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CA 2854424 A1 2013/05/16

(21) 2 854 424

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2012/11/08
(87) Date publication PCT/PCT Publication Date: 2013/05/16
(85) Entrée phase nationale/National Entry: 2014/05/02
(86) N° demande PCT/PCT Application No.: EP 2012/072143
(87) N° publication PCT/PCT Publication No.: 2013/068464
(30) Priorité/Priority: 2011/11/09 (EP11008927.3)

(51) Cl.Int./Int.Cl. *C07D 231/12* (2006.01), *A61K 31/415* (2006.01), *A61P 29/00* (2006.01)

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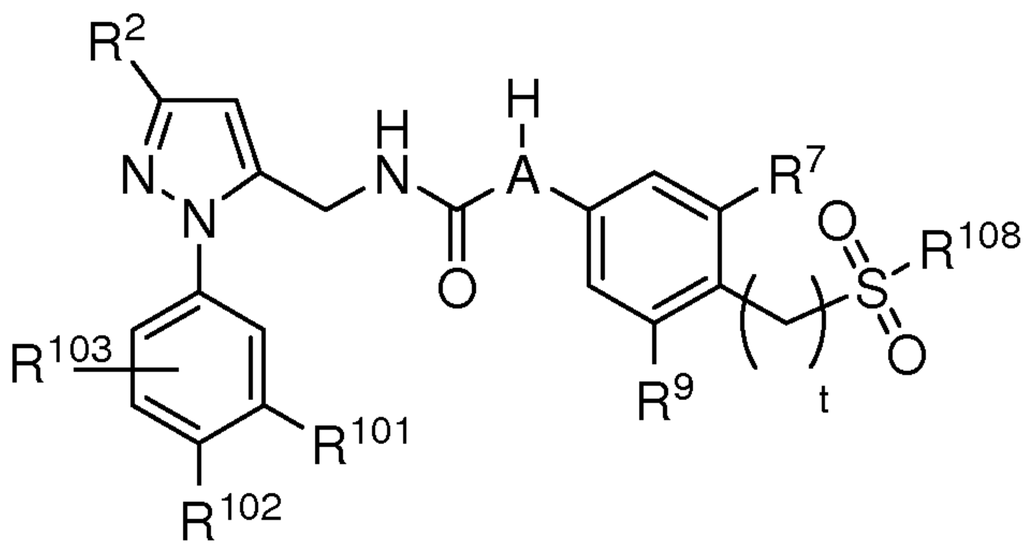
(54) Titre : DERIVES DE CARBOXAMIDE ET D'UREE A BASE DE PYRAZOLYLE SUBSTITUE PORTANT UN FRAGMENT PHENYLE REMPLACE PAR UN GROUPE CONTENANT SO_2 COMME LIGANDS DES RECEPTEURS VANILLOIDES

(54) Title: SUBSTITUTED PYRAZOLYL-BASED CARBOXAMIDE AND UREA DERIVATIVES BEARING A PHENYL MOIETY SUBSTITUTED WITH AN SO_2-CONTAINING GROUP AS VANILLOID RECEPTOR LIGANDS



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(57) Abrégé/Abstract:
The invention relates to substituted pyrazolyl-based carboxamide and urea derivatives bearing a phenyl moiety substituted with a $S0_2$-containing group as vanilloid receptor ligands, to pharmaceutical compositions containing these compounds and also to these compounds for use in the treatment and/or prophylaxis of pain and further diseases and/or disorders.

CA 2854424 A1 2013/05/16

(21) 2 854 424

(13) A1

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 May 2013 (16.05.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/068464 A1

(51) **International Patent Classification**:
C07D 231/12 (2006.01) *A61P 29/00* (2006.01)
A61K 31/415 (2006.01)

(21) **International Application Number**:
PCT/EP2012/072143

(22) **International Filing Date**:
8 November 2012 (08.11.2012)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
11008927.3 9 November 2011 (09.11.2011) EP

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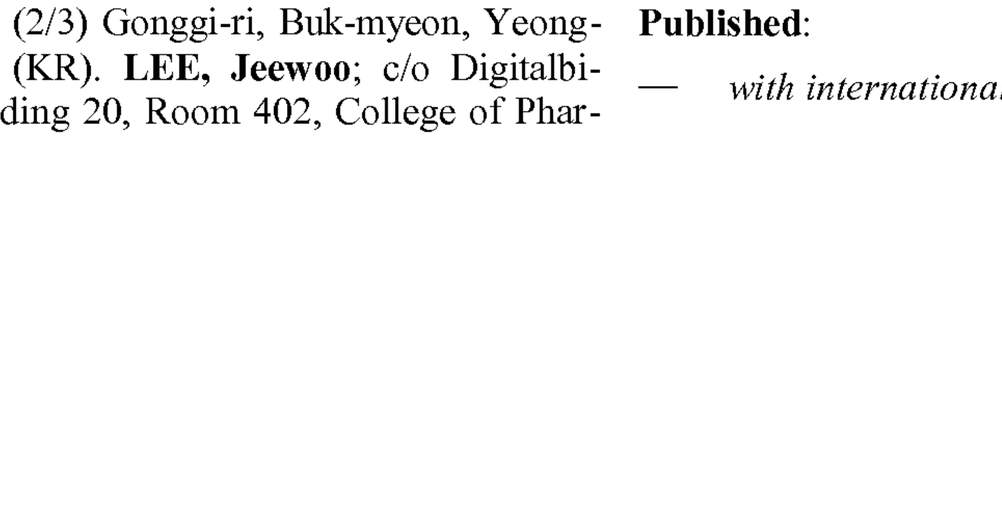
(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

(54) Title: SUBSTITUTED PYRAZOLYL-BASED CARBOXAMIDE AND UREA DERIVATIVES BEARING A PHENYL MOIETY SUBSTITUTED WITH AN SO2-CONTAINING GROUP AS VANILLOID RECEPTOR LIGANDS



(T)

(57) Abstract: The invention relates to substituted pyrazolyl-based carboxamide and urea derivatives bearing a phenyl moiety substituted with a SO_2-containing group as vanilloid receptor ligands, to pharmaceutical compositions containing these compounds and also to these compounds for use in the treatment and/or prophylaxis of pain and further diseases and/or disorders.

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Substituted pyrazolyl-based carboxamide and urea derivatives bearing a phenyl moiety substituted with an SO_2-containing group as vanilloid receptor ligands

FIELD OF THE INVENTION

The invention relates to substituted pyrazolyl-based carboxamide and urea derivatives bearing a phenyl moiety substituted with a SO_2-containing group as vanilloid receptor ligands, to pharmaceutical compositions containing these compounds and also to these compounds for use in the treatment and/or prophylaxis of pain and further diseases and/or disorders.

BACKGROUND OF THE INVENTION

The treatment of pain, in particular of neuropathic pain, is very important in medicine. There is a worldwide demand for effective pain therapies. The urgent need for action for a patient-focused and target-oriented treatment of chronic and non-chronic states of pain, this being understood to mean the successful and satisfactory treatment of pain for the patient, is also documented in the large number of scientific studies which have recently appeared in the field of applied analgesics or basic research on nociception.

The subtype 1 vanilloid receptor (VR1/TRPV1), which is often also referred to as the capsaicin receptor, is a suitable starting point for the treatment of pain, in particular of pain selected from the group consisting of acute pain, chronic pain, neuropathic pain and visceral pain. This receptor is stimulated inter alia by vanilloids such as capsaicin, heat and protons and plays a central role in the formation of pain. In addition, it is important for a large number of further physiological and pathophysiological processes and is a suitable target for the therapy of a large number of further disorders such as, for example, migraine, depression, neurodegenerative diseases, cognitive disorders, states of anxiety, epilepsy, coughs, diarrhoea, pruritus, inflammations, disorders of the cardiovascular system, eating disorders, medication dependency, misuse of medication and urinary incontinence.

Compounds which have an affinity for the subtype 1 vanilloid receptor (VR1/TRPV1) are e.g. known from WO 2010/127855-A2 and WO 2010/127856-A2.

There is a demand for further compounds having comparable or better properties, not only with regard to affinity to vanilloid receptors 1 (VR1/TRPV1 receptors) per se (*potency, efficacy*).

Thus, it may be advantageous to improve the metabolic stability, the solubility in aqueous media or the permeability of the compounds. These factors can have a beneficial effect on oral bioavailability or can alter the PK/PD (pharmacokinetic/pharmacodynamic) profile; this can lead to a more beneficial period of effectiveness, for example.

A weak or non-existent interaction with transporter molecules, which are involved in the ingestion and the excretion of pharmaceutical compositions, is also to be regarded as an indication of improved bioavailability and at most low interactions of pharmaceutical compositions. Furthermore, the interactions with the enzymes involved in the decomposition and the excretion of pharmaceutical compositions should also be as low as possible, as such test results also suggest that at most low interactions or no interactions at all, of pharmaceutical compositions are to be expected.

It was therefore an object of the invention to provide novel compounds, preferably having advantages over the prior-art compounds. The compounds should be suitable in particular as pharmacological active ingredients in pharmaceutical compositions, preferably in pharmaceutical compositions for the treatment and/or prophylaxis of disorders or diseases which are at least partially mediated by vanilloid receptors 1 (VR1/TRPV1 receptors).

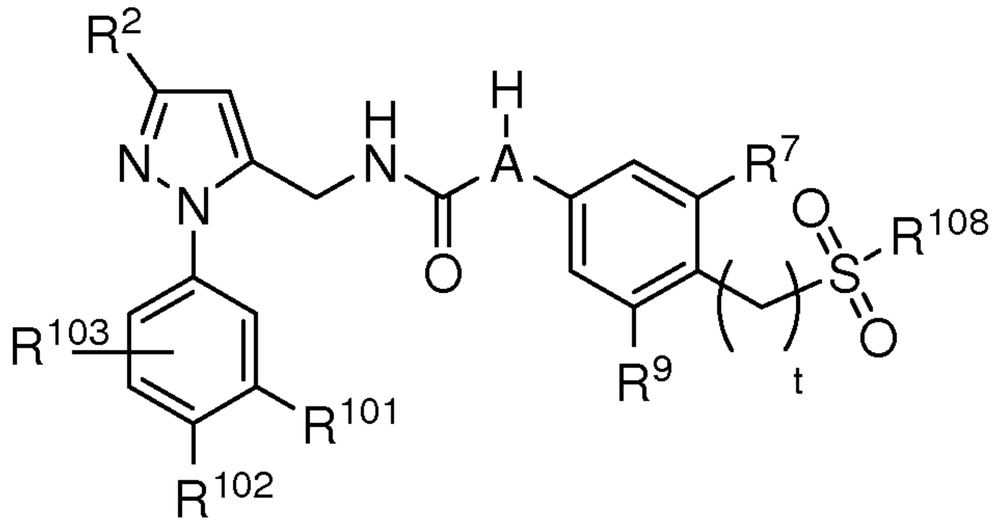
This object is achieved by the subject matter described herein.

It has surprisingly been found that the substituted compounds of general formula (T), as given below, display outstanding affinity to the subtype 1 vanilloid receptor (VR1/TRPV1 receptor) and are therefore particularly suitable for the prophylaxis and/or treatment of disorders or diseases which are at least partially mediated by vanilloid receptors 1 (VR1/TRPV1).

Particularly suitable are substituted compounds of general formula (T), as given below, that in addition to their activity with regard to the VR1-receptor show one or more additional advantageous properties, for example, suitable potency, suitable efficacy, no increase in body temperature and/or heat pain threshold; appropriate solubility in biologically relevant media such as aqueous media, in particular in aqueous media at a physiologically acceptable pH value, such as in buffer systems, for instance in phosphate buffer systems;

suitable metabolic stability and diversity (e.g. sufficient stability towards the oxidative capabilities of hepatic enzymes such as cytochrome P450 (CYP) enzymes and sufficient diversity with regard to the metabolic elimination via these enzymes); and the like.

The present invention therefore relates to a substituted compound of general formula (T),



(T),

in which

R^{101}, R^{102} and R^{103} are independently of one another selected from the group consisting of H, F, Cl, Br, CFH_2, CF_2H, CF_3, CN, CH_2-OH, CH_2CH_2-OH, CH_2-OCH_3, CH_2CH_2-OCH_3, $OCFH_2$, OCF_2H, OCF_3, OH, NH_2, a C_{1-4} alkyl, an O-C_{1-4} alkyl, a NH-C_{1-4} alkyl, and a $N(C_{1-4}$ alkyl$)_2$, wherein the C_{1-4} alkyl is in each case unsubstituted,

R^2 represents CF_3, an unsubstituted C_{1-4} alkyl or an unsubstituted C_{3-6} cycloalkyl,

R^7 and R^9 are independently of one another selected from the group consisting of H, F, Cl, Br, CFH_2, CF_2H, CF_3, CN, OH, OCF_3, a C_{1-4} alkyl, and an O-C_{1-4} alkyl, wherein the C_{1-4} alkyl is in each case unsubstituted,

A denotes N, CH or $C(CH_3)$,

t denotes 0, 1 or 2,

R^{108} represents C_{1-4} alkyl, which is unsubstituted or mono-, di- or trisubstituted with 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, OH, =O and OCH_3,

optionally in the form of a single stereoisomer or a mixture of stereoisomers, in the form of the free compound and/or a physiologically acceptable salt and/or a physiologically acceptable solvate thereof.

DETAILED DESCRIPTION

The term "single stereoisomer" preferably means in the sense of the present invention an individual enantiomer or diastereomer. The term "mixture of stereoisomers" means in the sense of this invention the racemate and mixtures of enantiomers and/or diastereomers in any mixing ratio.

The term "physiologically acceptable salt" preferably comprises in the sense of this invention a salt of at least one compound according to the present invention and at least one physiologically acceptable acid or base.

A physiologically acceptable salt of at least one compound according to the present invention and at least one physiologically acceptable acid preferably refers in the sense of this invention to a salt of at least one compound according to the present invention with at least one inorganic or organic acid which is physiologically acceptable - in particular when used in human beings and/or other mammals. Examples of physiologically acceptable acids are: hydrochloric acid, hydrobromic acid, sulphuric acid, methanesulphonic acid, p-toluenesulphonic acid, carbonic acid, formic acid, acetic acid, oxalic acid, succinic acid, tartaric acid, mandelic acid, fumaric acid, maleic acid, lactic acid, citric acid, glutamic acid, saccharic acid, monomethylsebacic acid, 5-oxoproline, hexane-1-sulphonic acid, nicotinic acid, 2, 3 or 4-aminobenzoic acid, 2,4,6-trimethylbenzoic acid, α-lipoic acid, acetyl glycine, hippuric acid, phosphoric acid, aspartic acid. Citric acid and hydrochloric acid are particularly preferred. Hydrochloride salts and citrate salts are therefore particularly preferred salts.

A physiologically acceptable salt of at least one compound according to the present invention and at least one physiologically acceptable base preferably refers in the sense of this invention to a salt of at least one compound according to the present invention as an anion with at least one preferably inorganic cation, which is physiologically acceptable – in particular when used in human beings and/or other mammals. Particularly preferred are the salts of the alkali and alkaline earth metals but also ammonium salts $[NH_xR_{4-x}]^+$, in which x = 0, 1, 2, 3 or 4 and R represents a branched or unbranched C_{1-4} alkyl residue, in particular (mono-) or (di)sodium, (mono-) or (di)potassium, magnesium or calcium salts.

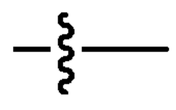
The terms "alkyl" and "C_{1-4} alkyl" preferably comprise in the sense of this invention acyclic saturated aliphatic hydrocarbon residues, which can be respectively branched or unbranched and can be unsubstituted or can be mono- or polysubstituted, e.g. mono-, di- or trisubstituted, and which contain 1 to 4, i.e. 1, 2, 3 or 4, carbon atoms, i.e. C_{1-4} aliphatic

residues, i.e. C_{1-4} alkanyls. Preferred C_{1-4} alkanyl residues are selected from the group consisting of methyl, ethyl, n-propyl, 2-propyl, n-butyl, isobutyl, sec.-butyl, and tert.-butyl.

In relation to the terms "alkyl" and "C_{1-4} alkyl", the term "monosubstituted" or "polysubstituted" such as di- or tri-substituted refers in the sense of this invention, with respect to the corresponding residues or groups, to the single substitution or multiple substitution, e.g. disubstitution or trisubstitution, of one or more hydrogen atoms each independently of one another by at least one substituent. The term "polysubstituted" such as di- or tri-substituted with respect to polysubstituted residues and groups such as di- or tri-substituted residues and groups includes the polysubstitution of these residues and groups either on different or on the same atoms, for example trisubstituted on the same carbon atom, as in the case of CF_3 or CH_2CF_3 or at various points, as in the case of $CH(OH)\text{-}CH_2CH_2\text{-}CHCl_2$. The multiple substitution can be carried out using the same or using different substituents.

The terms "cycloalkyl" and "C_{3-6} cycloalkyl" preferably mean for the purposes of this invention cyclic aliphatic (cycloaliphatic) hydrocarbons containing 3, 4, 5, or 6 carbon atoms, i.e. C_{3-6}-cycloaliphatic residues, wherein the hydrocarbons are saturated and which are unsubstituted. The cycloalkyl can be bound to the respective superordinate general structure via any desired and possible ring member of the cycloalkyl residue. Preferably, cycloalkyl is selected from the group consisting cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, more preferably from the group consisting of cyclopropyl and cyclobutyl. A particularly preferred cycloalkyl is cyclopropyl.

Within the scope of the present invention, the symbol



used in the formulae denotes a link of a corresponding residue to the respective superordinate general structure.

In a preferred embodiment of the compound according to the present invention

R^{101}, R^{102} and R^{103} are independently of one another selected from the group consisting of H, F, Cl, Br, CFH_2, CF_2H, CF_3, CN, $CH_2\text{-}OH$, $CH_2\text{-}OCH_3$, OCF_3, OH, CH_3, CH_2CH_3, $CH(CH_3)_2$, $O\text{-}CH_3$, $O\text{-}CH_2CH_3$, NH_2, $NH(CH_3)$, and $N(CH_3)_2$.

Preferably,

R^{101}, R^{102} and R^{103} are independently of one another selected from the group consisting of H, F, Cl, Br, CFH_2, CF_2H, CF_3, CN, CH_2-OH, CH_2-OCH_3, OCF_3, OH, CH_3, O-CH_3, O-CH_2CH_3, NH_2, $NH(CH_3)$, and $N(CH_3)_2$.

More preferably,

R^{101}, R^{102} and R^{103} are independently of one another selected from the group consisting of H, F, Cl, CFH_2, CF_2H, CF_3, CN, CH_2-OCH_3, OCF_3, CH_3, O-CH_3, O-CH_2CH_3 and $N(CH_3)_2$.

Even more preferably,

R^{101}, R^{102} and R^{103} are independently of one another selected from the group consisting of H, F, Cl, CFH_2, CF_2H, CF_3, OCF_3, CH_3, O-CH_3, and O-CH_2CH_3.

Still more preferably,

R^{101}, R^{102} and R^{103} are independently of one another selected from the group consisting of H, F, Cl, CF_3, OCF_3, CH_3 and O-CH_3.

Particularly,

R^{101}, R^{102} and R^{103} are independently of one another selected from the group consisting of H, F, Cl, CF_3 and O-CH_3.

Even more particularly preferred

R^{101}, R^{102} and R^{103} are independently of one another selected from the group consisting of H, F, Cl and O-CH_3.

In a preferred embodiment of the compound according to the present invention at least one of R^{101}, R^{102} and R^{103} is ≠ H.

In another preferred embodiment of the compound according to the present invention one or two of R^{101}, R^{102} and R^{103}, preferably R^{102} and/or R^{103}, denote(s) H.

In another preferred embodiment of the compound according to the present invention one of R^{101}, R^{102} and R^{103} represents H, preferably R^{103} represents H.

In another preferred embodiment of the compound according to the present invention

R^{101} and R^{102} are independently of one another selected from the group consisting of H, F, Cl, Br, CFH_2, CF_2H, CF_3, CN, CH_2-OH, CH_2-OCH_3, OCF_3, OH, CH_3, CH_2CH_3, $CH(CH_3)_2$, O-CH_3, O-CH_2CH_3, NH_2, $NH(CH_3)$, and $N(CH_3)_2$,

and R^{103} represents H.

Preferably,

R^{101} and R^{102} are independently of one another selected from the group consisting of H, F, Cl, Br, CFH_2, CF_2H, CF_3, CN, CH_2-OH, CH_2-OCH_3, OCF_3, OH, CH_3, O-CH_3, O-CH_2CH_3, NH_2, $NH(CH_3)$, and $N(CH_3)_2$, more preferably are independently of one another selected from the group consisting of H, F, Cl, CFH_2, CF_2H, CF_3, CN, CH_2-OCH_3, OCF_3, CH_3, O-CH_3, O-CH_2CH_3 and $N(CH_3)_2$, even more preferably are independently of one another selected from the group consisting of H, F, Cl, CFH_2, CF_2H, CF_3, OCF_3, CH_3, O-CH_3, and O-CH_2CH_3, still more preferably are independently of one another selected from the group consisting of H, F, Cl, CF_3, OCF_3, CH_3 and O-CH_3, in particular are independently of one another selected from the group consisting of H, F, Cl, CF_3 and O-CH_3, even more particularly preferred are independently of one another selected from the group consisting of H, F, Cl, and O-CH_3,

and R^{103} represents H.

In yet another preferred embodiment of the compound according to the present invention

R^{101} is selected from the group consisting of F, Cl, Br, CFH_2, CF_2H, CF_3, CN, CH_2-OH, CH_2-OCH_3, OCF_3, OH, CH_3, CH_2CH_3, $CH(CH_3)_2$, O-CH_3, O-CH_2CH_3, NH_2, $NH(CH_3)$, and $N(CH_3)_2$,

and both R^{102} and R^{103} represents H.

Preferably,

R^{101} is selected from the group consisting of F, Cl, Br, CFH_2, CF_2H, CF_3, CN, CH_2-OH, CH_2-OCH_3, OCF_3, OH, CH_3, O-CH_3, O-CH_2CH_3, NH_2, $NH(CH_3)$, and $N(CH_3)_2$, more preferably is selected from the group consisting of F, Cl, CFH_2, CF_2H, CF_3, CN, CH_2-OCH_3, OCF_3, CH_3, O-CH_3, O-CH_2CH_3 and $N(CH_3)_2$, even more preferably is selected from the group consisting of

F, Cl, CFH_2, CF_2H, CF_3, OCF_3, CH_3, O-CH_3, and O-CH_2CH_3, still more preferably is selected from the group consisting of F, Cl, CF_3, OCF_3, CH_3 and O-CH_3, in particular is selected from the group consisting of F, Cl, CF_3 and O-CH_3, even more particularly preferred is selected from the group consisting of F, Cl, and O-CH_3,

and both R^{102} and R^{103} represents H.

In still another preferred embodiment of the compound according to the present invention

R^{102} is selected from the group consisting of F, Cl, Br, CFH_2, CF_2H, CF_3, CN, CH_2-OH, CH_2-OCH_3, OCF_3, OH, CH_3, CH_2CH_3, $CH(CH_3)_2$, O-CH_3, O-CH_2CH_3, NH_2, $NH(CH_3)$, and $N(CH_3)_2$,

and both R^{101} and R^{103} represents H.

Preferably,

R^{102} is selected from the group consisting of F, Cl, Br, CFH_2, CF_2H, CF_3, CN, CH_2-OH, CH_2-OCH_3, OCF_3, OH, CH_3, O-CH_3, O-CH_2CH_3, NH_2, $NH(CH_3)$, and $N(CH_3)_2$, more preferably is selected from the group consisting of F, Cl, CFH_2, CF_2H, CF_3, CN, CH_2-OCH_3, OCF_3, CH_3, O-CH_3, O-CH_2CH_3 and $N(CH_3)_2$, even more preferably is selected from the group consisting of F, Cl, CFH_2, CF_2H, CF_3, OCF_3, CH_3, O-CH_3, and O-CH_2CH_3, still more preferably is selected from the group consisting of F, Cl, CF_3, OCF_3, CH_3 and O-CH_3, in particular is selected from the group consisting of F, Cl, CF_3 and O-CH_3, even more particularly preferred is selected from the group consisting of F, Cl, and O-CH_3,

and both R^{101} and R^{103} represents H.

In yet a further preferred embodiment of the compound according to the present invention

R^{101} is selected from the group consisting of F, Cl, Br, CFH_2, CF_2H, CF_3, CN, CH_2-OH, CH_2-OCH_3, OCF_3, OH, CH_3, CH_2CH_3, $CH(CH_3)_2$, O-CH_3, O-CH_2CH_3, NH_2, $NH(CH_3)$, and $N(CH_3)_2$,

R^{102} is selected from the group consisting of H, F, Cl, Br, CFH_2, CF_2H, CF_3, CN, CH_2-OH, CH_2-OCH_3, OCF_3, OH, CH_3, CH_2CH_3, $CH(CH_3)_2$, O-CH_3, O-CH_2CH_3, NH_2, $NH(CH_3)$, and $N(CH_3)_2$,

and R^{103} represents H.

Preferably,

R^{101} is selected from the group consisting of F, Cl, Br, CFH_2, CF_2H, CF_3, CN, CH_2-OH, CH_2-OCH_3, OCF_3, OH, CH_3, O-CH_3, O-CH_2CH_3, NH_2, $NH(CH_3)$, and $N(CH_3)_2$, more preferably is selected from the group consisting of F, Cl, CFH_2, CF_2H, CF_3, CN, CH_2-OCH_3, OCF_3, CH_3, O-CH_3, O-CH_2CH_3 and $N(CH_3)_2$, even more preferably is selected from the group consisting of F, Cl, CFH_2, CF_2H, CF_3, OCF_3, CH_3, O-CH_3, and O-CH_2CH_3, still more preferably is selected from the group consisting of F, Cl, CF_3, OCF_3, CH_3 and O-CH_3, in particular is selected from the group consisting of F, Cl, CF_3 and O-CH_3, even more particularly preferred is selected from the group consisting of F, Cl, and O-CH_3,

R^{102} is selected from the group consisting of H, F, Cl, Br, CFH_2, CF_2H, CF_3, CN, CH_2-OH, CH_2-OCH_3, OCF_3, OH, CH_3, O-CH_3, O-CH_2CH_3, NH_2, $NH(CH_3)$, and $N(CH_3)_2$, more preferably is selected from the group consisting of H, F, Cl, CFH_2, CF_2H, CF_3, CN, CH_2-OCH_3, OCF_3, CH_3, O-CH_3, O-CH_2CH_3 and $N(CH_3)_2$, even more preferably is selected from the group consisting of H, F, Cl, CFH_2, CF_2H, CF_3, OCF_3, CH_3, O-CH_3, and O-CH_2CH_3, still more preferably is selected from the group consisting of H, F, Cl, CF_3, OCF_3, CH_3 and O-CH_3, in particular is selected from the group consisting of H, F, Cl, CF_3 and O-CH_3, even more particularly preferred is selected from the group consisting of H, F, Cl, and O-CH_3,

and R^{103} represents H.

In yet another further preferred embodiment of the compound according to the present invention

R^{101} is selected from the group consisting of F, Br, CFH_2, CF_2H, CF_3, CN, CH_2-OH, CH_2-OCH_3, OCF_3, OH, CH_3, O-CH_3, O-CH_2CH_3, NH_2, $NH(CH_3)$, and $N(CH_3)_2$, more preferably is selected from the group consisting of F, CFH_2, CF_2H, CF_3, CN, CH_2-OCH_3, OCF_3, CH_3, O-CH_3, O-CH_2CH_3 and $N(CH_3)_2$, even more preferably is selected from the group consisting of F, CFH_2, CF_2H, CF_3, OCF_3, CH_3, O-CH_3, and O-CH_2CH_3, still more preferably is selected from the group consisting of F, CF_3, OCF_3, CH_3 and O-CH_3, in particular is selected from the group consisting of F, CF_3 and O-CH_3, even more particularly preferred is selected from the group consisting of F and O-CH_3,

and both R^{102} and R^{103} represents H.

In still another further preferred embodiment of the compound according to the present invention

R^{101} is selected from the group consisting of F, Br, CFH_2, CF_2H, CF_3, CN, CH_2-OH, CH_2-OCH_3, OCF_3, OH, CH_3, CH_2CH_3, $CH(CH_3)_2$, O-CH_3, O-CH_2CH_3, NH_2, $NH(CH_3)$, and $N(CH_3)_2$,

R^{102} is selected from the group consisting of H, F, Cl, Br, CFH_2, CF_2H, CF_3, CN, CH_2-OH, CH_2-OCH_3, OCF_3, OH, CH_3, CH_2CH_3, $CH(CH_3)_2$, O-CH_3, O-CH_2CH_3, NH_2, $NH(CH_3)$, and $N(CH_3)_2$,

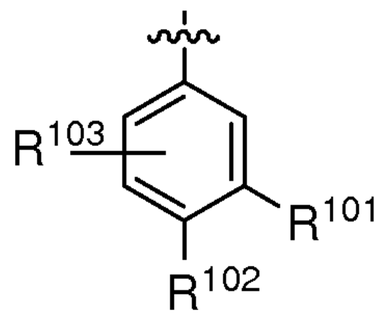
and R^{103} represents H.

Preferably,

R^{101} is selected from the group consisting of F, Br, CFH_2, CF_2H, CF_3, CN, CH_2-OH, CH_2-OCH_3, OCF_3, OH, CH_3, O-CH_3, O-CH_2CH_3, NH_2, $NH(CH_3)$, and $N(CH_3)_2$, more preferably is selected from the group consisting of F, CFH_2, CF_2H, CF_3, CN, CH_2-OCH_3, OCF_3, CH_3, O-CH_3, O-CH_2CH_3 and $N(CH_3)_2$, even more preferably is selected from the group consisting of F, CFH_2, CF_2H, CF_3, OCF_3, CH_3, O-CH_3, and O-CH_2CH_3, still more preferably is selected from the group consisting of F, CF_3, OCF_3, CH_3 and O-CH_3, in particular is selected from the group consisting of F, CF_3 and O-CH_3, even more particularly preferred is selected from the group consisting of F and O-CH_3,

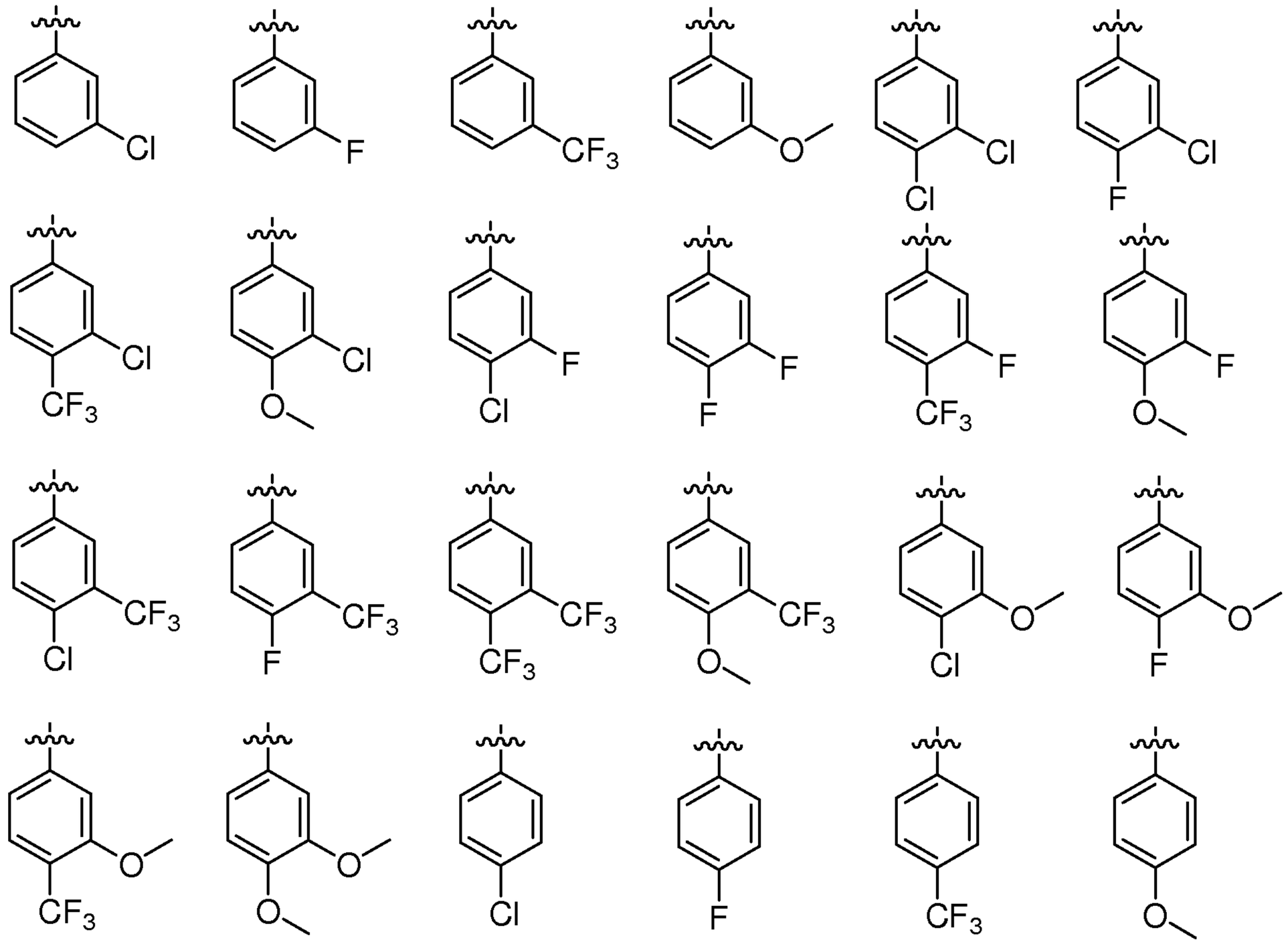
R^{102} is selected from the group consisting of H, F, Cl, Br, CFH_2, CF_2H, CF_3, CN, CH_2-OH, CH_2-OCH_3, OCF_3, OH, CH_3, O-CH_3, O-CH_2CH_3, NH_2, $NH(CH_3)$, and $N(CH_3)_2$, more preferably is selected from the group consisting of H, F, Cl, CFH_2, CF_2H, CF_3, CN, CH_2-OCH_3, OCF_3, CH_3, O-CH_3, O-CH_2CH_3 and $N(CH_3)_2$, even more preferably is selected from the group consisting of H, F, Cl, CFH_2, CF_2H, CF_3, OCF_3, CH_3, O-CH_3, and O-CH_2CH_3, still more preferably is selected from the group consisting of H, F, Cl, CF_3, OCF_3, CH_3 and O-CH_3, in particular is selected from the group consisting of H, F, Cl, CF_3 and O-CH_3, even more particularly preferred is selected from the group consisting of H, F, Cl, and O-CH_3,

In another particularly preferred embodiment according to the present invention the part structure (TS2)



(TS2),

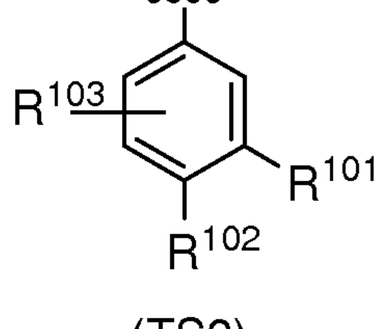
is selected from the group consisting of



,

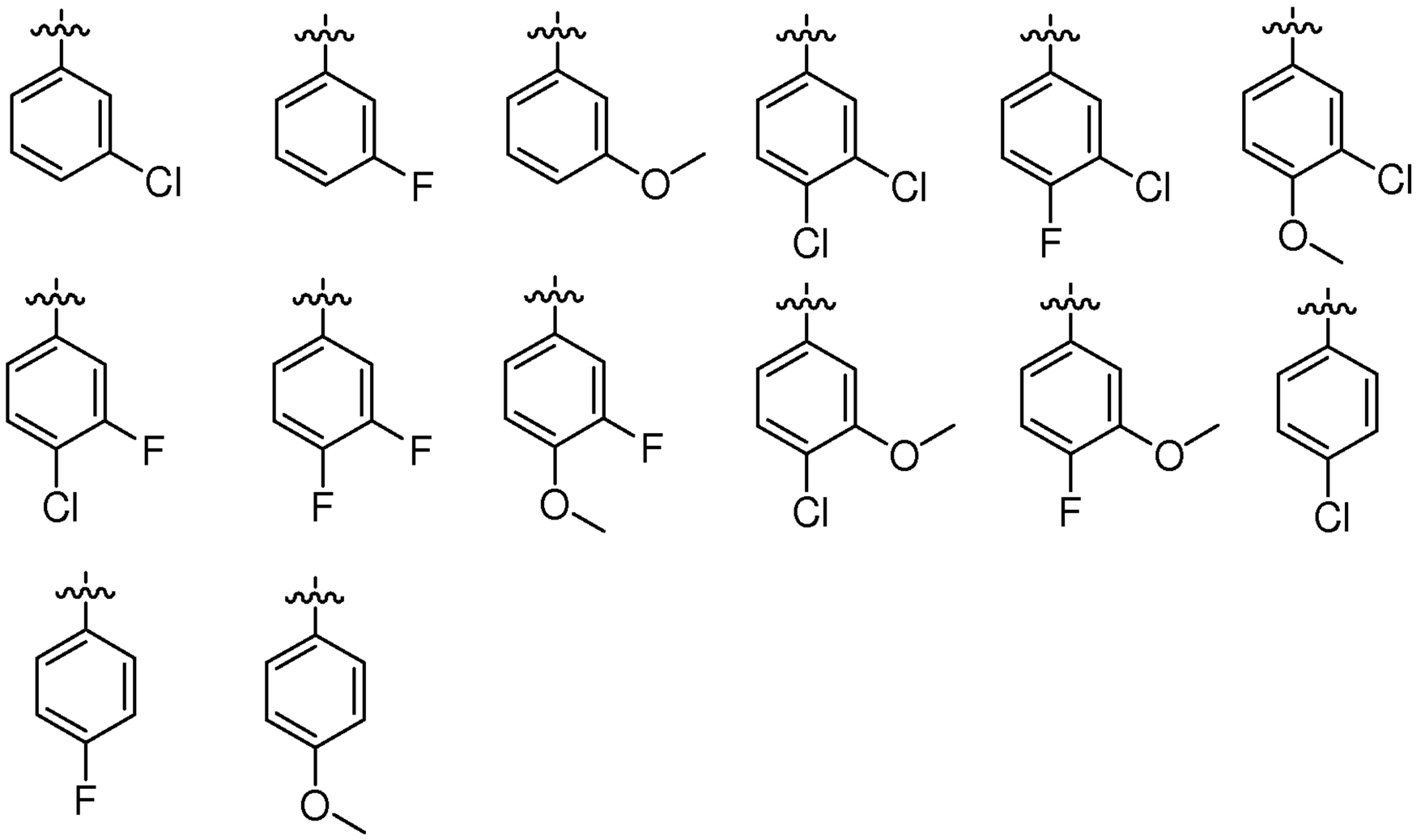
in particular when t denotes 0, 1 or 2, preferably denotes 1 or 2, and A denotes N.

Even more particularly preferred, the part structure (TS2)



(TS2),

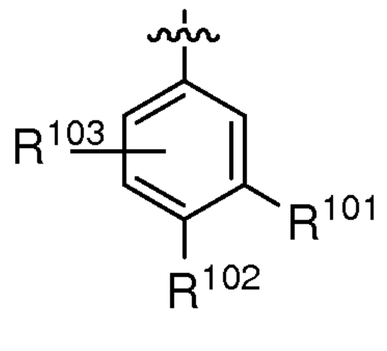
is selected from the group consisting of



,

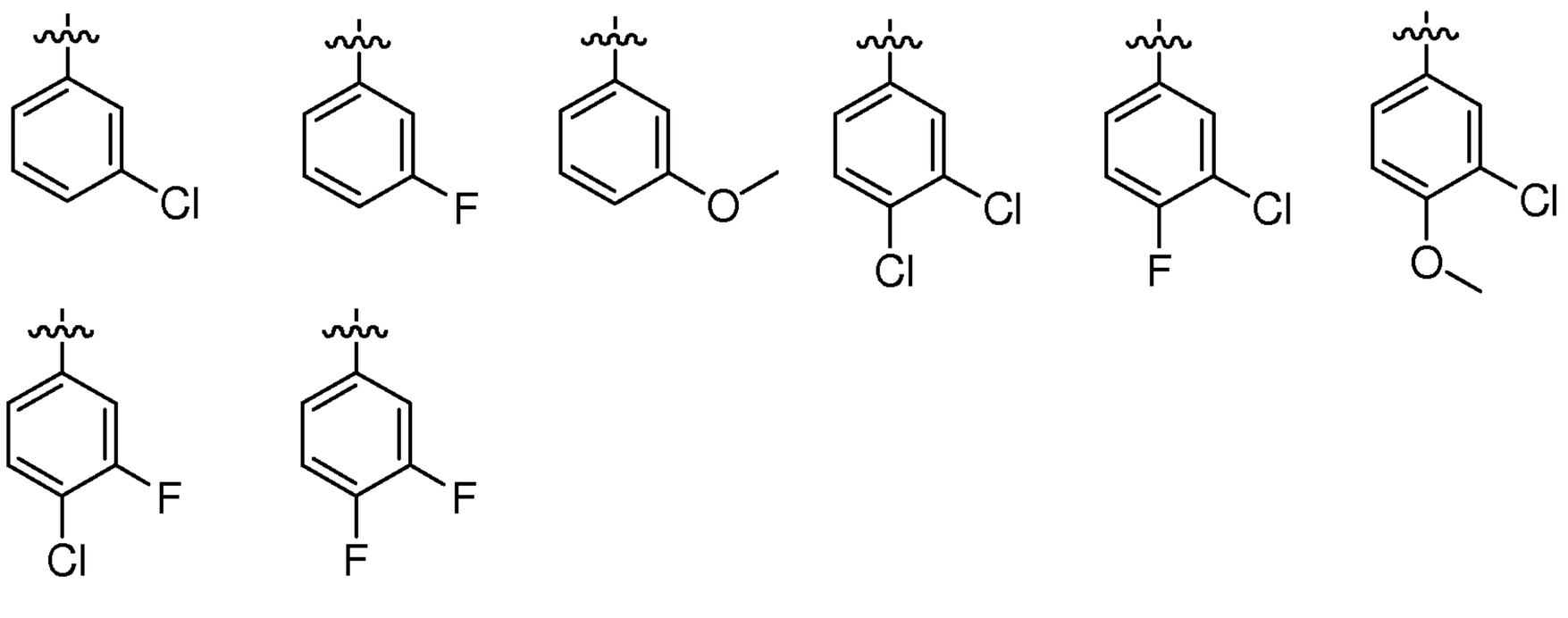
in particular when t denotes 0, 1 or 2, preferably denotes 1 or 2, and A denotes N.

Most preferred, the part structure (TS2)



(TS2),

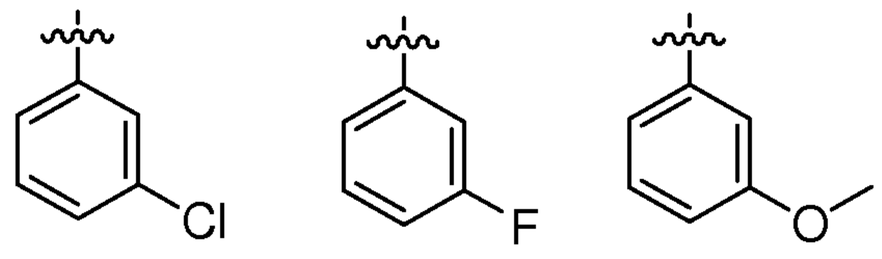
is selected from the group consisting of



,

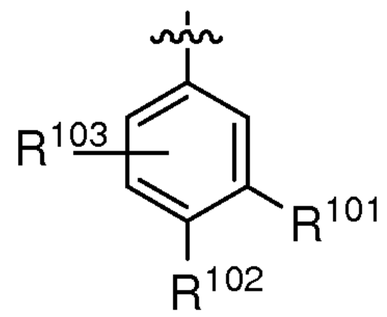
in particular when t denotes 0, 1 or 2, preferably denotes 1 or 2, and A denotes N,

preferably is selected from the group consisting of



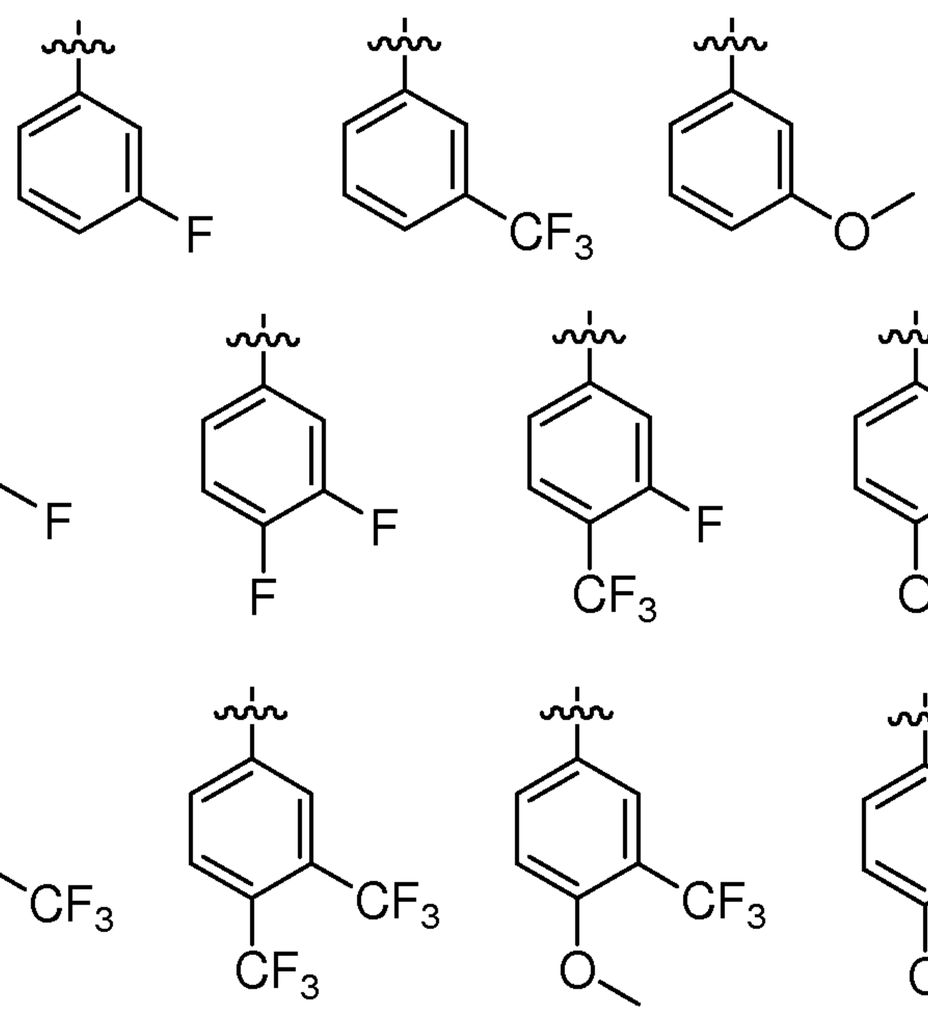
in particular when t denotes 0, 1 or 2, preferably denotes 1 or 2, and A denotes N.

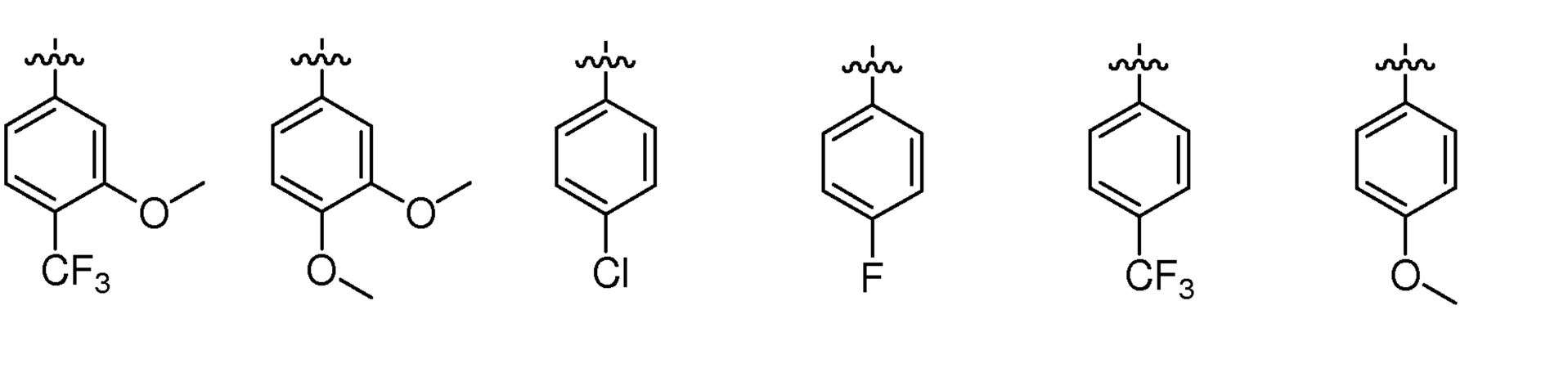
In another particularly preferred embodiment according to the present invention the part structure (TS2)



(TS2),

is selected from the group consisting of

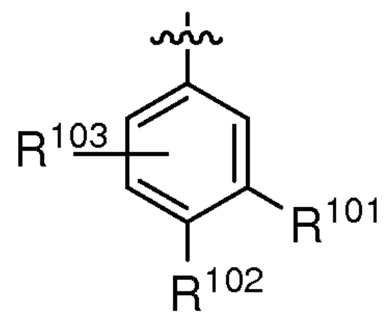




,

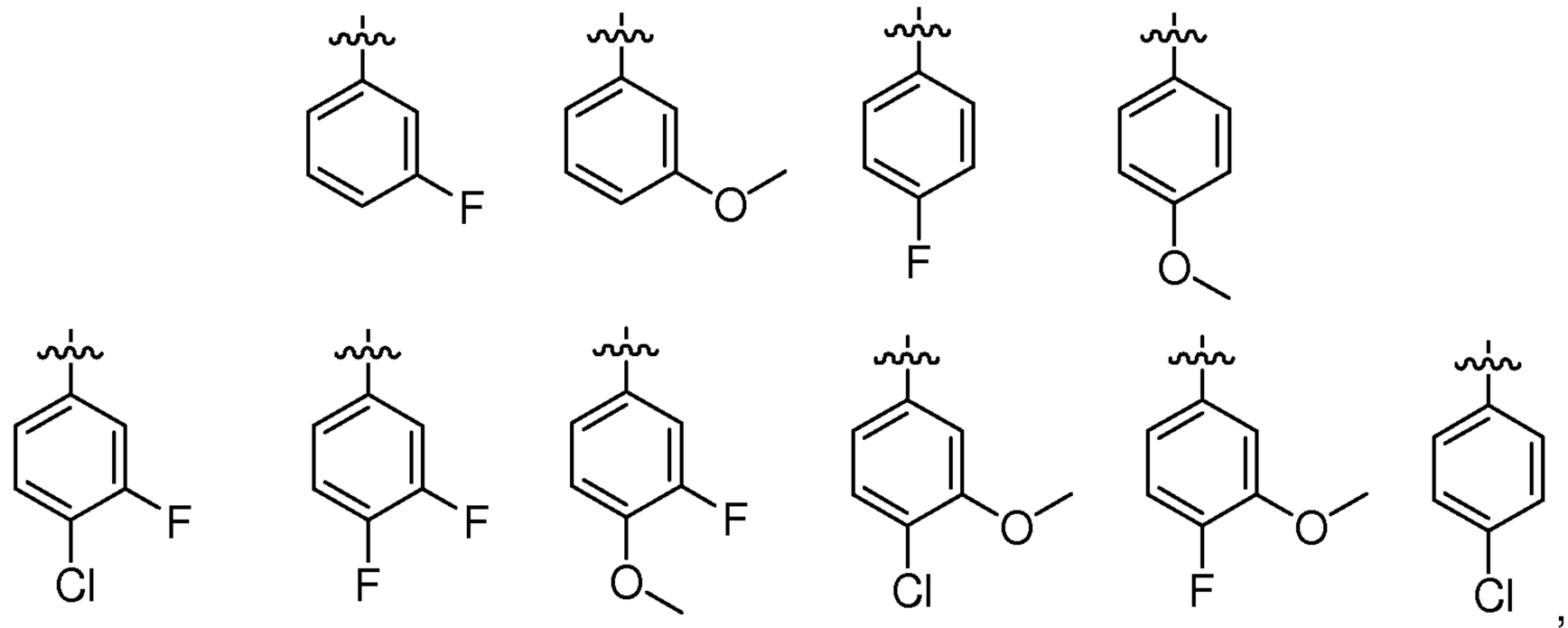
in particular when t denotes 0, 1 or 2, preferably denotes 1 or 2, and A denotes CH or $C(CH_3)$.

Even more particularly preferred, the part structure (TS2)



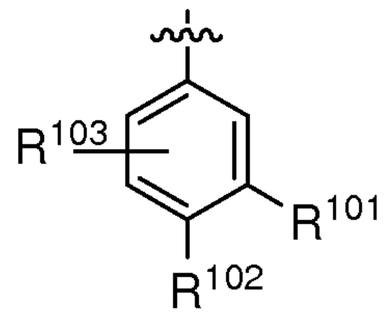
(TS2),

is selected from the group consisting of



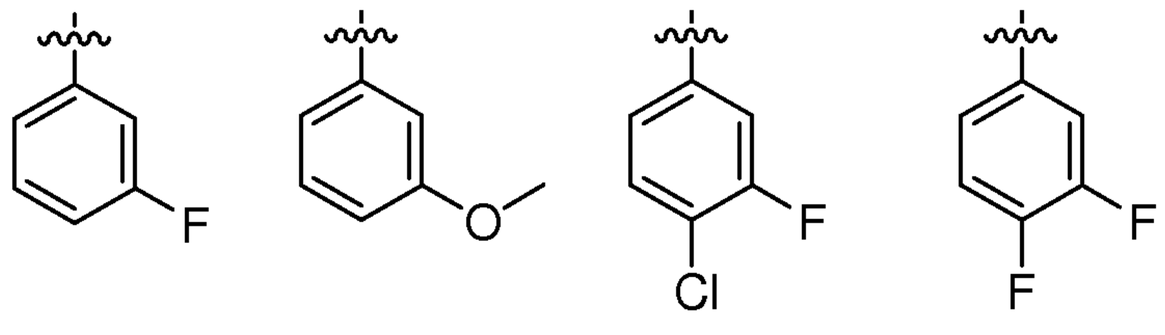
in particular when t denotes 1 or 2, preferably denotes 1 or 2, and A denotes CH or $C(CH_3)$.

Most preferred, the part structure (TS2)



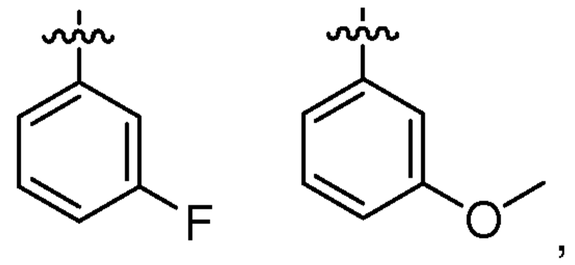
(TS2),

is selected from the group consisting of



in particular when t denotes 1 or 2, preferably denotes 1 or 2, and A denotes CH or $C(CH_3)$,

preferably is selected from the group consisting of



in particular when t denotes 1 or 2, preferably denotes 1 or 2, and A denotes CH or $C(CH_3)$.

In another preferred embodiment of the compound according to the present invention

R^2 represents CF_3, methyl, ethyl, n-propyl, 2-propyl, n-butyl, iso-butyl, sec.-butyl, tert.-butyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

Preferably,

R^2 represents CF_3, 2-propyl, n-butyl, iso-butyl, sec.-butyl, tert.-butyl, cyclopropyl, or cyclobutyl.

More preferably,

R^2 represents CF_3, tert.-butyl or cyclopropyl.

In a particularly preferred embodiment of the compound according to the present invention R^2 represents CF_3.

In another particularly preferred embodiment of the compound according to the present invention R^2 represents tert.-butyl.

In another particularly preferred embodiment of the compound according to the present invention R^2 represents cyclopropyl.

In a further preferred embodiment of the compound according to the present invention

R^7 and R^9 are independently of one another selected from the group consisting of H, F, Cl, Br, CF_3, CN, OH, OCF_3, CH_3, CH_2CH_3, $CH(CH_3)_2$, O-CH_3, and O-CH_2CH_3.

Preferably,

R^7 and R^9 are independently of one another selected from the group consisting of H, F, Cl, CF_3, CN, OH, OCF_3, CH_3, O-CH_3, and O-CH_2CH_3.

More preferably,

R^7 and R^9 are independently of one another selected from the group consisting of H, F, Cl, CF_3, O-CH_3, and O-CH_2CH_3.

Even more preferably,

R^7 and R^9 are independently of one another selected from the group consisting of H, F, Cl, and O-CH_3, still more preferably are independently of one another selected from the group consisting of H, F and Cl.

In yet a further preferred embodiment of the compound according to the present invention at least one of R^7 and R^9 is ≠ H.

In a further preferred embodiment of the compound according to the present invention R^9 denotes H.

In yet another preferred embodiment of the compound according to the present invention

R^7 is selected from the group consisting of F, Cl, Br, CF_3, CN, OH, OCF_3, CH_3, CH_2CH_3, $CH(CH_3)_2$, O-CH_3, and O-CH_2CH_3, preferably is selected from the group consisting of F, Cl, CF_3, CN, OH, OCF_3, CH_3, O-CH_3, and O-CH_2CH_3, more preferably is selected from the group consisting of F, Cl, CF_3, O-CH_3, and O-CH_2CH_3, even more preferably is selected from the group consisting of F, Cl, and O-CH_3, still more preferably is selected from the group consisting of F and Cl,

and R^9 represents H.

In another preferred embodiment of the compound according to the present invention

A denotes N or C(CH_3).

In a particularly preferred embodiment of the compound according to the present invention A denotes N.

In another particularly preferred embodiment of the compound according to the present invention A denotes $C(CH_3)$.

In another preferred embodiment of the compound according to the present invention

t denotes 1 or 2.

In a particularly preferred embodiment of the compound according to the present invention

t denotes 1.

In another particularly preferred embodiment of the compound according to the present invention

t denotes 2.

In a further preferred embodiment of the compound according to the present invention

t denotes 1 or 2, preferably 1,

A denotes N,

R^{101} is selected from the group consisting of H, F, Cl, Br, CFH_2, CF_2H, CF_3, CN, CH_2-OH, CH_2-OCH_3, OCF_3, OH, CH_3, CH_2CH_3, $CH(CH_3)_2$, O-CH_3, O-CH_2CH_3, NH_2, $NH(CH_3)$ and $N(CH_3)_2$; preferably is selected from the group consisting of H, F, Cl, CFH_2, CF_2H, CF_3, CN, CH_2-OCH_3, OCF_3, CH_3, O-CH_3, O-CH_2CH_3 and $N(CH_3)_2$; more preferably is selected from the group consisting of H, F, Cl, CFH_2, CF_2H, CF_3, OCF_3, CH_3, O-CH_3, and O-CH_2CH_3; even more preferably is selected from the group consisting of H, F, Cl, CF_3, OCF_3, CH_3 and O-CH_3; still more preferably is selected from the group consisting of H, F, Cl, CF_3 and O-CH_3; in particular is selected from the group consisting of H, F, Cl, and O-CH_3; most preferred denotes F or Cl;

and

R^{102} and R^{103} are independently of one another selected from the group consisting of H, F, Cl, Br, CFH_2, CF_2H, CF_3, CN, CH_2-OH, CH_2-OCH_3, OCF_3, OH, CH_3, CH_2CH_3,

$CH(CH_3)_2$, O-CH_3, O-CH_2CH_3, NH_2, $NH(CH_3)$ and $N(CH_3)_2$; preferably are independently of one another selected from the group consisting of H, F, Cl, CFH_2, CF_2H, CF_3, CN, CH_2-OCH_3, OCF_3, CH_3, O-CH_3, O-CH_2CH_3 and $N(CH_3)_2$; more preferably are independently of one another selected from the group consisting of H, F, Cl, CFH_2, CF_2H, CF_3, OCF_3, CH_3, O-CH_3, and O-CH_2CH_3; even more preferably are independently of one another selected from the group consisting of H, F, Cl, CF_3, OCF_3, CH_3 and O-CH_3; still more preferably are independently of one another selected from the group consisting of H, F, Cl, CF_3 and O-CH_3; in particular are independently of one another selected from the group consisting of H, F, Cl, and O-CH_3; most preferred denote independently of one another F or Cl;

or

t denotes 0, 1 or 2, preferably 1 or 2, more preferably 1,

A denotes CH or $C(CH_3)$, preferably $C(CH_3)$,

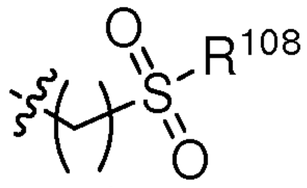
R^{101} is selected from the group consisting of H, F, Br, CFH_2, CF_2H, CF_3, CN, CH_2-OH, CH_2-OCH_3, OCF_3, OH, CH_3, CH_2CH_3, $CH(CH_3)_2$, O-CH_3, O-CH_2CH_3, NH_2, $NH(CH_3)$ and $N(CH_3)_2$; preferably is selected from the group consisting of H, F, CFH_2, CF_2H, CF_3, CN, CH_2-OCH_3, OCF_3, CH_3, O-CH_3, O-CH_2CH_3 and $N(CH_3)_2$; more preferably is selected from the group consisting of H, F, CFH_2, CF_2H, CF_3, OCF_3, CH_3, O-CH_3, and O-CH_2CH_3; even more preferably is selected from the group consisting of H, F, CF_3, OCF_3, CH_3 and O-CH_3; still more preferably is selected from the group consisting of H, F, CF_3 and O-CH_3; in particular is selected from the group consisting of H, F and O-CH_3; most preferred denotes F;

and

R^{102} and R^{103} are independently of one another selected from the group consisting of H, F, Cl, Br, CFH_2, CF_2H, CF_3, CN, CH_2-OH, CH_2-OCH_3, OCF_3, OH, CH_3, CH_2CH_3, $CH(CH_3)_2$, O-CH_3, O-CH_2CH_3, NH_2, $NH(CH_3)$ and $N(CH_3)_2$; preferably are independently of one another selected from the group consisting of H, F, Cl, CFH_2, CF_2H, CF_3, CN, CH_2-OCH_3, OCF_3, CH_3, O-CH_3, O-CH_2CH_3 and $N(CH_3)_2$; more preferably are independently of one another selected from the group consisting of H, F, Cl, CFH_2, CF_2H, CF_3, OCF_3, CH_3, O-CH_3, and O-CH_2CH_3; even more preferably are independently of one another selected from the group consisting of H, F, Cl, CF_3, OCF_3, CH_3 and O-CH_3; still more preferably are independently of one another selected from the group consisting of H, F, Cl, CF_3 and O-CH_3;

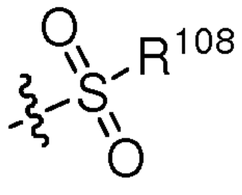
in particular are independently of one another selected from the group consisting of H, F, Cl, and O-CH_3; most preferred denote independently of one another F or Cl.

In a further preferred embodiment of the compound according to the present invention the part structure (TS1)

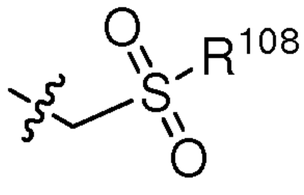


(TS1)

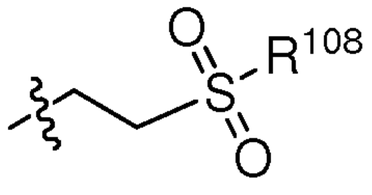
represents the part structure (PT1), (PT2) or (PT3),



(PT1),



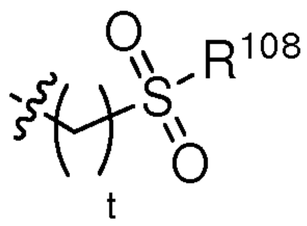
(PT2),



(PT3),

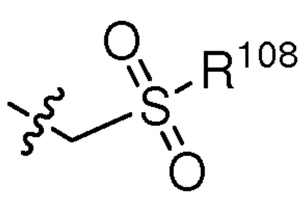
wherein R^{108} represents an unsubstituted C_{1-4} alkyl, preferably CH_3 or CH_2CH_3, more preferably CH_3.

Preferably, the part structure (TS1)

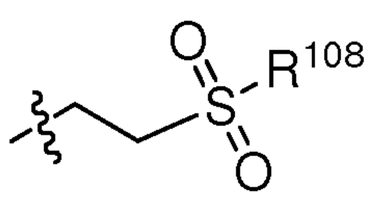


(TS1)

represents the part structure (PT2) or (PT3),



(PT2),



(PT3),

wherein R^{108} represents CH_3 or CH_2CH_3, preferably CH_3.

In a particularly preferred embodiment of the compound according to the present invention the

A denotes N,

and R^{101} is selected from the group consisting of H, F, Cl, Br, CFH_2, CF_2H, CF_3, CN, CH_2-OH, CH_2-OCH_3, OCF_3, OH, CH_3, CH_2CH_3, $CH(CH_3)_2$, O-CH_3, O-CH_2CH_3, NH_2, $NH(CH_3)$, and $N(CH_3)_2$,

and R^{102} and R^{103} are independently of one another selected from the group consisting of H, F, Cl, Br, CFH_2, CF_2H, CF_3, CN, CH_2-OH, CH_2-OCH_3, OCF_3, OH, CH_3, CH_2CH_3, $CH(CH_3)_2$, O-CH_3, O-CH_2CH_3, NH_2, $NH(CH_3)$, and $N(CH_3)_2$,

preferably, wherein at least one of R^{101}, R^{102} and R^{103} is ≠ H,

or

A denotes CH or $C(CH_3)$, preferably $C(CH_3)$,

and R^{101} is selected from the group consisting of H, F, Br, CFH_2, CF_2H, CF_3, CN, CH_2-OH, CH_2-OCH_3, OCF_3, OH, CH_3, CH_2CH_3, $CH(CH_3)_2$, O-CH_3, O-CH_2CH_3, NH_2, $NH(CH_3)$, and $N(CH_3)_2$,

and R^{102} and R^{103} are independently of one another selected from the group consisting of H, F, Cl, Br, CFH_2, CF_2H, CF_3, CN, CH_2-OH, CH_2-OCH_3, OCF_3, OH, CH_3, CH_2CH_3, $CH(CH_3)_2$, O-CH_3, O-CH_2CH_3, NH_2, $NH(CH_3)$, and $N(CH_3)_2$,

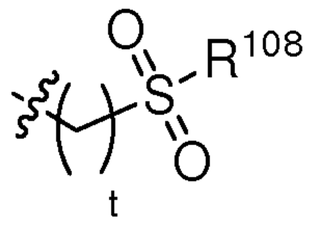
preferably, wherein at least one of R^{101}, R^{102} and R^{103} is ≠ H,

R^2 represents CF_3, tert.-butyl or cyclopropyl,

R^7 and R^9 are independently of one another selected from the group consisting of H, F, Cl, Br, CF_3, CN, OH, OCF_3, CH_3, CH_2CH_3, $CH(CH_3)_2$, O-CH_3, and O-CH_2CH_3,

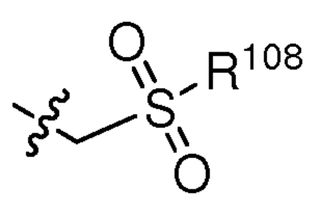
preferably, wherein at least one of R^7 and R^9 is ≠ H,

the part structure (TS1)

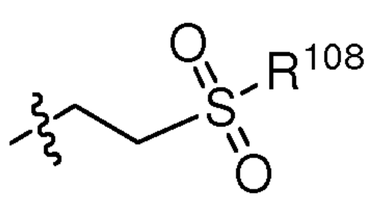


(TS1)

represents the part structure (PT2) or (PT3),



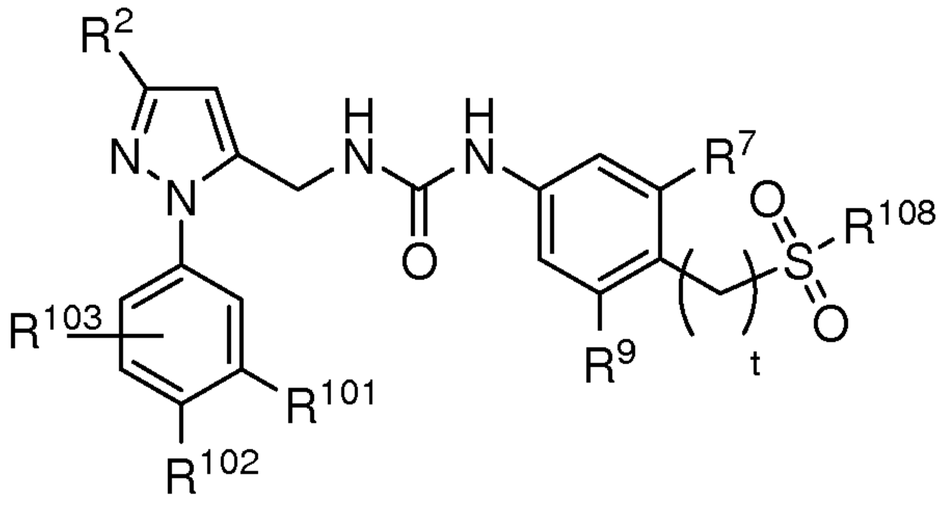
(PT2),



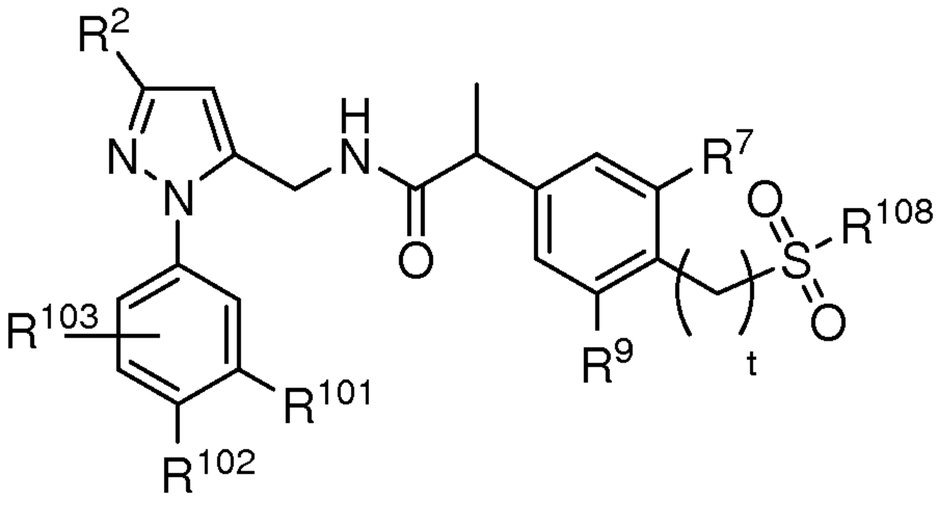
(PT3)

wherein R^{108} represents CH_3 or CH_2CH_3, preferably CH_3.

Preferred embodiments of the compound according to the invention of general formula (T) have general formulae (T0-a) and/or (T0-b):



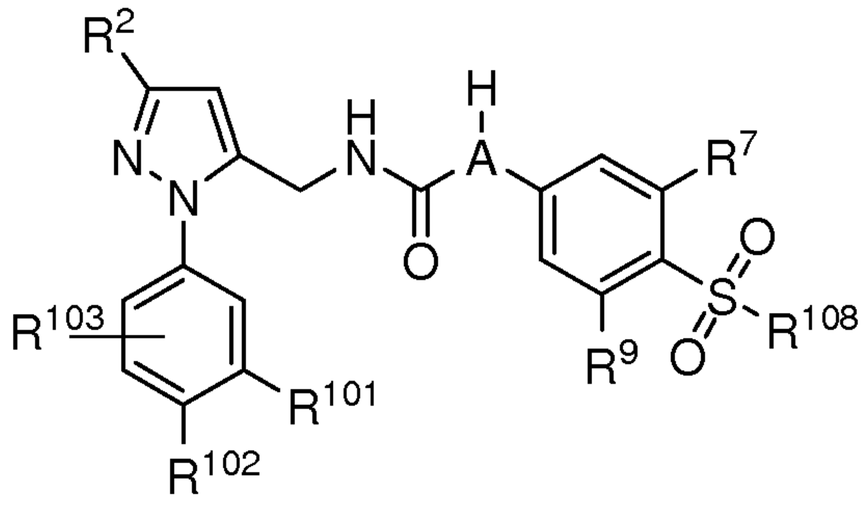
(T0-a)



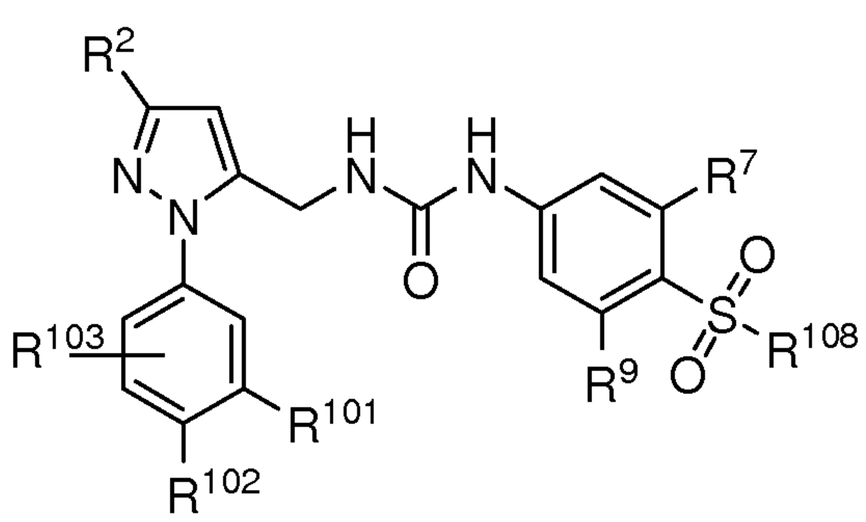
(T0-b),

wherein the particular radicals, variables and indices have the meanings described herein in connection with the compounds according to the invention and preferred embodiments thereof.

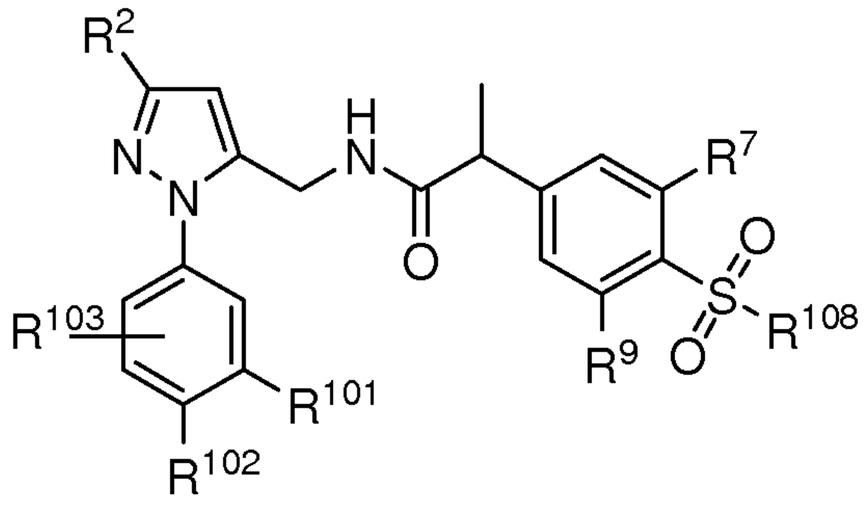
Further preferred embodiments of the compound according to the invention of general formula (T) have general formulae (T1-a), (T1-a-1) and/or (T1-a-2):



(T1-a),



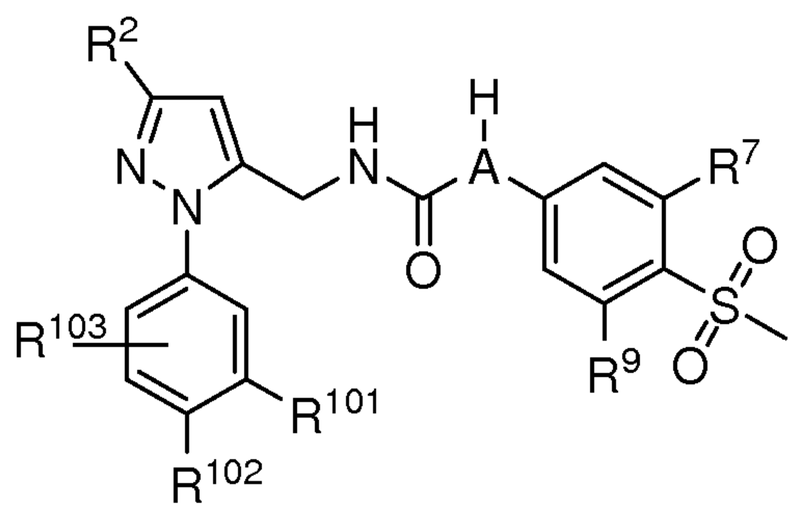
(T1-a-1),



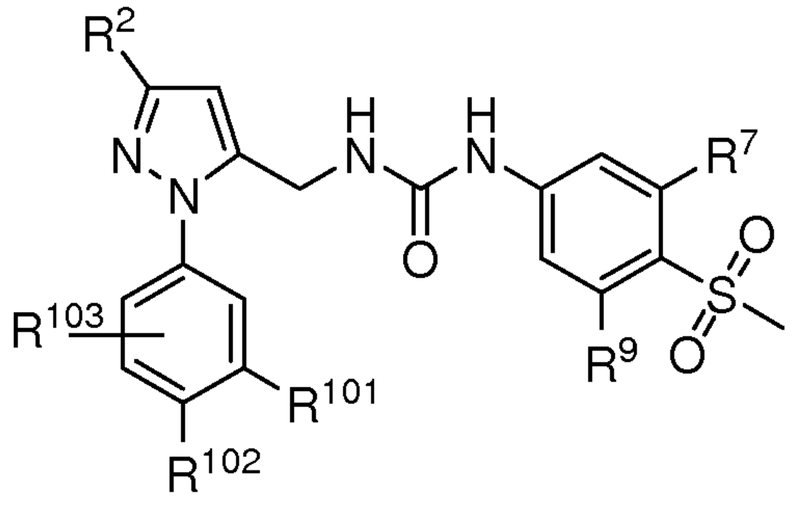
(T1-a-2),

wherein the particular radicals, variables and indices have the meanings described herein in connection with the compounds according to the invention and preferred embodiments thereof.

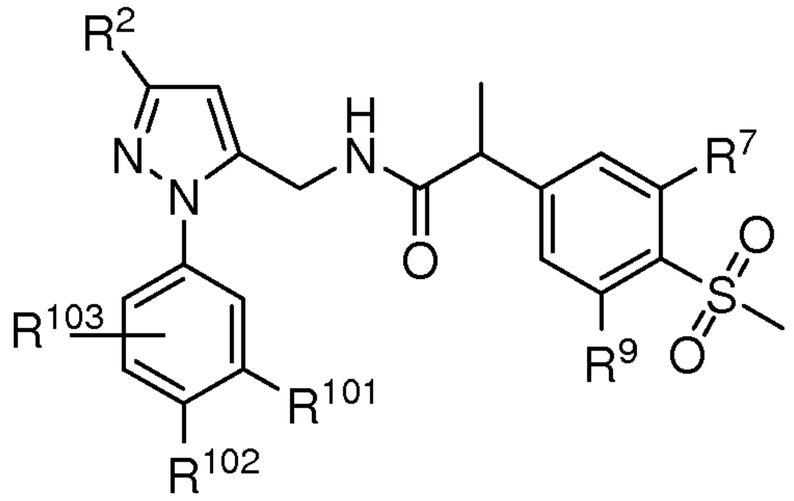
Moreover, preferred embodiments of the compound according to the invention of general formula (T) have general formulae (T1-b), (T1-b-1) and/or (T1-b-2):



(T1-b),



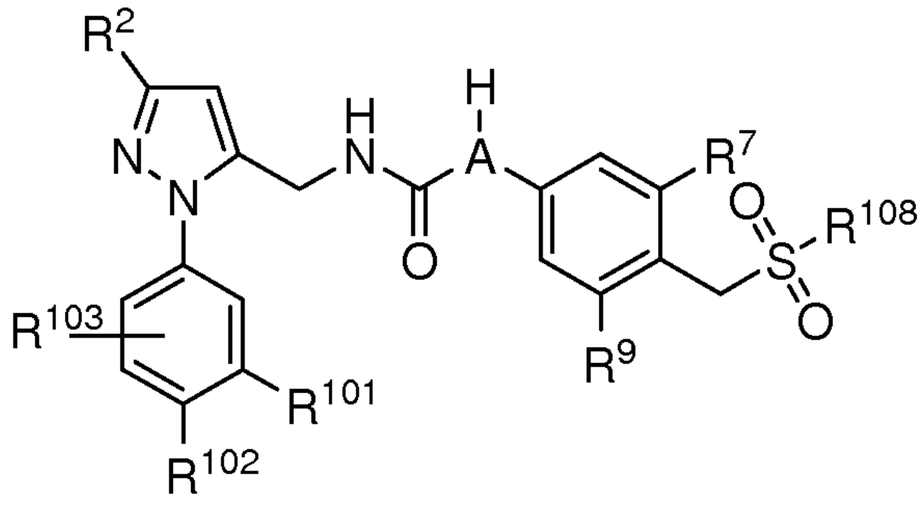
(T1-b-1),



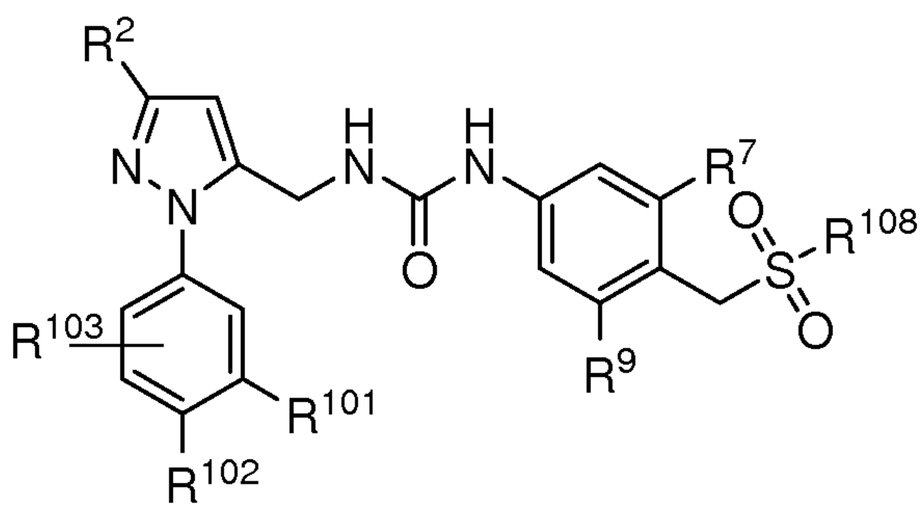
(T1-b-2),

wherein the particular radicals, variables and indices have the meanings described herein in connection with the compounds according to the invention and preferred embodiments thereof.

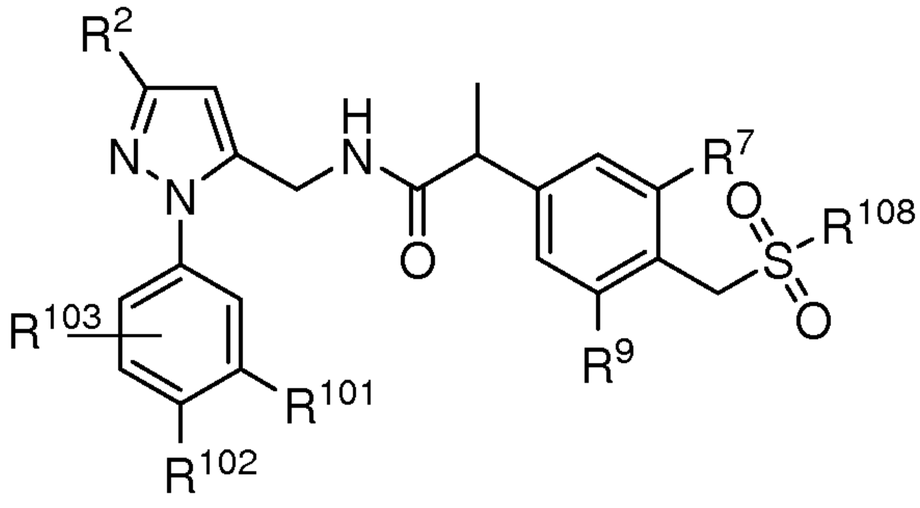
Further preferred embodiments of the compound according to the invention of general formula (T) have general formulae (T2-a), (T2-a-1) and/or (T2-a-2):



(T2-a),



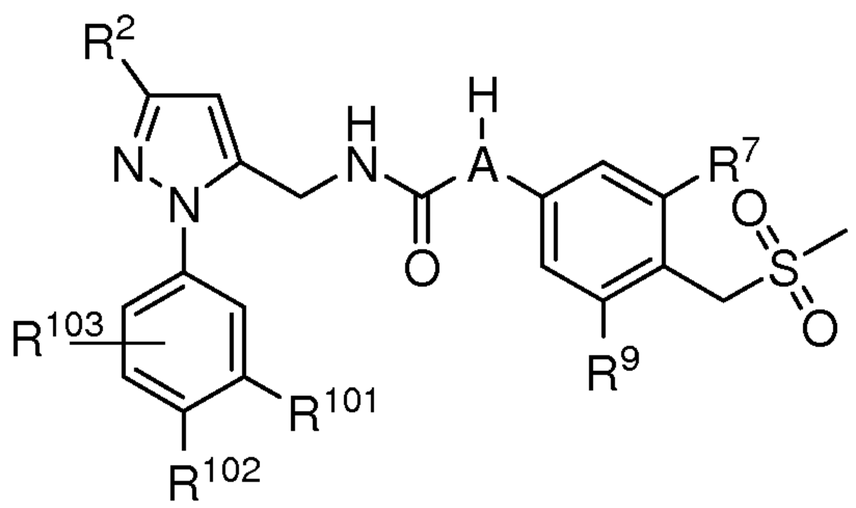
(T2-a-1),



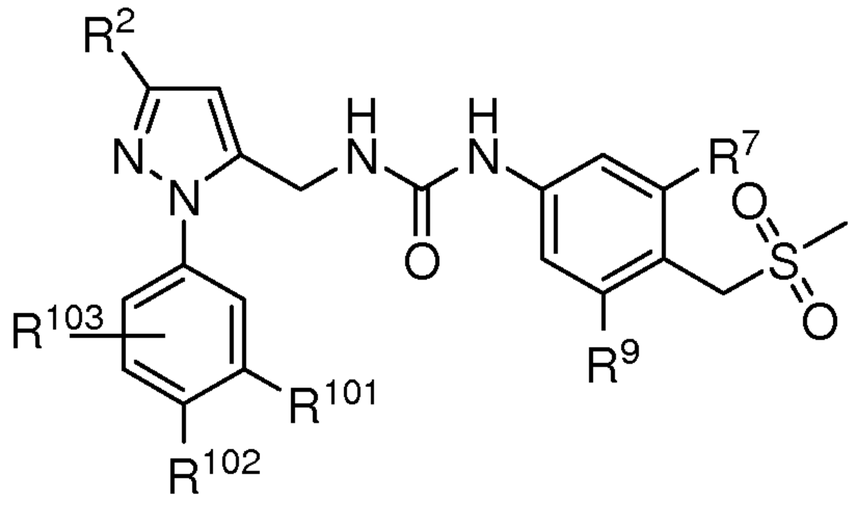
(T2-a-2),

wherein the particular radicals, variables and indices have the meanings described herein in connection with the compounds according to the invention and preferred embodiments thereof.

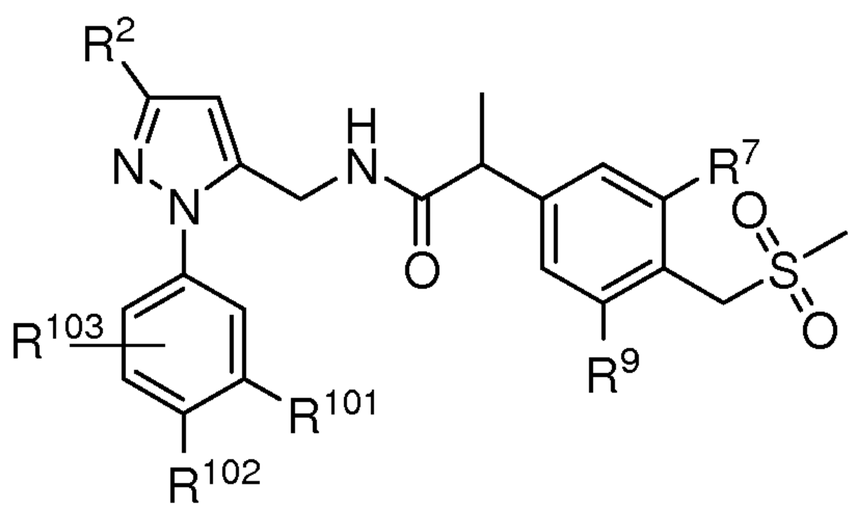
Moreover, preferred embodiments of the compound according to the invention of general formula (T) have general formulae (T2-b), (T2-b-1) and/or (T2-b-2):



(T2-b),



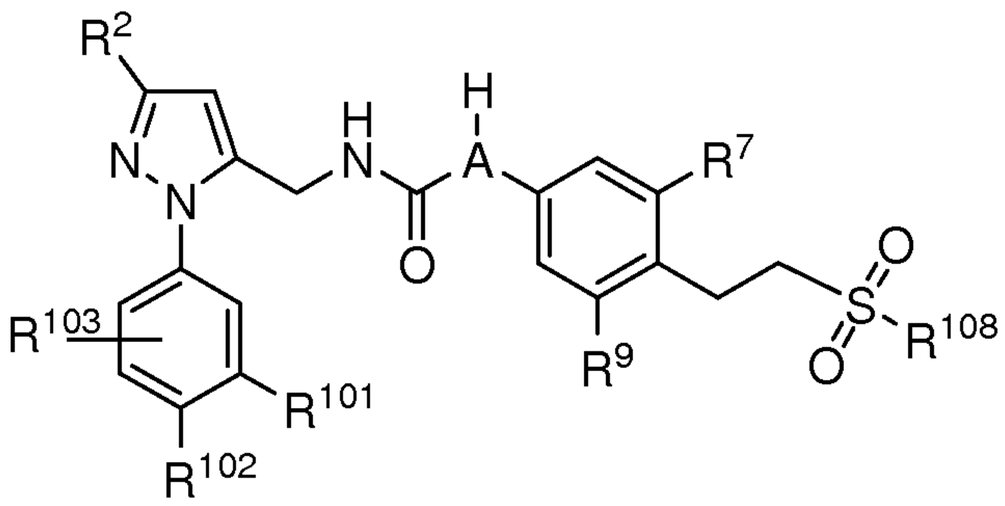
(T2-b-1),



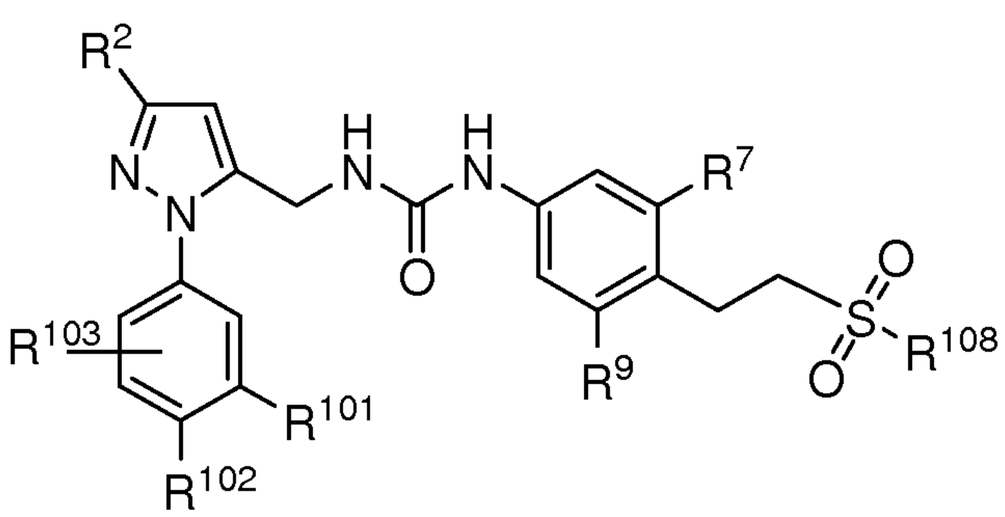
(T2-b-2),

wherein the particular radicals, variables and indices have the meanings described herein in connection with the compounds according to the invention and preferred embodiments thereof.

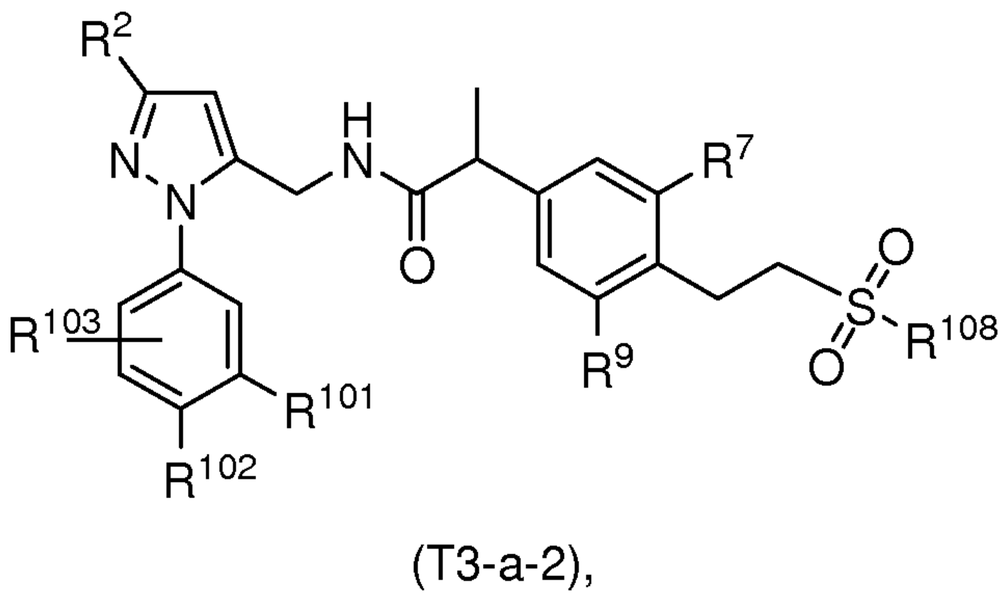
Further preferred embodiments of the compound according to the invention of general formula (T) have general formulae (T3-a), (T3-a-1) and/or (T3-a-2):



(T3-a),



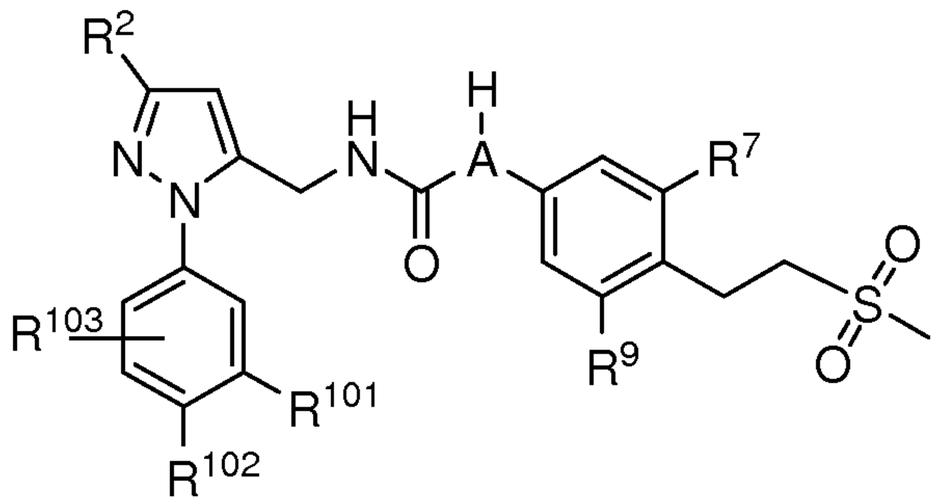
(T3-a-1),



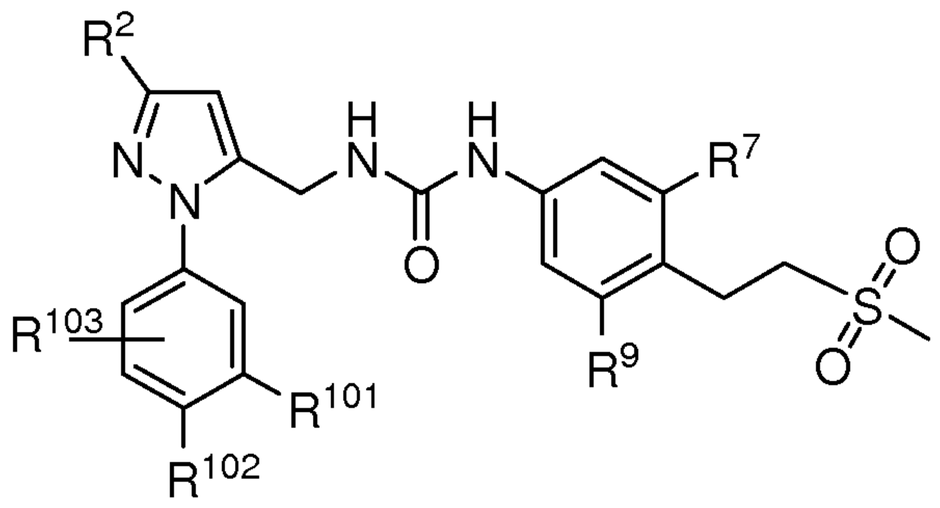
(T3-a-2),

wherein the particular radicals, variables and indices have the meanings described herein in connection with the compounds according to the invention and preferred embodiments thereof.

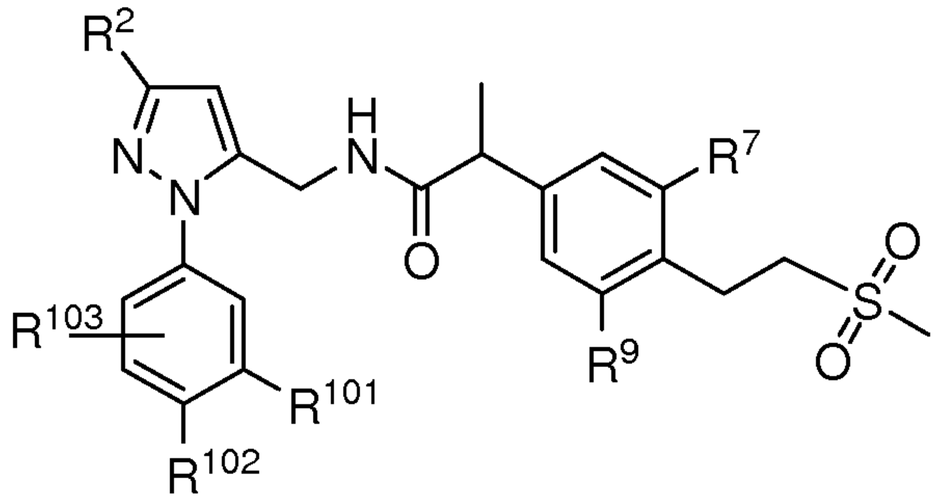
Moreover, preferred embodiments of the compound according to the invention of general formula (T) have general formulae (T3-b), (T3-b-1) and/or (T3-b-2):



(T3-b),



(T3-b-1),



(T3-b-2),

wherein the particular radicals, variables and indices have the meanings described herein in connection with the compounds according to the invention and preferred embodiments thereof.

Especially preferred embodiments of the compound of the present invention have general formulae (T2-a), (T2-a-1), (T2-a-2), (T2-b), (T2-b-1) (T2-b-2), (T3-a), (T3-a-1), (T3-a-2), (T3-b), (T3-b-1) and/or (T3-b-2).

In particularly preferred embodiments of the present invention radical R^{101} in the compound of general formula (T), (T0-a), (T0-b), (T1-a), (T1-a-1), (T1-a-2), (T1-b), (T1-b-1), (T1-b-2), (T2-a), (T2-a-1), (T2-a-2), (T2-b), (T2-b-1), (T2-b-2), (T3-a), (T3-a-1), (T3-a-2), (T3-b), (T3-b-

1), and/or (T3-b-2), represents F, Cl, CF_3 or O-CH_3, preferably F or Cl, most preferably Cl – preferably when R^{103} is H and R^{102} represents H, F, Cl, CF_3 or OCH_3, more preferably when R^{103} is H and R^{102} represents H, F or Cl, even more preferably when both R^{102} and R^{103} denote H -, and the remaining particular radicals, variables and indices have the meanings described herein in connection with the compounds according to the invention and preferred embodiments thereof.

In further particularly preferred embodiments of the present invention radical R^{101} in the compound of general formula (T), (T1-a), (T1-a-1), (T1-b), (T1-b-1), (T2-a), (T2-a-1), (T2-b), (T2-b-1), (T3-a), (T3-a-1), (T3-b) and/or (T3-b-1) represents F, Cl, CF_3 or O-CH_3, preferably F or Cl, most preferably Cl – preferably when R^{103} is H and R^{102} represents H, F, Cl, CF_3 or OCH_3, more preferably when R^{103} is H and R^{102} represents H, F or Cl, even more preferably when both R^{102} and R^{103} denote H - , and the remaining particular radicals, variables and indices have the meanings described herein in connection with the compounds according to the invention and preferred embodiments thereof.

In further particularly preferred embodiments of the present invention radical R^{101} in the compound of general formula (T), (T1-a), (T1-a-2), (T1-b), (T1-b-2), (T2-a), (T2-a-2), (T2-b), (T2-b-2), (T3-a), (T3-a-2), (T3-b) and/or (T3-b-2) represents F, CF_3 or O-CH_3, preferably F – preferably when R^{103} is H and R^{102} represents H, F, Cl, CF_3 or OCH_3, more preferably when R^{103} is H and R^{102} represents H, F or Cl, even more preferably when both R^{102} and R^{103} denote H - , and the remaining particular radicals, variables and indices have the meanings described herein in connection with the compounds according to the invention and preferred embodiments thereof.

Particularly preferred are compounds according to the invention from the group

D1 N-[[5-tert-Butyl-2-(3-chlorophenyl)-2H-pyrazol-3-yl]-methyl]-2-(3-fluoro-4-methylsulfonyl-phenyl)-propionamide;

D2 N-[[2-(3-Chlorophenyl)-5-(trifluoromethyl)-2H-pyrazol-3-yl]-methyl]-2-(3-fluoro-4-methylsulfonyl-phenyl)-propionamide;

D3 2-(3-Fluoro-4-methylsulfonyl-phenyl)-N-[[2-(3-fluorophenyl)-5-(trifluoromethyl)-2H-pyrazol-3-yl]-methyl]-propionamide;

D4 N-[[2-(3-Chloro-4-fluoro-phenyl)-5-(trifluoromethyl)-2H-pyrazol-3-yl]-methyl]-2-(3-fluoro-4-methylsulfonyl-phenyl)-propionamide;

D5 2-(3-Chloro-4-methylsulfonyl-phenyl)-N-[[2-(3-chlorophenyl)-5-(trifluoromethyl)-2H-pyrazol-3-yl]-methyl]-propionamide;

D6 N-[[2-(3-Chlorophenyl)-5-(trifluoromethyl)-2H-pyrazol-3-yl]-methyl]-2-[3-fluoro-4-(methylsulfonyl-methyl)-phenyl]-propionamide;

D7 N-[[5-tert-Butyl-2-(3-chlorophenyl)-2H-pyrazol-3-yl]-methyl]-2-[3-fluoro-4-(methylsulfonyl-methyl)-phenyl]-propionamide;

D8 N-[[5-tert-Butyl-2-(3-chloro-4-fluoro-phenyl)-2H-pyrazol-3-yl]-methyl]-2-[3-fluoro-4-(methylsulfonyl-methyl)-phenyl]-propionamide;

D9 N-[[5-tert-Butyl-2-(3-fluorophenyl)-2H-pyrazol-3-yl]-methyl]-2-[3-fluoro-4-(methylsulfonyl-methyl)-phenyl]-propionamide;

D10 2-[3-Fluoro-4-(methylsulfonyl-methyl)-phenyl]-N-[[2-(3-fluorophenyl)-5-(trifluoromethyl)-2H-pyrazol-3-yl]-methyl]-propionamide;

D11 N-[[5-tert-Butyl-2-(4-fluorophenyl)-2H-pyrazol-3-yl]-methyl]-2-[3-fluoro-4-(methylsulfonyl-methyl)-phenyl]-propionamide;

D12 2-[3-Fluoro-4-(methylsulfonyl-methyl)-phenyl]-N-[[2-(4-fluorophenyl)-5-(trifluoromethyl)-2H-pyrazol-3-yl]-methyl]-propionamide;

D13 N-[[5-tert-Butyl-2-(3,4-difluoro-phenyl)-2H-pyrazol-3-yl]-methyl]-2-[3-fluoro-4-(methylsulfonyl-methyl)-phenyl]-propionamide;

D14 N-[[2-(3,4-Difluoro-phenyl)-5-(trifluoromethyl)-2H-pyrazol-3-yl]-methyl]-2-[3-fluoro-4-(methylsulfonyl-methyl)-phenyl]-propionamide;

D15 N-[[2-(3,5-Difluoro-phenyl)-5-(trifluoromethyl)-2H-pyrazol-3-yl]-methyl]-2-[3-fluoro-4-(methylsulfonyl-methyl)-phenyl]-propionamide;

D16 N-[[5-tert-Butyl-2-[3-(methoxymethyl)-phenyl]-2H-pyrazol-3-yl]-methyl]-2-[3-fluoro-4-(methylsulfonyl-methyl)-phenyl]-propionamide;

D17 N-[[5-tert-Butyl-2-(3-dimethylamino-phenyl)-2H-pyrazol-3-yl]-methyl]-2-[3-fluoro-4-(methylsulfonyl-methyl)-phenyl]-propionamide;

D18 N-[[5-tert-Butyl-2-(3-fluoro-5-methyl-phenyl)-2H-pyrazol-3-yl]-methyl]-2-[3-fluoro-4-(methylsulfonyl-methyl)-phenyl]-propionamide;

D19 N-[[5-tert-Butyl-2-(3-cyano-phenyl)-2H-pyrazol-3-yl]-methyl]-2-[3-fluoro-4-(methylsulfonyl-methyl)-phenyl]-propionamide;

D20 N-[[5-tert-Butyl-2-[3-(difluoro-methyl)-phenyl]-2H-pyrazol-3-yl]-methyl]-2-[3-fluoro-4-(methylsulfonyl-methyl)-phenyl]-propionamide;

D21 N-[[5-tert-Butyl-2-(3-methoxyphenyl)-2H-pyrazol-3-yl]-methyl]-2-[3-fluoro-4-(methylsulfonyl-methyl)-phenyl]-propionamide;

D22 2-[3-Fluoro-4-(methylsulfonyl-methyl)-phenyl]-N-[[2-(3-methoxyphenyl)-5-(trifluoromethyl)-2H-pyrazol-3-yl]-methyl]-propionamide;

D23 N-[[5-tert-Butyl-2-[3-(trifluoromethyl)phenyl]-2H-pyrazol-3-yl]-methyl]-2-[3-fluoro-4-(methylsulfonyl-methyl)-phenyl]-propionamide;

D24 N-[[5-tert-Butyl-2-(m-tolyl)-2H-pyrazol-3-yl]-methyl]-2-[3-fluoro-4-(methylsulfonyl-methyl)-phenyl]-propionamide;

D25 2-[3-Fluoro-4-(methylsulfonyl-methyl)-phenyl]-N-[[2-(4-methoxyphenyl)-5-(trifluoromethyl)-2H-pyrazol-3-yl]-methyl]-propionamide;

D26 1-[[2-(3-Chlorophenyl)-5-cyclopropyl-2H-pyrazol-3-yl]-methyl]-3-[3-fluoro-4-(2-methylsulfonyl-ethyl)-phenyl]-urea;

D27 1-[[2-(3-Chlorophenyl)-5-(trifluoromethyl)-2H-pyrazol-3-yl]-methyl]-3-[3-fluoro-4-(2-methylsulfonyl-ethyl)-phenyl]-urea;

D28 1-[[2-(3-Chloro-4-fluoro-phenyl)-5-(trifluoromethyl)-2H-pyrazol-3-yl]-methyl]-3-[3-fluoro-4-(2-methylsulfonyl-ethyl)-phenyl]-urea;

D29 1-[[5-tert-Butyl-2-(3-chlorophenyl)-2H-pyrazol-3-yl]-methyl]-3-[3-fluoro-4-(2-methylsulfonyl-ethyl)-phenyl]-urea;

D30 1-[[5-tert-Butyl-2-(3-fluorophenyl)-2H-pyrazol-3-yl]-methyl]-3-[3-fluoro-4-(2-methylsulfonyl-ethyl)-phenyl]-urea;

D31 1-[[5-tert-Butyl-2-(3,5-difluoro-phenyl)-2H-pyrazol-3-yl]-methyl]-3-[3-fluoro-4-(2-methylsulfonyl-ethyl)-phenyl]-urea;

D32 1-[3-Fluoro-4-(2-methylsulfonyl-ethyl)-phenyl]-3-[[2-(m-tolyl)-5-(trifluoromethyl)-2H-pyrazol-3-yl]-methyl]-urea; and

D33 1-[3-Fluoro-4-(2-methylsulfonyl-ethyl)-phenyl]-3-[[2-(3-isopropyl-phenyl)-5-(trifluoromethyl)-2H-pyrazol-3-yl]-methyl]-urea;

optionally in the form of a single stereoisomer or a mixture of stereoisomers, in the form of the free compound and/or a physiologically acceptable salt thereof.

Furthermore, preference may be given to compounds according to the invention that cause a 50% displacement of capsaicin, which is present at a concentration of 100 nM, in a FLIPR assay with CHO K1 cells which were transfected with the human VR1 gene at a concentration of less than 2 000 nM, preferably less than 1 000 nM, particularly preferably less than 300 nM, most particularly preferably less than 100 nM, even more preferably less than 75 nM, additionally preferably less than 50 nM, most preferably less than 10 nM.

In the process, the Ca^{2+} influx is quantified in the FLIPR assay with the aid of a Ca^{2+}-sensitive dye (type Fluo-4, Molecular Probes Europe BV, Leiden, the Netherlands) in a fluorescent imaging plate reader (FLIPR, Molecular Devices, Sunnyvale, USA), as described hereinafter.

The substituted compounds according to the invention and corresponding stereoisomers and also the respective corresponding acids, bases, salts and solvates are toxicologically safe and are therefore suitable as pharmaceutical active ingredients in pharmaceutical compositions.

The present invention therefore further relates to a pharmaceutical composition containing at least one compound according to the invention, in each case if appropriate in the form of one of its pure stereoisomers, in particular enantiomers or diastereomers, its racemates or in the form of a mixture of stereoisomers, in particular the enantiomers and/or diastereomers, in any desired mixing ratio, or respectively in the form of a corresponding salt, or respectively in the form of a corresponding solvate, and also if appropriate one or more pharmaceutically compatible auxiliaries.

These pharmaceutical compositions according to the invention are suitable in particular for vanilloid receptor 1-(VR1/TRPV1) regulation, preferably for vanilloid receptor 1-(VR1/TRPV1) inhibition and/or for vanilloid receptor 1-(VR1/TRPV1) stimulation, i.e. they exert an agonistic or antagonistic effect.

Likewise, the pharmaceutical compositions according to the invention are preferably suitable for the prophylaxis and/or treatment of disorders or diseases which are mediated, at least in part, by vanilloid receptors 1.

The pharmaceutical composition according to the invention is suitable for administration to adults and children, including toddlers and babies.

The pharmaceutical composition according to the invention may be found as a liquid, semisolid or solid pharmaceutical form, for example in the form of injection solutions, drops, juices, syrups, sprays, suspensions, tablets, patches, capsules, plasters, suppositories, ointments, creams, lotions, gels, emulsions, aerosols or in multiparticulate form, for example in the form of pellets or granules, if appropriate pressed into tablets, decanted in capsules or suspended in a liquid, and also be administered as much.

In addition to at least one substituted compound according to the invention, if appropriate in the form of one of its pure stereoisomers, in particular enantiomers or diastereomers, its racemate or in the form of mixtures of the stereoisomers, in particular the enantiomers or diastereomers, in any desired mixing ratio, or if appropriate in the form of a corresponding salt or respectively in the form of a corresponding solvate, the pharmaceutical composition

according to the invention conventionally contains further physiologically compatible pharmaceutical auxiliaries which can for example be selected from the group consisting of excipients, fillers, solvents, diluents, surface-active substances, dyes, preservatives, blasting agents, slip additives, lubricants, aromas and binders.

The selection of the physiologically compatible auxiliaries and also the amounts thereof to be used depend on whether the pharmaceutical composition is to be applied orally, subcutaneously, parenterally, intravenously, intraperitoneally, intradermally, intramuscularly, intranasally, buccally, rectally or locally, for example to infections of the skin, the mucous membranes and of the eyes. Preparations in the form of tablets, dragées, capsules, granules, pellets, drops, juices and syrups are preferably suitable for oral application; solutions, suspensions, easily reconstitutable dry preparations and also sprays are preferably suitable for parenteral, topical and inhalative application. The substituted compounds according to the invention used in the pharmaceutical composition according to the invention in a repository in dissolved form or in a plaster, agents promoting skin penetration being added if appropriate, are suitable percutaneous application preparations. Orally or percutaneously applicable preparation forms can release the respective substituted compound according to the invention also in a delayed manner.

The pharmaceutical compositions according to the invention are prepared with the aid of conventional means, devices, methods and process known in the art, such as are described for example in „Remington's Pharmaceutical Sciences", A.R. Gennaro (Editor), 17th edition, Mack Publishing Company, Easton, Pa, 1985, in particular in Part 8, Chapters 76 to 93. The corresponding description is introduced herewith by way of reference and forms part of the disclosure. The amount to be administered to the patient of the respective substituted compounds according to the invention of the above-indicated general formula I may vary and is for example dependent on the patient's weight or age and also on the type of application, the indication and the severity of the disorder. Conventionally 0.001 to 100 mg/kg, preferably 0.05 to 75 mg/kg, particularly preferably 0.05 to 50 mg of at least one such compound according to the invention are applied per kg of the patient's body weight.

The pharmaceutical composition according to the invention is preferably suitable for the treatment and/or prophylaxis of one or more disorders and/or diseases selected from the group consisting of pain, preferably pain selected from the group consisting of acute pain, chronic pain, neuropathic pain, visceral pain and joint pain; hyperalgesia; allodynia; causalgia; migraine; depression; nervous affection; axonal injuries; neurodegenerative diseases, preferably selected from the group consisting of multiple sclerosis, Alzheimer's

disease, Parkinson's disease and Huntington's disease; cognitive dysfunctions, preferably cognitive deficiency states, particularly preferably memory disorders; epilepsy; respiratory diseases, preferably selected from the group consisting of asthma, bronchitis and pulmonary inflammation; coughs; urinary incontinence; overactive bladder (OAB); disorders and/or injuries of the gastrointestinal tract; duodenal ulcers; gastric ulcers; irritable bowel syndrome; strokes; eye irritations; skin irritations; neurotic skin diseases; allergic skin diseases; psoriasis; vitiligo; herpes simplex; inflammations, preferably inflammations of the intestine, the eyes, the bladder, the skin or the nasal mucous membrane; diarrhoea; pruritus; osteoporosis; arthritis; osteoarthritis; rheumatic diseases; eating disorders, preferably selected from the group consisting of bulimia, cachexia, anorexia and obesity; medication dependency; misuse of medication; withdrawal symptoms in medication dependency; development of tolerance to medication, preferably to natural or synthetic opioids; drug dependency; misuse of drugs; withdrawal symptoms in drug dependency; alcohol dependency; misuse of alcohol and withdrawal symptoms in alcohol dependency; for diuresis; for antinatriuresis; for influencing the cardiovascular system; for increasing vigilance; for the treatment of wounds and/or burns; for the treatment of severed nerves; for increasing libido; for modulating movement activity; for anxiolysis; for local anaesthesia and/or for inhibiting undesirable side effects, preferably selected from the group consisting of hyperthermia, hypertension and bronchoconstriction, triggered by the administration of vanilloid receptor 1 (VR1/TRPV1 receptor) agonists, preferably selected from the group consisting of capsaicin, resiniferatoxin, olvanil, arvanil, SDZ-249665, SDZ-249482, nuvanil and capsavanil.

Particularly preferably, the pharmaceutical composition according to the invention is suitable for the treatment and/or prophylaxis of one or more disorders and/or diseases selected from the group consisting of pain, preferably of pain selected from the group consisting of acute pain, chronic pain, neuropathic pain, visceral pain and joint pain; migraine; depression; neurodegenerative diseases, preferably selected from the group consisting of multiple sclerosis, Alzheimer's disease, Parkinson's disease and Huntington's disease; cognitive dysfunctions, preferably cognitive deficiency states, particularly preferably memory disorders; inflammations, preferably inflammations of the intestine, the eyes, the bladder, the skin or the nasal mucous membrane; urinary incontinence; overactive bladder (OAB); medication dependency; misuse of medication; withdrawal symptoms in medication dependency; development of tolerance to medication, preferably development of tolerance to natural or synthetic opioids; drug dependency; misuse of drugs; withdrawal symptoms in drug dependency; alcohol dependency; misuse of alcohol and withdrawal symptoms in alcohol dependency.

Most particularly preferably, the pharmaceutical composition according to the invention is suitable for the treatment and/or prophylaxis of pain, preferably of pain selected from the group consisting of acute pain, chronic pain, neuropathic pain and visceral pain.

The present invention further relates to a substituted compound according to the present invention and also if appropriate to a substituted compound according to the present invention and one or more pharmaceutically acceptable auxiliaries for use in vanilloid receptor 1-(VR1/TRPV1) regulation, preferably for use in vanilloid receptor 1-(VR1/TRPV1) inhibition and/or vanilloid receptor 1-(VR1/TRPV1) stimulation.

The present invention therefore further relates to a substituted compound according to the present invention and also if appropriate to a substituted compound according to the present invention and one or more pharmaceutically acceptable auxiliaries for use in the prophylaxis and/or treatment of disorders and/or diseases which are mediated, at least in part, by vanilloid receptors 1.

In particular, the present invention therefore further relates to a substituted compound according to the present invention and also if appropriate to a substituted compound according to the present invention and one or more pharmaceutically acceptable auxiliaries for use in the prophylaxis and/or treatment of disorders and/or diseases selected from the group consisting of pain, preferably pain selected from the group consisting of acute pain, chronic pain, neuropathic pain, visceral pain and joint pain; hyperalgesia; allodynia; causalgia; migraine; depression; nervous affection; axonal injuries; neurodegenerative diseases, preferably selected from the group consisting of multiple sclerosis, Alzheimer's disease, Parkinson's disease and Huntington's disease; cognitive dysfunctions, preferably cognitive deficiency states, particularly preferably memory disorders; epilepsy; respiratory diseases, preferably selected from the group consisting of asthma, bronchitis and pulmonary inflammation; coughs; urinary incontinence; overactive bladder (OAB); disorders and/or injuries of the gastrointestinal tract; duodenal ulcers; gastric ulcers; irritable bowel syndrome; strokes; eye irritations; skin irritations; neurotic skin diseases; allergic skin diseases; psoriasis; vitiligo; herpes simplex; inflammations, preferably inflammations of the intestine, the eyes, the bladder, the skin or the nasal mucous membrane; diarrhoea; pruritus; osteoporosis; arthritis; osteoarthritis; rheumatic diseases; eating disorders, preferably selected from the group consisting of bulimia, cachexia, anorexia and obesity; medication dependency; misuse of medication; withdrawal symptoms in medication dependency; development of tolerance to medication, preferably to natural or synthetic opioids; drug

dependency; misuse of drugs; withdrawal symptoms in drug dependency; alcohol dependency; misuse of alcohol and withdrawal symptoms in alcohol dependency; for diuresis; for antinatriuresis; for influencing the cardiovascular system; for increasing vigilance; for the treatment of wounds and/or burns; for the treatment of severed nerves; for increasing libido; for modulating movement activity; for anxiolysis; for local anaesthesia and/or for inhibiting undesirable side effects, preferably selected from the group consisting of hyperthermia, hypertension and bronchoconstriction, triggered by the administration of vanilloid receptor 1 (VR1/TRPV1 receptor) agonists, preferably selected from the group consisting of capsaicin, resiniferatoxin, olvanil, arvanil, SDZ-249665, SDZ-249482, nuvanil and capsavanil.

Most particularly preferred is a substituted compound according to the present invention and also if appropriate to a substituted compound according to the present invention and one or more pharmaceutically acceptable auxiliaries for use in the prophylaxis and/or treatment of pain, preferably of pain selected from the group consisting of acute pain, chronic pain, neuropathic pain and visceral pain.

The present invention further relates to the use of at least one substituted compound according to the present invention and also if appropriate to the use of at least one substituted compound according to the present invention of one or more pharmaceutically acceptable auxiliaries for the preparation of a pharmaceutical composition for vanilloid receptor 1-(VR1/TRPV1) regulation, preferably for vanilloid receptor 1-(VR1/TRPV1) inhibition and/or for vanilloid receptor 1-(VR1/TRPV1) stimulation, and, further for the prophylaxis and/or treatment of disorders and/or diseases which are mediated, at least in part, by vanilloid receptors 1, such as e.g. disorders and/or diseases selected from the group consisting of pain, preferably pain selected from the group consisting of acute pain, chronic pain, neuropathic pain, visceral pain and joint pain; hyperalgesia; allodynia; causalgia; migraine; depression; nervous affection; axonal injuries; neurodegenerative diseases, preferably selected from the group consisting of multiple sclerosis, Alzheimer's disease, Parkinson's disease and Huntington's disease; cognitive dysfunctions, preferably cognitive deficiency states, particularly preferably memory disorders; epilepsy; respiratory diseases, preferably selected from the group consisting of asthma, bronchitis and pulmonary inflammation; coughs; urinary incontinence; overactive bladder (OAB); disorders and/or injuries of the gastrointestinal tract; duodenal ulcers; gastric ulcers; irritable bowel syndrome; strokes; eye irritations; skin irritations; neurotic skin diseases; allergic skin diseases; psoriasis; vitiligo; herpes simplex; inflammations, preferably inflammations of the intestine, the eyes, the bladder, the skin or the nasal mucous membrane; diarrhoea; pruritus;

osteoporosis; arthritis; osteoarthritis; rheumatic diseases; eating disorders, preferably selected from the group consisting of bulimia, cachexia, anorexia and obesity; medication dependency; misuse of medication; withdrawal symptoms in medication dependency; development of tolerance to medication, preferably to natural or synthetic opioids; drug dependency; misuse of drugs; withdrawal symptoms in drug dependency; alcohol dependency; misuse of alcohol and withdrawal symptoms in alcohol dependency; for diuresis; for antinatriuresis; for influencing the cardiovascular system; for increasing vigilance; for the treatment of wounds and/or burns; for the treatment of severed nerves; for increasing libido; for modulating movement activity; for anxiolysis; for local anaesthesia and/or for inhibiting undesirable side effects, preferably selected from the group consisting of hyperthermia, hypertension and bronchoconstriction, triggered by the administration of vanilloid receptor 1 (VR1/TRPV1 receptor) agonists, preferably selected from the group consisting of capsaicin, resiniferatoxin, olvanil, arvanil, SDZ-249665, SDZ-249482, nuvanil and capsavanil.

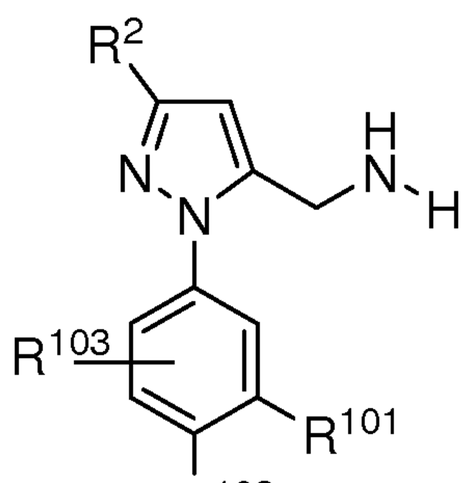
Another aspect of the present invention is a method for vanilloid receptor 1-(VR1/TRPV1) regulation, preferably for vanilloid receptor 1-(VR1/TRPV1) inhibition and/or for vanilloid receptor 1-(VR1/TRPV1) stimulation, and, further, a method of treatment and/or prophylaxis of disorders and/or diseases, which are mediated, at least in part, by vanilloid receptors 1, in a mammal, preferably of disorders and/or diseases selected from the group consisting of pain, preferably pain selected from the group consisting of acute pain, chronic pain, neuropathic pain, visceral pain and joint pain; hyperalgesia; allodynia; causalgia; migraine; depression; nervous affection; axonal injuries; neurodegenerative diseases, preferably selected from the group consisting of multiple sclerosis, Alzheimer's disease, Parkinson's disease and Huntington's disease; cognitive dysfunctions, preferably cognitive deficiency states, particularly preferably memory disorders; epilepsy; respiratory diseases, preferably selected from the group consisting of asthma, bronchitis and pulmonary inflammation; coughs; urinary incontinence; overactive bladder (OAB); disorders and/or injuries of the gastrointestinal tract; duodenal ulcers; gastric ulcers; irritable bowel syndrome; strokes; eye irritations; skin irritations; neurotic skin diseases; allergic skin diseases; psoriasis; vitiligo; herpes simplex; inflammations, preferably inflammations of the intestine, the eyes, the bladder, the skin or the nasal mucous membrane; diarrhoea; pruritus; osteoporosis; arthritis; osteoarthritis; rheumatic diseases; eating disorders, preferably selected from the group consisting of bulimia, cachexia, anorexia and obesity; medication dependency; misuse of medication; withdrawal symptoms in medication dependency; development of tolerance to medication, preferably to natural or synthetic opioids; drug dependency; misuse of drugs; withdrawal symptoms in drug dependency; alcohol dependency; misuse of alcohol and

withdrawal symptoms in alcohol dependency; for diuresis; for antinatriuresis; for influencing the cardiovascular system; for increasing vigilance; for the treatment of wounds and/or burns; for the treatment of severed nerves; for increasing libido; for modulating movement activity; for anxiolysis; for local anaesthesia and/or for inhibiting undesirable side effects, preferably selected from the group consisting of hyperthermia, hypertension and bronchoconstriction, triggered by the administration of vanilloid receptor 1 (VR1/TRPV1 receptor) agonists, preferably selected from the group consisting of capsaicin, resiniferatoxin, olvanil, arvanil, SDZ-249665, SDZ-249482, nuvanil and capsavanil, which comprises administering an effective amount of at least one substituted compound according to the invention to the mammal.

The effectiveness against pain can be shown, for example, in the *Bennett* or *Chung* model (Bennett, G.J. and Xie, Y.K., A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man, Pain 1988, 33(1), 87-107; Kim, S.H. and Chung, J.M., An experimental model for peripheral neuropathy produced by segmental spinal nerve ligation in the rat, Pain 1992, 50(3), 355-363), by tail flick experiments (e.g. according to D'Amour und Smith (J. Pharm. Exp. Ther. 72, 74 79 (1941)) or by the formalin test (e.g. according to D. Dubuisson et al., Pain 1977, 4, 161-174).

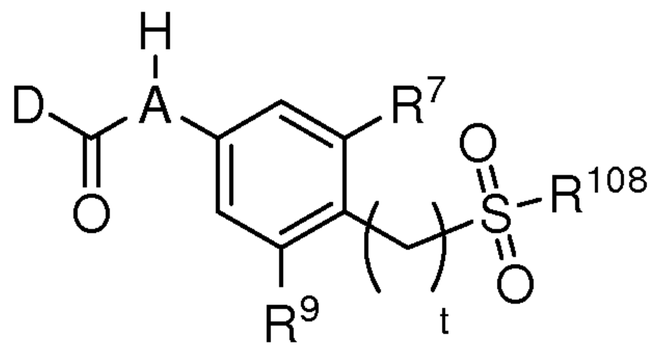
The present invention further relates to processes for preparing substituted compounds according to the invention.

In particular, the compounds according to the present invention of can be prepared by a process according to which at least one compound of general formula (T-II),



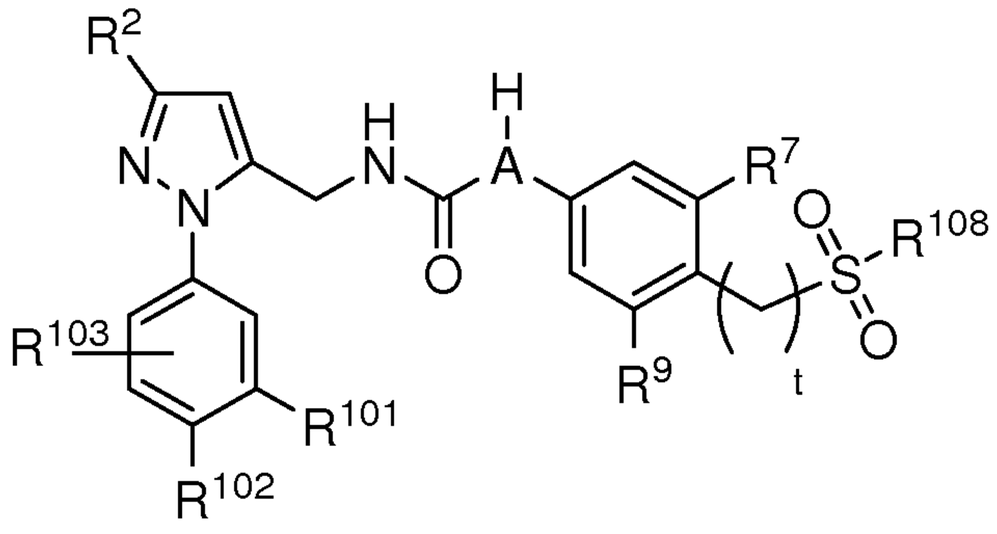
(T-II),

in which R^{101}, R^{102}, R^{103} and R^2 have one of the foregoing meanings, is reacted in a reaction medium, if appropriate in the presence of at least one suitable coupling reagent, if appropriate in the presence of at least one base, with a compound of general formula (T-III) with D = OH or Hal,



(T-III),

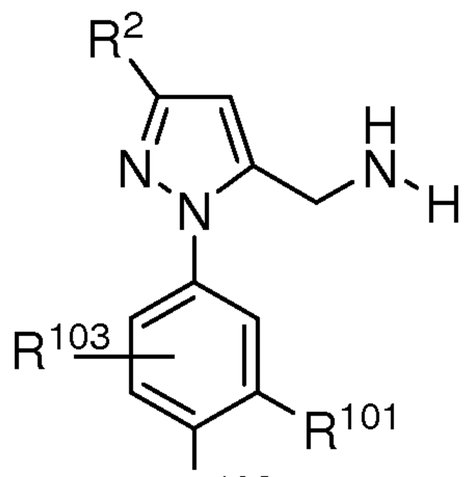
in which Hal represents a halogen, preferably Br or Cl, and R^7, R^9, R^{108} and t each have one of the foregoing meanings and A denotes CH or $C(CH_3)$, in a reaction medium, if appropriate in the presence of at least one suitable coupling reagent, if appropriate in the presence of at least one base, to form a compound of general formula (T),



(T),

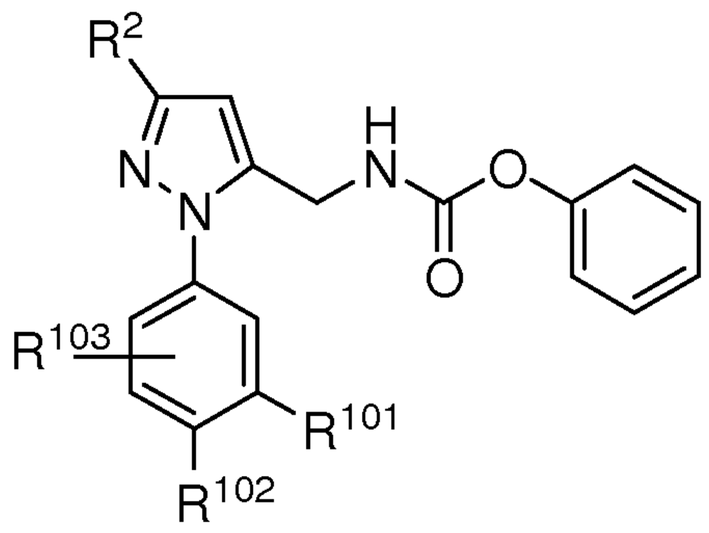
in which A represents CH or $C(CH_3)$ and R^{101}, R^{102}, R^{103} and R^2 as well as R^7, R^9, R^{108} and t have one of the foregoing meanings;

or in that at least one compound of general formula (T-II),



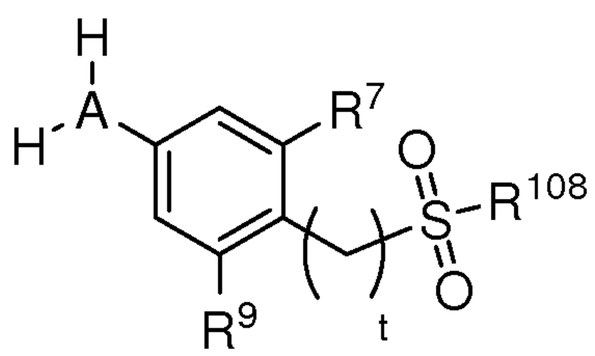
(T-II),

in which R^{101}, R^{102}, R^{103} and R^2 have one of the foregoing meanings, is reacted to form a compound of general formula (T-IV),



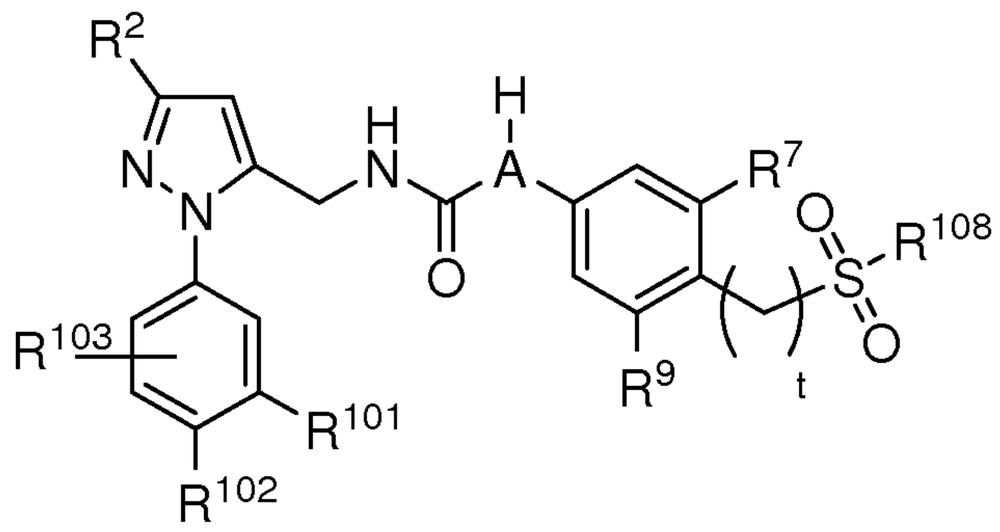
(T-IV),

in which R^{101}, R^{102}, R^{103} and R^2 have one of the foregoing meanings, in a reaction medium, in the presence of phenyl chloroformiate, if appropriate in the presence of at least one base and/or at least one coupling reagent, and said compound is if appropriate purified and/or isolated, and a compound of general formula (T-IV) is reacted with a compound of general formula (T-V),



(T-V),

in which R^7, R^9, R^{108} and t have one of the foregoing meanings, and A denotes N, in a reaction medium, if appropriate in the presence of at least one suitable coupling reagent, if appropriate in the presence of at least one base, to form a compound of general formula (T),



(T),

in which A represents N and R^{101}, R^{102}, R^{103} and R^2 as well as R^7, R^9, R^{108} and t have one of the foregoing meanings.

The reaction of compounds of the above-indicated general formula (T-II) with carboxylic acids of the above-indicated general formula (T-III), particularly with D = OH, to form compounds of the above-indicated general formula (T) is carried out preferably in a reaction medium selected from the group consisting of diethyl ether, tetrahydrofuran, acetonitrile, methanol, ethanol, (1,2)-dichloroethane, dimethylformamide, dichloromethane and corresponding mixtures, if appropriate in the presence of at least one coupling reagent, preferably selected from the group consisting of 1-benzotriazolyloxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (BOP), dicyclohexylcarbodiimide (DCC), N‘-(3-dimethylaminopropyl)-N-ethylcarbodiimide (EDCI), diisopropylcarbodiimide, 1,1‘-carbonyldiimidazole (CDI), N-[(dimethylamino)-1H-1, 2, 3-triazolo[4, 5-b]pyridino-1-yl-methylene]-N-methylmethanaminium hexafluorophosphate N-oxide (HATU), O-(benzotriazol-1-yl)-N,N,N‘,N‘-tetramethyluronium hexafluorophosphate (HBTU), O-(benzotriazol-1-yl)-N,N,N‘,N‘-tetramethyluronium tetrafluoroborate (TBTU), N-hydroxybenzotriazole (HOBt) and 1-hydroxy-7-azabenzotriazole (HOAt), if appropriate in the presence of at least one organic base, preferably selected from the group consisting of triethylamine, pyridine, dimethylaminopyridine, N-methylmorpholine and diisopropylethylamine, preferably at temperatures of from -70 ℃ to 100 ℃.

Alternatively, the reaction of compounds of the above-indicated general formulae (T-II) with carboxylic acid halides of the above-indicated general formula (T-III) with D = Hal, in which Hal represents a halogen as the leaving group, preferably a chlorine or bromine atom, to form compounds of the above-indicated general formula (T) is carried out in a reaction medium preferably selected from the group consisting of diethyl ether, tetrahydrofuran, acetonitrile, methanol, ethanol, dimethylformamide, dichloromethane and corresponding mixtures, if appropriate in the presence of an organic or inorganic base, preferably selected from the group consisting of triethylamine, dimethylaminopyridine, pyridine and diisopropylamine, at temperatures of from -70 ℃ to 100 ℃.

The compounds of the above-indicated formulae (T-II), (T-III), (T-IV), and (T-V) are each commercially available and/or can be prepared using conventional processes known to the person skilled in the art. In particular, processes to prepare these compounds are e.g. disclosed in WO 2010/127855-A2, and WO 2010/127856-A2. The corresponding parts of these references are hereby deemed to be part of the disclosure.

All reactions which can be applied for synthesizing the compounds according to the present invention can each be carried out under the conventional conditions with which the person skilled in the art is familiar, for example with regard to pressure or the order in which the

components are added. If appropriate, the person skilled in the art can determine the optimum procedure under the respective conditions by carrying out simple preliminary tests. The intermediate and end products obtained using the reactions described hereinbefore can each be purified and/or isolated, if desired and/or required, using conventional methods known to the person skilled in the art. Suitable purifying processes are for example extraction processes and chromatographic processes such as column chromatography or preparative chromatography. All of the process steps of the reaction sequences which can be applied for synthesizing the compounds according to the present invention as well as the respective purification and/or isolation of intermediate or end products, can be carried out partly or completely under an inert gas atmosphere, preferably under a nitrogen atmosphere.

The substituted compounds according to the invention can be isolated both in the form of their free bases, and also in the form of corresponding salts, in particular physiologically acceptable salts, and further in the form of a solvate such as hydrate.

The free bases of the respective substituted compounds according to the invention can be converted into the corresponding salts, preferably physiologically acceptable salts, for example by reaction with an inorganic or organic acid, preferably with hydrochloric acid, hydrobromic acid, sulphuric acid, methanesulphonic acid, p-toluenesulphonic acid, carbonic acid, formic acid, acetic acid, oxalic acid, succinic acid, tartaric acid, mandelic acid, fumaric acid, maleic acid, lactic acid, citric acid, glutamic acid, saccharic acid, monomethylsebacic acid, 5-oxoproline, hexane-1-sulphonic acid, nicotinic acid, 2, 3 or 4-aminobenzoic acid, 2,4,6-trimethylbenzoic acid, α-lipoic acid, acetyl glycine, hippuric acid, phosphoric acid and/or aspartic acid. The free bases of the respective inventive substituted compounds and of corresponding stereoisomers can likewise be converted into the corresponding physiologically acceptable salts using the free acid or a salt of a sugar additive, such as for example saccharin, cyclamate or acesulphame.

Accordingly, the substituted compounds according to the invention such as the free acids of the substituted compounds according to the invention can be converted into the corresponding physiologically acceptable salts by reaction with a suitable base. Examples include the alkali metal salts, alkaline earth metals salts or ammonium salts $[NH_xR_{4-x}]^+$, in which x = 0, 1, 2, 3 or 4 and R represents a branched or unbranched C_{1-4} alkyl residue.

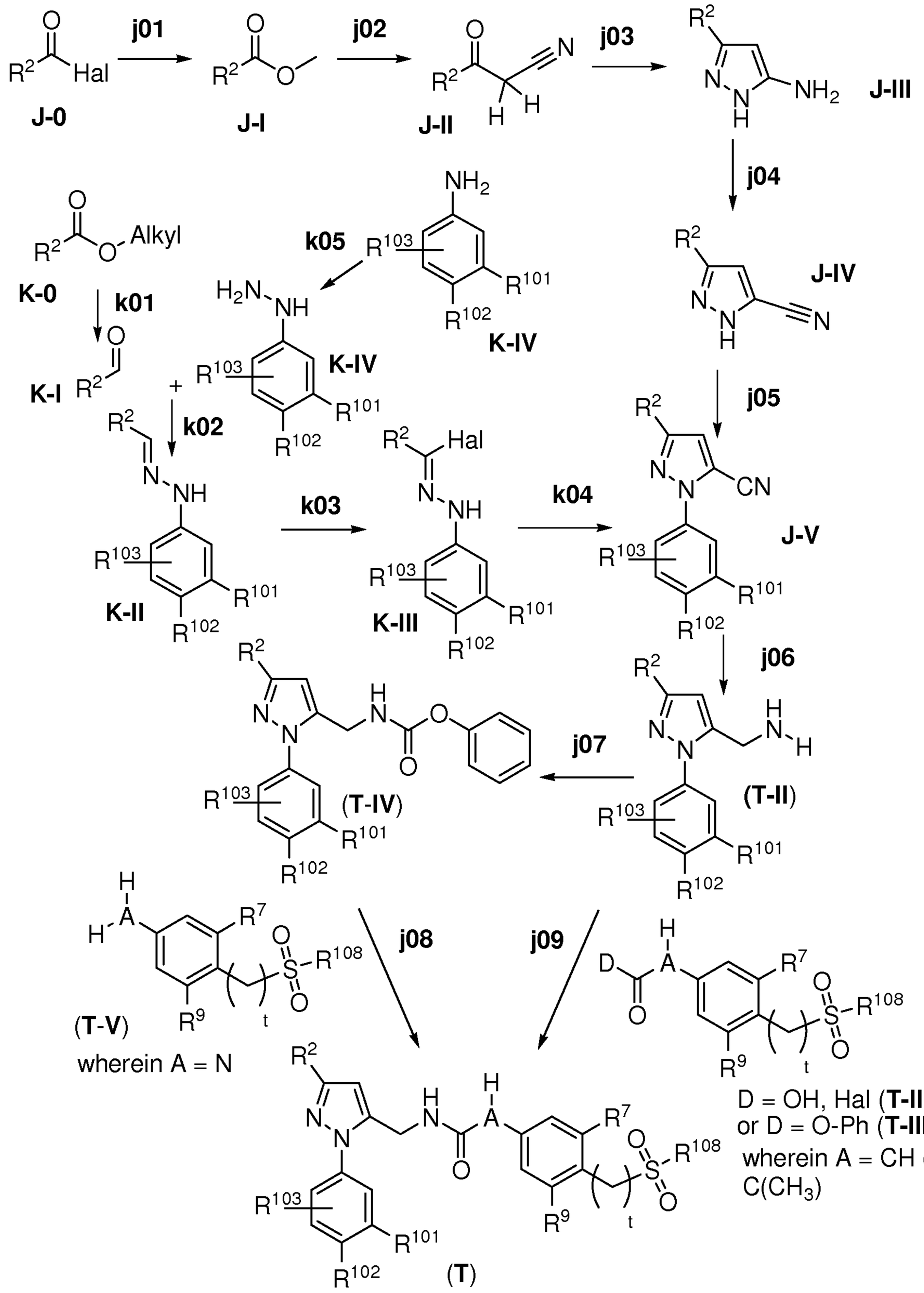
The substituted compounds according to the invention and of corresponding stereoisomers can if appropriate, like the corresponding acids, the corresponding bases or salts of these

compounds, also be obtained in the form of their solvates, preferably in the form of their hydrates, using conventional methods known to the person skilled in the art.

If the substituted compounds according to the invention are obtained, after preparation thereof, in the form of a mixture of their stereoisomers, preferably in the form of their racemates or other mixtures of their various enantiomers and/or diastereomers, they can be separated and if appropriate isolated using conventional processes known to the person skilled in the art. Examples include chromatographic separating processes, in particular liquid chromatography processes under normal pressure or under elevated pressure, preferably MPLC and HPLC processes, and also fractional crystallisation processes. These processes allow individual enantiomers, for example diastereomeric salts formed by means of chiral stationary phase HPLC or by means of crystallisation with chiral acids, for example (+)-tartaric acid, (-)-tartaric acid or (+)-10-camphorsulphonic acid, to be separated from one another.

The chemicals and reaction components used in the reactions and schemes described below are available commercially or in each case can be prepared by conventional methods known to the person skilled in the art.

General reaction scheme 1 (Scheme 1):



In step **j01** an acid halide **J-0**, in which Hal preferably represents Cl or Br, can be esterified using methanol to form the compound **J-I** by means of methods with which the person skilled in the art is familiar.

In step **j02** the methyl pivalate **J-I** can be converted into an oxoalkylnitrile **J-II** by means of methods known to the person skilled in the art, such as for example using acetonitrile CH_3-CN, if appropriate in the presence of a base.

In step **j03** the compound **J-II** can be converted into an amino-substituted pyrazolyl derivative **J-III** by means of methods known to the person skilled in the art, such as for example using hydrazine hydrate, with cyclization.

In step **j04** the amino compound **J-III** can first be converted into a diazonium salt by means of methods known to the person skilled in the art, such as for example using nitrite, and the diazonium salt can be converted into a cyano-substituted pyrazolyl derivative **J-IV** with elimination of nitrogen using a cyanide, if appropriate in the presence of a coupling reagent.

In step **j05** the compound **J-IV** can be substituted in the N position by means of methods known to the person skilled in the art, for example using a halide of part structure (TS2), i.e. Hal-(TS2), if appropriate in the presence of a base and/or a coupling reagent, wherein Hal is preferably Cl, Br or I, or using a boronic acid $B(OH)_2$(TS2) or a corresponding boronic acid ester, if appropriate in the presence of a coupling reagent and/or a base and the compound **J-V** can in this way be obtained.

Alternatively, a second synthesis pathway, in which in step **k01** an ester **K-0** is first reduced to form the aldehyde **K-I** by means of methods known to the person skilled in the art, for example using suitable hydrogenation reagents such as metal hydrides, is suitable for preparing the compound **J-V**.

In step **k02** the aldehyde **K-I** can then be reacted with a hydrazine **K-V**, which can be obtained in step **k05**, starting from the primary amine **K-IV**, by means of methods known to the person skilled in the art, to form the hydrazine **K-II** by means of methods known to the person skilled in the art with elimination of water.

In step **k03** the hydrazine **K-II** can be halogenated, preferably chlorinated, by means of methods known to the person skilled in the art with the double bond intact, such as for

example using a chlorination reagent such as NCS, and the compound **K-III** can in this way be obtained.

In step **k04** the hydrazonoyl halide **K-III** can be converted into a cyano-substituted compound **J-V** by means of methods known to the person skilled in the art, such as for example using a halogen-substituted nitrile, with cyclisation.

In step **j06** the compound **J-V** can be hydrogenated by means of methods known to the person skilled in the art, for example using a suitable catalyst such as palladium/activated carbon or using suitable hydrogenation reagents, and the compound (**T-II**) can in this way be obtained.

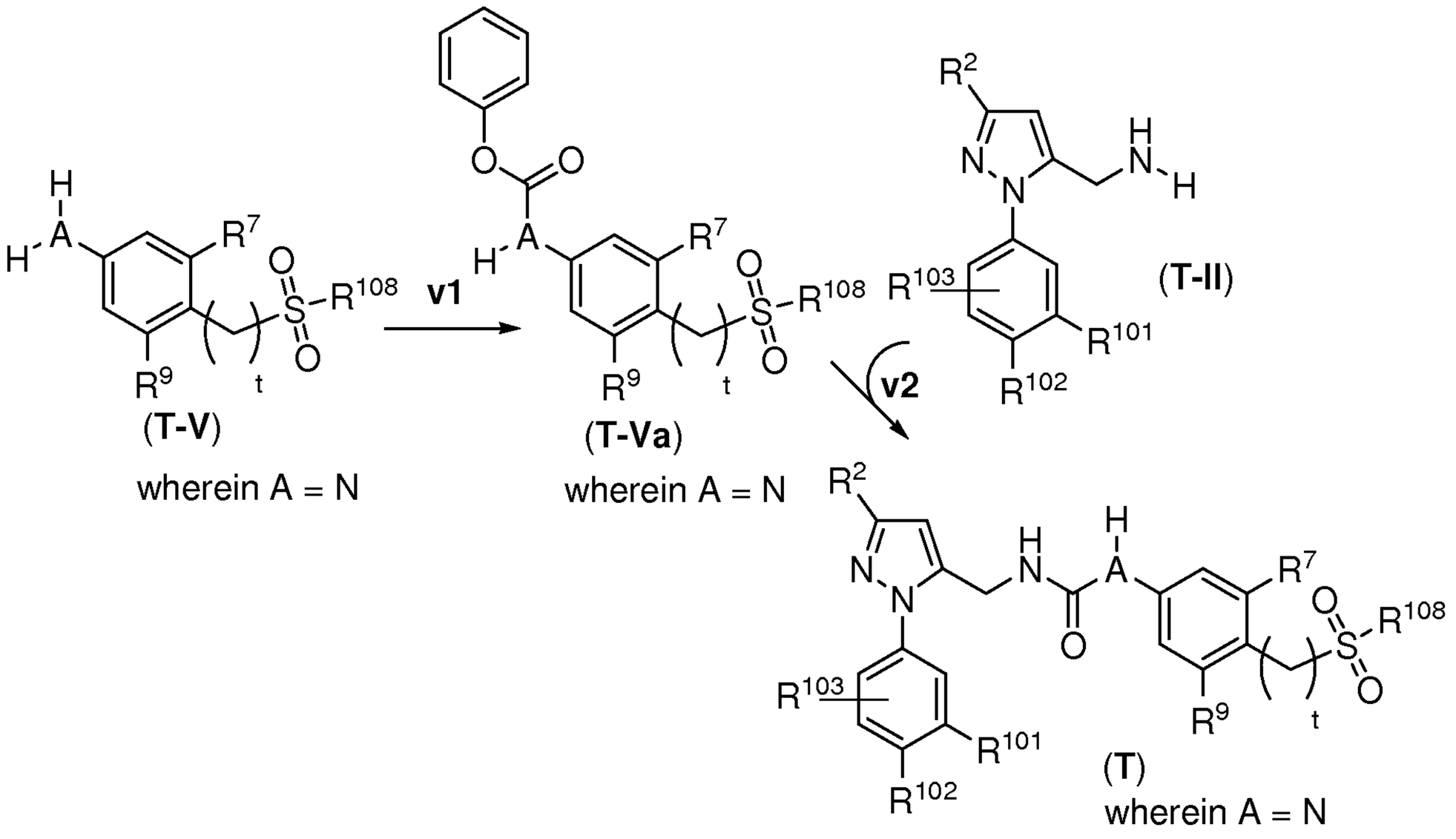
In step **j07** the compound (**T-II**) can be converted into the compound (**T-IV**) by means of methods known to the person skilled in the art, such as for example using phenyl chloroformate, if appropriate in the presence of a coupling reagent and/or a base. In addition to the methods disclosed in the present document for preparing unsymmetrical ureas using phenyl chloroformate, there are further processes with which the person skilled in the art is familiar, based on the use of activated carbonic acid derivatives or isocyanates, if appropriate.

In step **j08** the amine (**T-V**) can be converted into the urea compound (**T**) (wherein A = N). This can be achieved by reaction with (**T-IV**) by means of methods with which the person skilled in the art is familiar, if appropriate in the presence of a base.

In step **j09** the amine (**T-II**) can be converted into the amide (**T**) (wherein A = CH or $C(CH_3)$). This can for example be achieved by reaction with an acid halide, preferably a chloride of formula (**T-III**) with D = Hal by means of methods with which the person skilled in the art is familiar, if appropriate in the presence of a base or by reaction with an acid of formula (**T-III**) with D = OH, if appropriate in the presence of a suitable coupling reagent, for example HATU or CDI, if appropriate with the addition of a base. Further, the amine (**T-II**) may be converted into the amide (**T**) (wherein A = CH or $C(CH_3)$) by reaction of a compound (**T-IIIa**) by means of methods with which the person skilled in the art is familiar, if appropriate in the presence of a base.

The compounds according to general formula (**T**), wherein A = N, may be further prepared by a reaction sequence according to general reaction scheme 2.

General reaction scheme 2 (scheme 2)



In step **v1** the compound (**T-V**) can be converted into the compound (**T-Va**) by means of methods known to the person skilled in the art, such as for example using phenyl chloroformate, if appropriate in the presence of a coupling reagent and/or a base. In addition to the methods disclosed in the present document for preparing unsymmetrical ureas using phenyl chloroformate, there are further processes with which the person skilled in the art is familiar, based on the use of activated carbonic acid derivatives or isocyanates, if appropriate.

In step **v2** the amine (**T-II**) can be converted into the urea compound (**T**) (wherein A = N). This can be achieved by reaction with (**T-Va**) by means of methods with which the person skilled in the art is familiar, if appropriate in the presence of a base.

The methods with which the person skilled in the art is familiar for carrying out the reaction steps **j01** to **j09** and also **k01** to **k05** as well as **v1** and **v2** may be inferred from the standard works on organic chemistry such as, for example, J. March, Advanced Organic Chemistry, Wiley & Sons, 6th edition, 2007; F. A. Carey, R. J. Sundberg, Advanced Organic Chemistry, Parts A and B, Springer, 5th edition, 2007; team of authors, Compendium of Organic Synthetic Methods, Wiley & Sons. In addition, further methods and also literature references can be issued by the common databases such as, for example, the Reaxys® database of Elsevier, Amsterdam, NL or the SciFinder® database of the American Chemical Society, Washington, US.

EXAMPLES

The following examples further illustrate the invention but are not to be construed as limiting its scope.

The indication „equivalents“ ("eq." or “eq” or “equiv.” or “equiv”) means molar equivalents, „RT“ or “rt” means room temperature (23 ± 7 °C), „M“ are indications of concentration in mol/l, „aq.“ means aqueous, „sat.“ means saturated, „sol.“ means solution, "conc." means concentrated.

Further abbreviations:

d	days
AcOH	acetic acid
BH_3•$S(CH_3)_2$	borane-methyl sulfide complex (BH_3-DMS)
brine	saturated aqueous sodium chloride solution
n-BuLi	n-butyllithium
CC	column chromatography on silica gel
DBU	1,8-diazabicyclo[5.4.0]undec-7-en
DCM	dichloromethane
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
EDCI	N-ethyl-N‘-(3-dimethylaminopropyl)carbodiimide hydrochloride
ether	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
h	hour(s)
GC	gas chromatography
HBTU	O-(benzotriazol-1-yl)-N,N,N‘,N‘-tetramethyluronium hexafluorophosphate
HOBt	N-hydroxybenzotriazole
H_2O	water
m/z	mass-to-charge ratio
MeOH	methanol
min or min.	minutes
MS	mass spectrometry
TEA	triethylamine
Pd / C	palladium on charcoal

TBTU	O-(benzotriazol-1-yl)-N,N,N‘,N‘-tetramethyluronium tetrafluoroborate
TLC	thin layer chromatography
TFA	trifluoroacetic acid
THF	tetrahydrofuran
v/v	volume to volume
w/w	weight in weight

The yields of the compounds prepared were not optimized.

All temperatures are uncorrected.

All starting materials which are not explicitly described were either commercially available (the details of suppliers such as for example Acros, Avocado, Aldrich, Apollo, Bachem, Fluka, FluoroChem, Lancaster, Manchester Organics, MatrixScientific, Maybridge, Merck, Rovathin, Sigma, TCI, Oakwood, etc. can be found in the Symyx® Available Chemicals Database of MDL, San Ramon, US or the SciFinder® Database of the ACS, Washington DC, US, respectively, for example) or the synthesis thereof has already been described precisely in the specialist literature (experimental guidelines can be found in the Reaxys® Database of Elsevier, Amsterdam, NL or the SciFinder® Database of the ACS, Washington DC, US, repspectively, for example) or can be prepared using the conventional methods known to the person skilled in the art.

The stationary phase used for the column chromatography was silica gel 60 (0.04 - 0.063 mm) from E. Merck, Darmstadt.

The mixing ratios of solvents or eluents for chromatography are specified in v/v.

All the intermediate products and exemplary compounds were analytically characterized by means of ^{1}H-NMR spectroscopy. In addition, mass spectrometry tests (MS, m/z for $[M+H]^{+}$) were carried out for all the exemplary compounds and selected intermediate products.

Synthesis of selected intermediate products:

1. Synthesis of (3-tert-butyl-1-(3-chlorophenyl)-1H-pyrazol-5-yl)methanamine (steps **j01-j06**)

Step **j01**: Pivaloyl chloride (**J-0**) (1 eq., 60 g) was added dropwise to a solution of methanol (120 mL) within 30 min at 0 °C and the mixture was stirred for 1 h at room temperature. After the addition of water (120 mL), the separated organic phase was washed with water (120 mL), dried over sodium sulphate and codistilled with dichloromethane (150 mL). The liquid product **J-I** was able to be obtained at 99 % purity (57 g).

Step **j02**: NaH (50 % in paraffin oil) (1.2 equivalents, 4.6 g) was dissolved in 1,4-dioxane (120 mL) and the mixture was stirred for a few minutes. Acetonitrile (1.2 equivalents, 4.2 g) was added dropwise within 15 min and the mixture was stirred for a further 30 min. The methyl pivalate (**J-I**) (1 equivalents, 10 g) was added dropwise within 15 min and the reaction mixture was refluxed for 3 h. After complete reaction, the reaction mixture was placed in iced water (200 g), acidified to pH 4.5 and extracted with dichloromethane (12 x 250 mL). The combined organic phases were dried over sodium sulphate, distilled and after recrystallisation from n-hexane (100 mL) 5 g of the product (**J-II**) (51 % yield) was able to be obtained as a solid brown substance.

Step **j03**: At room temperature 4,4-dimethyl-3-oxopentanenitrile (**J-II**) (1 equivalents, 5 g) was taken up in ethanol (100 mL), mixed with hydrazine hydrate (2 equivalents, 4.42 g) and refluxed for 3 h. The residue obtained after removal of the ethanol by distillation was taken up in water (100 mL) and extracted with ethyl acetate (300 mL). The combined organic phases were dried over sodium sulphate, the solvent was removed under vacuum and the product (**J-III**) (5 g, 89 % yield) was obtained as a light red solid after recrystallisation from n-hexane (200 mL).

Step **j04**: 3-Tert-butyl-1H-pyrazol-5-amine (**J-III**) (1 equivalents, 40 g) was dissolved in diluted HCl (120 mL of HCl in 120 mL of water) and mixed dropwise with $NaNO_2$ (1.03 equivalents, 25 g in 100 mL) at 0 - 5 °C over a period of 30 min. After stirring for 30 minutes, the reaction mixture was neutralised with Na_2CO_3. A diazonium salt obtained by reaction of KCN (2.4 equivalents, 48 g), water (120 mL) and CuCN (1.12 equivalents, 31 g) was added dropwise to the reaction mixture within 30 min and the mixture was stirred for a further 30 min at 75 °C. After complete reaction, the reaction mixture was extracted with ethyl acetate (3 x 500 mL), the combined organic phases were dried over sodium sulphate and the solvent was removed under vacuum. The purification (silica gel: 100-200 mesh, eluent: 20 % ethyl

acetate/n-hexane) of the residue by column chromatography produced a white solid (**J-IV**) (6.5 g, 15 %).

Step **j05** (*method 1*):
3-tert.-butyl-1H-pyrazol-5-carbonitrile (**J-IV**) (10 mmol) was added to a suspension of NaH (60 %) (12.5 mmol) in dimethylformamide (20 mL) at room temperature while stirring. After stirring for 15 minutes, 1-iodo-3-chlorobenzene (37.5 mmol) was added dropwise to this reaction mixture at room temperature. After stirring for 30 min at 100 °C, the reaction mixture was mixed with water (150 mL) and extracted with dichloromethane (3 x 75 mL). The combined organic extracts were washed with water (100 mL) and sat. NaCl solution (100 mL) and dried over magnesium sulphate. After removal of the solvent under vacuum, the residue was purified by column chromatography (silica gel: 100-200 mesh, eluent: various mixtures of ethyl acetate and cyclohexane as the mobile solvent) and the product **J-V** was obtained.

Step **j05** (*method 2):*
A mixture of 3-tert-butyl-1H-pyrazol-5-carbonitrile (**J-IV**) (10 mmol), a boronic acid $B(OH)_2$(3-chlorophenyl) or a corresponding boronic acid ester (20 mmol) and copper (II) acetate (15 mmol) is placed in dichloromethane (200 mL), mixed with pyridine (20 mmol) while stirring at room temperature and the mixture is stirred for 16 h. After removal of the solvent under vacuum, the residue obtained is purified by column chromatography (silica gel: 100-200 mesh, eluent: various mixtures of ethyl acetate and cyclohexane as the mobile solvent) and the product **J-V** is in this way obtained.

Step **j06**: (*method 1):*
J-V was dissolved together with palladium on carbon (10 %, 500 mg) and concentrated HCl (3 mL) in methanol (30 mL) and exposed to a hydrogen atmosphere for 6 h at room temperature. The reaction mixture was filtered over celite and the filtrate was concentrated under vacuum. The residue was purified by means of flash chromatography (silica gel: 100-200 mesh, eluent: ethyl acetate) and the product (**U-II**) was in this way obtained.

Step **j06**: (*method 2):*
J-V was dissolved in tetrahydrofuran (10 mL) and BH_3•$S(CH_3)_2$ (2.0 M in tetrahydrofuran, 3 mL, 3 equivalents) was added thereto. The reaction mixture was heated to reflux for 8 h, aq. 2 N HCl (2 N) was added thereto and the reaction mixture was refluxed for a further 30 minutes. The reaction mixture was mixed with aq. NaOH solution (2N) and washed with ethyl acetate. The combined organic phases were washed with sat. aq. NaCl solution and dried

over magnesium sulphate. The solvent is removed under vacuum and the residue is purified by column chromatography (silica gel: 100-200 mesh, eluent: various mixtures of dichloromethane and methanol as the mobile solvent) and the product (**U-II**) is in this way obtained.

The following further intermediate products were/can be synthesised in a similar manner using the process described hereinbefore under **1.**:

(3-tert-butyl-1-(3-fluorophenyl)-1H-pyrazol-5-yl)methanamine
(3-tert-butyl-1-(4-fluorophenyl)-1H-pyrazol-5-yl)methanamine
(3-tert-butyl-1-(3-chloro-4-fluorophenyl)-1H-pyrazol-5-yl)methanamine
(3-tert-butyl-1-(3,4-difluorophenyl)-1H-pyrazol-5-yl)methanamine
(3-tert-butyl-1-(3,5-difluorophenyl)-1H-pyrazol-5-yl)methanamine
(3-tert-butyl-1-((3-difluoromethyl)phenyl)-1H-pyrazol-5-yl)methanamine
(3-tert-butyl-1-(3-trifluoromethylphenyl)-1H-pyrazol-5-yl)methanamine
(3-tert-butyl-1-(3-fluoro-5-methylphenyl)-1H-pyrazol-5-yl)methanamine
(3-tert-butyl-1-(3-methylphenyl)-1H-pyrazol-5-yl)methanamine
(3-tert-butyl-1-(3-cyanophenyl)-1H-pyrazol-5-yl)methanamine
(3-tert-butyl-1-(3-methoxymethylphenyl)-1H-pyrazol-5-yl)methanamine
(3-tert-butyl-1-(3-methoxyphenyl)-1H-pyrazol-5-yl)methanamine
(3-tert-butyl-1-(3-dimethylaminophenyl)-1H-pyrazol-5-yl)methanamine

2. Synthesis of 1-(3-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl-methanamine (steps **k01**-**k05** and **j06**)

Step **k01**: LAlH (lithium aluminium hydride) (0.25 equivalents, 0.7g) was dissolved in dry diethyl ether (30 mL) under a protective gas atmosphere and stirred for 2 h at room temperature. The suspension obtained was taken up in diethyl ether (20 mL). Ethyl-2,2,2-trifluoroacetate (**K-0**) (1 equivalent, 10 g) was taken up in dry diethyl ether (20 mL) and added dropwise to the suspension at -78 °C over a period of 1 h. The mixture was then the stirred for a further 2 h at -78 °C. ethanol (95 %) (2.5 mL) was then added dropwise, the reaction mixture was heated to room temperature and placed on iced water (30 mL) with concentrated H_2SO_4 (7.5 mL). The organic phase was separated and concentrated under vacuum and the reaction product **K-I** was immediately introduced into the next reaction step **k02**.

Step **k05**: 3-chloroaniline (**K-IV**) (1 equivalent, 50 g) was dissolved at -5 to 0 °C in concentrated HCl (300 mL) and stirred for 10 min. A mixture of $NaNO_2$ (1.2 equivalents, 32.4 g), water (30 mL), $SnCl_2 \bullet 2H_2O$ (2.2 equivalents, 70.6 g) and concentrated HCl (100 mL) was added dropwise over a period of 3 h while maintaining the temperature. After stirring for a further 2 h at -5 to 0 °C, the reaction mixture was set to pH 9 using NaOH solution and extracted with ethyl acetate (250 mL). The combined organic phases were dried over magnesium sulphate and the solvent was removed under vacuum. The purification by column chromatography (silica gel: 100-200 mesh, eluent: 8 % ethyl acetate/n-hexane) produced 40 g (72 %) of (3-chlorophenyl)hydrazine (**K-IV**) as a brown oil.

Step **k02**: The aldehyde (**K-I**) (2 equivalents, 300 mL) obtained from **k01** and (3-chlorophenyl)hydrazine (**K-IV**) (1 equivalent, 20 g) were placed in ethanol (200 mL) and refluxed for 5 h. The solvent was removed under vacuum, the residue was purified by column chromatography (silica gel: 100-200 mesh, eluent: n-hexane) and the product (25 g, 72 %) **K-II** was obtained as a brown oil.

Step **k03**: The hydrazine **K-II** (1 equivalent, 25 g) was dissolved in dimethylformamide (125 mL). N-chlorosuccinimide (1.3 equivalents, 19.5 g) was added portionwise at room temperature within 15 min and the mixture was stirred for 3 h. The dimethylformamide was removed by distillation and the residue was taken up in ethyl acetate. The ethyl acetate was removed under vacuum, the residue obtained was purified by column chromatography (silica gel: 100-200 mesh, eluent: n-hexane) and the product **K-III** (26.5 g, 92 %) was obtained as a pink-coloured oil.

Step **k04**: At room temperature the hydrazonoyl chloride **K-III** (1 equivalent, 10 g) was taken up in toluene (150 mL) and mixed with 2-chloroacrylonitrile (2 equivalents, 6.1 mL) and triethylamine (2 equivalents, 10.7 mL). This reaction mixture was stirred for 20 h at 80 °C. The mixture was then diluted with water (200 mL) and the phases were separated. The organic phase was dried over magnesium sulphate and the solvent was removed under vacuum. The residue was purified by means of column chromatography (silica gel: 100-200 mesh, eluent: 5 % ethyl acetate/n-hexane) and the product (5.5 g, 52 %) was obtained as a white solid **J-V**.

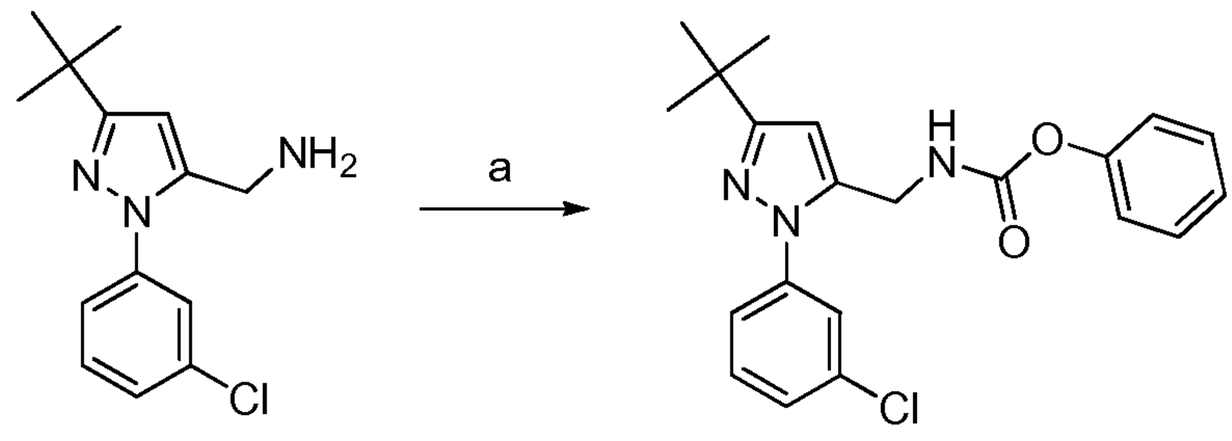
Step **j06** (*method 3*):
The carbonitrile **J-V** (1 equivalent, 1 g) was dissolved in methanolic ammonia solution (150 mL, 1:1) and hydrogenated in an H-cube (10 bar, 80 °C, 1 mL/min, 0.25 mol/L). After removal

of the solvent under vacuum, (1-(3-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl)methanamine (**II**) was able to be obtained as a white solid (0.92 g, 91 %).

The following further intermediate products were/can be synthesized in a similar manner using the process described hereinbefore under **2.**:

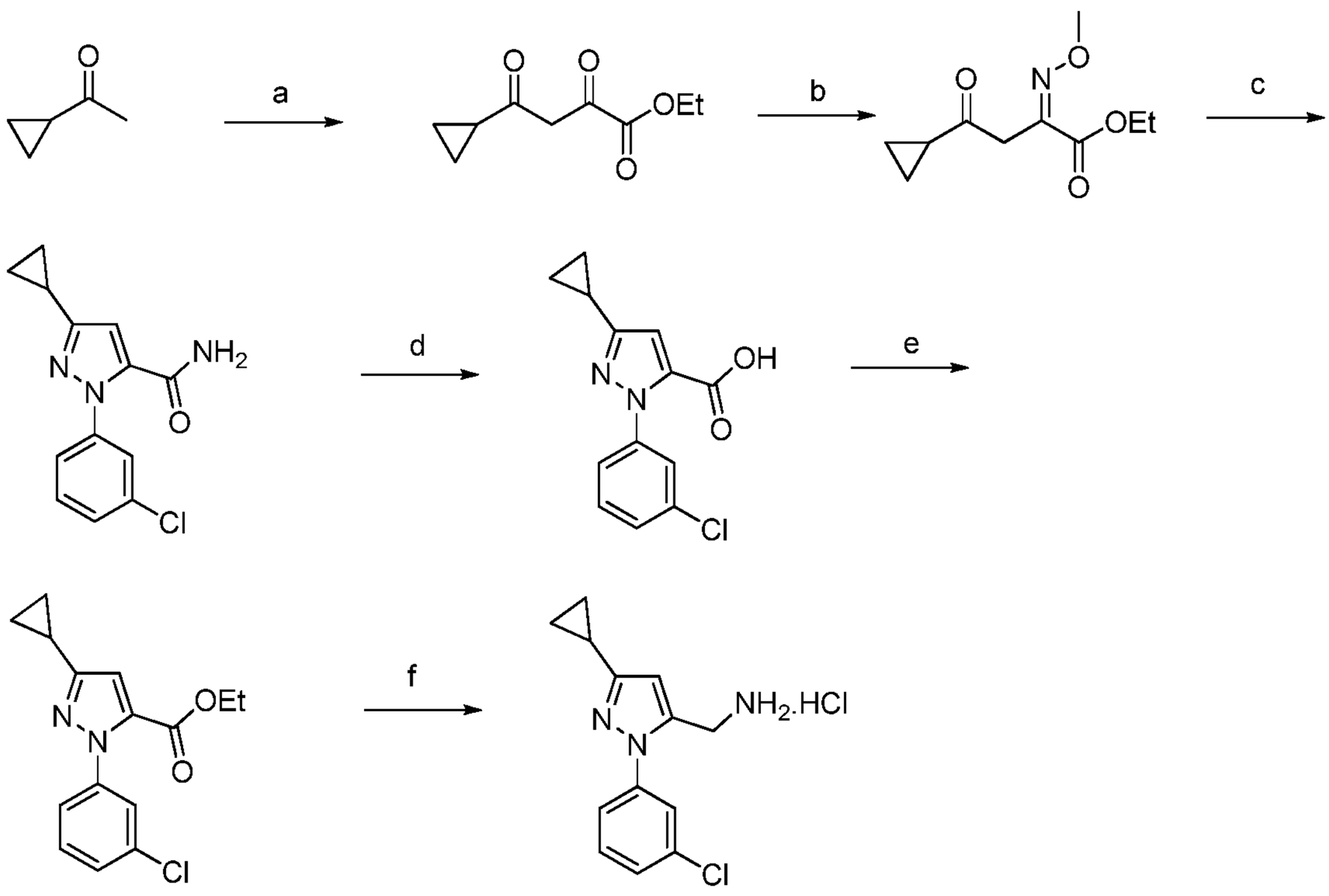
(1-(3-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl)methanamine
(1-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl)methanamine
(1-(3-chloro-4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl)methanamine
(1-(3,4-difluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl)methanamine

3. Preparation of methyl phenyl (3-tert-butyl-1-(3-chlorophenyl)-1H-pyrazol-5-yl)methylcarbamate



Step **a:** To a solution of (3-tert-butyl-1-(3-chlorophenyl)-1H-pyrazol-5-yl)methanamine (5 g, 18 mmol) in dimethylformamide (25 mL), potassium carbonate (9.16 g, 66 mmol, 3.5 eq) was added and cooled the contents to 0℃. Then phenyl chloroformate (3.28 g (2.65 mL), 20 mmol, 1.1 equivalents) was added dropwise for 15 minutes and the overall reaction mixture was stirred for another 15 minutes at 0 ℃. Progress of the reaction was monitored by TLC (20 % ethyl acetate-n-hexane). On completion of the reaction, reaction contents were filtered, filtrate was diluted with cold water (100 mL) and the product extracted with ethyl acetate (3 × 25 mL). Combined organic layer was washed with brine solution (100 mL), dried over sodium sulphate and concentrated under reduced pressure. Crude obtained was purified by column chromatography (silica gel: 100-200 mesh, eluent: 10% ethyl acetate in n-hexane) to yield the required product as a white solid (3.2 g, 45 %).

4. Preparation of (1-(3-chlorophenyl)-3-cyclopropyl-1H-pyrazol-5-yl)methanamine hydrochloride



Step **a***:* To a solution of sodium ethoxide (freshly prepared by dissolving sodium (1 g, 8.2 mmol, 1.2 equivalents) in ethanol (30 mL)), diethyl oxalate (0.92 mL, 6.85 mmol, 1 equivalent) was added at room temperature followed by addition of cyclopropyl methyl ketone (0.74 mL, 7.5 mmol, 1.1 equivalents) dropwise at 0 ℃. The reaction mixture was slowly warmed to room temperature and stirred for 3 h. Ice cold water (10 mL) was added and ethanol was evaporated under reduced pressure. The residual aqueous layer was diluted with 2 N aq. HCl (15mL) and extracted with diethyl ether (2 × 25 mL). The organic layer was washed with brine solution and dried over sodium sulphate, filtered and concentrated to give a pale brown liquid (400 mg, 31 %).

Step **b***:* To a solution of step-**a** product (200 mg, 0.543 mmol, 1 equivalent) in ethanol (8 mL), methoxylamine hydrochloride (30 % solution in water, 0.4 mL, 0.651 mmol, 1.2 equivalents) was added at room temperature and the reaction mixture stirred for 1 h. ethanol was evaporated under reduced pressure and the residual aqueous layer was extracted with ethyl acetate (15 mL). The organic layer was washed with water (10 mL), brine solution (10 mL), dried over sodium sulphate, filtered and concentrated under reduced pressure to give a pale yellow liquid (180 mg, 78 %).

Step **c***:* A mixture of step-**b** product (1.1 g, 5.164 mmol, 1 equivalent) and 3-chlorophenyl hydrazine hydrochloride (1.84 g, 10.27 mmol, 2 equivalents) was taken in acetic acid (20

mL), 2-methoxy ethanol (10 mL) and the reaction mixture was heated at 105 °C for 3 h. Solvent was evaporated and the residue was extracted with ethyl acetate (60 mL). The organic layer washed with water (10 mL), brine solution (10 mL), dried over sodium sulphate, filtered and concentrated under reduced pressure to give a residue. Purification by column chromatography (silica gel: 100-200 mesh; eluent: ethyl acetate-petroleum ether (4:96)) afforded a pale brown semi solid (1.15g, 77 %).

Step **d***:* To a solution of step-**c** product (2.5 g, 8.62 mmol, 1 eq) in tetrahydrofuran (15 mL) – methanol (9 mL) – water (3 mL), lithium hydroxide (1.08 g, 25.71 mmol, 3 equivalents) was added at 0 °C and the reaction mixture was stirred for 2 h at room temperature. Solvent was evaporated and pH of the residue was adjusted to ~3 sing 2 N aqueous HCl (1.2 mL). The acidic aqueous layer was extracted with ethyl acetate (2 × 60 mL); the combined organic layer washed with water (10 mL), brine solution (10 mL), dried over sodium sulphate, filtered and concentrated under reduced pressure to give an off white solid (1.4 g, 62 %).

Step **e***:* To a solution of step-**d** product (1.4 g, 5.34 mmol, 1 equivalent) in 1,4-dioxane (30 mL), pyridine (0.25 mL, 3.2 mmol, 0.6 equivalents) and di-tert-butyl dicarbonate (1.4 mL, 6.37 mmol, 1.2 equivalents) were added at 0 °C and the resulting mixture was stirred for 30 minutes at the same temperature. Ammonium bicarbonate (0.84 g, 10.63 mmol, 2 equivalents) was added at 0 °C and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with water (10 mL) and the aqueous layer was extracted with ethyl acetate (2 × 30 mL). The organic layer was washed with 2N HCl (20 mL), water (10 mL), brine solution (10 mL), dried over sodium sulphate, filtered and concentrated under reduced pressure to give a residue. Purification by column chromatography (silica gel: 100-200 mesh; eluent: ethyl acetate-petroleum ether (16:84)) gave a white solid (1 g, 72 %).

Step **f***:* To a solution of step-**e** product (2 g, 7.66 mmol, 1 equivalent) in tetrahydrofuran (25 mL), BH_3.DMS (1.44 mL, 15.32 mmol, 2 equivalents) was added at 0 °C and the reaction mixture was heated at 70°C for 3 h. The reaction mixture was cooled to 0 °C and methanol (15 mL) was added and reaction mixture heated at reflux for 1 h. The reaction mixture was brought to room temperature and solvent was evaporated under reduced pressure. The residue was dissolved in ether (15 mL), cooled to 0 °C and a solution of HCl in 1,4-dioxane (3 mL) was added (pH of the reaction mixture ~4). The precipitated solid was filtered and washed with diethyl ether (5 mL, thrice) to give the hydrochloride salt compound as a white solid (600 mg, 28 %).

Synthesis of exemplary compounds:

1. *Preparation of amides (A = CH or $C(CH_3)$)*

General directions for reacting amines of general formula (**T-II**) with carboxylic acids of general formula or carboxylic acid derivatives of general formula (**T-III**) to form compounds of general formula (**T**), wherein A = CH or $C(CH_3)$ (amides), as in scheme 1 (step **j09**).

1.1 Method A:

The acid of general formula (**T-III**) (1 equivalent), the amine of general formula (**T-II**) (1.2 equivalents) and EDCI (1.2 equivalents) are stirred in DMF (10 mmol of acid/20 mL) for 12 hours at RT and water is subsequently added thereto. The reaction mixture is repeatedly extracted with EtOAc, the aqueous phase is saturated with NaCl and subsequently reextracted with EtOAc. The combined organic phases are washed with 1 N HCl and brine, dried over magnesium sulphate and the solvent is removed under vacuum. The residue is purified by means of flash chromatography (SiO_2, EtOAc/hexane in different ratios such as 1:2) and the product (**T**) is in this way obtained.

1.2 Method B:

The acid of general formula (**T-III**) (1 equivalent) and the amine of general formulae (**T-II**) (1.1 equivalents) are dissolved in dichloromethane (1 mmol of acid in 6 mL) and mixed with EDCI (1.5 equivalents), HOBt (1.4 equivalents) and triethylamine (3 equivalents) at 0 °C. The reaction mixture is stirred for 20 h at room temperature and the crude product is purified by means of column chromatography (SiO_2, n-hexane/EtOAc in different ratios such as 2:1) and (**T**) is in this way obtained.

1.3 Method C:

The acid of general formula (**T-III**) (1 equivalent) is first mixed with a chlorinating agent, preferably with thionyl chloride and the mixture obtained in this way is boiled under reflux and the acid (**T-III**) is in this way converted into the corresponding acid chloride. The amine of general formulae (**T-II**) (1.1 equivalents) is dissolved in dichloromethane (1 mmol of acid in 6 mL) and mixed with triethylamine (3 equivalents) at 0 °C. The reaction mixture is stirred for 20 h at room temperature and the crude product is purified by means of column

chromatography (SiO_2, n-hexane/EtOAc in different ratios such as 2:1) and (**T**) is in this way obtained.

1.4 Method D:

The phenyl ester (**T-IIIa**) (1 equivalent) and the corresponding amine (**T-II**) (1.1 equivalents) are dissolved in THF (10 mmol of the reaction mixture in 120 mL) and stirred for 16 h at room temperature after addition of DBU (1.5 equivalents). After removal of the solvent under vacuum, the residue obtained is purified by means of flash chromatography (SiO_2, EtOAc/hexane in different ratios such as 1:1) and (**T**) is in this way obtained.

The exemplary compounds D1-D10 were obtained using one of the methods described hereinbefore. The exemplary compounds D11-D25 can be obtained using one of the methods described hereinbefore.

2. *Preparation of ureas (A = N)*

General directions for reacting amines of general formula (**T-II**) or (**T-V**) with phenyl chloroformate to form compounds of formula (**T-IV**) or (**T-Va**) (scheme 1, step **j07** and scheme 2, **step v1**) and subsequent reaction of compounds of formula (**T-IV**) with amines of general formula (**T-V**) (scheme 1, step **j08**) or of compounds of formula (**T-Va**) with amines of general formula (**T-II**) (scheme 2, step **v2**) to form compounds of general formula (**T**), wherein A = N:

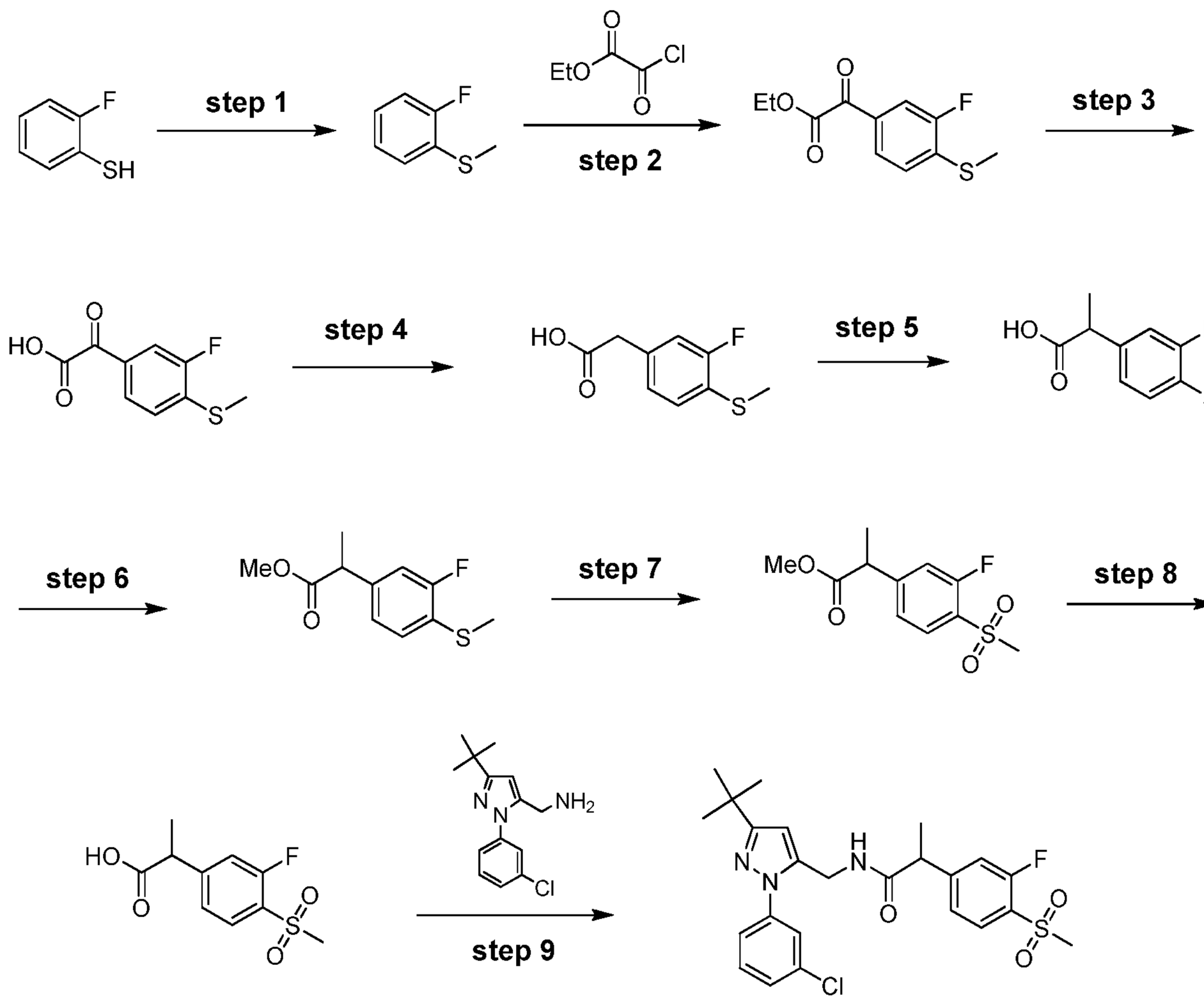
Step **j07**/step **v1**: The amine of general formula (**T-II**) or (**T-V**) (1 equivalent) is placed in dichloromethane (10 mmol of amine in 70 mL) and phenyl chloroformate (1.1 equivalents) is added thereto at room temperature and the mixture is stirred for 30 min. After removal of the solvent under vacuum, the residue is purified by means of flash chromatography (SiO_2, diethyl ether/hexane in different ratios such as 1:2) and (**T-IV**) or (**T-Va**) is in this way obtained.

Step **j08**/step **v2**: The carbamic acid phenyl ester (**T-IV**) or (**T-Va**) obtained (1 equivalent) and the corresponding amine (**T-V**) or (**T-II**) (1.1 equivalents) are dissolved in THF (10 mmol of the reaction mixture in 120 mL) and stirred for 16 h at room temperature after addition of DBU (1.5 equivalents). After removal of the solvent under vacuum, the residue obtained is purified by means of flash chromatography (SiO_2, EtOAc/hexane in different ratios such as 1:1) and (**T**) is in this way obtained.

The exemplary compounds D26-D29, D31 and D33 were obtained using one of the methods described hereinbefore. The exemplary compounds D30 and D32 can be prepared by using one of the methods described hereinbefore.

Detailed synthesis of selected exemplary compounds

Synthesis of example D1: N-[[5-tert-Butyl-2-(3-chlorophenyl)-2H-pyrazol-3-yl]-methyl]-2-(3-fluoro-4-methylsulfonyl-phenyl)-propionamide



Step 1: To 2-fluorobenzenethiol (4.8 g (3.6 mL), 0.03 mol), sodium hydroxide (1.8 g) was added at room temperature. Dimethyl sulphide (4.7 g, 1 eq) was neutralized with potassium carbonate and added to the above contents at room temperature. The overall reaction mixture was stirred for 3 h at room temperature. Progress of the reaction was monitored by TLC (5% ethyl acetate/hexane, R_f~0.8). On completion of the reaction, cold water was added to the contents and the compound extracted with ethyl acetate (2 × 50 mL). Combined extract was dried over sodium sulfate and concentrated under reduced pressure to (2-fluorophenyl)(methyl)sulfane as a pale blue colored liquid (5 g, crude). The crude obtained was directly used for the next step.

Step 2: To a solution of $AlCl_3$ (9.2 g, 0.06 mol, 2 eq) in chloroform (50 mL) cooled at 0ºC, ethyl (chlorocarbonyl)formate (7.3 g, 0.05 mol, 1.6 eq) was added drop wise and the reaction mixture was stirred for 30–45 min at the same temperature. (2-fluorophenyl)(methyl)sulfane

(5 g, crude) was added at 0ºC and the reaction mixture was stirred for 4 h at room temperature. Progress of the reaction was monitored by TLC (5% ethyl acetate in n-hexane, R_f~0.5). On completion of the reaction, crushed ice was added and the mixture was stirred for some time. The organic layer was separated and the aqueous layer was extracted with DCM (2 × 50 mL). The combined extract was washed with $NaHCO_3$ solution, dried over sodium sulfate and concentrated under reduced pressure to yield ethyl 2-(3-fluoro-4-(methylthio)phenyl)-2-oxoacetate as an yellow colored liquid (5.5 g).

Step 3: To a solution of ethyl 2-(3-fluoro-4-(methylthio)phenyl)-2-oxoacetate (5.5 g, 0.02 mol) in toluene (55 mL, 10 times), 3 M sodium hydroxide solution (9.09 mL) was added at 50ºC and the reaction mixture was stirred for 3 h at the same temperature. Progress of the reaction was monitored by TLC (30% ethyl acetate/hexane, R_f~0.1). On completion of the reaction, the contents were cooled to 0ºC, the mixture was acidified with diluted HCl and the solid precipitated was filtered. The crude 2-(3-fluoro-4-(methylthio)phenyl)-2-oxoacetic acid obtained as an yellow colored solid (4.5 g, crude) was directly used for the next step.

Step 4: 2-(3-Fluoro-4-(methylthio)phenyl)-2-oxoacetic acid (4.5 g, crude) was added to hydrazine hydrate (5.1 mL, 5 eq) at –50ºC. The contents were heated to 80ºC, KOH (2.7 g, 2.3 eq) was added and the overall reaction mixture was stirred for 12 h at 100ºC. Progress of the reaction was monitored by TLC (50% ethyl acetate/hexane, R_f~0.8). On completion of the reaction, to the contents was added water and ethyl acetate and the layers were separated. The aqueous layer was acidified with diluted HCl at 0–5ºC, the precipitate was filtered and dried to yield 2-(3-fluoro-4-(methylthio)phenyl)acetic acid as a white colored solid (3 g, 71%).

Step 5: 2-(3-Fluoro-4-(methylthio)phenyl)acetic acid (3 g, 0.01 mol) was dissolved in dry THF (60 mL) and the mixture was cooled to –78ºC. Lithium bis(trimethylsilyl)amide (45 mL, 3 eq) was added at –78ºC and the mixture was stirred for 1 h at the same temperature. Methyl iodide (0.93 mL, 1 eq) was added at –78ºC, the mixture was allowed to come to room temperature and stirred for 3 h at the same temperature. Progress of the reaction was monitored by TLC (50% ethyl acetate/hexane, R_f~0.5). Although the reaction had not been completed the mixture was worked-up. The reaction contents were quenched with saturated ammonium chloride solution at 0ºC. The contents were acidified with diluted HCl, the organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 50 mL). the combined extract was dried over sodium sulfate, concentrated under reduced pressure and the crude obtained was purified by column chromatography (10% ethyl acetate/hexane) to yield 2-(3-fluoro-4-(methylthio)phenyl)propanoic acid as an yellow solid (1 g, 31%).

Step 6: To a solution of 2-(3-fluoro-4-(methylthio)phenyl)propanoic acid (1 g, 0.009 mol) in acetone (10 mL), potassium carbonate (0.63 g) was added at room temperature. DMS (0.58 g, 1 eq) was neutralized with potassium carbonate and filtered. The filtered DMS was added to the above contents and the overall reaction mixture was stirred for 2 h at room temperature. Progress of the reaction was monitored by TLC (20% ethyl acetate/hexane, R_f~0.9). On completion of the reaction, the mixture was filtered and the filtrate was concentrated under reduced pressure. The residue obtained was taken in water and the compound extracted with ethyl acetate (2 × 25 mL). The combined extract was dried over sodium sulfate, concentrated under reduced pressure and the crude product obtained as brown colored liquid (1 g) was directly used for the next step.

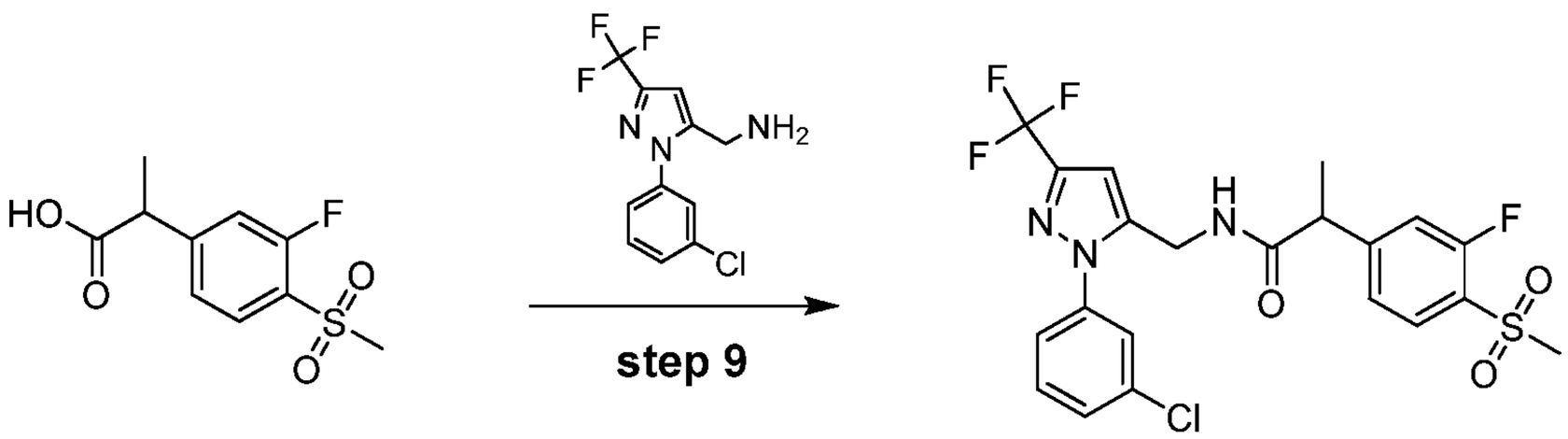
Step 7: Formic acid (6.5 mL, 1 eq) was added to methyl 2-(3-fluoro-4-(methylthio)phenyl)propanoate (1 g, crude) and the mixture cooled to 0ºC. Hydrogen peroxide (1.4 mL, 3 eq) was added drop wise at 0ºC and the reaction mixture was stirred overnight at room temperature. Progress of the reaction was monitored by TLC (20% ethyl acetate/hexane, R_f~0.4). On completion of the reaction, the contents were cooled to 0ºC, water was added and the mixture was extracted with ethyl acetate (2 × 25 mL). The combined extract was washed with $NaHCO_3$ solution, dried over sodium sulfate and concentrated under reduced pressure to yield methyl 2-(3-fluoro-4-(methylsulfonyl)phenyl)propanoate as colorless thick liquid (1 g, crude). The crude product obtained was directly used for the next step.

Step 8: To a solution of methyl 2-(3-fluoro-4-(methylsulfonyl)phenyl)propanoate (2.1 g, 0.008 mol) in methanol (21 mL, 10 times), a solution of sodium hydroxide (0.32 g, 1 eq) in water (3 mL) was added at 0ºC. The contents were allowed to come to room temperature and the mixture was stirred for 2 h. Progress of the reaction was monitored by TLC (50% ethyl acetate/hexane, R_f~0.1). On completion of the reaction, methanol was distilled off completely and the residue obtained was taken in water. The contents were acidified to a pH of 4 with diluted HCl, the precipitate was filtered and dried to yield 2-(3-fluoro-4-(methylsulfonyl)phenyl)propanoic acid as a white colored solid (1.7 g, 85%).

Step 9: To a solution of (3-tert-butyl-1-(3-chloro-4-fluorophenyl)-1H-pyrazol-5-yl)methanamine (49 mg, 0.189 mmol) in DCM (1.3 mL) at room temperature and under nitrogen atmosphere was added 1-chloro-N,N,2-trimethyl-1-propenylamine (48 µL, 0.369 mmol), After 1 h of stirring were added 2-(3-fluoro-4-(methylsulfonyl)phenyl)propanoic acid (93 mg, 0.378 mmol) and N-ethyldiisopropylamine (0.11 mL, 0.662 mmol). The reaction mixture was stirred overnight at room temperature, washed with $NaHCO_3$ solution (2 x 10 mL), dried over sodium sulfate and concentrated under reduced pressure. The obtained crude product was purified by column chromatography (eluent: ethyl acetate/cyclohexane

(2:1)) to give pure N-[[5-tert-butyl-2-(3-chlorophenyl)-2H-pyrazol-3-yl]-methyl]-2-(3-fluoro-4-methylsulfonyl-phenyl)-propionamide (example compound D1) (66 mg, 71%).

Synthesis of example D2: N-[[2-(3-Chlorophenyl)-5-(trifluoromethyl)-2H-pyrazol-3-yl]-methyl]-2-(3-fluoro-4-methylsulfonyl-phenyl)-propionamide

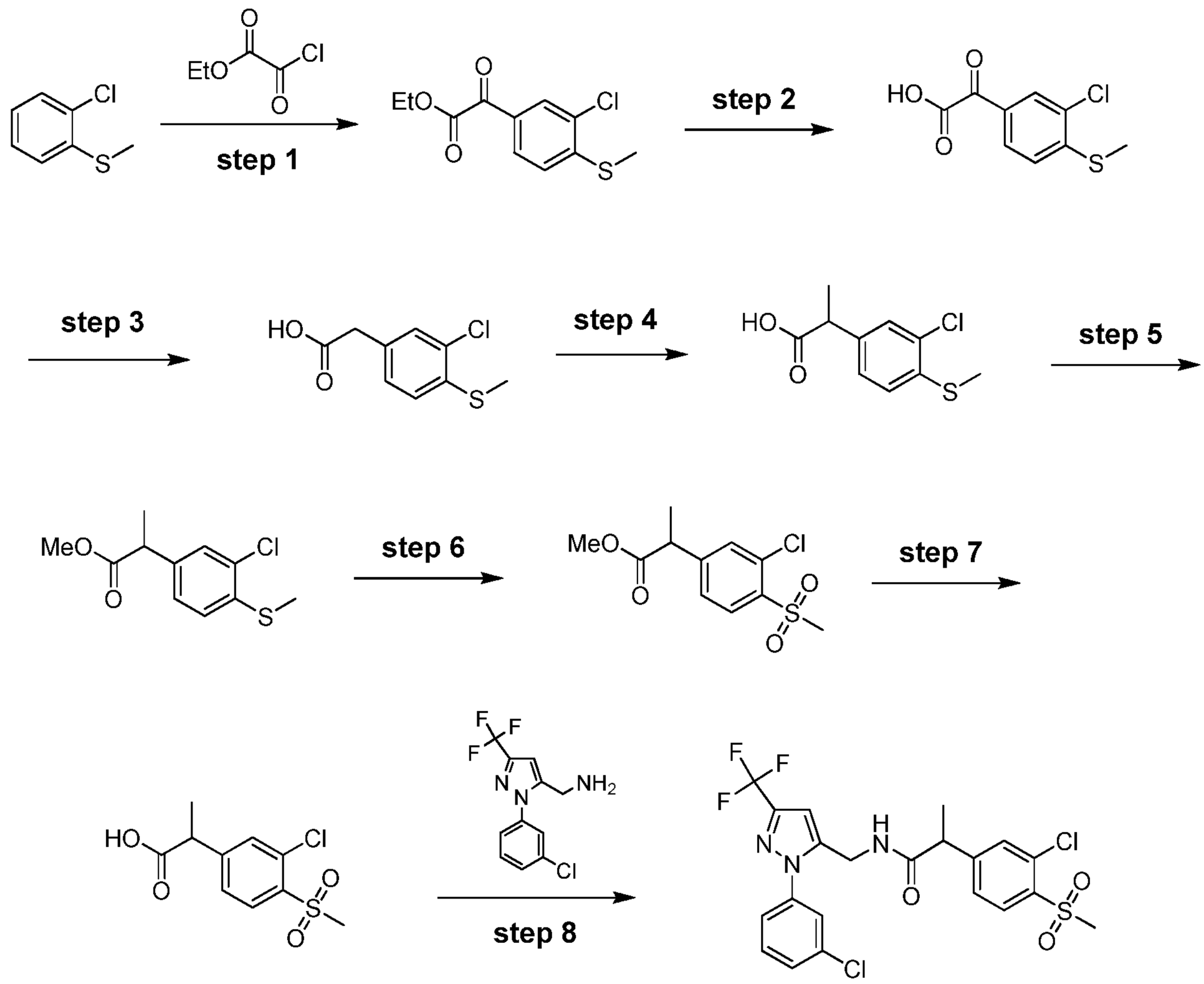


Steps 1-8: as described for **example D1**

Step 9: To a solution of 2-(3-fluoro-4-(methylsulfonyl)phenyl)propanoic acid (60 mg, 0.244 mmol) in THF(1.9 mL) was added 1-hydroxybenzotriazole (32 mg, 0.244 mmol), O-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (78 mg, 0.244 mmol), N-ethyldiisopropylamine (0.083 mL, 0.488 mmol) and (1-(3-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl)methanamine (67 mg, 0.244 mmol). The solution was stirred for 48 h at room temperature. The reaction mixture was concentrated in vacuo and purified by column chromatography (ethyl acetate/cyclohexane (2:1)) to give pure N-[[2-(3-chlorophenyl)-5-(trifluoromethyl)-2H-pyrazol-3-yl]-methyl]-2-(3-fluoro-4-methylsulfonyl-phenyl)-propionamide (example compound D2) (93 mg, 76 %).

Exemplary compounds D3 and **D4** were prepared in a similar manner.

Synthesis of example D5: 2-(3-Chloro-4-methylsulfonyl-phenyl)-N-[[2-(3-chlorophenyl)-5-(trifluoromethyl)-2H-pyrazol-3-yl]-methyl]-propionamide



Step 1: To a well stirred solution of $AlCl_3$ (16.58 g, 2 eq) in chloroform (100 mL), ethyl (chlorocarbonyl)formate (10.02 g (8.35 mL), 1.6 eq) was added at 0°C and the contents were allowed to stir for 30 min. Then (2-chlorophenyl)(methyl)sulfane (10 g (8.33 mL), 0.06 mol) was added at 0°C and the overall reaction mass was allowed to stir for 3 – 4 h at room temperature. Progress of the reaction was monitored by TLC (5% ethyl acetate/hexane, R_f~0.3). On completion of the reaction, crushed ice was added and the contents were allowed to stir for 10 min. The organic layer was separated and the aqueous layer was extracted with DCM (2 × 100 mL). The combined extract was dried over sodium sulfate and concentrated under reduced pressure to yield ethyl 2-(3-chloro-4-(methylthio)phenyl)-2-oxoacetate as a pale yellow colored liquid (12 g, 73%).

Step 2: A solution of ethyl 2-(3-chloro-4-(methylthio)phenyl)-2-oxoacetate (12 g, 0.49 mol) in toluene (120 mL, 10 times) was heated to 50°C. 3M NaOH solution (2.23 g, 1.2 eq) was added drop wise at 50°C and the contents were allowed to reflux for 3 h at 60°C. Progress of the reaction was monitored by TLC (50% ethyl acetate/hexane, R_f~0.1). On completion of the reaction, toluene was distilled off and the residue obtained was taken in ice cold water. Then the contents were acidified with diluted HCl at 0°C and allowed to stir for 1 h at room temperature. The precipitate was filtered and dried to yield 2-(3-chloro-4-(methylthio)phenyl)-2-oxoacetic acid as an yellow colored solid (10 g, 93%).

Step 3: To hydrazine hydrate (10 g, 5 eq) cooled at –50°C, 2-(3-chloro-4-(methylthio)phenyl)-2-oxoacetic acid (10 g, 0.04 mol) was added. The contents were initially warmed to room temperature and slowly heated to 80°C. Then KOH (5.59 g, 2.3 eq) was added portion wise at 80°C and the overall reaction mass was allowed to reflux for 12 – 16 h at the same temperature. Progress of the reaction was monitored by TLC (50% ethyl acetate/hexane, R_f~0.4). On completion of the reaction, the reaction contents were diluted with a mixture of water and ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 100 mL). Then the aqueous layer was acidified with diluted HCl and allowed to stir for 1 h at room temperature. The precipitate was filtered and dried to yield 2-(3-chloro-4-(methylthio)phenyl)acetic acid as a white colored solid (8 g, 85%).

Step 4: 2-(3-chloro-4-(methylthio)phenyl)acetic acid (2 g, 0.009 mol) was taken in THF (20 mL, 10 times) and cooled to –78°C. Lithium bis(trimethylsilyl)amide (27.77 mL, 3 eq) was added drop wise at –78°C and allowed to stir for 2 h at the same temperature. Then methyl iodide (1.31 g, 1 eq) was added drop wise at –78°C and the overall reaction mass was allowed to stir for 3 h at the same temperature. Progress of the reaction was monitored by TLC (50% ethyl acetate/hexane, R_f~0.2). As the reaction was not completed, reaction mass was warmed to room temperature and allowed to stir for 10 h. Again TLC was monitored and still the reaction was not completed. Then the reaction contents were quenched with saturated ammonium chloride solution and acidified with diluted HCl. THF layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 50 mL). The combined extract was dried over sodium sulfate, concentrated under reduced pressure and the crude obtained was purified by column chromatography (10% ethyl acetate/n-hexane) to yield 2-(3-chloro-4-(methylthio)phenyl)propanoic acid as a pale yellow colored solid (1.2 g, 53%).

Step 5: To a solution of 2-(3-chloro-4-(methylthio)phenyl)propanoic acid (3.5 g, 0.015 mol) in acetone (35 mL), potassium carbonate (2.06 g, 0.01mol, 1 eq) was added at room temperature. DMS (1.91 g, 1 eq) was neutralized with potassium carbonate and filtered. The filtered DMS was added to the above contents and the overall reaction mixture was stirred for 2 h at room temperature. Progress of the reaction was monitored by TLC (50% ethyl acetate/hexane, R_f~0.9). On completion of the reaction, filtered the contents and the filtrate was concentrated under reduced pressure. The residue obtained was taken in water and the compound extracted with ethyl acetate (2 × 100 mL). The combined extract was dried over sodium sulfate, concentrated under reduced pressure and the crude product obtained as brown colored liquid (3.5 g) was directly used for the next step.

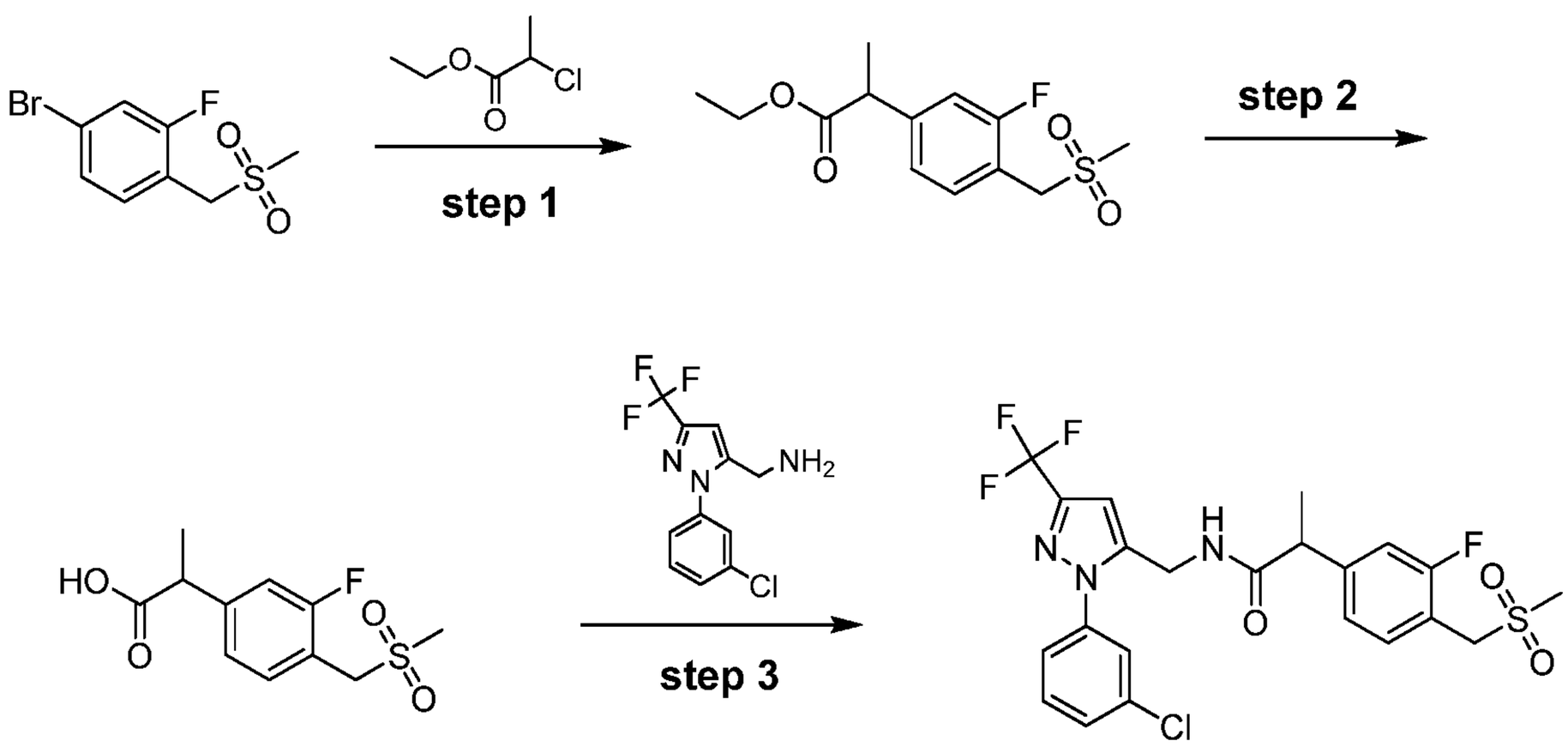
Step 6: Formic acid (20.8 mL, 1 eq) was added to methyl 2-(3-chloro-4-(methylthio)phenyl)propanoate (3.2 g, crude) and cooled to 0ºC. Hydrogen peroxide (4.48 mL, 3 eq) was added drop wise at 0ºC and the reaction mass was stirred for overnight at room temperature. Progress of the reaction was monitored by TLC (30% ethyl acetate/hexane, R_f~0.3). On completion of the reaction, the contents were cooled to 0ºC, water was added and the mixture was extracted with ethyl acetate (2 × 100 mL). The combined extract was washed with $NaHCO_3$ solution, dried over sodium sulfate and concentrated under reduced pressure to obtain methyl 2-(3-chloro-4-(methylsulfonyl)phenyl)propanoate as a colorless thick liquid (3.2 g, crude). Crude product obtained was directly used for the next step.

Step 7: To a solution of methyl 2-(3-chloro-4-(methylsulfonyl)phenyl)propanoate (3.2 g, crude) in methanol (32 mL, 10 times), a solution of sodium hydroxide (0.46 g, 1 eq) in water (5 mL) was added at 0ºC. The contents were warmed to room temperature and allowed to stir for 2 h. Progress of the reaction was monitored by TLC (50% ethyl acetate/hexane, R_f~0.1). On completion of the reaction, methanol was distilled off completely and the residue obtained was taken in water. The contents were acidified to a pH of 4 and diluted with HCl at 0ºC, the precipitate was filtered and dried to yield 2-(3-chloro-4-(methylsulfonyl)phenyl)propanoic acid as a white colored solid (2.7 g, 88%).

Step 8: To a solution of 2-(3-chloro-4-(methylsulfonyl)phenyl)propanoic acid (60 mg, 0.229 mmol) in THF (1.9 mL) was added 1-hydroxybenzotriazole (30 mg, 0.229 mmol), O-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (74 mg, 0.229 mmol), N-ethyldiisopropylamine (0.078 mL, 0.458 mmol) and (1-(3-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl)methanamine (63 mg, 0.229 mmol). The solution was stirred for 48 h at room temperature. The reaction mixture was concentrated in vacuo and purified by column

chromatography (eluent: ethyl acetate/cyclohexane (1:2)) to give 2-(3-chloro-4-methylsulfonyl-phenyl)-N-[[2-(3-chlorophenyl)-5-(trifluoromethyl)-2H-pyrazol-3-yl]-methyl]-propionamide (example compound D5) (100 mg, 84 %).

Synthesis of example D6: N-[[2-(3-Chlorophenyl)-5-(trifluoromethyl)-2H-pyrazol-3-yl]-methyl]-2-[3-fluoro-4-(methylsulfonyl-methyl)-phenyl]-propionamide



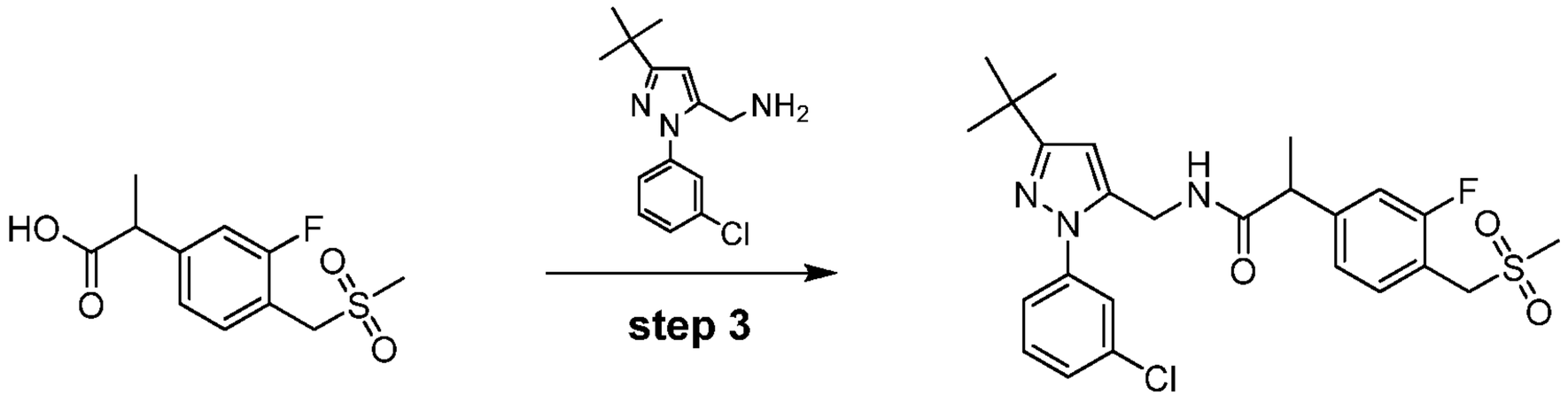
Step 1: To a stirred solution of 4-bromo-2-fluoro-1-(methylsulfonylmethyl)benzene (2 g, 7.487 mmol) in dimethylformamide (11 mL) were added ethyl 2-chloropropionate (1.24 mL,9.733 mmol), manganese (822 mg, 14.974 mmol) and (2,2'-bipyridine)nickel(II)-dibromide (196 mg, 0.524 mmol). Trifluoroacetic acid (4 drops) was added. The reaction mixture was stirred overnight at 60 ˚C. After cooling down to room temperature, the mixture was hydrolyzed by 1N HCl (30 mL) and extracted with ethyl acetate (3 x 50 mL). The organic layer was dried over magnesium sulfate and filtered. The solvent was removed in vacuo. The crude was purified by CC (eluent: ethyl acetate/cyclohexane (1:1)) to give ethyl 2-(3-fluoro-4-(methylsulfonylmethyl)phenyl)propanoate (966 mg, 45 %).

Step 2: To a stirred solution of ethyl 2-(3-fluoro-4-(methylsulfonylmethyl)phenyl)propanoate (950 mg, 3.295 mmol) in co-solvent with tetrahydrofuran and water (1:1) were added lithium hydroxide (236 mg, 9.885 mmol). The reaction mixture was refluxed for overnight, then cooled to room temperature, diluted with water (25 mL) and diethyl ether (25 mL). After phase separation the aqueous layer was acidified by HCl to a pH = 3 and extracted with DCM (3 x 50 mL). The organic layer was dried over magnesium sulfate and filtered. The solvent of the filtrate was removed in vacuo to give 2-(3-fluoro-4-(methylsulfonylmethyl)-phenyl)propanoic acid (846 mg, 99 %).

Step 3: To a stirred solution of 2-(3-fluoro-4-(methylsulfonylmethyl)phenyl)propanoic acid (68 mg, 0.231 mmol) and (1-(3-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl)methanamine (60 mg, 0.231 mmol) in THF (1.8 mL) were added O-(1H-Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluorborat (73 mg, 0.231 mmol), 1-hydroxybenzotriazole (30 mg, 0.231 mmol) and N-ethyldiisopropylamine (0.078 mL, 0.462 mmol). The reaction mixture was stirred for 48 h at room temperature, concentrated in vacuo and the residue was purified by CC (eluent: ethyl acetate/cyclohexane (3:2)) to give N-[[2-(3-Chlorophenyl)-5-(trifluoromethyl)-2H-pyrazol-3-yl]-methyl]-2-[3-fluoro-4-(methylsulfonyl-methyl)-phenyl]-propionamide (83 mg, 69%).

Exemplary compound D10 was prepared analogously according to **D6.**

Synthesis of example D7: N-[[5-tert-Butyl-2-(3-chlorophenyl)-2H-pyrazol-3-yl]-methyl]-2-[3-fluoro-4-(methylsulfonyl-methyl)-phenyl]-propionamide

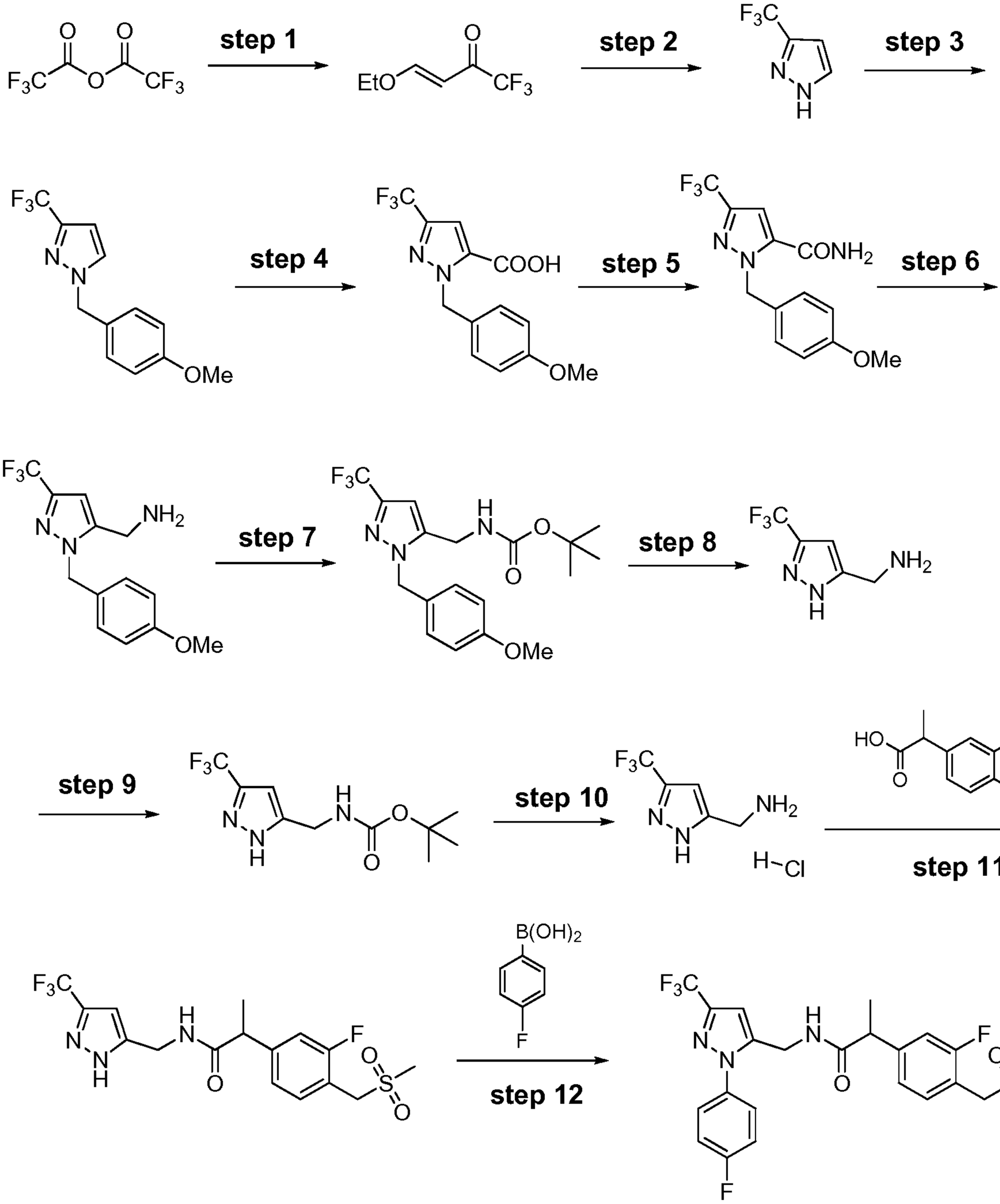


Steps 1-2: as described for **example compound D6**

Step 3: To a stirred solution of 2-(3-fluoro-4-(methylsulfonylmethyl)phenyl)propanoic acid (60 mg, 0.231 mmol) and (3-tert-butyl-1-(3-chlorophenyl)-1H-pyrazol-5-yl)methanamine (60 mg, 0.231 mmol) in THF (1.8 mL) were added O-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluorborat (73 mg, 0.231 mmol), 1-hydroxybenzotriazole (30 mg, 0.231 mmol) and N-ethyldiisopropylamine (0.078 mL, 0.462 mmol). The reaction mixture was stirred for 48 h at room temperature, concentrated in vacuo and the residue was purified by CC (eluent: ethyl acetate/cyclohexane (3:2)) to give N-[[5-tert-butyl-2-(3-chlorophenyl)-2H-pyrazol-3-yl]-methyl]-2-[3-fluoro-4-(methylsulfonyl-methyl)-phenyl]-propionamide (94 mg, 80%).

Exemplary compounds D8, D9, D11, D13, D16–D21, D23 and **24** were prepared in a similar manner or may be prepared analogously according to **D7.**

Synthesis of example D12: 2-[3-Fluoro-4-(methylsulfonyl-methyl)-phenyl]-N-[[2-(4-fluorophenyl)-5-(trifluoromethyl)-2H-pyrazol-3-yl]-methyl]-propionamide



Step 1: DMAP (4.25 g, 34 mmol) was added to DCM (3 L) and the contents were cooled to -10°C. Trifluoroacetic anhydride (765 g , 3.2 mol) was added followed by ethyl vinyl ether (250 g, 3.04 mol) which was added drop wise for 45 min at – 10°C. Then the overall reaction

mixture was stirred for 8 h at 0°C and later overnight at room temperature. Progress of the reaction was monitored by TLC (10% ethyl acetate/hexane, R_f~0.7). On completion of the reaction, the reaction contents were treated with saturated $NaHCO_3$ solution (600 mL) and the organic layer was separated. The aqueous layer was extracted with DCM (2 × 500 mL). The combined organic layer was washed with water (2 × 1 L), dried over sodium sulfate and concentrated under reduced pressure to give (E)-4-ethoxy-1,1,1-trifluorobut-3-en-2-one as a brown colored liquid (450 g, crude).

Step 2: Hydrazine dihydrochloride (225 g, 2.14 mol) in ethanol (1400 mL) was stirred well. TEA (185.4 mL, 1.34 mol) was added drop wise for 45 min at ambient temperature. Then (E)-4-ethoxy-1,1,1-trifluorobut-3-en-2-one (225 g, crude) was added drop wise at room temperature and the overall reaction mixture was refluxed overnight. Progress of the reaction was monitored by TLC (20 % ethyl acetate/hexane, Rf~0.4). On completion of the reaction, ethanol was distilled off completely, residue was taken in ice water (500 mL) and the product extracted with ethyl acetate (2 × 400 mL). Combined extract was washed with ice water (300 mL), dried over sodium sulfate and concentrated under reduced pressure to yield 3-(trifluoromethyl)-1H-pyrazole as a off white solid (175 g,crude).

Step 3: NaH (33.08 g (19.85 mol, 60 %) was washed with n-hexane, then dry DMF (500 mL) was added drop wise under N_2 atmosphere and the mixture was stirred well. A solution of 3-(trifluoromethyl)-1H-pyrazole (75 g, 0.55 mol) in DMF (125 mL) was added drop wise under N_2 atmosphere. Then a solution of 4-methoxylbenzyl chloride (86.3 g, 0.55 mol) in DMF (125 mL) was added drop wise and the overall reaction mixture was allowed to stir for 12 h at room temperature. Progress of the reaction was monitored by TLC (10 % ethyl acetate/hexane, R_f~0.4). On completion of the reaction, the reaction contents were poured into ice water (500 mL) and the product was extracted with ethyl acetate (2 × 400 mL). The ethyl acetate layer was washed with 2N HCl (2 x 200ml). Then the contents were dried over sodium sulfate and concentrated under reduced pressure. The obtained crude was purified by CC with 10% ethyl acetate/n-hexane to yield 1-(4-methoxybenzyl)-3-(trifluoromethyl)-1H-pyrazole as a brown colored liquid (98 g, 70 %).

Step 4: Diisopropyl amine (28.4 mol, 39.4 mL) was taken in THF (500 mL), stirred well and cooled to 0°C. n-BuLi (234.4 mL) was added drop wise at 0°C and the mixture was stirred for 1 h at 0°C. Then the contents were cooled to –78°C, a solution of 1-(4-methoxybenzyl)-3-(trifluoromethyl)-1H-pyrazole (62 g, 0.24 mol) in THF (200 mL) was added drop wise for 30 min and the contents were stirred for another h at –78°C. Then dry CO_2 gas was bubbled through the reaction mixture for 1.5 h. Progress of the reaction was monitored by TLC (10 %

ethyl acetate/hexane, R_f~0.1). On completion of the reaction, the reaction contents were poured into ice water (300 mL) and the aqueous layer was extracted with ethyl acetate (2 × 200 mL) in basic condition. The aqueous layer was acidified with 20% HCl solution and extracted with ethyl acetate (2 × 200 mL). The combined organic layer was dried over sodium sulfate and concentrated under reduced pressure to yield 1-(4-methoxybenzyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylic acid as an off white solid (40 g, 55 %).

Step 5: To a solution of 1-(4-methoxybenzyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylic acid (50 g, 0.16 mol) in DCM (750 mL), a catalytic amount of DMF was added and the mixture was cooled to 0℃. Thionyl chloride (61 mL, 0.83 mol) was added drop wise for 30 min at 0℃. The overall reaction mixture was heated to reflux and maintained for 2 h. Progress of the reaction was monitored by TLC (10 % ethyl acetate/hexane, R_f~0.4). On disappearance of the starting material, DCM was distilled off completely. Above prepared acid chloride was dissolved in DCM (500 mL) and added drop wise to aqueous ammonia solution (700 mL) at 0℃. The overall reaction mixture was allowed to stir for 1 h and the progress of the reaction was monitored by TLC (10% ethyl acetate/hexane, R_f~0.7). On completion of the reaction, ice cold water (200 mL) was added and the product was extracted with ethyl acetate (2 × 200 mL). The combined organic layer was dried over sodium sulfate and concentrated under reduced pressure to yield 1-(4-methoxybenzyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide as an off white solid (37 g, crude). Crude obtained was directly used for the next step.

Step 6: LAH (4.7 g, 0.12 mol) was charged into a flask. THF (250 mL) was added at 0℃. Then a solution of 1-(4-methoxybenzyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (37 g, 0.12 mol) in THF (120 mL) was added drop wise for 30 min at 0℃ and reaction mixture was heated to reflux for 5 h. Progress of the reaction was monitored by TLC (50 % ethyl acetate/hexane, R_f~0.2). As the reaction was not completd, LAH (2.3 g) was added again and the mixture was refluxed for another 4 h. After completion of the reaction, the reaction contents were slowly added to saturated sodium sulfate (1 L) solution and filtered over celite and the product was extracted with ethyl acetate (2 × 500 mL). The combined extract was dried over sodium sulfate and concentrated under reduced pressure to obtain the crude (1-(4-methoxybenzyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl)methanamine as an off white solid (32.5 g, crude). The crude obtained was directly used for the next step.

Step 7: To a solution of (1-(4-methoxybenzyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl)methanamine (80 g, 0.28 mol) in DCM (600 mL) cooled at 0℃, TEA (30.2 mL, 0.026 mol) was added drop wise for 10 min. Then Boc anhydride (62.5 mL, 0.28 mol) was added drop

wise for 20 – 30 min at 0°C. The overall reaction mixture was stirred for 30 min at 0°C and stirred for 1 h at room temperature. Progress of the reaction was monitored by TLC (20 % ethyl acetate/hexane, R_f~0.6). On completion of the reaction, DCM was distilled off completely, the residue was taken in ice water (500 mL) and the product extracted with ethyl acetate (2 × 300 mL). The combined extract was dried over sodium sulfate and concentrated under reduced pressure. The crude obtained was recrystallized from n-hexane (200 mL) to yield tert-butyl (1-(4-methoxybenzyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl)methylcarbamate as an off white solid (80 g, 74 %).

Step 8: To a stirred solution of tert-butyl (1-(4-methoxybenzyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl)methylcarbamate (20 g, 0.052 mol) in toluene (300 mL) cooled to 0°C was added aluminum chloride (17.34 g, 0.129 mol) portion wise for 30 min. The reaction mixture was slowly heated to 50 – 60°C and allowed to stir for 2 h at the same temperature. Progress of the reaction was monitored by TLC (20 % ethyl acetate/hexane, R_f~0.1). On completion of the reaction, the reaction contents were treated with diluted HCl, ice cold water (300 mL) was added and the mixture was extracted with ethyl acetate (2 × 100 mL). The aqueous layer was basified with sodium hydroxide solution and extracted with ethyl acetate and dried over sodium sulfate and concentrated under reduced pressure to give (3-(trifluoromethyl)-1H-pyrazol-5-yl)methanamine as a brown colored solid (4.6 g, crude). The crude obtained was directly used for the next step.

Step 9: (3-(Trifluoromethyl)-1H-pyrazol-5-yl)methanamine (7 g, 42.4 mmol) was dissolved in DCM (7 mL) at room temperature, then to that TEA (5.86 mL, 72.4 mmol) was added at room temperature and the mixture was stirred for 10 min and cooled to 0-5°C. $(Boc)_2O$ (9.24 g, 42.4 mmol) was added drop wise to reaction mixture for 30 min and maintained for 3 h at 0-5°C. Progress of the reaction was monitored by the TLC (30 % ethyl acetate/n-hexane). On completion of the reaction, the reaction mixture was brought to room temperature for 2 h and the DCM was distilled off, the residue obtained was treated with water (50 mL) and extracted with ethyl acetate (100 mL). The combined organic layer was dried over sodium sulphate, and the solvent evaporated under vacuum. The obtained crude was purified with CC to yield tert-butyl (3-(trifluoromethyl)-1H-pyrazol-5-yl)methylcarbamate as a white colored solid (5 g, 44 %).

Step 10: To a stirred solution of tert-butyl (3-(trifluoromethyl)-1H-pyrazol-5-yl)methyl-carbamate (5 g, 18.8 mmol) in MeOH (36 mL) was added HCl in 2-propanol (5.8 mL, 29.2 mmol) and the mixture was stirred for 48 h at room temperature. The reaction mixture was concentrated in vacuo, diethylether (20 mL) was added and the obtained precipitate filtered

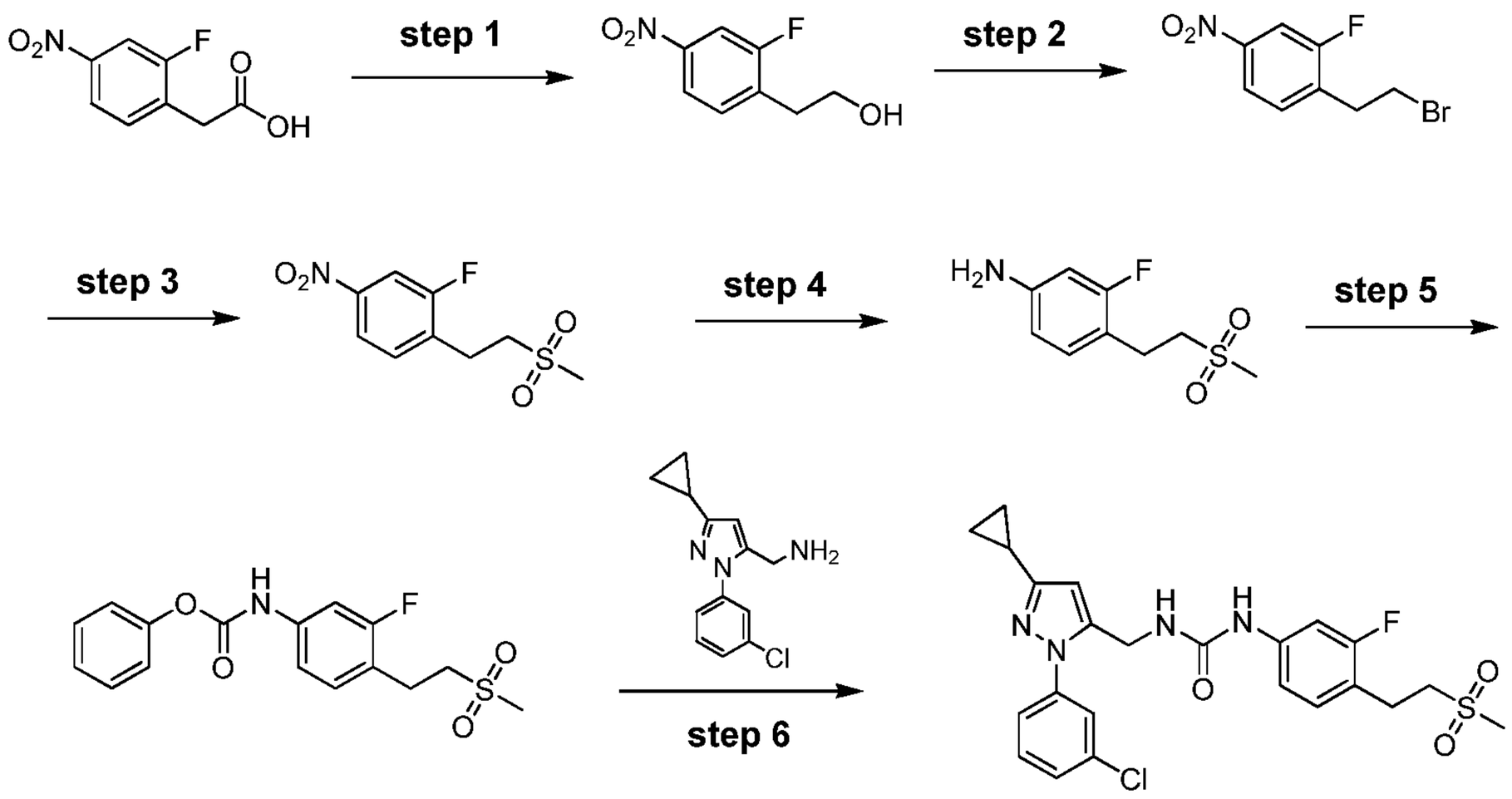
off and washed with diethylether (5 mL). After drying (3-(trifluoromethyl)-1H-pyrazol-5-yl)methanamine hydrochloride was obtained (3.67 g, 97 %).

Step 11: To a stirred solution of (3-(trifluoromethyl)-1H-pyrazol-5-yl)methanamine hydrochloride (194 mg, 0.96 mmol) and 2-(3-fluoro-4-(methylsulfonylmethyl)phenyl)propanoic acid (250 mg, 0.96 mmol) in THF (7.4 mL) were added O-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluorborat (308 mg, 0.96 mmol), 1-hydroxybenzotriazole (135 mg, 0.96 mmol) and N-ethyldiisopropylamine (0.491 mL, 2.881 mmol). The reaction mixture was stirred for overnight at room temperature, concentrated in vacuo, purified by CC (eluent: ethyl acetate/cyclohexane (9:1)) to give 2-(3-fluoro-4-(methylsulfonylmethyl)phenyl)-N-((3-(trifluoromethyl)-1H-pyrazol-5-yl)methyl)propanamide (335 mg, 86 %).

Step 12: 4-Fluorophenylboronic acid (41 mg, 0.295 mmol), 2-(3-fluoro-4-(methylsulfonylmethyl)phenyl)-N-((3-(trifluoromethyl)-1H-pyrazol-5-yl)methyl)propanamide (60 mg, 0.147 mmol) and copper(II)-acetate (0.021 mL, 0.221 mmol) were added to DCM (2.2 mL). At room temperature was added pyridine (0.238 mL, 2.946 mmol) and the mixture was stirred for overnight. The reaction mixture was concentrated in vacuo, the solid obtained was purified by CC (eluent: cyclohexane/ethyl acetate (1:2)) to afford 2-[3-fluoro-4-(methylsulfonyl-methyl)-phenyl]-N-[[2-(4-fluorophenyl)-5-(trifluoromethyl)-2H-pyrazol-3-yl]-methyl]-propionamide (55 mg, 75 %).

Exemplary compounds D14, **D15**, **D22** and **D25** were prepared in a similar manner or may be prepared analogously according to **D12.**

Synthesis of example D26: 1-[[2-(3-Chlorophenyl)-5-cyclopropyl-2H-pyrazol-3-yl]-methyl]-3-[3-fluoro-4-(2-methylsulfonyl-ethyl)-phenyl]-urea



Step 1: To a stirred solution of 2-(2-fluoro-4-nitrophenyl)acetic acid (1g, 5.02 mmol) in tetrahydrofuran (10 mL) was added $BH_3 \bullet S(CH_3)_2$ (7.5 mL, 7.53 mmol) at 0°C. The reaction mixture was allowed to stir at room temperature for 10 h. Then reaction mixture was cooled to 0°C and the excess of borane was quenched with methanol (10 mL). The reaction mixture was concentrated under reduced pressure to obtain a crude compound which was purified by CC (eluent: ethyl acetate/n-hexane (1:1)) to give 2-(2-fluoro-4-nitrophenyl)ethanol (0.89 g, 95 %).

Step 2: 2-(2-Fluoro-4-nitrophenyl)ethanol (0.89 g, 4.8 mmol) was added to a stirred solution of 48% aqueous hydrobromic acid (0.77g, 9.62 mmol) and concentrated sulfuric acid (0.25 mL) under cooling. The reaction mixture was heated to 100°C for 3 h. The reaction mixture was diluted with water (25 mL) and was extracted with ethyl acetate (3 x 25 mL). The combined organic layer was washed with brine (25 mL) and dried over anhydrous magnesium sulfate and concentrated under reduced pressure to afford the crude compound. The crude was purified by CC (eluent: 5% ethyl acetate in n-hexane) to afford 1-(2-bromoethyl)-2-fluoro-4-nitrobenzene (1 g, 85 %).

Step 3: To a stirred solution of 1-(2-bromoethyl)-2-fluoro-4-nitrobenzene (1 g, 4.03 mmol) in isopropanol (15 mL) was added sodium methane sulfinate (2.05g, 20.16 mmol) at room temperature. The reaction mixture was heated to 70°C for 10 h. The reaction mixture was cooled to room temperature and was concentrated under reduced pressure to obtain a crude

compound which was filtered off and the residue was washed with water (2 x 5 mL) to obtain pure 2-fluoro-1-(2-(methylsulfonyl)ethyl)-4-nitrobenzene (700 mg, 70 %).

Step 4: 2-Fluoro-1-(2-(methylsulfonyl)ethyl)-4-nitrobenzene (700 mg, 2.83 mmol) was dissolved in ethyl acetate (7 mL), and to the solution was added (10 %) Pd / C (70 mg) under argon atmosphere which was subjected to hydrogenation in a Parr apparatus and the reaction was continued to stir for 2 h. The reaction mixture was filtered through celite and was washed thoroughly with ethyl acetate and was concentrated under reduced pressure to obtain 3-fluoro-4-(2-(methylsulfonyl)ethyl)aniline (590 mg, 96 %).

Step 5: To a stirred solution of 3-fluoro-4-(2-(methylsulfonyl)ethyl)aniline (200 mg, 0.92 mmol) in acetone / DMF (3 mL + 1.27 mL), pyridine (0.222 mL, 2.76 mmol) was added dropwise phenyl chloroformate (0.152 mL, 1.197 mmol) at 0°C and the mixture was stirred at room temperature for 1 h. The acetone was evaporated and the residue was diluted with DCM (30 mL). The mixture was washed with saturated $NaHCO_3$ solution (15 mL) and the organic layer extracted with DCM (2 x 20 mL). The combined organic layer was dried over magnesium sulfate and concentrated in vacuo to give pure phenyl 3-fluoro-4-(2-(methylsulfonyl)ethyl)phenylcarbamate (260 mg, 84 %).

Step 6: To a stirred solution of phenyl 3-fluoro-4-(2-(methylsulfonyl)ethyl)phenylcarbamate (90 mg, 0.267 mmol) and (1-(3-chlorophenyl)-3-cyclopropyl-1H-pyrazol-5-yl)methanamine (70 mg, 0.286 mmol) in THF (4 mL) was added N-ethyldiisopropylamine (0.087 mL, 0.507 mmol) and stirred for 1 h in a microwave (150 °C, 7 bar). The reaction mixture was concentrated in vacuo and purified by CC (eluent: ethyl acetate/cyclohexane (2:1)) to give 1-[[2-(3-chlorophenyl)-5-cyclopropyl-2H-pyrazol-3-yl]-methyl]-3-[3-fluoro-4-(2-methylsulfonyl-ethyl)-phenyl]-urea (30 mg, 23 %).

Exemplary compounds D27 - D33 were prepared in a similar manner or may be prepared analogously according to **D26.**

Mass spectrometric data are cited hereinafter by way of example for the following exemplary compounds (Table 1):

Table 1

Exemplary compound	[M+H]
D1	492.0
D2	504.3
D3	488.1
D4	522.1
D5	520.2
D6	518.2
D7	506.3
D8	524.0
D9	490.2
D10	502.1
D12	502.1
D14	520.1
D15	520.1
D26	491.1
D27	519.1
D28	537.0
D29	507.2
D30	491.2
D31	509.2
D32	499.1
D33	527.2

Pharmacological methods

I. Functional testing carried out on the vanilloid receptor 1 (VRI/TRPV1 receptor)

The agonistic or antagonistic effect of the substances to be tested on the rat-species vanilloid receptor 1 (VR1/TRPV1) can be determined using the following assay. In this assay, the influx of Ca^{2+} through the receptor channel is quantified with the aid of a Ca^{2+}-sensitive dye (type Fluo-4, Molecular Probes Europe BV, Leiden, the Netherlands) in a fluorescent imaging plate reader (FLIPR, Molecular Devices, Sunnyvale, USA).

Method:

Complete medium: 50 mL HAMS F12 nutrient mixture (Gibco Invitrogen GmbH, Karlsruhe, Germany) with 10 % by volume of FCS (foetal calf serum, Gibco Invitrogen GmbH, Karlsruhe, Germany, heat-inactivated); 2mM L-glutamine (Sigma, Munich, Germany); 1 % by weight of AA solution (antibiotic/antimyotic solution, PAA, Pasching, Austria) and 25 ng/mL NGF medium (2.5 S, Gibco Invitrogen GmbH, Karlsruhe, Germany)

Cell culture plate: Poly-D-lysine-coated, black 96-well plates having a clear base (96-well black/clear plate, BD Biosciences, Heidelberg, Germany) are additionally coated with laminin (Gibco Invitrogen GmbH, Karlsruhe, Germany), the laminin being diluted with PBS (Ca-Mg-free PBS, Gibco Invitrogen GmbH, Karlsruhe, Germany) to a concentration of 100 µg/mL. Aliquots having a laminin concentration of 100 µg/mL are removed and stored at -20 °C. The aliquots are diluted with PBS in a ratio of 1:10 to 10 µg/mL of laminin and respectively 50 µL of the solution are pipetted into a recess in the cell culture plate. The cell culture plates are incubated for at least two hours at 37 °C, the excess solution is removed by suction and the recesses are each washed twice with PBS. The coated cell culture plates are stored with excess PBS which is not removed until just before the feeding of the cells.

Preparation of the cells:

The vertebral column is removed from decapitated rats and placed immediately into cold HBSS buffer (Hank's buffered saline solution, Gibco Invitrogen GmbH, Karlsruhe, Germany), i.e. buffer located in an ice bath, mixed with 1 % by volume (per cent by volume) of an AA solution (antibiotic/antimyotic solution, PAA, Pasching, Austria). The vertebral column is cut longitudinally and removed together with fasciae from the vertebral canal. Subsequently, the dorsal root ganglia (DRG) are removed and again stored in cold HBSS buffer mixed with 1 % by volume of an AA solution. The DRG, from which all blood remnants and spinal nerves

have been removed, are transferred in each case to 500 µL of cold type 2 collagenase (PAA, Pasching, Austria) and incubated for 35 minutes at 37 °C. After the addition of 2.5 % by volume of trypsin (PAA, Pasching, Austria), incubation is continued for 10 minutes at 37 °C. After complete incubation, the enzyme solution is carefully pipetted off and 500 µL of complete medium are added to each of the remaining DRG. The DRG are respectively suspended several times, drawn through cannulae No. 1, No. 12 and No. 16 using a syringe and transferred to a 50 mL Falcon tube which is filled up to 15 mL with complete medium. The contents of each Falcon tube are respectively filtered through a 70 µm Falcon filter element and centrifuged for 10 minutes at 1,200 rpm and room temperature. The resulting pellet is respectively taken up in 250 µL of complete medium and the cell count is determined.

The number of cells in the suspension is set to 3×10^5 per mL and 150 µL of this suspension are in each case introduced into a recess in the cell culture plates coated as described hereinbefore. In the incubator the plates are left for two to three days at 37 °C, 5 % by volume of CO_2 and 95 % relative humidity. Subsequently, the cells are loaded with 2 µM of Fluo-4 and 0.01 % by volume of Pluronic F127 (Molecular Probes Europe BV, Leiden, the Netherlands) in HBSS buffer (Hank's buffered saline solution, Gibco Invitrogen GmbH, Karlsruhe, Germany) for 30 min at 37 °C, washed 3 times with HBSS buffer and after further incubation for 15 minutes at room temperature used for Ca^{2+} measurement in a FLIPR assay. The Ca^{2+}-dependent fluorescence is in this case measured before and after the addition of substances (λex = 488 nm, λem = 540 nm). Quantification is carried out by measuring the highest fluorescence intensity (FC, fluorescence counts) over time.

FLIPR assay:

The FLIPR protocol consists of 2 substance additions. First the compounds to be tested (10 µM) are pipetted onto the cells and the Ca^{2+} influx is compared with the control (capsaicin 10 µM). This provides the result in % activation based on the Ca^{2+} signal after the addition of 10 µM of capsaicin (CP). After 5 minutes' incubation, 100 nM of capsaicin are applied and the Ca^{2+} influx is also determined.

Desensitising agonists and antagonists lead to suppression of the Ca^{2+} influx. The % inhibition is calculated compared to the maximum achievable inhibition with 10 µM of capsazepine.

Triple analyses (n=3) are carried out and repeated in at least 3 independent experiments (N=4).

Starting from the percentage displacement caused by different concentrations of the compounds to be tested of general formula I, IC_{50} inhibitory concentrations which cause a 50-% displacement of capsaicin were calculated. K_i values for the test substances were obtained by conversion by means of the Cheng-Prusoff equation (Cheng, Prusoff; Biochem. Pharmacol. 22, 3099-3108, 1973).

II. Functional testing carried out on the vanilloid receptor 1 (VRI/TRPV1 receptor)

The agonistic or antagonistic effect of the substances to be tested on the vanilloid receptor 1 (VR1) can also be determined using the following assay. In this assay, the influx of Ca^{2+} through the channel is quantified with the aid of a Ca^{2+}-sensitive dye (type Fluo-4, Molecular Probes Europe BV, Leiden, the Netherlands) in a fluorescent imaging plate reader (FLIPR, Molecular Devices, Sunnyvale, USA).

Method:

Chinese hamster ovary cells (CHO K1 cells, European Collection of Cell Cultures (ECACC) United Kingdom) are stably transfected with the VR1 gene. For functional testing, these cells are plated out on poly-D-lysine-coated black 96-well plates having a clear base (BD Biosciences, Heidelberg, Germany) at a density of 25,000 cells/well. The cells are incubated overnight at 37 °C and 5 % CO_2 in a culture medium (Ham's F12 nutrient mixture, 10 % by volume of FCS (foetal calf serum), 18 µg/ml of L-proline). The next day the cells are incubated with Fluo-4 (Fluo-4 2 µM, 0.01 % by volume of Pluronic F127, Molecular Probes in HBSS (Hank's buffered saline solution), Gibco Invitrogen GmbH, Karlsruhe, Germany) for 30 minutes at 37 °C. Subsequently, the plates are washed three times with HBSS buffer and after further incubation for 15 minutes at RT used for Ca^{2+} measurement in a FLIPR assay. The Ca^{2+}-dependent fluorescence is measured before and after the addition of the substances to be tested (λex wavelength = 488 nm, λem = 540 nm). Quantification is carried out by measuring the highest fluorescence intensity (FC, fluorescence counts) over time.

FLIPR assay:

The FLIPR protocol consists of 2 substance additions. First the compounds to be tested (10 µM) are pipetted onto the cells and the Ca^{2+} influx is compared with the control (capsaicin 10 µM) (% activation based on the Ca^{2+} signal after the addition of 10 µM of capsaicin). After 5 minutes' incubation, 100 nM of capsaicin are applied and the Ca^{2+} influx is also determined.

Desensitising agonists and antagonists led to suppression of the Ca^{2+} influx. The % inhibition is calculated compared to the maximum achievable inhibition with 10 µM of capsazepine.

Starting from the percentage displacement caused by different concentrations of the compounds to be tested of general formula I, IC_{50} inhibitory concentrations which cause a 50-per cent displacement of capsaicin were calculated. K_i values for the test substances were obtained by conversion by means of the Cheng-Prusoff equation (Cheng, Prusoff; Biochem. Pharmacol. 22, 3099-3108, 1973).

Pharmacological data

The affinity of the compounds according to the invention for the vanilloid receptor 1 (VR1/TRPV1 receptor) was determined as described hereinbefore (pharmacological method I or II).

The compounds according to the invention display outstanding affinity to the VR1/TRPV1 receptor (Table 2).

In Table 2 the abbreviations below have the following meanings:

Cap = capsaicin
AG = agonist

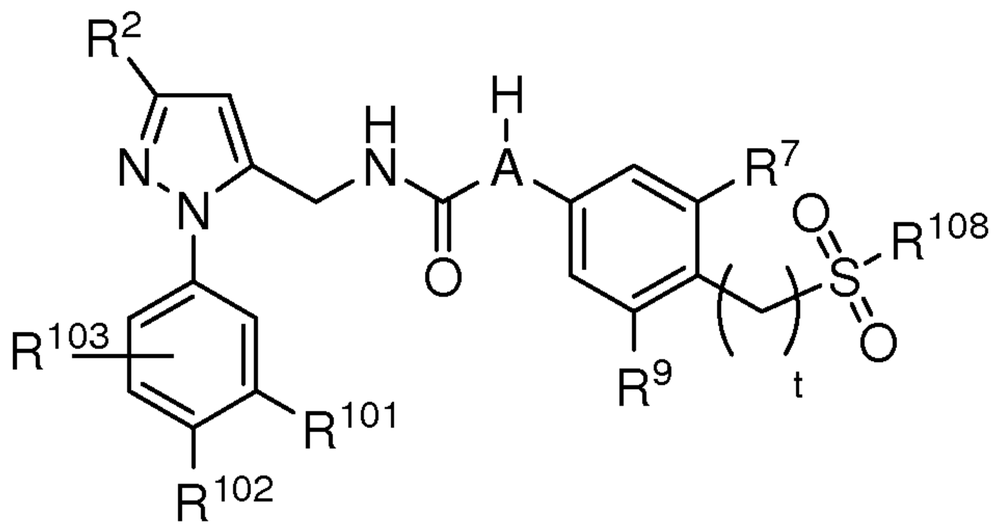
The value after the „@“symbol indicates the concentration at which the inhibition (as a percentage) was respectively determined.

Table 2

Compound according to Example	***(f)* Ki (human being) [nM] Cap**
D1	AG
D2	73
D3	55% @ 5 µM
D4	41
D5	7
D6	38
D7	27
D8	48
D9	30
D10	75
D26	42
D27	40
D28	32
D29	13
D31	15
D33	4

Patent claims:

1. A substituted compound of general formula (T),



(T),

in which

R^{101}, R^{102} and R^{103} are independently of one another selected from the group consisting of H, F, Cl, Br, CFH_2, CF_2H, CF_3, CN, CH_2-OH, CH_2CH_2-OH, CH_2-OCH_3, CH_2CH_2-OCH_3, $OCFH_2$, OCF_2H, OCF_3, OH, NH_2, a C_{1-4} alkyl, an O-C_{1-4} alkyl, a NH-C_{1-4} alkyl, and a N(C_{1-4} alkyl)$_2$, wherein the C_{1-4} alkyl is in each case unsubstituted,

R^2 represents CF_3, an unsubstituted C_{1-4} alkyl or an unsubstituted C_{3-6} cycloalkyl,

R^7 and R^9 are independently of one another selected from the group consisting of H, F, Cl, Br, CFH_2, CF_2H, CF_3, CN, OH, OCF_3, a C_{1-4} alkyl, and an O-C_{1-4} alkyl, wherein the C_{1-4} alkyl is in each case unsubstituted,

A denotes N, CH or C(CH_3),

t denotes 0, 1 or 2,

R^{108} represents C_{1-4} alkyl, which is unsubstituted or mono-, di- or trisubstituted with 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, OH, =O and OCH_3,

optionally in the form of a single stereoisomer or a mixture of stereoisomers, in the form of the free compound and/or a physiologically acceptable salt thereof.

2. The compound according to claim 1, characterized in that

R^2 represents CF_3, tert.-butyl or cyclopropyl.

3. The compound according to claim 1 or 2, characterized in that

R^{101}, R^{102} and R^{103} are independently of one another selected from the group consisting of H, F, Cl, Br, CFH_2, CF_2H, CF_3, CN, CH_2-OH, CH_2-OCH_3, OCF_3, OH, CH_3, CH_2CH_3, $CH(CH_3)_2$, O-CH_3, O-CH_2CH_3, NH_2, $NH(CH_3)$, and $N(CH_3)_2$.

4. The compound according to any of the preceding claims, characterized in that

t denotes 1 or 2,

A denotes N,

R^{101} is selected from the group consisting of H, F, Cl, Br, CFH_2, CF_2H, CF_3, CN, CH_2-OH, CH_2-OCH_3, OCF_3, OH, CH_3, CH_2CH_3, $CH(CH_3)_2$, O-CH_3, O-CH_2CH_3, NH_2, $NH(CH_3)$ and $N(CH_3)_2$, and

R^{102} and R^{103} are independently of one another selected from the group consisting of H, F, Cl, Br, CFH_2, CF_2H, CF_3, CN, CH_2-OH, CH_2-OCH_3, OCF_3, OH, CH_3, CH_2CH_3, $CH(CH_3)_2$, O-CH_3, O-CH_2CH_3, NH_2, $NH(CH_3)$ and $N(CH_3)_2$,

or

t denotes 0, 1 or 2,

A denotes CH or $C(CH_3)$,

R^{101} is selected from the group consisting of H, F, Br, CFH_2, CF_2H, CF_3, CN, CH_2-OH, CH_2-OCH_3, OCF_3, OH, CH_3, CH_2CH_3, $CH(CH_3)_2$, O-CH_3, O-CH_2CH_3, NH_2, $NH(CH_3)$ and $N(CH_3)_2$, and

R^{102} and R^{103} are independently of one another selected from the group consisting of H, F, Cl, Br, CFH_2, CF_2H, CF_3, CN, CH_2-OH, CH_2-OCH_3, OCF_3, OH, CH_3, CH_2CH_3, $CH(CH_3)_2$, O-CH_3, O-CH_2CH_3, NH_2, $NH(CH_3)$ and $N(CH_3)_2$.

5. The compound according to any of the preceding claims, characterized in that

R^{101} is selected from the group consisting of H, F, Br, CFH_2, CF_2H, CF_3, CN, CH_2-OH, CH_2-OCH_3, OCF_3, OH, CH_3, CH_2CH_3, $CH(CH_3)_2$, O-CH_3, O-CH_2CH_3, NH_2, $NH(CH_3)$ and $N(CH_3)_2$, and

R^{102} and R^{103} are independently of one another selected from the group consisting of H, F, Cl, Br, CFH_2, CF_2H, CF_3, CN, CH_2-OH, CH_2-OCH_3, OCF_3, OH, CH_3, CH_2CH_3, $CH(CH_3)_2$, O-CH_3, O-CH_2CH_3, NH_2, $NH(CH_3)$ and $N(CH_3)_2$.

6. The compound according to any of the preceding claims, characterized in that

at least one of R^{101}, R^{102} and R^{103} is ≠ H.

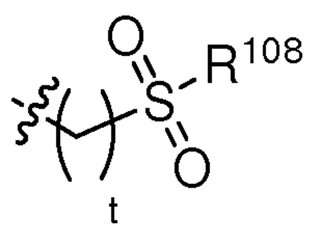
7. The compound according to any of the preceding claims, characterized in that

R^7 and R^9 are independently of one another selected from the group consisting of H, F, Cl, Br, CF_3, CN, OH, OCF_3, CH_3, CH_2CH_3, $CH(CH_3)_2$, O-CH_3, and O-CH_2CH_3.

8. The compound according to any of the preceding claims, characterized in that

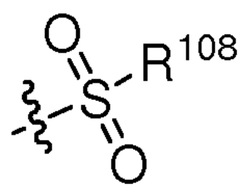
at least one of R^7 and R^9 is ≠ H.

9. The compound according to any of the preceding claims, characterized in that the part structure (TS1)

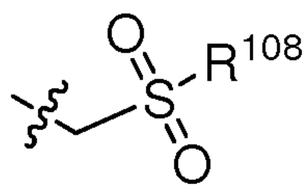


(TS1)

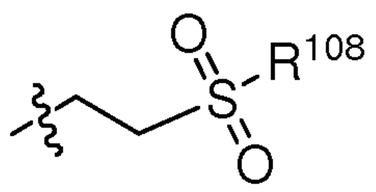
represents the part structure (PT1), (PT2) or (PT3),



(PT1),



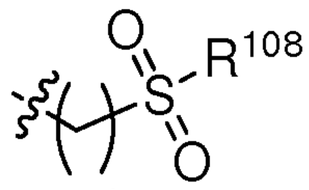
(PT2),



(PT3),

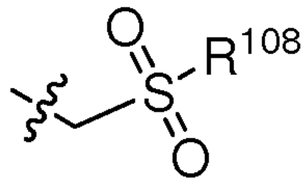
wherein R^{108} represents an unsubstituted C_{1-4} alkyl.

10. The compound according to any of the preceding claims, characterized in that the part structure (TS1)

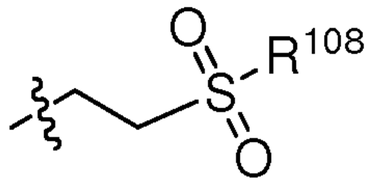


(TS1)

represents the part structure (PT2) or (PT3),



(PT2),



(PT3),

wherein R^{108} represents CH_3 or CH_2CH_3.

11. The compound according to any of the preceding claims, characterized in that

A denotes N or $C(CH_3)$.

12. The compound according to any one of claims 1-4, 6-8 and 10, characterized in that

A denotes N,

and R^{101} is selected from the group consisting of H, F, Cl, Br, CFH_2, CF_2H, CF_3, CN, CH_2-OH, CH_2-OCH_3, OCF_3, OH, CH_3, CH_2CH_3, $CH(CH_3)_2$, O-CH_3, O-CH_2CH_3, NH_2, $NH(CH_3)$, and $N(CH_3)_2$,

and R^{102} and R^{103} are independently of one another selected from the group consisting of H, F, Cl, Br, CFH_2, CF_2H, CF_3, CN, CH_2-OH, CH_2-OCH_3, OCF_3, OH, CH_3, CH_2CH_3, $CH(CH_3)_2$, O-CH_3, O-CH_2CH_3, NH_2, $NH(CH_3)$, and $N(CH_3)_2$,

or

A denotes CH or $C(CH_3)$,

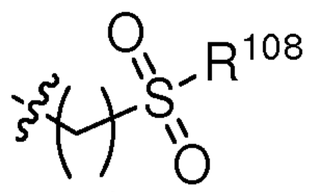
and R^{101} is selected from the group consisting of H, F, Br, CFH_2, CF_2H, CF_3, CN, CH_2-OH, CH_2-OCH_3, OCF_3, OH, CH_3, CH_2CH_3, $CH(CH_3)_2$, O-CH_3, O-CH_2CH_3, NH_2, $NH(CH_3)$, and $N(CH_3)_2$,

and R^{102} and R^{103} are independently of one another selected from the group consisting of H, F, Cl, Br, CFH_2, CF_2H, CF_3, CN, CH_2-OH, CH_2-OCH_3, OCF_3, OH, CH_3, CH_2CH_3, $CH(CH_3)_2$, O-CH_3, O-CH_2CH_3, NH_2, $NH(CH_3)$, and $N(CH_3)_2$,

R^2 represents CF_3, tert.-butyl or cyclopropyl,

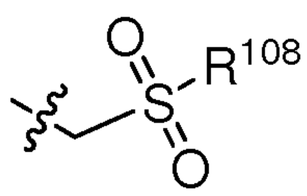
R^7 and R^9 are independently of one another selected from the group consisting of H, F, Cl, Br, CF_3, CN, OH, OCF_3, CH_3, CH_2CH_3, $CH(CH_3)_2$, O-CH_3, and O-CH_2CH_3,

the part structure (TS1)

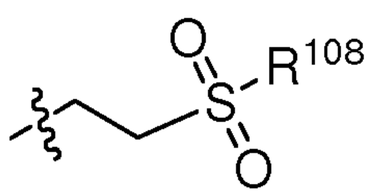


(TS1)

represents the part structure (PT2) or (PT3),



(PT2),



(PT3)

wherein R^{108} represents CH_3 or CH_2CH_3.

13. The compound according to any one of the preceding claims, selected from the group consisting of

D1 N-[[5-tert-Butyl-2-(3-chlorophenyl)-2H-pyrazol-3-yl]-methyl]-2-(3-fluoro-4-methylsulfonyl-phenyl)-propionamide;

D2 N-[[2-(3-Chlorophenyl)-5-(trifluoromethyl)-2H-pyrazol-3-yl]-methyl]-2-(3-fluoro-4-methylsulfonyl-phenyl)-propionamide;

D3 2-(3-Fluoro-4-methylsulfonyl-phenyl)-N-[[2-(3-fluorophenyl)-5-(trifluoromethyl)-2H-pyrazol-3-yl]-methyl]-propionamide;

D4 N-[[2-(3-Chloro-4-fluoro-phenyl)-5-(trifluoromethyl)-2H-pyrazol-3-yl]-methyl]-2-(3-fluoro-4-methylsulfonyl-phenyl)-propionamide;

D5 2-(3-Chloro-4-methylsulfonyl-phenyl)-N-[[2-(3-chlorophenyl)-5-(trifluoromethyl)-2H-pyrazol-3-yl]-methyl]-propionamide;

D6 N-[[2-(3-Chlorophenyl)-5-(trifluoromethyl)-2H-pyrazol-3-yl]-methyl]-2-[3-fluoro-4-(methylsulfonyl-methyl)-phenyl]-propionamide;

D7 N-[[5-tert-Butyl-2-(3-chlorophenyl)-2H-pyrazol-3-yl]-methyl]-2-[3-fluoro-4-(methylsulfonyl-methyl)-phenyl]-propionamide;

D8 N-[[5-tert-Butyl-2-(3-chloro-4-fluoro-phenyl)-2H-pyrazol-3-yl]-methyl]-2-[3-fluoro-4-(methylsulfonyl-methyl)-phenyl]-propionamide;

D9 N-[[5-tert-Butyl-2-(3-fluorophenyl)-2H-pyrazol-3-yl]-methyl]-2-[3-fluoro-4-(methylsulfonyl-methyl)-phenyl]-propionamide;

D10 2-[3-Fluoro-4-(methylsulfonyl-methyl)-phenyl]-N-[[2-(3-fluorophenyl)-5-(trifluoromethyl)-2H-pyrazol-3-yl]-methyl]-propionamide;

D11 N-[[5-tert-Butyl-2-(4-fluorophenyl)-2H-pyrazol-3-yl]-methyl]-2-[3-fluoro-4-(methylsulfonyl-methyl)-phenyl]-propionamide;

D12 2-[3-Fluoro-4-(methylsulfonyl-methyl)-phenyl]-N-[[2-(4-fluorophenyl)-5-(trifluoromethyl)-2H-pyrazol-3-yl]-methyl]-propionamide;

D13 N-[[5-tert-Butyl-2-(3,4-difluoro-phenyl)-2H-pyrazol-3-yl]-methyl]-2-[3-fluoro-4-(methylsulfonyl-methyl)-phenyl]-propionamide;

D14 N-[[2-(3,4-Difluoro-phenyl)-5-(trifluoromethyl)-2H-pyrazol-3-yl]-methyl]-2-[3-fluoro-4-(methylsulfonyl-methyl)-phenyl]-propionamide;

D15 N-[[2-(3,5-Difluoro-phenyl)-5-(trifluoromethyl)-2H-pyrazol-3-yl]-methyl]-2-[3-fluoro-4-(methylsulfonyl-methyl)-phenyl]-propionamide;

D16 N-[[5-tert-Butyl-2-[3-(methoxymethyl)-phenyl]-2H-pyrazol-3-yl]-methyl]-2-[3-fluoro-4-(methylsulfonyl-methyl)-phenyl]-propionamide;

D17 N-[[5-tert-Butyl-2-(3-dimethylamino-phenyl)-2H-pyrazol-3-yl]-methyl]-2-[3-fluoro-4-(methylsulfonyl-methyl)-phenyl]-propionamide;

D18 N-[[5-tert-Butyl-2-(3-fluoro-5-methyl-phenyl)-2H-pyrazol-3-yl]-methyl]-2-[3-fluoro-4-(methylsulfonyl-methyl)-phenyl]-propionamide;

D19 N-[[5-tert-Butyl-2-(3-cyano-phenyl)-2H-pyrazol-3-yl]-methyl]-2-[3-fluoro-4-(methylsulfonyl-methyl)-phenyl]-propionamide;

D20 N-[[5-tert-Butyl-2-[3-(difluoro-methyl)-phenyl]-2H-pyrazol-3-yl]-methyl]-2-[3-fluoro-4-(methylsulfonyl-methyl)-phenyl]-propionamide;

D21 N-[[5-tert-Butyl-2-(3-methoxyphenyl)-2H-pyrazol-3-yl]-methyl]-2-[3-fluoro-4-(methylsulfonyl-methyl)-phenyl]-propionamide;

D22 2-[3-Fluoro-4-(methylsulfonyl-methyl)-phenyl]-N-[[2-(3-methoxyphenyl)-5-(trifluoromethyl)-2H-pyrazol-3-yl]-methyl]-propionamide;

D23 N-[[5-tert-Butyl-2-[3-(trifluoromethyl)phenyl]-2H-pyrazol-3-yl]-methyl]-2-[3-fluoro-4-(methylsulfonyl-methyl)-phenyl]-propionamide;

D24 N-[[5-tert-Butyl-2-(m-tolyl)-2H-pyrazol-3-yl]-methyl]-2-[3-fluoro-4-(methylsulfonyl-methyl)-phenyl]-propionamide;

D25 2-[3-Fluoro-4-(methylsulfonyl-methyl)-phenyl]-N-[[2-(4-methoxyphenyl)-5-(trifluoromethyl)-2H-pyrazol-3-yl]-methyl]-propionamide;

D26 1-[[2-(3-Chlorophenyl)-5-cyclopropyl-2H-pyrazol-3-yl]-methyl]-3-[3-fluoro-4-(2-methylsulfonyl-ethyl)-phenyl]-urea;

D27 1-[[2-(3-Chlorophenyl)-5-(trifluoromethyl)-2H-pyrazol-3-yl]-methyl]-3-[3-fluoro-4-(2-methylsulfonyl-ethyl)-phenyl]-urea;

D28 1-[[2-(3-Chloro-4-fluoro-phenyl)-5-(trifluoromethyl)-2H-pyrazol-3-yl]-methyl]-3-[3-fluoro-4-(2-methylsulfonyl-ethyl)-phenyl]-urea;

D29 1-[[5-tert-Butyl-2-(3-chlorophenyl)-2H-pyrazol-3-yl]-methyl]-3-[3-fluoro-4-(2-methylsulfonyl-ethyl)-phenyl]-urea;

D30 1-[[5-tert-Butyl-2-(3-fluorophenyl)-2H-pyrazol-3-yl]-methyl]-3-[3-fluoro-4-(2-methylsulfonyl-ethyl)-phenyl]-urea;

D31 1-[[5-tert-Butyl-2-(3,5-difluoro-phenyl)-2H-pyrazol-3-yl]-methyl]-3-[3-fluoro-4-(2-methylsulfonyl-ethyl)-phenyl]-urea;

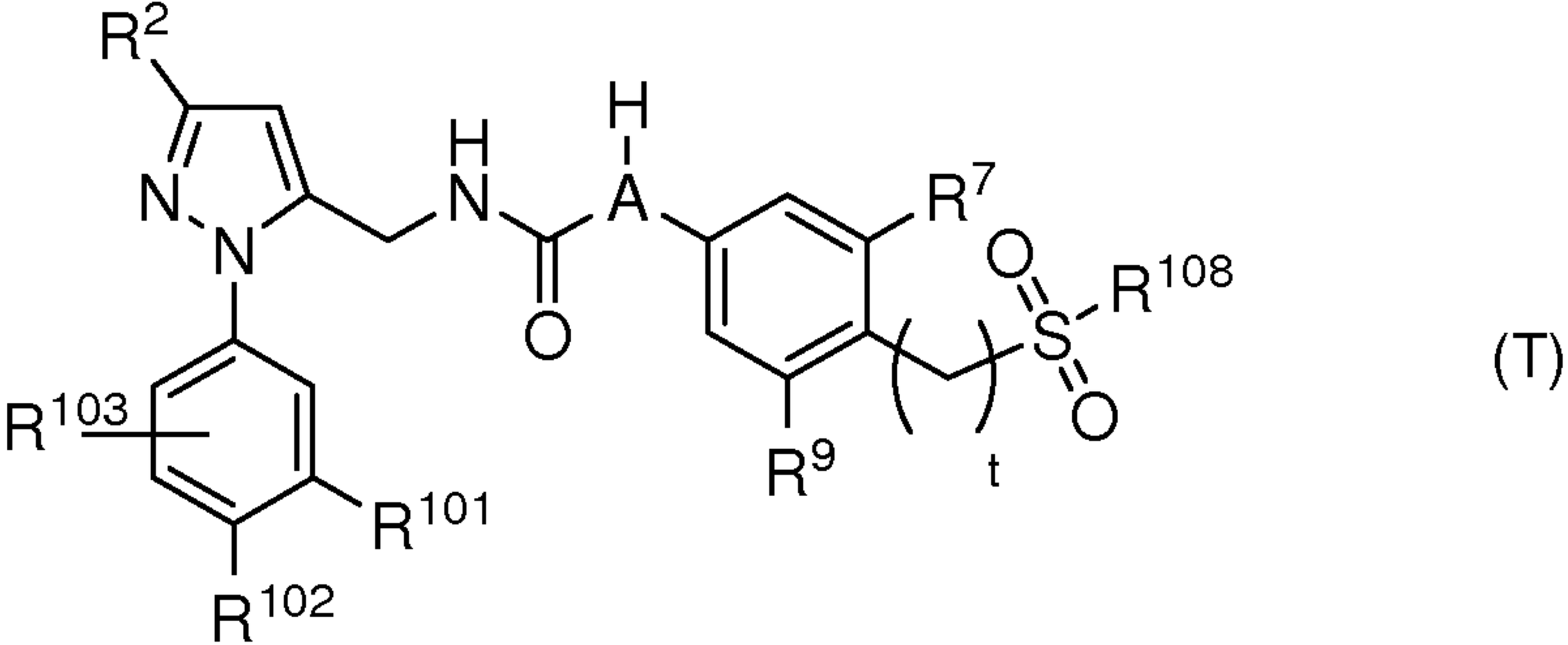
D32 1-[3-Fluoro-4-(2-methylsulfonyl-ethyl)-phenyl]-3-[[2-(m-tolyl)-5-(trifluoromethyl)-2H-pyrazol-3-yl]-methyl]-urea; and

D33 1-[3-Fluoro-4-(2-methylsulfonyl-ethyl)-phenyl]-3-[[2-(3-isopropyl-phenyl)-5-(trifluoromethyl)-2H-pyrazol-3-yl]-methyl]-urea;

optionally in the form of a single stereoisomer or a mixture of stereoisomers, in the form of the free compound and/or a physiologically acceptable salt thereof.

14. A pharmaceutical composition comprising at least one substituted compound according to any one of claims 1 to 13.

15. A substituted compound according to any one of claims 1 to 13 for use in the treatment and/or prophylaxis of one or more diseases and/or disorders selected from the group consisting of pain, preferably of pain selected from the group consisting of acute pain, chronic pain, neuropathic pain, visceral pain and joint pain; hyperalgesia; allodynia; causalgia; migraine; depression; nervous affection; axonal injuries; neurodegenerative diseases, preferably selected from the group consisting of multiple sclerosis, Alzheimer's disease, Parkinson's disease and Huntington's disease; cognitive dysfunctions, preferably cognitive deficiency states, particularly preferably memory disorders; epilepsy; respiratory diseases, preferably selected from the group consisting of asthma, bronchitis and pulmonary inflammation; coughs; urinary incontinence; overactive bladder (OAB); disorders and/or injuries of the gastrointestinal tract; duodenal ulcers; gastric ulcers; irritable bowel syndrome; strokes; eye irritations; skin irritations; neurotic skin diseases; allergic skin diseases; psoriasis; vitiligo; herpes simplex; inflammations, preferably inflammations of the intestine, the eyes, the bladder, the skin or the nasal mucous membrane; diarrhoea; pruritus; osteoporosis; arthritis; osteoarthritis; rheumatic diseases; eating disorders, preferably selected from the group consisting of bulimia, cachexia, anorexia and obesity; medication dependency; misuse of medication; withdrawal symptoms in medication dependency; development of tolerance to medication, preferably to natural or synthetic opioids; drug dependency; misuse of drugs; withdrawal symptoms in drug dependency; alcohol dependency; misuse of alcohol and withdrawal symptoms in alcohol dependency; for diuresis; for antinatriuresis; for influencing the cardiovascular system; for increasing vigilance; for the treatment of wounds and/or burns; for the treatment of severed nerves; for increasing libido; for modulating movement activity; for anxiolysis; for local anaesthesia and/or for inhibiting undesirable side effects, preferably selected from the group consisting of hyperthermia, hypertension and bronchoconstriction, triggered by the administration of vanilloid receptor 1 (VR1/TRPV1 receptor) agonists, preferably selected from the group consisting of capsaicin, resiniferatoxin, olvanil, arvanil, SDZ-249665, SDZ-249482, nuvanil and capsavanil.



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