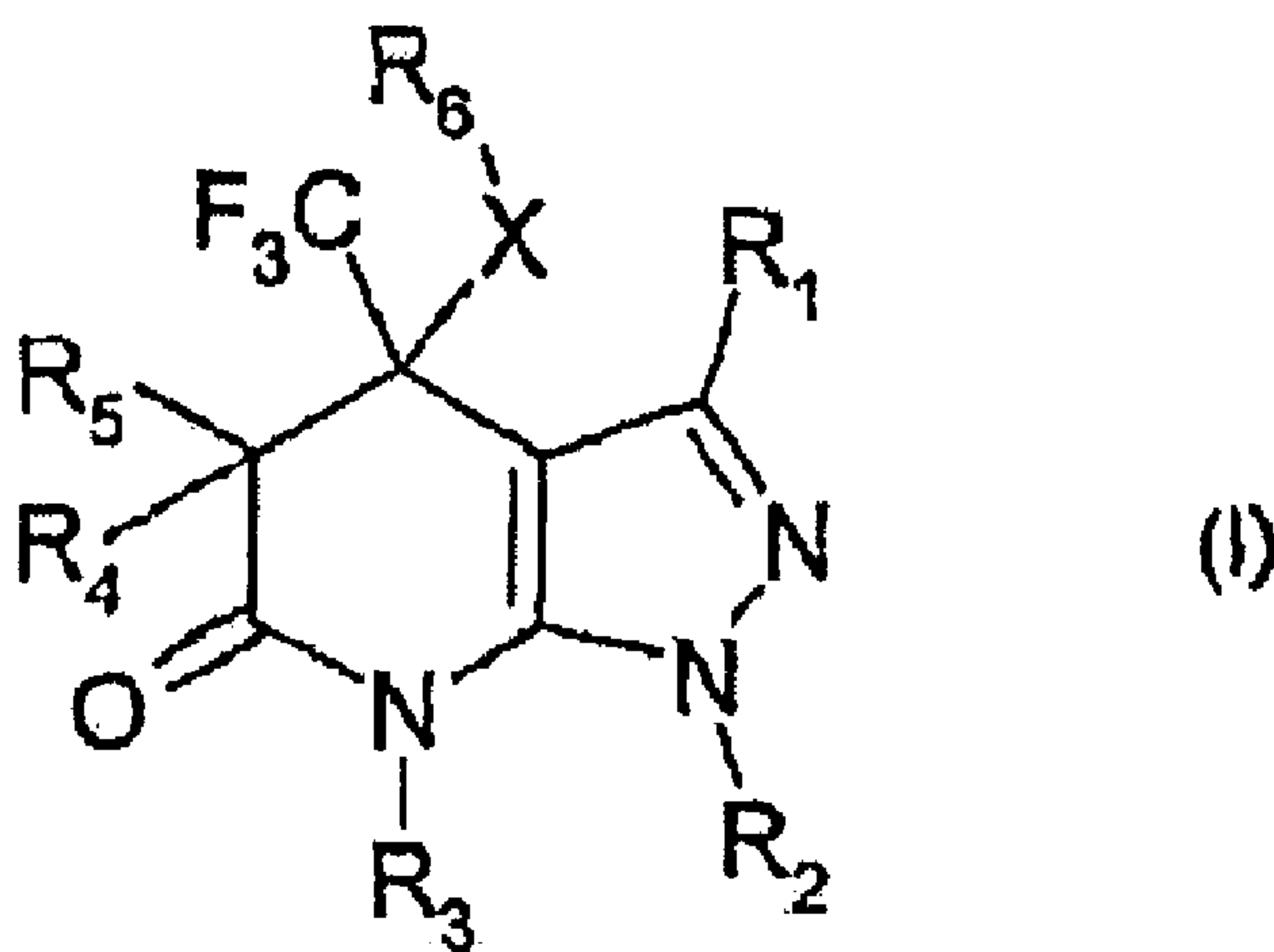




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(54) Title: PYRAZOLOPYRIDINONE DERIVATIVES AS LPA RECEPTOR ANTAGONISTS



(57) **Abrégé/Abstract:**

The present invention relates to pyrazolopyridinone derivatives according to formula (I)

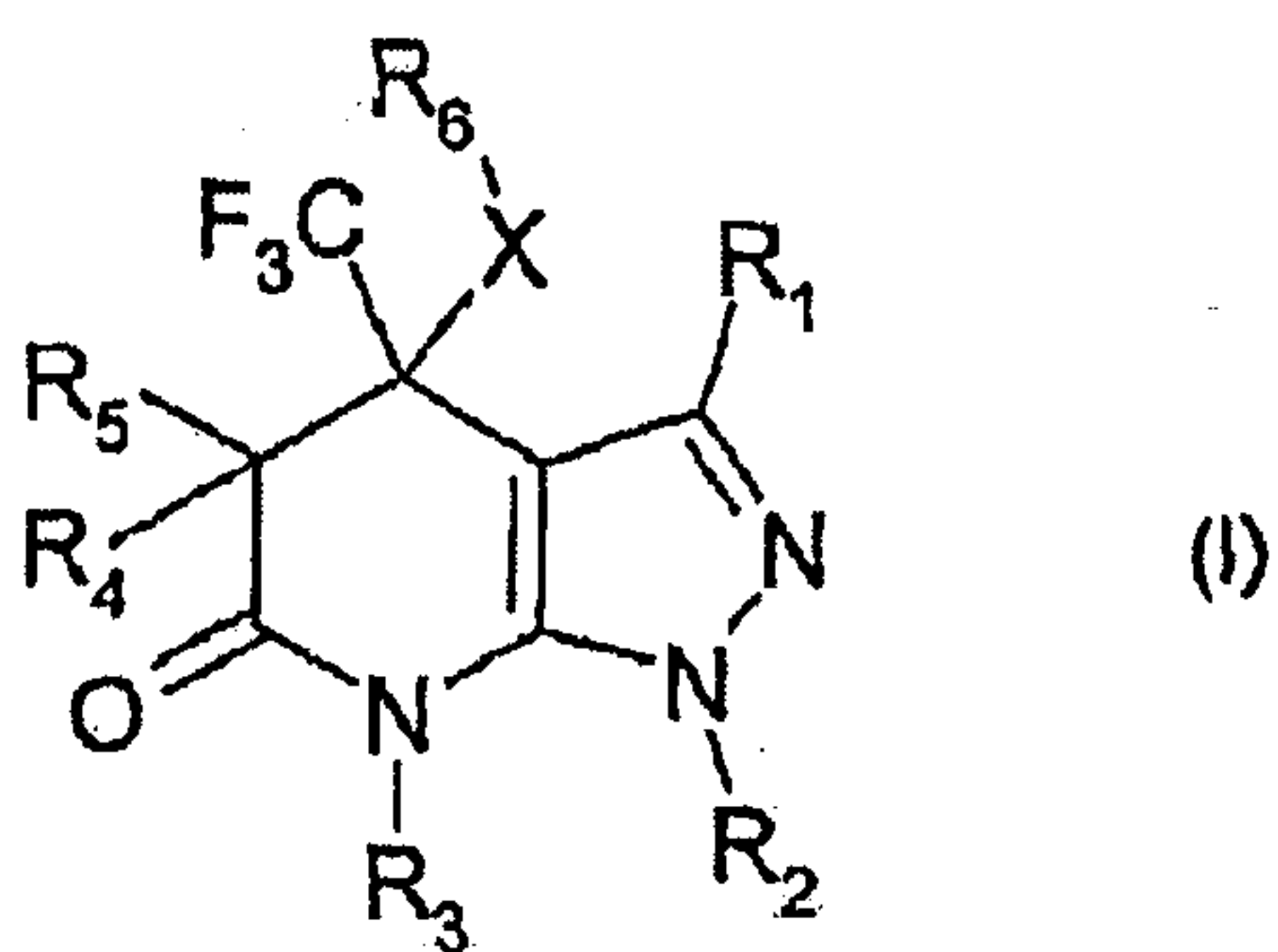
(see formula I)

and a process of manufacturing thereof, wherein R<sub>1</sub>-R<sub>2</sub> are as described herein. These pyrazolopyridinone derivatives can be used as LPA receptor antagonists for the treatment of various herein disclosed diseases.

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## Abstract

The present invention relates to pyrazolopyridinone derivatives according to formula (I)



- 5 and a process of manufacturing thereof, wherein  $R_1$ - $R_2$  are as described herein. These pyrazolopyridinone derivatives can be used as LPA receptor antagonists for the treatment of various herein disclosed diseases.

## Pyrazolopyridinone derivatives as LPA receptor antagonists

### Description

#### Technical field

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The present invention relates to novel pyrazolopyridinone derivatives that act as LPA receptor antagonists and a process of manufacturing thereof.

#### Prior art

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Lysophosphatidic acid (LPA) is a small glycerophospholipid (molecular weight: 430–480 Da) that is present in all eukaryotic tissues at low concentrations, relative to major phospholipid species, and at higher concentrations (sub-micromolar range) in blood plasma. In 1996, the first high-affinity, cognate cell surface receptor for LPA was identified (LPA1) (1). This quickly led to the identification of two additional, closely related receptors (LPA2 and LPA3) and the recent identification of two more, somewhat divergent, receptors (LPA4 and LPA5). All five receptors are type I, rhodopsin-like G protein–coupled receptors (GPCRs) that differ in their tissue distribution and downstream signaling pathways (see Choi JW et al., Annu. Rev. Pharmacol. Toxicol. 2010, 50: 157-186).

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Because of this heterogeneity of receptor subtypes, expression patterns, and effector pathways, the effects of LPA are diverse and widespread, regulating many biological processes. A great deal of information regarding these biological roles was derived from genetic deletion studies. To date, knockout mice have been reported for four of the five known receptors (LPA1–4), as well as the major LPA-generating enzyme, autotaxin (ATX) (2, 3). These mutant mice, in addition to emerging classes of chemical tools, have transitioned observations made through the use of in vitro studies into medically relevant contexts. It is difficult to discuss LPA without some mention of the structurally similar lipid sphingosine 1-phosphate (S1P). S1P was also discovered to be an extracellular signaling lipid when its first cognate receptor (S1P1) was deorphanized in 1998 (4). Although they represent distinct signaling systems, similarities between these two lipids extend to their tissue distribution and concentration, homology and effector pathways of their cognate receptors, and the broad range of their biological roles. However, because LPA and S1P signaling have become such a robust research area in recent years,

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this review focuses specifically on biological roles of LPA. Comprehensive reviews of S1P signaling can be found elsewhere (5, 6).

5 Since the early twentieth century, lysophospholipids have been known to have biological activity, but these effects were long thought to be the result of nonspecific detergent-like disruptions of the plasma membrane. These studies, however, were performed at very high, nonphysiological concentrations. It is now known that the effects of LPA at physiological concentrations are mediated by five bona fide, high-affinity cognate receptors (LPA1–LPA5) and perhaps by additional recently  
10 proposed or as yet unidentified receptors (16–18).

LPA1 is the first high-affinity receptor identified for LPA (1) (reviewed in 16, 17). The mammalian *LPAR1* gene (human chromosomal locus 9q31.3) encodes an approximately 41-kDa protein consisting of 364 amino acids with 7 putative  
15 transmembrane domains. In mice, the open reading frame is encoded on two of five exons with a conserved intron (shared with *Lpar2* and *Lpar3*) that interrupts transmembrane domain 6. One reported variant of *Lpar1* (mrec1.3), which may be produced by alternative exon usage or splicing, results in an 18-amino-acid deletion of the N terminus (19). The biological significance of this variant has not been  
20 established.

Wide expression of *Lpar1* is observed in adult mice, with clear presence in at least brain, uterus, testis, lung, small intestine, heart, stomach, kidney, spleen, thymus, placenta, and skeletal muscle (20, 21). *LPAR1* is also widely expressed in humans (22). Expression of *Lpar1* is more spatially restricted during embryonic  
25 development but is enriched in the brain (23). In particular, the developing nervous system is a major locus for *Lpar1* expression, where it is spatially and temporally regulated (reviewed in 17, 20). During embryogenesis, central nervous system (CNS) expression is restricted to the neocortical neurogenic region called the ventricular zone (VZ) and superficially in a layer that includes the meninges (1). The  
30 VZ disappears at the end of cortical neurogenesis, just prior to birth, but *Lpar1* expression continues in the postnatal brain, where it is apparent in cells present within developing white matter tracts and coincides with myelination (24). In situ hybridization reveals *Lpar1* expression in oligodendrocytes and Schwann cells, the myelinating cells of the CNS and peripheral nervous system, respectively (24, 25).

LPA1 couples with and activates three types of Gproteins: *Gai/o*, *Gaq/11*, and *Gα12/13* (26, 27). LPA1 activation induces a range of cellular responses: cell proliferation and survival, cell migration, and cytoskeletal changes; altered cell-cell contact through serum-response element activation,  $Ca^{2+}$  mobilization, and adenylyl cyclase inhibition; and activation of mitogen-activated protein kinase, phospholipase C, Akt, and Rho pathways (reviewed in 16, 17, 20).

The targeted disruption of *Lpar1* in mice revealed unanticipated *in vivo* functions of this receptor (28). *Lpar1*<sup>-/-</sup> mice show 50% perinatal lethality in a mixed (C57Bl/6J x 129) genetic background and further decreased survival in pure (C57Bl/6J or Balb/cByJ) genetic backgrounds (J. Chun, unpublished observations). Survivors have a reduced body size, craniofacial dysmorphism with blunted snouts, and increased apoptosis in sciatic nerve Schwann cells (28, 29). Defective suckling, attributed to olfactory defects, likely accounts for perinatal lethality. Small fractions of *Lpar1*<sup>-/-</sup> embryos have exencephaly (~5%) or frontal cephalic hemorrhage (~2.5%). Loss of LPA response in embryonic neuroblasts and fibroblasts demonstrates nonredundant functions and roles for *Lpar1* *in vivo* (28, 30). In addition, during colony expansion of the original line (28), an *Lpar1*<sup>-/-</sup> substrain arose spontaneously, which was called the "Málaga variant" and exhibits more severe developmental brain defects (31).

*Lpar2* was identified from GenBank searches of orphan GPCR genes because of its ~60% amino acid similarity to *Lpar1*. In humans, *LPAR2* (chromosomal locus 19p12) encodes a protein that has a predicted amino acid sequence of 348 residues, yielding a calculated molecular mass of ~39 kDa (32).

The expression pattern of *Lpar2* is relatively restricted spatiotemporally compared to that of *Lpar1* (20, 22). In mouse, *Lpar2* is highly expressed in kidney, uterus, and testis and moderately expressed in lung; and lower levels of expression are found in stomach, spleen, thymus, brain, and heart (20). *Lpar2* is also expressed in embryonic brain but decreases within a week after birth (20). In human tissues, high expression of *LPAR2* is detected in testis and leukocytes, with moderate expression found in prostate, spleen, thymus, and pancreas (22). In cancer cells, aberrant expression of *LPAR2* has been reported in several cases, suggesting a tumor promoting role for LPA2.

LPA2 couples to the *Gai/o*, *Gα11/q*, and *Gα12/13* family of heterotrimeric G proteins. These G proteins convey signals through downstream molecules that

include Ras, mitogen activated protein kinase, phosphatidylinositol 3-kinase, Rac, phospholipase C, diacylglycerol, and Rho, which is similar to LPA1 (28). LPA2 is a bona fide high affinity cognate LPA receptor (33). Activation of LPA2 signaling is generally associated with such processes as cell survival (34, 35) and cell migration (36–38). As a consequence, LPA2 signaling has emerged as a potential factor for cancer metastasis (see below) (39–41).

Interestingly, several reports have provided evidence for the interaction of LPA2 signaling with other pathways. For example, LPA2 promotes cell migration through interactions with focal adhesion molecule TRIP6 (42, 43), and several PDZ proteins and zinc finger proteins are also reported to interact directly with the carboxyl-terminal tail of LPA2 (44). In addition, LPA2-mediated signaling can provide inhibitory effects on the epidermal growth factor-induced migration and invasion of pancreatic cancer cells through the Gα12/13 /Rho pathway (45). These studies provide evidence that LPA2 signaling has cross-regulation between classical G protein signaling cascades and other signaling pathways to regulate the efficiency and specificity of signal transduction.

Mouse knockout studies demonstrate that *Lpar2*<sup>-/-</sup> mutant animals are viable, grossly normal, and born at normal Mendelian ratios without sexual bias, but *Lpar1*<sup>-/-</sup>/*Lpar2*<sup>-/-</sup> mutants have an exacerbation of the frontal hematomas present in the *Lpar1*<sup>-/-</sup> mutant (28, 30). In addition, primary fibroblasts and embryonic cortical cells from the double-null mutants show vastly reduced responses to exogenous LPA (30, 46).

*Lpar3* was discovered as an orphan GPCR gene using degenerate PCR-based cloning and homology searches (47, 48). *LPAR3* (human chromosomal locus 1p22.3-p31.1) encodes a ~40-kDa GPCR that is ~50% identical to mouse LPA1 and LPA2 in amino acid sequence. Expression of *LPAR3* has been observed in human heart, testis, prostate, pancreas, lung, ovary, and brain (47, 48) and is most abundant in mouse testis, kidney, lung, small intestine, heart, stomach, spleen, brain, and thymus (20). Interestingly, it has been shown that, in the murine uterus, *Lpar3* mRNA is exclusively expressed in the luminal endometrial epithelium at the window of implantation (49) and that its expression is regulated by progesterone and estrogen (50).

Like LPA1 and LPA2, LPA3 can couple with *Gai/o* and *Gαq* to mediate LPA-induced phospholipase C activation, Ca<sup>2+</sup> mobilization, adenylyl cyclase inhibition

and activation, and mitogen activated protein kinase activation (27). However, LPA3 is unable to couple with G $\alpha$ 12/13 and therefore does not mediate cell rounding in neuronal cells in which G $\alpha$ 12/13 and Rho are involved (27). Also, LPA3 is not as responsive as LPA1 and LPA2 to LPA species with saturated acyl chains but has a relatively high affinity for 2-acyl-LPA containing unsaturated fatty acids (47, 51).

*Lpar3*<sup>-/-</sup> mice are viable and grossly normal, but female nulls show a striking phenotype in the reproductive system (49) (see below). However, despite the fact that LPA3 is expressed in the frontal cortex, hippocampus, and amygdala (47, 48), no phenotypes related to LPA3 loss in the nervous system have been reported to date.

LPA4 was originally identified as a putative GPCR from an analysis of the expressed sequence tag database (52, 53) and was found to be a specific receptor for LPA through ligand screening (54). LPA4 is structurally distinct from classical LPA and S1P receptors that share significant homology and is more closely related to P2Y purinergic receptors. It does not, however, respond to any nucleotides or nucleosides tested (52, 54). In humans, the *LPAR4* gene is located on chromosome X, region q13-q21.1, and contains an intronless open reading frame of 1113 base pairs encoding 370 amino acids with a calculated molecular mass of ~42 kDa (52, 53). LPA4 has a specific binding affinity to 18:1-LPA with a *K<sub>d</sub>* value of 44.8 nM but not to other lysophospholipids and related lipids such as S1P and SPC (54). LPA4 prefers structural analogs of LPA with a rank order of 18:1- > 18:0- > 16:0- > 14:0- > 1-alkyl- > 1-alkenyl-LPA (54).

Among 16 human tissues examined with quantitative real-time PCR, *LPAR4* mRNA is ubiquitously expressed and specifically abundant in the ovary (54). Among mouse tissues examined with Northern blot and real-time PCR, *Lpar4* mRNA is expressed in heart, skin, thymus, ovary, developing brain, and embryonic fibroblasts (3, 55). Whole mount in situ hybridization detected *Lpar4* mRNA in limb buds, somites, facial processes, and developing brain (23).

In LPA4-overexpressing cells, LPA induces morphological changes such as cell rounding and stress fiber formation through the G $\alpha$ 12/13 and Rho/Rho-kinase pathways (55, 56), as observed in LPA1-, LPA2-, and LPA5-expressing cells. Additionally, Rho-kinase-mediated cell aggregation and N-cadherin-dependent cell adhesion are observed in LPA4-expressing cells (56). LPA induces intracellular cAMP accumulation through G $\alpha$ s, and Ca<sup>2+</sup> mobilization through G $\alpha$ q/11 and G $\alpha$ i

(55, 56). Notably,  $G_{\alpha s}$ -coupling is not reported for classical LPA receptors. Recently, LPA4-deficient mice have been reported, although they display no apparent abnormalities (3). However, LPA4 has a suppressive effect on cell motility in that (a) LPA4 deficiency enhances migratory response to LPA in fibroblasts and  
5 (b) heterologous expression of LPA4 suppresses LPA1-dependent migration of B103 cells and LPA-induced migration and invasion of colon cancer cells (3).

Recently, an orphan GPCR (GPR92) was identified as an LPA receptor and was renamed LPA5 to reflect this identity (57, 58). Human *LPAR5* is located on  
10 chromosome 12p13.31 and encodes a ~41 kDa protein consisting of 372 amino acids. Like other LPA receptors (LPA1–4), LPA5 also belongs to the rhodopsin-GPCR family and, although structurally different from LPA1–3, it shares 35% homology with LPA4 (58). *Lpar5* is broadly expressed in murine tissues such as embryonic brain, small intestine, skin, spleen, stomach, thymus, lung, heart, liver,  
15 and embryonic stem cells (57, 58).

LPA induces neurite retraction and stress fiber formation in LPA5-expressing cells by coupling to  $G_{\alpha 12/13}$  and increases intracellular calcium levels by activation of  $G_{\alpha q}$  (58). Furthermore, LPA increases cAMP levels and inositol phosphate production in LPA5-expressing cells (57, 58). Recently, two other lipid-derived  
20 molecules (farnesyl pyrophosphate and *N*-arachidonylglycin) were characterized as LPA5 ligands (59). In this study, farnesyl-pyrophosphate activated  $G_{\alpha q/11}$ - and  $G_{\alpha s}$ -mediated signaling, whereas *N*-arachidonylglycin was able to activate only  $G_{\alpha q/11}$ -mediated signaling. It has been suggested that those ligands interact differently with the ligand-binding pocket of LPA5 (59). However, subsequent  
25 studies confirm that LPA5 is a bona fide LPA receptor that can also be activated by farnesyl pyrophosphate at much higher concentrations relative to 18:1-LPA, leaving open the question of the biological relevance of these alternative ligands (60, 61).

Recently, three more orphan GPCRs have been published as new, putative  
30 LPA receptors: GPR87, P2Y5, and P2Y10 (62–64). Each of these orphan GPCRs belongs to the purinergic receptor P2Y family and is more closely related to LPA4 and LPA5 than to LPA1–3. Of these, P2Y5 is likely to join the LPA receptor family as LPA6, based on recent published and unpublished data. P2Y5 was identified as a critical mediator for human hair growth and is a causal gene of a rare familial form  
35 of human hair loss (63, 63a), and recent studies of this putative LPA6 support

activation of this receptor by uncharacteristically high concentrations of LPA [EC<sub>50</sub> in the low micromolar range for some assays (65)]. This suggests an identity of P2Y<sub>5</sub> as a relatively low-affinity LPA receptor, distinct from LPA<sub>1-5</sub> (65), perhaps requiring a distinct ligand or other explanations. GPR87 and P2Y<sub>10</sub> were reported to increase intracellular Ca<sup>2+</sup> mobilization using a promiscuous Gα<sub>16</sub> fusion system (62, 64). P2Y<sub>10</sub>-Gα<sub>16</sub> also can induce Ca<sup>2+</sup> transients by S1P as well as LPA (EC<sub>50</sub> = 53 and 130 nM, respectively) (62). More detailed investigations are required to confirm these three candidates as bona fide LPA receptors. Non-GPCR LPA receptors have been reported, but their validity remains to be established (66).

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- 35

Further prior art is as follows:

Balicki R (Polish Journal of Chemistry 1983, 57: 789-797) relates to the abnormal cyclocondensation of ethyl-4,4,4-trifluoroacetoacetate with aminopyrazoles. The scientific paper discloses compound 2 of the present invention (page 792, scheme 4, compound 14). The article, however, does not disclose the application of the therein disclosed compounds as medicaments.

WO 2003/062392 discloses methods of treating conditions associated with an EDG receptor. The compounds disclosed structurally differ from the compounds of the present invention.

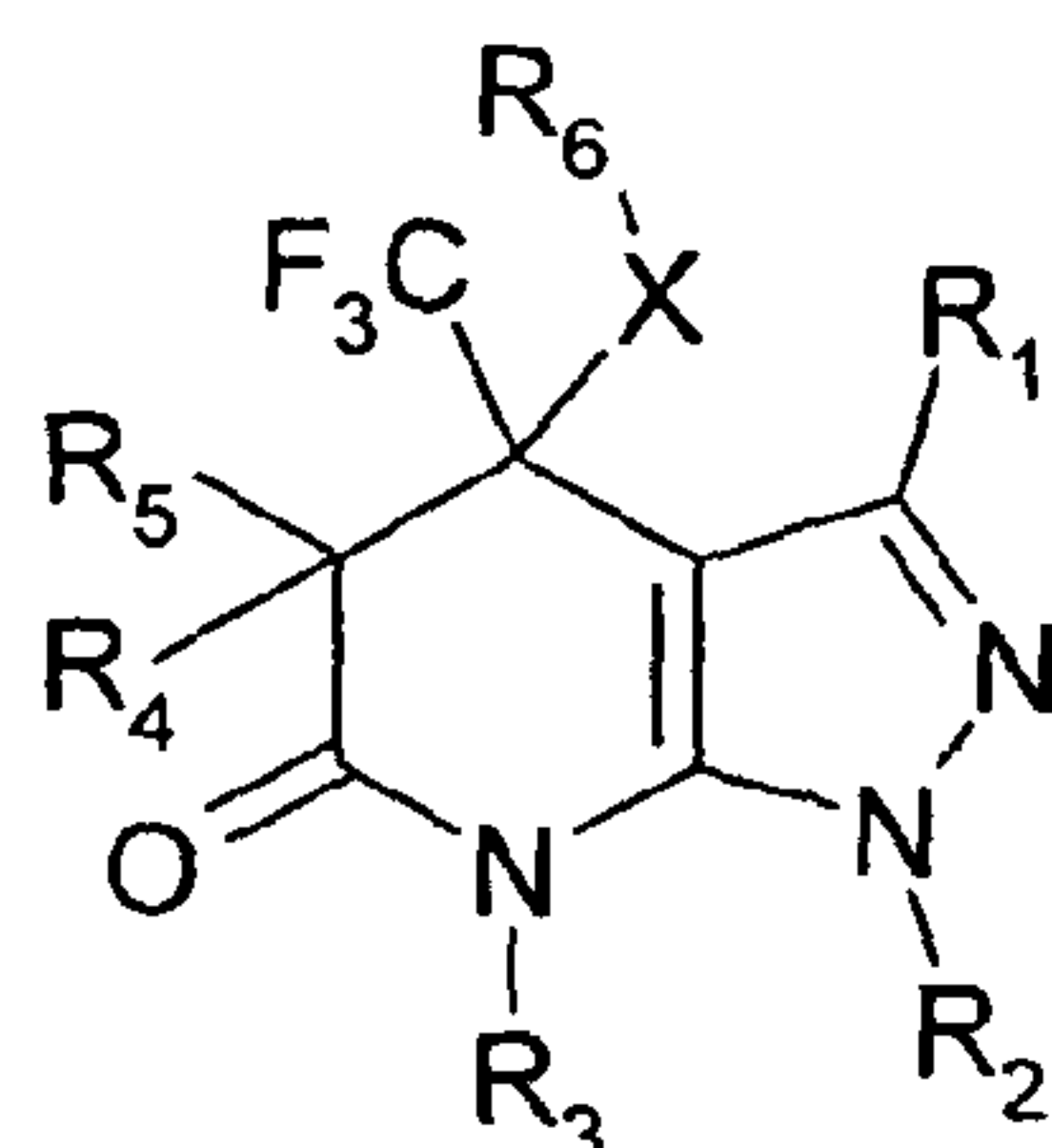
WO 2009/135590 describes acylamino-substituted fused cyclopentanecarboxylic acid derivatives and their use as pharmaceuticals. The compounds disclosed structurally differ from the compounds of the present invention.

The citation of any reference in this application is not an admission that the reference is relevant prior art to this application.

#### Description of the invention

The present invention has the object to provide novel LPA receptor antagonists.

The object of the present invention has surprisingly been solved in one aspect by providing compounds of formula (I)



(I)

wherein:

R<sub>1</sub> denotes aryl, heteroaryl, cycloalkyl, heterocyclyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocyclalkyl, which can optionally be substituted with one or more substituents selected from alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halogen, -F, -Cl, -Br, -I, -CN, -CF<sub>3</sub>, -N<sub>3</sub>, -

NH<sub>2</sub>, -NHZ1, -NZ2Z3, -NO<sub>2</sub>, -OH, -OCF<sub>3</sub>, -SH, -O-SO<sub>3</sub>H, -  
 OP(O)(OH)<sub>2</sub>, -CHO, -COOH, -C(O)NH<sub>2</sub>, -SO<sub>3</sub>H, -P(O)(OH)<sub>2</sub>, -C(O)-  
 Z4, -C(O)O-Z5, -C(O)NH-Z6, -C(O)NZ7Z8, -O-Z9, -O(-Z10-O)<sub>a</sub>-H  
 (a = 1, 2, 3, 4, 5), -O(-Z11-O)<sub>b</sub>-Z12 (b = 1, 2, 3, 4, 5), -OC(O)-Z13, -  
 5 OC(O)-O-Z14, -OC(O)-NHZ15, -O-C(O)-NZ16Z17, -  
 OP(O)(OZ18)(OZ19), -OSi(Z20)(Z21)(Z22), -OS(O<sub>2</sub>)-Z23, -NHC(O)-  
 NH<sub>2</sub>, -NHC(O)-Z24, -NZ25C(O)-Z26, -NH-C(O)-O-Z27, -NH-C(O)-  
 NH-Z28, -NH-C(O)-NZ29Z30, -NZ31-C(O)-O-Z32, -NZ33-C(O)-  
 NH-Z34, -NZ35-C(O)-NZ36Z37, -NHS(O<sub>2</sub>)-Z38, -NZ39S(O<sub>2</sub>)-Z40, -  
 10 S-Z41, -S(O)-Z42, -S(O<sub>2</sub>)-Z43, -S(O<sub>2</sub>)NH-Z44, -S(O<sub>2</sub>)NZ45Z46, -  
 S(O<sub>2</sub>)O-Z47, -P(O)(OZ48)(OZ49), -Si(Z50)(Z51)(Z52), -C(NH)-NH<sub>2</sub>, -  
 C(NZ53)-NH<sub>2</sub>, -C(NH)-NHZ54, -C(NH)-NZ55Z56, -C(NZ57)-NHZ58,  
 -C(NZ59)-NZ60Z61, -NH-C(O)-NH-O-Z62, -NH-C(O)-NZ63-O-Z64,  
 -NZ65-C(O)-NZ66-O-Z67, -N(-C(O)-NH-O-Z68)<sub>2</sub>, -N(-C(O)-NZ69-  
 15 O-Z70)<sub>2</sub>, -N(-C(O)-NH-O-Z71)(-C(O)-NZ72-O-Z73), -C(S)-Z74, -  
 C(S)-O-Z75, -C(S)-NH-Z76, -C(S)-NZ77Z78, -C(O)-NH-O-Z79, -  
 C(O)-NZ80-O-Z81, -C(S)-NH-O-Z82, -C(S)-NZ83-O-Z84, -C(O)-  
 NH-NH-Z85, -C(O)-NH-NZ86Z87, -C(O)-NZ88-NZ89Z90, -C(S)-  
 NH-NH-Z91, -C(S)-NH-NZ92Z93, -C(S)-NZ94-NZ95Z96, -C(O)-  
 20 C(O)-O-Z97, -C(O)-C(O)-NH<sub>2</sub>, -C(O)-C(O)-NHZ98, -C(O)-C(O)-  
 NZ99Z100, -C(S)-C(O)-O-Z101, -C(O)-C(S)-O-Z102, -C(S)-C(S)-  
 O-Z103, -C(S)-C(O)-NH<sub>2</sub>, -C(S)-C(O)-NHZ104, -C(S)-C(O)-  
 NZ105Z106, -C(S)-C(S)-NH<sub>2</sub>, -C(S)-C(S)-NHZ107, -C(S)-C(S)-  
 NZ108Z109, -C(O)-C(S)-NH<sub>2</sub>, -C(O)-C(S)-NHZ110, -C(O)-C(S)-  
 25 NZ111Z112";  
 wherein Z1, Z2, Z3, Z4, Z5, Z6, Z7, Z8, Z9, Z10, Z11, Z12, Z13, Z14,  
 Z15, Z16, Z17, Z18, Z19, Z20, Z21, Z22, Z23, Z24, Z25, Z26, Z27, Z28,  
 Z29, Z30, Z31, Z32, Z33, Z34, Z35, Z36, Z37, Z38, Z39, Z40, Z41, Z42,  
 Z43, Z44, Z45, Z46, Z47, Z48, Z49, Z50, Z51, Z52, Z53, Z54, Z55, Z56,  
 30 Z57, Z58, Z59, Z60, Z61, Z62, Z63, Z64, Z65, Z66, Z67, Z68, Z69, Z70,  
 Z71, Z72, Z73, Z74, Z75, Z76, Z77, Z78, Z79, Z80, Z81, Z82, Z83, Z84,  
 Z85, Z86, Z87, Z88, Z89, Z90, Z91, Z92, Z93, Z94, Z95, Z96, Z97, Z98,  
 Z99, Z100, Z101, Z102, Z103, Z104, Z105, Z106, Z107, Z108, Z109,  
 Z110, Z111, Z112 are independently from each other selected from the  
 35 group consisting of: „alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl,

heterocyclalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl" and wherein alternatively Z7, Z8 and/or Z16, Z17 and/or Z29, Z30 and/or Z36, Z37 and/or Z45, Z46 and/or Z55, Z56 and/or Z60, Z61 and/or Z77, Z78 and/or Z86, Z87 and/or Z89, Z90 and/or Z92, Z93 and/or Z95, Z96 and/or Z99, Z100 and/or Z105, Z106 and/or Z108, Z109 and/or Z111, Z112 respectively together can also form „heterocycl“;

R<sub>2</sub> denotes H or alkyl,

R<sub>3</sub> denotes H or alkyl,

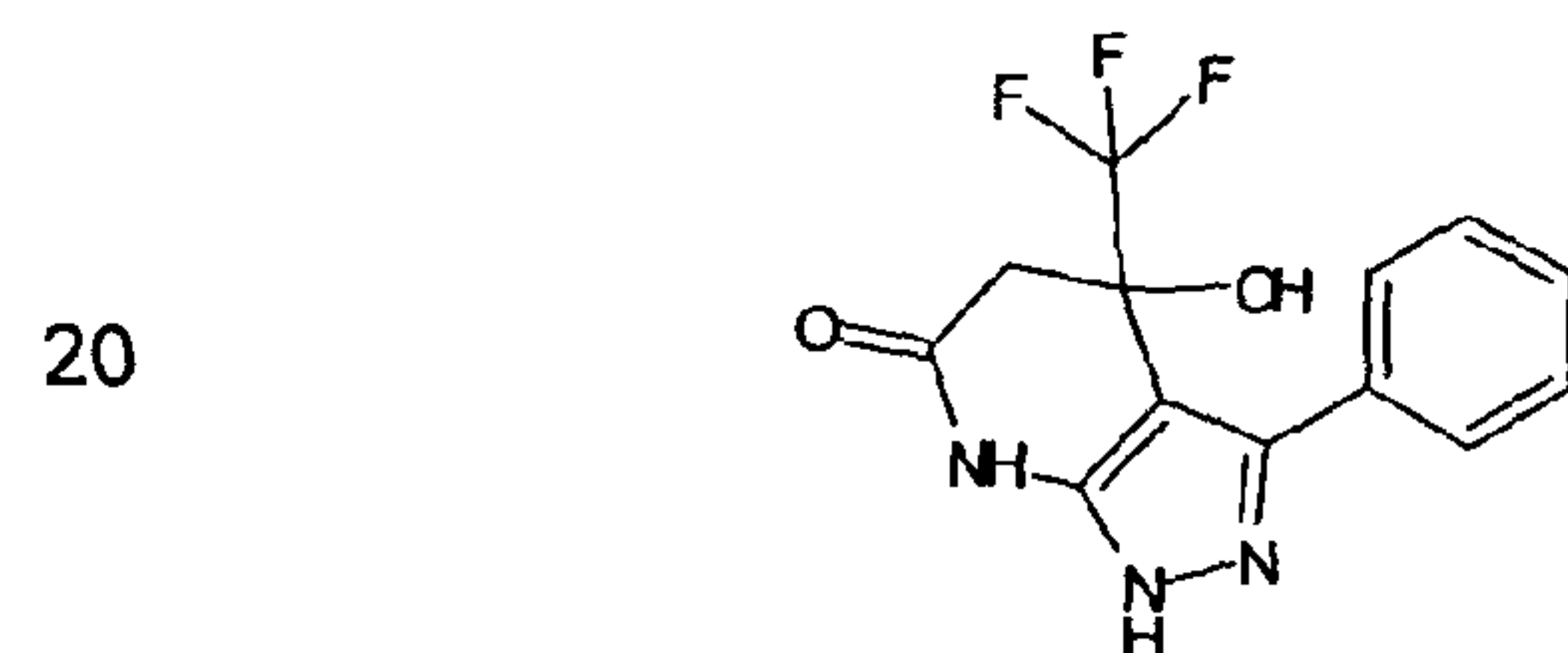
R<sub>4</sub>, R<sub>5</sub> independently from each other denote H, alkyl, OH-alkyl, alkoxy, halogen, F, Cl, Br, I, CN, NHR, NH<sub>2</sub>, NR<sub>2</sub>, S-alkyl or NH-alkyl-OH, wherein R independently from each other denotes alkyl, aryl, heteroaryl, cycloalkyl or heterocyclalkyl; or

R<sub>4</sub> and R<sub>5</sub> together form cycloalkyl or heterocyclalkyl,

R<sub>6</sub> denotes H or alkyl,

X denotes O, NH or N-alkyl,

with the proviso that the following compound is excluded from formula (I):



and the physiologically acceptable salts, solvates, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

25

In a preferred embodiment, a compound according to formula (I) is provided, wherein:

R<sub>1</sub> denotes aryl, heteroaryl, cycloalkyl or arylalkyl, preferably phenyl, thiophenyl, furanyl, pyrazolyl, pyridinyl, indolyl or benzyl, which can optionally be substituted with one or more substituents selected from halogen, F, Cl, Br, I, CF<sub>3</sub>, alkyl, methyl, alkoxy or methoxy,

30

and the physiologically acceptable salts, solvates, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

35

In a preferred embodiment, a compound according to formula (I) and above embodiment is provided, wherein:

5             $R_2$         denotes H, methyl or ethyl,  
              and the physiologically acceptable salts, solvates, tautomers and  
              stereoisomers thereof, including mixtures thereof in all ratios.

In a preferred embodiment, a compound according to formula (I) and above embodiments is provided, wherein:

10            $R_3$         denotes H, methyl or ethyl,  
              and the physiologically acceptable salts, solvates, tautomers and  
              stereoisomers thereof, including mixtures thereof in all ratios.

In a preferred embodiment, a compound according to formula (I) and above embodiments is provided, wherein:

15            $R_4, R_5$     independently from each other denote H, alkyl, OH-alkyl, alkoxy,  
                          methyl, ethyl, hydroxy-ethyl or methoxy,  
              and the physiologically acceptable salts, solvates, tautomers and  
              stereoisomers thereof, including mixtures thereof in all ratios.

20           In a preferred embodiment, a compound according to formula (I) and above  
embodiments is provided, wherein:

$R_6$         denotes H,  
              and the physiologically acceptable salts, solvates, tautomers and  
              stereoisomers thereof, including mixtures thereof in all ratios.

25           In a preferred embodiment, a compound according to formula (I) and above  
embodiments is provided, wherein:

              X        denotes O,  
              and the physiologically acceptable salts, solvates, tautomers and  
30            stereoisomers thereof, including mixtures thereof in all ratios.

In a preferred embodiment, a compound according to formula (I) and above  
embodiments is provided, wherein:

35            $R_1$         denotes aryl, heteroaryl, cycloalkyl or arylalkyl, preferably phenyl,  
                          thiophenyl, furanyl, pyrazolyl, pyridinyl, indolyl or benzyl, which can

optionally be substituted with one or more substituents selected from halogen, F, Cl, Br, I, CF<sub>3</sub>, alkyl, methyl, alkoxy or methoxy,

R<sub>2</sub> denotes H, methyl or ethyl,

R<sub>3</sub> denotes H, methyl or ethyl,

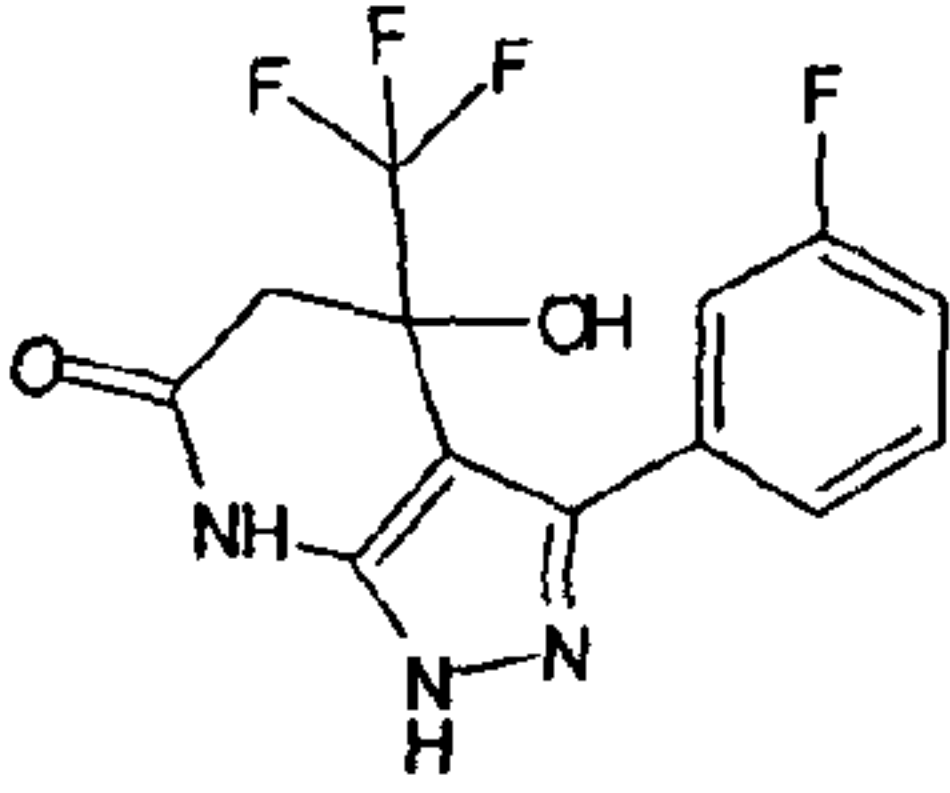
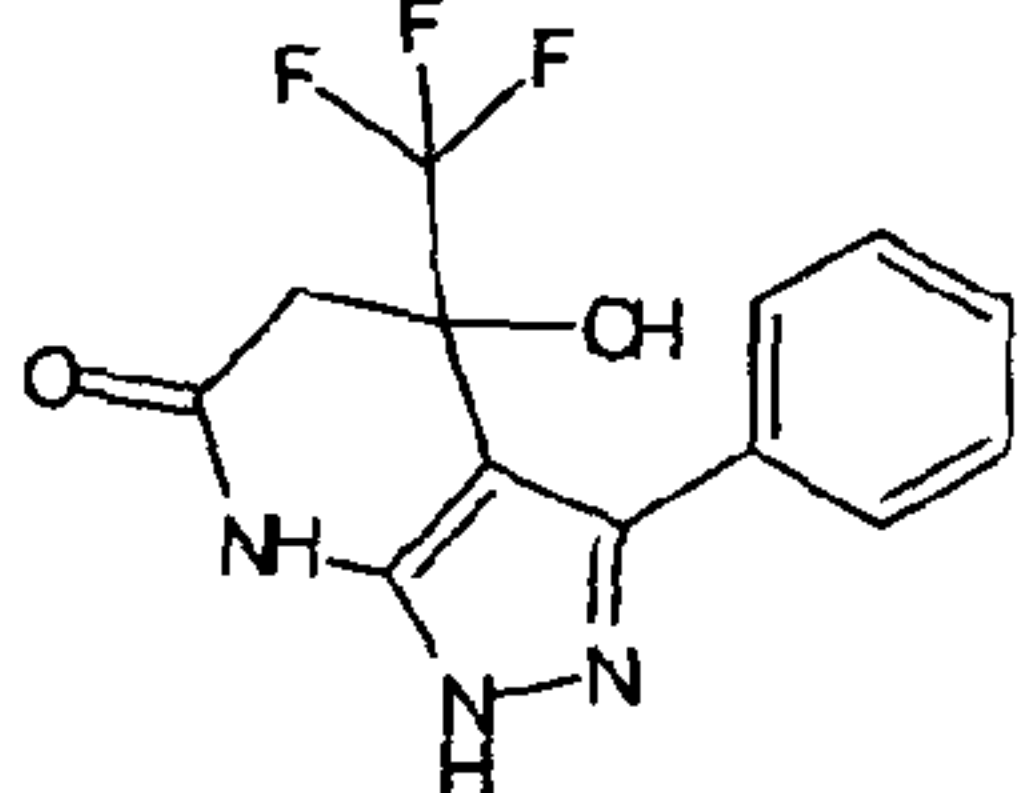
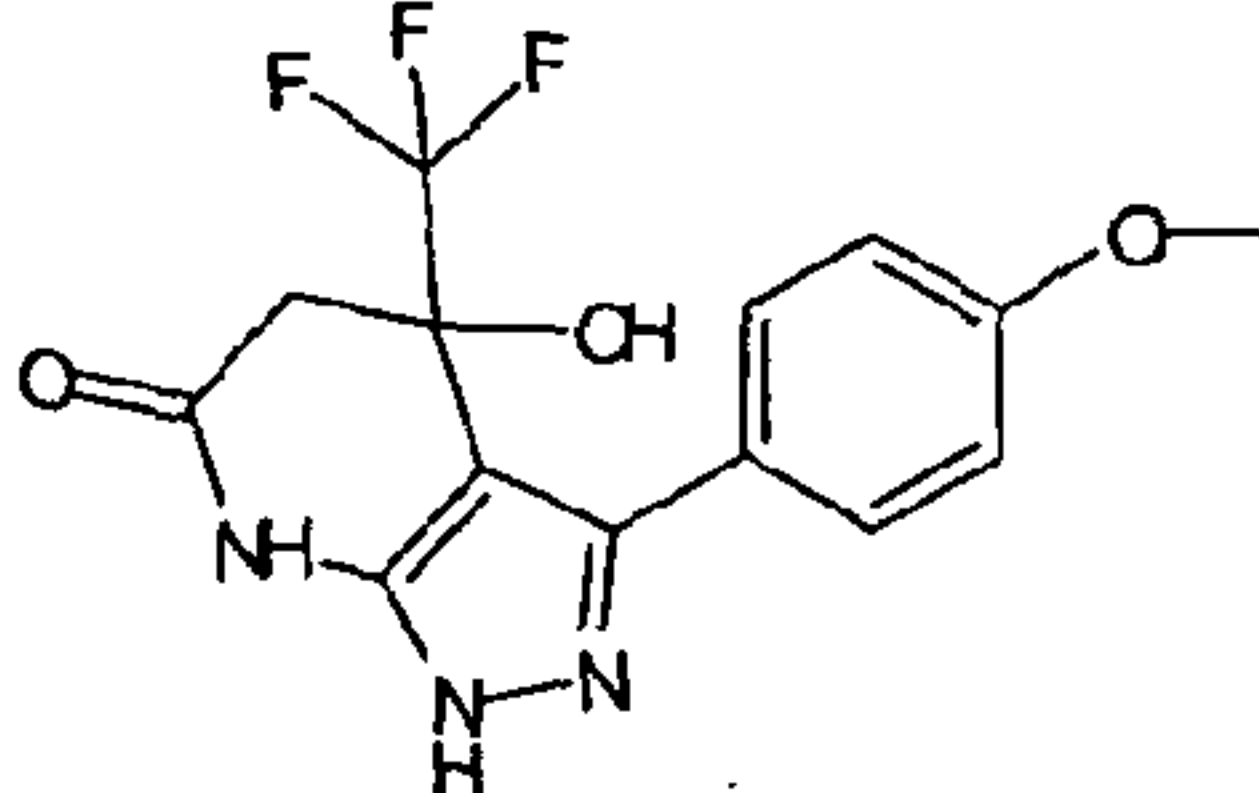
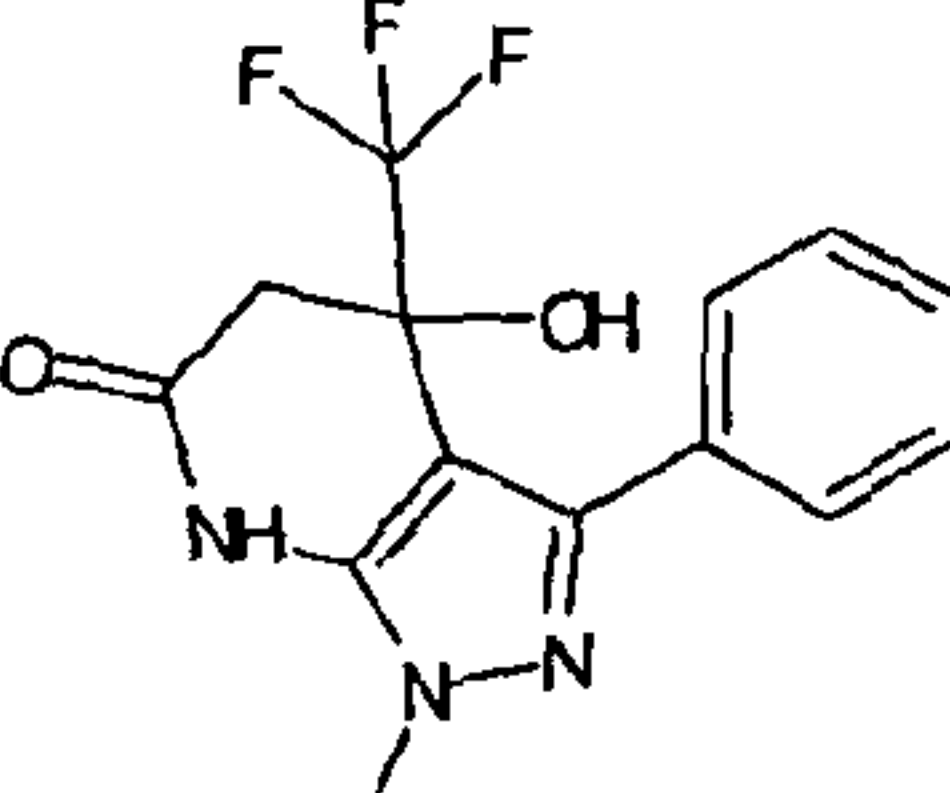
5 R<sub>4</sub>, R<sub>5</sub> independently from each other denote H, alkyl, OH-alkyl, alkoxy, methyl, ethyl, hydroxy-ethyl or methoxy,

R<sub>6</sub> denotes H,

X denotes O,

and the physiologically acceptable salts, solvates, tautomers and  
10 stereoisomers thereof, including mixtures thereof in all ratios.

In another aspect, the object of the present invention has surprisingly been solved by providing a compound selected from the group consisting of:

|    |   |                                                                                      |                                                                                                  |
|----|---|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| 15 | 1 |  | 3-(3-Fluoro-phenyl)-4-hydroxy-4-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-b]pyridin-6-one  |
| 20 | 2 |  | 4-Hydroxy-3-phenyl-4-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-b]pyridin-6-one             |
| 25 | 3 |  | 4-Hydroxy-3-(4-methoxy-phenyl)-4-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-b]pyridin-6-one |
| 30 | 4 |  | 4-Hydroxy-1-methyl-3-phenyl-4-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-b]pyridin-6-one    |
| 35 |   |                                                                                      |                                                                                                  |

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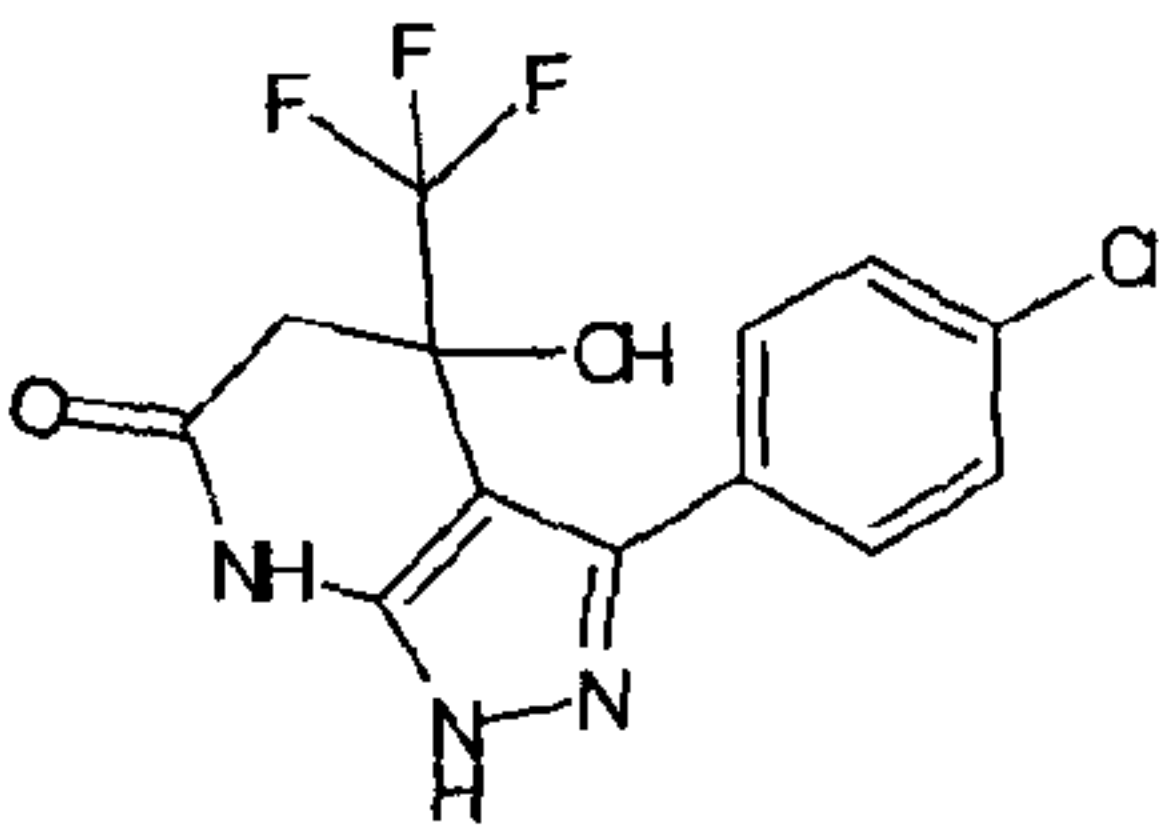
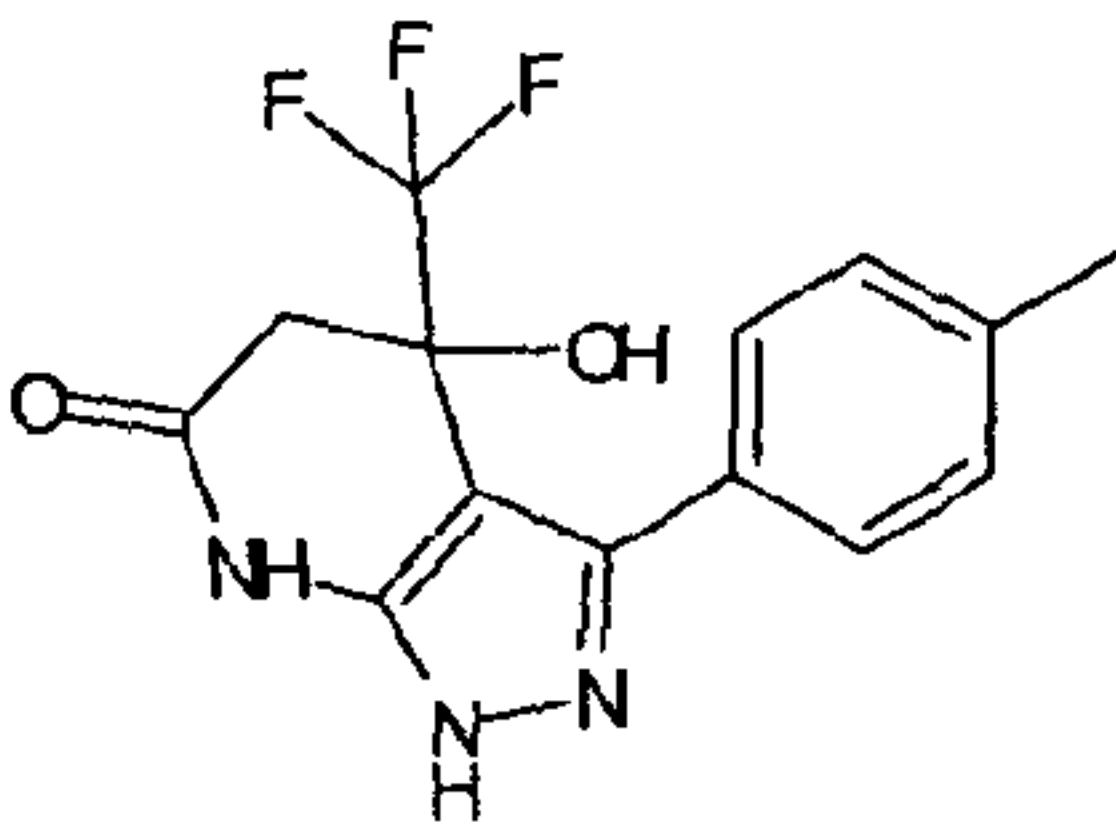
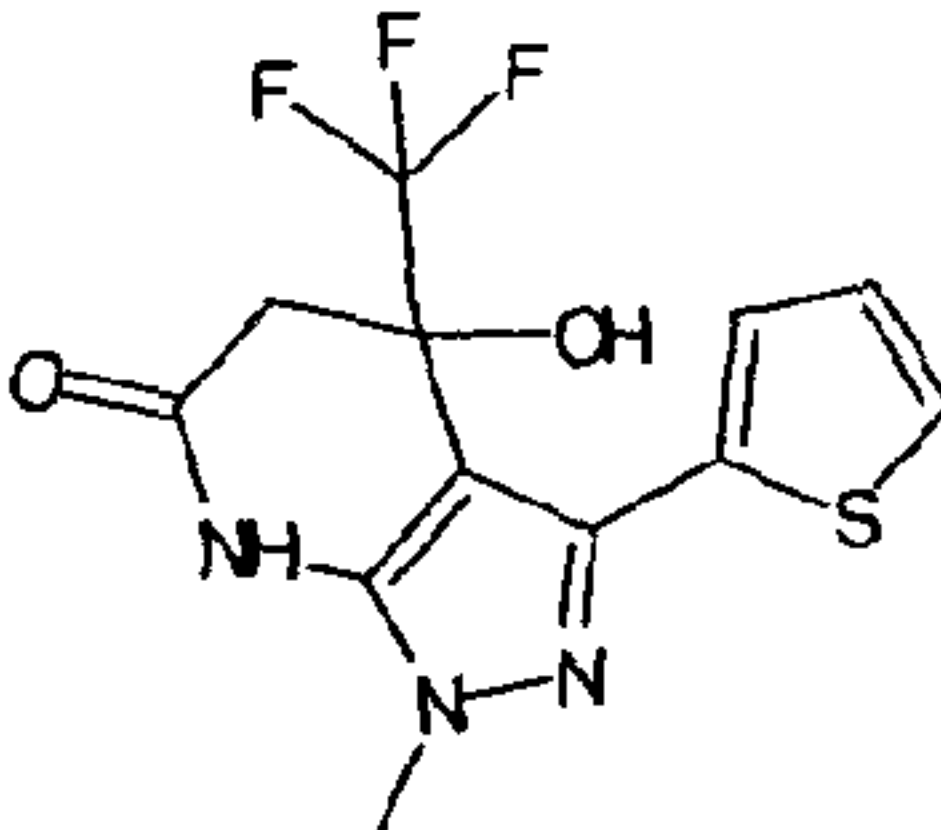
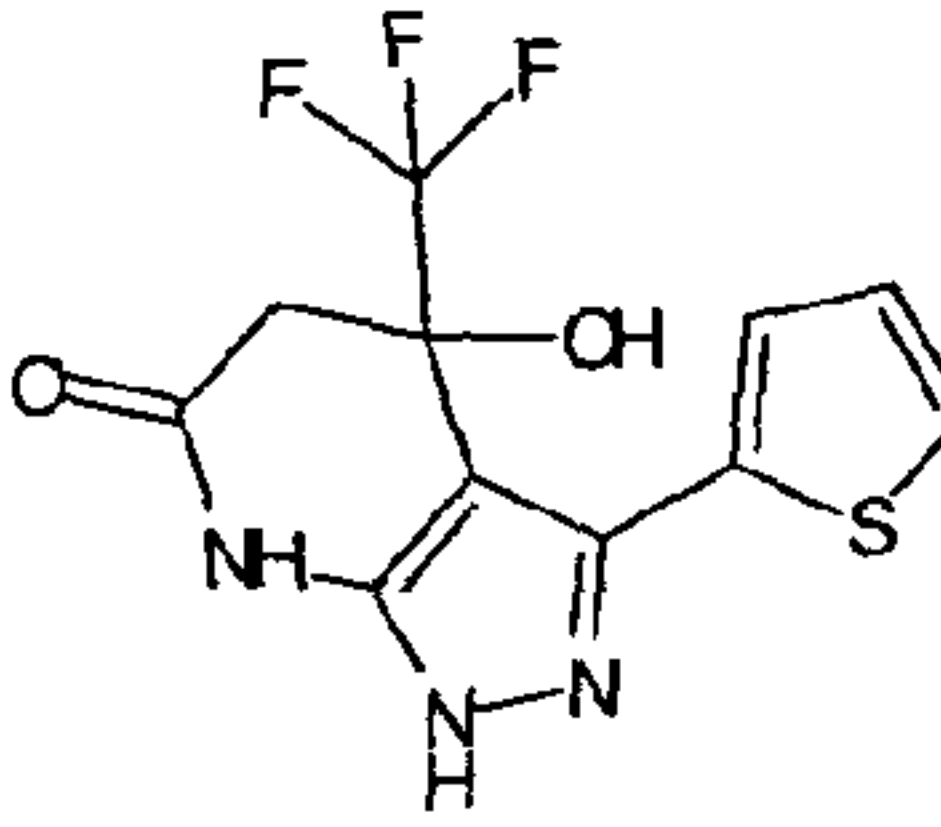
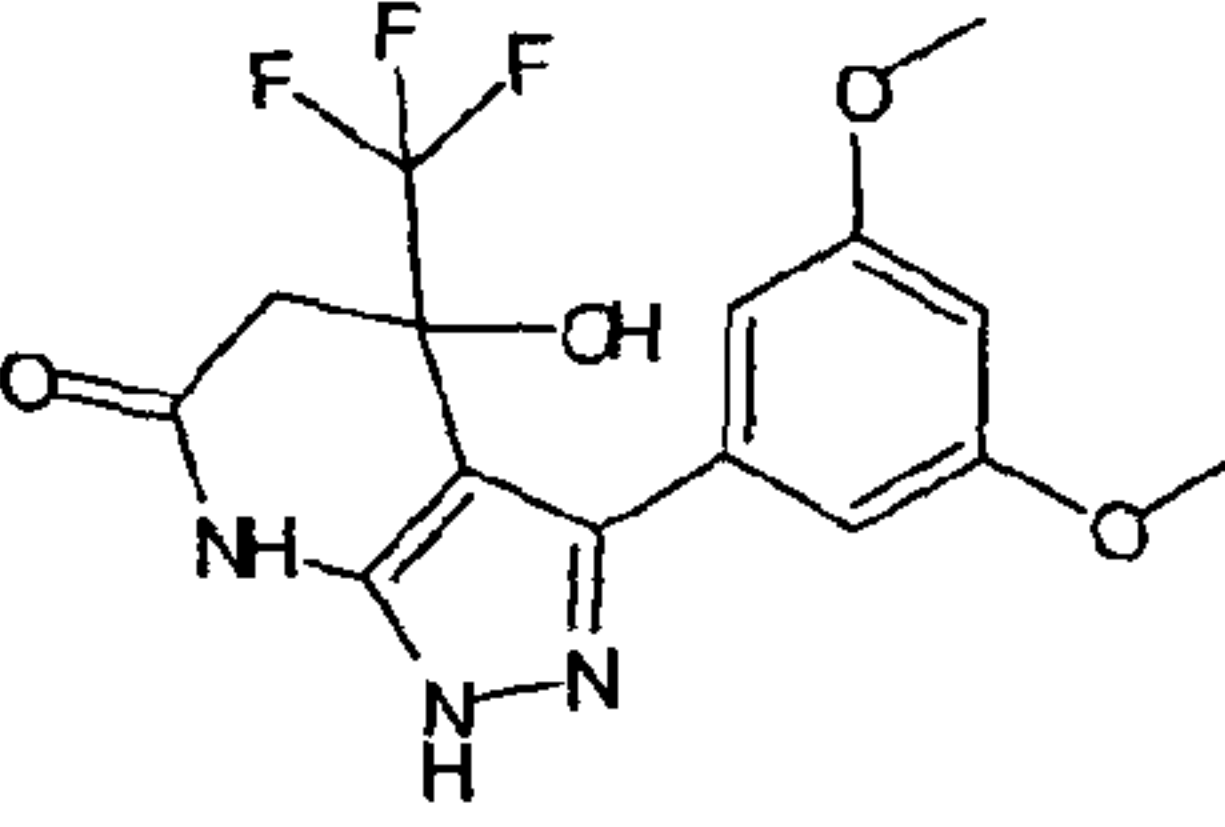
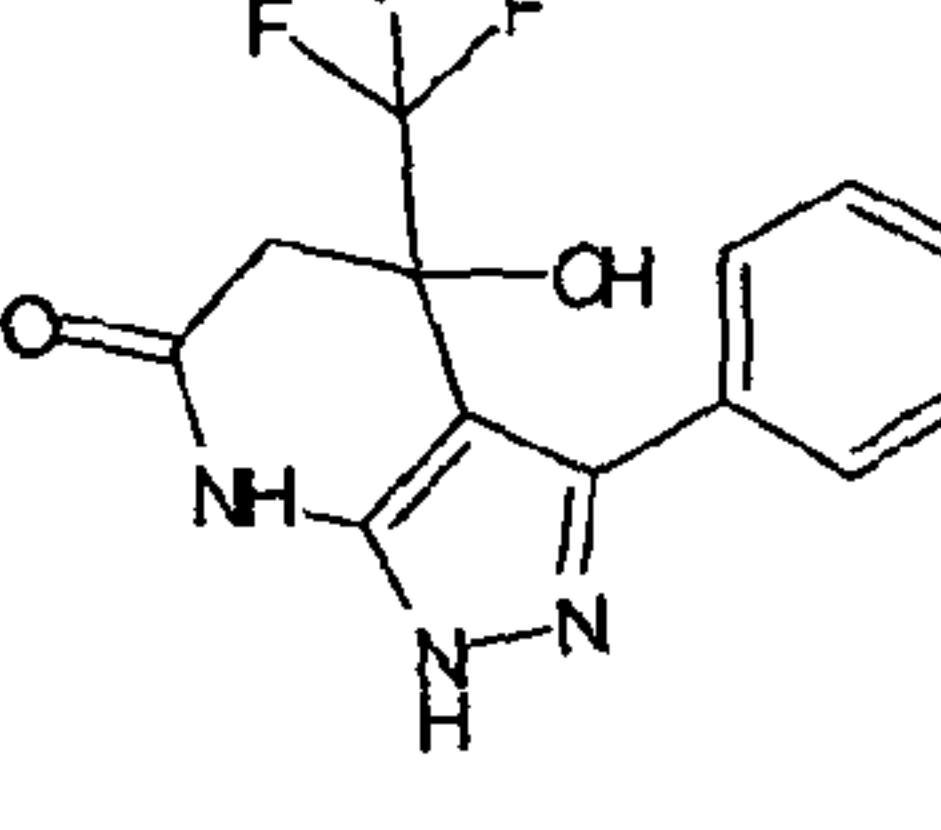
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|----|--------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| 5  |    | 3-(4-Chloro-phenyl)-4-hydroxy-4-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-b]pyridin-6-one      |
| 6  |   | 4-Hydroxy-3-p-tolyl-4-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-b]pyridin-6-one                |
| 7  |  | 4-Hydroxy-1-methyl-3-thiophen-2-yl-4-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-b]pyridin-6-one |
| 8  |  | 4-Hydroxy-3-thiophen-2-yl-4-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-b]pyridin-6-one          |
| 9  |  | 3-(3,5-Dimethoxy-phenyl)-4-hydroxy-4-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-b]pyridin-6-one |
| 10 |  | (-)-4-Hydroxy-3-phenyl-4-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-b]pyridin-6-one             |

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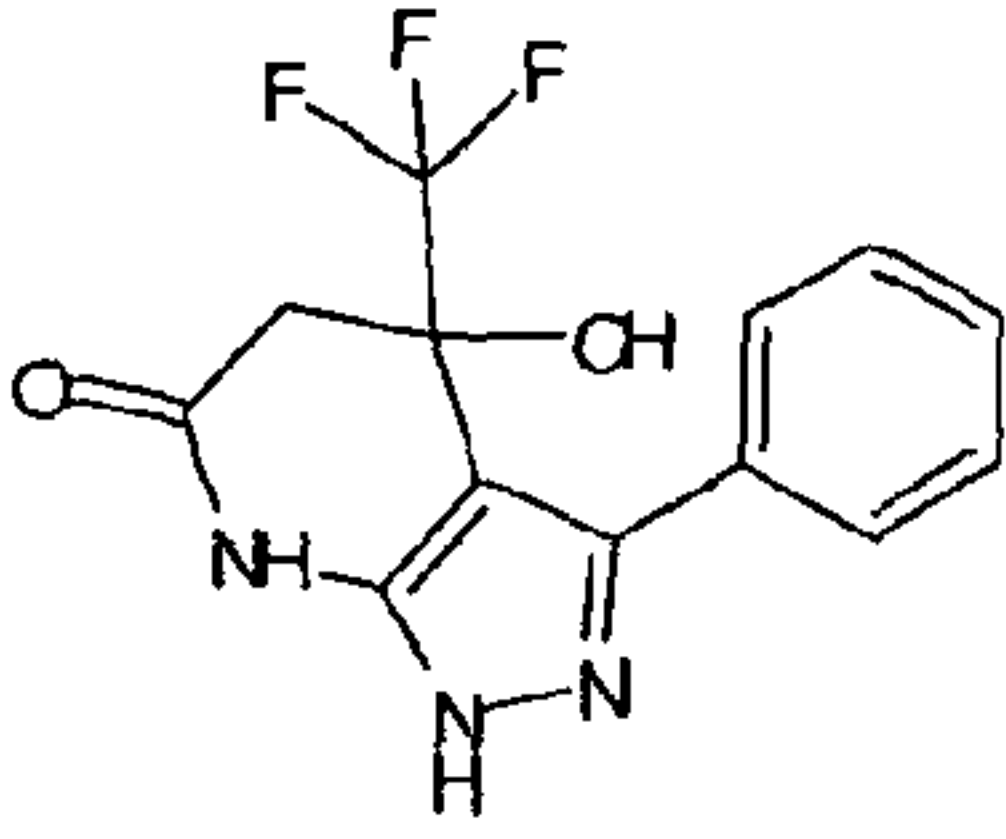
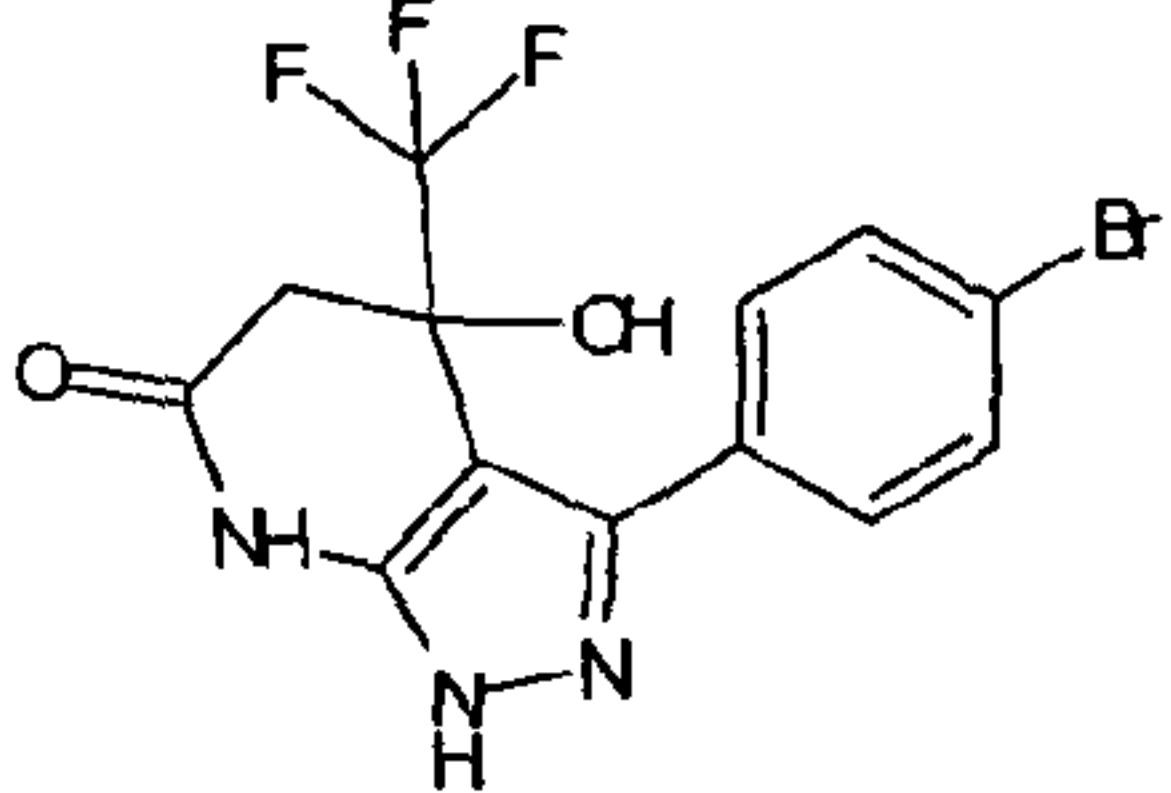
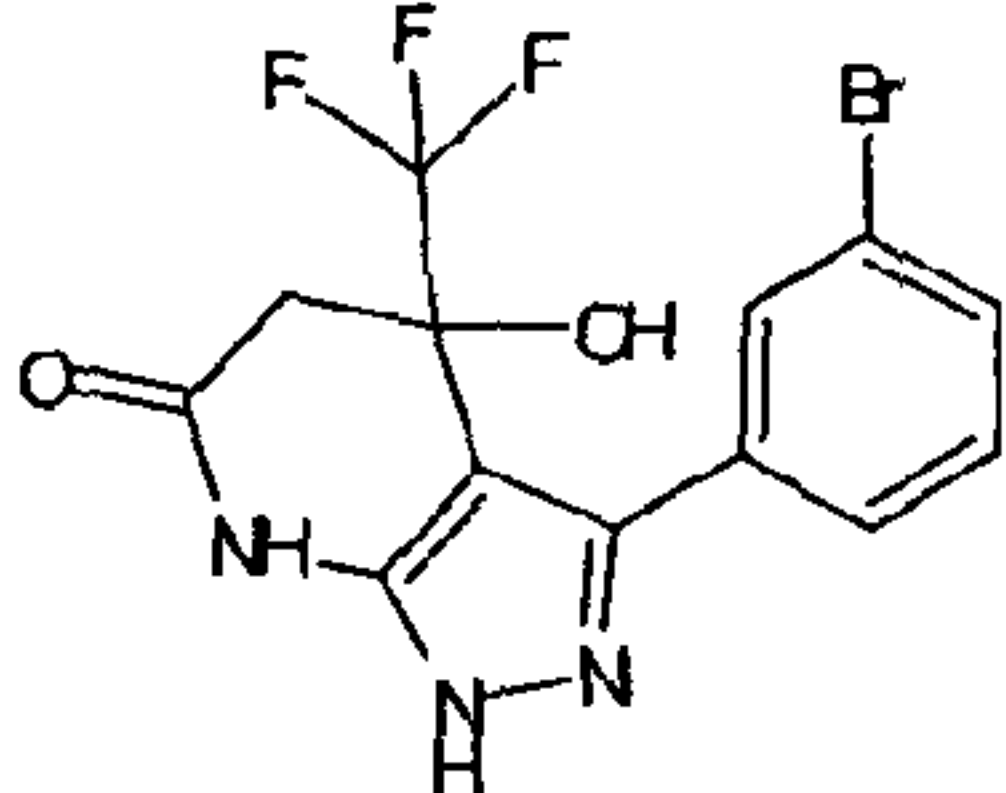
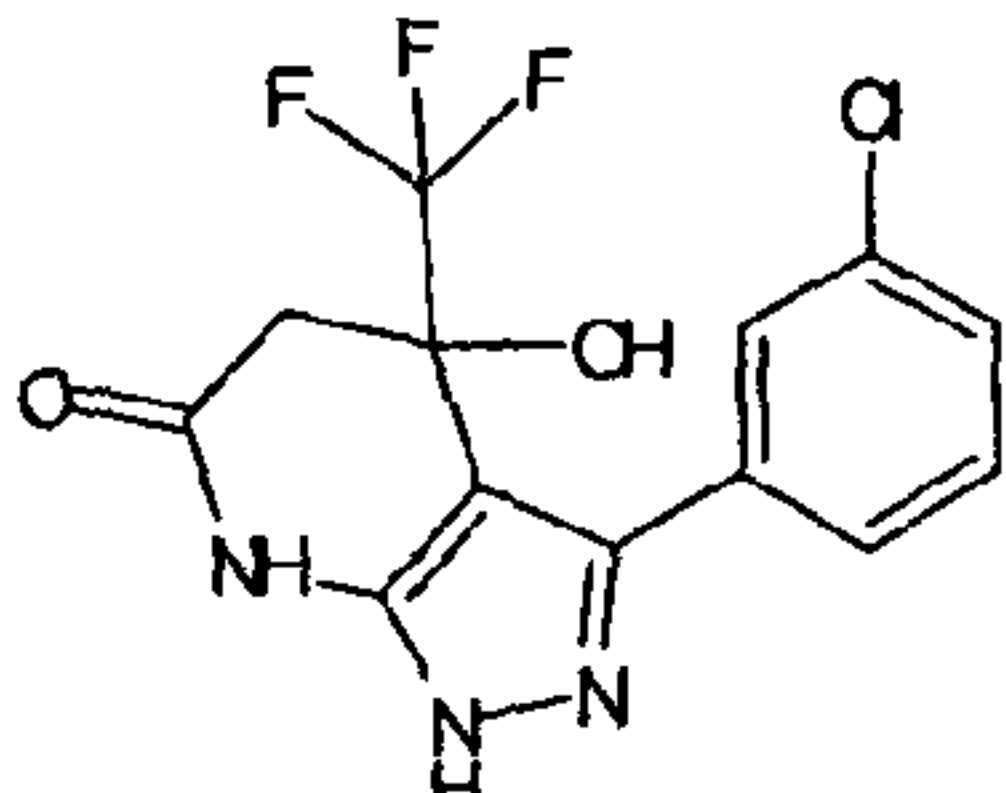
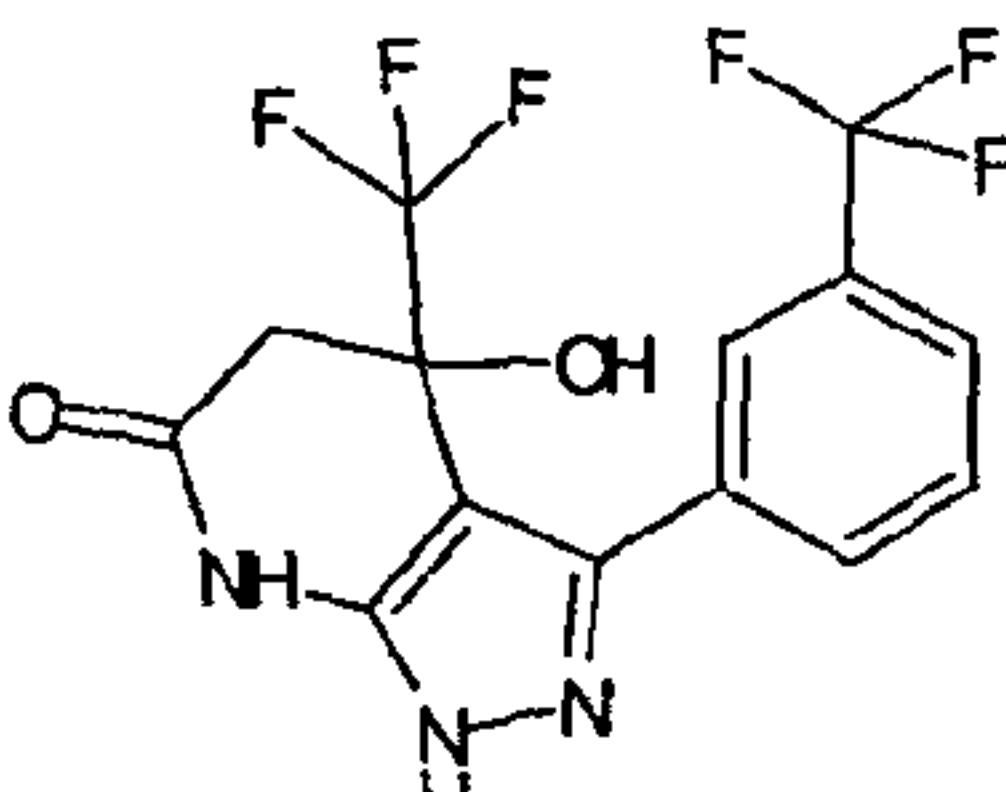
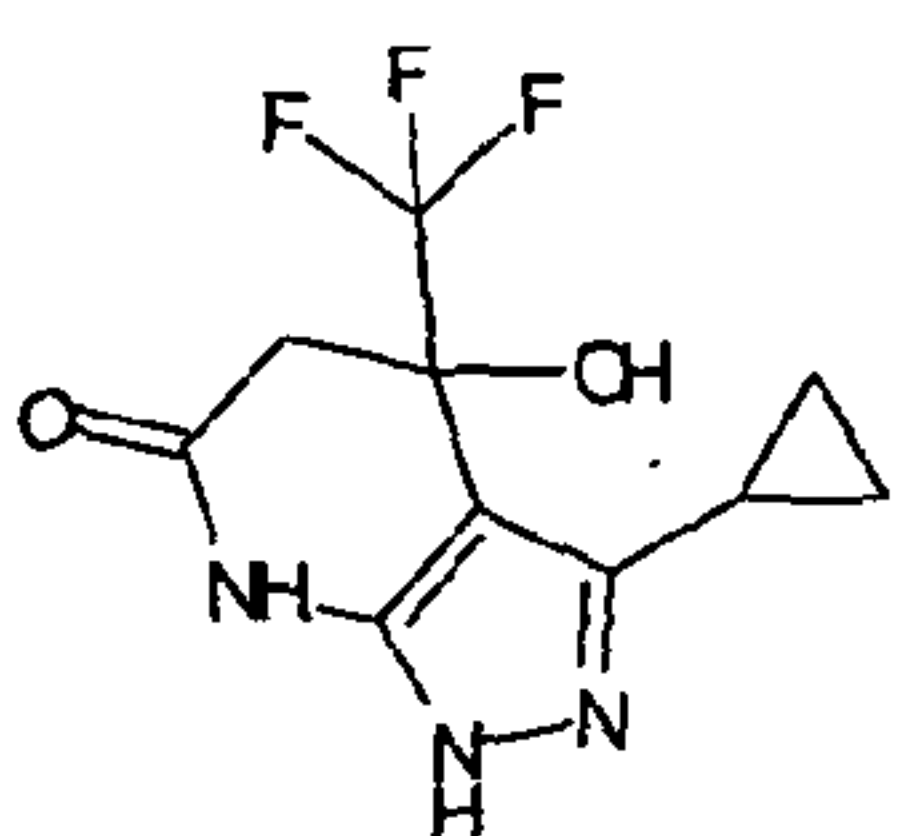
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|    |                                                                                      |                                                                                                         |
|----|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|
| 11 |    | (+)-4-Hydroxy-3-phenyl-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one                 |
| 12 |   | 3-(4-Bromo-phenyl)-4-hydroxy-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one           |
| 13 |  | 3-(3-Bromo-phenyl)-4-hydroxy-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one           |
| 14 |  | 3-(3-Chloro-phenyl)-4-hydroxy-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one          |
| 15 |  | 4-Hydroxy-4-trifluoromethyl-3-(3-trifluoromethyl-phenyl)-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one |
| 16 |  | 3-Cyclopropyl-4-hydroxy-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one                |

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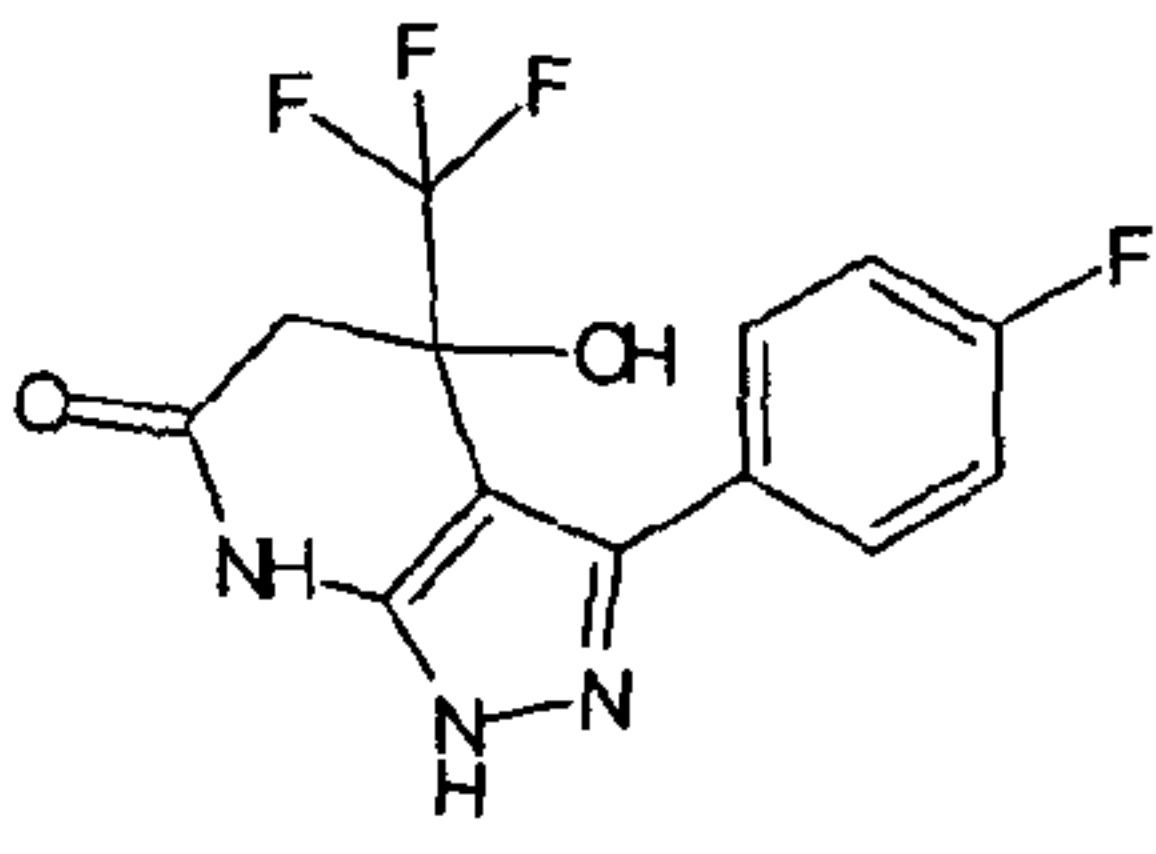
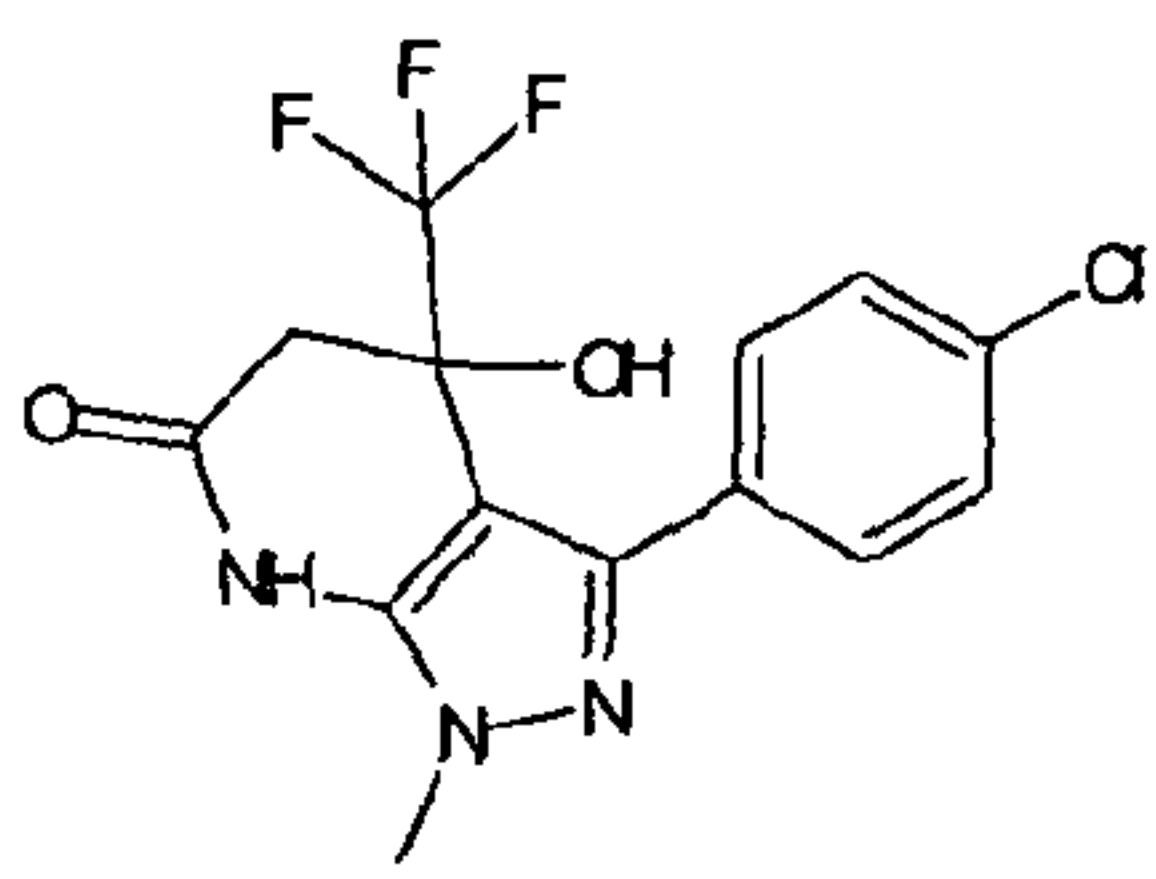
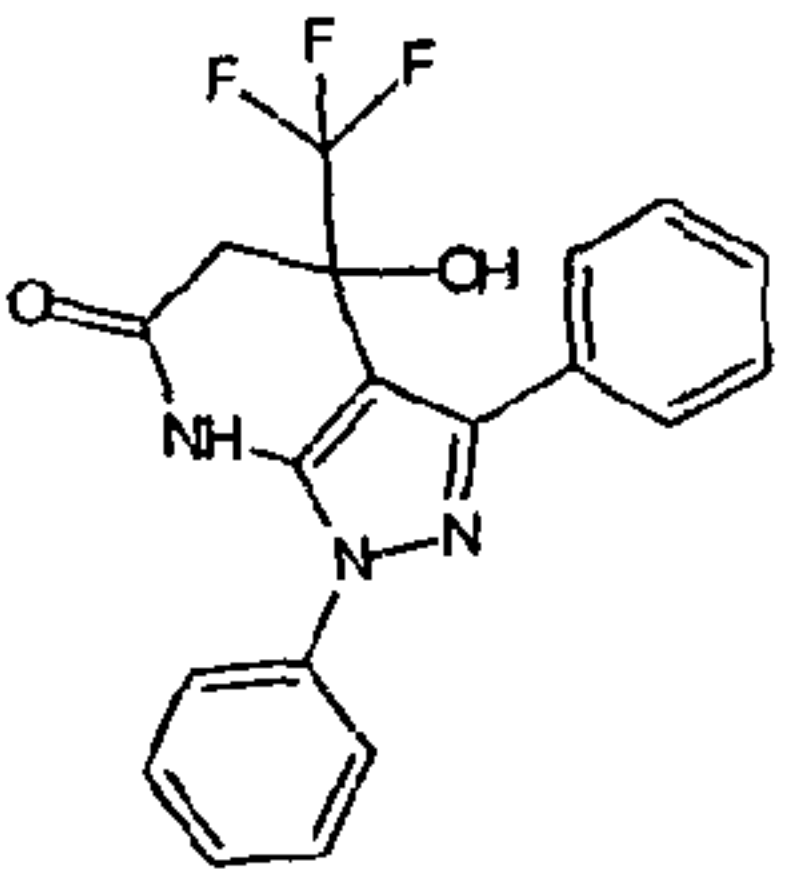
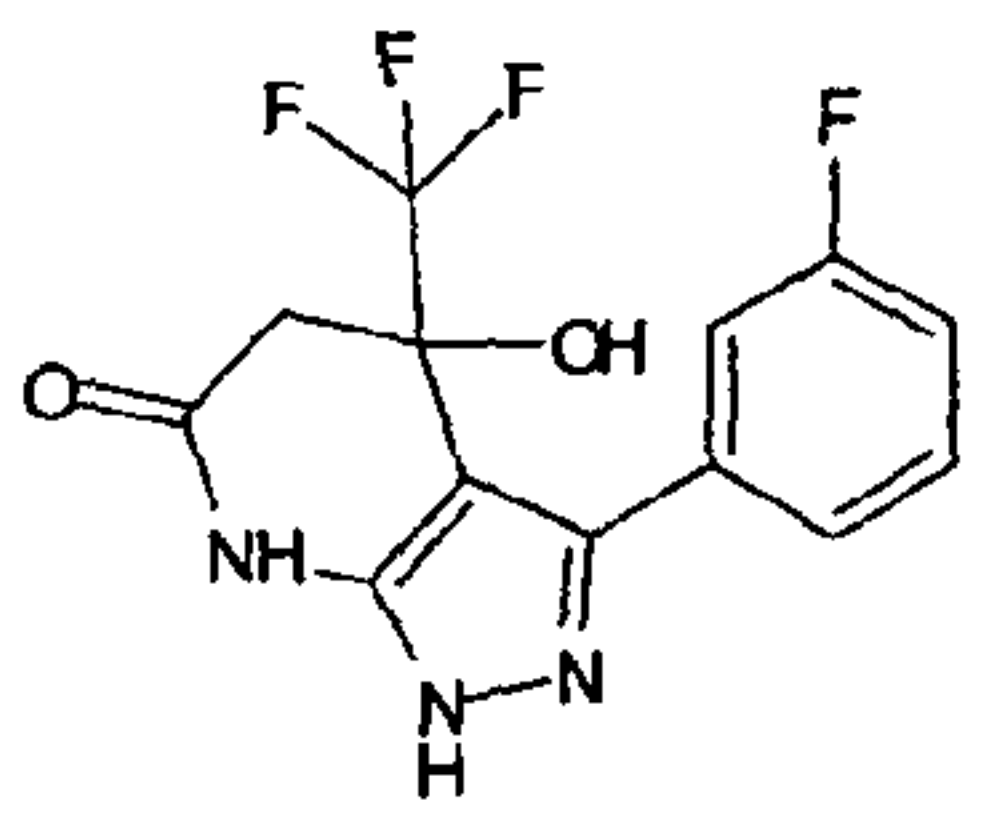
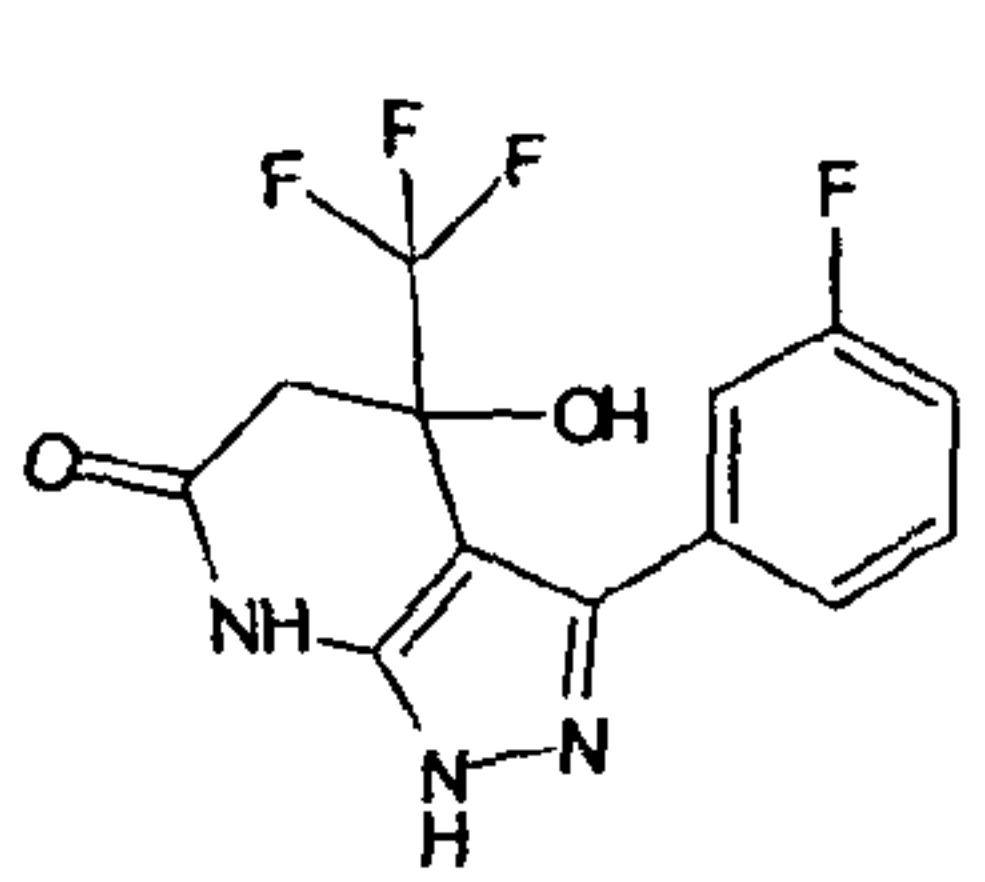
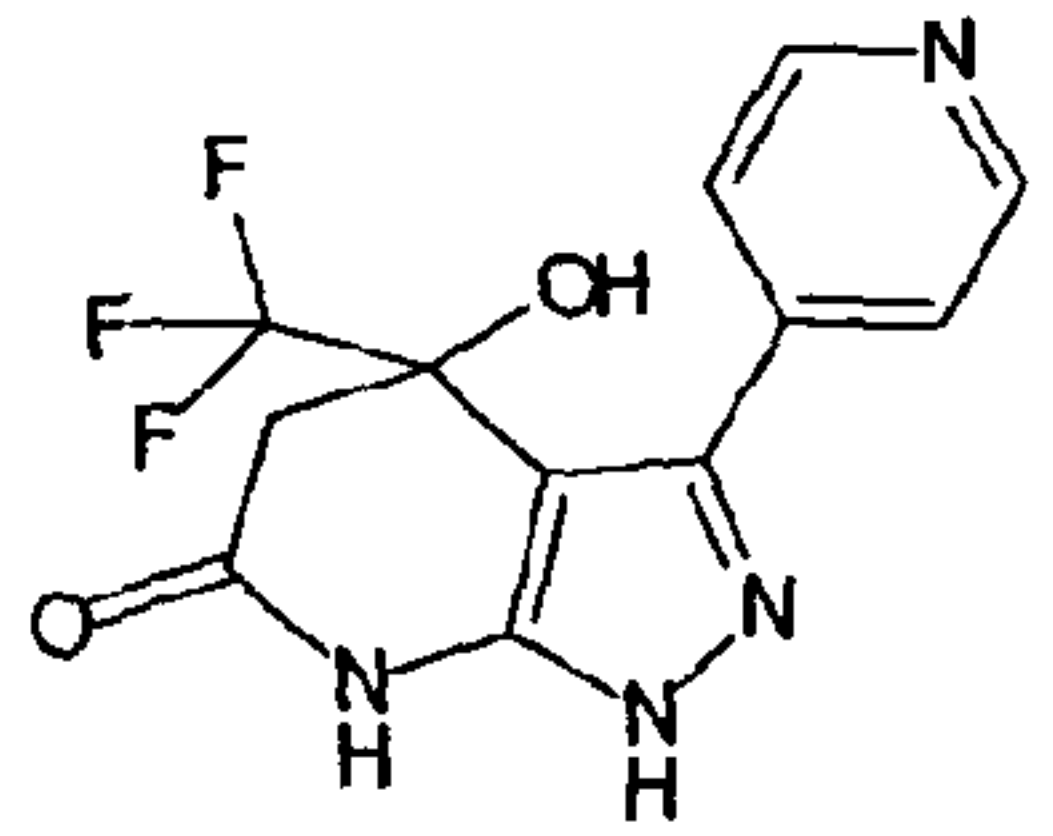
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|    |                                                                                      |                                                                                                                              |
|----|--------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|
| 17 |    | 3-(4-Fluoro-phenyl)-<br>4-hydroxy-4-<br>trifluoromethyl-<br>1,4,5,7-tetrahydro-<br>pyrazolo[3,4-<br>b]pyridin-6-one          |
| 18 |   | 3-(4-Chloro-phenyl)-<br>4-hydroxy-1-methyl-<br>4-trifluoromethyl-<br>1,4,5,7-tetrahydro-<br>pyrazolo[3,4-<br>b]pyridin-6-one |
| 19 |  | 4-Hydroxy-1,3-<br>diphenyl-4-<br>trifluoromethyl-<br>1,4,5,7-tetrahydro-<br>pyrazolo[3,4-<br>b]pyridin-6-one                 |
| 20 |  | (-)-3-(3-Fluoro-<br>phenyl)-4-hydroxy-4-<br>trifluoromethyl-<br>1,4,5,7-tetrahydro-<br>pyrazolo[3,4-<br>b]pyridin-6-one      |
| 21 |  | (+)-3-(3-Fluoro-<br>phenyl)-4-hydroxy-4-<br>trifluoromethyl-<br>1,4,5,7-tetrahydro-<br>pyrazolo[3,4-<br>b]pyridin-6-one      |
| 22 |  | 4-Hydroxy-3-pyridin-<br>4-yl-4-trifluoromethyl-<br>1,4,5,7-tetrahydro-<br>pyrazolo[3,4-<br>b]pyridin-6-one                   |

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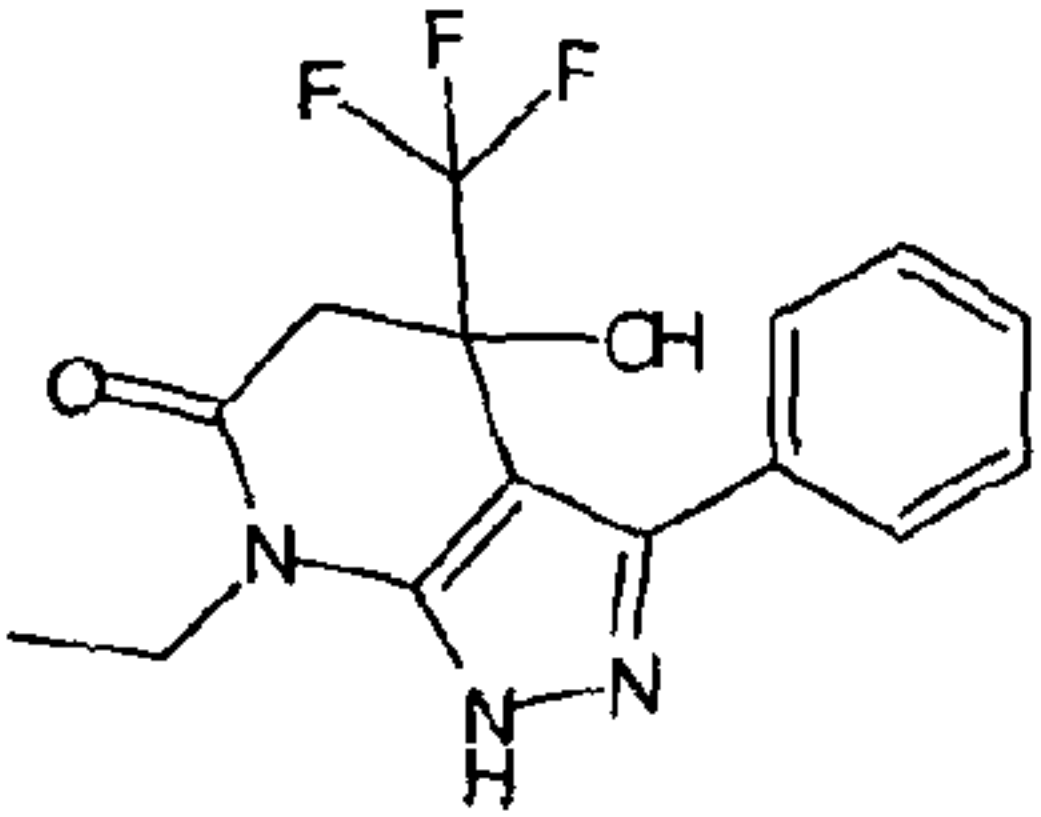
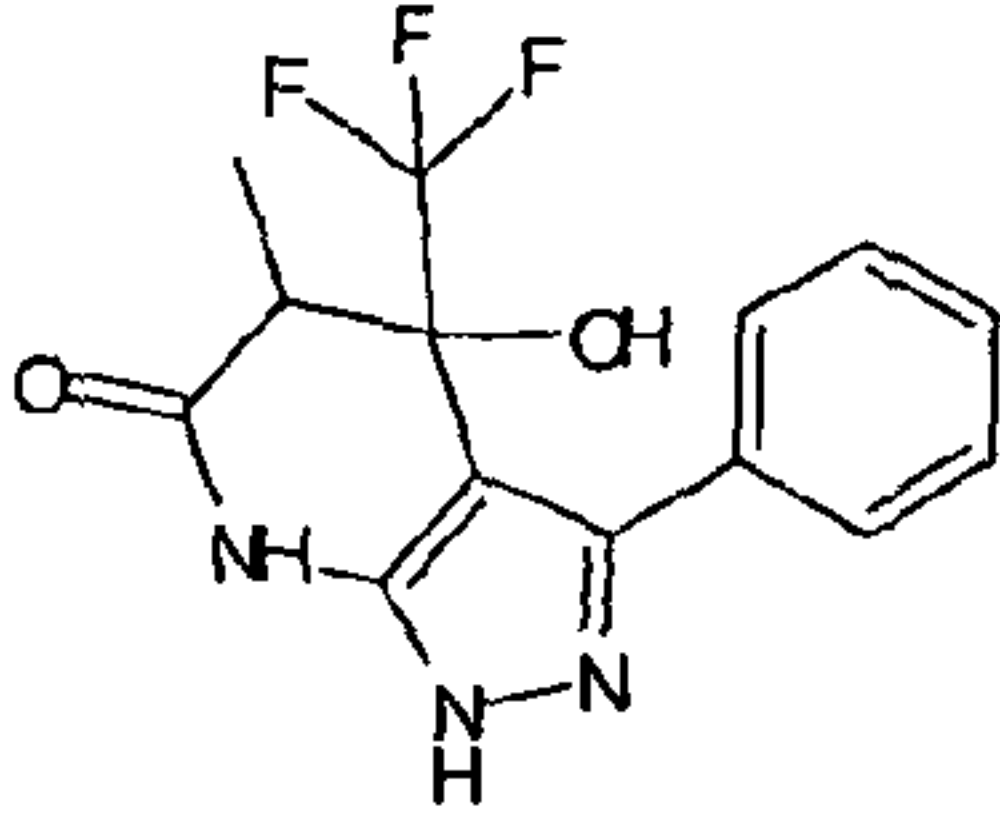
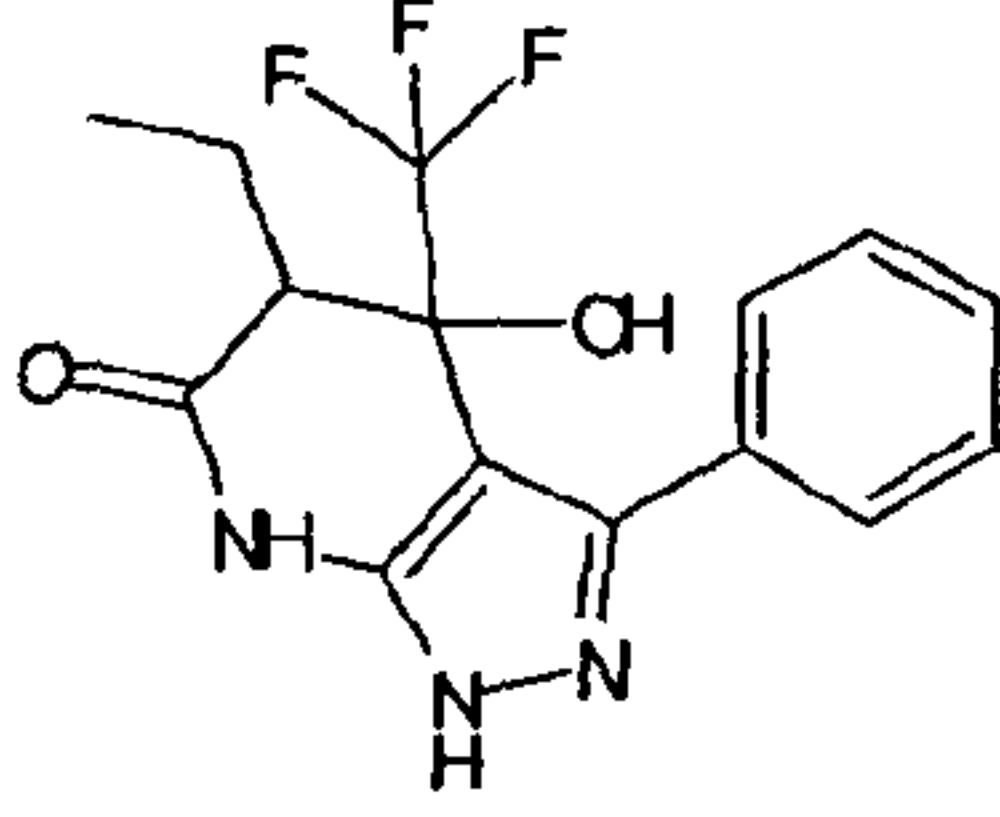
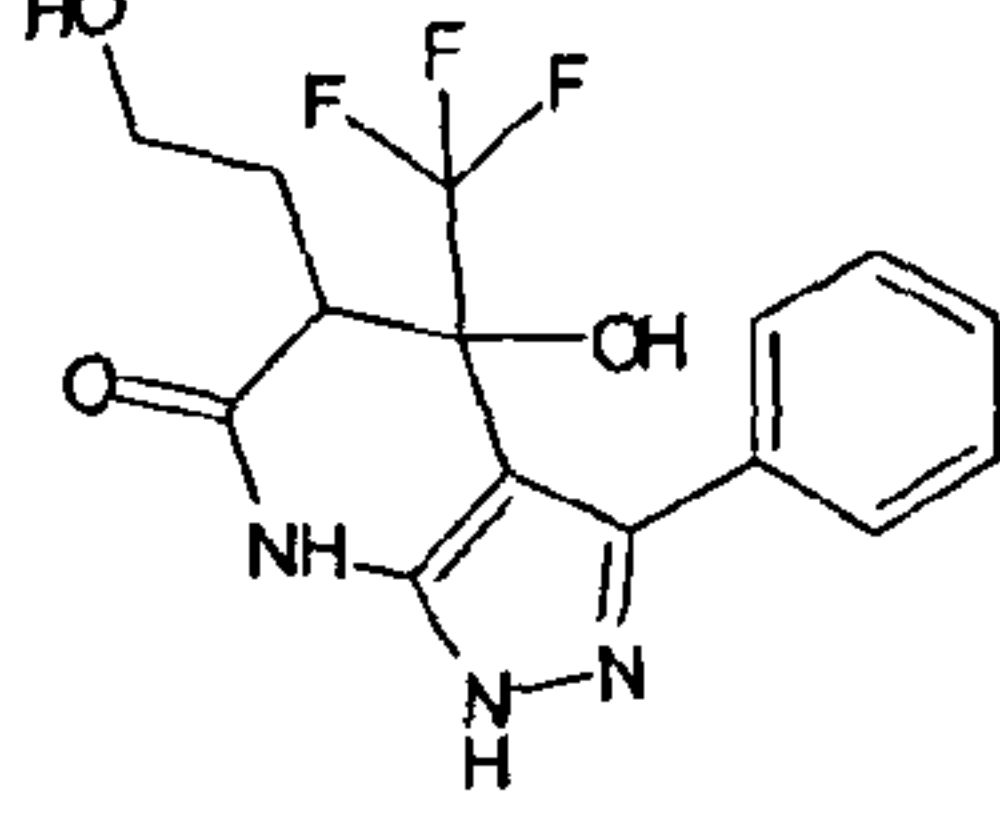
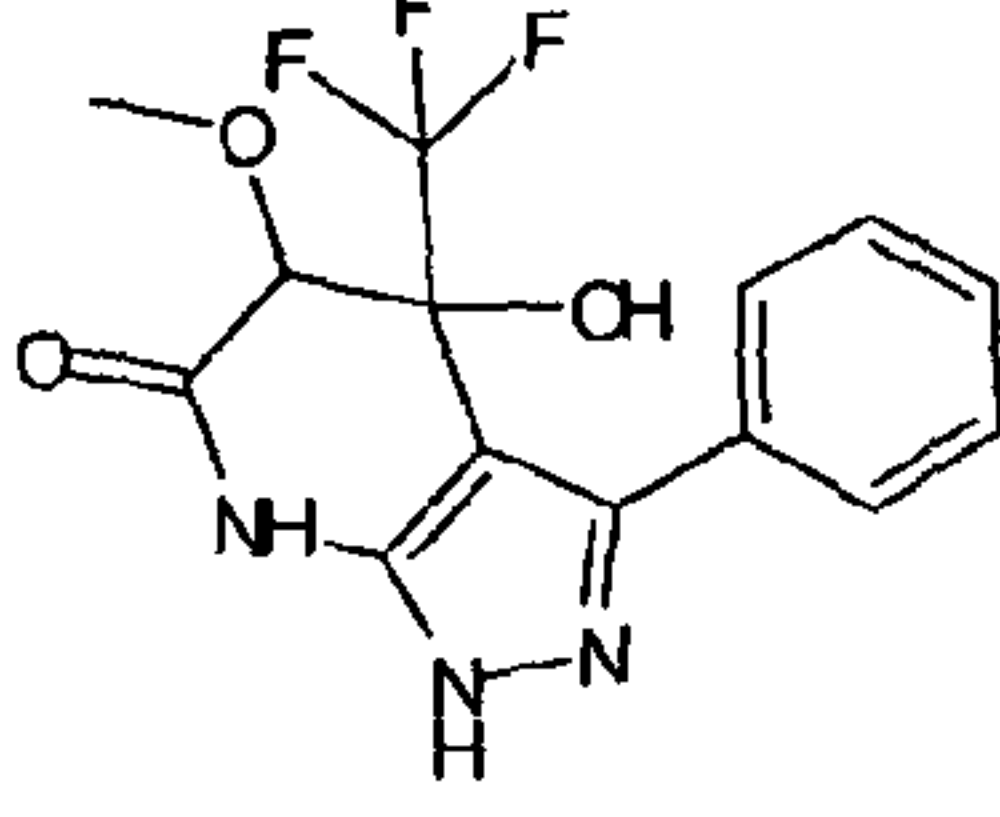
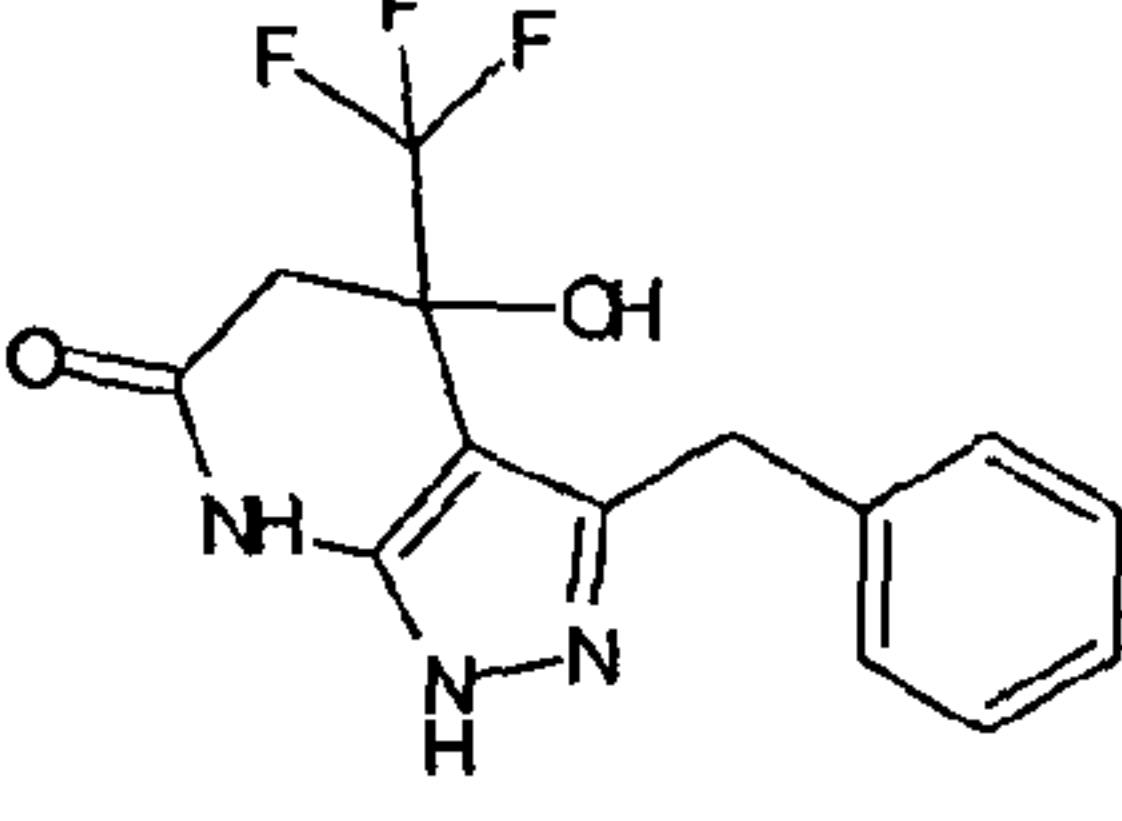
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|    |                                                                                      |                                                                                                         |
|----|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|
| 23 |    | 4-Hydroxy-7-ethyl-3-phenyl-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one             |
| 24 |   | 4-Hydroxy-5-methyl-3-phenyl-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one            |
| 25 |  | 4-Hydroxy-5-ethyl-3-phenyl-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one             |
| 26 |  | 4-Hydroxy-5-(2-hydroxy-ethyl)-3-phenyl-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one |
| 27 |  | 4-Hydroxy-5-methoxy-3-phenyl-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one           |
| 28 |  | 3-Benzyl-4-hydroxy-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one                     |

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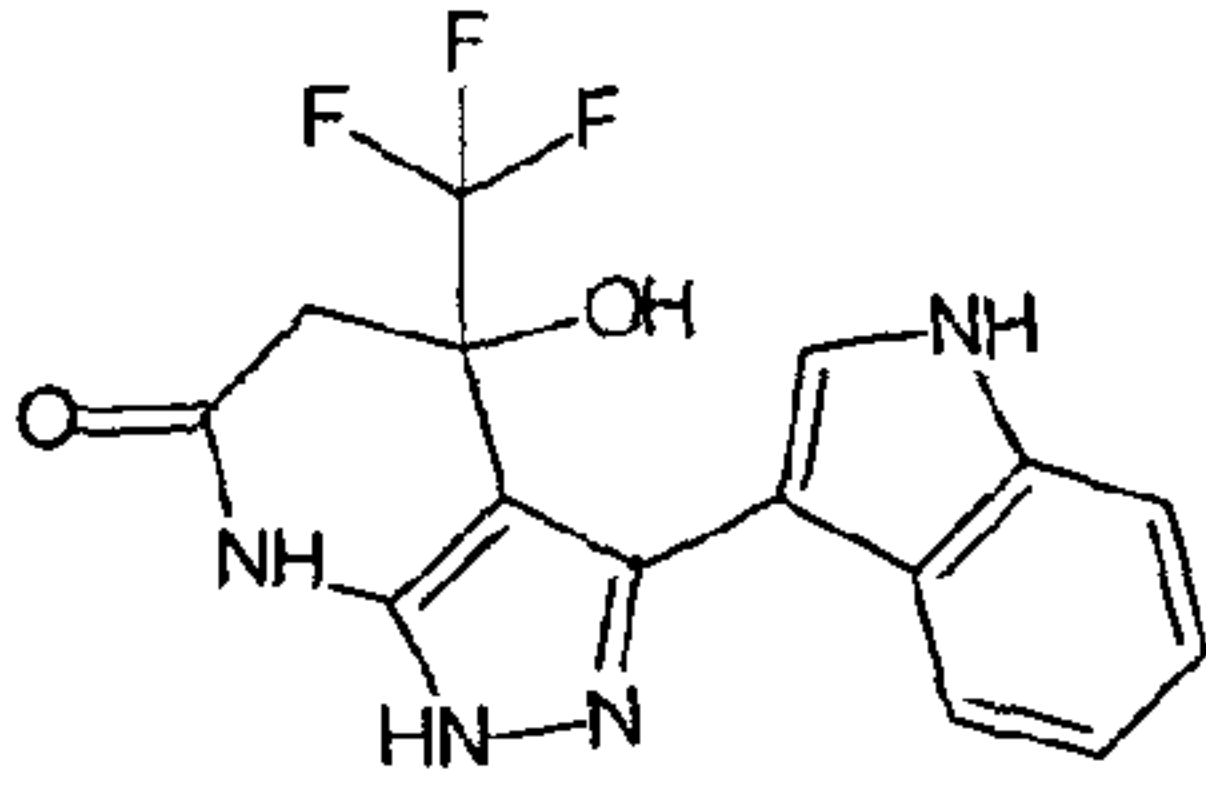
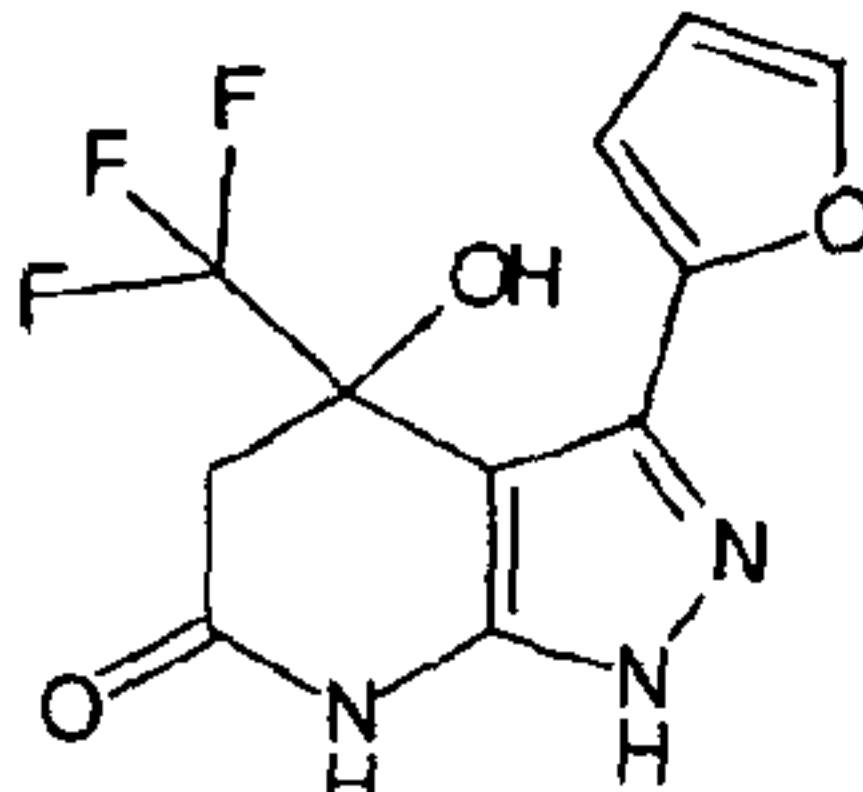
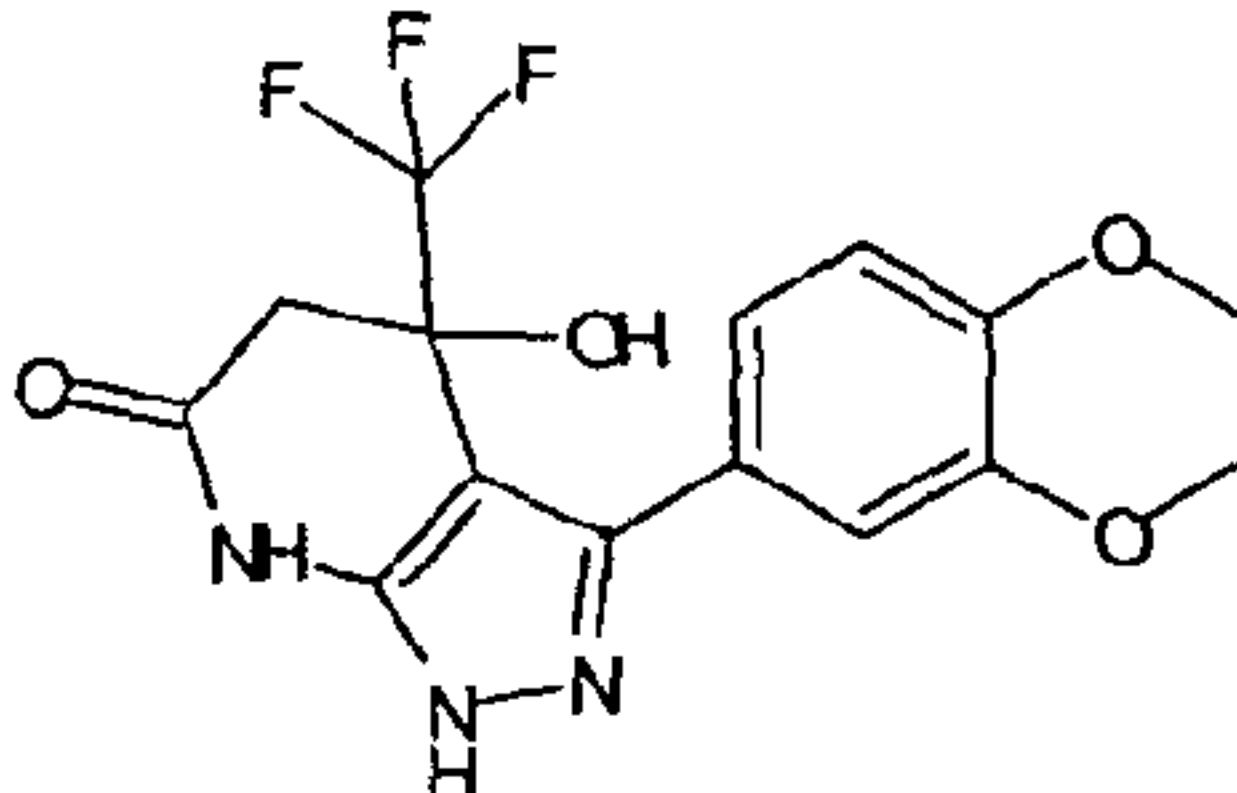
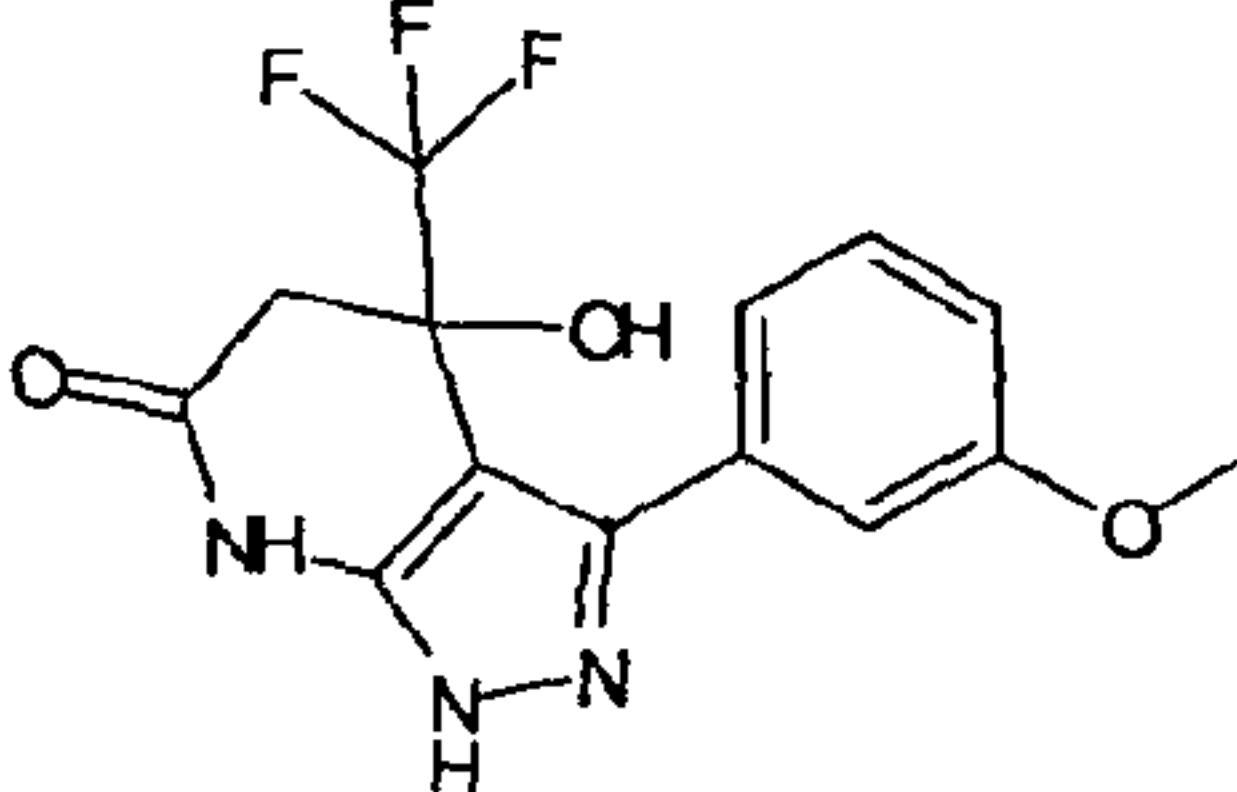
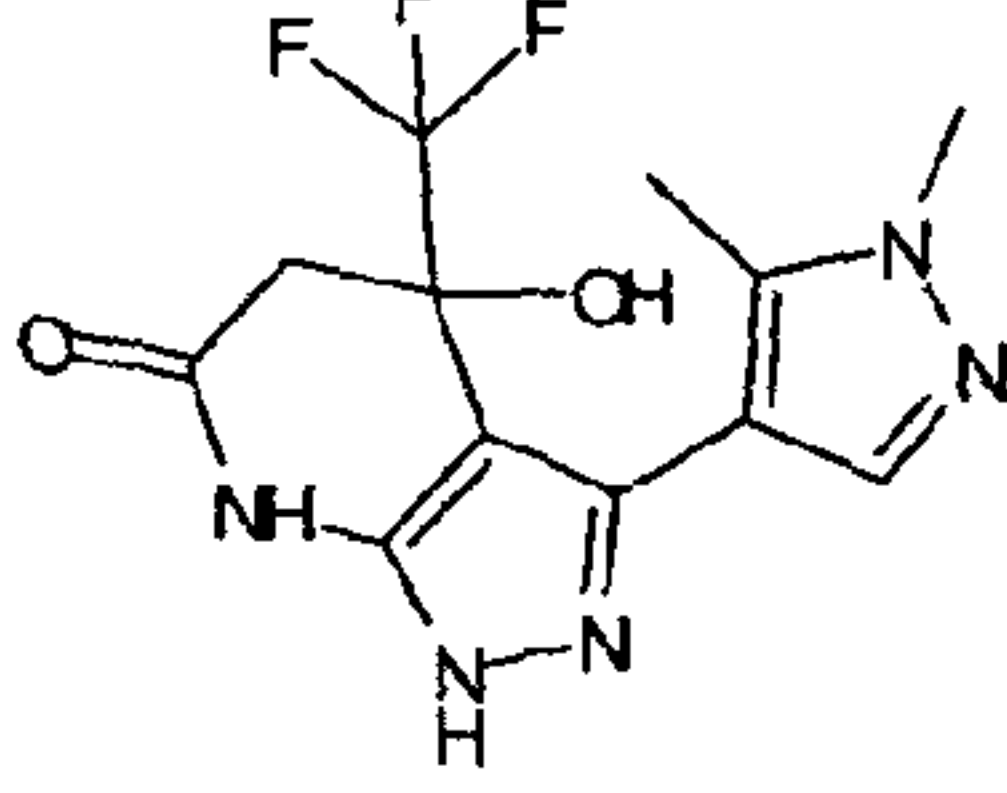
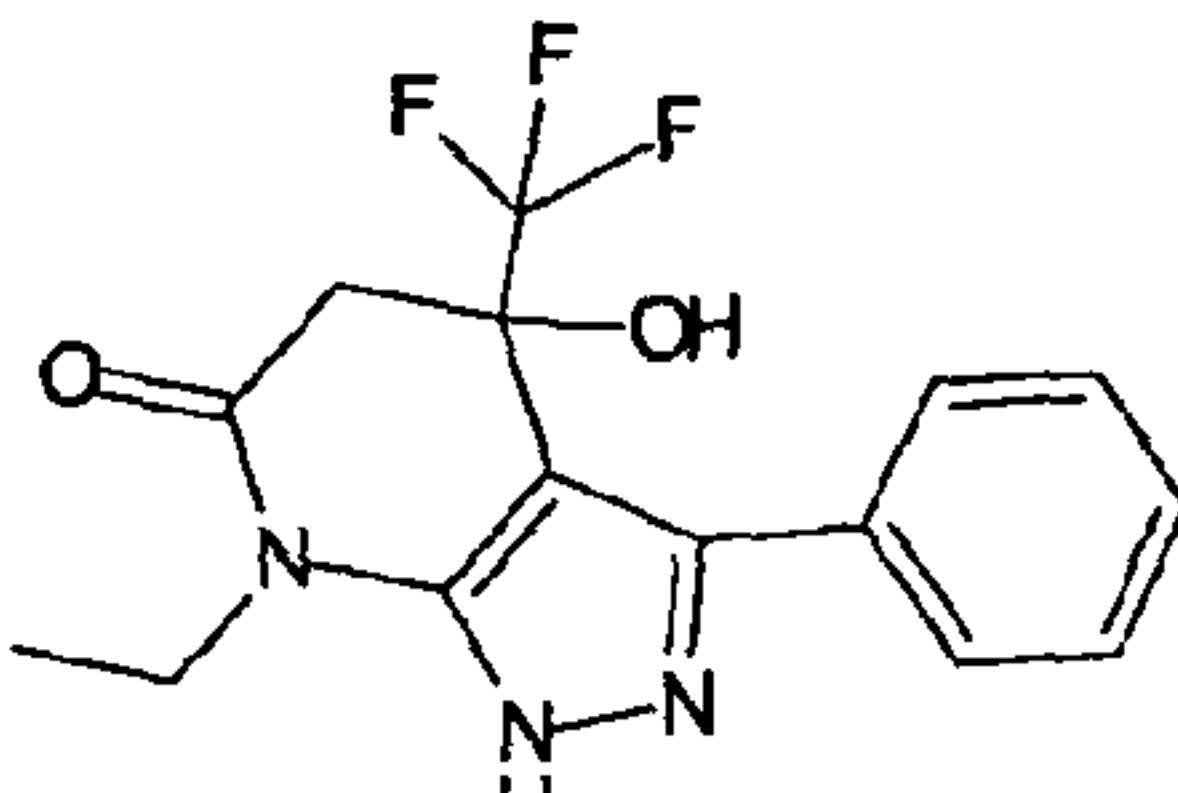
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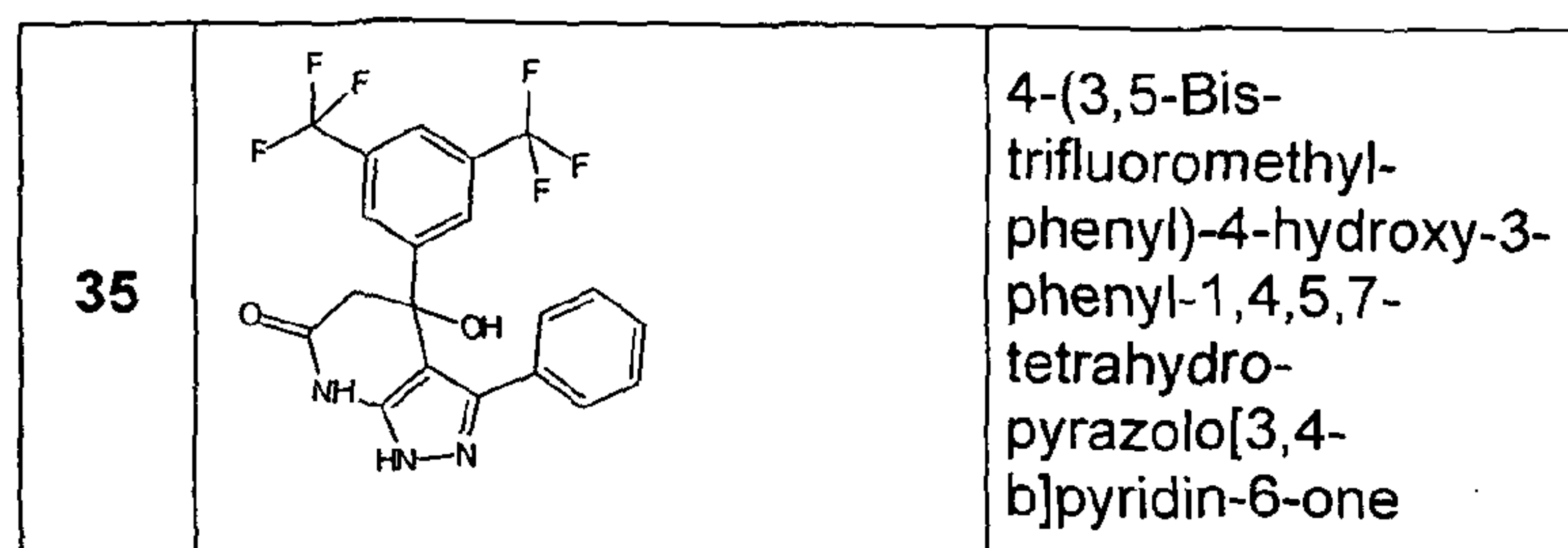
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|    |                                                                                      |                                                                                                             |
|----|--------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|
| 29 |    | 4-Hydroxy-3-(1H-indol-3-yl)-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one                |
| 30 |   | 3-Furan-2-yl-4-hydroxy-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one                     |
| 31 |  | 3-(3,4-Dimethoxyphenyl)-4-hydroxy-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one          |
| 32 |  | 4-Hydroxy-3-(3-methoxyphenyl)-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one              |
| 33 |  | 3-(1,5-Dimethyl-1H-pyrazol-4-yl)-4-hydroxy-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one |
| 34 |  | 7-Ethyl-4-hydroxy-3-phenyl-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one                 |

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5



and the physiologically acceptable salts, solvates, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

10

For the avoidance of doubt, if chemical name and chemical structure of the above illustrated compounds do not correspond by mistake, the chemical structure is regarded to unambiguously define the compound.

15

All the above generically or explicitly disclosed compounds, including preferred subsets/embodiments of the herein disclosed formula (I) and Compounds 1 to 35, are hereinafter referred to as compounds of the (present) invention.

20

The nomenclature as used herein for defining compounds, especially the compounds according to the invention, is in general based on the rules of the IUPAC organization for chemical compounds and especially organic compounds.

The terms indicated for explanation of the above compounds of the invention always, unless indicated otherwise in the description or in the claims, have the following meanings:

25

The term "unsubstituted" means that the corresponding radical, group or moiety has no substituents.

The term "substituted" means that the corresponding radical, group or moiety has one or more substituents. Where a radical has a plurality of substituents, and a selection of various substituents is specified, the substituents are selected independently of one another and do not need to be identical.

30

The terms "alkyl" or "A" as well as other groups having the prefix "alk" for the purposes of this invention refer to acyclic saturated or unsaturated hydrocarbon radicals which may be branched or straight-chain and preferably have 1 to 8 carbon atoms, i.e. C<sub>1</sub>-C<sub>8</sub>-alkanyls, C<sub>2</sub>-C<sub>8</sub>-alkenyls and C<sub>2</sub>-C<sub>8</sub>-alkynyls. Alkenyls have at least one C-C double bond and alkynyls at least one C-C triple bond. Alkynyls may additionally also have at least one C-C double bond. Examples of suitable alkyl radicals are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl,

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n-pentyl, iso-pentyl, neo-pentyl, tert-pentyl, 2- or 3-methyl-pentyl, n-hexyl, 2-hexyl, isohexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, n-undecyl, n-dodecyl, n-tetradecyl, n-hexadecyl, n-octadecyl, n-icosanyl, n-docosanyl, ethylenyl (vinyl), propenyl ( $-\text{CH}_2\text{CH}=\text{CH}_2$ ;  $-\text{CH}=\text{CH}-\text{CH}_3$ ,  $-\text{C}(\text{=CH}_2)-\text{CH}_3$ ), butenyl, pentenyl, hexenyl, heptenyl, octenyl, octadienyl, octadecenyl, octadec-9-enyl, icosenyl, icos-11-enyl, (Z)-icos-11-enyl, docosyl, docos-13-enyl, (Z)-docos-13-enyl, ethynyl, propynyl ( $-\text{CH}_2-\text{C}\equiv\text{CH}$ ,  $-\text{C}\equiv\text{C}-\text{CH}_3$ ), butynyl, pentynyl, hexynyl, heptynyl, octynyl. Especially preferred is  $\text{C}_{1-4}$ -alkyl. A  $\text{C}_{1-4}$ -alkyl radical is for example a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl.

The term "cycloalkyl" for the purposes of this invention refers to saturated and partially unsaturated non-aromatic cyclic hydrocarbon groups/radicals, having 1 to 3 rings, that contain 3 to 20, preferably 3 to 12, most preferably 3 to 8 carbon atoms. The cycloalkyl radical may also be part of a bi- or polycyclic system, where, for example, the cycloalkyl radical is fused to an aryl, heteroaryl or heterocyclyl radical as defined herein by any possible and desired ring member(s). The bonding to the compounds of the general formula can be effected via any possible ring member of the cycloalkyl radical. Examples of suitable cycloalkyl radicals are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl, cyclohexenyl, cyclopentenyl and cyclooctadienyl. Especially preferred are  $\text{C}_3$ - $\text{C}_9$ -cycloalkyl and  $\text{C}_4$ - $\text{C}_8$ -cycloalkyl. A  $\text{C}_4$ - $\text{C}_8$ -cycloalkyl radical is for example a cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl.

The term "heterocyclyl" or "heterocycle" for the purposes of this invention refers to a mono- or polycyclic system of 3 to 20, preferably 5 or 6 to 14 ring atoms comprising carbon atoms and 1, 2, 3, 4, or 5 heteroatoms, in particular nitrogen, oxygen and/or sulfur which are identical or different. The cyclic system may be saturated, mono- or polyunsaturated but may not be aromatic. In the case of a cyclic system consisting of at least two rings the rings may be fused or spiro- or otherwise connected. Such "heterocyclyl" radicals can be linked via any ring member. The term "heterocyclyl" also includes systems in which the heterocycle is part of a bi- or polycyclic saturated, partially unsaturated and/or aromatic system, such as where the heterocycle is fused to an "aryl", "cycloalkyl", "heteroaryl" or "heterocyclyl" group as defined herein via any desired and possible ring member of the heterocyclyl radical. The bonding to the compounds of the general formula can be effected via any possible ring member of the heterocyclyl radical. Examples of suitable "heterocyclyl" radicals are pyrrolidinyl, thiapyrrolidinyl, piperidinyl, piperazinyl,

oxapiperaziny, oxapiperidiny, oxadiazoly, tetrahydrofury, imidazolidiny, thiazolidiny, tetrahydropyrany, morpholiny, tetrahydrothiopheny, dihydropyrany, indoliny, indolinylmethyl, imidazolidiny, 2-aza-bicyclo[2.2.2]octany.

5 The term "aryl" for the purposes of this invention refers to a mono- or polycyclic aromatic hydrocarbon systems having 3 to 14, preferably 5 to 14, more preferably 5 to 10 carbon atoms. The term "aryl" also includes systems in which the aromatic cycle is part of a bi- or polycyclic saturated, partially unsaturated and/or aromatic system, such as where the aromatic cycle is fused to an "aryl", "cycloalkyl", "heteroaryl" or "heterocyclyl" group as defined herein via any desired and possible  
10 ring member of the aryl radical. The bonding to the compounds of the general formula can be effected via any possible ring member of the aryl radical. Examples of suitable "aryl" radicals are phenyl, biphenyl, naphthyl, 1-naphthyl, 2-naphthyl and anthracenyl, but likewise indanyl, indenyl, or 1,2,3,4-tetrahydronaphthyl. The most preferred aryl is phenyl.

15 The term "heteroaryl" for the purposes of this invention refers to a 3 to 15, preferably 5 to 14, more preferably 5-, 6- or 7-membered mono- or polycyclic aromatic hydrocarbon radical which comprises at least 1, where appropriate also 2, 3, 4 or 5 heteroatoms, preferably nitrogen, oxygen and/or sulfur, where the heteroatoms are identical or different. The number of nitrogen atoms is preferably 0,  
20 1, 2, or 3, and that of the oxygen and sulfur atoms is independently 0 or 1. The term "heteroaryl" also includes systems in which the aromatic cycle is part of a bi- or polycyclic saturated, partially unsaturated and/or aromatic system, such as where the aromatic cycle is fused to an "aryl", "cycloalkyl", "heteroaryl" or "heterocyclyl" group as defined herein via any desired and possible ring member of the heteroaryl  
25 radical. The bonding to the compounds of the general formula can be effected via any possible ring member of the heteroaryl radical. Examples of suitable "heteroaryl" are acridiny, benzdioxiny, benzimidazoly, benzisoxazoly, benzodioxoly, benzofurany, benzothiadiazoly, benzothiazoly, benzothiény, benzoxazoly, carbazoly, cinnoliny, dibenzofurany, dihydrobenzothiény, furany, furazany, furyl, imidazoly, indazoly, indoliny, indoliziny, indoly, isobenzylfurany, isoindoly,  
30 isoquinoliny, isoquinoly, isothiazoly, isoxazoly, naphthyridiny, oxadiazoly, oxazoly, phenaziny, phenothiaziny, phenoxaziny, phthalaziny, pteridiny, puriny, pyraziny, pyrazoly, pyridaziny, pyridiny, pyridyl, pyrimidiny, pyrimidyl, pyrroly, quinazoliny, quinoliny, quinoly, quinoxaliny, tetrazoly, thiadiazoly, thiazoly, thienyl, thiopheny, triaziny, triazoly.  
35

For the purposes of the present invention, the terms "alkyl-cycloalkyl", "cycloalkylalkyl", "alkyl-heterocyclyl", "heterocyclylalkyl", "alkyl-aryl", "arylalkyl", "alkyl-heteroaryl" and "heteroarylalkyl" mean that alkyl, cycloalkyl, heterocycl, aryl and heteroaryl are each as defined above, and the cycloalkyl, heterocyclyl, aryl and heteroaryl radical is bonded to the compounds of the general formula via an alkyl radical, preferably C<sub>1</sub>-C<sub>8</sub>-alkyl radical, more preferably C<sub>1</sub>-C<sub>4</sub>-alkyl radical.

The term "alkyloxy" or "alkoxy" for the purposes of this invention refers to an alkyl radical according to above definition that is attached to an oxygen atom. The attachment to the compounds of the general formula is via the oxygen atom. Examples are methoxy, ethoxy and n-propyloxy, propoxy, isopropoxy. Preferred is "C<sub>1</sub>-C<sub>4</sub>-alkyloxy" having the indicated number of carbon atoms.

The term "cycloalkyloxy" or "cycloalkoxy" for the purposes of this invention refers to a cycloalkyl radical according to above definition that is attached to an oxygen atom. The attachment to the compounds of the general formula is via the oxygen atom. Examples are cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy, cyclooctyloxy. Preferred is "C<sub>3</sub>-C<sub>8</sub>cycloalkyloxy" having the indicated number of carbon atoms.

The term "heterocycliloxy" for the purposes of this invention refers to a heterocyclyl radical according to above definition that is attached to an oxygen atom. The attachment to the compounds of the general formulae is via the oxygen atom. Examples are pyrrolidinyloxy, thiapyrrolidinyloxy, piperidinyloxy, piperazinyloxy.

The term "aryloxy" for the purposes of this invention refers to an aryl radical according to above definition that is attached to an oxygen atom. The attachment to the compounds of the general formula is via the oxygen atom. Examples are phenyloxy, 2-naphthyloxy, 1-naphthyloxy, biphenyloxy, indanyloxy. Preferred is phenyloxy.

The term "heteroaryloxy" for the purposes of this invention refers to a heteroaryl radical according to above definition that is attached to an oxygen atom. The attachment to the compounds of the general formula is via the oxygen atom. Examples are pyrrolyloxy, thienyloxy, furyloxy, imidazolyloxy, thiazolyloxy.

The term "carbonyl" or "carbonyl moiety" for the purposes of this invention refers to a -C(O)- group.

The term "alkylcarbonyl" for the purposes of this invention refers to a "alkyl-C(O)-" group, wherein alkyl is as defined herein.

The term "alkoxycarbonyl" or "alkyloxycarbonyl" for the purposes of this

invention refers to a "alkyl-O-C(O)-" group, wherein alkyl is as defined herein.

The term "alkoxyalkyl" for the purposes of this invention refers to a "alkyl-O-alkyl-" group, wherein alkyl is as defined herein.

5 The term "haloalkyl" for the purposes of this invention refers to an alkyl group as defined herein comprising at least one carbon atom substituent with at least one halogen as defined herein.

10 The term "halogen", "halogen atom", "halogen substituent" or "Hal" for the purposes of this invention refers to one or, where appropriate, a plurality of fluorine (F, fluoro), bromine (Br, bromo), chlorine (Cl, chloro), or iodine (I, iodo) atoms. The designations "dihalogen", "trihalogen" and "perhalogen" refer respectively to two, three and four substituents, where each substituent can be selected independently from the group consisting of fluorine, chlorine, bromine and iodine. "Halogen" preferably means a fluorine, chlorine or bromine atom. Fluorine is most preferred, when the halogens are substituted on an alkyl (haloalkyl) or alkoxy group (e.g. CF<sub>3</sub> and CF<sub>3</sub>O).

15 The term "hydroxyl" or "hydroxy" means an OH group.

20 The term "composition", as in pharmaceutical composition, for the purposes of this invention is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier.

25 The terms "administration of" and "administering a" compound should be understood to mean providing a compound of the invention or a prodrug of a compound of the invention to the individualist need.

30 As used herein, the term "effective amount" refers to any amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician. Furthermore, the term "therapeutically effective amount" means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a

35

disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function.

5 All stereoisomers of the compounds of the invention are contemplated, either in a mixture or in pure or substantially pure form. The compounds of the invention can have asymmetric centers at any of the carbon atoms. Consequently, they can exist in the form of their racemates, in the form of the pure enantiomers and/or diastereomers or in the form of mixtures of these enantiomers and/or diastereomers. The mixtures may have any desired mixing ratio of the stereoisomers.

10 Thus, for example, the compounds of the invention which have one or more centers of chirality and which occur as racemates or as diastereomer mixtures can be fractionated by methods known per se into their optical pure isomers, i.e. enantiomers or diastereomers. The separation of the compounds of the invention can take place by column separation on chiral or nonchiral phases or by  
15 recrystallization from an optionally optically active solvent or with use of an optically active acid or base or by derivatization with an optically active reagent such as, for example, an optically active alcohol, and subsequent elimination of the radical.

The compounds of the invention may be present in the form of their double bond isomers as "pure" E or Z isomers, or in the form of mixtures of these double bond  
20 isomers.

Where possible, the compounds of the invention may be in the form of the tautomers, such as keto-enol tautomers.

It is likewise possible for the compounds of the invention to be in the form of any desired prodrugs such as, for example, esters, carbonates, carbamates, ureas,  
25 amides or phosphates, in which cases the actually biologically active form is released only through metabolism. Any compound that can be converted in vivo to provide the bioactive agent (i.e. compounds of the invention) is a prodrug within the scope and spirit of the invention.

Various forms of prodrugs are well known in the art and are described for  
30 instance in:

- (i) Wermuth CG et al., Chapter 31: 671-696, The Practice of Medicinal Chemistry, Academic Press 1996;
- (ii) Bundgaard H, Design of Prodrugs, Elsevier 1985; and
- (iii) Bundgaard H, Chapter 5: 131-191, A Textbook of Drug Design and  
35 Development, Harwood Academic Publishers 1991.

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It is further known that chemical substances are converted in the body into metabolites which may where appropriate likewise elicit the desired biological effect - in some circumstances even in more pronounced form.

5 Any biologically active compound that was converted in vivo by metabolism from any of the compounds of the invention is a metabolite within the scope and spirit of the invention.

10 The compounds of the invention can, if they have a sufficiently basic group such as, for example, a secondary or tertiary amine, be converted with inorganic and organic acids into salts. The pharmaceutically acceptable salts of the compounds of the invention are preferably formed with hydrochloric acid, hydrobromic acid, iodic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, p-toluenesulfonic acid, carbonic acid, formic acid, acetic acid, sulfoacetic acid, trifluoroacetic acid, oxalic acid, malonic acid, maleic acid, succinic acid, tartaric acid, racemic acid, malic acid, 15 embonic acid, mandelic acid, fumaric acid, lactic acid, citric acid, taurocholic acid, glutaric acid, stearic acid, glutamic acid or aspartic acid. The salts which are formed are, inter alia, hydrochlorides, chlorides, hydrobromides, bromides, iodides, sulfates, phosphates, methanesulfonates, tosylates, carbonates, bicarbonates, formates, acetates, sulfoacetates, triflates, oxalates, malonates, maleates, succinates, tartrates, malates, embonates, mandelates, fumarates, lactates, citrates, glutarates, stearates, aspartates and glutamates. The stoichiometry of the salts formed from the compounds of the invention may moreover be an integral or non-integral multiple of one.

25 The compounds of the invention can, if they contain a sufficiently acidic group such as, for example, the carboxy, sulfonic acid, phosphoric acid or a phenolic group, be converted with inorganic and organic bases into their physiologically tolerated salts. Examples of suitable inorganic bases are ammonium, sodium hydroxide, potassium hydroxide, calcium hydroxide, and of organic bases are 30 ethanolamine, diethanolamine, triethanolamine, ethylenediamine, t-butylamine, t-octylamine, dehydroabietylamine, cyclohexylamine, dibenzylethylene-diamine and lysine. The stoichiometry of the salts formed from the compounds of the invention can moreover be an integral or non-integral multiple of one.

35 It is likewise possible for the compounds of the invention to be in the form of their solvates and, in particular, hydrates which can be obtained for example by

crystallization from a solvent or from aqueous solution. It is moreover possible for one, two, three or any number of solvate or water molecules to combine with the compounds of the invention to give solvates and hydrates.

5 By the term "solvate" is meant a hydrate, an alcoholate, or other solvate of crystallization.

It is known that chemical substances form solids which exist in different order states which are referred to as polymorphic forms or modifications. The various modifications of a polymorphic substance may differ greatly in their physical properties. The compounds of the invention can exist in various polymorphic forms and certain modifications may moreover be metastable. All these polymorphic forms  
10 of the compounds are to be regarded as belonging to the invention.

The compounds of the invention are surprisingly characterized by a strong and/or selective inhibition of LPA receptors, preferably LPA receptor 1, LPA receptor  
15 2, LPA receptor 3, LPA receptor 4, LPA receptor 5 or LPA receptor 6, most preferably LPA receptor 2.

Due to their surprisingly strong and/or selective receptor inhibition, the compounds of the invention can be advantageously administered at lower doses compared to other less potent or selective inhibitors of the prior art while still  
20 achieving equivalent or even superior desired biological effects. In addition, such a dose reduction may advantageously lead to less or even no medicinal adverse effects. Further, the high inhibition selectivity of the compounds of the invention may translate into a decrease of undesired side effects on its own regardless of the dose applied.

25 The compounds of the invention being LPA receptor inhibitors generally have an inhibition constant  $IC_{50}$  of less than about 10  $\mu M$ , and preferably less than about 1  $\mu M$ .

The compounds according to the invention preferably exhibit an advantageous biological activity, which is easily demonstrated in enzyme-based assays, for  
30 example assays as described herein. In such enzyme-based assays, the compounds according to the invention preferably exhibit and cause an inhibiting effect, which is usually documented by  $IC_{50}$  values in a suitable range, preferably in the micromolar range and more preferably in the nanomolar range.

As discussed herein, the LPA receptor signaling pathways are relevant for  
35 various diseases. Accordingly, the compounds according to the invention are useful

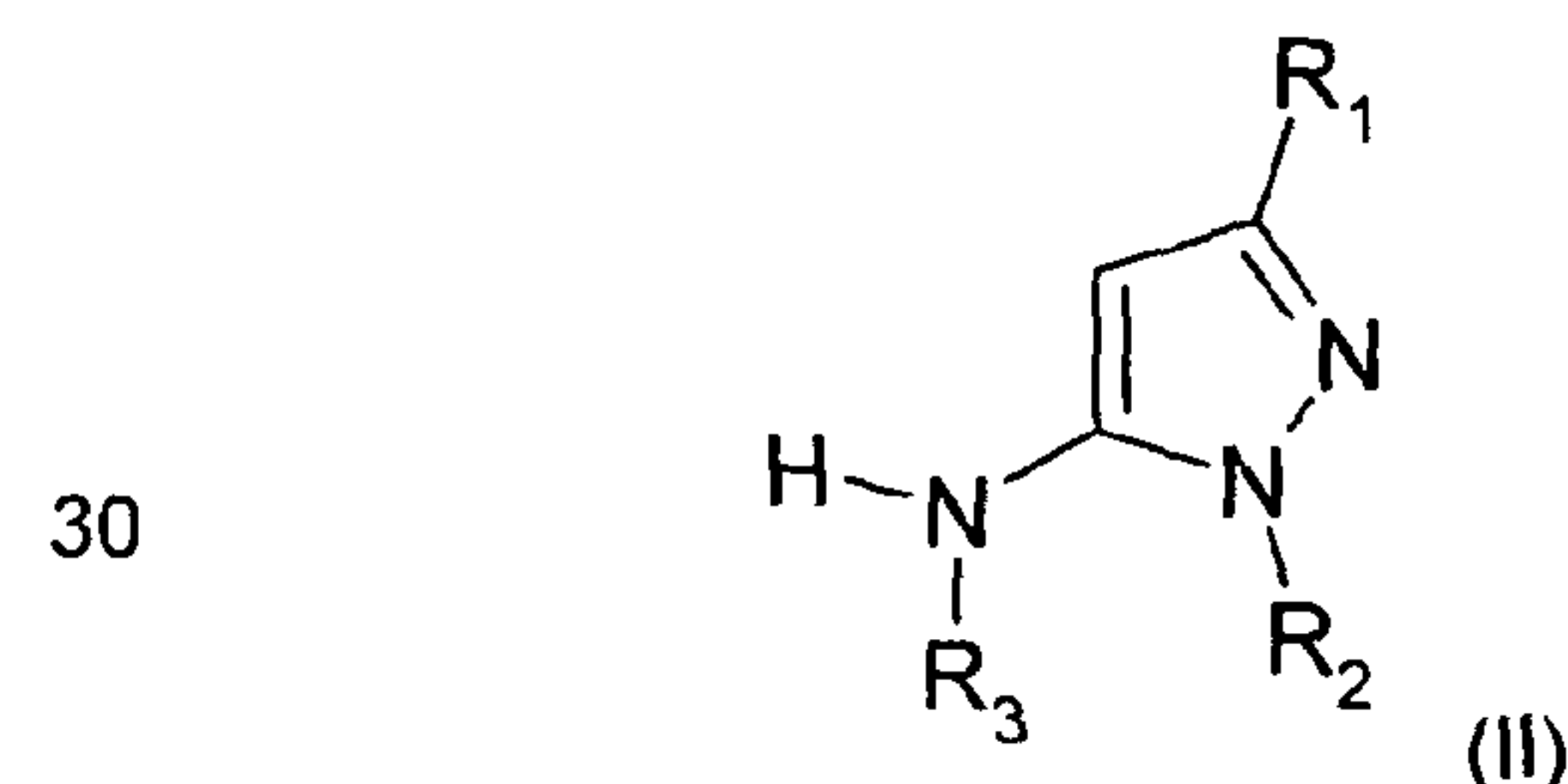
in the prophylaxis and/or treatment of diseases that are dependent on the said signaling pathways by interaction with one or more of the said signaling pathways. The present invention therefore relates to compounds according to the invention as promoters or inhibitors, preferably as inhibitors, of the signaling pathways described  
5 herein, particularly the LPA receptor signaling pathways.

The object of the present invention has surprisingly been solved in another aspect by providing the use of a compound of the invention for modulating, preferably inhibiting, LPA receptor mediated biological activity, preferably LPA  
10 receptor 1, LPA receptor 2, LPA receptor 3, LPA receptor 4, LPA receptor 5 or LPA receptor 6 mediated biological activity, most preferably LPA receptor 2 mediated biological activity.

The terms "inhibiting, inhibition and/or retardation" are intended to refer for the  
15 purposes of the present invention to as follows: "partial or complete inhibiting, inhibition and/or retardation". In this case, it is within the specialist knowledge of the average person skilled in the art to measure and determine such inhibiting, inhibition, and/or retardation by means of the usual methods of measurement and determination. Thus, a partial inhibiting, inhibition and/or retardation, for example,  
20 can be measured and determined in relation to a complete inhibiting, inhibition and/or retardation.

The object of the present invention has surprisingly been solved in another aspect by providing a process for manufacturing a compound of the invention,  
25 comprising the steps of:

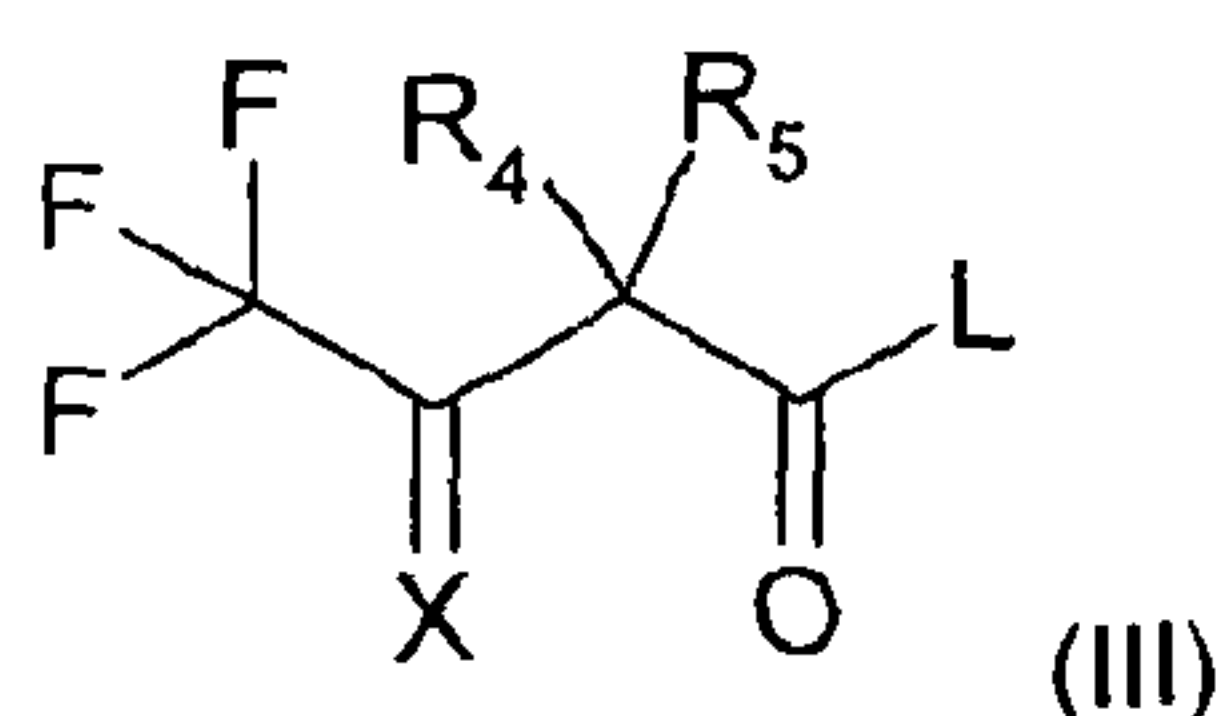
(a) reacting a compound of formula (II)



wherein R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> have the meaning as defined above,

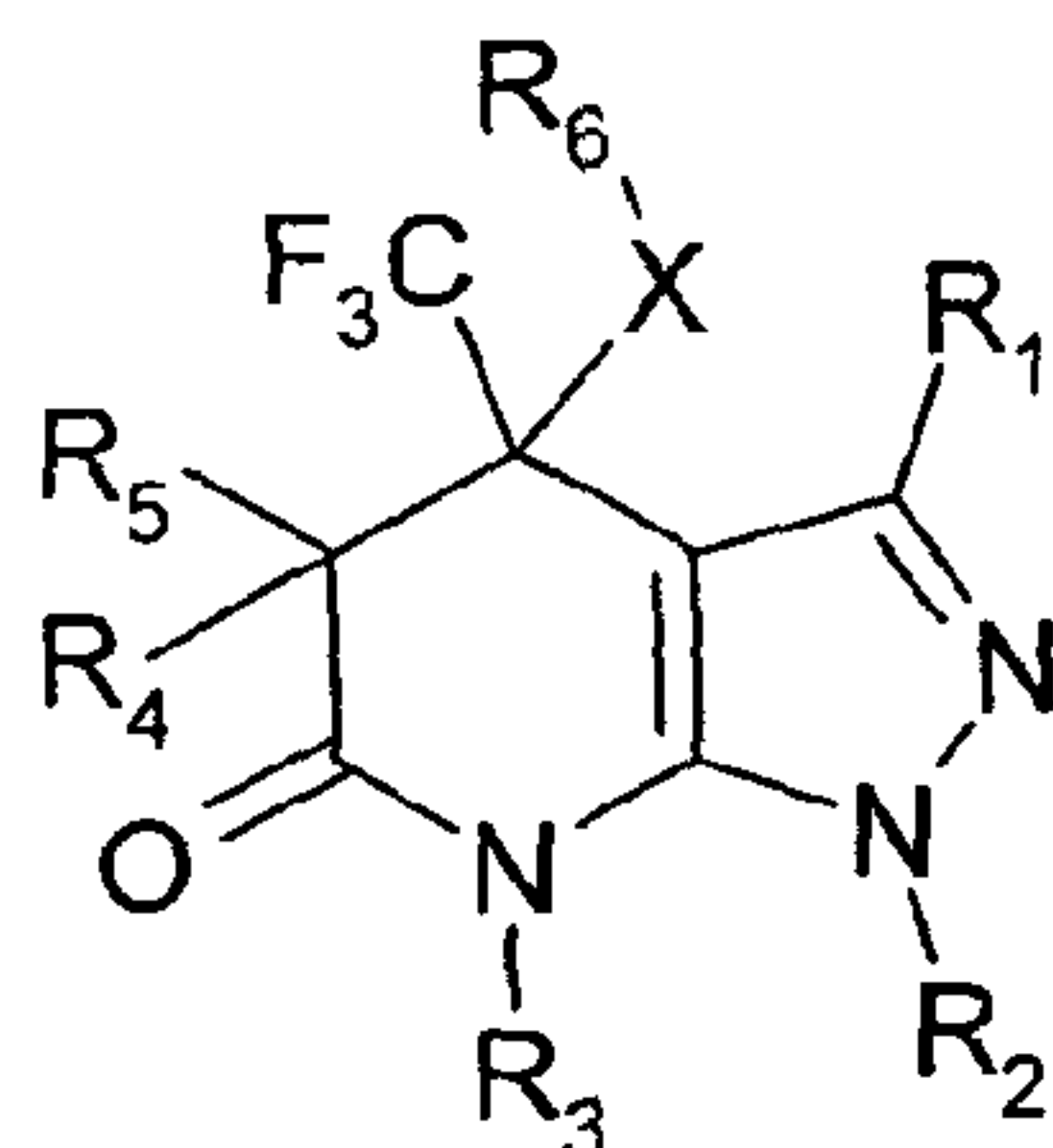
35 with a compound of formula (III)

34



5 wherein  $R_4$ ,  $R_5$  and  $X$  have the meaning as defined above and  $L$  denotes a leaving group,

to yield a compound of formula (I)



10 15 wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_6$  and  $X$  have the meaning as defined above,

and, optionally,

20 b) converting residue  $R_6$  as defined above into another residue  $R_6$  as defined above, e.g. by introducing an alkyl group,

and optionally

25 c) converting a base or an acid of the compound of formula (I) into a salt thereof.

30 In the course of this invention, a "leaving group" is a molecular fragment that departs with a pair of electrons in heterolytic bond cleavage. Leaving groups can be anions or neutral molecules. Common anionic leaving groups are halides such as  $\text{Cl}^-$ ,  $\text{Br}^-$ , and  $\text{I}^-$ , and sulfonate esters, such as *para*-toluenesulfonate or "tosylate" ( $\text{TsO}^-$ ). Common neutral molecule leaving groups are water ( $\text{H}_2\text{O}$ ), ammonia ( $\text{NH}_3$ ), and alcohols ( $\text{ROH}$ ).

35 The ability of a leaving group to depart is correlated with the  $\text{p}K_a$  of the conjugate acid, with lower  $\text{p}K_a$  being associated with better leaving group ability.

The correlation is not perfect because leaving group ability is a kinetic phenomenon, relating to a reaction's rate, whereas  $pK_a$  is a thermodynamic phenomenon, describing the position of an equilibrium. Nevertheless, it is a general rule that more highly stabilized anions act as better leaving groups.

Consistent with this rule, strong bases such as alkoxide ( $RO^-$ ), hydroxide ( $HO^-$ ), and amide ( $R_2N^-$ ) are poor leaving groups.

Preferred leaving groups in the course of the present invention are the following:

| Leaving groups ordered approximately in decreasing ability to leave |                                                               |
|---------------------------------------------------------------------|---------------------------------------------------------------|
| *R-N <sub>2</sub> <sup>+</sup>                                      | diazonium salts                                               |
| R-OR' <sub>2</sub> <sup>+</sup>                                     |                                                               |
| R-OSO <sub>2</sub> C <sub>4</sub> F <sub>9</sub>                    | nonaflates                                                    |
| R-OSO <sub>2</sub> CF <sub>3</sub>                                  | triflates                                                     |
| R-OSO <sub>2</sub> F                                                | fluorosulfonates                                              |
| R-OTs, R-OMs, etc.                                                  | tosylates, mesylates, and similar                             |
| R-I                                                                 | iodides                                                       |
| R-Br                                                                | bromides                                                      |
| R-OH <sub>2</sub> <sup>+</sup>                                      | (Conjugate acid of an alcohol)                                |
| R-Cl                                                                | chlorides, and acyl chloride when attached to carbonyl carbon |
| R-OHR' <sup>+</sup>                                                 | Conjugate acid of an ether                                    |
| R-ONO <sub>2</sub> , R-OPO(OH) <sub>2</sub>                         | nitrates, phosphates, and other inorganic esters              |
| R-SR' <sub>2</sub> <sup>+</sup>                                     |                                                               |
| R-NR' <sub>3</sub> <sup>+</sup>                                     | tetraalkylammonium Salts                                      |
| R-F                                                                 | fluorides                                                     |
| R-OCOR                                                              | esters, and acid anhydrides when attached to carbonyl carbon  |
| R-NH <sub>3</sub> <sup>+</sup>                                      | ammonium salts                                                |

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|       |                                                                    |
|-------|--------------------------------------------------------------------|
| R-OAr | phenoxides                                                         |
| R-OH  | alcohols, and carboxylic acids<br>when attached to carbonyl carbon |
| R-OR  | ethers, and esters when attached<br>to carbonyl carbon             |

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It is uncommon for groups such as  $H^-$  (hydrides),  $R_3C^-$  (alkyl anions, R=alkyl or H), or  $R_2N^-$  (amides, R=alkyl or H) to depart with a pair of electrons because of the instability of these bases.

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Some crude products were subjected to standard chromatography using solvent mixtures containing methanol, ethanol, isopropanol, n-hexane, cyclohexane, dichloromethane, n-heptane or petrol ether, respectively.

20

For a further detailed description of the manufacturing processes, please refer also to the examples and the following general description of the preferred conditions.

25

A physiologically acceptable salt of a compound of the invention can also be obtained by isolating and/or treating the compound of the invention obtained by the described reaction with an acid or a base.

30

The compounds of the invention and also the starting materials for their preparation are, are prepared by methods as described in the examples or by methods known per se, as described in the literature (for example in standard works, such as Houben-Weyl, Methoden der Organischen Chemie [Methods of Organic Chemistry], Georg Thieme Verlag, Stuttgart; Organic Reactions, John Wiley & Sons, Inc., New York), to be precise under reaction conditions which are known and suitable for the said reactions. Use can also be made here of variants which are known per se, but are not mentioned here in greater detail.

35

The starting materials for the claimed process may, if desired, also be formed in situ by not isolating them from the reaction mixture, but instead immediately converting them further into the compounds of the invention. On the other hand, it is possible to carry out the reaction stepwise.

Preferably, the reaction of the compounds is carried out in the presence of a suitable solvent, which is preferably inert under the respective reaction conditions. Examples of suitable solvents are hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as trichlorethylene, 1,2-dichloroethane, tetrachloromethane, chloroform or dichloromethane; alcohols, such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF) or dioxane; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether or ethylene glycol dimethyl ether (diglyme); ketones, such as acetone or butanone; amides, such as acetamide, dimethylacetamide, dimethylformamide (DMF) or N-methyl pyrrolidinone (NMP); nitriles, such as acetonitrile; sulfoxides, such as dimethyl sulfoxide (DMSO); nitro compounds, such as nitromethane or nitrobenzene; esters, such as ethyl acetate, or mixtures of the said solvents or mixtures with water. Polar solvents are in general preferred. Examples for suitable polar solvents are chlorinated hydrocarbons, alcohols, glycol ethers, nitriles, amides and sulfoxides or mixtures thereof. More preferred are amides, especially dimethylformamide (DMF).

As stated above, the reaction temperature is between about -100° C and 300° C, depending on the reaction step and the conditions used.

Reaction times are generally in the range between some minutes and several days, depending on the reactivity of the respective compounds and the respective reaction conditions. Suitable reaction times are readily determinable by methods known in the art, for example reaction monitoring. Based on the reaction temperatures given above, suitable reaction times generally lie in the range between 10 min and 48 hrs.

A base of a compound of the invention can be converted into the associated acid-addition salt using an acid, for example by reaction of equivalent amounts of the base and the acid in a preferably inert solvent, such as ethanol, followed by evaporation. Suitable acids for this reaction are, in particular, those which give physiologically acceptable salts. Thus, it is possible to use inorganic acids, for example sulfuric acid, sulfurous acid, dithionic acid, nitric acid, hydrohalic acids, such as hydrochloric acid or hydrobromic acid, phosphoric acids, such as, for example, orthophosphoric acid, sulfamic acid, furthermore organic acids, in particular aliphatic, alicyclic, araliphatic, aromatic or heterocyclic monobasic or polybasic carboxylic, sulfonic or sulfuric acids, for example formic acid, acetic acid,

propionic acid, hexanoic acid, octanoic acid, decanoic acid, hexadecanoic acid, octadecanoic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane- or ethanesulfonic acid, ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, trimethoxybenzoic acid, adamantanecarboxylic acid, p-toluenesulfonic acid, glycolic acid, embonic acid, chlorophenoxyacetic acid, aspartic acid, glutamic acid, proline, glyoxylic acid, palmitic acid, parachlorophenoxyisobutyric acid, cyclohexanecarboxylic acid, glucose 1-phosphate, naphthalenemono- and -disulfonic acids or laurylsulfuric acid.

Salts with physiologically unacceptable acids, for example picrates, can be used to isolate and/or purify the compounds of the invention.

On the other hand, compounds of the invention can be converted into the corresponding metal salts, in particular alkali metal salts or alkaline earth metal salts, or into the corresponding ammonium salts, using bases (for example sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate). Suitable salts are furthermore substituted ammonium salts, for example the dimethyl-, diethyl- and diisopropylammonium salts, monoethanol-, diethanol- and diisopropanolammonium salts, cyclohexyl- and dicyclohexylammonium salts, dibenzylethylenediammonium salts, furthermore, for example, salts with arginine or lysine.

If desired, the free bases of the compounds of the invention can be liberated from their salts by treatment with strong bases, such as sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate, so long as no further acidic groups are present in the molecule. In the cases where the compounds of the invention have free acid groups, salt formation can likewise be achieved by treatment with bases. Suitable bases are alkali metal hydroxides, alkaline earth metal hydroxides or organic bases in the form of primary, secondary or tertiary amines.

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Every reaction step described herein can optionally be followed by one or more working up procedures and/or isolating procedures. Suitable such procedures are known in the art, for example from standard works, such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart). Examples for such procedures include, but are not limited to

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evaporating a solvent, distilling, crystallization, fractionised crystallization, extraction procedures, washing procedures, digesting procedures, filtration procedures, chromatography, chromatography by HPLC and drying procedures, especially drying procedures in vacuo and/or elevated temperature.

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The object of the present invention has surprisingly been solved in another aspect by providing a medicament comprising at least one compound of the invention. In a preferred embodiment, such medicament in addition explicitly comprises compound 2 (4-Hydroxy-3-phenyl-4-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-b]pyridin-6-one) of the present invention.

10

The object of the present invention has surprisingly been solved in another aspect by providing a medicament comprising at least one compound of the invention for use in the treatment and/or prophylaxis of physiological and/or pathophysiological conditions selected from the group consisting of: "cancer, tumour, malignant tumours, benign tumours, solid tumours, sarcomas, carcinomas, hyperproliferative disorders, carcinoids, Ewing sarcomas, Kaposi sarcomas, brain tumours, tumours originating from the brain and/or the nervous system and/or the meninges, gliomas, glioblastomas, neuroblastomas, stomach cancer, kidney cancer, kidney cell carcinomas, prostate cancer, prostate carcinomas, connective tissue tumours, soft tissue sarcomas, pancreas tumours, liver tumours, head tumours, neck tumours, laryngeal cancer, oesophageal cancer, thyroid cancer, osteosarcomas, retinoblastomas, thymoma, testicular cancer, lung cancer, lung adenocarcinoma, small cell lung carcinoma, bronchial carcinomas, breast cancer, mamma carcinomas, intestinal cancer, colorectal tumours, colon carcinomas, rectum carcinomas, gynaecological tumours, ovary tumours/ovarian tumours, uterine cancer, cervical cancer, cervix carcinomas, cancer of body of uterus, corpus carcinomas, endometrial carcinomas, urinary bladder cancer, urogenital tract cancer, bladder cancer, skin cancer, epithelial tumours, squamous epithelial carcinoma, basaliomas, spinaliomas, melanomas, intraocular melanomas, leukaemias, monocyte leukaemia, chronic leukaemias, chronic myelotic leukaemia, chronic lymphatic leukemia, acute leukaemias, acute myelotic leukaemia, acute lymphatic leukemia, lymphomas, ophthalmic diseases, choroidal neovascularization, diabetic retinopathy, inflammatory diseases, arthritis, neurodegeneration, transplant rejection, metastatic growth, fibrosis, restenosis, HIV infection, atherosclerosis,

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inflammation, heart failure, cardiomyopathy, myocardial infarction, myocardial remodeling, vascular remodeling, hypertension, peripheral arterial occlusive disease, restenosis, thrombosis, vascular permeability disorders, inflammatory diseases, rheumatoid arthritis, osteoarthritis, renal diseases, renal papillary  
5 necrosis, renal failure, pulmonary diseases, chronic obstructive pulmonary disease, asthma, acute respiratory distress syndrome, immunological diseases, allergic diseases, tumor growth, metastasis, metabolic diseases, fibrotic diseases, pulmonary fibrosis, cardiac fibrosis, vascular fibrosis, perivascular fibrosis, renal fibrosis, liver fibrosis, fibrosing skin conditions, psoriasis, pain, pruritus, retinal  
10 ischemia/reperfusion damage, macular degeneration, psychiatric disorders, neurodegenerative diseases, cerebral nerve disorders, peripheral nerve disorders, endocrinic disorders, hyperthyroidism, scarring disorders or for cardioprotection or renoprotection and disorders of wound healing, angiogenesis, cardiovascular system, bone, CNS and/or PNS." In a preferred embodiment, such medicament in  
15 addition explicitly comprises compound 2 (4-Hydroxy-3-phenyl-4-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-b]pyridin-6-one) of the present invention. A corresponding use for the preparation of a medicament for the treatment and/or prophylaxis of the aforementioned conditions is intended to be comprised. A corresponding method of treatment administering at least one compound of the  
20 invention to a patient in need thereof is also intended to be comprised.

Compounds of the invention may be used in combination with one or more other active substances (ingredients, drugs) in the treatment, prevention, suppression or amelioration of diseases or conditions for which compounds of the invention or the  
25 other substances have utility. Typically the combination of the drugs is safer or more effective than either drug alone, or the combination is safer or more effective than would it be expected based on the additive properties of the individual drugs. Such other drug(s) may be administered, by a route and in an amount commonly used contemporaneously or sequentially with a compound of the invention. When a  
30 compound of the invention is used contemporaneously with one or more other drugs, a combination product containing such other drug(s) and the compound of the invention is preferred. However, combination therapy also includes therapies in which the compound of the invention and one or more other drugs are administered on different overlapping schedules. It is contemplated that when used in  
35 combination with other active ingredients, the compound of the present invention or

the other active ingredient or both may be used effectively in lower doses than when each is used alone. Accordingly, the pharmaceutical compositions of the present invention include those that contain one or more other active ingredients, in addition to a compound of the invention.

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Examples of other active substances (ingredients, drugs) that may be administered in combination with a compound of the invention, and either administered separately or in the same pharmaceutical composition, include, but are not limited to the compounds classes and specific compounds listed in Table 1:

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| <b>Table 1</b> |                             |                                                                                                                                                                                                                                                   |
|----------------|-----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 15             | Alkylating agents           | Cyclophosphamide<br>Busulfane<br>Ifosfamide<br>Melphalane<br>Hexamethylmelamine<br>Thiotepa<br>Chlorambucil<br>Dacarbazine<br>Carmustine                                                                                                          |
|                |                             | Lomustine<br>Procarbazine<br>Altretamine<br>Estramustinphosphate<br>Mechlorethamine<br>Streptozocine<br>Temozolomide<br>Semustine                                                                                                                 |
| 20             | Platinum agents             | Cisplatin<br>Oxaliplatin<br>Spiroplatin<br>Carboxyphthalatoplatinum<br>Tetraplatin<br>Orniplatin<br>Iproplatin                                                                                                                                    |
|                |                             | Carboplatin<br>ZD-0473 (AnorMED)<br>Lobaplatin (AeternaZentaris)<br>Satraplatin (Johnson<br>Matthey)<br>BBR-3464 (Hoffmann-La<br>Roche)<br>SM-11355 (Sumitomo)<br>AP-5280 (Access)                                                                |
| 25             | Antimetabolites             | Azacytidine<br>Gemcitabine<br>Capecitabine<br>5-Fluoruracil<br>Floxuridine<br>2-Chlordesoxyadenosine<br>6-Mercaptopurine<br>6-Thioguanine<br>Cytarabine<br>2-Fluordesoxycytidine<br>Methotrexate<br>Idatrexate                                    |
|                |                             | Tomudex<br>Trimetrexate<br>Deoxycoformycine<br>Fludarabine<br>Pentostatine<br>Raltitrexede<br>Hydroxyurea<br>Decitabine (SuperGen)<br>Clofarabine (Bioenvision)<br>Irofulven (MGI Pharma)<br>DMDC (Hoffmann-La Roche)<br>Ethinylcytidine (Taiho ) |
| 30             | Topoisomerase<br>inhibitors | Amsacrine<br>Epirubicine<br>Etoposide<br>Teniposide or Mitoxantrone                                                                                                                                                                               |
|                |                             | Rubitecane (SuperGen)<br>Exatecanmesylate (Daiichi)<br>Quinamed (ChemGenex)<br>Gimatecane (Sigma- Tau)                                                                                                                                            |

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|    |                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|----|-----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 5  |                       | Irinotecane (CPT-11)<br>7-Ethyl-10-hydroxycamptothecine<br>Topotecane<br>Dexrazoxanet (TopoTarget)<br>Pixantrone (Novuspharma)<br>Rebeccamycin-Analogue (Exelixis)<br>BBR-3576 (Novuspharma)                                                                                                                                                                                                                                                                                                          | Diflomotecane (Beaufour-Ipsen)<br>TAS-103 (Taiho)<br>Elsamitrucine (Spectrum)<br>J-107088 (Merck & Co)<br>BNP-1350 (BioNumerik)<br>CKD-602 (Chong Kun Dang)<br>KW-2170 (Kyowa Hakko)                                                                                                                                                                                                                                                                                                                                           |
| 10 | Antitumor antibiotics | Dactinomycin (Actinomycin D)<br>Doxorubicin (Adriamycin)<br>Deoxyrubicin<br>Valrubicin<br>Daunorubicin (Daunomycin)<br>Epirubicin<br>Therarubicin<br>Idarubicin<br>Rubidazole<br>Plicamycin<br>Porfiriomycin<br>Cyanomorpholinodoxorubicin<br>Mitoxantron (Novantron)                                                                                                                                                                                                                                 | Amonafide<br>Azonafide<br>Anthrapyrazole<br>Oxantrazole<br>Losoxantrone<br>Bleomycinsulfate (Blenoxan)<br>Bleomycinacid<br>Bleomycin A<br>Bleomycin B<br>Mitomycin C<br>MEN-10755 (Menarini)<br>GPX-100 (Gem Pharmaceuticals)                                                                                                                                                                                                                                                                                                  |
| 15 |                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 20 | Antimitotic agents    | Paclitaxel<br>Docetaxel<br>Colchicin<br>Vinblastine<br>Vincristine<br>Vinorelbine<br>Vindesine<br>Dolastatine 10 (NCI)<br>Rhizoxine (Fujisawa)<br>Mivobuline (Warner-Lambert)<br>Cemadotone (BASF)<br>RPR 109881A (Aventis)<br>TXD 258 (Aventis)<br>Epothilon B (Novartis)<br>T 900607 (Tularik)<br>T 138067 (Tularik)<br>Cryptophycin 52 (Eli Lilly)<br>Vinflunine (Fabre)<br>Auristatine PE (Teikoku Hormone)<br>BMS 247550 (BMS)<br>BMS 184476 (BMS)<br>BMS 188797 (BMS)<br>Taxoprexine (Protarga) | SB 408075<br>(GlaxoSmithKline)<br>E7010 (Abbott)<br>PG-TXL (Cell Therapeutics)<br>IDN 5109 (Bayer)<br>A 105972 (Abbott)<br>A 204197 (Abbott)<br>LU 223651 (BASF)<br>D 24851 (ASTA Medica)<br>ER-86526 (Eisai)<br>Combretastatine A4 (BMS)<br>Isohomohalichondrin-B (PharmaMar)<br>ZD 6126 (AstraZeneca)<br>PEG-Paclitaxel (Enzon)<br>AZ10992 (Asahi)<br>IDN-5109 (Indena)<br>AVLB (Prescient NeuroPharma)<br>Azaepothilon B (BMS)<br>BNP- 7787 (BioNumerik)<br>CA-4-Prodrug (OXiGENE)<br>Dolastatin-10 (Nrh)<br>CA-4 (OXiGENE) |
| 25 |                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 30 |                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 35 | Aromatase inhibitors  | Aminoglutethimide<br>Letrozole                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Exemestane<br>Atamestane (BioMedicines)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

|    |                                                                             |                                                                                                                                                                   |
|----|-----------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    | Anastrozole<br>Formestane                                                   | YM-511 (Yamanouchi)                                                                                                                                               |
|    |                                                                             |                                                                                                                                                                   |
|    | Thymidylatesynthas<br>e inhibitors                                          | Pemetrexed (Eli Lilly)<br>ZD-9331 (BTG)                                                                                                                           |
|    |                                                                             | Nolatrexed (Eximias)<br>CoFactor™ (BioKeys)                                                                                                                       |
| 5  | DNA antagonists                                                             | Trabectedine (PharmaMar)<br>Glufosfamide (Baxter<br>International)<br>Albumin + 32P (Isotope<br>Solutions)<br>Thymectacine (NewBiotics)<br>Edotreotide (Novartis) |
|    |                                                                             | Mafosfamide (Baxter<br>International)<br>Apaziquone (Spectrum<br>Pharmaceuticals)<br>O6-Benzylguanine (Paligent)                                                  |
| 10 | Farnesyltransferase<br>inhibitors                                           | Arglabine (NuOncology Labs)<br>lonafarnibe (Schering-<br>Plough)<br>BAY-43-9006 (Bayer)                                                                           |
|    |                                                                             | Tipifarnibe (Johnson &<br>Johnson)<br>Perillylalcohol (DOR<br>BioPharma)                                                                                          |
|    | Pump inhibitors                                                             | CBT-1 (CBA Pharma)<br>Tariquidar (Xenova)<br>MS-209 (Schering AG)                                                                                                 |
| 15 |                                                                             | Zosuquidar-Trihydrochloride<br>(Eli Lilly)<br>Biricodar-Dicitrate (Vertex)                                                                                        |
|    | Histoneacetyltransf<br>erases inhibitors                                    | Tacedinaline (Pfizer)<br>SAHA (Aton Pharma)<br>MS-275 (Schering AG)                                                                                               |
|    |                                                                             | Pivaloyloxymethylbutyrate<br>(Titan)<br>Depsipeptide (Fujisawa)                                                                                                   |
| 20 | Metalloproteinase<br>inhibitors /<br>Ribonucleosideredu<br>ktase inhibitors | Neovastat (Aeterna<br>Laboratories)<br>Marimastat (British Biotech)<br>Galliummaltolate (Titan)<br>Triapine (Vion)                                                |
|    |                                                                             | CMT -3 (CollaGenex)<br>BMS-275291 (Celltech)<br>Tezacitabine (Aventis)<br>Didox (Molecules for Health)                                                            |
|    | TNF-alpha agonists/<br>antagonists                                          | Virulizine (Lorus<br>Therapeutics)<br>CDC-394 (Celgene)                                                                                                           |
| 25 |                                                                             | Revimide (Celgene)                                                                                                                                                |
|    | Endotheline-A<br>receptor<br>antagonists                                    | Atrasentane (Abbot)<br>ZD-4054 (AstraZeneca)                                                                                                                      |
|    |                                                                             | YM-598 (Yamanouchi)                                                                                                                                               |
|    | Retinoic acid<br>receptor agonists                                          | Fenretinide (Johnson &<br>Johnson)<br>LGD-1550 (Ligand)                                                                                                           |
| 30 |                                                                             | Alitretinoin (Ligand)                                                                                                                                             |
|    | Immunomodulators                                                            | Interferon<br>Oncophage (Antigenics)<br>GMK (Progenics)<br>Adenocarcinoma vaccine<br>(Biomira)<br>CTP-37 (AVI BioPharma)                                          |
| 35 |                                                                             | Dexosome therapy (Anosys)<br>Pentrix (Australian Cancer<br>Technology)<br>JSF-154 (Tragen)<br>Cancer vaccine (Intercell)<br>Noreline (Biostar)                    |

|    |                                       |                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                             |
|----|---------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 5  |                                       | JRX-2 (Immuno-Rx)<br>PEP-005 (Peplin Biotech)<br>Synchrovax vaccine (CTL<br>Immuno)<br>Melanoma vaccine (CTL<br>Immuno)<br>p21-RAS vaccine (GemVax)                                                                                                                                                                                                                      | BLP-25 (Biomira)<br>MGV (Progenics)<br>13-Alethine (Dovetail)<br>CLL-Thera (Vasogen)                                                                                                                                                                                                                        |
| 10 | Hormonal and anti-<br>hormonal agents | Estrogens<br>Conjugated Estrogens<br>Ethinylestradiole<br>Chlorotrianisen<br>Idenestrole<br>Hydroxyprogesteroncaproate<br>Medroxyprogesterone<br>Testosterone<br>Testosteronpropionate<br>Fluoxymesterone<br>Methyltestosterone<br>Diethylstilbestrole<br>Megestrole<br>Tamoxifen<br>Toremofine<br>Dexamethasone                                                         | Prednisone<br>Methylprednisolone<br>Prednisolone<br>Aminoglutethimide<br>Leuprolide<br>Goserelin<br>Leuporelin<br>Cetrorelix<br>Bicalutamide<br>Flutamide<br>Octreotide<br>Nilutamide<br>Mitotane<br>P-04 (Novogen)<br>2-Methoxyestradiol<br>(EntreMed)<br>Arzoxifen (Eli Lilly)                            |
| 20 | Photodynamic<br>agents                | Talaporfine (Light Sciences)<br>Theralux (Theratechnologies)<br>Motexafin Gadolinium<br>(Pharmacyclics)                                                                                                                                                                                                                                                                  | Pd-Bacteriopheophorbide<br>(Yeda)<br>Lutetium-Texaphyrine<br>(Pharmacyclics)<br>Hypericine                                                                                                                                                                                                                  |
| 25 | Tyrosinkinase<br>inhibitors           | Imatinib (Novartis)<br>Leflunomid<br>(Sugen/Pharmacia)<br>ZDI839 (AstraZeneca)<br>Erlotinib (Oncogene Science)<br>Canertjinib (Pfizer)<br>Squalamin (Genaera)<br>SU5416 (Pharmacia)<br>SU6668 (Pharmacia)<br>ZD4190 (AstraZeneca)<br>ZD6474 (AstraZeneca)<br>Vatalanib (Novartis)<br>PKI166 (Novartis)<br>GW2016 (GlaxoSmithKline)<br>EKB-509 (Wyeth)<br>EKB-569 (Wyeth) | Kahalid F (PharmaMar)<br>CEP- 701 (Cephalon)<br>CEP-751 (Cephalon)<br>MLN518 (Millenium)<br>PKC412 (Novartis)<br>Phenoxodiol O<br>Trastuzumab (Genentech)<br>C225 (ImClone)<br>rhu-Mab (Genentech)<br>MDX-H210 (Medarex)<br>2C4 (Genentech)<br>MDX-447 (Medarex)<br>ABX-EGF (Abgenix)<br>IMC-1C11 (ImClone) |
| 35 | Different agents                      | SR-27897 (CCK-A inhibitor,<br>Sanofi-Synthelabo)<br>Tocladesine (cyclic-AMP                                                                                                                                                                                                                                                                                              | BCX-1777 (PNP inhibitor,<br>BioCryst)<br>Ranpirnase (Ribonuclease                                                                                                                                                                                                                                           |

|    |                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 5  | <p>agonist, Ribapharm)<br/> Alvocidib (CDK inhibitor, Aventis)<br/> CV-247 (COX-2-Inhibitor, Ivy Medical)<br/> P54 (COX-2 inhibitor, Phytopharm)<br/> CapCell™ (CYP450 stimulans, Bavarian Nordic)<br/> GCS-100 (gal3 antagonist, GlycoGenesys)<br/> G17DT immunogen (Gastrin inhibitor, Aphton)<br/> Efaproxiral (Oxygenator, Allos Therapeutics)<br/> PI-88 (Heparanase inhibitor, Progen)</p> | <p>stimulans, Alfacell)<br/> Galarubicin (RNA synthesis inhibitor, Dong-A)<br/> Tirapazamin (reducing agent, SRI International)<br/> N-Acetylcystein (reducing agent, Zambon)<br/> R-Flurbiprofen (NF-kappaB inhibitor, Encore)<br/> 3CPA (NF-kappaB inhibitor, Active Biotech)<br/> Seocalcitol (Vitamin-D receptor agonist, Leo)<br/> 131-I-TM-601 (DNA antagonist, TransMolecular)<br/> Eflornithin (ODC inhibitor, ILEX Oncology)</p> |
| 10 | <p>Tesmilifen (Histamine antagonist, YM BioSciences)<br/> Histamine (Histamine-H2 receptor agonist, Maxim)<br/> Tiazofurin (IMPDH inhibitor, Ribapharm)</p>                                                                                                                                                                                                                                      | <p>Minodronic acid (Osteoclasts inhibitor, Yamanouchi)<br/> Indisulam (p53 stimulans, Eisai)</p>                                                                                                                                                                                                                                                                                                                                          |
| 15 | <p>Cilengitide (Integrine antagonist, Merck KGaA)<br/> SR-31747 (IL-1 antagonist, Sanofi-Synthelabo)<br/> CCI-779 (mTOR kinase inhibitor, Wyeth)</p>                                                                                                                                                                                                                                             | <p>Aplidin (PPT inhibitor, PharmaMar)<br/> Rituximab (CD20 antibody, Genentech)<br/> Gemtuzumab (CD33 antibody, Wyeth Ayerst)</p>                                                                                                                                                                                                                                                                                                         |
| 20 | <p>Exisulind (PDE-V inhibitor, Cell Pathways)<br/> CP-461 (PDE-V inhibitor, Cell Pathways)<br/> AG-2037 (GART inhibitor, Pfizer)</p>                                                                                                                                                                                                                                                             | <p>PG2 (Hematopoiesis enhancer, Pharmagenesis)<br/> Immunol™ (Triclosan oral irrigation, Endo)<br/> Triacetyluridine (Uridine prodrug, Wellstat)</p>                                                                                                                                                                                                                                                                                      |
| 25 | <p>WX-UK1 (Plasminogen activator inhibitor, Willex)<br/> PBI-1402 (PMN stimulans, ProMetic LifeSciences)<br/> Bortezomib (Proteasome inhibitor, Millennium)<br/> SRL-172 (T-cell stimulans, SR Pharma)</p>                                                                                                                                                                                       | <p>SN-4071 (sarcoma agent, Signature BioScience)<br/> TransMID-107™<br/> (Immunotoxine, KS Biomedix)<br/> PCK-3145 (Apoptosis enhancer, Procyon)</p>                                                                                                                                                                                                                                                                                      |
| 30 | <p>TLK-286 (Glutathione-S-transferase inhibitor, Telik)<br/> PT-100 (Growth factor agonist, Point Therapeutics)<br/> Midostaurin (PKC inhibitor, Novartis)<br/> Bryostatin-1 (PKC stimulans, GPC Biotech)</p>                                                                                                                                                                                    | <p>Doranidazole (Apoptosis enhancer, Pola)<br/> CHS-828 (cytotoxic agent, Leo)<br/> trans-Retinoic acid (Differentiator, NIH)<br/> MX6 (Apoptosis enhancer, MAXIA)</p>                                                                                                                                                                                                                                                                    |
| 35 | <p>CDA-II (Apoptosis enhancer,</p>                                                                                                                                                                                                                                                                                                                                                               | <p>Apomin (Apoptosis enhancer, ILEX Oncology)<br/> Urocidine (Apoptosis enhancer, Bioniche)</p>                                                                                                                                                                                                                                                                                                                                           |

|  |                                                                                                         |                                                                                                 |
|--|---------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
|  | Everlife)<br>SDX-101 (Apoptosis<br>enhancer, Salmedix)<br>Ceflatonin (Apoptosis<br>enhancer, ChemGenex) | Ro-31-7453 (Apoptosis<br>enhancer, La Roche)<br>Brostallicin (Apoptosis<br>enhancer, Pharmacia) |
|--|---------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|

5

In a preferred embodiment, a compound of the invention is administered in combination with one or more known anti-tumor agents, such as the following: estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxics, antiproliferative agents, prenyl proteintransferase inhibitors, HMG-CoA-reductase inhibitors, HIV protease inhibitors, reverse transcriptase inhibitors, angiogenesis inhibitors. The compounds of the present inventions are particularly suitable for administration at the same time as radiotherapy.

The compounds of the invention are in particular well suited for administration in combination with radiotherapy. The synergistic effects of VEGF inhibition in combination with radiotherapy are known to the skilled artisan (WO 00/61186).

The term "estrogen receptor modulators" in the course of the present invention refers to compounds that interfere with or inhibit the binding of estrogen to estrogen receptor – independently from the mode of action. Non-limiting examples of estrogen receptor modulators are tamoxifen, raloxifen, idoxifen, LY353381, LY 117081, toremifen, fulvestrant, 4-[7-(2,2-Dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyloxy)ethoxy]phenyl]-2H-1-benzopyran-3-yl)]phenyl-2,2-dimethyl-propanoate, 4,4'-Dihydroxybenzophenon-2,4-dinitrophenylhydrazone and SH646.

The term "androgen receptor modulators" in the course of the present invention refers to compounds that interfere with or inhibit the binding of androgens to androgen receptor – independently from the mode of action. Non-limiting examples of androgen receptor modulators are finasteride and other 5alpha-reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole and abirateron acetate.

The term "retinoid receptor modulators" in the course of the present invention refers to compounds that interfere with or inhibit the binding of retinoids to retinoid receptor – independently from the mode of action. Non-limiting examples of retinoid receptor modulators are bexaroten, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid, alpha-difluoromethylornithine, ILX23-7553, trans-N-(4'-Hydroxyphenyl)retinamide and N-4-carboxyphenylretinamide.

The term "cytotoxics" in the course of the present invention refers to compounds that primarily trigger cell death through direct action on cell function(s) or which

interfere with or inhibit cell myosis, such as alkylating agents, tumor necrosis factors, intercalating agents, microtubule inhibitors and topoisomerase inhibitors. Non-limiting examples of cytotoxics are tirapazimin, sertenef, cachectine, ifosfamide, tasonermine, lonidamine, carboplatin, altretamine, prednimustine, dibromodulcit, 5 ranimustine, fotemustine, nedaplatin, oxaliplatin, temozolomide, heptaplatin, estramustin, improsulfan-tosylate, trofosfamide, nimustine, dibrospidium-chloride, pumitepa, lobaplatin, satraplatin, profiromycin, cisplatin, irofulven, dexifosfamide, cis-amindichloro(2-methylpyridine)platin, benzylguanine, glufosfamide, GPX100, (trans,trans,trans)-bis-mu-(hexane-1,6-diamine)-mu-[diamine-platin(II)]bis- 10 [diamine(chloro)platin(II)]-tetrachloride, diarizidinylspermine, arsenium trioxide, 1-(11-Dodecylamino-10-hydroxyundecyl)-3,7-dimethylxanthine, zorubicin, idarubicin, daunorubicin, bisantren, mitoxantron, pirarubicin, pinafide, valrubicine, amrubicine, antineoplaston, 3'-desamino-3'-morpholino-13-desoxo-10-hydroxycarminomycin, annamycin, galarubicin, elinafide, MEN10755 and 4-desmethoxy-3-desamino-3- 15 aziridiny-4-methylsulfonyl-daunorubicin (WO 00/50032).

Non-limiting examples of microtubule inhibitors are paclitaxel, vindesine-sulfate, 3',4'-dideshydro-4'-desoxy-8'-norvincal leukoblastine, docetaxol, rhizoxine, dolastatine, mivobuline-isethionate, auristatine, cemadotine, RPR109881, BMS184476, vinflunine, cryptophycine, 2,3,4,5,6-pentafluoro-N-(3-fluoro-4- 20 methoxyphenyl)-benzenesulfonamide, anhydrovinblastine, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline-t-butylamide, TDX258 and BMS188797.

Non-limiting examples of topoisomerase inhibitors are topotecane, hycaptamine, irinotecane, rubitecane, 6-ethoxypropionyl-3',4'-O-exo-benzylidene-chartreusine, 9-methoxy-N,N-dimethyl-5-nitropyrzolo[3,4,5-kl]acridine-2-(6H)propanamine, 1- 25 amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo-[de]-pyrano-[3',4':b,7]indolizino[1,2b]quinoline-10,13(9H,15H)-dione, lurtotecane, 7-[2-(N-isopropylamino)ethyl]-(20S)camptothecine, BNP1350, BNPI1100, BN80915, BN80942, etoposide-phosphate, teniposide, sobuzoxane, 2'-dimethylamino-2'-desoxy-etoposide, GL331, N-[2-(dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6H- 30 pyrido[4,3-b]carbazole-1-carboxamide, asulacrine, (5a,5aB,8aa,9b)-9-[2-[N-[2-(dimethylamino)ethyl]-N-methylamino]ethyl]-5-[4-hydroxy-3,5-dimethoxyphenyl]-5,5a,6,8,8a,9-hexahydrofuro(3',4':6,7)naphtho(2,3-d)-1,3-dioxol-6-one, 2,3-(methylenedioxy)-5-methyl-7-hydroxy-8-methoxybenzo[c]phenanthridinium, 6,9-bis[(2-aminoethyl)amino]-benzo[g]isoquinoline-5,10-dione, 5-(3-aminopropylamino)- 35 7,10-dihydroxy-2-(2-hydroxyethylaminomethyl)-6H-pyrzolo[4,5,1-de]-acridine-6-

one, N-[1-[2(diethylamino)ethylamino]-7-methoxy-9-oxo-9H-thioxane-then-4-ylmethyl]formamide, N-(2-(dimethyl-amino)-ethyl)acridine-4-carboxamide, 6-[[2-(dimethylamino)-ethyl]amino]-3-hydroxy-7H-indeno[2,1-c]quinolin-7-one and dimesna.

5 Non-limiting examples of antiproliferative agents are antisense RNA- and antisense-DNA oligonucleotides, such as G3139, ODN698, RVASKRAS, GEM231 and INX3001, as well as antimetabolites such as enocitabine, carmofur, tegafur, pentostatine, doxifluridine, trimetrexate, fludarabine, capecitabine, galocitabine, cytarabin-ocfosfate, fosteabine sodiumhydrate, raltitrexed, paltitrexide, emitfur, 10 tiazofurine, decitabine, nolatrexed, pemetrexed, nelzarabine, 2'-desoxy-2'-methylidencytidine, 2'-fluoromethylen-2'-desoxycytidine, N-[5-(2,3-dihydrobenzofuryl)sulfonyl]-N'-(3,4-dichlorophenyl)urea, N6-[4-desoxy-4-[N2-[2(E),4(E)-tetradecadienoyl]glycylamino]-L-glycero-B-L-manno-heptopyranosyl]adenine, aplidine, ecteinascidine, troxacitabine, 4-[2-amino-4-oxo- 15 4,6,7,8-tetrahydro-3H-pyrimidino[5,4-b][1,4]thiazine-6-yl-(S)-ethyl]-2,5-thienoyl-L-glutaminic acid, aminopterin, 5-fluorouracil, alanosine, 11-acetyl-8-(carbamoyloxymethyl)-4-formyl-6-methoxy-14-oxa-1,11-diaza-tetracyclo-(7.4.1.0.0)-tetradeca-2,4,6-trien-9-ylacetic acid ester, swainsonine, lometrexole, dexrazoxane, methioninase, 2'-cyan-2'-desoxy-N4-palmitoyl-1-B-D-arabinofuranosylcytosine and 20 3-aminopyridine-2-carboxaldehyde-thiosemicarbazone.

"Antiproliferative agents" also comprises monoclonal antibodies against growth factors that have not been listed under "angiogenesis inhibitors", such as trastuzumab, as well as tumor suppressor genes, such as p53.

25 In another aspect of the invention, a medicament according to above aspects and embodiments is provided, wherein in such medicament comprises at least one additional pharmacologically active substance (drug, ingredient).

In a preferred embodiment the at least one pharmacologically active substance is a substance as described herein.

30

In another aspect of the invention, a medicament according to above aspects and embodiments is provided, wherein the medicament is applied before and/or during and/or after treatment with at least one additional pharmacologically active substance.

35

In a preferred embodiment the at least one pharmacologically active substance is a substance as described herein.

5 In another aspect of the invention, a pharmaceutical composition comprising a therapeutically effective amount of at least one compound of the invention is provided.

10 In a preferred embodiment, the pharmaceutical composition contains at least one additional compound selected from the group consisting of physiologically acceptable excipients, auxiliaries, adjuvants, diluents, carriers and/or additional pharmaceutically active substance other than the compounds of the invention.

15 In another aspect of the invention, a pharmaceutical composition is disclosed which comprises at least one compound of the invention, at least one pharmacologically active substance other than the compounds of the invention as described herein; and a pharmaceutically acceptable carrier.

20 A further embodiment of the present invention is a process for the manufacture of said pharmaceutical compositions, characterized in that one or more compounds according to the invention and one or more compounds selected from the group consisting of solid, liquid or semiliquid excipients, auxiliaries, adjuvants, diluents, carriers and pharmaceutically active agents other than the compounds according to the invention, are converted in a suitable dosage form.

25 In another aspect of the invention, a kit is provided comprising a therapeutically effective amount of at least one compound of the invention and/or at least one pharmaceutical composition as described herein and a therapeutically effective amount of at least one further pharmacologically active substance other than the compounds of the invention.

30 The pharmaceutical compositions of the present invention may be administered by any means that achieve their intended purpose. For example, administration may be by oral, parenteral, topical, enteral, intravenous, intramuscular, inhalant, nasal, intraarticular, intraspinal, transtracheal, transocular, subcutaneous, intraperitoneal, transdermal, or buccal routes. Alternatively, or concurrently, administration may be by the oral route. The dosage administered will be dependent upon the age, health, 35 and weight of the recipient, kind of concurrent treatment, if any, frequency of

treatment, and the nature of the effect desired. Parenteral administration is preferred. Oral administration is especially preferred.

Suitable dosage forms include, but are not limited to capsules, tablets, pellets, dragees, semi-solids, powders, granules, suppositories, ointments, creams, lotions, inhalants, injections, cataplasms, gels, tapes, eye drops, solution, syrups, aerosols, suspension, emulsion, which can be produced according to methods known in the art, for example as described below:

tablets: mixing of active ingredient/s and auxiliaries, compression of said mixture into tablets (direct compression), optionally granulation of part of mixture before compression.

capsules: mixing of active ingredient/s and auxiliaries to obtain a flowable powder, optionally granulating powder, filling powders/granulate into opened capsules, capping of capsules.

semi-solids (ointments, gels, creams): dissolving/dispersing active ingredient/s in an aqueous or fatty carrier; subsequent mixing of aqueous/fatty phase with complementary fatty/ aqueous phase, homogenization (creams only).

suppositories (rectal and vaginal): dissolving/dispersing active ingredient/s in carrier material liquified by heat (rectal: carrier material normally a wax; vaginal: carrier normally a heated solution of a gelling agent), casting said mixture into suppository forms, annealing and withdrawal suppositories from the forms.

aerosols: dispersing/dissolving active agent/s in a propellant, bottling said mixture into an atomizer.

In general, non-chemical routes for the production of pharmaceutical compositions and/or pharmaceutical preparations comprise processing steps on suitable mechanical means known in the art that transfer one or more compounds of the invention into a dosage form suitable for administration to a patient in need of such a treatment. Usually, the transfer of one or more compounds of the invention into such a dosage form comprises the addition of one or more compounds, selected from the group consisting of carriers, excipients, auxiliaries and pharmaceutical active ingredients other than the compounds of the invention.

Suitable processing steps include, but are not limited to combining, milling, mixing, granulating, dissolving, dispersing, homogenizing, casting and/or compressing the respective active and non-active ingredients. Mechanical means for performing said processing steps are known in the art, for example from Ullmann's Encyclopedia of

Industrial Chemistry, 5th Edition. In this respect, active ingredients are preferably at least one compound of the invention and one or more additional compounds other than the compounds of the invention, which show valuable pharmaceutical properties, preferably those pharmaceutical active agents other than the compounds of the invention, which are disclosed herein.

Particularly suitable for oral use are tablets, pills, coated tablets, capsules, powders, granules, syrups, juices or drops, suitable for rectal use are suppositories, suitable for parenteral use are solutions, preferably oil-based or aqueous solutions, furthermore suspensions, emulsions or implants, and suitable for topical use are ointments, creams or powders. The compounds of the invention may also be lyophilised and the resultant lyophilisates used, for example, for the preparation of injection preparations. The preparations indicated may be sterilised and/or comprise assistants, such as lubricants, preservatives, stabilisers and/or wetting agents, emulsifiers, salts for modifying the osmotic pressure, buffer substances, dyes, flavours and/or a plurality of further active ingredients, for example one or more vitamins.

Suitable excipients are organic or inorganic substances, which are suitable for enteral (for example oral), parenteral or topical administration and do not react with the compounds of the invention, for example water, vegetable oils, benzyl alcohols, alkylene glycols, polyethylene glycols, glycerol triacetate, gelatine, carbohydrates, such as lactose, sucrose, mannitol, sorbitol or starch (maize starch, wheat starch, rice starch, potato starch), cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, magnesium stearate, talc, gelatine, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, polyvinyl pyrrolidone and/or vaseline.

If desired, disintegrating agents may be added such as the above-mentioned starches and also carboxymethyl-starch, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate. Auxiliaries include, without limitation, flow-regulating agents and lubricants, for example, silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with suitable coatings, which, if desired, are resistant to gastric juices. For this purpose, concentrated saccharide solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In order to produce coatings resistant

to gastric juices or to provide a dosage form affording the advantage of prolonged action, the tablet, dragee or pill can comprise an inner dosage and an outer dosage component the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer, which serves to resist  
5 disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, acetyl alcohol, solutions of suitable cellulose preparations such as acetyl-cellulose phthalate, cellulose  
10 acetate or hydroxypropylmethyl-cellulose phthalate, are used. Dye stuffs or pigments may be added to the tablets or dragee coatings, for example, for identification or in order to characterize combinations of active compound doses.

Suitable carrier substances are organic or inorganic substances which are suitable for enteral (e.g. oral) or parenteral administration or topical application and  
15 do not react with the novel compounds, for example water, vegetable oils, benzyl alcohols, polyethylene glycols, gelatin, carbohydrates such as lactose or starch, magnesium stearate, talc and petroleum jelly. In particular, tablets, coated tablets, capsules, syrups, suspensions, drops or suppositories are used for enteral administration, solutions, preferably oily or aqueous solutions, furthermore  
20 suspensions, emulsions or implants, are used for parenteral administration, and ointments, creams or powders are used for topical application. The compounds of the invention can also be lyophilized and the lyophilizates obtained can be used, for example, for the production of injection preparations.

The preparations indicated can be sterilized and/or can contain excipients such  
25 as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for affecting the osmotic pressure, buffer substances, colorants, flavourings and/or aromatizers. They can, if desired, also contain one or more further active compounds, e.g. one or more vitamins.

Other pharmaceutical preparations, which can be used orally include push-fit  
30 capsules made of gelatine, as well as soft, sealed capsules made of gelatine and a plasticizer such as glycerol or sorbitol. The push-fit capsules can contain the active compounds in the form of granules, which may be mixed with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are preferably

dissolved or suspended in suitable liquids, such as fatty oils, or liquid paraffin. In addition, stabilizers may be added.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally include aqueous solutions, suitably  
5 flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-  
10 pyrrolidone or gelatine.

Suitable formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form, for example, water-soluble salts and alkaline solutions. In addition, suspensions of the active compounds as appropriate oily injection suspensions may be administered. Suitable lipophilic solvents or  
15 vehicles include fatty oils, for example, sesame oil, or synthetic fatty acid esters, for example, ethyl oleate or triglycerides or polyethylene glycol-400 (the compounds are soluble in PEG-400).

Aqueous injection suspensions may contain substances, which increase the viscosity of the suspension, including, for example, sodium carboxymethyl cellulose, sorbitol, and/or dextran, optionally, the suspension may also contain stabilizers.  
20

For administration as an inhalation spray, it is possible to use sprays in which the active ingredient is either dissolved or suspended in a propellant gas or propellant gas mixture (for example CO<sub>2</sub> or chlorofluorocarbons). The active ingredient is advantageously used here in micronized form, in which case one or  
25 more additional physiologically acceptable solvents may be present, for example ethanol. Inhalation solutions can be administered with the aid of conventional inhalers.

Possible pharmaceutical preparations, which can be used rectally include, for example, suppositories, which consist of a combination of one or more of the active  
30 compounds with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, or paraffin hydrocarbons. In addition, it is also possible to use gelatine rectal capsules, which consist of a combination of the active compounds with a base. Possible base materials include, for example, liquid triglycerides, polyethylene glycols, or paraffin hydrocarbons.

For use in medicine, the compounds of the present invention will be in the form of pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds of the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid.

Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic bases, e.g. quaternary ammonium salts.

The pharmaceutical preparations can be employed as medicaments in human and veterinary medicine. As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician. Furthermore, the term "therapeutically effective amount" means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function. Said therapeutic effective amount of one or more of the compounds of the invention is known to the skilled artisan or can be easily determined by standard methods known in the art.

The compounds of the invention and the additional active substances are generally administered analogously to commercial preparations. Usually, suitable doses that are therapeutically effective lie in the range between 0.0005 mg and 1000 mg, preferably between 0.005 mg and 500 mg and especially between 0.5 mg and 100 mg per dose unit. The daily dose is preferably between about 0.001 mg/kg and 10 mg/kg of body weight.

Those of skill will readily appreciate that dose levels can vary as a function of the specific compound, the severity of the symptoms and the susceptibility of the subject to side effects. Some of the specific compounds are more potent than

others. Preferred dosages for a given compound are readily determinable by those of skill in the art by a variety of means. A preferred means is to measure the physiological potency of a given compound.

5           For the purpose of the present invention, all mammalian species are regarded as being comprised. In a preferred embodiment, such mammals are selected from the group consisting of "primate, human, rodent, equine, bovine, canine, feline, domestic animals, cattle, livestock, pets, cow, sheep, pig, goat, horse, pony, donkey, hinny, mule, hare, rabbit, cat, dog, guinea pig, hamster, rat, mouse". More  
10           preferably, such mammals are humans. Animal models are of interest for experimental investigations, providing a model for treatment of human diseases.

          The specific dose for the individual patient depends, however, on the multitude of factors, for example on the efficacy of the specific compounds employed, on the  
15           age, body weight, general state of health, the sex, the kind of diet, on the time and route of administration, on the excretion rate, the kind of administration and the dosage form to be administered, the pharmaceutical combination and severity of the particular disorder to which the therapy relates. The specific therapeutic effective dose for the individual patient can readily be determined by routine experimentation,  
20           for example by the doctor or physician, which advises or attends the therapeutic treatment.

          In the case of many disorders, the susceptibility of a particular cell to treatment with the subject compounds may be determined by in vitro testing. Typically a culture of the cell is combined with a subject compound at varying concentrations for  
25           a period of time sufficient to allow the active agents to show a relevant reaction, usually between about one hour and one week. For in vitro testing, cultured cells from a biopsy sample may be used.

          Even without further details, it is assumed that a person skilled in the art will be able to utilise the above description in the broadest scope. The preferred  
30           embodiments should therefore merely be regarded as descriptive disclosure, which is absolutely not limiting in any way.

          Above and below, all temperatures are indicated in °C. In the following examples, "conventional work-up" means that, if necessary, the solvent is removed, water is added if necessary, the pH is adjusted, if necessary, to between 2 and 10,  
35           depending on the constitution of the end product, the mixture is extracted with ethyl

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acetate or dichloromethane, the phases are separated, the organic phase is washed with saturated  $\text{NaHCO}_3$  solution, if desired with water and saturated  $\text{NaCl}$  solution, is dried over sodium sulfate, filtered and evaporated, and the product is purified by chromatography on silica gel, by preparative HPLC and/or by crystallisation. The purified compounds are, if desired, freeze-dried.

List of Abbreviations and Acronyms:

AcOH acetic acid, anh anhydrous, atm atmosphere(s), BOC tert-butoxycarbonyl  
CDI 1,1'-carbonyl diimidazole, conc concentrated, d day(s), dec decomposition,  
DIAD diisopropyl azodicarboxylate, DMAC NN-dimethylacetamide, DMPU 1,3-  
dimethyl-3,4,5,6-tetrahydro-2(H)-pyrimidinone, DMF NN-dimethylformamide, DMSO  
dimethylsulfoxide, DPPA diphenylphosphoryl azide, EDCI 1-(3-  
dimethylaminopropyl)-3-ethylcarbodiimide, EtOAc ethyl acetate, EtOH ethanol  
(100%),  $\text{Et}_2\text{O}$  diethyl ether,  $\text{Et}_3\text{N}$  triethylamine, h hour(s), MeOH methanol, pet. ether  
petroleum ether (boiling range 30-60°C),  $\text{PPh}_3$  triphenylphosphine, temp.  
temperature, THF tetrahydrofuran, TFA trifluoroAcOH, Tf trifluoromethanesulfonyl.

The invention is explained in more detail by means of the following examples without, however, being restricted thereto.

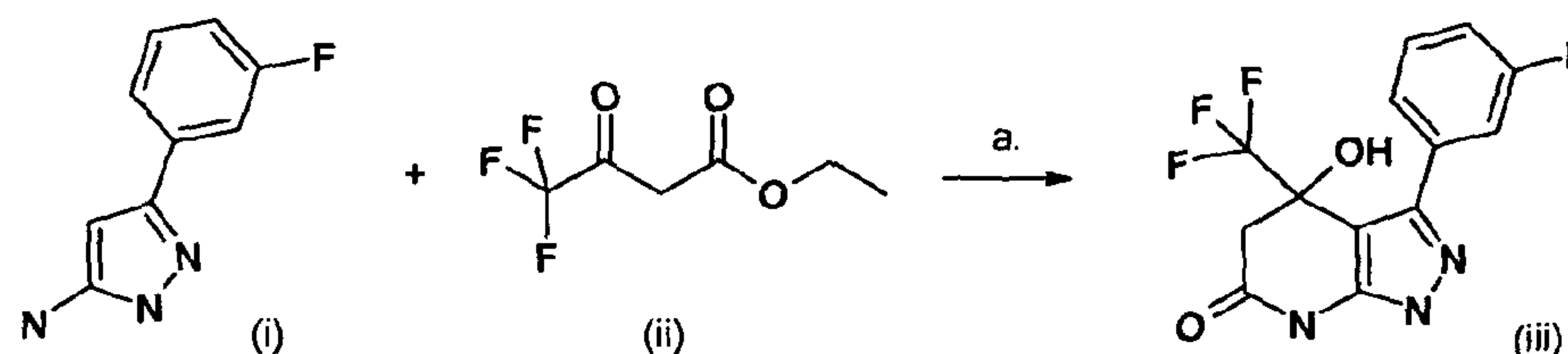
Examples**I. Synthesis of selected compounds of the invention**

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Example 1

3-(3-Fluoro-phenyl)-4-hydroxy-4-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-b]pyridin-6-one

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15

a. 5-(3-Fluoro-phenyl)-2H-pyrazol-3-ylamine (i) (100 mg, 0.56 mmol) was dissolved in glacial acetic acid (1 mL), Ethyl-4,4,4-trifluoroacetate (0.12 mL, 0.84 mmol) was added at RT and stirring was continued for 2.5 h at 120°C. The mixture was evaporated to dryness and the isomeric mixture was directly purified by preparative HPLC (Agilent 1100 Series, Chromolith prep RP-18e, 100-25). A colorless solid (110 mg, 0.35 mmol, 62 %) was obtained, characterized as compound (iii).

20

In analogy to this procedure the following compounds of the invention were synthesized: compounds 2, 3, 5, 6, 8, 9, 12, 13, 14, 15, 16, 17, 22 and 28 to 33.

25

Alternative Synthesis:

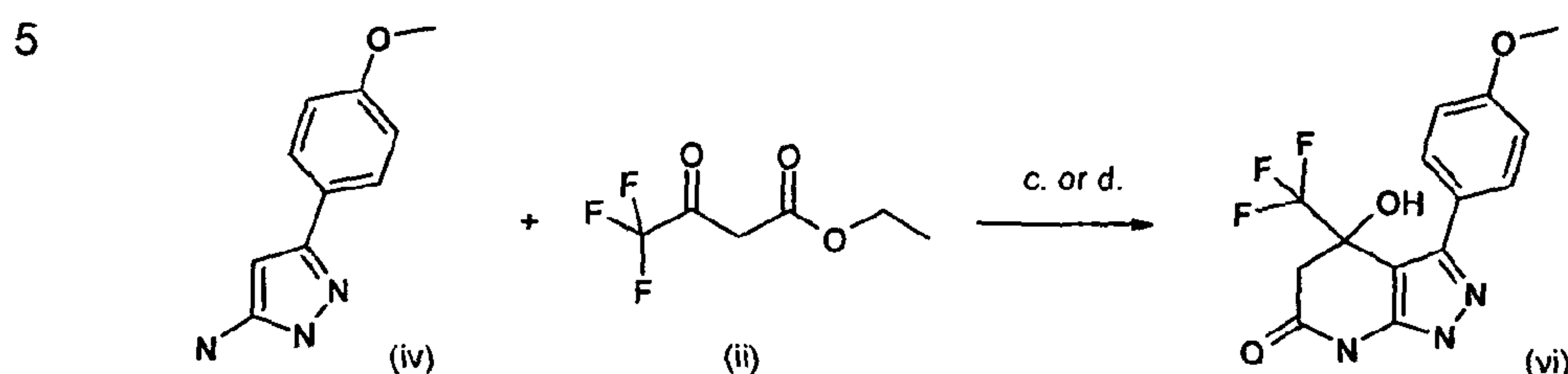
b. 5-(3-Fluoro-phenyl)-2H-pyrazol-3-ylamine (i) (100 mg, 0.56 mmol) was dissolved in ethanol or isopropanol (1 mL), Ethyl-4,4,4-trifluoroacetate (0.12 mL, 0.84 mmol) was added at RT and the mixture was stirred for additional 4 h at reflux. The mixture was evaporated to dryness and directly purified by silica gel flash chromatography (Dichloromethane/Ethyl acetate). A colorless compound (iii) was obtained (92 mg, 0.29 mmol, 52 %).

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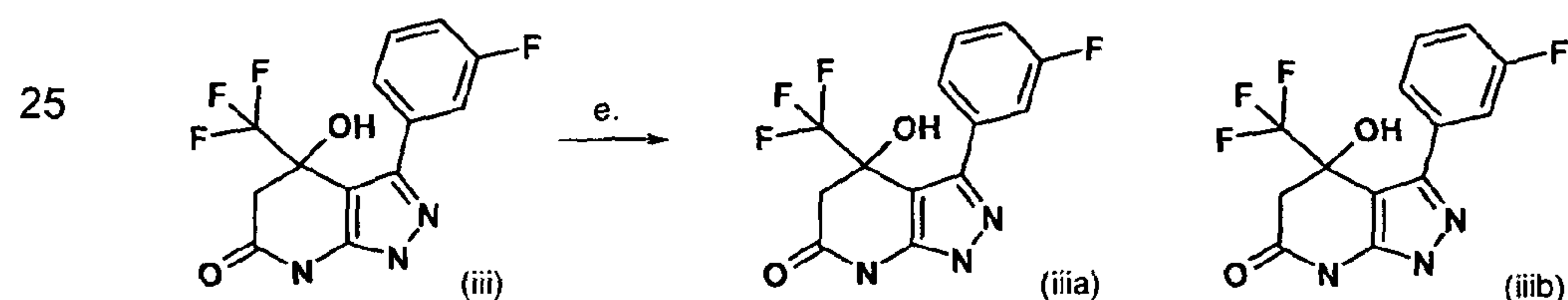
Example 2

3-(3-Methoxy-phenyl)-4-hydroxy-4-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-b]pyridin-6-one



c. 5-(4-Methoxy-phenyl)-2H-pyrazol-3-ylamine (iv) (100 mg, 0.53 mmol) was dissolved in toluene (1 mL), Ethyl-4,4,4-trifluoroacetoacetat (0.12 mL, 0.78 mmol) was added by RT and stirring was continued for 2.5 h at 120°C. The mixture was evaporated to dryness and directly purified by silica gel flash chromatography (Methanol/Dioxan). A colorless compound (vi) was obtained (72.5 mg, 0.22 mmol, 42).

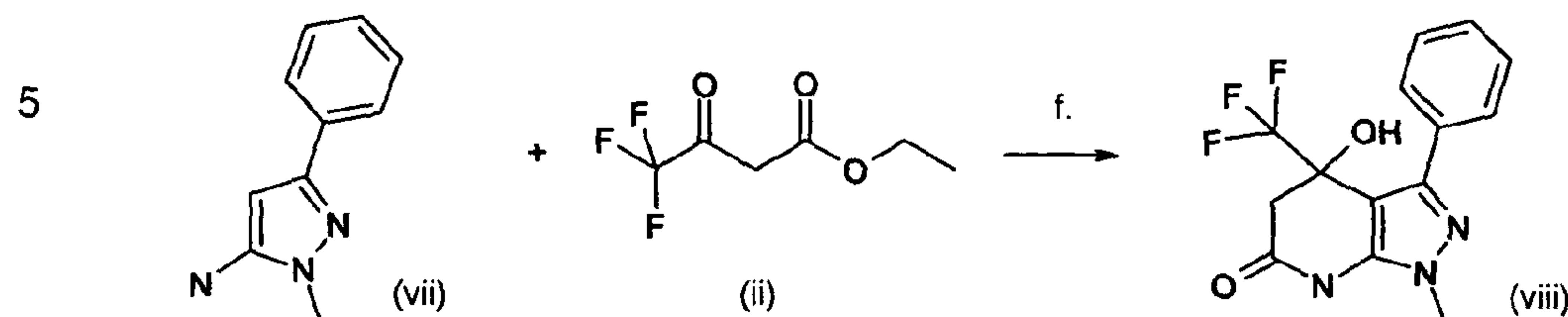
d. 5-(4-Methoxy-phenyl)-2H-pyrazol-3-ylamine (iv) (100 mg, 0.53 mmol) and Ethyl-4,4,4-trifluoroacetoacetat (0.12 mL, 0.78 mmol) was stirred without solvent for 2.5 h at 120°C. The mixture was evaporated to dryness and directly purified by silica gel flash chromatography (Methanol/Dioxan). A colorless solid (74.0 mg, 0.23 mmol, 43 %) was obtained, characterized as compound (vi).

Example 3

e. 50 mg of the racemic mixture (iii) was dissolved in ethanol (5 mL) and separated into enantiomers by chiral HPLC (column: 5x50cm Chiralpak AD, 20µm, flow rate: 120mL/min, n-Heptan/Ethanol 70/30). Compounds (iiiia) (21 mg) and (iiib) (22 mg) were obtained [compounds 20 (amount of rotation:  $[\alpha]_D^{20} = -31.5 \pm 3.3 (^{\circ})$  mL/(dm\*g), c=1.53 g/L in MeOH) and compound 21 (amount of rotation:  $[\alpha]_D^{20} = +32.0 \pm 3.1 (^{\circ})$  mL/(dm\*g), c=1.65 g/L in MeOH)].

Example 4

4-Hydroxy-1-methyl-3-phenyl-4-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-b]pyridin-6-one



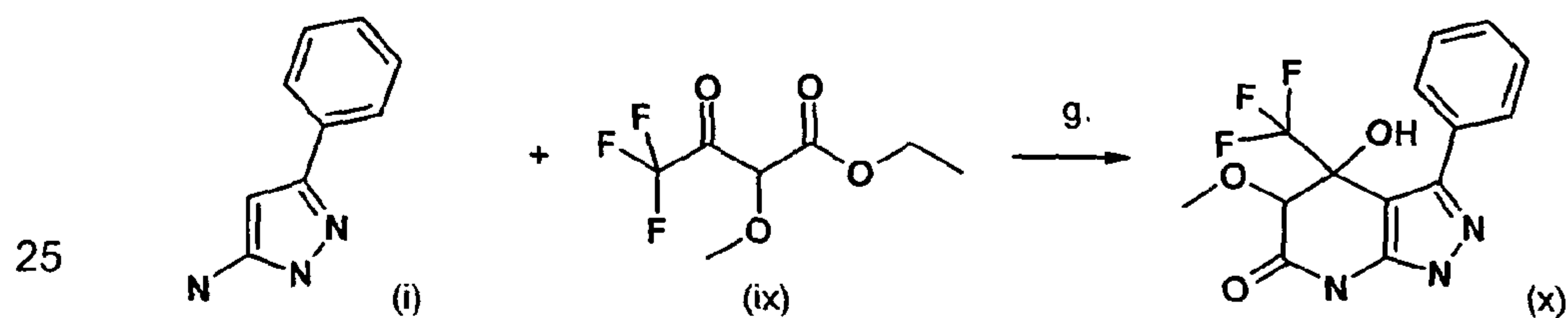
f. 2-Methyl-5-phenyl-2H-pyrazol-3-ylamine (vii) (100 mg, 0.58 mmol) was dissolved in glacial acetic acid (1 mL), ethyl-4,4,4-trifluoroacetate (0.13 mL, 0.85 mmol) was added at RT and stirring was continued for 2.5 h at 120°C. The mixture was evaporated to dryness and the isomeric mixture was directly purified by preparative HPLC (Agilent 1100 Series, Chromolith prep RP-18e, 100-25). A colorless solid (29 mg, 0.09 mmol, 16 %) was obtained, characterized as compound (viii).

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In analogy to this procedure the following compounds of the invention were synthesized: compounds 4, 7, 18 and 19.

Example 5

20 4-Hydroxy-5-methoxy-3-phenyl-4-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-b]pyridin-6-one



g. 5-Phenyl-2H-pyrazol-3-ylamine (i) (100 mg, 0.62 mmol) was dissolved in glacial acetic acid (1 mL), 4,4,4-Trifluoro-2-methoxy-3-oxo-butyric acid ethyl ester (95%, 0.17 mL, 0.92 mmol) was added at RT and stirring was continued for 15 h at 120°C. The mixture was evaporated to dryness and the isomeric mixture was directly purified by preparative HPLC (Agilent 1100 Series, Chromolith prep RP-18e, 100-25). A colorless solid (92 mg, 0.28 mmol, 46 %) was obtained, characterized as compound (x).

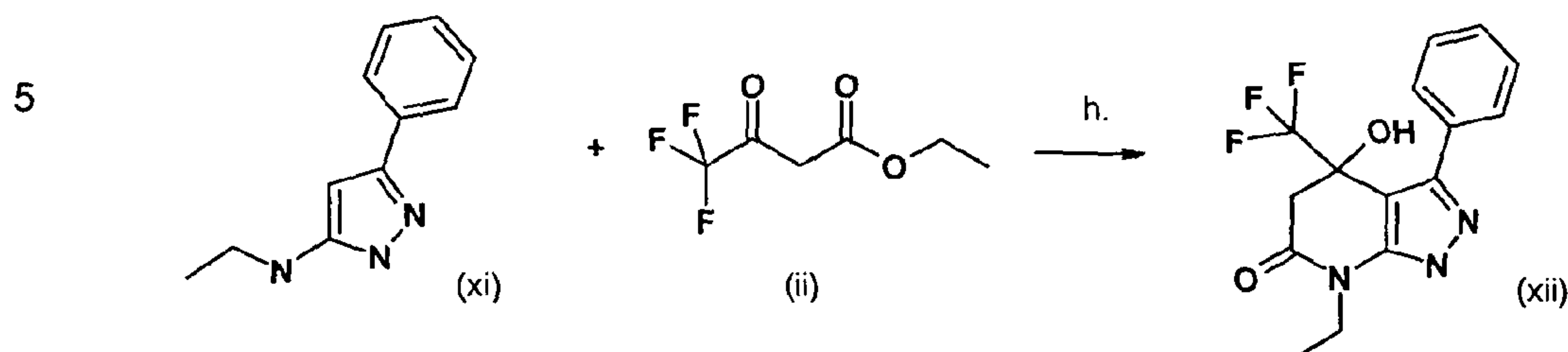
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In analogy to this procedure the following compounds of the invention were synthesized: compounds 24 to 27.

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**Example 6**

4-Hydroxy-5-methoxy-3-phenyl-4-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-b]pyridin-6-one



10 **h.** Ethyl-(5-phenyl-2H-pyrazol-3-yl)-amine (xi) (100 mg, 0.53 mmol, synthesized according to Journal of Heterocyclic Chemistry 1988, 25: 1387-90) was dissolved in glacial acetic acid (1 mL), Ethyl-4,4,4-trifluoroacetoacetate (0.12 mL, 0.80 mmol) was added at RT and stirring was continued for 4 h at 120°C. The mixture was

15 evaporated to dryness and directly purified by silica gel flash chromatography (Methanol/Dioxan). A colorless solid (113 mg, 0.35 mmol, 66 %) was obtained, characterized as compound (xii).

## II. Physicochemical characterization of the compounds of the invention

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Table 2

| Compound | Chemical name                                                                                  | MW [g/mol] | [M + 1] <sup>+</sup> | HPLC Rt [min] <sup>1</sup> | HPLC/MS Rt [min] <sup>2</sup> | NMR or amount of rotation                                                                                                                                                                                                            |
|----------|------------------------------------------------------------------------------------------------|------------|----------------------|----------------------------|-------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 25<br>1  | 3-(3-Fluorophenyl)-4-hydroxy-4-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-b]pyridin-6-one | 315,23     | 316                  | 3,15                       | 1,800                         | <sup>1</sup> H NMR (400 MHz, DMSO) δ 12.91 (s, 1H), 10.69 (s, 1H), 7.81-7.75 (m, 1H), 7.70 (d, J = 8.0, 1H), 7.49 (td, J = 8.1, 6.4, 1H), 7.24 (td, J = 8.3, 2.0, 1H), 7.12 (s, 1H), 3.01 (d, J = 16.5, 1H), 2.80 (d, J = 16.5, 1H). |

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|    |   |                                                                                                |        |     |      |       |                                                                                                                                                                                              |
|----|---|------------------------------------------------------------------------------------------------|--------|-----|------|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 5  | 2 | 4-Hydroxy-3-phenyl-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one            | 297,24 | 298 |      | 1,618 | <sup>1</sup> H NMR (300 MHz, DMSO) δ 12.75 (s, 1H), 10.63 (s, 1H), 7.84 (dd, J = 8.0, 1.5, 2H), 7.48-7.36 (m, 3H), 6.93 (s, 1H), 2.98 (d, J = 16.6, 1H), 2.79 (d, J = 16.5, 1H).             |
| 10 | 3 | 4-Hydroxy-3-(4-methoxyphenyl)-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one | 327,26 | 328 | 3,04 | 1,764 | <sup>1</sup> H NMR (400 MHz, DMSO) δ 12.64 (s, 1H), 10.62 (s, 1H), 7.80 (d, J = 8.9, 2H), 7.00 (d, J = 8.9, 2H), 6.95 (s, 1H), 3.79 (s, 3H), 2.97 (d, J = 16.5, 1H), 2.77 (d, J = 16.4, 1H). |
| 15 | 4 | 4-Hydroxy-1-methyl-3-phenyl-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one   | 311,26 | 312 | 3,15 | 1,822 | <sup>1</sup> H NMR (400 MHz, DMSO) δ 11.05 (s, 1H), 7.99-7.95 (m, 2H), 7.38-7.26 (m, 3H), 7.01 (s, 1H), 3.74 (s, 3H), 3.06 (d, J = 16.3, 1H), 2.82 (d, J = 16.4, 1H).                        |
| 20 | 5 | 3-(4-Chlorophenyl)-4-hydroxy-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one  | 331,68 | 333 | 3,41 | 1,926 | <sup>1</sup> H NMR (400 MHz, DMSO) δ 12.85 (s, 1H), 10.68 (s, 1H), 7.87 (d, J = 8.6, 2H), 7.52 (d, J = 8.6, 2H), 7.05 (s, 1H), 2.99 (d, J = 16.6, 1H), 2.79 (d, J = 16.5, 1H).               |
| 25 | 6 | 4-Hydroxy-3-p-tolyl-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one           | 311,26 | 312 | 3,23 | 1,855 | <sup>1</sup> H NMR (400 MHz, DMSO) δ 12.68 (s, 1H), 10.62 (s, 1H), 7.74 (d, J = 8.1, 2H), 7.24 (d, J = 8.1, 2H), 6.92 (s, 1H), 2.97 (d, J = 16.5, 1H), 2.77 (d, J = 16.4, 1H), 2.33 (s, 3H). |
| 30 |   |                                                                                                |        |     |      |       |                                                                                                                                                                                              |
| 35 |   |                                                                                                |        |     |      |       |                                                                                                                                                                                              |

|    |    |                                                                                                     |        |     |      |       |                                                                                                                                                                                                                 |
|----|----|-----------------------------------------------------------------------------------------------------|--------|-----|------|-------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 5  | 7  | 4-Hydroxy-1-methyl-3-thiophen-2-yl-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one | 317,29 | 318 | 3,12 | 1,816 |                                                                                                                                                                                                                 |
| 10 | 8  | 4-Hydroxy-3-thiophen-2-yl-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one          | 303,26 | 304 | 2,75 | 1,672 | <sup>1</sup> H NMR (400 MHz, DMSO) $\delta$ 12.85 (s, 1H), 10.64 (s, 1H), 7.69-7.59 (m, 2H), 7.14-7.10 (m, 1H), 7.01 (s, 1H), 2.99 (d, $J = 16.4$ , 1H), 2.76 (d, $J = 16.4$ , 1H).                             |
| 15 | 9  | 3-(3,5-Dimethoxyphenyl)-4-hydroxy-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one  | 357,29 | 358 | 3,25 | 1,822 | <sup>1</sup> H NMR (400 MHz, DMSO) $\delta$ 12.79 (s, 1H), 10.65 (s, 1H), 7.13 (d, $J = 2.2$ , 2H), 7.06 (s, 1H), 6.53 (t, $J = 2.2$ , 1H), 3.77 (s, 6H), 2.99 (d, $J = 16.6$ , 1H), 2.79 (d, $J = 16.4$ , 1H). |
| 20 |    |                                                                                                     |        |     |      |       |                                                                                                                                                                                                                 |
| 25 | 10 | (S)-4-Hydroxy-3-phenyl-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one             | 297,24 | 298 | 2,93 | 1,721 | Amount of rotation: $[\alpha]_D^{20} = -26.4 \pm 1.9$ ( $^{\circ}$ ) mL/(dm <sup>2</sup> g), $c=2.70$ g/L in MeOH                                                                                               |
| 30 | 11 | (R)-4-Hydroxy-3-phenyl-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one             | 297,24 | 298 | 2,91 | 1,723 | Amount of rotation: $[\alpha]_D^{20} = +26.0 \pm 2.2$ ( $^{\circ}$ ) mL/(dm <sup>2</sup> g), $c=2.85$ g/L in MeOH                                                                                               |

|    |           |                                                                                                         |        |         |      |       |                                                                                                                                                                                                                                    |
|----|-----------|---------------------------------------------------------------------------------------------------------|--------|---------|------|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 5  | <b>12</b> | 3-(4-Bromophenyl)-4-hydroxy-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one            | 376,13 | 376,378 | 3,39 | 1,901 |                                                                                                                                                                                                                                    |
| 10 | <b>13</b> | 3-(3-Bromophenyl)-4-hydroxy-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one            | 376,13 | 376,378 | 3,36 | 1,870 | <sup>1</sup> H NMR (400 MHz, DMSO) δ 12.92 (s, 1H), 10.71 (s, 1H), 8.12 (t, J = 1.7, 1H), 7.85 (d, J = 8.1, 1H), 7.61 (dd, J = 8.0, 1.0, 1H), 7.42 (t, J = 7.9, 1H), 7.13 (s, 1H), 3.00 (d, J = 16.6, 1H), 2.79 (d, J = 16.4, 1H). |
| 15 | <b>14</b> | 3-(3-Chlorophenyl)-4-hydroxy-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one           | 331,68 | 333     | 3,28 | 1,838 | <sup>1</sup> H NMR (400 MHz, DMSO) δ 12.93 (s, 1H), 10.72 (s, 1H), 7.99 (s, 1H), 7.84-7.78 (m, 1H), 7.51-7.47 (m, 2H), 7.15 (s, 1H), 3.01 (d, J = 16.5, 1H), 2.80 (d, J = 16.5, 1H).                                               |
| 20 | <b>15</b> | 4-Hydroxy-4-trifluoromethyl-3-(3-trifluoromethyl-phenyl)-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one | 365,23 | 366     | 3,49 | 1,947 | <sup>1</sup> H NMR (400 MHz, DMSO) δ 13.04 (s, 1H), 10.75 (s, 1H), 8.34 (s, 1H), 8.14 (d, J = 7.9, 1H), 7.78 (d, J = 7.8, 1H), 7.71 (t, J = 7.8, 1H), 7.21 (s, 1H), 3.03 (d, J = 16.6, 1H), 2.81 (d, J = 16.4, 1H).                |
| 25 | <b>16</b> | 3-Cyclopropyl-4-hydroxy-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-                   | 261,20 | 262     | 1,84 | 1,455 |                                                                                                                                                                                                                                    |
| 30 |           |                                                                                                         |        |         |      |       |                                                                                                                                                                                                                                    |
| 35 |           |                                                                                                         |        |         |      |       |                                                                                                                                                                                                                                    |

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|           |                                                                                                        |        |     |      |       |                                                                                                                                                                                     |
|-----------|--------------------------------------------------------------------------------------------------------|--------|-----|------|-------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|           | one                                                                                                    |        |     |      |       |                                                                                                                                                                                     |
| <b>17</b> | 3-(4-Fluorophenyl)-4-hydroxy-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one          | 315,23 | 316 | 2,99 | 1,804 | <sup>1</sup> H NMR (400 MHz, DMSO) $\delta$ 12.80 (s, 1H), 10.67 (s, 1H), 7.91-7.85 (m, 2H), 7.33-7.27 (m, 2H), 7.03 (s, 1H), 2.98 (d, $J = 16.4$ , 1H), 2.79 (d, $J = 16.4$ , 1H). |
| <b>18</b> | 3-(4-Chlorophenyl)-4-hydroxy-1-methyl-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one | 345,71 | 347 | 3,63 | 2,068 |                                                                                                                                                                                     |
| <b>19</b> | 4-Hydroxy-1,3-diphenyl-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one                | 373,33 | 374 | 3,95 | 2,205 |                                                                                                                                                                                     |
| <b>20</b> | (S)-3-(3-Fluorophenyl)-4-hydroxy-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one      | 315,23 | 316 | 2,96 | 1,812 | Amount of rotation:<br>[ $\alpha$ ] <sub>D</sub> <sup>20</sup> = $-31.5 \pm 3.3$<br>(°) mL/(dm <sup>3</sup> g),<br>c=1.53 g/L in MeOH                                               |

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|    |    |                                                                                                    |        |     |              |              |                                                                                                                                                                                                                                                                            |
|----|----|----------------------------------------------------------------------------------------------------|--------|-----|--------------|--------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 5  | 21 | (R)-3-(3-Fluoro-phenyl)-4-hydroxy-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one | 315,23 | 316 | 2,99         | 1,811        | Amount of rotation:<br>[ $\alpha$ ] <sub>D</sub> <sup>20</sup> = +32.0 ± 3.1<br>(°) mL/(dm*g),<br>c=1.65 g/L in MeOH                                                                                                                                                       |
| 10 | 22 | 4-Hydroxy-3-pyridin-4-yl-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one          | 298,22 | 299 |              | 1,267        | <sup>1</sup> H NMR (400 MHz, DMSO) $\delta$<br>13.17 (s, 1H),<br>10.76 (s, 1H), 8.66 (d, J = 5.8, 2H),<br>7.91 (d, J = 5.8, 2H), 7.25 (s, 1H),<br>3.05 (d, J = 16.6, 1H), 2.83 (d, J = 16.5, 1H).                                                                          |
| 15 | 23 | 4-Hydroxy-7-ethyl-3-phenyl-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one        | 325,29 | 326 |              | 1,896        |                                                                                                                                                                                                                                                                            |
| 20 | 24 | 4-Hydroxy-5-methyl-3-phenyl-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one       | 311,27 | 312 | 2,83<br>3,01 | 1,76<br>1,81 |                                                                                                                                                                                                                                                                            |
| 25 | 25 | 4-Hydroxy-5-ethyl-3-phenyl-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one        | 325,29 | 326 | 3,15         | 1,81         | <sup>1</sup> H NMR (400 MHz, DMSO, one diastereomer) $\delta$<br>12.67 (s, 1H),<br>10.42 (s, 1H),<br>7.93-7.77 (m, 2H),<br>7.52-7.31 (m, 3H),<br>6.67 (s, 1H), 2.50-2.46 (m, 2H, covered by DMSO-signal),<br>2.05-1.93 (m, 1H),<br>1.37-1.26 (m, 1H),<br>0.91 (t, J = 7.8, |
| 30 |    |                                                                                                    |        |     |              |              |                                                                                                                                                                                                                                                                            |
| 35 |    |                                                                                                    |        |     |              |              |                                                                                                                                                                                                                                                                            |

|              |           |                                                                                                         |        |     |      |                                                                                                                                                                                                                                                                                          |
|--------------|-----------|---------------------------------------------------------------------------------------------------------|--------|-----|------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 5            |           |                                                                                                         |        |     |      | 3H).                                                                                                                                                                                                                                                                                     |
| 10           | <b>26</b> | 4-Hydroxy-5-(2-hydroxy-ethyl)-3-phenyl-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one | 341,29 | 342 | 2,64 | 1,7<br><sup>1</sup> H NMR (400 MHz, DMSO, d-TFA exchanged) $\delta$ 7.91-7.80 (m, 2H), 7.55-7.38 (m, 3H), 3.69-3.52 (m, 2H), 2.87 (dd, $J = 9.3$ , 4.5, 1H), 2.28-2.17 (m, 1H), 1.65-1.55 (m, 1H).                                                                                       |
| 15           | <b>27</b> | 4-Hydroxy-5-methoxy-3-phenyl-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one           | 327,27 | 328 | 3,09 | 1,79<br><sup>1</sup> H NMR (400 MHz, DMSO, d-TFA exchanged) $\delta$ 7.91-7.87 (m, 2H), 7.50-7.38 (m, 3H), 3.70 (s, 1H), 3.52 (s, 3H).                                                                                                                                                   |
| 20           | <b>28</b> | 3-Benzyl-4-hydroxy-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one                     | 311,27 | 312 | 3,04 | 1,81                                                                                                                                                                                                                                                                                     |
| 25<br><br>30 | <b>29</b> | 4-Hydroxy-3-(1H-indol-3-yl)-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one            | 336,27 | 337 | 2,72 | 1,72<br><sup>1</sup> H NMR (400 MHz, DMSO) $\delta$ 12.39 (s, 1H), 11.40 (s, 1H), 10.57 (s, 1H), 7.84 (d, $J = 2.7$ , 1H), 7.77 (d, $J = 8.0$ , 1H), 7.45 (d, $J = 8.0$ , 1H), 7.18-7.13 (m, 1H), 7.11-7.06 (m, 1H), 6.81 (s, 1H), 2.96 (d, $J = 16.5$ , 1H), 2.78 (d, $J = 16.3$ , 1H). |

|    |    |                                                                                                             |        |     |      |      |                                                                                                                                                                                                                                    |
|----|----|-------------------------------------------------------------------------------------------------------------|--------|-----|------|------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 5  | 30 | 3-Furan-2-yl-4-hydroxy-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one                     | 287,2  | 288 | 2,37 | 1,66 | <sup>1</sup> H NMR (500 MHz, DMSO) δ 12.98 (s, 1H), 10.65 (s, 1H), 7.79 (d, J = 1.3, 1H), 7.07 (d, J = 3.4, 1H), 7.00 (s, 1H), 6.62 (dd, J = 3.4, 1.8, 1H), 2.98 (d, J = 16.5, 1H), 2.78 (d, J = 16.4, 1H).                        |
| 10 | 31 | 3-(3,4-Dimethoxyphenyl)-4-hydroxy-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one          | 357,29 | 358 | 2,77 | 1,69 | <sup>1</sup> H NMR (400 MHz, DMSO) δ 12.66 (s, 1H), 10.60 (s, 1H), 7.58 (d, J = 2.0, 1H), 7.44 (dd, J = 8.4, 2.1, 1H), 7.07 (s, 1H), 7.01 (d, J = 8.4, 1H), 3.78 (d, J = 8.5, 6H), 2.98 (d, J = 16.5, 1H), 2.80 (d, J = 16.5, 1H). |
| 15 | 32 | 4-Hydroxy-3-(3-methoxyphenyl)-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one              | 327,26 | 328 | 2,69 | 1,75 |                                                                                                                                                                                                                                    |
| 20 | 33 | 3-(1,5-Dimethyl-1H-pyrazol-4-yl)-4-hydroxy-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one | 315,25 | 316 | 2,61 | 1,49 | <sup>1</sup> H NMR (400 MHz, DMSO) δ 12.28 (s, 1H), 10.59 (s, 1H), 7.53 (s, 1H), 6.63 (s, 1H), 3.76 (s, 3H), 2.89 (d, J = 16.4, 1H), 2.75 (d, J = 16.4, 1H), 2.24 (s, 3H).                                                         |
| 25 | 34 | 7-Ethyl-4-hydroxy-3-phenyl-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one                 | 325,29 | 326 | 3,31 | 1,94 |                                                                                                                                                                                                                                    |
| 30 |    |                                                                                                             |        |     |      |      |                                                                                                                                                                                                                                    |
| 35 |    |                                                                                                             |        |     |      |      |                                                                                                                                                                                                                                    |

|   |    |                                                                                                       |        |     |      |      |  |
|---|----|-------------------------------------------------------------------------------------------------------|--------|-----|------|------|--|
| 5 | 35 | 4-(3,5-Bis-trifluoromethyl-phenyl)-4-hydroxy-3-phenyl-1,4,5,7-tetrahydro-pyrazolo[3,4-b]pyridin-6-one | 441,33 | 442 | 4,29 | 2,37 |  |
|---|----|-------------------------------------------------------------------------------------------------------|--------|-----|------|------|--|

**<sup>1</sup> HPLC-Method (nonpolar)**

10 Solvent A: Water + 0,1% TFA  
 Solvent B: Acetonitrile+ 0,08% TFA  
 Flow: 1,5 ml/min

Gradient: 0,0 min 20% B  
 5,0 min 100% B  
 15 5,5 min 100% B  
 6,0 min 20% B  
 6,5 min 20% B

Column: Chromolith Performance RP18e 100-3

**<sup>2</sup> HPLC/MS-Method (polar)**

20 Solvent A: Water + 0,05 % Formic Acid  
 Solvent B: Acetonitrile + 0,04 % Formic Acid  
 Flow: 2,4 ml/min, wavelength : 220nm

Gradient: 0,0 min 4 % B  
 2,8 min 100 % B  
 25 3,3 min 100% B  
 3,4 min 4% B

Column: Chromolith® Speed ROD RP-18e 50-4.6 mm

30

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**III. Biological Assays**Description of the LPA2R Assay5      Reagents

## Cell culture

|    |                         |                                    |
|----|-------------------------|------------------------------------|
|    | cell line               | U2OS, recombinant expressing LPA2R |
|    | McCoy's Medium          | Invitrogen # 26600-021             |
| 10 | DMEM                    | Gibco #41965                       |
|    | Penicillin/Streptomycin | Gibco #15140                       |
|    | FCS                     | PAA # A15-043                      |
|    | Geneticin               | Invitrogen #10131-027              |
|    | PBS                     | Gibco                              |
| 15 | HEPES                   | Gibco #15630-056                   |
|    | HyQ-Tase                | HyClone #SV30030.01                |

## Assay

|    |                                                                 |                            |
|----|-----------------------------------------------------------------|----------------------------|
|    | 10 x HBSS                                                       | Gibco #14065               |
| 20 | 1 M HEPES                                                       | Merck #1.10110             |
|    | NaCl                                                            | Merck #1.06404             |
|    | KCl                                                             | Merck #1.04936             |
|    | MgSO <sub>4</sub> x 7H <sub>2</sub> O                           | Merck #1.05886             |
|    | CaCl <sub>2</sub> x 2H <sub>2</sub> O                           | Merck #1.02382             |
| 25 | D(+)-Glucose x 1H <sub>2</sub> O                                | Merck #1.04074             |
|    | BSA, fatty acid free                                            | Roche #10 77 58 35 001     |
|    | ligand (LPA), 1-Oleoyl-2-Hydroxy-sn-Glycero-3-Phosphate, Avanti | #857130P                   |
|    | probenecid, water soluble                                       | Invitrogen #P36400         |
|    | detection solution (calcium dye)                                | Bulk Kit (Mol.Dev. #R8141) |
| 30 | mikro plate 384 blk, cl.bottom                                  | Falcon # 353692            |

**Cell cultivation / propagation**

|    |                    |                                           |
|----|--------------------|-------------------------------------------|
|    | medium             | McCoy's Medium, 10% FCS, 1mg/ml Genitacin |
| 5  | culture conditions | 37°C, 5% CO <sub>2</sub> in T75 flasks    |
|    | harvesting         | washing with PBS                          |
|    |                    | detaching with 1 mL HyQ-Tase per flask    |
|    |                    | incubation 5 min                          |
|    |                    | addition of 10 mL medium                  |
| 10 |                    | centrifugation                            |
|    |                    | re-suspension with 10 mL culture medium   |

**LPA2R-calciumflux assay protocol**

- 15 The assay detects intra cellular calcium which is generated by cells upon activation of the LPA2 receptor by its ligand LPA. This transient calcium mobilisation can be monitored using a commercial calcium detection kit (e.g. from Molecular Devices). The main component of such a kit is a dye, which becomes fluorescent when calcium is present – a transient fluorescence signal after laddition of a ligand to a
- 20 test well are the result. Readers like the FLIPR (from Molecular Devevices) can be used to monitor such transient "Ca-flux" signals.
- The signals are calculated according to peak maximum minus base line.
- Compounds which are antogonists of LPA lead to a decreased mobilisation of intracellular calcium and thus to a lower signal. The assay is performed in
- 25 microplates (384 wells per plate).

The assay itself is run according to the following procedure:

- 50 uL seed cells (10000cells/well in DMEM buffer)
- Incubate 24h at 37°C, 10% CO<sub>2</sub>
- 30 aspirate medium
- 50 uL add calcium dye 1x HBSS/HEPES buffer
- incubate 1h at 37°C („loading“)
- equilibrate 10 min at RT
- 5 uL add compounds in HEPES buffer
- 35 shake 10 sec. @ 1000 rpm

incubate 15 min at RT

**20 uL** add LPA (in the FLIPR Tetra) in KREBS-Puffer/BSA & measurement

5 The cells are seeded in DMEM buffer (DMEM, 10% FCS, 10 mM HEPES, 1% Pen/Strep).

Dye loading is done in HBSS/HEPES buffer (100 mL 10x HBSS + 20 mL 1M HEPES + 880 mL water, pH 7.4)

The LPA is added in Krebs/BSA buffer (120 mM NaCl, 5 mM KCl, 0,62 mM MgSO<sub>4</sub>, 1,8 mM CaCl<sub>2</sub>, 10 mM HEPES, 6 mM D(+)-Glucose, 0.2% BSA, pH 7.4).

10 The compounds are pre-diluted in HEPES buffer (20 mM, pH 7.4), whereby the final DMSO content in the assay is kept at 1%. The compounds are pre-diluted in order to generate dose response series on the microplates. The dose response series consist of 10 concentrations for each compound from 30 uM final to 1 nM final. From all compound wells the resulting signals are referred to control wells (located on each plate besides the compound wells) in terms of %activity.

$$\%activity = \frac{(\text{readout}_{\text{compound}} - \text{readout}_{\text{blank}})}{(\text{readout}_{\text{full}} - \text{readout}_{\text{blank}})} * 100$$

20

From these %activity values - along with the corresponding compound concentrations - IC50 values are fitted for each compound using standard fitting programs such as Graphpad Prism. Here the method "log(inhibitor) vs. response -- Variable slope" is used.

25

#### **Reader settings (FLIPR Tetra)**

ExcWLength:470\_495

Em.Wlength: 515\_575

30

Gain: 50

Exp. Time: 0,4

Exc.Intensity:80

READ with TF

35

First read interval: 1,00 s

Number of first reads: 240  
Reads before dispense: 10  
Second read interval: 1,00 s  
Number of second reads: 0  
5 Save Images: No

**Table 3**

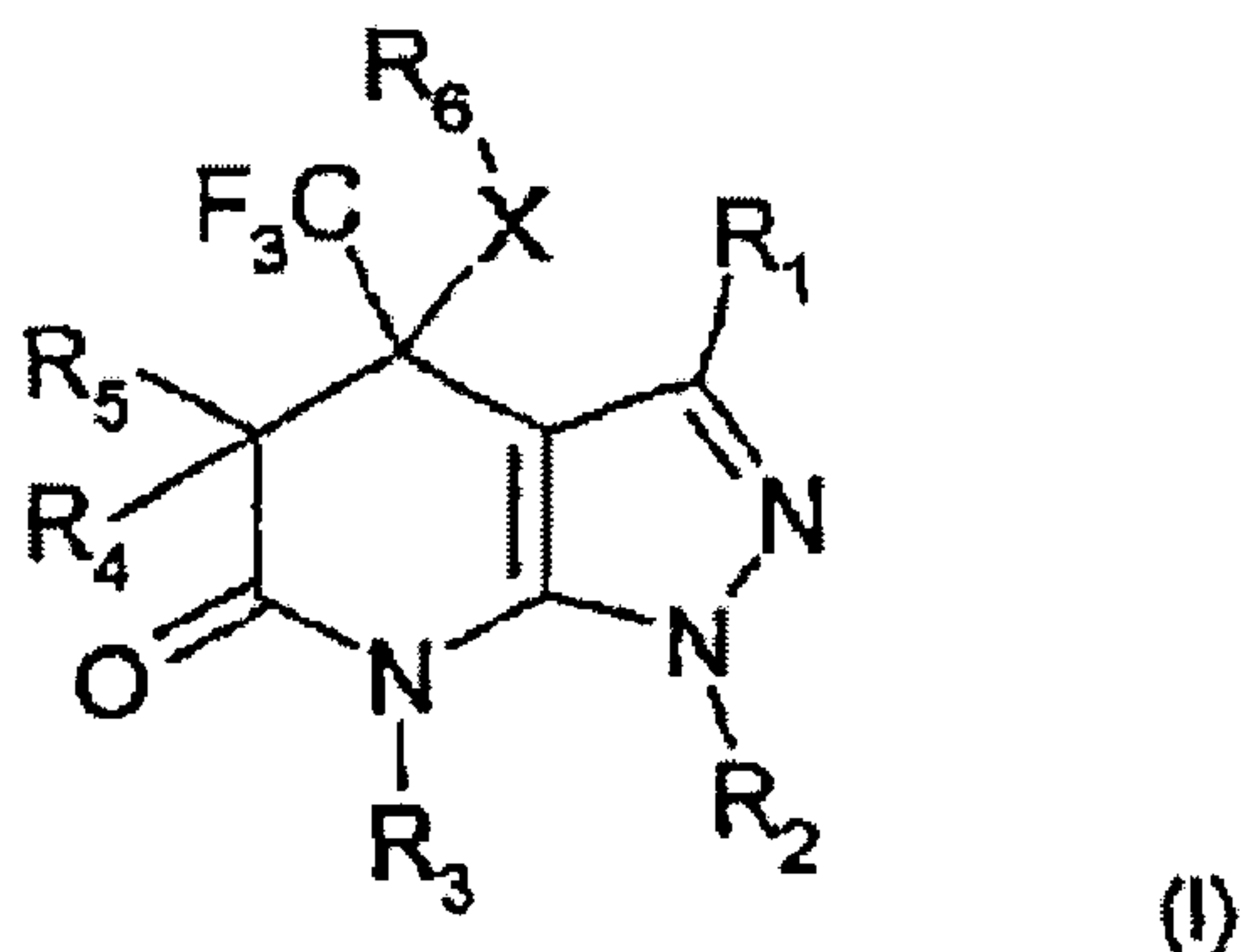
|    | Compound | IC50<br>A = > 10 $\mu$ M<br>B = 1-10 $\mu$ M<br>C = < 1 $\mu$ M |
|----|----------|-----------------------------------------------------------------|
|    |          |                                                                 |
| 10 | 1        | C                                                               |
|    | 2        | C                                                               |
|    | 3        | C                                                               |
| 15 | 4        | A                                                               |
|    | 5        | B                                                               |
|    | 6        | C                                                               |
| 20 | 7        | A                                                               |
|    | 8        | C                                                               |
|    | 9        | C                                                               |
| 25 | 10       | C                                                               |
|    | 11       | A                                                               |
|    | 12       | A                                                               |
| 30 | 13       | C                                                               |
|    | 14       | C                                                               |
|    | 15       | C                                                               |
| 35 | 16       | A                                                               |

73

|    |    |   |
|----|----|---|
| 5  | 17 | C |
|    | 18 | A |
|    | 19 | A |
|    | 20 | C |
|    | 21 | A |
| 10 | 22 | C |
|    | 23 |   |
|    | 24 | B |
|    | 25 | A |
|    | 26 | A |
| 15 | 27 | A |
|    | 28 | A |
|    | 29 | A |
|    | 30 | A |
|    | 31 | C |
| 20 | 32 | B |
|    | 33 | B |
|    | 34 | A |
|    | 35 | A |
|    |    |   |
| 25 |    |   |
|    |    |   |
|    |    |   |
|    |    |   |
|    |    |   |
| 30 |    |   |
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|    |    |   |
|    |    |   |
| 35 |    |   |
|    |    |   |
|    |    |   |
|    |    |   |
|    |    |   |

CLAIMS:

1. A compound of formula (I)



wherein

- 5             $R_1$             denotes aryl, heteroaryl, cycloalkyl, heterocyclyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocyclalkyl, which can optionally be substituted with one or more substituents selected from alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl,
- 10            halogen, -F, -Cl, -Br, -I, -CN, -CF<sub>3</sub>, -N<sub>3</sub>, -NH<sub>2</sub>, -NHZ1, -NZ2Z3, -NO<sub>2</sub>, -OH, -OCF<sub>3</sub>, -SH, -O-SO<sub>3</sub>H, -OP(O)(OH)<sub>2</sub>, -CHO, -COOH, -C(O)NH<sub>2</sub>, -SO<sub>3</sub>H, -P(O)(OH)<sub>2</sub>, -C(O)-Z4, -C(O)O-Z5, -C(O)NH-Z6, -C(O)NZ7Z8, -O-Z9, -O(-Z10-O)<sub>a</sub>-H, a = 1, 2, 3, 4 or 5, -O(-Z11-O)<sub>b</sub>-Z12, b = 1, 2, 3, 4 or 5, -OC(O)-Z13,
- 15            -OC(O)-O-Z14, -OC(O)-NHZ15, -O-C(O)-NZ16Z17, -OP(O)(OZ18)(OZ19), -OSi(Z20)(Z21)(Z22), -OS(O<sub>2</sub>)-Z23, -NHC(O)-NH<sub>2</sub>, -NHC(O)-Z24, -NZ25C(O)-Z26, -NH-C(O)-O-Z27, -NH-C(O)-NH-Z28, -NH-C(O)-NZ29Z30, -NZ31-C(O)-O-Z32, -NZ33-C(O)-NH-Z34, -NZ35-C(O)-NZ36Z37, -NHS(O<sub>2</sub>)-Z38,
- 20            -NZ39S(O<sub>2</sub>)-Z40, -S-Z41, -S(O)-Z42, -S(O<sub>2</sub>)-Z43, -S(O<sub>2</sub>)NH-Z44, -S(O<sub>2</sub>)NZ45Z46, -S(O<sub>2</sub>)O-Z47, -P(O)(OZ48)(OZ49), -Si(Z50)(Z51)(Z52), -C(NH)-NH<sub>2</sub>, -C(NZ53)-NH<sub>2</sub>, -C(NH)-NHZ54,

-C(NH)-NZ55Z56, -C(NZ57)-NHZ58, -C(NZ59)-NZ60Z61, -NH-  
 C(O)-NH-O-Z62, -NH-C(O)-NZ63-O-Z64, -NZ65-C(O)-NZ66-O-  
 Z67, -N(-C(O)-NH-O-Z68)<sub>2</sub>, -N(-C(O)-NZ69-O-Z70)<sub>2</sub>,  
 -N(-C(O)-NH-O-Z71)(-C(O)-NZ72-O-Z73), -C(S)-Z74, -C(S)-O-  
 5 Z75, -C(S)-NH-Z76, -C(S)-NZ77Z78, -C(O)-NH-O-Z79, -C(O)-  
 NZ80-O-Z81, -C(S)-NH-O-Z82, -C(S)-NZ83-O-Z84, -C(O)-NH-  
 NH-Z85, -C(O)-NH-NZ86Z87, -C(O)-NZ88-NZ89Z90, -C(S)-NH-  
 NH-Z91, -C(S)-NH-NZ92Z93, -C(S)-NZ94-NZ95Z96, -C(O)-  
 C(O)-O-Z97, -C(O)-C(O)-NH<sub>2</sub>, -C(O)-C(O)-NHZ98, -C(O)-C(O)-  
 10 NZ99Z100, -C(S)-C(O)-O-Z101, -C(O)-C(S)-O-Z102, -C(S)-  
 C(S)-O-Z103, -C(S)-C(O)-NH<sub>2</sub>, -C(S)-C(O)-NHZ104, -C(S)-  
 C(O)-NZ105Z106, -C(S)-C(S)-NH<sub>2</sub>, -C(S)-C(S)-NHZ107, -C(S)-  
 C(S)-NZ108Z109, -C(O)-C(S)-NH<sub>2</sub>, -C(O)-C(S)-NHZ110, -C(O)-  
 C(S)-NZ111Z112;  
 15 wherein Z1, Z2, Z3, Z4, Z5, Z6, Z7, Z8, Z9, Z10, Z11, Z12, Z13,  
 Z14, Z15, Z16, Z17, Z18, Z19, Z20, Z21, Z22, Z23, Z24, Z25,  
 Z26, Z27, Z28, Z29, Z30, Z31, Z32, Z33, Z34, Z35, Z36, Z37,  
 Z38, Z39, Z40, Z41, Z42, Z43, Z44, Z45, Z46, Z47, Z48, Z49,  
 Z50, Z51, Z52, Z53, Z54, Z55, Z56, Z57, Z58, Z59, Z60, Z61,  
 20 Z62, Z63, Z64, Z65, Z66, Z67, Z68, Z69, Z70, Z71, Z72, Z73,  
 Z74, Z75, Z76, Z77, Z78, Z79, Z80, Z81, Z82, Z83, Z84, Z85,  
 Z86, Z87, Z88, Z89, Z90, Z91, Z92, Z93, Z94, Z95, Z96, Z97,  
 Z98, Z99, Z100, Z101, Z102, Z103, Z104, Z105, Z106, Z107,  
 Z108, Z109, Z110, Z111, Z112 are independently from each  
 25 other selected from the group consisting of: alkyl, cycloalkyl,  
 cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl,  
 heteroaryl, heteroarylalkyl and wherein alternatively Z7, Z8  
 and/or Z16, Z17 and/or Z29, Z30 and/or Z36, Z37 and/or Z45,  
 Z46 and/or Z55, Z56 and/or Z60, Z61 and/or Z77, Z78 and/or  
 30 Z86, Z87 and/or Z89, Z90 and/or Z92, Z93 and/or Z95, Z96

and/or Z99, Z100 and/or Z105, Z106 and/or Z108, Z109 and/or Z111, Z112 respectively together can also form heterocyclyl;

R<sub>2</sub> denotes H or alkyl,

R<sub>3</sub> denotes H or alkyl,

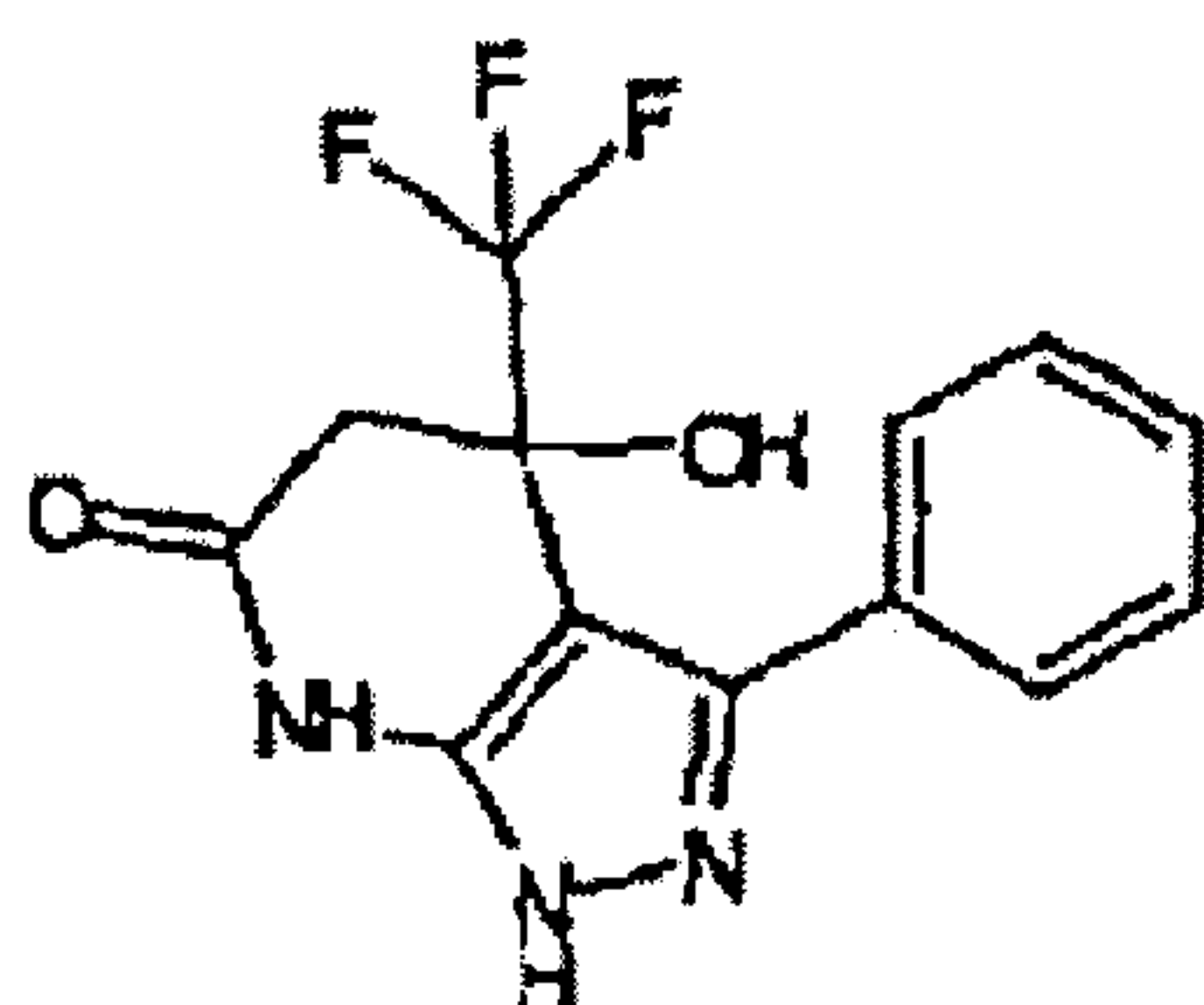
5 R<sub>4</sub>, R<sub>5</sub> independently from each other denote H, alkyl, OH-alkyl, alkoxy, halogen, F, Cl, Br, I, CN, NHR, NH<sub>2</sub>, NR<sub>2</sub>, S-alkyl or NH-alkyl-OH, wherein R independently from each other denotes alkyl, aryl, heteroaryl, cycloalkyl or heterocyclyl; or

R<sub>4</sub> and R<sub>5</sub> together form cycloalkyl or heterocyclyl,

10 R<sub>6</sub> denotes H or alkyl,

X denotes O, NH or N-alkyl,

with the proviso that the following compound is excluded from formula (I):



15 or a physiologically acceptable salt, solvate, tautomer or stereoisomer thereof, or a mixture thereof in any ratio.

2. The compound according to claim 1, wherein

R<sub>1</sub> denotes aryl, heteroaryl, cycloalkyl or arylalkyl, which can optionally be substituted with one or more substituents selected from halogen, F, Cl, Br, I, CF<sub>3</sub>, alkyl or alkoxy, or a

physiologically acceptable salt, solvate, tautomer or stereoisomer thereof, or a mixture thereof in any ratio.

3. The compound according to claim 1 or 2, wherein

$R_2$  denotes H, methyl or ethyl,

5 or a physiologically acceptable salt, solvate, tautomer or stereoisomer thereof, or a mixture thereof in any ratio.

4. The compound according to any one of claims 1 to 3, wherein

$R_3$  denotes H, methyl or ethyl,

10 or a physiologically acceptable salt, solvate, tautomer or stereoisomer thereof, or a mixture thereof in any ratio.

5. The compound according to any one of claims 1 to 4, wherein

$R_4, R_5$  independently from each other denote H, alkyl, OH-alkyl, or alkoxy,

15 or a physiologically acceptable salt, solvate, tautomer or stereoisomer thereof, or a mixture thereof in any ratio.

6. The compound according to any one of claims 1 to 5, wherein

$R_1$  denotes aryl, heteroaryl, cycloalkyl or arylalkyl, which can optionally be substituted with one or more substituents selected from halogen, F, Cl, Br, I,  $CF_3$ , alkyl or alkoxy,

20  $R_2$  denotes H, methyl or ethyl,

$R_3$  denotes H, methyl or ethyl,

$R_4, R_5$  independently from each other denote H, alkyl, OH-alkyl, alkoxy,

$R_6$  denotes H,

X denotes O,  
or a physiologically acceptable salt, solvate, tautomer or  
stereoisomer thereof, or a mixture thereof in any ratio.

7. The compound according to claim 2, wherein

5 R1 denotes phenyl, thiophenyl, furanyl, pyrazolyl, pyridinyl, indolyl  
or benzyl, which can optionally be substituted with one or more  
substituents selected from halogen, F, Cl, Br, I, CF<sub>3</sub>, alkyl or  
alkoxy,

10 or a physiologically acceptable salt, solvate, tautomer or  
stereoisomer thereof, or a mixture thereof in any ratio.

8. The compound according to claim 5, wherein

R<sub>4</sub>, R<sub>5</sub> independently from each other denote methyl, ethyl, hydroxy-  
ethyl or methoxy,

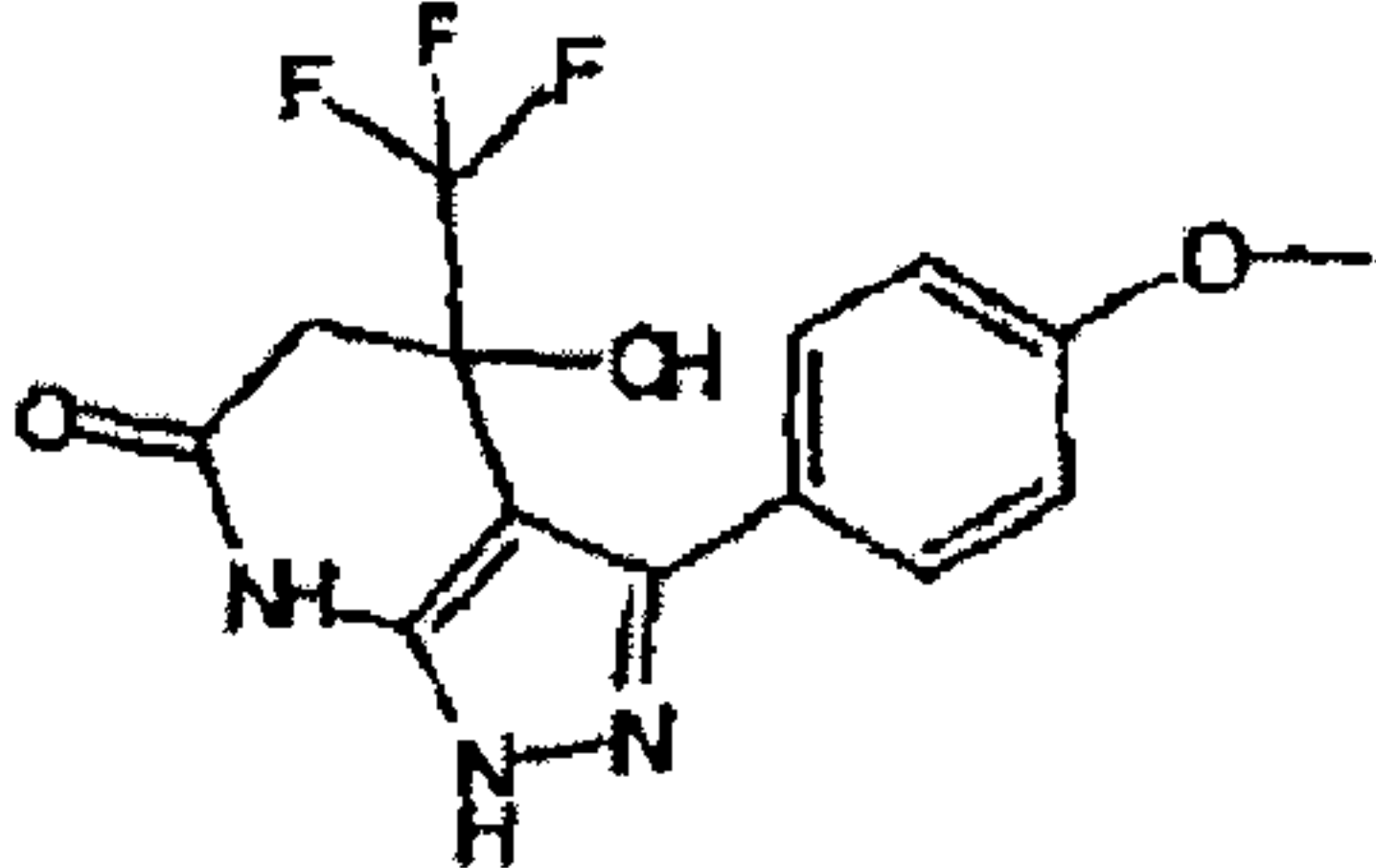
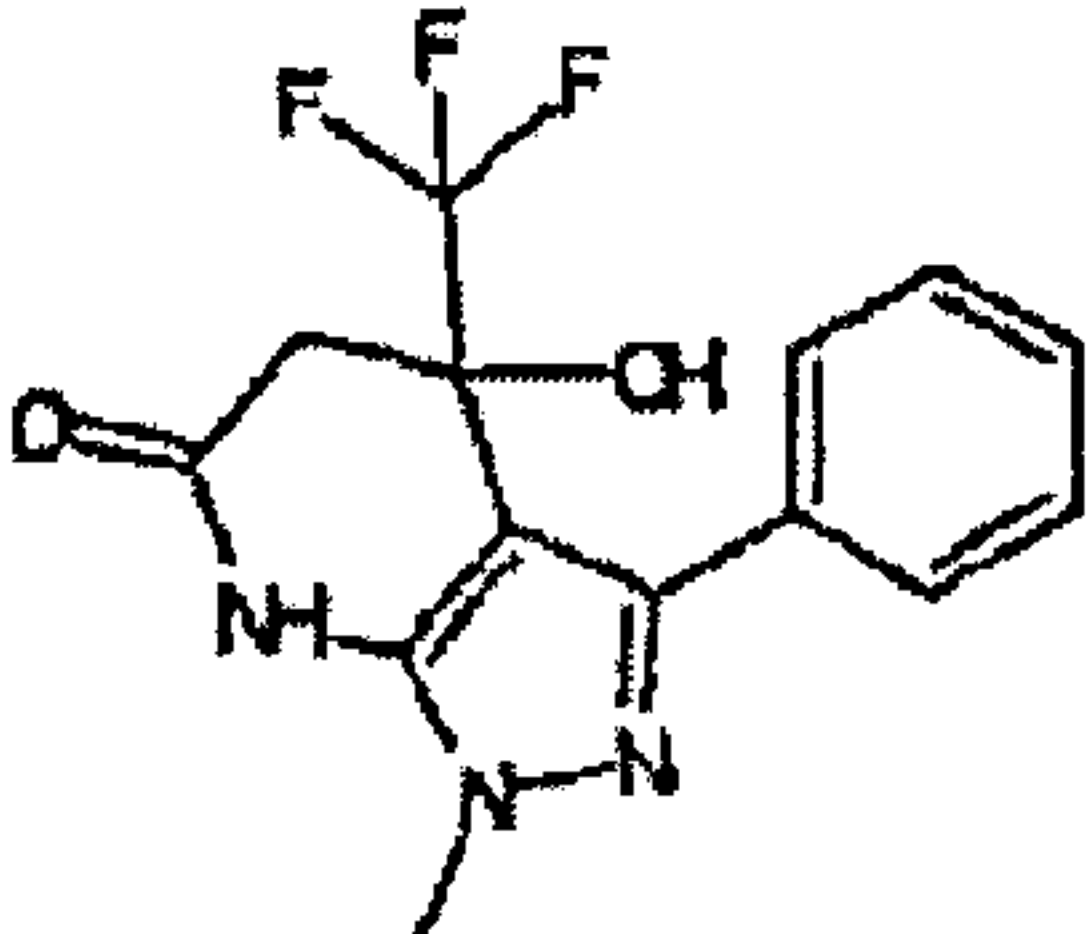
15 or a physiologically acceptable salt, solvate, tautomer or  
stereoisomer thereof, or a mixture thereof in any ratio.

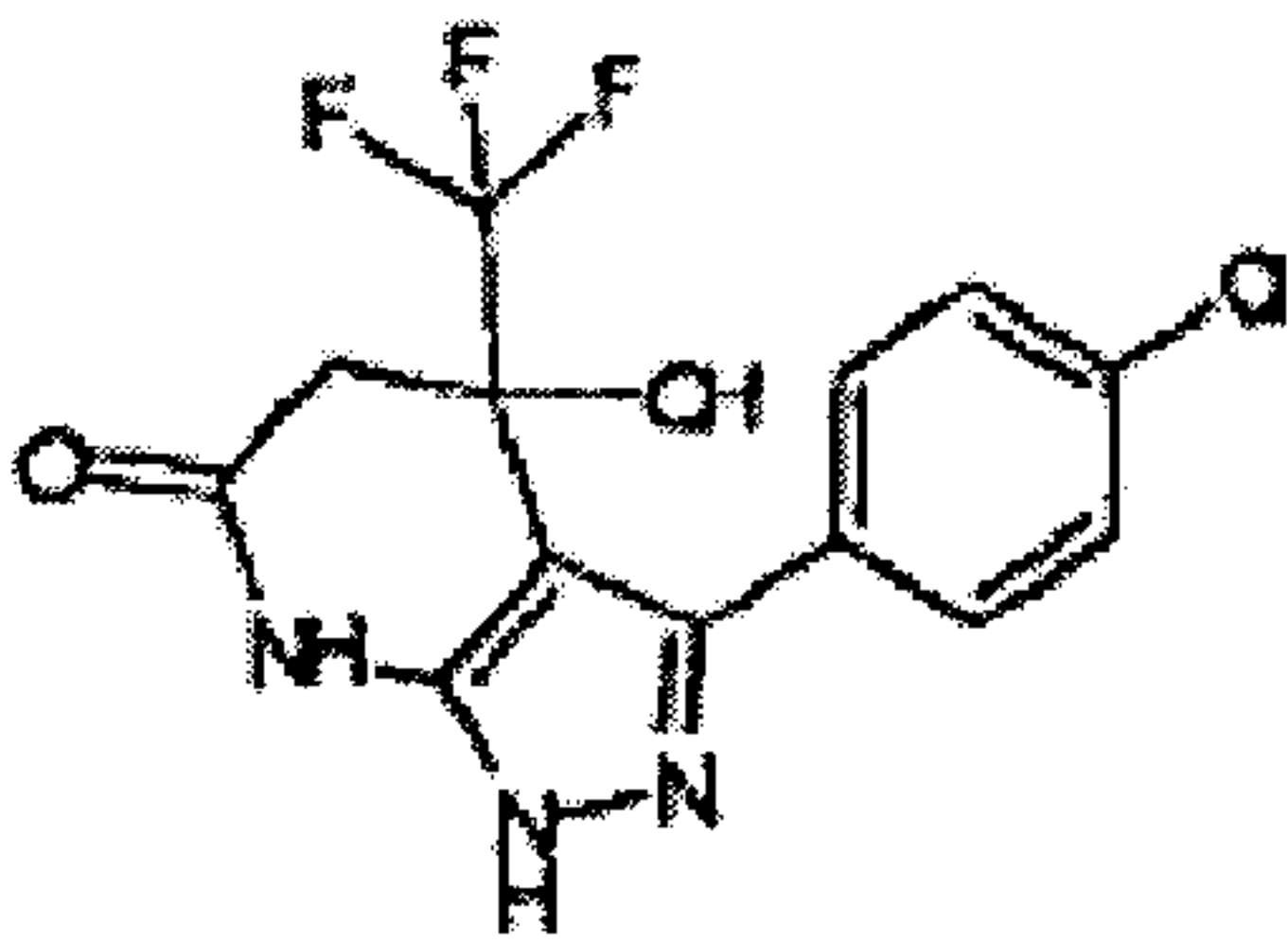
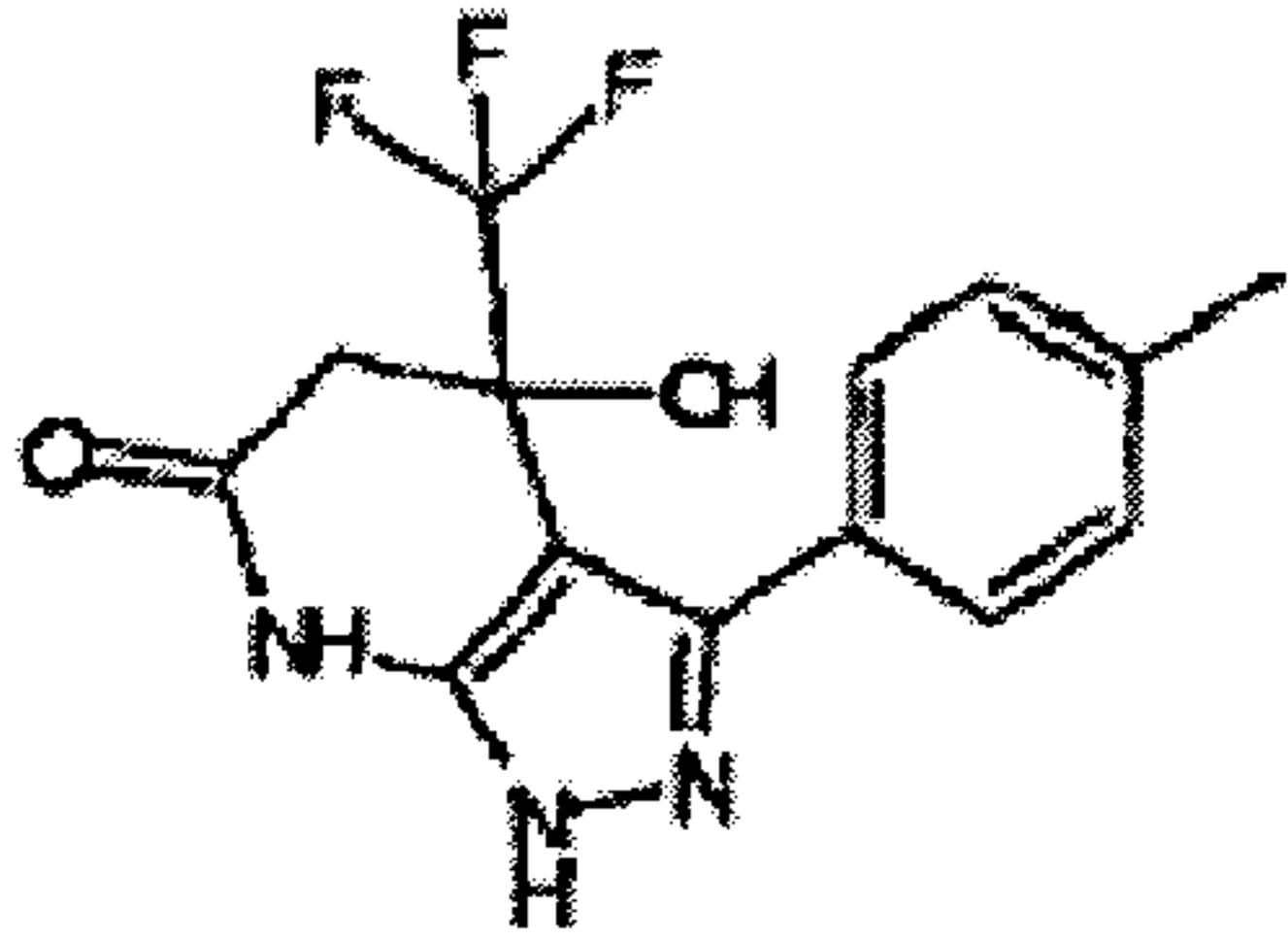
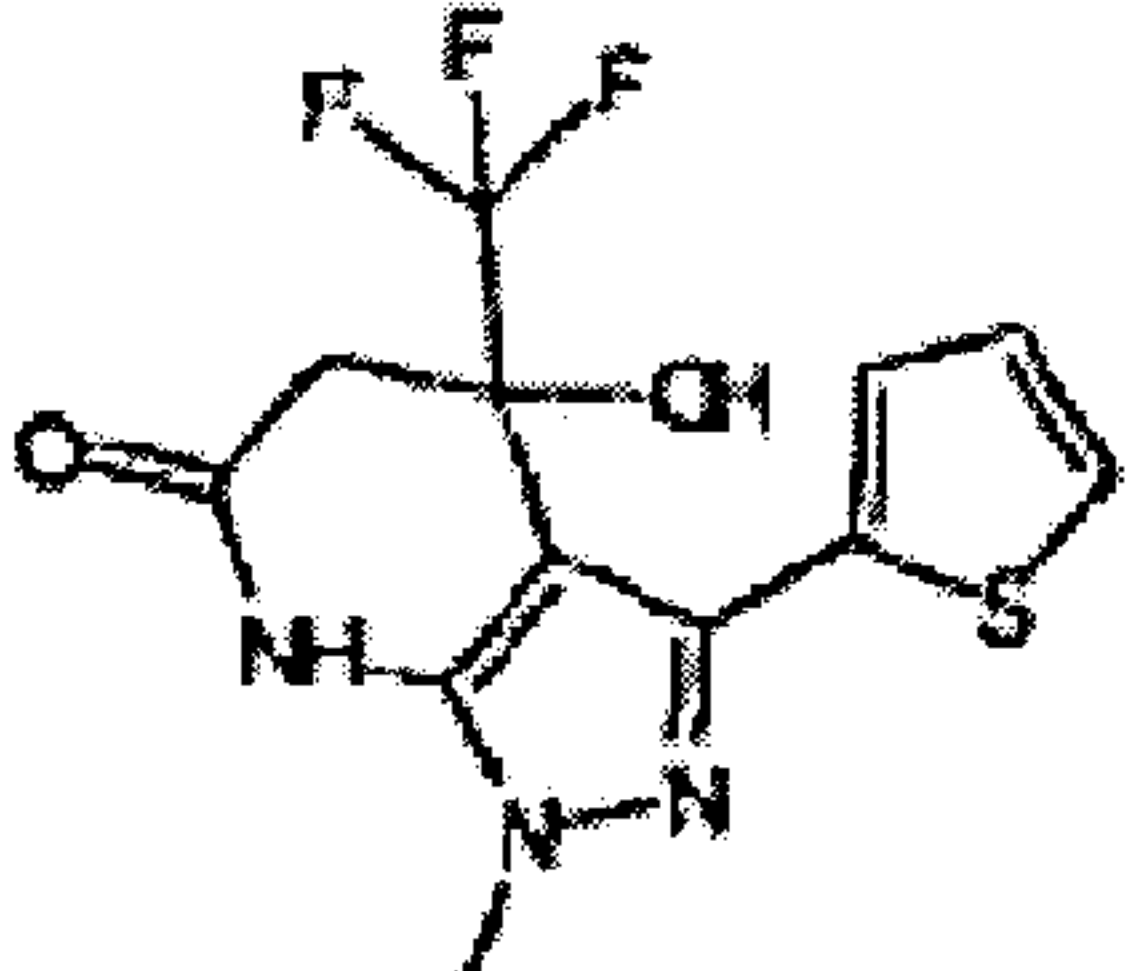
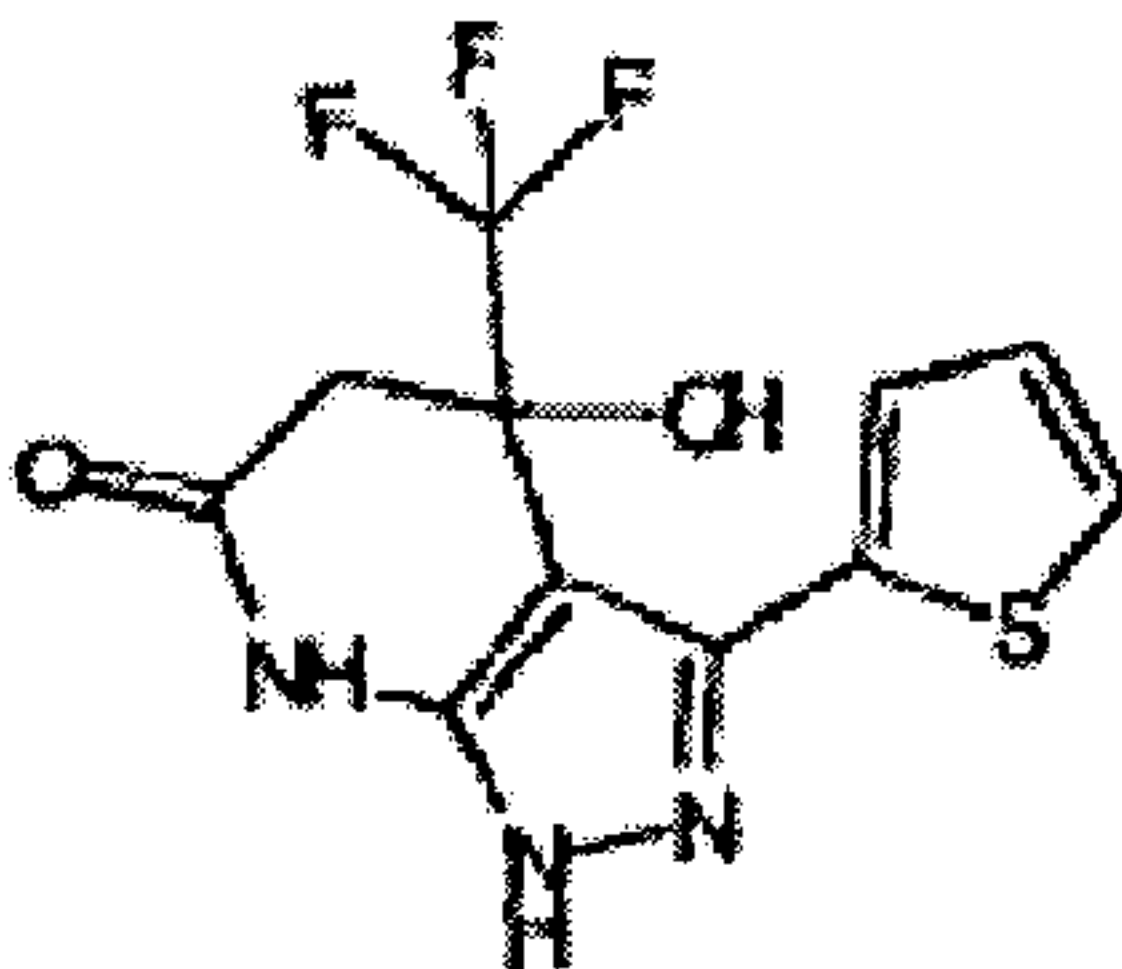
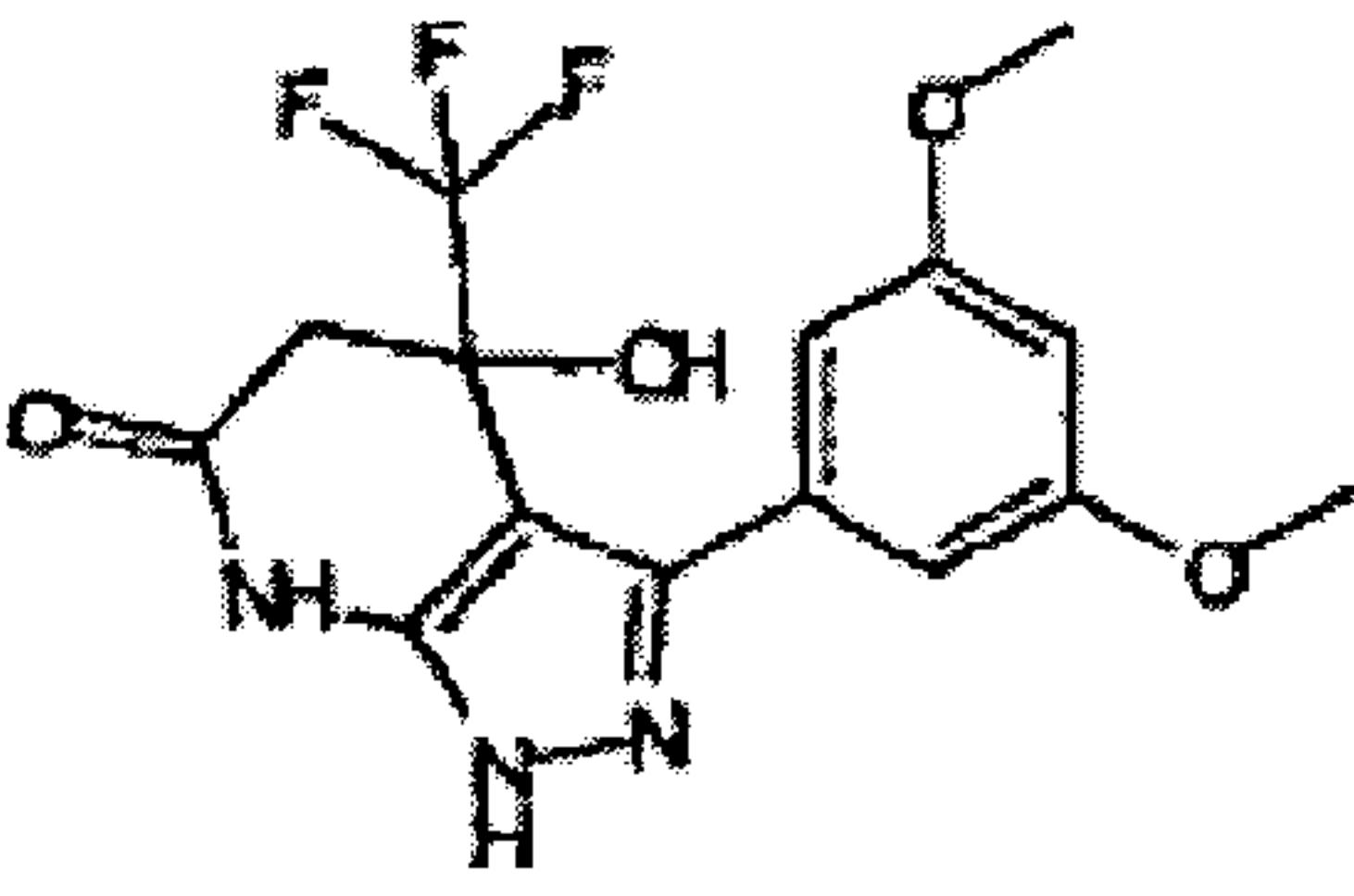
9. The compound according to claim 6, wherein

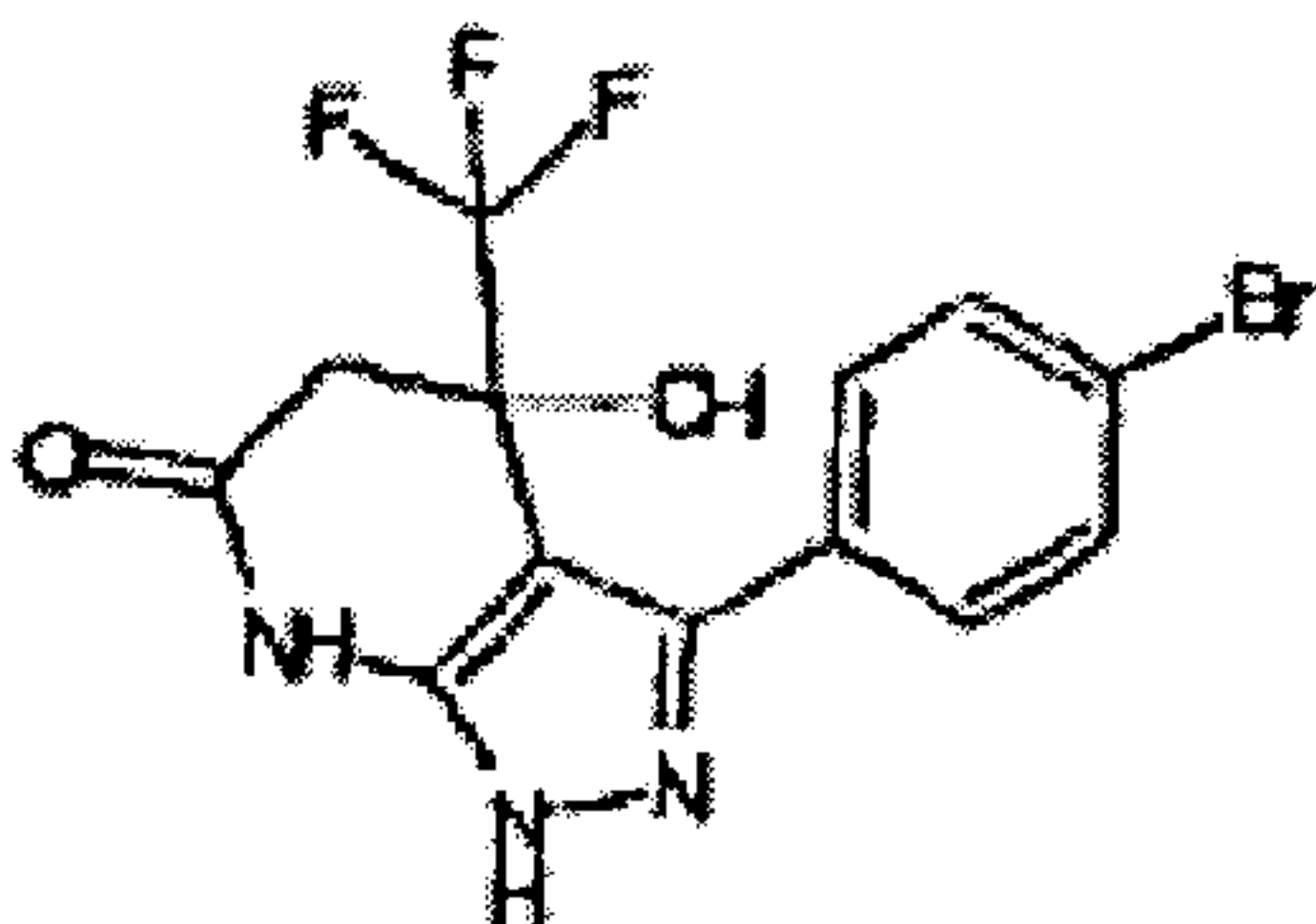
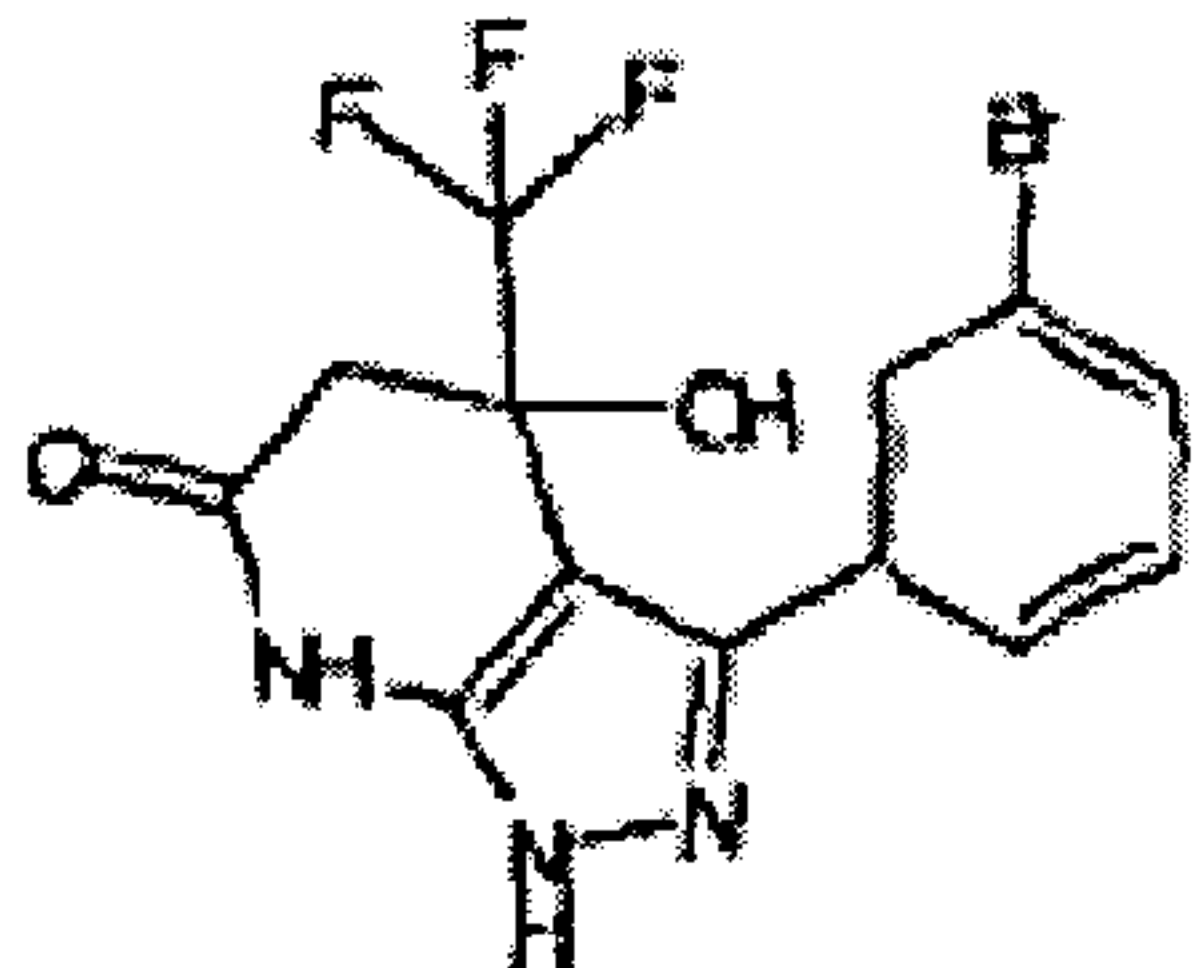
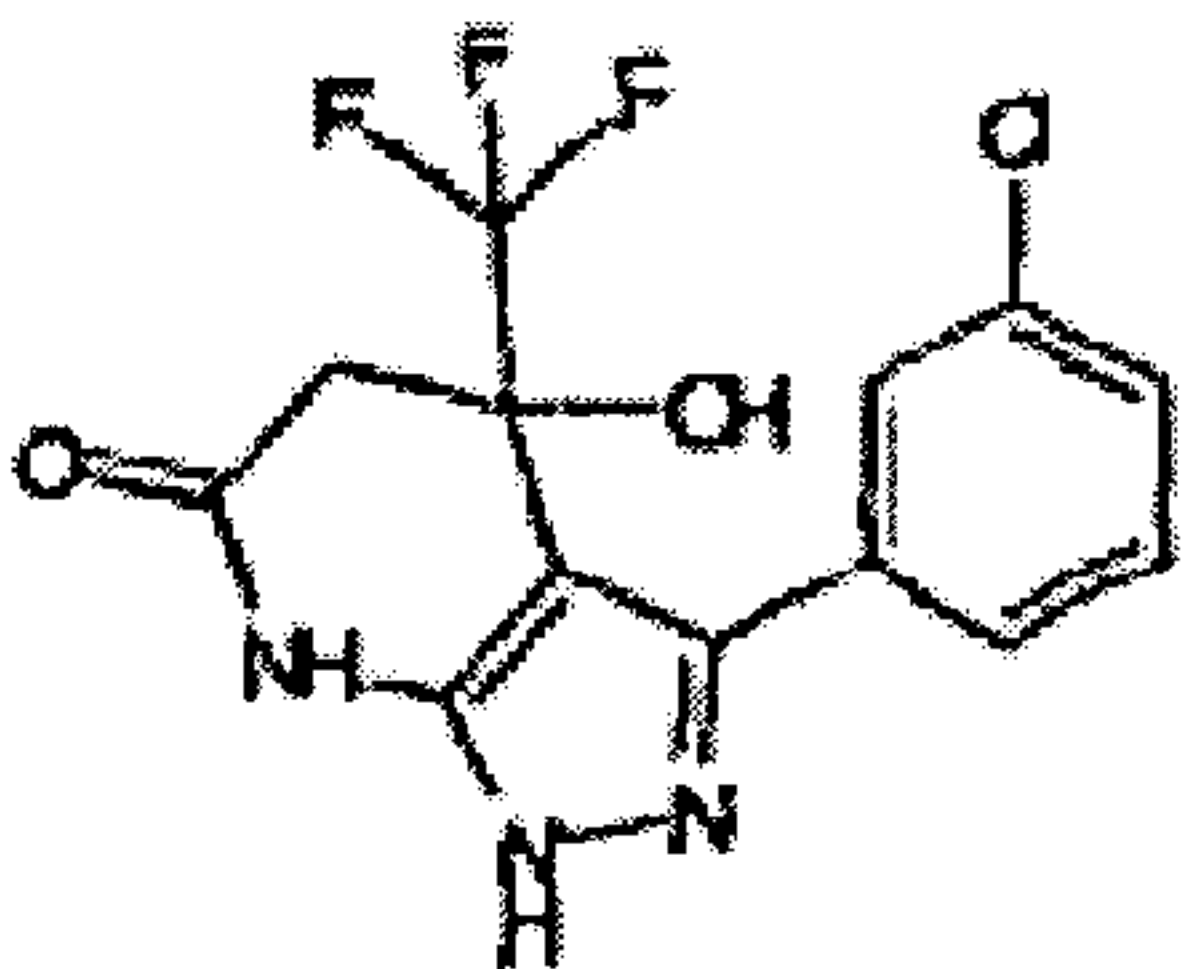
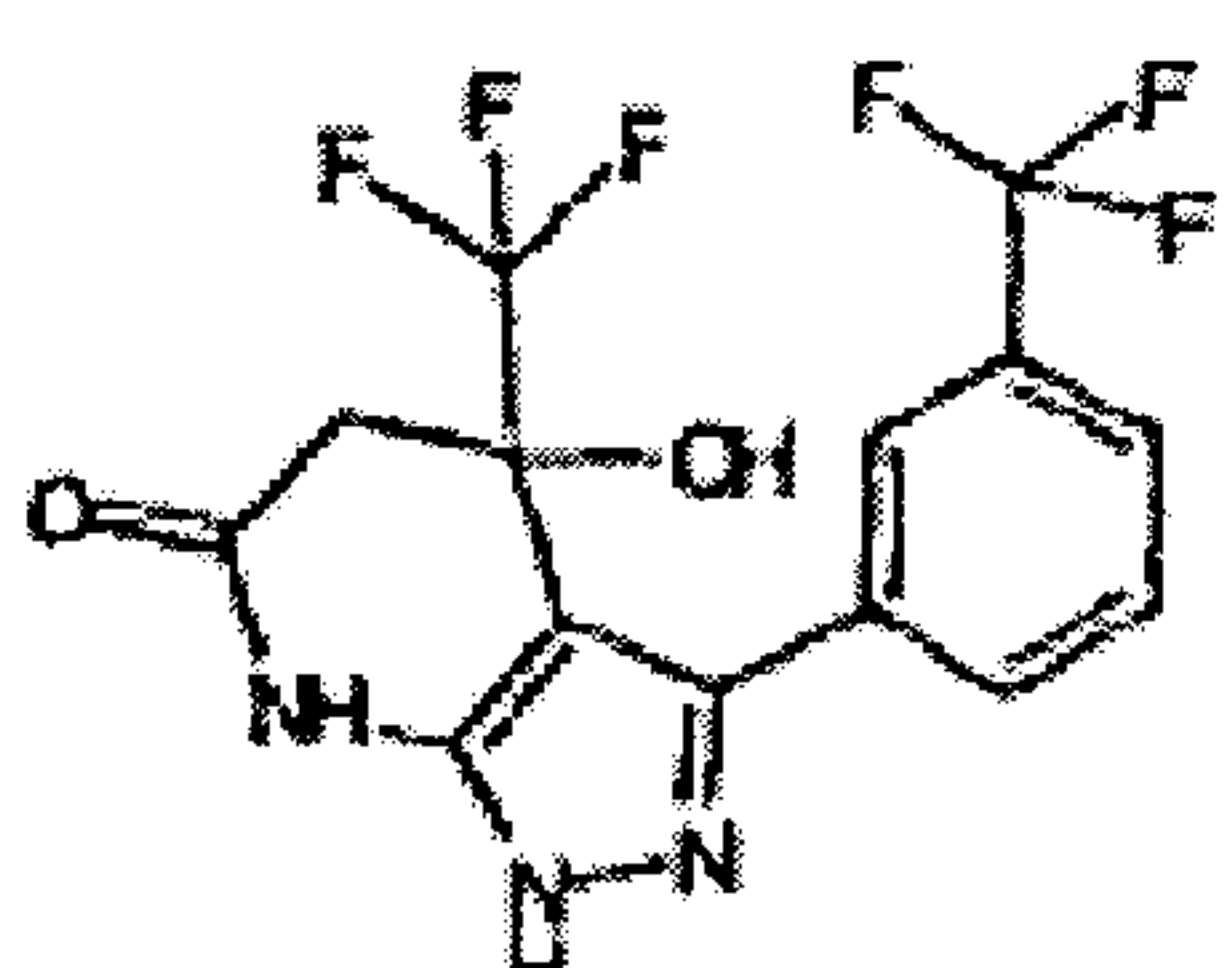
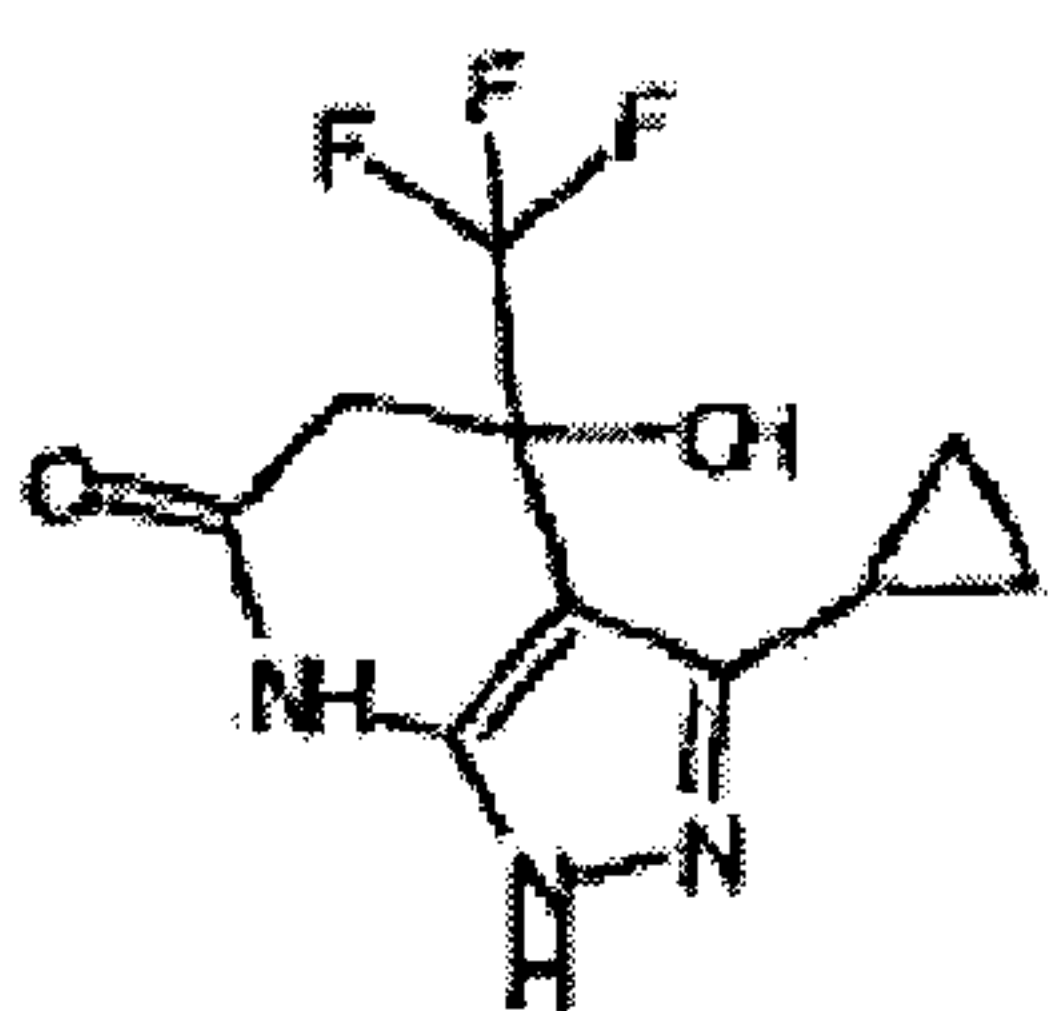
R1 denotes phenyl, thiophenyl or benzyl, which can optionally be  
substituted with one or more substituents selected from halogen,  
F, Cl, Br, I, CF<sub>3</sub>, methyl or methoxy,

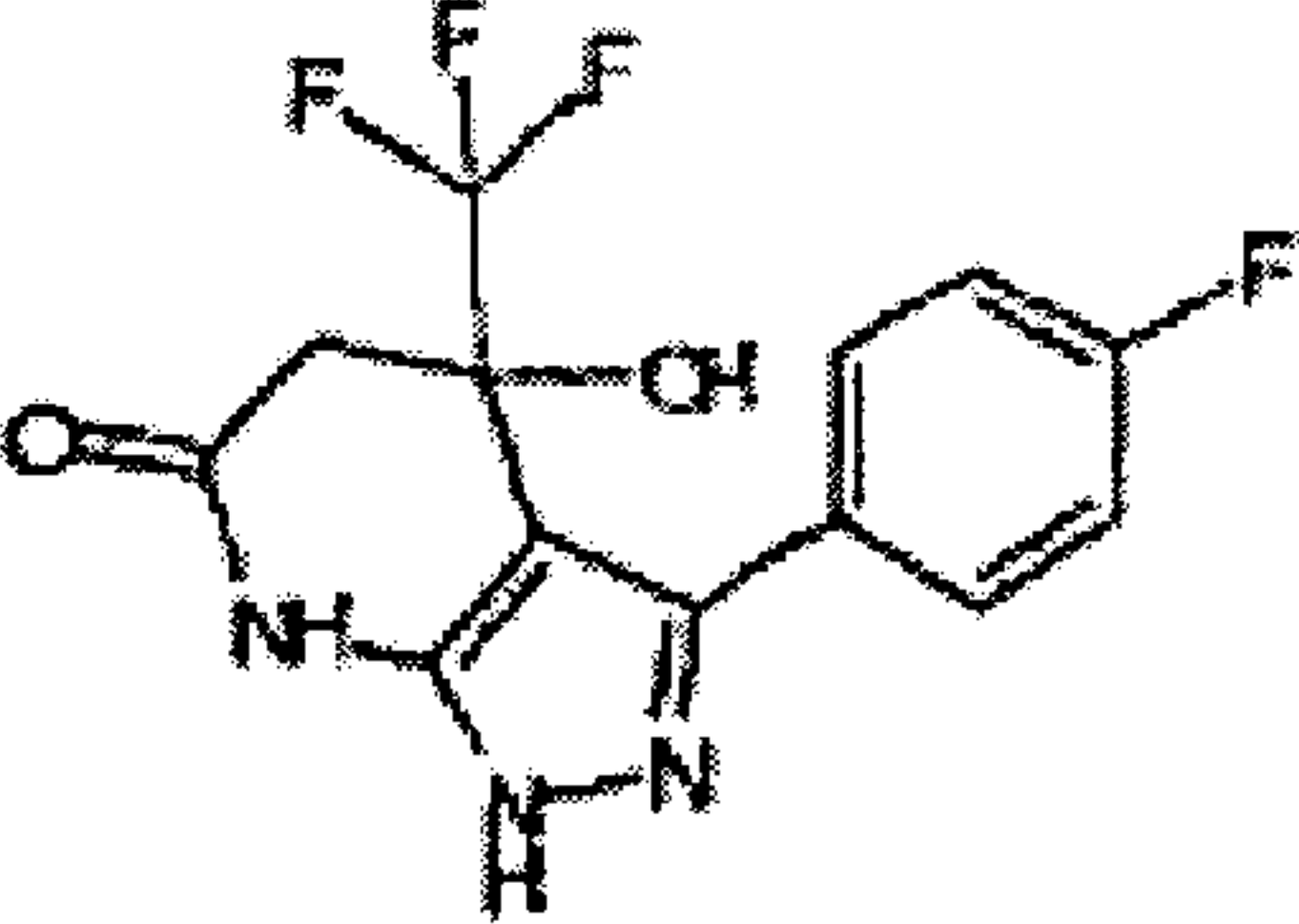
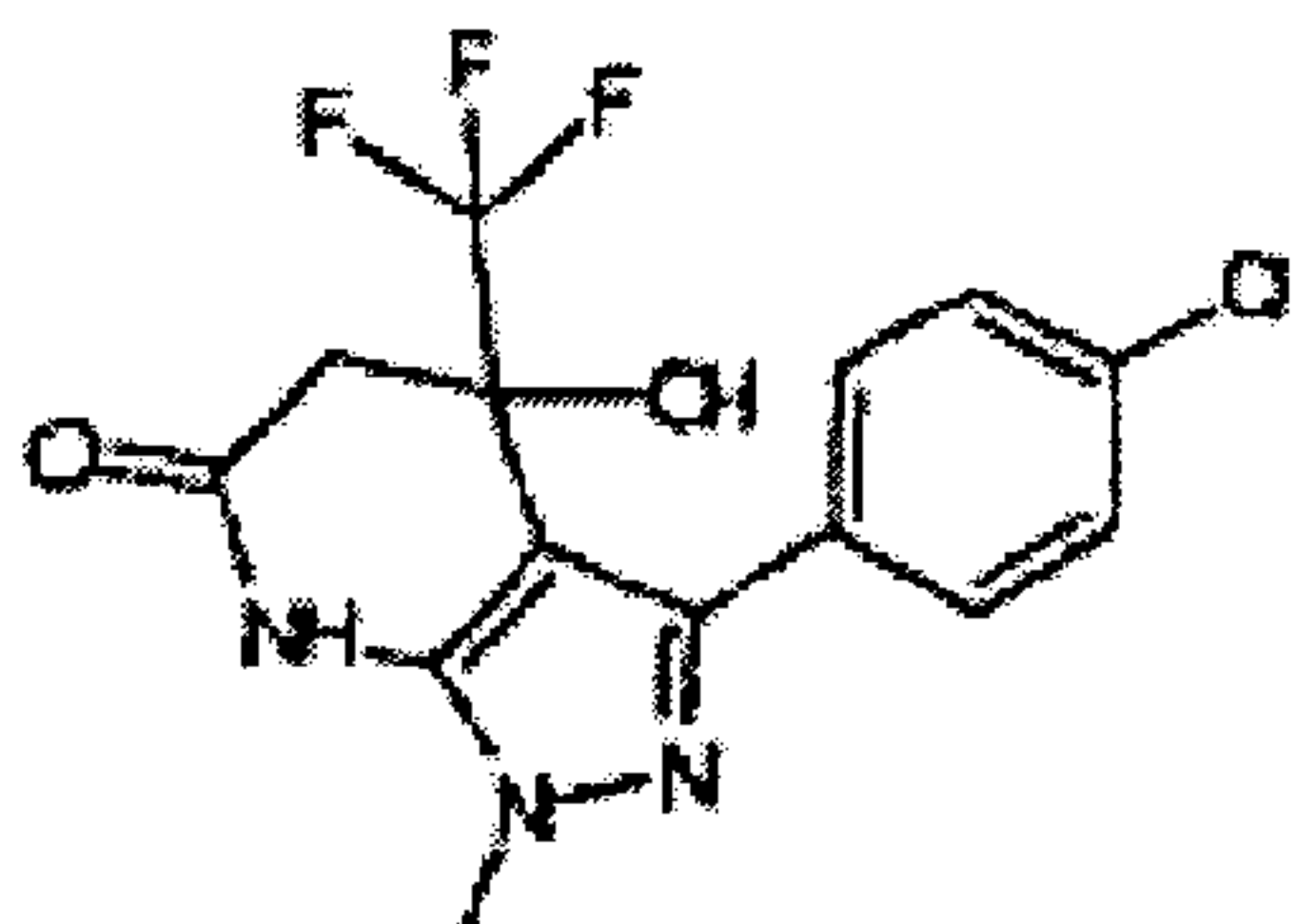
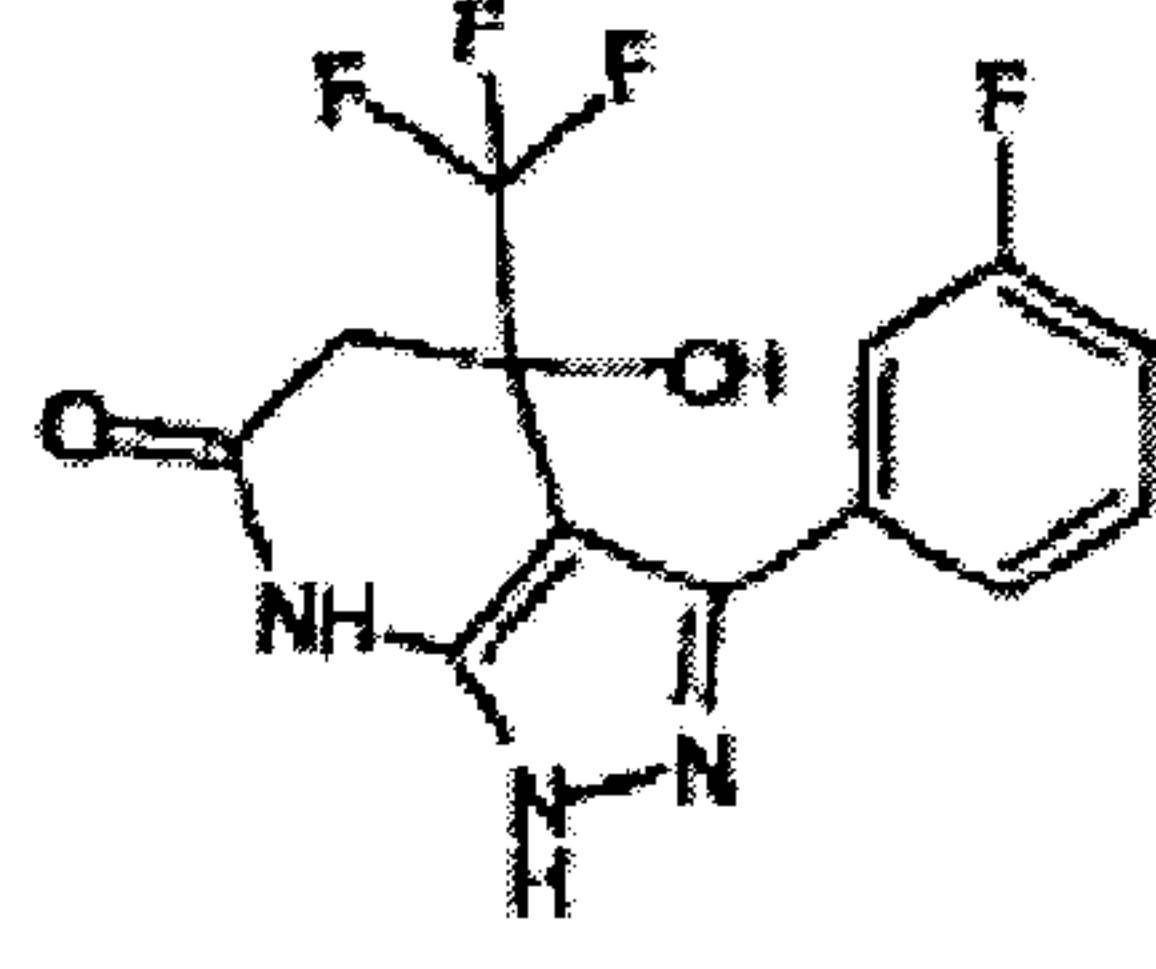
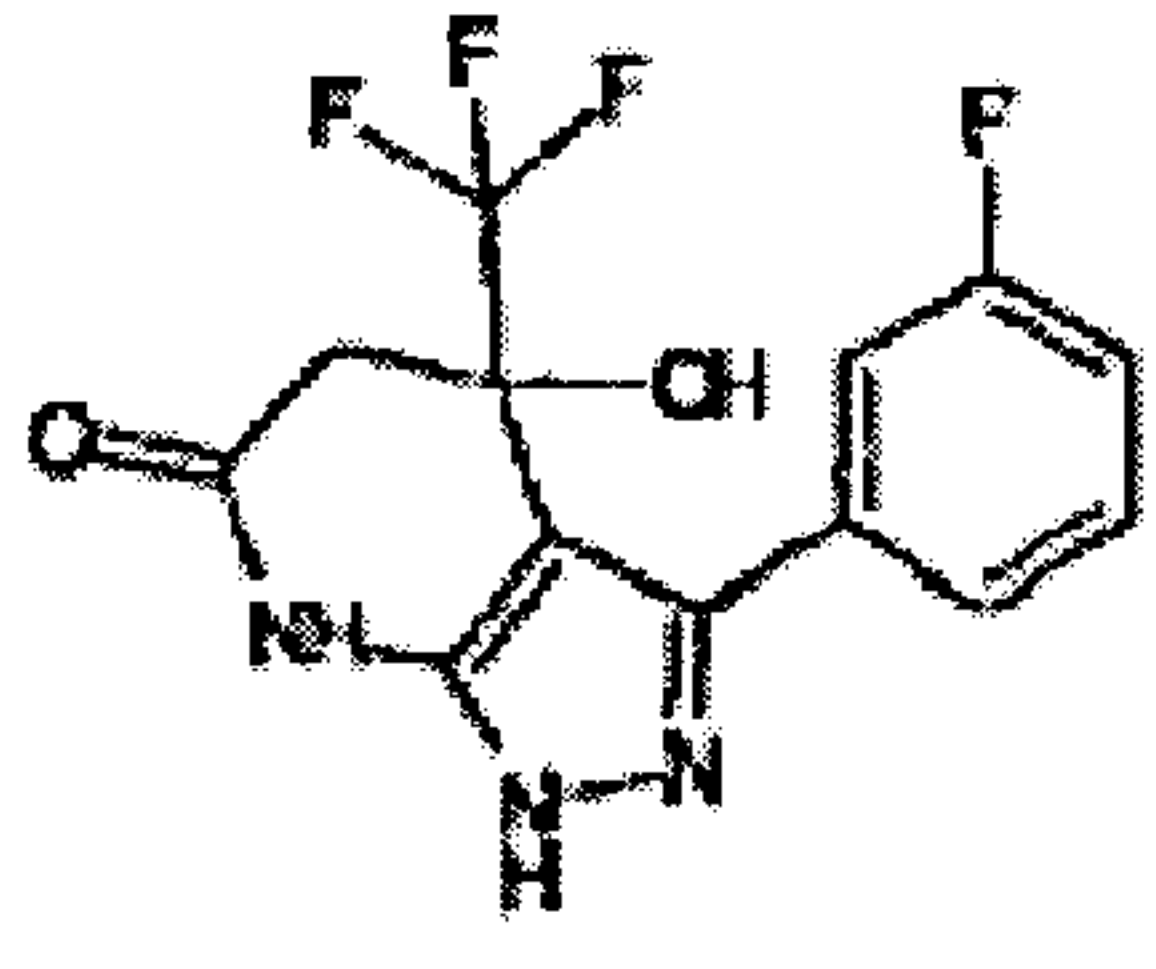
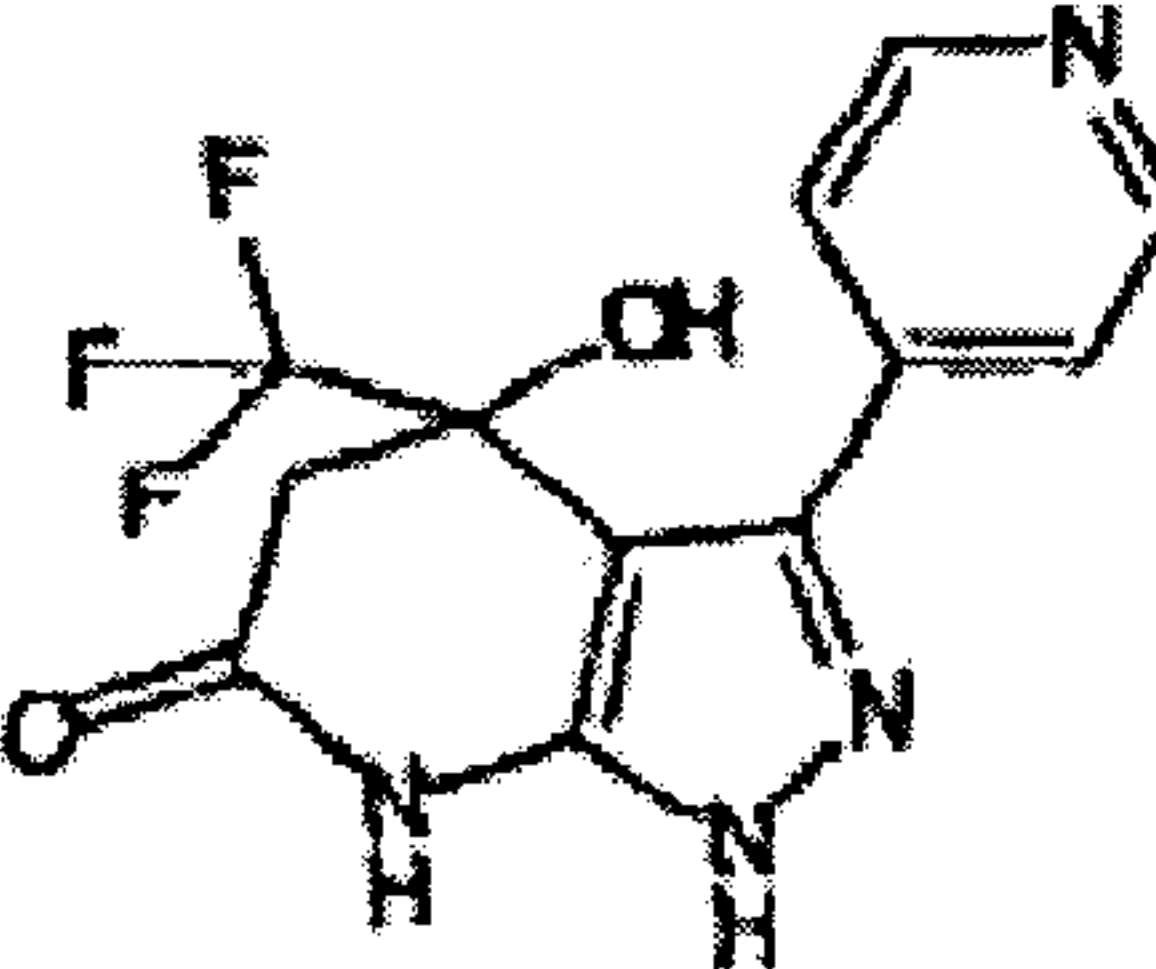
20 or a physiologically acceptable salt, solvate, tautomer or  
stereoisomer thereof, or a mixture thereof in any ratio.

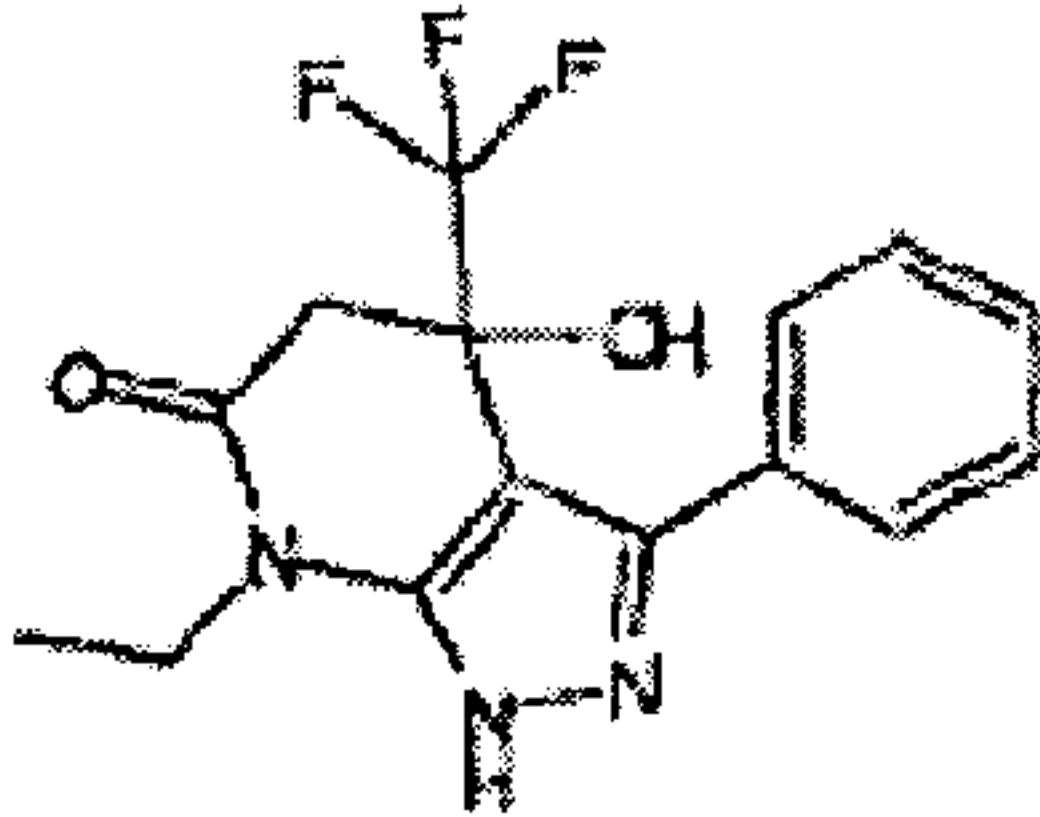
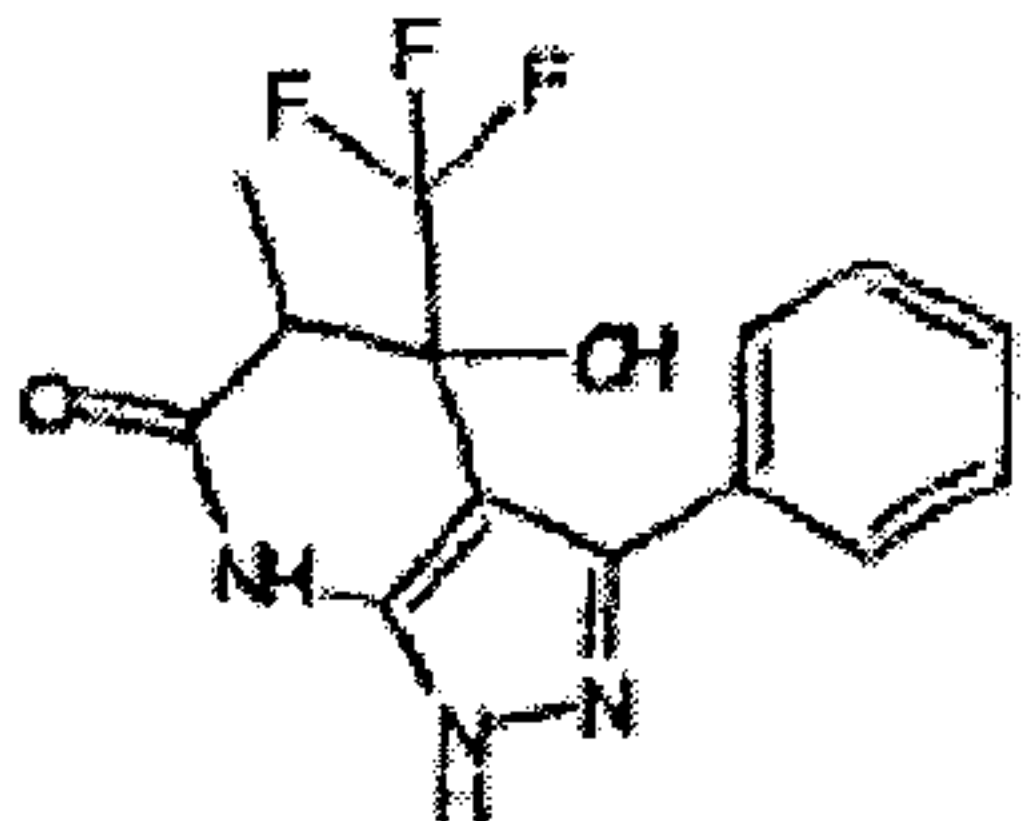
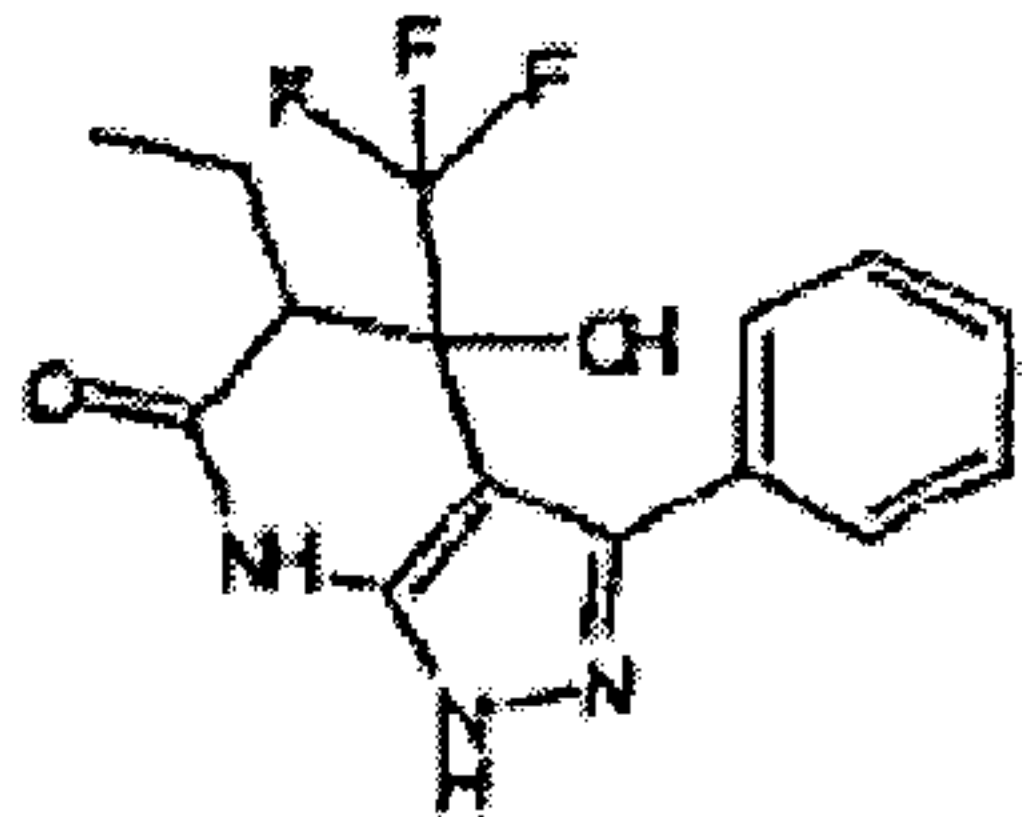
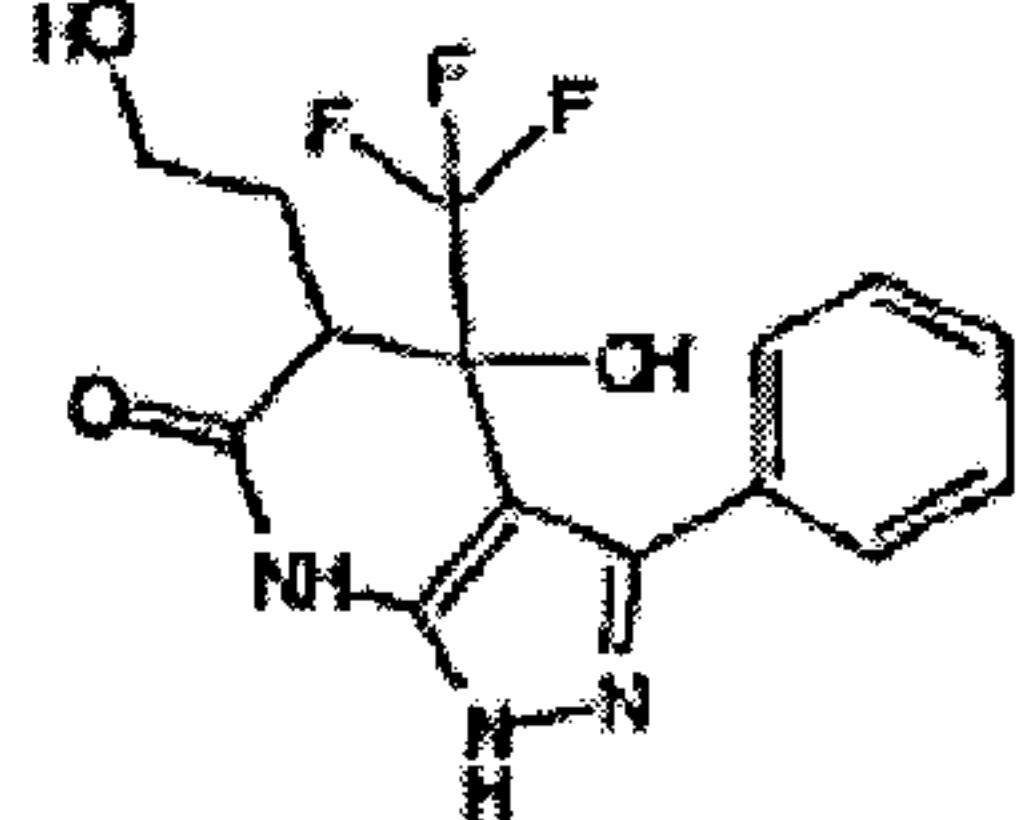
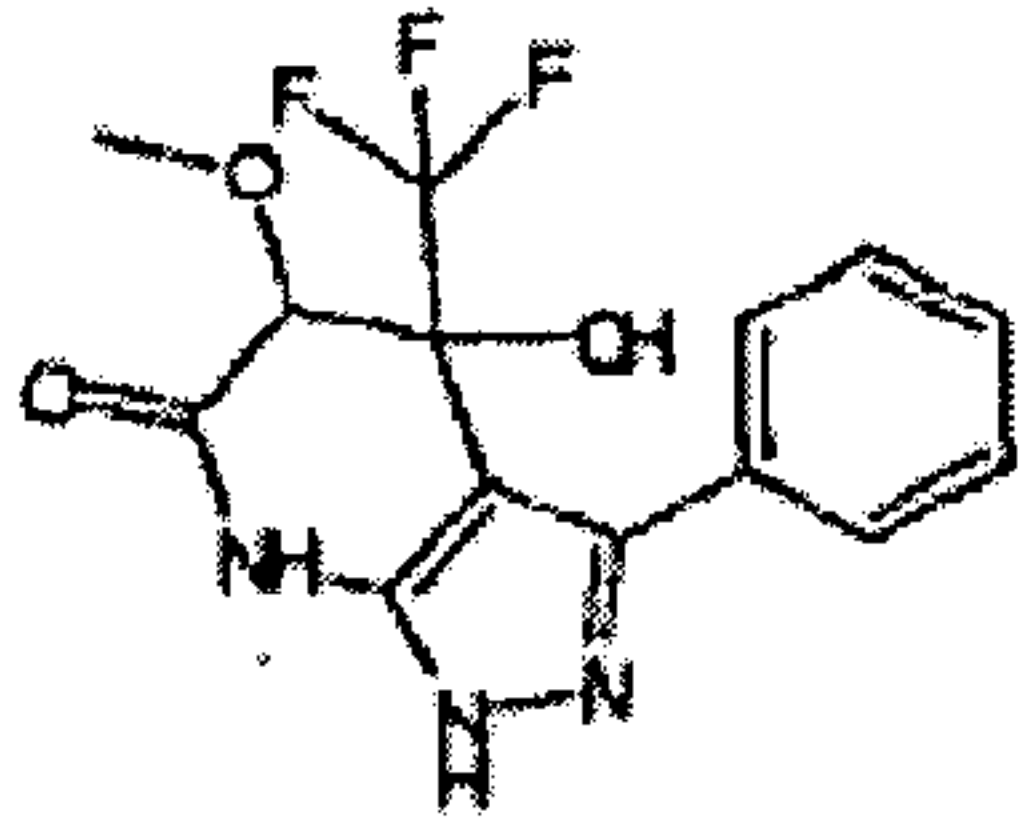
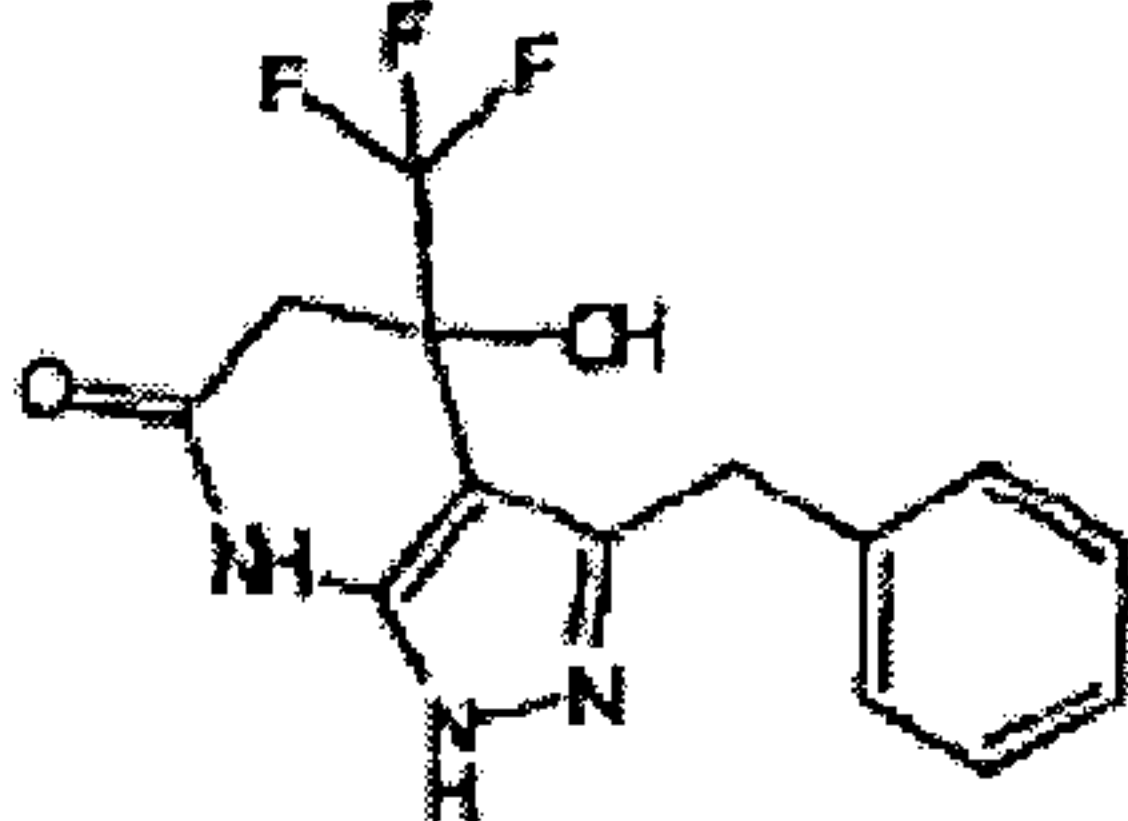
10. The compound according to any one of claims 1 to 9, which is:

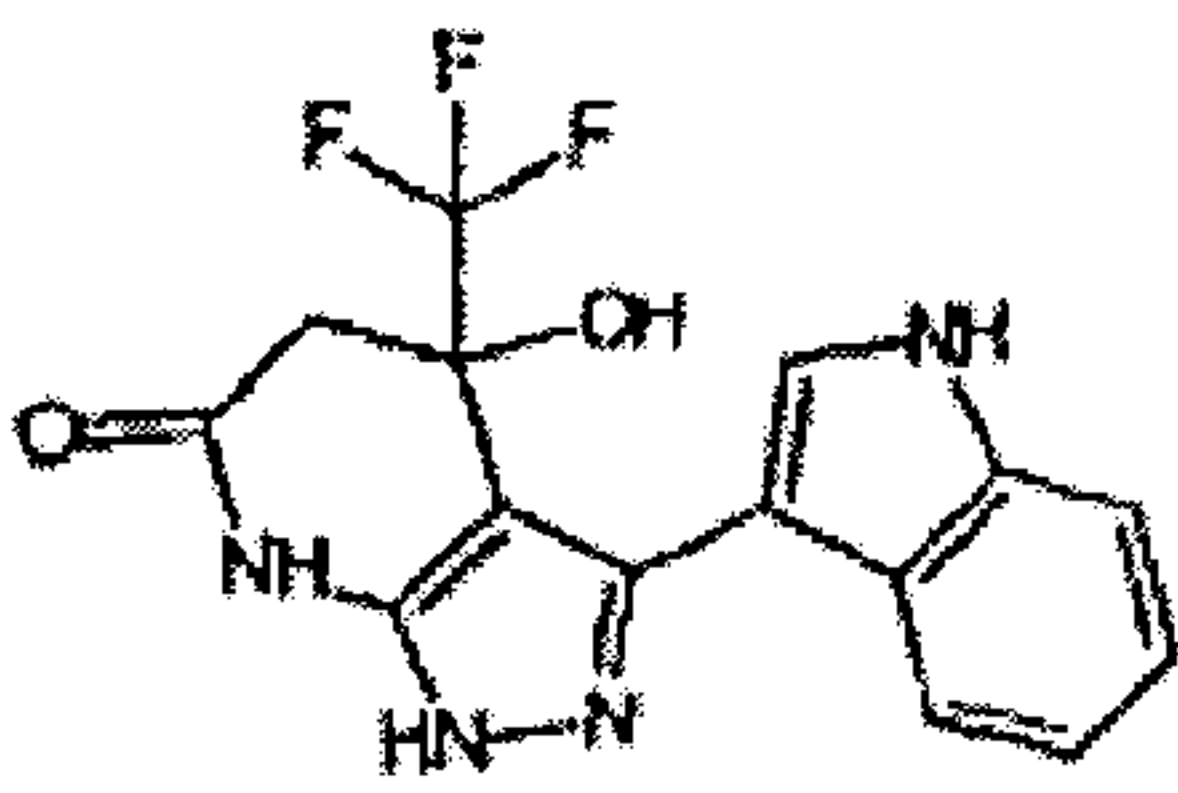
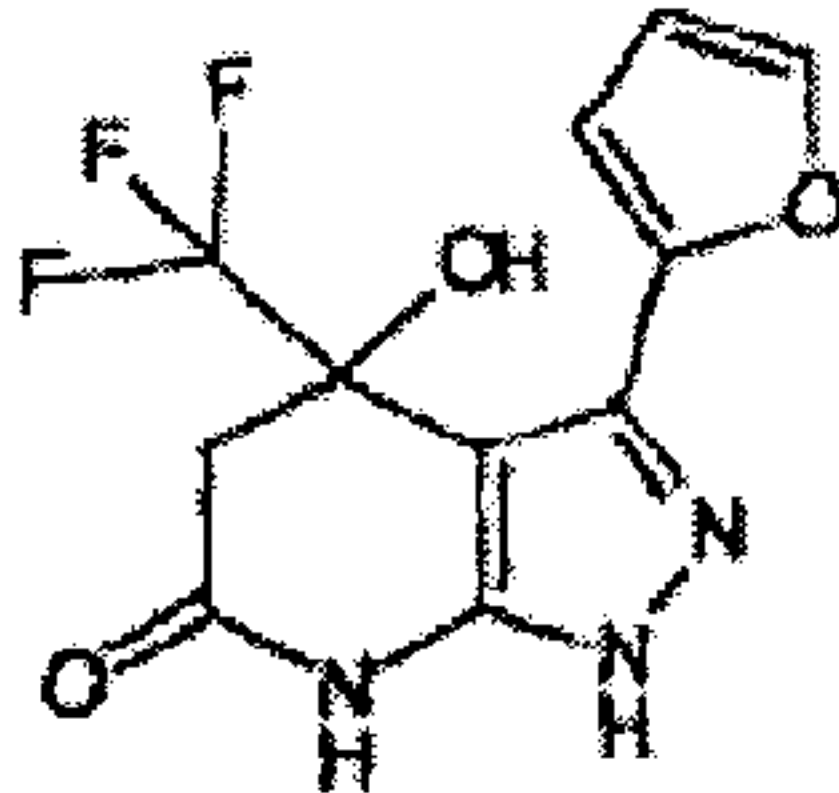
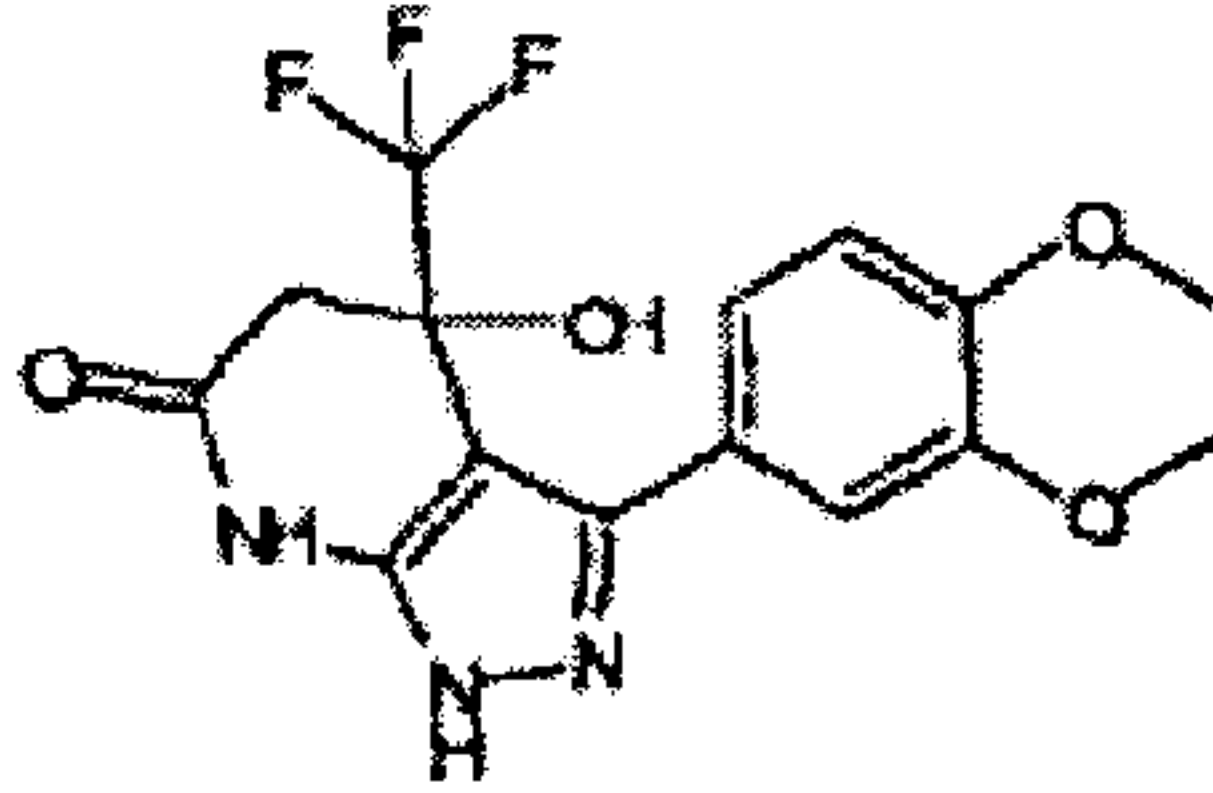
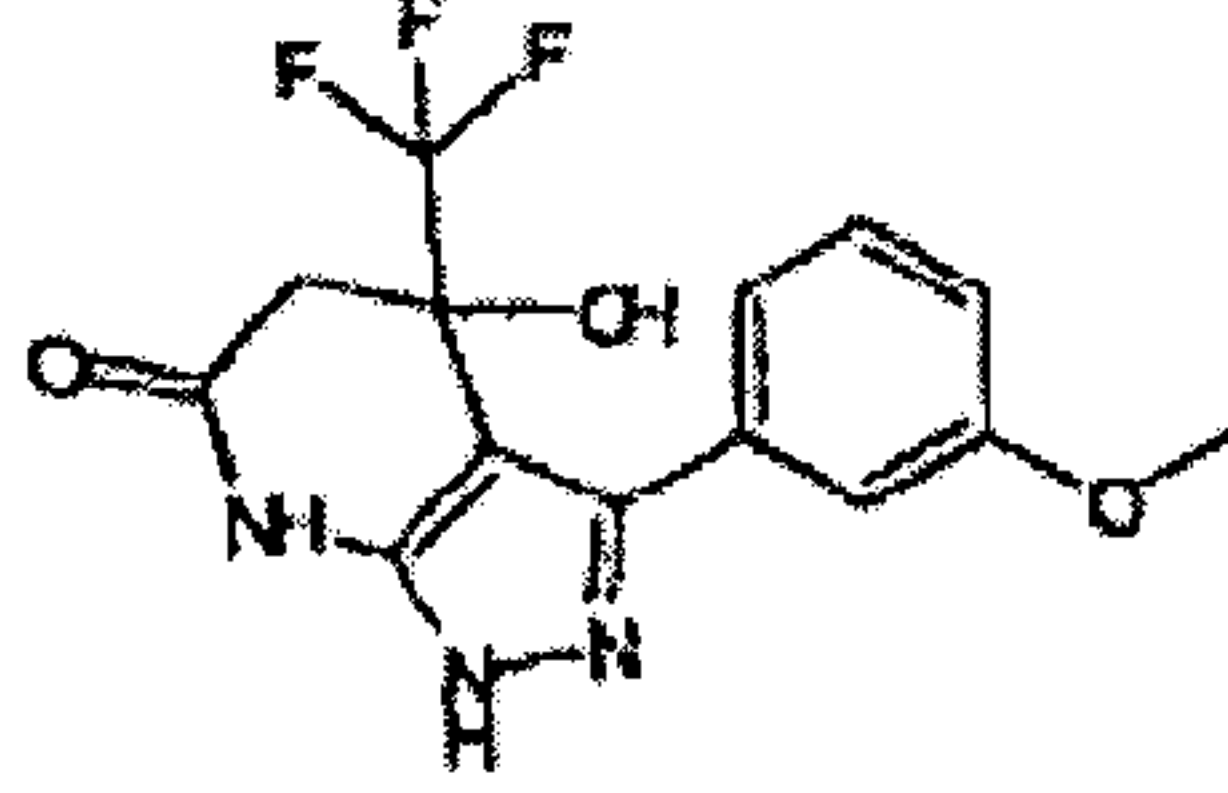
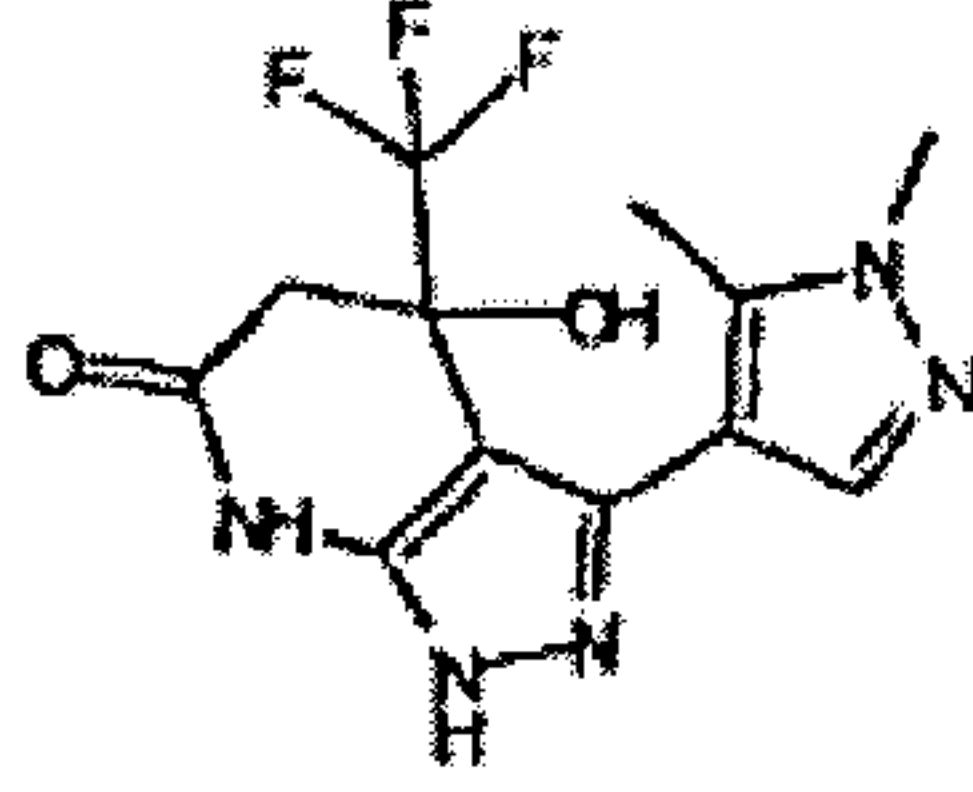
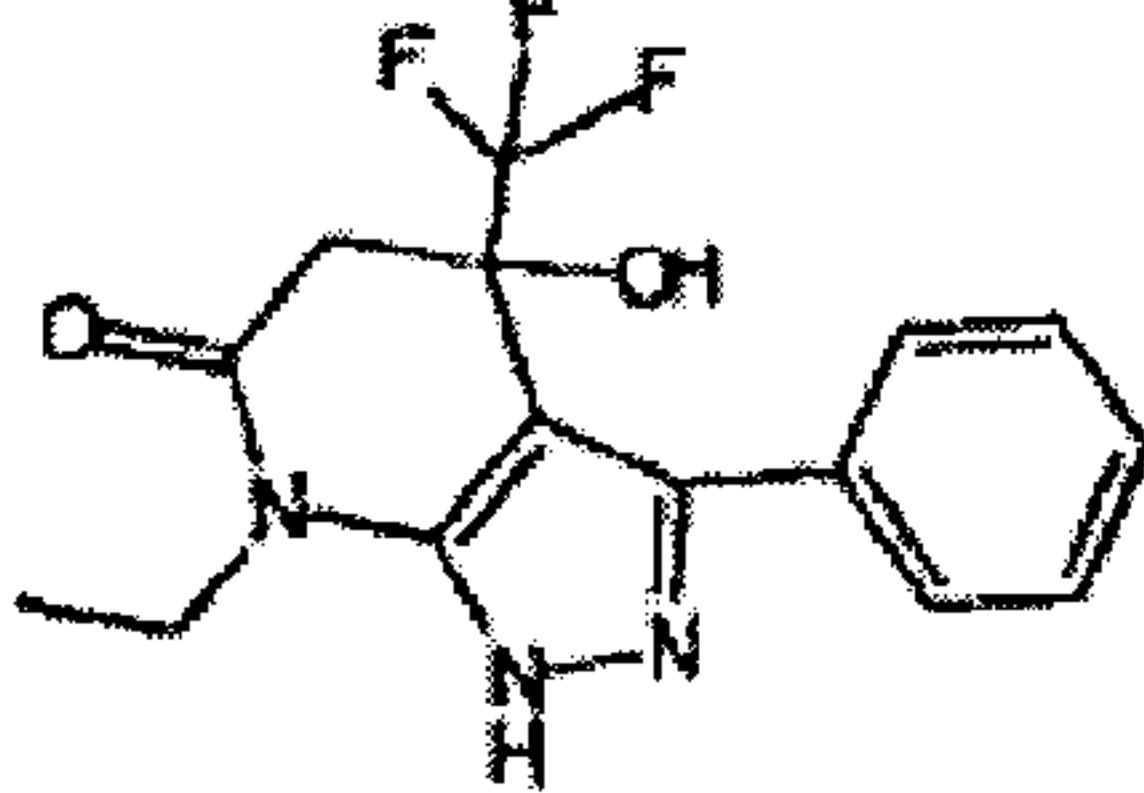
|   |                                                                                     |                                                                                                  |
|---|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| 3 |   | 4-Hydroxy-3-(4-methoxy-phenyl)-4-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-b]pyridin-6-one |
| 4 |  | 4-Hydroxy-1-methyl-3-phenyl-4-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-b]pyridin-6-one    |

|   |                                                                                      |                                                                                                                          |
|---|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|
| 5 |    | 3-(4-Chloro-phenyl)-<br>4-hydroxy-4-<br>trifluoromethyl-<br>1,4,5,7-tetrahydro-<br>pyrazolo[3,4-<br>b]pyridin-6-one      |
| 6 |   | 4-Hydroxy-3-p-tolyl-4-<br>trifluoromethyl-<br>1,4,5,7-tetrahydro-<br>pyrazolo[3,4-<br>b]pyridin-6-one                    |
| 7 |  | 4-Hydroxy-1-methyl-<br>3-thiophen-2-yl-4-<br>trifluoromethyl-<br>1,4,5,7-tetrahydro-<br>pyrazolo[3,4-<br>b]pyridin-6-one |
| 8 |  | 4-Hydroxy-3-<br>thiophen-2-yl-4-<br>trifluoromethyl-<br>1,4,5,7-tetrahydro-<br>pyrazolo[3,4-<br>b]pyridin-6-one          |
| 9 |  | 3-(3,5-Dimethoxy-<br>phenyl)-4-hydroxy-4-<br>trifluoromethyl-<br>1,4,5,7-tetrahydro-<br>pyrazolo[3,4-<br>b]pyridin-6-one |

|    |                                                                                      |                                                                                                                                  |
|----|--------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| 12 |    | 3-(4-Bromo-phenyl)-<br>4-hydroxy-4-<br>trifluoromethyl-<br>1,4,5,7-tetrahydro-<br>pyrazolo[3,4-<br>b]pyridin-6-one               |
| 13 |   | 3-(3-Bromo-phenyl)-<br>4-hydroxy-4-<br>trifluoromethyl-<br>1,4,5,7-tetrahydro-<br>pyrazolo[3,4-<br>b]pyridin-6-one               |
| 14 |  | 3-(3-Chloro-phenyl)-<br>4-hydroxy-4-<br>trifluoromethyl-<br>1,4,5,7-tetrahydro-<br>pyrazolo[3,4-<br>b]pyridin-6-one              |
| 15 |  | 4-Hydroxy-4-<br>trifluoromethyl-3-(3-<br>trifluoromethyl-<br>phenyl)-1,4,5,7-<br>tetrahydro-<br>pyrazolo[3,4-<br>b]pyridin-6-one |
| 16 |  | 3-Cyclopropyl-4-<br>hydroxy-4-<br>trifluoromethyl-<br>1,4,5,7-tetrahydro-<br>pyrazolo[3,4-<br>b]pyridin-6-one                    |

|    |                                                                                      |                                                                                                                              |
|----|--------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|
| 17 |    | 3-(4-Fluoro-phenyl)-<br>4-hydroxy-4-<br>trifluoromethyl-<br>1,4,5,7-tetrahydro-<br>pyrazolo[3,4-<br>b]pyridin-6-one          |
| 18 |   | 3-(4-Chloro-phenyl)-<br>4-hydroxy-1-methyl-<br>4-trifluoromethyl-<br>1,4,5,7-tetrahydro-<br>pyrazolo[3,4-<br>b]pyridin-6-one |
| 20 |   | (-)-3-(3-Fluoro-<br>phenyl)-4-hydroxy-4-<br>trifluoromethyl-<br>1,4,5,7-tetrahydro-<br>pyrazolo[3,4-<br>b]pyridin-6-one      |
| 21 |  | (+)-3-(3-Fluoro-<br>phenyl)-4-hydroxy-4-<br>trifluoromethyl-<br>1,4,5,7-tetrahydro-<br>pyrazolo[3,4-<br>b]pyridin-6-one      |
| 22 |  | 4-Hydroxy-3-pyridin-<br>4-yl-4-trifluoromethyl-<br>1,4,5,7-tetrahydro-<br>pyrazolo[3,4-<br>b]pyridin-6-one                   |

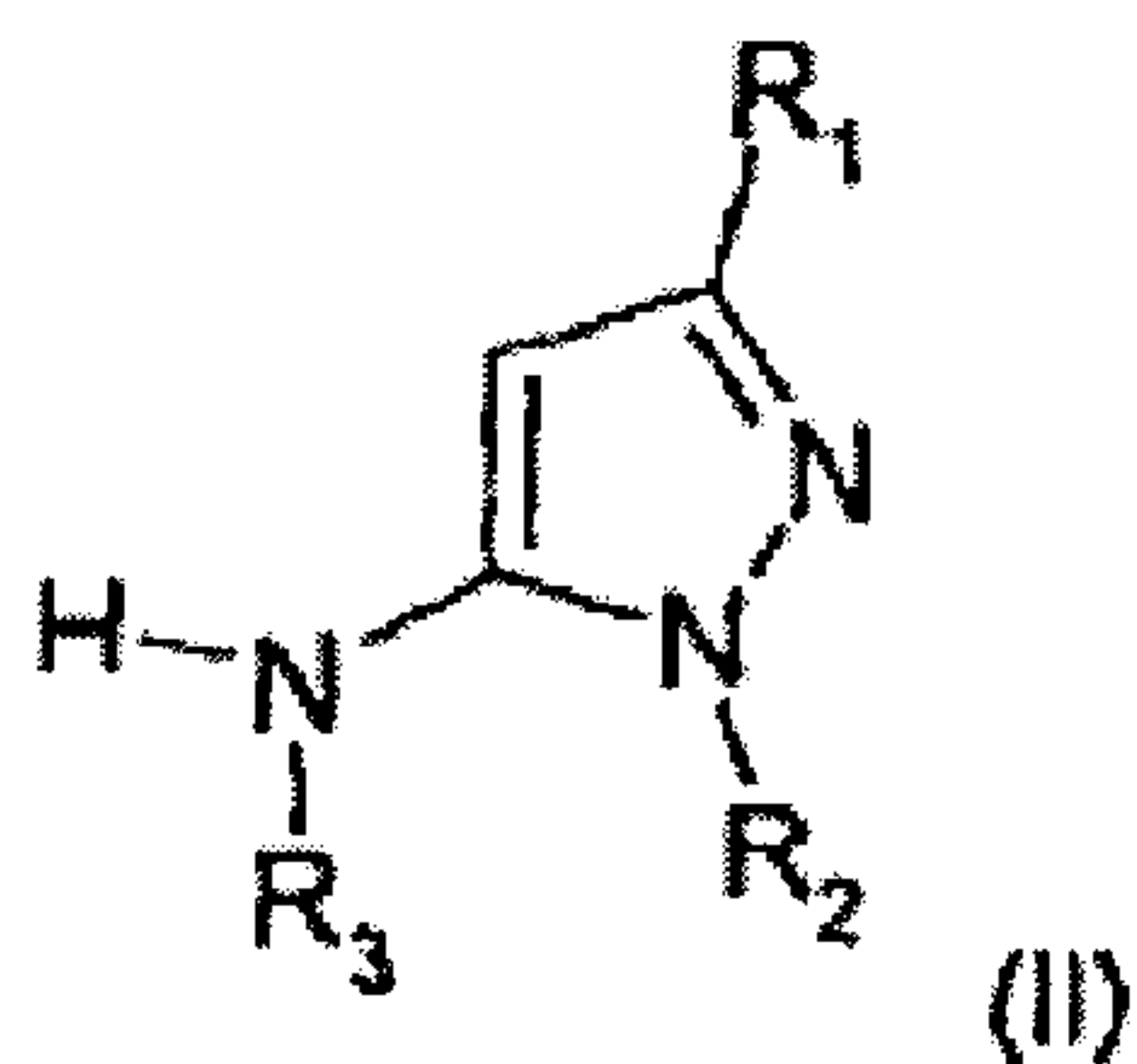
|    |                                                                                      |                                                                                                         |
|----|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|
| 23 |    | 4-Hydroxy-7-ethyl-3-phenyl-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one             |
| 24 |   | 4-Hydroxy-5-methyl-3-phenyl-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one            |
| 25 |  | 4-Hydroxy-5-ethyl-3-phenyl-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one             |
| 26 |  | 4-Hydroxy-5-(2-hydroxy-ethyl)-3-phenyl-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one |
| 27 |  | 4-Hydroxy-5-methoxy-3-phenyl-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one           |
| 28 |  | 3-Benzyl-4-hydroxy-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one                     |

|    |                                                                                      |                                                                                                             |
|----|--------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|
| 29 |    | 4-Hydroxy-3-(1H-indol-3-yl)-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one                |
| 30 |   | 3-Furan-2-yl-4-hydroxy-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one                     |
| 31 |  | 3-(3,4-Dimethoxyphenyl)-4-hydroxy-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one          |
| 32 |  | 4-Hydroxy-3-(3-methoxyphenyl)-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one              |
| 33 |  | 3-(1,5-Dimethyl-1H-pyrazol-4-yl)-4-hydroxy-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one |
| 34 |  | 7-Ethyl-4-hydroxy-3-phenyl-4-trifluoromethyl-1,4,5,7-tetrahydropyrazolo[3,4-b]pyridin-6-one                 |

or a physiologically acceptable salt, solvate, tautomer or stereoisomer thereof, or a mixture thereof in any ratio.

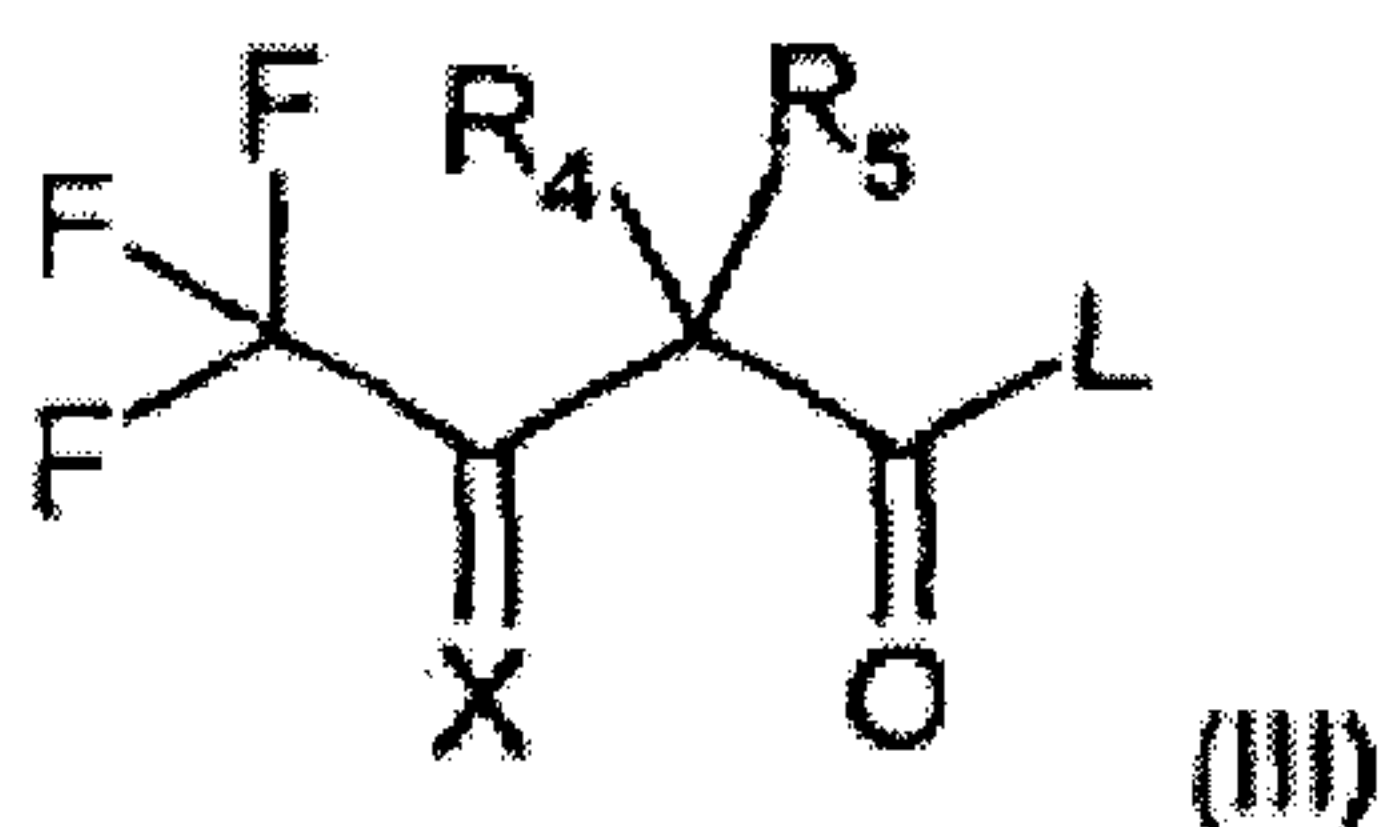
11. Process for manufacturing a compound of formula (I) comprising the steps of:

- 5 (a) reacting a compound of formula (II)



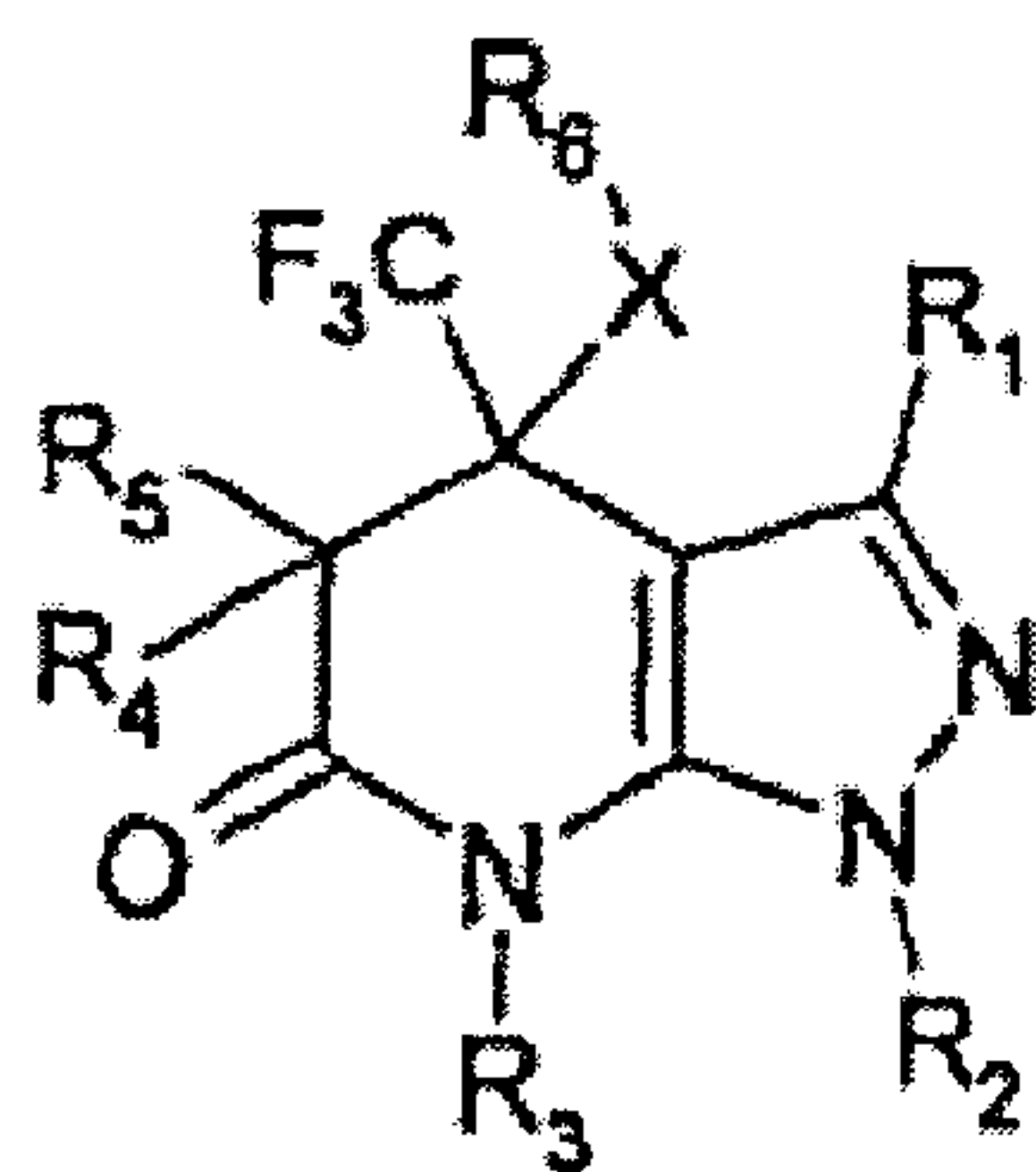
wherein  $R_1$ ,  $R_2$  and  $R_3$  have the meaning as defined in claim 1,

with a compound of formula (III)



- 10 wherein  $R_4$ ,  $R_5$  and  $X$  have the meaning as defined in claim 1, and  $L$  denotes a leaving group,

to yield a compound of formula (I)



wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_6$  and  $X$  have the meaning as defined in claim 1,

and, optionally,

- 5      b) converting residue  $R_6$  as defined in claim 1 into another residue  $R_6$  as defined above,

and optionally

- c) converting a base or an acid of the compound of formula (I) into a salt thereof.

- 10    12. Use of a compound according to any one of claims 1 to 10 for inhibiting LPA receptor mediated biological activity.

13. The use according to claim 12, wherein the LPA receptor mediated biological activity is LPA receptor 1, LPA receptor 2, LPA receptor 3, LPA receptor 4, LPA receptor 5 or LPA receptor 6 mediated biological activity.

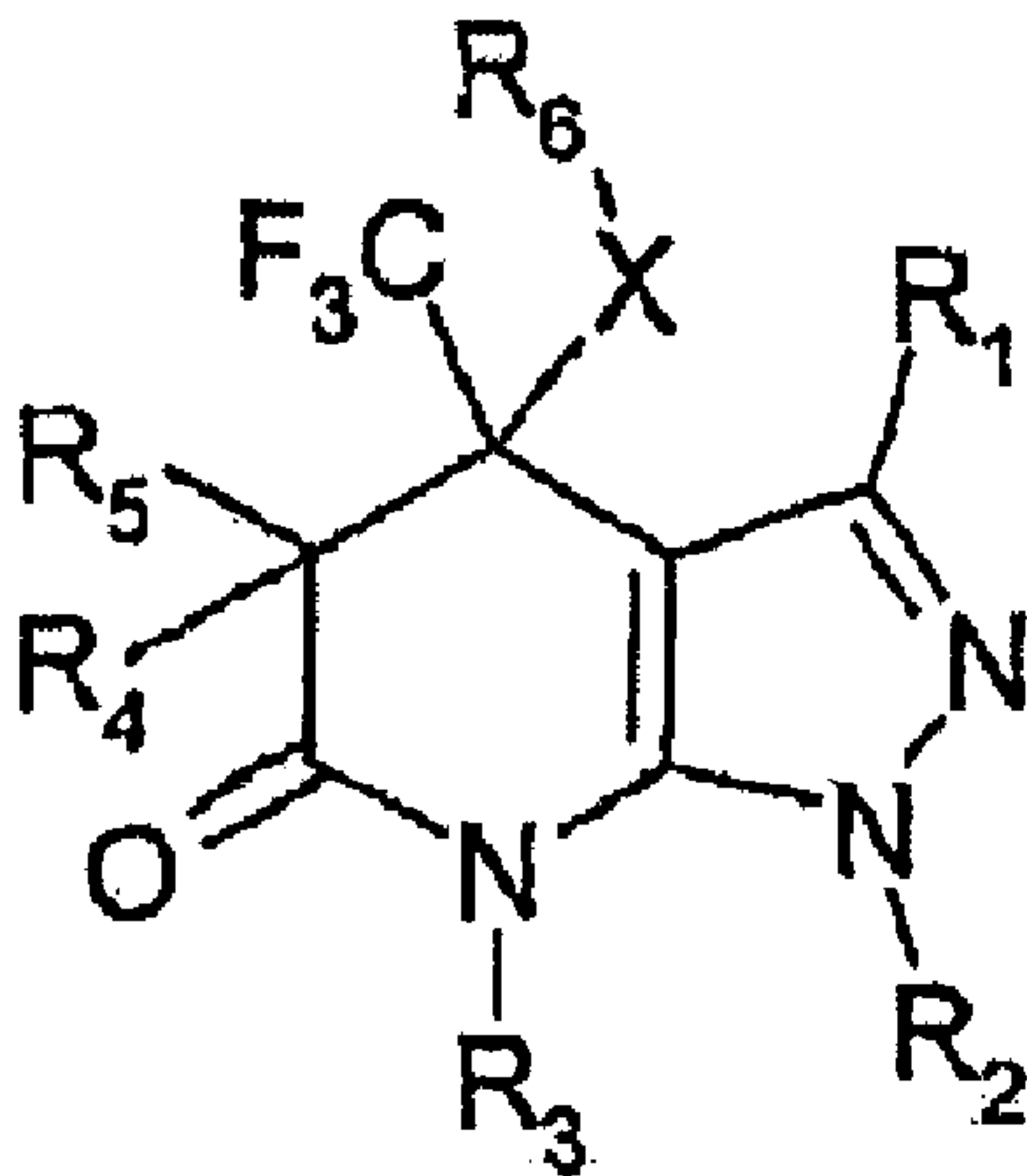
- 15    14. The use according to claim 12, wherein the LPA receptor mediated biological activity is LPA receptor 2 mediated biological activity.

15. A pharmaceutical composition comprising at least one compound according to any one of claims 1 to 10, or a physiologically acceptable salt, solvate, tautomer or stereoisomer thereof, or a mixture thereof in any ratio, and at least one additional compound selected from the group consisting of
- 20

physiologically acceptable excipients, auxiliaries, adjuvants, diluents, carriers and/or additional pharmaceutically active substance other than the compounds according to any one of claims 1 to 10.

16. The pharmaceutical composition according to claim 15 for use in the treatment or prophylaxis of physiological and/or pathophysiological conditions selected from the group consisting of: cancer, tumour, malignant tumours, benign tumours, solid tumours, sarcomas, carcinomas, hyperproliferative disorders, carcinoids, Ewing sarcomas, Kaposi sarcomas, brain tumours, tumours originating from the brain and/or the nervous system and/or the meninges, gliomas, glioblastomas, neuroblastomas, stomach cancer, kidney cancer, kidney cell carcinomas, prostate cancer, prostate carcinomas, connective tissue tumours, soft tissue sarcomas, pancreas tumours, liver tumours, head tumours, neck tumours, laryngeal cancer, oesophageal cancer, thyroid cancer, osteosarcomas, retinoblastomas, thymoma, testicular cancer, lung cancer, lung adenocarcinoma, small cell lung carcinoma, bronchial carcinomas, breast cancer, mamma carcinomas, intestinal cancer, colorectal tumours, colon carcinomas, rectum carcinomas, gynaecological tumours, ovary tumours/ovarian tumours, uterine cancer, cervical cancer, cervix carcinomas, cancer of body of uterus, corpus carcinomas, endometrial carcinomas, urinary bladder cancer, urogenital tract cancer, bladder cancer, skin cancer, epithelial tumours, squamous epithelial carcinoma, basaliomas, spinaliomas, melanomas, intraocular melanomas, leukaemias, monocyte leukaemia, chronic leukaemias, chronic myelotic leukaemia, chronic lymphatic leukemia, acute leukaemias, acute myelotic leukaemia, acute lymphatic leukemia, lymphomas, opthalmic diseases, choroidal neovascularization, diabetic retinopathy, inflammatory diseases, arthritis, neurodegeneration, transplant rejection, metastatic growth, fibrosis, restenosis, HIV infection, atherosclerosis, inflammation, heart failure, cardiomyopathy, myocardial infarction, myocardial remodeling, vascular remodeling, hypertension, peripheral arterial occlusive disease,

- restenosis, thrombosis, vascular permeability disorders, inflammatory diseases, rheumatoid arthritis, osteoarthritis, renal diseases, renal papillary necrosis, renal failure, pulmonary diseases, chronic obstructive pulmonary disease, asthma, acute respiratory distress syndrome, immunological diseases, allergic diseases, tumor growth, metastasis, metabolic diseases, fibrotic diseases, pulmonary fibrosis, cardiac fibrosis, vascular fibrosis, perivascular fibrosis, renal fibrosis, liver fibrosis, fibrosing skin conditions, psoriasis, pain, pruritus, retinal ischemia/reperfusion damage, macular degeneration, psychiatric disorders, neurodegenerative diseases, cerebral nerve disorders, peripheral nerve disorders, endocrinic disorders, hyperthyroidism, scarring disorders or for cardioprotection or renoprotection and disorders of wound healing, angiogenesis, cardiovascular system, bone, CNS or PNS.
- 5
- 10
- 15
- 20
17. The pharmaceutical composition according to claim 15 or 16, further comprising at least one additional pharmacologically active substance.
18. The pharmaceutical composition according to claim 15 or 16, which is for application before and/or during and/or after treatment with at least one additional pharmacologically active substance.
19. Kit comprising at least one compound according to any one of claims 1 to 10, or at least one pharmaceutical composition according to claim 15 and at least one further pharmacologically active substance other than the compounds according to any one of claims 1 to 10.



(I)