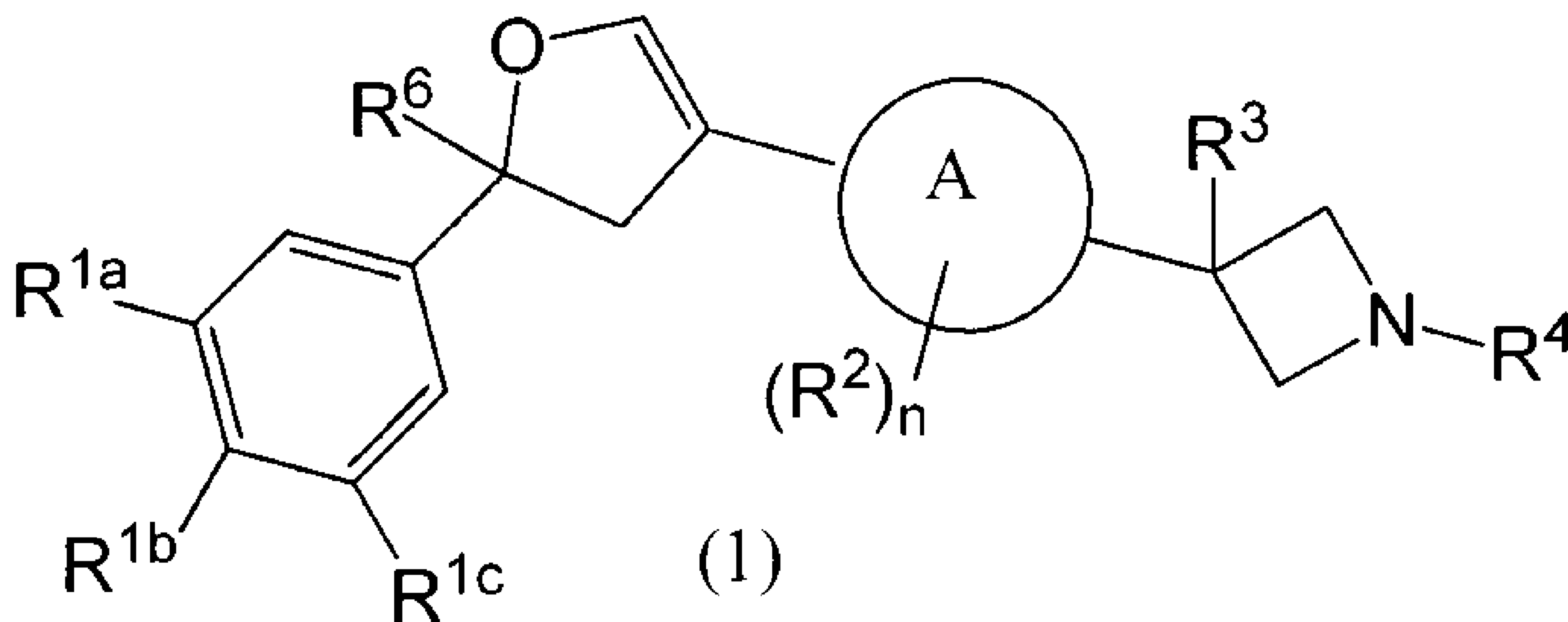




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(54) **Titre : DERIVES DE DIHYDROFURANE A SUBSTITUTION AZETIDINE EN TANT QU'AGENTS ANTIPARASITAIRES**
(54) **Title: DIHYDROFURAN AZETIDINE DERIVATIVES AS ANTIPARASITIC AGENTS**



(57) **Abrégé/Abstract:**

This invention recites dihydrofuran substituted azetidine derivatives of Formula (1) stereoisomers thereof, veterinarily acceptable salts thereof, compositions thereof, and their use as a parasiticide in mammals and birds. The substituents A, R^{1a}, R^{1b}, R^{1c}, R², R³, R⁴, R⁶, and n are as described herein.



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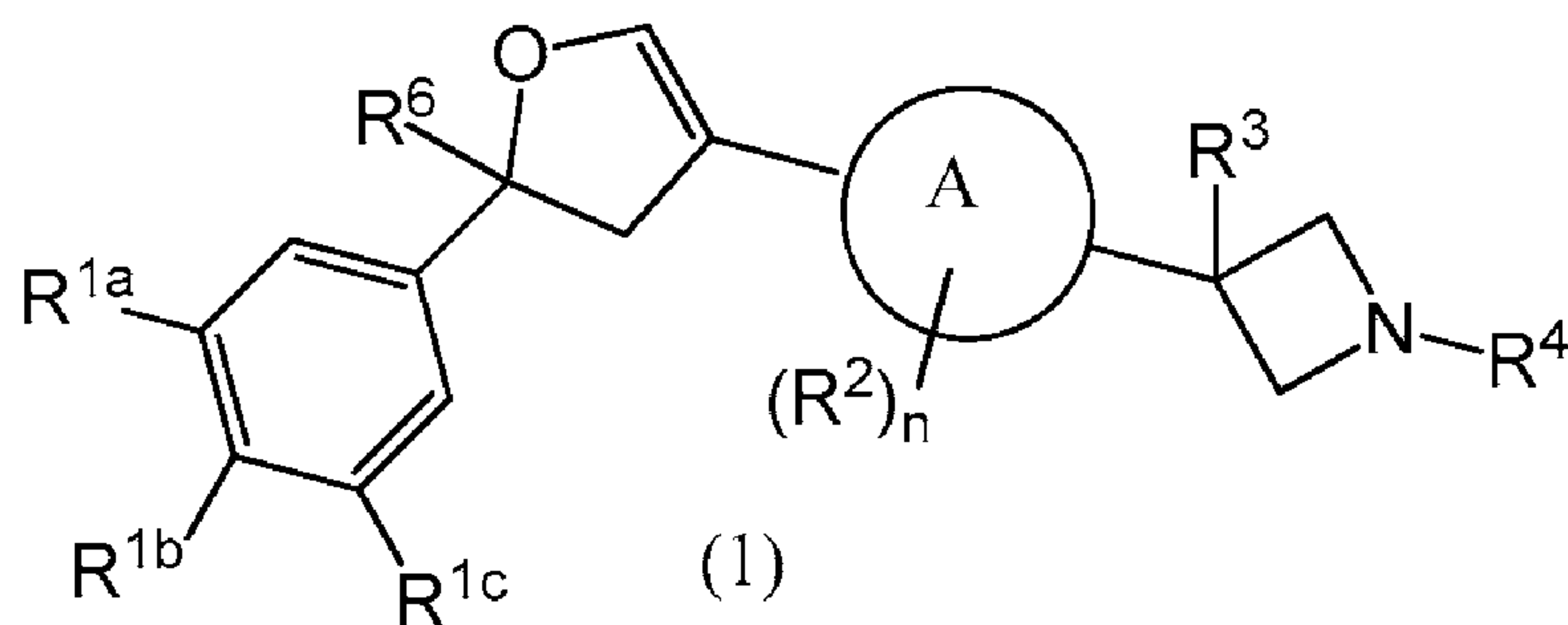
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ily acceptable salts thereof, compositions thereof, and their use as a parasiticide in mammals and birds. The substituents A, R^{1a}, R^{1b},
R^{1c}, R², R³, R⁴, R⁶, and n are as described herein.

FIELD OF THE INVENTION

35 Isoxazoline derivatives have been disclosed in the art as having insecticidal and acaricidal activity. For example, WO2007/105814, WO2008/122375, and WO2009/035004 recite certain alkylene linked amides. Further, WO2007/075459 discloses phenyl isoxazolines substituted with 5- to 6-membered heterocycles. WO2011/101229 discloses certain dihydrofuran

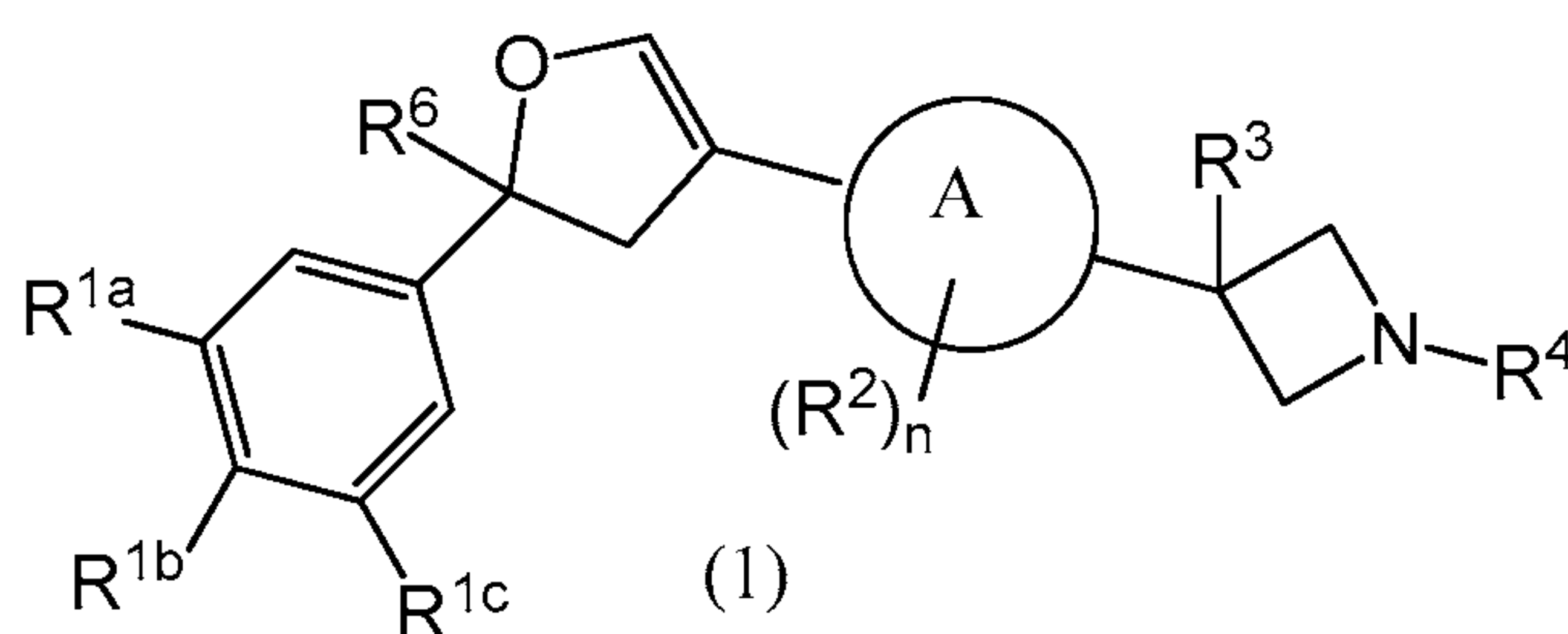
derivatives as antiparasitic agents. However, the citations do not exemplify a dihydrofuran substituted phenyl azetidine, nor does the prior art indicate that such compounds would be useful against a spectrum of parasitic species, regardless of morphological lifecycle stages, in animals.

5 Despite the availability of effective, broad spectrum antiparasitic agents, there remains a need for a safer, convenient, efficacious, and environmentally friendly product that will overcome the ever-present threat of resistance development.

The present invention overcomes one or more of the various
10 disadvantages of, or improves upon, the properties of existing compounds. In particular the present invention develops new isoxazoline substituted phenyl azetidines which demonstrate such properties.

SUMMARY

15 The present invention provides Formula (1) compounds, stereoisomers thereof, pharmaceutical or veterinarily acceptable salts thereof, which act as parasiticides, in particular, ectoparasiticides; therefore may be used to treat acarids and insect infection and infestation in animals. In addition, the invention contemplates the control and prevention endoparasites in animals. The present
20 invention also contemplates the control and treatment of tick borne diseases, for example, Lyme disease, canine and bovine anaplasmosis, canine ehrlichiosis, canine rickettsiosis, canine and bovine babesiosis, epizootic bovine abortion, and theileriosis. Thus, according to the invention, there is provided a compound of Formula (1)



25 wherein

A is phenyl, naphthyl, or heteroaryl where said heteroaryl contains 1 to 4 heteroatoms each independently selected from N, O and S;

R^{1a} , R^{1b} , and R^{1c} are each independently hydrogen, halo, hydroxyl, cyano, nitro, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_0 - C_3 alkyl C_3 - C_6 cycloalkyl, C_1 - C_6 haloalkoxy, $-C(O)NH_2$, $-SF_5$, or $-S(O)_pR$;

R^2 is halo, cyano, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, nitro, hydroxyl, $-C(O)NR^aR^b$,
5 C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, $-S(O)_pR$, or $-OR$;

R^3 is hydrogen, halo, hydroxyl, cyano, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_0 - C_3 alkyl C_3 - C_6 cycloalkyl, $-C(O)NH_2$, nitro, $-SC(O)R$, $-C(O)NR^aR^b$, C_0 - C_3 alkyl NR^aR^4 , $-NR^aNR^bR^4$, $-NR^aOR^b$, $-ONR^aR^b$, N_3 , $-NHR^4$, $-OR$, or $-S(O)_pR$;

R^4 is hydrogen, C_1 - C_6 alkyl, C_0 - C_6 alkyl C_3 - C_6 cycloalkyl, $-C(O)R^5$, $-C(S)R^5$,
10 $-C(O)NR^aR^5$, $-C(O)C(O)NR^aR^5$, $-S(O)_pR^c$, $-S(O)_2NR^aR^5$, $-C(NR^7)R^5$, $-C(NR^7)NR^aR^5$, C_0 - C_6 alkylphenyl, C_0 - C_6 alkylheteroaryl, or C_0 - C_6 alkylheterocycle;

R^5 is hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_0 - C_6 alkyl C_3 - C_6 cycloalkyl, C_0 - C_6 alkylphenyl, C_0 - C_6 alkylheteroaryl, or C_0 - C_6 alkylheterocycle;

R^6 is cyano, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, $-C(O)NR^aR^b$, C_2 - C_6 alkenyl,
15 C_2 - C_6 alkynyl, C_2 - C_6 haloalkenyl, or C_2 - C_6 haloalkynyl;

R^7 is hydrogen, C_1 - C_6 alkyl, hydroxyl, cyano, nitro, $-S(O)_pR^c$, or C_1 - C_6 alkoxy;

R is C_1 - C_6 alkyl or C_3 - C_6 cycloalkyl each optionally substituted by at least one halo;

R^a is hydrogen, C_1 - C_6 alkyl, or C_0 - C_3 alkyl C_3 - C_6 cycloalkyl; wherein the alkyl and alkylcycloalkyl is optionally substituted by cyano or at least one halo substituent;
20

R^b is hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_0 - C_3 alkylphenyl, C_0 - C_3 alkylheteroaryl, or C_0 - C_3 alkylheterocycle, each optionally substituted,
25 where chemically possible, with at least one substituent selected from hydroxyl, cyano, halo, or $-S(O)_pR$;

R^c is C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkyl C_3 - C_6 cycloalkyl, C_0 - C_3 alkyl C_3 - C_6 cycloalkyl, C_0 - C_3 alkylphenyl, C_0 - C_3 alkylheteroaryl, or C_0 - C_3 alkylheterocycle each optionally substituted with at least one substituent
30 selected from cyano, halo, hydroxyl, oxo, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, C_1 - C_6 haloalkyl, $-S(O)_pR$, $-SH$, $-S(O)_pNR^aR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$, $-SC(O)R^b$, $-SCN$, or $-C(O)NR^aR^b$;

each of R^4 and R^5 C_1 - C_6 alkyl or C_0 - C_6 alkyl C_3 - C_6 cycloalkyl can be optionally and independently substituted by at least one substituent selected

from C₁-C₆alkyl, cyano, halo, hydroxyl, C₁-C₆hydroxyalkyl, oxo, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₁-C₆alkyl, C₁-C₆haloalkyl, -S(O)_pR^c, -SH, -S(O)_pNR^aR^b, -NR^aR^b, -NR^aC(O)R^b, -SC(O)R^c, -SCN, or -C(O)NR^aR^b; and

wherein R⁴ and R⁵ C₀-C₆alkylphenyl, C₀-C₆alkylheteroaryl, or

- 5 C₀-C₆alkylheterocycle moiety can be further optionally substituted with at least one substituent selected from C₁-C₆alkyl, cyano, halo, oxo, =S, =NR⁷, hydroxyl, C₁-C₆hydroxyalkyl, C₁-C₆alkoxy, C₁-C₆alkyl, C₁-C₆haloalkyl, -SH, -S(O)_pR, and C₁-C₆haloalkoxy;

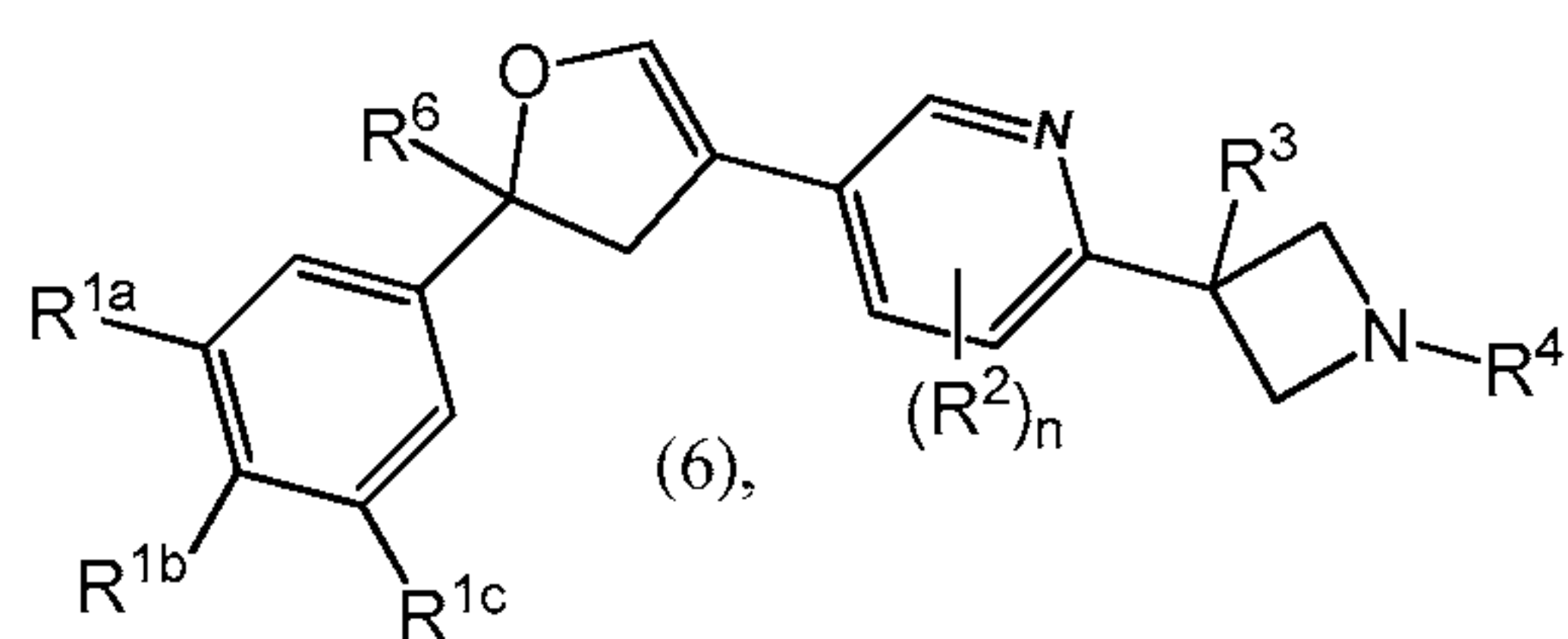
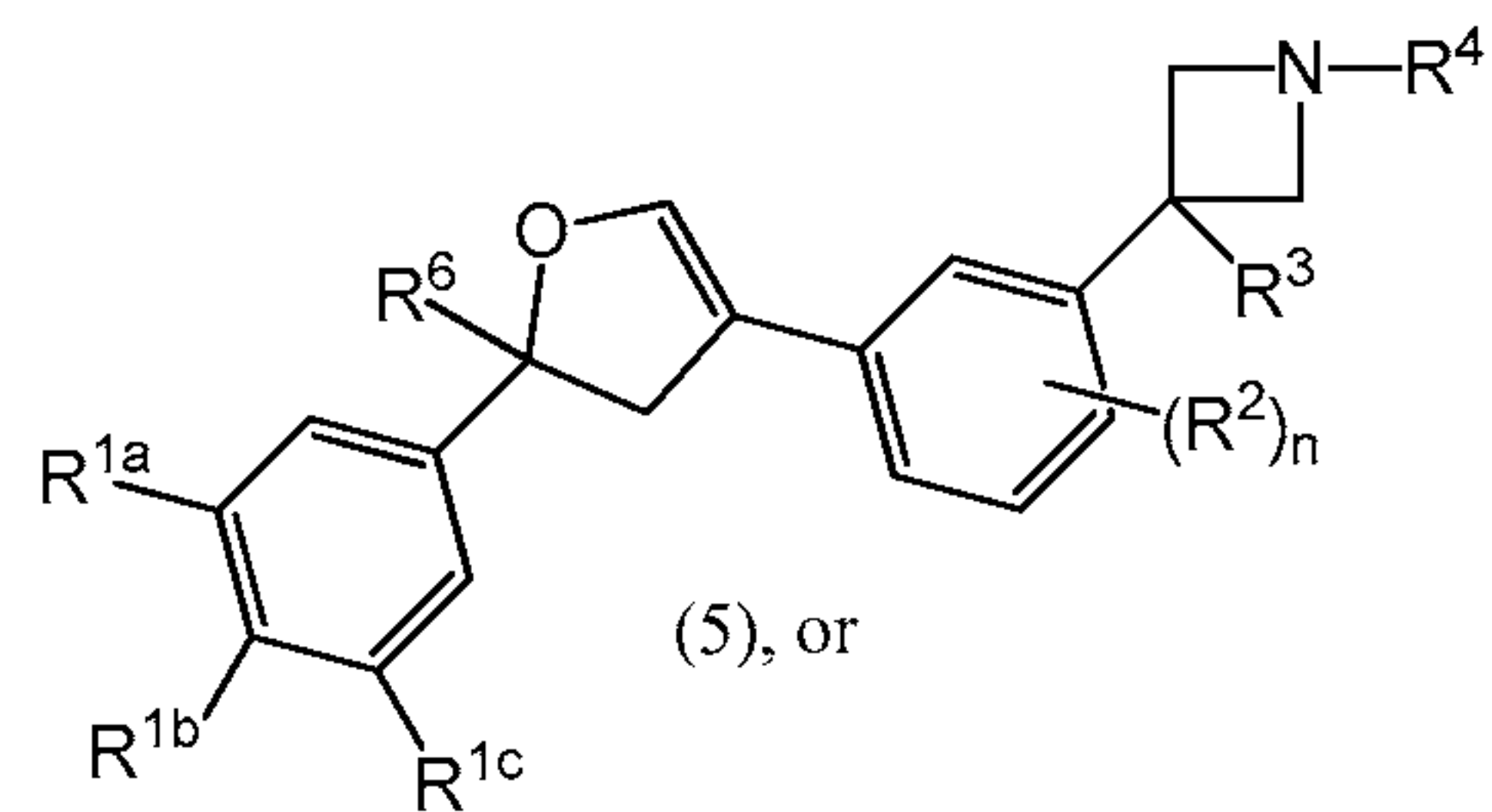
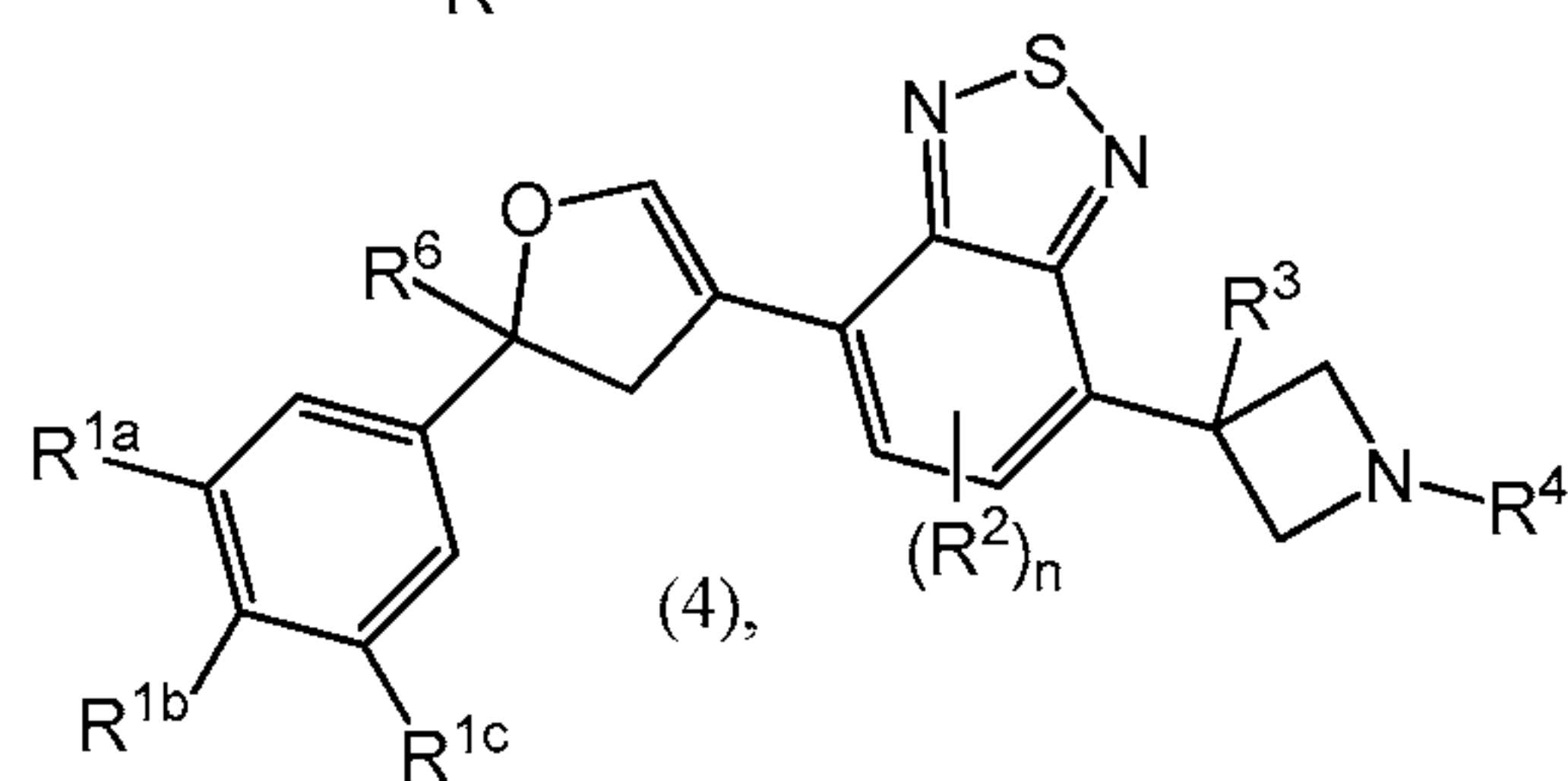
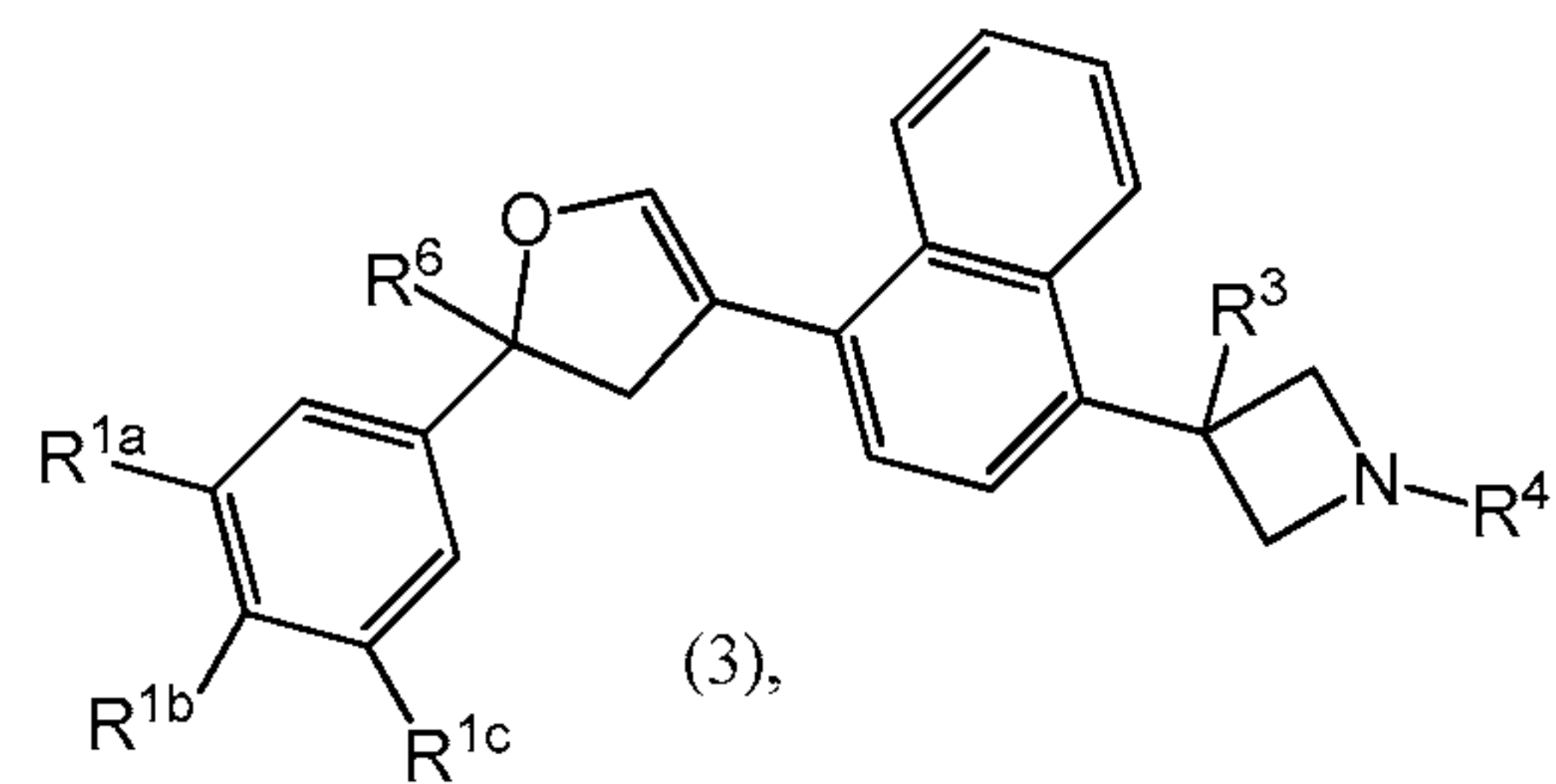
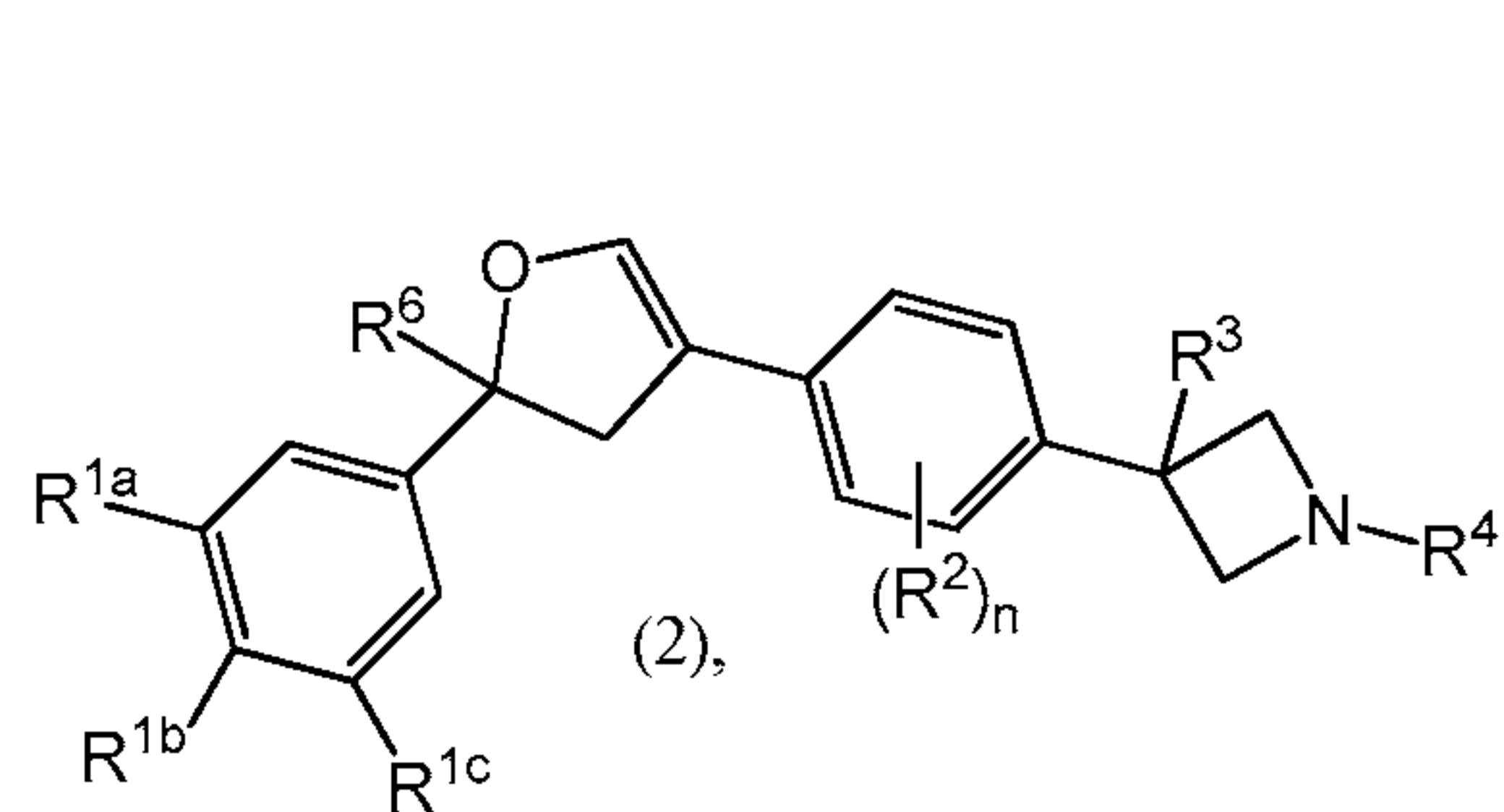
- 10 n is the integer 0, 1, or 2, and when n is 2, each R² may be identical or different from each other; and

p is the integer 0, 1, or 2;

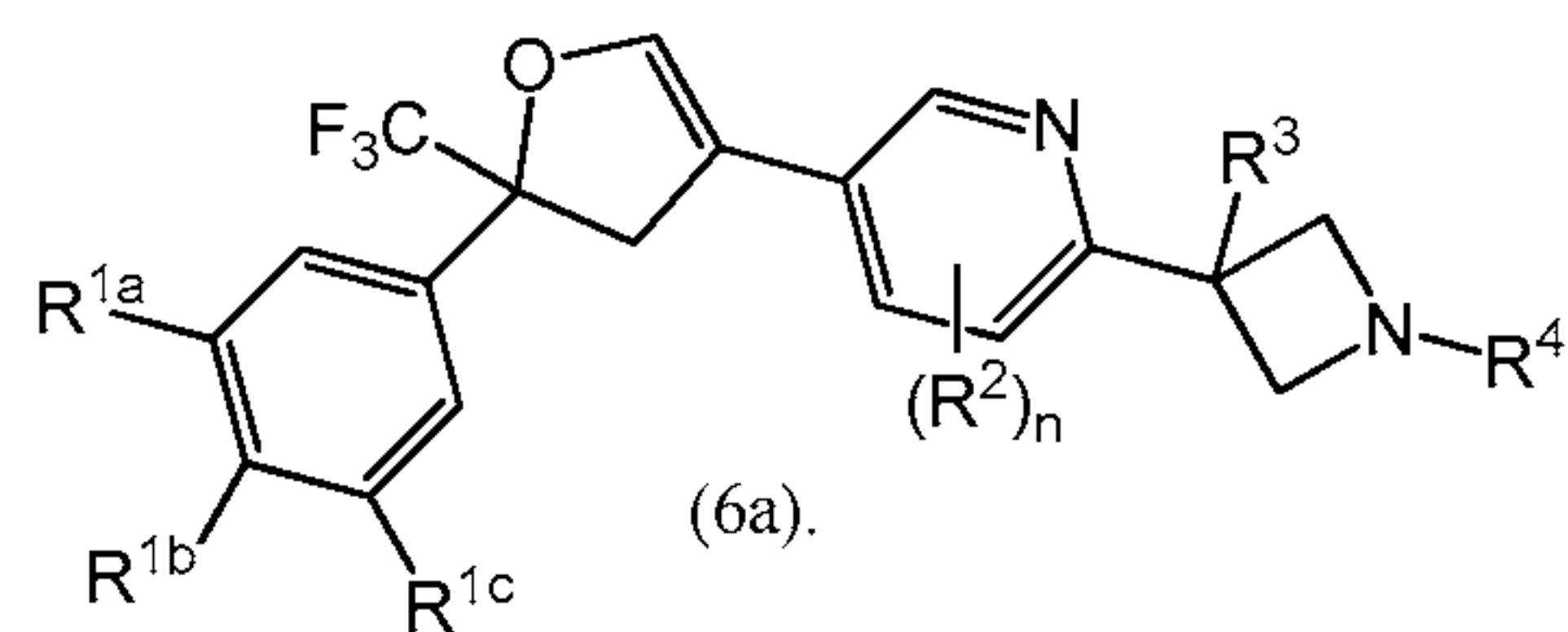
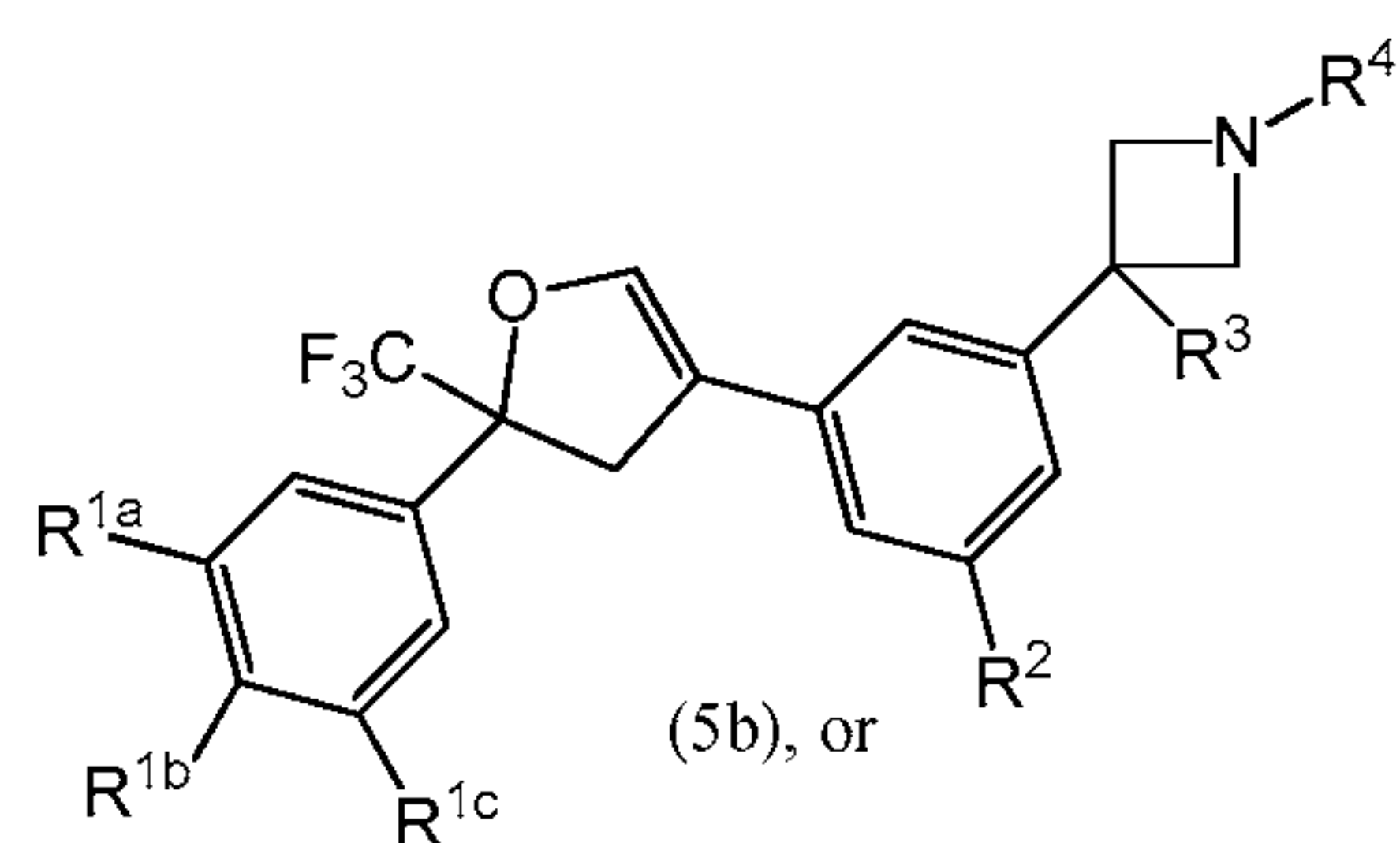
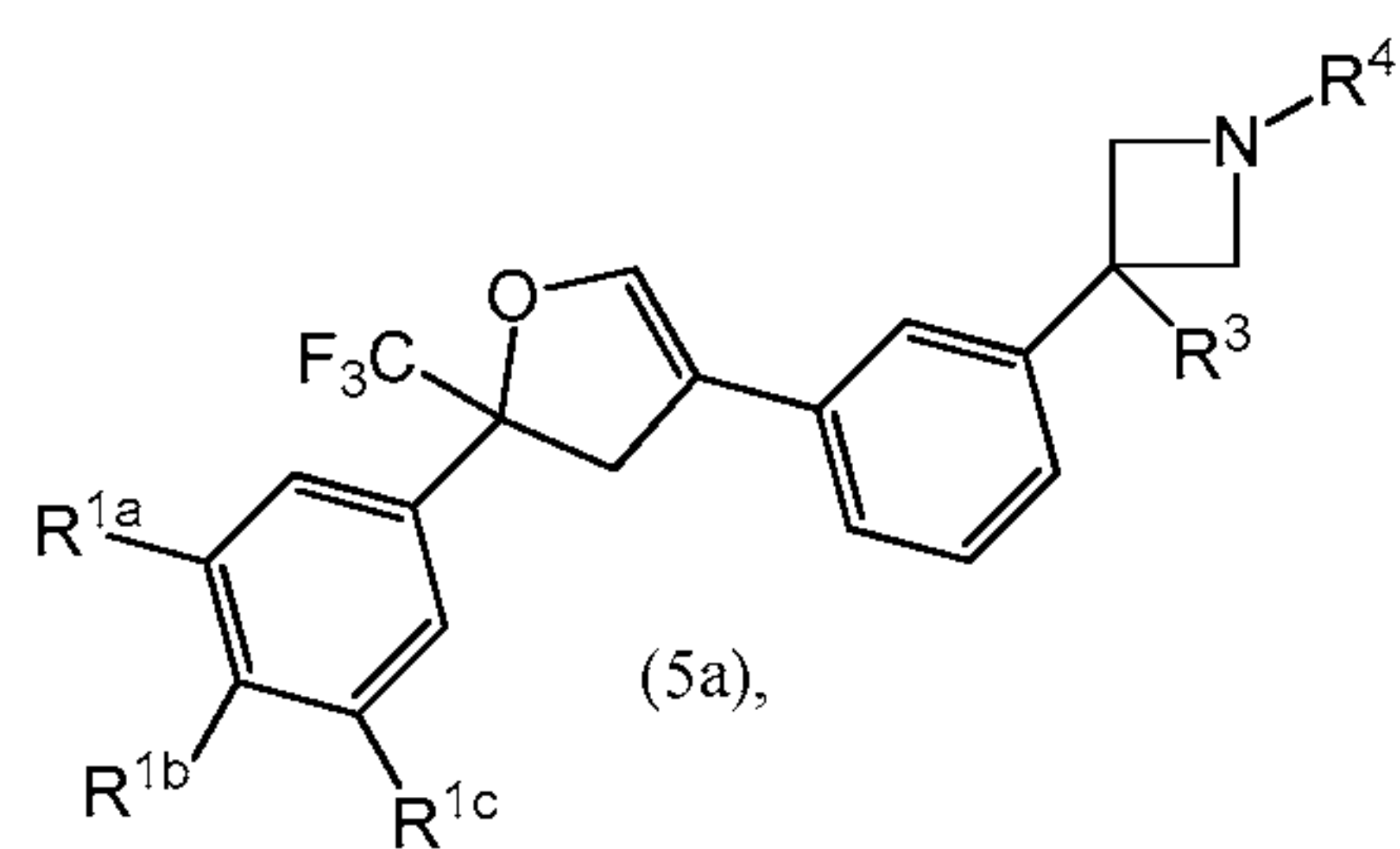
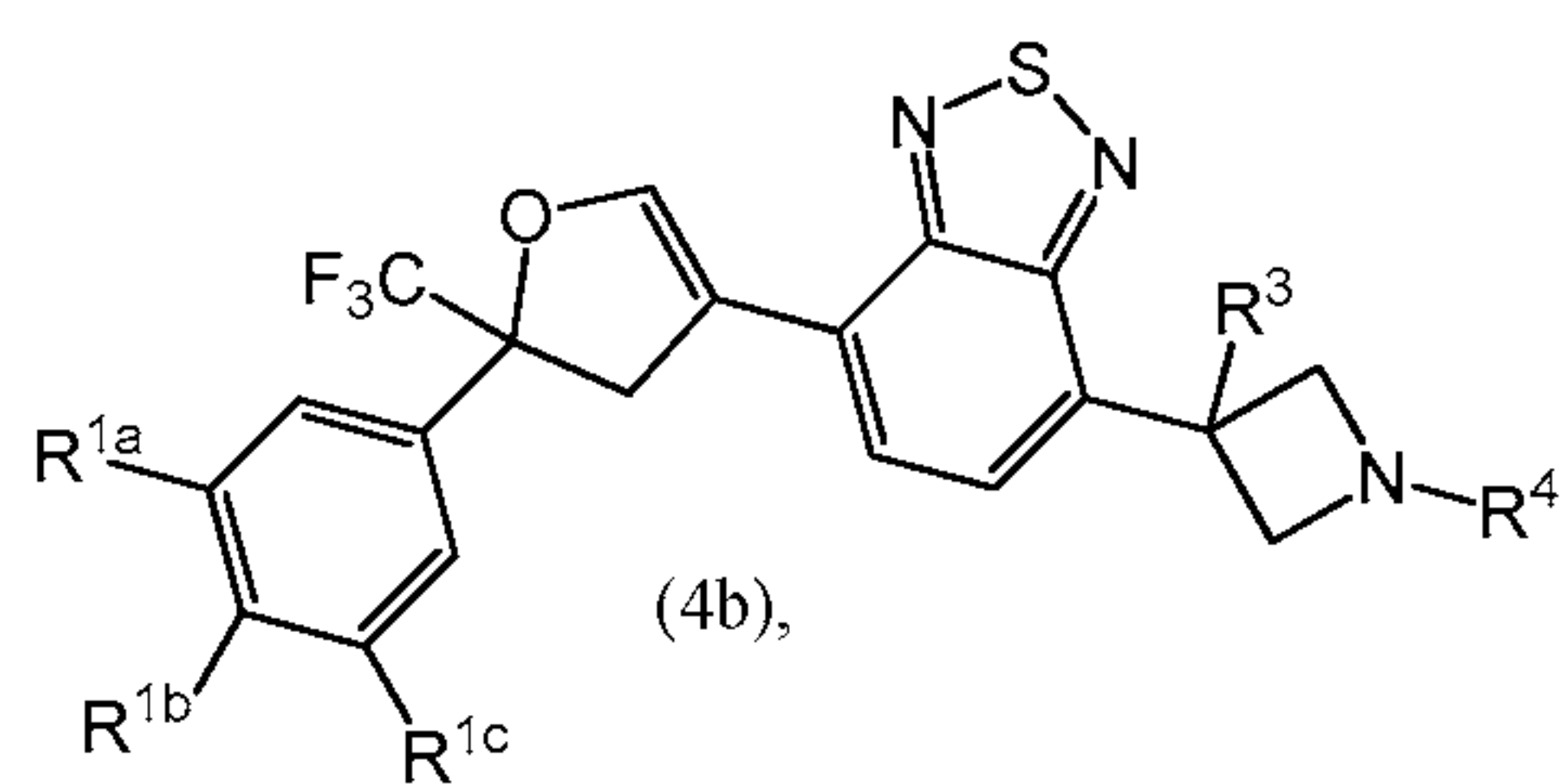
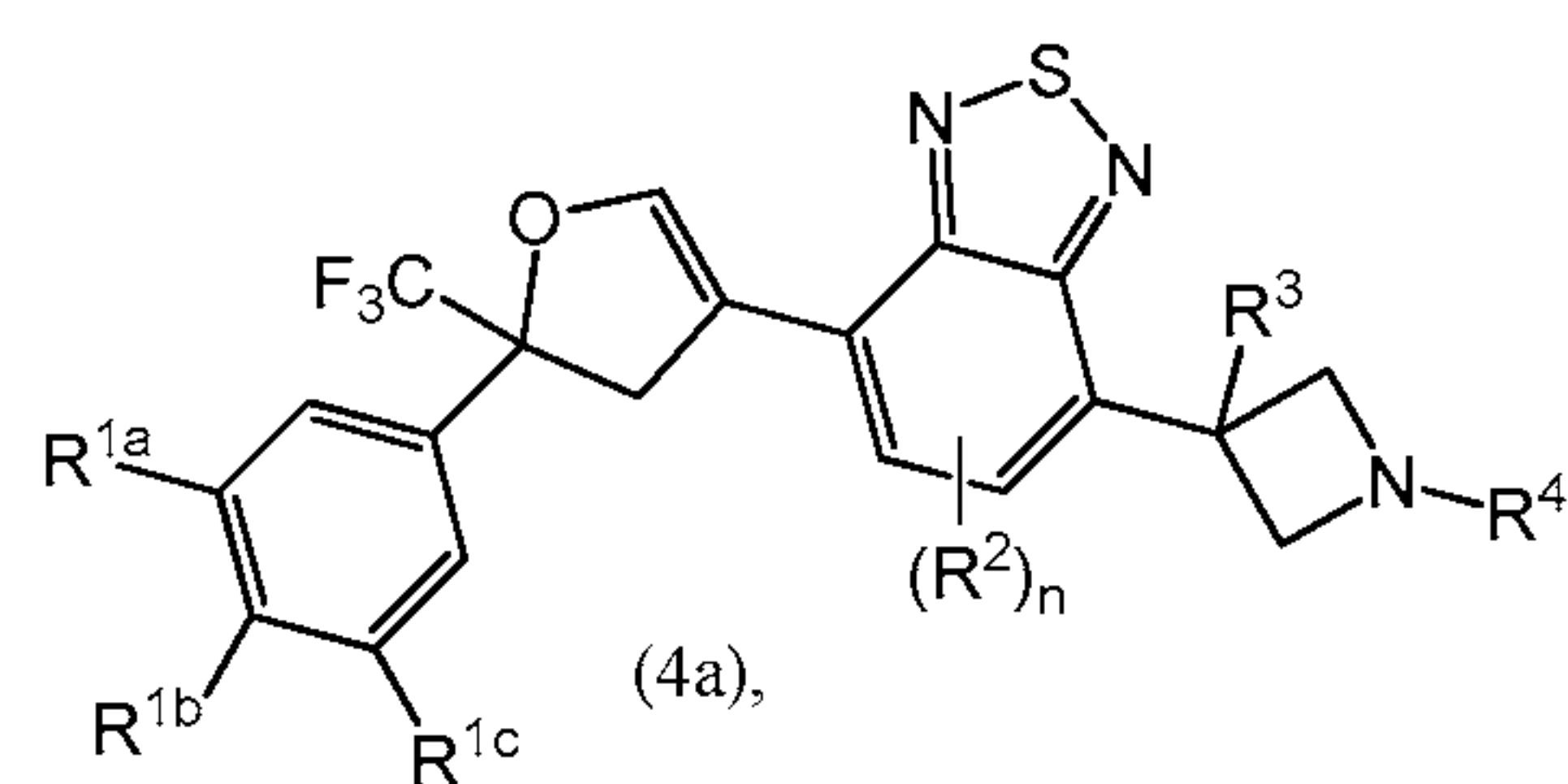
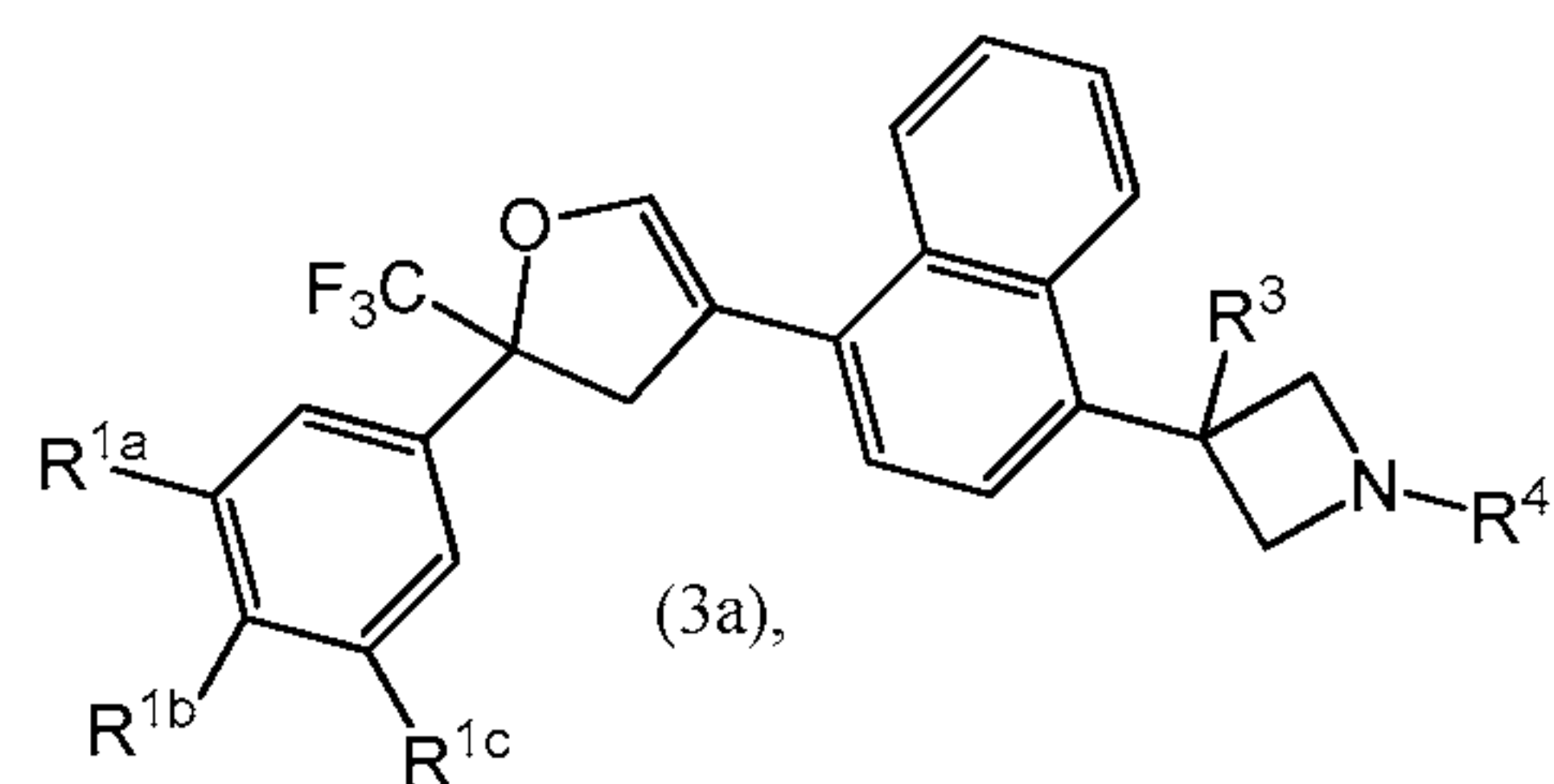
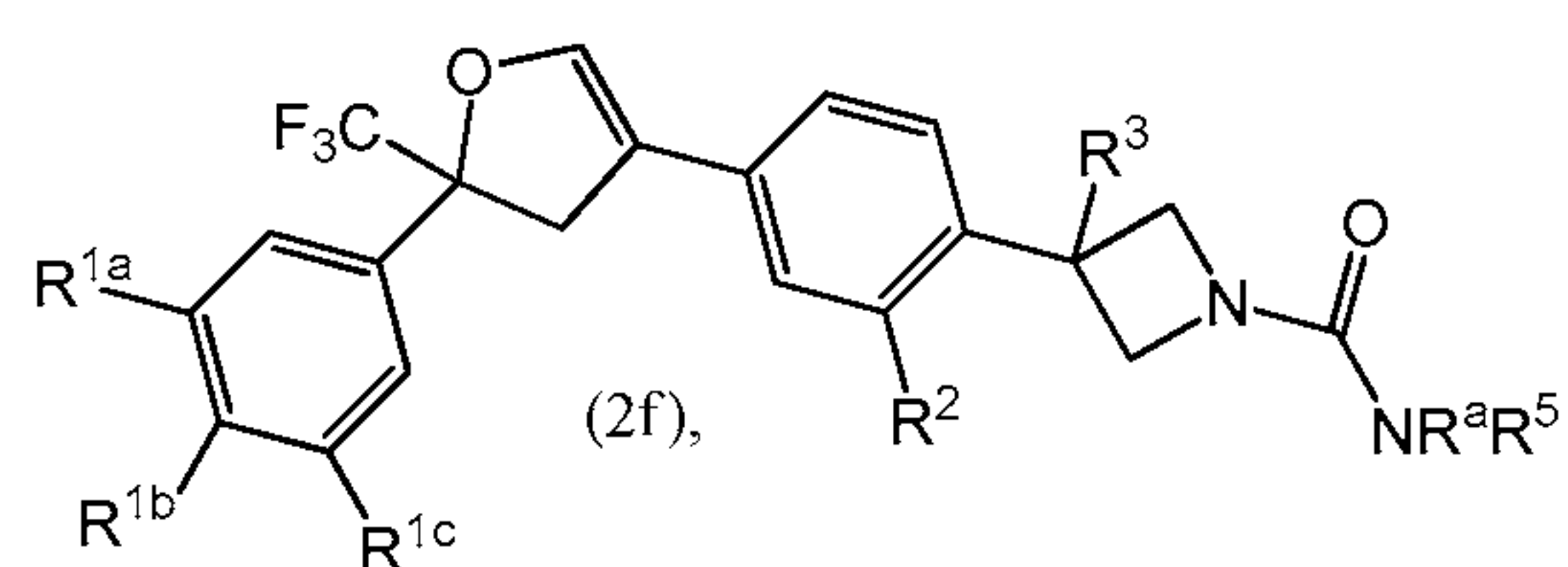
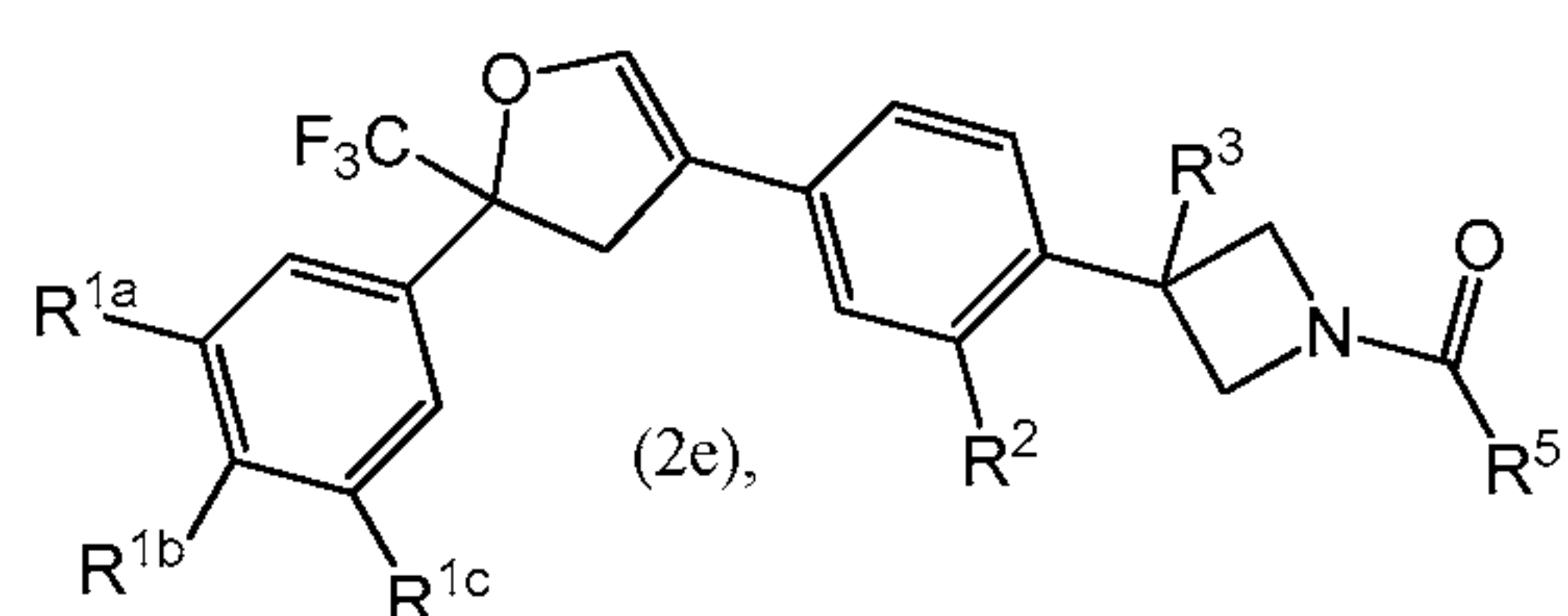
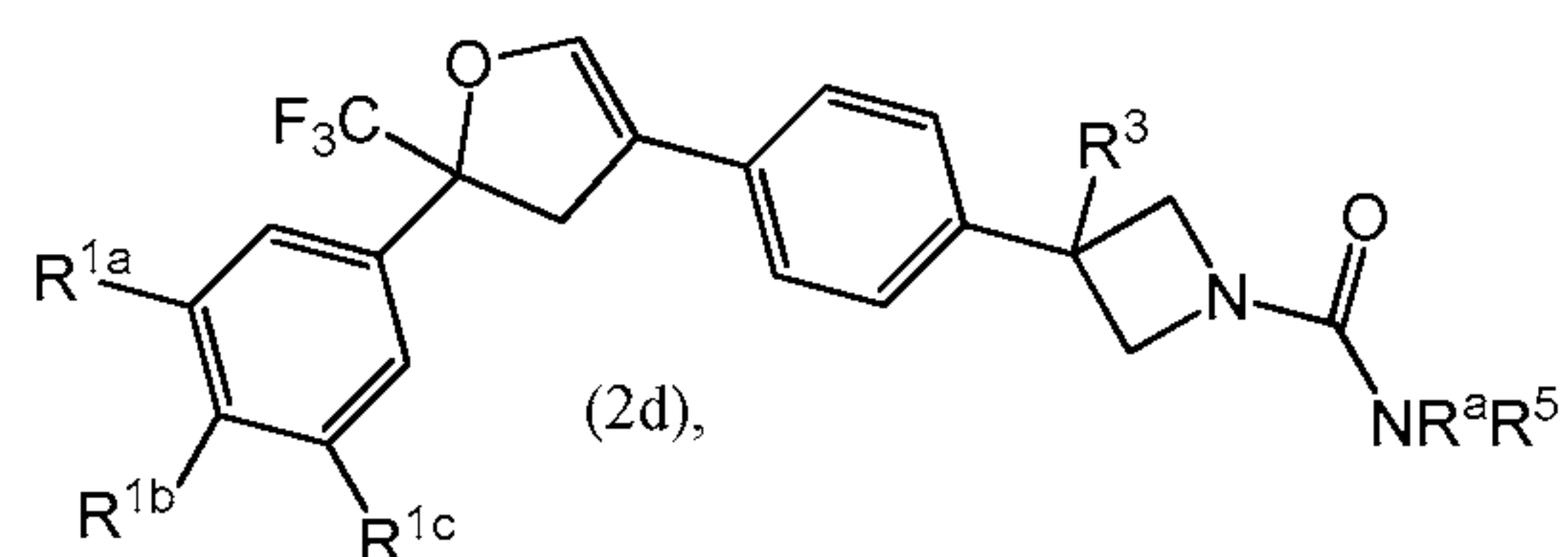
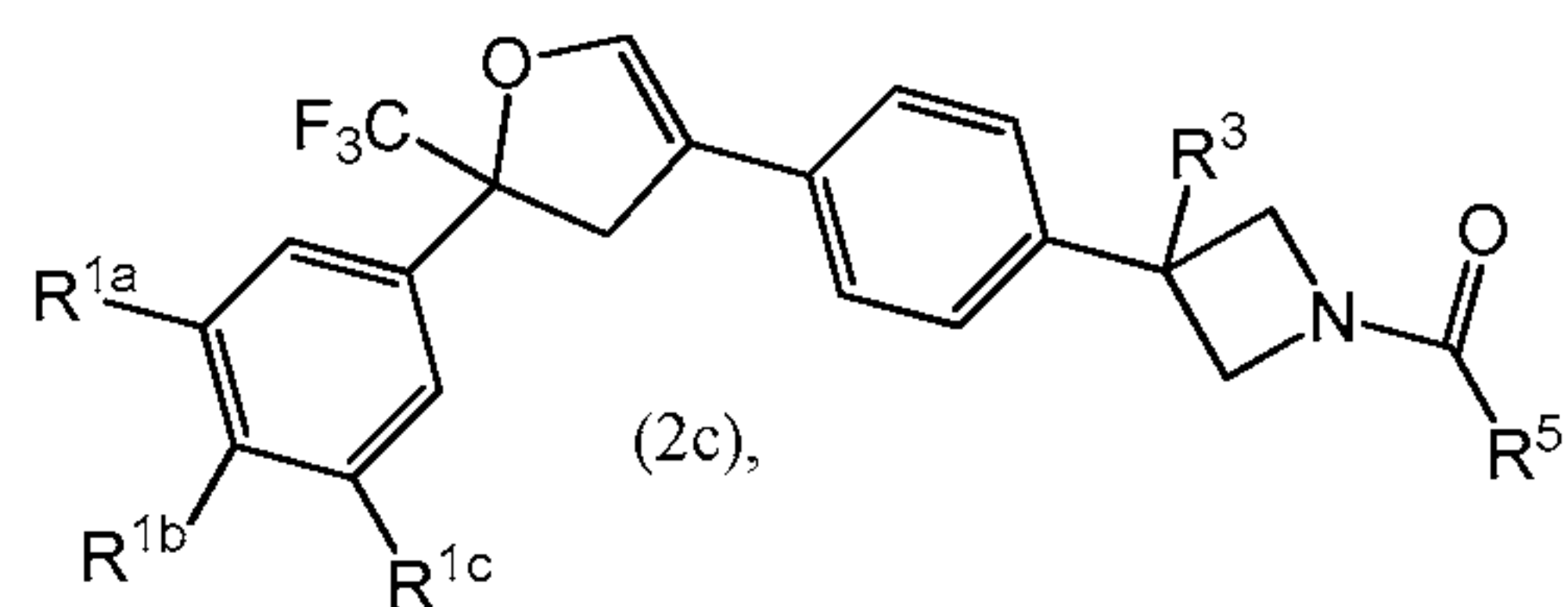
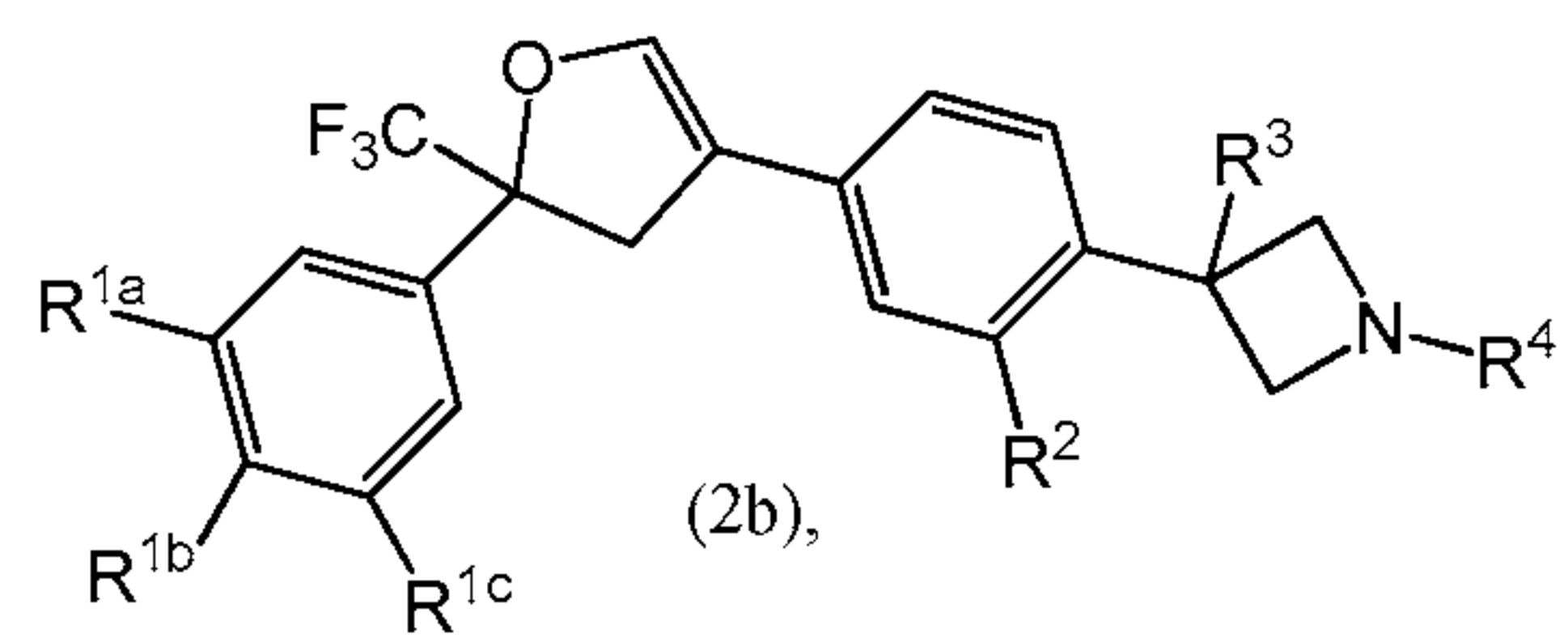
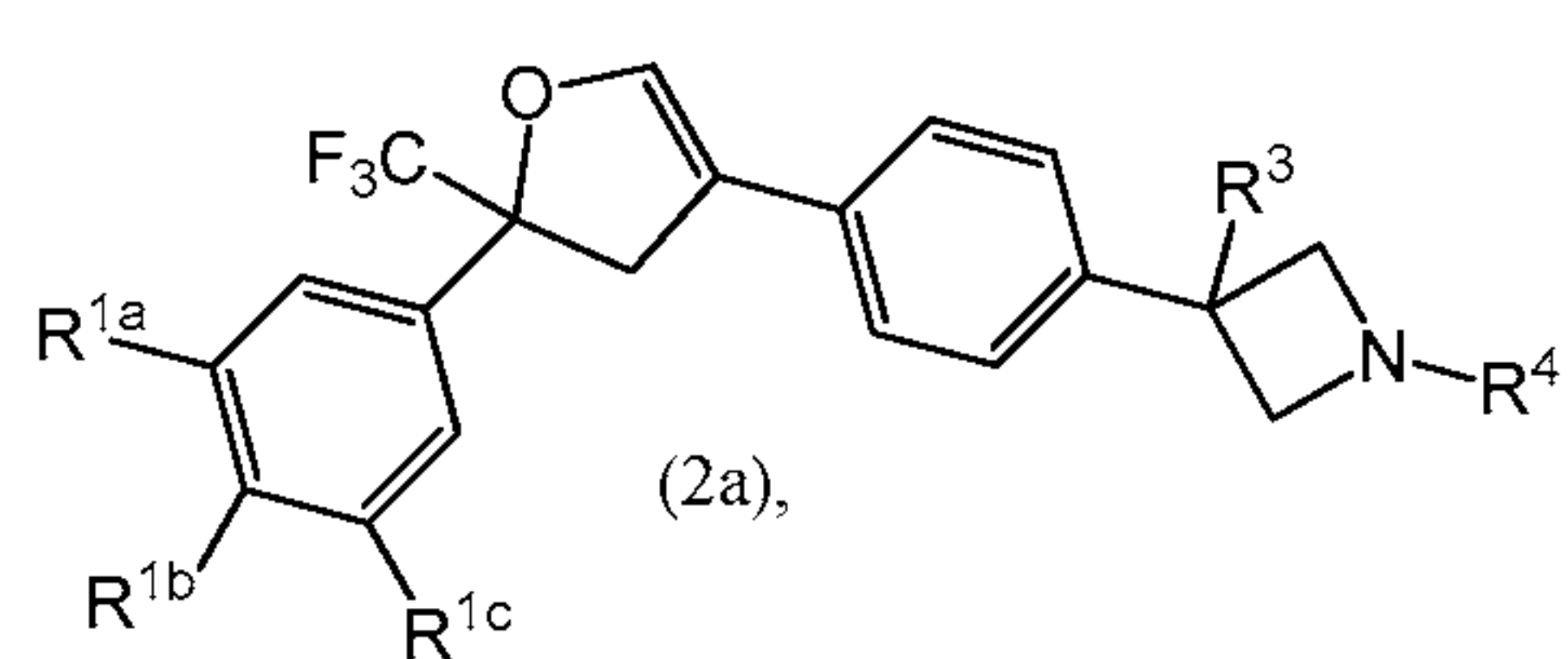
stereoisomers thereof, and pharmaceutically or veterinarily acceptable salts thereof.

- In another aspect of the invention, A is phenyl, naphthyl, pyridinyl, 15 pyrimidinyl, pyrazolyl, imidazolyl pyrrolyl, furanyl, thiophenyl, triazolyl, tetrazolyl, thiazolyl, isoxazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, pyridazinyl, pyrazinyl, benzofuranyl, benzothiophenyl, indolyl, benzimidazolyl, indazolyl, benzotriazolyl, thieno[2,3-c]pyridine, thieno[3,2-b]pyridine, and benzo[1,2,5]thiadiazole. In another aspect of the invention, A is phenyl, naphthyl, pyridinyl, pyrimidinyl, 20 pyrazolyl, triazolyl, tetrazolyl, thiazolyl, isoxazolyl, benzofuranyl, benzothiophenyl, indolyl, and benzo[1,2,5]thiadiazole. In another aspect of the invention, A is phenyl, naphthyl, pyridinyl, pyrazolyl, triazolyl, isoxazolyl, benzofuranyl, and benzo[1,2,5]thiadiazole. In another aspect of the invention, A is phenyl, naphthyl, pyridinyl, pyrazolyl, and benzo[1,2,5]thiadiazole. In another 25 aspect of the invention, A is phenyl, pyridinyl, naphthyl, or benzo[1,2,5]thiadiazole. In another aspect of the invention A is phenyl or pyridinyl. In another aspect of the invention A is phenyl. In another aspect of the invention A is pyridinyl. In another aspect of the invention, A is naphthyl. In yet another aspect of the invention, A is benzo[1,2,5]thiadiazole.

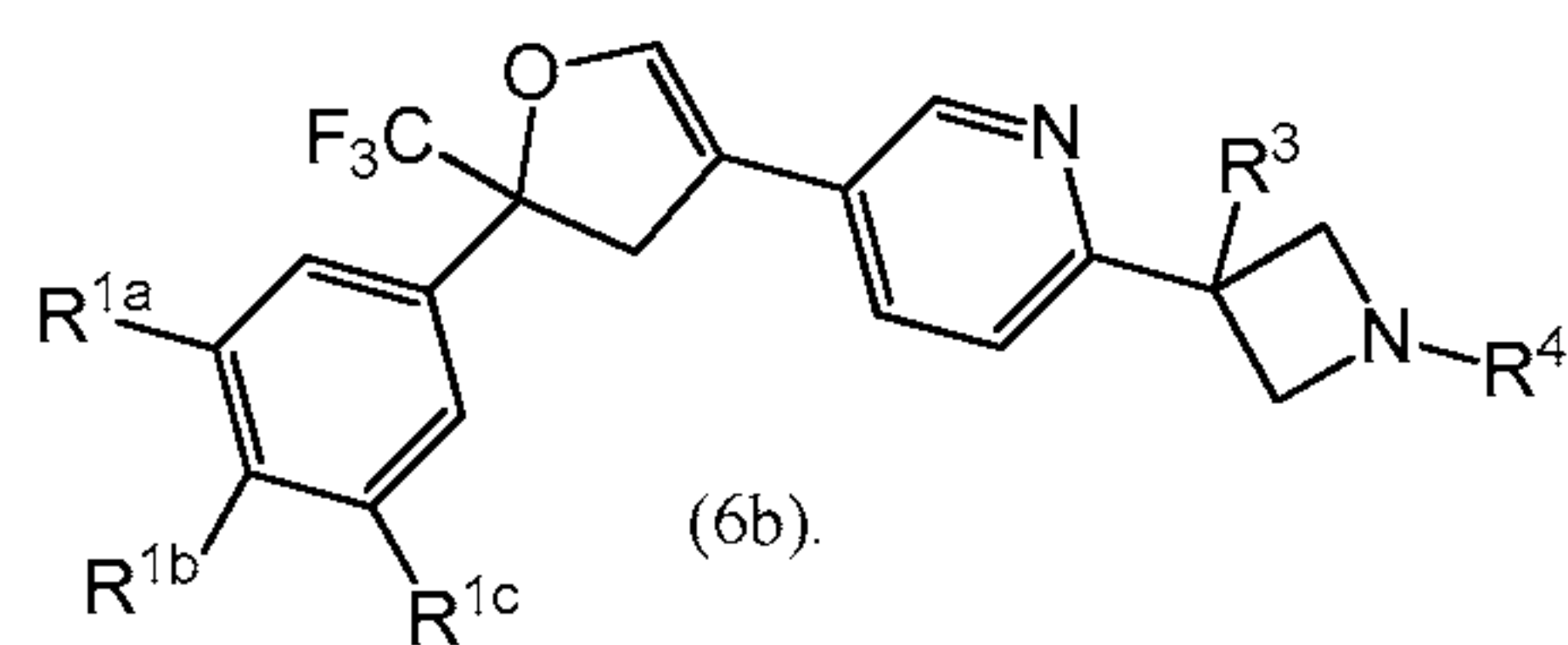
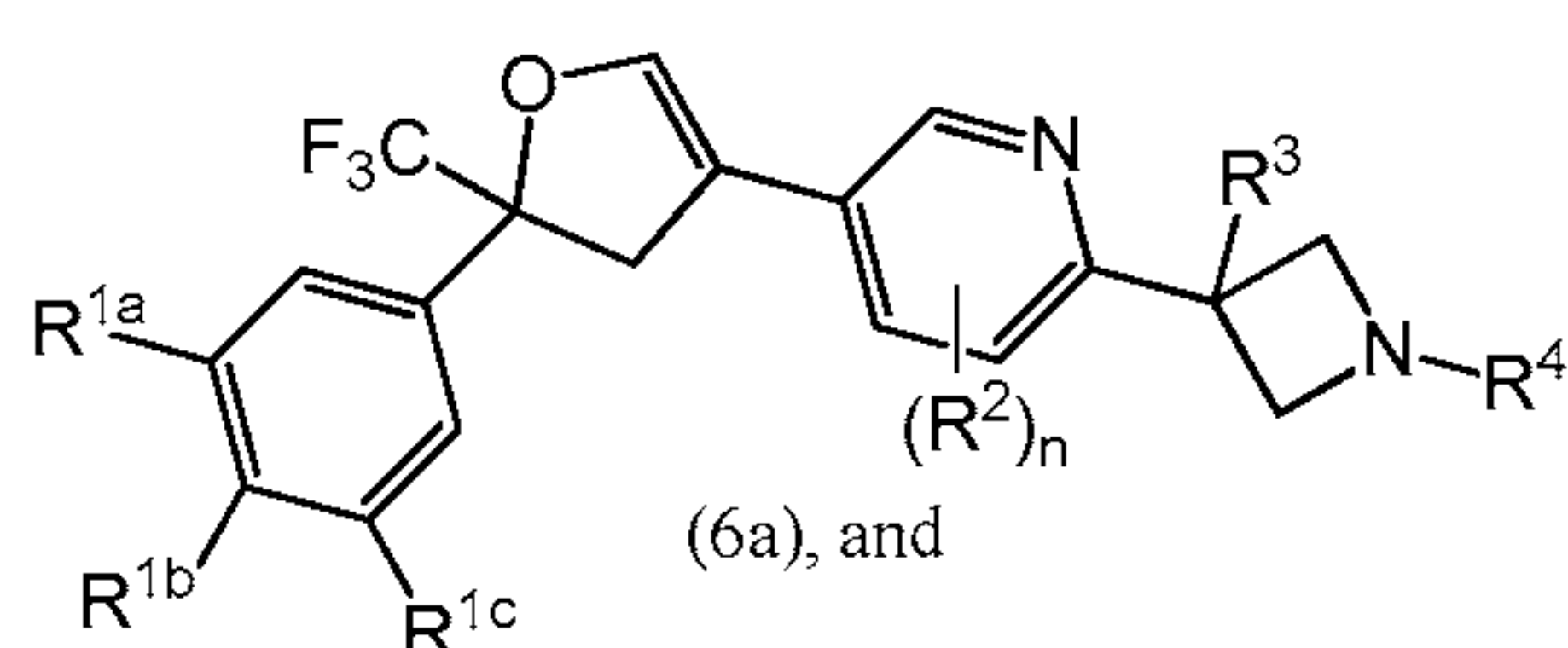
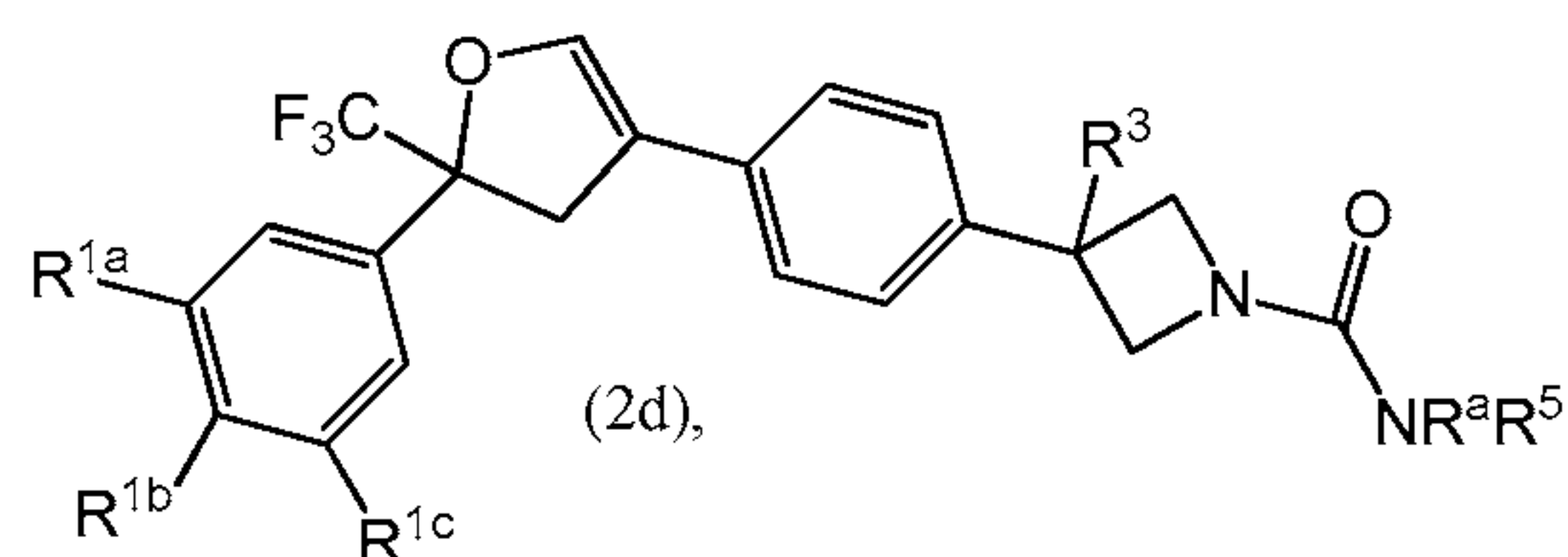
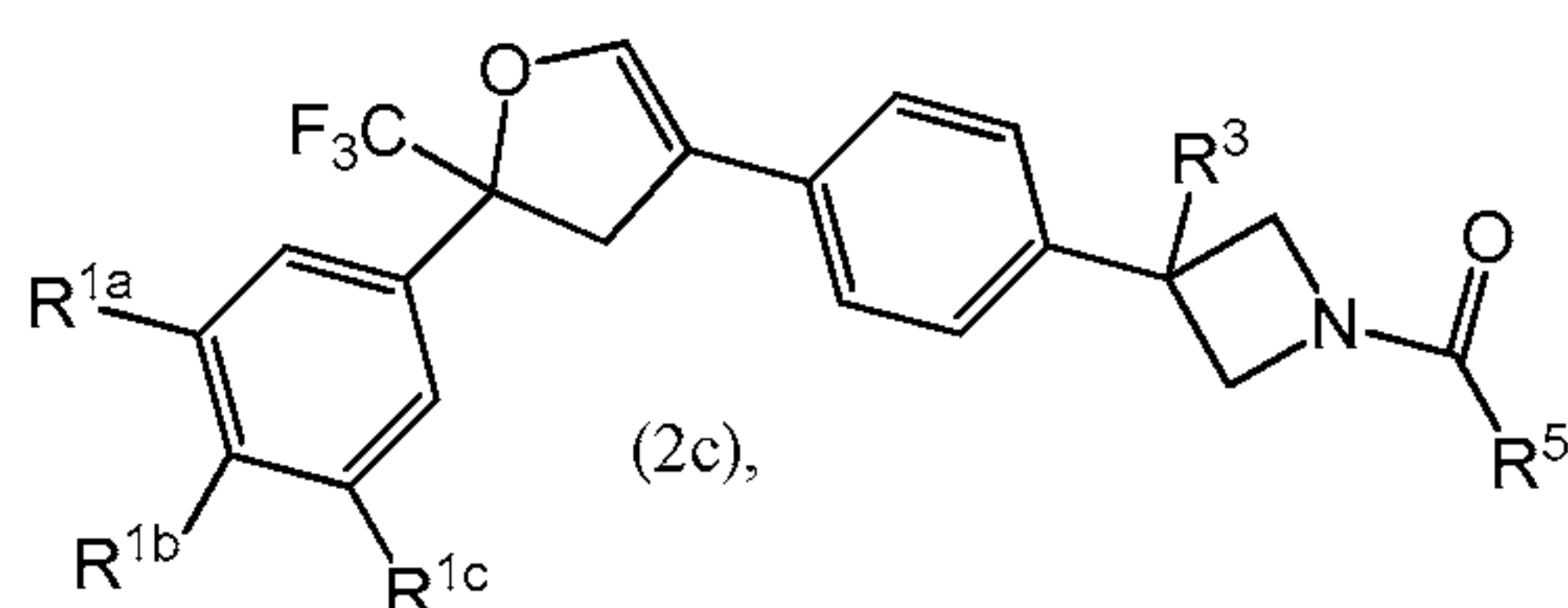
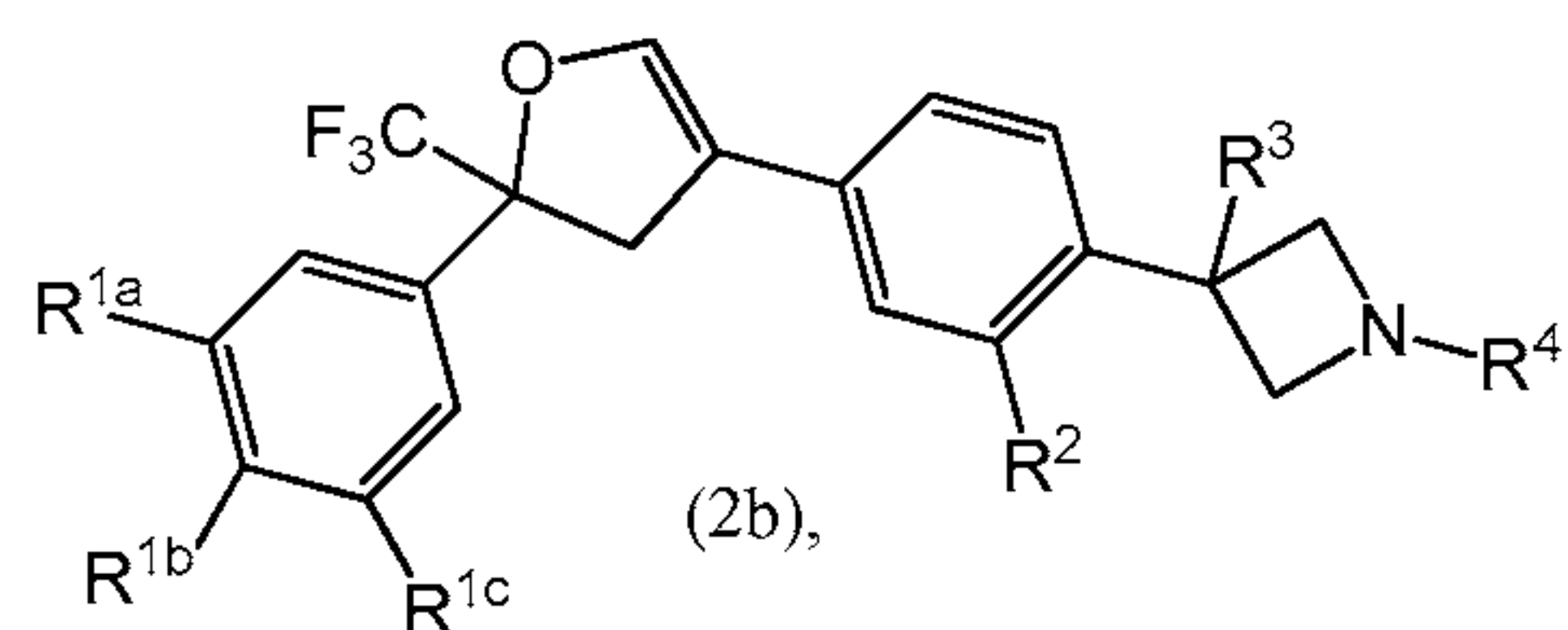
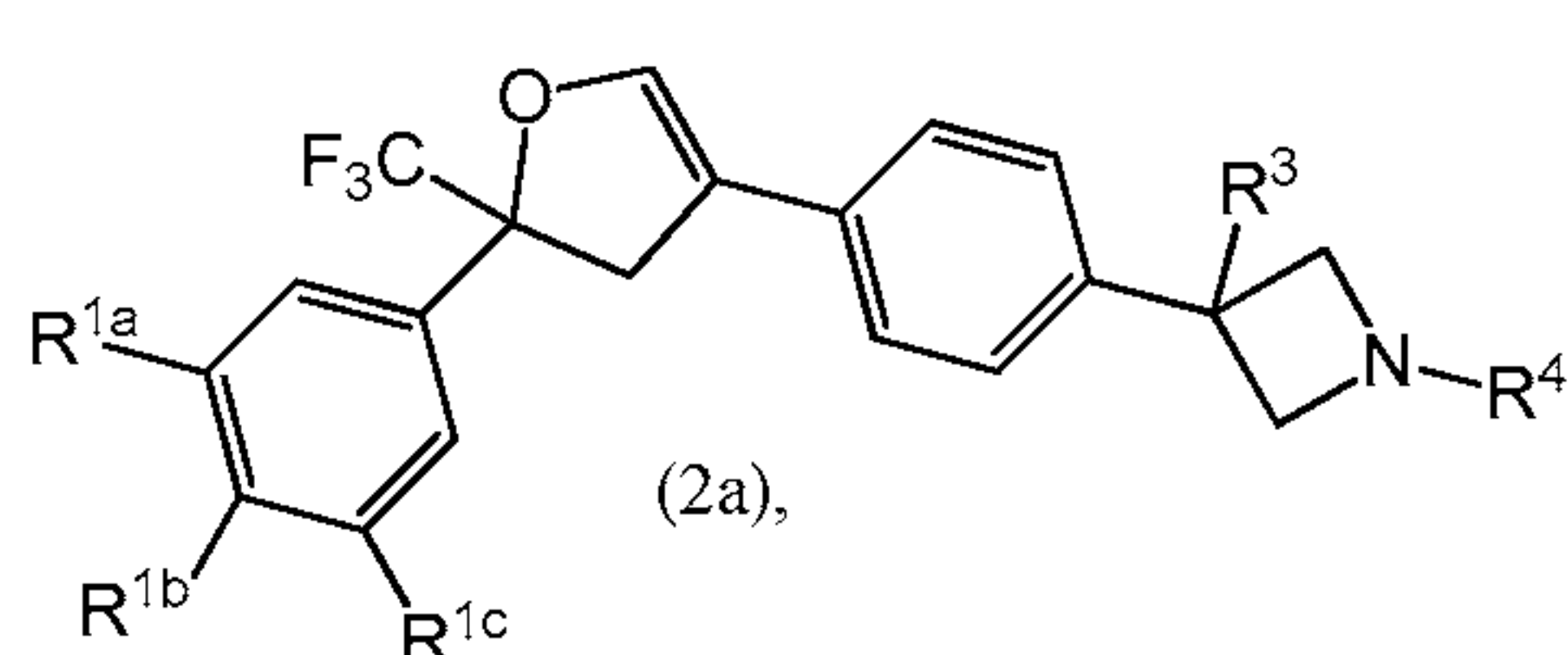
- 30 In another aspect of the invention are compounds of Formula (2), (3), (4), (5), and (6)



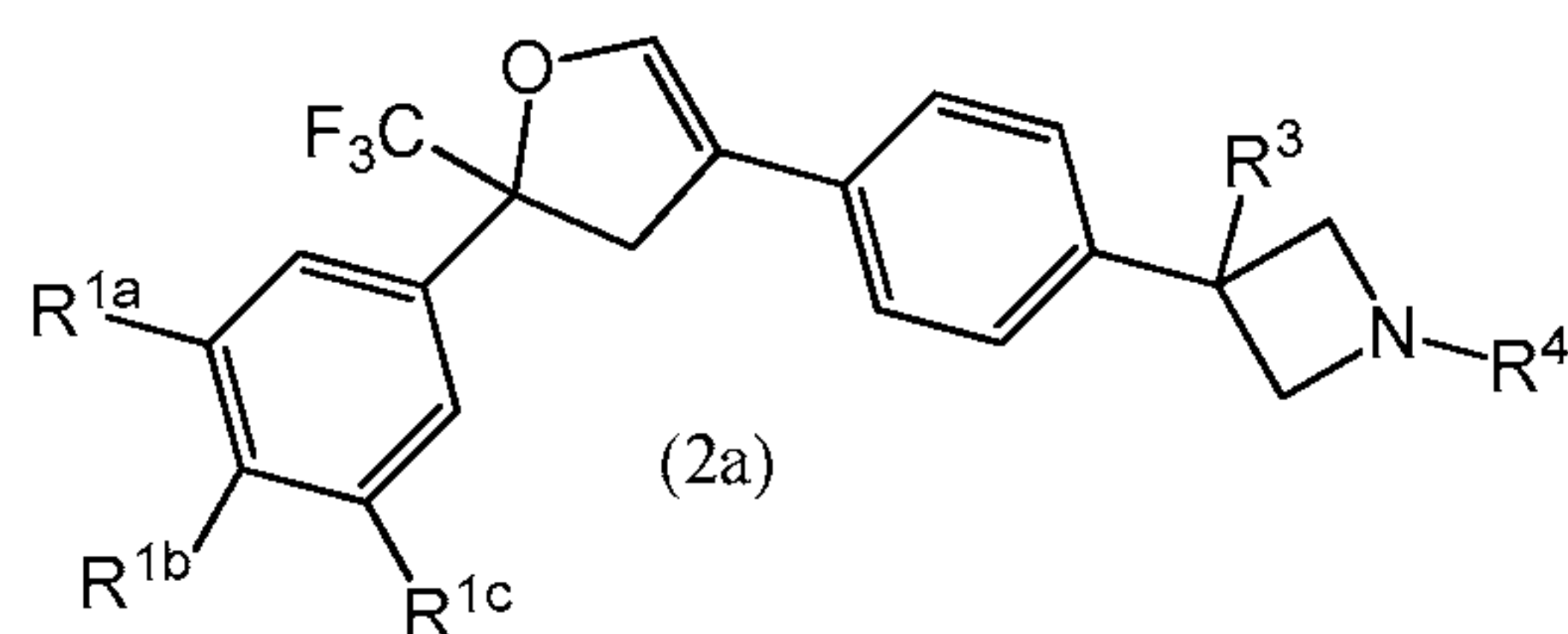
In yet another aspect of the invention are compounds of Formula (2a), (2b), (2c), (2d), (2e), (2f), (3a), (4a), (4b), (5a), (6a), and (6b).



In yet another aspect of the invention are compounds of Formula (2a), (2b), (2c), (2d), (6a), and (6b).

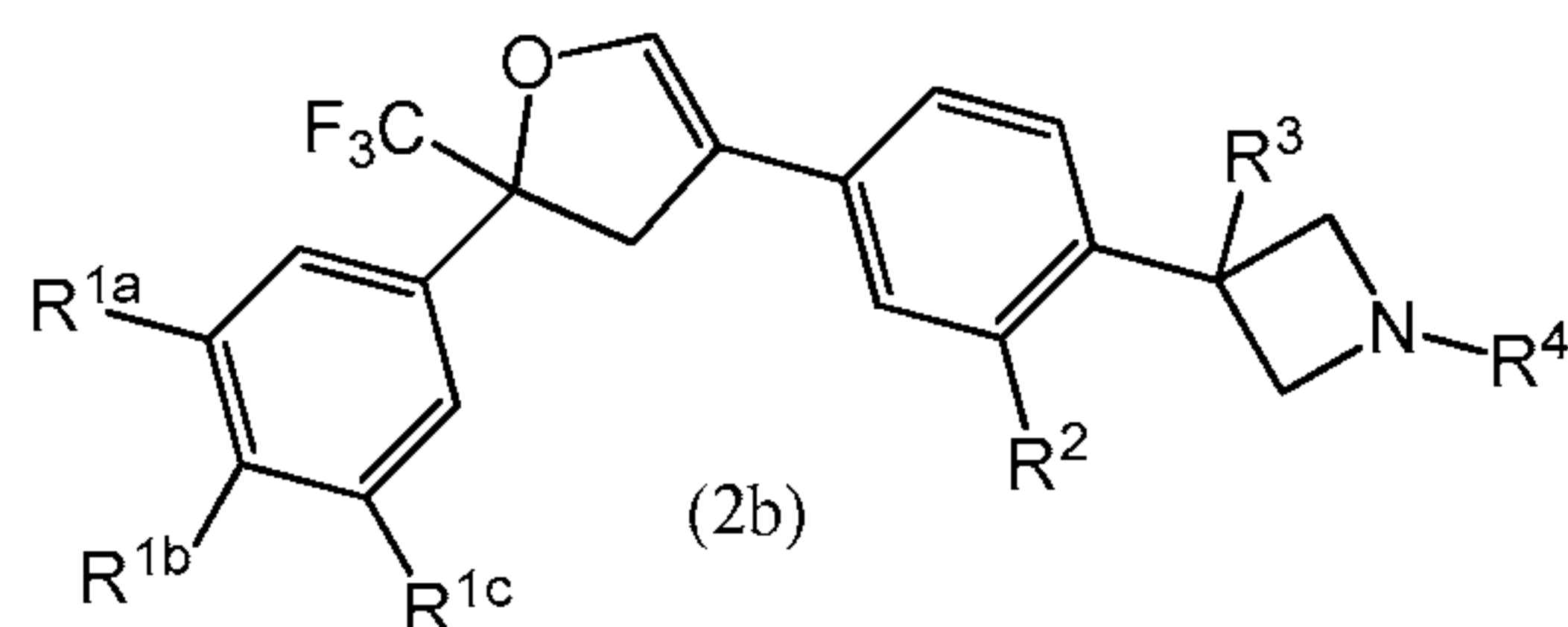


In yet another aspect of the invention are compounds of Formula (2a).

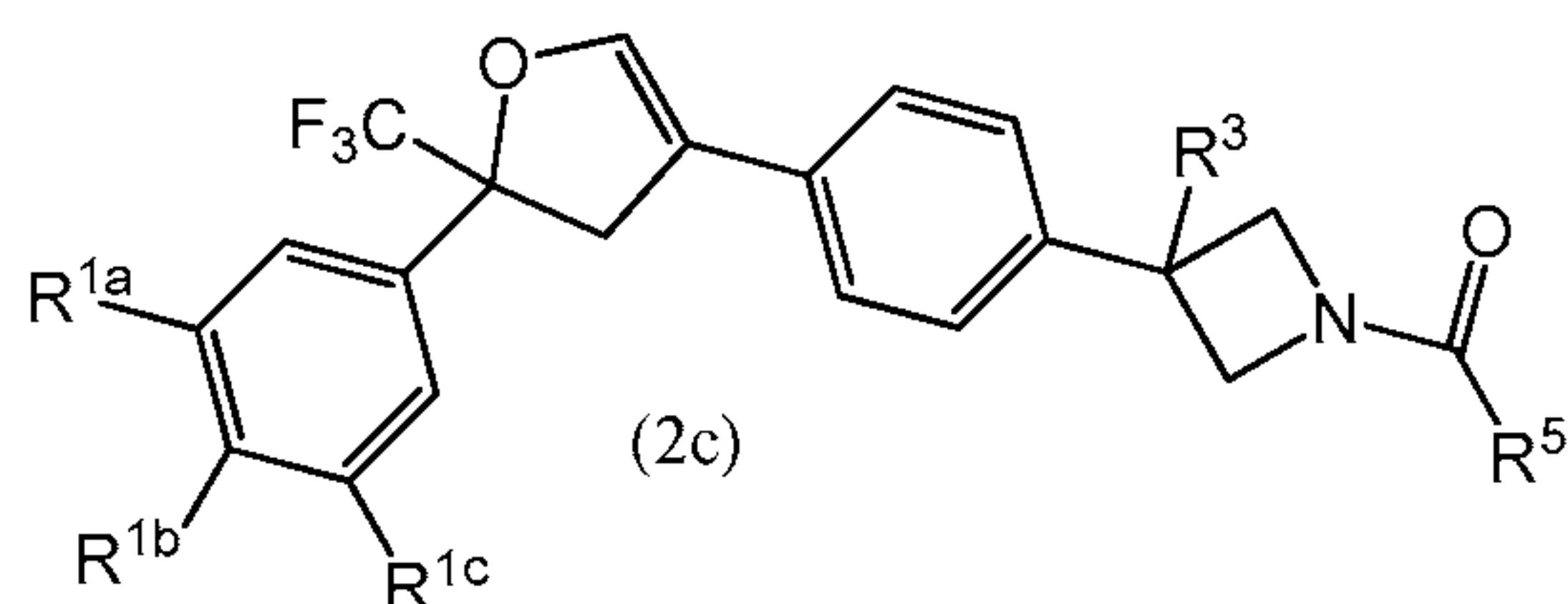


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In yet another aspect of the invention are compounds of Formula (2b).



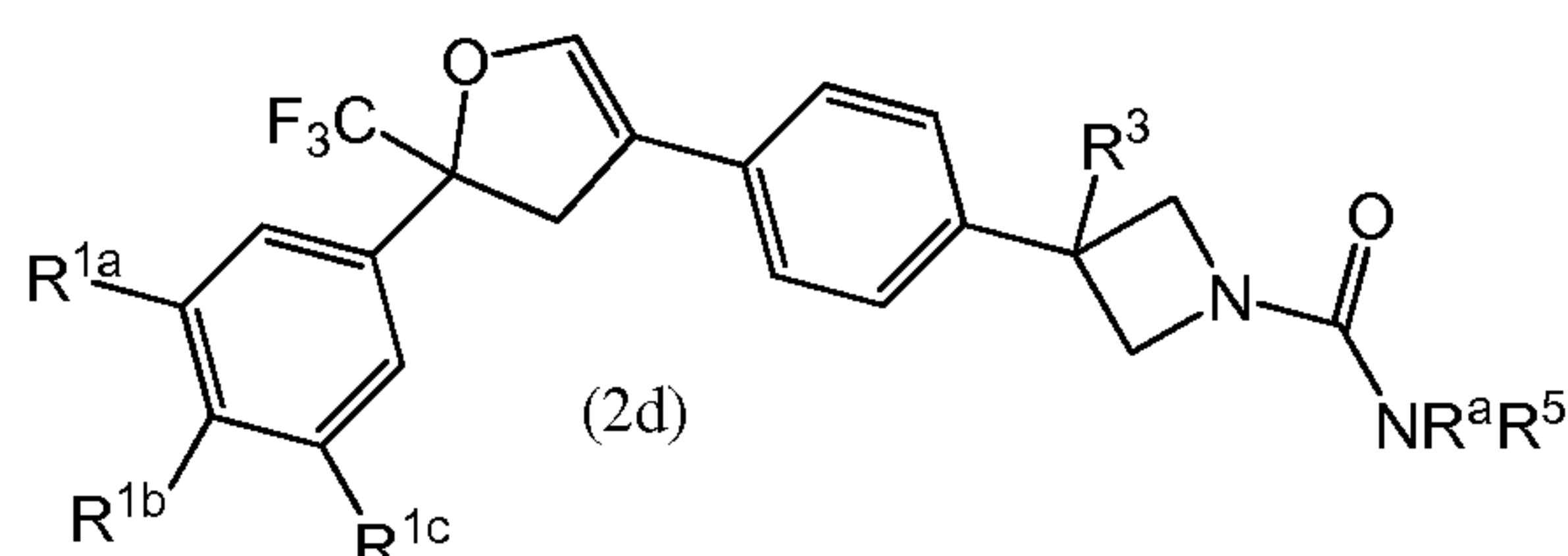
In yet another aspect of the invention are compounds of Formula (2c).



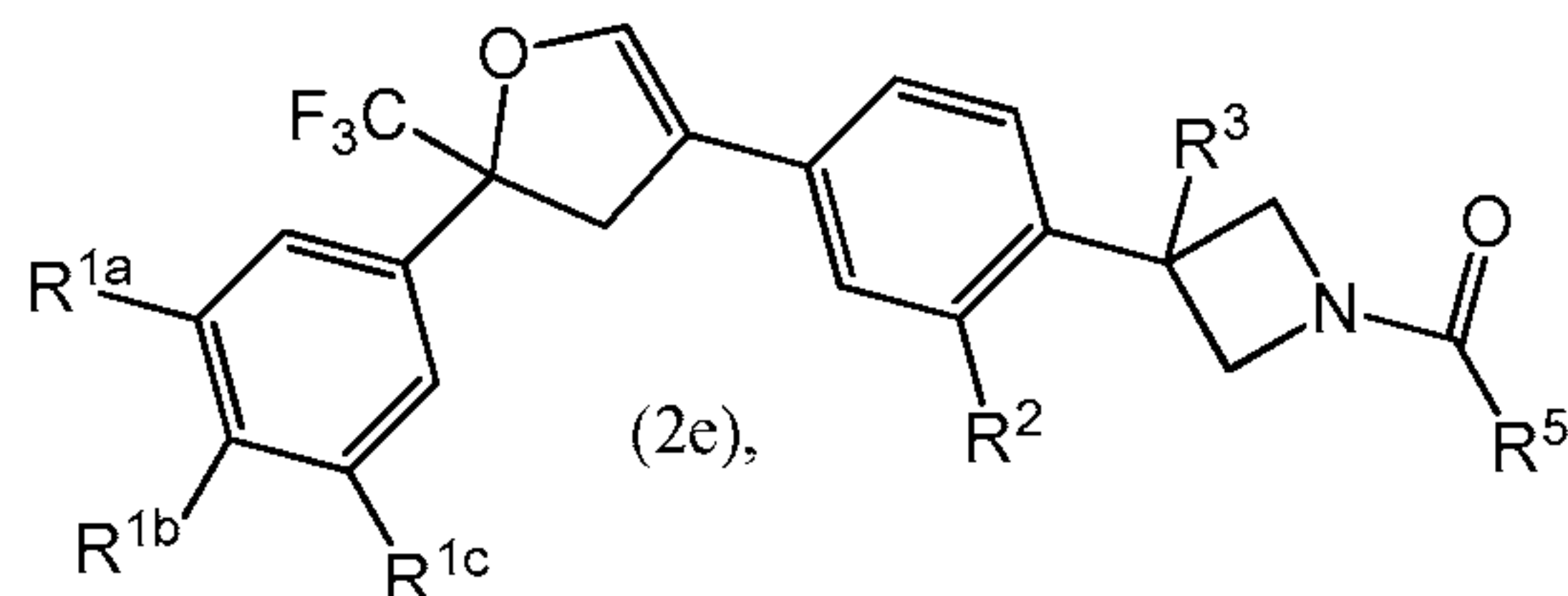
10 In yet another aspect of the invention are Formula (2c) compounds selected from 1-(3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydrofuran-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylsulfonyl)ethanone;

- 1-(3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydrofuran-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropan-1-one;
- 1-(3-{4-[5-(3,4,5-trichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-furan-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-2-methanesulfonyl-ethanone;
- 5 1-(3-Fluoro-3-{4-[5-(3,4,5-trichloro-phenyl)-5-trifluoromethyl-4,5-di-hydro-furan-3-yl]-phenyl}-azetidin-1-yl)-2-methyl-propan-1-one;
- 1-(3-{4-[5-(3,5-dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-furan-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-2-methanesulfonyl-ethanone; and
- 10 1-(3-{4-[5-(3,5-dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-furan-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-2-methyl-propan-1-one, stereoisomers thereof, and pharmaceutically or veterinarily acceptable salts thereof.

In yet another aspect of the invention are compounds of Formula (2d).

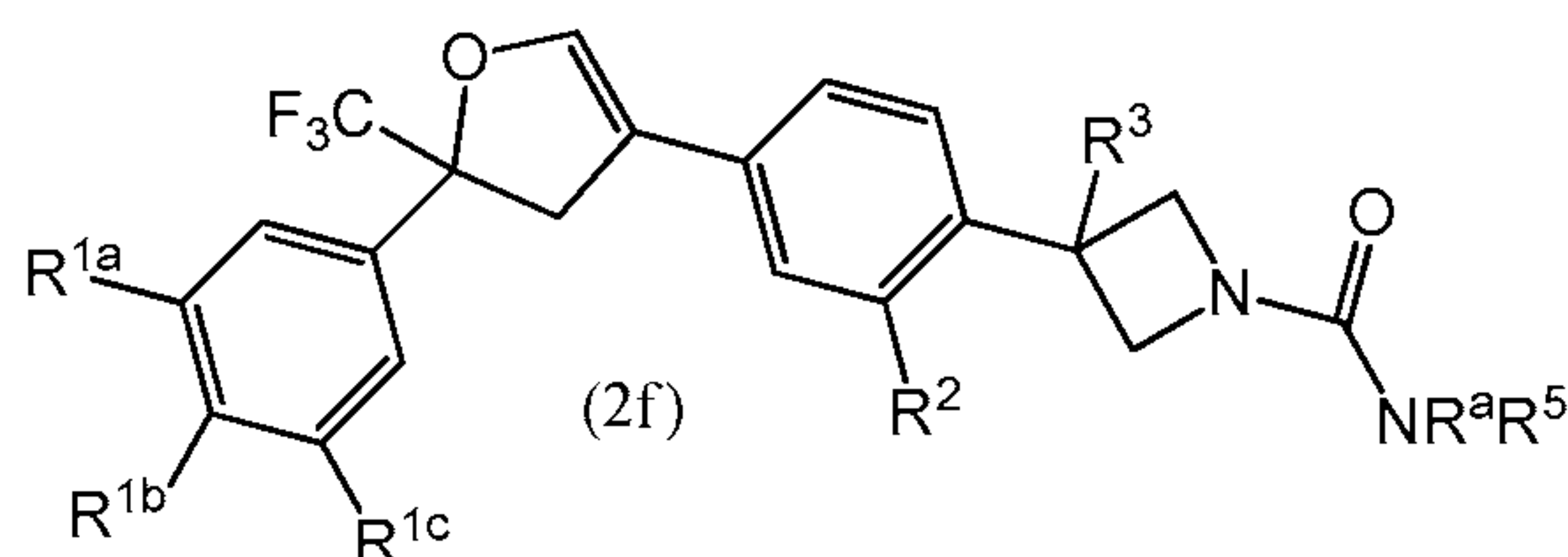


In yet another aspect of the invention are compounds of Formula (2e).

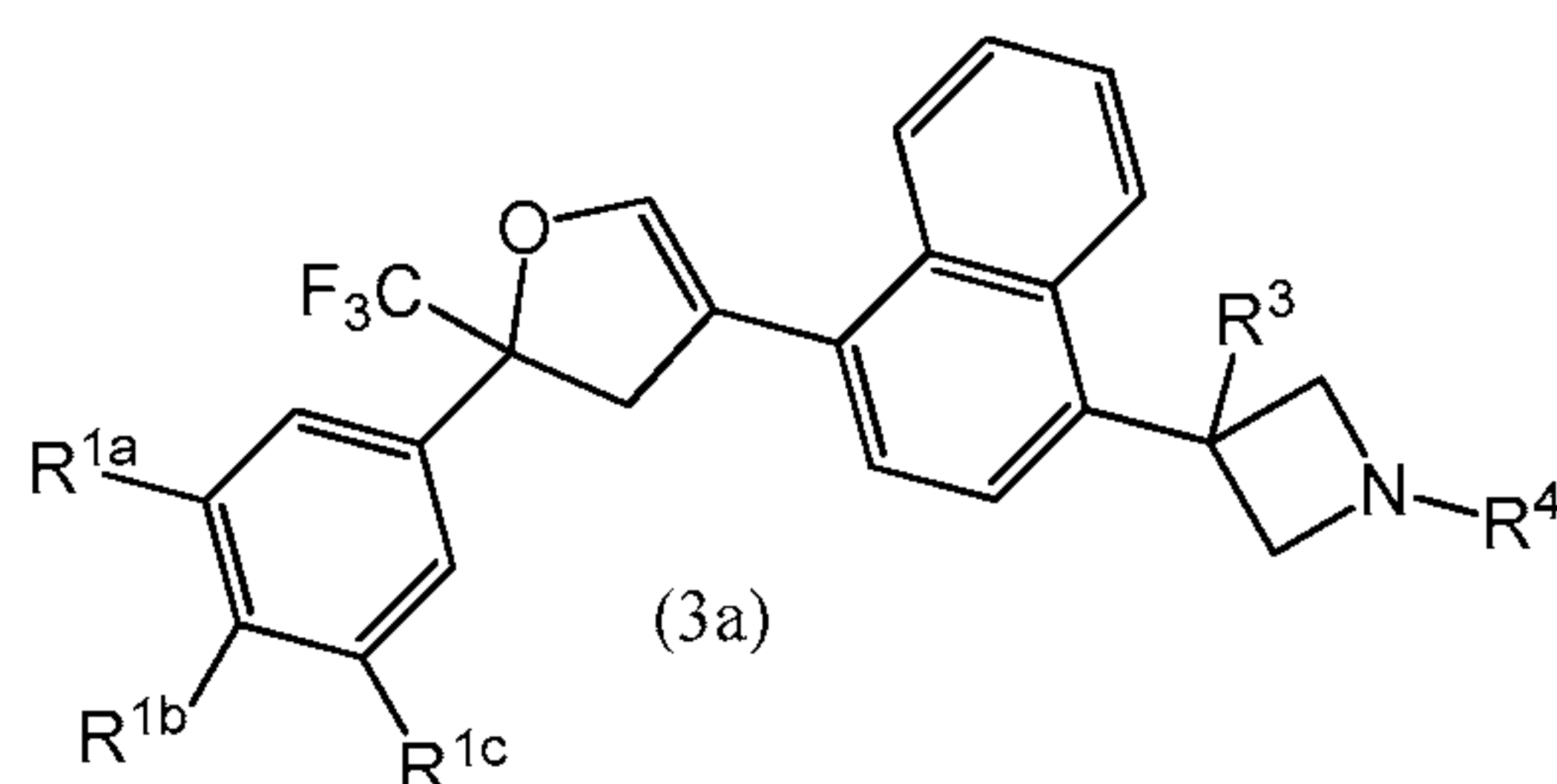


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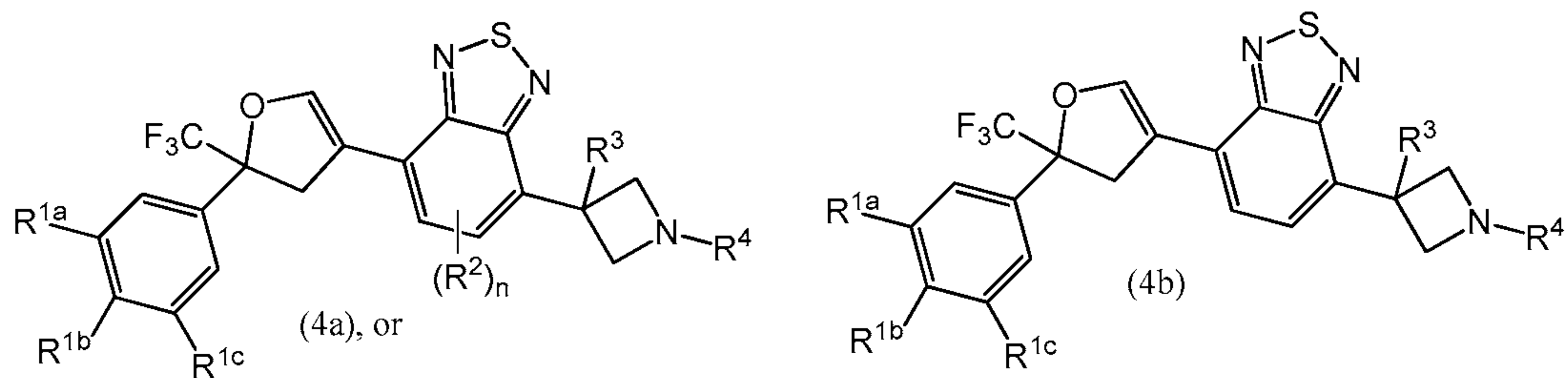
In another aspect of the invention are compounds of Formula (2f).



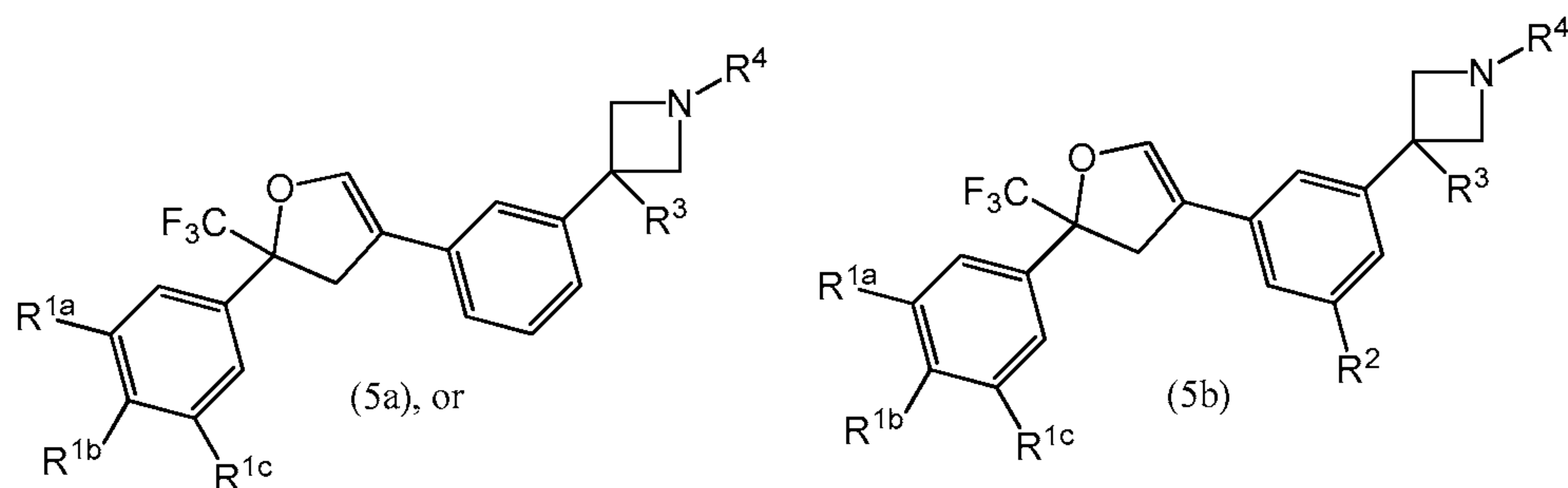
In another aspect of the invention are compounds of Formula (3a).



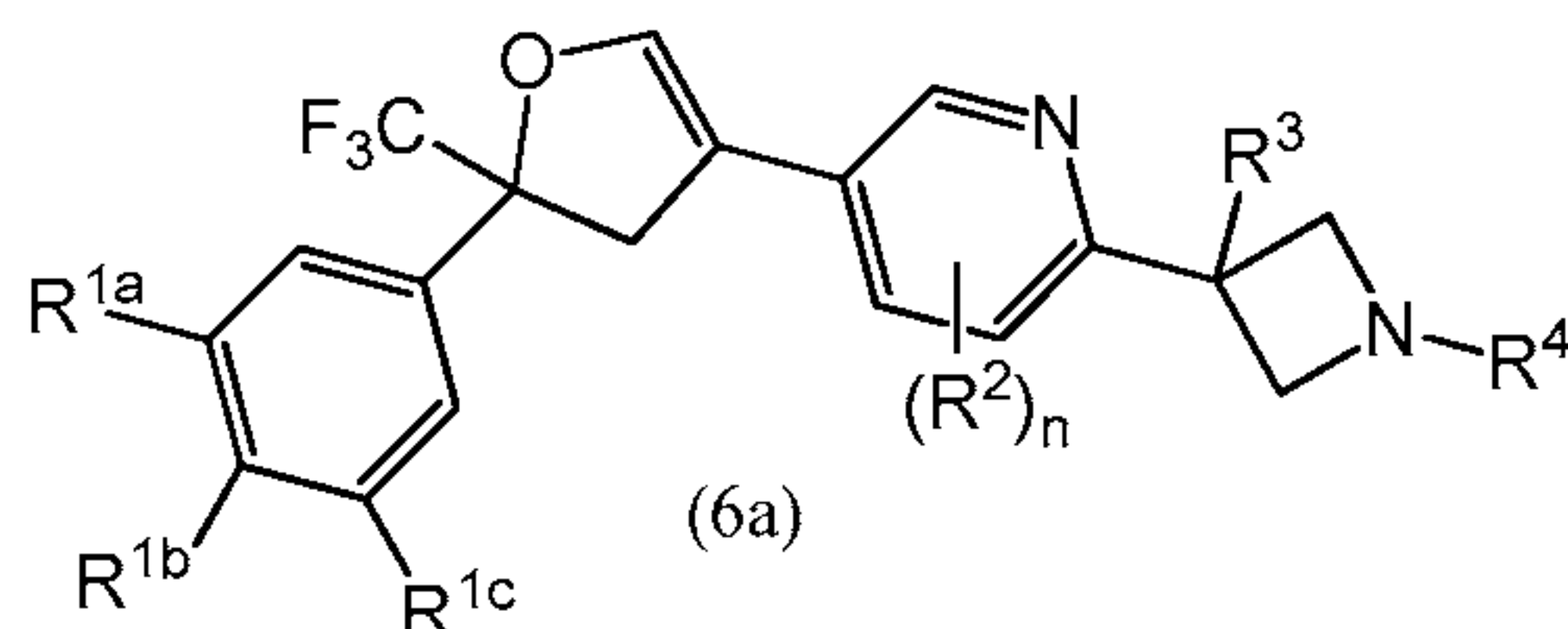
In another aspect of the invention are compounds of Formula (4a) and (4b).



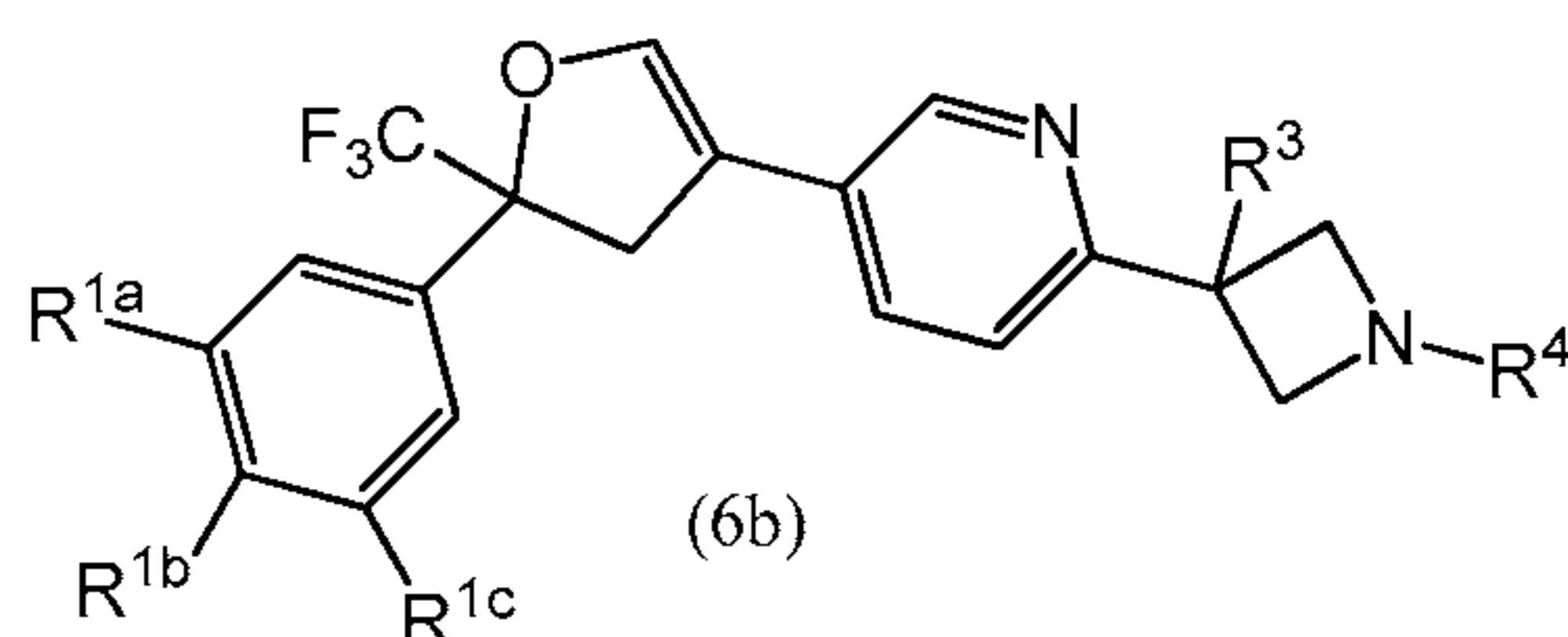
5 In another aspect of the invention are compounds of Formula (5a) and (5b).



In yet another aspect of the invention are compounds of Formula (6a).



10 In yet another aspect of the invention are compounds of Formula (6b).



In another aspect of the invention, each of R^{1a} , R^{1b} , and R^{1c} are independently selected from hydrogen, halo, hydroxyl, cyano, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_0 - C_3 alkyl C_3 - C_6 cycloalkyl, $-S(O)_pR$, and $-SF_5$. In yet another aspect of the invention, each of R^{1a} , R^{1b} , and R^{1c} are independently selected from hydrogen, halo, hydroxyl, cyano, C_1 - C_6 haloalkyl, and C_0 - C_3 alkyl C_3 - C_6 cycloalkyl. In yet another aspect of the invention, each of R^{1a} , R^{1b} , and R^{1c} are independently selected from hydrogen, halo, hydroxyl, cyano, and C_1 - C_6

haloalkyl. In yet another aspect of the invention, each of R^{1a} , R^{1b} , and R^{1c} are independently selected from hydrogen, fluoro, chloro, bromo, cyano, and C_1 - C_6 haloalkyl. In yet another aspect of the invention, each of R^{1a} , R^{1b} , and R^{1c} are independently selected from hydrogen, fluoro, chloro, bromo, and C_1 - C_6 haloalkyl. In yet another aspect of the invention, each of R^{1a} , R^{1b} , and R^{1c} are independently selected from hydrogen, fluoro, chloro, bromo, and $-CF_3$. In yet another aspect of the invention, each of R^{1a} , R^{1b} , and R^{1c} are independently selected from hydrogen, fluoro, chloro, and $-CF_3$.

In yet another aspect of the invention, the integer n of $(R^2)_n$ is 2. When the integer n is 2, then each R^2 may be identical or different from each other. In yet another aspect of the invention, the integer n of $(R^2)_n$ is 1. In yet another aspect of the invention, the integer n of $(R^2)_n$ is 0.

In yet another aspect of the invention, R^2 is selected from halo, cyano, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, hydroxyl, $-C(O)NR^aR^b$, C_2 - C_6 alkenyl, or $-OR$. In yet another aspect of the invention, R^2 is selected from halo, cyano, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, hydroxyl, $-C(O)NR^aR^b$, or $-OR$. In yet another aspect of the invention, R^2 is selected from halo, cyano, C_1 - C_6 alkyl, $-C(O)NR^aR^b$, or hydroxyl. In yet another aspect of the invention, R^2 is selected from halo, cyano, $-C(O)NR^aR^b$, or hydroxyl. In yet another aspect of the invention, R^2 is selected from cyano or $-C(O)NR^aR^b$, or hydroxyl. In yet another aspect of the invention, R^2 is selected from cyano. In yet another aspect of the invention, R^2 is selected from $-C(O)NR^aR^b$.

In another aspect of the invention, R^3 is hydrogen, halo, hydroxyl, cyano, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_0 - C_3 alkyl C_3 - C_6 cycloalkyl, $-C(O)NH_2$, $-SC(O)R$, $-C(O)NR^aR^b$, C_0 - C_3 alkyl NR^aR^4 , $-NR^aNR^bR^4$, $-NR^aOR^b$, $-ONR^aR^b$, N_3 , $-NHR^4$, $-OR$, or $-S(O)_pR$. In yet another aspect of the invention, R^3 is hydrogen, halo, hydroxyl, cyano, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_0 - C_3 alkyl C_3 - C_6 cycloalkyl, $-C(O)NH_2$, $-C(O)NR^aR^b$, C_0 - C_3 alkyl NR^aR^4 , $-NR^aNR^bR^4$, $-NR^aOR^b$, $-ONR^aR^b$, N_3 , $-NHR^4$, or $-S(O)_pR$. In yet another aspect of the invention, R^3 is hydrogen, halo, hydroxyl, cyano, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_0 - C_3 alkyl C_3 - C_6 cycloalkyl, $-C(O)NH_2$, $-C(O)NR^aR^b$, C_0 - C_3 alkyl NR^aR^4 , $-NR^aNR^bR^4$, $-NHR^4$, N_3 , or $-S(O)_pR$. In yet another aspect of the invention, R^3 is hydrogen, halo, hydroxyl, cyano, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_0 - C_3 alkyl C_3 - C_6 cycloalkyl, $-C(O)NH_2$, $-C(O)NR^aR^b$, $-$

NHR⁴, N₃, or -S(O)_pR. In yet another aspect of the invention, R³ is hydrogen, halo, hydroxyl, cyano, C₁-C₆alkyl, C₁-C₆haloalkyl, C₀-C₃alkylC₃-C₆cycloalkyl, -C(O)NH₂, or N₃.

In yet another aspect of the invention, R³ is hydrogen, halo, hydroxyl, cyano, C₁-C₆alkyl, C₁-C₆haloalkyl, or N₃. In yet another aspect of the invention, R³ is hydrogen, halo, hydroxyl, cyano, C₁-C₆alkyl, or N₃. In yet another aspect of the invention, R³ is hydrogen, halo, hydroxyl, cyano, or N₃. In yet another aspect of the invention, R³ is hydrogen, fluoro, chloro, bromo, N₃, hydroxyl, or cyano. In yet another aspect of the invention, R³ is hydrogen, fluoro, chloro, N₃, hydroxyl, or cyano. In yet another aspect of the invention, R³ is hydrogen. In yet another aspect of the invention, R³ is fluoro. In yet another aspect of the invention, R³ is chloro. In yet another aspect of the invention, R³ is hydroxyl. In yet another aspect of the invention, R³ is cyano. In yet another aspect of the invention, R³ is N₃.

In another aspect of the invention, R⁴ is C₁-C₆alkyl, C₀-C₆alkylC₃-C₆cycloalkyl, -C(O)R⁵, -C(S)R⁵, -C(O)NR^aR⁵, -C(O)C(O)NR^aR⁵, -S(O)_pR^c, -S(O)₂NR^aR⁵, -C(NR⁷)R⁵, -C(NR⁷)NR^aR⁵, C₀-C₆alkylheteroaryl, or C₀-C₆alkylheterocycle; wherein each of R⁴ and R⁵ C₁-C₆alkyl or C₀-C₆alkylC₃-C₆cycloalkyl can be optionally and independently substituted as described herein, and wherein each of R^a, R^c, R⁴ and R⁵ substituents can be optionally and independently substituted as described herein. In yet another aspect of the invention, R⁴ is -C(O)R⁵, -C(O)NR^aR⁵, -S(O)_pR^c, -C(S)R⁵, -S(O)₂NR^aR⁵, -C(NR⁷)R⁵, or -C(NR⁷)NR^aR⁵, and wherein each of R^a, R^c, and R⁵ substituents can be optionally and independently substituted as described herein. In yet another aspect of the invention, R⁴ is -C(O)R⁵, or -C(O)NR^aR⁵, and wherein each of R^a and R⁵ substituents can be optionally and independently substituted as described herein.

In yet another aspect of the invention, when R⁴ is -C(O)R⁵, then R⁵ is hydrogen, C₁-C₆alkyl, C₀-C₆alkylC₃-C₆cycloalkyl, C₀-C₆alkylphenyl, C₀-C₆alkylheteroaryl, or C₀-C₆alkylheterocycle, wherein said R⁵ C₁-C₆alkyl or C₀-C₆alkylC₃-C₆cycloalkyl can be optionally and independently substituted by at least one substituent selected from cyano, halo, hydroxyl, oxo, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₁-C₆haloalkyl, -S(O)_pR^c, -SH, -S(O)_pNR^aR^b, -NR^aR^b, -NR^aC(O)R^b, -SC(O)R^c, -SCN, or -C(O)NR^aR^b, where said R⁵ C₀-C₆alkylphenyl,

C₀-C₆alkylheteroaryl, or C₀-C₆alkylheterocycle moiety can be further optionally substituted with at least one substituent selected from cyano, halo, hydroxyl, C₁-C₆alkoxy, C₁-C₆alkyl, C₁-C₆haloalkyl, -SH, -S(O)_pR, and C₁-C₆haloalkoxy. The R^a and R^c substituents are also optionally substituted with at least one

5 substituent as defined herein.

In yet another aspect of the invention, when R⁴ is -C(O)R⁵, then R⁵ is hydrogen, C₁-C₆alkyl, C₀-C₆alkylC₃-C₆cycloalkyl, or C₀-C₆alkylheteroaryl, where said C₀-C₆alkylC₃-C₆cycloalkyl or C₀-C₆alkylheteroaryl moieties are optionally substituted as defined herein.

10 In yet another aspect of the invention, when R⁴ is -C(O)R⁵, then R⁵ is methyl, ethyl, propyl, isopropyl, isobutyl, n-butyl, t-butyl, cyclopropyl, cyclobutyl, cyclopentyl, -CH₂-cyclopropyl, -CH₂-cyclobutyl, -CH₂-cyclopentyl, -(CH₂)₂-cyclopropyl, -(CH₂)₂-cyclobutyl, -(CH₂)₂-cyclopentyl, pyrazolyl, -CH₂-pyrazolyl, -(CH₂)₂-pyrazolyl, pyridinyl, -CH₂-pyridinyl, -(CH₂)₂-pyridinyl,

15 wherein the alkyl (for example, methyl, ethyl, and propyl), cycloalkyl (for example, cyclopropyl and cyclobutyl) or alkylcycloalkyl (for example, -CH₂-cyclopropyl and -(CH₂)₂-cyclobutyl) can be optionally and independently substituted as defined herein.

In yet another aspect of the invention, when R⁴ is -C(O)R⁵, then R⁵ is

20 methyl, ethyl, propyl, isopropyl, isobutyl, n-butyl, t-butyl, cyclopropyl, cyclobutyl, cyclopentyl, -CH₂-cyclopropyl, -CH₂-cyclobutyl, -CH₂-cyclopentyl, -(CH₂)₂-cyclopropyl, -(CH₂)₂-cyclobutyl, -(CH₂)₂-cyclopentyl, pyrazolyl, -CH₂-pyrazolyl, -(CH₂)₂-pyrazolyl, pyridinyl, -CH₂-pyridinyl, -(CH₂)₂-pyridinyl, wherein the alkyl (for example, methyl, ethyl, and propyl), cycloalkyl (for

25 example, cyclopropyl and cyclobutyl) or alkylcycloalkyl (for example, -CH₂-cyclopropyl and -(CH₂)₂-cyclobutyl) can be optionally and independently substituted by at least one substituent selected from cyano, halo, hydroxyl, oxo, methoxy, -CF₃, ethoxy, -S(O)_pR, -SCH₃, -SCH₂CH₃, -NH₂, -NHCH₃, -NHCH₂CH₃, -NH(CH₂)₂CH₃, -NHcyclopropyl, -NHcyclobutyl, -NHCH₂cyclopropyl,

30 -NHCH₂cyclobutyl, -NR^aC(O)R^b, or -C(O)NH₂.

In yet another aspect of the invention, when R⁴ is -C(O)R⁵, then R⁵ is methyl, ethyl, propyl, isopropyl, isobutyl, cyclopropyl, cyclobutyl, cyclopentyl, -CH₂-cyclopropyl, -CH₂-cyclobutyl, -CH₂-cyclopentyl, pyrazolyl, -CH₂-pyrazolyl, pyridinyl, -CH₂-pyridinyl, wherein the alkyl (for example, methyl, ethyl, and

isopropyl), cycloalkyl (for example, cyclopropyl and cyclobutyl) or alkylcycloalkyl (for example, -CH₂-cyclopropyl) can be optionally and independently substituted by at least one substituent selected from cyano, halo, hydroxyl, oxo, -CF₃, S(O)_pR, methoxy, ethoxy, -SCH₃, -NH₂, -NHCH₃, -NHCH₂CH₃, -NHcyclopropyl, -NHcyclobutyl, -NHC(O)H, or -C(O)NH₂.

In yet another aspect of the invention, when R⁴ is -C(O)R⁵, then R⁵ is methyl, ethyl, propyl, isopropyl, isobutyl, cyclopropyl, cyclobutyl, cyclopentyl, -CH₂-cyclopropyl, -CH₂-cyclobutyl, -CH₂-cyclopentyl, pyrazolyl, -CH₂-pyrazolyl, pyridinyl, -CH₂-pyridinyl, wherein the alkyl (for example, methyl, ethyl, and isopropyl), cycloalkyl (for example, cyclopropyl and cyclobutyl) or alkylcycloalkyl (for example, -CH₂cyclopropyl) can be optionally and independently substituted by at least one substituent selected from cyano, halo, hydroxyl, oxo, -CF₃, methoxy, -SCH₃, S(O)_pR, -NH₂, -NHCH₃, -NHCH₂CH₃, -NHcyclopropyl, -NHC(O)H, or -C(O)NH₂.

In yet another aspect of the invention, when R⁴ is -C(O)R⁵, then R⁵ is oxetane, thiatane, azetidine, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, -CH₂-oxetane, -CH₂-thiatane, -CH₂-azetidine, or -CH₂-tetrahydrofuran, each of which are optionally substituted as defined herein. In yet another aspect of the invention, when R⁴ is -C(O)R⁵, then R⁵ is oxetane, thiatane, azetidine, tetrahydrofuran, tetrahydrothiophene, -CH₂-oxetane, -CH₂-thiatane, or -CH₂-azetidine, each of which are optionally substituted as defined herein. In yet another aspect of the invention, when R⁴ is -C(O)R⁵, then R⁵ is oxetane, thiatane, or azetidine, each of which are optionally substituted as defined herein. In yet another aspect of the invention, when R⁴ is -C(O)R⁵, then R⁵ is -CH₂-oxetane, -CH₂-thiatane, or -CH₂-azetidine, each of which are optionally substituted as defined herein.

In yet another aspect of the invention, when R⁴ is -C(O)R⁵, then R⁵ is pyrazole, imidazole, isoxazole, oxazole, isothiazole, thiazole, triazole, pyridine, pyridazine, pyrazine, or pyrimidine, each of the which are optionally substituted as defined herein.

In yet another aspect of the invention, when R⁴ is -C(O)R⁵, then R⁵ is

C₁-C₆alkyl, C₂-C₆alkenyl, or C₀-C₆alkylC₃-C₆cycloalkyl, wherein each of C₁-C₆alkyl or C₀-C₆alkylC₃-C₆cycloalkyl is optionally substituted with at least one substituent selected from cyano, halo, hydroxyl, -S(O)_pR^c, C₁-C₆alkoxy, -S(O)_pNR^aR^b, or -SC(O)R^c; pyrazole, pyridine, oxazole, pyridazine, triazole, azetidine, thiatane, wherein each heterocycle and heteroaryl moiety are optionally substituted further with at least one substituent selected from fluoro, hydroxyl, methyl, and oxo; where p, R^a, R^b, and R^c are as defined herein.

In yet another aspect of the invention, when R⁴ is -C(O)NR^aR⁵, then R^a is hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, -CH₂-cyclopropyl, -CH₂-cyclobutyl, -CH₂-cyclopentyl, -(CH₂)₂-cyclopropyl, -(CH₂)₂-cyclobutyl, or -(CH₂)₂-cyclopentyl; wherein the alkyl (for example methyl and propyl), cycloalkyl (for example, cyclopropyl and cyclopentyl), or the alkylcycloalkyl (for example, -CH₂-cyclopropyl, -CH₂-cyclopentyl, and -(CH₂)₂-cyclobutyl) are optionally substituted by cyano or at least one halo substituent; and R⁵ is as defined herein.

In yet another aspect of the invention, when R⁴ is -C(O)NR^aR⁵, then R^a is hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, -CH₂-cyclopropyl, -CH₂-cyclobutyl, -CH₂-cyclopentyl; wherein the alkyl (for example, methyl and propyl), cycloalkyl (for example, cyclopropyl and cyclopentyl), or the alkylcycloalkyl (for example, -CH₂-cyclopropyl and -CH₂-cyclopentyl) are optionally substituted by cyano or at least one halo substituent; and R⁵ is as defined herein.

In yet another aspect of the invention, when R⁴ is -C(O)NR^aR⁵, then R^a is hydrogen or methyl and R⁵ is selected from hydrogen, methyl, ethyl, propyl, cyclopropyl, and C₀-C₆alkylheterocycle, wherein the alkyl and alkylheterocycle moiety are each optionally substituted as described herein.

In yet another aspect of the invention, when R⁴ is -S(O)_pR^c, the integer p is 2, and R^c is as defined herein, and said R^c substituent is optionally substituted with at least one substituent as defined herein. In yet another aspect of the invention, when R⁴ is -S(O)_pR^c, the integer p is 2, R^c is C₁-C₆alkyl optionally substituted with at least one substituent as defined herein. In yet another aspect of the invention, when R⁴ is -S(O)_pR^c, the integer p is 2, R^c is C₁-C₆alkyl optionally substituted with at least one substituent selected from cyano or halo. In yet another aspect of the invention, when R⁴ is -S(O)_pR^c, the integer p is 2,

and R^c is C_1 - C_6 alkyl. In yet another aspect of the invention, when R^4 is $-S(O)_pR^c$, the integer p is 2, and R^c is methyl, ethyl, propyl, or isopropyl. In yet another aspect of the invention, when R^4 is $-S(O)_pR^c$, the integer p is 2, and R^c is methyl or ethyl.

5 In yet another aspect of the invention, R^6 is cyano, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, or $-C(O)NH_2$. In yet another aspect of the invention, R^6 is cyano, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl. In yet another aspect of the invention, R^6 is cyano, methyl, ethyl, or C_1 - C_6 haloalkyl. In yet another aspect of the invention, R^6 is cyano, methyl, or C_1 - C_6 haloalkyl. In yet another aspect of the invention, R^6 is
10 cyano or C_1 - C_6 haloalkyl. In yet another aspect of the invention, R^6 is C_1 - C_6 haloalkyl. In yet another aspect of the invention, R^6 is $-CF_3$, $-CHF_2$, $-CH_2F$, and $-CF_2Cl$. In yet another aspect of the invention, R^6 is $-CF_3$, $-CHF_2$, and $-CH_2F$. In yet another aspect of the invention, R^6 is $-CF_3$.

In yet another aspect of the invention, R is methyl, ethyl, propyl, isopropyl,
15 cyclopropyl, cyclobutyl, or cyclopentyl. In yet another aspect of the invention, R is methyl, ethyl, isopropyl, cyclopropyl, or cyclobutyl.

In yet another aspect of the invention, R^a is hydrogen, methyl, ethyl, propyl, isopropyl, or isobutyl, each alkyl moiety is optionally substituted as defined herein. In yet another aspect of the invention, R^a is hydrogen, methyl,
20 ethyl, propyl, or isopropyl, each alkyl moiety is optionally substituted as defined herein. In yet another aspect of the invention, R^a is hydrogen, methyl, or ethyl, each alkyl is optionally substituted as defined herein.

In yet another aspect of the invention, R^a is hydrogen, methyl, ethyl, propyl, isopropyl, isobutyl, cyclopropyl, cyclobutyl, cyclopentyl, $-CH_2$ -cyclopropyl,
25 or $-CH_2$ -cyclobutyl, each alkyl, cycloalkyl, and alkylcycloalkyl moiety is optionally substituted as defined herein. In yet another aspect of the invention, R^a is hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, $-CH_2$ -cyclopropyl, or $-CH_2$ -cyclobutyl, each alkyl, cycloalkyl, and alkylcycloalkyl moiety is optionally substituted as defined herein. In yet another aspect of the
30 invention, R^a is hydrogen, methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, $-CH_2$ -cyclopropyl, or $-CH_2$ -cyclobutyl, each alkyl, cycloalkyl, and alkylcycloalkyl moiety is optionally substituted as defined herein.

In another aspect of the invention, R^b is hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_0 - C_3 alkylphenyl, or C_0 - C_3 alkylheteroaryl. In yet another aspect

of the invention, R^b is hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, or C_0 - C_3 alkylheteroaryl. In yet another aspect of the invention, R^b is hydrogen, C_1 - C_6 alkyl, or C_3 - C_6 cycloalkyl. In yet another aspect of the invention, R^b is hydrogen, methyl, ethyl, isopropyl, propyl, isobutyl, cyclopropyl, or cyclobutyl.

5 In yet another aspect of the invention is a composition that comprises a) a Formula (1) compound, stereoisomers thereof, or a veterinarily or pharmaceutically acceptable salt thereof, and (b) a veterinarily or pharmaceutically acceptable excipient, diluent, or carrier. The variables R^{1a} , R^{1b} , R^{1c} , R^2 , R^3 , R^4 , R^6 , and n are as defined herein. Preferably, the composition
10 comprises a therapeutically effective amount of a Formula (1) compound, stereoisomer thereof, or veterinarily or pharmaceutically acceptable salt thereof, and a veterinarily or pharmaceutically acceptable excipient, diluent, or carrier. The composition may comprise at least one additional veterinary agent. Preferred additional veterinary agents include endoparasitocides, endectocides,
15 ectoparasitocides, insecticides, and anthelmintics, and are described herein.

The composition may comprise at least one additional veterinary agent. Preferred additional veterinary agents include endoparasitocides, endectocides, ectoparasitocides, insecticides, and anthelmintics, and are described herein. In one aspect of the invention, the additional veterinary agent is selected from
20 amitraz, amino acetonitriles, anthelmintics (e.g., albendazole, cambendazole, fenbendazole, flubendazole, mebendazole, octadepsipeptides, oxfendazole, oxibendazole, paraherquamide, parbendazole, piperazines, praziquantel, thiabendazole, tetramisole, triclabendazole, levamisole, pyrantel pamoate, oxantel, morantel, and the like), avermectins (e.g., abamectin, doramectin,
25 emamectin, eprinomectin, ivermectin, moxidectin, selamectin, and the like), milbemycin, milbemycin oxime, demiditraz, diethylcarbamazine, fipronil, hydroprene, kinoprene, methoprene, metaflumizone, niclosamide, permethrin, pyrethrins, pyriproxyfen, and spinosad. In another aspect of the invention, the additional agent is selected from an amino acetonitrile, albendazole,
30 cambendazole, fenbendazole, flubendazole, mebendazole, oxfendazole, oxibendazole, paraherquamide, parbendazole, praziquantel, thiabendazole, tetramisole, triclabendazole, levamisole, pyrantel pamoate, oxantel, morantel, abamectin, doramectin, emamectin, eprinomectin, ivermectin, moxidectin, selamectin, milbemycin, milbemycin oxime, demiditraz, diethylcarbamazine,

fipronil, hydroprene, kinoprene, methoprene, metaflumizone, niclosamide, pyriproxyfen, and spinosad. In yet another aspect of the invention, the additional agent is selected from an amino acetonitrile, paraherquamide, praziquantel, abamectin, doramectin, emamectin, eprinomectin, ivermectin, moxidectin, 5 selamectin, milbemycin, and milbemycin oxime. In yet another aspect of the invention, the additional agent is selected from abamectin, doramectin, emamectin, eprinomectin, ivermectin, moxidectin, selamectin, milbemycin, and milbemycin oxime. In yet another aspect of the invention, the additional agent is selected from abamectin, doramectin, eprinomectin, ivermectin, moxidectin, 10 selamectin, milbemycin, and milbemycin oxime. In yet another aspect of the invention, the additional agent is selected from moxidectin, selamectin, and milbemycin oxime. In yet another aspect of the invention, the additional agent is selected from moxidectin and milbemycin oxime.

In yet another aspect of the invention is the use of a Formula (1) 15 compound for the manufacture of a medicament.

In yet another aspect of the invention is a method for treating a parasitic infection or infestation in an animal that includes the step of administering to said animal, in need of such treatment, a therapeutically effective amount of a compound of the present invention, stereoisomer thereof, or veterinarily 20 acceptable salt thereof. In one aspect, the animal is a mammal, specifically a companion animal (for example, dog, cat, or horse) or livestock (for example, sheep, goat, cattle, and pig). In another aspect, the animal is a bird, specifically, fowl (for example, chicken, turkey, duck, and geese). In another aspect, the animal is a fish. The compounds of the present invention, and compositions 25 thereof, can be administered to the animal orally or topically. The compounds of the present invention, and compositions thereof, can also be administered to the animal by intramuscular-, intraperitoneal-, or subcutaneous-injection. Preferably, the compounds of the present invention, and compositions thereof, can be administered to the animal orally or topically.

30 In yet another aspect of the invention is a method for treating a parasitic infection or infestation in an animal that includes the step of administering to said animal, in need of such treatment, a therapeutically effective amount of a compound of the present invention, stereoisomer thereof, or veterinarily acceptable salt thereof, in combination with at least one additional veterinary

agent. In one aspect, the animal is a mammal, specifically a companion animal (for example, dog, cat, or horse) or livestock (for example, sheep, goat, cattle, and pig). In another aspect, the animal is a bird, specifically, fowl (for example, chicken, turkey, duck, and geese). In another aspect, the animal is a fish. The compounds of the present invention, and compositions thereof, can be administered to the animal orally or topically. The compounds of the present invention, and compositions thereof, can also be administered to the animal by intramuscular-, intraperitoneal-, or subcutaneous-injection. Preferably, the compounds of the present invention, and compositions thereof, can be administered to the animal orally or topically. Equally preferred, the compounds of the present invention can be administered by injection.

Compounds of the present invention alone, or in combination with an additional veterinary agent(s) may be administered as (a) a single veterinary composition which comprises a compound of the present invention, stereoisomer thereof, veterinarily acceptable salt thereof, and optionally, at least one additional veterinary agent as described herein and a veterinarily acceptable excipient, diluent, or carrier; or (b) two separate veterinary compositions comprising (i) a first composition comprising a compound of the present invention, stereoisomer thereof, veterinarily acceptable salt thereof, and a veterinarily acceptable excipient, diluent, or carrier, and (ii) a second composition comprising at least one additional veterinary agent, as described herein and a veterinarily acceptable excipient, diluent, or carrier. The veterinary compositions may be administered simultaneously or sequentially and in any order.

25

DEFINITIONS

For purposes of the present invention, as described and claimed herein, the following terms and phrases are defined as follows:

“Additional veterinary agent(s)” as used herein, unless otherwise indicated, refers to other veterinary or pharmaceutical compounds or products that provide a therapeutically effective amount of said agents that are useful for the treatment of a parasitic infection in an animal, as described herein.

30

“Alkoxy”, as used herein, unless otherwise indicated, refers to an oxygen moiety having a further alkyl substituent. The alkyl portion (i.e., alkyl moiety) of an alkoxy group has the same definition as below. Non-limiting examples include:

- 5 -OCH₃, -OCH₂CH₃, and the like.

"Alkyl", as used herein, unless otherwise indicated, refers to saturated monovalent hydrocarbon alkane radicals of the general formula C_nH_{2n+1}. The alkane radical may be straight or branched and may be unsubstituted or substituted. For example, the term “(C₁-C₆)alkyl” refers to a monovalent, straight or branched aliphatic group containing 1 to 6 carbon atoms. Non-exclusive examples of (C₁-C₆) alkyl groups include, but are not limited to methyl, ethyl, propyl, isopropyl, sec-butyl, t-butyl, n-propyl, n-butyl, i-butyl, s-butyl, n-pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, neopentyl, 3,3-dimethylpropyl, 2-methylpentyl, hexyl, and the like. The alkyl moiety may be attached to the chemical moiety by any one of the carbon atoms of the aliphatic chain. Alkyl groups are optionally substituted as described herein. Further when used in compound words such as alkylphenyl, said alkyl moiety has the same meaning as herein defined and may be attached to the chemical moiety by any one of the carbon atoms of the aliphatic chain. Non-limiting examples of the compound word, alkylphenyl include: C₁alkylphenyl is -CH₂phenyl, C₂alkylphenyl is -CH₂CH₂phenyl, C₀phenyl is phenyl, and the like.

“Alkenyl” as used herein, unless otherwise indicated, refers to a straight or branched aliphatic hydrocarbon chain having 2- to 6-carbon atoms and containing at least one carbon-carbon double bond (for example -C=C-, or -C=CH₂). Non-exclusive examples of alkenyl include: ethenyl, 1-propenyl, 2-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-pentenyl, and the like.

“Alkynyl” as used herein, unless otherwise indicated, refers to straight or branched aliphatic hydrocarbon chain having 2- to 6-carbon atoms and containing at least one carbon-carbon triple bond (for example, -C≡C- or -C≡CH). Non-exclusive examples of alkynyl include: ethynyl, 2-propynyl, 1-methyl-2-propynyl, 2-butyne, 3-butyne, 2-methyl-3-butyne, and the like.

“Animal(s)”, as used herein, unless otherwise indicated, refers to an individual animal that is a mammal, bird, or fish. Specifically, mammal refers to a vertebrate animal that is human and non-human, which are members of the

taxonomic class Mammalia. Non-exclusive examples of non-human mammals include companion animals and livestock. Non-exclusive examples of a companion animal include: dog, cat, llama, and horse. Preferred companion animals are dog, cat, and horse. More preferred is dog. Non-exclusive
5 examples of livestock include: swine, camel, rabbits, goat, sheep, deer, elk, bovine (cattle), and bison. Preferred livestock is cattle and swine. Specifically, bird refers to a vertebrate animal of the taxonomic class Aves. Birds are feathered, winged, bipedal, endothermic, and egg-laying. Non-exclusive examples of bird include, poultry (e.g., chicken, turkey, duck, and geese), all of
10 which are also referred to herein as fowl. Specifically, fish refers to the taxonomic class Chondrichthyes (cartilaginous fishes, e.g., sharks and rays) and Osteichthyes (bony fishes) which live in water, have gills or mucus-covered skin for respiration, fins, and may have scales. Non-exclusive examples of fish include shark, salmon, trout, whitefish, catfish, tilapia, sea bass, tuna, halibut,
15 turbot, flounder, sole, striped bass, eel, yellowtail, grouper, and the like.

"Carbocyclic", as used herein, unless otherwise indicated, refers to a partially saturated or saturated 5- to 7-membered ring containing only carbon atoms and can be monocyclic or part of a fused ring or spiro ring moiety. Examples of carbocyclic rings include cyclopentane, cyclohexane, and
20 cycloheptane. The carbocyclic ring is optionally substituted as described herein.

"Chiral", as used herein, unless otherwise indicated, refers to the structural characteristic of a molecule that makes it impossible to superimpose it on its mirror image, (e.g., "R" and "S" enantiomers). The term is also depicted as an asterisk (i.e.,*) in the Examples and preparations and refers to a chiral center
25 which includes both the S and R enantiomers.

"Compounds of the present invention", as used herein, unless otherwise indicated, refers to compounds of Formula (1) compounds, and stereoisomers thereof.

"Cycloalkyl", as used herein, unless otherwise indicated, includes fully
30 saturated or partially saturated carbocyclic alkyl moieties. Non-limiting examples of partially saturated cycloalkyls include: cyclopropene, cyclobutene, cycloheptene, cyclooctene, cyclohepta-1,3-diene, and the like. Preferred cycloalkyls are 3- to 6-membered saturated monocyclic rings including cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. The cycloalkyl group may

be attached to the chemical moiety by any one of the carbon atoms within the carbocyclic ring. Cycloalkyl groups are optionally substituted with at least one substituent. Further when used in compound words such as alkylcycloalkyl, said alkyl and cycloalkyl moiety has the same meaning as herein defined and may be

5 attached to the chemical moiety by any one of the carbon atoms of the aliphatic chain. Examples of C₀-C₆alkylC₃-C₆cycloalkyl include, methylcyclopropane (C₁alkylC₃cycloalkyl or -CH₂cyclopropane), ethylcyclopropane (C₂alkylC₃cycloalkyl or -CH₂CH₂cyclopropane), methylcyclobutane (C₁alkylC₄cycloalkyl or -CH₂cyclobutane), ethylcyclobutane (C₂alkylC₄cycloalkyl or -CH₂CH₂cyclobutane), methylcyclohexane (C₁alkylC₆cycloalkyl or -CH₂cyclohexane), and the like. C₀alkylC₃-C₆cycloalkyl is C₃-C₆cycloalkyl. Cycloalkyl moieties are optionally substituted as described herein

“Halogen” or “halo”, as used herein, unless otherwise indicated, refers to fluorine, chlorine, bromine and iodine. Further, when used in compound words

15 such as “haloalkyl”, “haloalkoxy”, “haloalkenyl”, or “haloalkynyl”, said alkyl, alkoxy, alkenyl, and alkynyl may be partially or fully substituted with halogen atoms which may be the same or different and said alkyl, alkoxy, alkenyl, and alkynyl moiety has the same meaning as above and may be attached to the chemical moiety by any one of the carbon atoms of the aliphatic chain.

20 Examples of “haloalkyl” include F₃C-, ClCH₂-, CF₃CH₂- and CF₃CCl₂-, and the like. The term “haloalkoxy” is defined analogously to the term “haloalkyl”. Examples of “haloalkoxy” include CF₃O-, CCl₃CH₂O-, HCF₂CH₂CH₂O- and CF₃CH₂O-, and the like. The term “haloalkenyl” is defined analogously to the term “haloalkyl” except that the aliphatic chain contains at least one carbon-carbon double bond. Examples of “haloalkenyl” include CF₃C=C-, CCl₃C=C-, HCF₂C=C- and CF₃C=CC-, and the like. The term “haloalkynyl” is defined analogously to the term “haloalkyl” except that the aliphatic chain contains at least one carbon-carbon triple bond. Examples of “haloalkynyl” include CF₃C≡C-, CCl₃C≡C-, HCF₂C≡C- and CF₃C≡CC-, and the like.

30 “Heteroaryl” or “Het”, as used herein, unless otherwise indicated, refers to a 5- to 6-membered aromatic monocyclic ring or an 8- to 10-membered fused aromatic ring where said monocyclic- and fused-ring moiety contains one or more heteroatoms each independently selected from N, O, or S, preferably from one to four heteroatoms. Non-exclusive examples of monocyclic heteroaryls

include pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, thiazolyl, isoxazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, and the like. Non-exclusive examples of fused heteroaryls include: benzofuranyl, benzothiophenyl, indolyl, benzimidazolyl, indazolyl, 5 benzotriazolyl, thieno[2,3-c]pyridine, thieno[3,2-b]pyridine, benzo[1,2,5]thiadiazole, and the like. The heteroaryl group may be attached to the chemical moiety by any one of the carbon atoms or nitrogen heteroatoms within the monocyclic or fused ring. Further when used in compound words such as alkylheteroaryl, said alkyl and heteroaryl moiety have the same meaning as 10 herein defined and may be attached to the chemical moiety by any one of the carbon atoms of the aliphatic chain. For example, C₀alkylheteroaryl is heteroaryl, C₁alkylheteroaryl is -CH₂heteroaryl, C₂alkylheteroaryl is -CH₂CH₂heteroaryl, and the like. Heteroaryls are optionally substituted as described herein.

15 “Heterocycle”, as used herein, unless otherwise indicated, refers to a partially saturated or saturated 3- to 7-membered monocyclic ring containing one or more heteroatoms each independently selected from N, O, or S, preferably from one to four heteroatoms. The heterocyclic ring can be part of a fused ring or spiro-ring moiety. Non-exclusive examples of heterocycle include oxirane, 20 thiarane, aziridine, oxetane, azetidine, thiatane, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, tetrahydropyrane, piperidine, piperazine, tetrahydropyridine, 2H-azirine, 2,3-dihydro-azete, 3,4-dihydro-2H-pyrrole, and the like. The heterocycle group may be attached to the chemical moiety by any one of the carbon atoms or nitrogen heteroatoms within the ring. Further when 25 used in compound words such as alkylheterocycle, said alkyl and heterocycle moiety have the same meaning as herein defined and may be attached to the chemical moiety by any one of the carbon atoms of the aliphatic chain. For example, C₀alkylheterocycle is heterocycle, C₁alkylheterocycle is -CH₂heterocycle, C₂alkylheterocycle is -CH₂CH₂heterocycle, and the like. 30 Heterocycles are optionally substituted as described herein.

“Optionally substituted”, is used herein interchangeably with the phrase substituted or unsubstituted. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group, and each substitution is independent of the other. An optionally

substituted group also may have no substituents. Therefore, the phrase “optionally substituted with at least one substituent” means that the number of substituents may vary from zero up to a number of available positions for substitution.

5 “Parasite(s)”, as used herein, unless otherwise indicated, refers to endoparasites and ectoparasites. Endoparasites are parasites that live within the body of its host and include helminths (e.g., trematodes, cestodes, and nematodes) and protozoa. Ectoparasites are organisms of the Arthropoda phylum (e.g., arachnids, insects, and crustaceans (e.g., copepods-sea lice)
10 which feed through or upon the skin of its host. Preferred arachnids are of the order Acarina, e.g., ticks and mites. Preferred insects are midges, fleas, mosquitos, biting flies (stable fly, horn fly, blow fly, horse fly, and the like), bed bugs, and lice. Preferred compounds of the present invention can be used for the treatment of parasites, i.e., treatment of a parasitic infection or infestation.

15 “Protecting group” or “Pg”, as used herein, unless otherwise indicated, refers to a substituent that is commonly employed to block or protect an amine on the compound thereby protecting its functionality while allowing for the reaction of other functional groups on the compound. Non-exclusive examples of an amine-protecting group include: acyl groups (e.g., formyl, acetyl,
20 chloroacetyl, trichloro-acetyl, *o*-nitrophenylacetyl, *o*-nitrophenoxycetyl, trifluoroacetyl, acetoacetyl, 4-chlorobutyryl, isobutyryl, *o*-nitrocinnamoyl, picolinoyl, acylisothiocyanate, aminocaproyl, benzoyl, and the like), acyloxy groups (e.g., 1-*tert*-butyloxycarbonyl (Boc), methoxycarbonyl, 9-fluorenyl-methoxycarbonyl, 2,2,2-trifluoroethoxycarbonyl, 2-trimethylsilylethoxycarbonyl,
25 vinylloxycarbonyl, allyloxycarbonyl, 1,1 –dimethyl-propynyloxycarbonyl, benzyloxy-carbonyl, *p*-nitrobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl, and the like), diphenylmethane, and benzylcarbmates.

 “Therapeutically effective amount”, as used herein, unless otherwise indicated, refers to an amount of the compounds of the present invention that (i)
30 treat the particular parasitic infection or infestation, (ii) attenuates, ameliorates, or eliminates one or more symptoms of the particular parasitic infection or infestation, or (iii) prevents or delays the onset of one or more symptoms of the particular parasitic infection or infestation described herein.

"Treatment", "treating", and the like, as used herein, unless otherwise indicated, refers to reversing, alleviating, or inhibiting the parasitic infection, infestation, or condition. As used herein, these terms also encompass, depending on the condition of the animal, preventing the onset of a disorder or condition, or of symptoms associated with a disorder or condition, including
5 reducing the severity of a disorder or condition or symptoms associated therewith prior to affliction with said infection or infestation. Thus, treatment can refer to administration of the compounds of the present invention to an animal that is not at the time of administration afflicted with the infection or infestation.
10 Treating also encompasses preventing the recurrence of an infection or infestation or of symptoms associated therewith as well as references to "control" (e.g., kill, repel, expel, incapacitate, deter, eliminate, alleviate, minimize, and eradicate).

"Veterinary acceptable" as used herein, unless otherwise indicated,
15 indicates that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, composition, and/or the animal being treated therewith. The term "pharmaceutically" acceptable has the same meaning as that recited for "veterinarily" acceptable.

20

DETAILED DESCRIPTION

The present invention provides Formula (1) compounds, stereoisomers thereof, as well as veterinary compositions that are useful as antiparasitic agents for animals, in particular, compounds that act as ectoparasiticides.

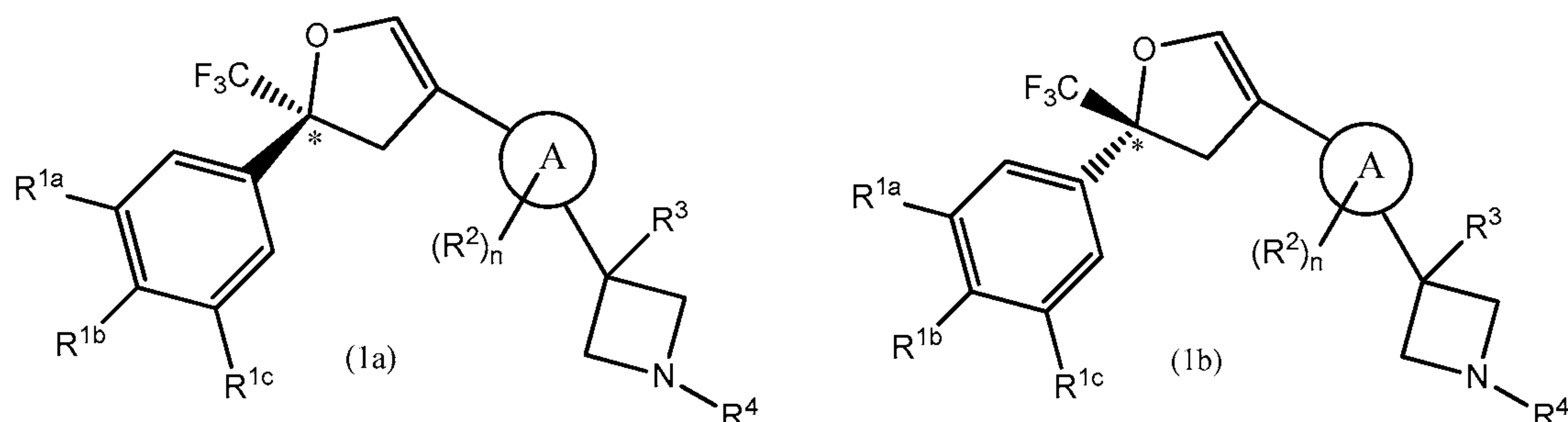
25 Compounds of the present invention may be synthesized by synthetic routes that include processes analogous to those well known in the chemical arts, particularly in light of the description contained herein. The starting materials are generally available from commercial sources such as Aldrich Chemicals (Milwaukee, Wis.) or are readily prepared using methods well known
30 to those skilled in the art (e.g., prepared by methods generally described in Louis F. Fieser and Mary Fieser, "Reagents for Organic Synthesis", 1; 19, Wiley, New York (1967, 1999 ed.), or Beilsteins Handbuch der organischen Chemie, 4, Aufl. ed. Springer-Verlag, Berlin, including supplements (also available *via* the Beilstein online database)). For illustrative purposes, the reaction schemes

depicted below demonstrate potential routes for synthesizing compounds of the present invention, and key intermediates. For a more detailed description of the individual reaction steps, see the Examples section below. A skilled artisan will appreciate that other suitable starting materials, reagents, and synthetic routes
5 may be used to synthesize the compounds of the present invention and a variety of derivatives thereof. Further, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional chemistry well known to the skilled artisan.

Compounds of the present invention described herein contain at least one
10 asymmetric or chiral center; and, therefore, exist in different stereoisomeric forms. The R and S configurations are based upon knowledge of known chiral inversion/retention chemistry. Unless specified otherwise, it is intended that all stereoisomeric forms of the compounds of the present invention as well as mixtures thereof, including racemic mixtures and diastereomeric mixtures, form
15 part of the present invention.

Enantiomeric mixtures can be separated into their individual enantiomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as chromatography and/or fractional crystallization. A more detailed description of techniques that can be used to resolve
20 stereoisomers of compounds from their racemic mixture can be found in Jean Jacques Andre Collet, Samuel H. Wilen, Enantiomers, Racemates and Resolutions, John Wiley and Sons, Inc. (1981).

Compounds of this invention can exist as one or more stereoisomers. The various stereoisomers include enantiomers, diastereomers and atropisomers.
25 One skilled in the art will appreciate that one stereoisomer may be more active and/or may exhibit beneficial effects when enriched relative to the other stereoisomer(s) or when separated from the other stereoisomer(s). Additionally, the skilled artisan knows how to separate, enrich, and/or to selectively prepare said stereoisomers. The compounds of the invention may be present as a
30 mixture of stereoisomers, individual stereo isomers or as an optically active form. For example, two possible enantiomers of Formula 1 are depicted as Formula 1a and Formula 1b involving the spirocyclic isoxazoline chiral center identified with an asterisk (*). Molecular depictions drawn herein follow standard conventions for depicting stereochemistry.



For illustrative purposes, the reaction schemes depicted below demonstrate potential routes for synthesizing key intermediates and compounds of the present invention. For a more detailed description of the individual reaction steps, see the Examples section below. Those skilled in the art will appreciate that other suitable starting materials, reagents, and synthetic routes may be used to synthesize the intermediates and compounds of the present invention and a variety of derivatives thereof. Further, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional chemistry. Schemes 1-10 outline the general procedures useful for the preparation and isolation of compounds of the present invention. It is to be understood, however, that the invention, as fully described herein and as recited in the claims, is not intended to be limited by the details of the following schemes or modes of preparation.

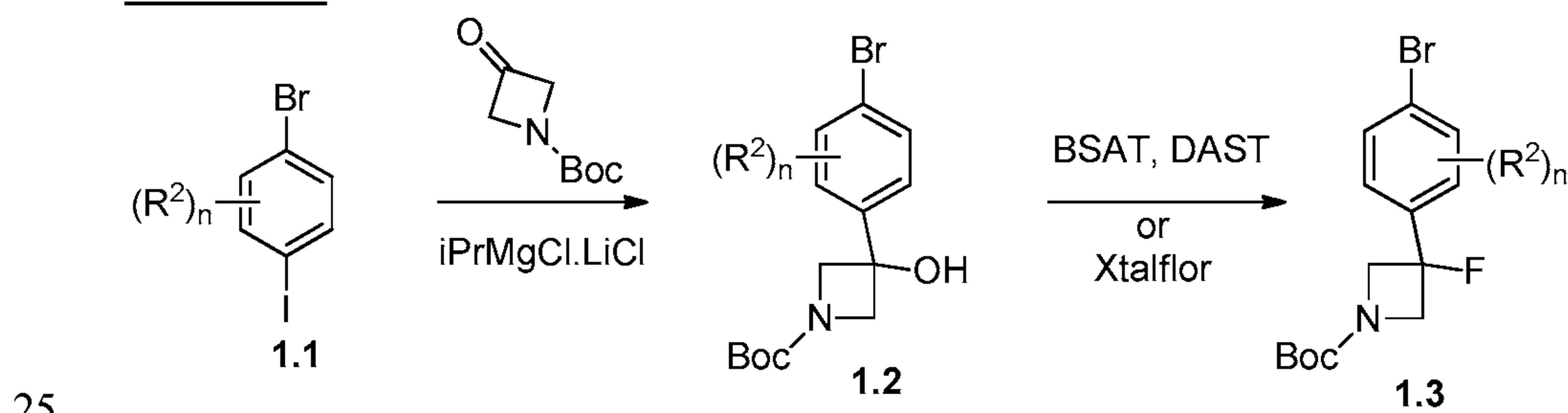
In the preparation of compounds of the present invention, protection of remote functionality of intermediates from undesired reactions can be accomplished with a protecting group. The term "protecting group" or "Pg" refers to a substituent that is commonly employed to block or protect a particular functionality while reacting other functional groups on the compound. For example, an amine-protecting group is a substituent attached to an amine that blocks or protects the amine-functionality of the compound or intermediate. Suitable amine protecting groups include: 1-*tert*-butoxycarbonyl (Boc), acyl groups including: formyl, acetyl, chloroacetyl, trichloro-acetyl, *o*-nitrophenylacetyl, *o*-nitrophenoxyacetyl, trifluoroacetyl, acetoacetyl, 4-chlorobutyryl, isobutyryl, *o*-nitrocinnamoyl, picolinoyl, acylisothiocyanate, aminocaproyl, benzoyl, and the like; and acyloxy groups including: methoxycarbonyl, 9-fluorenyl-methoxycarbonyl, 2,2,2-trifluoroethoxycarbonyl, 2-trimethylsilylethoxycarbonyl, vinyloxycarbonyl, allyloxycarbonyl, 1,1 -dimethyl-

propynyloxycarbonyl, benzyloxy-carbonyl, p-nitrobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl, and the like. Similarly, diphenylmethane and benzylcarbamates can be used as amine protecting groups. Suitable protecting groups and their respective uses are readily determined by one skilled in the art.

- 5 For a general description of protecting groups and their use, see T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991.

In the Schemes and Examples below, the following catalysts/reactants and miscellaneous abbreviations include: N,N-dimethyl formamide (DMF); dimethyl acetamide (DMA); tetrahydrofuran (THF); trifluoroacetic acid (TFA);
 10 dimethyl ether (DME); triphenylphosphine palladium (Pd(PPh₃)₄); N,N,N',N'-Tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (HATU); isopropylmagnesium chloride (iPrMgCl); t-butyloxycarbonyl (BOC); n-butyllithium (n-BuLi); triethylamine (Et₃N); dichloromethane (CH₂Cl₂); Bis(2-methoxyethylaminosulfur trifluoride (BSAT); diethyaminosulfur trifluoride (DAST);
 15 dichloroethane (DCE); palladium(II)[1,3-bis(diphenylphosphino)propane] (PD dppp); carbonyldiimidazole (CDI); tetrabutylammonium fluoride (TBAF); 4-dimethylaminopyridine (DMAP); Bis(1,5-cyclooctadienediiridium(1) dichloride ([Ir(COD)]₂); 4,4-di-tert-butyl bipyridine (dtbpy); bis(pinacolato)diboron (B₂pin₂); trimethylsilyldiazomethane (TMSCHN₂); and isopropylamine (iPrNH₂);
 20 triethyl amine (TEA); dichloromethane (DCM); methanol (MeOH); potassium hexamethyldisilazane (KHMDs); dimethylsulfoxide (DMSO); N,N-diisopropylethylamine (DIPEA); and propane phosphonic acid anhydride (T₃P).

Scheme 1

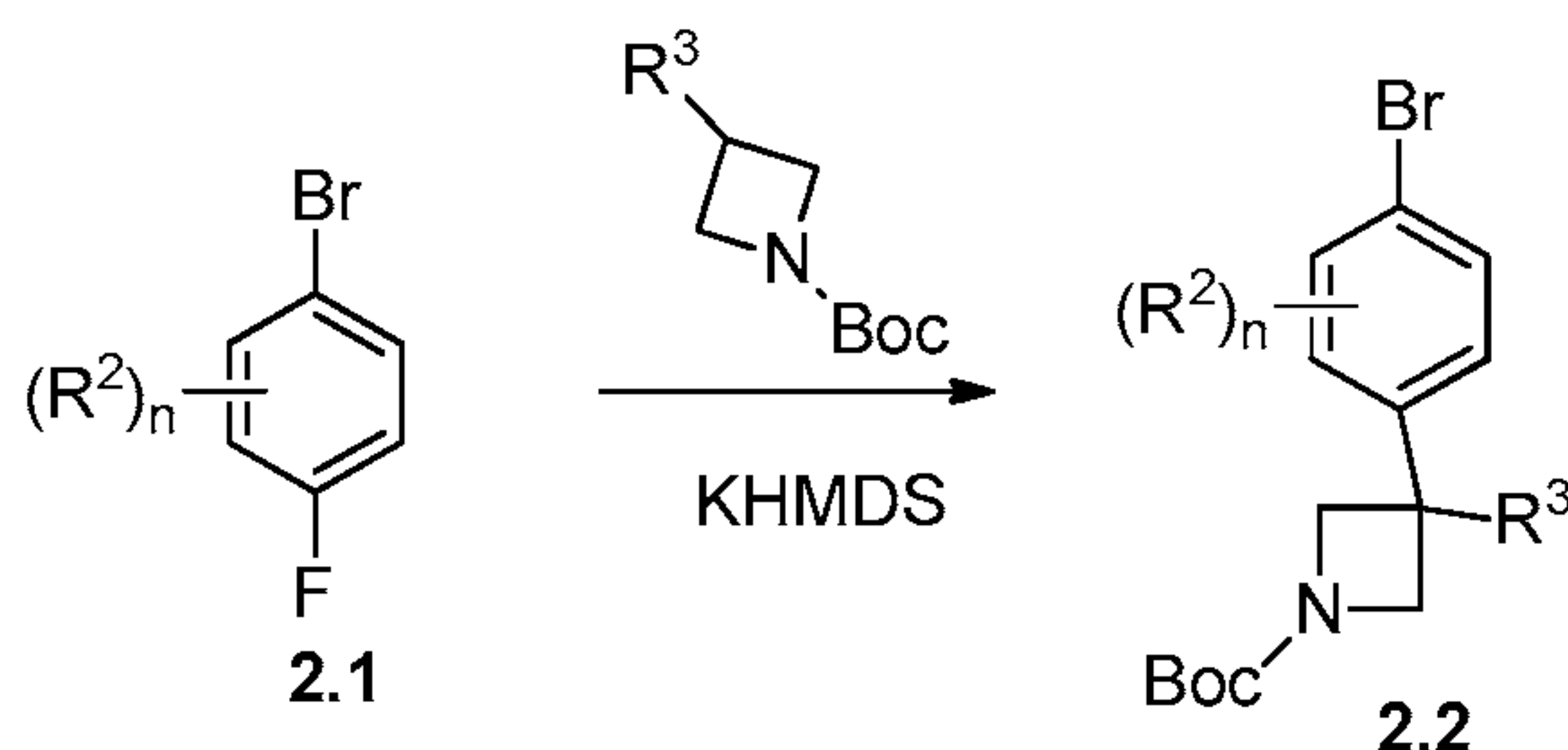


R² and n are as defined herein.

Compounds of Formula **2.2** (below) can be prepared using methods illustrated in Scheme 1. Selective Grignard metallation of the
 30 bromoiodobenzene **1.1** and addition to a protected azetidinone provides the

phenylazetidine derivatives **1.2**. The hydroxyl functionality can be further manipulated such as by treatment with a fluorinating agent (BAST, DAST or Xtalflor) to provide additional analogs of the phenylazetidines **1.3**.

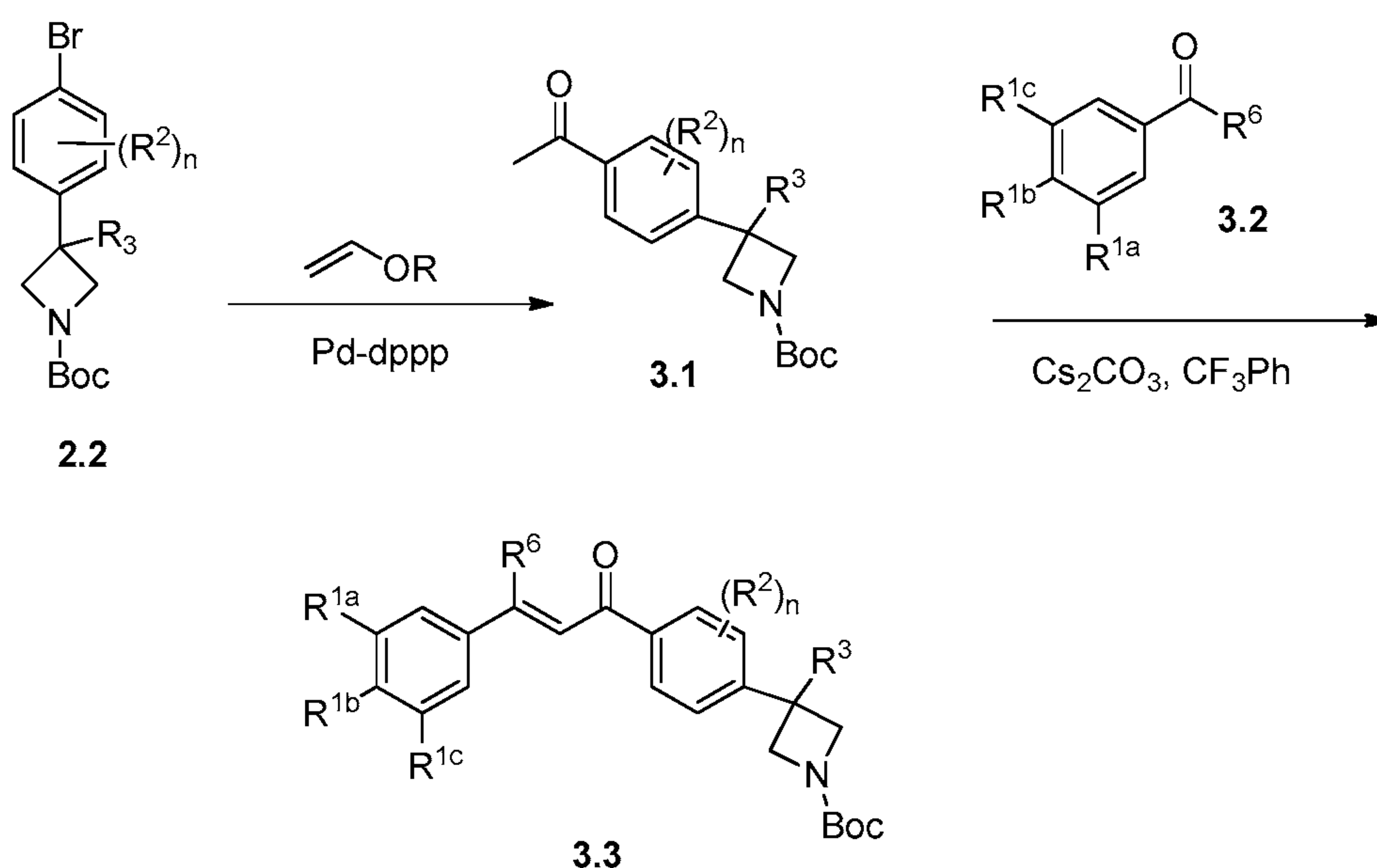
5 Scheme 2



R^2 , R^3 , and n are as defined herein.

Alternatively, compounds of Formula **2.2** can prepared using methods illustrated in Scheme 2. When R^3 is an electron withdrawing group (CN, CO_2R , SO_2R , etc), deprotonation of the azetidine ring can be accomplished by treatment with KHMDS. This metallated species can then undergo $\text{S}_{\text{N}}\text{Ar}$ displacement reaction of the fluorine of the bromofluorobenzene **2.1** to provide substituted azetidine analogs of Formula **2.2**. Other substituted phenylazetidines can be purchased from commercial sources or prepared using procedures analogous to those found in literature (see for example: WO2012017359 or Justus Liebigs Annalen der Chemie (1961), 647 83-91).

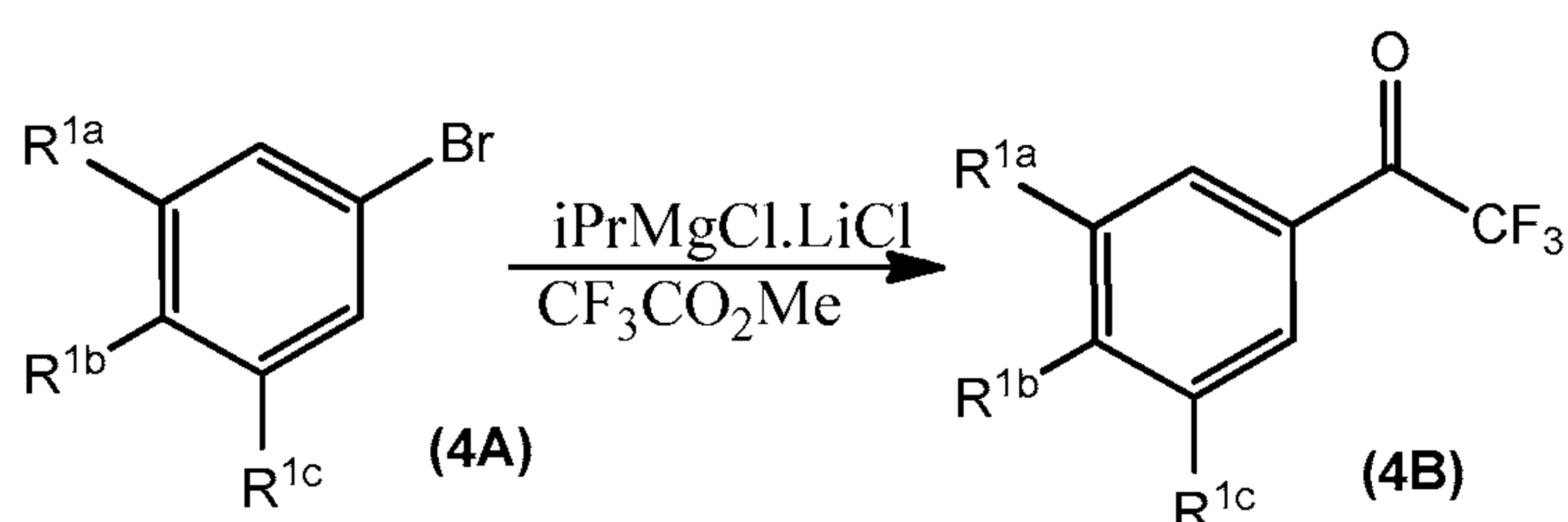
Scheme 3



R, R^{1a}, R^{1b}, R^{1c}, R², R³, R⁶, and n are as defined herein.

Compounds of Formula **3.3** can be prepared using methods illustrated by Scheme 3. Palladium catalyzed condensation of the bromophenylazetidine **2.2** with a vinyl ether provides the acetophenone **3.1** which can undergo
 5 condensation with a substituted phenylketone derivative **3.2** in the presence of a base such as cesium carbonate to give the enone **3.3**. The phenylketone derivative can be prepared by reacting bromobenzene with an ethyl ester in the presence of a Grignard reagent.

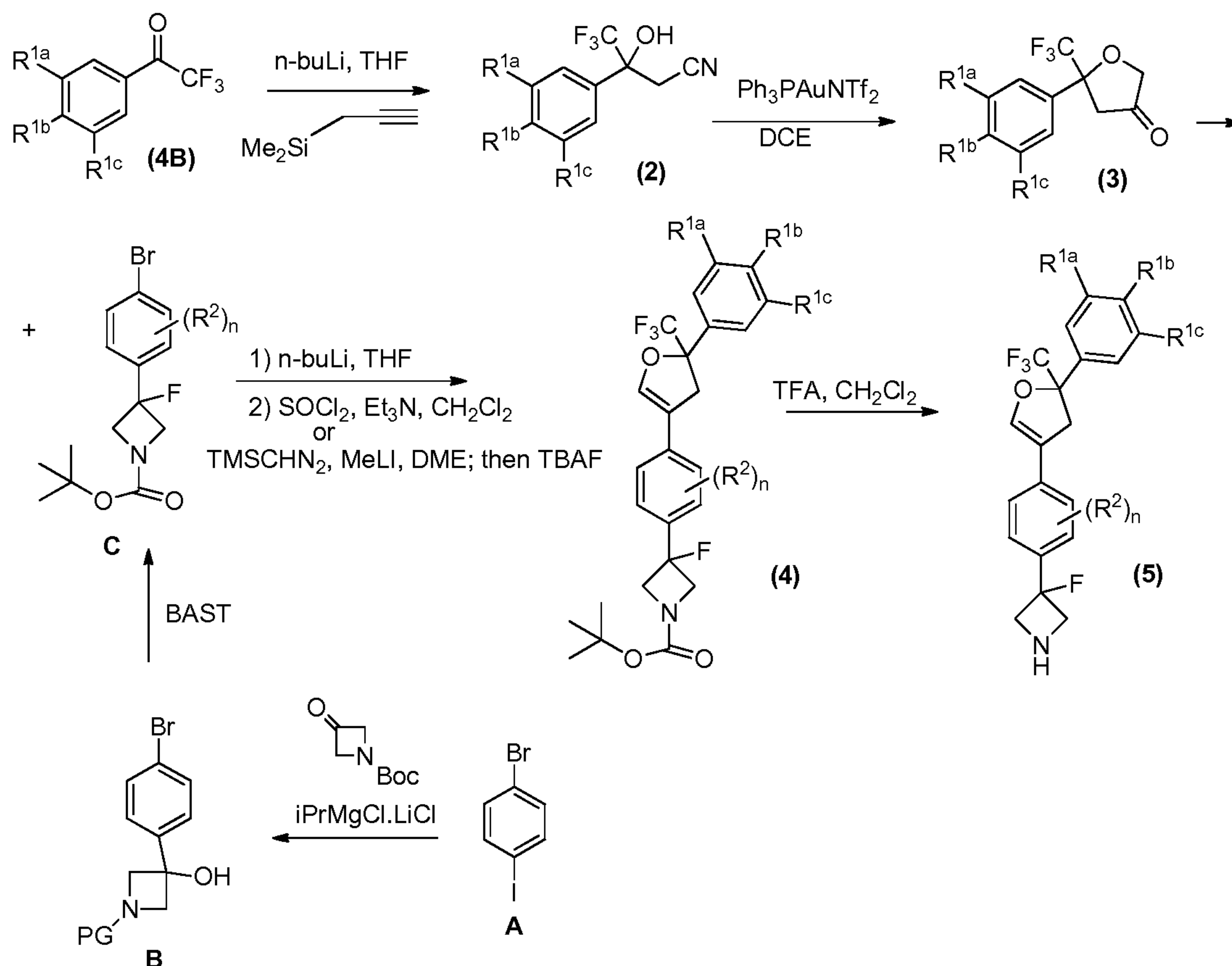
10 Scheme 4



The requisite trifluorophenylethanone derivatives **4B** can be prepared
 15 according to Scheme 4. Metallation of the aryl bromide **4A** under modified Grignard conditions and addition to ethyl 2,2,2-trifluoroacetate provides the substituted trifluorophenyl-ethanones **4B**.

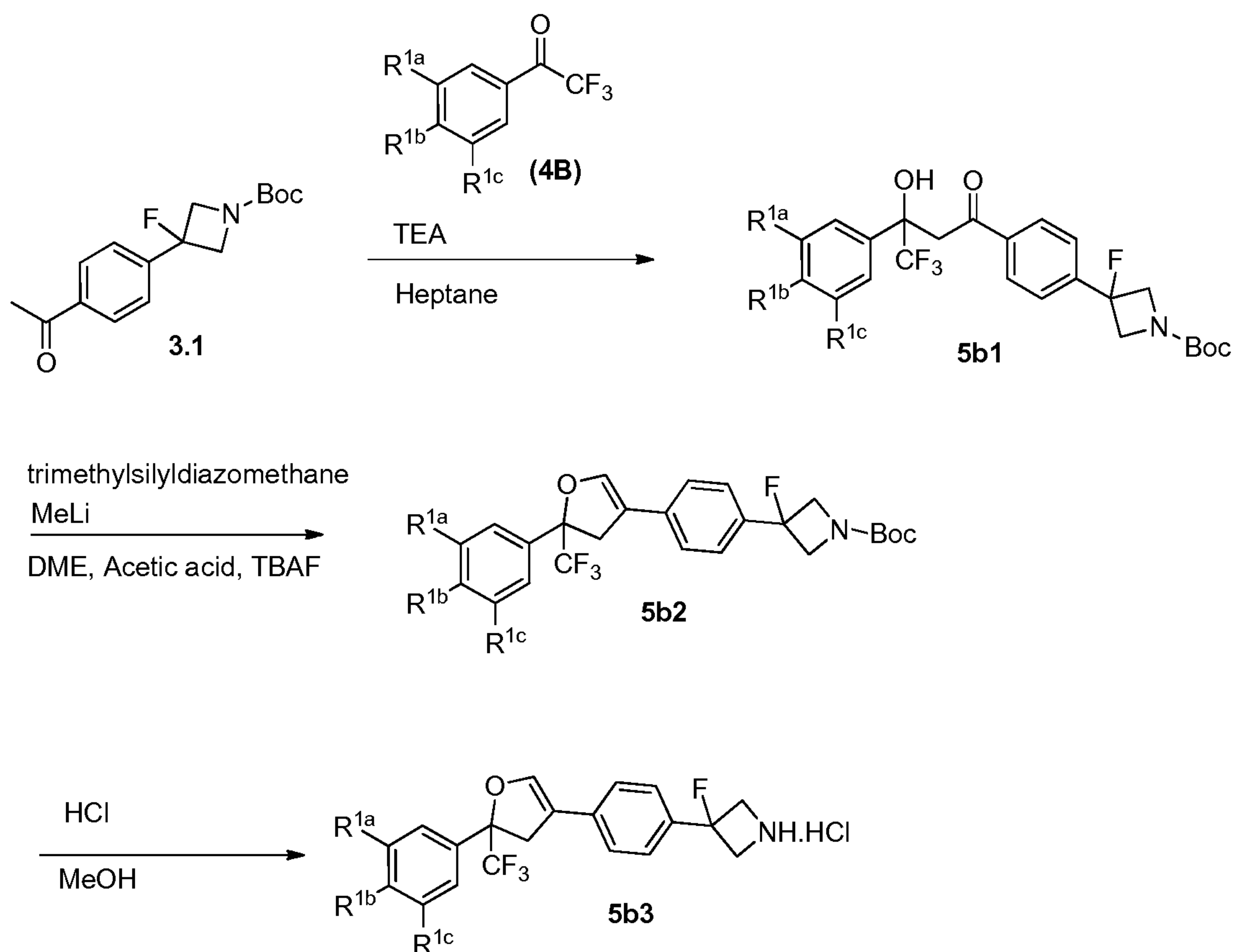
Scheme 5a

20



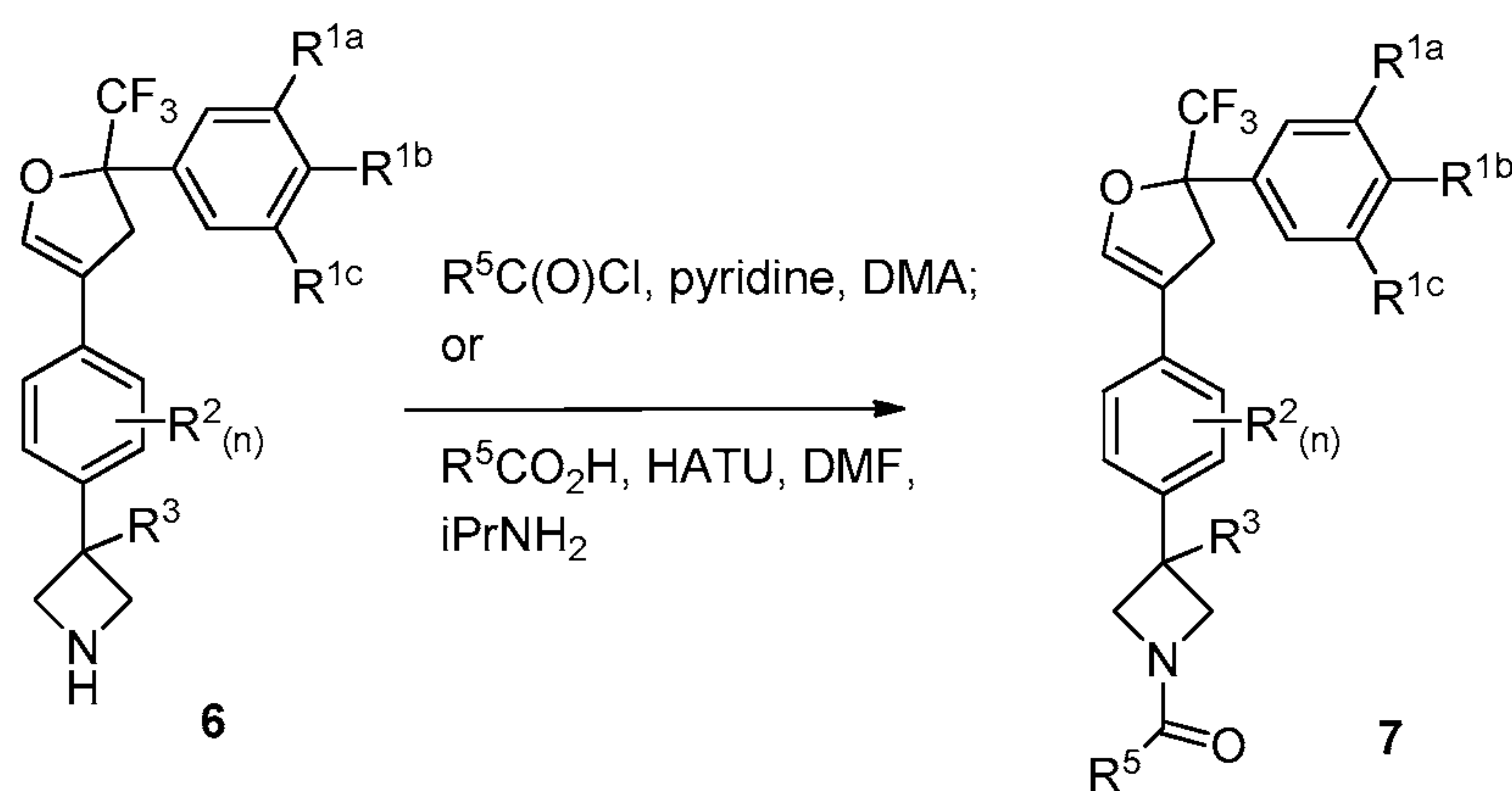
- Scheme 5a describes the preparation of the 2,3-dihydrofuran compounds from the bromophenyl azetidine **C** and the dihydrofuranone **3**. The
- 5 dihydrofuranone **3** is prepared by a two step procedure, initially involving the addition of trimethylsilylpropyne to the aryl olefin **4B** in the presence of a strong base and a subsequent hydrative cyclization of the resulting alcohol **2** in the presence of a suitable Lewis acid as described in *J. Am. Chem. Soc.*, 2010, 132 (10), pp 3258-3259. Halogen-metal exchange mediated addition of the
- 10 bromophenyl azetidine **C** to the dihydrofuranone **3** affords the 2,3-dihydrofuran **4**. Removal of the Boc protecting group can be achieved by treatment with trifluoroacetic acid to provide azetidine **5**. The bromophenyl azetidine **C** can be prepared by metallation of bromoiodobenzene **A** under modified Grignard conditions, condensation with a protected azetidinone to form the
- 15 hydroxyazetidinone **B** and fluorination of **B** with a fluorinating agent such as BAST, DAST or Xtalfluor.

Scheme 5b



Condensation of the acetophenone **3.1** with a substituted trifluoroacetophenone **(4B)** in the presence of a base such as triethylamine provides the beta-hydroxyketone **5b1**. Condensation of **5b1** with trimethylsilyldiazomethane and subsequent cyclization provides the dihydrofuran **5b2**. Removal of the Boc protecting group can be accomplished with acidic conditions such as HCl in methanol or trifluoroacetic acid to provide the azetidine **5b3**.

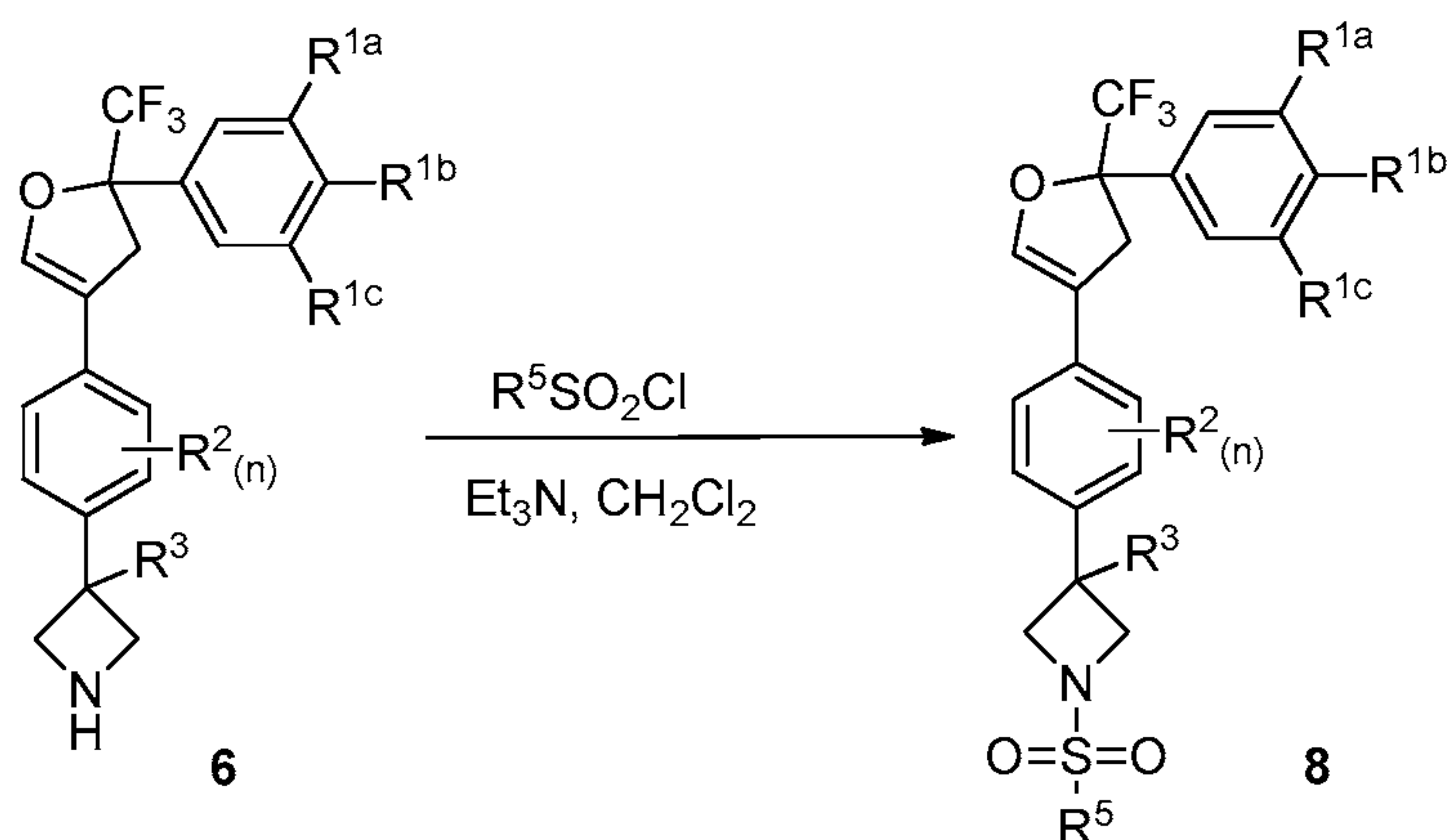
10

Scheme 6

R^{1a} , R^{1b} , R^{1c} , R^2 , R^3 , R^5 , and n are as defined herein.

Amide analogs of the azetidine ring can be prepared as shown in Scheme 6. Acylation of the azetidine ring can be accomplished by reaction of the azetidine **6** with an acid chloride in pyridine/DMA or by a condensation with a carboxylic acid utilizing a condensing agent such as HATU or HOBt to afford compound **7**.

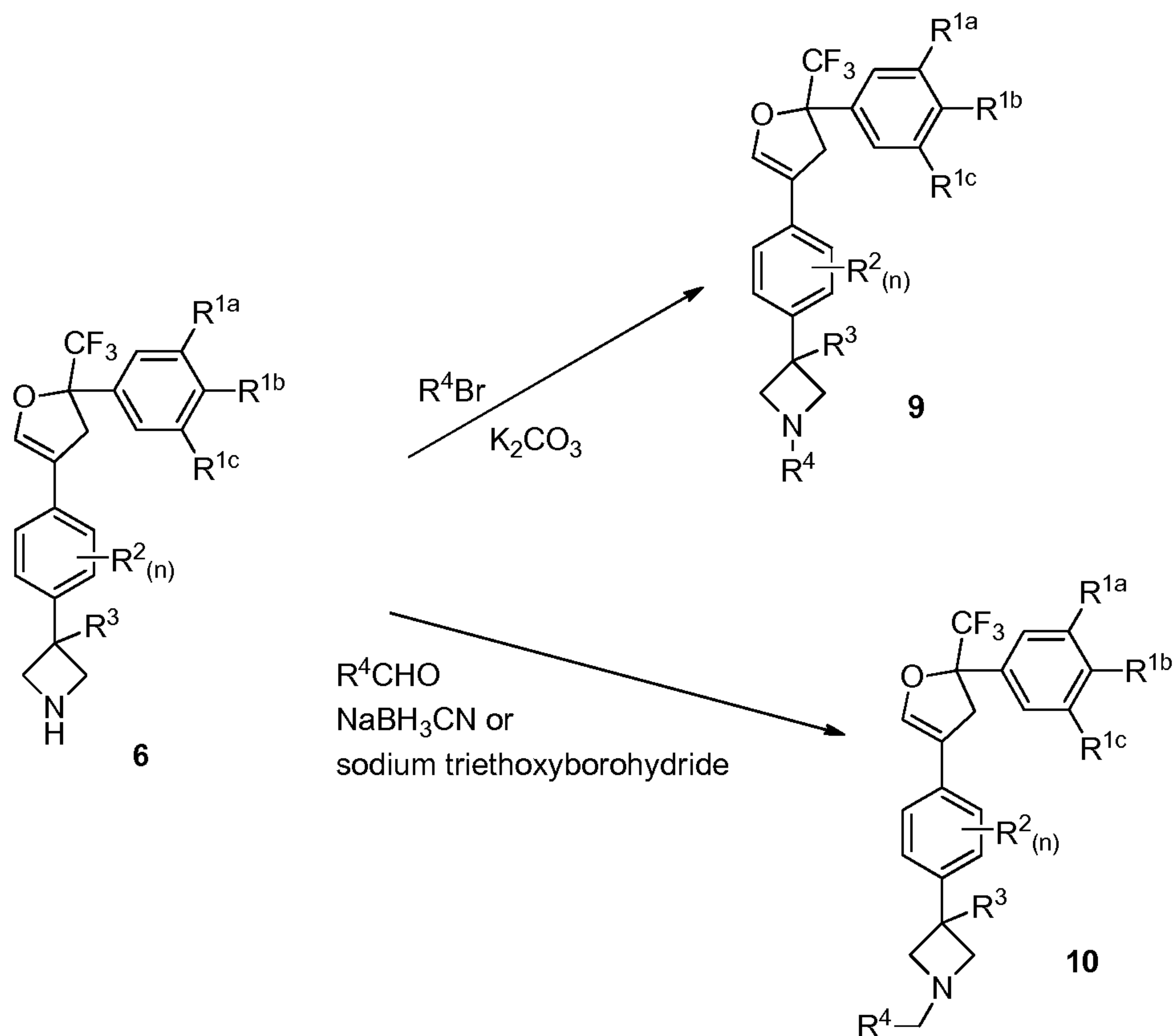
Scheme 7



R^{1a} , R^{1b} , R^{1c} , R^2 , R^3 , R^5 , and n are as defined herein.

Sulfonamide analogs of the azetidine ring can be prepared as shown in Scheme 7. Reaction of azetidine **6** with sulfonyl chlorides in the presence of triethylamine can give the desired sulfonamides **8**.

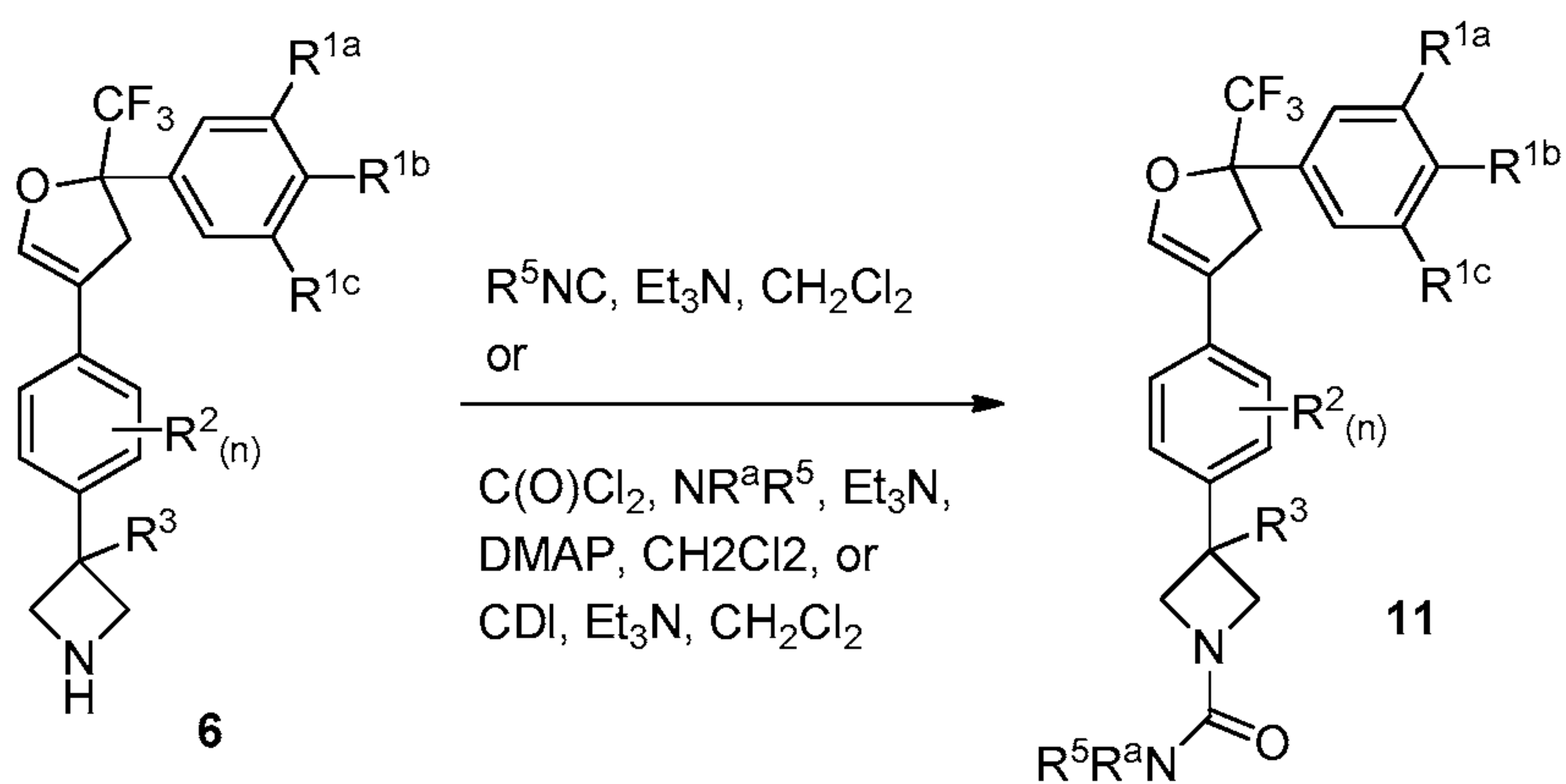
Scheme 8



R^{1a}, R^{1b}, R^{1c}, R², R³, R⁴, and n are as defined herein.

Compounds in which R⁴ is alkyl or substituted alkyl can be prepared from the azetidine **6** by standard alkylation chemistry or by reductive amination with the corresponding aldehydes as shown in Scheme 8.

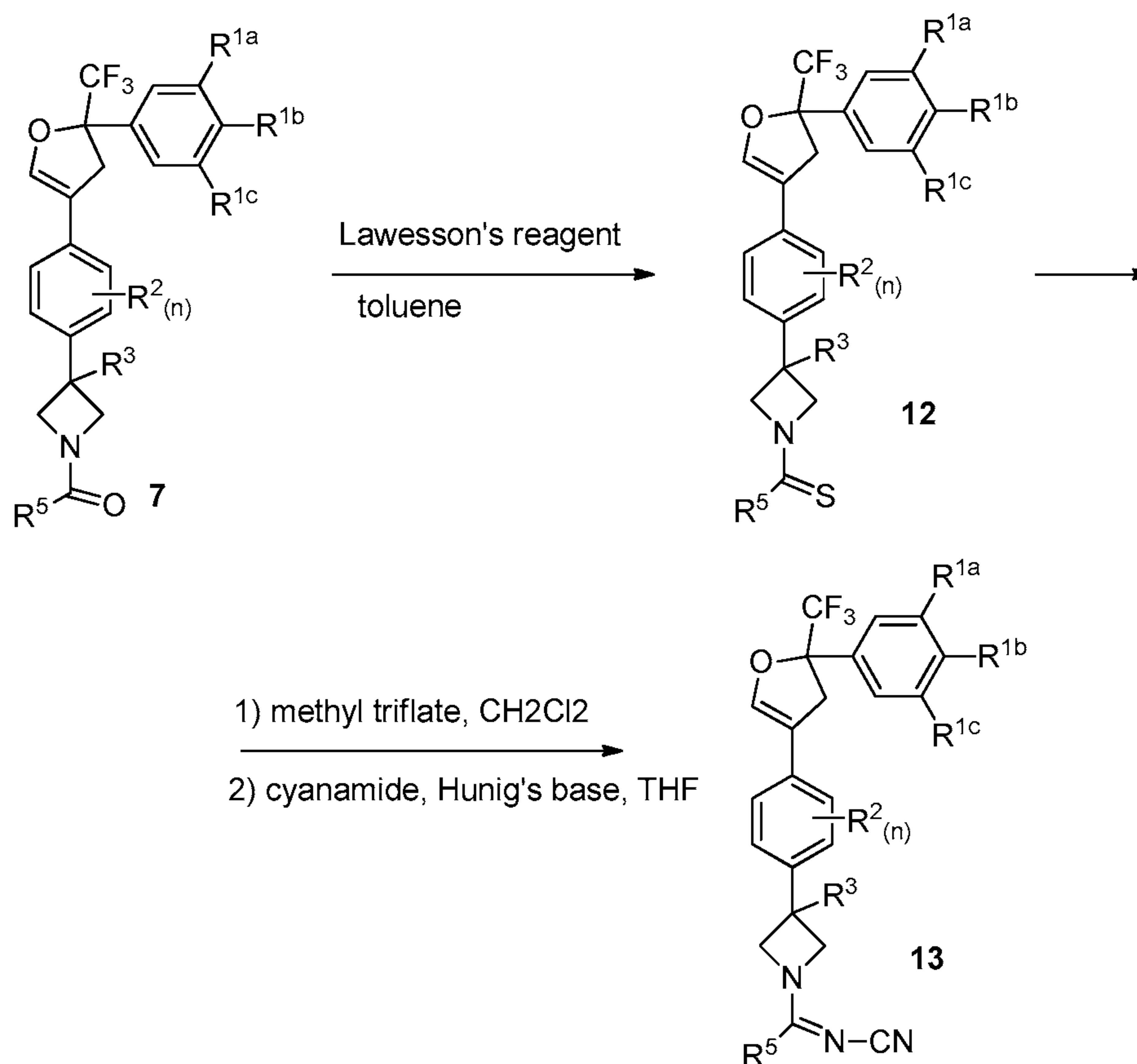
Scheme 9



R^{1a}, R^{1b}, R^{1c}, R², R³, R^a, R⁵, and n are as defined herein.

Urea analogs can be prepared as shown in Scheme 9. Reaction of the azetidine **6** with an isocyanate or preformed carbamoyl chloride in the presence of a tertiary amine base provides the ureas.

5 Scheme 10



Thioamide **12** can be prepared by treatment of amide **7** with Lawesson's reagent in refluxing toluene. Methyl triflate can be added to thioamide **12** in a solvent such as CH₂Cl₂ to form a thioimide intermediate as a solution.

- 10 Cyanamide and Hunig's base in THF can be subsequently added directly to the thioimide solution to afford cyanamide **13**.

One skilled in the art will recognize that, in some cases, after the introduction of a given reagent as it is depicted in the schemes, it may be necessary to perform additional routine synthetic steps not described in detail to complete the synthesis of Formula (1) compounds.

The present invention includes all veterinarily acceptable isotopically-labelled Formula (1) compounds wherein one or more atoms are replaced by

atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature.

Examples of isotopes suitable for inclusion in the compounds of the present invention include isotopes of hydrogen, such as ^2H and ^3H , carbon, such as ^{11}C , ^{13}C and ^{14}C , chlorine, such as ^{36}Cl , fluorine, such as ^{18}F , iodine, such as ^{123}I and ^{125}I , nitrogen, such as ^{13}N and ^{15}N , oxygen, such as ^{15}O , ^{17}O and ^{18}O , and sulphur, such as ^{35}S .

The skilled person will appreciate that the compounds of the present invention could be made by methods other than those herein described, by adaptation of the methods herein described and/or adaptation of methods known in the art, for example the art described herein, or using standard textbooks such as "Comprehensive Organic Transformations - A Guide to Functional Group Transformations", RC Larock, Wiley-VCH (1999 or later editions).

The Formula (1) compounds are useful as ectoparasitic and endoparasitic agents, therefore, another embodiment of the present invention is a veterinary or pharmaceutical composition comprising a therapeutically effective amount of a Formula (1) compound, stereoisomer thereof, and a veterinary or pharmaceutically acceptable excipient, diluent or carrier. The compounds of the present invention (including the compositions and processes used therein) may also be used in the manufacture of a medicament for the therapeutic applications described herein.

A typical formulation is prepared by mixing a Formula (1) compound with a carrier, diluent or excipient. Suitable carriers, diluents and excipients are well known to those skilled in the art and include materials such as carbohydrates, waxes, water soluble and/or swellable polymers, hydrophilic or hydrophobic materials, gelatin, oils, solvents, water, and the like. The particular carrier, diluent or excipient used will depend upon the means and purpose for which the compound of the present invention is being applied. Solvents are generally selected based on solvents recognized by persons skilled in the art as safe to be administered to an animal. The formulations may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring

agents and other known additives to provide an elegant presentation of the drug (i.e., a compound of the present invention or veterinary composition thereof) or aid in the manufacturing of the veterinary or pharmaceutical product (i.e., medicament).

5 The formulations can be prepared using conventional dissolution and mixing procedures. Such compositions and methods for their preparation may be found, for example, in 'Remington's Veterinary Sciences', 19th Edition (Mack Publishing Company, 1995; and "Veterinary Dosage Forms: Tablets, Vol. 1", by H. Lieberman and L. Lachman, Marcel Dekker, N.Y., 1980 (ISBN 0-8247-6918-
10 X). For example, the bulk drug substance (i.e., compound of the present invention or stabilized form of the compound (e.g., complex with a cyclodextrin derivative or other known complexation agent)) is dissolved in a suitable solvent in the presence of one or more other excipients. The compounds of the present invention are typically formulated into veterinary or pharmaceutical dosage forms
15 to provide an easily controllable dosage form for administration. Compounds of the present invention can also be admixed with animal feed.

 The compounds may be administered alone or in a formulation appropriate to the specific use envisaged, the particular species of host animal being treated and the parasite involved. Generally, they will be administered as
20 a formulation in association with one or more veterinarily or pharmaceutically acceptable salts, excipients, diluents, or carriers. The term "excipient", "diluent" or "carrier" is used herein to describe any ingredient other than the Formula (1) compounds or any additional antiparasitic agent. The choice of excipient, diluent, or carrier will to a large extent depend on factors such as the particular mode of
25 administration, the effect of the excipient, carrier, or diluent on solubility and stability, nature of the dosage form, and animal specie.

 The methods by which the compounds of the present invention may be administered include oral, topical, and injectable (subcutaneous, intraperitoneal, and intramuscular) administration. The preferred method of administration of the
30 Formula (1) compounds is in an oral solid dosage form or oral liquid dosage form. Equally preferred is topical administration.

 The Formula (1) compounds can be administered orally by capsule, bolus, tablet, powders, lozenges, chews, multi and nanoparticulates, gels, solid solution, films, sprays, liquid form, or admixed with food. Oral administration is

the preferred method of administration and as such it is desirable to develop active Formula (1) compounds that are particularly suited to such formulations. Such formulations may be employed as fillers in soft or hard capsules, tablets, or chews, and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, N-methylpyrrolidone, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid forms include suspensions, solutions, syrups, drenches and elixirs. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet. Oral drenches are commonly prepared by dissolving or suspending the active ingredient in a suitable medium. Feed admixtures can be prepared for livestock and fish. Oral formulations can comprise from about 0.5 mg/kg to 50 mg/kg of a Formula (1) compound, and preferably about 1 mg/kg to 30 mg/kg of a Formula (1) compound. Depending upon the host specie treated and the parasite being treated, dose adjustments can be made.

The compounds may be administered topically to the skin or mucosa, that is dermally or transdermally. This is a preferred method of administration and as such it is desirable to develop active Formula (1) compounds that are particularly suited to such formulations, for example liquid forms. Typical formulations for this purpose include pour-on, spot-on, multi-spot-on, stripe-on, comb-on, roll-on, dip, spray, mousse, shampoo, powder formulation, gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibers, bandages and micro emulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, N-methyl formamide, glycol monomethyl ethers, polyethylene glycol, propylene glycol, and the like. Penetration enhancers may be incorporated - see, for example, J Pharm Sci, 88 (10), 955-958 by Finnin and Morgan (October 1999). Pour-on or spot-on formulations may be prepared by dissolving the active ingredients in an acceptable liquid carrier vehicle such as butyl digol, liquid paraffin or a non-volatile ester, optionally with the addition of a volatile component such as propan-2-ol or a glycol ether. Alternatively, pour-on, spot-on or spray formulations can be prepared by encapsulation, to leave a residue of active agent on the surface of the animal, this effect may ensure that the Formula (1) compounds have increased persistence of action and are more durable, for

example they may be more water fast. Topical formulations of the combination contemplated herein can comprise from about 0.5 mg/kg to 50 mg/kg of a Formula (1) compound, and preferably about 1 mg/kg to 10 mg/kg of a Formula (1) compound. The compositions suitable for spot-on application according to
5 the invention can be prepared by conventional mixing means. The volume of the applied composition can be from about 0.5 mL/kg to 5 mL/kg and preferably from about 1 mL/kg to 3mL/kg. Similarly, dose can be adjusted.

The compounds of the present invention can also be administered topically via a support matrix for example, a synthetic or natural resin, plastic,
10 cloth, leather, or other such polymeric system in the shape of a collar or ear tag. Said collar or ear tag may be coated, impregnated, layered, by any means so as to provide a veterinarily or pharmaceutically acceptable amount of a compound of the present invention alone, or with a veterinarily or pharmaceutically acceptable excipient, diluent, or carrier, and optionally an additional veterinary
15 agent, or veterinarily or pharmaceutically acceptable salt thereof.

Agents may be added to the formulations of the present invention to improve the persistence of such formulations on the surface of the animal to which they are applied, for example to improve their persistence on the coat of the animal. It is particularly preferred to include such agents in a formulation
20 which is to be applied as a pour-on or spot-on formulation. Examples of such agents include acrylic copolymers and in particular fluorinated acrylic copolymers. A particular suitable reagent is the trademark reagent "Foraperle" (Redline Products Inc, Texas, USA). Certain topical formulations may include unpalatable additives to minimize oral exposure.

Injectable formulations may be prepared in the form of a sterile solution, which may contain other substances, for example enough salts or glucose to make the solution isotonic with blood. Acceptable liquid carriers include vegetable oils such as sesame oil, glycerides such as triacetin, esters such as benzyl benzoate, isopropyl myristate and fatty acid derivatives of propylene
30 glycol, as well as organic solvents such as pyrrolidin-2-one and glycerol formal. The formulations are prepared by dissolving or suspending compounds of the present invention alone or with an additional veterinary agent in the liquid carrier such that the final formulation contains from about 0.01 to 50% by weight of the

active ingredients, preferably from about 0.01% to about 10% by weight of the active ingredients.

Suitable devices for injection include needle (including micro needle) injectors, needle-free injectors and infusion techniques. Subcutaneous
5 formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dry powder form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water. The preparation of
10 subcutaneous formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard veterinary techniques well known to those skilled in the art. The solubility of compounds of Formula (1) used in the preparation of subcutaneous solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-
15 enhancing agents.

Such formulations are prepared in a conventional manner in accordance with standard medicinal or veterinary practice. Further, these formulations will vary with regard to the weight of active compound contained therein, depending on the species of host animal to be treated, the severity and type of infection or
20 infestation, and the body weight of the animal.

For fish, compounds of the present invention can be formulated for oral administration by way of feed admixture. For example, the compounds of the present invention can be formulated in a food product (e.g., pellets) that can be easily dispersed to fish as a feeding agent. Further, a compound of the present
25 invention can be administered topically by immersing the fish into an aqueous environment containing at least one of the compounds of the present invention. For example, fish may be transferred into a tank for treatment or caused to pass from one holding zone into another. The compounds of the present invention may also be administered directly to the water containing the fish. The
30 compound of the present invention can be in any dispersible formulation such that upon introduction to water the compound dissolves into the solution. Alternatively, the compounds of the present invention can be administered by injection. Preferable injection routes for treatment of fish are intraperitoneal or intramuscular. The injectable formulations include any liquid suspension, such as

oils, aqueous solutions, or oil and water emulsions. The compounds of the present invention can also be co-administered with additional agents, antigens, adjuvants, carriers, diluents or nutrients.

The Formula (1) compounds are also active against all or individual
5 developmental stages of animal pests showing normal sensitivity, as well as those showing resistance to widely used parasitocides.

As described herein, compounds of the present invention may be administered alone or in combination with at least one additional veterinary agent including insecticides, acaricides, anthelmintics, fungicides, nematocides,
10 antiprotozoals, bactericides, and growth regulators to form a multi-component agent giving an even broader spectrum of veterinary utility. Thus, the present invention also pertains to a composition comprising an effective amount of a Formula (1) compound, a stereoisomer thereof, and an effective amount of at least one additional veterinary agent and can further comprise one or more of a
15 veterinarily or pharmaceutically acceptable excipient, diluent, or carrier.

The following list of additional veterinary agents together with which the compounds of the present invention can be used is intended to illustrate the possible combinations, but not to impose any limitation. Non-limiting examples of additional veterinary agents include: amitraz, arylpyrazoles as recited in
20 publications WO1998/24767 and WO2005/060749, amino acetonitriles, anthelmintics (e.g., albendazole, cambendazole, fenbendazole, flubendazole, mebendazole, octadepsipeptides, oxfendazole, oxibendazole, paraherquamide (2-desoxoparaherquamide, derquantel), parbendazole, piperazines, praziquantel, thiabendazole, tetramisole, triclabendazole, levamisole, pyrantel
25 pamoate, oxantel, morantel, and the like), indoxacarb and derivatives thereof, avermectins (e.g., abamectin, doramectin, emamectin, eprinomectin, ivermectin, moxidectin, selamectin, and the like), milbemycin, milbemycin oxime, DEET, demiditraz, diethylcarbamazine, fipronil, insect growth regulators (e.g., hydroprene, kinoprene, methoprene, pyriproxyfen, and the like), metaflumizone,
30 niclosamide, permethrin, pyrethrins, spinosad, and formamidines (e.g., demiditraz, amitraz, and the like). In certain instances, combinations of a Formula (1) compound with an additional veterinary agent(s) can result in a greater-than-additive effect. Reducing the quantity of active ingredients released in the environment while ensuring effective pest control is always desirable.

It may be desirable to administer a compound of the present invention, stereoisomers thereof, alone or in a composition comprising a veterinarily acceptable excipient, diluent, or carrier, for example, for the purpose of treating a particular parasitic infection or infestation or condition associated therewith. It is
 5 within the scope of the present invention that two or more veterinary compositions, at least one of which contains a Formula (1) compound in accordance with the invention, and the other, an additional veterinary agent, may conveniently be combined in the form of a kit suitable for coadministration of the compositions.

10 The compounds of the present invention (including the compositions and processes used therein) may also be used in the manufacture of a medicament for the therapeutic applications described herein.

The compounds of the present invention, stereoisomers thereof, and compositions comprising a therapeutically effective amount of a Formula (1)
 15 compound and a veterinarily acceptable excipient, diluent, or carrier are useful as parasitocides (endo-and ecto-parasites) for the control and treatment of infections or infestations manifested by said parasite in an animal. The compounds of the present invention have utility as an ectoparasiticide, in particular, as an acaricide and insecticide. They may, in particular, be used in
 20 the fields of veterinary medicine, livestock husbandry, fish farming, and the maintenance of public health: against acarids and insects which are parasitic upon vertebrates, particularly warm-blooded vertebrates, including companion animals, livestock, and birds. The compounds of the present invention are also parasitocides for cold-blooded fish. Some non-limiting examples of acaride and
 25 insect parasites include: ticks (e.g., *Ixodes spp.*, *Rhipicephalus spp.*, *Boophilus spp.*, *Amblyomma spp.*, *Hyalomma spp.*, *Haemaphysalis spp.*, *Dermacentor spp.*, *Ornithodoros spp.*, and the like); mites (e.g., *Dermanyssus spp.*, *Sarcoptes spp.*, *Psoroptes spp.*, *Chorioptes spp.*, *Demodex spp.*, and the like); chewing and sucking lice (e.g., *Damalinia spp.*, *Linognathus spp.*, and the like); fleas
 30 (e.g., *Siphonaptera spp.*, *Ctenocephalides spp.*, and the like); biting flies and midges (e.g., *Tabanidae spp.*, *Haematobia spp.*, *Stomoxys spp.*, *Dermatobia spp.*, *Simuliidae spp.*, *Ceratopogonidae spp.*, *Psychodidae spp.*, and the like), and bed bugs (e.g., *Cimicidae spp.*, particularly, *Cimex lectularius*). In another example, ectoparasites of the crustacean order copepod, more particularly of the

genera *Lepeophtheirus* (especially the salmon louse, *Lepeophtheirus salmonis*) and/or *Caligus* (e.g., *C. elongates*, *C. rogercreysii*, *C. teres*, *C. flexispina*, and the like), particularly sea lice, can be treated with a compound of the present invention. The compounds of the invention can also be used for the treatment of
5 endoparasites, for example, heartworms, roundworms, hookworms, whipworms, and tapeworms.

The compounds of the present invention and compositions comprising compounds of the present invention in conjunction with at least one other veterinary agent are of particular value in the control of ectoparasites,
10 endoparasites, and insects which are injurious to, or spread or act as vectors of diseases in animals. The ectoparasites, insects, and endoparasites which can be treated with a combination of a Formula (1) compound and an additional veterinary agent include those as herein before described and including helminthes of the phylum platyhelminthes (e.g., trematodes, eucestoda, and
15 cestoda), and nemathelminthes (e.g., nematodes).

Any of the compounds of the present invention, or a suitable combination of a compound of the present invention and optionally, with at least one additional veterinary agent may be administered directly to the animal and/or indirectly by applying it to the local environment in which the animal dwells.
20 Direct administration includes contacting the skin, fur, or feathers of a subject animal or bird with the compound(s), or by feeding or injecting the compounds into the animal or bird.

The Formula (1) compounds, stereoisomers thereof, and combinations with at least one additional veterinary agent, as described herein, are of value for
25 the treatment and control of the various lifecycle stages of insects and parasites including egg, nymph, larvae, juvenile and adult stages.

The present invention also relates to a method of administering a compound of the present invention alone or in combination with at least one additional veterinary agent, and optionally a veterinarily or pharmaceutically
30 acceptable excipient, diluent, or carrier, to animals in good health comprising the application to said animal to reduce or eliminate the potential for human parasitic infection or infestation from parasites carried by the animal and to improve the environment in which the animal and human inhabit.

The reactions set forth below were done generally under a positive pressure of argon or nitrogen or with a drying tube, at ambient temperature (unless otherwise stated), in anhydrous solvents, and the reaction flasks were fitted with rubber septa for the introduction of substrates and reagents *via* syringe. Glassware was oven dried and/or heat dried. Analytical thin layer chromatography (TLC) was performed using glass-backed silica gel 60 F 254 precoated plates and eluted with appropriate solvent ratios (v/v). Reactions were assayed by TLC or LCMS and terminated as judged by the consumption of starting material. Visualization of the TLC plates was done with UV light (254 nm wavelength) or with an appropriate TLC visualizing solvent and activated with heat. Flash column chromatography (Still et al., J. Org. Chem. 43, 2923, (1978)) was performed using silica gel (RediSep Rf) or various MPLC systems, such as Biotage or ISCO purification system.

Conventional methods and/or techniques of separation and purification known to one of ordinary skill in the art can be used to isolate the compounds of the present invention, as well as the various intermediates related thereto. Such techniques will be well-known to one of ordinary skill in the art and may include, for example, all types of chromatography (high pressure liquid chromatography (HPLC), column chromatography using common adsorbents such as silica gel, and thin-layer chromatography (TLC), recrystallization, and differential (i.e., liquid-liquid) extraction techniques.

The compound structures in the examples below were confirmed by one or more of the following methods: proton magnetic resonance spectroscopy, and mass spectroscopy. Proton magnetic resonance (^1H NMR) spectra were determined using a Bruker spectrometer operating at a field strength of 400 megahertz (MHz). Chemical shifts are reported in parts per million (PPM, δ) downfield from an internal tetramethylsilane standard. Mass spectra (MS) data were obtained using Agilent mass spectrometer with atmospheric pressure chemical ionization. Method: Acquity HPLC with chromatography performed on a Waters BEH C18 column (2.1 x 50 mm, 1.7 μm) at 50°C. The mobile phase was a binary gradient of acetonitrile (containing 0.1% trifluoroacetic acid) and water (5–100%).

Embodiments of the present invention are illustrated by the following Examples. It is to be understood, however, that the embodiments of the

invention are not limited to the specific details of these Examples, as other variations thereof will be known, or apparent in light of the instant disclosure, to one of ordinary skill in the art.

5

EXAMPLES

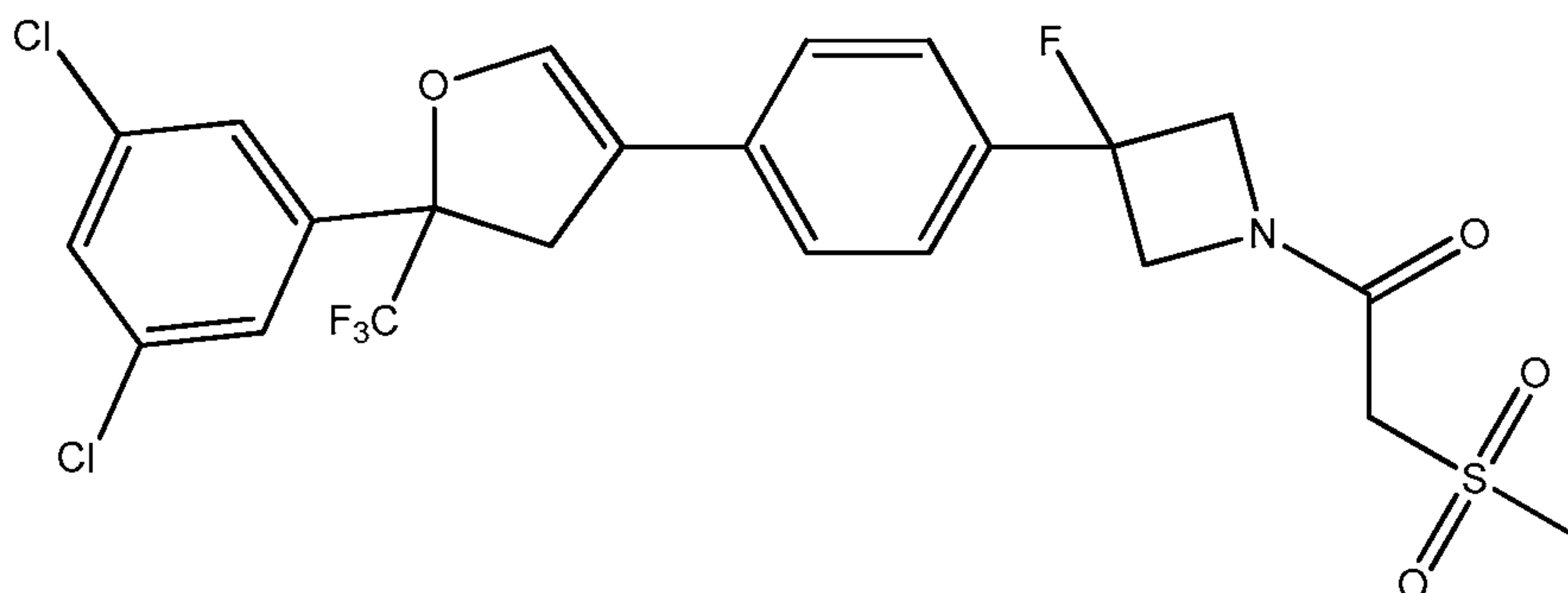
One skilled in the art will also recognize that Formula (1) compounds and the intermediates described herein can be subjected to various electrophilic, nucleophilic, radical, organometallic, oxidation, and reduction reactions to add substituents or modify existing substituents.

10

The following examples can be prepared according to the schemes presented herein. It is to be understood, however, that the invention, as fully described herein and as recited in the claims, is not intended to be limited by the details of the following schemes or modes of preparation.

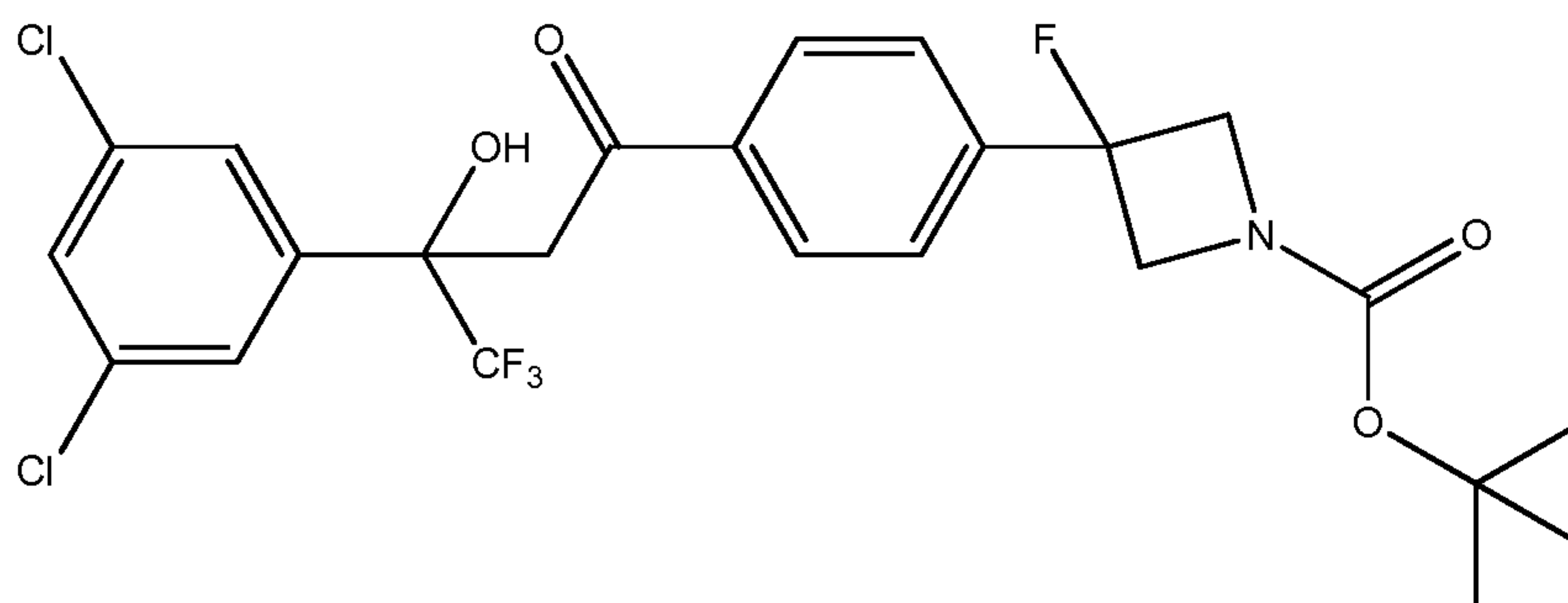
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Example 1. 1-(3-{4-[5-(3,5-dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-furan-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-2-methanesulfonyl-ethanone



Preparation 1 for Example 1, Intermediate 1, 3-{4-[3-(3,5-dichloro-phenyl)-4,4,4-trifluoro-3-hydroxy-butyryl]-phenyl}-3-fluoro-azetidine-1-carboxylic acid tert-butyl ester

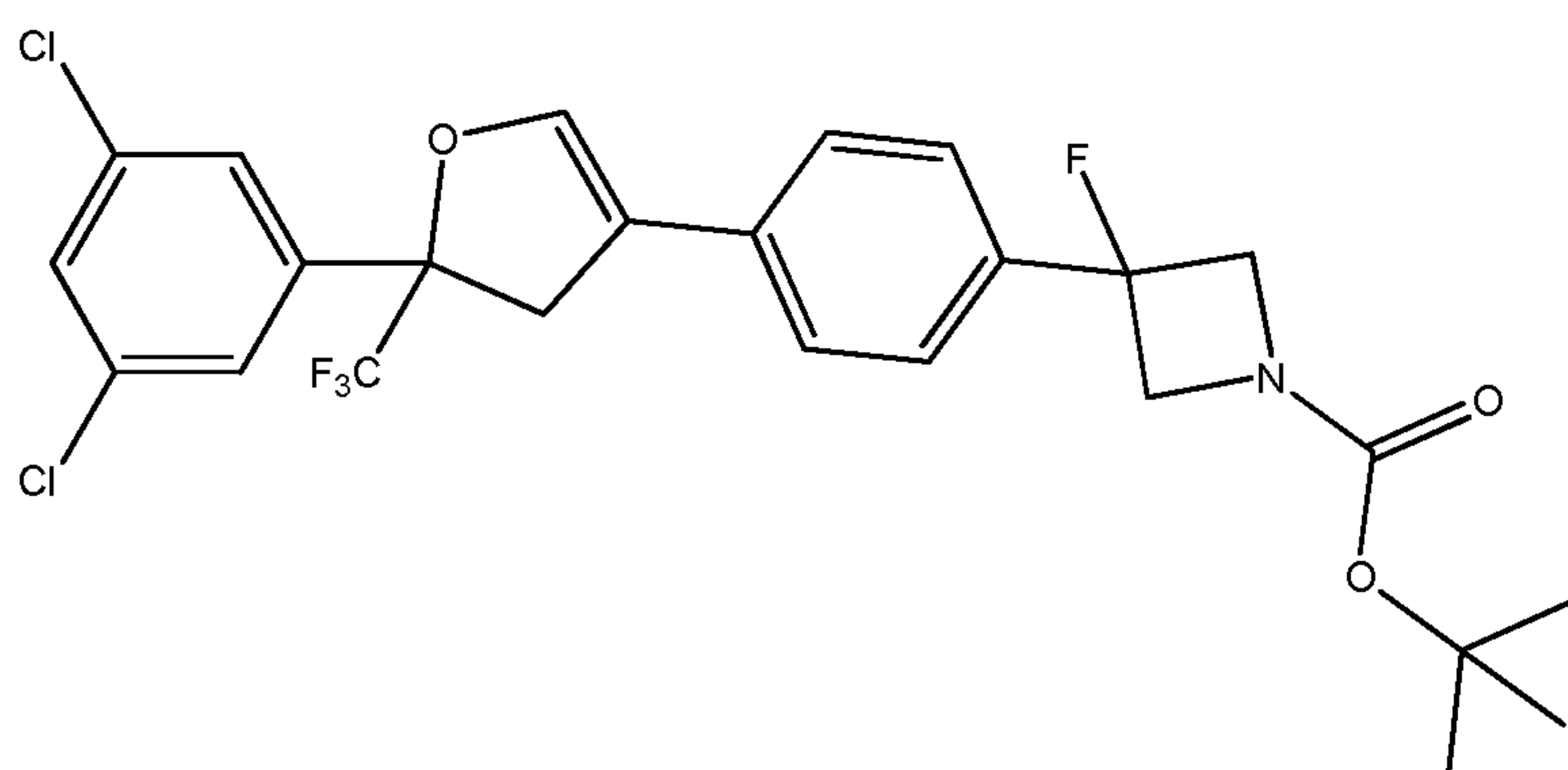
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In a clean and dry seal tube, to a stirred solution of 3-(4-acetyl-phenyl)-3-fluoro-azetidine-1-carboxylic acid tert-butyl ester (4g, 13.652mmol, 1eq.) in

heptane (40mL) was added 1-(3,5-dichlorophenyl)-2,2,2-trifluoro-ethanone (6.60gm, 27.304mmol, 2eq.) followed by addition of triethyl amine (TEA, 3.80ml, 27.304mmol, 2eq.) at room temperature. Resulting reaction mixture was heated at 60°C for 16 hours. After maximum consumption of starting material, reaction mixture was cooled to room temperature, solid precipitated out. Solid was filtered over Buchner funnel and washed with heptane (2 x 30mL) and n-Pentane (70mL) and dried under reduced pressure to get product as white solid. Yield: - 5.0g (68.31%). ¹H NMR (400 MHz, CDCl₃)δ: 1.47 (s, 9H), 3.68 (d, *J* = 17.36 Hz, 1H), 3.85 (d, *J* = 17.44 Hz, 1H), 4.17-4.24 (m, 2H), 4.39-4.47 (m, 2H), 5.69 (s, 1H), 7.33-7.35 (m, 1H), 7.48 (d, *J* = 1.16 Hz, 2H), 7.62 (d, *J* = 8.44 Hz, 2H), 7.98 (d, *J* = 8.28 Hz, 2H). LC-MS (*m/z*): = 534.0 (M-H).

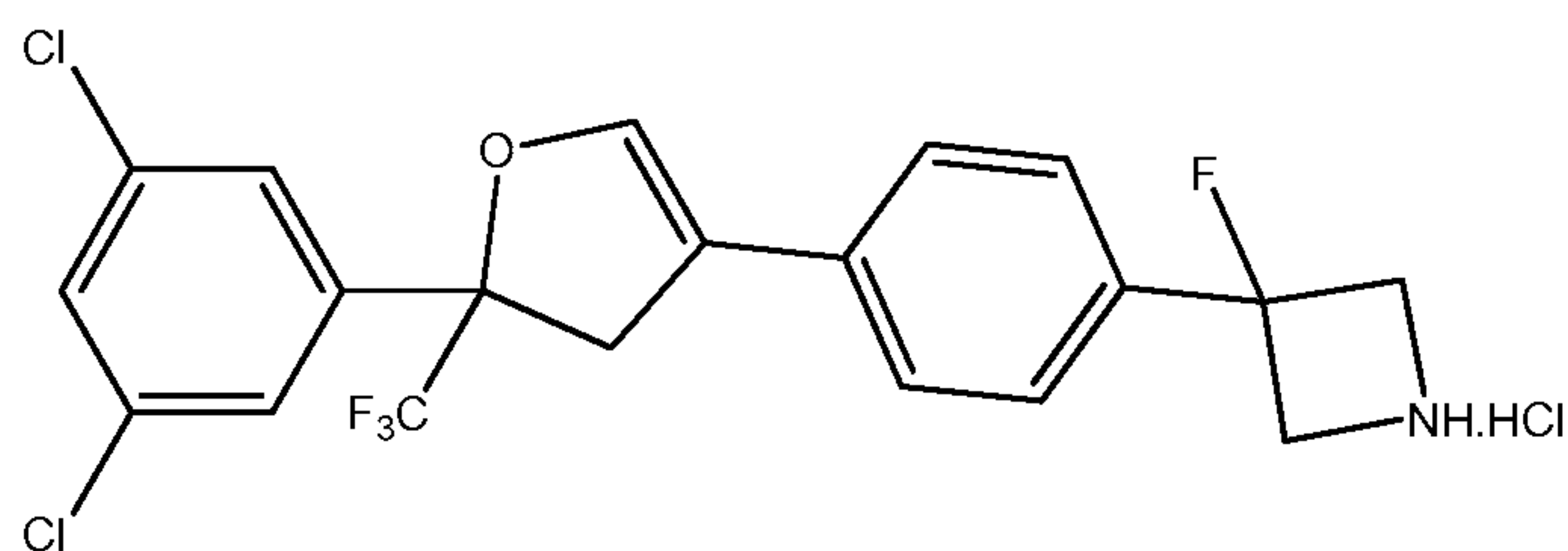
Preparation 2 for Example 1, Intermediate 2, 3-{4-[5-(3,5-dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-furan-3-yl]-phenyl}-3-fluoro-azetidine-1-carboxylic acid tert-butyl ester



To a stirred solution of trimethylsilyldiazomethane (2M in diethyl ether, 18.64mL, 37.289mmol) in 1,2-dimethoxyethane (DME, 100mL) was added methyl lithium (1.6M in diethyl ether, 23.32mL, 37.289mmol) at -78°C over period of 10 minutes and stirred reaction mixture for 30 minutes at -78°C. Pre-dissolved 3-{4-[3-(3,5-dichloro-phenyl)-4,4,4-trifluoro-3-hydroxy-butyryl]-phenyl}-3-fluoro-azetidine-1-carboxylic acid tert-butyl ester (Example 1, Intermediate 1) (5g, 9.322mmol, 1eq.) in DME (50 mL) was added at -78°C in drop wise manner over period of 10 minutes. Resulting reaction mixture was stirred for 1 hour at same temperature and then at room temperature for 2 hours. Acetic acid (1.60mL, 27.967mmol, 3 eq.) was added at room temperature over period of 5 minutes followed by addition of TBAF (27.92mL, 27.967mmol, 3 eq.) at room temperature over period of 10 minutes. After consumption of starting material,

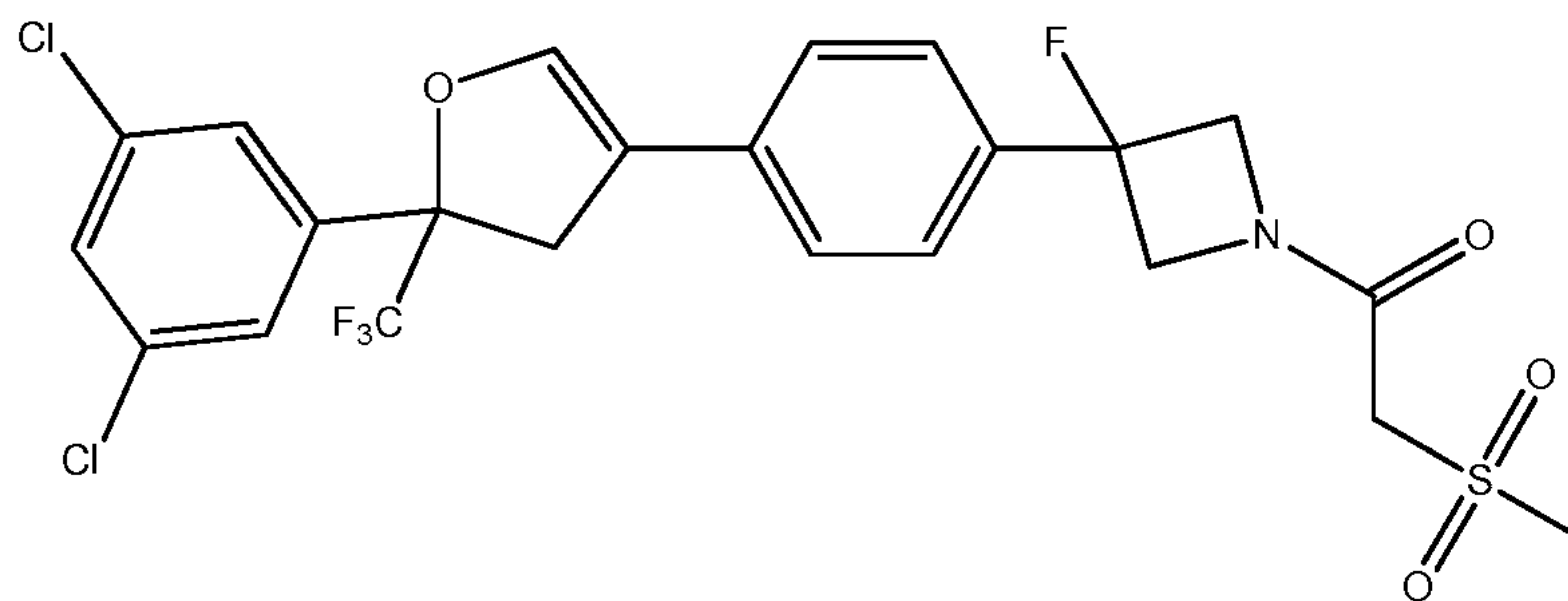
reaction mixture was quenched with water (150mL) and extracted with ethyl acetate (5 x 150mL). Combined organic layer was dried over sodium sulphate and concentrated in *vacuo* to get orange semisolid (6.1g, crude). Crude was purified by column chromatography using 100-200mesh silica gel. Desired compound was eluted in 10% ethyl acetate in hexane to afford off white semisolid (1.6g, Impure). The product was again purified by trituration using DCM: pentane (1: 5, 2 x 20mL) to afford product as off white solid (0.45g, 9.18%). Yield: - 0.45g (9.18%). ¹H NMR (400 MHz, CDCl₃)δ: 1.46 (s, 9H), 3.20 (d, *J* = 17.24 Hz, 1H), 3.30 (d, *J* = 17.24 Hz, 1H), 4.14-4.21 (m, 2H), 4.33-4.41 (m, 2H), 7.32-7.38 (m, 4H), 7.40 (t, *J* = 1.78 Hz, 1H), 7.52 (d, *J* = 1.36 Hz, 2H). LC-MS (*m/z*): = 529.9 (M-H).

Preparation 3 for Example 1, Intermediate 3, 3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydrofuran-3-yl)phenyl)-3-fluoroazetidine hydrochloride



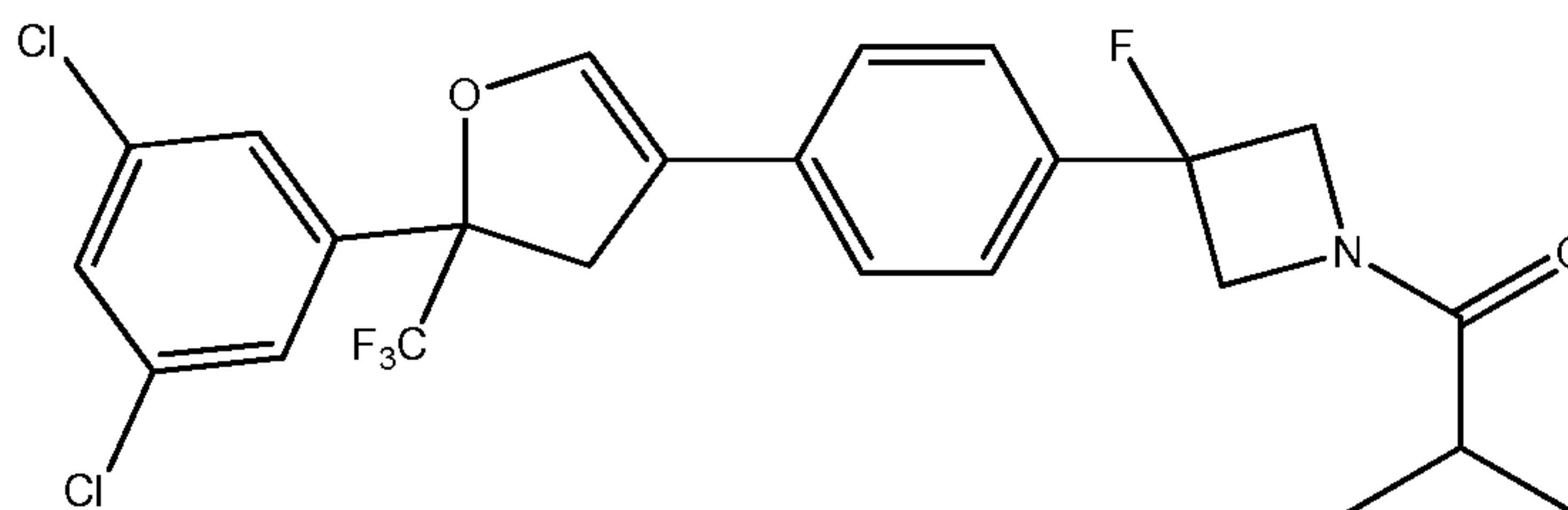
To a stirred solution of 3-{4-[5-(3,5-dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-furan-3-yl]-phenyl}-3-fluoro-azetidine-1-carboxylic acid tert-butyl ester (Example 1, Intermediate 2) (0.45g, 0.845mmol) in MeOH (10mL) was purged HCl gas for 1 hour at room temperature. After consumption of starting material, reaction mixture concentrated in *vacuo* to get pale yellow semisolid (0.49g, crude), which was triturated with n-pentane (2 x 5mL) to get off product as white solid. Yield: 0.36g, 98.53%. ¹H NMR (400 MHz, DMSO-d₆)δ: 3.20 (d, *J* = 17.16Hz, 1H), 3.64 (d, *J* = 17.16Hz, 1H), 4.30-4.54 (m, 4H), 7.29 (d, *J* = 7.96Hz, 2H), 7.48 (s, 1H), 7.52 (d, *J* = 8Hz, 2H), 7.69-7.71(m, 3H), 9.36 (bs, 2H).

Example 1. 1-(3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydrofuran-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylsulfonyl)ethanone



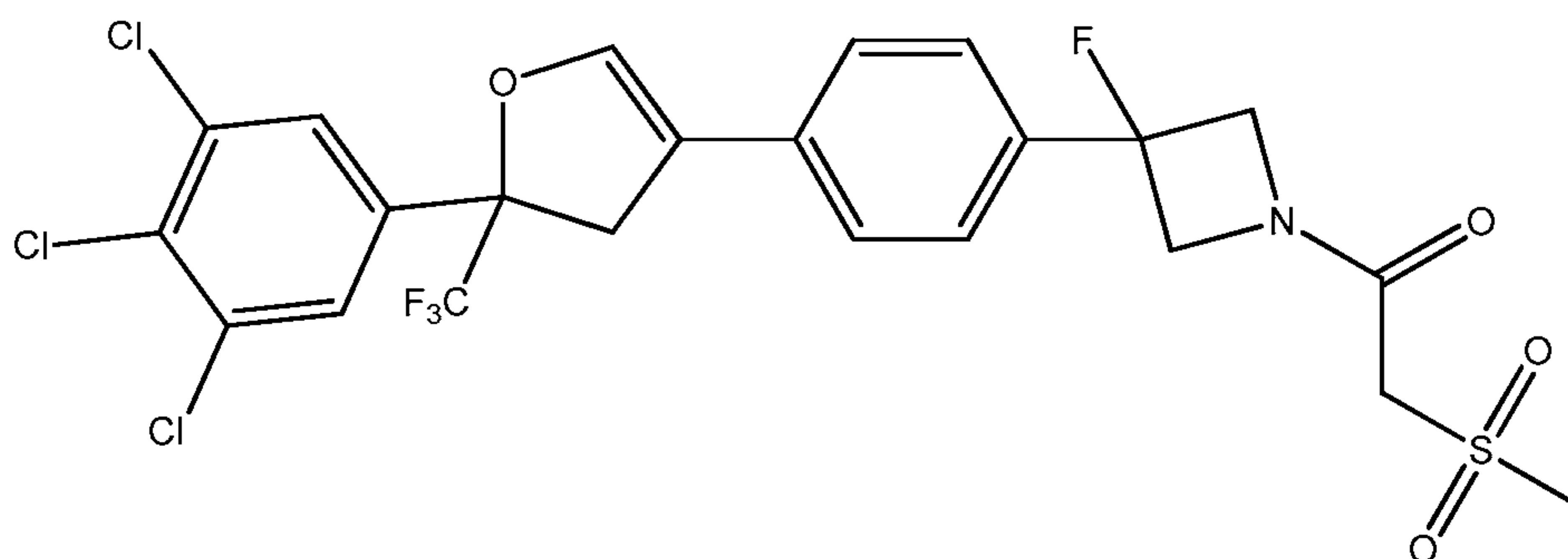
To a stirred solution of 3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydrofuran-3-yl)phenyl)-3-fluoroazetidine hydrochloride (Example 1, Intermediate 3) (0.25g, 0.535mmol) in THF (5mL) was added DIPEA (0.933mL, 5.35mmol) at room temperature and stirred for 10 minutes at room temperature. Methane sulfonyl acetic acid (0.147g, 1.07mmol), T₃P (50% solution in ethyl acetate, 1.6mL, 2.675mmol) were added at room temperature. Resulting reaction mixture was stirred for 16 hours at room temperature under nitrogen atmosphere. After complete consumption of starting material, reaction mixture was quenched with water (20mL) and extracted with ethyl acetate (5 x 25mL). Combined organic layer was washed with saturated solution of NaHCO₃ (2 x 100mL), dried over sodium sulphate and concentrated in *vacuo* to get pale yellow oil (0.32g, crude). Crude was purified by column chromatography using 100-200 mesh silica gel. Desired product gets eluted in 0.6% MeOH in DCM to afford white semisolid (0.160g), which was triturated with DCM: n-pentane (1:10; 2x 5mL) to afford product as off white solid. Yield: 0.145g (49.15%). ¹H NMR (400 MHz, DMSO-d₆)δ: 3.11 (s, 3H), 3.20 (d, *J* = 17.16 Hz, 1H), 3.65 (d, *J* = 17.12 Hz, 1H), 4.24(s, 2H), 4.34 (d, *J* = 21.6 Hz, 2H), 4.70 (d, *J* = 21.52Hz, 2H), 7.27 (d, *J* = 7.96 Hz, 2H), 7.47 (d, *J* = 9.36 Hz, 2H), 7.73 (d, *J* = 3.92 Hz, 3H). LC-MS (*m/z*): = 550.1 (M-H). HPLC purity: 98.75%.

Example 2. 1-(3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydrofuran-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropan-1-one



This compound was similarly prepared to that of Example 1, except that isobutyric acid was used in place of methane sulfonyl acetic acid. Yield: 70mg (65.21%). ¹H NMR (400 MHz, DMSO-d₆)δ: 0.98-1.13(m, 6H), 2.51-2.55 (m, 1H), 3.20 (d, *J* = 17.16 Hz, 1H), 3.65(d, *J* = 17.16 Hz, 1H), 4.23 (d, *J* = 21.92 Hz, 2H), 4.60 (d, *J* = 21.76Hz, 2H), 7.26 (d, *J* = 8.04 Hz, 2H), 7.45-7.48 (m, 3H), 7.70-7.71 (m, 3H). LC-MS (*m/z*): = 502.0 (M+H). HPLC purity: 98.70%.

Example 3. 1-(3-{4-[5-(3,4,5-trichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-furan-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-2-methanesulfonyl-ethanone



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Preparation 1 for Example 3, Intermediate 1, 3-{4-[3-(3,4,5-trichloro-phenyl)-4,4,4-trifluoro-3-hydroxy-butyryl]-phenyl}-3-fluoro-azetidine-1-carboxylic acid tert-butyl ester, was prepared similarly to Example 1, Intermediate 1, except that 1-(3,4,5-trichlorophenyl)- 2,2,2-trifluoro-ethanone was used in place of 1-(3,5-dichlorophenyl)- 2,2,2-trifluoro-ethanone. Yield: 8.2g (93.5%). ¹H NMR (400 MHz, CDCl₃)δ: 1.47 (s, 9H), 3.68 (d, *J* = 17.36 Hz, 1H), 3.84 (d, *J* = 17.44 Hz, 1H), 4.17-4.24 (m, 2H), 4.39-4.47 (m, 2H), 5.70 (s, 1H), 7.61-7.63 (m, 4H), 7.98 (d, *J* = 8.28 Hz, 2H). LC-MS (*m/z*): = 568.0 (M-H).

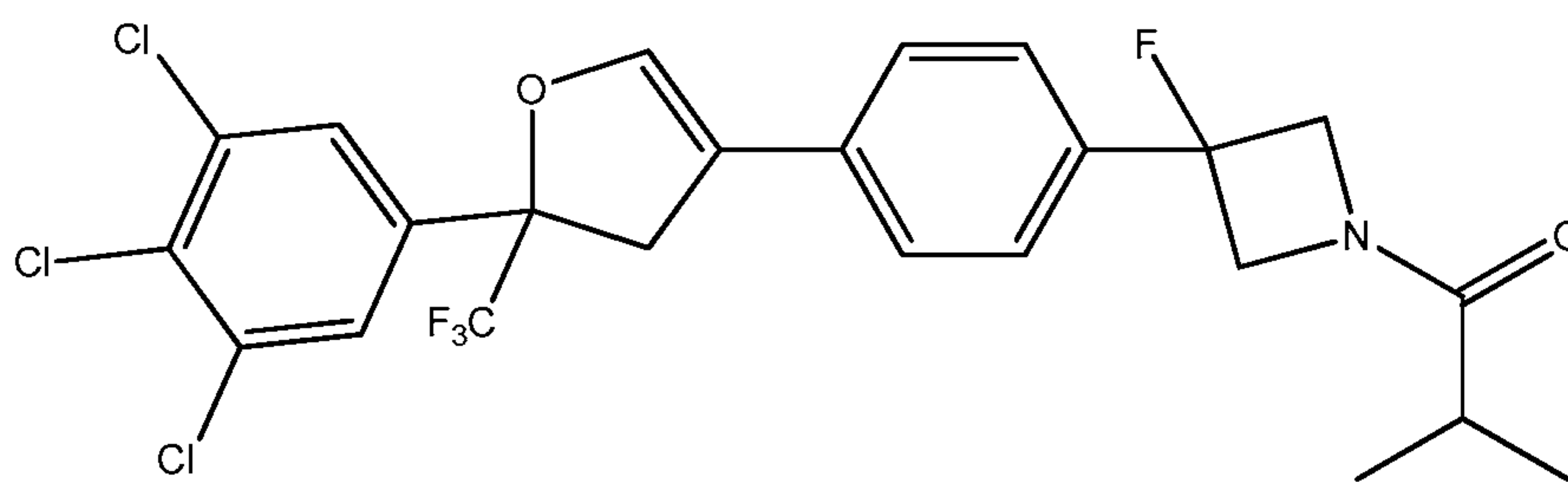
Preparation 2 for Example 3, Intermediate 2, 3-{4-[5-(3,4,5-trichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-furan-3-yl]-phenyl}-3-fluoro-azetidine-1-carboxylic acid tert-butyl ester, was prepared similarly to Example 1, Intermediate 2, except that 3-{4-[3-(3,4,5-trichloro-phenyl)-4,4,4-trifluoro-3-hydroxy-butyryl]-phenyl}-3-fluoro-azetidine-1-carboxylic acid tert-butyl ester was used in place of 3-{4-[3-(3,5-dichloro-phenyl)-4,4,4-trifluoro-3-hydroxy-butyryl]-phenyl}-3-fluoro-azetidine-1-carboxylic acid tert-butyl ester. Yield: 0.995g (13.72%). ¹H NMR (400 MHz, CDCl₃)δ: 1.46 (s, 9H), 3.21 (d, *J* = 17.24 Hz, 1H), 3.31 (d, *J* = 17.8 Hz, 2H), 4.15 (d, *J* = 10.28 Hz, 1H), 4.20 (d, *J* = 10.28 Hz,

1H), 4.35 (d, $J = 10.2$ Hz, 1H), 4.40 (d, $J = 10.24$ Hz, 1H), 7.33-7.37 (m, 4H), 7.65 (s, 2H). LC-MS (m/z): = 563.8 (M-H).

Preparation 3 for Example 3, Intermediate 3, 3-fluoro-3-{4-[5-(3,4,5-trichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-furan-3-yl]-phenyl}-azetidine hydrochloride, was prepared similarly to Example 1, Intermediate 3, except that 3-{4-[5-(3,4,5-trichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-furan-3-yl]-phenyl}-3-fluoro-azetidine-1-carboxylic acid tert-butyl ester was used in place of 3-{4-[5-(3,5-dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-furan-3-yl]-phenyl}-3-fluoro-azetidine-1-carboxylic acid tert-butyl ester. Yield: 0.580g (Crude, used as such in next step.) ^1H NMR (400 MHz, DMSO- d_6) δ : 3.22 (d, $J = 17.16$ Hz, 1H), 3.68 (d, $J = 17.16$ Hz, 1H), 4.39-4.53 (m, 4H), 7.30 (d, $J=8.2$ Hz, 2H), 7.54 (d, $J=8.16$ Hz, 2H), 7.60(s, 1H), 7.93 (s, 2H), 9.33 (bs, 1H), 9.76 (bs, 1H). LC-MS (m/z): = 465.8(M+H).

Example 3 was prepared similarly to that of Example 1, except that Example 3, Intermediate 3 was reacted with methane sulfonyl acetic acid . Yield: 0.170g (29.74%). ^1H NMR (400 MHz, DMSO- d_6) δ : 3.11 (s, 3H), 3.22 (d, $J = 17.24$ Hz, 1H), 3.70 (d, $J = 17.16$ Hz, 1H), 4.24(s, 2H), 4.34 (d, $J = 21.64$ Hz, 2H), 4.70 (d, $J = 21.6$ Hz, 2H), 7.28 (d, $J = 8.12$ Hz, 2H), 7.47 (d, $J = 8.24$ Hz, 2H), 7.58 (s, 1H), 7.92 (s, 2H). LC-MS (m/z): = 583.8 (M-H). HPLC purity: 99.64%.

Example 4. 1-(3-fluoro-3-{4-[5-(3,4,5-trichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-furan-3-yl]-phenyl}-azetidin-1-yl)-2-methyl-propan-1-one

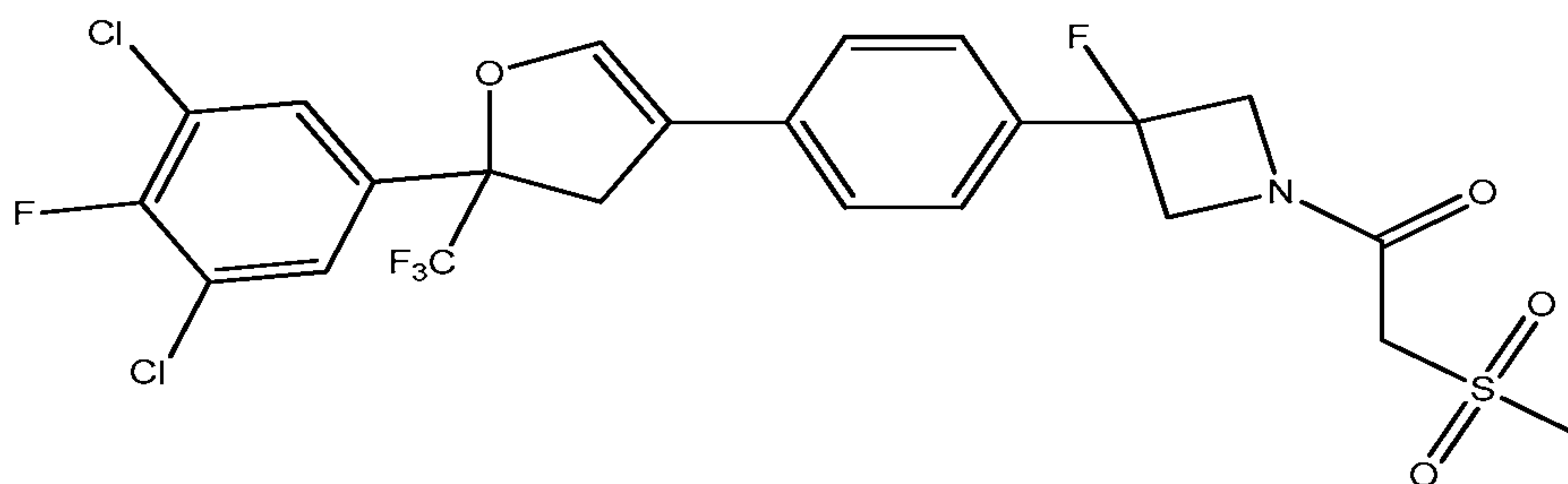


25

This compound was prepared similarly to Example 3, except that isobutyric acid was used in place of methane sulfonyl acetic acid. Yield: 0.115g (26.71%). ^1H NMR (400 MHz, DMSO- d_6) δ : 0.97-1.01 (m, 6H), 2.52-2.55 (m, 1H), 3.19 (d, $J = 17.24$ Hz, 1H), 3.69(d, $J = 17.16$ Hz, 1H), 4.24 (d, $J = 22.08$ Hz,

2H), 4.60 (d, $J = 21.88\text{Hz}$, 2H), 7.27 (d, $J = 8\text{ Hz}$, 2H), 7.47 (d, $J = 8.16\text{ Hz}$, 2H), 7.59 (s, 1H), 7.92 (s, 2H). LC-MS (m/z): = 535.9 (M+H). HPLC purity: 98.71%.

Example 5. 1-(3-{4-[5-(3,5-dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-furan-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-2-methanesulfonyl-ethanone



Preparation 1 for Example 5, Intermediate 1, tert-butyl 3-(4-(3-(3,5-dichloro-4-fluorophenyl)-4,4,4-trifluoro-3-hydroxybutanoyl)phenyl)-3-fluoroazetidine-1-carboxylate, was prepared similarly to Example 1, Intermediate 1, except that 1-(3,5-dichloro-4-fluoro-phenyl)-2,2,2-trifluoro-ethanone was used in place of 1-(3,5-dichloro phenyl)- 2,2,2-trifluoro-ethanone. Yield: 7.97g (93.65.4%). ^1H NMR (400 MHz, CDCl_3) δ : 1.47 (s, 9H), 3.68 (d, $J = 17.36\text{ Hz}$, 1H), 3.83 (d, $J = 17.44\text{ Hz}$, 1H), 4.17-4.24 (m, 2H), 4.39-4.48 (m, 2H), 5.72 (s, 1H), 7.57 (d, $J = 6.08\text{ Hz}$, 2H), 7.63 (d, $J = 8.44\text{ Hz}$, 2H), 7.98(d, $J = 8.16\text{ Hz}$, 2H). LC-MS (m/z): = 551.8 (M-H).

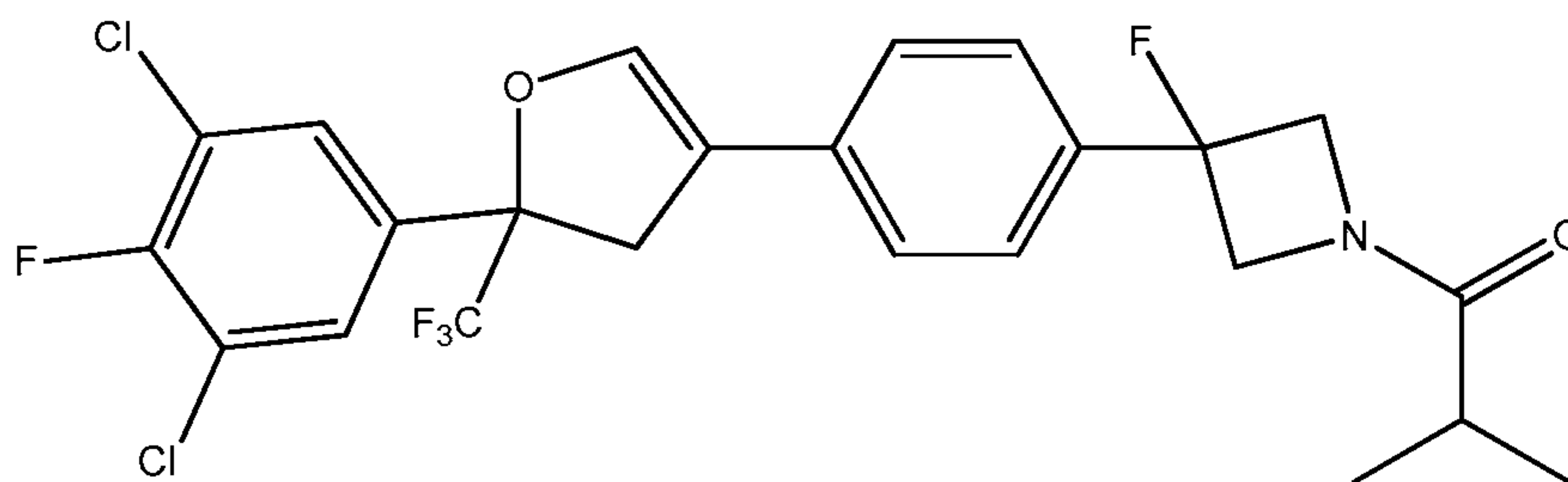
Preparation 2 for Example 5, Intermediate 2, tert-butyl 3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydrofuran-3-yl)phenyl)-3-fluoroazetidine-1-carboxylate, was prepared similarly to Example 1, Intermediate 2, except that tert-butyl 3-(4-(3-(3,5-dichloro-4-fluorophenyl)-4,4,4-trifluoro-3-hydroxybutanoyl)phenyl)-3-fluoroazetidine-1-carboxylate was used in place of 3-{4-[3-(3,5-dichloro-phenyl)-4,4,4-trifluoro-3-hydroxy-butyryl]-phenyl}-3-fluoroazetidine-1-carboxylic acid tert-butyl ester. Yield: 0.58g (7.34%). ^1H NMR (400 MHz, CDCl_3) δ : 1.46 (s, 9H), 3.20 (d, $J = 17.28\text{ Hz}$, 1H), 3.29-3.33 (m, 2H), 4.14-4.21 (m, 2H), 4.33-4.41 (m, 2H), 7.33-7.38(m, 4H), 7.59 (d, $J = 6.08\text{ Hz}$, 2H). LC-MS (m/z): = 548.0 (M-H).

Preparation 3 for Example 5, Intermediate 3, 3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydrofuran-3-yl)phenyl)-3-fluoroazetidine

hydrochloride, was prepared similarly to Example 1, Intermediate 3, except that tert-butyl 3-(4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydrofuran-3-yl)phenyl)-3-fluoroazetidine-1-carboxylate was used in place of 3-{4-[5-(3,5-dichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-furan-3-yl]-phenyl}-3-fluoro-azetidine-1-carboxylic acid tert-butyl ester. Yield: 0.45g (95.74%). ¹H NMR (400 MHz, DMSO-d₆)δ: 3.22 (d, *J* = 17.2Hz, 1H), 3.68 (d, *J* = 17.16Hz, 1H), 4.42-4.52 (m, 4H), 7.29 (d, *J* = 8.04Hz, 2H), 7.52-7.56 (m, 3H), 7.88 (d, *J* = 6.36Hz, 2H), 9.33(bs, 1H), 9.74 (bs, 1H). LC-MS (*m/z*): = 449.9(M+H)

Example 5 was prepared similarly to that of Example 1, except that Example 5, Intermediate 3 was reacted with methane sulfonyl acetic acid. Yield: 0.120g (46.82%). ¹H NMR (400 MHz, DMSO-d₆)δ: 3.11 (s, 3H), 3.21 (d, *J* = 17.2 Hz, 1H), 3.68 (d, *J* = 17.16 Hz, 1H), 4.24(s, 2H), 4.34 (d, *J* = 21.68 Hz, 2H), 4.70 (d, *J* = 21.60 Hz, 2H), 7.27 (d, *J* = 8.12 Hz, 2H), 7.46 (d, *J* = 8.28 Hz, 2H), 7.55 (s, 1H), 7.88 (d, *J* = 6.4 Hz, 2H). LC-MS (*m/z*): = 567.8 (M-H). HPLC purity: 99.31%.

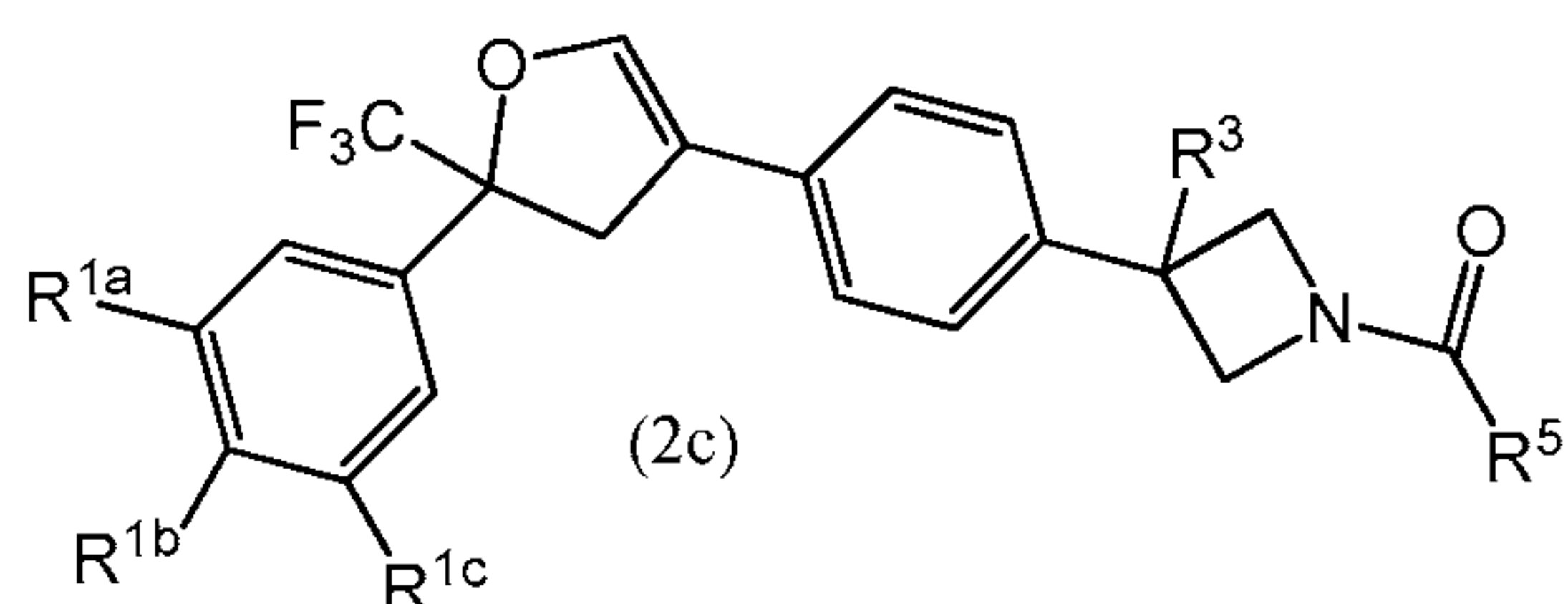
Example 6. 1-(3-{4-[5-(3,5-dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-furan-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-2-methyl-propan-1-one



This compound was prepared similarly to Example 5, except that isobutyric acid was used in place of methane sulfonyl acetic acid. Yield: 0.110g (47.05%). ¹H NMR (400 MHz, CDCl₃)δ: 0.97-1.01 (m, 6H), 2.52-2.55 (m, 1H), 3.20 (d, *J* = 17.24 Hz, 1H), 3.68(d, *J* = 17.16 Hz, 1H), 4.24 (d, *J* = 22.08 Hz, 2H), 4.60 (d, *J* = 21.88Hz, 2H), 7.27 (d, *J* = 8 Hz, 2H), 7.47 (d, *J* = 8.16 Hz, 2H), 7.55 (s, 1H), 7.86 (d, *J* = 6.36Hz, 2H). LC-MS (*m/z*): = 517.8 (M-H). HPLC purity: 98.62%.

In addition to the 6 examples described above, the following examples are also contemplated and can prepared by the methods and Schemes described

herein. The Examples in Table 1 of Formula 2c can be prepared according to the schemes presented herein,

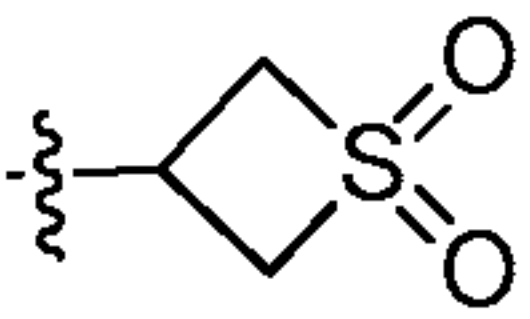
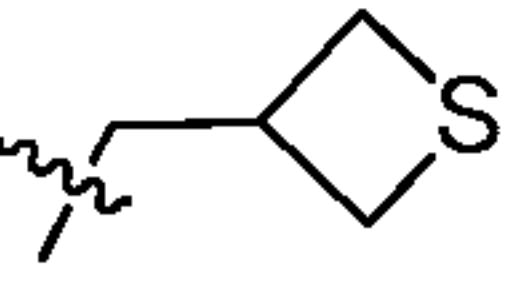
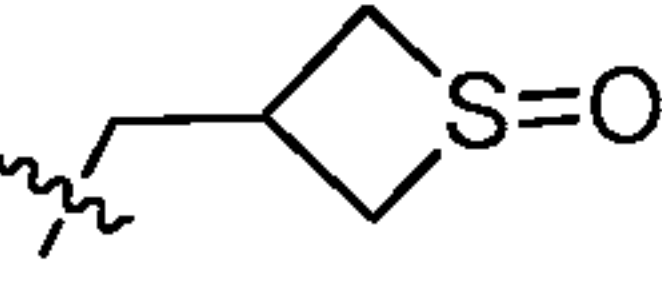
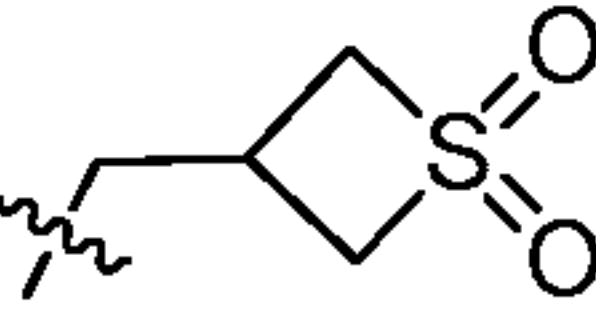
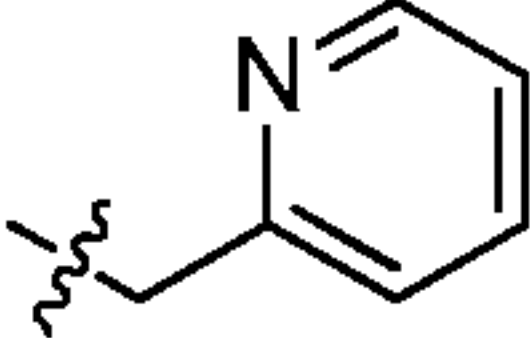
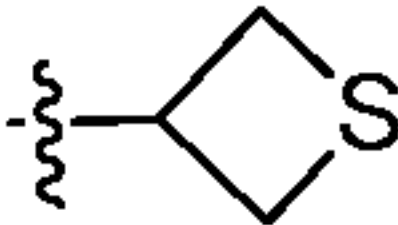


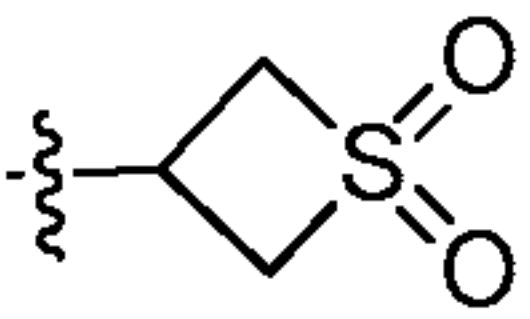
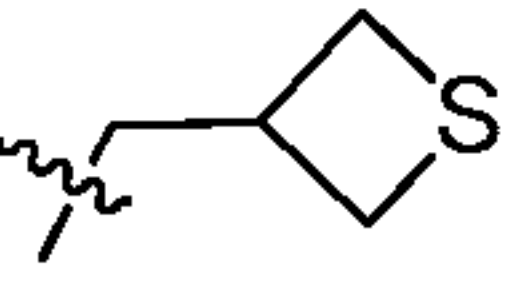
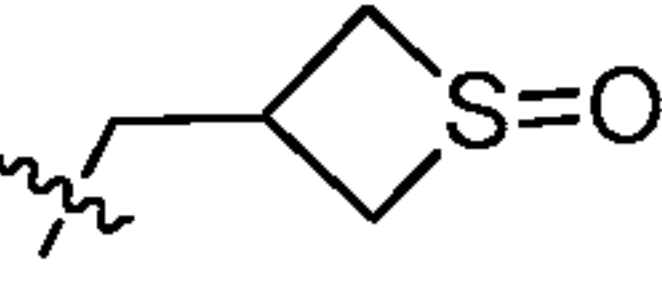
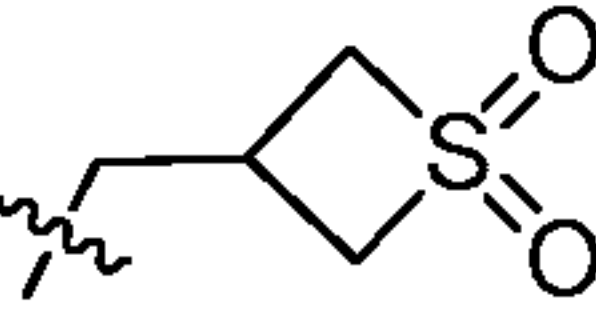
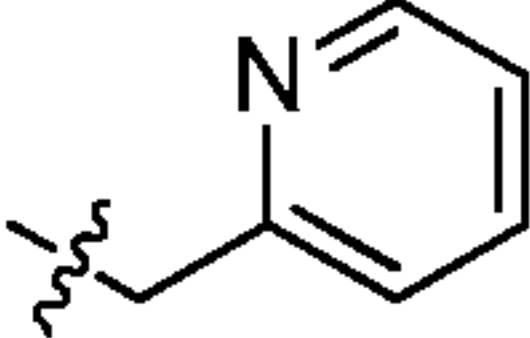
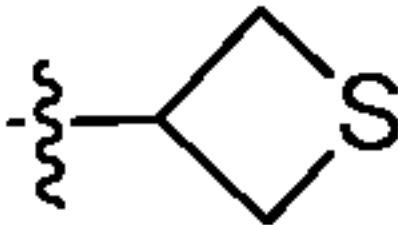
wherein R³ is fluoro (a), hydroxyl (b), or cyano (c).

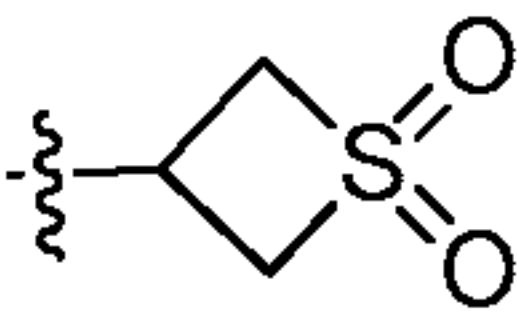
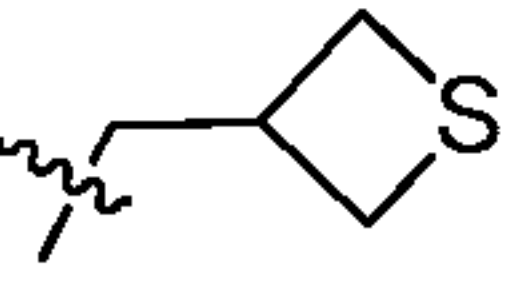
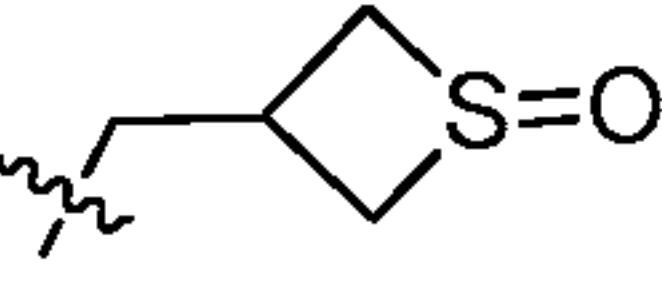
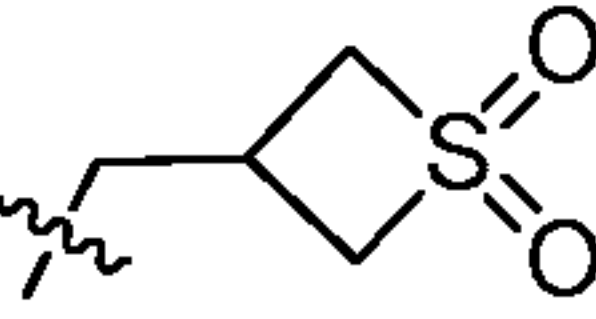
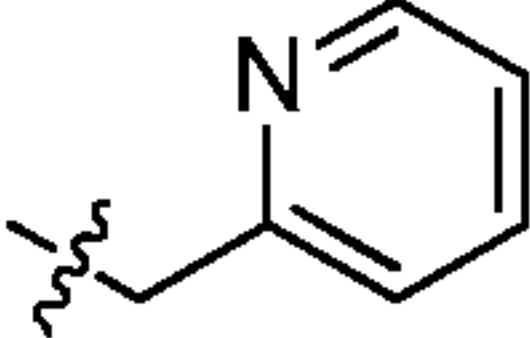
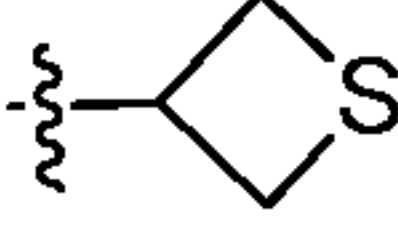
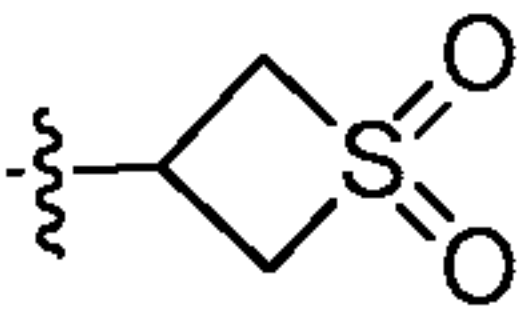
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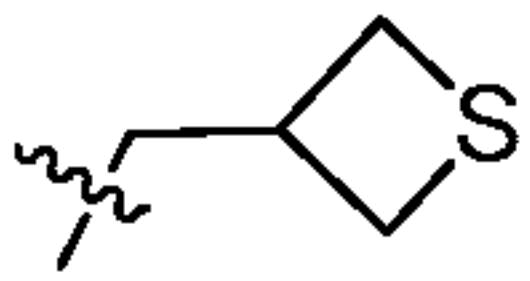
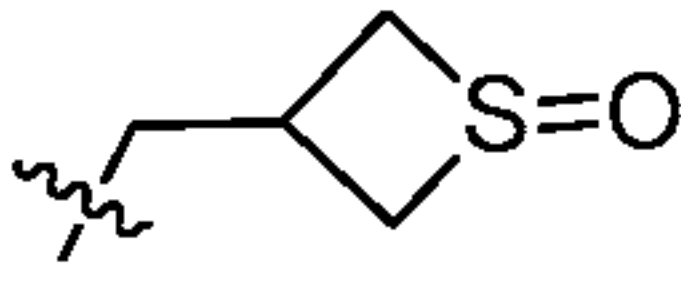
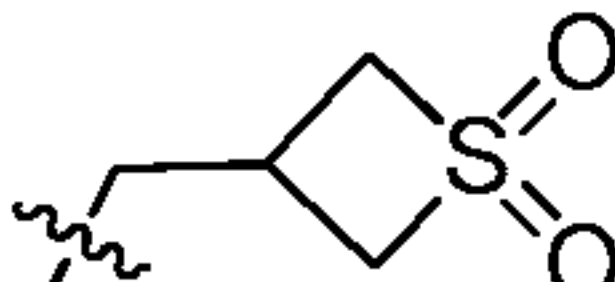
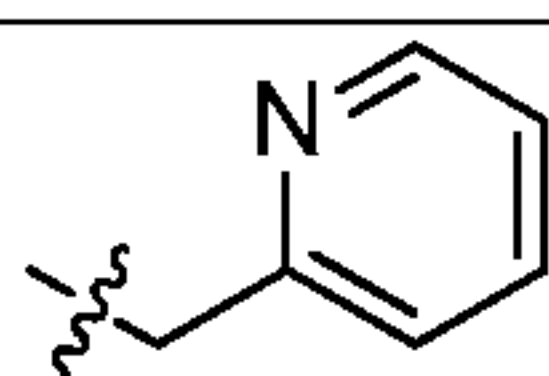
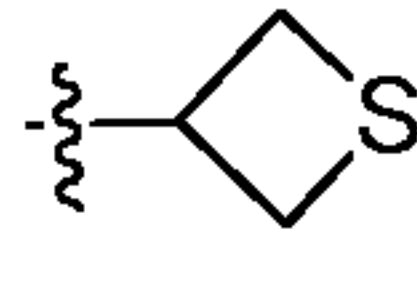
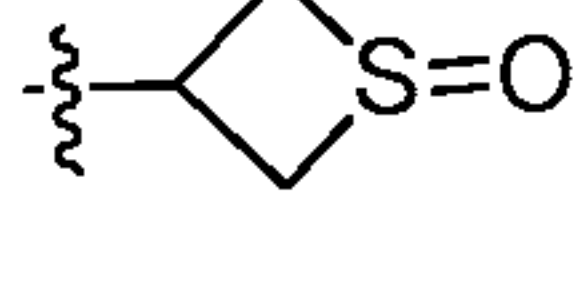
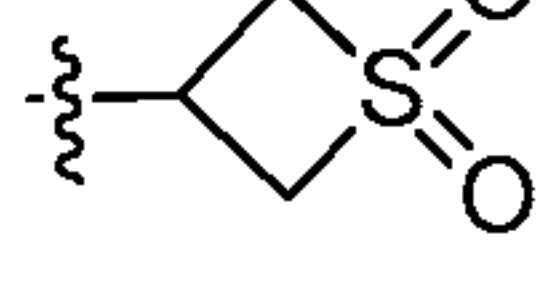
Table 1

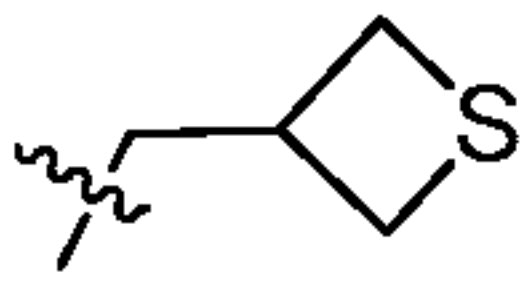
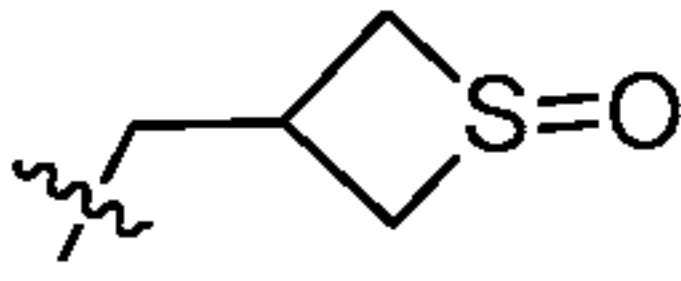
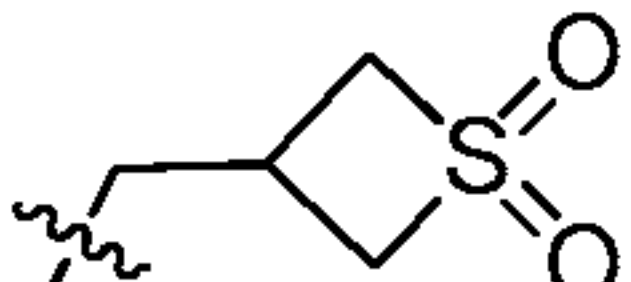
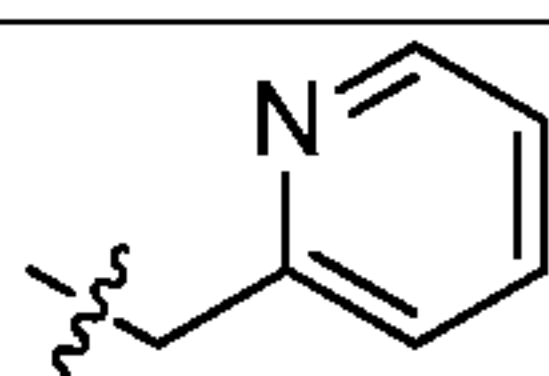
Example #	R ^{1a}	R ^{1b}	R ^{1c}	R ⁵
7a,b,c	Cl	Cl	Cl	methyl
8a,b,c	Cl	Cl	Cl	cyclopropyl
9 a,b,c	Cl	Cl	Cl	-NHCH ₃
10 a,b,c	Cl	Cl	Cl	-NHCH ₂ CH ₃
11 a,b,c	Cl	Cl	Cl	-NH-cyclopropyl
12 a,b,c	Cl	Cl	Cl	-CH ₂ -cyclopropyl
13 b,c	Cl	Cl	Cl	isopropyl
14 a,b,c	Cl	Cl	Cl	ethyl
15 a,b,c	Cl	Cl	Cl	propyl
16a,b,c	Cl	Cl	Cl	-CH ₂ CN
17a,b,c	Cl	Cl	Cl	-CH ₂ SCH ₃
18a,b,c	Cl	Cl	Cl	-CH ₂ OCH ₃
19a,b,c	Cl	Cl	Cl	cyclobutyl
20a,b,c	Cl	Cl	Cl	-CH ₂ CF ₃
21a,b,c	Cl	Cl	Cl	-NH ₂
22a,b,c	Cl	Cl	Cl	-CH ₂ S(O)CH ₃
23b,c	Cl	Cl	Cl	-CH ₂ S(O) ₂ CH ₃
24a,b,c	Cl	Cl	Cl	-S(O) ₂ CH ₃
25a,b,c,	Cl	Cl	Cl	-CH ₂ OH
26a,b,c	Cl	Cl	Cl	n-butyl
27a,b,c	Cl	Cl	Cl	
28a,b,c	Cl	Cl	Cl	

29a,b,c	Cl	Cl	Cl	
30a,b,c	Cl	Cl	Cl	
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32a,b,c	Cl	Cl	Cl	
33a,b,c	Cl	Cl	Cl	
34 a,b,c	Cl	H	Cl	methyl
35 a,b,c	Cl	H	Cl	cyclopropyl
36 a,b,c	Cl	H	Cl	-NHCH ₃
37 a,b,c	Cl	H	Cl	-NHCH ₂ CH ₃
38 a,b,c	Cl	H	Cl	-NH-cyclopropyl
39 a,b,c	Cl	H	Cl	-CH ₂ -cyclopropyl
40 b,c	Cl	H	Cl	isopropyl
41 a,b,c	Cl	H	Cl	ethyl
42 a,b,c	Cl	H	Cl	propyl
43 a,b,c	Cl	H	Cl	-CH ₂ CN
44 a,b,c	Cl	H	Cl	-CH ₂ SCH ₃
45 a,b,c	Cl	H	Cl	-CH ₂ OCH ₃
46 a,b,c	Cl	H	Cl	cyclobutyl
47 a,b,c	Cl	H	Cl	-CH ₂ CF ₃
48 a,b,c	Cl	H	Cl	-NH ₂
49 a,b,c	Cl	H	Cl	-CH ₂ S(O)CH ₃
50 b,c	Cl	H	Cl	-CH ₂ S(O) ₂ CH ₃
51 a,b,c	Cl	H	Cl	-S(O) ₂ CH ₃
52 a,b,c	Cl	H	Cl	-CH ₂ OH
53 a,b,c	Cl	H	Cl	n-butyl
54 a,b,c	Cl	H	Cl	
55 a,b,c	Cl	H	Cl	

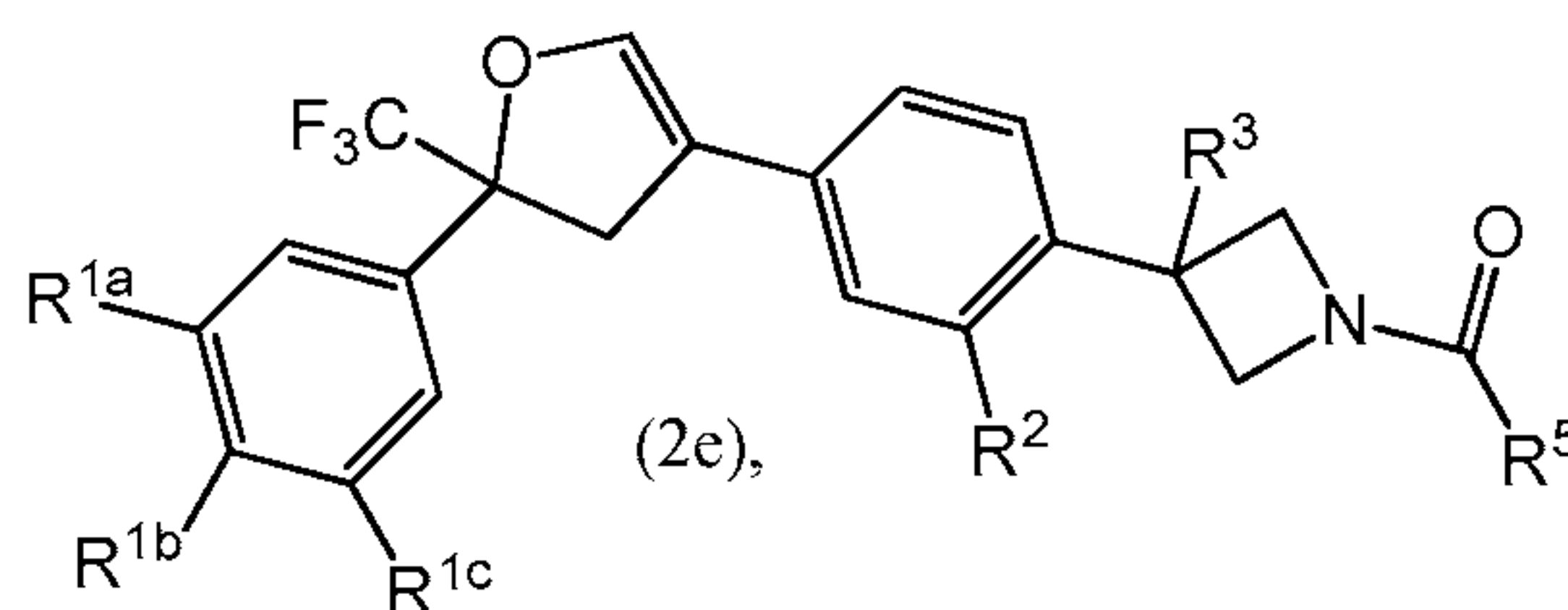
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61 a,b,c	Cl	F	Cl	-NH ₂
62 a,b,c	Cl	F	Cl	methyl
63 a,b,c	Cl	F	Cl	cyclopropyl
64 a,b,c	Cl	F	Cl	-NHCH ₃
65 a,b,c	Cl	F	Cl	-NHCH ₂ CH ₃
66 a,b,c	Cl	F	Cl	-NH-cyclopropyl
67 a,b,c	Cl	F	Cl	CH ₂ -cyclopropyl
68 b,c	Cl	F	Cl	isopropyl
69 a,b,c	Cl	F	Cl	ethyl
70 a,b,c	Cl	F	Cl	propyl
71 a,b,c	Cl	F	Cl	-CH ₂ CN
72 a,b,c	Cl	F	Cl	-CH ₂ SCH ₃
73 a,b,c	Cl	F	Cl	-CH ₂ OCH ₃
74 a,b,c	Cl	F	Cl	cyclobutyl
75 a,b,c	Cl	F	Cl	-CH ₂ CF ₃
76 a,b,c	Cl	F	Cl	-CH ₂ S(O)CH ₃
77 b,c	Cl	F	Cl	-CH ₂ S(O) ₂ CH ₃
78 a,b,c	Cl	F	Cl	-S(O) ₂ CH ₃
79 a,b,c	Cl	F	Cl	-CH ₂ OH
80 a,b,c	Cl	F	Cl	n-butyl
81 a,b,c	Cl	F	Cl	
82 a,b,c	Cl	F	Cl	

83 a,b,c	Cl	F	Cl	
84 a,b,c	Cl	F	Cl	
85 a,b,c	Cl	F	Cl	
86 a,b,c	Cl	F	Cl	
87 a,b,c	Cl	F	Cl	
88 a,b,c	Cl	H	CF ₃	-NH ₂
89 a,b,c	Cl	H	CF ₃	methyl
90 a,b,c	Cl	H	CF ₃	cyclopropyl
91 a,b,c	Cl	H	CF ₃	-NHCH ₃
92 a,b,c	Cl	H	CF ₃	-NHCH ₂ CH ₃
93 a,b,c	Cl	H	CF ₃	-NH-cyclopropyl
94 a,b,c	Cl	H	CF ₃	CH ₂ -cyclopropyl
95 a,b,c	Cl	H	CF ₃	isopropyl
96 a,b,c	Cl	H	CF ₃	ethyl
97 a,b,c	Cl	H	CF ₃	propyl
98 a,b,c	Cl	H	CF ₃	-CH ₂ CN
99 a,b,c	Cl	H	CF ₃	-CH ₂ SCH ₃
100 a,b,c	Cl	H	CF ₃	-CH ₂ OCH ₃
101 a,b,c	Cl	H	CF ₃	cyclobutyl
102 a,b,c	Cl	H	CF ₃	-CH ₂ CF ₃
103 a,b,c	Cl	H	CF ₃	-CH ₂ S(O)CH ₃
104 a,b,c	Cl	H	CF ₃	-CH ₂ S(O) ₂ CH ₃
105 a,b,c	Cl	H	CF ₃	-S(O) ₂ CH ₃
106 a,b,c	Cl	H	CF ₃	-CH ₂ OH
107 a,b,c	Cl	H	CF ₃	
108 a,b,c	Cl	H	CF ₃	
109 a,b,c	Cl	H	CF ₃	

110 a,b,c	Cl	H	CF ₃	
111 a,b,c	Cl	H	CF ₃	
112 a,b,c	Cl	H	CF ₃	
113 a,b,c	Cl	H	CF ₃	
114 a,b,c	Cl	H	Cl	n-butyl
115 a,b,c	Cl	Cl	CF ₃	-NH ₂
116 a,b,c	Cl	Cl	CF ₃	methyl
117 a,b,c	Cl	Cl	CF ₃	cyclopropyl
118 a,b,c	Cl	Cl	CF ₃	-NHCH ₃
119 a,b,c	Cl	Cl	CF ₃	-NHCH ₂ CH ₃
120 a,b,c	Cl	Cl	CF ₃	-NH-cyclopropyl
121 a,b,c	Cl	Cl	CF ₃	CH ₂ -cyclopropyl
122 a,b,c	Cl	Cl	CF ₃	isopropyl
123 a,b,c	Cl	Cl	CF ₃	ethyl
124 a,b,c	Cl	Cl	CF ₃	propyl
125 a,b,c	Cl	Cl	CF ₃	-CH ₂ CN
126 a,b,c	Cl	Cl	CF ₃	-CH ₂ SCH ₃
127 a,b,c	Cl	Cl	CF ₃	-CH ₂ OCH ₃
128 a,b,c	Cl	Cl	CF ₃	cyclobutyl
129 a,b,c	Cl	Cl	CF ₃	-CH ₂ CF ₃
130 a,b,c	Cl	Cl	CF ₃	-CH ₂ S(O)CH ₃
131 a,b,c	Cl	Cl	CF ₃	-CH ₂ S(O) ₂ CH ₃
132 a,b,c	Cl	Cl	CF ₃	-S(O) ₂ CH ₃
133 a,b,c	Cl	Cl	CF ₃	-CH ₂ OH
134 a,b,c	Cl	Cl	CF ₃	n-butyl
135 a,b,c	Cl	Cl	CF ₃	
136 a,b,c	Cl	Cl	CF ₃	
137 a,b,c	Cl	Cl	CF ₃	

138 a,b,c	Cl	Cl	CF ₃	
139 a,b,c	Cl	Cl	CF ₃	
140 a,b,c	Cl	Cl	CF ₃	
141 a,b,c	Cl	Cl	CF ₃	

In addition to the compounds of Table 1 of Formula 2c, similar compounds can be prepared from Formula (2e)



- 5 wherein R² is selected from chloro, bromo, cyano, and fluoro.

BIOLOGICAL ASSAYS

The biological activity of the compounds of the present invention can be tested against fleas, ticks, flies, and or sea lice using the test methods described below.

Horn Fly (*Haematobia irritans*) Feed Assay

Formula (1) compounds can be dissolved in DMSO and aliquots added to citrated bovine blood in a membrane covered Petri dish. Approximately ten horn flies are placed onto each Petri dish and covered. The flies are allowed to feed on the treated blood cell. Flies are held at approximately 80°F with a minimum of approximately 50% relative humidity. Flies are examined for knockdown and mortality at approximately 2 and 24 hours. Endpoint data is recorded as a lethal dose 90% (LD⁹⁰) in µg/mL.

Stable Fly (*Stomoxys calcitrans*) Topical Assay

Formula (1) compounds can be dissolved in acetone, and 1 µL of the solution placed on the thorax of an anesthetized fly (n=10). The flies are allowed

to recover, and are incubated for 24 hours at room temperature. Flies are examined for knockdown and mortality at 2 and 24 hours. Endpoint data is recorded as lethal dose 90% (LD⁹⁰) in µg/fly.

5 Flea (*Ctenocephalides felis*) Membrane Feed Assay-Adult

Formula (1) compounds were dissolved in DMSO and aliquots added to citrated bovine blood in a membrane covered Petri dish pre-warmed to 37°C. Feeding tubes containing approximately 30-35 adult fleas are placed onto the Petri dishes. The fleas are allowed to feed for approximately 2 hours. Fleas are observed for knockdown and/or death at approximately 2 and 24 hours. Endpoint data is recorded as a lethal dose 90% (LD⁹⁰) in µg/mL. Examples 1-6 had LD⁹⁰ values > 3 µg/mL.

Soft Tick (*Ornithodoros turicata*) Blood Feed Assay

15 Formula (1) compounds can be dissolved in dimethylsulfoxide (DMSO) and aliquots added to citrated bovine blood in a membrane covered Petri dish. The Petri dish is placed on a warming tray. Approximately 5 nymph stage ticks are placed onto the membrane, covered, and left to feed. Fed ticks are removed and placed into a Petri dish with sand. Fed ticks are observed at approximately 20 24, 48 and 72 hours for paralysis and/or death. Endpoint data is recorded as an ED¹⁰⁰ and/or an LD¹⁰⁰ in µg/mL. Positive control is fipronil and DMSO for the negative control.

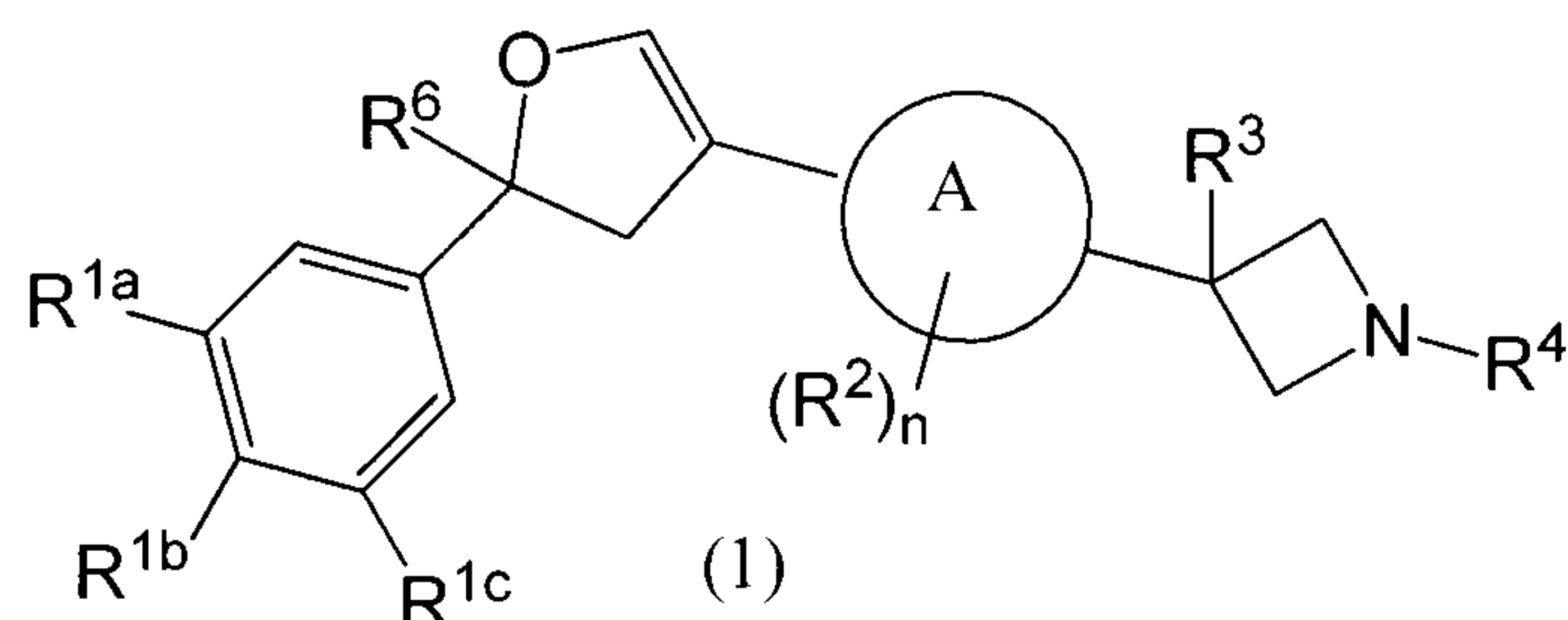
Copepod (*Lepeophtheirus salmonis*) BioAssay

25 Formula (1) compounds can be dissolved in sea water. Negative control is sea water and positive control is emamectin benzoate. Ten pre-adult/adult salmon lice are exposed for 24 hours. Lice are monitored for motility and endpoint data is recorded as an Effective Concentration 100% (EC¹⁰⁰) based on immotility.

30

We claim:

1. A compound of Formula (1)



wherein

A is phenyl, naphthyl, or heteroaryl where said heteroaryl contains 1 to 4 heteroatoms each independently selected from N, O and S;

R^{1a}, R^{1b}, and R^{1c} are each independently hydrogen, halo, hydroxyl, cyano, nitro, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₀-C₃alkylC₃-C₆cycloalkyl, C₁-C₆haloalkoxy, -C(O)NH₂, -SF₅, or -S(O)_pR;

R² is halo, cyano, C₁-C₆alkyl, C₁-C₆haloalkyl, nitro, hydroxyl, -C(O)NR^aR^b, C₂-C₆alkenyl, C₂-C₆alkynyl, -S(O)_pR, or -OR;

R³ is hydrogen, halo, hydroxyl, cyano, C₁-C₆alkyl, C₁-C₆haloalkyl, C₀-C₃alkylC₃-C₆cycloalkyl, -C(O)NH₂, nitro, -SC(O)R, -C(O)NR^aR^b, C₀-C₃alkylNR^aR⁴, -NR^aNR^bR⁴, -NR^aOR^b, -ONR^aR^b, N₃, -NHR⁴, -OR, or -S(O)_pR;

R⁴ is hydrogen, C₁-C₆alkyl, C₀-C₆alkylC₃-C₆cycloalkyl, -C(O)R⁵, -C(S)R⁵, -C(O)NR^aR⁵, -C(O)C(O)NR^aR⁵, -S(O)_pR^c, -S(O)₂NR^aR⁵, -C(NR⁷)R⁵, -C(NR⁷)NR^aR⁵, C₀-C₆alkylphenyl, C₀-C₆alkylheteroaryl, or C₀-C₆alkylheterocycle;

R⁵ is hydrogen, C₁-C₆alkyl, C₂-C₆alkenyl, C₀-C₆alkylC₃-C₆cycloalkyl, C₀-C₆alkylphenyl, C₀-C₆alkylheteroaryl, or C₀-C₆alkylheterocycle;

R⁶ is cyano, C₁-C₆alkyl, C₁-C₆haloalkyl, -C(O)NR^aR^b, C₂-C₆alkenyl, C₂-C₆alkynyl, C₂-C₆haloalkenyl, or C₂-C₆haloalkynyl;

R⁷ is hydrogen, C₁-C₆alkyl, hydroxyl, cyano, nitro, -S(O)_pR^c, or C₁-C₆alkoxy;

R is C₁-C₆alkyl or C₃-C₆cycloalkyl each optionally substituted by at least one halo;

R^a is hydrogen, C₁-C₆alkyl, or C₀-C₃alkylC₃-C₆cycloalkyl; wherein the alkyl and alkylcycloalkyl is optionally substituted by cyano or at least one halo substituent;

R^b is hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_0 - C_3 alkylphenyl, C_0 - C_3 alkylheteroaryl, or C_0 - C_3 alkylheterocycle, each optionally substituted, where chemically possible, with at least one substituent selected from hydroxyl, cyano, halo, or $-S(O)_pR$;

R^c is C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkyl C_3 - C_6 cycloalkyl, C_0 - C_3 alkyl C_3 - C_6 cycloalkyl, C_0 - C_3 alkylphenyl, C_0 - C_3 alkylheteroaryl, or C_0 - C_3 alkylheterocycle each optionally substituted with at least one substituent selected from cyano, halo, hydroxyl, oxo, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, C_1 - C_6 haloalkyl, $-S(O)_pR$, $-SH$, $-S(O)_pNR^aR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$, $-SC(O)R^b$, $-SCN$, or $-C(O)NR^aR^b$;

each of R^4 and R^5 C_1 - C_6 alkyl or C_0 - C_6 alkyl C_3 - C_6 cycloalkyl can be optionally and independently substituted by at least one substituent selected from C_1 - C_6 alkyl, C_1 - C_6 hydroxyalkyl, cyano, halo, hydroxyl, oxo, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, C_1 - C_6 haloalkyl, $-S(O)_pR^c$, $-SH$, $-S(O)_pNR^aR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$, $-SC(O)R^c$, $-SCN$, or $-C(O)NR^aR^b$; and

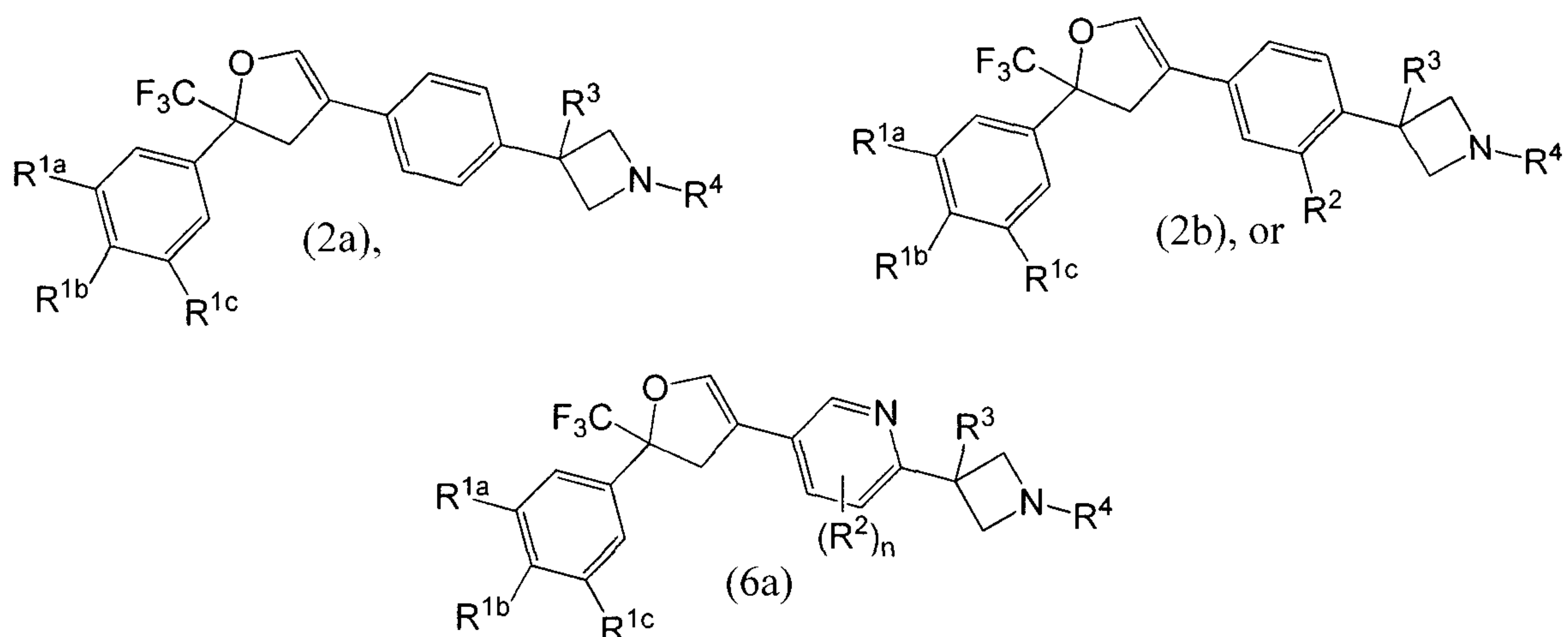
wherein R^4 and R^5 C_0 - C_6 alkylphenyl, C_0 - C_6 alkylheteroaryl, or C_0 - C_6 alkylheterocycle moiety can be further optionally substituted with at least one substituent selected from C_1 - C_6 alkyl, C_1 - C_6 hydroxyalkyl, cyano, halo, oxo, $=S$, $=NR^7$, hydroxyl, C_1 - C_6 alkoxy, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, $-SH$, $-S(O)_pR$, and C_1 - C_6 haloalkoxy;

n is the integer 0, 1, or 2, and when n is 2, each R^2 may be identical or different from each other; and

p is the integer 0, 1, or 2;

or a stereoisomer thereof, or a pharmaceutically or veterinarily acceptable salt thereof.

2. The compound of Claim 1 having Formula (2a), (2b), or (6a)



wherein

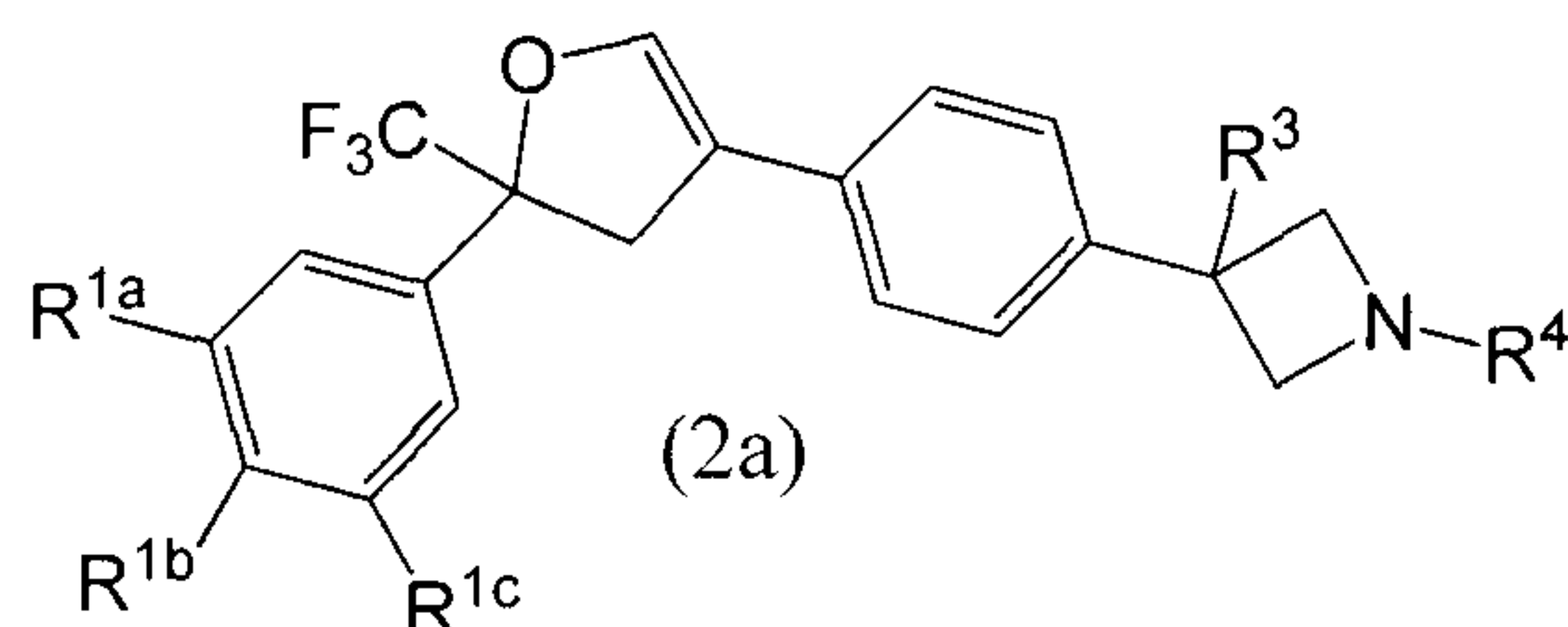
R^{1a} , R^{1b} , and R^{1c} are each independently selected from hydrogen, halo, hydroxyl, and C_1 - C_6 haloalkyl;

R^2 is halo, cyano, hydroxyl, $-C(O)NR^aR^b$, or $-OR$; and

R^3 is hydrogen, halo, hydroxyl, N_3 , or cyano;

or a stereoisomer thereof, or a pharmaceutically or veterinarily acceptable salt thereof.

3. The compound of Claim 2 having Formula (2a)



wherein

R^{1a} , R^{1b} , and R^{1c} are each independently selected from hydrogen, halo, and C_1 - C_6 haloalkyl; and

R^3 is hydrogen, halo, hydroxyl, or cyano;

or a stereoisomer thereof, or a pharmaceutically or veterinarily acceptable salt thereof.

4. The compound of claim 3 wherein

R^4 is $-C(O)R^5$, $-C(O)NR^aR^5$, $-S(O)_pR^c$, $-C(S)R^5$, $-S(O)_2NR^aR^5$, $-C(NR^7)R^5$; or $-C(NR^7)NR^aR^5$;

or a stereoisomer thereof, or a pharmaceutically or veterinarily acceptable salt thereof.

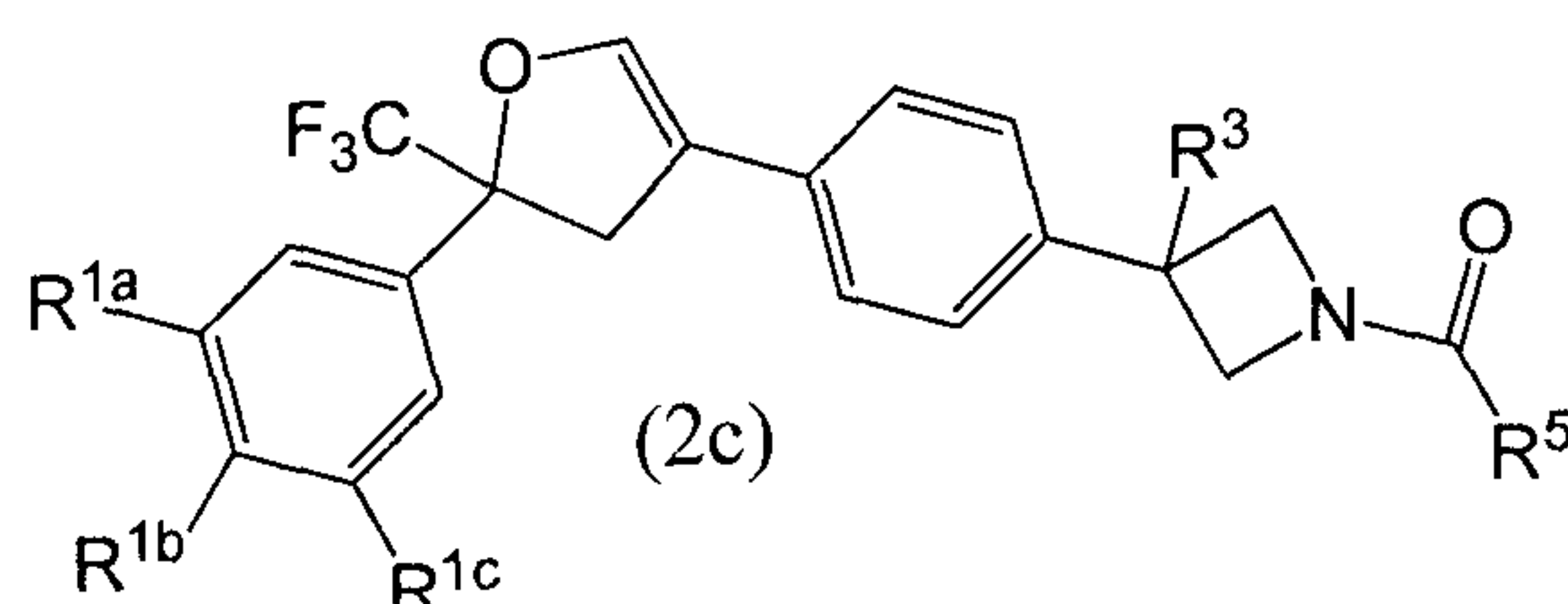
5. The compound of claim 4 wherein

R^{1a} , R^{1b} , and R^{1c} are each independently selected from hydrogen, chloro, fluoro, bromo, and C_1 - C_6 haloalkyl; and

R^4 is $-C(O)R^5$, $-C(O)NR^aR^5$, or $-C(NR^7)R^5$;

or a stereoisomer thereof, or a pharmaceutically or veterinarily acceptable salt thereof.

6. The compound of Claim 5 of Formula (2a) having Formula (2c)



wherein

R^{1a} , R^{1b} , and R^{1c} are each independently selected from hydrogen, chloro, fluoro, and C_1 - C_6 haloalkyl;

or a stereoisomer thereof, or a pharmaceutically or veterinarily acceptable salt thereof.

7. The compound that is 1-(3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydrofuran-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-(methylsulfonyl)ethanone; or a stereoisomer thereof, or a pharmaceutically or veterinarily acceptable salt thereof.

8. The compound that is 1-(3-(4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydrofuran-3-yl)phenyl)-3-fluoroazetidin-1-yl)-2-methylpropan-1-one; or a stereoisomer thereof, or a pharmaceutically or veterinarily acceptable salt thereof.

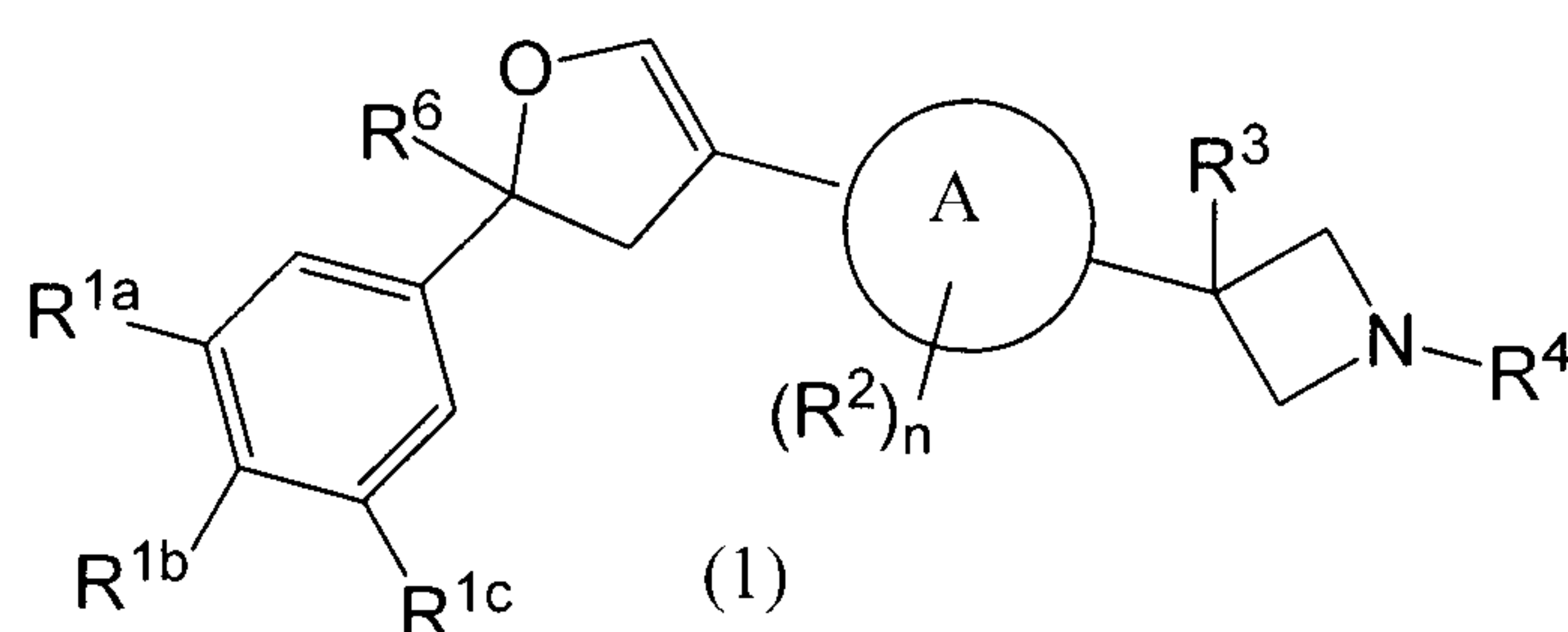
9. The compound that is 1-(3-{4-[5-(3,4,5-trichloro-phenyl)-5-trifluoromethyl-4,5-dihydro-furan-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-2-methanesulfonyl-ethanone; or a stereoisomer thereof, or a pharmaceutically or veterinarily acceptable salt thereof.

10. The compound that is 1-(3-Fluoro-3-{4-[5-(3,4,5-trichloro-phenyl)-5-trifluoromethyl-4,5-di-hydro-furan-3-yl]-phenyl}-azetidin-1-yl)-2-methyl-propan-1-one; or a stereoisomer thereof, or a pharmaceutically or veterinarily acceptable salt thereof.

11. The compound that is 1-(3-{4-[5-(3,5-dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-furan-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-2-methanesulfonyl-ethanone; or a stereoisomer thereof, or a pharmaceutically or veterinarily acceptable salt thereof.

12. The compound that is 1-(3-{4-[5-(3,5-dichloro-4-fluoro-phenyl)-5-trifluoromethyl-4,5-dihydro-furan-3-yl]-phenyl}-3-fluoro-azetidin-1-yl)-2-methylpropan-1-one; or a stereoisomer thereof, or a pharmaceutically or veterinarily acceptable salt thereof.

13. A pharmaceutical or veterinary composition comprising a compound of Formula (1)



wherein

A is phenyl, naphthyl, or heteroaryl where said heteroaryl contains 1 to 4 heteroatoms each independently selected from N, O and S;

R^{1a} , R^{1b} , and R^{1c} are each independently hydrogen, halo, hydroxyl, cyano, nitro, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_0 - C_3 alkyl C_3 - C_6 cycloalkyl, C_1 - C_6 haloalkoxy, $-C(O)NH_2$, $-SF_5$, or $-S(O)_pR$;

R^2 is halo, cyano, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, nitro, hydroxyl, $-C(O)NR^aR^b$, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, $-S(O)_pR$, or $-OR$;

R^3 is hydrogen, halo, hydroxyl, cyano, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_0 - C_3 alkyl C_3 - C_6 cycloalkyl, $-C(O)NH_2$, nitro, $-SC(O)R$, $-C(O)NR^aR^b$, C_0 - C_3 alkyl NR^aR^4 , $-NR^aNR^bR^4$, $-NR^aOR^b$, $-ONR^aR^b$, N_3 , $-NHR^4$, $-OR$, or $-S(O)_pR$;

R^4 is hydrogen, C_1 - C_6 alkyl, C_0 - C_6 alkyl C_3 - C_6 cycloalkyl, $-C(O)R^5$, $-C(S)R^5$, $-C(O)NR^aR^5$, $-C(O)C(O)NR^aR^5$, $-S(O)_pR^c$, $-S(O)_2NR^aR^5$, $-C(NR^7)R^5$, $-C(NR^7)NR^aR^5$, C_0 - C_6 alkylphenyl, C_0 - C_6 alkylheteroaryl, or C_0 - C_6 alkylheterocycle;

R^5 is hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_0 - C_6 alkyl C_3 - C_6 cycloalkyl, C_0 - C_6 alkylphenyl, C_0 - C_6 alkylheteroaryl, or C_0 - C_6 alkylheterocycle;

R^6 is cyano, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, $-C(O)NR^aR^b$, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_2 - C_6 haloalkenyl, or C_2 - C_6 haloalkynyl;

R^7 is hydrogen, C_1 - C_6 alkyl, hydroxyl, cyano, nitro, $-S(O)_pR^c$, or C_1 - C_6 alkoxy;

R is C_1 - C_6 alkyl or C_3 - C_6 cycloalkyl each optionally substituted by at least one halo;

R^a is hydrogen, C_1 - C_6 alkyl, or C_0 - C_3 alkyl C_3 - C_6 cycloalkyl; wherein the alkyl and alkylcycloalkyl is optionally substituted by cyano or at least one halo substituent;

R^b is hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_0 - C_3 alkylphenyl, C_0 - C_3 alkylheteroaryl, or C_0 - C_3 alkylheterocycle, each optionally substituted, where chemically possible, with at least one substituent selected from hydroxyl, cyano, halo, or $-S(O)_pR$;

R^c is C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkyl C_3 - C_6 cycloalkyl, C_0 - C_3 alkyl C_3 - C_6 cycloalkyl, C_0 - C_3 alkylphenyl, C_0 - C_3 alkylheteroaryl, or C_0 - C_3 alkylheterocycle each optionally substituted with at least one substituent selected from cyano, halo, hydroxyl, oxo, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, C_1 - C_6 haloalkyl, $-S(O)_pR$, $-SH$, $-S(O)_pNR^aR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$, $-SC(O)R^b$, $-SCN$, or $-C(O)NR^aR^b$;

each of R^4 and R^5 C_1 - C_6 alkyl or C_0 - C_6 alkyl C_3 - C_6 cycloalkyl can be optionally and independently substituted by at least one substituent selected from C_1 - C_6 alkyl, C_1 - C_6 hydroxyalkyl, cyano, halo, hydroxyl, oxo, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, C_1 - C_6 haloalkyl, $-S(O)_pR^c$, $-SH$, $-S(O)_pNR^aR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$, $-SC(O)R^c$, $-SCN$, or $-C(O)NR^aR^b$; and

wherein R^4 and R^5 C_0 - C_6 alkylphenyl, C_0 - C_6 alkylheteroaryl, or C_0 - C_6 alkylheterocycle moiety can be further optionally substituted with at least one substituent selected from C_1 - C_6 alkyl, C_1 - C_6 hydroxyalkyl, cyano, halo, oxo, $=S$, $=NR^7$, hydroxyl, C_1 - C_6 alkoxy, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, $-SH$, $-S(O)_pR$, and C_1 - C_6 haloalkoxy;

n is the integer 0, 1, or 2, and when n is 2, each R^2 may be identical or different from each other; and

p is the integer 0, 1, or 2;

or a stereoisomer thereof, or a pharmaceutically or veterinarily acceptable salt thereof, and wherein the composition further comprises a pharmaceutically or veterinarily acceptable excipient, diluent, or carrier.

14. The pharmaceutical or veterinary composition of claim 13 wherein the compound, stereoisomer, or pharmaceutically or veterinarily acceptable salt is as defined in claim 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

15. The pharmaceutical or veterinary composition of claim 13 or 14 for the treatment of a parasitic infection or infestation in an animal.

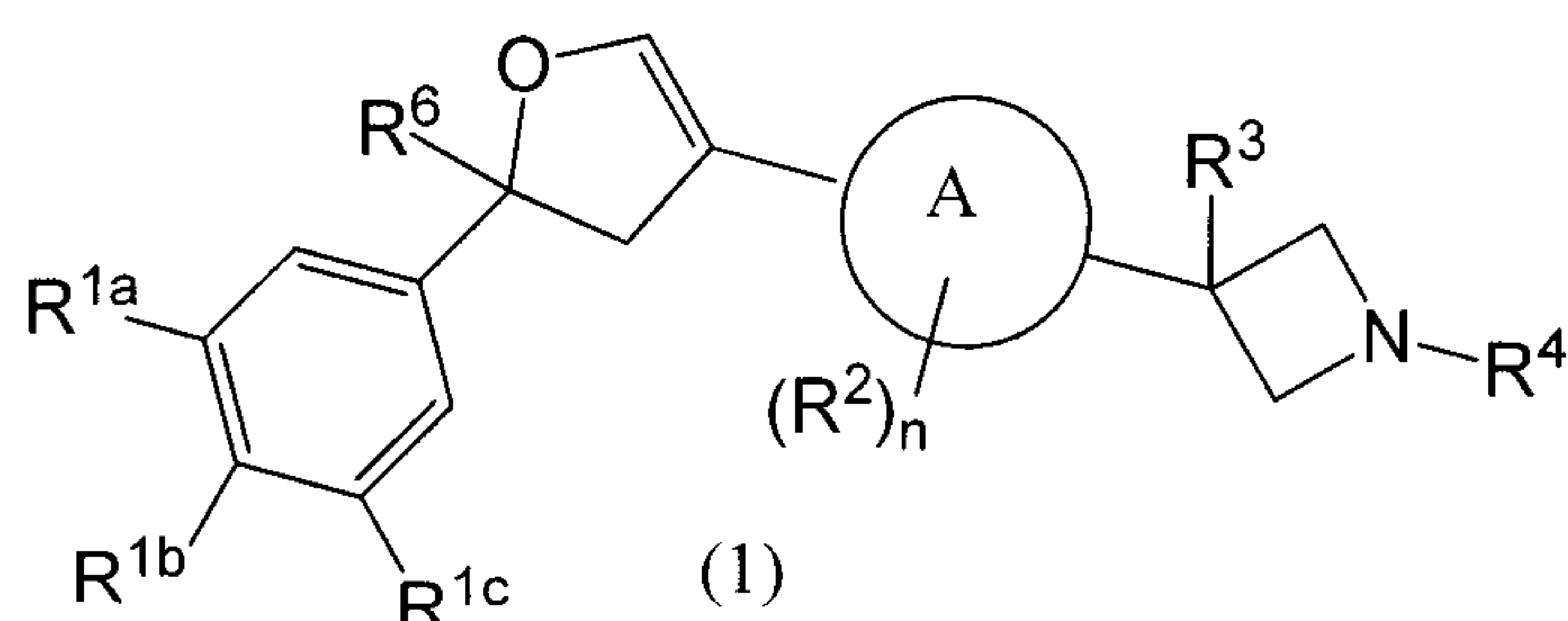
16. The pharmaceutical or veterinary composition of claim 13, 14 or 15 further comprising at least one additional veterinary agent.

17. The pharmaceutical or veterinary composition of claim 16 wherein said additional veterinary agent is selected from the group consisting of abamectin, ivermectin, avermectin, moxidectin, emamectin, eprinomectin, selamectin, doramectin, nemadectin, albendazole, cambendazole, fenbendazole, flubendazole, mebendazole, oxfenbendazole, oxibendazole, parbendazole, tetramisole, levamisole, pyrantel pamoate, oxantel, morantel, indoxacarb, closantel, triclabendazole, clorsulon, refoxanide, niclosamide, praziquantel, epsiprantel, 2-desoxoparaherquamide, pyripole, pyrafluprole, lufenuron, spiromesifen, tebufenozide, spinosad, spinetoram, imidacloprid, dinotefuran, metaflumizone, thibendiamide, chlorantraniliprole, indoxacarb, pyridalyl, pyrimidifen, pyrifluquinazon, milbemycin oxime, milbemycin, DEET, demiditraz, amitraz, fipronil, methoprene, hydroprene, novaluron, lufenuron, permethrin, and pyrethrin, or mixtures thereof.

18. The pharmaceutical or veterinary composition of Claim 17 wherein said additional veterinary agent is milbemycin oxime or moxidectin.

19. The pharmaceutical or veterinary composition of claim 13, 14, 15, 16, 17 or 18 which is for administration to the animal topically, orally, or by injection.

20. Use of a compound of Formula (1) for the treatment of a parasitic infection or infestation in an animal



wherein

A is phenyl, naphthyl, or heteroaryl where said heteroaryl contains 1 to 4 heteroatoms each independently selected from N, O and S;

R^{1a} , R^{1b} , and R^{1c} are each independently hydrogen, halo, hydroxyl, cyano, nitro, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_0 - C_3 alkyl/ C_3 - C_6 cycloalkyl, C_1 - C_6 haloalkoxy, $-C(O)NH_2$, $-SF_5$, or $-S(O)_pR$;

R^2 is halo, cyano, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, nitro, hydroxyl, $-C(O)NR^aR^b$, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, $-S(O)_pR$, or $-OR$;

R^3 is hydrogen, halo, hydroxyl, cyano, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_0 - C_3 alkyl C_3 - C_6 cycloalkyl, $-C(O)NH_2$, nitro, $-SC(O)R$, $-C(O)NR^aR^b$, C_0 - C_3 alkyl NR^aR^4 , $-NR^aNR^bR^4$, $-NR^aOR^b$, $-ONR^aR^b$, N_3 , $-NHR^4$, $-OR$, or $-S(O)_pR$;

R^4 is hydrogen, C_1 - C_6 alkyl, C_0 - C_6 alkyl C_3 - C_6 cycloalkyl, $-C(O)R^5$, $-C(S)R^5$, $-C(O)NR^aR^5$, $-C(O)C(O)NR^aR^5$, $-S(O)_pR^c$, $-S(O)_2NR^aR^5$, $-C(NR^7)R^5$, $-C(NR^7)NR^aR^5$, C_0 - C_6 alkylphenyl, C_0 - C_6 alkylheteroaryl, or C_0 - C_6 alkylheterocycle;

R^5 is hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_0 - C_6 alkyl C_3 - C_6 cycloalkyl, C_0 - C_6 alkylphenyl, C_0 - C_6 alkylheteroaryl, or C_0 - C_6 alkylheterocycle;

R^6 is cyano, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, $-C(O)NR^aR^b$, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_2 - C_6 haloalkenyl, or C_2 - C_6 haloalkynyl;

R^7 is hydrogen, C_1 - C_6 alkyl, hydroxyl, cyano, nitro, $-S(O)_pR^c$, or C_1 - C_6 alkoxy;

R is C_1 - C_6 alkyl or C_3 - C_6 cycloalkyl each optionally substituted by at least one halo;

R^a is hydrogen, C_1 - C_6 alkyl, or C_0 - C_3 alkyl C_3 - C_6 cycloalkyl; wherein the alkyl and alkylcycloalkyl is optionally substituted by cyano or at least one halo substituent;

R^b is hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_0 - C_3 alkylphenyl, C_0 - C_3 alkylheteroaryl, or C_0 - C_3 alkylheterocycle, each optionally substituted, where chemically possible, with at least one substituent selected from hydroxyl, cyano, halo, or $-S(O)_pR$;

R^c is C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkyl C_3 - C_6 cycloalkyl, C_0 - C_3 alkyl C_3 - C_6 cycloalkyl, C_0 - C_3 alkylphenyl, C_0 - C_3 alkylheteroaryl, or C_0 - C_3 alkylheterocycle each optionally substituted with at least one substituent selected from cyano, halo, hydroxyl, oxo, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, C_1 - C_6 haloalkyl, $-S(O)_pR$, $-SH$, $-S(O)_pNR^aR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$, $-SC(O)R^b$, $-SCN$, or $-C(O)NR^aR^b$;

each of R^4 and R^5 C_1 - C_6 alkyl or C_0 - C_6 alkyl C_3 - C_6 cycloalkyl can be optionally and independently substituted by at least one substituent selected from C_1 - C_6 alkyl, C_1 - C_6 hydroxyalkyl, cyano, halo, hydroxyl, oxo, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, C_1 - C_6 haloalkyl, $-S(O)_pR^c$, $-SH$, $-S(O)_pNR^aR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$, $-SC(O)R^c$, $-SCN$, or $-C(O)NR^aR^b$; and

wherein R^4 and R^5 C_0 - C_6 alkylphenyl, C_0 - C_6 alkylheteroaryl, or C_0 - C_6 alkylheterocycle moiety can be further optionally substituted with at least one substituent selected from C_1 - C_6 alkyl, C_1 - C_6 hydroxyalkyl, cyano, halo, oxo, $=S$, $=NR^7$,

hydroxyl, C₁-C₆alkoxy, C₁-C₆alkyl, C₁-C₆haloalkyl, -SH, -S(O)_pR, and C₁-C₆haloalkoxy;

n is the integer 0, 1, or 2, and when n is 2, each R² may be identical or different from each other; and

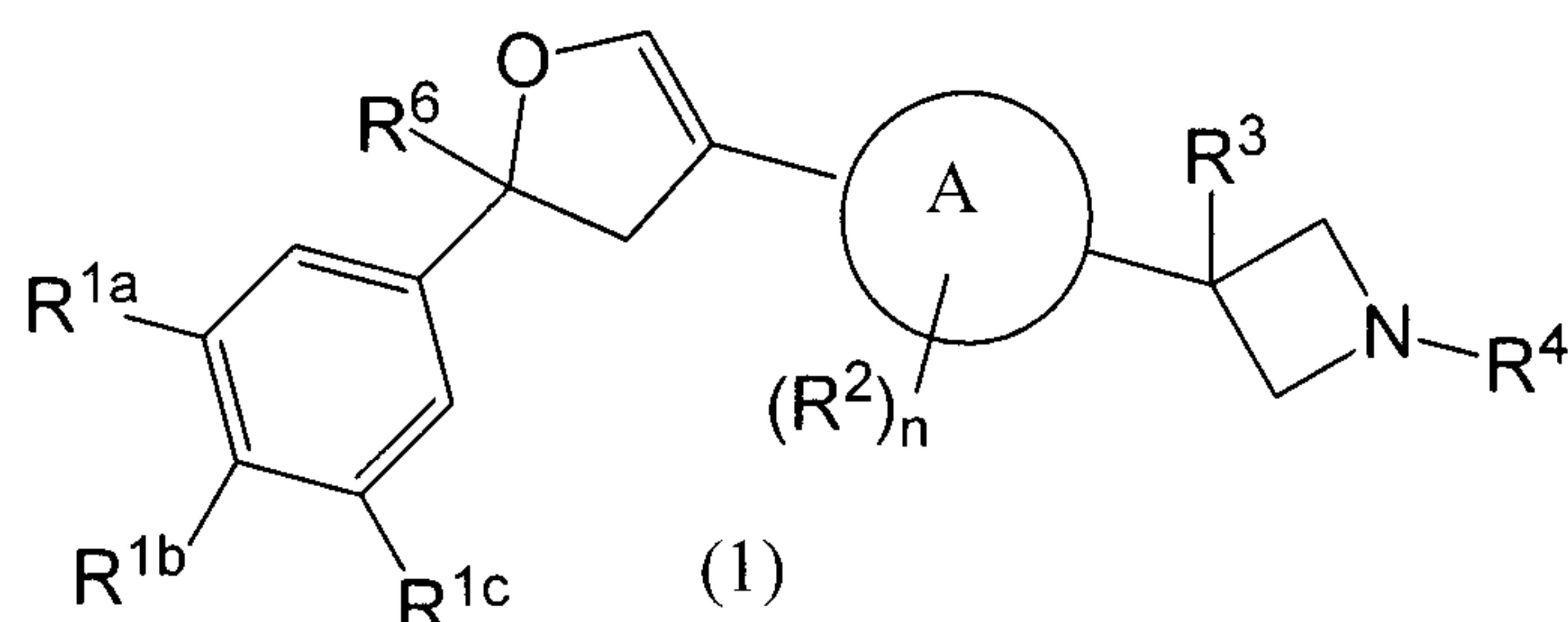
p is the integer 0, 1, or 2;

or a stereoisomer thereof, or a pharmaceutically or veterinarily acceptable salt thereof.

21. The use of claim 20 wherein the compound, stereoisomer, or pharmaceutically or veterinarily acceptable salt is as defined in claim 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

22. The use of claim 20 or 21 wherein the compound, stereoisomer, or pharmaceutically or veterinarily acceptable salt is for administration to the animal topically, orally, or by injection.

23. Use of a compound of Formula (1) in the manufacture of a medicament for the treatment of a parasitic infection or infestation in an animal



wherein

A is phenyl, naphthyl, or heteroaryl where said heteroaryl contains 1 to 4 heteroatoms each independently selected from N, O and S;

R^{1a}, R^{1b}, and R^{1c} are each independently hydrogen, halo, hydroxyl, cyano, nitro, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₀-C₃alkylC₃-C₆cycloalkyl, C₁-C₆haloalkoxy, -C(O)NH₂, -SF₅, or -S(O)_pR;

R² is halo, cyano, C₁-C₆alkyl, C₁-C₆haloalkyl, nitro, hydroxyl, -C(O)NR^aR^b, C₂-C₆alkenyl, C₂-C₆alkynyl, -S(O)_pR, or -OR;

R³ is hydrogen, halo, hydroxyl, cyano, C₁-C₆alkyl, C₁-C₆haloalkyl, C₀-C₃alkylC₃-C₆cycloalkyl, -C(O)NH₂, nitro, -SC(O)R, -C(O)NR^aR^b, C₀-C₃alkylNR^aR⁴, -NR^aNR^bR⁴, -NR^aOR^b, -ONR^aR^b, N₃, -NHR⁴, -OR, or -S(O)_pR;

R⁴ is hydrogen, C₁-C₆alkyl, C₀-C₆alkylC₃-C₆cycloalkyl, -C(O)R⁵, -C(S)R⁵, -C(O)NR^aR⁵, -C(O)C(O)NR^aR⁵, -S(O)_pR^c, -S(O)₂NR^aR⁵, -

$C(NR^7)R^5$, $-C(NR^7)NR^aR^5$, C_0-C_6 alkylphenyl, C_0-C_6 alkylheteroaryl, or C_0-C_6 alkylheterocycle;

R^5 is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_0-C_6 alkyl C_3-C_6 cycloalkyl, C_0-C_6 alkylphenyl, C_0-C_6 alkylheteroaryl, or C_0-C_6 alkylheterocycle;

R^6 is cyano, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-C(O)NR^aR^b$, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkenyl, or C_2-C_6 haloalkynyl;

R^7 is hydrogen, C_1-C_6 alkyl, hydroxyl, cyano, nitro, $-S(O)_pR^c$, or C_1-C_6 alkoxy;

R is C_1-C_6 alkyl or C_3-C_6 cycloalkyl each optionally substituted by at least one halo;

R^a is hydrogen, C_1-C_6 alkyl, or C_0-C_3 alkyl C_3-C_6 cycloalkyl; wherein the alkyl and alkylcycloalkyl is optionally substituted by cyano or at least one halo substituent;

R^b is hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_0-C_3 alkylphenyl, C_0-C_3 alkylheteroaryl, or C_0-C_3 alkylheterocycle, each optionally substituted, where chemically possible, with at least one substituent selected from hydroxyl, cyano, halo, or $-S(O)_pR$;

R^c is C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkyl C_3-C_6 cycloalkyl, C_0-C_3 alkyl C_3-C_6 cycloalkyl, C_0-C_3 alkylphenyl, C_0-C_3 alkylheteroaryl, or C_0-C_3 alkylheterocycle each optionally substituted with at least one substituent selected from cyano, halo, hydroxyl, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_6 haloalkyl, $-S(O)_pR$, $-SH$, $-S(O)_pNR^aR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$, $-SC(O)R^b$, $-SCN$, or $-C(O)NR^aR^b$;

each of R^4 and R^5 C_1-C_6 alkyl or C_0-C_6 alkyl C_3-C_6 cycloalkyl can be optionally and independently substituted by at least one substituent selected from C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, cyano, halo, hydroxyl, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_6 haloalkyl, $-S(O)_pR^c$, $-SH$, $-S(O)_pNR^aR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$, $-SC(O)R^c$, $-SCN$, or $-C(O)NR^aR^b$; and

wherein R^4 and R^5 C_0-C_6 alkylphenyl, C_0-C_6 alkylheteroaryl, or C_0-C_6 alkylheterocycle moiety can be further optionally substituted with at least one substituent selected from C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, cyano, halo, oxo, $=S$, $=NR^7$, hydroxyl, C_1-C_6 alkoxy, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-SH$, $-S(O)_pR$, and C_1-C_6 haloalkoxy;

n is the integer 0, 1, or 2, and when n is 2, each R^2 may be identical or different from each other; and

p is the integer 0, 1, or 2;

or a stereoisomer thereof, or a pharmaceutically or veterinarily acceptable salt thereof.

24. The use of claim 23 wherein the compound, stereoisomer, or pharmaceutically or veterinarily acceptable salt is as defined in claim 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

25. The use of claim 23 or 24 wherein the medicament is for administration to the animal topically, orally, or by injection.

