Innovation, Sciences et Développement économique Canada
Office de la Propriété Intellectuelle du Canada

Innovation, Science and Economic Development Canada
Canadian Intellectual Property Office

CA 3079770 A1 2019/05/02

(21) 3 079 770

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2018/10/17
(87) Date publication PCT/PCT Publication Date: 2019/05/02
(85) Entrée phase nationale/National Entry: 2020/04/21
(86) N° demande PCT/PCT Application No.: EP 2018/078398
(87) N° publication PCT/PCT Publication No.: 2019/081299
(30) Priorité/Priority: 2017/10/24 (EP17197937.0)

(51) Cl.Int./Int.Cl. *C07D 401/14* (2006.01), *A61K 31/4196* (2006.01), *A61P 13/12* (2006.01), *A61P 5/12* (2006.01), *A61P 9/00* (2006.01), *C07D 403/06* (2006.01), *C07D 403/14* (2006.01), *C07D 405/14* (2006.01), *C07D 407/14* (2006.01), *C07D 409/14* (2006.01), *C07D 417/14* (2006.01), *C07D 487/10* (2006.01), ...

(71) Demandeur/Applicant:
BAYER PHARMA AKTIENGESELLSCHAFT, DE

(72) Inventeurs/Inventors:
COLLIN-KROPELIN, MARIE-PIERRE, DE;
KOLKHOF, PETER, DE;
NEUBAUER, THOMAS, DE;

(54) Titre : DERIVES DE TRIAZOLE SUBSTITUES PAR UNE AMINE ET UTILISATIONS ASSOCIEES
(54) Title: AMINE SUBSTITUTED TRIAZOLE DERIVATIVES AND USES THEREOF

(57) Abrégé/Abstract:
The present invention relates to novel amine substituted 1,2,4-triazole derivatives, to processes for the preparation of such compounds, to pharmaceutical compositions containing such compounds, and to the use of such compounds or compositions for the treatment and/or prevention of diseases, in particular for the treatment and/or prevention of renal and cardiovascular diseases.

(21) 3 079 770

(13) A1

(51) Cl.Int./Int.Cl. (suite/continued) *C07D 491/048* (2006.01), *C07D 491/107* (2006.01), *C07D 495/10* (2006.01)

(72) Inventeurs(suite)/Inventors(continued): FURSTNER, CHANTAL, DE; POOK, ELISABETH, DE; TINEL, HANNA, DE; SCHMECK, CARSTEN, DE; WASNAIRE, PIERRE, DE; SCHIRMER, HEIKO, DE; LUSTIG, KLEMENS, DE

(74) Agent: SMART & BIGGAR IP AGENCY CO.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
02 May 2019 (02.05.2019)

WIPO | PCT

(10) International Publication Number
WO 2019/081299 A1

(51) International Patent Classification:

C07D 401/14 (2006.01)	*C07D 491/048* (2006.01)
C07D 405/14 (2006.01)	*C07D 491/107* (2006.01)
C07D 403/06 (2006.01)	*C07D 495/10* (2006.01)
C07D 403/14 (2006.01)	*A61P 5/12* (2006.01)
C07D 407/14 (2006.01)	*A61P 9/00* (2006.01)
C07D 409/14 (2006.01)	*A61P 13/12* (2006.01)
C07D 417/14 (2006.01)	*A61K 31/4196* (2006.01)
C07D 487/10 (2006.01)	

(21) International Application Number:
PCT/EP2018/078398

(22) International Filing Date:
17 October 2018 (17.10.2018)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
17197937.0 24 October 2017 (24.10.2017) EP

(71) Applicant: **BAYER PHARMA AKTIENGESELLSCHAFT** [DE/DE]; Müllerstr. 178, 13353 Berlin (DE).

(72) Inventors: **COLLIN-KRÖPELIN, Marie-Pierre**; Katernberger Schulweg 52, 42113 Wuppertal (DE). **KOLKHOF, Peter**; Falkenberg 121, 42113 Wuppertal (DE). **NEUBAUER, Thomas**; Kleiberweg 5c, 42111 Wuppertal (DE). **FÜRSTNER, Chantal**; Arnoldstr. 33, 45478 Mülheim/Ruhr (DE). **POOK, Elisabeth**; Im Lehmbruch 24, 42109 Wuppertal (DE). **TINEL, Hanna**; In der Beek 16, 42113 Wuppertal (DE). **SCHMECK, Carsten**; Carl-Friedrich-Goerdeler-Straße 24, 45472 Mülheim (DE). **WASNAIRE, Pierre**; Am Botanischen Garten 41, 40225 Düsseldorf (DE). **SCHIRMER, Heiko**; Dingshauser Straße 51a, 42655 Solingen (DE). **LUSTIG, Klemens**; Falkenberg 159, 42113 Wuppertal (DE).

(74) Agent: **BIP PATENTS**; Alfred-Nobel-Str. 10, 40789 Monheim am Rhein NRW (DE).

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

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

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

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

WO 2019/081299 A1

(54) **Title:** AMINE SUBSTITUTED TRIAZOLE DERIVATIVES AND USES THEREOF

(57) **Abstract:** The present invention relates to novel amine substituted 1,2,4-triazole derivatives, to processes for the preparation of such compounds, to pharmaceutical compositions containing such compounds, and to the use of such compounds or compositions for the treatment and/or prevention of diseases, in particular for the treatment and/or prevention of renal and cardiovascular diseases.

AMINE SUBSTITUTED TRIAZOLE DERIVATIVES AND USES THEREOF

The present invention relates to novel amine substituted 1,2,4-triazole derivatives, to processes for the preparation of such compounds, to pharmaceutical compositions containing such compounds, and to the use of such compounds or compositions for the treatment and/or prevention of diseases, in particular for the treatment and/or prevention of renal and cardiovascular diseases.

The liquid content of the human body is subject to various physiological control mechanisms, the purpose of which is to keep it constant (volume homeostasis). In the process, both the volume filling of the vascular system and also the osmolarity of the plasma are continuously recorded by appropriate sensors (baroreceptors and osmoreceptors). The information which these sensors supply to the relevant centers in the brain regulates drinking behaviour and controls fluid excretion via the kidneys by means of humoral and neural signals. The peptide hormone vasopressin is of central importance in this [Schrier R.W., Abraham W.T., *New Engl. J. Med.* 341, 577-585 (1999)].

Vasopressin is produced in specialized endocrine neurons in the *Nucleus supraopticus* and *N. paraventricularis* in the wall of the third ventricle (hypothalamus) and is transported from there along the neural processes into the posterior lobes of the hypophysis (neurohypophysis). There the hormone is released into the bloodstream in response to stimulus. A loss of volume, *e.g.* as a result of acute bleeding, heavy sweating, prolonged thirst or diarrhoea, is a stimulus for intensified release of the hormone. Conversely, the secretion of vasopressin is inhibited by an increase in the intravascular volume, *e.g.* as a result of increased fluid intake.

Vasopressin exerts its action mainly via binding to three receptors, which are classified as V1a, V1b and V2 receptors and which belong to the family of G protein-coupled receptors. V1a receptors are mainly located on the cells of the vascular smooth musculature. Their activation gives rise to vasoconstriction, as a result of which the peripheral resistance and blood pressure rise. Apart from this, V1a receptors are also detectable in the liver. V1b receptors (also named V3 receptors) are detectable in the central nervous system. Together with corticotropin-releasing hormone (CRH), vasopressin regulates the basal and stress-induced secretion of adrenocorticotropic hormone (ACTH) via the V1b receptor. V2 receptors are located in the distal tubular epithelium and the epithelium of the collecting tubules in the kidney. Their activation renders these epithelia permeable to water. This phenomenon is due to the incorporation of aquaporins (special water channels) in the luminal membrane of the epithelial cells.

The importance of vasopressin for the reabsorption of water from the urine in the kidney becomes clear from the clinical picture of diabetes insipidus, which is caused by a deficiency of the hormone, *e.g.* owing to hypophysis damage. Patients who suffer from this disease excrete up to 20 liters of urine per 24 hours if they are not given replacement hormone. This volume corresponds to about 10% of the primary urine. Because of its great importance for the reabsorption of water from

the urine, vasopressin is also synonymously referred to as antidiuretic hormone (ADH). Consequently, pharmacological inhibition of the action of vasopressin/ADH on the V2 receptor results in increased urine excretion. In contrast to the action of other diuretics (thiazides and loop diuretics), however, V2 receptor antagonists cause increased water excretion, without substantially increasing the excretion of electrolytes. This means that with V2 antagonist drugs, volume homeostasis can be restored without affecting electrolyte homeostasis. Hence, drugs with V2 antagonistic activity appear particularly suitable for the treatment of all disease conditions which are associated with an overloading of the body with water, without the electrolytes being adequately increased in parallel.

A significant electrolyte abnormality is measurable in clinical chemistry as hyponatremia (sodium concentration < 135 mmol/L); it is the most important electrolyte abnormality in hospital patients, with an incidence of about 5% or 250 000 cases per year in the US alone. If the plasma sodium concentration falls below 115 mmol/L, comatose states and death are imminent. Depending on the underlying cause, a distinction is made between hypovolemic, euvolemic and hypervolemic hyponatremia. The forms of hypervolemia with edema formation are clinically significant. Typical examples of these are the syndrome of inappropriate ADH/vasopressin secretion (SIADH) (*e.g.* after craniocerebral trauma or as paraneoplasia in carcinomas) and hypervolemic hyponatremia in liver cirrhosis, various renal diseases and heart failure [De Luca L. et al., *Am. J. Cardiol.* 96 (suppl.), 19L-23L (2005)]. In particular, patients with heart failure, in spite of their relative hyponatremia and hypervolemia, often display elevated vasopressin levels, which are seen as the consequence of a generally disturbed neurohumoral regulation in heart failure [Francis G.S. et al., *Circulation* 82, 1724-1729 (1990)].

The disturbed neurohormonal regulation essentially manifests itself in an elevation of the sympathetic tone and inappropriate activation of the renin-angiotensin-aldosterone system. While the inhibition of these components by beta-receptor blockers on the one hand and by ACE inhibitors or angiotensin-receptor blockers on the other is now an inherent part of the pharmacological treatment of heart failure, the inappropriate elevation of vasopressin secretion in advanced heart failure is at present still not adequately treatable. Apart from the retention of water mediated by V2 receptors and the unfavourable hemodynamic consequences associated therewith in terms of increased backload, the emptying of the left ventricle, the pressure in the pulmonary blood vessels and cardiac output are also adversely affected by V1a-mediated vasoconstriction. Furthermore, on the basis of experimental data in animals, a direct hypertrophy-promoting action on the heart muscle is also attributed to vasopressin. In contrast to the renal effect of volume expansion, which is mediated by activation of V2 receptors, the direct action on the heart muscle is triggered by activation of V1a receptors.

For these reasons, agents which inhibit the action of vasopressin on the V2 and/or the V1a receptor appear suitable for the treatment of heart failure. In particular, compounds with combined activity

on both vasopressin receptors (V1a and V2) should have both desirable renal as well as hemodynamic effects and thus offer an especially ideal profile for the treatment of patients with heart failure. The provision of such combined vasopressin antagonists also appears to make sense inasmuch as a volume diminution mediated solely via V2 receptor blockade can entail the stimulation of osmoreceptors and, as a result, may lead to a further compensatory increase in vasopressin release. Through this, in the absence of a component simultaneously blocking the V1a receptor, the harmful effects of vasopressin, such as for example vasoconstriction and heart muscle hypertrophy, could be further intensified [Saghi P. et al., *Europ. Heart J.* 26, 538-543 (2005)].

V1a receptors are mainly located on vascular smooth muscle cells (VSMC) but also on cardiomyocytes, fibroblasts and specialized renal cells like glomerular mesangial cells or cells of the macula densa which control the release of renin [Wasilewski MA, Myers VD, Recchia FA, Feldman AM, Tilley DG, Cell Signal., 28(3), 224-233, (2016)]. The activation of VSMC V1a receptor by vasopressin gives rise to intracellular calcium release and according vasoconstriction. Therefore, stimulation of VSMC V1a receptors causes increased vascular resistance and increased cardiac afterload. Cardiac output is adversely affected by V1a-mediated vasoconstriction. The increase in afterload and direct stimulation of V1a receptors on cardiomyocytes can lead to cardiac hypertrophy and remodeling including fibrosis. Mice with cardiac-specific overexpression of V1a receptor develop cardiac hypertrophy leading to dilation and left ventricular dysfunction, suggesting an essential role for V1a receptor in the development of heart failure [Li X, Chan TO, Myers V, Chowdhury I, Zhang XQ, Song J, Zhang J, Andrel J, Funakoshi H, Robbins J, Koch WJ, Hyslop T, Cheung JY, Feldman AM, Circulation.; 124, 572-581 (2011)].

V1a receptor is also expressed in the renal cortical and medullary vasculature, where it mediates vasoconstriction of renal vessels and affecting overall renal blood flow. Thus, the activation of V1a receptor can decrease renal medullary blood flow inducing further pathological processes as tissue hypoxia, reduced oxygen and accordingly energy supply for tubular transport processes as well as direct damages of mesangial and macula densa cells. It has been demonstrated that mesangial V1a receptor activation mediates TGFβ signaling and causes an increase in production of collagen IV. While this signaling contributes extracellular matrix accumulation and remodeling in the kidney, similar signaling pathways are believed to occur in cardiac cells especially after myocardial infarction, which emphasizes the central role of V1a receptor in the development of hypertrophic and fibrotic processes in response to pathophysiological elevated vasopressin levels [Wasilewski MA, Myers VD, Recchia FA, Feldman AM, Tilley DG. Arginine vasopressin receptor signaling and functional outcomes in heart failure. Cell Signal., 28(3), 224-233 (2016)].

Since V1a receptors are mainly expressed on VSMCs and thus participating in vascular function, a link to vascular diseases as peripheral arterial disease (PAD) including claudication and critical limb ischemia as well as coronary microvascular dysfunction (CMD) is conceivable.

Apart from this, V1a receptors are also expressed on human platelets and in the liver. The meaning of platelet V1a receptors is not fully understood although vasopressin induces aggregation of human platelets via V1a receptor at high concentrations ex vivo. Therefore, inhibition of vasopressin-induced platelet aggregation by V1a receptor antagonists is a useful pharmacological ex vivo assay making use of human tissue endogenously expressing the V1a receptor [Thibonnier M, Roberts JM, J Clin Invest.; 76:1857-1864, (1985)].

Vasopressin stimulates gluconeogenesis and glycogenolysis via activation of the hepatic V1a receptor. Animal studies have shown that vasopressin impairs glucose tolerance which could be inhibited by a V1a receptor antagonist thereby providing a link of vasopressin receptor V1a to diabetes mellitus. [Taveau C, Chollet C, Waeckel L, Desposito D, Bichet DG, Arthus MF, Magnan C, Philippe E, Paradis V, Foufelle F, Hainault I, Enhorning S, Velho G, Roussel R, Bankir L, Melander O, Bouby N. Vasopressin and hydration play a major role in the development of glucose intolerance and hepatic steatosis in obese rats. Diabetologia., 58(5), 1081-1090, (2015)]. Vasopressin was shown to contribute to the development of albuminuria and to diabetes-induced nephropathy in animal models which is consistent with epidemiological findings in humans.

It was found recently that vasopressin also seems to play a causal role in the development of preeclampsia. Chronic infusion of vasopressin during pregnancy in mice is sufficient to induce all of the major maternal and fetal phenotypes associated with human preeclampsia, including pregnancy-specific hypertension [Santillan MK, Santillan DA, Scroggins SM, Min JY, Sandgren JA, Pearson NA, Leslie KK, Hunter SK, Zamba GK, Gibson-Corley KN, Grobe JL. Vasopressin in preeclampsia: a novel very early human pregnancy biomarker and clinically relevant mouse model. Hypertension. 64(4), 852-859, (2014)].

Vasopressin levels can be elevated in women with dysmenorrhoea (a gynecological disorder which is characterised by cyclical cramping pelvic pain) during menstruation, which appear to increase myometrial smooth muscle contraction. It was found recently that a selective vasopressin V1a receptor antagonist (relcovaptan/SR-49059) can reduce intrauterine contractions elicited by vasopressin.

For these reasons, agents which inhibit the action of vasopressin on the V1a receptor appear suitable for the treatment of several cardiovascular diseases. In particular, agents which inhibit the action of vasopressin selectively on the V1a receptor offer an especially ideal profile for the treatment of otherwise normovolemic patients, i.e. those which are not eligible for decongestion by e.g. high doses of loop diuretics or V2 antagonists, and where induced aquaresis via V2 inhibition may be undesired.

Certain 4-phenyl-1,2,4-triazol-3-yl derivatives have been described in WO 2005/063754-A1 and WO 2005/105779-A1 to act as vasopressin V1a receptor antagonists that are useful for the treatment of gynecological disorders, notably menstrual disorders such as dysmenorrhea.

In WO 2011/104322-A1, a particular group of bis-aryl-bonded 1,2,4-triazol-3-ones, including 5-phenyl-1,2,4-triazol-3-yl and 1-phenyl-1,2,3-triazol-4-yl derivatives thereof, has been disclosed as antagonists of vasopressin V1a and/or V2 receptors being useful for the treatment and/or prevention of cardiovascular diseases.

In WO 2016/071212-A1 certain 5-(hydroxyalkyl)-1-phenyl-1,2,4-triazole derivatives have been disclosed, which act as potent antagonists of both vasopressin V1a and V2 receptors and, in addition, exhibit significantly enhanced aquaretic potency in vivo after oral application.

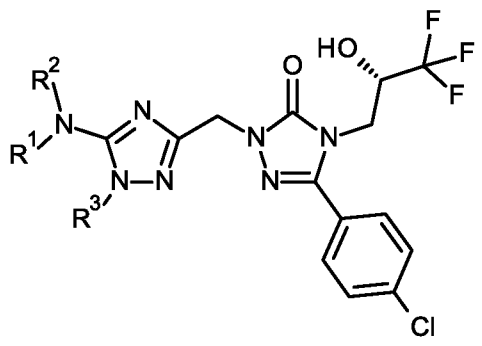
In WO 2017/191107-A1 and WO 2017/191102-A1 certain 5-(carboxamide)-1-phenyl-1,2,4-triazole derivatives as well as in WO 2017/191114-A1 specific 5-(hydroxyalkyl)-1-heteroaryl-1,2,4-triazole derivatives have been described, which represent highly potent and selective antagonists of the V1a receptor and are particularly useful for the treatment and/or prevention of renal and cardiovascular diseases in subjects which do not suffer from fluid overload and who therefore should not be decongested.

Further novel 5-(carboxamide)-substituted, 5-(fluoroalkyl)-substituted and 3-(hydroxyalkyl)-substituted 1,2,4-triazole derivatives have been disclosed as antagonists of vasopressin V2 and/or V1a receptors in WO 2017/191105-A1, WO 2017/191112-A1, WO 2017/191115-A1 and WO 2018/073144-A1.

It was an object of the present invention to provide novel compounds which act as potent selective or dual V1a/V2 receptor antagonists and as such are suitable for the treatment and/or prevention of diseases, more particularly for the treatment and/or prevention of renal and cardiovascular disorders.

The compounds of the present invention have valuable pharmacological properties and can be used for the prevention and/or treatment of various diseases and disease-induced states in humans and other mammals.

The invention provides compounds of the general formula (I)



(I),

in which

R^1 represents hydrogen or methyl,

R^2 represents C_1-C_5-alkyl or a 5- or 6-membered heterocyclyl,

where alkyl may be substituted by 1 to 2 substituents independently of one another selected from the group consisting of fluorine, hydroxy, amino, aminocarbonyl, aminosulfonyl, difluoromethyl, trifluoromethyl, methoxy, ethoxy, C_3-C_6-cycloalkyl, 4- to 7-membered heterocyclyl, methylsulfonyl, methylcarbonylamino, 2,2,2-trifluoroethylaminocarbonyl, methylsulfonylamino and C_1-C_4-alkoxycarbonyl,

wherein heterocyclyl may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of oxo, chlorine, fluorine, hydroxy, formyl, aminocarbonyl, methyl, methoxy, trifluoromethyl, methylcarbonyl, methylsulfonyl and C_1-C_4-alkoxycarbonyl,

and

wherein cycloalkyl may be substituted by one substituent hydroxyl,

and

where heterocyclyl may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of oxo, chlorine, fluorine, hydroxy, aminocarbonyl, methyl, methoxy, trifluoromethyl, methylcarbonyl, methylsulfonyl and C_1-C_4-alkoxycarbonyl,

or

R^1 and R^2 together with the nitrogen atom to which they are attached form a 4- to 6-membered heterocyclyl, 6-oxo-2,5,7-triazaspiro[3.4]octan-2-yl, hexahydro-4H-furo[3,2-b]pyrrol-4-yl, 2,2-dioxido-2-thia-6-azaspiro[3.3]hept-6-yl or 2-oxa-6-azaspiro[3.3]hept-6-yl,

where heterocyclyl may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of oxo, chlorine, fluorine, hydroxy, aminocarbonyl, methyl, methoxy, trifluoromethyl, methylcarbonyl, methylsulfonyl and C_1-C_4-alkoxycarbonyl,

R^3 represents phenyl, pyridinyl or 3,3,3-trifluoroprop-1-yl,

where phenyl may be substituted by one substituent selected from the group consisting of chlorine, fluorine and trifluoromethyl,

and

where pyridinyl may be substituted by one substituent selected from the group consisting of chlorine, fluorine, trifluoromethyl and trifluoromethoxy,

and pharmaceutically acceptable salts thereof, solvates thereof and the solvates of the salts thereof.

The term "substituted" means that one or more hydrogen atoms on the designated atom or group are replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded. Combinations of substituents and/or variables are permissible.

The term "optionally substituted" means that the number of substituents can be equal to or different from zero. Unless otherwise indicated, it is possible that optionally substituted groups are substituted with as many optional substituents as can be accommodated by replacing a hydrogen atom with a non-hydrogen substituent on any available carbon atom or heteroatom.

When groups in the compounds according to the invention are substituted, it is possible for said groups to be mono-substituted or poly-substituted with substituent(s), unless otherwise specified. Within the scope of the present invention, the meanings of all groups which occur repeatedly are independent from one another. It is possible that groups in the compounds according to the invention are substituted with one, two or three identical or different substituents.

The term "comprising" when used in the specification includes "consisting of".

If within the present text any item is referred to as "as mentioned herein", it means that it may be mentioned anywhere in the present text.

The terms as mentioned in the present text have the following meanings:

C_1-C_5-Alkyl represents a straight-chain or branched alkyl radical having 1 to 5 carbon atoms, preferably 1 to 3 carbon atoms (C_1-C_3-alkyl), by way of example and with preference methyl, ethyl, n-propyl, isopropyl, 2-methylprop-1-yl, n-butyl, *tert*-butyl and 2,2-dimethylprop-1-yl.

4- to 6-membered heterocyclyl in the definition of the combination of the radicals R^1 and R^2 represents a saturated or partially unsaturated monocyclic radical having 4 to 6 ring atoms which is bound via a nitrogen atom and which may contain one additional heteroatom from the group consisting of S, O and N, where a nitrogen atom may also form an N-oxide, by way of example and with preference azetidinyl, pyrrolidinyl, pyrazolidinyl, 1,3-oxazolidinyl, piperidinyl, piperazinyl, morpholinyl and thiomorpholinyl, preferred are azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl and thiomorpholinyl.

4- to 7-membered heterocyclyl as a substituent on alkyl in the definition of the radical R^2 represents a saturated or partially unsaturated monocyclic radical having 4 to 7 ring atoms and up to 2 heteroatoms from the group consisting of S, O and N, where a nitrogen atom may also form an N-oxide, by way of example and with preference azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, pyrazolidinyl, tetrahydrofuranyl, thiolanyl, 1,3-oxazolidinyl, imidazolidinyl, piperidinyl, piperazinyl, tetrahydropyranyl, tetrahydrothiopyranyl, 1,3-dioxanyl, 1,4-dioxanyl, morpholinyl, thiomorpholinyl, 1,2-thiazinanyl, azepanyl, hexahydroazepinyl and hexahydro-1,4-diazepinyl, preferred are

oxetan-3-yl, thietan-3-yl, pyrrolidin-1-yl, pyrrolidin-2-yl, 1,3-oxazolidin-5-yl, imidazolidin-1-yl, piperidin-4-yl, 1,2-thiazinan-2-yl and azepan-4-yl.

5- or 6-membered heterocyclyl in the definition of the radical R^2 represents a saturated or partially unsaturated monocyclic radical having 5 or 6 ring atoms and up to 2 heteroatoms from the group consisting of S, O and N, where a nitrogen atom may also form an N-oxide, by way of example and with preference pyrrolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, tetrahydropyranyl, morpholinyl and thiomorpholinyl, preferred are pyrrolidin-3-yl and piperidin-5-yl.

C_1-C_4-alkoxycarbonyl represents a straight-chain or branched alkoxy radical having 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms (C_1-C_3-alkoxy) which is linked via a carbonyl group, by way of example and with preference methoxycarbonyl, ethoxycarbonyl, *n*-propoxycarbonyl, isopropoxycarbonyl, *n*-butoxycarbonyl and tert-butoxycarbonyl.

C_3-C_6-cycloalkyl represents a monocyclic cycloalkyl group having 3 to 6 carbon atoms, cycloalkyl which may be mentioned by way of example and with preference being cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

It is possible for the compounds of general formula (I) to exist as isotopic variants. The invention therefore includes one or more isotopic variant(s) of the compounds of general formula (I), particularly deuterium-containing compounds of general formula (I).

The term "Isotopic variant" of a compound or a reagent is defined as a compound exhibiting an unnatural proportion of one or more of the isotopes that constitute such a compound.

The term "Isotopic variant of the compound of general formula (I)" is defined as a compound of general formula (I) exhibiting an unnatural proportion of one or more of the isotopes that constitute such a compound.

The expression "unnatural proportion" means a proportion of such isotope which is higher than its natural abundance. The natural abundances of isotopes to be applied in this context are described in "Isotopic Compositions of the Elements 1997", Pure Appl. Chem., 70(1), 217-235, 1998.

Examples of such isotopes include stable and radioactive isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine, bromine and iodine, such as ^{2}H (deuterium), ^{3}H (tritium), ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{32}P, ^{33}P, ^{33}S, ^{34}S, ^{35}S, ^{36}S, ^{18}F, ^{36}Cl, ^{82}Br, ^{123}I, ^{124}I, ^{125}I, ^{129}I and ^{131}I, respectively.

With respect to the treatment and/or prevention of the disorders specified herein the isotopic variant(s) of the compounds of general formula (I) preferably contain deuterium ("deuterium-containing compounds of general formula (I)"). Isotopic variants of the compounds of general formula (I) in which one or more radioactive isotopes, such as ^{3}H or ^{14}C, are incorporated are useful e.g. in drug and/or substrate tissue distribution studies. These isotopes are particularly

preferred for the ease of their incorporation and detectability. Positron emitting isotopes such as ^{18}F or ^{11}C may be incorporated into a compound of general formula (I). These isotopic variants of the compounds of general formula (I) are useful for in vivo imaging applications. Deuterium-containing and ^{13}C-containing compounds of general formula (I) can be used in mass spectrometry analyses (H. J. Leis et al., Curr. Org. Chem., 1998, 2, 131) in the context of preclinical or clinical studies.

Isotopic variants of the compounds of general formula (I) can generally be prepared by methods known to a person skilled in the art, such as those described in the schemes and/or examples herein, by substituting a reagent for an isotopic variant of said reagent, preferably for a deuterium-containing reagent. Depending on the desired sites of deuteration, in some cases deuterium from D_2O can be incorporated either directly into the compounds or into reagents that are useful for synthesizing such compounds (Esaki et al., Tetrahedron, 2006, 62, 10954; Esaki et al., Chem. Eur. J., 2007, 13, 4052). Deuterium gas is also a useful reagent for incorporating deuterium into molecules. Catalytic deuteration of olefinic bonds (H. J. Leis et al., Curr. Org. Chem., 1998, 2, 131; J. R. Morandi et al., J. Org. Chem., 1969, 34 (6), 1889) and acetylenic bonds (N. H. Khan, J. Am. Chem. Soc., 1952, 74 (12), 3018; S. Chandrasekhar et al., Tetrahedron Letters, 2011, 52, 3865) is a direct route for incorporation of deuterium. Metal catalysts (i.e. Pd, Pt, and Rh) in the presence of deuterium gas can be used to directly exchange deuterium for hydrogen in functional groups containing hydrocarbons (J. G. Atkinson et al., US Patent 3966781). A variety of deuterated reagents and synthetic building blocks are commercially available from companies such as for example C/D/N Isotopes, Quebec, Canada; Cambridge Isotope Laboratories Inc., Andover, MA, USA; and CombiPhos Catalysts, Inc., Princeton, NJ, USA. Further information on the state of the art with respect to deuterium-hydrogen exchange is given for example in Hanzlik et al., J. Org. Chem. 55, 3992-3997, 1990; R. P. Hanzlik et al., Biochem. Biophys. Res. Commun. 160, 844, 1989; P. J. Reider et al., J. Org. Chem. 52, 3326-3334, 1987; M. Jarman et al., Carcinogenesis 16(4), 683-688, 1995; J. Atzrodt et al., Angew. Chem., Int. Ed. 2007, 46, 7744; K. Matoishi et al., Chem. Commun. 2000, 1519−1520; K. Kassahun et al., WO2012/112363.

The term “deuterium-containing compound of general formula (I)” is defined as a compound of general formula (I), in which one or more hydrogen atom(s) is/are replaced by one or more deuterium atom(s) and in which the abundance of deuterium at each deuterated position of the compound of general formula (I) is higher than the natural abundance of deuterium, which is about 0.015%. Particularly, in a deuterium-containing compound of general formula (I) the abundance of deuterium at each deuterated position of the compound of general formula (I) is higher than 10%, 20%, 30%, 40%, 50%, 60%, 70% or 80%, preferably higher than 90%, 95%, 96% or 97%, even more preferably higher than 98% or 99% at said position(s). It is understood that the abundance of

deuterium at each deuterated position is independent of the abundance of deuterium at other deuterated position(s).

The selective incorporation of one or more deuterium atom(s) into a compound of general formula (I) may alter the physicochemical properties (such as for example acidity [C. L. Perrin, et al., J. Am. Chem. Soc., 2007, 129, 4490; A. Streitwieser et al., J. Am. Chem. Soc., 1963, 85, 2759;], basicity [C. L. Perrin et al., J. Am. Chem. Soc., 2005, 127, 9641; C. L. Perrin, et al., J. Am. Chem. Soc., 2003, 125, 15008; C. L. Perrin in Advances in Physical Organic Chemistry, 44, 144], lipophilicity [B. Testa et al., Int. J. Pharm., 1984, 19(3), 271]) and/or the metabolic profile of the molecule and may result in changes in the ratio of parent compound to metabolites or in the amounts of metabolites formed. Such changes may result in certain therapeutic advantages and hence may be preferred in some circumstances. Reduced rates of metabolism and metabolic switching, where the ratio of metabolites is changed, have been reported (A. E. Mutlib et al., Toxicol. Appl. Pharmacol., 2000, 169, 102; D. J. Kushner et al., Can. J. Physiol. Pharmacol., 1999, 77, 79). These changes in the exposure to parent drug and metabolites can have important consequences with respect to the pharmacodynamics, tolerability and efficacy of a deuterium-containing compound of general formula (I). In some cases deuterium substitution reduces or eliminates the formation of an undesired or toxic metabolite and enhances the formation of a desired metabolite (e.g. Nevirapine: A. M. Sharma et al., Chem. Res. Toxicol., 2013, 26, 410; Efavirenz: A. E. Mutlib et al., Toxicol. Appl. Pharmacol., 2000, 169, 102). In other cases the major effect of deuteration is to reduce the rate of systemic clearance. As a result, the biological half-life of the compound is increased. The potential clinical benefits would include the ability to maintain similar systemic exposure with decreased peak levels and increased trough levels. This could result in lower side effects and enhanced efficacy, depending on the particular compound's pharmacokinetic/ pharmacodynamic relationship. ML-337 (C. J. Wenthur et al., J. Med. Chem., 2013, 56, 5208) and Odanacatib (K. Kassahun et al., WO2012/112363) are examples for this deuterium effect. Still other cases have been reported in which reduced rates of metabolism result in an increase in exposure of the drug without changing the rate of systemic clearance (e.g. Rofecoxib: F. Schneider et al., Arzneim. Forsch. / Drug. Res., 2006, 56, 295; Telaprevir: F. Maltais et al., J. Med. Chem., 2009, 52, 7993). Deuterated drugs showing this effect may have reduced dosing requirements (e.g. lower number of doses or lower dosage to achieve the desired effect) and/or may produce lower metabolite loads.

A compound of general formula (I) may have multiple potential sites of attack for metabolism. To optimize the above-described effects on physicochemical properties and metabolic profile, deuterium-containing compounds of general formula (I) having a certain pattern of one or more deuterium-hydrogen exchange(s) can be selected. Particularly, the deuterium atom(s) of deuterium-containing compound(s) of general formula (I) is/are attached to a carbon atom and/or is/are

located at those positions of the compound of general formula (I), which are sites of attack for metabolizing enzymes such as e.g. cytochrome P_{450}.

Where the plural form of the word compounds, salts, polymorphs, hydrates, solvates and the like, is used herein, this is taken to mean also a single compound, salt, polymorph, isomer, hydrate, solvate or the like.

By "stable compound' or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The compounds of the present invention optionally contain one asymmetric centre, depending upon the location and nature of the various substituents desired. It is possible that one asymmetric carbon atom is present in the (R) or (S) configuration, which can result in racemic mixtures. In certain instances, it is possible that asymmetry also be present due to restricted rotation about a given bond, for example, the central bond adjoining two substituted aromatic rings of the specified compounds. Preferred compounds are those which produce the more desirable biological activity. Separated, pure or partially purified isomers and stereoisomers or racemic mixtures of the compounds of the present invention are also included within the scope of the present invention. The purification and the separation of such materials can be accomplished by standard techniques known in the art.

The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example, by the formation of diastereoisomeric salts using an optically active acid or base or formation of covalent diastereomers. Examples of appropriate acids are tartaric, diacetyltartaric, ditoluoyltartaric and camphorsulfonic acid. Mixtures of diastereoisomers can be separated into their individual diastereomers on the basis of their physical and/or chemical differences by methods known in the art, for example, by chromatography or fractional crystallisation. The optically active bases or acids are then liberated from the separated diastereomeric salts. A different process for separation of optical isomers involves the use of chiral chromatography (*e.g.*, HPLC columns using a chiral phase), with or without conventional derivatisation, optimally chosen to maximise the separation of the enantiomers. Suitable HPLC columns using a chiral phase are commercially available, such as those manufactured by Daicel, *e.g.*, Chiracel OD and Chiracel OJ, for example, among many others, which are all routinely selectable. Enzymatic separations, with or without derivatisation, are also useful. The optically active compounds of the present invention can likewise be obtained by chiral syntheses utilizing optically active starting materials. In order to distinguish different types of isomers from each other reference is made to IUPAC Rules Section E (Pure Appl Chem 45, 11-30, 1976).

The present invention includes all possible stereoisomers of the compounds of the present invention as single stereoisomers, or as any mixture of said stereoisomers, *e.g.* (R)- or (S)- isomers,

in any ratio. Isolation of a single stereoisomer, *e.g.* a single enantiomer or a single diastereomer, of a compound of the present invention is achieved by any suitable state of the art method, such as chromatography, especially chiral chromatography, for example.

In the context of the present invention, the term "enantiomerically pure" is to be understood as meaning that the compound in question with respect to the absolute configuration of the chiral centre is present in an enantiomeric excess of more than 95%, preferably more than 97%. The enantiomeric excess, ee, is calculated here by evaluating of the corresponding HPLC chromatogram on a chiral phase using the formula below:

$$ee = [E^A\,(\text{area\%}) - E^B\,(\text{area\%})] \times 100\% / [E^A\,(\text{area\%}) + E^B\,(\text{area\%})]$$

(E^A: major enantiomer, E^B: minor enantiomer)

Further, it is possible for the compounds of the present invention to exist as tautomers. The present invention includes all possible tautomers of the compounds of the present invention as single tautomers, or as any mixture of said tautomers, in any ratio.

Further, the compounds of the present invention can exist as N-oxides, which are defined in that at least one nitrogen of the compounds of the present invention is oxidised. The present invention includes all such possible N-oxides.

The present invention also covers useful forms of the compounds of the present invention, such as metabolites, hydrates, solvates, salts, in particular pharmaceutically acceptable salts, and/or co-precipitates.

The compounds of the present invention can exist as a hydrate, or as a solvate, wherein the compounds of the present invention contain polar solvents, in particular water, methanol or ethanol for example, as structural element of the crystal lattice of the compounds. It is possible for the amount of polar solvents, in particular water, to exist in a stoichiometric or non-stoichiometric ratio. In the case of stoichiometric solvates, *e.g.* a hydrate, hemi-, (semi-), mono-, sesqui-, di-, tri-, tetra-, penta- *etc.* solvates or hydrates, respectively, are possible. The present invention includes all such hydrates or solvates. Hydrates are preferred solvates in the context of the present invention.

Further, it is possible for the compounds of the present invention to exist in free form, *e.g.* as a free base, or as a free acid, or as a zwitterion, or to exist in the form of a salt. Said salt may be any salt, either an organic or inorganic addition salt, particularly any pharmaceutically acceptable organic or inorganic addition salt, which is customarily used in pharmacy, or which is used, for example, for isolating or purifying the compounds of the present invention.

The term “pharmaceutically acceptable salt" refers to an inorganic or organic acid addition salt of a compound of the present invention. For example, see S. M. Berge, *et al.* “Pharmaceutical Salts,” J. Pharm. Sci. 1977, 66, 1-19.

A suitable pharmaceutically acceptable salt of the compounds of the present invention may be, for example, an acid-addition salt of a compound of the present invention bearing a nitrogen atom, in a chain or in a ring, for example, which is sufficiently basic, such as an acid-addition salt with an inorganic acid, or "mineral acid", such as hydrochloric, hydrobromic, hydroiodic, sulfuric, sulfamic, bisulfuric, phosphoric, or nitric acid, for example, or with an organic acid, such as formic, acetic, acetoacetic, pyruvic, trifluoroacetic, propionic, butyric, hexanoic, heptanoic, undecanoic, lauric, benzoic, salicylic, 2-(4-hydroxybenzoyl)-benzoic, camphoric, cinnamic, cyclopentanepropionic, digluconic, 3-hydroxy-2-naphthoic, nicotinic, pamoic, pectinic, 3-phenylpropionic, pivalic, 2-hydroxyethanesulfonic, itaconic, trifluoromethanesulfonic, dodecylsulfuric, ethanesulfonic, benzenesulfonic, para-toluenesulfonic, methanesulfonic, 2-naphthalenesulfonic, naphthalinedisulfonic, camphorsulfonic acid, citric, tartaric, stearic, lactic, oxalic, malonic, succinic, malic, adipic, alginic, maleic, fumaric, D-gluconic, mandelic, ascorbic, glucoheptanoic, glycerophosphoric, aspartic, sulfosalicylic, or thiocyanic acid, for example.

Further, another suitably pharmaceutically acceptable salt of a compound of the present invention which is sufficiently acidic, is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium, magnesium or strontium salt, or an aluminium or a zinc salt, or an ammonium salt derived from ammonia or from an organic primary, secondary or tertiary amine having 1 to 20 carbon atoms, such as ethylamine, diethylamine, triethylamine, ethyldiisopropylamine, monoethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, dimethylaminoethanol, diethylaminoethanol, tris(hydroxymethyl)aminomethane, procaine, dibenzylamine, *N*-methylmorpholine, arginine, lysine, 1,2-ethylenediamine, *N*-methylpiperidine, *N*-methyl-glucamine, *N,N*-dimethyl-glucamine, *N*-ethyl-glucamine, 1,6-hexanediamine, glucosamine, sarcosine, serinol, 2-amino-1,3-propanediol, 3-amino-1,2-propanediol, 4-amino-1,2,3-butanetriol, or a salt with a quarternary ammonium ion having 1 to 20 carbon atoms, such as tetramethylammonium, tetraethylammonium, tetra(*n*-propyl)ammonium, tetra(*n*-butyl)ammonium, *N*-benzyl-*N,N,N*-trimethylammonium, choline or benzalkonium.

Those skilled in the art will further recognise that it is possible for acid addition salts of the claimed compounds to be prepared by reaction of the compounds with the appropriate inorganic or organic acid via any of a number of known methods. Alternatively, alkali and alkaline earth metal salts of acidic compounds of the present invention are prepared by reacting the compounds of the present invention with the appropriate base via a variety of known methods.

The present invention includes all possible salts of the compounds of the present invention as single salts, or as any mixture of said salts, in any ratio.

In the present text, in particular in the Experimental Section, for the synthesis of intermediates and of examples of the present invention, when a compound is mentioned as a salt form with the

corresponding base or acid, the exact stoichiometric composition of said salt form, as obtained by the respective preparation and/or purification process, is, in most cases, unknown.

Unless specified otherwise, suffixes to chemical names or structural formulae relating to salts, such as "hydrochloride", "trifluoroacetate", "sodium salt", or "x HCl", "x CF_3COOH", "x Na^+", for example, mean a salt form, the stoichiometry of which salt form not being specified.

This applies analogously to cases in which synthesis intermediates or example compounds or salts thereof have been obtained, by the preparation and/or purification processes described, as solvates, such as hydrates, with (if defined) unknown stoichiometric composition.

Furthermore, the present invention includes all possible crystalline forms, or polymorphs, of the compounds of the present invention, either as single polymorph, or as a mixture of more than one polymorph, in any ratio.

Furthermore, the present invention also embraces prodrugs of the compounds of the invention. The term “prodrugs” denotes compounds which may themselves be biologically active or inactive but which during their residence time in the body are converted (metabolically or by hydrolysis, for example) into compounds of the invention.

Preference is given to compounds of the general formula (I) in which

R^1 represents hydrogen or methyl,

R^2 represents C_1-C_5-alkyl, pyrrolidin-3-yl or piperidin-5-yl,

where alkyl may be substituted by 1 to 2 substituents independently of one another selected from the group consisting of fluorine, hydroxy, amino, aminocarbonyl, aminosulfonyl, difluoromethyl, trifluoromethyl, methoxy, ethoxy, C_3-C_6-cycloalkyl, oxetan-3-yl, thietan-3-yl, pyrrolidin-1-yl, pyrrolidin-2-yl, 1,3-oxazolidin-5-yl, imidazolidin-1-yl, piperidin-4-yl, 1,2-thiazinan-2-yl, azepan-4-yl, methylsulfonyl, methylcarbonylamino, 2,2,2-trifluoroethylaminocarbonyl, methylsulfonylamino and C_1-C_4-alkoxycarbonyl,

wherein oxetan-3-yl, thietan-3-yl, pyrrolidin-1-yl, pyrrolidin-2-yl, 1,3-oxazolidin-5-yl, imidazolidin-1-yl, piperidin-4-yl, 1,2-thiazinan-2-yl and azepan-4-yl may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of oxo, chlorine, fluorine, hydroxy, formyl, aminocarbonyl, methyl, methoxy, trifluoromethyl, methylcarbonyl, methylsulfonyl and C_1-C_4-alkoxycarbonyl,

and

wherein cycloalkyl may be substituted by one substituent hydroxyl,

and

where pyrrolidin-3-yl and piperidin-5-yl may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of oxo, chlorine, fluorine, hydroxy, aminocarbonyl, methyl, methoxy, trifluoromethyl, methylcarbonyl, methylsulfonyl and C_1-C_4-alkoxycarbonyl,

or

R^1 and R^2 together with the nitrogen atom to which they are attached form azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, 6-oxo-2,5,7-triazaspiro[3.4]octan-2-yl, hexahydro-4H-furo[3,2-b]pyrrol-4-yl, 2,2-dioxido-2-thia-6-azaspiro[3.3]hept-6-yl or 2-oxa-6-azaspiro[3.3]hept-6-yl,

where azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl and thiomorpholinyl may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of oxo, chlorine, fluorine, hydroxy, aminocarbonyl, methyl, methoxy, trifluoromethyl, methylcarbonyl, methylsulfonyl and C_1-C_4-alkoxycarbonyl,

R^3 represents phenyl, pyridinyl or 3,3,3-trifluoroprop-1-yl,

where phenyl may be substituted by one substituent selected from the group consisting of chlorine, fluorine and trifluoromethyl,

and

where pyridinyl may be substituted by one substituent selected from the group consisting of chlorine, fluorine, trifluoromethyl and trifluoromethoxy,

and pharmaceutically acceptable salts thereof, solvates thereof and the solvates of the salts thereof.

Preference is also given to compounds of the general formula (I) in which

R^1 represents hydrogen or methyl,

R^2 represents C_1-C_5-alkyl, pyrrolidin-3-yl or piperidin-5-yl,

where alkyl may be substituted by 1 to 2 substituents independently of one another selected from the group consisting of fluorine, hydroxy, amino, aminocarbonyl, aminosulfonyl, trifluoromethyl, methoxy, C_3-C_6-cycloalkyl, oxetan-3-yl, thietan-3-yl, pyrrolidin-1-yl, pyrrolidin-2-yl, 1,3-oxazolidin-5-yl, imidazolidin-1-yl, piperidin-4-yl, 1,2-thiazinan-2-yl, azepan-4-yl, methylsulfonyl, methylcarbonylamino, 2,2,2-trifluoroethylaminocarbonyl, methylsulfonylamino and C_1-C_4-alkoxycarbonyl,

wherein oxetan-3-yl, thietan-3-yl, pyrrolidin-1-yl, pyrrolidin-2-yl, 1,3-oxazolidin-5-yl, imidazolidin-1-yl, piperidin-4-yl, 1,2-thiazinan-2-yl and azepan-4-yl may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of oxo, hydroxy, formyl, methyl and C_1-C_4-alkoxycarbonyl,

and

wherein cycloalkyl may be substituted by one substituent hydroxyl,

and

where pyrrolidin-3-yl and piperidin-5-yl may be substituted by 1 or 2 substituents of oxo,

or

R^1 and R^2 together with the nitrogen atom to which they are attached form azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, 6-oxo-2,5,7-triazaspiro[3.4]octan-2-yl, hexahydro-4H-furo[3,2-b]pyrrol-4-yl, 2,2-dioxido-2-thia-6-azaspiro[3.3]hept-6-yl or 2-oxa-6-azaspiro[3.3]hept-6-yl,

where azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl and thiomorpholinyl may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of oxo, fluorine, hydroxy, aminocarbonyl, methyl, methoxy, trifluoromethyl, methylcarbonyl and methylsulfonyl,

R^3 represents phenyl, pyridinyl or 3,3,3-trifluoroprop-1-yl,

where phenyl may be substituted by one substituent selected from the group consisting of chlorine, fluorine and trifluoromethyl,

and

where pyridinyl may be substituted by one substituent selected from the group consisting of chlorine, fluorine and trifluoromethyl,

and pharmaceutically acceptable salts thereof, solvates thereof and the solvates of the salts thereof.

Preference is also given to compounds of the general formula (I) in which

R^1 represents hydrogen,

R^2 represents 2-hydroxy-2-methyl-prop-1-yl or 2-amino-2-methyl-prop-1-yl,

or

R^1 and R^2 together with the nitrogen atom to which they are attached form piperazinyl or 1,1-dioxidothiomorpholinyl,

where piperazinyl is substituted by 1 or 2 substituents independently of one another selected from the group consisting of oxo, methyl and trifluoromethyl,

R^3 represents phenyl or pyridin-2-yl,

where phenyl is substituted by one substituent trifluoromethyl in ortho-position to the point of attachment of the phenyl to the 1,2,4-triazolyl-ring,

and

where pyridin-2-yl may be substituted by one substituent selected from the group consisting of chlorine, fluorine and trifluoromethyl in ortho-position to the point of attachment of the pyridin-2-yl to the 1,2,4-triazolyl-ring,

and pharmaceutically acceptable salts thereof, solvates thereof and the solvates of the salts thereof.

Preference is also given to compounds of the general formula (I) in which

R^1 represents hydrogen,

R^2 represents 2-hydroxy-2-methyl-prop-1-yl or 2-amino-2-methyl-prop-1-yl,

or

R^1 and R^2 together with the nitrogen atom to which they are attached form 3,3-dimethyl-piperazin-1-yl, 3-trifluoromethyl-piperazin-1-yl or 1,1-dioxidothiomorpholinyl,

R^3 represents pyridin-2-yl,

where pyridin-2-yl is substituted by one substituent selected from the group consisting of chlorine and trifluoromethyl in ortho-position to the point of attachment of the pyridin-2-yl to the 1,2,4-triazolyl-ring,

and pharmaceutically acceptable salts thereof, solvates thereof and the solvates of the salts thereof.

Preference is also given to compounds of the general formula (I) in which

R^1 represents hydrogen,

R^2 represents methyl,

where methyl is substituted by one substituent selected from the group consisting of cyclopropyl, cyclobutyl and thietan-3-yl,

wherein thietan-3-yl is substituted by 2 substituents oxo,

and

wherein cyclopropyl and cyclobutyl are substituted by one substituent hydroxyl,

or

R^1 and R^2 together with the nitrogen atom to which they are attached form azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl or 2,2-dioxido-2-thia-6-azaspiro[3.3]hept-6-yl,

where azetidinyl, pyrrolidinyl, piperidinyl and piperazinyl may be substituted by 1 or 2 substituents independently of one another selected from the group consisting of fluorine, hydroxy, methyl, trifluoromethyl, methylcarbonyl and methylsulfonyl,

R^3 represents phenyl,

where phenyl may be substituted by one substituent selected from the group consisting of chlorine and fluorine in ortho-position or meta-position to the point of attachment of the phenyl to the 1,2,4-triazolyl-ring,

and pharmaceutically acceptable salts thereof, solvates thereof and the solvates of the salts thereof.

Preference is also given to compounds of the general formula (I) in which

R^1 represents hydrogen,

R^2 represents methyl,

where methyl is substituted by one substituent cyclopropyl,

wherein cyclopropyl is substituted by one substituent hydroxyl,

or

R^1 and R^2 together with the nitrogen atom to which they are attached form azetidinyl, pyrrolidinyl, piperazinyl or 2,2-dioxido-2-thia-6-azaspiro[3.3]hept-6-yl,

where azetidinyl and pyrrolidinyl are substituted by one substituent hydroxy and by one substituent trifluoromethyl,

and

where piperazinyl is substituted by one substituent methylcarbonyl,

R^3 represents phenyl,

where phenyl may be substituted by one substituent selected from the group consisting of chlorine and fluorine in ortho-position or meta-position to the point of attachment of the phenyl to the 1,2,4-triazolyl-ring,

and pharmaceutically acceptable salts thereof, solvates thereof and the solvates of the salts thereof.

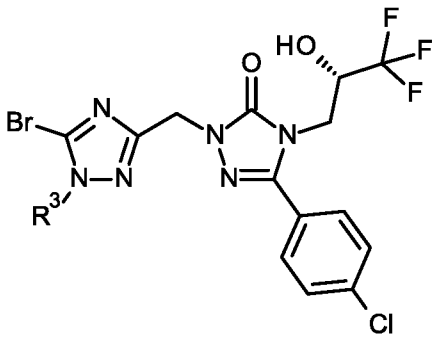
In a particular further embodiment of the first aspect, the present invention covers combinations of two or more of the above mentioned embodiments under the heading “further embodiments of the first aspect of the present invention”.

The present invention covers any sub-combination within any embodiment or aspect of the present invention of compounds of general formula (I).

The present invention covers the compounds of general formula (I) which are disclosed in the Example Section of this text, infra.

The invention further provides a process for preparing the compounds of the general formula (I), or the pharmaceutically acceptable salts thereof, solvates thereof or the solvates of the salts thereof, wherein

[A] the compounds of the formula



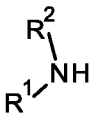
(II),

in which

R^3 has the meaning as defined for the compounds of general formula (I) given above,

wherein the hydroxy group in the formula (II) may be protected with a tert-butyl-(dimethyl)silyl group at the beginning of the reaction and which is cleaved under the reaction conditions,

are reacted with compounds of the formula



(III),

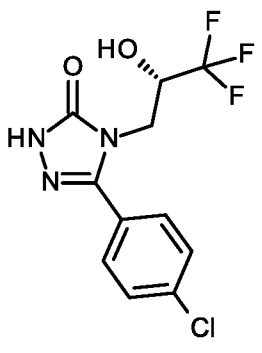
in which

R^1 and R^2 have the meaning as defined for the compounds of general formula (I) given above,

to give compounds of the general formula (I)

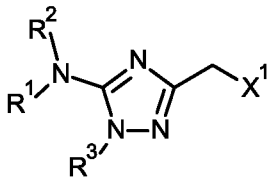
or

[B] the compound of the formula



(IV),

is reacted with compounds of the formula



(V),

in which

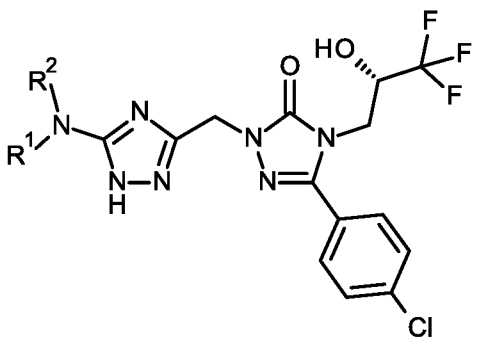
X^1 represents bromine or chlorine, and

R^1, R^2 and R^3 have the meaning as defined for the compounds of general formula (I) given above,

to give compounds of the general formula (I)

or

[C] the compounds of the formula



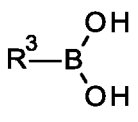
(VI),

in which

R^1 and R^2 together with the nitrogen atom to which they are attached form a 4- to 6-membered heterocyclyl,

where heterocyclyl may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of oxo, chlorine, fluorine, hydroxy, aminocarbonyl, methyl, methoxy, trifluoromethyl, methylcarbonyl, methylsulfonyl and C_1-C_4-alkoxycarbonyl,,

are reacted with compounds of the formula

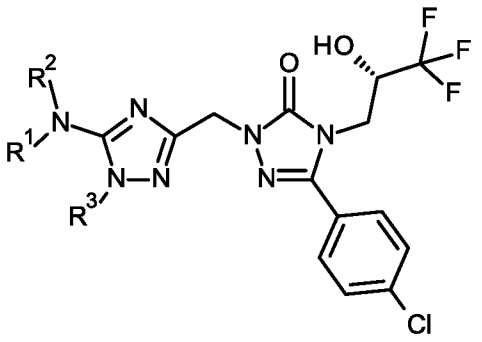


(VII),

in which

R^3 has the meaning as defined for the compounds of general formula (I) given above,

under Chan-Lam coupling conditions to give compounds of the formula



(Ia),

in which

R^1 and R^2 together with the nitrogen atom to which they are attached form a 4- to 6-membered heterocyclyl,

where heterocyclyl may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of oxo, chlorine, fluorine, hydroxy, aminocarbonyl, methyl, methoxy, trifluoromethyl, methylcarbonyl, methylsulfonyl and C_1-C_4-alkoxycarbonyl,

and

R^3 has the meaning as defined for the compounds of general formula (I) given above,

each [A], [B] and [C] optionally followed, where appropriate, by (*i*) separating the compounds of the general formula (I) thus obtained into their respective diastereomers, and/or (*ii*) converting the compounds of the general formula (I) into their respective pharmaceutically acceptable salts thereof, solvates thereof or the solvates of the salts thereof by treatment with the corresponding solvents and/or acids or bases.

The compounds of the formula (Ia) are a subset of the compounds of general formula (I).

The present invention covers methods of preparing compounds of the present invention of general formula (I), said methods comprising the steps as described in the Experimental Section herein.

The schemes and procedures described below illustrate synthetic routes to the compounds of general formula (I) of the invention and are not intended to be limiting. It is clear to the person skilled in the art that the order of transformations as exemplified in schemes 1, 2 and 3 can be modified in various ways. The order of transformations exemplified in these schemes is therefore not intended to be limiting. In addition, interconversion of any of the substituents R^1, R^2 and R^3 can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, halogenation, metallation, substitution or other reactions known to the person

skilled in the art. These transformations include those which introduce a functionality which allows for further interconversion of substituents. Appropriate protecting groups and their introduction and cleavage are well-known to the person skilled in the art (see for example T.W. Greene and P.G.M. Wuts in *Protective Groups in Organic Synthesis*, 3rd edition, Wiley 1999). Specific examples are described in the subsequent paragraphs.

The reaction according to process [A] is generally carried out by reacting a compound of the formula (II) with a compound of the formula (III) in an inert solvent or without solvent, if the compound of the formula (III) is a liquid, optionally in the presence of a base and optionally in a microwave, preferably in a temperature range from +20°C to +200°C, more preferably at +80°C to +180°C. The reactions can be carried out at atmospheric, at elevated or at reduced pressure (for example at from 0.5 to 5 bar); in general, the reactions are carried out at atmospheric pressure.

Inert solvents for the process step (II) + (III) → (I) are, for example, halogenated hydrocarbons such as dichloromethane, trichloromethane, carbon tetrachloride, trichloroethylene or chlorobenzene, hydrocarbons such as benzene, toluene, xylene, pentane, hexane, cyclohexane or mineral oil fractions, or dipolar aprotic solvents such as acetone, methyl ethyl ketone, ethyl acetate or acetonitrile. Preference is given to using acetonitrile.

Suitable bases for process step (II) + (III) → (I) are, for example, organic amines such as triethylamine, *N*-methylmorpholine, *N*-methylpiperidine, *N,N*-diisopropylethylamine or pyridine. Preference is given to using *N,N*-diisopropylethylamine.

The reaction according to process [B] is generally carried out by reacting a compound of the formula (IV) with a compound of the formula (V) in an inert solvent in the presence of a base and an optional alkylation catalyst, preferably in a temperature range of from -20°C to +150°C, more preferably at from 0°C to +80°C. The reactions can be carried out at atmospheric, at elevated or at reduced pressure (for example at from 0.5 to 5 bar); in general, the reactions are carried out at atmospheric pressure.

Inert solvents for the process step (IV) + (V) → (I) are, for example, halogenated hydrocarbons such as dichloromethane, trichloromethane, carbon tetrachloride, trichloroethylene or chlorobenzene, ethers such as diethyl ether, diisopropyl ether, methyl *tert*-butyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane or bis-(2-methoxyethyl) ether, hydrocarbons such as benzene, toluene, xylene, pentane, hexane, cyclohexane or mineral oil fractions, or dipolar aprotic solvents such as acetone, methyl ethyl ketone, ethyl acetate, acetonitrile, *N,N*-dimethylformamide (DMF), *N,N*-dimethylacetamide (DMA), dimethyl sulfoxide (DMSO), *N,N'*-dimethylpropyleneurea (DMPU), *N*-methylpyrrolidinone (NMP) or pyridine. It is also possible to use mixtures of the solvents mentioned. Preference is given to using tetrahydrofuran, acetonitrile, acetone or dimethylformamide.

Suitable bases for process step (IV) + (V) → (I) are the customary inorganic or organic bases. These preferably include alkali metal hydroxides such as, for example, lithium hydroxide, sodium hydroxide or potassium hydroxide, alkali metal or alkaline earth metal carbonates such as lithium carbonate, sodium carbonate, potassium carbonate, calcium carbonate or cesium carbonate, alkali metal alkoxides such as sodium methoxide or potassium methoxide, sodium ethoxide or potassium ethoxide or sodium *tert*-butoxide or potassium *tert*-butoxide, alkali metal hydrides such as sodium hydride or potassium hydride, amides such as sodium amide, lithium bis(trimethylsilyl)amide or potassium bis(trimethylsilyl)amide or lithium diisopropylamide, or organic amines such as triethylamine, *N*-methylmorpholine, *N*-methylpiperidine, *N,N*-diisopropylethylamine, pyridine, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or 1,4-diazabicyclo[2.2.2]octane (DABCO®). Preference is given to using potassium carbonate or cesium carbonate or sodium hydride. Here, the base is employed in an amount of from 1 to 5 mol, preferably in an amount of from 1 to 2.5 mol, based on 1 mole of the compound of the formula (IV).

These process steps (IV) + (V) → (I) may optionally be carried out in an advantageous manner with addition of alkylation catalysts such as, for example, lithium bromide, sodium iodide, potassium iodide, tetra-*n*-butylammonium bromide or benzyltriethylammonium chloride.

The Chan-Lam coupling reaction according to process [C] is generally carried out in inert solvents, in the presence of a copper catalyst and an amine base, optionally in a microwave, preferably in a temperature range from +20°C to +120°C, more preferably at +20°C to +70°C. The reactions can be carried out at atmospheric, at elevated or at reduced pressure (for example at from 0.5 to 5 bar); in general, the reactions are carried out at atmospheric pressure.

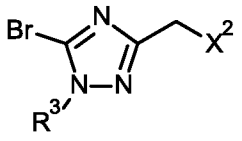
Inert solvents for the process step (VI) + (VII) → (I) are, for example, dichloromethane, 1,2-dichloroethane, methyl *tert*-butyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, toluene, pyridine, ethyl acetate, acetonitrile or *N,N*-dimethylformamide, or a mixture of these solvents. Preferably, pyridine is used both as solvent and base.

Suitable copper catalysts for the process step (VI) + (VII) → (I) are, for example, copper(II)salts, such as copper(II)acetate, copper(II)trifluoromethanesulfonate or copper(II)bromide. Preferably, copper(II)acetate is used.

Suitable amine bases for process step (VI) + (VII) → (I) are, for example, triethylamine, *N,N*-diisopropylethylamine, pyridine and 4-(*N,N*-dimethylamino)pyridine. Preferably, pyridine is used both as solvent and base.

["Chan-Lam coupling" conditions; see, for instance, D. M. T. Chan et al., *Tetrahedron Lett.* 44 (19), 3863-3865 (2003); J. X. Qiao and P. Y. S. Lam, *Synthesis*, 829-856 (2011); K. S. Rao and T.-S. Wu, *Tetrahedron* 68, 7735-7754 (2012)].

The compounds of the formula (II) are known or can be prepared by reacting the compound of the formula (IV) with compounds of the formula



(VIII),

in which

X^2 represents bromine or chlorine, and

R^3 has the meaning as defined for the compounds of general formula (I) given above.

The reaction is generally carried out by reacting a compound of the formula (IV) with a compound of the formula (VIII) in an inert solvent in the presence of a base and an optional alkylation catalyst, preferably in a temperature range of from -20°C to +150°C, more preferably at from 0°C to +80°C. The reactions can be carried out at atmospheric, at elevated or at reduced pressure (for example at from 0.5 to 5 bar); in general, the reactions are carried out at atmospheric pressure.

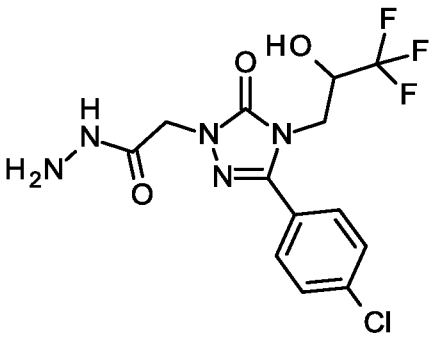
Inert solvents for the process step (IV) + (VIII) → (II) are, for example, halogenated hydrocarbons such as dichloromethane, trichloromethane, carbon tetrachloride, trichloroethylene or chlorobenzene, ethers such as diethyl ether, diisopropyl ether, methyl *tert*-butyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane or bis-(2-methoxyethyl) ether, hydrocarbons such as benzene, toluene, xylene, pentane, hexane, cyclohexane or mineral oil fractions, or dipolar aprotic solvents such as acetone, methyl ethyl ketone, ethyl acetate, acetonitrile, *N,N*-dimethylformamide (DMF), *N,N*-dimethylacetamide (DMA), dimethyl sulfoxide (DMSO), *N,N'*-dimethylpropyleneurea (DMPU), *N*-methylpyrrolidinone (NMP) or pyridine. It is also possible to use mixtures of the solvents mentioned. Preference is given to using tetrahydrofuran, acetonitrile, acetone or dimethylformamide.

Suitable bases for process step (IV) + (VIII) → (II) are the customary inorganic or organic bases. These preferably include alkali metal hydroxides such as, for example, lithium hydroxide, sodium hydroxide or potassium hydroxide, alkali metal or alkaline earth metal carbonates such as lithium carbonate, sodium carbonate, potassium carbonate, calcium carbonate or cesium carbonate, alkali metal alkoxides such as sodium methoxide or potassium methoxide, sodium ethoxide or potassium ethoxide or sodium *tert*-butoxide or potassium *tert*-butoxide, alkali metal hydrides such as sodium hydride or potassium hydride, amides such as sodium amide, lithium bis(trimethylsilyl)amide or potassium bis(trimethylsilyl)amide or lithium diisopropylamide, or organic amines such as triethylamine, *N*-methylmorpholine, *N*-methylpiperidine, *N,N*-diisopropylethylamine, pyridine, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or 1,4-diazabicyclo[2.2.2]octane (DABCO®). Preference is given to using potassium carbonate or cesium

carbonate or sodium hydride. Here, the base is employed in an amount of from 1 to 5 mol, preferably in an amount of from 1 to 2.5 mol, based on 1 mole of the compound of the formula (IV).

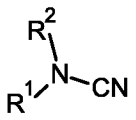
These process steps (IV) + (VIII) → (II) may optionally be carried out in an advantageous manner with addition of alkylation catalysts such as, for example, lithium bromide, sodium iodide, potassium iodide, tetra-*n*-butylammonium bromide or benzyltriethylammonium chloride.

The compounds of the formula (VI) are known or can be prepared by reacting the compound of the formula



(IX)

with compounds of the formula



(X),

in which

R^1 and R^2 together with the nitrogen atom to which they are attached form a 4- to 6-membered heterocyclyl,

where heterocyclyl may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of oxo, chlorine, fluorine, hydroxy, aminocarbonyl, methyl, methoxy, trifluoromethyl, methylcarbonyl, methylsulfonyl and C_1-C_4-alkoxycarbonyl.

The reaction is generally carried out by reacting a compound of the formula (IX) with a compound of the formula (X) in an inert solvent in the presence of a base, optionally in a microwave, preferably in a temperature range of from -20°C to +150°C, more preferably at from +20°C to +150°C. The reactions can be carried out at atmospheric, at elevated or at reduced pressure (for example at from 0.5 to 5 bar); in general, the reactions are carried out at atmospheric pressure.

Inert solvents for the process step (IX) + (X) → (VI) are, for example alkohols such as methanol, ethanol, propanol, 1-butanol. Preference is given to 1-butanol.

Suitable bases for process step (IX) + (X) → (VI) are the customary inorganic bases or organic bases. These preferably include alkali metal or alkaline earth metal carbonates such as lithium carbonate, sodium carbonate, potassium carbonate, calcium carbonate or cesium carbonate, or alkali metal alkoxides such as sodium methoxide or potassium methoxide, sodium ethoxide or potassium ethoxide, or alkali metal hydrides such as sodium hydride in methanol or ethanol. Preference is given to using potassium carbonate.

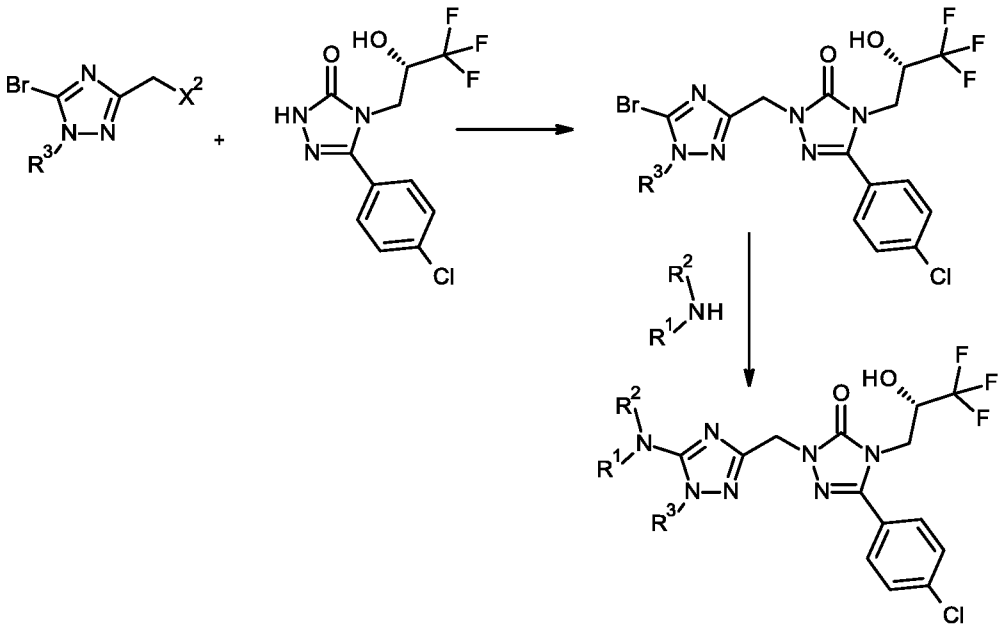
The compound of the formula (IV) can be synthesized by the procedures described in Int. Pat. Appl. WO 2011/104322.

The compound of the formula (IX) can be synthesized by the procedures described in Int. Pat. Appl. WO 2016/071212.

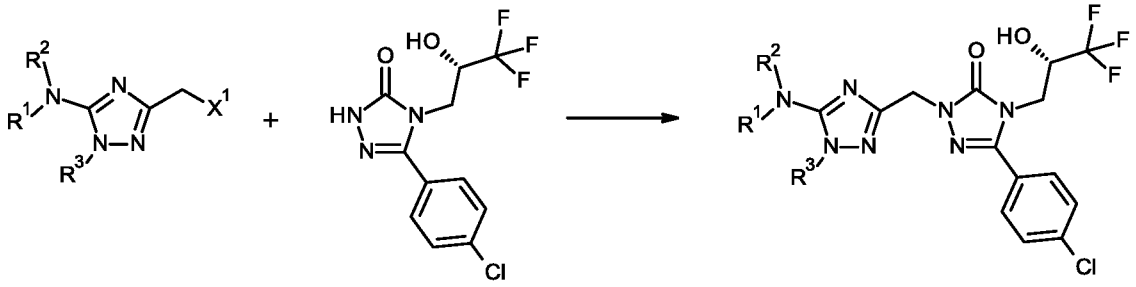
The compounds of the formula (III), (V), (VII), (VIII) and (X) are either commercially available, known from the literature, or can be prepared from readily available starting materials by adaptation of standard methods described in the literature. Detailed procedures and literature references for preparing the starting materials can also be found in the Experimental Part in the section on the preparation of the starting materials and intermediates.

The preparation of the compounds of the invention may be illustrated by means of the following synthetic schemes:

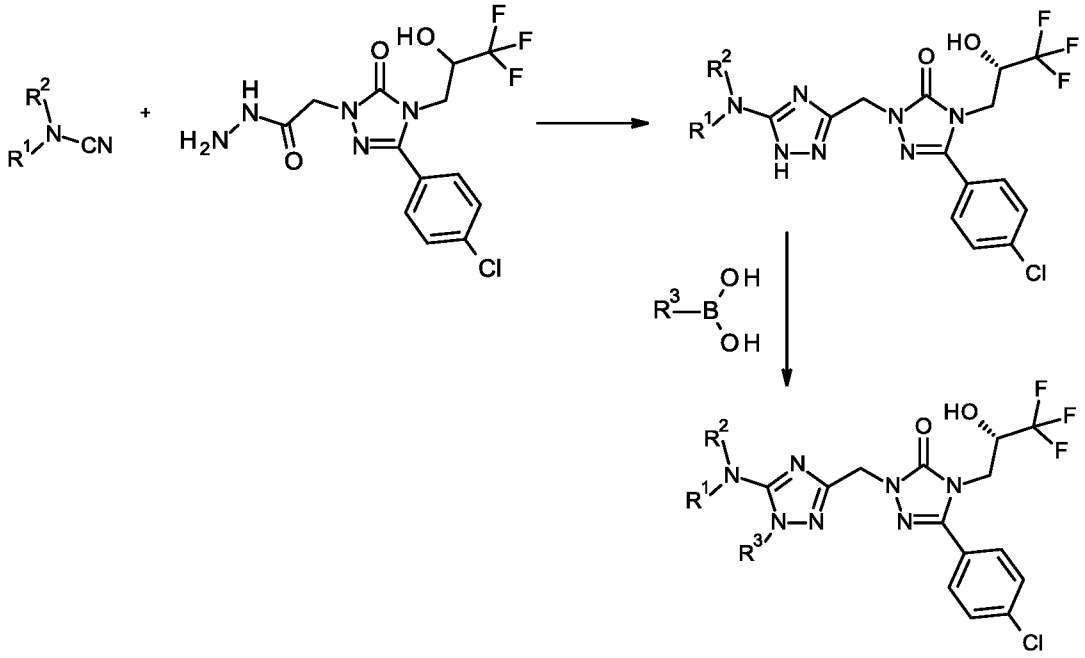
Scheme 1



Scheme 2



Scheme 3



The compounds of general formula (I) of the present invention can be converted to any salt, preferably pharmaceutically acceptable salts, as described herein, by any method which is known to the person skilled in the art. Similarly, any salt of a compound of general formula (I) of the present invention can be converted into the free compound, by any method which is known to the person skilled in the art.

The compounds of the present invention have valuable pharmacological properties and can be used for the prevention and/or treatment of various diseases and disease-induced states in humans and other mammals. Compounds of general formula (I) of the present invention demonstrate a valuable pharmacological spectrum of action and pharmacokinetic profile, both of which could not have been predicted. Compounds of the present invention have surprisingly been found to effectively inhibit the vasopressin V1a receptor and it is possible therefore that said compounds be used for the treatment and/or prevention of diseases, preferably renal and cardiovascular diseases in humans and animals.

In the context of the present invention, the term "treatment" or "treating" includes inhibiting, delaying, relieving, mitigating, arresting, reducing, or causing the regression of a disease, disorder, condition, or state, the development and/or progression thereof, and/or the symptoms thereof. The term "prevention" or "preventing" includes reducing the risk of having, contracting, or experiencing a disease, disorder, condition, or state, the development and/or progression thereof, and/or the symptoms thereof. The term prevention includes prophylaxis. Treatment or prevention of a disorder, disease, condition, or state may be partial or complete.

Throughout this document, for the sake of simplicity, the use of singular language is given preference over plural language, but is generally meant to include the plural language if not otherwise stated. For example, the expression "A method of treating a disease in a patient, comprising administering to a patient an effective amount of a compound of the general formula (I)" is meant to include the simultaneous treatment of more than one disease as well as the administration of more than one compound of the general formula (I).

The compounds of the present invention are potent selective or dual antagonists of vasopressin V1a and V2 receptors. The compounds of the invention are therefore expected to be highly valuable as therapeutic agents for the treatment and/or prevention of diseases, in particular for the treatment and/or prevention of cardiovascular and renal diseases.

The compounds according to the invention are suitable for the treatment and/or prevention of renal diseases, in particular of acute and chronic kidney diseases, diabetic kidney diseases, and of acute and chronic renal failure. The general terms 'renal disease' or 'kidney disease' describe a class of conditions in which the kidneys fail to filter and remove waste products from the blood. There are two major forms of kidney disease: acute kidney disease (acute kidney injury, AKI) and chronic kidney disease (CKD). The compounds according to the invention may further be used for the treatment and/or prevention of sequelae of acute kidney injury arising from multiple insults such as ischemia-reperfusion injury, radiocontrast administration, cardiopulmonary bypass surgery, shock and sepsis. In the sense of the present invention, the term renal failure or renal insufficiency comprises both acute and chronic manifestations of renal insufficiency, as well as underlying or related kidney diseases such as renal hypoperfusion, intradialytic hypotension, obstructive uropathy, glomerulopathies, IgA nephropathy, glomerulonephritis, acute glomerulonephritis, glomerulosclerosis, tubulointerstitial diseases, nephropathic diseases such as primary and congenital kidney disease, nephritis, Alport syndrome, kidney inflammation, immunological kidney diseases such as kidney transplant rejection, immune complex-induced kidney diseases, nephropathy induced by toxic substances, contrast medium-induced nephropathy; minimal change glomerulonephritis (lipoid); Membranous glomerulonephritis; focal segmental glomerulosclerosis (FSGS); hemolytic uremic syndrome (HUS), amyloidosis, Goodpasture's syndrome, Wegener's granulomatosis, Purpura Schönlein-Henoch, diabetic and non-diabetic nephropathy, pyelonephritis,

renal cysts, nephrosclerosis, hypertensive nephrosclerosis and nephrotic syndrome, which can be characterized diagnostically, for example, by abnormally reduced creatinine and/or water excretion, abnormally increased blood concentrations of urea, nitrogen, potassium and/or creatinine, altered activity of renal enzymes such as, for example, glutamyl synthetase, altered urine osmolarity or urine volume, increased microalbuminuria, macroalbuminuria, lesions of glomeruli and arterioles, tubular dilatation, hyperphosphataemia and/or the need for dialysis. The present invention also comprises the use of the compounds according to the invention for the treatment and/or prevention of sequelae of renal insufficiency, for example pulmonary edema, heart failure, uraemia, anaemia, electrolyte disturbances (*e.g.* hyperkalaemia, hyponatraemia) and disturbances in bone and carbohydrate metabolism. The compounds according to the invention are also suitable for the treatment and/or prevention of polycystic kidney disease (PCKD) and of the syndrome of inadequate ADH secretion (SIADH).

Cardiovascular diseases in this context that may be treated and/or prevented with the compounds of the invention include, but are not limited to, the following: acute and chronic heart failure including worsening chronic heart failure (or hospitalization for heart failure) and including congestive heart failure, arterial hypertension, resistant hypertension, arterial pulmonary hypertension, coronary heart disease, stable and unstable angina pectoris, atrial and ventricular arrhythmias, disturbances of atrial and ventricular rhythm and conduction disturbances, for example atrioventricular blocks of degree I-III (AVB I-III), supraventricular tachyarrhythmia, atrial fibrillation, atrial flutter, ventricular fibrillation, ventricular flutter, ventricular tachyarrhythmia, torsade-de-pointes tachycardia, atrial and ventricular extrasystoles, AV-junction extrasystoles, sick-sinus syndrome, syncopes, AV-node re-entry tachycardia and Wolff-Parkinson-White syndrome, acute coronary syndrome (ACS), autoimmune heart diseases (pericarditis, endocarditis, valvulitis, aortitis, cardiomyopathies), shock such as cardiogenic shock, septic shock and anaphylactic shock, aneurysms, Boxer cardiomyopathy (premature ventricular contraction), furthermore thromboembolic diseases and ischaemias such as peripheral perfusion disturbances, reperfusion injury, arterial and venous thromboses, myocardial insufficiency, endothelial dysfunction, micro- and macrovascular damage (vasculitis) and for preventing restenoses such as after thrombolysis therapies, percutaneous transluminal angioplasty (PTA), percutaneous transluminal coronary angioplasty (PTCA), heart transplantation and bypass operations, arteriosclerosis, disturbances of lipid metabolism, hypolipoproteinaemias, dyslipidemias, hypertriglyceridemias, hyperlipidemias and combined hyperlipidemias, hypercholesterolaemias, abetalipoproteinaemia, sitosterolemia, xanthomatosis, Tangier disease, adipositas, obesity, metabolic syndrome, transitory and ischemic attacks, stroke, inflammatory cardiovascular diseases, peripheral and cardiac vascular diseases, peripheral circulation disorders, spasms of the coronary arteries and peripheral arteries, and edema such as, for example, pulmonary edema, cerebral edema, renal edema and heart failure-related edema.

In the sense of the present invention, the term heart failure also includes more specific or related disease forms such as right heart failure, left heart failure, global insufficiency, ischemic cardiomyopathy, dilatative cardiomyopathy, congenital heart defects, heart valve defects, heart failure with heart valve defects, mitral valve stenosis, mitral valve insufficiency, aortic valve stenosis, aortic valve insufficiency, tricuspidal stenosis, tricuspidal insufficiency, pulmonary valve stenosis, pulmonary valve insufficiency, combined heart valve defects, heart muscle inflammation (myocarditis), chronic myocarditis, acute myocarditis, viral myocarditis, diabetic heart failure, alcohol-toxic cardiomyopathy, cardiac storage diseases, heart failure with preserved ejection fraction (HFpEF or diastolic heart failure), and heart failure with reduced ejection fraction (HFrEF or systolic heart failure).

The compounds of the present invention may be particularly useful for the treatment and/or prevention of the cardiorenal syndrome (CRS) and its various subtypes. This term embraces certain disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other. CRS has been sub-classified into five types based upon the organ that initiated the insult as well as the acuity and chronicity of the disease (type 1: development of renal insufficiency resulting from acute decompensated heart failure; type 2: chronic congestive heart failure resulting in progressive renal dysfunction; type 3: acute cardiac dysfunction resulting from an abrupt fall in renal function; type 4: chronic kidney disease leading to cardiac remodeling; type 5: systemic disease involving both the heart and the kidneys) [see, for example, M. R. Kahn et al., *Nature Rev. Cardiol.* 10, 261-273 (2013)].

The compounds according to the invention are also suitable for the treatment and/or prevention of polycystic kidney disease (PCKD) and of the syndrome of inadequate ADH secretion (SIADH). Furthermore, the compounds of the invention are suitable for use as a diuretic for the treatment of edemas and in electrolyte disorders, in particular in hypervolemic and euvolemic hyponatremia.

Moreover, the compounds according to the invention may be used for the treatment and/or prevention of peripheral arterial disease (PAD) including claudication and including critical limb ischemia coronary microvascular dysfunction (CMD) including CMD type 1-4, primary and secondary Raynaud's phenomenon, microcirculation disturbances, claudication, peripheral and autonomic neuropathies, diabetic microangiopathies, diabetic retinopathy, diabetic limb ulcers, gangrene, CREST syndrome, erythematous disorders, rheumatic diseases and for promoting wound healing.

Furthermore, the compounds of the invention are suitable for treating urological diseases and diseases of the male and female urogenital system such as, for example, benign prostatic syndrome (BPS), benign prostatic hyperplasia (BPH), benign prostatic enlargement (BPE), bladder outlet obstruction (BOO), lower urinary tract syndromes (LUTS), neurogenic overactive bladder (OAB), interstitial cystitis (IC), urinary incontinence (UI) such as, for example, mixed, urge, stress and

overflow incontinence (MUI, UUI, SUI, OUI), pelvic pains, erectile dysfunction, dysmenorrhea and endometriosis.

The compounds according to the invention may also be used for the treatment and/or prevention of inflammatory diseases, asthmatic diseases, chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), acute lung injury (ALI), alpha-1-antitrypsin deficiency (AATD), pulmonary fibrosis, pulmonary emphysema (*e.g.* smoking-induced pulmonary emphysema) and cystic fibrosis (CF). In addition, the compounds of the invention may be used for the treatment and/or prevention of pulmonary arterial hypertension (PAH) and other forms of pulmonary hypertension (PH), including pulmonary hypertension associated with left ventricular disease, HIV infection, sickle cell anaemia, thromboembolism (CTEPH), sarcoidosis, chronic obstructive pulmonary disease (COPD) or pulmonary fibrosis.

Additionally, the compounds according to the invention may be used for the treatment and/or prevention of liver cirrhosis, ascites, diabetes mellitus and diabetic complications such as, for example, neuropathy and nephropathy.

Further, the compounds of the invention are suitable for the treatment and/or prevention of central nervous disorders such as anxiety states, depression, glaucoma, cancer such as in particular pulmonary tumors, and circadian rhythm misalignment such as jet lag and shift work.

Furthermore, the compounds according to the invention may be useful for the treatment and/or prevention of pain conditions, diseases of the adrenals such as, for example, pheochromocytoma and adrenal apoplexy, diseases of the intestine such as, for example, Crohn's disease and diarrhea, menstrual disorders such as, for example, dysmenorrhea, endometriosis, preterm labor and tocolysis.

Due to their activity and selectivity profile, the compounds of the present invention are believed to be particularly suitable for the treatment and/or prevention of acute and chronic kidney diseases including diabetic nephropathy, acute and chronic heart failure, preeclampsia, peripheral arterial disease (PAD), coronary microvascular dysfunction (CMD), Raynaud's syndrome, dysmenorrhea, cardiorenal syndrome, hypervolemic and euvolemic hyponatremia, liver cirrhosis, ascites, edema and the syndrome of inadequate ADH secretion (SIADH).

The diseases mentioned above have been well characterized in humans, but also exist with a comparable etiology in other mammals, and may be treated in those with the compounds and methods of the present invention.

Thus, the present invention further relates to the use of the compounds according to the invention for the treatment and/or prevention of diseases, especially of the aforementioned diseases.

The present invention further relates to the use of the compounds according to the invention for preparing a pharmaceutical composition for the treatment and/or prevention of diseases, especially of the aforementioned diseases.

The present invention further relates to the use of the compounds according to the invention in a method for the treatment and/or prevention of diseases, especially of the aforementioned diseases.

The present invention further relates to a method for the treatment and/or prevention of diseases, especially of the aforementioned diseases, by using an effective amount of at least one of the compounds according to the invention.

In accordance with another aspect, the present invention covers pharmaceutical combinations, in particular medicaments, comprising at least one compound of general formula (I) of the present invention and at least one or more further active ingredients, in particular for the treatment and/or prevention of diseases, especially of the aforementioned diseases.

Particularly, the present invention covers a pharmaceutical combination, which comprises:

- one or more first active ingredients, in particular compounds of general formula (I) as defined aforementioned, and
- one or more further active ingredients, in particular for the treatment and/or prevention of diseases, especially of the aforementioned diseases.

The term "combination" in the present invention is used as known to persons skilled in the art, it being possible for said combination to be a fixed combination, a non-fixed combination or a kit-of-parts.

A "fixed combination" in the present invention is used as known to persons skilled in the art and is defined as a combination wherein, for example, a first active ingredient, such as one or more compounds of general formula (I) of the present invention, and a further active ingredient are present together in one unit dosage or in one single entity. One example of a "fixed combination" is a pharmaceutical composition wherein a first active ingredient and a further active ingredient are present in admixture for simultaneous administration, such as in a formulation. Another example of a "fixed combination" is a pharmaceutical combination wherein a first active ingredient and a further active ingredient are present in one unit without being in admixture.

A non-fixed combination or "kit-of-parts" in the present invention is used as known to persons skilled in the art and is defined as a combination wherein a first active ingredient and a further active ingredient are present in more than one unit. One example of a non-fixed combination or kit-of-parts is a combination wherein the first active ingredient and the further active ingredient are present separately. It is possible for the components of the non-fixed combination or kit-of-parts to

be administered separately, sequentially, simultaneously, concurrently or chronologically staggered.

The compounds of the present invention can be administered as the sole pharmaceutical agent or in combination with one or more other pharmaceutically active ingredients where the combination causes no unacceptable adverse effects. The present invention also covers such pharmaceutical combinations. For example, the compounds of the present invention can be combined with known agents for the treatment and/or prevention of diseases, especially of the aforementioned diseases.

In particular, the compounds of the present invention may be used in fixed or separate combination with

- antithrombotic agents, for example and preferably from the group of platelet aggregation inhibitors, anticoagulants and profibrinolytic substances;
- blood pressure lowering agents, for example and preferably from the group of calcium antagonists, angiotensin AII antagonists, ACE inhibitors, NEP inhibitors, vasopeptidase inhibitors, endothelin antagonists, renin inhibitors, alpha-blockers, beta-blockers, mineralocorticoid receptor antagonists and diuretics;
- antidiabetic agents (hypoglycemic or antihyperglycemic agents), such as for example and preferably insulin and derivatives, sulfonylureas, biguanides, thiazolidinediones, acarbose, DPP4 inhibitors, GLP-1 analogues, or SGLT inhibitors (gliflozins).
- organic nitrates and NO-donors, for example sodium nitroprusside, nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, molsidomine or SIN-1, and inhalational NO;
- compounds that inhibit the degradation of cyclic guanosine monophosphate (cGMP), for example inhibitors of phosphodiesterases (PDE) 1, 2, 5 and/or 9, in particular PDE-5 inhibitors such as sildenafil, vardenafil, tadalafil, udenafil, dasantafil, avanafil, mirodenafil, lodenafil, CTP-499 or PF-00489791;
- positive-inotropic agents, such as for example cardiac glycosides (digoxin) and beta-adrenergic and dopaminergic agonists such as isoproterenol, adrenalin, noradrenalin, dopamine or dobutamine;
- natriuretic peptides, such as for example atrial natriuretic peptide (ANP, anaritide), B-type natriuretic peptide or brain natriuretic peptide (BNP, nesiritide), C-type natriuretic peptide (CNP) or urodilatin;
- calcium sensitizers, such as for example and preferably levosimendan;

- NO- and heme-independent activators of soluble guanylate cyclase (sGC for example and with preference the compounds described in WO 01/19355, WO 01/19776, WO 01/19778, WO 01/19780, WO 02/070462 and WO 02/070510;
- NO-independent, but heme-dependent stimulators of guanylate cyclase (sGC), for example and with preference the compounds described in WO 00/06568, WO 00/06569, WO 02/42301, WO 03/095451, WO 2011/147809, WO 2012/004258, WO 2012/028647 and WO 2012/059549;
- agents, that stimulates the synthesis of cGMP, for example and with preference sGC modulators, for example and with preference riociguat, cinaciguat, vericiguat or BAY 1101042;
- inhibitors of human neutrophil elastase (HNE), such as for example sivelestat or DX-890 (reltran);
- compounds inhibiting the signal transduction cascade, in particular tyrosine and/or serine/threonine kinase inhibitors, such as for example nintedanib, dasatinib, nilotinib, bosutinib, regorafenib, sorafenib, sunitinib, cediranib, axitinib, telatinib, imatinib, brivanib, pazopanib, vatalanib, gefitinib, erlotinib, lapatinib, canertinib, lestaurtinib, pelitinib, semaxanib or tandutinib;
- compounds influencing the energy metabolism of the heart, such as for example and preferably etomoxir, dichloroacetate, ranolazine or trimetazidine, or full or partial adenosine A1 receptor agonists as GS-9667 (previously known as CVT-3619), capadenoson and neladenoson bialanate (BAY 1067197);
- compounds influencing the heart rate, such as for example and preferably ivabradine;
- cardiac myosin activators, such as for example and preferably omecamtiv mecarbil (CK-1827452);
- anti-inflammatory drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid (aspirin), ibuprofen and naproxen, glucocorticoids, NEP inhibitors, 5-aminosalicylic acid derivatives, leukotriene antagonists, TNF-alpha inhibitors and chemokine receptor antagonists such as CCR1, 2 and/or 5 inhibitors;
- fat metabolism altering agents, for example and preferably from the group of thyroid receptor agonists, cholesterol synthesis inhibitors, such as for example and preferably HMG-CoA-reductase or squalene synthesis inhibitors, ACAT inhibitors, CETP inhibitors, MTP inhibitors, PPAR-alpha, PPAR-gamma and/or PPAR-delta agonists, cholesterol absorption inhibitors, lipase inhibitors, polymeric bile acid adsorbers, bile acid reabsorption inhibitors and lipoprotein(a) antagonists.

Antithrombotic agents are preferably to be understood as compounds from the group of platelet aggregation inhibitors, anticoagulants and profibrinolytic substances.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a platelet aggregation inhibitor, for example and preferably aspirin, clopidogrel, ticlopidine or dipyridamole.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a thrombin inhibitor, for example and preferably ximelagatran, dabigatran, melagatran, bivalirudin or enoxaparin.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a GPIIb/IIIa antagonist, for example and preferably tirofiban or abciximab.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a factor Xa inhibitor, for example and preferably rivaroxaban, apixaban, otamixaban, fidexaban, razaxaban, fondaparinux, idraparinux, DU-176b, PMD-3112, YM-150, KFA-1982, EMD-503982, MCM-17, MLN-1021, DX 9065a, DPC 906, JTV 803, SSR-126512 or SSR-128428.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with heparin or a low molecular weight (LMW) heparin derivative.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a vitamin K antagonist, for example and preferably coumarin.

Blood pressure lowering agents are preferably to be understood as compounds from the group of calcium antagonists, angiotensin AII antagonists, ACE inhibitors, NEP inhibitors, vasopeptidase inhibitors, endothelin antagonists, renin inhibitors, alpha-blockers, beta-blockers, mineralocorticoid receptor antagonists and diuretics.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a calcium antagonist, for example and preferably nifedipine, amlodipine, verapamil or diltiazem.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with an alpha-1-receptor blocker, for example and preferably prazosin or tamsulosin.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a beta-blocker, for example and preferably propranolol, atenolol, timolol, pindolol, alprenolol, oxprenolol, penbutolol, bupranolol, metipranolol, nadolol, mepindolol, carazolol, sotalol, metoprolol, betaxolol, celiprolol, bisoprolol, carteolol, esmolol, labetalol, carvedilol, adaprolol, landiolol, nebivolol, epanolol or bucindolol.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with an angiotensin AII receptor antagonist, for example and preferably losartan, candesartan, valsartan, telmisartan, irbesartan, olmesartan, eprosartan, embursartan or azilsartan.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a vasopeptidase inhibitor or inhibitor of neutral endopeptidase (NEP), such as for example and preferably sacubitril, omapatrilat or AVE-7688.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a dual angiotensin AII receptor antagonist/NEP inhibitor (ARNI), for example and preferably LCZ696.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with an ACE inhibitor, for example and preferably enalapril, captopril, lisinopril, ramipril, delapril, fosinopril, quinopril, perindopril, benazepril or trandopril.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with an endothelin antagonist, for example and preferably bosentan, darusentan, ambrisentan, tezosentan, sitaxsentan, avosentan, macitentan or atrasentan.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a renin inhibitor, for example and preferably aliskiren, SPP-600 or SPP-800.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a mineralocorticoid receptor antagonist, for example and preferably finerenone, spironolactone, canrenone, potassium canrenoate, eplerenone, esaxerenone (CS-3150), or apararenone (MT-3995), CS-3150, or MT-3995.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a diuretic, such as for example and preferably furosemide, bumetanide, piretanide, torsemide, bendroflumethiazide, chlorothiazide, hydrochlorothiazide, xipamide, indapamide, hydroflumethiazide, methyclothiazide, polythiazide, trichloromethiazide, chlorothalidone, metolazone, quinethazone, acetazolamide, dichlorophenamide, methazolamide, glycerine, isosorbide, mannitol, amiloride or triamterene.

Fat metabolism altering agents are preferably to be understood as compounds from the group of CETP inhibitors, thyroid receptor agonists, cholesterol synthesis inhibitors such as HMG-CoA-reductase or squalene synthesis inhibitors, ACAT inhibitors, MTP inhibitors, PPAR-alpha, PPAR-gamma and/or PPAR-delta agonists, cholesterol absorption inhibitors, polymeric bile acid adsorbers, bile acid reabsorption inhibitors, lipase inhibitors and lipoprotein(a) antagonists.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a CETP inhibitor, for example and preferably dalcetrapib, anacetrapib, BAY 60-5521 or CETP-vaccine (Avant).

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a thyroid receptor agonist, for example and preferably D-thyroxin, 3,5,3'-triiodothyronin (T3), CGS 23425 or axitirome (CGS 26214).

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with an HMG-CoA-reductase inhibitor from the class of statins, for example and preferably lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin or pitavastatin.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a squalene synthesis inhibitor, for example and preferably BMS-188494 or TAK-475.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with an ACAT inhibitor, for example and preferably avasimibe, melinamide, pactimibe, eflucimibe or SMP-797.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with an MTP inhibitor, for example and preferably implitapide, R-103757, BMS-201038 or JTT-130.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a PPAR-gamma agonist, for example and preferably pioglitazone or rosiglitazone.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a PPAR-delta agonist, for example and preferably GW 501516 or BAY 68-5042.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a cholesterol absorption inhibitor, for example and preferably ezetimibe, tiqueside or pamaqueside.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a lipase inhibitor, for example and preferably orlistat.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a polymeric bile acid adsorber, for example and preferably cholestyramine, colestipol, colesolvam, CholestaGel or colestimide.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a bile acid reabsorption inhibitor, for example and preferably ASBT (= IBAT) inhibitors such as AZD-7806, S-8921, AK-105, BARI-1741, SC-435 or SC-635.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a lipoprotein(a) antagonist, for example and preferably gemcabene calcium (CI-1027) or nicotinic acid.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a TGFbeta antagonist, by way of example and with preference pirfenidone or fresolimumab.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with HIF-PH inhibitors, by way of example and with preference molidustat or roxadustat.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a CCR2 antagonist, by way of example and with preference CCX-140.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a TNFalpha antagonist, by way of example and with preference adalimumab.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a galectin-3 inhibitor, by way of example and with preference GCS-100.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a BMP-7 agonist, by way of example and with preference THR-184.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a NOX1/4 inhibitor, by way of example and with preference GKT-137831.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a medicament which affects the vitamin D metabolism, by way of example and with preference cholecalciferol or paracalcitol.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a cytostatic agent, by way of example and with preference cyclophosphamide.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with an immunosuppressive agent, by way of example and with preference ciclosporin.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a phosphate binder, by way of example and with preference sevelamer or lanthanum carbonate.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a calcimimetic for therapy of hyperparathyroidism.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with agents for iron deficit therapy, by way of example and with preference iron products.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with agents for the therapy of hyperurikaemia, by way of example and with preference allopurinol or rasburicase.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with glycoprotein hormone for the therapy of anaemia, by way of example and with preference erythropoietin.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with biologics for immune therapy, by way of example and with preference abatacept, rituximab, eculizumab or belimumab.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with Jak inhibitors, by way of example and with preference ruxolitinib, tofacitinib, baricitinib, CYT387, GSK2586184, lestaurtinib, pacritinib (SB1518) or TG101348.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with prostacyclin analogs for therapy of microthrombi.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with an alkali therapy, by way of example and with preference sodium bicarbonate.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with an mTOR inhibitor, by way of example and with preference everolimus or rapamycin.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with an NHE3 inhibitor, by way of example and with preference AZD1722.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with an eNOS modulator, by way of example and with preference sapropterin.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with a CTGF inhibitor, by way of example and with preference FG-3019.

In a preferred embodiment of the invention, the compounds according to the invention are administered in combination with antidiabetics (hypoglycemic or antihyperglycemic agents), such as for example and preferably insulin and derivatives, sulfonylureas such as tolbutamide, carbutamide, acetohexamide, chlorpropamide, glipizide, gliclazide, glibenclamide, glyburide, glibornuride, gliquidone, glisoxepide, glyclopyramide, glimepiride, JB253 and JB558, meglitinides such as repaglinide and nateglinide, biguanides such as metformin and buformin, thiazolidinediones such as rosiglitazone and pioglitazone, alpha-glucosidase inhibitors such as miglitol, acarbose and voglibose, DPP4 inhibitors such as vildagliptin, sitagliptin, saxagliptin, linagliptin, alogliptin, septagliptin and teneligliptin, GLP-1 analogues such as exenatide (also exendin-4, liraglutide, lixisenatide and taspoglutide, or SGLT inhibitors (gliflozins) such as canagliflozin, dapagliflozin and empagliflozin.

In a particularly preferred embodiment, the compounds of the present invention are administered in combination with one or more additional therapeutic agents selected from the group consisting of diuretics, angiotensin AII antagonists, ACE inhibitors, beta-receptor blockers, mineralocorticoid receptor antagonists, antidiabetics, organic nitrates and NO donors, activators and stimulators of the soluble guanylate cyclase (sGC), and positive-inotropic agents.

In a further particularly preferred embodiment, the compounds of the present invention are administered in combination with one or more additional therapeutic agents selected from the group consisting of diuretics, angiotensin AII antagonists, ACE inhibitors, beta-receptor blockers, mineralocorticoid receptor antagonists, antidiabetics, organic nitrates and NO donors, activators and stimulators of the soluble guanylate cyclase (sGC), positive-inotropic agents, antiinflammatory agents, immunosuppressive agents, phosphate binders and/or compounds which modulate vitamin D metabolism.

Thus, in a further embodiment, the present invention relates to pharmaceutical compositions comprising at least one of the compounds according to the invention and one or more additional thera-

peutic agents for the treatment and/or prevention of diseases, especially of the aforementioned diseases.

Furthermore, the compounds of the present invention may be utilized, as such or in compositions, in research and diagnostics, or as analytical reference standards and the like, which are well known in the art.

When the compounds of the present invention are administered as pharmaceuticals, to humans and other mammals, they can be given *per se* or as a pharmaceutical composition containing, for example, 0.1% to 99.5% (more preferably, 0.5% to 90%) of active ingredient in combination with one or more pharmaceutically acceptable excipients.

Thus, in another aspect, the present invention relates to pharmaceutical compositions comprising at least one of the compounds according to the invention, conventionally together with one or more inert, non-toxic, pharmaceutically acceptable excipients, and to the use thereof for the treatment and/ or prevention of diseases, especially of the aforementioned diseases.

It is possible for the compounds according to the invention to have systemic and/or local activity. For this purpose, they can be administered in a suitable manner, such as, for example, via the oral, parenteral, pulmonary, nasal, sublingual, lingual, buccal, rectal, vaginal, dermal, transdermal, conjunctival, otic route or as an implant or stent.

For these administration routes, it is possible for the compounds according to the invention to be administered in suitable administration forms.

For oral administration, it is possible to formulate the compounds according to the invention to dosage forms known in the art that deliver the compounds of the invention rapidly and/or in a modified manner, such as, for example, tablets (uncoated or coated tablets, for example with enteric or controlled release coatings that dissolve with a delay or are insoluble), orally-disintegrating tablets, films/wafers, films/lyophylisates, capsules (for example hard or soft gelatine capsules), sugar-coated tablets, granules, pellets, powders, emulsions, suspensions, aerosols or solutions. It is possible to incorporate the compounds according to the invention in crystalline and/or amorphised and/or dissolved form into said dosage forms.

Parenteral administration can be effected with avoidance of an absorption step (for example intravenous, intraarterial, intracardial, intraspinal or intralumbal) or with inclusion of absorption (for example intramuscular, subcutaneous, intracutaneous, percutaneous or intraperitoneal). Administration forms which are suitable for parenteral administration are, inter alia, preparations for injection and infusion in the form of solutions, suspensions, emulsions, lyophylisates or sterile powders.

Examples which are suitable for other administration routes are pharmaceutical forms for inhalation [inter alia powder inhalers, nebulizers], nasal drops, nasal solutions, nasal sprays;

tablets/films/wafers/capsules for lingual, sublingual or buccal administration; suppositories; eye drops, eye ointments, eye baths, ocular inserts, ear drops, ear sprays, ear powders, ear-rinses, ear tampons; vaginal capsules, aqueous suspensions (lotions, mixturae agitandae), lipophilic suspensions, emulsions, ointments, creams, transdermal therapeutic systems (such as, for example, patches), milk, pastes, foams, dusting powders, implants or stents.

The compounds according to the invention can be incorporated into the stated administration forms. This can be effected in a manner known per se by mixing with pharmaceutically suitable excipients. Pharmaceutically suitable excipients include, inter alia,

- fillers and carriers (for example cellulose, microcrystalline cellulose (such as, for example, Avicel®), lactose, mannitol, starch, calcium phosphate (such as, for example, Di-Cafos®)),
- ointment bases (for example petroleum jelly, paraffins, triglycerides, waxes, wool wax, wool wax alcohols, lanolin, hydrophilic ointment, polyethylene glycols),
- bases for suppositories (for example polyethylene glycols, cacao butter, hard fat),
- solvents (for example water, ethanol, iso-propanol, glycerol, propylene glycol, medium chain-length triglycerides fatty oils, liquid polyethylene glycols, paraffins),
- surfactants, emulsifiers, dispersants or wetters (for example sodium dodecyl sulfate), lecithin, phospholipids, fatty alcohols (such as, for example, Lanette®), sorbitan fatty acid esters (such as, for example, Span®), polyoxyethylene sorbitan fatty acid esters (such as, for example, Tween®), polyoxyethylene fatty acid glycerides (such as, for example, Cremophor®), polyoxethylene fatty acid esters, polyoxyethylene fatty alcohol ethers, glycerol fatty acid esters, poloxamers (such as, for example, Pluronic®),
- buffers, acids and bases (for example phosphates, carbonates, citric acid, acetic acid, hydrochloric acid, sodium hydroxide solution, ammonium carbonate, trometamol, triethanolamine),
- isotonicity agents (for example glucose, sodium chloride),
- adsorbents (for example highly-disperse silicas),
- viscosity-increasing agents, gel formers, thickeners and/or binders (for example polyvinylpyrrolidone, methylcellulose, hydroxypropylmethylcellulose, hydroxypropyl-cellulose, carboxymethylcellulose-sodium, starch, carbomers, polyacrylic acids (such as, for example, Carbopol®); alginates, gelatine),
- disintegrants (for example modified starch, carboxymethylcellulose-sodium, sodium starch glycolate (such as, for example, Explotab®), cross- linked polyvinylpyrrolidone, croscarmellose-sodium (such as, for example, AcDiSol®)),

- flow regulators, lubricants, glidants and mould release agents (for example magnesium stearate, stearic acid, talc, highly-disperse silicas (such as, for example, Aerosil®)),
- coating materials (for example sugar, shellac) and film formers for films or diffusion membranes which dissolve rapidly or in a modified manner (for example polyvinylpyrrolidones (such as, for example, Kollidon®), polyvinyl alcohol, hydroxypropylmethylcellulose, hydroxypropylcellulose, ethylcellulose, hydroxypropyl-methylcellulose phthalate, cellulose acetate, cellulose acetate phthalate, polyacrylates, polymethacrylates such as, for example, Eudragit®)),
- capsule materials (for example gelatine, hydroxypropylmethylcellulose),
- synthetic polymers (for example polylactides, polyglycolides, polyacrylates, polymethacrylates (such as, for example, Eudragit®), polyvinylpyrrolidones (such as, for example, Kollidon®), polyvinyl alcohols, polyvinyl acetates, polyethylene oxides, polyethylene glycols and their copolymers and blockcopolymers),
- plasticizers (for example polyethylene glycols, propylene glycol, glycerol, triacetine, triacetyl citrate, dibutyl phthalate),
- penetration enhancers,
- stabilisers (for example antioxidants such as, for example, ascorbic acid, ascorbyl palmitate, sodium ascorbate, butylhydroxyanisole, butylhydroxytoluene, propyl gallate),
- preservatives (for example parabens, sorbic acid, thiomersal, benzalkonium chloride, chlorhexidine acetate, sodium benzoate),
- colourants (for example inorganic pigments such as, for example, iron oxides, titanium dioxide),
- flavourings, sweeteners, flavour- and/or odour-masking agents.

The present invention furthermore relates to a pharmaceutical composition which comprise at least one compound according to the invention, conventionally together with one or more pharmaceutically suitable excipient(s), and to their use according to the present invention.

Based upon standard laboratory techniques known to evaluate compounds useful for the treatment of cardiovascular and renal disorders, by standard toxicity tests and by standard pharmacological assays for the determination of treatment of the conditions identified above in mammals, and by comparison of these results with the results of known active ingredients or medicaments that are used to treat these conditions, the effective dosage of the compounds of the present invention can readily be determined for treatment of each desired indication. The amount of the active ingredient to be administered in the treatment of one of these conditions can vary widely according to such

considerations as the particular compound and dosage unit employed, the mode of administration, the period of treatment, the age and sex of the patient treated, and the nature and extent of the condition treated.

The total amount of the active ingredient to be administered will generally range from about 0.001 mg/kg to about 200 mg/kg body weight per day, and preferably from about 0.01 mg/kg to about 20 mg/kg body weight per day. Clinically useful dosing schedules will range from one to three times a day dosing to once every four weeks dosing. In addition, it is possible for "drug holidays", in which a patient is not dosed with a drug for a certain period of time, to be beneficial to the overall balance between pharmacological effect and tolerability. It is possible for a unit dosage to contain from about 0.5 mg to about 1500 mg of active ingredient, and can be administered one or more times per day or less than once a day. The average daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous and parenteral injections, and use of infusion techniques will preferably be from 0.01 to 200 mg/kg of total body weight. Illustratively, the compound of the present invention may be administered parenterally at a dose of about 0.001 mg/kg to about 10 mg/kg, preferably of about 0.01 mg/kg to about 1 mg/kg of body weight. In oral administration, an exemplary dose range is about 0.01 to 100 mg/kg, preferably about 0.01 to 20 mg/kg, and more preferably about 0.1 to 10 mg/kg of body weight. Ranges intermediate to the above-recited values are also intended to be part of the invention.

Of course the specific initial and continuing dosage regimen for each patient will vary according to the nature and severity of the condition as determined by the attending diagnostician, the activity of the specific compound employed, the age and general condition of the patient, time of administration, route of administration, rate of excretion of the drug, drug combinations, and the like. The desired mode of treatment and number of doses of a compound of the present invention or a pharmaceutically acceptable salt or ester or composition thereof can be ascertained by those skilled in the art using conventional treatment tests.

The following exemplary embodiments illustrate the invention. The invention is not restricted to the examples.

The percentages in the following tests and examples are, unless stated otherwise, by weight; parts are by weight. Solvent ratios, dilution ratios and concentrations reported for liquid/liquid solutions are each based on volume.

EXPERIMENTAL SECTION

EXPERIMENTAL SECTION - GENERAL PART

NMR peak forms are stated as they appear in the spectra, possible higher order effects have not been considered.

Chemical names were generated using the ACD/Name software from ACD/Labs. In some cases generally accepted names of commercially available reagents were used in place of ACD/Name generated names.

The following table 1 lists the abbreviations used in this paragraph and in the Examples section as far as they are not explained within the text body. Other abbreviations have their meanings customary *per se* to the skilled person.

Table 1: Abbreviations

The following table lists the abbreviations used herein.

Abbreviation	Meaning
abs	absolut
br	broad (^{1}H-NMR signal)
conc.	concentrated
CI	chemical ionisation
d	doublet (^{1}H-NMR signal)
d	day(s)
DAD	diode array detector
DCM	dichloromethane
dd	double-doublet
DMSO	dimethylsulfoxide
ESI	electrospray (ES) ionisation
h	hour(s)
HPLC	high performance liquid chromatography
LC-MS	liquid chromatography mass spectrometry
m	multiplet (^{1}H-NMR signal)
min	minute(s)
MS	mass spectrometry
MTBE	methyl-tert-butylether
NMR	nuclear magnetic resonance spectroscopy: chemical shifts (δ) are given in ppm. The chemical shifts were corrected by setting the DMSO signal to 2.50 ppm unless otherwise stated.
of th.	of theory

PDA	Photo Diode Array
R_t	retention time (as measured either with HPLC or UPLC) in minutes
s	singlet (^{1}H-NMR signal)
SQD	Single-Quadrupole-Detector
t	triplet (^{1}H-NMR signal)
td	triple-doublet (^{1}H-NMR signal)
THF	tetrahydrofuran
UPLC	ultra performance liquid chromatography

The various aspects of the invention described in this application are illustrated by the following examples which are not meant to limit the invention in any way.

The example testing experiments described herein serve to illustrate the present invention and the invention is not limited to the examples given.

All reagents, for which the synthesis is not described in the experimental part, are either commercially available, or are known compounds or may be formed from known compounds by known methods by a person skilled in the art.

The compounds and intermediates produced according to the methods of the invention may require purification. Purification of organic compounds is well known to the person skilled in the art and there may be several ways of purifying the same compound. In some cases, no purification may be necessary. In some cases, the compounds may be purified by crystallization. In some cases, impurities may be stirred out using a suitable solvent. In some cases, the compounds may be purified by chromatography, particularly flash column chromatography, using for example prepacked silica gel cartridges, e.g. Biotage SNAP cartidges KP-Sil® or KP-NH® in combination with a Biotage autopurifier system (SP4® or Isolera Four®) and eluents such as gradients of hexane/ethyl acetate or DCM/methanol. In some cases, the compounds may be purified by preparative HPLC using for example a Waters autopurifier equipped with a diode array detector and/or on-line electrospray ionization mass spectrometer in combination with a suitable prepacked reverse phase column and eluents such as gradients of water and acetonitrile which may contain additives such as trifluoroacetic acid, formic acid or aqueous ammonia.

In some cases, purification methods as described above can provide those compounds of the present invention which possess a sufficiently basic or acidic functionality in the form of a salt, such as, in the case of a compound of the present invention which is sufficiently basic, a trifluoroacetate or formate salt for example, or, in the case of a compound of the present invention which is sufficiently acidic, an ammonium salt for example. A salt of this type can either be transformed into its free base or free acid form, respectively, by various methods known to the

person skilled in the art, or be used as salts in subsequent biological assays. It is to be understood that the specific form (e.g. salt, free base etc.) of a compound of the present invention as isolated and as described herein is not necessarily the only form in which said compound can be applied to a biological assay in order to quantify the specific biological activity.

In the case of the synthesis intermediates and working examples of the invention described hereinafter, any compound specified in the form of a salt of the corresponding base or acid is generally a salt of unknown exact stoichiometric composition, as obtained by the respective preparation and/or purification process. Unless specified in more detail, additions to names and structural formulae, such as "hydrochloride", "trifluoroacetate", "sodium salt" or "x HCl", "x CF_3COOH", "x Na^+" should not therefore be understood in a stoichiometric sense in the case of such salts, but have merely descriptive character with regard to the salt-forming components present therein.

This applies correspondingly if synthesis intermediates or working examples or salts thereof were obtained in the form of solvates, for example hydrates, of unknown stoichiometric composition (if they are of a defined type) by the preparation and/or purification processes described.

HPLC and LC-MS methods:

Method 1 (LC-MS)

MS instrument type: Agilent Technologies 6130 Quadrupole LC-MS; HPLC instrument type: Agilent Technologies 1260 Infinity; column: Waters XSelect (C18, 30 x 2.1 mm, 3.5µ); flow: 1 ml/min; column temp: 35°C; eluent A: 0.1% formic acid in acetonitrile; eluent B: 0.1% formic acid in water; lin. gradient: t = 0 min 5% A, t = 1.6 min 98% A, t = 3 min 98% A; detection: DAD (220-320 nm); detection: MSD (ESI pos/neg) mass range: 100 – 800; detection: ELSD (PL-ELS 2100): gas flow 1.2 ml/min, gas temp: 70°C, nebulizer: 50°C.

Method 2 (LC-MS)

Instrument: Waters ACQUITY SQD UPLC System; Column: Waters Acquity UPLC HSS T3 1.8 µ 50 x 1 mm; eluent A: 1 l water + 0.25 ml 99% formic acid, eluent B: 1 l acetonitrile + 0.25 ml 99% formic acid; gradient: 0.0 min 90% A → 1.2 min 5% A → 2.0 min 5% A; oven: 50°C; flow rate: 0.40 ml/min; UV detection: 208-400 nm.

Method 3 (LC-MS)

Instrument MS: Thermo Scientific FT-MS; Instrument type UHPLC+: Thermo Scientific UltiMate 3000; Column: Waters, HSST3, 2.1 x 75 mm, C18 1.8 µm; eluent A: 1 l water + 0.01% formic acid; eluent B: 1 l acetonitrile + 0.01% formic acid; gradient: 0.0 min 10% B → 2.5 min 95% B →

3.5 min 95% B; oven: 50°C; flow rate: 0.90 ml/min; UV detection: 210 nm/ optimum integration path 210-300 nm.

Method 4 (LC-MS)

Instrument: Waters ACQUITY SQD UPLC System; Column: Waters Acquity UPLC HSS T3 1.8 µ 50 x 1 mm; eluent A: 1 l water + 0.25 ml 99% formic acid, Eluent B: 1 l acetonitrile + 0.25 ml 99% formic acid; gradient: 0.0 min 95% A → 6.0 min 5% A → 7.5 min 5% A; oven: 50°C; flow rate: 0.35 ml/min; UV detection: 210-400 nm.

Method 5 (preparative HPLC)

Column: Chromatorex or Reprosil C18 10 µm; 125 x 30 mm, Flow: 75 ml/min, Run time: 20 min, Detection at 210 nm, Eluent A: water + 0.1% formic acid, Eluent B: acetonitrile + 0.1% formic acid or trifluoroacetic acid; Gradient: 3 min 10% B; 17.5 min 95% B; 19.5 min 100% B, 20 min 10% B.

Method 6 (LC-MS)

instrument type: Reveleris™ Flash Chromatography System; columns: GraceResolv™ Silica Cartridge; 4 g, flow 5 ml/min; 12 g, flow 16 ml/min; 40 g, flow 50 ml/min; 80 g, flow 100 ml/min; 120 g, flow 160 ml/min and Davisil™ Chromatographic Silica Media (LC60A 20-45 micron); 300 g, flow 70 ml/min; 500 g, flow 70 ml/min; eluents: see experiment; detection: UV (200-360 nm), ELSD.

Method 7 (LC-MS)

MS instrument type: Agilent Technologies 6130 Quadrupole LC-MS; HPLC instrument type: Agilent Technologies 1260 Infinity; column: Waters XSelect (C18, 50 x 2.1 mm, 3.5µ); flow: 0.8 ml/min; column temperature: 35°C; eluent A: 0.1% formic acid in acetonitrile; eluent B: 0.1% formic acid in water; linear gradient: t = 0 min 5% A, t = 3.5 min 98% A, t = 6 min 98% A; detection: DAD (220-320 nm); detection: MSD (ESI pos/neg) mass range: 100 – 800; detection: ELSD (PL-ELS 2100): gas flow: 1.2 ml/min, gas temperature: 70°C, nebulizer: 50°C.

Method 8 (LC-MS)

instrument type: Reveleris™ Flash Chromatography System; columns: Reveleris™ C18 Flash Cartridge; 4 g, flow 18 ml/min; 12 g, flow 30 ml/min; 40 g, flow 40 ml/min; 80 g, flow 60 ml/min; 120 g, flow 80 ml/min; eluent A: 0.1% formic acid in acetonitrile; eluent B: 0.1% formic acid in water; gradient: t = 0 min 5% A, t = 1 min 5% A, t = 13 min 100% A, t = 16 min 100% A; detection: UV (200-360 nm), ELSD.

Method 9 (LC-MS)

MS instrument type: Agilent Technologies LC/MSD SL; HPLC instrument type: Agilent Technologies 1100 Series; column: Waters XSelect (C18, 50 x 2.1 mm, 3.5µ; flow: 0.8 ml/min; column temp: 25°C; eluent A: 95% acetonitrile + 5% ammoniumbicarbonate in water; eluent B: 10 mmM ammoniumbicarbonate in water pH = 9.0; linear gradient: t = 0 min 5% A, t = 3.5min 98% A, t = 6 min 98% A; detection: DAD (220-320 nm); detection: MSD (ESI pos/neg) mass range: 100-800.

Method 10 (LC-MS)

Instrument: Agilent MS Quad 6150; HPLC: Agilent 1290; Column: Waters Acquity UPLC HSS T3 1.8 µ 50 x 2.1 mm; eluent A: 1 l water + 0.25 ml 99%ige formic acid, eluent B: 1 l acetonitrile + 0.25 ml 99%ige formic acid; gradient: 0.0 min 90% A → 0.3 min 90% A → 1.7 min 5% A → 3.0 min 5% A oven: 50°C; flow rate: 1.20 ml/min; UV-detection: 205 – 305 nm.

Method 11 (LC-MS)

Instrument: Waters Prep LC-MS System, Column: Phenomenex Kinetex C18 5µm 100 x 30 mm; eluent A: water, eluent B: acetonitrile, flow: 65 ml/min plus 5ml 2% formic acid in water, room temperature, UV detection: 200-400 nm, gradient: 0.0 min 10% B, 2 min 20% B, 2.2 min 60% B, 7 min 92% B, 7.5 min 92% B.

Method 12 (LC-MS)

Instrument MS: Waters (Micromass) Quattro Micro; Instrument Waters UPLC Acquity; Column: Waters BEH C18 1.7 µ 50 x 2.1 mm; eluent A: 1 l water + 0.01 mol ammonium formiat, eluent B: 1 l acetonitrile; gradient: 0.0 min 95% A, 0.1 min 95% A, 2.0 min 15% A, 2.5 min 15% A, 2.51 min 10% A, 3.0 min 10% A; oven: 40°C; flow rate: 0.5 ml/min; UV-detection: 210 nm

Method 13 (Preparative HPLC)

Column: Chromatorex C18 10µm 125 x 30 mm, water-acetonitrile-gradient with 0.05% trifluoroacetic acid : 0-3 min. 25% acetonitrile, 3-7 min. gradient to 50% acetonitrile, 7-13 min. gradient to 60% acetonitrile, 12-13 min. 75% acetonitrile, 13-17 min. isocratic 75% acetonitrile; flow: 50ml/min

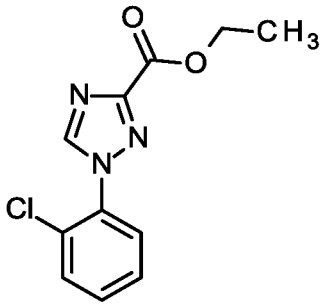
Microwave:

The microwave reactor used was an Initiator^{+} microwave system with robot sixty from Biotage®.

EXPERIMENTAL SECTION – STARTING MATERIALS AND INTERMEDIATES

Example 1A

Ethyl 1-(2-chlorophenyl)-1H-1,2,4-triazole-3-carboxylate



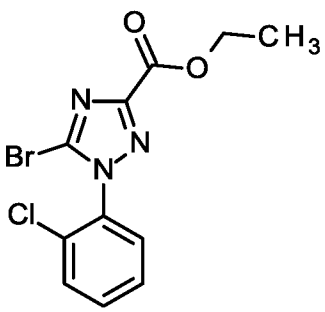
A suspension of 2-chloroaniline (6.1 g, 47.5 mmol, 5.0 ml) in a mixture of water (25 ml) and concentrated hydrochloric acid (14.1 g, 143 mmol, 13.9 ml) was cooled to 0°C. A solution of sodium nitrite (3.3 g, 47.5 mmol) in water (5 ml) was added maintaining the temperature between 0°C and 5°C. Stirring was continued for 5 min at 0°C. This solution was added drop wise to a mixture of acetic acid sodium salt (25.4 g, 309 mmol) and ethyl 2-isocyanoacetate (4.8 g, 42.8 mmol, 4.7 ml) in a mixture of water (50 ml) and methanol (5 ml). The reaction mixture was stirred at 0°C for 30 min and was allowed to warm to room temperature. Stirring was continued for 18 h. Ethyl acetate (50 ml) was added and layers were separated. Aqueous layer was extracted with ethyl acetate (3x50 ml). Combined organic extracts were dried with sodium sulfate and solvents were removed *in vacuo*. Flash column chromatography (Method 6; 500 g; heptane, 30%-40% ethyl acetate) afforded 6.5 g (25.8 mmol; 60% of th.) of the title compound.

LC-MS (Method 1): R_t = 1.81 min; m/z = 252 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d6) δ = 9.15 (s, 1H), 7.84 - 7.71 (m, 2H), 7.70 - 7.56 (m, 2H), 4.37 (q, 2H), 1.33 (t, 3H).

Example 2A

Ethyl 5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazole-3-carboxylate



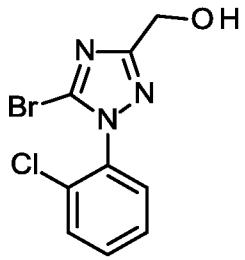
Under argon atmosphere sodium hydride (4.1 g, 101 mmol; 60% in mineral oil) was added to ethyl 1-(2-chlorophenyl)-1H-1,2,4-triazole-3-carboxylate (Example 1A, 8.5 g, 33.8 mmol) and N-bromosuccinimide (30.1 g, 169 mmol) in tetrahydrofuran (dry) (175 ml). Reaction mixture was stirred at room temperature for 16 h and at 50°C for 16 h. Reaction mixture was allowed to cool to room temperature and was diluted with ethyl acetate (100 ml) and ethanol (10 ml). The reaction mixture was poured out in saturated aqueous ammonium chloride (100 ml). Layers were separated and aqueous layer was extracted with ethyl acetate (3x100 ml). Combined organic layers were dried with sodium sulfate. Solvents were removed *in vacuo*. Purification by flash column chromatography (Method 6; 500 g; heptane, 25%-35% ethyl acetate) afforded 11.3 g (32.9 mmol; 97% of th.) of the title compound.

LC-MS (Method 1): R_t = 1.99 min; m/z = 330/332 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d6) δ = 7.88 - 7.79 (m, 2H), 7.73 (td, 1H), 7.64 (td, 1H), 4.38 (q, 2H), 1.32 (t, 3H).

Example 3A

[5-Bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methanol



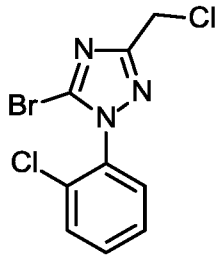
Under nitrogen atmosphere at 0°C to a solution of ethyl 5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazole-3-carboxylate (Example 2A, 1.5 g, 4.54 mmol) in tetrahydrofuran (dry) (15 ml) and ethanol (abs) (15 ml) were added lithium chloride (0.769 g, 18.15 mmol) and sodium borohydride (0.687 g, 18.15 mmol). Reaction mixture was allowed to warm to room temperature and stirring was continued for 18 h. Reaction mixture was slowly added to saturated aqueous ammonium chloride (50 ml). Ethyl acetate (50 ml) was added and layers were separated. Aqueous layer was extracted with ethyl acetate (2x50 ml). Combined organic layers were dried with sodium sulfate and solvents were removed *in vacuo*. Flash column chromatography (Method 6; 80 g; heptane, 30%-60% ethyl acetate) afforded 0.93 g (3.22 mmol; 71% of th.) of the title compound.

LC-MS (Method 1): R_t = 1.67 min; m/z = 288/290 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d6) δ = 7.80 - 7.73 (m, 1H), 7.70 - 7.53 (m, 3H), 5.49 (t, 1H), 4.48 (d, 2H).

Example 4A

5-Bromo-3-(chloromethyl)-1-(2-chlorophenyl)-1H-1,2,4-triazole



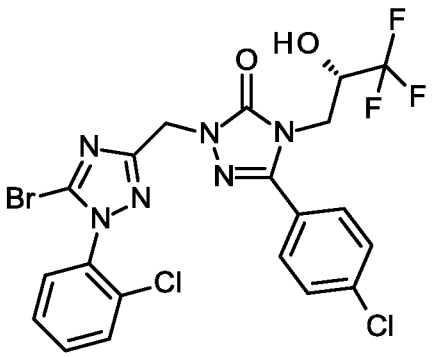
Under argon and at 0°C, a solution of [5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methanol (Example 3A, 7.00 g, 24.3 mmol) in dichloromethane (140 ml) was treated portionwise with phosphorous pentachloride (10.1 g, 48.5 mmol). The resulting mixture was stirred 2 h at room temperature and diluted with a ice-water mixture. The aqueous phase was extracted twice with dichloromethane. The combined organice layers were extracted twice with a saturated solution of sodium carbonate, dried over magnesium sulfate and evaporated affording 7.81 g (quant.) of the title compound which was used as such without further purification

LC-MS (Method 3): R_t = 1.82 min; MS (ESIpos): m/z = 305.9 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.91-7.48 (m, 4H), 4.83 (s, 2H).

Example 5A

2-{[5-Bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



A solution of 5-bromo-3-(chloromethyl)-1-(2-chlorophenyl)-1H-1,2,4-triazole (Example 4A, 7.81 g, 25.5 mmol) in acetonitrile (83 ml) was treated with 5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (synthesis described as Example 5A in WO 2011/104322-A1, 7.46 g, 24.2 mmol), potassium carbonate (6.70 g, 48.5 mmol) and potassium iodide (402 mg, 2.42 mmol). The resulting mixture was heated at reflux for 6 h and diluted with water. The aqueous phase was extracted with ethyl acetate. The combined organice layers were washed with a saturated solution of sodium chloride, dried over magnesium sulfate and evaporated.

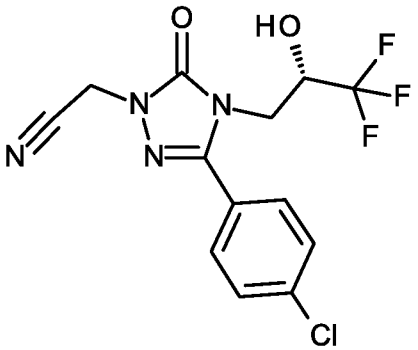
The residue was purified by flash chromatography over silica gel (cyclohexane / ethyl acetate gradient) affording 6.86 g (48% of th.) of the title compound.

LC-MS (Method 3): R_t = 2.04 min; MS (ESIpos): m/z = 577.0 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.85-7.52 (m, 8H), 6.90 (d, 1H), 5.17-5.05 (m, 2H), 4.30 (br ddd, 1H), 4.10-3.77 (m, 2H).

Example 6A

{3-(4-Chlorophenyl)-5-oxo-4-[(2*S*)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1*H*-1,2,4-triazol-1-yl}acetonitrile



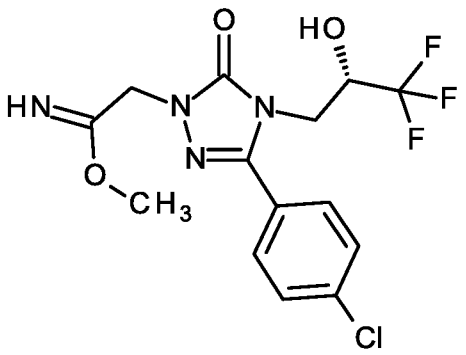
In a 2 l reaction vessel, 100 g (273 mmol) of {3-(4-chlorophenyl)-5-oxo-4-[(2*S*)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1*H*-1,2,4-triazol-1-yl}acetic acid (synthesis described as Example 8A in WO 2010/105770-A1, 43.3 g, 547 mmol) of pyridine and 33 mg (0.3 mmol) of 4-dimethylaminopyridine were dissolved in 300 ml THF. The resulting solution was treated at 5°C with 52.8 g (438 mmol) of 2,2-dimethylpropanoylchloride over 15 minutes and the resulting mixture was stirred at room temperature for 2.5 hours. After cooling to 0°C, 183 ml of 28% aqueous ammonia solution was added over 1 h while the solution temperature was kept between 10°C and 20°C and at the resulting mixture then stirred at 5°C for an additional time period of 1 h. 500 ml methyl tert-butylether and 300 ml 20% aqueous citric acid were then added while keeping the internal temperature between 10°C and 20°C. The phases were the separated and the organic phase was washed with 300 ml of 20% aqueous citric acid followed by 300 ml saturated aqueous sodium hydrogencarbonate solution and finally with 300 ml of 10% aqueous sodium chloride solution. The organic phase was evaporated at 60°C under reduced pressure until an oily residue was obtained. 300 ml THF was then added and the solution was evaporated again until an oily solution was obtained. This operation was repeated a second time. The oil residue was retaken in 360 ml THF and treated with 172 g (820 mmol) trifluoroacetic acid anhydride over 20 min at a temperature between 10°C and 20°C. The resulting solution was then stirred at room temperature for 1 h. 720 ml 4-methyl-2-pentanone and 650 ml 7.5% aqueous sodium hydroxide solution were added at a temperature between 10°C and 20°C. Finally the pH-value was adjusted to pH = 9.5

using 7.5% aqueous sodium hydroxide solution. After phase separation, the organic phase was washed twice with 450 ml 10% aqueous sodium chloride solution. The organic phase was evaporated at a temperature of 80°C under reduced pressure while 1200 ml n-heptane was added. The formed suspension was cooled to 20°C and a solid formed which was filtered off and washed with 200 ml n-heptane and then dried under reduced pressure (50°C, 30 mbar) affording 88 g (93% of th.) of {3-(4-chlorophenyl)-5-oxo-4-[(2*S*)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1*H*-1,2,4-triazol-1-yl}acetonitrile as a solid.

^{1}H-NMR (400 MHz, DMSO-d6): δ [ppm] = 7.78 (d, 2H), 7.55 (d, 2H), 6.91 (d, 1H), 5.17 (s, 2 H), 4.34-4.23 (m, 1 H), 3.98 (dd, 1H), 3.81 (dd, 1H).

Example 7A

Methyl-2-{3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluor-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}ethanimidate

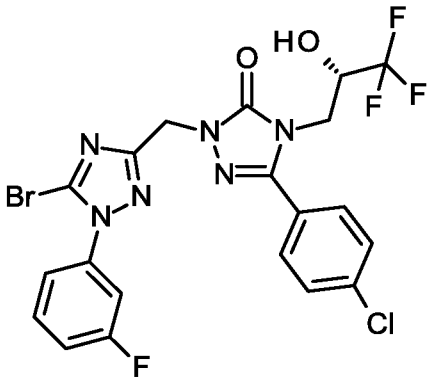


In a 4 l reaction vessel, 200 g (576.9 mmol) of {3-(4-chlorophenyl)-5-oxo-4-[(2*S*)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1*H*-1,2,4-triazol-1-yl}acetonitrile (Example 6A) in 1600 ml methanol was treated with 5.2 g (28 mmol) sodium methanolate (30% in methanol) and the resulting mixture was stirred at 50°C for 2.5 hours. The solution was then evaporated at 50°C under reduced pressure until an oily solution was obtained. 2000 ml methyl tert-butylether was added and the solution was concentrated until a volume of 800 ml was achieved. 3000 ml n-heptane was then added and a suspension was formed. After cooling at 20°C, the solid was filtered and washed with 500 ml n-heptane and then dried under reduced pressure (50°C, 30 mbar) affording 175 g (80% of th.) of methyl 2-{3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}ethanimidate as a solid.

^{1}H-NMR (400 MHz, DMSO-d6): δ [ppm] = 8.01 (s, 1H), 7.78 (d, 2H), 7.62 (d, 2H), 6.93 (br. s, 1H), 4.50 (s, 2 H), 4.35-4.23 (m, 1 H), 3.96 (dd, 1H), 3.81 (dd, 1H), 3.67 (s, 3 H).

Example 8A

2-{[5-Bromo-1-(3-fluorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



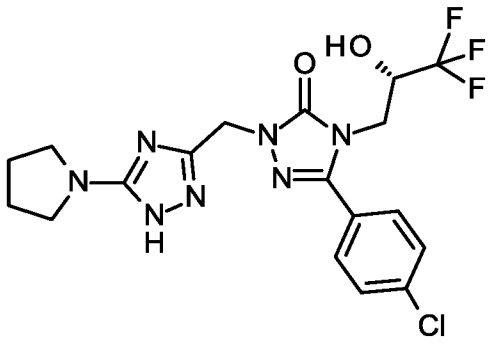
5-(4-Chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (synthesis described as Example 5A in WO 2011/104622-A1, 709 mg, 2.30 mmol), potassium carbonate (637 mg, 4.61 mmol) and catalytic amounts of potassium iodide were dissolved in 17 ml of acetonitrile. To this mixture, 5-bromo-3-(chloromethyl)-1-(3-fluorophenyl)-1H-1,2,4-triazole (Example 52A, 703 mg, 2.42 mmol) was added at room temperature. The mixture was stirred at 70°C for 4 h. After cooling to room temperature, the reaction mixture was diluted with 20 ml of water and extracted twice with 20 ml ethyl acetate. The combined organic phases were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by chromatography (silica gel, cyclohexane/ethyl acetate gradient) to afford 293 mg (23% of th.) of the title compound.

LC-MS (Method 2): R_t = 1.09 min; MS (ESIpos): m/z = 560 $[M+H]^+$

^{1}H-NMR (500 MHz, DMSO-d6) δ [ppm]: -0.121 (0.41), -0.008 (3.95), 0.006 (3.45), 0.116 (0.40), 1.160 (3.60), 1.174 (7.22), 1.188 (3.64), 1.235 (0.37), 1.987 (13.68), 2.361 (0.36), 2.635 (0.36), 3.829 (1.81), 3.848 (2.04), 3.858 (2.46), 3.877 (2.63), 3.992 (2.49), 3.998 (2.73), 4.007 (1.30), 4.022 (5.03), 4.027 (1.91), 4.036 (3.35), 4.050 (1.10), 4.292 (1.40), 4.305 (1.35), 4.622 (0.53), 5.099 (16.00), 6.899 (5.05), 6.912 (5.03), 7.431 (1.19), 7.436 (1.45), 7.448 (2.42), 7.453 (2.92), 7.465 (1.54), 7.471 (1.76), 7.494 (1.06), 7.520 (2.75), 7.536 (3.34), 7.601 (1.08), 7.607 (2.14), 7.612 (3.85), 7.618 (10.48), 7.626 (2.84), 7.631 (6.75), 7.635 (14.52), 7.648 (2.55), 7.652 (2.90), 7.665 (2.99), 7.681 (1.28), 7.754 (11.66), 7.772 (9.18).

Example 9A

5-(4-Chlorophenyl)-2-{[5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2*S*)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



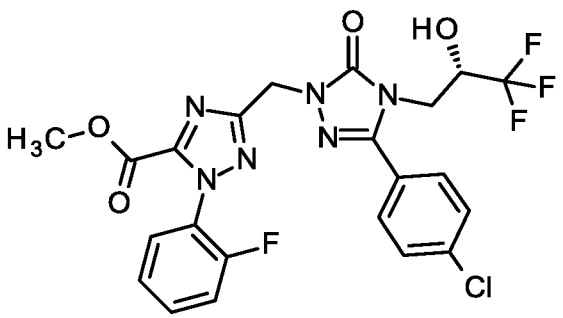
To a solution of 2-{3-(4-chlorophenyl)-5-oxo-4-[(2*S*)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1*H*-1,2,4-triazol-1-yl}acetohydrazide (Example 2A in WO 2016/071212 A1, 600 mg, 1.58 mmol) and pyrrolidine-1-carbonitrile (0.955 ml, 9.48 mmol) in 1-butanol (18 ml) was added potassium carbonate (109.2 mg, 0.79 mmol) at room temperature. The reaction mixture was stirred at 150°C for 2.5 h under microwave irradiation. After cooling, the reaction mixture was concentrated *in vacuo*, diluted with dichloromethane and water. After phase separation, the aqueous phase was extracted twice with dichloromethane. The combined organic phases were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude was purified by preparative HPLC (Method 5) affording 285 mg (0.62 mmol, 39% of th.) of the title compound.

LC-MS (Method 2): R_t = 0.84 min; MS [ESIpos]: m/z = 458 $(M+H)^+$

^{1}H-NMR (500 MHz, DMSO-d6) δ [ppm]: 7.72 -7.77 (m, 2 H), 7.60 -7.64 (m, 2 H), 6.89 (br. s., 1 H), 4.80 -4.89 (m, 2 H), 4.25 - 4.33 (m, 1 H), 3.98 (dd, 1 H), 3.84 (dd, 1 H), 3.26 -3.34 (m, 4 H), 1.88 - 1.93 (m, 4 H)

Example 10A

Methyl 3-({3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1-(2-fluorophenyl)-1H-1,2,4-triazole-5-carboxylate



A solution of methyl 2-{3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}ethanimidate (Example 7A, 1.00 g, 2.64 mmol) in tetrahydrofuran (20 ml) was cooled to 0°C and treated with methyl chloro(oxo)acetate (270 µl, 2.9 mmol) followed by N,N-diisopropylethylamine (0.5 ml, 2.9 mmol). The resulting mixture was stirred for 30 min.

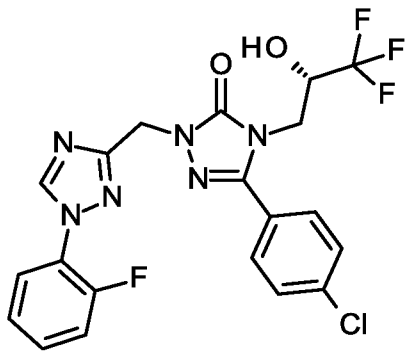
(2-Fluorophenyl)hydrazine hydrochloride (1:1) (472 mg, 2.90 mmol) and N,N-diisopropylethylamine (0.5 ml, 2.9 mmol) were added, the reaction mixture was warmed up to room temperature and stirred for 30 min, followed by 2 h at 80°C in a sealed vial under microwave irradiation. The reaction mixture was evaporated and the crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 983 mg (67% of th.) of the title compound.

LC-MS (Method 3): R_t = 1.94 min; MS (ESIpos): m/z = 541 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 3.776 (1.07), 3.793 (16.00), 3.823 (0.85), 3.847 (0.93), 3.859 (1.17), 3.883 (1.27), 3.991 (1.20), 3.999 (1.35), 4.028 (0.85), 4.036 (0.81), 5.182 (8.11), 6.902 (2.22), 6.918 (2.23), 7.379 (0.90), 7.398 (2.00), 7.417 (1.18), 7.473 (0.83), 7.495 (1.40), 7.520 (1.09), 7.615 (4.48), 7.620 (2.00), 7.631 (2.65), 7.636 (6.14), 7.643 (1.67), 7.649 (1.19), 7.658 (1.19), 7.663 (1.16), 7.677 (1.69), 7.681 (1.57), 7.696 (0.82), 7.701 (0.77), 7.751 (5.34), 7.756 (1.88), 7.767 (1.57), 7.772 (3.95).

Example 11A

5-(4-Chlorophenyl)-2-{[1-(2-fluorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



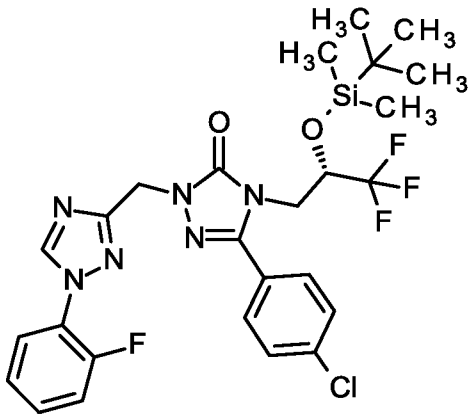
A solution of methyl 3-({3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1-(2-fluorophenyl)-1H-1,2,4-triazole-5-carboxylate (Example 10A, 900 mg, 1.66 mmol) in tetrahydrofuran (42 ml) was treated with an aqueous sodium hydroxid solution (21 ml, 1.0 M, 21 mmol) and stirred for 10 min. The pH of the reaction mixture was adjusted to pH = 1 with aqueous hydrochlorid acid (1 M) and stirred for 10 min. Ethyl acetate (20 ml) was added. Layers were separated and the aqueous layer was extracted with ethyl acetate. Combined organic extracts were washed with brine, dried over sodium sulfate and solvents were removed *in vacuo*. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 800 mg (quant.) of the title compound

LC-MS (Method 10): R_t = 1.32 min; MS (ESIpos): m/z = 483 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.008 (1.08), 0.008 (0.91), 1.157 (1.43), 1.175 (2.88), 1.193 (1.46), 1.988 (5.29), 3.288 (1.65), 3.819 (1.58), 3.843 (1.78), 3.855 (2.27), 3.879 (2.50), 3.985 (2.27), 3.994 (2.52), 4.003 (0.67), 4.021 (2.76), 4.030 (1.56), 4.039 (1.43), 4.299 (1.25), 4.316 (1.15), 5.139 (16.00), 6.907 (4.44), 6.923 (4.48), 7.386 (1.26), 7.392 (1.00), 7.396 (1.28), 7.399 (1.81), 7.407 (2.45), 7.415 (1.67), 7.420 (1.77), 7.428 (1.88), 7.521 (4.05), 7.524 (4.60), 7.532 (2.84), 7.538 (3.20), 7.542 (2.51), 7.546 (2.95), 7.553 (3.64), 7.555 (3.87), 7.601 (1.11), 7.607 (7.65), 7.612 (2.88), 7.624 (3.60), 7.629 (10.71), 7.635 (1.53), 7.737 (2.04), 7.743 (10.79), 7.748 (3.51), 7.759 (4.61), 7.764 (8.13), 7.775 (3.37), 7.778 (3.25), 7.796 (1.87), 8.971 (5.16), 8.977 (5.17).

Example 12A

4-[(2S)-2-{[tert-Butyl(dimethyl)silyl]oxy}-3,3,3-trifluoropropyl]-5-(4-chlorophenyl)-2-{[1-(2-fluorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-2,4-dihydro-3H-1,2,4-triazol-3-one

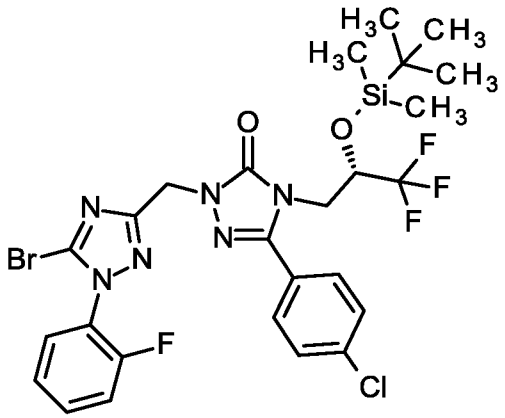


5-(4-Chlorophenyl)-2-{[1-(2-fluorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 11A, 750 mg, 1.55 mmol), 1H-imidazole (529 mg, 7.77 mmol) and tert-butyl(dimethyl)silyl trifluoromethanesulfonate (780 µl, 3.4 mmol) were dissolved in N,N-dimethylformamide (8.0 ml, 100 mmol) and stirred at room temperature for 16 h. The reaction mixture was heated to 60°C for additional 16 h. After addition of tert-butyl(dimethyl)silyl trifluoromethanesulfonate (780 µl, 3.4 mmol), the reaction mixture was heated to 60°C for additional 16 h. The reaction mixture was evaporated and the crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 772 mg (83% of th.) of the title compound.

LC-MS (Method 10): R_t = 1.77 min; MS (ESIpos): m/z = 443.2

Example 13A

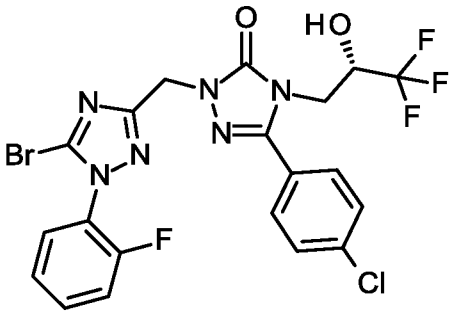
2-{[5-Bromo-1-(2-fluorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-2-{[tert-butyl(dimethyl)-silyl]oxy}-3,3,3-trifluoropropyl]-5-(4-chlorophenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one



A solution of 4-[(2S)-2-{[tert-butyl(dimethyl)silyl]oxy}-3,3,3-trifluoropropyl]-5-(4-chlorophenyl)-2-{[1-(2-fluorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 12A, 772 mg, 1.29 mmol) in tetrahydrofuran (20 ml) was treated with sodium hydride (310 mg, 60% purity, 7.76 mmol) and stirred for 5 min. 1,3-Dibromo-5,5-dimethylimidazolidine-2,4-dione (1.48 g, 5.17 mmol) was added and stirred for 2 h under reflux. Water was then added and the resulting mixture was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 860 mg (98% of th.) of the title compound which was directly submitted to the next step.

Example 14A

2-{[5-Bromo-1-(2-fluorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



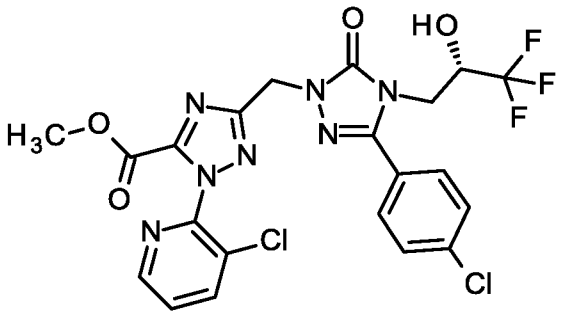
A solution of 2-{[5-bromo-1-(2-fluorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-2-{[tert-butyl(dimethyl)silyl]oxy}-3,3,3-trifluoropropyl]-5-(4-chlorophenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 13A, 860 mg, 1.27 mmol) in tetrahydrofuran (5.0 ml) was treated with a solution of tetra-n-butylammoniumfluoride in tetrahydrofuran (1.5 ml, 1.0 M, 1.5 mmol). The resulting mixture was stirred for 30 min at roomtemperature. Purification by preparative HPLC (Method 5) and lyophilisation of the product containing fractions afforded 510 mg (71% of th.) of the title compound.

LC-MS (Method 10): R_t = 1.30 min; MS (ESIpos): m/z = 561 $[M+H]^+$, 563 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.041 (0.58), -0.008 (2.30), 0.842 (0.83), 3.287 (1.07), 3.819 (1.56), 3.843 (1.79), 3.855 (2.27), 3.879 (2.46), 3.986 (2.28), 3.995 (2.65), 4.023 (1.62), 4.031 (1.60), 4.291 (1.31), 4.307 (1.23), 5.119 (16.00), 6.895 (4.53), 6.910 (4.62), 7.430 (1.72), 7.447 (3.82), 7.468 (2.29), 7.548 (1.32), 7.552 (1.50), 7.571 (2.36), 7.574 (3.01), 7.577 (1.93), 7.596 (2.09), 7.599 (1.91), 7.611 (1.07), 7.617 (7.85), 7.622 (3.32), 7.634 (3.41), 7.639 (10.70), 7.645 (2.13), 7.674 (0.88), 7.678 (1.50), 7.686 (2.68), 7.691 (3.51), 7.696 (2.68), 7.706 (4.07), 7.709 (5.68), 7.714 (2.15), 7.719 (1.04), 7.725 (1.57), 7.728 (3.19), 7.748 (1.69), 7.754 (10.77), 7.759 (4.01), 7.771 (3.07), 7.776 (7.94), 7.782 (1.55).

Example 15A

Methyl 3-({3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1-(3-chloropyridin-2-yl)-1H-1,2,4-triazole-5-carboxylate



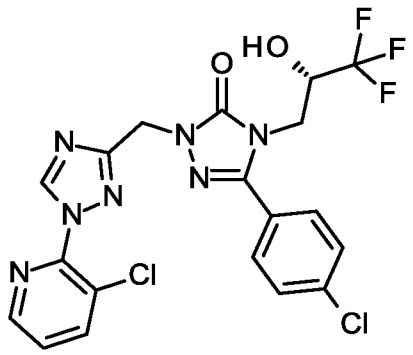
A solution of methyl 2-{3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}ethanimidate (Example 7A, 150 mg, 396 µmol) in tetrahydrofuran (3 ml) was cooled to 0°C and treated with methyl chloro(oxo)acetate (44 µl, 480 µmol). The resulting mixture was stirred for 30 min. 3-Chloro-2-hydrazinylpyridine (62.5 mg, 436 µmol) and N,N-diisopropylethylamine (280 µl, 1.6 mmol) were added, the reaction mixture was warmed up to room temperature and stirred for 1 h, followed by 1 h at 120°C in a sealed vial under microwave irradiation. The reaction mixture was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 25.3 mg (11% of th.) of the title compound.

LC-MS (Method 3): R_t = 1.82 min; MS (ESIpos): m/z = 558 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.141 (0.80), 1.237 (1.11), 2.085 (1.99), 3.288 (0.69), 3.311 (16.00), 3.822 (0.98), 3.846 (1.08), 3.859 (1.38), 3.883 (1.47), 3.991 (1.44), 3.999 (1.56), 4.028 (1.00), 4.036 (0.95), 4.297 (0.83), 4.315 (0.79), 5.218 (8.81), 6.907 (2.55), 6.923 (2.56), 7.614 (3.93), 7.636 (5.41), 7.749 (7.03), 7.760 (2.42), 7.771 (5.68), 7.780 (2.16), 8.324 (1.73), 8.327 (2.19), 8.344 (1.63), 8.347 (2.04), 8.599 (1.77), 8.603 (2.22), 8.611 (1.85), 8.614 (2.14).

Example 16A

5-(4-Chlorophenyl)-2-{[1-(3-chloropyridin-2-yl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



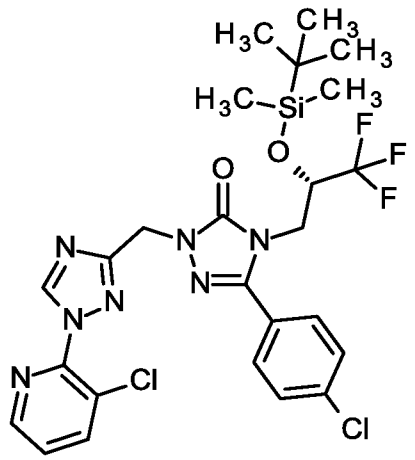
A solution of methyl 3-({3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1-(3-chloropyridin-2-yl)-1H-1,2,4-triazole-5-carboxylate (Example 15A, 180 mg, 322 µmol) in tetrahydrofuran (12 ml) was treated with an aqueous sodium hydroxid solution (7.3 ml, 5.0 M, 37 mmol) and stirred for 10 min. The pH of the reaction mixture was adjusted to pH = 1 with aqueous hydrochlorid acid (1 M) and stirred for 20 min. Ethyl acetate (20 ml) was added. Layers were separated and aqueous layer was extracted with ethyl acetate. Combined organic extracts were washed with brine, dried over sodium sulfate and evaporated. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 130 mg (81% of th.) of the title compound.

LC-MS (Method 10): R_t = 1.21 min; MS (ESIpos): m/z = 500 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.008 (1.20), 0.008 (1.24), 1.157 (0.88), 1.175 (1.77), 1.193 (0.90), 1.988 (3.25), 3.289 (1.71), 3.817 (1.56), 3.841 (1.77), 3.854 (2.25), 3.878 (2.45), 3.983 (2.24), 3.991 (2.51), 4.021 (2.17), 4.027 (1.55), 4.039 (0.87), 4.297 (1.25), 4.314 (1.19), 5.150 (16.00), 6.909 (4.56), 6.924 (4.58), 7.602 (1.17), 7.608 (8.03), 7.613 (3.03), 7.625 (3.53), 7.630 (11.04), 7.636 (1.68), 7.657 (3.81), 7.669 (3.90), 7.677 (3.98), 7.689 (4.10), 7.735 (1.85), 7.742 (11.09), 7.747 (3.46), 7.758 (3.07), 7.763 (7.91), 7.769 (1.08), 8.285 (3.90), 8.289 (4.12), 8.306 (3.75), 8.309 (3.73), 8.579 (3.99), 8.582 (4.05), 8.590 (3.99), 8.594 (3.78), 9.068 (10.80).

Example 17A

4-[(2S)-2-{[tert-Butyl(dimethyl)silyl]oxy}-3,3,3-trifluoropropyl]-5-(4-chlorophenyl)-2-{[1-(3-chloropyridin-2-yl)-1H-1,2,4-triazol-3-yl]methyl}-2,4-dihydro-3H-1,2,4-triazol-3-one

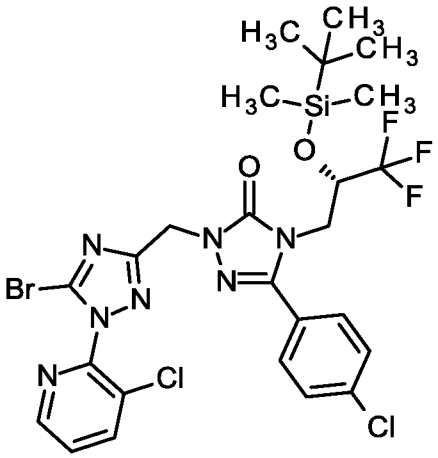


5-(4-Chlorophenyl)-2-{[1-(3-chloropyridin-2-yl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 16A, 120 mg, 240 µmol), 1H-imidazole (131 mg, 1.92 mmol) and tert-butyl(chloro)dimethylsilane (79.5 mg, 528 µmol) were dissolved in N,N-dimethylformamide (4.0 ml) and stirred at room temperature for 16 h. The reaction mixture was heated to 60°C for additional 16 h. After addition of tert-butyl(dimethyl)silyl trifluoromethanesulfonate (170 µl, 720 µmol), the reaction mixture was heated to 60°C for additional 16 h. The reaction mixture was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 144 mg (97% of th.) of the title compound.

LC-MS (Method 3): R_t = 2.60 min; MS (ESIpos): m/z = 614.1 $[M+H]^+$

Example 18A

2-{[5-Bromo-1-(3-chloropyridin-2-yl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-2-{[tert-butyl-(dimethyl)silyl]oxy}-3,3,3-trifluoropropyl]-5-(4-chlorophenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one



A solution of 4-[(2S)-2-{[tert-butyl(dimethyl)silyl]oxy}-3,3,3-trifluoropropyl]-5-(4-chlorophenyl)-2-{[1-(3-chloropyridin-2-yl)-1H-1,2,4-triazol-3-yl]methyl}-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 17A, 140 mg, 228 µmol) in tetrahydrofuran (17 ml) was treated with sodium hydride

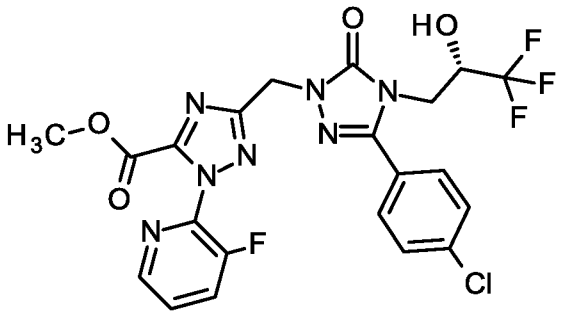
(54.7 mg, 60% purity, 1.37 mmol) and stirred for 5 min. 1,3-Dibromo-5,5-dimethylimidazolidine-2,4-dione (261 mg, 911 µmol) was added and stirred for 5 h under reflux. 1,3-Dibromo-5,5-dimethylimidazolidine-2,4-dione (261 mg, 911 µmol) was added and the reaxtion mixture was stirred for 5 h under reflux and 72 h at room temperature. Water was added and the resulting mixture was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 148 mg (94% of th.) of the title compound.

LC-MS (Method 3): R_t = 2.75 min; MS (ESIpos): m/z = 703 $[M+H]^+$, 705 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.227 (5.46), -0.013 (4.25), 0.706 (1.40), 0.714 (16.00), 5.142 (1.32), 5.163 (1.32), 7.633 (1.24), 7.655 (1.89), 7.735 (1.94), 7.756 (1.25), 7.790 (0.61), 7.801 (0.62), 7.810 (0.64), 7.822 (0.66), 8.376 (0.64), 8.380 (0.67), 8.397 (0.61), 8.401 (0.61), 8.666 (0.64), 8.670 (0.65), 8.678 (0.64), 8.682 (0.62).

Example 19A

Methyl 3-({3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1-(3-fluoropyridin-2-yl)-1H-1,2,4-triazole-5-carboxylate



A solution of methyl 2-{3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}ethanimidate (Example 7A, 1.00 g, 2.64 mmol) in tetrahydrofuran (20 ml) was cooled to 0°C and treated with methyl chloro(oxo)acetate (270 µl, 2.9 mmol). The resulting mixture was stirred for 30 min. 3-Fluoro-2-hydrazinylpyridine (369 mg, 2.90 mmol) and N,N-diisopropylethylamine (510 µl, 2.9 mmol) were added, the reaction mixture was warmed up to room temperature and stirred for 1 h, followed by 1 h at 120°C in a sealed vial under microwave irradiation. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 680 mg (48% of th.) of the title compound.

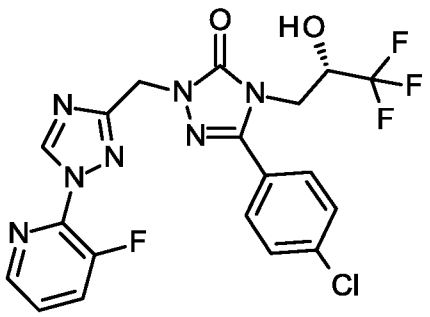
LC-MS (Method 3): R_t = 1.78 min; MS (ESIpos): m/z = 542 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 3.808 (16.00), 3.821 (1.05), 3.844 (0.95), 3.857 (1.15), 3.881 (1.24), 3.990 (1.20), 3.998 (1.28), 4.027 (0.81), 4.035 (0.78), 5.217 (8.13), 6.907 (2.33), 6.923 (2.34), 7.614 (3.78), 7.618 (1.47), 7.630 (1.62), 7.635 (5.20), 7.751 (5.36), 7.756 (1.78), 7.768 (1.53), 7.773 (3.96), 7.794 (0.74), 7.806 (1.20), 7.816 (1.57), 7.827 (1.42), 7.837 (0.87),

8.135 (0.90), 8.138 (0.95), 8.156 (1.02), 8.159 (1.71), 8.162 (1.23), 8.180 (0.81), 8.184 (0.82), 8.485 (1.74), 8.496 (1.69).

Example 20A

5-(4-Chlorophenyl)-2-{[1-(3-fluoropyridin-2-yl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



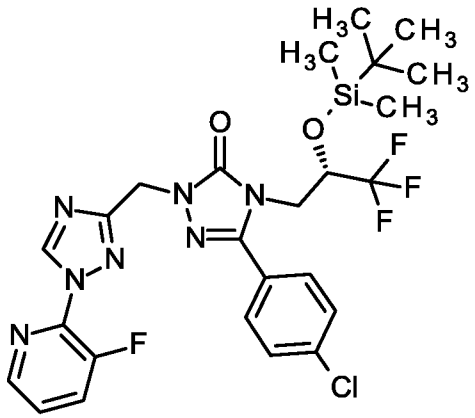
A solution of methyl 3-({3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1-(3-fluoropyridin-2-yl)-1H-1,2,4-triazole-5-carboxylate (Example 19A, 700 mg, 80% purity, 1.03 mmol) in tetrahydrofuran (10 ml) was treated with an aqueous sodium hydroxid solution (1.6 ml, 1.0 M, 1.6 mmol) and stirred for 10 min. The pH of the reaction mixture was adjusted to pH = 1 with aqueous hydrochlorid acid (1 M) and stirred for 10 min. Ethyl acetate (20 ml) was added. Layers were separated and aqueous layer was extracted with ethyl acetate. Combined organic extracts were washed with brine, dried with sodium sulfate and solvents were removed *in vacuo*. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 490 mg (88% of th.) of the title compound

LC-MS (Method 3): R_t = 1.68 min; MS (ESIpos): m/z = 484 $[M+H]^+$

^{1}H-NMR (500 MHz, DMSO-d6) δ [ppm]: -0.007 (1.02), 0.007 (0.97), 3.289 (0.87), 3.825 (1.64), 3.844 (1.82), 3.854 (2.20), 3.874 (2.32), 3.989 (2.30), 3.996 (2.50), 4.018 (1.65), 4.025 (1.60), 4.290 (0.79), 4.303 (1.25), 4.309 (1.10), 4.316 (1.16), 5.157 (16.00), 5.640 (0.95), 6.916 (4.36), 6.929 (4.41), 7.599 (0.78), 7.603 (1.35), 7.608 (8.01), 7.612 (3.52), 7.616 (1.62), 7.621 (3.48), 7.625 (10.23), 7.630 (1.75), 7.648 (1.59), 7.656 (2.01), 7.657 (2.13), 7.665 (3.28), 7.672 (2.21), 7.674 (2.40), 7.682 (1.79), 7.696 (0.74), 7.738 (1.68), 7.743 (9.92), 7.747 (3.63), 7.756 (3.08), 7.760 (7.70), 7.765 (1.29), 8.088 (1.84), 8.091 (2.00), 8.105 (1.90), 8.107 (2.39), 8.109 (2.49), 8.112 (2.16), 8.126 (1.76), 8.129 (1.84), 8.439 (3.75), 8.441 (2.79), 8.448 (3.68), 8.451 (2.59), 9.160 (8.72).

Example 21A

4-[(2S)-2-{[tert-Butyl(dimethyl)silyl]oxy}-3,3,3-trifluoropropyl]-5-(4-chlorophenyl)-2-{[1-(3-fluoropyridin-2-yl)-1H-1,2,4-triazol-3-yl]methyl}-2,4-dihydro-3H-1,2,4-triazol-3-one

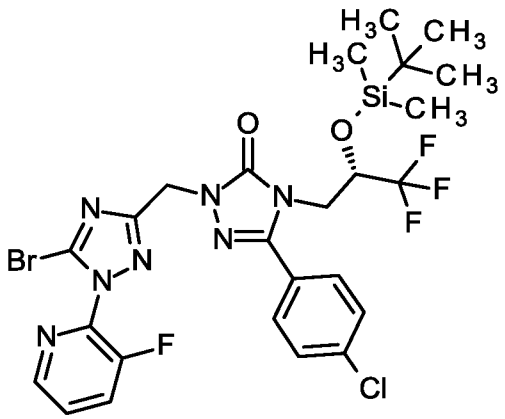


5-(4-Chlorophenyl)-2-{[1-(3-fluoropyridin-2-yl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 20A, 482 mg, 995 µmol), 1H-imidazole (203 mg, 2.99 mmol) and tert-butyl(dimethyl)silyl trifluoromethanesulfonate (340 µl, 1.5 mmol) were dissolved in N,N-dimethylformamide (8.0 ml) and stirred at room temperature for 16 h. The reaction mixture was heated to 60°C for additional 16 h. After addition of tert-butyl(dimethyl)silyl trifluoromethanesulfonate (340 µl, 1.5 mmol) the reaction mixture was heated to 60°C for additional 16 h. The reaction mixture was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 468 mg (78% of th.) of the title compound.

LC-MS (Method 3): R_t = 2.57 min; MS (ESIpos): m/z = 598.2 $[M+H]^+$

Example 22A

2-{[5-Bromo-1-(3-fluoropyridin-2-yl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-2-{[tert-butyl-(dimethyl)silyl]oxy}-3,3,3-trifluoropropyl]-5-(4-chlorophenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one



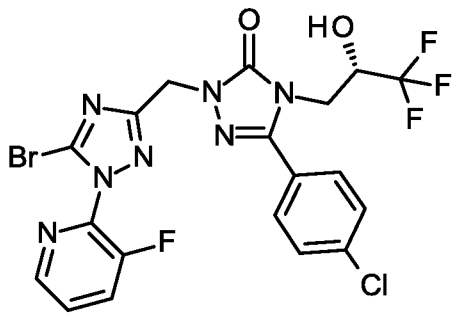
A solution of 4-[(2S)-2-{[tert-butyl(dimethyl)silyl]oxy}-3,3,3-trifluoropropyl]-5-(4-chlorophenyl)-2-{[1-(3-fluoropyridin-2-yl)-1H-1,2,4-triazol-3-yl]methyl}-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 21A, 465 mg, 777 µmol) in tetrahydrofuran (17 ml) was treated with sodium hydride (111 mg, 60%, 4.7 mmol) and stirred for 5 min. 1,3-Dibromo-5,5-dimethylimidazolidine-2,4-dione

(889 mg, 3.11 mmol) was added and stirred for 5 h under reflux. 1,3-Dibromo-5,5-dimethylimidazolidine-2,4-dione (889 mg, 3.11 mmol) was added and the reaxtion mixture was stirred for 5 h under reflux and 72 h at room temperature. Water was added and the resulting mixture was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 303 mg (57% of th.) of the title compound which was directly submitted to the next step.

LC-MS (Method 3): R_t = 2.67 min; MS (ESIpos): m/z = 676 $[M+H]^+$

Example 23A

2-{[5-Bromo-1-(3-fluoropyridin-2-yl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



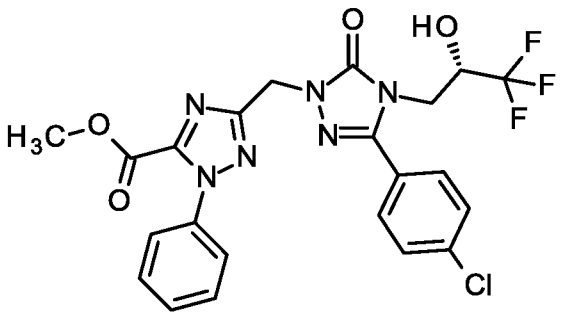
A solution of 2-{[5-bromo-1-(3-fluoropyridin-2-yl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-2-{[tert-butyl(dimethyl)silyl]oxy}-3,3,3-trifluoropropyl]-5-(4-chlorophenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 22A, 302 mg, 446 µmol) in tetrahydrofuran (6.0 ml) was treated with a solution of tetra-*N*-butylammoniumfluoride in tetrahydrofuran (540 µl, 1.0 M, 540 µmol) and stirred for 30 min at room temperature. The reaction mixture was evaporated and the residue was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 218 mg (87% of th.) of the title compound.

LC-MS (Method 3): R_t = 1.84 min; MS (ESIpos): m/z = 562 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.041 (1.95), -0.008 (1.44), 0.008 (1.18), 0.842 (2.83), 3.815 (1.56), 3.839 (1.75), 3.852 (2.21), 3.876 (2.41), 3.984 (2.34), 3.992 (2.64), 4.020 (1.70), 4.029 (1.61), 4.299 (1.07), 5.148 (16.00), 6.898 (1.77), 6.913 (1.78), 7.609 (1.02), 7.615 (8.12), 7.620 (2.87), 7.631 (3.34), 7.636 (11.08), 7.643 (1.51), 7.746 (1.68), 7.752 (11.13), 7.757 (3.47), 7.769 (2.91), 7.774 (7.98), 7.780 (1.08), 7.838 (1.56), 7.848 (2.43), 7.859 (3.42), 7.870 (2.83), 7.880 (1.91), 8.190 (1.94), 8.194 (2.02), 8.212 (2.27), 8.215 (3.69), 8.218 (2.45), 8.236 (1.78), 8.239 (1.79), 8.558 (3.72), 8.570 (3.63).

Example 24A

Methyl 3-({3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1-phenyl-1H-1,2,4-triazole-5-carboxylate



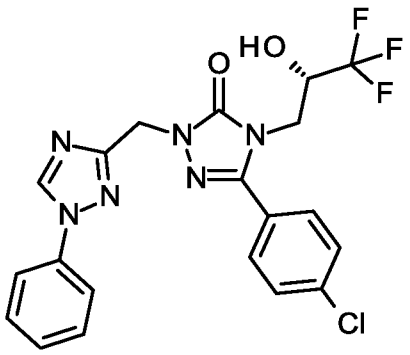
A solution of methyl 2-{3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}ethanimidate (Example 7A, 300 mg, 792 µmol) in tetrahydrofuran (6 ml) was cooled to 0°C and treated with methyl chloro(oxo)acetate (80 µl, 870 µmol). The resulting mixture was stirred for 30 min. Phenylhydrazine (86 µl, 870 µmol) and N,N-diisopropylethylamine (150 µl, 870 µmol) were added, the reaction mixture was warmed up to room temperature and stirred for 1 h, followed by 1 h at 120°C in a sealed vial under microwave irradiation. The reaction mixture was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 347 mg (84% of th.) of the title compound.

LC-MS (Method 3): R_t = 1.31 min; MS (ESIpos): m/z = 523 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.008 (1.05), 1.157 (1.22), 1.175 (2.47), 1.192 (1.26), 1.988 (4.57), 3.288 (0.82), 3.777 (16.00), 3.820 (0.81), 3.844 (0.90), 3.857 (1.15), 3.881 (1.24), 3.988 (1.12), 3.996 (1.28), 4.021 (1.42), 4.033 (0.83), 4.038 (1.30), 5.153 (7.84), 6.904 (2.25), 6.920 (2.27), 7.522 (1.30), 7.526 (1.70), 7.534 (3.96), 7.540 (7.60), 7.547 (3.74), 7.552 (4.57), 7.560 (2.14), 7.572 (1.28), 7.577 (0.94), 7.612 (3.85), 7.617 (1.46), 7.628 (1.60), 7.633 (5.25), 7.749 (5.32), 7.754 (1.71), 7.765 (1.44), 7.770 (3.89).

Example 25A

5-(4-Chlorophenyl)-2-[(1-phenyl-1H-1,2,4-triazol-3-yl)methyl]-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



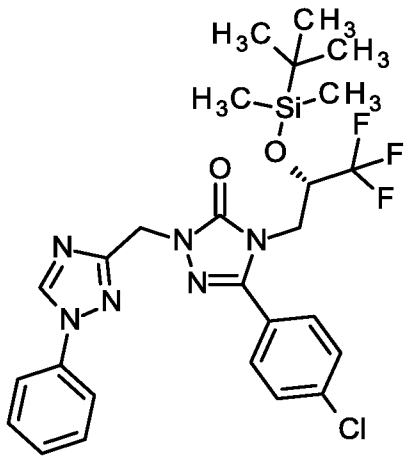
A solution of methyl 3-({3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1-phenyl-1H-1,2,4-triazole-5-carboxylate (Example 24A, 300 mg, 574 µmol) in tetrahydrofuran (14 ml) was treated with an aqueous sodium hydroxid solution (1.4 ml, 5.0 M, 7.2 mmol) and stirred for 10 min. The pH of the reaction mixture was adjusted to pH = 1 with aqueous hydrochlorid acid (1 M) and stirred for 20 min. Ethyl acetate (20 ml) was added. Layers were separated and aqueous layer was extracted with ethyl acetate. Combined organic extracts were washed with brine, dried over sodium sulfate and solvents were removed *in vacuo*. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 254 mg (95% of th.) of the title compound.

LC-MS (Method 10): R_t = 1.28 min; MS (ESIpos): m/z = 509 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.008 (1.99), 0.008 (2.07), 1.175 (0.78), 1.356 (2.57), 1.909 (2.75), 1.988 (1.12), 3.820 (1.56), 3.844 (1.77), 3.857 (2.29), 3.881 (2.50), 3.987 (2.30), 3.995 (2.59), 4.023 (1.72), 4.032 (1.60), 4.301 (1.18), 4.317 (1.12), 5.122 (16.00), 6.909 (3.55), 6.924 (3.56), 7.402 (1.55), 7.421 (4.09), 7.437 (1.54), 7.440 (2.64), 7.539 (4.72), 7.543 (2.24), 7.559 (7.46), 7.573 (1.57), 7.578 (4.21), 7.596 (0.98), 7.603 (7.86), 7.607 (2.98), 7.619 (3.26), 7.624 (10.98), 7.630 (1.65), 7.733 (1.57), 7.739 (10.90), 7.744 (3.49), 7.756 (2.93), 7.761 (8.08), 7.767 (1.11), 7.820 (7.57), 7.834 (1.94), 7.839 (6.75), 7.842 (5.29), 9.242 (11.46).

Example 26A

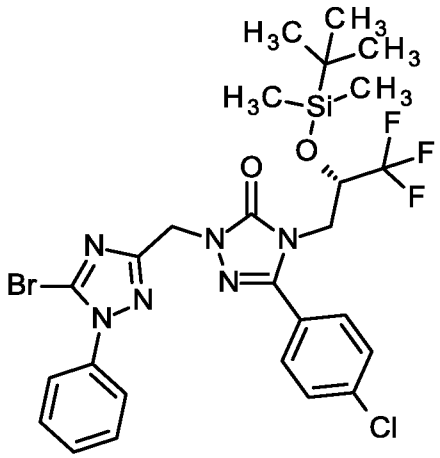
4-[(2S)-2-{[tert-Butyl(dimethyl)silyl]oxy}-3,3,3-trifluoropropyl]-5-(4-chlorophenyl)-2-[(1-phenyl-1H-1,2,4-triazol-3-yl)methyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



5-(4-Chlorophenyl)-2-[(1-phenyl-1H-1,2,4-triazol-3-yl)methyl]-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 25A, 240 mg, 516 µmol), 1H-imidazole (105 mg, 1.55 mmol) and tert-butyl(chloro)dimethylsilane (117 mg, 774 µmol) were dissolved in N,N-dimethylformamide (4.0 ml, 52 mmol) and stirred at room temperature for 16 h. The reaction mixture was heated to 60°C for additional 16 h. After addition of tert-butyl(dimethyl)silyl trifluoromethanesulfonate (140 µl, 620 µmol) the reaction mixture was heated to 60°C for additional 16 h. The reaction mixture was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 236 mg (79% of th.) of the title compound which was directly submitted to the next step.

Example 27A

2-[(5-Bromo-1-phenyl-1H-1,2,4-triazol-3-yl)methyl]-4-[(2S)-2-{[tert-butyl(dimethyl)silyl]oxy}-3,3,3-trifluoropropyl]-5-(4-chlorophenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one

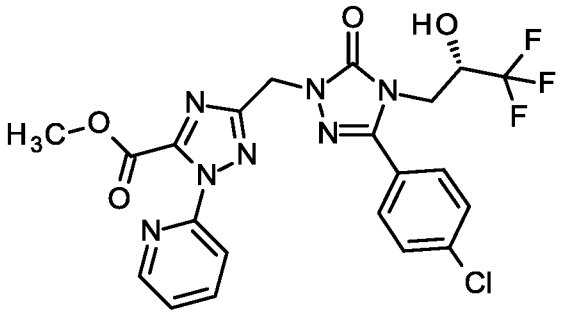


A solution of [4-[(2S)-2-{[tert-butyl(dimethyl)silyl]oxy}-3,3,3-trifluoropropyl]-5-(4-chlorophenyl)-2-[(1-phenyl-1H-1,2,4-triazol-3-yl)methyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 26A, 236 mg, 408 µmol) in tetrahydorfuran (17 ml) was treated with sodium hydride (350 µl, 7.0 M, 2.4 mmol) and stirred for 5 min. 1,3-Dibromo-5,5-dimethylimidazolidine-2,4-dione (466 mg, 1.63

mmol) was added and stirred for 5 h under reflux. 1,3-Dibromo-5,5-dimethylimidazolidine-2,4-dione (466 mg, 1.63 mmol) was added and the reaxtion mixture was stirred for 5 h under reflux and 72 h at room temperature. Water was added and the reaction mixture was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 217 mg (80% of th.) of the title compound which was directly submitted to the next step.

Example 28A

Methyl 3-({3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1-(pyridin-2-yl)-1H-1,2,4-triazole-5-carboxylate



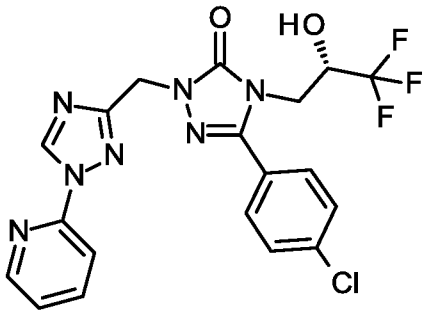
A solution of methyl 2-{3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}ethanimidate (Example 7A; 1.00 g, 2.64 mmol) in tetrahydrofuran (20 ml) was cooled to 0°C and treated with methyl chloro(oxo)acetate (270 µl, 2.9 mmol). The resulting mixture was stirred for 30 min. 2-Hydrazinylpyridine hydrochloride (1:1) (423 mg, 2.90 mmol) and N,N-diisopropylethylamine (1.0 ml, 5.8 mmol) were added, the reaction mixture was warmed up to room temperature and stirred for 30 min, followed by 1 h at 120°C in a sealed vial under microwave irradiation. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 483 mg (33% of th.) of the title compound.

LC-MS (Method 3): R_t = 1.79 min; MS (ESIpos): m/z = 524 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 3.820 (0.78), 3.844 (1.02), 3.858 (16.00), 3.880 (1.25), 3.990 (1.15), 3.998 (1.28), 4.026 (0.81), 4.035 (0.78), 5.187 (7.66), 6.905 (2.15), 6.921 (2.27), 7.564 (1.07), 7.577 (1.17), 7.583 (1.19), 7.595 (1.26), 7.608 (3.70), 7.613 (1.40), 7.625 (1.82), 7.629 (4.90), 7.743 (0.97), 7.750 (5.02), 7.755 (1.55), 7.766 (1.45), 7.771 (3.70), 7.815 (1.92), 7.835 (2.21), 8.099 (0.94), 8.103 (0.94), 8.118 (1.49), 8.122 (1.54), 8.138 (0.77), 8.142 (0.75), 8.527 (1.25), 8.532 (1.40), 8.539 (1.33), 8.544 (1.33).

Example 29A

5-(4-Chlorophenyl)-2-{[1-(pyridin-2-yl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



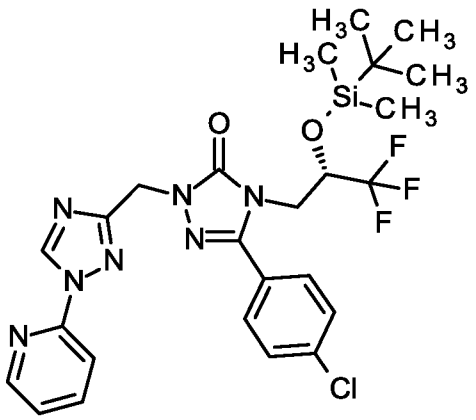
A solution of methyl 3-({3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1-(pyridin-2-yl)-1H-1,2,4-triazole-5-carboxylate (Example 28A, 435 mg, 830 µmol) in tetrahydrofuran (5.0 ml) was treated with an aqueous sodium hydroxid solution (1.2 ml, 1.0 M, 1.2 mmol) and stirred for 5 min. The pH of the reaction mixture was adjusted to pH = 1 with aqueous hydrochlorid acid (1 M) and stirred for 5 min. The reaction mixture was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 423 mg (98% of th.) of the title compound.

LC-MS (Method 3): R_t = 1.76 min; MS (ESIpos): m/z = 466 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 3.291 (0.87), 3.824 (1.59), 3.847 (1.85), 3.859 (4.49), 3.884 (2.54), 3.990 (2.45), 3.999 (2.76), 4.027 (1.72), 4.035 (1.68), 4.289 (0.79), 4.305 (1.35), 4.313 (1.16), 4.322 (1.28), 5.153 (16.00), 5.187 (1.38), 6.920 (4.82), 6.936 (4.52), 7.474 (2.22), 7.486 (2.41), 7.493 (2.47), 7.505 (2.42), 7.596 (1.14), 7.603 (7.03), 7.607 (3.64), 7.619 (3.03), 7.624 (9.72), 7.630 (2.48), 7.736 (1.56), 7.742 (9.98), 7.759 (2.91), 7.763 (7.51), 7.771 (1.51), 7.822 (3.73), 7.843 (4.40), 8.056 (1.77), 8.061 (1.87), 8.076 (2.84), 8.080 (3.09), 8.096 (1.49), 8.099 (1.64), 8.532 (2.64), 8.534 (2.82), 8.537 (2.83), 8.544 (2.69), 8.546 (2.80), 8.549 (2.63), 9.337 (7.69).

Example 30A

4-[(2S)-2-{[tert-Butyl(dimethyl)silyl]oxy}-3,3,3-trifluoropropyl]-5-(4-chlorophenyl)-2-{[1-(pyridin-2-yl)-1H-1,2,4-triazol-3-yl]methyl}-2,4-dihydro-3H-1,2,4-triazol-3-one

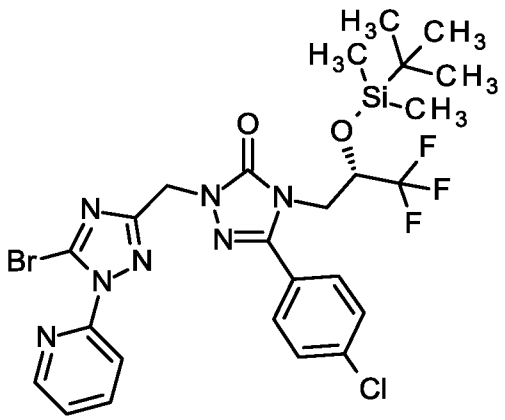


5-(4-Chlorophenyl)-2-{[1-(pyridin-2-yl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 29A, 414 mg, 888 µmol), 1H-imidazole (181 mg, 2.66 mmol) and tert-butyl(dimethyl)silyl trifluoromethanesulfonate (310 µl, 1.3 mmol) were dissolved in N,N-dimethylformamide (7.0 ml, 91 mmol) and stirred at room temperature for 16 h. The reaction mixture was heated to 60°C for additional 16 h. After addition of tert-butyl(dimethyl)silyl trifluoromethanesulfonate (310 µl, 1.3 mmol) the reaction mixture was heated to 60°C for additional 16 h. The reaction mixture was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 400 mg (78% of th.) of the title compound which was directly submitted to the next step.

LC-MS (Method 2): R_t = 1.38 min; MS (ESIpos): m/z = 580 $[M+H]^+$

Example 31A

2-{[5-Bromo-1-(pyridin-2-yl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-2-{[tert-butyl(dimethyl)-silyl]oxy}-3,3,3-trifluoropropyl]-5-(4-chlorophenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one

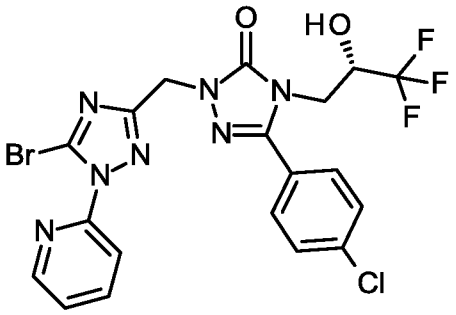


A solution of 4-[(2S)-2-{[tert-butyl(dimethyl)silyl]oxy}-3,3,3-trifluoropropyl]-5-(4-chlorophenyl)-2-{[1-(pyridin-2-yl)-1H-1,2,4-triazol-3-yl]methyl}-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 30A, 399 mg, 688 µmol) in tetrahydrofuran (17 ml) was treated with sodium hydride (99 mg, 60%, 4.1 mmol) and stirred for 5 min. 1,3-Dibromo-5,5-dimethylimidazolidine-2,4-dione (787 mg, 2.75 mmol) was added and stirred for 5 h under reflux. 1,3-Dibromo-5,5-dimethylimidazolidine-2,4-dione (787 mg, 2.75 mmol) was added and the reaxtion mixture was stirred for 5 h under reflux and 72 h at room temperature. Water was added and the reaction mixture was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 288 mg (58% of th.) of the title compound which was directly submitted to the next step.

LC-MS (Method 3): R_t = 2.72 min; MS (ESIpos): m/z = 658 $[M+H]^+$, 661 $[M+H]^+$

Example 32A

2-{[5-Bromo-1-(pyridin-2-yl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



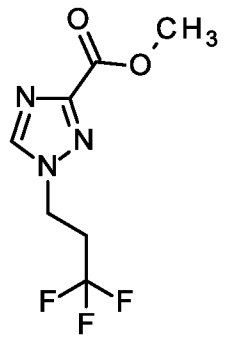
A solution of 2-{[5-bromo-1-(pyridin-2-yl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-2-{[tert-butyl(dimethyl)silyl]oxy}-3,3,3-trifluoropropyl]-5-(4-chlorophenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 31A, 288 mg, 402 µmol) in tetrahydrofuran (5.0 ml) was treated with tetra-*N*-butylammoniumfluoride (480 µl, 1.0 M, 480 µmol). The resulting mixture was stirred for 30 min at room temperature. The reaction mixture was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 125 mg (53% of th.) of the title compound.

LC-MS (Method 3): R_t = 1.81 min; MS (ESIpos): m/z = 544 $[M+H]^+$, 546 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.041 (1.78), 0.843 (2.61), 3.291 (1.16), 3.819 (1.64), 3.843 (1.89), 3.858 (3.76), 3.879 (2.55), 3.988 (2.34), 3.996 (2.65), 4.024 (1.67), 4.033 (1.60), 4.297 (1.29), 4.315 (1.22), 5.124 (16.00), 5.153 (0.78), 5.187 (1.12), 6.903 (4.64), 6.919 (4.87), 7.608 (3.83), 7.612 (9.77), 7.617 (3.38), 7.620 (3.14), 7.623 (3.39), 7.629 (6.34), 7.633 (11.66), 7.639 (3.80), 7.641 (3.23), 7.742 (0.80), 7.748 (2.04), 7.754 (11.52), 7.760 (6.94), 7.771 (3.60), 7.776 (8.87), 7.780 (5.92), 8.103 (2.27), 8.108 (2.24), 8.123 (3.41), 8.128 (3.32), 8.142 (1.88), 8.147 (1.83), 8.630 (2.81), 8.633 (2.83), 8.635 (2.66), 8.641 (2.44), 8.643 (2.84), 8.645 (2.67), 8.647 (2.44).

Example 33A

Methyl 1-(3,3,3-trifluoropropyl)-1H-1,2,4-triazole-3-carboxylate



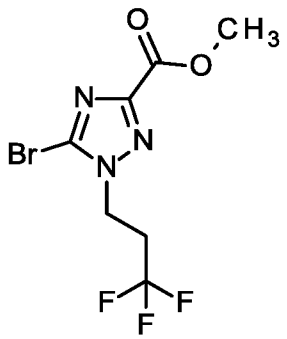
Methyl 1H-1,2,4-triazole-3-carboxylate (8.11 g, 63.8 mmol) was dissolved in N,N-dimethylformamide (41 ml) and cooled to 0°C. Sodium hydride (3.32 g, 60% purity, 82.9 mmol)

was added and the reaction mixture was stirred for 30 min at 0°C. After 1,1,1-trifluoro-3-iodopropane (15.0 g, 67.0 mmol) was added and the resulting mixture was stirred for 16 h at room temperarture. Saturated ammonium chloride solution and ethyl acetate were added. Layers were separated and aqueous layer was extracted with ethyl acetate. Combined organic extracts were washed with brine, dried over sodium sulfate and solvents were removed *in vacuo*. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 2.56 g (18% of th.) of the title compound

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 2.904 (0.96), 2.921 (2.07), 2.932 (2.97), 2.938 (1.52), 2.948 (5.97), 2.959 (3.22), 2.966 (3.45), 2.976 (5.83), 2.987 (1.41), 2.993 (3.06), 3.004 (1.93), 3.021 (0.94), 3.331 (1.18), 4.556 (8.10), 4.573 (16.00), 4.590 (7.72), 8.776 (11.85).

Example 34A

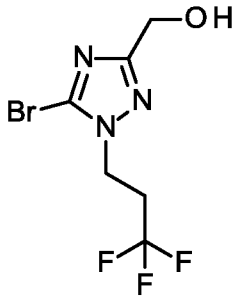
Methyl 5-bromo-1-(3,3,3-trifluoropropyl)-1H-1,2,4-triazole-3-carboxylate



Methyl 1-(3,3,3-trifluoropropyl)-1H-1,2,4-triazole-3-carboxylate (Example 33A, 1.30 g, 5.83 mmol), 1-bromopyrrolidine-2,5-dione (5.18 g, 29.1 mmol) and sodium hydride (699 mg, 60%, 17.5 mmol) were dissolved in tetrahydrofuran (33 ml, 400 mmol) and stirred at 60°C for 16 h. Aqueous ammonium chloride solution and ethyl acetate were added. Layers were separated and aqueous layer was extracted with ethyl acetate. Combined organic extracts were washed with brine, dried over sodium sulfate and evaporated. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 2.56 g (18% of th.) of the title compound

Example 35A

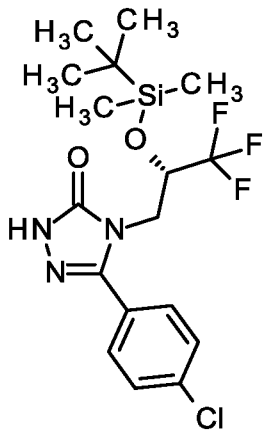
[5-Bromo-1-(3,3,3-trifluoropropyl)-1H-1,2,4-triazol-3-yl]methanol



Methyl 5-bromo-1-(3,3,3-trifluoropropyl)-1H-1,2,4-triazole-3-carboxylate (Example 34A, 2.00 g, 5.30 mmol) was dissolved in ethanol (20 ml, 340 mmol) and tetrahydrofuran (20 ml). Lithium chloride (1.12 g, 26.5 mmol) and sodium borohydride (1.00 g, 26.5 mmol) were added to the reaction mixture and stirred for 17 h at room temperature. The reaction mixture was diluted with ethyl acetate and saturated ammonium chloride solution and stirred for 30min. Layers were separated and aqueous layer was extracted with ethyl acetate. Combined organic extracts were washed with brine, dried over magnesium sulfate and solvents were removed *in vacuo*. The crude product was triturated with ethyl acetate/diethyl ether (1/1) and a few drops of methanol. The organic layer was decanted of and dried *in vacuo* to afford the title product. The crude product was directly used in the next step.

Example 36A

4-[(2S)-2-{[Ttert-butyl(dimethyl)silyl]oxy}-3,3,3-trifluoropropyl]-5-(4-chlorophenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one



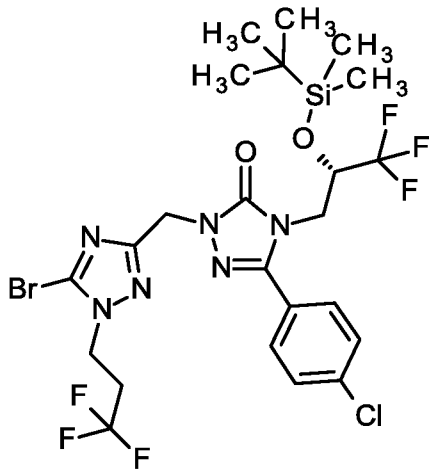
To a solution of 5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (synthesis described as Example 5A in WO 2011/104622-A1, 5.00 g, 16.3 mmol) in 20 ml N,N-dimethylformamide was added tert-butyl(chloro)dimethylsilane (4.90 g, 32.5 mmol) and 1H-imidazole (4.43 g, 65.0 mmol). The mixture was stirred for 18 h at room temperature. To this mixture 80 ml of a saturated sodiumcarbonat solution were added and stirring was continued for 30 min. To this solution 1 N hydrochloric acid was added until pH 7 was reached. The mixture was extracted twice with 50 ml of ethyl acetate. The combined organic

phases were dried over sodium sulfate, filtered and concentrated in vacuo. The crude product was purified by chromatography (silica gel, cyclohexane/ethyl acetate gradient) to afford 1.35 g (20% of th.) of the title compound.

LC-MS (Method 2): R_t = 1.33 min; MS (ESIpos): m/z = 422 $[M+H]^+$

Example 37A

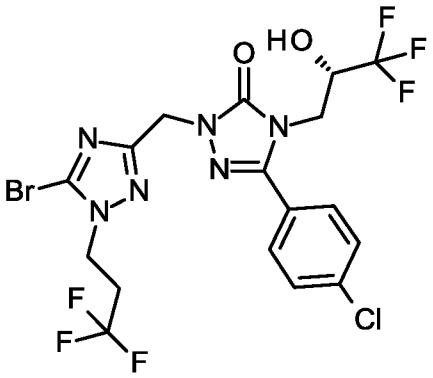
2-{[5-Bromo-1-(3,3,3-trifluoropropyl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-2-{[tert-butyl-(dimethyl)silyl]oxy}-3,3,3-trifluoropropyl]-5-(4-chlorophenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one



4-[(2S)-2-{[tert-Butyl(dimethyl)silyl]oxy}-3,3,3-trifluoropropyl]-5-(4-chlorophenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 36A, 924 mg, 2.19 mmol), [5-bromo-1-(3,3,3-trifluoropropyl)-1H-1,2,4-triazol-3-yl]methanol (Example 35A, 400 mg, 1.46 mmol) and triphenylphosphine (459 mg, 1.75 mmol) were dissolved in tetrahydrofuran (12 ml, 150 mmol) and cooled down to 0°C. Dipropan-2-yl (E)-diazene-1,2-dicarboxylate (354 mg, 1.75 mmol) was added and the reaction mixture was stirred for 1 h at room temperature. Dipropan-2-yl (E)-diazene-1,2-dicarboxylate (174 mg, 0.88 mmol) was added and the reaction mixture was stirred for 20 min at 60°C. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 992 mg (66% of th.) of the title compound.

Example 38A

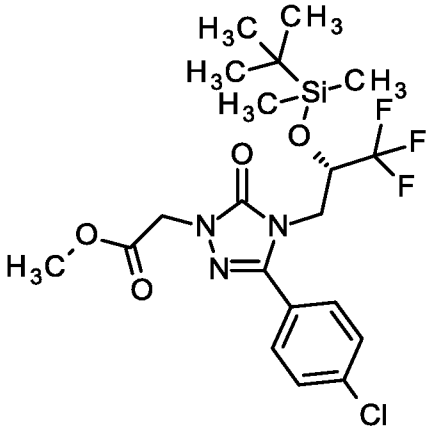
2-{[5-Bromo-1-(3,3,3-trifluoropropyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



A solution of 2-{[5-bromo-1-(3,3,3-trifluoropropyl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-2-{[tert-butyl(dimethyl)silyl]oxy}-3,3,3-trifluoropropyl]-5-(4-chlorophenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 37A, 941 mg, 1.39 mmol) in tetrahydrofuran (2.0 ml) was treated with a solution of tetra-n-butylammonium fluoride in tetrahydrofuran (1.7 ml, 1.0 M, 1.7 mmol). The reaction mixture was stirred for 1 h at room temperature and purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 358 mg (46% of th.) of the title compound

Example 39A

Methyl {4-[(2S)-2-{[tert-butyl(dimethyl)silyl]oxy}-3,3,3-trifluoropropyl]-3-(4-chlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl}acetate

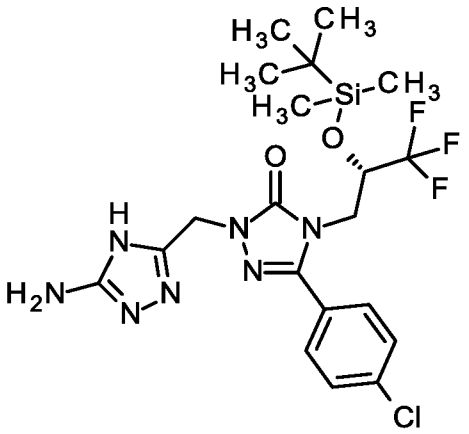


To a solution of 4-[(2S)-2-{[tert-butyl(dimethyl)silyl]oxy}-3,3,3-trifluoropropyl]-5-(4-chlorophenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (synthesis described as Example 7A in WO 2011/104622-A1,, 6.60 g, 15.6 mmol) in 50 ml acetonitrile was added caesium carbonate (6.12 g, 18.8 mmol) and dropwise methyl chloroacetate (1.5 ml, 17 mmol). The mixture was heated under reflux for 1 h and an additional 3 h at room temperature. To this mixture 80 ml water were added. The mixture was extracted twice with 50 ml of ethyl acetate. The combined organic phases were dried over sodium sulfate, filtered and concentrated in vacuo. The crude product was used witout further purification. 8.32 g (quant.) of the title compound were obtained.

LC-MS (Method 2): R_t = 1.39 min; MS (ESIpos): m/z = 494 $[M+H]^+$

Example 40A

2-[(5-Amino-4H-1,2,4-triazol-3-yl)methyl]-4-[(2S)-2-{[tert-butyl(dimethyl)silyl]oxy}-3,3,3-trifluoropropyl]-5-(4-chlorophenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one

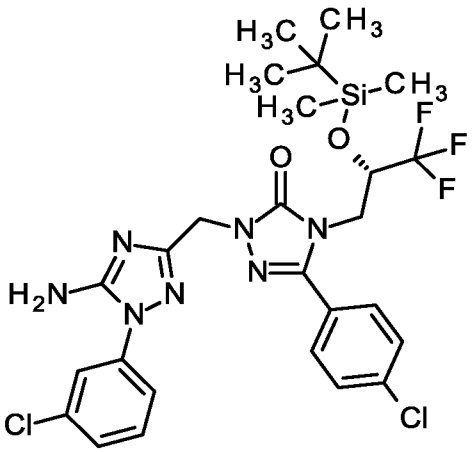


To a solution of sodium methanolate (5.7 ml, 30% purity, 31 mmol) in 20 ml methanol was added hydrazinecarboximidamide hydrochloride (1:1) (3.40 g, 30.8 mmol) at room temperature. To this mixture, methyl {4-[(2S)-2-{[tert-butyl(dimethyl)silyl]oxy}-3,3,3-trifluoropropyl]-3-(4-chlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl}acetate (Example 39A, 3.80 g, 7.69 mmol) dissolved in 10 ml methanol was. The mixture was heated to reflux for 45 min. After cooling to room temperature the solution was diluted with water, 10 ml of a saturated sodium carbonat solution were added and the mixture was extracted twice with 20 ml of ethyl acetate. The combined organic phases were dried over sodium sulfate, filtered and concentrated in vacuo. The crude product was purified by chromatography (silica gel, cyclohexane/ethyl acetate gradient) to afford 1.50 g (38% of th.) of the title compound.

LC-MS (Method 2): R_t = 1.14 min; MS (ESIpos): m/z = 518 $[M+H]^+$

Example 41A

2-{[5-Amino-1-(3-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-2-{[tert-butyl(dimethyl)-silyl]oxy}-3,3,3-trifluoropropyl]-5-(4-chlorophenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one

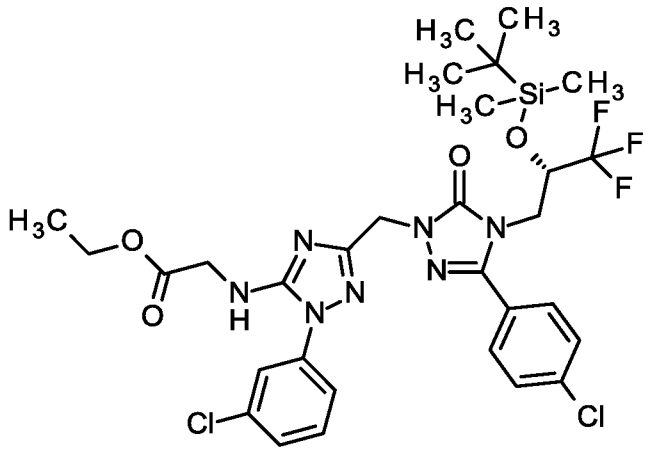


2-[(5-Amino-4H-1,2,4-triazol-3-yl)methyl]-4-[(2S)-2-{[tert-butyl(dimethyl)silyl]oxy}-3,3,3-trifluoropropyl]-5-(4-chlorophenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 40A, 500 mg, 965 µmol), copper(II)acetate (263 mg, 1.45 mmol), 20 mg of molsieves 3A and (3-chlorophenyl)boronic acid (302 mg, 1.93 mmol) were stirred at 60°C in 5 ml of pyridine for 10 h. After cooling to room temperature the mixture was filtered through a pad of celite. After elution with ethyl acetate, the organic phase was washed twice with water, dried over sodium sulfate, filtered and reduced in vacuo. The crude product was purified by chromatography (silica gel, cyclohexane/ethyl acetate gradient) to afford 464 mg (76% of th.) of the title compound.

LC-MS (Method 2): R_t = 1.39 min; MS (ESIpos): m/z = 628 $[M+H]^+$

Example 42A

Ethyl N-[3-({4-[(2S)-2-{[tert-butyl(dimethyl)silyl]oxy}-3,3,3-trifluoropropyl]-3-(4-chlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1-(3-chlorophenyl)-1H-1,2,4-triazol-5-yl]glycinate



A solution of 2-{[5-amino-1-(3-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-2-{[tert-butyl(dimethyl)silyl]oxy}-3,3,3-trifluoropropyl]-5-(4-chlorophenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 41A, 50.0 mg, 79.5 µmol) in 1 ml of tetrahydrofuran was added slowly to a

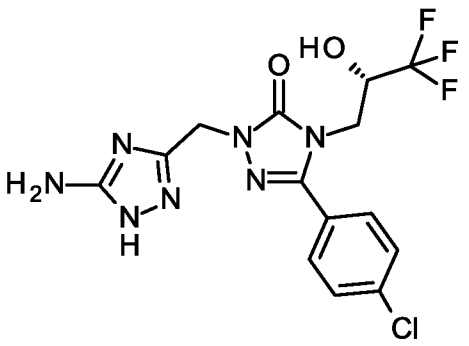
suspension of sodium hydride (6.36 mg, 60% purity, 159 µmol) in 1 ml of tetrahydrofuran at 0°C. After stirring for 10 min, ethyl bromoacetate (11 µl, 95 µmol) was added and the reaction mixture was stirred at room temperature for 18 h. The mixture was diluted with water and extracted twice with 20 ml of ethyl acetate. The combined organic phases were dried over sodium sulfate, filtered and concentrated in vacuo. The crude product was purified by chromatography (silica gel, cyclohexane/ethyl acetate gradient) to afford 25 mg (39% of th.) of the title compound.

LC-MS (Method 2): R_t = 1.48 min; MS (ESIpos): m/z = 714 $[M+H]^+$

1H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.209 (5.30), -0.009 (5.92), 0.008 (1.78), 0.714 (1.45), 0.725 (16.00), 1.073 (1.77), 1.090 (3.63), 1.108 (1.92), 1.144 (1.71), 1.162 (3.54), 1.180 (1.76), 3.357 (0.64), 3.375 (1.86), 3.392 (1.83), 3.410 (0.59), 3.976 (0.54), 3.984 (1.13), 3.999 (1.15), 4.031 (0.52), 4.041 (0.47), 4.050 (0.55), 4.061 (0.54), 4.078 (1.80), 4.096 (1.54), 4.113 (0.50), 4.805 (0.43), 4.845 (1.12), 4.879 (1.17), 4.918 (0.45), 7.250 (0.59), 7.489 (0.86), 7.494 (0.68), 7.500 (0.55), 7.505 (0.74), 7.543 (0.88), 7.548 (1.97), 7.569 (0.92), 7.620 (1.35), 7.642 (2.07), 7.720 (1.98), 7.741 (1.26).

Example 43A

2-[(5-Amino-1H-1,2,4-triazol-3-yl)methyl]-5-(4-chlorophenyl)-4-[(2*S*)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



At 0°C, to a solution of sodium methoxide (5.06 ml, 27.25 mmol, 30% in methanol, ~ 5.4 M solution), in methanol (17 ml), was added portionwise aminoguanidine hydrochloride (3.012 g, 27.25 mmol). To this suspension was added dropwise a solution of methyl {3-(4-chlorophenyl)-5-oxo-4-[(2*S*)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1*H*-1,2,4-triazol-1-yl}acetate (example 1A in WO 2016/071212 A1, 4.139 g, 10.90 mmol). The reaction mixture was stirred at room temperature for 10 min, then at reflux for 4 hours. After cooling, the reaction mixture was concentrated *in vacuo*, diluted with ethyl acetate and the resulting mixture was washed with saturated aqueous sodium carbonate solution. After phase separation, the organic phase was concentrated *in vacuo* and diluted with dichloromethane and aqueous hydrochloric acid (100 ml, 1 M). After additional phase separation, the organic phase was discarded. The remaining aqueous phase was slightly basified with aqueous sodium hydroxide and extracted twice with ethyl acetate.

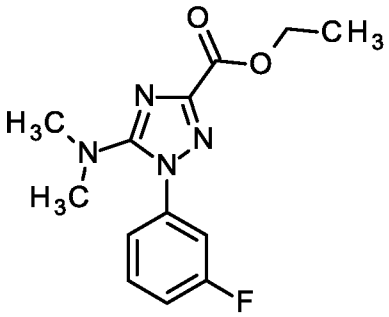
After phase separation, the organic phase was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resulting solid was dried under high vacuum, affording 3.25 g (8.05 mmol, 73.8% of Th.) of of the title compound.

LC-MS (Method 2): R_t = 0.76 min; MS [ESIpos]: m/z = 404 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 11.85 (br. s., 1 H), 7.77 - 7.71 (m, 2 H), 7.58 - 7.64 (m, 2 H), 6.93 (d, 1 H), 5.95 (br. s., 2 H), 4.74 (br. s., 2 H), 4.24 - 4.34 (m, 1 H), 3.97 (dd, 1 H), 3.82 (dd, 1 H)

Example 44A

Ethyl 5-(dimethylamino)-1-(3-fluorophenyl)-1H-1,2,4-triazole-3-carboxylate



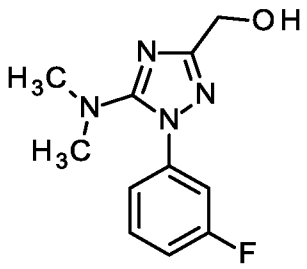
In a sealed reaction vessel (stainless steel; 25 ml) a suspension of dimethylamine (6.02 mmol, 3.01 ml; 2 M in trahydrofuran), ethyl 5-bromo-1-(3-fluorophenyl)-1H-1,2,4-triazole-3-carboxylate (Example 52A, 0.86 g, 2.74 mmol) and potassium carbonate (1.25 g, 9.04 mmol) in acetonitrile (dry) (15 ml) was stirred at 50°C overnight. Reaction mixture was allowed to cool to room temperature. Ethyl acetate (50 ml) and a mixture of water (10 ml) and brine (10 ml) were added. Layers were separated and aqueous layer was extracted with ethyl acetate (3x50 ml). Combined organic extracts were dried with sodium sulfate and solvents were removed *in vacuo*. 0.75 g (2.70 mmol; 98% of th.) of the title compound were obtained.

LC-MS (Method 1): R_t = 1.88 min; m/z = 279 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d6) δ [ppm]: 7.58 - 7.33 (m, 3H), 7.20 - 7.07 (m, 1H), 4.48 (q, 2H), 2.87 (s, 6H), 1.42 (t, 3H).

Example 45A

[5-(Dimethylamino)-1-(3-fluorophenyl)-1H-1,2,4-triazol-3-yl]methanol



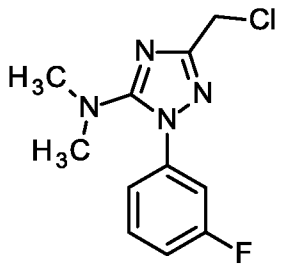
Under nitrogen atmosphere at 0°C lithium aluminum hydride (5.13 mmol, 2.14 ml; 2.4 M in tetrahydrofuran) was added to a solution of ethyl 5-(dimethylamino)-1-(3-fluorophenyl)-1H-1,2,4-triazole-3-carboxylate (Example 53A, 1.36 g, 4.89 mmol) in tetrahydrofuran (dry) (25 ml). Reaction mixture was stirred at 0°C for 5 min. Reaction mixture was poured out in an ice cold mixture of saturated aqueous ammonium chloride (25 ml) and ethyl acetate (50 ml). Layers were separated. Organic layer was extracted with ethyl acetate (3x50 ml). Combined organic layers were dried with sodium sulfate and solvents were removed *in vacuo*. Flash column chromatography (Method 6; 80 g; dichloromethane, 3%-5% methanol) afforded 0.60 g (2.54 mmol; 52% of th.) of the title compound.

LC-MS (Method 1): R_t = 1.56 min; m/z = 237 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d6) δ [ppm]: 7.49 - 7.32 (m, 3H), 7.11 - 7.02 (m, 1H), 4.67 (s, 2H), 2.84 (s, 6H), 2.62 - 2.53 (m, 1H).

Example 46A

3-(Chloromethyl)-1-(3-fluorophenyl)-N,N-dimethyl-1H-1,2,4-triazol-5-amine



Under nitrogen atmosphere at 0°C to a solution of [5-(dimethylamino)-1-(3-fluorophenyl)-1H-1,2,4-triazol-3-yl]methanol (Example 54A, 0.60 g, 2.54 mmol) in dichloromethane (25 ml) was added phosphorus pentachloride (1.06 g, 5.08 mmol). The reaction mixture was stirred at 0°C for 5 min and was allowed to warm to room temperature. Stirring was continued overnight. Reaction mixture was poured out in a mixture of water (10 ml) and saturated aqueous sodium hydrogencarbonate (10 ml). Layers were separated and the aqueous layer was extracted with dichloromethane (3x30 ml). Combined organic layers were washed with water (2x10 ml) and dried with sodium sulfate. Solvents were removed *in vacuo*. Flash column chromatography (Method 6;

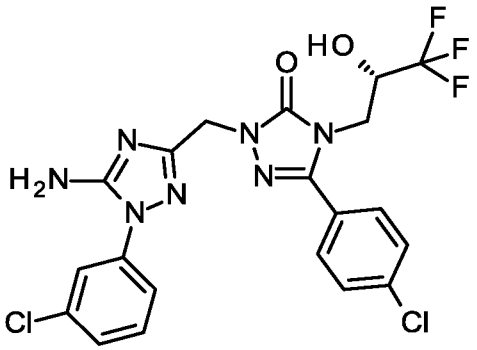
80 g; heptane, 20%-30% ethyl acetate) afforded 0.50 g (1.98 mmol; 78% of th.) of the title compound.

LC-MS (Method 7): R_t = 2.75 min; m/z = 255 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d6) δ [ppm]: 7.49 - 7.30 (m, 3H), 7.15 - 7.01 (m, 1H), 4.53 (s, 2H), 2.85 (s, 6H).

Example 47A

2-{[5-Amino-1-(3-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2*S*)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



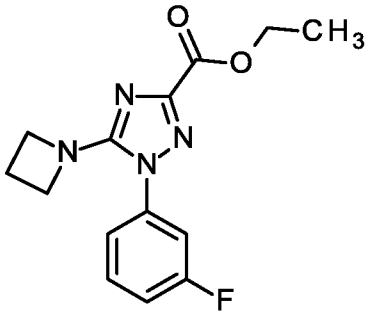
To a solution of 2-[(5-amino-1H-1,2,4-triazol-3-yl)methyl]-5-(4-chlorophenyl)-4-[(2*S*)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 43A, 1.7 g, 4.21 mmol) in pyridine (13 ml) were added (3-chlorophenyl)boronic acid (1.317 g, 8.42 mmol) and copper(II) acetate (1.53 g, 8.42 mmol). The reaction mixture was stirred at room temperature for 5 days, then diluted with ethyl acetate and quenched with aqueous hydrochloric acid (1 M). After phase separation, the aqueous phase was extracted twice with ethyl acetate. The combined organic phases were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was first purified by preparative HPLC [Chromatorex C18, 10 µm, 125 x 30 mm, water-acetonitrile-gradient 0.05% trifluoroacetic acid]. A second purification by preparative chiral SFC [sample preparation: 1.46 g (purity 90%) dissolved in 60 ml of a mixture of methanol/ethanol/acetonitrile; injection volume: 2 ml; column: Daicel Chiralcel® OX-H 5 µm, 250 x 20 mm; eluent: carbon dioxide/methanol 70:30; flow rate: 80 ml/min; temperature: 40°C; UV detection: 210 nm] afforded 1.10 g (2.04 mmol, 48.6% of th.) of the title compound.

LC-MS (Method 4): R_t = 3.06 min; MS [ESIpos]: m/z = 514 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.72 - 7.78 (m, 2 H), 7.60 - 7.64 (m, 2 H), 7.58 (t, 1 H), 7.49 - 7.56 (m, 2 H), 7.41 - 7.45 (m, 1 H), 6.90 (d, 1 H), 6.64 (s, 2 H), 4.79 - 4.89 (m, 2 H), 4.24 - 4.35 (m, 1 H), 3.99 (dd, 1 H), 3.84 (dd, 1 H)

Example 48A

Ethyl 5-(azetidin-1-yl)-1-(3-fluorophenyl)-1H-1,2,4-triazole-3-carboxylate

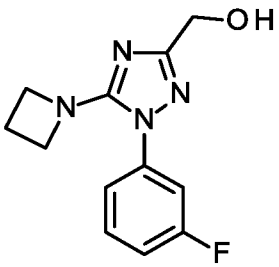


Azetidine (0.46 g, 8.05 mmol, 0.54 ml) was added to a mixture ethyl 5-bromo-1-(3-fluorophenyl)-1H-1,2,4-triazole-3-carboxylate (Example 52A, 1.15 g, 3.66 mmol) and potassium carbonate (1.67 g, 12.08 mmol) in acetonitrile (dry) (40 ml). The reaction mixture was stirred at 50°C overnight. Reaction mixture was allowed to cool to room temperature. Ethyl acetate (100 ml) and a mixture of water (25 ml) and brine (25 ml) were added. Layers were separated and aqueous layer was extracted with ethyl acetate (3x50 ml). Combined organic extracts were dried with sodium sulfate and solvents were removed *in vacuo*. 1.10 g (3.33 mmol; 91% of th.) of the title compound with a purity of 88% according to LC-MS were obtained.

LC-MS (Method 1): R_t = 1.89 min; m/z = 291 $(M+H)^+$

Example 49A

[5-(Azetidin-1-yl)-1-(3-fluorophenyl)-1H-1,2,4-triazol-3-yl]methanol

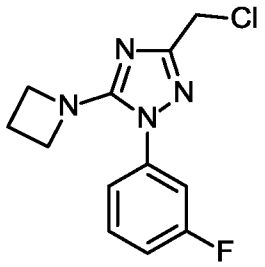


Under nitrogen atmosphere at 0°C lithium aluminum hydride (3.98 mmol, 1.66 ml; 2.4 M in tetrahydrofuran) was added drop wise to a solution of ethyl 5-(azetidin-1-yl)-1-(3-fluorophenyl)-1H-1,2,4-triazole-3-carboxylate (Example 48A, 1.10 g, 3.79 mmol) in tetrahydrofuran (20 ml). Reaction mixture was stirred at 0°C for 5 min and was poured out in an ice cold mixture of saturated aqueous ammonium chloride (25 ml) and ethyl acetate (50 ml). Layers were separated. Organic layer was extracted with ethyl acetate (2x100 ml). Combined organic layers were dried with sodium sulfate and solvents were removed *in vacuo*. Flash column chromatography (Method 6; 80 g; dichloromethane, 2%-4% methanol) afforded 0.69 g (2.79 mmol; 74% of th.) of the title compound.

LC-MS (Method 1): R_t = 1.60 min; m/z = 249 $(M+H)^+$

Example 50A

5-(Azetidin-1-yl)-3-(chloromethyl)-1-(3-fluorophenyl)-1H-1,2,4-triazole



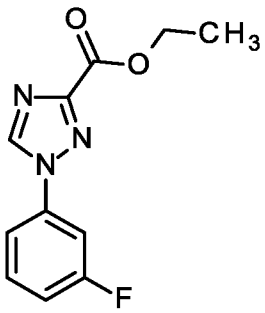
Under nitrogen atmosphere at 0°C to a solution of [5-(azetidin-1-yl)-1-(3-fluorophenyl)-1H-1,2,4-triazol-3-yl]methanol (Example 49A, 0.69 g, 2.79 mmol) in dichloromethane (25 ml) was added phosphorus pentachloride (1.16 g, 5.58 mmol). The reaction mixture was stirred at 0°C for 5 min and was allowed to warm to room temperature. Stirring was continued overnight. Reaction mixture was poured out in a mixture of water (10 ml) and saturated aqueous sodium hydrogencarbonate (10 ml). Layers were separated and the aqueous layer was extracted with dichloromethane (3x30 ml). Combined organic layers were washed with water (2x10 ml) and dried with sodium sulfate. Solvents were removed *in vacuo*. Flash column chromatography (Method 6; 80 g; heptane, 20%-30% ethyl acetate) afforded 0.42 g (1.57 mmol; 56% of th.) of the title compound.

LC-MS (Method 7): R_t = 2.78 min; m/z = 267 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d6) δ [ppm]: 7.42 (td, 1H), 7.36 - 7.25 (m, 2H), 7.06 (tdd, 1H), 4.53 (s, 2H), 4.02 - 3.92 (m, 4H), 2.41 - 2.28 (m, 2H).

Example 51A

Ethyl 1-(3-fluorophenyl)-1H-1,2,4-triazole-3-carboxylate



A solution of 3-fluoroaniline (5.80 g, 52.2 mmol, 5.0 ml) in a mixture of water (25 ml) and concentrated hydrochloric acid (15.43 g, 157 mmol, 15.28 ml) was cooled to 0°C. A solution of sodium nitrite (3.60 g, 52.2 mmol) in water (5 ml) was added maintaining the temperature between 0°C and 5°C. Stirring was continued for 5 min at 0°C. This solution was added drop wise to a

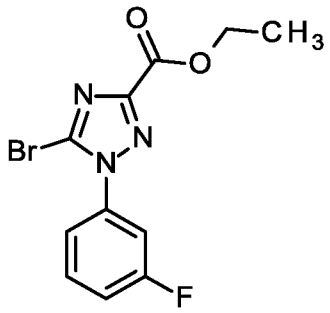
mixture of acetic acid sodium salt (27.8 g, 339 mmol) and ethyl 2-isocyanoacetate (5.31 g, 47.0 mmol, 5.13 ml) in a mixture of water (50 ml) and methanol (5 ml). The reaction mixture was stirred at 0°C for 30 min and was allowed to warm to room temperature. Stirring was continued for 18 h. Ethyl acetate (100 ml) was added. Layers were separated. Aqueous layer was extracted with ethyl acetate (3x100 ml). Combined organic extracts were dried with sodium sulfate and solvents were removed *in vacuo*. For purification the material was combined with a second batch of crude ethyl 1-(3-fluorophenyl)-1H-1,2,4-triazole-3-carboxylate obtained from the conversion of 3-fluoroaniline (2.90 g, 26.1 mmol, 2.5 ml). Flash column chromatography (Method 6; 500 g; heptane, 10%-50% ethyl acetate) and subsequent trituration in diisopropyl ether afforded 6.91 g (29.4 mmol; 38% of th. based on 78.3 mmol) of the title compound.

LC-MS (Method 1): R_t = 1.81 min; m/z = 252 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d6) δ [ppm]: 9.50 (s, 1H), 7.90 - 7.76 (m, 2H), 7.66 (td, 1H), 7.42 - 7.29 (m, 1H), 4.40 (q, 2H), 1.36 (t, 3H).

Example 52A

Ethyl 5-bromo-1-(3-fluorophenyl)-1H-1,2,4-triazole-3-carboxylate



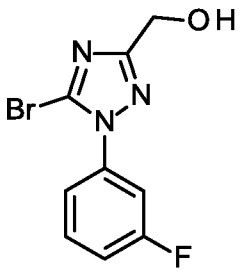
In a 250 ml-round bottom flask under argon atmosphere sodium hydride (2.42 g, 60.6 mmol; 60% in mineral oil) was added to a suspension of ethyl 1-(3-fluorophenyl)-1H-1,2,4-triazole-3-carboxylate (Example 51A, 4.75 g, 20.2 mmol) and N-bromosuccinimide (18.0 g, 101 mmol) in tetrahydrofuran (dry) (100 ml). Reaction mixture was stirred at room temperature for 10 min and at reflux for 5 h. The mixture was allowed to cool to room temperature, diluted with ethyl acetate (100 ml) and was poured out in saturated aqueous ammonium chloride (100 ml). Layers were separated and aqueous layer was extracted with ethyl acetate (3x100 ml). Combined organic layers were dried with sodium sulfate. Solvents were removed *in vacuo*. The residue was absorbed on isolute. Purification by flash column chromatography (Method 6; 500 g; heptane, 25%-35% ethyl acetate and Method 6; 500 g; heptane, 20%-35% ethyl acetate) afforded 4.49 g (24.3 mmol; 71% of th.) of the title compound.

LC-MS (Method 1): R_t = 1.94 min; m/z = 314/316 $(M+H)^+$

1H-NMR (300 MHz, DMSO-d6) δ [ppm]: 7.76 - 7.61 (m, 2H), 7.59 - 7.42 (m, 2H), 4.35 (q, 2H), 1.30 (t, 3H).

Example 53A

[5-Bromo-1-(3-fluorophenyl)-1H-1,2,4-triazol-3-yl]methanol

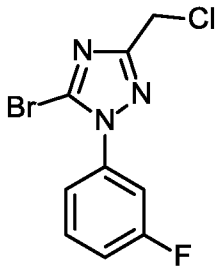


At 0°C under nitrogen atmosphere to a solution of ethyl 5-bromo-1-(3-fluorophenyl)-1H-1,2,4-triazole-3-carboxylate (Example 52A, 4.38 g, 13.9 mmol) in a mixture of tetrahydrofuran (dry) (50 ml) and ethanol (abs) (50 ml) were added lithium chloride (2.36 g, 55.8 mmol) and sodium borohydride (2.11 g, 55.8 mmol). Reaction mixture was allowed to warm to room temperature and stirring was continued for 18 h. The reaction mixture was diluted with ethyl acetate (50 ml) and was poured out in aqueous saturated ammonium chloride. Layers were separated and aqueous layer was extracted with ethyl acetate (3x50 ml). Combined organic layers were dried with sodium sulfate and solvents were removed *in vacuo*. Reversed phase flash column chromatography (Method 8; 120 g) afforded 0.9 g (3.3 mmol; 24% of th.) of the title compound.

LC-MS (Method 1): R_t = 1.64 min; m/z = 272/274 $(M+H)^+$

Example 54A

5-Bromo-3-(chloromethyl)-1-(3-fluorophenyl)-1H-1,2,4-triazole



Phosphorus pentachloride (1.4 g, 6.7 mmol) was added to a solution of 5-bromo-1-(3-fluorophenyl)-1H-1,2,4-triazol-3-yl]methanol (Example 53A, 0.9 g, 3.3 mmol) in dichloromethane (50 ml). The solution was stirred at room temperature for 1 h. The reaction mixture was washed with saturated aqueous ammonium chloride. The organic layer was dried with sodium sulfate and solvents were removed *in vacuo*. The crude product was absorbed on isolute. Purification by flash

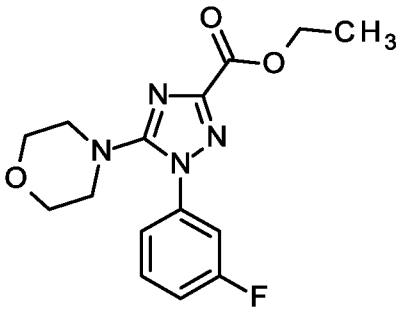
column chromatography (Method 6; 80 g; heptane, 0%-20% ethyl acetate) afforded 0.76 g (2.6 mmol; 79% of th.) of title compound.

LC-MS (Method 9): R_t = 3.38 min; m/z = 290/292 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d6) δ [ppm]: 7.71 - 7.43 (m, 4H), 4.81 (s, 2H).

Example 55A

Ethyl 1-(3-fluorophenyl)-5-(morpholin-4-yl)-1H-1,2,4-triazole-3-carboxylate



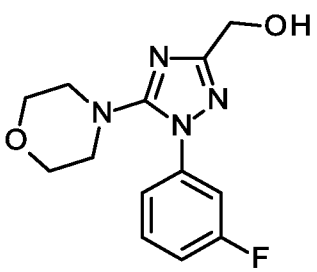
Under nitrogen atmosphere morpholine (0.50 g, 5.76 mmol, 0.50 ml) was added to a mixture of ethyl 5-bromo-1-(3-fluorophenyl)-1H-1,2,4-triazole-3-carboxylate (Example 52A, 1.72 g, 5.49 mmol) and potassium carbonate (0.76 g, 5.49 mmol) in dimethyl sulfoxide (dry) (20 ml). The reaction mixture was stirred at 50°C overnight. Reaction mixture was allowed to cool to room temperature and was partitioned between water (10 ml) and a mixture of diethyl ether (100 ml) and ethyl acetate (20 ml). Layers were separated and aqueous layer was extracted with ethyl acetate (3x50 ml). Combined organic layers were dried with sodium sulfate. Solvents were removed *in vacuo* Purification by reversed phase flash column chromatography (Method 8; 120 g) afforded 1.05 g (3.28 mmol; 60% of th.) of the title compound.

LC-MS (Method 1): R_t = 1.86 min; m/z = 321 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d6) δ [ppm]: 7.56 - 7.43 (m, 3H), 7.13 (tdd, 1H), 4.49 (q, 2H), 3.78 - 3.71 (m, 4H), 3.28 - 3.19 (m, 4H), 1.43 (t, 3H).

Example 56A

[1-(3-Fluorophenyl)-5-(morpholin-4-yl)-1H-1,2,4-triazol-3-yl]methanol



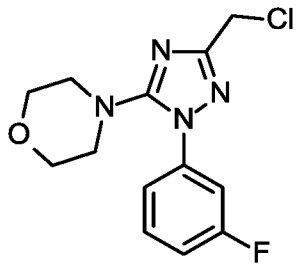
At 0°C under nitrogen atmosphere to a solution of ethyl 1-(3-fluorophenyl)-5-(morpholin-4-yl)-1H-1,2,4-triazole-3-carboxylate (Example 55A, 1.05 g, 3.28 mmol) in a mixture of tetrahydrofuran (dry) (10 ml) and ethanol (abs) (10 ml) were added lithium chloride (0.556 g, 13.11 mmol) and sodium borohydride (0.496 g, 13.11 mmol). Reaction mixture was allowed to warm to room temperature and stirring was continued overnight. Reaction mixture was diluted with tetrahydrofuran (dry) (10 ml) and ethanol (abs) (10 ml). Lithium chloride (1.668 g, 39.31 mmol) and sodium borohydride (1.488 g, 39.31 mmol) were added. Stirring at room temperature was continued for 48 h. Reaction mixture was diluted with ethyl acetate (20 ml) and was poured out in saturated aqueous ammonium chloride (20 ml). Layers were separated and aqueous layer was extracted with ethyl acetate (3x20 ml). Combined organic layers were dried with sodium sulfate and solvents were removed *in vacuo*. Residue was absorbed on isolute. Flash column chromatography (Method 6; 80 g; dichloromethane, 2%-4% methanol) afforded 0.56 g (2.00 mmol; 61% of th.) of the title compound.

LC-MS (Method 1): R_t = 1.61 min; m/z = 279 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d6) δ [ppm]: 7.54 - 7.39 (m, 3H), 7.07 (tdd, 1H), 4.69 (d, 2H), 3.80 - 3.72 (m, 4H), 3.19 (dd, 4H), 2.57 (t, 1H).

Example 57A

4-[3-(Chloromethyl)-1-(3-fluorophenyl)-1H-1,2,4-triazol-5-yl]morpholine



Under nitrogen atmosphere at 0°C to a solution of [1-(3-fluorophenyl)-5-(morpholin-4-yl)-1H-1,2,4-triazol-3-yl]methanol (Example 56A, 0.55 g, 1.98 mmol) in dichloromethane (dry) (15 ml) was added phosphorus pentachloride (0.82 g, 3.95 mmol). The reaction mixture was stirred at 0°C for 5 min and was allowed to warm to room temperature. Stirring was continued overnight. Reaction mixture was poured out in a mixture of ice-water (20 ml) and saturated aqueous sodium hydrogencarbonate (20 ml). Layers were separated and aqueous layer was extracted with dichloromethane (3x20 ml). Combined organic layers were washed with water (2x10 ml) and dried with sodium sulfate. Solvents were removed *in vacuo*. 0.57 g (1.92 mmol; 97% of th.) of the title compound were obtained.

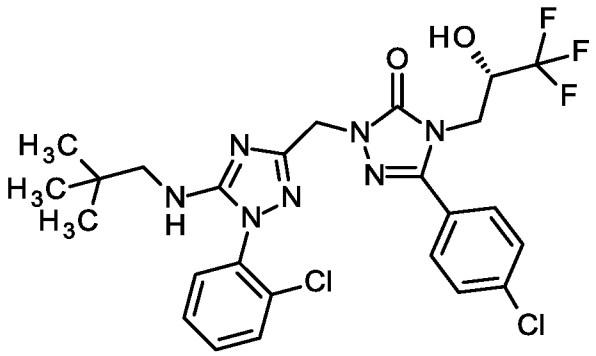
LC-MS (Method 7): R_t = 2.73 min; m/z = 297 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d6) δ [ppm]: 7.57 - 7.40 (m, 3H), 7.16 - 7.04 (m, 1H), 4.56 (s, 2H), 3.80 - 3.71 (m, 4H), 3.27 - 3.18 (m, 4H).

EXPERIMENTAL SECTION – EXAMPLES

Example 1

5-(4-Chlorophenyl)-2-({1-(2-chlorophenyl)-5-[(2,2-dimethylpropyl)amino]-1H-1,2,4-triazol-3-yl}methyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



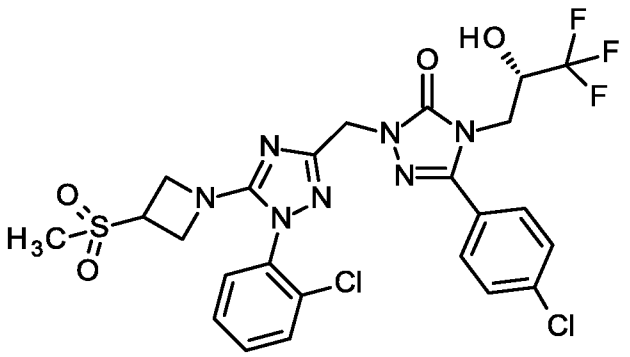
A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 100 mg, 173 µmol) in acetonitrile (330 µl) was treated with N,N-diisopropylethylamine (450 µl, 2.6 mmol) and 2,2-dimethylpropan-1-amine (151 mg, 1.73 mmol). The resulting mixture was heated for 5 h at 180°C under microwave irradiation and evaporated. The residue was purified by preparative HPLC (Method 5) affording 65.5 mg (65% of th.) of the title compound.

LC-MS (Method 3): R_t = 2.14 min; MS (ESIpos): m/z = 584.1 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.42 - 7.81 (m, 8H), 6.88 (d, 1H), 6.38 (t, 1H), 4.76 - 4.92 (m, 2H), 4.20 - 4.40 (m, 1H), 3.77 - 4.08 (m, 2H), 3.04 (br d, 2H), 0.83 (s, 9H).

Example 2

5-(4-Chlorophenyl)-2-({1-(2-chlorophenyl)-5-[3-(methylsulfonyl)azetidin-1-yl]-1H-1,2,4-triazol-3-yl}methyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



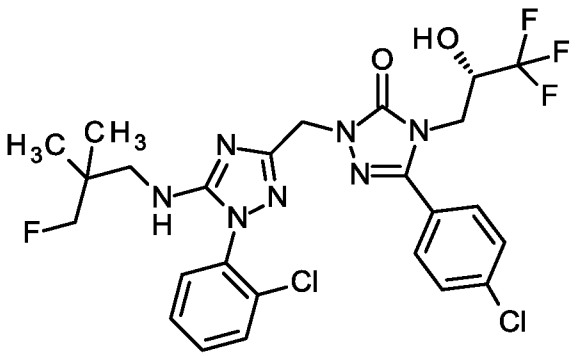
A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 100 mg, 173 µmol) in acetonitrile (330 µl) was treated with N,N-diisopropylethylamine (450 µl, 2.6 mmol) and 3-(methylsulfonyl)azetidine (234 mg, 1.73 mmol). The resulting mixture was heated for 5 h at 180°C under microwave irradiation and evaporated. The residue was purified by preparative HPLC (Method 5) affording 21.2 mg (19% of th.) of the title compound.

LC-MS (Method 3): R_t = 1.74 min; MS (ESIpos): m/z = 632.1 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.45 - 7.85 (m, 8H), 6.89 (d, 1H), 4.84 - 5.01 (m, 2H), 4.16 - 4.45 (m, 2H), 3.75 - 4.11 (m, 6H), 2.96 (s, 3H).

Example 3

5-(4-Chlorophenyl)-2-({1-(2-chlorophenyl)-5-[(3-fluoro-2,2-dimethylpropyl)amino]-1H-1,2,4-triazol-3-yl}methyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



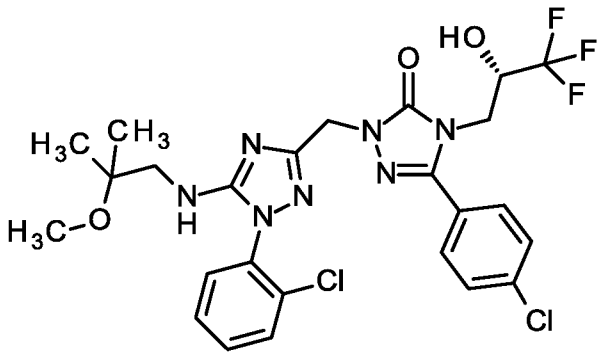
A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 100 mg, 173 µmol) in acetonitrile (330µl) was treated with N,N-diisopropylethylamine (450 µl, 2.6 mmol) and 3-fluoro-2,2-dimethylpropan-1-amine (182 mg, 1.73 mmol). The resulting mixture was heated for 5 h at 180°C under microwave irradiation. The reaction mixture was evaporated and purified by preparative HPLC (Method 5) affording 36.5 mg (35% of th.) of the title compound.

LC-MS (Method 3): R_t = 2.05 min; MS (ESIpos): m/z = 602.1 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.43 - 7.80 (m, 8H), 6.87 (d, 1H), 6.49 (t, 1H), 4.76 - 4.93 (m, 2H), 4.44 - 4.22 (m, 1H), 4.12 (d, 2H), 3.73 - 4.03 (m, 2H), 3.17 (br d, 2H), 0.85 (2 s, 6H).

Example 4

5-(4-Chlorophenyl)-2-({1-(2-chlorophenyl)-5-[(2-methoxy-2-methylpropyl)amino]-1H-1,2,4-triazol-3-yl}methyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



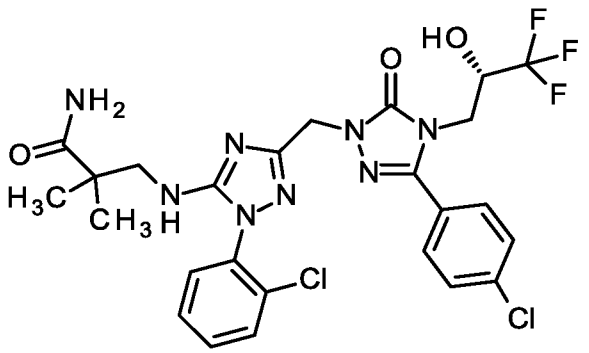
A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 100 mg, 173 µmol) in acetonitrile (330 µl) was treated with N,N-diisopropylethylamine (450 µl, 2.6 mmol) and 2-methoxy-2-methylpropan-1-amine (178 mg, 1.73 mmol). The resulting mixture was heated for 5 h at 180°C under microwave irradiation and evaporated. The residue was purified by preparative HPLC (Method 5) affording 82.5 mg (79% of th.) of the title compound.

LC-MS (Method 2): R_t = 1.05 min; MS (ESIpos): m/z = 600.2 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.44 - 7.81 (m, 8H), 6.87 (d, 1H), 6.12 (t, 1H), 4.77 - 4.93 (m, 2H), 4.29 (br ddd, 1H), 3.78 - 4.08 (m, 2H), 3.30 - 3.19 (m, 2H, overlapping with HDO peak), 3.06 (s, 3H), 1.05 (s, 6H).

Example 5

3-{[1-(2-Chlorophenyl)-3-({3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1H-1,2,4-triazol-5-yl]amino}-2,2-dimethylpropanamide



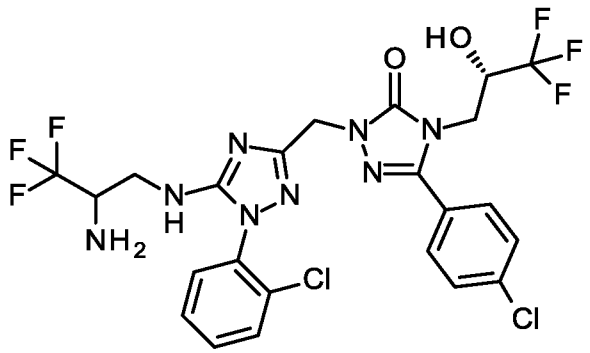
A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 100 mg, 173 µmol) in acetonitrile (330 µl) was treated with N,N-diisopropylethylamine (450 µl, 2.6 mmol) and 3-amino-2,2-dimethylpropanamide (201 mg, 1.73 mmol). The resulting mixture was heated for 5 h at 180°C under microwave irradiation and evaporated. The residue was purified by preparative HPLC (Method 5), followed by a second preparative HPLC (Daicel Chiralcel® OZ-H 5 µm, 250 x 20 mm, iso-hexane/ethanol: 55/45) and finally by preparative HPLC (Method 5) affording 30.4 mg (29% of th.) of the title compound.

LC-MS (Method 3): R_t = 1.67 min; MS (ESIpos): m/z = 613.1 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.93-6.75 (m, 11H), 6.38-5.87 (m, 1H), 5.00-4.86 (m, 2H), 4.29 (br m, 1H), 4.07-3.69 (m, 2H), 3.49-3.16 (m, 2H, overlapping with HDO peak), 1.34-0.83 (m, 6H).

Example 6

2-{[5-{[2-Amino-3,3,3-trifluoropropyl]amino}-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (*diastereomeric mixture*)



A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 100 mg, 173 µmol)in acetonitrile (330 µl) was treated with N,N-diisopropylethylamine (450 µl, 2.6 mmol) and 3,3,3-trifluoropropane-1,2-diamine dihydrochloride (174 mg, 865 µmol). The resulting mixture was heated for 8 h at 180°C under microwave irradiation and evaporated. The residue was purified by preparative HPLC (Method 5) affording 40.0 mg (37% of th.) of the title compound as a mixture of diastereomers.

The two diastereomers were separated by preparative chiral HPLC [sample preparation: 31.2 mg dissolved in 2 ml 2-propanol; injection volume: 400 µl; column: Daicel Chiralcel® OZ-H 5 µm, 250 x 20 mm; eluent: iso-hexane/2-propanol 60:40; flow rate: 15 ml/min; temperature: 40°C; UV

detection: 220 nm]. After separation, 12 mg of diastereomer 1 (Example 7), which eluted first, and 13 mg of diastereomer 2 (Example 8), which eluted later, were isolated.

Example 7

2-{[5-{[2-Amino-3,3,3-trifluoropropyl]amino}-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (*diastereomer 1*)

Analytical chiral HPLC: R_t = 5.11 min, e.e. = 100% [column: Daicel Chiralcel® OZ-H 5 µm, 250 x 4.6 mm; eluent: iso-hexane/2-propanol 50:50 + 0.2% diethylamine; flow rate: 1.0 ml/min; temperature: 45°C; UV detection: 220 nm].

LC-MS (Method 3): R_t = 1.72 min; MS (ESIpos): m/z = 625.1 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.81-7.43 (m, 8H), 6.91 (d, 1H), 6.59 (t, 1H), 4.89 (d, 2H), 4.42-4.19 (m, 1H), 4.09-3.75 (m, 2H), 3.63-3.44 (m, 2H), 3.23-3.05 (m, 1H), 1.99 (br d, 2H).

Example 8

2-{[5-{[2-Amino-3,3,3-trifluoropropyl]amino}-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (*diastereomer 2*)

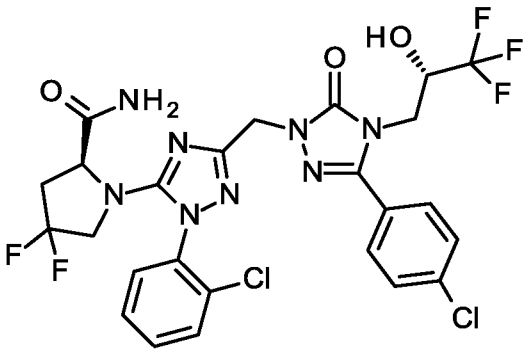
Analytical chiral HPLC: R_t = 6.30 min, e.e. = 100% [column: Daicel Chiralcel® OZ-H 5 µm, 250 x 4.6 mm; eluent: iso-hexane/2-propanol 50:50 + 0.2% diethylamine; flow rate: 1.0 ml/min; temperature: 45°C; UV detection: 220 nm].

LC-MS (Method 3): R_t = 1.73 min; MS (ESIpos): m/z = 625.1 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.82-7.43 (m, 8H), 6.92 (d, 1H), 6.59 (br t, 1H), 4.96-4.80 (m, 2H), 4.29 (br ddd, 1H), 4.07-3.72 (m, 2H), 3.60-3.43 (m, 2H), 3.23-3.04 (m, 1H), 2.00 (br d, 2H).

Example 9

1-[1-(2-Chlorophenyl)-3-({3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1H-1,2,4-triazol-5-yl]-4,4-difluoro-L-prolinamide



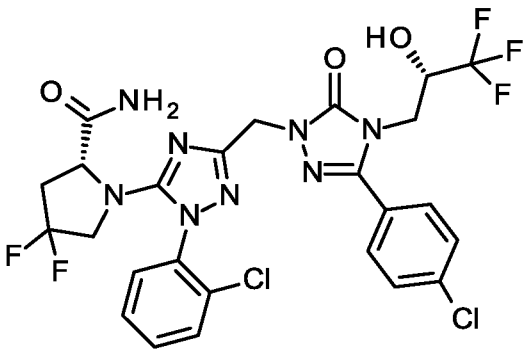
A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 100 mg, 173 µmol) in acetonitrile (330 µl) was treated with N,N-diisopropylethylamine (450 µl, 2.6 mmol) and 4,4-difluoro-L-prolinamide hydrochloride (1:1) (323 mg, 1.73 mmol). The resulting mixture was heated for 16 h at 180°C under microwave irradiation and diluted with DMSO. The solution was purified by preparative HPLC (Method 5) affording 43.5 mg (37% of th.) of the title compound.

LC-MS (Method 3): R_t = 1.79 min; MS (ESIpos): m/z = 647.1 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.89-6.74 (m, 11H), 5.09-4.67 (m, 2H), 4.63-4.17 (m, 2H), 4.06-3.72 (m, 2H), 3.69-3.34 (m, 2H, overlapping with HDO), 2.96-2.59 (m, 1H), 2.44-2.16 (m, 1H).

Example 10

1-[1-(2-Chlorophenyl)-3-({3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1H-1,2,4-triazol-5-yl]-4,4-difluoro-D-prolinamide



A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 100 mg, 173 µmol) in acetonitrile (330 µl) was treated with N,N-diisopropylethylamine (450 µl, 2.6 mmol) and 4,4-difluoro-D-prolinamide hydrochloride (1:1) (323 mg, 1.73 mmol). The resulting

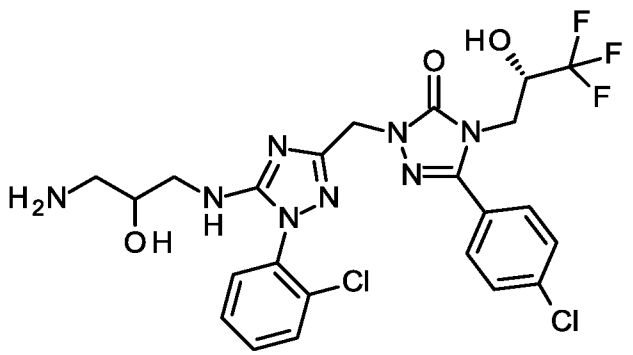
mixture was heated for 16 h at 180°C under microwave irradiation and evaporated. The residue was purified by preparative HPLC (Method 5) affording 50.9 mg (45% of th.) of the title compound.

LC-MS (Method 3): R_t = 1.78 min; MS (ESIpos): m/z = 647.1 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.80-6.83 (m, 11H), 5.03-4.81 (m, 2H), 4.66-4.15 (m, 2H), 4.10-3.71 (m, 2H), 3.66-3.34 (m, 2H, overlapping with HDO peak), 2.94-2.62 (m, 1H), 2.45-2.19 (m, 1H).

Example 11

2-{[5-{[3-Amino-2-hydroxypropyl]amino}-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (*diastereomeric mixture*)



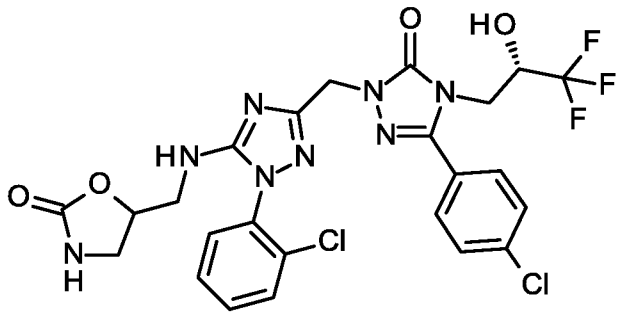
A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 300 mg, 519 µmol) in acetonitrile (15 ml) was treated with N,N-diisopropylethylamine (190 µl, 1.1 mmol) and 1,3-diaminopropan-2-ol (468 mg, 5.19 mmol). The resulting mixture was heated for 5 h at 180°C under microwave irradiation, combined with a 20 mg test reaction and evaporated. The residue was purified by preparative HPLC (Method 5) affording 246 mg (75% of th.) of the title compound as a mixture of diastereomers.

LC-MS (Method 3): R_t = 1.18 min; MS (ESIpos): m/z = 587.1 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 8.31 (s, 1H), 7.87-7.38 (m, 8H), 6.70-6.49 (m, 1H), 5.08-4.71 (m, 2H), 4.51-3.54 (m, 4H), 3.40-3.06 (m, 2H), 2.82-2.59 (m, 1H).

Example 12

5-(4-Chlorophenyl)-2-{[1-(2-chlorophenyl)-5-({[2-oxo-1,3-oxazolidin-5-yl]methyl}amino)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (*diastereomeric mixture*)



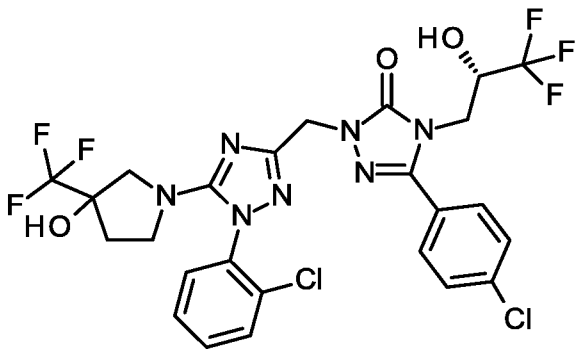
A solution of 2-{[5-{[3-amino-2-hydroxypropyl]amino}-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 11, 233 mg, 0.40 mmol) in (3.1 ml) was treated with 1,1'-carbonyldiimidazole (71 mg, 0.44 mmol). The resulting mixture was stirred 2 h at roomtemperatur and heated at refluxed overnight. The reaction mixture was combined with a 10 mg test reaction, diluted with DMSO and purified by preparative HPLC (Method 5) affording 57 mg (23% of th.) of the title compound as a mixture of diastereomers.

LC-MS (Method 3): R_t = 1.60 min; MS (ESIpos): m/z = 613.1 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm] = 7.79-7.43 (m, 9H), 6.93-6.77 (m, 2H), 4.97-4.79 (m, 2H), 4.74-4.61 (m, 1H), 4.29 (br ddd, 1H), 4.06-3.77 (m, 2H), 3.51-3.22 (m, 4H, overlapping with HDO peak).

Example 13

5-(4-Chlorophenyl)-2-({1-(2-chlorophenyl)-5-[3-hydroxy-3-(trifluoromethyl)pyrrolidin-1-yl]-1H-1,2,4-triazol-3-yl}methyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (*diastereomeric mixture*)



A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 150 mg, 259 µmol) in acetonitrile (500 µl) was treated with N,N-diisopropylethylamine (680 µl, 3.9 mmol) and 3-(trifluoromethyl)pyrrolidin-3-ol hydrochloride (1:1) (497 mg, 2.59 mmol). The resulting mixture was heated for 5 h at 180°C under microwave irradiation and evaporated. The

residue was purified by preparative HPLC (Method 5) affording 131 mg (77% of th.) of the title compound as a mixture of diastereomers.

The two diastereomers were separated by preparative chiral HPLC [sample preparation: 111 mg dissolved in 4 ml ethanol; injection volume: 150 µl; column: Daicel Chiralpak® IA 5 µm, 250 x 20 mm; eluent: iso-hexane/ethanol 40:60; flow rate: 15 ml/min; temperature: 25°C; UV detection: 210 nm]. After separation, 50 mg of diastereomer 1 (Example 14), which eluted first, and 52 mg of diastereomer 2 (Example 15), which eluted later, were isolated.

Example 14

5-(4-Chlorophenyl)-2-({1-(2-chlorophenyl)-5-[3-hydroxy-3-(trifluoromethyl)pyrrolidin-1-yl]-1H-1,2,4-triazol-3-yl}methyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (*diastereomer 1*)

Analytical chiral HPLC: R_t = 2.29 min, e.e. = 100% [column: Daicel Chiraltek® IA 3 µm, 100 x 4.6 mm; eluent: iso-hexane/ethanol 50:50; flow rate: 1.0 ml/min; temperature: 25°C; UV detection: 220 nm].

LC-MS (Method 3): R_t = 1.94 min; MS (ESIpos): m/z = 652.1 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.84-7.42 (m, 8H), 6.88 (d, 1H), 6.49 (s, 1H), 5.02-4.76 (m, 2H), 4.29 (br ddd, 1H), 4.10-3.71 (m, 2H), 3.47-3.13 (m, 4H, overlapping with HDO peak), 2.22-1.81 (m, 2H).

Example 15

5-(4-Chlorophenyl)-2-({1-(2-chlorophenyl)-5-[3-hydroxy-3-(trifluoromethyl)pyrrolidin-1-yl]-1H-1,2,4-triazol-3-yl}methyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (*diastereomer 2*)

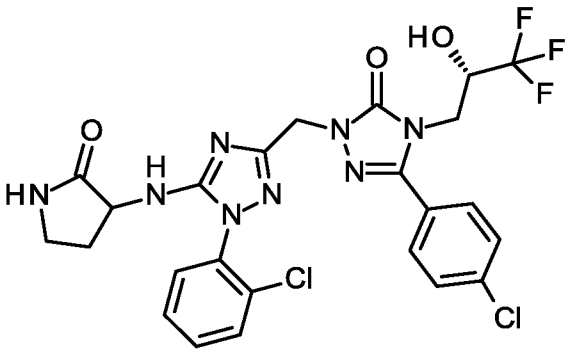
Analytical chiral HPLC: R_t = 4.21 min, e.e. = 100% [column: Daicel Chiraltek® IA 3 µm, 100 x 4.6 mm; eluent: iso-hexane/ethanol 50:50; flow rate: 1.0 ml/min; temperature: 25°C; UV detection: 220 nm].

LC-MS (Method 3): R_t = 1.94 min; MS (ESIpos): m/z = 652.1 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.84-7.42 (m, 8H), 6.88 (d, 1H), 6.49 (s, 1H), 4.98-4.77 (m, 2H), 4.29 (br ddd, 1H), 4.06-3.76 (m, 2H), 3.43-3.17 (m, 4H, overlapping with HDO peak), 2.20-1.84 (m, 2H).

Example 16

5-(4-Chlorophenyl)-2-{[1-(2-chlorophenyl)-5-{[2-oxopyrrolidin-3-yl]amino}-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (*diastereomeric mixture*)



A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 300 mg, 519 µmol) in acetonitrile (2.0 ml) was treated with N,N-diisopropylethylamine (190 µl, 1.1 mmol) and 3-aminopyrrolidin-2-one (519 mg, 5.19 mmol). The resulting mixture was heated for 5 h at 150°C under microwave irradiation and diluted with DMSO. The resulting solution was purified by preparative HPLC (Method 5) affording 110 mg (33% of th.) of the title compound as a mixture of diastereomers.

The two diastereomers were separated by preparative chiral HPLC [sample preparation: 100 mg dissolved in 4 ml acetonitrile; injection volume: 300 µl; column: Daicel Chiralcel® OX-H 5 µm, 250 x 20 mm; eluent: iso-hexane/ethanol 50:50; flow rate: 20 ml/min; temperature: 25°C; UV detection: 220 nm]. After separation, 24 mg of diastereomer 1 (Example 17), which eluted first, and 33 mg of diastereomer 2 (Example 18), which eluted later, were isolated.

Example 17

5-(4-Chlorophenyl)-2-{[1-(2-chlorophenyl)-5-{[2-oxopyrrolidin-3-yl]amino}-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (*diastereomer 1*)

Analytical chiral HPLC: R_t = 1.94 min, e.e. = 100% [column: Daicel Chiralcel® OX 3 µm, 50 x 4.6 mm; eluent: iso-hexane/ethanol 50:50; flow rate: 1.0 ml/min; temperature: 25°C; UV detection: 220 nm].

LC-MS (Method 3): R_t = 1.61 min; MS (ESIpos): m/z = 597.1 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.83-7.44 (m, 9H), 6.89 (d, 1H), 6.70 (d, 1H), 4.95-4.76 (m, 2H), 4.41-4.21 (m, 2H), 4.05-3.77 (m, 2H), 3.14 (br dd, 2H), 2.41-2.26 (m, 1H), 1.98-1.82 (m, 1H).

Example 18

5-(4-Chlorophenyl)-2-{[1-(2-chlorophenyl)-5-{[2-oxopyrrolidin-3-yl]amino}-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (*diastereomer 2*)

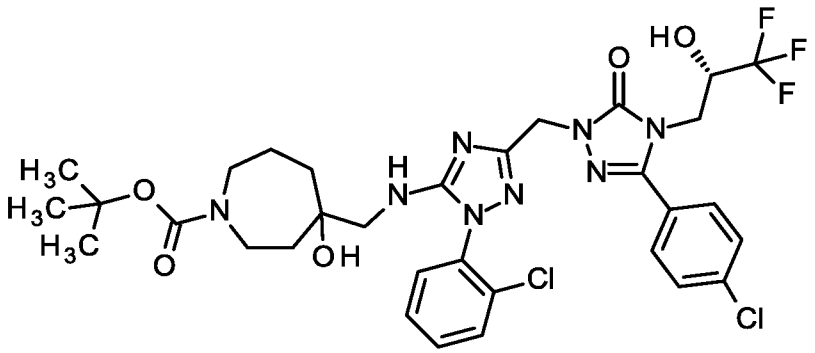
Analytical chiral HPLC: R_t = 2.648 min, e.e. = 98.7% [column: Daicel Chiralcel® OX 3 µm, 50 x 4.6 mm; eluent: iso-hexane/ethanol 50:50; flow rate: 1.0 ml/min; temperature: 25°C; UV detection: 220 nm].

LC-MS (Method 3): R_t = 1.60 min; MS (ESIpos): m/z = 597.1 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.82-7.43 (m, 9H), 6.89 (d, 1H), 6.70 (d, 1H), 4.86 (s, 2H), 4.40-4.21 (m, 2H), 4.06-3.78 (m, 2H), 3.15 (dd, 2H), 2.40-2.27 (m, 1H), 2.01-1.83 (m, 1H)

Example 19

tert-Butyl 4-({[1-(2-chlorophenyl)-3-({3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1H-1,2,4-triazol-5-yl]amino}methyl)-4-hydroxyazepane-1-carboxylate (*diastereomeric mixture*)



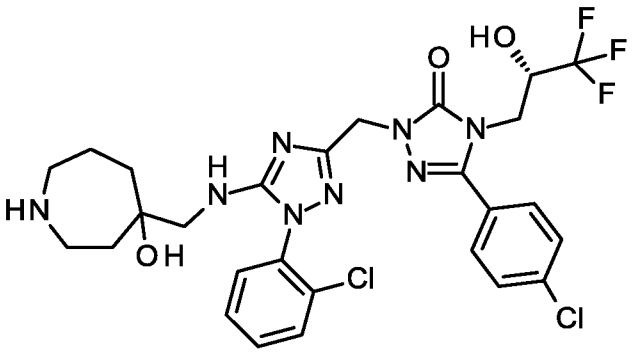
A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 200 mg, 346 µmol) in acetonitrile (1.3 ml) was treated with N,N-diisopropylethylamine (130 µl, 730 µmol) and tert-butyl 4-(aminomethyl)-4-hydroxyazepane-1-carboxylate (532 mg, 2.18 mmol). The resulting mixture was heated for 5 h at 180°C under microwave irradiation and diluted with DMSO. The resulting solution was purified by preparative HPLC (Method 5) affording 81.3 mg (32% of th.) of the title compound as a mixture of diastereomers.

LC-MS (Method 3): R_t = 2.14 min; MS (ESIpos): m/z = 741.2 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.83-7.44 (m, 8H), 6.88 (d, 1H), 6.28 (br d, 1H), 4.96-4.77 (m, 2H), 4.72-4.60 (m, 1H), 4.30 (br ddd, 1H), 4.04-3.77 (m, 2H), 3.60-2.92 (m, 6H, overlap with HDO peak), 1.97-1.16 (m, 15H).

Example 20

5-(4-Chlorophenyl)-2-{[1-(2-chlorophenyl)-5-({4-hydroxyazepan-4-yl]methyl}amino)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (*diastereomeric mixture*)



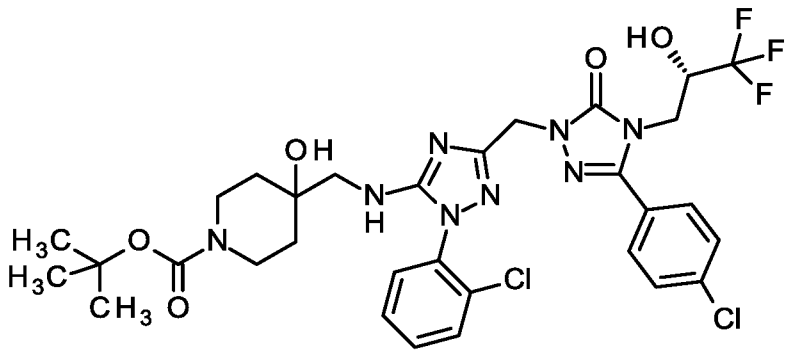
tert-Butyl 4-({[1-(2-chlorophenyl)-3-({3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1H-1,2,4-triazol-5-yl]amino}methyl)-4-hydroxyazepane-1-carboxylate (Example 19, 200 mg, 270 µmol) in a solution of hydrogen chloride in dioxane (5 ml, 4N, 20 mmol,) was stirred overnight at room temperature. The reaction mixture was evaporated and purified by preparative HPLC (Method 5) affording 52.4 mg (30% of th.) of the title compound as a mixture of diastereomers.

LC-MS (Method 12): R_t = 1.47 min; MS (ESIpos): m/z = 641.0 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 8.36 (s, 1H), 7.86-7.43 (m, 8H), 6.33 (br t, 1H), 4.95-4.76 (m, 2H), 4.29 (br ddd, 1H), 4.06-3.72 (m, 2H), 3.31-3.11 (m, 2H, overlapping with HDO peak), 3.05-2.71 (m, 4H), 1.84-1.42 (m, 6H).

Example 21

tert-Butyl 4-({[1-(2-chlorophenyl)-3-({3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1H-1,2,4-triazol-5-yl]amino}methyl)-4-hydroxypiperidine-1-carboxylate



A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 150 mg, 259 µmol) in acetonitrile (1.0 ml) was treated with N,N-diisopropylethylamine (95 µl, 540 µmol) and tert-butyl 4-(aminomethyl)-4-hydroxypiperidine-1-carboxylate (597 mg, 2.59 mmol). The resulting mixture was heated for 5 h at 150°C under microwave irradiation and diluted with

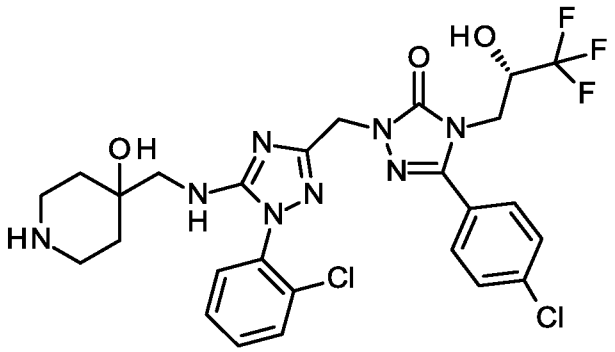
DMSO. The resulting solution was purified by preparative HPLC (Method 5) affording 29.0 mg (15% of th.) of the title compound.

LC-MS (Method 3): R_t = 2.10 min; MS (ESIneg): m/z = 725.1 $[M-H]^-$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.83-7.37 (m, 8H), 6.88 (d, 1H), 6.32 (t, 1H), 5.01-4.63 (m, 3H), 4.30 (br ddd, 1H), 4.11-3.48 (m, 4H), 3.26-2.79 (m, 4H), 1.56-1.18 (m, 13H).

Example 22

5-(4-Chlorophenyl)-2-{[1-(2-chlorophenyl)-5-{[(4-hydroxypiperidin-4-yl)methyl]amino}-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



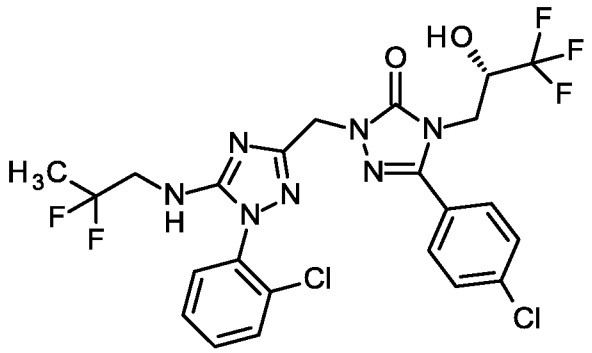
tert-Butyl 4-({[1-(2-chlorophenyl)-3-({3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1H-1,2,4-triazol-5-yl]amino}methyl)-4-hydroxypiperidine-1-carboxylate (Example 21, 30.0 mg, 41.2 µmol) in a solution of hydrogen chloride in dioxane (5 ml, 4N, 20 mmol,) was stirred 72 h at room temperature. The reaction mixture was evaporated and purified by preparative HPLC (Method 5) affording 10.6 mg (41% of th.) of the title compound.

LC-MS (Method 2): R_t = 0.72 min; MS (ESIpos): m/z = 627.4 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 8.35 (br s, 1H), 8.05-7.36 (m, 8H), 6.38 (t, 1H), 4.86 (d, 2H), 4.48-3.69 (m, 3H), 3.35-2.70 (m, 6H, overlapping with HDO), 1.75-1.24 (m, 4H).

Example 23

5-(4-Chlorophenyl)-2-({1-(2-chlorophenyl)-5-[(2,2-difluoropropyl)amino]-1H-1,2,4-triazol-3-yl}methyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



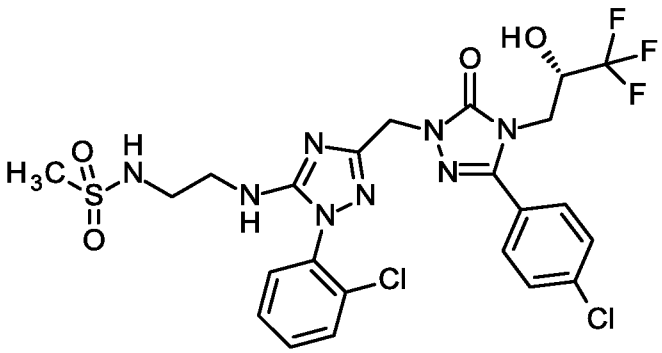
A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 150 mg, 259 µmol) in acetonitrile (1.0 ml) was treated with N,N-diisopropylethylamine (680 µl, 3.9 mmol) and 2,2-difluoropropan-1-amine hydrochloride (1:1) (341 mg, 2.59 mmol). The resulting mixture was heated for 8 h at 180°C under microwave irradiation and diluted with DMSO. The resulting solution was purified by preparative HPLC (Method 5) affording 43.6 mg (28% of th.) of the title compound.

LC-MS (Method 3): R_t = 1.93 min; MS (ESIpos): m/z = 592.1 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.80-7.43 (m, 8H), 6.99 (t, 1H), 6.87 (d, 1H), 4.95-4.80 (m, 2H), 4.36-4.20 (m, 1H), 4.05-3.77 (m, 2H), 3.62 (td, 2H), 1.56 (t, 3H).

Example 24

N-(2-{[1-(2-Chlorophenyl)-3-({3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1H-1,2,4-triazol-5-yl]amino}ethyl)-methanesulfonamide



A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 150 mg, 259 µmol) in acetonitrile (1.0 ml, 19 mmol) was treated with N,N-diisopropylethylamine (680 µl, 3.9 mmol) and N-(2-aminoethyl)methanesulfonamide hydrochloride (1:1) (453 mg, 2.59 mmol). The resulting mixture was heated for 5 h at 180°C under microwave irradiation and diluted with

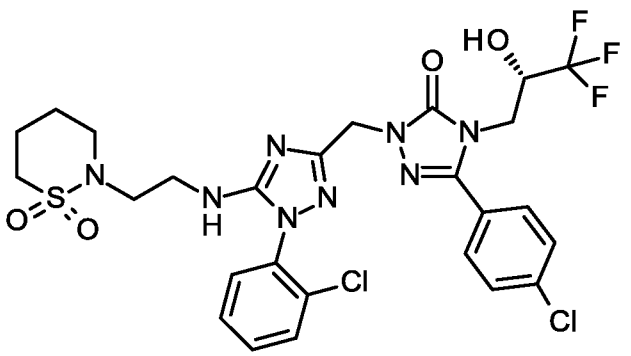
DMSO. The resulting solution was purified by preparative HPLC (Method 5) affording 112 mg (68% of th.) of the title compound.

LC-MS (Method 2): R_t = 0.94 min; MS (ESIpos): m/z = 635.2 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.83-7.44 (m, 8H), 7.07-6.83 (m, 2H), 6.52 (t, 1H), 4.94-4.78 (m, 2H), 4.28 (br ddd, 1H), 4.09-3.75 (m, 2H), 3.46-2.99 (m, 4H, overlap with HDO peak), 2.86 (s, 3H).

Example 25

5-(4-Chlorophenyl)-2-{[1-(2-chlorophenyl)-5-{[2-(1,1-dioxido-1,2-thiazinan-2-yl)ethyl]amino}-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



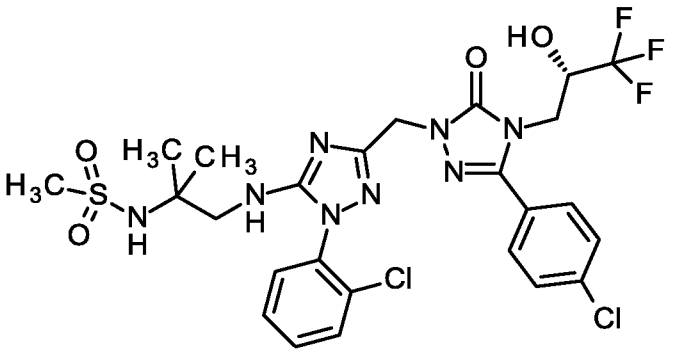
A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 150 mg, 259 µmol) in acetonitrile (1.0 ml) was treated with N,N-diisopropylethylamine (95 µl, 540 µmol) and 2-(1,1-dioxido-1,2-thiazinan-2-yl)ethanamine (462 mg, 2.59 mmol). The resulting mixture was heated for 5 h at 150°C under microwave irradiation and diluted with DMSO. The resulting solution was purified by preparative HPLC (Method 5) affording 64.1 mg (37% of th.) of the title compound.

LC-MS (Method 2): R_t = 1.03 min; MS (ESIpos): m/z = 675.0 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.83-7.43 (m, 8H), 6.88 (d, 1H), 6.52 (t, 1H), 4.95-4.78 (m, 2H), 4.30 (br ddd, 1H), 4.05-3.77 (m, 2H), 3.35-3.24 (m, 4H, overlapping with HDO peak), 3.22-3.14 (m, 2H), 3.05-2.97 (m, 2H), 2.05-1.79 (m, 2H), 1.54-1.37 (m, 2H).

Example 26

N-(1-{[1-(2-Chlorophenyl)-3-({3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1H-1,2,4-triazol-5-yl]amino}-2-methylpropan-2-yl)methanesulfonamide



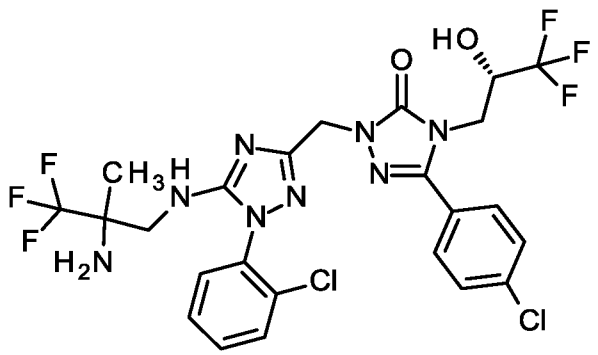
A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 150 mg, 259 µmol) in acetonitrile (1.0 ml) was treated with N,N-diisopropylethylamine (680 µl, 3.9 mmol) and N-(1-amino-2-methylpropan-2-yl)methanesulfonamide hydrochloride (1:1) (526 mg, 2.59 mmol). The resulting mixture was heated for 5 h at 150°C under microwave irradiation and diluted with methanol. The resulting solution was purified by preparative HPLC (Method 5) affording 106 mg (62% of th.) of the title compound.

LC-MS (Method 2): R_t = 1.03 min; MS (ESIpos): m/z = 663.0 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.81-7.44 (m, 8H), 6.98-6.78 (m, 2H), 6.43 (t, 1H), 4.95-4.76 (m, 2H), 4.28 (br ddd, 1H), 4.05-3.75 (m, 2H), 3.41-3.16 (m, 2H, overlap with water peak), 2.88 (s, 3H), 1.23 (s, 6H).

Example 27

2-{[5-{[2-Amino-3,3,3-trifluoro-2-methylpropyl]amino}-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (*diastereomeric mixture*)



A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 150 mg, 259 µmol) in acetonitrile (1.0 ml) was treated with N,N-diisopropylethylamine (680 µl, 3.9 mmol) and 3,3,3-trifluoro-2-methylpropane-1,2-diamine hydrochloride (1:1) (463 mg, 2.59 mmol).

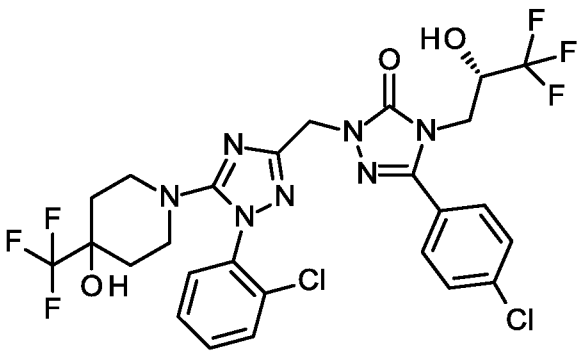
The resulting mixture was heated for 8 h at 180°C under microwave irradiation and diluted with DMSO. The resulting solution was purified by preparative HPLC (Method 5) affording 48.9 mg (29% of th.) of the title compound as a diastereomeric mixture.

LC-MS (Method 3): R_t = 1.78 min; MS (ESIpos): m/z = 639.1 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.79-7.45 (m, 8H), 6.94 (br d, 1H), 6.51-6.39 (m, 1H), 4.97-4.78 (m, 2H), 4.29 (br ddd, 1H), 4.06-3.75 (m, 2H), 3.46-3.36 (m, 2H, overlapping with HDO peak), 2.16 (br. s, 2H), 1.11 (s, 3H).

Example 28

5-(4-Chlorophenyl)-2-({1-(2-chlorophenyl)-5-[4-hydroxy-4-(trifluoromethyl)piperidin-1-yl]-1H-1,2,4-triazol-3-yl}methyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



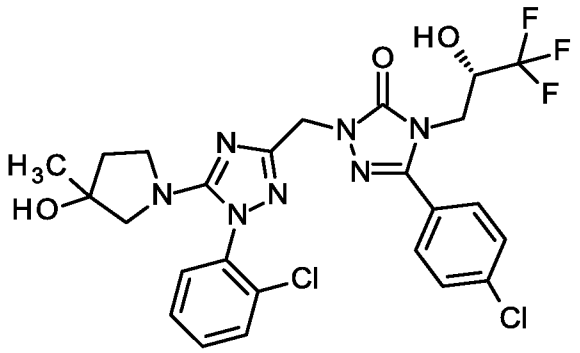
A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 150 mg, 259 µmol) in acetonitrile (1.0 ml) was treated with N,N-diisopropylethylamine (95 µl, 540 µmol) and 4-(trifluoromethyl)piperidin-4-ol (439 mg, 2.59 mmol). The resulting mixture was heated for 5 h at 180°C under microwave irradiation and diluted with DMSO. The resulting solution was purified by preparative HPLC (Method 5) affording 119 mg (69% of th.) of the title compound.

LC-MS (Method 3): R_t = 2.10 min; MS (ESIpos): m/z = 666.1 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.84-7.42 (m, 8H), 6.87 (d, 1H), 6.02 (s, 1H), 5.05-4.72 (m, 2H), 4.29 (br ddd d, 1H), 4.09-3.72 (m, 2H), 3.51-3.19 (m, 2H, overlapping with HDO peak), 3.14-2.75 (m, 2H), 1.95-1.24 (m, 4H).

Example 29

5-(4-Chlorophenyl)-2-({1-(2-chlorophenyl)-5-[3-hydroxy-3-methylpyrrolidin-1-yl]-1H-1,2,4-triazol-3-yl}methyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (*diastereomeric mixture*)



A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 150 mg, 259 µmol) in acetonitrile (1.5 ml) was treated with N,N-diisopropylethylamine (95 µl, 540 µmol) and 3-methylpyrrolidin-3-ol (262 mg, 2.59 mmol). The resulting mixture was heated for 5 h at 150°C under microwave irradiation. The reaction mixture was purified by preparative HPLC (Method 5) affording 92.1 mg (59% of th.) of the title compound as a mixture of diastereomers.

The two diastereomers were separated by preparative chiral HPLC [sample preparation: 61 mg dissolved in 5 ml ethanol; injection volume: 500 µl; column: Daicel Chiralcel® OX-H 5 µm, 250 x 20 mm; eluent: iso-hexane/ethanol 40:60; flow rate: 15 ml/min; temperature: 25°C; UV detection: 210 nm]. After separation, 21 mg of diastereomer 1 (Example 30), which eluted first, and 20 mg of diastereomer 2 (Example 31), which eluted later, were isolated.

Example 30

5-(4-Chlorophenyl)-2-({1-(2-chlorophenyl)-5-[3-hydroxy-3-methylpyrrolidin-1-yl]-1H-1,2,4-triazol-3-yl}methyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (*diastereomer 1*)

Analytical chiral HPLC: R_t = 2.43 min, e.e. = 99.0% [column: Daicel Chiralcel® OX 3 µm, 50 x 4.6 mm; eluent: iso-hexane/ethanol 50:50; flow rate: 1.0 ml/min; temperature: 25°C; UV detection: 220 nm].

LC-MS (Method 3): R_t = 1.75 min; MS (ESIpos): m/z = 598.1 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.92-7.39 (m, 8H), 6.88 (d, 1H), 4.97-4.61 (m, 3H), 4.29 (br ddd, 1H), 4.10-3.71 (m, 2H), 3.28-2.78 (m, 4H, overlapping with HDO peak), 1.79-1.61 (m, 2H), 1.17 (s, 3H).

Example 31

5-(4-Chlorophenyl)-2-({1-(2-chlorophenyl)-5-[3-hydroxy-3-methylpyrrolidin-1-yl]-1H-1,2,4-triazol-3-yl}methyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (*diastereomer 2*)

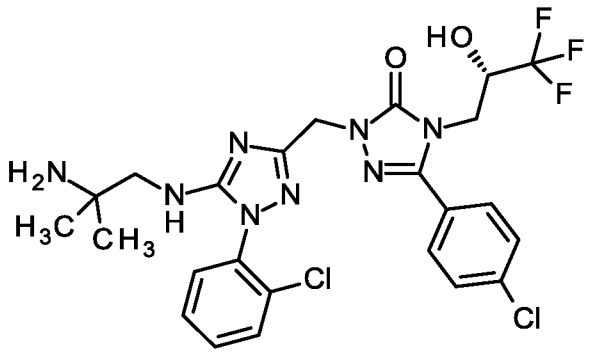
Analytical chiral HPLC: R_t = 4.03 min, e.e. = 97.6% [column: Daicel Chiralcel® OX 3 µm, 50 x 4.6 mm; eluent: iso-hexane/ethanol 50:50; flow rate: 1.0 ml/min; temperature: 25°C; UV detection: 220 nm].

LC-MS (Method 2): R_t = 0.97 min; MS (ESIpos): m/z = 598.3 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.80-7.43 (m, 8H), 6.88 (d, 1H), 4.92-4.69 (m, 3H), 4.29 (br ddd, 1H), 4.06-3.78 (m, 2H), 3.30-2.82 (m, 4H, overlapping with HDO peak), 1.74-1.66 (m, 2H), 1.17 (s, 3H).

Example 32

2-({5-[(2-Amino-2-methylpropyl)amino]-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl}methyl)-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



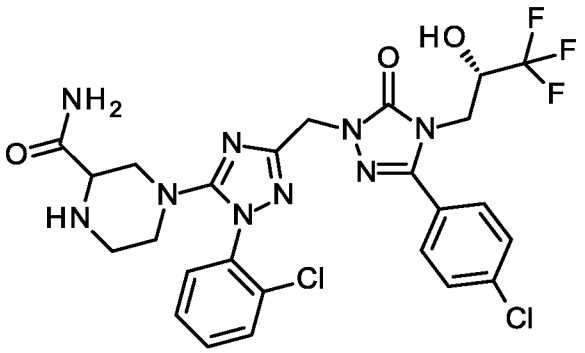
A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 1.50 g, 2.59 mmol) in acetonitrile (10 ml) was treated with N,N-diisopropylethylamine (950 µl, 5.4 mmol) and 2-methylpropane-1,2-diamine (2.7 ml, 26 mmol). The resulting mixture was heated for 5 h at 180°C under microwave irradiation. The reaction mixture was purified by preparative HPLC (Method 5) affording 1.32 g (82% of th.) of the title compound.

LC-MS (Method 12): R_t = 1.51 min; MS (ESIpos): m/z = 585.0 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 8.28 (br s, 1H), 7.85-7.38 (m, 8H), 6.67 (br t, 1H), 4.96-4.76 (m, 2H), 4.30 (br ddd, 1H), 4.07-3.74 (m, 2H), 3.70-2.95 (m, 2H, overlapping with HDO peak), 1.08 (s, 6H).

Example 33

4-[1-(2-Chlorophenyl)-3-({3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1H-1,2,4-triazol-5-yl]piperazine-2-carboxamide (*diastereomeric mixture*)



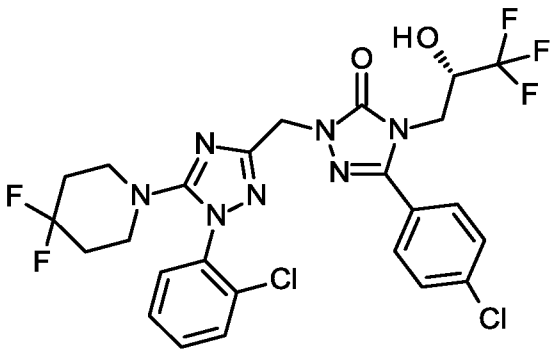
A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 150 mg, 259 µmol) in acetonitrile (500 µl) was treated with N,N-diisopropylethylamine (95 µl, 540 µmol) and piperazine-2-carboxamide (335 mg, 2.59 mmol). The resulting mixture was heated for 5 h at 180°C under microwave irradiation and diluted with DMSO. The resulting solution was purified by preparative HPLC (Method 5) affording 54.6 mg (34% of th.) of the title compound as a mixture of diastereomers.

LC-MS (Method 2): R_t = 0.72 min; MS (ESIpos): m/z = 626.2 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.79-7.42 (m, 9H), 7.24-7.02 (m, 2H), 6.88 (br d, 1H), 4.90 (d, 2H), 4.29 (br ddd, 1H), 4.08-3.93 (m, 1H), 3.84 (dd, 1H), 3.45 (br d, 1H, overlapping with HDO peak), 3.19-2.60 (m, 6H, overlapping with HDO peak).

Example 34

5-(4-Chlorophenyl)-2-{[1-(2-chlorophenyl)-5-(4,4-difluoropiperidin-1-yl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 150 mg, 259 µmol) in acetonitrile (500 µl, 9.5 mmol) was treated with N,N-diisopropylethylamine (200 µl, 1.1 mmol) and 4,4-difluoropiperidine hydrochloride (1:1) (409 mg, 2.59 mmol). The resulting mixture was heated for 5 h at 180°C under microwave irradiation and diluted with DMSO. The

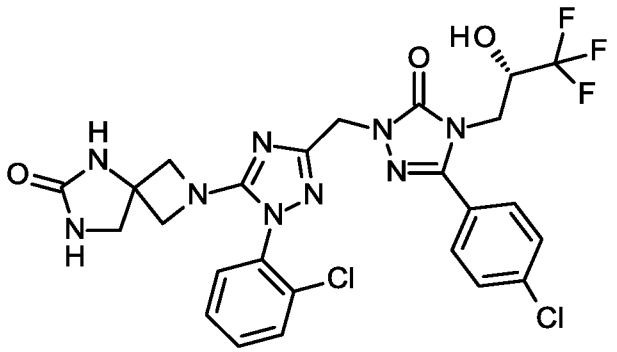
resulting solution was purified by preparative HPLC (Method 5) affording 121 mg (75% of th.) of the title compound.

LC-MS (Method 2): R_t = 1.15 min; MS (ESIpos): m/z = 618.2 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.80-7.47 (m, 8H), 6.87 (d, 1H), 5.02-4.83 (m, 2H), 4.29 (br ddd, 1H), 4.09-3.75 (m, 2H), 3.27-3.13 (m, 4H), 1.99-1.82 (m, 4H).

Example 35

2-[1-(2-Chlorophenyl)-3-({3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1H-1,2,4-triazol-5-yl]-2,5,7-triazaspiro[3.4]octan-6-one



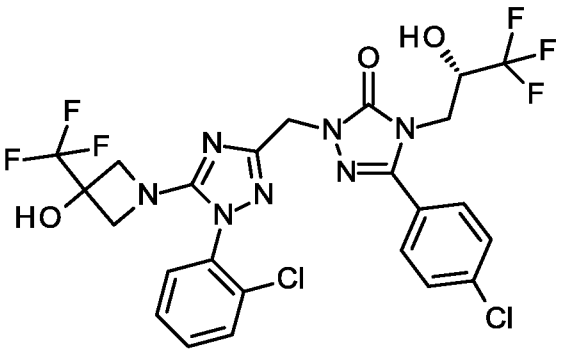
A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 150 mg, 259 µmol) in acetonitrile (500 µl, 9.5 mmol) was treated with N,N-diisopropylethylamine (200 µl, 1.1 mmol) and 2,5,7-triazaspiro[3.4]octan-6-one (330 mg, 2.59 mmol). The resulting mixture was heated for 5 h at 180°C under microwave irradiation and diluted with DMSO. The resulting solution was purified by preparative HPLC (Method 5) affording 66.2 mg (39% of th.) of the title compound.

LC-MS (Method 2): R_t = 0.88 min; MS (ESIpos): m/z = 624.3 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.85-7.43 (m, 8H), 7.06-6.78 (m, 2H), 6.30 (br s, 1H), 4.89 (d, 2H), 4.29 (br ddd, 1H), 4.08-3.62 (m, 6H), 3.51-3.42 (m, 2H, overlapping with HDO peak).

Example 36

5-(4-Chlorophenyl)-2-({1-(2-chlorophenyl)-5-[3-hydroxy-3-(trifluoromethyl)azetidin-1-yl]-1H-1,2,4-triazol-3-yl}methyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



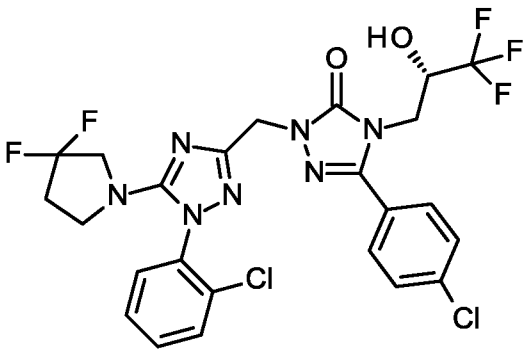
A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 150 mg, 259 µmol) in acetonitrile (500 µl) was treated with N,N-diisopropylethylamine (200 µl, 1.1 mmol) and 3-(trifluoromethyl)azetidin-3-ol (366 mg, 2.59 mmol). The resulting mixture was heated for 5 h at 180°C under microwave irradiation and diluted with DMSO. The resulting solution was purified by preparative HPLC (Method 5) affording 48.5 mg (29% of th.) of the title compound.

LC-MS (Method 2): R_t = 1.06 min; MS (ESIpos): m/z = 638.2 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.81-7.47 (m, 8H), 7.35 (br s, 1H), 6.88 (br s, 1H), 4.99-4.84 (m, 2H), 4.29 (br ddd, 1H), 4.05-3.72 (m, 6H).

Example 37

5-(4-Chlorophenyl)-2-{[1-(2-chlorophenyl)-5-(3,3-difluoropyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



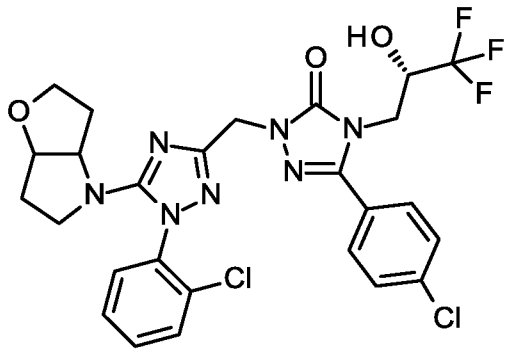
A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 150 mg, 259 µmol) in acetonitrile (500 µl) was treated with N,N-diisopropylethylamine (95 µl, 540 µmol) and 3,3-difluoropyrrolidine (278 mg, 2.59 mmol). The resulting mixture was heated for 5 h at 180°C under microwave irradiation and diluted with DMSO. The resulting solution was purified by preparative HPLC (Method 5) affording 121 mg (77% of th.) of the title compound.

LC-MS (Method 2): R_t = 1.11 min; MS (ESIpos): m/z = 604.2 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.86-7.44 (m, 8H), 6.88 (br s, 1H), 5.19-4.80 (m, 2H), 4.29 (br ddd, 1H), 4.09-3.76 (m, 2H), 3.62-3.19 (m, 4H, overlapping with HDO peak), 2.49-2.28 (m, 2H).

Example 38

5-(4-Chlorophenyl)-2-{[1-(2-chlorophenyl)-5-(hexahydro-4H-furo[3,2-b]pyrrol-4-yl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



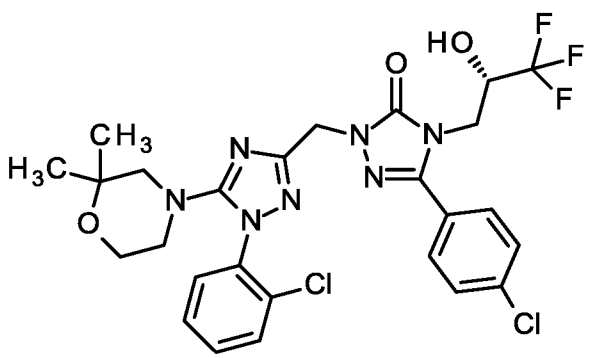
A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 150 mg, 259 µmol) in acetonitrile (500 µl) was treated with N,N-diisopropylethylamine (95 µl, 540 µmol) and hexahydro-2H-furo[3,2-b]pyrrole (294 mg, 2.59 mmol). The resulting mixture was heated for 5 h at 180°C under microwave irradiation and diluted with DMSO. The resulting solution was purified by preparative HPLC (Method 5) affording 118 mg (75% of th.) of the title compound.

LC-MS (Method 2): R_t = 1.04 min; MS (ESIpos): m/z = 610.2 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm] : 7.82-7.44 (m, 8H), 6.87 (t, 1H), 4.98-4.79 (m, 2H), 4.47-4.19 (m, 3H), 4.06-3.78 (m, 2H), 3.74-3.56 (m, 2H), 3.20-2.76 (m, 2H), 2.05-1.67 (m, 4H).

Example 39

5-(4-Chlorophenyl)-2-{[1-(2-chlorophenyl)-5-(2,2-dimethylmorpholin-4-yl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



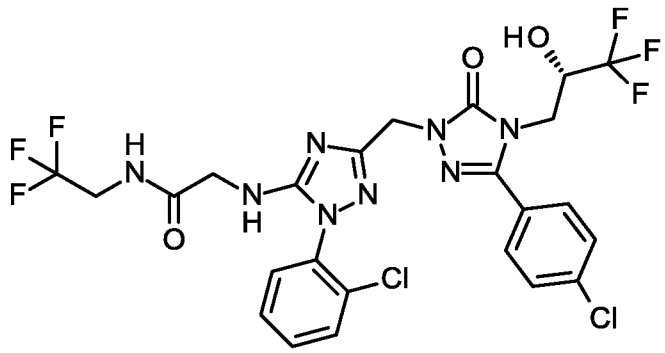
A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 130 mg, 225 µmol) in acetonitrile (200 µl) was treated with N,N-diisopropylethylamine (590 µl, 3.4 mmol) and 2,2-dimethylmorpholine hydrochloride (1:1) (341 mg, 2.25 mmol). The resulting mixture was heated for 3 h at 180°C under microwave irradiation and diluted with DMSO. The resulting solution was purified by preparative HPLC (Method 5) affording 119 mg (86% of th.) of the title compound.

LC-MS (Method 2): R_t = 1.11 min; MS (ESIpos): m/z = 612.3 $[M+H]^+$

^{1}H-NMR (500 MHz, DMSO-d6) δ [ppm]: 7.81-7.50 (m, 8H), 6.88 (d, 1H), 4.98-4.85 (m, 2H), 4.36-4.22 (m, 1H), 4.04-3.78 (m, 2H), 3.58-3.48 (m, 2H), 3.01-2.93 (m, 2H), 2.82 (s, 2H), 0.98 (s, 6H).

Example 40

N^2-[1-(2-Chlorophenyl)-3-({3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1H-1,2,4-triazol-5-yl]-N-(2,2,2-trifluoroethyl)glycinamide



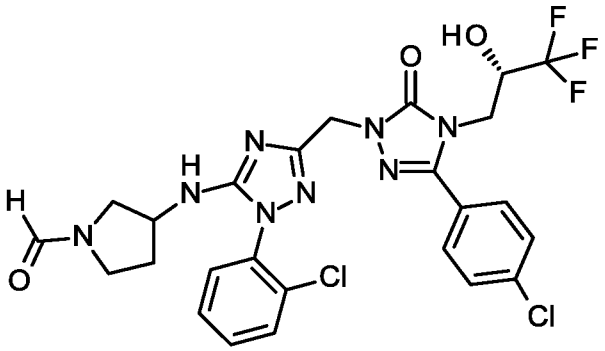
A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 150 mg, 259 µmol) in acetonitrile (500 µl) was treated with N,N-diisopropylethylamine (95 µl, 540 µmol) and N-(2,2,2-trifluoroethyl)glycinamide (405 mg, 2.59 mmol). The resulting mixture was heated for 5 h at 180°C under microwave irradiation and diluted with DMSO. The resulting solution was purified by preparative HPLC (Method 5) affording 75.0 mg (44% of th.) of the title compound.

LC-MS (Method 2): R_t = 1.01 min; MS (ESIpos): m/z = 653.3 $[M+H]^+$

^{1}H-NMR (500 MHz, DMSO-d6) δ [ppm]: 8.45 (t, 1H), 7.78-7.47 (m, 8H), 6.88 (d, 1H), 6.73 (t, 1H), 4.92-4.77 (m, 2H), 4.29 (br ddd, 1H), 4.06-3.77 (m, 6H).

Example 41

3-{[1-(2-Chlorophenyl)-3-({3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1H-1,2,4-triazol-5-yl]amino}pyrrolidine-1-carbaldehyde (*diastereomeric mixture*)



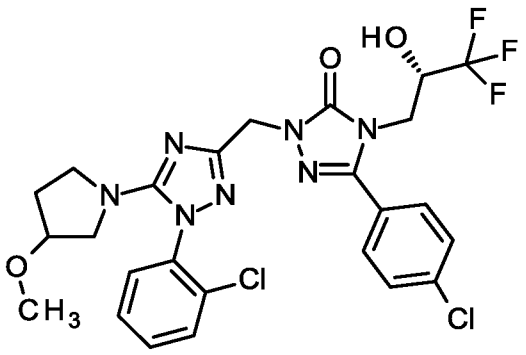
A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 150 mg, 259 µmol) in acetonitrile (1.5 ml) was treated with N,N-diisopropylethylamine (95 µl, 540 µmol) and 3-aminopyrrolidine-1-carbaldehyde (296 mg, 2.59 mmol). The resulting mixture was heated for 5 h at 150°C under microwave irradiation and evaporated. The residue was purified by preparative HPLC (Method 5) affording 54.8 mg (32% of th.) of the title compound as a mixture of diastereomers.

LC-MS (Method 2): R_t = 0.91 min; MS (ESIpos): m/z = 611.3 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 8.28 (br d, 1H), 7.96-7.44 (m, 9H), 6.88 (d, 1H), 4.87 (d, 2H), 4.40-3.72 (m, 4H), 3.28-2.79 (m, 4H, overlapping with HDO peak), 2.11-1.89 (m, 1H), 1.81-1.59 (m, 1H).

Example 42

5-(4-Chlorophenyl)-2-({1-(2-chlorophenyl)-5-[3-methoxypyrrolidin-1-yl]-1H-1,2,4-triazol-3-yl}methyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (*diastereomeric mixture*)



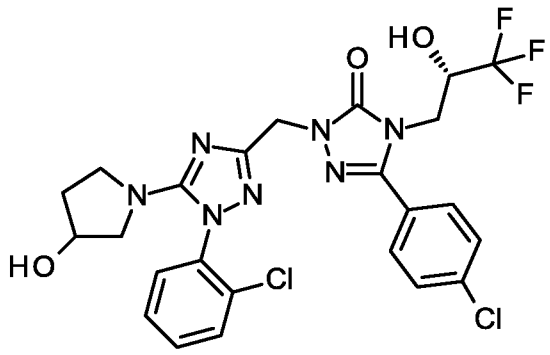
A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 150 mg, 259 µmol) in acetonitrile (1.5 ml) was treated with N,N-diisopropylethylamine (95 µl, 540 µmol) and 3-methoxypyrrolidine hydrochloride (1:1) (357 mg, 2.59 mmol). The resulting mixture was heated for 8 h at 150°C under microwave irradiation and diluted with water. The resulting solution was purified by preparative HPLC (Method 5) affording 91.0 mg (59% of th.) of the title compound as a mixture of diastereomers.

LC-MS (Method 2): R_t = 1.06 min; MS (ESIpos): m/z = 598.3 $[M-H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.87-7.35 (m, 8H), 6.88 (d, 1H), 4.97-4.75 (m, 2H), 4.29 (br ddd, 1H), 4.07-3.76 (m, 3H), 3.24-2.94 (m, 7H), 1.98-1.72 (m, 2H).

Example 43

5-(4-Chlorophenyl)-2-({1-(2-chlorophenyl)-5-[3-hydroxypyrrolidin-1-yl]-1H-1,2,4-triazol-3-yl}methyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (*diastereomeric mixture*)



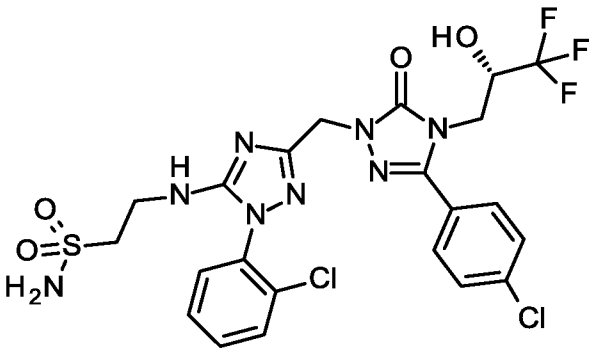
A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 150 mg, 259 µmol) in acetonitrile (1.5 ml) was treated with N,N-diisopropylethylamine (95 µl, 540 µmol) and pyrrolidin-3-ol (210 µl, 2.6 mmol). The resulting mixture was heated for 5 h at 150°C under microwave irradiation and diluted with water. The resulting solution was purified by preparative HPLC (Method 5) affording 45.6 mg (30% of th.) of the title compound as a mixture of diastereomers.

LC-MS (Method 2): R_t = 0.94 min; MS (ESIpos): m/z = 584.2 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.82-7.42 (m, 8H), 6.88 (d, 1H), 4.95-4.82 (m, 3H), 4.39-4.12 (m, 2H), 4.06-3.76 (m, 2H), 3.27-2.83 (m, 4H, overlapping with HDO peak), 1.92-1.61 (m, 2H).

Example 44

2-{[1-(2-Chlorophenyl)-3-({3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1H-1,2,4-triazol-5-yl]amino}ethanesulfonamide



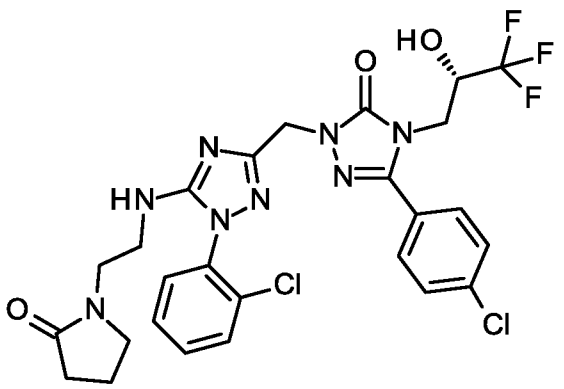
A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 150 mg, 259 µmol) in acetonitrile (1.5 ml) was treated with N,N-diisopropylethylamine (95 µl, 540 µmol) and 2-aminoethanesulfonamide (322 mg, 2.59 mmol). The resulting mixture was heated for 5 h at 150°C and 14 h at 180°C under microwave irradiation and evaporated. The reaction volume was concentrated to 1ml, and 2-aminoethanesulfonamide (322 mg, 2.59 mmol) was added. The resulting mixture was stirred 2 h at 200°C and diluted with DMSO. The resulting solution was purified by preparative HPLC (Method 5) affording 19.5 mg (12% of th.) of the title compound.

LC-MS (Method 2): R_t = 0.89 min; MS (ESIpos): m/z = 621.0 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.80-7.43 (m, 8H), 6.92-6.80 (m, 3H), 6.57 (t, 1H), 4.96-4.81 (m, 2H), 4.29 (br ddd, 1H), 4.07-3.77 (m, 2H), 3.65-3.50 (m, 2H), 3.27-3.15 (m, 2H).

Example 45

5-(4-Chlorophenyl)-2-{[1-(2-chlorophenyl)-5-{[2-(2-oxopyrrolidin-1-yl)ethyl]amino}-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



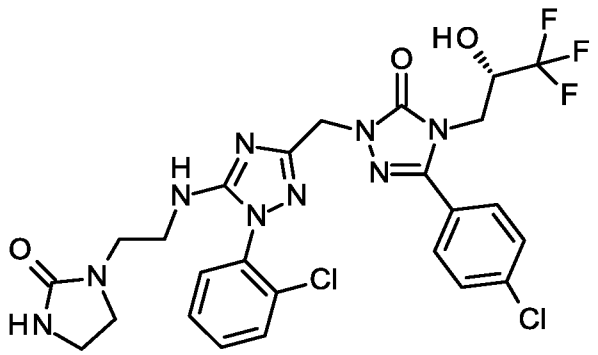
A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 150 mg, 259 µmol) in acetonitrile (1.5 ml) was treated with N,N-diisopropylethylamine (95 µl, 540 µmol) and 1-(2-aminoethyl)pyrrolidin-2-one (333 mg, 2.59 mmol). The resulting mixture was heated for 5 h at 150°C under microwave irradiation and evaporated. The residue was purified by preparative HPLC (Method 5) affording 85.0 mg (50% of th.) of the title compound.

LC-MS (Method 2): R_t = 0.95 min; MS (ESIpos): m/z = 625.3 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.82-7.42 (m, 8H), 6.90 (br s, 1H), 6.48 (br t, 1H), 4.86 (d, 2H), 4.31 (br ddd, 1H), 4.06-3.78 (m, 2H), 3.63-3.22 (m, 6H, overlapping with HDO), 2.14-2.03 (m, 2H), 1.79 (quin, 2H).

Example 46

5-(4-Chlorophenyl)-2-{[1-(2-chlorophenyl)-5-{[2-(2-oxoimidazolidin-1-yl)ethyl]amino}-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



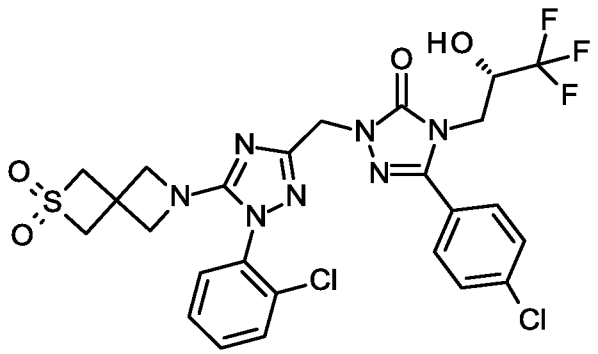
A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 150 mg, 259 µmol) in acetonitrile (1.5 ml) was treated with N,N-diisopropylethylamine (95 µl, 540 µmol) and 1-(2-aminoethyl)imidazolidin-2-one (335 mg, 2.59 mmol). The resulting mixture was heated for 5 h at 150°C under microwave irradiation and evaporated. The residue was purified by preparative HPLC (Method 5) affording 115 mg (64% of th.) of the title compound.

LC-MS (Method 2): R_t = 0.88 min; MS (ESIpos): m/z = 626.1 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.81-7.41 (m, 8H), 6.89 (d, 1H), 6.47 (t, 1H), 6.22 (s, 1H), 4.86 (d, 2H), 4.30 (br ddd, 1H), 4.06-3.76 (m, 2H), 3.36-3.06 (m, 8H, overlapping with HDO peak).

Example 47

5-(4-Chlorophenyl)-2-{[1-(2-chlorophenyl)-5-(2,2-dioxido-2-thia-6-azaspiro[3.3]hept-6-yl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



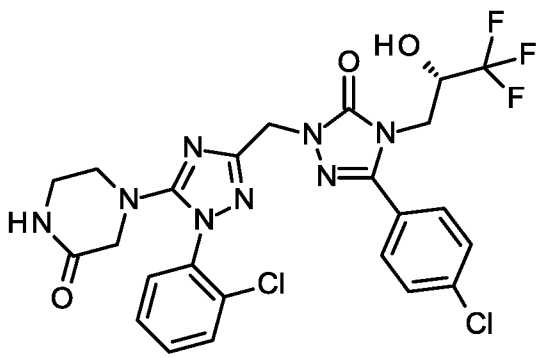
A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 80.0 mg, 138 µmol) in acetonitrile (800 µl) was treated with N,N-diisopropylethylamine (51 µl, 290 µmol) and 2-thia-6-azaspiro[3.3]heptane 2,2-dioxide (102 mg, 692 µmol). The resulting mixture was heated for 5 h at 180°C under microwave irradiation and diluted with DMSO. The resulting solution was purified by preparative HPLC (Method 5) affording 27.8 mg (31% of th.) of the title compound.

LC-MS (Method 2): R_t = 1.00 min; MS (ESIpos): m/z = 644.2 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.81-7.46 (m, 8H), 6.88 (d, 1H), 4.89 (d, 2H), 4.46-4.21 (m, 5H), 4.06-3.78 (m, 6H).

Example 48

4-[1-(2-Chlorophenyl)-3-({3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1H-1,2,4-triazol-5-yl]piperazin-2-one



A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 100

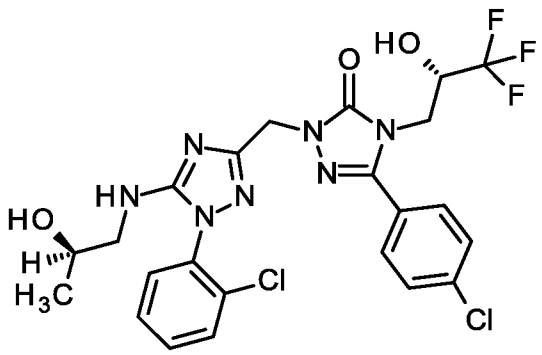
mg, 173 µmol) in acetonitrile (1.0 ml) was treated with N,N-diisopropylethylamine (63 µl, 360 µmol) and piperazin-2-one (120 µl, 1.7 mmol). The resulting mixture was heated for 8 h at 150°C under microwave irradiation and diluted with DMSO. The resulting solution was purified by preparative HPLC (Method 5) affording 70.8 mg (69% of th.) of the title compound.

LC-MS (Method 2): R_t = 0.91 min; MS (ESIpos): m/z = 597.3 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 8.01 (br s, 1H), 7.82-7.46 (m, 8H), 6.88 (d, 1H), 4.92 (d, 2H), 4.29 (br ddd, 1H), 4.08-3.77 (m, 2H), 3.59 (s, 2H), 3.29-3.03 (m, 4H, overlapping with HDO peak).

Example 49

5-(4-Chlorophenyl)-2-{[1-(2-chlorophenyl)-5-{[(2R)-2-hydroxypropyl]amino}-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



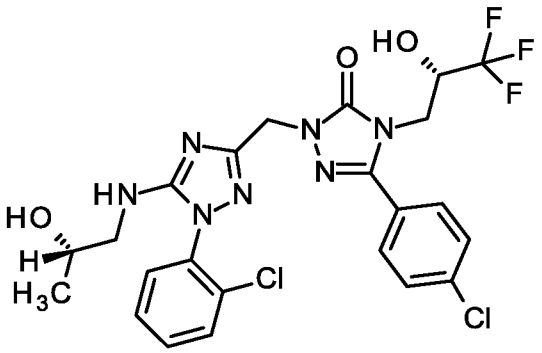
A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 60.0 mg, 104 µmol) in N-methylpyrrolidone (1.5 ml) was treated with N,N-diisopropylethylamine (54 µl, 310 µmol) and (2R)-1-aminopropan-2-ol (82 µl, 1.0 mmol). The resulting mixture was heated for 5 h at 160°C and 2 h at 180°C under microwave irradiation. The reaction mixture was combined with a 20 mg test reaction and evaporated. The residue was retaken in ethyl acetate and washed with a saturated solution of sodium chloride. The organic phase was dried over magnesium sulfate, evaporated and purified by preparative HPLC (Method 5) affording 47.3 mg (78% of th.) of the title compound.

LC-MS (Method 2): R_t = 0.96 min; MS (ESIpos): m/z = 572.3 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.80-7.43 (m, 8H), 6.88 (d, 1H), 6.31 (t, 1H), 4.94-4.80 (m, 2H), 4.69 (d, 1H), 4.29 (br ddd, 1H), 4.06-3.67 (m, 3H), 3.21-3.02 (m, 2H), 1.01 (d, 3H).

Example 50

5-(4-Chlorophenyl)-2-{[1-(2-chlorophenyl)-5-{[(2S)-2-hydroxypropyl]amino}-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



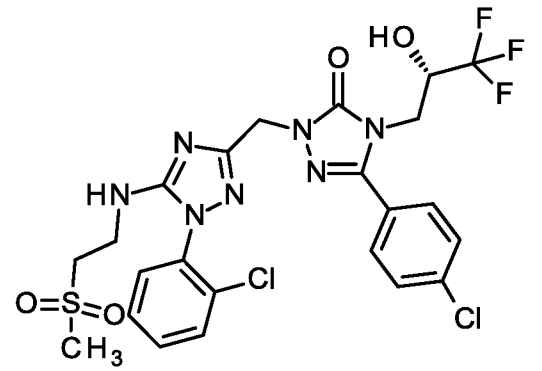
A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 80.0 mg, 138 µmol) in N-methylpyrrolidone (2.0 ml) was treated with N,N-diisopropylethylamine (72 µl, 420 µmol) and (2S)-1-aminopropan-2-ol (110 µl, 1.4 mmol). The resulting mixture was heated for 5 h at 160°C under microwave irradiation and evaporated. The residue was retaken in ethyl acetate and washed with a saturated solution of sodium chloride. The organic phase was dried over magnesium sulfate, evaporated and was purified by preparative HPLC (Method 5) affording 31.0 mg (39% of th.) of the title compound.

LC-MS (Method 2): R_t = 0.96 min; MS (ESIpos): m/z = 572.3 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.80-7.42 (m, 8H), 6.88 (d, 1H), 6.31 (t, 1H), 4.86 (d, 2H), 4.68 (d, 1H), 4.29 (br ddd, 1H), 4.05-3.68 (m, 3H), 3.23-3.02 (m, 2H), 1.01 (d, 3H).

Example 51

5-(4-Chlorophenyl)-2-{[1-(2-chlorophenyl)-5-{[2-(methylsulfonyl)ethyl]amino}-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 150 mg, 259 µmol) in acetonitrile (1.5 ml) was treated with N,N-diisopropylethylamine (95 µl, 540 µmol) and 2-(methylsulfonyl)ethanamine (320 mg, 2.59 mmol). The resulting mixture was heated for 5 h at 150°C, 12 h at 180°C and 5 h at 200°C under microwave irradiation. The reaction

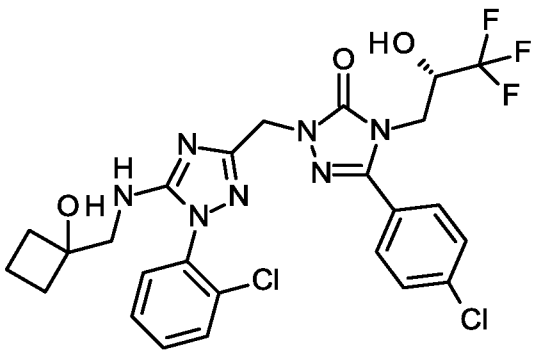
mixture was purified by preparative HPLC (Method 5) affording 23.4 mg (15% of th.) of the title compound.

LC-MS (Method 2): R_t = 0.94 min; MS (ESIpos): m/z = 620.2 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.80-7.44 (m, 8H), 6.88 (d, 1H), 6.69 (t, 1H), 4.98-4.84 (m, 2H), 4.29 (br ddd, 1H), 4.06-3.79 (m, 2H), 3.60 (q, 2H), 3.39-3.26 (m, 2H, overlapping with HDO peak), 2.97 (s, 3H).

Example 52

5-(4-Chlorophenyl)-2-{[1-(2-chlorophenyl)-5-{[(1-hydroxycyclobutyl)methyl]amino}-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



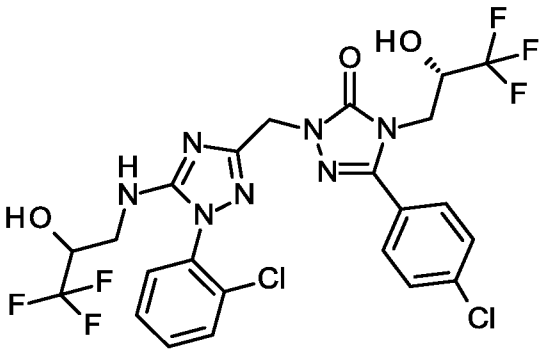
A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 60.0 mg, 104 µmol) in N-methylpyrrolidone (900 µl) was treated with N,N-diisopropylethylamine (54 µl, 310 µmol) and 1-(aminomethyl)cyclobutanol (105 mg, 1.04 mmol). The resulting mixture was heated for 5 h at 160°C under microwave irradiation and evaporated. The residue was retaken in ethyl acetate and washed with a saturated solution of sodium chloride. The organic phase was dried over magnesium sulfate, evaporated and was purified by preparative HPLC (Method 5) affording 50.1 mg (81% of th.) of the title compound.

LC-MS (Method 2): R_t = 1.01 min; MS (ESIpos): m/z = 598.2 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.82-7.42 (m, 8H), 6.89 (d, 1H), 6.12 (t, 1H), 5.30 (s, 1H), 4.97-4.75 (m, 2H), 4.30 (br ddd, 1H), 4.10-3.71 (m, 2H), 3.44-3.17 (m, 2H, overlapping with HDO peak), 2.12-1.73 (m, 4H), 1.66-1.29 (m, 2H).

Example 53

5-(4-Chlorophenyl)-2-{[1-(2-chlorophenyl)-5-{[3,3,3-trifluoro-2-hydroxypropyl]amino}-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (*diastereomeric mixture*)



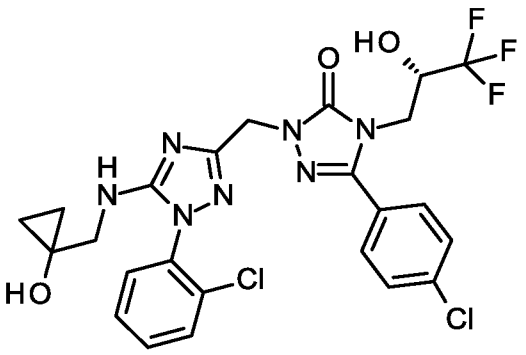
A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 80.0 mg, 138 µmol) in acetonitrile (800 µl) was treated with N,N-diisopropylethylamine (51 µl, 290 µmol) and 3-amino-1,1,1-trifluoropropan-2-ol (357 mg, 2.77 mmol). The resulting mixture was heated for 5 h at 150°C under microwave irradiation. The raction mixture was purified by preparative HPLC (Method 5) affording 36.0 mg (39% of th.) of the title compound as a mixture of diastereomers.

LC-MS (Method 4): R_t = 3.22 min; MS (ESIpos): m/z = 626.0 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.81-7.44 (m, 8H), 6.88 (d, 1H), 6.68 (t, 1H), 6.41 (dd, 1H), 4.95-4.83 (m, 2H), 4.36-4.16 (m, 2H), 4.05-3.78 (m, 2H), 3.54-3.19 (m, 2H, overlapping with HDO peak).

Example 54

5-(4-Chlorophenyl)-2-{[1-(2-chlorophenyl)-5-{[(1-hydroxycyclopropyl)methyl]amino}-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 150 mg, 259 µmol) in acetonitrile (1.5 ml) was treated with N,N-diisopropylethylamine (95 µl, 540 µmol) and 1-(aminomethyl)cyclopropanol (226 mg, 2.59 mmol). The resulting mixture was heated

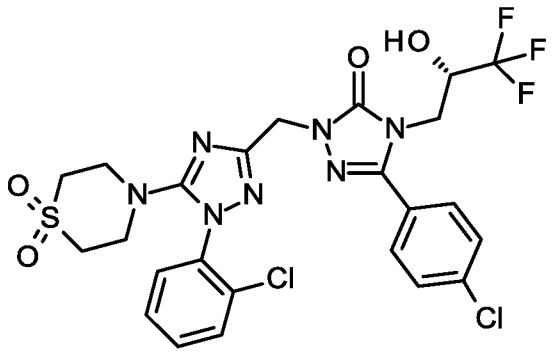
for 5 h at 150°C under microwave irradiation. The reaction mixture was purified by preparative HPLC (Method 5) affording 47.1 mg (31% of th.) of the title compound.

LC-MS (Method 2): R_t = 0.95 min; MS (ESIpos): m/z = 584.1 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.83-7.44 (m, 8H), 6.88 (d, 1H), 6.33 (t, 1H), 5.41 (s, 1H), 4.94-4.77 (m, 2H), 4.39-4.19 (m, 1H), 4.06-3.74 (m, 2H), 3.36 (d, 2H), 0.59-0.40 (m, 4H).

Example 55

5-(4-Chlorophenyl)-2-{[1-(2-chlorophenyl)-5-(1,1-dioxidothiomorpholin-4-yl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



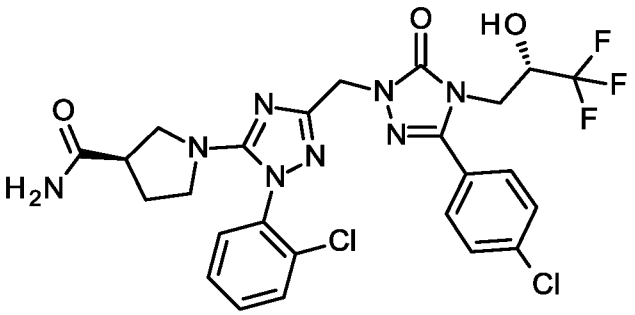
A solution of 2-{[5-bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 200 mg, 346 µmol) in acetonitrile (2.0 ml) was treated with N,N-diisopropylethylamine (130 µl, 730 µmol) and thiomorpholine 1,1-dioxide (935 mg, 6.92 mmol). The resulting mixture was heated for 12 h at 180°C under microwave irradiation and diluted with water. The resulting solution was purified by preparative HPLC (Method 5) affording 105 mg (48% of th.) of the title compound.

LC-MS (Method 2): R_t = 0.96 min; MS (ESIpos): m/z = 632.0 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.83-7.46 (m, 8H), 6.87 (d, 1H), 5.02-4.86 (m, 2H), 4.27 (br ddd, 1H), 4.06-3.77 (m, 2H), 3.61-3.45 (m, 4H, overlapping with HDO peak), 3.20-3.06 (m, 4H).

Example 56

(3R)-1-[1-(2-Chlorophenyl)-3-({3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1H-1,2,4-triazol-5-yl]pyrrolidine-3-carboxamide



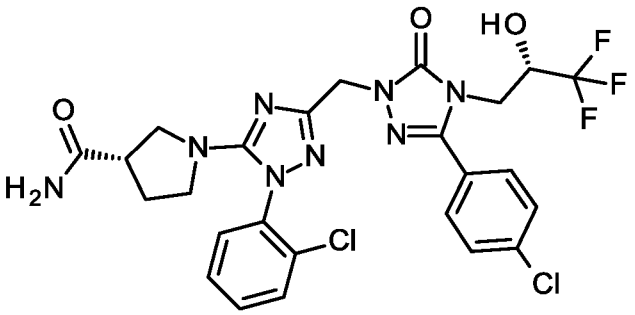
2-{[5-Bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 82.0 mg, 142 µmol), (3R)-pyrrolidine-3-carboxamide (162 mg, 1.42 mmol), N,N-diisopropylethylamine (250 µl, 1.4 mmol) were dissolved in acetonitrile (1.5 ml) and strirred for 5 h at 180°C in a sealed vial under microwave irradiation, followed by 5 h at 180°C. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 40.4 mg (44% of th.) of the title compound.

LC-MS (Method 10): R_t = 1.17 min; MS (ESIpos): m/z = 611 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.008 (1.89), 1.848 (1.44), 1.869 (1.70), 1.879 (2.35), 1.899 (2.25), 1.927 (1.12), 1.945 (2.01), 1.957 (2.48), 1.975 (2.01), 1.989 (1.12), 2.366 (0.59), 2.816 (0.84), 2.835 (2.43), 2.854 (3.41), 2.874 (2.36), 2.892 (0.72), 3.080 (1.73), 3.118 (2.59), 3.143 (3.88), 3.162 (4.13), 3.195 (2.77), 3.288 (3.52), 3.806 (2.08), 3.829 (2.38), 3.842 (2.94), 3.866 (3.08), 3.971 (3.07), 3.979 (3.30), 4.008 (2.12), 4.016 (1.96), 4.284 (1.85), 4.301 (1.71), 4.815 (1.28), 4.855 (7.65), 4.860 (8.00), 4.867 (6.52), 4.907 (0.97), 6.875 (6.99), 6.891 (5.56), 7.375 (4.02), 7.469 (1.86), 7.484 (4.60), 7.503 (3.77), 7.529 (2.79), 7.534 (3.06), 7.549 (4.48), 7.553 (4.69), 7.568 (2.62), 7.611 (12.50), 7.632 (16.00), 7.643 (6.82), 7.664 (4.12), 7.746 (12.52), 7.767 (9.05).

Example 57

(3S)-1-[1-(2-Chlorophenyl)-3-({3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1H-1,2,4-triazol-5-yl]pyrrolidine-3-carboxamide



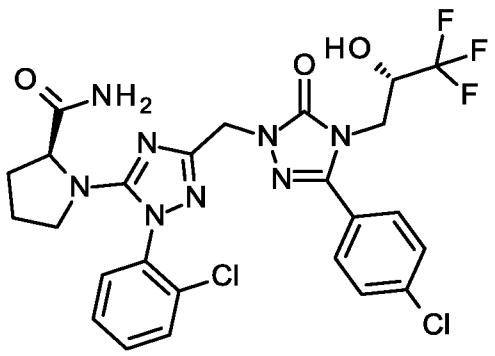
2-{[5-Bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 86.7 mg, 150 µmol), (3S)-pyrrolidine-3-carboxamide (245 mg, 70% purity, 1.50 mmol), N,N-diisopropylethylamine (260 µl, 1.5 mmol) were dissolved in acetonitrile (1.5 ml) and stirred for 5 h at 180°C in a sealed vial under microwave irradiation, followed by 5 h at 180°C. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 44.8 mg (49% of th.) of the title compound.

LC-MS (Method 3): R_t = 1.62 min; MS (ESIpos): m/z = 611 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.008 (1.62), 0.008 (1.34), 1.849 (1.01), 1.860 (0.82), 1.869 (1.26), 1.879 (1.92), 1.900 (1.90), 1.928 (0.80), 1.946 (1.57), 1.958 (2.07), 1.975 (1.71), 1.989 (0.93), 2.836 (2.03), 2.855 (2.94), 2.874 (2.11), 3.081 (1.17), 3.119 (1.95), 3.138 (2.34), 3.143 (3.13), 3.162 (3.29), 3.196 (1.83), 3.290 (1.31), 3.806 (1.79), 3.830 (2.05), 3.843 (2.56), 3.867 (2.76), 3.971 (2.42), 3.979 (2.76), 4.008 (1.76), 4.016 (1.65), 4.285 (1.38), 4.301 (1.32), 4.816 (0.73), 4.855 (5.49), 4.861 (8.53), 4.868 (4.81), 4.908 (0.69), 6.882 (6.41), 6.892 (3.67), 6.898 (3.65), 7.374 (3.28), 7.465 (1.54), 7.469 (1.63), 7.484 (4.19), 7.488 (4.28), 7.503 (3.37), 7.507 (3.35), 7.529 (2.40), 7.534 (2.91), 7.549 (3.83), 7.554 (4.46), 7.568 (2.23), 7.573 (2.08), 7.605 (1.62), 7.612 (11.61), 7.616 (6.56), 7.628 (4.88), 7.633 (16.00), 7.639 (4.44), 7.643 (6.17), 7.647 (5.54), 7.663 (3.85), 7.667 (3.57), 7.741 (1.93), 7.747 (11.88), 7.752 (3.60), 7.764 (3.33), 7.768 (8.58), 7.775 (1.14).

Example 58

1-[1-(2-Chlorophenyl)-3-({3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1H-1,2,4-triazol-5-yl]-L-prolinamide



2-{[5-Bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 80.0 mg, 85% purity, 118 µmol), L-prolinamide (134 mg, 1.18 mmol), N,N-diisopropylethylamine (43 µl, 250 µmol) were dissolved in acetonitrile (670 µl) and stirred for 5 h at 180°C in a sealed vial under microwave irradiation, followed by 5 h at 180°C. The crude product was purified by preparative HPLC

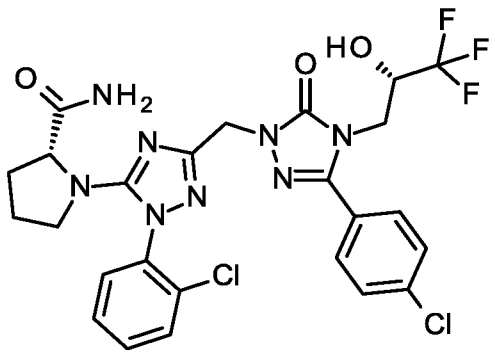
(Method 5). Lyophilisation of the product containing fractions afforded 51.2 mg (64% of th.) of the title compound.

LC-MS (Method 10): R_t = 1.20 min; MS (ESIpos): m/z = 611 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.008 (2.43), 0.008 (2.79), 1.709 (1.75), 1.732 (3.22), 1.748 (3.49), 1.765 (1.94), 1.774 (1.43), 1.783 (1.60), 1.804 (1.46), 1.815 (1.70), 2.019 (1.50), 2.028 (0.94), 2.038 (1.60), 2.050 (1.44), 2.061 (0.87), 2.070 (1.32), 3.018 (0.82), 3.287 (2.55), 3.791 (1.51), 3.815 (1.77), 3.828 (2.25), 3.851 (2.42), 3.956 (2.34), 3.964 (2.65), 3.993 (1.79), 4.000 (1.74), 4.288 (1.69), 4.863 (14.19), 6.898 (5.13), 6.914 (5.31), 6.944 (1.62), 7.458 (1.10), 7.475 (2.30), 7.493 (1.85), 7.526 (2.60), 7.530 (3.04), 7.545 (3.65), 7.550 (3.88), 7.564 (2.24), 7.569 (2.29), 7.610 (8.69), 7.631 (16.00), 7.650 (3.88), 7.721 (1.04), 7.745 (11.06), 7.750 (3.67), 7.762 (3.65), 7.767 (7.76).

Example 59

1-[1-(2-Chlorophenyl)-3-({3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1H-1,2,4-triazol-5-yl]-D-prolinamide



2-{[5-Bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 66.0 mg, 85% purity, 97.0 µmol), D-prolinamide (111 mg, 970 µmol), N,N-diisopropylethylamine (35 µl, 200 µmol) were dissolved in acetonitrile (550 µl) and stirred for 5 h at 180°C in a sealed vial under microwave irradiation, followed by 4 h at 190°C. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 50.1 mg (82% of th.) of the title compound.

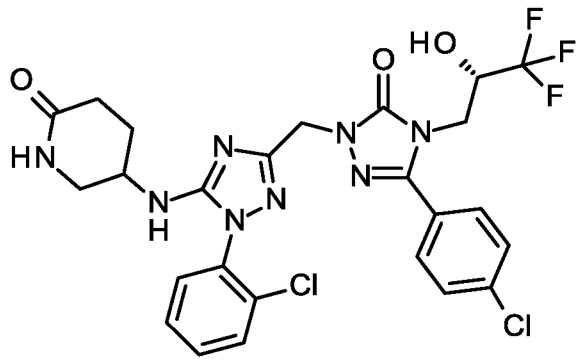
LC-MS (Method 10): R_t = 1.19 min; MS (ESIpos): m/z = 611 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.008 (0.95), 1.708 (1.89), 1.731 (3.64), 1.748 (3.95), 1.766 (2.06), 1.775 (1.46), 1.785 (1.72), 1.795 (1.27), 1.805 (1.60), 1.816 (1.91), 1.826 (1.45), 1.832 (1.35), 1.843 (0.68), 1.998 (0.78), 2.019 (1.75), 2.028 (1.07), 2.037 (1.80), 2.048 (1.66), 2.060 (0.98), 2.068 (1.39), 3.014 (0.85), 3.288 (2.54), 3.795 (1.80), 3.819 (2.10), 3.831 (2.63), 3.855 (2.82), 3.960 (2.81), 3.968 (3.10), 3.996 (2.02), 4.005 (1.91), 4.279 (1.90), 4.296 (1.80),

4.808 (2.25), 4.848 (7.18), 4.863 (1.98), 4.875 (8.00), 4.915 (2.57), 6.874 (5.41), 6.890 (5.63), 6.900 (1.22), 6.916 (1.50), 6.935 (1.84), 7.455 (1.12), 7.474 (2.56), 7.494 (2.05), 7.526 (2.59), 7.530 (2.76), 7.545 (4.17), 7.550 (4.35), 7.565 (2.54), 7.569 (2.39), 7.600 (1.81), 7.606 (9.34), 7.611 (4.28), 7.623 (5.33), 7.628 (16.00), 7.633 (7.83), 7.650 (4.01), 7.653 (3.77), 7.735 (2.42), 7.741 (12.65), 7.746 (5.07), 7.758 (4.00), 7.763 (9.19), 7.768 (2.26).

Example 60

5-{[1-(2-Chlorophenyl)-3-({3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1H-1,2,4-triazol-5-yl]amino}piperidin-2-one (*diastereomeric mixture*)



2-{[5-Bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 120 mg, 85% purity, 176 µmol), (5R)-5-aminopiperidin-2-one (190 µl, 90% purity, 1.8 mmol), N,N-diisopropylethylamine (92 µl, 530 µmol) were dissolved in acetonitrile (1.0 ml) and stirred for 5 h at 180°C in a sealed vial under microwave irradiation, followed by 10 h at 160°C. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 79.3 mg (66% of th.) of the title compound as a mixture of diastereomers.

LC-MS (Method 2): R_t = 0.87 min; MS (ESIpos): m/z = 611 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.008 (1.41), 0.008 (1.26), 1.179 (0.91), 1.695 (1.42), 1.708 (1.31), 1.722 (1.63), 1.732 (1.86), 1.745 (1.18), 1.752 (0.73), 1.990 (1.16), 1.994 (1.18), 2.012 (2.09), 2.023 (2.89), 2.027 (3.77), 2.049 (3.58), 2.060 (5.55), 2.064 (5.01), 2.068 (3.47), 2.086 (3.94), 2.104 (2.35), 2.127 (0.83), 2.191 (1.18), 2.207 (1.65), 2.212 (1.62), 2.226 (1.20), 3.158 (1.37), 3.175 (2.20), 3.191 (2.95), 3.208 (1.76), 3.215 (1.89), 3.230 (3.02), 3.244 (2.09), 3.264 (1.37), 3.278 (0.95), 3.288 (1.37), 3.672 (1.75), 3.687 (2.45), 3.703 (1.70), 3.808 (1.91), 3.832 (2.22), 3.845 (2.92), 3.869 (3.26), 3.970 (3.28), 3.979 (3.67), 4.006 (2.31), 4.015 (2.19), 4.283 (1.84), 4.299 (1.92), 4.819 (1.67), 4.859 (9.47), 4.869 (10.15), 4.883 (1.96), 4.909 (1.48), 5.754 (7.55), 6.531 (2.28), 6.540 (2.64), 6.546 (4.19), 6.559 (2.80), 6.873 (5.31), 6.889 (5.27), 7.349 (1.19), 7.477 (1.36), 7.481 (2.15), 7.485 (1.52), 7.494 (2.83), 7.501 (7.27), 7.514 (4.70),

7.518 (4.79), 7.524 (1.76), 7.531 (1.80), 7.536 (9.35), 7.538 (9.31), 7.540 (6.85), 7.551 (4.10), 7.554 (7.17), 7.559 (5.41), 7.566 (1.88), 7.571 (3.12), 7.576 (3.27), 7.588 (6.48), 7.603 (1.86), 7.610 (10.74), 7.614 (4.87), 7.626 (4.54), 7.631 (15.22), 7.637 (2.69), 7.651 (1.74), 7.653 (1.77), 7.667 (3.69), 7.672 (6.57), 7.683 (1.42), 7.688 (2.53), 7.691 (4.32), 7.734 (2.58), 7.740 (16.00), 7.745 (5.53), 7.757 (4.52), 7.761 (11.69), 7.768 (1.75).

The two diastereomers were separated by preparative chiral HPLC [sample preparation: 79 mg dissolved in 5 ml iso-propanol; injection volume: 0.35 ml; column: Daicel Chiralcel® OD-H 5 µm, 250 x 30 mm; eluent: iso-hexane/ iso-propanol 50:50; flow rate: 15 ml/min; temperature: 25°C; UV detection: 210 nm]. 27.3 mg of diastereomer 1 (Example 61), which eluted first, and 12.0 mg of diastereomer 2 (Example 62), which eluted later, were isolated.

Example 61

5-{[1-(2-Chlorophenyl)-3-({3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1H-1,2,4-triazol-5-yl]amino}piperidin-2-one (*diastereomer 2*)

Analytical chiral HPLC: R_t = 2.56 min, d.e. = 99% [column: Chiraltek OD-3 50 x 4.6 mm; eluent: iso-hexane/ iso-propanol 50/50, flow rate: 1 ml/min; UV detection: 210 nm].

LC-MS (Method 2): R_t = 0.88 min; MS (ESIpos): m/z = 611 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.008 (1.59), 0.779 (1.19), 0.798 (2.58), 0.817 (2.19), 0.822 (7.38), 0.839 (7.82), 0.847 (2.29), 0.865 (4.10), 0.883 (2.07), 1.009 (2.63), 1.038 (14.81), 1.053 (1.11), 1.087 (16.00), 1.141 (0.89), 1.146 (1.04), 1.159 (0.83), 1.236 (1.64), 1.242 (1.46), 1.261 (1.04), 1.289 (1.30), 1.308 (0.90), 1.396 (1.51), 1.406 (0.96), 1.426 (1.28), 1.444 (0.81), 1.694 (0.95), 1.707 (0.93), 1.721 (1.17), 1.731 (1.33), 1.744 (0.79), 1.874 (0.66), 1.990 (0.91), 2.011 (1.45), 2.026 (2.57), 2.049 (2.51), 2.060 (3.88), 2.063 (3.45), 2.086 (2.72), 2.104 (1.57), 3.158 (0.92), 3.175 (1.50), 3.191 (2.07), 3.208 (1.33), 3.214 (1.35), 3.228 (2.08), 3.243 (1.48), 3.262 (0.95), 3.289 (1.18), 3.670 (1.25), 3.685 (1.75), 3.701 (1.24), 3.807 (1.27), 3.831 (1.46), 3.844 (1.84), 3.868 (1.98), 3.971 (1.97), 3.979 (2.15), 4.007 (1.42), 4.016 (1.30), 4.281 (1.10), 4.298 (1.12), 4.819 (1.06), 4.858 (6.12), 4.869 (6.16), 4.909 (1.08), 6.531 (1.41), 6.546 (2.65), 6.561 (1.40), 6.873 (3.63), 6.889 (3.69), 7.477 (0.76), 7.481 (0.87), 7.493 (0.97), 7.501 (2.67), 7.514 (2.95), 7.518 (3.00), 7.536 (6.55), 7.554 (4.64), 7.559 (3.38), 7.571 (1.87), 7.576 (1.85), 7.589 (4.50), 7.603 (1.44), 7.610 (6.38), 7.614 (2.71), 7.626 (3.29), 7.631 (8.60), 7.637 (1.61), 7.667 (2.28), 7.672 (3.70), 7.684 (1.09), 7.691 (2.75), 7.733 (1.70), 7.739 (8.68), 7.744 (3.21), 7.756 (2.83), 7.761 (6.31), 7.767 (1.26), 10.496 (0.75), 10.552 (2.11), 10.616 (2.38).

Example 62

5-{[1-(2-Chlorophenyl)-3-({3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1H-1,2,4-triazol-5-yl]amino}piperidin-2-one

(*diastereomer 1*)

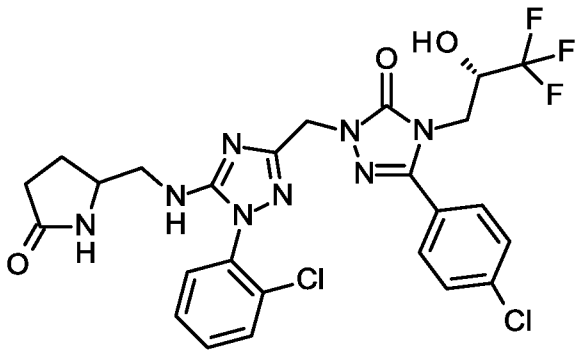
Analytical chiral HPLC: R_t = 5.34 min, d.e. = 99% [column: Chiraltek OD-3 50 x 4.6 mm; eluent: iso-hexane/ iso-propanol 50/50, flow rate: 1 ml/min; UV detection: 210 nm].

LC-MS (Method 4): R_t = 2.67 min; MS (ESIpos): m/z = 611 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.008 (1.66), 0.008 (1.41), 0.779 (0.97), 0.798 (2.07), 0.817 (1.60), 0.822 (5.32), 0.840 (5.68), 0.847 (2.10), 0.865 (4.06), 0.883 (2.10), 0.988 (0.69), 1.010 (2.16), 1.038 (10.86), 1.053 (1.05), 1.087 (16.00), 1.141 (0.76), 1.290 (1.13), 1.308 (0.86), 1.396 (1.49), 1.407 (0.89), 1.426 (1.13), 1.731 (0.94), 1.874 (0.77), 2.012 (1.02), 2.027 (1.80), 2.049 (1.78), 2.060 (2.77), 2.086 (2.13), 2.104 (1.13), 2.206 (0.84), 3.174 (1.10), 3.191 (1.44), 3.206 (0.84), 3.215 (0.91), 3.230 (1.50), 3.245 (1.05), 3.673 (0.87), 3.687 (1.22), 3.703 (0.88), 3.811 (1.02), 3.834 (1.20), 3.847 (1.54), 3.871 (1.70), 3.969 (1.74), 3.977 (1.96), 4.005 (1.24), 4.013 (1.18), 4.282 (0.98), 4.299 (0.96), 4.819 (0.74), 4.858 (4.57), 4.868 (5.01), 4.908 (0.75), 6.531 (1.03), 6.546 (2.01), 6.559 (1.43), 6.873 (2.98), 6.889 (3.01), 7.481 (1.00), 7.494 (1.52), 7.501 (3.51), 7.514 (2.26), 7.518 (2.27), 7.536 (4.83), 7.554 (3.43), 7.559 (2.55), 7.571 (1.36), 7.576 (1.35), 7.588 (3.23), 7.610 (5.52), 7.626 (2.69), 7.631 (7.53), 7.653 (0.96), 7.667 (1.85), 7.672 (3.28), 7.691 (2.09), 7.734 (1.43), 7.740 (8.14), 7.746 (2.88), 7.757 (2.41), 7.762 (5.92), 7.768 (1.12), 10.553 (1.18), 10.616 (1.79).

Example 63

5-(4-Chlorophenyl)-2-{[1-(2-chlorophenyl)-5-({[5-oxopyrrolidin-2-yl]methyl}amino)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (*diastereomeric mixture*)



2-{[5-Bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 120 mg, 85% purity, 176 µmol), 5-(aminomethyl)pyrrolidin-2-one (224 mg, 90% purity, 1.76 mmol), N,N-diisopropylethylamine (92 µl, 530 µmol) were dissolved in acetonitrile (1.0 ml) and stirred for 5 h at 180°C in a sealed vial under microwave irradiation, followed by 10 h at 160°C. The crude

product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 78.6 mg (73% of th.) of the title compound as a mixture of diastereomers.

LC-MS (Method 2): R_t = 0.87 min; MS (ESIpos): m/z = 611 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.141 (1.96), 1.179 (1.06), 1.679 (0.74), 1.695 (1.76), 1.709 (1.70), 1.723 (2.07), 1.732 (2.41), 1.745 (1.37), 1.752 (0.87), 1.991 (1.46), 2.012 (2.57), 2.027 (4.70), 2.050 (4.64), 2.060 (7.04), 2.086 (6.60), 2.104 (2.86), 2.117 (0.88), 2.127 (0.91), 3.143 (0.85), 3.158 (1.67), 3.175 (2.76), 3.192 (3.70), 3.208 (2.24), 3.215 (2.41), 3.230 (3.81), 3.245 (2.60), 3.263 (1.66), 3.278 (1.03), 3.289 (1.22), 3.672 (2.31), 3.688 (3.19), 3.703 (2.21), 3.810 (1.93), 3.834 (2.30), 3.847 (2.97), 3.870 (3.22), 3.970 (3.29), 3.979 (3.77), 4.007 (2.32), 4.016 (2.21), 4.282 (1.89), 4.300 (1.98), 4.819 (1.85), 4.859 (11.34), 4.869 (11.01), 4.909 (1.71), 5.754 (10.86), 6.532 (2.67), 6.547 (4.96), 6.561 (2.60), 6.874 (6.26), 6.890 (6.30), 7.478 (1.31), 7.481 (1.66), 7.494 (1.68), 7.501 (4.87), 7.514 (5.12), 7.518 (5.51), 7.537 (12.14), 7.555 (8.57), 7.560 (6.22), 7.571 (3.48), 7.576 (3.75), 7.589 (8.26), 7.603 (2.25), 7.610 (11.74), 7.614 (5.36), 7.626 (5.36), 7.631 (16.00), 7.667 (4.31), 7.672 (6.92), 7.684 (1.73), 7.691 (5.28), 7.734 (2.76), 7.740 (15.48), 7.761 (11.22).

The two diastereomers were separated by preparative chiral HPLC [sample preparation: 79 mg dissolved in 5 ml iso-propanol; injection volume: 0.40 ml; column: Daicel Chiralcel® OD-H 5 µm, 250 x 30 mm; eluent: iso-hexane/ iso-propanol 50:50; flow rate: 15 ml/min; temperature: 25°C; UV detection: 210 nm]. 26.5 mg of diastereomer 1 (Example 64), which eluted first, and 32.1 mg of diastereomer 2 (Example 65), which eluted later, were isolated.

Example 64

5-(4-Chlorophenyl)-2-{[1-(2-chlorophenyl)-5-({[5-oxopyrrolidin-2-yl]methyl}amino)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (*diastereomer 1*)

Analytical chiral HPLC: R_t = 2.61 min, d.e. = 99% [column: Chiraltek OD-3 50 x 4.6 mm; eluent: iso-hexane/ iso-propanol 50/50, flow rate: 1 ml/min; UV detection: 210 nm].

LC-MS (Method 2): R_t = 0.87 min; MS (ESIpos): m/z = 611 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.008 (3.29), 0.008 (3.00), 0.798 (0.98), 0.822 (1.86), 0.840 (2.00), 0.847 (0.85), 0.865 (1.33), 0.883 (0.71), 0.988 (1.32), 1.003 (1.37), 1.010 (0.87), 1.030 (1.59), 1.038 (3.67), 1.045 (1.56), 1.087 (4.61), 1.135 (1.09), 1.147 (1.67), 1.157 (1.54), 1.175 (2.07), 1.236 (2.16), 1.679 (0.82), 1.695 (1.74), 1.708 (1.66), 1.723 (2.10), 1.732 (2.36), 1.745 (1.40), 1.752 (0.92), 1.989 (1.63), 2.012 (2.58), 2.027 (4.56), 2.049 (4.47), 2.060 (6.92), 2.064 (6.23), 2.086 (4.94), 2.104 (2.83), 2.127 (0.99), 3.141 (0.92), 3.157 (1.76), 3.174 (2.79), 3.190 (3.72), 3.206 (2.20), 3.215 (2.31), 3.230 (3.87), 3.244 (2.77), 3.263 (1.74), 3.278 (1.24), 3.288 (1.73), 3.673 (2.20), 3.687 (3.15), 3.703 (2.23), 3.811 (2.25), 3.834 (2.59), 3.847 (3.28),

3.871 (3.51), 3.969 (3.40), 3.977 (3.80), 4.006 (2.41), 4.014 (2.28), 4.282 (1.90), 4.299 (1.87), 4.323 (0.87), 4.819 (1.86), 4.858 (11.38), 4.868 (11.39), 4.908 (1.81), 5.754 (6.08), 6.531 (2.61), 6.546 (4.83), 6.560 (2.55), 6.872 (6.62), 6.888 (6.67), 7.478 (1.45), 7.481 (1.64), 7.494 (1.78), 7.499 (4.14), 7.501 (4.69), 7.514 (5.32), 7.518 (5.38), 7.536 (11.48), 7.541 (7.76), 7.554 (8.15), 7.560 (5.70), 7.571 (3.35), 7.577 (3.54), 7.587 (8.15), 7.603 (2.16), 7.610 (11.46), 7.615 (4.58), 7.626 (5.32), 7.631 (15.56), 7.637 (2.67), 7.667 (4.06), 7.672 (6.40), 7.684 (1.70), 7.691 (4.87), 7.734 (2.86), 7.740 (16.00), 7.746 (5.32), 7.757 (4.68), 7.762 (11.48), 7.768 (1.76), 10.616 (0.61).

Example 65

5-(4-Chlorophenyl)-2-{[1-(2-chlorophenyl)-5-({[5-oxopyrrolidin-2-yl]methyl}amino)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (*diastereomer 2*)

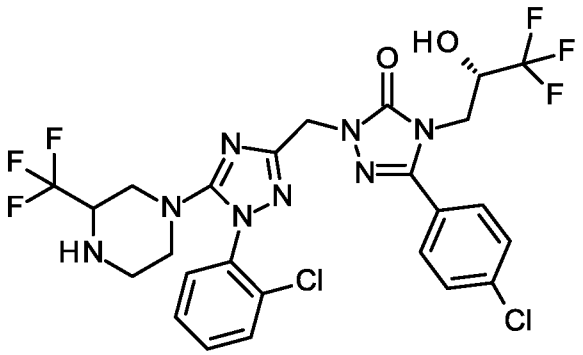
Analytical chiral HPLC: R_t = 4.83 min, d.e. = 99% [column: Chiraltek OD-3 50 x 4.6 mm; eluent: iso-hexane/ iso-propanol 50/50, flow rate: 1 ml/min; UV detection: 210 nm].

LC-MS (Method 2): R_t = 0.87 min; MS (ESIpos): m/z = 611 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.008 (1.18), 0.779 (1.20), 0.798 (2.33), 0.817 (1.78), 0.822 (5.87), 0.840 (6.21), 0.847 (2.15), 0.865 (4.07), 0.883 (2.11), 1.010 (2.19), 1.038 (11.81), 1.088 (16.00), 1.141 (0.88), 1.147 (0.89), 1.173 (1.00), 1.236 (1.01), 1.290 (1.06), 1.308 (0.80), 1.397 (1.50), 1.407 (0.90), 1.416 (0.78), 1.426 (1.15), 1.731 (0.88), 2.012 (0.95), 2.027 (1.71), 2.049 (1.67), 2.060 (2.60), 2.064 (2.30), 2.086 (1.86), 2.104 (1.05), 3.175 (1.01), 3.192 (1.37), 3.208 (0.87), 3.215 (0.91), 3.229 (1.38), 3.244 (0.96), 3.686 (1.16), 3.702 (0.82), 3.808 (0.83), 3.832 (0.95), 3.845 (1.19), 3.868 (1.28), 3.971 (1.25), 3.980 (1.39), 4.008 (0.91), 4.016 (0.84), 4.819 (0.72), 4.859 (4.11), 4.870 (4.09), 4.909 (0.73), 5.754 (0.79), 6.532 (0.93), 6.546 (1.74), 6.561 (0.90), 6.873 (2.36), 6.889 (2.38), 7.499 (1.52), 7.501 (1.73), 7.514 (1.97), 7.518 (2.00), 7.536 (4.33), 7.540 (2.87), 7.554 (3.10), 7.559 (2.23), 7.571 (1.24), 7.577 (1.22), 7.590 (2.98), 7.610 (4.27), 7.614 (1.77), 7.626 (2.10), 7.631 (5.78), 7.637 (1.02), 7.668 (1.53), 7.672 (2.44), 7.688 (1.25), 7.691 (1.84), 7.733 (1.09), 7.739 (5.87), 7.745 (1.99), 7.756 (1.79), 7.761 (4.21), 10.552 (1.42), 10.616 (2.03).

Example 66

5-(4-Chlorophenyl)-2-({1-(2-chlorophenyl)-5-[(3-(trifluoromethyl)piperazin-1-yl]-1H-1,2,4-triazol-3-yl}methyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (*diastereomeric mixture*)



2-{[5-Bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 120 mg, 85% purity, 176 µmol), 2-(trifluoromethyl)piperazine (163 mg, 1.06 mmol), N,N-diisopropylethylamine (92 µl, 530 µmol) were dissolved in acetonitrile (1.0 ml) and stirred for 15 h at 180°C in a sealed vial under microwave irradiation. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 68.5 mg (58% of th.) of the title compound as a mixture of diastereomers.

LC-MS (Method 10): R_t = 1.37 min; MS (ESIpos): m/z = 651 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.008 (5.07), 0.008 (4.57), 1.147 (1.03), 1.157 (1.17), 1.175 (2.24), 1.192 (1.27), 1.235 (1.62), 1.259 (0.68), 1.552 (1.31), 1.581 (4.76), 1.611 (1.54), 1.907 (1.23), 1.923 (1.76), 1.941 (2.93), 1.958 (3.34), 1.975 (2.75), 1.988 (3.47), 1.993 (1.81), 2.009 (0.96), 2.366 (0.86), 2.710 (0.88), 3.101 (4.66), 3.114 (6.22), 3.128 (4.49), 3.286 (3.43), 3.335 (4.55), 3.364 (8.35), 3.393 (4.02), 3.812 (2.15), 3.835 (2.46), 3.848 (3.47), 3.859 (0.90), 3.872 (3.47), 3.884 (0.78), 3.974 (3.16), 3.982 (3.67), 4.010 (2.26), 4.020 (2.61), 4.038 (0.72), 4.280 (1.95), 4.874 (1.54), 4.914 (12.08), 4.922 (12.08), 4.962 (1.50), 5.115 (2.83), 6.868 (6.52), 6.884 (6.61), 6.896 (1.29), 6.912 (1.15), 7.520 (1.27), 7.524 (1.44), 7.538 (4.21), 7.542 (4.25), 7.557 (4.94), 7.561 (4.86), 7.566 (3.02), 7.572 (4.62), 7.585 (3.73), 7.591 (6.73), 7.600 (8.04), 7.605 (7.79), 7.613 (12.39), 7.618 (8.76), 7.624 (4.86), 7.629 (5.27), 7.634 (15.90), 7.641 (4.68), 7.683 (0.86), 7.707 (5.46), 7.711 (5.39), 7.727 (4.70), 7.731 (4.92), 7.740 (16.00), 7.745 (5.33), 7.756 (5.58), 7.761 (11.49), 7.768 (1.99), 7.775 (3.04).

The two diastereomers were separated by preparative chiral HPLC [sample preparation: 52.3 mg dissolved in 1.5ml ethanol; injection volume: 1.0 ml; column: Daicel Chiralpak® IA 5 µm, 250 x 20 mm; eluent: iso-hexane/ ethanol 50:50; flow rate: 15 ml/min; temperature: 25°C; UV detection: 220 nm]. 12.0 mg of diastereomer 1 (Example 67), which eluted first, and 13.0 mg of diastereomer 2 (Example 68), which eluted later, were isolated.

Example 67

5-(4-Chlorophenyl)-2-({1-(2-chlorophenyl)-5-[3-(trifluoromethyl)piperazin-1-yl]-1H-1,2,4-triazol-

3-yl}methyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (*diastereomer 1*)

Analytical chiral HPLC: R_t = 6.00 min, d.e. = 99% [column: Chiralpak® IA 250 x 4.6 mm; eluent: iso-hexane/ ethanol 50/50 + 0.2% diethylamine, flow rate: 1 ml/min; UV detection: 210 nm].

LC-MS (Method 2): R_t = 1.01 min; MS (ESIpos): m/z = 651 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.008 (2.09), 0.008 (2.01), 0.822 (0.69), 0.840 (0.72), 1.038 (1.33), 1.087 (2.06), 2.563 (1.94), 2.580 (1.32), 2.593 (1.26), 2.601 (0.85), 2.757 (1.97), 2.765 (2.19), 2.789 (1.57), 2.796 (1.61), 2.833 (1.49), 2.841 (1.50), 2.864 (2.92), 2.871 (2.40), 2.877 (3.26), 2.889 (2.12), 2.900 (4.49), 2.907 (4.56), 2.917 (3.06), 2.930 (5.68), 3.090 (2.69), 3.121 (2.14), 3.288 (2.90), 3.398 (2.69), 3.429 (2.42), 3.436 (2.14), 3.812 (1.97), 3.835 (2.23), 3.848 (2.86), 3.872 (3.10), 3.973 (2.95), 3.982 (3.37), 4.009 (2.13), 4.018 (2.01), 4.278 (1.59), 4.295 (1.53), 4.877 (1.64), 4.917 (10.38), 4.927 (10.34), 4.967 (1.65), 6.867 (5.00), 6.883 (5.01), 7.505 (1.38), 7.508 (1.59), 7.523 (4.16), 7.527 (4.45), 7.542 (3.99), 7.546 (4.02), 7.555 (2.82), 7.560 (3.48), 7.574 (3.96), 7.579 (4.72), 7.593 (2.20), 7.598 (2.00), 7.606 (1.63), 7.612 (10.11), 7.617 (4.22), 7.627 (8.19), 7.634 (16.00), 7.640 (2.78), 7.646 (4.02), 7.650 (3.61), 7.699 (5.16), 7.703 (5.11), 7.719 (4.22), 7.723 (4.13), 7.731 (2.54), 7.737 (14.28), 7.742 (4.67), 7.754 (3.91), 7.759 (10.05), 7.765 (1.49).

Example 68

5-(4-Chlorophenyl)-2-({1-(2-chlorophenyl)-5-[3-(trifluoromethyl)piperazin-1-yl]-1H-1,2,4-triazol-3-yl}methyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (*diastereomer 2*)

Analytical chiral HPLC: R_t = 7.54 min, d.e. = 99% [column: Chiralpak® IA 250 x 4.6 mm; eluent: iso-hexane/ ethanol 50/50 + 0.2% diethylamine, flow rate: 1 ml/min; UV detection: 210 nm].

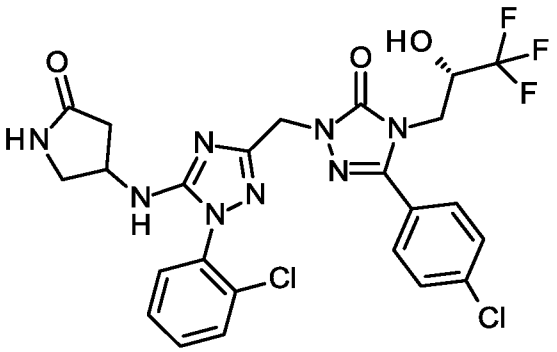
LC-MS (Method 2): R_t = 1.01 min; MS (ESIpos): m/z = 651 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.008 (2.66), 0.008 (2.32), 0.798 (0.84), 0.817 (0.81), 0.822 (1.67), 0.840 (1.83), 0.847 (0.99), 0.865 (1.36), 0.883 (0.71), 1.010 (0.68), 1.038 (2.74), 1.087 (4.07), 1.147 (1.00), 1.172 (0.92), 1.235 (2.61), 2.563 (2.17), 2.593 (1.38), 2.765 (2.31), 2.790 (1.67), 2.796 (1.71), 2.834 (1.58), 2.841 (1.58), 2.865 (3.06), 2.872 (2.51), 2.878 (3.36), 2.890 (2.26), 2.900 (4.68), 2.908 (4.79), 2.918 (3.27), 2.931 (5.74), 3.092 (2.82), 3.123 (2.25), 3.288 (3.30), 3.398 (2.85), 3.428 (2.56), 3.812 (2.02), 3.836 (2.34), 3.849 (2.96), 3.872 (3.21), 3.972 (3.09), 3.981 (3.50), 4.009 (2.23), 4.018 (2.10), 4.276 (1.69), 4.879 (1.13), 4.919 (11.99), 4.925 (11.90), 4.965 (1.14), 6.869 (5.00), 6.884 (5.00), 7.505 (1.38), 7.508 (1.62), 7.523 (4.32), 7.527 (4.56), 7.542 (4.12), 7.546 (4.17), 7.555 (2.92), 7.560 (3.59), 7.574 (4.15), 7.579 (4.88), 7.593 (2.31), 7.598 (2.11), 7.606 (1.73), 7.612 (10.34), 7.617 (4.55), 7.626 (7.56), 7.634 (16.00),

7.640 (3.13), 7.645 (4.37), 7.650 (3.76), 7.699 (5.30), 7.703 (5.26), 7.719 (4.39), 7.723 (4.34), 7.731 (2.81), 7.738 (14.53), 7.742 (5.15), 7.754 (4.23), 7.759 (10.34), 7.765 (1.65), 10.616 (0.57).

Example 69

5-(4-Chlorophenyl)-2-{[1-(2-chlorophenyl)-5-{[5-oxopyrrolidin-3-yl]amino}-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (*diastereomeric mixture*)



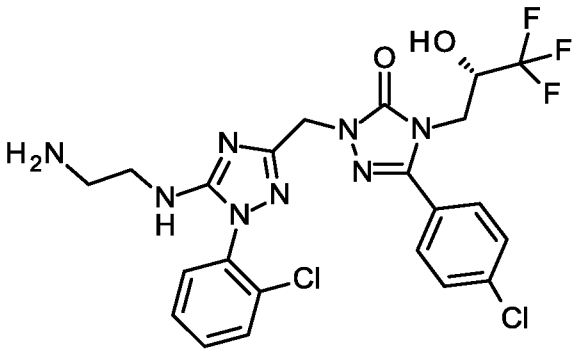
2-{[5-Bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 120 mg, 85% purity, 176 µmol), 4-aminopyrrolidin-2-one hydrochloride (1:1) (241 mg, 1.76 mmol), N,N-diisopropylethylamine (400 µl, 2.3 mmol) were dissolved in acetonitrile (1.0 ml) and N-methyl-2-pyrrolidone (1.0 ml) and stirred for 5 h at 180°C in a sealed vial under microwave irradiation, followed by 5 h at 180°C. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 12.7 mg (11% of th.) of the title compound.

LC-MS (Method 2): R_t = 0.87 min; MS (ESIpos): m/z = 597 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.796 (0.97), 1.178 (3.06), 1.235 (2.97), 2.128 (2.46), 2.138 (2.40), 2.170 (3.23), 2.180 (3.34), 2.422 (3.58), 2.443 (4.02), 2.463 (3.29), 2.695 (1.66), 3.085 (3.19), 3.096 (3.34), 3.110 (3.63), 3.121 (3.62), 3.287 (2.46), 3.503 (3.29), 3.521 (4.07), 3.528 (3.72), 3.546 (3.11), 3.806 (2.32), 3.830 (2.81), 3.843 (3.57), 3.867 (3.77), 3.969 (3.90), 3.977 (4.33), 4.005 (2.70), 4.013 (2.65), 4.284 (2.55), 4.363 (2.85), 4.381 (2.69), 4.829 (1.12), 4.872 (11.26), 4.878 (11.94), 4.920 (1.19), 5.754 (4.63), 6.856 (6.21), 6.875 (10.64), 6.892 (6.85), 7.466 (1.15), 7.485 (4.51), 7.498 (11.99), 7.503 (13.38), 7.516 (3.84), 7.529 (4.11), 7.535 (4.01), 7.555 (11.28), 7.564 (4.68), 7.571 (3.17), 7.611 (11.30), 7.632 (15.61), 7.656 (7.13), 7.675 (5.43), 7.741 (16.00), 7.762 (11.85).

Example 70

2-({5-[(2-Aminoethyl)amino]-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl}methyl)-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



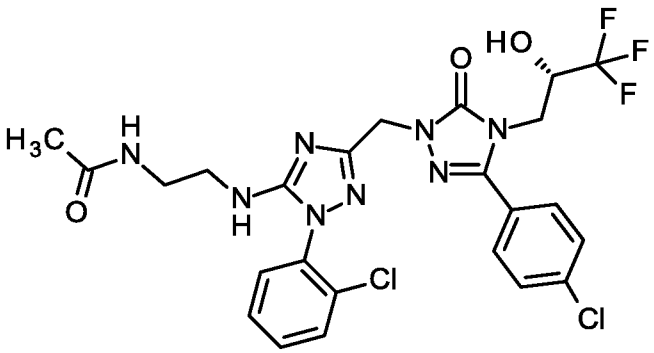
2-{[5-Bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 120 mg, 85% purity, 176 µmol), N-(2-aminoethyl)acetamide (190 µl, 90% purity, 1.8 mmol), N,N-diisopropylethylamine (92 µl, 530 µmol) were dissolved in acetonitrile (1.0 ml) and stirred for 5 h at 180°C in a sealed vial under microwave irradiation. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 56.6 mg (51% of th.) of the title compound.

LC-MS (Method 2): R_t = 0.71 min; MS (ESIpos): m/z = 557 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.177 (0.75), 1.235 (0.72), 2.328 (0.43), 2.670 (0.58), 2.710 (0.47), 2.813 (3.87), 2.828 (7.64), 2.843 (4.27), 3.243 (1.09), 3.302 (2.99), 3.315 (6.56), 3.330 (6.41), 3.663 (0.80), 3.801 (2.77), 3.825 (3.10), 3.837 (3.83), 3.861 (3.97), 3.963 (4.09), 3.970 (4.67), 3.999 (3.04), 4.007 (2.96), 4.300 (2.05), 4.316 (2.54), 4.333 (1.77), 4.831 (0.85), 4.873 (15.50), 4.914 (0.90), 6.681 (3.00), 7.474 (1.51), 7.491 (4.24), 7.508 (5.44), 7.511 (5.30), 7.532 (6.15), 7.536 (7.68), 7.540 (7.83), 7.549 (6.33), 7.554 (5.66), 7.560 (3.80), 7.566 (2.94), 7.570 (2.21), 7.612 (11.66), 7.634 (15.14), 7.661 (5.04), 7.665 (5.45), 7.685 (4.83), 7.761 (16.00), 7.782 (11.93), 7.975 (0.47), 8.291 (2.05).

Example 71

N-(2-{[1-(2-Chlorophenyl)-3-({3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1H-1,2,4-triazol-5-yl]amino}ethyl)acetamide



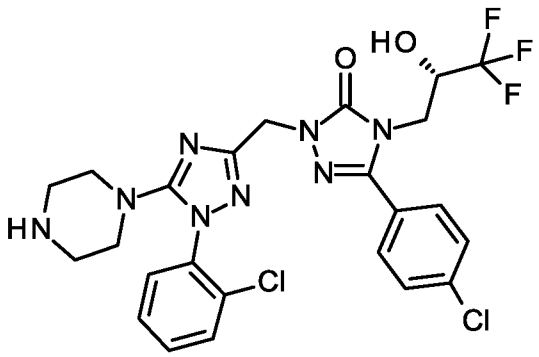
2-{[5-Bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 120 mg, 85% purity, 176 µmol), N-(2-aminoethyl)acetamide (190 µl, 90% purity, 1.8 mmol), N,N-diisopropylethylamine (92 µl, 530 µmol) were dissolved in acetonitrile (1.0 ml) and stirred for 5 h at 180°C in a sealed vial under microwave irradiation. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 56.6 mg (51% of th.) of the title compound.

LC-MS (Method 2): R_t = 0.88 min; MS (ESIpos): m/z = 599 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.744 (1.43), 1.752 (16.00), 3.157 (1.61), 3.172 (2.31), 3.186 (1.44), 3.206 (1.38), 3.220 (2.11), 3.235 (1.53), 3.809 (0.70), 3.833 (0.81), 3.845 (1.02), 3.869 (1.10), 3.970 (1.08), 3.979 (1.19), 4.007 (0.77), 4.859 (4.04), 4.865 (4.06), 5.754 (2.35), 6.478 (0.87), 6.493 (1.76), 6.506 (0.80), 6.892 (1.83), 6.908 (1.83), 7.487 (1.10), 7.491 (1.22), 7.502 (3.42), 7.507 (4.19), 7.521 (0.98), 7.525 (1.50), 7.532 (0.78), 7.544 (1.44), 7.551 (1.05), 7.560 (1.02), 7.567 (0.79), 7.610 (3.82), 7.615 (1.39), 7.626 (1.58), 7.632 (5.22), 7.660 (1.89), 7.663 (1.95), 7.682 (1.56), 7.746 (5.30), 7.752 (1.60), 7.763 (1.53), 7.768 (3.82), 7.846 (1.24).

Example 72

5-(4-Chlorophenyl)-2-{[1-(2-chlorophenyl)-5-(piperazin-1-yl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



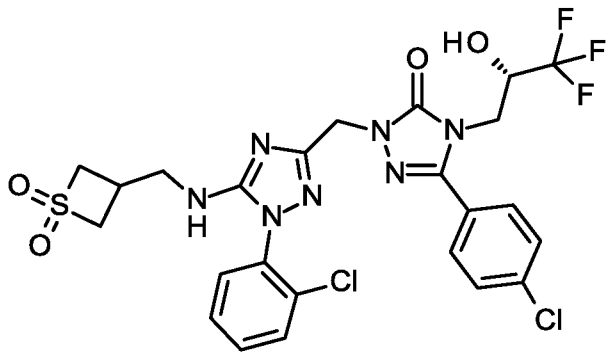
2-{[5-Bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 120 mg, 85% purity, 176 µmol), piperazine (152 mg, 1.76 mmol), N,N-diisopropylethylamine (92 µl, 530 µmol) were dissolved in acetonitrile (1.0 ml) and stirred for 1 h at 100°C in a sealed vial under microwave irradiation, followed by 5 h at 120°C. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 87.9 mg (83% of th.) of the title compound.

LC-MS (Method 10): R_t = 0.93 min; MS (ESIpos): m/z = 583 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.148 (0.80), 2.327 (0.70), 2.365 (0.80), 2.611 (11.55), 2.623 (15.15), 2.636 (12.52), 2.710 (0.74), 2.988 (14.02), 2.995 (12.86), 3.000 (15.89), 3.012 (12.02), 3.313 (1.58), 3.810 (2.53), 3.834 (2.85), 3.846 (3.61), 3.870 (3.86), 3.971 (3.86), 3.980 (4.41), 4.008 (2.82), 4.016 (2.61), 4.288 (2.23), 4.853 (1.41), 4.894 (13.47), 4.900 (13.38), 4.940 (1.38), 5.754 (4.92), 6.885 (0.76), 7.497 (1.64), 7.511 (4.41), 7.515 (4.83), 7.530 (4.88), 7.536 (6.14), 7.542 (4.39), 7.556 (4.67), 7.561 (5.39), 7.575 (2.29), 7.580 (2.05), 7.599 (6.80), 7.603 (6.74), 7.613 (11.97), 7.622 (5.41), 7.634 (15.35), 7.685 (5.82), 7.704 (4.77), 7.708 (4.58), 7.741 (16.00), 7.762 (11.53), 8.182 (11.02).

Example 73

5-(4-Chlorophenyl)-2-{[1-(2-chlorophenyl)-5-{[(1,1-dioxidothietan-3-yl)methyl]amino}-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



2-{[5-Bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 120 mg, 85% purity, 176 µmol), 1-(1,1-dioxidothietan-3-yl)methanamine (238 mg, 1.76 mmol), N,N-diisopropylethylamine (92 µl, 530 µmol) were dissolved in acetonitrile (3.0 ml) and stirred for 5 h at 180°C in a sealed vial under microwave irradiation, followed by 1 h a 180°C. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 38.2 mg (34% of th.) of the title compound.

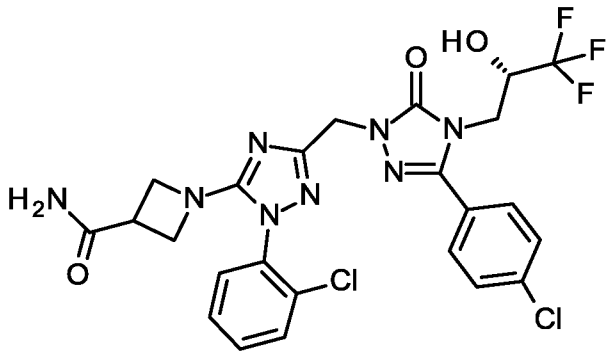
LC-MS (Method 10): R_t = 1.22 min; MS (ESIpos): m/z = 632 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.149 (0.60), -0.008 (5.59), 0.008 (4.89), 0.146 (0.58), 2.753 (1.19), 2.763 (1.44), 2.777 (2.12), 2.792 (1.48), 2.801 (1.28), 3.420 (4.63), 3.436 (7.33), 3.453 (4.30), 3.808 (2.25), 3.832 (2.61), 3.845 (3.35), 3.869 (3.66), 3.887 (4.22), 3.901 (4.27), 3.915 (2.25), 3.923 (5.67), 3.930 (2.74), 3.937 (5.36), 3.969 (3.42), 3.977 (3.83), 4.006 (2.45), 4.014 (2.31), 4.136 (5.14), 4.160 (5.72), 4.172 (4.67), 4.196 (3.84), 4.283 (1.90), 4.300 (1.83), 4.825 (2.40), 4.865 (10.95), 4.879 (10.95), 4.919 (2.38), 5.753 (10.74), 6.823 (2.58), 6.838 (5.37), 6.853 (2.64), 6.867 (6.79), 6.883 (6.84), 7.477 (0.80), 7.480 (0.87), 7.496 (3.43), 7.499 (4.09), 7.507 (6.72), 7.514 (15.04), 7.526 (2.54), 7.538 (3.79), 7.546 (2.64), 7.553 (2.24), 7.558 (4.35),

7.566 (3.06), 7.573 (2.76), 7.580 (2.20), 7.600 (1.63), 7.607 (11.32), 7.611 (4.88), 7.623 (5.00), 7.628 (15.95), 7.634 (3.09), 7.674 (5.52), 7.677 (5.84), 7.695 (4.83), 7.732 (2.61), 7.738 (16.00), 7.743 (5.85), 7.755 (4.53), 7.760 (11.82), 7.766 (2.23).

Example 74

1-[1-(2-Chlorophenyl)-3-({3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1H-1,2,4-triazol-5-yl]azetidine-3-carboxamide



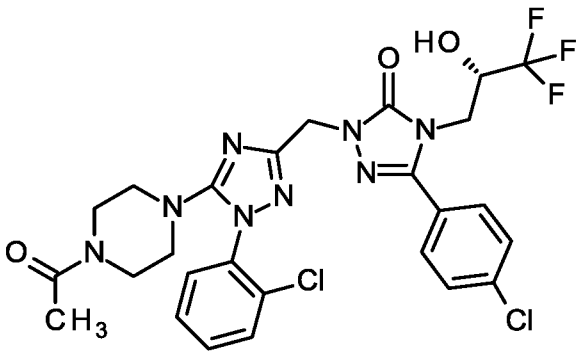
2-{[5-Bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 120 mg, 85% purity, 176 µmol), azetidine-3-carboxamide (177 mg, 1.76 mmol), N,N-diisopropylethylamine (92 µl, 530 µmol) were dissolved in acetonitrile (3.0 ml) and stirred for 7 h at 180°C in a sealed vial under microwave irradiation. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 66.4 mg (60% of th.) of the title compound.

LC-MS (Method 10): R_t = 1.14 min; MS (ESIpos): m/z = 597 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.008 (3.24), 0.008 (3.11), 3.264 (0.74), 3.287 (3.19), 3.302 (5.34), 3.340 (1.08), 3.707 (1.89), 3.726 (10.63), 3.732 (12.70), 3.749 (16.00), 3.768 (1.41), 3.807 (2.07), 3.831 (2.38), 3.844 (2.95), 3.867 (3.19), 3.973 (3.13), 3.982 (3.46), 4.010 (2.17), 4.018 (2.04), 4.287 (1.71), 4.304 (1.62), 4.844 (1.17), 4.883 (11.80), 4.889 (11.97), 4.928 (1.05), 5.754 (10.08), 6.881 (6.12), 6.897 (6.17), 6.965 (3.77), 7.322 (3.79), 7.481 (1.61), 7.484 (1.82), 7.499 (4.35), 7.503 (4.75), 7.518 (3.72), 7.522 (3.91), 7.547 (2.61), 7.551 (3.54), 7.566 (4.19), 7.571 (5.30), 7.585 (2.33), 7.590 (2.36), 7.606 (7.01), 7.612 (12.96), 7.617 (4.76), 7.625 (5.38), 7.629 (8.42), 7.634 (14.88), 7.640 (2.49), 7.672 (5.45), 7.676 (5.79), 7.692 (4.03), 7.695 (4.15), 7.742 (2.67), 7.749 (14.15), 7.754 (4.99), 7.765 (3.98), 7.770 (10.40), 7.776 (1.55).

Example 75

2-{[5-(4-Acetylpiperazin-1-yl)-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



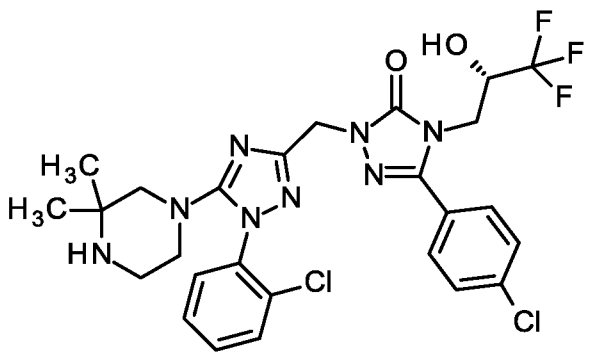
2-{[5-Bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 120 mg, 85% purity, 176 µmol), 1-(piperazin-1-yl)ethanone (220 µl, 1.8 mmol), N,N-diisopropylethylamine (65 µl, 370 µmol) were dissolved in acetonitrile (1.0 ml) and stirred for 5 h at 180°C in a sealed vial under microwave irradiation. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 80.4 mg (71% of th.) of the title compound.

LC-MS (Method 10): R_t = 1.22 min; MS (ESIpos): m/z = 625 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.008 (1.60), 0.008 (1.50), 1.157 (1.17), 1.175 (2.34), 1.192 (1.20), 1.940 (16.00), 1.988 (4.30), 3.065 (3.78), 3.072 (3.15), 3.286 (1.39), 3.344 (1.73), 3.362 (3.14), 3.370 (2.95), 3.389 (1.36), 3.812 (0.69), 3.836 (0.78), 3.849 (1.00), 3.872 (1.08), 3.974 (0.99), 3.982 (1.14), 4.020 (1.65), 4.038 (1.03), 4.910 (3.95), 4.917 (3.91), 6.869 (2.04), 6.885 (2.05), 7.528 (1.51), 7.532 (1.63), 7.547 (1.44), 7.551 (1.49), 7.558 (1.15), 7.563 (1.33), 7.578 (1.49), 7.583 (1.76), 7.597 (0.83), 7.602 (0.78), 7.613 (3.72), 7.618 (1.41), 7.629 (1.85), 7.634 (6.89), 7.638 (2.83), 7.652 (1.40), 7.657 (1.30), 7.700 (1.85), 7.705 (1.79), 7.720 (1.58), 7.724 (1.46), 7.741 (5.19), 7.746 (1.58), 7.757 (1.39), 7.762 (3.67).

Example 76

5-(4-Chlorophenyl)-2-{[1-(2-chlorophenyl)-5-(3,3-dimethylpiperazin-1-yl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



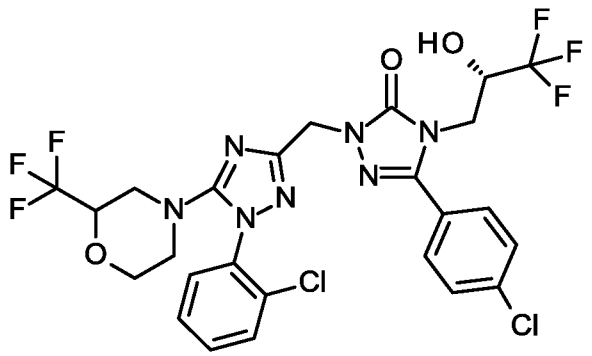
2-{[5-Bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 120 mg, 85% purity, 176 µmol), 2,2-dimethylpiperazine (201 mg, 1.76 mmol), N,N-diisopropylethylamine (65 µl, 370 µmol) were dissolved in acetonitrile (1.0 ml) and stirred for 5 h at 180°C in a sealed vial under microwave irradiation. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 80.3 mg (74% of th.) of the title compound.

LC-MS (Method 10): R_t = 0.96 min; MS (ESIpos): m/z = 613 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.874 (16.00), 1.157 (0.62), 1.175 (1.23), 1.193 (0.64), 1.988 (2.18), 2.687 (0.99), 2.699 (1.39), 2.712 (1.25), 2.751 (4.49), 2.956 (1.17), 2.965 (1.17), 2.970 (1.40), 2.982 (0.97), 3.850 (0.68), 3.873 (0.73), 3.973 (0.74), 3.982 (0.84), 4.020 (0.93), 4.038 (0.57), 4.903 (2.40), 4.911 (2.35), 7.525 (0.86), 7.529 (0.92), 7.544 (0.91), 7.548 (0.98), 7.557 (0.77), 7.571 (0.84), 7.576 (0.99), 7.614 (3.01), 7.620 (1.58), 7.635 (3.49), 7.692 (1.03), 7.696 (1.01), 7.712 (0.82), 7.716 (0.78), 7.739 (2.96), 7.744 (0.92), 7.756 (0.82), 7.761 (2.09), 8.187 (3.06).

Example 77

5-(4-Chlorophenyl)-2-({1-(2-chlorophenyl)-5-[2-(trifluoromethyl)morpholin-4-yl]-1H-1,2,4-triazol-3-yl}methyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



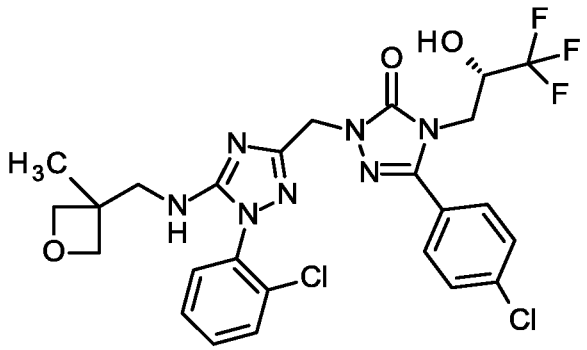
2-{[5-Bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 120 mg, 208 µmol), 2-(trifluoromethyl)morpholine hydrochloride (1:1) (199 mg, 1.04 mmol), N,N-diisopropylethylamine (290 µl, 1.7 mmol) were dissolved in acetonitrile (3.0 ml) and stirred for 5 h at 180°C in a sealed vial under microwave irradiation. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 56.0 mg (41% of th.) of the title compound as a mixture of diastereomers.

LC-MS (Method 10): R_t = 1.44 min; MS (ESIpos): m/z = 652 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.149 (0.66), -0.008 (6.02), 0.008 (5.39), 0.146 (0.64), 2.085 (8.52), 2.977 (3.54), 2.988 (1.46), 3.003 (3.88), 3.008 (5.21), 3.015 (2.39), 3.020 (2.13), 3.034 (3.86), 3.040 (2.39), 3.048 (1.81), 3.130 (2.91), 3.160 (1.78), 3.287 (2.61), 3.444 (2.70), 3.474 (2.36), 3.512 (1.35), 3.519 (1.64), 3.541 (2.93), 3.548 (2.82), 3.569 (1.66), 3.576 (1.33), 3.815 (1.90), 3.839 (2.39), 3.852 (5.24), 3.876 (4.49), 3.975 (2.74), 3.984 (3.05), 4.012 (1.93), 4.021 (1.85), 4.164 (1.04), 4.171 (1.39), 4.180 (1.38), 4.189 (1.84), 4.197 (1.43), 4.206 (1.27), 4.213 (1.00), 4.275 (1.49), 4.894 (1.18), 4.934 (10.22), 4.942 (9.53), 4.983 (1.07), 5.754 (4.21), 6.863 (5.82), 6.879 (5.87), 7.517 (1.55), 7.520 (1.78), 7.535 (4.52), 7.539 (4.70), 7.554 (4.03), 7.558 (4.02), 7.569 (2.93), 7.574 (3.63), 7.589 (4.20), 7.594 (5.00), 7.608 (3.57), 7.613 (12.28), 7.618 (3.97), 7.630 (4.40), 7.635 (15.02), 7.641 (2.25), 7.655 (5.50), 7.660 (5.21), 7.675 (4.03), 7.679 (3.77), 7.711 (5.46), 7.715 (5.27), 7.731 (6.41), 7.737 (16.00), 7.742 (4.55), 7.754 (3.95), 7.759 (10.38), 7.765 (1.35).

Example 78

5-(4-Chlorophenyl)-2-{[1-(2-chlorophenyl)-5-{[(3-methyloxetan-3-yl)methyl]amino}-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



2-{[5-Bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 120 mg, 85% purity, 176 µmol), 1-(3-methyloxetan-3-yl)methanamine (178 mg, 1.76 mmol), N,N-diisopropylethylamine (65 µl, 370 µmol) were dissolved in acetonitrile (1.0 ml) and stirred for 6 h at 160°C in a sealed vial under microwave irradiation. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 40.0 mg (38% of th.) of the title compound.

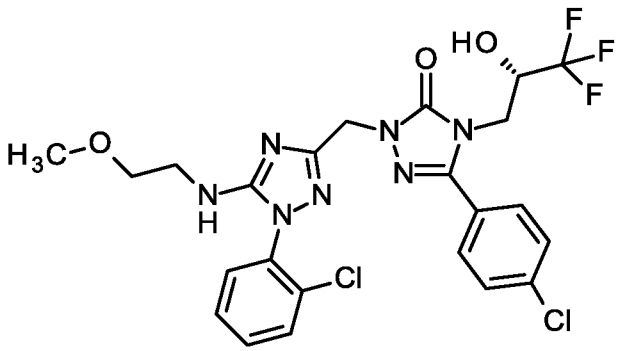
LC-MS (Method 10): R_t = 1.25 min; MS (ESIpos): m/z = 598 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.008 (3.07), 0.008 (2.43), 1.091 (16.00), 1.157 (1.62), 1.175 (3.22), 1.192 (1.64), 1.988 (5.53), 3.232 (3.68), 3.250 (5.62), 3.254 (6.25), 3.268 (4.58), 3.287 (1.73), 3.524 (4.79), 3.543 (4.21), 3.808 (0.88), 3.832 (1.04), 3.844 (1.28), 3.868 (1.39), 3.971 (1.34), 3.979 (1.48), 4.003 (0.79), 4.007 (0.99), 4.016 (0.98), 4.021 (1.61), 4.038 (1.32), 4.825 (1.64), 4.838 (3.28), 4.851 (1.61), 4.866 (5.45), 4.871 (5.39), 6.877 (2.63), 6.892 (2.64),

7.469 (0.73), 7.472 (0.79), 7.487 (2.06), 7.491 (2.15), 7.506 (1.81), 7.510 (1.76), 7.529 (1.21), 7.534 (1.57), 7.549 (1.84), 7.554 (2.30), 7.568 (1.12), 7.573 (1.07), 7.585 (2.69), 7.589 (2.29), 7.604 (2.10), 7.608 (2.34), 7.613 (5.05), 7.618 (1.84), 7.629 (2.19), 7.634 (6.68), 7.641 (0.99), 7.656 (2.53), 7.660 (2.52), 7.676 (1.93), 7.680 (1.77), 7.739 (1.13), 7.745 (6.69), 7.750 (2.12), 7.761 (1.86), 7.766 (4.72).

Example 79

5-(4-Chlorophenyl)-2-({1-(2-chlorophenyl)-5-[(2-methoxyethyl)amino]-1H-1,2,4-triazol-3-yl}methyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



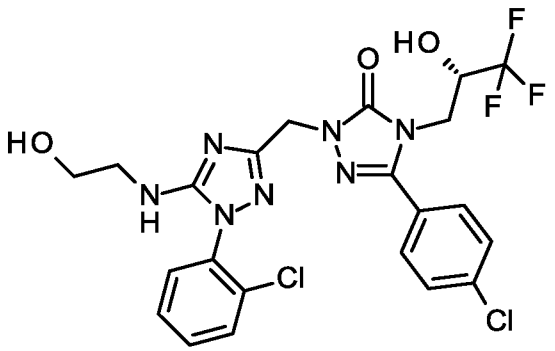
2-{[5-Bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 78.0 mg, 135 µmol) was dissolved in 2 ml of acetonitrile. 2-methoxyethanamine (113 µl, 1.30 mmol) and N,N-diisopropylethylamine (49 µl, 280 µmol) were added and the mixture was stirred under microvawe radiation at 150°C for 1 h. Additional 2-methoxyethanamine (200 µl, 2.3 mmol) was added and the mixture was stirred under microvawe radiation at 150°C for 4 h. After cooling to room temperature, the mixture was diluted with 2 ml of water and extracted twice with 10 ml ethyl acetate. The combined organic phases were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by preparative HPLC (Method 5) to afford 38.5 mg (50% of th.) of the title compound.

LC-MS (Method 2): R_t = 1.00 min; MS (ESIpos): m/z = 572 $[M+H]^+$

^{1}H-NMR (500 MHz, DMSO-d6) δ [ppm]: -0.120 (0.54), -0.007 (5.78), 0.006 (4.40), 0.117 (0.53), 1.077 (1.33), 1.091 (2.69), 1.105 (1.33), 1.236 (0.47), 2.361 (0.51), 2.635 (0.49), 3.207 (16.00), 3.323 (2.17), 3.335 (2.29), 3.346 (1.05), 3.363 (0.47), 3.377 (1.40), 3.390 (3.52), 3.402 (3.06), 3.415 (1.03), 3.814 (0.61), 3.833 (0.67), 3.843 (0.82), 3.862 (0.86), 3.972 (0.84), 3.979 (0.96), 4.002 (0.66), 4.009 (0.61), 4.292 (0.43), 4.824 (0.51), 4.856 (2.91), 4.865 (2.84), 4.897 (0.50), 6.442 (0.70), 6.454 (1.41), 6.465 (0.67), 6.875 (1.07), 6.886 (1.08), 7.482 (3.06), 7.488 (2.36), 7.509 (0.30), 7.527 (0.82), 7.534 (0.72), 7.543 (0.99), 7.549 (0.80), 7.555 (0.62), 7.561 (0.55), 7.613 (2.99), 7.630 (3.87), 7.658 (1.92), 7.675 (1.29), 7.744 (3.83), 7.761 (2.95).

Example 80

5-(4-Chlorophenyl)-2-({1-(2-chlorophenyl)-5-[(2-hydroxyethyl)amino]-1H-1,2,4-triazol-3-yl}methyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



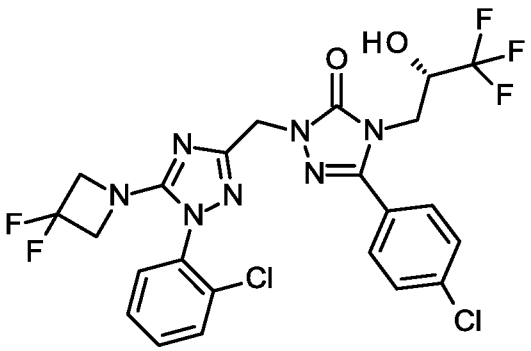
2-{[5-Bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 100 mg, 173 µmol) was dissolved in 2 ml of acetonitrile. 2-Aminoethanol (261 µl, 4.30 mmol) and N,N-diisopropylethylamine (63 µl, 360 µmol) were added and the mixture was stirred under microwave radiation at 150°C for 3 h. After cooling to room temperature, the mixture was diluted with 2 ml of water and extracted twice with 10 ml ethyl acetate. The combined organic phases were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by preparative HPLC (Method 5) to afford 52 mg (54% of th.) of the title compound.

LC-MS (Method 2): R_t = 0.91 min; MS (ESIpos): m/z = 558 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.008 (1.01), 0.008 (0.97), 3.162 (2.52), 3.175 (2.60), 3.221 (2.36), 3.237 (7.13), 3.252 (7.83), 3.267 (3.29), 3.440 (3.29), 3.455 (7.94), 3.470 (7.24), 3.486 (2.48), 3.807 (2.09), 3.830 (2.36), 3.843 (2.94), 3.867 (3.18), 3.969 (3.14), 3.978 (3.68), 4.006 (2.36), 4.015 (2.21), 4.077 (0.74), 4.090 (0.74), 4.295 (1.51), 4.643 (3.25), 4.657 (6.97), 4.671 (3.14), 4.814 (1.36), 4.854 (11.78), 4.861 (11.78), 4.900 (1.36), 6.326 (2.52), 6.341 (5.35), 6.355 (2.48), 6.887 (4.96), 7.466 (0.66), 7.469 (0.66), 7.485 (3.10), 7.489 (3.87), 7.496 (5.93), 7.501 (8.68), 7.503 (14.76), 7.510 (1.51), 7.514 (2.05), 7.524 (3.91), 7.532 (2.44), 7.539 (1.98), 7.544 (4.15), 7.547 (1.90), 7.552 (2.83), 7.558 (2.71), 7.566 (2.09), 7.605 (1.28), 7.611 (11.23), 7.616 (3.84), 7.627 (4.30), 7.632 (15.65), 7.639 (2.01), 7.658 (5.00), 7.660 (5.50), 7.677 (3.10), 7.679 (4.73), 7.740 (2.17), 7.746 (16.00), 7.752 (4.61), 7.763 (3.95), 7.768 (11.58), 7.775 (1.39).

Example 81

5-(4-Chlorophenyl)-2-{[1-(2-chlorophenyl)-5-(3,3-difluoroazetidin-1-yl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



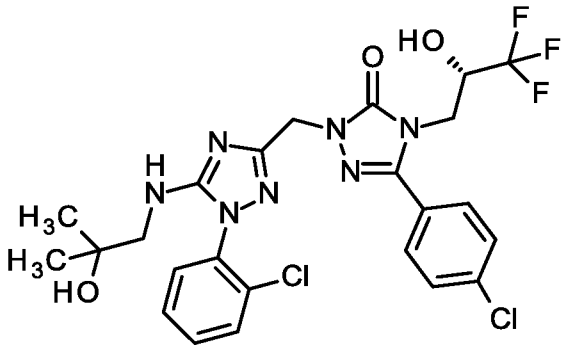
2-{[5-Bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 80.0 mg, 138 µmol) was dissolved in 2 ml of acetonitrile. 3,3-difluoroazetidine hydrochloride (1:1) (180 mg, 1.38 mmol) and N,N-diisopropylethylamine (240 µl, 1.38 mmol) were added and the mixture was stirred under microwave radiation at 120°C for 2 h. Additional 3,3-difluoroazetidine hydrochloride (1:1) (180 mg, 1.38 mmol) and N,N-diisopropylethylamine (240 µl, 1.38 mmol) were added and the mixture was stirred at 85°C for 48 h in a closed vial. After cooling to room temperature, the mixture was diluted with 5 ml of water and extracted twice with 10 ml ethyl acetate. The combined organic phases were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by chromatography (SiO2, cyclohexane/ethyl acetate gradient) to afford 34 mg (42% of th.) of the title compound.

LC-MS (Method 2): R_t = 1.09 min; MS (ESIpos): m/z = 590 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.149 (1.13), -0.008 (14.17), 0.008 (8.32), 1.744 (2.31), 1.821 (0.78), 1.853 (4.83), 1.866 (3.95), 1.872 (3.36), 3.814 (2.15), 3.838 (2.47), 3.851 (3.30), 3.875 (3.36), 3.976 (3.14), 3.985 (3.33), 4.013 (2.42), 4.021 (2.12), 4.044 (1.64), 4.137 (4.97), 4.168 (8.99), 4.198 (4.72), 4.282 (1.80), 4.886 (1.10), 4.926 (13.29), 4.930 (12.72), 4.970 (0.91), 6.875 (6.07), 6.891 (6.01), 7.501 (2.17), 7.505 (2.23), 7.520 (5.21), 7.523 (5.05), 7.539 (4.13), 7.542 (4.05), 7.573 (3.19), 7.577 (3.60), 7.592 (4.81), 7.597 (5.29), 7.615 (13.15), 7.636 (15.30), 7.661 (6.23), 7.665 (5.66), 7.680 (5.61), 7.686 (7.46), 7.690 (6.04), 7.706 (4.46), 7.710 (3.97), 7.744 (16.00), 7.749 (4.81), 7.761 (4.48), 7.765 (10.98).

Example 82

5-(4-Chlorophenyl)-2-({1-(2-chlorophenyl)-5-[(2-hydroxy-2-methylpropyl)amino]-1H-1,2,4-triazol-3-yl}methyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



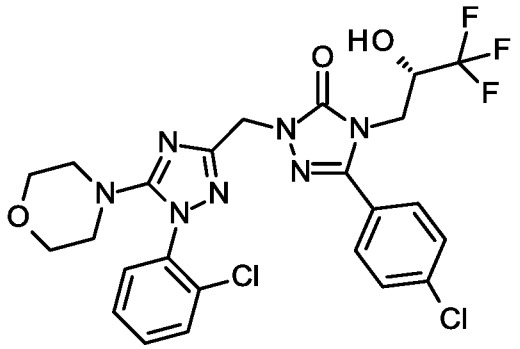
2-{[5-Bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 80.0 mg, 138 µmol) was dissolved in 2 ml of acetonitrile. 1-Amino-2-methylpropan-2-ol (123 mg, 1.38 mmol) and N,N-diisopropylethylamine (51 µl, 290 µmol) were added and the mixture was stirred under microwave radiation at 150°C for 1 h. Additional 1-amino-2-methylpropan-2-ol (123 mg, 1.38 mmol) and N,N-diisopropylethylamine (51 µl, 290 µmol) were added and the mixture was stirred under microwave radiation at 150°C for further 2 h. After cooling to room temperature, the mixture was diluted with 5 ml of water and extracted twice with 10 ml ethyl acetate. The combined organic phases were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by preparative HPLC (Method 5) to afford 48.5 mg (60% of th.) of the title compound.

LC-MS (Method 2): R_t = 1.01 min; MS (ESIpos): m/z = 586 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.008 (0.68), 0.008 (0.63), 1.049 (16.00), 1.073 (2.08), 1.091 (4.06), 1.108 (2.06), 1.125 (0.17), 1.158 (3.43), 1.908 (0.12), 2.709 (1.03), 3.168 (1.72), 3.183 (1.73), 3.357 (0.69), 3.375 (1.99), 3.392 (1.95), 3.410 (0.64), 3.803 (0.43), 3.827 (0.50), 3.840 (0.62), 3.864 (0.68), 3.965 (0.62), 3.973 (0.69), 4.002 (0.43), 4.010 (0.42), 4.287 (0.33), 4.640 (3.77), 4.813 (0.29), 4.853 (2.41), 4.860 (2.41), 4.900 (0.29), 4.980 (0.40), 6.112 (0.49), 6.127 (1.03), 6.142 (0.48), 6.880 (1.32), 6.896 (1.33), 7.486 (0.17), 7.502 (0.66), 7.506 (0.79), 7.521 (3.14), 7.537 (1.00), 7.544 (0.57), 7.556 (0.97), 7.564 (0.67), 7.571 (0.60), 7.579 (0.46), 7.611 (2.33), 7.633 (3.27), 7.680 (1.13), 7.699 (0.94), 7.739 (3.29), 7.743 (1.03), 7.755 (0.86), 7.760 (2.32).

Example 83

5-(4-Chlorophenyl)-2-{[1-(2-chlorophenyl)-5-(morpholin-4-yl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



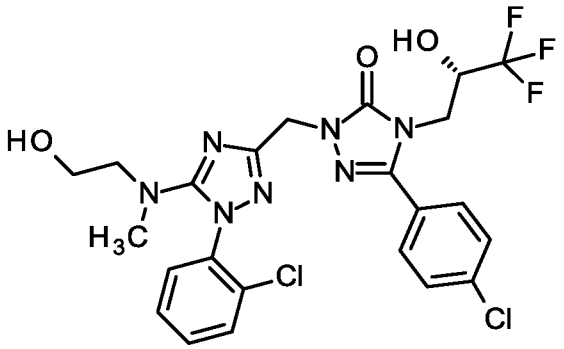
2-{[5-Bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 82.0 mg, 142 µmol) was dissolved in 2 ml of acetonitrile. Morpholine (120 µl, 1.4 mmol) and N,N-diisopropylethylamine (52 µl, 300 µmol) were added and the mixture was stirred under microwave radiation at 140°C for 1 h. Additional morpholine (120 µl, 1.4 mmol) and N,N-diisopropylethylamine (52 µl, 300 µmol) were added and the mixture was stirred under microwave radiation at 140°C for 1 h. After cooling to room temperature, the mixture was diluted with 5 ml of water and extracted twice with 10 ml ethyl acetate. The combined organic phases were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by preparative HPLC (Method 5) to afford 51 mg (62% of th.) of the title compound.

LC-MS (Method 2): R_t = 1.03 min; MS (ESIpos): m/z = 584 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.008 (2.75), 0.008 (2.48), 1.073 (7.78), 1.091 (16.00), 1.108 (8.08), 3.024 (8.34), 3.036 (10.57), 3.048 (9.21), 3.357 (2.71), 3.375 (7.92), 3.392 (7.72), 3.410 (2.55), 3.494 (9.33), 3.507 (10.42), 3.518 (8.40), 3.811 (1.50), 3.834 (1.70), 3.847 (2.16), 3.871 (2.34), 3.972 (2.28), 3.981 (2.65), 4.009 (1.66), 4.018 (1.60), 4.290 (1.03), 4.869 (1.01), 4.908 (8.69), 4.915 (8.69), 4.955 (0.99), 6.880 (2.73), 7.500 (1.09), 7.504 (1.25), 7.518 (3.43), 7.522 (3.56), 7.537 (3.43), 7.541 (3.35), 7.546 (2.51), 7.551 (3.15), 7.566 (3.21), 7.571 (3.96), 7.585 (1.78), 7.589 (1.50), 7.607 (1.07), 7.613 (8.28), 7.619 (6.81), 7.624 (4.61), 7.630 (3.56), 7.635 (12.08), 7.643 (3.54), 7.692 (4.02), 7.696 (3.58), 7.711 (3.37), 7.715 (2.99), 7.735 (1.62), 7.741 (11.66), 7.746 (3.52), 7.758 (2.95), 7.763 (8.24), 7.769 (1.09).

Example 84

5-(4-Chlorophenyl)-2-({1-(2-chlorophenyl)-5-[(2-hydroxyethyl)(methyl)amino]-1H-1,2,4-triazol-3-yl}methyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



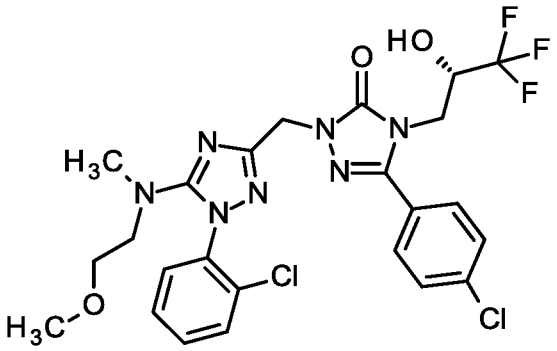
2-{[5-Bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 82.0 mg, 142 µmol) was dissolved in 2 ml of acetonitrile. 2-(Methylamino)ethanol (57 µl, 710 µmol) and N,N-diisopropylethylamine (52 µl, 300 µmol) were added and the mixture was stirred under microwave radiation at 150°C for 2 h. Additional 2-(methylamino)ethanol (57 µl, 710 µmol) and N,N-diisopropylethylamine (52 µl, 300 µmol) were added and the mixture was stirred under microwave radiation at 150°C for further 1.5 h. After cooling to room temperature, the mixture was diluted with 5 ml of water and extracted twice with 10 ml ethyl acetate. The combined organic phases were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by preparative HPLC (Method 5) to afford 50 mg (62% of th.) of the title compound.

LC-MS (Method 2): R_t = 0.97 min; MS (ESIpos): m/z = 572 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.008 (1.50), 0.008 (1.19), 1.073 (6.89), 1.091 (14.03), 1.108 (7.00), 2.366 (0.21), 2.695 (16.00), 3.162 (0.31), 3.175 (0.34), 3.199 (1.33), 3.215 (3.34), 3.230 (1.89), 3.357 (2.30), 3.375 (6.88), 3.392 (7.03), 3.410 (4.45), 3.424 (2.42), 3.440 (0.80), 3.805 (0.68), 3.828 (0.77), 3.841 (0.96), 3.865 (1.04), 3.967 (0.93), 3.976 (1.06), 4.004 (0.68), 4.012 (0.63), 4.278 (0.48), 4.638 (1.31), 4.651 (2.89), 4.664 (1.25), 4.818 (0.53), 4.858 (3.79), 4.866 (3.74), 4.906 (0.51), 6.871 (1.79), 6.886 (1.81), 7.472 (0.52), 7.476 (0.60), 7.490 (1.59), 7.495 (1.62), 7.509 (1.49), 7.513 (1.45), 7.520 (1.06), 7.525 (1.31), 7.540 (1.43), 7.545 (1.75), 7.559 (0.81), 7.563 (0.69), 7.603 (2.16), 7.608 (2.40), 7.611 (3.94), 7.616 (1.39), 7.622 (1.56), 7.627 (2.55), 7.633 (5.27), 7.650 (1.91), 7.653 (1.71), 7.669 (1.51), 7.673 (1.30), 7.741 (5.41), 7.746 (1.52), 7.758 (1.36), 7.763 (3.77).

Example 85

5-(4-Chlorophenyl)-2-({1-(2-chlorophenyl)-5-[(2-methoxyethyl)(methyl)amino]-1H-1,2,4-triazol-3-yl}methyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



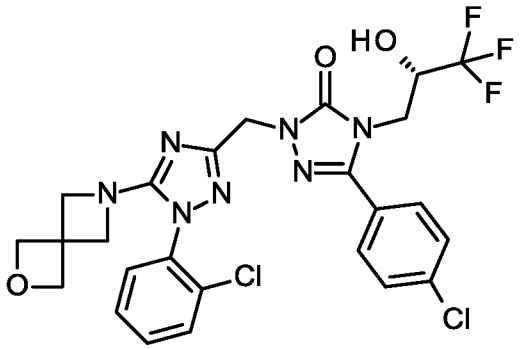
2-{[5-Bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, 82.0 mg, 142 µmol) was dissolved in 2 ml of acetonitrile. 2-Methoxy-N-methylethanamine (126 mg, 1.42 mmol) and N,N-diisopropylethylamine (52 µl, 300 µmol) were added and the mixture was stirred under microwave radiation at 150°C for 2 h. Additional 2-methoxy-N-methylethanamine (126 mg, 1.42 mmol) and N,N-diisopropylethylamine (52 µl, 300 µmol) were added and the mixture was stirred under microwave radiation at 150°C for further 2 h. After cooling to room temperature, the mixture was diluted with 5 ml of water and extracted twice with 10 ml ethyl acetate. The combined organic phases were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by preparative HPLC (Method 5) to afford 60 mg (72% of th.) of the title compound.

LC-MS (Method 2): R_t = 1.07 min; MS (ESIpos): m/z = 586 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.008 (0.59), 1.073 (3.51), 1.091 (7.17), 1.108 (3.63), 2.366 (0.16), 2.681 (13.35), 2.710 (0.20), 3.148 (16.00), 3.162 (1.82), 3.175 (1.82), 3.331 (4.20), 3.340 (3.00), 3.357 (1.51), 3.375 (3.55), 3.392 (3.51), 3.410 (1.16), 3.807 (0.61), 3.830 (0.70), 3.843 (0.92), 3.867 (0.96), 3.968 (0.87), 3.976 (0.98), 4.004 (0.62), 4.013 (0.60), 4.063 (0.12), 4.076 (0.33), 4.089 (0.33), 4.278 (0.51), 4.825 (0.49), 4.864 (3.33), 4.874 (3.29), 4.913 (0.48), 5.119 (0.73), 6.868 (1.86), 6.884 (1.86), 6.897 (0.26), 6.913 (0.23), 7.482 (0.44), 7.498 (1.25), 7.501 (1.27), 7.516 (1.17), 7.520 (1.16), 7.527 (0.83), 7.532 (1.00), 7.546 (1.18), 7.551 (1.37), 7.565 (0.62), 7.570 (0.59), 7.612 (4.31), 7.628 (2.21), 7.633 (4.73), 7.639 (1.03), 7.656 (1.55), 7.660 (1.45), 7.676 (1.23), 7.680 (1.15), 7.738 (4.57), 7.754 (1.62), 7.759 (3.30), 7.774 (0.64), 7.794 (0.13).

Example 86

5-(4-Chlorophenyl)-2-{[1-(2-chlorophenyl)-5-(2-oxa-6-azaspiro[3.3]hept-6-yl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



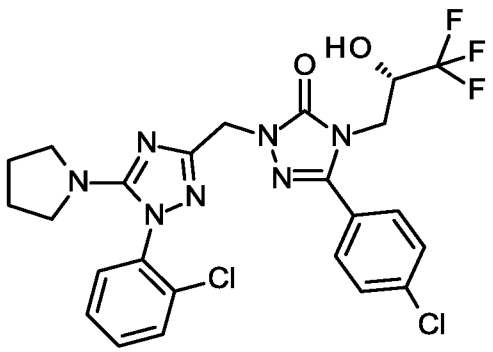
2-{[5-Bromo-1-(2-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 5A, intermediate 17, 82.0 mg, 142 µmol) was dissolved in 2 ml of acetonitrile. 2-Oxa-6-azaspiro[3.3]heptane ethanedioate (1:1) (131 mg, 692 µmol) and N,N-diisopropylethylamine (240 µl, 1.4 mmol) were added and the mixture was stirred at 80°C for 5 d in a closed vial. Additional 2-oxa-6-azaspiro[3.3]heptane ethanedioate (1:1) (131 mg, 692 µmol) and N,N-diisopropylethylamine (240 µl, 1.4 mmol) were added and the mixture was stirred at 80°C for further 2 d. After cooling to room temperature, the mixture was diluted with 5 ml of water and extracted twice with 10 ml ethyl acetate. The combined organic phases were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by preparative HPLC (Method 5) to afford 11 mg (13% of th.) of the title compound.

LC-MS (Method 2): R_t = 0.99 min; MS (ESIpos): m/z = 596 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.008 (1.01), 0.008 (0.91), 1.073 (1.92), 1.091 (3.85), 1.109 (1.82), 2.328 (0.61), 2.366 (0.81), 2.665 (0.51), 2.670 (0.61), 2.675 (0.51), 2.710 (0.81), 3.357 (1.11), 3.375 (2.03), 3.392 (1.92), 3.410 (0.71), 3.811 (0.81), 3.834 (0.91), 3.847 (1.32), 3.871 (10.43), 3.973 (1.11), 3.981 (1.11), 4.010 (0.71), 4.280 (0.61), 4.558 (16.00), 4.869 (4.56), 4.874 (4.56), 6.876 (2.23), 6.892 (2.23), 7.486 (0.61), 7.490 (0.61), 7.505 (1.92), 7.510 (1.01), 7.523 (1.62), 7.527 (1.62), 7.555 (0.71), 7.560 (1.72), 7.570 (2.13), 7.574 (3.75), 7.577 (3.04), 7.590 (1.32), 7.594 (2.73), 7.599 (0.81), 7.607 (0.61), 7.614 (4.15), 7.618 (1.42), 7.630 (1.82), 7.635 (5.87), 7.641 (0.81), 7.669 (1.72), 7.673 (2.23), 7.683 (0.51), 7.693 (1.62), 7.734 (0.81), 7.739 (5.87), 7.745 (1.62), 7.756 (1.42), 7.761 (4.05), 7.768 (0.51).

Example 87

5-(4-Chlorophenyl)-2-{[1-(2-chlorophenyl)-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



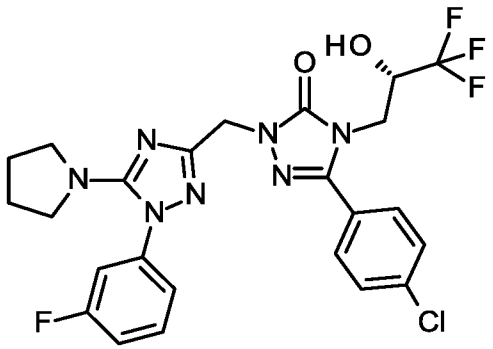
To a solution of 5-(4-chlorophenyl)-2-{[5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2*S*)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (example 9A, 100 mg, 0.22 mmol) in pyridine (2.8 ml) were added (2-chlorophenyl)boronic acid (68.3 mg, 0.44 mmol) and copper(II) acetate (79.3 mg, 0.44 mmol). The reaction mixture was stirred at room temperature for 3 days, after which extra boronic acid (34.2 mg, 0.22 mmol) was added due to incomplete conversion. After stirring for five additional days, the reaction mixture was diluted with MTBE and then quenched with aqueous hydrochloric acid (0.5 M). After phase separation, the aqueous phase was extracted twice with MTBE. The combined organic phases were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by preparative HPLC (Method 13), affording 3.05 mg (4.8 µmol, 90% purity, 2.2% of th.) of the title compound.

LC-MS (Method 3): R_t = 1.38 min; MS [ESIpos]: m/z = 568 $(M+H)^+$

^{1}H-NMR (500 MHz, DMSO-d_6) δ [ppm]: 7.73 - 7.78 (m, 2 H), 7.60 - 7.66 (m, 4 H), 7.55 (td, 1 H), 7.48 (m, 1 H), 6.85 - 6.91 (m, 1 H), 4.82 - 4.90 (m, 2 H), 4.25 - 4.33 (m, 1 H), 3.99 (dd, 1 H), 3.84 (dd, 1 H), 3.00 - 3.12 (m, 4 H), 1.71 - 1.78 (m, 4 H)

Example 88

5-(4-Chlorophenyl)-2-{[1-(3-fluorophenyl)-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2*S*)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



To a solution of 5-(4-chlorophenyl)-2-{[5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2*S*)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 9A, 100 mg, 0.22 mmol) in pyridine (2.8 ml) were added (3-fluorophenyl)boronic acid (61.1 mg, 0.44 mmol) and

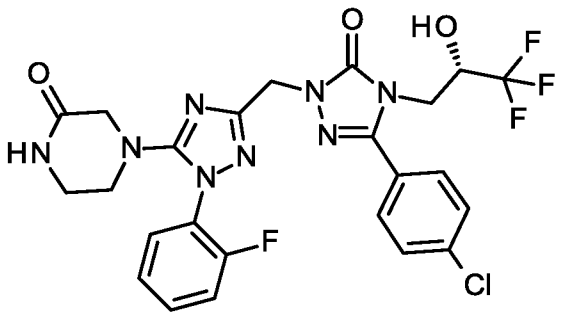
copper(II) acetate (79.3 mg, 0.44 mmol). The reaction mixture was stirred at room temperature for 4 days. The reaction mixture was then diluted with MTBE and quenched with aqueous hydrochloric acid (0.5 M). After phase separation, the aqueous phase was extracted twice with MTBE. The combined organic phases were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by preparative HPLC (Method 13), affording 3.9 mg (0.01 mmol, 3.0% of th.) of the title compound.

LC-MS (Method 4): R_t = 3.49 min; MS [ESIpos]: m/z = 552 $(M+H)^+$

^{1}H-NMR (500 MHz, DMSO-d6) δ [ppm]: 7.73 - 7.77 (m, 2 H), 7.60 - 7.64 (m, 2 H), 7.54 (td, 1 H), 7.36 (dt, 1 H), 7.26 - 7.33 (m, 2 H), 6.87 (br. s., 1 H), 4.83 - 4.91 (m, 2 H), 4.29 (br. s., 1 H), 3.99 (dd, 1 H), 3.84 (dd, 1 H), 3.11 - 3.17 (m, 4 H), 1.75 - 1.81 (m, 4 H)

Example 89

4-[3-({3-(4-Chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1-(2-fluorophenyl)-1H-1,2,4-triazol-5-yl]piperazin-2-one



2-{[5-bromo-1-(2-fluorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 14A, 80.0 mg, 85% purity, 121 µmol), piperazin-2-one (121 mg, 1.21 mmol), N,N-diisopropylethylamine (44 µl, 250 µmol) were dissolved in acetonitrile (1.0 ml) and stirred for 5 h at 180°C in a sealed vial under microwave irradiation, followed by 5 h at 180°C. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 60.5 mg (86% of th.) of the title compound.

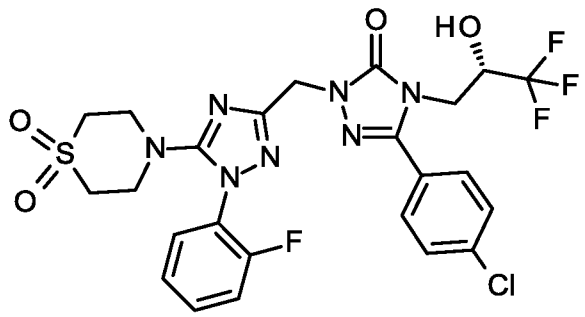
LC-MS (Method 12): R_t = 1.59 min; MS (ESIpos): m/z = 581 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.008 (1.80), 3.109 (1.98), 3.121 (3.47), 3.127 (4.06), 3.135 (3.03), 3.142 (2.28), 3.263 (4.34), 3.277 (5.26), 3.289 (4.25), 3.622 (16.00), 3.807 (1.39), 3.830 (1.60), 3.843 (1.94), 3.867 (2.05), 3.973 (2.02), 3.982 (2.16), 4.010 (1.41), 4.018 (1.28), 4.283 (1.13), 4.300 (1.03), 4.927 (11.53), 6.877 (3.84), 6.893 (3.77), 7.370 (1.40), 7.373 (1.38), 7.389 (3.00), 7.392 (2.91), 7.408 (1.80), 7.411 (1.73), 7.470 (1.27), 7.473 (1.25), 7.491 (2.04), 7.495 (2.33), 7.499 (1.39), 7.517 (1.79), 7.520 (1.56), 7.579 (1.08), 7.583 (1.29), 7.592 (1.42), 7.596 (2.04), 7.604 (2.51), 7.611 (8.08), 7.616 (3.94), 7.623 (3.31), 7.628 (4.77), 7.632 (9.80),

7.639 (2.08), 7.643 (3.16), 7.647 (2.35), 7.662 (1.38), 7.667 (1.05), 7.738 (1.99), 7.744 (9.65), 7.750 (2.80), 7.761 (2.82), 7.766 (6.78), 8.017 (2.75).

Example 90

5-(4-Chlorophenyl)-2-{[5-(1,1-dioxidothiomorpholin-4-yl)-1-(2-fluorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



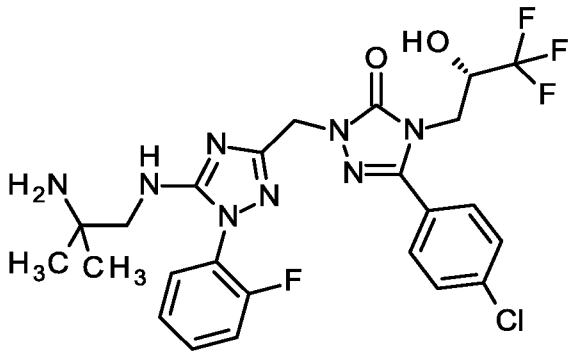
2-{[5-Bromo-1-(2-fluorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 14A, 80.0 mg, 85% purity, 121 µmol), thiomorpholine 1,1-dioxide (164 mg, 1.21 mmol), N,N-diisopropylethylamine (44 µl, 250 µmol) were dissolved in acetonitrile (1.0 ml) and stirred for 5 h at 180°C in a sealed vial under microwave irradiation, followed by 2 h at 180°C. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 69.5 mg (93% of th.) of the title compound.

LC-MS (Method 12): R_t = 1.74 min; MS (ESIpos): m/z = 616 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.008 (2.11), 0.008 (1.90), 3.133 (7.24), 3.145 (9.33), 3.159 (8.05), 3.289 (1.61), 3.535 (8.10), 3.549 (8.79), 3.562 (7.11), 3.810 (1.94), 3.833 (2.16), 3.846 (2.78), 3.870 (2.95), 3.973 (2.75), 3.982 (3.09), 4.009 (1.94), 4.019 (1.81), 4.276 (1.49), 4.294 (1.40), 4.905 (0.92), 4.945 (11.78), 4.949 (11.90), 4.989 (0.85), 6.866 (5.75), 6.881 (5.81), 7.375 (1.88), 7.378 (2.05), 7.397 (4.26), 7.413 (2.42), 7.417 (2.52), 7.479 (1.68), 7.482 (1.86), 7.500 (2.84), 7.504 (3.53), 7.508 (2.12), 7.525 (2.71), 7.529 (2.54), 7.575 (1.37), 7.580 (1.58), 7.588 (1.65), 7.593 (2.40), 7.610 (12.41), 7.614 (5.56), 7.619 (1.85), 7.626 (5.01), 7.631 (15.14), 7.637 (2.14), 7.698 (2.16), 7.702 (2.19), 7.717 (4.10), 7.721 (4.08), 7.732 (2.73), 7.738 (16.00), 7.743 (5.14), 7.755 (3.69), 7.760 (10.18), 7.766 (1.35).

Example 91

2-({5-[(2-Amino-2-methylpropyl)amino]-1-(2-fluorophenyl)-1H-1,2,4-triazol-3-yl}methyl)-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



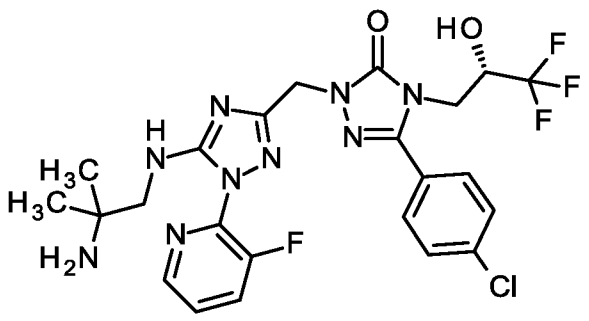
2-{[5-Bromo-1-(2-fluorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 14A, 80.0 mg, 85% purity, 121 µmol), 2-methylpropane-1,2-diamine (107 mg, 1.21 mmol), N,N-diisopropylethylamine (44 µl, 250 µmol) were dissolved in acetonitrile (690 µl) and stirred for 5 h at 180°C in a sealed vial under microwave irradiation, followed by 5 h at 180°C. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 56.9 mg (78% of th.) of the title compound.

LC-MS (Method 10): R_t = 0.93 min; MS (ESIneg): m/z = 567 $[M-H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.008 (1.19), 0.008 (0.68), 1.089 (16.00), 3.260 (2.29), 3.274 (2.22), 3.799 (0.73), 3.823 (0.84), 3.836 (0.98), 3.860 (1.06), 3.963 (1.09), 3.972 (1.24), 3.999 (0.82), 4.008 (0.75), 4.867 (5.30), 6.795 (0.76), 7.332 (0.63), 7.336 (0.71), 7.351 (1.37), 7.355 (1.41), 7.370 (0.91), 7.374 (0.97), 7.427 (0.67), 7.449 (1.19), 7.454 (0.72), 7.472 (0.87), 7.475 (0.88), 7.523 (1.69), 7.537 (1.02), 7.542 (2.61), 7.546 (1.74), 7.556 (1.03), 7.561 (1.24), 7.566 (0.91), 7.609 (3.76), 7.614 (1.39), 7.625 (1.54), 7.631 (5.13), 7.637 (0.78), 7.740 (0.67), 7.746 (4.92), 7.751 (1.59), 7.763 (1.34), 7.768 (3.66).

Example 92

2-({5-[(2-Amino-2-methylpropyl)amino]-1-(3-fluoropyridin-2-yl)-1H-1,2,4-triazol-3-yl}methyl)-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



2-{[5-Bromo-1-(3-fluoropyridin-2-yl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 23A, 60.0 mg, 107

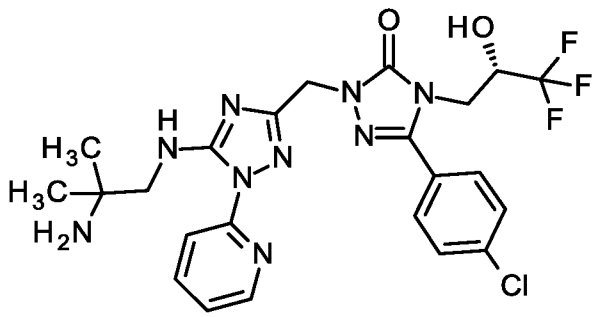
µmol), 2-methylpropane-1,2-diamine (110 µl, 1.1 mmol), N,N-diisopropylethylamine (39 µl, 220 µmol) were dissolved in acetonitrile (1.0 ml) and stirred for 5 h at 180°C in a sealed vial under microwave irradiation, followed by 1 h at 180°C. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 26.4 mg (43% of th.) of the title compound.

LC-MS (Method 3): R_t = 1.16 min; MS (ESIpos): m/z = 570 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.109 (16.00), 3.357 (2.14), 3.372 (2.08), 3.805 (0.59), 3.829 (0.66), 3.842 (0.83), 3.866 (0.88), 3.969 (0.91), 3.977 (1.03), 4.005 (0.66), 4.014 (0.63), 4.891 (5.31), 7.523 (0.65), 7.525 (0.71), 7.535 (1.14), 7.544 (0.75), 7.546 (0.85), 7.555 (0.65), 7.605 (2.81), 7.610 (1.36), 7.621 (1.57), 7.627 (4.42), 7.739 (4.12), 7.745 (1.44), 7.756 (1.18), 7.761 (3.12), 7.982 (0.70), 8.006 (0.81), 8.009 (0.77), 8.030 (0.66), 8.366 (1.44), 8.378 (1.45).

Example 93

2-({5-[(2-Amino-2-methylpropyl)amino]-1-(pyridin-2-yl)-1H-1,2,4-triazol-3-yl}methyl)-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



2-{[5-Bromo-1-(pyridin-2-yl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 32A, 60.0 mg, 93% purity, 102 µmol), 2-methylpropane-1,2-diamine (110 µl, 1.0 mmol), N,N-diisopropylethylamine (37 µl, 210 µmol) were dissolved in acetonitrile (1.0 ml) and stirred for 5 h at 180°C in a sealed vial under microwave irradiation, followed by 1 h at 180°C. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 57.0 mg (99% of th.) of the title compound.

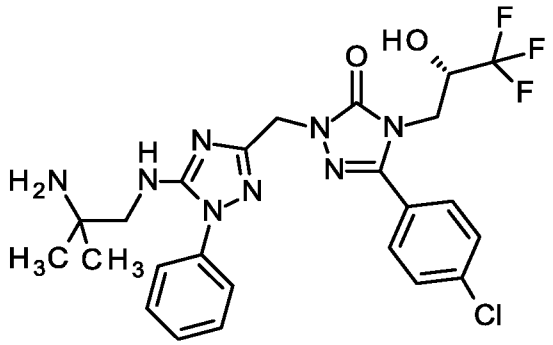
LC-MS (Method 3): R_t = 1.25 min; MS (ESIpos): m/z = 552 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.260 (1.01), 1.276 (16.00), 1.477 (1.07), 3.626 (2.77), 3.642 (2.72), 3.836 (0.70), 3.859 (0.89), 3.872 (1.11), 3.895 (1.10), 3.995 (1.14), 4.004 (1.33), 4.032 (0.83), 4.041 (0.80), 4.310 (0.70), 4.883 (0.93), 4.923 (4.05), 4.931 (3.96), 4.970 (0.63), 7.324 (1.00), 7.326 (1.00), 7.336 (1.10), 7.338 (1.23), 7.342 (1.23), 7.344 (1.08), 7.355 (1.11), 7.357 (1.04), 7.612 (3.55), 7.617 (1.46), 7.628 (1.85), 7.633 (4.85), 7.639 (0.90), 7.705 (1.89), 7.726 (2.18), 7.739 (0.99), 7.745 (5.00), 7.750 (1.71), 7.762 (1.74), 7.767 (3.60), 7.997 (0.92),

8.001 (0.92), 8.015 (1.26), 8.017 (1.41), 8.019 (1.41), 8.036 (0.81), 8.041 (0.79), 8.133 (2.19), 8.473 (1.32), 8.475 (1.46), 8.478 (1.47), 8.486 (1.39), 8.487 (1.49), 8.490 (1.38), 8.530 (0.76), 8.546 (1.60), 8.563 (0.79).

Example 94

2-({5-[(2-Amino-2-methylpropyl)amino]-1-phenyl-1H-1,2,4-triazol-3-yl}methyl)-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



2-[(5-Bromo-1-phenyl-1H-1,2,4-triazol-3-yl)methyl]-4-[(2S)-2-{[tert-butyl(dimethyl)silyl]oxy}-3,3,3-trifluoropropyl]-5-(4-chlorophenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 27A; 80.0 mg, 103 µmol), 2-methylpropane-1,2-diamine (91.1 mg, 1.03 mmol) and N,N-diisopropylethylamine (38 µl, 220 µmol) were dissolved in acetonitrile (590 µl) and stirred for 5 h at 160°C in a sealed vial under microwave irradiation, followed by 4 h at 190°C. The reaction mixture was evaporated and the residue was purified by preparative HPLC (Method 5).

The residue was retaken in tetrahydrofuran (1.0 ml), treated with a solution of tetra-n-butylammonium fluoride in tetrahydrofuran (110 µl, 1.0 M, 110 µmol) and stirred for 1 h at room temperature. The reaction mixture was purified by preparative HPLC (Method 5) followed by flash chromatography (silica gel, dichloromethane/methanol, 8/2) affording 55.6 mg (89% of th.) of the title compound.

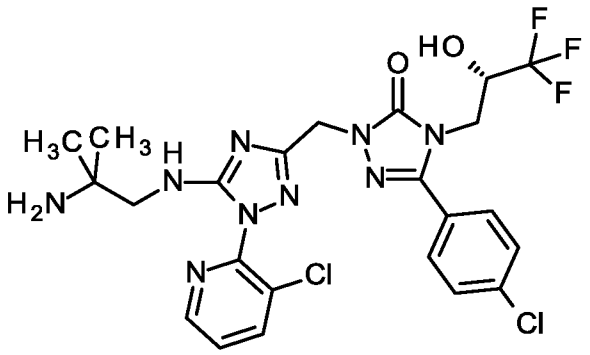
LC-MS (Method 3): R_t = 0.92 min; MS (ESIpos): m/z = 551 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.918 (1.34), 0.936 (3.26), 0.955 (1.62), 1.088 (16.00), 1.225 (0.74), 1.301 (0.80), 1.319 (0.78), 1.337 (0.91), 3.141 (0.68), 3.163 (0.65), 3.184 (0.74), 3.329 (0.73), 3.800 (0.70), 3.823 (0.79), 3.836 (0.99), 3.860 (1.07), 3.966 (1.08), 3.975 (1.26), 4.002 (0.81), 4.011 (0.75), 4.309 (0.64), 4.873 (5.53), 7.390 (0.67), 7.396 (1.10), 7.406 (0.60), 7.412 (0.94), 7.509 (0.91), 7.525 (0.99), 7.530 (3.44), 7.543 (5.52), 7.547 (8.74), 7.564 (0.99), 7.606 (3.56), 7.610 (1.22), 7.622 (1.57), 7.627 (4.69), 7.741 (0.83), 7.747 (5.39), 7.752 (1.60), 7.764 (1.44), 7.768 (3.90).

Example 95

2-({5-[(2-Amino-2-methylpropyl)amino]-1-(3-chloropyridin-2-yl)-1H-1,2,4-triazol-3-yl}methyl)-

5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



2-{[5-Bromo-1-(3-chloropyridin-2-yl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-2-{[tert-butyl(dimethyl)silyl]oxy}-3,3,3-trifluoropropyl]-5-(4-chlorophenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 18A, 73.0 mg, 105 µmol), 2-methylpropane-1,2-diamine (110 µl, 1.1 mmol) and N,N-diisopropylethylamine (55 µl, 320 µmol) were dissolved in acetonitrile (1.5 ml) and stirred for 8 h at 180°C in a sealed vial under microwave irradiation, followed by 10 h at 160°C.

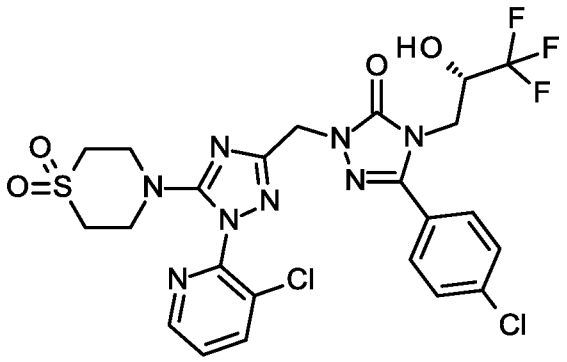
The reaction mixture was cooled to room temperature, a solution of tetra-n-butylammonium fluoride in tetrahydrofuran (160 µl, 1.0 M, 160 µmol) was added and stirred for 1 h at room temperature. The reaction mixture was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded the crude product, which was dissolved in ethyl acetate and washed with sat. aqueous sodium bicarbonate solution. The combined organic solutions were dried over magnesium sulfate and concentrated in vacuo to afford 20.8 mg (34% of th.) of the title compound.

LC-MS (Method 3): R_t = 1.17 min; MS (ESIpos): m/z = 586 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.008 (1.09), 0.008 (0.73), 1.015 (16.00), 1.157 (1.46), 1.175 (2.80), 1.193 (1.54), 1.236 (2.18), 1.988 (4.60), 3.189 (2.24), 3.203 (2.18), 3.800 (0.69), 3.824 (0.79), 3.837 (0.98), 3.861 (1.03), 3.966 (1.10), 3.975 (1.27), 4.003 (1.23), 4.011 (0.82), 4.021 (1.25), 4.039 (1.18), 4.876 (5.85), 6.870 (0.87), 7.565 (1.54), 7.577 (1.59), 7.585 (1.65), 7.597 (1.84), 7.607 (3.45), 7.612 (1.37), 7.624 (1.64), 7.628 (4.64), 7.635 (0.79), 7.734 (0.92), 7.741 (4.54), 7.746 (1.56), 7.757 (1.40), 7.762 (3.27), 8.198 (1.62), 8.202 (1.66), 8.218 (1.59), 8.222 (1.52), 8.532 (1.67), 8.536 (1.66), 8.544 (1.66), 8.548 (1.53).

Example 96

5-(4-Chlorophenyl)-2-{[1-(3-chloropyridin-2-yl)-5-(1,1-dioxidothiomorpholin-4-yl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



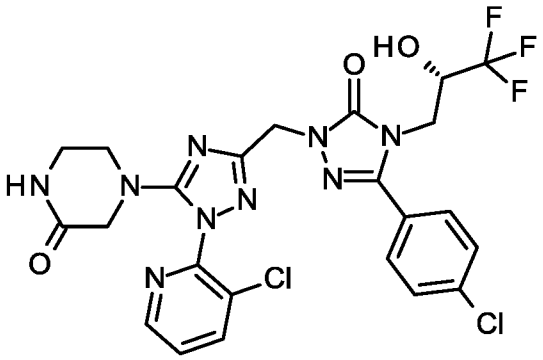
2-{[5-Bromo-1-(3-chloropyridin-2-yl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-2-{[tert-butyl(dimethyl)silyl]oxy}-3,3,3-trifluoropropyl]-5-(4-chlorophenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 18A, 75.0 mg, 108 µmol), thiomorpholine 1,1-dioxide (146 mg, 1.08 mmol) and N,N-diisopropylethylamine (57 µl, 320 µmol) were dissolved in acetonitrile (1.5 ml) and stirred for 8 h at 180°C in a sealed vial under microwave irradiation. The reaction mixture was cooled to room temperature, treated with a solution of tetra-n-butylammonium fluoride in tetrahydrofuran (130 µl, 1.0 M, 130 µmol) and stirred for 1 h at room temperature. The reaction mixture was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 61.0 mg (88% of th.) of the title compound.

LC-MS (Method 10): R_t = 1.18 min; MS (ESIpos): m/z = 633 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.008 (1.91), 3.114 (9.54), 3.126 (12.43), 3.140 (10.56), 3.288 (2.34), 3.540 (10.67), 3.553 (11.82), 3.566 (9.45), 3.808 (2.25), 3.832 (2.58), 3.844 (3.26), 3.868 (3.55), 3.970 (3.35), 3.978 (3.75), 4.006 (2.35), 4.015 (2.25), 4.277 (1.89), 4.294 (1.80), 4.906 (1.54), 4.946 (12.54), 4.954 (12.42), 4.994 (1.54), 6.869 (6.92), 6.885 (6.96), 7.602 (1.72), 7.608 (11.39), 7.613 (4.30), 7.625 (5.36), 7.630 (15.64), 7.636 (2.39), 7.686 (4.93), 7.698 (5.10), 7.707 (5.23), 7.718 (5.52), 7.730 (2.87), 7.736 (16.00), 7.742 (5.09), 7.753 (4.78), 7.758 (11.36), 7.764 (1.65), 8.292 (5.57), 8.296 (5.71), 8.312 (5.30), 8.316 (5.14), 8.600 (5.77), 8.604 (5.72), 8.612 (5.77), 8.616 (5.26).

Example 97

4-[3-({3-(4-Chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1-(3-chloropyridin-2-yl)-1H-1,2,4-triazol-5-yl]piperazin-2-one



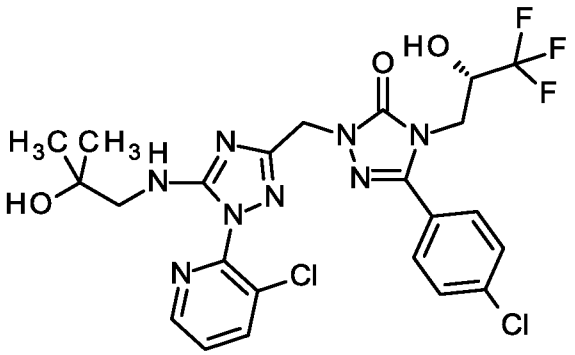
2-{[5-Bromo-1-(3-chloropyridin-2-yl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-2-{[tert-butyl(dimethyl)silyl]oxy}-3,3,3-trifluoropropyl]-5-(4-chlorophenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 18A, 75.0 mg, 108 µmol), piperazin-2-one (108 mg, 1.08 mmol) and N,N-diisopropylethylamine (57 µl, 320 µmol) were dissolved in acetonitrile (1.5 ml) and stirred for 8 h at 180°C in a sealed vial under microwave irradiation. The reaction mixture was cooled to room temperature, treated with a solution of tetra-n-butylammonium fluoride in tetrahydrofuran (130 µl, 1.0 M, 130 µmol) and stirred for 1 h at room temperature. The reaction mixture was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 52.3 mg (80% of th.) of the title compound.

LC-MS (Method 10): R_t = 1.09 min; MS (ESIpos): m/z = 598 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.008 (1.74), 0.008 (1.04), 3.122 (1.87), 3.134 (3.30), 3.140 (3.95), 3.148 (3.05), 3.155 (2.23), 3.263 (4.53), 3.278 (5.43), 3.290 (4.99), 3.586 (16.00), 3.806 (1.31), 3.829 (1.54), 3.842 (1.84), 3.866 (1.95), 3.971 (1.90), 3.979 (2.07), 4.008 (1.33), 4.017 (1.18), 4.283 (1.10), 4.300 (0.99), 4.886 (0.73), 4.926 (8.04), 4.931 (7.69), 4.970 (0.57), 6.880 (3.89), 6.896 (3.83), 7.603 (1.28), 7.609 (6.84), 7.614 (2.43), 7.625 (3.11), 7.631 (9.10), 7.637 (1.21), 7.682 (3.05), 7.694 (3.14), 7.702 (3.19), 7.714 (3.32), 7.735 (1.88), 7.742 (9.40), 7.747 (2.80), 7.758 (2.65), 7.763 (6.55), 8.055 (2.64), 8.284 (3.27), 8.288 (3.33), 8.304 (3.07), 8.308 (2.87), 8.593 (3.41), 8.597 (3.36), 8.604 (3.27), 8.608 (2.96).

Example 98

5-(4-Chlorophenyl)-2-({1-(3-chloropyridin-2-yl)-5-[(2-hydroxy-2-methylpropyl)amino]-1H-1,2,4-triazol-3-yl}methyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



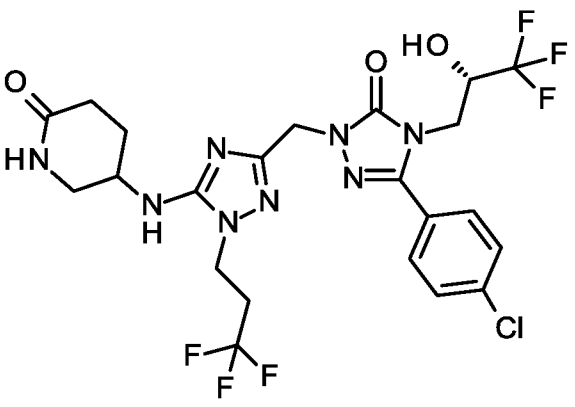
2-{[5-Bromo-1-(3-chloropyridin-2-yl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-2-{[tert-butyl(dimethyl)silyl]oxy}-3,3,3-trifluoropropyl]-5-(4-chlorophenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 18A, 73.0 mg, 105 µmol), 1-amino-2-methylpropan-2-ol and N,N-diisopropylethylamine (55 µl, 320 µmol) were dissolved in acetonitrile (1.5 ml) and stirred for 8 h at 180°C in a sealed vial under microwave irradiation. The reaction mixture was cooled to room temperature, treated with a solution of in tetra-n-butylammonium fluoride in tetrahydrofuran (160 µl, 1.0 M, 160 µmol) and stirred for 1 h at room temperature. The reaction mixture was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 51.2 mg (83% of th.) of the title compound.

LC-MS (Method 3): R_t = 1.75 min; MS (ESIpos): m/z = 597 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.074 (16.00), 3.225 (2.19), 3.239 (2.16), 3.843 (0.64), 3.866 (0.69), 3.975 (0.74), 4.620 (3.08), 4.867 (2.35), 4.876 (2.32), 6.737 (1.06), 6.883 (1.29), 6.899 (1.30), 7.550 (0.91), 7.562 (0.93), 7.570 (0.95), 7.582 (0.99), 7.608 (2.10), 7.613 (0.80), 7.625 (0.96), 7.629 (2.96), 7.734 (2.98), 7.739 (1.06), 7.750 (0.83), 7.755 (2.16), 8.194 (0.90), 8.198 (0.94), 8.214 (0.87), 8.218 (0.87), 8.523 (0.94), 8.527 (0.98), 8.535 (0.97), 8.538 (0.93).

Example 99

5-{[3-({3-(4-Chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1-(3,3,3-trifluoropropyl)-1H-1,2,4-triazol-5-yl]amino}piperidin-2-one (*diastereomeric mixture*)



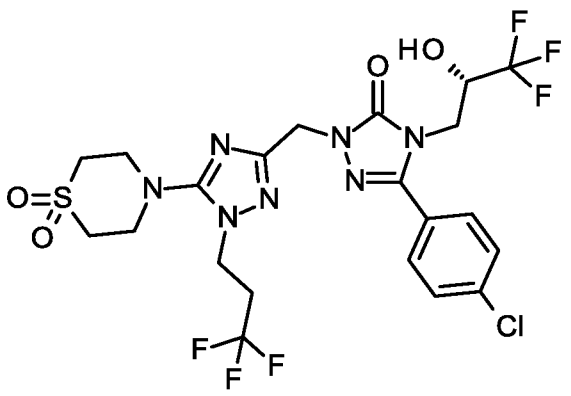
2-{[5-Bromo-1-(3,3,3-trifluoropropyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 38A, 100 mg, 177 µmol), (5R)-5-aminopiperidin-2-one (203 mg, 1.77 mmol), N,N-diisopropylethylamine (93 µl, 530 µmol) were dissolved in acetonitrile (3.0 ml) and stirred for 8 h at 170°C in a sealed vial under microwave irradiation, followed by 5 h at 180°C. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 66.4 mg (56% of th.) of the title compound as a mixture of diastereomers.

LC-MS (Method 10): R_t = 1.11 min; MS (ESIpos): m/z = 597 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.008 (1.47), 1.665 (0.69), 1.680 (1.46), 1.695 (1.47), 1.709 (2.26), 1.718 (1.72), 1.731 (0.94), 2.035 (1.28), 2.057 (3.09), 2.065 (3.27), 2.086 (3.62), 2.097 (3.36), 2.105 (4.39), 2.119 (1.80), 2.137 (1.86), 2.154 (2.45), 2.178 (1.14), 2.192 (0.69), 2.220 (0.79), 2.240 (1.03), 2.265 (1.37), 2.280 (0.73), 2.654 (1.13), 2.671 (1.98), 2.682 (3.12), 2.700 (3.92), 2.710 (3.50), 2.719 (2.76), 2.728 (3.58), 2.746 (1.95), 2.756 (1.20), 3.057 (0.69), 3.189 (4.29), 3.204 (7.46), 3.219 (4.10), 3.681 (1.91), 3.696 (2.41), 3.711 (1.64), 3.801 (2.31), 3.824 (3.04), 3.837 (3.69), 3.861 (3.58), 3.960 (3.47), 3.969 (3.66), 3.996 (2.32), 4.005 (2.22), 4.082 (4.46), 4.100 (6.99), 4.119 (5.34), 4.137 (2.85), 4.155 (1.61), 4.275 (2.13), 4.713 (1.57), 4.752 (7.73), 4.764 (7.53), 4.778 (2.48), 4.787 (1.72), 4.806 (1.18), 6.608 (1.50), 6.625 (1.42), 6.703 (2.05), 6.718 (3.85), 6.732 (1.81), 6.864 (5.76), 6.880 (5.56), 7.388 (1.50), 7.605 (9.91), 7.626 (14.18), 7.696 (6.32), 7.717 (16.00), 7.734 (5.12), 7.739 (10.69).

Example 100

5-(4-Chlorophenyl)-2-{[5-(1,1-dioxidothiomorpholin-4-yl)-1-(3,3,3-trifluoropropyl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



2-{[5-Bromo-1-(3,3,3-trifluoropropyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 38A, 70.0 mg, 124 µmol), thiomorpholine 1,1-dioxide (168 mg, 1.24 mmol), N,N-diisopropylethylamine (65 µl, 370 µmol) were dissolved in acetonitrile (3.0 ml) and stirred for 5 h at 180°C in a sealed vial under microwave irradiation, followed by 15 h at 180°C. The crude product was purified by preparative

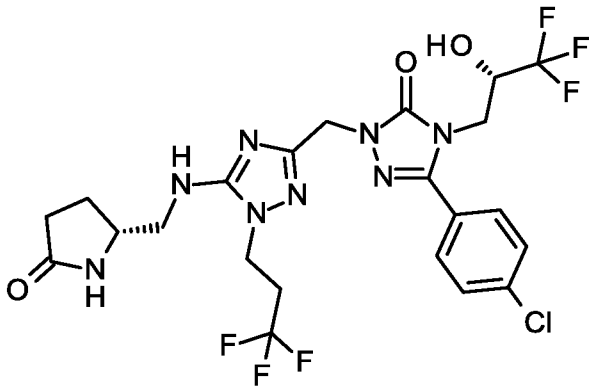
HPLC (Method 5 followed by Method 11). Lyophilisation of the product containing fractions afforded 33.0 mg (41% of th.) of the title compound.

LC-MS (Method 10): R_t = 1.22 min; MS (ESIpos): m/z = 618 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 2.847 (0.97), 2.875 (0.93), 3.275 (1.74), 3.287 (2.81), 3.301 (2.33), 3.311 (16.00), 3.514 (2.16), 3.522 (2.10), 3.528 (2.20), 3.541 (1.73), 3.870 (0.76), 4.212 (1.36), 4.229 (2.45), 4.247 (1.41), 4.891 (2.53), 4.905 (2.53), 6.861 (1.41), 6.877 (1.43), 7.607 (2.62), 7.612 (0.87), 7.624 (1.26), 7.629 (3.81), 7.718 (3.94), 7.723 (1.08), 7.734 (0.97), 7.739 (2.55).

Example 101

5-(4-Chlorophenyl)-2-{[5-({[(2R)-5-oxopyrrolidin-2-yl]methyl}amino)-1-(3,3,3-trifluoropropyl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



2-{[5-Bromo-1-(3,3,3-trifluoropropyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (60.0 mg, 106 µmol), (5R)-5-(aminomethyl)pyrrolidin-2-one (Example 38A, 122 mg, 1.06 mmol), N,N-diisopropylethylamine (56 µl, 320 µmol) were dissolved in acetonitrile (3.0 ml) and stirred for 10 h at 170°C in a sealed vial under microwave irradiation, followed by 5 h at 180°C. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 39.0 mg (58% of th.) of the title compound.

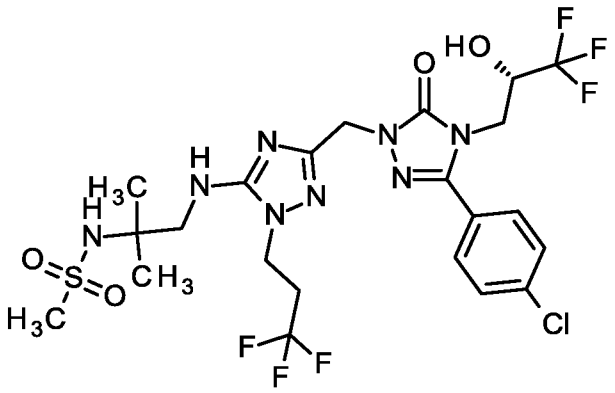
LC-MS (Method 10): R_t = 1.13 min; MS (ESIpos): m/z = 597 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.665 (0.69), 1.681 (1.74), 1.695 (1.59), 1.709 (2.70), 1.718 (2.08), 1.732 (1.15), 2.034 (1.31), 2.052 (2.40), 2.057 (3.41), 2.062 (3.78), 2.064 (3.75), 2.076 (1.41), 2.083 (4.04), 2.086 (3.92), 2.097 (3.96), 2.106 (5.15), 2.119 (2.09), 2.131 (1.66), 2.137 (2.13), 2.143 (1.55), 2.154 (3.06), 2.178 (1.24), 2.671 (1.43), 2.681 (2.17), 2.690 (1.40), 2.700 (3.61), 2.710 (2.68), 2.718 (2.70), 2.727 (3.49), 2.738 (1.26), 2.746 (2.25), 2.756 (1.23), 3.189 (4.84), 3.204 (8.91), 3.219 (4.98), 3.682 (2.06), 3.697 (2.69), 3.711 (1.93), 3.802 (2.13),

3.825 (2.46), 3.838 (3.13), 3.862 (3.37), 3.959 (3.12), 3.968 (3.48), 3.995 (2.17), 4.004 (2.08), 4.082 (4.67), 4.101 (7.52), 4.119 (4.32), 4.258 (1.06), 4.274 (1.78), 4.290 (1.65), 4.714 (1.87), 4.753 (10.74), 4.764 (10.84), 4.802 (1.86), 6.703 (2.30), 6.718 (4.75), 6.732 (2.22), 6.865 (6.16), 6.880 (6.15), 7.599 (1.49), 7.605 (10.30), 7.610 (4.03), 7.621 (4.85), 7.626 (15.15), 7.632 (2.35), 7.695 (6.92), 7.711 (3.02), 7.717 (16.00), 7.723 (4.98), 7.734 (4.54), 7.739 (10.79), 7.745 (1.47).

Example 102

N-(1-{[3-({3-(4-Chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1-(3,3,3-trifluoropropyl)-1H-1,2,4-triazol-5-yl]amino}-2-methylpropan-2-yl)methanesulfonamide



2-{[5-Bromo-1-(3,3,3-trifluoropropyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 38A, 60.0 mg, 106 µmol), N-(1-amino-2-methylpropan-2-yl)methanesulfonamide hydrochloride (1:1) (216 mg, 1.06 mmol), N,N-diisopropylethylamine (280 µl, 1.6 mmol) were dissolved in acetonitrile (3.0 ml) and stirred for 10 h at 180°C in a sealed vial under microwave irradiation, followed by 5 h at 180°C. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 36.5 mg (48% of th.) of the title compound.

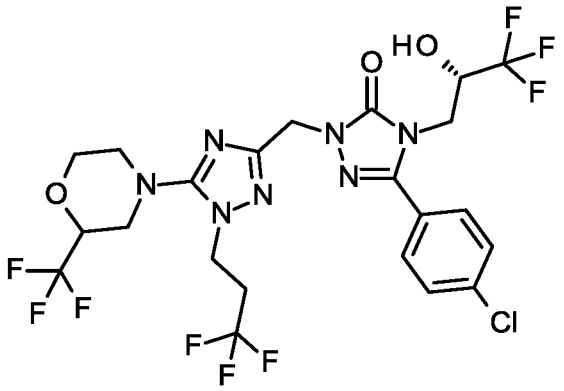
LC-MS (Method 10): R_t = 1.25 min; MS (ESIpos): m/z = 649 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.238 (16.00), 2.692 (0.73), 2.709 (1.41), 2.720 (0.86), 2.727 (0.95), 2.738 (1.32), 2.755 (0.75), 2.903 (14.75), 3.790 (0.67), 3.814 (0.78), 3.827 (1.07), 3.850 (1.08), 3.948 (1.04), 3.957 (1.18), 3.984 (0.74), 3.994 (0.70), 4.131 (1.72), 4.148 (3.18), 4.165 (1.61), 4.435 (0.69), 4.698 (1.04), 4.737 (3.03), 4.765 (3.00), 4.804 (1.03), 4.994 (1.03), 6.628 (0.75), 6.644 (1.55), 6.659 (0.74), 6.845 (1.84), 6.861 (1.85), 6.965 (3.64), 7.603 (3.43), 7.620 (1.65), 7.625 (5.40), 7.631 (1.06), 7.695 (0.84), 7.702 (4.80), 7.706 (1.78), 7.718 (1.96), 7.723 (3.46), 8.522 (0.63).

Example 103

5-(4-Chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2-({5-[2-(trifluoromethyl)morpholin-

4-yl]-1-(3,3,3-trifluoropropyl)-1H-1,2,4-triazol-3-yl}methyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (*diastereomeric mixture*)



2-{[5-Bromo-1-(3,3,3-trifluoropropyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 38A, 90.0 mg, 160 µmol), (2S)-2-(trifluoromethyl)morpholine (248 mg, 1.60 mmol), N,N-diisopropylethylamine (83 µl, 480 µmol) were dissolved in acetonitrile (3.0 ml) and stirred for 5 h at 180°C in a sealed vial under microwave irradiation, followed by 5 h at 180°C. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 97.0 mg (95% of th.) of the title compound as a mixture of diastereomers.

The two diastereomers were separated by preparative chiral HPLC [sample preparation: 95 mg dissolved in 3 ml methyl-tert-butylether; injection volume: 0.40 ml; column: Daicel Chiralpak® IA 5 µm, 250 x 20 mm; eluent: methyl-tert-butylether / methanol 90:10; flow rate: 15 ml/min; temperature: 30°C; UV detection: 220 nm]. 38 mg of diastereomer 1 (Example 104), which eluted first, and 40 mg of diastereomer 2 (Example 105), which eluted later, were isolated.

LC-MS (Method 10): R_t = 1.41 min; MS (ESIpos): m/z = 638 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.008 (2.49), 0.008 (2.34), 2.823 (0.99), 2.834 (1.40), 2.851 (2.71), 2.862 (1.65), 2.869 (1.84), 2.879 (2.66), 2.897 (1.51), 2.907 (0.93), 2.944 (1.99), 2.969 (3.28), 2.974 (3.59), 2.999 (3.97), 3.027 (1.15), 3.033 (1.01), 3.201 (2.27), 3.232 (1.70), 3.285 (2.28), 3.337 (2.32), 3.367 (1.93), 3.754 (0.95), 3.760 (1.15), 3.782 (2.24), 3.789 (2.17), 3.814 (2.38), 3.837 (1.56), 3.851 (2.07), 3.874 (2.23), 3.969 (2.13), 3.978 (2.40), 4.005 (3.10), 4.014 (1.66), 4.028 (1.73), 4.222 (4.02), 4.239 (7.97), 4.256 (4.42), 4.396 (0.84), 4.403 (1.14), 4.412 (1.10), 4.421 (1.52), 4.428 (1.15), 4.438 (1.00), 4.845 (1.23), 4.884 (7.50), 4.895 (7.42), 4.935 (1.22), 5.754 (16.00), 6.860 (4.12), 6.876 (4.11), 7.609 (6.75), 7.614 (2.70), 7.625 (3.40), 7.630 (9.88), 7.636 (1.54), 7.712 (1.82), 7.718 (9.94), 7.723 (3.25), 7.735 (2.79), 7.739 (6.65).

Example 104

5-(4-Chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2-({5-[2-(trifluoromethyl)morpholin-

4-yl]-1-(3,3,3-trifluoropropyl)-1H-1,2,4-triazol-3-yl}methyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (*diastereomer 1*)

Analytical chiral HPLC: R_t = 4.85 min, d.e. = 100% [column: Daicel Chiralpak® IA 5µm 250 x 4.6 mm; eluent: methyl-tert-butylether/ methanol 90/10+ 0.2% diethylamine, flow rate: 1 ml/min; UV detection: 270 nm].

LC-MS (Method 10): R_t = 1.42 min; MS (ESIpos): m/z = 638 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.008 (4.84), 0.008 (2.17), 1.181 (1.52), 1.187 (16.00), 2.825 (1.74), 2.835 (2.33), 2.852 (4.22), 2.863 (2.70), 2.870 (2.94), 2.881 (4.02), 2.898 (2.34), 2.909 (1.45), 2.944 (3.29), 2.970 (5.40), 2.974 (4.94), 3.000 (6.16), 3.008 (2.51), 3.028 (2.16), 3.037 (1.67), 3.202 (3.29), 3.228 (2.44), 3.287 (2.99), 3.339 (3.43), 3.367 (2.76), 3.754 (1.62), 3.760 (1.86), 3.782 (3.57), 3.789 (3.32), 3.815 (3.53), 3.838 (2.51), 3.852 (3.08), 3.875 (3.25), 3.969 (3.47), 3.979 (3.73), 4.006 (4.57), 4.015 (2.55), 4.028 (2.51), 4.222 (6.36), 4.240 (11.89), 4.257 (6.51), 4.275 (1.94), 4.397 (1.54), 4.403 (1.89), 4.413 (1.83), 4.421 (2.34), 4.429 (1.75), 4.439 (1.56), 4.445 (1.21), 4.846 (2.08), 4.885 (11.35), 4.896 (10.80), 4.936 (2.00), 4.947 (3.09), 6.862 (6.21), 6.878 (6.03), 7.603 (2.20), 7.609 (10.63), 7.614 (4.23), 7.625 (5.24), 7.631 (15.39), 7.637 (2.17), 7.712 (3.47), 7.718 (15.35), 7.724 (4.89), 7.735 (4.28), 7.740 (10.13), 7.746 (1.33), 11.670 (1.11).

Example 105

5-(4-Chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2-({5-[2-(trifluoromethyl)morpholin-4-yl]-1-(3,3,3-trifluoropropyl)-1H-1,2,4-triazol-3-yl}methyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (*diastereomer 2*)

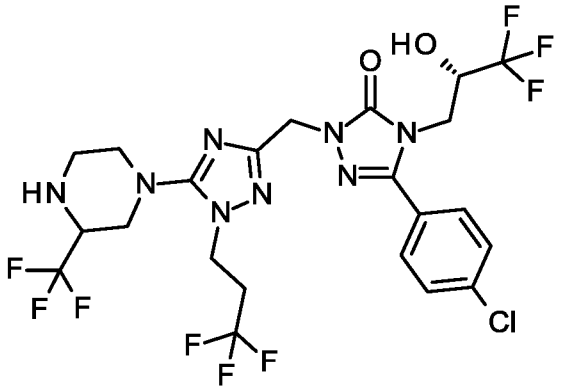
Analytical chiral HPLC: R_t = 6.11 min, d.e. = 100% [column: Daicel Chiralpak® IA 5µm 250 x 4.6 mm; eluent: methyl-tert-butylether/ methanol 90/10+ 0.2% diethylamine, flow rate: 1 ml/min; UV detection: 270 nm].

LC-MS (Method 10): R_t = 1.42 min; MS (ESIpos): m/z = 638 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.008 (2.43), 0.008 (1.74), 1.187 (16.00), 2.825 (1.34), 2.835 (1.88), 2.852 (3.64), 2.863 (2.23), 2.869 (2.46), 2.880 (3.54), 2.897 (2.04), 2.908 (1.28), 2.945 (2.67), 2.974 (5.03), 3.001 (5.22), 3.025 (1.85), 3.033 (1.51), 3.202 (3.03), 3.232 (2.30), 3.287 (1.78), 3.338 (3.09), 3.367 (2.57), 3.755 (1.28), 3.761 (1.55), 3.783 (2.98), 3.790 (2.91), 3.815 (3.16), 3.838 (2.08), 3.852 (2.69), 3.875 (2.90), 3.970 (2.86), 3.979 (3.21), 4.006 (4.11), 4.016 (2.19), 4.030 (2.29), 4.223 (5.26), 4.240 (10.34), 4.257 (5.81), 4.396 (1.16), 4.403 (1.54), 4.413 (1.50), 4.421 (2.06), 4.428 (1.55), 4.438 (1.37), 4.445 (1.09), 4.846 (1.54), 4.885 (9.66), 4.896 (9.54), 4.936 (1.59), 4.947 (3.35), 6.861 (5.63), 6.877 (5.64), 7.610 (8.78), 7.631 (12.84), 7.713 (2.24), 7.719 (12.87), 7.740 (8.79), 11.670 (1.30).

Example 106

5-(4-Chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2-({5-[3-(trifluoromethyl)piperazin-1-yl]-1-(3,3,3-trifluoropropyl)-1H-1,2,4-triazol-3-yl}methyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (*diastereomeric mixture*)



2-{[5-Bromo-1-(3,3,3-trifluoropropyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 38A, 60.0 mg, 106 µmol), (2S)-2-(trifluoromethyl)piperazine (164 mg, 1.06 mmol), N,N-diisopropylethylamine (56 µl, 320 µmol) were dissolved in acetonitrile (3.0 ml) and stirred for 5 h at 180°C in a sealed vial under microwave irradiation, followed by 10 h at 180°C. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 49.7 mg (72% of th.) of the title compound as a mixture of diastereomers.

LC-MS (Method 10): R_t = 1.30 min; MS (ESIpos): m/z = 637 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.008 (1.24), 2.786 (1.67), 2.803 (3.28), 2.813 (3.51), 2.820 (2.82), 2.831 (5.89), 2.841 (3.71), 2.848 (5.01), 2.859 (5.28), 2.876 (5.36), 2.889 (4.41), 2.904 (2.56), 2.912 (4.12), 2.919 (3.86), 2.942 (6.04), 2.955 (5.07), 2.975 (2.48), 3.088 (2.87), 3.116 (2.06), 3.235 (2.67), 3.242 (2.96), 3.264 (2.41), 3.271 (2.38), 3.288 (1.38), 3.554 (1.60), 3.563 (1.57), 3.573 (1.51), 3.811 (2.12), 3.835 (2.43), 3.848 (3.13), 3.871 (3.39), 3.968 (3.20), 3.977 (3.56), 4.005 (2.22), 4.013 (2.16), 4.177 (5.87), 4.194 (11.44), 4.212 (5.54), 4.276 (1.72), 4.291 (1.62), 4.833 (2.03), 4.873 (11.36), 4.884 (11.26), 4.924 (2.02), 6.864 (6.54), 6.880 (6.58), 7.602 (1.56), 7.608 (10.18), 7.613 (3.95), 7.625 (4.99), 7.630 (15.11), 7.636 (2.29), 7.713 (2.51), 7.719 (16.00), 7.724 (4.98), 7.736 (4.09), 7.741 (10.83), 7.747 (1.53).

The two diastereomers were separated by preparative chiral HPLC [sample preparation: 45.4 mg dissolved in 3 ml methyl-tert-butylether; injection volume: 0.4 ml; column: Daicel Chiralpak® IA 5 µm, 250 x 20 mm; eluent: methyl-tert-butylether/methanol 90:10; flow rate: 15 ml/min; temperature: 30°C; UV detection: 220 nm]. 20 mg of diastereomer 1 (Example 107), which eluted first, and 20.0 mg of diastereomer 2 (Example 108), which eluted later, were isolated.

Example 107

5-(4-Chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2-({5-[3-(trifluoromethyl)piperazin-1-yl]-1-(3,3,3-trifluoropropyl)-1H-1,2,4-triazol-3-yl}methyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (*diastereomer 1*)

Analytical chiral HPLC: R_t = 10.15 min, d.e. = 99% [column: Chiralpak® IA 250 x 20 mm; eluent: iso-hexane/ iso-propanol 50/50, methyl-tert-butylether/methanol 90:10; flow rate: 15 ml/min; temperature: 30°C; UV detection: 220 nm].

LC-MS (Method 10): R_t = 1.29 min; MS (ESIpos): m/z = 637 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.182 (2.05), 1.186 (16.00), 1.427 (2.89), 2.786 (1.30), 2.803 (2.23), 2.813 (2.40), 2.831 (3.65), 2.841 (2.49), 2.849 (3.13), 2.858 (3.54), 2.878 (3.42), 2.888 (3.13), 2.911 (2.87), 2.918 (2.50), 2.941 (3.79), 2.955 (3.41), 3.087 (1.85), 3.115 (1.30), 3.235 (1.82), 3.242 (1.98), 3.264 (1.85), 3.271 (1.86), 3.288 (1.75), 3.554 (1.12), 3.574 (1.02), 3.811 (1.28), 3.834 (1.48), 3.847 (1.85), 3.871 (1.94), 3.967 (2.01), 3.976 (2.16), 4.004 (1.37), 4.013 (1.28), 4.176 (3.60), 4.194 (6.61), 4.211 (3.19), 4.277 (1.12), 4.833 (1.22), 4.872 (6.58), 4.884 (6.31), 4.923 (1.12), 4.947 (3.33), 6.866 (3.27), 6.881 (3.16), 7.603 (1.27), 7.608 (5.64), 7.625 (2.87), 7.630 (8.05), 7.713 (1.89), 7.719 (8.50), 7.724 (3.35), 7.735 (2.42), 7.740 (5.78), 11.671 (1.38).

Example 108

5-(4-Chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2-({5-[(3-(trifluoromethyl)piperazin-1-yl]-1-(3,3,3-trifluoropropyl)-1H-1,2,4-triazol-3-yl}methyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (*diastereomer 2*)

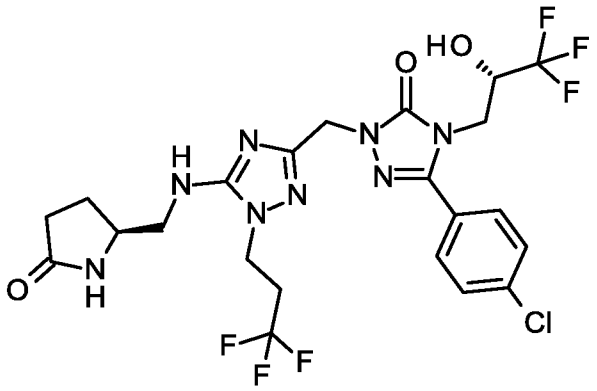
Analytical chiral HPLC: R_t = 12.03 min, d.e. = 99% [column: Chiralpak® IA 250 x 20 mm; eluent: iso-hexane/ iso-propanol 50/50, methyl-tert-butylether/methanol 90:10; flow rate: 15 ml/min; temperature: 30°C; UV detection: 220 nm].

LC-MS (Method 10): R_t = 1.29 min; MS (ESIpos): m/z = 637 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.008 (2.55), 0.008 (1.11), 1.181 (1.70), 1.187 (16.00), 1.427 (0.91), 2.786 (1.13), 2.802 (2.00), 2.813 (2.19), 2.820 (1.87), 2.830 (3.32), 2.841 (2.37), 2.848 (3.11), 2.852 (2.49), 2.858 (2.80), 2.876 (3.27), 2.882 (2.10), 2.889 (2.28), 2.905 (1.66), 2.912 (2.27), 2.919 (2.22), 2.942 (3.50), 2.954 (2.96), 2.975 (1.33), 3.088 (1.59), 3.116 (1.09), 3.233 (1.55), 3.241 (1.62), 3.263 (1.55), 3.271 (1.51), 3.287 (1.61), 3.811 (1.18), 3.834 (1.37), 3.848 (1.67), 3.871 (1.74), 3.968 (1.78), 3.977 (1.87), 4.005 (1.20), 4.014 (1.09), 4.177 (3.38), 4.194 (6.04), 4.212 (2.88), 4.833 (1.19), 4.872 (6.15), 4.884 (5.81), 4.923 (1.14), 4.947 (2.99), 6.863 (3.41), 6.879 (3.27), 7.602 (1.28), 7.608 (5.84), 7.613 (2.29), 7.625 (2.95), 7.630 (8.26), 7.636 (1.11), 7.713 (1.97), 7.719 (8.47), 7.724 (2.64), 7.736 (2.44), 7.741 (5.57), 11.670 (1.06).

Example 109

5-(4-Chlorophenyl)-2-{[5-({[(2S)-5-oxopyrrolidin-2-yl]methyl}amino)-1-(3,3,3-trifluoropropyl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



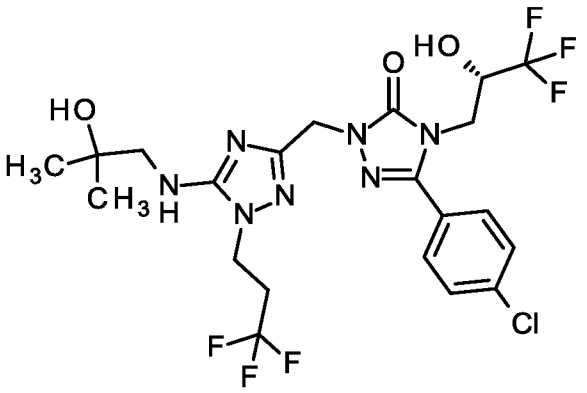
2-{[5-Bromo-1-(3,3,3-trifluoropropyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 38A, 60.0 mg, 106 µmol), (5S)-5-(aminomethyl)pyrrolidin-2-one (122 mg, 1.06 mmol), N,N-diisopropylethylamine (56 µl, 320 µmol) were dissolved in acetonitrile (3.0 ml) and stirred for 8 h at 170°C in a sealed vial under microwave irradiation, followed by 5 h at 180°C. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 44.1 mg (69% of th.) of the title compound.

LC-MS (Method 10): R_t = 1.13 min; MS (ESIpos): m/z = 597 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.008 (1.22), 1.664 (0.74), 1.680 (1.82), 1.694 (1.72), 1.708 (2.97), 1.717 (2.29), 1.730 (1.24), 2.034 (1.44), 2.056 (3.80), 2.064 (4.04), 2.085 (4.54), 2.096 (4.25), 2.105 (5.86), 2.119 (2.23), 2.137 (2.34), 2.153 (3.17), 2.177 (1.24), 2.653 (0.74), 2.670 (1.57), 2.682 (2.32), 2.699 (3.64), 2.710 (2.98), 2.718 (2.97), 2.727 (3.54), 2.746 (2.42), 2.754 (1.30), 2.774 (0.71), 3.188 (5.32), 3.203 (9.85), 3.218 (5.46), 3.289 (2.70), 3.665 (0.78), 3.681 (2.30), 3.695 (3.08), 3.710 (2.14), 3.799 (2.21), 3.822 (2.58), 3.835 (3.23), 3.859 (3.48), 3.960 (3.40), 3.969 (3.73), 3.997 (2.38), 4.006 (2.20), 4.081 (5.76), 4.100 (9.36), 4.117 (5.26), 4.274 (1.95), 4.291 (1.81), 4.711 (2.56), 4.750 (10.68), 4.767 (10.55), 4.806 (2.52), 6.702 (2.64), 6.716 (5.31), 6.731 (2.49), 6.863 (6.50), 6.879 (6.44), 7.599 (1.98), 7.604 (10.44), 7.609 (4.34), 7.621 (5.47), 7.626 (15.19), 7.632 (2.32), 7.695 (7.82), 7.710 (3.75), 7.716 (16.00), 7.721 (5.31), 7.733 (4.79), 7.738 (10.63), 7.744 (1.52).

Example 110

5-(4-Chlorophenyl)-2-({5-[(2-hydroxy-2-methylpropyl)amino]-1-(3,3,3-trifluoropropyl)-1H-1,2,4-triazol-3-yl}methyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



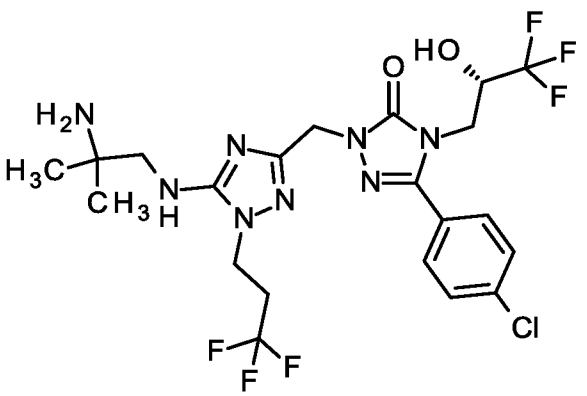
2-{[5-Bromo-1-(3,3,3-trifluoropropyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 38A, 60.0 mg, 106 µmol), 1-amino-2-methylpropan-2-ol (94.9 mg, 1.06 mmol), N,N-diisopropylethylamine (56 µl, 320 µmol) were dissolved in acetonitrile (3.0 ml) and stirred for 5 h at 160°C and 3 h at 170°C in a sealed vial under microwave irradiation, followed by 5 h at 180°C. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 49.3 mg (81% of th.) of the title compound.

LC-MS (Method 10): R_t = 1.25 min; MS (ESIpos): m/z = 572 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.072 (16.00), 2.695 (0.83), 2.723 (0.81), 3.163 (1.92), 3.177 (1.82), 3.831 (0.69), 3.854 (0.74), 3.954 (0.72), 3.962 (0.83), 4.144 (1.16), 4.161 (1.98), 4.179 (1.10), 4.758 (2.22), 4.767 (2.19), 7.606 (2.02), 7.610 (0.81), 7.622 (0.94), 7.627 (3.00), 7.715 (3.10), 7.720 (1.04), 7.731 (0.83), 7.736 (2.12).

Example 111

2-({5-[(2-Amino-2-methylpropyl)amino]-1-(3,3,3-trifluoropropyl)-1H-1,2,4-triazol-3-yl}methyl)-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



2-{[5-Bromo-1-(3,3,3-trifluoropropyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 38A, 50.0 mg, 88.7 µmol), 2-methylpropane-1,2-diamine (78.2 mg, 887 µmol), N,N-diisopropylethylamine (46 µl, 270

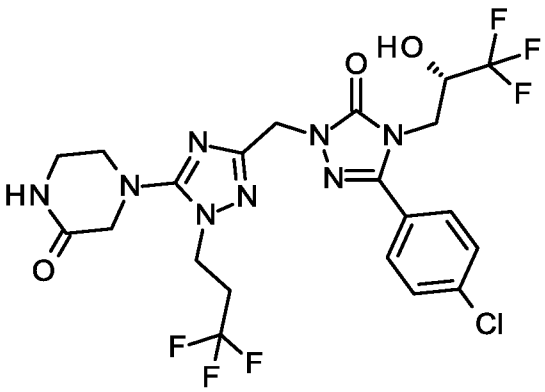
µmol) were dissolved in acetonitrile (3.0 ml) and stirred for 5 h at 160°C and 3 h at 170°C in a sealed vial under microwave irradiation, followed by 5 h at 180°C. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 37.1 mg (73% of th.) of the title compound.

LC-MS (Method 10): R_t = 0.93 min; MS (ESIpos): m/z = 571 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.132 (16.00), 2.695 (0.65), 2.711 (1.15), 2.723 (0.76), 2.730 (0.82), 2.740 (1.07), 2.758 (0.68), 3.288 (2.28), 3.302 (2.18), 3.793 (0.67), 3.816 (0.75), 3.829 (0.96), 3.853 (1.00), 3.951 (1.02), 3.960 (1.17), 3.987 (0.75), 3.996 (0.70), 4.144 (1.55), 4.162 (2.54), 4.179 (1.46), 4.763 (5.74), 7.603 (2.96), 7.608 (1.32), 7.620 (1.43), 7.625 (4.26), 7.714 (0.82), 7.720 (4.68), 7.725 (1.55), 7.737 (1.30), 7.742 (3.27).

Example 112

4-[3-({3-(4-Chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1-(3,3,3-trifluoropropyl)-1H-1,2,4-triazol-5-yl]piperazin-2-one



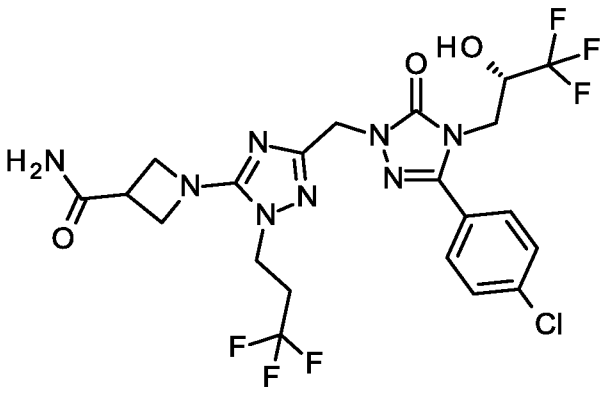
2-{[5-Bromo-1-(3,3,3-trifluoropropyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 38A, 80.0 mg, 142 µmol), piperazin-2-one (142 mg, 1.42 mmol), acetonitrile (3.0 ml) were dissolved in N,N-diisopropylethylamine (74 µl, 430 µmol) and stirred for 8 h at 180°C in a sealed vial under microwave irradiation. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 50.1 mg (59% of th.) of the title compound.

LC-MS (Method 10): R_t = 1.15 min; MS (ESIpos): m/z = 583 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 2.838 (1.08), 2.866 (1.04), 3.259 (1.50), 3.267 (1.53), 3.298 (2.23), 3.312 (16.00), 3.841 (0.76), 3.865 (0.81), 3.966 (0.77), 3.974 (0.86), 4.191 (1.44), 4.208 (2.69), 4.226 (1.36), 4.871 (2.95), 4.878 (2.94), 6.877 (1.48), 6.893 (1.48), 7.608 (2.62), 7.613 (1.05), 7.625 (1.19), 7.630 (3.78), 7.724 (3.82), 7.728 (1.25), 7.740 (1.03), 7.745 (2.62), 8.002 (1.17).

Example 113

1-[3-({3-(4-Chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1-(3,3,3-trifluoropropyl)-1H-1,2,4-triazol-5-yl]azetidine-3-carboxamide



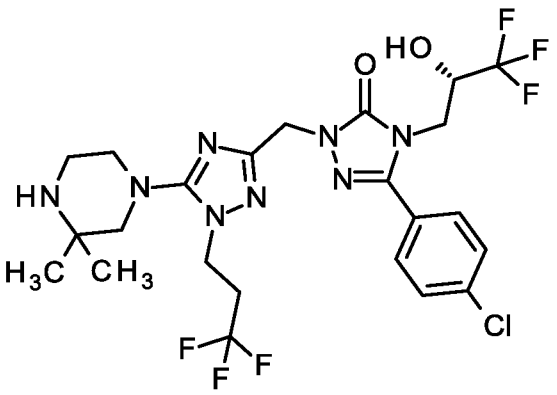
2-{[5-Bromo-1-(3,3,3-trifluoropropyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 38A, 60.0 mg, 106 µmol), azetidine-3-carboxamide (107 mg, 1.06 mmol), N,N-diisopropylethylamine (56 µl, 320 µmol) were dissolved in acetonitrile (3.0 ml) and stirred for 12 h at 160°C in a sealed vial under microwave irradiation. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 33.0 mg (52% of th.) of the title compound.

LC-MS (Method 10): R_t = 1.12 min; MS (ESIpos): m/z = 583 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 2.366 (1.23), 2.710 (1.41), 2.722 (0.97), 2.739 (1.94), 2.750 (2.76), 2.767 (4.98), 2.778 (3.17), 2.784 (3.45), 2.795 (4.70), 2.812 (2.66), 2.823 (1.58), 2.840 (0.77), 3.289 (5.09), 3.400 (0.92), 3.421 (2.53), 3.438 (3.81), 3.455 (2.20), 3.460 (2.48), 3.476 (0.95), 3.798 (2.43), 3.821 (2.86), 3.834 (3.53), 3.858 (3.71), 3.962 (3.86), 3.971 (4.22), 3.999 (3.02), 4.008 (3.12), 4.026 (6.72), 4.043 (11.71), 4.061 (6.29), 4.076 (5.24), 4.094 (14.19), 4.112 (11.68), 4.117 (11.55), 4.139 (11.73), 4.158 (4.24), 4.278 (2.35), 4.294 (2.17), 4.751 (1.69), 4.790 (13.32), 4.797 (12.93), 4.836 (1.38), 6.876 (6.88), 6.891 (6.80), 7.044 (4.40), 7.455 (4.37), 7.607 (11.09), 7.623 (5.50), 7.628 (15.64), 7.729 (16.00), 7.733 (6.98), 7.745 (4.93), 7.750 (11.45).

Example 114

5-(4-Chlorophenyl)-2-{[5-(3,3-dimethylpiperazin-1-yl)-1-(3,3,3-trifluoropropyl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



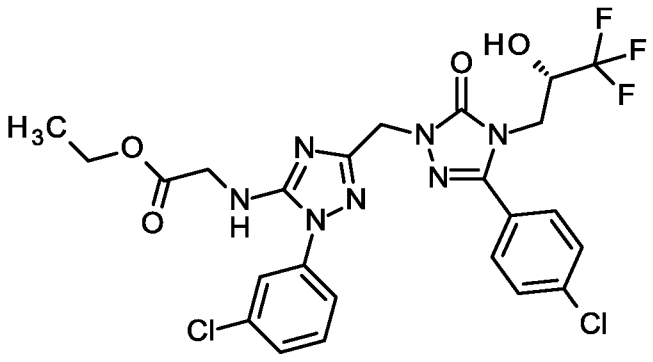
2-{[5-Bromo-1-(3,3,3-trifluoropropyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 38A, 50.0 mg, 88.7 µmol), 2,2-dimethylpiperazine (101 mg, 887 µmol), N,N-diisopropylethylamine (31 µl, 180 µmol) were dissolved in acetonitrile (3.0 ml) and stirred for 5 h at 180°C in a sealed vial under microwave irradiation. The crude product was purified by preparative HPLC (Method 5). Lyophilisation of the product containing fractions afforded 41.3 mg (78% of th.) of the title compound.

LC-MS (Method 10): R_t = 0.94 min; MS (ESIpos): m/z = 587 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.008 (0.86), 1.019 (0.58), 1.153 (15.69), 1.157 (16.00), 2.781 (4.58), 2.797 (0.86), 2.808 (0.99), 2.825 (1.75), 2.836 (1.10), 2.842 (1.19), 2.852 (1.67), 2.870 (1.02), 2.880 (0.69), 2.947 (7.67), 3.810 (0.90), 3.833 (1.04), 3.846 (1.28), 3.870 (1.34), 3.967 (1.40), 3.976 (1.56), 4.003 (1.03), 4.013 (0.96), 4.171 (2.25), 4.189 (4.10), 4.206 (1.97), 4.270 (0.70), 4.287 (0.84), 4.815 (0.66), 4.854 (4.25), 4.864 (4.11), 4.903 (0.63), 7.609 (3.75), 7.614 (1.86), 7.625 (1.82), 7.630 (5.45), 7.716 (1.13), 7.722 (5.66), 7.727 (2.28), 7.739 (1.60), 7.743 (3.97), 8.224 (1.54).

Example 115

Ethyl N-[1-(3-chlorophenyl)-3-({3-(4-chlorophenyl)-5-oxo-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1H-1,2,4-triazol-5-yl]glycinate



Ethyl N-[3-({4-[(2S)-2-{[tert-butyl(dimethyl)silyl]oxy}-3,3,3-trifluoropropyl]-3-(4-chlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl}methyl)-1-(3-chlorophenyl)-1H-1,2,4-triazol-5-

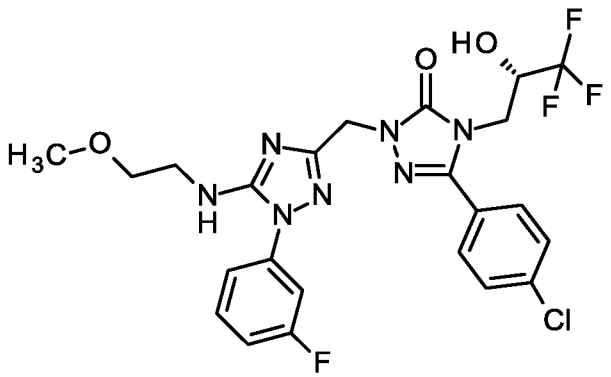
yl]glycinate (Example 42A, 25.0 mg, 35.0 µmol) was dissolved in 0.5 ml of tetrahydrofuran and colled to 0°C. A tetra-n-butylammoniumfluorid solution (1M in THF; 42 µl, 42 µmol) was added and stirring was continued at room temperature for 15 min. For purification, the mixture was purified by preparative HPLC (Method 5) to afford 16.0 mg (76% of th.) of the title compound.

LC-MS (Method 2): R_t = 1.11 min; MS (ESIpos): m/z = 600 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.149 (0.90), -0.009 (10.28), 0.008 (7.56), 0.146 (0.92), 1.073 (5.34), 1.090 (11.00), 1.108 (5.50), 1.131 (7.27), 1.149 (16.00), 1.157 (1.08), 1.166 (7.36), 1.174 (1.35), 1.192 (0.63), 1.236 (3.61), 1.988 (2.02), 2.327 (1.12), 2.669 (1.10), 2.674 (0.74), 3.357 (1.91), 3.375 (5.32), 3.392 (5.16), 3.410 (1.66), 3.804 (1.03), 3.828 (1.26), 3.841 (1.53), 3.865 (1.66), 3.963 (1.91), 3.976 (5.16), 3.992 (4.58), 4.020 (0.70), 4.052 (2.09), 4.070 (6.73), 4.088 (6.53), 4.106 (2.09), 4.283 (0.83), 4.813 (0.81), 4.853 (5.92), 4.860 (5.68), 4.900 (0.74), 6.866 (2.02), 6.880 (1.91), 7.242 (1.14), 7.257 (2.40), 7.273 (1.03), 7.472 (1.35), 7.475 (1.64), 7.480 (1.44), 7.491 (3.03), 7.495 (3.84), 7.500 (2.63), 7.508 (2.54), 7.513 (2.96), 7.516 (1.57), 7.552 (3.77), 7.574 (6.31), 7.579 (2.38), 7.591 (1.55), 7.604 (6.04), 7.609 (1.97), 7.620 (2.54), 7.625 (8.06), 7.632 (0.88), 7.725 (1.39), 7.731 (8.21), 7.736 (2.47), 7.748 (2.13), 7.753 (5.63).

Example 116

5-(4-Chlorophenyl)-2-({1-(3-fluorophenyl)-5-[(2-methoxyethyl)amino]-1H-1,2,4-triazol-3-yl}methyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



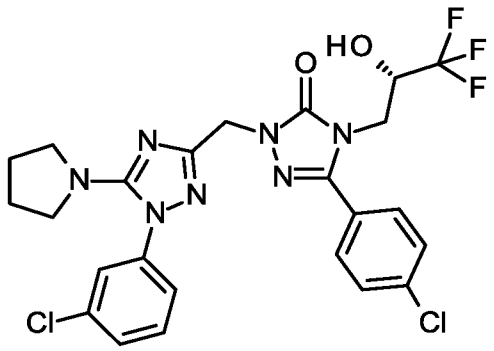
2-{[5-Bromo-1-(3-fluorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 8A, 87.0 mg, 155 µmol) was dissolved in 2 ml of acetonitrile. 2-Methoxyethanamine (130 µl, 1.5 mmol) and N,N-diisopropylethylamine (57 µl, 330 µmol) were added and the mixture was stirred under microwave radiation at 150°C for 1.5 h. After cooling to room temperature, the mixture was diluted with 2 ml of water and extracted twice with 10 ml ethyl acetate. The combined organic phases were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by preparative HPLC (Method 5) to afford 58 mg (67% of th.) of the title compound.

LC-MS (Method 2): R_t = 1.01 min; MS (ESIpos): m/z = 556 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.149 (0.27), -0.008 (2.35), 0.008 (2.16), 0.146 (0.28), 1.073 (0.93), 1.091 (1.88), 1.108 (0.94), 2.366 (0.29), 2.670 (0.20), 2.709 (0.29), 3.230 (16.00), 3.357 (0.36), 3.375 (1.26), 3.388 (1.37), 3.392 (1.44), 3.402 (1.81), 3.414 (0.85), 3.450 (1.90), 3.463 (2.62), 3.477 (0.66), 3.811 (0.48), 3.834 (0.54), 3.847 (0.69), 3.871 (0.74), 3.974 (0.68), 3.983 (0.78), 4.010 (0.49), 4.019 (0.47), 4.286 (0.33), 4.827 (0.29), 4.866 (2.89), 4.872 (2.84), 4.911 (0.29), 6.743 (0.55), 6.757 (1.15), 6.771 (0.53), 6.870 (1.16), 6.886 (1.17), 7.219 (0.35), 7.234 (0.62), 7.239 (0.73), 7.259 (0.39), 7.322 (0.85), 7.333 (0.93), 7.342 (0.65), 7.347 (1.01), 7.353 (1.75), 7.531 (0.57), 7.546 (0.65), 7.551 (0.92), 7.568 (0.90), 7.589 (0.40), 7.607 (2.58), 7.612 (0.87), 7.624 (1.08), 7.628 (3.65), 7.738 (3.74), 7.743 (1.07), 7.755 (0.95), 7.760 (2.65).

Example 117

5-(4-Chlorophenyl)-2-{[1-(3-chlorophenyl)-5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2*S*)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



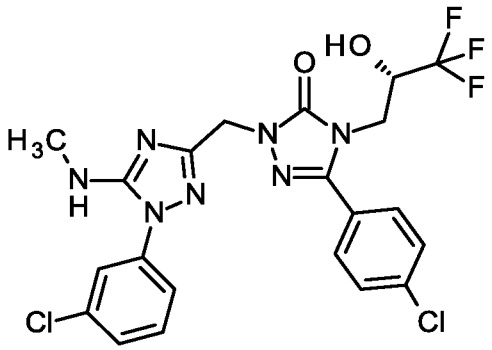
To a solution of 5-(4-chlorophenyl)-2-{[5-(pyrrolidin-1-yl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2*S*)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 9A, 100 mg, 0.22 mmol) in pyridine (2.8 ml) were added (3-chlorophenyl)boronic acid (68.3 mg, 0.44 mmol) and copper(II) acetate (79.3 mg, 0.44 mmol). The reaction mixture was stirred at room temperature for 4 days. The reaction mixture was then diluted with MTBE and quenched with aqueous hydrochloric acid (0.5 M). After phase separation, the aqueous phase was extracted twice with MTBE. The combined organic phases were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by preparative HPLC (Method 13), affording 5.2 mg (0.01 mmol, 4.1% of th.) of the title compound.

LC-MS (Method 4): R_t = 3.71 min; MS [ESIpos]: m/z = 568 $(M+H)^+$

^{1}H-NMR (500 MHz, DMSO-d6) δ [ppm]: 7.75 (br. d, 2 H), 7.62 (br. d, 2 H), 7.48 - 7.58 (m, 3 H), 7.43 (dt, 1 H), 6.87 (br. s., 1 H), 4.82 - 4.91 (m, 2 H), 4.25 - 4.34 (m, 1 H), 3.99 (dd, 1 H), 3.84 (dd, 1 H), 3.10 – 3.16 (m, 4 H), 1.74 - 1.82 (m, 4 H)

Example 118

5-(4-Chlorophenyl)-2-{[1-(3-chlorophenyl)-5-(methylamino)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2*S*)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



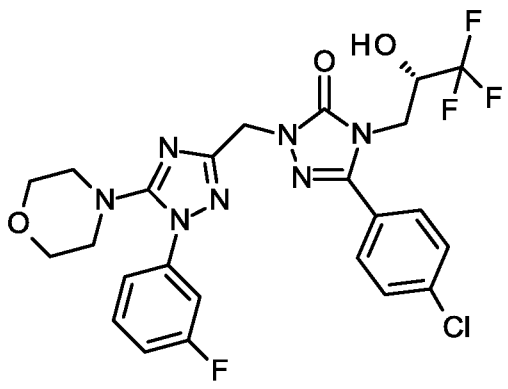
To a solution of 2-{[5-amino-1-(3-chlorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2*S*)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 47A, 30mg, 58 µmol) in N,N-dimethylformamide (1 ml) was added caesium carbonate (20.9 mg, 64 µmol). After 20 minutes of stirring at room temperature, iodomethane (4 µl, 64 µmol) was added and the reaction mixture was stirred for 15 min at 100°C under microwave irradiation. After cooling, the reaction mixture was concentrated *in vacuo*. The crude product was purified by preparative HPLC (Chromatorex C18, 10µm, 125 x 30 mm, water-acetonitrile-gradient 0.05% trifluoroacetic acid), affording the title compound (1.9 mg, 3.6 µmol, 6.1% of Th.).

LC-MS (Method 2): Rt = 1.08 min; MS [ESIpos]: m/z = 528 $(M+H)^+$

^{1}H-NMR (500 MHz, DMSO-d6) δ [ppm]: 7.75 (br. d, 2 H), 7.62 (br. d, 2 H), 7.55 (t, 1 H), 7.53 (d, 1 H), 7.48 (br. s, 1 H), 7.45 (td, 1 H), 6.88 (br. s., 1 H), 6.68 - 6.75 (m, 1 H), 4.83 - 4.91 (m, 2 H), 4.25 - 4.34 (m, 1 H), 4.00 (dd, 1 H), 3.84 (dd, 1 H), 2.81 (d, 3 H)

Example 119

5-(4-Chlorophenyl)-2-{[1-(3-fluorophenyl)-5-(morpholin-4-yl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



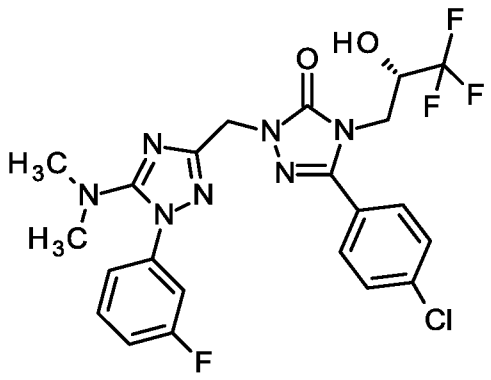
5-(4-Chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (synthesis described as Example 5A in WO 2011/104622-A198.7 mg, 321 µmol), potassium carbonate (88.7 mg, 642 µmol) and catalytic amounts ofpotassium iodide were dissolved in 4 ml of acetonitrile. To this mixture, 4-[3-(chloromethyl)-1-(3-fluorophenyl)-1H-1,2,4-triazol-5-yl]morpholine (Example 57A, 100 mg, 337 µmol) was added at room temperature. The mixture was stirred under reflux for 2.5 h. After cooling to room temperature, the suspension was filtered and the obtained solution was concentrated in vacuo. The crude product was purified by preparative HPLC (Method 5) to afford 103 mg (57% of th.) of the title compound.

LC-MS (Method 2): R_t = 1.03 min; MS (ESIpos): m/z = 568 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.149 (1.20), -0.008 (16.00), 0.008 (14.08), 0.146 (1.05), 1.073 (3.31), 1.091 (6.71), 1.108 (3.40), 1.147 (0.72), 2.085 (1.20), 2.327 (1.68), 2.366 (1.77), 2.523 (6.04), 2.669 (1.53), 2.709 (1.72), 3.036 (7.62), 3.048 (10.16), 3.059 (8.10), 3.357 (1.25), 3.375 (3.31), 3.392 (3.31), 3.410 (1.10), 3.620 (8.48), 3.632 (10.11), 3.643 (7.52), 3.813 (1.44), 3.837 (1.63), 3.850 (2.11), 3.874 (2.25), 3.976 (2.30), 3.986 (2.63), 4.013 (1.63), 4.022 (1.49), 4.291 (1.34), 4.936 (9.92), 4.939 (10.16), 4.979 (0.53), 6.878 (4.60), 7.257 (1.10), 7.284 (2.11), 7.302 (1.29), 7.502 (2.44), 7.514 (2.63), 7.522 (2.11), 7.534 (5.89), 7.558 (1.96), 7.573 (2.25), 7.579 (2.78), 7.594 (2.59), 7.609 (7.62), 7.614 (3.78), 7.625 (3.40), 7.631 (10.01), 7.733 (1.82), 7.739 (10.49), 7.745 (3.88), 7.756 (3.07), 7.761 (7.52).

Example 120

5-(4-Chlorophenyl)-2-{[5-(dimethylamino)-1-(3-fluorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



5-(4-Chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (synthesis described as Example 5A in WO 2011/104622-A1, 97.9 mg, 318 µmol), potassium carbonate (88.0 mg, 637 µmol) and catalytic amounts of potassium iodide were dissolved in 4 ml of acetonitrile. To this mixture, 3-(bromomethyl)-1-(3-fluorophenyl)-N,N-dimethyl-1H-1,2,4-triazol-5-amine (Example 46A, 100 mg, 334 µmol) was added at room temperature. The mixture was stirred under reflux for 3 h. After cooling to room temperature, the suspension was filtered and

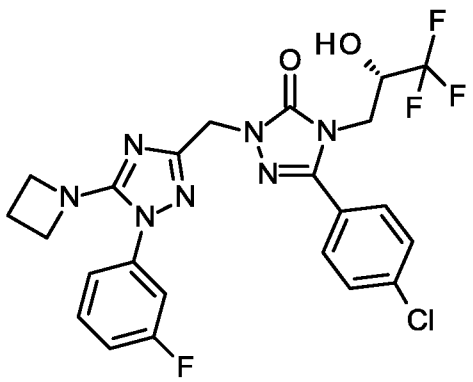
the obtained solution was concentrated in vacuo. The crude product was purified by preparative HPLC (Method 5) to afford 129 mg (76% of th.) of the title compound.

LC-MS (Method 2): R_t = 1.04 min; MS (ESIpos): m/z = 526 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.149 (0.45), -0.008 (5.68), 0.008 (4.84), 0.146 (0.45), 2.710 (0.58), 2.732 (16.00), 3.872 (0.54), 3.975 (0.52), 3.984 (0.61), 4.894 (2.55), 6.879 (0.86), 7.393 (0.60), 7.410 (1.24), 7.414 (1.27), 7.436 (0.57), 7.555 (0.55), 7.572 (0.64), 7.609 (1.62), 7.626 (0.77), 7.631 (2.22), 7.742 (2.28), 7.747 (0.84), 7.758 (0.66), 7.763 (1.64).

Example 121

2-{[5-(Azetidin-1-yl)-1-(3-fluorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



5-(4-Chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (synthesis described as Example 5A in WO 2011/104622-A1, 94.2 mg, 306 µmol), potassium carbonate (84.6 mg, 612 µmol) and catalytic amounts of potassium iodide were dissolved in 3 ml of acetonitrile. To this mixture, 5-(azetidin-1-yl)-3-(bromomethyl)-1-(3-fluorophenyl)-1H-1,2,4-triazole (Example 50A, 100 mg, 321 µmol) was added at room temperature. The mixture was stirred under reflux for 3 h. After cooling to room temperature, the suspension was filtered and the obtained solution was concentrated in vacuo. The crude product was purified by preparative HPLC (Method 5) to afford 121 mg (73% of th.) of the title compound.

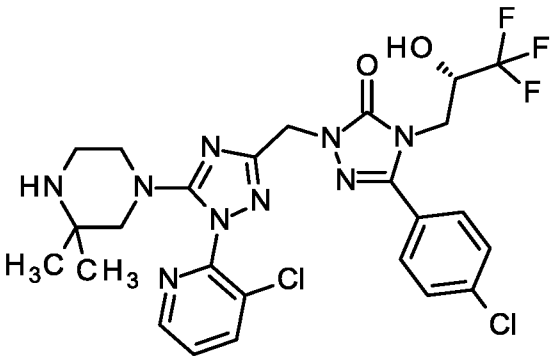
LC-MS (Method 2): R_t = 1.08 min; MS (ESIpos): m/z = 538 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.171 (0.02), -0.031 (0.29), -0.016 (0.10), -0.014 (0.17), 0.124 (0.02), 2.180 (0.07), 2.198 (0.22), 2.217 (0.31), 2.236 (0.23), 2.255 (0.07), 2.305 (0.04), 2.344 (0.05), 2.495 (0.22), 2.498 (0.22), 2.500 (0.24), 2.502 (0.27), 2.505 (0.31), 2.508 (0.39), 2.510 (0.55), 2.518 (16.00), 2.523 (0.37), 2.525 (0.17), 2.647 (0.04), 2.687 (0.05), 3.787 (0.72), 3.806 (1.02), 3.825 (0.74), 3.848 (0.17), 3.953 (0.16), 3.961 (0.19), 3.989 (0.13), 3.998 (0.11), 4.270 (0.08), 4.830 (0.03), 4.870 (0.92), 4.910 (0.02), 6.861 (0.29), 7.218 (0.08), 7.221 (0.08), 7.236 (0.14), 7.240 (0.16), 7.258 (0.08), 7.264 (0.09), 7.295 (0.38), 7.298 (0.32), 7.305 (0.13),

7.315 (0.26), 7.317 (0.29), 7.324 (0.17), 7.329 (0.08), 7.505 (0.10), 7.523 (0.16), 7.526 (0.19), 7.543 (0.19), 7.548 (0.11), 7.563 (0.09), 7.586 (0.56), 7.591 (0.20), 7.603 (0.25), 7.608 (0.78), 7.614 (0.10), 7.713 (0.14), 7.719 (0.80), 7.724 (0.24), 7.735 (0.22), 7.741 (0.57).

Example 122

5-(4-Chlorophenyl)-2-{[1-(3-chloropyridin-2-yl)-5-(3,3-dimethylpiperazin-1-yl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



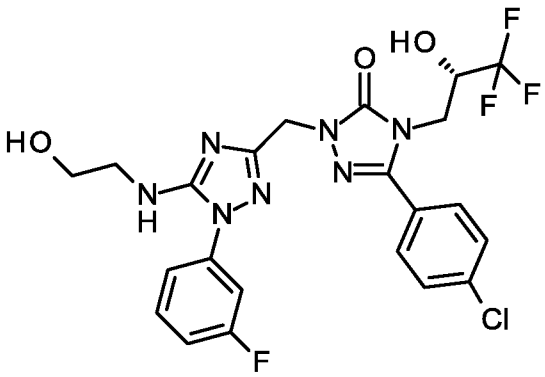
A solution of 2-{[5-bromo-1-(3-chloropyridin-2-yl)-1H-1,2,4-triazol-3-yl]methyl}-4-[(2S)-2-{[tert-butyl(dimethyl)silyl]oxy}-3,3,3-trifluoropropyl]-5-(4-chlorophenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 18A, 75.0 mg, 108 µmol) in acetonitrile (1.5 ml) was treated with 2,2-dimethylpiperazine (124 mg, 1.08 mmol) and N,N-diisopropylethylamine (57 µl, 320 µmol). The resulting mixture was stirred 8 h at 180°C under microwave irradiation. The reaction mixture was cooled to room temperature, treated with a solution of tetra-n-butylammonium fluoride in tetrahydrofuran (110 µl, 1.0 M, 110 µmol) and stirred for 30 min at room temperature. Purification by preparative HPLC (Method 4) and further purification by flash chromatography (silica gel, eluent dichloromethane/methanol gradient) afforded 39.0 mg (67% of th.) of the title compound.

LC-MS (Method 12): R_t = 1.49 min; MS (ESIpos): m/z = 611.9 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 8.60 (dd, 1H), 8.28 (dd, 1H), 7.79-7.56 (m, 5H), 6.89 (br s, 1H), 5.01-4.83 (m, 2H), 4.39-4.21 (m, 1H), 4.06-3.93 (m, 1H), 3.84 (dd, 1H), 3.50 (br s, 1H), 3.04-2.90 (m, 2H), 2.77 (s, 2H), 2.74-2.65 (m, 2H), 0.88 (s, 6H).

Example 123

5-(4-Chlorophenyl)-2-({1-(3-fluorophenyl)-5-[(2-hydroxyethyl)amino]-1H-1,2,4-triazol-3-yl}methyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



2-{[5-Bromo-1-(3-fluorophenyl)-1H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-4-[(2S)-3,3,3-trifluoro-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 14A, 100 mg, 178 µmol) was dissolved in 2 ml of acetonitrile. 2-aminoethanol (110 µl, 1.8 mmol) and N,N-diisopropylethylamine (65 µl, 370 µmol) were added and the mixture was stirred under microwave radiation at 150°C for 1.5 h. After cooling to room temperature, the mixture was diluted with 2 ml of water and extracted twice with 10 ml ethyl acetate. The combined organic phases were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by preparative HPLC (Method 5) to afford 64 mg (66% of th.) of the title compound.

LC-MS (Method 2): R_t = 0.94 min; MS (ESIpos): m/z = 542 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.008 (6.53), 0.008 (6.10), 1.073 (7.20), 1.091 (14.92), 1.108 (7.43), 3.280 (2.59), 3.295 (8.46), 3.357 (2.57), 3.375 (7.22), 3.392 (7.17), 3.410 (2.29), 3.500 (3.67), 3.514 (9.60), 3.529 (8.76), 3.544 (2.75), 3.809 (2.11), 3.832 (2.36), 3.845 (2.96), 3.869 (3.23), 3.974 (2.87), 3.982 (3.26), 4.010 (2.06), 4.019 (1.90), 4.286 (1.49), 4.705 (4.22), 4.719 (9.38), 4.733 (3.99), 4.823 (1.08), 4.862 (12.72), 4.867 (12.72), 4.906 (1.10), 6.659 (2.38), 6.673 (5.02), 6.688 (2.38), 6.874 (6.37), 6.890 (6.42), 7.212 (1.54), 7.230 (3.00), 7.236 (3.28), 7.256 (1.74), 7.362 (6.81), 7.368 (4.33), 7.381 (4.97), 7.393 (3.78), 7.527 (2.29), 7.544 (2.98), 7.548 (4.01), 7.565 (3.92), 7.585 (1.86), 7.607 (11.39), 7.629 (15.66), 7.742 (16.00), 7.747 (4.65), 7.763 (11.42).

EXPERIMENTAL SECTION – BIOLOGICAL ASSAYS

Abbreviations and Acronyms:

Acc. No.	accession number
AVP	arginine vasopressin
B_{max}	maximal ligand binding capacity
BSA	bovine serum albumin
cAMP	cyclic adenosine monophosphate
Cat. No.	catalogue number
cDNA	complementary deoxyribonucleic acid
CHO	chinese hamster ovary
CRE	cAMP response element
Ct	cycle threshold
DMEM/F12	Dulbecco's modified Eagle's medium / Ham's F12 medium (1:1)
DNA	deoxyribonucleic acid
DMSO	dimethylsulfoxide
DTT	dithiothreitol
EC_{50}	half-maximal effective concentration
EDTA	ethylenediamine-tetraacetic acid
FAM	carboxyfluorescein succinimidyl ester
f.c.	final concentration
FCS	fetal calf serum
HEPES	4-(2-hydroxyethyl)piperazine-1-ethanesulfonic acid
IC_{50}	half-maximal inhibitory concentration
K_d	dissociation constant
K_i	dissociation constant of an inhibitor
mRNA	messenger ribonucleic acid
PBS	phosphate buffered saline
PEG	polyethylene glycol
p.o.	*per os*, peroral
RNA	ribonucleic acid
RTPCR	real-time polymerase chain reaction
SPA	scintillation proximity assay
TAMRA	carboxytetramethylrhodamine
TRIS; Tris	2-amino-2-hydroxymethylpropane-1,3-diol

Demonstration of the activity of the compounds of the present invention may be accomplished through *in vitro, ex vivo*, and *in vivo* assays that are well known in the art. For example, to demonstrate the activity of the compounds of the present invention, the following assays may be used.

B-1. Cellular in vitro assay for determining vasopressin receptor activity

The identification of agonists and antagonists of the V1a and V2 vasopressin receptors from humans, rats and dogs as well as the quantification of the activity of the compounds of the invention is carried out using recombinant cell lines. These cell lines originally derive from a hamster's ovary epithelial cell (Chinese Hamster Ovary, CHO K1, ATCC: American Type Culture Collection, Manassas, VA 20108, USA). The test cell lines constitutively express the human, rat or dog V1a or V2 receptors. In case of the $G_{\alpha q}$-coupled V1a receptors, cells are also stably transfected with a modified form of the calcium-sensitive photoproteins aequorin (human and rat V1a) or obelin (dog V1a), which, after reconstitution with the cofactor coelenterazine, emit light when there are increases in free calcium concentrations [Rizzuto R, Simpson AW, Brini M, Pozzan T, *Nature* 358, 325-327 (1992); Illarionov BA, Bondar VS, Illarionova VA, Vysotski ES, *Gene* 153 (2), 273-274 (1995)]. The resulting vasopressin receptor cells react to stimulation of the recombinantly expressed V1a receptors by intracellular release of calcium ions, which can be quantified by the resulting photoprotein luminescence. The G_s-coupled V2 receptors are stably transfected into cell lines expressing the gene for firefly luciferase under control of a CRE-responsible promoter. Activation of V2 receptors induces the activation of the CRE-responsive promoter *via* cAMP increase, thereby inducing the expression of firefly luciferase. The light emitted by photoproteins of V1a cell lines as well as the light emitted by firefly luciferase of V2 cell lines corresponds to the activation or inhibition of the respective vasopressin receptor. The bioluminescence of the cell lines is detected using a suitable luminometer [Milligan G, Marshall F, Rees S, *Trends in Pharmacological Sciences* 17, 235-237 (1996)].

Test procedure:

Vasopressin V1a receptor cell lines:

On the day before the assay, the cells are plated out in culture medium (DMEM/F12, 2% FCS, 2 mM glutamine, 10 mM HEPES, 5 µg/ml coelenterazine) in 384-well microtiter plates and kept in a cell incubator (96% humidity, 5% v/v CO_2, 37°C). On the day of the assay, test compounds in various concentrations are placed for 10 minutes in the wells of the microtiter plate before the agonist [Arg^8]-vasopressin at EC_{50} concentration is added. The resulting light signal is measured immediately in a luminometer.

Vasopressin V2 receptor cell lines:

On the day before the assay, the cells are plated out in culture medium (DMEM/F12, 2% FCS, 2 mM glutamine, 10 mM HEPES) in 384-well microtiter plates and kept in a cell incubator (96%

humidity, 5% v/v CO_2, 37°C). On the day of the assay, test compounds in various concentrations and the agonist [Arg^8]-vasopressin at EC_{50} concentration are added together to the wells, and plates are incubated for 3 hours in a cell incubator. Upon addition of the cell lysis reagent Triton™ and the substrate luciferin, luminescence of firefly luciferase is measured in a luminometer.

Table 1A below lists individual IC_{50} values for the compounds of the invention (including racemic mixtures as well as separated enantiomers) that were obtained from cell lines transfected with the human V1a or V2 receptor:

Table 1A:

Example No.	**IC_{50} hV1a [µM]**	**IC_{50} hV2 [µM]**	**ratio IC_{50} hV2/hV1a**
1	0.00075	0.00185	2.5
2	0.00043	0.00084	1.9
3	0.00062	0.00215	3.5
4	0.00230	0.00477	2.1
5	0.00064	0.00380	6.0
6	0.00039	0.00345	8.9
7	0.00022	0.00112	5.2
8	0.00031	0.00169	5.5
9	0.00089	0.01675	18.8
10	0.00063	0.01823	29.2
11	0.00093	0.00465	5.0
12	0.00120	0.00245	2.0
13	0.00035	0.00225	6.5
14	0.00096	0.00585	6.1
15	0.00340	0.01140	3.4
16	0.00033	0.00082	2.5
17	0.00050	0.00190	3.8
18	0.00081	0.00135	1.7
19	0.00255	0.03800	14.9
20	0.00042	0.01200	28.6
21	0.00200	0.03550	17.8
22	0.00046	0.01200	26.1

Example No.	IC_{50} hV1a [µM]	IC_{50} hV2 [µM]	ratio IC_{50} hV2/hV1a
23	0.00125	0.00120	1.0
24	0.00040	0.00102	2.6
25	0.00043	0.00086	2.0
26	0.00040	0.00220	5.6
27	0.00035	0.00128	3.7
28	0.00066	0.01000	15.3
29	0.00105	0.00490	4.7
30	0.00038	0.00270	7.2
31	0.00108	0.00835	7.7
32	0.00035	0.02475	71.2
33	0.00037	0.00925	25.2
34	0.00046	0.00875	19.0
35	0.00048	0.00605	12.6
36	0.00082	0.00175	2.1
37	0.00044	0.00133	3.1
38	0.00040	0.00355	8.9
39	0.00058	0.01800	31.0
40	0.00072	0.00720	10.1
41	0.00093	0.00740	8.0
42	0.00048	0.00190	4.0
43	0.00042	0.00440	10.5
44	0.00034	0.00116	3.5
45	0.00245	0.01300	5.3
46	0.00065	0.00547	8.5
47	0.00096	0.00563	5.8
48	0.00064	0.01042	16.3
49	0.00063	0.00194	3.1
50	0.00047	0.00208	4.5
51	0.00071	0.00175	2.5

Example No.	IC_{50} hV1a [µM]	IC_{50} hV2 [µM]	ratio IC_{50} hV2/hV1a
52	0.00065	0.00083	1.3
53	0.00052	0.00185	3.6
54	0.00054	0.00156	2.9
55	0.00039	0.02600	67.1
56	0.00073	0.00565	7.7
57	0.00074	0.00490	6.6
58	0.00165	0.02200	13.3
59	0.00230	0.03950	17.2
60	0.00044	0.00540	12.3
61	0.00135	0.01005	7.4
62	0.00130	0.00945	7.3
63	0.00042	0.00580	14.0
64	0.00080	0.00435	5.5
65	0.00063	0.00645	10.2
66	0.00037	0.00690	18.9
67	0.00116	0.02200	19.0
68	0.00045	0.01350	30.3
69	0.00105	0.00435	4.2
70	0.00090	0.02200	24.4
71	0.00044	0.00240	5.5
72	0.00058	0.01750	30.2
73	0.00113	0.00950	8.4
74	0.00048	0.00360	7.5
75	0.00081	0.00890	11.0
76	0.00042	0.04500	108.4
77	0.00150	0.03900	26.0
78	0.00079	0.00163	2.1
79	0.00032	0.00219	6.8
80	0.00036	0.00279	7.8

Example No.	IC_{50} hV1a [µM]	IC_{50} hV2 [µM]	ratio IC_{50} hV2/hV1a
81	0.00160	0.01767	11.0
82	0.00086	0.00647	7.5
83	0.00056	0.01430	25.7
84	0.00083	0.01200	14.4
85	0.00058	0.00976	16.9
86	0.00098	0.00666	6.8
87	0.00241	0.02680	11.1
88	0.00559	0.01185	2.1
89	0.00545	0.08050	14.8
90	0.00880	0.24750	28.1
91	0.00115	0.10550	91.7
92	0.04150	3.05000	73.5
93	0.02800	3.15000	112.5
94	0.00430	0.09550	22.2
95	0.00086	0.72750	845.9
96	0.00100	0.40750	407.5
97	0.00056	0.09950	176.9
98	0.00190	0.14500	76.3
99	0.01015	0.35000	34.5
100	0.33000	3.80000	11.5
101	0.02950	0.51000	17.3
102	0.00390	0.12300	31.5
103	0.03000	0.24500	8.2
104	0.03050	0.36500	12.0
105	0.02200	0.18000	8.2
106	0.02650	0.31000	11.7
107	0.04350	0.78500	18.1
108	0.01070	0.08400	7.9
109	0.00940	0.38500	41.0

Example No.	IC_{50} hV1a [µM]	IC_{50} hV2 [µM]	ratio IC_{50} hV2/hV1a
110	0.00140	0.17000	121.4
111	0.01850	2.75000	148.7
112	0.11450	0.81000	7.1
113	0.03700	0.36000	9.7
114	0.01025	1.80000	175.6
115	0.00586	0.00207	0.4
116	0.00135	0.00198	1.5
117	0.06650	0.01920	0.3
118	0.01645	0.00104	0.1
119	0.00779	0.01713	2.2
120	0.00466	0.00819	1.8
121	0.00640	0.00612	1.0
122	0.00097	1.55000	1606.2
123	0.00215	0.00459	2.1

B-2. Radioactive binding assay

IC_{50} and K_i values can be determined in radioactive binding assays using membrane fractions of recombinant human embryonic kidney cell line 293 (HEK293) or CHO-K1 cell lines expressing the respective human vasopressin V1a and V2 receptors.

Human recombinant vasopressin V1a receptors expressed in HEK293 cells are used in 50 mM Tris-HCl buffer, pH 7.4, 5 mM $MgCl_2$, 0.1% BSA using standard techniques. Aliquots of prepared membranes are incubated with test compounds in various concentrations in duplicates and 0.03nM [^{125}I]Phenylacetyl-D-Tyr(Me)-Phe-Gln-Asn-Arg-Pro-Arg-Tyr-NH_2 for 120 minutes at 25°C. Non-specific binding is estimated in the presence of 1 µM [Arg^8]Vasopressin. Receptors are filtered and washed, the filters are then counted to determine [^{125}I]Phenylacetyl-D-Tyr(Me)-Phe-Gln-Asn-Arg-Pro-Arg-Tyr-NH_2 specifically bound.

CHO-K1 cells stably transfected with a plasmid encoding human vasopressin V2 receptor are used to prepare membranes in 50 mM Tris-HCl buffer, pH 7.4, 10 mM $MgCl_2$, 0.1% BSA using standard techniques. Aliquots of prepared membrane are incubated with test compounds in various concentrations in duplicates and 4 nM [^{3}H](Arg^8)-Vasopressin for 120 minutes at 25°C. Non-specific binding is estimated in the presence of 1 mM (Arg^8)-vasopressin. Membranes are filtered

and washed 3 times and the filters are counted to determine [^{3}H](Arg$_8$)-Vasopressin specifically bound.

IC_{50} values are determined by a non-linear, least squares regression analysis using MathIQTM (ID Business Solutions Ltd., UK). The inhibition constant K_i is calculated using the equation of Cheng and Prusoff (Cheng, Y., Prusoff, W.H., Biochem. Pharmacol. 22:3099-3108, 1973).

B-3. Cellular in vitro assay for detecting the action of vasopressin V1a receptor antagonists on the regulation of pro-fibrotic genes

The cell line H9C2 (American Type Culture Collection ATCC No. CRL-1446), described as a cardiomyocyte type isolated from rat cardiac tissue, endogenously expresses the vasopressin V1a receptor AVPR1A in high copy number, whereas AVPR2 expression cannot be detected. Likewise, the cell line NRK49F (ATCC No. CRL1570) isolated from rat kidney tissue, shows similar expression pattern of high AVPR1A mRNA expression and diminishing AVPR2 expression. For cell assays detecting the inhibition of AVPR1A receptor-dependent regulation of gene expression by receptor antagonists, the procedure is as follows:

H9C2 cells or NRK49F cells are seeded in 6-well microtiter plates for cell culture at a cell density of 50 000 cells/ well in 2.0 ml of Opti-MEM medium (Invitrogen Corp., Carlsbad, CA, USA, Cat. No. 11058-021) and held in a cell incubator (96% humidity, 8% v/v CO_2, 37°C). After 24 hours, sets of three wells (triplicate) are charged with vehicle solution (negative control) and vasopressin solution ([Arg8]-vasopressin acetate, Sigma, Cat. No. V9879), or test compound (dissolved in vehicle: water with 20% v/v ethanol) and vasopressin solution. In the cell culture, the final vasopressin concentration is 1 nM. The test compound solution is added to the cell culture in small volumes, so that a final concentration of 0.03% of ethanol in the cell assay is not exceeded. After an incubation time of 5 hours, the culture supernatant is drawn off under suction, the adherent cells are lysed in 350 µl of RLT buffer (Qiagen, Cat. No. 79216), and the RNA is isolated from the lysate using the RNeasy kit (Qiagen, Cat. No. 74104). This is followed by DNAse digestion (Invitrogen, Cat. No. 18068-015), cDNA synthesis (Promaga, ImProm-II Reverse Transcription System, Cat. No. A3800) and Reverse Transcription Polymerase Chain Reaction (RTPCR) (pPCR MasterMix RT-QP2X-03-075, Eurogentec, Seraing, Belgium). All procedures take place in accordance with the working protocols of the test reagents' manufacturers. The primer sets for the RTPCR are selected on the basis of the mRNA gene sequences (NCBI GenBank Entrez Nucleotide Data Base) using the Primer3Plus program with 6-FAM TAMRA-labelled probes. The RTPCR for determining the relative mRNA expression in the cells of the various assay batches is carried out using the Applied Biosystems ABI Prism 7700 Sequence Detector in 384-well microtiter plate format in accordance with the instrument operating instructions. The relative gene expression is represented by the delta-delta Ct value [Applied Biosystems, User Bulletin No. 2 ABI Prism 7700 SDS, December 11, 1997 (updated 10/2001)] with reference to the level of expression of the

ribosomal protein L-32 gene (GenBank Acc. No. NM_013226) and the threshold Ct value of Ct = 35.

B-4. Inhibition of vasopressin induced aggregation of human platelets

Human platelets endogenously express the V1a receptor. It was found that relatively high vasopressin concentrations (ca. 50-100 nM) stimulate platelet aggregation ex vivo. Therefore, platelets enriched from human blood may serve as a V1a expressing tissue for pharmacological studies with corresponding high concentrations of vasopressin antagonists.

Human blood is collected in a 10 mM trisodium citrate solution by venous puncture from nonsmoking healthy volunteers (n=4-8) who were drug free for at least 1 week. Platelet-rich plasma (PRP) is obtained by centrifuging the blood sample at 140 g for 20 min at 4°C. The resulting pellet is further centrifuged (15.000 rpm, 2 min) to produce platelet-poor plasma (PPP). Platelet aggregation is measured turbidimetrically using an aggregometer (APACT 4). The reaction is followed by monitoring changes in light transmission on 178 µL PRP aliquots, under continuous stirring at 37°C, against PPP control. Various concentrations of vasopressin antagonists (in 2 µL) are added to PRP 5 min before the addition of 20 µL Arg-vasopressin (final concentration 100 nM. The inhibitory effects of the compounds are determined by measuring the height of the aggregation wave from the bottom of the shape change compared with the control response. IC50 values are calculated a dose-response inhibition curve by an iterative nonlinear regression program

B-5. Effects on the contraction of isolated rat vessel rings

Isolated aorta

Test compounds can be investigated on isolated aortic rings from male Wistar rats endogenously expressing the V1a receptor. Male Wistar rats are euthanized using carbon dioxide. The aorta is removed and placed in ice-cold Krebs-Henseleit buffer of following composition (in mmol/l): NaCl 112, KCl 5.9, $CaCl_2$ 2.0, $MgCl_2$ 1.2, NaH_2PO_4 1.2, $NaHCO_3$ 25, glucose 11.5. The aorta is cut into 3 mm rings and transferred to 20 ml organ baths containing Krebs-Henseleit solution equilibrated with 95% O_2, 5% CO_2 at 37°C. For recording of isometric tension the rings are mounted between two hooks. The resting tension is adjusted to 3 g. After an equilibration period, each experiment is started by exposing the preparation to K+ (50 mM) Krebs-Henseleit solution. The aortic rings are than pre-contracted using 1 nmol/l Arg-vasopressin. After a stable contraction is established, a cumulative dose response curve of the test compound is constructed. The stabilized contraction induced by Arg-vasopressin is defined as 100% tension. The relaxation is expressed as percentage tension.

Isolated A. renalis

Male Wistar rats (200-250 g) are euthanized using carbon dioxide. The A. renalis is removed and placed in ice-cold Krebs-Henseleit buffer of following composition (in mmol/l): NaCl 112, KCl

5.9, $CaCl_2$ 2.0, $MgCl_2$ 1.2, NaH_2PO_4 1.2, $NaHCO_3$ 25, glucose 11.5. For measurement of isometric tension, ring segments, 2 mm in length, are mounted in a small vessel chamber myograph (Danish Myo Technology A/S, Denmark) using two tungsten wires fixed to mounting jaws. One mounting jaw is attached to a micrometer, allowing control of vessel circumference. The other mounting jaw is attached to a force transducer for measurement of tension development. The whole preparation is kept in a chamber with physiological salt solution at 37°C, bubbled with oxygen. After a 30 min equilibration period, the vessels are stretched to their optimal lumen diameter for active tension development which is determined based on the internal circumference-wall tension ratio. The internal circumference is set to 90% of what the vessels would have if they are exposed to a passive tension equivalent to that produced by a transmural pressure of 100 mmHg.

Afterwards, the vessels are washed three times with Krebs-Henseleit buffer and left to equilibrate for 30 min. The contractility is then tested by a twofold exposure to a high K^+ solution (50 mmol/l KCl). After washing with Krebs-Henseleit buffer the vessels are then pre-contracted using 1 nmol/l Arg-vasopressin. After a stable contraction is established, a cumulative dose response curve of the test compound is constructed. The stabilized contraction induced by Arg-vasopressin is defined as 100% tension. The relaxation is expressed as percentage tension.

B-6. In vivo assay for detecting cardiovascular effects: blood pressure measurement in anaesthetized rats (vasopressin 'challenge' model)

Male Sprague-Dawley rats (250-350 g body weight) are used under ketamine/ xylazine/ pentobarbital injection anaesthesia. Polyethylene tubes (PE-50, Intramedic®), prefilled with heparin-containing (500 IU/ml) isotonic sodium chloride solution, are introduced into the jugular vein and the femoral vein and then tied in. Arg-vasopressin (SIGMA) is injected *via* one venous access, with the aid of a syringe; the test substance is administered *via* the second venous access. For determination of the systolic blood pressure, a pressure catheter (Millar SPR-320 2F) is tied into the carotid artery. The arterial catheter is connected to a pressure transducer which feeds its signals to a recording computer equipped with suitable recording software. In a typical experiment, the experimental animal is administered 3-4 successive bolus injections at intervals of 10-15 min with a defined amount of Arg-vasopressin (30 ng/kg) in isotonic sodium chloride solution. When the blood pressure has reached initial levels again, the test substance is administered as a bolus, with subsequent continuous infusion, in a suitable solvent. After this, at defined intervals (10-15 min), the same amount of Arg-vasopressin as at the start is administered again. On the basis of the blood pressure values, a determination is made of the extent to which the test substance counteracts the hypertensive effect of Arg-vasopressin. Control animals only receive solvent instead of the test substance.

Following intravenous administration, the compounds of the invention, in comparison to the solvent controls, bring about an inhibition of the blood pressure increase caused by Arg-vasopressin.

B-7. In vivo assay for detecting cardiovascular effects: diuresis investigations in conscious rats kept in metabolism cages

Wistar rats (220-450 g body weight) are kept with free access to feed (Altromin) and drinking water. During the experiment, the animals are kept with free access to drinking water for 4 to 8 or up to 24 hours individually in metabolism cages suitable for rats of this weight class (Tecniplast Deutschland GmbH, D-82383 Hohenpeißenberg). At the beginning of the experiment, the animals are administered the test substance in a volume of 1 to 3 ml/kg body weight of a suitable solvent by means of gavage into the stomach. Control animals only receive solvent. Controls and substance tests are carried out in parallel on the same day. Control groups and substance-dose groups each consist of 4 to 8 animals. During the experiment, the urine excreted by the animals is collected continuously in a receiver at the base of the cage. The volume of urine per time unit is determined separately for each animal, and the concentration of urinary electrolytes is measured by standard methods of flame photometry. Before the beginning of the experiment, the body weight of the individual animals is determined.

B-8. In vivo assay for detecting protective renal effects: Acute ischemia/reperfusion injury model in rodents

Laboratory bred male C57Bl/6J mice 6-8 weeks old are obtained from Taconic Biosciences, male 6-8 weeks old Sprague Dawley® rat are obtained from Charles River. Both rats and mice are maintained under standard laboratory conditions, 12 hour light-dark cycles with access to normal chow and drinking water at libitum. For the ischemia reperfusion injury model a total of 10-12 rats or mice is used in each control and experimental group.

Animals are anesthetized with continuous inhaled isoflurane. A right nephrectomy is performed through a right flank incision 7 days before the ischemic procedures in the contralateral kidneys. For renal ischemia a left flank incision is made. Renal vessels are exposed by dissection of the left renal pedicle. Non-traumatic vascular clamps are used to stop blood flow (artery and vein) during 45 min (rats) or 25 min (mice) of ischemia. Reperfusion is established by removing the clamps. The abdominal wall (muscular layer and skin) is closed with 5.0 polypropylene sutures. Temgesic® (Buprenorphin, 0.025 mg/kg s.c.) is applied as an analgesic.

Urine of each animal is collected in metabolic cages over night before sacrifice at 24h post ischemia. Upon sacrifice, blood samples are obtained under terminal anesthesia. After centrifugation of the blood samples, serum is isolated. Both serum creatinine and serum urea are measured via clinical biochemistry analyzer (Pentra 400). For the assessment of serum and urinary kidney injury biomarkers (Neutrophil gelatinase-associated lipocalin [NGAL], kidney injury molecule- 1 [KIM-1] and Osteopontin) ELISA's are performed according to the manufacturers protocol. Both urinary creatinine and albumin are measured to determine the albumin/creatinine ratio.

Total RNA is isolated from kidneys. Left kidneys are snap-frozen in liquid nitrogen at sacrifice. Kidney tissue is then homogenized and RNA is obtained. Total RNA is transcribed to cDNA. Using TaqMan real-time PCR renal NGAL, Osteopontin, KIM-1, Nephrin and Podocin mRNA expression is analyzed in whole kidney tissue.

Differences between groups are analyzed by one-way ANOVA with Dunnett's corrections for multiple comparisons. Statistical significance is defined as $p < 0.05$. All statistical analyses are done using GraphPad Prism 6.

B-9. In vivo assay for detecting cardiovascular effects: hemodynamic investigations in anaesthetized dogs

Male beagle dogs (Beagle, Marshall BioResources, USA) with a weight of between 10 and 15 kg are anesthetized with pentobarbital (30 mg/kg iv, Narcoren®, Merial, Germany) for the surgical interventions and the hemodynamic and functional investigation termini. Pancuroniumbromide (Pancuronium Inresa, Inresa, Germany, 2-4 mg/animal i.v.) serves additionally as a muscle relaxant. The dogs are intubated and ventilated with an oxygen/ambient air mixture (30/70%), about 2,5-4 L/min. Ventilation takes place using a ventilator from GE Healthcare (Avance, Germany) and is monitored using a carbon dioxide analyzer (-Datex Ohmeda). The anesthesia is maintained by continual infusion of pentobarbital (50 µg/kg/min); fentanyl is used as an analgesic (10 µg/kg/h).

In preparatory interventions, the dogs are fitted with a cardiac pacemaker. At start of experiment, a cardiac pacemaker from Biotronik (Logos®, Germany) is implanted into a subcutaneous skin pocket and is contacted with the heart via a pacemaker electrode (Siello S60®, Biotronik, Germany) which is advanced through the external jugular vein, with illumination, into the right ventricle.

Thereafter accesses are removed and the dog wakes spontaneously from the anesthesia. After a further 7 days, the above-described pacemaker is activated and the heart is stimulated at a frequency of 220 beats per minute.

The actual drug testing experiments take place 28 days after the beginning of pacemaker stimulation, using the following instrumentation:

- Introduction of a bladder catheter for bladder relief and for measuring the flow of urine
- Attachment of electrocardiography (ECG) leads to the extremities for ECG measurement
- Introduction of a sheath introducer filled with sodium chloride solution into the femoral artery. This tube is connected to a pressure sensor (Braun Melsungen, Melsungen, Germany) for measuring the systemic blood pressure

- Introduction of a Millar Tip catheter (type 350 PC, Millar Instruments, Houston, USA) through a port secured in the carotid artery, for measuring cardiac hemodynamics .
- Introduction of a Swan-Ganz catheter (CCOmbo 7.5F, Edwards, Irvine, USA) via the jugular vein into the pulmonary artery, for measuring the cardiac output, oxygen saturation, pulmonary arterial pressures and central venous pressure
- Siting of a venous catheter in the cephalic vein, for infusing pentobarbital, for liquid replacement and for blood sampling (determination of the plasma levels of substance or other clinical blood values)
- Siting of a venous catheter in the saphenous vein, for infusing fentanyl and for administration of substance
- Infusion of vasopressin (Sigma) in increasing dosage, up to a dose of 4 mU/kg/min. The pharmacological substances are then tested with this dosage.

The primary signals are amplified if necessary (ACQ7700, Data Sciences International, USA or Edwards-Vigilance-Monitor, Edwards, Irvine, USA) and subsequently fed into the Ponemah system (Data Sciences International, USA) for evaluation. The signals are recorded continuously throughout the experimental period, and are further processed digitally by said software, and averaged over 30 seconds.

Although the invention has been disclosed with reference to specific embodiments, it is apparent that other embodiments and variations of the invention may be devised by others skilled in the art without departing from the true spirit and scope of the invention. The claims are intended to be construed to include all such embodiments and equivalent variations.

C) **Working examples of pharmaceutical compositions**

The substances according to the invention can be converted to pharmaceutical preparations as follows:

Tablet:

Composition:

100 mg of the compound of Example 1, 50 mg of lactose (monohydrate), 50 mg of maize starch, 10 mg of polyvinylpyrrolidone (PVP 25) (from BASF, Germany) and 2 mg of magnesium stearate.

Tablet weight 212 mg. Diameter 8 mm, radius of curvature 12 mm.

Production:

The mixture of the compound of Example 1, lactose and starch is granulated with a 5% strength solution (m/m) of the PVP in water. After drying, the granules are mixed with the magnesium stearate for 5 min. This mixture is compressed in a conventional tabletting press (see above for format of the tablet).

Oral suspension:

Composition:

1000 mg of the compound of Example 1, 1000 mg of ethanol (96%), 400 mg of Rhodigel (xanthan gum) (from FMC, USA) and 99 g of water.

10 ml of oral suspension correspond to a single dose of 100 mg of the compound of the invention.

Production:

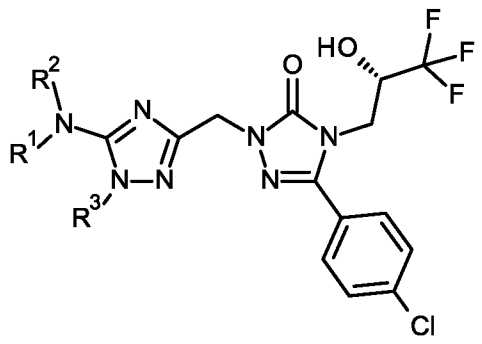
The Rhodigel is suspended in ethanol, and the compound of Example 1 is added to the suspension. The water is added while stirring. The mixture is stirred for about 6 h until swelling of the Rhodigel is complete.

Sterile i.v. solution:

The compound according to the invention is dissolved at a concentration below saturation solubility in a physiologically acceptable solvent (for example isotonic sodium chloride solution, glucose solution 5% and/or PEG 400 solution 30%). The solution is sterilized by filtration and filled into sterile and pyrogen-free injection containers.

CLAIMS:

1. A compound of general formula (I)



(I),

in which

R^1 represents hydrogen or methyl,

R^2 represents C_1-C_5-alkyl or a 5- or 6-membered heterocyclyl,

where alkyl may be substituted by 1 to 2 substituents independently of one another selected from the group consisting of fluorine, hydroxy, amino, aminocarbonyl, aminosulfonyl, difluoromethyl, trifluoromethyl, methoxy, ethoxy, C_3-C_6-cycloalkyl, 4- to 7-membered heterocyclyl, methylsulfonyl, methylcarbonylamino, 2,2,2-trifluoroethylaminocarbonyl, methylsulfonylamino and C_1-C_4-alkoxycarbonyl,

wherein heterocyclyl may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of oxo, chlorine, fluorine, hydroxy, formyl, aminocarbonyl, methyl, methoxy, trifluoromethyl, methylcarbonyl, methylsulfonyl and C_1-C_4-alkoxycarbonyl,

and

wherein cycloalkyl may be substituted by one substituent hydroxyl,

and

where heterocyclyl may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of oxo, chlorine, fluorine, hydroxy, aminocarbonyl, methyl, methoxy, trifluoromethyl, methylcarbonyl, methylsulfonyl and C_1-C_4-alkoxycarbonyl,

or

R^1 and R^2 together with the nitrogen atom to which they are attached form a 4- to 6-membered heterocyclyl, 6-oxo-2,5,7-triazaspiro[3.4]octan-2-yl, hexahydro-4H-furo[3,2-b]pyrrol-4-yl, 2,2-dioxido-2-thia-6-azaspiro[3.3]hept-6-yl or 2-oxa-6-azaspiro[3.3]hept-6-yl,

where heterocyclyl may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of oxo, chlorine, fluorine, hydroxy, aminocarbonyl, methyl, methoxy, trifluoromethyl, methylcarbonyl, methylsulfonyl and C_1-C_4-alkoxycarbonyl,

R^3 represents phenyl, pyridinyl or 3,3,3-trifluoroprop-1-yl,

where phenyl may be substituted by one substituent selected from the group consisting of chlorine, fluorine and trifluoromethyl,

and

where pyridinyl may be substituted by one substituent selected from the group consisting of chlorine, fluorine, trifluoromethyl and trifluoromethoxy,

or one of the pharmaceutically acceptable salts thereof, solvates thereof or solvates of the salts thereof.

2. A compound of general formula (I) according to Claim 1, characterized in that

R^1 represents hydrogen or methyl,

R^2 represents C_1-C_5-alkyl, pyrrolidin-3-yl or piperidin-5-yl,

where alkyl may be substituted by 1 to 2 substituents independently of one another selected from the group consisting of fluorine, hydroxy, amino, aminocarbonyl, aminosulfonyl, difluoromethyl, trifluoromethyl, methoxy, ethoxy, C_3-C_6-cycloalkyl, oxetan-3-yl, thietan-3-yl, pyrrolidin-1-yl, pyrrolidin-2-yl, 1,3-oxazolidin-5-yl, imidazolidin-1-yl, piperidin-4-yl, 1,2-thiazinan-2-yl, azepan-4-yl, methylsulfonyl, methylcarbonylamino, 2,2,2-trifluoroethylaminocarbonyl, methylsulfonylamino and C_1-C_4-alkoxycarbonyl,

wherein oxetan-3-yl, thietan-3-yl, pyrrolidin-1-yl, pyrrolidin-2-yl, 1,3-oxazolidin-5-yl, imidazolidin-1-yl, piperidin-4-yl, 1,2-thiazinan-2-yl and azepan-4-yl may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of oxo, chlorine, fluorine, hydroxy, formyl, aminocarbonyl, methyl, methoxy, trifluoromethyl, methylcarbonyl, methylsulfonyl and C_1-C_4-alkoxycarbonyl,

and

wherein cycloalkyl may be substituted by one substituent hydroxyl,

and

where pyrrolidin-3-yl and piperidin-5-yl may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of oxo, chlorine, fluorine, hydroxy, aminocarbonyl, methyl, methoxy, trifluoromethyl, methylcarbonyl, methylsulfonyl and C_1-C_4-alkoxycarbonyl,

or

R^1 and R^2 together with the nitrogen atom to which they are attached form azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, 6-oxo-2,5,7-triazaspiro[3.4]octan-2-yl, hexahydro-4H-furo[3,2-b]pyrrol-4-yl, 2,2-dioxido-2-thia-6-azaspiro[3.3]hept-6-yl or 2-oxa-6-azaspiro[3.3]hept-6-yl,

where azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl and thiomorpholinyl may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of oxo, chlorine, fluorine, hydroxy, aminocarbonyl, methyl, methoxy, trifluoromethyl, methylcarbonyl, methylsulfonyl and C_1-C_4-alkoxycarbonyl,

R^3 represents phenyl, pyridinyl or 3,3,3-trifluoroprop-1-yl,

where phenyl may be substituted by one substituent selected from the group consisting of chlorine, fluorine and trifluoromethyl,

and

where pyridinyl may be substituted by one substituent selected from the group consisting of chlorine, fluorine, trifluoromethyl and trifluoromethoxy,

or one of the pharmaceutically acceptable salts thereof, solvates thereof or solvates of the salts thereof.

3. A compound of general formula (I) according to Claim 1 or 2, characterized in that

R^1 represents hydrogen or methyl,

R^2 represents C_1-C_5-alkyl, pyrrolidin-3-yl or piperidin-5-yl,

where alkyl may be substituted by 1 to 2 substituents independently of one another selected from the group consisting of fluorine, hydroxy, amino, aminocarbonyl, aminosulfonyl, trifluoromethyl, methoxy, C_3-C_6-cycloalkyl, oxetan-3-yl, thietan-3-yl, pyrrolidin-1-yl, pyrrolidin-2-yl, 1,3-oxazolidin-5-yl, imidazolidin-1-yl, piperidin-4-yl, 1,2-thiazinan-2-yl, azepan-4-yl, methylsulfonyl, methylcarbonylamino, 2,2,2-trifluoroethylaminocarbonyl, methylsulfonylamino and C_1-C_4-alkoxycarbonyl,

wherein oxetan-3-yl, thietan-3-yl, pyrrolidin-1-yl, pyrrolidin-2-yl, 1,3-oxazolidin-5-yl, imidazolidin-1-yl, piperidin-4-yl, 1,2-thiazinan-2-yl and azepan-4-yl may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of oxo, hydroxy, formyl, methyl and C_1-C_4-alkoxycarbonyl,

and

wherein cycloalkyl may be substituted by one substituent hydroxyl,

and

where pyrrolidin-3-yl and piperidin-5-yl may be substituted by 1 or 2 substituents of oxo,

or

R^1 and R^2 together with the nitrogen atom to which they are attached form azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, 6-oxo-2,5,7-triazaspiro[3.4]octan-2-yl, hexahydro-4H-furo[3,2-b]pyrrol-4-yl, 2,2-dioxido-2-thia-6-azaspiro[3.3]hept-6-yl or 2-oxa-6-azaspiro[3.3]hept-6-yl,

where azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl and thiomorpholinyl may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of oxo, fluorine, hydroxy, aminocarbonyl, methyl, methoxy, trifluoromethyl, methylcarbonyl and methylsulfonyl,

R^3 represents phenyl, pyridinyl or 3,3,3-trifluoroprop-1-yl,

where phenyl may be substituted by one substituent selected from the group consisting of chlorine, fluorine and trifluoromethyl,

and

where pyridinyl may be substituted by one substituent selected from the group consisting of chlorine, fluorine and trifluoromethyl,

or one of the pharmaceutically acceptable salts thereof, solvates thereof or solvates of the salts thereof.

4. A compound of general formula (I) according to Claim 1, 2 or 3, characterized in that

R^1 represents hydrogen,

R^2 represents 2-hydroxy-2-methyl-prop-1-yl or 2-amino-2-methyl-prop-1-yl,

or

R^1 and R^2 together with the nitrogen atom to which they are attached form piperazinyl or 1,1-dioxidothiomorpholinyl,

where piperazinyl is substituted by 1 or 2 substituents independently of one another selected from the group consisting of oxo, methyl and trifluoromethyl,

R^3 represents phenyl or pyridin-2-yl,

where phenyl is substituted by one substituent trifluoromethyl in ortho-position to the point of attachment of the phenyl to the 1,2,4-triazolyl-ring,

and

where pyridin-2-yl may be substituted by one substituent selected from the group consisting of chlorine, fluorine and trifluoromethyl in ortho-position to the point of attachment of the pyridin-2-yl to the 1,2,4-triazolyl-ring,

or one of the pharmaceutically acceptable salts thereof, solvates thereof or solvates of the salts thereof.

5. The compound of the general formula (I) according to Claim 1, 2 or 3, characterized in that

R^1 represents hydrogen,

R^2 represents methyl,

where methyl is substituted by one substituent selected from the group consisting of cyclopropyl, cyclobutyl and thietan-3-yl,

wherein thietan-3-yl is substituted by 2 substituents oxo,

and

wherein cyclopropyl and cyclobutyl are substituted by one substituent hydroxyl,

or

R^1 and R^2 together with the nitrogen atom to which they are attached form azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl or 2,2-dioxido-2-thia-6-azaspiro[3.3]hept-6-yl,

where azetidinyl, pyrrolidinyl, piperidinyl and piperazinyl may be substituted by 1 or 2 substituents independently of one another selected from the group consisting of fluorine, hydroxy, methyl, trifluoromethyl, methylcarbonyl and methylsulfonyl,

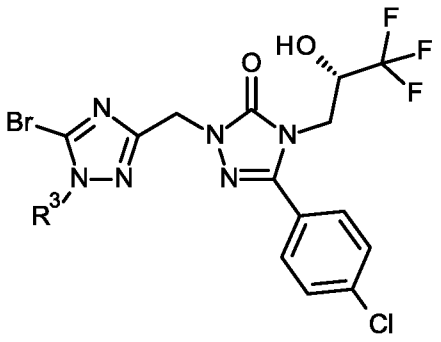
R^3 represents phenyl,

where phenyl may be substituted by one substituent selected from the group consisting of chlorine and fluorine in ortho-position or meta-position to the point of attachment of the phenyl to the 1,2,4-triazolyl-ring,

or one of the pharmaceutically acceptable salts thereof, solvates thereof or solvates of the salts thereof.

6. Process for preparing a compound of the general formula (I) or one of the pharmaceutically acceptable salts thereof, solvates thereof or solvates of the salts thereof according to Claim 1, characterized in that

[A] a compound of the formula



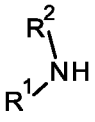
(II),

in which

R^3 has the meaning as defined for the compounds of general formula (I) given in Claim 1,

wherein the hydroxy group in the formula (II) may be protected with a tert-butyl-(dimethyl)silyl group at the beginning of the reaction and which is cleaved under the reaction conditions,

is reacted with a compound of the formula



(III),

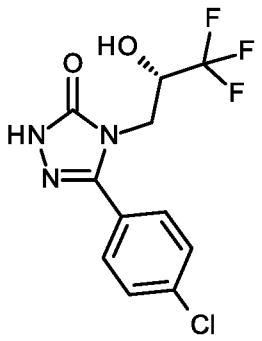
in which

R^1 and R^2 have the meaning as defined for the compounds of general formula (I) given in Claim 1,

to give a compound of the general formula (I)

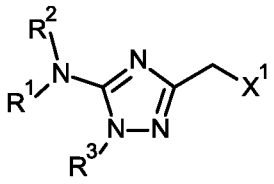
or

[B] a compound of the formula



(IV),

is reacted with a compound of the formula



(V),

in which

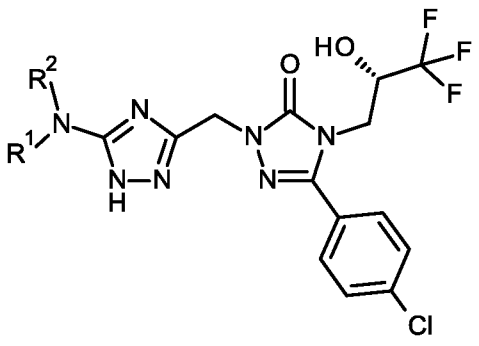
X^1 represents bromine or chlorine, and

R^1, R^2 and R^3 have the meaning as defined for the compounds of general formula (I) given in Claim 1,

to give a compound of the general formula (I)

or

[C] a compound of the formula



(VI),

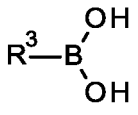
in which

R^1 and R^2 together with the nitrogen atom to which they are attached form a 4- to 6-membered heterocyclyl,

where heterocyclyl may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of oxo, chlorine, fluorine, hydroxy,

aminocarbonyl, methyl, methoxy, trifluoromethyl, methylcarbonyl, methylsulfonyl and C_1-C_4-alkoxycarbonyl,,

is reacted with a compound of the formula

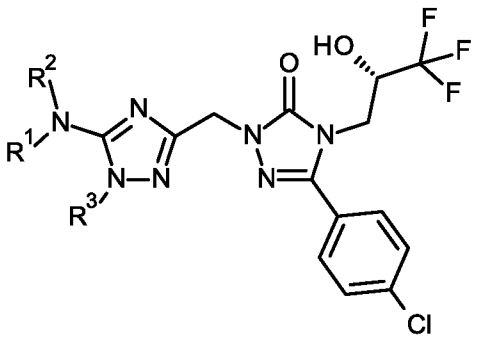


(VII),

in which

R^3 has the meaning as defined for the compounds of general formula (I) given in Claim 1,

under Chan-Lam coupling conditions to give a compound of the formula



(Ia),

in which

R^1 and R^2 together with the nitrogen atom to which they are attached form a 4- to 6-membered heterocyclyl,

where heterocyclyl may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of oxo, chlorine, fluorine, hydroxy, aminocarbonyl, methyl, methoxy, trifluoromethyl, methylcarbonyl, methylsulfonyl and C_1-C_4-alkoxycarbonyl,

and

R^3 has the meaning as defined for the compounds of general formula (I) given in Claim 1,

each [A], [B] and [C] optionally followed, where appropriate, by (*i*) separating the compound of the general formula (I) thus obtained into their respective diastereomers, and/or (*ii*) converting the compound of the general formula (I) into their respective pharmaceutically acceptable salts thereof, solvates thereof or the solvates of the salts thereof by treatment with the corresponding solvents and/or acids or bases.

7. Compound for use as defined in any of Claims 1 to 5 for the treatment and/or prevention of diseases.

8. Compound as defined in any of Claims 1 to 5 for use in a method for the treatment and/or prevention of acute and chronic kidney diseases including diabetic nephropathy, acute and chronic heart failure, preeclampsia, peripheral arterial disease (PAD), coronary microvascular dysfunction (CMD), Raynaud's syndrome, dysmenorrhea, cardiorenal syndrome, hypervolemic and euvolemic hyponatremia, liver cirrhosis, ascites, edema and the syndrome of inadequate ADH secretion (SIADH).

9. Use of a compound as defined in any of Claims 1 to 5 for the manufacture of a pharmaceutical composition for the treatment and/or prevention of acute and chronic kidney diseases including diabetic nephropathy, acute and chronic heart failure, preeclampsia, peripheral arterial disease (PAD), coronary microvascular dysfunction (CMD), Raynaud's syndrome dysmenorrhea, cardiorenal syndrome, hypervolemic and euvolemic hyponatremia, liver cirrhosis, ascites, edema and the syndrome of inadequate ADH secretion (SIADH).

10. Pharmaceutical composition comprising a compound as defined in any of Claims 1 to 5 and one or more pharmaceutically acceptable excipients.

11. Pharmaceutical composition of Claim 10 comprising one or more first active ingredients, in particular compounds of general formula (I) according to any one of claims 1 to 5, and one or more further active ingredients, in particular one or more additional therapeutic agents selected from the group consisting of diuretics, angiotensin AII antagonists, ACE inhibitors, beta-receptor blockers, mineralocorticoid receptor antagonists, organic nitrates, NO donors, activators and stimulators of the soluble guanylate cyclase, and positive-inotropic agents, antiinflammatory agents, immunosuppressive agents, phosphate binders and/or compounds which modulate vitamin D metabolism.

12. The pharmaceutical composition as defined in Claim 10 or 11 for the treatment and/or prevention of acute and chronic kidney diseases including diabetic nephropathy, acute and chronic heart failure, preeclampsia, peripheral arterial disease (PAD), coronary microvascular dysfunction (CMD), Raynaud's syndrome, dysmenorrhea, cardiorenal syndrome, hypervolemic and euvolemic hyponatremia, liver cirrhosis, ascites, edema and the syndrome of inadequate ADH secretion (SIADH).

13. Method for the treatment and/or prevention of acute and chronic kidney diseases including diabetic nephropathy, acute and chronic heart failure, preeclampsia, peripheral arterial disease (PAD) and coronary microvascular dysfunction (CMD), Raynaud's syndrome dysmenorrhea, cardiorenal syndrome, hypervolemic and euvolemic hyponatremia, liver cirrhosis, ascites, edema and the syndrome of inadequate ADH secretion (SIADH) in a

human or other mammal, comprising administering to a human or other mammal in need thereof a therapeutically effective amount of one or more compounds as defined in any of Claims 1 to 5, or of a pharmaceutical composition as defined in any of Claims 10 to 11.