-yloxy)phenyl)methanone hydrochloride** (compound 7o)

Synthesis according to General procedure C (Scheme 3)

25 **(6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl)(4-(1-(3,3,3-trifluoropropyl)azetidin-3-yloxy)phenyl)methanone hydrochloride** (compound 7p)

Synthesis according to General procedure A (Scheme 1)

(6-hydroxy-2-(4-hydroxy-2-methylphenyl)benzo[b]thiophen-3-yl)(4-(1-propylazetidin-3-yloxy)phenyl)methanone hydrochloride (compound 7q)

Synthesis according to General Procedure E (Scheme 5, route C)

30

(6-hydroxy-2-(4-hydroxy-3-methylphenyl)benzo[b]thiophen-3-yl)(4-(1-propylazetidin-3-yloxy)phenyl)methanone hydrochloride (compound 7r)

Synthesis according to General Procedure E (Scheme 5, route C)

(2-(4-fluoro-3-methylphenyl)-6-hydroxybenzo[b]thiophen-3-yl)(4-(1-propylazetidin-3-yloxy)phenyl)methanone hydrochloride (compound 7s)

Synthesis according to General Procedure E (Scheme 5, route C)

5

(2-(3,5-difluorophenyl)-6-hydroxybenzo[b]thiophen-3-yl)(4-(1-propylazetidin-3-yloxy)phenyl)methanone hydrochloride (compound 7t)

Synthesis according to General Procedure E (Scheme 5, route C)

10 **(3-fluoro-4-(1-propylazetidin-3-yloxy)phenyl)(6-hydroxy-2-(4-hydroxyphenyl)-benzo[b]thiophen-3-yl)methanone hydrochloride** (compound 7u)

Synthesis according to General Procedure E (Scheme 5, route C)

15 **4-(3-(2-chlorophenyl)-4-(4-(1-isobutylazetidin-3-yloxy)phenyl)isoxazol-5-yl)-phenol hydrochloride** (compound 7w = 9b)

Synthesis according to General procedure A (Scheme 1)

4-(3-(2-chlorophenyl)-4-(4-(1-((tetrahydrofuran-3-yl)methyl)azetidin-3-yloxy)-phenyl)isoxazol-5-yl)phenol hydrochloride (compound 7x)

20 Synthesis according to General procedure A (Scheme 1)

4-(3-(2-chlorophenyl)-4-(4-(1-(cyclopropylmethyl)azetidin-3-yloxy)phenyl)-isoxazol-5-yl)phenol hydrochloride (compound 7y = 9c)

Synthesis according to General procedure A (Scheme 1)

25

4-(3-(2-chlorophenyl)-4-(4-(1-(cyclobutylmethyl)azetidin-3-yloxy)phenyl)-isoxazol-5-yl)phenol hydrochloride (compound 7z = 9d)

Synthesis according to General procedure A (Scheme 1)

30 **4-(3-(2-chlorophenyl)-4-(4-(1-(3-fluoropropyl)azetidin-3-yloxy)phenyl)isoxazol-5-yl)phenol hydrochloride** (compound 7aa = 9e)

Synthesis according to General procedure A (Scheme 1)

4-(3-(2-chloro-6-methylphenyl)-4-(4-(1-propylazetidin-3-yloxy)phenyl)isoxazol-5-yl)phenol 2,2,2-trifluoroacetate (compound 7ab)

Synthesis according to General procedure F (Scheme 6, route A)

5 **4-(3-(2,3-dimethylphenyl)-4-(4-(1-propylazetidin-3-yloxy)phenyl)isoxazol-5-yl)phenol 2,2,2-trifluoroacetate** (compound 7ac)

Synthesis according to General procedure F (Scheme 6, route A)

10 **4-(3-(2-ethylphenyl)-4-(4-(1-propylazetidin-3-yloxy)phenyl)isoxazol-5-yl)phenol 2,2,2-trifluoroacetate** (compound 7ad)

Synthesis according to General procedure F (Scheme 6, route A)

4-(3-(4-methyl-1,2,3-thiadiazol-5-yl)-4-(4-(1-propylazetidin-3-yloxy)phenyl)isoxazol-5-yl)phenol hydrochloride (compound 7ae)

15 Synthesis according to General Procedure G (Scheme 6, route B)

4-(3',5'-dimethyl-4-(4-(1-propylazetidin-3-yloxy)phenyl)-3,4'-biisoxazol-5-yl)phenol hydrochloride (compound 7af)

Synthesis according to General Procedure G (Scheme 6, route B)

20

(3-(2-chlorophenyl)-5-(4-hydroxyphenyl)isoxazol-4-yl)(4-(1-(3-fluoropropyl)azetidin-3-yloxy)phenyl)methanone 2,2,2-trifluoroacetate (compound 7ah = 8f)

Synthesis according to General procedure C (Scheme 3)

25

(5-(4-hydroxyphenyl)-3-phenylisoxazol-4-yl)(4-(1-propylazetidin-3-yloxy)phenyl)methanone hydrochloride (compound 7ai)

Synthesis according to General procedure B (Scheme 2)

30 **(5-(4-hydroxyphenyl)-3-o-tolylisoxazol-4-yl)(4-(1-propylazetidin-3-yloxy)phenyl)methanone hydrochloride** (compound 7aj)

Synthesis according to General procedure B (Scheme 2)

(3-(2,6-difluorophenyl)-5-(4-hydroxyphenyl)isoxazol-4-yl)(4-(1-propylazetidin-3-yloxy)phenyl)methanone hydrochloride (compound 7ak = 8g)

Synthesis according to General procedure B (Scheme 2)

5 **(5-(4-hydroxyphenyl)-3-(1-methyl-1H-pyrrol-2-yl)isoxazol-4-yl)(4-(1-propylazetidin-3-yloxy)phenyl)methanone hydrochloride** (compound 7al)

Synthesis according to General procedure B (Scheme 2)

10 **(5-(4-hydroxyphenyl)-3-(3-methylpyridin-2-yl)isoxazol-4-yl)(4-(1-propylazetidin-3-yloxy)phenyl)methanone hydrochloride** (compound 7am)

Synthesis according to General procedure B (Scheme 2)

(5-(4-hydroxyphenyl)-3-(3-methylthiophen-2-yl)isoxazol-4-yl)(4-(1-propylazetidin-3-yloxy)phenyl)methanone hydrochloride (compound 7an)

15 Synthesis according to General procedure B (Scheme 2)

(3-(2-chlorophenyl)-5-phenyl)isoxazol-4-yl)(4-(1-propylazetidin-3-yloxy)-phenyl)methanone hydrochloride (compound 7ao)

Synthesis according to General procedure B (Scheme 2)

20

(3-(2-chlorophenyl)-5-(3-hydroxyphenyl)isoxazol-4-yl)(4-(1-propylazetidin-3-yloxy)phenyl)methanone hydrochloride (compound 7ap)

Synthesis according to General procedure B (Scheme 2)

25 **(3-(2-chlorophenyl)-5-(1H-pyrrol-3-yl)isoxazol-4-yl)(4-(1-propylazetidin-3-yloxy)phenyl)methanone 2,2,2-trifluoroacetate** (compound 7aq)

Synthesis according to General procedure B (Scheme 2)

30 **(5-(4-aminophenyl)-3-(2-chlorophenyl)isoxazol-4-yl)(4-(1-propylazetidin-3-yloxy)phenyl)methanone 2,2,2-trifluoroacetate** (compound 7ar)

Synthesis according to General procedure B (Scheme 2)

(3-(2-chlorophenyl)-5-(1H-indazol-4-yl)isoxazol-4-yl)(4-(1-propylazetidin-3-yl-oxy)phenyl)methanone 2,2,2-trifluoroacetate (compound 7as)

Synthesis according to General procedure B (Scheme 2)

5 **(3-(2-chlorophenyl)-5-(4-hydroxyphenyl)isoxazol-4-yl)(3-fluoro-4-(1-propyl-azetidin-3-yloxy)phenyl)methanone hydrochloride** (compound 7at)

Synthesis according to General procedure B (Scheme 2)

10 **4-(3-(2-chlorophenyl)-4-(4-(1-propylazetidin-3-yloxy)phenyl)isoxazol-5-yl)-phenol hydrochloride** (compound 7au)

Synthesis according to Scheme 7

To a solution of 4-(3-(2-chlorophenyl)-4-(hydroxy(4-(1-propylazetidin-3-yloxy)-phenyl)methyl)isoxazol-5-yl)phenol (79 mg, 0.161 mmol) in methylene chloride (5 ml) was added triethylsilane (39 μ l, 0.241 mmol). The reaction mixture was cooled
15 to 0°C and trifluoroacetic acid (1.195 ml, 16.1 mmol) was added. The mixture was stirred at room temperature for 2 h. Then water and saturated NaHCO₃ solution were added. The mixture was extracted with ethyl acetate. The combined organic layers were dried (Na₂SO₄) and concentrated. The crude product was purified by prep. HPLC (10-60% acetonitrile/water + 3% TFA). To the product-containing
20 fractions 4N HCl (0.5 ml) was added and the mixture was freeze-dried to give the target compound as a white solid (60 mg, 70% yield).

4-(3-(2-chlorophenyl)-4-(hydroxy(4-(1-propylazetidin-3-yloxy)phenyl)methyl)isoxazol-5-yl)phenol (compound 7av = 9f)

25 Synthesis according to Scheme 7

To a solution of (3-(2-chlorophenyl)-5-(4-hydroxyphenyl)isoxazol-4-yl)(4-(1-propyl-azetidin-3-yloxy)phenyl)methanone (100 mg, 0.190 mmol) in ethanol was added sodium borohydride (144 mg, 3.81 mmol). The reaction mixture was stirred at reflux for 48 h. Then water was added and the mixture was extracted with ethyl
30 acetate. The combined organic layers were dried (Na₂SO₄) and concentrated. The crude product was purified by column chromatography over silica (elution with methylene chloride/methanol/triethylamine 95:5:0.1) to give the desired product as free base (60 mg, 43% yield)

4-(3-(2-chlorophenyl)-4-(methoxy(4-(1-propylazetidin-3-yloxy)phenyl)methyl)-isoxazol-5-yl)phenol (compound 7aw)

Synthesis according to Scheme 7

- 5 To a solution of 4-(3-(2-chlorophenyl)-4-(4-(1-propylazetidin-3-yloxy)phenyl)isoxazol-5-yl)phenol (35 mg, 0.071 mmol) in acetonitrile (3 ml) was added hydrogen chloride (0.71 mmol) and methanol (2 ml). The mixture was stirred at room temperature for 16 h. Then NaHCO₃ was added and the mixture was extracted with ethyl acetate. The combined organic layers were dried (Na₂SO₄) and
- 10 concentrated. The crude product was purified by column chromatography over silica (elution with methylene chloride/methanol/ammonia 95:5:0.1). The product-containing fractions were concentrated, redissolved in acetonitrile/water and freeze-dried to give the desired compound as a white solid (20 mg, 48% yield).

15 **4-(3-(2-chlorophenyl)-4-(1-(4-(1-propylazetidin-3-yloxy)phenyl)vinyl)isoxazol-5-yl)phenol** (compound 7ax)

Synthesis according to Scheme 7

- To a cooled (0°C) solution of (3-(2-chlorophenyl)-5-(4-hydroxyphenyl)isoxazol-4-yl)(4-(1-propylazetidin-3-yloxy)phenyl)methanone (76 mg, 0.155 mmol) in
- 20 anhydrous THF (2 ml), under a nitrogen atmosphere, was added methyllithium (0.971 ml, 1.554 mmol). The mixture was stirred for 2 h at room temperature. Then water was added and the mixture was extracted with ethyl acetate. The combined organic layers were dried (Na₂SO₄) and concentrated. The crude product was purified by column chromatography over silica (elution with methylene chloride/-
- 25 methanol/ammonia 95:5:0.1). The obtained intermediate (50 mg) was dissolved in acetonitrile (2 ml) and a few drops of concentrated HCl were added. The mixture was stirred at room temperature for 2 h. Then NaHCO₃ was added and the mixture was extracted with ethyl acetate. The combined organic layers were dried (Na₂SO₄) and concentrated. The crude product was purified by column
- 30 chromatography over silica (elution with methylene chloride/methanol/ammonia 95:5:0.1). The purified product was dissolved in acetonitrile/water and was freeze-dried to give the desired product as a white solid (39 mg, 38% yield).

(3-(4-hydroxyphenyl)-5-o-tolylisoxazol-4-yl)(4-(1-propylazetidin-3-yloxy)-phenyl)methanone hydrochloride (compound 7az = 8h)

Synthesis according to General procedure B (Scheme 2)

5 **(5-(2-fluorophenyl)-3-(3-hydroxyphenyl)isoxazol-4-yl)(4-(1-propylazetidin-3-yloxy)phenyl)methanone hydrochloride** (compound 7ba)

Synthesis according to Scheme 6, route D

10 **(5-(4-hydroxyphenyl)-3-o-tolylisothiazol-4-yl)(4-(1-propylazetidin-3-yloxy)-phenyl)methanone hydrochloride** (compound 7bb)

Synthesis according to Scheme 8

7-methoxy-3-phenyl-4-(4-(1-propylazetidin-3-yloxy)benzyl)-2H-chromen-2-one (compound 7bf)

15 Synthesis according to General procedure A (Scheme 1)

The title compound was obtained as white solid (75 mg; 85% yield).

¹H-NMR (400 MHz, CDCl₃) 0.90 (t, 3H), 1.39 (m, 2H), 2.46 (t, 2H), 3.03 (m, 2H), 3.80 (m, 2H), 3.88 (s, 3H), 3.99 (s, 2H), 4.72 (m, 1H), 6.62 (d, 2H), 6.75 (d, 1H), 6.82 (d, 1H), 6.98 (d, 2H), 7.23 (d, 2H), 7.31 (d, 1H), 7.38 (m, 3H).

20

Example 11

The antagonistic activity of compounds on the estrogen receptors was determined in an *in vitro* bioassay with recombinant Chinese Hamster Ovary (CHO) cells stably co-transfected with the human estrogen receptor α (hER α), the rat oxytocin promoter (RO) and the luciferase reporter gene (LUC). The potency of a test
25 compound to antagonize the transactivation of the enzyme luciferase by 17 β -estradiol and mediated *via* the estrogen receptors hER α is expressed as IC₅₀ in mol/l and/or as pIC₅₀ (-log(IC₅₀)) and/or as percentage (%) relative to the IC₅₀ of the standard anti-estrogen ICI 164,384 (potency test compound = (IC₅₀ ICI
30 164,384 / IC₅₀ test compound) $\times$ 100%). The antagonistic efficacy, *i.e.* the amount of maximal inhibition of the 17 β -estradiol activated receptor by a compound, is expressed as fraction relative to the maximal inhibition as induced by the standard anti-estrogen ICI 164,384 (efficacy test compound = (maximal inhibition test

compound / maximal inhibition ICI 164,384)). A more detailed description of the methodology can be found in De Gooyer *et al.*, *Steroids*, 68 (2003) 21-30.

In certain embodiments, compounds of the present invention are antagonistic at
5 ER α with a pIC₅₀ >7.

Example 12

To what extent compounds are capable of stimulating proliferation in ER-positive, tamoxifen-resistant breast cancer cells is tested in a 7-day *in vitro* proliferation
10 assay using MCF-7H cells. More specifically, this *in vitro* bioassay is used to determine the efficacy (fraction of maximal response), pEC₅₀, and relative potency of the compound to induce proliferation by comparing the data for this compound with those of the reference compound 17 β -estradiol (E2) in the same test.

15

A more detailed description of the method used is as follows.

Cell culture: The human epithelial breast cancer cell line MCF-7H (origin: Hubrecht Laboratory, Utrecht, The Netherlands) was routinely maintained in complete medium which is a 1:1 mixture of Ham's F12 medium and Dulbecco's
20 Modified Eagle Medium (DMEM; Invitrogen, Carlsbad, USA) without phenol red and enriched with 5% fetal calf serum (FCS; Hyclone, Utah, USA), 100 μ g/ml streptomycin and 100 units/ml penicillin adapted to contain:

	SOD DIHYD PHOS 2H ₂ O EP	0.0706618	g/L
	DISOD HYD PHOS ANHYD EP	0.07102	g/L
25	CUPRIC SULPH ANHYD	0.0008	g/L
	L-GLUTAMINE	1.085	g/L
	D-BIOTIN EP+	0.0000037	g/L
	SODIUM PYRUVATE	0.165	g/L
	SOD SELENITE 5H ₂ O	0.000447	g/L
30	MERCAPTOETHANOL	0.0023	g/L
	ETHANOLAMINE HCL	0.00198	g/L
	BOVINE INSULINE	0.0005	g/L

Cells were grown in 80 cm² culture flasks (Nunc, Roskilde, Denmark) and kept in an atmosphere of 5% CO₂-95% air at 37 degrees Celsius. Cells were subcultured when they reached about 80-90% confluence, resulting in one passage a week. Subculturing includes detaching the cells using trypsin/EDTA and diluting the cell suspension 10 times.

Methyl-³H-thymidine incorporation assay: MCF-7H cells were starved overnight in assay medium containing 5% charcoal-treated (CT) bovine calf serum (BCS; Hyclone) instead of FCS and a final concentration of 1.0 µg/ml bovine insulin, the day before plating. Cells were plated in assay medium containing 5% CT BCS, in white 24-wells plates (Perkin Elmer, Shelton, USA), at a density of 7.5x10³ cells per well, each well containing 630 µL assay medium. Cells were allowed to attach and spread for 24 h before stimulation with reference and/or test compound(s). After a stimulation period of 7 days, 0.25 µCi/well of methyl-³H-thymidine (GE Healthcare Limited, Buckinghamshire, UK) was added per well. Cultures were maintained in an atmosphere of 5% CO₂-95% air at 37 degrees Celsius. After overnight incubation, excess methyl-³H-thymidine was aspirated and the cells were washed with phosphate-buffered saline (PBS). After 1 h of incubation with 1 ml scintillation fluid Microscint-20 (Perkin Elmer), radioactivity was measured in a Packard TOP-count NXT microplate scintillation counter (Perkin Elmer).

17β-Estradiol (E2) and Ethynyl Estradiol (EE) induce proliferation of MCF-7H breast cancer cells in the picomolar range and with full efficacy (efficacy of E2 is 1.0 by definition; data for selected compounds are given in Table 1).

Table 1: *In vitro* data for selected reference compounds in MCF-7H breast cancer cell proliferation assay

Compound	% E2	Efficacy (fractional to E2)
E2	100 ^a	1.00 ^a
EE	137	0.99
Tamoxifen	0.008	0.58
4OHT ^b	2.3	0.49
Raloxifene	21.1	0.33
Arzoxifene	99.1	0.34

Droloxifene	5.9	0.38
Fulvestrant	18.9	0.02

^a per definition; data for test compounds are normalized against those for E2

5 ^b 4-OH-tamoxifen is a potent pharmacologically active metabolite of tamoxifen

In certain embodiments, compounds of the present invention show an efficacy equal to or <0.10 in the MCF-7H breast cancer cell proliferation assay.

10 Example 13

To what extent compounds are capable of stabilizing or downregulating (destabilizing) the estrogen receptor alpha in ER-positive breast cancer cells is tested in an *in vitro* assay using T47D cells. More specifically, this *in vitro* bioassay is used to determine the efficacy (fraction of maximal response) of the compound
15 by comparing the data for this compound with those of the reference compound ICI 182,780 (fulvestrant) in the same test (downregulation of fulvestrant is 100% by definition). 4-OH-Tamoxifen is included as an example of a compound that stabilizes ER α protein levels in the cell (data for selected compounds are given in Table 2).

20

A more detailed description of the method used is as follows.

Cell culture. The human epithelial breast cancer cell line T47D (origin: ATCC) was routinely maintained in a 1:1 mixture of Ham's F12 medium and Dulbecco's Modified Eagle Medium (Gibco) enriched with 5% fetal calf serum (Hyclone), 10
25 mM HEPES pH 7.5 and 100 μ g/ml penicillin-streptomycin solution. Cells were grown in 80 cm² culture flasks (Nunc, Roskilde, Denmark) and kept in an atmosphere of 5% CO₂-95% air at 37 degrees Celsius. Cells were subcultured when they reached about 80-90% confluence, resulting in one passage a week. Subculturing includes detaching the cells using Cell Dissociation Buffer [Sigma]
30 and subsequent inoculation at 1:5 or 1:10 in a new Roux flask (175 cc) and/or plating out in NunclonTM Surface 96 wells microplates. The culture medium needs to be refreshed on day three or four of the incubation, if applicable.

Determination of ER α protein levels: T47D cells in the microplates are incubated with 1E-5 M test compound for 24 hours. The supernatant in all wells is carefully aspirated. Cells are lysed on the microplate and cell lysates are probed for ER α content using an ER α ELISA assay kit (Active Motif).

5

Table 2: *In vitro* data for selected reference compounds in the ER α downregulation assay in T47D breast cancer cells

	<u>Compound</u>	<u>Downregulation (% of fulvestrant)</u>
10	Fulvestrant	100 ^a
	4OHT ^b	- 330 ^c
	Raloxifene	- 39 ^c
	Vehicle (1% DMSO)	0 ^d

15 ^a per definition; data for test compounds are normalized against those for fulvestrant

^b 4-OH-tamoxifen is a potent pharmacologically active metabolite of tamoxifen

^c a negative number indicates upregulation or stabilization of the receptor

^d compound-induced effects are normalized against a vehicle control

20

In certain embodiments, compounds of the present invention show a minimum of 20% downregulation of ER α in the T47D breast cancer cell assay.

Example 14

25 Rapid Rat PK

This test was used to determine the pharmacokinetic parameters (AUC(0-6h), C_{max} and T_{max}) after oral administration of compounds in male (intact or castrated) or female (intact or ovariectomized) rats (*Rattus Norvegicus*).

After oral administration of a compound at 20 μ mol/kg, blood was collected at
 30 various time points (0.5, 1, 2, 3, 4 and 6 hours after compound administration) via the tail vein. Plasma samples were pooled per time point, after which the concentration was determined in plasma by means of LC-MS. Pharmacokinetic parameters (AUC(0-6h), C_{max} and T_{max}) were derived from the obtained

concentration versus time curves using the non-compartmental analysis module in Animals! or WinNonlin.

In certain embodiments, compounds of the present invention are orally
5 bioavailable in the rat with an AUC(0-6h) >1 μ M.h.

Table 3. Biological and physicochemical data of cpds. according to Formulae 6

compound	ER α pIC50 (a)	yield (%)	purity (%)	HPLC Rf (min)	HPLC method	MS- ESI [M+H]	azetidine NMR H-3 ppm
6a	9.1	17	95.7	2.07	A	404.1	5.12 (m, br) (MeOD)
6b	9.1	44	98	14.83	E	432.2	5.05, 5.15 (2xm, br) (DMSO)
6c	9.6	62	98	2.19	A	448.1	4.95 (m, br) (DMSO)
6d	8.8	19	99	2.13	A	460	5.05, 5.15(2xm, br)(DMSO)
6e	8.8	24	99	2.05	A	460	
6f	7.8	82	89.4	5.49	D		5.12 (m) (MeOD)
6g	9.6	23	99.8	2.67	A	461.1	4.97, 5.09 (2xm, br) (DMSO)
6h	9.2	50	99.7	2.78	A	475.2	4.96, 5.08 (2xm, br) (DMSO)
6i	9.0	35	99.4	2.69	A	475.2	4.70 (m) (MeOD)
6j	9.4	32	100	0.93	B		4.65, 5.05 (2xm, br) (DMSO)
6k	9.3	15	99	0.96	B		4.94, 5.04 (2xm, br) (DMSO)
6l	9.2	16	100	1.08	B		4.98, 5.08 (2xm, br) (DMSO)
6m	8.7	61	97.7	2.60	A	489.2	5.05, 5.15 (2xm, br) (DMSO)
6n	8.4	39	98.8	0.84	B	489.3	4.8 (m, br) (DMSO)
6o	7.6	53	100	2.79	B	458.19	4.91 (m, br) (DMSO)
6p	8.4	49	99	2.46	B	444.20	4.92 (m, br) (DMSO)
6q	9.6	46	98	0.93	B	414.3	4.85, 4.95 (2xm, br) (DMSO)
6r	8.8	60	98	2.43	A	442.3	5.12 (m, br) (DMSO)
6s	8.6	42	95	2.75	C	460.1	4.70 (m) (CDCl ₃)
6t	8.5	78	98	2.69	C	474.1	4.90 (m) (CDCl ₃)
6u	7.5	46	93	1.82, 1.99	C	398.22	4.82-5.17 (4xm, br) (DMSO)
6v	9.3	58	97	2.66	C	414.19	4.90, 5.09 (2xm, br) (DMSO)
6w	8.3	64	97	1.49, 1.58	B	414.4	5.01 (2xm, br) (DMSO)
6x	8.1	46	100	1.53, 1.58	B	404.1	5.01 (m, br) (DMSO)

10 (a) See Example 11

A: UPLC BEH C18, 1.7 μ m, 2.1x100 mm (0 to 60% acetonitrile/water/5% TFA)

B: UPLC BEH C18, 1.7 μ m, 2.1x100 mm (40 to 80% acetonitrile/water/5% TFA)

C: LCMS Xbridge, C18, 3.5 μ m, 3.5x20 mm (0 to 100% acetonitrile/water/5% TFA)

D: Luna C18, 3 μ m, 100x2 mm (25% acetonitrile/75% water)

E: Luna C18, 3 μ m, 100x2 mm (0-80% acetonitrile/5% TFA)

5 Table 4. Biological and physicochemical data of cpds. according to Formulae 7

cpd	ER α pIC50 (a)	DR (%) (b)	yield (%)	purity (%)	HPLC Rf (min)	HPLC method	MS- ESI [M+H]	azetidine NMR H-3 ppm
7a	9.1	53	44	98	14.83	E	432.2	5.05, 5.15 (2xm, br) (DMSO)
7b	9.2	68	21	99.3	2.20	A	430.1	4.98 (m, br) (MeOD)
7c	9.6	7 ^(c)	62	98	2.19	A	448.1	4.95 (m, br) (DMSO)
7d	8.7	48	18	97.2	1.91	A	432	5.10 (m, br)(DMSO)
7e	8.7	96	34	99.3	10.80	F	444	5.2 (m, br)(MeOD)
7f	8.6	88	60	98.2	0.67	B	450	5.16 (m,br)(MeOD)
7g	8.4	46	26	99	11.88	G		5.06, 5.12 (2xm, br)(DMSO)
7h	8.8	79	19	99	2.13	A	460	5.05, 5.15 (2xm, br)(DMSO)
7i	8.6	66	62	98.8	2.07	A	458	5.09 (2xm, br)(DMSO)
7j	8.6	98	2	98.8	2.07	A	478	5.13 (m, br)(DMSO)
7k	8.7	57	14	94.4	2.12	A	490	5.05, 5.14 (2xm, br)(DMSO)
7l	9.1	30	15	99.4	2.07	A	472	5.09 (m, br)(DMSO)
7m	9.0	73	24	99.3	2.24	A	474	5.11 (m, br)(MeOD)
7n	8.9	77	36	99.6	2.28	A	486	5.11 (m, br)(MeOD)
7o	8.3	73	39	96.4	1.98	A	502	5.14 (m, br)(MeOD)
7p	8.3	35	14	95.1	2.21	A	514	
7q	8.9	64	14	91.7	8.71	G		5.12 (m, br)(MeOD)
7r	8.7	94	14	99.2	9.64	F		5.09 (m, br)(MeOD)
7s	8.3	101	25	98.9	10.90	F		5.13 (m, br)(MeOD)
7t	8.7	98	27	97	10.82	F		5.24 (m, br)(MeOD)
7u	9.1	78	48	96.4	8.91	F		5.22 (m, br)(MeOD)
7v	9.6	57	23	99.8	2.67	A	461.1	4.97, 5.09 (2xm, br) (DMSO)
7w	9.5	32	62	99.9	2.74	A	475.2	4.72 (m) (MeOD)
7x	9.3	66	61	98.4	2.52	A	503.2	4.72 (m) (MeOD)
7y	9.5	57	23	99.1	2.65	A	473.2	4.63 (m) (MeOD)
7z	9.4	58	42	100	2.84	A		4.74 (m) (MeOD)
7aa	9.0	93	29	100	2.72	A		5.10 (m) (MeOD)
7ab	9.4	86	17	98	1.00	B		5.00 (m, br) (DMSO)
7ac	8.8	94	39	100	1.04	B		5.02 (m, br) (DMSO)
7ad	9.0	92	80	100	1.19	B		5.04 (m, br) (DMSO)
7ae	7.9	99	58	99.4	2.50	A	449.2	5.12, 5.22 (2xm, br) (DMSO)
7af	8.5	92	12	96.4	2.31	A	446.2	5.05, 5.24 (2xm, br) (DMSO)
7ag	8.7	81	61	97.7	2.60	A	489.2	5.05, 5.15 (2xm, br) (DMSO)
7ah	8.6	94	16	97	2.54	A	507.1	5.10 (m, br) (DMSO)
7ai	8.1	96	65	99.8	0.80	B	455.3	5.05, 5.16 (2xm, br) (DMSO)

7aj	8.5	100	59	99.1	0.85	B	469.3	5.01, 5.15 (2xm, br) (DMSO)
7ak	8.5	93	46	99.4	0.77	B	491.2	5.05, 5.15 (2xm, br) (DMSO)
7al	8.1	100	30	99.5	0.70	B	457.9	5.15 (m, br) (DMSO)
7am	7.6	93	26	99.7	2.34	A	470.2	5.18 (m) (MeOD)
7an	8.7	98	30	96	2.71	A	475.2	5.07, 5.17 (2xm, br) (DMSO)
7ao	7.6	80	34	98.7				4.62 (m) (CDCl ₃)
7ap	8.7	90	67	100	2.65	A	489.3	5.10 (m, br) (DMSO)
7aq	7.6	78	42	99	2.40	A	462.2	5.14 (m) (CDCl ₃)
7ar	7.7	82	16	97.4	0.70	B	488.2	5.15 (m) (CDCl ₃)
7as	7.4	55	36	98.8	2.55	A	513.2	5.05 (m, br) (DMSO)
7at	8.8	101	82	98.5	0.94	B	507.2	5.10 (m, br) (DMSO)
7au	9.0	89	70	99.7	2.74	A	475.2	4.85, 5.00 (2xm, br) (DMSO)
7av	7.6	84	43	99.5	2.27	A	491.2	4.65 (m) (CDCl ₃)
7aw	8.1	64	48	93.4	0.90	B	505.2	4.70 (m) (CDCl ₃)
7ax	9.1	33	38	99.3	0.99	B	487.2	4.69 (m) (CDCl ₃)
7ay	8.4	62	39	98.8	0.84	B	489.3	4.8 (m, br) (DMSO)
7az	8.2	88	21	99.5	1.15	B	469.3	5.04, 5.15 (2xm, br) (DMSO)
7ba	7.8	51	27	99	2.47	A	473.3	5.05, 5.15 (2xm, br) (DMSO)
7bb	8.7	90	45	98	1.32	B	485.3	5.09 (m, br) (DMSO)
7bc	9.6	47	46	98	0.93	B	414.3	4.85, 4.95 (2xm, br) (DMSO)
7bd	7.6	75	53	100	2.79	B	458.19	4.91 (m, br) (DMSO)
7be	8.4	58	49	99	2.46	B	444.20	4.92 (m, br) (DMSO)
7bf	7.2	33	85	95	0.95	B	456.3	4.72 (m, br) (DMSO)
7bg	7.5	75	46	93	1.82, 1.99	C	398.22	4.82-5.17 (4xm, br) (DMSO)
7bh	9.3	-5 ^(d)	58	97	2.66	C	414.19	4.90, 5.09 (2xm, br) (DMSO)
7bi	8.3	63	64	97	1.49, 1.58	B	414.4	5.01 (2xm, br) (DMSO)
7bj	8.1	63	46	100	1.53, 1.58	B	404.1	5.01 (m, br) (DMSO)

(a) See Example 11

(b) See Example 13

- 5 (c) The corresponding analogue of compound 7c in which the N-propylazetidiny-3-oxy side chain is replaced by a piperidylethyloxy side chain (*i.e.* compound LY-335562, described as Example 18 in US patent 5,488,058) shows downregulation of -199% (*i.e.* upregulation of 199%).

- 10 (d) Downregulation of -5% means upregulation of 5%. The corresponding analogue of compound 7bh in which the N-propylazetidiny-3-oxy side chain is replaced by a dimethylaminoethyloxy side chain (*i.e.* 4-hydroxy-tamoxifen) shows down-regulation of -343% (*i.e.* upregulation of 343%).

A: UPLC BEH C18, 1.7 μ m, 2.1x100 mm (0 to 60% acetonitrile/water/5% TFA)

- 15 B: UPLC BEH C18, 1.7 μ m, 2.1x100 mm (40 to 80% acetonitrile/water/5% TFA)

C: LCMS Xbridge, C18, 3.5 μ m, 3.5x20 mm (0 to 100% acetonitrile/water/5% TFA)

D: Luna C18, 3 μ m, 100x2 mm (25% acetonitrile/75% water)

E: Luna C18, 3um, 100x2 mm (0-80% acetonitrile/5% TFA)
F: HPLC BEH C18 5um Luna column (10 to 60% acetonitrile/water 5%TFA)
G: HPLC BEH C18 5um Luna column (10 to 70% acetonitrile/water 5%TFA)

5

Table 5. Biological and physicochemical data of cpds. according to Formulae 8

cpd	ERα pIC50 (a)	MCF7 ia (b)	DR (%) (c)	yield (%)	purity (%)	HPLC Rf (min)	HPLC method	MS- ESI [M+H]	azetidine NMR H-3 ppm
8a	9.1	0.10	53	44	98	14.83	E	432.2	5.05, 5.15 (2xm, br) (DMSO)
(d)8c	8.8	0.05	79	19	99	2.13	A	460	5.05, 5.15 (2xm, br)(DMSO)
8d	9.6	0.02	57	23	99.8	2.67	A	461.1	4.97, 5.09 (2xm, br) (DMSO)
8e	8.7	0.07	81	61	97.7	2.60	A	489.2	5.05, 5.15 (2xm, br) (DMSO)
8f	8.6	0.06	94	16	97	2.54	A	507.1	5.10 (m, br) (DMSO)
8g	8.5	0.07	93	46	99.4	0.77	B	491.2	5.05, 5.15 (2xm, br) (DMSO)
8h	8.2	0.08	88	21	99.5	1.15	B	469.3	5.04, 5.15 (2xm, br) (DMSO)
8i	8.7	0.03	90	45	98	1.32	B	485.3	5.09 (m, br) (DMSO)
8j	9.6	0.06	47	46	98	0.93	B	414.3	4.85, 4.95 (2xm, br) (DMSO)
8k	7.5	0.08	75	46	93	1.82, 1.99	C	398.22	4.82-5.17 (4xm, br) (DMSO)

- (a) See Example 11
10 (b) See Example 12
(c) See Example 13
(d) See comment (c) to cpd. 7c in Table 4

- A: UPLC BEH C18, 1.7 um, 2.1x100 mm (0 to 60% acetonitrile/water/5% TFA)
15 B: UPLC BEH C18, 1.7 um, 2.1x100 mm (40 to 80% acetonitrile/water/5% TFA)
C: LCMS Xbridge, C18, 3.5 um, 3.5x20 mm (0 to 100% acetonitrile/water/5% TFA)
D: Luna C18, 3um, 100x2 mm (25% acetonitrile/75% water)
E: Luna C18, 3um, 100x2 mm (0-80% acetonitrile/5% TFA)

20

Table 6. Biological and physicochemical data of cpds. according to Formulae 9

cpd	ERα pIC50 (a)	MCF7 (b)	DR (%) (c)	RRat AUC (μM.h) (d)	RRat Cmax (μM) (d)	yield (%)	purity (%)	HPLC Rf (min)	HPLC metho d	MS- ESI [M+H]	azetidine NMR H-3 ppm
9a	9.6	0.02	57	2.05	0.57	23	99.8	2.67	A	461.1	4.97, 5.09 (2xm, br) (DMSO)
9b	9.5		32	1.55	0.52	62	99.9	2.74	A	475.2	4.72 (m)

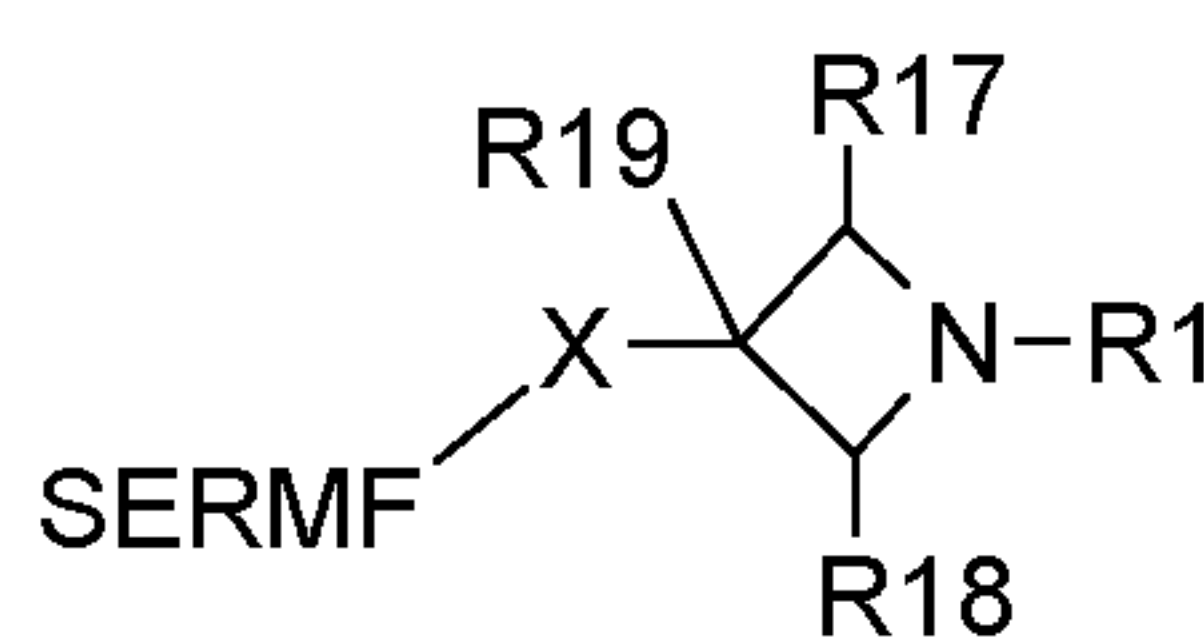
											(MeOD)
9c	9.5		57	1.20	0.29	23	99.1	2.65	A	473.2	4.63 (m) (MeOD)
9d	9.4		58	1.03	0.35	42	100	2.84	A		4.74 (m) (MeOD)
9e	9.0		93	3.58	0.99	29	100	2.72	A		5.10 (m) (MeOD)
9f	7.6		84	3.80	0.99	43	99.5	2.27	A	491.2	4.65 (m) (CDCl ₃)
9g	7.5	0.08	75	1.97	0.45	46	93	1.82, 1.99	C	398.22	4.82-5.17 (4xm, br) (DMSO)
9h	8.3		63	1.07	0.23	64	97	1.49, 1.58	B	414.4	5.01 (2xm, br) (DMSO)

- (a) See Example 11
- (b) See Example 12
- (c) See Example 13
- 5 (d) See Example 14

A: UPLC BEH C18, 1.7 um, 2.1x100 mm (0 to 60% acetonitrile/water/5% TFA)
B: UPLC BEH C18, 1.7 um, 2.1x100 mm (40 to 80% acetonitrile/water/5% TFA)
C: LCMS Xbridge, C18, 3.5 um, 3.5x20 mm (0 to 100% acetonitrile/water/5% TFA)

CLAIMS

1. N-substituted azetidine derivative of the following Formula 1



Formula 1

wherein

SERMF is a Selective Estrogen Receptor Modulator fragment;

10 X is no atom, O, S, CH₂, carbonyl, N-R5;

R1 is H, (C1-8)alkyl, (C3-8)cycloalkyl, (C3-6)heterocycloalkyl, (C2-6)alkenyl, (C2-6)alkynyl, (C1-4)alkylcarbonyl, (C1-4)alkoxy(C2-4)alkyl, (C3-6)cycloalkyl-(C1-3)alkyl, (C3-6)heterocycloalkyl(C1-3)alkyl, each independently optionally substituted with one or more halogen, nitrile, hydroxyl or (C1-2)alkyl;

15 R5 is H, (C1-3)alkyl, optionally substituted with one or more fluorine;

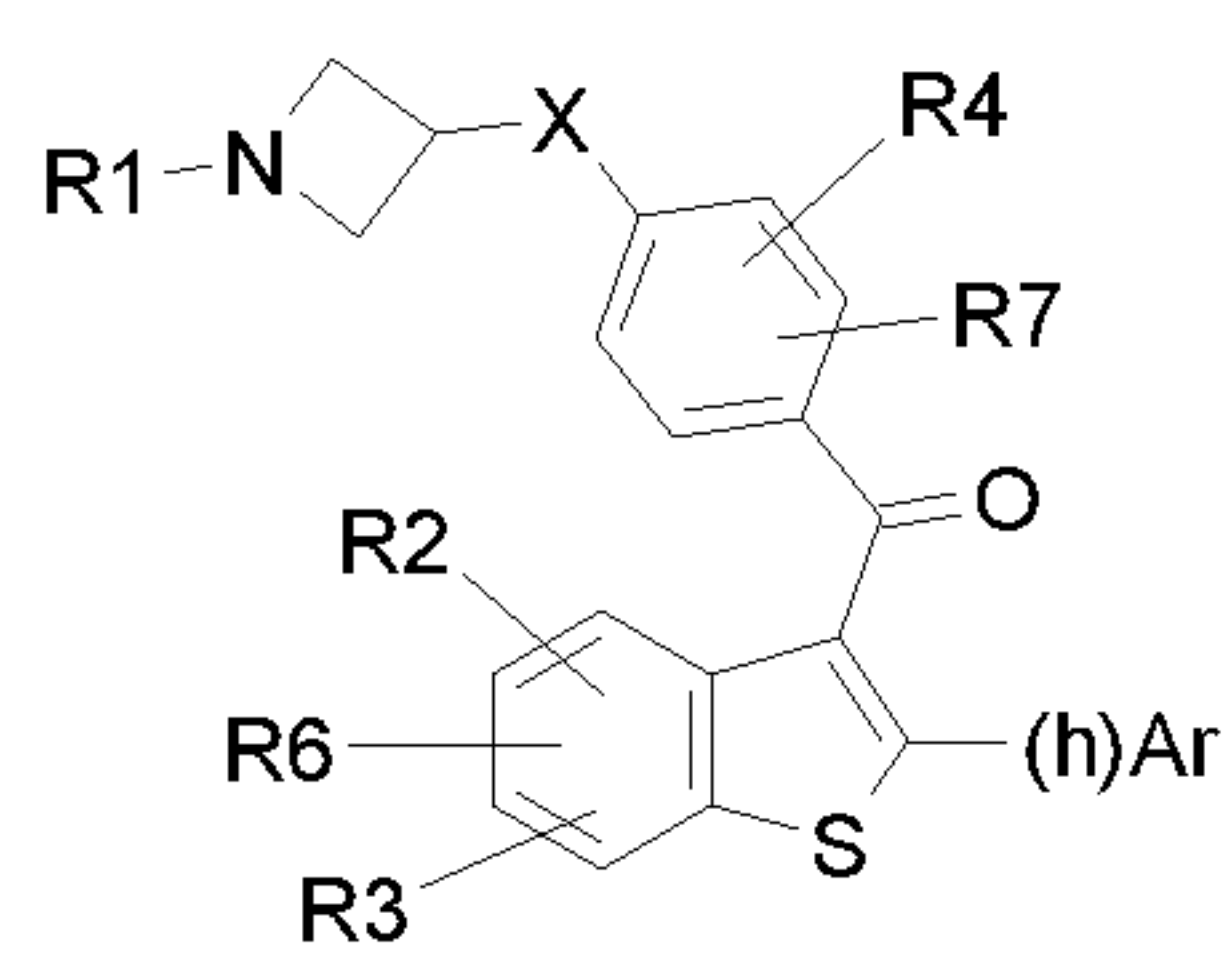
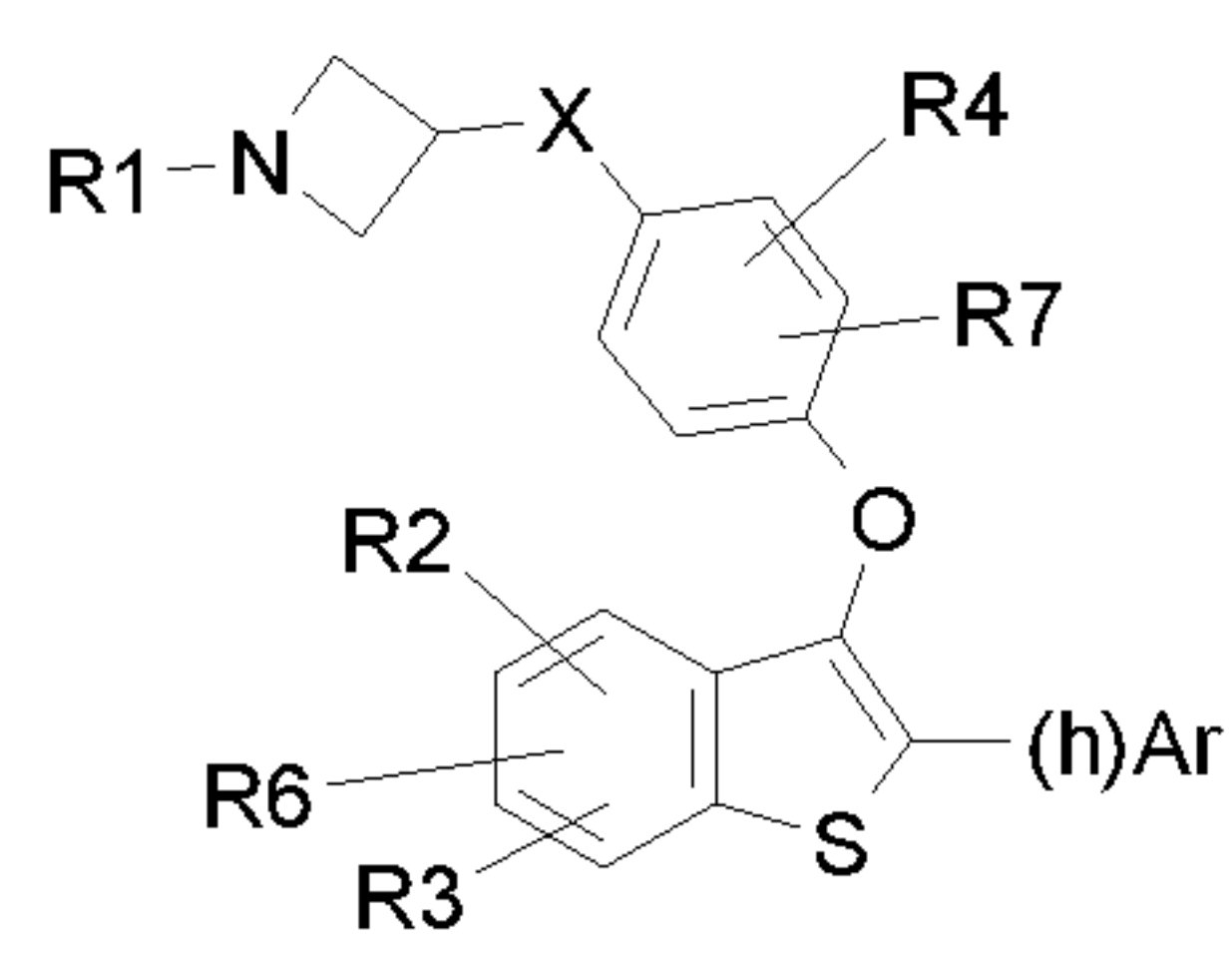
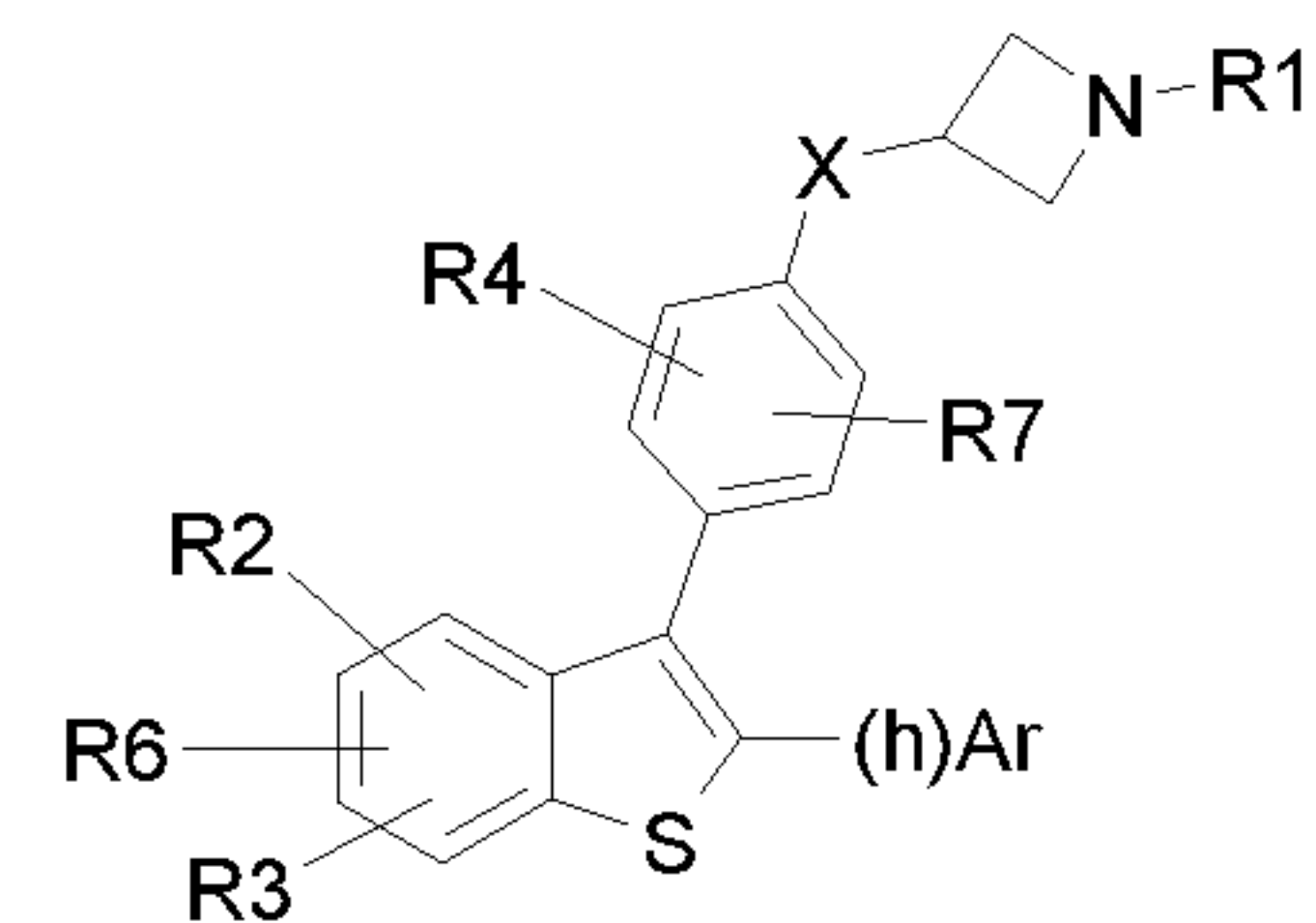
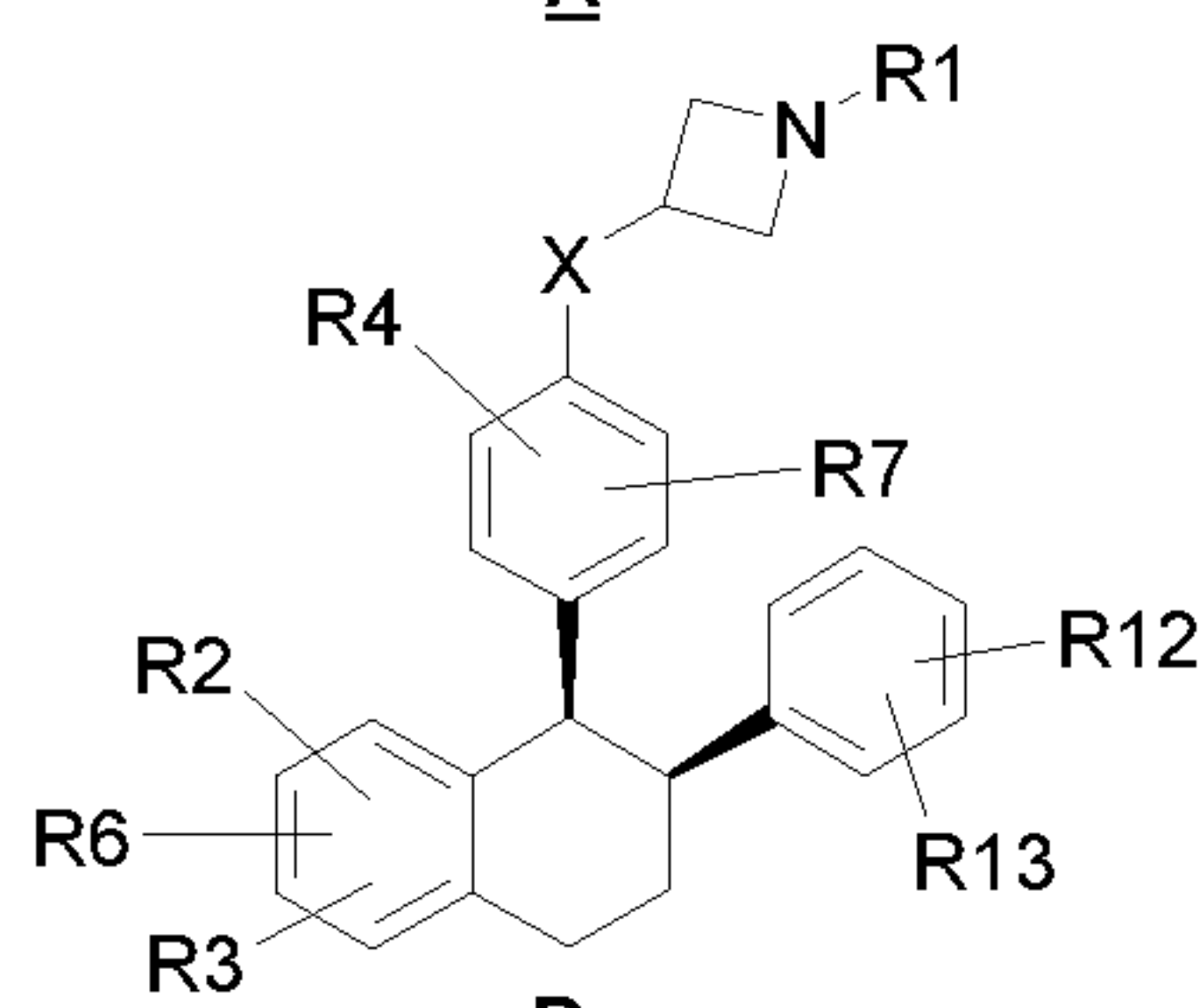
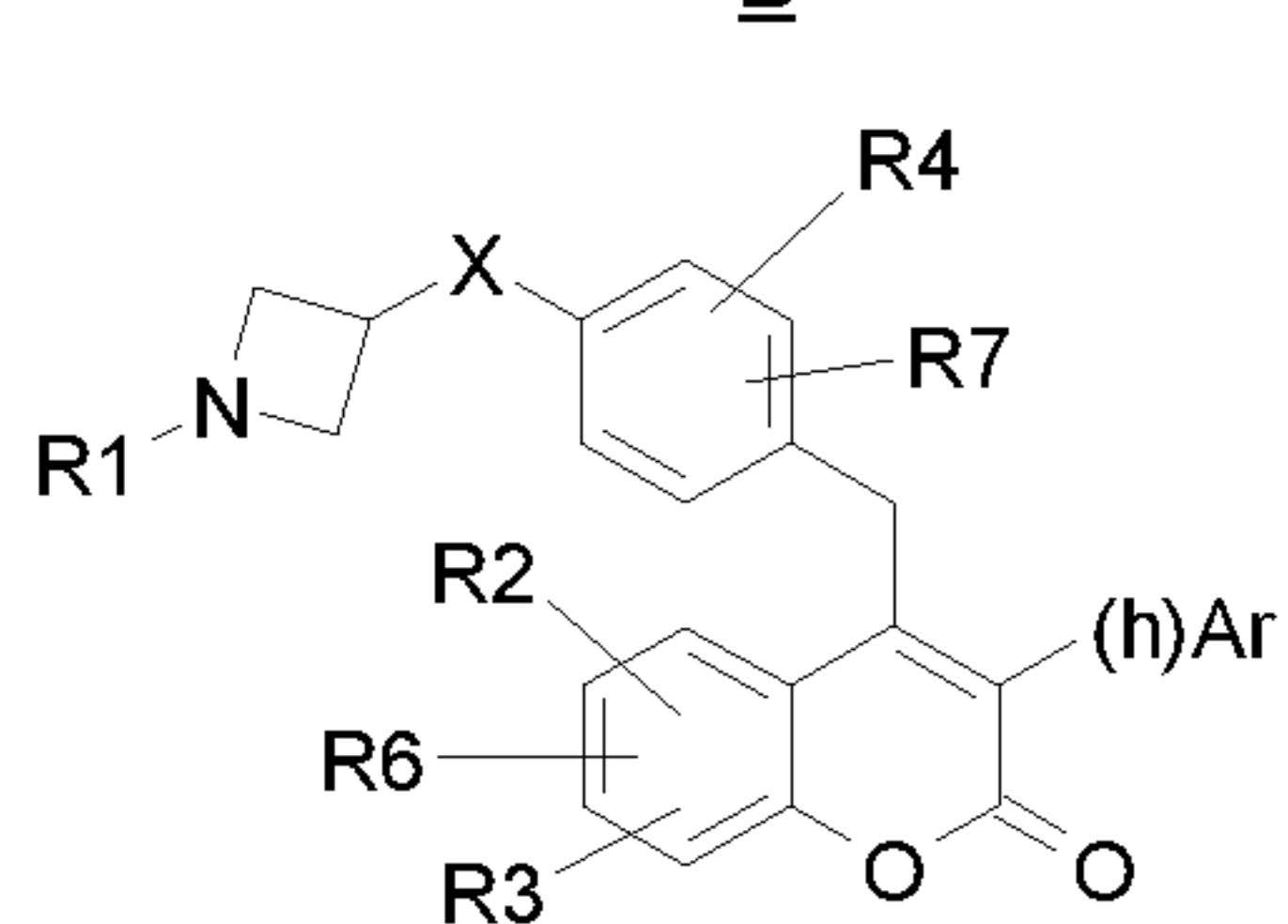
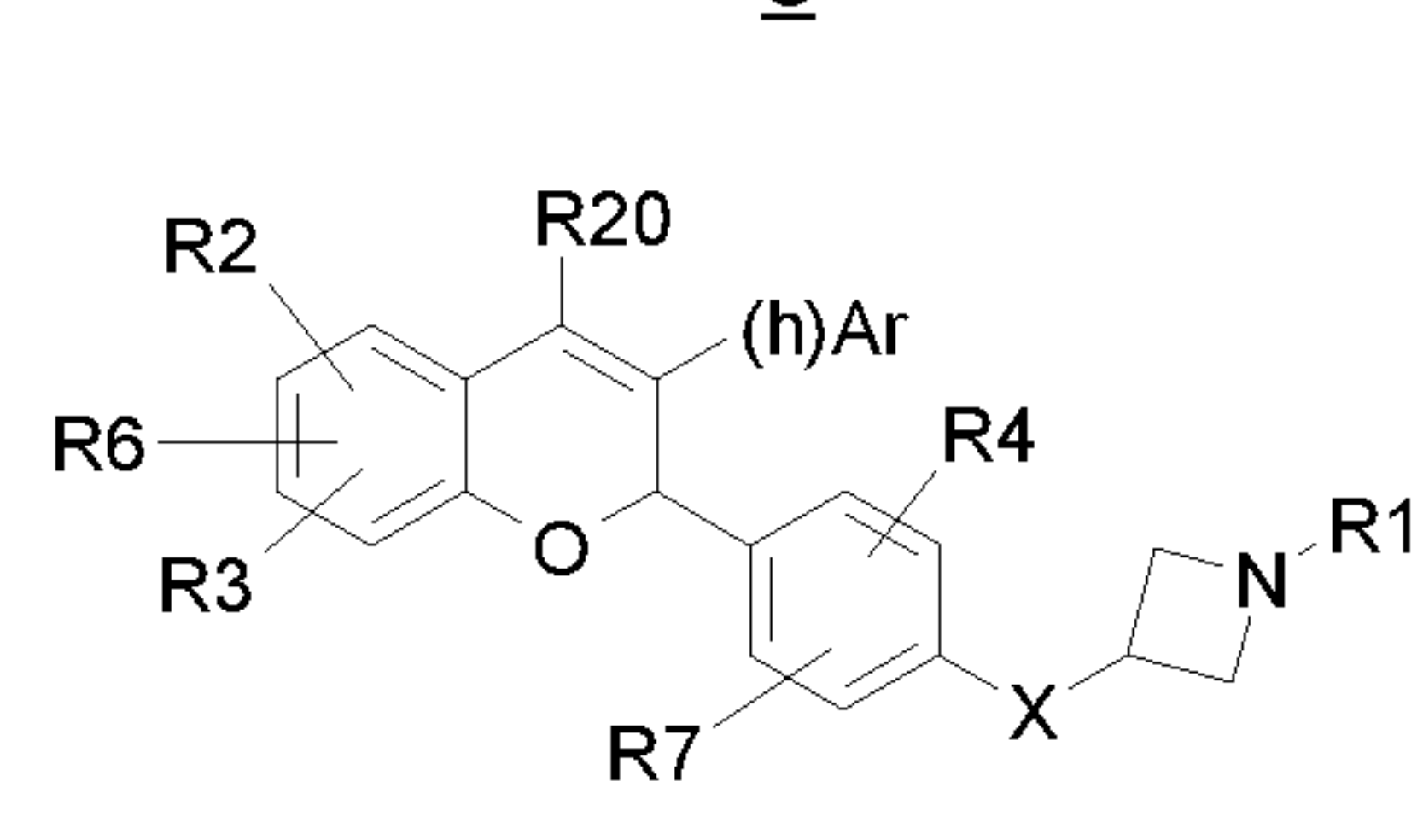
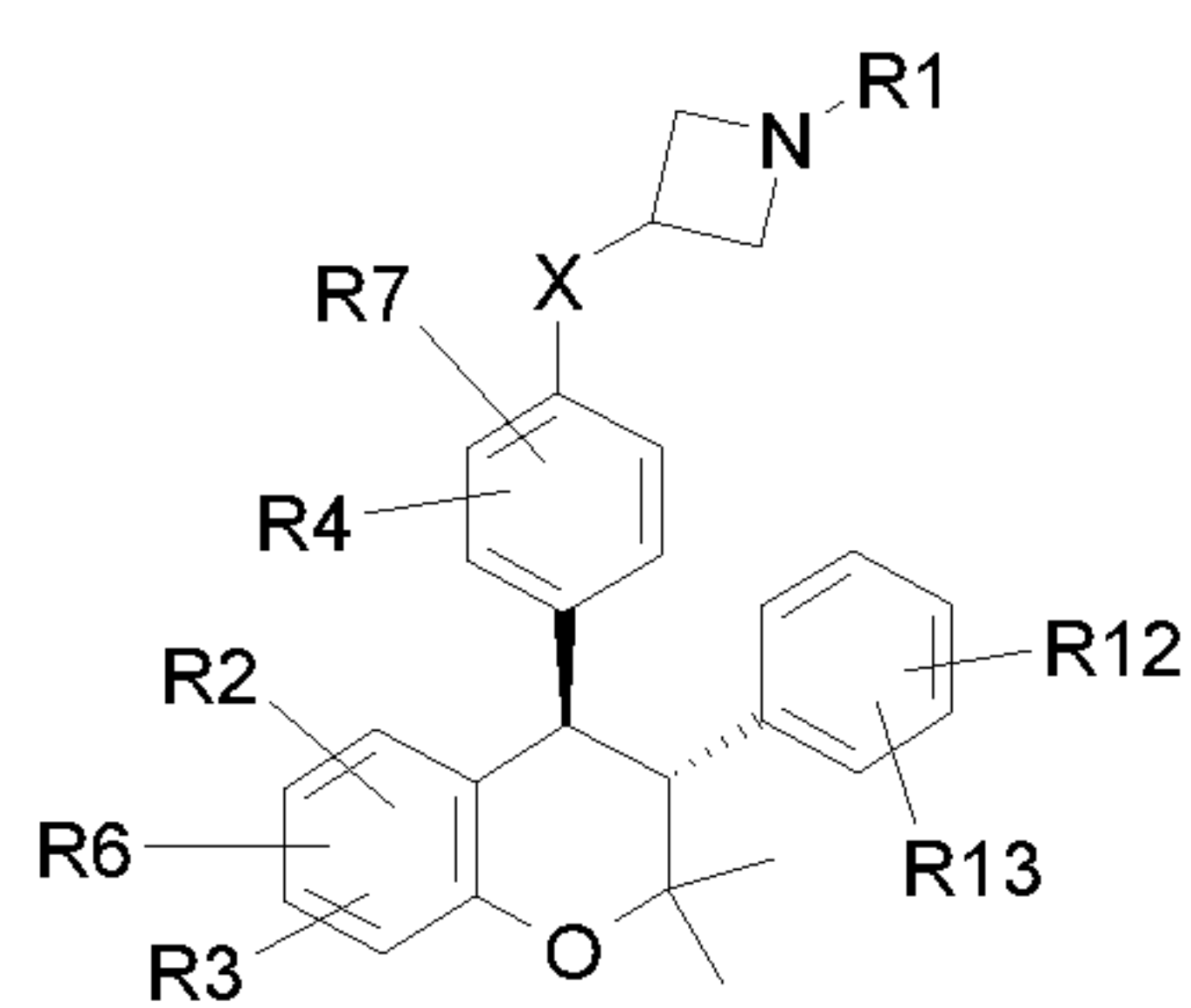
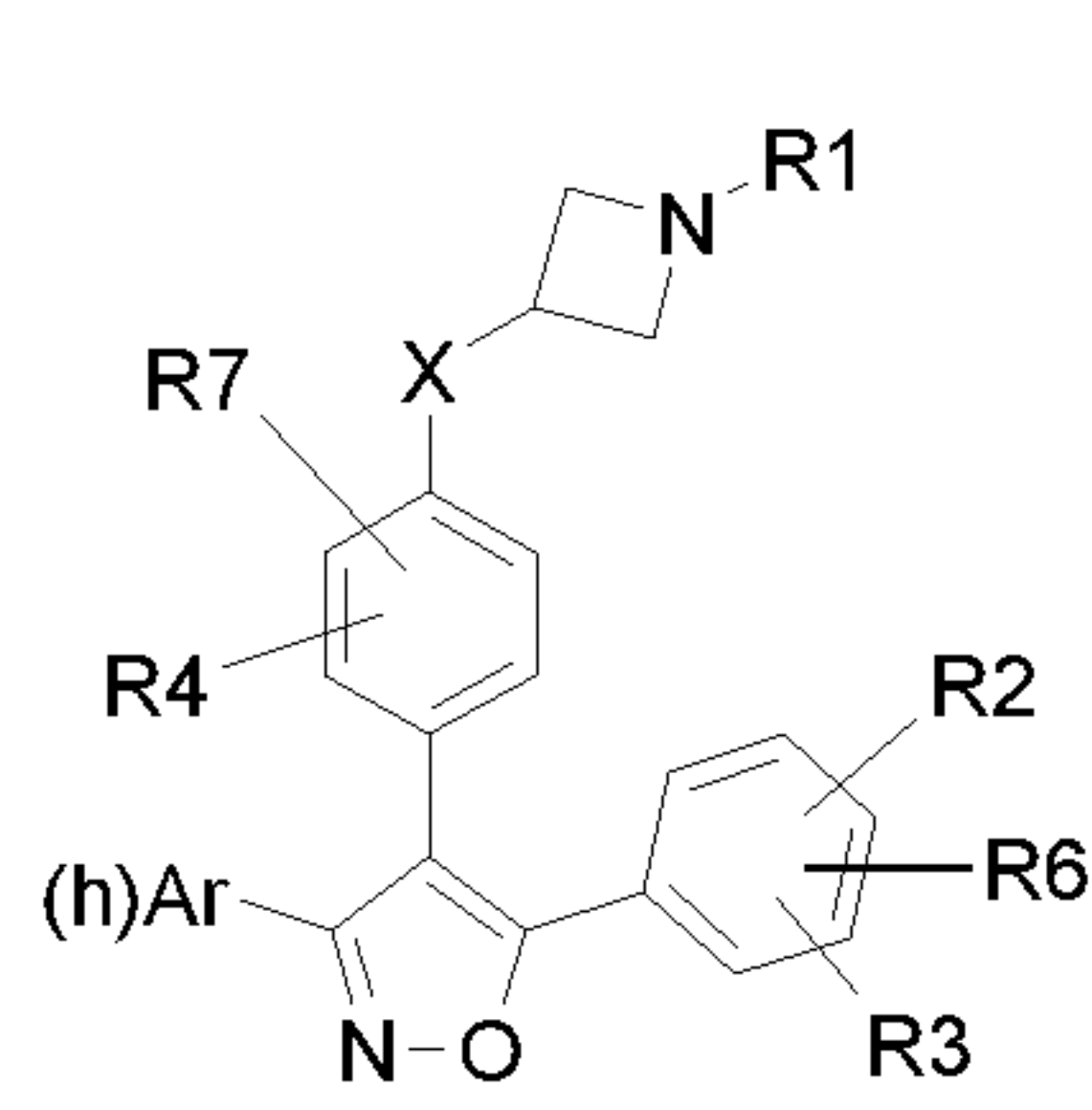
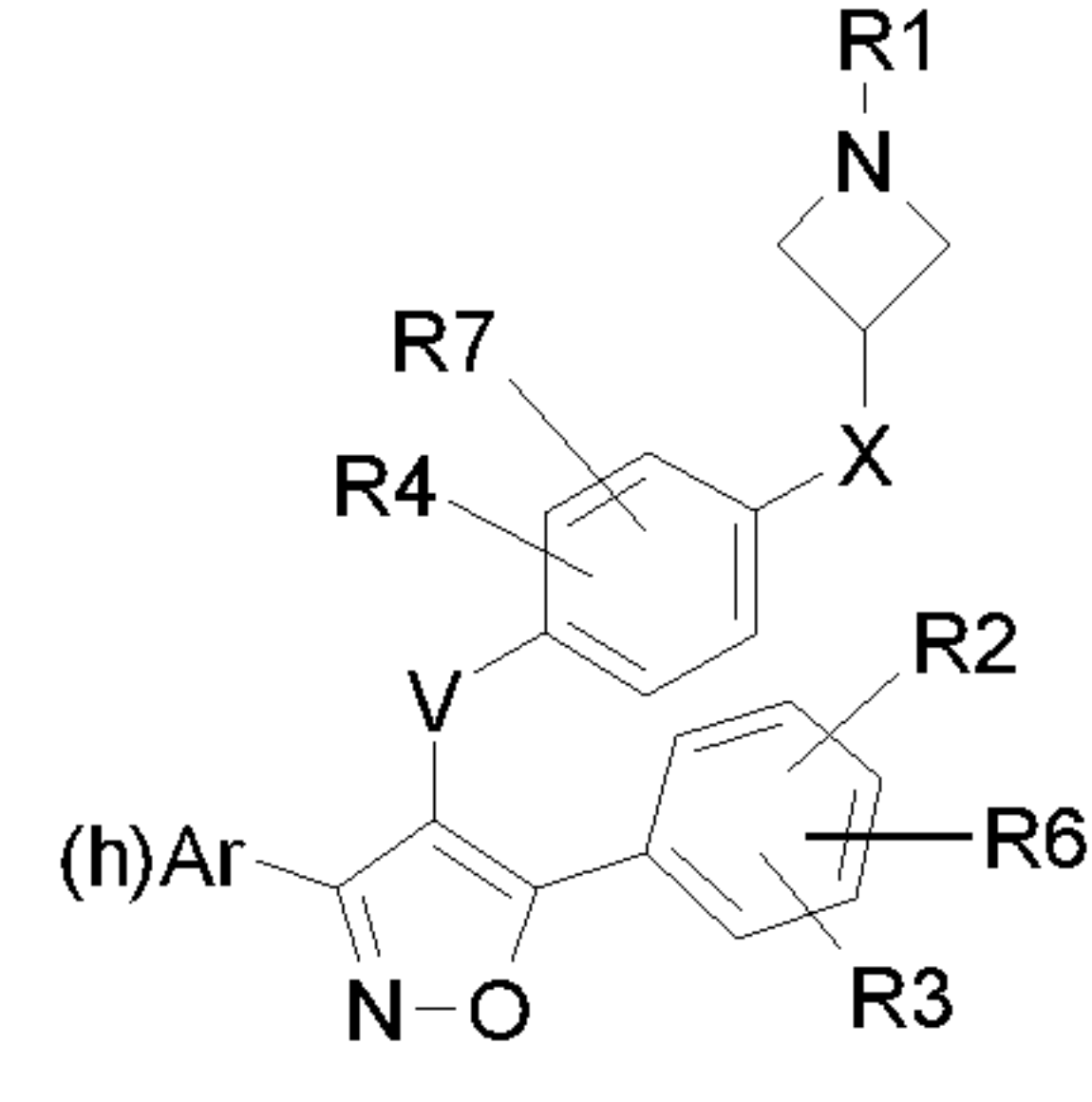
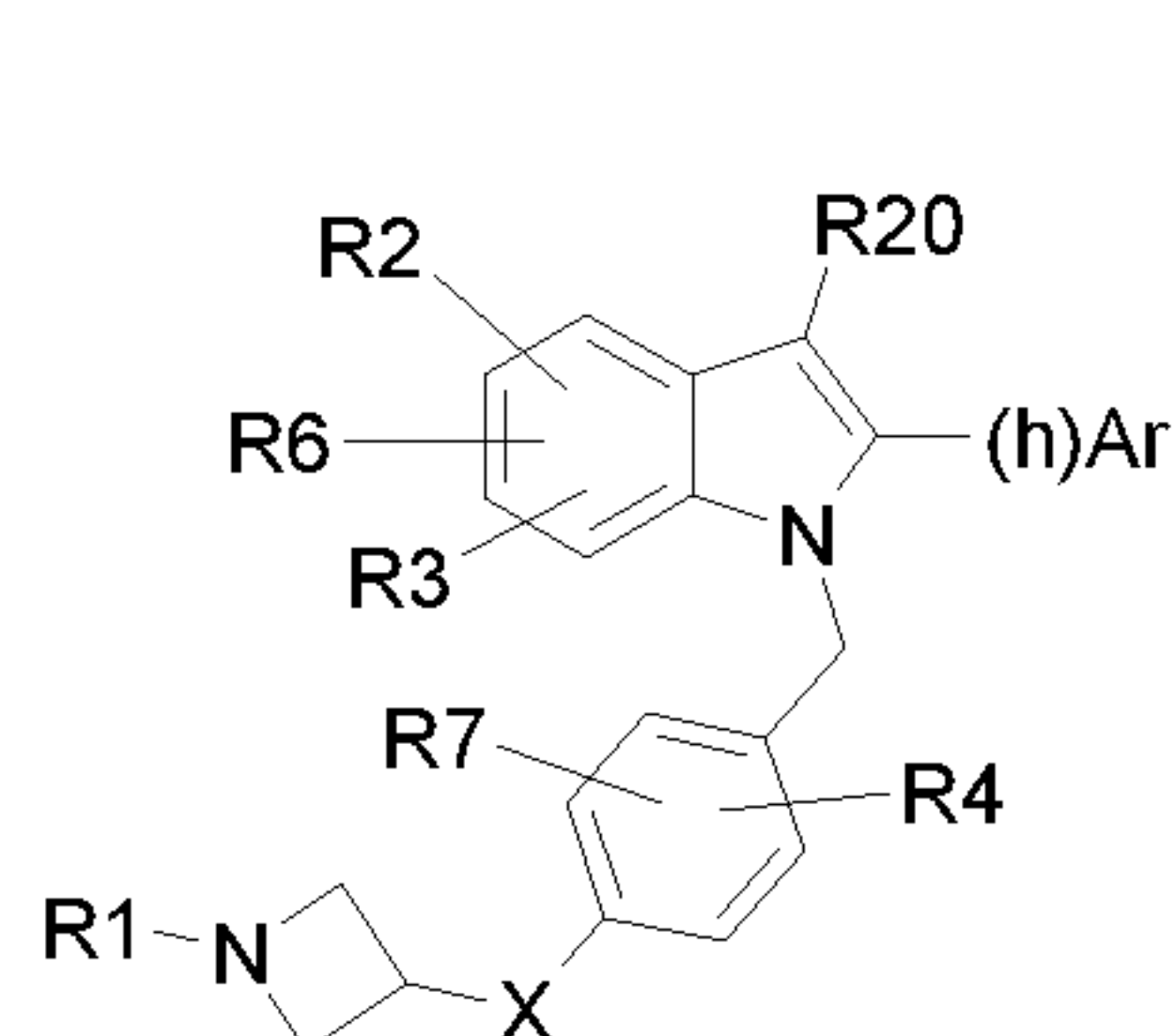
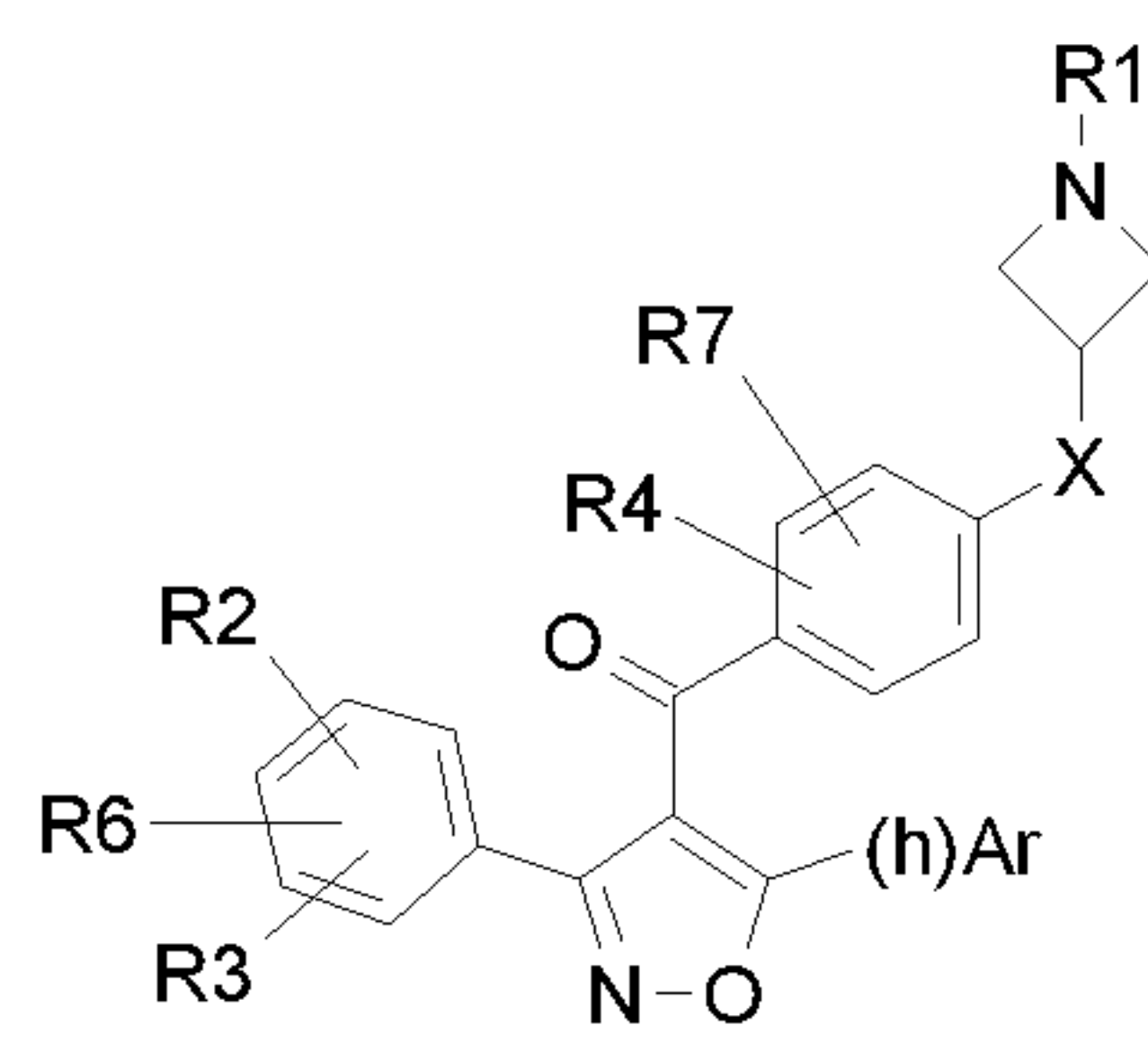
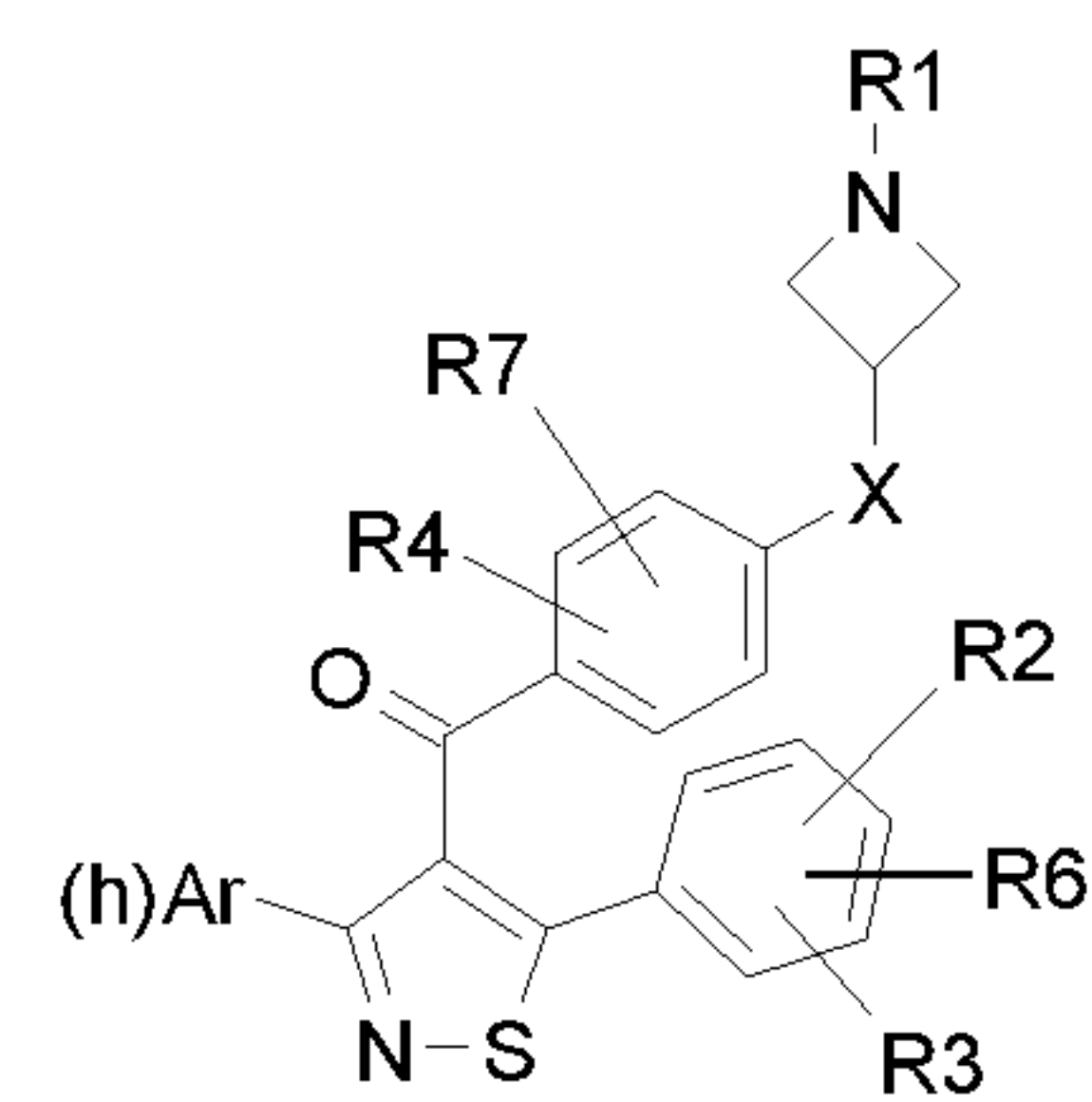
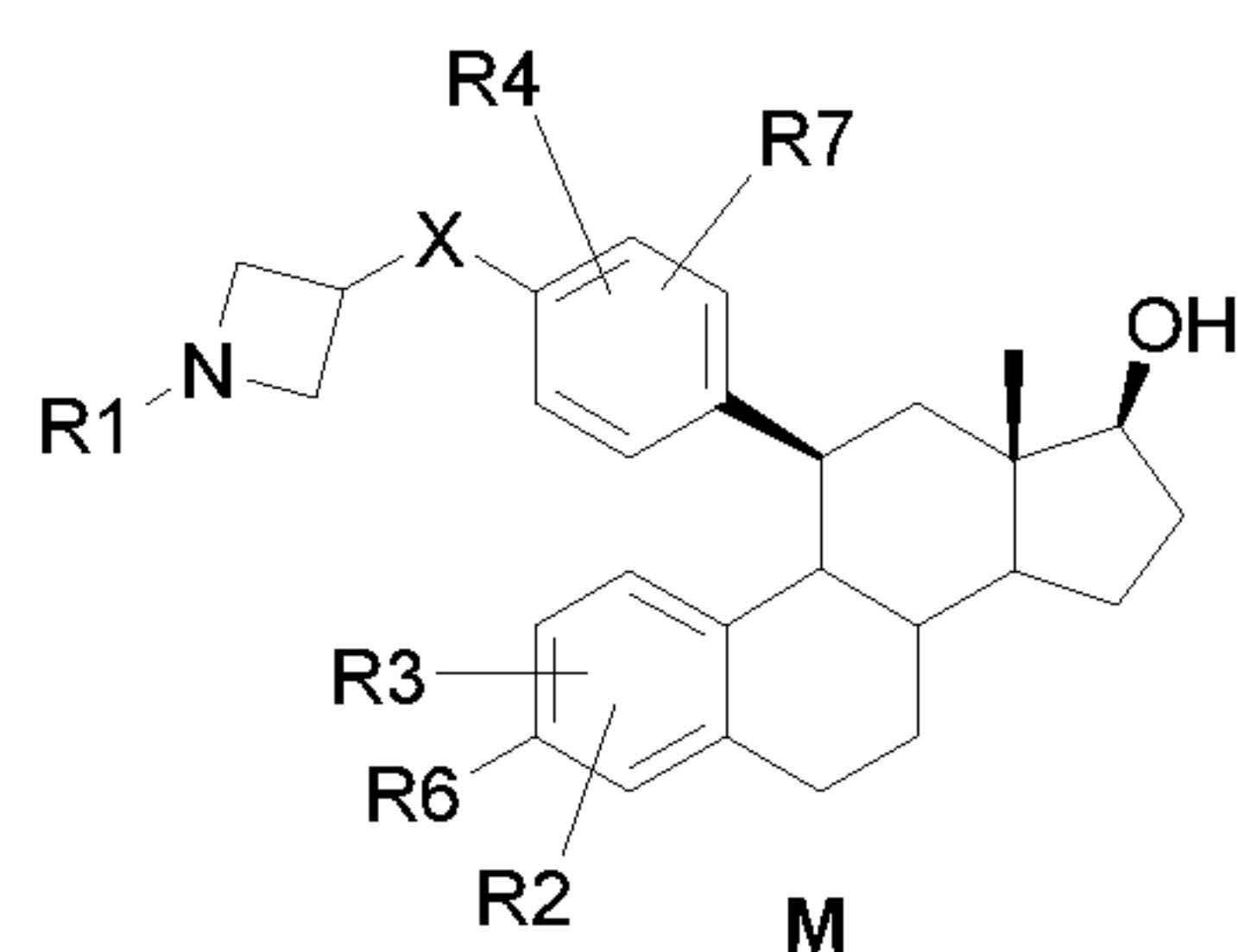
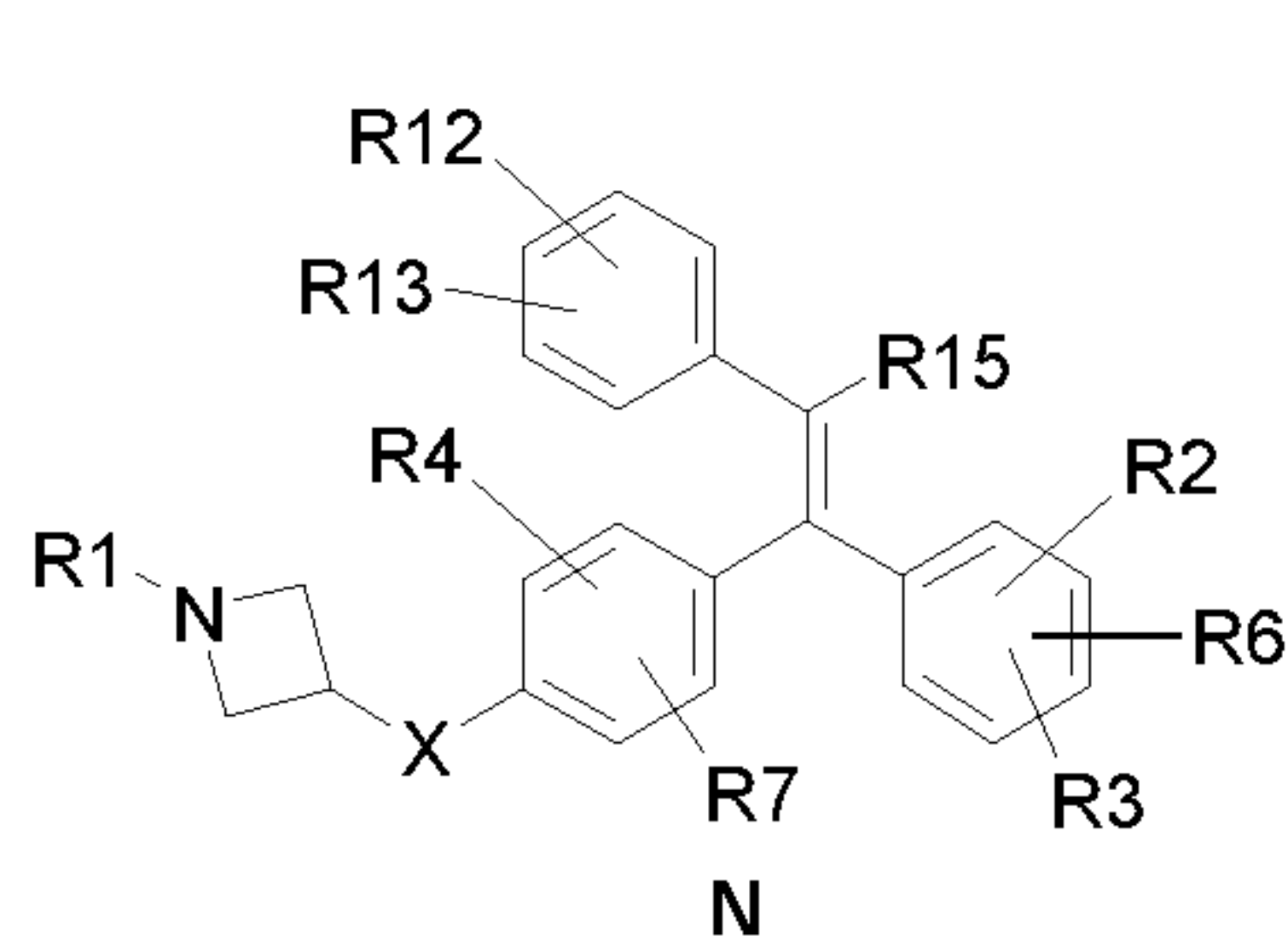
R17, R18 and R19 are independently of each other H, fluorine, nitrile or (C1-3)-alkyl, optionally substituted with one or more fluorine;

or a prodrug, isotopically-labelled derivative or pharmaceutically acceptable salt thereof.

20

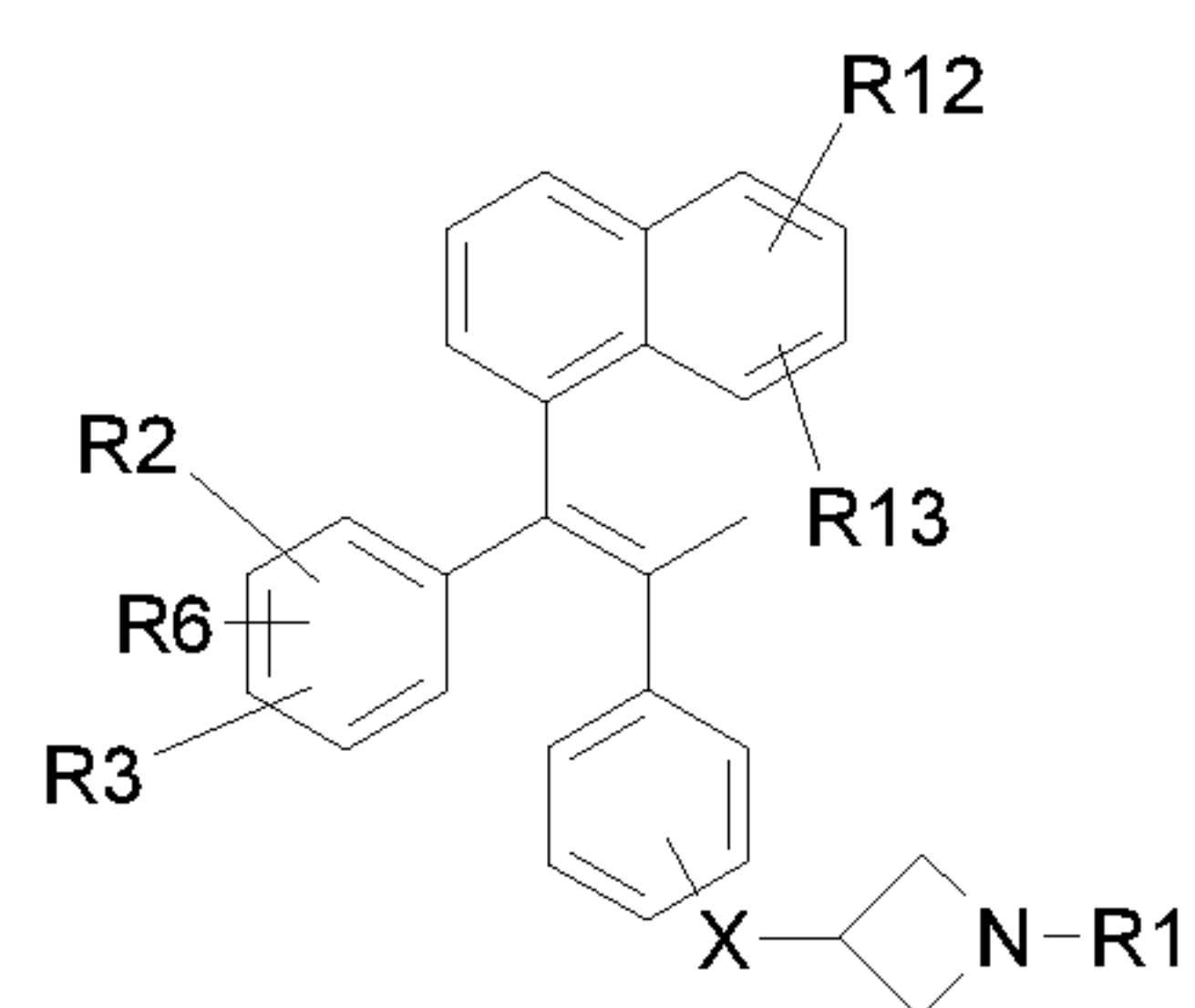
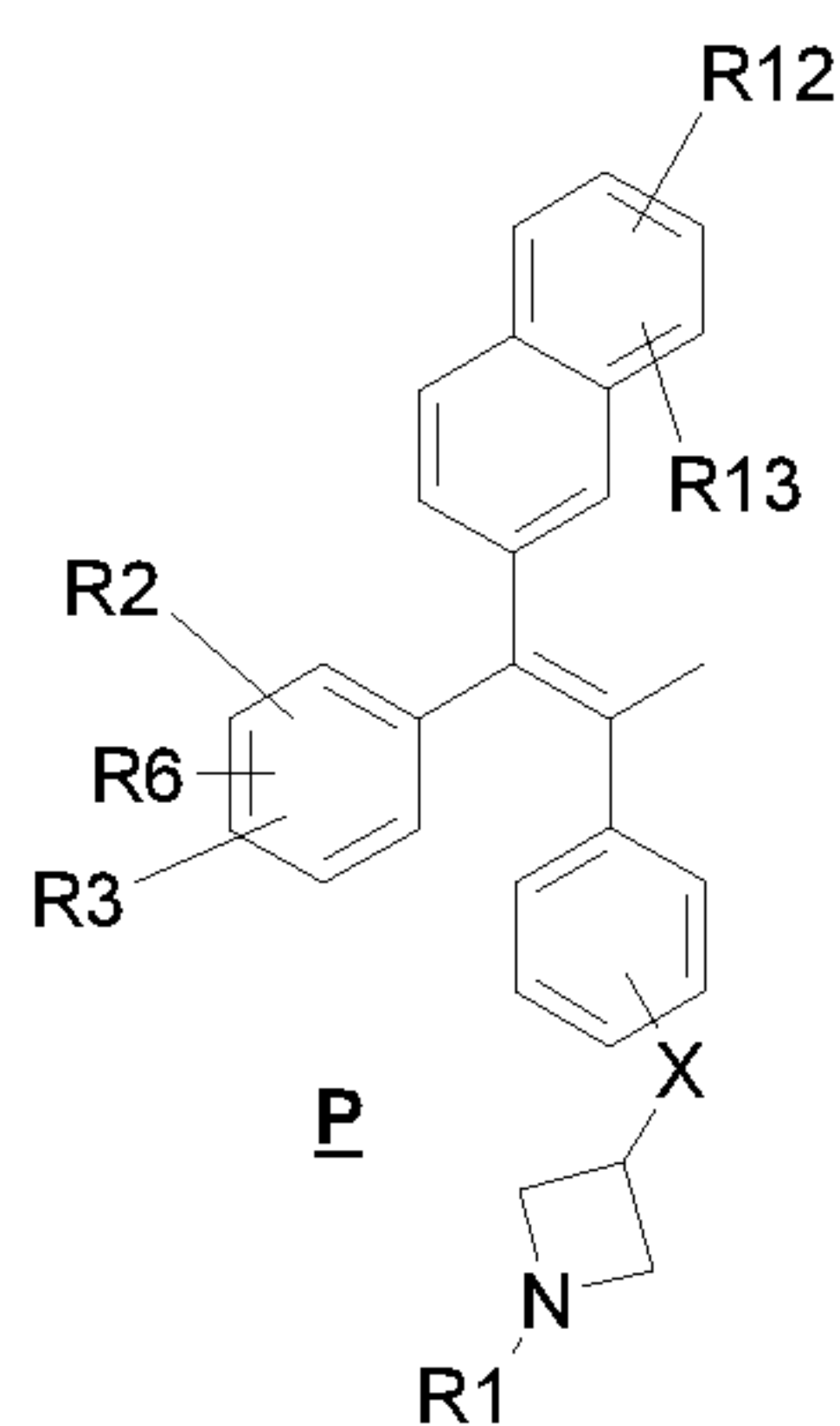
2. An N-substituted azetidine derivative according to claim 1 selected from the group consisting of compounds according to any one of Formulae 3

80

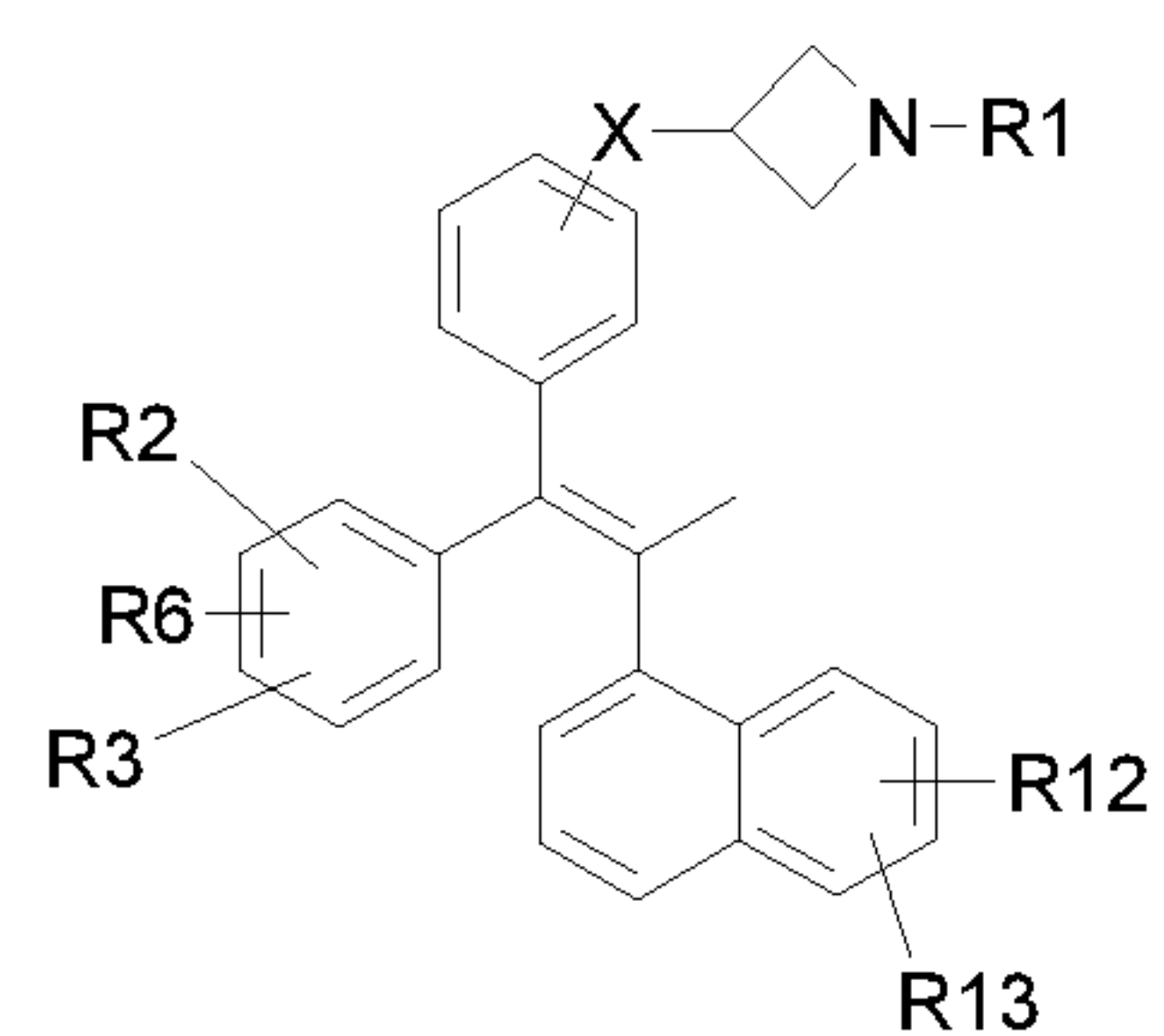
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Formulae 3

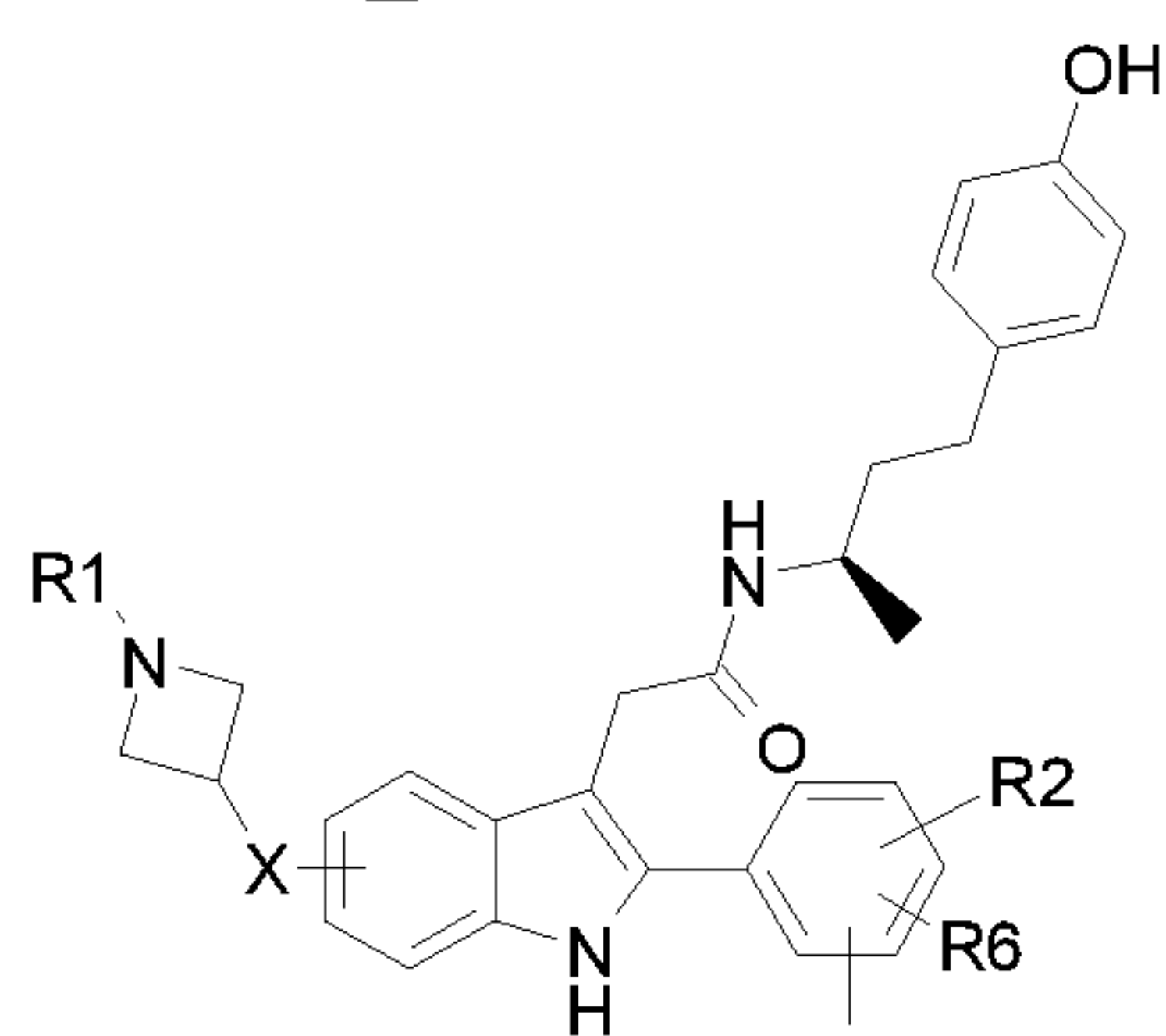
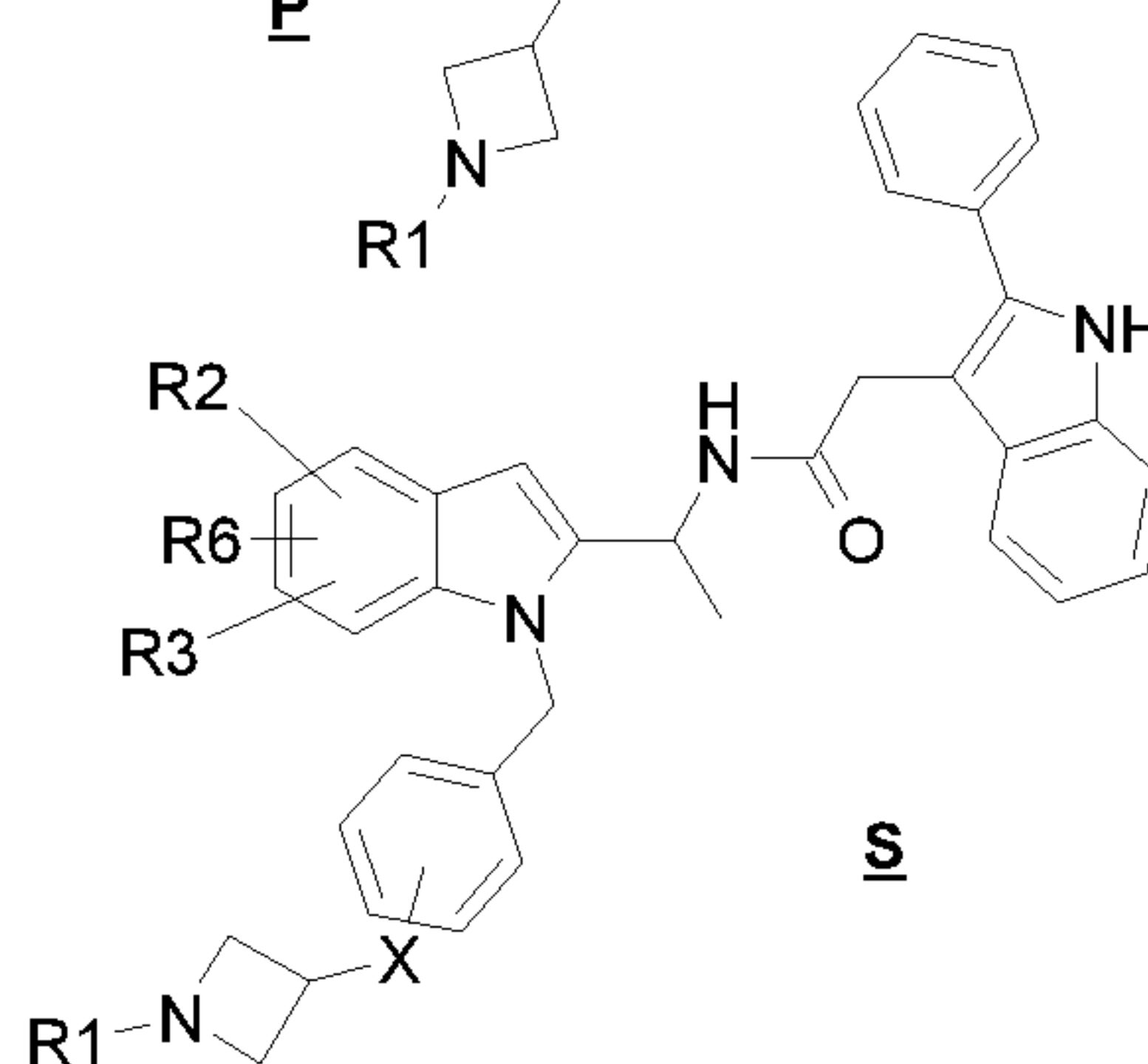
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O

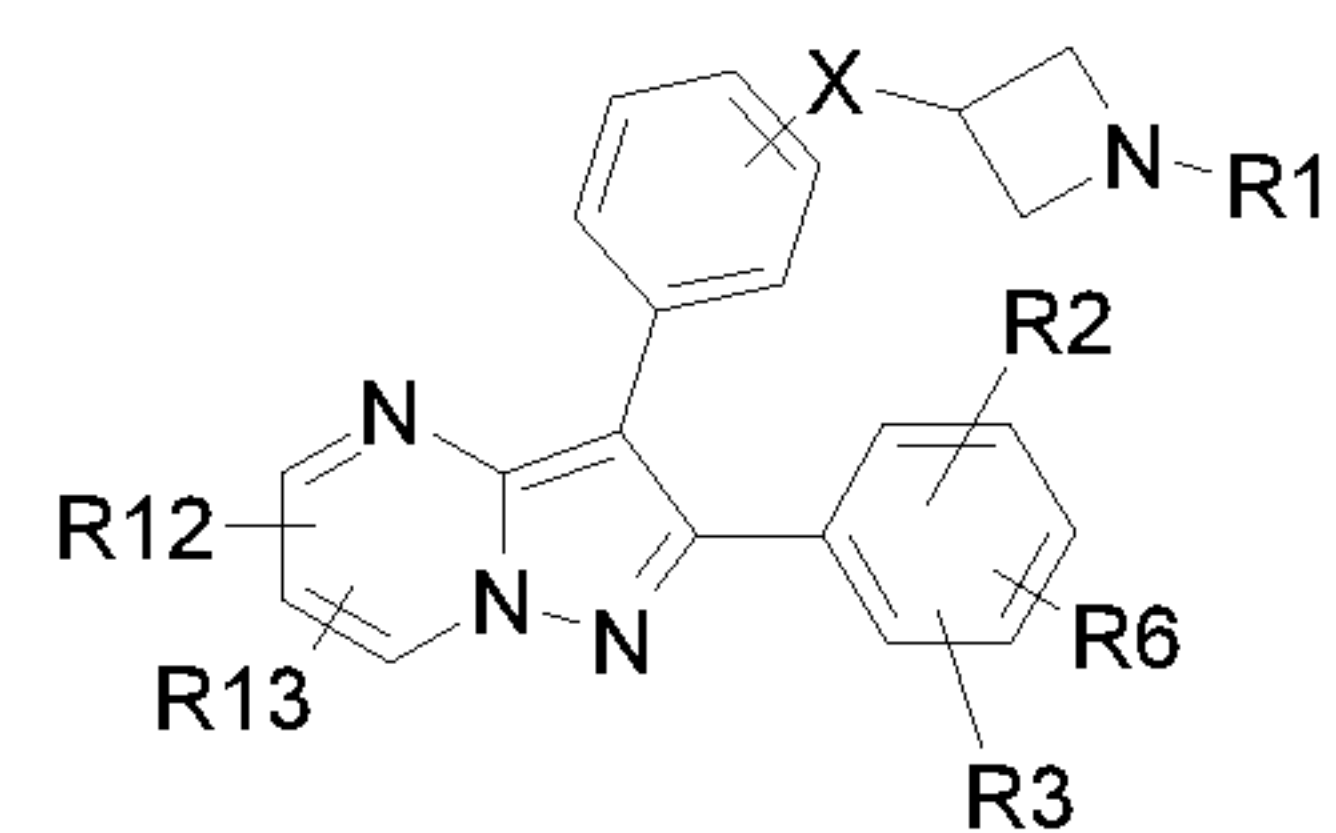
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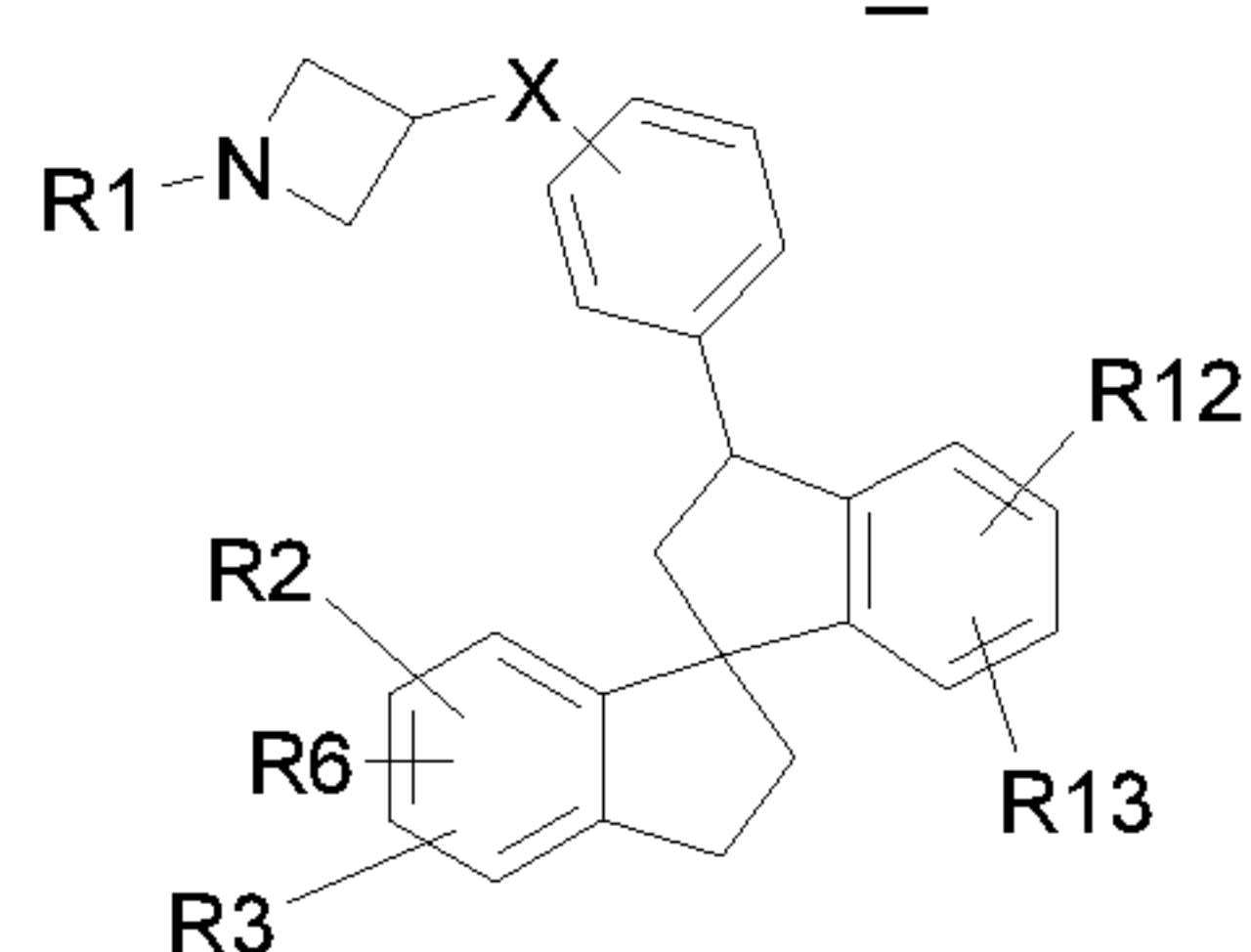
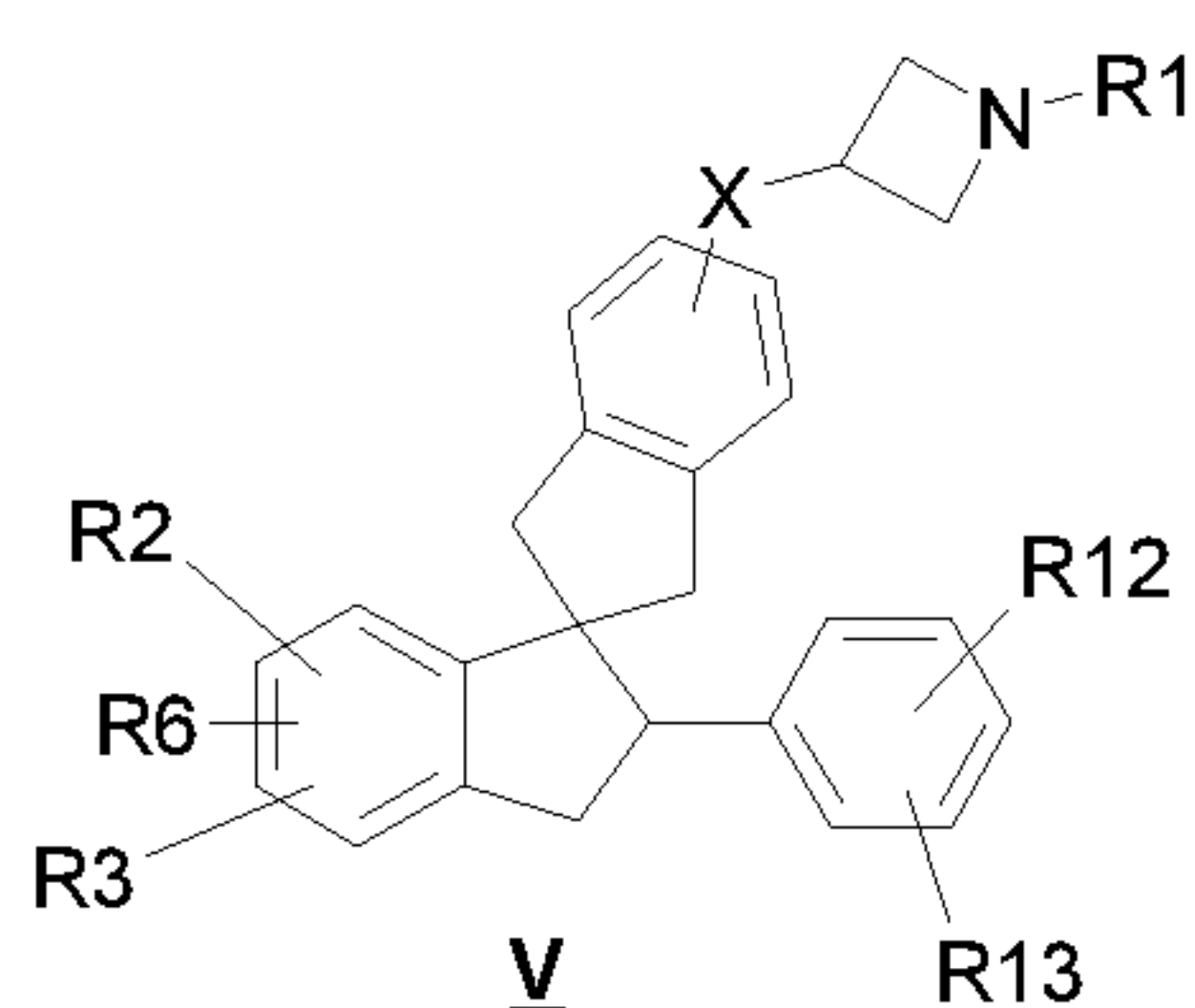
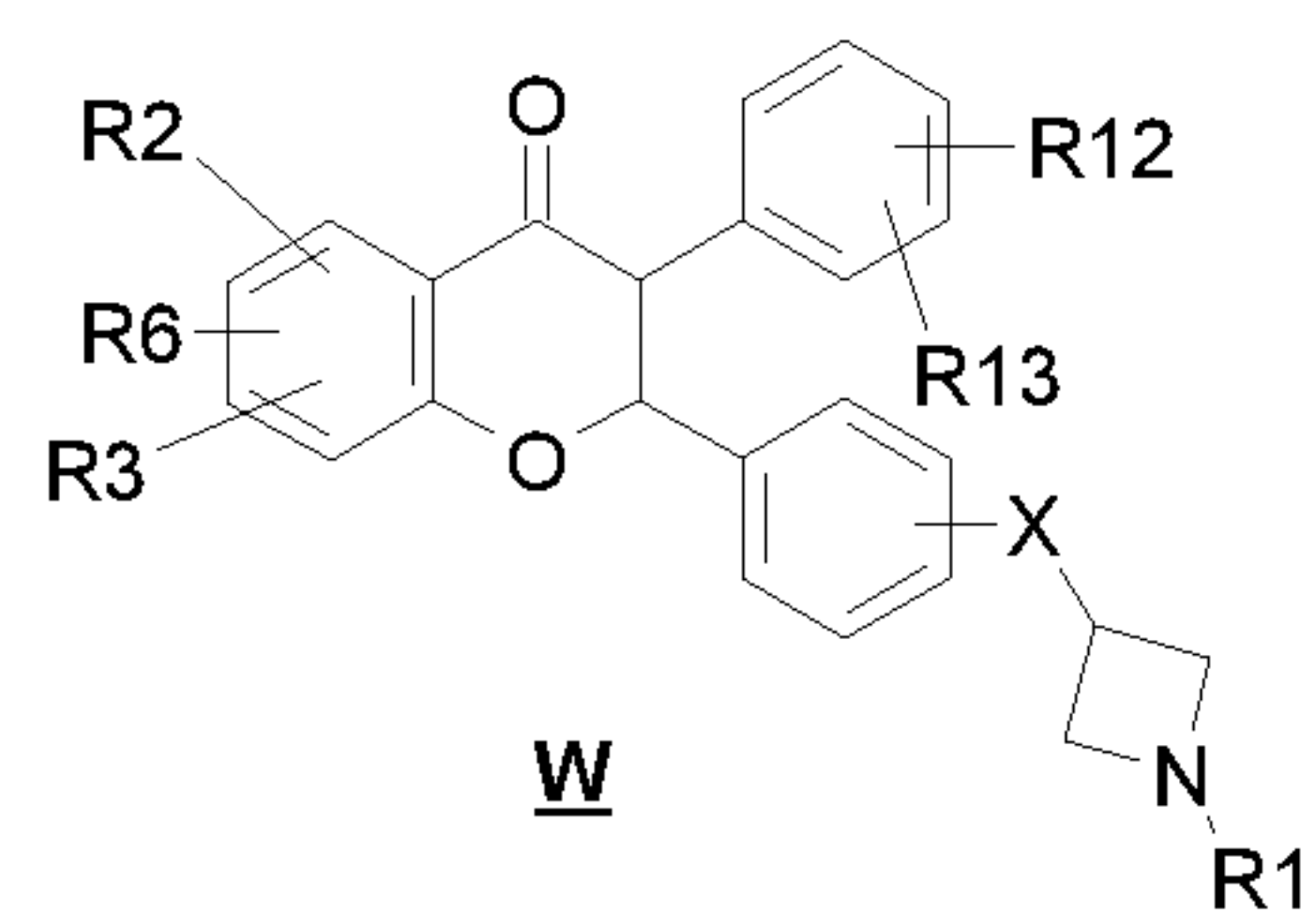
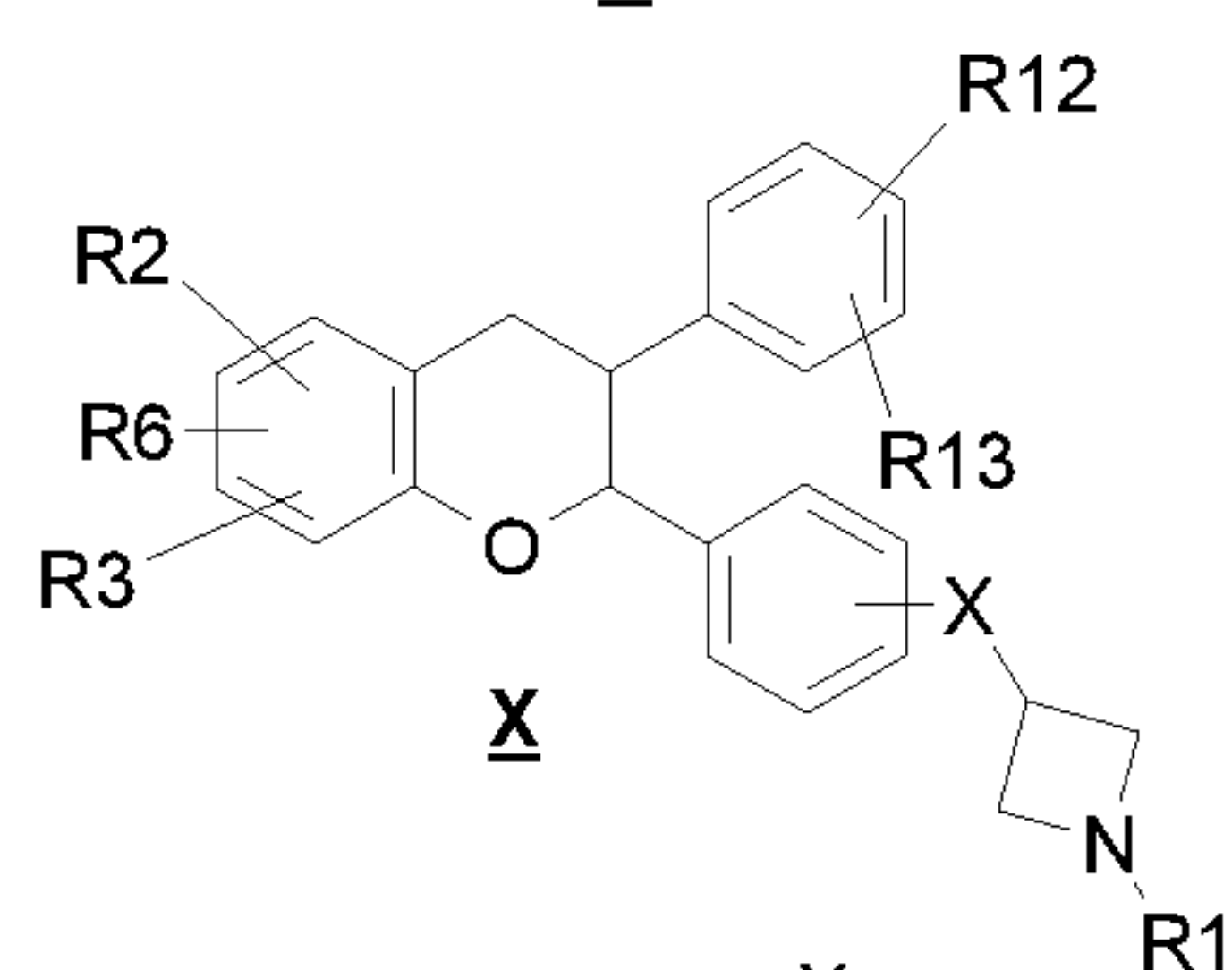
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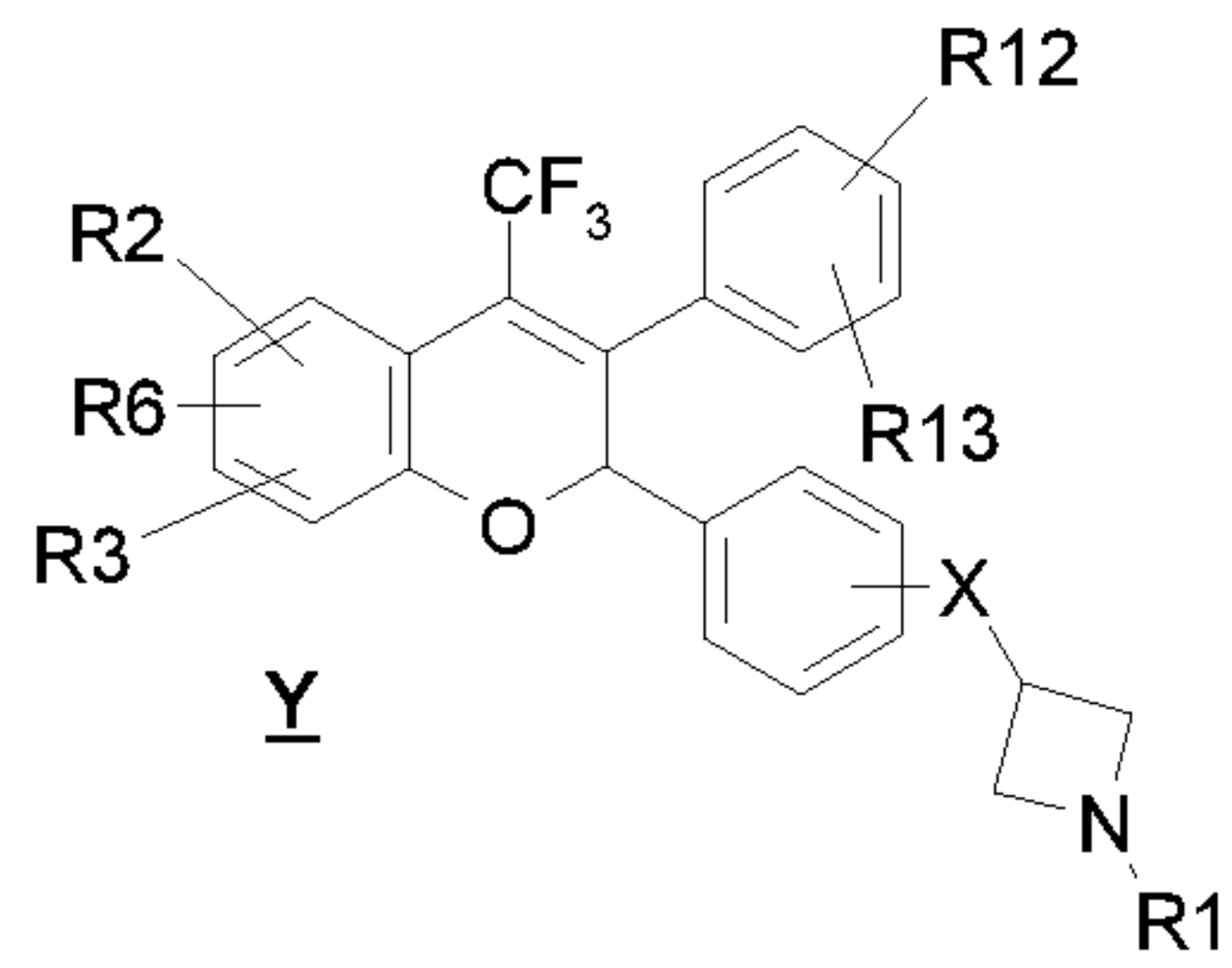
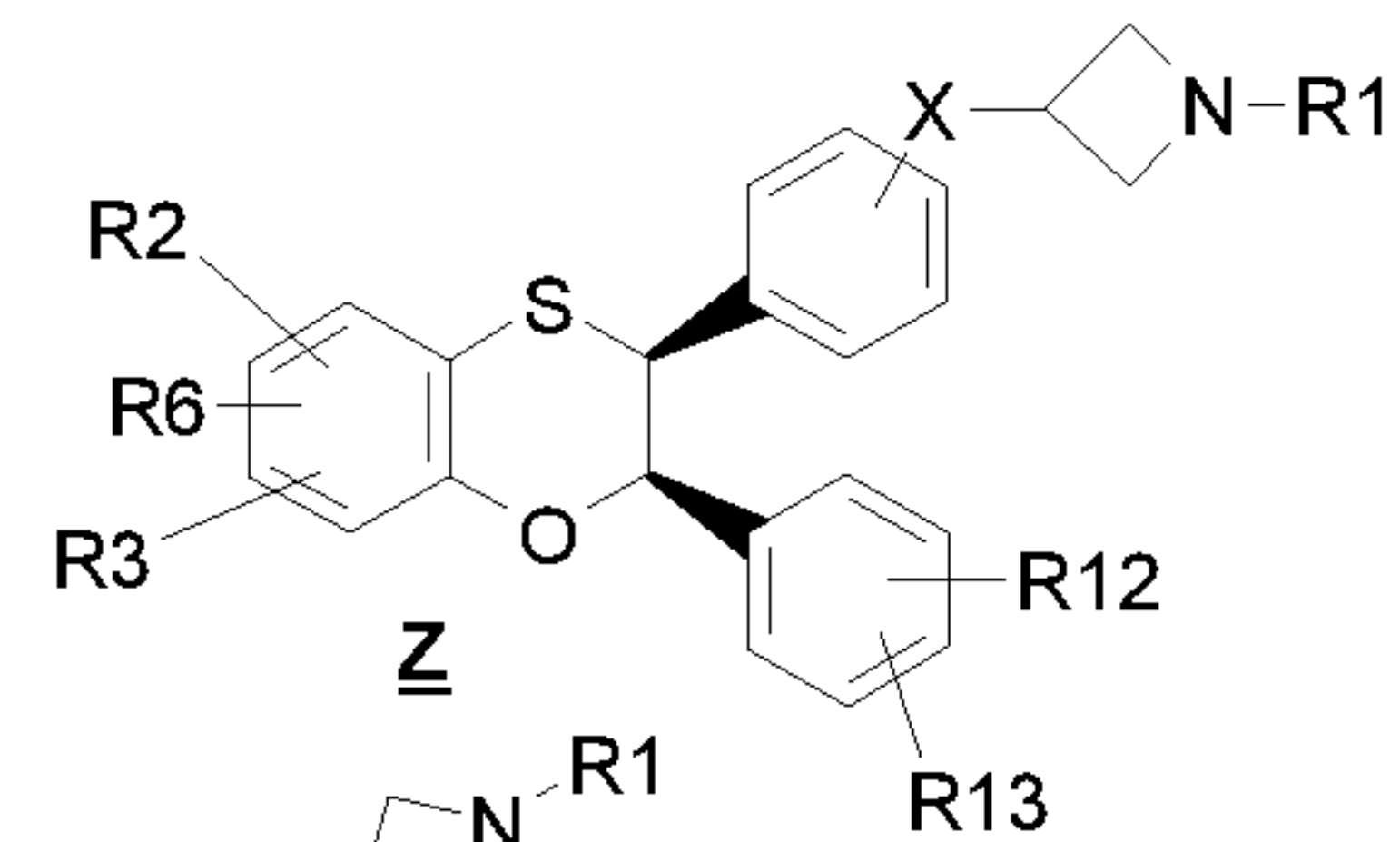
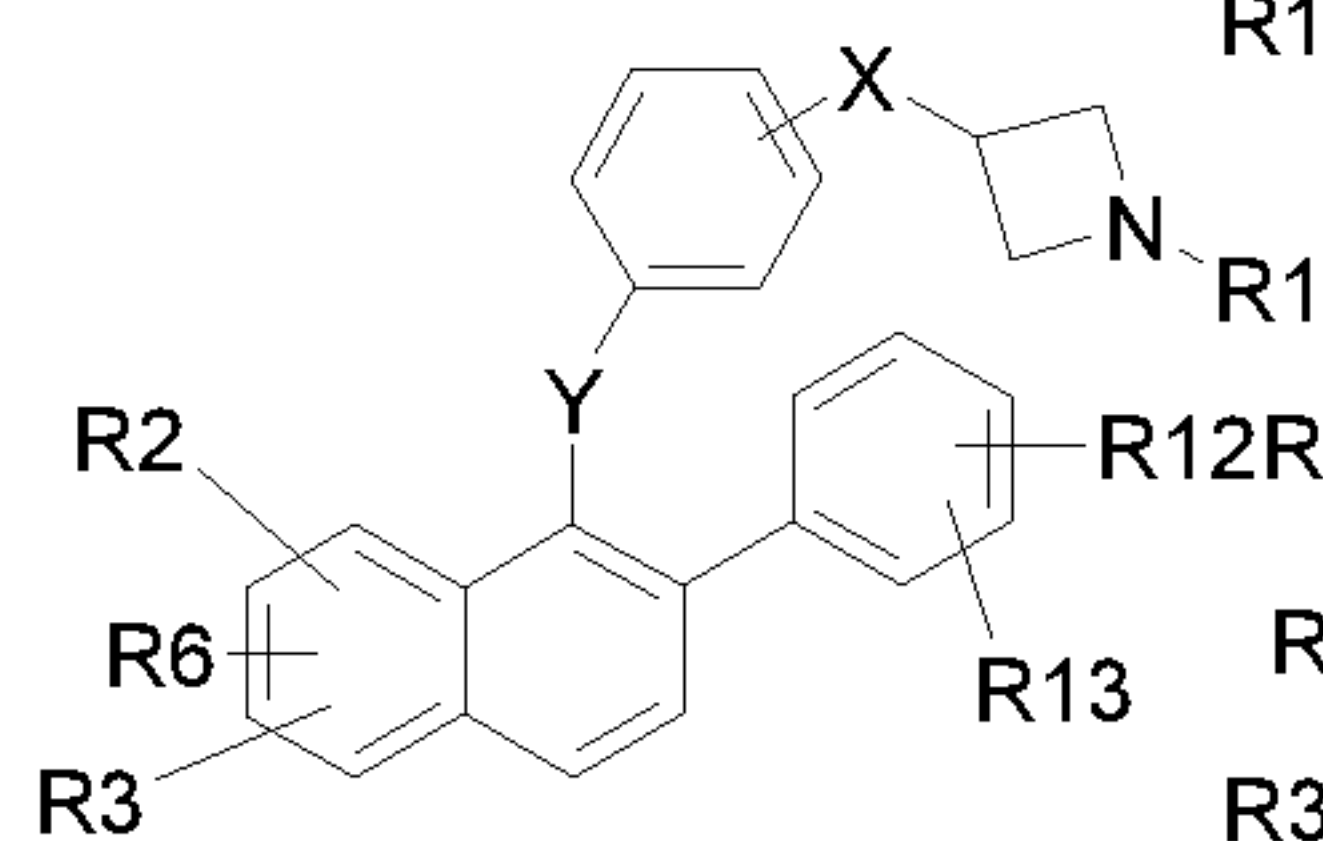
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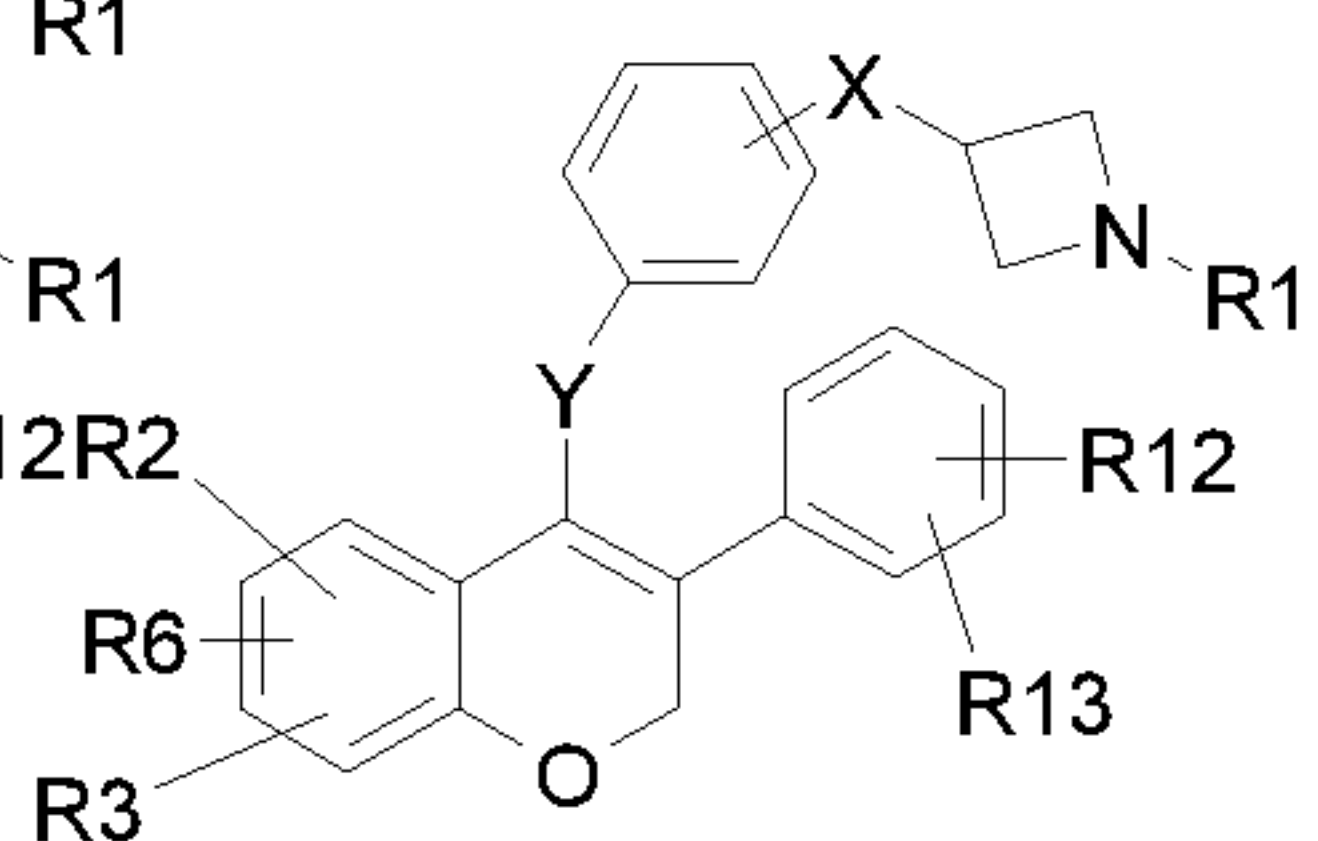
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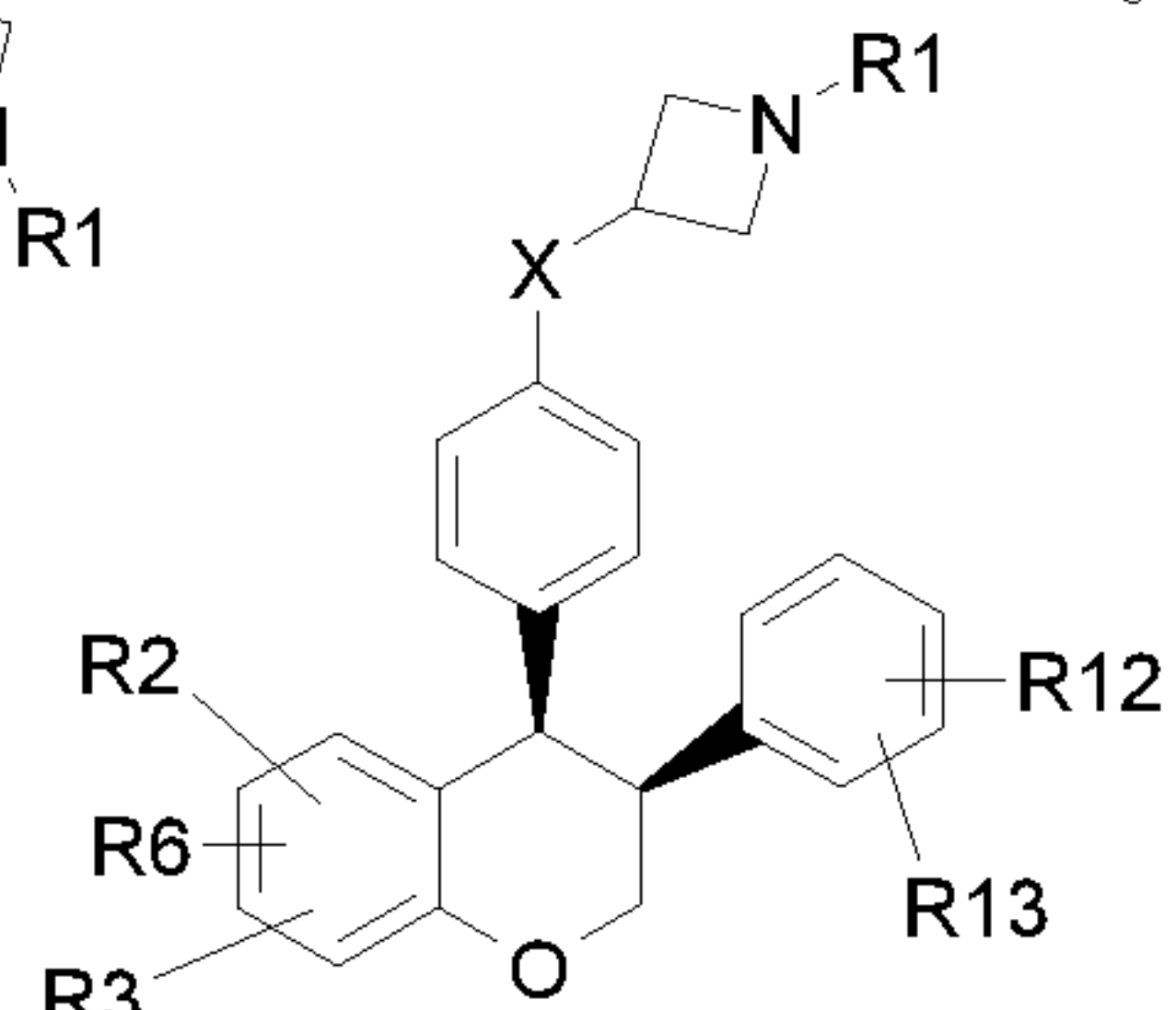
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YZ

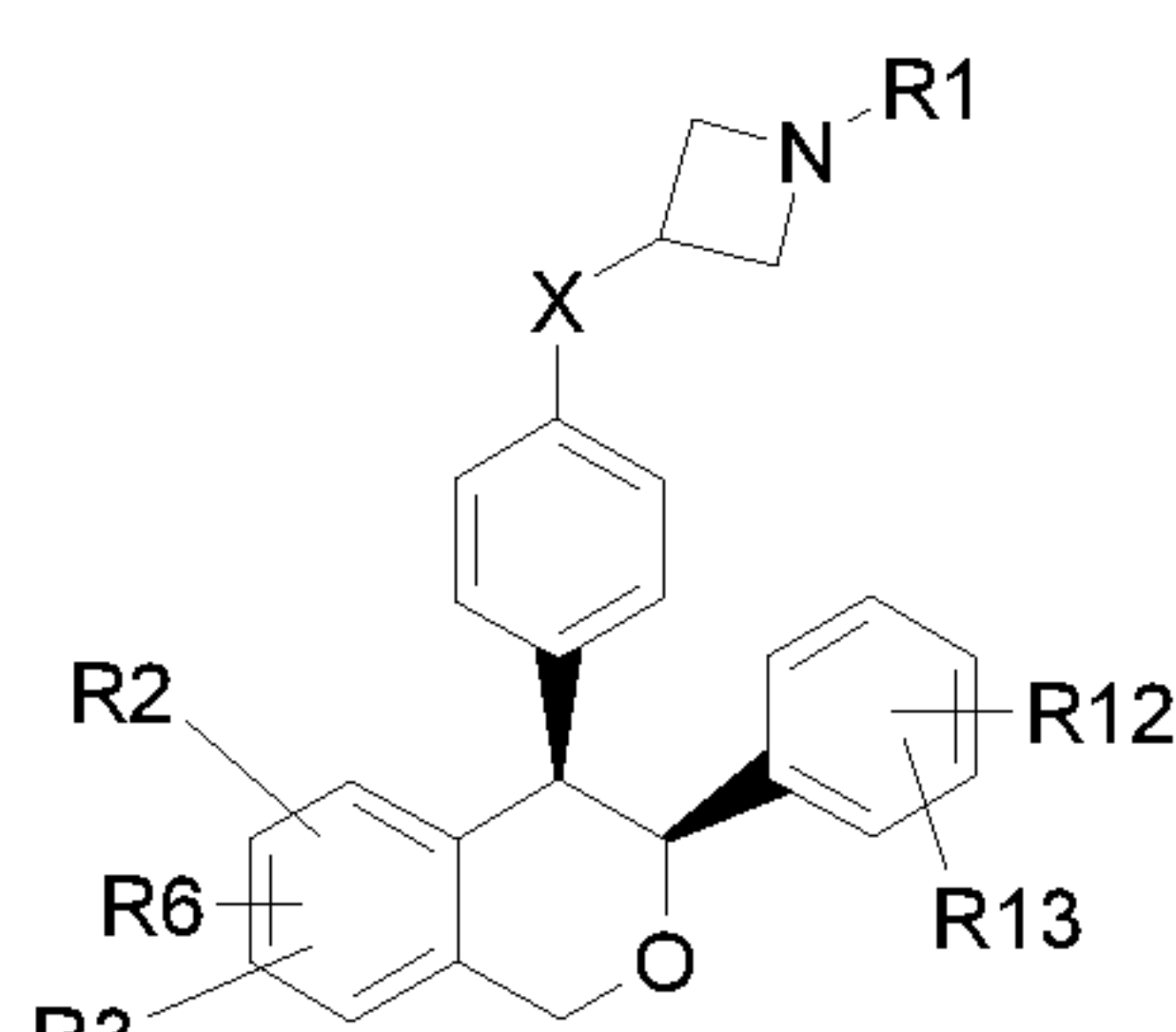
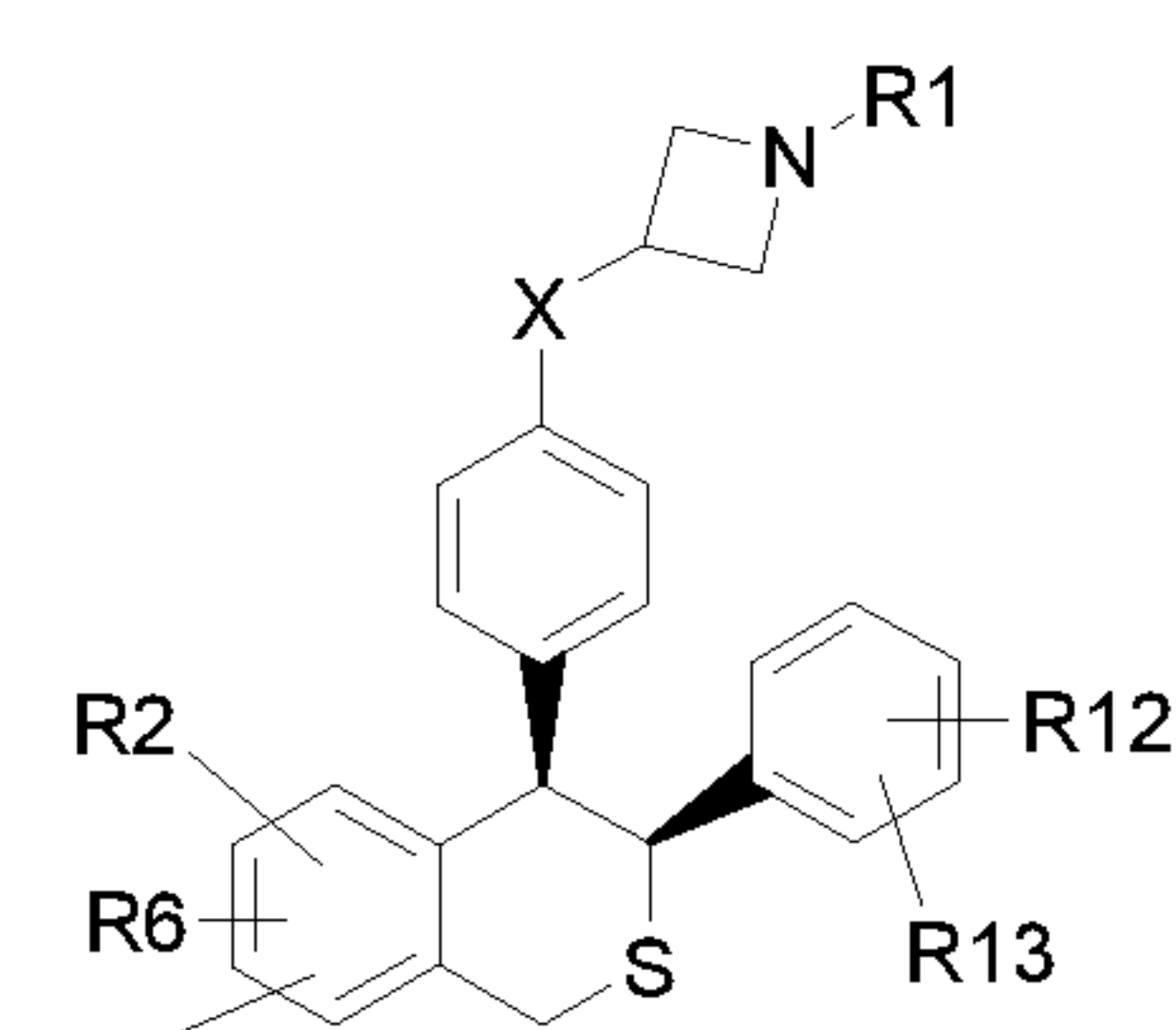
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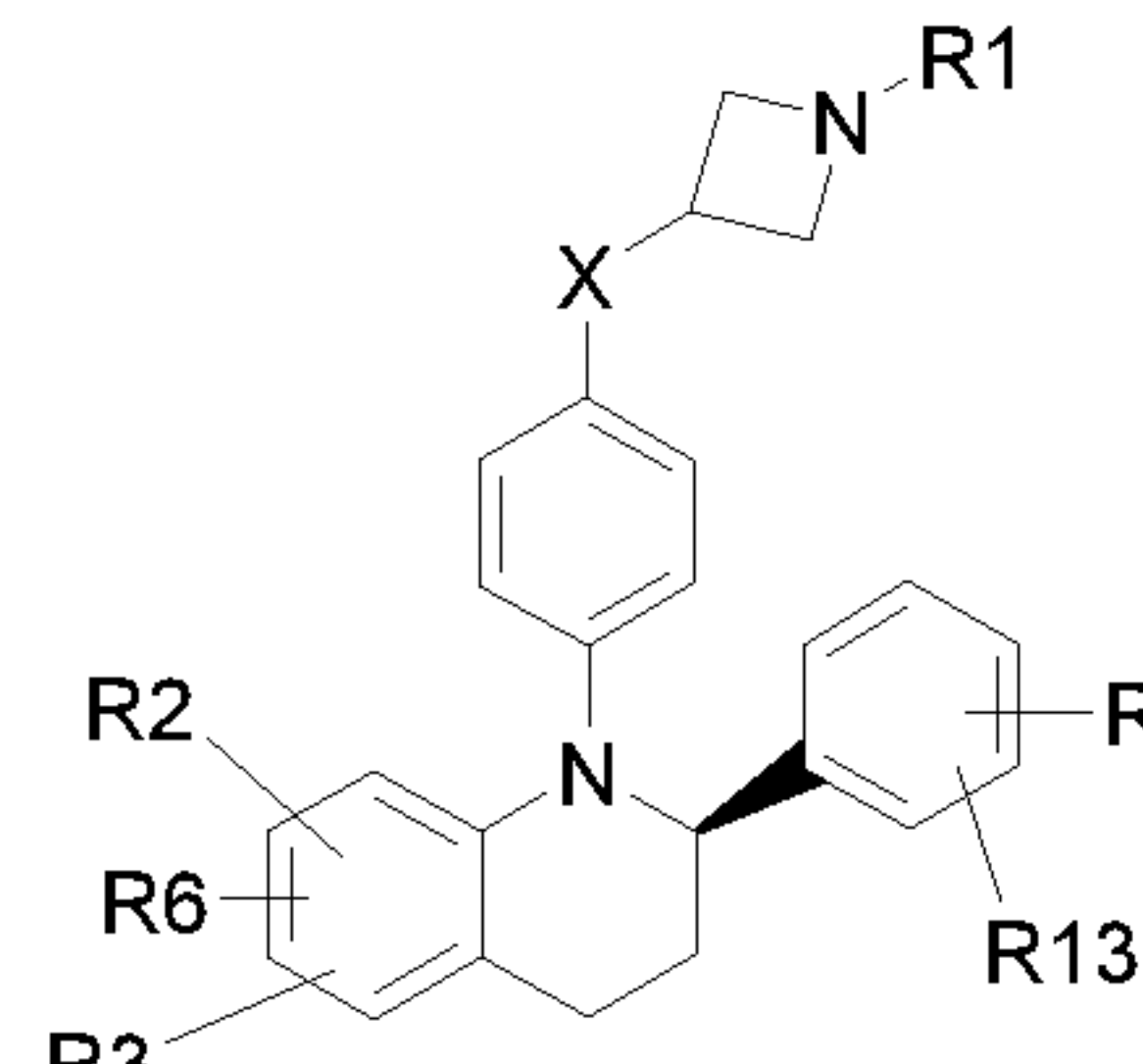
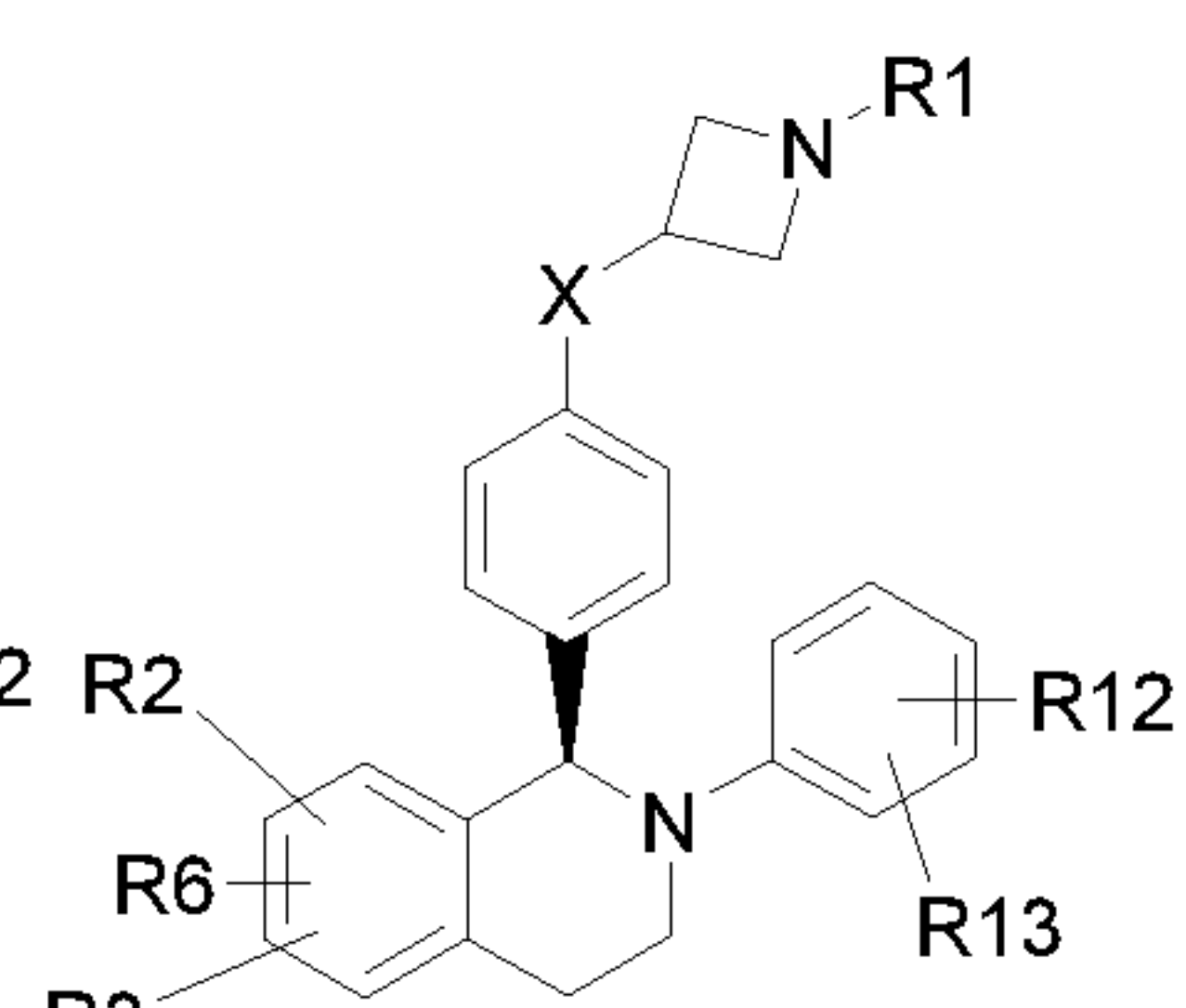
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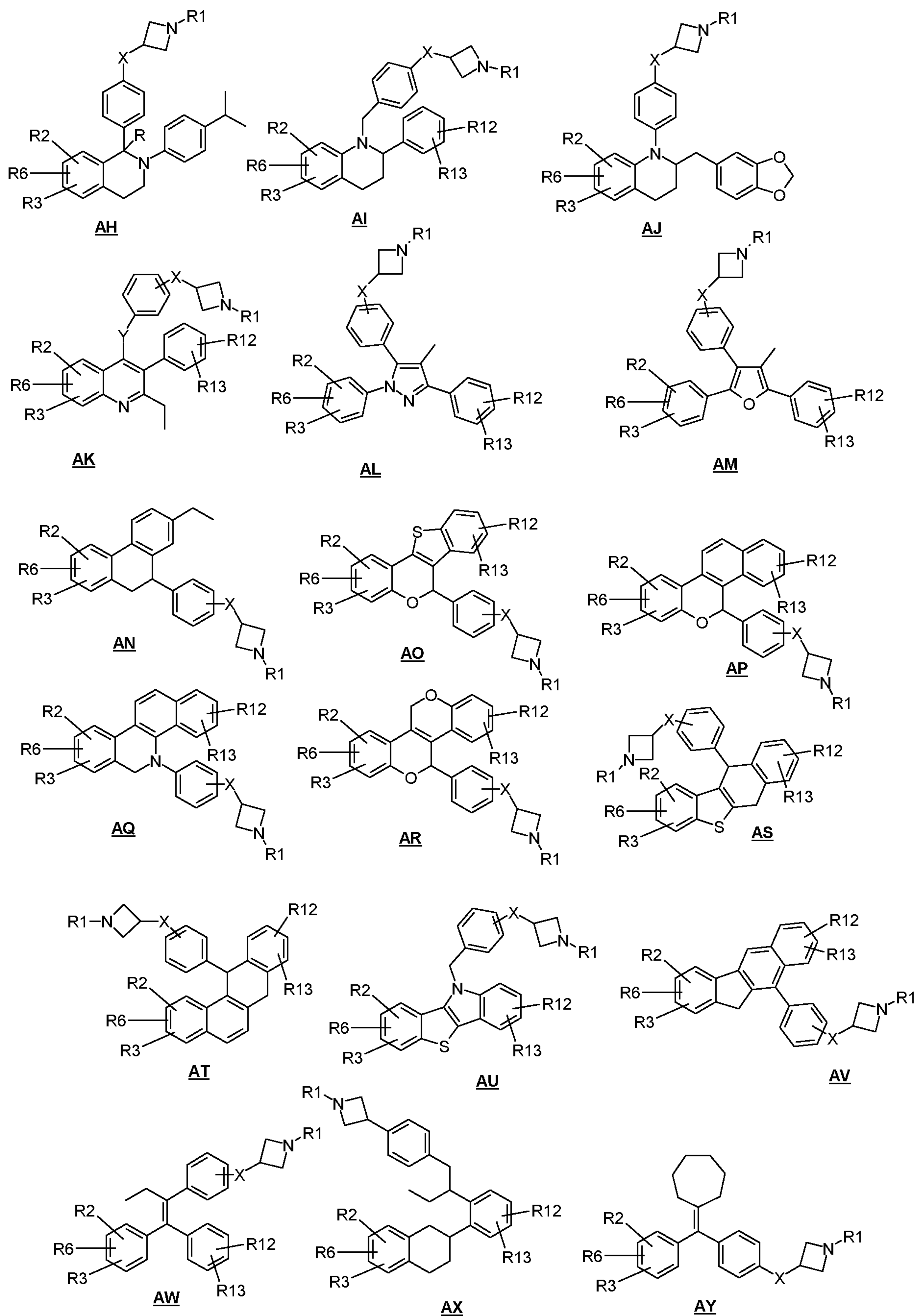
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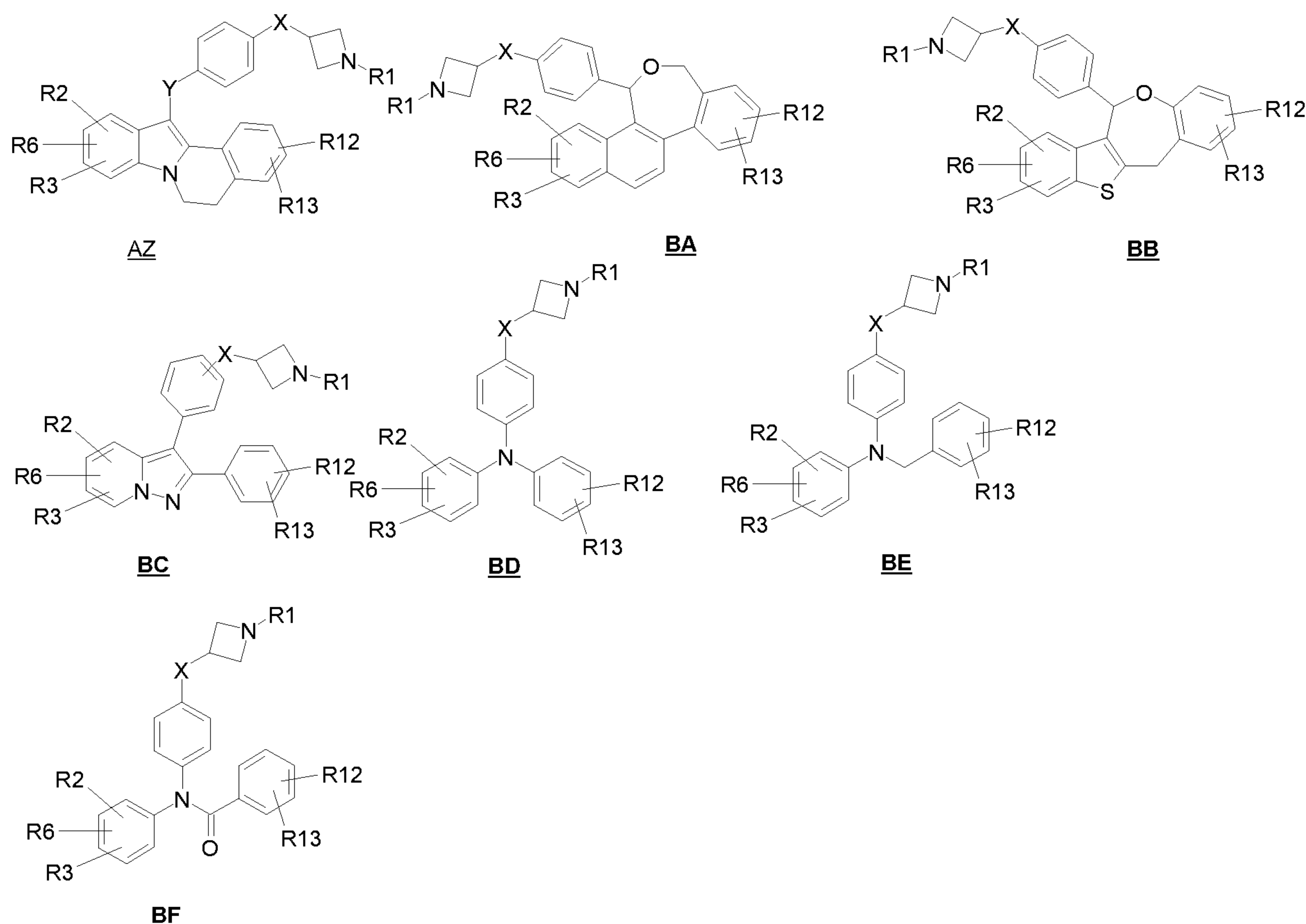
AD

AE

AF

AG





Formulae 3

wherein

- 5 R1 is (C1-8)alkyl, (C3-8)cycloalkyl, (C3-6)heterocycloalkyl, (C2-6)alkenyl, (C2-6)alkynyl, (C1-4)alkylcarbonyl, (C1-4)alkoxy(C2-4)alkyl, (C3-6)cycloalkyl(C1-3)-alkyl, (C3-6)heterocycloalkyl(C1-3)alkyl, each independently optionally substituted with one or more halogen, nitrile, hydroxyl or (C1-2)alkyl;
- X is no atom, O, S, CH₂, carbonyl, N-R5;
- 10 (h)Ar is a (hetero)aromatic ring, optionally substituted with R12 and R13;
- R2 and R3 are independently of each other H, fluorine, chlorine, (C1-3)alkyl, (C1-3)alkoxy, (C1-3)alkylthio, CF₃ or nitrile;
- R4 and R7 are independently of each other H, fluorine, chlorine, (C1-2)alkyl, CF₃ or nitrile;
- 15 R12 is H, fluorine, chlorine, (C1-2)alkyl, (C1-2)alkoxy, nitrile or hydroxyl;
- R13 is H, fluorine, chlorine, (C1-3)alkyl, (C1-3)alkoxy, (C1-3)alkylthio, CF₃ or nitrile;
- R6 is H, hydroxyl, amine or (C1-6)alkoxy;

R6 and R2 may be linked to form a (hetero)aromatic ring which is optionally substituted with fluorine, chlorine or (C1-3)alkyl;

R5 is H, (C1-3)alkyl, optionally substituted with one or more fluorine;

V is O, S, CH₂, CHOH, CH(C1-3)alkoxy, C=CH₂, carbonyl, N-R16;

5 R15 is H, halogen, nitro, nitrile or (C1-6)alkyl, optionally substituted with one or more halogen;

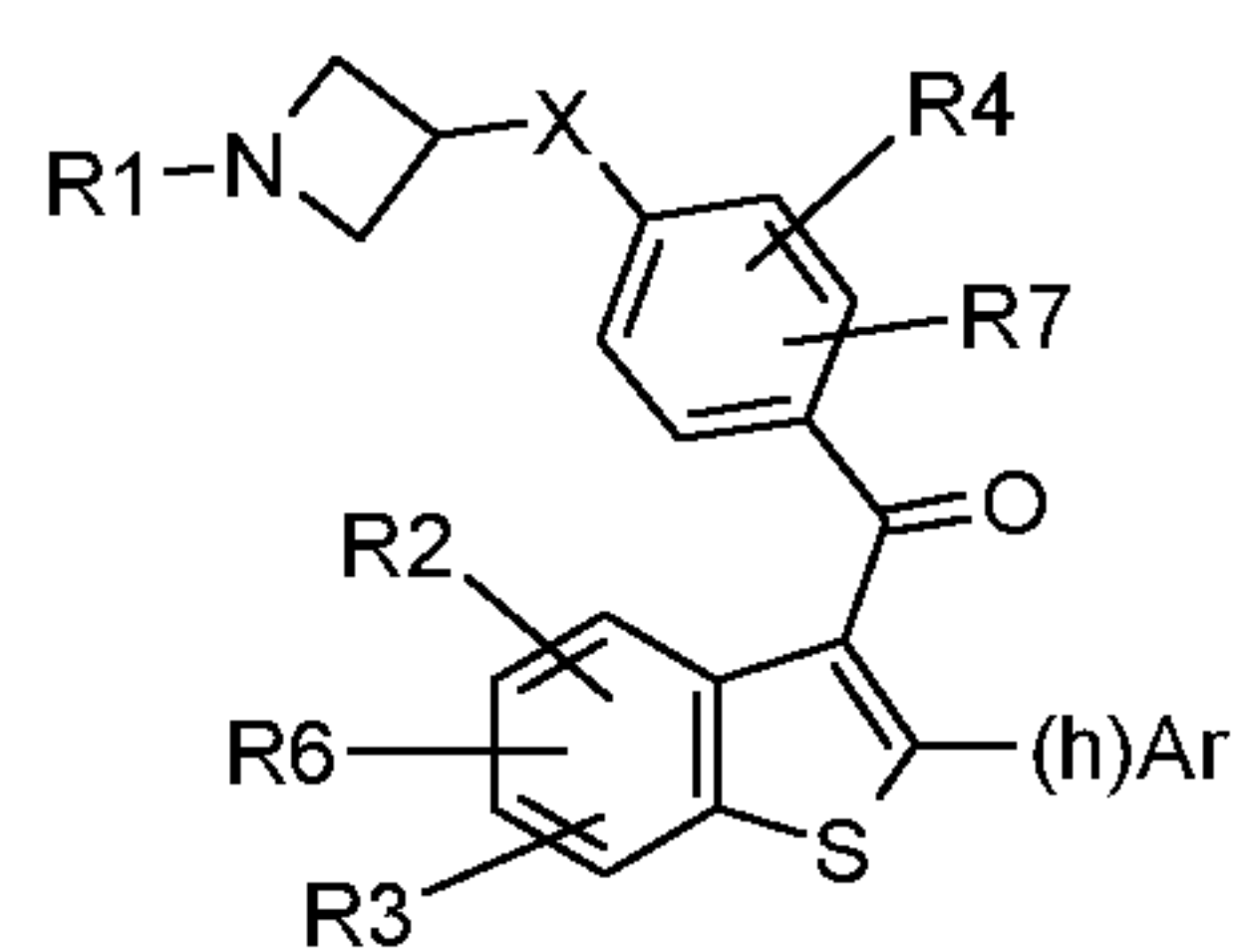
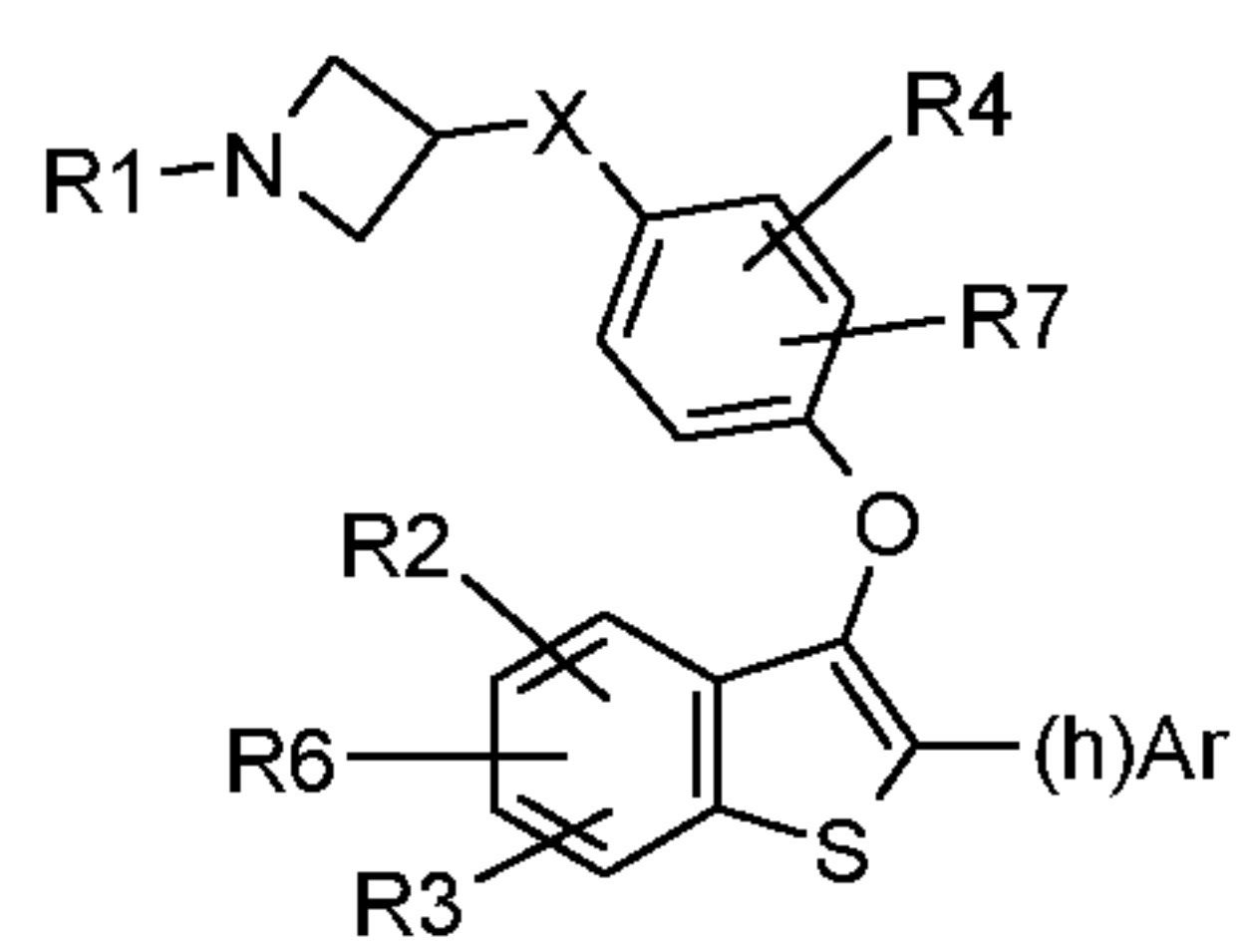
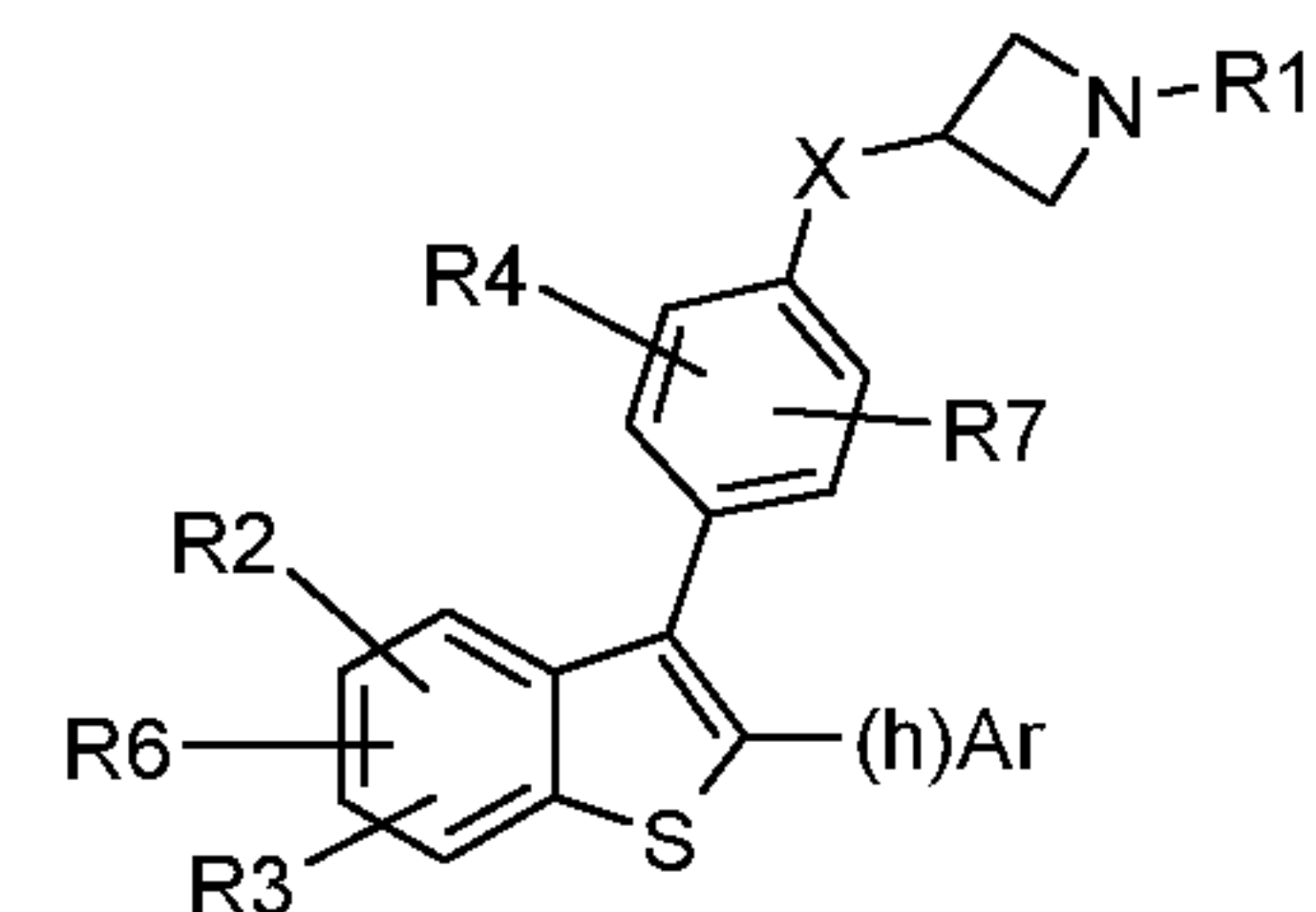
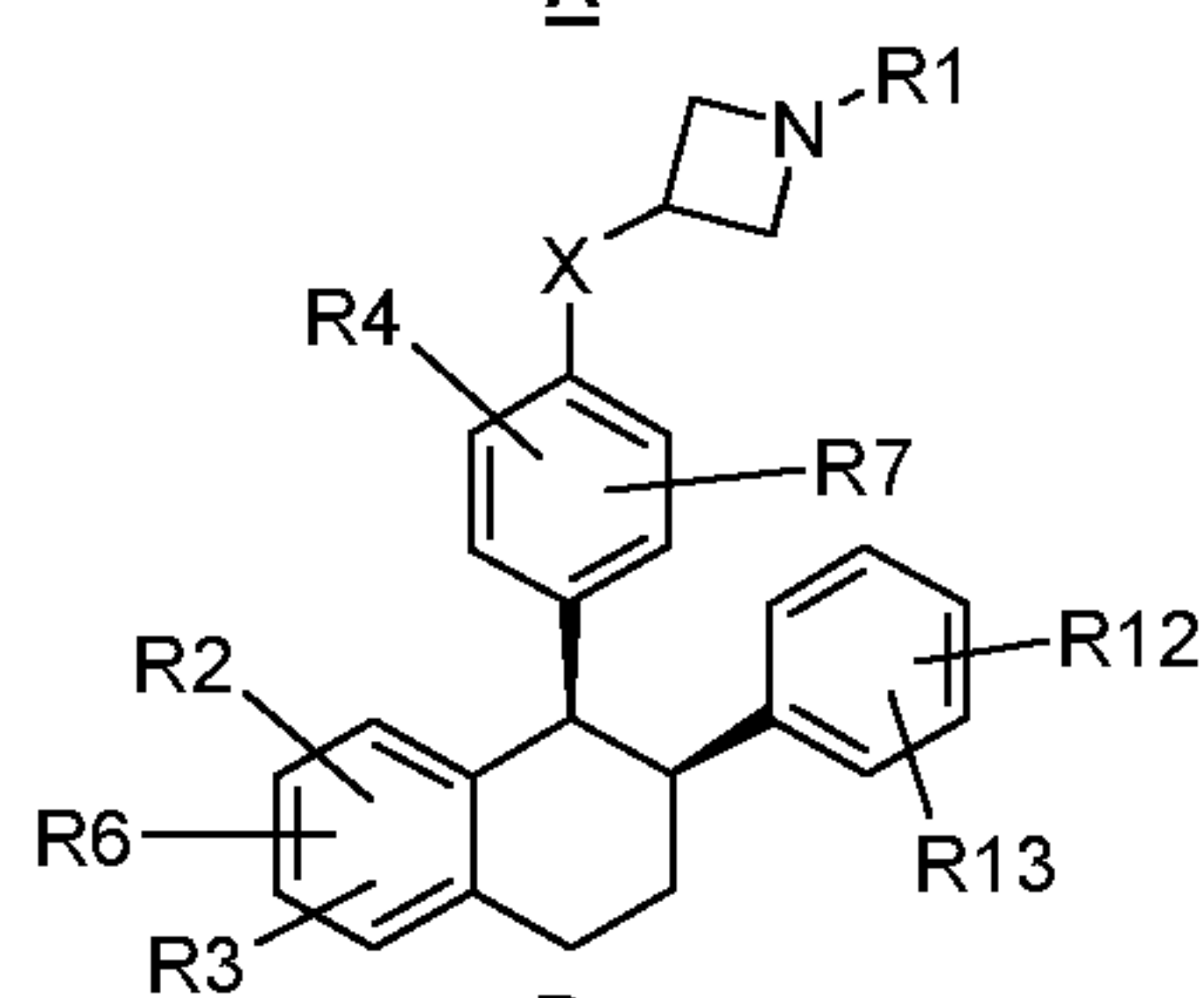
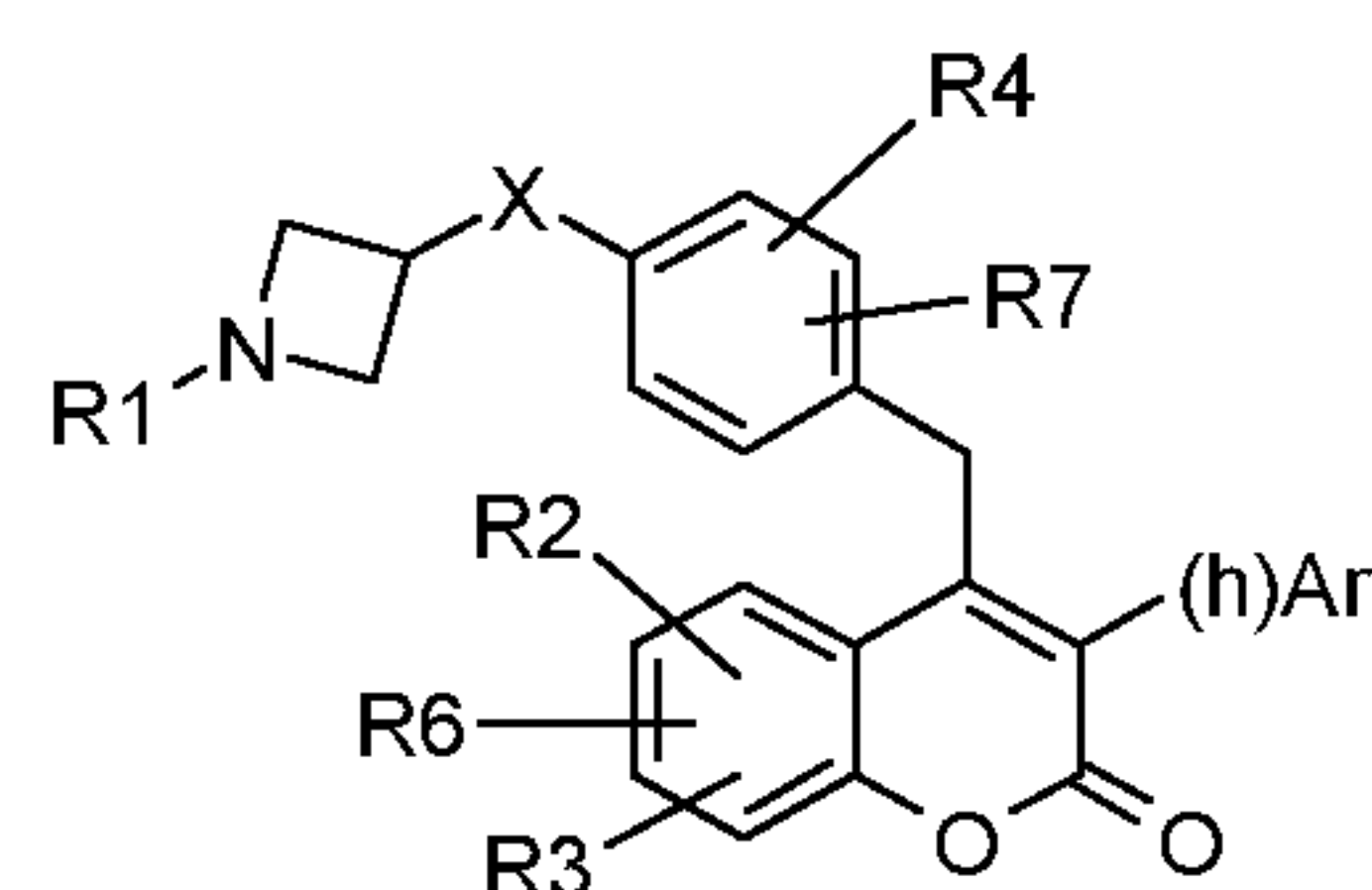
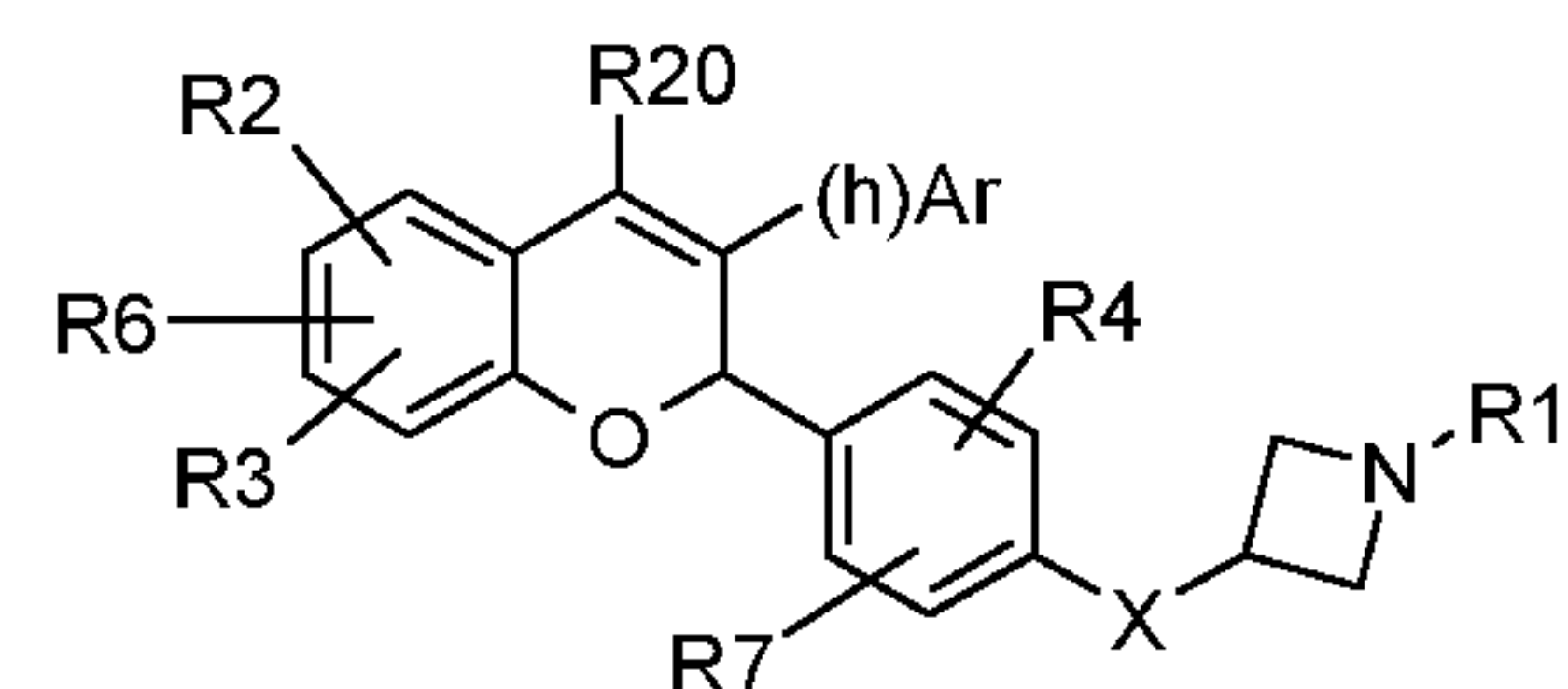
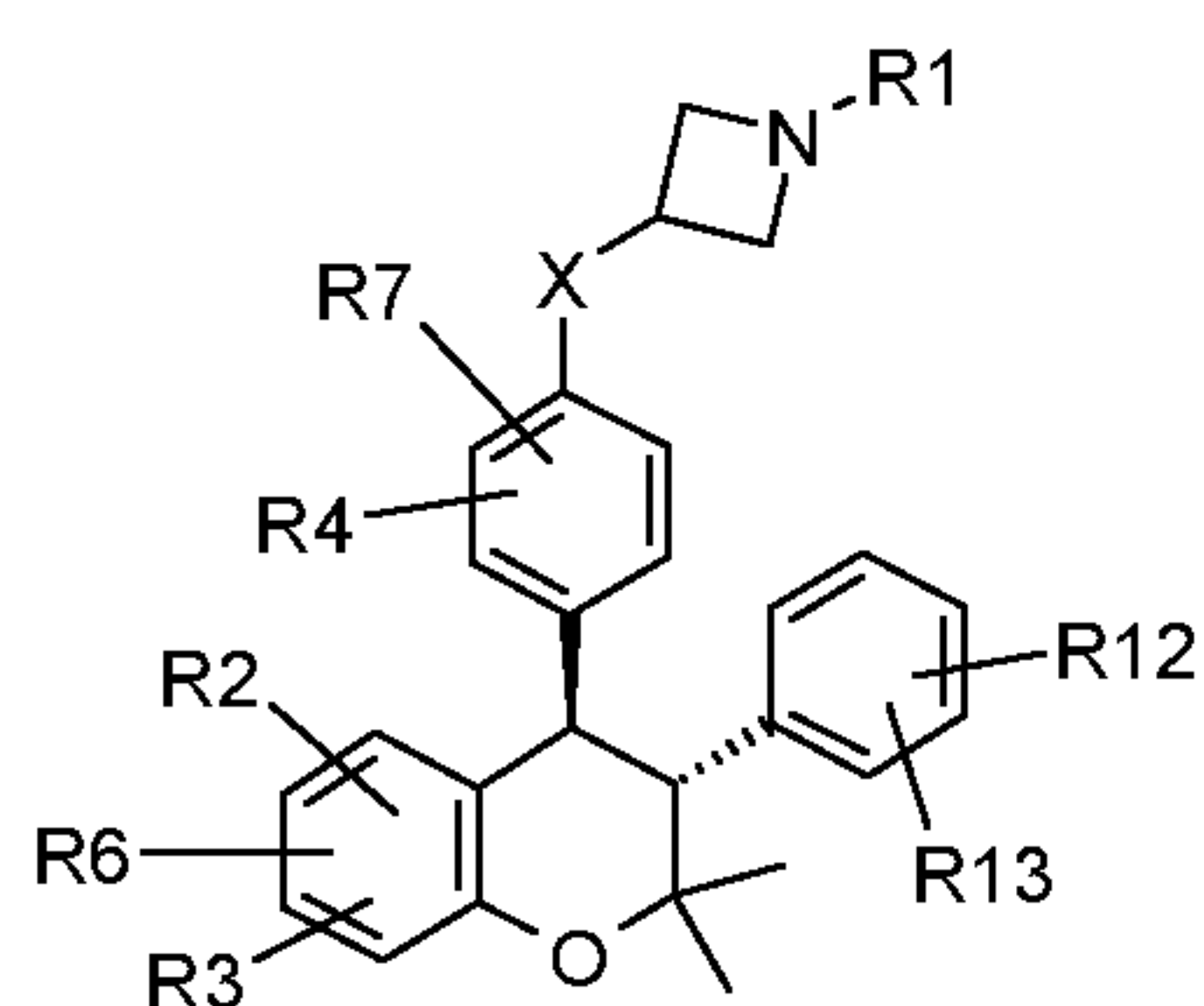
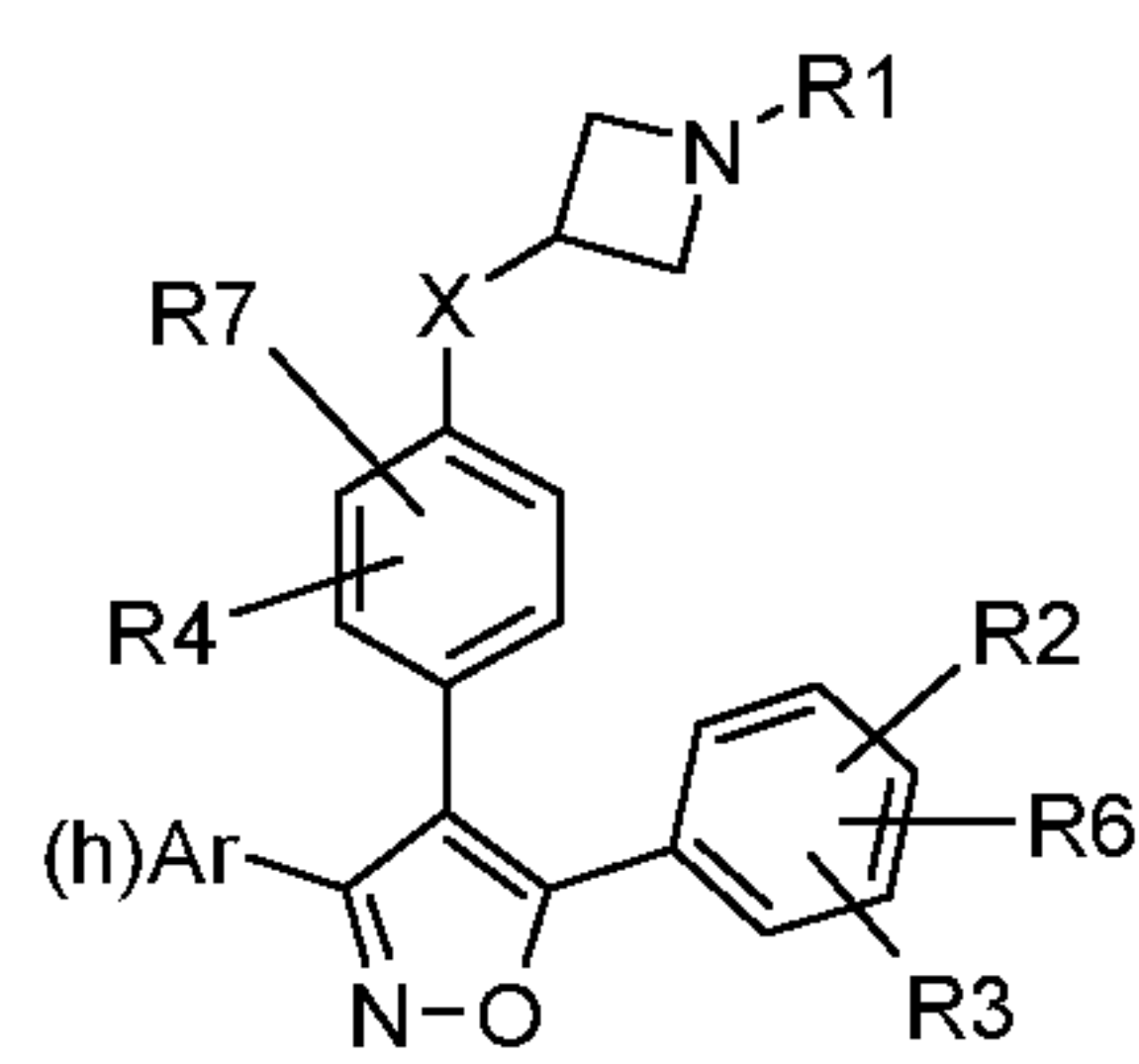
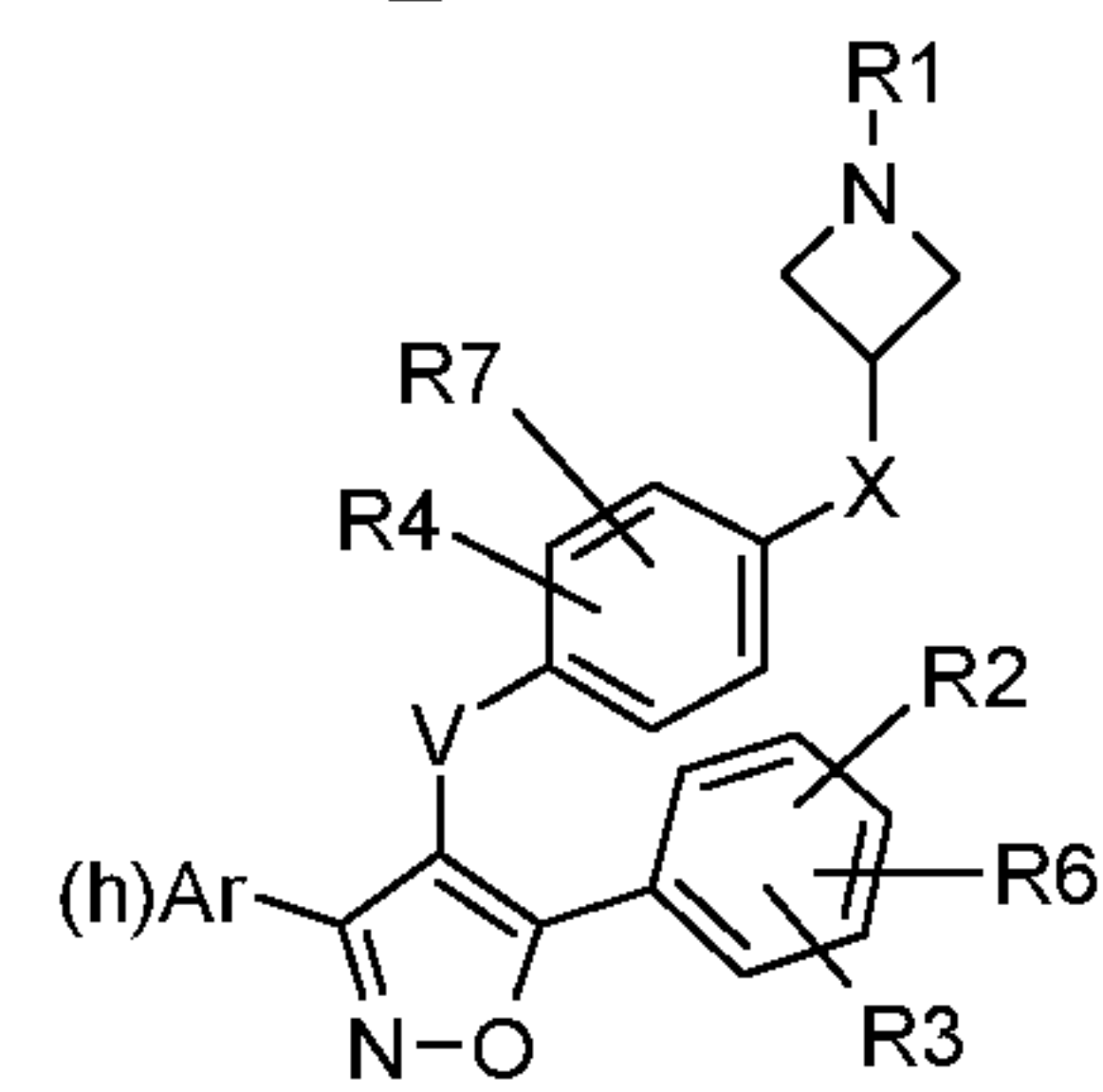
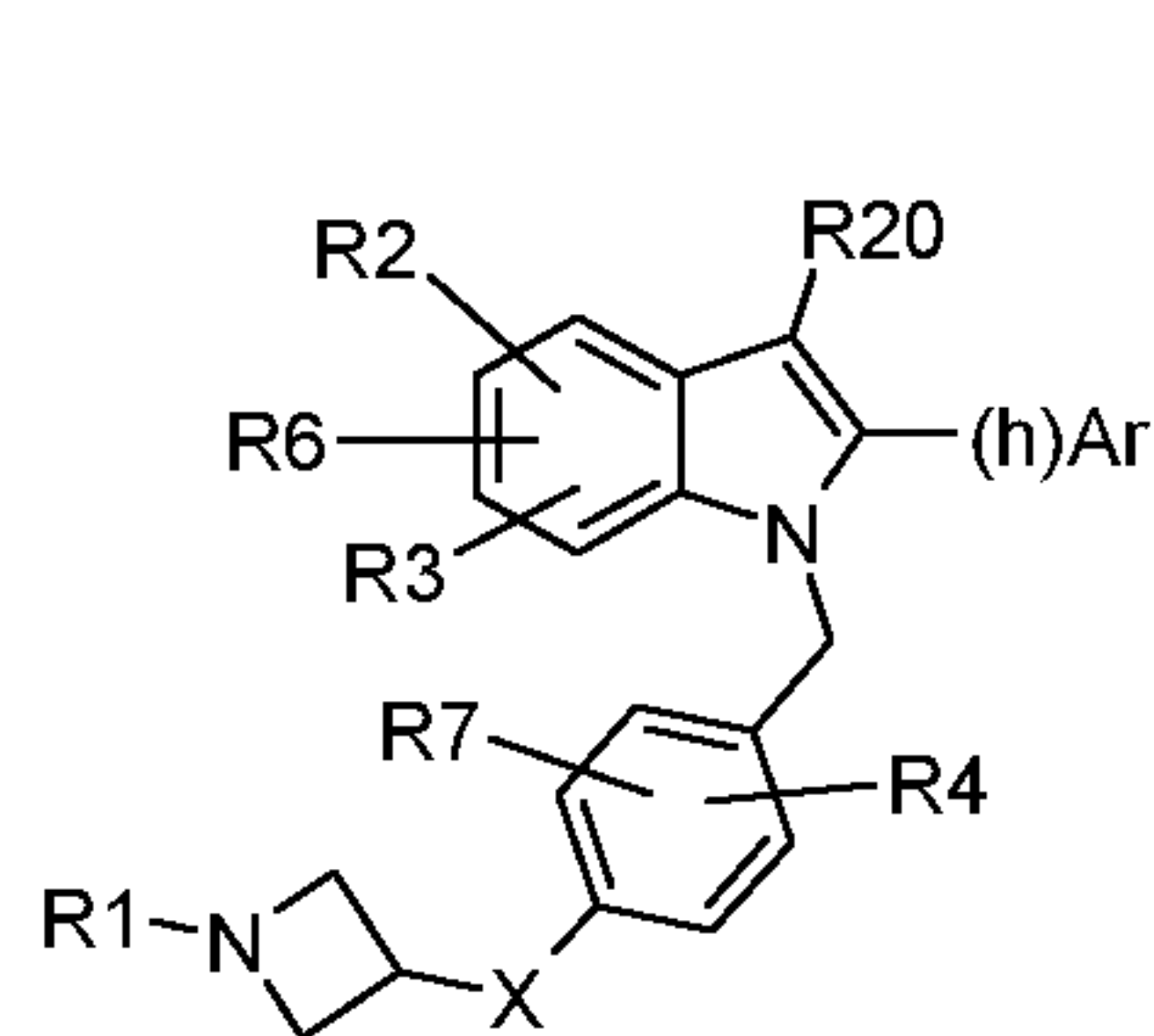
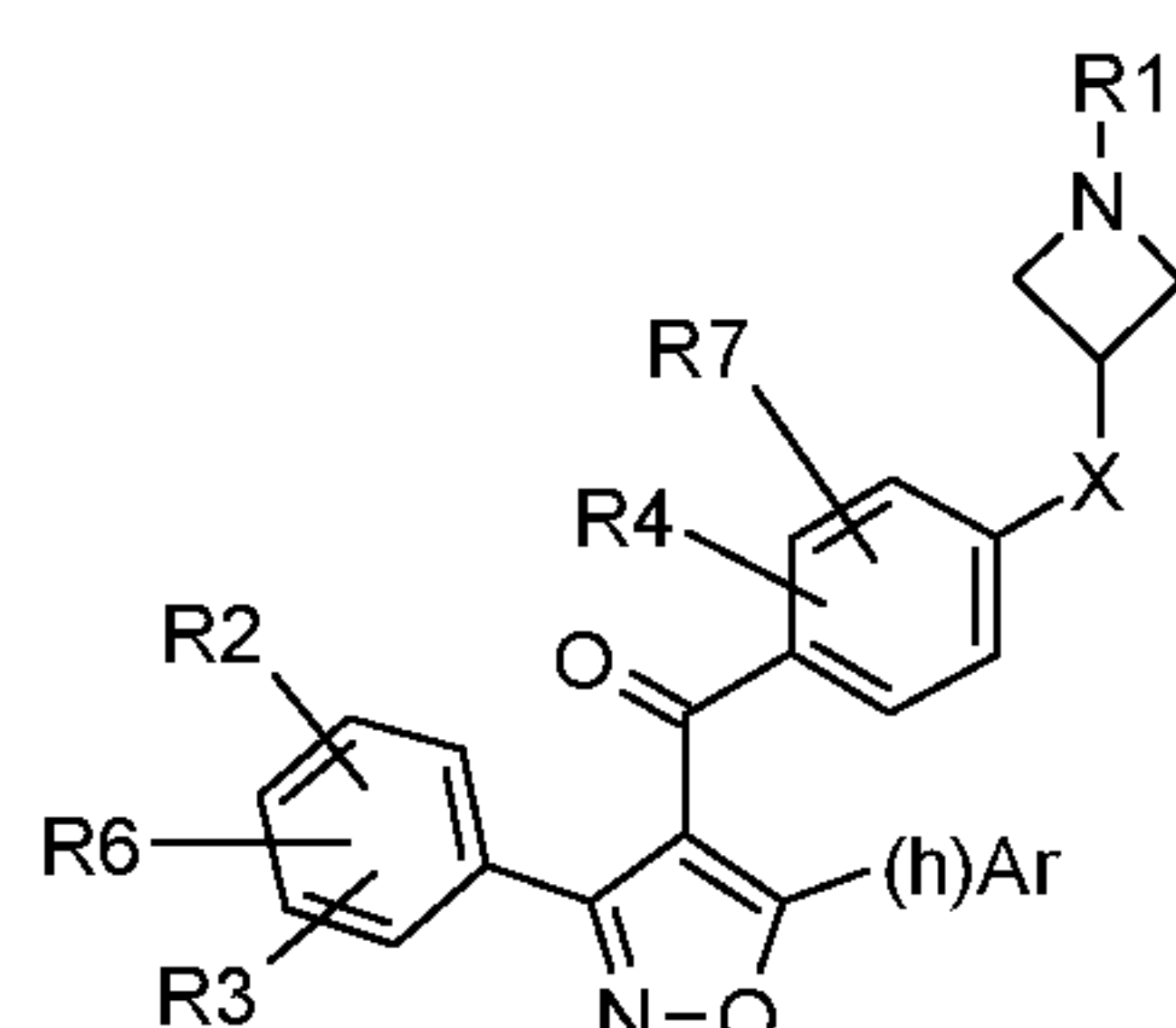
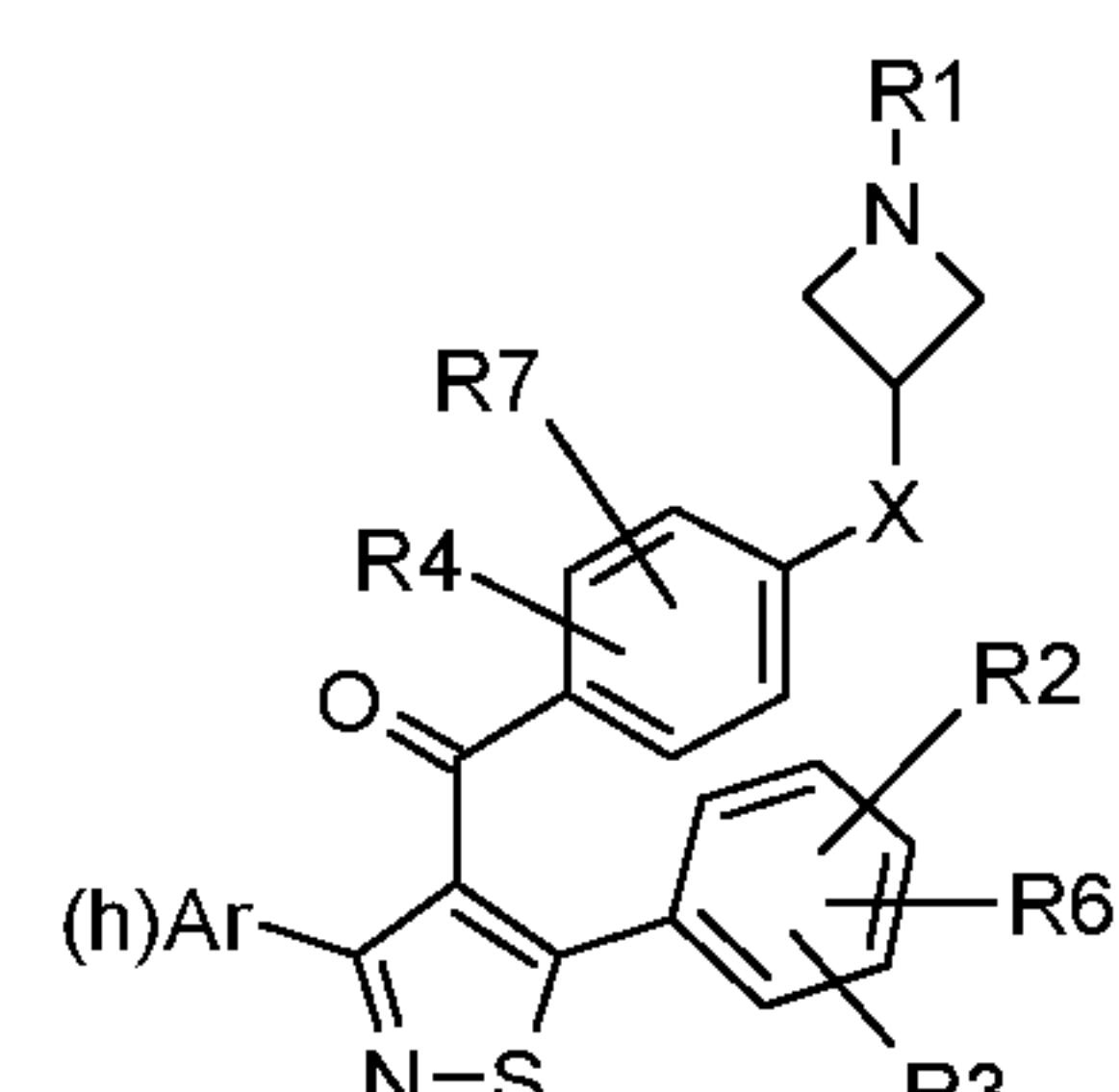
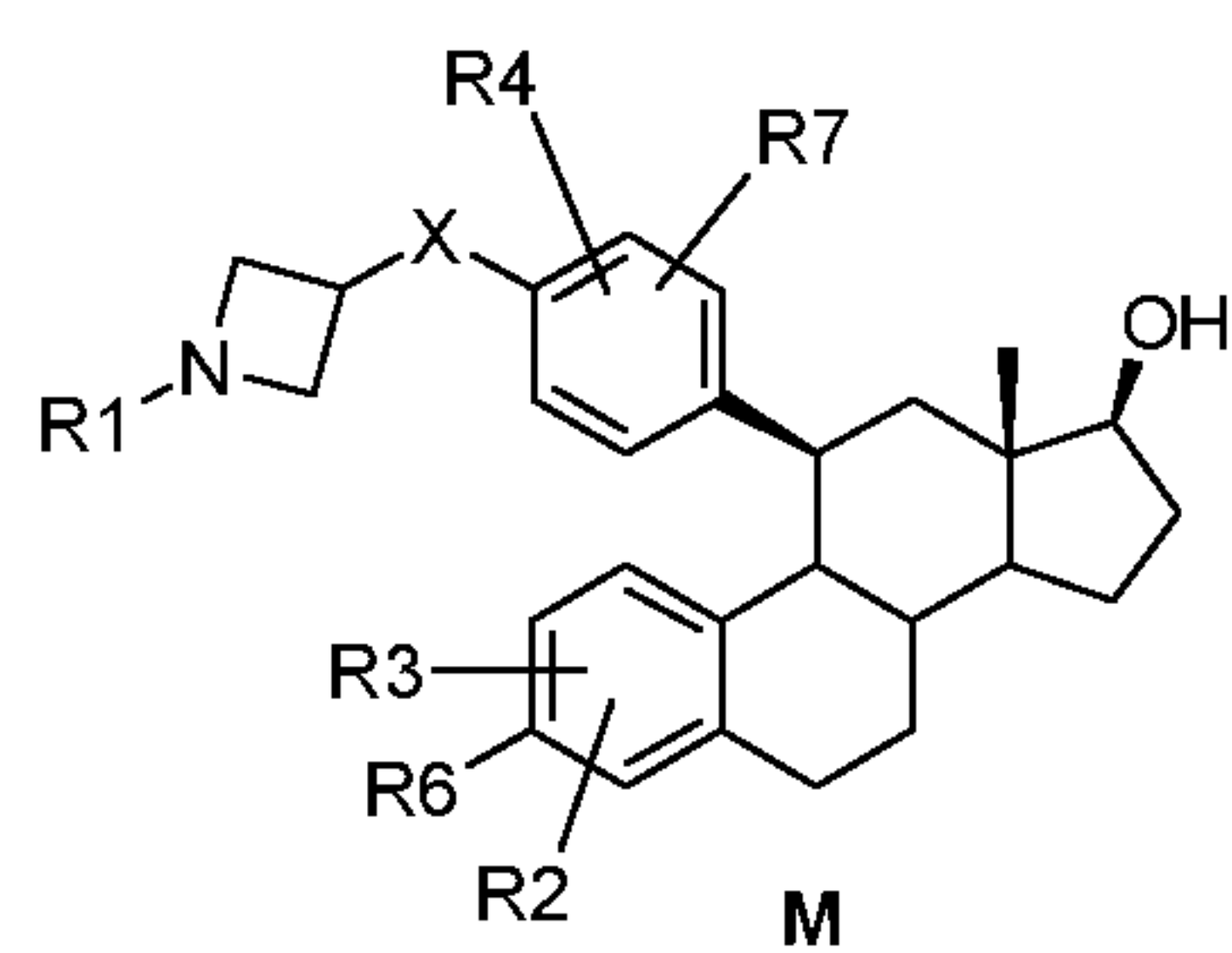
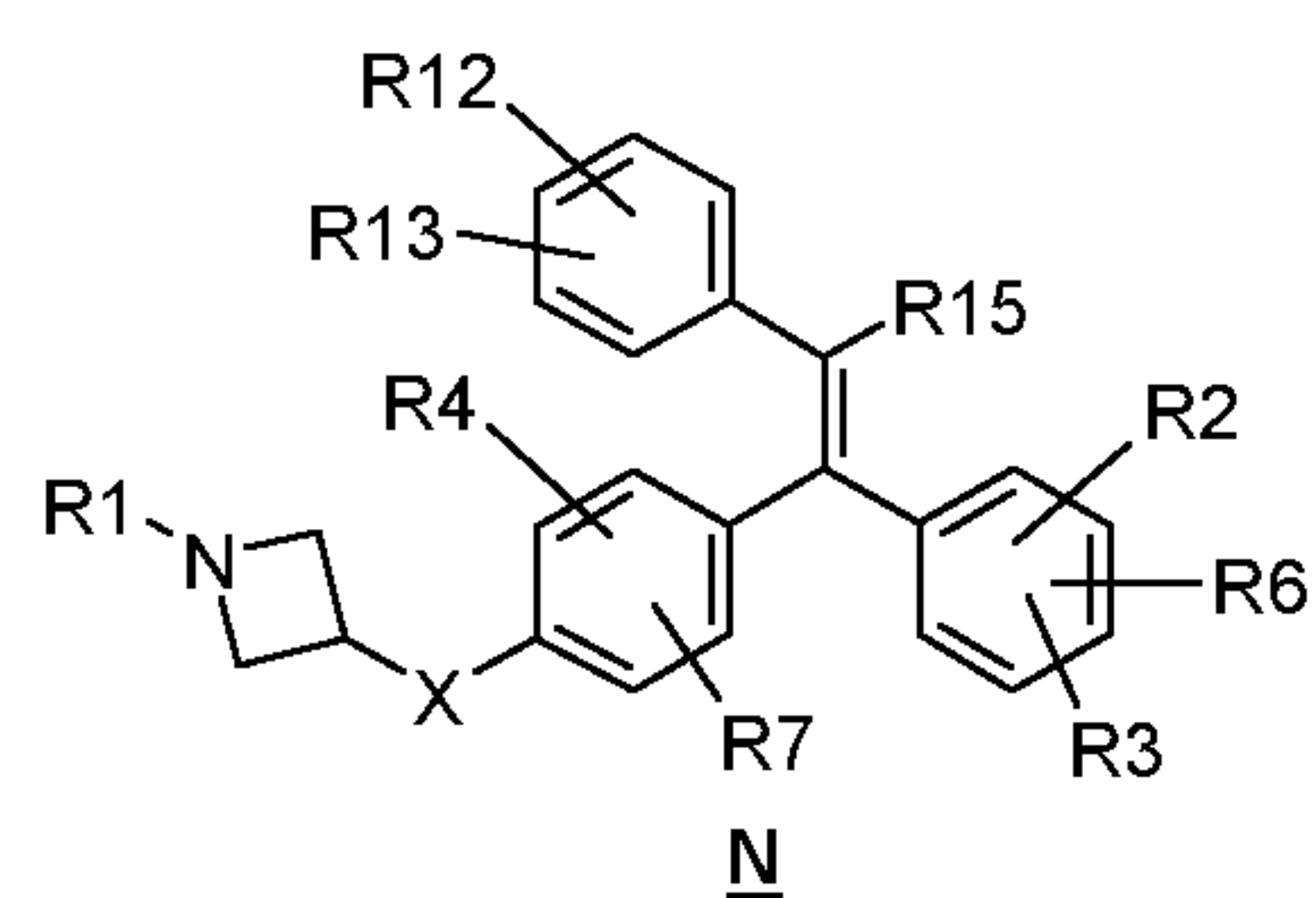
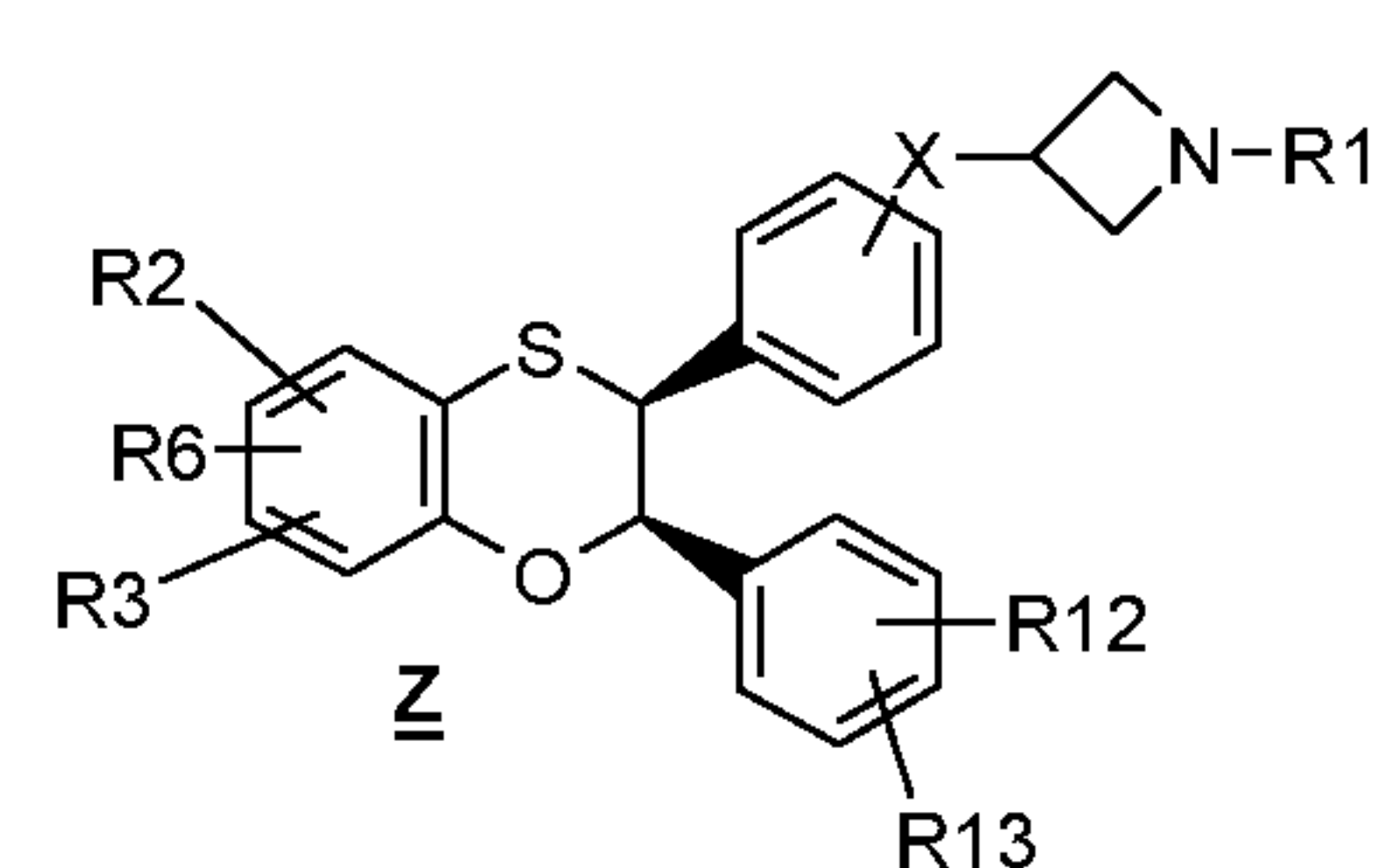
R16 is H, (C1-4)alkyl, (C1-4)alkenyl, optionally substituted with one or more halogen;

R20 is (C1-3)alkyl, optionally substituted with one or more fluorine.

10

3. An N-substituted azetidine derivative according to claim 1 selected from the group consisting of compounds according to any one of Formulae 4

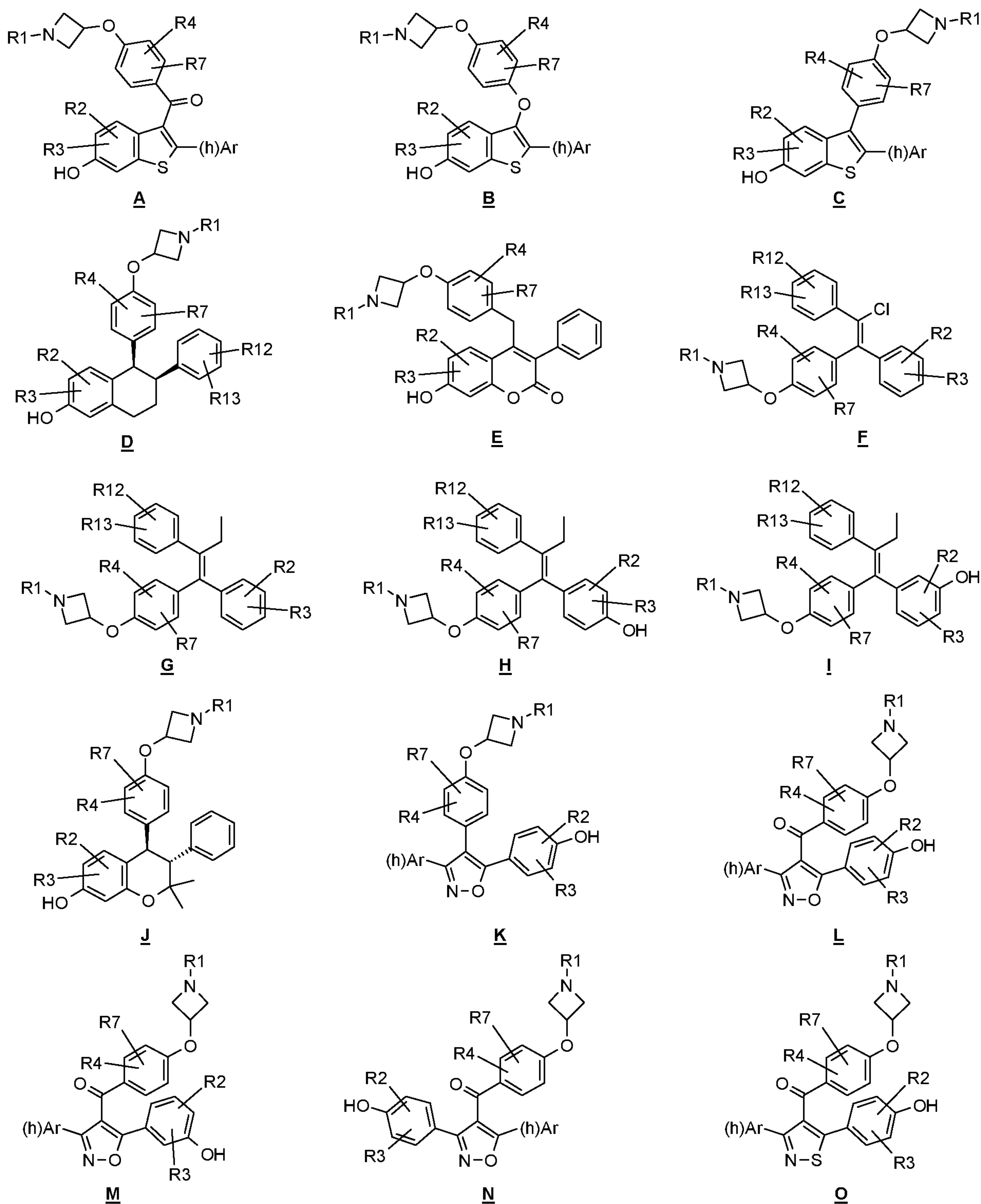
85

ABCDEFGHIJKLMNZ

Formulae 4

5 wherein

- R1 is (C1-8)alkyl, (C3-8)cycloalkyl, (C3-6)heterocycloalkyl, (C2-6)alkenyl, (C2-6)alkynyl, (C1-4)alkylcarbonyl, (C1-4)alkoxy(C2-4)alkyl, (C3-6)cycloalkyl(C1-3)-alkyl, (C3-6)heterocycloalkyl(C1-3)alkyl, each independently optionally substituted with one or more halogen, nitrile, hydroxyl or (C1-2)alkyl;
- 5 X is no atom, O, S, CH₂, carbonyl, N-R5;
- (h)Ar is a (hetero)aromatic ring, optionally substituted with R12 and R13;
- R2 and R3 are independently of each other H, fluorine, chlorine, (C1-3)alkyl, (C1-3)alkoxy, (C1-3)alkylthio, CF₃ or nitrile;
- R4 and R7 are independently of each other H, fluorine, chlorine, (C1-2)alkyl,
- 10 CF₃ or nitrile;
- R12 is H, fluorine, chlorine, (C1-2)alkyl, (C1-2)alkoxy, nitrile or hydroxyl;
- R13 is H, fluorine, chlorine, (C1-3)alkyl, (C1-3)alkoxy, (C1-3)alkylthio, CF₃ or nitrile;
- R6 is H, hydroxyl, amine or (C1-6)alkoxy;
- 15 R6 and R2 may be linked to form a (hetero)aromatic ring which is optionally substituted with fluorine, chlorine or (C1-3)alkyl;
- R5 is H, (C1-3)alkyl, optionally substituted with one or more fluorine;
- V is O, S, CH₂, CHOH, CH(C1-3)alkoxy, C=CH₂, carbonyl, N-R16;
- R15 is H, halogen, nitro, nitrile or (C1-6)alkyl, optionally substituted with one or
- 20 more halogen;
- R16 is H, (C1-4)alkyl, (C1-4)alkenyl, optionally substituted with one or more halogen;
- R20 is (C1-3)alkyl, optionally substituted with one or more fluorine.
- 25 4. An N-substituted azetidine derivative according to claim 1 selected from the group consisting of compounds according to any one of Formulae 5



Formulae 5

wherein

- 5 R1 is (C1-8)alkyl, (C3-8)cycloalkyl, (C3-6)heterocycloalkyl, (C2-6)alkenyl, (C2-6)alkynyl, (C1-4)alkylcarbonyl, (C1-4)alkoxy(C2-4)alkyl, (C3-6)cycloalkyl(C1-3)-

alkyl, (C3-6)heterocycloalkyl(C1-3)alkyl, each independently optionally substituted with one or more halogen, nitrile, hydroxyl or (C1-2)alkyl;

(h)Ar is a (hetero)aromatic ring, optionally substituted with R12 and R13;

5 R2 and R3 are independently of each other H, fluorine, chlorine, (C1-3)alkyl, (C1-3)alkoxy, (C1-3)alkylthio, CF₃ or nitrile;

R4 and R7 are independently of each other H, fluorine, chlorine, (C1-2)alkyl, CF₃ or nitrile;

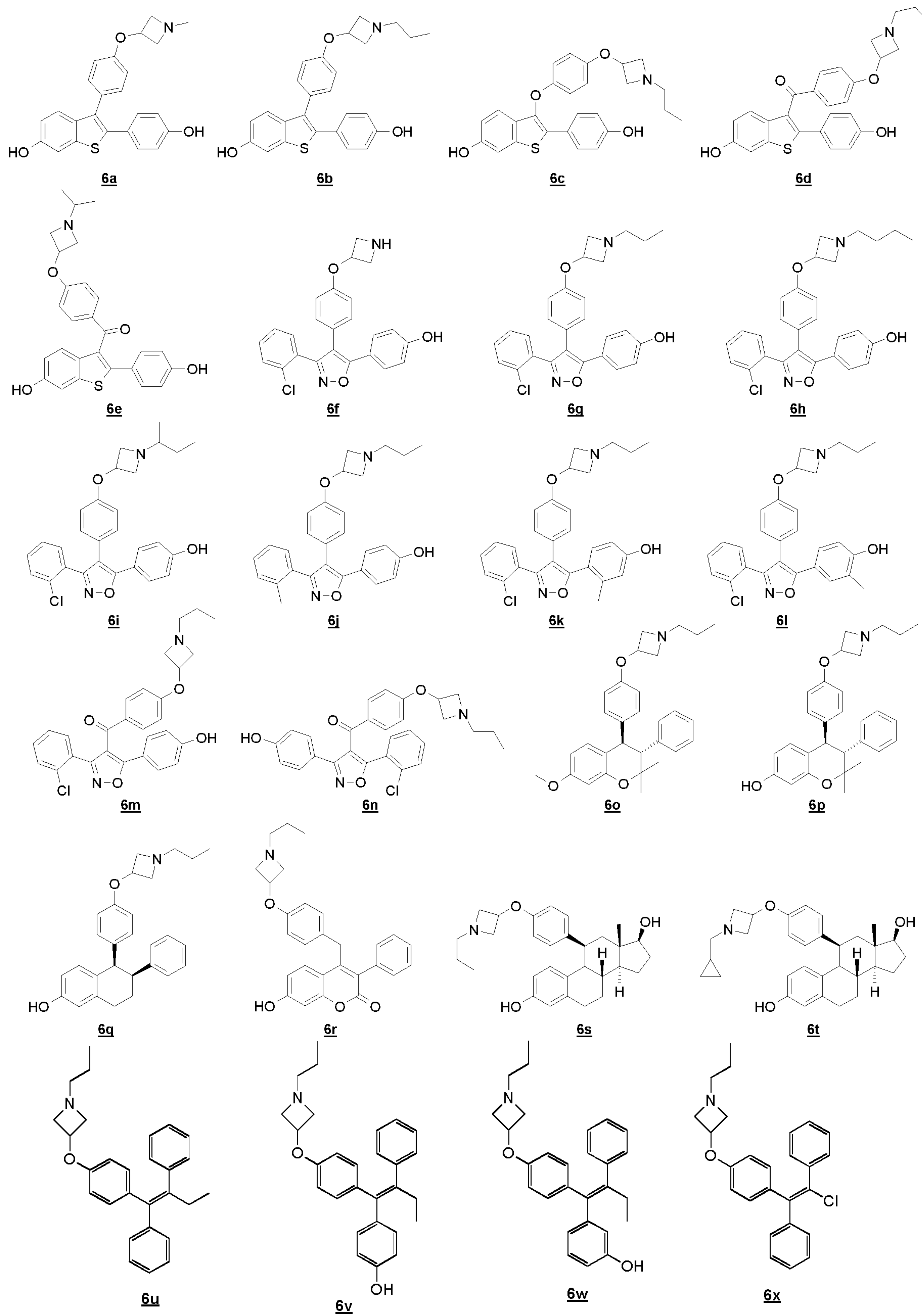
R12 is H, fluorine, chlorine, (C1-2)alkyl, (C1-2)alkoxy, nitrile or hydroxyl;

10 R13 is H, fluorine, chlorine, (C1-3)alkyl, (C1-3)alkoxy, (C1-3)alkylthio, CF₃ or nitrile;

R6 is H, hydroxyl, amine or (C1-6)alkoxy;

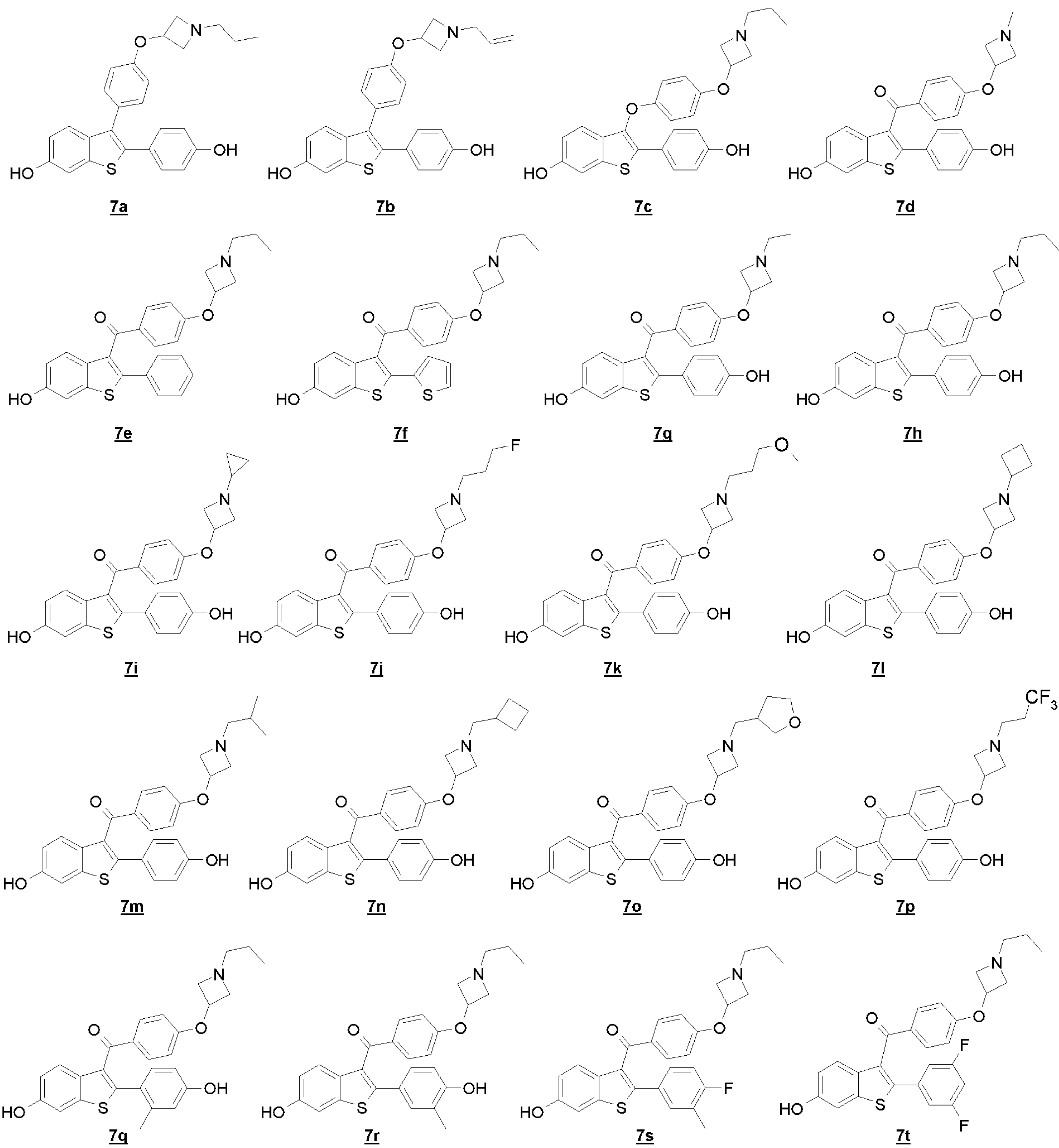
R6 and R2 may be linked to form a (hetero)aromatic ring which is optionally substituted with fluorine, chlorine or (C1-3)alkyl.

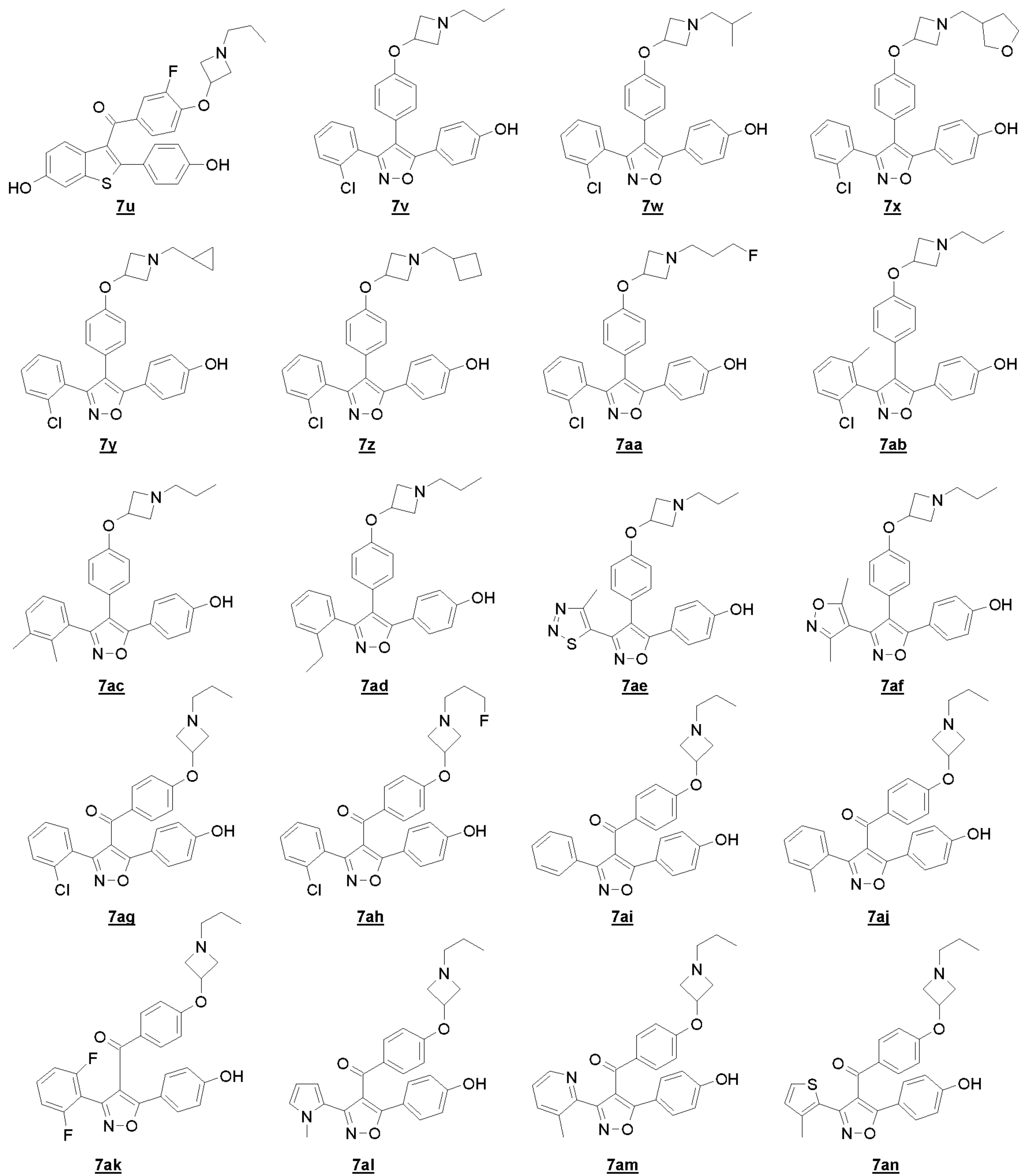
- 15 5. An N-substituted azetidine derivative according to claim 1 selected from the group consisting of compounds according to any one of Formulae 6



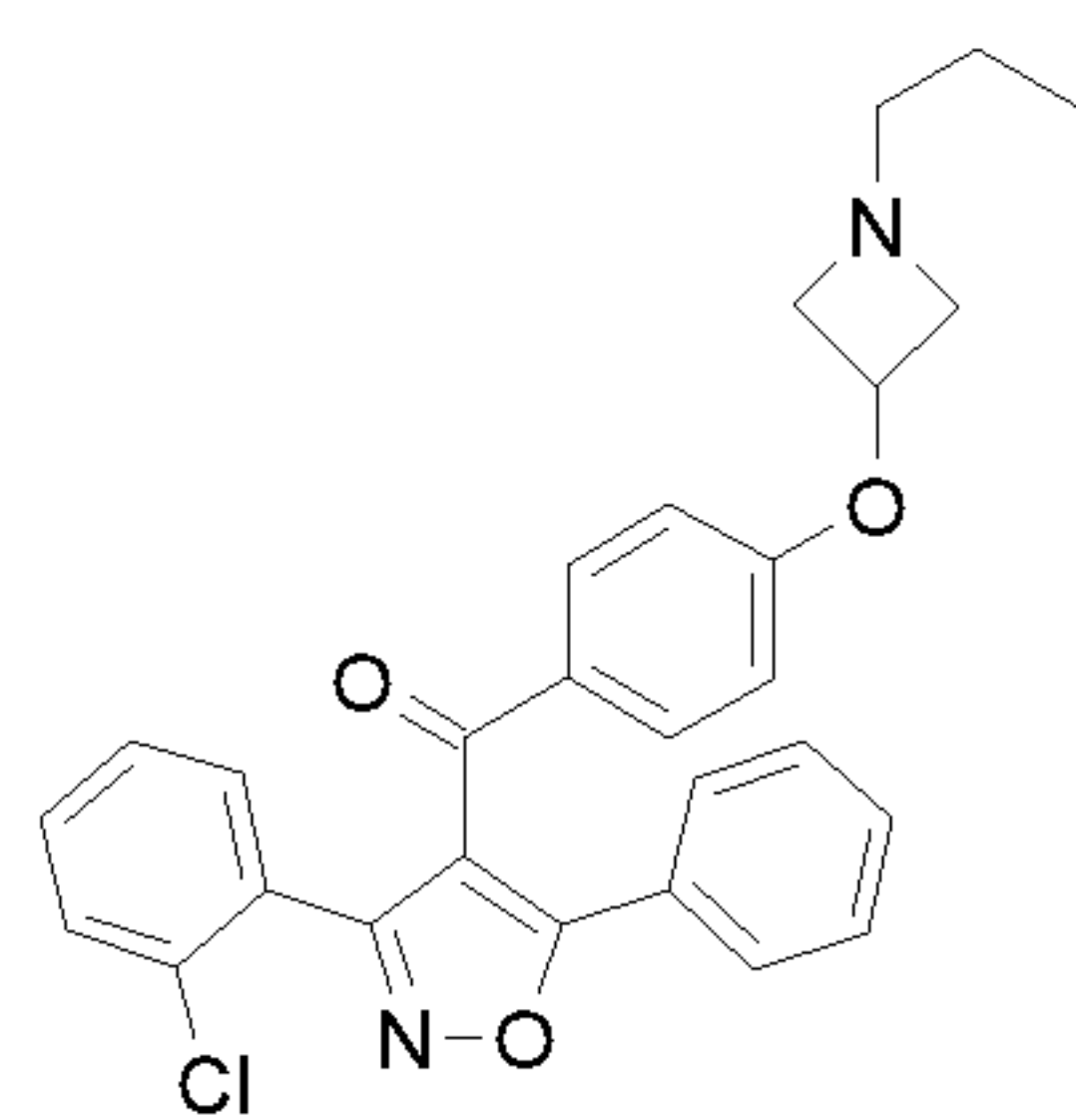
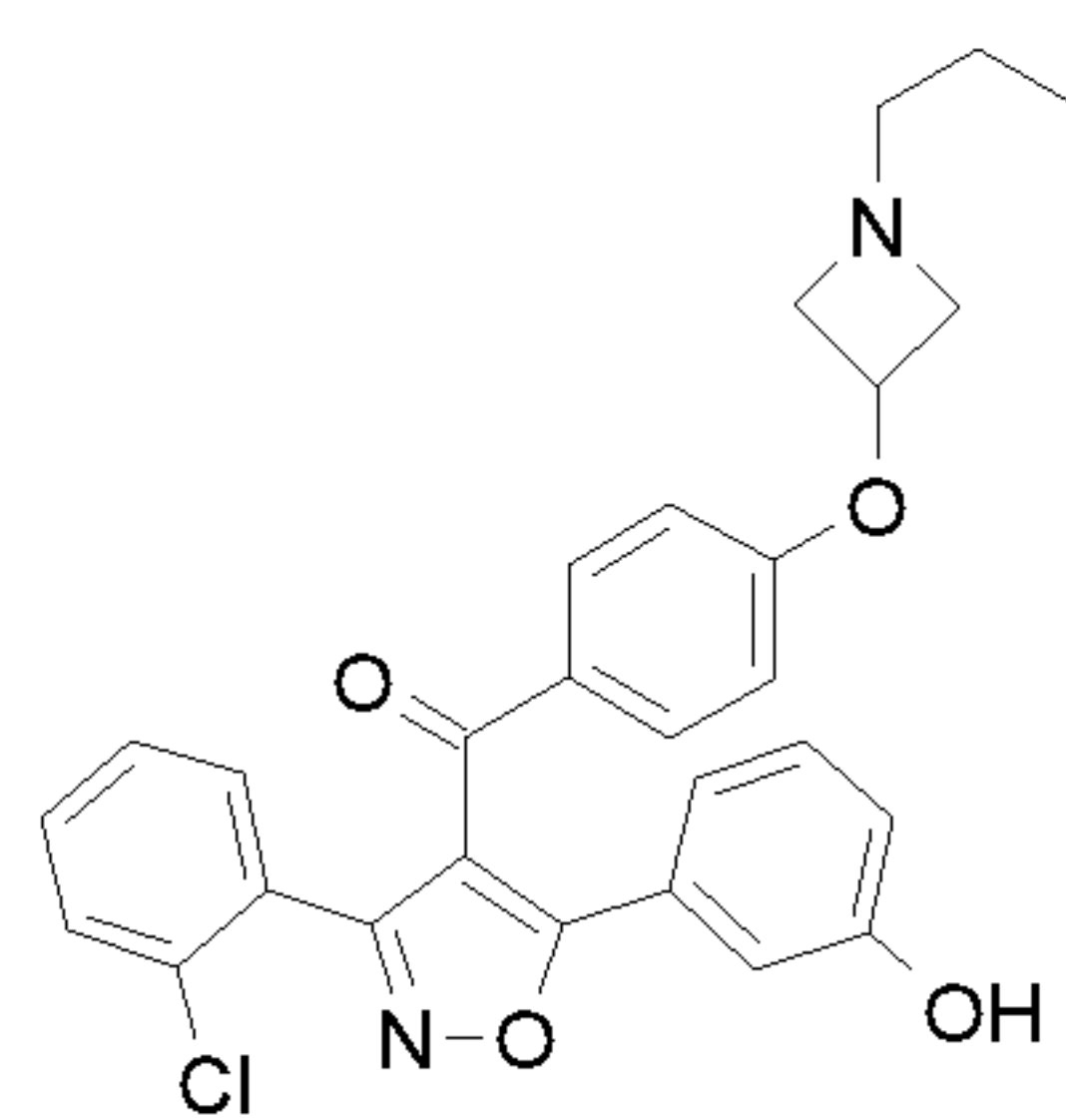
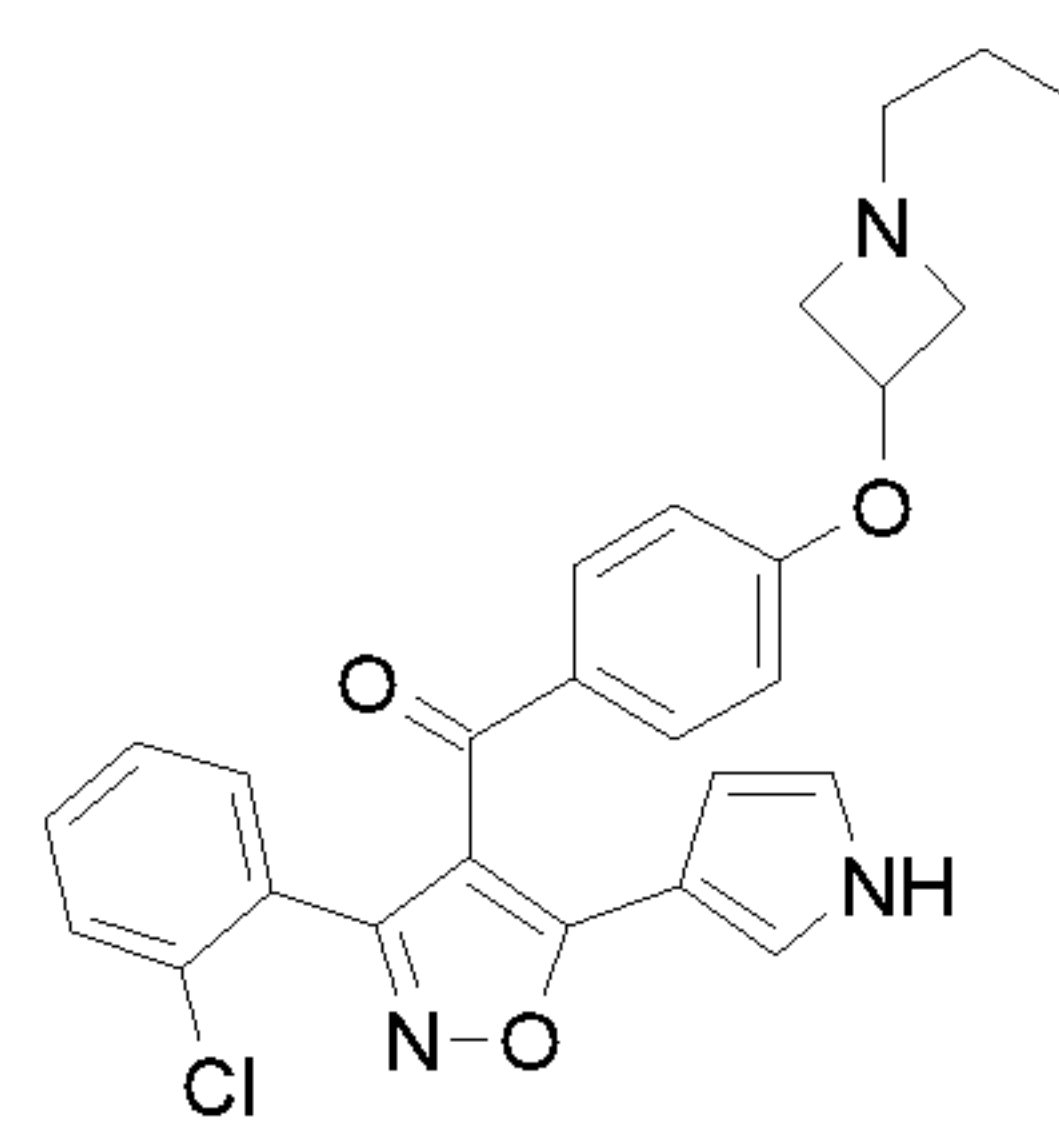
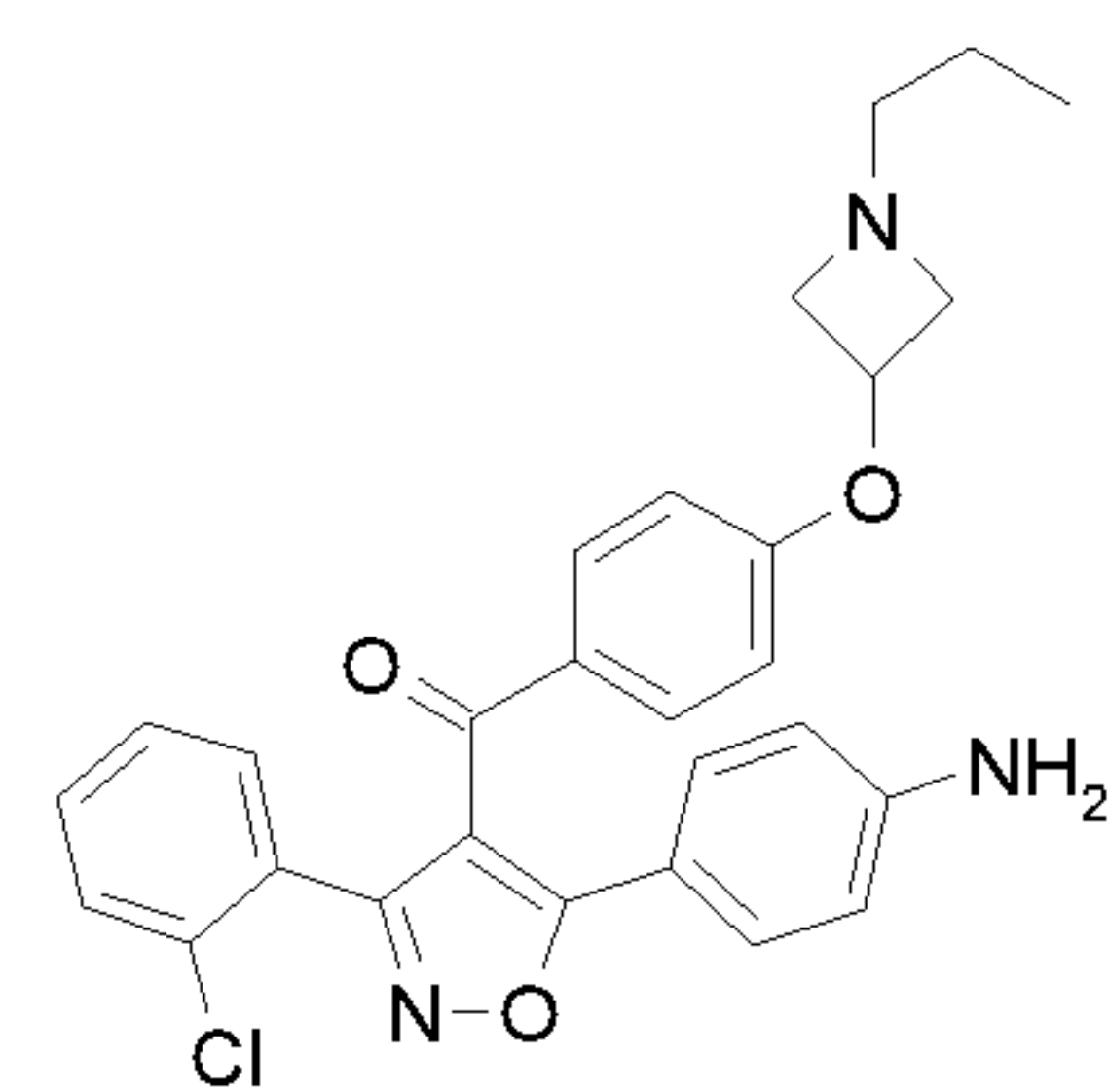
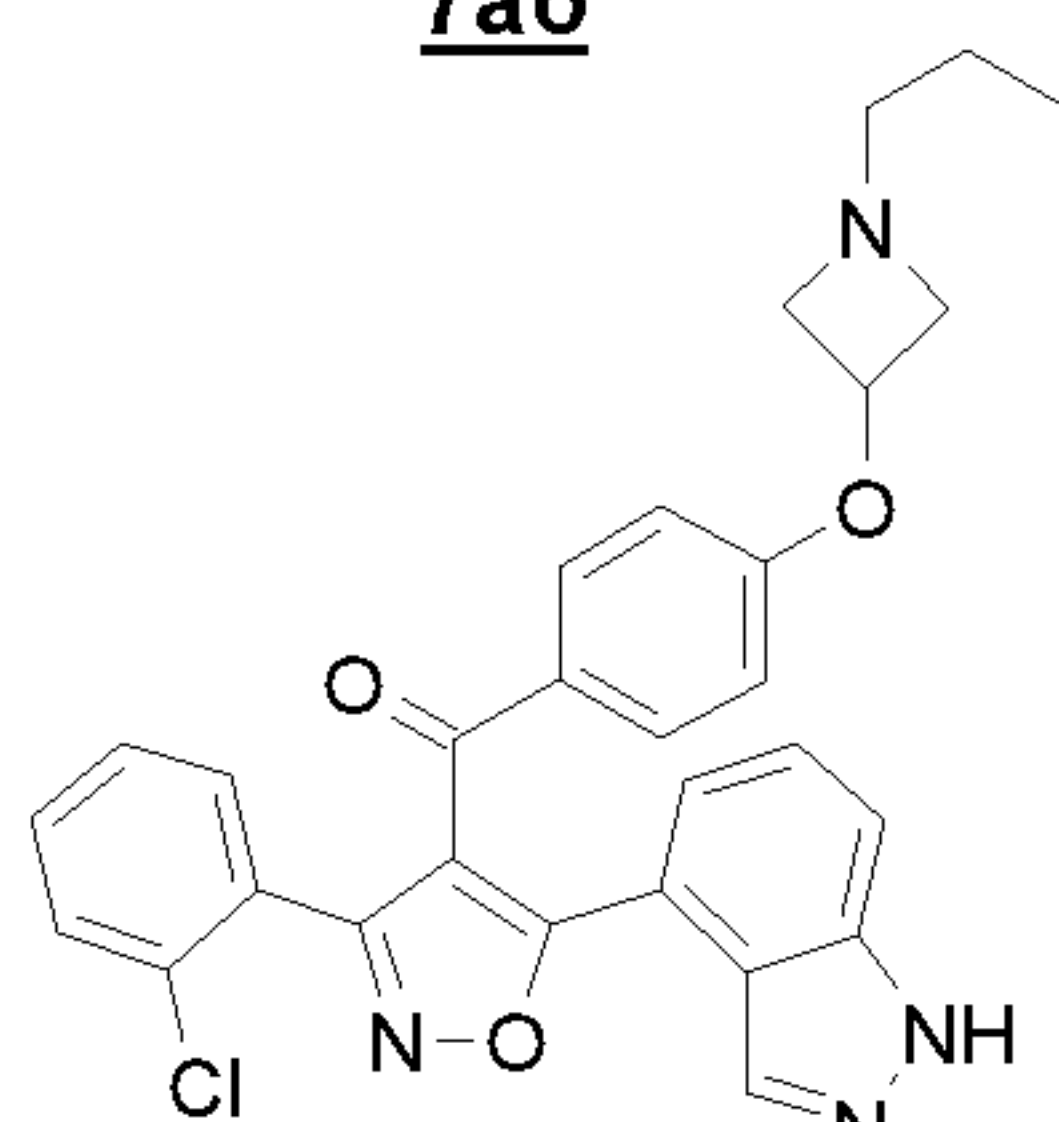
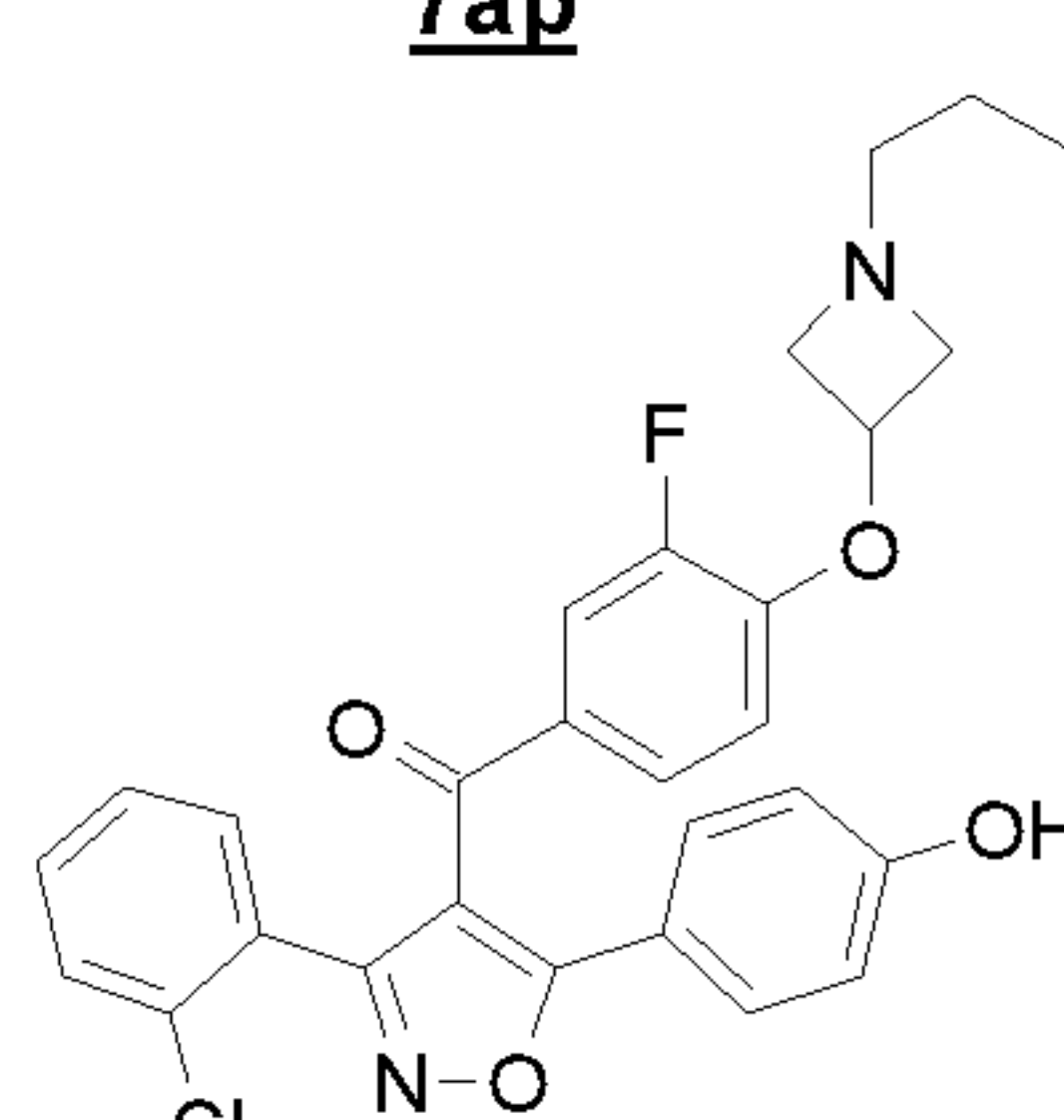
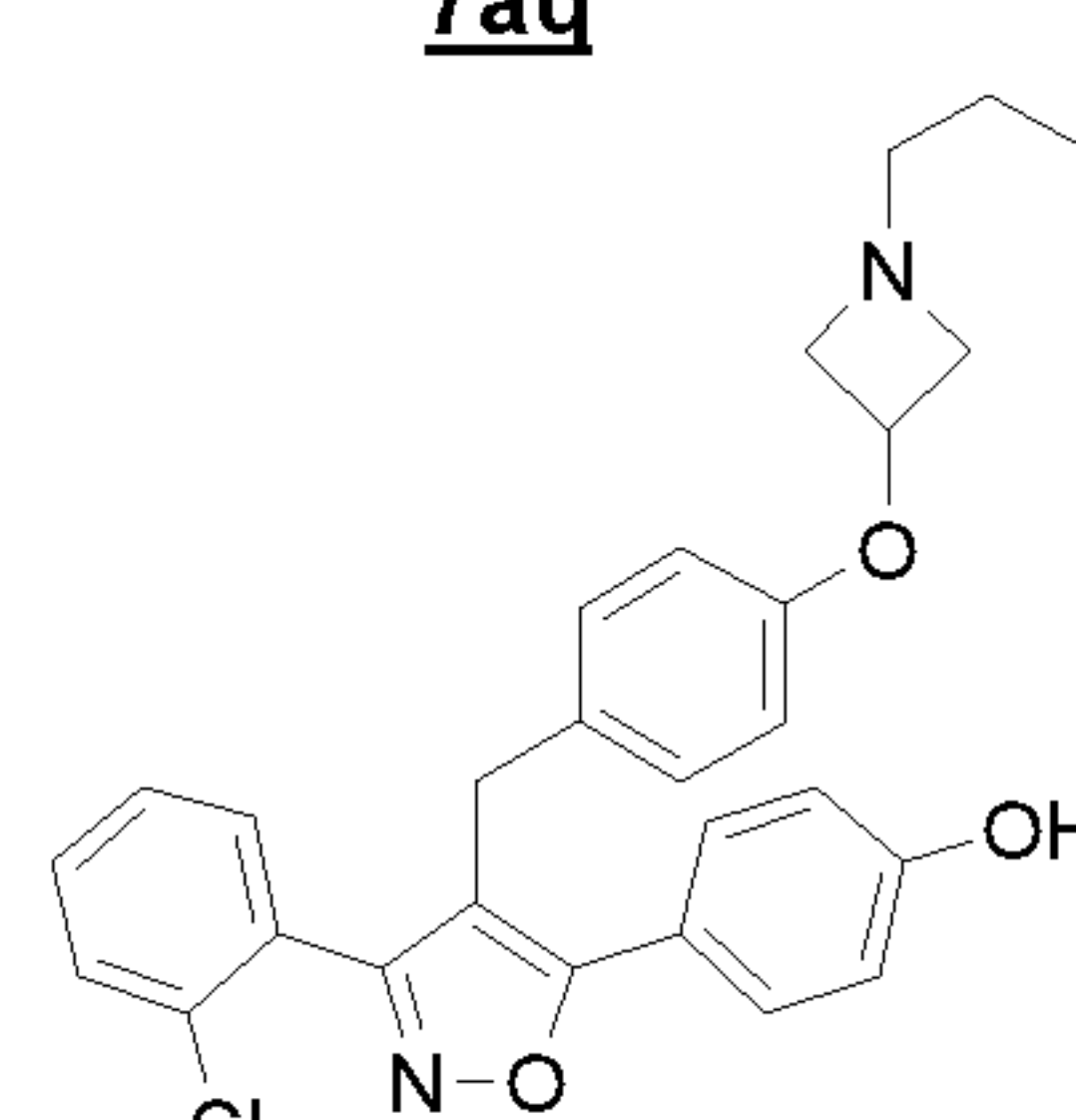
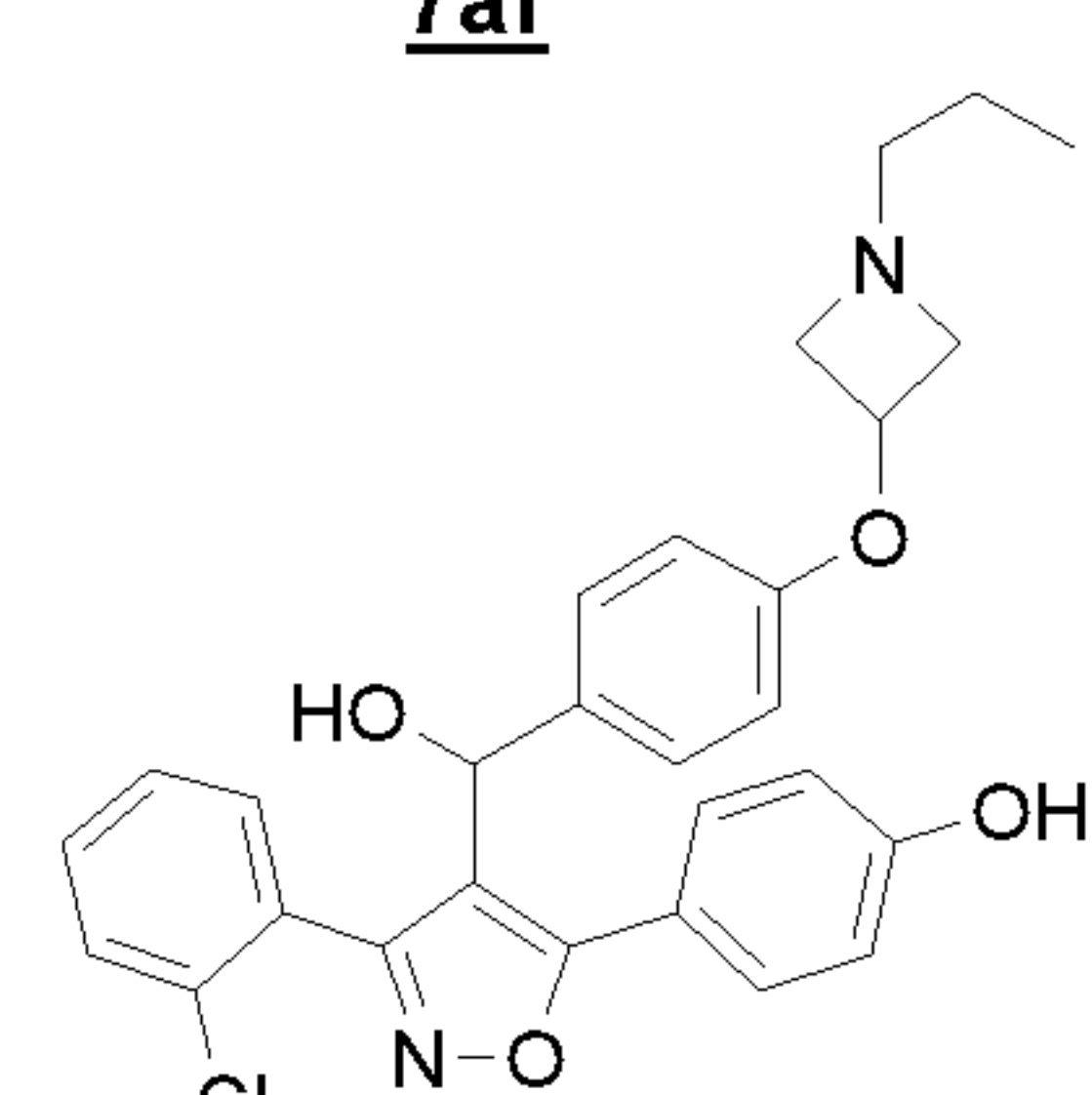
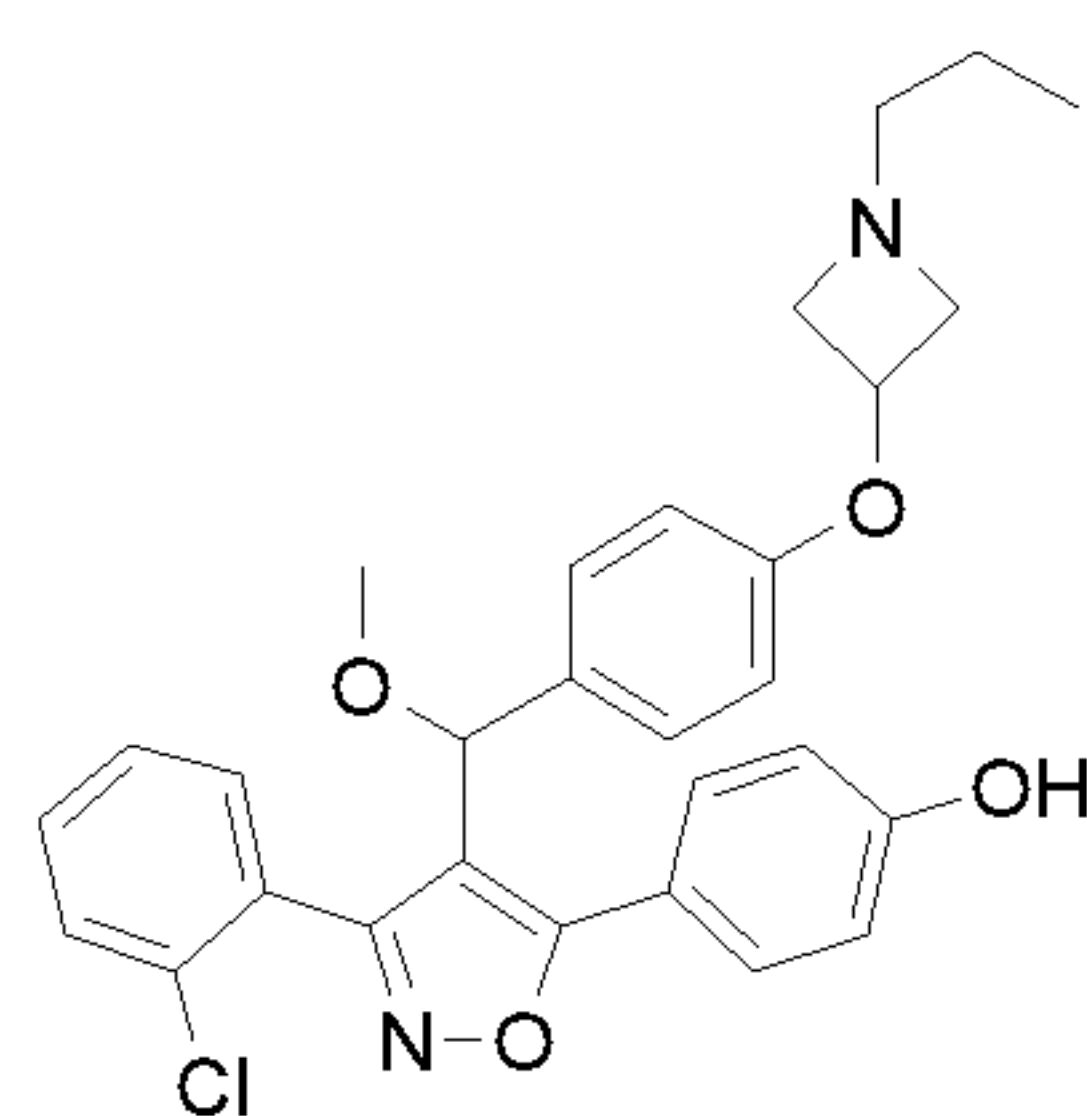
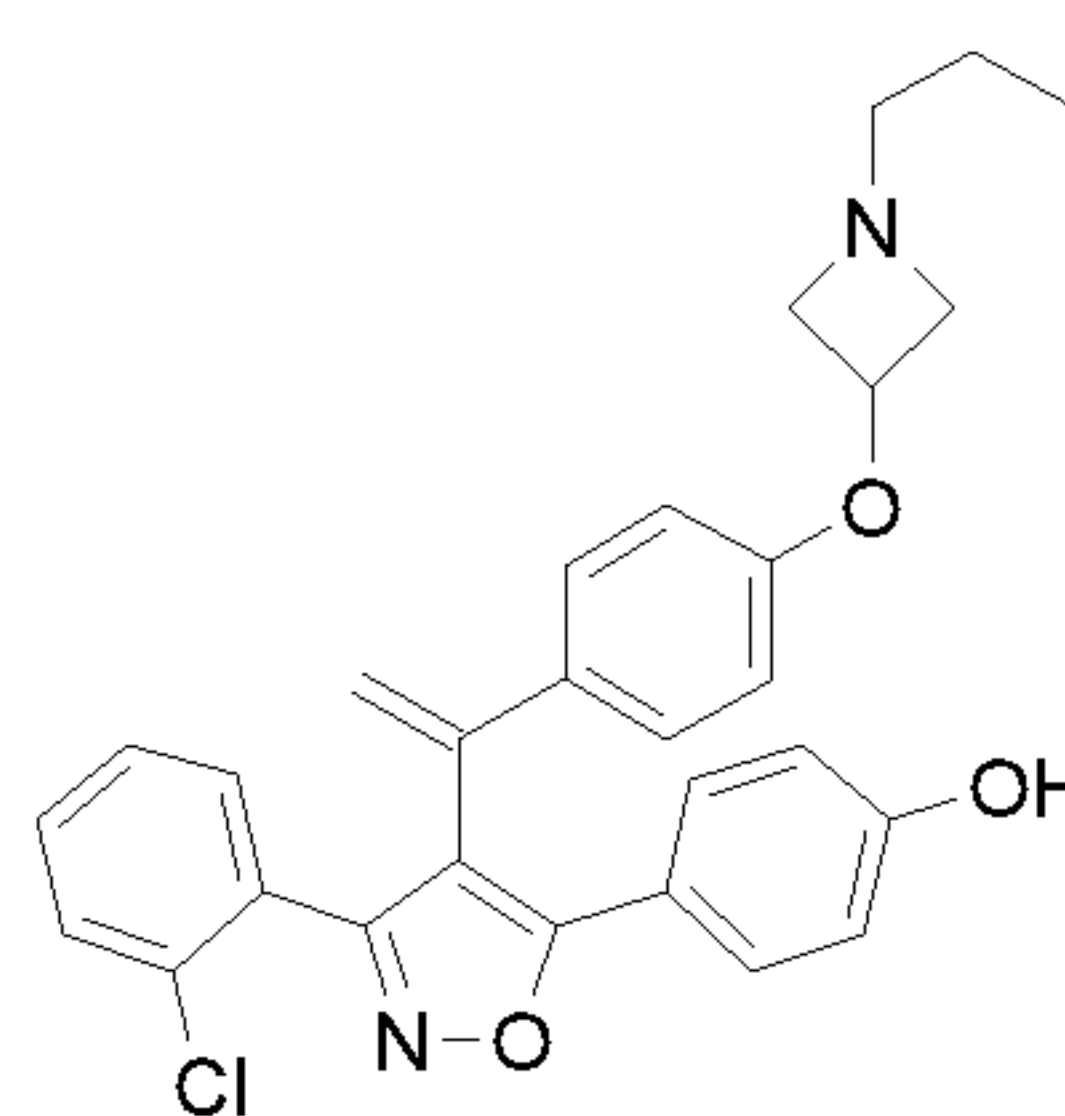
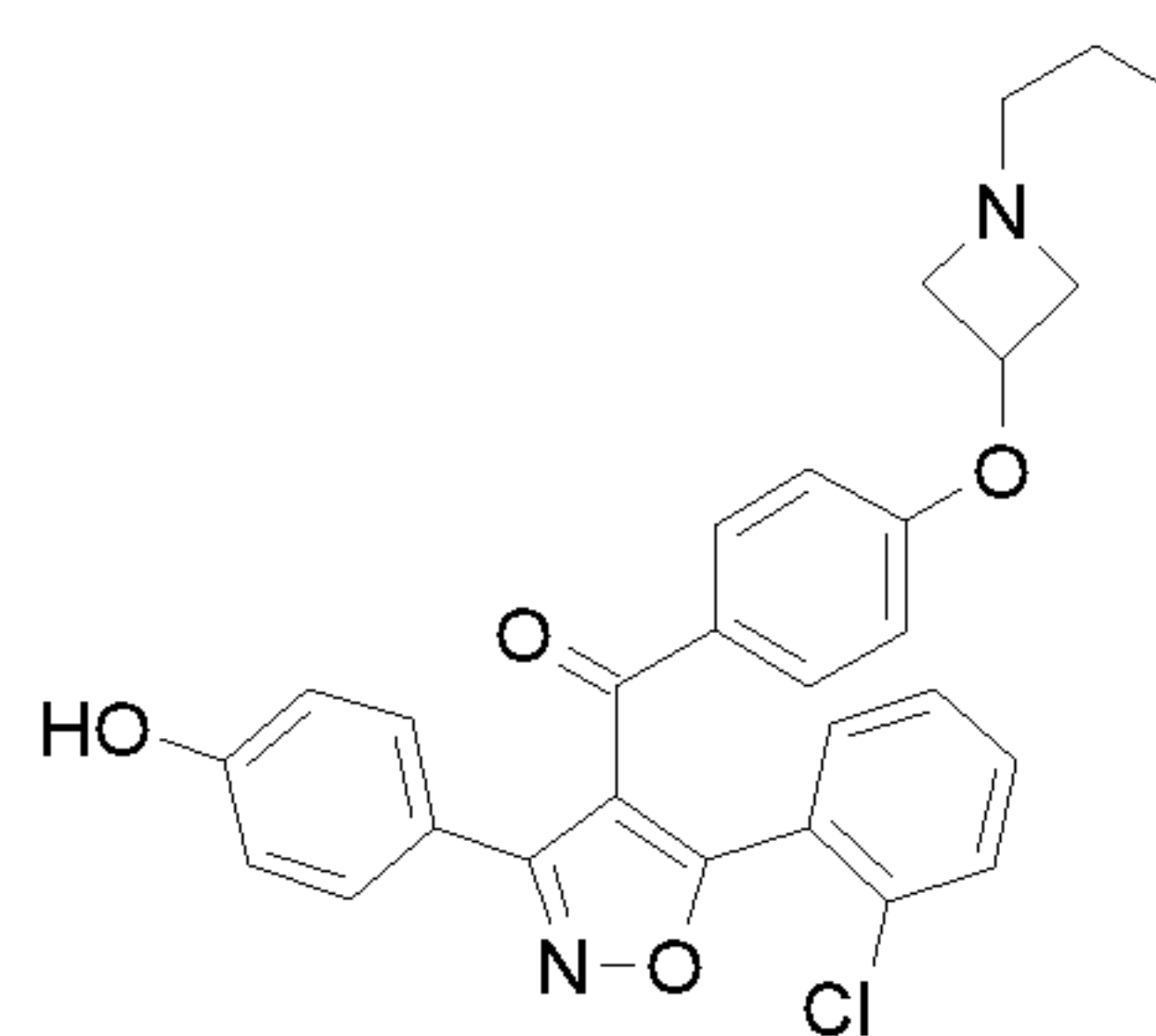
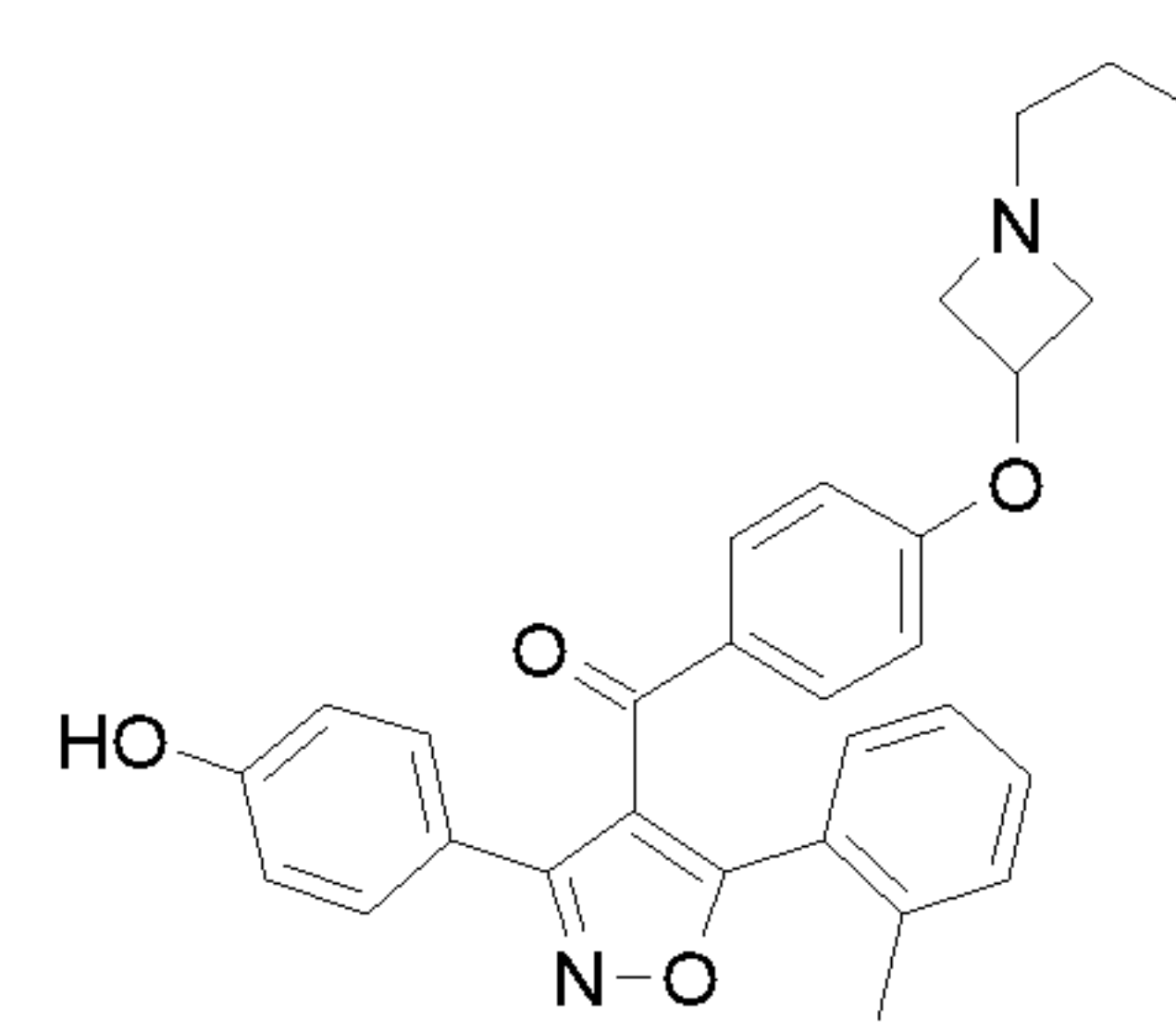
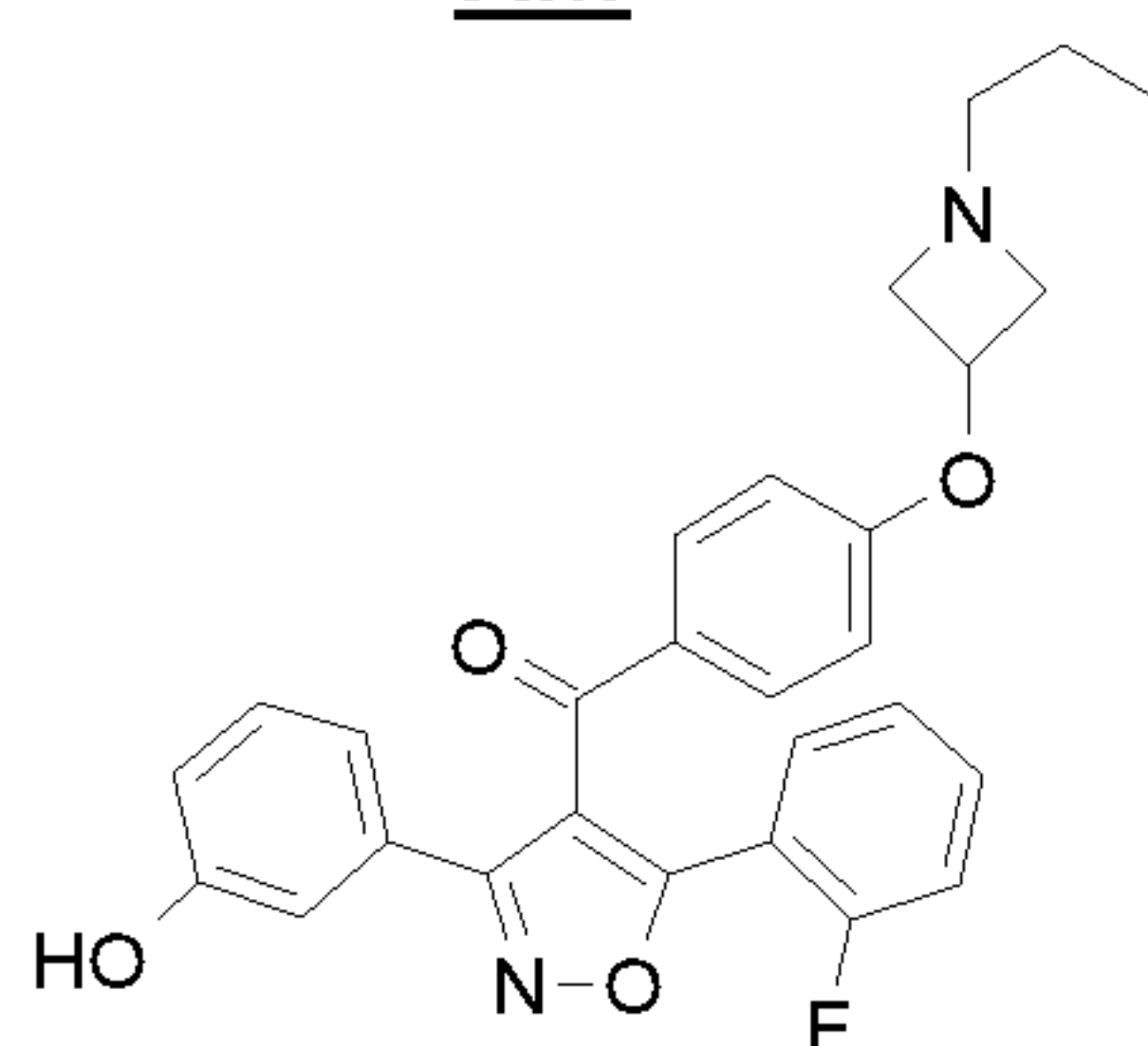
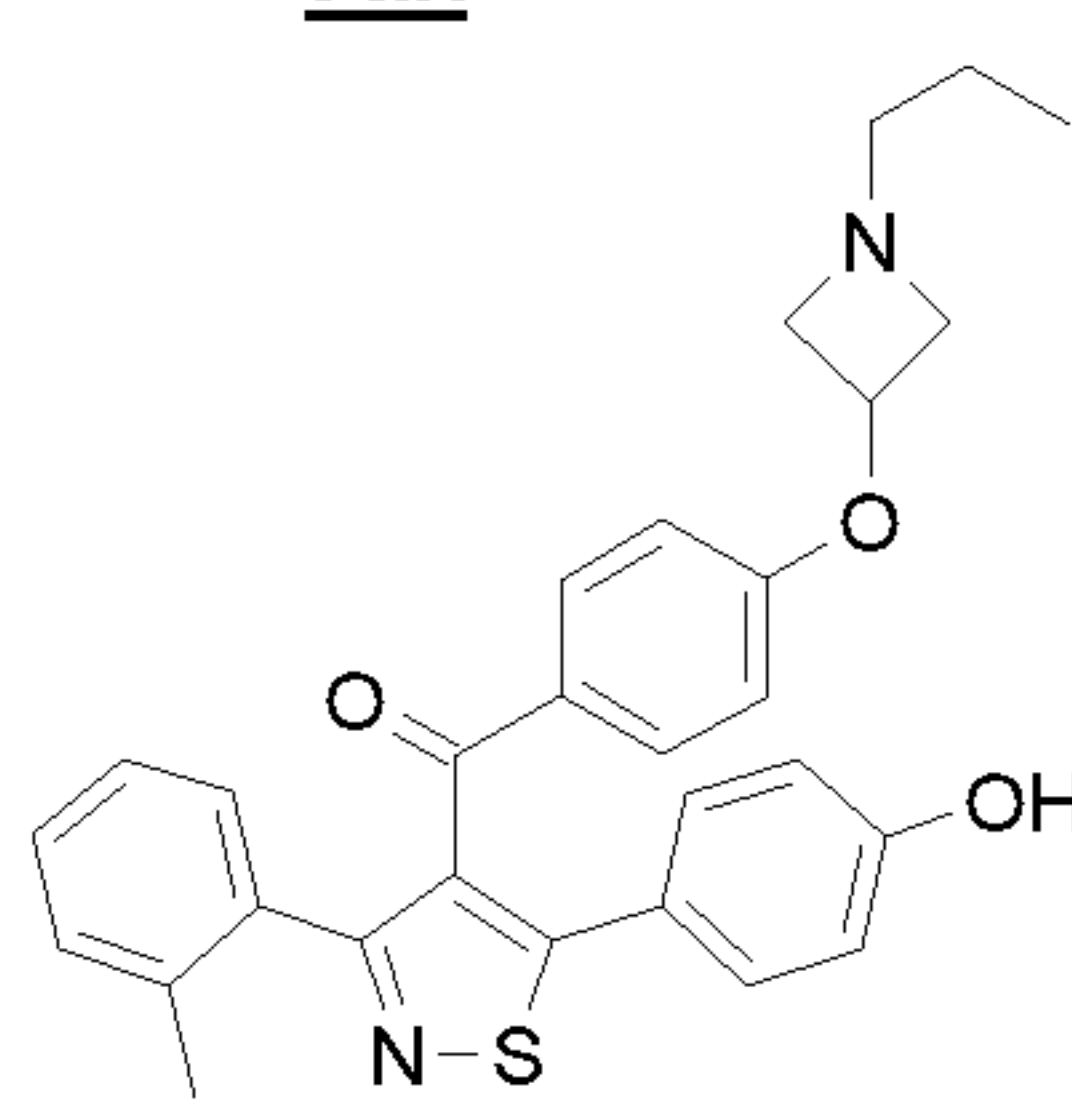
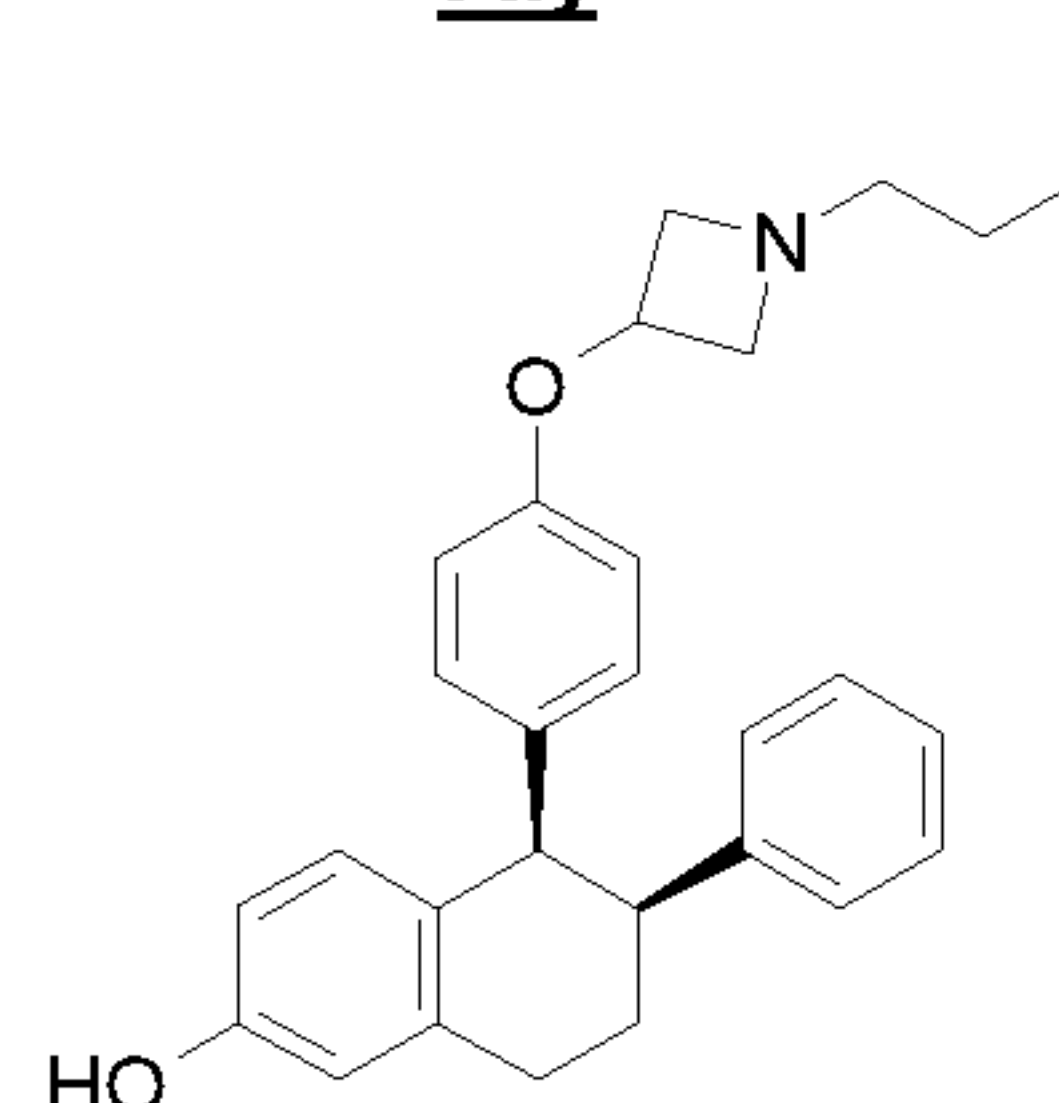
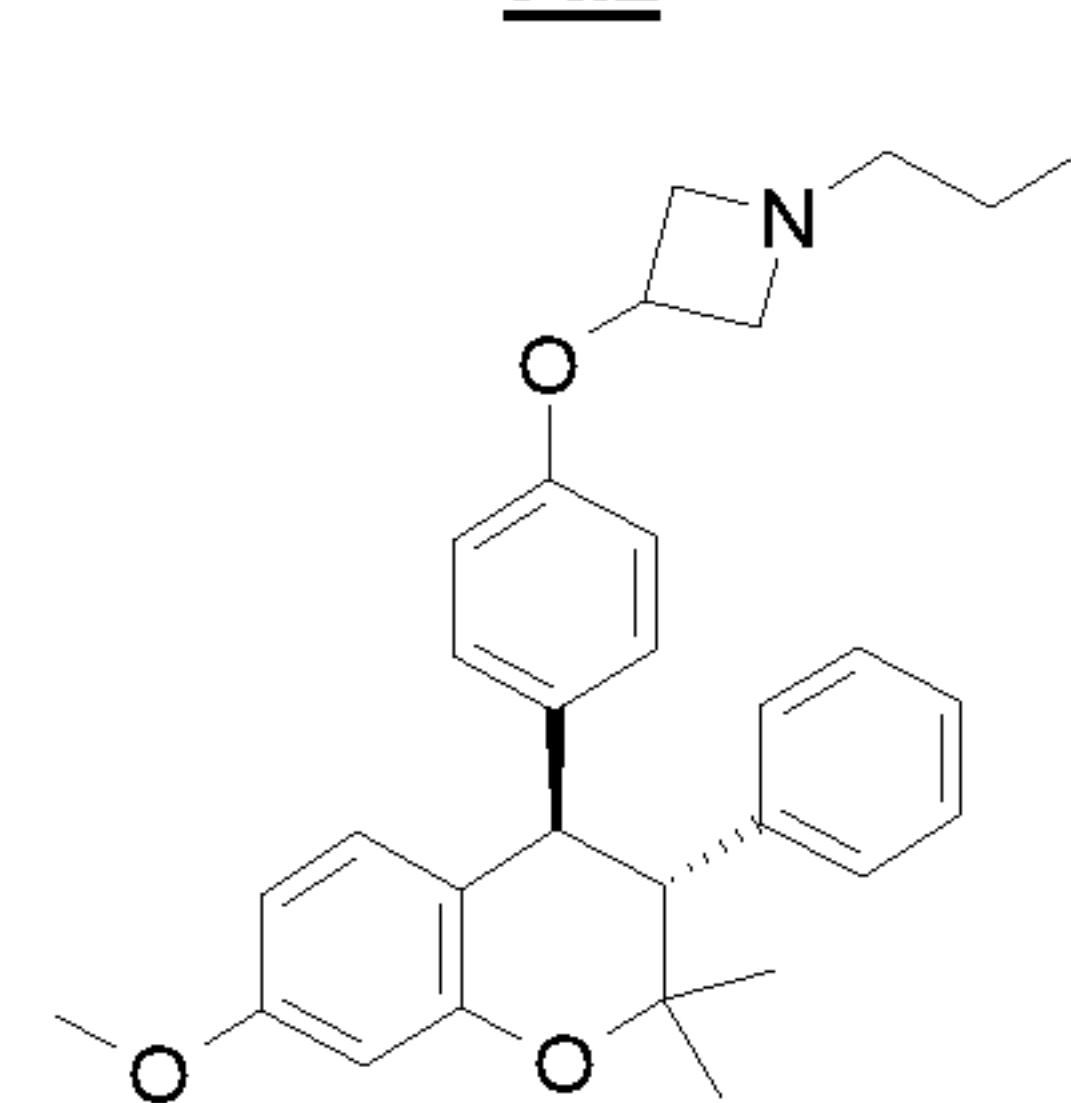
Formulae 6

6. An N-substituted azetidine derivative according to claim 1 selected from the group consisting of compounds according to any one of Formulae 7

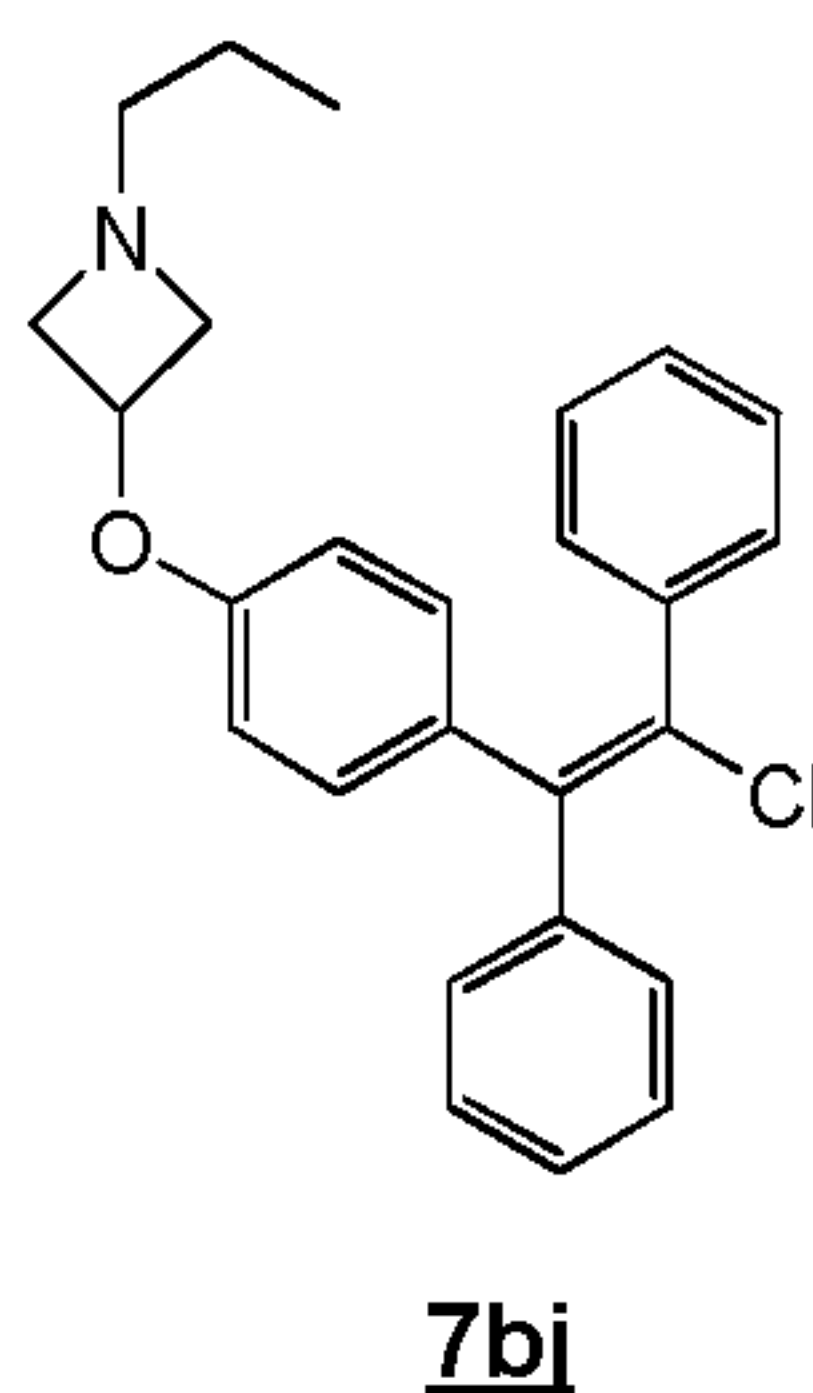
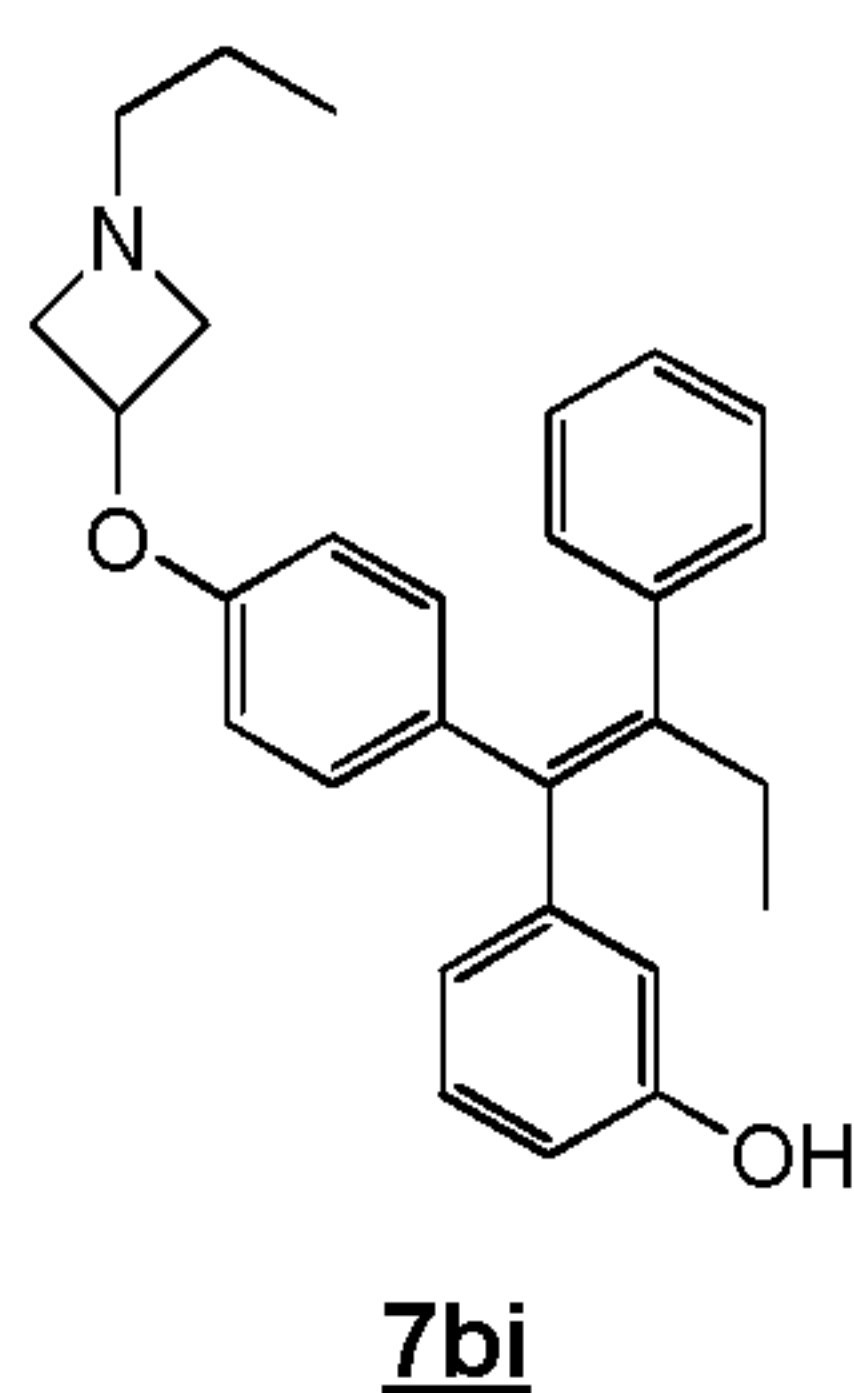
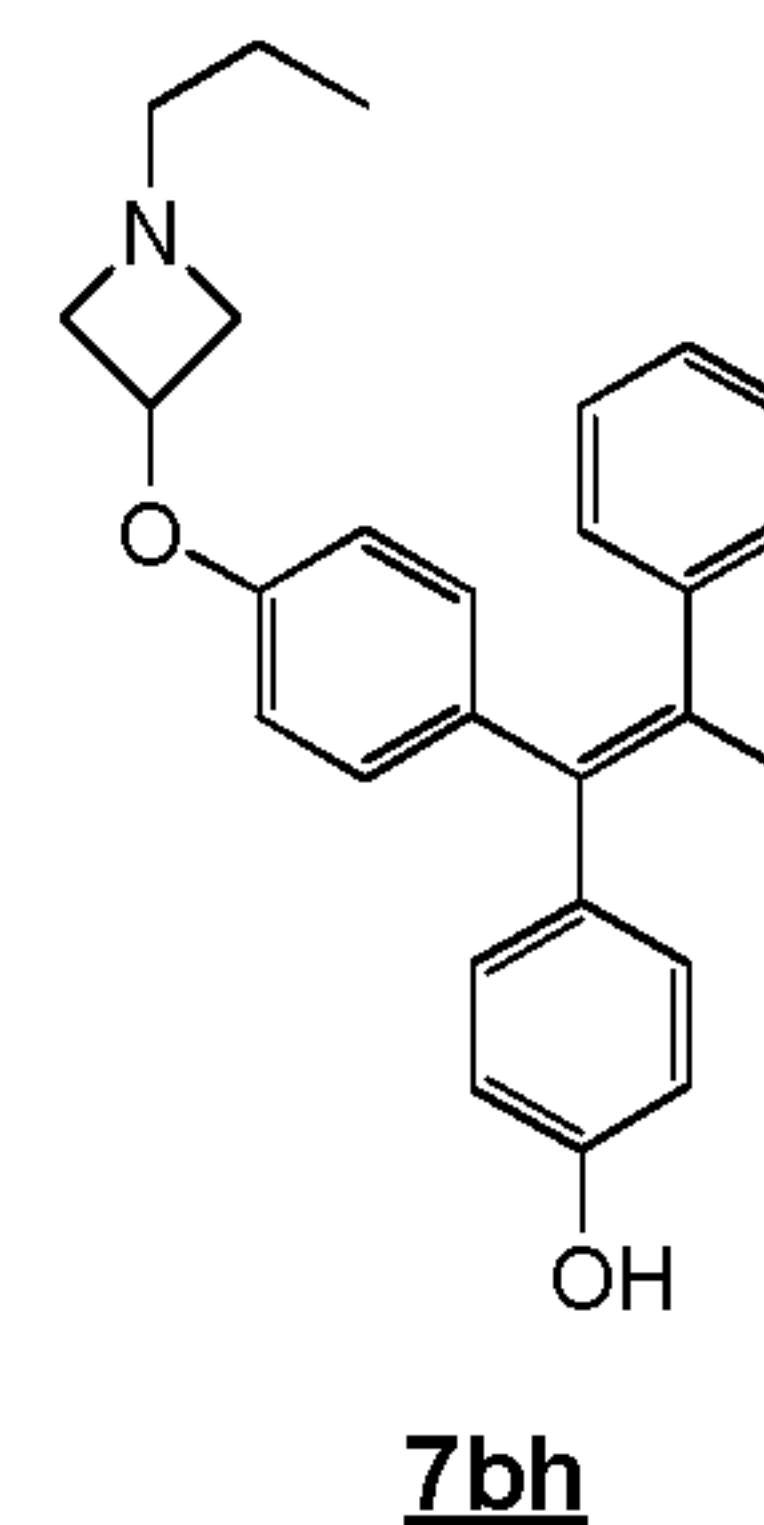
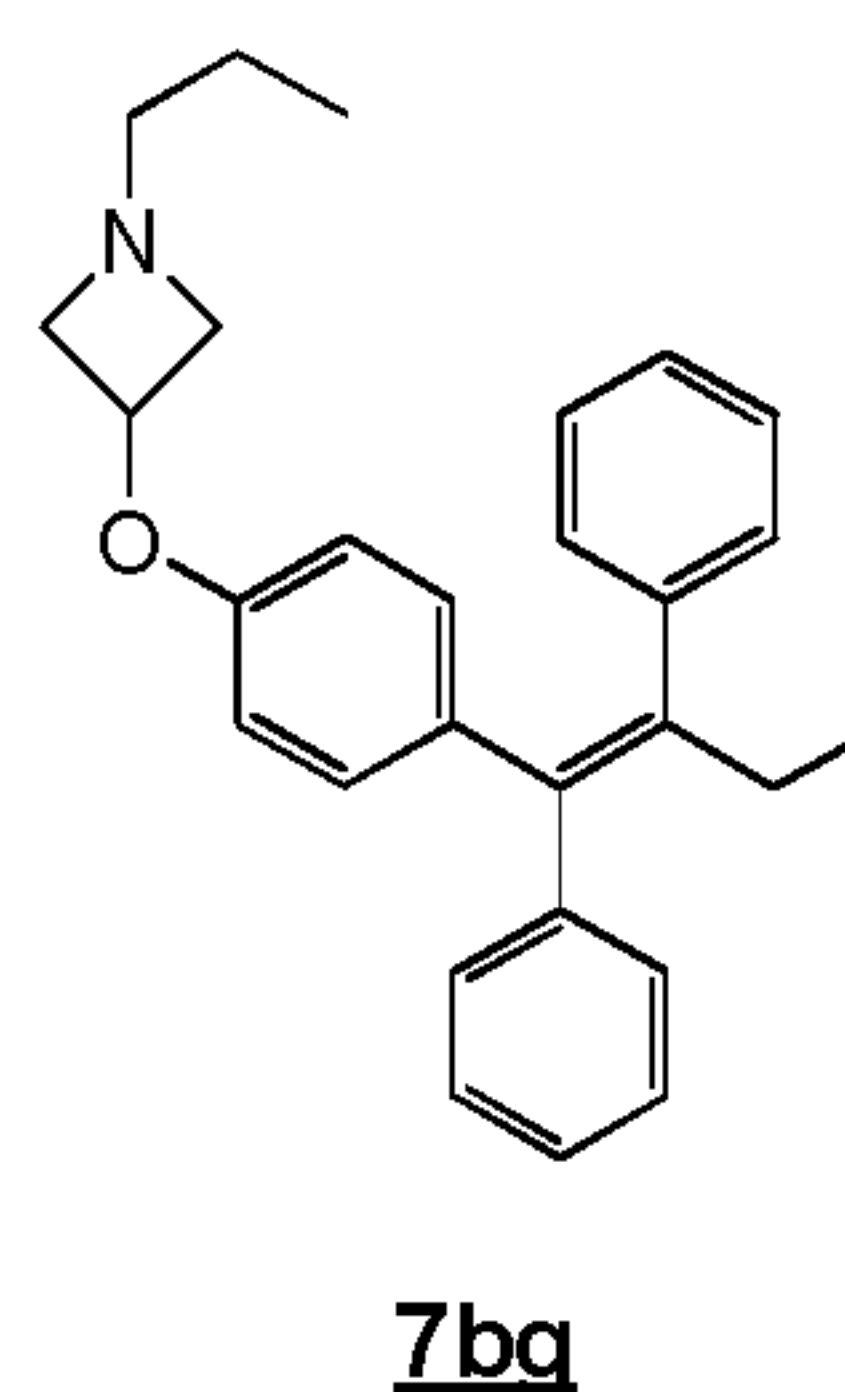
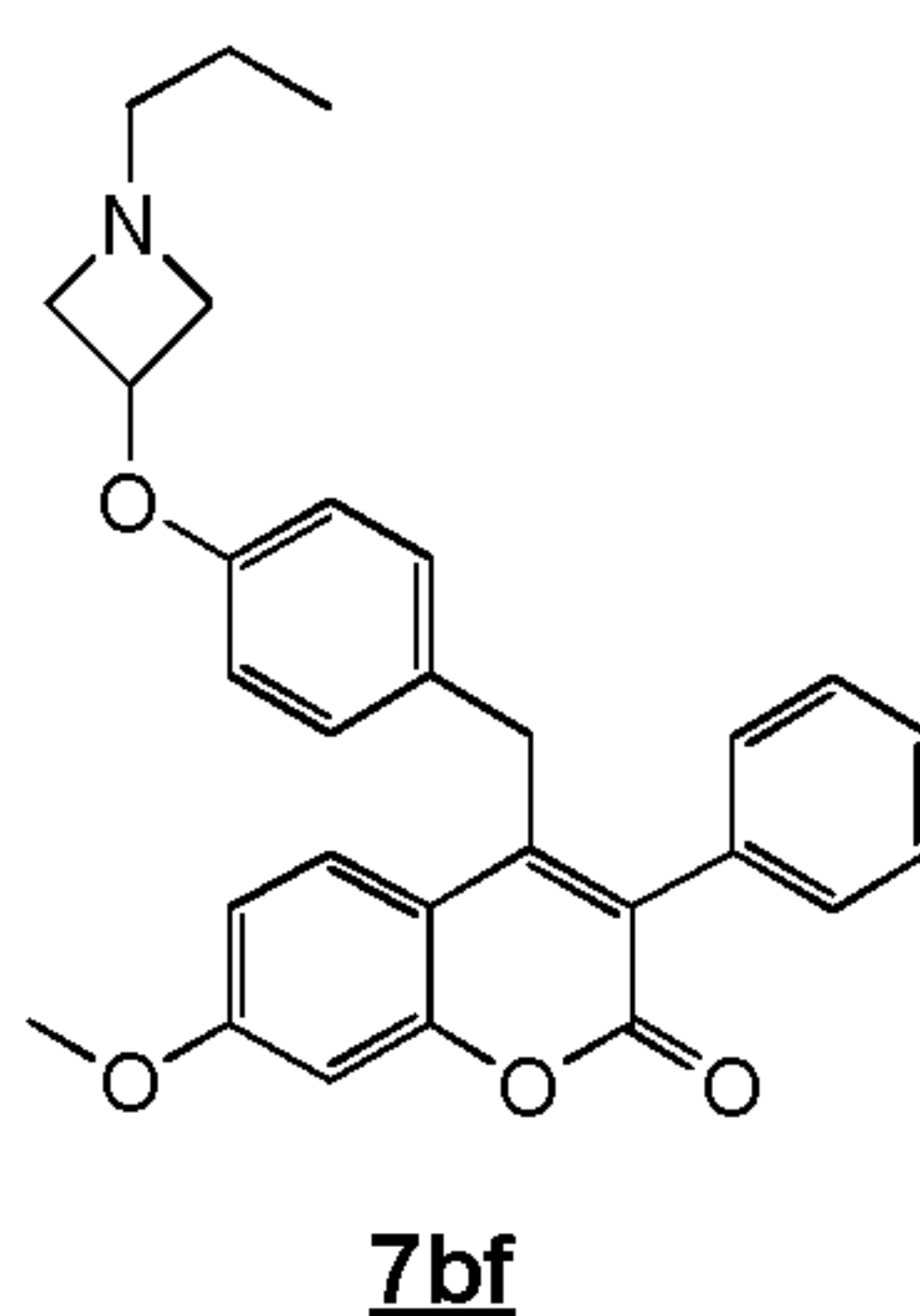
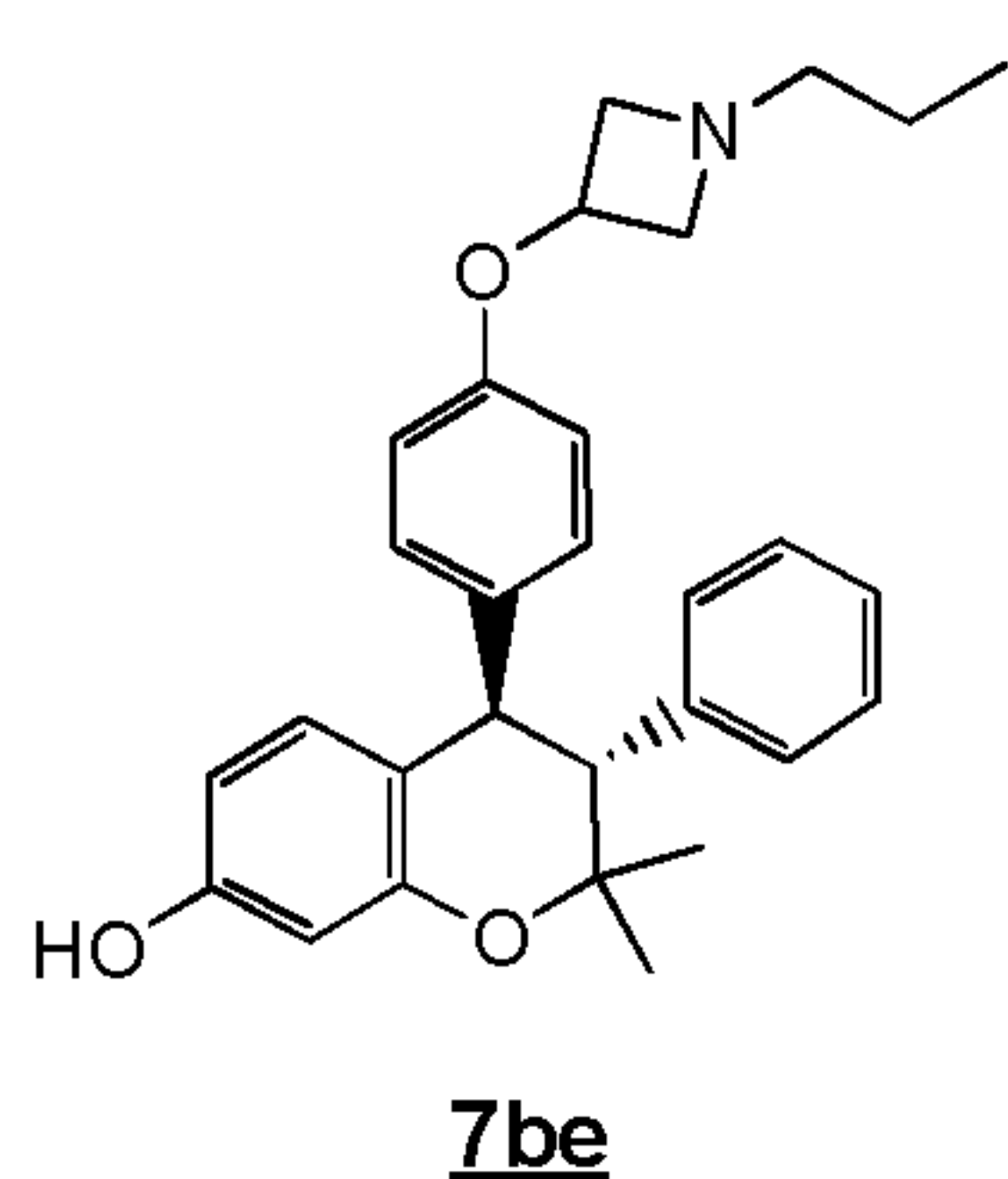




Formulae 7

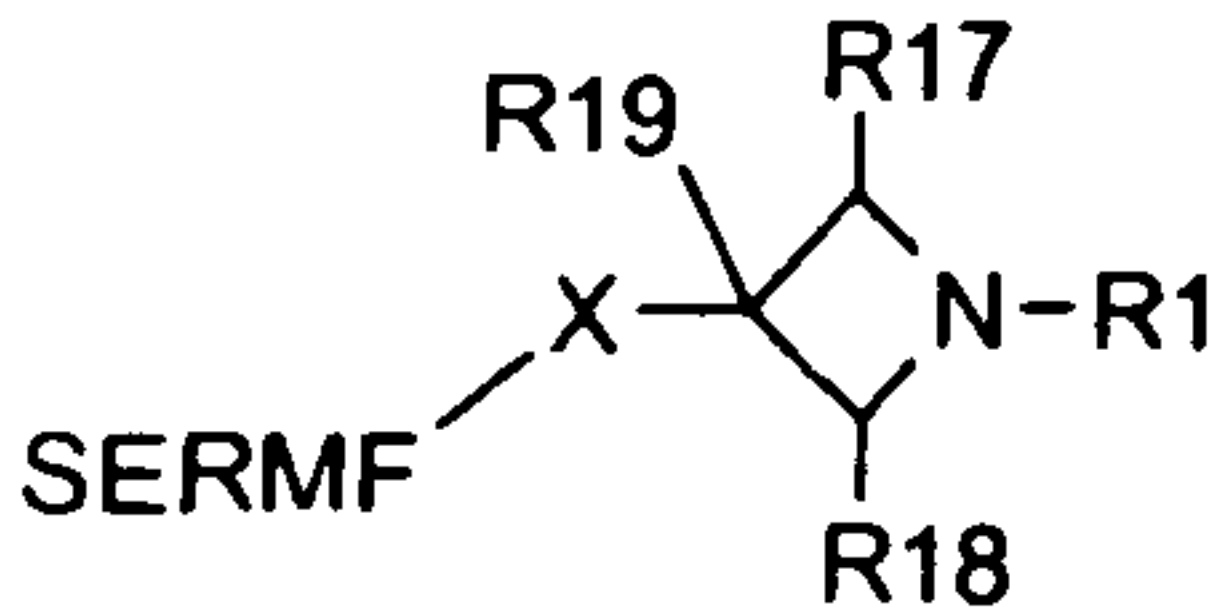
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Formulae 7



Formulae 7

7. A pharmaceutical composition comprising an N-substituted azetidine derivative
 5 according to any one of claims 1 to 6 and a pharmaceutically acceptable
 excipient.
8. An N-substituted azetidine derivative according to any one of claims 1 to 6 for
 use in therapy.
- 10 9. An N-substituted azetidine derivative according to any one of claims 1 to 6 for
 use in the treatment or prevention of ovulatory dysfunction, uterine cancer,
 endometrium cancer, ovarian cancer, endometriosis, osteoporosis, prostate
 cancer, benign prostatic hypertrophy, and breast cancer, in particular ER-
 15 positive breast cancer, more in particular ER-positive hormone treatment-
 resistant breast cancer.
10. The N-substituted azetidine derivative according to claim 9 for use in the
 treatment of ER-positive, tamoxifen-resistant breast cancer.



(I)