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(54) Title: 3-AZABICYCLO [3.1.0] HEXANE DERIVATIVES AS VANILLOID RECEPTOR LIGANDS

(57) Abstract: The present invention relates to 3-azabicyclo[3.1.0]hexane derivatives, which are useful as vanilloid receptor (VR) ligands, methods of treating diseases, conditions and/or disorders modulated by vanilloid receptors with them, and processes for preparing them.



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3-AZABICYCLO [3.1.0] HEXANE DERIVATIVES AS VANILLOID RECEPTOR LIGANDS

This application claims the benefit of Indian Application No. 125/MUM/2008, filed on January 17, 2008 and U.S. Provisional Application No. 61/025,042, filed on January 31, 2008, all of which are hereby incorporated by reference.

Field of the Invention

The present invention relates to 3-azabicyclo[3.1.0] hexane derivatives, which can be used as vanilloid receptor (VR) ligands, methods of treating diseases, conditions and/or disorders modulated by vanilloid receptors with them, and processes for preparing them.

Background of the Invention

Pain is the most common symptom for which patients seek medical advice and treatment. Pain can be acute or chronic. While acute pain is usually self-limiting, chronic pain 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 K. M. Foley, *Pain*, in "Cecil Textbook of Medicine", J. C. Bennett and F. Plum eds., 20th ed., (1996), 100-107. The sensation of pain can be triggered by stimuli including chemical, mechanical, thermal, and proton (pH <6) modalities. The sensory neurons which mediate the response to these harmful stimuli are known as "nociceptors". Nociceptors are primary sensory afferent neurons (C and A δ fibers) that are activated by a wide variety of noxious stimuli as above.

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. There is a large body of evidence relating activity at vanilloid receptors (VR1) to pain processing. (V. Di Marzo *et al.*, *Current Opinion in Neurobiology.*, (2002), 12, 372-379).

The lipophilic vanilloid, Capsaicin (8-methyl-N-vanillyl-6-nonenamides) is known to stimulate pain pathways through the release of a variety of sensory afferent neurotransmitters via a specific cell surface capsaicin receptor, cloned as the first vanilloid receptor (VR1 now known as TRPV1) Caterina MJ, *et.al.*, *Science.*, (2000), 288, (5464): 306-13.). Capsaicin is the main pungent component in hot pepper. Hot pepper has been used historically not only as a spice, but also as a traditional medicine in the treatment of gastric disorders orally, and

applied locally for the relief of pain and inflammation. CAP has a wide spectrum of biological actions and not only exhibits effects on the cardiovascular and respiratory systems, but also induces pain and irritancy on local application. CAP, however, after such induction of pain induces desensitization, both to CAP itself and also to other noxious stimuli, thereby stopping the pain. The intradermal administration of capsaicin is characterized by an initial burning or hot sensation followed by a prolonged period of analgesia. The analgesic component of VR1 receptor activation is thought to be mediated by a capsaicin-induced desensitization of the primary sensory afferent terminal. Based on this property, CAP and its analogues such as olvanil, nuvanil, DA-5018, SDZ-249482, and resiniferatoxin are either used or are under development as analgesic agents or therapeutic agents for urinary incontinence or skin disorders. (Wrigglesworth and Walpole, *Drugs of the Future.*, (1998) 23, 531-538).

VR1 is widely expressed in non-neuronal tissues in various organs, and the functional roles of VR1 in various systems are not properly understood at this time. An increasing number of animal studies have revealed the possible involvement of VR1 receptors in a number of pathologies. Based on this information VR1 is now being considered as a molecular target for various indications such as migraine, arthralgia, diabetic neuropathy, neurodegeneration, neurotic skin disorder, stroke, cardiac pain arising from an ischemic myocardium, Huntington's disease, memory deficits, restricted brain function, amyotrophic lateral sclerosis (ALS), dementia, urinary bladder hypersensitiveness, urinary incontinence, vulvodynia, pruritic conditions such as uremic pruritus, irritable bowel syndrome including gastro-esophageal reflux disease, enteritis, ileitis, stomach-duodenal ulcer, inflammatory bowel disease including Crohn's disease, celiac disease and inflammatory diseases such as pancreatitis, and in respiratory disorders such as allergic and non-allergic rhinitis, asthma or chronic obstructive pulmonary disease, irritation of skin, eye or mucous membrane, dermatitis, and in non specific disorders such as ferveescence, retinopathy, muscle spasms, emesis, dyskinesias and depression. Specifically VR1 antagonists are likely to be useful in multiple sub-types of pain such as acute, chronic, neuropathic pain or post-operative pain, as well as in pain due to neuralgia (*e.g.*, post herpetic neuralgia, trigeminal neuralgia, and in pain due to diabetic neuropathy, dental pain as well as cancer pain. Additionally, VR1 antagonists will also prove useful in the treatment of inflammatory pain conditions such as arthritis or osteoarthritis. VR1 antagonists hold potential benefit in diabetes, obesity,

urticaria, actinic keratosis, keratocanthoma, alopecia, Meniere's disease, tinnitus, hyperacusis and anxiety disorders.

One class of natural and synthetic compounds that modulate the function of VR1 have been characterized by the presence of a vanillyl (4-hydroxy 3-methoxybenzyl) group or a functionally equivalent group and the same have been widely studied and is extensively reviewed by Szallasi and Blumberg, *Pharmacological reviews*,. (1999), 51, 159-212.

Various vanilloid agonists and antagonists have been developed for the treatment of pain; the agonists work through desensitizing the receptor while antagonists block its stimulation by pathophysiological ligands. The first antagonist Capsazepine was synthesized by Novartis.

There are other VR1 antagonists, which are at the clinical or preclinical stage, for example, AZD-1386, NGD-8243/MK-2295, SB-705498 are at various stages of clinical development whereas Amore Pacific's PAC-20030, Neurogen's BCTC, Abbott's A-425619 and Amgen's AMG-9810 are in preclinical testing.

According to the following patent publications, 3-azabicyclo[3.1.0]hexane groups may be incorporated into certain compounds useful as sorbitol dehydrogenase inhibitors, modulators of CCR5 chemokine receptors, NK-3 receptor antagonists, and AKT protein kinase inhibitors.

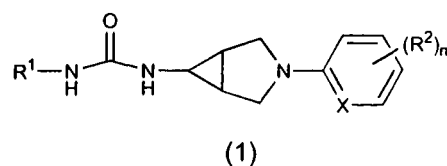
WO 00/59510 (US 6,414,149), WO 02/32411, WO 02/43762 and WO 05/037284, disclose aminopyrimidines as sorbitol dehydrogenase inhibitors and their combination with a statin, a GABA agonist, or a hypertensive agent. WO 02/34761 (US 2002/0094989) discloses pyrrolidine modulators of CCR5 chemokine receptors. US 2004/0002504 describe substituted sulfonamides as NK-3 receptor antagonists. WO 05/051304 discloses certain AKT protein kinase inhibitors. WO 06/123121 discloses Histone deacetylase inhibitors. WO 05/59510 discloses sorbitol dehydrogenase inhibitors. US 2003/0232739 disclose NOS inhibitors.

Vanilloid receptor modulating compounds are disclosed in US 6,933,311, US 6,939,891, US 7,037,927, US 2006/0100460, WO 02/08221, WO 02/16317, WO 02/16318, WO 02/16319, WO 04/103281, WO 04/108133, WO 04/111009, WO 06/044527, WO 03/080578 and WO 06/045498.

There still exists a need for safe and more effective vanilloid receptor modulators useful in the treatment of diseases, conditions, and/or disorders modulated by vanilloid receptors, including acute and chronic pain and neuropathic pain.

Summary of the Invention

The present invention relates to VR1 receptor ligands of general formula (1):



pharmaceutically acceptable salts, N-oxides, esters, tautomers or stereoisomers, thereof,

wherein,

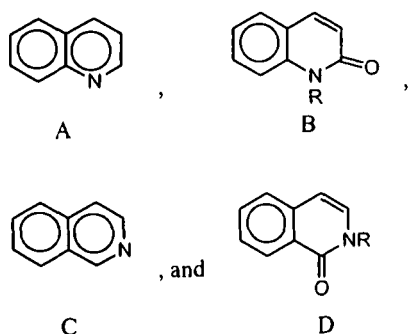
X is CH or N;

R¹ is selected from substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocyclic ring; wherein substituents are selected from nitro, haloalkyl, substituted or unsubstituted alkyl, linear or branched chain alkyl, fully or partially substituted haloalkyl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocyclic ring;

each occurrence of R² is independently selected from hydrogen, nitro, cyano, formyl, acetyl, halogen, hydroxyl, substituted or unsubstituted alkyl, fully or partially substituted haloalkyl, substituted or unsubstituted cycloalkyl or substituted or unsubstituted aryl;

'n' is an integer selected from 0 to 3;

with the proviso that R¹ is not



Where R in formulas A, B, C, and D can be any chemical moiety.

According to one embodiment, R¹ is unsubstituted aryl, preferably phenyl.

According to one embodiment, R¹ is substituted aryl. In this embodiment R¹ is substituted phenyl, wherein the substituents comprises of CF₃, methyl-1,3-thiazolyl, 5-tert-

butyl-1,3,4-oxadiazolyl, cyano-4,5-dihydroisoxazolyl, furyl, thienyl, thiophenyl, 1,3-thiazolyl, isoxazolyl, pyrazolyl, benzyl-1*H*-pyrazolyl, oxo-1,3-oxazolidinyl, -4,5-dihydroisoxazole-5-carboxylate, pyrrolidinyl, , morpholinyl, or [1,2,3]triazolyl.

According to another embodiment R^1 is substituted or unsubstituted heteroaryl or heterocyclic ring. In this embodiment R^1 group includes but not limited to thiadiazolyl, indazolyl, oxidiazolyl, isoindolyl, dihydroisoxazolyl, dioxo-2,3-dihydro-1*H*-isoindolyl, dihydro-3*H*-chromeno[4,3-*c*]isoxazolyl, dihydro-1,4-benzodioxinyl, benzimidazolyl, isoxazolyl, dihydrospiro [chromene-2 1'-cyclobutan]-yl, or pyridyl, each of which optionally substituted one or more times with halo (for eg., F, Cl, or Br), nitro, alkyl (for eg., methyl, or *t*-butyl), CF_3 , or nitrophenyl.

According to another embodiment X is CH.

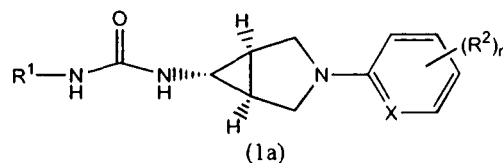
According to another embodiment X is N.

According to another embodiment R^2 is halogen, preferably fluorine; and 'n' is 1 or 2.

According to another embodiment R^2 is haloalkyl, preferably trifluoromethyl.

According to another embodiment 'n' is 0.

According to a preferred embodiment, the vanilloid receptor ligand is a compound of formula (1a):

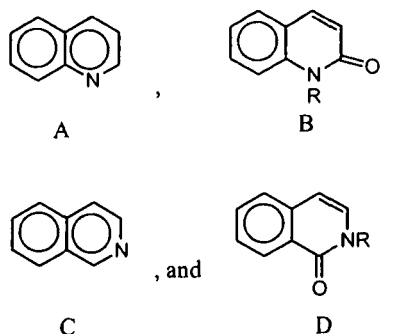


pharmaceutically acceptable salts, N-oxides, esters, tautomers or stereoisomers thereof,

wherein,

R^1 , R^2 , X and 'n' are the same as defined for formula (1).

with the proviso that R^1 is not



According to one embodiment, R¹ is unsubstituted aryl, preferably phenyl.

According to one embodiment, R¹ is substituted aryl. In this embodiment R¹ is substituted phenyl, wherein the substituents comprises of CF₃, methyl-1,3-thiazolyl, 5-*tert*-butyl-1,3,4-oxadiazolyl, cyano-4,5-dihydroisoxazolyl, furyl, thienyl, thiophenyl, 1,3-thiazolyl, isoxazolyl, pyrazolyl, benzyl-1*H*-pyrazolyl, oxo-1,3-oxazolidinyl, -4,5-dihydroisoxazole-5-carboxylate, pyrrolidinyl, , morpholinyl, or [1,2,3]triazolyl.

According to another embodiment R¹ is substituted or unsubstituted heteroaryl or heterocyclic ring. In this embodiment R¹ group includes but not limited to thiadiazolyl, indazolyl, oxidiazolyl, isoindolyl, dihydroisoxazolyl, dioxo-2,3-dihydro-1*H*-isoindolyl, dihydro-3*H*-chromeno[4,3-*c*]isoxazolyl, dihydro-1,4-benzodioxinyl, benzimidazolyl, isoxazolyl, dihydrospiro [chromene-2 1'-cyclobutan]-yl, or pyridyl, each of which optionally substituted one or more times with halo (for eg., F, Cl, or Br), nitro, alkyl (for eg., methyl, or *t*-butyl), CF₃, or nitrophenyl.

According to another embodiment X is CH.

According to another embodiment X is N.

According to another embodiment R² is halogen, preferably fluorine; and 'n' is 1 or 2.

According to another embodiment R² is haloalkyl, preferably trifluoromethyl.

According to another embodiment 'n' is 0.

Representative compounds of the present invention include those specified below and pharmaceutically acceptable salts thereof. The present invention should not be construed to be limited to them.

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(5-*tert*-butyl)thiadiazol-2-yl)urea (Compound No. 1),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(5-nitropyridin-2-yl) urea (Compound No. 2),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl] urea (Compound No. 3),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[(4-trifluoromethyl) phenyl] urea (Compound No. 4),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(1H-indazol-4-yl) urea (Compound No. 5),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(2-methyl-1,3-thiazol-4-yl)phenyl]urea (Compound No. 6),

1-[(1 α ,5 α ,6 α)-3-(4-Fluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(2-methyl-1,3-thiazol-4-yl)phenyl]urea (Compound No. 7),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(5-*tert*-butyl-1,3,4-oxadiazol-2-yl)phenyl]urea (Compound No. 8),

1-[(1 α ,5 α ,6 α)-3-(4-Fluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(5-*tert*-butyl-1,3,4-oxadiazol-2-yl)phenyl]urea (Compound No. 9),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(5-cyano-4,5-dihydroisoxazol-3-yl)phenyl]urea (Compound No. 10),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(2-furyl)-phenyl]urea (Compound No. 11),

1-[(1 α ,5 α ,6 α)-3-(4-Fluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(2-furyl)-phenyl]urea (Compound No. 12),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(2-thionyl)-phenyl]urea (Compound No. 13),

1-[(1 α ,5 α ,6 α)-3-(4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(2-thionyl)-phenyl]urea (Compound No. 14),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(1,3-thiazol-2-yl)phenyl]urea (Compound No. 15),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(3-isoxazol-3-yl)phenyl]urea (Compound No. 16),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(1-methyl-1*H*-pyrazol-3-yl)phenyl]urea (Compound No. 17),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(1-benzyl-1*H*-pyrazol-3-yl)phenyl]urea (Compound No. 18),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[2-(1*H*-1,2,4-triazol-1-yl)phenyl]urea (Compound No. 19),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(1*H*-1,2,4-triazol-1-yl)phenyl]urea (Compound No. 20),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[2-(1*H*-1,2,3-triazol-1-yl)phenyl]urea (Compound No. 21),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(2*H*-1,2,3-triazol-2-yl)phenyl]urea (Compound No. 22),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl)urea (Compound No. 23),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)urea (Compound No. 24),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-methyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl)urea (Compound No. 25),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-methyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)urea (Compound No. 26),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[2-(2-oxo-1,3-oxazolidin-3-yl)phenyl]urea (Compound No. 27),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-oxo-1,3-oxazolidin-3-yl)phenyl]urea (Compound No. 28),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[methyl 3-phenyl-4,5-dihydroisoxazole-5-carboxylate]urea (Compound No. 29),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-methyl-1*H*-benzimidazol-5-yl)urea (Compound No. 30),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(3*a*,4-dihydro-3*H*-chromeno[4,3-*c*]isoxazol-8-yl)urea (Compound No. 31),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2,3-dihydro-1,4-benzodioxin-6-yl)urea (Compound No. 32),

1-[(1 α ,5 α ,6 α)-3-(4-Fluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2,3-dihydro-1,4-benzodioxin-6-yl)urea (Compound No. 33),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(3,4-dihydrospiro[chromene-2,1'-cyclobutan]-4-yl)urea (Compound No. 34),

1-(5-Nitropyridin-2-yl)-3-{3-[(1 α ,5 α ,6 α)-3-(trifluoromethyl)pyridin-2-yl]-3-azabicyclo[3.1.0]hex-6-yl}urea (Compound No. 35),

1-[4-(Trifluoromethyl)phenyl]-3-{3-[(1 α ,5 α ,6 α)-3-(trifluoromethyl)pyridine-2-yl]-3-azabicyclo[3.1.0]hex-6-yl}urea (Compound No. 36),

1-[5-(4-Bromophenyl)-1,3,4-thiadiazol-2-yl]-3-{3-[(1 α ,5 α ,6 α)-3-(trifluoromethyl)pyridin-2-yl]-3-azabicyclo[3.1.0]hex-6-yl}urea (Compound No. 37),

1-[5-(*tert*-Butyl)-1,3,4-thiadiazol-2-yl]-3-{3-[(1 α ,5 α ,6 α)-3-(trifluoromethyl)pyridin-2-yl]-3-azabicyclo[3.1.0]hex-6-yl}urea (Compound No. 38),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-pyrrolidin-1-ylphenyl)urea (Compound No. 39),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-(2-thienyl)phenyl)urea (Compound No. 40),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-(1,3-thiazol-2-yl)phenyl)urea (Compound No. 41),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-isoxazol-3-ylphenyl)urea (Compound No. 42),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-morpholin-4-ylphenyl)urea (Compound No. 43),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(3-[1,2,3]triazol-1-yl phenyl urea (Compound No. 44),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-[1,2,3]triazol-2-yl-phenyl urea (Compound No. 45), and

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-pyrazol-1-yl-phenyl urea (Compound No. 46)

or pharmaceutically acceptable salts, N-oxides, esters, tautomers or stereoisomers thereof.

The present invention also provides a pharmaceutical composition comprising at least one compound of the present invention and a 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 of the present invention. The compound of the present invention 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.

Also provided herein is a method for preventing, ameliorating or treating a disease, disorder or syndrome mediated by VR1 in a subject in need thereof by administering to the subject a therapeutically effective amount of one or more compounds of the present invention or a pharmaceutical composition of the present invention. Non-limiting examples of diseases, disorders and syndromes which can be mediated by VR1 include but not limited to migraine, arthralgia, diabetic neuropathy, neurodegeneration, neurotic skin disorder, stroke, cardiac pain arising from an ischemic myocardium, Huntington's disease, memory deficits, restricted brain function, amyotrophic lateral sclerosis (ALS), dementia, urinary bladder hypersensitiveness, urinary incontinence, vulvodynia, pruritic conditions such as uremic pruritus, irritable bowel syndrome including gastro-esophageal reflux disease, enteritis, ileitis, stomach-duodenal ulcer, inflammatory bowel disease including Crohn's disease, celiac disease, inflammatory diseases (such as pancreatitis), respiratory disorders such as allergic and non-allergic rhinitis, asthma or chronic obstructive pulmonary disease (COPD), irritation of skin, eye or mucous membrane, dermatitis, ferveescence, retinopathy, muscle spasms, emesis, dyskinesias, depression, pain such as acute, chronic, neuropathic pain or post-operative pain, pain due to neuralgia or trigeminal neuralgia, pain due to diabetic neuropathy, dental pain, cancer pain, arthritis, osteoarthritis, diabetes, obesity, urticaria, actinic keratosis, keratocanthoma, alopecia, Meniere's disease, tinnitus, hyperacusis, anxiety disorders and

benign prostate hyperplasia. According to one preferred embodiment, the compounds of the present invention are administered to treat acute or chronic pain or neuropathic pain.

Detailed Description of the Invention

The present invention provides 3-azabicyclo [3.1.0] hexane derivatives, which can be used as vanilloid receptor ligands, and processes for the synthesis of these compounds. Pharmaceutically acceptable salts, pharmaceutically enantiomers, diastereomers, of these compounds having the same type of activity are also provided. Pharmaceutical compositions containing the described compounds together with pharmaceutically acceptable carriers, excipients or diluents, which can be used for the treatment of diseases, condition and/or disorders mediated by VR1 are further provided.

Definitions

The term "alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to eight carbon atoms, 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 "alkenyl" refers to an aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be a straight or branched chain having 2 to about 10 carbon atoms, e.g., ethenyl, 1-propenyl, 2-propenyl (allyl), iso-propenyl, 2-methyl-1-propenyl, 1-butenyl, and 2-butenyl.

The term "alkynyl" refers to a straight or branched chain 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), e.g., ethynyl, propynyl, and butynyl.

The term "alkoxy" denotes an alkyl group attached via an oxygen linkage to the rest of the molecule. Representative examples of such groups are -OCH₃ and -OC₂H₅.

The term "haloalkyl" refers to a group containing at least one halogen and an alkyl portion as defined above, that is, a haloalkyl is a substituted alkyl group that is substituted with one or more halogens. Exemplary haloalkyl groups include fluoromethyl, chloromethyl, fluoroethyl, chloroethyl, trifluoromethyl, and the like. Unless otherwise specified, a haloalkyl group has from 1 to 20 carbon atoms.

The term "cycloalkyl" denotes a non-aromatic mono or multicyclic ring system of 3 to about 12 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Examples of multicyclic cycloalkyl groups include, but are not limited to, perhydronaphthyl, adamantyl and norbornyl groups, bridged cyclic groups or spirobicyclic groups, e.g., spiro (4,4) non-2-yl.

The term "cycloalkylalkyl" refers to a cyclic ring-containing radical having 3 to about 8 carbon atoms directly attached to an alkyl group. 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. Non-limiting examples of such groups include cyclopropylmethyl, cyclobutylethyl, and cyclopentylethyl.

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, such as cyclopropenyl, cyclobutenyl, and cyclopentenyl.

The term "aryl" refers to an aromatic radical having 6 to 14 carbon atoms such as phenyl, naphthyl, tetrahydronaphthyl, indanyl, and biphenyl.

The term "arylalkyl" refers to an aryl group as defined above directly bonded to an alkyl group as defined above, e.g., $-\text{CH}_2\text{C}_6\text{H}_5$ and $-\text{C}_2\text{H}_5\text{C}_6\text{H}_5$.

The term "heterocyclic ring" or "heterocyclyl" or "heterocyclic group" refers to a stable 3- to 15-membered ring radical which consists of carbon atoms and from one to five heteroatoms selected from nitrogen, phosphorus, oxygen and sulfur. For purposes of this invention, the heterocyclic ring radical may be a monocyclic, bicyclic 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; and the ring radical may be partially or fully saturated (i.e., heterocyclic or heteroaryl). Examples of such heterocyclic ring radicals include, but are not limited to, azetidiny, acridiny, benzodioxolyl, benzodioxanyl, benzofurnyl, carbazolyl, cinnoliny, dioxolanyl, indoliziny, naphthyridiny, perhydroazepiny, phenaziny, phenothiaziny, phenoxaziny, phthalaziny, pyridyl, pteridiny, puriny, quinazolinyl, quinoxaliny, quinoliny, isoquinoliny, tetrazoyl, imidazolyl, tetrahydroisouinolyl, piperidiny, piperaziny, 2-oxopiperaziny, 2-oxopiperidiny, 2-oxopyrrolidiny, 2-oxoazepiny, azepiny, pyrrolyl, 4-piperidonyl, pyrrolidiny, pyraziny, pyrimidiny, pyridaziny, oxazolyl, oxazoliny,

oxasolidinyl, triazolyl, indanyl, isoxazolyl, isoxasolidinyl, morpholinyl, thiazolyl, thiazolinyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, octahydroindolyl, octahydroisoindolyl, quinolyl, isoquinolyl, decahydroisoquinolyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, benzooxazolyl, furyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, dioxaphospholanyl, oxadiazolyl, chromanyl, and isochromanyl. The heterocyclic ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

The term "heterocyclyl" refers to a heterocyclic ring radical as defined above. The heterocyclyl ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

The term "heterocyclylalkyl" refers to a heterocyclic ring radical directly bonded to an alkyl group. The heterocyclylalkyl radical may be attached to the main structure at any carbon atom in the alkyl group that results in the creation of a stable structure.

The term "heteroaryl" refers to an aromatic heterocyclic ring radical. The heteroaryl ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

The term "heteroarylalkyl" refers to a heteroaryl ring radical directly bonded to an alkyl group. The heteroarylalkyl radical may be attached to the main structure at any carbon atom in the alkyl group that results in the creation of a stable structure.

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 alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclylalkyl ring, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted guanidine, $-\text{COOR}^x$, $-\text{C(O)R}^x$, $-\text{C(S)R}^x$, $-\text{C(O)NR}^x\text{R}^y$, $-\text{C(O)ONR}^x\text{R}^y$, $-\text{NR}^x\text{CONR}^y\text{R}^z$, $-\text{N(R}^x\text{)SOR}^y$, $-\text{N(R}^x\text{)SO}_2\text{R}^y$, $-(=\text{N-N(R}^x\text{)R}^y)$, $-\text{NR}^x\text{C(O)OR}^y$, -

NR^xR^y , $-\text{NR}^x\text{C}(\text{O})\text{R}^y$, $-\text{NR}^x\text{C}(\text{S})\text{R}^y$, $-\text{NR}^x\text{C}(\text{S})\text{NR}^y\text{R}^z$, $-\text{SONR}^x\text{R}^y$, $-\text{SO}_2\text{NR}^x\text{R}^y$, $-\text{OR}^x$, $-\text{OR}^x\text{C}(\text{O})\text{NR}^y\text{R}^z$, $-\text{OR}^x\text{C}(\text{O})\text{OR}^y$, $-\text{OC}(\text{O})\text{R}^x$, $-\text{OC}(\text{O})\text{NR}^x\text{R}^y$, $-\text{R}^x\text{NR}^y\text{C}(\text{O})\text{R}^z$, $-\text{R}^x\text{OR}^y$, $-\text{R}^x\text{C}(\text{O})\text{OR}^y$, $-\text{R}^x\text{C}(\text{O})\text{NR}^y\text{R}^z$, $-\text{R}^x\text{C}(\text{O})\text{R}^y$, $-\text{R}^x\text{OC}(\text{O})\text{R}^y$, $-\text{SR}^x$, $-\text{SOR}^x$, $-\text{SO}_2\text{R}^x$, and $-\text{ONO}_2$, wherein 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 cycloalkenyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted heterocyclylalkyl ring, substituted or unsubstituted heteroarylalkyl, or 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" cannot be "substituted alkenyl".

The term "protecting group" or "PG" refers to a substituent that is employed to block or protect a particular functionality while other functional groups on the compound may remain reactive. For example, an "amino-protecting group" is a substituent attached to an amino group that blocks or protects the amino functionality in the compound. Suitable amino-protecting groups include, but are not limited to, acetyl, trifluoroacetyl, t-butoxycarbonyl (BOC), benzyloxycarbonyl (CBz) and 9-fluorenylmethylenoxycarbonyl (Fmoc). Similarly, a "hydroxy-protecting group" refers to a substituent of a hydroxy group that blocks or protects the hydroxy functionality. Suitable hydroxy-protecting groups include, but are not limited to, acetyl, benzyl, tetrahydropyranyl and silyl. A "carboxy-protecting group" refers to a substituent of the carboxy group that blocks or protects the carboxy functionality. Suitable carboxy-protecting groups include, but are not limited to, $-\text{CH}_2\text{CH}_2\text{SO}_2\text{Ph}$, cyanoethyl, 2-(trimethylsilyl)ethyl, 2-(trimethylsilyl)ethoxymethyl, 2-(p-toluenesulfonyl)ethyl, 2-(p-nitrophenylsulfenyl)ethyl, 2-(diphenylphosphino)-ethyl, and nitroethyl. For a general description of protecting groups and their use, see, T. W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York, (1991), 2nd ed.

The term "treating" or "treatment" of a state, disorder or condition includes:

(1) 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;

(2) 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

(3) relieving the disease, i.e., causing regression of the state, disorder or condition or at least one of its clinical or subclinical symptoms.

The benefit to a subject to be treated is either statistically significant or at least perceptible to the subject or to the physician.

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).

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" will vary depending on the compound, the disease and its severity and the age, weight, physical condition and responsiveness of the subject to be treated.

Pharmaceutically acceptable salts forming part of this invention include salts derived from inorganic bases (such as Li, Na, K, Ca, Mg, Fe, Cu, Zn, and Mn), salts of organic bases (such as N,N'-diacetylenediamine, glucamine, triethylamine, choline, hydroxide, dicyclohexylamine, metformin, benzylamine, trialkylamine, and thiamine), salts of chiral bases (such as alkylphenylamine, glycinol, and phenyl glycinol), salts of natural amino acids (such as glycine, alanine, valine, leucine, isoleucine, norleucine, tyrosine, cystine, cysteine, methionine, proline, hydroxy proline, histidine, ornithine, lysine, arginine, and serine), salts of non-natural amino acids (such as D-isomers or substituted amino acids), salts of guanidine, salts of substituted guanidine (wherein the substituents are selected from nitro, amino, alkyl, alkenyl, or alkynyl), ammonium salts, substituted ammonium salts, and aluminum salts. Other pharmaceutically acceptable salts include acid addition salts (where appropriate) such as sulphates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates (such as trifluoroacetate), tartrates, maleates, citrates, fumarates, succinates, palmoates, methanesulphonates, benzoates, salicylates, benzenesulfonates, ascorbates, glycerophosphates, and ketoglutarates. Yet other pharmaceutically acceptable salts include, but are not limited to, quaternary ammonium salts of the compounds of invention with alkyl halides or alkyl sulphates (such as MeI or (Me)₂SO₄).

Pharmaceutically acceptable solvates includes hydrates and other solvents of crystallization (such as alcohols). The compounds of the present invention may form solvates with low molecular weight solvents by methods known in the art.

Certain compounds of present invention are capable of existing in stereoisomeric forms (e.g. diastereomers and enantiomers) and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by known methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof. For example, both tautomeric forms of the following moiety are contemplated:



Pharmaceutical Compositions

The pharmaceutical composition of the present invention comprises at least one compound of the present invention and a pharmaceutically acceptable excipient (such as a pharmaceutically acceptable carrier or diluent). Preferably, the pharmaceutical composition comprises a therapeutically effective amount of the compound(s) of the present invention. The compound of the present invention 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.

Examples of suitable carriers include, but are not limited to, water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatin, lactose, terra alba, sucrose, dextrin, magnesium carbonate, sugar, cyclodextrin, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone.

The carrier or diluent may include a sustained release material, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax.

The pharmaceutical composition may also include one or more pharmaceutically acceptable auxiliary agents, wetting agents, emulsifying agents, suspending agents,

preserving agents, salts for influencing osmotic pressure, buffers, sweetening agents, flavoring agents, colorants, or any combination of the foregoing. The pharmaceutical composition of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the subject by employing procedures known in the art.

The pharmaceutical compositions of the present invention may be prepared by conventional techniques, e.g., as described in Remington: The Science and Practice of Pharmacy, 20th Ed., 2003 (Lippincott Williams & Wilkins). For example, the active compound can be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier, which may be in the form of an ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be a solid, semi-solid, or liquid material that acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container, for example, in a sachet.

The pharmaceutical compositions may be in conventional forms, for example, capsules, tablets, aerosols, solutions, suspensions or products for topical application.

The route of administration may be any route which effectively transports the active compound of the invention to the appropriate or desired site of action. Suitable routes of administration include, but are not limited to, oral, nasal, pulmonary, buccal, subdermal, intradermal, transdermal, parenteral, rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic (such as with an ophthalmic solution) or topical (such as with a topical ointment). The oral route is preferred.

Solid oral formulations include, but are not limited to, tablets, capsules (soft or hard gelatin), dragees (containing the active ingredient in powder or pellet form), troches and lozenges. Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, cornstarch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

A typical tablet that may be prepared by conventional tableting techniques may contain: (1) Core: Active compound (as free compound or salt thereof), 250 mg colloidal silicon dioxide (Aerosil®), 1.5 mg microcrystalline cellulose (Avicel®), 70 mg modified cellulose gum (Ac-Di-Sol®), and 7.5 mg magnesium stearate; (2) Coating: HPMC, approx. 9 mg Mywacett 9-40 T and approx. 0.9 mg acylated monoglyceride

Liquid formulations include, but are not limited to, syrups, emulsions, soft gelatin and sterile injectable liquids, such as aqueous or non-aqueous liquid suspensions or solutions.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Methods of Treatment

The present invention provides compounds and pharmaceutical formulations thereof that are useful in the treatment of diseases, conditions and/or disorders modulated by vanilloid VR1 receptor antagonists.

The present invention further provides a method of treating a disease, condition and/or disorder modulated by vanilloid receptor antagonists in a subject in need thereof by administering to the subject a therapeutically effective amount of a compound or a pharmaceutical composition of the present invention. The method is particularly useful for treating diseases, conditions and/or disorders modulated by VR1 receptor antagonists.

Diseases, conditions, and/or disorders that are modulated by vanilloid receptor antagonists include, but are not limited to, migraine, arthralgia, diabetic neuropathy, neurodegeneration, neurotic skin disorder, stroke, cardiac pain arising from an ischemic myocardium, Huntington's disease, memory deficits, restricted brain function, amyotrophic lateral sclerosis (ALS), dementia, urinary bladder hypersensitiveness, urinary incontinence, vulvodynia, pruritic conditions such as uremic pruritus, irritable bowel syndrome including gastro-esophageal reflux disease, enteritis, ileitis, stomach-duodenal ulcer, inflammatory bowel disease including Crohn's disease, celiac disease and inflammatory diseases such as pancreatitis, and in respiratory disorders such as allergic and non-allergic rhinitis, asthma or chronic obstructive pulmonary disease, irritation of skin, eye or mucous membrane, dermatitis, and in non specific disorders such as fervescence, retinopathy, muscle spasms, emesis, dyskinesias or depression. Specifically in multiple sub-types of pain such as acute, chronic, neuropathic pain or post-operative pain, as well as in pain due to neuralgia (e.g. post herpetic neuralgia, trigeminal neuralgia; and in pain due to diabetic neuropathy or dental pain as well as in cancer pain. Additionally, VR1 antagonists hold potential benefit in the treatment of inflammatory pain conditions e.g. arthritis, and osteoarthritis, diabetes, obesity, urticaria, actinic keratosis, keratocanthoma, alopecia, Meniere's disease, tinnitus, hyperacusis and anxiety disorders.

The method is also particularly useful for treating pain, urinary incontinence, ulcerative colitis, asthma, and inflammation.

As indicated above, the compounds of the present invention and their pharmaceutically acceptable salts have VR1 antagonistic activity and are useful for the treatment or prophylaxis of certain diseases or disorders mediated or associated with the activity of vanilloid receptor, including disorders such as pain, chronic pain, neuropathic pain, postoperative pain, rheumatoid arthritic pain, osteoarthritic pain, back pain, visceral pain, cancer pain, algesia, neuralgia, migraine, neuropathies, diabetic neuropathy, sciatica, HIV-related neuropathy, post-herpetic neuralgia, fibromyalgia, nerve injury, ischaemia, neurodegeneration, stroke, post stroke pain, multiple sclerosis, respiratory diseases, asthma, cough, COPD, inflammatory disorders, oesophagitis, gastroesophageal reflux disorder (GERD), irritable bowel syndrome, inflammatory bowel disease, pelvic hypersensitivity, urinary incontinence, cystitis, burns, psoriasis, emesis, stomach duodenal ulcer and pruritus.

Thus the invention also provides a compounds or a pharmaceutically acceptable salt thereof, for use as an active therapeutic substance, in particular in the treatment or prophylaxis of diseases or disorders mediated or associated with the activity of vanilloid receptor. In particular the invention provides a compound of formula (1) or a pharmaceutically acceptable salt thereof for use in the treatment or prophylaxis of pain.

The invention further provides a method of treatment or prophylaxis of diseases or disorders mediated or associated with the activity of vanilloid receptor, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of the present invention.

The invention provides for the use of a compound of the present invention or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof in the manufacture of a medicament for the treatment or prophylaxis of diseases or disorders mediated or associated with the activity of vanilloid receptor.

The compound of the present invention has potent analgesic and anti-inflammatory activity, and the pharmaceutical composition of the present invention thus may be employed to alleviate or relieve acute, chronic or inflammatory pains, suppress inflammation, or treat urinary incontinence (including urgent urinary incontinence).

In accordance with another aspect of the present invention, there is also provided a method for alleviating and/or treating migraine, arthralgia, diabetic neuropathy,

neurodegeneration, neurotic skin disorder, stroke, cardiac pain arising from an ischemic myocardium, Huntington's disease, memory deficits, restricted brain function, amyotrophic lateral sclerosis (ALS), dementia, urinary bladder hypersensitiveness, urinary incontinence, vulvodynia, pruritic conditions such as uremic pruritus, irritable bowel syndrome including gastro-esophageal reflux disease, enteritis, ileitis, stomach-duodenal ulcer, inflammatory bowel disease including Crohn's disease, celiac disease and inflammatory diseases such as pancreatitis, and in respiratory disorders such as allergic and non-allergic rhinitis, asthma or chronic obstructive pulmonary disease, irritation of skin, eye or mucous membrane, dermatitis, and in non specific disorders such as fervescence, retinopathy, muscle spasms, emesis, dyskinesias or depression. Specifically in multiple sub-types of pain such as acute, chronic, neuropathic pain or post-operative pain, as well as in pain due to neuralgia (e.g. post herpetic neuralgia, trigeminal neuralgia; and in pain due to diabetic neuropathy or dental pain as well as in cancer pain. Additionally in the treatment of inflammatory pain conditions e.g. arthritis, and osteoarthritis, diabetes, obesity, urticaria, actinic keratosis, keratocanthoma, alopecia, Meniere's disease, tinnitus, hyperacusis and anxiety disorders.

According to a preferred embodiment there is provided a method of treating pain in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound described herein. According to yet another preferred embodiment, pain is acute, chronic or post-operative pain. Yet another embodiment provides a method of treating neuropathic pain, urinary incontinence, ulcerative colitis, asthma or inflammation

The compounds of the present invention in pharmaceutical dosage forms may be used in the form of their pharmaceutically acceptable salts, and also may be used alone or in appropriate association, as well as in combination with other pharmaceutically active compounds.

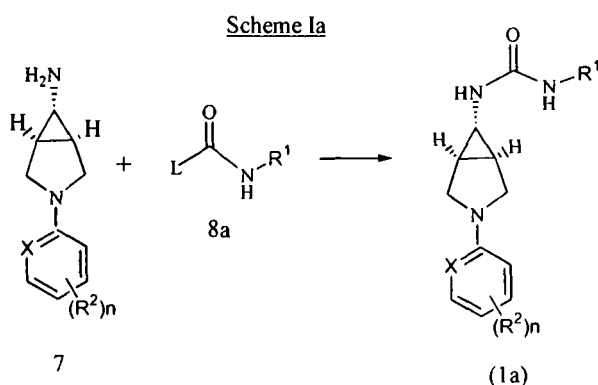
The compounds of the present invention (including the pharmaceutical compositions and processes used therein) may be used alone or in combination with other pharmaceutical agents in the manufacture of a medicament for the therapeutic applications described herein.

Methods of Preparation

The compounds described herein may be prepared by techniques known in the art. In addition, the compounds described herein may be prepared by following the reaction sequences as depicted in Schemes Ia, Ib, IIa, IIb, IIc and IId. Further, in the following schemes, where specific bases, acids, reagents, solvents, oxidizing agents, reducing agents,

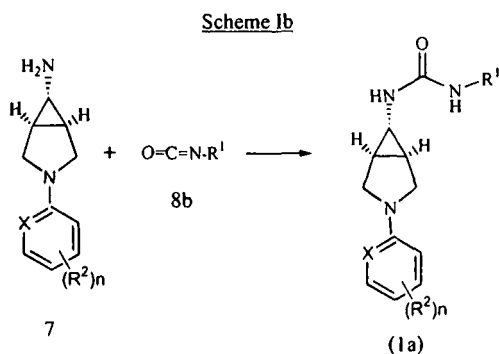
coupling agents, etc., are mentioned, it is understood that other bases, acids, reagents, solvents, oxidizing agents, reducing agents, coupling agents etc., known in the art may be also used and are therefore included within the present invention. Variations in reaction conditions, for example, temperature and/or duration of the reaction, which may be used as known in the art are also within the scope of the present invention. All the stereo isomers of the compounds in these schemes, unless otherwise specified, are also encompassed within the scope of this invention.

In one embodiment the compounds of formula (1a) wherein R^1 , R^2 , X and n are as defined in the general description, can be synthesized as shown in scheme Ia below.



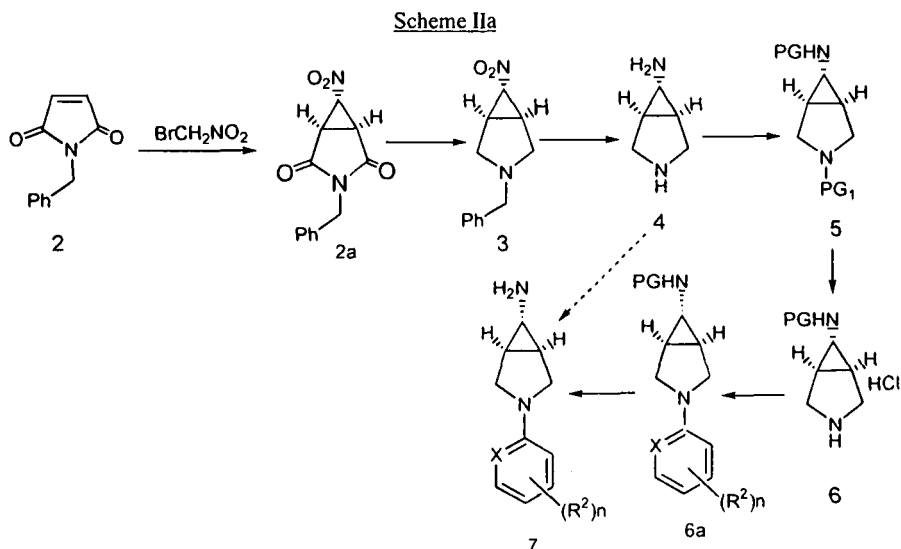
In the above general scheme Ia, a compound of formula 7 is reacted with a compound of formula 8a (wherein L is a leaving group, examples of leaving groups include, but are not limited to, halogen, aryloxy, alkoxy, imidazolyl, benzimidazolyl, tetrazolyl, benzotriazolyl, succinimidyl, preferably in the presence of a base (such as triethylamine or pyridine), to obtain the compound of formula (1a).

In another embodiment, the compounds of the formula (1a), wherein R^1 , R^2 , X and n are as defined in the general description, can be synthesized as shown in scheme Ib below.



In the above general scheme Ib, a compound of formula 7 is reacted with a compound of formula 8b, preferably in the presence of a base (such as triethylamine or pyridine), to obtain the compound of formula (1a).

In one embodiment the intermediate of formula 7, wherein R^2 , X and n are as defined in the general description, can be synthesized as shown in scheme IIa.

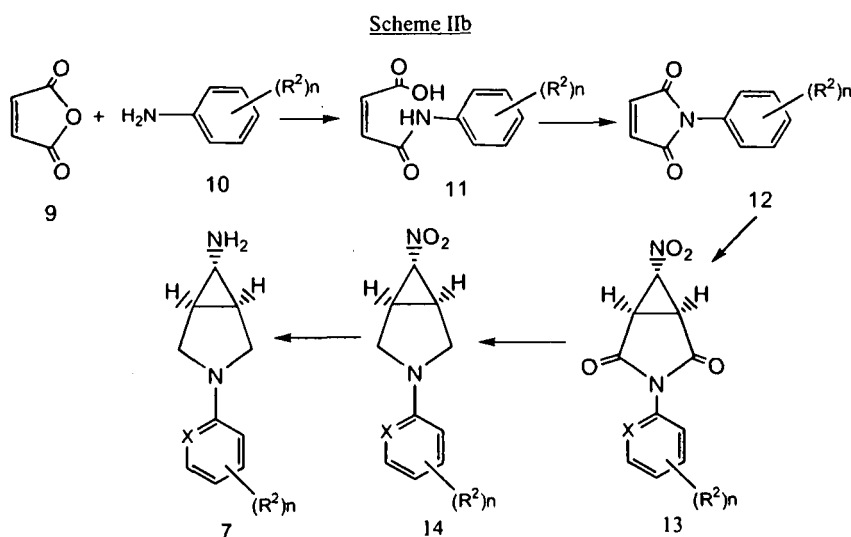


In the above general scheme IIa, compound of formula 2 is converted into intermediate 2a, for example, by reacting compound of formula 2 with bromonitromethane, preferably in the presence of a base (e.g., potassium carbonate, sodium carbonate, or a quaternary ammonium salt) and a solvent (e.g., dimethyl formamide). Compound of formula 2a is reduced to form compound of formula 3, such as by reacting compound of formula 2a with a reducing agent (such as lithium aluminum hydride, boranes, sodium borohydride, BF_3 (e.g., $\text{BF}_3 \cdot \text{OEt}_2$), or a mixture thereof) to give compound of formula 3. Compound of formula 3 can be reduced using reductive conditions such as hydrogenation in the presence of palladium (e.g., Pd/C), Raney nickel, iron/hydrochloric acid, or Raney nickel/hydrazine to obtain compound of formula 4. Compound of formula 4 can then be protected with a protecting group such as *t*-butoxy carbonyl (BOC), preferably in the presence of a base (e.g., triethylamine, sodium carbonate, potassium carbonate, or sodium hydroxide) in a suitable solvent (e.g., methanol, dichloromethane, chloroform, or ethyl acetate) to give compound of formula 5 where PG and PG_1 is protecting group. Deprotection of compound of formula 5 under acidic conditions, such as with dry hydrochloric acid or trifluoroacetic acid in a suitable solvent, such as ethyl acetate, methanol, or dichloromethane, provides compound of formula 6 (as a free base or acid addition salt thereof). Reaction of compound of formula 6

with an appropriately substituted phenyl, preferably in the presence of a base (such as triethylamine or potassium carbonate) or under metal catalyzed conditions (such as in presence of copper or palladium) provides compound of formula 6a. Deprotection of compound of formula 6a under acidic conditions, such as dry hydrochloric acid or trifluoroacetic acid in a suitable solvent (such as ethyl acetate, methanol, or dichloromethane), provides compound of formula 7.

Alternatively, compound of formula 4 can be reacted with an appropriately substituted phenyl, preferably in the presence of a base (such as triethylamine or potassium carbonate) or under metal catalyzed conditions (such as in presence of copper or palladium), to provide compound of formula 7.

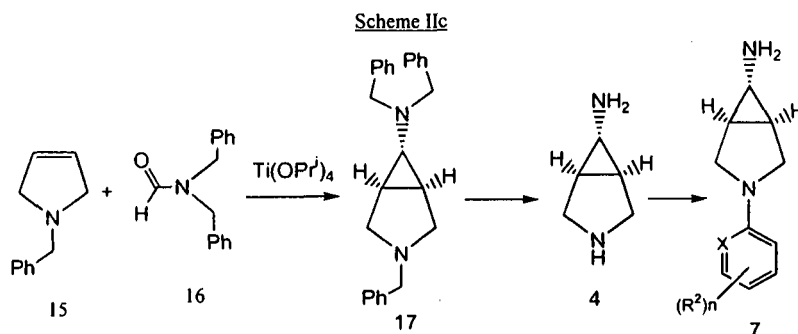
In yet another embodiment the compound of formula 7, wherein R^2 , X and n are as defined in the general description, can be synthesized as shown in scheme IIb.



Alternatively, the compound of formula 7 can be prepared by scheme IIb as shown above. Compound of formula 9 can be reacted with an appropriately substituted compound of formula 10, for example, in the presence or absence of acid (such as acetic acid), to form intermediate 11. Intermediate 11 can be cyclized with a dehydrating agent (such as acetic anhydride or dicyclohexylcarbodiimide (DCC)) to afford compound of formula 12. Compound of formula 12 can be converted to compound of formula 13, for example, by reaction with bromonitromethane, preferably in the presence of a base (e.g. potassium carbonate, sodium carbonate, or a quaternary ammonium salt). To prepare compound of formula 7, compound of formula 13 is reduced with a reducing agent (such as lithium aluminium hydride, boranes, or sodium borohydride, BF_3 (e.g., $BF_3 \cdot OEt_2$), or a mixture

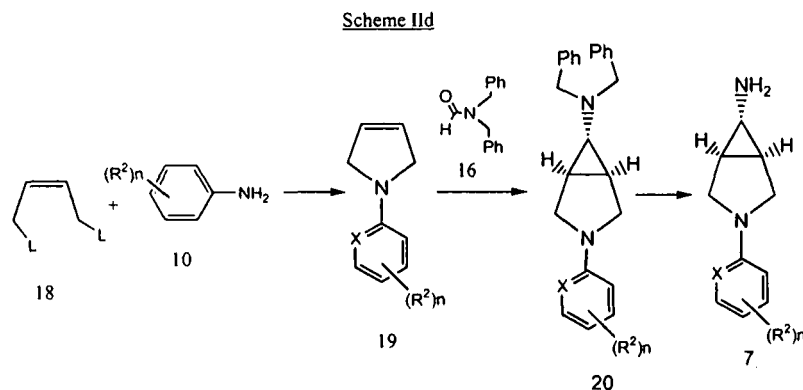
thereof) to give compound of formula 14. Compound of formula 14 can be reduced using reductive conditions (such as hydrogenation in the presence of palladium, Raney nickel, iron/hydrochloric acid, or Raney nickel /hydrazine) to obtain compound of formula 7.

In yet another embodiment the compound of formula 7, wherein R^2 , X and n are as defined in the general description, can be synthesized as shown in scheme IIc below.



Yet another method of preparing Compound of formula 7 is shown in scheme IIc above. Compound of formula 17 is obtained by reacting a N-benzylpyrroline of formula 15 with N,N-dibenzylformamide, for example, in the presence of $\text{Ti(OPr}^i\text{)}_4$, MeMgCl , and/or cyclohexylmagnesium bromide in a suitable solvent, such as THF, dimethoxyethane, or dioxane. Exhaustive debenzylation of compound of formula 17 using reductive conditions, such as hydrogenation in the presence of palladium, Raney nickel, iron/hydrochloric acid, or Raney nickel/hydrazine, provides compound of formula 4 *Chem. Eur.J.*, (2002), 8, 3789-3801. Reaction of compound of formula 4 with an appropriately substituted aryl/heteroaryl, aralkyl/heteroaralkyl halide, preferably in the presence of a base (such as triethylamine or potassium carbonate) or under metal catalyzed conditions (such as in presence of copper or palladium) provides compound of formula 7.

In yet another method, the intermediate of formula 7, wherein R^2 , X and n are as defined in the general description, can be synthesized as shown in scheme IId.



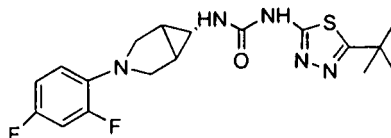
Compound of formulae 7 can also be synthesized as given in scheme IId shown above. Compound of formula 19 can be synthesized by reacting a compound of formula 18 wherein L is a leaving group (such as halogen, tosyl or mesyl group) with an amine of formula 10 in the absence or presence of base such as triethylamine, potassium carbonate. Compound of formula 19 can then be reacted with N,N-dibenzylformamide in the presence of titanium isopropoxide, methyl magnesium chloride or methyl magnesium bromide and cyclohexylmagnesium bromide or cyclohexylmagnesium chloride in solvents such as tetrahydrofuran, dimethoxyethane or dioxane to obtain compound of formula 20. Exhaustive debenzoylation of compound of formula 20 using reductive conditions such as hydrogenation in the presence of palladium, platinum or Raney nickel, can provide the compound of formula 7 *Chem. Eur.J.*, (2002), 8, 3789-3801.

The invention is explained in detail in the examples given below which are provided by way of illustration only and therefore should not be construed to limit the scope of the invention.

EXAMPLES

Example 1

Preparation of 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(5-*tert*-butyl) thiadiazol-2-yl)urea:



Step 1: Preparation of (2Z)-but-2-ene-1,4-diyl dimethanesulfonate:

To a solution of methanesulfonyl chloride (40 ml, 0.527 moles) in anhydrous dichloromethane (300 mL) is added slowly a mixture of *cis*-2-butene-1,4-diol (10.5 ml, 0.127 mol) and triethylamine (84 ml, 0.604 mol) at 0°C under nitrogen atmosphere and stirred for about 30-60 minutes. After the mixture is stirred for about 30 min more, it is then transferred to a separatory funnel and washed successively with chilled water, hydrochloric acid (10%), saturated sodium bicarbonate solution and saturated sodium chloride solution. The dichloromethane layer is separated and dried over anhydrous sodium sulfate. The removal of solvent in vacuum resulted in a yellow powder (10 g) obtained. IR (KBr) 2929, 1624, 1319, 1173, 1144, 1056, 1018, 934, 795 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 5.90 (m, 2H), 4.80 (d, 4H), 3.03 (s, 6H).

Step 2: 1-(2,4-difluorophenyl)-2,5-dihydro-1H-pyrrole:

To a solution of (2Z)-but-2-ene-1,4-diyl dimethanesulfonate (2.44 g, 10 mmol, step 1) in anhydrous dichloromethane (50 mL) at room temperature under nitrogen, 2,4-difluoroaniline (30.0 mmol) is added drop wise. The resulting solution is stirred overnight and then extracted with water. The organic layer is separated and dried with sodium sulfate. After removal of solvent, the residue is purified in pet ether: ethyl acetate (10%) to get pure product. IR (KBr): 3055, 2892, 2848, 1596, 1530, 1475, 1372, 1341, 1275, 1160, 1014, 1075, 1027, 906, 815 cm^{-1} . ^1H NMR (300 MHz, CDCl_3): δ 4.10 (s, 4H), 5.98 (s, 2H), 7.01-7.05 (m, 2H), 7.32-7.42 (m, 2H).

Step 3: 1 α ,5 α ,6 α -N,N-dibenzyl-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine:

A mixture of 1-(2,4-difluorophenyl)-2,5-dihydro-1H-pyrrole (10.0 mmol) and titanium (IV) isopropoxide (10.0 mmol) in tetrahydrofuran is titrated with methylmagnesium chloride (3M in tetrahydrofuran, 10.0 mmol), then a solution of N,N-dibenzyl formamide (10.0 mmol) in tetrahydrofuran is added in one portion. Cyclohexyl magnesium bromide (20.0 mmol, 2M in diethyl ether) is added at ambient temperature over about 50 minutes and reaction mixture is heated under reflux for about 15 minutes. The reaction mixture is diluted with tetrahydrofuran, brine solution is added. Precipitated inorganic salt is filtered. Organic layer is dried over sodium sulphate and concentrated. After removal of solvent, the residue is purified in pet ether: ethyl acetate (20%) to get pure product as yellow oil. IR (KBr) 3055, 2944, 2956, 1514, 1483, 1455, 1378, 1370, 1282, 1251, 1161, 1128, 1089, 1037, 962, 815 cm^{-1} . ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 1.44 (s, 2H), 1.86 (s, 1H), 3.15 (d, 2H, $J = 9.0$ Hz), 3.54 (d, 2H, $J = 9.0$ Hz) 3.67 (s, 4H), 6.53 (m, 2H), 6.93 (m, 2H), 7.26 (m, 10H).

Step 4: 1 α ,5 α ,6 α -tert-butyl [3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]carbamate:

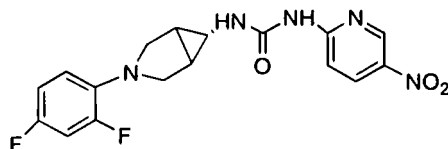
A suspension of 1 α , 5 α , 6 α -N,N-dibenzyl-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine in methanol (20 mL) and 10 % Pd/C (50% W/W) is hydrogenated in a *parr* hydrogenation apparatus for about 2-12 hours at room temperature. The reaction mixture is filtered through celite bed. To the filtrate (t-Boc) $_2$ O (20 mmol) is added and stirred at room temperature for about 2 hours. The reaction mixture is purified through silica gel column using mixture of pet ether and ethyl acetate as eluent to get pure product as white solid. IR (KBr) 3334, 3155, 2829, 2845, 1631, 1575, 1523, 1488, 1370, 1329, 1269, 1144, 1110, 1054, 1022, 916, 855 cm^{-1} . ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 1.45 (s, 9H), 1.76(s, 2 H), 2.58(s, 1H), 3.29 (d, 2H, $J = 9.0$ Hz), 3.80 (d, 2H, $J = 9.0$ Hz), 6.61 (m, 2H), 6.91 (m, 2H).

Step 5: 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(5-*tert*-butyl)thiadiazol-2-yl)urea:

To a solution of 1 α , 5 α , 6 α -*tert*-butyl [3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]carbamate (10 mmole) dissolved in ethyl acetate is added saturated solution of hydrochloric acid /ethyl acetate and stirred for about 2-3 hours. The residue obtained after removal of solvent is taken in dimethyl sulfoxide and triethylamine (20 mmol) is added followed by addition of phenyl (5-*tert*-butyl-1,3,4-thiadiazol-2-yl)carbamate (10 mmole). The reaction mixture is then stirred at room temperature for about 2-3 hours. The reaction mixture is poured on ice cold water. Solid precipitate out is filtered and leached in methanol to get pure product. mp 247-248 °C. IR (KBr) 3304, 2859, 1634, 1587, 1532, 1478, 1365, 1332, 1269, 1157, 1111, 1032, 912, 807 cm⁻¹. ¹H NMR (300 MHz, DMSO-d₆) δ 1.36 (9H, s), 1.80 (s, 2H), 2.57 (s, 1H), 3.19 (d, 2H, *J* = 9.0 Hz), 3.65 (d, 2H, *J* = 9.0 Hz), 6.75-7.15 (m, 3H), 10.85 (s, 1H). [M+H]⁺ = 394.

Example 2

Preparation of 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(5-nitropyridin-2-yl) urea:

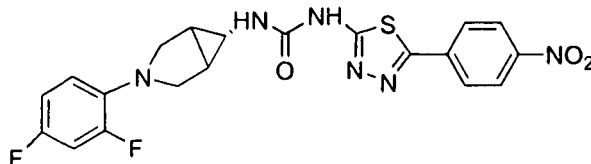


The title compound is prepared by the method as described in step 5 of the Example 1 from 1 α , 5 α , 6 α -*tert*-butyl [3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]carbamate and phenyl (5-nitropyridin-2-yl)carbamate. mp 231-232 °C. IR (KBr) 3304, 2859, 1634, 1587, 1532, 1478, 1365, 1332, 1269, 1157, 1111, 1032, 912, 807 cm⁻¹. ¹H NMR (300 MHz, DMSO-d₆): δ 1.84 (s, 2H), 2.63 (s, 1H), 3.23 (d, 2H, *J* = 9.0 Hz), 3.65 (d, 2H, *J* = 9.0 Hz), 6.77-6.79 (m, 1H), 6.90-6.96 (m, 1H), 7.08-7.21 (m, 2H), 7.76 (s, 1H), 7.79 (s, 1H), 8.49 (dd, 1H, *J* = 9.0 Hz, *J* = 2.7 Hz), 9.06 (s, 1H), 9.92 (s, 1H). [M+H]⁺ = 376

Example 3

Preparation of 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[5-(4-nitro phenyl)-1,3,4-thiadiazol-2-yl] urea:

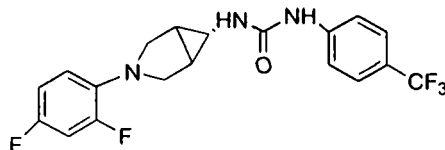
28



The title compound is prepared by the method as described in step 5 of the Example I from 1*α*, 5*α*, 6*α*-*tert*-butyl [3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]carbamate and phenyl [5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl]carbamate. mp 250 °C. IR (KBr) 3304, 2859, 1634, 1587, 1532, 1478, 1365, 1332, 1269, 1157, 1111, 1032, 912, 807 cm⁻¹. ¹H NMR (300 MHz, DMSO-d₆): δ 1.86 (s, 2H), 2.63 (s, 1H), 3.23 (d, 2H, *J* = 9.0 Hz), 3.66 (d, 2H, *J* = 9.0 Hz), 6.75-7.15 (m, 3H), 8.17 (2H, d, *J* = 7.8 Hz), 8.36 (2H, d, *J* = 7.8 Hz), 11.23 (s, 1H). [M+H]⁺ = 359.

Example 4

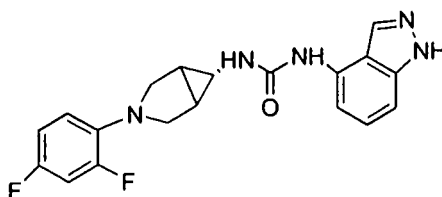
Preparation of 1-[(1*α*,5*α*,6*α*)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[(4-trifluoromethyl) phenyl] urea:



The title compound is prepared by the method as described in step 5 of the Example I from 1*α*, 5*α*, 6*α*-*tert*-butyl [3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]carbamate and phenyl-4-(trifluorophenyl)]carbamate. m.pt: 189-191 °C. IR (KBr) 3304, 2859, 1634, 1587, 1532, 1478, 1365, 1332, 1269, 1157, 1111, 1032, 912, 807 cm⁻¹. ¹H NMR (300 MHz, DMSO-d₆): δ 1.84 (s, 2H), 2.63 (s, 1H), 3.23 (d, 2H, *J* = 9.0 Hz), 3.65 (d, 2H, *J* = 9.0 Hz), 6.60 (s, 1H), 6.73-6.81 (m, 1H), 6.89-6.94 (m, 1H), 7.08-7.16 (m, 2H), 7.55-7.63 (m, 4H), 8.83(s, 1H). [M+H]⁺ = 398.

Example 5

Preparation of 1-[(1*α*,5*α*,6*α*)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(1*H*-indazol-4-yl) urea:



Step 1: 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(1-ethoxycarbonyl-1H-indazol-4-yl) urea:

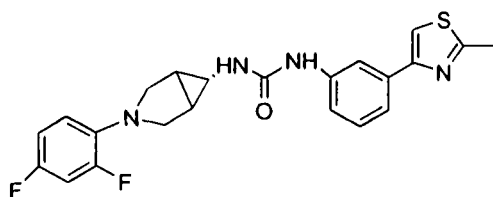
The title compound is prepared by the method as described in step 5 of the Example I from 1 α , 5 α , 6 α -*tert*-butyl [3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]carbamate and phenyl-4-(1-ethoxycarbonyl-1H-indazol-4-yl)carbamate. The product obtained after usual work up is taken ahead for next step.

Step 2: 1-[(α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(1H-indazol-4-yl) urea:

A mixture of N-[3-(2,4-difluoro)phenyl]-3-azabicyclo[3.1.0]-hex-6-yl-N'-(1-ethoxycarbonyl-1H-indazol-4-yl) urea (10 mmol) and sodium hydroxide (28 mmol) in a mixture of methanol and tetrahydrofuran is stirred at room temperature for about 4-5 hours. The crude product obtained after usual work up and extraction with ethyl acetate is purified through silica gel column to get desired product as buff colour solid. mp 233-234 °C. IR (KBr): 3293, 1642, 1561, 1512, 1477, 1360, 1327, 1269, 1245, 1138, 1101, 1024, 946, 855 cm⁻¹. ¹H NMR (300 MHz, DMSO-d₆): δ 1.80 (s, 2H), 2.59 (s, 1H), 3.21 (d, 2H, J = 9.0 Hz), 3.65 (d, 2H, J = 9.0 Hz), 6.60 (s, 1H), 6.76-6.78 (m, 1H), 6.90-6.92 (m, 1H), 7.04-7.20 (m, 2H), 7.69 (d, 1H, J = 8.1 Hz), 8.06 (s, 1H), 8.60 (s, 1H), 13.00 (s, 1H). [M+H]⁺ = 370

Example 6

Preparation of 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(2-methyl-1,3-thiazol-4-yl)phenyl]urea:



Step 1:- 2-bromo-1-(3-nitrophenyl)ethanone:

To a stirred solution of 3-nitro acetophenone (0.0121 mole) in diethyl ether at -5 to 0°C, bromine (0.0242 mole) is added at the same temperature and the reaction mixture is stirred at room temperature for 10 hours. The reaction mixture is then filtered, washed with diethyl ether followed by pet. ether (cold) and dried under vacuum. ¹H NMR (CDCl₃): δ 4.48 (s, 2H); 7.69 (m, 1H); 8.31 (dd, 1H); 8.45 (dd, 1H); 8.79 (s, 1H).

Step 2:- 2-methyl-4-(3-nitrophenyl)-1, 3-thiazole:

To a stirred solution of 2-bromo-1-(3-nitrophenyl)ethanone (0.002 mole) in 10 mL of ethanol is added thioacetamide (0.002 mole) followed by sodium sulphate (0.0023 mole) and refluxed the reaction mixture for 24 hours under nitrogen. The reaction mixture is diluted with ethanol (10 mL), filtered the solid and the filtrate is concentrated to get crude product which is purified by column chromatography. ^1H NMR (CDCl_3): δ 2.78 (s, 3H); 7.46 (s, 1H); 7.56 (t, 1H, $J = 5.4$ Hz); 8.16 (m, 2H); 8.69 (t, 1H). MS $[\text{M}+\text{H}]^+$: 221.65.

Step 3:- 3-(2-methyl-1,3-thiazol-4-yl)aniline:

To a stirred solution of 2-methyl-4-(3-nitrophenyl)-1, 3-thiazole (0.00318 mole) in 20 mL methanol, is added 0.1 g, (0.00348 mole) of Pd/C and the reaction mixture is subjected to hydrogenation at 60 psi for 6 hours. The reaction mixture is filtered to remove the catalyst and the filtrate is concentrated to get the desired product. ^1H NMR ($\text{DMSO}-d_6$): δ 2.49 (s, 3H); 5.13 (s, 2H); 6.48 (m, 1H); 7.01 (d, 2H, $J = 4.8$ Hz); 7.16 (s, 1H); 7.67 (s, 1H). MS $[\text{M}+\text{H}]^+$: 191.74.

Step 4:- phenyl[3-(2-methyl-1,3-thiazol-4-yl)phenyl]carbamate:

To a stirred solution of 3-(2-methyl-1,3-thiazol-4-yl)aniline (0.0010 mole) in DCM (10mL) is added phenyl chloroformate (0.0011 mole) and stirred the reaction mixture for 4 hours at room temperature. A solution of aq. NaHCO_3 is added to the reaction mixture and extracted with dichloromethane. The organic layer then dried over Na_2SO_4 and concentrated to get crude product and the crude is purified by column chromatography. ^1H NMR (CDCl_3): δ 2.7 (s, 3H); 7 (s, 1H); 7.2 (m, 2H); 7.3 (dd, 5H); 7.55 (d, 1H); 7.9 (s, 1H). MS $[\text{M}+\text{H}]^+$: 311.50.

Step 5:- 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(2-methyl-1,3-thiazol-4-yl)phenyl]urea:

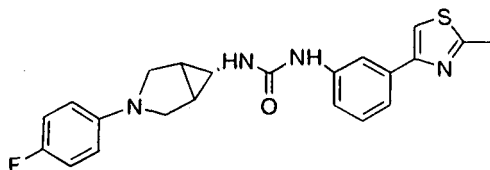
To a stirred solution of 3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine (0.0032 mole) in DMSO is added TEA (0.0032 mole) followed by a solution of phenyl[3-(2-methyl-1,3-thiazol-4-yl)phenyl]carbamate (0.0032 mole) in DMSO and stirred for 24 hours at room temperature. The reaction mixture is then diluted with ethyl acetate (20 mL) and washed water. The organic layer is then separated, dried over Na_2SO_4 and concentrated to get the crude material which is purified by column chromatography. ^1H NMR (CDCl_3): δ 1.7 (dd, 2H); 2.55 (d, 1H); 2.7 (s, 3H); 3.1 (d, 2H); 3.6 (d, 2H, $J = 8.7$ Hz); 6.4 (s, 1H); 6.8 (dd, 1H); 7.1 (dd, 1H); 7.2 (d, 1H, $J = 7.8$ Hz); 7.3 (d, 1H, $J = 6.9$ Hz); 7.4 (d, 2H, $J = 7.2$ Hz); 7.7

(s, 1H); 8 (s, 1H); 8.4 (s, 1H). IR (KBr) (cm^{-1}): 3296, 2928, 2857, 1651, 1609, 1568, 1515, 1321, 1133, 948, 797, 746.

MS $[\text{M}+\text{H}]^+$: 427. M. P. – 169°C.

Example 7

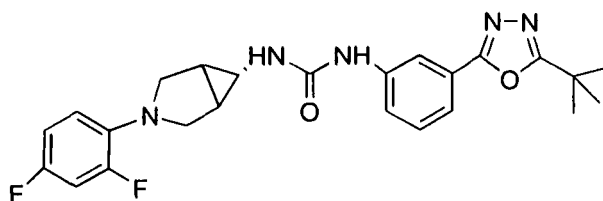
Preparation of 1-[(1 α ,5 α ,6 α)-3-(4-fluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(2-methyl-1,3-thiazol-4-yl)phenyl]urea:



The title compound is prepared by procedure as described in example 6, step 5 using phenyl[3-(2-methyl-1,3-thiazol-4-yl)phenyl]carbamate and 3-(4-fluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine. ^1H NMR ($\text{DMSO}-d_6$): δ 1.8 (s, 2H); 2.4 (s, 1H); 2.7 (s, 3H); 3.1 (d, 2H, $J = 9.3$ Hz); 3.5 (d, 2H, $J = 8.7$ Hz); 6.4 (dd, 3H); 6.5 (d, 2H, $J = 4.2$ Hz); 6.9 (d, 1H, $J = 9$ Hz); 7.2 (d, 1H, $J = 7.8$ Hz); 7.3 (d, 1H, $J = 6.6$ Hz); 7.7 (s, 1H); 8 (s, 1H); 8.4 (s, 1H). IR (KBr) (cm^{-1}): 3384, 3285, 2847, 1656, 1609, 1564, 1518, 1364, 1227, 1173, 811, 784, 751. MS $[\text{M}+\text{H}]^+$: 409.65. M. P. – 207 °C.

Example 8

Preparation of 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(5-*tert*-butyl-1,3,4-oxadiazol-2-yl)phenyl]urea:



Step 1:- 3-nitrobenzohydrazide:

To a stirred solution of ethyl 3-nitrobenzoate (0.015 mole) in absolute ethanol (25 mL), hydrazine hydrate (0.0194 mole) is added and the mixture is refluxed at 80°C for 24 hours. The reaction mixture is then cooled, filtered and washed with water. The aqueous layer is then extracted with ethyl acetate. Organic layer is dried over Na_2SO_4 and

concentrated to get crude product which is purified by column chromatography. ^1H NMR (D_2O): δ 4.62 (s, 2H); 7.75 (t, 1H, $J = 8.4$ Hz); 8.23 (d, 1H, $J = 7.2$ Hz); 8.35 (d, 1H, $J = 8.4$ Hz); 8.61 (s, 1H); 10.14 (s, 1H). MS $[\text{M}-1]$: 180.76.

Step 2:- N-(2,2-dimethylpropanoyl)-3-nitrobenzohydrazide:

To a stirred solution of 3-nitrobenzohydrazide (0.0082 mole) in DCM (25 mL), TEA (0.0183 mole) is added at 0°C . To the above, pivaloyl chloride (0.0098 mole) is added drop wise and stirred for 15 mins. , the ice bath is removed and stirred at room temperature overnight. The residue formed was filtered, washed with (20 mL) DCM. Filtrate and the washings are combined and concentrated to get crude product which is purified by column chromatography. ^1H NMR (CDCl_3): δ 1.50 (s, 9H); 7.58 (t, 1H, $J = 7.8$ Hz); 8.26 (d, 2H); 8.81 (s, 1H). MS $[\text{M}+\text{H}]^+$: 266.34.

Step 3:- 2-tert-butyl-5-(3-nitrophenyl)-1,3,4-oxadiazole:

To a stirred solution of N-(2,2-dimethylpropanoyl)-3-nitrobenzohydrazide (0.000377 mole) in 10 mL of Ethyl acetate, POCl_3 (0.00074 mole) is added and the mixture is stirred at room temperature for 16 hrs. The reaction mixture is then neutralized with aq. NaHCO_3 soln. at 0°C and extracted with ethyl acetate. The organic layer is then dried over Na_2SO_4 and concentrated to get the crude product which is purified by column chromatography. ^1H NMR (CDCl_3): δ 1.51 (s, 9H); 7.71 (t, 1H, $J = 7.8$ Hz); 8.39 (m, 2H); 8.81 (s, 1H).

Step 4:- 3-(5-tert-butyl-1,3,4-oxadiazol-2-yl)aniline:

To a solution of 2-tert-butyl-5-(3-nitrophenyl)-1,3,4-oxadiazole (0.7 g) in 50 mL of methanol, is added Pd/C (0.25 g) and the mixture is subjected to hydrogenation at 60 psi for 4 hrs. The catalyst is filtered, and the filtrate concentrated to obtain the crude product which is purified by column chromatography. ^1H NMR (CDCl_3): δ 1.30 (bs, 9H); 4.03 (s, 2H); 6.82 (s, 1H); 7.27 (s, 1H); 7.37 (s, 1H); 7.39 (s, 1H).

Step 5:- phenyl [3-(5-tert-butyl-1,3,4-oxadiazol-2-yl)phenyl]carbamate:

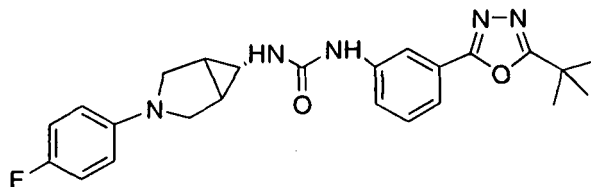
The title compound is prepared by the procedure as described in example 6, step 4 using 3-(5-tert-butyl-1,3,4-oxadiazol-2-yl)aniline and phenyl chloroformate. ^1H NMR (CDCl_3): δ 1.7 (s, 9H); 6.85 (dd, 2H); 7.25 (dddd, 3H); 7.35 (dd, 2H); 7.55 (dd, 2H); 8.15 (s, 1H).

Step 6:- 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(5-tert-butyl-1,3,4-oxadiazol-2-yl)phenyl]urea:

The title compound is prepared by the procedure as described in example 6, step 5 using phenyl [3-(5-*tert*-butyl-1,3,4-oxadiazol-2-yl)phenyl]carbamate and 3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine. ¹H NMR (DMSO- *d*₆): δ 1.4 (s, 9H); 1.7 (s, 2 H); 2.5 (d, 1H); 3.1 (d, 2H, *J* = 7.8 Hz); 3.6 (d, 2H, *J* = 9.3 Hz); 6.5 (s, 1H); 6.7 (dd, 1H); 6.9 (dd, 1H); 7.1 (dd, 1H, *J* = 9.3 Hz); 7.4 (dd, 1H, *J* = 7.8 Hz); 7.5 (ddd, 2H, *J* = 6.9 Hz); 8.1 (s, 1H); 8.7 (s, 1H). IR (KBr) (cm⁻¹): 3370, 2842, 1698, 1694, 1610, 1572, 1478, 1224, 1131, 1098, 947, 787, 683. MS [M+H]⁺ : 454.65. M. P. – 229 °C.

Example 9

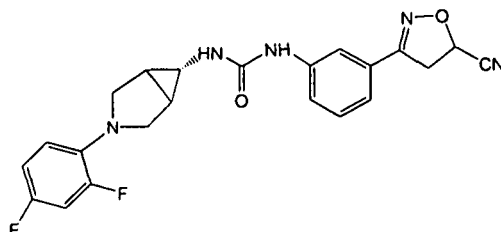
Preparation of 1-[(1 α ,5 α ,6 α)-3-(4-fluorophenyl)-3-azabicyclo [3.1.0]hex-6-yl]-3-[3-(5-*tert*-butyl-1,3,4-oxadiazol-2-yl)phenyl]urea:



The title compound is prepared by the procedure as described in example 6, step 5 using phenyl [3-(5-*tert*-butyl-1,3,4-oxadiazol-2-yl)phenyl]carbamate and 3-(4-fluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine. ¹H NMR (DMSO- *d*₆): δ 1.4 (s, 9H); 1.8 (s, 2H); 3.1(d, 3H, *J* = 7.8 Hz); 3.5 (d, 2H, *J* = 8.7 Hz); 6.5 (dd, 3H); 6.9 (t, 2H, *J* = 8.4 Hz); 7.4 (t, 1H, *J* = 7.5 Hz); 7.5 (dd, 2H, *J* = 7.5 Hz); 8.1 (s, 1H); 8.7 (s, 1H). IR (KBr) (cm⁻¹): 3371, 2818, 1693, 1610, 1572, 1543, 1478, 1306, 1220, 1162, 1089, 787, 719. MS [M+H]⁺ : 436.80. M. P. – 224 °C.

Example 10

Preparation of 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(5-cyano-4,5-dihydroisoxazol-3-yl)phenyl]urea:



Step 1:- 3-(3-nitrophenyl)-4,5-dihydroisoxazole-5-carbonitrile

To a solution of 3-nitrobenzaldehyde oxime (0.0030 mole) in acetonitrile (10 mL), acrylonitrile (0.0032mole) is added followed by the addition of ceric ammonium nitrate

(0.0065 mole) and the reaction mixture is stirred at room temperature. After Completion of reaction 20 ml of water added and extracted with ethyl acetate. The organic layer is dried over Na₂SO₄, Concentrated and purified by column chromatography. ¹H NMR (CDCl₃): δ 3.85 (dd, 2H); 5.45 (t, 1H); 7.65 (d, 1H); 8 (d, 1H); 8.35 (d, 1H); 8.4 (s, 1H).

Step 2:- 3-(3-aminophenyl)-4,5-dihydroisoxazole-5-carbonitrile:

The title compound is prepared by procedure as described in example 6, step 3 using 3-(3-nitrophenyl)-4,5-dihydroisoxazole-5-carbonitrile. ¹H NMR (DMSO- *d*₆): δ 3.1 (t, 1H); 3.50 (d, 2H); 5.3 (s, 2H); 6.6 (dd, 1H); 6.7 (dd, 1H); 6.9 (s, 1H); 7.0 (dd, 1H). MS [M+H]⁺: 188.5.

Step 3:- phenyl[3-(5-cyno-4,5-dihydroisoxazole-3-yl)phenyl]carbamate:

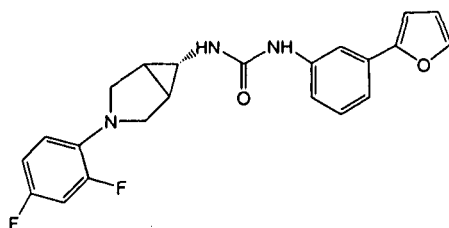
The title compound is prepared by procedure as described in example 6, step 4 using 3-(3-aminophenyl)-4,5-dihydroisoxazole-5-carbonitrile and phenyl chloroformate. ¹H NMR CDCl₃): δ 3.75 (d, 2H); 5.3 (t, 1H); 6.85 (dd, 2H); 6.80 (dd, 1H); 7.2 (m, 5H); 7.4 (d, 1H); 7.8 (s, 1H).

Step 4:- 1-[(1α,5α,6α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(5-cyano-4,5-dihydroisoxazol-3-yl)phenyl]urea:

The title compound is prepared by procedure as described in example 6, step 5 using 3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine and phenyl[3-(5-cyno-4,5-dihydroisoxazole-3-yl)phenyl]carbamate. ¹H NMR (DMSO- *d*₆): δ 2.54 (d, 1H); 3.1 (d, 3H, J = 8.7 Hz); 3.6 (d, 3 H, J = 9.3 Hz); 3.8 (d, 2H, J = 7.8 Hz); 5.7 (dd, 1H); 6.4 (ddd, 1H); 6.7 (dd, 1H); 6.8 (dd, 1H); 7 (dd, 1H); 7.2 (dd, 1H, J = 7.2 Hz); 7.3 (dd, 1H); 7.4 (d, 1H); 7.8 (s, 1H); 8.5 (s, 1H). IR (KBr) (cm⁻¹): 3328, 2853, 1654, 1562, 1518, 1362, 1227, 1135, 948, 796, 689. MS [M+1]⁺: 424.72. M. P. - 210 °C.

Example 11

Preparation of 1-[(1α,5α,6α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(2-furyl)phenyl]urea:



Step 1:- 3-(2-furyl)aniline:

To a solution of 3-bromoaniline (0.000581 mole) in 1,4-dioxane (5 mL) is added 2-furanboronic acid (0.000697 mole) followed by Bis(dichloro)triphenyl phosphoryl palladium (II) (0.000029 mole) and stirred the reaction mixture for half an hour at RT. 1M Na₂CO₃ solution (0.00174 mole) is added and heated the reaction mixture at 80°C for 2 hrs. The reaction mixture is then quenched with water and extracted with ethyl acetate. The organic layer is dried over Na₂SO₄, concentrated and purified by column chromatography. ¹H NMR (DMSO- *d*₆): δ 5.17 (s, 2H); 6.44 (d, 1H, J = 9Hz); 6.51(d, 1H); 6.71(d, 1H); 6.80 (d, 1H, J = 9Hz); 6.87 (s, 1H); 6.99 (t, 1H, J= 9 Hz); 7.66 (s, 1H).

Step 2:- phenyl [3-(2-furyl)phenyl]carbamate:

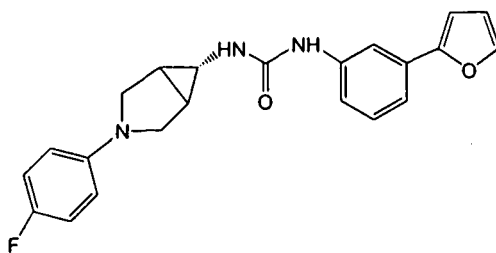
The title compound is prepared by procedure as described in example 6, step 4 using 3-(2-furyl)aniline and phenyl chloroformate. ¹H NMR (DMSO- *d*₆): δ 6.57 (d, 1H); 6.87 (d, 1H); 7.11-7.27 (m, 3H); 7.37-7.44 (m, 5H); 7.73 (s, 1H); 7.88 (s, 1H); 10.32 (s, 1H).

Step3:- 1-[(1α,5α,6α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(2-furyl)phenyl]urea

The title compound is prepared by procedure as described in example 6, step 5 using 3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine and phenyl [3-(2-furyl)phenyl]carbamate. ¹H NMR (DMSO- *d*₆): δ 1.76 (s, 2H); 2.50 (s, 1H); 3.19 (d, 2H, J = 9 Hz); 3.64 (d, 2H, J = 9 Hz); 6.45 (d, 1H); 6.56 (d, 1H); 6.76-6.90 (m, 3H); 7.06 (m, 1H); 7.23 (m, 3H); 7.71 (s, 1H); 7.83 (s, 1H); 8.48 (s, 1H). IR (KBr) (cm⁻¹): 3435, 2926, 2851, 1650, 1614, 1565, 1517, 1359, 1228, 1134, 1014, 948, 790, 737. MS [M+H]⁺: 412.41. mp.: 159°C.

Example 12

Preparation of 1-[(1α,5α,6α)-3-(4-fluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(2-furyl)phenyl]urea:

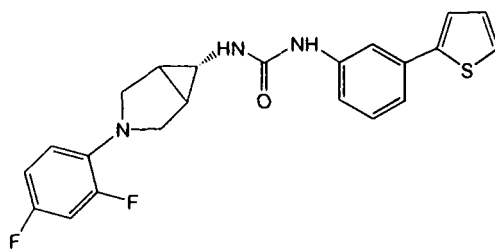


The title compound is prepared by procedure as described in example 6, step 5 using 3-(4-fluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine and phenyl [3-(2-

furyl)phenyl]carbamate. ^1H NMR (DMSO- d_6): δ 1.82 (s, 2H); 2.50 (s, 1H); 3.16 (d, 2H, $J = 9$ Hz); 3.55 (d, 2H, $J = 9$ Hz); 6.40-6.55 (m, 4H); 6.81 (s, 1H); 6.98 (t, 2H); 7.23 (m, 3H); 7.71 (s, 1H); 7.83 (m, 1H); 8.46 (s, 1H). IR (KBr) (cm^{-1}): 3295, 2848, 1648, 1613, 1580, 1519, 1364, 1227, 1155, 1014, 814, 785, 691. mp.: 180°C.

Example 13

Preparation of 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(2-thiophenyl)phenyl]urea:



Step 1:- 3-(2-thienyl)aniline:

The title compound is prepared by procedure as described in example 11, step 1 using 3-bromo aniline (0.000581 mole) and 2-thiophene boronic acid (0.000639 mole). ^1H NMR (DMSO- d_6): δ 5.20 (s, 2H); 6.46 (d, 1H, $J = 9$ Hz); 6.76-6.81 (m, 2H); 6.99-7.08 (m, 2H); 7.31 (s, 1H); 7.44 (s, 1H).

Step 2:- phenyl [3-(2-thienyl)phenyl]carbamate:

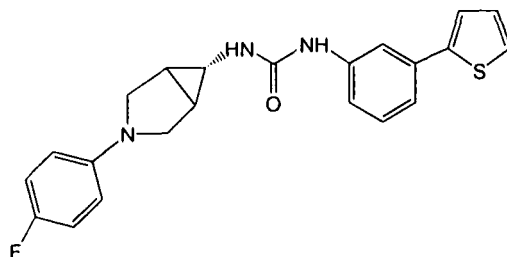
The title compound is prepared by procedure as described in example 6, step 4 using 3-(2-thienyl)aniline and phenyl chloroformate. ^1H NMR (DMSO- d_6): δ 6.57 (s, 1H); 6.86 (s, 1H); 7.20- 7.27 (m, 3H); 7.36- 7.43 (m, 5H);n 7.73 (s, 1H); 7.88 (s, 1H); 10.30 (s, 1H).

Step3:-1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(2-thionyl)phenyl]urea

The title compound is prepared by procedure as described in example 6, step 5 using 3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine and phenyl [3-(2-thienyl)phenyl]carbamate ^1H NMR (DMSO- d_6): δ 1.76 (s, 2H); 2.49 (s, 1H); 3.19 (d, 2H, $J = 9$ Hz); 3.64 (d, 2H, $J = 9$ Hz); 6.45 (d, 1H); 6.74 (m, 1H); 6.89 (m, 1H); 7.10 (m, 2H); 7.20 (m, 3H); 7.39 (s, 1H); 7.52 (d, 1H, $J = 6$ Hz); 7.78 (s, 1H), 8.49 (s, 1H). IR (KBr) (cm^{-1}) $\therefore$ 3293, 2848, 1650, 1605, 1518, 1308, 1228, 1134, 948, 790, 704. mp.: 204°C.

Example 14

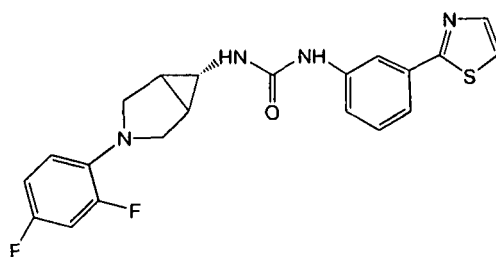
Preparation of 1-[(1 α ,5 α ,6 α)-3-(4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(2-thiophenyl)phenyl]urea:



The title compound is prepared by procedure as described in example 6, step 5 using 3-(4-fluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine and phenyl [3-(2-thienyl)phenyl]carbamate ^1H NMR (DMSO- d_6): δ 1.82 (s, 2H); 2.41 (s, 1H); 3.13 (d, 2H, J = 9 Hz); 3.55 (d, 2H, J = 9 Hz); 6.50 (m, 3H); 6.98 (t, 2H, J = 9 Hz); 7.10 (t, 1H, J = 6 Hz); 7.24 (m, 3H); 7.41 (s, 1H); 7.52 (d, 1H, J = 6 Hz); 7.79 (s, 1H); 8.49 (s, 1H). IR (KBr) (cm^{-1}) : 3289, 3049, 2841, 1650, 1606, 1566, 1518, 1364, 1226, 1168, 813, 784, 700. MS $[\text{M}+1]^+$: 394.69. mp.: 186°C.

Example 15

Preparation of 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(1,3-thiazol-2-yl)phenyl]urea:



Step 1:- 2-(3-nitrophenyl)-1,3-thiazole:

The title compound is prepared by procedure as described in example 11, step 1 using 2-bromo-1,3-thiazole (0.00304 mole) and 3-nitrophenyl boronic acid (0.00365 mole). ^1H NMR (DMSO- d_6): δ 7.76 (m, 1H); 7.91 (s, 1H); 8.01 (s, 1H); 8.27- 8.37 (m, 2H); 8.66 (s, 1H).

Step 2:- 3-(1,3-thiazol-2-yl)aniline

The title compound is prepared by procedure as described in example 6, step 3, using 2-(3-nitrophenyl)-1,3-thiazole. ^1H NMR (DMSO- d_6): δ 7.03 (s, 1H); 7.20 (s, 1H); 7.44 (m, 2H); 7.73 (s, 1H); 8.12 (d, 1H, $J = 9$ Hz).

Step 3:- phenyl [3-(1,3-thiazol-2-yl)phenyl]carbamate

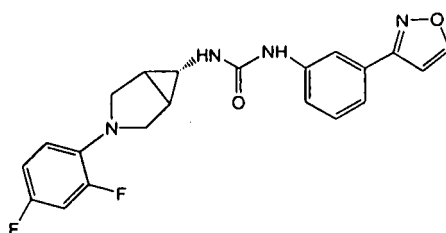
The title compound is prepared by procedure as described in example 6, step 4 using 3-(1,3-thiazol-2-yl)aniline and phenyl chloroformate. ^1H NMR (DMSO- d_6): δ 6.73 (d, 3H, $J = 9$ Hz); 7.10-7.55 (m, 7H); 8.25 (d, 1H); 9.32 (s, 1H).

Step 4:- 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(1,3-thiazol-2-yl)phenyl]urea:

The title compound is prepared by procedure as described in example 6, step 5 using 3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine and phenyl [3-(1,3-thiazol-2-yl)phenyl]carbamate. ^1H NMR (DMSO- d_6): δ 1.77 (s, 2H); 2.56 (s, 1H); 3.19 (d, 2H, $J = 9$ Hz); 3.65 (d, 2H, $J = 9$ Hz); 6.48 (s, 1H); 6.76 (m, 1H); 6.89 (m, 1H); 7.09 (t, 1H); 7.31-7.48 (m, 3H); 7.75 (s, 1H); 7.87 (s, 1H); 8.15 (s, 1H); 8.61 (s, 1H). IR (KBr) (cm^{-1}): 3296, 2928, 2857, 1651, 1609, 1568, 1515, 1321, 1133, 948, 797, 746. mp. 201°C.

Example 16

Preparation of 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(3-isoxazol-3-yl)phenyl]urea:



Step 1:- 3-(dimethylamino)-1-(3-nitrophenyl)prop-2-en-1-one:

To a solution of 1-(3-nitrophenyl)ethanone (0.01212 mole) in toluene (50 mL), diisopropyl ethyl amine (0.02424 mole), or dimethylformamide dimethyl acetal (0.024 mole) are added and refluxed the reaction mixture for 4 hrs. The reaction mixture is then cooled to room temperature, quenched with water and extracted with ethyl acetate. The organic layer is then dried over Na_2SO_4 and concentrated. The crude material is then triturated with ethyl acetate and decanted the solvent to get pure product. ^1H NMR (DMSO- d_6): δ 2.97 (s, 3H);

3.19 (s, 3H); 5.90 (d, 1H, J = 12 Hz); 7.71 (t, 1H, J = 9 Hz); 7.81 (d, 1H, J = 12 Hz); 8.32 (t, 2H, J = 6 Hz); 8.61 (s, 1H).

Step 2:- 3-(3-nitrophenyl)isoxazole:

To a solution of 3-(dimethylamino)-1-(3-nitrophenyl)prop-2-en-1-one (0.0068 mole) in methanol (20 mL), hydroxyl amine hydrochloride (0.01362 mole) is added and refluxed the reaction mixture for 3 hrs. Methanol is evaporated from the reaction mixture under vacuum; water is added to the residue and extracted with ethyl acetate. The organic layer is then dried over Na₂SO₄ and concentrated. ¹H NMR (DMSO- *d*₆): δ 7.37 (s, 1H); 7.83 (t, 1H, J = 9 Hz); 8.33 (d, 2H, J = 9 Hz); 8.67 (s, 1H); 8.77 (s, 1H).

Step 3:- 3-isoxazol-3-ylaniline:

The title compound is prepared by procedure as described in example 6, step 3, using 3-(3-nitrophenyl)isoxazole. ¹H NMR (DMSO- *d*₆): δ 7.41 (s, 1H); 7.88 (t, 1H); 8.28 (d, 2H); 8.64 (s, 1H); 8.78 (s, 1H); 10.17 (s, 2H).

Step 4:- phenyl (3-isoxazol-3-ylphenyl)carbamate:

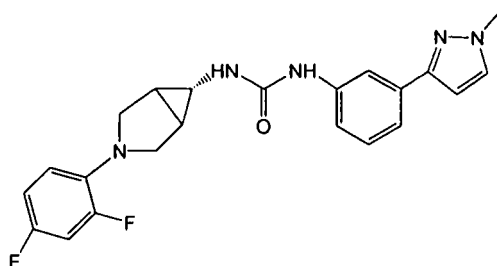
The title compound is prepared by procedure as described in example 6, step 4 using 3-isoxazol-3-ylaniline and phenyl chloroformate. ¹H NMR (CDCl₃): δ 3.89 (s, 1H); 7.23 (m, 5H); 7.34 (d, 2H); 7.42 (m, 4H).

Step 5:- 1-[(1α,5α,6α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(3-isoxazol-3-yl)phenyl)urea:

The title compound is prepared by procedure as described in example 6, step 5 using 3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine and phenyl (3-isoxazol-3-ylphenyl)carbamate. ¹H NMR (DMSO- *d*₆): δ 1.77 (s, 2H); 2.50 (s, 1H); 3.22 (d, 2H, J = 9 Hz); 3.65 (d, 2H, J = 9 Hz); 6.53 (d, 1H); 6.74 (m, 1H); 6.87 (m, 2H); 7.06 (m, 1H); 7.36-7.42 (m, 3H); 8.01 (s, 1H); 8.62 (s, 2H). IR (KBr) (cm⁻¹): 3328, 2853, 1654, 1562, 1518, 1362, 1227, 1135, 948, 796, 689. mp.: 142°C

Example 17

Preparation of 1-[(1α,5α,6α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(1-methyl-1*H*-pyrazol-3-yl)phenyl]urea:



Step 1:- 3-(dimethylamino)-1-(3-nitrophenyl)prop-2-en-1-one:

The title compound is prepared by procedure as described in example 11, step 1.

Step 2:- 3-(3-nitrophenyl)-1H-pyrazole:

The title compound is prepared by procedure as described in example 11, step 2 using 3-(dimethylamino)-1-(3-nitrophenyl)prop-2-en-1-one (0.00582 mole) and hydrazine hydrate (0.00582 mole). ¹H NMR (DMSO- *d*₆): δ 6.94 (s, 1H); 7.71 (t, 1H, *J* = 6 Hz); 7.88 (s, 1H); 8.13 (d, 1H, *J* = 9 Hz); 8.27 (d, 1H, *J* = 9 Hz); 8.62 (s, 1H); 13.63 (bs, 1H).

Step 3:- 1-methyl-3-(3-nitrophenyl)-1H-pyrazole:

The title compound is prepared by procedure as described in example 20, step 1 using 3-(3-nitrophenyl)-1H-pyrazole. Crude compound is taken for further reaction.

Step 4:- 3-(1-methyl-1H-pyrazol-3-yl)aniline:

The title compound is prepared by procedure as described in example 11, step 3 using 1-methyl-3-(3-nitrophenyl)-1H-pyrazole. ¹H NMR (DMSO- *d*₆): δ 3.83 (s, 3H); 5.14 (bs, 2H); 6.46 (d, 2H, *J* = 9 Hz); 6.88 (d, 1H, *J* = 6 Hz); 6.99 (m, 2H); 7.63 (s, 1H).

Step 5:- phenyl [3-(1-methyl-1H-pyrazol-3-yl)phenyl]carbamate:

The title compound is prepared by procedure as described in example 6, step 4 using and phenyl chloroformate and 3-(1-methyl-1H-pyrazol-3-yl)aniline. ¹H NMR (DMSO- *d*₆): δ 3.29 (s, 3H); 7.11 (s, 1H); 7.23 (d, 2H, *J* = 6 Hz); 7.35- 7.43 (m, 5H); 7.47- 63 (m, 1H); 8.17 (s, 1H); 8.58 (s, 1H); 10.34 (s, 1H).

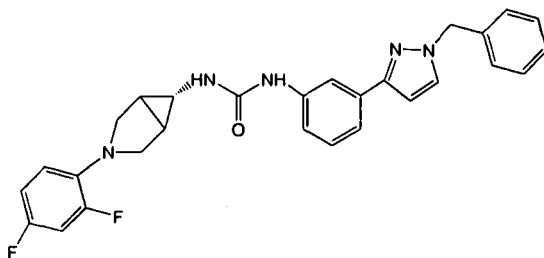
Step 6:- 1-[(1α,5α,6α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(1-methyl-1H-pyrazol-3-yl)phenyl]urea:

The title compound is prepared by procedure as described in example 6, step 5 using 3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine and phenyl [3-(1-methyl-1H-pyrazol-3-yl)phenyl]carbamate. ¹H NMR (CDCl₃): δ 1.76 (s, 2H); 2.53 (s, 1H); 3.19 (d, 2H, *J* = 9 Hz); 3.64 (d, 2H, *J* = 9 Hz); 3.86 (s, 3H); 6.39 (s, 1H); 6.55 (s, 1H); 6.74 (m, 1H); 7.06-

7.29 (m, 4H); 7.68 (s, 1H); 7.87 (s, 1H); 8.42 (s, 1H). IR (KBr) (cm^{-1}): 3389, 3295, 1651, 1612, 1570, 1478, 1360, 1217, 1134, 1051, 947, 795, 758, 724. MS $[M+1]^+$: 410.60. mp.: 147°C.

Example 18

Preparation of 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(1-benzyl-1H-pyrazol-3-yl)phenyl]urea:



Step 1:- 3-(dimethylamino)-1-(3-nitrophenyl)prop-2-en-1-one:

The title compound is prepared by procedure as described in example 11 step 1.

Step 2:- 3-(3-nitrophenyl)-1H-pyrazole:

The title compound is prepared by procedure as described in example 17, step 2.

Step 3:- 1-benzyl-3-(3-nitrophenyl)-1H-pyrazole:

The title compound is prepared by procedure as described in example 17, step 3 using 3-(3-nitrophenyl)-1H-pyrazole and benzyl bromide (0.00528 mole) and this crude compound is taken for further reaction.

Step 4:- 3-(1-benzyl-1H-pyrazol-3-yl)aniline:

The title compound is prepared by procedure as described in example 6, step 3 using 1-benzyl-3-(3-nitrophenyl)-1H-pyrazole. ^1H NMR ($\text{DMSO}-d_6$): δ 5.07 (s, 2H); 5.32 (s, 2H); 6.43 (d, 1H, $J = 9$ Hz); 6.55 (s, 1H); 6.86 (d, 1H, $J = 9$ Hz); 6.96-7.01 (d, 1H, $J = 7.8$ Hz); 7.21-7.32 (m, 6H); 7.82 (s, 1H).

Step 5:- phenyl [3-(1-benzyl-1H-pyrazol-3-yl)phenyl]carbamate:

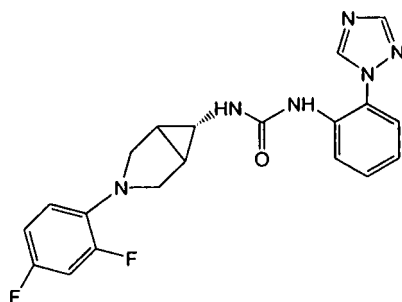
The title compound is prepared by procedure as described in example 6, step 4 using phenyl chloroformate and 3-(1-benzyl-1H-pyrazol-3-yl)aniline and this crude compound is taken for further reaction.

Step 6:- 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]- 3-[3-(1-benzyl-1H-pyrazol-3-yl)phenyl]urea:

The title compound is prepared by procedure as described in example 6, step 5 using 3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine and phenyl [3-(1-benzyl-1H-pyrazol-3-yl)phenyl]carbamate. ¹H NMR (DMSO- *d*₆): δ 1.75 (s, 2H); 2.49 (s, 1H); 3.18(d, 2H, J = 9 Hz); 3.63 (d, 2H, J= 9 Hz); 5.35 (s, 2H); 6.62 (s, 1H); 6.73 (m, 1H); 6.89 (s, 1H); 7.07-7.32 (m, 10H); 7.85 (s, 2H); 8.45 (s, 1H). IR (KBr) (cm⁻¹): 3389, 3300, 2924, 2855, 1655, 1574, 1514, 1478, 1333, 1217, 1133, 1051, 947, 851, 796, 722. MS [M+1]⁺ : 486.74. mp.: 112°C.

Example 19

Preparation of 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]- 3-[2-(1H-1,2,4-triazol-1-yl)phenyl]urea:



Step 1:- 1-(2-nitrophenyl)-1H-1,2,4-triazole:

To a stirred solution of 1-fluoro-2-nitrobenzene (0.0141 mole) in DMSO(10 mL), 1H-1,2,4-triazole (0.0156 mole) is added and heated to 80°C for 1 h. On completion of the reaction, water is added to the reaction mixture and extracted with ethyl acetate. The organic layer is dried over Na₂SO₄, concentrated and purified by column chromatography. H NMR (DMSO- *d*₆): δ 7.73 (m, 1H); 7.88 (s, 2H); 8.16 (d, 1H, J = 9 Hz); 8.24 (s, 1H); 9.11 (s, 1H).

Step 2:- 2-(1H-1,2,4-triazol-1-yl)aniline:

The title compound is prepared by procedure as described in example 6, step 3 using 1-(2-nitrophenyl)-1H-1,2,4-triazole. Crude compound is taken for further reaction.

Step 3:-phenyl [2-(1H-1,2,4-triazol-1-yl)phenyl]carbamate:

The title compound is prepared by procedure as described in example 6, step 4 using and phenyl chloroformate and 2-(1H-1,2,4-triazol-1-yl)aniline. ¹H NMR (DMSO- *d*₆): δ 7.06

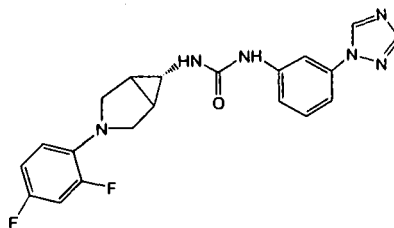
(d, 2H, J = 6 Hz); 7.20 (t, 1H, J = 6 Hz); 7.36 (t, 3H); 7.47-7.57 (m, 2H); 7.71 (d, 1H); 8.27 (s, 1H); 8.93 (s, 1H); 9.75 (s, 1H).

Step 4:- 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]- 3-[2-(1H-1,2,4-triazol-1-yl)phenyl]urea:

The title compound is prepared by procedure as described in example 6, step 5 using 3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine and phenyl [2-(1H-1,2,4-triazol-1-yl)phenyl]carbamate. ¹H NMR (DMSO- *d*₆): δ 1.72 (s, 2H); 2.50 (s, 1H); 3.17 (d, 2H, J = 9 Hz); 3.61 (d, 2H, J = 9 Hz); 6.75 (m, 1H); 6.89 (m, 1H); 7.10 (m, 3H); 7.41 (t, 2H); 8.11 (d, 1H); 8.26 (s, 1H); 8.93 (s, 1H). IR (KBr) (cm⁻¹) : 3334, 3240, 3101, 2936, 2870, 1688, 1598, 1514, 1452, 1342, 1276, 1135, 1061, 947, 755. mp.: 207°C.

Example 20

Preparation of 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]- 3-[3-(1H-1,2,4-triazol-1-yl)phenyl]urea:



Step 1:- 1-(3-nitrophenyl)-1H-1,2,4-triazole:

To a stirred solution of 1-Iodo-3-nitrobenzene (0.01418 mole) in DMF (20 mL), CuI (0.00141 mole), N,N-Dimethyl ethylenediamine (0.00283 mole), Tripotassium phosphate (0.0283 mole) and 1,2,4-triazole (0.0156 mole) are added and heated at 110°C for 8 hrs. On completion of reaction, water is added to the reaction mixture and extracted with ethyl acetate. The organic layer is dried over Na₂SO₄, concentrated and purified by column chromatography. ¹H NMR (DMSO- *d*₆) δ 7.82 (t, 2H); 8.23 (d, 1H; J = 6 Hz); 8.35 (d, 1H; J = 6 Hz); 8.68 (s, 1H); 9.51 (s, 1H).

Step 2:- 3-(1H-1,2,4-triazol-1-yl)aniline:

The title compound is prepared by procedure as described in example 6, step 3 using 1-(3-nitrophenyl)-1H-1,2,4-triazole. Crude compound is taken for further reaction.

Step 3:- phenyl [3-(1H-1,2,4-triazol-1-yl)phenyl]carbamate:

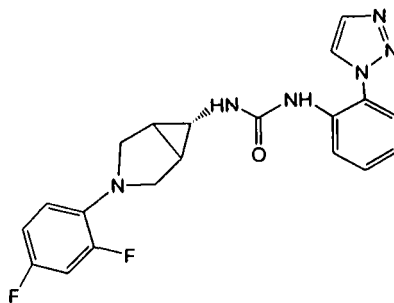
The title compound is prepared by procedure as described in example 6, step 4 using and phenyl chloroformate and 3-(1*H*-1,2,4-triazol-1-yl)aniline. ¹H NMR (DMSO- *d*₆): δ 7.21 (m, 3H); 7.39-7.49 (m, 5H); 8.07 (s, 1H); 8.21 (s, 1H); 9.23 (s, 1H); 10.51 (s, 1H).

Step 4:- 1-[(1α,5α,6α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]- 3-[3-(1H-1,2,4-triazol-1-yl)phenyl]urea:

The title compound is prepared by procedure as described in example 6, step 5 using 3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine and phenyl [3-(1*H*-1,2,4-triazol-1-yl)phenyl]carbamate. ¹H NMR (DMSO- *d*₆): δ 1.77 (s, 2H); 2.50 (s, 1H); 3.19 (d, 2H, *J* = 9 Hz); 3.64 (d, 2H, *J* = 9 Hz); 6.53 (s, 1H); 6.76 (m, 1H); 6.89 (m, 1H); 7.09 (m, 1H); 7.36 (s, 3H); 8.03 (s, 1H); 8.19 (s, 1H); 8.68 (s, 1H); 9.18 (s, 1H). IR (KBr) (cm⁻¹): 3313, 3105, 2848, 1639, 1603, 1518, 1315, 1227, 1138, 949, 790, 725. mp.: 187°C.

Example 21

Preparation of 1-[(1α,5α,6α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]- 3-[2-(1*H*-1,2,3-triazol-1-yl)phenyl]urea:



Step 1:- 1-(2-nitrophenyl)-1H-1,2,3-triazole:

To a stirred solution of 1-fluoro-2-nitrobenzene (0.0141mole) in DMSO, 1*H*-1,2,3-triazole (0.0156 mole) is added and heated at 80°C for 1 hrs. On completion of reaction, water is added and extracted with ethyl acetate. The organic layer is dried over Na₂SO₄, concentrated and purified by column chromatography. ¹H NMR (DMSO- *d*₆): δ 7.80-7.86 (m, 2H); 7.92-7.99 (m, 2H); 8.18 (d, 1H, *J* = 9 Hz); 8.70 (s, 1H).

Step 2:- 2-(1H-1,2,3-triazol-1-yl)aniline:

The title compound is prepared by procedure as described in example 6, step 3 using 1-(2-nitrophenyl)-1*H*-1,2,3-triazole. Crude compound is taken for reaction.

Step 3:- phenyl [2-(1H-1,2,3-triazol-1-yl)phenyl]carbamate:

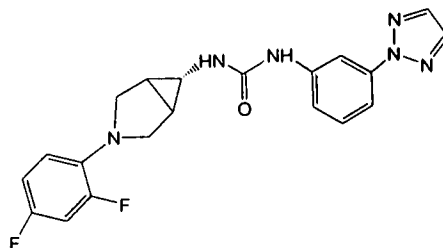
The title compound is prepared by procedure as described in example 6, step 4 using and phenyl chloroformate and 2-(1*H*-1,2,3-triazol-1-yl)aniline and this crude compound is taken for further reaction.

*Step 4:- 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[2-(1*H*-1,2,3-triazol-1-yl)phenyl]urea:*

The title compound is prepared by procedure as described in example 6, step 5 using 3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine and phenyl [2-(1*H*-1,2,3-triazol-1-yl)phenyl]carbamate. ¹H NMR (DMSO- *d*₆): δ 1.69 (s, 2H); 2.53 (s, 1H); 3.16 (d, 2H, *J* = 9 Hz); 3.62 (d, 2H, *J* = 9 Hz); 6.74 (m, 1H); 6.89 (m, 1H); 7.09-7.16 (m, 3H); 7.42 (m, 2H); 8.00 (s, 1H); 8.13 (d, 1H); 8.51 (s, 1H). IR (KBr) (cm⁻¹): 3433, 3107, 2981, 2827, 1687, 1595, 1516, 1451, 1343, 1229, 1137, 947, 848, 756. mp.: 138°C.

Example 22

Preparation of 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(2*H*-1,2,3-triazol-2-yl)phenyl]urea:



*Step 1:- 2-(3-nitrophenyl)-2*H*-1,2,3-triazole:*

To a stirred solution of 1-Iodo-3-nitrobenzene (0.01418 mole) in DMF (20 mL), CuI (0.00141 mole), N,N-Dimethyl ethylenediamine (0.00283 mole), tripotassium phosphate (0.0283 mole) and 1,2,3-triazole (0.0156 mole) are added and heated to 110°C for 8 hrs. On completion of reaction, water is added and extracted with ethyl acetate. The organic layer is dried over Na₂SO₄, concentrated and purified by column chromatography. ¹H NMR (DMSO- *d*₆): δ 7.83 (t, 1H, *J* = 9 Hz); 8.23 (s, 3H); 8.44 (d, 1H, *J* = 6 Hz); 8.69 (s, 1H).

*Step 2:- 3-(2*H*-1,2,3-triazol-2-yl)aniline:*

The title compound is prepared by procedure as described in example 6, step 3 using 2-(3-nitrophenyl)-2*H*-1,2,3-triazole. Crude compound is taken for reaction.

*Step 3:- phenyl [3-(2*H*-1,2,3-triazol-yl)phenyl]carbamate:*

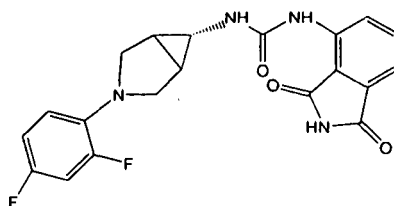
The title compound is prepared by procedure as described in example 6, step 4 using and phenyl chloroformate and 3-(2H-1,2,3-triazol-2-yl)aniline. ¹H NMR (DMSO- *d*₆): δ 7.23 (m, 3H); 7.40-7.50 (m, 4H); 7.69 (s, 1H); 8.10 (s, 2H); 8.35 (s, 1H); 10.53 (s, 1H).

Step 4: 1-[(1α,5α,6α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(2H-1,2,3-triazol-2-yl)phenyl]urea:

The title compound is prepared by procedure as described in example 6, step 5 using 3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine and phenyl [3-(2H-1,2,3-triazol-yl)phenyl]carbamate. ¹H NMR (DMSO- *d*₆): δ 1.78 (s, 2H); 2.56 (s, 1H); 3.19 (d, 2H, *J* = 9 Hz); 3.65 (d, 2H, *J* = 9 Hz); 6.51 (s, 1H); 6.76-6.90 (m, 2H); 7.10 (t, 1H); 7.32-7.37 (m, 2H); 7.52 (d, 1H); 8.07(s, 2H); 8.32 (s, 1H); 8.71 (s, 1H). IR (KBr) (cm⁻¹) : 3341, 3290, 2849, 1651, 1605, 1571, 1518, 1306, 1227, 1134, 948, 847, 788, 724. mp. :171°C.

Example 23

Preparation of 1-[(1α,5α,6α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-H-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl)urea:



Step 1:- 4-amino-1H-isoindole-1,3(2H)-dione:

The title compound is prepared by procedure as described in example 6, step 3 using 4-nitro-1H-isoindole-1,3(2H)-dione. This crude compound is taken for further reaction.

Step 2:- phenyl (1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl)carbamate:

The title compound is prepared by procedure as described in example 6, step 4 using and phenyl chloroformate and 4-amino-1H-isoindole-1,3(2H)-dione. ¹H NMR (DMSO- *d*₆): δ 7.25- 7.27 (m, 3H); 7.41 (t, 2H); 7.53 (d, 1H); 7.79 (t, 1H, *J* =9 Hz); 8.16 (d, 1H, *J* =9 Hz); 9.51 (s, 1H); 11.46 (s, 1H).

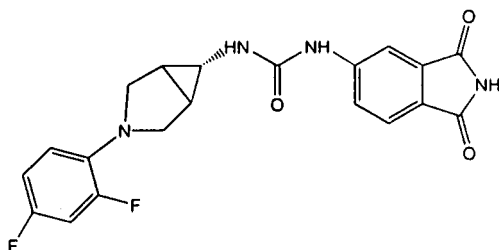
Step 3:- 1-[(1α,5α,6α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]- 3-(2-H-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl)urea:

The title compound is prepared by procedure as described in example 6, step 5 using 3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine and phenyl (1,3-dioxo-2,3-

dihydro-1*H*-isoindol-4-yl)carbamate. ¹H NMR (DMSO- *d*₆): δ 1.84 (s, 2H); 2.53 (s, 1H); 3.21 (d, 2H, *J* = 9 Hz); 3.73 (d, 2H); 6.73 (m, 1H); 6.88 (t, 1H); 7.10 (t, 1H, *J* = 9 Hz); 7.31 (d, 1H, *J* = 6 Hz); 7.64 (t, 1H, *J* = 6 Hz); 7.90 (s, 1H); 8.56 (m, 1H); 8.9 (s, 1H); 11.29 (bs, 1H). IR (KBr) (cm⁻¹): 3329, 3277, 3022, 1750, 1727, 1614, 1537, 1516, 1481, 1306, 1279, 1159, 1066, 948, 794, 745. mp.: > 250°C.

Example 24

Preparation of 1-[(1*α*,5*α*,6*α*)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-*H*-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)urea:



Step 1:- 5-amino-1H-isoindole-1,3(2H)-dione:

The title compound is prepared by procedure as described in example 6, step 3 using 5-nitro-1*H*-isoindole-1,3(2*H*)-dione. Crude compound is taken for further reaction.

Step 2:- phenyl (1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)carbamate:

The title compound is prepared by procedure as described in example 6, step 4 using and phenyl chloroformate and 5-amino-1*H*-isoindole-1,3(2*H*)-dione.

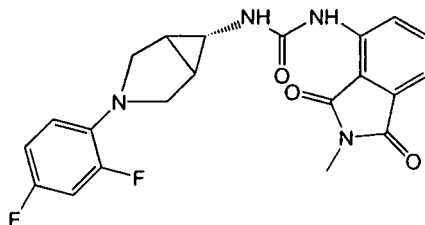
¹H NMR (DMSO- *d*₆): δ 7.25-7.27 (m, 3H); 7.41 (t, 2H); 7.53 (d, 1H); 7.79 (t, 1H, *J* = 9 Hz); 8.16 (t, 1H, *J* = 9 Hz); 9.51 (s, 1H); 11.46 (s, 1H).

Step 3:- 1-[(1α,5α,6α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-HS-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)urea:

The title compound is prepared by procedure as described in example 6, step 5 using 3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine and phenyl (1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)carbamate. ¹H NMR (DMSO- *d*₆): δ 1.79 (s, 2H); 2.58 (s, 1H); 3.22 (d, 2H, *J* = 9 Hz); 3.67 (d, 2H, *J* = 9Hz); 6.73 (m, 2H); 6.90 (t, 1H); 7.09- 7.10 (m, 1H); 7.64 (s, 2H); 7.99 (s, 1H); 9.09 (s, 1H). IR (KBr) (cm⁻¹): 3329, 3277, 1750, 1726, 1614, 1537, 1516, 1481, 1306, 1279, 1159, 1066, 948, 794, 745. mp.: > 250°C.

Example 25

Preparation of 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-methyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl)urea:



Step 1: 2-methyl-4-nitro-1H-isoindole-1,3(2H)-dione:

To a stirred solution of 4-nitro-1*H*-isoindole-1,3(2*H*)-dione (0.00520 mole) in DMF (5 mL), NaH (0.000528 mole) is added at 0°C and stirred the reaction mixture at RT for 30 min. To the above at 0°C, methyl iodide (0.000528 mole) is added and stirred for 2 h at room temperature. On completion of reaction, the reaction mixture is quenched with water, extracted with ethyl acetate and the organic layer dried and concentrated to get the desired product. ¹H NMR (DMSO- *d*₆): δ 3.04 (s, 3H); 8.04 (t, 1H, *J* = 9 Hz); 8.14 (d, 1H, *J* = 9 Hz); 8.25 (d, 1H, *J* = 6 Hz).

Step 2: 4-amino-2-methyl-1H-isoindole-1,3(2H)-dione:

The title compound is prepared by procedure as described in example 6, step 3 using 2-methyl-4-nitro-1*H*-isoindole-1,3(2*H*)-dione. ¹H NMR (DMSO- *d*₆): δ 2.96 (s, 3H); 6.42 (bs, 2H); 6.94 -6.97 (m, 2H); 7.38 (t, 1H, *J* = 9 Hz).

Step 3:- phenyl (2-methyl-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl)carbamate:

The title compound is prepared by procedure as described in example 6, step 4 using phenyl chloroformate and 4-amino-2-methyl-1*H*-isoindole-1,3(2*H*)-dione. ¹H NMR (DMSO- *d*₆): δ 3.02 (s, 3H); 7.24- 7.45 (m, 5H); 7.55 (d, 1H, *J* = 6 Hz); 7.78 (t, 1H, *J* = 9 Hz); 8.11 (d, 1H, *J* = 9 Hz); 9.54 (s, 1H). MS [M+H]⁺: 207.56.

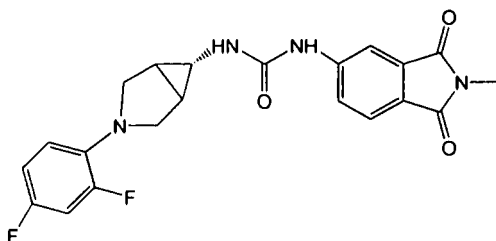
Step 4:- 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-methyl-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl)urea:

The title compound is prepared by procedure as described in example 6, step 5 using 3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine and phenyl (2-methyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl)carbamate. ¹H NMR (DMSO- *d*₆): δ 1.82 (s, 2H); 2.53 (s, 1H); 3.00 (s, 3H); 3.21(d, 2H, *J* = 9 Hz); 3.70 (d, 2H, *J* = 9 Hz); 6.75 (m, 1H); 6.90 (m, 1H); 7.11 (t, 1H, *J* = 9Hz); 7.34 (d, 1H,

$J = 9$ Hz); 7.63 (t, 1H); 7.90 (bs, 1H); 8.54 (d, 1H); 8.73 (bs, 1H). IR (KBr) (cm^{-1}): 3329, 3279, 3022, 1751, 1727, 1614, 1538, 1516, 1483, 1306, 1279, 1159, 1066, 948, 794, 745. MS $[M+1]^+$: 413. mp.: 244°C.

Example 26

Preparation of 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-methyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)urea:



Step 1:-2-methyl-4-nitro-1H-isoindole-1,3(2H)-dione:

The title compound is prepared by procedure as described in example 25, step 1 using 4-nitro-1*H*-isoindole-1,3(2*H*)-dione. ^1H NMR (DMSO- d_6): δ 3.08 (s, 3H); 8.10 (d, 1H, $J = 9$ Hz); 8.48 (s, 1H); 8.62 (d, 1H, $J = 6$ Hz).

Step 2:- 5-amino-2-methyl-1H-isoindole-1,3(2H)-dione:

The title compound is prepared by procedure as described in example 6, step 3 using 2-methyl-4-nitro-1*H*-isoindole-1,3(2*H*)-dione. ^1H NMR (DMSO- d_6): δ 2.94 (s, 3H); 6.47 (bs, 2H); 6.76 (d, 1H, $J = 6$ Hz); 6.91(s, 1H); 7.45 (d, 1H, $J = 9$ Hz).

Step 3:- phenyl (2-methyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)carbamate:

The title compound is prepared by procedure as described in example 6, step 4 using phenyl chloroformate and 5-amino-2-methyl-1*H*-isoindole-1,3(2*H*)-dione. ^1H NMR (DMSO- d_6): δ 3.00 (s, 3H); 7.24- 7.29 (m, 3H); 7.40 (t, 2H, $J = 9$ Hz); 7.81 (s, 2H); 7.98 (s, 1H); 10.90 (s, 1H).

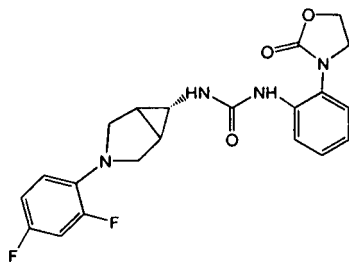
Step 4:- 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-methyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)urea:

The title compound is prepared by procedure as described in example 6, step 5 using 3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine and phenyl (2-methyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)carbamate. ^1H NMR (DMSO- d_6): δ 1.78 (s, 2H); 2.50 (s, 1H); 2.98 (s, 3H); 3.21 (d, 2H, $J = 9$ Hz); 3.64 (d, 2H, $J = 9$ Hz); 6.74 (m, 1H); 6.76 (m, 2H); 7.10 (m, 1H); 7.62-7.67 (m, 2H);

8.04 (s, 1H); 9.26 (s, 1H). IR (KBr) (cm^{-1}): 3328, 3279, 1750, 1728, 1615, 1537, 1516, 1483, 1306, 1279, 1159, 1065, 948, 796, 745. mp.: 202°C.

Example 27

Preparation of 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[2-(2-oxo-1,3-oxazolidin-3-yl)phenyl]urea:



Step 1:- 3-(2-nitrophenyl)-1,3-oxazolidin-2-one:

The title compound is prepared by procedure as described in example 19, step 1 using 1,3-oxazolidin-2-one and 1-fluoro-2-nitrobenzene. ^1H NMR ($\text{DMSO}-d_6$): δ 4.15 (t, 2H, $J = 9$ Hz); 4.49 (t, 2H, $J = 9$ Hz); 7.47 (t, 1H, $J = 9$ Hz); 7.63 (d, 1H); 7.75 (t, 1H); 7.97 (d, 1H, $J = 6$ Hz).

Step 2:- 3-(2-aminophenyl)-1,3-oxazolidin-2-one:

The title compound is prepared by procedure as described in example 6, step 3 using 3-(2-nitrophenyl)-1,3-oxazolidin-2-one. Crude compound is taken for further reaction.

Step 3:- phenyl [2-(2-oxo-1,3-oxazolidin-3-yl)phenyl]carbamate:

The title compound is prepared by procedure as described in example 6, step 4 using and phenyl chloroformate and 3-(2-aminophenyl)-1,3-oxazolidin-2-one. ^1H NMR ($\text{DMSO}-d_6$): δ 3.91 (t, 2H, $J = 9$ Hz); 4.46 (t, 2H, $J = 9$ Hz); 6.71 (d, 1H); 7.17-7.41(m, 7H); 7.76 (d, 1H); 9.72 (s, 1H).

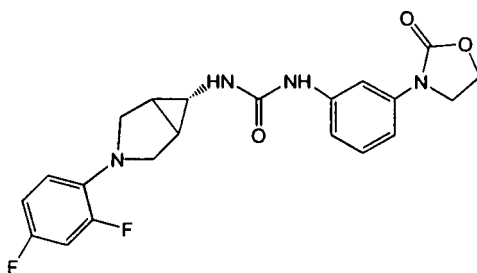
Step 4:- 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]- 3-[2-(2-oxo-1,3-oxazolidin-3-yl)phenyl]urea:

The title compound is prepared by procedure as described in example 6, step 5 using 3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine and phenyl [2-(2-oxo-1,3-oxazolidin-3-yl)phenyl]carbamate. ^1H NMR ($\text{DMSO}-d_6$): δ 1.77 (s, 2H); 2.49 (s, 1H); 3.22 (d, 2H); 3.63 (d, 2H); 3.84 (m, 2H); 4.46 (m, 2H); 6.75 (m, 1H); 6.82 (m, 1H); 6.96 (m, 2H);

7.14 (m, 1H); 7.28(m, 2H); 7.82 (s, 1H); 8.10 (m, 1H). IR (KBr) (cm^{-1}): 3413, 3328, 2906, 2867, 1740, 1688, 1599, 1515, 1457, 1358, 1219, 1139, 1032, 946, 763. mp.: 126°C.

Example 28

Preparation of 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-oxo-1,3-oxazolidin-3-yl)phenyl]urea:



Step 1:- 3-(3-nitrophenyl)-1,3-oxazolidin-2-one

The title compound is prepared by procedure as described in example 20, step 1 using 1,3-oxazolidin-2-one. ^1H NMR (DMSO- d_6): δ 4.14 (t, 2H, $J = 7.2$ Hz); 4.56 (t, 2H, $J = 8.7$ Hz); 7.55 (t, 1H, $J = 8.4$ Hz); 7.97 (d, 1H, $J = 6.6$ Hz); 8.14 (d, 1H, $J = 6.7$ Hz); 8.20 (s, 1H).

Step 2:- 3-(3-aminophenyl)-1,3-oxazolidin-2-one:

The title compound is prepared by procedure as described in example 6, step 3 using 3-(3-nitrophenyl)-1,3-oxazolidin-2-one. ^1H NMR (DMSO- d_6): δ 3.95 (t, 2H, $J = 7.2$ Hz); 4.37 (t, 2H, $J = 8.1$ Hz); 5.16 (bs, 2H); 6.29 (d, 1H, $J = 6.9$ Hz); 6.13 (d, 1H, $J = 7.8$ Hz); 6.82 (bs, 1H); 6.96 (t, 1H, $J = 7.8$ Hz). MS $[\text{M}+\text{H}]^+$: 179.75.

Step 3:- phenyl [3-(2-oxo-1,3-oxazolidin-3-yl)phenyl]carbamate:

The title compound is prepared by procedure as described in example 6, step 4 using and phenyl chloroformate and 3-(3-aminophenyl)-1,3-oxazolidin-2-one. ^1H NMR (DMSO- d_6): δ 4.01 (t, 2H, $J = 7.2$ Hz); 4.21 (t, 2H, $J = 8.1$ Hz); 6.72 (d, 1H, $J = 7.8$ Hz); 7.21 (m, 5H); 7.39 (t, 2H, $J = 7.2$ Hz); 7.79 (s, 1H); 10.27 (s, 1H).

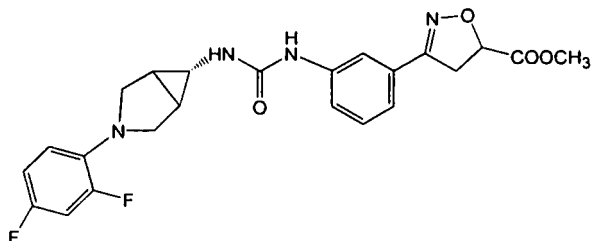
Step 4:- 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]- 3-(2-oxo-1,3-oxazolidin-3-yl)phenyl]urea:

The title compound is prepared by procedure as described in example 6, step 5 using 3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine and phenyl [3-(2-oxo-1,3-oxazolidin-3-yl)phenyl]carbamate. ^1H NMR (DMSO- d_6): δ 1.75 (bs, 2H); 3.91 (d, 2H, $J = 8.4$ Hz); 3.64 (d, 2H, $J = 6.6$ Hz); 4.01 (t, 2H, $J = 8.4$ Hz); 4.41 (t, 2H, $J = 8.1$ Hz); 6.73 (s ,

1H); 6.75 (m, 1H); 6.89 (m, 1H); 7.06 (bs, 1H); 7.18 (m, 4H); 7.66 (s, 1H); 8.49 (s, 1H). IR (KBr) (cm^{-1}): 3290, 3058, 2848, 1643, 1567, 1511, 1358, 1269, 1225, 1135, 1099, 1025, 946, 848, 792, 724. MS $[\text{M}+\text{H}]^+$: 415.50. mp.: Decomposes above 230°C.

Example 29

Preparation of 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[methyl 3-phenyl-4,5-dihydroisoxazole-5-carboxylate]urea:



Step 1:- 3-nitrobenzaldehyde oxime:

To a stirred solution of 3-nitrobenzaldehyde (0.0198 moles) in ethanol (35 mL), hydroxylamine hydrochloride (0.023 mole) is added and the reaction mixture neutralized to pH 8 by the addition of sat. NaHCO_3 and the reaction mixture is stirred at room temperature for 3 hrs. The reaction mixture is diluted with water, extracted with ethyl acetate and the organic layer concentrated to get the desired compound. ^1H NMR ($\text{DMSO}-d_6$): δ 7.68 (t, 1H, $J = 7.8$ Hz); 8.02 (d, 1H, $J = 7.8$ Hz); 8.20 (d, 1H, $J = 8.4$ Hz); 8.30 (s, 1H); 8.39 (s, 1H); 11.64 (s, 1H). MS ($\text{M}-\text{H}$): 165.28.

Step 2:- methyl 3-(3-nitrophenyl)-4,5-dihydroisoxazole-5-carboxylate:

To a stirred solution of 3-nitrobenzaldehyde oxime (0.014 mole) in acetonitrile (20 mL), methyl acrylate (0.014 mole) is added followed by ceric ammonium nitrate (0.0342 mole) and the mixture is stirred at room temperature for 18 hrs. The reaction mixture is diluted with ethyl acetate and washed with water. The organic layer is dried over Na_2SO_4 , concentrated and purified by column chromatography. ^1H NMR (CDCl_3): δ 3.68-3.77 (m, 3H); 3.81-3.91 (m, 2H); 5.34 – 5.41 (m, 1H); 7.75 (t, 1H, $J = 9.6$ Hz); 8.11 (d, 1H, 7.2 Hz); 8.31(d, 1H, 7.8 Hz); 8.40 (s, 1H). MS ($\text{M}+\text{H}^+$): 251. 57.

Step 3:- methyl 3-(3-aminophenyl)-4,5-dihydroisoxazole-5-carboxylate:

The title compound is prepared by procedure as described in example 6, step 3 using methyl 3-(3-nitrophenyl)-4,5-dihydroisoxazole-5-carboxylate. ^1H NMR ($\text{DMSO}-d_6$): δ 3.34-

3.52 (m, 2H); 3.69 (s, 3H); 5.18-5.26 (m, 3H); 6.63 (d, 1H, $J = 7.2$ Hz); 6.75(d, 1H, $J = 7.2$ Hz); 6.88(s, 1H); 7.06(t, 1H, $J = 7.8$ Hz). MS ($M+H$)⁺: 220.

Step 4:- methyl 3-{3-[(phenoxy carbonyl)amino]phenyl}-4,5-dihydroisoxazole-5-carboxylate:

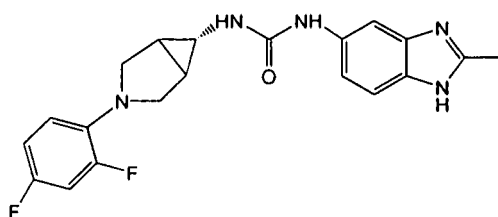
The title compound is prepared by procedure as described in example 6, step 4 using and phenyl chloroformate and methyl 3-(3-aminophenyl)-4,5-dihydroisoxazole-5-carboxylate. ¹H NMR (DMSO- *d*₆): δ 3.61 (m, 2H); 3.69- 3.78(s, 3H); 5.28(m, 1H); 7.21(t, 3H, $J = 8.4$ Hz); 7.30 (m, 1H); 7.41 (d, 3H); 7.55 (d, 1H); 7.89 (s, 1H); 10.36 (s, 1H). MS ($M+H$)⁺: 341.22.

Step 5:- 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[methyl 3-phenyl-4,5-dihydroisoxazole-5-carboxylate]urea:

The title compound is prepared by procedure as described in example 6, step 5 using 3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine and methyl 3-{3-[(phenoxy carbonyl) amino]phenyl}-4,5-dihydroisoxazole-5-carboxylate. ¹H NMR (DMSO- *d*₆): δ 2.49 (m, 2H); 3.21 (m, 3H); 3.32-3.71 (m, 7H); 5.23 (m, 1H); 6.47 (d, 1H, $J = 1.5$ Hz); 6.74 (m, 1H); 6.89 (m, 1H); 7.19 (d, 2H, $J = 7.8$ Hz); 7.29 (t, 1H, $J = 7.2$ Hz); 7.45 (d, 1H, $J = 6.9$ Hz); 7.81 (s, 1H), 8.53 (s, 1H). IR (KBr) (cm⁻¹): 3378, 2850- 2955, 1751, 1658, 1556, 1515, 1346, 1225, 1000- 1100, 948. MS ($M+H$): 475. 01. mp.: 206°C.

Example 30

Preparation of 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-methyl-1*H*-benzimidazol-5-yl)urea:



Step 1:-N-(2-amino-5-nitrophenyl)acetamide:

To a stirred solution of 4-nitrobenzene-1,2-diamine (0.032679 mole) in DMF (50 mL), triethyl amine (0.0980392 mole) is added followed by the dropwise addition of acetyl chloride (0.049019 mole) at 10-15°C and maintained for 4 -5 hrs. The reaction mixture is then poured in ice water and extracted with 5% methanol in DCM. The organic layer is then concentrated and purified by column chromatography. ¹H NMR (DMSO- *d*₆): δ 2.06 (s, 3H);

6.49 (s, 2H); 6.70 (d, 1H, $J = 8.7$ Hz); 7.8 (d, 1H, $J = 8.7$ Hz); 8.2 (s, 1H); 9.18 (s, 1H). MS $[M+H]^+$: 196.57.

Step 2:- 2-methyl-5-nitro-1H-benzimidazole:

To a stirred solution of *N*-(2-amino-5-nitrophenyl)acetamide (0.01026 mole) in ethyl acetate, POCl₃ (0.0205 mole) is added at room temperature and stirred overnight. Excess POCl₃ is distilled off from the reaction mixture, water is added, basified with solid NaCO₃, and the solid precipitated out is filtered and purified by column chromatography. ¹H NMR (DMSO- *d*₆): δ 2.55 (s, 3H); 7.60 (m, 1H); 8.03 (m, 1H); 8.35 (m, 1H); 12.87 (s, 1H). MS $[M+H]^+$: 178.67.

Step 3:- 2-methyl-1H-benzimidazol-5-amine:

The title compound is prepared by procedure as described in example 6, step 3 using 2-methyl-5-nitro-1H-benzimidazole. ¹H NMR (DMSO- *d*₆): δ 2.4 (s, 3H); 6.43 (d, 1H, $J = 8.4$ Hz); 6.57 (s, 1H); 7.12 (d, 1H, $J = 8.4$ Hz). MS $[M+H]^+$: 148.47.

Step 4:- phenyl (2-methyl-1H-benzimidazol-5-yl)carbamate:

The title compound is prepared by procedure as described in example 6, step 4 using and phenyl chloroformate and 2-methyl-1H-benzimidazol-5-amine. ¹H NMR (DMSO- *d*₆): δ 2.44 (s, 3H); 7.21 (m, 4H); 7.38 (m, 4H); 7.69 (bs, 1H); 10.10 (bs, 1H). MS $[M+H]^+$: 268.47.

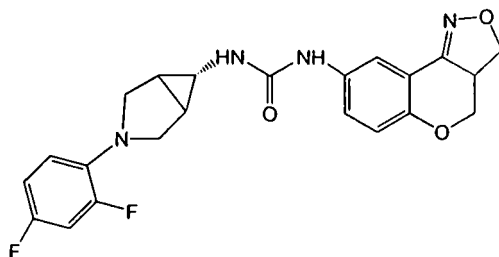
Step 5:- 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-methyl-1H-benzimidazol-5-yl)urea:

The title compound is prepared by procedure as described in example 6, step 5 using 3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine and phenyl (2-methyl-1H-benzimidazol-5-yl)carbamate. ¹H NMR (DMSO- *d*₆): δ 1.75 (s, 2H); 2.44 (s, 3H); 2.55 (s, 1H); 3.21 (d, 2H, $J = 8.1$ Hz); 3.65 (d, 2H, $J = 8.4$ Hz); 6.36 (s, 1H); 6.75 (m, 1H); 6.92 (m, 1H); 7.07 (t, 1H, $J = 9.3$ Hz); 7.27 (d, 1H, $J = 8.1$ Hz); 7.69 (s, 1H); 8.32 (s, 1H). IR (KBr) (cm⁻¹): 3293, 2922, 2849, 1643, 1596, 1511, 1385, 1225, 1135, 1023, 946, 792, 724. MS $[M+H]^+$: 384.17. mp.: Decomposes above 206°C.

Example 31

Preparation of 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(3a,4-dihydro-3H-chromeno[4,3-*c*]isoxazol-8-yl)urea:

55



Step 1:- 2-(allyloxy)-5-nitrobenzaldehyde:

To a stirred solution of 2-hydroxy-5-nitrobenzaldehyde (0.00598 mole) in DMF (10 mL), potassium carbonate (0.00778 mole) and allyl bromide (0.00718 mole) are added and stirred at room temperature for 24 hrs. Water is added to the reaction mixture and extracted with ethyl acetate. The organic layer is dried over Na_2SO_4 , concentrated and Purified by column chromatography.

Step 2:- 2-(allyloxy)-5-nitrobenzaldehyde oxime:

To a stirred solution of 2-(allyloxy)-5-nitrobenzaldehyde (0.00436 mole) in ethanol (5 mL), hydroxyl amine hydrochloride (0.0524 mole) is added, the pH adjusted to 7 using sodium carbonate solution (0.00218 mole) and stirred the reaction mixture at room temperature for 6 hrs. Ethanol is evaporated from the reaction mixture on rotavapor, water is added to the residue and extracted with ethyl acetate. The organic layer is dried over Na_2SO_4 and concentrated to get the crude compound, which is taken for further reaction. ^1H NMR (CDCl_3): δ 4.51 (d, 2H); 5.32 (t, 1H, $J = 9$ Hz); 5.42 (s, 1H); 6.03 (m, 1H); 7.19 (d, 1H, $J = 9$ Hz); 7.81 (d, 1H, $J = 9$ Hz); 8.39 (s, 1H).

Step 3:- 8-nitro-3a,4-dihydro-3H-chromeno[4,3-c]isoxazole:

To a stirred solution of 2-(allyloxy)-5-nitrobenzaldehyde oxime (0.00452 mole) in acetonitrile (15 mL), ceric ammonium nitrate (0.00904 mole) is added and stirred the reaction mixture at room temperature for 3 hrs. Water is added to the reaction mixture, extracted with ethyl acetate and concentrated the organic layer to get the desired compound, which is purified by column chromatography. ^1H NMR ($\text{DMSO}-d_6$): δ 3.90-3.97 (m, 2H); 4.25 (t, 1H, $J = 9$ Hz); 4.69 (t, 1H); 4.86 (m, 1H); 7.21 (d, 1H, $J = 9$ Hz); 8.20 (d, 1H); 8.40 (s, 1H).

Step 4:- 3a,4-dihydro-3H-chromeno[4,3-c]isoxazol-8-amine:

The title compound is prepared by procedure as described in example 6, step 3 using 8-nitro-3a,4-dihydro-3H-chromeno[4,3-c]isoxazole. ¹H NMR (DMSO- *d*₆): δ 4.25-4.30 (m, 3H); 4.60 (m, 2H); 6.97 (d, 1H); 7.12- 7.22 (m, 2H); 8.28 (bs, 2H).

Step 5:- phenyl 3a,4-dihydro-3H-chromeno[4,3-c]isoxazol-8-ylcarbamate:

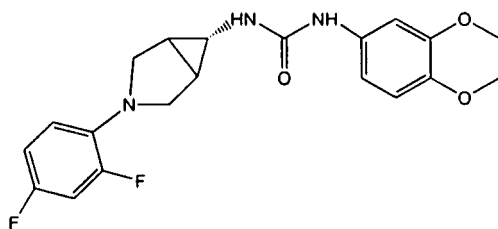
The title compound is prepared by procedure as described in example 6, step 4 using and phenyl chloroformate and 3a,4-dihydro-3H-chromeno[4,3-c]isoxazol-8-amine. ¹H NMR (DMSO- *d*₆): δ 3.83-4.069 (m, 3H); 4.66 (m, 2H); 6.96 (d, 1H, *J* = 9 Hz); 7.19-7.23 (m, 3H); 7.23-7.40 (m, 3H); 7.84 (s, 1H); 10.21 (s, 1H).

Step 6: 1-[(1α,5α,6α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(3a,4-dihydro-3H-chromeno[4,3-c]isoxazol-8-yl)urea:

The title compound is prepared by procedure as described in example 6, step 5 using 3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine and phenyl 3a,4-dihydro-3H-chromeno[4,3-c]isoxazol-8-ylcarbamate. ¹H NMR (DMSO- *d*₆): δ 1.75 (s, 2H); 2.50 (s, 1H); 3.18 (d, 2H, *J* = 9 Hz); 3.64 (d, 2H, *J* = 9Hz); 3.83-4.03 (m, 3H); 4.61 (m, 2H); 6.39 (s, 1H); 6.73 (m, 1H); 6.88 (m, 2H); 7.08 (m, 1H); 7.32 (m, 1H); 7.79 (s, 1H); 8.36(s, 1H). IR (KBr) (cm⁻¹): 3359, 3039, 2929, 2873, 1679, 1582, 1541, 1487, 1306, 1202, 1104, 947, 829, 800, 725. mp.; >250°C.

Example 32

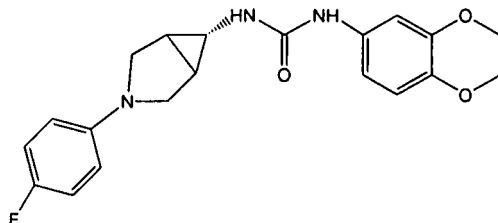
Preparation of 1-[(1α,5α,6α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2,3-dihydro-1,4-benzodioxin-6-yl)urea:



The title compound is prepared by procedure as described in example 6, step 5 using 3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine and phenyl 2,3-dihydro-1,4-benzodioxin-6-ylcarbamate. ¹H NMR (DMSO- *d*₆): δ 1.73 (s, 2H); 2.50 (s, 1H); 3.18 (d, 2H, *J* = 9 Hz); 3.66 (d, 2H, *J* = 9 Hz); 4.17 (d, 4H, *J* = 6 Hz); 6.31 (s, 1H); 6.70- 6.80 (m, 3H); 6.89 (t, 1H, *J* = 9 Hz); 7.05 (s, 1H); 7.12 (t, 1H, *J* = 9 Hz); 8.16 (s, 1H). IR (KBr) (cm⁻¹): 3392, 3301, 3049, 2939, 2864, 1646, 1595, 1562, 1509, 1314, 1207, 1131, 1068, 854, 802, 724. mp: 188°C.

Example 33

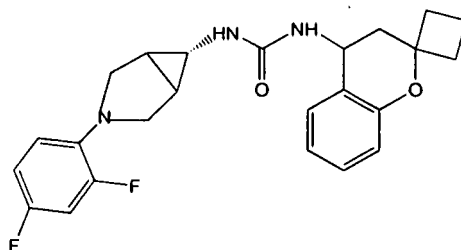
Preparation of 1-[(1 α ,5 α ,6 α)-3-(4-fluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2,3-dihydro-1,4-benzodioxin-6-yl)urea:



The title compound is prepared by procedure as described in example 6, step 5 using 3-(4-fluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine and phenyl 2,3-dihydro-1,4-benzodioxin-6-ylcarbamate. ¹H NMR (DMSO- *d*₆): δ 1.79 (s, 2H); 2.50 (s, 1H); 3.21(d, 2H, J = 9 Hz); 3.49 (d, 2H, J = 9 Hz); 4.16 (d, 4H, J = 6 Hz); 6.34 (s, 1H); 6.51-6.55 (m, 2H); 6.72 (m, 2H); 6.99-7.05(m, 3H); 8.16(s, 1H). IR (KBr) (cm⁻¹): 3390, 3295, 2897, 1648, 1597, 1555, 1512, 1314, 1209, 1159, 1068, 817. MS [M+H]⁺: 370. mp.: 219°C.

Example 34

Preparation of 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(3,4-dihydrospiro[chromene-2,1'-cyclobutan]-4-yl)urea:

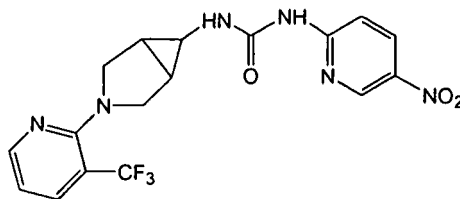


The title compound is prepared by procedure as described in example 6, step 5 using 3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine and phenyl 3,4-dihydrospiro[chromene-2,1'-cyclobutan]-4-ylcarbamate. ¹H NMR (DMSO- *d*₆): δ 1.72 (s, 2H); 1.83 (m, 2H); 2.08 (m, 2H); 2.26 (m, 2H); 2.53 (s, 1H); 3.19 (d, 2H, J = 9 Hz); 3.64 (d, 2H, J = 9 Hz); 3.65 (m, 1H); 4.88 (m, 1H); 6.27 (m, 2H); 6.71 (m, 2H); 6.84 (m, 2H); 7.03-7.13 (m, 3H). IR (KBr) (cm⁻¹): 3429, 2937, 1629, 1574, 1516, 1310, 1274, 1142, 1018, 951, 750. mp.: 128°C.

Example 35

Preparation of 1-(5-nitropyridin-2-yl)-3-[(1 α ,5 α ,6 α)-3-(3-(trifluoromethyl)pyridin-2-yl)-3-azabicyclo[3.1.0]hex-6-yl]urea:

58



Step 1: 1 α ,5 α ,6 α -6-amino-3-azabicyclo [3.1.0] hexane hydrochloride

Step a: 2-Benzyl-4-nitrohexahydrocyclopropa[c]azole-1,3-dione:

To a well-stirred suspension of N-benzyl maleimide (5.0 g, 26.7 mmol), bromonitromethane (7.48 g, 52.4 mmol), celite (5.0 g), and molecular sieve 4A (5.0 g) in dimethyl formamide (50.0 mL), anhydrous potassium carbonate (7.4 g, 53.4 mmol) is added in portions at -30° to -25°C and stirred for 3-4 hrs. Water (500 mL) is added to the reaction mixture and acidified to pH 5-6 with 10% aq. HCl solution. Ethyl acetate (100 mL) is added and the mixture is filtered through celite bed. The layers are separated and the organic layer is washed with water (2 x 25 mL), dried over anhydrous sodium sulfate, and concentrated to give crude product (4.5 g). The crude product is then purified through silica gel column using ethyl acetate: pet. ether (2:8), to give 2.1 gm of product as light yellow product. IR (KBr):- 3086, 1789, 1707, 1560, 1433, 1405, 1360, 1173, 1017, 883 cm⁻¹. ¹H NMR (300 MHz, DMSO-d₆): δ 3.74 (s, 2H), 4.40 (s, 2H), 5.57 (s, 1H), 7.23-7.35 (m, 5H).

Step b: 1 α ,5 α ,6 α -(6-amino-3-benzyl)-3-azabicyclo [3.1.0] hexane:

To a well-stirred suspension of 2-benzyl-4-nitrohexahydrocyclopropa[c]azole-1,3-dione (2.0 g, 8.12 mmol) in dry THF (20.0 mL) sodium borohydride (0.92 g, 24.36 mmol) is added at -20° C. BF₃·Et₂O (3.0 mL, 24.36 mmol) is then added slowly at the same temperature. Reaction mixture is then stirred for 7-8 hrs at room temperature and then treated with methanol (5.0 mL), diluted with water (100 mL), and extracted with ethyl acetate (3 x 25 mL). The combined organic layers are washed with water and dried over anhydrous sodium sulfate. Removal of solvent under vacuum gave 1.7 g product as white solid which is treated with ethyl acetate saturated with hydrochloric acid to isolate the product as a hydrochloride salt. IR (KBr):- 3076, 1782, 1717, 1562, 1442, 1401, 1363, 1178, 1017, 883 cm⁻¹. ¹H NMR (300 MHz, DMSO-d₆): δ 2.91 (s, 2H), 3.42 (s, 4H), 4.34 (s, 2H), 5.37 (s, 1H), 7.43-7.62 (m, 5H).

Step c: 1 α ,5 α ,6 α -6-amino-3-azabicyclo [3.1.0] hexane:

A suspension of 1 α ,5 α ,6 α -(6-amino-3-benzyl)-3-azabicyclo [3.1.0] hexane (500 mg), 10% Pd/C (100 mg) and triethylamine (1.0 mL) in methanol (10 mL) is hydrogenated in a

Parr apparatus at 60-70 psi of hydrogen gas. The catalyst is removed by filtration on celite bed. Removal of solvent under vacuum gave 200 mg of product as brown oil.

Step d: 1 α ,5 α ,6 α -[6-(tert)-butyloxycarbamoyl-3-(tert)-butyloxycarbonyl]-3-azabicyclo [3.1.0] hexane :

A solution of 1 α ,5 α ,6 α -6-amino-3-azabicyclo [3.1.0] hexane (200 mg, 2.0 mmol), Boc anhydride (100 mg) and triethylamine (0.5 mL) in methanol (5 mL) is stirred at room temperature for 2-3 hrs. Removal of solvent under vacuum gave 280 mg of product as light yellow solid. ¹H NMR (300 MHz, CDCl₃):- δ 1.42 (s, 9H), 1.44 (s, 9H), 1.56 (s, 2H), 2.28(s,1H), 3.32-3.40 (m, 2H), 3.64-3.67 (m, 2H), 4.75 (s, 1H).

Step e: 1 α , 5 α , 6 α -6-amino-3-azabicyclo [3.1.0] hexane hydrochloride:

A solution of 1 α , 5 α , 6 α -[6-(tert)-butyloxycarbamoyl-3-(tert)-butyloxycarbonyl]-3-azabicyclo [3.1.0] hexane (280 mg) and ethyl acetate saturated with HCl (5.0 mL) is stirred at room temperature for 5-6 hrs. The residue obtained after removal of solvent is washed with dry ether to give 180 mg of product as white solid. ¹H NMR (300 MHz, CD₃OD):- δ 2.31(s, 2H), 2.82 (s, 1H), 3.57 (s, 4H).

Step 2:- 1 α ,5 α ,6 α -[6-amino-3-(3-trifluoromethyl pyrid-2-yl)]-3-azabicyclo [3.1.0] hexane

A solution of intermediate 1 (600 mg, 6.12 mmol) and triethylamine (2.0 mL) in dimethyl sulfoxide (5.0 mL) is added 2-chloro-3-trifluoromethyl pyridine (1.44 g, 6.95 mmol) and stirred at room temperature for 15-16 hrs. Reaction mixture is diluted with water (100 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers are washed with water and dried over anhydrous sodium sulfate, the residue obtained after removal of solvent is purified through silica gel column using 10% methanol in chloroform as an eluent to get 300 mg of product as brown oil. ¹H NMR (300 MHz, DMSO-d₆):- δ 1.73 (brs, 3H), 2.17 (s, 1H), 3.52 (d, 2H, *J* = 10.2 Hz), 3.70 (d, 2H, *J* = 10.2Hz), 7.12 (d, 1H, *J* = 9.3 Hz), 7.60 (d, 1H, *J* = 8.7 Hz), 8.24 (s, 1H).

Step 3:- phenyl (5-nitropyridin-2-yl)carbamate:

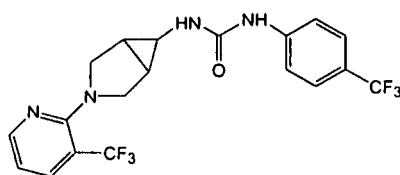
Phenyl chloroformate (0.0021 mole) in chloroform is cooled to 0°C. 5-nitropyridin-2-amine (0.0010 mole) is taken in dry THF, this is added dropwise to the reaction mass at 0°C. Reaction mass is stirred at room temperature overnight. Chloroform is removed. Crude product is washed with diethyl ether and dried.

Step 4:- 1-(5-nitropyridin-2-yl)-3-((1 α ,5 α ,6 α)-3-[3-(trifluoromethyl)pyridin-2-yl]-3-azabicyclo[3.1.0]hex-6-yl}urea:

To a stirred solution of 3-[3-(trifluoromethyl)pyridin-2-yl]-3-azabicyclo[3.1.0]hexan-6-amine (0.00041 mole) in DMSO (1 mL), TEA (0.00041 mole) is added followed by a solution of phenyl (5-nitropyridin-2-yl)carbamate (0.00045 mole) in DMSO added dropwise to the reaction mixture at room temperature and stirred overnight. The reaction mixture is then diluted with water, the solid precipitated out is stirred in water for 1 h, filtered, solid stirred in diethyl ether for 1 h filtered and dried. ¹H NMR (DMSO- *d*₆): δ 1.82 (s, 2H); 2.32 (s, 1H); 3.57 (d, 2H, *J* = 9.9 Hz); 3.92 (d, 2H, *J* = 10.8 Hz); 6.62 (s, 1H); 6.87 (m, 1H); 7.59 (m, 3H); 7.95 (d, 1H, *J* = 7.8 Hz); 8.36 (d, 1H); 8.85 (s, 1H). IR (KBr) (cm⁻¹): 3376, 2964, 1654, 1599, 1552, 1454, 1325, 1230, 1161, 1105, 1067, 1031, 847, 767. MS [M+H]⁺: 409.04. mp.: 183- 184°C.

Example 36

Preparation of 1-[4-(trifluoromethyl)phenyl]-3-((1 α ,5 α ,6 α)-3-[3-(trifluoromethyl)pyridine-2-yl]-3-azabicyclo[3.1.0]hex-6-yl}urea:



Step 1:- phenyl [4-(trifluoromethyl)phenyl]carbamate:

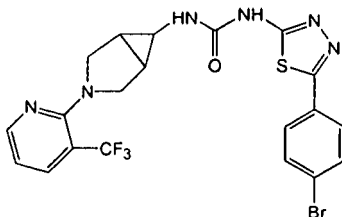
The title compound is prepared by procedure as described in example 35, step 2 using 4-(trifluoromethyl)aniline.

Step 2:- 1-[4-(trifluoromethyl)phenyl]-3-((1 α ,5 α ,6 α)-3-[3-(trifluoromethyl)pyridine-2-yl]-3-azabicyclo[3.1.0]hex-6-yl}urea

The title compound is prepared by procedure as described in example 35, step 3 using 3-[3-(trifluoromethyl)pyridine-2-yl]-3-azabicyclo[3.1.0]hexan-6-amine and phenyl[4-(trifluoromethyl)phenyl]carbamate. ¹H NMR (DMSO- *d*₆): δ 1.89 (s, 2H); 2.38 (s, 1H); 3.59 (d, 2H, *J* = 9.6 Hz); 3.92 (d, 2H, *J* = 10.5 Hz); 6.88 (m, 1H); 7.77 (m, 2H); 7.96 (d, 1H, *J* = 7.5 Hz); 8.37 (d, 1H, *J* = 4.2 Hz); 8.49(dd, 1H); 9.08 (d, 1H, *J* = 3 Hz); 9.93 (s, 1H). IR (KBr) (cm⁻¹): 3431, 3228, 2982, 1690, 1596, 1548, 1457, 1342, 1305, 1257, 1117, 1098, 1023, 839, 761. MS [M+H]⁺: 431.22 mp.: 235- 236°C.

Example 37

Preparation of 1-[5-(4-bromophenyl)-1,3,4-thiadiazol-2-yl]-3-[(1 α ,5 α ,6 α)-3-[3-(trifluoromethyl)pyridin-2-yl]-3-azabicyclo[3.1.0]hex-6-yl]urea:



Step 1:- phenyl [5-(4-bromophenyl)-1,3,4-thiadiazol-2-yl]carbamate:

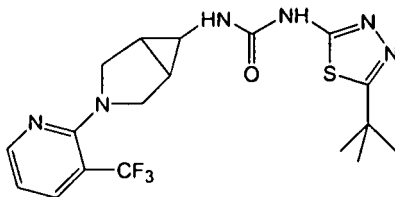
The title compound is prepared by procedure as described in example 30, step 2 using 5-(4-bromophenyl)-1,3,4-thiadiazol-2-amine. ¹H NMR (DMSO- *d*₆): δ 7.31 (m, 3H); 7.47 (m, 2H); 7.74 (m, 2H); 7.88 (m, 2H); 8.32 (s, 1H).

Step3:-1-[5-(4-bromophenyl)-1,3,4-thiadiazol-2-yl]-3-[(1 α ,5 α ,6 α)-3-[3-(trifluoromethyl)pyridin-2-yl]-3-azabicyclo[3.1.0]hex-6-yl]urea:

The title compound is prepared by procedure as described in example 35, step 3 using 3-[3-(trifluoromethyl)pyridin-2-yl]-3-azabicyclo[3.1.0]hexan-6-amine and phenyl [5-(4-bromophenyl)-1,3,4-thiadiazol-2-yl]carbamate. ¹H NMR (CDCl₃): δ 1.94 (s, 2H); 2.7 (s, 1H); 3.65 (d, 2H, *J* = 10.2 Hz); 4.13 (d, 2H, *J* = 10.2 Hz); 6.70 (s, 1H); 7.61 -7.41 (m, 7H); 8.28 (bs, 1H). IR (KBr) (cm⁻¹): 3387, 2918, 1711, 1722, 1593, 1559, 1448, 1300, 1242, 1106, 1073, 984, 828, 773, 751. MS [*M*]⁺: 525.34. mp.: 242- 244°C.

Example 38

Preparation of 1-[5-(tert-butyl)-1,3,4-thiadiazol-2-yl]-3-[(1 α ,5 α ,6 α)-3-[3-(trifluoromethyl)pyridin-2-yl]-3-azabicyclo[3.1.0]hex-6-yl]urea:



Step 1:- phenyl (5-tert-butyl-1,3,4-thiadiazol-2-yl)carbamate:

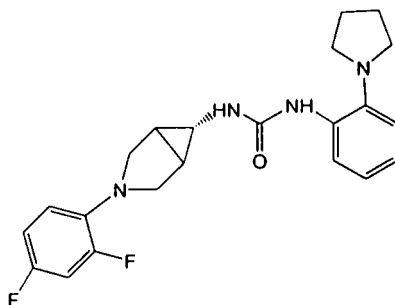
The title compound is prepared by procedure as described in example 35, step 2 using 5-tert-butyl-1,3,4-thiadiazol-2-amine. ¹H NMR (DMSO- *d*₆): δ 1.39 (s, 9H); 7.28 (m, 3H); 7.45 (m, 2H); 12.6 (s, 1H).

Step 3:- 1-[5-(tert-butyl)-1,3,4-thiadiazol-2-yl]-3-{(1 α ,5 α ,6 α)-3-[3-(trifluoromethyl)pyridin-2-yl]-3-azabicyclo[3.1.0]hex-6-yl}urea:

The title compound is prepared by procedure as described in example 35, step 3 using 3-[3-(trifluoromethyl)pyridin-2-yl]-3-azabicyclo[3.1.0]hexan-6-amine and phenyl (5-*tert*-butyl-1,3,4-thiadiazol-2-yl)carbamate. ¹H NMR (DMSO- *d*₆): δ 1.36 (s, 9H); 1.85 (s, 2H); 2.34 (s, 1H); 3.57 (d, 2H, *J* = 9.9 Hz); 3.92 (d, 2H, *J* = 9.9 Hz); 6.87 (m, 2H); 7.95 (d, 1H, *J* = 7.5 Hz); 8.36 (d, 1H); 10.77 (bs, 1H). IR (KBr) (cm⁻¹): 3396, 2964, 2875, 1717, 1594, 1560, 1518, 1448, 1365, 1300, 1237, 1106, 1030, 808, 774, 751. MS [M-H]⁺: 425.31. mp.: > 250°C.

Example 39

Preparation of 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-pyrrolidin-1-ylphenyl)urea:



Step 1:- 1-(2-nitrophenyl)pyrrolidine:

To the stirred solution of 1-fluoro-2-nitrobenzene (0.0141mole) in DMSO, potassium fluoride (0.0170 mole), and then pyrrolidine (0.0141mole) is added and heated to 60°C for 2 hours. After completion of reaction water is added, extracted in ethyl acetate to get pure product. ¹H NMR (DMSO- *d*₆): δ 1.8 (m, 4H); 2.2 (t, 2H); 3.2 (t, 2H); 7.6 – 7.8 (m, 3H); 8.2 (d, 1H, *J* = 9 Hz).

Step 2:- 2-pyrrolidin-1-ylaniline:

The title compound is prepared by procedure as described in example 6, step 3 by using 1-(2-nitrophenyl)pyrrolidine. Crude compound is taken for further reaction.

Step 3:- phenyl (2-pyrrolidin-1-ylphenyl)carbamate

The title compound is prepared by procedure as described in example 6, step 4 by using phenyl chloroformate and 2-pyrrolidin-1-ylaniline. ¹H NMR (DMSO- *d*₆): δ 1.84 – 1.89

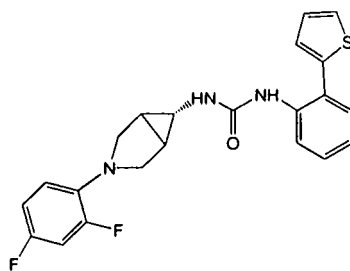
(m, 3H); 2.10 (bs, 1H); 3.05 (bs, 1H); 3.27 (bs, 1H); 3.81 (s, 2H); 6.71 – 6.79 (m, 2H); 7.07 – 7.29 (m, 5H); 7.26 – 7.41 (m, 2H); 9.31 (s, 1H).

Step 4:- 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-pyrrolidin-1-ylphenyl)urea:

The title compound is prepared by procedure as described in example 6, step 5 by using 3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine and phenyl (2-pyrrolidin-1-ylphenyl)carbamate. ¹H NMR (DMSO- *d*₆): δ 1.77 (s, 2H); 1.89 (s, 4H); 2.4 (s, 1H); 2.99 (m, 4H); 3.24 (m, 2H); 3.66 (m, 2H); 6.77 (m, 1H); 6.90 (m, 3H); 7.04 – 7.12 (m, 3H); 7.74 (m, 1H); 7.88 (m, 1H). IR (KBr) (cm⁻¹): 3421, 1682, 1605, 1510, 1430, 1315, 1294, 1236, 1159, 1130, 922, 854, 769. mp.: 185°C.

Example 40

Preparation of 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-(2-thienyl)phenyl)urea:



Step 1:- 2-(2-thienyl)aniline:

The title compound is prepared by procedure as described in example 11, step 1 by using 2-bromo aniline (0.000581 mole) and 2-thiophene boronic acid (0.000639 mole). ¹H NMR (DMSO- *d*₆): δ 5.04 (s, 2H); 6.58 (t, 1H, *J* = 7.8 Hz); 6.77 (d, 1H, *J* = 8.4 Hz); 7.02 (t, 1H, *J* = 6.9 Hz); 7.12 (m, 2H); 7.22 (d, 1H, *J* = 3.6 Hz); 7.51 (d, 1H, *J* = 5.4 Hz).

Step 2:- phenyl [2-(2-thienyl)phenyl]carbamate:

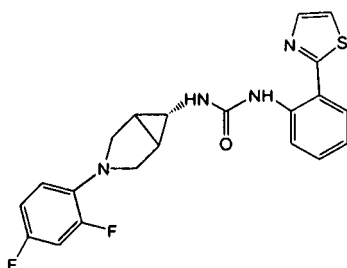
The title compound is prepared by procedure as described in example 6, step 4 by using phenyl chloroformate and 2-(2-thienyl)aniline. ¹H NMR (DMSO- *d*₆): δ 7.08 – 7.17 (m, 3H); 7.32 – 7.44 (m, 7H); 7.63 (m, 2H); 9.58 (bs, 1H).

Step 3:- 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-(2-thienyl)phenyl)urea:

The title compound is prepared by procedure as described in example 6, step 5 by using 3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine and phenyl [2-(2-thienyl)phenyl]carbamate. ^1H NMR (DMSO- d_6): δ 1.71 (s, 2H); 2.4 (s, 1H); 3.15 (m, 2H); 3.54 (m, 2H); 6.70 (m, 1H); 6.87 (m, 2H); 7.05 (m, 1H); 7.08 (m, 1H); 7.14 (m, 1H); 7.26 (m, 2H); 7.36 (m, 1H); 7.57 (m, 1H); 7.61 (m, 1H); 7.81 (d, 1H). IR (KBr) (cm^{-1}): 3324, 1645, 1580, 1513, 1477, 1333, 1227, 1135, 1099, 948, 848, 755. mp.: 110°C.

Example 41

Preparation of 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-(1,3-thiazol-2-yl)phenyl)urea:



Step 1:- 2-(2-nitrophenyl)-1,3-thiazole:

The title compound is prepared by procedure as described in example 11, step 1 by using 2-bromo-1,3-thiazole (0.00314 mole) and 2-nitrophenyl boronic acid (0.00285 mole). ^1H NMR (DMSO- d_6): δ 7.78 (m, 1H); 7.92 (s, 1H); 8.1 (s, 1H); 8.30 – 8.39 (m, 2H); 8.7 (d, 1H).

Step 2:- 2-(1,3-thiazol-2-yl)aniline:

The title compound is prepared by procedure as described in example 6, step 3 by using 2-(2-nitrophenyl)-1,3-thiazole. Crude compound is taken for further reaction.

Step 3:- phenyl [2-(1,3-thiazol-2-yl)phenyl]carbamate:

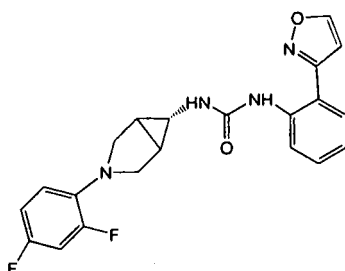
The title compound is prepared by procedure as described in example 6, step 4 by using phenyl chloroformate and 2-(1,3-thiazol-2-yl)aniline. ^1H NMR (DMSO- d_6): δ 7.22 – 7.40 (m, 4H); 7.40 – 7.52 (m, 3H); 7.91- 7.97 (m, 2H); 8.06 (s, 1H); 8.23 (d, 1H, $J = 8.7$ Hz); 11.89 (bs, 1H).

Step 4:- 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-(1,3-thiazol-2-yl)phenyl)urea

The title compound is prepared by procedure as described in example 6, step 5 by using 3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine and phenyl [2-(1,3-thiazol-2-yl)phenyl]carbamate. ^1H NMR (DMSO- d_6): δ 1.85 (m, 2H); 2.4 (s, 1H); 3.21 (m, 2H); 3.70 (m, 2H); 6.79 (m, 1H); 6.91 (m, 1H); 7.05 (m, 2H); 7.37 (m, 2H); 7.82 (m, 3H); 8.37 (d, 1H, $J = 8.7$ Hz); 11.03 (s, 1H). IR (KBr) (cm^{-1}): 3326, 1627, 1568, 1515, 1479, 1437, 1361, 1277, 1230, 1136, 1052, 946, 745, 761. MS $[\text{M}]^+$: 413.02. mp.: 170°C.

Example 42

Preparation of 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-isoxazol-3-ylphenyl)urea:



Step 1:- 3-(dimethylamino)-1-(2-nitrophenyl)prop-2-en-1-one:

To the stirred solution of 1-(2-nitrophenyl)ethanone (0.01212 mole) in toluene, diisopropyl ethylamine (0.02424 mole) and dimethyl acetal (0.02420 mole) is added and refluxed for 4 h. Quenched in water, extracted in ethyl acetate and concentrated. Solid obtained is washed with ethyl acetate. ^1H NMR (DMSO- d_6): δ 2.98 (s, 3H); 3.2 (s, 3H); 5.91(d, 1H, $J = 12$ Hz); 7.72 (t, 1H, $J = 9$ Hz); 7.82 (d, 1H, $J = 12$ Hz); 8.33 (t, 2H, $J = 6$ Hz); 8.42 (s, 1H).

Step 2:- 3-(2-nitrophenyl)isoxazole:

To the stirred solution of 3-(dimethylamino)-1-(2-nitrophenyl)prop-2-en-1-one (0.0454 mole) in methanol, hydroxyl amine hydrochloride (0.03538 mole) is added and refluxed for 3 h. solvent is removed under vacuum, water is added, extracted in ethyl acetate and concentrated. ^1H NMR (DMSO- d_6): δ 6.94 (s, 1H); 7.75- 7.90 (m, 3H); 8.06 (d, 1H, $J = 7.8$ Hz); 8.71 (s, 1H).

Step 3:- 2-isoxazol-3-ylaniline:

The title compound is prepared by procedure as described in example 6, step 3 by using 3-(2-nitrophenyl)isoxazole. Crude compound is taken for further reaction.

Step 4:- phenyl (2-isoxazol-3-ylphenyl)carbamate:

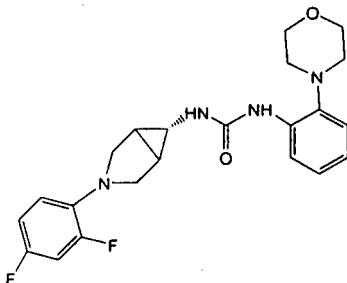
The title compound is prepared by procedure as described in example 6, step 4 by using phenyl chloroformate and 2-isoxazol-3-ylaniline. ¹H NMR (DMSO- *d*₆): δ 6.88 (s, 1H); 7.13- 7.21 (m, 3H); 7.38 (m, 3H); 7.52 (m, 2H); 7.80(d, 1H, J = 7.8 Hz); 8.69 (m, 1H); 9.81 (bs, 1H).

Step 5:- 1-[(1α,5α,6α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-isoxazol-3-ylphenyl)urea:

The title compound is prepared by procedure as described in example 6, step 5 using 3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine and phenyl (2-isoxazol-3-ylphenyl)carbamate. ¹H NMR (DMSO- *d*₆): δ 1.8 (s, 2H); 2.4 (s, 1H); 3.1 (d, 2H); 3.6 (d, 2H); 6.6 (m, 6H); 7.4 (t, 1H); 7.7 (d, 1H); 8.9 (d, 1H); 8.0 (m, 1H); 8.7 (bs, 1H). IR (KBr) (cm⁻¹): 3326, 1627, 1568, 1515, 1466, 1361, 1277, 1136, 1052, 1024, 946, 845, 761. M. P.: 201 °C.

Example 43

Preparation of 1-[(1 α,5 α,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-morpholin-4-ylphenyl)urea:

*Step 1:- 4-(2-nitrophenyl)morpholine:*

To the stirred solution of 1-fluoro-2-nitrobenzene (0.0141mole) in DMSO, potassium fluoride (0.0170 mole), and then morpholine (0.0141mole) is added and heated to 60°C for 2 hours. After completion of reaction water is added, extracted in ethyl acetate to get pure product. ¹H NMR (DMSO- *d*₆): δ 3.0 (m, 4H); 3.9 (m, 4H); 6.8 (t, 1H); 7.0 (d, 1H); 7.2 (t, 1H); 7.4 (d, 1H).

Step 2:- 2-morpholin-4-ylaniline:

The title compound is prepared by procedure as described in example 6, step 3 by using 4-(2-nitrophenyl)morpholine. ¹H NMR (DMSO- *d*₆): δ 2.72 (m, 4H); 3.72 (m, 4H); 4.75

(s, 2H); 6.51 (t, 1H, J = 7.8 Hz); 6.64(d, 1H, J = 6.9 Hz); 6.78 (t, 1H, J = 8.4 Hz); 6.86 (d, 1H, J = 7.8 Hz).

Step 3:- phenyl (2-morpholin-4-ylphenyl)carbamate:

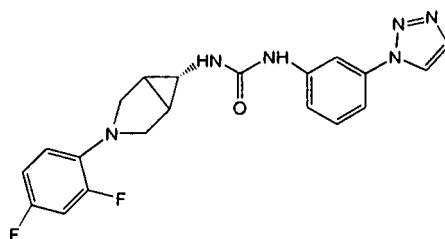
The title compound is prepared by procedure as described in example 6, step 4 by using phenyl chloroformate and 2-morpholin-4-ylaniline. ¹H NMR (DMSO- *d*₆): δ 2.78 (m, 4H); 3.73 (m, 4H); 6.55 (t, 1H, J = 7.8 Hz); 6.65 (d, 1H, J = 9 Hz); 6.79 (t, 1H, J = 9 Hz); 6.87 (d, 1H, J = 7.8 Hz); 7.2 – 7.3 (m, 5H); 9.5 (bs, 1H).

Step 4:- 1-[(1α,5α,6α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-morpholin-4-ylphenyl)urea::

The title compound is prepared by procedure as described in example 6, step 5 by using 3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine and phenyl (2-morpholin-4-ylphenyl)carbamate. ¹H NMR (CDCl₃): δ 1.79 (s, 2H); 2.55 (s, 1H); 2.74 (m, 4H); 3.23 (d, 2H, J = 8.7 Hz); 3.68 (d, 2H, J = 9.3 Hz); 3.78 (m, 4H); 6.76 (m, 1H); 6.89 (m, 1H); 7.00 (t, 1H, J = 7.8 Hz); 7.12 – 7.14 (m, 3H); 7.32 (m, 1H); 7.80 (s, 1H); 8.06 (d, 1H, J = 7.5 Hz). IR (KBr) (cm⁻¹): 3283, 1640, 1596, 1550, 1513, 1449, 1360, 1229, 1114, 1100, 948, 848, 757. mp.: 189°C.

Example 44

Preparation of 1-[(1α,5α,6α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(3-[1,2,3]triazol-1-yl phenyl) urea:



Step 1:1-(3-Nitro phenyl)-1H-1,2,3-triazole:

To a stirred solution of 3-Nitro iodobenzene (2 g, 0.0141 mole) in 15 mL DMF, is added Copper iodide 0.27 g, (0.00141 mole), tripotassium phosphate (6.01 g, 0.0283 mole), N,N-dimethyl ethylene diamine 0.249 g, 0.00283 mol) followed by 1,2,3-Triazole 1.07 g, 0.0156 mole) and the reaction is heated at 80°C for 4 h. The reaction is poured in to ice cold water, extracted with ethyl acetate, concentrated and purified by column chromatography in

ethyl acetate in chloroform to get 1.0 g of 1-(3-Nitro phenyl)-1H-1,2,3-triazole and 0.6 g of 2-(3-Nitro phenyl)-1H-1,2,3-triazole. ^1H NMR (DMSO- d_6): δ 7.92 (s, 2H); 8.30 (d, 1H, J = 6.0 Hz); 8.39 (d, 1H, J = 6.0 Hz); 8.73 (s, 1H), 9.06 (s, 1H) ;

Step 2: 3-(1,2,3-triazol-1-yl)-phenylamine:

To a stirred solution of 1-(3-Nitro phenyl)-1H-1,2,3-triazole (1.0 g) in 20 mL methanol, is added 0.3 g of Pd/C and the reaction mixture is subjected to hydrogenation at 60 psi for 4 hrs. The reaction mixture is filtered to remove the catalyst and the filtrate is concentrated to get the desired product.

Step 3: (3-[1,2,3]-triazol-1-yl-phenyl)-carbamic acid phenyl ester:

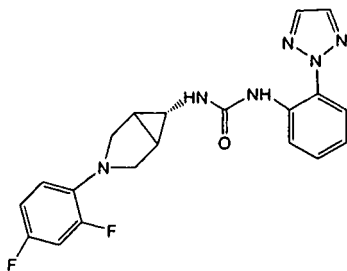
To a stirred solution of 3-(1,2,3-triazol-1-yl)-phenylamine (0.6 g, 0.00377 mole) in DCM (10mL) is added phenyl chloroformate (0.596 g, 0.00377 mole) and stirred the reaction mixture for 4 hrs at room temperature. A solution of aq. NaHCO_3 is added to the reaction mixture and extracted with dichloromethane. The organic layer is then dried over Na_2SO_4 and concentrated. The crude product is purified by column chromatography to get 250 mg of the desired product. ^1H NMR (CDCl_3): δ 7.18 (m, 3H); 7.40 (m, 2H); 7.54 (br s, 3H); 7.95 (s, 1H); 8.15 (s, 1H); 8.76 (s, 1H); 10.57 (s, 1H).

Step 4: 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(3-[1,2,3] triazol-1-yl-phenyl urea:

To a stirred solution of [(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine (67 mg, 0.00032 mole) in DMSO (5mL) is added TEA (0.00032 mole) followed by a solution of (3-[1,2,3]- triazol-1-yl- phenyl)-carbamic acid phenyl ester (0.00032 mole) in DMSO and stirred for 24 h at room temperature. The reaction mixture is then diluted with ethyl acetate (20 mL) washed with water. The organic layer is then separated, dried over NaSO_4 and concentrated to get the crude material which is purified by column chromatography. ^1H NMR (CDCl_3): δ 1.78 (s, 2H); 2.50 (s, 1H); 3.19 (d, 2H, J = 9.0Hz); 3.64 (d, 2H, J = 9.0Hz); 6.57 (s, 1H); 6.74-6.90 (m, 2H); 7.1 (t, 1H); 7.4 (m, 3H); 7.93 (s, 1H); 8.11 (s, 1H); 8.72 (s, 2H). mp: 195°C;

Example 45

Preparation of 1-[(1 α ,5 α ,6 α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-[1,2,3]triazol-2-yl-phenyl urea:



Step 1:-2-(2-Nitro phenyl)-2H-1,2,3-triazole:

To a stirred solution of 2-Fluoro Nitrobenzene (2 g, 0.0141 mole) in 15 mL DMSO, is added Potassium fluoride 0.82 g, (0.0141 mole), followed by 1,2,3-Triazole (0.978 g, 0.0141 mole) and the reaction is heated at 60°C for 2 h. The reaction is poured in to ice cold water, extracted with ethyl acetate, concentrated and purified by column chromatography in ethylacetate in chloroform to get 1.0 g of 2-(2-Nitro phenyl)-2H-1,2,3-triazole and 0.6 g of 1-(2-Nitro phenyl)-1H-1,2,3-triazole. ¹H NMR (DMSO- *d*₆): δ 7.70 (t, 1H, J = 6.0 Hz); 7.88 (t, 1H, J = 9.0 Hz); 7.97 (d, 1H, J = 9.0 Hz); 8.06 (d, 1H, J = 6.0 Hz); 8.18 (s, 2H).

Step 2: 2-(1,2,3-triazol-2-yl)-phenylamine:

To a stirred solution of 2-(2-nitrophenyl)-2H-1,2,3-triazole (1.0 g) in 20 mL methanol, is added 0.3 g of Pd/C and the reaction mixture is subjected to hydrogenation at 60 psi for 4 hrs. The reaction mixture is filtered to remove the catalyst and the filtrate is concentrated to get the desired product.

Step 3: (2-[1,2,3]-triazol-2-yl-phenyl)-carbamic acid phenyl ester:

To a stirred solution of 2-(1,2,3-triazol-2-yl)-phenylamine (0.6 g, 0.00377 mole) in DCM (10mL) is added phenyl chloroformate (0.596 g, 0.00377 mole) and stirred the reaction mixture for 4 hrs at room temperature. A solution of aq. NaHCO₃ is added to the reaction mixture and extracted with dichloromethane. The organic layer is then dried over Na₂SO₄ and concentrated. The crude product is purified by column chromatography to get 250 mg of the desired product. ¹H NMR (CDCl₃): δ 7.11 (d, 2H); 7.20 (t, 1H, J = 6.0 Hz); 7.33-7.41 (m, 3H); 7.51 (t, 1H, J = 6.0 Hz); 7.82 (m, 2H); 8.20 (s, 2H); 10.06 (s, 1H).

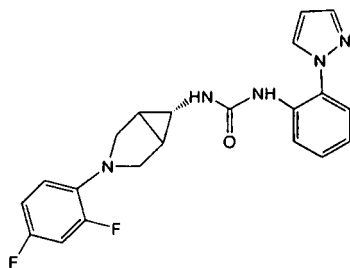
Step 4:- 1-[(1α,5α,6α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-[1,2,3]triazol-2-yl-phenyl) urea:

To a stirred solution of [(1α,5α,6α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]]hexan-6-amine (67 mg, 0.00032 mole) in DMSO (5mL) is added TEA (0.00032 mole) followed by a solution of (2-[1,2,3]-triazol-2-yl-phenyl)-carbamic acid

phenyl ester (0.00032 mole) in DMSO and stirred for 24 h at room temperature. The reaction mixture is then diluted with ethyl acetate (20 mL) washed with water. The organic layer is then separated, dried over NaSO₄ and concentrated to get the crude material which is purified by column chromatography. ¹H NMR (CDCl₃): δ 1.79 (s, 2H); 2.50 (s, 1H); 3.22 (d, 2H, J = 9.0 Hz); 3.66 (d, 2H, J = 9.0 Hz); 6.79-6.91 (m, 2H); 7.14 (m, 2H); 7.31-7.36 (m, 2H); 7.72 (m, 1H); 8.17 (s, 2H); 8.23 (d, 1H, J = 6.0 Hz); 9.01 (s, 1H). IR (KBr) (cm⁻¹): 3434, 3314, 3256, 3099, 2982, 2865, 1686, 1526, 1513, 1449, 1332, 1269, 1135, 950, 752. mp.: 156°C;

Example 46

Preparation of 1-[(1α,5α,6α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-pyrazol-1-yl-phenyl) urea:



To a stirred solution of [(1α,5α,6α)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine (67 mg, 0.00032 mole) in DMSO (5mL) is added TEA (0.00032 mole) followed by a solution of (2-pyrazol-1-yl-phenyl)-carbamic acid phenyl ester (89 mg, 0.00032 mole) in DMSO and stirred for 24 h at room temperature. The reaction mixture is then diluted with ethyl acetate (20 mL) washed with water. The organic layer is then separated, dried over NaSO₄ and concentrated to get the crude material which is purified by column chromatography. ¹H NMR (CDCl₃): δ 1.76 (s, 2H); 2.49 (s, 1H); 3.19 (d, 2H, J = 9.0 Hz); 3.66 (d, 2H, J = 9.0 Hz); 6.57 (s, 1H); 6.77-6.90 (m, 2H); 7.08-7.29 (m, 3H); 7.31 (t, 1H); 7.40 (d, 1H, J = 6.0 Hz); 7.75 (s, 1H); 8.12 (d, 1H, J = 9.0 Hz); 8.35 (s, 1H). mp.: 198°C;

Example 47

Screening for TRPV1 antagonist using ⁴⁵Calcium uptake assay

The inhibition of TRPV1 receptor activation was followed as inhibition of capsaicin induced cellular uptake of radioactive calcium which represents calcium influx exclusively through the plasma membrane associated TRPV1 receptor.

Materials:

A stock solution of capsaicin was made in ethanol and test compounds were prepared in 100% DMSO. Stock solutions are diluted to appropriate final concentrations in assay buffer keeping the final DMSO concentration between 0.1% and 0.55%. ^{45}Ca was used at a final concentration of 2.5 $\mu\text{Ci/ml}$ (^{45}Ca , ICN). Assay buffer was composed of F-12 DMEM medium supplemented with 1.8 mM CaCl_2 (final conc.) and 0.1% Bovine serum albumin.(BSA from SIGMA) The wash buffer was Tyrodes solution supplemented with 0.1% BSA and 1.8 mM calcium. Lysis buffer contained 50 mM Tris-HCl, pH7.5, 150 mM NaCl, 1% Triton X-100, 0.5% deoxycholate and 0.1% Sodium dodecyl sulphate (SDS, SIGMA).

Method:

The assay was carried out with some modifications of the procedure as described by Toth A *et. al.*, *Life Sciences.*, (2003), 73, 487-498,. Human TRPV1 expressing CHO cells are grown in F-12 DMEM (Dulbecco's modified Eagle's medium –GIBCO) medium with 10% FBS (fetal bovine serum Hyclone), 1% penicillin-streptomycin solution, and 400 $\mu\text{g} / \text{ml}$ of G-418. Cells were seeded 48 h prior to the assay in 96 well plates to obtain ~ 50,000 cells per well on the day of experiment. Plates were incubated at 37°C in the presence of 5 % CO_2 . Cells were then washed twice with 200 μl of assay buffer and re-suspended in 144 μl of the same. Assay was carried out at 30°C in total volume of 200 μl . Test compounds were added to the cells fifteen minutes before addition of capsaicin. The final concentration of capsaicin in the assay was 250 nM. After 5 minutes of agonist treatment, the drug was washed out and the wells were rinsed with 300 μl of ice cold wash buffer 3X. The cells were lysed in 50 μl lysis buffer for 20 min. 40 μl of cell lysate was mixed with 150 μl of Microscint PS, left overnight for equilibration. Radioactivity in samples was measured as counts per minute (cpm) using Packard Biosciences Top Count. The drug / vehicle / capsaicin treated ^{45}Ca uptake values were normalized over basal ^{45}Ca value. Data was expressed as % inhibition of ^{45}Ca uptake by test compound with respect to maximum ^{45}Ca uptake induced by capsaicin alone. IC_{50} value was calculated from dose response curve by nonlinear regression analysis using GraphPadPRISM software. The results summarized in the Table-1 below.

Table-1:

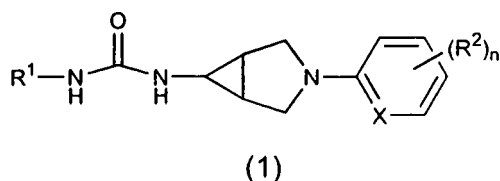
Compound No.	% inhibition at 300 nM conc.	Compound No.	% inhibition at 300 nM conc.	Compound No.	% inhibition at 300 nM conc.
1	2.08	14	2.36	27	8.09
2	1.86	15	1.59	29	1.37
3	2.92	16	7.93	31	2.35
4	4.94	17	8.66	34	0.38

6	2.22	18	7.46	35	16.01
7	8.89	19	16.20	36	10.21
8	14.70	23	0.84	37	7.15
9	5.04	24	0.27	38	3.40
10	0.35	25	13.80		
12	2.60	26	3.63	42	16.82**
13	12.36	28	5.14**	43	6.93**
20	9.10*	39	0.00**	44	4.62**
21	6.27*	40	25.41**	45	14.29**
22	16.45*	41	3.35**	46	1.36**

* = % inhibition at 3 μ M and ** = % inhibition at 1 μ M.

We Claim:

1. A compound of general formula (1)



pharmaceutically acceptable salts, N-oxides, esters, tautomers or stereoisomers thereof,

wherein,

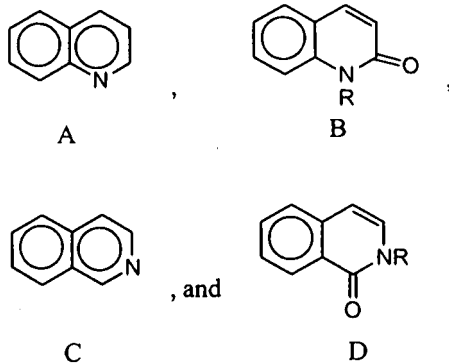
X is CH or N;

R^1 is selected from substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocyclic ring; wherein substituents are selected from nitro, haloalkyl, substituted or unsubstituted alkyl, linear or branched chain alkyl, fully or partially substituted haloalkyl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocyclic ring;

each occurrence of R^2 is independently selected from hydrogen, nitro, cyano, formyl, acetyl, halogen, hydroxyl, substituted or unsubstituted alkyl, fully or partially substituted haloalkyl, substituted or unsubstituted cycloalkyl or substituted or unsubstituted aryl;

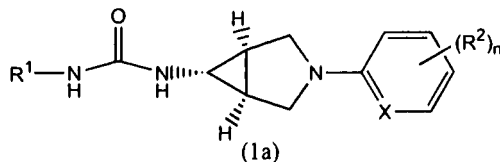
'n' is an integer selected from 0 to 3;

with the proviso that R^1 is not



where R in formulas A, B, C, and D is any chemical moiety.

2. A compound of general formula (1a)



pharmaceutically acceptable salts, N-oxides, esters, tautomers, or stereoisomers, wherein,

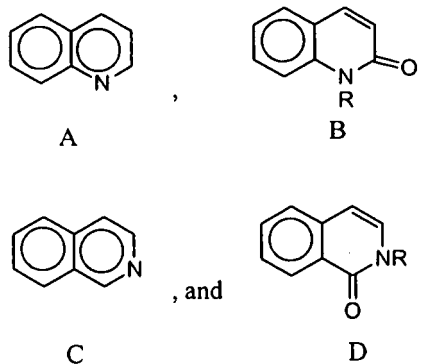
X is CH or N;

R¹ is selected from substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocyclic ring; wherein substituents are selected from nitro, haloalkyl, substituted or unsubstituted alkyl, linear or branched chain alkyl, fully or partially substituted haloalkyl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocyclic ring;

each occurrence of R² is independently selected from hydrogen, nitro, cyano, formyl, acetyl, halogen, hydroxyl, substituted or unsubstituted alkyl, fully or partially substituted haloalkyl, substituted or unsubstituted cycloalkyl or substituted or unsubstituted aryl;

'n' is an integer selected from 0 to 3;

with the proviso that R¹ is not



where R in formulas A, B, C, and D is any chemical moiety.

3. The compound according to claim 1 or 2, wherein R¹ is substituted or unsubstituted aryl.
4. The compound according to claim 1, 2 or 3, wherein aryl is unsubstituted phenyl.
5. The compound according to claim 1, 2 or 3, wherein aryl is substituted phenyl.
6. The compound according to any of claims 1-6, wherein R¹ is unsubstituted phenyl.
7. The compound according to claim 6, wherein the substituents to the phenyl group in R¹ are selected from CF₃, methyl-1,3-thiazolyl, 5-*tert*-butyl-1,3,4-oxadiazolyl, cyano-4,5-dihydroisoxazolyl, furyl, thienyl, thiophenyl, 1,3-thiazolyl, isoxazolyl, pyrazolyl, benzyl-1*H*-pyrazolyl, oxo-1,3-oxazolidinyl, -4,5-dihydroisoxazole-5-carboxylate, pyrrolidinyl, morpholinyl, or [1,2,3]triazolyl.
8. The compound according to claim 1, 2, 4, or 5, wherein R¹ is substituted or unsubstituted heteroaryl or heterocyclic ring.
9. The compound according to any of claims 8, wherein heteroaryl or heterocyclic ring is thiadiazolyl, indazolyl, oxidiazolyl, isoindolyl, dihydroisoxazolyl, dioxo-2,3-dihydro-1*H*-isoindolyl, dihydro-3*H*-chromeno[4,3-*c*]isoxazolyl, dihydro-1,4-benzodioxinyl, benzimidazolyl, isoxazolyl, dihydrospiro[chromene-2 1'-cyclobutan]-yl, or pyridyl.
10. The compound according to claim 9, wherein the substituents to the heteroaryl or heterocyclic group in R¹ are one or more of halo, nitro, alkyl, CF₃, or nitrophenyl.
11. The compound according to claim 10, wherein halo is fluorine.
12. The compound according to claim 10, wherein the alkyl substituent in R¹ is methyl or *tert*-butyl.
13. The compound according to any of claims 1-12, wherein X is CH.
14. The compound according to any of claims 1-12, wherein X is N.
15. The compound according to any of claims 1-14, wherein R² is halogen.
16. The compound according to claim 15, wherein R² is fluorine.

17. The compound according to claim 15, wherein R² is haloalkyl.
18. The compound according to claim 17, wherein R² is trifluoromethyl.
19. The compound according to any of claims 1-18, wherein n is 1.
20. The compound according to any of claims 1-18, wherein n is 2.
21. The compound according to any of claims 1-14, wherein n is 0.
22. A compound selected from:

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(5-*tert*-butyl) thiadiazol-2-yl)urea (Compound No. 1),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(5-nitropyridin-2-yl) urea (Compound No. 2),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[5-(4-nitro phenyl)-1,3,4-thiadiazol-2-yl] urea (Compound No. 3),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[(4-trifluoromethyl) phenyl] urea (Compound No. 4),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(1H-indazol-4-yl) urea (Compound No. 5),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(2-methyl-1,3-thiazol-4-yl)phenyl]urea (Compound No. 6),

1-[(1 α ,5 α ,6 α)-3-(4-Fluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(2-methyl-1,3-thiazol-4-yl)phenyl]urea (Compound No. 7),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(5-*tert*-butyl-1,3,4-oxadiazol-2-yl)phenyl]urea (Compound No. 8),

1-[(1 α ,5 α ,6 α)-3-(4-Fluorophenyl)-3-azabicyclo [3.1.0]hex-6-yl]-3-[3-(5-*tert*-butyl-1,3,4-oxadiazol-2-yl)phenyl]urea (Compound No. 9),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(5-cyano-4,5-dihydroisoxazol-3-yl)phenyl]urea (Compound No. 10),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(2-furyl)phenyl]urea (Compound No. 11),

1-[(1 α ,5 α ,6 α)-3-(4-Fluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(2-furyl)phenyl]urea (Compound No. 12),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(2-thionyl)phenyl]urea (Compound No. 13),

1-[(1 α ,5 α ,6 α)-3-(4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(2-thionyl)phenyl]urea (Compound No. 14),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(1,3-thiazol-2-yl)phenyl]urea (Compound No. 15),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(3-isoxazol-3-yl)phenyl]urea (Compound No. 16),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(1-methyl-1*H*-pyrazol-3-yl)phenyl]urea (Compound No. 17),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(1-benzyl-1*H*-pyrazol-3-yl)phenyl]urea (Compound No. 18),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[2-(1*H*-1,2,4-triazol-1-yl)phenyl]urea (Compound No. 19),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(1*H*-1,2,4-triazol-1-yl)phenyl]urea (Compound No. 20),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[2-(1*H*-1,2,3-triazol-1-yl)phenyl]urea (Compound No. 21),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[3-(2*H*-1,2,3-triazol-2-yl)phenyl]urea (Compound No. 22),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl)urea (Compound No. 23),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)urea (Compound No. 24),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-methyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl)urea (Compound No. 25),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-methyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)urea (Compound No. 26),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[2-(2-oxo-1,3-oxazolidin-3-yl)phenyl]urea (Compound No. 27),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-oxo-1,3-oxazolidin-3-yl)phenyl]urea (Compound No. 28),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-[methyl 3-phenyl-4,5-dihydroisoxazole-5-carboxylate]urea (Compound No. 29),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-methyl-1*H*-benzimidazol-5-yl)urea (Compound No. 30),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(3a,4-dihydro-3*H*-chromeno[4,3-*c*]isoxazol-8-yl)urea (Compound No. 31),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2,3-dihydro-1,4-benzodioxin-6-yl)urea (Compound No. 32),

1-[(1 α ,5 α ,6 α)-3-(4-Fluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2,3-dihydro-1,4-benzodioxin-6-yl)urea (Compound No. 33),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(3,4-dihydrospiro[chromene-2,1'-cyclobutan]-4-yl)urea (Compound No. 34),

1-(5-Nitropyridin-2-yl)-3-[(1 α ,5 α ,6 α)-3-[3-(trifluoromethyl)pyridin-2-yl]-3-azabicyclo[3.1.0]hex-6-yl]urea (Compound No. 35),

1-[4-(Trifluoromethyl)phenyl]-3-[(1 α ,5 α ,6 α)-3-[3-(trifluoromethyl)pyridine-2-yl]-3-azabicyclo[3.1.0]hex-6-yl]urea (Compound No. 36),

1-[5-(4-Bromophenyl)-1,3,4-thiadiazol-2-yl]-3-[(1 α ,5 α ,6 α)-3-[3-(trifluoromethyl)pyridin-2-yl]-3-azabicyclo[3.1.0]hex-6-yl]urea (Compound No. 37),

1-[5-(tert-Butyl)-1,3,4-thiadiazol-2-yl]-3-[(1 α ,5 α ,6 α)-3-[3-(trifluoromethyl)pyridin-2-yl]-3-azabicyclo[3.1.0]hex-6-yl]urea (Compound No. 38),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-pyrrolidin-1-ylphenyl)urea (Compound No. 39),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-(2-thienyl)phenyl)urea (Compound No. 40),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-(1,3-thiazol-2-yl)phenyl)urea (Compound No. 41),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-isoxazol-3-ylphenyl)urea (Compound No. 42),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-morpholin-4-ylphenyl)urea (Compound No. 43),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(3-[1,2,3]triazol-1-yl-phenyl urea (Compound No.44),

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-[1,2,3]triazol-2-yl-phenyl urea (Compound No.45), and

1-[(1 α ,5 α ,6 α)-3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-pyrazol-1-yl)-phenyl urea (Compound No.46)

or a pharmaceutically acceptable salt thereof, an N-oxide thereof, an ester thereof, a tautomer thereof, or a stereoisomer thereof.

23. A pharmaceutical composition comprising a compound according to any one of claims 1 to 22 and one or more pharmaceutically acceptable carriers, diluents or excipients.

24. A method for preventing, ameliorating or treating diseases, disorders or syndromes mediated by a vanilloid receptor comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 22.
25. The method according to claim 24, wherein the vanilloid receptor mediated disease, disorder or syndrome is a pain or inflammatory disease, disorder or syndrome mediated by VR1.
26. The method according to claim 24 or 25, wherein the disease, disorder or syndrome is selected from pain, acute pain, chronic pain, nociceptive pain, neuropathic pain, post-operative pain, dental pain, cancer pain, cardiac pain arising from an ischemic myocardium, pain due to migraine, arthralgia, neuropathies, neuralgia, trigeminal neuralgia, nerve injury, diabetic neuropathy, neurodegeneration, retinopathy, neurotic skin disorder, stroke, urinary bladder hypersensitiveness, urinary incontinence, vulvodynia, gastrointestinal disorders such as irritable bowel syndrome (IBS), gastro-esophageal reflux disease (GERD), enteritis, ileitis, stomach-duodenal ulcer, inflammatory bowel disease, Crohn's disease, celiac disease, an inflammatory disease such as pancreatitis, respiratory disorder such as allergic and non-allergic rhinitis, asthma or chronic obstructive pulmonary disease, irritation of skin, eye or mucous membrane, dermatitis, pruritic conditions such as uremic pruritus, fervescence, muscle spasms, emesis, dyskinesias, depression, Huntington's disease, memory deficits, restricted brain function, amyotrophic lateral sclerosis (ALS), dementia, arthritis, osteoarthritis, diabetes, obesity, urticaria, actinic keratosis, keratocanthoma, alopecia, Meniere's disease, tinnitus, hyperacusis, anxiety disorders and benign prostate hyperplasia.
27. The method according to claim 26, wherein the pain is acute pain.
28. The method according to claim 26, wherein the pain is chronic pain.
29. The method according to claim 26, wherein the pain is post-operative pain.
30. A method of treating neuropathic pain in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1 to 22.

31. A method of treating urinary incontinence in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1 to 22.
32. A method of treating overactive bladder or benign prostate hyperplasia in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1 to 22.
33. A method of treating ulcerative colitis in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1 to 22.
34. A method of treating asthma in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1 to 22.
35. A method of treating inflammation in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1 to 22.