



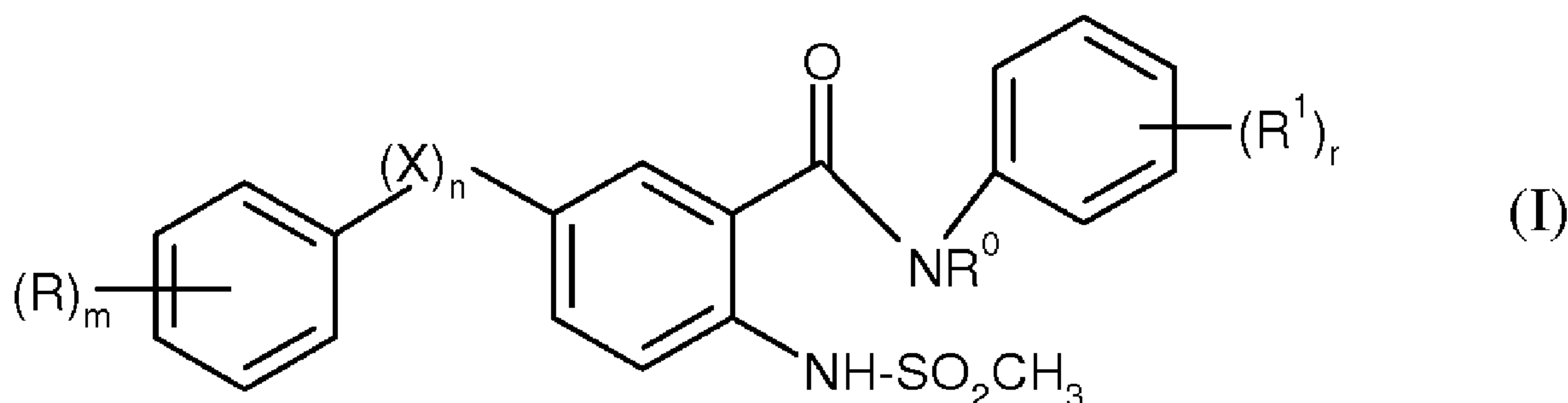
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(54) Titre : NOUVEAUX COMPOSES SULFONYLAMINO BENZAMIDE
(54) Title: NEW SULFONYLAMINO BENZAMIDE COMPOUNDS



(57) Abrégé/Abstract:

The present invention relates to a new compound of formula (I) wherein the variables have the meaning as indicated in the claims; or an enantiomer or salt thereof. The compounds of formula (I) are useful in the control of parasites, in particular endoparasites, in and on vertebrates.

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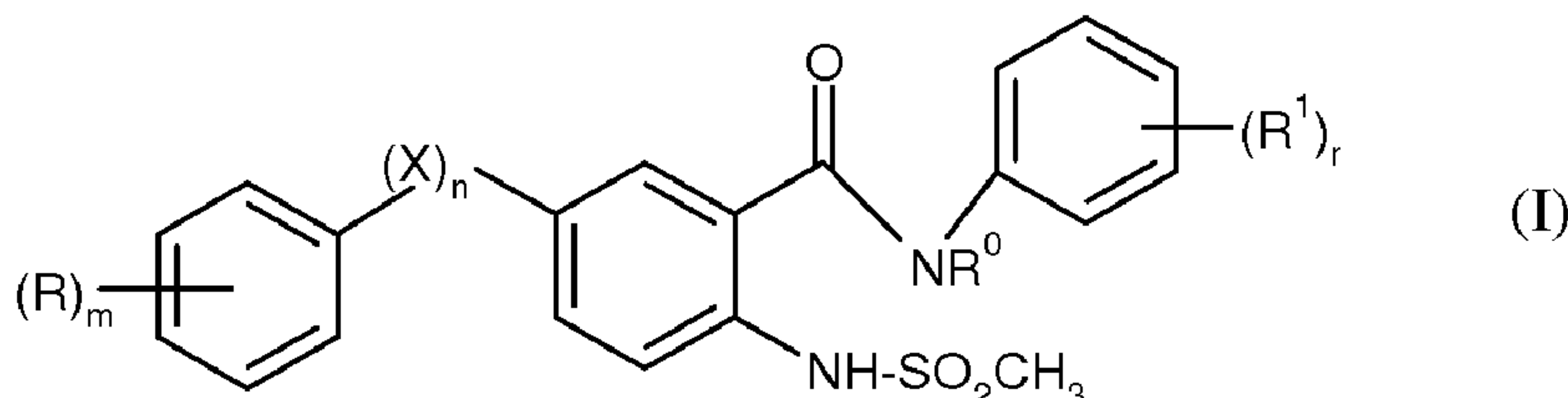
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(57) Abstract: The present invention relates to a new compound of formula (I) wherein the variables have the meaning as indicated in the claims; or an enantiomer or salt thereof. The compounds of formula (I) are useful in the control of parasites, in particular endoparasites, in and on vertebrates.

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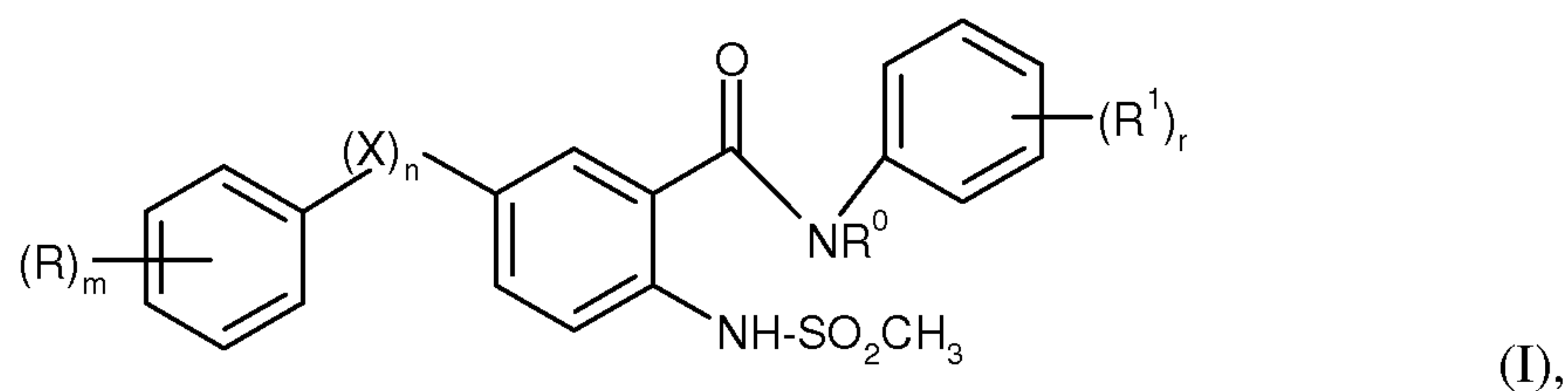
NEW SULFONYLAMINO BENZAMIDE COMPOUNDS

The present invention relates to novel sulfonylaminobenzamide compounds and their use in the control of endoparasites, for example heartworms, in warm-blooded animals.

Heartworm (*Dirofilaria immitis*) is a parasitic roundworm that is spread from host to host through the bites of mosquitoes. The definite host is the dog but it can also infect cats and other warm-blooded animals. Although commonly being called “heartworm” the adult worms actually reside in the pulmonary arterial system (lung arteries) for the most part, and the primary effect on the health of the animal is damage to the lung vessels and tissue. Occasionally, adult heartworms migrate to the right heart and even the great veins in heavy infections. Heartworm infection may result in serious disease for the host.

Heartworm infections may be combatted with arsenic-based compounds; the treatment is time-consuming, cumbersome and often only partly successful. Accordingly, the main focus is on the prevention of heartworm infections. Heartworm prevention is currently performed exclusively by year round periodical administration of a macrocyclic lactone such as ivermectin, moxidectin or milbemycin oxim to the dog, cat or else warm-blooded animal. Unfortunately, upcoming resistancy of *Dirofilaria immitis* against macrocyclic lactones has been observed in certain parts of the USA. Accordingly, there is a strong need for finding new classes of compounds which are effectively controlling heartworm infections either by way of prophylaxis or by direct killing of the different stages of heartworms. It now has been found surprisingly that a group of novel sulfonylaminobenzamide compounds effectively controls endoparasites including heartworms effectively on warm-blooded animals.

The present invention therefore according to one embodiment concerns a compound of formula



or a salt or an enantiomer thereof, wherein X is O, S, NR² C(O), C(CN) or CH=CH,

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R^0 is H, C₁-C₄-alkyl or hydroxyl;

n is 0 or 1,

each R is independently halogen; C₁-C₆-alkyl; C₁-C₆-haloalkyl; C₃-C₆-cycloalkyl; C₃-C₆-halocycloalkyl; amino; N-mono- or N,N-di-C₁-C₄-alkylamino; hydroxy; C₁-C₆-alkoxy;

5 C₁-C₆-haloalkoxy; C₁-C₆-alkylthio; C₁-C₆-haloalkylthio; C₁-C₆-alkyl-sulfinyl; C₁-C₆-haloalkylsulfinyl; C₁-C₆-alkylsulfonyl; C₁-C₆-haloalkylsulfonyl; SF₅; tri-C₁-C₄-alkylsilyl; C₁-C₆-alkoxycarbonyl; aminocarbonyl; N-mono- or N,N-di-C₁-C₆-alkylaminocarbonyl; aminosulfonyl; N-mono- or N,N-di-C₁-C₆-alkylaminosulfonyl; N-C₁-C₆-alkylsulfonylamino; C₁-C₆-alkoxycarbonylamino; N-C₁-C₄-alkyl-N-C₁-C₆-alkoxycarbonylamino; cyano; nitro; or C₃-C₆-heterocyclyl which is unsubstituted or substituted by halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₃-C₆-cycloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, amino, cyano or nitro;

m is an integer from 0 to 4;

each R^1 is independently halogen; C₁-C₆-alkyl; C₁-C₆-haloalkyl; C₃-C₆-cycloalkyl; C₃-C₆-halocycloalkyl; C₁-C₆-alkoxy; C₁-C₆-haloalkoxy; C₁-C₆-alkylthio; C₁-C₆-haloalkylthio; C₁-C₆-alkyl-sulfinyl; C₁-C₆-haloalkylsulfinyl; C₁-C₆-alkylsulfonyl; C₁-C₆-haloalkylsulfonyl; SF₅; amino; N-mono- or N,N-di-C₁-C₆-alkylamino; tri-C₁-C₄-alkylsilyl; C₁-C₆-alkoxycarbonyl; aminocarbonyl; N-mono- or N,N-di-C₁-C₆-alkylaminocarbonyl; N,N-di-C₁-C₄-alkylamino-C₁-C₄-alkylaminocarbonyl; aminosulfonyl; N-mono- or N,N-di-C₁-C₆-alkylaminosulfonyl; N-C₁-C₆-alkylsulfonylamino; C₁-C₆-alkoxycarbonylamino; N-C₁-C₄-alkyl-N-C₁-C₆-alkoxycarbonylamino; cyano; nitro; hydroxy; B(OH)₂; or phenyl, benzoyl, C₃-C₆-heterocyclyl, C₃-C₆-heterocycloxy or C₆-C₈-benzoheterocyclyl, which is each unsubstituted or substituted by halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₃-C₆-cycloalkyl; C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, amino, cyano or nitro; and

25 r is an integer of from 1 to 4.

The invention also provides a composition comprising a compound of formula (I), or a salt or enantiomer thereof, and at least one carrier, for example a surfactant, a solid diluent and/or a liquid diluent.

30 In one embodiment, this invention also provides a composition for controlling parasites, in particular endoparasites, comprising a biologically effective amount of a

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compound of formula (I), or a salt thereof, and at least one additional component selected from the group consisting of a surfactant, a solid diluent and a liquid diluent, said composition optionally further comprising a biologically effective amount of at least one additional pharmaceutically or veterinary active compound or agent.

5 This invention also provides a method for controlling parasites comprising contacting the parasites or their environment with a pharmaceutically or veterinary effective amount of a compound of formula (I), an enantiomer or a salt thereof, (e.g., as a composition described herein). This invention also relates to such method wherein the parasites or their environment are contacted with a composition comprising a
10 pharmaceutically or veterinary effective amount of a compound of formula (I), an enantiomer or a salt thereof, and at least one additional component selected from the group consisting of a surfactant, a solid diluent and a liquid diluent, said composition optionally further comprising a pharmaceutically or veterinary effective amount of at least one additional pharmaceutically or veterinary active compound or agent.

15 This invention also provides a method for protecting an animal from a parasitic pest comprising administering to the animal a parasitically effective amount of a compound of formula (I), an enantiomer or a salt thereof.

DETAILS OF THE INVENTION

20 In the above recitations, the term "alkyl", used either alone or in compound words such as "alkylthio", "haloalkylthio", "haloalkyl", "N-alkylamino", "N,N-di-alkylamino and the like includes straight-chain or branched alkyl, such as, methyl, ethyl, n-propyl, i-propyl, n-, iso-, sec.- or tert.-butyl or the different pentyl or hexyl isomers.

 The term "alkoxy" used either alone or in compound words such as "haloalkoxy",
25 "alkoxycarbonyl" includes, for example, methoxy, ethoxy, n-propyloxy, isopropyloxy and the different butoxy, pentoxy and hexyloxy isomers. "Alkylthio" includes branched or straight-chain alkylthio moieties such as methylthio, ethylthio, and the different propylthio, butylthio, pentylthio and hexylthio isomers.

 "Alkylsulfinyl" includes both enantiomers of an alkylsulfinyl group. Examples of
30 "alkylsulfinyl" include $\text{CH}_3\text{S(O)-}$, $\text{CH}_3\text{CH}_2\text{S(O)-}$, $\text{CH}_3\text{CH}_2\text{CH}_2\text{S(O)-}$, $(\text{CH}_3)_2\text{CHS(O)-}$ and the different butylsulfinyl, pentylsulfinyl and hexylsulfinyl isomers.

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Alkylcarbonyl" denotes a straight-chain or branched alkyl moieties bonded to a C(=O) moiety. Examples of "alkylcarbonyl" include $\text{CH}_3\text{C}(=\text{O})-$, $\text{CH}_3\text{CH}_2\text{CH}_2\text{C}(=\text{O})-$ and $(\text{CH}_3)_2\text{CHC}(=\text{O})-$. Examples of "alkoxycarbonyl" include $\text{CH}_3\text{OC}(=\text{O})-$, $\text{CH}_3\text{CH}_2\text{OC}(=\text{O})$, $\text{CH}_3\text{CH}_2\text{CH}_2\text{OC}(=\text{O})-$, $(\text{CH}_3)_2\text{CHOC}(=\text{O})-$ and the different butoxy- or
 5 pentoxycarbonyl isomers, for example tert.-butoxycarbonyl (Boc). Examples of "alkoxycarbonylamino" or N-alkoxycarbonyl,N-alkylamino include tert.-butoxycarbonylamino and N-tert.-butoxycarbonyl,N-methylamino. Examples of "N-mono- or N,N-di-alkylaminocarbonyl" include "N-methylaminocarbonyl", "N-ethylaminocarbonyl, N-methyl-N-ethylaminocarbonyl, N,N-di-methylaminocarbonyl or
 10 N,N-di-ethylaminocarbonyl. Examples of "alkylcarbonylamino" include ", "methylcarbonylamino" or "ethylcarbonylamino".

Examples of "alkylsulfonyl" include $\text{CH}_3\text{S}(\text{O})_2-$, $\text{CH}_3\text{CH}_2\text{S}(\text{O})_2-$, $\text{CH}_3\text{CH}_2\text{CH}_2\text{S}(\text{O})_2-$, $(\text{CH}_3)_2\text{CHS}(\text{O})_2-$, and the different butylsulfonyl, pentylsulfonyl and hexylsulfonyl isomers. Examples of "N-mono- or N,N-di-alkylaminosulfonyl" include
 15 "N-methylaminosulfonyl", "N-ethylaminosulfonyl, N-methyl-N-ethylaminosulfonyl, N,N-di-methylaminosulfonyl or N,N-di-ethylaminosulfonyl. Examples of "alkylsulfonylamino" include ", "methylsulfonylamino" or "ethylsulfonylamino".

"Cycloalkyl" includes, for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The term "alkylcycloalkyl" denotes alkyl substitution on a cycloalkyl moiety
 20 and includes, for example, ethylcyclopropyl, i-propylcyclobutyl, 3-methylcyclopentyl and 4-methylcyclohexyl.

The term "halogen", either alone or in compound words such as "haloalkyl", includes fluorine, chlorine, bromine or iodine. Further, when used in compound words such as "haloalkyl", said alkyl may be partially or fully substituted with halogen atoms
 25 which may be the same or different. Examples of "haloalkyl" include $\text{F}_3\text{C}-$, ClCH_2- , CF_3CH_2- and CF_3CCl_2- . The terms "halocycloalkyl", "haloalkoxy", "haloalkylthio", and the like, are defined analogously to the term "haloalkyl". Examples of "haloalkoxy" include $\text{CF}_3\text{O}-$, $\text{CF}_3\text{CF}_2\text{-O-}$, $\text{CF}_3\text{CH}_2\text{O-}$, $\text{CCl}_3\text{CH}_2\text{O-}$, $\text{CF}_3\text{CHFCH}_2\text{O-}$ and $\text{HCF}_2\text{CH}_2\text{CH}_2\text{O-}$; and Examples of "haloalkylthio" include $\text{CCl}_3\text{S-}$, $\text{CF}_3\text{S-}$, $\text{CCl}_3\text{CH}_2\text{S-}$
 30 and $\text{ClCH}_2\text{CH}_2\text{CH}_2\text{S-}$. Examples of "haloalkylsulfinyl" include $\text{CF}_3\text{S}(\text{O})-$, $\text{CCl}_3\text{S}(\text{O})-$,

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CF₃CH₂S(O)- and CF₃CF₂S(O)-. Examples of "haloalkylsulfonyl" include CF₃S(O)₂-, CCl₃S(O)₂-, CF₃CH₂S(O)₂- and CF₃CF₂S(O)₂-.

The total number of carbon atoms in a substituent group is indicated by the "C_i-C_j" prefix where i and j are integers. For example, C₁-C₄ alkylsulfonyl designates methylsulfonyl through butylsulfonyl.

When a compound is substituted with a substituent bearing a subscript that indicates the number of said substituents can exceed 1, said substituents (when they exceed 1) are independently selected from the group of defined substituents, e.g., (R₂)_n, n is 1 or 2. "Aromatic" indicates that each of the ring atoms is essentially in the same plane and has ap-orbital perpendicular to the ring plane, and in which (4n + 2) π electrons, where n is a positive integer, are associated with the ring to comply with Hückel's rule.

The terms "heterocyclyl", "heterocyclic ring" or "heterocycle" denote a ring in which at least one atom forming the ring backbone is not carbon, e.g., nitrogen, oxygen sulfur or a group S(O) or S(O₂). Typically a heterocyclic ring contains no more than 4 nitrogens, no more than 2 oxygens and no more than 2 sulfurs. In addition, the heterocyclic ring may contain a group -C(O)-, -S(O)- or -S(O₂)-. Unless otherwise indicated, a heterocyclic ring can be a saturated, partially unsaturated, or fully unsaturated ring. When a fully unsaturated heterocyclic ring satisfies Hückel's rule, then said ring is also called a "heteroaromatic ring" or "heteroaryl" substituent. Unless otherwise indicated, heterocyclic rings and ring systems can be attached through any available carbon or nitrogen by replacement of a hydrogen on said carbon or nitrogen.

The term heterocyclyl, either alone or in compound words such as heterocyclyloxy may be, for example a 5- or 6-membered heterocyclic radical having from 1 to 4, preferably from 1 to 3 same or different heteroatoms selected from the group consisting of N, O and S, which is further unsubstituted or substituted.

The term heterocyclyl may denote, for example, a 5- or 6-membered heteroaryl radical having from 1 to 4, preferably from 1 to 3 same or different heteroatoms selected from the group consisting of N, O and S, which is further unsubstituted or substituted by one or more substituents as mentioned below. The heteroaryl radical is preferably substituted by 0 to 3, in particular 0, 1 or 2 substituents from the group as defined below.

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Examples of suitable substituents of the heteroaryl are halogen, hydroxy, C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₃-C₆-cycloalkyl, C₁-C₆-haloalkyl, C₁-C₆-alkoxy, C₁-C₆-haloalkoxy, C₁-C₆-alkylthio, C₁-C₆-alkylsulfinyl, C₁-C₆-alkylsulfonyl, cyano, nitro, amino, N-mono- or N,N-di-C₁-C₆-alkylamino, C₃-C₆-cycloalkylamino, COOH, C₁-C₆-alkoxycarbonyl, C₂-C₆-alkylcarbonyl, C₁-C₆-alkylcarbonylamino, aminocarbonyl, N-mono- or N,N-di-C₁-C₆-alkylaminocarbonyl, aminosulfonyl, or N-mono- or N,N, di-C₁-C₄-alkylaminosulfonyl.

Examples of a 5- or 6-membered heteroaryl radicals include a thienyl, pyrrolyl, furyl, oxazolyl, thiazolyl, pyridyl or pyrimidinyl radical which is each unsubstituted or substituted, for example, by halogen, C₁-C₂-alkyl, C₁-C₂-haloalkyl, C₃-C₆-cycloalkyl or C₁-C₄-alkoxycarbonyl.

The term heterocyclyl may further denote a 3 to 6-membered heterocycloalkyl radical having from 1 to 3 same or different heteroatoms selected from the group consisting of N, O and S, which is further unsubstituted or substituted by one or more substituents as defined above for heterocyclyl. The heterocycloalkylene radical is preferably substituted by 0 to 3, in particular 0, 1 or 2 substituents from the group as defined above. Examples are tetrahydrofuranyl, pyrrolidinyl, morpholinyl, piperidinyl or piperazinyl which is each unsubstituted or substituted by halogen, C₁-C₂-alkyl, C₁-C₂-haloalkyl or C₁-C₂-alkoxy.

Examples of heterocyclyloxy are 2-, 3- or 4-pyridyloxy or pyrimidin-4-yloxy, which is each unsubstituted or substituted by halogen, C₁-C₂-alkyl, C₃-C₆-cycloalkyl, C₁-C₂-haloalkyl or C₁-C₂-alkoxy.

Examples of C₆-C₈-benzoheterocyclyl are benzoxazolyl, benzthiazolyl or indolyl, which may each be unsubstituted or substituted, for example, by halogen, C₁-C₂-alkyl, C₁-C₂-haloalkyl or C₁-C₂-alkoxy.

Concerning the variables contained in the compounds of formula (I), the following meanings and preferences apply.

The variable m is preferably an integer from 1 to 4, more preferably an integer 1, 2 or 3, even more preferably an integer 1 or 2 and in particular 1.

Each R is independently preferably halogen; C₁-C₄-alkyl; C₁-C₄-haloalkyl; amino; C₁-C₄-alkoxy; C₁-C₄-haloalkoxy; C₁-C₄-haloalkylthio; C₁-C₄-alkylsulfonyl; C₁-C₄-

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haloalkylsulfonyl; tri-C₁-C₂-alkylsilyl; C₁-C₄-alkoxycarbonyl; N-mono- or N,N-di-C₁-C₄-alkylaminocarbonyl; aminosulfonyl; N-mono- or N,N-di-C₁-C₄-alkylaminosulfonyl; N-C₁-C₂-alkyl-N-C₁-C₄-alkoxycarbonylamino; cyano; nitro; or 5- or 6-membered heterocycloalkyl comprising 1 or 2 same or different heteroatoms selected from O, S and N,
 5 which is unsubstituted or substituted by halogen, C₁-C₂-alkyl, C₁-C₂-haloalkyl or C₁-C₂-alkoxy.

Each R is independently more preferably halogen; C₁-C₂-alkyl; C₁-C₄-haloalkyl; amino; C₁-C₄-alkoxy; C₁-C₄-haloalkoxy; C₁-C₄-alkylsulfonyl; C₁-C₄-haloalkylsulfonyl; trimethylsilyl; C₁-C₄-alkoxycarbonyl; N,N-di-C₁-C₂-alkylaminocarbonyl; aminosulfonyl;
 10 N,N-di-C₁-C₂-alkylaminosulfonyl; N-C₁-C₂-alkyl-N-C₁-C₄-alkoxycarbonylamino; cyano; nitro; or a heterocycloalkyl radical selected from the group consisting of tetrahydrofuranyl, pyrrolidinyl, morpholinyl and piperidinyl.

Each R is independently particularly preferably halogen, C₁-C₂-alkyl, C₁-C₂-haloalkyl, C₁-C₂-alkoxy, C₁-C₂-haloalkoxy or cyano, and especially chlorine, fluorine or
 15 CF₃. Specific preferred substituents (R)_m are 2-, 3- or 4-Cl, 4-CF₃, 3,5-di-Cl, 3,5-di-CF₃, 2,4,6-tri-Cl, 3,4,5-tri-Cl, 2-Cl-4-CF₃, 2-CF₃-4-Cl, 2,6-di-Cl-4-CF₃, in particular 4-Cl.

The variable r is preferably an integer 1, 2 or 3 and more preferably 2 or 3.

Each R¹ is independently preferably halogen; C₁-C₄-alkyl; C₁-C₄-haloalkyl; C₃-C₆-cycloalkyl; C₁-C₄-alkoxy; C₁-C₄-haloalkoxy; C₁-C₄-haloalkylthio; SF₅; N,N-di-C₁-C₄-alkylamino-C₁-C₄-alkylaminocarbonyl; N-C₁-C₄-alkylsulfonylamino; cyano; nitro;
 20 hydroxy; B(OH)₂, morpholino; or phenyl, benzoyl, pyridyloxy, pyrimidinyl or benzothiazolyl, which is each unsubstituted or substituted by halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₃-C₆-cycloalkyl or C₁-C₄-alkoxy.

Each R¹ is independently more preferably halogen; C₁-C₂-alkyl; C₁-C₃-haloalkyl; C₁-C₂-alkoxy; C₁-C₃-haloalkoxy; C₁-C₂-haloalkylthio; SF₅; nitro or hydroxy.
 25

Each R¹ is independently particularly preferably halogen, methyl, C₁-C₃-haloalkyl, methoxy, C₁-C₃-haloalkoxy, SCF₃, SF₅, nitro or hydroxy and especially halogen or CF₃. Specific preferred substituents (R)_m are 3,4,5-tri-Cl, 3,5-di-CF₃-4-Cl, 3,5-di-CF₃.
 30

According to one preferred embodiment of the invention r is an integer 1, 2 or 3, and each R¹ is independently halogen; C₁-C₂-alkyl; C₁-C₃-haloalkyl; C₁-C₂-alkoxy; C₁-

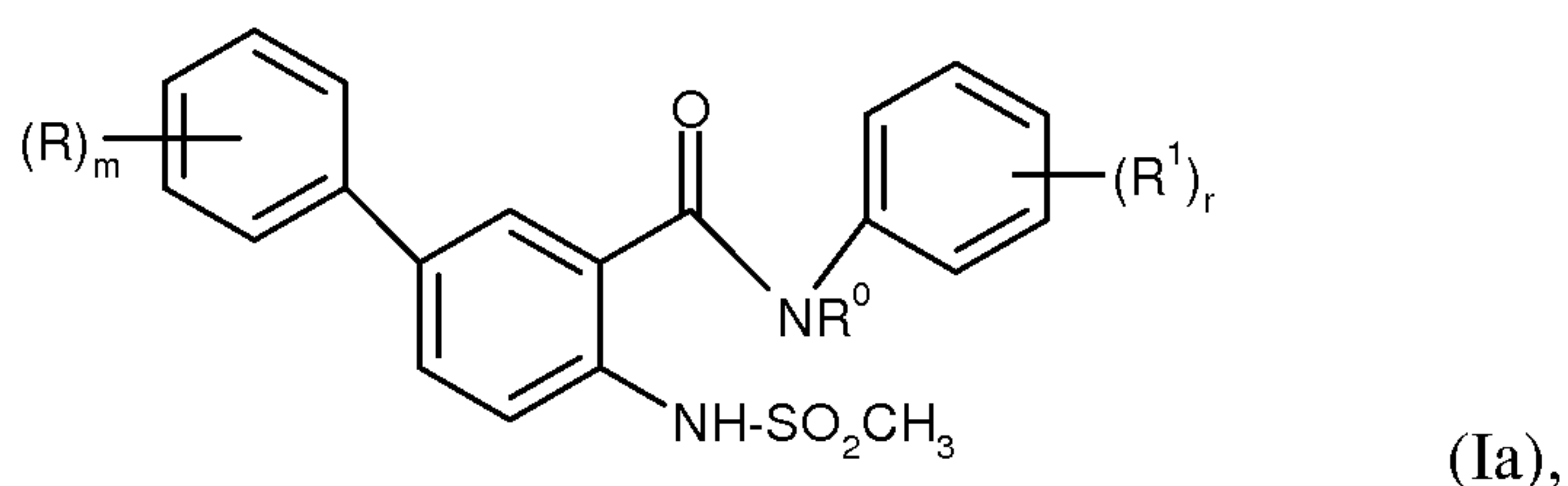
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C₃-haloalkoxy; C₁-C₂-haloalkylthio; SF₅; nitro or hydroxy. According to one particularly preferred embodiment of the invention r is an integer 2 or 3, and each R¹ is independently halogen; or C₁-C₃-haloalkyl.

The variable X preferably denotes O.

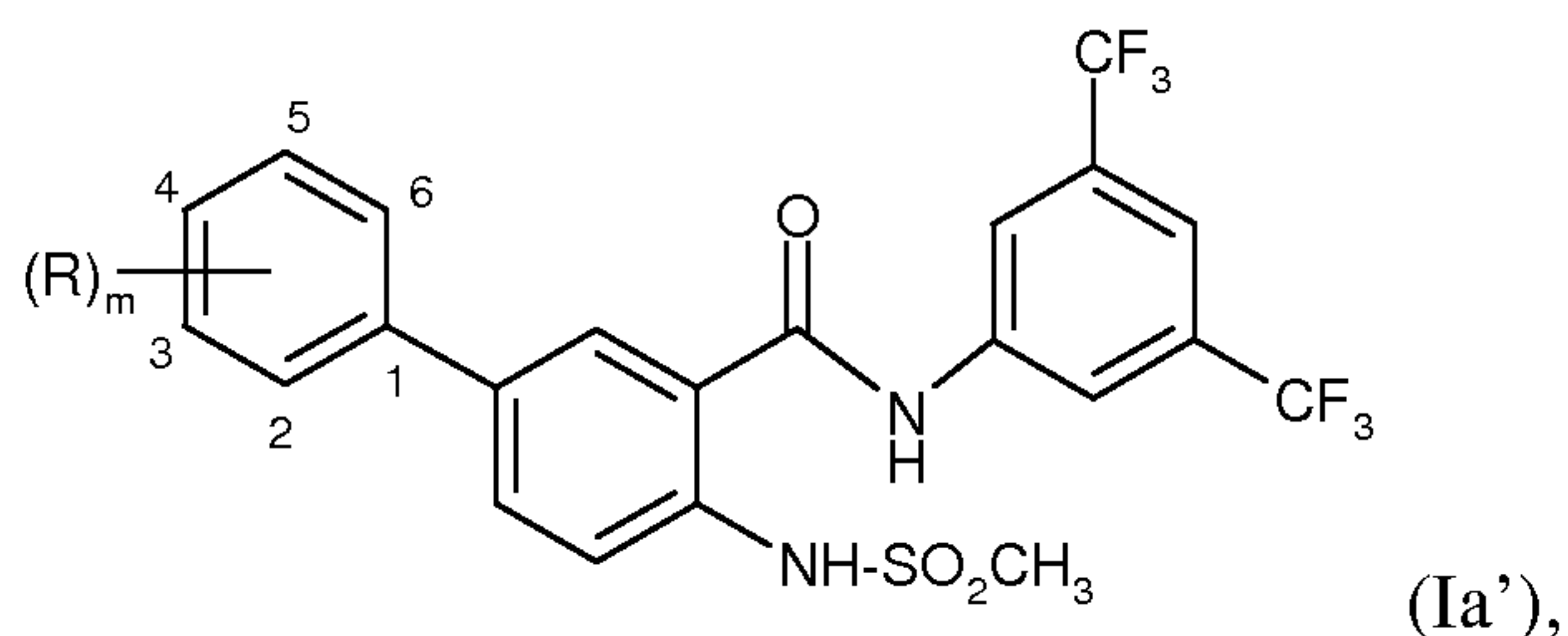
5 R⁰ is preferably H or methyl, in particular H.

One embodiment of the present invention concerns a compound of formula



wherein R, R⁰, R¹, m and r each have the above given meanings including the preferences. A preferred embodiment relates to a compound of formula (Ia), wherein R⁰ is H, m is 1, 2 or 3, especially 1 or 2, r is 2 or 3, especially 2, and for R and R¹ each the above-given meanings and preferences apply. A particular preferred embodiment relates to a compound of formula (Ia), wherein R⁰ is H, m is 1 or 2, r is 2 or 3, each R is independently halogen, C₁-C₂-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₁-C₄-alkylsulfonyl, trimethylsilyl, N,N-di-C₁-C₂-alkylaminosulfonyl, N-C₁-C₂-alkyl-N-C₁-C₄-alkoxycarbonylamino, cyano, nitro, or pyrrolidinyl, and each R¹ is independently C₁-C₄-haloalkyl. An especially preferred embodiment relates to a compound of formula (Ia), wherein R⁰ is H, m is 1 or 2, r is 2, each R is independently halogen or CF₃, and R¹ is CF₃.

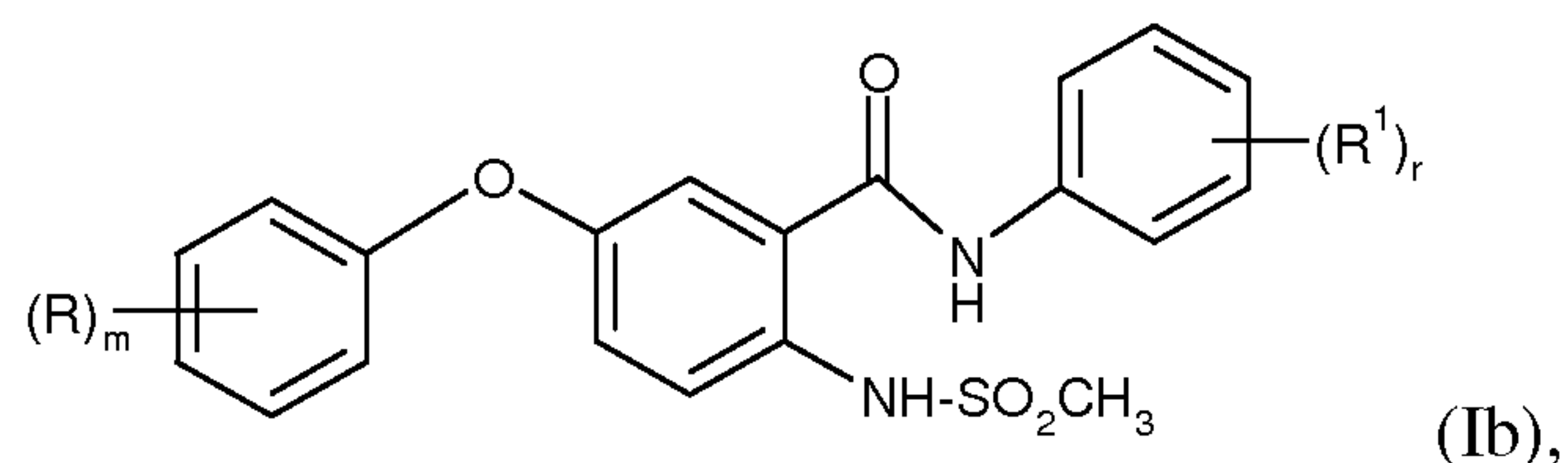
A preferred embodiment of the present invention concerns a compound of formula



wherein for R and m each the above given meanings and preferences apply.

A further embodiment of the present invention concerns a compound of formula

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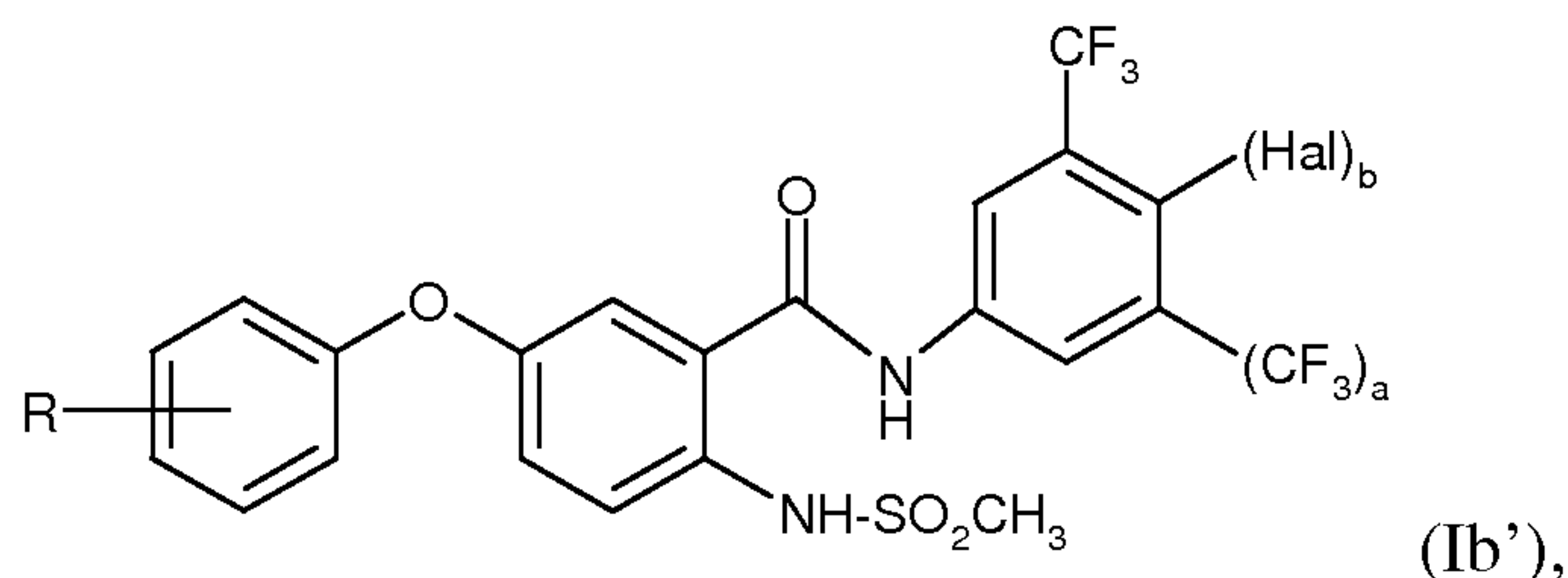
wherein for R, R¹, m and r each the above given meanings and preferences apply.

A preferred embodiment relates to a compound of formula (Ib), wherein m is 1 or 2, especially 1, r is 2 or 3, and for R and R¹ each the above-given meanings and preferences

5 apply. A particular preferred embodiment relates to a compound of formula (Ia), wherein m is 1, r is 2 or 3, each R is halogen, C₁-C₃-haloalkyl, C₁-C₂-alkoxy or cyano, and each R¹ is independently halogen, C₁-C₂-alkyl, C₁-C₃-haloalkyl, C₁-C₂-alkoxy, C₁-C₃-haloalkoxy, C₁-C₂-haloalkylthio, SF₅, nitro or hydroxy. An especially preferred embodiment relates to a compound of formula (Ib), wherein m is 1, r is 2 or 3, R is

10 halogen or CF₃, in particular chlorine, and each R¹ is halogen or CF₃.

A further preferred embodiment of the present invention concerns a compound of formula



wherein the variables a and b are each independently 0 or 1, (Hal) is halogen, and R is

15 halogen or CF₃, in particular halogen. In the above formula (Ib') one of the variables a and b is preferably 1 and the other one is 0 or 1.

A salt of a compound or formula (I) may be produced in known manner. Acid addition salts, for example, are obtainable by treatment with a suitable acid or a suitable ion exchange reagent, and salts with bases are obtainable by treatment with a suitable

20 base or a suitable ion exchange reagent.

Salts of compounds of formula (I) can be converted into the free compounds by the usual means, acid addition salts e.g. by treating with a suitable basic composition or with a suitable ion exchange reagent, and salts with bases e.g. by treating with a suitable acid or a suitable ion exchange reagent.

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Salts of compounds of formula (I) can be converted into other salts of compounds of the formula (I) in a known manner; acid addition salts can be converted for example into other acid addition salts, e.g. by treating a salt of an inorganic acid, such as a hydrochloride, with a suitable metal salt, such as a sodium, barium, or silver salt, of an acid, e.g. with silver acetate, in a suitable solvent, in which a resulting inorganic salt, e.g. silver chloride, is insoluble and thus precipitates out from the reaction mixture.

Depending on the method and/or reaction conditions, the compounds of formula (I) with salt-forming characteristics can be obtained in free form or in the form of salts. Compounds of formula (I) can also be obtained in the form of their hydrates and/or also can include other solvents, used for example where necessary for the crystallisation of compounds present in solid form.

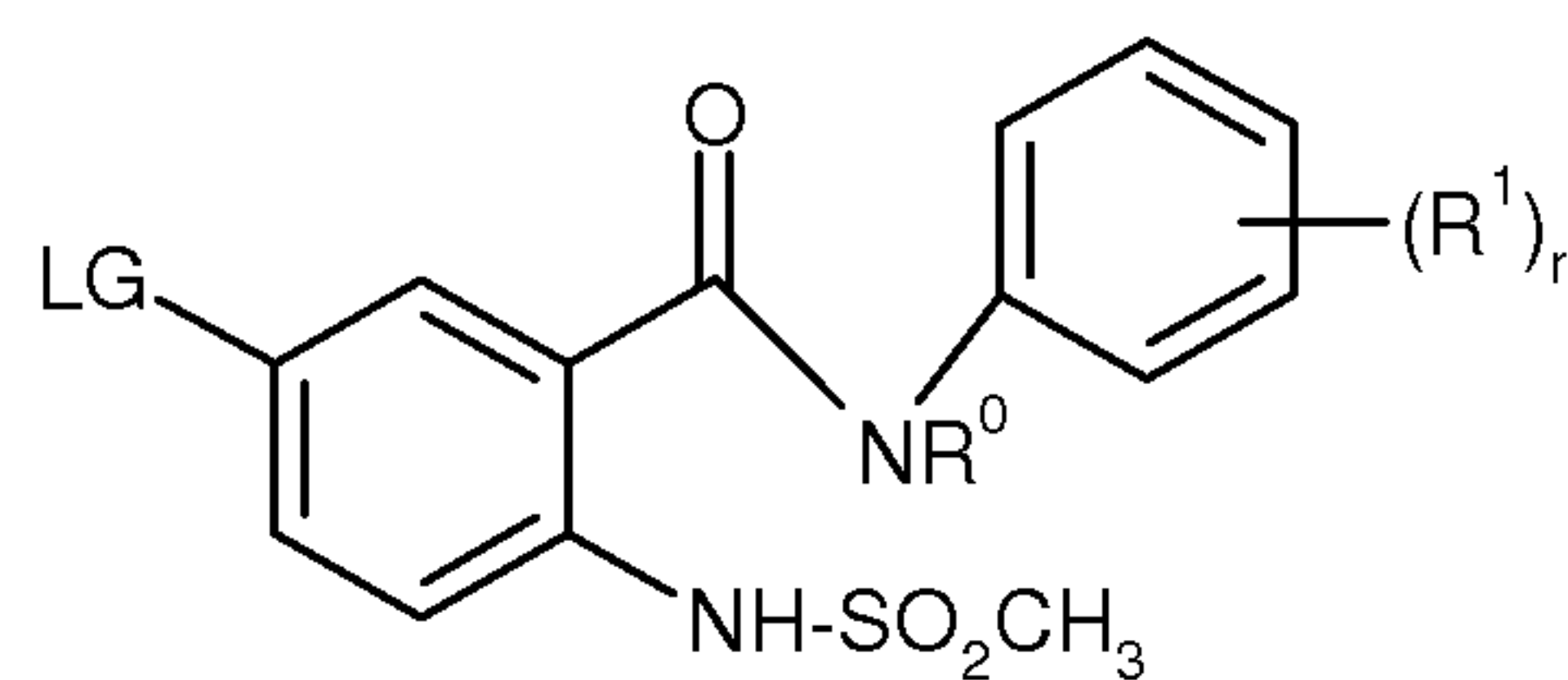
As mentioned before, the compounds of formula (I) may be optionally present as optical and/or geometric isomers or as a mixture thereof. The invention relates both to the pure isomers and to all possible isomeric mixtures, and is hereinbefore and hereinafter understood as doing so, even if stereochemical details are not specifically mentioned in every case.

Diastereoisomeric mixtures of compounds of formula (I), which are obtainable by the process or in another way, may be separated in known manner, on the basis of the physical-chemical differences in their components, into the pure diastereoisomers, for example by fractional crystallisation, distillation and/or chromatography.

Splitting of mixtures of enantiomers, that are obtainable accordingly, into the pure isomers, may be achieved by known methods, for example by recrystallisation from an optically active solvent, by chromatography on chiral adsorbents, e.g. high-pressure liquid chromatography (HPLC) on acetyl cellulose, with the assistance of appropriate micro-organisms, by cleavage with specific immobilised enzymes, through the formation of inclusion compounds, e.g. using chiral crown ethers, whereby only one enantiomer is complexed.

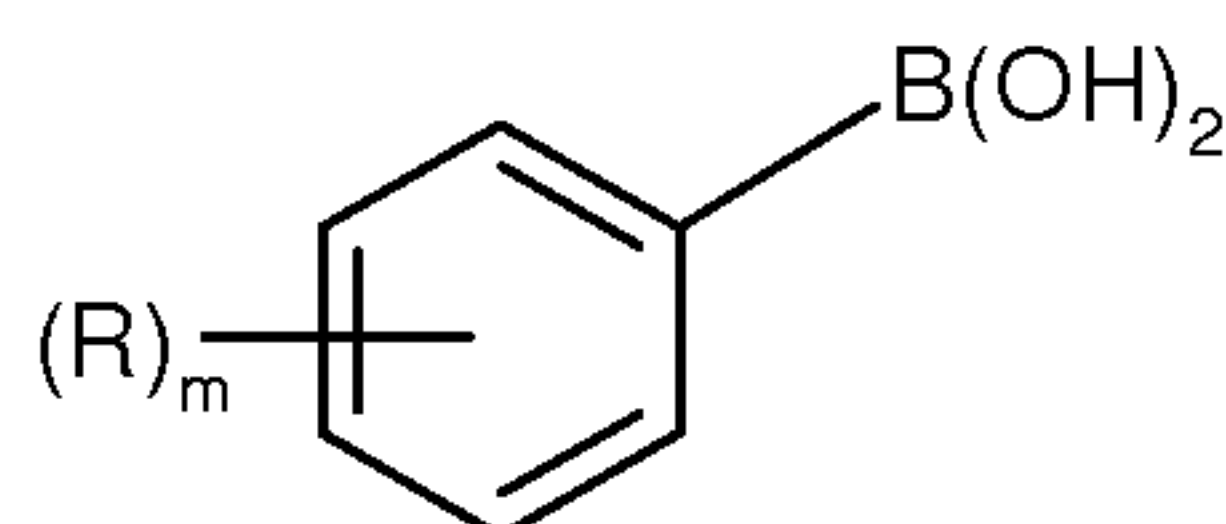
The compounds of the formula (I), wherein n is 0, may be prepared, for example, by reaction of a compound of formula

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(II)

wherein R^0 , R^1 and r are each as defined above and LG is a leaving group, for example halogen such as bromine, with a compound of formula

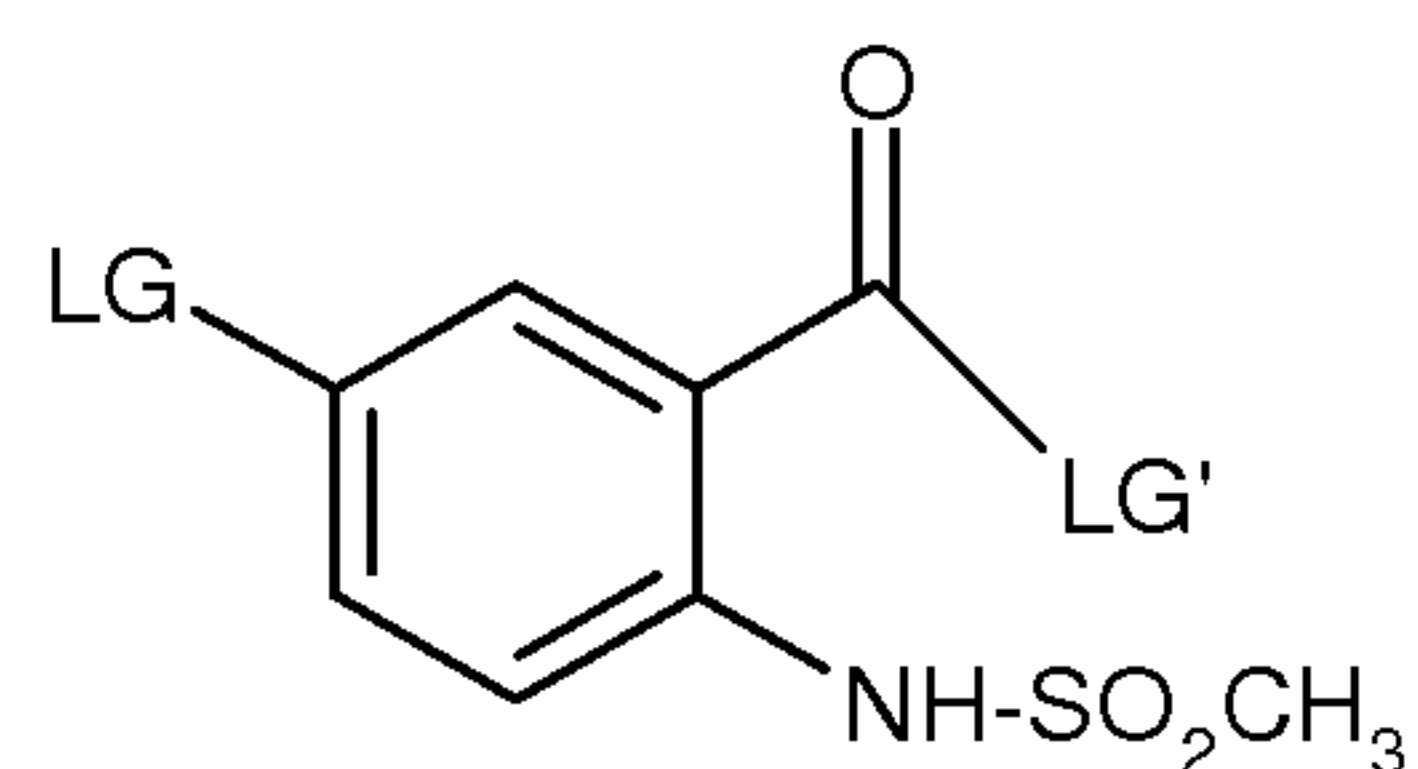


(III),

5

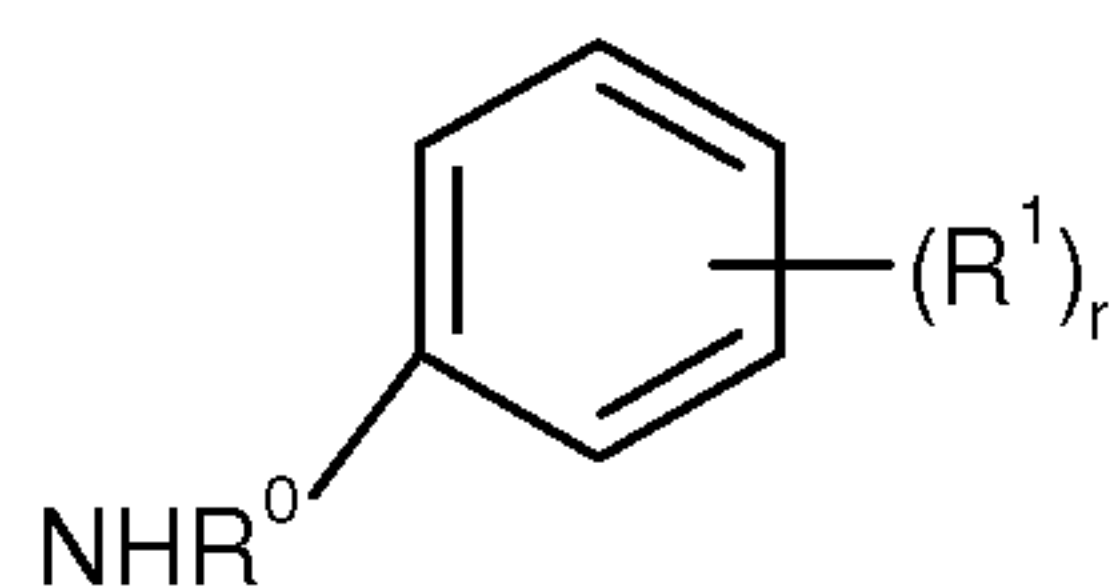
in the presence of a palladium catalyst, wherein R and m are each as defined above. The details of this palladium-catalyzed carbon-carbon bond forming reaction, called Suzuki reaction, are known from textbooks of organic chemistry.

10 The compounds of formula (II) are known or may be prepared according to known processes, for example by reacting a compound of formula



(IV)

with a compound of formula



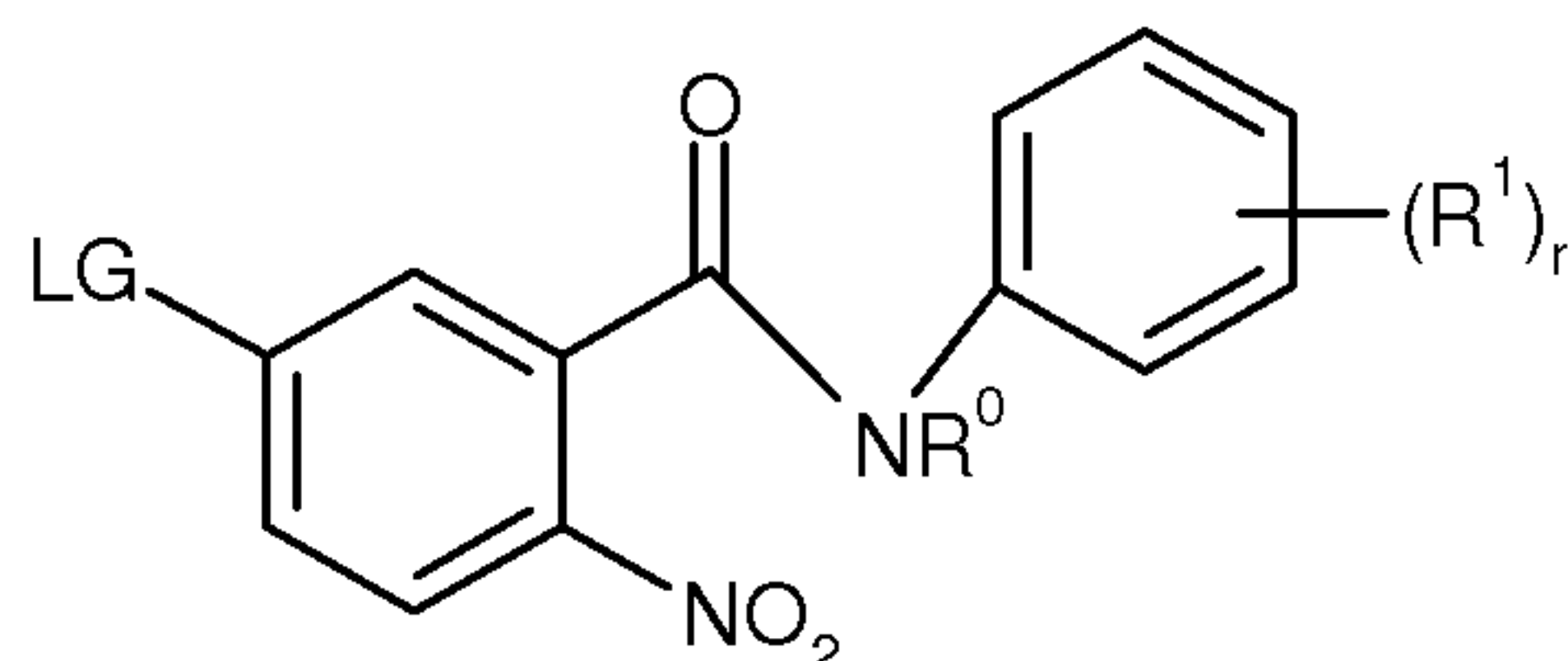
(V),

15 wherein LG' is a leaving group, for example halogen, C_1 - C_2 -alkoxy or hydroxyl, and the further variables each have the above mentioned meaning. The amide formation from an carboxylic acid or an derivative thereof with an amine is known from textbooks of organic chemistry. The compounds of formula (IV) are known or may be prepared according to known processes, for example by reacting the corresponding amine with

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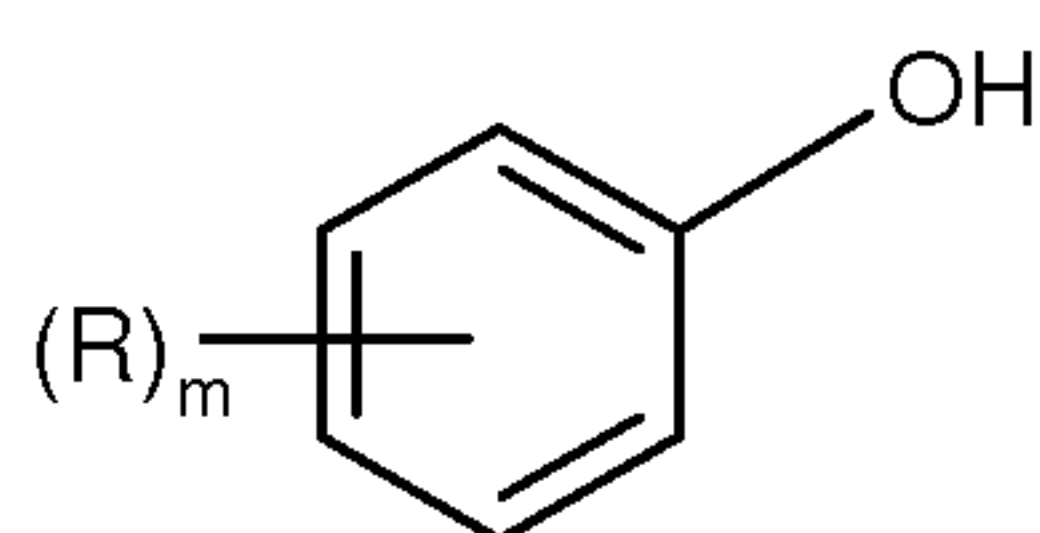
methane sulfonyl chloride in known manner. The compounds of formula (III) and (V) are known compounds which are commercially available.

The compounds of the formula (I), wherein n is 1 and X is O, may be prepared, for example, by reaction of a compound of formula



(VI)

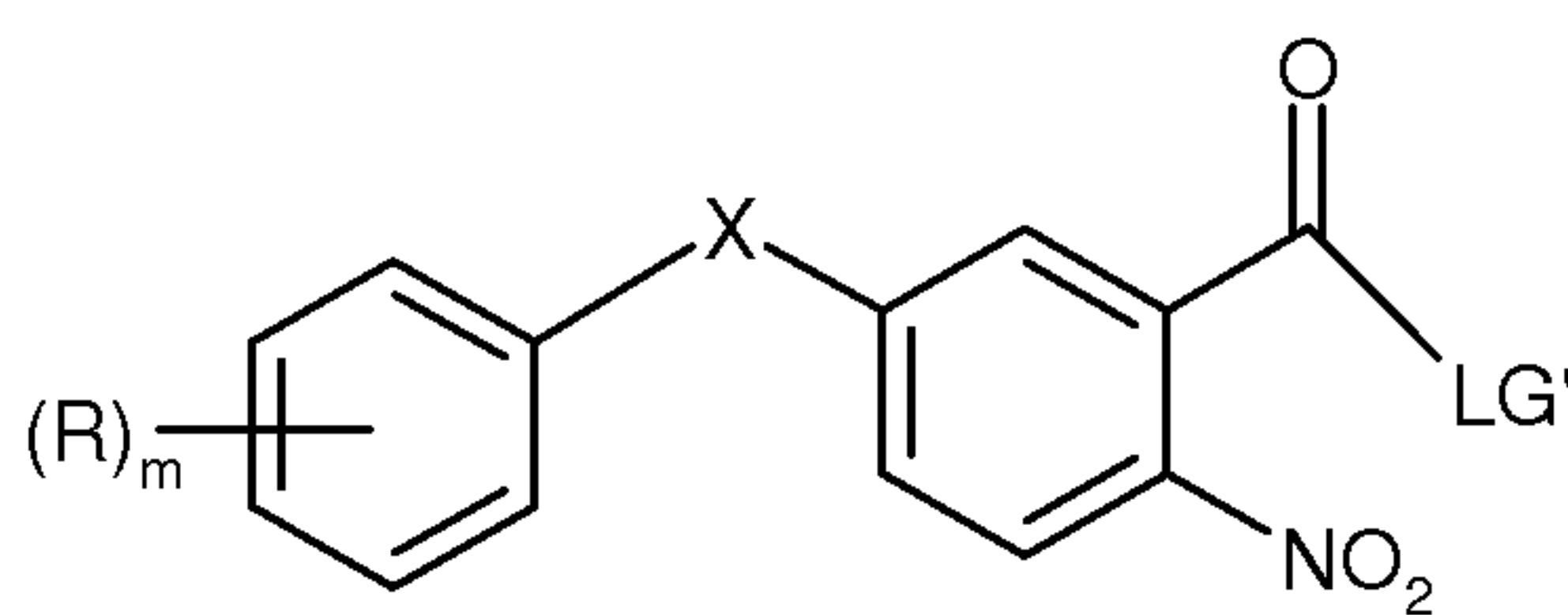
with a compound of formula



(VII),

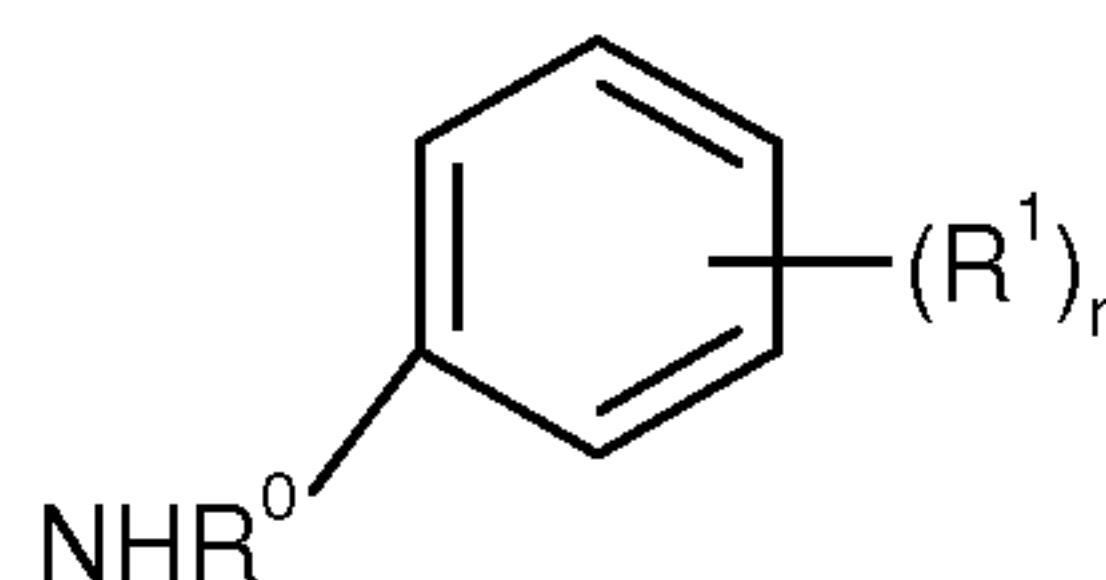
wherein the variables are as defined above, followed by the reduction of the nitro group and further reacting the resulting amine with methane sulfonyl chloride. The details of these reactions are known from textbooks of organic chemistry. The compounds of formula (VI) may be prepared in analogy to the compounds of formula (II). The compounds of formula (VII) are known per se and are commercially available.

The compounds of the formula (I), wherein n is 1 may also be prepared by reaction of a compound of formula



(VIII)

with a compound of formula



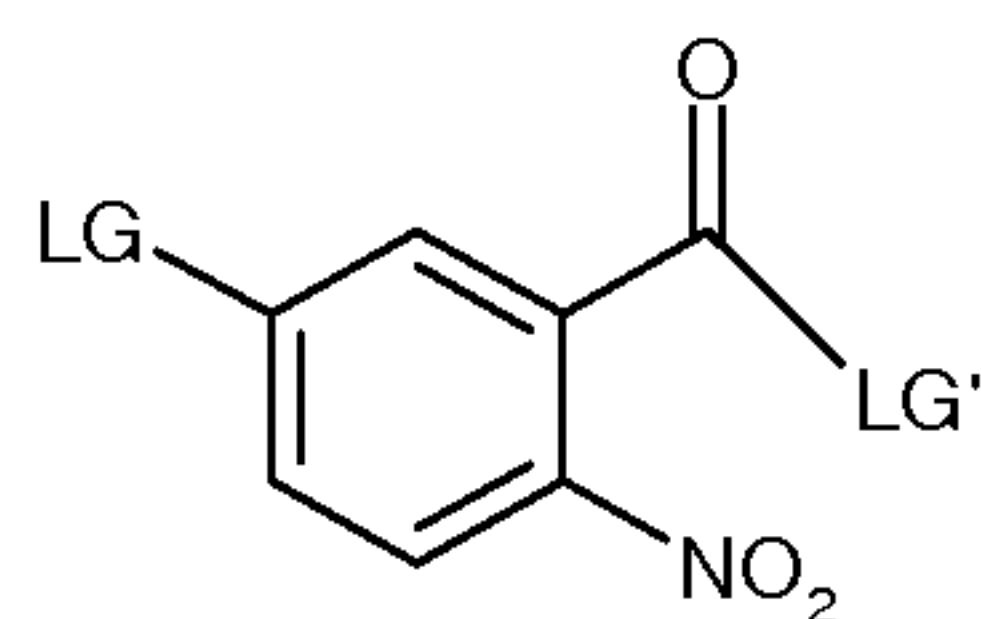
(V),

wherein the variables each have the above given meaning, followed by the reduction of the nitro group and further reacting the resulting amine with methane sulfonyl chloride. In

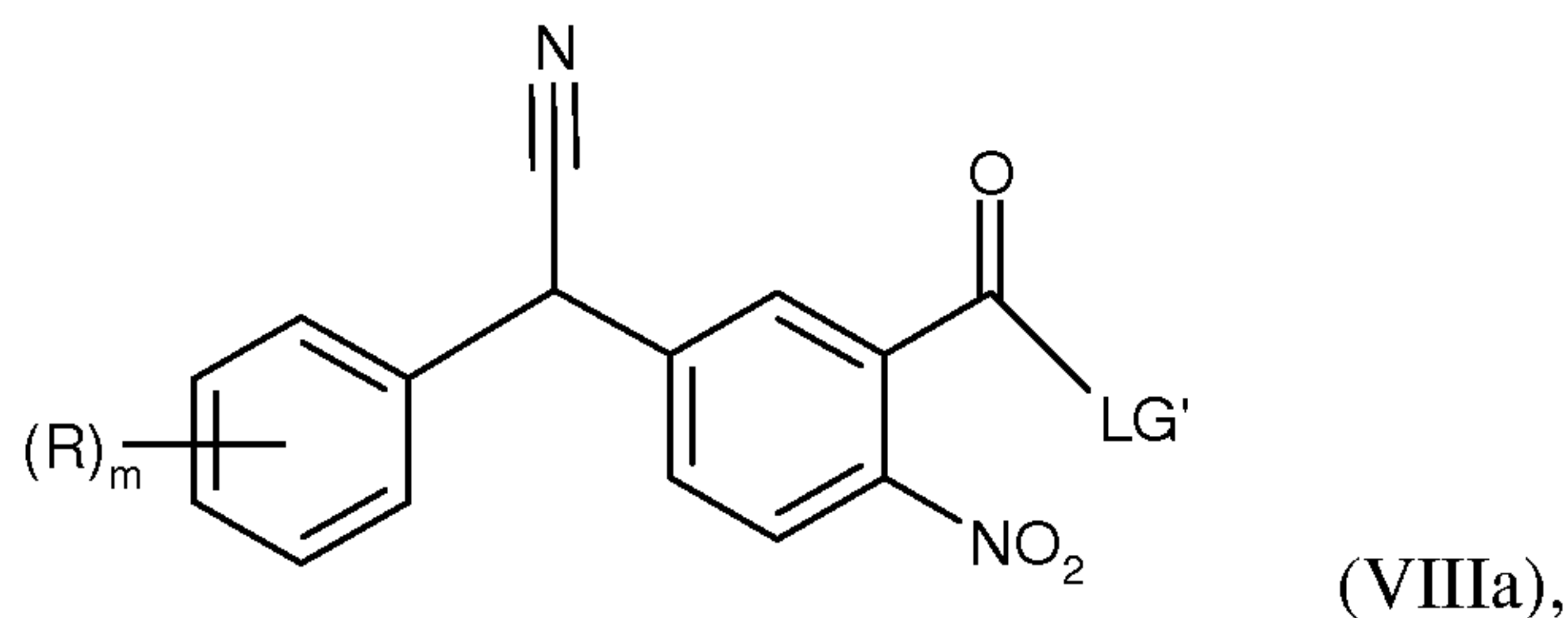
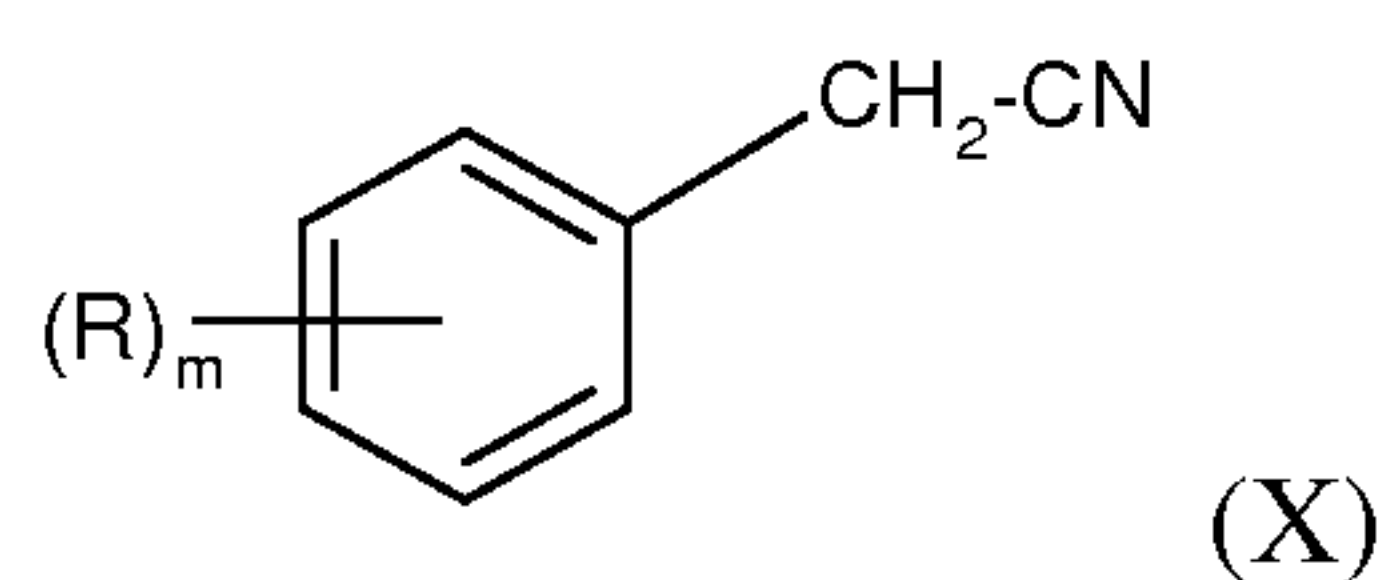
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the alternative, the nitro group of the compound of formula (VIII) may first of all be reduced and the resulting amino group be reacted with methane sulfonyl chloride, before the reaction with the compound of formula (V) is performed.

The compounds of formula (VIII) may be prepared in a manner known per se, for example by reaction of a compound of formula

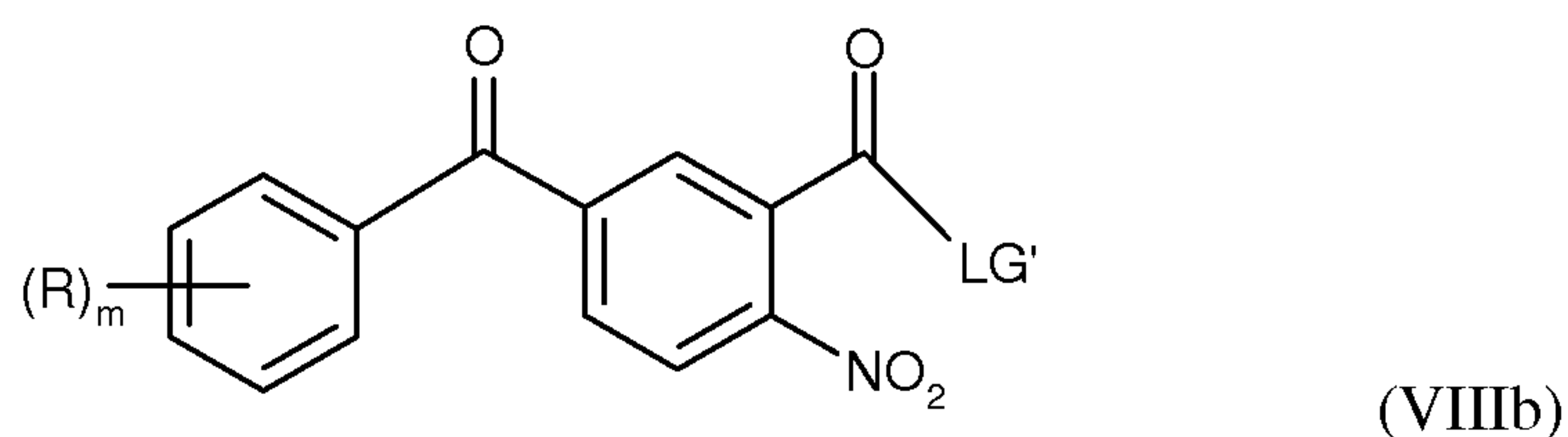


(IX) with a compound of formula



yielding a compound of formula

which may, for example, be further transformed to a compound of formula



by the action with a strong base such as lithium hydroxide in an aqueous medium.

The Examples further illustrate the different synthesis methods.

The compounds of formula (I) according to the invention are notable for their broad activity spectrum and are valuable active ingredients for use in pest control, including in particular the control of endoparasites, especially helminths, in and on warm-blooded animals, especially productive livestock and pets, whilst being well-tolerated by warm-blooded animals and fish.

Productive livestock includes mammals such as, for example, cattle, horses, sheep, pigs, goats, donkeys, rabbits, deer, as well as birds, for example chickens, geese, turkeys, ducks and exotic birds.

Pets include, for example, dogs, cats and hamsters, in particular dogs and cats.

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The compounds of formula (I) of the present invention are effective against helminths, in which the endoparasitic nematodes and trematodes may be the cause of serious diseases of mammals and poultry. Typical nematodes of this indication are: *Filariidae*, *Setariidae*, *Haemonchus*, *Trichostrongylus*, *Ostertagia*, *Nematodirus*,
 5 *Cooperia*, *Ascaris*, *Bunostomum*, *Oesophagostomum*, *Charbertia*, *Trichuris*, *Strongylus*, *Trichonema*, *Dictyocaulus*, *Capillaria*, *Heterakis*, *Toxocara*, *Ascaridia*, *Oxyuris*, *Ancylostoma*, *Uncinaria*, *Toxascaris* and *Parascaris*. The trematodes include, in particular, the family of *Fasciolidae*, especially *Fasciola hepatica*.

It could also be shown surprisingly and unexpectedly that the compositions of the
 10 present invention have exceptionally high efficacy against nematodes that are resistant to many active substances. This can be demonstrated, for example *in vitro* by the LDA test.

Certain pests of the species *Nematodirus*, *Cooperia* and *Oesophagostomum* infest the intestinal tract of the host animal, while others of the species *Haemonchus* and *Ostertagia* are parasitic in the stomach and those of the species *Dictyocaulus* are parasitic
 15 in the lung tissue. Parasites of the families and may be found in the internal cell tissue and in the organs, e.g. the heart, the blood vessels, the lymph vessels and the subcutaneous tissue. A particularly notable parasite is the heartworm of the dog, *Dirofilaria immitis*.

The compounds of formula (I) according to the present invention are highly effective against these parasites.

20 The pests which may be controlled by the compounds of formula (I) of the present invention also include those from the class of *Cestoda* (tapeworms), e.g. the families *Mesocestoidae*, especially of the genus *Mesocestoides*, in particular *M. lineatus*; *Dipylidiidae*, especially *Dipylidium caninum*, *Joyeuxiella* spp., in particular *Joyeuxiella pasquali*, and *Diplopylidium* spp., and *Taeniidae*, especially *Taenia pisiformis*, *Taenia cervi*, *Taenia ovis*, *Taenia hydatigena*, *Taenia multiceps*, *Taenia taeniaeformis*, *Taenia serialis*, and *Echinococcus* spp., most preferably *Taenia hydatigena*, *Taenia ovis*, *Taenia multiceps*, *Taenia serialis*; *Echinococcus granulosus* and *Echinococcus multilocularis*.
 25

Furthermore, the compounds of formula (I) are suitable for the control of human pathogenic parasites. Of these, typical representatives that appear in the digestive tract are
 30 those of the genus *Ancylostoma*, *Necator*, *Ascaris*, *Strongyloides*, *Trichinella*, *Capillaria*, *Trichuris* and *Enterobius*. The compounds of the present invention are also effective

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against parasites of the genus *Wuchereria*, *Brugia*, *Onchocerca* and *Loa* from the family of *Dracunculus* and parasites of the genus *Strongyloides* and *Trichinella*, which infect the gastrointestinal tract in particular.

5 The good endoparasitocidal activity of the compounds of formula (I) corresponds to a mortality rate of at least 50-60%, in particular at least 80% and especially at least 90% of the endoparasites mentioned.

Administration of the compounds of formula (I) according to the invention may be effected therapeutically or preferably prophylactically.

10 Application of the compounds of formula (I) according to the invention to the animals to be treated may take place, for example, topically, perorally, parenterally or subcutaneously. A preferred embodiment of the invention relates to compounds of formula (I) for parenteral use or, in particular, for peroral use.

Preferred application forms for usage on warm-blooded animals in the control of nematodes/ helminths comprise solutions; emulsions including classical emulsions, 15 microemulsions and self-emulsifying compositions, that are waterless organic, preferably oily, compositions which form emulsions – together with body fluids - upon addition to an animal body; suspensions (drenches); pour-on formulations; food additives; powders; tablets including effervescent tablets; boli; capsules including micro-capsules; and chewable treats; whereby the physiological compatibility of the formulation excipients 20 must be taken into consideration. Particularly preferred application forms are tablets, capsules, food additives or chewable treats.

The compounds of formula (I) of the present invention are employed in unmodified form or preferably together with adjuvants conventionally used in the art of formulation and may therefore be processed in a known manner to give, for example, 25 emulsifiable concentrates, directly dilutable solutions, dilute emulsions, soluble powders, powder mixtures, granules or microencapsulations in polymeric substances. As with the compositions, the methods of application are selected in accordance with the intended objectives and the prevailing circumstances.

30 The formulation, i.e. the agents, preparations or compositions containing the one or more active ingredients and optionally a solid or liquid adjuvant, are produced in a manner known *per se*, for example by intimately mixing and/or grinding the active

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ingredients with the adjuvants, for example with solvents, solid carriers and/or surface-active compounds (surfactants).

The solvents in question may be: alcohols, such as ethanol, propanol or butanol, and glycols and their ethers and esters, such as propylene glycol, dipropylene glycol
5 ether, ethylene glycol, ethylene glycol monomethyl or -ethyl ether, ketones, such as cyclohexanone, isophorone or diacetanol alcohol, strong polar solvents, such as N-methyl-2-pyrrolidone, dimethyl sulfoxide or dimethylformamide, or water, vegetable oils, such as rape, castor, coconut, or soybean oil, and also, if appropriate, silicone oils.

Suitable surfactants are, for example, non-ionic surfactants, such as, for example,
10 nonylphenolpolyethoxyethanols; castor oil polyglycol ethers, for example macrogol glycerolhydroxystearate 40; polyethylene glycols; polypropylene/polyethylene oxide adducts; or fatty acid esters of polyoxyethylene sorbitan, e.g. polyoxyethylene sorbitan monooleate.

Solid carriers, for example for tablets and boli, may be chemically modified
15 polymeric natural substances that are soluble in water or in alcohol, such as starch, cellulose or protein derivatives (e.g. methyl cellulose, carboxymethyl cellulose, ethylhydroxyethyl cellulose, proteins such as zein, gelatin and the like), as well as synthetic polymers, such as polyvinyl alcohol, polyvinyl pyrrolidone etc. The tablets also contain fillers (e.g. starch, microcrystalline cellulose, sugar, lactose etc.), glidants and
20 disintegrants.

If the anthelmintics are present in the form of feed concentrates, then the carriers used are e.g. performance feeds, feed grain or protein concentrates. Such feed concentrates or compositions may contain, apart from the active ingredients, also additives, vitamins, antibiotics, chemotherapeutics or other pesticides, primarily
25 bacteriostats, fungistats, coccidiostats, or even hormone preparations, substances having anabolic action or substances which promote growth, which affect the quality of meat of animals for slaughter or which are beneficial to the organism in another way.

Suitable compositions of the compounds of formula (I) may also contain further additives, such as stabilisers, antioxidants, for example tocopherols like α -tocopherol,
30 anti-foaming agents, viscosity regulators, binding agents, colors or tackifiers, as well as other active ingredients, in order to achieve special effects. Preferably, the composition

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comprises from 0.001 to 1 % w/v of one or more antioxidants. If desired, the formulations of the present invention may comprise a color, for example in an amount of from 0.001 to 1 % w/v.

As a rule, an anthelmintic composition according to the invention contains 0.1 to 99 % by weight, especially 0.1 to 95 % by weight of a compound of formula (I), 99.9 to 1 % by weight, especially 99.8 to 5 % by weight of a solid or liquid admixture, including 0 to 25 % by weight, especially 0.1 to 25 % by weight of a surfactant.

In each of the processes according to the invention for pest control or in each of the pest control compositions according to the invention, the compounds of formula (I) can be used in all of their steric configurations or in mixtures thereof.

The invention also includes a method of prophylactically protecting warm-blooded animals, especially productive livestock and pets, in particular dogs or cats, against parasitic helminths, which is characterised in that a compound of formula (I) or the active ingredient formulation prepared therefrom is administered to the warm-blooded animal as an additive to the feed, or to the drinks or also in solid or liquid form, orally or by injection or parenterally. The invention also includes the compounds of formula (I) according to the invention for usage in one of the said processes.

The compounds of formula (I) according to the invention may be used alone or in combination with other biocides. They may be combined with pesticides having the same sphere of activity e.g. to increase activity, or with substances having another sphere of activity e.g. to broaden the range of activity. It can also be sensible to add so-called repellents.

The following Examples illustrate the invention further.

Analysis of the purified samples is in each case done using a Waters Autopurification (HPLC/MS) system with a reversed phase column using method B described below. The samples are characterized by m/z and retention time. The above-given retention times relate in each case to the use of a solvent system comprising two different solvents, solvent A: H₂O + 0.01% HCOOH, and solvent B: CH₃CN + 0.01% HCOOH).

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- Method B: column Waters XTerra MS C18 5 μ m, 50X4.6mm (Waters), flow rate of 3.00 mL/min with a time-dependent gradient as given in the Table:

Time [min]	A [%]	B [%]
0	90	10
0.5	90	10
2.5	5	95
2.8	5	95
2.9	90	10
3.0	90	10

5

Example 1: Synthesis of N-(3,5-bis(trifluoromethyl)phenyl)-2'-chloro-4-(methylsulfonamido)-4'-(trifluoromethyl)-[1,1'-biphenyl]-3-carboxamide (Ex. 1.13 in Table 1)

Step A: Methyl 5-bromo-2-(methylsulfonamido) benzoate.

- 10 A N₂ degassed solution of methyl 2-amino-5-bromobenzoate (2.8 g) in 10 mL 1 pyridine was cooled to 0°C before the drop wise addition of methane sulfonyl chloride (0.9 mL). The reaction mixture was stirred overnight at rt, then diluted with 50 mL ethyl acetate. The organic layer was washed with a saturated solution of Na₂CO₃, with brine, then dried over MgSO₄ and evaporated to dryness (yield: 82%). LCMS (method B): 305.6 (M-H)⁻ at
- 15 1.55 min.

Step B: 5-Bromo-2-(methylsulfonamido)benzoic acid

- Methyl 5-bromo-2-(methylsulfonamido) benzoate (3.15 g) was suspended in THF (20 mL, 1/1). NaOH 4 N (6.9 mL) was added and the reaction mixture was stirred 4h at
- 20 reflux. Upon completion, the reaction mixture was treated with 2N HCl (1mL) and extracted twice with ethyl acetate. Combined organic layers were washed with H₂O, brine, dried over Na₂SO₄, filtered and evaporated to dryness. The title product was pure enough by LCMS to be engaged into next step without further purification. (yield: 66%) LCMS (method B): 291.64 (M-H)⁻ at 1.2 min.

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Step C: N-(3,5-bis(trifluoromethyl)phenyl)-5-bromo-2-(methylsulfonamido)benzamide.

5-Bromo-2-(methylsulfonamido) benzoic acid (2.4 g) was treated with thionyl chloride (23 mL) at reflux for 4h. Excess SOCl₂ was removed under vacuum. CH₂Cl₂ (20 mL) was added to the acyl chloride. At 0°C, 3,5-bis(trifluoromethyl)aniline (1.4 mL) and NEt₃ (5.68 mL) in 10 mL CH₂Cl₂ were added slowly. The reaction mixture was allowed to warm up and it was stirred at rt overnight. The reaction mixture was diluted with 30 mL CH₂Cl₂. 20 mL HCl 2 N and 20 mL H₂O were added, and the mixture was stirred until a yellow precipitate is formed. The precipitate was filtered off and dried under high vacuum before analysis (yield: 67%).

LCMS (method B): 502.93 (M-H)⁻ at 1.99 min.

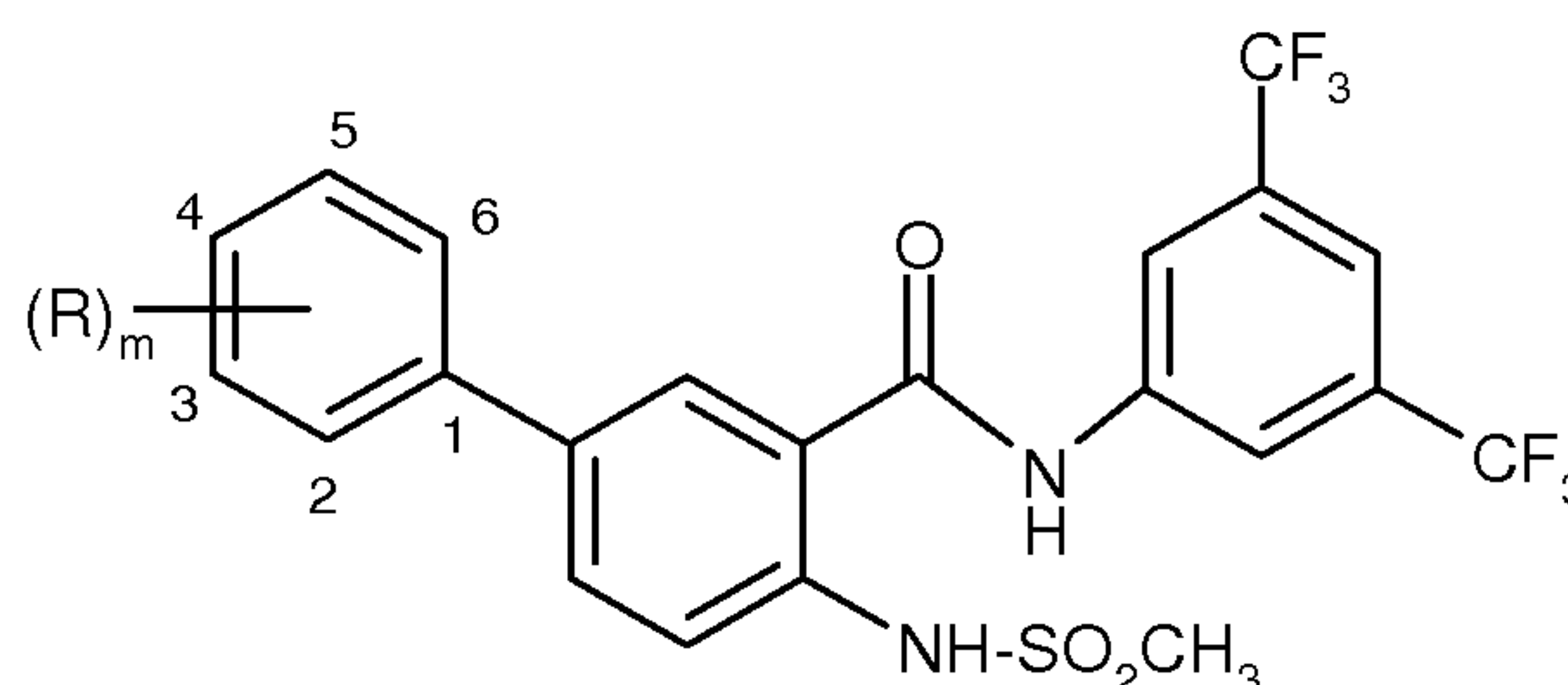
Step D: Synthesis of N-(3,5-bis(trifluoromethyl)phenyl)-2'-chloro-4-(methylsulfonamido)-4'-(trifluoromethyl)-[1,1'-biphenyl]-3-carboxamide.

To a solution of N-(3,5-bis(trifluoromethyl) phenyl)-5-bromo-2-(methylsulfonamido) benzamide (0.5 g) and 2-Chloro-4(trifluoromethyl)benzeneboronic acid (286 mg) under N₂ in dioxane/H₂O (4 mL, 1/1) was added Na₂CO₃ (636 mg) and (1,1'-bis-diphenylphosphino-ferrocene)palladium-II-dichloride (Pd(dppf)Cl₂.CH₂Cl₂, 366 mg). The reaction mixture was stirred for 1h at 85°C. It was diluted with ethyl acetate, filtered through celite. The filtrate was washed with H₂O, brine, dried over Na₂SO₄, filtered and evaporated to dryness.

The crude mixture was purified by flash chromatography eluting with a gradient of 100% heptane to 60% heptane/40% ethyl acetate to offer the title compound in 37% yield.

LCMS (method C): 604.7 (M+H)⁺ at 2.32 min.

The substances named in the following Table 1 are prepared analogously to the above-described method. The compounds are of formula



wherein the meaning of (R)_m, is given in Table 1.

The following physical data are obtained according to the above-described HPLC/MS characterization process.

5 Table 1:

Ex. No.	(R) _m	m/z: [M+H ⁺]	R _t [min] (Method)	Physical state
1.1	4-CF ₃	570.7	2.27 (B)	Powder
1.2	2,5-di-Cl	570.6	2.34 (B)	Powder
1.3	3-(pyrrolidin-1-yl)	571.8	2.40 (B)	Powder
1.4	4-N-tert-butoxycarbonyl,N-methylamino	631.7	2.32 (B)	Powder
1.5	3,5-di-Cl	570.8	2.40 (B)	Powder
1.6	2-F-3-Cl	554.7	2.25 (B)	Powder
1.7	3-NO ₂ -4-methyl	561.7	2.17 (B)	Powder
1.8	3-Si(CH ₃) ₃	574.7	2.53 (B)	Solid
1.9	3,5-di-CH ₃	530.8	2.33 (B)	Powder
1.10	2,3,4,5-tetra-F	574.8	2.20 (B)	Powder
1.11	4-CN	527.7	2.01 (B)	Powder
1.12	3-CF ₃ -4-Cl	604.7	2.34 (B)	Foam
1.13	2-Cl-4-CF ₃	604.7	2.32 (B)	Powder
1.14	3,5-di-CF ₃	638.7	2.38 (B)	Powder
1.15	4-isopropylsulfonyl	608.7	1.98 (B)	Powder
1.16	3-N,N-diethylaminocarbonyl	601.8	2.00 (B)	Powder
1.17	3-N,N-dimethylaminosulfonyl	609.9	1.97 (B)	Foam
1.18	3-trifluoromethoxy-5-amino	601.9	2.10 (B)	Powder
1.19	3,4,5-tri-Cl	604.7	2.52 (B)	Powder
1.20	4-pentafluoroethoxy	636.9	2.43 (B)	Powder
1.21	3,4,5-tri-F	556.9	2.20 (B)	Powder
1.22	2,4,6-tri-Cl	604.8	2.36 (B)	Powder
1.23	2,6-di-Cl-4-CF ₃	638.8	2.34 (B)	Powder

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1.24	3-CF ₃ -4-Br	614.8	2.30 (B)	Powder
1.25	2-Cl-4-CF ₃	682.7	2.42 (B)	Solid
1.26	2,4,6-tri-CH ₃	543.01 (M-H)-	2.36 (B)	Foam

Example 2: 5-(4-Chlorophenoxy)-2-(methylsulfonamido)-N-(3,4,5-trichlorophenyl) benzamide (Ex. 2.1 in Table 2)

- 5 Step A: 5-Chloro-2-nitro-N-(3,4,5-trichlorophenyl) benzamide. 5-chloro-2-nitrobenzoic acid (10 g) was treated with thionyl chloride (7.2 mL) at reflux for 4h. Excess SOCl₂ was removed under vacuum. CH₂Cl₂ (100 mL) was added to the acyl chloride. At 0°C, 3,4,5-trichloroaniline (9.7 g) and NEt₃ (13.8 mL) in 100 mL CH₂Cl₂ were added slowly. The reaction mixture was allowed to warm up and it was stirred at room temperature (RT) overnight.

The reaction mixture was diluted with 200 mL diethyl ether. 10 mL HCl 2 N and 200 mL H₂O were added, and the mixture was stirred until a yellow precipitate is formed. The precipitate was filtered off and dried under high vacuum before analysis (yield: 66%).

- 15 LCMS (method B): 380.59 (M+H)⁺ at 1.97 min.

Step B: 5-(4-Chlorophenoxy)-2-nitro-N-(3,4,5-trichlorophenyl) benzamide.

- 5-Chloro-2-nitro-N-(3,4,5-trichlorophenyl) benzamide (8.77 g), K₂CO₃ (6.7 g) and 4-chlorophenol (3.26 g) in DMA were heated at 140°C during 14h. The reaction mixture was poured in H₂O (100 mL), the precipitate was filtered off, dried under high vacuum to afford a brown solid (yield: 55%).

LCMS (method B): 468.45 (M-H)⁻ at 2.25 min.

Step C: 2-Amino-5-(4-chlorophenoxy)-N-(3,4,5-trichlorophenyl) benzamide.

- 25 Under N₂, 5-(4-chlorophenoxy)-2-nitro-N-(3,4,5-trichlorophenyl) benzamide (13.2 g) in 80 mL EtOH/H₂O (3/1) was treated with Fe (10.9 g) and HCl 25% (0.6 mL) and the reaction mixture was stirred at RT for 4 h. When the reduction was completed, the

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reaction mixture was filtered on a plug of celite and washed with ethyl acetate. The filtrate was evaporated under vacuum. Ethyl acetate was added, and the organic layer was washed with brine, dried over MgSO_4 , and evaporated to dryness (yield: 89%).

LCMS (method B): 442.54 ($\text{M}+\text{H}$)⁺ at 2.41 min.

5

Step D: 5-(4-Chlorophenoxy)-2-(methylsulfonamido)-N-(3,4,5-trichlorophenyl) benzamide

To N_2 degassed solution of 2-amino-5-(4-chlorophenoxy)-N-(3,4,5-trichlorophenyl) benzamide (9 g) in 50 mL of CH_2Cl_2 , pyridine (8.2 mL) was added. The mixture was cooled to 0°C before the drop wise addition of methane sulfonyl chloride (1.6 mL). The reaction mixture was stirred overnight at RT, then diluted with additional 50 mL CH_2Cl_2 . The organic layer was washed with a saturated solution of Na_2CO_3 , with brine, then dried over MgSO_4 and evaporated to dryness (yield: 81%).

LCMS (method B): 518.5 ($\text{M}+\text{H}$)⁺ at 2.27 min.

15

Example 3: 5-((4-Chlorophenyl) (cyano) methyl) -2- (methylsulfonamido) -N- (3, 4, 5-trichlorophenyl) benzamide (Ex. 2.7 in Table 2)

Step A: Methyl 5-((4-chlorophenyl) (cyano) methyl) -2- nitrobenzoate.

NaH (140 mg) was suspended in 10 mL DMF. 2-(4- chlorophenyl) acetonitrile (600 mg) in 2 mL DMF was added drop wise at 0°C to the reaction mixture, then allowed to stir at rt for 2h. The mixture was cooled to 0°C before adding drop wise methyl 5- chloro -2- nitrobenzoate (1.024 g) dissolved in 1.5 mL DMF. The reaction was stirred 2h at 0°C, then overnight at RT. Diisopropyl ether was added, and the mixture was washed with H_2O , brine, dried over Na_2SO_4 , filtered and evaporated to dryness. The crude product was purified on a semi-preparative HPLC to offer the title compound in 12% yield.

LCMS (method B): 328.84 ($\text{M}-\text{H}$)⁻ at 1.75 min.

Step B: Methyl 2-amino -5- ((4- chlorophenyl) (cyano) methyl) benzoate

Methyl 5-((4-chlorophenyl) (cyano) methyl) -2- nitrobenzoate was reduced in a similar manner as step C of Example 2 (yield: 96%).

LCMS (method B): 300.88 ($\text{M}+\text{H}$)⁺ at 1.72 min.

30

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Step C: Methyl 5-((4-Chlorophenyl) (cyano) methyl)-2-(methanesulfonamido) benzoate
Methyl 2-amino-5-((4-chlorophenyl) (cyano) methyl) benzoate was sulfonylated in a similar manner as step D of Example 2 (yield: 55%).

5 LCMS (method B): 376.76 (M-H)⁻ at 1.71 min.

Step D: 5-((4-Chlorophenyl) (cyano) methyl)-2-(methanesulfonamido) benzoic acid

Methyl 5-((4-chlorophenyl)(cyano)methyl)-2-(methanesulfonamido)benzoate (50 mg) was suspended in MeOH/ H₂O (1 mL, 1/1). NaOH (6 mg) was added and the reaction mixture
10 was stirred overnight at RT. Upon completion, the reaction mixture was treated with 2N HCl (1mL) and extracted twice with Ethyl acetate. Combined organic layers were washed with H₂O, brine, dried over Na₂SO₄, filtered and evaporated to dryness. The title product was pure enough by LCMS to be engaged into next step without further purification.
LCMS (method B): 362.71 (M-H)⁻ at 1.52 min.

15

Step E: 5-((4-Chlorophenyl)(cyano)methyl)-2-(methanesulfonamido)-N-(3,4,5-trichlorophenyl) benzamide

5- ((4-chlorophenyl) (cyano) methyl)-2-(methanesulfonamido) benzoic acid (48 mg) was dissolved in CH₂Cl₂ (1.5 mL). 3,4,5 trichloroaniline (31 mg), benzotriazol-1-yl-oxytri-
20 pyrrolidinophosphonium hexafluorophosphate (Pybop, 75 mg), and diisopropylethylamine (DIPEA, 69 μL) were added. The reaction mixture was stirred at RT overnight. H₂O was added and the mixture was extracted with CH₂Cl₂. Combined organic layers were washed with saturated solution of Na₂CO₃, brine, filtered and evaporated to dryness. The crude product was purified on a semi-preparative HPLC to
25 offer the title compound in 46% yield.
LCMS (method B): 539.58 (M-H)⁻ at 2.15 min.

Example 4: 5-(4-Chlorobenzoyl)-2-(methanesulfonamido)-N-(3,4,5-trichlorophenyl)benzamide (Ex. 2.6 in Table 2)

30 Step A: 5-(4-Chlorobenzoyl)-2-nitrobenzoic acid.

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Methyl 5-((4-chlorophenyl)(cyano)methyl)-2-nitrobenzoate (150 mg, see Step A Example 3) was treated with LiOH (6 eq.) in THF/H₂O (4/1, 5 mL) at rt overnight. Additional 6 eq. of LiOH were added. The reaction was completed after 72h. HCl 2N was added until reaching pH 1-2, and then the reaction mixture was extracted twice with ethyl acetate. Combined organic layers were washed with H₂O, brine, dried over Na₂SO₄, filtered and evaporated to dryness. The title compound was pure enough for use in step B. LCMS (method B): 303.85 (M-H)⁻ at 1.54 min.

Step B: 5-(4-Chlorobenzoyl)-2-nitro-N-(3,4,5-trichlorophenyl)benzamide.

5-(4-Chlorobenzoyl)-2-nitrobenzoic acid was treated in a similar manner as described Example 3, step E (yield: 71%).
LCMS (method B): 480.57 (M-H)⁻ at 2.20 min.

Step C: 2-Amino-5-(4-chlorobenzoyl)-N-(3,4,5-trichlorophenyl)benzamide.

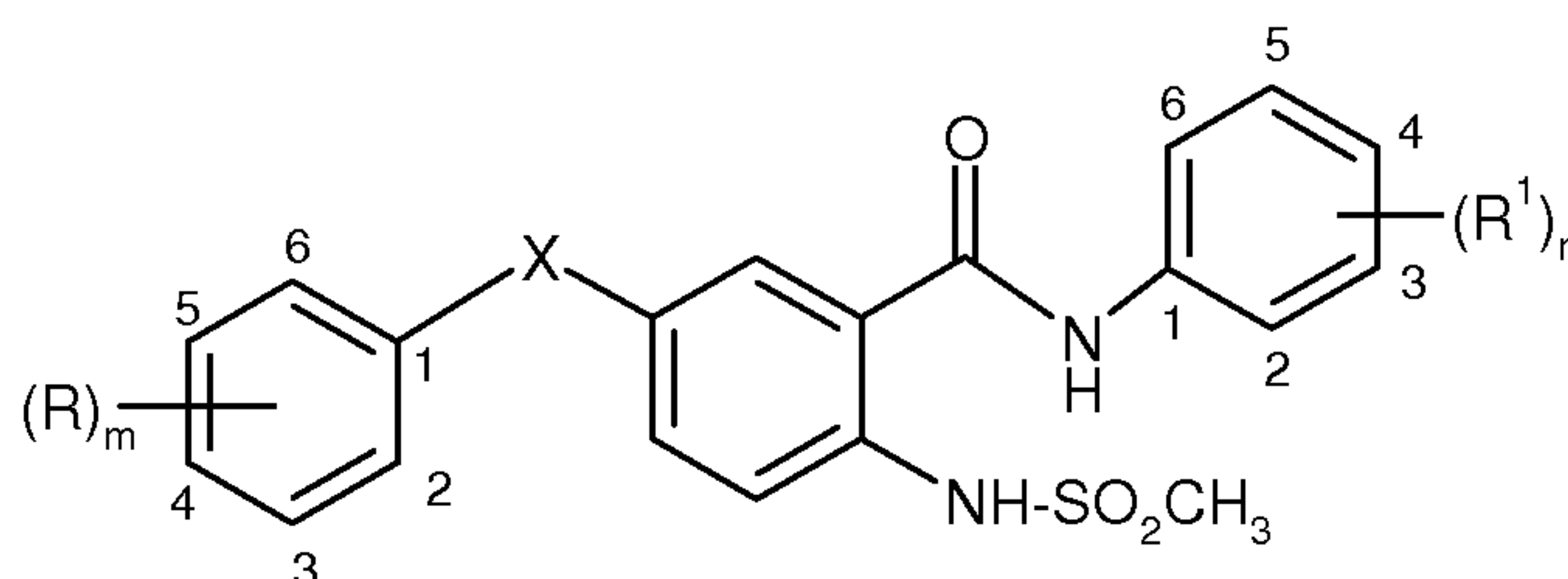
5-(4-Chlorobenzoyl)-2-nitro-N-(3,4,5-trichlorophenyl)benzamide was treated in a similar manner as described in Example 3, step B (yield: 93%).
LCMS (method B): 450.61 (M-H)⁻ at 2.31 min.

Step D: 5-(4-Chlorobenzoyl)-2-(methylsulfonamido)-N-(3,4,5-

trichlorophenyl)benzamide.

2-Amino-5-(4-chlorobenzoyl)-N-(3,4,5-trichlorophenyl)benzamide was treated in a similar manner as described in Example 2, step D (yield: 18%).
LCMS (method B): 530.5 (M+H)⁺ at 2.23 min.

The substances named in the following Table 2 are prepared analogously to the above-described methods. The compounds are of formula



wherein the meaning of $(R^1)_r$, $(R)_m$, and X are given in Table 2

The following physical data are obtained according to the above-described HPLC/MS characterization process.

5 Table 2:

Ex. No.	$(R)_m$	$(R^1)_r$	X	m/z: $[M+H]^+$	R_t [min] (Method)	R_t [min] (Method)
2.1	4-Cl	3,4,5-tri-Cl	O	518.5	2.27 (B)	Solid
2.2	H	3,4,5-tri-Cl	O	484.6	2.16 (B)	Powder
2.3	4-Cl	3,4,5-tri-Cl	NH	517.5	2.13 (B)	Powder
2.4	4-Cl	3,4,5-tri-Cl	S	534.5	2.38 (B)	Solid
2.5	H	3,4,5-tri-Cl	NH	483.7	1.98 (B)	Solid
2.6	4-Cl	3,4,5-tri-Cl	C(O)	530.6	2.23 (B)	Solid
2.7	4-Cl	3,4,5-tri-Cl	C(CN)	541.5	2.15 (B)	Foam
2.8	4-Br	3,5-di- CF_3	O	596.9	2.23 (B)	Foam
2.9	4-CN	3,5-di- CF_3	O	543.9	1.98 (B)	Gum
2.10	3,5-di- CF_3	3,5-di- CF_3	O	654.9	2.31 (B)	Solid
2.11	2-Cl	3,5-di- CF_3	O	552.9	2.19 (B)	Gum
2.12	3-Cl	3,5-di- CF_3	O	552.9	2.14 (B)	Solid
2.13	4- CF_3	3,5-di- CF_3	O	586.9	2.22 (B)	Oil
2.14	3-OCH ₃	3,5-di- CF_3	CH=C H	558,8	2.21(B)	Solid
2.15	4-Cl	3,4-di-Cl	O	484 $[M-H]^-$	2.11 (B)	Solid
2.16	4-Cl	4-OCF ₃	O	500.7	2.03 (B)	Powder
2.17	4-Cl	3- CF_3 -4-OCH ₃	O	514.6	1.94 (B)	Powder
2.18	4-Cl	4-SF ₅	O	542.5	2.04 (B)	Solid
2.19	4-Cl	3,4,5-tri-F	O	470.6	1.96 (B)	Solid
2.20	4-Cl	3-B(OH) ₂	O	460.7	2.01 (B)	Oil
2.21	4-Cl	3- CF_3 -4-Br	O	562.5	2.10 (B)	Oil

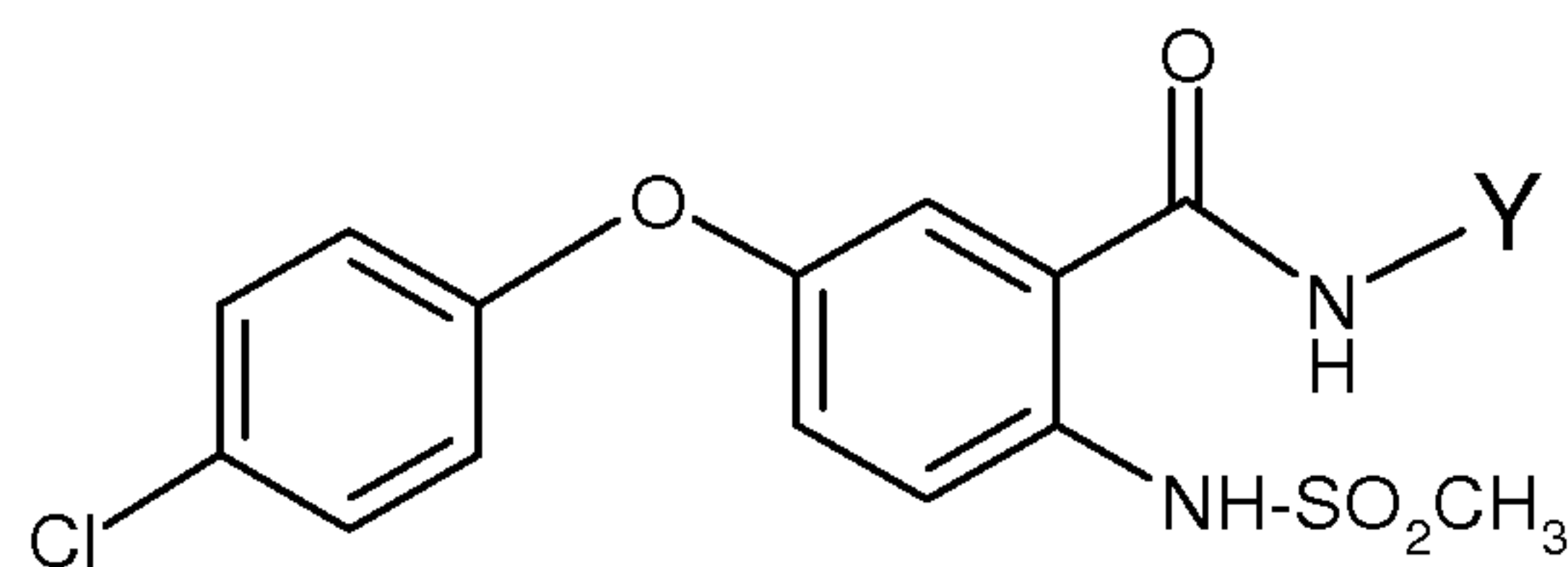
-26-

2.22	4-Cl	4-CF(CF ₃) ₂ -2,6-di-CH ₃	O	612.7	2.18 (B)	Oil
2.23	4-Cl	2,3,4-tri-Cl	O	518.6	2.12 (B)	Oil
2.24	4-Cl	4-cyclohexyl	O	498.8	2.35 (B)	Oil
2.25	4-Cl	4-OCF ₂ CHF(CF ₃)-2,5-di-Cl	O	650.6	2.19 (B)	Solid
2.26	4-Cl	3,5-di-CF ₃	O	552.6	2.14 (B)	Solid
2.27	4-Cl	3-CF ₃ -4-Cl	O	518.6	2.09 (B)	Solid
2.28	4-Cl	4-NO ₂ -2-Cl	O	495.6	1.93 (B)	Oil
2.29	4-Cl	4-SCF ₃	O	516.7	2.17 (B)	Oil
2.30	4-Cl	2,4,5-tri-F	O	470.7	1.93 (B)	Oil
2.31	4-Cl	3,5-di-F-4-Cl	O	486.7	2.10 (B)	Oil
2.32	4-Cl	2-(N-morpholino)	O	501.8	1.97 (B)	Oil
2.33	4-Cl	2,3,4-tri-F	O	470.8	1.96 (B)	Oil
2.34	4-Cl	3,4-di-F	O	452.8	2.00 (B)	Oil
2.35	4-Cl	3,5-di-F	O	452.8	2.02(B)	Foam
2.36	4-Cl	2,3,5-tri-F	O	470.8	1.99 (B)	Foam
2.37	4-Cl	3,5-di-Cl-4-F	O	502.7	2.21 (B)	Oil
2.38	4-Cl	3,5-di-Cl	O	484.7	2.23 (B)	Oil
2.39	4-Cl	4-NO ₂	O	461.8	2.42 (B)	Powder
2.40	4-Cl	3-Cl-4-Br	O	528.7	2.15 (B)	Solid
2.41	4-Cl	2-(N,N-diethylamino)-ethyl-aminocarbonyl	O	559.0	1.21 (B)	Oil
2.42	4-Cl	3-Cl-4-J	O	576.6	2.17 (B)	Oil
2.43	4-Cl	2-F-4-Br	O	512.7	2.00 (B)	Crystal
2.44	4-Cl	3,4-di-Br	O	572.6	2.14 (B)	Solid
2.45	4-Cl	3,5-di-Cl-4-Br	O	562.6	2.19 (B)	Oil
2.46	4-Cl	3,5-di-Cl-4-CH ₃	O	498.8	2.30 (B)	Oil
2.47	4-Cl	3,5-di-Cl-4-OH	O	500.6	1.83 (B)	Oil
2.48	4-Cl	3,5-di-CF ₃ -4-Br	O	630.5	2.30 (B)	Solid
2.49	4-Cl	3,5-di-Cl-4-OCH ₃	O	514.6	2.12 (B)	Foam

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2.50	4-Cl	4-CF(CF ₃) ₂	O	584.8	2.23 (B)	Foam
2.51	4-Cl	3-CF ₃	O	484.9	2.03 (B)	Foam
2.52	4-Cl	3-OCF ₃	O	500.8	2.06 (B)	Foam
2.53	4-Cl	3-CHF ₂	O	466.8	1.90 (B)	Foam
2.54	4-Cl	3-SF ₅	O	542.9	1.97 (B)	Powder
2.55	4-Cl	4-CF ₃	O	484.8	2.04 (B)	Powder
2.56	4-Cl	3,5-di-CF ₃ -4-Cl	O	586.8	2.28 (B)	Powder
2.57	4-Cl	3,5-di-Cl-2-OH	O	500.6	1.94 (B)	Oil
2.58	4-Cl	2-CH ₃ SO ₂ NH-4,5-di-Cl	O	577.7	1.89(B)	Powder

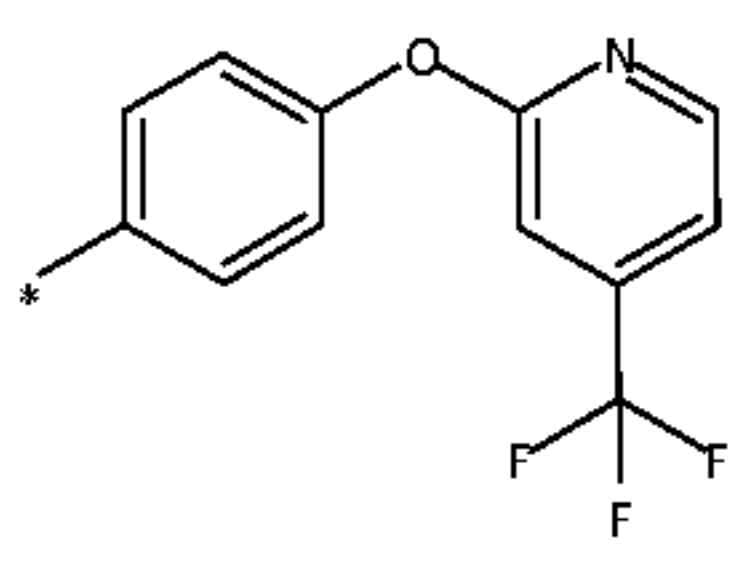
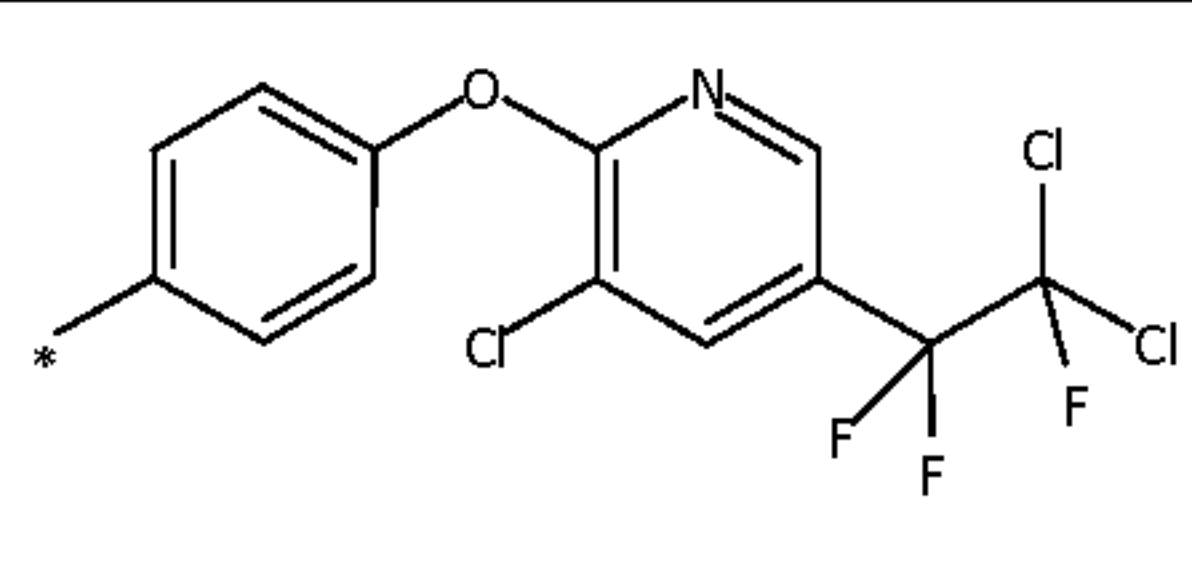
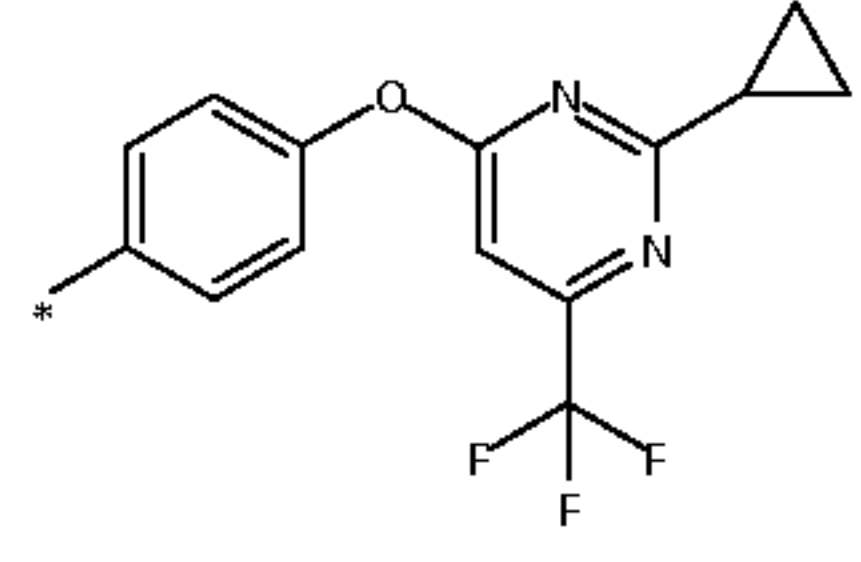
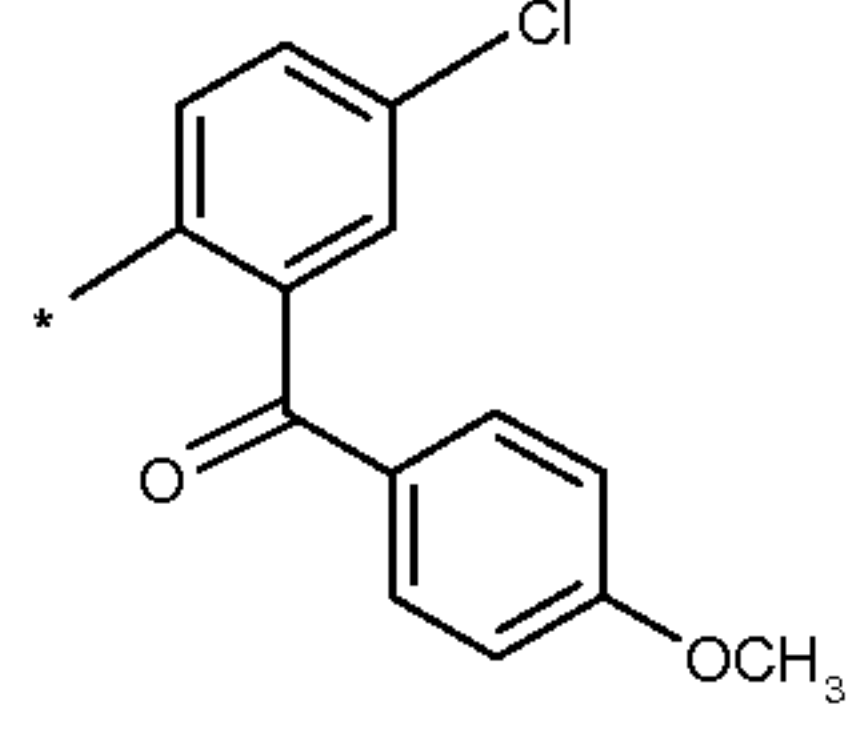
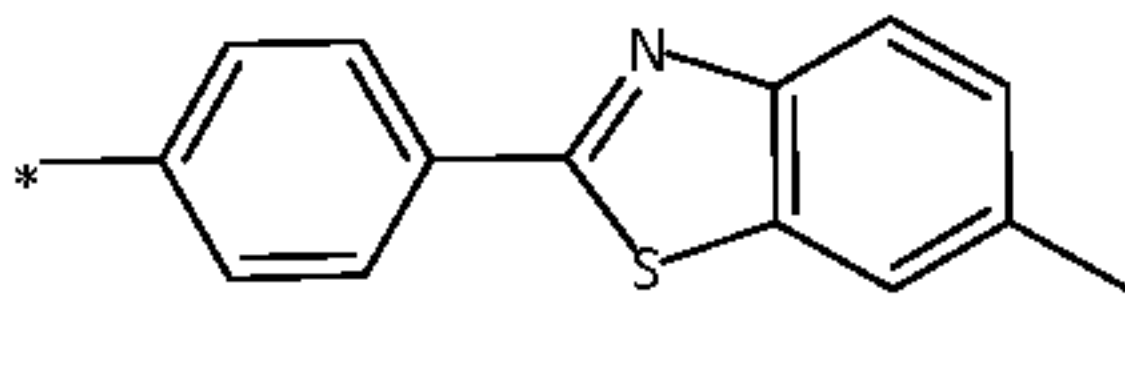
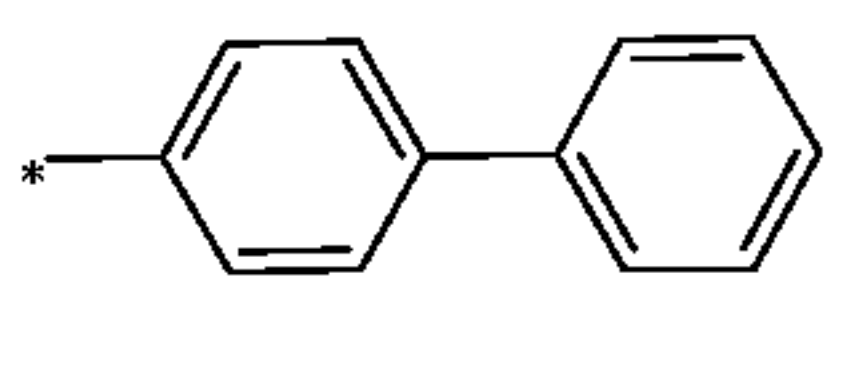
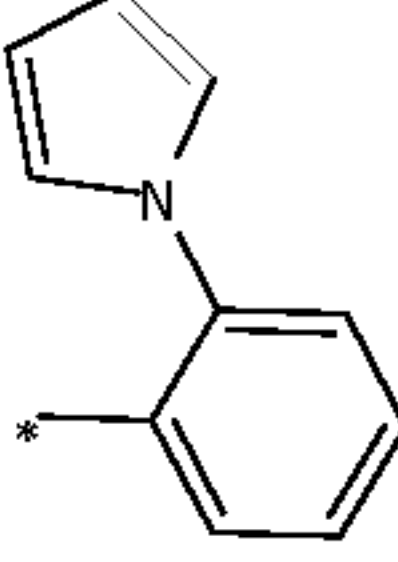
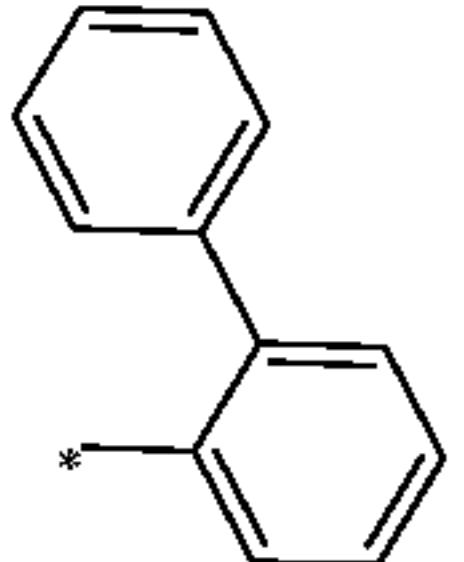
The substances named in the following Table 3 are prepared analogously to the above-described methods. The compounds are of formula

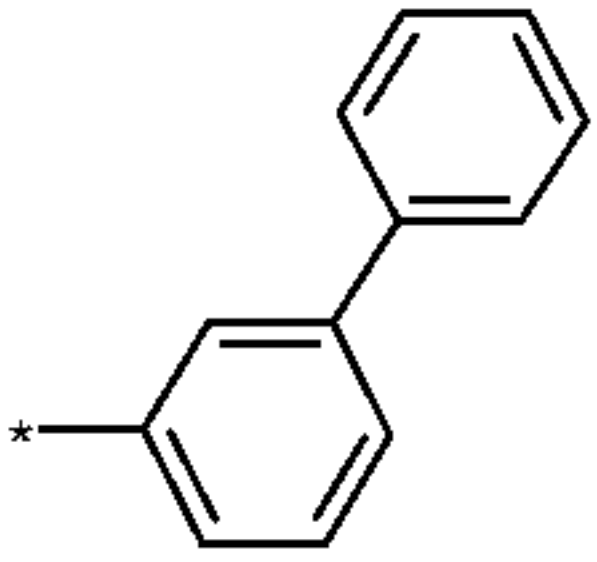
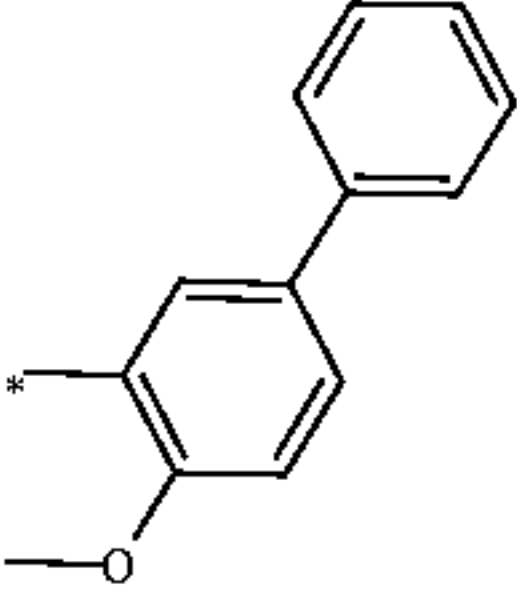


- 5 wherein the meaning Y is given in Table 3. The following physical data are obtained according to the above-described HPLC/MS characterization process.

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Table 3:

Ex. No.	Y	m/z: [M+H ⁺]	R _t [min] (Method)	R _t [min] (Method)
3.1		577.7	2.09 (B)	Powder
3.2		711.6	2.34 (B)	Powder
3.3		618.8	2.22 (B)	Powder
3.4		584.7	2.19 (B)	Solid
3.5		563.8	2.38 (B)	Solid
3.6		492.9	2.18 (B)	Solid
3.7		481.8	1.91 (B)	Solid
3.8		492.8	1.98 (B)	Solid

3.9		492.8	2.10 (B)	Solid
3.10		522.8	2.14 (B)	Solid

Biological Examples:

5 **Gastro-intestinal Larval Development Assay**

Freshly harvested and cleaned nematode eggs are used to seed a suitably formatted well plate containing the test substances to be evaluated for antiparasitic activity and media allowing the full development of eggs through to 3rd instar larvae. The plates are incubated for 6 days at 25°C and 60% relative humidity. Egg-hatching and ensuing larval development are recorded to identify a possible nematocidal activity. Efficacy is expressed in percent reduced egg hatch, reduced development of L3, or paralysis & death of larvae at any stage. Compounds Nos. 1.9-1.13, 1.21-1.23, 1.25, 1.26, 2.13, 2.50, 2.51 and 2.54 reached $\geq 60\%$ efficacy at 10ppm, and are therefore considered active.

15

Dirofilaria immitis microfilaria assay

Freshly harvested and cleaned *Dirofilaria immitis* microfilariae are prepared from blood from donor animals dogs. The microfilariae are then distributed in formatted microplates containing the test substances to be evaluated for antiparasitic activity. The plates are incubated for 48 hours at 25°C and 60% relative humidity (RH). Motility of microfilariae is then recorded to determine efficacy. Efficacy is expressed in percent reduced motility as compared to the control and standards. Compounds Nos. 1.1-1.25, 2.1-2.58, and 3.1-3.10 showed an efficacy above 50% at 10 ppm, and are therefore considered active.

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Acanthocheilonema viteae in Gerbil

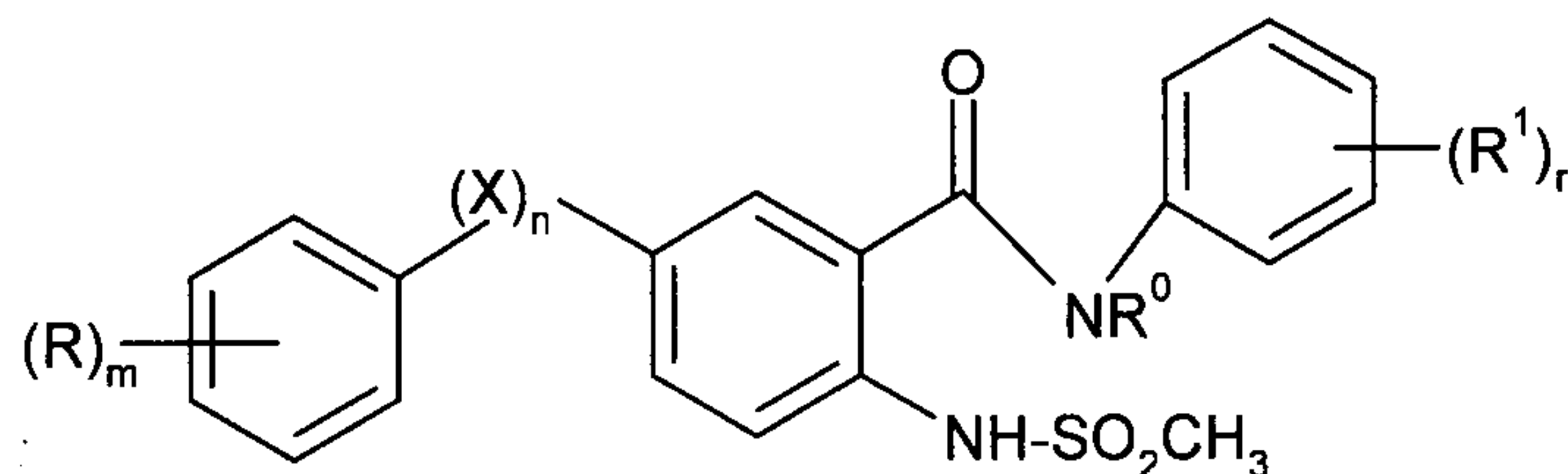
Gerbils are artificially infected with 80 L3 larvae of *A. viteae* by subcutaneous injection. Treatment by gavage with the formulated test compounds occurs consecutively day 5 to day 9 after infection. Eighty-four days after infection, gerbils are bled for counting circulating microfilariae, using a Fuchs-Rosenthal counting chamber and microscope. Only test groups with an average of circulating microfilariae at least 50% lower than in the placebo treated group are fully dissected to recover adult worms. Efficacy is expressed as a % reduction in worm numbers in comparison with the placebo treated group, using the Abbot's formula. Compound No. 1.5, 1.10, 1.13, 1.17, 2.1, 2.21, 2.26 and 2.51 showed an efficacy above 80% at 10 mg/kg.

Adult liver fluke-in vitro assay

Freshly harvested adult *Fasciola hepatica* from cattle or sheep livers were distributed in 12-well plates (1 fluke per well) with 4 mL of RPMI complete medium and kept in an incubator at 37°C for approximately 12 hours. After renewal of the medium, the viability of the flukes is determined by video-registration of the movement of the individual flukes (pre-value). Test compounds are added at a concentration of 100 µg/mL and the movements of the flukes are measured after 6 and 24 hours. Efficacy is expressed as percent reduced movement based on the pre-value and the untreated control. In this test the following examples showed more than >90% efficacy after 6 h and >95% after 24 h are considered as positive: 1.5, 1.10, 1.13, 2.19, 2.21, 2.26, and 2.48.

CLAIMS

1. A compound of formula



5 (I),

or a salt or an enantiomer thereof, wherein X is O, S, NH, C(O), C(CN) or CH=CH,

R⁰ is H, C₁-C₄-alkyl or hydroxyl;

n is 0 or 1,

10 each R is independently halogen; C₁-C₆-alkyl; C₁-C₆-haloalkyl; C₃-C₆-cycloalkyl; C₃-C₆-halocycloalkyl; amino; N-mono- or N,N-di-C₁-C₄-alkylamino; hydroxy; C₁-C₆-alkoxy; C₁-C₆-haloalkoxy; C₁-C₆-alkylthio; C₁-C₆-haloalkylthio; C₁-C₆-alkyl-sulfinyl; C₁-C₆-haloalkylsulfinyl; C₁-C₆-alkylsulfonyl; C₁-C₆-haloalkylsulfonyl; SF₅; tri-C₁-C₄-alkylsilyl; C₁-C₆-alkoxycarbonyl; aminocarbonyl; N-mono- or N,N-di-C₁-C₆-alkylaminocarbonyl; aminosulfonyl; N-mono- or N,N-di-C₁-C₆-alkylaminosulfonyl; N-C₁-C₆-alkylsulfonylamino; C₁-C₆-alkoxycarbonylamino; N-C₁-C₄-alkyl-N- C₁-C₆-alkoxycarbonylamino; cyano; nitro; or C₃-C₆-heterocyclyl which is unsubstituted or substituted by halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₃-C₆-cycloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, amino, cyano or nitro;

20 m is an integer from 0 to 4;

each R¹ is independently halogen; C₁-C₆-alkyl; C₁-C₆-haloalkyl; C₃-C₆-cycloalkyl; C₃-C₆-halocycloalkyl; C₁-C₆-alkoxy; C₁-C₆-haloalkoxy; C₁-C₆-alkylthio; C₁-C₆-haloalkylthio; C₁-C₆-alkyl-sulfinyl; C₁-C₆-haloalkylsulfinyl; C₁-C₆-alkylsulfonyl; C₁-C₆-haloalkylsulfonyl; SF₅; amino;

25 N-mono- or N,N-di-C₁-C₆-alkylamino; tri-C₁-C₄-alkylsilyl; C₁-C₆-alkoxycarbonyl; aminocarbonyl; N-mono- or N,N-di-C₁-C₆-alkylaminocarbonyl; N,N-di-C₁-C₄-alkylamino-C₁-C₄-alkylaminocarbonyl; aminosulfonyl; N-mono- or N,N-di-C₁-C₆-alkylaminosulfonyl; N-C₁-C₆-alkylsulfonylamino; C₁-C₆-alkoxycarbonylamino; N-

C₁-C₄-alkyl-N-C₁-C₆-alkoxycarbonylamino; cyano; nitro; hydroxy; B(OH)₂; or phenyl, benzoyl, C₃-C₆-heterocyclyl, C₃-C₆-heterocycloxy or C₆-C₈-benzoheterocyclyl, which is each unsubstituted or substituted by halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₃-C₆-cycloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, amino, cyano or
 5 nitro; and
 r is an integer of from 1 to 4.

2. A compound of formula (I) according to claim 1, wherein each R is independently halogen; C₁-C₄-alkyl; C₁-C₄-haloalkyl; amino; C₁-C₄-alkoxy; C₁-C₄-haloalkoxy; C₁-C₄-haloalkylthio; C₁-C₄-alkylsulfonyl; C₁-C₄-haloalkylsulfonyl; tri-
 10 haloalkoxy; C₁-C₄-haloalkylthio; C₁-C₄-alkylsulfonyl; C₁-C₄-haloalkylsulfonyl; tri-C₁-C₂-alkylsilyl; C₁-C₄-alkoxycarbonyl; N-mono- or N,N-di-C₁-C₄-alkylamino-carbonyl; aminosulfonyl; N-mono- or N,N-di-C₁-C₄-alkylaminosulfonyl; N-C₁-C₂-alkyl-N-C₁-C₄-alkoxycarbonylamino; cyano; nitro; or 5- or 6-membered heterocycloalkyl comprising 1 or 2 same or different heteroatoms of O, S or N, which
 15 is unsubstituted or substituted by halogen, C₁-C₂-alkyl, C₁-C₂-haloalkyl or C₁-C₂-alkoxy.

3. A compound of formula (I) according to claim 1, wherein each R is halogen, C₁-C₂-alkyl, C₁-C₂-haloalkyl, C₁-C₂-alkoxy, C₁-C₂-haloalkoxy or cyano.
 20

4. A compound of formula (I) according to claim 3, wherein each R is chlorine, fluorine or CF₃.

5. A compound of formula (I) according to any one of claims 1 to 4, wherein m
 25 is an integer 1, 2 or 3.

6. A compound of formula (I) according to any one of claims 1 to 5, wherein each R¹ is independently halogen; C₁-C₄-alkyl; C₁-C₄-haloalkyl; C₃-C₆-cycloalkyl; C₁-C₄-alkoxy; C₁-C₄-haloalkoxy; C₁-C₄-haloalkylthio; SF₅; N,N-di-C₁-C₄-alkylamino-C₁-C₄-alkylaminocarbonyl; N-C₁-C₄-alkylsulfonylamino; cyano; nitro;
 30 hydroxy; B(OH)₂, morpholino; or phenyl, benzoyl, pyridyloxy, pyrimidinyloxy or

benzothiazoloyl, which is each unsubstituted or substituted by halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₃-C₆-cycloalkyl or C₁-C₄-alkoxy.

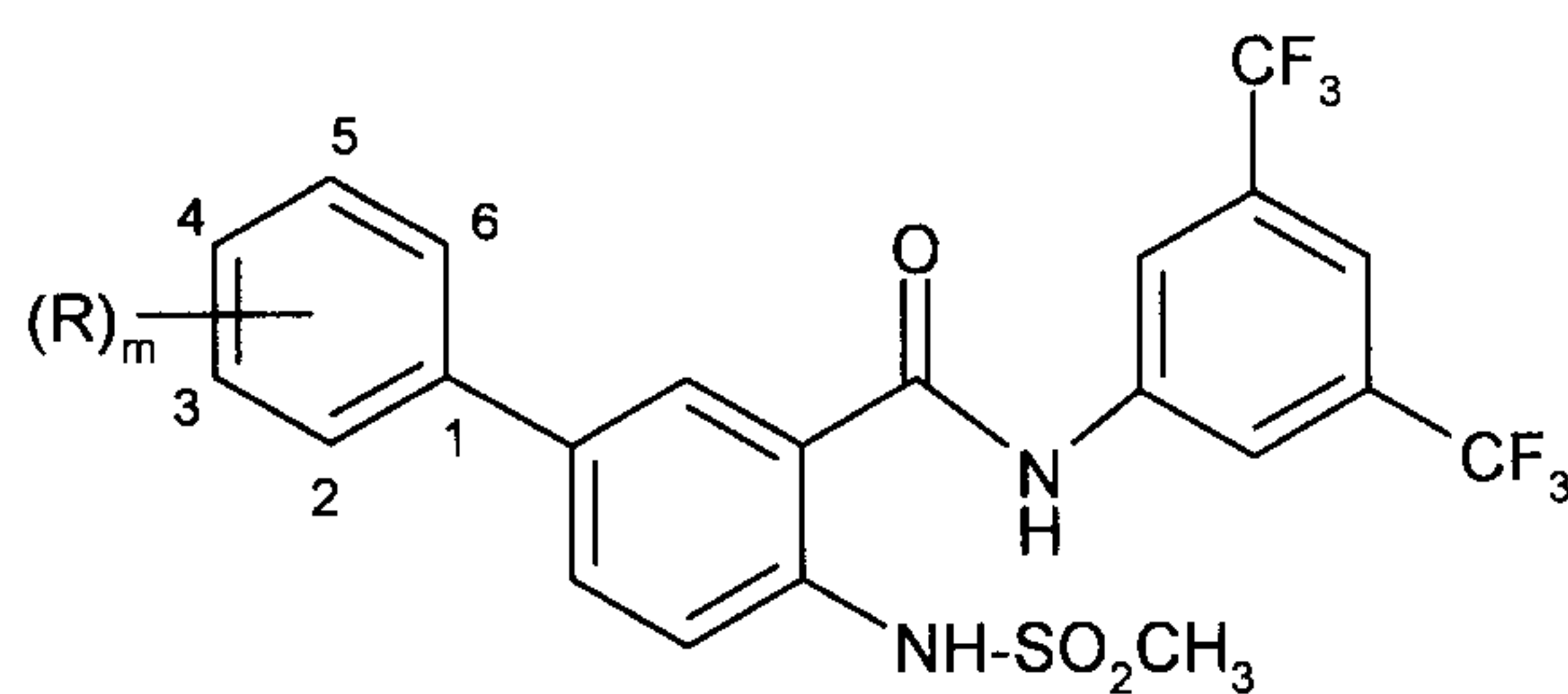
7. A compound of formula (I) according to any one of claims 1 to 5, wherein
 5 each R¹ is independently halogen; C₁-C₂-alkyl; C₁-C₃-haloalkyl; C₁-C₂-alkoxy; C₁-C₃-haloalkoxy; C₁-C₂-haloalkylthio; SF₅; nitro; or hydroxy.

8. A compound of formula (I) according to claim 7, wherein each R¹ is
 10 independently halogen or CF₃

9. A compound of formula (I) according to any one of claims 1 to 8, wherein r is
 an integer of 1, 2 or 3.

10. A compound of formula (I) according to any one of claims 1 to 9, wherein R⁰
 15 is H, m is 0 or 1 and X is O.

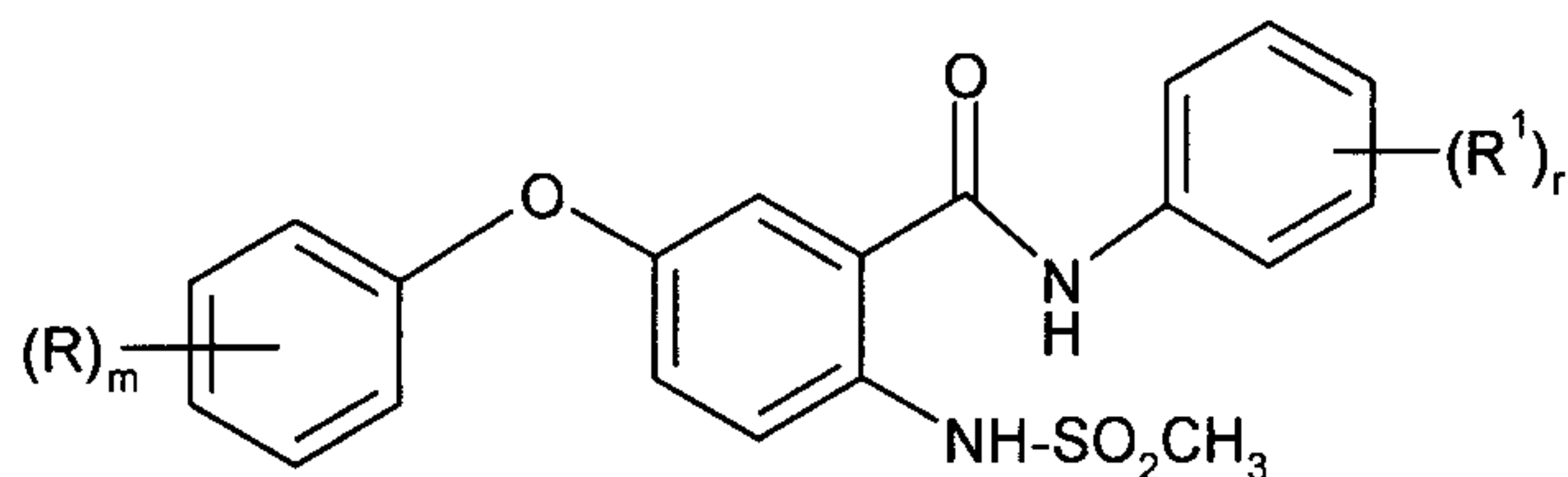
11. A compound according to claim 1 of formula



(Ia'),

20 wherein R and m are each as defined in claim 1.

12. A compound according to claim 1 of formula



(Ib),

25 wherein R, R¹, m and r are each as defined in claim 1.

13. A compound of formula (Ib) according to claim 12, wherein m is an integer 1 or 2, r is an integer 2 or 3, each R is independently halogen or CF₃, and each R¹ is independently halogen or CF₃.

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14. A Composition for the control of parasites, which contains as active ingredient at least one compound of formula (I) according to any one of claims 1 to 13, in addition to one or more pharmaceutically acceptable carrier or dispersant.

10 15. A compound of formula (I) according to any one of claims 1 to 13 for use in the control of endoparasites in or on warm-blooded animals.

16. A use of a veterinary effective amount of at least one compound of formula (I) as defined according to any one of claims 1 to 13 for controlling endoparasites, in
15 or on warm-blooded animals.

17. A use of a compound of formula (I) as defined according to any one of claims 1 to 13 in the preparation of a veterinary or pharmaceutical composition against endoparasites in or on warm-blooded animals.

20

18. A compound of formula (I) as defined according to any one of claims 1 to 13 for use in the manufacture of a veterinary or pharmaceutical composition for control of endoparasites in or on warm-blooded animals.