



HU000028493T2

(19) **HU****MAGYARORSZÁG**
Szellemi Tulajdon Nemzeti Hivatala(11) Lajstromszám: **E 028 493**(13) **T2**

EURÓPAI SZABADALOM SZÖVEGÉNEK FORDÍTÁSA

(21) Magyar ügyszám: **E 13 745477**(22) A bejelentés napja: **2013. 06. 10.**

(96) Az európai bejelentés bejelentési száma:

EP 20130745477

(97) Az európai bejelentés közzétételi adatai:

EP 2718284 A1 **2013. 12. 19.**

(97) Az európai szabadalom megadásának meghirdetési adatai:

EP 2718284 B1 **2015. 11. 18.**(51) Int. Cl.: **C07D 403/12** (2006.01)**A61K 3141/96** (2006.01)**A61P 29/00** (2006.01)**C07D 249/12** (2006.01)**C07D 401/04** (2006.01)**C07D 409/14** (2006.01)**C07D 417/10** (2006.01)**C07D 417/12** (2006.01)**C07D 413/10** (2006.01)**C07D 405/12** (2006.01)**C07D 401/10** (2006.01)**C07D 403/04** (2006.01)**C07D 403/10** (2006.01)

(86) A nemzetközi (PCT) bejelentési szám:

PCT/IB 13/054752

(87) A nemzetközi közzétételi szám:

WO 13186692

(30) Elsőbbségi adatok:

MM17332012	2012. 06. 15.	IN
201261668146 P	2012. 07. 05.	US
MM33192012	2012. 11. 19.	IN
201261735679 P	2012. 12. 11.	US
MM03872013	2013. 02. 08.	IN
201361792225 P	2013. 03. 15.	US

(72) Feltaláló(k):

GHARAT, Laxmikant Atmaram, Thane
(West)Maharashtra 400601 (IN)
MUTHUKAMAN, Nagarajan, ErodeTamil Nadu 638151
(IN)
KHAIRATKAR-JOSHI, Neelima, Thane (W)Maharashtra
400602 (IN)
KATTIGE, Vidya Ganapati, Thane (W)Maharashtra
400607 (IN)

(73) Jogosult(ak):

Glenmark Pharmaceuticals S.A., 2300 La
Chaux-de-Fonds (CH)

(74) Képviselő:

ARINOVA Szabadalmi és Védjegy Iroda,
Budapest

(54)

Triazonon vegyületek MPGES-1 inhibitorokként

Az európai szabadalom ellen, megadásának az Európai Szabadalmi Közlönyben való meghirdetésétől számított kilenc hónapon belül, felszólalást lehet benyújtani az Európai Szabadalmi Hivatalnál. (Európai Szabadalmi Egyezmény 99. cikk(1))

A fordítást a szabadalmas az 1995. évi XXXIII. törvény 84/H. §-a szerint nyújtotta be. A fordítás tartalmi helyességét a Szellemi Tulajdon Nemzeti Hivatala nem vizsgálta.



(11) **EP 2 718 284 B1**

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention
of the grant of the patent:
18.11.2015 Bulletin 2015/47

(21) Application number: **13745477.3**

(22) Date of filing: **10.06.2013**

(51) Int Cl.:
C07D 403/12 ^(2006.01) **C07D 401/04** ^(2006.01)
C07D 401/10 ^(2006.01) **C07D 403/04** ^(2006.01)
C07D 403/10 ^(2006.01) **C07D 405/12** ^(2006.01)
C07D 409/14 ^(2006.01) **C07D 413/10** ^(2006.01)
C07D 417/10 ^(2006.01) **C07D 417/12** ^(2006.01)
C07D 249/12 ^(2006.01) **A61K 31/4196** ^(2006.01)
A61P 29/00 ^(2006.01)

(86) International application number:
PCT/IB2013/054752

(87) International publication number:
WO 2013/186692 (19.12.2013 Gazette 2013/51)

(54) **TRIAZOLONE COMPOUNDS AS mPGES-1 INHIBITORS**

TRIAZOLONVERBINDUNGEN ALS MPGES-1-INHIBITOREN

COMPOSÉS TRIAZOLONE UTILISÉS COMME INHIBITEURS DE LA MPGES-1

(84) Designated Contracting States:
**AL AT BE BG CH CY CZ DE DK EE ES FI FR GB
GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO
PL PT RO RS SE SI SK SM TR**

(30) Priority: **15.06.2012 IN MM17332012**
05.07.2012 US 201261668146 P
19.11.2012 IN MM33192012
11.12.2012 US 201261735679 P
08.02.2013 IN MM03872013
15.03.2013 US 201361792225 P

(43) Date of publication of application:
16.04.2014 Bulletin 2014/16

(73) Proprietor: **Glenmark Pharmaceuticals S.A.**
2300 La Chaux-de-Fonds (CH)

(72) Inventors:
• **GHARAT, Laxmikant Atmaram**
Thane (West)
Maharashtra 400601 (IN)

- **MUTHUKAMAN, Nagarajan**
Erode
Tamil Nadu 638151 (IN)
- **KHAIRATKAR-JOSHI, Neelima**
Thane (W)
Maharashtra 400602 (IN)
- **KATTIGE, Vidya Ganapati**
Thane (W)
Maharashtra 400607 (IN)

(74) Representative: **HGF Limited**
Belgrave Hall
Belgrave Street
Leeds LS2 8DD (GB)

(56) References cited:
WO-A1-2004/058731 WO-A1-2006/117657
GB-A- 1 068 083 US-A1- 2002 045 651

Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

EP 2 718 284 B1

DescriptionTechnical Field

5 **[0001]** The present application relates to triazolone compounds as mPGES-1 inhibitors.

Background of the Invention

10 **[0002]** There are many diseases or disorders that are inflammatory in their nature. One of the major problems associated with existing treatments of inflammatory conditions is inadequate efficacy and/or the prevalence of side effects. Inflammatory diseases that affect the population include asthma, inflammatory bowel disease, rheumatoid arthritis, osteoarthritis, rhinitis, conjunctivitis and dermatitis. Inflammation is also a common cause of pain.

15 **[0003]** The enzyme cyclooxygenase (COX) converts arachidonic acid to an unstable intermediate, prostaglandin H₂ (PGH₂), which is further converted to other prostaglandins, including PGE₂, PGF_{2α}, PGD₂, prostacyclin and thromboxane A₂. These arachidonic acid metabolites are known to have pronounced physiological and pathophysiological activity, including pro-inflammatory effects. The COX enzyme exists in two forms, one that is constitutively expressed in many cells and tissues (COX-1), and another that in most cells and tissues is induced by pro-inflammatory stimuli, such as cytokines, during an inflammatory response (COX-2).

20 **[0004]** Among all prostaglandin metabolites, PGE₂ is particularly known to be a strong pro-inflammatory mediator, and is also known to induce fever and pain. Consequently, numerous drugs have been developed with a view to inhibiting the formation of PGE₂, including "NSAIDs" (non-steroidal anti-inflammatory drugs) and "coxibs" (selective COX-2 inhibitors). These drugs act predominantly by inhibition of COX-1 and/or COX-2, thereby reducing the formation of PGE₂. However, the inhibition of COXs has the disadvantage of reducing the formation of all metabolites of PGH₂, thereby decreasing the beneficial properties of some of the metabolites. In view of this, drugs which act by inhibition of COXs are suspected to cause adverse biological effects. For example, the non-selective inhibition of COXs by NSAIDs may give rise to gastrointestinal side-effects and affect platelet and renal function. Even the selective inhibition of COX-2 by coxibs, whilst reducing such gastrointestinal side-effects, is believed to give rise to cardiovascular problems.

25 **[0005]** A combination of pharmacological, genetic and neutralizing antibody approaches demonstrates the importance of PGE₂ in inflammation. The conversion of PGH₂ to PGE₂ by prostaglandin E synthases (PGES) may, therefore, represent a pivotal step in the propagation of inflammatory stimuli. There are two microsomal prostaglandin E synthases (mPGES-1 and mPGES-2), and one cytosolic prostaglandin E synthase (cPGES). mPGES-1 is an inducible PGES after exposure to pro-inflammatory stimuli. mPGES-1 is induced in the periphery and CNS by inflammation, and represents therefore a target for acute and chronic inflammatory disorders. PGE₂ is a major prostanoid, produced from arachidonic acid liberated by phospholipases (PLAs), which drives the inflammatory processes. Arachidonic acid is transformed by the action of prostaglandin H synthase (PGH synthase, cyclooxygenase) into PGH₂ which is a substrate for mPGES-1, the terminal enzyme transforming PGH₂ to the pro-inflammatory PGE₂.

30 **[0006]** Agents that are capable of inhibiting the action of mPGES-1, and thus reducing the formation of the specific arachidonic acid metabolite PGE₂, are beneficial in the treatment of inflammation. Further, agents that are capable of inhibiting the action of the proteins involved in the synthesis of the leukotrienes are also beneficial in the treatment of asthma and COPD.

35 **[0007]** Blocking the formation of PGE₂ in animal models of inflammatory pain results in reduced inflammation, pain and fever response (Kojima et. al, The Journal of Immunology 2008, 180, 8361-6; Xu et. al., The Journal of Pharmacology and Experimental Therapeutics 2008, 326, 754-63). In abdominal aortic aneurism, inflammation leads to connective tissue degradation and smooth muscle apoptosis ultimately leading to aortic dilation and rupture. In animals lacking mPGES-1 a slower disease progression and disease severity has been demonstrated (Wang et. al., Circulation, 2008, 117, 1302-1309).

40 **[0008]** Several lines of evidence indicate that PGE₂ is involved in malignant growth. PGE₂ facilitates tumor progression by stimulation of cellular proliferation and angiogenesis and by modulation of immunosuppression. In support of a role for PGE₂ in cancers, genetic deletion of mPGES-1 in mice suppresses intestinal tumorigenesis (Nakanishi et. al., Cancer Research 2008, 68(9), 3251-9). In human beings, mPGES-1 is also upregulated in cancers such as colorectal cancer (Schroder, Journal of Lipid Research 2006, 47, 1071-80).

45 **[0009]** Myositis is a chronic muscle disorder characterized by muscle weakness and fatigue. Proinflammatory cytokines and prostanoids have been implicated in the development of myositis. In skeletal muscle tissue from patients suffering from myositis an increase in cyclooxygenases and mPGES-1 has been demonstrated, implicating mPGES-1 as a target for treating this condition. (Korotkova, Annals of the Rheumatic Diseases 2008, 67, 1596- 1602).

50 **[0010]** In atherosclerosis, inflammation of the vasculature leads to atheroma formation that eventually may progress into infarction. In patients with carotid atherosclerosis an increase in mPGES-1 in plaque regions has been reported (Gomez-Hernandez Atherosclerosis 2006, 187, 139-49). In an animal model of atherosclerosis, mice lacking the mPGES-

1 receptor were found to show a retarded atherogenesis and a concomitant reduction in macrophage-derived foam cells together with an increase in vascular smooth muscle cells (Wang, Proceedings of National Academy of Sciences 2006, 103(39), 14507-12).

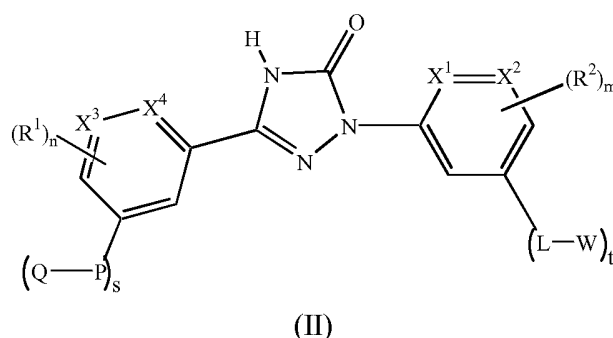
[0011] GB 1,068,083 discloses Δ^3 -1,2,4-triazoline derivatives having pharmacological properties, and in particular anti-inflammatory, antipyretic or analgesic activity. International Publication Nos. WO 2006/063466, WO 2007/059610, WO 2010/034796, WO 2010/100249, WO 2012/055995, WO 2012/110860 and WO 2013/038308 disclose numerous heterocyclic compounds which are stated to be inhibitors of the microsomal prostaglandin E synthase- 1 (mPGES-1) enzyme.

[0012] The present application is directed to compounds that act as inhibitors of the mPGES-1 enzyme and, therefore, are useful for the treatment of pain and inflammation in a variety of diseases or conditions.

Summary of the Invention

[0013] Embodiments relating to groups R^1 , R^2 , m, n, s, t, P, L, Q and W (and groups defined therein) are described hereinafter in relation to the compounds of formula (II), formula (III) and formula (IV).

[0014] The invention provides a compound of formula (II)



or a pharmaceutically acceptable salt thereof, wherein,

X^1 , X^2 , X^3 and X^4 are each independently selected from CH and N;

each occurrence of L is independently selected from $-\text{CH}_2\text{NHC(O)}-$ and $-\text{CH}_2\text{NHS(O)}_2-$;

each occurrence of P is independently selected from $-\text{CH}_2\text{NHC(O)}-$ and $-\text{CH}_2\text{NHS(O)}_2-$;

each occurrence of Q is independently selected from C_{1-8} alkyl, halo C_{1-8} alkyl, C_{1-8} alkoxy C_{1-8} alkyl, hydroxy C_{1-8} alkyl, carboxyl C_{1-8} alkyl, C_{3-12} cycloalkyl, C_{6-14} aryl, 3-15 membered heterocyclyl, and 5-14 membered heteroaryl;

each occurrence of W is independently selected from isopropyl, *tert*-butyl, trifluoromethyl, 1-fluoro-2-methylpropan-2-yl, 1-hydroxy-2-methylpropan-2-yl and cyclopropyl.

each occurrence of R^1 is independently selected from halogen, cyano, C_{1-8} alkyl, C_{1-8} alkoxy, halo C_{1-8} alkoxy C_{1-8} alkyl, halo C_{1-8} alkyl, C_{3-6} cycloalkyl, 5 membered heterocyclyl C_{1-8} alkyl, 5 membered heteroaryl, 5 membered heteroaryl C_{1-8} alkyl, and $-\text{C}\equiv\text{CR}$;

each occurrence of R^2 is independently selected from halogen, cyano, C_{1-8} alkyl, C_{1-8} alkoxy, halo C_{1-8} alkyl, C_{3-6} cycloalkyl, 5 membered heteroaryl, $-\text{C(O)NHR}$, $-\text{NHC(O)R}$, $-\text{S(O)}_2\text{NHR}$ and $-\text{C}\equiv\text{CR}$;

each occurrence of R is independently selected from C_{1-8} alkyl, C_{3-12} cycloalkyl, and C_{6-14} aryl;

'm' is an integer ranging from 0 to 3, both inclusive;

'n' is an integer ranging from 0 to 3, both inclusive;

's' is an integer ranging from 0 to 1, both inclusive; and

't' is an integer ranging from 0 to 1, both inclusive;

with the provisos that (i) 's' and 't' are not '0' simultaneously, and (ii) 'm' and 'n' are not '0' simultaneously.

[0015] The compounds of formula (II) may involve one or more embodiments. It is to be understood that the embodiments below are illustrative of the present invention and are not intended to limit the claims to the specific embodiments exemplified. It is also to be understood that the embodiments defined herein may be used independently or in conjunction with any definition of any other embodiment defined herein. Thus the invention contemplates all possible combinations and permutations of the various independently described embodiments. For example, the invention provides compounds of formula (II) as defined above wherein X^1 , X^2 , X^3 and X^4 are CH (according to an embodiment defined below), 'm' is 0, 1 or 2 (according to another embodiment defined below), and 's' is 0 any 't' is 1 (according to another embodiment

defined below).

[0016] According to one embodiment, specifically provided are compounds of formula (II), in which X¹, X², X³ and X⁴ are CH.

[0017] According to another embodiment, specifically provided are compounds of formula (II), in which X¹ is N and X², X³ and X⁴ are CH.

[0018] According to yet another embodiment, specifically provided are compounds of formula (II), in which X² is N and X¹, X³ and X⁴ are CH.

[0019] According to yet another embodiment, specifically provided are compounds of formula (II), in which X³ is N and X¹, X² and X⁴ are CH.

[0020] According to yet another embodiment, specifically provided are compounds of formula (II), in which each occurrence of L is -CH₂NHC(O)-.

[0021] According to yet another embodiment, specifically provided are compounds of formula (II), in which each occurrence of P is -CH₂NHC(O)-.

[0022] According to yet another embodiment, specifically provided are compounds of formula (II), in which each occurrence of R¹ is independently selected from cyano, halogen (e.g. F, Cl or Br), C₁₋₈alkyl (e.g. methyl), haloC₁₋₈alkyl (e.g. trifluoromethyl or difluoromethyl), C₁₋₈alkoxy (e.g. methoxy), haloC₁₋₈alkoxyC₁₋₈alkyl (e.g. (2,2,2-trifluoroethoxy)methyl), C₃₋₆cycloalkyl (e.g. cyclopropyl), 5 membered heterocyclylC₁₋₈alkyl (e.g. (pyrrolidin-1-yl)methyl), 5 membered heteroaryl (e.g. 4-methylthiophenyl, 5-isopropyl-1,3,4-oxadiazol-2-yl), 5 membered heteroarylC₁₋₈alkyl (e.g. (3,5-dimethyl-1H-pyrazol-1-yl)methyl) and -C≡CR.

[0023] According to yet another embodiment, specifically provided are compounds of formula (II), in which each occurrence of R¹ is independently selected from cyano, Cl, F, CHF₂, CF₃, OCH₃, CH₃, (2,2,2-trifluoroethoxy)methyl, cyclopropyl, (pyrrolidin-1-yl)methyl, 4-methylthiophenyl, 5-isopropyl-1,3,4-oxadiazol-2-yl, (3,5-dimethyl-1H-pyrazol-1-yl)methyl and -C≡CR. In this embodiment R is isopropyl, *tert*-butyl, cyclopropyl, 4-chloro-2-fluorophenyl, 3-chloro-2-fluorophenyl, 3-(trifluoromethyl)phenyl or 2-chloro-4-(trifluoromethyl)phenyl.

[0024] According to yet another embodiment, specifically provided are compounds of formula (II), in which each occurrence of R¹ is independently selected from cyano, Cl, F, CHF₂, CF₃, OCH₃, CH₃, (2,2,2-trifluoroethoxy)methyl, cyclopropyl, (pyrrolidin-1-yl)methyl, 4-methylthiophenyl, 5-isopropyl-1,3,4-oxadiazol-2-yl, (3,5-dimethyl-1H-pyrazol-1-yl)methyl, 3,3-dimethylbut-1-ynyl, 2-cyclopropylethynyl, (2,5-dichlorophenyl)ethynyl, (4-chloro-2-fluorophenyl)ethynyl, (3-chloro-2-fluorophenyl)ethynyl, (3-(trifluoromethyl)phenyl)ethynyl and (2-chloro-4-(trifluoromethyl)phenyl)ethynyl.

[0025] According to yet another embodiment, specifically provided are compounds of formula (II), in which each occurrence of R¹ is independently cyano, Cl, F, CHF₂, CF₃, OCH₃, CH₃, (2,2,2-trifluoroethoxy)methyl, cyclopropyl, (pyrrolidin-1-yl)methyl, 4-methylthiophenyl, 5-isopropyl-1,3,4-oxadiazol-2-yl, (3,5-dimethyl-1H-pyrazol-1-yl)methyl, 3,3-dimethylbut-1-ynyl, 2-cyclopropylethynyl, (2,5-dichlorophenyl)ethynyl, (4-chloro-2-fluorophenyl)ethynyl, (3-chloro-2-fluorophenyl)ethynyl, (3-(trifluoromethyl)phenyl)ethynyl or (2-chloro-4-(trifluoromethyl)phenyl)ethynyl; and 'n' is 1 or 2.

[0026] According to yet another embodiment, specifically provided are compounds of formula (II), in which 'n' is 0, 1 or 2.

[0027] According to yet another embodiment, specifically provided are compounds of formula (II), in which each occurrence of R² is independently selected from cyano, halogen (e.g. F, Cl or Br), C₁₋₈alkyl (e.g. methyl), haloC₁₋₈alkyl (e.g. trifluoromethyl), C₁₋₈alkoxy (e.g. methoxy), 5 membered heteroaryl (e.g. 3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl), -C(O)NHR, -NHC(O)R and -C≡CR.

[0028] According to yet another embodiment, specifically provided are compounds of formula (II), in which each occurrence of R² is independently -C(O)NHR, -NHC(O)R or -C≡CR. In this embodiment R is isopropyl, *tert*-butyl, cyclopropyl, 4-chloro-2-fluorophenyl, 3-chloro-2-fluorophenyl, 3-(trifluoromethyl)phenyl, 2-chloro-4-(trifluoromethyl)phenyl, 3-(difluoromethyl)-4-fluorophenyl or 3-(difluoromethyl)phenyl.

[0029] According to yet another embodiment, specifically provided are compounds of formula (II), in which each occurrence of R² is independently cyano, Cl, F, CH₃, CF₃, OCH₃, 3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl, cyclopropanecarboxamido, 3,3-dimethylbut-1-ynyl, 2-cyclopropylethynyl, -CONH-[3-(trifluoromethyl)phenyl], -CONH-[3-(difluoromethyl)-4-fluorophenyl] or -CONH-[3-(difluoromethyl)phenyl].

[0030] According to yet another embodiment, specifically provided are compounds of formula (II), in which each occurrence of R² is independently cyano, Cl, F, CH₃, CF₃, OCH₃, 3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl, cyclopropanecarboxamido, 3,3-dimethylbut-1-ynyl, 2-cyclopropylethynyl, -CONH-[3-(trifluoromethyl)phenyl], -CONH-[3-(difluoromethyl)-4-fluorophenyl] or -CONH-[3-(difluoromethyl)phenyl]; and 'm' is 1 or 2.

[0031] According to yet another embodiment, specifically provided are compounds of formula (II), in which 'm' is 0, 1 or 2.

[0032] According to yet another embodiment, specifically provided are compounds of formula (II), in which W is isopropyl, *tert*-butyl, trifluoromethyl, 1-fluoro-2-methylpropan-2-yl, 1-hydroxy-2-methylpropan-2-yl or cyclopropyl; 't' is 1; and 's' is 0.

[0033] According to yet another embodiment, specifically provided are compounds of formula (II), in which each occurrence of Q is C₁₋₈alkyl (e.g. isopropyl or *tert*-butyl), haloC₁₋₈alkyl (e.g. trifluoromethyl or 1-fluoro-2-methylpropan-2-yl), C₁₋₈alkoxyC₁₋₈alkyl (e.g. 1-methoxy-2-methylpropan-2-yl), hydroxyC₁₋₈alkyl (e.g. 1-hydroxyl-2-methylpropan-2-yl).

yl), C₃₋₁₂cycloalkyl (e.g. cyclopropyl, cyclobutyl or cyclopentyl), C₆₋₁₄aryl (e.g. 2-fluorophenyl), 3-15 membered heterocyclyl (e.g. tetrahydrofuranyl, tetrahydrofuran-2-yl, (S)-tetrahydrofuran-2-yl or (R)-tetrahydrofuran-2-yl) or 5-14 membered heteroaryl (e.g. isoxazolyl or 1-methyl-1*H*-imidazole-2-yl).

[0034] According to yet another embodiment, specifically provided are compounds of formula (II), in which each occurrence of Q is isopropyl, *tert*-butyl, trifluoromethyl, 1-fluoro-2-methylpropan-2-yl, 1-methoxy-2-methylpropan-2-yl, 1-hydroxy-2-methylpropan-2-yl, cyclopropyl, cyclobutyl, cyclopentyl, 2-fluorophenyl, tetrahydrofuranyl, tetrahydrofuranyl, tetrahydrofuran-2-yl, (S)-tetrahydrofuran-2-yl, (R)-tetrahydrofuran-2-yl, isoxazolyl or 1-methyl-1*H*-imidazole-2-yl.

[0035] According to yet another embodiment, specifically provided are compounds of formula (II), in which Q is isopropyl, *tert*-butyl, trifluoromethyl, 1-fluoro-2-methylpropan-2-yl, 1-methoxy-2-methylpropan-2-yl, 1-hydroxy-2-methylpropan-2-yl, cyclopropyl, cyclobutyl, cyclopentyl, 2-fluorophenyl, tetrahydrofuranyl, tetrahydrofuranyl, tetrahydrofuran-2-yl, (S)-tetrahydrofuran-2-yl, (R)-tetrahydrofuran-2-yl, isoxazolyl or 1-methyl-1*H*-imidazole-2-yl; 's' is 1; and 't' is 0.

[0036] According to yet another embodiment, specifically provided are compounds of formula (II), in which 's' is 0 and 't' is 1.

[0037] According to yet another embodiment, specifically provided are compounds of formula (II), in which 's' is 1 and 't' is 0.

[0038] According to yet another embodiment, specifically provided are compounds of formula (II), in which 's' is 1 and 't' is 1.

[0039] According to yet another embodiment, specifically provided are compounds of formula (II), in which each occurrence of R is independently selected from C₁₋₈alkyl (e.g. isopropyl or *tert*-butyl), C₃₋₁₂cycloalkyl (e.g. cyclopropyl) and C₆₋₁₄aryl (e.g. 4-chloro-2-fluorophenyl, 3-chloro-2-fluorophenyl, 3-(trifluoromethyl)phenyl, 2-chloro-4-(trifluoromethyl)phenyl, 3-(difluoromethyl)-4-fluorophenyl or 3-(difluoromethyl)phenyl).

[0040] According to yet another embodiment, specifically provided are compounds of formula (II), in which each occurrence of R is phenyl optionally substituted with one or more substituents selected from Cl, F, CH₃, trifluoromethyl and difluoromethyl.

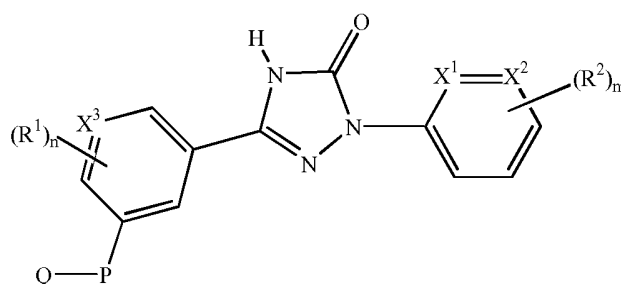
[0041] According to yet another embodiment, specifically provided are compounds of formula (II), in which each occurrence of R is independently isopropyl, *tert*-butyl, cyclopropyl, 4-chloro-2-fluorophenyl, 3-chloro-2-fluorophenyl, 3-(trifluoromethyl)phenyl, 2-chloro-4-(trifluoromethyl)phenyl, 3-(difluoromethyl)-4-fluorophenyl or 3-(difluoromethyl)phenyl.

[0042] According to an embodiment, specifically provided are compounds of formula (II) that exhibit an IC₅₀ value of less than 500 nM, preferably less than 100 nM, more preferably less than 50 nM with respect to mPGES-1 inhibition.

[0043] Further embodiments relating to groups R¹, R², m, n, s, t, P, L, Q and W (and groups defined therein) are described herein in relation to the compounds of formula (III) or formula (IV). It is to be understood that these embodiments are not limited to use in conjunction with formula (III) or formula (IV), but apply independently and individually to the compounds of formula (II). For example, in an embodiment described hereinafter, the invention specifically provides compounds of formula (III) or formula (IV) in which 'n' is 0, 1 or 2, and consequently there is also provided a compound of formula (II) in which 'n' is 0, 1 or 2.

[0044] The invention also provides a compound of formula (III).

[0045] Accordingly the invention provides the compound of formula (III)



(III)

or a pharmaceutically acceptable salt thereof,
wherein,

X¹, X² and X³ are each independently selected from CH and N;

P is selected from -CH₂NHC(O)- and -CH₂NHS(O)₂-;

Q is selected from C₁₋₈alkyl, haloC₁₋₈alkyl, C₁₋₈alkoxyC₁₋₈alkyl, hydroxyC₁₋₈alkyl, carboxylC₁₋₈alkyl, C₃₋₁₂cycloalkyl,

C₆₋₁₄aryl, 3-15 membered heterocyclyl, and 5-14 membered heteroaryl;

each occurrence of R¹ is independently selected from halogen, cyano, C₁₋₈alkyl, C₁₋₈alkoxy, haloC₁₋₈alkyl and C₃₋₆cycloalkyl;

each occurrence of R² is independently selected from halogen, cyano, C₁₋₈alkyl, C₁₋₈alkoxy, haloC₁₋₈alkyl, C₃₋₆cycloalkyl, 5 membered heteroaryl, -C(O)NHR, -NHC(O)R, -S(O)₂NHR and -C≡CR;

each occurrence of R is independently selected from C₁₋₈alkyl, C₃₋₁₂cycloalkyl, and C₆₋₁₄aryl;

'm' is an integer ranging from 0 to 3, both inclusive; and

'n' is an integer ranging from 0 to 3, both inclusive;

with the proviso that 'm' and 'n' are not '0' simultaneously.

[0046] The compounds of formula (III) may involve one or more embodiments. It is to be understood that the embodiments below are illustrative of the present invention and are not intended to limit the claims to the specific embodiments exemplified. It is also to be understood that the embodiments defined herein may be used independently or in conjunction with any definition of any other embodiment defined herein. Thus the invention contemplates all possible combinations and permutations of the various independently described embodiments. For example, the invention provides compounds of formula (III) as defined above wherein X¹, X² and X³ are CH (according to an embodiment defined below), 'm' is 0, 1 or 2 (according to another embodiment defined below) and 'n' is 0, 1 or 2 (according to another embodiment defined below).

[0047] According to one embodiment, specifically provided are compounds of formula (III), in which X¹, X² and X³ are CH.

[0048] According to another embodiment, specifically provided are compounds of formula (III), in which X¹ is N and X² and X³ are CH.

[0049] According to yet another embodiment, specifically provided are compounds of formula (III), in which X² is N and X¹ and X³ are CH.

[0050] According to yet another embodiment, specifically provided are compounds of formula (III), in which X³ is N and X¹ and X² are CH.

[0051] According to yet another embodiment, specifically provided are compounds of formula (III), in which P is -CH₂NHC(O)-.

[0052] According to yet another embodiment, specifically provided are compounds of formula (III), in which each occurrence of R¹ is independently selected from cyano, halogen (e.g. F, Cl or Br), C₁₋₈alkyl (e.g. methyl), haloC₁₋₈alkyl (e.g. trifluoromethyl or difluoromethyl), C₁₋₈alkoxy (e.g. methoxy) and C₃₋₆cycloalkyl (e.g. cyclopropyl).

[0053] According to yet another embodiment, specifically provided are compounds of formula (III), in which each occurrence of R¹ is independently selected from cyano, Cl, F, CHF₂, CF₃, OCH₃, CH₃ and cyclopropyl.

[0054] According to yet another embodiment, specifically provided are compounds of formula (III), in which each occurrence of R¹ is independently cyano, Cl, F, CHF₂, CF₃, OCH₃, CH₃ or cyclopropyl; and 'n' is 1 or 2.

[0055] According to yet another embodiment, specifically provided are compounds of formula (III), in which 'n' is 0, 1 or 2.

[0056] According to yet another embodiment, specifically provided are compounds of formula (III), in which each occurrence of R² is independently selected from cyano, halogen (e.g. F, Cl or Br), C₁₋₈alkyl (e.g. methyl), haloC₁₋₈alkyl (e.g. trifluoromethyl), C₁₋₈alkoxy (e.g. methoxy), 5 membered heteroaryl (e.g. 3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl), -C(O)NHR, -NHC(O)R and -C≡CR.

[0057] According to yet another embodiment, specifically provided are compounds of formula (III), in which each occurrence of R² is independently -C(O)NHR, -NHC(O)R and -C≡CR. In this embodiment R is isopropyl, *tert*-butyl, cyclopropyl, 4-chloro-2-fluorophenyl, 3-chloro-2-fluorophenyl, 3-(trifluoromethyl)phenyl, 2-chloro-4-(trifluoromethyl)phenyl, 3-(difluoromethyl)-4-fluorophenyl or 3-(difluoromethyl)phenyl.

[0058] According to yet another embodiment, specifically provided are compounds of formula (III), in which each occurrence of R² is independently cyano, Cl, F, CH₃, CF₃, OCH₃, 3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl, cyclopropanecarboxamido, 3,3-dimethylbut-1-ynyl, 2-cyclopropylethynyl, -CONH-[3-(trifluoromethyl)phenyl], -CONH-[3-(difluoromethyl)-4-fluorophenyl] or -CONH-[3-(difluoromethyl)phenyl].

[0059] According to yet another embodiment, specifically provided are compounds of formula (III), in which R² is independently cyano, Cl, F, CH₃, CF₃, OCH₃, 3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl, cyclopropanecarboxamido, 3,3-dimethylbut-1-ynyl, 2-cyclopropylethynyl, -CONH-[3-(trifluoromethyl)phenyl], -CONH-[3-(difluoromethyl)-4-fluorophenyl] or -CONH-[3-(difluoromethyl)phenyl]; and 'm' is 1 or 2.

[0060] According to yet another embodiment, specifically provided are compounds of formula (III), in which 'm' is 0, 1 or 2.

[0061] According to yet another embodiment, specifically provided are compounds of formula (III), in which Q is C₁₋₈alkyl (e.g. isopropyl or *tert*-butyl), haloC₁₋₈alkyl (e.g. trifluoromethyl or 1-fluoro-2-methylpropan-2-yl), C₁₋₈alkoxyC₁₋₈alkyl (e.g. 1-methoxy-2-methylpropan-2-yl), hydroxyC₁₋₈alkyl (e.g. 1-hydroxy-2-methylpropan-2-yl), C₃₋₁₂cycloalkyl (e.g. cyclopropyl, cyclobutyl or cyclopentyl), C₆₋₁₄aryl (e.g. 2-fluorophenyl), 3-15 membered heterocyclyl

(e.g. tetrahydrofuranyl, tetrahydrofuran-2-yl, (S)-tetrahydrofuran-2-yl or (R)-tetrahydrofuran-2-yl) or 5-14 membered heteroaryl (e.g. isoxazolyl or 1-methyl-1*H*-imidazole-2-yl).

[0062] According to yet another embodiment, specifically provided are compounds of formula (III), in which Q is isopropyl, *tert*-butyl, trifluoromethyl, 1-fluoro-2-methylpropan-2-yl, 1-methoxy-2-methylpropan-2-yl, 1-hydroxy-2-methylpropan-2-yl, cyclopropyl, cyclobutyl, cyclopentyl, 2-fluorophenyl, tetrahydrofuranyl, tetrahydrofuran-2-yl, (S)-tetrahydrofuran-2-yl, (R)-tetrahydrofuran-2-yl, isoxazolyl or 1-methyl-1*H*-imidazole-2-yl.

[0063] According to yet another embodiment, specifically provided are compounds of formula (III), in which each occurrence of R is independently selected from C₁₋₈alkyl (e.g. isopropyl or *tert*-butyl), C₃₋₁₂cycloalkyl (e.g. cyclopropyl) and C₆₋₁₄aryl (e.g. 4-chloro-2-fluorophenyl, 3-chloro-2-fluorophenyl, 3-(trifluoromethyl)phenyl, 2-chloro-4-(trifluoromethyl)phenyl, 3-(difluoromethyl)-4-fluorophenyl or 3-(difluoromethyl)phenyl).

[0064] According to yet another embodiment, specifically provided are compounds of formula (III), in which each occurrence of R is phenyl optionally substituted with one or more substituents selected from Cl, F, CH₃, trifluoromethyl and difluoromethyl.

[0065] According to yet another embodiment, specifically provided are compounds of formula (III), in which each occurrence of R is independently isopropyl, *tert*-butyl, cyclopropyl, 4-chloro-2-fluorophenyl, 3-chloro-2-fluorophenyl, 3-(trifluoromethyl)phenyl, 2-chloro-4-(trifluoromethyl)phenyl, 3-(difluoromethyl)-4-fluorophenyl or 3-(difluoromethyl)phenyl.

[0066] According to yet another embodiment, specifically provided are compounds of formula (III), in which:

each R¹ is, independently, cyano, Cl, F, CHF₂, CF₃, OCH₃, CH₃ or cyclopropyl;

each R² is, independently, cyano, Cl, F, CH₃, CF₃ or OCH₃;

P is -CH₂NHC(O)-;

'm' is 1 or 2;

'n' is 0, 1 or 2; and

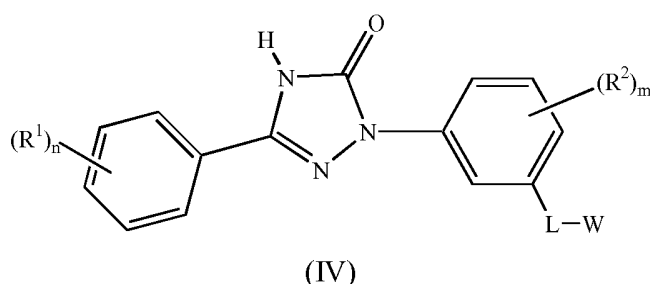
Q is isopropyl, *tert*-butyl, trifluoromethyl, 1-fluoro-2-methylpropan-2-yl, 1-methoxy-2-methylpropan-2-yl, 1-hydroxy-2-methylpropan-2-yl, cyclopropyl, cyclobutyl, cyclopentyl, 2-fluorophenyl, tetrahydrofuranyl, tetrahydrofuran-2-yl, (S)-tetrahydrofuran-2-yl, (R)-tetrahydrofuran-2-yl, isoxazolyl or 1-methyl-1*H*-imidazole-2-yl.

[0067] According to an embodiment, specifically provided are compounds of formula (III) which exhibit an IC₅₀ value of less than 500 nM, preferably less than 100 nM, more preferably less than 50 nM with respect to mPGES-1 inhibition.

[0068] Further embodiments relating to groups R¹, R², m, n, s, t, P, L, Q and W (and groups defined therein) are described herein in relation to the compounds of formula (II) or formula (IV). It is to be understood that these embodiments are not limited to use in conjunction with formula (II) or formula (IV), but apply independently and individually to the compounds of formula (III). For example, in an embodiment described hereinafter, the invention specifically provides compounds of formula (II) or formula (IV) in which 'n' is 0, 1 or 2, and consequently there is also provided a compound of formula (III) in which 'n' is 0, 1 or 2.

[0069] The invention also provides a compound of formula (IV).

[0070] Accordingly the invention provides the compound of formula (IV)



or a pharmaceutically acceptable salt thereof, wherein,

L is selected from -CH₂NHC(O)- and -CH₂NHS(O)₂;

W is selected from isopropyl, *tert*-butyl, trifluoromethyl, 1-fluoro-2-methylpropan-2-yl, 1-hydroxy-2-methylpropan-2-yl and cyclopropyl.

each occurrence of R¹ is independently selected from halogen, cyano, C₁₋₈alkyl, C₁₋₈alkoxy, haloC₁₋₈alkoxyC₁₋₈alkyl, haloC₁₋₈alkyl, C₃₋₆cycloalkyl, 5 membered heterocyclylC₁₋₈alkyl, 5 membered heteroaryl, 5 membered

heteroarylC₁₋₈alkyl, and - C≡C_R;

each occurrence of R² is independently selected from halogen, cyano, C₁₋₈alkyl, C₁₋₈alkoxy and haloC₁₋₈alkyl;

each occurrence of R is independently selected from C₁₋₈alkyl, C₃₋₁₂cycloalkyl, and C₆₋₁₄aryl;

'm' is an integer ranging from 0 to 3, both inclusive; and

'n' is an integer ranging from 0 to 3, both inclusive;

with the proviso that 'm' and 'n' are not '0' simultaneously.

[0071] The compounds of formula (IV) may involve one or more embodiments. It is to be understood that the embodiments below are illustrative of the present invention and are not intended to limit the claims to the specific embodiments exemplified. It is also to be understood that the embodiments defined herein may be used independently or in conjunction with any definition of any other embodiment defined herein. Thus the invention contemplates all possible combinations and permutations of the various independently described embodiments. For example, the invention provides compounds of formula (IV) as defined above wherein L is -CH₂NHC(O)- (according to an embodiment defined below), 'm' is 0, 1 or 2 (according to another embodiment defined below), and 'n' is 0, 1 or 2 (according to another embodiment defined below).

[0072] According to one embodiment, specifically provided are compounds of formula (IV), in which L is -CH₂NHC(O)-.

[0073] According to another embodiment, specifically provided are compounds of formula (IV), in which each occurrence of R¹ is independently selected from cyano, halogen (e.g. F, Cl or Br), C₁₋₈alkyl (e.g. methyl), haloC₁₋₈alkyl (e.g. trifluoromethyl or difluoromethyl), C₁₋₈alkoxy (e.g. methoxy), haloC₁₋₈alkoxyC₁₋₈alkyl (e.g. (2,2,2-trifluoroethoxy)methyl), 5 membered heterocyclylC₁₋₈alkyl (e.g. (pyrrolidin-1-yl)methyl), 5 membered heteroaryl (e.g. 4-methylthiophenyl, 5-isopropyl-1,3,4-oxadiazol-2-yl), 5 membered heteroarylC₁₋₈alkyl (e.g. (3,5-dimethyl-1H-pyrazol-1-yl)methyl) and -C≡CR.

[0074] According to yet another embodiment, specifically provided are compounds of formula (IV), in which each occurrence of R¹ is independently selected from cyano, Cl, F, CHF₂, CF₃, OCH₃, CH₃, (2,2,2-trifluoroethoxy)methyl, (pyrrolidin-1-yl)methyl, 4-methylthiophenyl, 5-isopropyl-1,3,4-oxadiazol-2-yl, (3,5-dimethyl-1H-pyrazol-1-yl)methyl and -C≡CR. In this embodiment R is isopropyl, *tert*-butyl, cyclopropyl, 4-chloro-2-fluorophenyl, 3-chloro-2-fluorophenyl, 3-(trifluoromethyl)phenyl or 2-chloro-4-(trifluoromethyl)phenyl.

[0075] According to yet another embodiment, specifically provided are compounds of formula (IV), in which each occurrence of R¹ is independently selected from cyano, Cl, F, CHF₂, CF₃, OCH₃, CH₃, (2,2,2-trifluoroethoxy)methyl, (pyrrolidin-1-yl)methyl, 4-methylthiophenyl, 5-isopropyl-1,3,4-oxadiazol-2-yl, (3,5-dimethyl-1H-pyrazol-1-yl)methyl, 3,3-dimethylbut-1-ynyl, 2-cyclopropylethynyl, (2,5-dichlorophenyl)ethynyl, (4-chloro-2-fluorophenyl)ethynyl, (3-chloro-2-fluorophenyl)ethynyl, (3-(trifluoromethyl)phenyl)ethynyl and (2-chloro-4-(trifluoromethyl)phenyl)ethynyl.

[0076] According to yet another embodiment, specifically provided are compounds of formula (IV), in which each occurrence of R¹ is independently cyano, Cl, F, CHF₂, CF₃, OCH₃, CH₃, (2,2,2-trifluoroethoxy)methyl, (pyrrolidin-1-yl)methyl, 4-methylthiophenyl, 5-isopropyl-1,3,4-oxadiazol-2-yl, (3,5-dimethyl-1H-pyrazol-1-yl)methyl, 3,3-dimethylbut-1-ynyl, 2-cyclopropylethynyl, (2,5-dichlorophenyl)ethynyl, (4-chloro-2-fluorophenyl)ethynyl, (3-chloro-2-fluorophenyl)ethynyl, (3-(trifluoromethyl)phenyl)ethynyl or (2-chloro-4-(trifluoromethyl)phenyl)ethynyl; and 'n' is 1 or 2.

[0077] According to yet another embodiment, specifically provided are compounds of formula (IV), in which 'n' is 0, 1 or 2.

[0078] According to yet another embodiment, specifically provided are compounds of formula (IV), in which each occurrence of R² is independently selected from cyano, halogen (e.g. F, Cl or Br), C₁₋₈alkyl (e.g. methyl), haloC₁₋₈alkyl (e.g. trifluoromethyl) and C₁₋₈alkoxy (e.g. methoxy).

[0079] According to yet another embodiment, specifically provided are compounds of formula (IV), in which each occurrence of R² is independently cyano, Cl, F, CH₃, CF₃ or OCH₃.

[0080] According to yet another embodiment, specifically provided are compounds of formula (IV), in which each occurrence of R² is independently cyano, Cl, F, CH₃, CF₃ or OCH₃; and 'm' is 1 or 2.

[0081] According to yet another embodiment, specifically provided are compounds of formula (IV), in which 'm' is 0, 1 or 2.

[0082] According to yet another embodiment, specifically provided are compounds of formula (IV), in which each occurrence of R is independently selected from C₁₋₈alkyl (e.g. isopropyl or *tert*-butyl), C₃₋₁₂cycloalkyl (e.g. cyclopropyl) and C₆₋₁₄aryl (e.g. 4-chloro-2-fluorophenyl, 3-chloro-2-fluorophenyl, 3-(trifluoromethyl)phenyl, 2-chloro-4-(trifluoromethyl)phenyl, 3-(difluoromethyl)-4-fluorophenyl or 3-(difluoromethyl)phenyl).

[0083] According to yet another embodiment, specifically provided are compounds of formula (IV), in which each occurrence of R is phenyl optionally substituted with one or more substituents selected from Cl, F, trifluoromethyl and difluoromethyl.

[0084] According to yet another embodiment, specifically provided are compounds of formula (IV), in which each occurrence of R is independently isopropyl, *tert*-butyl, cyclopropyl, 4-chloro-2-fluorophenyl, 3-chloro-2-fluorophenyl, 3-(trifluoromethyl)phenyl, 2-chloro-4-(trifluoromethyl)phenyl, 3-(difluoromethyl)-4-fluorophenyl or 3-(difluoromethyl)phenyl).

[0085] According to yet another embodiment, specifically provided are compounds of formula (IV), in which:

each occurrence of R¹ is independently Cl, F, CHF₂, CF₃, OCH₃, CH₃, 3,3-dimethylbut-1-ynyl, 2-cyclopropylethynyl, (2,5-dichlorophenyl)ethynyl, (4-chloro-2-fluorophenyl)ethynyl, 3-chloro-2-fluorophenyl)ethynyl, 3-(trifluoromethyl)phenyl)ethynyl or 2-chloro-4-(trifluoromethyl)phenyl)ethynyl;

each occurrence of R² is independently Cl, F, CH₃, CF₃ or OCH₃;

L is -CH₂NHC(O)-;

'm' is 1 or 2;

'n' is 0, 1 or 2; and

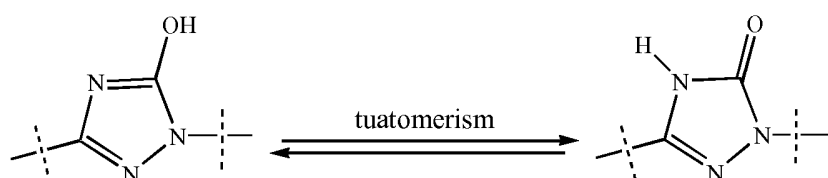
W is isopropyl, *tert*-butyl, trifluoromethyl, 1-fluoro-2-methylpropan-2-yl, 1-hydroxy-2-methylpropan-2-yl or cyclopropyl.

[0086] According to an embodiment, specifically provided are compounds of formula (IV) that exhibit an IC₅₀ value of less than 500 nM, preferably less than 100 nM, more preferably less than 50 nM with respect to mPGES-1 inhibition.

[0087] It should be understood that the formulas (I), (II), (III) and (IV), structurally encompass all geometrical isomers, stereoisomers, enantiomers and diastereomers, *N*-oxides, and pharmaceutically acceptable salts that may be contemplated from the chemical structure of the genera described herein.

[0088] Compounds of the present invention include the compounds in Examples 1-192.

[0089] According to an embodiment, the compounds of formula (II), formula (III) or formula (IV) structurally encompass all tautomeric forms whether such tautomer exists in equilibrium or predominantly in one form. Such tautomeric form may be different or the same when the compound is bound to the mPGES-1 enzyme.



[0090] The present application also provides a pharmaceutical composition that includes at least one compound described herein and at least one pharmaceutically acceptable excipient (such as a pharmaceutically acceptable carrier or diluent). Preferably, the pharmaceutical composition comprises a therapeutically effective amount of at least one compound described herein. The compounds described herein may be associated with a pharmaceutically acceptable excipient (such as a carrier or a diluent) or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container.

[0091] The compounds and pharmaceutical compositions of the present invention are useful for inhibiting the activity of mPGES-1, which is related to a variety of disease states.

[0092] The present disclosure further provides a method of inhibiting mPGES-1 in a subject in need thereof by administering to the subject one or more compounds described herein in an amount effective to cause inhibition of such receptor.

Detailed Description of the Invention

Definitions

[0093] The terms "halogen" or "halo" means fluorine (fluoro), chlorine (chloro), bromine (bromo), or iodine (iodo).

[0094] The term "alkyl" refers to a hydrocarbon chain radical that includes solely carbon and hydrogen atoms in the backbone, containing no unsaturation, having from one to eight carbon atoms (i.e. C₁₋₈alkyl), and which is attached to the rest of the molecule by a single bond, e.g., methyl, ethyl, n-propyl, 1-methylethyl (isopropyl), n-butyl, n-pentyl, and 1,1-dimethylethyl (t-butyl). The term "C₁₋₆ alkyl" refers to an alkyl chain having 1 to 6 carbon atoms. The term "C₁₋₄alkyl" refers to an alkyl chain having 1 to 4 carbon atoms. Unless set forth or recited to the contrary, all alkyl groups described or claimed herein may be straight chain or branched, substituted or unsubstituted.

[0095] The term "alkenyl" refers to a hydrocarbon chain containing from 2 to 10 carbon atoms (i.e. C₂₋₁₀alkenyl) and including at least one carbon-carbon double bond. Examples of alkenyl groups include ethenyl, 1-propenyl, 2-propenyl (allyl), *iso*-propenyl, 2-methyl-1-propenyl, 1-butenyl, and 2-butenyl. Unless set forth or recited to the contrary, all alkenyl groups described or claimed herein may be straight chain or branched, substituted or unsubstituted.

[0096] The term "alkynyl" refers to a hydrocarbyl radical having at least one carbon-carbon triple bond, and having 2 to about 12 carbon atoms (with radicals having 2 to about 10 carbon atoms being preferred i.e. C₂₋₁₀alkynyl). Examples of alkynyl groups include ethynyl, propynyl, and butynyl. Unless set forth or recited to the contrary, all alkynyl groups

described or claimed herein may be straight chain or branched, substituted or unsubstituted.

[0097] The term "alkoxy" denotes an alkyl group attached via an oxygen linkage to the rest of the molecule (i.e. C₁₋₈alkoxy). Representative examples of such groups are -OCH₃ and -OC₂H₅. Unless set forth or recited to the contrary, all alkoxy groups described or claimed herein may be straight chain or branched, substituted or unsubstituted.

[0098] The term "alkoxyalkyl" or "alkyloxyalkyl" refers to an alkoxy or alkyloxy group as defined above directly bonded to an alkyl group as defined above (i.e. C₁₋₈alkoxyC₁₋₈alkyl or C₁₋₈alkyloxyC₁₋₈alkyl). Examples of such alkoxyalkyl moiety include -CH₂OCH₃ and -CH₂OC₂H₅. Unless set forth or recited to the contrary, all alkoxyalkyl groups described herein may be straight chain or branched, substituted or unsubstituted.

[0099] The term "haloalkyl" refers to at least one halo group (selected from F, Cl, Br or I), linked to an alkyl group as defined above (i.e. haloC₁₋₈alkyl). Examples of such haloalkyl moiety include trifluoromethyl, difluoromethyl and fluoromethyl groups. Unless set forth or recited to the contrary, all haloalkyl groups described herein may be straight chain or branched, substituted or unsubstituted.

[0100] The term "haloalkoxy" refers to an alkoxy group substituted with one or more halogen atoms (i.e. haloC₁₋₈alkoxy). Examples of "haloalkoxy" include fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, pentafluoroethoxy, pentachloroethoxy, chloromethoxy, dichloromethoxy, trichloromethoxy and 1-bromoethoxy. Unless set forth or recited to the contrary, all haloalkoxy groups described herein may be straight chain or branched, substituted or unsubstituted.

[0101] The term "haloalkoxyalkyl" refers to haloalkoxy group as defined above directly bonded to an alkyl group as defined above (i.e. haloC₁₋₈alkoxyC₁₋₈alkyl). Examples of "haloC₁₋₈alkoxyC₁₋₈alkyl" include (2,2,2-trifluoroethoxy)methyl or (2,2-difluoroethoxy)methyl. Unless set forth or recited to the contrary, all haloalkoxyalkyl groups described herein may be straight chain or branched, substituted or unsubstituted.

[0102] The term "hydroxyalkyl" refers to an alkyl group as defined above wherein one to three hydrogen atoms on different carbon atoms is/are replaced by hydroxyl groups (i.e. hydroxyC₁₋₈alkyl). Examples of hydroxyalkyl moieties include -CH₂OH, -C₂H₄OH and -CH(OH)C₂H₄OH. Unless set forth or recited to the contrary, all hydroxyalkyl groups described herein may be straight chain or branched, substituted or unsubstituted.

[0103] The term "carboxyl" means the group -COOH.

[0104] The term "carboxylalkyl" refers to C₁₋₈alkyl group as defined above wherein at least one of the hydrogen atoms of the C₁₋₈alkyl group is replaced by a carboxyl group (i.e. "carboxylC₁₋₈alkyl"). Examples of carboxylalkyl moieties include carboxylmethyl (-CH₂-COOH), carboxylethyl (-CH₂-CH₂-COOH), carboxylisopropyl (-C(CH₃)₂-COOH) and carboxylterbutyl (-C(CH₃)₂CH₂-COOH). Unless set forth or recited to the contrary, all carboxylalkyl groups described herein may be straight chain or branched, substituted or unsubstituted.

[0105] The term "cycloalkyl" denotes a non-aromatic mono or multicyclic ring system of 3 to about 12 carbon atoms, (i.e. C₃₋₁₂cycloalkyl). Examples of monocyclic cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Examples of multicyclic cycloalkyl groups include, perhydronaphthyl, adamantyl and norbornyl groups, bridged cyclic groups or spirobicyclic groups, e.g., spiro(4,4)non-2-yl. The term "C₃₋₆cycloalkyl" refers to the cyclic ring having 3 to 6 carbon atoms. Unless set forth or recited to the contrary, all cycloalkyl groups described or claimed herein may be substituted or unsubstituted.

[0106] The term "cycloalkylalkyl" refers to a non-aromatic cyclic ring-containing radical having 3 to about 8 carbon atoms directly attached to an alkyl group (i.e. C₃₋₈cycloalkylC₁₋₈alkyl). The cycloalkylalkyl group may be attached to the main structure at any carbon atom in the alkyl group that results in the creation of a stable structure. Examples of such groups include cyclopropylmethyl, cyclobutylethyl, and cyclopentylethyl. Unless set forth or recited to the contrary, all cycloalkylalkyl groups described or claimed herein may be substituted or unsubstituted.

[0107] The term "cycloalkenyl" refers to a cyclic ring-containing radical having 3 to about 8 carbon atoms with at least one carbon-carbon double bond, (i.e. C₃₋₈cycloalkenyl). Examples of "cycloalkenyl" include cyclopropenyl, cyclobutenyl, and cyclopentenyl. Unless set forth or recited to the contrary, all cycloalkenyl groups described or claimed herein may be substituted or unsubstituted.

[0108] The term "cycloalkenylalkyl" refers to a non-aromatic cyclic ring-containing radical having 3 to about 8 carbon atoms with at least one carbon-carbon double bond, directly attached to an alkyl group, (i.e. C₃₋₈cycloalkenylC₁₋₈alkyl). Unless set forth or recited to the contrary, all cycloalkenylalkyl groups described or claimed herein may be substituted or unsubstituted.

[0109] The term "aryl" refers to an aromatic radical having 6 to 14 carbon atoms (i.e. C₆₋₁₄aryl), including monocyclic, bicyclic and tricyclic aromatic systems, such as phenyl, naphthyl, tetrahydronaphthyl, indanyl, and biphenyl. Unless set forth or recited to the contrary, all aryl groups described or claimed herein may be substituted or unsubstituted.

[0110] The term "aryloxy" refers to an aryl group as defined above attached via an oxygen linkage to the rest of the molecule (i.e. C₆₋₁₄aryloxy). Examples of aryloxy moieties include, phenoxy and naphthoxy. Unless set forth or recited to the contrary, all aryloxy groups described herein may be substituted or unsubstituted.

[0111] The term "arylalkyl" refers to an aryl group as defined above directly bonded to an alkyl group as defined above, i.e. C₆₋₁₄arylC₁₋₈alkyl, such as -CH₂C₆H₅ and -C₂H₄C₆H₅. Unless set forth or recited to the contrary, all arylalkyl groups

described or claimed herein may be substituted or unsubstituted.

[0112] The term "heterocyclic ring" or "heterocyclyl" unless otherwise specified refers to substituted or unsubstituted non-aromatic 3 to 15 membered ring radical (i.e. 3 to 15 membered heterocyclyl) which consists of carbon atoms and from one to five hetero atoms selected from nitrogen, phosphorus, oxygen and sulfur. The heterocyclic ring radical may be a mono-, bi- or tricyclic ring system, which may include fused, bridged or spiro ring systems, and the nitrogen, phosphorus, carbon, oxygen or sulfur atoms in the heterocyclic ring radical may be optionally oxidized to various oxidation states. In addition, the nitrogen atom may be optionally quaternized; also, unless otherwise constrained by the definition the heterocyclic ring or heterocyclyl may optionally contain one or more olefinic bond(s). Examples of such heterocyclic ring radicals include azepinyl, azetidiny, benzodioxolyl, benzodioxanyl, chromanyl, dioxolanyl, dioxaphospholanyl, decahydroisoquinolyl, indanyl, indoliny, isoindoliny, isochromanyl, isothiazolidinyl, isoxazolidinyl, morpholiny, oxazoliny, oxazolidinyl, oxadiazolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, octahydroindolyl, octahydroisoindolyl, perhydroazepinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, piperidinyl, phenothiazinyl, phenoxazinyl, quinclidinyl, tetrahydroisquinolyl, tetrahydrofuryl or tetrahydrofuranyl, tetrahydropyranyl, thiazoliny, thiazolidinyl, thiamorpholiny, thiamorpholiny sulfoxide and thiamorpholiny sulfone. Unless set forth or recited to the contrary, all heterocyclyl groups described or claimed herein may be substituted or unsubstituted.

[0113] The term "heterocyclylalkyl" refers to a heterocyclic ring radical directly bonded to an alkyl group (i.e. 3 to 15 membered heterocyclylC₁₋₈alkyl). Unless set forth or recited to the contrary, all heterocyclylalkyl groups described or claimed herein may be substituted or unsubstituted.

[0114] The term "heteroaryl" unless otherwise specified refers to substituted or unsubstituted 5 to 14 membered aromatic heterocyclic ring radical with one or more heteroatom(s) independently selected from N, O or S (i.e. 5 to 14 membered heteroaryl). The heteroaryl may be a mono-, bi- or tricyclic ring system. Examples of such heteroaryl ring radicals include oxazolyl, isoxazolyl, imidazolyl, furyl, indolyl, isoindolyl, pyrrolyl, triazolyl, triazinyl, tetrazoyl, thienyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrazolyl, benzofuranyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, benzothienyl, benzopyranyl, carbazolyl, quinoliny, isoquinoliny, quinazoliny, cinnoliny, naphthyridinyl, pteridinyl, purinyl, quinoxaliny, quinolyl, isoquinolyl, thiadiazolyl, indoliziny, acridiny, phenazinyl and phthalazinyl. Unless set forth or recited to the contrary, all heteroaryl groups described or claimed herein may be substituted or unsubstituted.

[0115] The term "heteroarylalkyl" refers to a heteroaryl ring radical directly bonded to an alkyl group (i.e. 5 to 14 membered heterarylC₁₋₈alkyl). Unless set forth or recited to the contrary, all heteroarylalkyl groups described or claimed herein may be substituted or unsubstituted.

[0116] Unless otherwise specified, the term "substituted" as used herein refers to substitution with any one or any combination of the following substituents: hydroxy, halogen, carboxyl, cyano, nitro, oxo (=O), thio (=S), substituted or unsubstituted alkyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted hydroxyl alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted haloalkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted guanidine, -COOR^x, -C(O)R^x, -C(S)R^x, -C(O)NR^xR^y, -C(O)ONR^xR^y, -NR^xCONR^yR^z, -N(R^x)SOR^y, -N(R^x)SO₂R^y, -(=N-N(R^x)R^y), -NR^xC(O)OR^y, -NR^xR^y, -NR^xC(O)R^y, -NR^xC(S)R^y, -NR^xC(S)NR^yR^z, -SONR^xR^y, -SO₂NR^xR^y, -OR^x, -OC(O)NR^yR^z, -OC(O)OR^y, -OC(O)R^x, -OC(O)NR^xR^y, -SR^x, -SOR^x, -SO₂R^x, and -ONO₂, wherein each occurrence of R^x, R^y and R^z are independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl, and substituted or unsubstituted heterocyclic ring. The substituents in the aforementioned "substituted" groups cannot be further substituted. For example, when the substituent on "substituted alkyl" is "substituted aryl", the substituent on "substituted aryl" can be unsubstituted alkenyl but cannot be "substituted alkenyl".

[0117] The term "pharmaceutically acceptable salt" includes salts prepared from pharmaceutically acceptable bases or acids including inorganic or organic bases and inorganic or organic acids. Examples of such salts include acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, *N*-methylglucamine ammonium salt, oleate, oxalate, pamoate (embonate), palmitate, pantothenate, phosphate, diphosphate, polygalacturonate, salicylate, stearate, sulfate, subacetate, succinate, tannate, tartrate, teo-clate, tosylate, triethiodide and valerate. Examples of salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, mangamous, potassium, sodium, and zinc.

[0118] The term "treating" or "treatment" of a state, disorder or condition includes: (a) preventing or delaying the appearance of clinical symptoms of the state, disorder or condition developing in a subject that may be afflicted with or predisposed to the state, disorder or condition but does not yet experience or display clinical or subclinical symptoms of the state, disorder or condition; (b) inhibiting the state, disorder or condition, i.e., arresting or reducing the development of the disease or at least one clinical or subclinical symptom thereof; or (c) relieving the disease, i.e., causing regression of the state, disorder or condition or at least one of its clinical or subclinical symptoms.

[0119] The term "subject" includes mammals (especially humans) and other animals, such as domestic animals (e.g., household pets including cats and dogs) and non-domestic animals (such as wildlife).

[0120] A "therapeutically effective amount" means the amount of a compound that, when administered to a subject for treating a state, disorder or condition, is sufficient to effect such treatment. The "therapeutically effective amount" may vary depending on the compound, the disease and its severity and the age, weight, physical condition and responsiveness of the subject to be treated.

[0121] The sensation of pain can be triggered by any number of physical or chemical stimuli and the sensory neurons which mediate the response to this harmful stimulus are termed as "nociceptors". Nociceptors are primary sensory afferent (C and A δ fibers) neurons that are activated by a wide variety of noxious stimuli including chemical, mechanical, thermal, and proton (pH<6) modalities. Nociceptors are the nerves which sense and respond to parts of the body which suffer from damage. They signal tissue irritation, impending injury, or actual injury. When activated, they transmit pain signals (via the peripheral nerves as well as the spinal cord) to the brain.

[0122] The term "chronic pain" usually refers to pain which persists for 3 months or longer and can lead to significant changes in a patient's personality, lifestyle, functional ability and overall quality of life. Chronic pain can be classified as either nociceptive or neuropathic. Nociceptive pain includes tissue injury-induced pain and inflammatory pain such as that associated with arthritis. Neuropathic pain is caused by damage to the sensory nerves of the peripheral or central nervous system and is maintained by aberrant somatosensory processing. The pain is typically well localized, constant, and often with an aching or throbbing quality. Visceral pain is the subtype of nociceptive pain that involves the internal organs. It tends to be episodic and poorly localized. Nociceptive pain is usually time limited, meaning when the tissue damage heals, the pain typically resolves (arthritis is a notable exception in that it is not time limited).

Pharmaceutical Compositions

[0123] The compounds of the invention are typically administered in the form of a pharmaceutical composition. Such compositions can be prepared using procedures known in the pharmaceutical art and comprise at least one compound of the invention. The pharmaceutical composition of the present patent application comprises one or more compounds described herein and one or more pharmaceutically acceptable excipients. Typically, the pharmaceutically acceptable excipients are approved by regulatory authorities or are generally regarded as safe for human or animal use. The pharmaceutically acceptable excipients include carriers, diluents, glidants and lubricants, preservatives, buffering agents, chelating agents, polymers, gelling agents, viscosifying agents, and solvents.

[0124] Examples of suitable carriers include water, salt solutions, alcohols, polyethylene glycols, peanut oil, olive oil, gelatin, lactose, terra alba, sucrose, dextrin, magnesium carbonate, sugar, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid, lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, fatty acid esters, and polyoxyethylene.

[0125] The pharmaceutical composition may also include one or more pharmaceutically acceptable auxiliary agents, wetting agents, suspending agents, preserving agents, buffers, sweetening agents, flavoring agents, colorants or any combination of the foregoing.

[0126] The pharmaceutical compositions may be in conventional forms, for example, capsules, tablets, solutions, suspensions, injectables or products for topical application. Further, the pharmaceutical composition of the present invention may be formulated so as to provide a desired release profile.

[0127] Administration of the compounds of the invention, in pure form or in an appropriate pharmaceutical composition, can be carried out using any of the accepted routes of administration of pharmaceutical compositions. The route of administration may be any route which effectively transports the active compound of the patent application to the appropriate or desired site of action. Suitable routes of administration include oral, nasal, buccal, dermal, intradermal, transdermal, parenteral, rectal, subcutaneous, intravenous, intraurethral, intramuscular, or topical.

[0128] Solid oral formulations include tablets, capsules (soft or hard gelatin), dragees (containing the active ingredient in powder or pellet form), troches and lozenges.

[0129] Liquid formulations include syrups, emulsions, and sterile injectable liquids, such as suspensions or solutions.

[0130] Topical dosage forms of the compounds include ointments, pastes, creams, lotions, powders, solutions, eye or ear drops, and impregnated dressings, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration.

[0131] The pharmaceutical compositions of the present patent application may be prepared by conventional tech-

niques, e.g., as described in Remington: The Science and Practice of Pharmacy, 20th Ed., 2003 (Lippincott Williams & Wilkins).

[0132] Suitable doses of the compounds for use in treating the diseases and disorders described herein can be determined by those skilled in the relevant art. Therapeutic doses are generally identified through a dose ranging study in humans based on preliminary evidence derived from animal studies. Doses are generally sufficient to result in a desired therapeutic benefit without causing unwanted side effects. Mode of administration, dosage forms, and suitable pharmaceutical excipients can also be well used and adjusted by those skilled in the art. All changes and modifications are envisioned within the scope of the present patent application.

[0133] In another embodiment, the present invention relates to a pharmaceutical composition comprising a compound as described herein, a second therapeutic agent, and optionally a pharmaceutically-acceptable excipient. In one embodiment, the pharmaceutical composition includes a compound as described herein and a second therapeutic agent, wherein each of the compound described herein and the second therapeutic agent is formulated in admixture with a pharmaceutically-acceptable excipient.

Medical Uses

[0134] Compounds of the present invention are particularly useful because they may inhibit the activity of prostaglandin E synthases (and particularly microsomal prostaglandin E synthase-1 (mPGES-1)), i.e., they prevent, inhibit, or suppress the action of mPGES-1 or a complex of which the mPGES-1 enzyme forms a part, and/or may elicit mPGES-1 modulating effect. Compounds of the invention are thus useful in the treatment of those conditions treatable by inhibition of a PGES, and particularly mPGES-1.

[0135] Compounds of the invention are thus expected to be useful in the treatment of inflammation. The term "inflammation" will be understood by those skilled in the art to include any condition characterized by a localized or a systemic protective response, which may be elicited by physical trauma, infection, chronic diseases, such as those mentioned hereinbefore, and/or chemical and/or physiological reactions to external stimuli (e.g. as part of an allergic response). Any such response, which may serve to destroy, dilute or sequester both the injurious agent and the injured tissue, may be manifest by, for example, heat, swelling, pain, redness, dilation of blood vessels and/or increased blood flow.

[0136] The term "inflammation" is also understood to include any inflammatory disease, disorder or condition per se, any condition that has an inflammatory component associated with it, and/or any condition characterized by inflammation as a symptom, including, *inter alia*, acute, chronic, ulcerative, specific, allergic, infection by pathogens, immune reactions due to hypersensitivity, entering foreign bodies, physical injury, and necrotic inflammation, and other forms of inflammation known to those skilled in the art. The term thus also includes, for the purposes of this invention, inflammatory pain, pain generally and/or fever.

[0137] The compounds of the present invention may also be useful in the treatment of asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, inflammatory bowel disease, irritable bowel syndrome, inflammatory pain, chronic pain, acute pain, fever, migraine, headache, low back pain, fibromyalgia, myofascial disorders, viral infections (e.g. influenza, common cold, herpes zoster, hepatitis C and AIDS), bacterial infections, fungal infections, dysmenorrhea, burns, surgical or dental procedures, malignancies (e.g. breast cancer, colon cancer, and prostate cancer), hyperprostaglandin E syndrome, classic Bartter syndrome, atherosclerosis, gout, arthritis, osteoarthritis, juvenile arthritis, rheumatoid arthritis, juvenile onset rheumatoid arthritis, rheumatic fever, ankylosing spondylitis, Hodgkin's disease, systemic lupus erythematosus, vasculitis, pancreatitis, nephritis, bursitis, conjunctivitis, iritis, scleritis, uveitis, wound healing, dermatitis, eczema, psoriasis, stroke, diabetes mellitus, neurodegenerative disorders such as Alzheimer's disease and multiple sclerosis, autoimmune diseases, allergic disorders, rhinitis, ulcers, mild to moderately active ulcerative colitis, familial adenomatous polyposis, coronary heart disease, sarcoidosis and any other disease with an inflammatory component.

[0138] Compounds of the invention may also have effects that are not linked to inflammatory mechanisms, such as in the reduction of bone loss in a subject. Conditions that may be mentioned in this regard include osteoporosis, osteoarthritis, Paget's disease and/or periodontal diseases.

[0139] By virtue of the mPGES-1 inhibitory activity of compounds of the present invention, the compounds are useful for the relief of pain, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, migraine (acute and prophylactic treatment), toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, juvenile rheumatoid arthritis, degenerative joint diseases (osteoarthritis), acute gout and ankylosing spondylitis, acute, subacute and chronic musculoskeletal pain syndromes such as bursitis, burns, injuries, and pain following surgical (post-operative pain) and dental procedures as well as the preemptive treatment of surgical pain. The pain may be mild pain, moderate pain, severe pain, musculoskeletal pain, complex regional pain syndrome, neuropathic pain, back pain such as acute visceral pain, neuropathies, acute trauma, chemotherapy - induced mononeuropathy pain states, polyneuropathy pain states (such as diabetic peripheral neuropathy & chemotherapy induced neuropathy), autonomic neuropathy

pain states, peripheric nervous system (PNS) lesion or central nervous system (CNS) lesion or disease related pain states, polyradiculopathies of cervical, lumbar or sciatica type, cauda equina syndrome, piriformis syndrome, paraplegia, quadriplegia, pain states related to various Polyneuritis conditions underlying various infections, chemical injuries, radiation exposure, underlying disease or deficiency conditions (such as beriberi, vitamin deficiencies, hypothyroidism, porphyria, cancer, HIV, autoimmune disease such as multiple sclerosis and spinal-cord injury, fibromyalgia, nerve injury, ischaemia, neurodegeneration, stroke, post stroke pain, inflammatory disorders, oesophagitis, gastroesophageal reflux disorder (GERD), irritable bowel syndrome, inflammatory bowel disease, pelvic hypersensitivity, urinary incontinence, cystitis, stomach duodenal ulcer, muscle pain, pain due to colicky and referred pain. Compounds of the present invention may also be useful for the treatment or prevention of endometriosis, hemophilic arthropathy and Parkinson's disease.

[0140] Compounds of the present invention will also inhibit prostanoid-induced smooth muscle contraction by preventing the synthesis of contractile prostanoids and hence may be of use in the treatment of dysmenorrhea, premature labor and asthma.

[0141] In addition, the compounds of the present invention may inhibit cellular neoplastic transformations and metastatic tumor growth and hence can be used in the treatment of cancer, and pain associated with cancer. Furthermore, the present invention provides preferred embodiments of the uses as described herein, in which cancer includes Acute Lymphoblastic Leukemia, Acute Myeloid Leukemia, Adolescents Cancer, Adrenocortical Carcinoma, Anal Cancer, Appendix Cancer, Astrocytomas, Atypical Teratoid, Basal Cell Carcinoma, Bile Duct Cancer, Extrahepatic, Bladder Cancer, Bone Cancer, Brain Stem Glioma, Brain Tumor, Breast Cancer, Bronchial Tumors, Burkitt Lymphoma, Carcinoid Tumor, Carcinoma of Unknown Primary, Cardiac (Heart) Tumors, Central Nervous System tumors, Cervical Cancer, Childhood Cancers, Chordoma, Chronic Lymphocytic Leukemia, Chronic Myelogenous Leukemia, Chronic Myeloproliferative Disorders, Colon Cancer, Colorectal Cancer, Craniopharyngioma, Cutaneous T-Cell Lymphoma, Duct Bile Extrahepatic cancer, Ductal Carcinoma In Situ, Embryonal Tumors, Central Nervous System cancer, Endometrial Cancer, Ependymoma, Esophageal Cancer, Esthesioneuroblastoma, Ewing Sarcoma, Extracranial Germ Cell Tumor, Extragonadal Germ Cell Tumor, Extrahepatic Bile Duct Cancer, Eye Cancer, Fibrous Histiocytoma of Bone, Malignant, and Osteosarcoma, Gall bladder Cancer, Gastric (Stomach) Cancer, Gastrointestinal Carcinoid Tumor, Gastrointestinal Stromal Tumors, Germ Cell Tumor, Gestational Trophoblastic Tumor, Glioma, Hairy Cell Leukemia, Head and Neck Cancer, Heart Cancer, Hepatocellular (Liver) Cancer, Histiocytosis, Langerhans Cell, Hodgkin Lymphoma, Hypopharyngeal Cancer, Intraocular Melanoma, Islet Cell Tumors, Pancreatic Neuroendocrine Tumors, Kaposi Sarcoma, Kidney cancer, Langerhans Cell Histiocytosis, Laryngeal Cancer, Acute Lymphoblastic Leukemia, Acute Myeloid Leukemia, Chronic Lymphocytic Leukemia, Chronic Myelogenous Leukemia, Hairy Cell Leukemia, Lip and Oral Cavity Cancer, Liver Cancer, Lobular Carcinoma In Situ, Lung Cancer, AIDS-Related Lymphoma, Cutaneous T-Cell Lymphoma, Hodgkin Lymphoma, Non-Hodgkin Lymphoma, Primary Central Nervous System (CNS) Lymphoma, Macroglobulinemia, Waldenström, Male Breast Cancer, Malignant Fibrous Histiocytoma of Bone and Osteosarcoma, Melanoma, Merkel Cell Carcinoma, Mesothelioma, Malignant, Metastatic Squamous Neck Cancer with Occult Primary, Midline Tract Carcinoma Involving NUT Gene, Mouth Cancer, Multiple Endocrine Neoplasia Syndromes, Multiple Myeloma/Plasma Cell Neoplasm, Mycosis Fungoides, Myelodysplastic Syndromes, Myelodysplastic/Myeloproliferative Neoplasms, Myelogenous Leukemia, Chronic, Myeloid Leukemia Acute, Multiple Myeloma, Chronic Myeloproliferative Disorders, Nasal Cavity and Paranasal Sinus Cancer, Nasopharyngeal Cancer, Neuroblastoma, Non-Hodgkin Lymphoma, Non-Small Cell Lung Cancer, Oral Cancer, Oral Cavity Cancer, Lip and, Oropharyngeal Cancer, Osteosarcoma and Malignant Fibrous Histiocytoma of Bone, Ovarian Cancer, Pancreatic Cancer, Papillomatosis, Paraganglioma, Paranasal Sinus and Nasal Cavity Cancer, Parathyroid Cancer, Penile Cancer, Pharyngeal Cancer, Pheochromocytoma, Pituitary Tumor, Plasma Cell Neoplasm/Multiple Myeloma, Pleuropulmonary Blastoma, Pregnancy and Breast Cancer, Primary Central Nervous System (CNS) Lymphoma, Prostate Cancer, Rectal Cancer, Renal Cell (Kidney) Cancer, Renal Pelvis and Ureter, Transitional Cell Cancer, Retinoblastoma, Rhabdomyosarcoma, Salivary Gland Cancer, Ewing Sarcoma, Kaposi Sarcoma, Osteosarcoma, Rhabdomyosarcoma, Soft Tissue Sarcoma, Uterine Sarcoma, Sézary Syndrome, Skin Cancer, Small Cell Lung Cancer, Small Intestine Cancer, Soft Tissue Sarcoma, Squamous Cell Carcinoma, Squamous Neck Cancer with Occult Primary, Metastatic, Stomach (Gastric) Cancer, T-Cell Lymphoma, Cutaneous, Testicular Cancer, Throat Cancer, Thymoma and Thymic Carcinoma, Thyroid Cancer, Transitional Cell Cancer of the Renal Pelvis and Ureter, Trophoblastic Tumor, Gestational, Unknown Primary, Carcinoma of, Ureter and Renal Pelvis, Transitional Cell Cancer, Urethral Cancer, Uterine Cancer, Endometrial, Uterine Sarcoma, Vaginal Cancer, Vulvar Cancer, Waldenström, Macroglobulinemia, Wilms Tumor and Women's Cancers.

[0142] The compounds of the present invention may be useful in the treatment of disease, disorder, syndrome or condition selected from the group consisting of inflammation, asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, inflammatory bowel disease, irritable bowel syndrome, pain, inflammatory pain, chronic pain, acute pain, fever, migraine, headache, low back pain, fibromyalgia, myofascial disorders, viral infections, influenza, common cold, herpes zoster, hepatitis C, AIDS, bacterial infections, fungal infections, dysmenorrhea, burns, surgical or dental procedures, malignancies hyperprostaglandin E syndrome, classic Bartter syndrome, synovitis, atherosclerosis, gout, arthritis, osteoarthritis, juvenile arthritis, rheumatoid arthritis, juvenile onset rheumatoid arthritis, rheumatic fever, ankylosing spond-

ylitis, Hodgkin's disease, systemic lupus erythematosus, vasculitis, pancreatitis, nephritis, bursitis, conjunctivitis, iritis, scleritis, uveitis, wound healing, dermatitis, eczema, psoriasis, stroke, diabetes mellitus, cancer, neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis and multiple sclerosis, autoimmune diseases, allergic disorders, rhinitis, ulcers, mild to moderately active ulcerative colitis, familial adenomatous polyposis, coronary heart disease, and sarcoidosis.

[0143] The compounds of the present invention may be useful in the treatment of pain, chronic pain, acute pain, rheumatoid arthritic pain or osteoarthritic pain.

[0144] The compounds of the present invention may be useful in the treatment of inflammation, neurodegenerative disorders such as Parkinson's disease, Alzheimer's disease and amyotrophic lateral sclerosis.

[0145] The compounds of the present invention may be useful in the treatment prevention or management of the cancer.

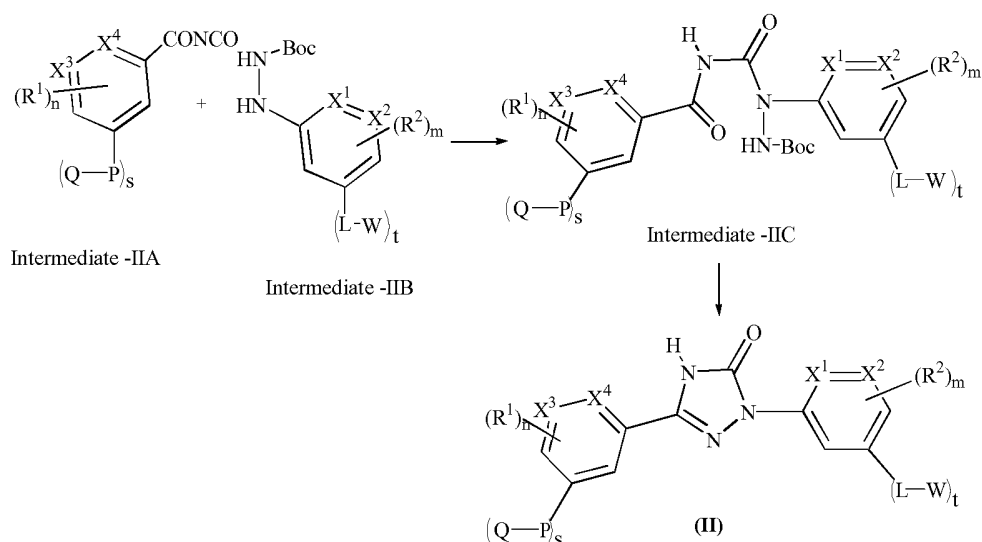
[0146] Compounds of the present invention are indicated both in the therapeutic and/or prophylactic treatment of the above-mentioned conditions. For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated. The daily dosage of the compound of the invention may be in the range from 0.05 mg/kg to 100 mg/kg.

General Methods of Preparation

[0147] The compounds described herein, including compounds of general formula (II), (III), and (IV) and specific examples can be prepared using techniques known to one skilled in the art through the reaction sequences depicted in Synthetic Scheme-I, Synthetic Scheme-II, Synthetic Scheme-III, Synthetic Scheme-IV, Synthetic Scheme-V, Synthetic Scheme-VI, Synthetic Scheme-VII, Synthetic Scheme-VIII, Synthetic Scheme-IX, Synthetic Scheme-X and Synthetic Scheme-XI as well as by other methods. Furthermore, in the following schemes, where specific acids, bases, reagents, coupling agents, solvents, etc. are mentioned, it is understood that other suitable acids, bases, reagents, coupling agents etc. may be used and are included within the scope of the present invention. Modifications to reaction conditions, for example, temperature, duration of the reaction or combinations thereof, are envisioned as part of the present invention. The compounds obtained by using the general reaction sequences may be of insufficient purity. These compounds can be purified by using any of the methods for purification of organic compounds known to persons skilled in the art, for example, crystallization or silica gel or alumina column chromatography using different solvents in suitable ratios. All possible geometrical isomers and stereo isomers are envisioned within the scope of this invention.

[0148] The compound of formula (II) can be prepared following the synthetic steps depicted in Synthetic Scheme-II (wherein R¹, R², L, P, Q, W, X¹, X², X³, X⁴, m, n, s and t are as defined with respect to a compound of formula (II)).

Synthetic Scheme-II

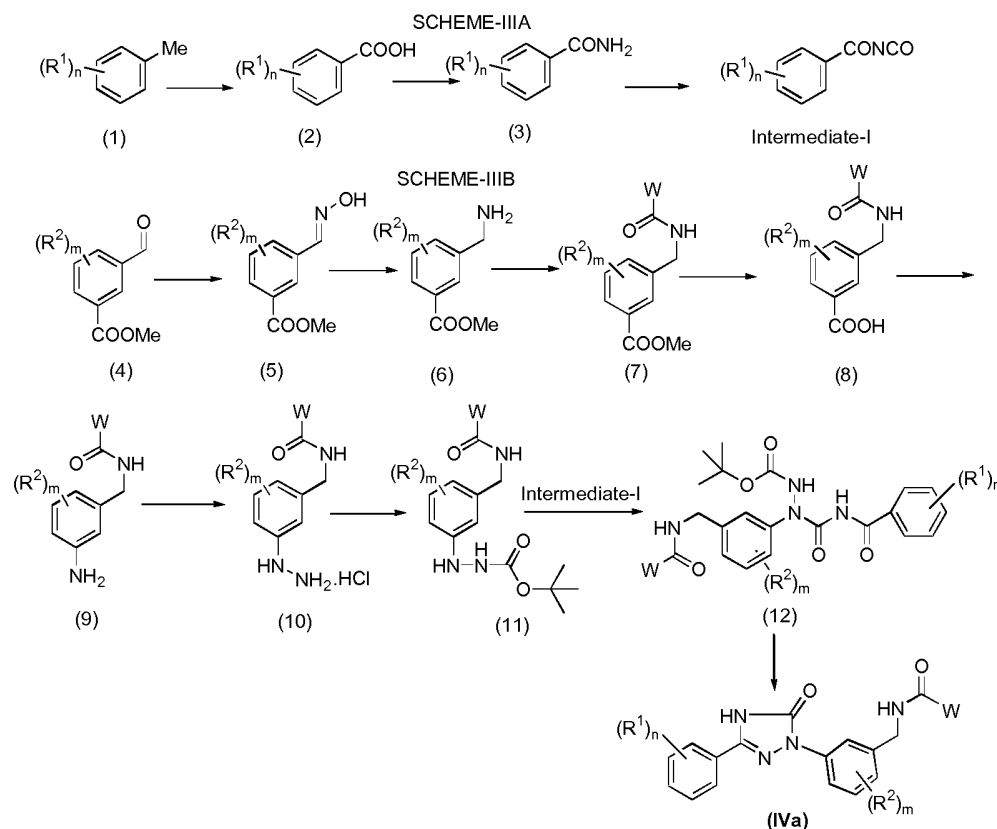


[0149] An Isocyanate compound of formula (Intermediate-IIA) may be obtained from a corresponding acid, amide or acid halide derivative. A compound of formula (Intermediate-IIA) can be treated with (or coupled to) a compound of formula (Intermediate-IIB) to form a compound of formula (Intermediate-IIC). A compound of formula (Intermediate-IIC) can be treated with an acid such as an organic acid (e.g. TFA, CSA or methane sulphonic acid) at room temperature to obtain a compound of formula (II). According to the process, the compound of formula (Intermediate-IIA) can be reacted

with the compound of formula (Intermediate-IIB) in a solvent such as DCM, toluene or EDC. According to the process, the compound of formula Intermediate-IIC may be isolated or not isolated.

[0150] An approach for the preparation of compound of formula (IVa) is schematically represented in Synthetic Scheme-III (wherein R¹, R², W, m, and n are as defined with respect to a compound of formula (IV)).

Synthetic Scheme-III



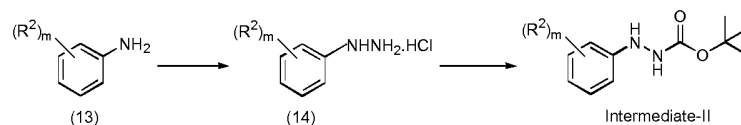
[0151] A compound of formula (1) (Scheme-III A) can be converted to a compound of formula (2) by using general oxidation methods known in the art using oxidizing agents such as KMnO₄, CrO₃, K₂Cr₂O₇ etc. A compound of formula (2) can be converted to a compound of formula (3) by using reaction conditions such as oxalyl chloride/NH₃, thionyl chloride/ NH₃ or EDCI/NH₄Cl. A compound of formula (3) can be treated with oxalyl chloride in solvents such as EDC or toluene to obtain Intermediate-I (Scheme-III A).

[0152] A compound of formula (5) (Scheme-III B) can be prepared from a compound of formula (4) according to known procedures in the literature and can be further converted to a compound of formula (6) by known reducing agents such as Fe/HCl or Zn/HCl. A compound of formula (6) can be converted to a compound of formula (7) by reacting it with aromatic or aliphatic carbonyl chloride using solvent such as dry THF. A compound of formula (7) can be converted to a compound of formula (8) by hydrolysis, for example with NaOH, KOH or LiOH. A compound of formula (8) can be treated with NaN₃ and conc. H₂SO₄ (e.g., at about 50°C) to give a compound of formula (9). A compound of formula (9) can be converted to a compound of formula (10) by reaction with an aqueous solution of sodium nitrite and a solution of stannous chloride in conc. HCl. A compound of formula (10) can be converted to a compound of formula (11) by using an aqueous solution of inorganic bases such as Na₂CO₃ or K₂CO₃ and BOC anhydride in a solvent such as THF or DMF. A compound of formula (11) can be treated with Intermediate-I to obtain a compound of formula (12). The compound of formula (11) can be reacted with the Intermediate-I in an aprotic solvent such as DCM, toluene or EDC to obtain the compound of formula (12). A compound of formula (12) can be treated with organic acid to obtain compound of formula (IVa) (Scheme-III B). The organic acid used in the conversion of the compound of formula (12) may be TFA, CSA or methane sulphonic acid.

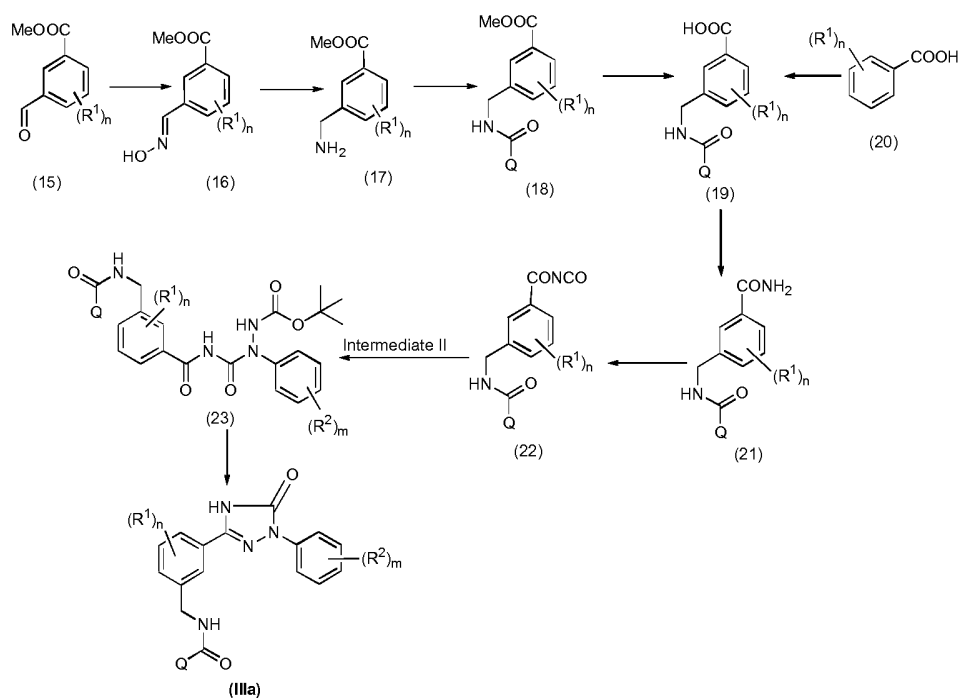
[0153] An approach for the preparation of compound of formula (IIIa) is schematically represented in Synthetic Scheme-IV (wherein R¹, R², Q, m, and n are as defined with respect to a compound of formula (III)).

Synthetic Scheme-IV

SCHEME-IVA



SCHEME-IVB

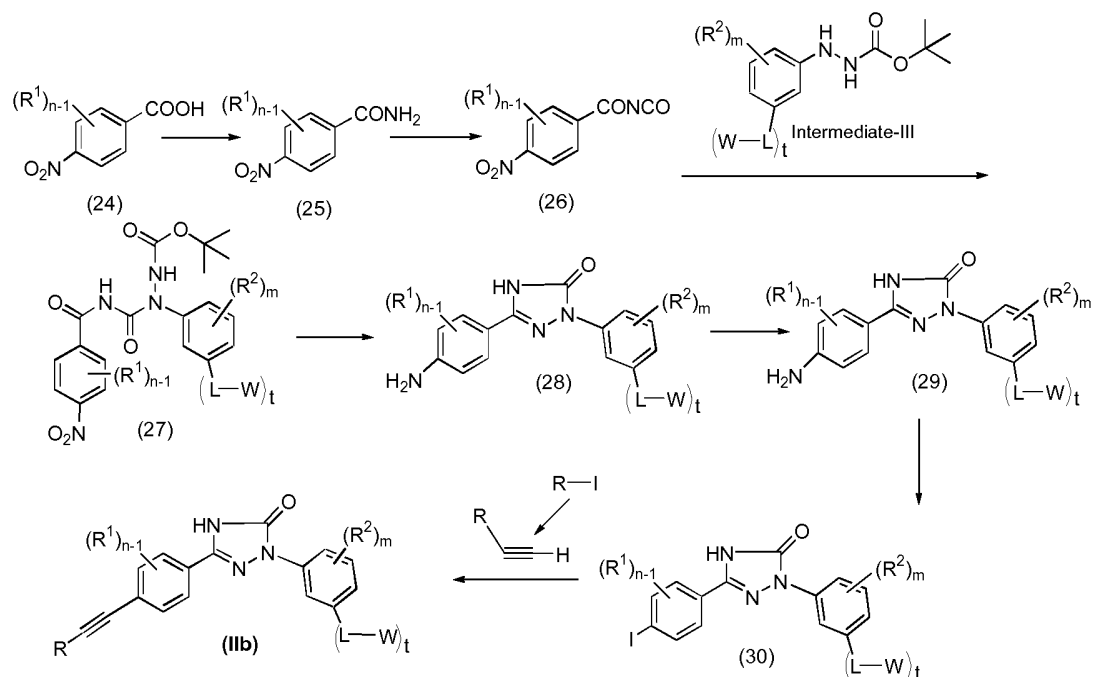


[0154] A compound of formula (13) can be converted to a compound of formula (14) by reaction with an aqueous solution of sodium nitrite and a solution of stannous chloride in conc. HCl, which can be further converted to Intermediate-II by using BOC protection methods known in the art of synthesis in the presence of inorganic bases such as Na₂CO₃, K₂CO₃ by using aprotic solvents such as THF, DMF at 0-100°C. A compound of formula (19) can be prepared from a compound of formula (15) by following the reaction steps as given in scheme IIB for a compound of formula (8). Also, a compound of formula (19) can be directly prepared from a compound of formula (20) by using 2,2,2-trifluoro-N-(hydroxymethyl)acetamide and sulphuric acid. A compound of formula (19) can be converted to a compound of formula (21) by using reaction conditions such as oxalyl chloride/NH₃, thionyl chloride/NH₃ or EDCI/NH₄Cl, which can be further treated with oxalyl chloride in a solvent such as EDC or toluene to give a compound of formula (22).

[0155] A compound of formula (22) can be treated with Intermediate-II to obtain a compound of formula (23). The compound of formula (22) can be treated with the Intermediate-II in an aprotic solvent, such as DCM, toluene or EDC to obtain a compound of formula (23). A compound of formula (23) can be treated with organic acid to obtain compound of formula (IIIa). The organic acid used in the conversion of a compound of formula (23) may be TFA, CSA or methane sulphonic acid. The compound of formula (IIIa) can be converted to a free amine for further amide derivatization by procedures known in the art of synthesis.

[0156] An approach for the preparation of compound of formula (IIb) is schematically represented in Synthetic Scheme-V (wherein L, W, R¹, R², R, t, m, and n are as defined with respect to a compound of formula (II)).

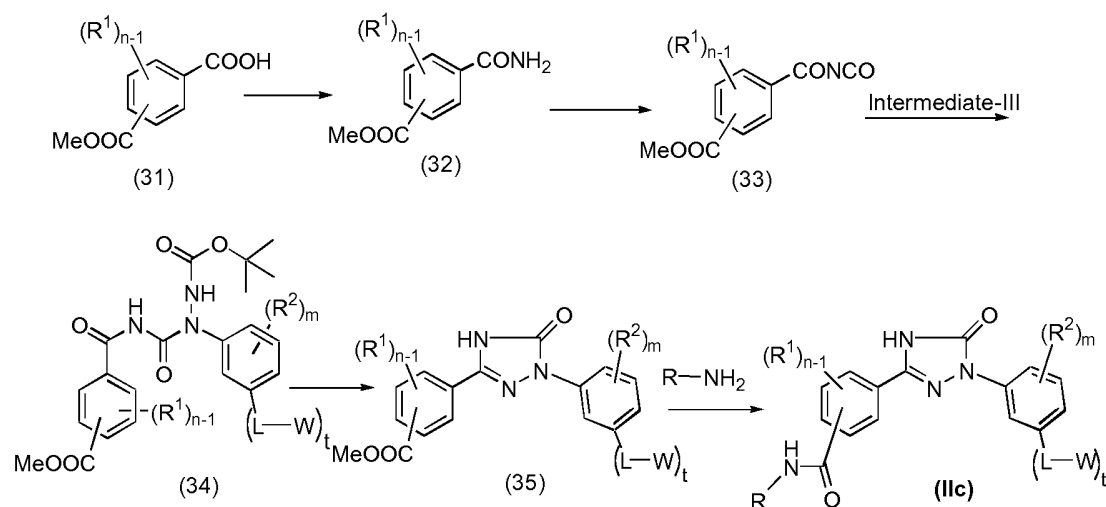
Synthetic Scheme-V



[0157] A compound of formula (24) can be converted to a compound of formula (25) by using reaction conditions such as oxalyl chloride/NH₃, thionyl chloride/NH₃ or EDCI/NH₄Cl, which can be further treated with oxalyl chloride in a solvent such as EDC or toluene to give a compound of formula (26). A compound of formula (26) can be treated with Intermediate-III in an aprotic solvent, such as DCM, toluene or EDC to obtain a compound of formula (27), which then further treated with an organic acid, such as TFA, CSA or methane sulphonic acid at room temperature give a compound of formula (28). A compound of formula (28) can be converted to a compound of formula (29) by reduction methods known in the art of synthesis such as Pd/C, Fe-HCl or Raney Nickel in a solvent such as MeOH or EtOH, which can be further converted to a compound of formula (30) by iodination using KI followed by diazotization using PTSA and NaNO₂. A compound of formula (30) can be converted to a compound of formula (IIb) by a sequence of transformations such as transition metal catalyzed reactions for example Sonogashira coupling.

[0158] An approach for the preparation of compound of formula (IIc) is schematically represented in Synthetic Scheme-VI (wherein L, W, R¹, R², R, m, and n are as defined with respect to a compound of formula (II)).

Synthetic Scheme-VI



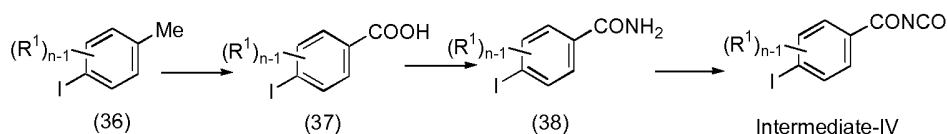
[0159] A compound of formula (31) can be converted to a compound of formula (32) by using standard conditions such as oxalyl chloride/ NH_3 , thionyl chloride/ NH_3 or EDCI/ NH_4Cl , which can be further treated with oxalyl chloride in a solvent, such as EDC or toluene to give a compound of formula (33). A compound of formula (33) can be treated with (or coupled to) Intermediate-III in an aprotic solvent, such as DCM, toluene or EDC to obtain a compound of formula (34), which when further treated with organic acid, such as TFA, CSA or methane sulphonic acid at room temperature give a compound of formula (35). A compound of formula (35) can be prepared from a compound of formula (35) by using trimethyl aluminum and solvents such as toluene, xylene or EDC at a temperature of 0-100°C.

[0160] Alternatively, the methyl ester of a compound of formula (35) can be converted to its acid derivative under hydrolysis condition, which can be further treated with the amines of the formula R-NH_2 to give compound of formula (35) using standard coupling conditions such as EDCI, HBTU, TBTU, DCC etc.

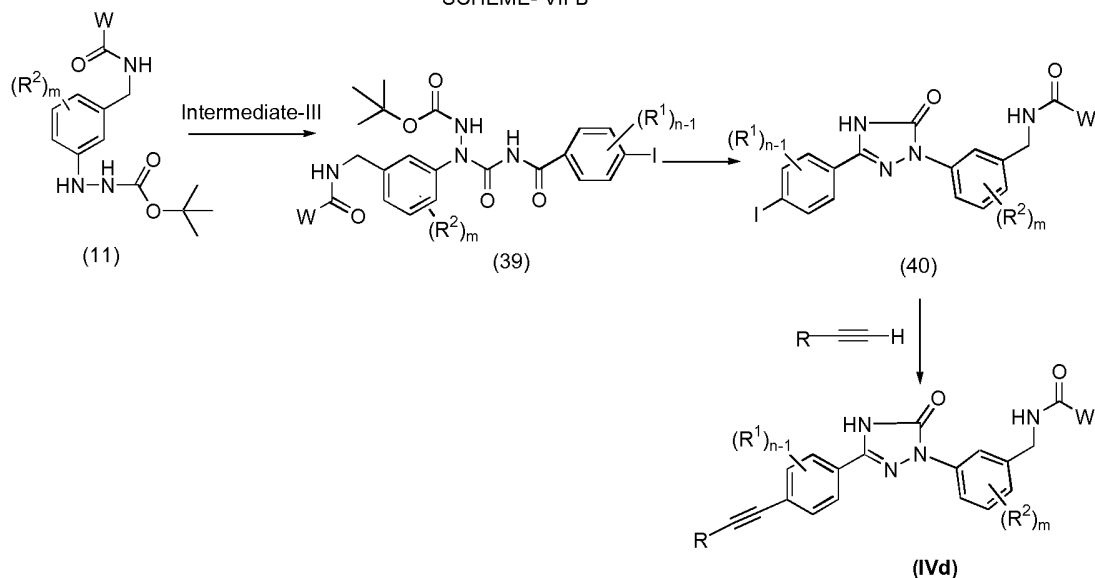
[0161] An approach for the preparation of a compound of formula (IVd) is schematically represented in Synthetic Scheme-VII (wherein R^1 , R^2 , R, W, m, and n are as defined with respect to a compound of formula (IV)).

Synthetic Scheme-VII

SCHEME- VII A



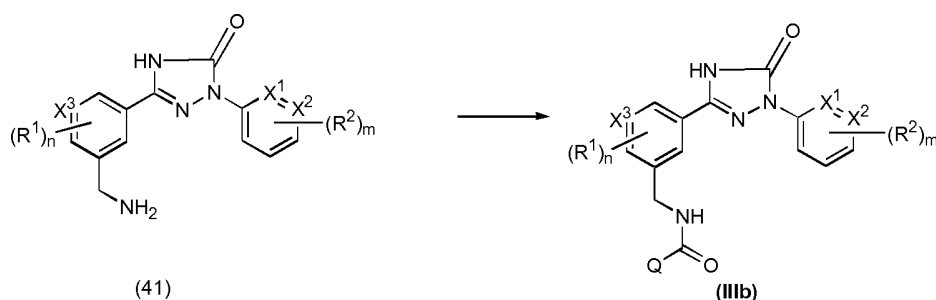
SCHEME- VII B



[0162] A compound of formula (36) can be converted to Intermediate-IV by following the same reaction steps as for Intermediate-I described in scheme IIIA. A compound of formula (11) can be treated with Intermediate-IV in an aprotic solvent, such as DCM, toluene or EDC to obtain a compound of formula (39), which when further treated with organic acid, such as TFA, CSA or methane sulphonic acid at room temperature give a compound of formula (40). A compound of formula (40) can be converted to a compound of formula (IVd) by a sequence of transformations such as transition metal catalyzed reactions for example Sonogashira coupling.

[0163] In another approach, the compound of formula (IIIb) can be prepared following the synthetic steps depicted in Synthetic Scheme-VIII (wherein X^1 , X^2 , X^3 , R^1 , R^2 , Q, m and n are as defined with respect to a compound of formula (III)).

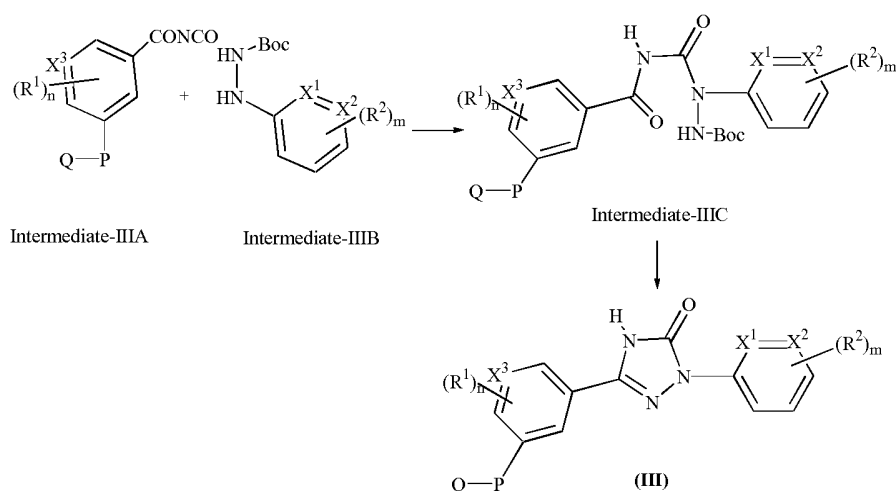
Synthetic Scheme-VIII



[0164] A compound of formula (41) can be reacted with Q-C(O)LG (wherein LG represents a suitable leaving group (e.g., OH or Cl or Br or O-alkyl)) under suitable reaction conditions to obtain a compound of formula (IIIb). When LG represents Cl the reaction can be performed in a suitable solvent such as DMF, DCM or THF in the temperature range of 0-120°C, optionally in the presence of a suitable base such as DIPEA or Et₃N. Furthermore, when LG represents O-alkyl the reaction can be performed with a suitable reagent such as trimethylaluminium or a strong base such as sodium hydride (NaH) in a suitable solvent such as toluene or DMF. When LG represents OH, the reaction can be performed with a suitable coupling reagent known in the art, for example, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) in a suitable solvent such as DMF or tetrahydrofuran (THF) in the temperature range of 0-120°C, optionally in the presence of a suitable base such as DIPEA (diisopropylethyl amine) or Et₃N. Alternatively, the reaction can be performed using a suitable reagent such as isobutyl chloroformate, oxalyl chloride or thionyl chloride in a suitable solvent such as DMF, DCM or THF, in the presence of a suitable base such as DIPEA or Et₃N.

[0165] In another approach, the compound of formula (III) can be prepared following the synthetic steps depicted in Synthetic Scheme-IX (wherein R¹, R², P, Q, X¹, X², X³, m and n are as defined with respect to a compound of formula (III)).

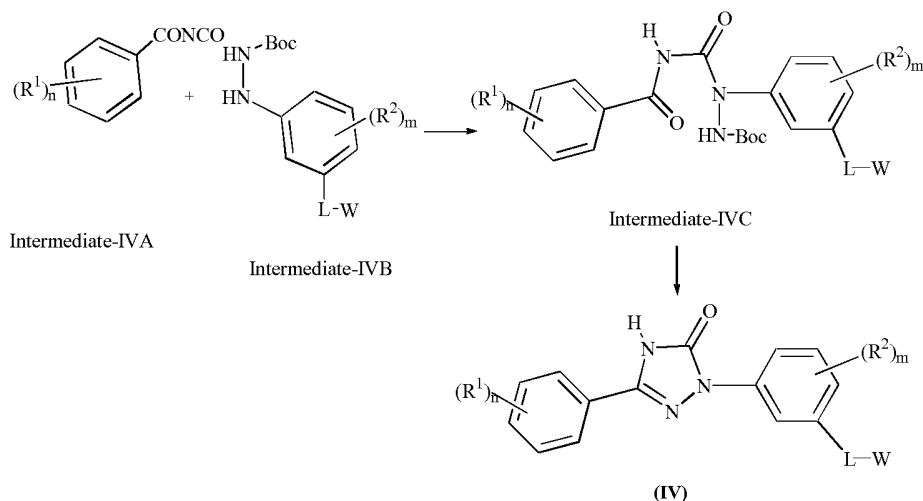
Synthetic Scheme-IX



[0166] An isocyanate compound of formula (Intermediate-III A) may be obtained from a corresponding acid, amide or acid halide derivative. A compound of formula (Intermediate-III A) can be reacted with a compound of formula (Intermediate-III B) to form a compound of formula (Intermediate-III C) and the compound of formula (Intermediate-III C) can be converted to a compound of formula (III). According to the process, the compound of formula (Intermediate-III A) can be reacted with the compound of formula (Intermediate-III B) in a solvent such as DCM, toluene or EDC. According to the process, the compound of formula (Intermediate-III C) may be isolated or not isolated. According to the process, the compound of formula (Intermediate-III C) is converted to compound of formula (III) using an acid. The acid used in the process can be an organic acid such as TFA, CSA or methane sulphonic acid.

[0167] In another approach, the compound of formula (IV) can be prepared following the synthetic steps depicted in Synthetic Scheme-X (wherein R¹, R², L, W, m and n are as defined with respect to a compound of formula (IV)).

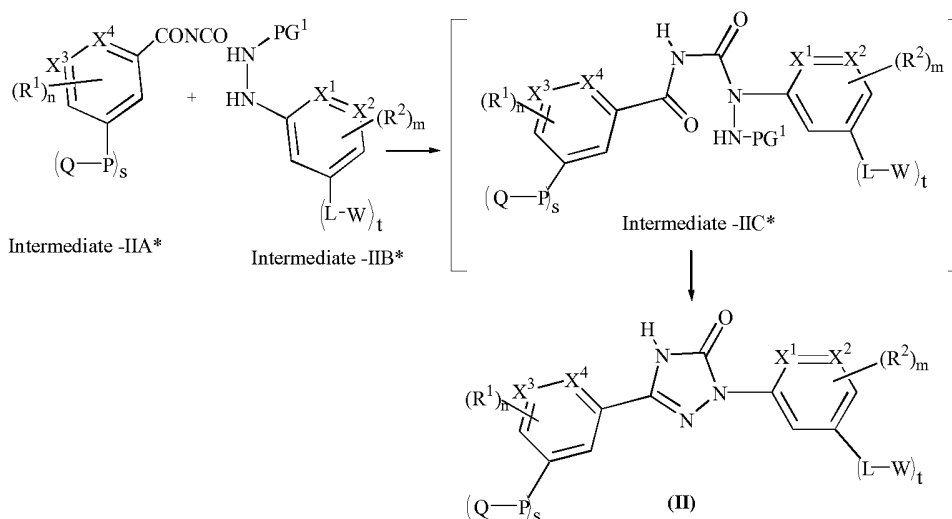
Synthetic Scheme-X



[0168] An isocyanate compound of formula (Intermediate-IVA) may be obtained from a corresponding acid, amide or acid halide derivative. A compound of formula (Intermediate-IVA) can be reacted with a compound of formula (Intermediate-IVB) to form a compound of formula (Intermediate-IVC) and the compound of formula (Intermediate-IVC) can be converted to a compound of formula (IV). According to the process, the compound of formula (Intermediate-IVA) can be reacted with the compound of formula (Intermediate-IVB) in solvent such as DCM, toluene or EDC. According to the process, the compound of formula (Intermediate-IVC) may be isolated or not isolated. According to the process, the compound of formula (Intermediate-IVC) is converted to a compound of formula (IV) using an acid. The acid used in the process can be an organic acid such as TFA, CSA or methane sulphonic acid.

[0169] In another approach, the compound of formula (II) can be prepared following the synthetic steps depicted in Synthetic Scheme-XI (wherein R^1 , R^2 , L , P , Q , W , X^1 , X^2 , X^3 , X^4 , m , n , s and t are as defined with respect to a compound of formula (II) and PG^1 represents an amine protecting group such as *tert*-Butoxycarbonyl (Boc) or carboxybenzyl (Cbz) or benzyl.

Synthetic Scheme-XI



[0170] An isocyanate compound of formula (Intermediate-IIA*) may be obtained from a corresponding acid, amide or acid halide derivative. A compound of formula (Intermediate-IIA*) can be reacted with a compound of formula (Interme-

diolate-IIB*) to form a compound of formula (Intermediate-IIC*) and the compound of formula (Intermediate-IIC*) can be converted to the compound of formula (II). According to the process, the compound of formula (Intermediate-IIA*) can be reacted with the compound of formula (Intermediate-IIB*) in a solvent such as DCM, toluene or EDC. According to the process, the compound of formula Intermediate-IIC* may be isolated or not isolated. According to the process, the compound of formula (Intermediate-IIC*) is converted to compound of formula (II) using an acid. The acid used in the process can be an organic acid such as TFA, CSA or methane sulphonic acid.

[0171] Q, W or other substituents (e.g. R¹ or R²) if present in the formula (II), (III) or (IV) may be transformed into another chemical group at a chemically compatible stage of the synthetic sequence, in the presence of a suitable reagent by following the procedures known in the art of organic synthesis to obtain the final compound of formula (II), (III) or (IV).

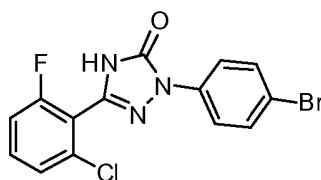
Experimental

[0172] Unless otherwise stated, work-up includes distribution of the reaction mixture between the organic and aqueous phase indicated within parentheses, separation of layers and drying the organic layer over sodium sulphate (Na₂SO₄), filtration and evaporation of the solvent under reduced pressure. Purification, unless otherwise mentioned, includes purification by silica gel chromatographic techniques, in suitable solvents of a suitable polarity as the mobile phase. Abbreviations used in the description of the chemistry and in the examples that follow are: AIBN: Azobisisobutyronitrile; NBS: N-Bromosuccinimide; CCl₄: Carbon tetrachloride; CSA: Camphor sulphonic acid; TFA: Trifluoro acetic acid; NaHCO₃: Sodium bicarbonate; PCl₅: Phosphorous pentachloride; POCl₃: Phosphorous oxychloride; NaO^tBu: Sodium *O-tert* butyl; K₂CO₃: Potassium carbonate; DIPEA: *N,N*-Diisopropylethylamine; LDA: Lithium diisopropylamide; TEA: Triethylamine; TBAF: Tetra-*n*-butylammonium fluoride; DCC: *N,N'*-Dicyclohexylcarbodiimide; HOBT: 1-Hydroxybenzotriazole; TBTU: *O*-(Benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate; HBTU: *O*-(Benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate; EDCI: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; BOP: (Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate; Boc/BOC: *tert*-Butoxycarbonyl; BOC anhydride: Di-*tert*-butyl dicarbonate; Cbz: Benzyloxycarbonyl; DAST: Diethylaminosulfur trifluoride; PTSA: *p*-Toluenesulfonic acid; DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene; DCM or MDC: Dichloromethane; DEE: Diethylether; DMSO: Dimethyl sulfoxide; THF: Tetrahydrofuran; EDC: Ethylene dichloride; EtOAc or EA: Ethyl acetate; CHCl₃: Chloroform; MeOH: Methanol; RT: Room temperature; h: hours.

Intermediate-1

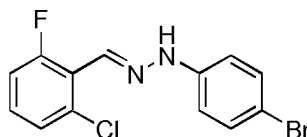
2-(4-Bromophenyl)-5-(2-chloro-6-fluorophenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one

[0173]



Step-1:- Preparation of (2*E*)-1-(4-bromophenyl)-2-(2-chloro-6-fluorobenzylidene) hydrazine

[0174]

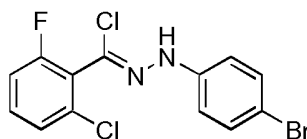


[0175] To a solution of 2-chloro-6-fluorobenzaldehyde (1.0 g, 6.32 mmol) in ethanol was added (4-bromophenyl)hydrazine (1.7 g, 7.59 mmol) and aq. solution of NaHCO₃ (0.637 g, 4.59 mmol). The reaction mixture was stirred at RT for 5-6 h. The reaction mass was quenched in water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and concentrated. The obtained crude product was purified by column chromatography on silica gel, eluting with 4.6 % EA: pet. ether to afford 0.650 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 6.98 (d, *J* = 7.8 Hz, 2H), 7.23-7.40 (m, 5H), 8.07 (s, 1H), 10.87 (br s, 1H). MS (*m/z*): 329.17 (*M*+H)⁺.

EP 2 718 284 B1

Step-2:- Preparation of *N*-(4-bromophenyl)-2-chloro-6-fluorobenzenecarbohydrazonoyl chloride

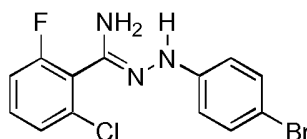
[0176]



[0177] To a solution of (2*E*)-1-(4-bromophenyl)-2-(2-chloro-6-fluorobenzylidene) hydrazine (0.300 g, 1.32 mmol) in benzene (10 mL) was added PCl₅ (0.330 g, 1.58 mmol). The reaction mixture was stirred at RT for 18 h. The reaction mass was quenched in water, neutralized with NaHCO₃ and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and concentrated to afford 0.110 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 7.17 (d, *J* = 8.7 Hz, 2H), 7.41 (d, *J* = 8.7 Hz, 3H), 7.45-7.61 (m, 2H), 10.26 (s, 1H). MS (*m/z*): 361.34 (M-H)⁺.

Step-3:- Preparation of *N'*-(4-bromophenyl)-2-chloro-6-fluorobenzenecarbohydrazonamide

[0178]



[0179] To a cold solution of *N'*-(4-bromophenyl)-2-chloro-6-fluorobenzenecarbohydrazonoyl chloride (0.070 g, 0.267 mmol) in dry THF was added aq. ammonia. The reaction mass was stirred at 0-5°C for 2-3 h. The reaction mass was quenched in water, neutralized with dilute acetic acid and extracted with DCM. The organic layer was dried over anhydrous sodium sulphate and concentrated to afford 0.040 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 6.29 (br s, 2H), 6.80 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 9.3 Hz, 2H), 7.28-7.50 (m, 3H), 8.33 (s, 1H).

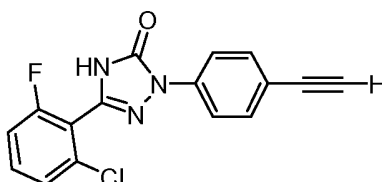
Step-4:- Preparation of 2-(4-bromophenyl)-5-(2-chloro-6-fluorophenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one

[0180] To a cold solution of *N'*-(4-bromophenyl)-2-chloro-6-fluorobenzenecarbohydrazonamide (0.050 g, 0.146 mmol) in CHCl₃ was added pyridine (0.5 mL) and phosgene (1.0 mL) at 0-5°C. The reaction mass was stirred at 0-5°C for 2-3 h. The reaction mass was quenched in water, neutralized with dilute acetic acid and extracted with DCM. The organic layer was dried over anhydrous sodium sulphate and concentrated. The obtained crude product was purified with column chromatography on silica gel eluting with 1.0 % MeOH: DCM to afford 0.020 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 7.50 (t, *J* = 8.7 Hz, 1H), 7.56-7.71 (m, 4H), 7.89 (d, *J* = 9.3 Hz, 2H), 12.69 (s, 1H). MS (*m/z*): 368.15 (M)⁺.

Intermediate-2

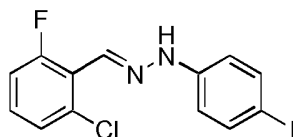
5-(2-Chloro-6-fluorophenyl)-2-(4-ethynylphenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one

[0181]



Step-1:- Preparation of (1*E*)-1-(2-chloro-6-fluorobenzylidene)-2-(4-iodophenyl)hydrazine

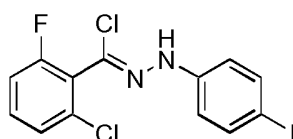
[0182]



[0183] To a solution of (4-iodophenyl)hydrazine (1.0 g, 4.27 mmol) in ethanol (10 mL) was slowly added solution of 2-chloro-6-fluorobenzaldehyde (0.675 g, 4.27 mmol) in ethanol (10 mL). The reaction mass was stirred at RT for 5-6 h. The reaction mass was quenched in water and extracted with ethyl acetate. The organic layer was concentrated to afford 1.2 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 6.87 (d, *J* = 8.4 Hz, 2H), 7.26-7.36 (m, 3H), 7.53 (d, *J* = 9.0 Hz, 2H), 8.06 (s, 1H), 10.84 (s, 1H). MS (*m/z*): 374.87 (M)⁺.

Step-2:- Preparation of 2-chloro-6-fluoro-*N*-(4-iodophenyl)benzenecarbohydrazonoyl chloride

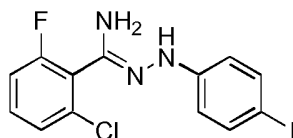
[0184]



[0185] The title compound was prepared according to the procedure described in step-2 of Intermediate-1 using (1*E*)-1-(2-chloro-6-fluorobenzylidene)-2-(4-iodophenyl)hydrazine (1.2 g, 3.20 mmol), PCl₅ (0.990 g, 4.8 mmol) and benzene (20 mL) to afford 1.0 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 7.00 (d, *J* = 8.7 Hz, 2H), 7.41 (d, *J* = 8.7 Hz, 1H), 7.48-7.60 (m, 4H), 10.22 (s, 1H).

Step-3:- Preparation of 2-chloro-6-fluoro-*N'*-(4-iodophenyl)benzenecarbohydrazonamide

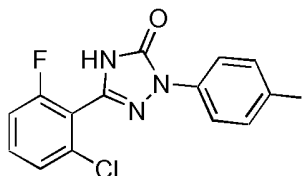
[0186]



[0187] The title compound was prepared according to the procedure described in step-3 of Intermediate-1 by using 2-chloro-6-fluoro-*N'*-(4-iodophenyl)benzenecarbohydrazonoyl chloride (1.00 g, 2.44 mmol), aq. ammonia (2.0 mL) and dry THF (10 mL) to afford 0.900 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 6.28 (br s, 2H), 6.70 (d, *J* = 8.4 Hz, 2H), 7.27 (t, *J* = 8.7 Hz, 1H), 7.36-7.42 (m, 3H), 7.45-7.51 (m, 1H), 8.33 (s, 1H).

Step-4:- Preparation of 5-(2-chloro-6-fluorophenyl)-2-(4-iodophenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one

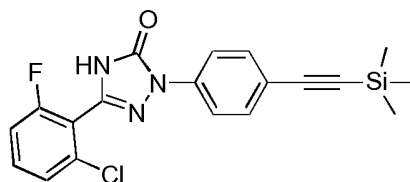
[0188]



[0189] The title a compound was prepared according to the procedure described in step-4 of Intermediate-1 using 2-chloro-6-fluoro-*N'*-(4-iodophenyl)benzene carbohydrazonamide (0.900 g, 2.31 mmol), pyridine (0.65 mL, 5.79 mmol), phosgene (2.50 mL, 4.63 mmol) and CHCl₃ (20 mL). The obtained crude product was purified with column chromatography on silica gel eluting with 1.0 % MeOH: DCM to afford 0.400 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 7.47 (t, *J* = 9.0 Hz, 2H), 7.54-7.82 (m, 5H), 12.62 (s, 1H). MS (*m/z*): 414.25 (M-H)⁻.

Step-5:- Preparation of 5-(2-chloro-6-fluorophenyl)-2-{4-[(trimethylsilyl)ethynyl] phenyl}-2,4-dihydro-3*H*-1,2,4-triazol-3-one

[0190]



[0191] To a solution of 5-(2-chloro-6-fluorophenyl)-2-(4-iodophenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (0.200 g, 0.483 mmol) in DMSO (2 mL) was added ethynyl(trimethyl)silane (0.071 g, 0.724 mmol), copper iodide (0.005 g, 0.007 mmol), bis(triphenylphosphine) palladium(II) chloride (0.200 g, mmol) and TEA (2.0 mL). The reaction mass was stirred at RT for 24 h. The reaction mass was quenched in water and neutralized with dilute acetic acid and extracted with DCM. The organic layer was dried over anhydrous sodium sulphate and concentrated to afford 0.200 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 2.31 (s, 9H), 7.44-7.47 (m, 3H), 7.54-7.71 (m, 3H), 7.94-8.01 (m, 1H), 77.95 (br s, 1H). MS (m/z): 384.29 (M-H)⁻.

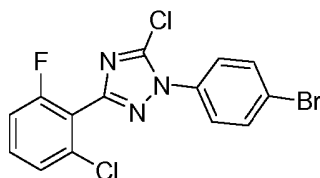
Step-6:- Preparation of 5-(2-chloro-6-fluorophenyl)-2-(4-ethynylphenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one

[0192] To a solution of 5-(2-chloro-6-fluorophenyl)-2-{4-[(trimethylsilyl)ethynyl] phenyl}-2,4-dihydro-3*H*-1,2,4-triazol-3-one (0.200 g, 0.570 mmol) in DCM was added TBAF (0.362 g, 1.11 mmol). The reaction mass was stirred at RT for 2-3 h. The reaction mass was quenched in water and filtered through celite bed and concentrated. The obtained crude product was purified with column chromatography on silica gel eluting with 2.0 % MeOH: DCM to afford 0.400 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 4.21 (s, 1H), 7.50 (t, *J* = 9.3 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 3H), 7.67-7.71 (m, 1H), 7.96 (d, *J* = 8.1 Hz, 2H), 12.69 (br s, 1H).

Intermediate-3

1-(4-bromophenyl)-5-chloro-3-(2-chloro-6-fluorophenyl)-1*H*-1,2,4-triazole

[0193]



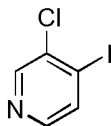
[0194] To 2-(4-bromophenyl)-5-(2-chloro-6-fluorophenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Intermediate-1, 0.100 g, 0.271 mmol) was added POCl₃. The reaction mass was refluxed for 48 h. The reaction mass was quenched in water, basified with NaHCO₃ and extracted with ethyl acetate and concentrated. The obtained crude product was purified with column chromatography on silica gel eluting with 0.5 % EA: DCM to afford 0.110 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 7.44 (t, *J* = 9.3 Hz, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.60-7.68 (m, 1H), 7.72 (d, *J* = 9.0 Hz, 2H), 7.85 (d, *J* = 8.7 Hz, 2H). MS (m/z): 388.22 (M+H)⁺.

Intermediate-4

3-Chloro-4-iodopyridine

[0195]

EP 2 718 284 B1

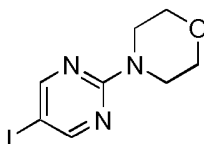


[0196] To a cold solution of 3-chloro pyridine (1.0 g, 8.88 mmol) in THF (30.0 mL) was added LDA (5.9 mL, 8.88 mmol) at -75°C. The reaction mixture was stirred at -75°C for 4 h. Iodine (2.2 g, 8.88 mmol) was added and continued stirring at -75°C for 1 h. The reaction mixture was quenched in water at -70°C, extracted with ethyl acetate and concentrated to afford 0.500 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 8.01 (d, *J* = 5.1 Hz, 1H), 8.14 (d, *J* = 4.8 Hz, 1H), 8.63 (s, 1H).

Intermediate-5

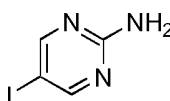
4-(5-Iodopyrimidin-2-yl)morpholine

[0197]



Step-1:- Preparation of 5-iodopyrimidin-2-amine

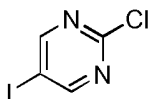
[0198]



[0199] To a solution of pyrimidin-2-amine (1.0 g, 0.010 mol) in DMSO (10 mL) was added iodine (3.2 g, 0.012 mol). The reaction mixture was stirred at 120°C for 1 h. The reaction mass was quenched in water and excess of iodine was neutralised with sodium metabisulphate. The reaction mass was extracted with ethyl acetate and concentrated to afford 0.400 g of the desired product.

Step-2:- Preparation of 2-chloro-5-iodopyrimidine

[0200]



[0201] To a solution of 5-iodopyrimidin-2-amine (10.0 g, 0.045 mol) in acetonitrile (150 mL) was added CuCl₂ (11.57 g, 0.067 mol) and *tert*-butyl nitrite (6.99 g, 0.067 mol). The reaction mass was heated at 70°C for 5-6 h. The reaction mass was diluted with ether and the solid obtained was filtered off. The obtained product was purified with column chromatography on silica gel eluting with DCM to afford 1.700 g of the desired product.

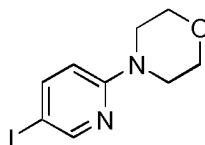
Step-3:- Preparation of 4-(5-iodopyrimidin-2-yl)morpholine

[0202] The mixture of 2-chloro-5-iodopyrimidine (0.200 g, 0.836 mmol) in morpholine (3.0 mL) was refluxed for 2-3 h. The reaction mass was quenched in water and the solid obtained was filtered off. The obtained solid was dried to afford 0.180 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.63(s, 8H), 8.52 (s, 2H); MS (*m/z*): 292.25 (M+H)⁺.

Intermediate-6

4-(5-Iodopyridin-2-yl)morpholine

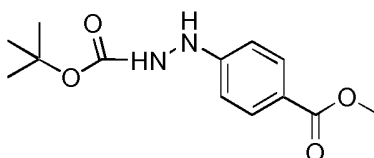
[0203]



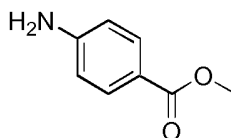
[0204] A solution of 2-chloro-5-iodo pyridine (0.200 g, 0.836 mmol) in morpholine (3.0 mL) was refluxed for 12-15 h. The reaction mass was quenched in ice and the solid obtained was filtered off to afford 0.170 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.40 (t, *J* = 4.8 Hz, 4H), 3.67 (t, *J* = 4.5 Hz, 4H), 6.74 (d, *J* = 8.7 Hz, 1H), 7.77-7.81 (m, 1H), 8.28 (s, 1H).

Intermediate-7*tert*-Butyl 2-[4-(methoxycarbonyl)phenyl]hydrazinecarboxylate

[0205]

Step-1:- Preparation of methyl 4-aminobenzoate

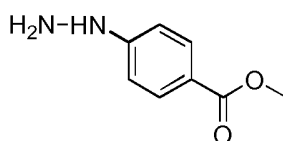
[0206]



[0207] To a solution of 4-amino benzoic acid (20.0 g, 0.14 mol) in methanol (400 mL) was added conc. sulphuric acid (40 mL). The reaction mass was stirred at RT for 6-7 h. The reaction mass was quenched with water and basified with NaHCO₃ and extracted with DCM. The organic layer was dried over anhydrous sodium sulphate and concentrated to afford 15.0 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.72 (s, 3H), 5.96 (br s, 2H), 6.55 (d, *J* = 8.1 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 2H) MS (*m/z*): 152.21 (*M*+H)⁺.

Step-2:- Preparation of methyl 4-hydrazinylbenzoate

[0208]



[0209] To a cold solution of methyl 4-aminobenzoate (15.0 g, 0.099 mol) in conc. HCl was added aq. solution of sodium nitrite (7.5 g, 0.109 mmol) at 0-5°C. The reaction mass was stirred at RT for 1-2 h. The reaction mass was cooled to

EP 2 718 284 B1

0°C and stannous chloride (0.049 g, 0.210 mmol) was added and further stirred at RT for 2-3 h. The reaction mass was filtered to afford 17.0 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.77 (s, 3H), 7.03 (d, *J* = 8.4 Hz, 2H), 7.82 (d, *J* = 8.4 Hz, 2H), 10.69 (br s, 2H); MS (*m/z*): 167.28 (M+H)⁺.

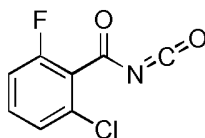
Step-3:- Preparation of tert-butyl 2-[4-(methoxycarbonyl)phenyl]hydrazinecarboxylate

[0210] To a solution of methyl 4-hydrazinylbenzoate (10.0 g, 0.049 mol) in DCM (150 mL) was added TEA (10 mL) and BOC anhydride (10.7 g, 0.049 mmol). The reaction mass was stirred at RT for 12 h. The reaction mass was quenched in water and extracted with DCM. The organic layer was dried over anhydrous sodium sulphate and concentrated. The obtained solid was washed with pentane to afford 6.5 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.40 (s, 9H), 3.74 (s, 3H), 6.65 (d, *J* = 8.4 Hz, 2H), 7.74 (d, *J* = 8.7 Hz, 2H), 8.31 (s, 1H), 8.93 (br s, 1H).

Intermediate-8

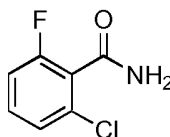
2-Chloro-6-fluorobenzoyl isocyanate

[0211]



Step-1:- Preparation 2-chloro-6-fluorobenzamide

[0212]



[0213] A solution of 2-chloro-6-fluorobenzonitrile (8.0 g, 51.61 mmol) in conc. sulphuric acid (50 mL) was heated at 60-70°C for 6-7 h. The reaction mass was quenched in water and extracted with DCM. The organic layer was dried over anhydrous sodium sulphate and concentrated to afford 5.5 g of desired product.

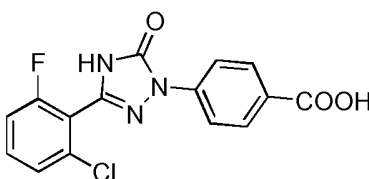
Step-2:- Preparation of 2-chloro-6-fluorobenzoyl isocyanate

[0214] To a solution of 2-chloro-6-fluorobenzamide (2.0 g, 0.011 mmol) in EDC (10 mL) was added oxalyl chloride (2.18 g, 0.017 mmol). The reaction mass was refluxed for 24 h. Excess of solvent was removed under vacuum to afford 2.0 g of desired product.

Intermediate-9

4-[3-(2-Chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl]benzoic acid

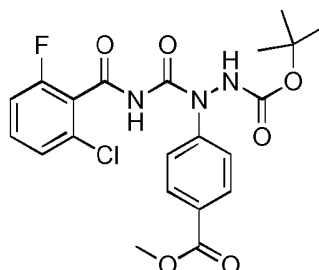
[0215]



EP 2 718 284 B1

Step-1:- Preparation of *tert*-butyl 2-[(2-chloro-6-fluorobenzoyl)carbamoyl]-2-[4-(methoxycarbonyl)phenyl]hydrazinecarboxylate

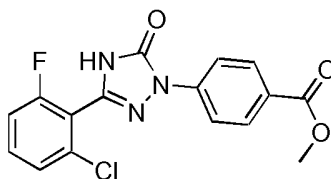
[0216]



[0217] To a solution of *tert*-butyl 2-[4-(methoxycarbonyl)phenyl]hydrazinecarboxylate (Intermediate-7, 2.0 g, 7.54 mmol) in DCM (15 mL) was added 2-chloro-6-fluorobenzoyl isocyanate (Intermediate-8, 1.50 g, 7.54 mmol). The reaction mass was stirred at RT for 2 h. Excess of solvent was removed under vacuum to afford 3.0 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.42 (s, 9H), 3.83 (s, 3H), 7.24-7.46 (m, 5H), 7.94 (d, *J* = 7.2 Hz, 2H), 9.91 (br s, 1H), 11.34-11.39 (br m, 1H); MS (*m/z*): 464.06 (M-H)⁺.

Step-2:- Preparation of methyl 4-[3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]benzoate

[0218]



[0219] To a solution of *tert*-butyl 2-[(2-chloro-6-fluorobenzoyl)carbamoyl]-2-[4-(methoxycarbonyl)phenyl]hydrazinecarboxylate (3.0 g, 6.45 mmol) in DCM (30 mL) was added trifluoro acetic acid (2.0 mL). The reaction mass was stirred at RT for 2-3 h. Excess of solvent was removed at low temperature. The reaction mass was quenched in ice and filtered off to afford 2.0 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.86 (s, 3H), 7.51-7.60 (m, 2H), 7.70 (br s, 1H), 8.09 (br s, 4H), 12.79 (br s, 1H); MS (*m/z*): 348.55 (M+H)⁺.

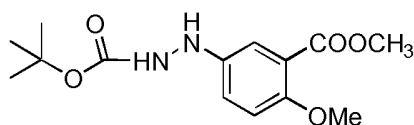
Step-3:- Preparation of 4-[3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]benzoic acid

[0220] To a solution of methyl 4-[3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]benzoate (2.0 g, 5.76 mmol) in THF: water (5 mL:10 mL) was added sodium hydroxide (0.691 g, 17.27 mmol). The reaction mass was stirred at RT for 3 h. The reaction mass was diluted with water and washed the aqueous layer with diethyl ether and toluene. The aqueous layer was cooled to 15°C and acidified with dilute HCl. The reaction mass was filtered off to afford 1.0 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 7.50 (t, *J* = 9.0 Hz, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.67-7.74 (m, 1H), 8.06 (s, 4H), 12.77 (br s, 1H).

Intermediate-10

tert-Butyl 2-[4-methoxy-3-(methoxycarbonyl)phenyl]hydrazinecarboxylate

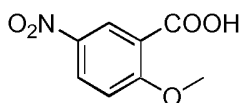
[0221]



EP 2 718 284 B1

Step-1:- Preparation of 2-methoxy-5-nitrobenzoic acid

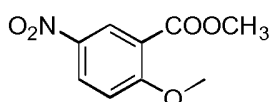
[0222]



[0223] To a solution of 2-chloro-5-nitrobenzoic acid (3.0 g, 0.14 mol) in methanol (500 mL) was added sodium methoxide (28.1 g, 0.520 mol). The reaction mass was refluxed for 15 h. Excess of solvent was removed under vacuum and the reaction mass was diluted with water and acidified with dilute HCl to obtain solid which was filtered off to afford 25.0 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.96 (s, 3H), 7.36 (d, *J* = 9.3 Hz, 1H), 8.37 (d, *J* = 9.0 Hz, 1H), 8.45 (s, 1H), 13.32 (br s, 1H); MS (*m/z*): 198.25 (M+H)⁺.

Step-2:- Preparation of methyl 2-methoxy-5-nitrobenzoate

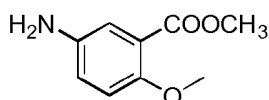
[0224]



[0225] To a solution of 2-methoxy-5-nitrobenzoic acid (25.0 g, 0.12 mol) in DMF (100 mL) was added K₂CO₃ (26.3 g, 0.19 mol). The reaction mass was stirred at 80°C for 1 h followed by addition of methyl iodide (12.3 mL, 0.19 mol). The reaction mass was further stirred at 80°C for 5-6 h. The reaction mass was filtered and the obtained filtrate was concentrated. The residue was further diluted with water and obtained solid was filtered off to afford 20.0 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.83 (s, 3H), 3.97 (s, 3H), 7.38 (d, *J* = 9.3 Hz, 1H), 8.41 (dd, *J* = 2.4 Hz & 2.4 Hz, 1H), 8.47 (s, 1H); MS (*m/z*): 212.44 (M+H)⁺.

Step-3:- Preparation of methyl 5-amino-2-methoxybenzoate

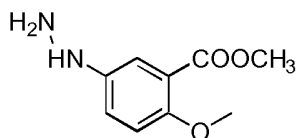
[0226]



[0227] A solution of methyl 2-methoxy-5-nitrobenzoate (20.0g, 0.097 mol) in methanol (300 mL) and 10% Pd/C (5.0 g) was stirred under hydrogen atmosphere under 70-80 psi pressure in Parr apparatus for 4-5 h. The reaction mass was filtered and the obtained filtrate was concentrated to afford 15.0 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.67 (s, 3H), 3.74 (s, 3H), 4.96 (br s, 2H), 6.75 (dd, *J* = 2.4 Hz, 1H), 6.85 (d, *J* = 8.7 Hz, 1H), 6.92 (s, 1H); MS (*m/z*): 182.25 (M+H)⁺.

Step-4:- Preparation of methyl 5-hydrazinyl-2-methoxybenzoate

[0228]



[0229] The title compound was prepared according to the procedure described in step-2 of Intermediate-7 by using methyl 5-amino-2-methoxybenzoate (15.0 g, 0.082 mol), stannous chloride (37.25 g, 0.16 mmol), sodium nitrite (6.28

g, 0.091 mmol), conc.HCl (400 mL) and water (100 mL) to afford 14.0 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.75 (s, 6H), 7.09 (m, 1H), 7.20-7.23 (m, 1H), 7.34 (s, 1H), 10.20 (br s, 2H) ; MS (m/z): 197.27 (M+H)⁺.

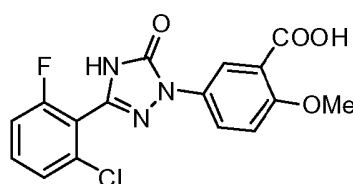
Step-5:- Preparation of *tert*-butyl 2-[4-(methoxycarbonyl)phenyl]hydrazinecarboxylate

[0230] The title compound was prepared according to the procedure described in step-3 of Intermediate-7 by using methyl 5-hydrazinyl-2-methoxybenzoate (10.0 g, 0.051 mol), DCM (150 mL), TEA (10 mL) and BOC anhydride (11.2 g, 0.051 mmol) to afford 2.0 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.43 (s, 9H), 3.71 (s, 3H), 3.79 (s, 3H), 6.81-6.85 (m, 1H), 6.97-6.99 (m, 2H), 7.45 (s, 1H), 8.78 (s, 1H) ; MS (m/z): 295.19 (M-H)⁻.

Intermediate-11

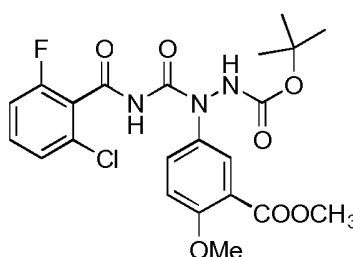
5-[3-(2-Chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-2-methoxy benzoic acid

[0231]



Step-1:- Preparation *tert*-butyl 2-[(2-chloro-6-fluorobenzoyl)carbamoyl]-2-[4-methoxy-3-(methoxycarbonyl)phenyl]hydrazinecarboxylate

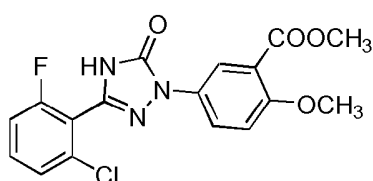
[0232]



[0233] The title compound was prepared according to the procedure described in step-1 of Intermediate-9 by using 2-chloro-6-fluorobenzoyl isocyanate (Intermediate-8, 2.0 g, 6.75 mmol), *tert*-butyl 2-[4-methoxy-3-(methoxycarbonyl)phenyl]hydrazinecarboxylate (Intermediate-10, 1.61 g, 8.18 mmol) and DCM (30 mL) to afford 3.0 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.40 (s, 9H), 3.81 (s, 6H), 7.13-7.83 (m, 6H), 9.6 (br s, 1H), 11.13 (br s, 1H); MS (m/z): 494.05 (M-H)⁻.

Step-2:- Preparation of methyl 5-[3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-2-methoxybenzoate

[0234]



[0235] The title compound was prepared according to the procedure described in step-2 of Intermediate-9 by using

EP 2 718 284 B1

tert-butyl 2-[(2-chloro-6-fluorobenzoyl)carbamoyl]-2-[4-methoxy-3-(methoxycarbonyl)phenyl]hydrazinecarboxylate (3.0 g, 6.06 mmol), DCM (30 mL) and trifluoro acetic acid (3.0 mL) to afford 2.0 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.80 (s, 3H), 3.84 (s, 3H), 7.28 (d, *J* = 9.3 Hz, 1H), 7.49 (t, *J* = 8.7 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.65-7.73 (m, 1H), 8.06 (d, *J* = 9.0 Hz, 1H), 8.18 (s, 1H), 12.62 (s, 1H); MS (*m/z*): 376.27 (M-H)⁻.

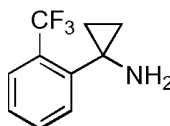
Step-3:- Preparation of 5-[3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*,2,4-triazol-1-yl]-2-methoxybenzoic acid

[0236] The title compound was prepared according to the procedure described in step-3 of Intermediate-9 by using of methyl 5-[3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-2-methoxybenzoate (1.5 g, 3.97 mol) and sodium hydroxide (0.320 g, 7.95 mmol) to afford 0.700 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.84 (s, 3H), 7.24 (t, *J* = 9.3 Hz, 1H), 7.48 (t, *J* = 8.7 Hz, 1H), 7.57 (d, *J* = 8.7 Hz, 1H), 7.65-7.72 (m, 1H), 8.00 (d, *J* = 8.7 Hz, 1H), 8.17 (s, 1H), 12.60 (s, 1H), 12.85 (br s, 1H).

Intermediate-12

1 - [2 -(Trifluoromethyl)phenyl]cyclopropanamine

[0237]

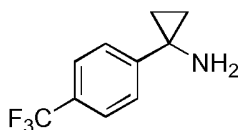


[0238] To a cold solution of 2-(trifluoromethyl)benzonitrile (1.0 g, 0.58 mmol) in diethyl ether (20 mL) was added titanium isopropoxide (2.0 g, 0.70 mmol) at -70°C and ethyl magnesium bromide (4.30 mL, 12.86 mmol). The reaction mass was stirred at RT for 2-3 h. Followed by addition of boron trifluoride solution (1.5 mL) and continued stirring for 2 h at RT. The reaction mass was quenched in 1N HCl and basified with NaOH solution. The obtained crude product was further purified by column chromatography on silica gel eluting with 1% EtOAC: DCM eluent to afford 0.250 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 0.82-0.84 (s, 2H), 0.91-0.93 (br s, 2H), 2.24 (br s, 2H), 7.41 (t, *J* = 6.6 Hz, 1H), 7.58-7.67 (m, 3H).

Intermediate-13

1-[4-(Trifluoromethyl)phenyl]cyclopropanamine

[0239]



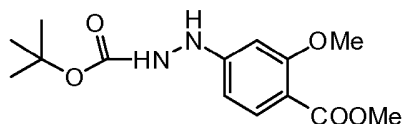
[0240] The title compound was prepared according to the procedure described in Intermediate-12 by using of 4-(trifluoromethyl)benzonitrile (1.0 g, 0.58 mmol), diethyl ether (20 mL), titanium isopropoxide (2.0 g, 0.70 mmol), ethyl magnesium bromide (4.30 mL, 12.86 mmol) and boron trifluoride solution (1.5 mL) to afford 0.210 g of desired product. ¹H NMR (CDCl₃): δ 1.05 (s, 2H), 1.60 (s, 2H), 1.78 (s, 2H), 7.36 (d, *J* = 7.8 Hz, 2H), 7.55 (d, *J* = 8.1 Hz, 2H).

Intermediate-14

tert-Butyl 2-(3-methoxy-4-(methoxycarbonyl)phenyl)hydrazinecarboxylate

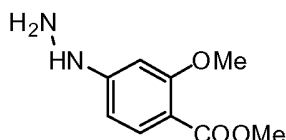
[0241]

EP 2 718 284 B1



Step-1:- Preparation of methyl 4-hydrazinyl-2-methoxybenzoate

[0242]



[0243] The title compound was prepared according to the procedure described in step-2 of Intermediate-7 by using methyl 4-amino-2-methoxybenzoate (10.0 g, 0.055 mol), stannous chloride (31.00 g, 0.138 mmol), sodium nitrite (4.57 g, 0.066 mmol), 6 N HCl (200 mL) and water (100 mL) to afford 14.0 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.73 (s, 3H), 3.80 (s, 3H), 6.51 (d, *J* = 8.4 Hz, 1H), 6.69 (s, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 8.75 (br s, 1H), 10.28 (br hump, 2H); MS (*m/z*): 197.01 (*M*+H)⁺.

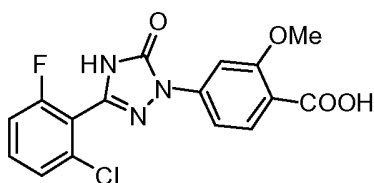
Step-2:- Preparation of *tert*-butyl 2-(3-methoxy-4-(methoxycarbonyl)phenyl)hydrazine carboxylate

[0244] The title compound was prepared according to the procedure described in step-3 of Intermediate-7 by using methyl 4-hydrazinyl-2-methoxybenzoate (5.0 g, 0.025 mol), DCM (70 mL), TEA (5.0 mL) and BOC anhydride (6.11 g, 0.028 mmol) to afford 3.50 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.40 (s, 9H), 3.68 (s, 3H), 3.72 (s, 3H), 6.26 (s, 2H), 7.59 (d, *J* = 8.7 Hz, 1H), 8.26 (s, 1H), 8.94 (s, 1H); MS (*m/z*): 297.02 (*M*+H)⁺.

Intermediate-15

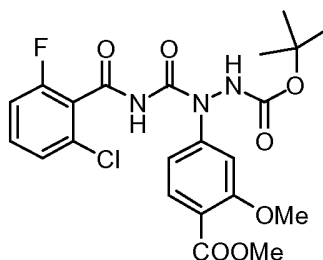
4-(3-(2-Chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzoic acid

[0245]



Step-1:- Preparation of *tert*-butyl 2-((2-chloro-6-fluorobenzoyl)carbamoyl)-2-(3-methoxy-4-(methoxycarbonyl)phenyl)hydrazinecarboxylate

[0246]

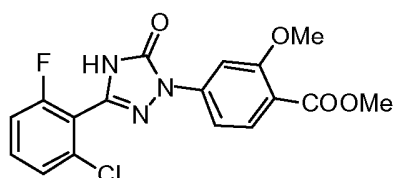


EP 2 718 284 B1

[0247] The title compound was prepared according to the procedure described in step-1 of Intermediate-9 by using 2-chloro-6-fluorobenzoyl isocyanate (Intermediate-8, 2.0 g, 6.75 mmol), *tert*-butyl 2-(3-methoxy-4-(methoxycarbonyl)phenyl)hydrazinecarboxylate (Intermediate-14, 2.0 g, 10.10 mmol) and DCM (30 mL) to afford 3.0 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.42 (s, 9H), 3.76 (s, 6H), 6.99 (d, *J* = 8.1 Hz, 1H), 7.11 (s, 1H), 7.2-7.50 (m, 4H), 9.88 (s, 1H), 11.32 (s, 1H); MS (*m/z*): 493.92 (M-H)⁻.

Step-2:- Preparation of methyl 4-(3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzoate

[0248]



[0249] The title compound was prepared according to the procedure described in step-2 of Intermediate-9 by using *tert*-butyl 2-((2-chloro-6-fluorobenzoyl)carbamoyl)-2-(3-methoxy-4-(methoxycarbonyl)phenyl)hydrazinecarboxylate (3.0 g, 6.06 mmol), DCM (30 mL) and trifluoro acetic acid (2.0 mL) to afford 2.0 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.81 (s, 3H), 3.85 (s, 3H), 7.34-7.73 (m, 6H), 12.80 (s, 1H); MS (*m/z*): 376.16 (M-H)⁻.

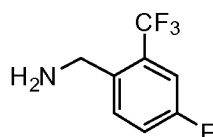
Step-3:- Preparation of 4-(3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzoic acid

[0250] The title compound was prepared according to the procedure described in step-3 of Intermediate-9 by using methyl 4-(3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzoate (1.0 g, 2.65 mol) and sodium hydroxide (0.210 g, 5.30 mmol) to afford 0.600 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.84 (s, 3H), 7.59 (t, *J* = 7.8 Hz, 2H), 7.67-7.75 (m, 3H), 7.81 (d, *J* = 8.4 Hz, 1H), 12.58 (br, 1H), 12.80 (s, 1H); MS (*m/z*): 362.21 (M-H)⁻.

Intermediate-16

(4-Fluoro-2-(trifluoromethyl)phenyl)methanamine

[0251]

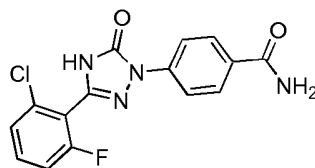


[0252] To a solution of 4-fluoro-2-(trifluoromethyl)benzonitrile (2.0 g) in ethanol (10.0 mL) was added Raney Ni (catalytic amount). The reaction mixture was subjected for hydrogenation in Parr apparatus under 50 psi for 2-3 h. The reaction mass was filtered through celite and the filtrate was concentrated to afford 0.400 g of desired product. ¹H NMR (CDCl₃): δ 3.98 (s, 2H), 7.24 (t, *J* = 9.0 Hz, 1H), 7.34 (d, *J* = 8.7 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 1H); MS [*M*+*H*]⁺ :194.03.

Intermediate-17

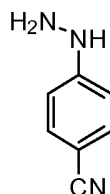
4-(3-(2-Chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzamide

[0253]



Step-1:- Preparation of 4-hydrazinylbenzonitrile

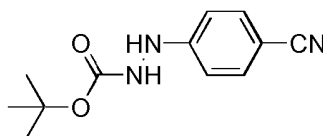
[0254]



[0255] To a cold solution of 4-cyanoaniline (6.0 g, 0.050 mol) in conc. HCl was added aq. solution of sodium nitrite (3.85 g, 0.055 mmol) at -15°C. The reaction mass was stirred at 0-10°C for 15 minutes and filtered off to remove insolubles. The filtrate was added to stannous chloride in conc. HCl (24.0 g, 0.166 mmol). The reaction mass was stirred at -15°C for 30 minutes. The reaction mass was filtered to afford 5.2 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 7.04 (d, 2H), 7.70 (d, 2H), 9.17 (br s, 1H), 10.66 (br s, 2H).

Step-2:- Preparation of *tert*-butyl 2-(4-cyanophenyl)hydrazinecarboxylate

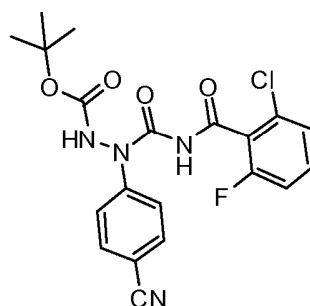
[0256]



[0257] The title compound was prepared according to the procedure described in step-3 of Intermediate-7 by using 4-hydrazinylbenzonitrile (10.0 g, 0.059 mmol), BOC anhydride (14.5 g, 0.065 mmol), TEA and DCM to afford 12.0 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.41 (s, 9H), 6.70 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 8.48 (br s, 1H), 9.00 (br s, 1H); (M+H)⁺. 233.94.

Step-3:- Preparation of *tert*-butyl 2-((2-chloro-6-fluorobenzoyl)carbamoyl)-2-(4-cyanophenyl)hydrazinecarboxylate

[0258]



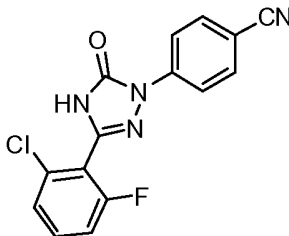
[0259] To a solution of *tert*-butyl 2-(4-cyanophenyl)hydrazinecarboxylate (2.5 g, 0.01 mmol) in DCM (15 mL) was added 2-chloro-6-fluorobenzoyl isocyanate (Intermediate-8, 2.56 g, 0.012 mmol). The reaction mass was stirred at RT for 2 h. Excess of solvent was removed under vacuum to afford 4.0 g of desired product. ¹H NMR (300 MHz, DMSO

EP 2 718 284 B1

d_6): δ 1.42 (s, 9H), 7.25-7.38 (m, 2H), 7.47-7.60 (m, 3H), 7.82-7.85 (m, 2H), 9.96 (br s, 1H), 11.43 (br s, 1H); MS (m/z): 431.02 (M+H)⁺.

Step-4:- Preparation of 4-(3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)benzonitrile

[0260]



[0261] The title compound was prepared according to the procedure described in step-2 of Intermediate-9 by using *tert*-butyl 2-((2-chloro-6-fluorobenzoyl)carbamoyl)-2-cyanophenylhydrazinecarboxylate (4.0 g, 00.009 mol), DCM (30 mL), trifluoro acetic acid (5.0 mL) to afford 2.2 g of desired product. ¹H NMR (300 MHz, DMSO d_6): δ 7.50 (t, 1H), 7.58 (d, 1H), 7.70 (q, 1H), 7.95 (d, J = 8.7 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H), 12.80 (br s, 1H); MS (m/z): 331.80 (M+H)⁺.

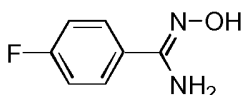
Step-5:- Preparation of 4-(3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)benzamide

[0262] A solution of 4-(3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)benzonitrile (1.0 g, 0.003 mol) in conc. sulphuric acid (10 mL) was heated to 70°C for 15 h. The reaction mixture was quenched in ice water. The reaction mass was basified till pH ~ 6 -6.5 with dilute NaOH. The obtained solid was filtered off, washed with water and suck dried to afford 0.300 g of desired product. ¹H NMR (300 MHz, DMSO d_6): δ 7.36 (br s, 1H), 7.84 (t, 1H), 7.57 (d, 1H), 7.67 (d, 1H), 7.98 (m, 5H), 12.70 (br s, 1H); MS (m/z): 333.11 (M+H)⁺.

Intermediate-18

4-Fluoro-*N*'-hydroxybenzimidamide

[0263]



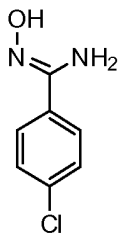
[0264] To a solution of 4-fluorobenzonitrile (0.500 g, 4.13 mmol) in ethanol (3 mL) was added hydroxyl amine HCl (0.427g, 6.19 mmol) and potassium carbonate (1.14g, 8.26 mmol). The reaction mass was stirred at RT for 15-17 h. Excess of solvent was removed under vacuum. The obtained residue was diluted with water, acidified with dilute HCl and extracted with DCM. The organic layer was separated, dried over anhydrous sodium sulphate and concentrated to afford 0.450 g of desired product. ¹H NMR (300 MHz, DMSO d_6): δ 5.84 (br s, 2H), 7.17-7.27 (m, 2H), 7.68-7.73 (m, 2H), 9.64 (br s, 1H); MS (m/z): 155.13 (M+H)⁺.

Intermediate-19

4-Chloro-*N*'-hydroxybenzimidamide

[0265]

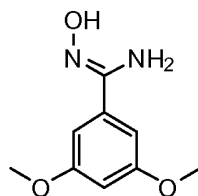
EP 2 718 284 B1



[0266] To a solution of 4-chloro benzonitrile (1.000 g, 7.26 mmol) in ethanol (20 mL) was added hydroxyl amine HCl (0.752 g, 10.90 mmol) and potassium carbonate (3.00 g, 21.80 mmol). The reaction mass was refluxed for 10-12 h. Excess of solvent was removed under vacuum and the residue was diluted with water, acidified with dilute HCl. Precipitate obtained was filtered off and sucked dried to afford 0.500 g of desired product. ^1H NMR (300 MHz, DMSO d_6): δ 5.88 (br s, 2H), 7.42 (d, J = 8.1 Hz, 2H), 7.68 (d, J = 8.4 Hz, 2H), 9.70 (br s, 1H); MS (m/z): 171.13 (M+H) $^+$.

Intermediate-20

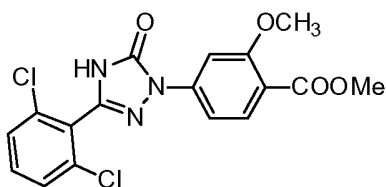
N'-Hydroxy-3,5-dimethoxybenzimidamide



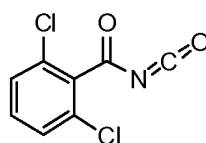
[0268] The title compound was prepared according to the procedure described in Intermediate-19 by using 3,5-dimethoxy benzonitrile (1.00 g, 6.13 mmol), hydroxyl amine HCl (0.634 g, 9.23 mmol) and potassium carbonate (2.53g, 18.40 mmol), ethanol (20 mL) to afford 0.400 g of desired product. ^1H NMR (300 MHz, DMSO d_6): δ 3.75 (s, 6H), 5.79 (s, 2H), 6.49 (s, 1H), 6.84 (s, 2H), 9.62 (br s, 1H); MS (m/z): 197.11 (M+H) $^+$.

Intermediate-21

Methyl 4-(3-(2,6-dichlorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzoate



Step-1:- Preparation of 2,6-dichlorobenzoyl isocyanate

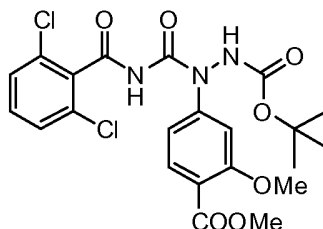


EP 2 718 284 B1

[0271] The title compound was prepared according to the procedure described in step-2 of Intermediate-8 by using 2,6-dichlorobenzamide (1.00 g, 5.26 mmol), oxalyl chloride (0.795 g, 6.31 mmol) and toluene (10 mL) to afford 1.00 g of desired product.

Step-2:- Preparation of *tert*-butyl 2-((2,6-dichlorobenzoyl)carbamoyl)-2-(3-methoxy-4-(methoxycarbonyl)phenyl)hydrazinecarboxylate

[0272]



[0273] The title compound was prepared according to the procedure described in step-1 of Intermediate-9 by using 2,6-dichlorobenzoyl isocyanate (1.0 g, 3.38 mmol), *tert*-butyl 2-(3-methoxy-4-(methoxycarbonyl)phenyl)hydrazinecarboxylate (Intermediate-14, 0.805 g, 3.72 mmol) and DCM (20 mL) to afford 1.5 g of desired product. ^1H NMR (300 MHz, DMSO d_6): δ 1.42 (s, 9H), 3.76 (s, 6H), 6.99 (d, J = 6.0 Hz, 1H), 7.10 (s, 1H), 7.60-7.37 (m, 3H), 7.67 (d, J = 7.8 Hz, 1H), 9.86 (br s, 1H), 11.30 (br s, 1H).

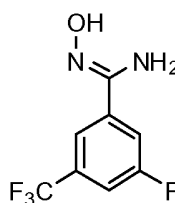
Step-3:- Preparation of methyl 4-(3-(2,6-dichlorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzoate

[0274] The title compound was prepared according to the procedure described in step-2 of Intermediate-9 by using *tert*-butyl 2-((2,6-dichlorobenzoyl)carbamoyl)-2-(3-methoxy-4-(methoxycarbonyl)phenyl)hydrazinecarboxylate (1.5 g, 2.2 mmol), DCM (50 mL) and trifluoro acetic acid (5.0 mL) to afford 0.900 g of desired product. ^1H NMR (300 MHz, DMSO d_6): δ 3.78 (s, 3H), 3.84 (s, 3H), 7.62- 7.30 (m, 5H), 7.82 (d, J = 8.7 Hz, 1H), 12.76 (br s, 1H); MS (m/z): 393.85 ($M+H$) $^+$.

Intermediate-22

3-Fluoro-*N'*-hydroxy-5-(trifluoromethyl)benzimidamide

[0275]



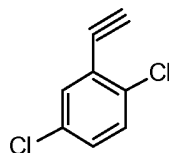
[0276] The title compound was prepared according to the procedure described in Intermediate-19 by using 3-fluoro-5-(trifluoromethyl)benzonitrile (2.00 g, 10.0 mmol), hydroxyl amine .HCl (1.09 g, 15 mmol) and potassium carbonate (2.2 g, 15 mmol), ethanol (20 mL) to afford 0.900 g of the desired product. ^1H NMR (300 MHz, DMSO d_6): δ 6.10 (s, 2H), 7.69 (d, J = 7.8 Hz, 1H), 7.79 (d, J = 10.2 Hz, 1H), 10.03 (s, 1H); MS (m/z): 223.17 ($M+H$) $^+$.

Intermediate-23

1,4-Dichloro-2-ethynylbenzene

[0277]

EP 2 718 284 B1

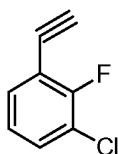


[0278] The title compound was prepared according to the procedure described in step-5 and step-6 of Intermediate-2 by using 1,4-dichloro-2-iodobenzene (1.0 g, 3.6 mmol), ethynyl(trimethyl)silane (0.541 g, 5.5 mmol), copper iodide (0.027 g, 0.14 mmol), bis(triphenylphosphine) palladium(II) chloride (0.050 g, 0.072 mmol), TBAF (catalytic) and DCM to afford 0.550 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 4.73 (s, 1H), 7.50 (d, *J* = 8.7 Hz, 1H), 7.58 (d, *J* = 8.7 Hz, 1H), 7.71 (s, 1H).

Intermediate-24

1-Chloro-3-ethynyl-2-fluorobenzene

[0279]

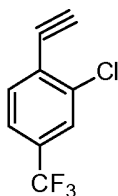


[0280] The title compound was prepared according to the procedure described in step-5 and step-6 of Intermediate-2 by using 1-chloro-2-fluoro-3-iodobenzene (1.0 g, 3.9 mmol), ethynyl(trimethyl)silane (0.541 g, 5.5 mmol), copper iodide (0.027 g, 0.14 mmol), bis(triphenylphosphine) palladium(II) chloride (0.050 g, 0.072 mmol), TBAF (catalytic) and DCM to afford 0.500 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 4.66 (s, 1H), 7.25 (t, *J* = 8.4 Hz, 1H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.65 (t, *J* = 7.8 Hz, 1H).

Intermediate-25

2-Chloro-1-ethynyl-4-(trifluoromethyl)benzene

[0281]



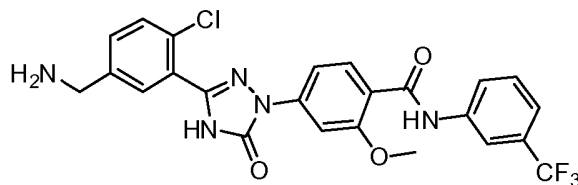
[0282] The title compound was prepared according to the procedure described in step-5 and step-6 of Intermediate-2 by using 2-chloro-1-iodo-4-(trifluoromethyl)benzene (1.0 g, 3.2 mmol), ethynyl(trimethyl)silane (0.541 g, 5.5 mmol), copper iodide (0.027 g, 0.14 mmol), bis(triphenylphosphine) palladium(II) chloride (0.050 g, 0.072 mmol), TBAF (catalytic) and DCM to afford 0.525 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 4.88 (s, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 8.01 (s, 1H).

Intermediate-26

4-(3-(5-(Aminomethyl)-2-chlorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxy-*N*-(3-(trifluoromethyl)phenyl)benzamide

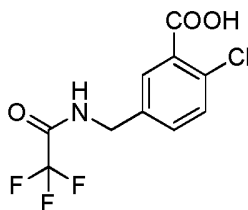
[0283]

EP 2 718 284 B1



Step 1: Preparation of 2-chloro-5-[[[(trifluoroacetyl)amino]methyl]benzoic acid

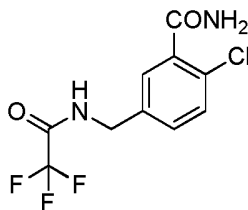
[0284]



[0285] To a solution of 2-chlorobenzoic acid (0.500 g, 3.49 mmol) in conc. H_2SO_4 was added 2,2,2-trifluoro-*N*-(hydroxymethyl)acetamide (0.547 g, 3.49 mmol). The mixture was stirred at RT for 16 h. The reaction mixture was poured into ice-water and stirred for 2 h. The precipitate obtained was collected by filtration, dried and re-crystallized from toluene/butan-2-one (7:1) to afford 0.800 g of the title product. ^1H NMR (300 MHz, DMSO d_6): δ 4.42 (d, J = 6.0 Hz, 2H), 7.43 (d, J = 9.9 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.71 (s, 1H), 10.06 (br s, 1H), 13.47 (br s, 1H); MS (m/z): 280.18 (M-H) $^-$.

Step 2: Preparation of 2-chloro-5-((2,2,2-trifluoroacetamido)methyl)benzamide

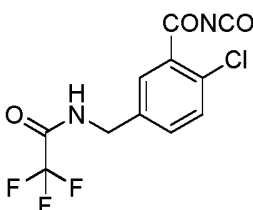
[0286]



[0287] To a cold solution of 2-chloro-5-[[[(trifluoroacetyl)amino]methyl]benzoic acid (1.50 g, 5.33 mmol) in THF : DCM (20:10 mL) was added oxalyl chloride (0.6 mL, 6.40 mmol) and DMF (2-3 drop) at 0°C. The reaction mixture was stirred at RT for 2 h and concentrated. A solution of the concentrated mass in THF (15 mL) was treated with ammonia gas (purged through reaction mass) at 0°C and the reaction mixture was stirred at RT for 1 h. The reaction mixture was diluted with ethyl acetate. The reaction mixture was washed with water, dilute HCl and brine. The organic layer was separated, dried, filtered and concentrated to afford 0.800 g of the desired product. ^1H NMR (300 MHz, DMSO d_6): δ 4.39 (s, 2H), 7.30- 7.34 (m, 2H), 7.46 (d, J = 7.8 Hz, 1H), 7.63 (s, 1H), 7.90 (s, 1H), 10.06 (s, 1H).

Step 3: Preparation of 2-chloro-5-((2,2,2-trifluoroacetamido)methyl)benzoyl isocyanate

[0288]

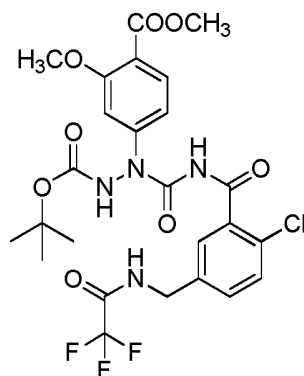


EP 2 718 284 B1

[0289] The title compound was prepared according to the procedure described in step-2 of Intermediate-8 by using 2-chloro-5-((2,2,2-trifluoroacetamido)methyl)benzamide (0.700 g, 2.5 mmol), oxalyl chloride (0.3 mL, 3.0 mmol) and EDC (30 mL) to afford 0.700 g of the desired product.

Step 4: Preparation of *tert*-butyl 2-((2-chloro-5-((2,2,2-trifluoroacetamido)methyl) benzoyl)carbamoyl)-2-(3-methoxy-4-(methoxycarbonyl)phenyl)hydrazinecarboxylate

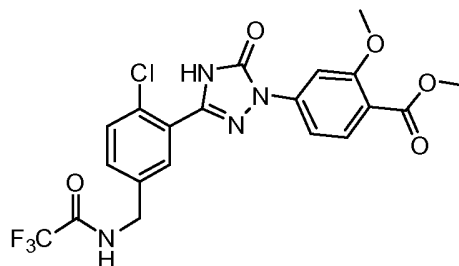
[0290]



[0291] The title compound was prepared according to the procedure described in step-1 of Intermediate-9 by using 2-chloro-5-((2,2,2-trifluoroacetamido)methyl)benzoyl isocyanate (0.700 g, 2.2 mmol), *tert*-butyl 2-(3-methoxy-4-(methoxycarbonyl)phenyl) hydrazinecarboxylate (Intermediate-14, 0.675 mL, 2.20 mmol) and DCM (30 mL) to afford 1.2 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.39 (s, 9H), 3.09 (m, 6H), 4.48 (s, 2H), 6.22- 6.26 (m, 2H), 7.13- 7.76 (m, 4H), 8.94 (s, 1H), 10.08 (s, 1H), 11.02 (s, 1H); MS (*m/z*): (*M*)⁺.602.72.

Step 5: Preparation of methyl 4-(3-(2-chloro-5-((2,2,2-trifluoroacetamido)methyl) phenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzoate

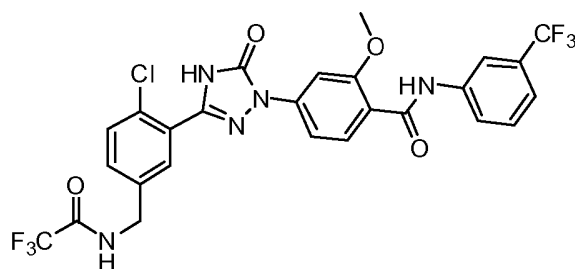
[0292]



[0293] The title compound was prepared according to the procedure described in step-2 of Intermediate-9 by using *tert*-butyl 2-((2-chloro-5-((2,2,2-trifluoroacetamido)methyl) benzoyl)carbamoyl)-2-(3-methoxy-4-(methoxycarbonyl)phenyl)hydrazinecarboxylate (1.20 g, 1.99 mmol), TFA (2 mL) and DCM (20 mL) to afford 0.280 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.78 (s, 3H), 3.85 (s, 3H), 4.46 (d, *J* = 6.0 Hz, 2H), 7.51 (t, *J* = 8.1 Hz, 1H), 7.65- 7.68 (m, 3H), 7.78- 7.84 (m, 2H), 10.09 (m, 1H), 12.70 (br s, 1H); MS (*m/z*): (*M*)⁺.484.95.

Step 6: Preparation of 4-(3-(2-chloro-5-((2,2,2-trifluoroacetamido)methyl)phenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxy-*N*-(3-(trifluoromethyl)phenyl)benzamide

[0294]



[0295] To a solution of methyl 4-(3-(2-chloro-5-((2,2,2-trifluoroacetamido) methyl)phenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-2-methoxybenzoate (0.200 g, 0.413 mmol) in dry toluene (3 mL) was added 3-(trifluoromethyl)aniline (0.100 g, 0.619 mmol) followed by addition of trimethyl aluminium (2M solution in toluene) (2 mL). The reaction mass was refluxed for 3-4 h. The reaction mass was quenched in water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and concentrated to afford 0.170 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.95 (s, 3H), 4.46 (d, *J* = 6.0 Hz, 2H), 7.56 (t, *J* = 6.0 Hz, 2H), 7.59- 7.85 (m, 6H), 7.96 (d, *J* = 7.8 Hz, 1H), 8.26 (s, 1H), 10.09 (s, 1H), 10.37 (s, 1H), 12.65 (s, 1H); MS (*m/z*): (*M*)⁺.614.08.

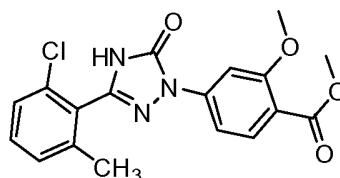
Step 7: Preparation of 4-(3-(5-(aminomethyl)-2-chlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-2-methoxy-*N*-(3-(trifluoromethyl)phenyl)benzamide

[0296] To a solution of 4-(3-(2-chloro-6-((2,2,2-trifluoroacetamido)methyl)phenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-2-methoxy-*N*-(3-(trifluoromethyl)phenyl)benzamide (0.150 g, 0.24 mmol) in THF was added aq. KOH (0.028 g, 0.48 mmol). The mixture was stirred at RT for 3-4 h. The reaction mixture was poured into water and extracted in DCM. Organic layer was dried and concentrated to afford 0.080 g of the title product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.92-3.96 (m, 5H), 7.43- 7.61 (m, 5H), 7.70- 7.85 (m, 3H), 7.97 (m, 2H), 8.26 (s, 1H), 10.35 (m, 1H).

Intermediate-27

Methyl 4-(3-(2-chloro-6-methylphenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-2-methoxybenzoate

[0297]



Step 1: Preparation of 2-chloro-6-methylbenzamide

[0298]

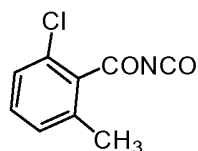


[0299] A solution of 2-chloro-6-methylbenzonitrile (2.0 g) in conc. sulphuric acid (10 mL) was heated at 100°C for 3-4 h. The reaction mass was quenched in ice-water and the solid obtained was filtered. The precipitate was suck dried to afford 1.5 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 2.28 (s, 3H), 7.21- 7.27 (m, 3H), 7.65 (s, 1H), 7.91 (s, 1H).

Step 2: Preparation of 2-chloro-6-methylbenzoyl isocyanate

[0300]

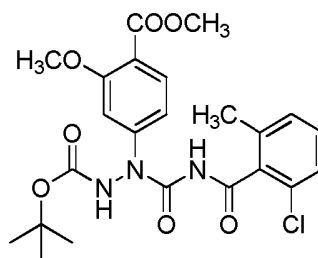
EP 2 718 284 B1



[0301] The title compound was prepared according to the procedure described in step-2 of Intermediate-8 by using 2-chloro-6-methylbenzamide (1.0 g, 5.9 mmol), oxalyl chloride (0.894 g, 7.1 mmol) and EDC (20 mL) to afford 1.00 g of the desired product.

Step 3: Preparation of *tert*-butyl 2-((2-chloro-6-methylbenzoyl)carbamoyl)-2-(3-methoxy-4-(methoxycarbonyl)phenyl)hydrazinecarboxylate

[0302]



[0303] The title compound was prepared according to the procedure described in step-1 of Intermediate-9 by using 2-chloro-6-methylbenzoyl isocyanate (0.793 g, 4.06 mmol), *tert*-butyl 2-(3-methoxy-4-(methoxycarbonyl)phenyl)hydrazinecarboxylate (Intermediate - 14, 1.2 g, 4.06 mmol) and DCM (30 mL) to afford 1.5 g of the desired product.

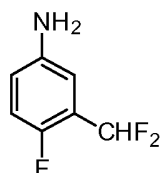
Step 4: Preparation of methyl 4-(3-(2-chloro-6-methylphenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzoate

[0304] The title compound was prepared according to the procedure described in step-2 of Intermediate-9 by using *tert*-butyl 2-((2-chloro-6-methylbenzoyl)carbamoyl)-2-(3-methoxy-4-(methoxycarbonyl)phenyl)hydrazinecarboxylate (2.0 g), TFA (5 mL) and DCM (30 mL) to afford 0.700 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 2.31 (s, 3H), 3.78 (s, 3H), 3.84 (s, 3H), 7.40 (s, 1H), 7.49 (s, 2H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.75 (s, 1H), 7.81 (d, *J* = 8.7 Hz, 1H), 12.54 (s, 1H); MS (*m/z*): 373.95 (*M*+*H*)⁺.

Intermediate-28

3-(Difluoromethyl)-4-fluoroaniline

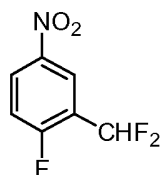
[0305]



Step 1: Preparation of 2-(difluoromethyl)-1-fluoro-4-nitrobenzene

[0306]

EP 2 718 284 B1



[0307] A solution of 2-fluoro-5-nitrobenzaldehyde (3.0 g, 17 mmol) in DCM (50 mL) was added DAST (3.42 g, 21 mmol) and stirred at RT for 18 h under nitrogen atmosphere. The reaction mass was quenched in ice-water and extracted with DCM. The organic layer was dried and concentrated to afford 2.5 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 7.31 (s, 1H), 7.69 (t, *J* = 8.7 Hz, 1H), 8.46-8.50 (m, 2H).

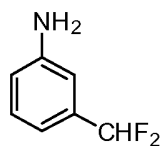
Step 2: Preparation of 3-(difluoromethyl)-4-fluoroaniline

[0308] A solution of 2-(difluoromethyl)-1-fluoro-4-nitrobenzene (1.2 g, 6.2 mmol) in methanol (20 mL) was added iron powder (4.8 g, 24.8 mmol) followed by conc. HCl (5 mL) dropwise. The reaction mass was stirred at RT for 1-2 h. The reaction mass was quenched in ice-water, basified with NaHCO₃ and extracted with DCM. The organic layer was dried and concentrated to afford 0.800 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 5.25 (s, 2H), 6.66-6.73 (m, 2H), 6.86- 7.04 (m, 2H).

Intermediate-29

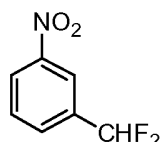
3-(Difluoromethyl)aniline

[0309]



Step 1: Preparation of 1-(difluoromethyl)-3-nitrobenzene

[0310]



[0311] The title compound was prepared according to the procedure described in step-1 of Intermediate-28 by using 3-nitrobenzaldehyde (2.0 g, 13 mmol), DAST (2.55 g, 15 mmol) and DCM (30 mL) to afford 1.5 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 7.21 (s, 1H), 7.83 (t, *J* = 8.1 Hz, 1H), 8.05 (m, 1H), 8.40 (br s, 2H).

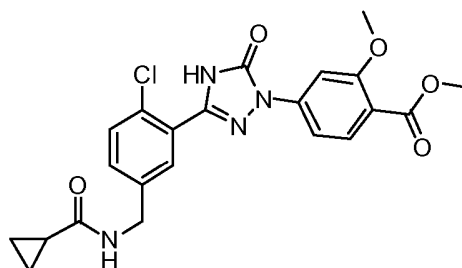
Step 2: Preparation of 3-(difluoromethyl)aniline

[0312] The title compound was prepared according to the procedure described in step-2 of Intermediate-28 by using 1-(difluoromethyl)-3-nitrobenzene (1.0 g, 5.0 mmol), Iron powder (3.0 g, 15.0 mmol), conc. HCl (5 mL) and methanol (20 mL) to afford 0.700 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 5.36 (br s, 2H), 6.62- 6.82 (m, 4H), 7.11 (t, *J* = 7.8 Hz, 1H); MS (m/z): 144.05 (M+H)⁺.

Intermediate-30

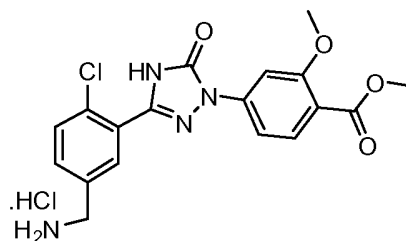
Methyl 4-(3-(2-chloro-5-(cyclopropanecarboxamidomethyl)phenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzoate

[0313]



Step 1: Preparation of methyl 4-(3-(5-(aminomethyl)-2-chlorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzoate hydrochloride

[0314]



[0315] A solution of methyl 4-(3-(2-chloro-5-((2,2,2-trifluoroacetamido)methyl)phenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzoate (step-5 of Intermediate-26, 0.500 g) in methanol (20 mL) was added conc. HCl (5 mL) dropwise. The reaction mass was refluxed for 24 h. The reaction mass was concentrated to afford 0.450 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.78 (s, 3H), 3.85 (s, 3H), 4.10 (d, *J* = 5.4 Hz, 2H), 7.63 (d, *J* = 9.0 Hz, 1H), 7.74- 7.84 (m, 4H), 7.94 (s, 1H), 8.57 (s, 2H), 12.81 (s, 2H); MS (*m/z*): 388.96 (*M*+*H*)⁺.

Step 2: Preparation of methyl 4-(3-(2-chloro-5-(cyclopropanecarboxamidomethyl)phenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzoate

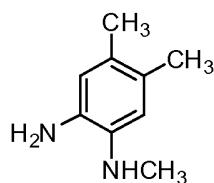
[0316] A solution of methyl 4-(3-(5-(aminomethyl)-2-chlorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzoate hydrochloride (0.500 g, 1.29 mmol) in THF (20 mL) was added DIPEA (2 mL) and cyclopropyl carbonyl chloride (0.201 g, 1.9 mmol) under nitrogen atmosphere. The reaction mass was stirred at RT for 2-4 h. The reaction mass was quenched in water, extracted with DCM and concentrated to afford 0.400 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 0.69 (m, 4H), 1.60 (s, 1H), 3.79 (s, 3H), 3.86 (s, 3H), 4.33 (d, *J* = 5.4 Hz, 2H), 7.41- 7.54 (m, 3H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.73 (s, 1H), 7.79 (d, 1H), 8.71 (m, H); MS (*m/z*): 456.97 (*M*+*H*)⁺.

Intermediate-31

*N*¹,4,5-Trimethylbenzene-1,2-diamine

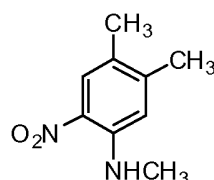
[0317]

EP 2 718 284 B1



Step 1: Preparation of *N*¹,4,5-trimethyl-2-nitroaniline

[0318]



[0319] A solution of 4,5-dimethyl-2-nitroaniline (2.00 g, 12 mmol) in toluene (25 mL) was added NaOH (1.93 g, 48 mmol). The reaction mass was stirred at 100°C for 1 h, followed by addition of dimethyl sulphate (4.6 g, 36 mmol) and reaction mass was stirred at RT for 24 h. The reaction mass was quenched in water, extracted with DCM and concentrated to afford 1.5 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 2.11 (s, 3H), 2.24 (d, *J* = 7.8 Hz, 3H), 2.92 (s, 3H), 6.77 (m, 1H), 7.79 (m, 1H), 8.06 (s, 1H); MS (*m/z*): 180.92 (*M*+H)⁺.

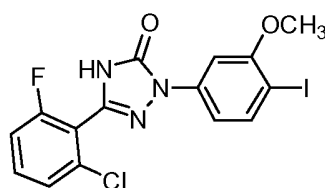
Step 2: Preparation of *N*¹,4,5-trimethylbenzene-1,2-diamine

[0320] The title compound was prepared according to the procedure described in step-2 of Intermediate-28 by using *N*¹,4,5-trimethyl-2-nitroaniline (0.350 g, 1.9 mmol), methanol (20 mL), Iron powder (1.75 g, 9.75 mmol), conc. HCl (5 mL) to afford 0.120 g of desired product.

Intermediate-32

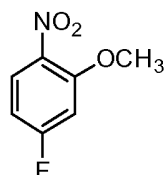
3-(2-Chloro-6-fluorophenyl)-1-(4-iodo-3-methoxyphenyl)-1*H*-1,2,4-triazol-5(4*H*)-one

[0321]



Step-1:- Preparation of 4-fluoro-2-methoxy-1-nitrobenzene

[0322]



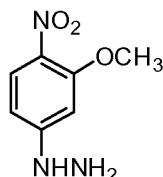
[0323] To a solution of 4-fluoro-2-hydroxy-1-nitrobenzene (5.0 g, 31.8 mmol) in DMF (10 mL) was added K₂CO₃ (13.1 g, 95.4 mmol). The reaction mixture was stirred at RT for 1 h followed by addition of methyl iodide (9.93 g, 69.9 mmol) and the reaction mixture was stirred at 60°C for 2 h. The reaction mass was concentrated and quenched in water. The

EP 2 718 284 B1

reaction mass was basified with saturated sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and concentrated to afford 4.5 g of desired product. ^1H NMR (300 MHz, DMSO d_6): δ 3.93 (s, 3H), 6.97 (t, J = 7.8 Hz, 1H), 7.31 (d, J = 8.7 Hz, 1H), 8.02 (s, 1H).

Step-2:- Preparation of (3-methoxy-4-nitrophenyl)hydrazine

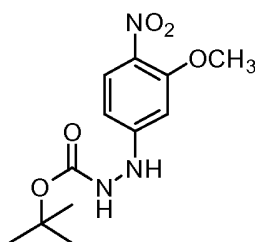
[0324]



[0325] To a solution of 4-fluoro-2-methoxy-1-nitrobenzene (2.5 g, 14.60 mmol) in ethanol (25 mL) was added hydrazine hydrate (2.1 g, 43.8 mmol). The reaction mixture was refluxed for 3-4 h. The reaction mixture was concentrated to afford 2.0 g of desired product. ^1H NMR (300 MHz, DMSO d_6): δ 3.84 (s, 3H), 4.46 (s, 2H), 6.31 (d, J = 9.3 Hz, 1H), 6.50 (s, 1H), 7.83 (d, J = 9.3 Hz, 1H), 8.25 (s, 1H); MS (m/z): (184.01 M) $^+$.

Step-3:- Preparation of *tert*-butyl 2-(3-methoxy-4-nitrophenyl)hydrazinecarboxylate

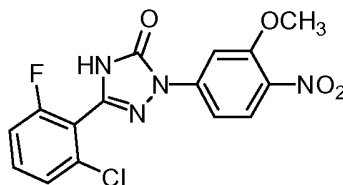
[0326]



[0327] The title compound was prepared according to the procedure described in step-3 of Intermediate-7 by using (3-methoxy-4-nitrophenyl)hydrazine (0.500 g, 2.68 mmol), BOC anhydride (0.703 g, 3.22 mmol), sodium carbonate (0.426 g, 4.02 mmol) and DCM to afford 0.200 g of desired product. ^1H NMR (300 MHz, DMSO d_6): δ 1.36 (s, 9H), 3.81 (s, 3H), 6.25- 6.29 (m, 2H), 7.87 (d, J = 8.7 Hz, 1H), 7.78 (s, 1H), 9.12 (s, 1H); MS (m/z): 283.88 (M) $^+$.

Step-4:- Preparation of 3-(2-chloro-6-fluorophenyl)-1-(3-methoxy-4-nitrophenyl)-1*H*-1,2,4-triazol-5(4*H*)-one

[0328]

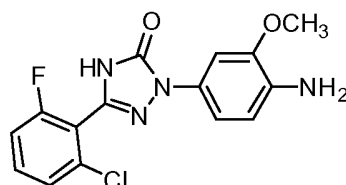


[0329] The title compound was prepared according to the procedure described in step-1 and step-2 of Intermediate-9 by using *tert*-butyl 2-(3-methoxy-4-nitrophenyl) hydrazinecarboxylate (1.0 g) and 2-chloro-6-fluorobenzoyl isocyanate (Intermediate-8, 1.0 g), TFA (5 mL) and DCM (40 mL) to afford 0.900 g of desired product. ^1H NMR (300 MHz, DMSO d_6): δ 3.96 (s, 3H), 7.51 (t, J = 8.7 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.68- 7.73 (m, 2H), 7.88 (s, 1H), 8.09 (d, J = 8.7 Hz, 1H), 12.93 (s, 1H); MS (m/z): 363 (M) $^-$.

EP 2 718 284 B1

Step-5:- Preparation of 1-(4-amino-3-methoxyphenyl)-3-(2-chloro-6-fluorophenyl)-1*H*-1,2,4-triazol-5(4*H*)-one

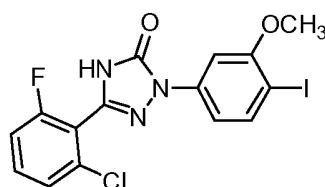
[0330]



[0331] The title compound was prepared according to the procedure described in step-2 of Intermediate- 28 by using 3-(2-chloro-6-fluorophenyl)-1-(3-methoxy-4-nitrophenyl)-1*H*-1,2,4-triazol-5(4*H*)-one (0.100 g), iron powder (catalytic), conc.HCl (5-6 drops) and methanol (5 mL) to afford 0.070 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.77 (s, 3H), 4.81 (s, 2H), 6.66 (d, *J* = 8.7 Hz, 1H), 7.17 (d, *J* = 8.1 Hz, 1H), 7.26 (s, 1H), 7.50- 7.57 (m, 2H), 7.68 (m, 1H), 12.39 (s, 1H).

Step-6:- Preparation of 3-(2-chloro-6-fluorophenyl)-1-(4-iodo-3-methoxyphenyl)-1*H*-1,2,4-triazol-5(4*H*)-one

[0332]

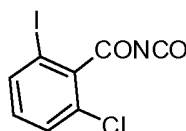


[0333] To a solution of 1-(4-amino-3-methoxyphenyl)-3-(2-chloro-6-fluorophenyl)-1*H*-1,2,4-triazol-5(4*H*)-one (0.280 g, 0.83 mmol) in acetonitrile (5.0 ml) was added PTSA (0.477 g, 2.51 mmol). The reaction mass was stirred at RT for 1h followed by addition of potassium iodide (0.347 g, 2.0 mmol) and sodium nitrite (0.115 g, 1.67 mmol) at 0-5°C and further stirred for 2h. Excess solvent was removed under vacuum and the residue reaction mass was quenched in water and extracted with ethyl acetate. The organic layer was washed with sodium metabisulphate and concentrated to obtain a crude product, which was further purified by column chromatography on silica gel eluting with 10% EtOAc: pet. ether to afford 0.200 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.85 (s, 3H), 7.40 (d, *J* = 8.7 Hz, 1H), 7.46- 7.74 (m, 4H), 7.83 (d, *J* = 8.1 Hz, 1H), 12.71 (br s, 1H); MS (*m/z*): 445.84 (*M*+*H*)⁺.

Intermediate-33

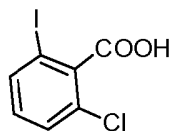
2-Chloro-6-iodobenzoyl isocyanate

[0334]



Step-1:- Preparation of 2-chloro-6-iodobenzoic acid

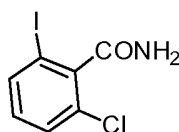
[0335]



[0336] To the cold solution of 2-amino-6-chlorobenzoic acid (2.0 g, 11.6 mmol) in conc. HCl (10 mL) was added aq. solution of sodium nitrite (0.8 g, 11.6 mmol) at 0°C followed by addition of solution of potassium iodide (2.88 g, 17.4 mmol) in water and conc. sulphuric acid (1 mL). The reaction mixture was refluxed for 2 h. The reaction mass was washed with sodium metabisulphate solution and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and concentrated to afford 2.0 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 7.08 (t, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.76 (d, *J* = 7.8 Hz, 1H), 8.37 (br s, 1H); MS (*m/z*): 280.59 (M)⁻.

Step-2:- Preparation of 2-chloro-6-iodobenzamide

[0337]



[0338] The title compound was prepared according to the procedure described in step-2 of Intermediate-26 by using 2-chloro-6-iodobenzoic acid (2.7 g, 9.6 mmol), oxalyl chloride (1.4 g, 11.5 mmol), ammonia gas, THF (20 mL) and DCM (10 mL) to afford 2.3 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 7.11 (t, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.73 (s, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 8.00 (s, 1H); MS (*m/z*): 281.98 (M+H)⁺.

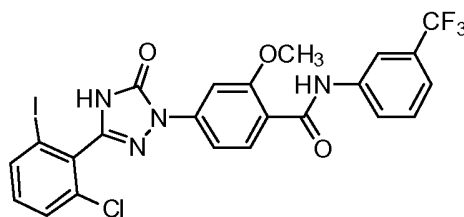
Step-3:- Preparation of 2-chloro-6-iodobenzoyl isocyanate

[0339] The title compound was prepared according to the procedure described in step-2 of Intermediate-8 by using 2-chloro-6-iodobenzamide (1.0 g, 3.5 mmol), oxalyl chloride (0.538 g, 4.2 mmol) and EDC (20 mL) to afford 1.00 g of the desired product.

Intermediate-34

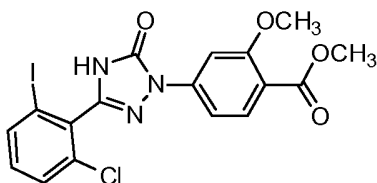
4-(3-(2-Chloro-6-iodophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxy-*N*-(3-(trifluoromethyl)phenyl)benzamide

[0340]



Step-1:- Preparation of methyl 4-(3-(2-chloro-6-iodophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzoate

[0341]



[0342] The title compound was prepared according to the procedure described in step-1 and step-2 of Intermediate-9 by using *tert*-butyl 2-(3-methoxy-4-(methoxycarbonyl)phenyl) hydrazinecarboxylate (Intermediate-14, 1.0g) and 2-chloro-6-iodobenzoyl isocyanate (Intermediate-33, 1.0 g), TFA (5 mL) and DCM (40 mL) to afford 0.900 g of desired product. ^1H NMR (300 MHz, DMSO d_6): δ 3.78 (s, 3H), 3.85 (s, 3H), 3.37 (t, J = 7.8 Hz, 1H), 7.63 (d, J = 9.0 Hz, 1H), 7.70- 7.81 (m, 3H), 8.00 (d, J = 7.8 Hz, 1H), 12.65 (br s, 1H); MS (m/z): 285.75 ($M+H$) $^+$.

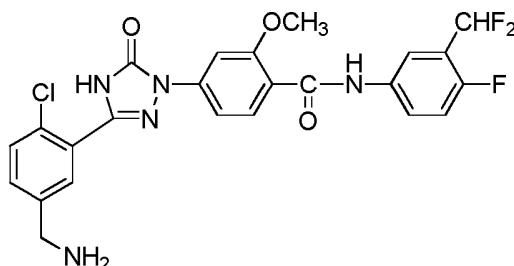
Step-2:- Preparation of 4-(3-(2-chloro-6-iodophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxy-*N*-(3-(trifluoromethyl)phenyl)benzamide

[0343] The title compound was prepared by following the procedure as described for step-6 of Intermediate-26 by using methyl 4-(3-(2-chloro-6-iodophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzoate (0.100 g, 0.206 mmol), 3-(trifluoromethyl)aniline (0.041 g, 0.247 mmol), trimethyl aluminium (2M solution in toluene) (0.5 mL), dry toluene (10.0 mL) to afford 0.075 g of desired product. ^1H NMR (300 MHz, DMSO d_6): δ 3.95 (s, 3H), 7.19- 8.03 (m, 9H), 8.25 (s, 1H), 10.36 (s, 1H), 12.65 (s, 1H); MS (m/z): 614.98 ($M+H$) $^+$.

Intermediate-35

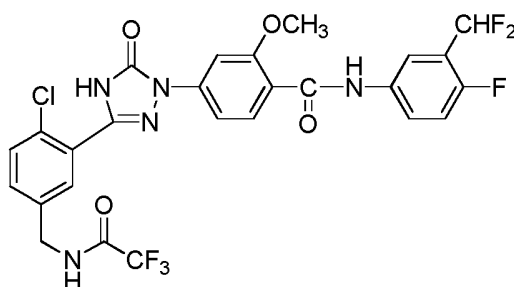
4-(3-(5-(Aminomethyl)-2-chlorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-*N*-(3-(difluoromethyl)-4-fluorophenyl)-2-methoxybenzamide

[0344]



Step-1:- Preparation of 4-(3-(2-chloro-5-((2,2,2-trifluoroacetamido)methyl)phenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-*N*-(3-(difluoromethyl)-4-fluorophenyl)-2-methoxybenzamide

[0345]



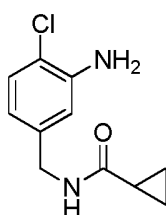
[0346] The title compound was prepared by following the procedure as described for step-6 of Intermediate-26 by using methyl 4-(3-(2-chloro-6-((2,2,2-trifluoroacetamido) methyl) phenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-

methoxybenzoate (Step-5 of Intermediate-26, 0.100 g, 0.20 mmol), 3-(difluoromethyl)-4-fluoroaniline (0.050 g, 0.30 mmol), trimethyl aluminium (2M solution in toluene) (1 mL) to afford 0.070 g of desired product. ^1H NMR (300 MHz, DMSO d_6): δ 3.95 (s, 3H), 4.47 (s, 2H), 6.71 (m, 1H), 7.04 (m, 1H), 7.34- 7.40 (m, 1H), 7.50- 7.54 (m, 1H), 7.65- 7.70 (m, 3H), 7.79- 7.87 (m, 3H), 8.12 (s, 1H), 10.09 (m, 1H), 10.28 (s, 1H), 12.67 (brs, 1H); MS (m/z): 614.04 (M+H) $^+$. Step-2:- Preparation of 4-(3-(5-(aminomethyl)-2-chlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-N-(3-(difluoromethyl)-4-fluorophenyl)-2-methoxybenzamide The solution of 4-(3-(2-chloro-5-((2,2,2-trifluoroacetamido)methyl)phenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-N-(3-(difluoromethyl)-4-fluorophenyl)-2-methoxybenzamide (0.070 g, 0.11 mmol) in 20% aq. KOH (10 mL) and aq. NH_3 (2 mL) was stirred for 24 h at RT. Excess of solvent was removed under vacuum and filtered off to afford 0.015 g of desired product.

Intermediate-36

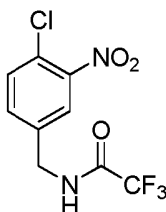
N-(3-Amino-4-chlorobenzyl)cyclopropanecarboxamide

[0347]



Step-1:- Preparation of *N*-(4-chloro-3-nitrobenzyl)-2,2,2-trifluoroacetamide

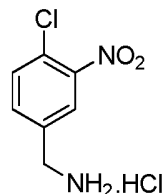
[0348]



[0349] To a solution of 1-chloro-2-nitrobenzene (10.0 g, 0.063 mmol) in conc. sulphuric acid (150 mL) was added *N*-hydroxy methyl trifluoro acetamide (9.98 g, 0.069 mmol). The reaction mixture was heated at 70-80°C for 24 h. The reaction mass was quenched in ice cold water, neutralised with sodium hydroxide and extracted with DCM. The organic layer was concentrated and the obtained crude product was purified by column chromatography on silica gel eluting with 4% EtOAc: pet. ether to afford 5.5 g of desired product. ^1H NMR (300 MHz, DMSO d_6): 4.48 (d, J = 3.9 Hz, 2H), 7.62- 7.64 (m, 1H), 7.72- 7.78 (m, 1H), 7.97- 8.01 (m, 1H), 10.09 (brs, 1H).

Step-2:- Preparation of (4-chloro-3-nitrophenyl)methanamine hydrochloride

[0350]



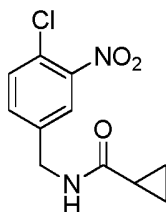
[0351] To a solution of *N*-(4-chloro-3-nitrobenzyl)-2,2,2-trifluoroacetamide (0.800 g) in methanol (20 mL) was added

EP 2 718 284 B1

conc. HCl (2.0 ml). The reaction mass was refluxed for 18 h. Excess solvent was removed under vacuum to afford 0.700 g of desired product. ^1H NMR (300 MHz, DMSO d_6): δ 7.18 (s, 1H), 7.35 (s, 1H), 7.52 (s, 1H), 7.86 (s, 2H), 8.28 (s, 1H), 8.72 (br s, 2H).

Step-3:- Preparation of N-(4-chloro-3-nitrobenzyl)cyclopropanecarboxamide

[0352]



[0353] The title compound was prepared by following the procedure as described in step-2 of Intermediate-30 by using (4-chloro-3-nitrophenyl)methanamine hydrochloride (0.700 g, 3.14 mmol), cyclopropylcarbonyl chloride (0.490 g, 4.71 mmol), DIPEA (3.0 mL) and THF (15 mL) to afford 0.400 g of desired product. ^1H NMR (300 MHz, DMSO d_6): δ 0.69 (d, J = 6.0 Hz, 2H), 1.55- 1.61 (m, 1H), 4.33 (d, J = 6.0 Hz), 7.55 (d, J = 7.8 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.87 (s, 1H), 8.68 (br s, 1H); MS (m/z): 255.09 (M+H) $^+$.

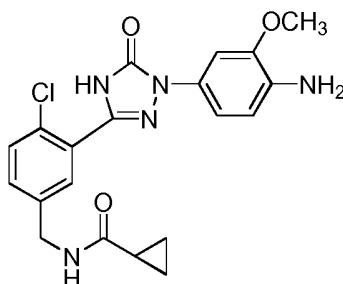
Step-4:- Preparation of N-(3-amino-4-chlorobenzyl)cyclopropanecarboxamide

[0354] The title compound was prepared by following the procedure as described in step-2 of Intermediate-28 by using N-(4-chloro-3-nitrobenzyl)cyclopropanecarboxamide (0.400 g), methanol (10 mL), iron powder (catalytic) and conc.HCl (5 mL). The reaction mass was refluxed for 2 h. The reaction mass was quenched in water and basified with NaHCO_3 and extracted with DCM. The organic layer was dried over anhydrous sodium sulphate and concentrated to afford 0.200 g of desired product. ^1H NMR (300 MHz, DMSO d_6): δ 0.65 (d, J = 8.4 Hz, 4H), 1.57 (m, 1H), 4.11 (d, J = 5.4 Hz, 2H), 5.34 (s, 2H), 6.41 (d, J = 7.2 Hz, 1H), 7.10 (d, J = 7.8 Hz, 1H), 8.50 (br s, 1H); MS (m/z): 225.07 (M+H) $^+$.

Intermediate-37

N-(3-(1-(4-Amino-3-methoxyphenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4-chlorobenzyl)cyclopropanecarboxamide

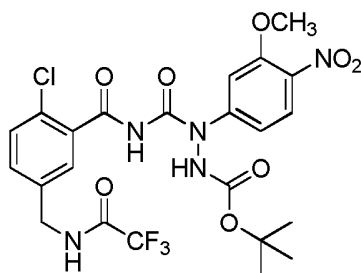
[0355]



Step-1:- Preparation of *tert*-butyl 2-((2-chloro-5-((2,2,2-trifluoroacetamido) methyl)benzoyl)carbamoyl)-2-(3-methoxy-4-nitrophenyl)hydrazinecarboxylate

[0356]

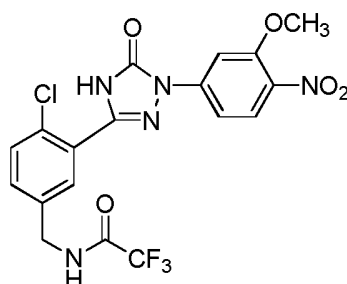
EP 2 718 284 B1



[0357] The title compound was prepared according to the procedure described in step-1 of Intermediate-9 by using 2-chloro-5-((2,2,2-trifluoroacetamido)methyl)benzoyl isocyanate (step-3 of Intermediate-26, 1.400 g, 4.57 mmol), *tert*-butyl 2-(3-methoxy-4-nitrophenyl)hydrazinecarboxylate (step-3 of Intermediate-32, 1.30 g, 4.57 mmol) and DCM 30 mL to afford 2.0 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.33- 1.46 (m, 9H), 3.87 (s, 3H), 4.40 (s, 2H), 7.06 (d, *J* = 8.4 Hz, 1H), 7.32- 7.36 (m, 3H), 7.45- 7.52 (m, 1H), 7.96 (d, *J* = 8.7 Hz, 1H), 9.92 (s, 1H), 10.07 (brs, 1H), 11.13 (br s, 1H); MS (*m/z*): 589.69 (M)⁺.

Step-2:- Preparation of *N*-(4-chloro-3-(1-(3-methoxy-4-nitrophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide

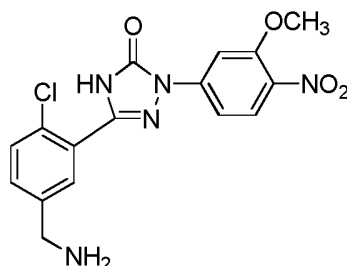
[0358]



[0359] The title compound was prepared according to the procedure described in step-2 of Intermediate-9 by using *tert*-butyl 2-((2-chloro-5-((2,2,2-trifluoroacetamido) methyl)benzoyl)carbonyl)-2-(3-methoxy-4-nitrophenyl)hydrazinecarboxylate (2.0 g, 4.23 mmol), TFA (30 mL) and DCM (5 mL) to afford 1.300 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.96 (s, 3H), 4.47 (d, *J* = 5.4 Hz, 2H), 7.54 (d, *J* = 8.7 Hz, 1H), 7.67- 7.74 (m, 3H), 7.93 (s, 1H), 8.10 (d, *J* = 9.0 Hz, 1H), 10.11 (m, 1H), 12.86 (br s, 1H); MS (*m/z*): 471.88 (M+H)⁺.

Step-3:- Preparation of 3-(5-(aminomethyl)-2-chlorophenyl)-1-(3-methoxy-4-nitrophenyl)-1*H*-1,2,4-triazol-5(4*H*)-one

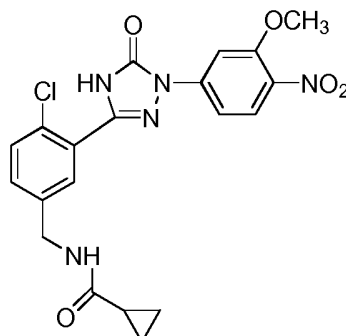
[0360]



[0361] The solution of *N*-(4-chloro-3-(1-(3-methoxy-4-nitrophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide (0.500 g, 1.06 mmol) in 20% aq. KOH (20 mL) was stirred for 2-3 h at RT. Excess of solvent was removed under vacuum and filtered off remaining reaction mass to afford 0.400 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.80 (br s, 2H), 3.72 (s, 2H), 3.91 (s, 3H), 7.27- 7.39 (m, 2H), 7.78 (d, *J* = 9.9 Hz, 2H), 8.98 (d, *J* = 8.7 Hz, 1H), 8.25 (s, 1H); MS (*m/z*): 375.91 (M)⁺.

Step-4:- Preparation of *N*-(4-chloro-3-((3-methoxy-4-nitrophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)cyclopropanecarboxamide

[0362]



[0363] The title compound was prepared according to the procedure as described in step-2 Intermediate-30 by using 3-(5-(aminomethyl)-2-chlorophenyl)-1-(3-methoxy-4-nitrophenyl)-1*H*-1,2,4-triazol-5(4*H*)-one (0.500 g, 1.33 mmol), cyclopropylcarbonyl chloride (0.207 g, 1.99 mmol), DIPEA (2.0 mL) and THF (30 mL) to afford 0.300 g of crude product which was triturated with methanol: DEE to afford 0.300 g of pure product. ¹H NMR (300 MHz, DMSO *d*₆): δ 0.69 (s, 4H), 1.60 (m, 1H), 3.97 (s, 3H), 4.33 (d, *J* = 5.4 Hz, 2H), 7.42- 7.55 (m 3H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.87 (s, 1H), 8.12 (d, *J* = 8.7 Hz, 1H), 8.69- 8.71 (m, 1H), 12.83 (s, 1H); MS (*m/z*): 442.14 (M-H)⁺.

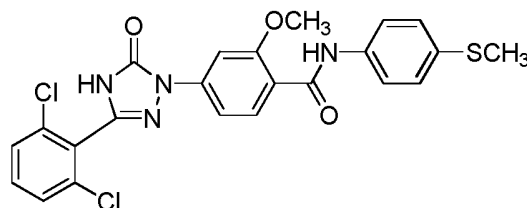
Step-5:- Preparation of *N*-(3-(1-(4-amino-3-methoxyphenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-4-chlorobenzyl)cyclopropanecarboxamide

[0364] The title compound was prepared according to the procedure as described in step-2 Intermediate-28 by using *N*-(4-chloro-3-(1-(3-methoxy-4-nitrophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)cyclopropanecarboxamide (0.500 g, 1.12 mmol), iron powder (catalytic amount), methanol (20 mL), conc. HCl (5.0 mL) to afford 0.350 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 0.69 (s, 4H), 1.22 (br s, 2H), 1.60 (m, 1H), 3.97 (s, 3H), 4.33 (d, *J* = 5.4 Hz, 2H), 7.45- 7.58 (m, 3H), 7.70 (d, *J* = 9.3 Hz, 1H), 7.87 (s, 1H), 8.13 (d, *J* = 9.0 Hz, 1H), 8.71 (m, 1H), 12.30 (br s, 1H); MS (*m/z*): 414.09 (M+H)⁺.

Intermediate-38

4-(3-(2,6-Dichlorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxy-*N*-(4-(methylthio)phenyl)benzamide

[0365]

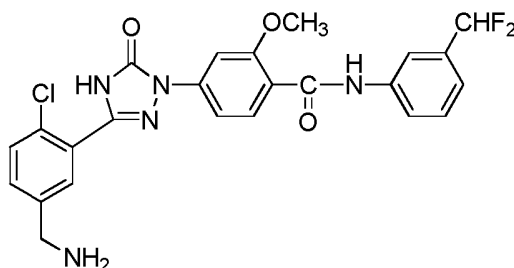


[0366] The title compound was prepared according to the procedure as described for step-6 of Intermediate-26 by using methyl 4-(3-(2,6-dichlorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzoate (Intermediate-21, 0.150 g, 0.380 mmol), 4-(methylthio)aniline (0.079 g, 0.570 mmol), trimethyl aluminium (2M solution in toluene) (1 mL) and dry toluene (5.0 mL) to afford 0.080 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 2.46 (s, 3H), 3.94 (s, 3H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.69- 7.72 (m, 6H), 7.78 (d, *J* = 6.9 Hz, 1H), 7.82 (s, 1H), 10.06 (s, 1H), 12.76 (br s, 1H); MS (*m/z*): 501.0 (M)⁺.

Intermediate-39

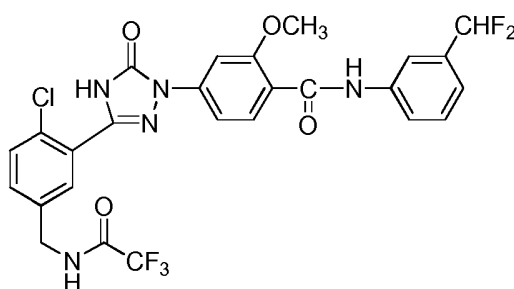
4-(3-(5-(Aminomethyl)-2-chlorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-*N*-(3-(difluoromethyl)phenyl)-2-methoxybenzamide

[0367]



Step-1:- Preparation of 4-(3-(2-chloro-5-((2,2,2-trifluoroacetamido)methyl)phenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-*N*-(3-(difluoromethyl)phenyl)-2-methoxybenzamide

[0368]



[0369] The title compound was prepared according to the procedure described in step-6 of Intermediate-26 by using methyl 4-(3-(2-chloro-5-((2,2,2-trifluoroacetamido)methyl)phenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzoate (step-5 of Intermediate-26, 0.100g, 0.20 mmol), 3-(difluoromethyl)aniline (Intermediate-29, 0.045 g, 0.30 mmol), trimethyl aluminium (2M solution in toluene) (1.0 mL) and dry toluene (5.0 mL) to afford 0.080 g of crude product which was triturated with methanol: DCM: ether to afford 0.080 g of pure product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.95 (s, 3H), 4.47 (d, *J* = 5.7 Hz, 2H), 7.05 (m, 1H), 7.30 (m, 1H), 7.50 (d, *J* = 7.8 Hz, 2H), 7.70 (m, 3H), 7.80 (d, *J* = 6.3 Hz, 3H), 8.08 (s, 1H), 10.11 (br s, 1H), 10.28 (s, 1H), 12.72 (br s, 1H); MS (*m/z*): 596.12 (*M*+*H*)⁺.

Step-2:- Preparation of 4-(3-(5-(aminomethyl)-2-chlorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-*N*-(3-(difluoromethyl)phenyl)-2-methoxybenzamide

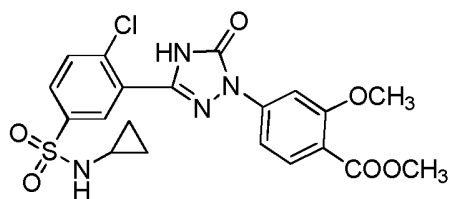
[0370] The solution of 4-(3-(2-chloro-5-((2,2,2-trifluoroacetamido)methyl)phenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-*N*-(3-(difluoromethyl)phenyl)-2-methoxybenzamide (0.070 g, 0.11 mmol) in 20% aq. KOH (10 mL) and aq. NH₃ (2 mL) was stirred for 24 h at RT. Excess of solvent was removed under vacuum and filtered off to afford 0.015 g of desired product.

Intermediate-40

Methyl 4-(3-(2-chloro-5-(*N*-cyclopropylsulfamoyl)phenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzoate

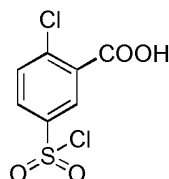
[0371]

EP 2 718 284 B1



Step-1:- Preparation of 2-chloro-5-(chlorosulfonyl)benzoic acid

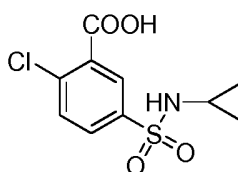
[0372]



[0373] To a solution of 2-chlorobenzoic acid (5.0 g, 31.93 mmol) was slowly added chlorosulphonic acid (25 mL). The reaction mixture was heated at 100°C for 5-6 h, followed by stirring at RT for 24 h. The reaction mass was quenched in ice cold water slowly and the solid obtained was filtered off, washed with water and dried to afford 4.0 g of pure product. ¹H NMR (300 MHz, DMSO *d*₆): δ 7.50 (d, *J* = 7.8 Hz, 1H), 7.68 (d, *J* = 8.1 Hz, 1H), 7.96 (d, *J* = 1.5 Hz, 1H), 12.69-12.94 (br s, 1H).

Step-2:- Preparation of 2-chloro-5-(*N*-cyclopropylsulfamoyl)benzoic acid

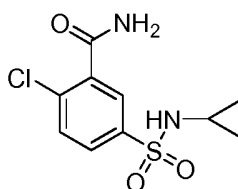
[0374]



[0375] To a solution of 2-chloro-5-(chlorosulfonyl)benzoic acid (4.0 g, 15.68 mmol) in DCM (60 mL) was added cyclopropyl amine (1.8 g, 31.57 mmol) and the reaction mixture was stirred at RT for 16 h. The reaction mass was concentrated and the residue was diluted with ice cold water and acidified with dilute HCl. The crude solid was filtered off, washed with water and dried to afford 3.0 g of pure product. ¹H NMR (300 MHz, DMSO *d*₆): δ 0.37 (s, 2H), 0.49 (d, *J* = 5.4 Hz, 2H), 2.12-2.13 (m, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 8.13 (s, 1H), 8.18 (s, 1H), 13.92 (br s, 1H).

Step-3:- Preparation of 2-chloro-5-(*N*-cyclopropylsulfamoyl)benzamide

[0376]

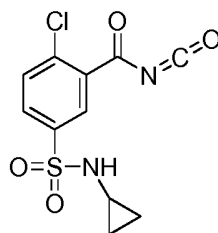


[0377] The title compound was prepared by following procedure as described for step-2 of Intermediate -26 by using 2-chloro-5-(*N*-cyclopropylsulfamoyl)benzoic acid (3.0 g, 10.0 mmol), DCM (30 mL), oxalyl chloride, ammonia gas (1.2 mL, 13.0 mmol), DMF (2-3 drop) and THF (40 mL) to afford 2.500 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 0.41 (m, 2H), 0.47-0.51 (m, 2H), 2.12 (m, 2H), 7.74- 7.82 (m, 4H), 8.11 (br s, 2H); MS (*m/z*): 273.00 (M-H)⁺.

EP 2 718 284 B1

Step-4:- Preparation of 2-chloro-5-(*N*-cyclopropylsulfamoyl)benzoyl isocyanate

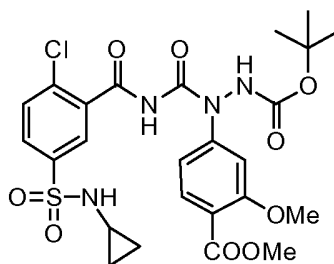
[0378]



[0379] To a solution of 2-chloro-5-(*N*-cyclopropylsulfamoyl)benzamide (1.50 g, 5.46 mmol) in EDC (20 mL) was added oxalyl chloride (0.59 mL, 6.55 mmol). The reaction mass was refluxed for 1-2 h. Excess of solvent was removed under vacuum to afford 1.5 g of desired product.

Step-5:- Preparation of *tert*-butyl 2-((2-chloro-5-(*N*-cyclopropylsulfamoyl) benzoyl)carbamoyl)-2-(3-methoxy-4-(methoxycarbonyl)phenyl) hydrazinecarboxylate

[0380]



[0381] To a solution of *tert*-butyl 2-(3-methoxy-4-(methoxycarbonyl)phenyl) hydrazinecarboxylate (Intermediate 14, 1.5 g, 5.08 mmol) in DCM (20 mL) was added 2-chloro-5-(*N*-cyclopropylsulfamoyl)benzoyl isocyanate (1.6 g, 5.32 mmol). The reaction mass was stirred at RT for 2 h. Excess of solvent was removed under vacuum to afford 0.500 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 0.50 (m, 4H), 1.41 (s, 9H), 2.11 (m, 1H), 3.68-3.75 (m, 6H), 7.59 (d, *J* = 8.7 Hz, 1H), 7.78- 7.87 (m, 4H), 8.10 (m, 2H), 8.27 (s, 1H), 8.95 (s, 1H).

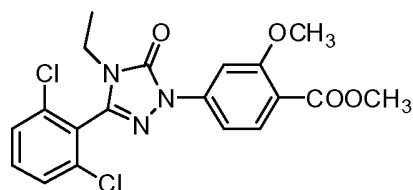
Step-6:- Preparation of methyl 4-(3-(2-chloro-5-(*N*-cyclopropylsulfamoyl)phenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzoate

[0382] The title compound was prepared according to the procedure described in step-2 of Intermediate-9 by using *tert*-butyl 2-((2-chloro-5-(*N*-cyclopropylsulfamoyl) benzoyl)carbamoyl)-2-(3-methoxy-4-(methoxycarbonyl)phenyl) hydrazinecarboxylate (0.500 g, 0.83 mmol), TFA (2 mL) and DCM (10 mL) to afford 0.100 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 0.40 (m, 2H), 0.52 (d, *J* = 5.4 Hz, 2H), 2.18 (m, 1H), 3.77 (s, 3H), 3.85 (s, 3H), 7.65 (d, *J* = 9.0 Hz, 1H), 7.82 (d, *J* = 8.1 Hz, 2H), 7.93 (s, 2H), 8.18 (s, 2H), 12.8 (br s, 1H); MS (*m/z*): 478.97 (M+H)⁺.

Intermediate-41

Methyl 4-(3-(2,6-dichlorophenyl)-4-ethyl-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzoate

[0383]

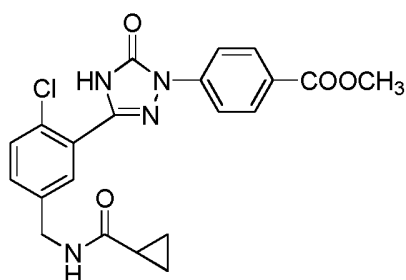


[0384] To a solution of methyl 4-(3-(2,6-dichlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-2-methoxybenzoate (Intermediate-21, 0.100 g, 0.25 mmol) in dry DMF (3 mL) was added NaH (0.012 g, 0.30 mmol) at 0°C and the reaction mixture was stirred for 20-30 minutes. Ethyl bromide (0.028 g, 0.25 mmol) was added and the reaction mixture was further stirred at 60°C for 5-6 h. The reaction mass was quenched with water and extracted in ethyl acetate. The organic layer was dried and concentrated to afford 0.040 g of the crude product which was further purified by column chromatography in basic alumina eluting with 0.5-1.0 % methanol : DCM to afford 0.040 g of pure product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.13 (t, 3H), 3.54-3.56 (m, 2H), 3.78 (s, 3H), 3.86 (s, 3H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.77 (m, 4H), 7.84 (d, *J* = 8.4 Hz, 1H); MS (*m/z*): 421.95 (M+H)⁺.

Intermediate-42

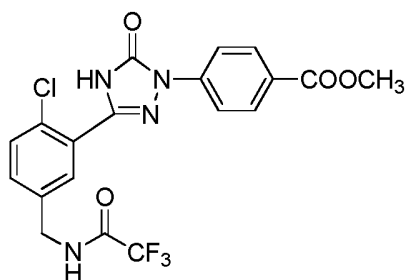
Methyl 4-(3-(2-chloro-5-(cyclopropanecarboxamidomethyl)phenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)benzoate

[0385]



Step-1:- Preparation of methyl 4-(3-(2-chloro-5-((2,2,2-trifluoroacetamido) methyl)phenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)benzoate

[0386]

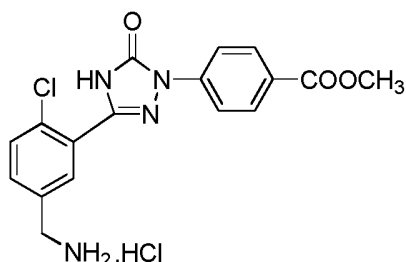


[0387] The title compound was prepared according to the procedure described in step-1 and step-2 of Intermediate-9 by using 2-chloro-5-((2,2,2-trifluoroacetamido)methyl)benzoyl isocyanate (step-3 of Intermediate-26, 1.300 g, 4.2 mmol) and *tert*-butyl 2-[4-(methoxycarbonyl)phenyl]hydrazinecarboxylate (Intermediate-7, 1.150g, 3.8 mmol) in TFA (5-7 mL) and DCM (40 mL). The reaction mass was quenched with water and extracted with DCM. The organic layer was dried over anhydrous sodium sulphate and concentrated to afford 1.300 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.84 (s, 3H), 4.44 (d, *J* = 5.7 Hz, 2H), 7.49 (t, 1H), 7.66 (d, *J* = 8.7 Hz, 2H), 8.04-8.13 (m, 4H), 10.07 (m, 1H), 12.69 (s, 1H); MS (*m/z*): 453.14 (M-H)⁻.

EP 2 718 284 B1

Step-2:- Preparation of methyl 4-(3-(5-(aminomethyl)-2-chlorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzoate hydrochloride

[0388]



[0389] The title compound was prepared according to the procedure described in step-1 of Intermediate-30 by using methyl 4-(3-(2-chloro-5-((2,2,2-trifluoroacetamido) methyl)phenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzoate (1.00 g, 2.19 mmol), methanol (20 mL) and HCl (10 mL) to afford 1.00 g of desired product.

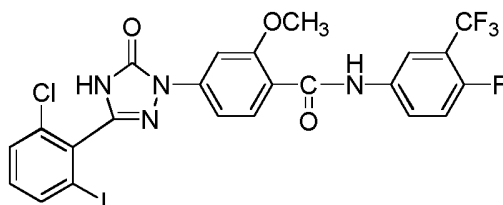
Step-3:- Preparation of methyl 4-(3-(2-chloro-5-(cyclopropanecarboxamidomethyl) phenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzoate

[0390] The title compound was prepared by following the procedure as described for step- 2 of Intermediate-30 by using methyl 4-(3-(5-(aminomethyl)-2-chlorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzoate hydrochloride (0.250 g, 0.5 mmol), cyclopropane carbonyl chloride (0.108 g, 1.0 mmol), DIPEA (2.0 mL), THF (10 mL) to afford 0.200 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.05 (s, 2H), 1.60 (m, 2H), 3.14 (m, 1H), 3.87 (s, 3H), 4.33 (d, *J* = 5.7 Hz, 2H), 7.41- 7.61 (m, 4H), 8.11-8.17 (m, 3H), 8.69 (m, 1H), 12.65 (br s, 1H); MS (*m/z*): 427.14 (*M*+*H*)⁺.

Intermediate-43

4-(3-(2-Chloro-6-iodophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-*N*-(4-fluoro-3-(trifluoromethyl)phenyl)-2-methoxybenzamide

[0391]



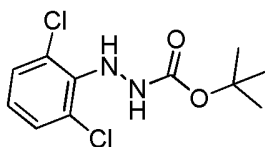
[0392] The title compound was prepared by following the procedure as described for step- 6 of Intermediate-26 by using methyl 4-(3-(2-chloro-6-iodophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzoate (step-1 of Intermediate-34, 0.100 g, 0.20 mmol), 4-fluoro-3-(trifluoromethyl)aniline (0.044 g, 0.34 mmol), trimethyl aluminium (2M solution in toluene) (1.0 mL) and dry toluene (8.0 mL) to afford 0.020 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.94 (s, 3H), 3.78 (t, 1H), 7.52 (t, 2H), 7.71-7.82 (m, 3H), 8.03 (d, *J* = 6.6 Hz, 2H), 10.38 (s, 1H), 12.69 (br s, 1H).

Intermediate-44

tert-Butyl 2-(2,6-dichlorophenyl)hydrazinecarboxylate

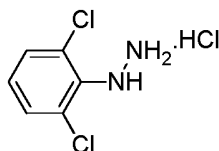
[0393]

EP 2 718 284 B1



Step-1:- Preparation of (2,6-dichlorophenyl)hydrazine hydrochloride

[0394]



[0395] To a cold solution of 2,6-dichloroaniline (10.0 g, 61.72 mmol) in conc. HCl was added aqueous solution of sodium nitrite (5.11 g, 74.00 mmol) at -15°C. The reaction mass was stirred at 0-10°C for 15 minutes. The reaction mass was filtered off to remove insolubles and stannous chloride in conc. HCl (34.7 g, 150 mmol) was added to the filtrate. The reaction mass was further stirred at -15°C for 30 min and filtered to afford 15.00 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 7.18- 7.28 (m, 1H), 7.39- 7.52 (m, 2H), 10.30 (br s, 3H); MS (m/z): 176.90 (M)⁺.

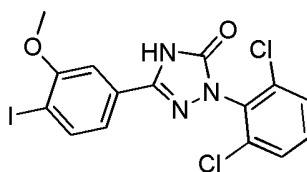
Step-2:- Preparation of *tert*-butyl 2-(2,6-dichlorophenyl)hydrazinecarboxylate

[0396] To the cold solution of (2,6-dichlorophenyl)hydrazine hydrochloride (15.0 g, 84.0 mmol) in THF (50 mL) was added aqueous solution of K₂CO₃ (23.3 g, 169 mmol) and BOC anhydride solution in THF (20.3 g, 93.00 mmol) at 0°C. The reaction mass was stirred at RT for 12 h. The reaction mass was quenched in water and extracted with DCM. The organic layer was dried over anhydrous sodium sulphate and concentrated. The obtained solid was washed with pentane to afford 6.5 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.34 (s, 9H), 6.85 (m, 1H), 7.06 (s, 1H), 7.27 (d, *J* = 7.8 Hz, 2H), 9.01 (s, 1H); MS (m/z): 276.88 (M-H)⁺.

Intermediate-45

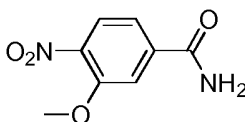
1-(2,6-Dichlorophenyl)-3-(4-iodo-3-methoxyphenyl)-1*H*-1,2,4-triazol-5(4*H*)-one

[0397]



Step-1:- Preparation of 3-methoxy-4-nitrobenzamide

[0398]



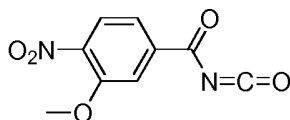
[0399] To a cold solution of 3-methoxy-4-nitrobenzoic acid (2.0 g, 10.10 mmol) in THF (25 mL) was added oxalyl chloride (1.1 mL, 12.1 mmol) and DMF (2-3 drop) at 0°C. The reaction mixture was stirred at RT for 2 h and concentrated. The solution of the concentrated mass in THF (15 mL) was treated with ammonia gas (purged through reaction mass) at 0°C and the reaction mixture was stirred at RT for 1 h. The reaction mass was diluted with ethyl acetate, washed with

EP 2 718 284 B1

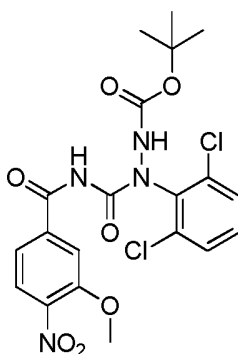
water, dilute HCl and brine. The organic layer was separated, dried, filtered and concentrated. The concentrate was used for the next step without further purification. ^1H NMR (300 MHz, DMSO d_6): δ 3.97 (s, 3H), 7.56 (d, J = 8.1 Hz, 1H), 7.72- 7.75 (m, 2H), 7.94 (d, J = 8.4 Hz, 1H), 8.25 (s, 1H); MS (m/z): 195.98 (M) $^-$.

Step-2:- Preparation of 3-methoxy-4-nitrobenzoyl isocyanate

[0400]



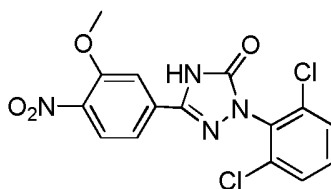
[0401] To a solution of 3-methoxy-4-nitrobenzamide (1.00 g, 5.10 mmol) in EDC (10 mL) was added oxalyl chloride (0.64 g, 6.12 mmol). The reaction mass was refluxed for 24 h. Excess of solvent was removed under vacuum to afford 1.0 g of desired product. **Step-3:-** Preparation of *tert*-butyl 2-(2,6-dichlorophenyl)-2-((3-methoxy-4-nitrobenzoyl) carbamoyl)hydrazinecarboxylate



[0402] To a solution of *tert*-butyl 2-(2,6-dichlorophenyl) hydrazinecarboxylate (Intermediate-44, 1.2 g, 4.5 mmol) in DCM (20 mL) was added 3-methoxy-4-nitrobenzoyl isocyanate (1.0 g, 4.5 mmol). The reaction mass was stirred at RT for 2 h. Excess of solvent was removed under vacuum to afford 1.5 g of desired product. ^1H NMR (300 MHz, DMSO d_6): δ 1.35 (s, 9H), 3.97 (s, 3H), 7.89 (m, 1H), 7.27- 7.35 (m, 2H), 7.55 (d, 1H), 7.62-7.75 (m, 1H), 7.94 (d, 1H), 8.26 (s, 1H), 9.03 (s, 1H); MS (m/z): 496.78 (M-H) $^-$.

Step-4:- Preparation of 1-(2,6-dichlorophenyl)-3-(3-methoxy-4-nitrophenyl)-1*H*-1,2,4-triazol-5(4*H*)-one

[0403]

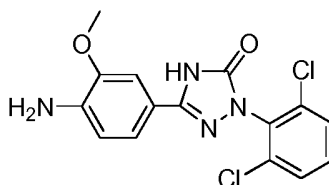


[0404] To a solution of *tert*-butyl 2-(2,6-dichlorophenyl)-2-((3-methoxy-4-nitrobenzoyl) carbamoyl)hydrazinecarboxylate (1.0 g, 2.002 mmol) in DCM (20 mL) was added trifluoro acetic acid (2.0 mL). The reaction mass was stirred at RT for 2-3 h. Excess of solvent was removed at low temperature. The reaction mass was quenched in ice and filter off to afford 0.200 g of desired product. ^1H NMR (300 MHz, DMSO d_6): δ 3.98 (s, 3H), 7.56- 7.62 (m, 2H), 7.69- 7.75 (m, 3H), 8.02 (d, J = 8.4 Hz, 1H), 11-12 (br s, 1H); MS (m/z): 382.07 (M+H) $^+$.

EP 2 718 284 B1

Step-5:- Preparation of 3-(4-amino-3-methoxyphenyl)-1-(2,6-dichlorophenyl)-1*H*-1,2,4-triazol-5(4*H*)-one

[0405]



[0406] To a solution of 1-(2,6-dichlorophenyl)-3-(3-methoxy-4-nitrophenyl)-1*H*-1,2,4-triazol-5(4*H*)-one (0.200 g, 0.52 mmol) in methanol (10 mL) was added iron powder (0.060 g, 1.84 mmol) and conc. HCl (2 mL). The reaction mixture was stirred at RT for 2 h. The reaction mass was quenched in water, basified with saturated sodium bicarbonate solution and extracted with DCM. The organic layer was dried over anhydrous sodium sulphate and concentrated to afford 0.150 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.80 (s, 3H), 5.34 (s, 2H), 6.66 (d, *J* = 7.8 Hz, 1H), 7.18- 7.21 (m, 2H), 7.58 (m, 1H), 7.69 (d, *J* = 7.8 Hz, 2H), 12.27 (s, 1H); MS (*m/z*): 351.05 (M)⁺.

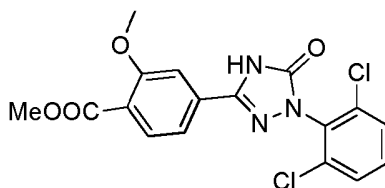
Step-6:- Preparation of 1-(2,6-dichlorophenyl)-3-(4-iodo-3-methoxyphenyl)-1*H*-1,2,4-triazol-5(4*H*)-one

[0407] To a solution of 3-(4-amino-3-methoxyphenyl)-1-(2,6-dichlorophenyl)-1*H*-1,2,4-triazol-5(4*H*)-one (0.300 g, 0.85 mmol) in acetonitrile (20 mL) was added PTSA (0.488 g, 2.56 mmol). The reaction mixture was stirred at RT for 2 h, followed by addition of aqueous solution of NaNO₂ (0.118 g, 1.170 mmol) and KI (0.284 g, 1.70 mmol). The reaction mixture was stirred at RT for 2 h. The reaction mass was concentrated and quenched in water. The reaction mass was washed with sodium metabisulphite solution and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and concentrated to afford 0.220 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.89 (s, 3H), 7.23 (d, *J* = 7.8 Hz, 1H), 7.40 (s, 1H), 7.61 (m, 1H), 7.71- 7.73 (m, 2H), 7.92 (d, *J* = 8.4 Hz, 1H), 12.74 (s, 1H); MS (*m/z*): 461.93 (M)⁺.

Intermediate-46

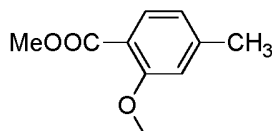
Methyl 4-(1-(2,6-dichlorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2-methoxybenzoate

[0408]



Step-1:- Preparation of methyl 2-methoxy-4-methylbenzoate

[0409]



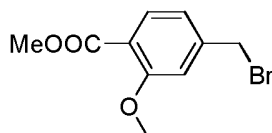
[0410] To a solution of 2-hydroxy-4-methylbenzoic acid (10.00 g, 65 mmol) in DMF (10 mL) was added K₂CO₃ (13.6 g, 98 mmol). The reaction mixture was stirred at 60°C for 1 h. Methyl iodide (14.0 g, 98 mmol) was added to the reaction mixture and was stirred at 60°C for 18 h. The reaction mass was quenched in water and concentrated. The reaction mass was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and concentrated

EP 2 718 284 B1

to afford 10.00 g of desired product. ^1H NMR (300 MHz, DMSO d_6): δ 2.34 (s, 3H), 3.74 (s, 3H), 3.79 (s, 3H), 6.81 (d, $J = 7.2$ Hz, 1H), 6.97 (s, 1H), 7.56 (d, $J = 7.8$ Hz, 1H); MS (m/z): 180.95 (M+H) $^+$.

Step-2:- Preparation of methyl 4-(bromomethyl)-2-methoxybenzoate

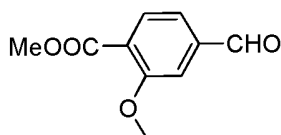
[0411]



[0412] To a solution of methyl 2-methoxy-4-methylbenzoate (10.00 g, 55 mmol) in CCl_4 (150 mL) were added NBS (11.8 g, 66 mmol) and AIBN (0.100 g). The reaction mixture was refluxed for 18 h. The reaction mass was diluted with diethyl ether and washed with 25% NaOH solution. The organic layer was dried over anhydrous sodium sulphate and concentrated to afford 10.00 g of desired product. ^1H NMR (300 MHz, DMSO d_6): δ 3.77 (m, 6H), 4.68 (s, 2H), 7.06 (d, $J = 7.8$ Hz, 1H), 7.23 (s, 1H), 7.61 (d, $J = 7.8$ Hz, 1H); MS (m/z): 259.13 (M) $^+$.

Step-3:- Preparation of methyl 4-formyl-2-methoxybenzoate

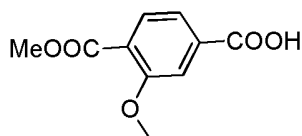
[0413]



[0414] To a solution of sodium methoxide (0.260 g, 4.82 mmol) in methanol (200 mL) was added nitromethane (4.03 g, 11.58 mmol) under nitrogen atmosphere and the reaction mixture was stirred and reflux for 30 minutes. Methyl 4-(bromomethyl)-2-methoxybenzoate (10.00 g, 9.65 mmol) in methanol was added and the reaction mixture was refluxed for 7-8 h. The reaction mass was concentrated and diluted with CHCl_3 . The diluted reaction mass was washed with 2N NaOH solution. The organic layer was dried over anhydrous sodium sulphate and concentrated to afford 6.00 g of desired product. ^1H NMR (300 MHz, DMSO d_6): δ 3.83 (m, 6H), 7.36 (d, $J = 6.6$ Hz, 2H), 7.79 (d, $J = 7.8$ Hz, 1H), 10.04 (s, 1H).

Step-4:- Preparation of 3-methoxy-4-(methoxycarbonyl)benzoic acid

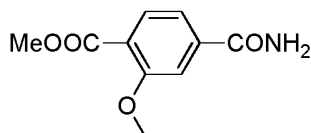
[0415]



[0416] To a cold solution of methyl 4-formyl-2-methoxybenzoate (6.0 g, 7.73 mmol) in acetone (50 mL) was added aqueous sulphamic acid solution (4.5 g, 11.59 mmol) and aqueous sodium chlorite solution (4.04 g, 11.59 mmol) at 0-5°C. The reaction mixture was stirred at RT for 3-4 h. Excess of solvent was removed under vacuum. The obtained residue was diluted with water and basified with saturated sodium bicarbonate solution. The aqueous layer was washed with diethyl ether to remove organic impurities and the obtained aqueous layer was again acidified with conc. HCl. The solid obtained was filtered and suck dried to afford 2.00 g of desired product. ^1H NMR (300 MHz, DMSO d_6): δ 3.80 (s, 3H), 3.87 (s, 3H), 7.55- 7.59 (m, 2H), 7.70 (d, $J = 7.8$ Hz, 1H), 13.37 (s, 1H); MS (m/z): 210.97 (M+H) $^+$.

Step-5:- Preparation of methyl 4-carbamoyl-2-methoxybenzoate

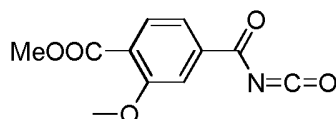
[0417]



[0418] The title compound was prepared according to the procedure described in step-2 of Intermediate-26 by using 3-methoxy-4-(methoxycarbonyl)benzoic acid (2.00 g, 9.52 mmol), oxalyl chloride (1.02 g, 11.42 mmol), ammonia gas and THF (25 mL) to afford 1.40 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.79 (s, 3H), 3.87 (s, 3H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.57 (s, 2H), 7.68 (d, *J* = 7.8 Hz, 1H), 8.14 (s, 1H); MS (*m/z*): 209.99 (M)⁺.

Step-6:- Preparation of methyl 4-(isocyanatocarbonyl)-2-methoxybenzoate

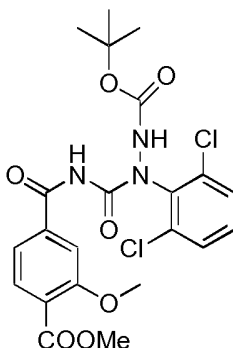
[0419]



[0420] The title compound was prepared according to the procedure described in step-2 of Intermediate-8 by using methyl 4-carbamoyl-2-methoxybenzoate (1.4 g, 6.69 mmol), oxalyl chloride (0.72 mL, 8.03 mmol) and EDC (10 mL) to afford 1.00 g of the desired product.

Step-7:- Preparation of *tert*-butyl 2-(2,6-dichlorophenyl)-2-((3-methoxy-4-(methoxycarbonyl)benzoyl)carbamoyl)hydrazinecarboxylate

[0421]



[0422] The title compound was prepared according to the procedure described in step-1 of Intermediate-9 by using methyl 4-(isocyanatocarbonyl)-2-methoxybenzoate (0.84 g, 3.61 mmol), *tert*-butyl 2-(2,6-dichlorophenyl)hydrazinecarboxylate (Intermediate-44, 1.0 g, 3.61 mmol) and DCM (20 mL) to afford 1.50 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.35 (s, 9H), 3.80 (s, 3H), 3.87 (s, 3H), 7.28- 7.42 (m, 6H), 9.57 (s, 1H), 10.85 (s, 1H); MS (*m/z*): 511.73 (M)⁺.

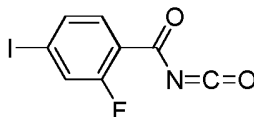
Step-8:- Preparation of methyl 4-(1-(2,6-dichlorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2-methoxybenzoate

[0423] The title compound was prepared according to the procedure described in step-2 of Intermediate-9 by using *tert*-butyl 2-(2,6-dichlorophenyl)-2-((3-methoxy-4-(methoxycarbonyl) benzoyl)carbamoyl)hydrazinecarboxylate (1.5 g, 2.9 mmol), DCM (20 mL) and trifluoro acetic acid (2.0 mL) to afford 0.600 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.80 (s, 3H), 3.80 (s, 3H), 7.49- 7.71 (m, 3H), 7.74- 7.79 (m, 3H), 12.85 (s, 1H); MS (*m/z*): 393.95 (M)⁺.

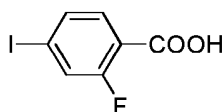
Intermediate-47

2-Fluoro-4-iodobenzoyl isocyanate

[0424]

Step-1:- Preparation of 2-fluoro-4-iodobenzoic acid

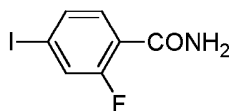
[0425]



[0426] A solution of sodium dichromate (25.2 g, 84.0 mmol) in acetic acid (100 mL) was stirred for 10 min, followed by addition of 2-fluoro-4-iodo-1-methylbenzene (10.0 g, 42 mmol). The reaction mixture was stirred for 5 min followed by slow addition of conc. H_2SO_4 (60 mL) for 1-2 h. The reaction mixture stirred at 90-100°C for 7-8 h. The reaction mixture was cooled and quenched with ice water. The reaction mass was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and concentrated to afford 5.0 g of the desired product. ^1H NMR (300 MHz, DMSO d_6): δ 7.58 (t, J = 8.4 Hz, 1H), 7.67 (d, J = 7.5 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 13 (br s, 1H); MS (m/z): 264.99 (M-H) $^-$.

Step-2:- Preparation of 2-fluoro-4-iodobenzamide

[0427]



[0428] The title compound was prepared according to the procedure described in step-2 of Intermediate-26 by using 2-fluoro-4-iodobenzoic acid (5.00 g, 18.0 mmol), oxalyl chloride (2.0 mL, 22.0 mmol), ammonia gas, DCM (100 mL) and THF (100 mL) to afford 2.00 g of the desired product. ^1H NMR (300 MHz, DMSO d_6): δ 7.40 (t, J = 7.8 Hz, 1H), 7.63-7.76 (m, 1H); MS (m/z): 266.19 (M+H) $^+$.

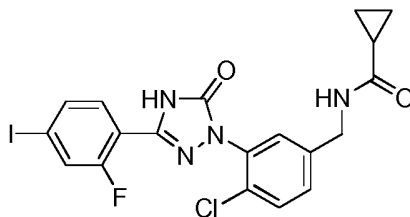
Step-3:- Preparation of 2-fluoro-4-iodobenzoyl isocyanate

[0429] The title compound was prepared according to the procedure described in step-2 of Intermediate-8 by using 2-fluoro-4-iodobenzamide (0.500 g, 1.8 mmol), oxalyl chloride (0.285 g, 2.2 mmol) and EDC (10 mL) to afford 0.350 g of the desired product.

Intermediate-48

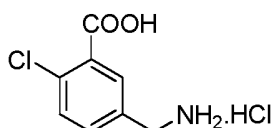
N-(4-Chloro-3-(3-(2-fluoro-4-iodophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)benzyl)cyclopropanecarboxamide

[0430]



Step-1:- Preparation of 5-(aminomethyl)-2-chlorobenzoic acid hydrochloride

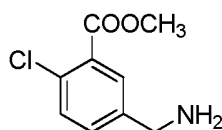
[0431]



[0432] To a solution of 2-chloro-5-((2,2,2-trifluoroacetamido)methyl)benzoic acid (step-1 of Intermediate-26, 10.0 g, 35.50 mmol) in methanol (100 mL) was added conc. HCl (10 mL). The reaction mixture was refluxed for 18 h. The reaction mixture was concentrated and crude reaction mixture was used for next step.

Step-2:- Preparation of methyl 5-(aminomethyl)-2-chlorobenzoate

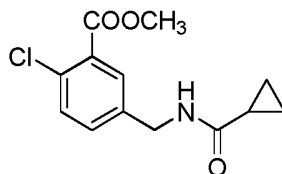
[0433]



[0434] To a solution of 5-(aminomethyl)-2-chlorobenzoic acid hydrochloride (17.0 g, 76.5 mmol) in methanol (200 mL) was added conc. H₂SO₄ (15 mL). The reaction mixture was refluxed for 15 h. The reaction mixture was concentrated and water was added. The aq. solution was basified with sodium bicarbonate. The reaction mixture was extracted with 10% MeOH: DCM and concentrated to afford 15.0 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 2.1 (br s, 2H), 3.73 (s, 2H), 3.85 (s, 3H), 7.50 (s, 2H), 7.77 (s, 1H); MS (m/z): 200.05 (M+H)⁺.

Step-3:- Preparation of methyl 2-chloro-5-(cyclopropanecarboxamidomethyl)benzoate

[0435]

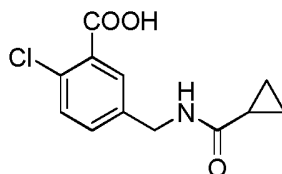


[0436] To a solution of methyl 5-(aminomethyl)-2-chlorobenzoate (15.0 g, 75 mmol) in dry THF (150 mL) was added DIPEA (15 mL) under nitrogen atmosphere. Cyclopropanecarbonyl chloride was added to the reaction mixture at 10°C and (11.81 g, 113 mmol). The reaction mixture was stirred at RT for 5-6 h. The reaction mixture was quenched with ice water and extracted with ethyl acetate. The organic layer was washed with dilute HCl, followed with sodium bicarbonate solution and concentrated to afford 10.0 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 0.69 (m, 4H), 1.59 (m, 1H), 3.86 (s, 3H), 4.29 (d, *J* = 6.0 Hz, 2H), 7.43 (d, *J* = 6.6 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.67 (s, 1H), 8.64 (br s, 1H); MS (m/z): 268.16 (M+H)⁺.

EP 2 718 284 B1

Step-4:- Preparation of 2-chloro-5-(cyclopropanecarboxamidomethyl)benzoic acid

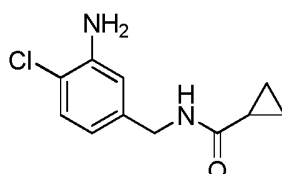
[0437]



[0438] To a solution of methyl 2-chloro-5-(cyclopropanecarboxamidomethyl)benzoate (10.0 g, 30 mmol) in THF: methanol (10:20 mL) was added aqueous solution of NaOH (6.0 g, 140 mmol). The reaction mixture was refluxed for 3-5 h. The reaction mixture was concentrated, diluted with water and acidified with dilute HCl. The reaction mixture was extracted with 10% MeOH: DCM and concentrated to afford 4.0 g of desired product. ^1H NMR (300 MHz, DMSO d_6): δ 0.67 (m, 4H), 1.59 (m, 1H), 4.28 (d, J = 6.0 Hz, 2H), 7.37- 7.50 (m, 2H), 7.65 (s, 1H), 8.64 (m, 1H), 13.40 (br s, 1H).

Step-5:- Preparation of N-(3-amino-4-chlorobenzyl)cyclopropanecarboxamide

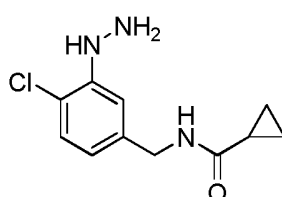
[0439]



[0440] To a solution of 2-chloro-5-(cyclopropanecarboxamidomethyl)benzoic acid (5.0 g, 19 mmol) in conc. H_2SO_4 (30 mL) was added NaN_3 (1.4 g, 21 mmol) lotwise at 50°C . The reaction mixture was stirred at 50°C for 18 h. The reaction mass was quenched with ammonia and ice water. The solid obtained was filtered and suck dried to afford 3.0 g of desired product. ^1H NMR (300 MHz, DMSO d_6): δ 0.66 (m, 4H), 1.56 (m, 1H), 4.12 (d, J = 6.0 Hz, 2H), 5.27 (s, 2H), 6.41 (d, J = 6.9 Hz, 1H), 6.61 (s, 1H), 7.10 (d, J = 8.4 Hz, 1H), 8.48 (m, 1H); MS (m/z): 225.22 ($\text{M}+\text{H}$) $^+$.

Step-6:- Preparation of N-(4-chloro-3-hydrazinylbenzyl)cyclopropanecarboxamide

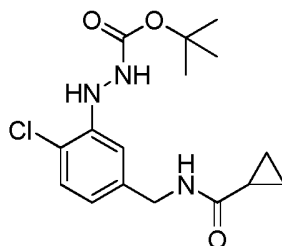
[0441]



[0442] To a cold solution of N-(3-amino-4-chlorobenzyl)cyclopropanecarboxamide (2.00 g, 8.90 mmol) in conc. HCl (25 mL) was added aqueous solution of sodium nitrite (0.676 g, 9.7 mmol) at -20°C to -25°C . The reaction mass was stirred at -20°C to -25°C for 30 min, followed by addition of stannous chloride solution (5.0 g, 22.2 mmol) in conc. HCl slowly. The reaction mass was stirred at -20°C to -25°C for 1 h. The reaction mass was basified with aqueous NaOH at below 0°C . The reaction mass was diluted with water, extracted with 10% MeOH: DCM and concentrated to afford 1.6 g of desired product. ^1H NMR (300 MHz, DMSO d_6): δ 0.66 (m, 4H), 1.58 (m, 1H), 4.10 (s, 2H), 4.18 (d, J = 5.4 Hz, 2H), 6.47 (m, 2H), 7.11 (m, 2H), 8.51 (br s, 1H); MS (m/z): 240.05 ($\text{M}+\text{H}$) $^+$.

Step-7:- Preparation of *tert*-butyl 2-(2-chloro-5-(cyclopropanecarboxamidomethyl) phenyl)hydrazinecarboxylate

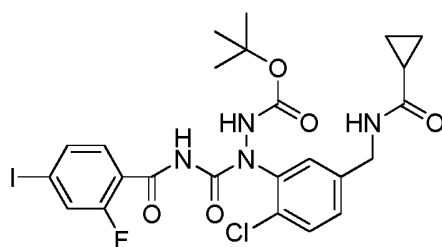
[0443]



[0444] To a cold solution of *N*-(4-chloro-3-hydrazinylbenzyl)cyclopropanecarboxamide (1.60 g, 6.69 mmol) in acetonitrile (20 mL) was added aqueous solution of Na_2CO_3 (1.06 g, 10.04 mmol) and BOC anhydride (1.06 g, 7.36 mmol). The reaction mass was stirred at RT for 12 h. The reaction mass was quenched in water and extracted with ethyl acetate and concentrated to afford 1.00 g of the crude product which was further purified by column chromatography using basic alumina eluting with 0.3% MeOH: DCM to afford 0.900 g of pure product. ^1H NMR (300 MHz, DMSO d_6): δ 0.63 (m, 4H), 1.40 (s, 9H), 1.54 (m, 1H), 4.15 (d, J = 6.0 Hz, 2H), 6.59 (m, 2H), 7.17 (d, J = 7.8 Hz, 1H), 7.31 (s, 1H), 8.51 (m, 1H), 8.87 (s, 1H); MS (m/z): 338.41 (M-H) $^-$.

Step-8:- Preparation of *tert*-butyl 2-(2-chloro-5-(cyclopropanecarboxamidomethyl) phenyl)-2-((2-fluoro-4-iodobenzoyl)carbamoyl)hydrazinecarboxylate

[0445]



[0446] The title compound was prepared according to the procedure described in step-1 of Intermediate-9 by using 2-fluoro-4-iodobenzoyl isocyanate (Intermediate-47, 0.500 g, 1.71 mmol), *tert*-butyl 2-(2-chloro-5-(cyclopropanecarboxamidomethyl)phenyl)hydrazine carboxylate (0.582 g, 1.71 mmol) and DCM (20 mL) to afford 0.200 g of the desired product. ^1H NMR (300 MHz, DMSO d_6): δ 0.69 (m, 4H), 1.42 (s, 9H), 1.56 (m, 1H), 4.17 (d, J = 5.7 Hz, 2H), 6.58- 6.63 (m, 2H), 7.18 (d, J = 8.1 Hz, 1H), 7.30 (m, 3H), 7.63- 7.79 (m, 2H), 8.53 (m, 1H), 8.90 (s, 1H); MS (m/z): 630.85 (M+H) $^+$.

Step-9:- Preparation of *N*-(4-chloro-3-(3-(2-fluoro-4-iodophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)benzyl)cyclopropanecarboxamide

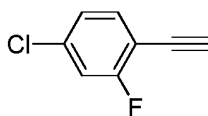
[0447] To a solution of *tert*-butyl 2-(2-chloro-5-(cyclopropanecarboxamidomethyl)phenyl)-2-((2-fluoro-4-iodobenzoyl)carbamoyl)hydrazinecarboxylate (0.200 g, 0.31 mmol) in DCM (10 mL) was added trifluoro acetic acid (1.0 mL). The reaction mass was stirred at RT for 12 h and refluxed for 15 h. The reaction mass was cooled to RT, basified with NaHCO_3 (pH =8), extracted with DCM and concentrated to afford 0.110 g of desired product. ^1H NMR (300 MHz, DMSO d_6): δ 0.68 (m, 4H), 1.59 (m, 1H), 4.32 (d, J = 5.7 Hz, 2H), 7.38 (d, J = 8.4 Hz, 1H), 7.45 (s, 1H), 7.51- 7.63 (m, 2H), 7.75 (d, J = 8.1 Hz, 1H), 7.88 (d, J = 10.2 Hz, 1H), 8.68 (m, 1H), 12.43 (brs, 1H); MS (m/z): 513.01 (M+H) $^+$.

Intermediate-49

4-Chloro-1-ethynyl-2-fluorobenzene

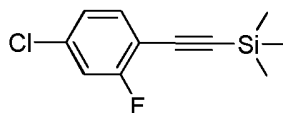
[0448]

EP 2 718 284 B1



Step-1:- Preparation of ((4-chloro-2-fluorophenyl)ethynyl)trimethylsilane

[0449]



[0450] To a solution of 4-chloro-2-fluoro-1-iodobenzene (2.0 g, 7.8 mmol) in DMSO (10 mL) was added ethynyl(trimethyl)silane (1.14 g, 11.0 mmol), copper iodide (0.029 g, 0.15 mmol), bis(triphenylphosphine) palladium(II) chloride (0.218 g, 0.3 mmol) and TEA (1 mL). The reaction mass was stirred at RT for 4-5 h. The reaction mass quenched in water, passed through celite bed and extracted with ethyl acetate and concentrated to afford 1.0 g of desired product.

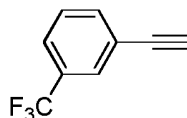
Step-2:- Preparation of 4-chloro-1-ethynyl-2-fluorobenzene

[0451] To a solution of ((4-chloro-2-fluorophenyl)ethynyl)trimethylsilane (1.0 g, 4.42 mmol) in DCM (20 mL) was added TBAF (catalytic) and reaction mixture was stirred for 1-2 h at RT. The reaction mass was quenched in water, extracted with DCM and concentrated to afford 0.900 g of the crude product which was further purified by column chromatography eluting with pet. ether to afford 0.500 g of pure product. ^1H NMR (300 MHz, DMSO d_6): δ 4.60 (s, 1H), 7.32 (d, J = 8.1 Hz, 1H), 7.56- 7.61 (m, 2H).

Intermediate-50

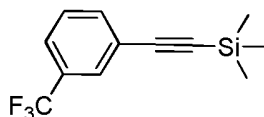
1-Ethynyl-3-(trifluoromethyl)benzene

[0452]



Step-1:- Preparation of trimethyl((3-(trifluoromethyl)phenyl)ethynyl)silane

[0453]



[0454] To a solution of 1-iodo-3-(trifluoromethyl)benzene (1.0 g, 3.6 mmol) in ethyl acetate (20 mL) was added ethynyl(trimethyl)silane (0.540 g, 5.5 mmol), copper iodide (0.042 g, 0.22 mmol), bis(triphenylphosphine) palladium(II) chloride (0.129 g, 0.18 mmol) and TEA (2.2 mL, 14.7 mmol). The reaction mass stirred at 50-60°C for 24 h. The reaction mass was quenched in water, extracted with ethyl acetate and concentrated to afford 0.500 g of desired product. ^1H NMR (300 MHz, DMSO d_6): δ 0.26 (s, 9H), 7.44 (t, J = 7.8 Hz, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.62 (d, J = 7.2 Hz, 1H), 7.72 (s, 1H).

Step-2:- Preparation of 1-ethynyl-3-(trifluoromethyl)benzene

[0455] To a solution of trimethyl((3-(trifluoromethyl)phenyl)ethynyl)silane (0.500 g, 2.06 mmol) in ethanol (10 mL) was added potassium carbonate (0.253g, 1.8 mmol) and the reaction mixture was stirred at RT for 18 h. The reaction mass was quenched in water, neutralized with dil. HCl and extracted with hexane and concentrated to afford 0.200 g of the

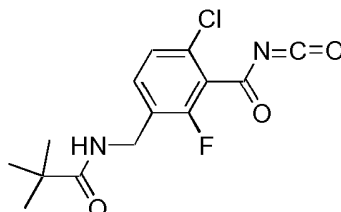
EP 2 718 284 B1

crude product which was further purified by column chromatography using silica (60-120 mesh) eluting with pet. ether to afford 0.500 g of pure product. ^1H NMR (300 MHz, DMSO d_6): δ 4.41 (s, 1H), 7.64 (d, J = 7.5 Hz, 1H), 7.77- 7.81 (m, 3H).

Intermediate-51

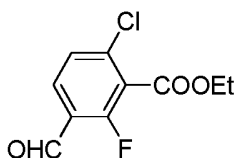
6-Chloro-2-fluoro-3-(pivalamidomethyl)benzoyl isocyanate

[0456]



Step-1:- Preparation of ethyl 6-chloro-2-fluoro-3-formylbenzoate

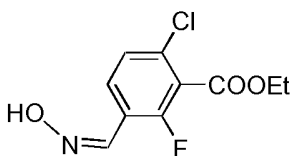
[0457]



[0458] To a cold solution of ethyl 2-chloro-6-fluorobenzoate (0.500 g, 24.7 mmol) in THF (35 mL) was added LDA (6.6g, 61.8 mmol) at -78°C . The reaction mixture was stirred for 2 h at same temperature, followed by addition of DMF (2.7 g, 37 mmol). The reaction mixture was further stirred for 2 h at same temperature. The reaction mass was quenched in dilute HCl, extracted with ethyl acetate and concentrated to afford crude product which was further purified by column chromatography eluting with EtOAC: pet.ether to afford 2.00 g of pure product. ^1H NMR (300 MHz, DMSO d_6): δ 1.31 (t, 3H), 4.42 (q, 2H), 7.94- 7.99 (m, 2H), 10.14 (s, 1H).

Step-2:- Preparation of ethyl 6-chloro-2-fluoro-3-((hydroxyimino)methyl)benzoate

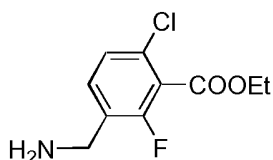
[0459]



[0460] To a solution of ethyl 6-chloro-2-fluoro-3-formylbenzoate (1.1 g, 4.0 mmol) in MeOH (5 mL) was added (aq. solution) hydroxyl amine (4 mL) and the reaction mixture was heated at 60°C for 2-3 h. The reaction mass was concentrated and extracted with EtOAC. The organic layer was washed with brine and concentrated to afford 0.900 g of the product. ^1H NMR (300 MHz, DMSO d_6): δ 1.31 (t, J = 6.9 Hz, 3H), 4.40 (q, J = 6.6 Hz, 2H), 7.47 (d, J = 9.0 Hz, 1H), 7.86 (t, J = 8.1 Hz, 1H), 8.20 (s, 1H), 11.89 (br s, 1H).

Step-3:- Preparation of ethyl 3-(aminomethyl)-6-chloro-2-fluorobenzoate

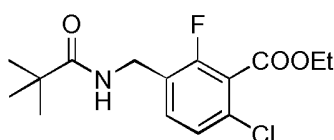
[0461]



[0462] To a solution of ethyl 6-chloro-2-fluoro-3-((hydroxyimino)methyl)benzoate (0.800 g, 3.26 mmol) in MeOH (5 mL) was added Zn (0.850 g, 13.06 mmol), followed by dropwise addition of conc. HCl (catalytic) and the reaction mixture was heated at 60°C for 2-3 h. Excess of solvent was removed under vacuum and the residue was diluted with water and basified with NaHCO₃, extracted with EtOAc and concentrated to afford 0.600 g of the product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.31 (t, *J* = 7.2 Hz, 3H), 3.76 (s, 2H), 4.38 (q, *J* = 6.9 Hz, 2H), 7.41 (d, *J* = 8.1 Hz, 1H), 7.65 (t, *J* = 8.1 Hz, 1H).

Step-4:- Preparation of ethyl 6-chloro-2-fluoro-3-(pivalamidomethyl)benzoate

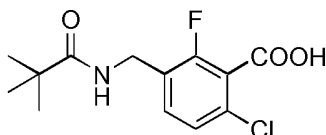
[0463]



[0464] To a solution of ethyl 3-(aminomethyl)-6-chloro-2-fluorobenzoate (0.540 g, 2.5 mmol) in THF (5 mL) was added pivaloyl chloride (0.335 g, 2.79 mmol) and TEA (0.1 mL) and the reaction mixture was stirred for 2-3 h at RT. Excess of solvent was removed under vacuum and the residue was diluted with water, extracted with EtOAc and concentrated to afford 0.500 g of the product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.11 (s, 9H), 1.31 (t, *J* = 7.5 Hz, 3H), 4.26 (d, *J* = 5.1 Hz, 2H), 4.39 (q, *J* = 6.6 Hz, 2H), 7.33- 7.43 (m, 2H), 8.13 (m, 1H).

Step-5:- Preparation of 6-chloro-2-fluoro-3-(pivalamidomethyl)benzoic acid

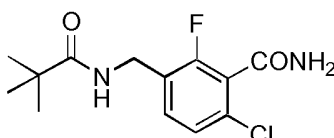
[0465]



[0466] The title compound was prepared according to the procedure described in step-4 of Intermediate-48 by using ethyl 6-chloro-2-fluoro-3-(pivalamidomethyl)benzoate (0.800 g) THF: methanol (2:2 mL) and aqueous solution of NaOH (1.0 g) to afford 0.500 g of the product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.11 (s, 9H), 4.26 (d, *J* = 5.4 Hz, 2H), 7.26- 7.38 (m, 2H), 8.14 (m, 1H), 14.07 (br s, 1H).

Step-6:- Preparation of 6-chloro-2-fluoro-3-(pivalamidomethyl)benzamide

[0467]



[0468] The title compound was prepared according to the procedure described in step-2 of Intermediate-26 by using 6-chloro-2-fluoro-3-(pivalamidomethyl)benzoic acid (0.400 g, 1.39 mmol), THF (25 mL), oxalyl chloride (0.14 mL, 1.67 mmol) and ammonia gas to afford 0.220 g of the product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.12 (s, 9H), 4.25 (d, *J* = 5.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.82 (s, 1H), 8.12 (br s, 2H); MS (*m/z*): 287.01 (M+H⁺).

EP 2 718 284 B1

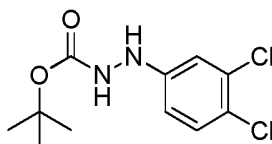
Step-7:- Preparation of 6-chloro-2-fluoro-3-(pivalamidomethyl)benzoyl isocyanate

[0469] To a solution of 6-chloro-2-fluoro-3-(pivalamidomethyl)benzamide (0.300 g, 1.04 mmol) in EDC (10 mL) was added oxalyl chloride (0.11 mL, 1.25 mmol). The reaction mass was heated at 60-70°C for 4-5 h. Excess of solvent was removed under vacuum to afford 1.0 g of desired product.

Intermediate-52

tert-Butyl 2-(3,4-dichlorophenyl)hydrazinecarboxylate

[0470]

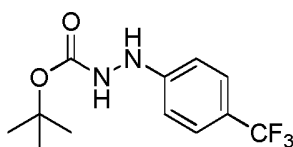


[0471] The title compound was prepared according to the procedure described in step-3 of Intermediate-7 by using (3,4-dichlorophenyl)hydrazine hydrochloride (1.00 g, 4.6 mmol), BOC anhydride (1.22 g, 5.6 mmol), Na₂CO₃ (1.24 g, 11.7 mmol), acetonitrile (20 mL) and water (10 mL) to afford 0.700 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.40 (s, 9H), 6.62 (d, *J* = 8.7 Hz, 1H), 6.77 (s, 1H), 7.34 (d, *J* = 8.7 Hz, 1H), 8.02 (s, 1H), 8.91 (s, 9H).

Intermediate-53

tert-Butyl 2-(4-(trifluoromethyl)phenyl)hydrazinecarboxylate

[0472]

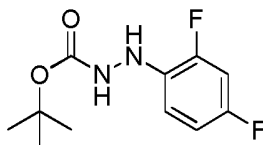


[0473] The title compound was prepared according to the procedure described in step-3 of Intermediate-7 by using 4-(trifluoromethyl)phenylhydrazine hydrochloride (1.00 g, 5.6 mmol), BOC anhydride (1.46 g, 6.8 mmol), Na₂CO₃ (0.900 g, 8.5 mmol), acetonitrile (20 mL) and water (10 mL) to afford 0.600 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.41 (s, 9H), 6.74 (d, *J* = 8.7 Hz, 2H), 7.45 (d, *J* = 9.0 Hz, 2H), 8.23 (s, 1H), 8.94 (br s, 1H).

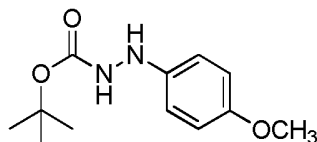
Intermediate-54

tert-Butyl 2-(2,4-difluorophenyl)hydrazinecarboxylate

[0474]



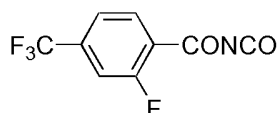
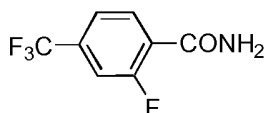
[0475] The title compound was prepared according to the procedure described in step-3 of Intermediate-7 by using (2,4-difluorophenyl)hydrazine hydrochloride (1.00 g, 5.54 mmol), BOC anhydride (1.81 g, 8.31 mmol), Na₂CO₃ (1.46 g, 13.85 mmol), acetonitrile (20 mL) and water (10 mL) to afford 0.500 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.40 (s, 9H), 6.70-6.72 (m, 1H), 6.90 (t, *J* = 8.1 Hz, 1H), 7.07-7.14 (m, 1H), 7.47 (s, 1H), 8.83 (br s, 1H).

Intermediate-55*tert*-Butyl 2-(4-methoxyphenyl)hydrazinecarboxylate**[0476]**

[0477] The title compound was prepared according to the procedure described in step-3 of Intermediate-7 by using (4-methoxyphenyl)hydrazine hydrochloride (1.00 g, 5.72 mmol), BOC anhydride (1.8 g, 8.59 mmol), Na₂CO₃ (1.51 g, 14.31 mmol), acetonitrile (20 mL) and water (10 mL) to afford 0.400 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.39 (s, 9H), 3.64 (s, 3H), 6.60 (d, *J* = 7.8 Hz, 2H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.18 (br s, 1H), 8.68 (br s, 1H).

Intermediate-56

2-Fluoro-4-(trifluoromethyl)benzoyl isocyanate

[0478]Step-1:- Preparation of 2-fluoro-4-(trifluoromethyl)benzamide**[0479]**

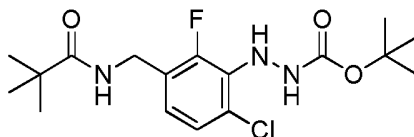
[0480] The title compound was prepared according to the procedure described in step-2 of Intermediate-26 by using 2-fluoro-4-(trifluoromethyl)benzoic acid (1.5 g), THF (25 mL), oxalyl chloride (0.5 mL) and ammonia gas to afford 1.35 g of the product. ¹H NMR (300 MHz, DMSO *d*₆): δ 7.65 (d, *J* = 8.4 Hz, 1H), 7.77- 7.84 (m, 3H), 7.96 (br s, 1H); MS (*m/z*): 208.06 (*M*⁺).

Step-2:- Preparation of 2-fluoro-4-(trifluoromethyl)benzoyl isocyanate

[0481] The title compound was prepared according to the procedure described in step-2 of Intermediate-8 by using 2-fluoro-4-(trifluoromethyl)benzamide (0.200 g, 0.96 mmol), EDC (10 mL) and oxalyl chloride (0.1 mL, 1.15 mmol) to afford 0.200 g of the product.

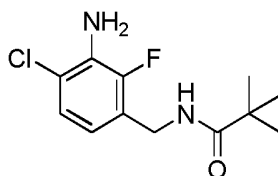
Intermediate-57*tert*-Butyl 2-(6-chloro-2-fluoro-3-(pivalamidomethyl)phenyl)hydrazinecarboxylate**[0482]**

EP 2 718 284 B1



Step-1:- Preparation of *N*-(3-amino-4-chloro-2-fluorobenzyl)pivalamide

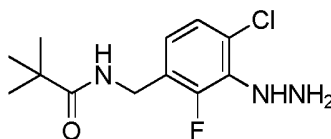
[0483]



[0484] To a solution of 6-chloro-2-fluoro-3-(pivalamidomethyl)benzoic acid (step-5 of Intermediate-51, 1.0 g, 3.48 mmol) in conc. sulphuric acid (10.0 mL) was added sodium azide (0.271 g, 4.18 mmol). The reaction mass was stirred at 50-60°C for 18 h. The reaction mass was quenched in ammonia solution (cold) and solid obtained was filtered and suck dried to afford 0.570 g of the product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.11 (s, 9H), 4.21 (d, *J* = 5.7 Hz, 2H), 5.30 (s, 2H), 6.39 (t, *J* = 7.8 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 7.98 (m, 1H); MS (*m/z*): 259.12 (M+H⁺).

Step-2:- Preparation of *N*-(4-chloro-2-fluoro-3-hydrazinylbenzyl)pivalamide

[0485]



[0486] The title compound was prepared according to the procedure described in step-2 of Intermediate-7 by using *N*-(3-amino-4-chloro-2-fluorobenzyl)pivalamide (0.500 g, 1.93 mmol), sodium nitrite (0.200 g, 2.90 mmol), stannous chloride.H₂O (4.84 g, 1.09 mmol), conc. HCl (20.0 g) and water (3 mL) to afford 0.300 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.12 (s, 9H), 4.23(d, *J* = 5.4 Hz, 2H), 4.34 (br s, 2H), 5.91 (s, 1H), 6.65 (t, *J* = 7.8 Hz, 1H), 8.02 (m, 1H); MS (*m/z*): 274.08 (M+H⁺).

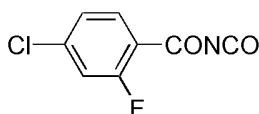
Step-3:- Preparation of *tert*-butyl 2-(6-chloro-2-fluoro-3-(pivalamidomethyl)phenyl) hydrazinecarboxylate

[0487] The title compound was prepared according to the procedure described in step-3 of Intermediate-7 by using *N*-(4-chloro-2-fluoro-3-hydrazinylbenzyl)pivalamide (0.300 g, 1.09 mmol), BOC anhydride (0.360 g, 1.64 mmol), Na₂CO₃ (0.231 g, 2.18 mmol), acetonitrile (10 mL) and water (5 mL) to afford 0.150 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.11 (s, 9H), 1.37 (s, 9H), 4.20 (d, *J* = 5.7 Hz, 2H), 6.64 (m, 1H), 7.06 (br s, 2H), 8.00 (br s, 1H), 8.98 (s, 1H).

Intermediate-58

4-Chloro-2-fluorobenzoyl isocyanate

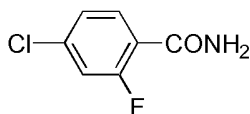
[0488]



EP 2 718 284 B1

Step-1:- Preparation of 4-chloro-2-fluorobenzamide

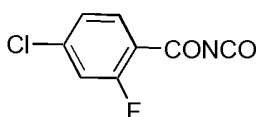
[0489]



[0490] The title compound was prepared according to the procedure described in step-2 of Intermediate-26 by using 4-chloro-2-fluoro benzoic acid (1.5 g), THF (25 mL), oxalyl chloride (0.5 mL) and ammonia gas to afford 1.45 g of the product. ¹H NMR (300 MHz, DMSO *d*₆): δ 7.36 (d, *J* = 6.3 Hz, H), 7.53 (dd, *J* = 8.7 Hz, 1H), 7.64- 7.76 (m, 3H).

Step-2:- Preparation of 4-chloro-2-fluorobenzoyl isocyanate

[0491]

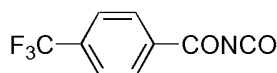


[0492] The title compound was prepared according to the procedure described in step-2 of Intermediate-8 by using 4-chloro-2-fluorobenzamide (0.200 g, 1.26 mmol), EDC (10 mL) and oxalyl chloride (0.14 mL, 1.15 mmol) to afford 0.200 g of the product.

Intermediate -59

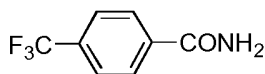
4-(Trifluoromethyl)benzoyl isocyanate

[0493]



Step-1:- Preparation of 4-(trifluoromethyl)benzamide

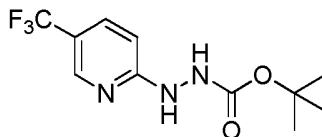
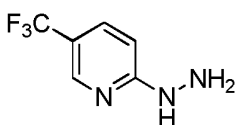
[0494]



[0495] To a cold solution of 4-(trifluoromethyl)benzonitrile (0.500 g, 2.92 mmol) in DMSO (6.0 mL) was added H₂O₂ (50%) (5 mL) at 0°C, followed by portion-wise addition of K₂CO₃ (0.121 g, 0.87 mmol). The reaction mass was allowed to attain RT and stirred for 1 h. The reaction mass was quenched in ice water and extracted with DCM and concentrated to afford 0.300 g of product. ¹H NMR (400 MHz, DMSO *d*₆): δ 7.60 (br s, 1H), 7.82 (d, *J* = 7.5 Hz, 2H), 8.05 (d, *J* = 6.6 Hz, 2H), 8.17 (br s, 1H); MS (*m/z*): 190.11 (*M*+H⁺).

Step-2:- Preparation of 4-(trifluoromethyl)benzoyl isocyanate

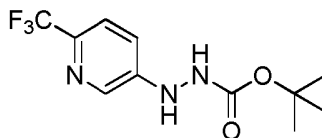
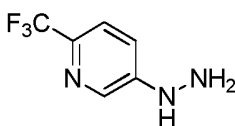
[0496] The title compound was prepared according to the procedure described in step-2 of Intermediate-8 by using 4-(trifluoromethyl)benzamide (0.200 g, 1.05 mmol), EDC (10 mL) and oxalyl chloride (0.15 mL, 1.58 mmol) to afford 0.200 g of the product.

Intermediate-60*tert*-Butyl 2-(5-(trifluoromethyl)pyridin-2-yl)hydrazinecarboxylate**[0497]**Step-1:- Preparation of 2-hydrazinyl-5-(trifluoromethyl)pyridine**[0498]**

[0499] To a solution of 2-chloro-5-(trifluoromethyl)pyridine (1.5 g, 8.26 mmol) in ethanol (20.0 mL) was added hydrazinehydrate (1.21 g, 24.79 mmol). The reaction mass was refluxed for 5-6 h. The reaction mass was concentrated and quenched in ice water and solid obtained was filtered and suck dried to afford 0.700 g of the product. ¹H NMR (300 MHz, DMSO *d*₆): δ 4.32 (br s, 2H), 6.78 (d, *J* = 8.8 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 8.25 (br s, 2H); MS (*m/z*): 178.15 (*M*+*H*⁺).

Step-2:- Preparation of *tert*-butyl 2-(5-(trifluoromethyl)pyridin-2-yl)hydrazinecarboxylate

[0500] The title compound was prepared according to the procedure described in step-3 of Intermediate-7 by using 2-hydrazinyl-5-(trifluoromethyl)pyridine (0.700 g, 3.95 mmol), BOC anhydride (1.3 g, 5.9 mmol), Na₂CO₃ (0.838 g, 7.90 mmol), acetonitrile (15 mL) and water (7 mL) to afford 0.500 g of desired product. ¹H NMR (400 MHz, DMSO *d*₆): δ 1.40 (s, 9H), 6.62 (d, *J* = 8.8 Hz, 1H), 7.83 (dd, *J* = 8.0 Hz, 1H), 8.37 (s, 1H), 8.95 (s, 1H), 9.01 (brs, 1H); MS (*m/z*): 278.00 (*M*+*H*⁺).

Intermediate-61*tert*-Butyl 2-(6-(trifluoromethyl)pyridin-3-yl)hydrazinecarboxylate**[0501]**Step-1:- Preparation of 5-hydrazinyl-2-(trifluoromethyl)pyridine**[0502]**

[0503] To a cold solution of 6-(trifluoromethyl)pyridin-3-amine (1.5 g, 9.25 mmol) in 4N HCl (60.0 mL) was added aqueous solution of NaNO₂ (0.766 g, 11.11 mmol) at 0°C. The reaction mass was stirred at same temperature for 30

EP 2 718 284 B1

minutes. The reaction mass was added to a solution of $\text{SnCl}_2 \cdot \text{H}_2\text{O}$ in 4N HCl at 80°C and further continued stirring for 5-6 h at same temperature. The reaction mass was cooled, basified and extracted with DCM. The organic layer was dried and concentrated to afford 0.700 g of the product. ^1H NMR (300 MHz, DMSO d_6): δ 4.29 (br s, 2H), 7.18 (dd, J = 8.6 Hz, 1H), 7.51 (d, J = 8.8 Hz, 1H), 7.68 (s, 1H), 8.13 (d, J = 2.4 Hz, 1H); MS (m/z): 178.15 ($\text{M}+\text{H}^+$).

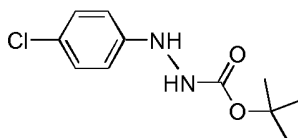
Step-2:- Preparation of *tert*-butyl 2-(6-(trifluoromethyl)pyridin-3-yl)hydrazinecarboxylate

[0504] The title compound was prepared according to the procedure described in step-3 of Intermediate-7 by using 5-hydrazinyl-2-(trifluoromethyl)pyridine (0.700 g, 3.95 mmol), BOC anhydride (1.3 g, 5.9 mmol), Na_2CO_3 (0.838 g, 7.90 mmol), acetonitrile (15 mL) and water (7 mL) to afford 0.400 g of desired product. ^1H NMR (400 MHz, DMSO d_6): δ 1.31 (s, 9H), 7.10 (dd, J = 8.0 Hz, 1H), 7.64 (d, J = 8.6 Hz, 1H), 8.09 (d, J = 2.3 Hz, 1H), 8.55 (br s, 1H), 9.08 (br s, 1H); MS (m/z): 278.05 ($\text{M}+\text{H}^+$).

Intermediate-62

tert-Butyl 2-(4-chlorophenyl)hydrazinecarboxylate

[0505]

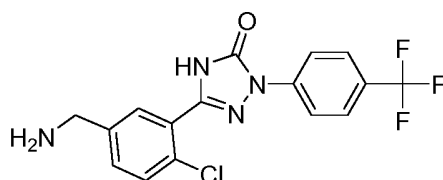


[0506] The title compound was prepared according to the procedure described in step-3 of Intermediate-7 by using (4-chlorophenyl)hydrazine hydrochloride (1.5 g, 10.5 mmol), BOC anhydride (2.7 g, 12.6 mmol), Na_2CO_3 (2.23 g, 21.03 mmol), acetonitrile (20 mL) and water (10 mL) to afford 0.900 g of desired product.

Intermediate-63

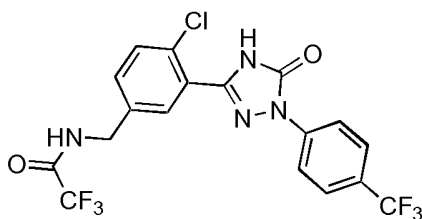
3-(5-(Aminomethyl)-2-chlorophenyl)-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,4-triazol-5(4*H*)-one

[0507]



Step-1:- Preparation of *N*-(4-chloro-3-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide

[0508]



[0509] To a solution of *tert*-butyl 2-(4-(trifluoromethyl)phenyl)hydrazinecarboxylate (Intermediate-53, 1.00 g, 3.63 mmol) in DCM (20 mL), 2-chloro-5-((2,2,2-trifluoroacetamido)methyl)benzoyl isocyanate (step-3 of Intermediate-26, 1.30

EP 2 718 284 B1

g, 4.03 mmol) was added and the reaction mass was stirred at RT for 2 h. After completion of reaction, excess of solvent was removed under reduced pressure to obtain 0.700 g of the crude product. To a solution of obtained crude product in DCM (5.0 mL), TFA (5.0 mL) was added and the reaction mass was stirred at RT for 2-3 h. Excess of the solvent was removed from the reaction mass under reduced pressure and the reaction mass was quenched in ice and filtered to obtain 0.700 g of the desired title product. ¹H NMR (300 MHz, DMSO *d*₆): δ 4.45 (d, 1H), 7.50 (d, *J* = 4.8 Hz, 1H), 7.65-7.68 (m, 2H), 8.85 (d, *J* = 6.6 Hz, 2H), 8.18 (d, *J* = 6.3 Hz, 2H), 10.05 (s, 1H), 12.69 (s, 1H); MS (*m/z*): 463.17

(*M-H*)⁻.

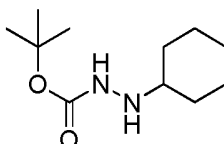
Step-2:- Preparation of 3-(5-(aminomethyl)-2-chlorophenyl)-1-(4-(trifluoromethyl) phenyl)-1*H*-1,2,4-triazol-5(4*H*)-one

[0510] To a solution of *N*-(4-chloro-3-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide (0.400 g, 0.861 mmol) in THF (5.0 mL) was added KOH aqueous solution (0.096 g, 1.72 mmol) and the reaction mass was stirred at RT for 3-4 h. The reaction mass was quenched in water and extracted with ethyl acetate and concentrated to afford 0.200 g of the desired product.

Intermediate-64

tert-Butyl 2-Cyclohexyl hydrazinecarboxylate

[0511]

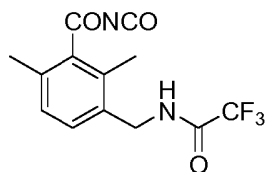


[0512] The title compound was prepared according to the procedure described in step-3 of Intermediate-7 by using cyclohexyl hydrazine hydrochloride (1.00 g, 6.6 mmol), BOC anhydride (1.73 g, 7.9 mmol), Na₂CO₃ (1.75 g, 16.6 mmol), acetonitrile (20 mL) and water (10 mL) to afford 0.500 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 0.95-1.02 (m, 2H), 1.07-1.14 (m, 2H), 1.16 (s, 9H), 1.39-1.51 (m, 2H), 1.67-1.98 (m, 2H), 2.61 (m, 1H), 8.16 (br s, 1H), 8.75 (br s, 1H). MS (*m/z*): 214.79 (*M*⁺).

Intermediate-65

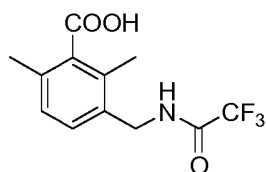
3-((2,2,2-Trifluoroacetamido)methyl)-2,6-dimethylbenzoyl isocyanate

[0513]



Step-1:- Preparation of 3-((2,2,2-trifluoroacetamido)methyl)-2,6-dimethylbenzoic acid

[0514]

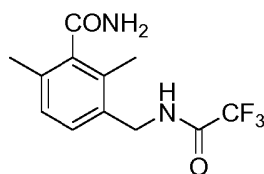


EP 2 718 284 B1

[0515] To a solution of 2,6-dimethyl benzoic acid (6.8 g, 0.045 mmol) in conc.H₂SO₄ (100 mL), 2,2,2-trifluoro-*N*-(hydroxymethyl)acetamide (7.1 g, 0.049 mmol) was added and the reaction mixture was stirred at RT for 24 h. After completion of the reaction, the reaction mass was quenched in ice water and stirred for 15 minutes. The obtained solid product was filtered and dried to afford 7.0 g of the desired title product. ¹H NMR (300 MHz, DMSO *d*₆): δ 2.26 (s, 6H), 4.36 (t, *J* = 12.3 Hz, 2H), 7.09 (m, 1H), 7.15 (m, 1H), 9.89-9.94 (m, 1H).

Step-2:- Preparation of 3-((2,2,2-trifluoroacetamido)methyl)-2,6-dimethylbenzamide

[0516]



[0517] The title compound was prepared according to the procedure described in step-2 of Intermediate-26 by using 3-((2,2,2-trifluoroacetamido)methyl)-2,6-dimethylbenzoic acid (1.0 g), oxalyl chloride (1.0 mL), THF (50 mL) and ammonia gas to afford 0.800 g of the desired product.

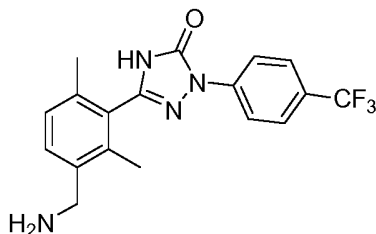
Step-3:- Preparation of 3-((2,2,2-trifluoroacetamido)methyl)-2,6-dimethylbenzoyl isocyanate

[0518] The title compound was prepared according to the procedure described in step-2 of Intermediate-8 by using 3-((2,2,2-trifluoroacetamido)methyl)-2,6-dimethylbenzamide (1.0 g, 3.6 mmol), oxalyl chloride and EDC (10 mL) to afford 0.900 g of the desired product.

Intermediate-66

5-(3-(Aminomethyl)-2,6-dimethylphenyl)-2-(4-(trifluoromethyl)phenyl)-2*H*-1,2,4-triazol-3(4*H*)-one

[0519]

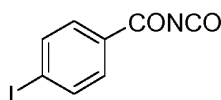


[0520] To a solution of *N*-(3-(1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2,4-dimethylbenzyl)-2,2,2-trifluoroacetamide (Example-106, 0.800 g, 1.74 mmol) in THF (10 mL), aqueous solution of KOH was added and the reaction mass was stirred at RT for 3-4 h. After completion of the reaction, the reaction mass was quenched with water and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulphate and concentrated to afford 0.200 g of the desired product. MS (*m/z*): 362.86 (*M*+*H*)⁺.

Intermediate-67

4-Iodobenzoyl isocyanate

[0521]

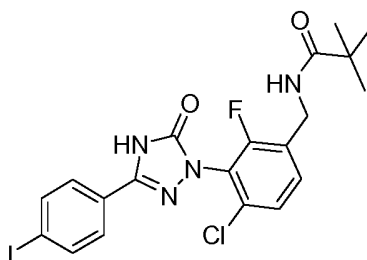


EP 2 718 284 B1

[0522] The title compound was prepared according to the procedures described in step-2 and step-3 of Intermediate-26 by using 4-iodo benzoic acid (2.0 g), oxalyl chloride (1.0 ml), ammonia gas, DCM (20 mL), THF (20 mL) to afford 1.5 g of the desired product. ^1H NMR (400 MHz, DMSO d_6): δ 7.17 (br s, 1H), 7.64 (d, 2H), 8.01 (s, 2H); MS (m/z): 461.14 (M+H) $^+$.

Intermediate-68

N-(4-Chloro-2-fluoro-3-(4,5-dihydro-3-(4-iodophenyl)-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide

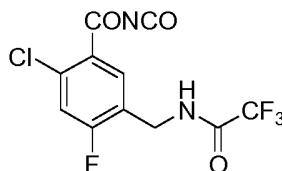


[0524] The title compound was prepared according to the procedure described in Example-83 by using *tert*-butyl 2-(6-chloro-2-fluoro-3-(pivalamidomethyl)phenyl)hydrazinecarboxylate (Intermediate-57, 0.250g), 4-iodobenzoyl isocyanate (Intermediate-67, 0.250 g), DCM (10 mL) and trifluoro acetic acid (0.5 mL) to afford 0.150 g of the desired product. ^1H NMR (400 MHz, DMSO d_6): δ 1.19 (s, 9H), 4.30 (d, J = 3.3 Hz, 2H), 7.39 (m, 1H), 7.45 (d, 1H), 7.62 (d, 2H), 7.90 (d, J = 3.6 Hz, 2H), 8.19 (t, 1H), 13.0 (br s, 1H); MS (m/z): 528.98 (M+H) $^+$.

Intermediate-69

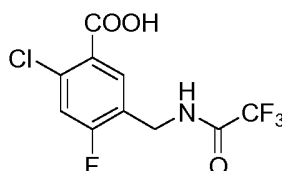
5-((2,2,2-Trifluoroacetamido)methyl)-2-chloro-4-fluorobenzoyl isocyanate

[0525]



Step-1:- Preparation of 5-((2,2,2-trifluoroacetamido)methyl)-2-chloro-4-fluorobenzoic acid

[0526]

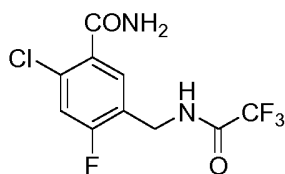


[0527] The title compound was prepared according to the procedure described in step-1 of Intermediate-26 by using 2-chloro-4-fluorobenzoic acid (5.0 g, 0.002 mmol), 2,2,2-trifluoro-*N*-(hydroxymethyl)acetamide (4.0 g, 0.002 mmol) and conc. H_2SO_4 (50 mL) to afford 4.0 g of the desired product. ^1H NMR (400 MHz, DMSO d_6): δ 4.44 (d, J = 12.0 Hz, 2H), 7.59 (m, 1H), 7.92 (m, 1H), 10.0 (br s, 1H), 13.5 (br s, 1H).

EP 2 718 284 B1

Step-2:- Preparation of 5-((2,2,2-trifluoroacetamido)methyl)-2-chloro-4-fluorobenzamide

[0528]



[0529] The title compound was prepared according to the procedure described in step-2 of Intermediate-26 by using 5-((2,2,2-trifluoroacetamido)methyl)-2-chloro-4-fluorobenzoic acid (1.0 g), oxalyl chloride (1.0 mL), THF (50 mL) and ammonia gas to afford 0.800 g of the desired product. ^1H NMR (400 MHz, DMSO d_6): δ 4.53 (m, 2H), 7.43 (m, 1H), 7.44 (m, 2H), 7.48 (m, 1H), 10.0 (br s, 1H); MS (m/z): 297.10 (M-H) $^-$.

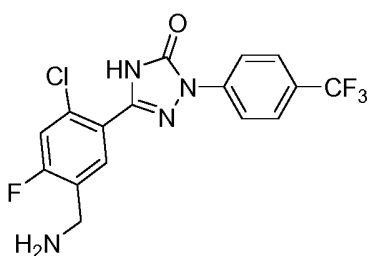
Step-3:- Preparation of 5-((2,2,2-trifluoroacetamido)methyl)-2-chloro-4-fluorobenzoyl isocyanate

[0530] The title compound was prepared according to the procedure described in step-2 of Intermediate-8 by using 5-((2,2,2-trifluoroacetamido)methyl)-2-chloro-4-fluorobenzamide (1.0 g, 3.6 mmol), oxalyl chloride (1.0 mL) and EDC (10 mL) to afford 0.750 g of the desired product.

Intermediate-70

5-(5-(Aminomethyl)-2-chloro-4-fluorophenyl)-2-(4-(trifluoromethyl)phenyl)-2H-1,2,4-triazol-3(4H)-one

[0531]

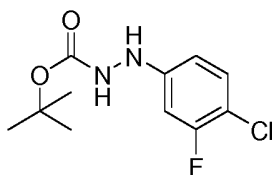


[0532] The title compound was prepared according to the procedure described in Intermediate-66 by using *N*-(4-chloro-2-fluoro-5-(1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1H-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide (Example-113, 0.100 g, 0.207 mmol), KOH (0.034 g, 0.622 mol), water (5 mL) and THF (5.0 mL) to afford 0.080 g of the desired product.

Intermediate-71

tert-Butyl 2-(4-chloro-3-fluorophenyl)hydrazinecarboxylate

[0533]



[0534] The title compound was prepared according to the procedure described in step-3 of Intermediate-7 by using 4-chloro-3-fluorophenylhydrazine hydrochloride (1.00 g), BOC anhydride (1.5g), Na_2CO_3 (0.900 g, 8.5 mmol), acetonitrile

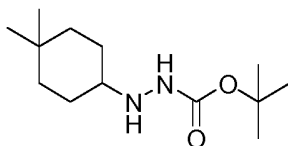
EP 2 718 284 B1

(20 mL) and water (10 mL) to afford 0.600 g of the desired product.

Intermediate-72

4,4-Dimethyl tert-butyl 2-cyclohexyl hydrazinecarboxylate

[0535]

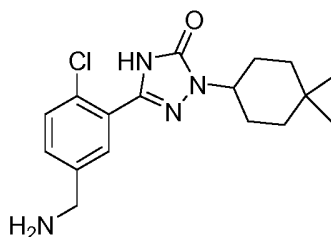


The title compound was prepared according to the procedure described in step-3 of Intermediate-7 by using 4,4-dimethylcyclohexylhydrazine hydrochloride (1.00 g), BOC anhydride (1.5g), Na_2CO_3 (0.900 g, 8.5 mmol), acetonitrile (20 mL) and water (10 mL) to afford 0.600 g of the desired product.

Intermediate-73

5-(5-(Aminomethyl)-2-chlorophenyl)-2-(4,4-dimethylcyclohexyl)-2H-1,2,4-triazol-3(4H)-one

[0537]

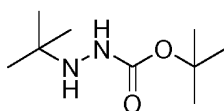


The title compound was prepared according to the procedure described in Intermediate-66 by using *N*-(4-chloro-3-(4,5-dihydro-1-(4,4-dimethylcyclohexyl)-5-oxo-1H-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide (Example-117, 0.150 g, 0.348 mmol), KOH (0.039 g, 0.696 mol), water (2 mL) and THF (5.0 mL) to afford 0.100 g of the desired product.

Intermediate-74

tert-Butyl 2-*tert*-butylhydrazinecarboxylate

[0539]



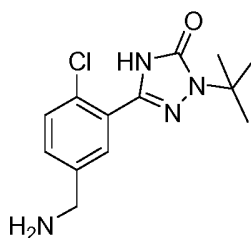
The title compound was prepared according to the procedure described in step-3 of Intermediate-7 by using *tert*-butylhydrazine (1.00 g), BOC anhydride (1.5g), Na_2CO_3 (0.900 g, 8.5 mmol), acetonitrile (20 mL) and water (10 mL) to afford 0.600 g of the desired product.

Intermediate-75

2-*tert*-Butyl-5-(5-(aminomethyl)-2-chlorophenyl)-2H-1,2,4-triazol-3(4H)-one

[0541]

EP 2 718 284 B1

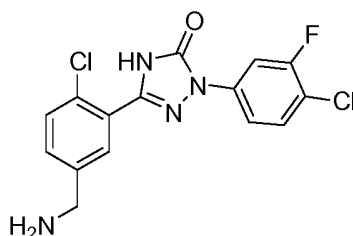


[0542] The title compound was prepared according to the procedure described in Intermediate-66 by using *N*-(3-(1-*tert*-butyl-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-4-chlorobenzyl)-2,2,2-trifluoroacetamide (Example-120, 0.400 g, 1.062 mmol), KOH (0.119 g, 2.12 mmol), water (5 mL) and THF (5.0 mL) to afford 0.300 g of the desired product.

Intermediate-76

5-(5-(Aminomethyl)-2-chlorophenyl)-2-(4-chloro-3-fluorophenyl)-2*H*-1,2,4-triazol-3(4*H*)-one

[0543]

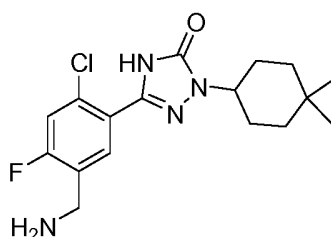


[0544] The title compound was prepared according to the procedure described in Intermediate-66 by using *N*-(4-chloro-3-(1-(4-chloro-3-fluorophenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide (Example-116, 0.400 g, 0.890 mmol), KOH (0.099 g, 1.78 mmol), water (2 mL) and THF (4.0 mL) to afford 0.300 g of the desired product.

Intermediate-77

5-(5-(Aminomethyl)-2-chloro-4-fluorophenyl)-2-(4,4-dimethylcyclohexyl)-2*H*-1,2,4-triazol-3(4*H*)-one

[0545]

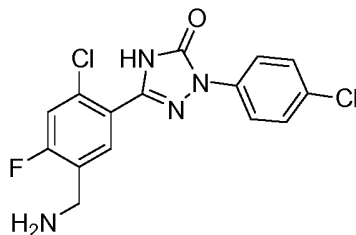


[0546] The title compound was prepared according to the procedure described in Intermediate-66 by using *N*-(4-chloro-2-fluoro-5-(4,5-dihydro-1-(4,4-dimethylcyclohexyl)-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide (Example-124, 1.0 g), KOH (1.0 g), water (5 mL) and THF (40.0 mL) to afford 0.700 g of the desired product.

Intermediate-78

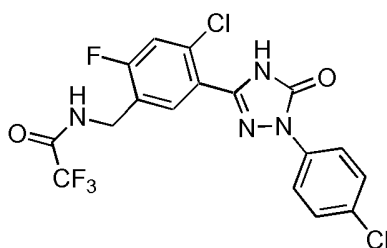
5-(5-(Aminomethyl)-2-chloro-4-fluorophenyl)-2-(4-chlorophenyl)-2*H*-1,2,4-triazol-3(4*H*)-one

[0547]



Step-1:- Preparation of *N*-(4-chloro-5-(1-(4-chlorophenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2-fluorobenzyl)-2,2,2-trifluoroacetamide

[0548]



[0549] The title compound was prepared according to the procedure described in Example-83 by using 5-((2,2,2-trifluoroacetamido)methyl)-2-chloro-4-fluorobenzoyl isocyanate (Intermediate-69, 0.400 g), *tert*-butyl 2-(4-chlorophenyl)hydrazinecarboxylate (Intermediate-62, 0.400 g), DCM (20 mL) and trifluoro acetic acid (5.0 mL) to afford 0.250 g of the desired product.

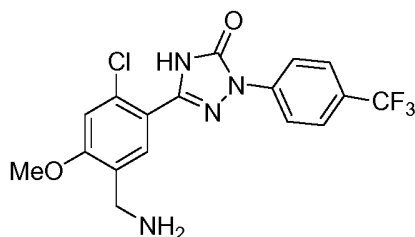
Step-2:- Preparation of 5-(5-(aminomethyl)-2-chloro-4-fluorophenyl)-2-(4-chlorophenyl)-2*H*-1,2,4-triazol-3(4*H*)-one

[0550] The title compound was prepared according to the procedure described in Intermediate-66 by using *N*-(4-chloro-5-(1-(4-chlorophenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2-fluorobenzyl)-2,2,2-trifluoroacetamide (0.160 g), KOH (0.050 g), water (2 mL) and THF (10.0 mL) to afford 0.070 g of the desired product.

Intermediate-79

5-(5-(Aminomethyl)-2-chloro-4-methoxyphenyl)-2-(4-(trifluoromethyl)phenyl)-2*H*-1,2,4-triazol-3(4*H*)-one

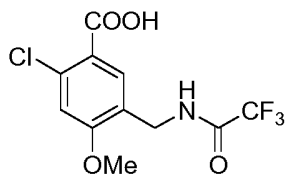
[0551]



Step-1:- Preparation of 5-((2,2,2-trifluoroacetamido)methyl)-2-chloro-4-methoxybenzoic acid

[0552]

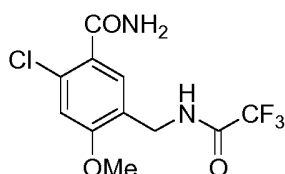
EP 2 718 284 B1



[0553] The title compound was prepared according to the procedure described in step-1 of Intermediate-26 by using 2-chloro-4-methoxybenzoic acid (0.060 g), 2,2,2-trifluoro-*N*-(hydroxymethyl)acetamide (0.050 g) and H₂SO₄ (2 mL) to afford 0.040 g of the desired product.

Step-2:- Preparation of 5-((2,2,2-trifluoroacetamido)methyl)-2-chloro-4-methoxybenzamide

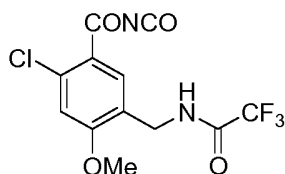
[0554]



[0555] The title compound was prepared according to the procedure described in step-2 of Intermediate-26 by using 5-((2,2,2-trifluoroacetamido)methyl)-2-chloro-4-methoxybenzoic acid (1.0 g), oxalyl chloride (1.0 mL), THF (50 mL) and ammonia gas to afford 0.800 g of the desired product.

Step-3:- Preparation of 5-((2,2,2-trifluoroacetamido)methyl)-2-chloro-4-methoxybenzoyl isocyanate

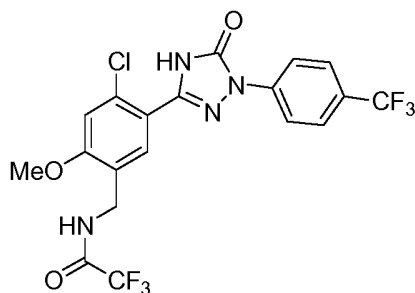
[0556]



[0557] The title compound was prepared according to the procedure described in step-2 of Intermediate-8 by using 5-((2,2,2-trifluoroacetamido)methyl)-2-chloro-4-methoxybenzamide (1.0 g, 3.6 mmol), oxalyl chloride (1.0 mL) and EDC (10 mL) to afford 0.750 g of the desired product.

Step-4:- Preparation of *N*-(4-chloro-5-(1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2-methoxybenzyl)-2,2,2-trifluoroacetamide

[0558]



[0559] The title compound was prepared according to the procedure described in Example-83 by using 5-((2,2,2-

EP 2 718 284 B1

trifluoroacetamido)methyl)-2-chloro-4-methoxybenzoyl isocyanate (0.500 g), *tert*-butyl 2-(4-(trifluoromethyl)phenyl)hydrazinecarboxylate (Intermediate-53, 0.450 g), DCM (20 mL), and trifluoro acetic acid (5.0 mL) to afford 0.180 g of the desired product.

5 Step-5:- Preparation of 5-(5-(aminomethyl)-2-chloro-4-methoxyphenyl)-2-(4-(trifluoromethyl)phenyl)-2*H*-1,2,4-triazol-3(4*H*)-one

10 **[0560]** The title compound was prepared according to the procedure described in Intermediate-66 by using *N*-(4-chloro-5-(1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2-methoxybenzyl)-2,2,2-trifluoroacetamide (0.200 g), water (5 mL), KOH (0.200 g) and THF (10.0 mL) to afford 0.150 g of the desired product.

Intermediate-80

15 *tert*-Butyl 2-[4-fluoro-3-(trifluoromethyl)phenyl]hydrazinecarboxylate

[0561]



25 Step1:- Preparation of 1-(4-fluoro-3-(trifluoromethyl)phenyl)hydrazine

[0562]



35 **[0563]** The title compound was prepared according to the procedure described in step-1 of Intermediate-61 by using 4-fluoro-3-(trifluoromethyl)aniline (3.0 g, 0.016 mmol), NaNO₂ (1.73 g, 0.025 mmol), SnCl₂·2H₂O (9.39 g, 0.041 mmol) and conc. HCl (100 mL) to afford 2.0 g of the desired product.

40 Step-2:- Preparation of *tert*-butyl 2-[4-fluoro-3-(trifluoromethyl)phenyl]hydrazinecarboxylate

45 **[0564]** The title compound was prepared according to the procedure described in step-3 of Intermediate-7 by using 1-(4-fluoro-3-(trifluoromethyl)phenyl)hydrazine (1.00 g), BOC anhydride (1.5g), Na₂CO₃ (0.900 g, 8.5 mmol), acetonitrile (20 mL) and water (10 mL) to afford 0.600 g of the desired product. ¹H NMR (300 MHz, CDCl₃): δ 1.40 (s, 9H), 6.86-6.94 (m, 2H), 7.26- 7.32 (m, 1H), 7.98 (s, 1H), 8.95 (s, 1H); MS (m/z): 436.55 (M⁺H)⁺.

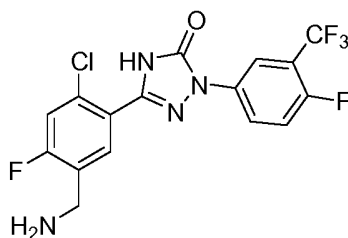
Intermediate-81

50 5-(5-(Aminomethyl)-2-chloro-4-fluorophenyl)-2-(4-fluoro-3-(trifluoromethyl)phenyl)-2*H*-1,2,4-triazol-3(4*H*)-one

[0565]

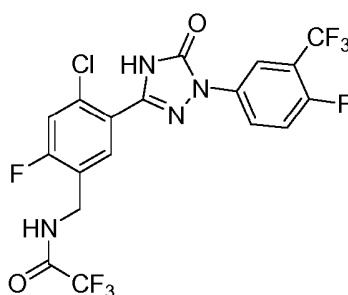
55

EP 2 718 284 B1



Step-1:- Preparation of *N*-(4-chloro-2-fluoro-5-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide

[0566]



[0567] The title compound was prepared according to the procedure described in Example-83 by using 5-((2,2,2-trifluoroacetamido)methyl)-2-chloro-4-fluorobenzoyl isocyanate (Intermediate-69, 0.400 g), *tert*-butyl 2-[4-fluoro-3-(trifluoromethyl)phenyl]hydrazinecarboxylate (Intermediate-80, 0.400 g), DCM (20 mL) and TFA (5.0 mL) to afford 0.200 g of the desired product.

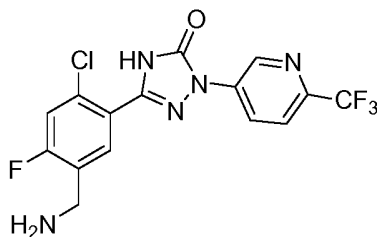
Step-2:- Preparation of 5-(5-(aminomethyl)-2-chloro-4-fluorophenyl)-2-(4-fluoro-3-(trifluoromethyl)phenyl)-2*H*-1,2,4-triazol-3(4*H*)-one

[0568] The title compound was prepared according to the procedure described in Intermediate-66 by using *N*-(4-chloro-3-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide (0.400 g), KOH (0.100 g) and THF (10.0 mL) to afford 0.150 g of desired product.

Intermediate-82

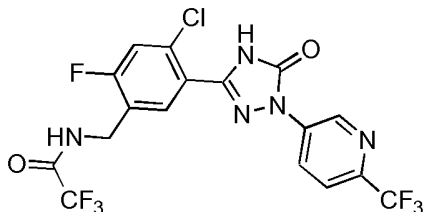
5-(5-(Aminomethyl)-2-chloro-4-fluorophenyl)-2-(6-(trifluoromethyl)pyridin-3-yl)-2*H*-1,2,4-triazol-3(4*H*)-one

[0569]



Step-1:- Preparation of *N*-(4-chloro-2-fluoro-5-(1-(6-(trifluoromethyl)pyridin-3-yl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide

[0570]



[0571] The title compound was prepared according to the procedure described in Example-83 by using 5-((2,2,2-trifluoroacetamido)methyl)-2-chloro-4-fluorobenzoyl isocyanate (Intermediate-69, 0.350 g), *tert*-butyl 2-[6-(trifluoromethyl)pyridin-3-yl]hydrazinecarboxylate (Intermediate-61, 0.350 g), DCM (20 mL) and TFA (5.0 mL) to afford 0.250 g of the desired product.

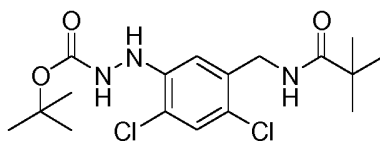
Step-2:- Preparation of 5-(5-(aminomethyl)-2-chloro-4-fluorophenyl)-2-(6-(trifluoromethyl)pyridin-3-yl)-2*H*-1,2,4-triazol-3(4*H*)-one

[0572] The title compound was prepared according to the procedure described in Intermediate-66 by using *N*-(4-chloro-2-fluoro-5-(1-(6-(trifluoromethyl)pyridin-3-yl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide (0.500 g), KOH (0.200 g), water (5 mL) and THF (10.0 mL) to afford 0.150 g of desired product.

Intermediate-83

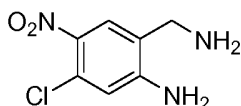
tert-Butyl 2-(2,4-dichloro-5-((2,2-dimethylpropanoyl)amino)methyl)phenyl) hydrazinecarboxylate

[0573]



Step-1:- Preparation of 2-(aminomethyl)-5-chloro-4-nitrobenzenamine

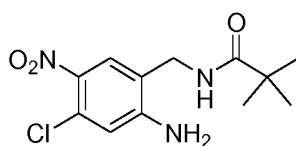
[0574]



[0575] To a solution of 2-amino-4-chloro-5-nitrobenzamide (3.0 g, 13.7 mmol) in dry THF (50 mL), borane dimethyl sulphide complex (1.56 g, 20.6 mmol) was added at RT and the reaction mass was refluxed for 24 h. The reaction mass was cooled to RT and dilute HCl was added till it became acidic. Further, the reaction mixture was stirred for 1 h and then the reaction mixture was basified with dilute NaOH and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulphate and concentrated to afford 2.0 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.58 (s, 2H), 6.72 (br s, 3H), 8.04 (br s, 1H); MS (m/z): 200.28 (M-H).

Step-2:- Preparation of *N*-(2-amino-4-chloro-5-nitrobenzyl)pivalamide

[0576]

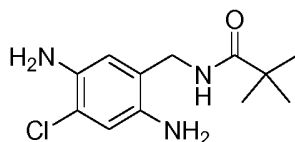


EP 2 718 284 B1

[0577] To a solution of 2-(aminomethyl)-5-chloro-4-nitrobenzenamine (2.5 g, 12.25 mmol) in THF (35 mL), TEA (3.0 mL) and pivaloyl chloride (1.96 mL, 14.7 mmol) were added and the reaction mass was stirred at RT for 5 h. The reaction mass was quenched with water and extracted with ethyl acetate. The organic layer was washed with dilute HCl and dilute sodium bicarbonate solution, separated, dried over anhydrous sodium sulphate and concentrated to afford 2.0 of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.12 (s, 9H), 4.30 (d, *J* = 5.4 Hz, 2H), 7.81 (d, *J* = 9.9 Hz, 1H), 7.96 (d, *J* = 6.3 Hz, 1H), 8.21 (m, 1H).

Step3:- Preparation of *N*-(2,5-diamino-4-chlorobenzyl)pivalamide

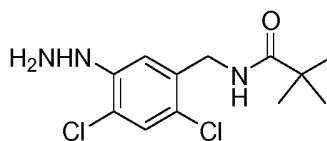
[0578]



[0579] To a solution of *N*-(2-amino-4-chloro-5-nitrobenzyl)pivalamide (2.0 g, 6.9 mmol) in methanol (20 mL), Raney Ni (2.0 g) and hydrazine hydrate (5.0 mL) were added and the reaction mass was stirred at RT for 3 h. After the completion of the reaction, the reaction mass was filtered through celite pad and obtained filtrate was concentrated to afford 1.5 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.11 (s, 9H), 3.97 (br d, 2H), 4.52 (br d, 2H), 5.44 (br s, 2H), 6.50 (d, *J* = 11.4 Hz, 2H), 7.88 (m, 1H).

Step-4:- Preparation of *N*-(2,4-dichloro-5-hydrazinylbenzyl)-2,2-dimethylpropanamide

[0580]



[0581] The title compound was prepared according to the procedure described in step-1 of Intermediate-61 by using *N*-(2,5-diamino-4-chlorobenzyl)pivalamide (1.5 g, 5.8 mmol), NaNO₂ (0.481 g, 6.9 mmol), SnCl₂·2H₂O (3.20 g, 14.5 mmol), conc. HCl (50 mL) to afford 1.0 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.11 (s, 9H), 4.44 (m, 2H), 6.53 (m, 1H), 7.18 (m, 1H), 7.99 (m, 1H), 10.23 (s, 1H).

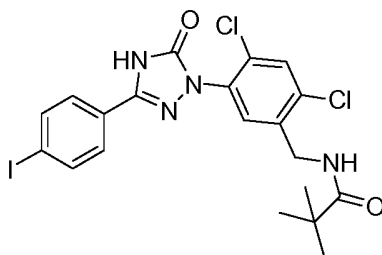
Step-5:- Preparation of *tert-butyl* 2-(2,4-dichloro-5-(((2,2-dimethylpropanoyl) amino)methyl)phenyl)hydrazinecarboxylate

[0582] The title compound was prepared according to the procedure described in step-3 of Intermediate-7 by using *N*-(2,4-dichloro-5-hydrazinylbenzyl)-2,2-dimethylpropanamide (1.0 g, 3.6 mmol), BOC anhydride (0.958 g, 4.39 mmol), Na₂CO₃ (0.776 g, 7.32 mmol), acetonitrile (10 mL) and water (5 mL) to afford 0.500 g of the desired product.

Intermediate-84

N-(2,4-Dichloro-5-(4,5-dihydro-3-(4-iodophenyl)-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide

[0583]

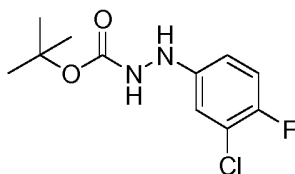


[0584] The title compound was prepared according to the procedure described in Example-83 by using 4-iodobenzoyl isocyanate (Intermediate-67, 0.300 g, 0.800 mmol), *tert*-butyl 2-(2,4-dichloro-5-((2,2-dimethylpropanoyl)amino)methyl)phenylhydrazine carboxylate (Intermediate-83, 0.397g, 1.6 mmol), DCM (20 mL), trifluoro acetic acid (5.0 mL) to afford 0.150 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.09 (s, 9H), 4.31 (d, *J* = 4.2 Hz, 2H), 7.40- 7.58 (m, 2H), 7.61- 7.78 (m, 2H), 7.93-8.02 (br d, 2H), 8.17 (m, 1H).

Intermediate-85

tert-Butyl 2-(3-chloro-4-fluorophenyl)hydrazinecarboxylate

[0585]

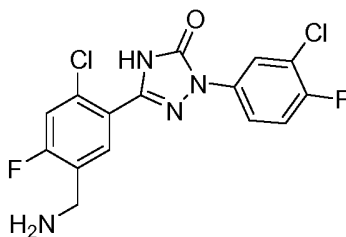


[0586] The title compound was prepared according to the procedure described in step-3 of Intermediate-7 by using 1-(3-chloro-4-fluorophenyl)hydrazine (3.0 g, 0.015 mmol), BOC anhydride (3.6 g, 0.16 mmol), Na₂CO₃ (2.40 g, 0.022 mmol), acetonitrile (30 mL) and water (5 mL) to afford 1.3 g of the desired product. ¹H NMR (300 MHz, CDCl₃): δ 1.38 (s, 9H), 6.60 (m, 1H), 6.67 (m, 1H), 7.13- 7.20 (m, 1H), 7.77 (s, 1H), 8.85 (s, 1H).

Intermediate-86

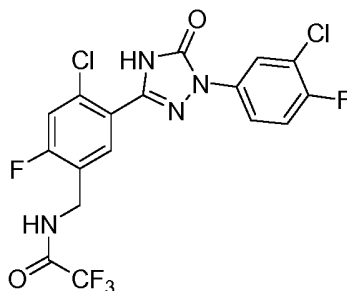
5-(5-(Aminomethyl)-2-chloro-4-fluorophenyl)-2-(3-chloro-4-fluorophenyl)-2*H*-1,2,4-triazol-3(4*H*)-one

[0587]



Step-1:- Preparation of *N*-(4-chloro-5-(1-(3-chloro-4-fluorophenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2-fluorobenzyl)-2,2,2-trifluoroacetamide

[0588]



[0589] The title compound was prepared according to the procedure described in Example-83 by using 5-((2,2,2-trifluoroacetamido)methyl)-2-chloro-4-fluorobenzoyl isocyanate (Intermediate-69, 0.300 g), *tert*-butyl 2-(3-chloro-4-fluorophenyl)hydrazinecarboxylate (Intermediate-85, 0.300 g), DCM (20 mL) and trifluoro acetic acid (5.0 mL) to afford 0.200 g of the desired product.

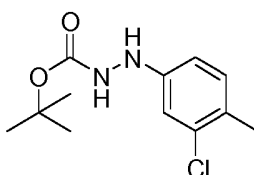
Step-2:- Preparation of 5-(5-(aminomethyl)-2-chloro-4-fluorophenyl)-2-(3-chloro-4-fluorophenyl)-2*H*-1,2,4-triazol-3(4*H*)-one

[0590] The title compound was prepared according to the procedure described in Intermediate-66 by using *N*-(4-chloro-5-(1-(3-chloro-4-fluorophenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2-fluorobenzyl)-2,2,2-trifluoroacetamide (0.300 g), KOH (0.100 g), water (2 ml) and THF (10.0 mL) to afford 0.100 g of the desired product.

Intermediate-87

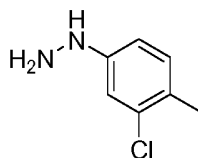
tert-Butyl 2-(3-chloro-4-methylphenyl)hydrazinecarboxylate

[0591]



Step-1:- Preparation of 1-(3-chloro-4-methylphenyl)hydrazine

[0592]



[0593] The title compound was prepared according to the procedure described in step-1 of Intermediate-61 by using 3-chloro-4-methylaniline (6.0 g, 0.0420 mmol), NaNO₂ (8.56 g, 0.050 mmol), SnCl₂·2H₂O (23.7 g, 0.105 mmol) and conc. HCl (100 mL) to afford 4.5 g of the desired product.

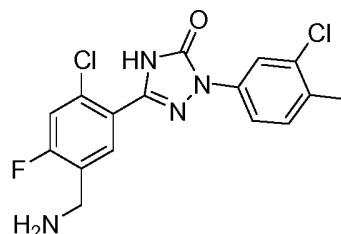
Step-2:- Preparation of *tert*-butyl 2-(3-chloro-4-methylphenyl)hydrazine carboxylate

[0594] The title compound was prepared according to the procedure described in step-3 of Intermediate-7 by using 1-(3-chloro-4-methylphenyl)hydrazine (4.5 g, 0.028 mmol), BOC anhydride (6.8 g, 0.032 mmol), Na₂CO₃ (4.50 g, 0.041 mmol), acetonitrile (30 mL) and water (5 mL) to afford 1.300 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.40 (s, 9H), 2.17 (s, 3H), 6.53 (d, *J* = 10.4 Hz, 1H), 6.63 (s, 1H), 7.08 (d, *J* = 10.82 Hz, 1H), 7.67 (s, 1H), 8.80 (s, 1H).

Intermediate-88

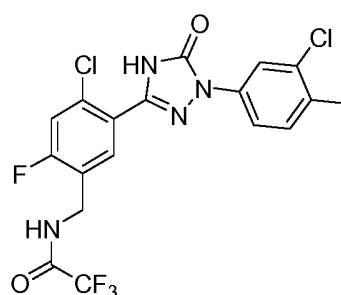
5-(5-(Aminomethyl)-2-chloro-4-fluorophenyl)-2-(3-chloro-4-methylphenyl)-2H-1,2,4-triazol-3(4H)-one

[0595]



Step-1:- Preparation of *N*-(4-chloro-5-(1-(3-chloro-4-methylphenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2-fluorobenzyl)-2,2,2-trifluoroacetamide

[0596]



[0597] The title compound was prepared according to the procedure described in Example-83 by using 5-((2,2,2-trifluoroacetamido)methyl)-2-chloro-4-fluorobenzoyl isocyanate (Intermediate-69, 0.300 g), *tert*-butyl 2-(3-chloro-4-methylphenyl)hydrazinecarboxylate (Intermediate-87, 0.300 g), DCM (20 mL) and trifluoro acetic acid (5.0 mL) to afford 0.200 g of the desired product.

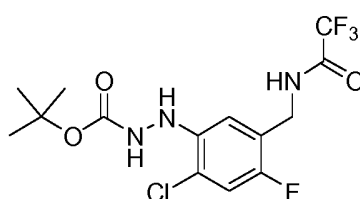
Step-2:- Preparation of 5-(5-(aminomethyl)-2-chloro-4-fluorophenyl)-2-(3-chloro-4-fluorophenyl)-2H-1,2,4-triazol-3(4H)-one

[0598] The title compound was prepared according to the procedure described in Intermediate-66 by using *N*-(4-chloro-5-(1-(3-chloro-4-methylphenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2-fluorobenzyl)-2,2,2-trifluoroacetamide (0.300 g), KOH (0.100 g), water (2 mL) and THF (10.0 mL) to afford 0.200 g of the desired product.

Intermediate-89

tert-Butyl 2-(2-chloro-4-fluoro-5-(((trifluoroacetyl)amino)methyl)phenyl)hydrazinecarboxylate

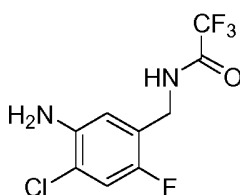
[0599]



EP 2 718 284 B1

Step-1:- Preparation of *N*-(5-amino-4-chloro-2-fluorobenzyl)-2,2,2-trifluoroacetamide

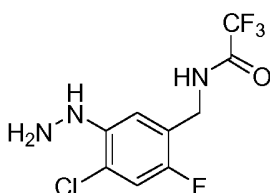
[0600]



[0601] The title compound was prepared according to the procedure described in step-1 of Intermediate-57 by using 5-((2,2,2-trifluoroacetamido)methyl)-2-chloro-4-fluorobenzoic acid (3.0 g), conc. H_2SO_4 and sodium azide (0.793 g, 0.012 mmol) to afford 2.1 g of the desired product.

Step-2:-Preparation of *N*-(4-chloro-2-fluoro-5-hydrazinylbenzyl)-2,2,2-trifluoroacetamide

[0602]



[0603] The title compound was prepared according to the procedure described in step-1 of Intermediate-61 by using *N*-(5-amino-4-chloro-2-fluorobenzyl)-2,2,2-trifluoroacetamide (2.0 g, 0.007 mmol), NaNO_2 (0.612 g, 0.008 mmol), $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (4.10 g, 0.018 mmol), and conc. HCl (100 mL) to afford 1.0 g of the desired product.

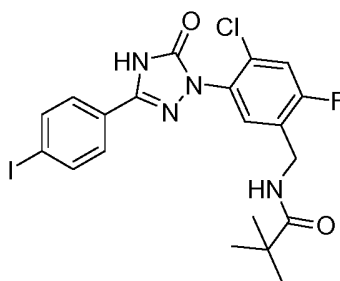
Step-3:- Preparation of *tert-butyl* 2-(2-chloro-4-fluoro-5-(((trifluoroacetyl)amino)methyl)phenyl)hydrazinecarboxylate

[0604] The title compound was prepared according to the procedure described in step-3 of Intermediate-7 by using *N*-(4-chloro-2-fluoro-5-hydrazinylbenzyl)-2,2,2-trifluoroacetamide (1.00 g, 3.5 mmol), BOC anhydride (1.14 g, 5.26 mmol), Na_2CO_3 (0.743 g, 7.01 mmol), acetonitrile (20 mL) and water (10 mL) to afford 0.600 g of the desired product.

Intermediate-90

N-(4-Chloro-2-fluoro-5-(4,5-dihydro-3-(4-iodophenyl)-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide

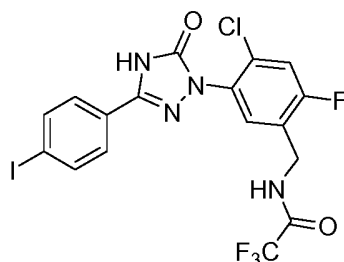
[0605]



EP 2 718 284 B1

Step-1:- Preparation of *N*-(4-chloro-2-fluoro-5-(4,5-dihydro-3-(4-iodophenyl)-5-oxo-1,2,4-triazol-1-yl)benzyl)-2,2,2-trifluoroacetamide

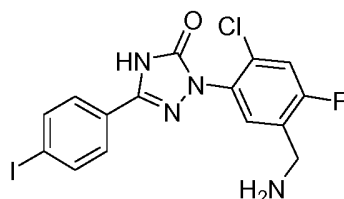
[0606]



[0607] The title compound was prepared according to the procedure described in Example-83 by using 4-iodobenzoyl isocyanate (Intermediate-67, 0.700 g, 1.8 mmol), *tert*-butyl 2-(2-chloro-4-fluoro-5-[(trifluoroacetyl)amino]methyl)phenyl)hydrazine carboxylate (Intermediate-89, 0.992 g, 3.63 mmol), DCM (50 mL), trifluoro acetic acid (5.0 mL) to afford 0.600 g of the desired product. ^1H NMR (300 MHz, DMSO d_6): δ 4.47 (s, 2H), 7.61 (d, J = 2.1 Hz, 3H), 7.86- 7.90 (br d, 3H), 10.05 (br s, 1H).

Step-2:- Preparation of 2-(5-(aminomethyl)-2-chloro-4-fluorophenyl)-5-(4-iodophenyl)-2*H*-1,2,4-triazol-3(4*H*)-one

[0608]



[0609] The title compound was prepared according to the procedure described in Intermediate-66 by using *N*-(4-chloro-2-fluoro-5-(4,5-dihydro-3-(4-iodophenyl)-5-oxo-1,2,4-triazol-1-yl)benzyl)-2,2,2-trifluoroacetamide (0.550 g, 1.01 mmol), KOH (0.285 g, 5.09 mmol), water (5 mL) and THF (15.0 mL) to afford 0.400 g of the desired product. ^1H NMR (300 MHz, DMSO d_6): δ 3.59 (m, 2H), 3.71 (s, 1H), 7.38 (d, J = 9.6 Hz, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.60- 7.69 (m, 4H).

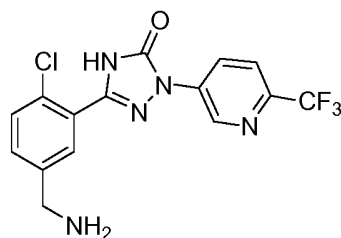
Step-3:- Preparation of *N*-(4-chloro-2-fluoro-5-(4,5-dihydro-3-(4-iodophenyl)-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide

[0610] The title compound was prepared according to the procedure described in step-2 of Intermediate-83 by using 2-(5-(aminomethyl)-2-chloro-4-fluorophenyl)-5-(4-iodophenyl)-2*H*-1,2,4-triazol-3(4*H*)-one (0.400 g, 0.900 mmol), pivaloyl chloride (0.2 mL, 1.35 mmol), DIPEA (2 mL), and THF (10 mL) to afford 0.300 g of the desired product. ^1H NMR (300 MHz, DMSO d_6): δ 1.10 (s, 9H), 4.30 (d, J = 5.4 Hz, 2H), 7.42-7.44 (m, 1H), 7.62- 7.66 (m, 3H), 7.88- 7.91 (br d, 1H), 8.14 (m, 1H); MS (m/z): 529.42 (M^+H^+).

Intermediate-91

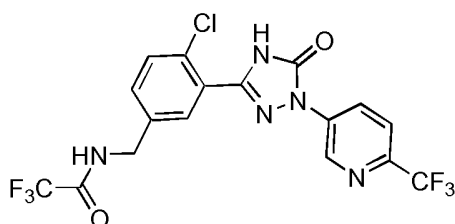
5-(5-(Aminomethyl)-2-chlorophenyl)-2-(6-(trifluoromethyl)pyridin-3-yl)-2*H*-1,2,4-triazol-3(4*H*)-one

[0611]



Step-1:- Preparation *N*-(4-chloro-3-(1-(6-(trifluoromethyl)pyridin-3-yl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide

[0612]



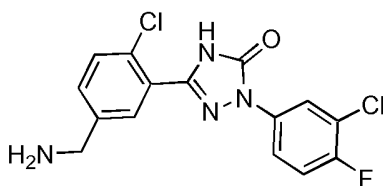
The title compound was prepared according to the procedure described in Example-83 by using 2-chloro-5-((2,2,2-trifluoroacetamido)methyl)benzoyl isocyanate (step-3 of Intermediate-26, 0.500 g, 1.55 mmol), *tert*-butyl 2-[6-(trifluoromethyl)pyridin-3-yl]hydrazinecarboxylate (Intermediate-61, 0.431 g, 1.55 mmol), DCM (50 mL) and trifluoroacetic acid (5.0 mL) to afford 0.500 g of the desired product.

Step-2:- Preparation of 5-(5-(aminomethyl)-2-chlorophenyl)-2-(6-(trifluoromethyl) pyridin-3-yl)-2*H*-1,2,4-triazol-3(4*H*)-one

The title compound was prepared according to the procedure described in Intermediate-66 by using *N*-(4-chloro-3-(1-(6-(trifluoromethyl)pyridin-3-yl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide (0.400 g), KOH (0.400 g), THF (5.0 mL), and water (5 mL) to afford 0.350 g of the desired product.

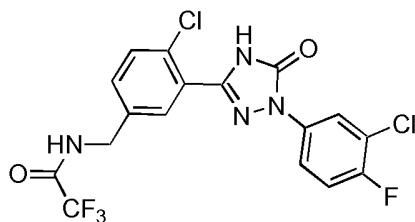
Intermediate-92

5-(5-(Aminomethyl)-2-chlorophenyl)-2-(3-chloro-4-fluorophenyl)-2*H*-1,2,4-triazol-3(4*H*)-one



Step-1:- Preparation of *N*-(4-chloro-3-(1-(3-chloro-4-fluorophenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide

[0616]



[0617] The title compound was prepared according to the procedure described in Example-83 by using 2-chloro-5-((2,2,2-trifluoroacetamido)methyl)benzoyl isocyanate (step-3 of Intermediate-26, 0.500 g, 1.55 mmol), *tert*-butyl 2-(3-chloro-4-fluorophenyl)hydrazinecarboxylate (Intermediate-85, 0.455 g, 1.55 mmol), DCM (20 mL) and trifluoro acetic acid (5.0 mL) to afford 0.200 g of the desired product.

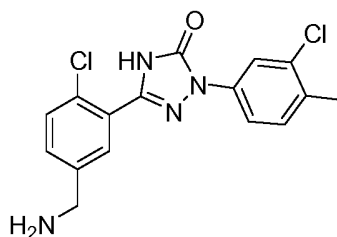
Step-2:- Preparation of 5-(5-(aminomethyl)-2-chlorophenyl)-2-(3-chloro-4-fluorophenyl)-2H-1,2,4-triazol-3(4H)-one

[0618] The title compound was prepared according to the procedure described in Intermediate-66 by using *N*-(4-chloro-3-(1-(3-chloro-4-fluorophenyl)-4,5-dihydro-5-oxo-1H-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide (0.300 g), KOH (0.300 g), water (5 mL) and THF (10.0 mL) to afford 0.150 g of the desired product.

Intermediate-93

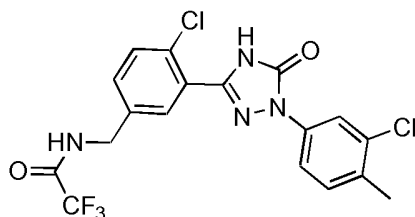
5-(5-(Aminomethyl)-2-chlorophenyl)-2-(3-chloro-4-methylphenyl)-2H-1,2,4-triazol-3(4H)-one

[0619]



Step-1:- Preparation of *N*-(4-chloro-3-(1-(3-chloro-4-methylphenyl)-4,5-dihydro-5-oxo-1H-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide

[0620]



[0621] The title compound was prepared according to the procedure described in Example-83 by using 2-chloro-5-((2,2,2-trifluoroacetamido)methyl)benzoyl isocyanate (step-3 of Intermediate-26, 0.500 g, 1.55 mmol), *tert*-butyl 2-(3-chloro-4-methylphenyl)hydrazinecarboxylate (Intermediate-87, 0.450 g, 1.55 mmol), DCM (20 mL) and trifluoro acetic acid (5.0 mL) to afford 0.180 g of the desired product.

Step-2:- Preparation of 5-(5-(aminomethyl)-2-chlorophenyl)-2-(3-chloro-4-methylphenyl)-2H-1,2,4-triazol-3(4H)-one

[0622] The title compound was prepared according to the procedure described in Intermediate-66 by using *N*-(4-chloro-3-(1-(3-chloro-4-methylphenyl)-4,5-dihydro-5-oxo-1H-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide (0.400

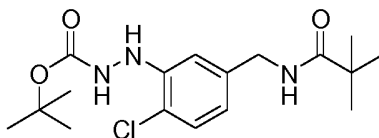
EP 2 718 284 B1

g), KOH (0.400 g), water (5 mL) and THF (10.0 mL) to afford 0.350 g of the desired product.

Intermediate-94

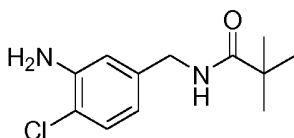
tert-Butyl 2-(2-chloro-5-[[2,2-dimethylpropanoyl]amino]methyl}phenyl) hydrazinecarboxylate

[0623]

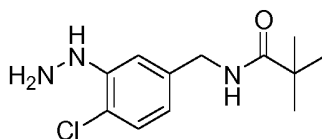


Step-1:- Preparation of N-(3-amino-4-chlorobenzyl)pivalamide

[0624]



The title compound was prepared according to the procedure described in step-2 of Intermediate-83 by using 5-(aminomethyl)-2-chlorobenzenamine (2.0 g), pivaloyl chloride (0.2 mL), TEA (2 mL) and THF(10 mL) to afford 2.0 g of the desired product. Step-2:- Preparation of N-(4-chloro-3-hydrazinylbenzyl)-2,2-dimethylpropanamide



The title compound was prepared according to the procedure described in step-1 of Intermediate-61 by using N-(3-amino-4-chlorobenzyl)pivalamide (1.80 g), NaNO₂ (0.62 g, 0.009 mmol), SnCl₂·2H₂O (4.2 g, 0.018 mmol) and conc. HCl (30 mL) to afford 1.5 g of the desired product.

Step-3:- Preparation of *tert*-butyl 2-(2-chloro-5-[[2,2-dimethylpropanoyl]amino]methyl} phenyl) hydrazinecarboxylate

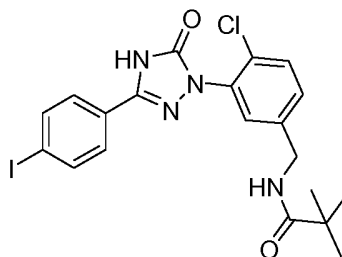
The title compound was prepared according to the procedure described in step-3 of Intermediate-7 by using N-(4-chloro-3-hydrazinylbenzyl)-2,2-dimethylpropanamide (1.5 g, 0.005 mmol), BOC anhydride (1.4 g, 0.006 mmol), Na₂CO₃ (0.922 g, 0.008 mmol), acetonitrile (30 mL) and water (5 mL) to afford 1.0 g of the desired product.

Intermediate-95

N-(4-Chloro-3-(4,5-dihydro-3-(4-iodophenyl)-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide

[0628]

EP 2 718 284 B1

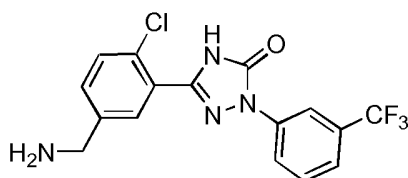


[0629] To a solution of *tert*-butyl 2-(2-chloro-5-[(2,2-dimethylpropanoyl)amino]methyl)phenyl hydrazine carboxylate (Intermediate-94, 0.450 g, 1.55 mmol) in DCM (20 mL) was added solution of 4-iodobenzoyl isocyanate (Intermediate-67, 0.500 g, 1.55 mmol) in DCM (10 mL) and the reaction mixture was stirred for 20 h at room temperature, followed by addition of trifluoro acetic acid (TFA, 3 mL) and further stirred for 20 h at same temperature. The reaction mass was quenched in water, extracted with DCM and concentrated to afford crude product which was purified by column chromatography eluting with MeOH: DCM to afford 0.180 g of the desired product.

Intermediate-96

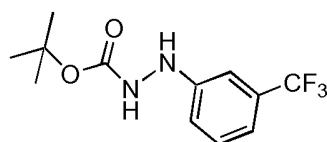
5-(5-(Aminomethyl)-2-chlorophenyl)-2-(3-(trifluoromethyl)phenyl)-2H-1,2,4-triazol-3(4H)-one

[0630]



Step1:- Preparation of *tert*-butyl 2-[3-(trifluoromethyl)phenyl]hydrazinecarboxylate

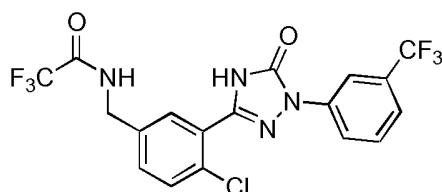
[0631]



[0632] The title compound was prepared according to the procedure described in step-3 of Intermediate-7 by using [3-(trifluoromethyl)phenyl]hydrazine hydrochloride (1.00 g, 0.0056 mol), BOC anhydride (1.4 g, 0.0067 mol), Na₂CO₃ (0.800 g, 0.008 mol), acetonitrile (10 mL) and water (2 mL) to afford 0.500 g of the desired product.

Step2:- Preparation of *N*-(4-chloro-3-(1-(3-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1H-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide

[0633]



[0634] The title compound was prepared according to the procedure described in Example-83 by using 2-chloro-

5-((2,2,2-trifluoroacetamido)methyl)benzoyl isocyanate (step-3 of Intermediate-26, 0.500 g, 1.55 mmol), *tert*-butyl 2-[3-(trifluoromethyl)phenyl]hydrazinecarboxylate (0.428 g, 1.55 mmol), DCM (20 mL) and trifluoro acetic acid (5.0 mL) to afford 0.400 g of the desired product.

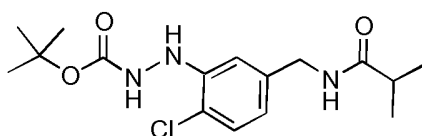
Step-3:- Preparation of 5-(5-(aminomethyl)-2-chlorophenyl)-2-(3-(trifluoromethyl)phenyl)-2*H*-1,2,4-triazol-3(4*H*)-one

[0635] The title compound was prepared according to the procedure described in Intermediate-66 by using *N*-(4-chloro-3-(1-(3-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide (0.400 g), KOH (0.200 g), water (2 mL) and THF (5.0 mL) to afford 0.200 g of the desired product.

Intermediate-97

tert-Butyl 2-(2-chloro-5-[[2-(methylpropanoyl)amino]methyl]phenyl)hydrazinecarboxylate

[0636]

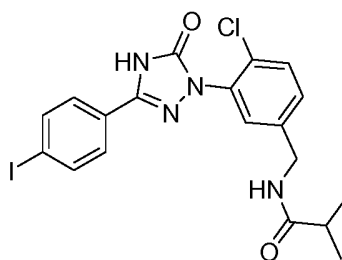


[0637] The title compound was prepared according to the procedure described in step-3 of Intermediate-7 by using *N*-(4-chloro-3-hydrazinylbenzyl)-2-methylpropanamide (2.5 g, 0.010 mol), BOC anhydride (2.5 g, 0.011 mol), Na₂CO₃ (1.6 g, 0.015 mol), acetonitrile (20 mL) and water (5 mL) to afford 1.500 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.03 (d, *J* = 6.6 Hz, 6H), 1.41 (s, 9H), 2.36-2.40 (m, 1H), 4.09 (d, *J* = 6.3 Hz, 1H), 4.15 (d, *J* = 5.4 Hz, 2H), 7.18 (d, *J* = 7.8 Hz, 2H), 7.32 (s, 1H), 8.24 (m, 2H); MS (*m/z*): 340.8 (M-H)⁻.

Intermediate-98

N-(4-Chloro-3-(4,5-dihydro-3-(4-iodophenyl)-5-oxo-1,2,4-triazol-1-yl)benzyl)isobutyramide

[0638]



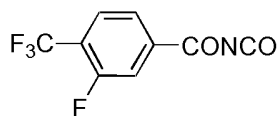
[0639] The title compound was prepared according to the procedure described in Example-83 by using 4-iodobenzoyl isocyanate (Intermediate-67, 1.500 g), *tert*-butyl 2-(2-chloro-5-[[2-(methylpropanoyl)amino]methyl]phenyl)hydrazinecarboxylate (Intermediate-97, 1.0 g), DCM (20 mL), and trifluoro acetic acid (5.0 mL) to afford 0.500 g of the desired product. ¹H NMR (400 MHz, DMSO *d*₆): δ 1.02 (d, *J* = 6.9 Hz, 6H), 2.44 (m, 1H), 4.28 (d, *J* = 8.7 Hz, 2H), 7.28 (br s, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.44 (s, 1H), 7.61 (d, *J* = 8.7 Hz, 1H), 7.91 (d, *J* = 8.1 Hz, 2H), 8.38 (m, 1H), 12.61 (m, 1H); MS (*m/z*): 495.7 (M-H)⁻.

Intermediate-99

3-Fluoro-4-(trifluoromethyl)benzoyl isocyanate

[0640]

EP 2 718 284 B1

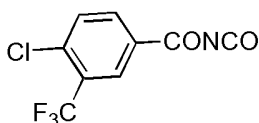


[0641] The title compound was prepared according to the procedure described in step-2 of Intermediate-8 by using 3-fluoro-4-(trifluoromethyl)benzamide (0.200 g), oxalyl chloride (0.025 mL) and EDC (15 mL) to afford 0.150 g of the desired product.

Intermediate-100

4-Chloro-3-(trifluoromethyl)benzoyl isocyanate

[0642]

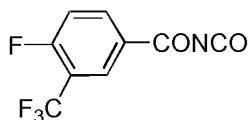


[0643] The title compound was prepared according to the procedure described in step-2 of Intermediate-8 by using 4-chloro-3-(trifluoromethyl)benzamide (0.200 g), oxalyl chloride (0.012 mL) and EDC (15 mL) to afford 0.150 g of the desired product.

Intermediate-101

4-Fluoro-3-(trifluoromethyl)benzoyl isocyanate

[0644]

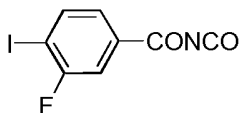


[0645] The title compound was prepared according to the procedure described in step-2 of Intermediate-8 by using 4-fluoro-3-(trifluoromethyl)benzamide (0.200 g), oxalyl chloride (0.012 mL) and EDC (15 mL) to afford 0.150 g of the desired product.

Intermediate-102

3-Fluoro-4-iodobenzoyl isocyanate

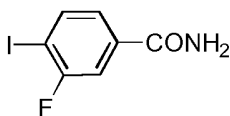
[0646]



Step-1:- Preparation of 3-fluoro-4-iodobenzamide

[0647]

EP 2 718 284 B1



[0648] To a solution of 3-fluoro-4-iodobenzonitrile (2.7 g, 0.010 mmol) in DMSO (6.0 mL), K_2CO_3 (0.450 g, 0.003 mmol) and 30% H_2O_2 (2.4 mL) were added at 0-10°C and the reaction mass was stirred at RT for 2 h. After completion of the reaction, the reaction mass was quenched in ice cold water. The obtained solid product was filtered off to afford 2.0 g of the desired title product. ^1H NMR (400 MHz, DMSO d_6): δ 7.48-7.51 (m, 2H), 7.66 (br s, 1H), 7.69-7.70 (m, 1H), 8.09 (brs, 1H).

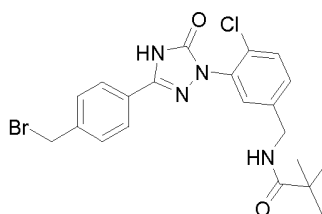
Step-2:- Preparation of 3-fluoro-4-iodobenzoyl isocyanate

[0649] The title compound was prepared according to the procedure described in step-2 of Intermediate-8 by using 3-fluoro-4-iodobenzamide (2.0 g), oxalyl chloride (0.120 mL) and EDC (25 mL) to afford 1.0 g of the desired product.

Intermediate-103

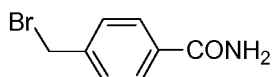
N-(3-(3-(4-(bromomethyl)phenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)-4-chlorobenzyl)pivalamide

[0650]



Step-1:-Preparation of 4-(bromomethyl)benzamide

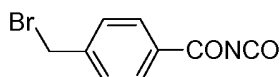
[0651]



[0652] Stirred the solution of 4-(bromomethyl)benzonitrile (1.5 g) in conc. H_2SO_4 at 100°C for 3-4 h. After completion of the reaction, the reaction mass was quenched in ice and filtered to afford 0.900 g of desired product. ^1H NMR (400 MHz, DMSO d_6): δ 4.71 (s, 2H), 7.26 (br s, 1H), 7.49 (d, J = 7.8 Hz, 2H), 7.82 (d, J = 7.8 Hz, 2H), 7.89 (br s, 1H); MS (m/z): 214.36 ($M+H$) $^+$.

Step-2:-Preparation of 4-(bromomethyl)benzoyl isocyanate

[0653]



[0654] The title compound was prepared according to the procedure described in step-2 of Intermediate-8 by using 4-(bromomethyl)benzamide (0.200 g), oxalyl chloride (0.012 mL) and EDC (15 mL) to afford 0.150 g of the desired product.

Step-3:- Preparation of *N*-(3-(3-(4-(bromomethyl)phenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)-4-chlorobenzyl)pivalamide

The title compound was prepared according to the procedure described in Example-83 by using 4-(bromomethyl)benzoyl isocyanate (0.150 g), *tert*-Butyl 2-(2-chloro-5-((2,2-dimethylpropanoyl)amino)methyl{phenyl}hydrazinecarboxylate (In-

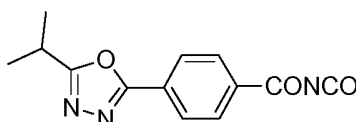
EP 2 718 284 B1

intermediate-94, 0.150 g), DCM (20 mL), and trifluoro acetic acid (5.0 mL) to afford 0.100 g of the desired product. ¹H NMR (400 MHz, DMSO *d*₆): δ 1.12 (s, 9H), 4.28 (br d, 2H), 4.75 (s, 2H), 7.34 (br d, 2H), 7.43 (br s, 1H), 7.60 (br d, 2H), 7.81 (br d, 2H), 8.17 (br s, 1H), 12.57 (s, 1H).

Intermediate-104

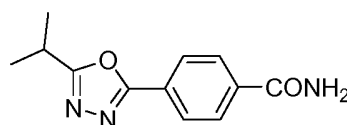
4-(5-isopropyl-1,3,4-oxadiazol-2-yl)benzoyl isocyanate

[0655]



Step1:- Preparation of 4-(5-isopropyl-1,3,4-oxadiazol-2-yl)benzamide

[0656]



[0657] The title compound was prepared according to the procedure described in step1 of Intermediate-59 by using 4-(5-isopropyl-1,3,4-oxadiazol-2-yl)benzonitrile (0.500 g, 2.34 mmol), 50% H₂O₂ (5.0 mL), K₂CO₃ (0.097 g, 0.070 mmol) to afford 0.250 g of desired product. ¹H NMR (400 MHz, DMSO *d*₆): δ 1.3(s, 3H), 1.35 (s, 3H), 3.33(m, 1H), 7.56 (br s, 1H), 8.06 (s, 4H), 8.16 (br s, 1H); MS (m/z): 232.30 (M+H)⁺.

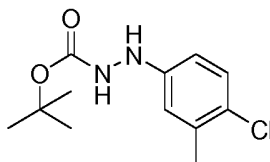
Step2:- Preparation of 4-(5-isopropyl-1,3,4-oxadiazol-2-yl)benzoyl isocyanate

[0658] The title compound was prepared according to the procedure described in step-2 of Intermediate-8 by using 4-(5-isopropyl-1,3,4-oxadiazol-2-yl)benzamide (0.200 g), oxalyl chloride (0.012 mL) and EDC (15 mL) to afford 0.150 g of the desired product.

Intermediate-105

tert-Butyl 2-(4-chloro-3-methylphenyl)hydrazinecarboxylate

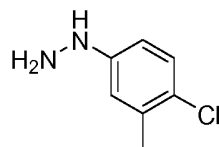
[0659]



Step-1:- Preparation of 1-(4-chloro-3-methylphenyl)hydrazine

[0660]

EP 2 718 284 B1



[0661] The title compound was prepared according to the procedure described in step-1 of Intermediate-61 by using *N*-(4-chloro-3-methylphenyl)hydrazine (2.0 g, 0.014 mmol), NaNO₂ (0.16 g, 0.0169 mmol), SnCl₂·2H₂O (7.93 g, 0.0352 mmol) and conc. HCl (30 mL) to afford 1.5 g of the desired product.

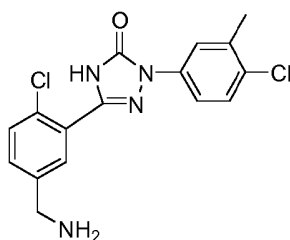
Step-2:- Preparation of *tert*-butyl 2-(4-chloro-3-methylphenyl)hydrazinecarboxylate

[0662] The title compound was prepared according to the procedure described in step-3 of Intermediate-7 by using 1-(4-chloro-3-methylphenyl)hydrazine (1.22 g, 0.011 mmol), BOC anhydride (2.0 g, 0.009 mmol), Na₂CO₃ (0.922 g, 0.008 mmol), acetonitrile (30 mL) and water (5 mL) to afford 1.0 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.40 (s, 9H), 2.21 (s, 3H), 6.49 (d, *J* = 8.4 Hz, 1H), 6.58 (s, 1H), 7.13 (d, *J* = 8.7 Hz, 1H), 7.65 (s, 1H), 8.78 (s, 1H).

Intermediate-106

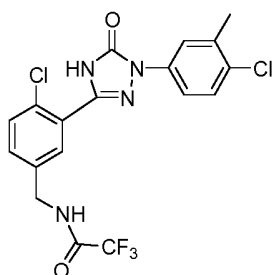
5-(5-(aminomethyl)-2-chlorophenyl)-2-(4-chloro-3-methylphenyl)-2*H*-1,2,4-triazol-3(4*H*)-one

[0663]



Step-1 :-Preparation of *N*-(4-chloro-3-(1-(4-chloro-3-methylphenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide

[0664]



[0665] The title compound was prepared according to the procedure described in Example-83 by using 2-chloro-5-((2,2,2-trifluoroacetamido)methyl)benzoyl isocyanate (step-3 of Intermediate-26, 1.0 g, 0.003 mmol), *tert*-butyl 2-(4-chloro-3-methylphenyl)hydrazinecarboxylate (Intermediate-105, 1.500 g), DCM (20 mL), and trifluoro acetic acid (5.0 mL) to afford 0.600 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 2.38 (s, 3H), 4.45 (d, *J* = 5.4 Hz, 2H), 7.53 (d, *J* = 9.3 Hz, 2H), 7.67 (s, 2H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.92 (s, 1H), 10.08 (t, 1H), 12.61 (s, 1H); MS (*m/z*): 445.31 (*M*+*H*)⁺.

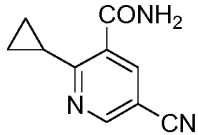
Step-2:- Preparation of 3-(5-(aminomethyl)-2-chlorophenyl)-1-(3-methoxy-4-nitrophenyl)-1*H*-1,2,4-triazol-5(4*H*)-one

[0666] The solution of *N*-(4-chloro-3-(1-(4-chloro-3-methylphenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide (0.550 g, 1.23 mmol) in 20% aq. KOH (20 mL) was stirred for 2-3 h at RT. Excess of solvent

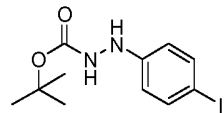
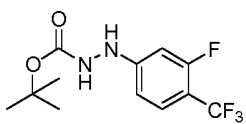
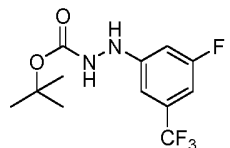
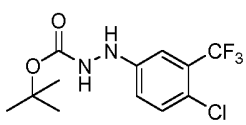
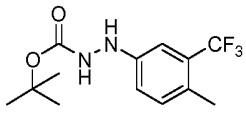
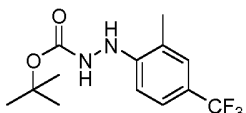
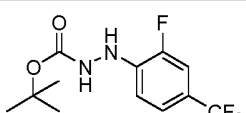
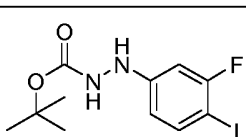
EP 2 718 284 B1

was removed under vacuum and filtered off remaining reaction mass to afford 0.400 g of desired product. MS (m/z): 349.34 (M)⁺.

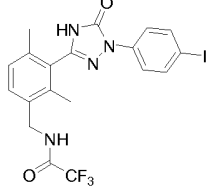
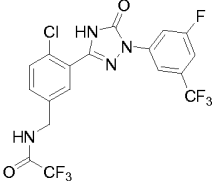
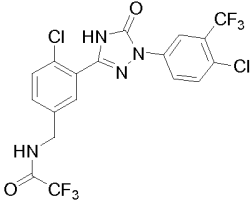
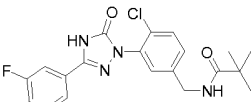
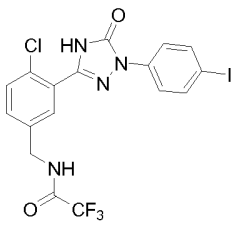
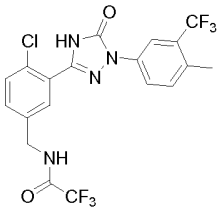
[0667] Intermediate-107 was prepared according to the procedure described for step-2 of Intermediate-26 by using 5-cyano-2-cyclopropylpyridine-3-carboxylic acid, oxalyl chloride, ammonia gas, DMF, THF and DCM.

No. & Chemical Structure	Chemical name and Characterization data
Intermediate-107 	5-cyano-2-cyclopropylpyridine-3-carboxamide. ¹ H NMR (300 MHz, DMSO <i>d</i> ₆): δ 107 (m, 4H), 2.49 (s, 1H), 7.82 (s, 1H), 8.13 (s, 1H), 8.20 (s, 2H), 8.87 (s, 1H); MS (m/z): 188.04 (M+H) ⁺ .

[0668] The Intermediate-108 to Intermediate-115 were prepared by following the procedure described for step-1 of Intermediate-61 by using corresponding amine, NaNO₂, SnCl₂·H₂O, 4N HCl and followed by following the procedure described for step-3 of Intermediate-7 using BOC anhydride, Na₂CO₃ in acetonitrile and water.

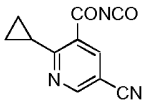
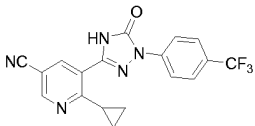
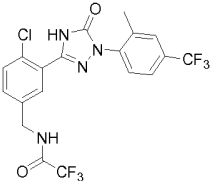
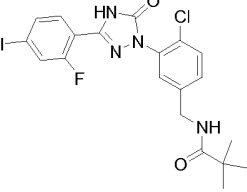
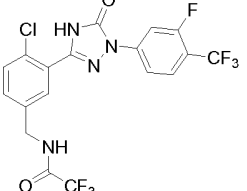
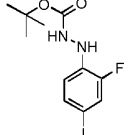
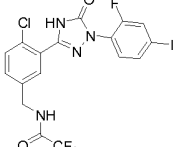
No.	Structure	Chemical name and Characterization data
Intermediate -108		<i>tert</i> -butyl 2-(4-iodophenyl)hydrazinecarboxylate. MS (m/z): 335.15 (M+H) ⁺ .
Intermediate -109		<i>tert</i> -butyl 2-[3-fluoro-4-(trifluoromethyl)phenyl]hydrazinecarboxylate. MS (m/z): 295.21 (M+H) ⁺ .
Intermediate -110		<i>tert</i> -butyl 2-[3-fluoro-5-(trifluoromethyl)phenyl]hydrazinecarboxylate. MS (m/z): 295.24 (M+H) ⁺ .
Intermediate -111		<i>tert</i> -butyl 2-[4-chloro-3-(trifluoromethyl)phenyl]hydrazinecarboxylate. ¹ H NMR (300 MHz, DMSO <i>d</i> ₆): δ 1.40 (s, 9H), 6.90 (d, <i>J</i> = 8.7 Hz, 1H), 7.01 (s, 1H), 7.45 (d, <i>J</i> = 9.0 Hz, 1H), 8.20 (s, 1H), 8.99 (br s, 1H).
Intermediate -112		<i>tert</i> -butyl 2-[4-methyl-3-(trifluoromethyl)phenyl]hydrazinecarboxylate. ¹ H NMR (300 MHz, DMSO <i>d</i> ₆): δ 1.40 (s, 9H), 2.28 (s, 3H), 6.80 (d, <i>J</i> = 8.4 Hz, 1H), 6.91 (s, 1H), 7.18 (d, <i>J</i> = 8.4 Hz, 1H), 7.84 (s, 1H), 8.88 (br s, 1H).
Intermediate -113		<i>tert</i> -butyl 2-[2-methyl-4-(trifluoromethyl)phenyl]hydrazinecarboxylate. MS (m/z): 291.12 (M+H) ⁺ .
Intermediate -114		<i>tert</i> -butyl 2-[2-fluoro-4-(trifluoromethyl)phenyl]hydrazinecarboxylate. ¹ H NMR (300 MHz, DMSO <i>d</i> ₆): δ 1.42 (s, 9H), 6.83 (t, 1H), 7.39 (d, <i>J</i> = 8.4 Hz, 1H), 7.44-7.48 (m, 1H), 8.28 (s, 1H), 9.03 (s, 1H).
Intermediate -115		<i>tert</i> -butyl 2-(3-fluoro-4-iodophenyl)hydrazinecarboxylate. MS (m/z): 351.14 (M-H) ⁻ .

[0669] The Intermediate-116 to Intermediate-128 was prepared by following the procedure described for Example-83 by using corresponding starting material mentioned in the table below, DCM and TFA.

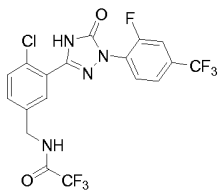
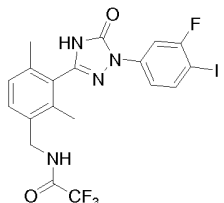
Starting material used	Intermediate No. and Structure	Intermediate chemical name and characterization data
Intermediate-65 + Intermediate-67	Intermediate-116 	<i>N</i> -(3-(4,5-dihydro-1-(4-iodophenyl)-5-oxo-1 <i>H</i> -1,2,4-triazol-3-yl)-2,4-dimethylbenzyl)-2,2,2-trifluoroacetamide. ¹ H NMR (300 MHz, DMSO <i>d</i> ₆): δ 2.19 (s, 3H), 2.21 (s, 3H), 4.41 (d, <i>J</i> = 4.8 Hz, 2H), 7.20 (d, <i>J</i> = 7.8 Hz, 1H), 7.29 (d, <i>J</i> = 7.8 Hz, 1H), 7.53-7.82 (m, 4H), 9.97 (s, 1H), 12.23 (s, 1H); MS (<i>m/z</i>): 517.301 (M+H) ⁺ .
Step 3 product of Intermediate-26 + Intermediate-110	Intermediate-117 	<i>N</i> -(4-chloro-3-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1 <i>H</i> -1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide. ¹ H NMR (300 MHz, DMSO <i>d</i> ₆): δ 4.46 (d, 2H), 7.51 (m, 1H), 7.60 (d, <i>J</i> = 9.3 Hz, 1H), 7.66-7.69 (m, 2H), 8.08 (d, <i>J</i> = 13.8 Hz, 1H), 8.16 (s, 1H), 10.09 (m, 1H), 12.84 (m, 1H).
Step-3 product of Intermediate-26 + Intermediate-111	Intermediate-118 	<i>N</i> -(4-chloro-3-(1-(4-chloro-3-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1 <i>H</i> -1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide. ¹ H NMR (300 MHz, DMSO <i>d</i> ₆): δ 4.46 (d, <i>J</i> = 6.0 Hz, 2H), 7.49 (d, <i>J</i> = 10.2 Hz, 1H), 7.67 (d, <i>J</i> = 8.4 Hz, 2H), 7.85 (d, <i>J</i> = 9.0 Hz, 1H), 8.24 (d, <i>J</i> = 8.7 Hz, 1H), 8.44 (s, 1H), 10.09 (t, 1H), 12.80 (s, 1H); MS (<i>m/z</i>): 499.31 (M+H) ⁺ .
Intermediate-94 + Intermediate-102	Intermediate-119 	<i>N</i> -(4-chloro-3-(3-(3-fluoro-4-iodophenyl)-4,5-dihydro-5-oxo-1 <i>H</i> -1,2,4-triazol-1-yl)benzyl)pivalamide. ¹ H NMR (300 MHz, DMSO <i>d</i> ₆): δ 1.12 (s, 9H), 4.28 (d, <i>J</i> = 8.4 Hz, 2H), 7.34 (d, <i>J</i> = 7.8 Hz, 1H), 7.43-7.49 (m, 2H), 7.59-7.67 (m, 2H), 8.02 (t, <i>J</i> = 7.2 Hz, 1H), 8.19 (t, 1H), 12.67 (s, 1H); MS (<i>m/z</i>): 529.05 (M+H) ⁺ .
Step-3 product of Intermediate-26 + Intermediate-67	Intermediate-120 	<i>N</i> -(4-chloro-3-(4,5-dihydro-1-(4-iodophenyl)-5-oxo-1 <i>H</i> -1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide. ¹ H NMR (300 MHz, DMSO <i>d</i> ₆): δ 4.44 (br s, 2H), 7.46-7.73 (m, 4H), 7.80 (s, 2H), 10.11 (s, 1H); MS (<i>m/z</i>): 523.09 (M+H) ⁺ .
Step-3 product of Intermediate-26 + Intermediate-112	Intermediate-121 	<i>N</i> -(4-chloro-3-(1-(3-(trifluoromethyl)-4-methylphenyl)-4,5-dihydro-5-oxo-1 <i>H</i> -1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide. ¹ H NMR (300 MHz, DMSO <i>d</i> ₆): δ 2.45 (s, 3H), 4.46 (d, <i>J</i> = 6.6 Hz, 2H), 7.49 (d, <i>J</i> = 7.8 Hz, 1H), 7.57 (d, <i>J</i> = 7.8 Hz, 1H), 7.68 (s, 2H), 8.10 (d, <i>J</i> = 8.7 Hz, 1H), 8.28 (s, 1H), 10.09 (br s, 1H), 12.69 (br s, 1H); MS (<i>m/z</i>): 476.91 (M+H) ⁺ .

EP 2 718 284 B1

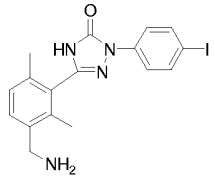
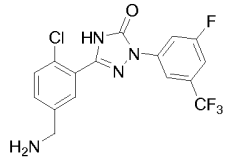
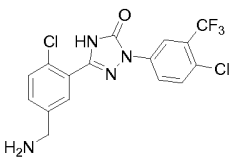
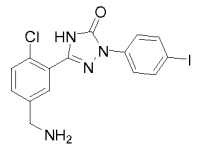
(continued)

Starting material used	Intermediate No. and Structure	Intermediate chemical name and characterization data
Intermediate-53 + 	Intermediate-122 	6-cyclopropyl-5-(1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1H-1,2,4-triazol-3-yl)pyridine-3-carbonitrile. ¹H NMR (300 MHz, DMSO <i>d</i>₆): δ 1.18 (m, 2H), 1.39 (m, 2H), 3.01 (m, 1H), 7.85 (d, <i>J</i> = 9.0 Hz, 2H), 8.20 (d, <i>J</i> = 7.8 Hz, 2H), 8.45 (s, 1H), 8.99 (s, 1H), 12.82 (br s, 1H); MS (<i>m/z</i>): 372.24 (M+H)⁺.
Step-3 product of Intermediate-26 + Intermediate-113	Intermediate-123 	<i>N</i>-(4-chloro-3-(1-(4-(trifluoromethyl)-2-methylphenyl)-4,5-dihydro-5-oxo-1H-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide. ¹H NMR (300 MHz, DMSO <i>d</i>₆): δ 2.39 (s, 3H), 4.44 (br d, 2H), 7.33-7.90 (m, 6H), 10.07 (br s, 1H), 12.51 (s, 1H); MS (<i>m/z</i>): 479.10 (M+H)⁺.
Intermediate-47 + Intermediate-94	Intermediate-124 	<i>N</i>-(4-chloro-3-(3-(2-fluoro-4-iodophenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide. ¹H NMR (300 MHz, DMSO <i>d</i>₆): δ 1.11 (s, 9H), 4.28 (d, <i>J</i> = 5.7 Hz, 2H), 7.34 (d, <i>J</i> = 8.4 Hz, 1H), 7.42 (s, 1H), 7.53-7.61 (m, 2H), 7.75 (d, <i>J</i> = 7.2 Hz, 1H), 7.89 (d, <i>J</i> = 9.3 Hz, 1H), 8.18 (t, 1H), 12.43 (s, 1H); MS (<i>m/z</i>): 529.0110 (M+H)⁺.
Step-3 product of Intermediate-26 + Intermediate-109	Intermediate-125 	<i>N</i>-(4-chloro-3-(1-(3-fluoro-4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1H-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide. ¹H NMR (300 MHz, DMSO <i>d</i>₆): δ 4.46 (d, <i>J</i> = 6.0 Hz, 2H), 7.50 (d, <i>J</i> = 8.7 Hz, 1H), 7.66 (s, 2H), 7.92-8.07 (m, 3H), 10.10 (t, 1H), 12.84 (m, 1H). <i>N</i>-(4-chloro-3-(1-(2-fluoro-4-iodophenyl)-4,5-
Step-3 product of Intermediate-26 + 	Intermediate-126 	dihydro-5-oxo-1H-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide. ¹H NMR (300 MHz, DMSO <i>d</i>₆): δ 4.44 (d, <i>J</i> = 5.1 Hz, 2H), 7.39-7.48 (m, 2H), 7.63 (br s, 2H), 7.74 (t, <i>J</i> = 8.4 Hz, 1H), 7.90 (d, <i>J</i> = 8.7 Hz, 1H), 10.08 (br s, 1H), 12.52 (s, 1H); MS (<i>m/z</i>): 540.98 (M+H)⁺.

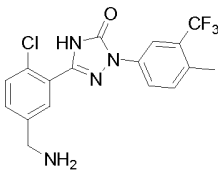
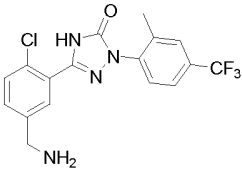
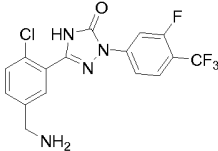
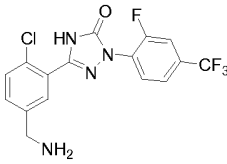
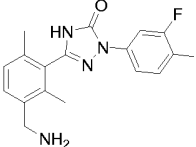
(continued)

Starting material used	Intermediate No. and Structure	Intermediate chemical name and characterization data
Step-3 product of Intermediate-26 + Intermediate-114	Intermediate-127 	<i>N</i> -(4-chloro-3-(1-(2-fluoro-4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1 <i>H</i> -1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide. ¹ H NMR (300 MHz, DMSO <i>d</i> ₆): δ 4.44 (m, 2H), 7.34 (s, 1H), 7.49 (m, 2H), 7.75 (d, <i>J</i> = 7.8 Hz, 1H), 7.79-7.98 (m, 2H), 10.10 (br s, 1H), 12.64 (m, 1H); MS (<i>m/z</i>): 483.12 (M+H) ⁺
Intermediate-65 + Intermediate-115	Intermediate-128 	<i>N</i> -(3-(1-(3-fluoro-4-iodophenyl)-4,5-dihydro-5-oxo-1 <i>H</i> -1,2,4-triazol-3-yl)-2,4-dimethylbenzyl)-2,2,2-trifluoroacetamide. MS (<i>m/z</i>): 535.01 (M+H) ⁺ .

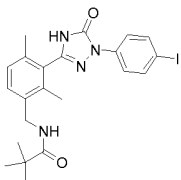
[0670] The Intermediate-129 to Intermediate-137 were prepared by following the procedure described in step-2 of Intermediate-106 by using corresponding starting material mentioned in the table below, KOH and water.

Starting material used	Intermediate No. and Structure	Intermediate chemical name and characterization data.
Intermediate-116	Intermediate-129 	5-(3-(aminomethyl)-2,6-dimethylphenyl)-2-(4-iodophenyl)-2 <i>H</i> -1,2,4-triazol-3(4 <i>H</i>)-one. ¹ H NMR (300 MHz, DMSO <i>d</i> ₆): δ 2.10 (s, 3H), 2.12 (s, 3H), 3.13 (br s, 2H), 3.66 (s, 2H), 6.98 (d, <i>J</i> = 8.4 Hz, 1H), 7.21 (d, <i>J</i> = 8.1 Hz, 1H), 7.57 (d, <i>J</i> = 8.1 Hz, 2H), 7.90 (d, <i>J</i> = 8.7 Hz, 2H).
Intermediate-117	Intermediate-130 	5-(5-(aminomethyl)-2-chlorophenyl)-2-(3-fluoro-5-(trifluoromethyl)phenyl)-2 <i>H</i> -1,2,4-triazol-3(4 <i>H</i>)-one
Intermediate-118	Intermediate-131 	5-(5-(aminomethyl)-2-chlorophenyl)-2-(4-chloro-3-(trifluoromethyl)phenyl)-2 <i>H</i> -1,2,4-triazol-3(4 <i>H</i>)-one
Intermediate-120	Intermediate-132 	5-(5-(aminomethyl)-2-chlorophenyl)-2-(4-iodophenyl)-2 <i>H</i> -1,2,4-triazol-3(4 <i>H</i>)-one. ¹ H NMR (300 MHz, DMSO <i>d</i> ₆): δ 3.36 (br s, 2H), 3.80 (br s, 2H), 7.41 (m, 1H), 7.47 (m, 1H), 7.6-7.72 (m, 2H), 7.77 (s, 1H), 7.87-7.90 (m, 2H).

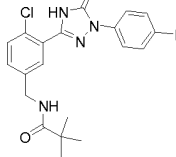
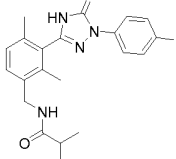
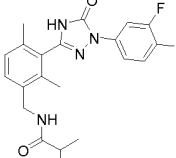
(continued)

Starting material used	Intermediate No. and Structure	Intermediate chemical name and characterization data.
Intermediate-121	Intermediate-133 	5-(5-(aminomethyl)-2-chlorophenyl)-2-(3-(trifluoromethyl)-4-methylphenyl)-2 <i>H</i> -1,2,4-triazol-3(4 <i>H</i>)-one. MS (m/z): 381.01 (M-H) ⁻ .
Intermediate-123	Intermediate-134 	5-(5-(aminomethyl)-2-chlorophenyl)-2-(4-(trifluoromethyl)-2-methylphenyl)-2 <i>H</i> -1,2,4-triazol-3(4 <i>H</i>)-one. MS (m/z): 383.15 (M+H) ⁺ .
Intermediate-125	Intermediate-135 	5-(5-(aminomethyl)-2-chlorophenyl)-2-(3-fluoro-4-(trifluoromethyl)phenyl)-2 <i>H</i> -1,2,4-triazol-3(4 <i>H</i>)-one. MS (m/z): 387.21 (M+H) ⁺ .
Intermediate-127	Intermediate-136 	5-(5-(aminomethyl)-2-chlorophenyl)-2-(2-fluoro-4-(trifluoromethyl)phenyl)-2 <i>H</i> -1,2,4-triazol-3(4 <i>H</i>)-one. MS (m/z): 387.06 (M+H) ⁺ .
Intermediate-128	Intermediate-137 	5-(3-(aminomethyl)-2,6-dimethylphenyl)-2-(3-fluoro-4-iodophenyl)-2 <i>H</i> -1,2,4-triazol-3(4 <i>H</i>)-one. MS (m/z): 439.24 (M+H) ⁺ .

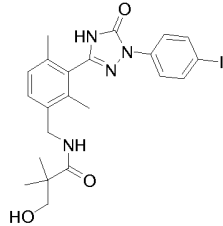
[0671] The Intermediate-138 to Intermediate-141 were prepared by following the procedure described in Example-108 by using corresponding starting material mentioned in the table below, TEA and THF.

Starting material used	Intermediate No. and Structure	Intermediate chemical name and characterization data
Intermediate-129 + Pivaloyl chloride	Intermediate-138 	<i>N</i> -(3-(4,5-dihydro-1-(4-iodophenyl)-5-oxo-1 <i>H</i> -1,2,4-triazol-3-yl)-2,4-dimethylbenzyl)pivalamide. ¹ H NMR (300 MHz, DMSO <i>d</i> ₆): δ 1.19 (s, 9H), 2.15 (s, 3H), 2.19 (s, 3H), 4.22 (d, 2H), 7.17-7.21 (m, 2H), 7.79 (m, 4H), 8.00 (m, 1H), 12.00 (s, 1H).

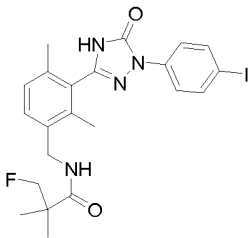
(continued)

Starting material used	Intermediate No. and Structure	Intermediate chemical name and characterization data
Intermediate-132 + Pivaloyl chloride	Intermediate-139 	<i>N</i> -(4-chloro-3-(4,5-dihydro-1-(4-iodophenyl)-5-oxo-1 <i>H</i> -1,2,4-triazol-3-yl)benzyl)pivalamide. ¹ H NMR (300 MHz, DMSO <i>d</i> ₆): δ 1.13 (s, 9H), 4.29 (d, <i>J</i> = 5.4 Hz, 2H), 7.41 (d, <i>J</i> = 8.4 Hz, 1H), 7.59 (s, 2H), 7.80 (q, <i>J</i> = 6.3 Hz, 4H), 8.19 (m, 1H), 12.59 (s, 1H); MS (<i>m/z</i>): 511.16 (M+H) ⁺ .
Intermediate-129 + Isopropyl chloride	Intermediate-140 	<i>N</i> -(3-(4,5-dihydro-1-(4-iodophenyl)-5-oxo-1 <i>H</i> -1,2,4-triazol-3-yl)-2,4-dimethylbenzyl)isobutyramide. ¹ H NMR (300 MHz, DMSO <i>d</i> ₆): δ 1.23 (s, 3H), 1.35 (s, 3H), 2.06 (s, 3H), 2.20 (s, 3H), 4.23 (br s, 2H), 7.08 (d, <i>J</i> = 7.8 Hz, 1H), 7.20 (d, <i>J</i> = 7.5 Hz, 1H), 7.74 (d, <i>J</i> = 8.7 Hz, 2H), 7.85 (d, <i>J</i> = 8.1 Hz, 2H), 8.17 (t, 1H).
Intermediate-137 + Isopropyl chloride	Intermediate-141 	<i>N</i> -(3-(1-(3-fluoro-4-iodophenyl)-4,5-dihydro-5-oxo-1 <i>H</i> -1,2,4-triazol-3-yl)-2,4-dimethylbenzyl)isobutyramide. MS (<i>m/z</i>): 509.02 (M+H) ⁺ .

[0672] The Intermediate-142 was prepared by following the procedure described in Example-107 by using Intermediate-129, THF, DMF, 3-methoxy-2,2-dimethylpropanoic acid, TBTU and TEA.

Starting material used	Intermediate No. and Structure	Intermediate chemical name and characterization data
Intermediate-129	Intermediate-142 	<i>N</i> -(3-(4,5-dihydro-1-(4-iodophenyl)-5-oxo-1 <i>H</i> -1,2,4-triazol-3-yl)-2,4-dimethylbenzyl)-3-hydroxy-2,2-dimethylpropanamide. ¹ H NMR (300 MHz, DMSO <i>d</i> ₆): δ 1.08 (m, 6H), 2.15 (s, 3H), 2.19 (s, 3H), 3.41 (m, 2H), 4.25 (d, 2H), 4.92 (m, 1H), 6.93 (d, <i>J</i> = 6.9 Hz, 1H), 7.15 (d, <i>J</i> = 8.7 Hz, 1H), 7.28 (d, <i>J</i> = 8.1 Hz, 1H), 7.79 (s, 3H), 7.92 (t, 1H), 12.25 (s, 1H); MS (<i>m/z</i>): 521.18 (M+H) ⁺ .

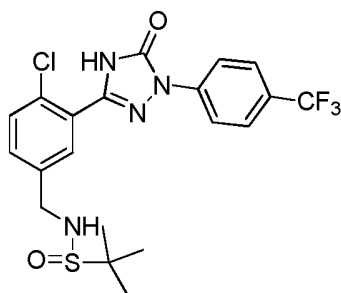
[0673] The Intermediate-143 was prepared by following the procedure described in step-2 of Example-134 by using Intermediate-142, DAST and THF.

Starting material used	Intermediate No and Structure	Intermediate chemical name and characterization data
Intermediate-142	Intermediate-143 	<i>N</i> -(3-(4,5-dihydro-1-(4-iodophenyl)-5-oxo-1 <i>H</i> -1,2,4-triazol-3-yl)-2,4-dimethylbenzyl)-3-fluoro-2,2-dimethylpropanamide. ¹ H NMR (300 MHz, DMSO <i>d</i> ₆): δ 1.08 (m, 6H), 2.15 (s, 3H), 2.19 (s, 3H), 3.34 (m, 2H), 4.25 (d, 2H), 6.91 (m, 1H), 7.15 (m, 1H), 7.25-7.27 (m, 1H), 7.79 (s, 3H), 8.08 (s, 1H), 12.24 (s, 1H); MS (<i>m/z</i>): 521.03 (<i>M</i> + <i>H</i>) ⁺ .

Intermediate-144

N-(4-Chloro-3-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)-2-methylpropane-2-sulfonamide

[0674]

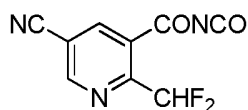


[0675] The title compound was prepared according to the procedure described in Example-108 by using 3-(5-(aminomethyl)-2-chlorophenyl)-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,4-triazol-5(4*H*)-one (Intermediate-63, 0.450 g, 1.22 mmol), 2-methylpropane-2-sulfinic chloride (0.205 g, 1.46 mmol), TEA (2.0 mL), DCM (10 mL) to afford 0.250 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.23 (s, 9H), 4.24 (m, 2H), 7.63-7.87 (m, 4H), 7.86 (d, *J* = 8.7 Hz, 2H), 8.19 (d, *J* = 9.0 Hz, 2H); MS (*m/z*): 472.095 (*M*+*H*)⁺.

Intermediate-145

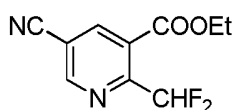
5-Cyano-2-(difluoromethyl)nicotinoyl isocyanate

[0676]



Step-1 :- Preparation of ethyl 5-cyano-2-(difluoromethyl)nicotinate

[0677]

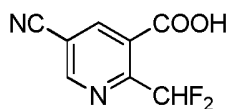


EP 2 718 284 B1

[0678] The title compound was prepared according to the procedure described in step-2 of Example-134 by using ethyl 5-cyano-2-formylnicotinate (6.0 g, 0.029 mmol), DAST (11.8 mL, 0.088 mmol), DCM (200 mL) to afford 3.5 g of desired product. MS (m/z): 227.06 (M+H)⁺.

Step-2 :-Preparation of 5-cyano-2-(difluoromethyl)nicotinic acid

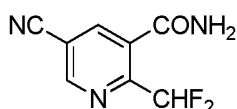
[0679]



[0680] To a solution of ethyl 5-cyano-2-(difluoromethyl)nicotinate (1.2 g, 5.3 mmol) in THF : water (20 mL : 5 mL) was added LiOH.H₂O (0.267 g, 6.3 mmol) at 0°C and the reaction mass was stirred for 40-60 minutes. The reaction mass was acidified with dil. HCl and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulphate and concentrated to afford 0.700 g of the desired product. ¹H NMR (300 MHz, DMSO d₆): δ 7.37-7.72 (t, J = 53.7 Hz, 1H), 8.24 (s, 1H), 9.30 (s, 1H), 14.25 (br s, 1H); MS (m/z): 199.34 (M+H)⁺.

Step-3 :-Preparation of 5-cyano-2-(difluoromethyl)nicotinamide

[0681]



[0682] To a solution of 5-cyano-2-(difluoromethyl)nicotinic acid (0.600 g, 3.0 mmol) in dry DMF (20 mL), TBTU (10.0 g, 3.33 mmol) was added at 0°C followed by slow addition of DIPEA (0.7 mL, 3.93 mmol). The reaction mass was stirred at 0°C for 1 h and ammonium chloride (3.33 g, 60.7 mmol) was added. The reaction mass was stirred at RT for 30-48 h. After completion of reaction quenched the reaction mass with DCM, filtered off solid to afford 0.500 g of the desired product. ¹H NMR (300 MHz, DMSO d₆): δ 8.16 (m, 1H), 8.63 (s, 1H), 9.22 (s, 1H).

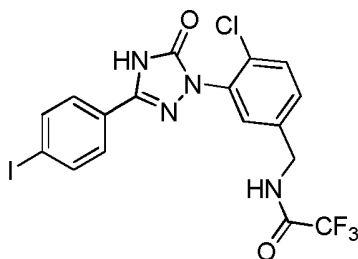
Step-4:- Preparation of 5-cyano-2-(difluoromethyl)nicotinoyl isocyanate

[0683] The title compound was prepared according to the procedure described in step-2 of Intermediate-8 by using 5-cyano-2-(difluoromethyl)nicotinamide (1.0 g), oxalyl chloride (3.2 g, 25.3 mmol) and DCM (20 mL) to afford 1.0 g of the desired product.

Intermediate-146

N-(4-Chloro-3-(3-(4-iodophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)-2,2,2-trifluoroacetamide

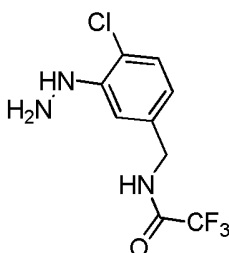
[0684]



EP 2 718 284 B1

Step-1:- Preparation *N*-(4-chloro-3-hydrazinylbenzyl)-2,2,2-trifluoroacetamide

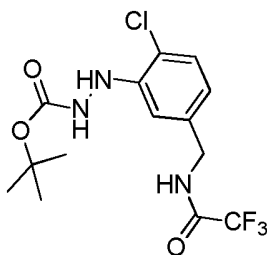
[0685]



[0686] To a cold solution of *N*-(3-amino-4-chlorobenzyl)-2,2,2-trifluoroacetamide (0.500 g, 0.017 mmol) in 6N HCl (50.0 mL), aqueous solution of NaNO₂ (1.29 g, 0.018 mmol) was added at 0°C and the reaction mass was stirred at 0-5°C for 30 min. The reaction mass was added to a solution of SnCl₂·H₂O (22.18 g, 0.98 mmol) in 6N HCl at 0-5°C and further continued stirring for 5-6 h at same temperature. The reaction mass was cooled, basified and extracted with DCM. The organic layer was separated, dried and concentrated to afford 0.700 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 4.22 (br s, 2H), 4.29 (d, *J* = 6.0 Hz, 2H), 6.42-6.67 (m, 2H), 7.14-7.16 (m, 2H), 9.98 (br s, 1H).

Step-2:- Preparation *tert*-butyl 2-(2-chloro-5-((2,2,2-trifluoroacetamido)methyl)phenyl) hydrazinecarboxylate

[0687]



[0688] The title compound was prepared according to the procedure described in step-3 of Intermediate-7 by using *N*-(4-chloro-3-hydrazinylbenzyl)-2,2,2-trifluoroacetamide (0.350 g, 1.3 mmol), BOC anhydride (0.316 g, 1.4 mmol), Na₂CO₃ (1.19 g, 1.9 mmol), acetonitrile (20 mL) and water (10 mL) to afford 0.500 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.41 (s, 9H), 4.28 (d, *J* = 5.7 Hz, 2H), 6.61-6.65 (m, 2H), 7.22 (d, *J* = 8.1 Hz, 1H), 7.41 (s, 1H), 9.91 (s, 1H), 9.97 (s, 1H).

Step-3:- Preparation of *N*-(4-chloro-3-(4,5-dihydro-3-(4-iodophenyl)-5-oxo-1,2,4-triazol-1-yl)benzyl)isobutyramide

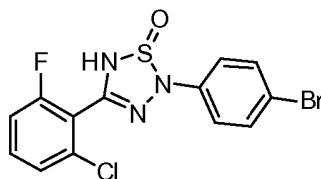
[0689] The title compound was prepared according to the procedure described in Example-83 by using 4-iodobenzoyl isocyanate (Intermediate-67, 1.500 g), *tert*-butyl 2-(2-chloro-5-((2,2,2-trifluoroacetamido)methyl)phenyl) hydrazinecarboxylate (1.0 g), DCM (20 mL), and trifluoro acetic acid (5.0 mL) to afford 0.500 g of the desired product. ¹H NMR (400 MHz, DMSO *d*₆): δ 4.44 (d, *J* = 6.0 Hz, 2H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.52 (s, 1H), 7.60-7.67 (m, 2H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 8.7 Hz, 2H), 10.09 (br s, 1H), 12.63 (s, 1H).

Examples

Comparative Example-1 2-(4-Bromophenyl)-4-(2-chloro-6-fluorophenyl)-2,5-dihydro-1,2,3,5-thiadiazole-1-oxide

[0690]

EP 2 718 284 B1

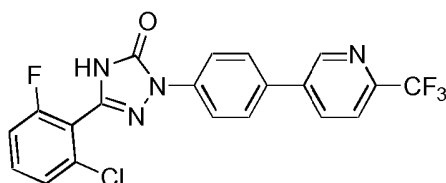


[0691] The title compound was prepared according to the procedure described in step-4 of Intermediate-1 using *N'*-(4-bromophenyl)-2-chloro-6-fluorobenzenecarbohydrazonamide (step-3 of Intermediate-1, 0.100 g, 0.292 mmol), CHCl_3 (10 mL), pyridine (2.0 mL) and thionyl chloride (1.0 mL). The obtained product was purified with column chromatography on silica gel eluting with 0.5 % MeOH: DCM to afford 0.050 g of the desired product. ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 7.45 (t, J = 6.9 Hz, 3H), 7.51-7.68 (m, 4H), 12.05 (br s, 1H); MS (m/z): 388.02 (M) $^-$.

Comparative Example-2

5-(2-Chloro-6-fluorophenyl)-2-{4-[6-(trifluoromethyl)pyridin-3-yl]phenyl}-2,4-dihydro-3*H*-1,2,4-triazol-3-one

[0692]

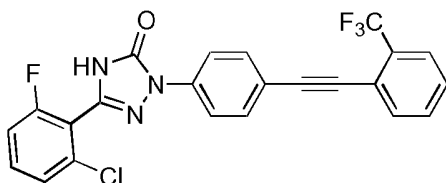


[0693] To a solution of 2-(4-bromophenyl)-5-(2-chloro-6-fluorophenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Intermediate-1, 0.100 g, 0.271 mmol) in DMSO (3.0 mL) was added [6-(trifluoromethyl)pyridin-3-yl]boronic acid (0.078 g, 0.40 mmol), K_2CO_3 (0.112 g, 0.81 mmol) and tetrakis(triphenyl)phosphine palladium (0) (0.062 g, 0.054 mmol). The reaction mass was stirred at 110°C for 24-48 h. The reaction mass was quenched in water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and concentrated. The obtained product was purified with column chromatography on silica gel eluting with 4-5 % EA: DCM to afford 0.030 g of the desired product. ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 7.38-7.48 (m, 1H), 7.61-7.63 (m, 1H), 7.88-7.99 (m, 4H), 8.01-8.17 (m, 2H), 8.41 (d, J = 7.8 Hz, 1H), 9.14 (s, 1H), 12.60 (br s, 1H). MS (m/z): 435.25 (M+H) $^+$.

Comparative Example-3

5-(2-Chloro-6-fluorophenyl)-2-(4-{[2-(trifluoromethyl)phenyl]ethynyl}phenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one

[0694]

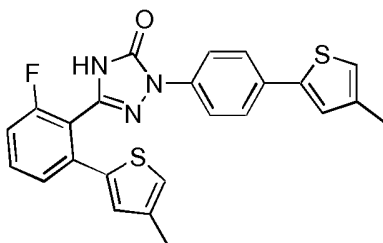


[0695] To a solution of 5-(2-chloro-6-fluorophenyl)-2-(4-ethynylphenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Intermediate-2, 0.100 g, 0.319 mmol) in DMSO was added 1-iodo-2-(trifluoromethyl)benzene (0.13 g, 0.479 mmol), TBAF (0.301 g, 0.958 mmol) and bis(triphenylphosphine)palladium(II) chloride (0.050 g, 0.071 mmol). The reaction mass was stirred at 110°C for 5-6 h. The reaction mass was quenched in water and extracted with DCM and concentrated. The obtained product was purified with column chromatography on silica gel eluting with 2.0 % EA: DCM to afford 0.040 g of the desired product. ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 7.50 (t, J = 9.3 Hz, 1H), 7.57-7.73 (m, 6H), 7.82 (br s, 2H), 8.02 (d, J = 8.7 Hz, 2H), 12.72 (br s, 1H). MS (m/z): 458.26 (M+H) $^+$.

Comparative Example-4

5-[2-Fluoro-6-(4-methylthiophen-2-yl)phenyl]-2-[4-(4-methylthiophen-2-yl)phenyl]-2,4-dihydro-3H-1,2,4-triazol-3-one

5 [0696]

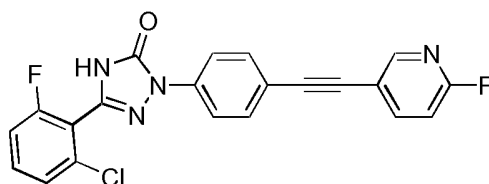


[0697] The title compound was prepared according to the procedure described in Example-2 using 2-(4-bromophenyl)-5-(2-chloro-6-fluorophenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (Intermediate-1, 0.100 g, 0.271 mmol), (4-methylthiophen-2-yl)boronic acid (0.059 g, 0.407 mmol), K_2CO_3 (0.112 g, 0.81 mmol), tetrakis(triphenyl phosphine) palladium (0) (0.062 g, 0.054 mmol) and DMSO (3.0 mL) to afford 0.020 g of desired product. ^1H NMR (300 MHz, $CDCl_3$): δ 2.29 (s, 6H), 6.86 (s, 1H), 6.91 (s, 2H), 7.13 (s, 1H), 7.21 (d, J = 9.3 Hz, 1H), 7.39 (d, J = 7.8 Hz, 1H), 7.48-7.55 (m, 1H), 7.61 (d, J = 8.1 Hz, 2H), 7.92 (d, J = 9.0 Hz, 2H), 9.27 (br s, 1H). MS (m/z): 384.88 (M-H) $^-$.

Comparative Example-5

5-(2-Chloro-6-fluorophenyl)-2-{4-[(6-fluoropyridin-3-yl)ethynyl]phenyl}-2,4-dihydro-3H-1,2,4-triazol-3-one

[0698]

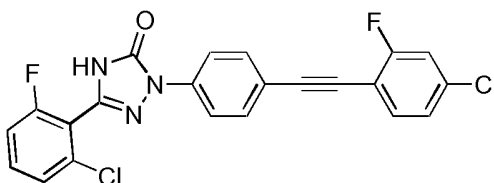


[0699] The title compound was prepared according to the procedure described in Example-3 using 5-(2-chloro-6-fluorophenyl)-2-(4-ethynylphenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (Intermediate-2, 0.100 g, 0.319 mmol), 2-fluoro-5-iodopyridine (0.106 g, 0.479 mmol), TBAF (0.201 g, 0.638 mmol), bis(triphenylphosphine)palladium(II) chloride (0.020 g, 0.028 mmol) and DMSO (3.0 mL). The obtained product was purified with column chromatography on silica gel eluting with 2.0 % MeOH: DCM to afford 0.030 g of the desired product. ^1H NMR (300 MHz, DMSO d_6): δ 7.30 (d, J = 7.5 Hz, 1H), 7.51 (t, J = 8.7 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.70 (d, J = 8.1 Hz, 3H), 8.03 (d, J = 8.4 Hz, 2H), 8.20 (t, J = 7.2 Hz, 1H), 8.49 (s, 1H), 12.73 (br s, 1H). MS (m/z): 407.33 (M-H) $^-$.

Comparative Example-6

5-(2-Chloro-6-fluorophenyl)-2-4-[(4-chloro-2-fluorophenyl)ethynyl]phenyl-2,4-dihydro-3H-1,2,4-triazol-3-one

[0700]

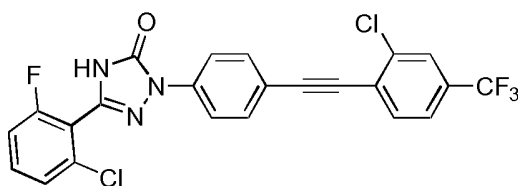


[0701] The title compound was prepared according to the procedure described in Example-3 using 5-(2-chloro-6-fluorophenyl)-2-(4-ethynylphenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Intermediate-2, 0.100 g, 0.319 mmol), 4-chloro-2-fluoro-1-iodobenzene (0.123 g, 0.479 mmol), TBAF (0.201 g, 0.638 mmol), bis(triphenylphosphine)palladium(II) chloride (0.020 g, 0.028 mmol) and DMSO (3.0 ml). The obtained crude product was purified with column chromatography on silica gel eluting with 1.0 % MeOH: DCM to afford 0.045 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 7.38 (d, *J* = 8.4 Hz, 1H), 7.50 (t, *J* = 8.7 Hz, 1H), 7.57-7.70 (m, 6H), 8.02 (d, *J* = 8.7 Hz, 2H), 12.74 (br s, 1H). MS (*m/z*): 442.38 (*M*⁺).

Comparative Example-7

5-(2-Chloro-6-fluorophenyl)-2-(4-{[2-chloro-4-(trifluoromethyl)phenyl]ethynyl}phenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one

[0702]

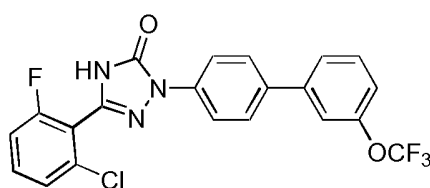


[0703] The title compound was prepared according to the procedure described in Example-3 using 5-(2-chloro-6-fluorophenyl)-2-(4-ethynylphenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Intermediate-2, 0.100 g, 0.319 mmol), 2-chloro-1-iodo-4-(trifluoromethyl)benzene (0.147 g, 0.479 mmol), TBAF (0.201 g, 0.638 mmol), bis(triphenylphosphine)palladium(II) chloride (0.020 g, 0.028 mmol) and DMSO (3.0 mL). The obtained product was purified with column chromatography on silica gel eluting with 1.0 % MeOH: DCM to afford 0.040 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 7.51 (d, *J* = 8.7 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.67-7.87 (m, 3H), 7.84 (t, *J* = 8.4 Hz, 2H), 8.05 (d, *J* = 8.4 Hz, 2H), 8.11 (s, 1H), 12.75 (br s, 1H). MS (*m/z*): 492.22 (*M*⁺).

Comparative Example-8

5-(2-Chloro-6-fluorophenyl)-2-[3'-(trifluoromethoxy)biphenyl-4-yl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one

[0704]

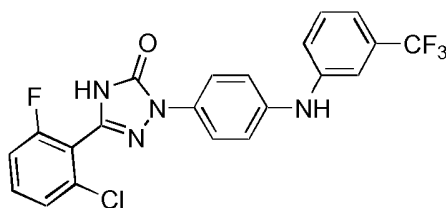


[0705] The title compound was prepared according to the procedure described in Example-2 using 5-(2-chloro-6-fluorophenyl)-2-(4-iodophenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (step-4 of Intermediate-2, 0.100 g, 0.242 mmol), [3-(trifluoromethoxy)phenyl]boronic acid (0.075 g, 0.363 mmol), K₂CO₃ (0.100 g, 0.726 mmol), tetrakis(triphenyl phosphine) palladium (0) (0.055 g, 0.048 mmol) and DMSO (3.0 mL) to afford 0.025 g of desired product. ¹H NMR (300 MHz, CDCl₃): δ 7.19 (d, *J* = 8.4 Hz, 1H), 7.35 (s, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 6.6 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 8.12 (d, *J* = 8.4 Hz, 2H), 10.01 (br s, 1H).

Comparative Example-9

5-(2-Chloro-6-fluorophenyl)-2-(4-{[3-(trifluoromethyl)phenyl]amino}phenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one

[0706]

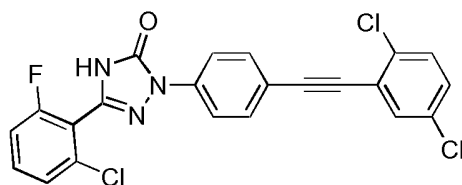


[0707] To a solution of 5-(2-chloro-6-fluorophenyl)-2-(4-iodophenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (step-4 of Intermediate-2, 0.100 g, 0.242 mmol) in toluene (5.0 mL) was added 3-(trifluoromethyl)aniline (0.076 g, 0.292 mmol), NaOtBu (0.035 g, 0.360 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.022 g, 0.024 mmol) and 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (0.021 g, 0.036 mmol). The reaction mixture was refluxed for 12 h. The reaction mass was quenched in water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and concentrated. The obtained product was purified with column chromatography on silica gel eluting with 10 % EA: DCM to afford 0.030 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 7.09 (d, *J* = 7.5 Hz, 1H), 7.20 (s, 1H), 7.24 (d, *J* = 5.7 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 1H), 7.41-7.59 (m, 3H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.81 (d, *J* = 8.7 Hz, 2H), 8.64 (s, 1H), 12.51 (s, 1H). MS (*m/z*): 449.31 (M+H)⁺.

Comparative Example-10

5-(2-Chloro-6-fluorophenyl)-2-{4-[(2,5-dichlorophenyl)ethynyl]phenyl}-2,4-dihydro-3H-1,2,4-triazol-3-one

[0708]

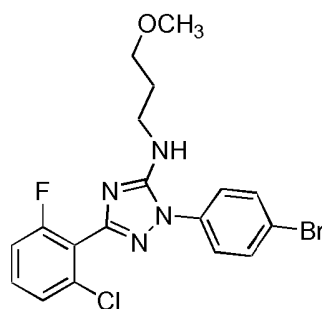


[0709] The title compound was prepared according to the procedure described in Example-3 using 5-(2-chloro-6-fluorophenyl)-2-(4-ethynylphenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (Intermediate-2, 0.100 g, 0.319 mmol), 1,4-dichloro-2-iodobenzene (0.130 g, 0.470 mmol), TBAF (0.201 g, 0.638 mmol), bis(triphenylphosphine)palladium(II) chloride (0.020 g, 0.028 mmol) and DMSO (3.0 mL). The obtained product was purified with column chromatography on silica gel eluting with 1.0 % MeOH: DCM to afford 0.040 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 7.50-7.72 (m, 7H), 7.82 (s, 1H), 8.05 (d, *J* = 8.7 Hz, 2H), 12.75 (br s, 1H). MS (*m/z*): 458.31 (M+).

Comparative Example-11

1-(4-Bromophenyl)-3-(2-chloro-6-fluorophenyl)-N-(3-methoxypropyl)-1H-1,2,4-triazol-5-amine

[0710]



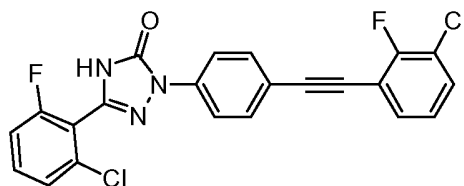
[0711] To a solution of 1-(4-bromophenyl)-5-chloro-3-(2-chloro-6-fluorophenyl)-1H-1,2,4-triazole (Intermediate-3, 0.100 g, 0.257 mmol) in DMF (3.0 mL) was added 3-methoxypropan-1-amine (0.035 g, 0.386 mmol) and DIPEA (1.0

mL). The reaction mass was stirred at 80°C for 5-6 h. The reaction mass was quenched in water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and concentrated to afford 0.040 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.92 (d, *J* = 5.4 Hz, 2H), 2.34 (t, *J* = 7.5 Hz, 2H), 3.28 (s, 3H), 3.56-3.64 (m, 2H), 5.69 (m, 1H), 7.06-7.15 (m, 1H), 7.22-7.49 (m, 2H), 7.54 (d, *J* = 10.2 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 2H). MS (*m/z*): 441.19 (M+H)⁺.

Comparative Example-12

1-(4-((3-Chloro-2-fluorophenyl)ethynyl)phenyl)-3-(2-chloro-6-fluorophenyl)-1*H*-1,2,4-triazol-5(4*H*)-one

[0712]

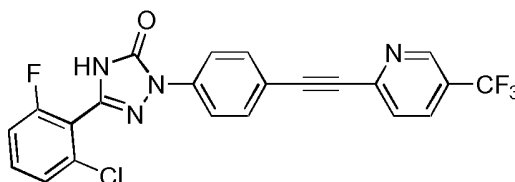


[0713] The title compound was prepared according to the procedure described in Example-3 using 5-(2-chloro-6-fluorophenyl)-2-(4-ethynylphenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Intermediate-2, 0.100 g, 0.319 mmol), 1-chloro-2-fluoro-3-iodobenzene (0.123 g, 0.470 mmol), TBAF (0.201 g, 0.638 mmol), bis(triphenylphosphine)palladium(II) chloride (0.020 g, 0.028 mmol) and DMSO (3.0 mL). The obtained product was purified with column chromatography on silica gel eluting with 1.0 % MeOH: DCM to afford 0.040 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 7.29 (t, *J* = 7.8 Hz, 1H), 7.50 (t, *J* = 8.7 Hz, 1H), 7.57-7.72 (m, 6H), 8.04 (d, *J* = 9.0 Hz, 2H), 12.74 (br s, 1H). MS (*m/z*): 442.35 (M⁺).

Comparative Example-13

5-(2-Chloro-6-fluorophenyl)-2-(4-[[5-(trifluoromethyl)pyridin-2-yl]ethynyl]phenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one

[0714]

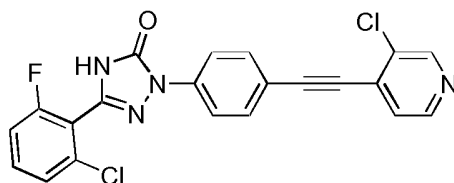


[0715] The title compound was prepared according to the procedure described in Example-3 using 5-(2-chloro-6-fluorophenyl)-2-(4-ethynylphenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Intermediate-2, 0.100 g, 0.319 mmol), 2-bromo-5-(trifluoromethyl)pyridine (0.108 g, 0.479 mmol), TBAF (0.201 g, 0.638 mmol), bis(triphenylphosphine)palladium(II) chloride (0.020 g, 0.028 mmol) and DMSO (3.0 mL). The obtained product was purified with column chromatography on silica gel eluting with 1.0 % MeOH: DCM to afford 0.030 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 7.51 (t, *J* = 8.7 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.70 (t, *J* = 6.3 Hz, 1H), 7.79 (d, *J* = 8.7 Hz, 2H), 7.89 (d, *J* = 8.1 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 2H), 8.29 (d, *J* = 7.8 Hz, 1H), 9.00 (s, 1H), 12.75 (br s, 1H). MS (*m/z*): 459.37 (M⁺).

Comparative Example-14

5-(2-Chloro-6-fluorophenyl)-2-{4-[(3-chloropyridin-4-yl)ethynyl]phenyl}-2,4-dihydro-3*H*-1,2,4-triazol-3-one

[0716]

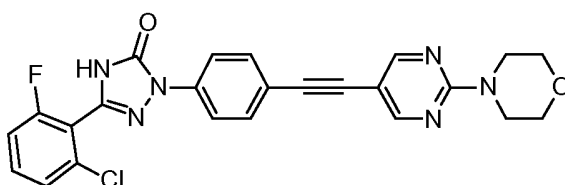


[0717] The title compound was prepared according to the procedure described in Example-3 using 5-(2-chloro-6-fluorophenyl)-2-(4-ethynylphenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (Intermediate-2, 0.100 g, 0.319 mmol), 3-chloro-4-iodopyridine (Intermediate-4, 0.114 g, 0.429 mmol), TBAF (0.201 g, 0.638 mmol), bis(triphenylphosphine)palladium(II) chloride (0.020 g, 0.028 mmol) and DMSO (3.0 mL). The obtained product was purified with column chromatography on silica gel eluting with 1.0 % MeOH: DCM to afford 0.035 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 7.49 (t, *J* = 8.7 Hz, 1H), 7.56 (d, *J* = 11.7 Hz, 2H), 7.60-7.77 (m, 3H), 8.08 (d, *J* = 8.4Hz, 2H), 8.57 (d, *J* = 5.1 Hz, 1H), 8.78 (s, 1H), 12.76 (br s, 1H). MS (*m/z*): 425.43 (*M*⁺).

Comparative Example-15

3-(2-Chloro-6-fluorophenyl)-1-(4-((2-morpholinopyrimidin-5-yl)ethynyl)phenyl)-1*H*-1,2,4-triazol-5(4*H*)-one

[0718]

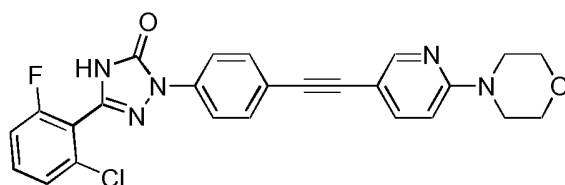


[0719] The title compound was prepared according to the procedure described in Example-3 using 5-(2-chloro-6-fluorophenyl)-2-(4-ethynylphenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (Intermediate-2, 0.100 g, 0.319 mmol), 4-(5-iodopyrimidin-2-yl)morpholine (Intermediate-5, 0.139 g, 0.470 mmol), TBAF (0.201 g, 0.638 mmol), bis(triphenylphosphine)palladium(II) chloride (0.020 g, 0.028 mmol) and DMSO (3.0 mL). The obtained product was purified with column chromatography on silica gel eluting with 2.0 % MeOH: DCM to afford 0.035 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.67 (br s, 4H), 3.76 (br s, 4H), 7.47-7.71 (m, 5H), 7.98 (d, *J* = 9.0 Hz, 2H), 8.58 (s, 2H), 12.69 (s, 1H).

Comparative Example-16

5-(2-Chloro-6-fluorophenyl)-2-(4-([6-(morpholin-4-yl)pyridin-3-yl]ethynyl)phenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one

[0720]



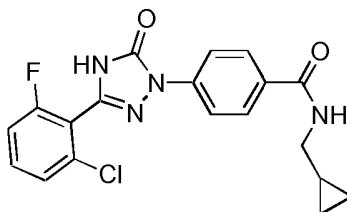
[0721] The title compound was prepared according to the procedure described in Example-3 using 5-(2-chloro-6-fluorophenyl)-2-(4-ethynylphenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (Intermediate-2, 0.100 g, 0.319 mmol), 4-(5-iodopyridin-2-yl)morpholine (Intermediate-6, 0.139 g, 0.470 mmol), TBAF (0.201 g, 0.638 mmol), bis(triphenylphosphine)palladium(II) chloride (0.020 g, 0.028 mmol) and DMSO (3.0 mL). The obtained product was purified with column chromatography on silica gel eluting with 2.0 % MeOH: DCM to afford 0.020 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.58-3.61 (m, 4H), 3.82-3.85 (br s, 4H), 6.64 (d, *J* = 8.7 Hz, 1H), 7.19 (t, *J* = 8.7 Hz, 1H), 7.36-7.47 (m, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.63-7.67 (m, 1H), 8.03 (d, *J* = 9.0 Hz, 2H), 8.38 (s, 1H), 10.14 (br s, 1H); MS (*m/z*):

473.64 (M-H)⁻.

Comparative Example-17

4-[3-(2-Chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-*N*-(cyclopropylmethyl)benzamide

[0722]

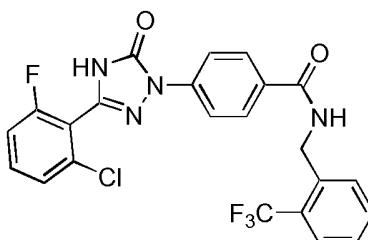


[0723] To a solution of 4-[3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]benzoic acid (Intermediate-9, 0.100 g, 0.290 mmol) in THF was added di-isopropyl ethyl amine (1.0 mL) and TBTU (0.193 g, 0.590 mmol). The reaction mass was stirred at RT for 1 h. 1-cyclopropylmethanamine (0.048 g, 0.440 mmol) was added to the reaction mass and further stirred at RT for 15 h. The reaction mass was quenched in water and extracted with ethyl acetate. The organic layer was washed with NaHCO₃ solution and water, dried over anhydrous sodium sulphate and concentrated to afford 0.025 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 0.23 (br s, 1H), 0.44 (d, *J* = 7.5 Hz, 1H), 0.83-0.85 (m, 1H), 1.06-1.024 (m, 1H), 1.31 (m, 1H), 3.14 (t, *J* = 5.7 Hz, 2H), 7.50 (t, *J* = 9.0 Hz, 1H), 7.58 (d, *J* = 7.2 Hz, 1H), 7.67-7.72 (m, 1H), 7.95-8.00 (m, 4H), 8.59 (m, 1H), 12.70 (br s, 1H); MS (*m/z*): 387.35 (M+H)⁺.

Comparative Example-18

4-[3-(2-Chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-*N*-[2-(trifluoromethyl)benzyl]benzamide

[0724]

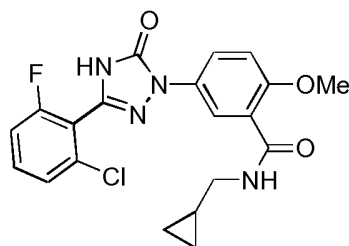


[0725] The mixture of methyl 4-[3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]benzoate (step-2 of Intermediate-9, 0.100 g, 0.280 mmol), 1-[2-(trifluoromethyl)phenyl]methanamine (0.075 g, 0.430 mmol), 1,2,4-triazole (0.004 g, 0.05 mmol) and DBU (0.009 g, 0.005 mmol) was heated at 80-90°C in seal tube for 15 h. The reaction mass was quenched in water and extracted with ethyl acetate. The organic layer was washed with dilute HCl and water, dried over anhydrous sodium sulphate and concentrated to afford 0.030 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 4.66-4.68 (d, *J* = 4.2 Hz, 2H), 7.45-7.75 (m, 7H), 8.05 (s, 4H), 9.16 (br s, 1H), 12.73 (br s, 1H); MS (*m/z*): 489.42 (M-H)⁻.

Comparative Example-19

5-[3-(2-Chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-*N*-(cyclopropylmethyl)-2-methoxybenzamide

[0726]

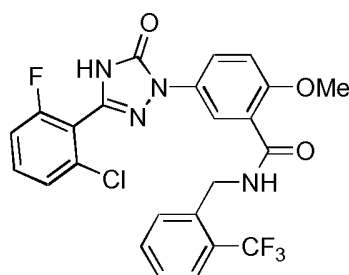


[0727] The title compound was prepared according to the procedure described in Example-17 by using 5-[3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl]-2-methoxybenzoic acid (Intermediate-11, 0.100 g, 0.270 mmol), THF (5 mL), di-isopropyl ethyl amine (1.0 mL), TBTU (0.177 g, 0.540 mmol) and 1-cyclopropylmethanamine (0.045 g, 0.410 mmol) to afford 0.035 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 0.23-0.24 (m, 2H), 0.41-0.44 (m, 2H), 1.03 (m, 1H), 3.17 (t, *J* = 7.2 Hz, 2H), 3.91 (s, 3H), 7.25 (d, *J* = 9.0 Hz, 1H), 7.49 (t, *J* = 8.7 Hz, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.65-7.70 (m, 1H), 7.98 (d, *J* = 9.0 Hz, 1H), 8.23 (s, 1H), 8.32 (m, 1H), 12.57 (s, 1H); MS (*m/z*): 415.23 (M-H)⁺.

Comparative Example-20

5-[3-(2-Chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl]-2-methoxy-*N*-[2-(trifluoromethyl)benzyl]benzamide

[0728]

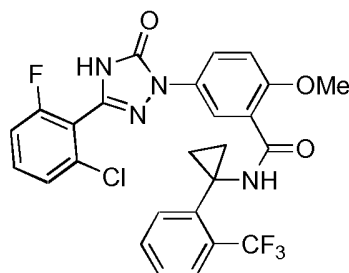


[0729] The title compound was prepared according to the procedure described in Example-17 by using 5-[3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl]-2-methoxybenzoic acid (Intermediate-11, 0.100 g, 0.270 mmol), THF (5 mL), di-isopropyl ethyl amine (1.0 mL), TBTU (0.177 g, 0.540 mmol) and 1-[2-(trifluoromethyl)phenyl]methanamine (0.072 g, 0.410 mmol) to afford 0.035 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.95 (s, 3H), 4.62-4.71 (br s, 2H), 7.30 (d, *J* = 8.7 Hz, 1H), 7.46-7.52 (m, 2H), 7.56-7.59 (m, 2H), 7.65-7.75 (m, 3H), 8.02 (dd, *J* = 2.4 Hz, 1H), 8.28 (s, 1H), 8.90 (br s, 1H), 12.58 (s, 1H); MS (*m/z*): 519.30 (M-H)⁺.

Comparative Example-21

5-[3-(2-Chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl]-2-methoxy-*N*-{1-[2-(trifluoromethyl)phenyl]cyclopropyl}benzamide

[0730]

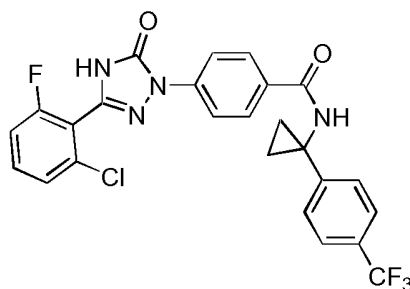


[0731] The title compound was prepared according to the procedure described in Example-17 by using 5-[3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-2-methoxybenzoic acid (Intermediate-11, 0.100 g, 0.270 mmol), THF (5 mL), di-isopropyl ethyl amine (1.0 mL), TBTU (0.177 g, 0.540 mmol) and 1-[2-(trifluoromethyl)phenyl]cyclopropanamine (Intermediate-12, 0.066 g, 0.329 mmol) to afford 0.025 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.26-1.28 (m, 4H), 3.91 (s, 3H), 7.24 (d, *J* = 9.3 Hz, 1H), 7.11-7.48 (m, 6H), 7.98 (t, *J* = 7.5 Hz, 2H), 8.27 (s, 1H), 8.74 (s, 1H), 12.56 (br s, 1H); MS (*m/z*): 545.31 (*M*-H)⁻.

Comparative Example-22

4-[3-(2-Chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-*N*-(1-[4-(trifluoromethyl)phenyl]cyclopropyl)benzamide

[0732]

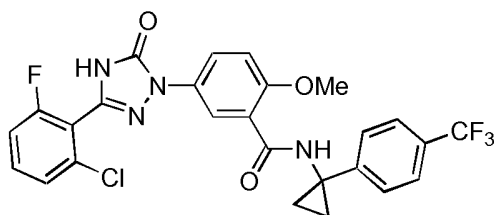


[0733] The title compound was prepared according to the procedure described in Example-17 by using 4-[3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]benzoic acid (Intermediate-9, 0.100 g, 0.290 mmol), THF (5 mL), di-isopropyl ethyl amine (2.0 mL), TBTU (0.193 g, 0.590 mmol) and 1-[4-(trifluoromethyl)phenyl]cyclopropanamine (Intermediate-13, 0.073 g, 0.350 mmol) to afford 0.030 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.35 (s, 4H), 7.36 (d, *J* = 7.8 Hz, 2H), 7.46-7.70 (m, 5H), 8.01 (s, 4H), 9.30 (s, 1H), 12-13 (br s, 1H); MS (*m/z*): 515.23 (*M*-H)⁻.

Comparative Example-23

5-[3-(2-Chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-2-methoxy-*N*-(1-[4-(trifluoromethyl)phenyl]cyclopropyl)benzamide

[0734]

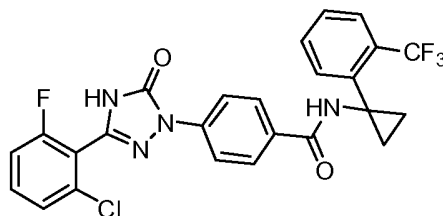


[0735] The title compound was prepared according to the procedure described in Example-17 by using 5-[3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-2-methoxybenzoic acid (Intermediate-11, 0.100 g, 0.270 mmol), THF (10 mL), di-isopropyl ethyl amine (10.0 mL), TBTU (0.177 g, 0.540 mmol) and 1-[4-(trifluoromethyl)phenyl]cyclopropanamine (Intermediate-13, 0.066 g, 0.320 mmol) to afford 0.025 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.23 (s, 4H), 3.94 (s, 3H), 7.26 (d, *J* = 9.0 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 3H), 7.30-7.48 (m, 4H), 7.99 (d, *J* = 9.3 Hz, 1H), 8.05 (s, 1H), 8.96 (s, 1H), 12.51 (br s, 1H); MS (*m/z*): 547.15 (*M*⁺).

Comparative Example-24

4-(3-(2-Chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-*N*-(1-(2-(trifluoromethyl)phenyl)cyclopropyl)benzamide

[0736]

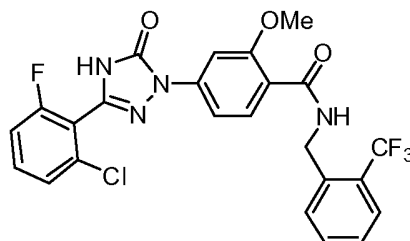


[0737] The title compound was prepared according to the procedure described in Example-17 by using 4-[3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]benzoic acid (Intermediate-9, 0.100 g, 0.290 mmol), THF (10 mL), di-isopropyl ethyl amine (10.0 mL), TBTU (0.177 g, 0.540 mmol) and 1-[2-(trifluoromethyl)phenyl] cyclopropanamine (Intermediate-12, 0.035 g, 0.350 mmol) to afford 0.020 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.23 (s, 2H), 1.31 (s, 2H), 7.59 (d, *J* = 7.2 Hz, 2H), 7.65-7.68 (m, 4H), 7.82 (d, *J* = 12.0 Hz, 2H), 7.88-8.02 (m, 3H), 8.77 (s, 1H), 12.60 (br s, 1H); MS (*m/z*): 517.03 (*M*⁺).

Comparative Example-25

4-[3-(2-Chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-2-methoxy-*N*-[2-(trifluoromethyl)benzyl]benzamide

[0738]



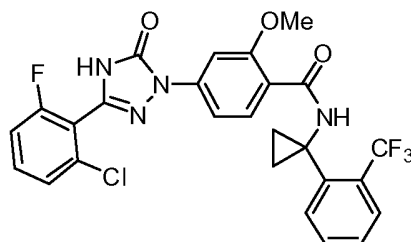
[0739] The title compound was prepared according to the procedure described in Example-17 by using 4-(3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzoic acid (Intermediate-15, 0.100 g, 0.270 mmol), THF (5 mL), di-isopropyl ethyl amine (1.0 mL), TBTU (0.177 g, 0.540 mmol) and 1-[2-(trifluoromethyl)phenyl] methanamine (0.072 g, 0.410 mmol) to afford 0.025 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.96 (s, 3H), 4.70 (d, *J* = 4.8 Hz, 2H), 7.45-7.50 (m, 3H), 7.57 (t, *J* = 8.4 Hz, 2H), 7.67 (t, *J* = 8.7 Hz, 2H), 7.71 (d, *J* = 9.3 Hz, 2H), 7.92 (d, *J* = 8.4 Hz, 1H), 8.80 (t, 1H), 12.77 (br s, 1H); MS (*m/z*): 519.43 (*M*-H)⁻.

Comparative Example-26

4-(3-(2-Chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxy-*N*-(1-(2-(trifluoromethyl)phenyl)cyclopropyl)benzamide

[0740]

EP 2 718 284 B1

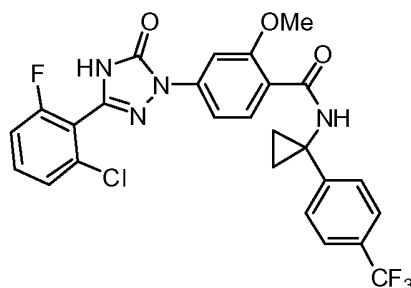


[0741] The title compound was prepared according to the procedure described in Example-17 by using 4-(3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzoic acid (Intermediate-15, 0.100 g, 0.270 mmol), THF (5 mL), di-isopropyl ethyl amine (2.0 mL), TBTU (0.177 g, 0.540 mmol) and 1-[2-(trifluoromethyl)phenyl] cyclopropanamine (Intermediate-12, 0.082 g, 0.410 mmol) to afford 0.020 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.27-1.31 (m, 4H), 3.90 (s, 3H), 7.47 (t, *J* = 8.1 Hz, 2H), 7.54-7.69 (m, 6H), 7.87 (t, *J* = 8.4 Hz, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 8.61 (s, 1H); MS (*m/z*): 547.15 (*M*⁺).

Comparative Example-27

4-(3-(2-Chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxy-*N*-(1-(4-(trifluoromethyl)phenyl)cyclopropyl)benzamide

[0742]

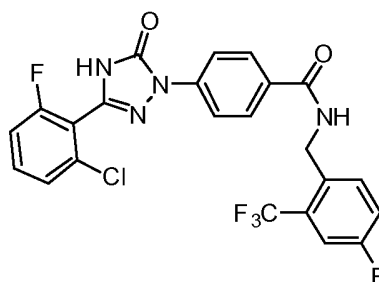


[0743] The title compound was prepared according to the procedure described in Example-17 by using 4-(3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzoic acid (Intermediate-15, 0.100 g, 0.270 mmol), THF (5 mL), di-isopropyl ethyl amine (2.0 mL), TBTU (0.177 g, 0.540 mmol) and 1-[4-(trifluoromethyl)phenyl] cyclopropanamine (Intermediate-13, 0.066 g, 0.320 mmol) to afford 0.020 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.37 (s, 4H), 3.95 (s, 3H), 7.42 (d, *J* = 7.8 Hz, 2H), 7.50 (t, *J* = 8.7 Hz, 1H), 7.63 (t, *J* = 7.8 Hz, 4H), 7.73 (t, *J* = 12.3 Hz, 3H), 8.85 (s, 1H), 12.50 (br s, 1H); MS (*m/z*): 546.99 (*M*⁺).

Comparative Example-28

4-(3-(2-Chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-*N*-(4-fluoro-2-(trifluoromethyl)benzyl)benzamide

[0744]

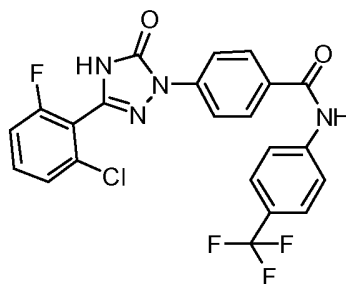


[0745] The title compound was prepared according to the procedure described in Example-17 by using 4-[3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]benzoic acid (Intermediate-9, 0.100 g, 0.30 mmol), THF (5 mL), di-isopropyl ethyl amine (2.0 mL), TBTU (0.177 g, 0.540 mmol) and 4-fluoro-2-trifluoromethyl benzylamine (0.089 g, 0.600 mmol) to afford 0.025 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 4.63 (d, *J* = 4.5 Hz, 2H), 7.48-7.50 (m, 6H), 8.05 (s, 4H), 9.16 (t, 1H), 12.67 (br, 1H); MS (*m/z*): 509.05 (M+H)⁺.

Comparative Example-29

4-(3-(2-Chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-*N*-(4-(trifluoromethyl)phenyl)benzamide

[0746]

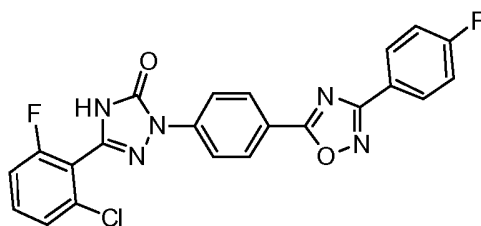


[0747] To a solution of 4-(3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzamide (Intermediate-17, 0.100 g, 0.301 mmol) in dry toluene (5 mL) was added 1-bromo-4-(trifluoromethyl)benzene (0.101 g, 0.451 mmol), sodium *tert*-butoxide (0.058 g, 0.602 mmol), tris(diphenylideneacetone)dipalladium(0) (0.005 g, 0.0006 mmol), 4,5-bis(diphenylphosphino) and 9,9-dimethylxanthene (0.005 g, 0.0009 mmol) under nitrogen atmosphere. The reaction mass was refluxed for 3-4 h. The reaction mass was quenched in water and extracted in ethyl acetate. The organic layer was concentrated to afford crude product which was purified by column chromatography to afford 0.015 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 7.40 (br s, 1H), 7.84 (t, *J* = 9 Hz, 1H), 7.55 (d, 1H), 7.72-7.75 (m, 3H), 8.02 (d, *J* = 8.1 Hz, 2H), 8.11 (br s, 3H) 10.61 (br s, 1H), 12.70 (br s, 1H). MS (*m/z*): 475.18 (M-H)⁻.

Comparative Example-30

3-(2-Chloro-6-fluorophenyl)-1-(4-(3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl)phenyl)-1*H*-1,2,4-triazol-5(4*H*)-one

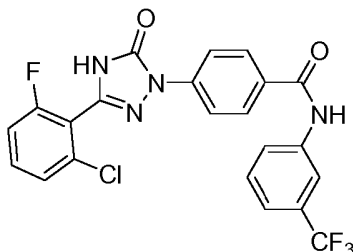
[0748]



[0749] To a solution of 4-fluoro-*N*-hydroxybenzimidamide (Intermediate-18, 0.073 g, 0.47 mmol) in dry DMF (3 mL) under nitrogen atmosphere was added 4-(3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzotriazole (step-4 of Intermediate-17, 0.100 g, 0.31 mmol) and ZnCl₂ (0.0087 g, 0.06 mmol). The reaction mass was heated at 100°C for 8-10 h. The reaction mass was quenched with water, extracted in DCM and column purified to afford 0.025 g of desired product. ¹H NMR (DMSO-*d*₆): δ 7.02 (br s, 1H), 7.33 (t, 1H), 7.45-7.54 (m, 2H), 7.61 (d, 1H), 7.70 (m, 1H), 7.83 (t, 1H), 8.09-8.17 (m, 2H), 8.26-8.30 (m, 2H), 12.81 (br s, 1H). MS (*m/z*): 452.05 [M+H]⁺.

Comparative Example-314-(3-(2-Chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-*N*-(3-(trifluoromethyl)phenyl)benzamide

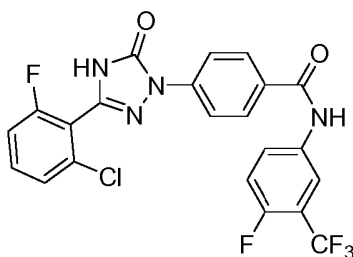
[0750]



[0751] To a solution of methyl 4-[3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]benzoate (step-2 of Intermediate-9, 0.100 g, 0.28 mmol) in dry toluene was added 3-trifluoromethyl aniline (0.070 g, 0.43 mmol) followed by addition of trimethyl aluminium (2M solution in toluene) (0.5 mL). The reaction mixture was refluxed for 1 h. The reaction mass was quenched in water and acidified with dilute HCl and extracted in DCM. The organic layer was dried over anhydrous sodium sulphate and concentrated to afford crude product, which was column purified to afford 0.040 g of desired product. ¹HNMR (DMSO-*d*₆): δ 7.45-7.54 (m, 2H), 7.59 (m, 2H), 7.72 (q, *J* = 6.3 Hz, 1H), 8.05-8.12 (m, 5H), 8.25 (s, 1H), 10.58 (br s, 1H), 12.77 (br s, 1H); MS (*m/z*): 477.08 [*M*+*H*]⁺.

Comparative Example-324-(3-(2-Chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-*N*-(4-fluoro-3-(trifluoromethyl)phenyl)benzamide

[0752]

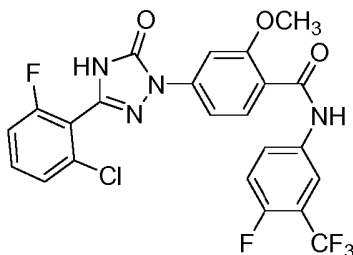


[0753] The title compound was prepared according to the procedure described in Example-31, by using methyl 4-[3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]benzoate (step-2 of Intermediate-9, 0.100 g, 0.28 mmol), 4-fluoro-3-trifluoromethyl aniline (0.077 g, 0.43 mmol) and trimethyl aluminium (2M solution in toluene) (0.5 mL) to afford 0.043 g of desired product. ¹HNMR (DMSO-*d*₆): δ 7.46-7.59 (m, 3H), 7.69 (t, *J* = 6.3 Hz, 1H), 8.11 (br s, 5H), 8.26 (m, 1H), 10.59 (br s, 1H), 12.72 (br s, 1H); MS (*m/z*): 495.07 [*M*+*H*]⁺.

Comparative Example-334-(3-(2-Chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-*N*-(4-fluoro-3-(trifluoromethyl)phenyl)-2-methoxybenzamide

[0754]

EP 2 718 284 B1

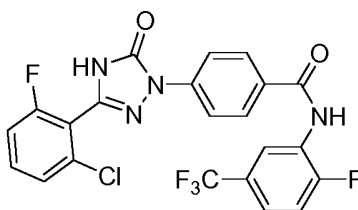


[0755] The title compound was prepared according to the procedure described in Example-31, by using methyl 4-((3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-2-methoxybenzoate (step-2 of Intermediate-15, 0.100 g, 0.26 mmol), 4-floro-3-trifloromethyl aniline (0.070 g, 1.5 mmol), trimethyl aluminium (2M solution in toluene) (0.5 mL) to afford 0.030 g of desired product. ¹HNMR (DMSO-*d*₆): δ 3.94 (s, 3H), 7.50-7.60 (m, 3H), 7.67-7.72 (m, 2H), 7.77-7.82 (m, 2H), 8.01 (m, 1H), 8.26 (m, 1H), 10.38 (br s, 1H), 12.80 (br s, 1H); MS (m/z): 525.17 [M+H]⁺.

Comparative Example-34

4-((3-(2-Chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-N-(2-fluoro-5-(trifluoromethyl)phenyl)benzamide

[0756]

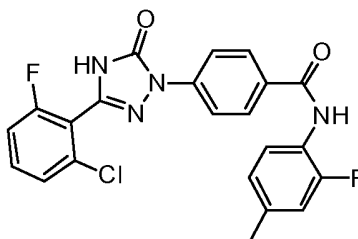


[0757] The title compound was prepared according to the procedure described in Example-31, by using methyl 4-((3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)benzoate (step-2 of Intermediate-9, 0.100g, 0.28 mmol), 2-fluoro-5-trifluoromethyl aniline (0.077 g, 0.43 mmol) and trimethyl aluminium (2M solution in toluene) (0.5 mL) to afford 0.050 g of desired product. ¹HNMR (DMSO-*d*₆): δ 7.48-7.61 (m, 3H), 7.68-7.73 (m, 2H), 8.08-8.12 (m, 5H), 10.41 (br s, 1H), 12.78 (br s, 1H); MS (m/z): 493.09 [M-H]⁻.

Comparative Example-35

4-((3-(2-Chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-N-(2-fluoro-4-methylphenyl)benzamide

[0758]

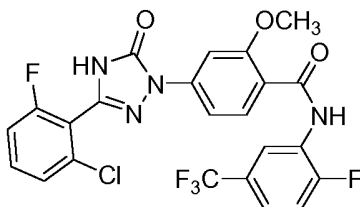


[0759] The title compound was prepared according to the procedure described in Example-31, by using methyl 4-((3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)benzoate (step-2 of Intermediate-9, 0.100 g, 0.28 mmol), 2-fluoro-4-methyl aniline (0.054 g, 0.43 mmol) and trimethyl aluminium (2M solution in toluene) (0.5 mL) to afford 0.055 g of desired product. ¹HNMR (DMSO-*d*₆): δ 2.30 (s, 3H), 7.00 (d, *J*=7.8 Hz, 1H), 7.11 (d, *J*= 11.7 Hz, 1H), 7.39-7.48 (m, 2H), 7.51-7.58 (d, 1H), 7.65-7.72 (m, 1H), 8.07 (br s, 4H), 10.04 (br s, 1H), 12.73 (br s, 1H); MS (m/z): 439.13 [M-H]⁻.

Comparative Example-36

4-(3-(2-Chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-*N*-(2-fluoro-5-(trifluoromethyl)phenyl)-2-methoxybenzamide

[0760]

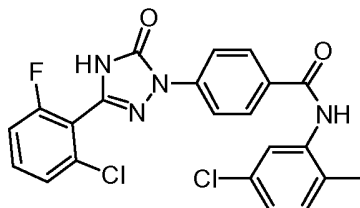


[0761] The title compound was prepared according to the procedure described in Example-31, by using methyl 4-(3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzoate (step-2 of Intermediate-15, 0.100 g, 0.26 mmol), 2-fluoro-5-trifluoromethyl aniline (0.070 g, 0.39 mmol) and trimethyl aluminium (2M solution in toluene (0.5 mL) to afford 0.049 g of desired product. ¹HNMR (DMSO-*d*₆): δ 4.05 (s, 3H), 7.50 (t, *J* = 8.4 Hz, 1H), 7.57-7.70 (m, 3H), 7.72-7.77 (m, 2H), 7.85 (s, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 8.67 (d, *J* = 6.3 Hz, 1H), 10.38 (br s, 1H), 12.82 (br s, 1H); MS (*m/z*): 525.15 [*M*+*H*]⁺.

Comparative Example-37

N-(5-Chloro-2-methylphenyl)-4-(3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzamide

[0762]

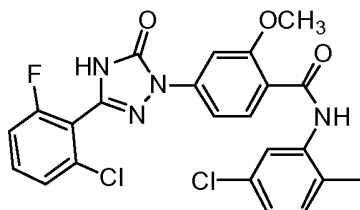


[0763] The title compound was prepared according to the procedure described in Example-31, by using methyl 4-[3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]benzoate (step-2 of Intermediate-9, 0.100 g, 0.28 mmol), 5-chloro-2-methyl aniline (0.062 g, 0.43 mmol) and trimethyl aluminium (2M solution in toluene) (0.5 mL) to afford 0.059 g of desired product. ¹HNMR (DMSO-*d*₆): δ 2.23 (s, 3H), 7.23 (d, *J* = 6.9 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.53 (m, 2H), 7.59 (m, 1H), 7.71 (m, 1H), 8.10 (br s, 4H), 9.98 (br s, 1H), 12.76 (br s, 1H); MS (*m/z*): 457.18 [*M*]⁺.

Comparative Example-38

N-(5-Chloro-2-methylphenyl)-4-(3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzamide

[0764]



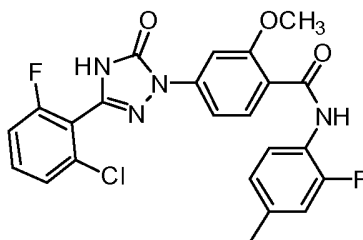
[0765] The title compound was prepared according to the procedure described in Example-31, by using methyl 4-(3-(2-

chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzoate (step-2 of Intermediate-15, 0.100 g, 0.26 mmol), 5-chloro-2-methyl aniline (0.057 g, 0.39 mmol) and trimethyl aluminium (2M solution in toluene) (0.5 mL) to afford 0.057 g of desired product. ¹HNMR (DMSO-*d*₆): δ 2.32 (s, 3H), 4.05 (s, 3H), 7.13 (d, *J* = 9.9 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 1H), 7.49 (t, 1H), 7.59 (d, 1H), 7.61-7.75 (m, 2H), 7.84 (s, 1H), 8.08 (d, *J* = 8.7 Hz, 1H), 8.19 (s, 1H), 9.94 (br s, 1H), 12.83 (br s, 1H); MS (*m/z*): 487.11 [*M*]⁺.

Comparative Example-39

4-(3-(2-Chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-*N*-(2-fluoro-4-methylphenyl)-2-methoxybenzamide

[0766]

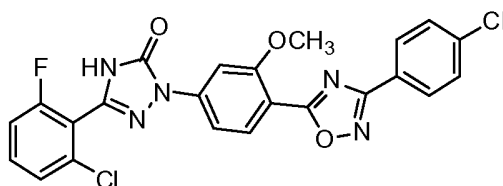


[0767] The title compound was prepared according to the procedure described in Example-31, by using methyl 4-(3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzoate (step-2 of Intermediate-15, 0.100 g, 0.26 mmol), 2-fluoro-4-methyl aniline (0.050 g, 0.39 mmol) and trimethyl aluminium (2M solution in toluene) (0.5 mL) to afford 0.047 g of desired product. ¹HNMR (DMSO-*d*₆): δ 2.30 (s, 3H), 4.03 (s, 3H), 7.02 (d, *J* = 8.1 Hz, 1H), 7.14 (d, *J* = 11.7 Hz, 1H), 7.51 (t, 1H), 7.58 (d, 1H), 7.65-7.75 (m, 2H), 7.85 (s, 1H), 8.04-8.10 (m, 2H), 10.07 (br s, 1H), 12.65 (br s, 1H); MS (*m/z*): 469.16 [*M-H*]⁻.

Comparative Example-40

3-(2-Chloro-6-fluorophenyl)-1-(4-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)-3-methoxyphenyl)-1*H*-1,2,4-triazol-5(4*H*)-one

[0768]

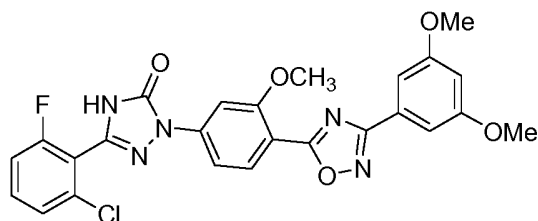


[0769] To a solution of 4-chloro-*N*-hydroxybenzimidamide (Intermediate-19, 0.069 g, 0.39 mmol) in dry toluene was added sodium hydride (0.016 g, 0.39 mmol). The reaction mixture was refluxed for 30 minutes followed by addition of methyl 4-(3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzoate (step-2 of Intermediate-15, 0.100 g, 0.26 mmol). The reaction mixture was refluxed for 5-6 h. The reaction mixture was quenched in water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and concentrated to afford crude product which was further purified by column chromatography to afford 0.015 g of desired product. ¹HNMR (DMSO-*d*₆): δ 3.98 (s, 3H), 7.45-7.48 (m, 1H), 7.54 (d, *J* = 8.1 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 3H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.95 (s, 1H), 8.10 (d, *J* = 8.4 Hz, 2H), 8.18 (d, *J* = 8.7 Hz, 1H), 12.90 (br s, 1H). MS [*M+H*]⁺: 499.89.

Comparative Example-41

3-(2-Chloro-6-fluorophenyl)-1-(4-(3-(3,5-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)-3-methoxyphenyl)-1*H*-1,2,4-triazol-5(4*H*)-one

[0770]

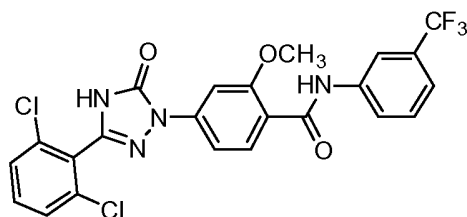


[0771] The title compound was prepared by following the procedure as described for Example-40 by using methyl 4-(3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzoate (step-2 of Intermediate -15, 0.100 g, 0.26 mmol), *N*'-hydroxy-3,5-dimethoxybenzimidamide (Intermediate-20, 0.077 g, 0.529 mmol), sodium hydride (0.006 g, 0.39 mmol) and dry THF (5.0 mL) at RT to afford 0.015 g of desired product. ¹HNMR (DMSO-*d*₆): δ 3.84 (s, 6H), 3.99 (s, 3H), 6.73 (s, 1H), 7.19 (s, 2H), 7.47 (t, *J* = 8.1 Hz, 1H), 7.56 (d, *J* = 8.4 Hz, 1H), 7.67 (t, *J* = 8.7 Hz, 1H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.93 (s, 1H), 8.19 (d, *J* = 8.7 Hz, 1H), 12.61 (br s, 1H); MS (*m/z*): 523.89 [*M*+]⁺.

Comparative Example-42

4-(3-(2,6-Dichlorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxy-*N*-(3-(trifluoromethyl)phenyl)benzamide

[0772]

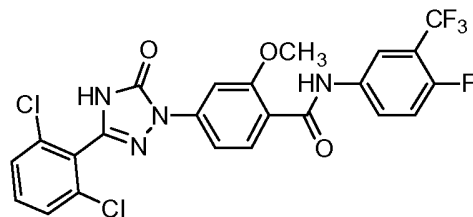


[0773] The title compound was prepared by following the procedure as described for Example-31 by using methyl 4-(3-(2,6-dichlorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzoate (Intermediate-21, 0.100 g, 0.25 mmol), 3-(trifluoromethyl)aniline (0.062 g, 0.38 mmol), trimethyl aluminium (2M solution in toluene) (0.5 mL) and dry toluene (5.0 mL) to afford 0.035 g of desired product. ¹HNMR (DMSO-*d*₆): δ 3.95 (s, 3H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.76-7.68 (m, 5H), 7.82 (t, *J* = 8.7 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 8.25 (s, 1H), 10.37 (s, 1H), 12.75 (br s, 1H); MS (*m/z*): 524.96 [*M*+]⁺.

Comparative Example-43

4-(3-(2,6-Dichlorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-*N*-(4-fluoro-3-(trifluoromethyl)phenyl)-2-methoxybenzamide

[0774]

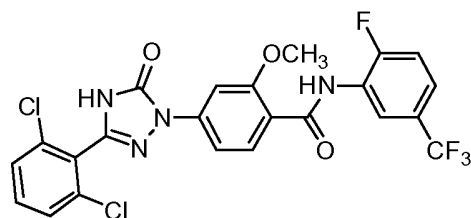


[0775] The title compound was prepared by following the procedure as described for Example-31 by using methyl 4-(3-(2,6-dichlorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzoate (Intermediate-21, 0.100 g, 0.25 mmol), 4-fluoro-3-(trifluoromethyl)aniline (0.069 g, 0.38 mmol), trimethyl aluminium (2M solution in toluene) (0.5 mL) and dry toluene (5.0 mL) to afford 0.050 g of desired product. ¹HNMR (DMSO-*d*₆): δ 4.09 (s, 3H), 7.52 (t, *J* = 9.6 Hz, 1H), 7.88-7.68 (m, 6H), 8.25 (s, 1H), 8.25 (d, *J* = 6.9 Hz, 1H), 10.37 (s, 1H), 12.74 (s, 1H); MS (*m/z*): 540.91[M]⁺.

Comparative Example-44

4-(3-(2,6-Dichlorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-*N*-(2-fluoro-5-(trifluoromethyl)phenyl)-2-methoxybenzamide

[0776]

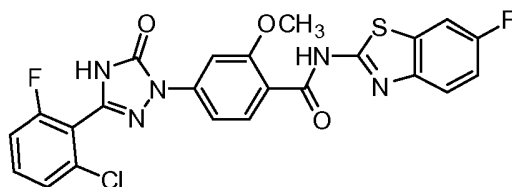


[0777] The title compound was prepared by following the procedure as described for Example-31 by using methyl 4-(3-(2,6-dichlorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzoate (Intermediate-21, 0.100 g, 0.25 mmol), 2-fluoro-5-(trifluoromethyl)aniline (0.069 g, 0.38 mmol), trimethyl aluminium (2M solution in toluene) (0.5 mL) and dry toluene (5.0 mL) to afford 0.035 g of desired product. ¹HNMR (DMSO-*d*₆): δ 4.06 (s, 3H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.77-7.68 (m, 5H), 7.84 (s, 1H), 8.09 (d, *J* = 8.7 Hz, 1H), 8.67 (d, *J* = 6.9 Hz, 1H), 10.38 (s, 1H), 12.79 (br s, 1H); MS (*m/z*): 540.92 [M+H]⁺.

Comparative Example-45

4-(3-(2-Chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-*N*-(6-fluorobenzo[d]thiazol-2-yl)-2-methoxybenzamide

[0778]



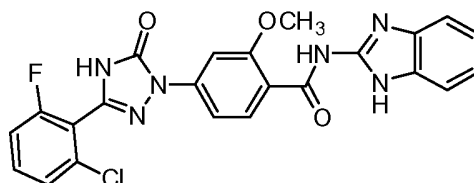
[0779] The title compound was prepared by following the procedure as described for Example-31 by using methyl 4-(3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzoate (step-2 of Intermediate-15, 0.100 g, 0.26 mmol), 6-fluorobenzo[d]thiazol-2-amine (0.067 g, 0.397 mmol), trimethyl aluminium (2M solution in toluene) (0.5 mL) and dry toluene (5.0 mL) to afford 0.050 g of desired product. ¹HNMR (DMSO-*d*₆): δ 3.99 (s, 3H), 7.32 (t, *J* = 7.2 Hz, 1H), 7.51 (t, *J* = 9.3 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.68-7.80 (m, 4H), 7.94 (t, *J* = 6.3 Hz, 2H), 11.98 (s, 1H),

12.83 (br s, 1H); MS (m/z): 512.97 [M-H]⁻.

Comparative Example-46

N-(1*H*-Benzo[d]imidazol-2-yl)-4-(3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzamide

[0780]

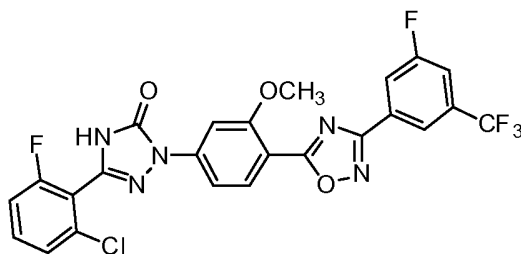


[0781] The title compound was prepared by following the procedure as described for Example-31 by using methyl 4-(3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzoate (step-2 of Intermediate-15, 0.100 g, 0.26 mmol), 1*H*-benzo[d]imidazol-2-amine (0.046 g, 0.34 mmol), trimethyl aluminium (2M solution in toluene) (0.5 mL) and dry toluene (5.0 mL) to afford 0.040 g of desired product. ¹HNMR (DMSO-*d*₆): δ 4.01 (s, 3H), 7.11 (m, 2H), 7.48-7.76 (m, 6H), 7.81 (s, 1H), 7.96 (d, *J* = 9.0 Hz, 1H), 11.16 (br s, 1H), 12.28 (br s, 1H), 12.76 (br s, 1H); MS (m/z): 478.90 [M]⁺

Comparative Example-47

3-(2-Chloro-6-fluorophenyl)-1-(4-(3-(3-fluoro-5-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)-3-methoxyphenyl)-1*H*-1,2,4-triazol-5(4*H*)-one

[0782]

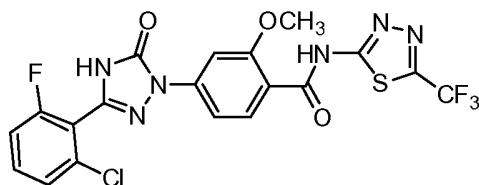


[0783] The title compound was prepared by following the procedure as described for Example-40 by using methyl 4-(3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzoate (step-2 of Intermediate-15, 0.100 g, 0.26 mmol), 3-fluoro-*N'*-hydroxy-5-(trifluoromethyl)benzimidamide (Intermediate-22, 0.088 g, 0.39 mmol), sodium hydride (0.017 g, 0.42 mmol) and dry THF (5.0 mL) at RT to afford 0.010 g of desired product. ¹HNMR (DMSO-*d*₆): δ 4.01 (s, 3H), 7.50 (m, 1H), 7.60 (m, 1H), 7.70 (m, 1H), 7.84 (m, 1H), 7.92 (br s, 1H), 8.02 (d, 1H), 8.18 (m, 2H), 8.25 (d, 1H), 12.95 (br s, 1H); MS (m/z): 550.07 [M]⁺.

Comparative Example-48

4-(3-(2-Chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxy-*N*-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)benzamide

[0784]

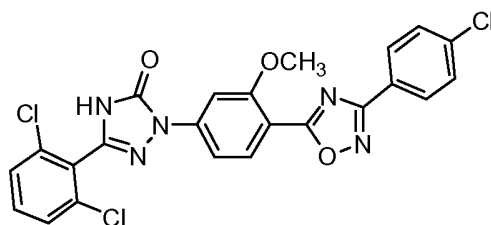


[0785] The title compound was prepared by following the procedure as described for Example-31 by using methyl 4-(3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-2-methoxybenzoate (step-2 of Intermediate -15, 0.100 g, 0.26 mmol), 5-(trifluoromethyl)-1,3,4-thiadiazol-2-amine (0.059 g, 0.34 mmol), trimethyl aluminium (2M solution in toluene) (0.5 mL) and dry toluene (5.0 mL) to afford 0.025 g of desired product. ¹HNMR (DMSO-*d*₆): δ 3.95 (s, 3H), 7.51 (t, *J* = 9.0 Hz, 1H), 7.87-7.76 (m, 3H), 7.78 (s, 1H), 7.85 (d, *J* = 8.7 Hz, 1H), 12.86 (br s, 2H); MS (*m/z*): 514.90 [M]⁺.

Comparative Example-49

1-(4-(3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl)-3-methoxyphenyl)-3-(2,6-dichlorophenyl)-1H-1,2,4-triazol-5(4H)-one

[0786]

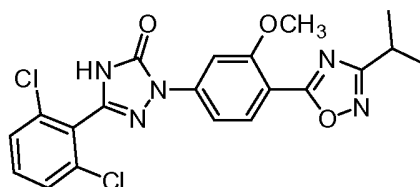


[0787] The title compound was prepared by following the procedure as described for Example-40 by using methyl 4-(3-(2,6-dichlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-2-methoxybenzoate (Intermediate-21, 0.100 g, 0.25 mmol), 4-chloro-*N'*-hydroxybenzimidamide (Intermediate-19, 0.064 g, 0.38 mmol), sodium hydride (0.020 g, 0.50 mmol) and dry THF (5.0 mL) at RT to afford 0.015 g of desired product. ¹HNMR (DMSO-*d*₆): δ 4.00 (s, 3H), 7.66-7.72 (m, 5H), 7.81 (d, *J* = 8.7 Hz, 1H), 7.89 (s, 1H), 8.10 (d, *J* = 8.4 Hz, 2H), 8.22 (d, *J* = 9.0 Hz, 1H), 12.82 (br s, 1H); MS (*m/z*): 515.84 [M+H]⁺.

Comparative Example-50

3-(2,6-Dichlorophenyl)-1-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)-3-methoxyphenyl)-1H-1,2,4-triazol-5(4H)-one

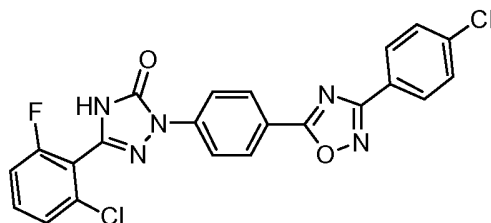
[0788]



[0789] The title compound was prepared by following the procedure as described for Example-40 by using methyl 4-(3-(2,6-dichlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-2-methoxybenzoate (Intermediate-21, 0.100 g, 0.25 mmol), *N'*-hydroxyisobutyrimidamide (0.077 g, 0.529 mmol), sodium hydride (0.020 g, 0.50 mmol) and dry THF (5.0 mL) at RT to afford 0.019 g of desired product. ¹HNMR (DMSO-*d*₆): δ 1.31 (d, *J* = 6.9 Hz, 6H), 3.12 (m, 1H), 3.95 (s, 3H), 7.65-7.78 (m, 4H), 7.56 (s, 1H), 8.09 (d, *J* = 8.7 Hz, 1H), 12.83 (br s, 1H); MS (*m/z*): 447.96 [M+H]⁺.

Comparative Example-513-(2-Chloro-6-fluorophenyl)-1-(4-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)phenyl)-1*H*-1,2,4-triazol-5(4*H*)-one

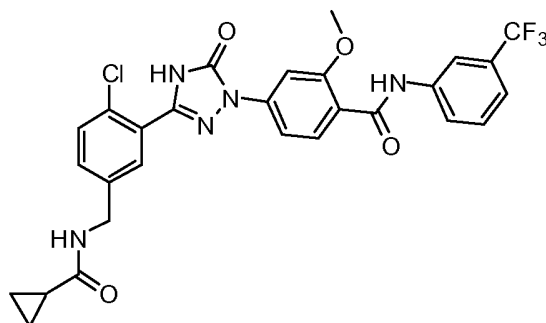
[0790]



[0791] The title compound was prepared by following the procedure as described for Example-40 by using methyl 4-[3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]benzoate (step-2 of Intermediate-9, 0.100 g, 0.28 mmol), 4-chloro-*N*'-hydroxybenzimidamide (Intermediate-19, 0.073 g, 0.43 mmol), sodium hydride (0.018 g, 0.43 mmol) and dry THF (5.0 mL) to afford 0.025 g of desired product. ¹H NMR (DMSO-*d*₆): δ 7.51 (t, *J* = 8.7 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.67-7.73 (m, 3H), 8.11 (d, *J* = 8.1 Hz, 2H), 8.24- 8.29 (m, 4H), 12.85 (br s, 1H); MS (*m/z*): 467.87 [M+H]⁺.

Comparative Example-524-(3-(2-Chloro-5-(cyclopropanecarboxamidomethyl)phenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxy-*N*-(3-(trifluoromethyl)phenyl)benzamide

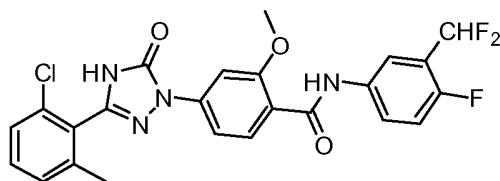
[0792]



[0793] The title compound was prepared by following the procedure as described for step- 2 of Intermediate-30 by using 4-(3-(5-(aminomethyl)-2-chlorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxy-*N*-(3-(trifluoromethyl)phenyl)benzamide (Intermediate-26 , 0.060 g, 0.11 mmol), cyclopropylcarbonyl chloride (0.019 g, 0.17 mmol), DIPEA (1 mL) and THF (5 mL) to afford 0.020 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.06 (m, 2H), 1.22 (m, 2H), 3.17 (m, 1H), 3.95 (s, 3H), 4.34 (d, *J* = 6.0 Hz, 2H), 7.44-7.84 (m, 8H), 7.95 (d, *J* = 9.0 Hz, 1H), 8.25 (s, 1H), 8.70 (m, 1H), 10.43 (m, 1H), 12.05 (m, 1H); MS (*m/z*): 584.35 (M+H⁺).

Comparative Example-534-(3-(2-Chloro-6-methylphenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-*N*-(3-(difluoromethyl)-4-fluorophenyl)-2-methoxybenzamide

[0794]

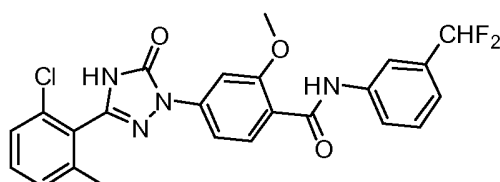


[0795] The title compound was prepared by following the procedure as described for Example-31 by using methyl 4-(3-(2-chloro-6-methylphenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-2-methoxybenzoate (Intermediate-27, 0.100 g, 0.268 mmol), 3-(difluoromethyl)-4-fluoroaniline (Intermediate-28, 0.065 g, 0.403 mmol), trimethyl aluminium (2M solution in toluene) (0.5 mL) and dry toluene (5.0 mL) to afford 0.025 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 2.32 (s, 3H), 3.94 (s, 3H), 7.05-7.41 (m, 3H), 7.50 (s, 2H), 7.68-7.88 (m, 4H), 8.11 (m, 1H), 10.27 (s, 1H), 12.53 (s, 1H); MS (m/z): 503.10 (M+H⁺).

Comparative Example-54

4-(3-(2-Chloro-6-methylphenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-N-(3-(difluoromethyl)phenyl)-2-methoxybenzamide

[0796]

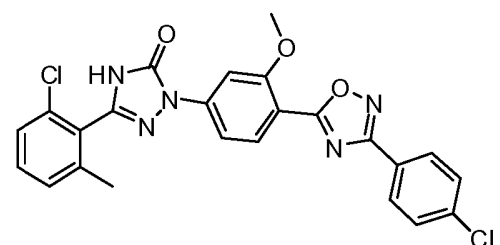


[0797] The title compound was prepared by following the procedure as described for Example-31 by using methyl 4-(3-(2-chloro-6-methylphenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-2-methoxybenzoate (Intermediate-27, 0.100 g, 0.268 mmol), 3-(difluoromethyl)aniline (Intermediate-29, 0.058 g, 0.40 mmol), trimethyl aluminium (2M solution in toluene) (0.5 mL) and dry toluene (5.0 mL) to afford 0.035 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 2.33 (s, 3H), 3.95 (s, 3H), 7.04 (m, 1H), 7.35 (d, 1H), 7.41 (m, 1H), 7.50 (m, 3H), 7.69 (d, *J* = 8.7 Hz, 1H), 7.77-7.82 (m, 3H), 8.07 (s, 1H), 10.25 (s, 1H), 12.52 (br s, 1H); MS (m/z): 485.06 (M+H⁺).

Comparative Example-55

3-(2-Chloro-6-methylphenyl)-1-(4-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)-3-methoxy phenyl)-1H-1,2,4-triazol-5(4H)-one

[0798]



[0799] The title compound was prepared by following the procedure as described for Example-40 by using methyl 4-(3-(2-chloro-6-methylphenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-2-methoxybenzoate (Intermediate-27, 0.100 g, 0.26 mmol), 4-chloro-N-hydroxybenzimidamide (Intermediate-19, 0.069 g, 0.40 mmol), sodium hydride (0.022 g, 0.53 mmol) and dry THF (5.0 mL) to afford 0.020 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 2.33 (s, 3H), 4.00 (s, 3H), 7.41 (m, 1H), 7.51 (s, 2H), 7.67 (d, *J* = 8.7 Hz, 2H), 7.83 (d, *J* = 8.7 Hz, 1H), 7.90 (s, 1H), 8.10 (d, *J* = 8.4 Hz,

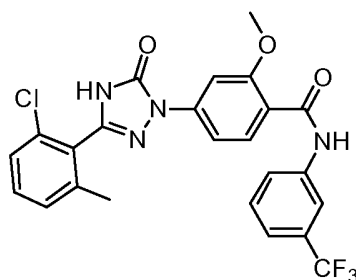
EP 2 718 284 B1

2H), 8.22 (d, $J = 8.7$ Hz, 1H), 12.63 (s, 1H); MS (m/z): 495.98 (M+H⁺).

Comparative Example-56

5 4-(3-(2-Chloro-6-methylphenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxy-*N*-(3-(trifluoromethyl)phenyl)benzamide

[0800]

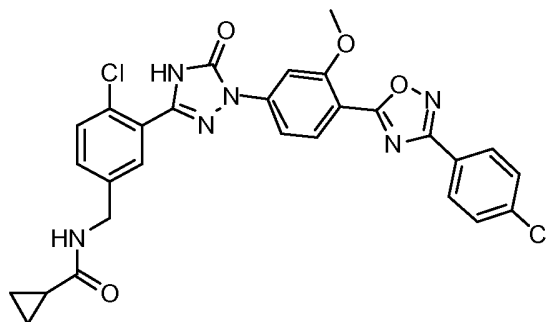


[0801] The title compound was prepared by following the procedure as described for Example-31 by using methyl 4-(3-(2-chloro-6-methylphenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzoate (Intermediate-27, 0.100 g, 0.268 mmol), 3-(trifluoromethyl)aniline (0.040 g, 0.403 mmol), trimethyl aluminium (2M solution in toluene) (0.5 mL) and dry toluene (5.0 mL) to afford 0.030 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 2.33 (s, 3H), 3.95 (s, 3H), 7.41-7.59 (m, 4H), 7.68 (t, $J = 6.9$ Hz, 1H), 7.75 (d, 1H), 7.77-7.82 (m, 2H), 7.95 (d, $J = 8.4$ Hz, 1H), 8.25 (s, 1H), 10.36 (s, 1H), 12.53 (br s, 1H); MS (m/z): 503.17 (M⁺).

Comparative Example-57

30 *N*-(4-Chloro-3-(1-(4-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)-3-methoxyphenyl)-5-oxo-4,5--dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)cyclopropanecarboxamide

[0802]

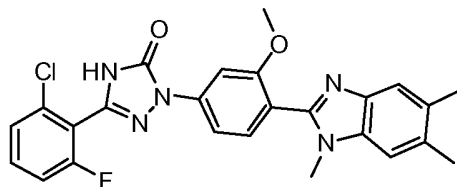


[0803] The title compound was prepared by following the procedure as described for Example-40 by using methyl 4-(3-(2-chloro-6-(cyclopropanecarboxamidomethyl)phenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzoate (Intermediate-30, 0.100 g, 0.21 mmol), 4-chloro-*N*'-hydroxybenzimidamide (Intermediate-19, 0.056 g, 0.32 mmol), sodium hydride (0.018 g, 0.43 mmol) and dry THF (5.0 mL) to afford 0.020 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.21 (m, 2H), 1.59 (m, 2H), 3.04 (m, 1H), 3.98 (s, 3H), 4.31 (m, 2H), 7.53 (m, 2H), 7.64 (m, 3H), 7.82 (m, 1H), 7.92 (m, 1H), 8.08 (m, 2H), 8.20 (m, 1H), 8.67 (s, 1H), 12.77 (br s, 1H); MS (m/z): 577.07 (M+H⁺).

Comparative Example-58

3-(2-Chloro-6-fluorophenyl)-1-(3-methoxy-4-(1,5,6-trimethyl-1*H*-benzo[d]imidazol-2-yl)phenyl)-1*H*-1,2,4-triazol-5(4*H*)-one

[0804]

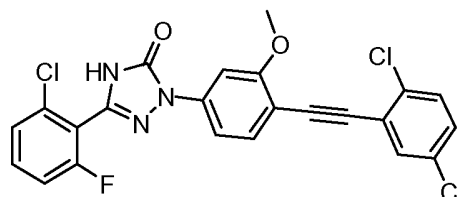


[0805] The title compound was prepared by following the procedure as described for Example-31 by using methyl 4-(3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxybenzoate (step-2 of Intermediate-15, 0.100 g, 0.26 mmol), *N*¹,4,5-trimethylbenzene-1,2-diamine (Intermediate-31, 0.048 g, 0.32 mmol), trimethyl aluminium (2M solution in toluene) (0.5 mL), dry toluene (5.0 mL) to afford 0.030 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 2.33 (s, 3H), 2.36 (s, 3H), 3.56 (s, 3H), 3.85 (s, 3H), 7.33 (s, 1H), 7.41 (s, 1H), 7.47-7.59 (m, 3H), 7.66-7.78 (m, 3H), 12.5 (br s, 1H); MS (*m/z*): 478.29 (*M*+*H*⁺).

Comparative Example-59

3-(2-Chloro-6-fluorophenyl)-1-(4-((2,5-dichlorophenyl)ethynyl)-3-methoxyphenyl)-1*H*-1,2,4-triazol-5(4*H*)-one

[0806]

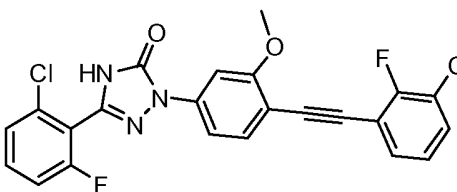


[0807] The title compound was prepared according to the procedure described in Example-3 using 3-(2-chloro-6-fluorophenyl)-1-(4-iodo-3-methoxyphenyl)-1*H*-1,2,4-triazol-5(4*H*)-one (Intermediate-32, 0.050 g, 0.11 mmol), 1,4-dichloro-2-ethynylbenzene (Intermediate-23, 0.029 g, 0.16 mmol), TBAF (0.101 g, 0.33 mmol), bis(triphenylphosphine)palladium(II) chloride (0.005 g, 0.04 mmol) and DMSO (3.0 mL) at 80°C to afford 0.010 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.89 (s, 3H), 7.49-7.56 (m, 3H), 7.59-7.73 (m, 6H), 12.90 (br s, 1H); MS (*m/z*): 487.95 (*M*+*H*⁺).

Comparative Example-60

1-(4-((3-Chloro-2-fluorophenyl)ethynyl)-3-methoxyphenyl)-3-(2-chloro-6-fluorophenyl)-1*H*-1,2,4-triazol-5(4*H*)-one

[0808]



[0809] The title compound was prepared according to the procedure described in Example-3 using 3-(2-chloro-6-fluorophenyl)-1-(4-iodo-3-methoxyphenyl)-1*H*-1,2,4-triazol-5(4*H*)-one (Intermediate-32, 0.050 g, 0.11 mmol), 1-chloro-

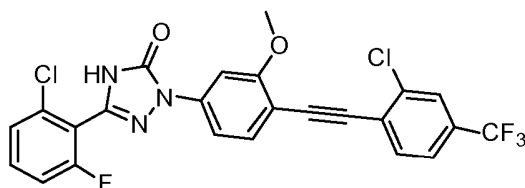
EP 2 718 284 B1

3-ethynyl-2-fluorobenzene (Intermediate-24, 0.033 g, 0.22 mmol), TBAF (0.080 g, 0.30 mmol), bis(triphenylphosphine)palladium(II) chloride (0.020 g, 0.022 mmol) and DMSO (3.0 ml) at 80°C to afford 0.015 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.89 (s, 3H), 7.28 (t, *J* = 7.8 Hz, 1H), 7.48 (t, *J* = 9.0 Hz, 1H), 7.56-7.70 (m, 7H), 12.79 (m, 1H); MS (*m/z*): 470.00 (M-H)⁻.

Comparative Example-61

1-4-((2-Chloro-4-(trifluoromethyl)phenyl)ethynyl)-3-methoxyphenyl)-3-(2-chloro-6-fluorophenyl)-1*H*-1,2,4-triazol-5(4*H*)-one

[0810]

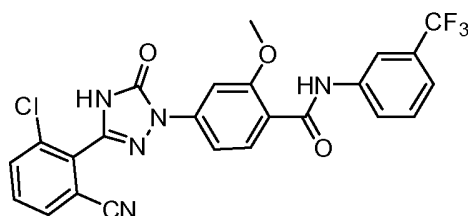


[0811] The title compound was prepared according to the procedure described in Example-3 using 3-(2-chloro-6-fluorophenyl)-1-(4-iodo-3-methoxyphenyl)-1*H*-1,2,4-triazol-5(4*H*)-one (Intermediate-32, 0.050 g, 0.11 mmol), 2-chloro-1-ethynyl-4-(trifluoromethyl)benzene (Intermediate-25, 0.044 g, 0.22 mmol), TBAF (0.080 g, 0.30 mmol), bis(triphenylphosphine)palladium(II) chloride (0.020 g, 0.022 mmol) and DMSO (3.0 mL) at 80°C to afford 0.012 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.89 (s, 3H), 7.52 (t, *J* = 9.0 Hz, 1H), 7.56-7.75 (m, 6H), 7.83 (d, *J* = 8.1 Hz, 1H), 8.02 (s, 1H), 12.78 (s, 1H); MS (*m/z*): 522.00 (M+H)⁺.

Comparative Example-62

4-(3-(2-Chloro-6-cyanophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxy-*N*-(3-(trifluoromethyl)phenyl)benzamide

[0812]

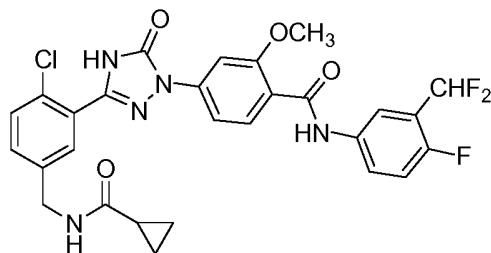


[0813] To a solution of 4-(3-(2-chloro-6-iodophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxy-*N*-(3-(trifluoromethyl)phenyl)benzamide (Intermediate-34, 0.130 g, 0.211 mmol) in DMF (5 mL) was added CuCN (0.020 g, 0.232 mmol) and reaction mixture was heated at 80°C for 4-5 h. The reaction mass was quenched with aq. KMnO₄ solution and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and concentrated to afford 0.015 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.95 (s, 3H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.59 (t, *J* = 8.4 Hz, 1H), 7.68 (d, *J* = 8.1 Hz, 1H), 7.80-7.86 (m, 3H), 7.95 (d, *J* = 8.7 Hz, 1H), 8.06-8.12 (m, 2H), 8.25 (s, 1H), 10.38 (s, 1H), 13.00 (br s, 1H); MS (*m/z*): 512.14 (M-H)⁻.

Example-63

4-(3-(2-Chloro-5-(cyclopropanecarboxamidomethyl)phenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-*N*-(3-(difluoromethyl)-4-fluorophenyl)-2-methoxybenzamide

[0814]

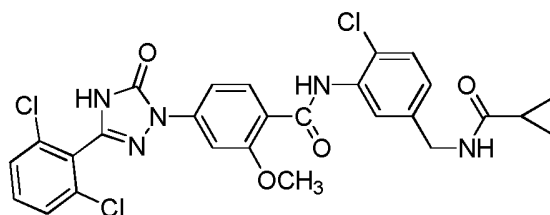


[0815] The title compound was prepared by following the procedure as described for step-2 of Intermediate-30, by using 4-(3-(5-(aminomethyl)-2-chlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-N-(3-(difluoromethyl)-4-fluorophenyl)-2-methoxybenzamide (Intermediate-35, 0.050 g, 0.09 mmol), cyclopropylcarbonyl chloride (0.016 g, 0.14 mmol), DIPEA (2.0 mL) and THF (5 mL) to afford 0.015 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 0.67 (s, 4H), 1.59 (m, 1H), 3.92 (s, 3H), 3.32 (d, *J* = 4.8 Hz, 2H), 7.03-7.33 (m, 1H), 7.35-7.47 (m, 3H), 7.62-7.68 (m, 2H), 7.76-7.84 (m, 2H), 8.09 (m, 2H), 8.70 (m, 1H), 10.28 (s, 1H), 12.69 (brs, 1H); MS (*m/z*): 586.12 (M+H)⁺.

Comparative Example-64

N-(2-Chloro-5-(cyclopropanecarboxamidomethyl)phenyl)-4-(3-(2,6-dichlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-2-methoxybenzamide

[0816]

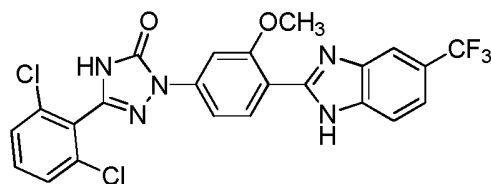


[0817] The title compound was prepared by following the procedure as described for Example-31 by using methyl 4-(3-(2,6-dichlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-2-methoxybenzoate (Intermediate-21, 0.100 g, 0.25 mmol), *N*-(3-amino-4-chlorobenzyl)cyclopropanecarboxamide (Intermediate-36, 0.085 g, 0.38 mmol), trimethyl aluminum (2M solution in toluene) (1 ml) and dry toluene (5.0 mL) to afford 0.020 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 0.68 (d, *J* = 8.1 Hz, 4H), 1.61 (m, 1H), 4.11 (s, 3H), 4.28 (d, *J* = 5.4 Hz, 2H), 7.04 (d, *J* = 6.9 Hz, 1H), 7.52 (d, *J* = 8.7 Hz, 1H), 7.71-7.79 (m, 4H), 7.88 (s, 1H), 8.19 (d, *J* = 9.0 Hz, 1H), 8.44 (s, 1H), 8.67 (m, 1H), 10.53 (s, 1H), 12.82 (br s, 1H); MS (*m/z*): 587.96 (M+H)⁺.

Comparative Example-65

3-(2,6-Dichlorophenyl)-1-(3-methoxy-4-(5-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)phenyl)-1H-1,2,4-triazol-5(4H)-one

[0818]



[0819] The title compound was prepared by following the procedure as described for Example-31 by using methyl 4-(3-(2,6-dichlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-2-methoxybenzoate (Intermediate-21, 0.150 g, 0.30

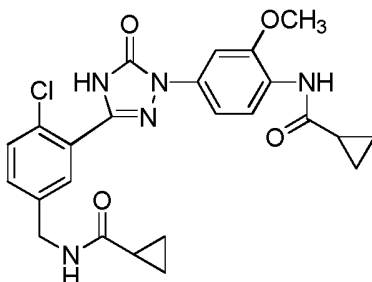
EP 2 718 284 B1

mmol), 4-(trifluoromethyl)benzene-1,2-diamine (0.081 g, 0.45 mmol), trimethyl aluminium (2M solution in toluene) (2 mL), dry toluene (5.0 mL) to afford 0.015 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 4.09 (s, 3H), 7.52 (s, 1H), 7.73-7.85 (m, 5H), 8.02-8.15 (m, 2H), 8.48 (m, 1H), 12.79 (br s, 1H), 13.33 (br s, 1H); MS (*m/z*): 520.14 (M+H)⁺.

Example-66

N-(4-Chloro-3-(1-(4-(cyclopropanecarboxamido)-3-methoxyphenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)cyclopropanecarboxamide

[0820]

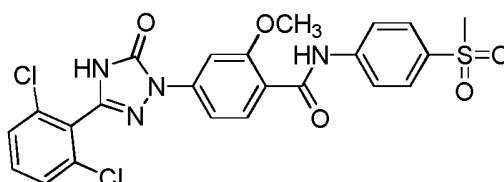


[0821] The title compound was prepared by following the procedure as described for step-2 of Intermediate-30 by using *N*-(3-(1-(4-amino-3-methoxyphenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-4-chlorobenzyl)cyclopropanecarboxamide (Intermediate-37, 0.050 g, 0.120 mmol), cyclopropylcarbonyl chloride (0.018 g, 0.180 mmol), DIPEA (2.0 mL) and THF (5 mL) to afford 0.015 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 0.69 (s, 4H), 0.77 (s, 4H), 1.60 (m, 1H), 2.08 (m, 1H), 3.88 (s, 3H), 4.33 (d, *J* = 5.4 Hz, 2H), 7.45 (m, 2H), 7.62 (s, 2H), 7.96 (d, *J* = 8.4 Hz, 1H), 8.69 (m, 1H), 9.49 (s, 1H), 12.54 (s, 1H); MS (*m/z*): 482.10 (M+H)⁺.

Comparative Example-67

4-(3-(2,6-Dichlorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxy-*N*-(4-(methylsulfonyl)phenyl)benzamide

[0822]

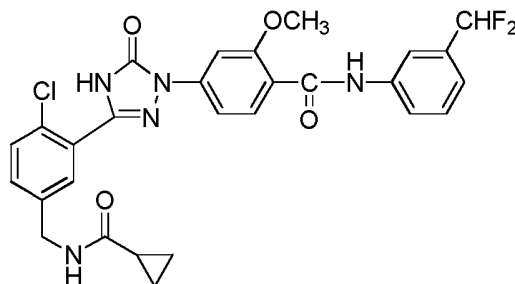


[0823] To a solution of 4-(3-(2,6-dichlorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxy-*N*-(4-(methylthio)phenyl)benzamide (Intermediate-38, 0.070 g, 0.13 mmol) in mixture of acetonitrile: water (3 mL:3 mL) was added oxone (0.053 g, 0.34 mmol). The reaction mass was stirred at RT for 24 h. The reaction mass was diluted with water and extracted with DCM. The organic layer was dried over anhydrous sodium sulphate and concentrated to afford 0.020 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.18 (s, 3H), 3.94 (s, 3H), 7.68-7.76 (m, 7H), 7.80 (d, *J* = 8.7 Hz, 1H), 7.90 (d, *J* = 8.7 Hz, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 10.48 (s, 1H), 12.76 (br s, 1H); MS (*m/z*): 531.14 (M+H)⁺.

Example-68

4-(3-(2-Chloro-5-(cyclopropanecarboxamidomethyl)phenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-*N*-(3-(difluoromethyl)phenyl)-2-methoxybenzamide

[0824]

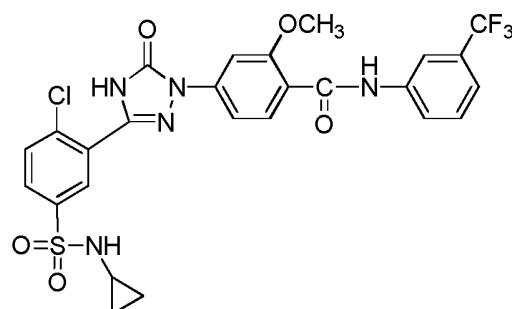


[0825] The title compound was prepared by following the procedure as described for step-2 of Intermediate-30 by using 4-(3-(5-(aminomethyl)-2-chlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-N-(3-(difluoromethyl)phenyl)-2-methoxybenzamide (Intermediate-39, 0.050 g, 0.10 mmol), cyclopropane carbonyl chloride (0.016 g, 0.15 mmol), DIPEA (2.0 mL) and THF (2 mL) to afford 0.015 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 0.68 (d, *J* = 8.7 Hz, 4H), 1.60 (m, 1H), 3.95 (s, 3H), 4.34 (d, *J* = 5.4 Hz, 2H), 7.05 (m, 1H), 7.29 (d, *J* = 7.9 Hz, 1H), 7.41-7.55 (m, 4H), 7.65 (d, *J* = 9.0 Hz, 1H), 7.74 (s, 1H), 7.82 (d, *J* = 8.7 Hz, 2H), 8.07 (s, 1H), 8.72 (m, 1H), 10.33 (s, 1H); MS (*m/z*): 566.29 (M-H)⁺.

Comparative Example-69

4-(3-(2-Chloro-5-(N-cyclopropylsulfamoyl)phenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-2-methoxy-N-(3-(trifluoromethyl)phenyl)benzamide

[0826]

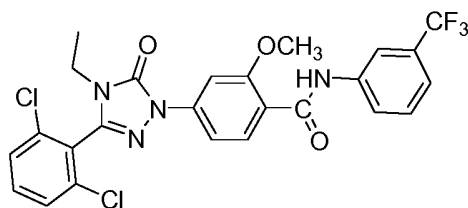


[0827] The title compound was prepared by following the procedure as described for Example-31 by using methyl 4-(3-(2-chloro-5-(N-cyclopropylsulfamoyl)phenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-2-methoxybenzoate (Intermediate-40, 0.040 g, 0.08 mmol), 3-(trifluoromethyl)aniline (0.020 g, 0.12 mmol), trimethyl aluminium (2M solution in toluene) (1 mL) and dry toluene (5.0 mL) to afford 0.015 g of crude product, which was purified by washing with methanol: DCM: DEE to afford 0.015 g of pure product. ¹H NMR (300 MHz, DMSO *d*₆): δ 0.42 (s, 2H), 0.54 (d, *J* = 5.4 Hz, 2H), 2.20 (m, 1H), 3.96 (s, 3H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.61 (t, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.80-7.84 (m, 2H), 7.96 (s, 3H), 8.18 (m, 2H), 8.26 (s, 1H), 10.40 (s, 1H), 12.88 (br s, 1H); MS (*m/z*): 606.13 (M-H)⁺.

Comparative Example-70

4-(3-(2,6-Dichlorophenyl)-4-ethyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-2-methoxy-N-(3-(trifluoromethyl)phenyl)benzamide

[0828]

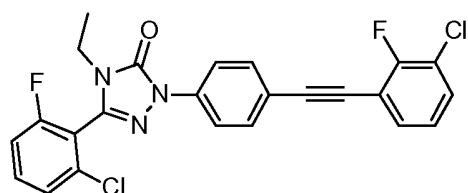


[0829] The title compound was prepared by following the procedure as described for Example-31 by using methyl 4-(3-(2,6-dichlorophenyl)-4-ethyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-2-methoxybenzoate (Intermediate-41, 0.040 g, 0.09 mmol), 3-(trifluoromethyl)aniline (0.010 g, 0.6 mmol), trimethyl aluminium (2M solution in toluene) (1 mL) and dry toluene (5.0 mL) to afford 0.015 g of crude product which was purified by column chromatography in basic alumina eluting with 0.2 % methanol: DCM to afford 0.015 g of pure product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.14 (t, 3H), 3.55-3.57 (m, 2H), 3.95 (s, 3H), 7.46 (m, 1H), 7.59 (t, 1H), 7.69-7.81 (m, 6H), 7.94 (m, 1H), 8.25 (s, 1H), 10.38 (s, 1H); MS (*m/z*): 551.11 (M+H)⁺.

Comparative Example-71

1-(4-((3-Chloro-2-fluorophenyl)ethynyl)phenyl)-3-(2-chloro-6-fluorophenyl)-4-ethyl-1H-1,2,4-triazol-5(4H)-one

[0830]

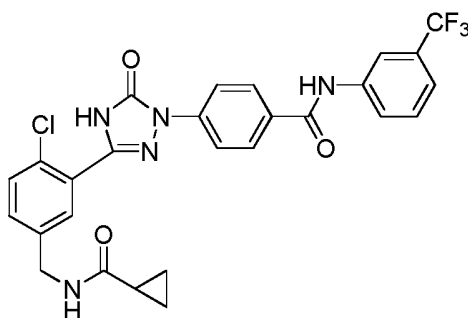


[0831] The title compound was prepared by following the procedure as described for Intermediate-41 by using 1-(4-((3-chloro-2-fluorophenyl)ethynyl)phenyl)-3-(2-chloro-6-fluorophenyl)-1H-1,2,4-triazol-5(4H)-one (Example-12, 0.070 g, 0.15 mmol), dry DMF (3 mL), NaH (0.010 g, 0.23 mmol) and ethyl bromide (0.026 g, 0.23 mmol) to afford 0.030 g of the crude product which was purified by column chromatography in basic alumina eluting with 0.2 % methanol: DCM to afford 0.030 g of pure product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.09 (t, 3H), 3.56 (m, 2H), 7.29 (t, 1H), 7.52-7.84 (m, 7H), 8.04 (d, *J* = 8.1 Hz, 2H); MS (*m/z*): 470.06 (M+H)⁺.

Example-72

4-(3-(2-Chloro-5-(cyclopropanecarboxamidomethyl)phenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-N-(3-(trifluoromethyl)phenyl)benzamide

[0832]



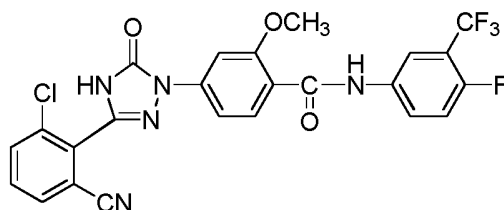
[0833] The title compound was prepared by following the procedure as described for Example-31 by using methyl 4-(3-(2-chloro-5-(cyclopropane carboxamidomethyl)phenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)benzoate (Interme-

diolate-42, 0.100 g, 0.24 mmol), 3-(trifluoromethyl)aniline (0.050 g, 0.36 mmol), trimethyl aluminium (2M solution in toluene) (1 mL) and dry toluene (8.0 mL). The reaction mass was quenched in water, extracted with DCM and the organic layer was concentrated to afford 0.010 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 0.70 (s, 4H), 1.62 (m, 1H), 4.33 (d, *J* = 6.3 Hz, 2H), 7.44-7.67 (m, 4H), 8.10-8.26 (m, 6H), 8.68 (m, 1H), 10.53 (s, 1H), 12.68 (br s, 1H); MS (*m/z*): 554.30 (M-H)⁻.

Comparative Example-73

4-(3-(2-Chloro-6-cyanophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-*N*-(4-fluoro-3-(trifluoromethyl)phenyl)-2-methoxybenzamide

[0834]

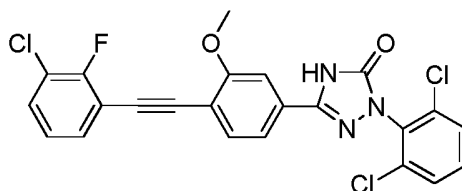


[0835] The title compound was prepared by following the procedure as described for Example-62 by using 4-(3-(2-chloro-6-iodophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-*N*-(4-fluoro-3-(trifluoromethyl)phenyl)-2-methoxybenzamide (Intermediate-43, 0.130 g, 0.21 mmol), DMF (4 mL) and CuCN (0.020 g, 0.23 mmol) to afford 0.030 g of crude product which was further purified by column chromatography in basic alumina eluting with 50 % methanol: DCM and few drops of 10 % ammonia to afford 0.030 g of pure product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.94 (s, 3H), 7.52 (t, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.81 (m, 3H), 8.05-8.12 (m, 3H), 8.26 (s, 1H), 10.40 (s, 1H), 13.01 (br s, 1H); MS (*m/z*): 532.12 (M+H)⁺.

Comparative Example-74

3-(4-((3-Chloro-2-fluorophenyl)ethynyl)-3-methoxyphenyl)-1-(2,6-dichlorophenyl)-1*H*-1,2,4-triazol-5(4*H*)-one

[0836]

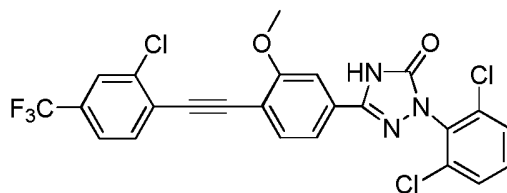


[0837] To a solution of 1-(2,6-dichlorophenyl)-3-(4-iodo-3-methoxyphenyl)-1*H*-1,2,4-triazol-5(4*H*)-one (Intermediate-45, 0.070 g, 0.15 mmol) in DMSO (3.0 mL) was added 1-chloro-3-ethynyl-2-fluorobenzene (Intermediate-24, 0.035 g, 0.22 mmol), TBAF (0.080 g, 0.30 mmol) and bis(triphenylphosphine)palladium(II) chloride (0.020 g, 0.022 mmol). The reaction mass was stirred at 80°C for 5-6 h. The reaction mass was quenched in water and extracted with DCM and concentrated. The obtained product was purified with column chromatography on silica gel eluting with 2.0 % EA: DCM to afford 0.020 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.92 (s, 3H), 7.29 (t, *J* = 8.4 Hz, 1H), 7.48-7.72 (m, 8H), 12-13 (br s, 1H); MS (*m/z*): 488.00 (M⁺).

Comparative Example-75

3-(4-((2-Chloro-4-(trifluoromethyl)phenyl)ethynyl)-3-methoxyphenyl)-1-(2,6-dichlorophenyl)-1*H*-1,2,4-triazol-5(4*H*)-one

[0838]

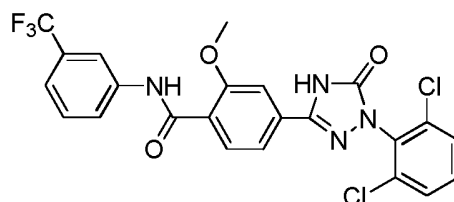


[0839] The title compound was prepared according to the procedure described in Example-3 using 1-(2,6-dichlorophenyl)-3-(4-iodo-3-methoxyphenyl)-1*H*-1,2,4-triazol-5(4*H*)-one (Intermediate-45, 0.070 g, 0.15 mmol), 2-chloro-1-ethynyl-4-(trifluoromethyl)benzene (Intermediate-25, 0.046 g, 0.22 mmol), TBAF (0.080 g, 0.30 mmol), bis(triphenylphosphine)palladium(II) chloride (0.020 g, 0.022 mmol) and DMSO (3.0 mL) at 80°C to afford 0.020 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.95 (s, 3H), 7.50-7.53 (m, 2H), 7.56-7.79 (m, 5H), 7.88 (d, *J* = 8.4 Hz, 1H), 8.05 (s, 1H), 12.04 (s, 1H); MS (*m/z*): 538.07 (*M*⁺).

Comparative Example-76

4-(1-(2,6-Dichlorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2-methoxy-*N*-(3-(trifluoromethyl)phenyl)benzamide

[0840]

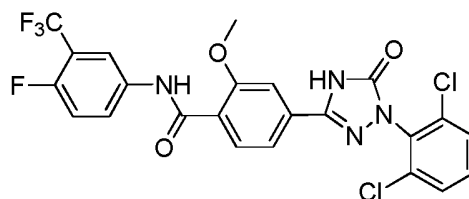


[0841] To a solution of methyl 4-(1-(2,6-dichlorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2-methoxybenzoate (Intermediate-46, 0.070g, 0.17 mmol) in dry toluene was added 3-(trifluoromethyl)aniline (0.043 g, 0.17mmol) followed by addition of trimethyl aluminum (2M solution in toluene) (0.5 mL). The reaction mixture was refluxed for 1 hr under inert atmosphere. The reaction mixture was brought to RT and quenched with water. Few drops of dilute HCl were added and the reaction mixture was extracted with DCM and concentrated. The obtained product was purified with column chromatography to afford 0.050 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.95 (s, 3H), 7.46 (d, *J* = 6.9 Hz, 1H), 7.54-7.65 (m, 4H), 7.72-7.76 (m, 3H), 7.94 (d, *J* = 8.4 Hz, 1H), 8.24 (s, 1H), 10.51 (s, 1H), 12.85 (s, 1H); MS (*m/z*): 523.04 (*M*⁺).

Comparative Example-77

4-(1-(2,6-Dichlorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-*N*-(4-fluoro-3-(trifluoromethyl)phenyl)-2-methoxybenzamide

[0842]

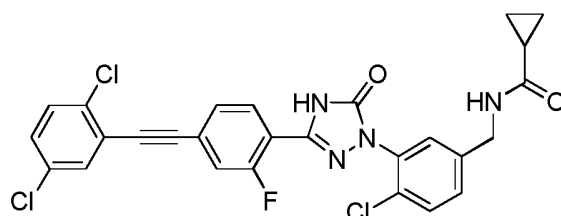


[0843] The title compound was prepared by following the procedure as described for step-6 of Intermediate-26 by using methyl 4-(1-(2,6-dichlorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2-methoxybenzoate (Intermediate-46, 0.070g, 0.17 mmol), 4-fluoro-3-(trifluoromethyl)aniline (0.048 g, 0.26 mmol), trimethyl aluminum (2M solution in toluene) (0.5 mL) and dry toluene (5.0 mL) to afford 0.040 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.95 (s, 3H), 7.49-7.64 (m, 4H), 7.72-7.76 (m, 3H), 7.99 (m, 1H), 8.25 (m, 1H), 10.52 (s, 1H), 12.86 (s, 1H); MS (*m/z*): 541.05 (*M*⁺).

Example-78

N-(4-Chloro-3-(3-(4-((2,5-dichlorophenyl)ethynyl)-2-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)cyclopropanecarboxamide

[0844]

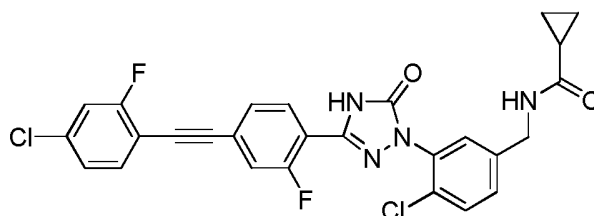


[0845] The title compound was prepared according to the procedure described in Example-3 by using *N*-(4-chloro-3-(3-(2-fluoro-4-iodophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)cyclopropanecarboxamide (Intermediate-48, 0.060 g, 0.10 mmol), 1,4-dichloro-2-ethynylbenzene (Intermediate-23, 0.026 g, 0.15 mmol), TBAF (0.064 g, 0.20 mmol), bis(triphenylphosphine)palladium(II) chloride (0.064 g, 0.20 mmol) and DMSO (3.0 mL) at 80°C to afford 0.020 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 0.68 (m, 4H), 1.60 (m, 1H), 4.33 (d, *J* = 5.7 Hz, 2H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.47 (s, 1H), 7.57-7.69 (m, 5H), 7.86-7.94 (m, 2H), 8.68 (m, 1H), 12.45 (br s, 1H); MS (*m/z*): 557.05 (*M*+*H*⁺).

Example-79

N-(4-Chloro-3-(3-(4-((4-chloro-2-fluorophenyl)ethynyl)-2-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)cyclopropanecarboxamide

[0846]

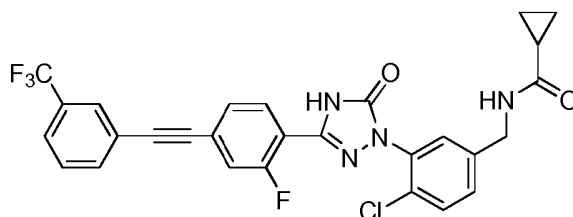


[0847] The title compound was prepared according to the procedure described in Example-3 using *N*-(4-chloro-3-(3-(2-fluoro-4-iodophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl) cyclopropanecarboxamide (Intermediate-48, 0.050 g, 0.097 mmol), 4-chloro-1-ethynyl-2-fluorobenzene (Intermediate-49, 0.022 g, 0.14 mmol), TBAF (0.061 g, 0.19 mmol), bis(triphenylphosphine)palladium(II) chloride (catalytic) and DMSO (1.0 mL) at 80°C to afford 0.025 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 0.65 - 0.68 (m, 4H), 1.60 (m, 1H), 4.32 (d, *J* = 6.0 Hz, 2H), 7.33-7.52 (m, 3H), 7.55-7.74 (m, 5H), 7.90 (m, 1H), 8.68 (m, 1H), 12.0 (br s, 1H); MS (*m/z*): 539.0 (*M*⁺).

Example-80

N-(4-Chloro-3-(3-(2-fluoro-4-((3-(trifluoromethyl)phenyl)ethynyl)phenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)cyclopropanecarboxamide

[0848]

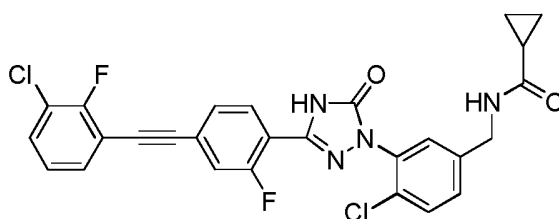


[0849] The title compound was prepared according to the procedure described in Example-3 by using *N*-(4-chloro-3-(3-(2-fluoro-4-iodophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl) cyclopropanecarboxamide (Intermediate-48, 0.050 g, 0.097 mmol), 1-ethynyl-3-(trifluoromethyl)benzene (Intermediate-50, 0.025 g, 0.14 mmol), TBAF (0.061 g, 0.19 mmol), bis(triphenylphosphine)palladium(II) chloride (catalytic) and DMSO (1.0 mL) at 80°C to afford 0.020 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 0.65-0.70 (m, 4H), 1.60 (m, 1H), 4.31 (d, *J* = 6.0 Hz, 2H), 7.28-7.41 (m, 2H), 7.51-7.61 (m, 4H), 7.67-7.97 (m, 4H), 8.68 (m, 1H), 12.0 (br s, 1H); MS (*m/z*): 555.05 (*M*+*H*⁺).

Example-81

N-(4-Chloro-3-(3-(4-((3-chloro-2-fluorophenyl)ethynyl)-2-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)cyclopropanecarboxamide

[0850]

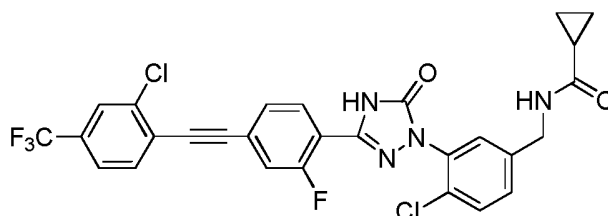


[0851] The title compound was prepared according to the procedure described in Example-3 using *N*-(4-chloro-3-(3-(2-fluoro-4-iodophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl) cyclopropanecarboxamide (Intermediate-48, 0.050 g, 0.097 mmol), 1-chloro-3-ethynyl-2-fluorobenzene (Intermediate-24, 0.022 g, 0.14 mmol), TBAF (0.061 g, 0.19 mmol), bis(triphenylphosphine)palladium(II) chloride (catalytic) and DMSO (1.0 mL) at 80°C to afford 0.030 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 0.69 (m, 4H), 1.60 (m, 1H), 4.33 (d, *J* = 5.7 Hz, 2H), 7.30-7.41 (m, 3H), 7.48-7.74 (m, 5H), 7.87-7.93 (m, 1H), 8.69 (m, 1H), 12.40- 12.58 (br s, 1H); MS (*m/z*): 539.36 (*M*⁺).

Example-82

N-(4-Chloro-3-(3-(4-((2-chloro-4-(trifluoromethyl)phenyl)ethynyl)-2-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)cyclopropanecarboxamide

[0852]



[0853] The title compound was prepared according to the procedure described in Example-3 by using *N*-(4-chloro-3-(3-(2-fluoro-4-iodophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl) cyclopropanecarboxamide (Intermediate-48, 0.060 g, 0.117 mmol), 2-chloro-1-ethynyl-4-(trifluoromethyl)benzene (Intermediate-25, 0.037 g, 0.175 mmol), TBAF

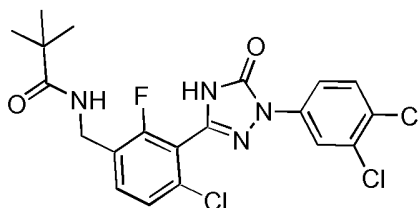
EP 2 718 284 B1

(0.073 g, 0.234 mmol), bis(triphenylphosphine)palladium(II) chloride (catalytic) and DMSO (1.0 mL) at 80°C to afford 0.030 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 0.66-0.69 (m, 4H), 1.60 (m, 1H), 4.33 (d, *J* = 6.0 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.48 (s, 1H), 7.62-7.64 (m, 2H), 7.73 (d, *J* = 11.4 Hz, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.92-7.97 (m, 2H), 8.09 (s, 1H), 8.69 (m, 1H), 12.00 (br s, 1H); MS (*m/z*): 589.14 (*M*⁺).

Example-83

N-(4-Chloro-3-(1-(3,4-dichlorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2-fluorobenzyl)pivalamide

[0854]

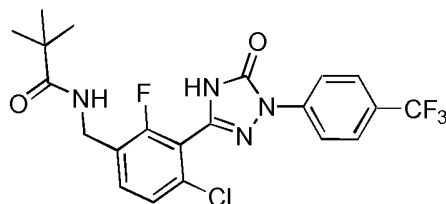


[0855] To a solution of *tert*-butyl 2-(3,4-dichlorophenyl)hydrazinecarboxylate (Intermediate-52, 0.060 g, 0.21 mmol) in DCM (10 mL) was added solution of 6-chloro-2-fluoro-3-(pivalamidomethyl)benzoyl isocyanate (Intermediate-51, 0.101 g, 0.32 mmol) in DCM and the reaction mixture was stirred for 20 h at room temperature, followed by addition of TFA (3 mL) and further stirred for 20 h at room temperature. The reaction mass was quenched in water, extracted with DCM and concentrated to afford crude product which was purified by column chromatography eluting with MeOH: DCM to afford 0.007 g of pure product. ¹H NMR (300 MHz, CDCl₃): δ 1.20 (s, 9H), 4.44 (d, *J* = 5.4 Hz, 2H), 6.20 (m, 1H), 7.29 (m, 1H), 7.41-7.49 (m, 2H), 7.91 (d, *J* = 8.1 Hz, 1H), 8.15 (s, 1H); MS (*m/z*): 471.26 (*M*⁺).

Example-84

N-(4-Chloro-2-fluoro-3-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide

[0856]

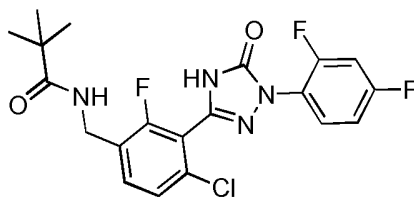


[0857] The title compound was prepared by following the procedure as described for Example-83 by using *tert*-butyl 2-(4-(trifluoromethyl)phenyl) hydrazinecarboxylate (Intermediate-53, 0.060 g, 0.21 mmol), 6-chloro-2-fluoro-3-(pivalamidomethyl)benzoyl isocyanate (Intermediate-51, 0.101 g, 0.32 mmol), DCM (10 mL) and TFA (3 mL) to afford 0.025 g of pure product. ¹H NMR (300 MHz, CDCl₃): δ 1.19 (s, 9H), 4.40 (m, 2H), 6.22 (m, 1H), 7.26 (m, 1H), 7.35 (m, 1H), 7.62 (d, *J* = 8.1 Hz, 2H), 8.12 (d, *J* = 7.8 Hz, 2H); MS (*m/z*): 471.18 (*M*⁺).

Example-85

N-(4-Chloro-3-(1-(2,4-difluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2-fluorobenzyl)pivalamide

[0858]

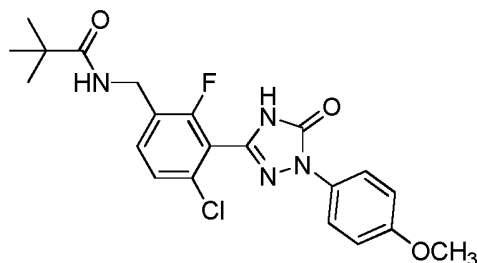


[0859] The title compound was prepared by following the procedure as described for Example-83 by using *tert*-butyl 2-(2,4-difluorophenyl)hydrazinecarboxylate (Intermediate-54, 0.060 g, 0.21 mmol), 6-chloro-2-fluoro-3-(pivalamidomethyl)benzoyl isocyanate (Intermediate-51, 0.101 g, 0.32 mmol), DCM (10 mL) and TFA (3 mL) to afford 0.018 g of pure product. ^1H NMR (300 MHz, CDCl_3): δ 1.16 (s, 9H), 4.38 (d, J = 5.4 Hz, 2H), 6.25 (m, 1H), 6.79- 6.82 (m, 1H), 6.90- 6.96 (m, 2H), 7.20-7.32 (m, 2H), 7.50-7.53 (m, 1H); MS (m/z): 437.26 ($\text{M}+\text{H}^+$).

Example-86

N-(4-Chloro-2-fluoro-3-(1-(4-methoxyphenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide

[0860]

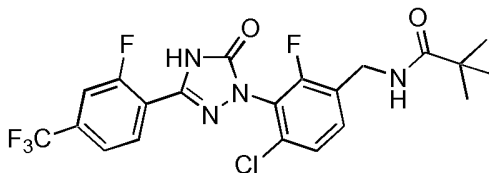


[0861] The title compound was prepared by following the procedure as described for Example-83 by using *tert*-butyl 2-(4-methoxyphenyl)hydrazinecarboxylate (Intermediate-55, 0.060 g, 0.21 mmol), 6-chloro-2-fluoro-3-(pivalamidomethyl)benzoyl isocyanate (Intermediate-51, 0.101 g, 0.32 mmol), DCM (10 mL) and TFA (3 mL) to afford 0.018 g of pure product. ^1H NMR (400 MHz, CDCl_3): δ 1.20 (s, 9H), 3.82 (s, 3H), 4.46 (d, J = 5.8 Hz, 2H), 6.12 (m, 1H), 6.95 (d, J = 8.9 Hz, 2H), 7.26-7.30 (m, 1H), 7.43 (t, J = 7.9 Hz, 1H), 7.82 (d, J = 8.9 Hz, 2H), 11.01 (br s, 1H); MS (m/z): 433.20 ($\text{M}+\text{H}^+$).

Example-87

N-(4-Chloro-2-fluoro-3-(3-(2-fluoro-4-(trifluoromethyl)phenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)pivalamide

[0862]

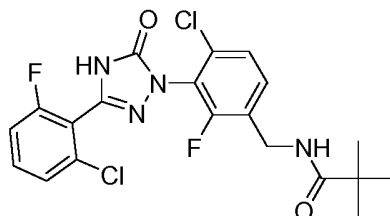


[0863] The title compound was prepared by following the procedure as described for Example-83 by using *tert*-butyl 2-(6-chloro-2-fluoro-3-(pivalamidomethyl)phenyl) hydrazinecarboxylate (Intermediate-57, 0.050 g, 0.13 mmol), 2-fluoro-4-(trifluoromethyl)benzoyl isocyanate (Intermediate-56, 0.10 g, 0.26 mmol), DCM (10 mL) and TFA (3 mL) to afford 0.030 g of pure product. ^1H NMR (400 MHz, CDCl_3): δ 1.20 (s, 9H), 4.48 (d, J = 5.7 Hz, 2H), 6.13 (m, 1H), 7.31 (d, J = 8.5 Hz, 1H), 7.41-7.51 (m, 3H), 8.12 (t, J = 7.9 Hz, 1H); MS (m/z): 489.20 ($\text{M}+\text{H}^+$).

Example-88

N-(4-Chloro-3-(3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-fluorobenzyl)pivalamide

[0864]

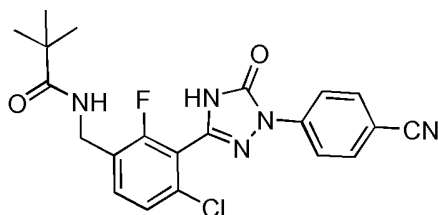


[0865] The title compound was prepared by following the procedure as described for Example-83 by using *tert*-butyl 2-(6-chloro-2-fluoro-3-(pivalamidomethyl)phenyl)hydrazinecarboxylate (Intermediate-57, 0.050 g, 0.13 mmol), 2-chloro-6-fluorobenzoyl isocyanate (Intermediate-8, 0.060 g, 0.26 mmol), DCM (10 mL) and TFA (3 mL) to afford 0.025 g of pure product. ¹H NMR (400 MHz, CDCl₃): δ 1.19 (s, 9H), 4.48 (m, 2H), 6.09 (m, 1H), 7.15 (t, *J* = 8.4 Hz, 1H), 7.32 (t, *J* = 8.2 Hz, 2H), 7.40-7.45 (m, 2H), 10.66 (br s, 1H); MS (*m/z*): 455.21 (M⁺).

Example-89

N-(4-chloro-3-(1-(4-cyanophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2-fluorobenzyl)pivalamide

[0866]

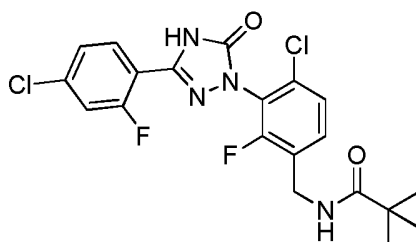


[0867] The title compound was prepared by following the procedure as described for Example-83 by using *tert*-butyl 2-(4-cyanophenyl)hydrazinecarboxylate (step-2 of Intermediate 17, 0.060 g, 0.25 mmol), 6-chloro-2-fluoro-3-(pivalamidomethyl)benzoyl isocyanate (Intermediate-51, 0.160 g, 0.51 mmol), DCM (10 mL) and TFA (3 mL) to afford 0.020 g of pure product. ¹H NMR (400 MHz, CDCl₃): δ 1.20 (s, 9H), 4.45 (d, *J* = 5.9 Hz, 2H), 6.19 (m, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.43 (t, *J* = 7.9 Hz, 1H), 7.73 (d, *J* = 8.8 Hz, 2H), 8.19 (d, *J* = 8.4 Hz, 2H), 10.72 (br s, 1H); MS (*m/z*): 426.27 (M-H⁺).

Example-90

N-(4-Chloro-3-(3-(4-chloro-2-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-fluorobenzyl)pivalamide

[0868]



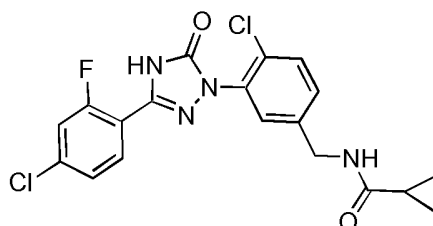
EP 2 718 284 B1

[0869] The title compound was prepared by following the procedure as described for Example-83 by using *tert*-butyl 2-(6-chloro-2-fluoro-3-(pivalamidomethyl)phenyl)hydrazinecarboxylate (Intermediate-57, 0.050 g, 0.13 mmol), 4-chloro-2-fluorobenzoyl isocyanate (Intermediate-58, 0.060 g, 0.26 mmol), DCM (10 mL) and TFA (3 mL) to afford 0.025 g of desired product. ¹H NMR (400 MHz, CDCl₃): δ 1.21 (s, 9H), 4.50 (t, *J* = 7.2 Hz, 2H), 6.07 (m, 1H), 7.22- 7.26 (m, 2H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.44 (t, *J* = 8.1 Hz, 1H), 7.93 (t, *J* = 8.6 Hz, 1H); MS (*m/z*): 455.08 (M⁺).

Example-91

N-(4-Chloro-3-(3-(4-chloro-2-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)cyclopropanecarboxamide

[0870]

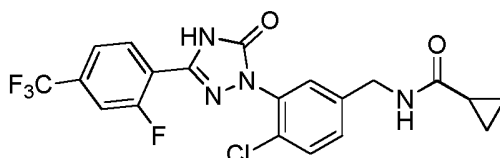


[0871] The title compound was prepared by following the procedure as described for Example-83 by using *tert*-butyl 2-(2-chloro-5-(cyclopropanecarboxamidomethyl) phenyl)hydrazinecarboxylate (step-7 of Intermediate-48, 0.060 g, 0.17 mmol), 4-chloro-2-fluorobenzoyl isocyanate (Intermediate-58, 0.035 g, 0.71 mmol), DCM (10 mL) and TFA (3 mL) to afford 0.040 g of desired product. ¹H NMR (400 MHz, DMSO *d*₆): δ 0.67-0.69 (m, 4H), 1.59 - 1.60 (m, 1H), 4.31 (d, *J* = 5.9 Hz, 2H), 7.36 (dd, *J* = 6.24 Hz, 1H), 7.45 (dd, *J* = 8.5 Hz, 2H), 7.59 (d, *J* = 8.3 Hz, 1H), 7.65 (d, *J* = 8.8 Hz, 1H), 7.83 (t, *J* = 8.3 Hz, 1H), 7.64 (t, *J* = 6 Hz, 1H), 12.51 (br s, 1H); MS (*m/z*): 421.08 (M⁺).

Example-92

N-(4-Chloro-3-(3-(2-fluoro-4-(trifluoromethyl)phenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)cyclopropanecarboxamide

[0872]

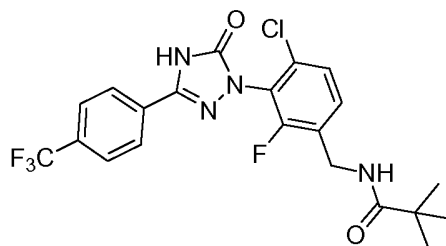


[0873] The title compound was prepared by following the procedure as described for Example-83 by using *tert*-butyl 2-(2-chloro-5-(cyclopropanecarboxamidomethyl) phenyl)hydrazinecarboxylate (step-7 of Intermediate-48, 0.060 g, 0.17 mmol), 2-fluoro-4-(trifluoromethyl)benzoyl isocyanate (Intermediate-56, 0.035 g, 0.82 mmol), DCM (10 mL) and TFA (3 mL) to afford 0.045 g of desired product. ¹H NMR (400 MHz, DMSO *d*₆): δ 0.67 (m, 4H), 1.60 (m, 1H), 4.3 (d, *J* = 5.9 Hz, 2H), 7.37 (d, *J* = 6.4 Hz, 1H), 7.46 (s, 1H), 7.60 (d, *J* = 8.3 Hz, 1H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.89 (d, *J* = 10.56 Hz, 1H), 8.05 (t, *J* = 7.7 Hz, 1H), 8.65 (t, *J* = 5.8 Hz, 1H), 12.6 (br s, 1H); MS (*m/z*): 454.98 (M⁺).

Example-93

N-(4-Chloro-2-fluoro-3-(5-oxo-3-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)pivalamide

[0874]

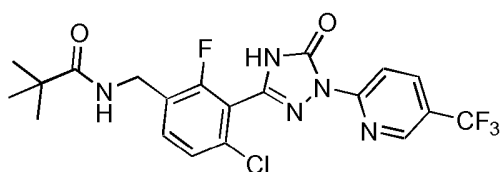


[0875] The title compound was prepared by following the procedure as described for Example-83 by using *tert*-butyl 2-(6-chloro-2-fluoro-3-(pivalamidomethyl)phenyl) hydrazinecarboxylate (Intermediate-57, 0.050 g, 0.13 mmol), 4-(trifluoromethyl) benzoyl isocyanate (Intermediate-59, 0.060 g, 0.26 mmol), DCM (10 mL) and TFA (3 mL) to afford 0.045 g of desired product. ^1H NMR (400 MHz, DMSO d_6): δ 1.12 (s, 9H), 4.30 (d, J = 4.4 Hz, 2H), 7.41 (t, J = 8 Hz, 1H), 7.53 (d, J = 8.5 Hz, 1H), 7.91 (d, J = 8.4 Hz, 2H), 8.0 (d, J = 8.2 Hz, 2H), 8.17 (t, J = 5.8 Hz, 1H), 12.9 (br s, 1H); MS (m/z): 471.10 ($M+H^+$).

Example-94

N-(4-Chloro-2-fluoro-3-(5-oxo-1-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydro-1H-1,2,4-triazol-3-yl)benzyl)pivalamide

[0876]

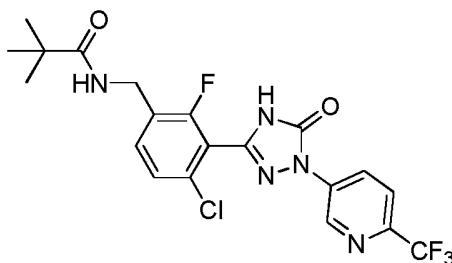


[0877] The title compound was prepared by following the procedure as described for Example-83 by using *tert*-butyl 2-(5-(trifluoromethyl)pyridin-2-yl)hydrazinecarboxylate (Intermediate-60, 0.050 g, 0.18 mmol), 6-chloro-2-fluoro-3-(pivalamidomethyl)benzoyl isocyanate (Intermediate-51, 0.120 g, 0.36 mmol), DCM (10 mL) and TFA (3 mL) to afford 0.012 g of desired product. ^1H NMR (400 MHz, DMSO d_6): δ 1.13 (s, 9H), 4.30 (d, J = 5.6 Hz, 2H), 7.11 (br s, 1H), 7.46 (t, J = 8 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H), 8.14 (m, 1H), 8.28 (d, J = 8.8 Hz, 1H), 8.35 (dd, J = 7.2 Hz, 1H), 8.87 (s, 1H); MS (m/z): 472.24 ($M+H^+$).

Example-95

N-(4-Chloro-2-fluoro-3-(5-oxo-1-(6-(trifluoromethyl)pyridin-3-yl)-4,5-dihydro-1H-1,2,4-triazol-3-yl)benzyl)pivalamide

[0878]



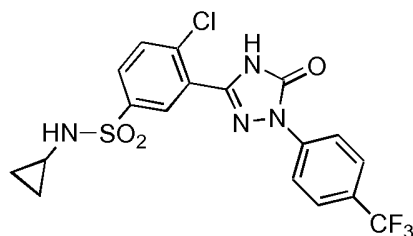
[0879] The title compound was prepared by following the procedure as described for Example-83 by using *tert*-butyl 2-(6-(trifluoromethyl)pyridin-3-yl) hydrazine carboxylate (Intermediate-61, 0.050 g, 0.18 mmol), 6-chloro-2-fluoro-3-(pivalamidomethyl)benzoyl isocyanate (Intermediate-51, 0.120 g, 0.36 mmol), DCM (10 mL) and TFA (3 mL) to afford 0.013 g of desired product. ^1H NMR (400 MHz, DMSO d_6): δ 1.13 (s, 9H), 4.30 (d, J = 5.6 Hz, 2H), 7.11 (br s, 1H), 7.46 (t, J = 8 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 8.16 (m, 1H), 8.56 (dd, J = 6.4 Hz, 1H), 9.30 (m, 1H);

MS (m/z): 472.26 (M+H⁺).

Comparative Example-96

4-Chloro-*N*-cyclopropyl-3-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzenesulfonamide

[0880]

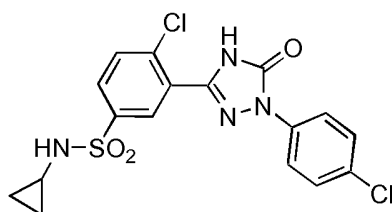


[0881] The title compound was prepared by following the procedure as described for Example-83 by using *tert*-butyl 2-(4-(trifluoromethyl)phenyl)hydrazinecarboxylate (Intermediate-53, 0.050 g, 0.18 mmol), 2-chloro-5-(*N*-cyclopropylsulfamoyl)benzoyl isocyanate (step-4 of Intermediate-40, 0.108 g, 0.36 mmol), DCM (10 mL) and TFA (3 mL) to afford 0.050 g of desired product. ¹H NMR (400 MHz, DMSO *d*₆): δ 0.40-0.42 (m, 2H), 0.50-0.54 (m, 2H), 2.17-2.21 (m, 1H), 7.85 (d, *J* = 8.8 Hz, 2H), 7.92-7.98 (m, 2H), 8.15-8.21 (m, 4H), 12.84 (s, 1H); MS (m/z): 457.15 (M+H⁺).

Comparative Example-97

4-Chloro-3-(1-(4-chlorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-*N*-cyclopropylbenzenesulfonamide

[0882]

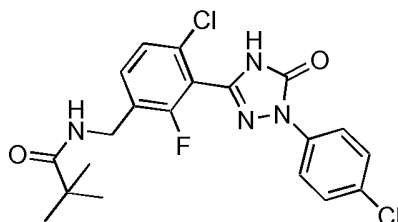


[0883] The title compound was prepared by following the procedure as described for Example-83 by using *tert*-butyl 2-(4-chlorophenyl)hydrazinecarboxylate (Intermediate-62, 0.050 g, 0.20 mmol), 2-chloro-5-(*N*-cyclopropylsulfamoyl)benzoyl isocyanate (step-4 of Intermediate-40, 0.123 g, 0.41 mmol), DCM (10 mL) and TFA (3 mL) to afford 0.025 g of pure product. ¹H NMR (400 MHz, DMSO *d*₆): δ 0.39-0.41 (m, 2H), 0.49-0.52 (m, 2H), 2.17- 2.20 (m, 1H), 7.52-7.55 (d, *J* = 8.0 Hz, 2H), 7.91-8.00 (m, 5H), 8.14 (m, 1H), 12.60 (br s, 1H); MS (m/z): 425.10 (M⁺).

Example-98

N-(4-Chloro-3-(1-(4-chlorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2-fluorobenzyl)pivalamide

[0884]



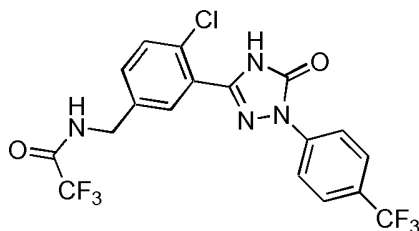
EP 2 718 284 B1

[0885] The title compound was prepared by following the procedure as described for Example-83 by using *tert*-butyl 2-(4-chlorophenyl)hydrazinecarboxylate (Intermediate-62, 0.050 g, 0.20 mmol), 6-chloro-2-fluoro-3-(pivalamidomethyl)benzoyl isocyanate (Intermediate-51, 0.130 g, 0.41 mmol), DCM (10 mL) and TFA (3 mL) to afford 0.040 g of pure product. ¹H NMR (400 MHz, DMSO *d*₆): δ 1.12 (s, 9H), 4.30 (d, *J* = 6.0 Hz, 2H), 7.24-7.47 (m, 2H), 7.52 (d, *J* = 7.2 Hz, 2H), 7.94 (d, *J* = 8.8 Hz, 2H), 8.16 (m, 1H), 12.10 (br s, 1H); MS (*m/z*): 437.16 (*M*⁺).

Example-99

N-(4-Chloro-3-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide

[0886]

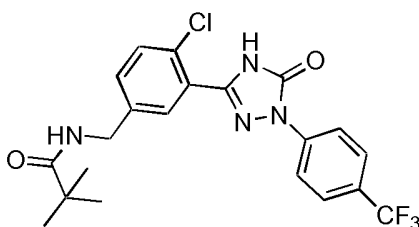


[0887] The title compound was prepared according to the procedure described for Example-83 by using *tert*-butyl 2-(4-(trifluoromethyl)phenyl)hydrazinecarboxylate (Intermediate-53, 1.00 g, 3.63 mmol), 2-chloro-5-((2,2,2-trifluoroacetamido)methyl)benzoyl isocyanate (step-3 of Intermediate-26, 1.30 g, 4.03 mmol), DCM (20 mL) and TFA (5.0 mL) to afford 0.700 g of the desired product. ¹H NMR (400 MHz, DMSO *d*₆): δ 4.44-4.46 (d, *J* = 6 Hz, 2H), 7.48-7.50 (d, *J* = 8.4 Hz, 1H), 7.65-7.68 (m, 2H), 7.84-7.86 (d, *J* = 8.8 Hz, 2H), 8.17-8.19 (d, *J* = 8.4 Hz, 2H), 10.05 (br s, 1H), 12.69 (br s, 1H); MS (*m/z*): 463.17 (*M*-H⁻).

Example-100

N-(4-Chloro-3-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide

[0888]

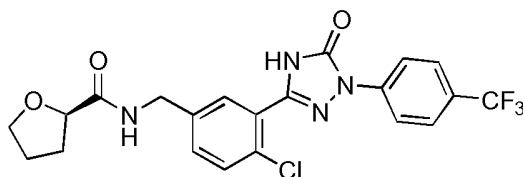


[0889] To a solution of 3-(5-(aminomethyl)-2-chlorophenyl)-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,4-triazol-5(4*H*)-one (Intermediate-63, 0.070 g, 0.189 mmol) in dry THF (5 mL) was added DIPEA (3 mL) and stirred for 20 minutes. The reaction mixture was cooled to 0°C and pivaloyl chloride (0.025 g, 0.283 mmol) was added and stirred for 3 h at RT. The reaction mass was quenched in water, extracted with DCM: MeOH and concentrated to afford of the crude product which was purified by column chromatography eluting with MeOH:DCM to afford 0.030 g of the desired title product. ¹H NMR (400 MHz, DMSO *d*₆): δ 1.12 (s, 9H), 4.28-4.30 (d, *J* = 6Hz, 2 H), 7.39-7.42 (d, *J* = 8. Hz, 1H), 7.59-7.61 (d, *J* = 6.4Hz, 2H), 7.84-7.86 (d, *J* = 8.8 Hz, 2H), 8.14-8.19 (m, 3H), 12.59 (br s, 1H); MS (*m/z*): 451.29 (*M*-H⁻).

Example-101

(*R*)-*N*-(4-Chloro-3-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)tetrahydrofuran-2-carboxamide

[0890]

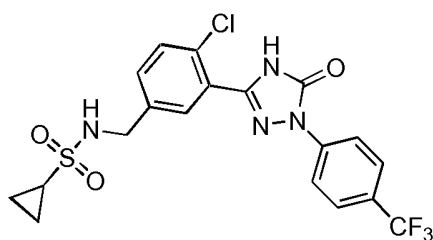


[0891] To a solution of 3-(5-(aminomethyl)-2-chlorophenyl)-1-(4-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-5(4H)-one (Intermediate-63, 0.070 g, 0.189 mmol) in dry THF: DMF (4: 1 mL) was added TBTU (0.182g, 0.567 mmol) and TEA (3 mL) and stirred for 1h under nitrogen atmosphere. To the reaction mixture (*R*)-(+)-tetrahydro-2-furoic acid (0.032 g, 0.283 mmol) was added and stirred for 18 h at room temperature. The reaction mass was quenched in water, extracted with ethyl acetate and concentrated to afford crude product which was purified by column chromatography eluting with MeOH: DCM to afford 0.025 g of the desired title product. ¹H NMR (400 MHz, DMSO *d*₆): δ 1.23 (s, 2H), 1.74-1.92 (m, 3H), 2.09-2.24, (m, 1H), 3.75-3.80 (m, 1H), 3.89-3.94 (m, 1H), 4.26-4.37 (m, 3H), 7.43-7.45 (d, *J* = 8.4 Hz, 1H), 7.61-7.63 (d, *J* = 8.4Hz, 2H), 7.85-7.87 (d, *J* = 8.8 Hz, 2H), 8.19-8.21 (d, *J* = 8.8Hz, 2H), 8.50-8.53 (m, 1H), 12.71 (br s, 1H); MS (*m/z*): 465.55 (M-H⁺).

Example-102

N-(4-Chloro-3-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1H-1,2,4-triazol-3-yl)benzyl)cyclopropanesulfonamide

[0892]

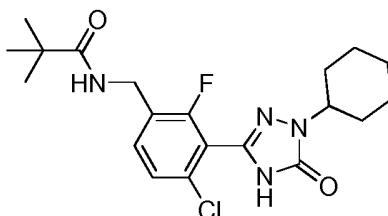


[0893] The title compound was prepared according to the procedure described in Example-100 by using 3-(5-(aminomethyl)-2-chlorophenyl)-1-(4-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-5(4H)-one (Intermediate-63, 0.070 g, 0.189 mmol), cyclopropanesulfonyl chloride (0.2 mL), DIPEA (3 mL), and dry THF (5 mL) to afford 0.029 g of pure product. ¹H NMR (400 MHz, DMSO *d*₆): δ 0.86-0.92 (m, 4H), 1.14-1.24 (m, 1H), 4.26-4.28 (d, *J* = 6.4 Hz, 2H), 7.57-7.60 (d, *J* = 8.4 Hz, 1H), 7.63-7.68 (d, *J* = 8.4Hz, 1H), 7.58-7.81 (m, 1H), 7.86-7.88 (d, *J* = 8.8 Hz, 2H), 8.19-8.21 (d, *J* = 8.4Hz, 2H), 12.89 (br s, 1H); MS (*m/z*): 471.30 (M-H⁺).

Comparative Example-103

N-(4-Chloro-3-(1-cyclohexyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-2-fluorobenzyl)pivalamide

[0894]



[0895] The title compound was prepared by following the procedure as described for Example-83 by using *tert*-butyl 2-(cyclohexyl)hydrazinecarboxylate (Intermediate-64, 0.050 g, 0.23 mmol), 6-chloro-2-fluoro-3-(pivalamidomethyl)benzoyl isocyanate (Intermediate-51, 0.225 g, 0.70 mmol), DCM (10 mL) and TFA (3 mL) to afford 0.015 g of pure product. ¹H NMR (400 MHz, DMSO *d*₆): δ 1.13 (s, 9H), 1.22-1.23 (m, 2H), 1.30-1.37 (m, 2H), 1.62-1.64 (m, 2H), 1.78-1.81 (m,

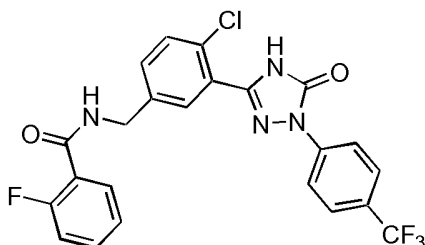
EP 2 718 284 B1

4H), 3.90-3.92 (m, 1H), 4.27-4.28 (d, $J = 4.8$ Hz, 2H), 7.37 -7.41 (t, 1H), 7.46-7.48 (d, 1H), 8.17 (br s, 1H); MS (m/z): 409.36 (M+H⁺).

Example-104

N-(4-Chloro-3-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)-2-fluorobenzamide

[0896]

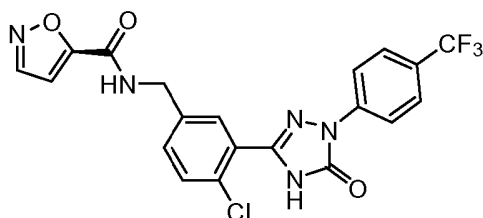


[0897] To a solution of 3-(5-(aminomethyl)-2-chlorophenyl)-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,4-triazol-5(4*H*)-one (Intermediate-63, 0.060 g, 0.162 mmol) in dry THF (5 mL) was added DIPEA (3 mL) and stirred for 20 minutes. The reaction mixture was cooled to 0°C and 2-fluorobenzoyl chloride (0.038 g, 0.243 mmol) was added and stirred for 3 h at room temperature. The reaction mass was quenched in water, extracted with DCM: MeOH and concentrated to afford crude product which was purified by column chromatography eluting with MeOH: DCM to afford 0.030 g of pure product. ¹H NMR (400 MHz, DMSO d_6): δ 4.50-4.52 (d, $J = 8$ Hz, 2H), 7.25-7.33 (m, 2H), 7.52-7.55 (m, 2H), 7.63-7.65 (m, 2H), 7.72-7.86 (d, $J = 2.4$ Hz, 1H), 7.83-7.86 (d, $J = 11.6$ Hz, 2H), 8.17-8.20 (d, $J = 11.6$ Hz, 2H), 8.95-8.99 (t, 1H), 12.69 (br s, 1H); MS (m/z): 491.17 (M+H⁺).

Example-105

N-(4-Chloro-3-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)isoxazole-5-carboxamide

[0898]

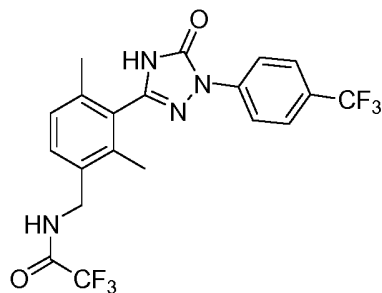


[0899] To a solution of 3-(5-(aminomethyl)-2-chlorophenyl)-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,4-triazol-5(4*H*)-one (Intermediate-63, 0.060 g, 0.162 mmol) in dry THF (5 mL) was added DIPEA (3 mL) and stirred for 20 minutes. The reaction mixture was cooled to 0°C and isoxazole-5-carboxyl chloride (0.032 g, 0.243 mmol) was added and stirred for 3 h at room temperature. The reaction mass was quenched in water, extracted with DCM: MeOH and concentrated to afford crude product which was purified by column chromatography eluting with MeOH: DCM to afford 0.030 g of pure product. ¹H NMR (400 MHz, DMSO d_6): δ 4.50-4.52 (d, $J = 8$ Hz, 2H), 7.09-7.10 (d, $J = 2$ Hz, 1H), 7.43-7.45 (d, $J = 8.4$ Hz, 1H), 7.50-7.53 (d, $J = 10.4$ Hz, 1H), 7.59-7.64 (d, $J = 18$ Hz, 1H), 7.82-7.85 (d, $J = 8.8$ Hz, 2H), 8.17-8.19 (d, $J = 8.4$ Hz, 2H), 8.74-8.75 (d, $J = 2$ Hz, 1H), 9.58-9.61 (t, 1H), 12.61-12.74 (br s, 1H); MS (m/z): 464.11 (M+H⁺).

Example-106

N-(3-(1-(4-(Trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2,4-dimethylbenzyl)-2,2,2-trifluoroacetamide

[0900]

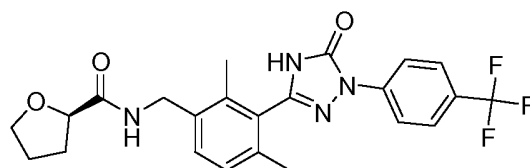


[0901] The title compound was prepared according to the procedure described in Example-83 by using *tert*-butyl 2-(4-(trifluoromethyl)phenyl)hydrazinecarboxylate (Intermediate-53, 1.00 g, 3.63 mmol), 3-((2,2,2-trifluoroacetamido)methyl)-2,6-dimethylbenzyl isocyanate (Intermediate-65, 1.00 g, 3.33 mmol), DCM (20 mL), trifluoro acetic acid (5.0 mL) to afford 0.700 g of the desired product. ^1H NMR (400 MHz, DMSO d_6): δ 2.20 (s, 3H), 2.22 (s, 3H), 4.40 (d, J = 4.2 Hz, 2H), 7.21 (d, J = 6.0 Hz, 1H), 7.29 (d, J = 6.0 Hz, 1H), 7.82 (d, J = 6.6 Hz, 1H), 8.17 (d, J = 6.6 Hz, 1H), 9.95 (t, J = 6.9 Hz, 1H), 12.32 (br s, 1H); MS (m/z): 457.26 ($M-H$) $^-$.

Example-107

(*R*)-*N*-(2,4-Dimethyl-3-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)tetrahydrofuran-2-carboxamide

[0902]

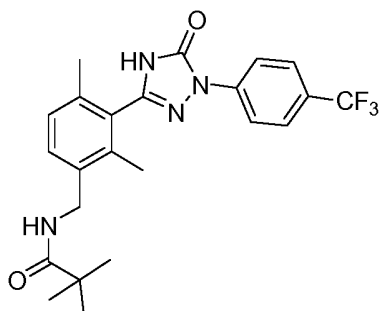


[0903] To a solution of 5-(3-(aminomethyl)-2,6-dimethylphenyl)-2-(4-(trifluoromethyl)phenyl)-2*H*-1,2,4-triazol-3(4*H*)-one (Intermediate-66, 0.050 g, 0.138 mmol) in dry THF:DMF (4 mL:1 mL), TBTU (0.132 g, 0.414 mmol) and TEA (1.0 mL) were added and the reaction mass was stirred for 1h under nitrogen atmosphere. To the reaction mass, (*R*)-(-)-tetrahydrofuran-2-carboxylic acid (0.024 g, 0.207 mmol) was added and stirred for 18 h at room temperature. After completion of the reaction, the reaction mass was quenched in water, extracted with ethyl acetate and concentrated to afford crude product which was purified by column chromatography by eluting with solution of 2% ammonia in 10% MeOH:DCM to afford 0.017 g of the title product. ^1H NMR (400 MHz, DMSO d_6): δ 1.79 (m, 3H), 1.87 (m, 3H), 2.20 (s, 6H), 3.74-3.79 (m, 1H), 3.88-3.92 (m, 1H), 4.25 (d, J = 4.5 Hz, 2H), 7.16 (d, J = 6.0 Hz, 1H), 7.25 (d, J = 6.0 Hz, 1H), 7.82 (d, J = 6.6 Hz, 1H), 8.17 (d, J = 6.3 Hz, 2H), 8.24 (t, J = 4.8 Hz, 2H), 12.30 (br s, 1H); MS (m/z): 461.14 ($M+H$) $^+$.

Example-108

N-(3-(1-(4-(Trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2,4-dimethylbenzyl)pivalamide

[0904]

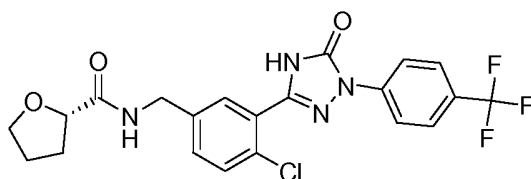


[0905] To a solution of 5-(3-(aminomethyl)-2,6-dimethylphenyl)-2-(4-(trifluoromethyl)phenyl)-2H-1,2,4-triazol-3(4H)-one (Intermediate-66, 0.050 g) in dry THF (5 mL), TEA (3 mL) was added and stirred the reaction mixture for 20 minutes. The reaction mixture was cooled to 0°C and pivaloyl chloride (0.05 g, 0.563 mmol) was added and stirred for 3 h at RT. After completion of the reaction, the reaction mass was quenched with water, extracted with DCM:MeOH. The organic layer was separated, concentrated, and purified by column chromatography to afford 0.012 g of the desired title product. ¹H NMR (400 MHz, DMSO *d*₆): δ 1.15 (s, 9H), 2.18 (s, 3H), 2.22 (s, 3H), 4.24 (d, *J* = 12.6 Hz, 2H), 7.19 (d, 1H), 7.25 (d, 1H), 7.84 (d, *J* = 5.7 Hz, 2H), 8.0 (t, 1H), 8.20 (d, *J* = 6.4 Hz, 2H), 12.30 (br s, 1H); MS (*m/z*): 447.20 (M+H)⁺.

Example-109

(S)-N-(4-Chloro-3-(1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1H-1,2,4-triazol-3-yl)benzyl)-tetrahydrofuran-2-carboxamide

[0906]

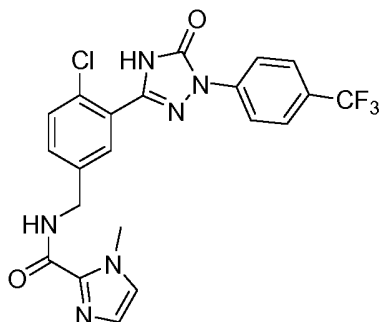


[0907] The title compound was prepared according to the procedure described in Example-107 by using 3-(5-(aminomethyl)-2-chlorophenyl)-1-(4-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-5(4H)-one (Intermediate-63, 0.070 g, 0.189 mmol), THF:DMF (5 mL:1 mL), (S)-(-) tetrahydrofuran-2-carboxylic acid (0.032 g, 0.283 mmol), TBTU (0.182 g, 0.567 mmol), and TEA (3.0 mL). The obtained crude was purified by column chromatography on basic alumina by eluting solution of 2% ammonia in 10.0 % MeOH:DCM to afford 0.010 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.80 (m, 3H), 2.15 (m, 1H), 3.75 (m, 1H), 3.94 (m, 1H), 4.27-4.32 (m, 3H), 7.42 (d, 1H), 7.60 (d, 2H), 7.85 (d, *J* = 5.4 Hz, 2H), 8.20 (d, *J* = 4.5 Hz, 2H), 8.52 (s, 1H), 12.50 (s, 1H); MS (*m/z*): 467.08 (M+H)⁺.

Example-110

N-(4-Chloro-3-(1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1H-1,2,4-triazol-3-yl)benzyl)-1-methyl-1H-imidazole-2-carboxamide

[0908]

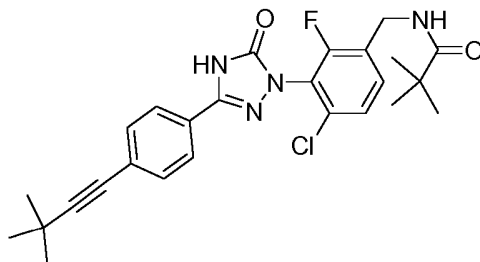


[0909] The title compound was prepared according to the procedure described in Example-108 by using 3-(5-(aminomethyl)-2-chlorophenyl)-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,4-triazol-5(4*H*)-one (Intermediate-63, 0.070 g, 0.189 mmol), 1-methyl-1*H*-imidazole-2-carbonyl chloride (0.026 g, 0.283 mmol), dry THF (5 mL), DIPEA (2 mL). The obtained crude was purified by column chromatography using 2% ammonia in 20 % MeOH:DCM as mobile phase to afford 0.020 g of the desired title product. ¹H NMR (300 MHz, DMSO *d*₆): δ 3.50 (s, 3H), 4.41 (d, *J* = 18.0 Hz, 1H), 6.99 (s, 1H), 7.43 (br, 2H), 7.67 (d, 1H), 7.78 (s, 1H), 8.28 (d, *J* = 4.5 Hz, 2H), 8.30 (s, 1H), 9.08 (t, 1H); MS (*m/z*): 477.10 (M+H)⁺.

Example-111

N-(4-Chloro-2-fluoro-3-(4,5-dihydro-3-(4-(3,3-dimethylbut-1-ynyl)phenyl)-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide

[0910]

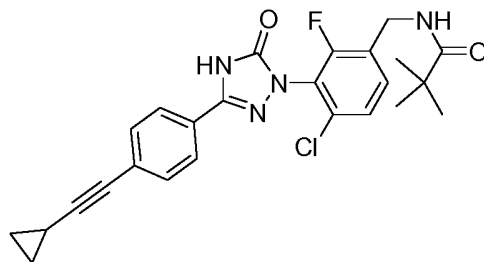


[0911] To a solution of *N*-(4-chloro-2-fluoro-3-(4,5-dihydro-3-(4-iodophenyl)-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide (Intermediate-68, 0.050 g, 0.094 mmol) in DMSO (3.0 mL), 3,3-dimethylbut-1-yne (0.011 g, 0.142 mmol), TBAF (0.074 g, 0.283 mmol) and bis(triphenylphosphine)palladium(II) chloride (0.020 g, 0.022 mmol) were added and the reaction mass was stirred at 80°C for 5-6 h. After completion of the reaction, the reaction mass was quenched with water and extracted with DCM and concentrated. The obtained crude product was purified with column chromatography on silica gel column and 2.0 % EA: DCM as mobile phase to afford 0.022 g of the desired title product. ¹H NMR (400 MHz, DMSO *d*₆): δ 1.09 (s, 9H), 1.25 (s, 9H), 4.31 (br s, 2H), 7.35-7.51 (m, 4H), 7.80 (d, *J* = 8.3 Hz, 2H), 8.18-8.20 (m, 1H); MS (*m/z*): 481.14 (M-H)⁻.

Example-112

N-(4-Chloro-3-(3-(4-(2-cyclopropylethynyl)phenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)-2-fluorobenzyl)pivalamide

[0912]

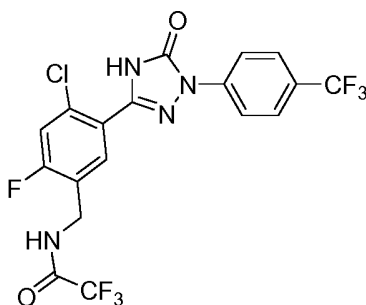


[0913] The title compound was prepared according to the procedure described in Example-111 by using *N*-(4-chloro-2-fluoro-3-(4,5-dihydro-3-(4-iodophenyl)-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide (Intermediate-68, 0.050 g, 0.094 mmol), ethynylcyclopropane (0.009 g, 0.142 mmol), TBAF (0.074 g, 0.283 mmol), bis(triphenylphosphine)palladium(II) chloride (0.003 g, 0.003 mmol) and DMSO (3.0 mL) to afford 0.018 g of the desired title product. ^1H NMR (400 MHz, DMSO d_6): δ 0.75 (m, 2H), 0.77-0.91 (m, 2H), 1.36 (s, 9H), 1.53-1.59 (m, 2H), 7.38 (t, J = 5.9 Hz, 1H), 7.46-7.52 (m, 3H), 8.79 (d, J = 4.4 Hz, 2H), 8.19 (t, J = 4.3 Hz, 1H); MS (m/z): 467.15 ($M+H$) $^+$.

Example-113

N-(4-Chloro-2-fluoro-5-(1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1H-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide

[0914]

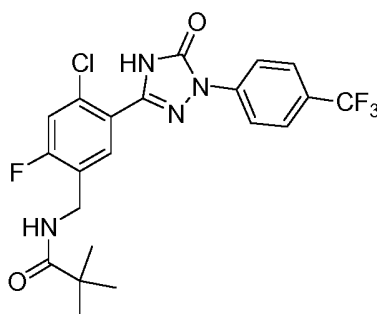


[0915] The title compound was prepared according to the procedure described in Example-83 by using *tert*-butyl 2-(4-(trifluoromethyl)phenyl)hydrazinecarboxylate (Intermediate-53, 0.300 g), 5-((2,2,2-trifluoroacetamido)methyl)-2-chloro-4-fluorobenzoyl isocyanate (Intermediate-69, 0.300 g), DCM (20 mL), trifluoro acetic acid (5.0 mL) to afford 0.030 g of the desired product. ^1H NMR (400 MHz, DMSO d_6): δ 4.49 (m, 2H), 7.74-7.77 (m, 1H), 7.78-7.80 (m, 1H), 7.87 (d, J = 5.1 Hz, 2H), 8.19 (d, J = 4.2 Hz, 2H), 10.06 (m, 1H), 12.76 (s, 1H); MS (m/z): 467.15 ($M+H$) $^+$.

Example-114

N-(4-Chloro-2-fluoro-5-(1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1H-1,2,4-triazol-3-yl)benzyl)pivalamide

[0916]



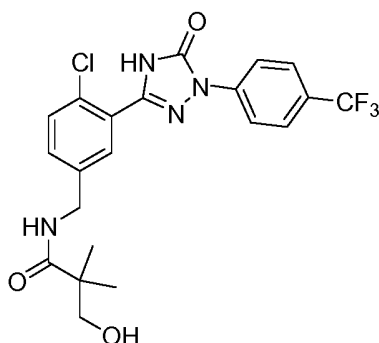
EP 2 718 284 B1

[0917] The title compound was prepared according to the procedure described in Example-108 by using 5-(5-(aminomethyl)-2-chloro-4-fluorophenyl)-2-(4-(trifluoromethyl)phenyl)-2H-1,2,4-triazol-3(4H)-one (Intermediate-70, 0.080 g, 0.206 mmol), pivaloyl chloride (0.027 g, 0.227 mmol), THF (5.0 mL) and TEA (0.2 mL) to afford 0.043 g of the desired product. ¹H NMR (400 MHz, DMSO *d*₆): δ 1.13 (s, 9H), 4.31-4.32 (m, 2H), 7.86 (d, *J* = 6.5 Hz, 2H), 8.13-8.18 (m, 3H), 12.70 (s, 1H); MS (*m/z*): 471.14 (M+H)⁺.

Example-115

N-(4-Chloro-3-(1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1H-1,2,4-triazol-3-yl)benzyl)-3-hydroxy-2,2-dimethylpropanamide

[0918]

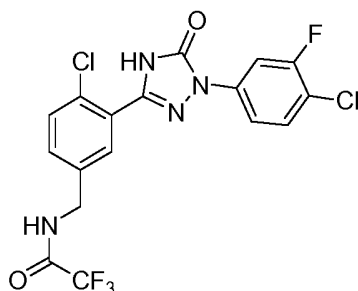


[0919] The title compound was prepared according to the procedure described in Example-107 by using 3-(5-(aminomethyl)-2-chlorophenyl)-1-(4-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-5(4H)-one (Intermediate-63, 0.100 g, 0.271 mmol), THF:DMF (5 mL:1 mL), 3-methoxy-2,2-dimethylpropanoic acid (0.053 g, 0.407 mmol), TBTU (0.261 g, 0.813 mmol), TEA (2.0 mL). The obtained crude was purified by column chromatography using basic alumina as stationary phase and eluting with the solution of 2% ammonia in 10.0% MeOH:DCM to afford 0.012 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.05 (s, 6H), 3.30 (s, 2H), 4.30 (d, *J* = 4.5 Hz, 1H), 4.36 (s, 1H), 7.53 (d, *J* = 6.3 Hz, 1H), 7.75 (s, 1H), 8.08 (t, *J* = 4.5 Hz, 1H), 8.21 (d, *J* = 6.3 Hz, 2H); MS (*m/z*): 469.04 (M+H)⁺.

Example-116

N-(4-Chloro-3-(1-(4-chloro-3-fluorophenyl)-4,5-dihydro-5-oxo-1H-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide

[0920]

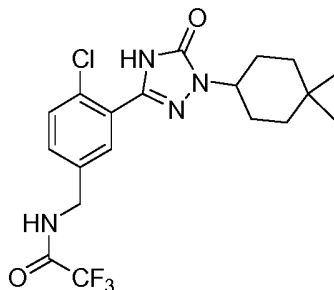


[0921] The title compound was prepared according to the procedure described in Example-83 by using *tert*-butyl 2-(4-chloro-3-fluorophenyl)hydrazinecarboxylate (Intermediate-71, 0.828 g, 0.003 mmol), 2-chloro-5-((2,2,2-trifluoroacetamido)methyl)benzoyl isocyanate (step-3 of Intermediate-26, 1.3 g, 0.043 mmol), DCM (20 mL), trifluoro acetic acid (5.0 mL) to afford 0.500 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 4.45 (d, 2H), 7.48 (d, *J* = 15.0 Hz, 1H), 7.68-7.83 (m, 3H), 7.85 (d, 1H), 7.99 (d, *J* = 17.1 Hz, 1H), 10.08 (d, *J* = 12.0 Hz, 1H), 12.73 (s, 1H).

Comparative Example-117

N-(4-Chloro-3-(4,5-dihydro-1-(4,4-dimethylcyclohexyl)-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide

[0922]

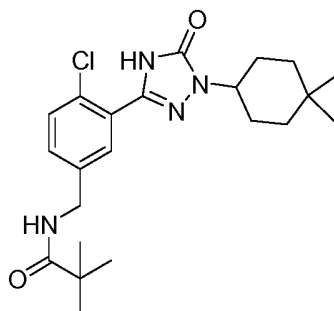


[0923] The title compound was prepared according to the procedure described in Example-83 by using 4,4-dimethyl *tert*-butyl 2-cyclohexyl hydrazinecarboxylate (Intermediate-72, 0.269 g, 1.1 mmol), 2-chloro-5-((2,2,2-trifluoroacetamido)methyl)benzoyl isocyanate (step-2 of Intermediate-26, 0.400 g, 1.2 mmol), DCM (20 mL), trifluoro acetic acid (5.0 mL) to afford 0.200 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.33 (s, 6H), 1.43-1.91 (m, 8H), 3.86-3.94 (m, 1H), 4.41 (d, *J* = 4.5 Hz, 2H), 7.38 (d, *J* = 7.5 Hz, 1H), 7.53 (s, 1H), 7.58 (d, *J* = 6.3Hz, 1H), 10.02-10.04 (m, 1H), 11.95 (s, 1H); MS (*m/z*): 431.17 (M+H)⁺.

Comparative Example-118

N-(4-Chloro-3-(4,5-dihydro-1-(4,4-dimethylcyclohexyl)-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide

[0924]

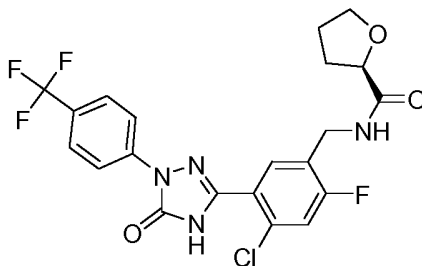


[0925] To a solution of 5-(5-(aminomethyl)-2-chlorophenyl)-2-(4,4-dimethylcyclohexyl)-2*H*-1,2,4-triazol-3(4*H*)-one (Intermediate-73, 0.070 g, 0.202 mmol) in dry THF (5.0 mL), DIPEA (2.0 mL) and pivaloyl chloride (0.30 g, 0.242 mmol) were added and the reaction mass was stirred at RT for 16 h. After completion of the reaction, the reaction mass was quenched with water and extracted with 10 % MeOH:DCM. The organic layer was washed with dilute HCl and concentrated. The obtained crude was purified with column chromatography on basic alumina by eluting with 2.0 % MeOH:DCM to afford 0.040 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.44 (s, 6H), 1.47 (s, 9H), 1.81-1.94 (m, 8H), 3.86-3.90 (m, 1H), 4.40 (s, 2H), 7.33 (d, *J* = 1.5 Hz, 1H), 7.45 (s, 1H), 7.50 (d, *J* = 2.1 Hz, 1H), 8.16 (t, 1H), 11.93 (s, 1H); MS (*m/z*): 419.21 (M+H)⁺.

Example-119

(*R*)-*N*-(4-chloro-2-fluoro-5-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)tetrahydrofuran-2-carboxamide

[0926]

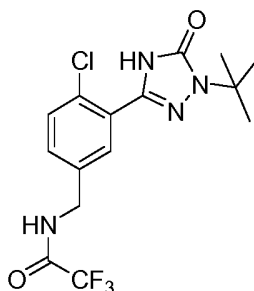


[0927] The title compound was prepared according to the procedure described in Example-107 by using 5-(5-(aminomethyl)-2-chloro-4-fluorophenyl)-2-(4-(trifluoromethyl)phenyl)-2H-1,2,4-triazol-3(4H)-one (Intermediate-70, 0.090 g, 0.233 mmol), THF:DMF (5 mL:1 mL), (R)-(-)-tetrahydrofuran-2-carboxylic acid (0.040 g, 0.349 mmol), TBTU (0.224 g, 0.699 mmol), and TEA (0.5 mL). The obtained crude was purified with column chromatography using basic alumina as stationary phase and 2% ammonia in 10.0 % MeOH:DCM solution as mobile phase to afford 0.015 g of the desired product. ¹H NMR (400 MHz, DMSO *d*₆): δ 1.78-1.91 (m, 2H), 2.09-2.15 (m, 1H), 3.74 (m, 1H), 3.88-3.94 (m, 1H), 4.28 (m, 1H), 4.43 (m, 2H), 7.65 (m, 2H), 7.86 (d, *J* = 8.72 Hz, 2H), 8.18 (d, *J* = 8.52 Hz, 2H), 8.45 (d, *J* = 16.0 Hz, 1H), 12.71 (s, 1H).

Comparative Example-120

N-(3-(1-*tert*-Butyl-4,5-dihydro-5-oxo-1H-1,2,4-triazol-3-yl)-4-chlorobenzyl)-2,2,2-trifluoroacetamide

[0928]

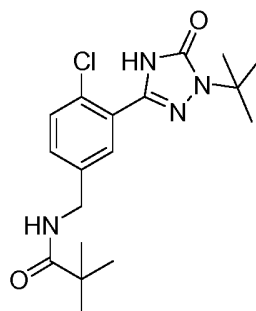


[0929] The title compound was prepared according to the procedure described in Example-83 by using *tert*-butyl 2-*tert*-butylhydrazinecarboxylate (Intermediate-74, 0.233 g, 1.2 mmol), 2-chloro-5-((2,2,2-trifluoroacetamido)methyl)benzoyl isocyanate (step-3 of Intermediate-26, 0.400 g, 1.2 mmol), DCM (10 mL), trifluoro acetic acid (5.0 mL) to afford 0.100 g of the desired product. ¹H NMR (400 MHz, DMSO *d*₆): δ 1.52 (s, 9H), 4.42 (s, 2H), 7.39 (d, 1H), 7.41 (s, 1H), 7.58 (d, *J* = 2.1 Hz, 2H), 10.0 (br s, 1H), 12.0 (br s, 1H); MS (*m/z*): 377.20 (*M*+H)⁺.

Comparative Example-121

N-(3-(1-*tert*-Butyl-4,5-dihydro-5-oxo-1H-1,2,4-triazol-3-yl)-4-chlorobenzyl)pivalamide

[0930]

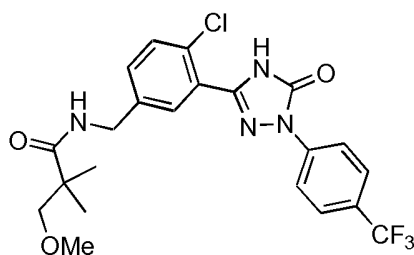


[0931] The title compound was prepared according to the procedure described in Example-108 by using 2-*tert*-butyl-5-(5-(aminomethyl)-2-chlorophenyl)-2*H*-1,2,4-triazol-3(4*H*)-one (Intermediate-75, 0.250 g), pivaloyl chloride (1.0 mL), DIPEA (2.0 mL), and dry THF (5 mL) to afford 0.180 g of desired product. ¹H NMR (400 MHz, DMSO *d*₆): δ 1.08 (s, 9H), 1.49 (s, 9H), 4.24 (d, *J* = 4.5 Hz, 2H), 7.32 (dd, *J* = 4.5 Hz, 3.6Hz, 2H), 7.43 (s, 1H), 7.50 (s, 1H), 8.14 (d, *J* = 4.5 Hz, 1H); MS (*m/z*): 365.20 (M+H)⁺.

Example-122

N-(4-Chloro-3-(1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)-3-methoxy-2,2-dimethylpropanamide

[0932]

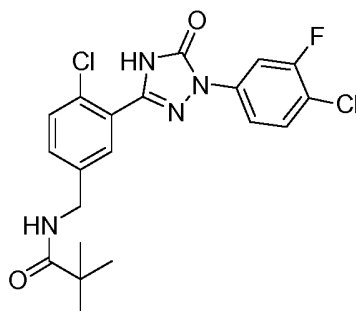


[0933] To a solution of 3-(5-(aminomethyl)-2-chlorophenyl)-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,4-triazol-5(4*H*)-one (Intermediate-63, 0.250 g, 0.678 mmol) in THF:DMF (5 mL:1 mL), TBTU (0.653 g, 2.3 mmol), TEA (4.0 mL) were added and the reaction mass was stirred at RT for 1 h. To the reaction mixture, 3-methoxy-2,2-dimethylpropanoic acid (0.134 g, 1.01 mmol) was added and stirring was continued at RT for 2 days. After completion of the reaction, the reaction mass was quenched with water and extracted with ethyl acetate. The organic layer was separated, dried and concentrated to obtain crude product. The obtained crude was purified with column chromatography on basic alumina by eluting with 5.0 % MeOH:DCM to afford 0.110 g of the desired product. ¹H NMR (400 MHz, DMSO *d*₆): δ 1.15 (s, 6H), 1.18 (s, 3H), 3.09 (t, 2H), 4.32 (d, *J* = 11.4Hz, 2H), 7.43 (dd, *J* = 4.5 Hz, 3.6Hz, 1H), 7.45 (d, 1H), 7.86 (d, *J* = 5.4 Hz, 2H), 8.15 (t, 1H), 8.20 (d, 2H), 12.50 (br s, 1H); MS (*m/z*): 483.20 (M+H)⁺.

Example-123

N-(4-Chloro-3-(1-(4-chloro-3-fluorophenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide

[0934]

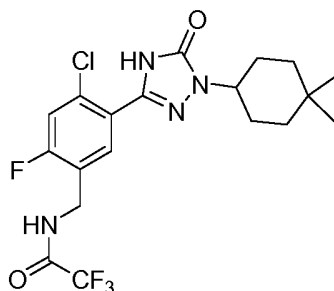


[0935] The title compound was prepared according to the procedure described in Example-108 by using 5-(5-(aminomethyl)-2-chlorophenyl)-2-(4-chloro-3-fluorophenyl)-2*H*-1,2,4-triazol-3(4*H*)-one (Intermediate-76, 0.250 g), pivaloyl chloride (1.0 mL), DIPEA (2.0 mL), dry THF (5 mL) to afford 0.110 g of the desired product. ¹H NMR (400 MHz, DMSO *d*₆): δ 1.24 (s, 9H), 4.30 (d, *J* = 14.7 Hz, 2H), 7.40 (dd, *J* = 4.5 Hz, 3.6 Hz, 1H), 7.43 (d, 1H), 7.60 (d, *J* = 5.4 Hz, 1H), 7.74 (d, 1H), 7.98 (d, 1H), 8.18 (t, *J* = 15.0 Hz, 1H), 12.70 (s, 1H); MS (*m/z*): 437.59 (*M*+*H*)⁺.

Comparative Example-124

N-(4-Chloro-2-fluoro-5-(4,5-dihydro-1-(4,4-dimethylcyclohexyl)-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide

[0936]

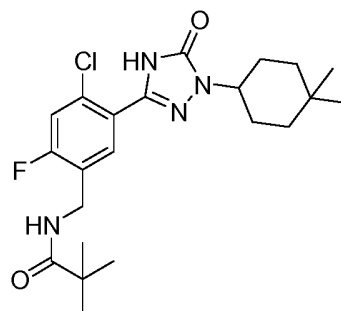


[0937] The title compound was prepared according to the procedure described in Example-83 by using 4,4-dimethyl *tert*-butyl 2-cyclohexyl hydrazinecarboxylate (Intermediate-72, 0.400g), 5-((2,2,2-trifluoroacetamido)methyl)-2-chloro-4-fluorobenzoyl isocyanate (Intermediate-69, 0.400 g), DCM (10 mL), trifluoro acetic acid (5.0 mL) to afford 0.150 g of the desired product. ¹H NMR (400 MHz, DMSO *d*₆): δ 0.93 (s, 6H), 1.32-1.35 (m, 2H), 1.36-1.46 (m, 2H), 1.59-1.62 (m, 2H), 1.83-1.87 (m, 2H), 3.89 (m, 1H), 4.42 (m, 2H), 7.72 (m, 2H), 10.0 (s, 1H), 12.01 (s, 1H); MS (*m/z*): 449.48 (*M*+*H*)⁺.

Comparative Example-125

N-(4-Chloro-2-fluoro-5-(4,5-dihydro-1-(4,4-dimethylcyclohexyl)-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide

[0938]

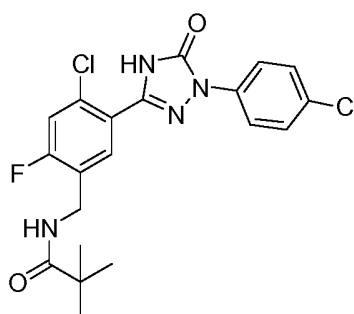


[0939] The title compound was prepared according to the procedure described in Example-108 by using 5-(5-(aminomethyl)-2-chloro-4-fluorophenyl)-2-(4,4-dimethylcyclohexyl)-2H-1,2,4-triazol-3(4H)-one (Intermediate-77, 0.200 g), pivaloyl chloride (0.5 mL), TEA (2.0 mL), dry THF (5 mL) to afford 0.033 g of the desired product. ¹H NMR (300 MHz, CDCl₃): δ 1.36 (s, 6H), 1.37 (s, 9H), 1.62 (m, 2H), 1.79 (m, 1H), 1.82 (m, 2H), 1.89 (m, 2H), 3.46-3.94 (m, 1H), 4.28 (s, 2H), 7.47 (d, *J* = 7.9 Hz, 1H), 7.59 (d, *J* = 9.72 Hz, 1H), 8.15 (m, 1H), 11.95 (s, 1H); MS (*m/z*): 436.55 (M+H)⁺.

Example-126

N-(4-Chloro-5-(1-(4-chlorophenyl)-4,5-dihydro-5-oxo-1H-1,2,4-triazol-3-yl)-2-fluorobenzyl)pivalamide

[0940]

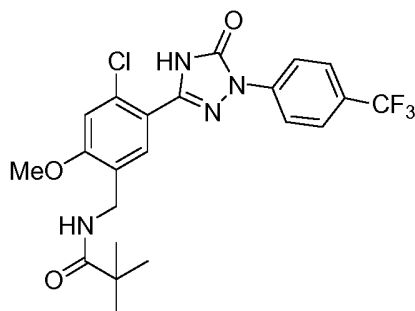


[0941] The title compound was prepared according to the procedure described in Example-108 by using 5-(5-(aminomethyl)-2-chloro-4-fluorophenyl)-2-(4-chlorophenyl)-2H-1,2,4-triazol-3(4H)-one (Intermediate-78, 0.120 g), pivaloyl chloride (0.5 mL), TEA (2.0 mL), dry THF (5 mL) to afford 0.033 g of the desired product. ¹H NMR (300 MHz, DMSO): δ 1.12 (s, 9H), 4.30 (br s, 2H), 7.53-7.63 (m, 4H), 7.95 (d, *J* = 12.8 Hz, 2H), 8.14 (s, 1H), 12.61 (s, 1H); MS (*m/z*): 437.47 (M+H)⁺.

Example-127

N-(4-Chloro-5-(1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1H-1,2,4-triazol-3-yl)-2-methoxybenzyl)pivalamide

[0942]

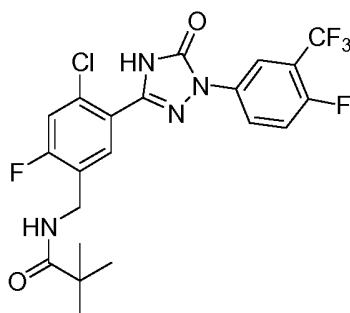


[0943] The title compound was prepared according to the procedure described in Example-108 by using 5-(5-(aminomethyl)-2-chloro-4-methoxyphenyl)-2-(4-(trifluoromethyl)phenyl)-2*H*-1,2,4-triazol-3(4*H*)-one (Intermediate-79, 0.200 g), pivaloyl chloride (0.2 mL), TEA (2.0 mL), dry THF (5 mL) to afford 0.015 g of the desired product. ¹H NMR (300 MHz, CDCl₃): δ 1.15 (s, 9H), 3.91 (s, 3H), 4.22 (m, 2H), 7.26 (s, 1H), 7.42 (s, 1H), 7.87 (m, 2H), 7.99 (m, 1H), 8.15 (m, 2H), 12.57 (s, 1H); MS (m/z): 483.38 (M+H)⁺.

Example-128

N-(4-Chloro-2-fluoro-5-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide

[0944]

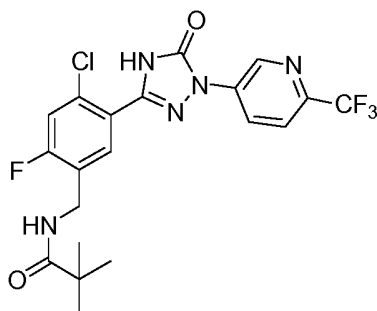


[0945] The title compound was prepared according to the procedure described in Example-108 by using 5-(5-(aminomethyl)-2-chloro-4-fluorophenyl)-2-(4-fluoro-3-(trifluoromethyl)phenyl)-2*H*-1,2,4-triazol-3(4*H*)-one (Intermediate-81, 0.300 g), pivaloyl chloride (0.3 mL), TEA (2.0 mL), dry THF (5 mL) to afford 0.065 g of the desired product. ¹H NMR (300 MHz, CDCl₃): δ 1.12 (s, 9H), 4.30 (m, 2H), 7.61-7.69 (m, 3H), 8.16 (br s, 1H), 8.25 (br s, 2H), 12.73 (s, 1H); MS (m/z): 489.47 (M+H)⁺.

Example-129

N-(4-Chloro-2-fluoro-5-(1-(6-(trifluoromethyl)pyridin-3-yl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide

[0946]

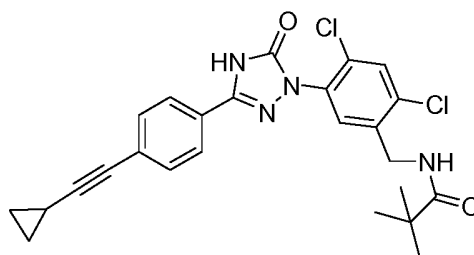


[0947] The title compound was prepared according to the procedure described in Example-108 by using 5-(5-(aminomethyl)-2-chloro-4-fluorophenyl)-2-(6-(trifluoromethyl)pyridin-3-yl)-2*H*-1,2,4-triazol-3(4*H*)-one (Intermediate-82, 0.300 g), pivaloyl chloride (0.3 mL), TEA (2.0 mL), dry THF (10 mL) to afford 0.050 g of the desired product. ¹H NMR (300 MHz, CDCl₃): δ 1.12 (s, 9H), 4.31 (d, *J* = 6.8 Hz, 2H), 7.63-7.71 (m, 2H), 8.05-8.07 (m, 1H), 8.16 (m, 1H), 8.55 (d, *J* = 13.2 Hz, 1H), 9.29 (s, 1H), 12.85 (s, 1H); MS (*m/z*): 472.41 (M+H)⁺.

Example-130

N-(2,4-Dichloro-5-(3-(4-(2-cyclopropylethynyl)phenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide

[0948]

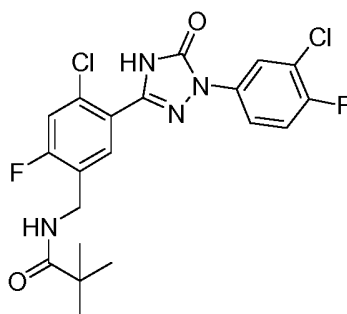


[0949] The title compound was prepared according to the procedure described in Example-111 using *N*-(2,4-dichloro-5-(4,5-dihydro-3-(4-iodophenyl)-5-oxo-1,2,4-triazol-1-yl)benzyl) pivalamide (Intermediate-84, 0.150 g, 0.028 mmol), ethynylcyclopropane (0.038 g, 0.56 mmol), TBAF (0.268 g, 0.85 mmol), bis(triphenylphosphine)palladium(II) chloride (catalytic) and DMSO (3.0 mL) to afford 0.050 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 0.77 (m, 2H), 0.93 (m, 2H), 1.21 (s, 9H), 1.58 (m, 1H), 4.32 (d, *J* = 6.3 Hz, 2H), 7.50-7.53 (m, 3H), 7.82-7.91 (m, 2H), 7.95 (s, 1H), 8.21 (m, 1H).

Example-131

N-(4-Chloro-5-(1-(3-chloro-4-fluorophenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2-fluorobenzyl)pivalamide

[0950]



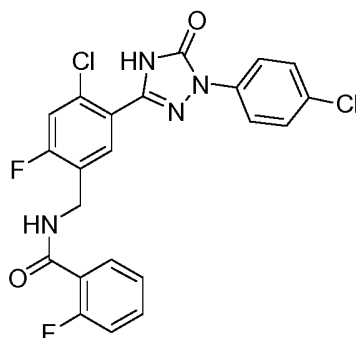
EP 2 718 284 B1

[0951] The title compound was prepared according to the procedure described in Example-108 by using 5-(5-(aminomethyl)-2-chloro-4-fluorophenyl)-2-(3-chloro-4-fluorophenyl)-2*H*-1,2,4-triazol-3(4*H*)-one (Intermediate-86, 0.300 g), pivaloyl chloride (0.3 mL), TEA (2.0 mL), dry THF (10 mL) to afford 0.083 g of the desired product. ¹H NMR (300 MHz, DMSO): δ 1.13 (s, 9H), 4.30 (d, *J* = 6.4 Hz, 2H), 7.53-7.66 (s, 3H), 7.91-8.15 (s, 3H), 12.67 (s, 1H); MS (*m/z*): 455.19 (M+H)⁺.

Example-132

N-(4-Chloro-5-(1-(4-chlorophenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2-fluorobenzyl)-2-fluorobenzamide

[0952]

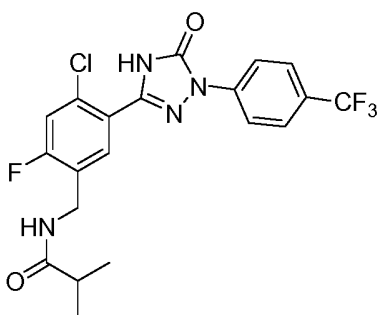


[0953] A mixture of 2-fluoro benzoic acid (0.400 g), thionyl chloride (20 mL) and DMF (cat. amt.) was refluxed for 5 h and excess of solvent was removed under reduced pressure to obtain crude product. The obtained crude product was added to the solution of 5-(5-(aminomethyl)-2-chloro-4-fluorophenyl)-2-(4-chlorophenyl)-2*H*-1,2,4-triazol-3(4*H*)-one (Intermediate-78, 0.250 g) and DIPEA (1.0 mL) in THF (20 mL) and the reaction mass was stirred for 3 h. After completion of reaction, reaction mass was quenched with water and extracted with ethyl acetate. The organic layer was separated, concentrated to afford 0.032 g of the desired product. ¹H NMR (300 MHz, DMSO): δ 4.53 (br s, 2H), 7.29 (m, 2H), 7.70 (m, 3H), 7.78 (m, 3H), 7.95 (br s, 2H), 8.94 (br s, 1H), 12.63 (br s, 1H); MS (*m/z*): 475.39 (M+H)⁺.

Example-133

N-(4-Chloro-2-fluoro-5-(1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)isobutyramide

[0954]

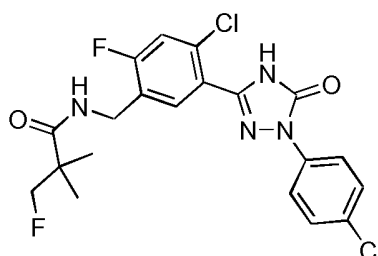


[0955] The title compound was prepared according to the procedure described in Example-108 by using 5-(5-(aminomethyl)-2-chloro-4-fluorophenyl)-2-(4-(trifluoromethyl)phenyl)-2*H*-1,2,4-triazol-3(4*H*)-one (Intermediate-70, 0.100 g), 2-methylpropanoyl chloride (0.1 mL), TEA (0.1 mL), dry THF (5 mL) to afford 0.028 g of the desired product. ¹H NMR (300 MHz, DMSO): δ 1.01 (s, 6H), 4.32 (d, *J* = 7.6 Hz, 2H), 7.67-7.71 (m, 2H), 7.85 (d, *J* = 11.2 Hz, 2H), 8.17 (d, *J* = 11.6 Hz, 2H), 8.36 (m, 1H), 12.73 (s, 1H); MS (*m/z*): 457.37 (M+H)⁺.

Example-134

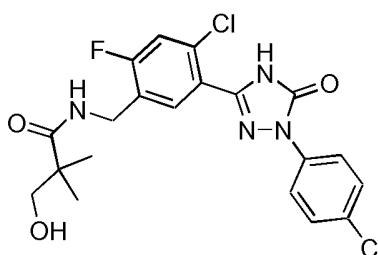
N-(4-Chloro-5-(1-(4-chlorophenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2-fluorobenzyl)-3-fluoro-2,2-dimethylpropanamide

[0956]



Step-1:- Preparation of *N*-(4-chloro-5-(1-(4-chlorophenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2-fluorobenzyl)-3-hydroxy-2,2-dimethylpropanamide

[0957]

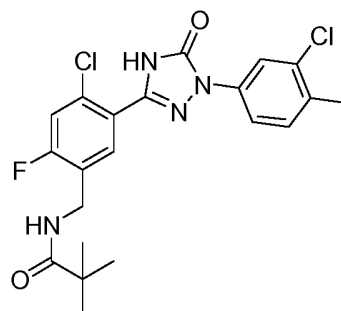


[0958] The title compound was prepared according to the procedure described in Example-107 by using 5-(5-(aminomethyl)-2-chloro-4-fluorophenyl)-2-(4-chlorophenyl)-2*H*-1,2,4-triazol-3(4*H*)-one (Intermediate-78, 0.250 g, 0.708 mmol), THF:DMF (5 mL: 1 mL), 3-hydroxy-2,2-dimethylpropanoic acid (0.091 g, 0.407 mmol), TBTU (0.340 g, 1.062 mmol), TEA (2.0 mL) to afford 0.150 g of the desired product. ¹H NMR (300 MHz, CDCl₃): δ 1.05 (s, 6H), 2.68 (s, 2H), 4.32 (d, *J* = 8.0 Hz, 2H), 7.53 (d, *J* = 12.0 Hz, 2H), 7.64-7.67 (m, 2H), 7.95-7.98 (m, 2H), 8.08 (br s, 1H); MS (*m/z*): 453.27 (*M*⁺*H*)⁺. Step-2:- Preparation *N*-(4-chloro-5-(1-(4-chlorophenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2-fluorobenzyl)-3-fluoro-2,2-dimethylpropanamide To a solution of *N*-(4-chloro-5-(1-(4-chlorophenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2-fluorobenzyl)-3-hydroxy-2,2-dimethylpropanamide (0.150 g, 0.330 mmol) in THF (5.0 mL), DAST (0.079 g, 0.495 mmol) was added at 0-5°C and stirred at RT for 5-6 h. After completion of the reaction, the reaction mass was quenched with water and extracted with ethyl acetate. The organic layer was separated, concentrated and the obtained crude was purified with column chromatography using basic alumina by eluting with solution of 2% ammonia in 10.0 % MeOH: DCM to afford 0.013 g of the desired product. ¹H NMR (300 MHz, CDCl₃): δ 1.13 (s, 6H), 4.32 (m, 3H), 4.46 (s, 1H), 7.55 (m, 2H), 7.69 (m, 2H), 7.94-7.97 (m, 2H), 8.31 (s, 1H), 12.61 (s, 1H); MS (*m/z*): 454.25 (*M*⁺*H*)⁺.

Example-135

N-(4-Chloro-5-(1-(3-chloro-4-methylphenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2-fluorobenzyl)pivalamide

[0959]

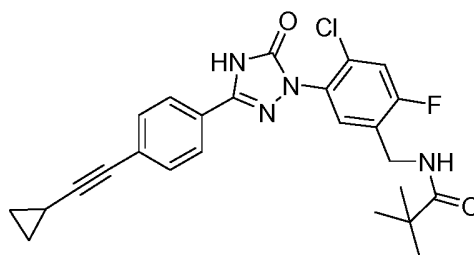


[0960] The title compound was prepared according to the procedure described in Example-108 by using 5-(5-(aminomethyl)-2-chloro-4-fluorophenyl)-2-(3-chloro-4-methylphenyl)-2H-1,2,4-triazol-3(4H)-one (Intermediate-88, 0.200 g), pivaloyl chloride (0.5 mL), TEA (2.0 mL), dry THF (5 mL) to afford 0.074 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.11 (s, 9H), 2.32 (s, 3H), 4.29 (d, *J* = 8.8 Hz, 2H), 7.43 (d, *J* = 11.6 Hz, 1H), 7.60-7.67 (m, 1H), 7.79 (d, *J* = 10.4 Hz, 1H), 7.96 (s, 1H), 8.15 (m, 1H), 12.60 (s, 1H); MS (*m/z*): 451.52 (M+H)⁺.

Example-136

N-(4-Chloro-5-(3-(4-(2-cyclopropylethynyl)phenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)-2-fluorobenzyl)pivalamide

[0961]

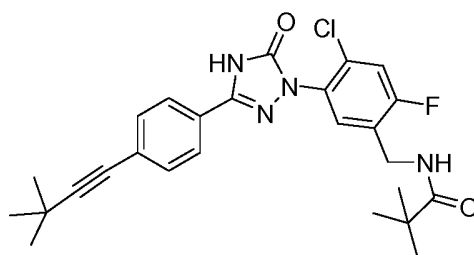


[0962] The title compound was prepared according to the procedure described in Example-111 using *N*-(4-chloro-2-fluoro-5-(4,5-dihydro-3-(4-iodophenyl)-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide (Intermediate-90, 0.200 g, 0.370 mmol), ethynylcyclopropane (0.050 g, 0.75 mmol), TBAF (0.360 g, 1.13 mmol), bis(triphenylphosphine)palladium(II) chloride (catalytic) and DMSO (3.0 mL) at 80°C to afford 0.080 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 0.77 (br s, 9H), 0.92 (br s, 2H), 1.10 (s, 3H), 1.57 (m, 1H), 4.30 (d, *J* = 5.4 Hz, 2H), 7.43-7.50 (m, 3H), 7.65 (d, *J* = 5.4 Hz, 2H), 7.77 (d, *J* = 5.1 Hz, 2H), 12.57 (br s, 1H); MS (*m/z*): 467.36 (M+H)⁺.

Example-137

N-(4-Chloro-2-fluoro-5-(4,5-dihydro-3-(4-(3,3-dimethylbut-1-ynyl)phenyl)-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide

[0963]



[0964] The title compound was prepared according to the procedure described in Example-111 using *N*-(4-chloro-2-

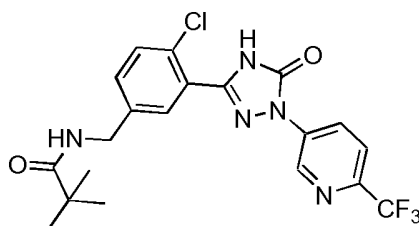
EP 2 718 284 B1

fluoro-5-(4,5-dihydro-3-(4-iodophenyl)-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide (Intermediate-90, 0.100 g, 0.189 mmol), 3,3-dimethylbut-1-yne (0.031 g, 0.378 mmol), TBAF (0.178g, 0.567 mmol), bis(triphenylphosphine)palladium(II) chloride (catalytic) and DMSO (3.0 mL) to afford 0.050 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.10 (s, 9H), 1.30 (s, 9H), 4.30 (d, *J* = 9.0Hz, 2H), 7.43-7.50 (m, 3H), 7.65 (d, *J* = 9.3Hz, 1H), 7.78 (d, *J* = 8.1Hz, 2H), 8.14 (br s, 1H), 12.60 (br s, 1H); MS (*m/z*): 483.29 (M+H)⁺.

Example-138

N-(4-Chloro-3-(1-(6-(trifluoromethyl)pyridin-3-yl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide

[0965]

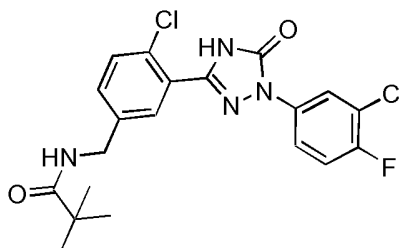


[0966] The title compound was prepared according to the procedure described in Example-108 by using 5-(5-(aminomethyl)-2-chlorophenyl)-2-(6-(trifluoromethyl)pyridin-3-yl)-2*H*-1,2,4-triazol-3(4*H*)-one (Intermediate-91, 0.350 g, 0.945 mmol), pivaloyl chloride (0.120 g, 0.945 mmol), DIPEA (2.0 mL), dry THF (10 mL) to afford 0.080 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.11 (s, 9H), 4.30 (d, *J* = 6.3 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.61-7.64 (m, 2H), 8.06 (d, *J* = 9.0 Hz, 1H), 8.19 (m, 1H), 8.58 (d, *J* = 8.4Hz, 1H), 9.32 (s, 1H), 12.82 (s, 1H); MS (*m/z*): 454.50 (M+H)⁺.

Example-139

N-(4-Chloro-3-(1-(3-chloro-4-fluorophenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide

[0967]

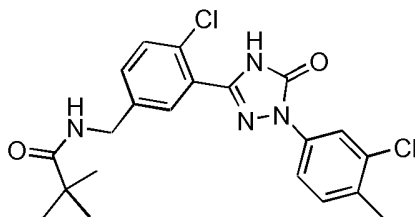


[0968] The title compound was prepared according to the procedure described in Example-108 by using 5-(5-(aminomethyl)-2-chlorophenyl)-2-(3-chloro-4-fluorophenyl)-2*H*-1,2,4-triazol-3(4*H*)-one (Intermediate-92, 0.300 g, 0.852 mmol), pivaloyl chloride (0.108 g, 0.852 mmol), DIPEA (2.0 mL), dry THF (10 mL) to afford 0.050 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.13 (s, 9H), 4.29 (d, *J* = 5.4 Hz, 2H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.52-7.59 (m, 3H), 7.91-8.18 (m, 3H), 12.65 (s, 1H); MS (*m/z*): 437.23 (M+H)⁺.

Example-140

N-(4-Chloro-3-(1-(3-chloro-4-methylphenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide

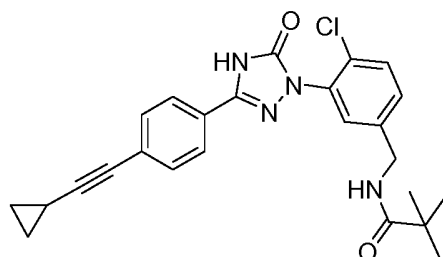
[0969]



[0970] The title compound was prepared according to the procedure described in Example-108 by using 5-(5-(aminomethyl)-2-chlorophenyl)-2-(3-chloro-4-methylphenyl)-2H-1,2,4-triazol-3(4H)-one (Intermediate-93, 0.350 g, 1.00 mmol), pivaloyl chloride (0.128 g, 1.0 mmol), DIPEA (2.0 mL), dry THF (10 mL) to afford 0.200 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.13 (s, 9H), 2.34 (s, 3H), 4.29 (d, *J* = 6.3 Hz, 2H), 7.39-7.47 (m, 2H), 7.58-7.61 (m, 2H), 7.82 (d, *J* = 8.7 Hz, 1H), 8.01 (s, 1H), 8.18 (t, 1H), 12.58 (s, 1H); MS (*m/z*): 433.19 (M+H)⁺.

Example-141

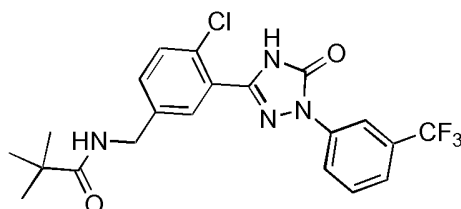
N-(4-Chloro-3-(3-(4-(2-cyclopropylethynyl)phenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide



[0972] To a solution of *N*-(4-chloro-3-(4,5-dihydro-3-(4-iodophenyl)-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide (Intermediate-95, 0.100 g, 0.196 mmol) in DMSO (3.0 mL), ethynylcyclopropane (0.035 g, 0.530 mmol), TBAF (0.150 g, 0.574) and bis(triphenylphosphine)palladium(II) chloride (catalytic) were added and the reaction mass was stirred at 80°C for 5-6 h. After completion of the reaction, the reaction mass was quenched with water and extracted with DCM and concentrated to afford 0.050 g of the desired title product. ¹H NMR (300 MHz, DMSO *d*₆): δ 0.76-.91 (m, 2H), 0.91-0.92 (m, 2H), 1.11 (s, 9H), 1.57 (m, 1H), 4.28 (br d, 2H), 7.31-7.34 (br d, 1H), 7.42 (br s, 1H), 7.47-7.50 (br m, 2H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 2H), 8.18 (s, 1H), 12.58 (s, 1H); MS (*m/z*): 449.52 (M+H)⁺.

Example-142

N-(4-Chloro-3-(1-(3-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1H-1,2,4-triazol-3-yl)benzyl)pivalamide

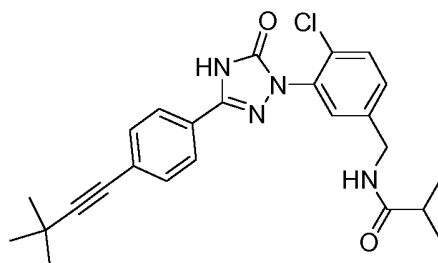


[0974] The title compound was prepared according to the procedure described in Example-108 by using 5-(5-(aminomethyl)-2-chlorophenyl)-2-(3-(trifluoromethyl)phenyl)-2H-1,2,4-triazol-3(4H)-one (Intermediate-96, 0.250 g, 0.678 mmol), pivaloyl chloride (0.3 mL), TEA (2.0 mL), and dry THF (5 mL) to afford 0.150 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.13 (s, 9H), 4.30 (d, *J* = 6.0 Hz, 2H), 7.41-7.43 (m, 1H), 7.59-7.62 (m, 3H), 7.71-7.76 (m, 1H), 8.19-8.29 (m, 3H), 12.68 (s, 1H); MS (*m/z*): 453.38 (M+H)⁺.

Example-143

N-(4-Chloro-3-(4,5-dihydro-3-(4-(3,3-dimethylbut-1-ynyl)phenyl)-5-oxo-1,2,4-triazol-1-yl)benzyl)isobutyramide

[0975]

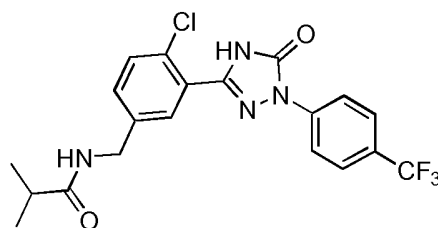


[0976] The title compound was prepared according to the procedure described in Example-111 by using *N*-(4-chloro-3-(4,5-dihydro-3-(4-iodophenyl)-5-oxo-1,2,4-triazol-1-yl)benzyl)isobutyramide (Intermediate-98, 0.060 g, 0.120 mmol), 3,3-dimethylbut-1-yne (0.014 g, 0.181 mmol), TBAF (0.094 g, 0.362 mmol), bis(triphenylphosphine)palladium (II)chloride (0.003 g, 0.003 mmol) and DMSO (3.0 mL) to afford 0.015 g of the desired product. ^1H NMR (400 MHz, DMSO d_6): δ 1.03 (s, 6H), 1.30 (s, 9H), 2.50 (m, 1H), 4.27 (d, J = 5.4 Hz, 2H), 7.35 (d, J = 8.7 Hz, 1H), 7.44-7.50 (m, 3H), 7.61 (d, J = 8.1Hz, 1H), 7.80 (d, J = 8.1 Hz, 2H), 8.38 (m, 1H); MS (m/z): 449.9 (M-H) $^-$.

Example-144

N-(4-Chloro-3-(1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)isobutyramide

[0977]

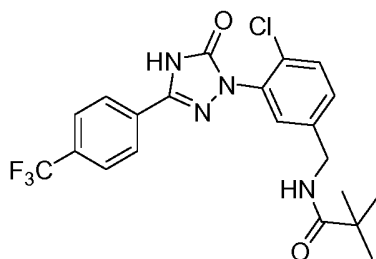


[0978] The title compound was prepared according to the procedure described in Example-108 by using 3-(5-(aminomethyl)-2-chlorophenyl)-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,4-triazol-5(4*H*)-one (Intermediate-63, 0.250 g, 0.678 mmol), isobutyryl chloride (0.108 g, 1.01 mmol), TEA (2.0 mL), and dry THF (5 mL) to afford 0.350 g of the desired product. ^1H NMR (300 MHz, DMSO d_6): δ 1.14 (d, J = 6.6 Hz, 6H), 2.41-2.43 (m, 1H), 4.30 (d, J = 6.3 Hz, 2H), 7.43 (d, J = 8.1 Hz, 1H), 7.61-7.64 (m, 2H), 7.86 (d, J = 9.3 Hz, 2H), 8.20 (d, J = 8.4 Hz, 2H), 8.38 (m, 1H), 12.69 (s, 1H); MS (m/z): 439.24 (M+H) $^+$.

Example-145

N-(4-Chloro-3-(3-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide

[0979]

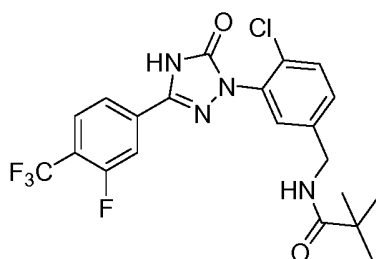


[0980] The title compound was prepared according to the procedure described in Example-83 by using *tert*-butyl 2-(2-chloro-5-((2,2-dimethylpropanoyl)amino)methyl)phenyl)hydrazinecarboxylate (Intermediate-94, 0.150 g, 0.420 mmol), 4-(trifluoromethyl)benzoyl isocyanate (Intermediate-59, 0.181 g, 0.84 mmol), DCM (15 mL), and trifluoro acetic acid (3.0 mL) to afford 0.070 g of the desired product. ^1H NMR (300 MHz, DMSO d_6): δ 1.13 (s, 9H), 4.29 (d, J = 5.4 Hz, 2H), 7.36 (d, J = 8.7 Hz, 1H), 7.45 (s, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.92 (d, J = 8.4 Hz, 2H), 8.06 (d, J = 8.4 Hz, 2H), 8.19 (m, 1H), 12.79 (s, 1H); MS (m/z): 456.59 (M+H) $^+$.

Example-146

N-(4-Chloro-3-(3-(3-fluoro-4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide

[0981]

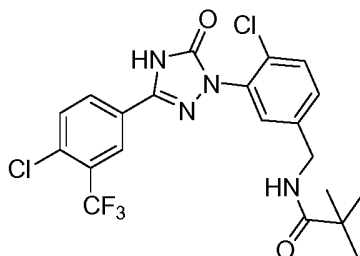


[0982] The title compound was prepared according to the procedure described in Example-83 by using 3-fluoro-4-(trifluoromethyl)benzoyl isocyanate (Intermediate-99, 2.0 g), *tert*-butyl 2-(2-chloro-5-((2,2-dimethylpropanoyl)amino)methyl)phenyl)hydrazinecarboxylate (Intermediate-94, 1.0 g), DCM (15 mL), and trifluoro acetic acid (3.0 mL) to afford 0.900 g of the desired product. ^1H NMR (300 MHz, DMSO d_6): δ 1.12 (s, 9H), 4.29 (d, J = 5.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 1H), 7.44 (s, 1H), 7.62 (d, J = 8.7 Hz, 1H), 7.86-8.10 (m, 3H), 8.19 (m, 1H), 12.86 (s, 1H); MS (m/z): 471.35 (M+H) $^+$.

Example-147

N-(4-Chloro-3-(3-(4-chloro-3-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide

[0983]



[0984] The title compound was prepared according to the procedure described in Example-83 by using 4-chloro-3-(trifluoromethyl)benzoyl isocyanate (Intermediate-100, 2.0 g), *tert*-butyl 2-(2-chloro-5-((2,2-dimethylpropanoyl)amino)methyl)phenyl)hydrazinecarboxylate (Intermediate-94, 1.0 g), DCM (15 mL), and trifluoro acetic acid (3.0 mL) to

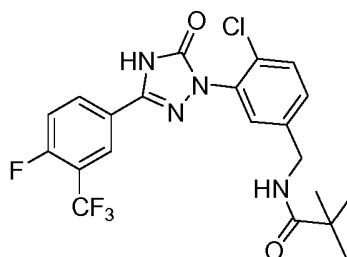
EP 2 718 284 B1

afford 0.900 g of the desired product. ^1H NMR (300 MHz, DMSO d_6): δ 1.12 (s, 9H), 4.29 (d, J = 5.1 Hz, 2H), 7.36 (d, J = 9.3 Hz, 1H), 7.43 (s, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 9.0 Hz, 1H), 8.10-8.18 (m, 2H), 8.27 (s, 1H), 12.82 (s, 1H); MS (m/z): 487.29 ($M+H$) $^+$.

Example-148

N-(4-Chloro-3-(3-(4-fluoro-3-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide

[0985]

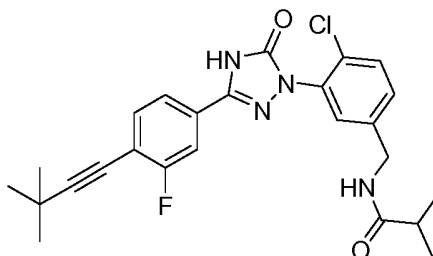


[0986] The title compound was prepared according to the procedure described in Example-83 by using 4-fluoro-3-(trifluoromethyl)benzoyl isocyanate (Intermediate-101, 0.196 g, 0.84 mmol), *tert*-butyl 2-(2-chloro-5-((2,2-dimethylpropanoyl)amino)methyl)phenylhydrazinecarboxylate (Intermediate-94, 0.150 g, 0.420 mmol), DCM (15 mL), and trifluoro acetic acid (3.0 mL) to afford 0.090 g of the desired product. ^1H NMR (300 MHz, DMSO d_6): δ 1.12 (s, 9H), 4.29 (d, J = 5.7 Hz, 2H), 7.35 (d, J = 8.4 Hz, 1H), 7.43 (s, 1H), 7.60 (d, J = 8.7 Hz, 1H), 7.70-7.76 (m, 1H), 8.19-8.23 (m, 3H), 12.76 (s, 1H); MS (m/z) : 471.32 ($M+H$) $^+$.

Example-149

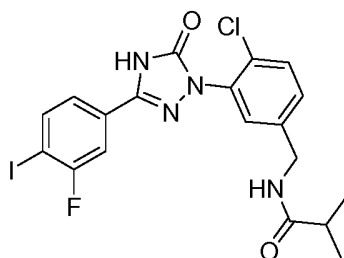
N-(4-Chloro-3-(3-(3-fluoro-4-(3,3-dimethylbut-1-ynyl)phenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)isobutyramide

[0987]



Step1:- Preparation of *N*-(4-chloro-3-(3-(3-fluoro-4-iodophenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)isobutyramide

[0988]



[0989] The title compound was prepared according to the procedure described in Example-83 by using 3-fluoro-4-iodobenzoyl isocyanate (Intermediate-102, 1.0 g), *tert*-butyl 2-(2-chloro-5-[(2-methylpropanoyl)amino]methyl)phenyl)hydrazinecarboxylate (Intermediate-97, 0.800 g), DCM (15 mL), and trifluoro acetic acid (3.0 mL) to afford 0.900 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.30 (s, 6H), 2.43-2.45 (m, 1H), 4.26 (m, 2H), 7.01 (m, 1H), 7.46-7.49 (m, 1H), 7.63-7.66 (m, 1H), 7.84-7.91 (m, 1H), 8.01-8.06 (m, 1H), 8.22 (s, 1H), 8.36 (br s, 1H), 12.66 (m, 1H); MS (m/z) : 515.21 (M+H)⁺.

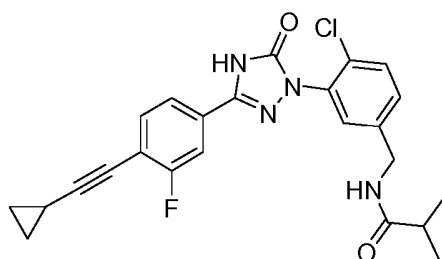
Step-2:- Preparation of *N*-(4-chloro-3-(3-(3-fluoro-4-(3,3-dimethylbut-1-ynyl)phenyl)phenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)isobutyramide

[0990] The title compound was prepared according to the procedure described in Example-111 by using *N*-(4-chloro-3-(3-(3-fluoro-4-iodophenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)isobutyramide (0.080 g, 0.155 mmol), 3,3-dimethylbut-1-yne (0.019 g, 0.233 mmol), TBAF (0.121 g, 0.466 mmol), bis(triphenylphosphine)palladium(II)chloride (0.004 g, 0.006 mmol) and DMSO (3.0 mL) to afford 0.009 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.02 (d, *J* = 6.9 Hz, 6H), 1.31 (s, 9H), 2.39-2.42 (m, 1H), 4.29 (d, *J* = 5.7 Hz, 2H), 7.35 (d, *J* = 7.5 Hz, 1H), 7.43 (s, 1H), 7.57-7.67 (m, 4H), 8.37 (m, 1H), 13.0 (br s, 1H); MS (m/z): 469.31 (M+H)⁺.

Example-150

N-(4-Chloro-3-(3-(4-(2-cyclopropylethynyl)-3-fluorophenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)isobutyramide

[0991]

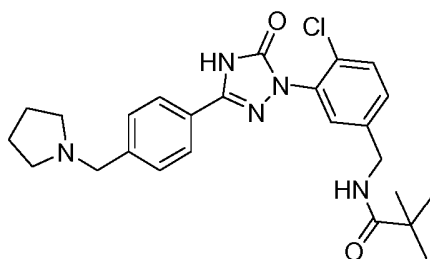


[0992] The title compound was prepared according to the procedure described in Example-111 by using *N*-(4-chloro-3-(3-(3-fluoro-4-iodophenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)isobutyramide (step 1 of Example-149, 0.080 g, 0.155 mmol), ethynylcyclopropane (0.019 g, 0.233 mmol), TBAF (0.121 g, 0.466 mmol), bis(triphenylphosphine)palladium(II)chloride (0.004 g, 0.006 mmol) and DMSO (3.0 mL) to afford 0.009 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 0.79-0.92 (m, 2H), 1.011 (m, 2H), 1.30 (s, 6H), 1.63 (m, 1H), 2.39 (m, 1H), 4.28 (d, *J* = 5.7 Hz, 2H), 7.35 (m, 1H), 7.43 (s, 1H), 7.57-7.67 (m, 4H), 8.37 (m, 1H); MS (m/z): 453.24 (M+H)⁺.

Example-151

N-(4-Chloro-3-(4,5-dihydro-5-oxo-3-(4-((pyrrolidin-1-yl)methyl)phenyl)-1,2,4-triazol-1-yl)benzyl)pivalamide

[0993]



[0994] To a cold solution of pyrrolidine (0.060 g, 0.830 mmol) in DMF was added NaH (0.034 g, 0.830 mmol) at 0°C and stirred the reaction mass for 1 h. Then solution of *N*-(3-(3-(4-(bromomethyl)phenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-

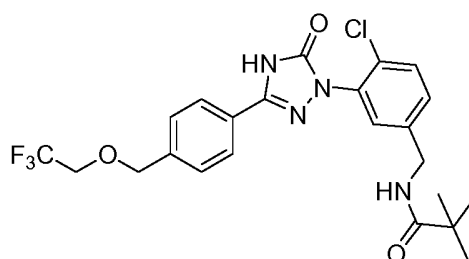
EP 2 718 284 B1

1-yl)-4-chlorobenzyl)pivalamide (Intermediate-103, 0.200 g, 0.419) in DMF was added at 0°C and continued stirring at 5-10°C for 2-3 h. The reaction mass was quenched in ice and pH adjusted to 6-7 and extracted with DCM. The organic layer was dried over anhydrous sodium sulphate and concentrated. The obtained crude product was purified by column chromatography on basic alumina, eluting with 5 % MeOH:DCM to afford 0.020 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.23 (s, 9H), 1.79 (br s, 4H), 2.53 (br s, 4H), 3.66 (s, 2H), 4.48 (d, *J* = 5.7 Hz, 2H), 6.08 (m, 1H), 7.26-7.54 (m, 5H), 7.79 (d, *J* = 7.8 Hz, 2H); MS (*m/z*): 468.51 (M+H)⁺.

Example-152

N-(3-(3-(4-((2,2,2-Trifluoroethoxy)methyl)phenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)-4-chlorobenzyl)pivalamide

[0995]

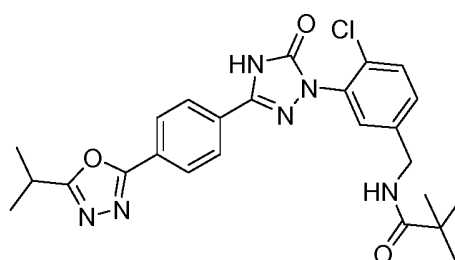


[0996] To a solution of 2,2,2-trifluoro ethanol (0.042 g, 0.410 mmol) in THF was added NaH (0.017 g, 0.041 mmol) at 10°C and continued stirring at RT for 1 h. Then solution of *N*-(3-(3-(4-(bromomethyl)phenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)-4-chlorobenzyl)pivalamide (Intermediate-103, 0.100 g, 0.041 mmol) in THF and TBAI (0.004 g, 0.0012 mmol) were added to the reaction mixture. The reaction mass was refluxed for 2-3 h. The reaction mass was quenched in ice and pH adjusted to 6-7 and extracted with DCM. The organic layer was dried over anhydrous sodium sulphate and concentrated to afford 0.060 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.12 (s, 9H), 4.11-4.17 (m, 2H), 4.28 (d, *J* = 5.4 Hz, 2H), 4.71 (s, 2H), 7.28 (d, *J* = 9.0 Hz, 1H), 7.41 (s, 1H), 7.46 (d, *J* = 7.8 Hz, 2H), 7.57 (d, *J* = 8.1 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 2H), 8.18 (t, 1H); MS (*m/z*): 497.31 (M+H)⁺.

Example-153

N-(4-Chloro-3-(4,5-dihydro-3-(4-(5-isopropyl-1,3,4-oxadiazol-2-yl)phenyl)-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide

[0997]

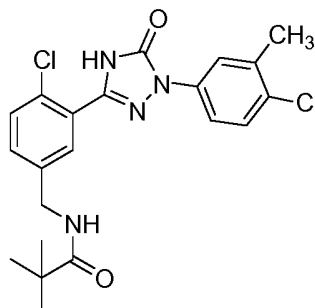


[0998] The title compound was prepared according to the procedure described in Example-83 by using 4-(5-isopropyl-1,3,4-oxadiazol-2-yl)benzoyl isocyanate (Intermediate-104, 0.196 g, 0.84 mmol), *tert*-butyl 2-(2-chloro-5-((2,2-dimethylpropanoyl)amino)methyl)phenylhydrazinecarboxylate (Intermediate-94, 0.150 g, 0.420 mmol), DCM (15 mL), and trifluoro acetic acid (3.0 mL) to afford 0.090 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.06 (s, 9H), 1.35 (s, 6H), 3.25 (m, 1H), 4.27 (d, *J* = 5.4 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.44 (s, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 8.01-8.04 (m, 2H), 8.10-8.17 (m, 3H), 12.73 (s, 1H); MS (*m/z*): 495.39 (M+H)⁺.

Example-154

N-(4-Chloro-3-(1-(4-chloro-3-methylphenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide

[0999]

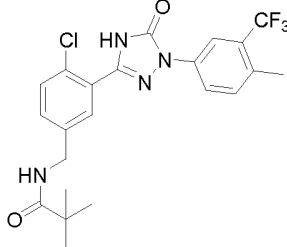
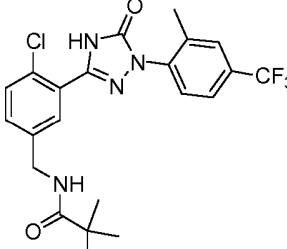
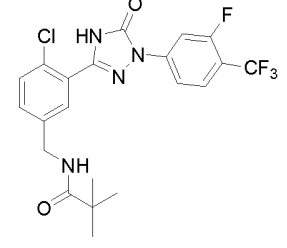
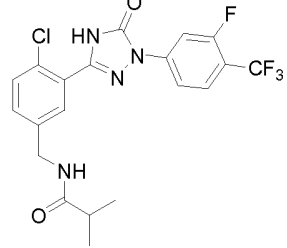
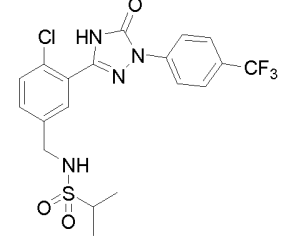


[1000] The title compound was prepared according to the procedure described in Example-108 by using 5-(5-(aminomethyl)-2-chlorophenyl)-2-(4-chloro-3-methylphenyl)-2*H*-1,2,4-triazol-3(4*H*)-one (Intermediate-106, 0.300 g, 0.859 mmol), pivaloyl chloride (0.130 g, 1.03 mmol), TEA (2.0 mL), dry THF (5 mL) to afford 0.140 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.13 (s, 9H), 2.37 (s, 3H), 4.29 (d, *J* = 5.7 Hz, 2H), 7.41 (d, *J* = 8.7 Hz, 1H), 7.51 (d, *J* = 8.7 Hz, 1H), 7.58 (s, 2H), 7.70 (br d, 1H), 7.91 (s, 1H), 8.20 (d, *J* = 6.0 Hz, 1H), 12.56 (s, 1H); MS (*m/z*) : 433.38 (M+H)⁺.

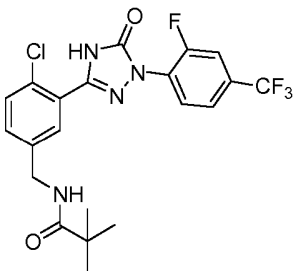
[1001] Example-155 to Example-163 were prepared by following the procedure described in Example-108 by using corresponding intermediates mentioned in table below, TEA and THF.

Intermediates used	Example No. and Structure	Example chemical name and characterization data
Intermediate-106 + Isobutyryl chloride	Example-155 	<i>N</i> -(4-Chloro-3-(1-(4-chloro-3-methylphenyl)-4,5-dihydro-5-oxo-1 <i>H</i> -1,2,4-triazol-3-yl)benzyl)isobutyramide. ¹ H NMR (300 MHz, DMSO <i>d</i> ₆): δ 1.02 (s, 3H), 1.05 (s, 3H), 2.38 (s, 3H), 4.29 (d, <i>J</i> = 6.0 Hz, 2H), 7.42 (d, <i>J</i> = 9.0 Hz, 1H), 7.52 (d, <i>J</i> = 8.7 Hz, 1H), 7.60 (s, 2H), 7.82 (br d, 1H), 7.91 (s, 1H), 8.38 (t, 1H), 12.57 (s, 1H); MS (<i>m/z</i>) : 433.30 (M+H) ⁺ .
Intermediate-130 + Pivaloyl chloride	Example-156 	<i>N</i> -(4-Chloro-3-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1 <i>H</i> -1,2,4-triazol-3-yl)benzyl)pivalamide. ¹ H NMR (300 MHz, DMSO <i>d</i> ₆): δ 1.13 (s, 9H), 4.30 (d, <i>J</i> = 6.3 Hz, 2H), 7.42 (d, <i>J</i> = 8.40 Hz, 1H), 7.61 (m, 3H), 8.09 (d, 1H), 8.14 (s, 1H), 8.20 (t, 1H), 12.80 (s, 1H); MS (<i>m/z</i>): 471.39 (M+H) ⁺ .
Intermediate-131 + Pivaloyl chloride	Example-157 	<i>N</i> -(4-Chloro-3-(1-(4-chloro-3-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1 <i>H</i> -1,2,4-triazol-3-yl)benzyl)pivalamide. ¹ H NMR (300 MHz, DMSO <i>d</i> ₆): δ 1.13 (s, 9H), 4.30 (d, <i>J</i> = 6.0 Hz, 2H), 7.42 (d, <i>J</i> = 7.20 Hz, 1H), 7.62 (d, <i>J</i> = 8.10 Hz, 2H), 7.86 (d, <i>J</i> = 8.7 Hz, 1H), 8.19-8.26 (m, 2H), 8.42 (s, 1H), 12.76 (s, 1H); MS (<i>m/z</i>) : 487.43 (M+H) ⁺ .

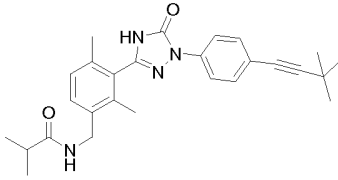
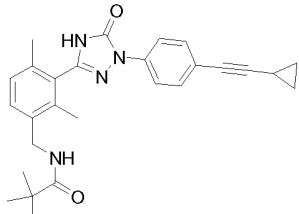
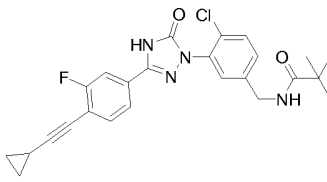
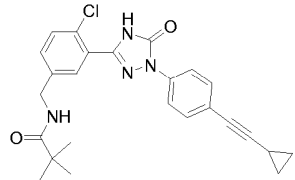
(continued)

Intermediates used	Example No. and Structure	Example chemical name and characterization data
Intermediate-133 + Pivaloyl chloride	<u>Example-158</u> 	<i>N</i>-(4-Chloro-3-(1-(3-(trifluoromethyl)-4-methylphenyl)-4,5-dihydro-5-oxo-1<i>H</i>-1,2,4-triazol-3-yl)benzyl)pivalamide. ¹H NMR (300 MHz, DMSO <i>d</i>₆): δ 1.13 (s, 9H), 2.46 (s, 3H), 4.31 (d, <i>J</i> = 5.7 Hz, 2H), 7.39 (d, <i>J</i> = 7.8 Hz, 2H), 7.57 (d, 2H), 7.68 (d, 2H), 7.80 (s, 1H), 12.47 (s, 1H); MS (<i>m/z</i>) : 467.22 (<i>M</i>+<i>H</i>)⁺.
Intermediate-134 + Pivaloyl chloride	<u>Example-159</u> 	<i>N</i>-(4-Chloro-3-(1-(4-(trifluoromethyl)-2-methylphenyl)-4,5-dihydro-5-oxo-1<i>H</i>-1,2,4-triazol-3-yl)benzyl)pivalamide. ¹H NMR (300 MHz, DMSO <i>d</i>₆): δ 1.12 (s, 9H), 2.39 (s, 3H), 4.28 (d, 2H), 7.43 (d, 1H), 7.55-7.60 (m, 3H), 8.12 (d, 1H), 8.20 (m, 1H), 8.29 (s, 1H), 12.65 (s, 1H); MS (<i>m/z</i>) : 467.15 (<i>M</i>+<i>H</i>)⁺.
Intermediate-135 + Pivaloyl chloride	<u>Example-160</u> 	<i>N</i>-(4-Chloro-3-(1-(3-fluoro-4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1<i>H</i>-1,2,4-triazol-3-yl)benzyl)pivalamide. ¹H NMR (300 MHz, DMSO <i>d</i>₆): δ 1.13 (s, 9H), 4.29 (d, <i>J</i> = 4.8 Hz, 2H), 7.43 (m, 1H), 7.60-7.61 (m, 2H), 7.91-7.94 (m, 1H), 7.98-8.06 (m, 2H), 8.19 (t, 1H); MS (<i>m/z</i>) : 471.18 (<i>M</i>+<i>H</i>)⁺.
Intermediate-135 + Isobutyryl chloride	<u>Example-161</u> 	<i>N</i>-(4-Chloro-3-(1-(3-fluoro-4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1<i>H</i>-1,2,4-triazol-3-yl)benzyl)isobutyramide. ¹H NMR (300 MHz, DMSO <i>d</i>₆): δ 1.02 (s, 3H), 1.05 (s, 3H), 2.43 (m, 1H), 4.29 (d, <i>J</i> = 6.6 Hz, 2H), 7.42 (d, <i>J</i> = 7.5 Hz, 1H), 7.60 (s, 1H), 7.63 (br s, 1H), 7.91 (t, <i>J</i> = 6.9 Hz, 1H), 7.99-8.08 (m, 2H), 8.40 (t, 1H); MS (<i>m/z</i>) : 455.01 (<i>M</i>+<i>H</i>)⁺.
Intermediate-63 + Isopropyl sulfonyl chloride	<u>Example-162</u> 	<i>N</i>-(4-Chloro-3-(1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1<i>H</i>-1,2,4-triazol-3-yl)benzyl)propane-2-sulfonamide. ¹H NMR (300 MHz, DMSO <i>d</i>₆): δ 1.22 (s, 3H), 1.24 (s, 3H), 3.17 (m, 1H), 4.23 (d, <i>J</i> = 6.0 Hz, 2H), 7.56 (d, <i>J</i> = 7.8 Hz, 1H), 7.65-7.72 (m, 3H), 7.87 (d, <i>J</i> = 8.4 Hz, 2H), 8.19 (d, <i>J</i> = 8.7 Hz, 2H), 12.72 (s, 1H); MS (<i>m/z</i>) : 475.15 (<i>M</i>+<i>H</i>)⁺.

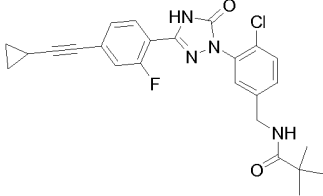
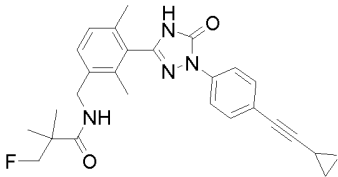
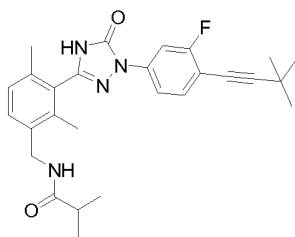
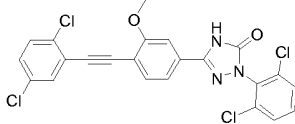
(continued)

Intermediates used	Example No. and Structure	Example chemical name and characterization data
Intermediate-136 + Pivaloyl chloride	Example-163 	<i>N</i> -(4-Chloro-3-(1-(2-fluoro-4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1 <i>H</i> -1,2,4-triazol-3-yl)benzyl)pivalamide. ¹ H NMR (300 MHz, DMSO <i>d</i> ₆): δ 1.12 (s, 9H), 7.28 (d, <i>J</i> = 5.7 Hz, 2H), 7.40 (d, <i>J</i> = 7.8 Hz, 1H), 7.57-7.62 (m, 2H), 7.75 (d, <i>J</i> = 7.8 Hz, 1H), 7.90-7.98 (m, 2H), 8.18 (t, 1H), 12.59 (s, 1H); MS (<i>m/z</i>) : 471.17 (M+H) ⁺ .

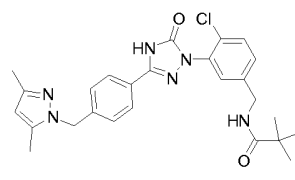
[1002] Example-164 to Example-171 were prepared by following the procedure described in Example-111 by using corresponding intermediates mentioned in table below, bis(triphenylphosphine)palladium(II) chloride, TBAF and DMSO.

Intermediates used	Example No. and Structure	Example chemical name and Characterization data
Intermediate-140 + 3,3-dimethylbut-1-yne	Example-164 	<i>N</i> -(3-(4,5-Dihydro-1-(4-(3,3-dimethylbut-1-ynyl)phenyl)-5-oxo-1 <i>H</i> -1,2,4-triazol-3-yl)-2,4-dimethylbenzyl)isobutyramide. ¹ H NMR (300 MHz, DMSO <i>d</i> ₆): δ 1.01 (s, 3H), 1.04 (s, 3H), 1.26 (s, 9H), 2.16 (s, 3H), 2.20 (s, 3H), 2.42 (m, 1H), 4.24 (d, <i>J</i> = 6.3 Hz, 2H), 7.17 (d, <i>J</i> = 7.8 Hz, 1H), 7.27 (d, <i>J</i> = 8.4 Hz, 1H), 7.43 (d, <i>J</i> = 8.7 Hz, 2H), 7.92 (d, <i>J</i> = 9.0 Hz, 2H), 8.19 (t, 1H), 12.23 (s, 1H); MS (<i>m/z</i>): 445.26 (M+H) ⁺ .
Intermediate-138 + Ethynylcyclopropane	Example-165 	<i>N</i> -(3-(1-(4-(2-Cyclopropylethynyl)phenyl)-4,5-dihydro-5-oxo-1 <i>H</i> -1,2,4-triazol-3-yl)-2,4-dimethylbenzyl)pivalamide. ¹ H NMR (300 MHz, DMSO <i>d</i> ₆): δ 0.73 (m, 2H), 0.88 (m, 2H), 1.14 (s, 9H), 1.54 (s, 3H), 2.16 (s, 3H), 2.19 (s, 3H), 4.23 (d, <i>J</i> = 6.0 Hz, 2H), 7.16 (d, <i>J</i> = 8.4 Hz, 1H), 7.23 (d, <i>J</i> = 7.8 Hz, 1H), 7.43 (d, <i>J</i> = 8.4 Hz, 2H), 7.91 (d, <i>J</i> = 9.0 Hz, 2H), 8.00 (t, 1H), 12.22 (s, 1H); MS (<i>m/z</i>) : 443.51 (M+H) ⁺ .
Intermediate-119 + Ethynylcyclopropane	Example-166 	<i>N</i> -(4-Chloro-3-(3-(4-(2-cyclopropylethynyl)-3-fluorophenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide. ¹ H NMR (300 MHz, DMSO <i>d</i> ₆): δ 0.80 (m, 2H), 0.93-0.95 (m, 2H), 1.12 (s, 9H), 1.63 (m, 1H), 4.28 (d, <i>J</i> = 6.3 Hz, 2H), 7.35 (d, <i>J</i> = 9.0 Hz, 1H), 7.43 (s, 1H), 7.59-7.67 (m, 4H), 8.19 (t, 1H), 12.66 (s, 1H); MS (<i>m/z</i>) : 467.24 (M+H) ⁺ .
Intermediate-139 + Ethynylcyclopropane	Example-167 	<i>N</i> -(4-Chloro-3-(1-(4-(2-cyclopropylethynyl)phenyl)-4,5-dihydro-5-oxo-1 <i>H</i> -1,2,4-triazol-3-yl)benzyl)pivalamide. ¹ H NMR (300 MHz, DMSO <i>d</i> ₆): δ 0.73 (m, 2H), 0.89 (m, 2H), 1.13 (s, 9H), 1.54 (m, 1H), 4.30 (d, 2H), 7.41-7.47 (m, 2H), 7.58 (s, 2H), 7.81 (m, 1H), 7.91 (d, <i>J</i> = 6.3 Hz, 2H), 8.18 (br s, 1H), 12.56 (s, 1H); MS (<i>m/z</i>): 449.30 (M+H) ⁺ .

(continued)

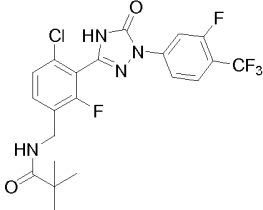
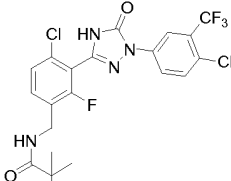
Intermediates used	Example No. and Structure	Example chemical name and Characterization data
Intermediate-124 + Ethynylcyclopropane	<u>Example-168</u> 	<i>N</i> -(4-Chloro-3-(3-(4-(2-cyclopropylethynyl)-2-fluorophenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide. ¹ H NMR (300 MHz, DMSO <i>d</i> ₆): δ 0.78 (m, 2H), 0.93 (m, 2H), 1.12 (s, 9H), 1.59 (m, 1H), 4.28 (d, <i>J</i> = 6.6 Hz, 2H), 7.34 (d, <i>J</i> = 8.4 Hz, 2H), 7.41 (m, 2H), 7.62 (d, <i>J</i> = 7.8 Hz, 1H), 7.75 (d, <i>J</i> = 7.8 Hz, 1H), 8.19 (t, 1H), 12.40 (s, 1H); MS (<i>m/z</i>) : 467.20 (M) ⁺ .
Intermediate-143 + Ethynylcyclopropane	<u>Example-169</u> 	<i>N</i> -(3-(1-(4-(2-Cyclopropylethynyl)phenyl)-4,5-dihydro-5-oxo-1 <i>H</i> -1,2,4-triazol-3-yl)-2,4-dimethylbenzyl)-3-fluoro-2,2-dimethylpropanamide. ¹ H NMR (300 MHz, DMSO <i>d</i> ₆): δ 0.74 (m, 2H), 0.85 (m, 2H), 1.15 (s, 6H), 1.54 (m, 1H), 2.15 (s, 3H), 2.19 (s, 3H), 4.27 (d, 2H), 4.43 (s, 1H), 4.49 (s, 1H), 7.17-7.24 (m, 2H), 7.43 (d, <i>J</i> = 8.4 Hz, 2H), 7.90 (d, <i>J</i> = 8.7 Hz, 2H), 8.16 (s, 1H), 12.22 (s, 1H); MS (<i>m/z</i>): 461.21 (M+H) ⁺ .
Intermediate-141 + 3,3-dimethylbut-1-yne	<u>Example-170</u> 	<i>N</i> -(3-(1-(3-Fluoro-4-(3,3-dimethylbut-1-ynyl)phenyl)-4,5-dihydro-5-oxo-1 <i>H</i> -1,2,4-triazol-3-yl)-2,4-dimethylbenzyl)isobutyramide. ¹ H NMR (300 MHz, DMSO <i>d</i> ₆): δ 1.01 (s, 3H), 1.04 (s, 3H), 1.23 (s, 9H), 2.15 (s, 3H), 2.20 (s, 3H), 4.25 (d, 2H), 7.18 (m, 1H), 7.26 (m, 1H), 7.51 (m, 1H), 7.84 (m, 2H), 8.19 (t, 1H), 12.35 (s, 1H); MS (<i>m/z</i>): 463.151 (M+H) ⁺ .
Intermediate-45 + 1,4-dichloro-2-ethynylbenzene	<u>Comparative Example-171</u> 	2-(2,6-Dichlorophenyl)-5-(4-(2-(2,5-dichlorophenyl)ethynyl)-3-methoxyphenyl)-2 <i>H</i> -1,2,4-triazol-3(4 <i>H</i>)-one. ¹ H NMR (300 MHz, DMSO <i>d</i> ₆): δ 3.92 (s, 3H), 7.54 (m, 4H), 7.58-7.69 (m, 4H), 7.75 (s, 1H), 12-13 (br s, 1H); MS (<i>m/z</i>): 506.01 (M+H) ⁺ .

[1003] Example-172 was prepared by following the procedure described in Intermediate-41 by using corresponding intermediates mentioned in table below, NaH and DMF.

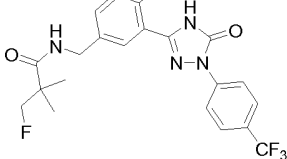
Intermediate used	Example No. and Structure	Example chemical name and characterization data
Intermediate-103 + 3,5-dimethyl-1 <i>H</i> -pyrazole	<u>Example-172</u> 	<i>N</i> -(4-Chloro-3-(4,5-dihydro-3-(4-((3,5-dimethyl-1 <i>H</i> -pyrazol-1-yl)methyl)phenyl)-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide. ¹ H NMR (300 MHz, DMSO <i>d</i> ₆): δ 1.11 (s, 9H), 2.10 (s, 3H), 2.15 (s, 3H), 4.28 (d, <i>J</i> = 5.1 Hz, 2H), 5.24 (s, 2H), 5.87 (s, 1H), 7.19 (d, <i>J</i> = 7.8 Hz, 2H), 7.32 (d, <i>J</i> = 8.7 Hz, 1H), 7.22 (s, 1H), 7.59 (d, <i>J</i> = 8.1 Hz, 1H), 7.79 (d, <i>J</i> = 7.5 Hz, 1H), 8.18 (t, 1H); MS (<i>m/z</i>) : 493.36 (M) ⁺ .

[1004] Example-173 and Example-174 were prepared by following the procedure as described in Example-83 by using corresponding intermediates mentioned in table below, TFA and DCM.

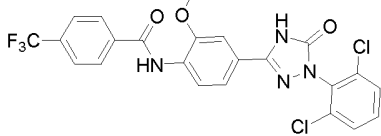
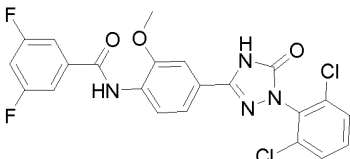
EP 2 718 284 B1

Intermediates used	Example No. and Structure	Example chemical name and characterization data
Intermediate-109 + Intermediate-51	Example-173 	<i>N</i>-(4-Chloro-2-fluoro-3-(1-(3-fluoro-4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1<i>H</i>-1,2,4-triazol-3-yl)benzyl)pivalamide. ¹H NMR (300 MHz, CDCl₃): δ 1.21 (s, 9H), 4.46 (d, <i>J</i> = 5.7 Hz, 2H), 6.21 (t, 1H), 6.42 (d, 1H), 7.32 (s, 1H), 7.42 (t, 1H), 7.65 (t, 1H), 7.96 (m, 2H); MS (<i>m/z</i>): 489.56 (M)⁺.
Intermediate-111 + Intermediate-51	Example-174 	<i>N</i>-(4-Chloro-3-(1-(4-chloro-3-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1<i>H</i>-1,2,4-triazol-3-yl)-2-fluorobenzyl)pivalamide. ¹H NMR (300 MHz, DMSO <i>d</i>₆): δ 1.13 (s, 9H), 4.30 (d, <i>J</i> = 6.0 Hz, 2H), 7.46 (d, <i>J</i> = 7.8 Hz, 1H), 7.55 (d, <i>J</i> = 8.1 Hz, 1H), 7.85 (d, <i>J</i> = 8.1 Hz, 1H), 8.20 (t, 2H), 8.41 (s, 1H), 12.90 (m, 1H); MS (<i>m/z</i>): 505.27 (M+H)⁺.

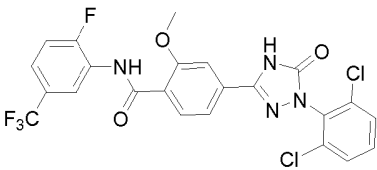
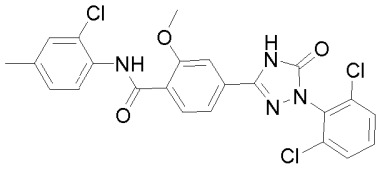
[1005] Example-175 was prepared by following the procedure as described in described for step-2 of Example-134 by using Example-115, DAST and THF.

Intermediates used	Example No. and Structure	Example chemical name and characterization data
Example-115	<u>Example-175</u> 	<i>N</i>-(4-Chloro-3-(1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1<i>H</i>-1,2,4-triazol-3-yl)benzyl)-3-fluoro-2,2-dimethylpropanamide. ¹H NMR (300 MHz, DMSO <i>d</i>₆): δ 1.15 (s, 6H), 4.33 (m, 4H), 7.41 (d, <i>J</i> = 7.2 Hz, 1H), 7.61 (d, <i>J</i> = 7.8 Hz, 2H), 7.85 (d, <i>J</i> = 9.3 Hz, 2H), 8.20 (d, <i>J</i> = 8.4 Hz, 2H), 8.35 (t, 1H), 12.71 (m, 1H); MS (<i>m/z</i>): 471.28 (M+H)⁺.

[1006] Example-176 to Example-179 were prepared by following the procedure as described for step-6 of Intermediate-26 by using corresponding intermediates used mentioned in table below, trimethyl aluminium (2M solution in toluene) and dry toluene.

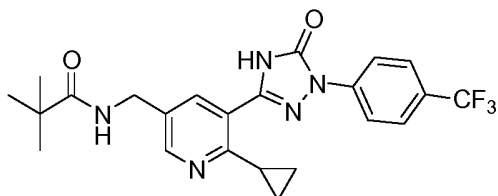
Intermediates used	Example No. and Structures	Example chemical name and characterization data
Step-5 of Intermediate-45 + methyl 4-(trifluoromethyl)benzoate	<u>Comparative Example-176</u> 	<i>N</i>-(4-(1-(2,6-Dichlorophenyl)-4,5-dihydro-5-oxo-1<i>H</i>-1,2,4-triazol-3-yl)-2-methoxyphenyl)-4-(trifluoromethyl)benzamide. ¹H NMR (300 MHz, DMSO <i>d</i>₆): δ 3.91 (s, 3H), 7.49-7.64 (m, 3H), 7.72-7.74 (m, 2H), 7.91 (d, <i>J</i> = 8.4 Hz, 2H), 7.98 (d, <i>J</i> = 8.4 Hz, 1H), 8.15 (d, <i>J</i> = 8.1 Hz, 2H), 9.90 (s, 1H), 12.70 (s, 1H); MS (<i>m/z</i>): 523.10 (M+H)⁺.
Step-5 of Intermediate-45 + methyl 3,5-difluorobenzoate	<u>Comparative Example-177</u> 	<i>N</i>-(4-(1-(2,6-Dichlorophenyl)-4,5-dihydro-5-oxo-1<i>H</i>-1,2,4-triazol-3-yl)-2-methoxyphenyl)-3,5-difluorobenzamide. ¹H NMR (300 MHz, DMSO <i>d</i>₆): δ 3.90 (s, 3H), 7.47-7.61 (m, 4H), 7.64-7.72 (m, 4H), 7.88 (d, <i>J</i> = 7.8 Hz, 1H), 9.86 (s, 1H), 12.69 (s, 1H); MS (<i>m/z</i>): 491.03 (M+H)⁺.

(continued)

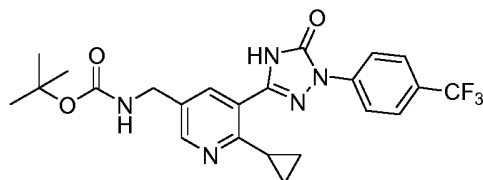
Intermediates used	Example No. and Structures	Example chemical name and characterization data
Intermediate- 46 + 2-fluoro-5-(trifluoromethyl) aniline	<u>Comparative Example-178</u> 	4-(1-(2,6-Dichlorophenyl)-4,5-dihydro-5-oxo-1H-1,2,4-triazol-3-yl)-N-(2-fluoro-5-(trifluoromethyl)phenyl)-2-methoxybenzamide. ¹ H NMR (300 MHz, DMSO <i>d</i> ₆): δ 4.06 (s, 3H), 7.60-7.65 (m, 5H), 7.55.-7.67 (m, 2H), 8.03 (d, <i>J</i> = 7.8 Hz, 1H), 8.60 (s, 1H), 10.44 (s, 1H), 12.90 (s, 1H); MS (<i>m/z</i>): 541.05 (M+H) ⁺ .
Intermediate-46 + 2-chloro-4-methyl aniline	<u>Comparative Example-179</u> 	N-(2-Chloro-4-methylphenyl)-4-(1-(2,6-dichlorophenyl)-4,5-dihydro-5-oxo-1H-1,2,4-triazol-3-yl)-2-methoxybenzamide. ¹ H NMR (300 MHz, DMSO <i>d</i> ₆): δ 2.30 (s, 3H), 4.13 (s, 3H), 7.20 (d, <i>J</i> = 8.7 Hz, 1H), 7.41 (s, 1H), 7.41-7.75 (m, 5H), 8.15 (d, <i>J</i> = 7.8 Hz, 1H), 8.30 (d, <i>J</i> = 8.4 Hz, 1H), 10.47 (s, 1H), 12.91 (s, 1H); MS (<i>m/z</i>): 503.00 (M+H) ⁺ .

Example-180

N-((6-Cyclopropyl-5-(1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1H-1,2,4-triazol-3-yl)pyridin-3-yl)methyl)pivalamide

[1007]

Step-1:- Preparation of *tert*-butyl (6-cyclopropyl-5-(1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1H-1,2,4-triazol-3-yl)pyridin-3-yl)methylcarbamate

[1008]

[1009] A solution of 6-cyclopropyl-5-(1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1H-1,2,4-triazol-3-yl)pyridine-3-carbonitrile (0.110 g) in ethanol (10 mL) and BOC anhydride (0.150 g), TEA (1.0 mL), Pd/C (catalytic amount) was stirred under hydrogen atmosphere under 35-40 psi pressure in Parr apparatus for 4-5 h. The reaction mass was filtered and the obtained filtrate was concentrated to afford 0.100 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 0.93-0.98 (m, 4H), 1.36 (s, 9H), 2.09 (m, 1H), 4.12 (d, *J* = 5.7 Hz, 2H), 7.51 (m, 1H), 7.69 (s, 1H), 7.88 (d, *J* = 8.4 Hz, 2H), 8.43 (d, *J* = 7.8 Hz, 2H); MS (*m/z*) : 476.13 (M+H)⁺.

EP 2 718 284 B1

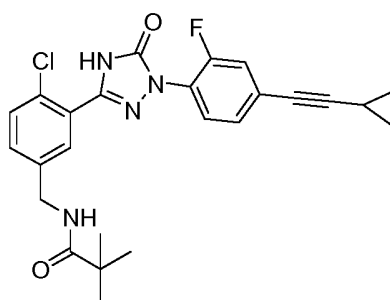
Step-2:- Preparation *N*-((6-cyclopropyl-5-(1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)pyridin-3-yl)methyl)pivalamide

[1010] Stirred a solution of *tert*-butyl (6-cyclopropyl-5-(1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)pyridin-3-yl)methylcarbamate (0.100 g) in EtOC:HCl (5.0 mL) for 6 h at RT. Excess of solvent was removed and added DCM (5.0 mL), TEA (0.5 mL) and pivaloyl chloride (0.045 g) under nitrogen atmosphere o the reaction mixture. The reaction mass was stirred at RT for 4 h. Excess of solvent was removed under vacuum and the residue was diluted with water, extracted with EtOAc and concentrated to afford 0.020 g of the product. ¹H NMR (300 MHz, DMSO *d*₆): δ 0.98 (m, 4H), 1.12 (s, 9H), 2.73 (m, 1H), 4.27 (d, *J* = 6.0 Hz, 2H), 7.78 (s, 1H), 7.85 (d, *J* = 8.7 Hz, 2H), 8.13 (t, 1H), 8.19 (d, *J* = 9.3 Hz, 2H), 8.40 (s, 1H), 12.75 (s, 1H); MS (*m/z*) : 460.30 (M+H)⁺

Example-181

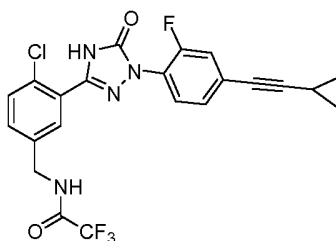
N-(4-Chloro-3-(1-(4-(2-cyclopropylethynyl)-2-fluorophenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide

[1011]



Step 1:- Preparation of *N*-(4-chloro-3-(1-(4-(2-cyclopropylethynyl)-2-fluorophenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide

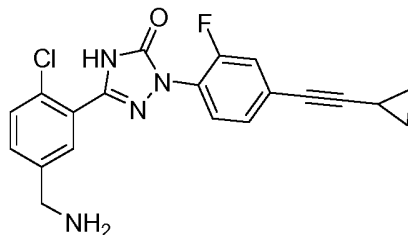
[1012]



[1013] The title compound was prepared according to the procedure described in Example-111 by using *N*-(4-chloro-3-(1-(2-fluoro-4-iodophenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide (Intermediate-126, 1.100 g, 3.88 mmol), ethynylcyclopropane (0.127 g, 1.93 mmol), TBAF (1.10 g, 3.88 mmol), bis(triphenylphosphine)palladium(II) chloride (0.036 g, 0.051 mmol) and DMSO (3.0 mL) to afford 0.400 g of the desired title product. ¹H NMR (400 MHz, DMSO *d*₆): δ 0.95 (m, 4H), 1.56 (m, 1H), 4.44 (br s, 2H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.42-7.46 (m, 2H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.65 (m, 3H), 10.12 (br s, 1H); MS (*m/z*): 479.11 (M+H)⁺.

Step 2:- Preparation of 5-(5-(aminomethyl)-2-chlorophenyl)-2-(4-(2-cyclopropylethynyl)-2-fluorophenyl)-2*H*-1,2,4-triazol-3(4*H*)-one

[1014]



[1015] The title compound was prepared by following the procedure as described in step-2 of Intermediate-106 by using *N*-(4-chloro-3-(1-(4-(2-cyclopropylethynyl)-2-fluorophenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide (0.300 g), KOH (0.300 g), water (2.0 mL), THF (10.0 mL) to afford 0.200 g of desired product. MS (*m/z*): 383.16 (*M*+*H*)⁺.

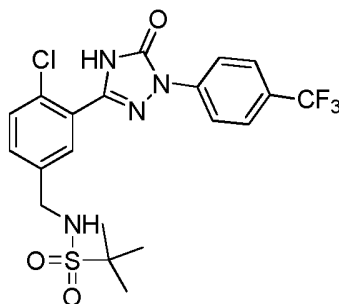
Step -3:-Preparation of *N*-(4-chloro-3-(1-(4-(2-cyclopropylethynyl)-2-fluorophenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide

[1016] The title compound was prepared according to the procedure described in Example-108 by using 5-(5-(aminomethyl)-2-chlorophenyl)-2-(4-(2-cyclopropylethynyl)-2-fluorophenyl)-2*H*-1,2,4-triazol-3(4*H*)-one (0.100 g, 0.266 mmol), pivaloyl chloride (0.040 g, 0.319 mmol), THF (10.0 mL) and TEA (2 mL) to afford 0.040 g of the desired product. ¹H NMR (400 MHz, DMSO *d*₆): δ 0.78 (m, 2H), 0.919 (m, 2H), 1.11 (br s, 9H), 1.56 (m, 1H), 4.28 (br d, 2H), 7.32-7.41 (m, 3H), 7.56 (br s, 3H), 8.16 (s, 1H), 12.46 (s, 1H); MS (*m/z*): 467.22 (*M*+*H*)⁺.

Example-182

N-(4-Chloro-3-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)-2-methylpropane-2-sulfonamide

[1017]

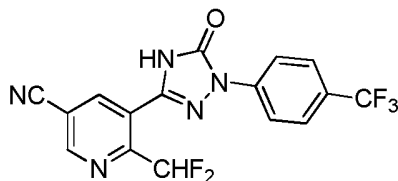


[1018] To a solution of *N*-(4-chloro-3-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)-2-methylpropane-2-sulfonamide (Intermediate-144, 0.075 g, 0.158 mmol) in mixture of DCM : acetonitrile : water (0.2 mL : 0.2 mL : 0.3 mL), sodium periodate (0.050 g, 0.238 mmol) and ruthenium chloride (0.001 g, 0.003 mmol) were added and the reaction mass was stirred at RT for 4 h. After completion of the reaction the reaction mass was filtered through celite bed and extracted with DCM. The organic layer was separated, dried over anhydrous sodium sulphate and concentrated. The obtained product was purified with column chromatography on neutral alumina eluting with 10 % MeOH: DCM to afford 0.020 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.30 (s, 9H), 4.31 (d, *J* = 6.0 Hz, 2H), 7.55-7.71 (m, 4H), 7.86 (d, *J* = 8.7 Hz, 2H), 8.19 (d, *J* = 9.0 Hz, 2H), 12.71 (s, 1H). MS (*m/z*): 489.04 (*M*+*H*)⁺.

Comparative Example-183

6-(Difluoromethyl)-5-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)nicotinonitrile

[1019]

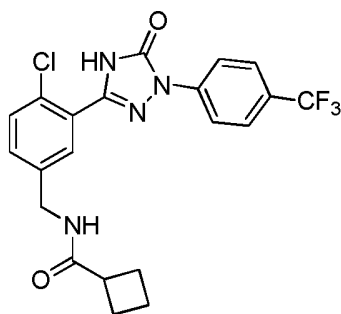


[1020] The title compound was prepared by following the procedure as described in Example-83 by using 5-cyano-2-(difluoromethyl)nicotinoyl isocyanate (Intermediate-145, 0.900 g, 4.03 mmol), *tert*-butyl 2-(4-(trifluoromethyl)phenyl)hydrazinecarboxylate (Intermediate-53, 1.0 g, 3.63 mmol), TFA (10 mL), DCM (40 mL) to afford 0.350 g of the desired product. ^1H NMR (300 MHz, DMSO d_6): δ 7.45-7.56 (t, J = 53.4 Hz, 1H), 7.90 (d, J = 9.3 Hz, 2H), 8.20 (d, J = 8.7 Hz, 2H), 8.77 (s, 1H), 9.32 (s, 1H), 13.01 (s, 1H); MS (m/z): 382.15 ($M+H$) $^+$.

Example-184

N-(4-Chloro-3-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1H-1,2,4-triazol-3-yl)benzyl)cyclobutanecarboxamide

[1021]

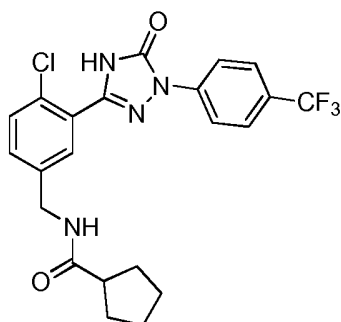


[1022] The title compound was prepared according to the procedure described in Example-108 by using 3-(5-(aminomethyl)-2-chlorophenyl)-1-(4-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-5(4H)-one (Intermediate-63, 0.100 g, 0.271 mmol), TEA (1.0 mL), DCM (10 mL), cyclobutanecarbonyl chloride (0.041 g, 0.352 mmol) to afford 0.020 g of the desired product. ^1H NMR (300 MHz, DMSO d_6): δ 2.05 (m, 6H), 3.08 (m, 1H), 4.29 (m, 2H), 7.44 (m, 1H), 7.60 (m, 2H), 7.86 (m, 2H), 8.17 (m, 3H), 12.69 (s, 1H); MS (m/z): 451.07 ($M+H$) $^+$.

Example-185

N-(4-Chloro-3-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1H-1,2,4-triazol-3-yl)benzyl)cyclopentanecarboxamide

[1023]



[1024] The title compound was prepared according to the procedure described in Example-17 by using 3-(5-(aminomethyl)-2-chlorophenyl)-1-(4-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-5(4H)-one (Intermediate-63, 0.100 g, 0.271 mmol), TEA (1.0 mL), DCM (10 mL), cyclopentanecarbonyl chloride (0.041 g, 0.352 mmol) to afford 0.020 g of the desired product. ^1H NMR (300 MHz, DMSO d_6): δ 2.05 (m, 6H), 3.08 (m, 1H), 4.29 (m, 2H), 7.44 (m, 1H), 7.60 (m, 2H), 7.86 (m, 2H), 8.17 (m, 3H), 12.69 (s, 1H); MS (m/z): 467.07 ($M+H$) $^+$.

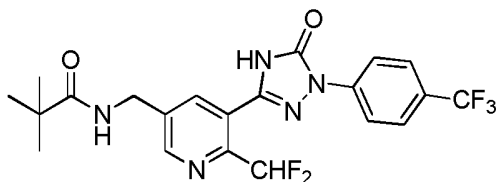
EP 2 718 284 B1

mmol), TEA (1.0 mL), TBTU (0.261 g, 0.813 mmol), THF : DMF (10 mL), cyclopentanecarboxylic acid (0.061 g, 0.542 mmol) to afford 0.025 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.50-1.76 (m, 8H), 2.62 (s, 1H), 4.30 (d, 2H), 7.45 (m, 1H), 7.61 (m, 2H), 7.85 (d, *J* = 9.6 Hz, 2H), 8.19 (d, *J* = 8.1 Hz, 2H), 8.40 (m, 1H), 12.69 (s, 1H); MS (*m/z*): 465.08 (M+H)⁺.

Example-186

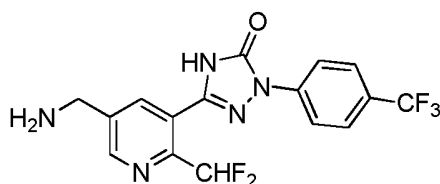
N-((6-(Difluoromethyl)-5-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyridin-3-yl)methyl)pivalamide

[1025]



Step-1:- Preparation of 3-(5-(aminomethyl)-2-(difluoromethyl)pyridin-3-yl)-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,4-triazol-5 (4*H*)-one

[1026]



[1027] The title compound was prepared according to the procedure described in Intermediate-16 by using 6-(difluoromethyl)-5-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)nicotinonitrile (Example-183, 0.050 g, 0.13 mmol), Raney Ni (catalytic amount), TEA (0.040 g, 0.39 mmol) in ethanol (20 mL) to afford 0.50 g of the desired product.

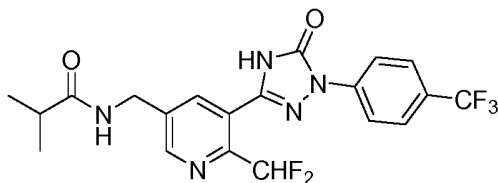
Step-2:- Preparation of *N*-((6-(difluoromethyl)-5-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyridin-3-yl)methyl)pivalamide

[1028] The title compound was prepared by following the procedure as described in Example-108 by using 3-(5-(aminomethyl)-2-(difluoromethyl)pyridin-3-yl)-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,4-triazol-5(4*H*)-one (0.50 g, 0.12 mmol), pivaloyl chloride (0.018 g, 0.14 mmol), TEA (0.038 g, 0.37 mmol) in DCM (10 mL) to afford 0.010 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.18 (s, 9H), 4.38 (s, 2H), 7.24-7.63 (m, 1H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.99 (s, 1H), 8.10 (d, *J* = 8.4 Hz, 2H), 8.61 (s, 1H); MS (*m/z*): 470.25 (M+H)⁺.

Example-187

N-((6-(Difluoromethyl)-5-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyridin-3-yl)methyl)isobutyramide

[1029]

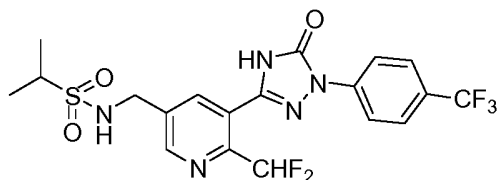


[1030] The title compound was prepared by following the procedure as described in Example-108 by using 3-(5-(aminomethyl)-2-(difluoromethyl)pyridin-3-yl)-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,4-triazol-5(4*H*)-one (step-1 of Example-186, 0.50 g, 0.12 mmol), isobutyryl chloride (0.017 g, 0.15 mmol), TEA (0.042 g, 0.41 mmol) and DCM (10 mL) to afford 0.015 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.14-1.21 (m, 6H), 2.47 (m, 1H), 4.47 (s, 2H), 7.32-7.54 (m, 1H), 7.72 (d, *J* = 8.7 Hz, 2H), 8.09 (br s, 1H), 8.18 (d, *J* = 7.8 Hz, 2H), 8.70 (s, 1H); MS (*m/z*): 456.14 (M+H)⁺.

Example-188

N-((6-(Difluoromethyl)-5-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyridin-3-yl)methyl)propane-2-sulfonamide

[1031]

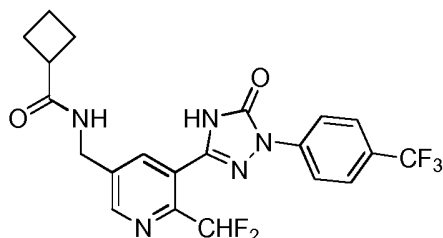


[1032] The title compound was prepared by following the procedure as described in Example-108 by using 3-(5-(aminomethyl)-2-(difluoromethyl)pyridin-3-yl)-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,4-triazol-5(4*H*)-one (step-1 of Example-186, 0.75 g, 0.19 mmol), isopropyl sulphonyl chloride (0.042 g, 0.29 mmol), TEA (0.059 g, 0.58 mmol), and DCM (10 mL) to afford 0.012 g of desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.32 (s, 3H), 1.35 (s, 3H), 3.15 (m, 1H), 4.36 (s, 2H), 7.26-7.66 (m, 3H), 8.08-8.11 (m, 3H), 8.65 (s, 1H); MS (*m/z*): 492.08 (M+H)⁺.

Example-189

N-((6-(Difluoromethyl)-5-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyridin-3-yl)methyl)cyclobutanecarboxamide

[1033]

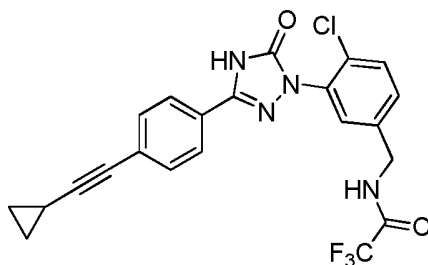


[1034] The title compound was prepared by following the procedure as described in Example-108 by using 3-(5-(aminomethyl)-2-(difluoromethyl)pyridin-3-yl)-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,4-triazol-5(4*H*)-one (step-1 of Example-186, 0.75 g, 0.19 mmol), cyclobutane carbonyl chloride (0.035 g, 0.29 mmol), TEA (0.059 g, 0.58 mmol) and DCM (10 mL) to afford 0.020 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 1.89-2.29 (m, 7H), 4.45 (s, 2H), 7.31-7.52 (m, 1H), 7.72 (d, *J* = 8.4 Hz, 2H), 8.05 (s, 1H), 8.18 (d, *J* = 8.4 Hz, 2H), 8.66 (s, 1H); MS (*m/z*): 468.26 (M+H)⁺.

Example-190

N-(4-Chloro-3-(3-(4-(cyclopropylethynyl)phenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)-2,2,2-trifluoroacetamide

[1035]

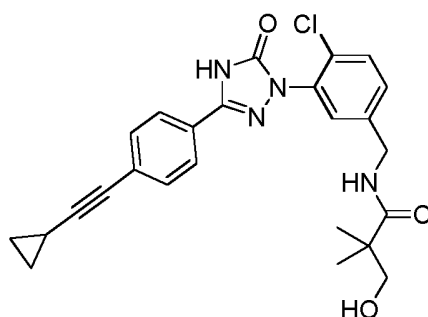


[1036] The title compound was prepared according to the procedure described in Example 111 using *N*-(4-chloro-3-(3-(4-iodophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)-2,2,2-trifluoroacetamide (Intermediate-146, 0.300 g, 0.568 mmol), ethynylcyclopropane (0.056 g, 0.852 mmol), TBAF (0.444 g, 1.72 mmol), bis(triphenylphosphine)palladium(II) chloride (0.016 g, 0.022 mmol) and DMSO (3.0 mL) to afford 0.020 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 0.75 (m, 2H), 0.90 (m, 2H), 1.55 (m, 1H), 4.43 (d, *J* = 6.0 Hz, 2H), 7.38 (d, *J* = 6.6 Hz, 1H), 7.46-7.51 (m, 3H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 2H), 10.06 (m, 1H), 12-13 (br s, 1H). MS (*m/z*): 461.12 (*M*+*H*)⁺.

Example-191

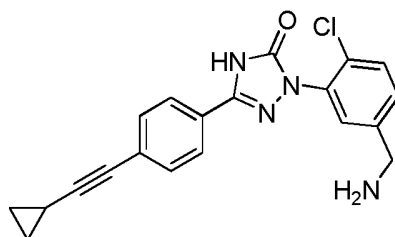
N-(4-Chloro-3-(3-(4-(cyclopropylethynyl)phenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)-3-hydroxy-2,2-dimethylpropanamide

[1037]



Step-1:-Preparation of 1-(5-(aminomethyl)-2-chlorophenyl)-3-(4-(cyclopropylethynyl)phenyl)-1*H*-1,2,4-triazol-5(4*H*)-one

[1038]



[1039] The title compound was prepared by following the procedure as described in step-2 of InteremEDIATE-106 by

using *N*-(4-chloro-3-(3-(4-(cyclopropylethynyl)phenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)-2,2,2-trifluoroacetamide (Example-190, 0.100 g), LiOH (0.100 g), water (2.0 mL), THF (10.0 mL) to afford 0.050 g of the desired product. MS (m/z): 365.83 (M+H)⁺.

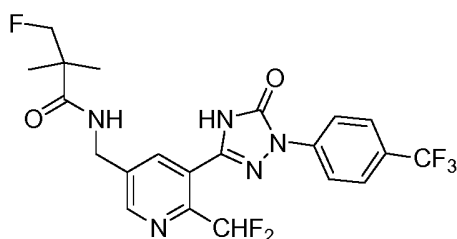
Step-2:- Preparation of *N*-(4-chloro-3-(3-(4-(cyclopropylethynyl)phenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)-3-hydroxy-2,2-dimethylpropanamide

[1040] The title compound was prepared according to the procedure described in Example-107 by using 1-(5-(aminomethyl)-2-chlorophenyl)-3-(4-(cyclopropylethynyl)phenyl)-1*H*-1,2,4-triazol-5(4*H*)-one (0.080 g, 0.228 mmol), DMF (5 mL), 3-methoxy-2,2-dimethylpropanoic acid (0.040 g, 0.342 mmol), BOP (0.151 g, 0.342 mmol), TEA (2.0 mL) to afford 0.010 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 0.75 (m, 2H), 0.83 (m, 2H), 1.10 (s, 6H), 1.51 (m, 1H), 3.34 (m, 2H), 4.31 (br s, 2H), 4.85 (m, 1H), 7.37-7.50 (m, 3H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.77-7.83 (m, 3H), 8.11 (br s, 1H), 12.56 (s, 1H); MS (m/z): 465.07 (M+H)⁺.

Example-192

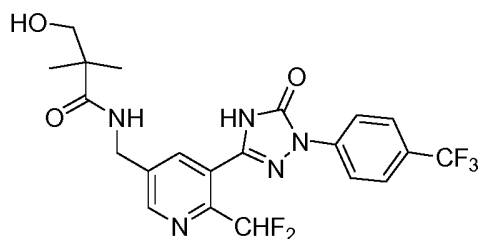
3-Fluoro-*N*-((6-(difluoromethyl)-5-(1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)pyridin-3-yl)methyl)-2,2-dimethylpropanamide

[1041]



Step-1:- Preparation of *N*-((6-(difluoromethyl)-5-(1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)pyridin-3-yl)methyl)-3-hydroxy-2,2-dimethylpropanamide

[1042]



[1043] The title compound was prepared by following the procedure as described in Example-107 by using 3-(5-(aminomethyl)-2-(difluoromethyl)pyridin-3-yl)-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,4-triazol-5(4*H*)-one (step-1 of Example-186, 0.130 g, 0.33 mmol), DMF (5 mL), 3-methoxy-2,2-dimethylpropanoic acid (0.060 g, 0.50 mmol), BOP (0.224 g, 0.50 mmol), TEA (2.0 mL) to afford 0.070 g of the desired product. MS (m/z): 486.22 (M+H)⁺.

Step-2:- Preparation of 3-fluoro-*N*-((6-(difluoromethyl)-5-(1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)pyridin-3-yl)methyl)-2,2-dimethylpropanamide

[1044] The title compound was prepared by following the procedure as described in step-2 of Example-134 by using *N*-((6-(difluoromethyl)-5-(1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)pyridin-3-yl)methyl)-3-hydroxy-2,2-dimethylpropanamide (0.060 g, 0.12 mmol), DAST (0.060 g, 0.37 mmol), DCM (10 mL) to afford 0.005 g of the desired product. ¹H NMR (300 MHz, DMSO *d*₆): δ 0.80 (br s, 6H), 4.22 (br s, 1H), 4.38-4.42 (m, 3H), 7.41-7.66 (m, 3H), 7.95 (br s, 1H), 8.08-8.11 (m, 2H), 8.61 (s, 1H); MS (m/z): 488.23 (M+H)⁺.

Pharmacological activity

In-vitro Protocol for Screening of mPGES-1 inhibitors:

[1045] mPGES-1 (Microsomal prostaglandin E synthase-1) is a microsomal enzyme that converts endoperoxide substrate PGH_2 (prostaglandin H_2) to product PGE_2 (prostaglandin E_2) by isomerization in the presence of reduced glutathione (GSH). mPGES-1 inhibitors were screened by assessing their ability to inhibit formation of PGE_2 from PGH_2 in the presence of mPGES-1 using an anti- PGE_2 antibody based detection method. Recombinant human mPGES-1 was generated in-house by expression in CHO cells (Ouellet M et al. (2002), Protein Expression and Purification 26: 489 - 495). The assay was set up using crude microsomal fractions at a protein concentration of 40-60 $\mu\text{g/mL}$. Test compounds were prepared in 100 % dimethyl sulfoxide (DMSO) to obtain 20 mM stock solution and then diluted using assay buffer comprising 0.1 M Potassium phosphate buffer with 2 mM EDTA. The final concentration of DMSO in the reaction was 0.5 % (v/v). Negative controls were comprised of all assay reagents except the enzyme. Positive controls were comprised of the enzyme reaction in the absence of any inhibitor. Test compounds were incubated for 10 minutes in assay buffer containing 2.5 mM GSH and mPGES-1 enzyme followed by addition of PGH_2 at a concentration of 15 μM for 1 minute. The reaction was stopped by addition of Stannous chloride (11mg/ml) and PGE_2 levels were measured (Masse F et al. (2005), Journal of Biomolecular Screening 10(6) 599 - 605; Goedken RE et al. (2008), Journal of Biomolecular Screening 13 (7): 619 - 625) by HTRF kit (CisBio)).

[1046] Inhibition of mPGES-1 enzyme activity was measured using the percent of reaction occurring in the positive control. Concentration response curves were plotted using percent inhibition of maximum enzyme reaction. The IC_{50} value was calculated from the concentration response curve by nonlinear regression analysis using GraphPad PRISM software.

[1047] The compounds prepared were tested using the above assay procedure and the results obtained are given in Table 1. Percentage inhibition at concentrations of 1.0 μM , 3.0 μM or 10.0 μM are given in the table along with IC_{50} (nM) details for selected examples. The compounds prepared were tested using the above assay procedure and were found to have IC_{50} less than 200nM, preferably less than 100nM, more preferably less than 50nM or most preferably less than 20nM.

[1048] The IC_{50} (nM) values of some of the compounds are set forth in Table 1 wherein "A" refers to an IC_{50} value of less than 50 nM, "B" refers to IC_{50} value in range of 50.01 to 100.0 nM and "C" refers to IC_{50} values more than 100 nM.

Table 1:

Sr. No.	Example No.	Percentage inhibition at			IC_{50} (nM)
		1 μM	3 μM	10 μM	
1.	Example-1	9.32	-	68.18	-
2.	Example-2	17.97	-	18.97	-
3.	Example-3	88.90	96.79	-	A
4.	Example-4	46.43	-	69.70	-
5.	Example-5	91.83	-	86.21	A
6.	Example-6	83.89	-	87.67	A
7.	Example-7	89.12	-	95.25	A
8.	Example-8	84.86	-	87.24	B
9.	Example-9	1.53	-	23.19	-
10.	Example-10	84.88	-	91.21	A
11.	Example-11	2.34	-	71.72	-
12.	Example-12	84.76	-	87.54	A
13.	Example-13	86.27	-	90.42	C
14.	Example-14	95.99	-	95.82	B
15.	Example-15	64.15	-	83.79	-
16.	Example-16	40.88	-	92.28	-

EP 2 718 284 B1

(continued)

5

10

15

20

25

30

35

40

45

50

55

Sr. No.	Example No.	Percentage inhibition at			IC ₅₀ (nM)
		1 μ M	3 μ M	10 μ M	
17.	Example-17	2.52	-	44.08	-
18.	Example-18	56.23	-	98.10	-
19.	Example-19	5.11	-	29.66	-
20.	Example-20	22.37	-	87.36	-
21.	Example-21	76.06	-	91.78	-
22.	Example-22	39.26	-	99.73	-
23.	Example-23	13.25	-	52.94	-
24.	Example-24	70.96	-	83.09	-
25.	Example-25	74.44	-	88.92	C
26.	Example-26	80.56	-	88.14	C
27.	Example-27	72.84	-	97.54	-
28.	Example-28	72.22	-	95.51	-
29.	Example-29	79.21	-	85.78	C
30.	Example-30	89.60	-	94.52	A
31.	Example-31	96.88	-	98.63	B
32.	Example-32	88.85	-	93.97	B
33.	Example-33	89.42	-	96.78	A
34.	Example-34	70.73	-	92.28	-
35.	Example-35	37.43	-	59.15	-
36.	Example-36	97.34	-	98.90	A
37.	Example-37	50.96	-	94.31	-
38.	Example-38	87.36	-	84.91	B
39.	Example-39	90.06	-	96.37	B
40.	Example-40	89.05	-	90.68	A
41.	Example-41	58.81	-	87.08	-
42.	Example-42	96.55	-	99.65	A
43.	Example-43	98.58	-	99.05	A
44.	Example-44	97.37	-	99.03	A
45.	Example-45	81.65	-	90.11	A
46.	Example-46	59.77	-	72.09	-
47.	Example-47	89.46	-	96.51	A
48.	Example-48	98.33	-	100.00	A
49.	Example-49	89.15	-	96.34	A
50.	Example-50	95.32	-	99.85	B
51.	Example-51	88.29	-	85.96	A
52.	Example-52	96.44	-	98.34	A
53.	Example-53	82.70	-	97.89	A

EP 2 718 284 B1

(continued)

Sr. No.	Example No.	Percentage inhibition at			IC ₅₀ (nM)
		1 μ M	3 μ M	10 μ M	
54.	Example-54	89.36	-	97.50	B
55.	Example-55	80.95	91.85	-	A
56.	Example-56	98.08	-	98.54	A
57.	Example-57	98.73	98.55	-	A
58.	Example-58	95.20	-	97.32	B
59.	Example-59	93.91	-	96.80	A
60.	Example-60	95.39	-	93.07	A
61.	Example-61	92.44	-	96.85	A
62.	Example-62	97.77	-	98.29	A
63.	Example-63	92.41	-	94.79	A
64.	Example-64	28.94	-	63.78	-
65.	Example-65	75.45	-	94.48	-
66.	Example-66	87.85	-	98.83	C
67.	Example-67	72.71	-	96.32	-
68.	Example-68	97.39	-	96.41	A
69.	Example-69	86.44	-	89.11	C
70.	Example-70	0.55	-	6.63	-
71.	Example-71	12.95	-	17.88	-
72.	Example-72	99.24	99.05	-	A
73.	Example-73	92.38	-	92.43	A
74.	Example-74	93.25	-	98.71	B
75.	Example-75	99.07	-	98.31	A
76.	Example-76	95.62	-	95.38	A
77.	Example-77	93.21	-	98.06	B
78.	Example-78	99.94	-	99.88	A
79.	Example-79	99.14	-	97.14	A
80.	Example-80	96.99	-	97.10	A
81.	Example-81	99.76	-	98.05	A
82.	Example-82	98.26	-	98.96	A
83.	Example-83	97.49	-	99.86	A
84.	Example-84	98.81	-	99.51	A
85.	Example-85	22.58	-	69.28	-
86.	Example-86	79.87	-	96.68	C
87.	Example-87	93.36	-	99.19	B
88.	Example-88	3.34	-	39.18	-
89.	Example-89	95.30	-	99.06	A
90.	Example-90	81.74	-	97.20	C

EP 2 718 284 B1

(continued)

Sr. No.	Example No.	Percentage inhibition at			IC ₅₀ (nM)
		1 μM	3 μM	10 μM	
91.	Example-91	66.15	-	94.31	-
92.	Example-92	76.02	-	99.37	C
93.	Example-93	96.83	-	99.60	A
94.	Example-94	87.02	-	100.00	c
95.	Example-95	98.71	-	99.04	A
96.	Example-96	52.25	-	68.70	-
97.	Example-97	20.19	-	6.88	-
98.	Example-98	97.52	-	99.45	A
99.	Example-99	95.30	-	98.55	A
100.	Example-100	99.97	-	98.56	A
101.	Example-101	94.97	-	98.18	A
102.	Example-102	96.52	-	98.03	A
103.	Example-103	19.92	-	51.12	-
104.	Example-104	96.91	-	99.50	A
105.	Example-105	73.88	-	95.96	C
106.	Example-106	92.03	-	96.77	C
107.	Example-107	56.07	-	90.50	-
108.	Example-108	89.82	-	99.72	C
109.	Example-109	97.10	-	97.15	B
110.	Example-110	47.19	-	95.07	-
111.	Example-111	87.20	-	96.15	A
112.	Example-112	99.53	-	99.83	A
113.	Example-113	99.30	-	99.06	A
114.	Example-114	99.06	-	98.39	A
115.	Example-115	96.49	-	98.22	A
116.	Example-116	97.97	-	95.50	A
117.	Example-117	67.93	-	95.02	-
118.	Example-118	76.25	-	87.82	C
119.	Example-119	88.70	-	94.30	A
120.	Example-120	11.45	-	46.01	-
121.	Example-121	16.28	-	72.53	-
122.	Example-122	92.22	-	93.49	A
123.	Example-123	93.78	-	100.00	A
124.	Example-124	27.96	-	88.96	-
125.	Example-125	79.87	-	94.99	-
126.	Example-126	100.00	-	99.29	A
127.	Example-127	32.43	-	58.48	-

EP 2 718 284 B1

(continued)

5

10

15

20

25

30

35

40

45

50

55

Sr. No.	Example No.	Percentage inhibition at			IC ₅₀ (nM)
		1 μ M	3 μ M	10 μ M	
128.	Example-128	91.83	-	89.35	A
129.	Example-129	93.50	-	92.14	A
130.	Example-130	96.56	-	97.79	B
131.	Example-131	100.00	-	99.23	A
132.	Example-132	91.76	-	89.83	A
133.	Example-133	98.00	-	97.89	A
134.	Example-134	91.45	-	93.88	A
135.	Example-135	92.26	-	98.89	A
136.	Example-136	95.06	-	94.79	A
137.	Example-137	93.36	-	93.06	A
138.	Example-138	93.30	-	92.91	A
139.	Example-139	93.94	-	99.06	A
140.	Example-140	97.36	-	98.11	A
141.	Example-141	97.57	-	97.48	A
142.	Example-142	97.25	-	93.98	A
143.	Example-143	99.21	-	90.70	A
144.	Example-144	97.49	-	92.73	A
145.	Example-145	94.24	-	98.86	A
146.	Example-146	100.00	-	99.73	A
147.	Example-147	98.64	-	97.61	A
148.	Example-148	98.91	-	97.78	A
149.	Example-149	98.34	-	94.61	A
150.	Example-150	98.38	-	99.52	A
151.	Example-151	64.96	-	95.89	-
152.	Example-152	96.01	-	100.00	A
153.	Example-153	93.94	-	99.65	B
154.	Example-154	95.18	-	100.00	A
155.	Example-155	99.74	-	97.08	A
156.	Example-156	98.50	-	99.25	A
157.	Example-157	98.54	-	96.46	A
158.	Example-158	99.05	-	99.70	A
159.	Example-159	75.40	-	96.76	C
160.	Example-160	96.62	-	97.33	A
161.	Example-161	98.04	-	99.36	A
162.	Example-162	99.35	-	99.33	A
163.	Example-163	91.82	-	98.66	A
164.	Example-164	98.30	-	97.19	A

EP 2 718 284 B1

(continued)

Sr. No.	Example No.	Percentage inhibition at			IC ₅₀ (nM)
		1 μ M	3 μ M	10 μ M	
165.	Example-165	97.91	-	99.51	A
166.	Example-166	99.68	-	100.00	A
167.	Example-167	99.03	-	98.43	A
168.	Example-168	100.00	-	98.89	A
169.	Example-169	95.54	-	99.17	C
170.	Example-170	99.83	-	98.87	A
171.	Example-171	95.22	-	99.60	A
172.	Example-172	91.86	-	99.04	C
173.	Example-173	96.77	-	98.95	A
174.	Example-174	99.90	-	100.00	A
175.	Example-175	99.44	-	99.44	A
176.	Example-176	45.84	-	89.54	-
177.	Example-177	29.89	-	71.07	-
178.	Example-178	42.72	-	91.55	-
179.	Example-179	50.59	-	95.17	-
180.	Example-180	72.34	-	92.51	C
181.	Example-181	88.24	-	94.28	A
182.	Example-182	92.94	-	94.05	A
183.	Example-183	41.55	-	85.5	-
184.	Example-184	98.59	-	94.26	A
185.	Example-185	96.06	-	98.3	A
186.	Example-186	96.84	-	98.02	A
187.	Example-187	98.63	-	97.51	A
188.	Example-188	89.49	-	99.32	B
189.	Example-189	96.17	-	98.48	A
190.	Example-190	100	-	100	A
191.	Example-191	93.5	-	100	C
192.	Example-192	99.3	-	99.31	A

Screening for mPGES-1 inhibitors using the A549 cell based assay

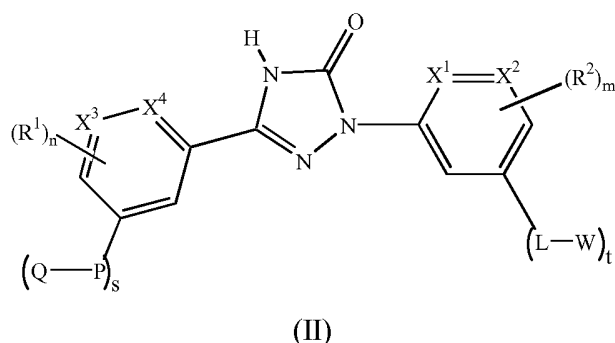
[1049] The inhibition of mPGES-1 enzyme in the A549 cell line was monitored as inhibition of IL-1 β induced PGE₂ release. A549 cells were maintained in DMEM medium with 10% FBS and 1% Penicillin-Streptomycin Solution in 5% CO₂ at 37°C. Cells were seeded 24 h prior to the assay in 96 well plates in DMEM containing 1% Penicillin-Streptomycin and 2% FBS so as to get ~ 40,000 cells per well on the day of experiment. The assay was carried out in a total volume of 200 μ L. Test compounds were dissolved in dimethyl sulfoxide (DMSO) to prepare 2 mM stock solution and then diluted using plain DMEM. The final concentration of DMSO in the reaction was 0.55% (v/v). Cells were treated with test compounds for 30 minutes followed by addition of IL- β at a final concentration of 10 ng/mL for 16-20 h. Plates were then centrifuged at 1000 rpm for 10 min at 4°C. Supernatants were collected and analyzed by the addition of PGE₂-D2 and anti-PGE₂ cryptate conjugate supplied by the CisBio HTRF kit in a 96 well half area Blackwell EIA/RIA plate. The assay plate was incubated overnight at 4-5° C before being read in an Artemis (K-101) (Japan) HTRF plate reader and levels

of PGE₂ calculated by extrapolation from the standard curve.

[1050] The concentration response curves were plotted as a percentage of maximal response obtained in the absence of test antagonist. The IC₅₀ value was calculated from the concentration response curve by nonlinear regression analysis using GraphPad PRISM software.

Claims

1. A compound of formula (II)



or a pharmaceutically acceptable salt thereof,
wherein,

X¹, X², X³ and X⁴ are each independently selected from CH and N;

each occurrence of L is independently selected from -CH₂NHC(O)- and -CH₂NHS(O)₂-;

each occurrence of P is independently selected from -CH₂NHC(O)- and -CH₂NHS(O)₂-;

each occurrence of Q is independently selected from C₁₋₈alkyl, haloC₁₋₈alkyl, C₁₋₈alkoxyC₁₋₈alkyl, hydroxyC₁₋₈alkyl, carboxyC₁₋₈alkyl, C₃₋₁₂cycloalkyl, C₆₋₁₄aryl, 3-15 membered heterocyclyl, and 5-14 membered heteroaryl;

each occurrence of W is independently selected from isopropyl, *tert*-butyl, trifluoromethyl, 1-fluoro-2-methylpropan-2-yl, 1-hydroxy-2-methylpropan-2-yl and cyclopropyl;

each occurrence of R¹ is independently selected from halogen, cyano, C₁₋₈alkyl, C₁₋₈alkoxy, haloC₁₋₈alkoxyC₁₋₈alkyl, haloC₁₋₈alkyl, C₃₋₆cycloalkyl, 5 membered heterocyclylC₁₋₈alkyl, 5 membered heteroaryl, 5 membered heteroarylC₁₋₈alkyl, and -C≡CR;

each occurrence of R² is independently selected from halogen, cyano, C₁₋₈alkyl, C₁₋₈alkoxy, haloC₁₋₈alkyl, C₃₋₆cycloalkyl, 5 membered heteroaryl, -C(O)NHR, -NHC(O)R, -S(O)₂NHR and -C≡CR;

each occurrence of R is independently selected from C₁₋₈alkyl, C₃₋₁₂cycloalkyl, and C₆₋₁₄aryl;

'm' is an integer ranging from 0 to 3, both inclusive;

'n' is an integer ranging from 0 to 3, both inclusive;

's' is an integer ranging from 0 to 1, both inclusive; and

't' is an integer ranging from 0 to 1, both inclusive;

with the provisos that (i) 's' and 't' are not '0' simultaneously, and (ii) 'm' and 'n' are not '0' simultaneously.

2. The compound according to claim 1, wherein X¹, X², X³ and X⁴ are CH.

3. The compound according to claim 1 or 2, wherein each occurrence of R¹ is independently cyano, Cl, F, CHF₂, CF₃, OCH₃, CH₃, (2,2,2-trifluoroethoxy)methyl, cyclopropyl, (pyrrolidin-1-yl)methyl, 4-methylthiophenyl, 5-isopropyl-1,3,4-oxadiazol-2-yl, (3,5-dimethyl-1*H*-pyrazol-1-yl)methyl, 3,3-dimethylbut-1-ynyl, 2-cyclopropylethynyl, (2,5-dichlorophenyl)ethynyl, (4-chloro-2-fluorophenyl)ethynyl, (3-chloro-2-fluorophenyl)ethynyl, (3-(trifluoromethyl)phenyl)ethynyl or (2-chloro-4-(trifluoromethyl)phenyl)ethynyl; and 'n' is 1 or 2.

4. The compound according to any one of claims 1 to 3, wherein each occurrence of R² is independently cyano, Cl, F, CH₃, CF₃, OCH₃, 3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl,

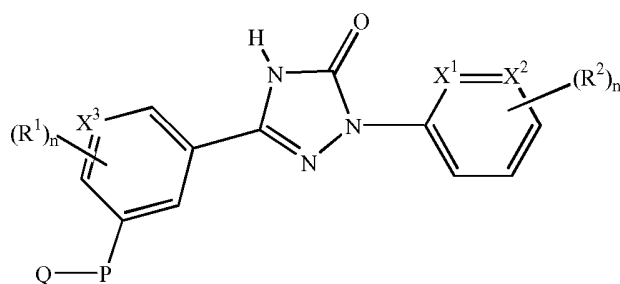
cyclopropanecarboxamido, 3,3-dimethylbut-1-ynyl, 2-cyclopropylethynyl, -CONH-[3-(trifluoromethyl)phenyl], -CONH-[3-(difluoromethyl)-4-fluorophenyl] or -CONH-[3-(difluoromethyl)phenyl]; and 'm' is 1 or 2.

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

Q is isopropyl, *tert*-butyl, trifluoromethyl, 1-fluoro-2-methylpropan-2-yl, 1-methoxy-2-methylpropan-2-yl, 1-hydroxy-2-methylpropan-2-yl, cyclopropyl, cyclobutyl, cyclopentyl, 2-fluorophenyl, tetrahydrofuranyl, tetrahydrofuran-2-yl, (S)-tetrahydrofuran-2-yl, (R)-tetrahydrofuran-2-yl, isoxazolyl or 1-methyl-1H imidazole-2-yl; 's' is 1; and 't' is 0.

6. The compound according to any one of claims 1 to 5, wherein 't' is 1; and 's' is 0.

7. The compound according to claim 1 of the formula (III)



(III)

or a pharmaceutically acceptable salt thereof,
wherein,

X¹, X² and X³ are each independently selected from CH and N;

P is selected from -CH₂NHC(O)- and -CH₂NHS(O)₂-;

Q is selected from C₁₋₈alkyl, haloC₁₋₈alkyl, C₁₋₈alkoxyC₁₋₈alkyl, hydroxyC₁₋₈alkyl, carboxylC₁₋₈alkyl, C₃₋₁₂cycloalkyl, C₆₋₁₄aryl, 3-15 membered heterocyclyl, and 5-14 membered heteroaryl;

each occurrence of R¹ is independently selected from halogen, cyano, C₁₋₈alkyl, C₁₋₈alkoxy, haloC₁₋₈alkyl and C₃₋₆cycloalkyl;

each occurrence of R² is independently selected from halogen, cyano, C₁₋₈alkyl, C₁₋₈alkoxy, haloC₁₋₈alkyl, C₃₋₆cycloalkyl, 5 membered heteroaryl, -C(O)NHR, -NHC(O)R, -S(O)₂NHR and -C≡CR;

each occurrence of R is independently selected from C₁₋₈alkyl, C₃₋₁₂cycloalkyl, and C₆₋₁₄aryl;

'm' is an integer ranging from 0 to 3, both inclusive; and

'n' is an integer ranging from 0 to 3, both inclusive; with the proviso that 'm' and 'n' are not '0' simultaneously.

8. The compound according to claim 7, wherein X¹, X², and X³ are CH.

9. The compound according to claim 7 or 8, wherein

each R¹ is, independently, cyano, Cl, F, CHF₂, CF₃, OCH₃, CH₃ or cyclopropyl;

each R² is, independently, cyano, Cl, F, CH₃, CF₃ or OCH₃;

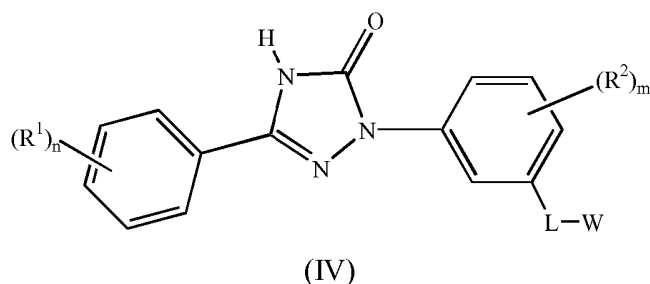
P is -CH₂NHC(O)-;

'm' is 1 or 2;

'n' is 0, 1 or 2; and

Q is isopropyl, *tert*-butyl, trifluoromethyl, 1-fluoro-2-methylpropan-2-yl, 1-methoxy-2-methylpropan-2-yl, 1-hydroxy-2-methylpropan-2-yl, cyclopropyl, cyclobutyl, cyclopentyl, 2-fluorophenyl, tetrahydrofuranyl, tetrahydrofuran-2-yl, (S)-tetrahydrofuran-2-yl, (R)-tetrahydrofuran-2-yl, isoxazolyl or 1-methyl-1H-imidazole-2-yl.

10. The compound according to claim 1 of the formula (IV)



or a pharmaceutically acceptable salt thereof,
wherein,

L is selected from -CH₂NHC(O)- and -CH₂NHS(O)₂;

W is selected from isopropyl, *tert*-butyl, trifluoromethyl, 1-fluoro-2-methylpropan-2-yl, 1-hydroxy-2-methylpropan-2-yl and cyclopropyl;

each occurrence of R¹ is independently selected from halogen, cyano, C₁₋₈alkyl, C₁₋₈alkoxy, haloC₁₋₈alkoxy, haloC₁₋₈alkyl, C₃₋₆cycloalkyl, 5 membered heterocyclyl, C₁₋₈alkyl, 5 membered heteroaryl, 5 membered heteroarylC₁₋₈alkyl, and -C≡CR;

each occurrence of R² is independently selected from halogen, cyano, C₁₋₈alkyl, C₁₋₈alkoxy and haloC₁₋₈alkyl;

each occurrence of R is independently selected from C₁₋₈alkyl, C₃₋₁₂cycloalkyl, and C₆₋₁₄aryl;

'm' is an integer ranging from 0 to 3, both inclusive; and

'n' is an integer ranging from 0 to 3, both inclusive; with the proviso that 'm' and 'n' are not '0' simultaneously.

11. The compound according to claim 10, wherein

each occurrence of R¹ is independently Cl, F, CHF₂, CF₃, OCH₃, CH₃, 3,3-dimethylbut-1-ynyl, 2-cyclopropylethynyl, (2,5-dichlorophenyl)ethynyl, (4-chloro-2-fluorophenyl)ethynyl, 3-chloro-2-fluorophenyl)ethynyl, 3-(trifluoromethyl)phenyl)ethynyl or 2-chloro-4-(trifluoromethyl)phenyl)ethynyl;

each occurrence of R² is independently Cl, F, CH₃, CF₃ or OCH₃;

L is -CH₂NHC(O)-;

'm' is 1 or 2;

'n' is 0, 1 or 2; and

W is isopropyl, *tert*-butyl, trifluoromethyl, 1-fluoro-2-methylpropan-2-yl, 1-hydroxy-2-methylpropan-2-yl or cyclopropyl.

12. The compound according to claim 1 selected from

4-(3-(2-Chloro-5-(cyclopropanecarboxamidomethyl)phenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-2-methoxy-N-(3-(trifluoromethyl)phenyl)benzamide;

N-(4-Chloro-3-(1-(4-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)-3-methoxyphenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)benzyl)cyclopropanecarboxamide;

4-(3-(2-Chloro-5-(cyclopropanecarboxamidomethyl)phenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-N-(3-(difluoromethyl)-4-fluorophenyl)-2-methoxybenzamide;

N-(4-Chloro-3-(1-(4-(cyclopropanecarboxamido)-3-methoxyphenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)benzyl)cyclopropanecarboxamide;

4-(3-(2-Chloro-5-(cyclopropanecarboxamidomethyl)phenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-N-(3-(difluoromethyl)phenyl)-2-methoxybenzamide;

4-(3-(2-Chloro-5-(cyclopropanecarboxamidomethyl)phenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-N-(3-(trifluoromethyl)phenyl)benzamide;

N-(4-Chloro-3-(3-(4-(2,5-dichlorophenyl)ethynyl)-2-fluorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)benzyl)cyclopropanecarboxamide;

N-(4-Chloro-3-(3-(4-(4-chloro-2-fluorophenyl)ethynyl)-2-fluorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)benzyl)cyclopropanecarboxamide;

N-(4-Chloro-3-(3-(2-fluoro-4-(3-(trifluoromethyl)phenyl)ethynyl)phenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)benzyl)cyclopropanecarboxamide;

N-(4-Chloro-3-(3-(4-(3-chloro-2-fluorophenyl)ethynyl)-2-fluorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-

yl)benzyl)cyclopropanecarboxamide;

N-(4-Chloro-3-(3-(4-((2-chloro-4-(trifluoromethyl)phenyl)ethynyl)-2-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)cyclopropanecarboxamide;

N-(4-Chloro-3-(1-(3,4-dichlorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2-fluorobenzyl)pivalamide;

5 *N*-(4-Chloro-2-fluoro-3-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide;

N-(4-Chloro-3-(1-(2,4-difluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2-fluorobenzyl)pivalamide;

N-(4-Chloro-2-fluoro-3-(1-(4-methoxyphenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide;

10 *N*-(4-Chloro-2-fluoro-3-(3-(2-fluoro-4-(trifluoromethyl)phenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)pivalamide;

N-(4-Chloro-3-(3-(2-chloro-6-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-fluorobenzyl)pivalamide;

N-(4-Chloro-3-(1-(4-cyanophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2-fluorobenzyl)pivalamide;

N-(4-Chloro-3-(3-(4-chloro-2-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-fluorobenzyl)pivalamide;

15 *N*-(4-Chloro-3-(3-(4-chloro-2-fluorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)cyclopropanecarboxamide;

N-(4-Chloro-3-(3-(2-fluoro-4-(trifluoromethyl)phenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)cyclopropanecarboxamide;

N-(4-Chloro-2-fluoro-3-(5-oxo-3-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)pivalamide;

20 *N*-(4-Chloro-2-fluoro-3-(5-oxo-1-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide;

N-(4-Chloro-2-fluoro-3-(5-oxo-1-(6-(trifluoromethyl)pyridin-3-yl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide;

N-(4-Chloro-3-(1-(4-chlorophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2-fluorobenzyl)pivalamide;

25 *N*-(4-Chloro-3-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide;

N-(4-Chloro-3-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide;

(*R*)-*N*-(4-Chloro-3-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)tetrahydrofuran-2-carboxamide;

30 *N*-(4-Chloro-3-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)cyclopropanesulfonamide;

N-(4-Chloro-3-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)-2-fluorobenzamide;

35 *N*-(4-Chloro-3-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)isoxazole-5-carboxamide;

N-(3-(1-(4-(Trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2,4-dimethylbenzyl)-2,2,2-trifluoroacetamide;

(*R*)-*N*-(2,4-Dimethyl-3-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)tetrahydrofuran-2-carboxamide;

40 *N*-(3-(1-(4-(Trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2,4-dimethylbenzyl)pivalamide;

(*S*)-*N*-(4-Chloro-3-(1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)-tetrahydrofuran-2-carboxamide;

N-(4-Chloro-3-(1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)-1-methyl-1*H*-imidazole-2-carboxamide;

45 *N*-(4-Chloro-2-fluoro-3-(4,5-dihydro-3-(4-(3,3-dimethylbut-1-ynyl)phenyl)-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide;

N-(4-Chloro-3-(3-(4-(2-cyclopropylethynyl)phenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)-2-fluorobenzyl)pivalamide;

50 *N*-(4-Chloro-2-fluoro-5-(1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide;

N-(4-Chloro-2-fluoro-5-(1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide;

N-(4-Chloro-3-(1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)-3-hydroxy-2,2-dimethylpropanamide;

55 *N*-(4-Chloro-3-(1-(4-chloro-3-fluorophenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide;

(*R*)-*N*-(4-chloro-2-fluoro-5-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-2,4-triazol-3-yl)benzyl)tetrahydrofuran-2-carboxamide;

N-(4-Chloro-3-(1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)-3-methoxy-2,2-dimethylpropanamide;
N-(4-Chloro-3-(1-(4-chloro-3-fluorophenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide;
N-(4-Chloro-5-(1-(4-chlorophenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2-fluorobenzyl)pivalamide;
5 *N*-(4-Chloro-5-(1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2-methoxybenzyl)pivalamide;
N-(4-Chloro-2-fluoro-5-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide;
10 *N*-(4-Chloro-2-fluoro-5-(1-(6-(trifluoromethyl)pyridin-3-yl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide;
N-(2,4-Dichloro-5-(3-(4-(2-cyclopropylethynyl)phenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide;
N-(4-Chloro-5-(1-(3-chloro-4-fluorophenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2-fluorobenzyl)pivalamide;
N-(4-Chloro-5-(1-(4-chlorophenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2-fluorobenzyl)-2-fluorobenzamide;
15 *N*-(4-Chloro-2-fluoro-5-(1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)isobutyramide;
N-(4-Chloro-5-(1-(4-chlorophenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2-fluorobenzyl)-3-fluoro-2,2-dimethylpropanamide;
20 *N*-(4-Chloro-5-(1-(3-chloro-4-methylphenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2-fluorobenzyl)pivalamide;
N-(4-Chloro-5-(3-(4-(2-cyclopropylethynyl)phenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)-2-fluorobenzyl)pivalamide;
N-(4-Chloro-2-fluoro-5-(4,5-dihydro-3-(4-(3,3-dimethylbut-1-ynyl)phenyl)-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide;
25 *N*-(4-Chloro-3-(1-(6-(trifluoromethyl)pyridin-3-yl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide;
N-(4-Chloro-3-(1-(3-chloro-4-fluorophenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide;
N-(4-Chloro-3-(1-(3-chloro-4-methylphenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide;
N-(4-Chloro-3-(3-(4-(2-cyclopropylethynyl)phenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide;
N-(4-Chloro-3-(1-(3-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide;
30 *N*-(4-Chloro-3-(4,5-dihydro-3-(4-(3,3-dimethylbut-1-ynyl)phenyl)-5-oxo-1,2,4-triazol-1-yl)benzyl)isobutyramide;
N-(4-Chloro-3-(1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)isobutyramide;
N-(4-Chloro-3-(3-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide;
N-(4-Chloro-3-(3-(3-fluoro-4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide;
35 *N*-(4-Chloro-3-(3-(4-chloro-3-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide;
N-(4-Chloro-3-(3-(4-fluoro-3-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide;
N-(4-Chloro-3-(3-(3-fluoro-4-(3,3-dimethylbut-1-ynyl)phenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)isobutyramide;
40 *N*-(4-Chloro-3-(3-(4-(2-cyclopropylethynyl)-3-fluorophenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)isobutyramide;
N-(4-Chloro-3-(4,5-dihydro-5-oxo-3-(4-((pyrrolidin-1-yl)methyl)phenyl)-1,2,4-triazol-1-yl)benzyl)pivalamide;
N-(3-(3-(4-((2,2,2-Trifluoroethoxy)methyl)phenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)-4-chlorobenzyl)pivalamide;
45 *N*-(4-Chloro-3-(4,5-dihydro-3-(4-(5-isopropyl-1,3,4-oxadiazol-2-yl)phenyl)-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide;
N-(4-Chloro-3-(1-(4-chloro-3-methylphenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide;
N-(4-Chloro-3-(1-(4-chloro-3-methylphenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)isobutyramide;
N-(4-Chloro-3-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide;
50 *N*-(4-Chloro-3-(1-(4-chloro-3-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide;
N-(4-Chloro-3-(1-(3-(trifluoromethyl)-4-methylphenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide;
N-(4-Chloro-3-(1-(4-(trifluoromethyl)-2-methylphenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide;
55 *N*-(4-Chloro-3-(1-(3-fluoro-4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide;
N-(4-Chloro-3-(1-(3-fluoro-4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)isobutyramide;

amide;

N-(4-Chloro-3-{5-oxo-1-[4-(trifluoromethyl)phenyl]-4,5-dihydro-1*H*-1,2,4-triazol-3-yl}benzyl)propane-2-sulfonamide;

N-(4-Chloro-3-(1-(2-fluoro-4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide;

N-(3-(4,5-Dihydro-1-(4-(3,3-dimethylbut-1-ynyl)phenyl)-5-oxo-1*H*-1,2,4-triazol-3-yl)-2,4-dimethylbenzyl)isobutyramide;

N-(3-(1-(4-(2-Cyclopropylethynyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2,4-dimethylbenzyl)pivalamide;

N-(4-Chloro-3-(3-(4-(2-cyclopropylethynyl)-3-fluorophenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide;

N-(4-Chloro-3-(1-(4-(2-cyclopropylethynyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide;

N-(4-Chloro-3-(3-(4-(2-cyclopropylethynyl)-2-fluorophenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide;

N-(3-(1-(4-(2-Cyclopropylethynyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2,4-dimethylbenzyl)-3-fluoro-2,2-dimethylpropanamide;

N-(3-(1-(3-Fluoro-4-(3,3-dimethylbut-1-ynyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2,4-dimethylbenzyl)isobutyramide;

N-(4-Chloro-3-(4,5-dihydro-3-(4-((3,5-dimethyl-1*H*-pyrazol-1-yl)methyl)phenyl)-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide;

N-(4-Chloro-2-fluoro-3-(1-(3-fluoro-4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide;

N-(4-Chloro-3-(1-(4-chloro-3-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2-fluorobenzyl)pivalamide;

N-(4-Chloro-3-(1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)-3-fluoro-2,2-dimethylpropanamide;

N-((6-Cyclopropyl-5-(1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)pyridin-3-yl)methyl)pivalamide;

N-(4-Chloro-3-(1-(4-(2-cyclopropylethynyl)-2-fluorophenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide;

N-(4-Chloro-3-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)-2-methylpropane-2-sulfonamide;

N-(4-Chloro-3-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)cyclobutanecarboxamide;

N-(4-Chloro-3-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)cyclopentanecarboxamide;

N-((6-(Difluoromethyl)-5-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyridin-3-yl)methyl)pivalamide;

N-((6-(Difluoromethyl)-5-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyridin-3-yl)methyl)isobutyramide;

N-((6-(Difluoromethyl)-5-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyridin-3-yl)methyl)propane-2-sulfonamide;

N-((6-(Difluoromethyl)-5-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyridin-3-yl)methyl)cyclobutanecarboxamide;

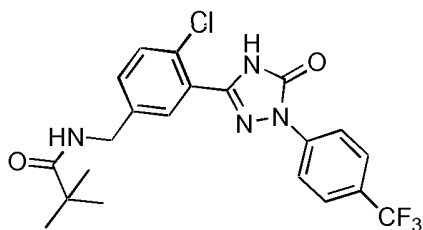
N-(4-Chloro-3-(3-(4-(cyclopropylethynyl)phenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)-2,2,2-trifluoroacetamide;

N-(4-Chloro-3-(3-(4-(cyclopropylethynyl)phenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)-3-hydroxy-2,2-dimethylpropanamide;

3-Fluoro-*N*-((6-(difluoromethyl)-5-(1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)pyridin-3-yl)methyl)-2,2-dimethylpropanamide;

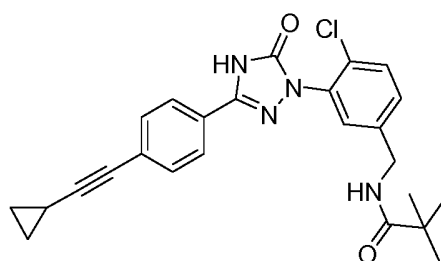
and pharmaceutically acceptable salts thereof.

13. The compound according to claim 1 of the formula



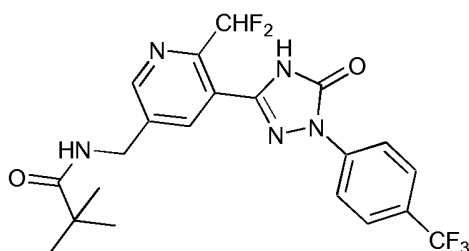
or a pharmaceutically acceptable salt thereof.

14. The compound according to claim 1 of the formula



or a pharmaceutically acceptable salt thereof.

15. The compound according to claim 1 of the formula



or a pharmaceutically acceptable salt thereof.

16. A compound according to claim 1 selected from

N-(4-Chloro-3-(5-oxo-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacetamide;

N-(4-Chloro-3-(4,5-dihydro-3-(4-iodophenyl)-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide;

and pharmaceutically acceptable salts thereof.

17. A pharmaceutical composition comprising a compound according to any one of claims 1 to 15 and a pharmaceutically acceptable excipient.

18. The pharmaceutical composition according to claim 17, wherein the pharmaceutically acceptable excipient is a carrier or diluent.

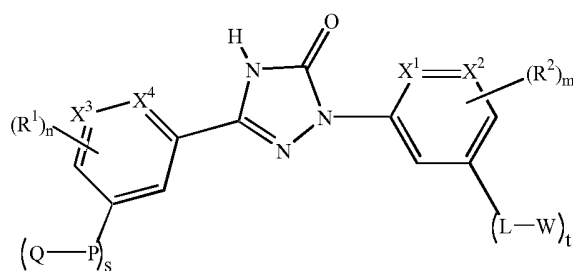
19. The compound according to any one of claims 1 to 15, for use in the prevention or treatment of a mPGES-1 mediated disease, disorder or syndrome in a subject.

20. The compound according to any one of claims 1 to 15, for use in the prevention or treatment of disease, disorder, syndrome or condition selected from the group consisting of inflammation, asthma, chronic obstructive pulmonary

disease, pulmonary fibrosis, inflammatory bowel disease, irritable bowel syndrome, pain, inflammatory pain, chronic pain, acute pain, fever, migraine, headache, low back pain, fibromyalgia, myofascial disorders, viral infections, influenza, common cold, herpes zoster, hepatitis C, AIDS, bacterial infections, fungal infections, dysmenorrhea, burns, surgical or dental procedures, malignancies hyperprostaglandin E syndrome, classic Bartter syndrome, synovitis, atherosclerosis, gout, arthritis, osteoarthritis, juvenile arthritis, rheumatoid arthritis, juvenile onset rheumatoid arthritis, rheumatic fever, ankylosing spondylitis, Hodgkin's disease, systemic lupus erythematosus, vasculitis, pancreatitis, nephritis, bursitis, conjunctivitis, iritis, scleritis, uveitis, wound healing, dermatitis, eczema, psoriasis, stroke, diabetes mellitus, cancer, neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis and multiple sclerosis, autoimmune diseases, allergic disorders, rhinitis, ulcers, mild to moderately active ulcerative colitis, familial adenomatous polyposis, coronary heart disease, and sarcoidosis.

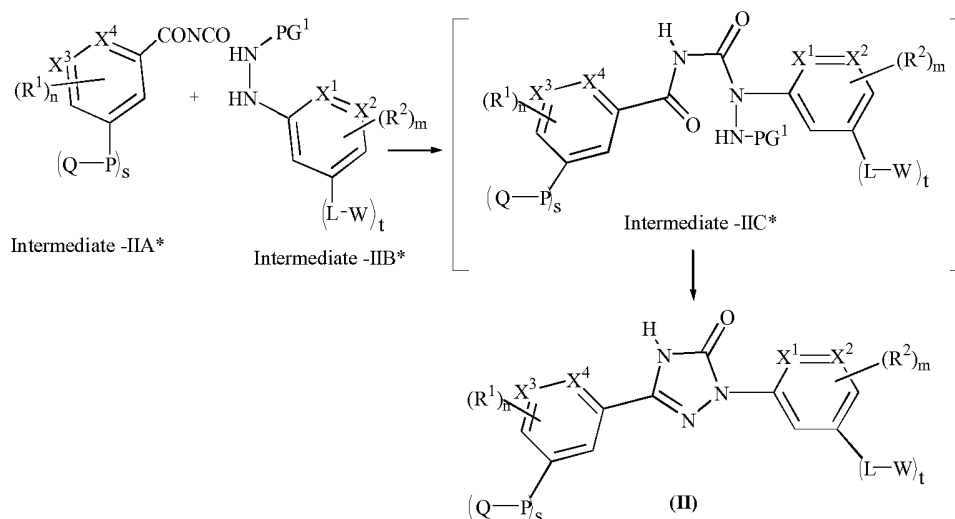
21. The compound according to any one of claims 1 to 15, for use in the prevention or treatment of a disease, disorder, syndrome or condition wherein the disease, disorder, syndrome or condition is pain, chronic pain, acute pain, rheumatoid arthritic pain or osteoarthritic pain.

22. A process for preparing a compound of formula (II) according to claim 1



(II)

or a pharmaceutically acceptable salt thereof, which comprises: reacting a compound of formula (Intermediate-IIA*) with a compound of formula (Intermediate-IIB*) to form a compound of formula (Intermediate-IIC*); and converting the compound of formula (Intermediate-IIC*) to a compound of formula (II):



wherein,

X^1 , X^2 , X^3 and X^4 are each independently selected from CH and N;
 each occurrence of L is independently selected from $-\text{CH}_2\text{NHC}(\text{O})_2-$ and $-\text{CH}_2\text{NHS}(\text{O})_2-$;
 each occurrence of P is independently selected from $-\text{CH}_2\text{NHC}(\text{O})-$ and $-\text{CH}_2\text{NHS}(\text{O})_2-$;
 each occurrence of Q is independently selected from $\text{C}_{1-8}\text{alkyl}$, $\text{haloC}_{1-8}\text{alkyl}$, $\text{C}_{1-8}\text{alkoxyC}_{1-8}\text{alkyl}$,

hydroxyC₁₋₈alkyl, carboxylC₁₋₈alkyl, C₃₋₁₂cycloalkyl, C₆₋₁₄aryl, 3-15 membered heterocyclyl, and 5-14 membered heteroaryl;

each occurrence of W is independently selected from isopropyl, *tert*-butyl, trifluoromethyl, 1-fluoro-2-methylpropan-2-yl, 1-hydroxy-2-methylpropan-2-yl and cyclopropyl;

each occurrence of R¹ is independently selected from halogen, cyano, C₁₋₈ alkyl, C₁₋₈alkoxy, haloC₁₋₈alkoxyC₁₋₈alkyl, haloC₁₋₈alkyl, C₃₋₆cycloalkyl, 5 membered heterocyclylC₁₋₈alkyl, 5 membered heteroaryl, 5 membered heteroarylC₁₋₈alkyl, and -C≡CR;

each occurrence of R² is independently selected from halogen, cyano, C₁₋₈alkyl, C₁₋₈alkoxy, haloC₁₋₈alkyl, C₃₋₆cycloalkyl, 5 membered heteroaryl, -C(O)NHR, -NHC(O)R, -S(O)₂NHR and -C≡CR;

each occurrence of R is independently selected from C₁₋₈alkyl, C₃₋₁₂cycloalkyl, and C₆₋₁₄aryl;

PG¹ represents an amine protecting group;

'm' is an integer ranging from 0 to 3, both inclusive;

'n' is an integer ranging from 0 to 3, both inclusive;

's' is an integer ranging from 0 to 1, both inclusive; and

't' is an integer ranging from 0 to 1, both inclusive;

with the provisos that (i) 's' any 't' are not '0' simultaneously; and (ii) that 'm' and 'n' are not '0' simultaneously.

23. The process according to claim 22, wherein the isocyanate of formula (Intermediate-IIA*) is obtained from the corresponding acid, amide or acid halide derivative.

24. The process according to claim 22, wherein a compound of formula (Intermediate-IIA*) is reacted with a compound of formula (Intermediate-IIB*) in DCM, toluene or EDC.

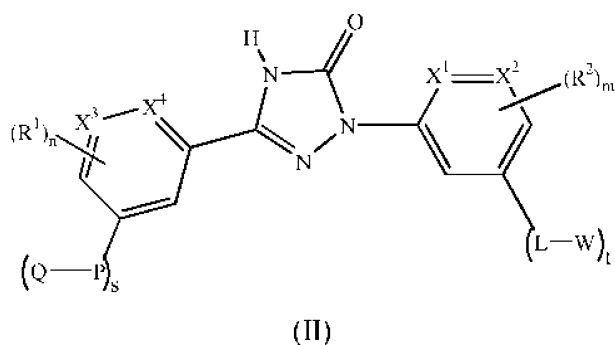
25. The process according to claim 22, wherein Intermediate-IIC* is not isolated.

26. The process according to claim 22, wherein PG¹ is *tert*-butoxycarbonyl.

27. The process according to claim 22, wherein a compound of formula (Intermediate-IIC*) is converted to compound of formula (II) using an organic acid.

Patentansprüche

1. Verbindung der Formel (II)



oder ein pharmazeutisch verträgliches Salz davon, wobei:

X¹, X², X³ und X⁴ jeweils unabhängig ausgewählt sind aus CH und N;

jedes L unabhängig ausgewählt ist aus -CH₂NHC(O)- und -CH₂NHS(O)₂-;

jedes P unabhängig ausgewählt ist aus -CH₂NHC(O)- und -CH₂NHS(O)₂-;

jedes Q unabhängig ausgewählt ist aus C₁₋₈-Alkyl, Halo-C₁₋₈-Alkyl, C₁₋₈-AlkoxyC₁₋₈-Alkyl, Hydroxy-C₁₋₈-Alkyl, Carboxyl-C₁₋₈-Alkyl, C₃₋₁₂-Cycloalkyl, C₆₋₁₄-Aryl, 3-15-gliedrigem Heterocyclyl und 5-14-gliedrigem Heteroaryl;

jedes W unabhängig ausgewählt ist aus Isopropyl, *tert*-Butyl, Trifluormethyl, 1-Fluor-2-methylpropan-2-yl, 1-Hydroxy-2-methylpropan-2-yl und Cyclopropyl;

jedes R¹ unabhängig ausgewählt ist aus Halogen, Cyano, C₁₋₈-Alkyl, C₁₋₈-Alkoxy, Halo-C₁₋₈-Alkoxy, C₁₋₈-Alkyl, Halo-C₁₋₈-Alkyl, C₃₋₆-Cycloalkyl, 5-gliedrigem Heterocyclyl-C₁₋₈-Alkyl, 5-gliedrigem Heteroaryl, 5-gliedrigem Heteroaryl-C₁₋₈-Alkyl und -C≡CR;

jedes R² unabhängig ausgewählt ist aus Halogen, Cyano, C₁₋₈-Alkyl, C₁₋₈-Alkoxy, Halo-C₁₋₈-Alkyl, C₃₋₆-Cycloalkyl, 5-gliedrigem Heteroaryl, -C(O)NHR, -NHC(O)R, S(O)₂NHR und -C≡CR;

jedes R unabhängig ausgewählt ist aus C₁₋₈-Alkyl, C₃₋₁₂-Cycloalkyl und C₆₋₁₄-Aryl;

'm' eine ganze Zahl zwischen 0 und 3 ist, jeweils inklusive;

'n' eine ganze Zahl zwischen 0 und 3 ist, jeweils inklusive;

's' eine ganze Zahl zwischen 0 und 1 ist, jeweils inklusive; und

't' eine ganze Zahl zwischen 0 und 1 ist, jeweils inklusive;

unter den Bedingungen, dass (i) 's' und 't' nicht gleichzeitig '0' sind und dass (ii) 'm' und 'n' nicht gleichzeitig '0' sind.

2. Verbindung nach Anspruch 1, wobei X¹, X², X³ und X⁴ CH sind.

3. Verbindung nach Anspruch 1 oder 2, wobei

jedes R¹ unabhängig Cyano, Cl, F, CHF₂, CF₃, OCH₃, CH₃, (2,2,2-Trifluorethoxy)methyl, Cyclopropyl, (Pyrrolidin-1-yl)methyl, 4-Methylthiophenyl, 5-Isopropyl-1,3,4-oxadiazol-2-yl, (3,5-Dimethyl-1-H-pyrazol-1-yl)methyl, 3,3-Dimethylbut-1-ynyl, 2-Cyclopropylethynyl, (2,5-Dichlorphenyl)ethynyl, (4-Chlor-2-fluorphenyl)ethynyl, (3-Chlor-2-fluorphenyl)ethynyl, (3-(Trifluormethyl)phenyl)ethynyl oder (2-Chlor-4-(trifluormethyl)phenyl)ethynyl ist; und 'n' 1 oder 2 ist.

4. Verbindung nach einem der Ansprüche 1 bis 3, wobei

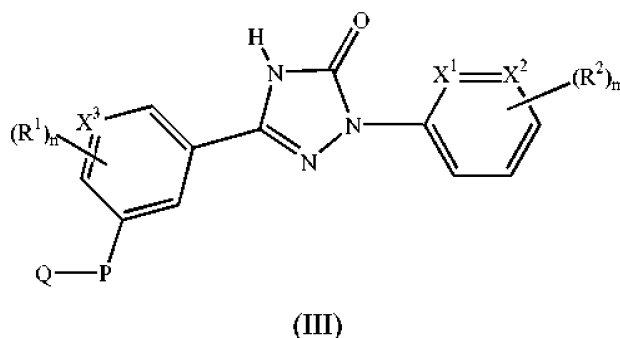
jedes R² unabhängig Cyano, Cl, F, CH₃, CF₃, OCH₃, 3-(4-Chlorphenyl)-1,2,4-oxadiazol-5-yl, Cyclopropanocarboxamido, 3,3-Dimethylbut-1-ynyl, 2-Cyclopropylethynyl, -CONH-[3-(Trifluormethyl)phenyl], -CONH-[3-(Difluormethyl)-4-fluorphenyl] oder -CONH-[3-(Difluormethyl)phenyl] ist; und 'm' 1 oder 2 ist.

5. Verbindung nach einem der Ansprüche 1 bis 4, wobei

Q Isopropyl, *tert*-Butyl, Trifluormethyl, 1-Fluor-2-methylpropan-2-yl, 1-Methoxy-2-methylpropan-2-yl, 1-Hydroxy-2-methylpropan-2-yl, Cyclopropyl, Cyclobutyl, Cyclopentyl, 2-Fluorphenyl, Tetrahydrofuranyl, Tetrahydrofuran-2-yl, (S)-Tetrahydrofuran-2-yl, (R)-Tetrahydrofuran-2-yl, Isoxazolyl oder 1-Methyl-1H-imidazol-2-yl ist; 's' 1 ist; und 't' 0 ist.

6. Verbindung nach einem der Ansprüche 1 bis 5, wobei 't' 1 ist; und 's' 0 ist.

7. Verbindung nach Anspruch 1 der Formel (III)



oder ein pharmazeutisch verträgliches Salz davon, wobei:

X¹, X² und X³ jeweils unabhängig ausgewählt sind aus CH und N;

P ausgewählt ist aus -CH₂NHC(O)- und -CH₂NHS(O)₂;

Q ausgewählt ist aus C₁₋₈-Alkyl, Halo-C₁₋₈-Alkyl, C₁₋₈-Alkoxy, C₁₋₈-Alkoxy, Hydroxy-C₁₋₈-Alkyl, Carboxyl-C₁₋₈-Alkyl, C₃₋₁₂-Cycloalkyl, C₆₋₁₄-Aryl, 3-15-gliedrigem Heterocyclyl und 5-14-gliedrigem Heteroaryl;

jedes R¹ unabhängig ausgewählt ist aus Halogen, Cyano, C₁₋₈-Alkyl, C₁₋₈-Alkoxy, Halo-C₁₋₈-Alkyl und C₃₋₆-Cycloalkyl;

EP 2 718 284 B1

jedes R^2 unabhängig ausgewählt ist aus Halogen, Cyano, C_{1-8} -Alkyl, C_{1-8} -Alkoxy, Halo- C_{1-8} -Alkyl, C_{3-6} -Cycloalkyl, 5-gliedrigem Heteroaryl, $-C(O)NHR$, $-NHC(O)R$, $S(O)_2NHR$ und $-C\equiv CR$;

jedes R unabhängig ausgewählt ist aus C_{1-8} -Alkyl, C_{3-12} -Cycloalkyl und C_{6-14} -Aryl;

'm' eine ganze Zahl zwischen 0 und 3 ist, jeweils inklusive; und

'n' eine ganze Zahl zwischen 0 und 3 ist, jeweils inklusive; unter der Bedingung, dass 'm' und 'n' nicht gleichzeitig '0' sind.

8. Verbindung nach Anspruch 7, wobei X^1 , X^2 und X^3 CH sind.

9. Verbindung nach Anspruch 7 oder 8, wobei:

jedes R^1 unabhängig Cyano, Cl, F, CHF_2 , CF_3 , OCH_3 , CH_3 oder Cyclopropyl ist;

jedes R^2 unabhängig Cyano, Cl, F, CH_3 , CF_3 oder OCH_3 ist;

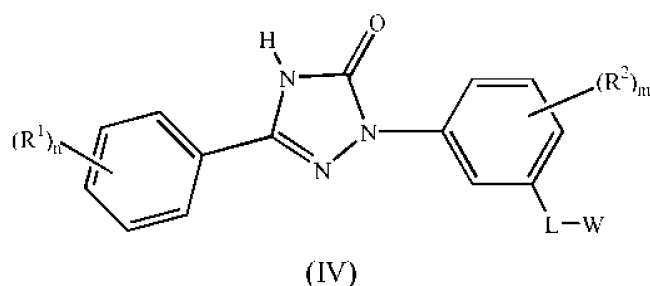
P- $CH_2NHC(O)$ - ist;

'm' 1 oder 2 ist;

'n' 0, 1 oder 2 ist; und

Q Isopropyl, *tert*-Butyl, Trifluormethyl, 1-Fluor-2-methylpropan-2-yl, 1-Methoxy-2-methylpropan-2-yl, 1-Hydroxy-2-methylpropan-2-yl, Cyclopropyl, Cyclobutyl, Cyclopentyl, 2-Fluorphenyl, Tetrahydrofuran-2-yl, Tetrahydrofuran-2-yl, (S)-Tetrahydrofuran-2-yl, (R)-Tetrahydrofuran-2-yl, Isoxazolyl oder 1-Methyl-1H-imidazol-2-yl ist.

10. Verbindung nach Anspruch 1 der Formel (IV)



oder ein pharmazeutisch verträgliches Salz davon, wobei:

L ausgewählt ist aus $-CH_2NHC(O)$ - und $-CH_2NHS(O)_2$;

W ausgewählt ist aus Isopropyl, *tert*-Butyl, Trifluormethyl, 1-Fluor-2-methylpropan-2-yl, 1-Hydroxy-2-methylpropan-2-yl und Cyclopropyl;

jedes R^1 unabhängig ausgewählt ist aus Halogen, Cyano, C_{1-8} -Alkyl, C_{1-8} -Alkoxy, Halo- C_{1-8} -Alkoxy, C_{1-8} -Alkyl, Halo- C_{1-8} -Alkyl, C_{3-6} -Cycloalkyl, 5-gliedrigem Heterocyclyl- C_{1-8} -Alkyl, 5-gliedrigem Heteroaryl- C_{1-8} -Alkyl und $-C\equiv CR$;

jedes R^2 unabhängig ausgewählt ist aus Halogen, Cyano, C_{1-8} -Alkyl, C_{1-8} -Alkoxy und Halo- C_{1-8} -Alkyl;

jedes R unabhängig ausgewählt ist aus C_{1-8} -Alkyl, C_{3-12} -Cycloalkyl und C_{6-14} -Aryl;

'm' eine ganze Zahl zwischen 0 und 3 ist, jeweils inklusive; und

'n' eine ganze Zahl zwischen 0 und 3 ist, jeweils inklusive.

11. Verbindung nach Anspruch 10, wobei:

jedes R^1 unabhängig Cl, F, CHF_2 , CF_3 , OCH_3 , CH_3 , 3,3-Dimethylbut-1-ynyl, 2-Cyclopropylethynyl, (2,5-Dichlorphenyl)ethynyl, (4-Chlor-2-fluorphenyl)ethynyl, 3-Chlor-2-fluorphenyl)ethynyl, 3-(Trifluormethyl)phenyl)ethynyl oder 2-Chlor-4-(trifluormethyl)phenyl)ethynyl ist;

jedes R^2 unabhängig Cl, F, CH_3 , CF_3 oder OCH_3 ist;

L- $CH_2NHC(O)$ - ist;

'm' 1 oder 2 ist;

'n' 0, 1 oder 2 ist; und

W Isopropyl, *tert*-Butyl, Trifluormethyl, 1-Fluor-2-methylpropan-2-yl, 1-Hydroxy-2-methylpropan-2-yl oder Cyclopropyl ist.

12. Verbindung nach Anspruch 1, ausgewählt aus:

4-(3-(2-Chlor-5-(cyclopropancarboxamidomethyl)phenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-methoxy-*N*-(3-(trifluormethyl)phenyl)benzamid;
 5 *N*-(4-Chlor-3-(1-(4-(3-(4-chlorphenyl)-1,2,4-oxadiazol-5-yl)-3-methoxyphenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)cyclopropancarboxamid;
 4-(3-(2-Chlor-5-(cyclopropancarboxamidomethyl)phenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-*N*-(3-(difluormethyl)-4-fluorphenyl)-2-methoxybenzamid;
 10 *N*-(4-Chlor-3-(1-(4-(cyclopropancarboxamido)-3-methoxyphenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)cyclopropancarboxamid
 4-(3-(2-Chlor-5-(cyclopropancarboxamidomethyl)phenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-*N*-(3-(difluormethyl)phenyl)-2-methoxybenzamid;
 4-(3-(2-Chlor-5-(cyclopropancarboxamidomethyl)phenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-*N*-(3-(trifluormethyl)phenyl)benzamid;
 15 *N*-(4-Chlor-3-(3-(4-((2,5-dichlorphenyl)ethynyl)-2-fluorphenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)cyclopropancarboxamid;
N-(4-Chlor-3-(3-(4-((4-chlor-2-fluorphenyl)ethynyl)-2-fluorphenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)cyclopropancarboxamid;
 20 *N*-(4-Chlor-3-(3-(2-fluor-4-((3-(trifluormethyl)phenyl)ethynyl)phenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)cyclopropancarboxamid;
N-(4-Chlor-3-(3-(4-((3-chlor-2-fluorphenyl)ethynyl)-2-fluorphenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)cyclopropancarboxamid;
N-(4-Chlor-3-(3-(4-((2-chlor-4-(trifluormethyl)phenyl)ethynyl)-2-fluorphenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)cyclopropancarboxamid;
 25 *N*-(4-Chlor-3-(1-(3,4-dichlorphenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2-fluorbenzyl)pivalamid;
N-(4-Chlor-2-fluor-3-(5-oxo-1-(4-(trifluormethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamid;
N-(4-Chlor-3-(1-(2,4-difluorphenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2-fluorbenzyl)pivalamid;
N-(4-Chlor-2-fluor-3-(1-(4-methoxyphenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamid;
 30 *N*-(4-Chlor-2-fluor-3-(3-(2-fluor-4-(trifluormethyl)phenyl)-5-oxo-4,5-dihydro-1*H*-1,2,3-triazol-1-yl)benzyl)pivalamid;
N-(4-Chlor-3-(3-(2-chlor-6-fluorphenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-fluorbenzyl)pivalamid;
N-(4-Chlor-3-(1-(4-cyanophenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2-fluorbenzyl)pivalamid;
N-(4-Chlor-3-(3-(4-chlor-2-fluorphenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-fluorbenzyl)pivalamid;
 35 *N*-(4-Chlor-3-(3-(4-chlor-2-fluorphenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)cyclopropancarboxamid;
N-(4-Chlor-3-(3-(2-fluor-4-(trifluormethyl)phenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)cyclopropancarboxamid;
N-(4-Chlor-2-fluor-3-(5-oxo-3-(4-(trifluormethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)pivalamid;
N-(4-Chlor-2-fluor-3-(5-oxo-1-(5-(trifluormethyl)pyridin-2-yl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamid;
 40 *N*-(4-Chlor-2-fluor-3-(5-oxo-1-(6-(trifluormethyl)pyridin-3-yl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamid;
N-(4-Chlor-3-(1-(4-Chlorphenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2-fluorbenzyl)pivalamid;
N-(4-Chlor-3-(5-oxo-1-(4-(trifluormethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoracetamide;
 45 *N*-(4-Chlor-3-(5-oxo-1-(4-(trifluormethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamid;
(R)-*N*-(4-Chlor-3-(5-oxo-1-(4-(trifluormethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)tetrahydrofuran-2-carboxamid;
N-(4-Chlor-3-(5-oxo-1-(4-(trifluormethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)cyclopropan-sulfonamid;
 50 *N*-(4-Chlor-3-(5-oxo-1-(4-(trifluormethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)-2-fluorbenzamid;
N-(4-Chlor-3-(5-oxo-1-(4-(trifluormethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)isoxazole-5-carboxamid;
N-(3-(1-(4-(Trifluormethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2,4-dimethylbenzyl)-2,2,2-trifluoroacetamid;
 55 *(R)*-*N*-(2,4-Dimethyl-3-(5-oxo-1-(4-(trifluormethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)tetrahydrofuran-2-carboxamid;
N-(3-(1-(4-(Trifluormethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2,4-dimethylbenzyl)pivalamid;

(S)-*N*-(4-Chlor-3-(1-(4-(trifluormethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)-tetrahydrofuran-2-carboxamid;

N-(4-Chlor-3-(1-(4-(trifluormethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)-1-methyl-1*H*-imidazol-2-carboxamid;

5 *N*-(4-Chlor-2-fluor-3-(4,5-dihydro-3-(4-(3,3-dimethylbut-1-ynyl)phenyl)-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamid;

N-(4-Chlor-3-(3-(4-(2-cyclopropylethynyl)phenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)-2-fluorbenzyl)pivalamid;

N-(4-Chlor-2-fluor-5-(1-(4-(trifluormethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoracetamid;

10 *N*-(4-Chlor-2-fluor-5-(1-(4-(trifluormethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamid;

N-(4-Chlor-3-(1-(4-(trifluormethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)-3-hydroxy-2,2-dimethylpropanamid;

N-(4-Chlor-3-(1-(4-chlor-3-fluorphenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoracetamid;

15 (R)-*N*-(4-Chlor-2-fluor-5-(5-oxo-1-(4-(trifluormethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)tetrahydrofuran-2-carboxamid;

N-(4-Chlor-3-(1-(4-(trifluormethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)-3-methoxy-2,2-dimethylpropanamid;

N-(4-Chlor-3-(1-(4-chlor-3-fluorphenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamid;

N-(4-Chlor-5-(1-(4-chlorphenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2-fluorbenzyl)pivalamid;

20 *N*-(4-Chlor-5-(1-(4-(trifluormethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2-methoxybenzyl)pivalamid;

N-(4-Chlor-2-fluor-5-(1-(4-fluor-3-(trifluormethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamid;

25 *N*-(4-Chlor-2-fluor-5-(1-(6-(trifluormethyl)pyridin-3-yl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamid;

N-(2,4-Dichlor-5-(3-(4-(2-cyclopropylethynyl)phenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamid;

N-(4-Chlor-5-(1-(3-chlor-4-fluorphenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2-fluorbenzyl)pivalamid;

N-(4-Chlor-5-(1-(4-chlorphenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2-fluorbenzyl)-2-fluorbenzamid;

N-(4-Chlor-2-fluor-5-(1-(4-(trifluormethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)isobutyramid;

30 *N*-(4-Chlor-5-(1-(4-chlorphenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2-fluorbenzyl)-3-fluor-2,2-dimethylpropanamid;

N-(4-Chlor-5-(1-(3-Chlor-4-methylphenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2-fluorbenzyl)pivalamid;

N-(4-Chlor-5-(3-(4-(2-cyclopropylethynyl)phenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)-2-fluorbenzyl)pivalamid;

35 *N*-(4-Chlor-2-fluor-5-(4,5-dihydro-3-(4-(3,3-dimethylbut-1-ynyl)phenyl)-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamid;

N-(4-Chlor-3-(1-(6-(trifluormethyl)pyridin-3-yl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamid ;

N-(4-Chlor-3-(1-(3-Chlor-4-fluorphenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamid;

N-(4-Chlor-3-(1-(3-Chlor-4-methylphenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamid;

N-(4-Chlor-3-(3-(4-(2-cyclopropylethynyl)phenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamid;

40 *N*-(4-Chlor-3-(1-(3-(trifluormethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamid;

N-(4-Chlor-3-(4,5-dihydro-3-(4-(3,3-dimethyl but-1-ynyl)phenyl)-5-oxo-1,2,4-triazol-1-yl)benzyl)isobutyramid;

N-(4-Chlor-3-(1-(4-(trifluormethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)isobutyramid;

N-(4-Chlor-3-(3-(4-(trifluormethyl)phenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamid;

N-(4-Chlor-3-(3-(3-fluor-4-(trifluormethyl)phenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamid;

45 *N*-(4-Chlor-3-(3-(4-chlor-3-(trifluormethyl)phenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamid;

N-(4-Chlor-3-(3-(4-fluor-3-(trifluormethyl)phenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamid;

N-(4-Chlor-3-(3-(3-fluor-4-(3,3-dimethylbut-1-ynyl)phenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)isobutyramid;

50 *N*-(4-Chlor-3-(3-(4-(2-cyclopropylethynyl)-3-fluorphenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)isobutyramid;

N-(4-Chlor-3-(4,5-dihydro-5-oxo-3-(4-((pyrrolidin-1-yl)methyl)phenyl)-1,2,4-triazol-1-yl)benzyl)pivalamid;

N-(3-(3-(4-((2,2,2-Trifluoroethoxy)methyl)phenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)-4-chlorbenzyl)pivalamid;

N-(4-Chlor-3-(4,5-dihydro-3-(4-(5-isopropyl-1,3,4-oxadiazol-2-yl)phenyl)-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamid;

55 *N*-(4-Chlor-3-(1-(4-chlor-3-methylphenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamid;

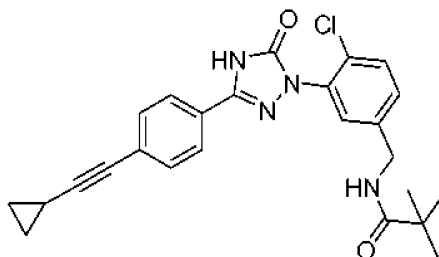
N-(4-Chlor-3-(1-(4-chlor-3-methylphenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)isobutyramid;

N-(4-Chlor-3-(1-(3-fluor-5-(trifluormethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamid;

N-(4-Chlor-3-(1-(4-chlor-3-(trifluormethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamid;

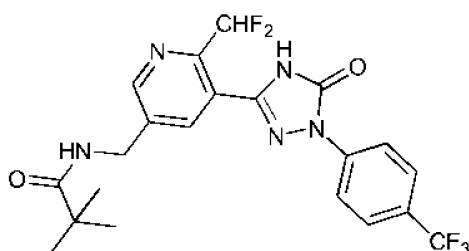
N-(4-Chlor-3-(1-(3-(trifluormethyl)-4-methylphenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamid;
N-(4-Chlor-3-(1-(4-(trifluormethyl)-2-methylphenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamid;
N-(4-Chlor-3-(1-(3-fluor-4-(trifluormethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamid;
N-(4-Chlor-3-(1-(3-fluor-4-(trifluormethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)isobutyramid;
5 *N*-(4-Chlor-3-(5-oxo-1-(4-(trifluormethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)propan-2-sulfonamid;
N-(4-Chlor-3-(1-(2-fluor-4-(trifluormethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamid;
N-(3-(4,5-Dihydro-1-(4-(3,3-dimethylbut-1-ynyl)phenyl)-5-oxo-1*H*-1,2,4-triazol-3-yl)-2,4-dimethylbenzyl)isobutyramid;
10 *N*-(3-(1-(4-(2-Cyclopropylethynyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2,4-dimethylbenzyl)pivalamid;
N-(4-Chlor-3-(3-(4-(2-cyclopropylethynyl)-3-fluorphenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamid;
N-(4-Chlor-3-(1-(4-(2-cyclopropylethynyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamid;
N-(4-Chlor-3-(3-(4-(2-cyclopropylethynyl)-2-fluorphenyl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamid;
15 *N*-(3-(1-(4-(2-Cyclopropylethynyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2,4-dimethylbenzyl)-3-fluor-2,2-dimethylpropanamid;
N-(3-(1-(3-Fluor-4-(3,3-dimethylbut-1-ynyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2,4-dimethylbenzyl)isobutyramid;
N-(4-Chlor-3-(4,5-dihydro-3-(4-((3,5-dimethyl-1*H*-pyrazol-1-yl)methyl)phenyl)-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamid;
20 *N*-(4-Chlor-2-fluor-3-(1-(3-fluor-4-(trifluormethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamid;
N-(4-Chlor-3-(1-(4-Chlor-3-(trifluormethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2-fluorbenzyl)pivalamid;
N-(4-Chlor-3-(1-(4-(trifluormethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)-3-fluor-2,2-dimethylpropanamid;
25 *N*-(6-Cyclopropyl-5-(1-(4-(trifluormethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)pyridin-3-yl)methyl)pivalamid;
N-(4-Chlor-3-(1-(4-(2-cyclopropylethynyl)-2-fluorphenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamid;
30 *N*-(4-Chlor-3-(5-oxo-1-(4-(trifluormethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)-2-methylpropan-2-sulfonamid;
N-(4-Chlor-3-(5-oxo-1-(4-(trifluormethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)cyclobutancarboxamid;
N-(4-Chlor-3-(5-oxo-1-(4-(trifluormethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)cyclopentancarboxamid;
35 *N*-(6-(Difluormethyl)-5-(5-oxo-1-(4-(trifluormethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyridin-3-yl)methyl)pivalamid;
N-(6-(Difluormethyl)-5-(5-oxo-1-(4-(trifluormethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyridin-3-yl)methyl)isobutyramid;
40 *N*-(6-(Difluormethyl)-5-(5-oxo-1-(4-(trifluormethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyridin-3-yl)methyl)propan-2-sulfonamid;
N-(6-(Difluormethyl)-5-(5-oxo-1-(4-(trifluormethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyridin-3-yl)methyl)cyclobutancarboxamid;
N-(4-Chlor-3-(3-(4-(cyclopropylethynyl)phenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)-2,2,2-trifluoroacetamid;
45 *N*-(4-Chlor-3-(3-(4-(cyclopropylethynyl)phenyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)-3-hydroxy-2,2-dimethylpropanamid;
3-Fluor-*N*-(6-(difluormethyl)-5-(1-(4-(trifluormethyl)phenyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)pyridin-3-yl)methyl)-2,2-dimethylpropanamid;
50 und pharmazeutisch verträglichen Salzen davon.

13. Verbindung nach Anspruch 1 der Formel



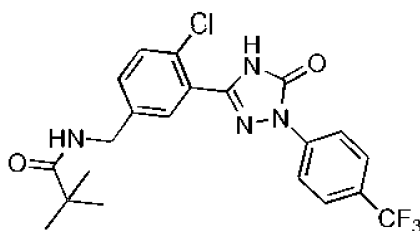
oder ein pharmazeutisch verträgliches Salz davon.

14. Verbindung nach Anspruch 1 der Formel



oder ein pharmazeutisch verträgliches Salz davon.

15. Verbindung nach Anspruch 1 der Formel



oder ein pharmazeutisch verträgliches Salz davon.

16. Verbindung nach Anspruch 1, ausgewählt aus:

N-(4-Chlor-3-(5-oxo-1-(4-(trifluormethyl)phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoracetamid;

N-(4-Chlor-3-(4,5-dihydro-3-(4-iodophenyl)-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamid;

und pharmazeutisch verträglichen Salzen davon.

17. Pharmazeutische Zusammensetzung, umfassend eine Verbindung nach einem der Ansprüche 1 bis 14 und einen pharmazeutisch verträglichen Arzneiträger.

18. Pharmazeutische Zusammensetzung nach Anspruch 17, wobei der pharmazeutisch verträgliche Arzneiträger ein Träger oder ein Verdünner ist.

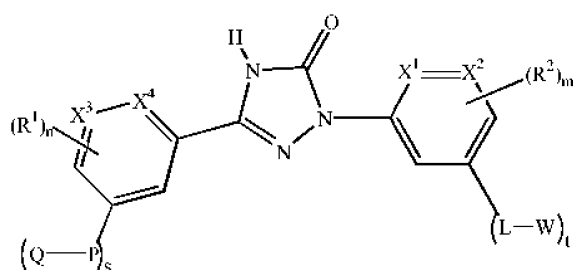
19. Verbindung nach einem der Ansprüche 1 bis 15 zur Verwendung in der Prävention oder Behandlung einer mPGES-1-vermittelten Erkrankung, Störung oder eines solchen Syndroms in einem Subjekt.

20. Verbindung nach einem der Ansprüche 1 bis 15 zur Verwendung in der Prävention oder Behandlung einer Erkrankung, Störung, eines Syndroms oder eines Zustands, die, das bzw. der ausgewählt ist aus der Gruppe bestehend aus Entzündung, Asthma, chronisch obstruktiver Lungenerkrankung, Lungenfibrose, entzündliche Darmerkrankung,

Reizdarmsyndrom, Schmerzen, Entzündungsschmerzen, chronische Schmerzen, akute Schmerzen, Fieber, Migräne, Kopfschmerzen, Kreuzschmerzen, Fibromyalgie, myofaszialen Störungen, viralen Infektionen, Influenza, Erkältung, Gürtelrose, Hepatitis C, AIDS, bakteriellen Infektionen, Pilzinfektionen, Dysmenorrhö, Prellungen, chirurgische oder dentale Eingriffe, Malignitäten, Hyperprostaglandin-E-Syndrom, klassisches Bartter-Syndrom, Synovitis, Atherosklerose, Gicht, Arthritis, Osteoarthritis, Juvenile Arthritis, Rheumatoide Arthritis, Juvenile Rheumatoide Arthritis, rheumatisches Fieber, Bechterew-Krankheit, Morbus Hodgkin, systemische Lupus erythematosus, Vasculitis, Pankreatitis, Nephritis, Bursitis, Konjunktivitis, Iritis, Skleritis, Uveitis, Wundheilung, Dermatitis, Ekzem, Psoriasis, Hirnschlag, Diabetes mellitus, Krebs, neurodegenerative Störungen wie etwa die Alzheimer-Krankheit, die Parkinson-Krankheit, amyotrophische Lateralsklerose und multiple Sklerose, Autoimmunerkrankungen, allergische Erkrankungen, Rhinitis, Geschwüre, mäßige bis moderat aktive Colitis ulcerosa, familiäre adenomatöse Polyposis, koronare Herzkrankheit und Sarkoidose.

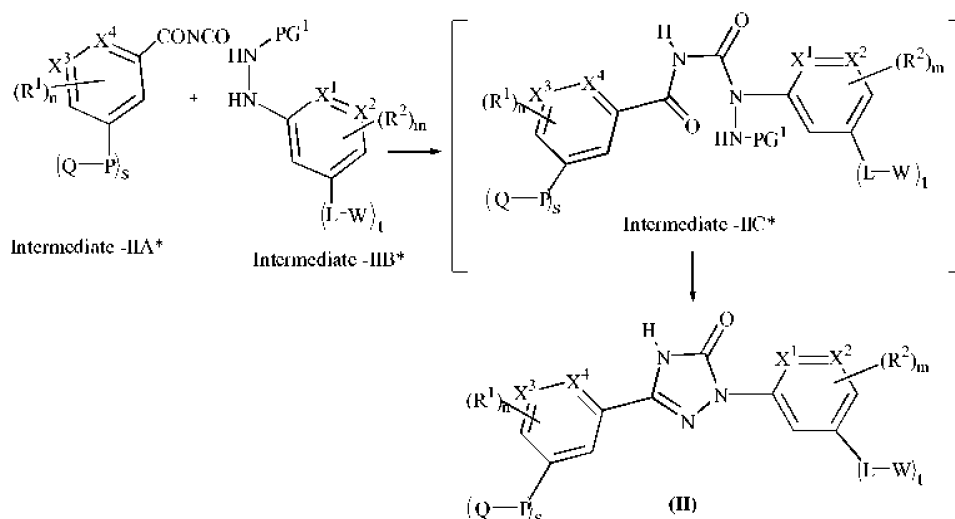
21. Verbindung nach einem der Ansprüche 1 bis 15 zur Verwendung in der Prävention oder Behandlung einer Erkrankung, Störung, eines Syndroms oder eines Zustands, wobei die Erkrankung, die Störung, das Syndrom oder der Zustand Schmerzen, chronische Schmerzen, akute Schmerzen, Schmerzen rheumatoider Arthritis oder osteoarthritische Schmerzen sind.

22. Verfahren zur Herstellung einer Verbindung der Formel (II) gemäß Anspruch 1



(II)

oder eines pharmazeutisch verträglichen Salzes davon, umfassend: in Reaktion bringen einer Verbindung der Formel (Intermediate-IIA*) mit einer Verbindung der Formel (Intermediate-IIB*), um eine Verbindung der Formel (Intermediate-IIC*) zu erzeugen; und Umwandeln der Verbindung der Formel (Intermediate-IIC*) in eine Verbindung der Formel (II):



wobei:

X¹, X², X³ und X⁴ jeweils unabhängig ausgewählt sind aus CH und N;

jedes L unabhängig ausgewählt ist aus $-\text{CH}_2\text{NHC(O)}-$ und $-\text{CH}_2\text{NHS(O)}_2-$;

jedes P unabhängig ausgewählt ist aus $-\text{CH}_2\text{NHC(O)}-$ und $-\text{CH}_2\text{NHS(O)}_2-$;

jedes Q unabhängig ausgewählt ist aus C_{1-8} -Alkyl, Halo- C_{1-8} -Alkyl, C_{1-8} -Alkoxy C_{1-8} -Alkyl, Hydroxy- C_{1-8} -Alkyl, Carboxyl- C_{1-8} -Alkyl, C_{3-12} -Cycloalkyl, C_{6-14} -Aryl, 3-15-gliedrigem Heterocyclyl und 5-14-gliedrigem Heteroaryl;

jedes W unabhängig ausgewählt ist aus Isopropyl, *tert*-Butyl, Trifluormethyl, 1-Fluor-2-methylpropan-2-yl, 1-Hydroxy-2-methylpropan-2-yl und Cyclopropyl;

jedes R^1 unabhängig ausgewählt ist aus Halogen, Cyano, C_{1-8} -Alkyl, C_{1-8} -Alkoxy, Halo- C_{1-8} -Alkoxy C_{1-8} -Alkyl, Halo- C_{1-8} -Alkyl, C_{3-6} -Cycloalkyl, 5-gliedrigem Heterocyclyl- C_{1-8} -Alkyl, 5-gliedrigem Heteroaryl, 5-gliedrigem Heteroaryl- C_{1-8} -Alkyl und $-\text{C}\equiv\text{CR}$;

jedes R^2 unabhängig ausgewählt ist aus Halogen, Cyano, C_{1-8} -Alkyl, C_{1-8} -Alkoxy, Halo- C_{1-8} -Alkyl, C_{3-6} -Cycloalkyl, 5-gliedrigem Heteroaryl, $-\text{C(O)NHR}$, $-\text{NHC(O)R}$, $\text{S(O)}_2\text{NHR}$ und $-\text{C}\equiv\text{CR}$;

jedes R unabhängig ausgewählt ist aus C_{1-8} -Alkyl, C_{3-12} -Cycloalkyl und C_{6-14} -Aryl;

PG^1 eine Aminschutzgruppe darstellt;

'm' eine ganze Zahl zwischen 0 und 3 ist, jeweils inklusive;

'n' eine ganze Zahl zwischen 0 und 3 ist, jeweils inklusive;

's' eine ganze Zahl zwischen 0 und 1 ist, jeweils inklusive; und

't' eine ganze Zahl zwischen 0 und 1 ist, jeweils inklusive;

unter den Bedingungen, dass (i) 's' und 't' nicht gleichzeitig '0' sind und dass (ii) 'm' und 'n' nicht gleichzeitig '0' sind.

23. Verfahren nach Anspruch 22, wobei das Isocyanat der Formel (Intermediate-IIA*) erhalten wird aus dem entsprechenden Säure-, Amid- oder Säurehalid-Derivat.

24. Verfahren nach Anspruch 22, wobei eine Verbindung der (Intermediate-IIA*) in Reaktion gebracht wird mit einer Verbindung der Formel (Intermediate-IIB*) in DCM, Toluol oder EDC.

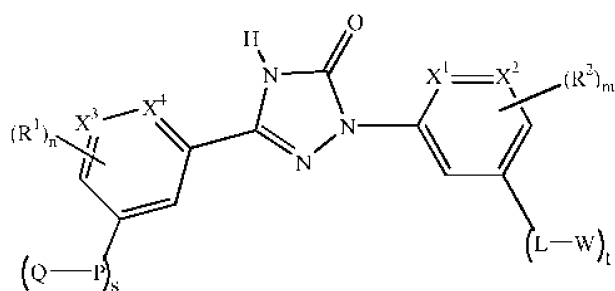
25. Verfahren nach Anspruch 22, wobei Intermediate-IIC* nicht isoliert ist.

26. Verfahren nach Anspruch 22, wobei PG^1 *tert*-Butoxycarbonyl ist.

27. Verfahren nach Anspruch 22, wobei eine Verbindung der Formel (Intermediate-IIC*) unter Verwendung einer organischen Säure in eine Verbindung der Formel (II) umgewandelt wird.

Revendications

1. Composé de formule (II),



(II)

ou sel pharmaceutiquement acceptable associé,

X^1 , X^2 , X^3 et X^4 étant chacun indépendamment choisi parmi CH et N ;

chaque occurrence de L étant indépendamment choisie parmi $-\text{CH}_2\text{NHC(O)}-$ et $-\text{CH}_2\text{NHS(O)}_2-$;

chaque occurrence de P étant indépendamment choisie parmi $-\text{CH}_2\text{NHC(O)}-$ et $-\text{CH}_2\text{NHS(O)}_2-$;

chaque occurrence de Q étant indépendamment choisie parmi C_{1-8} alkyle, halo C_{1-8} alkyle, C_{1-8} alkoxy C_{1-8} alkyle, hydroxy C_{1-8} alkyle, carboxyle C_{1-8} alkyle, C_{3-12} cycloalkyle, C_{6-14} aryle, hétérocyclyl à 3-15 chaînons, et hétéroa-

ryle à 5-14 chaînons ;

chaque occurrence de W étant indépendamment choisie parmi isopropyle, *tert*-butyle, trifluorométhyle, 1-fluoro-2-méthylpropan-2-yl, 1-hydroxy-2-méthylpropan-2-yl et cyclopropyle ;

chaque occurrence de R¹ étant sélectionnée choisie parmi halogène, cyano, C₁₋₈alkyle, C₁₋₈alkoxy, haloC₁₋₈alkoxyC₁₋₈alkyle, haloC₁₋₈alkyle, C₃₋₆cycloalkyle, hétérocyclylC₁₋₈alkyle à 5 chaînons, hétéroaryle à 5 chaînons, hétéroaryle₁₋₈alkyle à 5 chaînons, et -C≡CR ;

chaque occurrence de R² étant indépendamment choisie parmi halogène, cyano, C₁₋₈alkyle, C₁₋₈alkoxy, haloC₁₋₈alkyle, C₃₋₆cycloalkyle, hétéroaryle à 5 chaînons, -C(O)NHR, -NHC(O)R, S(O)₂NHR et -C≡CR ;

chaque occurrence de R étant indépendamment choisie parmi C₁₋₈alkyle, C₃₋₁₂cycloalkyle et C₆₋₁₄aryle ;

m étant un entier compris entre 0 et 3, tous deux inclus ;

n étant un entier compris entre 0 et 3, tous deux inclus ;

s étant un entier compris entre 0 et 1, tous deux inclus ; et

t étant un entier compris entre 0 et 1, tous deux inclus ;

à condition que (i) s et t ne soient pas 0 simultanément, et (ii) m et n ne soient pas 0 simultanément.

2. Composé selon la revendication 1, X¹, X², X³ et X⁴ étant CH.

3. Composé selon la revendication 2 :

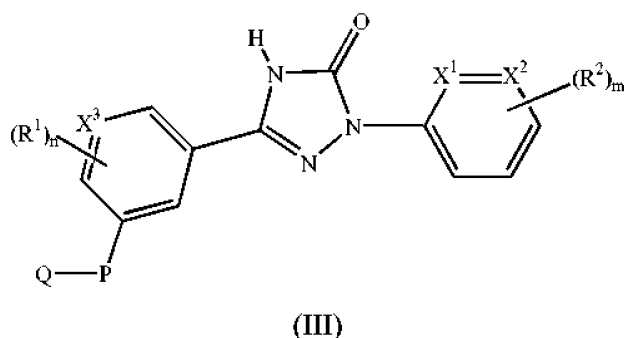
chaque occurrence de R¹ étant indépendamment cyano, Cl, F, CHF₂, CF₃, OCH₃, CH₃, (2,2,2-trifluoroéthoxy)méthyl, cyclopropyle, (pyrrolidine-1-yl)méthyl, 4-méthylthiophényle, 5-isopropyle-1,3,4-oxadiazol-2-yl, (3,5-diméthyl-1H-pyrazol-1-yl)méthyl, 3,3-diméthylbut-1-ynyle, 2-cyclopropyléthynyle, (2,5-dichlorophényl)éthynyle, (4-chloro-2-fluorophényl)éthynyle, (3-chloro-2-fluorophényl)éthynyle, (3-(trifluorométhyle)phényl)éthynyle ou (2-chloro-4-(trifluorométhyle)phényl)éthynyle ; et n étant 1 ou 2.

4. Composé selon l'une quelconque des revendications 1 à 3, chaque occurrence de R² étant indépendamment cyano, Cl, F, CH₃, CF₃, OCH₃, 3-(4-chlorophényl)-1,2,4-oxadiazol-5-yl, cyclopropanecarboxamido, 3,3-diméthylbut-1-ynyle, 2-cyclopropyléthynyle, -CONH-[3-(trifluorométhyle)phényle], -CONH-[3-(difluorométhyle)-4-fluorophényle] ou -CONH-[3-(difluorométhyle)phényle] ; et m étant 1 ou 2.

5. Composé selon l'une quelconque des revendications 1 à 4, Q étant isopropyle, *tert*-butyle, trifluorométhyle, 1-fluoro-2-méthylpropan-2-yl, 1-méthoxy-2-méthylpropan-2-yl, 1-hydroxy-2-méthylpropan-2-yl, cyclopropyle, cyclobutyle, cyclopentyle, 2-fluorophényl, tétrahydrofuranyl, tétrahydrofuranyl, tétrahydrofurane-2-yl, (S)-tétrahydrofurane-2-yl, (R)-tétrahydrofurane-2-yl, isoxazolyle ou 1-méthyl-1H-imidazole-2-yl ; s étant 1 ; et t étant 0.

6. Composé selon l'une quelconque des revendications 1 à 5, t étant 1 ; et s étant 0.

7. Composé selon la revendication 1, de formule (III)



ou sel pharmaceutiquement acceptable associé,

X¹, X² et X³ étant chacun indépendamment choisi parmi CH et N ;

P étant choisi parmi -CH₂NHC(O)- et -CH₂NHS(O)₂- ;

Q étant choisi parmi C₁₋₈alkyle, haloC₁₋₈alkyle, C₁₋₈alkoxyC₁₋₈alkyle, hydroxyC₁₋₈alkyle, carboxyleC₁₋₈alkyle,

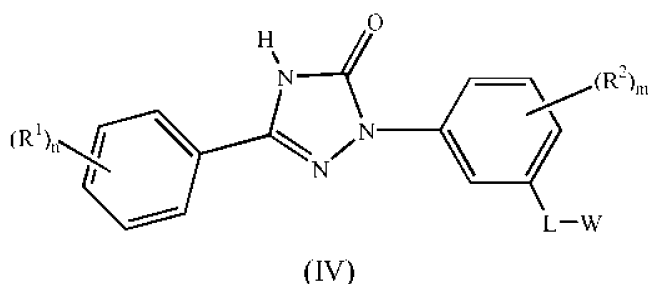
C₃₋₁₂cycloalkyle, C₆₋₁₄aryle, hétérocyclyle à 3-15 chaînons, et hétéroaryle à 5-14 chaînons ;
 chaque occurrence de R¹ étant indépendamment choisie parmi halogène, cyano, C₁₋₈alkyle, C₁₋₈alkoxy, haloC₁₋₈alkyle et C₃₋₆cycloalkyle ;
 chaque occurrence de R² étant indépendamment choisie parmi halogène, cyano, C₁₋₈alkyle, C₁₋₈alkoxy, haloC₁₋₈alkyle, C₃₋₆cycloalkyle, hétéroaryle à 5 chaînons, -C(O)NHR, -NHC(O)R, S(O)₂NHR et -C≡CR ;
 chaque occurrence de R étant indépendamment choisie parmi C₁₋₈alkyle, C₃₋₁₂cycloalkyle et C₆₋₁₄aryle ;
 m étant un entier compris entre 0 et 3, tous deux inclus ; et
 n étant un entier compris entre 0 et 3, tous deux inclus ; à condition que m et n ne soient pas 0 en même temps.

8. Composé selon la revendication 7, X¹, X² et X³ étant CH.

9. Composé selon la revendication 7 ou 8,

chaque R¹ étant, indépendamment, cyano, Cl, F, CHF₂, CF₃, OCH₃, CH₃ ou cyclopropyle ;
 chaque R² étant, indépendamment, cyano, Cl, F, CH₃, CF₃ ou OCH₃ ;
 P étant -CH₂NHC(O)- ;
 m étant 1 ou 2 ;
 n étant 0, 1 ou 2 ; et
 Q étant isopropyle, *tert*-butyle, trifluorométhyle, 1-fluoro-2-méthylpropan-2-yl, 1-méthoxy-2-méthylpropan-2-yl, 1-hydroxy-2-méthylpropan-2-yl, cyclopropyle, cyclobutyle, cyclopentyle, 2-fluorophényl, tétrahydrofuranyl, tétrahydrofuranyl, tétrahydrofurane-2-yl, (S)-tétrahydrofurane-2-yl, (R)-tétrahydrofurane-2-yl, isoxazolyl ou 1-méthyl-1*H*-imidazole-2-yl.

10. Composé selon la revendication 1, de formule (IV)



ou sel pharmaceutiquement acceptable associé,

L étant choisi parmi -CH₂NHC(O)- et -CH₂NHS(O)₂- ;
 W étant indépendamment choisi parmi isopropyle, *tert*-butyle, trifluorométhyle, 1-fluoro-2-méthylpropan-2-yl, 1-hydroxy-2-méthylpropan-2-yl et cyclopropyle ;
 chaque occurrence de R¹ étant sélectionnée choisie parmi halogène, cyano, C₁₋₈alkyle, C₁₋₈alkoxy, haloC₁₋₈alkyle, haloC₁₋₈alkoxy, C₃₋₆cycloalkyle, hétérocyclyle C₁₋₈alkyle à 5 chaînons, hétéroaryle à 5 chaînons, hétéroaryle C₁₋₈alkyle à 5 chaînons, et -C≡CR ;
 chaque occurrence de R² étant indépendamment choisie parmi halogène, cyano, C₁₋₈alkyle, C₁₋₈alkoxy et haloC₁₋₈alkyle ;
 chaque occurrence de R étant indépendamment choisie parmi C₁₋₈alkyle, C₃₋₁₂cycloalkyle et C₆₋₁₄aryle ;
 m étant un entier compris entre 0 et 3, tous deux inclus ; et
 n étant un entier compris entre 0 et 3, tous deux inclus ; à condition que m et n ne soient pas 0 en même temps.

11. Composé selon la revendication 10,

chaque occurrence de R¹ étant indépendamment Cl, F, CHF₂, CF₃, OCH₃, CH₃, 3, 3-diméthylbut-1-ynyle, 2-cyclopropyléthynyl, (2,5-dichlorophényl)éthynyl, (4-chloro-2-fluorophényl)éthynyl, 3-chloro-2-fluorophényl)éthynyl, 3-(trifluorométhyle)phényl)éthynyl ou 2-chloro-4-(trifluorométhyle)phényl)éthynyl ;
 chaque occurrence de R² étant indépendamment Cl, F, CH₃, CF₃ ou OCH₃ ;
 L étant -CH₂NHC(O)- ;
 m étant 1 ou 2 ;

n étant 0, 1 ou 2 ; et

W étant isopropyle, *tert*-butyle, trifluorométhyle, 1-fluoro-2-méthylpropan-2-yl, 1-hydroxy-2-méthylpropan-2-yl ou cyclopropyle.

5 12. Composé selon la revendication 1, choisi parmi

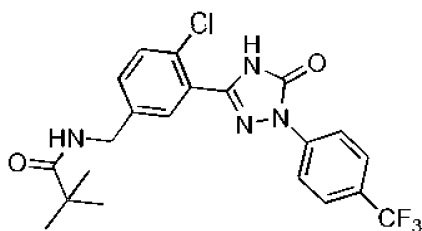
4-(3-(2-Chloro-5-(cyclopropanecarboxamidométhyle)phényl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-méthoxy-*N*-(3-(trifluorométhyle)phényl)benzamide ;
 10 *N*-(4-Chloro-3-(1-(4-(3-(4-chlorophényl)-1,2,4-oxadiazol-5-yl)-3-méthoxyphényl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)cyclopropanecarboxamide ;
 4-(3-(2-chloro-5-(cyclopropanecarboxamidométhyle)phényl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-*N*-(3-(difluorométhyle)-4-fluorophényl)-2-méthoxybenzamide ;
N-(4-Chloro-3-(1-(4-(cyclopropanecarboxamido)-3-méthoxyphényl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)cyclopropanecarboxamide ;
 15 4-(3-(2-chloro-5-(cyclopropanecarboxamidométhyle)phényl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-*N*-(3-(difluorométhyle)phényl)-2-méthoxybenzamide ;
 4-(3-(2-chloro-5-(cyclopropanecarboxamidométhyle)phényl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-*N*-(3-(trifluorométhyle)phényl)benzamide ;
N-(4-Chloro-3-(3-(4-(2,5-dichlorophényl)cthynyl)-2-fluorophényl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)cyclopropanecarboxamide ;
 20 *N*-(4-Chloro-3-(3-(4-(4-chloro-2-fluorophényl)ethynyl)-2-fluorophényl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)cyclopropanecarboxamide ;
N-(4-Chloro-3-(3-(2-fluoro-4-((3-(trifluorométhyle)phényl)cthynyl)phényl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)cyclopropanecarboxamide ;
 25 *N*-(4-Chloro-3-(3-(4-(3-chloro-2-fluorophényl)cthynyl)-2-fluorophényl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)cyclopropanecarboxamide ;
N-(4-Chloro-3-(3-(4-(2-chloro-4-(trifluorométhyle)phényl)cthynyl)-2-fluorophényl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)cyclopropanecarboxamide ;
N-(4-Chloro-3-(1-(3,4-dichlorophényl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2-fluorobenzyl)pivalamide ;
 30 *N*-(4-Chloro-2-fluoro-3-(5-oxo-1-(4-(trifluorométhyle)phényl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide ;
N-(4-Chloro-3-(1-(2,4-difluorophényl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2-fluorobenzyl)pivalamide ;
N-(4-Chloro-2-fluoro-3-(1-(4-méthoxyphényl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide ;
N-(4-Chloro-2-fluoro-3-(3-(2-fluoro-4-(trifluorométhyle)phényl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)pivalamide ;
 35 *N*-(4-Chloro-3-(3-(2-chloro-6-fluorophényl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-fluorobenzyl)pivalamide ;
N-(4-Chloro-3-(1-(4-cyanophényl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2-fluorobenzyl)pivalamide ;
N-(4-Chloro-3-(3-(4-chloro-2-fluorophényl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-2-fluorobenzyl)pivalamide ;
 40 *N*-(4-Chloro-3-(3-(4-chloro-2-fluorophényl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)cyclopropanecarboxamide ;
N-(4-Chloro-3-(3-(2-fluoro-4-(trifluorométhyle)phényl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)cyclopropanecarboxamide ;
 45 *N*-(4-Chloro-2-fluoro-3-(5-oxo-3-(4-(trifluorométhyle)phényl)-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)pivalamide ;
N-(4-Chloro-2-fluoro-3-(5-oxo-1-(5-(trifluorométhyle)pyridin-2-yl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide ;
N-(4-Chloro-2-fluoro-3-(5-oxo-1-(6-(trifluorométhyle)pyridin-3-yl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide ;
 50 *N*-(4-Chloro-3-(1-(4-chlorophényl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2-fluorobenzyl)pivalamide ;
N-(4-Chloro-3-(5-oxo-1-(4-(trifluorométhyle)phényl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacétamide ;
N-(4-Chloro-3-(5-oxo-1-(4-(trifluorométhyle)phényl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide ;
 55 (R)-*N*-(4-Chloro-3-(5-oxo-1-(4-(trifluorométhyle)phényl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)tetrahydrofuran-2-carboxamide ;
N-(4-Chloro-3-(5-oxo-1-(4-(trifluorométhyle)phényl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)cyclopropanesulfonamide ;

N-(4-Chloro-3-(5-oxo-1-(4-(trifluorométhyle)phényl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)-2-fluorobenzamide ;
N-(4-Chloro-3-(5-oxo-1-(4-(trifluorométhyle)phényl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)isoxazole-5-carboxamide ;
5 *N*-(3-(1-(4-(Trifluorométhyle)phényl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2,4-diméthylbenzyl)-2,2,2-trifluoroacétamide ;
(R)-*N*-(2,4-Diméthyl-3-(5-oxo-1-(4-(trifluorométhyle)phényl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)tetrahydrofuran-2-carboxamide ;
N-(3-(1-(4-(Trifluorométhyle)phényl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2,4-diméthylbenzyl)pivalamide ;
10 (S)-*N*-(4-Chloro-3-(1-(4-(trifluorométhyle)phényl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)-tetrahydrofuran-2-carboxamide ;
N-(4-Chloro-3-(1-(4-(trifluorométhyle)phényl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)-1-méthyl-1*H*-imidazole-2-carboxamide ;
N-(4-Chloro-2-fluoro-3-(4-(3,3-diméthylbut-1-ynyle)phényl)-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide ;
15 *N*-(4-Chloro-3-(3-(4-(2-cyclopropyléthynyl)phényl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)-2-fluorobenzyl)pivalamide ;
N-(4-Chloro-2-fluoro-5-(1-(4-(trifluorométhyle)phényl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacétamide ;
20 *N*-(4-Chloro-2-fluoro-5-(1-(4-(trifluorométhyle)phényl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide ;
N-(4-Chloro-3-(1-(4-(trifluorométhyle)phényl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)-3-hydroxy-2,2-diméthylpropanamide ;
N-(4-Chloro-3-(1-(4-chloro-3-fluorophényl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacétamide ;
25 (R)-*N*-(4-chloro-2-fluoro-5-(5-oxo-1-(4-(trifluorométhyle)phényl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)tetrahydrofuran-2-carboxamide ;
N-(4-Chloro-3-(1-(4-(trifluorométhyle)phényl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)-3-méthoxy-2,2-diméthylpropanamide ;
30 *N*-(4-Chloro-3-(1-(4-chloro-3-fluorophényl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide ,
N-(4-Chloro-5-(1-(4-chlorophényl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2-fluorobenzyl)pivalamide ;
N-(4-Chloro-5-(1-(4-(trifluorométhyle)phényl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2-méthoxybenzyl)pivalamide ;
N-(4-Chloro-2-fluoro-5-(1-(4-fluoro-3-(trifluorométhyle)phényl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide ;
35 *N*-(4-Chloro-2-fluoro-5-(1-(6-(trifluorométhyle)pyridin-3-yl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide ;
N-(2,4-Dichloro-5-(3-(4-(2-cyclopropyléthynyl)phényl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide ;
N-(4-Chloro-5-(1-(3-chloro-4-fluorophényl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2-fluorobenzyl)pivalamide ;
40 *N*-(4-Chloro-5-(1-(4-chlorophényl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2-fluorobenzyl)-2-fluorobenzamide ;
N-(4-Chloro-2-fluoro-5-(1-(4-(trifluorométhyle)phényl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)isobutyramide ;
45 *N*-(4-Chloro-5-(1-(4-chlorophényl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2-fluorobenzyl)-3-fluoro-2,2-diméthylpropanamide ;
N-(4-Chloro-5-(1-(3-chloro-4-méthylphényl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2-fluorobenzyl)pivalamide ;
N-(4-Chloro-5-(3-(4-(2-cyclopropyléthynyl)phényl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)-2-fluorobenzyl)pivalamide ;
50 *N*-(4-Chloro-2-fluoro-5-(4,5-dihydro-3-(4-(3,3-diméthylbut-1-ynyle)phényl)-5-oxo-1*H*-1,2,4-triazol-1-yl)benzyl)pivalamide ;
N-(4-Chloro-3-(1-(6-(trifluorométhyle)pyridin-3-yl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide ;
N-(4-Chloro-3-(1-(3-chloro-4-fluorophényl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide ,
55 *N*-(4-Chloro-3-(1-(3-chloro-4-méthylphényl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide ;
N-(4-Chloro-3-(3-(4-(2-cyclopropyléthynyl)phényl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide ;
N-(4-Chloro-3-(1-(3-(trifluorométhyle)phényl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide ;
N-(4-Chloro-3-(4,5-dihydro-3-(4-(3,3-diméthylbut-1-ynyle)phényl)-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide ;

yl)benzyl)isobutyramide ;
N-(4-Chloro-3-(1-(4-(trifluorométhyle)phényl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)isobutyramide ;
N-(4-Chloro-3-(3-(4-(trifluorométhyle)phényl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide ;
N-(4-Chloro-3-(3-(3-fluoro-4-(trifluorométhyle)phényl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide ;
 5 *N*-(4-Chloro-3-(3-(4-chloro-3-(trifluorométhyle)phényl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide ;
N-(4-Chloro-3-(3-(4-fluoro-3-(trifluorométhyle)phényl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide ;
N-(4-Chloro-3-(3-(3-fluoro-4-(3,3-diméthylbut-1-ynyle)phényl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)isobutyramide ;
N-(4-Chloro-3-(3-(4-(2-cyclopropyléthynyl)-3-fluorophényl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)isobutyramide ;
 10 *N*-(4-Chloro-3-(4,5-dihydro-5-oxo-3-(4-((pyrrolidin-1-yl)méthyle)phényl)-1,2,4-triazol-1-yl)benzyl)pivalamide ;
N-(3-(3-(4-((2,2,2-Trifluoroéthoxy)méthyle)phényl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)-4-chlorobenzyl)pivalamide ;
N-(4-Chloro-3-(4,5-dihydro-3-(4-(5-isopropyle-1,3,4-oxadiazol-2-yl)phényl)-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide ;
 15 *N*-(4-Chloro-3-(1-(4-chloro-3-méthylphényl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide ,
N-(4-Chloro-3-(1-(4-chloro-3-méthylphényl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)isobutyramide ;
N-(4-Chloro-3-(1-(3-fluoro-5-(trifluorométhyle)phényl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide ;
 20 *N*-(4-Chloro-3-(1-(4-chloro-3-(trifluorométhyle)phényl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide ;
N-(4-Chloro-3-(1-(3-(trifluorométhyle)-4-méthylphényl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide ;
N-(4-Chloro-3-(1-(4-(trifluorométhyle)-2-méthylphényl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide ;
 25 *N*-(4-Chloro-3-(1-(3-fluoro-4-(trifluorométhyle)phényl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide ;
N-(4-Chloro-3-(1-(3-fluoro-4-(trifluorométhyle)phényl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)isobutyramide ;
 30 *N*-(4-Chloro-3-(5-oxo-1-[4-(trifluorométhyle)phényl]-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)propane-2-sulfonamide ;
N-(4-Chloro-3-(1-(2-fluoro-4-(trifluorométhyle)phényl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide ;
N-(3-(4,5-Dihydro-1-(4-(3,3-diméthylbut-1-ynyle)phényl)-5-oxo-1*Y*-1,2,4-triazol-3-yl)-diméthylbenzyl)isobutyramide ;
 35 *N*-(3-(1-(4-(2-cyclopropyléthynyl)phényl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2,4-diméthylbenzyl)pivalamide ;
N-(4-Chloro-3-(3-(4-(2-cyclopropyléthynyl)-3-fluorophényl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide ;
 40 *N*-(4-Chloro-3-(1-(4-(2-cyclopropyléthynyl)phényl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)pivalamide ;
N-(4-Chloro-3-(3-(4-(2-cyclopropyléthynyl)-2-fluorophényl)-4,5-dihydro-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide ;
N-(3-(1-(4-(2-cyclopropyléthynyl)phényl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2,4-diméthylbenzyl)-3-fluoro-2,2-diméthylpropanamide ;
 45 *N*-(3-(1-(3-Fluoro-4-(3,3-diméthylbut-1-ynyle)phényl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2,4-diméthylbenzyl)isobutyramide ;
N-(4-Chloro-3-(4,5-dihydro-3-(4-((3,5-diméthyl-1*H*-pyrazol-1-yl)méthyle)phényl)-5-oxo-triazol-1-yl)benzyl)pivalamide ;
N-(4-Chloro-2-fluoro-3-(1-(3-fluoro-4-(trifluorométhyle)phényl)-4,5-dihydro-5-oxo-1*H*-triazole-3-yl)benzyl)pivalamide ;
 50 *N*-(4-Chloro-3-(1-(4-chloro-3-(trifluorométhyle)phényl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)-2-fluorobenzyl)pivalamide ;
N-(4-Chloro-3-(1-(4-(trifluorométhyle)phényl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)benzyl)-3-fluoro-2,2-diméthylpropanamide ;
 55 *N*-(6-cyclopropyle-5-(1-(4-(trifluorométhyle)phényl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)pyridin-3-yl)méthyle)pivalamide ;
N-(4-Chloro-3-(1-(4-(2-cyclopropyléthynyl)-2-fluorophényl)-4,5-dihydro-5-oxo-1*H*-triazole-3-yl)benzyl)pivalamide ;

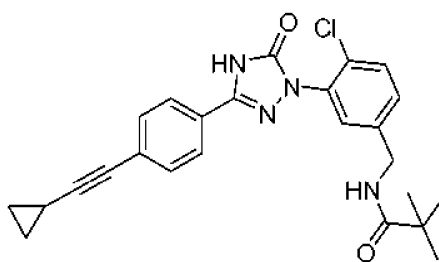
N-(4-Chloro-3-(5-oxo-1-(4-(trifluorométhyle)phényl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)-2-méthylpropane-2-sulfonamide ;
N-(4-Chloro-3-(5-oxo-1-(4-(trifluorométhyle)phényl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)cyclobutanecarboxamide ;
5 *N*-(4-Chloro-3-(5-oxo-1-(4-(trifluorométhyle)phényl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)cyclopentanecarboxamide ;
N-((6-(Difluorométhyle)-5-(5-oxo-1-(4-(trifluorométhyle)phényl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyridin-3-yl)méthyle)pivalamide ;
10 *N*-((6-(Difluorométhyle)-5-(5-oxo-1-(4-(trifluorométhyle)phényl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyridin-3-yl)méthyle)isobutyramide ;
N-((6-(Difluorométhyle)-5-(5-oxo-1-(4-(trifluorométhyle)phényl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyridin-3-yl)méthyle)propane-2-sulfonamide ;
N-((6-(Difluorométhyle)-5-(5-oxo-1-(4-(trifluorométhyle)phényl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyridin-3-yl)méthyle)cyclobutanecarboxamide ;
15 *N*-(4-Chloro-3-(3-(4-(cyclopropyléthynyl)phényl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)-2,2,2-trifluoroacétamide ;
N-(4-Chloro-3-(3-(4-(cyclopropyléthynyl)phényl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)benzyl)-3-hydroxy-2,2-diméthylpropanamide ;
20 3-Fluoro-*N*-((6-(difluorométhyle)-5-(1-(4-(trifluorométhyle)phényl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)pyridin-3-yl)méthyle)-2,2-diméthylpropanamide ;
et leurs sels pharmaceutiquement acceptables.

13. Composé selon la revendication 1, de formule



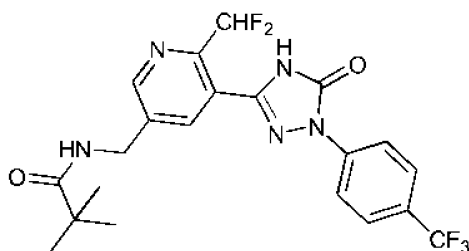
ou un sel associé pharmaceutiquement acceptable.

14. Composé selon la revendication 1, de formule



ou un sel associé pharmaceutiquement acceptable.

15. Composé selon la revendication 1, de formule



ou un sel associé pharmaceutiquement acceptable.

16. Composé selon la revendication 1, choisi parmi

N-(4-Chloro-3-(5-oxo-1-(4-(trifluorométhyle)phényl)-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)benzyl)-2,2,2-trifluoroacétamide ;
N-(4-Chloro-3-(4,5-dihydro-3-(4-iodophényl)-5-oxo-1,2,4-triazol-1-yl)benzyl)pivalamide ;
 et sels pharmaceutiquement acceptables associés.

17. Composition pharmaceutique comprenant un composé selon l'une quelconque des revendications 1 à 15 et un excipient pharmaceutiquement acceptable.

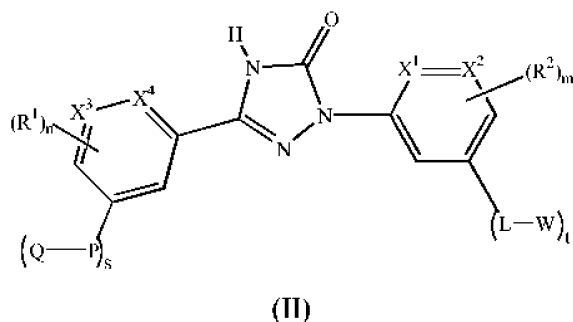
18. Composition pharmaceutique selon la revendication 17, l'excipient pharmaceutiquement acceptable étant un entraîneur ou un diluant.

19. Composé selon l'une quelconque des revendications 1 à 15, destiné à être utilisé dans la prévention ou le traitement d'une maladie, d'un trouble ou d'un syndrome médié par mPGES-1 chez un sujet.

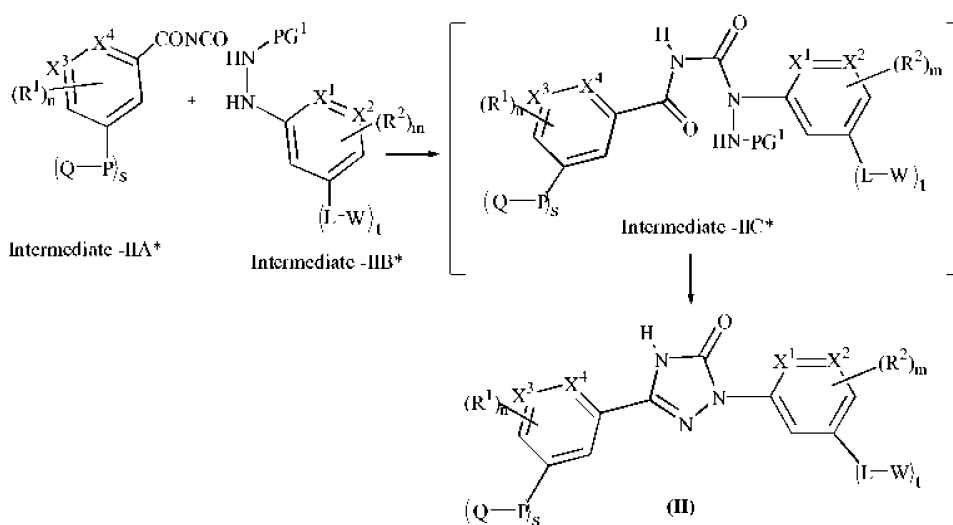
20. Composé selon l'une quelconque des revendications 1 à 15, destiné à être utilisé dans la prévention ou le traitement de maladies, troubles, syndromes ou conditions choisis dans le groupe constitué par inflammation, asthme, bronchopneumopathie chronique obstructive, fibrose pulmonaire, maladie inflammatoire de l'intestin, syndrome du côlon irritable, douleur, douleur inflammatoire, douleur chronique, douleur aiguë, fièvre, migraine, maux de tête, lombalgie, fibromyalgie, troubles myofasciaux, infections virales, grippe, rhume, zona, hépatite C, SIDA, infections bactériennes, infections fongiques, dysménorrhée, brûlures, procédures chirurgicales ou dentaires, syndrome d'hyperprostaglandine E à tumeurs malignes, syndrome de Bartter classique, synovite, athérosclérose, goutte, arthrite, arthrose, arthrite juvénile, polyarthrite rhumatoïde, arthrite rhumatoïde juvénile, fièvre rhumatismale aiguë, spondylarthrite ankylosante, maladie de Hodgkin, lupus érythémateux disséminé, vascularite, pancréatite, néphrite, bursite, conjonctivite, iritis, sclérite, uvéite, cicatrisation des plaies, dermatite, eczéma, psoriasis, accident vasculaire cérébral, diabète sucré, cancer, maladies neurodégénératives telles que maladie d'Alzheimer, maladie de Parkinson, sclérose latérale amyotrophique et sclérose en plaques, maladies auto-immunes, troubles allergiques, rhinite, ulcères, colite ulcéreuse légèrement à moyennement active, polypose adénomateuse familiale, maladie coronarienne et sarcoïdose.

21. Composé selon l'une quelconque des revendications 1 à 15, destiné à être utilisé dans la prévention ou le traitement d'une maladie, d'un trouble, d'un syndrome ou d'une condition, la maladie, le trouble, le syndrome ou la condition étant une douleur, une douleur chronique, une douleur aiguë, une douleur arthritique rhumatoïde ou une douleur arthrosique.

22. Procédé de préparation d'un composé de formule (II) selon la revendication 1



ou d'un sel pharmaceutiquement acceptable associé, comprenant les étapes consistant à : faire réagir un composé de formule (Intermediate-IIA*) avec un composé de formule (Intermediate-IIB*) pour former un composé de formule (Intermediate-IIC*) ; et convertir le composé de formule (Intermediate-IIC*) en un composé de formule (II) :



X¹, X², X³ et X⁴ étant chacun indépendamment choisi parmi CH et N ;

chaque occurrence de L étant indépendamment choisie parmi -CH₂NHC(O)- et -CH₂NHS(O)₂- ;

chaque occurrence de P étant indépendamment choisie parmi -CH₂NHC(O)- et -CH₂NHS(O)₂- ;

chaque occurrence de Q étant indépendamment choisie parmi C₁₋₈alkyle, haloC₁₋₈alkyle, C₁₋₈alkoxyC₁₋₈alkyle, hydroxyC₁₋₈alkyle, carboxyleC₁₋₈alkyle, C₃₋₁₂cycloalkyle, C₆₋₁₄aryle, hétérocyclyle à 3-15 chaînons, et hétéroaryle à 5-14 chaînons ;

chaque occurrence de W étant indépendamment choisie parmi isopropyle, *tert*-butyle, trifluorométhyle, 1-fluoro-2-méthylpropan-2-yl, 1-hydroxy-2-méthylpropan-2-yl et cyclopropyle ;

chaque occurrence de R¹ étant sélectionnée choisie parmi halogène, cyano, C₁₋₈alkyle, C₁₋₈alkoxy, haloC₁₋₈alkoxyC₁₋₈alkyle, haloC₁₋₈alkyle, C₃₋₆cycloalkyle, hétérocyclyleC₁₋₈alkyle à 5 chaînons, hétéroaryle à 5 chaînons, hétéroaryle₁₋₈alkyle à 5 chaînons, et -C≡CR ;

chaque occurrence de R² étant indépendamment choisie parmi halogène, cyano, C₁₋₈alkyle, C₁₋₈alkoxy, haloC₁₋₈alkyle, C₃₋₆cycloalkyle, hétéroaryle à 5 chaînons, -C(O)NHR, -NHC(O)R, S(O)₂NHR et -C≡CR ;

chaque occurrence de R étant indépendamment choisie parmi C₁₋₈alkyle, C₃₋₁₂cycloalkyle et C₆₋₁₄aryle ;

PG¹ représentant un groupe protecteur d'amine ;

m étant un entier compris entre 0 et 3, tous deux inclus ;

n étant un entier compris entre 0 et 3, tous deux inclus ;

s étant un entier compris entre 0 et 1, tous deux inclus ; et

t étant un entier compris entre 0 et 1, tous deux inclus ;

à condition que (i) s et t ne soient pas 0 simultanément, et (ii) m et n ne soient pas 0 simultanément.

23. Procédé selon la revendication 22, l'isocyanate de formule (Intermediate-IIA*) étant obtenu à partir de l'acide, amide ou dérivé d'halogénure d'acide correspondant.

EP 2 718 284 B1

24. Procédé selon la revendication 22, un composé de formule (Intermediate IA*) réagissant avec un composé de formule (Intermediate dIB*) dans du DEM, toluène ou EDE.
25. Procédé selon la revendication 22, Intermediate-IIC* n'étant pas isolée
26. Le procédé selon la revendication 22, PG¹ étant du *tert*-butoxycarbonyle.
27. Procédé selon la revendication 22, un composé de formule (Intermediate-IIC*) étant converti en composé de formule (II) à l'aide d'un acide organique.

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- GB 1068083 A [0011]
- WO 2006063466 A [0011]
- WO 2007059610 A [0011]
- WO 2010034796 A [0011]
- WO 2010100249 A [0011]
- WO 2012055995 A [0011]
- WO 2012110860 A [0011]
- WO 2013038308 A [0011]

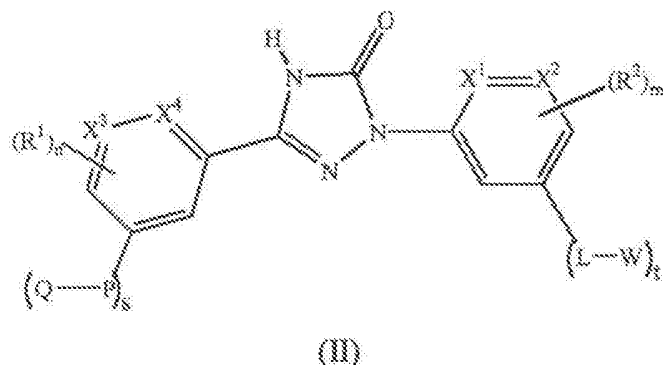
Non-patent literature cited in the description

- **KOJIMA.** *The Journal of Immunology*, 2008, vol. 180, 8361-6 [0007]
- **XU.** *The Journal of Pharmacology and Experimental Therapeutics*, 2008, vol. 326, 754-63 [0007]
- **WANG.** *Circulation*, 2008, vol. 117, 1302-1309 [0007]
- **NAKANISHI.** *Cancer Research*, 2008, vol. 68 (9), 3251-9 [0008]
- **SCHRODER.** *Journal of Lipid Research*, 2006, vol. 47, 1071-80 [0008]
- **KOROTKOVA.** *Annals of the Rheumatic Diseases*. 2008, vol. 67, 1596-1602 [0009]
- **GOMEZ-HERNANDEZ.** *Atherosclerosis*, 2006, vol. 187, 139-49 [0010]
- **WANG.** *Proceedings of National Academy of Sciences*, 2006, vol. 103 (39), 14507-12 [0010]
- Remington: The Science and Practice of Pharmacy. Lippincott Williams & Wilkins, 2003 [0131]
- **OUELLET M et al.** *Protein Expression and Purification*, 2002, vol. 26, 489-495 [1045]
- **MASSE F et al.** *Journal of Biomolecular Screening*, 2005, vol. 10 (6), 599-605 [1045]
- **GOEDKEN RE et al.** *Journal of Biomolecular Screening*, 2008, vol. 13 (7), 619-625 [1045]

TRIAZOLON VEGYÜLETEK MPGES-1 INHIBITOROKKÉNT

Szabadalmi igénypontok

1. A következő (II) általános képletű vegyület:



vagy annak egy gyógyszerészetileg elfogadható sója,
ahol,

X^1 , X^2 , X^3 és X^4 közül mindegyik jelentése egymástól függetlenül a következők közül van választva: CH és N;

L jelentése minden esetben egymástól függetlenül a következők közül van választva: $-CH_2NHC(O)-$ és $-CH_2NHS(O)_2-$;

P jelentése minden esetben egymástól függetlenül a következők közül van választva: $-CH_2NHC(O)-$ és $-CH_2NHS(O)_2-$;

Q jelentése minden esetben egymástól függetlenül a következők közül van választva: C_{1-8} -alkil, halogén- C_{1-8} -alkil, C_{1-8} -alkoxi- C_{1-8} -alkil, hidroxil- C_{1-8} -alkil, karboxil- C_{1-8} -alkil, C_{3-12} -cikloalkil, C_{6-14} -aril, 3-15 tagú heterociklil és 5-14 tagú heteroaril;

W jelentése minden esetben egymástól függetlenül a következők közül van választva: izopropil, *tert*-butil, trifluor-metil, 1-fluor-2-metil-propán-2-il, 1-hidroxil-2-metil-propán-2-il és ciklopropil;

R^1 jelentése minden esetben egymástól függetlenül a következők közül van választva: halogén, ciano, C_{1-8} -alkil, C_{1-8} -alkoxi, halogén- C_{1-8} -alkoxi- C_{1-8} -alkil, halogén- C_{1-8} -alkil, C_{3-6} -cikloalkil, 5 tagú heterociklil- C_{1-8} -alkil, 5 tagú heteroaril, 5 tagú heteroaril- C_{1-8} -alkil és $-C\equiv CR$;

R^2 jelentése minden esetben egymástól függetlenül a következők közül van választva: halogén, ciano, C_{1-8} -alkil, C_{1-8} -alkoxi, halogén- C_{1-8} -alkil, C_{3-6} -cikloalkil, 5 tagú heteroaril, $-C(O)NHR$, $-NHC(O)R$, $-S(O)_2NHR$ és $-C\equiv CR$;

R jelentése minden esetben egymástól függetlenül a következők közül van választva: C_{1-8} -alkil, C_{3-12} -cikloalkil és C_{6-14} -aril;

'm' jelentése egy egész szám, amely 0-tól 3-ig terjed, mindkét értéket beleértve;

'n' jelentése egy egész szám, amely 0-tól 3-ig terjed, mindkét értéket beleértve;

's' jelentése egy egész szám, amely 0-tól 1-ig terjed, mindkét értéket beleértve; és

't' jelentése egy egész szám, amely 0-tól 1-ig terjed, mindkét értéket beleértve;

azokkal a feltételekkel, hogy (i) 's' és 't' értéke egyidejűleg nem '0', és (ii) 'm' és 'n' értéke egyidejűleg nem '0'.

2. Vegyület az 1. igénypont szerint, ahol X^1 , X^2 , X^3 és X^4 jelentése CH.

3. Vegyület az 1. vagy 2. igénypont szerint, ahol

R^1 jelentése minden esetben egymástól függetlenül ciano, Cl, F, CHF_2 , CF_3 , OCH_3 , CH_3 , (2,2,2-trifluor-etoxi)metil, ciklopropil, (pirrolidin-1-il)metil, 4-metil-tiofenil, 5-izopropil-1,3,4-oxadiazol-2-il, (3,5-dimetil-1H-pirazol-1-il)metil, 3,3-dimetil-but-1-inil, 2-ciklopropil-etinil, (2,5-diklór-fenil)etinil, (4-klór-2-fluor-fenil)etinil, (3-klór-2-fluor-fenil)etinil, (3-(trifluor-metil)fenil)etinil vagy (2-klór-4-(trifluor-metil)fenil)etinil; és
'n' értéke 1 vagy 2.

4. Vegyület az 1.-től 3.-ig igénypontok bármelyike szerint, ahol

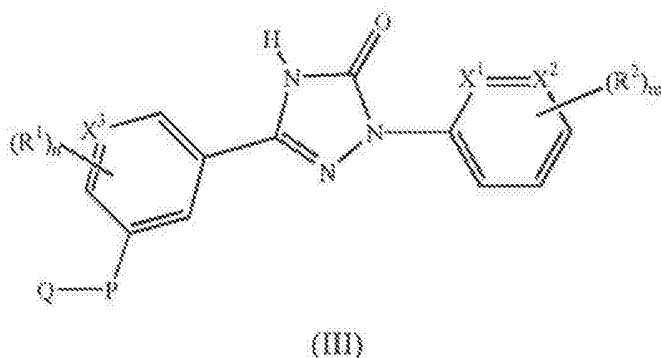
R^2 jelentése minden esetben egymástól függetlenül ciano, Cl, F, CH_3 , CF_3 , OCH_3 , 3-(4-klór-fenil)-1,2,4-oxadiazol-5-il, ciklopropán-karboxamido, 3,3-dimetil-but-1-inil, 2-ciklopropil-etinil, -CONH-[3-(trifluor-metil)fenil], -CONH-[3-(difluor-metil)-4-fluor-fenil] vagy -CONH-[3-(difluor-metil)fenil]; és
'm' értéke 1 vagy 2.

5. Vegyület az 1.-től 4.-ig igénypontok bármelyike szerint, ahol

Q jelentése izopropil, *tert*-butil, trifluor-metil, 1-fluor-2-metil-propán-2-il, 1-metoxi-2-metil-propán-2-il, 1-hidroxi-2-metil-propán-2-il, ciklopropil, ciklobutil, ciklopentil, 2-fluor-fenil, tetrahydrofuranil, tetrahydrofuranil, tetrahydrofuran-2-il, (S)-tetrahydrofuran-2-il, (R)-tetrahydrofuran-2-il, izoxazolil vagy 1-metil-1H-imidazol-2-il;
's' értéke 1; és 't' értéke 0.

6. Vegyület az 1.-től 5.-ig igénypontok bármelyike szerint, ahol 't' értéke 1; és 's' értéke 0.

7. Vegyület az 1. igénypont szerint, amely a következő (III) általános képletű:



vagy annak egy gyógyszerészetileg elfogadható sója,

ahol,

X^1 , X^2 , és X^3 közül mindegyik jelentése egymástól függetlenül a következők közül van választva: CH és N;

P jelentése a következők közül van választva: $-\text{CH}_2\text{NHC(O)}-$ és $-\text{CH}_2\text{NHS(O)}_2-$;

Q jelentése a következők közül van választva: C_{1-8} -alkil, halogén- C_{1-8} -alkil, C_{1-8} -alkoxi- C_{1-8} -alkil, hidroxi- C_{1-8} -alkil, karboxil- C_{1-8} -alkil, C_{3-12} -cikloalkil, C_{6-14} -aril, 3-15 tagú heterociklil és 5-14 tagú heteroaril;

R^1 jelentése minden esetben egymástól függetlenül a következők közül van választva: halogén, ciano, C_{1-8} -alkil, C_{1-8} -alkoxi, halogén- C_{1-8} -alkil és C_{3-6} -cikloalkil;

R^2 jelentése minden esetben egymástól függetlenül a következők közül van választva: halogén, ciano, C_{1-8} -alkil, C_{1-8} -alkoxi, halogén- C_{1-8} -alkil, C_{3-6} -cikloalkil, 5 tagú heteroaril, $-\text{C(O)NHR}$, $-\text{NHC(O)R}$, $-\text{S(O)}_2\text{NHR}$ és $-\text{C}\equiv\text{CR}$;

R jelentése minden esetben egymástól függetlenül a következők közül van választva: C_{1-8} -alkil, C_{3-12} -cikloalkil és C_{6-14} -aril;

'm' jelentése egy egész szám, amely 0-tól 3-ig terjed, mindkét értéket beleértve; és

'n' jelentése egy egész szám, amely 0-tól 3-ig terjed, mindkét értéket beleértve;

azzal a feltétellel, hogy 'm' és 'n' értéke egyidejűleg nem '0'.

8. Vegyület a 7. igénypont szerint, ahol X^1 , X^2 és X^3 jelentése CH.

9. Vegyület a 7. vagy 8. igénypont szerint, ahol

mindegyik R^1 jelentése, egymástól függetlenül, ciano, Cl, F, CHF_2 , CF_3 , OCH_3 , CH_3 vagy ciklopropil;

mindegyik R^2 jelentése, egymástól függetlenül, ciano, Cl, F, CH_3 , CF_3 , vagy OCH_3 ;

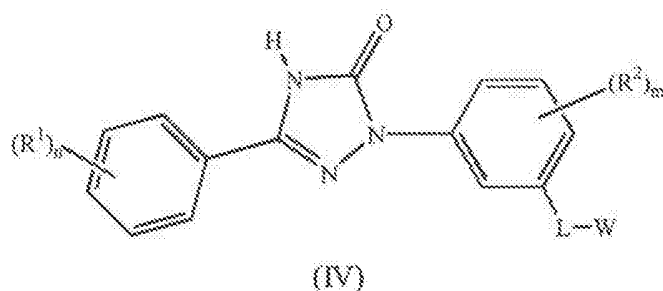
P jelentése $-CH_2NHC(O)-$;

'm' értéke 1 vagy 2;

'n' értéke 0, 1 vagy 2; és

Q jelentése izopropil, *tert*-butil, trifluor-metil, 1-fluor-2-metil-propán-2-il, 1-metoxi-2-metil-propán-2-il, 1-hidroxi-2-metil-propán-2-il, ciklopropil, ciklobutil, ciklopentil, 2-fluor-fenil, tetrahidrofuranil, tetrahidrofuranil, tetrahidrofuran-2-il, (S)-tetrahidrofuran-2-il, (R)-tetrahidrofuran-2-il, izoxazolil vagy 1-metil-1H-imidazol-2-il.

10. Vegyület az 1. igénypont szerint, amely a következő (IV) általános képletű:



vagy annak egy gyógyszerészetileg elfogadható sója,

ahol,

L jelentése a következők közül van választva: $-CH_2NHC(O)-$ és $-CH_2NHS(O)_2-$;

W jelentése a következők közül van választva: izopropil, *tert*-butil, trifluor-metil, 1-fluor-2-metil-propán-2-il, 1-hidroxi-2-metil-propán-2-il és ciklopropil;

R^1 jelentése minden esetben egymástól függetlenül a következők közül van választva: halogén, ciano, C_{1-8} -alkil, C_{1-8} -alkoxi, halogén- C_{1-8} -alkoxi- C_{1-8} -alkil, halogén- C_{1-8} -alkil, C_{3-6} -cikloalkil, 5 tagú heterociklik- C_{1-8} -alkil, 5 tagú heteroaril, 5 tagú heteroaril- C_{1-8} -alkil és $-C\equiv CR$;

R^2 jelentése minden esetben egymástól függetlenül a következők közül van választva: halogén, ciano, C_{1-8} -alkil, C_{1-8} -alkoxi és halogén- C_{1-8} -alkil;

R jelentése minden esetben egymástól függetlenül a következők közül van választva: C_{1-8} -alkil, C_{3-12} -cikloalkil és C_{6-14} -aril;

'm' jelentése egy egész szám, amely 0-tól 3-ig terjed, mindkét értéket beleértve; és

'n' jelentése egy egész szám, amely 0-tól 3-ig terjed, mindkét értéket beleértve;

azzal a feltétellel, hogy 'm' és 'n' értéke egyidejűleg nem '0'.

11. Vegyület a 10. igénypont szerint, ahol

R^1 jelentése minden esetben egymástól függetlenül Cl, F, CHF_2 , CF_3 , OCH_3 , CH_3 , 3,3-dimetil-but-1-inil, 2-ciklopropil-etinil, (2,5-diklór-fenil)etinil, (4-klór-2-fluor-fenil)etinil, 3-klór-2-fluor-fenil)etinil, 3-(trifluor-metil)fenil)etinil vagy 2-klór-4-(trifluor-metil)fenil)etinil;

R^2 jelentése minden esetben egymástól függetlenül Cl, F, CH_3 , CF_3 , vagy OCH_3 ;

L jelentése $-\text{CH}_2\text{NHC(O)}-$;

'm' értéke 1 vagy 2;

'n' értéke 0, 1 vagy 2; és

W jelentése izopropil, *tert*-butil, trifluor-metil, 1-fluor-2-metil-propán-2-il, 1-hidroxi-2-metil-propán-2-il vagy ciklopropil.

12. Vegyület az 1. igénypont szerint, amely a következők közül van választva:

- 4-(3-(2-Klór-5-(ciklopropán-karboxamido-metil)fenil)-5-oxo-4,5-dihidro-1*H*-1,2,4-triazol-1-il)-2-metoxi-*N*-(3-(trifluor-metil)fenil)benzamid;
- N*-(4-Klór-3-(1-(4-(3-(4-klór-fenil)-1,2,4-oxadiazol-5-il)-3-metoxi-fenil)-5-oxo-4,5-dihidro-1*H*-1,2,4-triazol-3-il)benzil)ciklopropán-karboxamid;
- 4-(3-(2-Klór-5-(ciklopropán-karboxamido-metil)fenil)-5-oxo-4,5-dihidro-1*H*-1,2,4-triazol-1-il)-*N*-(3-(difluor-metil)-4-fluor-fenil)-2-metoxi-benzamid;
- N*-(4-Klór-3-(1-(4-(ciklopropán-karboxamido)-3-metoxi-fenil)-5-oxo-4,5-dihidro-1*H*-1,2,4-triazol-3-il)benzil)ciklopropán-karboxamid;
- 4-(3-(2-Klór-5-(ciklopropán-karboxamido-metil)fenil)-5-oxo-4,5-dihidro-1*H*-1,2,4-triazol-1-il)-*N*-(3-(difluor-metil)fenil)-2-metoxi-benzamid;
- 4-(3-(2-Klór-5-(ciklopropán-karboxamido-metil)fenil)-5-oxo-4,5-dihidro-1*H*-1,2,4-triazol-1-il)-*N*-(3-(trifluor-metil)fenil)benzamid;
- N*-(4-Klór-3-(3-(4-((2,5-diklór-fenil)etinil)-2-fluor-fenil)-5-oxo-4,5-dihidro-1*H*-1,2,4-triazol-1-il)benzil)ciklopropán-karboxamid;
- N*-(4-Klór-3-(3-(4-((4-klór-2-fluor-fenil)etinil)-2-fluor-fenil)-5-oxo-4,5-dihidro-1*H*-1,2,4-triazol-1-il)benzil)ciklopropán-karboxamid;
- N*-(4-Klór-3-(3-(2-fluor-4-((3-(trifluor-metil)fenil)etinil)fenil)-5-oxo-4,5-dihidro-1*H*-1,2,4-triazol-1-il)benzil)ciklopropán-karboxamid;
- N*-(4-Klór-3-(3-(4-((3-klór-2-fluor-fenil)etinil)-2-fluor-fenil)-5-oxo-4,5-dihidro-1*H*-1,2,4-triazol-1-il)benzil)ciklopropán-karboxamid;
- N*-(4-klór-3-(3-(4-((2-klór-4-(trifluor-metil)fenil)etinil)-2-fluor-fenil)-5-oxo-4,5-dihidro-1*H*-1,2,4-triazol-1-il)benzil)ciklopropán-karboxamid;
- N*-(4-Klór-3-(1-(3,4-diklór-fenil)-5-oxo-4,5-dihidro-1*H*-1,2,4-triazol-3-il)-2-fluor-benzil)pivalamid;
- N*-(4-Klór-2-fluor-3-(5-oxo-1-(4-(trifluor-metil)fenil)-4,5-dihidro-1*H*-1,2,4-triazol-3-il)benzil)pivalamid;
- N*-(4-Klór-3-(1-(2,4-difluor-fenil)-5-oxo-4,5-dihidro-1*H*-1,2,4-triazol-3-il)-2-fluor-benzil)pivalamid;
- N*-(4-Klór-2-fluor-3-(1-(4-metoxi-fenil)-5-oxo-4,5-dihidro-1*H*-1,2,4-triazol-3-il)benzil)pivalamid;
- N*-(4-Klór-2-fluor-3-(3-(2-fluor-4-(trifluor-metil)fenil)-5-oxo-4,5-dihidro-1*H*-1,2,4-triazol-1-il)benzil)pivalamid;
- N*-(4-Klór-3-(3-(2-klór-6-fluor-fenil)-5-oxo-4,5-dihidro-1*H*-1,2,4-triazol-1-il)-2-fluor-benzil)pivalamid;
- N*-(4-Klór-3-(1-(4-ciano-fenil)-5-oxo-4,5-dihidro-1*H*-1,2,4-triazol-3-il)-2-fluor-benzil)pivalamid;

N-(4-Klór-3-(3-(4-klór-2-fluor-fenil)-5-oxo-4,5-dihidro-1*H*-1,2,4-triazol-1-il)-2-fluor-benzil)pivalamid;
N-(4-Klór-3-(3-(4-klór-2-fluor-fenil)-5-oxo-4,5-dihidro-1*H*-1,2,4-triazol-1-il)benzil)ciklopropán-karboxamid;
N-(4-Klór-3-(3-(2-fluor-4-(trifluor-metil)fenil)-5-oxo-4,5-dihidro-1*H*-1,2,4-triazol-1-il)benzil)ciklopropán-karboxamid;
N-(4-Klór-2-fluor-3-(5-oxo-3-(4-(trifluor-metil)fenil)-4,5-dihidro-1*H*-1,2,4-triazol-1-il)benzil)pivalamid;
N-(4-Klór-2-fluor-3-(5-oxo-1-(5-(trifluor-metil)piridin-2-il)-4,5-dihidro-1*H*-1,2,4-triazol-3-il)benzil)pivalamid;
N-(4-Klór-2-fluor-3-(5-oxo-1-(6-(trifluor-metil)piridin-3-il)-4,5-dihidro-1*H*-1,2,4-triazol-3-il)benzil)pivalamid;
N-(4-Klór-3-(1-(4-klór-fenil)-5-oxo-4,5-dihidro-1*H*-1,2,4-triazol-3-il)-2-fluor-benzil)pivalamid;
N-(4-Klór-3-(5-oxo-1-(4-(trifluor-metil)fenil)-4,5-dihidro-1*H*-1,2,4-triazol-3-il)benzil)-2,2,2-trifluor-acetamid;
N-(4-Klór-3-(5-oxo-1-(4-(trifluor-metil)fenil)-4,5-dihidro-1*H*-1,2,4-triazol-3-il)benzil)pivalamid;
(R)-*N*-(4-Klór-3-(5-oxo-1-(4-(trifluor-metil)fenil)-4,5-dihidro-1*H*-1,2,4-triazol-3-il)benzil)tetrahydrofuran-2-karboxamid;
N-(4-Klór-3-(5-oxo-1-(4-(trifluor-metil)fenil)-4,5-dihidro-1*H*-1,2,4-triazol-3-il)benzil)ciklopropán-szulfonamid;
N-(4-Klór-3-(5-oxo-1-(4-(trifluor-metil)fenil)-4,5-dihidro-1*H*-1,2,4-triazol-3-il)benzil)-2-fluor-benzamid;
N-(4-Klór-3-(5-oxo-1-(4-(trifluor-metil)fenil)-4,5-dihidro-1*H*-1,2,4-triazol-3-il)benzil)izoxazol-5-karboxamid;
N-(3-(1-(4-(Trifluor-metil)fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)-2,4-dimetil-benzil)-2,2,2-trifluor-acetamid;
(R)-*N*-(2,4-Dimetil-3-(5-oxo-1-(4-(trifluor-metil)fenil)-4,5-dihidro-1*H*-1,2,4-triazol-3-il)benzil)tetrahydrofuran-2-karboxamid;
N-(3-(1-(4-(Trifluor-metil)fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)-2,4-dimetil-benzil)pivalamid;
(S)-*N*-(4-Klór-3-(1-(4-(trifluor-metil)fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)benzil)-tetrahydrofuran-2-karboxamid;
N-(4-Klór-3-(1-(4-(trifluor-metil)fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)benzil)-1-metil-1*H*-imidazol-2-karboxamid;
N-(4-Klór-2-fluor-3-(4,5-dihidro-3-(4-(3,3-dimetil-but-1-inil)fenil)-5-oxo-1,2,4-triazol-1-il)benzil)pivalamid;
N-(4-Klór-3-(3-(4-(2-ciklopropil-etinil)fenil)-4,5-dihidro-5-oxo-1,2,4-triazol-1-il)-2-fluor-benzil)pivalamid;
N-(4-Klór-2-fluor-5-(1-(4-(trifluor-metil)fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)benzil)-2,2,2-trifluor-acetamid;
N-(4-Klór-2-fluor-5-(1-(4-(trifluor-metil)fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)benzil)pivalamid;
N-(4-Klór-3-(1-(4-(trifluor-metil)fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)benzil)-3-hidroxí-2,2-dimetil-propánamid;
N-(4-Klór-3-(1-(4-klór-3-fluor-fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)benzil)-2,2,2-trifluor-acetamid;
(R)-*N*-(4-Klór-2-fluor-5-(5-oxo-1-(4-(trifluor-metil)fenil)-4,5-dihidro-1*H*-1,2,4-triazol-3-il)benzil)tetrahydrofuran-2-karboxamid;

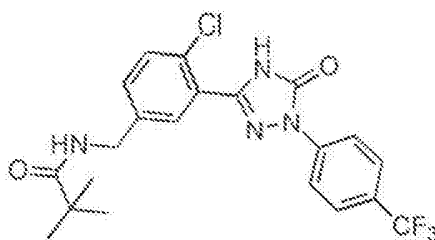
N-(4-Klór-3-(1-(4-(trifluor-metil)fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)benzil)-3-metoxi-2,2-dimetil-propánamid;
N-(4-Klór-3-(1-(4-klór-3-fluor-fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)benzil)pivalamid;
N-(4-Klór-5-(1-(4-klór-fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)-2-fluor-benzil)pivalamid;
N-(4-Klór-5-(1-(4-(trifluor-metil)fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)-2-metoxi-benzil)pivalamid;
N-(4-Klór-2-fluor-5-(1-(4-fluor-3-(trifluor-metil)fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)benzil)pivalamid;
N-(4-Klór-2-fluor-5-(1-(6-(trifluor-metil)piridin-3-il)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)benzil)pivalamid;
N-(2,4-Diklór-5-(3-(4-(2-ciklopropil-etinil)fenil)-4,5-dihidro-5-oxo-1,2,4-triazol-1-il)benzil)pivalamid;
N-(4-Klór-5-(1-(3-klór-4-fluor-fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)-2-fluor-benzil)pivalamid;
N-(4-Klór-5-(1-(4-klór-fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)-2-fluor-benzil)-2-fluor-benzamid;
N-(4-Klór-2-fluor-5-(1-(4-(trifluor-metil)fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)benzil)izobutiramid;
N-(4-Klór-5-(1-(4-klór-fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)-2-fluor-benzil)-3-fluor-2,2-dimetil-propánamid;
N-(4-Klór-5-(1-(3-klór-4-metil-fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)-2-fluor-benzil)pivalamid;
N-(4-Klór-5-(3-(4-(2-ciklopropil-etinil)fenil)-4,5-dihidro-5-oxo-1,2,4-triazol-1-il)-2-fluor-benzil)pivalamid;
N-(4-Klór-2-fluor-5-(4,5-dihidro-3-(4-(3,3-dimetil-but-1-inil)fenil)-5-oxo-1,2,4-triazol-1-il)benzil)pivalamid;
N-(4-Klór-3-(1-(6-(trifluor-metil)piridin-3-il)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)benzil)pivalamid;
N-(4-Klór-3-(1-(3-klór-4-fluor-fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)benzil)pivalamid;
N-(4-Klór-3-(1-(3-klór-4-metil-fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)benzil)pivalamid;
N-(4-Klór-3-(3-(4-(2-ciklopropil-etinil)fenil)-4,5-dihidro-5-oxo-1,2,4-triazol-1-il)benzil)pivalamid;
N-(4-Klór-3-(1-(3-(trifluor-metil)fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)benzil)pivalamid;
N-(4-Klór-3-(4,5-dihidro-3-(4-(3,3-dimetil-but-1-inil)fenil)-5-oxo-1,2,4-triazol-1-il)benzil)izobutiramid;
N-(4-Klór-3-(1-(4-(trifluor-metil)fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)benzil)izobutiramid;
N-(4-Klór-3-(3-(4-(trifluor-metil)fenil)-4,5-dihidro-5-oxo-1,2,4-triazol-1-il)benzil)pivalamid;
N-(4-Klór-3-(3-(3-fluor-4-(trifluor-metil)fenil)-4,5-dihidro-5-oxo-1,2,4-triazol-1-il)benzil)pivalamid;
N-(4-Klór-3-(3-(4-klór-3-(trifluor-metil)fenil)-4,5-dihidro-5-oxo-1,2,4-triazol-1-il)benzil)pivalamid;
N-(4-Klór-3-(3-(4-fluor-3-(trifluor-metil)fenil)-4,5-dihidro-5-oxo-1,2,4-triazol-1-il)benzil)pivalamid;

N-(4-Klór-3-(3-(3-fluor-4-(3,3-dimetil-but-1-inil)fenil)-4,5-dihidro-5-oxo-1,2,4-triazol-1-il)benzil)izobutiramid;
N-(4-Klór-3-(3-(4-(2-ciklopropil-etinil)-3-fluor-fenil)-4,5-dihidro-5-oxo-1,2,4-triazol-1-il)benzil)izobutiramid;
N-(4-Klór-3-(4,5-dihidro-5-oxo-3-(4-((pirrolidin-1-il)metil)fenil)-1,2,4-triazol-1-il)benzil)pivalamid;
N-(3-(3-(4-((2,2,2-Trifluor-etoxi)metil)fenil)-4,5-dihidro-5-oxo-1,2,4-triazol-1-il)-4-klór-benzil)pivalamid;
N-(4-Klór-3-(4,5-dihidro-3-(4-(5-izopropil-1,3,4-oxadiazol-2-il)fenil)-5-oxo-1,2,4-triazol-1-il)benzil)pivalamid;
N-(4-Klór-3-(1-(4-klór-3-metil-fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)benzil)pivalamid;
N-(4-Klór-3-(1-(4-klór-3-metil-fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)benzil)izobutiramid;
N-(4-Klór-3-(1-(3-fluor-5-(trifluor-metil)fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)benzil)pivalamid;
N-(4-Klór-3-(1-(4-klór-3-(trifluor-metil)fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)benzil)pivalamid;
N-(4-Klór-3-(1-(3-(trifluor-metil)-4-metil-fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)benzil)pivalamid;
N-(4-Klór-3-(1-(4-(trifluor-metil)-2-metil-fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)benzil)pivalamid;
N-(4-Klór-3-(1-(3-fluor-4-(trifluor-metil)fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)benzil)pivalamid;
N-(4-Klór-3-(1-(3-fluor-4-(trifluor-metil)fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)benzil)izobutiramid;
N-(4-Klór-3-{5-oxo-1-[4-(trifluor-metil)fenil]-4,5-dihidro-1*H*-1,2,4-triazol-3-il}benzil)propán-2-szulfonamid;
N-(4-Klór-3-(1-(2-fluor-4-(trifluor-metil)fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)benzil)pivalamid;
N-(3-(4,5-Dihidro-1-(4-(3,3-dimetil-but-1-inil)fenil)-5-oxo-1*H*-1,2,4-triazol-3-il)-2,4-dimetil-benzil)izobutiramid;
N-(3-(1-(4-(2-Ciklopropil-etinil)fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)-2,4-dimetil-benzil)pivalamid;
N-(4-Klór-3-(3-(4-(2-ciklopropil-etinil)-3-fluor-fenil)-4,5-dihidro-5-oxo-1,2,4-triazol-1-il)benzil)pivalamid;
N-(4-Klór-3-(1-(4-(2-ciklopropil-etinil)fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)benzil)pivalamid;
N-(4-Klór-3-(3-(4-(2-ciklopropil-etinil)-2-fluor-fenil)-4,5-dihidro-5-oxo-1,2,4-triazol-1-il)benzil)pivalamid;
N-(3-(1-(4-(2-Ciklopropil-etinil)fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)-2,4-dimetil-benzil)-3-fluor-2,2-dimetil-propánamid;
N-(3-(1-(3-Fluor-4-(3,3-dimetil-but-1-inil)fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)-2,4-dimetil-benzil)izobutiramid;
N-(4-Klór-3-(4,5-dihidro-3-(4-((3,5-dimetil-1*H*-pirazol-1-il)metil)fenil)-5-oxo-1,2,4-triazol-1-il)benzil)pivalamid;
N-(4-Klór-2-fluor-3-(1-(3-fluor-4-(trifluor-metil)fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)benzil)pivalamid;
N-(4-Klór-3-(1-(4-klór-3-(trifluor-metil)fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)-2-fluor-benzil)pivalamid;

N-(4-Klór-3-(1-(4-(trifluor-metil)fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)benzil)-3-fluor-2,2-dimetil-propánamid;
N-((6-Ciklopropil-5-(1-(4-(trifluor-metil)fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)piridin-3-il)metil)pivalamid;
N-(4-Klór-3-(1-(4-(2-ciklopropil-etinil)-2-fluor-fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)benzil)pivalamid;
N-(4-Klór-3-(5-oxo-1-(4-(trifluor-metil)fenil)-4,5-dihidro-1*H*-1,2,4-triazol-3-il)benzil)-2-metil-propán-2-szulfonamid;
N-(4-Klór-3-(5-oxo-1-(4-(trifluor-metil)fenil)-4,5-dihidro-1*H*-1,2,4-triazol-3-il)benzil)ciklobután-karboxamid;
N-(4-Klór-3-(5-oxo-1-(4-(trifluor-metil)fenil)-4,5-dihidro-1*H*-1,2,4-triazol-3-il)benzil)ciklopentán-karboxamid;
N-((6-(Difluor-metil)-5-(5-oxo-1-(4-(trifluor-metil)fenil)-4,5-dihidro-1*H*-1,2,4-triazol-3-il)piridin-3-il)metil)pivalamid;
N-((6-(Difluor-metil)-5-(5-oxo-1-(4-(trifluor-metil)fenil)-4,5-dihidro-1*H*-1,2,4-triazol-3-il)piridin-3-il)metil)izobutiramid;
N-((6-(Difluor-metil)-5-(5-oxo-1-(4-(trifluor-metil)fenil)-4,5-dihidro-1*H*-1,2,4-triazol-3-il)piridin-3-il)metil)propán-2-szulfonamid;
N-((6-(Difluor-metil)-5-(5-oxo-1-(4-(trifluor-metil)fenil)-4,5-dihidro-1*H*-1,2,4-triazol-3-il)piridin-3-il)metil)ciklobután-karboxamid;
N-(4-Klór-3-(3-(4-(ciklopropil-etinil)fenil)-5-oxo-4,5-dihidro-1*H*-1,2,4-triazol-1-il)benzil)-2,2,2-trifluor-acetamid;
N-(4-Klór-3-(3-(4-(ciklopropil-etinil)fenil)-5-oxo-4,5-dihidro-1*H*-1,2,4-triazol-1-il)benzil)-3-hidroxi-2,2-dimetil-propánamid;
 3-Fluor-*N*-((6-(difluor-metil)-5-(1-(4-(trifluor-metil)fenil)-4,5-dihidro-5-oxo-1*H*-1,2,4-triazol-3-il)piridin-3-il)metil)-2,2-dimetil-propánamid;

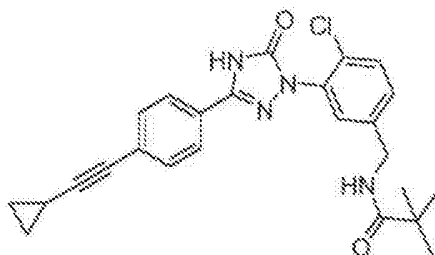
és azok gyógyszerészetileg elfogadható sói.

13. Vegyület az 1. igénypont szerint, amely a következő képletű:



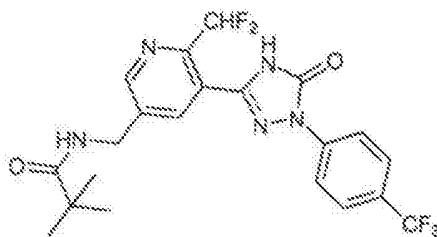
vagy annak egy gyógyszerészetileg elfogadható sója.

14. Vegyület az 1. igénypont szerint, amely a következő képletű:



vagy annak egy gyógyszerészetileg elfogadható sója.

15. Vegyület az 1. igénypont szerint, amely a következő képletű:



vagy annak egy gyógyszerészetileg elfogadható sója.

16. Vegyület az 1. igénypont szerint, amely a következők közül van választva:

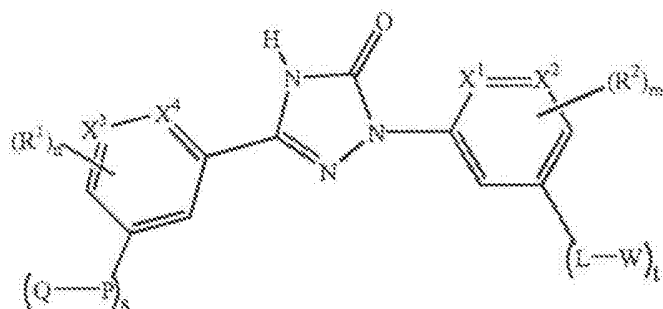
N-(4-Klór-3-(5-oxo-1-(4-(trifluorometil)fenil)-4,5-dihidro-1H-1,2,4-triazol-3-il)benzil)-2,2,2-trifluor-acetamid;

N-(4-Klór-3-(4,5-dihidro-3-(4-jód-fenil)-5-oxo-1,2,4-triazol-1-il)benzil)pivalamid;

és azok gyógyszerészetileg elfogadható sói.

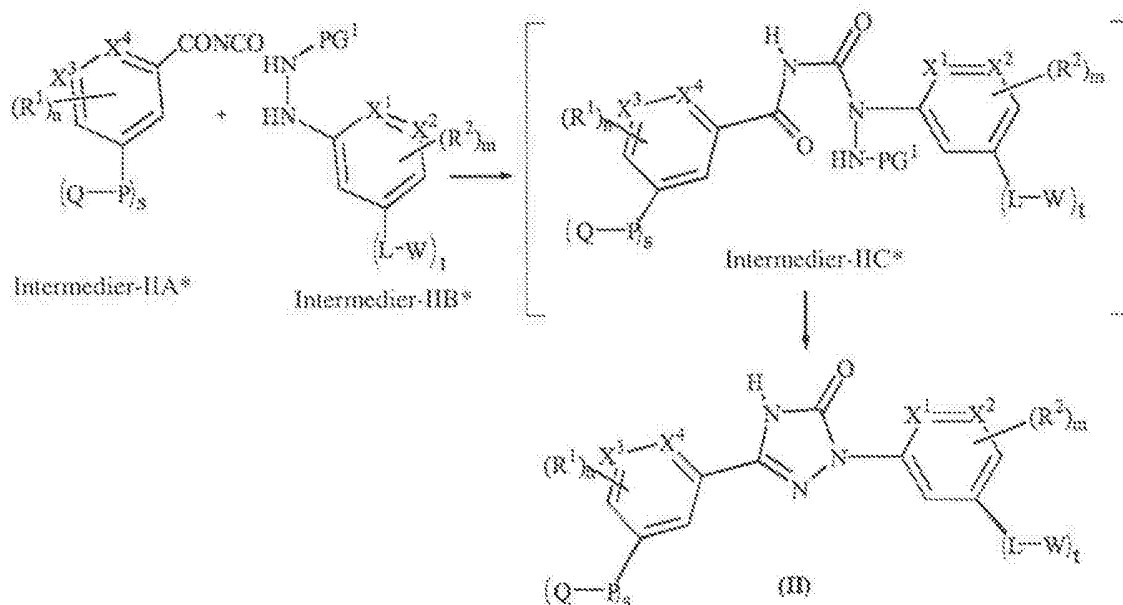
17. Gyógyszerészeti készítmény, amely tartalmaz egy az 1.-től 15.-ig igénypontok bármelyike szerinti vegyületet és egy gyógyszerészetileg elfogadható segédanyagot.
18. Gyógyszerészeti készítmény a 17. igénypont szerint, ahol a gyógyszerészetileg elfogadható segédanyag egy hordozó vagy hígító.
19. Vegyület az 1.-től 15.-ig igénypontok bármelyike szerint, alkalmazás céljából egy mPGES-1 által közvetített betegségnek, rendellenességnek vagy szindrómának a megelőzésében vagy kezelésében egy alanynál.
20. Vegyület az 1.-től 15.-ig igénypontok bármelyike szerint, alkalmazás céljából egy betegségnek, rendellenességnek, szindrómának vagy állapotnak a megelőzésében vagy kezelésében, amely a következőkből álló csoportból van választva: gyulladás, asztma, krónikus obstruktív tüdőbetegség, tüdőfibrozis, gyulladásos bélbetegség, irritábilis bél szindróma, fájdalom, gyulladásos fájdalom, krónikus fájdalom, akut fájdalom, láz, migrén, fejfájás, deréktáji fájdalom, fibromialgia, miofaszciális rendellenességek, vírusos fertőzések, influenza, nátha, herpesz zoster, hepatitisz C, AIDS, bakteriális fertőzések, gombás fertőzések, fájdalmas menstruáció (dysmenorrhea), égések, sebészeti vagy fogászati eljárások, malignitások, hiper-prosztaglandin E-szindróma, klasszikus Bartter-szindróma, szinovitisz, ateroszklerózis, köszvény, artritisz, oszteoarthritisz, juvenilis artritisz, reumatoid artritisz, juvenilis eredetű reumatoid artritisz, reumás láz, spondilitisz ankilopoetika (Bechterew-kór), Hodgkin-kór, szisztémás lupusz eritematózus, vaszkulitisz, hasnyálmirigy gyulladás (pankreatitisz), nefritisz, nyáktömlő gyulladás (burzitisz), kötőhártya gyulladás (konjunktivitisz), szívárványhártya gyulladás (iritisz), szkleritisz, uveagyulladás (uveitisz), sebgyógyulás, dermatitisz, ekcéma, pikkelysömör (pszoriázis), sztrók (stroke), diabétesz mellitusz, rák, neurodegeneratív rendellenességek, mint amilyen az Alzheimer-kór, Parkinson-kór, Amiotrófiás laterális szklerózis és szklerózis multiplex, autoimmun betegségek, allergiás rendellenességek, rinitisz, fekélyek, enyhétől mérsékeltig aktív ulceratív kolitisz, familiáris adenomatózus polipózis, szívkoszorúér betegség és szarkoidózis.
21. Vegyület az 1.-től 15.-ig igénypontok bármelyike szerint, alkalmazás céljából egy betegségnek, rendellenességnek, szindrómának vagy állapotnak a megelőzésében vagy kezelésében, ahol a betegség, rendellenesség, szindróma vagy állapot a következő: fájdalom, krónikus fájdalom, akut fájdalom, reumatoid artritisz általi fájdalom vagy oszteoarthritisz általi fájdalom.

22. Eljárás egy az 1. igénypont szerinti, következő (II) általános képletű vegyület előállítására:



(II)

vagy annak egy gyógyszerészetileg elfogadható sójának előállítására, amely eljárás magában foglalja a következőket: egy (Intermediér-IIA*) általános képletű vegyület reagáltatását egy (Intermediér-IIB*) általános képletű vegyülettel, hogy legyen kialakítva egy (Intermediér-IIC*) általános képletű vegyület; és az (Intermediér-IIC*) általános képletű vegyület konvertálása egy (II) általános képletű vegyületté:



ahol,

X^1 , X^2 , X^3 és X^4 közül mindegyik jelentése egymástól függetlenül a következők közül van választva: CH és N;

L jelentése minden esetben egymástól függetlenül a következők közül van választva: $-\text{CH}_2\text{NHC(O)}-$ és $-\text{CH}_2\text{NHS(O)}_2-$;

P jelentése minden esetben egymástól függetlenül a következők közül van választva: $-\text{CH}_2\text{NHC(O)}-$ és $-\text{CH}_2\text{NHS(O)}_2-$;

Q jelentése minden esetben egymástól függetlenül a következők közül van választva: C_{1-8} -alkil, halogén- C_{1-8} -alkil, C_{1-8} -alkoxi- C_{1-8} -alkil, hidrox- C_{1-8} -alkil, karboxil- C_{1-8} -alkil, C_{3-12} -cikloalkil, C_{6-14} -aril, 3-15 tagú heterociklil és 5-14 tagú heteroaril;

W jelentése minden esetben egymástól függetlenül a következők közül van választva: izopropil, *tert*-butil, trifluor-metil, 1-fluor-2-metil-propán-2-il, 1-hidrox-2-metil-propán-2-il és ciklopropil;

R^1 jelentése minden esetben egymástól függetlenül a következők közül van választva: halogén, ciano, C_{1-8} -alkil, C_{1-8} -alkoxi, halogén- C_{1-8} -alkoxi- C_{1-8} -alkil, halogén- C_{1-8} -alkil, C_{3-6} -cikloalkil, 5 tagú heterociklik- C_{1-8} -alkil, 5 tagú heteroaril, 5 tagú heteroaril- C_{1-8} -alkil és $-C\equiv CR$;

R^2 jelentése minden esetben egymástól függetlenül a következők közül van választva: halogén, ciano, C_{1-8} -alkil, C_{1-8} -alkoxi, halogén- C_{1-8} -alkil, C_{3-6} -cikloalkil, 5 tagú heteroaril, $-C(O)NHR$, $-NHC(O)R$, $-S(O)_2NHR$ és $-C\equiv CR$;

R jelentése minden esetben egymástól függetlenül a következők közül van választva: C_{1-8} -alkil, C_{3-12} -cikloalkil és C_{6-14} -aril;

PG^1 jelentése egy amin-védőcsoport;

'm' jelentése egy egész szám, amely 0-tól 3-ig terjed, mindkét értéket beleértve;

'n' jelentése egy egész szám, amely 0-tól 3-ig terjed, mindkét értéket beleértve;

's' jelentése egy egész szám, amely 0-tól 1-ig terjed, mindkét értéket beleértve; és

't' jelentése egy egész szám, amely 0-tól 1-ig terjed, mindkét értéket beleértve;

azokkal a feltételekkel, hogy (i) 's' és 't' értéke egyidejűleg nem '0', és (ii) hogy 'm' és 'n' értéke egyidejűleg nem '0'.

23. Eljárás a 22. igénypont szerint, ahol az (Intermedier-IIA*) általános képletű izocianát a megfelelő sav-, amid- vagy sav-halogenid-származékból van kapva.
24. Eljárás a 22. igénypont szerint, ahol egy (Intermedier-IIA*) általános képletű vegyület reagáltatva van egy (Intermedier-IIB*) általános képletű vegyülettel DCM-ben, toluolban vagy EDC-ben.
25. Eljárás a 22. igénypont szerint, ahol az Intermedier-IIC* nem izolált.
26. Eljárás a 22. igénypont szerint, ahol PG^1 jelentése *tert*-butoxi-karbonil.
27. Eljárás a 22. igénypont szerint, ahol egy (Intermedier-IIC*) általános képletű vegyület konvertálva van a (II) általános képletű vegyületté egy szerves sav alkalmazásával.