Abstract:
The methods and/or processes relating to substituted 3-azabicyclo[3.1.0] hexane vanilloid receptor ligands, methods of treating diseases, conditions and/or disorders modulated by vanilloid receptors with them, and processes for preparing them.

Title: 3-AZABICYCLO [3.1.0] HEXANE VANILLOID RECEPTOR LIGANDS, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM, AND PROCESSES FOR THEIR PREPARATION

Abstract: The present invention relates to substituted 3-azabicyclo [3.1.0] hexane derivatives, which are useful as vanilloid receptor ligands, methods of treating diseases, conditions and/or disorders modulated by vanilloid receptors with them, and processes for preparing them.
3-AZABICYCLO [3.1.0] HEXANE VANILLOID RECEPTOR LIGANDS, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM, AND PROCESSES FOR THEIR PREPARATION

This application claims the benefit of Indian Application Nos. 1136/MUM/2006 and 381/MUM/2007, filed July 17, 2006 and February 27, 2007, and U.S. Provisional Application No. 60/835,560, 60/893,675, and 60/974,715, filed August 3, 2006, March 8, 2007, and July 3, 2007, all of which are hereby incorporated by reference.

Field of the Invention

The present invention relates to substituted 3-azabicyclo [3.1.0] hexane derivatives, which are useful as vanilloid receptor 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 either 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 100-107, J. C. Bennett and F. Plum eds., 20th ed., 1996). The sensation of pain can be triggered by any number of physical or chemical stimuli and the sensory neurons which mediate the response to these harmful stimuli are known as "nociceptors". Nociceptors are primary sensory afferent (C and A δ fibers) neurons that are activated by a wide variety of noxious stimuli including chemical, mechanical, thermal, and proton (pH <6) modalities.

Moreover, 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) (V. Di Marzo et al., Current Opinion in Neurobiology Y2: 372-379, 2002) to pain processing.
The lipophilic vanilloid, Capsaicin (8-methyl-N-vanillyl-6-nonenamides; CAP) 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 (VRI now known as TRPV1) (Caterina MJ, et.al, Science , Apr 14; 288 (5464): 306-13, 2000). 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 upon local application. However, after induction of pain, CAP induces desensitization to both CAP itself and also to other noxious stimuli, thereby stopping the pain. The intradermal administration of CAP is characterized by an initial burning or hot sensation followed by a prolonged period of analgesia. The analgesic component of VRI 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 or have been used or under development as analgesic agents or therapeutic agents for urinary incontinence or skin disorders (Wrigglesworth and Walpole, Drugs of the Future, 23: pp 531-538, 1998).

VRI is widely expressed in non-neuronal tissues in various organ systems, and the functional roles of VRI in these systems are not properly understood at this time. An increasing number of animal studies have revealed the possible involvement of VRI receptors in a number of pathologies. Based on this information, VRI is 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 hypersensitivity, urinary incontinence, vulvodynia, pruritic conditions such as uremic pruritus, irritable bowel syndrome (IBS) including gastro-esophageal reflux disease (GERD), 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 and depression. Specifically VRI antagonists

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are 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, and 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, keratoacanthoma, alopecia, Meniere's disease, tinnitus, hyperacusis and anxiety disorders.

One class of natural and synthetic compounds that modulate the function of vanilloid Receptor (VR1) have been characterized by the presence of a vanillyl (4-hydroxy 3-methoxybenzyl) group or a functionally equivalent group and have been widely studied and is extensively reviewed by Szallasi and Blumberg (The Am. Soc. for Pharmacology and Experimental Therapeutics, Vol. 51, No. 2, 1999).

Various vanilloid agonists and antagonists have been developed for the treatment of pain. The agonists work by desensitizing the receptor, while antagonists block its stimulation by (patho) physiological ligands. The first antagonist, Capsazepine, was developed by Novartis.

Additional VR1 antagonists are currently in preclinical evaluation, for example, Amore Pacific's PAC-20030, Neurogen's BCTC, Abbott's A-425619 and Amgen's AMG-9810.


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):

$$R^1 - N - R^2 - N - R^3 - N - R^6$$

or is a prodrug thereof, a pharmaceutically acceptable salt thereof, an N-oxide thereof, an ester thereof, a pharmaceutically acceptable solvate thereof, a tautomer thereof, a stereoisomer thereof or a polymorph thereof, wherein:

- $X$ is O or S;
- $R^1$ is selected from

![Chemical structures A, B, C, D](image)

wherein $R^1$ is linked to the main structure through any carbon atom in the ring and is optionally substituted with one or more $R$ groups;

- each occurrence of $R$ and $R^6$ is independently selected from hydrogen, nitro, cyano, formyl, acetyl, halogen, -OR$^7$, -SR$^7$, oxo, thio, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclalkyl, -C(O)R$^7$, -C(O)O-R$^7$, -C(O)NR$^7$R$^8$, -NR$^7$R$^8$, -S(O)$_2$R, and a protecting group;
each occurrence of $R^7$ and $R^8$ is independently selected from hydrogen, nitro, halo, cyano, -OR, -SR, oxo, thio, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted aroyl, substituted or unsubstituted aryalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, -C(O)R, -C(O)O-R, -C(O)NR, -S(O)R, -S(O)NR, -S(O)NR, -NR, and a protecting group, or $R^7$ and $R^8$, when both are directly bound to the same nitrogen atom, are joined together with the nitrogen atom to which they are attached to form an optionally substituted 3 to 7 membered saturated or unsaturated cyclic ring, which optionally includes one or more heteroatoms selected from O, NR and S;

each occurrence of $R^a$ and $R^b$ is independently selected from hydrogen, halogen, nitro, cyano, formyl, acetyl, oxo, thio, -C(O)-R, -C(O)O-R, -C(O)NR, -S(O)R, -S(O)NR, -NR, a protecting group, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aroyl, substituted or unsubstituted aryalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, and substituted or unsubstituted heterocyclylalkyl;

each occurrence of $R^c$ and $R^d$ is independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aroyl, substituted or unsubstituted aryalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heterocyclylalkyl and a protecting group, or $R^c$ and $R^d$, when both are directly bound to the same nitrogen atom, are joined together with the nitrogen atom to which they are attached to form an optionally substituted 3 to 7 membered saturated or unsaturated cyclic ring, which optionally includes one or more heteroatoms selected from O, NR or S;
each occurrence of \( R^5 \) is independently selected from hydrogen and substituted or unsubstituted alkyl;

each occurrence of \( m \) is independently 0, 1 or 2;

\( R^2 \) and \( R^3 \) are independently selected from hydrogen, hydroxy and \( C_{1-6} \) alkyl; and

each occurrence of \( R^4 \) and \( R^5 \) is independently selected from hydrogen, halogen, and alkyl, or when \( R^4 \) and \( R^5 \) are bound to the same carbon atom, \( R^4 \) and \( R^5 \) together form oxo or thio.

According to one preferred embodiment, the compound of formula (I) meets one, two, or all of the following criteria:

(a) \( R^6 \) is not substituted or unsubstituted pyrimidine,

(b) \( R^6 \) is not a substituted or unsubstituted pyrrolidinealkyl, and

(c) \( R^1 \) is not a substituted or unsubstituted amino group.

Another preferred embodiment is a compound of formula (I) where \( X \) is O.

Further preferred is a compound of formula (I) where \( R^1 \) is an unsubstituted quinoline, quinolone, isoquinoline, or isoquinolone.

Further preferred is a compound of formula (I) where \( R^1 \) is a substituted or unsubstituted quinoline or isoquinoline attached to the nitrogen at position 5, 6, 7, or 8.

Further preferred is a compound of formula (I) where \( R^1 \) is

Further preferred is a compound of formula (I) where \( R^1 \) is hydrogen.

In a preferred embodiment, each \( R \) and \( R^6 \) is independently hydrogen, nitro, cyano, formyl, acetyl, halogen, or a substituted or unsubstituted group selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, aryl, arylalkyl, heteroaryl, heteroarylmethyl, heterocyclic group, or heterocyclylmethyl.

Further preferred is a compound of formula (I) wherein \( R^6 \) is a substituted or unsubstituted group selected from cycloalkyl, cycloalkylalkyl, cycloalkenyl, aryl, arylalkyl,
heteroaryl, heteroarylalkyl, heterocyclic group, and heterocyclylalkyl, wherein the optional substitution(s) are selected from alkyl, hydroxy, nitro, cyano, formyl, acetyl, halogen, or trihalo alkyl.

In another preferred embodiment, each R is independently hydrogen, nitro, cyano, formyl, acetyl, halogen, or a substituted or unsubstituted alkyl, and R⁶ is a substituted or unsubstituted group selected from cycloalkyl, cycloalkylalkyl, cycloalkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclic group, and heterocyclylalkyl, wherein the optional substitution(s) are selected from alkyl, hydroxy, nitro, cyano, formyl, acetyl, halogen, or trihalo alkyl.

Further preferred R⁶ is substituted or unsubstituted heteroaryl.

Further preferred is a compound of formula (I) where R⁶ is 3-chloropyridyl-3-yl.

Further preferred is a compound of formula (I) where R⁶ is 3-chloro,5-trifluoropyridyl-2-yi.

Further preferred is a compound of formula (I) where R⁶ is 5-trifluoromethylpyrid-2-yi.

Further preferred is a compound of formula (I) where R⁶ is 3-trifluoromethylpyrid-2-yi.

Further preferred is a compound of formula (I) where R⁶ is 3-nitropyrid-2-yl.

Further preferred is a compound of formula (I) where R⁶ is 4-t-butylbenzoyl.

According to one preferred embodiment, the VRI receptor ligand has the general formula (Ia):

\[ \text{Ia) } \]

or is a prodrug thereof, a pharmaceutically acceptable salt thereof, an N-oxide thereof, an ester thereof, a pharmaceutically acceptable solvate thereof, a tautomer thereof, a stereoisomer thereof or a polymorph thereof, wherein

X is O or -S-;

R², R³, R⁴ and R⁵ are hydrogen;

R⁶ is substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, C(O)R⁷, S(O)₂R⁷ or COOR⁷; and
R7 is substituted or unsubstituted aryl.

Further preferred embodiment is a compound of formula (Ia), wherein R6 is substituted with methyl, isopropyl, t-butyl, trifluoromethyl, bromo, chloro, fluoro, iodo, nitro, methoxy, cyclopropylmethoxy, difluoromethoxy, trifluoromethoxy, acetylamino, trifluoroacetylamino or methanesulfonylamino.

Further preferred is a compound of formula (Ia) wherein R6 is substituted or unsubstituted aryl.

Further preferred is a compound of formula (Ia) where R6 is selected from phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 2,6-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2,3,4-trifluorophenyl, 2,4,5-trifluorophenyl, 2,4,6-trifluorophenyl, 3,4,5-trifluorophenyl, 2-methoxyphenyl, 2-methoxyphenyl, 2-isopropylphenyl, 4-isopropylphenyl, 4-t-butyl phenyl, 2,4-dimethylphenyl, 2-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-difluoromethoxyphenyl, 2-trifluoromethoxyphenyl, 2-fluoro-5-methylphenyl, 2-cyclopropylmethoxyphenyl, 2-fluoro-3-trifluoromethylphenyl, 2-trifluoromethoxyphenyl, 2-fluoro-5-trifluoromethylphenyl, 2-fluoro-4-difluoromethoxyphenyl, or 2-fluoro-4-methylphenyl.

Further preferred is a compound of formula (Ia) wherein R6 is arylalkyl.

Further preferred is a compound of formula (Ia) where R6 is selected from benzyl, A-chlorobenzyl and 4-trifluoromethylbenzyl.

Further preferred is a compound of formula (Ia) where R6 is selected from A-chlorophenylsulfonyl, 4-trifluoromethylphenylsulfonyl, 4-fluorophenylsulfonyl, 2,6-dichlorophenylsulfonyl, 2,6-difluorophenylsulfonyl, 2,4-dibromophenylsulfonyl, 2,4-dichlorophenylsulfonyl, 2-trifluoromethyl phenylsulfonyl, 2-fluorophenylsulfonyl, 2-chlorophenylsulfonyl, 2-bromophenylsulfonyl, phenylsulfonyl, 4-bromophenylsulfonyl, A-iodophenylsulfonyl or 4-methylphenylsulfonyl.

Further preferred is a compound of formula (Ia) wherein R6 is -COR7.

Further preferred is a compound of formula (Ia) where R6 is selected from A-bromobenzoyl, 4-chlorobenzoyl, 3-fluorobenzoyl, 2-bromobenzoyl, 2-fluorobenzoyl, 2-chlorobenzoyl, 4-methyl benzoyl, 2-trifluoromethylbenzoyl, 4-trifluoromethyl benzoyl, 4-bromo benzoyl or 4-benzyl benzoyl.
Further preferred is a compound of formula (Ia) wherein $R_6$ is heteroaryl.

Further preferred is a compound of formula (Ia) where $R_6$ is selected from 3-(acetyl amino)pyridin-2-yl, 3-(trifluoroacetyl amino)pyridin-2-yl, 3-(methanesulphonyl amino) pyrid-2-yl, 3,5-dichloropyridin-2-yl, 3-bromopyridin-2-yl or 5-nitro-pyridin-2-yl.

Representative compounds of the present invention include those specified below and prodrugs thereof, pharmaceutically acceptable salts thereof, N-oxides thereof, esters thereof, solvates thereof, tautomers thereof, stereoisomers thereof and polymorphs thereof. The present invention should not be construed to be limited to the following examples.

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(3-acetylaminopyrid-2-yl)]-3-azabicyclo [3.1.0]hexane (Compound No. 1),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(3-trifluoroacetylaminopyrid-2-yl)]-3-azabicyclo [3.1.0]hexane (Compound No. 2),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(3-methanesulphonylaminopyrid-2-yl)]-3-azabicyclo [3.1.0]hexane (Compound No. 3),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(3,5-dichloropyrid-2-yl)]-3-azabicyclo [3.1.0]hexane (Compound No. 4),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(3-bromopyrid-2-yl)]-3-azabicyclo [3.1.0]hexane (Compound No. 5),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(5-nitropyrid-2-yl)]-3-azabicyclo [3.1.0]hexane (Compound No. 6),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2-fluorophenyl)]-3-azabicyclo [3.1.0]hexane (Compound No. 7),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(4-fluorophenyl)]-3-azabicyclo [3.1.0]hexane (Compound No. 8),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(4-isopropylphenyl)]-3-azabicyclo [3.1.0]hexane (Compound No. 9),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2-methoxyphenyl)]-3-azabicyclo [3.1.0]hexane (Compound No. 10),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(4-t-butylphenyl)]-3-azabicyclo [3.1.0]hexane (Compound No. 11),
1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2,4-dimethylphenyl)]-3-azabicyclo[3.1.0]hexane (Compound No. 12),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(4-trifluoromethyl)phenyl]-3-azabicyclo[3.1.0]hexane (Compound No. 13),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-((4-methoxy)phenyl)]-3-azabicyclo[3.1.0]hexane (Compound No. 14),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(3,4,5-trifluoro)phenyl]-3-azabicyclo[3.1.0]hexane (Compound No. 15),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2-difluoromethoxy)phenyl]-3-azabicyclo[3.1.0]hexane (Compound No. 16),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(3,4-difluoro)phenyl]-3-azabicyclo[3.1.0]hexane (Compound No. 17),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2-fluoro-5-methyl)phenyl]-3-azabicyclo[3.1.0]hexane (Compound No. 18),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(3-fluoro)phenyl]-3-azabicyclo[3.1.0]hexane (Compound No. 19),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(3-fluoro)phenyl]-3-azabicyclo[3.1.0]hexane (Compound No. 20),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2,4-difluoro)phenyl]-3-azabicyclo[3.1.0]hexane (Compound No. 21),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2,6-difluoro)phenyl]-3-azabicyclo[3.1.0]hexane (Compound No. 22),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2-fluoro-3-trifluoromethyl)phenyl]-3-azabicyclo[3.1.0]hexane (Compound No. 23),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2-trifluoromethoxy)phenyl]-3-azabicyclo[3.1.0]hexane (Compound No. 24),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2-trifluoromethyl)phenyl]-3-azabicyclo[3.1.0]hexane (Compound No. 25),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-[2-fluoro-(5-trifluoromethyl)phenyl]]-3-azabicyclo[3.1.0]hexane (Compound No. 26),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-[2-fluoro-(4-difluoromethoxy)phenyl]]-3-azabicyclo[3.1.0]hexane (Compound No. 27),
1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2,3,4-trifluoro)phenyl]-3-azabicyclo[3.1.0]hexane (Compound No. 28),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2,4,6-trifluoro)phenyl]-3-azabicyclo[3.1.0]hexane (Compound No. 29),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2,3-difluoro)phenyl]-3-azabicyclo[3.1.0]hexane (Compound No. 30),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2-fluoro-4-methylphenyl)]phenyl]-3-azabicyclo[3.1.0]hexane (Compound No. 31),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2-isopropyl)phenyl]-3-azabicyclo[3.1.0]hexane (Compound No. 32),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(3,5-difluorophenyl)]-3-azabicyclo[3.1.0]hexane (Compound No. 33),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2,4,5-trifluorophenyl)]-3-azabicyclo[3.1.0]hexane trifluoroacetate salt (Compound No. 35),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2,4-difluorophenyl)]-3-azabicyclo[3.1.0]hexane triflate salt (Compound No. 36),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2,4-difluorophenyl)]-3-azabicyclo[3.1.0]hexane hydrochloride salt (Compound No. 37),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2,4-difluorophenyl)]-3-azabicyclo[3.1.0]hexane mesylate salt (Compound No. 38),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(4-chlorophenyl)sulfonyl]-3-azabicyclo[3.1.0]hexane (Compound No. 39),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-[4-(trifluoromethyl)phenyl]sulfonyl]-3-azabicyclo[3.1.0]hexane (Compound No. 40),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(4-fluorophenyl)sulfonyl]-3-azabicyclo[3.1.0]hexane (Compound No. 41),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2,6-dichlorophenyl)sulfonyl]-3-azabicyclo[3.1.0]hexane (Compound No. 42),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2,6-difluorophenyl)sulfonyl]-3-azabicyclo[3.1.0]hexane (Compound No. 43),
1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2,4-dibromophenyl)sulfonyl]-3-azabicyclo [3.1.0]hexane (Compound No. 44),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2,4-dichlorophenyl)sulfonyl]-3-azabicyclo [3.1.0]hexane (Compound No. 45),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2-trifluoromethyl phenyl) sulfonyl]-3-azabicyclo [3.1.0]hexane (Compound No. 46),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2-fluorophenyl)sulfonyl]-3-azabicyclo [3.1.0]hexane (Compound No. 47),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2-chlorophenyl)sulfonyl]-3-azabicyclo [3.1.0]hexane (Compound No. 48),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2-bromophenyl)sulfonyl]-3-azabicyclo [3.1.0]hexane (Compound No. 49),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(phenylsulfonyl)]-3-azabicyclo [3.1.0]hexane (Compound No. 50),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(4-bromophenyl) sulfonyl]-3-azabicyclo [3.1.0]hexane (Compound No. 51),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(4-iodophenyl)sulfonyl)]-3-azabicyclo [3.1.0]hexane (Compound No. 52),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(4-methylphenyl)sulfonyl]-3-azabicyclo [3.1.0]hexane (Compound No. 53),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(4-bromobenzoyl)]-3-azabicyclo [3.1.0]hexane (Compound No. 54),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(4-chlorobenzoyl)]-3-azabicyclo [3.1.0]hexane (Compound No. 55),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(3-fluorobenzoyl)]-3-azabicyclo [3.1.0]hexane (Compound No. 56),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2-bromobenzoyl)]-3-azabicyclo [3.1.0]hexane (Compound No. 57),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2-fluorobenzoyl)]-3-azabicyclo [3.1.0]hexane (Compound No. 58),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2-chlorobenzoyl)]-3-azabicyclo [3.1.0]hexane (Compound No. 59),
1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(4-methylbenzoyl)]-3-azabicyclo[3.1.0]hexane (Compound No. 60),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2-trifluoromethyl) benzoyl]-3-azabicyclo [3.1.0]hexane (Compound No. 61),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(4-trifluoromethylbenzoyl)]-3-azabicyclo [3.1.0]hexane (Compound No. 62),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(4-bromobenzoyl)]-3-azabicyclo [3.1.0]hexane (Compound No. 63),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(4-benzylbenzoyl)]-3-azabicyclo [3.1.0]hexane (Compound No. 64),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(4-chlorobenzoyl)]-3-azabicyclo [3.1.0]hexane (Compound No. 65),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(4-trifluoromethylbenzoyl)]-3-azabicyclo [3.1.0]hexane (Compound No. 66),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-phenyl]-3-azabicyclo [3.1.0]hexane (Compound No. 67),

N-[3-(3-trifluoromethylpyridin-2-yl)]-3-azabicyclo[3.1.0]-hex-6-yl-N-isoquinolin-5-yl urea (Compound No. 68),

1α,5α,6α-[6-(5-isoquinolylaminocarboxamido)-3-(3-chloropyrid-2-yl)]-3-azabicyclo[3.1.0]hexane (Compound No. 69),

1α,5α,6α-[6-(5-isoquinolylaminocarboxamido)-3-(5-trifluoromethylpyrid-2-yl)]-3-azabicyclo [3.1.0]hexane (Compound No. 70),

1α,5α,6α-[6-(5-isoquinolylaminocarboxamido)-3-(3-chloro-5-trifluoromethylpyrid-2-yl)]-3-azabicyclo [3.1.0]hexane (Compound No. 71),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(3-chloro-5-trifluoromethylpyrid-2-yl)]-3-azabicyclo [3.1.0]hexane (Compound No. 72),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(3-nitropyrid-2-yl)]-3-azabicyclo [3.1.0]hexane (Compound No. 73),

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(4-t-butylbenzoyl)]-3-azabicyclo [3.1.0]hexane (Compound No. 74),

1-[3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-methyl-1-oxo-1,2-dihydroisoquinolin-5-yl)-urea (Compound No. 75),
**Table 1**

(R²=R³=R⁴=R⁵=H, X is O; * X is S)

<table>
<thead>
<tr>
<th>Comp. No</th>
<th>R⁶</th>
<th>Comp. No.</th>
<th>R⁶</th>
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<tbody>
<tr>
<td>1</td>
<td><img src="" alt="Chemical Structure" /></td>
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<td>35</td>
<td><img src="image" alt="Structure 35" /></td>
<td><img src="image" alt="Structure 36" /></td>
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</tr>
</tbody>
</table>
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.

The compounds and pharmaceutical compositions of the present invention are useful in the treatment of diseases, conditions and/or disorders modulated by vanilloid receptor antagonists.
The present invention further provides a method of treating a disease, condition and/or disorder modulated by a vanilloid VR1 receptor antagonist 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 present invention further provides a method of treating a disease, condition and/or disorder modulated by a vanilloid VR1 receptor antagonist in a subject in need thereof by administering to the subject a therapeutically effective amount of a compound of formula I, where R6 is a substituted pyrimidine, a substituted or unsubstituted aminoalkyl or a substituted pyrrolidinemethyl group, or a pharmaceutical composition comprising at least one such compound of formula I and a pharmaceutically acceptable excipient.

According to a preferred embodiment, provided herein is a method for preventing, ameliorating or treating diseases, disorders or syndromes mediated by a vanilloid receptor (especially the vanilloid VR1 receptor) comprising administering to the subject in need thereof a therapeutically effective amount of a compound of formula I or Ia.

According to a preferred embodiment, the disease, disorder or syndrome is pain or an inflammatory disease, disorder or syndrome mediated by VR1.

According to another preferred embodiment, 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, arthalgia, neuropathies, neuralgia, trigeminal neuralgia, nerve injury, diabetic neuropathy, neurodegeneration, retinopathy, neurotrophic 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.
In another preferred embodiment, the disease, disorder or syndrome is pain such as acute pain, chronic pain or post-operative pain.

In yet another preferred embodiment, the disease, disorder or syndrome is neuropathic pain.

In yet another preferred embodiment, the disease, disorder or syndrome is urinary incontinence.

In yet another preferred embodiment, the disease, disorder or syndrome is overactive bladder or benign prostate hyperplasia.

In yet another preferred embodiment, the disease, disorder or syndrome is ulcerative colitis.

In yet another preferred embodiment, the disease, disorder or syndrome is asthma.

In yet another embodiment, the disease, disorder or syndrome is inflammation.

Also provided herein are processes for preparing a compound of general formula (I) or (Ia).

The invention further provides intermediates useful in the preparation of the compounds of the present invention having the formula 26:

![Chemical Structure](image)

wherein R⁴ and R⁵ are hydrogen, and R⁶ is selected from phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 2,6-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2,3,4-trifluorophenyl, 2,4,5-trifluorophenyl, 2,4,6-trifluorophenyl, 3,4,5-trifluorophenyl, 2-methoxyphenyl, 4-methoxyphenyl, 2-isopropylphenyl, 4-isopropylphenyl, 4-fluoro-2-butyl phenyl, 2,4-dimethylphenyl, 2-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-difluoromethoxyphenyl, 2-trifluoromethoxyphenyl, 2-fluoro-5-methylphenyl, 2-cyclopropylmethoxyphenyl, 2-fluoro-3-trifluoromethylphenyl, 2-trifluoromethoxyphenyl, 2-fluoro-5-trifluoromethylphenyl, 2-fluoro-4-difluoromethoxyphenyl, 2-fluoro-4-methylphenyl,
The invention further provides intermediates useful in the preparation of the compounds of the present invention having the formula 6a:

wherein R⁴, R⁵, and R⁶ are as defined above for formula 26 and PG is an N-protecting group as defined hereinafter (also referred to as an amino-protecting group).

The invention further provides intermediates useful in the preparation of the compounds of the present invention having the formula 7:

wherein R⁴, R⁵, and R⁶ are as defined above for formula 26.

**Detailed Description of the Invention**

**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 "Ci6 alkyl" refers to an alkyl chain having 1 to 6 carbon atoms.

The term "aminoalkyl" refers to an amino group directly bonded to an alkyl group as defined above. The amino group is substituted or unsubstituted. The aminoalkyl group may be attached to the main structure at any carbon atom in the alkyl group.

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-l-propenyl, 1-butynyl, and 2-butynyl.

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 "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, perhydro- napththyl, adamantyl and norbornyl groups, bridged cyclic groups or sprirobicyclic 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 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" 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, azetidinyl, acridinyl, benzodioxolyl, benzodioxanyln, benzofurnyl, carbazolyl, cinnolinyl, dioxolanyl, indolizinyln, naphthyridinyln, perhydroazepinyln, phenazineyn, phenothiazinyl, phenoxyazinyl, phthalazinyl, pyridyl, pteridinyln, purinyln, quinazolinyln, quinoxalinyln, quinolininyln, isoquinolininyln, tetrazolyl, imidazolyl, tetrahydroisouinolyl, piperidinyln, piperazinyl, 2-oxopiperazinyln, 2-oxopiperidinyln, 2-oxopyrrolidinyln, 2-oxoazepinyln, azepinyln, pyrrolyln, 4-piperidonyln, pyrrolidinyln, pyrazinyl, pyrimidinyln, pyridazinyl, oxazolyl, oxazolinyln, oxasolidinyln, triazolyl, indanyl, isoazolyl, isoasolidinyln, morpholinyln, thiazolyl, thiazolinyln, thiazolidinyln, isothiazolyl, quinclidinyln, isothiazolidinyln, indolyl, isoindolyl, indolinyln, isoindolinyln, octahydroindolyl, octahydroisoindolyl, quinolyl, isoquinolyn, decahydroisoquinolyl, benzimidazolyl, thiazolyl, benzopyranyln, benzothiazolyl, benzooxazolyl, furyln, tetrahydrofurtyln, tetrahydrocrynanyln, thienc, benzothiencn, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfon, dioxaphospholanyln, oxadiazolyl, chromanyln, and isochromanyln. 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 "heteroarylmalkyl" refers to a heteroaryl ring radical directly bonded to an alkyl group. The heteroarylmalkyl 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, o xo (=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 heteroarylmalkyl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted guanidine, -COOR, -C(O)R, -C(S)R, -C(O)NR, -C(O)ONR, -NR<CONR, -N(R^2)SOR, -N(R^2)SO_2 R^3, -(=N-N(R^2)R^3), -NR^3C(O)OR, -NR^3R, -NR^3C(O)R, -NR^3C(S)R, -NR^3C(S)NR^4R^5, -SO_2NR^3R^4, -OR^4, -OR^3C(O)NR^4R^5, -OR^3C(O)OR^4, -OC(O)R^5, -OC(O)NR^4R^5, -R^5NR^4C(O)R, -R^5OR, -R^5C(O)Or, -R^5C(O)NR^4R^5, -R^5C(O)R, -R^5OC(O)R, -SR^4, -SOR^4, -SO_2R^4, and -ONO_2, wherein R^2, R^3 and R^4 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 heteroarylmalkyl, or substituted or unsubstituted heterocyclic ring. According to one embodiment, 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, -CH$_2$CH$_2$SO$_2$Ph, cyanoethyl, 2-(trimethylsilyl)ethyl, 2-(trimethylsilyl)ethoxymethyl, 2-(p-toluenesulfonyl)ethyl, 2-(p-nitrophenylsulfonyl)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.

The term "prodrug" means a compound that is transformed in vivo to yield a compound of Formula (I) or (Ia) or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms, such as through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

The term "treating" or "treatment" of a disease, state, disorder or condition includes:
(1) preventing or delaying the appearance of clinical symptoms of the disease, state, disorder or condition developing in a subject that may be afflicted with or predisposed to the disease, state, disorder or condition but does not yet experience or display clinical or subclinical symptoms of the state, disorder or condition;
(2) inhibiting the disease, 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 disease, 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 disease, state, disorder or condition, is sufficient to effect such treatment. The "therapeutically effective amount" will vary depending on the compound, the disease, state, disorder or condition and its severity, as well as 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'-diacetylthelyenediamine, glucamine, triethylamine, choline, hydroxide, dicyclohexylamine, metformin, benzylamine, trialkylamine, and thiamine), salts of chiral bases (such as alkylphenylamine, glycineol, and phenyl glycineol), 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, benzenesulphonates, 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 Me₂SO₄). The pharmaceutically acceptable salts of the present invention may be prepared by any of the conventional techniques known to a person of ordinary skill in the art, e.g., as described in Handbook of Pharmaceutical Salts-Properties, Selection and Use", P. Heinrich Stahl, Camille G. Wermuth [Eds.], VHCA and WILEY-VCH (2002).

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 moieties are contemplated:

\[
\begin{align*}
&\text{Pharmaceutical Compositions} \\
\text{The pharmaceutical composition of the present invention comprises at least one compound of the present invention and a pharmaceutically acceptable excipient (such as a pharmaceutically acceptable carrier or diluent). Preferably, the pharmaceutical composition comprises a therapeutically effective amount of the compound(s) of the present invention. The compound of the present invention may be associated with a pharmaceutically acceptable excipient (such as a carrier or a diluent) or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container.}
\end{align*}
\]

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 glycercylo monostearate or glycercyldistearate, 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.

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 tabletting 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 which may be treated by the compounds and compositions of the present invention 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 (IBS) including gastro-esophageal reflux disease (GERD), enteritis, ileitis, stomach-duodenal ulcer, inflammatory bowel disease including Crohn's disease, celiac disease and inflammatory diseases such as pancreatitis, 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. Non-limiting examples of types of pain modulated by vanilloid receptor antagonists include acute pain, chronic pain, neuropathic pain, post-operative pain, pain due to neuralgia (e.g., post-herpetic neuralgia or trigeminal neuralgia), pain due to diabetic neuropathy, dental pain and cancer pain. Other diseases, conditions, and/or disorders that are modulated by vanilloid receptor
antagonists include, but are not limited to, inflammatory pain conditions (e.g. arthritis and osteoarthritis), diabetes, obesity, urticaria, actinic keratosis, keratoacanthoma, alopecia, Meniere's disease, tinnitus, hyperacusis and anxiety disorders.

Another embodiment is a method of treating or preventing a disease or disorder mediated by or associated with the activity of the vanilloid receptor in a subject in need thereof (e.g., a mammal or human) by administering to the subject a therapeutically effective amount of the compound or pharmaceutical composition of the present invention. Such diseases and disorders include, but are not limited to, disorders such as pain, chronic pain, neuropathic pain, postoperative pain, rheumatoid arthritis 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, ischemia, neurodegeneration, stroke, post stroke pain, multiple sclerosis, respiratory diseases, asthma, cough, COPD, inflammatory disorders, oesophagitis, gastroesophageal reflux disorder (GERD), irritable bowel syndrome (IBS), inflammatory bowel disease, pelvic hypersensitivity, urinary incontinence, cystitis, burns, psoriasis, emesis, stomach duodenal ulcer and pruritus.

Yet another embodiment is a method of treating or preventing pain in a subject in need thereof by administering a therapeutically effective amount of the compound or pharmaceutical composition 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 a disease or disorder mediated or associated with the activity of vanilloid receptor.

The compounds of the present invention have potent analgesic and anti-inflammatory activity, and the pharmaceutical compositions of the present invention thus may be employed to alleviate or relieve acute, chronic or inflammatory pain, suppress inflammation, or treat urgent urinary incontinence.

The compounds of the present invention may be used alone or in appropriate association, as well as in combination with other pharmaceutically active compounds.

The compounds and the pharmaceutical compositions of the present invention may be used alone or in combination with other pharmaceutically active compounds in the manufacture of a medicament for the therapeutic applications described herein.
Methods of Preparation

The compounds of formula (I), wherein \( R_3 \) is H, \( X \) is O, and \( R_1, R_2, R_4, R_5, \) and \( R_6 \) are as defined in the general description, can be synthesized as shown in scheme Ia below. According to one embodiment, \( R_4 \) and \( R_5 \) are H or, when \( R_4 \) and \( R_5 \) are bound to the same carbon atom, together form an oxo or thio group.

Scheme Ia

As shown above in scheme Ia, a compound of formula 7 is reacted with a compound of formula 8a (where \( L \) is a leaving group, such as a halogen, aryloxy, alkoxy, imidazolyl, imidazolyl, benzimidazolyl, tetrazolyl, benzotetrazolyl, succinimidyl, o xo or pyridine) to obtain a compound of formula (I).

The group \( R_3 \) in the compound of formula (I) formed by scheme Ia can be converted to a different \( R_3 \) group, such as alkyl, or aryl benzoyl, by methods known in the art.

In another embodiment, the compounds of the formula (1), wherein \( R_2 \) and \( R_3 \) represent H and X, \( R_1, R_4, R_5 \) and \( R_6 \) are as defined in the general description, can be synthesized as shown in scheme Ib below.

Scheme Ib
As shown above in 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 (I).

According to a preferred embodiment of schemes Ia and Ib, \( R^1 \) is selected from

![Chemical structures](A.png)

According to another preferred embodiment of schemes Ia and Ib, \( R^1 \) is selected from formulas A and D.

In one embodiment, the intermediate of formula 7, wherein \( R^4 \) and \( R^5 \) represent H and \( R^6 \) is as defined as in the general description above, is synthesized as shown in scheme Ha.

Methods for the synthesis of compounds of formula 7 are outlined below in Schemes Ha through Hg. In each of these methods, \( R^6 \) may be a protecting group.

Scheme Ha
In the above general scheme Ha, a compound of formula 2 is converted into intermediate 2a, for example, by reacting a compound of formula 2 with bromoritromethane, preferably in the presence of a base such as potassium carbonate, sodium carbonate or a quaternary ammonium salt and a solvent such as dimethyl formamide. The compound of formula 2a is reduced to form a compound of formula 3, such as by reaction with a reducing agent such as lithium aluminum hydride, boranes, sodium borohydride, BF₃ (e.g., BF₃•OEt₂), or a mixture thereof. The compound of formula 3 is reduced, for example, 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 a compound of formula 4. The amine in the compound of formula 4 is then protected with a protecting group, such as t-butyloxy carbonyl (BOC), preferably in the presence of a base (such as triethyl amine, sodium carbonate, potassium carbonate or sodium hydroxide), in a suitable solvent (such as methanol, dichloromethane, chloroform or ethyl acetate) to give a compound of formula 5. The compound of formula 5 is deprotected (i.e., the protecting group PGi is selectively removed), for example, under acidic conditions, such as with dry hydrochloric acid or trifluoroacetic acid in a suitable solvent, such as ethyl acetate, methanol, or dichloromethane, to provide a compound of formula 6 (as a free base or acid addition salt thereof). The reaction of a compound of formula 6 with an appropriately substituted aryl/heteroaryl, aralkyl/heteroaralkyl halide (based on the desired R⁶
substituent), 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 a compound of formula 6a. The compound of formula 6a is deprotected (i.e., the protecting group PG is removed), for example, under acidic conditions, such as dry hydrochloric acid or trifluoroacetic acid in a suitable solvent such as ethyl acetate, methanol or dichloromethane to provide a compound of formula 7.

Alternatively, the compound of formula 4 is reacted 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 the presence of copper or palladium to provide a compound of formula 7 directly, without the use of protecting group chemistry.

In yet another embodiment, the compound of formula 7, wherein R4 and R5 represent H and R6 is as defined in the general description, is synthesized as shown in schemes lib

Scheme Hb

The compound of formula 9 is 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 is cyclized, for example, with a dehydrating agent, such as acetic anhydride or dicyclohexylcarbodiimide (DCC), to afford a compound of formula 12. The compound of formula 12 is converted to a compound of formula 13, for example, by reaction with bromo nitro methane, preferably in the presence of a base such as potassium carbonate, sodium carbonate, or a quaternary ammonium salt. To prepare a compound of formula 7 wherein R4 and R5 together
form an oxo group, the compound of formula 13 is reduced, for example, using reductive conditions such as hydrogenation in the presence of palladium, Raney nickel, iron/hydrochloric acid, or Raney nickel/hydrazine to obtain a compound of formula 7. To prepare a compound of formula 7 wherein $R^4$ and $R^5$ are hydrogen, the compound of formula 13 is reduced, for example, 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 a compound of formula 14. The compound of formula 14 is then reduced, for example, using reductive conditions such as hydrogenation in the presence of palladium, Raney nickel, iron/hydrochloric acid, or Raney nickel/hydrazine to obtain a compound of formula 7.

In yet another embodiment, the compound of formula 7 is synthesized as shown in scheme Hc.

Scheme Hc

The compound of formula 7, wherein $R^4$ and $R^5$ are hydrogen or together form an oxo group) can be prepared as shown in scheme Hc above, using the reaction conditions provided by

In yet another embodiment the compound of formula 7, wherein R⁴ and R⁵ represent H and R⁶ is as defined in the general description, is synthesized as shown in scheme Hd.

**Scheme Hd**

The compound of formula 21 is obtained by the reaction of a N-benzylpyrrolidine compound of formula 19 with N,N-dibenzylformamide, for example, in the presence of Ti(OPr)₄, MeMgCl, and/or cyclohexylmagnesium bromide in a suitable solvent such as tetrahydrofuran, dimethoxyethane, or dioxane. The exhaustive debenzylation of a compound of formula 21, for example, using reductive conditions, such as hydrogenation, in the presence of palladium, Raney nickel, iron/hydrochloric acid, or Raney nickel/hydrazine, provides a compound of formula 4 (Chem. Eur.J. 8(16), 3789-3801, 2002.). The reaction of a 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 a compound of formula 7.

In yet another method the compound of formula 7, wherein R⁴ and R⁵ represent H and R⁶ is as defined in the general description, is synthesized as shown in schemes He.
N-benzyl maleimide is reacted with an ylide of formula 22, for example, in a suitable solvent such as benzene, toluene, dichloromethane, or acetone under refluxing solvent conditions, to provide a mixture of endo (15a) and exo (15) isomers of a compound of formula 23. The endo and exo isomers are separated, for example, by column chromatography. The compounds of formula 15 and 15a are then converted to a compound of formula 7 and 7a, respectively, using for example the procedure described in Scheme Hc.

Yet another method of preparing compound of formula 7 (wherein $R^4$ and $R^5$ together form oxo groups and $R^6$ is as defined in the general description) is shown in scheme Hf below.

An amine compound of formula 7 is formed by reducing a nitro compound of formula 13, for example, using reductive conditions, such as hydrogenation in the presence of palladium or Raney nickel, iron/hydrochloric acid, or Raney nickel/hydrazine.
Yet another method of preparing a compound of formula 7, wherein R\textsuperscript{4} and R\textsuperscript{5} represent H and R\textsuperscript{6} is as defined in the general description, is shown in scheme Hg below.

**Scheme Hg**

The compound of formula 25 is synthesized by reacting a compound of formula 24 wherein L is a leaving group such as halogen, a toluenesulphonylate (tosylate) or methanesulphonylate (mesylate) group, with an amine of the formula R\textsuperscript{6}-NH\textsubscript{2} in the absence or presence of a base such as triethylamine or potassium carbonate. The compound of formula 25 is reacted with N,N-dibenzylformamide, preferably in the presence of titanium isopropoxide, methyl magnesium chloride, methyl magnesium bromide, cyclohexylmagnesium bromide, or cyclohexylmagnesium chloride, in a solvent such as tetrahydrofuran, dimethoxyethane or dioxane, to obtain a compound of formula 26. The exhaustive debenzylation of a compound of formula 26 for example using reductive conditions such as hydrogenation in the presence of palladium, platinum or Raney nickel, provides a compound of formula 7 (Chem. Eur. J. 8(16), 3789-3801, 2002).
A compound of formula 37 can be prepared using the procedure outlined in scheme III above. A compound of formula 33, where PG is an N-protecting group [examples include, but are not limited to, tert-butoxy carbonyl, benzyl carbamates (e.g., benzyl chloroformate), 9-fluorenemethyl carbamate (e.g., 9-fluorenemethyl chloroformate), and vinyl carbamate (e.g., vinyl chloroformate)], is reacted with a compound of formula 34 (wherein L is as defined above) to obtain a compound of formula 35. The reaction is preferably performed in the presence one or more bases, for example, triethylamine, pyridine, sodium carbonate, potassium carbonate or lithium carbonate, and in one or more solvents, for example, an aprotic polar solvent (e.g., dimethylsulfoxide, dimethylformamide, acetonitrile), a chlorinated solvent (e.g., dichloromethane, dichloroethane, chloroform), or a mixture thereof. The compound of formula 35 is deprotected, for example, by reacting it with a deprotecting agent such as para toluene sulphonic acid, methanesulphonic acid, piperidine, dichloroacetic acid or trifluoracetic acid, to form a compound of formula 36. The compound of formula 35 is deprotected in the presence of one or more bases, for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate or lithium carbonate in one or more solvent aprotic polar solvent such as tetrahydrofuran, diethylether or a mixture thereof. The compound of formula 36 is reacted with an arylsulfonyl halide, an aryl carbonyl halide, or an arylalkyl halide in presence of one or more bases such as triethylamine, pyridine, sodium carbonate, potassium carbonate or lithium carbonate, and in one or more aprotic polar solvents such as tetrahydrofuran, diethylether or a mixture thereof, to form a compound of formula 37.
Scheme IV

Step I

Scheme I

**Step II**

a) 

b) 

40

40a
Compounds of formula 43 and 44 can be prepared by the reaction scheme shown above. A compound of formula 4 is reacted with a compound of formula 38 in the presence of a base such as triethylamine or pyridine, in a polar aprotic solvent such as dimethylsulfoxide or dimethylformamide, to form a compound of formula 39. The compound of formula 39 is reacted with a protecting agent (wherein PG is as defined above) to form a compound of formula 40.

A compound of formula 43 can be prepared as follows: A compound of formula 40 (when R' is NO₂ and R'' is H) is reduced, for example, in the presence of a catalytic reducing agent (e.g., 10% palladium on carbon or platinum on carbon and hydrogen gas) or metal reducing agent (e.g., zinc/acetic acid or Fe/HCl), in the presence of a polar protic solvent such as methanol, ethanol, isopropanol or water to provide an amine compound of formula 41. The amine of the compound of formula 41 is reacted with methane sulfonyl chloride or trifluoroacetic anhydride or acetic anhydride to form a compound of formula 42 (wherein W is CO or SO₂ and R'' is CH₃ or CF₃ and PG is as defined earlier). The compound of formula 42 is deprotected, for example, by reaction with a deprotecting agent (e.g., para toluene sulphonic acid, methanesulphonic acid, piperidine, dichloroacetic acid or trifluoracetic acid) to form a compound of formula 42a. The compound of formula 42a is reacted with phenyl isoquinolin-5-yl carbamate, for example, in the presence of a base such as triethylamine, in a polar aprotic solvent such as dimethyl sulfoxide or dimethyl formamide, to form a compound of formula 43.

A compound of formula 44 can be prepared as follows: A compound of formula 40 (where R' is chloro or bromo and R'' is chloro or nitro) is deprotected, for example, by reacting it with a deprotecting agent, (e.g., para toluene sulphonic acid, methanesulphonic acid, piperidine, dichloroacetic acid or trifluoracetic acid), to form a compound of formula 40a. The compound of formula 40a and 42a are reacted with phenyl isoquinolin-5-yl carbamate in the presence of a base such as triethylamine, in a polar aprotic solvent, such as dimethyl sulfoxide or dimethyl formamide, to form a compound of formula 44.

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.

Intermediate 1

Intermediate 1: Preparation of 1α, 5α, 6α-6-amino-3-azabicyclo [3.1.0] hexane hydrochloride

Step 1: preparation of 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 4A molecular sieves (5.0 g) in dimethyl formamide (50.0 mL), anhydrous potassium carbonate (7.4 g, 53.4 mmol) was added in portions at -30° to -25 °C and stirred for 3-4 hrs. Water (500 mL) was added to the reaction mixture and acidified to a pH 5-6 with 10% aq. HCl solution. Ethyl acetate (100 mL) was added and the mixture was filtered through a bed of celite. The layers were separated and the organic layer was washed with water (2 x 25 mL), dried over anhydrous sodium sulfate, and concentrated to give crude product (4.5 g). The crude product was then purified through a silica gel column using ethyl acetate: petroleum ether (2:8), to give 2.1 gm of product as light yellow product. IR (KBr): 3086, 1789, 1707, 1562, 1401, 1360, 1173, 1017, 883 cm⁻¹. ¹H-NMR (300 MHz, DMSO-d₆): δ 3.74 (s, 2H), 4.40 (s, 2H), 5.57 (s, IH), 7.23-7.35 (m, 5H).

**Step 2: preparation of Ia, 5a, 6a-(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) was added at -20° C. BF₃-Et₂O (3.0 mL, 24.36 mmol) was then added slowly at the same temperature. The reaction mixture was then stirred for 7-8 hrs at room temperature and treated with methanol (5.0 mL), diluted with water (100 mL), and extracted with ethyl acetate (3 x 25 mL). The combined organic layers were washed with water and dried over anhydrous sodium sulfate. Removal of solvent under vacuum gave 1.7 g product as white solid which was 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, IH), 7.43-7.62 (m, 5H).

**Step 3: Preparation of Ia, 5a, 6a-6-amino-3-azabicyclo [3.1.0] hexane**

A suspension of 1α, 5α, 6α-(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) was hydrogenated in a Parr apparatus at 60-70 psi of hydrogen gas. The catalyst was removed by filtration on a bed of celite. Removal of solvent under vacuum gave 200 mg of the product as brown oil.
Step 4: Preparation of Ia, 5a, 6a-[6-(tert)-butyloxy carbamoyl-3-(tert)-butyloxy carbonyl]-3-azabicyclo[3.1.0]hexane

A solution of 1α, 5α, 6α-6-amino-3-azabicyclo [3.1.0]hexane (200 mg, 2.0 mmol), Boc anhydride (100 mg) and triethyl amine (0.5 mL) in methanol (5 mL) was stirred at room temperature for 2-3 hrs. Removal of solvent under vacuum gave 280 mg of product as light yellow solid. $^1$H-NMR (300 MHz, CDCl$_3$): δ 1.42 (s, 9H), 1.44 (s, 9H), 1.56 (s, 2H), 2.28 (s, IH), 3.32-3.40 (m, 2H), 3.64-3.67 (m, 2H), 4.75 (s, IH).

Step 5: Ia, 5a, 6a-6-amino-3-azabicyclo [3.1.0]hexane hydrochloride

A solution of 1α, 5α, 6α-6-(tert)-butyloxy carbamoyl-3-(tert)-butyloxy carbonyl]-3-azabicyclo [3.1.0]hexane (280 mg) and ethyl acetate saturated with HCl (5.0 mL) was stirred at room temperature for 5-6 hrs. The residue obtained after removal of solvent was washed with dry ether to give 180 mg of product as white solid. $^1$H-NMR (300 MHz, CD$_3$OD): δ 231 (s, 2H), 2.82 (s, IH), 3.57 (s, 4H).

Intermediate 2: Preparation of 3-(3-Nitropyridin-2-yl)-3-azabicyclo [3.1.0]hexan-6-amine

A solution of 1α, 5α, 6α-6-amino-3-azabicyclo [3.1.0]hexane hydrochloride (400 mg, 4.08 mmol) and triethylamine (2.0 mL) in dimethyl sulfoxide (5.0 mL) was added 2-chloro-3-nitro pyridine (1.05 g, 6.52 mmol) and stirred at room temperature for 15-16 hrs. Reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water and dried over anhydrous sodium sulfate, the residue obtained after removal of solvent was purified through silica gel column using 10% methanol in chloroform as an eluent to get 300 mg of product as brown oil.

$^1$H-NMR (300 MHz, DMSO-d$_6$): δ 1.73 (brs, 3H), 2.17 (s, IH), 3.52 (d, 2H, $J = 10.2$ Hz), 3.70 (d, 2H, $J = 10.2$Hz), 7.32 (d, IH, $J = 9.3$ Hz), 7.60 (d, IH, $J = 8.7$ Hz), 8.28 (s, IH).

Intermediate 3: Preparation of Tert-butyl 3-(3-Nitropyridin-2-yl)-3-azabicvclo [3.1.0]hex-6-yl carbamate

In the stirred solution of 3-(3-Nitropyridin-2-yl)-3-azabicyclo [3.1.0]hexan-6-amine (1 mmole) and Triethyl amine (1.5 mmoles) in methanol, a solution of Boc-anhydride in methanol was added at room temperature. Heat the reaction mass up to reflux temperature for 3-4 hrs. Distillate methanol and reaction mass was dissolved in ethyl acetate and extracted with
water. Compound was purified by column chromatography. $^1$H NMR (DMSO-$d_6$): $\delta$ 1.43 (9H, s); 1.82 (2H, s); 2.16 (IH, s); 3.60 (2H, d; 3.82 (2H, d) 4.70 (IH, s); 6.66 (IH, m) 7.99 (IH, d, d); 8.28 (IH, d). IR (KBr) (cm$^{-1}$): 2984, 1759, 1622, 1450, 1200, 1095,709. MS (M$^+$+I): 321

Intermediate 4: Preparation of Tert-butyl 3-(3-aminopyridin-2-yl)-3-azabicyclo[3.1.0]hex-6-ylcarbamate

A suspension of Tert-butyl 3-(3-nitropyridin-2-yl)-3-azabicyclo[3.1.0]hex-6-yl carbamate and 10% Pd on carbon was hydrogenated in a parr apparatus for 8-10 hours. Catalyst was removed by filtration, the filtrate obtained concentrated to give the product.

Intermediate 5: Preparation of (2Z)-but-2-ene-1,4-diyldimethanesulfonate

To a solution of methanesulfonyl chloride (40 ml, 0.527 moles) in 300 ml of anhydrous dichloromethane was added slowly a mixture of cis-1, 4-butenediol (10.5 ml, 0.127 mol) and triethylamine (84 ml, 0.604 mol) at 0°C under nitrogen atmosphere and stirred for 30-40 minutes. After the mixture was stirred for 30 min more, it was then transferred to a separatory funnel and washed successively with 200 ml each of chilled water, 10% HCl, saturated sodium bicarbonate solution and saturated sodium chloride solution. The dichloromethane layer was separated and dried over 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$^{-1}$. $^1$H-NMR (300 MHz, CDCl$_3$) 65.90 (m, 2H), 4.80 (d, 4H), 3.03 (s, 6H).

Intermediate 6: Preparation of N-3-azabicyclo[3.1.0]hex-6-yl-N'-isoquinolin-5-ylurea

Step 1: tert-butyl 6-[(isoquinolin-5-ylamino)carbonyl]amino]-3-azabicyclo[3.1.0]hexane-3-carboxylate

A solution of phenyl isoquinolin-5-yl carbamate (1 mmol) and tert-butyl 6-amino-3-azabicyclo[3.1.0] hexane-3-carboxylate (1 mmol) and triethylamine (2 mmol) in DMSO was stirred at room temperature 5-7 hours. Few drops of water were added in the reaction mixture. The solid precipitated was filtered, washed with water, and dried.

IR (KBr) (cm$^{-1}$): 3355, 3214, 2973, 1693, 1648, 1554, 1368, 1266, 1116. $^1$H NMR (CDCl$_3$): $\delta$ 1.39 (9H, s); 1.70-1.76 (2H, m); 2.26-2.32 (IH, m); 3.28-3.40 (2H, m); 3.53 (2H, d, $J = 11.2$ Hz); 6.85 (IH, m); 7.56-7.65 (IH, m); 7.76 (IH, d, $J = 7.2$ Hz); 7.84-7.90 (IH, s); 8.20-8.27 (IH, m); 8.53 (IH, $d, J = 4.8$ Hz); 8.61 (IH, s); 9.27 (IH, s).
Step 2: N-3-azabicyclo[3.1.0]hex-6-yl-N′-isoquinolin-5-ylurea

To a solution of tert-butyl 6-{[(isoquinolin-5-ylamino)carbonyl]amino}-3-azabicyclo[3.1.0]hexane-3-carboxylate (1.0 mmol) in tetrahydrofuran was added p-toluene sulphonic acid solution (3.0 mmol) at room temperature. Reaction mixture was stirred at same temperature for 6-7 hours. Excess solvent was evaporated under vacuum. The residue was treated with aq. NaOH solution to obtain the desired compound as a white solid.

$^1$H NMR (CDCl$_3$): 1.50-1.57 (2H, m); 2.26-2.32 (IH, m); 3.15 (2H, d, $J = 9.3$ Hz); 3.70 (2H, d, $J = 10.2$ Hz); 7.57 (IH, d, $J = 7.2$ Hz); 7.68 (IH, d, $J = 7.2$ Hz); 7.96 (IH, s); 8.22-8.34 (3H, m); 8.44-8.50 (IH, m); 9.22 (IH, s); 9.62 (IH, s). IR (KBr) (cm$^{-1}$): 3434, 1640, 1545, 1429, 1406, 645. MS (M+1): 267.26

Intermediate 7: Preparation of lot, 5α, 6α,6α-amino-3-(3-chloropyrid-2-yl)-3-azabicyclo[3.1.0]hexane

The compound 2,3-dichloro pyridine (720 mg, 4.98 mmol) was added to a solution of intermediate 1 (400 mg, 4.08 mmol) and triethylamine (2.0 mL) in dimethyl sulfoxide (5.0 mL) and stirred at 85-90°C for 15-16 hrs. The reaction mixture was cooled to room temperature, diluted with water (100 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water and dried over anhydrous sodium sulfate, the residue obtained after removal of solvent was purified through silica gel column using 10% methanol in chloroform as an eluent to produce 200 mg of product as brown oil. $^1$H-NMR (300 MHz, DMSO-d$_6$): $\delta$ 1.60 (s, 2H), 1.67 (bs, 2H), 2.62 (s, IH), 3.56-3.69 (m, 2H), 4.07-4.20 (m, 2H), 6.59(m, IH), 7.46 (m, IH), 8.05 (m, IH).

Intermediate 8: Preparation of 1α, 5α, 6α-[6-amino-3-(5-trifluoromethyl pyrid-2-yl)]-3-azabicyclo [3.1.0]hexane

The compound 2-chloro-5-trifluoromethyl pyridine (1.2 g, 6.63 mmol) was added to a solution of intermediate 1 (500 mg, 5.1 mmol) and triethylamine (2.0 mL) in dimethyl sulfoxide (5.0 mL) and stirred at room temperature for 15-16 hrs. The Reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water and dried over anhydrous sodium sulfate, the residue obtained after removal of solvent was purified through silica gel column using 10% methanol in chloroform as an eluent to produce 300 mg of product as brown oil. $^1$H-NMR (300 MHz, DMSO-d$_6$): $\delta$ 1.73 (brs, 3H),
2.17 (s, IH), 3.52 (d, 2H, J = 10.2 Hz), 3.70 (d, 2H, J = 10.2 Hz), 6.31 (d, IH, J = 9.3 Hz), 7.58 (d, IH, J = 8.7 Hz), 8.35 (s, IH).

Intermediate 9: Preparation of 1α, 5α, 6α-[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) was added 2-chloro-3-trifluoromethyl pyridine (1.44 g, 6.95 mmol) and stirred at room temperature for 15-16 hrs. Reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water and dried over anhydrous sodium sulfate, the residue obtained after removal of solvent was purified through silica gel column using 10% methanol in chloroform as an eluent to get 300 mg of product as brown oil. 

\[ \text{^1H-NMR (300 MHz, DMSO): } \delta 1.73 \text{ (brs, 3H), 2.17 (s, IH), 3.52 (d, 2H, } J = 10.2 \text{ Hz), 3.70 (d, 2H, } J = 10.2 \text{ Hz), 7.12 (d, IH, } J = 9.3 \text{ Hz), 7.60 (d, IH, } J = 8.7 \text{ Hz), 8.24 (s, IH).} \]

Intermediate 10: Preparation of 1α, 5α, 6α-[6-amino-3-(3-chloro-5-trifluoromethyl pyrid-2-yl)]-3-azabicyclo [3.1.0] hexane

A solution of intermediate 1 (400 mg, 4.08 mmol) and triethylamine (2.0 mL) in dimethyl sulfoxide (5.0 mL) was added 2,3-dichloro-5-trifluoromethyl pyridine (1.40 g, 6.52 mmol) and stirred at room temperature for 15-16 hrs. Reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water and dried over anhydrous sodium sulfate, the residue obtained after removal of solvent was purified through silica gel column using 10% methanol in chloroform as an eluent to get 300 mg of product as brown oil.

\[ \text{^1H-NMR (300 MHz, DMSO): } \delta 1.73 \text{ (brs, 3H), 2.17 (s, IH), 3.52 (d, 2H, } J = 10.2 \text{ Hz), 3.70 (d, 2H, } J = 10.2 \text{ Hz), 7.60 (m, IH), 8.22 (d, IH, } J = 7.2). \]

Intermediate 11: Preparation of 1α, 5α, 6α-[6-amino-3-(3-nitro pyrid-2-yl)]-3-azabicyclo [3.1.0] hexane

A solution of intermediate 1 (400 mg, 4.08 mmol) and triethylamine (2.0 mL) in dimethyl sulfoxide (5.0 mL) was added 2-chloro-3-nitro pyridine (1.05 g, 6.52 mmol) and stirred at room temperature for 15-16 hrs. Reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water and dried over anhydrous sodium sulfate, the residue obtained after removal of solvent was
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, IH), 3.52 (d, 2H, J = 10.2 Hz), 3.70 (d, 2H, J = 10.2 Hz), 7.32 (d, IH, J = 9.3 Hz), 7.60 (d, IH, J = 8.7 Hz), 8.28 (s, IH).

Intermediate 12: Preparation of 1α, 5α, 6α-[6-(tert-butylxycarbamoyl)-3-azabicyclo[3.1.0]hex-6-yl]carbamate

To a well stirred solution of intermediate 1 (400 mg, 4.08 mmol) and triethylamine (0.4 mL) in methanol (5.0 mL) was slowly added a solution of di-t-butyl carbonate (1.33 g, 6.12 mmol) at 0-5°C and stirred at room temperature 15-16 hrs. Reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water and dried over anhydrous sodium sulfate, the residue obtained after removal of solvent was purified through silica gel column using 2% methanol in chloroform as an eluent to get 200 mg of product as yellow oil. H-NMR (300 MHz, DMSO-d6): δ 1.42 (s, 9H), 1.48 (s, 2H), 2.10 (s, IH), 3.33 (m, 2H), 3.48 (m, 2H).

Example 1: Preparation of 1α, 5α, 6α-[6-(isoquinolylaminocarboxamido)-3-(3-acetyl amino)pyridin-2-yl]-3-azabicyclo [3.1.0]hex-6-ylcarbamate

Step 1: Preparation of 3-(acetyl amino) pyridin-2-yl]-3-azabicyclo [3.1.0] hex-6-ylcarbamate

To cold solution of Tert-butyl 3-(3-aminopyridin-2-yl)-3-azabicyclo [3.1.0] hex-6-ylcarbamate (1 mmole) and triethyl amine (2.mmoles) in dichloromethane (DCM), slowly acetic anhydride (1.1 mmoles) was add under stirring. Reaction was monitor at room temperature for 3-4 hrs. Dilute the reaction with cold water and organic layer was separated and desired compound was obtained by column chromatographic purification.

3H NMR (DMSO-d6): δ 1.38 (9H, s); 1.66 (2H, s); 2.02 (3H, s); 2.27 (IH, m); 3.43 (3H, m) 3.76 (2H, d); 6.68 (IH, m) 7.08 (IH, s); 7.33 (IH, d); 7.96 (IH, d); 9.35 (IH, s)

MS (M+H): 333.27

Step 2: Preparation of 1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(3-acetyl amino)pyridin-2-yl]-3-azabicyclo [3.1.0]hexane

To a stirred solution of N-[2-(6-amino-3-azabicyclo[3.1.0]hex-3-yl) pyridin-3-yl]-2, 2, 2-acetamide (1.0 mmol) and Triethylamine (1.5 mmoles) in dimethylsulfoxide (DMSO), was added a solution of phenyl isoquinolin-5-ylcarbamate (1.0 mmol) in DMSO at room temperature.
under stirring. Reaction mixture was then stirred at room temperature for 2-5 hrs. Reaction mixture was poured into cold water. The solid separated was filtered and dried to afford crude product. Purification through column chromatography gave pure product.

\[
{^1}H \text{ NMR (DMSO-} d_6): \delta 51.80 (2H, s); 2.04 (3H, s); 3.46 (2H, d); 3.88 (2H, d); 6.99 (IH, m) 6.83 (IH, m); 7.36 (IH, dd); 7.61 (IH, m); 7.75 (IH, dd); 7.89 (IH, d); 7.99 (IH, d) 8.24 (IH, dd); 8.54 (IH, m); 9.27 (1H, s); 9.39 (1H, s); IR (KBr) (cm\(^{-1}\)): 3271, 1638, 1533, 1451, 1242.758; MS (M\(^{+}\)): 403.25.
\]

Example 2: lot. 50\(\%\) 60\(\%\)-6-(5-isoquinolylaminocarboxamido)-3-(3-(trifluoroacetyl amino)pyrid-2-yl)-3-azabicyclo[3.1.0]hexane (Compound No. 2)

Step 1: Preparation of Tert-butyl 3-[3-(trifluoroacetyl amino) pyridin-2-yl]-3-azabicyclo [3.1.0] hex-6-ylcarbamate

To cold solution of Tert-butyl 3-(3-aminopyridin-2-yl)-3-azabicyclo [3.1.0] hex-6-ylcarbamate (1 mmole) and Triethyl amine (2 mmoles) in DCM was added slowly trifluoro acetic Anhydride (1.1 mmoles) under stirring. Reaction was stirred at room temperature for 3-4 hrs. Dilute the reaction with cold water and extract it with ethyl acetate. Organic layers were separated and desired compound was obtained by column chromatographic purification.

\[
{^1}H \text{ NMR (DMSO-} d_6): \delta 1.38 (9H, s); 1.70 (2H, s); 2.17 (IH, s); 3.16 (IH, s); 3.45 (2H, d) 3.75 (2H, d); 6.73 (IH, m,) 7.101 (IH, s) 7.43 (IH, d), 8.09 (IH d); 11.06 (IH, s). \text{ IR (KBr) (cm}^{-1}\text{)): 3273, 1671, 1509, 1332, 1287, 1113, 823; MS (M\(^{+}\)1): 387.19
\]

Step 2: Preparation of Ia, 5a, 6a-[6-(5-isoquinolylaminocarboxamido)-3-(3-(trifluoroacetyl amino) pyridin-2-yl)]-3-azabicyclo [3.1.0] hexane

To a stirred solution of 7V-[2-(6-amino-3-azabicyclo [3.1.0] hex-3-yl) pyridin-3-yl]-2, 2, 2-trifluoroacetamide (1 mmole) and triethylamine (1.5 mmoles) in DMSO, Add a solution of phenyl isoquinolin-5-ylcarbamate (1 mmole) in DMSO at room temperature under stirring. Reaction was monitored for 2-5 hrs at room temperature. Add reaction mass on cold water to offered desired product fit it and purify by Column chromatography.

\[
{^1}H \text{ NMR (DMSO-} d_6): \delta 51.85 (2H, s); 2.04 (3H, s); 3.51 (2H, d); 3.86 (2H, d); 6.47 (IH, m) 6.84 (IH, s); 7.44 (IH, dd); 7.59 (IH, t); 7.74 (IH, d); 7.86 (IH, d); 8.10 (IH, d); 8.24 (IH, dd); 8.52 (IH, d); 8.61 (IH, s); 9.27 (IH, s); 11.09 (IH, m); \text{ IR (KBr) (cm}^{-1}\text{)): 3374, 1638, 1717, 1594, 1550, 1459, 1225, 1157.757; MS (M\(^{+}\)1): 457.31.
\]

Example 3: Preparation of 1\(\alpha\), 5\(\alpha\), 6\(\alpha\)-[6-(5-isoquinolylaminocarboxamido)-3-(3-(methanesulphonylamo) pyridn-2-yl)]-3-azabicyclo [3.1.0] hexane (Compound No. 3)
Step 1: Preparation of Tert-butyl 3-{3-{(methanesulphonyl) amino} pyridin-2-yl}-3-azabicyclo [3.1.0] hex-6-ylcarbamate

To cold solution of tert-butyl 3-(3-aminopyridin-2-yl)-3-azabicyclo [3.1.0] hex-6-ylcarbamate (1.0 mmol) and Triethyl amine (2.mmoles) in DCM was added slowly methane sulphonyl chloride (1.1 mmol) under stirring. Reaction was stirred at room temperature for 3-4 hrs. Dilute the reaction with cold water and extract it with ethyl acetate. Organic layers were separated and desired compound was obtained by column chromatographic purification.

^1H NMR (DMSO- d6): δ 1.38 (9H, s); 1.70 (2H, s); 1.90 (1H, d); 2.17 (IH, s); 3.16 (IH, s); 3.12 (3H, s); 3.45 (2H, d) 3.75 (2H, d); 6.73 (IH, m,) 7.10 (IH, s,) 7.43 (IH, d); 8.09 (IH, d); 11.06 (IH, s); IR (KBr) (cm⁻¹): 3289, 1668, 1561, 1345, 1293, 1119, 823; MS (M+?): 369.24.

Step 2: Preparation of 1a, 5a, 6a-[6-(5-isoquinolylaminocarboxamido)-3-(3-(methanesulphonyl) amino) pyrid -2-yll]-3-azabicyclo [3.1.0]hexane

To a stirred solution of tert-butyl 3-{3-(methanesulphonyl) amino} pyridin-2-yl]-3-azabicyclo [3.1.0] hex-6-ylcarbamate (1.mmole) and Triethylamine (1.5 mmoles) in DMSO, Add a solution of phenyl isoquinolin-5-ylcarbamate (1.mmole) in DMSO at room temperature under stirring. Reaction was monitored for 2-5 hrs at room temperature. Add reaction mass on cold water to offered desired product fitter it and purify by Column chromatography.

^1H NMR (DMSO- d6): δ 1.89 (2H, s); 2.54 (IH, s); 2.64 (IH, s); 3.38 (3H, s); 3.58 (IH, d); 4.00 (IH, d); 5.75 (IH, s); 6.77 (IH, m); 6.85 (IH, s); 7.70 (3H, dd); 7.90 (IH, m); 8.23 (2H, m); 8.53 (IH, m); 8.62 (IH, s); 9.27 (IH, s); IR (KBr) (cm⁻¹): 3403, 1650, 1555, 1461, 1364, 1159,762; MS (M+?): 439.25.

Example 4: Preparation of 1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(3-(3,5-dichloro) pyrid -2-yll]-3-azabicyclo [3.1.0]hexane (Compound No. 4)

Step 1: Preparation of 3-(3, 5-dichloropyridin-2-yl)-3-azabicyclo [3.1.0]hexan-6-amine

The compound 2,3,5-trichloro pyridine (740 mg, 4.98 mmol) was added to a solution of 1α, 5α, 6α-6-amino-3-azabicyclo [3.1.0] hexane hydrochloride (400 mg, 4.08 mmol) and triethylamine (2.0 mL) in dimethyl sulfoxide (5.0 mL) and stirred at 85-90°C for 15-16 hrs. The reaction mixture was cooled to room temperature, diluted with water (100 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water and dried over anhydrous sodium sulfate; the residue obtained after removal of solvent was purified through silica gel column using 10% methanol in chloroform as an eluent to produce 200 mg of product as brown oil.
1H NMR (DMSO- $d_6$): δ 1.56 (2H, s); 1.18 (IH, s); 1.19 (IH, s); 3.86 (2H, bs, D$_2$O Exchangeable); 3.46 (3H, m); 6.78 (IH, s); 8.13 (IH, s); IR (KBr) (cm$^{-1}$): 3281, 1631, 1562, 131 1. 1299, 1102, 826; MS (M$^+$+): 243.03.

Step 2: Preparation of Ia, 5a, 6a-{6-(5-isoquinolylaminocarboxamido)-3-(3-(3-bromo) pyrid-2-yl)}-3-azabicyclo[3.1.0]hexane

A solution of 1α, 5α, 6α-[6-amino-3-(3,5-dichloropyrid-2-yl)-3-azabicyclo[3.1.0]hexane (100 mg, 0.40 mmol), phenyl isoquinolin-5-ylcarbamate (127 mg, 0.516 mmol) in dimethyl sulfoxide (5.0 mL) was stirred at room temperature for 12-13 hrs. The reaction mixture was diluted with water (50 mL), extracted with ethyl acetate (3 x 25mL). The combined organic layers were washed with water and dried over anhydrous sodium sulfate. The residue obtained after removal of solvent was purified through silica gel column 2.0 % methanol in chloroform as an eluent to get 50 mg of product as off white solid.

1H NMR (DMSO- $d_6$): δ 1.18 (2H, s); 2.55 (IH, m); 3.60 (2H, d); 4.10 (2H, d); 6.86 (IH, s); 7.60 (IH, m); 7.75 (IH, d); 7.87 (2H, dd) 8.15 (IH, d); 8.23 (IH, dd); 8.53 (IH, d); 8.60 (IH, s); 9.27 (IH, s); IR (KBr) (cm$^{-1}$): 3271, 1638, 1533, 1451, 1242,758; MS (M$^+$+): 418.32.

Example 5: Preparation of 1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(3-(3-bromo) pyrid-2-yl)]-3-azabicyclo [3.1.0]hexane (Compound No. 5)

Step 1: Preparation of 3-(3-bromopyridin-2-yl)-3-azabicyclo[3.1.0]hexan-6-amine

The compound 3-bromo-2-chloro pyridine (783 mg, 4.98 mmol) was added to a solution of 1α, 5α, 6α-3-amino-3-azabicyclo [3.1.0]hexane hydrochloride (400 mg, 4.08 mmol) and triethylamine (2.0 mL) in DMSO (5.0 mL) and stirred at 85-90°C for 15-16 hrs. The reaction mixture was cooled to room temperature, diluted with water (100 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water and dried over anhydrous sodium sulfate; the residue obtained after removal of solvent was purified through silica gel column using 10% methanol in chloroform as an eluent to produce 200 mg of product as brown oil.

1H NMR (DMSO- $d_6$): δ 1.56 (2H, s); 1.18 (IH, s); 1.19 (IH, s); 3.47 (2H, brs); 3.46 (3H, m); 6.54 (IH, m); 6.67 (IH, d); 8.00 (IH, d); IR (KBr) (cm$^{-1}$): 3265, 1601 1538, 1459, 1246,756; MS (M$^+$+): 255.28.

Step 2: Preparation of Ia, 5a, 6a-[6-(5-isoquinolylaminocarboxamido)-3-(3-(3-bromo) pyrid -2-y1)]-3-azabicyclo [3.1.0]hexane
A solution of 1a, 5a, 6a-[6-amino-3-(3-bromo pyrid-2-yl)]-3-azabicyclo[3.1.0] hexane (100 mg, 0.40 mmol), phenyl isoquinolin-5-ylcarbamate (127 mg, 0.51 16 mmol) in dimethyl sulfoxide (5.0 mL) was stirred at room temperature for 12-13 hrs. The reaction mixture was diluted with water (50 mL), extracted with ethyl acetate (3 x 25mL). The combined organic layers were washed with water and dried over anhydrous sodium sulfate. The residue obtained after removal of solvent was purified through silica gel column 2.0 % methanol in chloroform as an eluent to get 50 mg of product as off white solid.

1H NMR (DMSO- d$_6$): δ 1.82 (2H, s); 2.55 (IH, m); 3.54 (2H, d); 4.14 (2H, d); 6.72 (IH, m); 7.84 (IH, s); 7.60 (IH, t); 7.74 (IH, d); 7.87 (2H, dd); 8.15 (IH, d); 8.22 (IH, d); 8.53 (IH, d); 8.60 (IH, s), 9.27 (IH, s); IR (KBr) (cm$^{-1}$): 3271, 1638, 1533, 1451, 1242,758; MS (M$^+$+l): 425.40.

Example 6: Preparation of 1a, 5a, 6a-[6-(5-isoquinoxyaminocarboxamido)-3-(3-(5-nitro pyrid -2-yl)]-3-azabicyclo [3.1.0]hexane (Compound No. 6)

Step 1: Preparation of 3-(5-Nitropyridin-2-yl)-3-azabicyclo [3.1.0] hexan-6-amine

A solution of 1a, 5a, 6a-6-amino-3-azabicyclo [3.1.0] hexane hydrochloride (400 mg, 4.08 mmol) and triethylamine (2.0 mL) in dimethyl sulfoxide (5.0 mL) was added 2-chloro-5-nitro pyridine (1.05 g, 6.52 mmol) and stirred at room temperature for 15-16 hrs. Reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water and dried over anhydrous sodium sulfate, the residue obtained after removal of solvent was purified through silica gel column using 10% methanol in chloroform as an eluent to get 300 mg of product as brown oil.

1H NMR (DMSO- d$_6$): δ 1.56 (2H, s); 1.18 (IH, s); 1.19 (IH, s); 3.47 (2H, brs); 3.46 (3H, m); 6.54 (IH, m); 6.67 (IH, d); 8.00 (IH, d); IR (KBr) (cm$^{-1}$): 3289, 1638, 1568, 1345, 1299, 1109, 823; MS (M$^+$+l): 221.32.

Step 2: Preparation of 1a, 5a, 6a-[6-(5-isoquinoxyaminocarboxamido)-3-(3-(5-nitro pyrid -2-yl)]-3-azabicyclo [3.1.0]hexane

A solution of 1a, 5a, 6a-[6-amino-3-(5-nitro pyrid-2-yl)]-3-azabicyclo [3.1.0] hexane (100 mg, 0.40 mmol), phenyl isoquinolin-5-ylcarbamate (127 mg, 0.51 16 mmol) in dimethyl sulfoxide (5.0 mL) was stirred at room temperature for 12-13 hrs. The reaction mixture was diluted with water (50 mL), extracted with ethyl acetate (3 x 25mL). The combined organic layers were washed with water and dried over anhydrous sodium sulfate. The residue obtained
after removal of solvent was purified through silica gel column 2.0 % methanol in chloroform as an eluent to get 50 mg of product as light yellow solid.

\({}^1\text{H NMR (DMSO-}d_6\text{)}: \delta 1.99 (2H, s), 2.41 (IH, m), 3.69 (2H, d); 3.99 (2H, d); 5.09 (IH, d); 6.62 (IH, d); 6.92 (IH, s), 7.01 (IH, t); 7.77 (IH, d) 8.22 (2H, d); 8.54 (IH, d); 8.98 (IH, s) 8.60 (IH, s), 9.27 (IH, s); IR (KBr) (cm\(^{-1}\)): 3294, 1633, 1572, 1327, 1293, 1117, 820.

**M.S (M\({}^+\))**: 391.2

**Example 7**: Preparation of \(5\alpha,6\alpha\alpha\)-r-5-(isoquinolylaminocarboxamido)-3-(2-fluorophenyl)-3-azabicyclo[3.1.0]hexane (Compound No. 7)

**Step 1: Preparation of 1-(2-fluorophenyl)-2,5-dihydro-lH-pyrrole**

To a solution of \((2Z)\)-but-2-ene-1,4-diyl dimethanesulfonyl (2.44 g, 10 mmol) in 50 ml of anhydrous dichloromethane at room temperature under nitrogen, 2-fluoro aniline (30.0 mmol) was added drop wise. The resulting solution was stirred overnight and then extracted with 50 ml of water. The organic layer was separated and dried with sodium sulfate. After removal of solvent, the residue was 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\(^{-1}\); \({}^1\text{H NMR (300 MHz, CDCl}_{3}\text{)}: \delta 4.10(s, 2H), 5.98(s, 2H), 7.01-7.05 (m, 2H), 7.32-7.42(m, 2H).

**Step 2: Preparation of 1a, 5a, 6a-N,N-dibenzyl-3-(2-fluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine**

A mixture of 1-(2-fluorophenyl)-2,5-dihydro-l H-pyrrole (10.0 mmole) and titanium tetrapropoxide (10.0 mmol) in \(\text{THF}\) (5.0 ml) was treated with methylmagnesium chloride (3 M in \(\text{THF}\), 10.0 mmol), then a solution of N,N-dibenzyl formamide (10 mmol) in \(\text{THF}\) was added in one portion. Cyclohexyl magnesium bromide (2.0 mmol, 2 M in diethyl ether) was added at ambient temperature over 50 min and reaction mixture was heated under reflux for 15 min. the reaction mixture was diluted with 20 ml of \(\text{THF}\), 5 ml of brine solution was added. Precipitated inorganic salt was filtered. Organic layer was dried over sodium sulphate and concentrated. After removal of solvent, the residue was 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\(^{-1}\); \({}^1\text{H-NMR (300 MHz, DMSO-}d_6\text{)}: \delta 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 3: Preparation of 1a, 5a, 6a-tert-butyl \([3-(2-fluorophenyl)-3-azabicyclo[3.1.0]hexan-6-yl] carbamate**
A suspension of $1\alpha$, $5\alpha$, $6a$-$N,N$-dibenzyl-3-(2-fluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine in methanol (20ml) and 10% Pd/C (50% WAV) was hydrogenated in a parr hydrogenation apparatus for 2-12 hrs at room temperature. Progress of reaction was monitored by TLC. Reaction mixture was filtered through celite bed. To the filtrate BoC$_2$O (20 mmol) was added and stirred at room temperature for 2 hrs. Reaction mixture was 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$^{-1}$; $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 1.45 (s, 9H), 1.76(s, 2 H), 2.58(s, IH), 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 4: Preparation of 1a, 5a, 6a-[6-(5-isoquinolylaminocarboxamido)-3-(2-fluorophenyl)]-3-azabicyclo[3.1.0]hexane**

To a solution of 1a, 5a, 6a-tert-butyl [3-(2-fluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]carbamate (10 mmole) dissolved in ethyl acetate was added saturated solution of HCl/ ethyl acetate and stirred for 2-3 hours. The residue obtained after removal of solvent was taken in dimethyl sulfoxide and TEA (20 mmol) was added followed by addition of 5-amino isoquinolone phenyl carbamate (10mmole). Reaction mixture was then stirred at room temperature for 2-3 hrs. Reaction mixture was poured on ice cold water. Solid precipitate out was filtered and leached in methanol to get pure product.

IR (KBr) 3300, 3127, 2894, 2850, 1631, 1597, 1531, 1477, 1371, 1336, 1270, 1161, 1114, 1071, 1027, 906, 815 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$1.84 (s, 2H), 2.60 (s, IH), 3.37 (d, 2H, $J = 9.0$ Hz), 3.72 (d, 2H, $J = 9.0$ Hz), 6.73 (d, 2H, $J = 8.1$ Hz), 6.86 (s, IH), 7.02 (m, 2H), 7.60 (t, IH), 7.75 (d, IH), 7.90(d, IH), 8.23 (d, IH), 8.53 (d, IH), 8.61(s, IH), 9.27 (S, IH); m.p. is 225-227 °C.

**Example 8: Preparation of 1a, 5a, 6a-[6-(5-isoquinolylaminocarboxamido)-3-(4-fluorophenyl)]-3-azabicyclo[3.1.0]hexane (Compound No. 8)**

**Step 1: Preparation of 1-(4-fluorophenyl)-2,5-dihydro-IH-pyrrole**

This compound was prepared by the same method as described in step 1 of the example 7 from intermediate 5 and 4-fluoroaniline.

IR (KBr): 3098, 2817, 2807, 1545, 1531, 1470, 1346, 1261, 1161, 1154, 1071, 1017, 915, 806 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): δ4.14(s, 4H), 5.96(s, 2H), 6.51(d, 2H, $J = 8.4$ Hz), 7.45(d, 2H, $J = 8.7$ Hz).
Step 2: Preparation of Ia, 5a, 6a-N,N-dibenzyl-3-(4-fluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine

This compound was prepared by the same method as described in step 2 of the example 7 from 1α, 5α, 6αl-(4-fluorophenyl)-2,5-dihydro-1H-pyrole and N,N-dibenzyl formamide.

-IR (KBr) 3055, 2939, 2914, 1540, 1477, 1453, 1370, 1355, 1270, 1242, 1155, 1120, 1099, 967, 811 cm⁻¹; ¹H NMR (300 MHz, DMSOd₆) δ 1.56(s, 2H), 1.77(s, 2H), 3.05(d, 2H, J = 9.0 Hz), 3.30(d, 2H, J = 9.0 Hz) 3.57(s, 6H), 6.39(m, 2H), 6.89(m, 2H), 7.26-7.31(m, 10H).

Step 3: Preparation of Ia, 5a, 6a-tert-butyl [3-(4-fluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]carbamate

This compound was prepared by the same method as described in step 3 of the example 7 from α',N-dibenzyl-3-(4-fluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine.

IR (KBr) 3300, 3127, 2844, 2831, 1635, 1590, 1529, 1473, 1344, 1333, 1243, 1159, 1114, 1069, 1026, 916, 875 cm⁻¹; ¹H NMR (300 MHz, DMSOδ) δ 1.46 (s, 9H), 2.60(s, 2H), 2.60(s, 2H), 3.25(d, 2H, J = 9.0 Hz), 3.75(d, 2H, J = 9.0 Hz), 6.65(d, 2H, J = 9.0 Hz), 6.95(d, 2H, J = 9.0 Hz).

Step 4: Preparation of Ia, 5a, 6a-[6-(5-isoquinolylaminocarboxamido)-3-(4-fluorophenyl)]-3-azabicyclo[3.1.0]hexane

This compound was prepared by the same method as described in step 4 of the example 7 from 1α, 5α, 6α-tert-butyl [3-(4-fluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]carbamate and phenyl 7V-(isoquinolin-5-yl)carbamate.

IR (KBr) 3378, 3145, 2899, 2850, 1645, 1598, 1535, 1489, 1378, 1334, 1299, 1133, 1134, 1071, 1027, 956, 810 cm⁻¹; ¹H NMR (300 MHz, DMSOδ) 52.50(m, 2H), 3.23(d, 2H, J = 9.0 Hz), 3.76(d, 2H, J = 9.0 Hz), 6.40(d, 2H, J = 8.1 Hz), 6.55(t, 2H), 7.64-7.91(m, 4H), 8.33(s, 1H), 8.53(d, 1H), 9.31(s, 1H); m.p. is 226-228 °C

Example 9: Preparation of 1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(4-isopropylphenyl)]-3-azabicyclo[3.1.0]hexane (Compound No. 9)

Step 1: Preparation of f-I(4-isopropylphenyl)-2,5-dihydro-IH-pyrole

This compound was prepared by the same method as described in step 1 of the example 7 from intermediate 5 and 4-isopropylaniline.

IR (KBr): 3027, 2894, 2850, 1593, 1531, 1477, 1371, 1335, 1269, 1165, 1124, 1075, 1027, 909, 817 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ1.14(s, 6H), 4.00(s, 4H), 6.02(s, 2H), 6.42(d, 2H, J = 8.4 Hz), 7.04(d, 2H, J = 8.7 Hz).
Step 2: Preparation of Ia, 5a, 6a-N,N-dibenzyl-3-(4-isopropylphenyl)-3-azabicyclo[3.1.0]hexan-6-amine

This compound was prepared by the same method as described in step 2 of the example 7 from 1-(4-isopropylphenyl)-2,5-dihydro-1 H-pyrrole and N,N-dibenzylformamide.

-IR (KBr) 3044, 2976, 2914, 1530, 1477, 1450, 1377, 1355, 1249, 1242, 1190, 1120, 1088, 945, 810 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 1.27(s, 6H), 1.20(s, 2H), 1.30(s, 6H), 2.99 (d, 2H, J = 9.0 Hz), 3.34(d, 2H, J = 3.4 Hz), 3.57(s, 4H), 7.26-7.31(m, 10H).

Step 3: Preparation of Ia, 5a, 6a-tert-butyl [3-(4-isopropylphenyl)-3-azabicyclo[3.1.0]hex-6-yl]carbamate

This compound was prepared by the same method as described in step 3 of the example 7 from 1α, 5α, 6α-(N,N-dibenzyl-3-(4-isopropylphenyl)-3-azabicyclo[3.1.0]hexan-6-amine.

IR (KBr) 3332, 3178, 2894, 2855, 1640, 1543, 1531, 1476, 1370, 1339, 1279, 1165, 1114, 1065, 1033, 917, 856 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 1.24 (s, 9H), 1.33(s, 6H), 1.97(s, 2 H), 2.17(s, 1H), 3.13 (d, 2H, J = 9.0 Hz), 3.49 (d, 2H, J = 9.0 Hz), 6.45 (d, 2H, J = 9.0 Hz), 7.15 (m, 2H, J = 9.0 Hz).

Step 4: Preparation of Ia, 5a, 6a-[6-(5-isooquinolylaminocarboxamido)-3-(4-isopropylphenyl)]-3-azabicyclo [3.1.0]hexane

This compound was prepared by the same method as described in step 4 of the example 7 from 1α, 5α, 6α-tert-butyl [3-(4-isopropylphenyl)-3-azabicyclo[3.1.0]hex-6-yl]carbamate and phenyl 7V-(isoquinolin-5-yI)carbamate.

IR (KBr) 3296, 3093, 2956, 2864, 1649, 1568, 1519, 1483, 1360, 1336, 1265, 1248, 1169, 1101, 1027, 966, 827 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 1.13 (d, 6H, J = 7.0 Hz ), 1.86 (m, 2H), 2.73 (s, 1H), 3.16(d, 2H, J = 9.0 Hz), 3.58 (d, 2H, J = 9.0 Hz), 6.49 (d, 2H, J = 9.0 Hz), 6.88 (s, 1H), 7.02 (d, 2H), 7.58 (t, 1H), 7.75 (d, 1H), 7.88(d, 1H), 8.24 (d, 1H), 8.54 (d, 1H), 8.62 (s, 1H), 9.28(s, 1H); m.p. is 236-237 °C

Example 10: Preparation of 1α, 5α, 6α-r6-(5-isooquinolylaminocarboxamido)-3-(2-methoxyphenyl)-3-azabicyclo [3.1.0]hexane (Compound No. 10)

Step 1: Preparation of 1-(2-methoxy phenyl)-2,5-dihydro-1 H-pyrrole

This compound was prepared by the same method as described in step 1 of the example 7 from intermediate 5 and 2-methoxyaniline.

IR (KBr): 3044, 2855, 2847, 1593, 1520, 1475, 1368, 1321, 1270, 1161, 1114, 1071, 1027, 906, 815 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 3.81(d, 3H), 4.26(s, 4H), 5.89(s, 2H), 6.98(m, 2H), 7.25-7.30 (m, 2H).
Step 2: Preparation of Ia, 5a, 6a-N,N-dibenzyl-3-(2-methoxyphenyl)-3-azabicyclo[3.1.0]hexan-6-amine

This compound was prepared by the same method as described in step 2 of the example 7
from l-(2-methoxyphenyl)-2,5-dihydro-l H-pyrrole and N,N-dibenzyl formamide.

IR (KBr) 3027, 2891, 2844, 1597, 1531, 1466, 1370, 1237, 1234, 1154, 1109, 1000, 906, 815 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 1.49(s, 2H), 1.63(s, 1H), 3.32(s, 3H), 2.92(d, 2H, J = 9.0 Hz), 3.28(d, 2H, J = 9.0 Hz), 3.63 (s, 4H), 6.39(d, 2H), 6.73(d, 2H), 7.26-7.38(m, 10H).

Step 3: Preparation of Ia, 5a, 6a-tert-butyl [3-(2-methoxyphenyl)-3-azabicyclo[3.1.0]hex-6-yl]carbamate

This compound was prepared by the same method as described in step 3 of the example 7
from Ia, 5α, 6α-N,N-dibenzyl-3-(2-methoxyphenyl)-3-azabicyclo[3.1.0]hexan-6-amine.

IR (KBr) 3331, 3156, 2878, 2850, 1644, 1578, 1543, 1465, 1323, 1390, 1254, 1198, 1123, 1078, 1032, 909, 878 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 1.38 (s, 9H), 1.70(s, 2 H), 2.20( s, IH), 2.99 (d, 2H, J = 9.0 Hz), 3.67 (d, 2H, J = 9.0 Hz), 3.74 (s, 3H), 6.65 (d, 2H), 6.78 (m, 2H),

Step 4: Preparation of Ia, 5a, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2-methoxyphenyl)]-3-azabicyclo[3.1.0]hexane

This compound was prepared by the same method as described in step 4 of the example 7
from tert-butyl [3-(2-methoxyphenyl)-3-azabicyclo[3.1.0]hex-6-yl]carbamate and phenyl TV-
(isoquinolin-5-yl)carbamate.

IR (KBr) 3354, 3127, 2894, 2850, 1631, 1597, 1531, 1477, 1371, 1336, 1270, 1161, 1114, 1071, 1027, 906, 815 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 1.75 (m, 2H), 2.70 (s, IH), 3.07(d, 2H, J = 9.0 Hz), 3.76(s, 3H), 3.81(d, 2H, J = 9.0 Hz), 6.69-6.88 (m, 4H), 7.60 (t, IH), 7.74 (d, IH), 7.89 (d, IH), 8.25(d,IH), 8.53 (d, IH), 8.60 (s, IH), 9.27(s, IH); m.p. is 189-191 °C

Example 11: Preparation of 1α, 5α, 6α-tert-(5-isoquinolylaminocarboxamido)-3-(4-t-
butylphenyl)]-3-azabicyclo [3.1.0]hexane (Compound No. 11)

Step 1: Preparation of l-(4-t-butylphenyl)-2,5-dihydro-lH-pyrrole

This compound was prepared by the same method as described in step 1 of the example 7
from intermediate 5 and 4-t-butyl aniline.

IR (KBr): 3047, 2945, 2829, 2809, 1500, 1475, 1380, 1362, 1282, 1181, 1042, 1007, 943, 815 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.29(s, 9H), 4.10(s, 4H), 5.93(s, 2H), 6.48(d, 2H J = 9.0 Hz), 29.75 (d, 2H J = 9.0 Hz).
Step 2: Preparation of $\text{Ia, 5a, 6a-N,N-dibenzyl-3-(4-t-butylphenyl)-3-azabicyclo[3.1.0]hexan-6-amine}$

This compound was prepared by the same method as described in step 2 of the example 7 from $1-(4-t$-butylphenyl)-2,5-dihydro-$1H$-pyrrole and N,N-dibenzylformamide.

IR (KBr) 3010, 2947, 2900, 2893, 2876, 1576, 1544, 1480, 1388, 1336, 1289, 1156, 1114, 1074, 1027, 911, 803 cm$^{-1}$; $^1$H-NMR (300 MHz, DMSO-$d_6$) $\delta$ 1.22 (s, 9H), 1.88 (m, 2H), 2.51 (s, IH), 3.17 (d, 2H, $J = 9.0$ Hz), 3.58 (d, 2H, $J = 9.0$ Hz), 3.66 (s, 3H), 6.49 (d, 2H, $J = 9.0$ Hz), 6.89 (s, IH), 7.16 (d, 2H), 7.61 (t, IH), 7.75 (d, IH), 7.89 (d, IH), 8.24 (d, IH), 8.54 (d, IH), 8.62 (s, IH), 9.28 (s, IH); m.p. is 218-220 °C

Step 3: Preparation of $\text{Ia, 5a, 6a-tert-butyl [3-(4-t-butylphenyl)-3-azabicyclo[3.1.0]hex-6-yl]carbamate}$

This compound was prepared by the same method as described in step 3 of the example 1 from N,N-dibenzyl-3-(4-t-butyphenyl)-3-azabicyclo[3.1.0]hexan-6-amine.

IR (KBr) 3331, 3156, 2878, 2850, 1644, 1578, 1543, 1465, 1323, 1390, 1254, 1198, 1123, 1077, 1032, 909, 878 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 1.07 (s, 9H), 1.70 (s, 2H), 2.20 (s, IH), 2.99 (d, 2H, $J = 9.0$ Hz), 3.67 (d, 2H, $J = 9.0$ Hz), 3.74 (s, 3H), 6.65 (d, 2H), 6.78 (m, 2H), 7.71 (m, 10H).

Step 4: Preparation of $\text{Ia, 5a, 6a-[6-(5-isoquinolylaminocarboxamido)-3-(4-t-butylphenyl)]-3-azabicyclo[3.1.0]hexane}$

This compound was prepared by the same method as described in step 4 of the example 1 from l-α, 5α, 6α-tert-butyl [3-(4-t-butylphenyl)-3-azabicyclo[3.1.0]hex-6-yl]carbamate and phenyl N-(isoquinolin-5-yl)carbamate.

IR (KBr) 3314, 3042, 2958, 2828, 1633, 1582, 1520, 1478, 1362, 1268, 1248, 1164, 1030, 966, 813 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 1.22 (s, 9H), 1.88 (m, 2H), 2.51 (s, IH), 3.17 (d, 2H, $J = 9.0$ Hz), 3.58 (d, 2H, $J = 9.0$ Hz), 3.66 (s, 3H), 6.49 (d, 2H, $J = 9.0$ Hz), 6.89 (s, IH), 7.16 (d, 2H), 7.61 (t, IH), 7.75 (d, IH), 7.89 (d, IH), 8.24 (d, IH), 8.54 (d, IH), 8.62 (s, IH), 9.28 (s, IH); m.p. is 218-220 °C

Example 12: Preparation of 1α, 5α, 6α-f6-(5-isoquinolylaminocarboxamido)-3-(2,4-dimethylphenyl]-3-azabicyclo[3.1.0]hexane (Compound No. 12)

Step 1: Preparation of l(2,4-dimethylphenyl)-2,5-dihydro-lH-pyrrole

This compound was prepared by the same method as described in step 1 of the example 7 from intermediate 5 and 2,4-dimethylaniline.

IR (KBr): 3037, 2948, 2920, 1505, 1473, 1403, 1351, 1324, 1234, 1163, 1110, 1015, 941, 807 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.17 (d, 3H), 2.26 (d, 3H), 4.04 (s, 4H), 5.95 (s, 2H), 6.18 (s, IH), 6.86 (m, 3H).
Step 2: Preparation of Ia, 5a, 6a-N,N-dibenzyl-3-[(2,4-dimethyl)phenyl]-3-azabicyclo[3.1.0]hexan-6-amine

This compound was prepared by the same method as described in step 2 of the example 7 from 1-[(2,4-dimethyl)phenyl]-2,5-dihydro-1H-pyrrole and N,N-dibenzylformamide.

IR (KBr) 3055, 2890, 2850, 1589, 1527, 1460, 1344, 1336, 1269, 1154, 1114, 1092, 1000, 905, 815 cm\(^{-1}\); \(^1\)H NMR (300 MHz, DMSO-d\(_6\)) \(\delta\) 1.37(s, 2H), 1.50(s, 9H), 1.37(s, 2H), 1.50(s, 9H), 1.37(s, 2H), 1.50(s, 9H), 1.37(s, 2H), 1.50(s, 9H), 1.37(s, 2H), 1.50(s, 9H), 1.37(s, 2H), 1.50(s, 9H).

Step 3: Preparation of Ia, 5a, 6a-tert-butyl [3-(2,4-dimethylphenyl)-3-azabicyclo[3.1.0]hex-6-yl]carbamate

This compound was prepared by the same method as described in step 3 of the example 7 from N,N-dibenzyl-3-[2-(4-dimethylphenyl)-3-azabicyclo[3.1.0]hexan-6-amine.

IR (KBr) 3356, 3124 2812, 2878, 1645, 1592, 1544, 1470, 1370, 1336, 1290, 1162, 1117, 1078, 1027, 934, 876 cm\(^{-1}\); \(^1\)H-NMR (300 MHz, DMSO-d\(_6\)) \(\delta\) 1.25(s, 1H), 1.37(s, 1H), 1.50(s, 1H), 2.83(d, 2H, \(J = 9.0\) Hz), 3.23(d, 2H, \(J = 9.0\) Hz), 3.64(s, 4H), 6.74(s, 2H).

Step 4: Preparation of Ia, 5a, 6a-[6-(5-isoquinolylaminocarboxamido)-3-(2,4-dimethylphenyl)]-3-azabicyclo [3.1.0]hexane

This compound was prepared by the same method as described in step 4 of the example 7 from 1\(\alpha\), 5\(\alpha\), 6\(\alpha\)-tert-butyl [3-(2,4-dimethylphenyl)-3-azabicyclo[3.1.0]hex-6-yl]carbamate and phenyl 7\(\alpha\)-(isoquinolin-5-yl)carbamate.

IR (KBr) 3332, 3056, 2958, 2816, 1644, 1558, 1502, 1370, 1326, 1265, 1242, 1116, 1017, 861, 821 cm\(^{-1}\); \(^1\)H-NMR (300 MHz, DMSO-d\(_6\)) \(\delta\) 1.72(m, 6R), 2.19(d, 6H), 2.27(s, 1H), 2.50(d, 2H, \(J = 9.0\) Hz), 3.04(d, 2H, \(J = 9.0\) Hz), 6.80-6.92(m, 4H), 7.60(t, 1H), 7.74(d, 1H), 7.90(d, 1H), 8.25(d, 1H), 8.53-8.59(m, 2H), 9.27(s, 1H); m.p. is 190-192 \(^\circ\)C.

Example 13: Preparation of 1\(\alpha\), 5\(\alpha\), 6\(\alpha\)-[6-(5-isoquinolylaminocarboxamido)-3-(4-trifluoromethyl)phenyl]-3-azabicyclo [3.1.0]hexane (Compound No. 13)

Step 1: Preparation of l-[(4-trifluoromethyl)phenyl]-2,5-dihydro-lH-pyrrole

This compound was prepared by the same method as described in step 1 of the example 7 from intermediate 5 and 4-(trifluoromethyl)aniline.

IR (KBr): 3087, 2945, 2998, 1512, 1487, 1498, 1355, 1324, 1234, 1164, 1114, 1015, 941, 805 cm\(^{-1}\); \(^1\)H-NMR (300 MHz, CDCl\(_3\)) \(\delta\) 4.06(s, 4H), 5.99(s, 2H), 6.56(d, 2H, \(J = 9.0\) Hz), 6.76(d, 2H, \(J = 9.0\) Hz).
Step 2: Preparation of Ia, 5a, 6a-N,N-dibenzyl-3-{[4-(trifluoromethyl)phenyl]-3-azabicyclo[3.1.0]hexan-6-amine

This compound was prepared by the same method as described in step 2 of the example 7 from 1-[(4-trifluoromethyl)phenyl]-2,5-dihydro-1//-pyrrole and N,N-dibenzyl formamide.

IR (KBr) 3098, 2834, 2867, 1543, 1556, 1460, 1321, 1311, 1267, 1190, 1114, 1045, 1012, 945, 867 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 1.42(s, 2H), 1.52(s, 1H), 2.81(d, 2H, J = 9.0 Hz), 3.18(d, 2H, J = 9.0 Hz), 3.63(s, 4H), 6.76(m, 2H), 6.91(m, 2H), 7.33-7.39(m, 10H).

Step 3: Preparation of Ia, 5a, 6a-tert-butyl [3-(4-trifluoromethyl)phenyl]-3-azabicyclo[3.1.0]hexane-6-yl]carbamate

This compound was prepared by the same method as described in step 3 of the example 7 from N,N-dibenzyl-3-[(4-trifluoromethyl)phenyl]-3-azabicyclo[3.1.0]hexan-6-amine.

IR (KBr) 3312, 3178, 2856, 2843, 1676, 1591, 1578, 1423, 1344, 1336, 1255, 1156, 1198, 1034, 1019, 906, 823 cm⁻¹; ¹H-NMR (300 MHz, DMSO-d₆) δ 1.34 (s, 9H), 2.20(s, 2H), 2.50(s, 1H), 3.27 (d, 2H, J = 9.0 Hz), 3.72 (d, 2H, J = 9.0 Hz), 6.68 (d, 2H), 7.43 (d, 2H).

Step 4: Preparation of Ia, 5a, 6a-6-(5-isoquinolylaminocarboxamido)-3-(4-trifluoromethyl)phenyl]-3-azabicyclo[3.1.0]hexane

This compound was prepared by the same method as described in step 4 of the example 7 from 1α, 5α, 6a-tert-butyl [3-(4-trifluoromethyl)phenyl]-3-azabicyclo[3.1.0]hexan-6-yl]carbamate and phenyl N-(isoquinololin-5-yl)carbamate.

IR (KBr) 3356, 3078, 2989, 2834, 1678, 1545, 1502, 1378, 1321, 1267, 1244, 1118, 1055, 885, 809 cm⁻¹; ¹H-NMR (300 MHz, DMSO-d₆) δ 1.95 (m, 2H), 2.27 (s, 1H), 2.50(d, 2H, J = 9.0 Hz), 3.63 (d, 2H, J = 9.0 Hz), 6.65 (d, 2H J = 9.0 Hz), 6.90 (s,1H), 7.44 (d, 1H J = 9.0 Hz), 7.60 (t, 1H), 7.75 (d, 1H J = 9.0 Hz), 7.88 (d, 1H J = 9.0 Hz), 8.21 (d, 1H J = 9.0 Hz), 8.53 (d, 1H J = 9.0 Hz), 8.62(s, 1H), 9.27 (s, 1H). m.p. is 247-249 ⁰C

Example 14: Preparation of 1α, 5α, 6α-6-(5-isoquinolylaminocarboxamido)-3-[(4-methoxy)phenyl]-3-azabicyclo[3.1.0]hexane (Compound No. 14)

Step 1: Preparation of l-(4-methoxyphenyl)-2,5-dihydro-lH-pyrrole

This compound was prepared by the same method as described in step 1 of the example 7 from intermediate 5 and 4-methoxyaniline.

IR (KBr): 3043, 2942, 2919, 1500, 1474, 1413, 1344, 1328, 1232, 1160, 1111, 1012, 945, 807 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 3.36(s, 3H), 4.06(s, 4H), 5.97(s, 2H), 6.22(d, 2H), 7.12(d, 2H).
**Step 2: Preparation of Ia, 5a, 6a-N,N-dibenzyl-3-(4-methoxyphenyl)-3-azabicyclo[3.1.0]hexan-6-amine**

This compound was prepared by the same method as described in step 2 of the example 7 from 1-(4-methoxy)phenyl-2,5-dihydro-1-\(H\)-pyrrole and N,N-dibenzylformamide.

IR (KBr) 3043, 2944, 2911, 2841, 2875, 1514, 1483, 1358, 1244, 1161, 1037, 962, 815 cm\(^{-1}\).

\(\text{\(1^H\)NMR (300 MHz, DMSO-\(d_6\))} \delta\) 1.49 (s, 2H), 1.63 (s, 3H), 2.50 (s, 3H), 2.92 (d, 2H, \(J = 9.0\) Hz), 3.28 (d, 2H, \(J = 9.0\) Hz), 3.63 (s, 4H), 6.39 (d, 2H), 6.73 (d, 2H), 7.26-7.38 (m, 10H).

**Step 3: Preparation of Ia, 5a, 6a-tert-butyl [3-(4-methoxyphenyl)-3-azabicyclo[3.1.0]hex-6-yl]carbamate**

This compound was prepared by the same method as described in step 3 of the example 7 from N,N-dibenzyl-3-[[(4-methoxy)phenyl]-3-azabicyclo[3.1.0]hexan-6-amine.

IR (KBr) 3356, 3156, 2878, 2834, 1645, 1567, 1523, 1467, 1334, 1323, 1245, 1189, 1198, 1037, 1056, 934, 867 cm\(^{-1}\); \(\text{\(1^H\)NMR (300 MHz, DMSO-\(d_6\))} \delta\) 1.36 (s, 9H), 2.21 (s, 2H), 2.50 (s, 3H), 2.53 (s, 1H), 3.24 (d, 2H, \(J = 9.0\) Hz), 3.69 (d, 2H, \(J = 9.0\) Hz), 6.75 (d, 2H), 7.75 (d, 2H).

**Step 4: Preparation of Ia, 5a, 6a-[6-(5-isoquinolylaminocarboxamido)-3-(4-methoxy)phenyl]-3-azabicyclo[3.1.0]hexane**

This compound was prepared by the same method as described in step 4 of the example 7 from 1α, 5α, 6α-tert-butyl [3-(4-methoxy)phenyl]-3-azabicyclo[3.1.0]hex-6-yl]carbamate and phenyl N-(isoquinolin-5-yl)carbamate.

IR (KBr) 3329, 3127, 2894, 2850, 1631, 1597, 1531, 1477, 1371, 1336, 1270, 1161, 1114, 1071, 1027, 906, 815 cm\(^{-1}\); \(\text{\(1^H\)NMR (300 MHz, DMSO-\(d_6\))} \delta\) 1.87 (m, 2H), 2.51 (s, 1H), 3.11 (d, 2H, \(J = 9.0\) Hz), 3.57 (d, 2H, \(J = 9.0\) Hz), 3.66 (s, 3H), 6.52 (d, 2H, \(J = 9.0\) Hz), 6.78 (d, 2H, \(J = 9.0\) Hz), 6.86 (s, 1H), 7.58 (t, 1H), 7.75 (d, 1H), 7.89 (d, 1H), 8.23 (d, 1H), 8.53 (d, 1H), 8.60 (s, 1H), 9.28 (s, 1H); m.p. is 226-228 \(^{\circ}\)C

**Example 15: Iα, 5α, 6αr6-(5-isoquinolylaminocarboxamido)-3-(3,4,5-trifluoro)phenyl]-3-azabicyclo[3.1.0]hexane (Compound No. 15)**

**Step 1: Preparation of l-(3,4,5-trifluorophenyl)-2,5-dihydro-\(l\)-\(H\)-pyrrole**

This compound was prepared by the same method as described in step 1 of the example 7 from intermediate 5 and 3,4,5-trifluoroaniline.

IR (KBr) cm\(^{-1}\) 3044, 2989, 2898, 2866, 1658, 1545, 1599, 1434, 1321, 1244, 1265, 1120, 1044, 1078, 995, 827 cm\(^{-1}\); \(\text{\(1^H\)NMR (300 MHz, CDCl}_3)\): 4.27 (s, 4H), 5.88 (s, 2H), 6.77-6.89 (m, 2H).

**Step 2: Preparation of Ia, 5a, 6a-N,N-dibenzyl-3-(3,4,5-trifluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine**
This compound was prepared by the same method as described in step 2 of the example 7 from 1-(3,4,5-trifluorophenyl)-2,5-dihydro-1H-pyrrole and N,N-dibenzyl formamide.

IR (KBr) 3098, 2867, 2855, 1540, 1593, 1421, 1370, 1254, 1121, 1165, 1056, 1034, 986, 878 cm⁻¹; ¹H-NMR (300 MHz, DMSO-d₆) δ 1.45(s, 2H), 1.68(s, 1H), 3.12(d, 2H, J = 9.0 Hz), 3.44(d, 2H, J = 9.0 Hz), 3.63(s, 4H), 6.51(m, 1H), 7.27 (m, 1H), 7.27-7.38(m, 10H).

Step 3: Preparation of 1a, 5a, 6a-tert-butyl-3-(3,4,5-trifluorophenyl)-3-azabicyclo[3.1.0]hexan-6-yl carbamate

This compound was prepared by the same method as described in step 3 of the example 7 from 1α, 5α, 6α-7V, N-dibenzyl-3-(3,4,5-trifluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine.

IR (KBr) 3332, 3126, 2898, 2845, 1677, 1599, 1533, 1456, 1366, 1332, 1256, 1166, 1078, 1021, 9099, 8677 cm⁻¹; ¹H-NMR (300 MHz, DMSO-d₆) δ 3.55(s, 2H), 3.68(s, 2H), 1.69(s, 2H), 2.55(s, 1H), 3.32(d, 2H, J = 9.0 Hz), 3.45(d, 2H, J = 9.0 Hz), 6.95-7.10(m, 2H).

Step 4: Preparation of 1a, 5a, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(3,4,5-trifluorophenyl)-3-azabicyclo[3.1.0]hexane]

This compound was prepared by the same method as described in step 4 of the example 7 from 1α, 5α, 6α-[6-tert-butyl-3-(3,4,5-trifluorophenyl)-3-azabicyclo[3.1.0]hexan-6-yl carbamate and phenyl isoquinolin-5-yl carbamate.

IR (KBr) 3291, 3109, 3055, 2981, 2863, 1650, 1613, 1580, 1517, 1484, 1387, 1254, 1211, 1176, 1111, 1025, 916, 841, 828, 791 cm⁻¹; ¹H-NMR (300 MHz, DMSO-d₆) δ 1.92(s, 2H), 2.42(s, 1H), 3.35(d, 2H, J = 9.0 Hz), 3.55(d, 2H, J = 9.0 Hz), 6.45(m, 2H), 6.89(s, 1H), 7.61(t, 1H), 7.75(d, 1H), 7.90(d, 1H), 8.22(d, 1H), 8.54(d, 1H), 8.62(s, 1H), 9.28(s, 1H); m.p. is 211.3°C

Example 16: Preparation of 1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2-difluoromethoxy)phenyl]-3-azabicyclo[3.1.0]hexane (Compound No. 16)

Step 1: Preparation of 1-(2-difluoromethoxyphenyl)-2,5-dihydro-1H-pyrrole

This compound was prepared by the same method as described in step 1 of the example 7 from intermediate 5 and 2-difluoromethoxyaniline.

IR (KBr) 3039, 2939, 2840, 2847, 1620, 1537, 1522, 1477, 1306, 1352, 1270, 1184, 1035, 1009, 9755, 8253 cm⁻¹; ¹H NMR (3000 MHz, CDCl₃) δ 4.22(s, 4H), 5.89(s, 2H), 6.98(m, 2H), 7.1(s, 1H, J = 7.20 Hz), 7.25-7.30(m, 2H).

Step 2: Preparation of 1a, 5a, 6a-N,N-dibenzyl-3-(2-difluoromethoxyphenyl)-3-azabicyclo[3.1.0]hexan-6-amine

This compound was prepared by the same method as described in step 2 of the example 7 from 1-(2-difluoromethoxy)phenyl-2,5-dihydro-1H-pyrrole and N,N-dibenzyl formamide.
IR (KBr) 3032, 2878, 2887, 1534, 1521, 1489, 1367, 1334, 1232, 1178, 1154, 1067, 965, 817 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 1.44(s, 2H), 1.74(s, 1H), 3.05(d, 2H, J = 9.0 Hz), 6.77(d, 2H), 7.01 (t, IH, J = 9.0 Hz), 7.10(d, 2H), 7.22-7.35(m, 10H).

Step 3: Preparation of 1a, 5a, 6a-tert-butyl [3-(2-difluoromethoxy)phenyl]-3-azabicyclo[3.1.0]hex-6-yl]carbamate

This compound was prepared by the same method as described in step 3 of the example 7 from 1α, 5α, 6α,N,N-dibenzyl-3-(2-difluoromethoxyphenyl)-3-azabicyclo[3.1.0]hexan-6-amine.

IR (KBr) 3330, 3123, 2857, 2845, 1640, 1589, 1525, 1498, 1352, 1367, 1234, 1178, 1049, 1001, 915, 823 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 1.45(s, 2H), 1.74(s, 1H), 3.05(d, 2H, J = 9.0 Hz), 6.77(d, 2H), 7.01(t, IH, J = 9.0 Hz), 7.10(d, 2H), 7.22-7.35(m, 10H).

Step 4: Preparation of 1a, 5a, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2-difluoromethoxy)phenyl]-3-azabicyclo[3.1.0]hexane

This compound was prepared by the same method as described in step 4 of the example 7 from 1α, 5α, 6α-tert-butyl [3-(2-difluoromethoxy)phenyl]-3-azabicyclo[3.1.0]hex-6-yl]carbamate and phenyl 7V-(isoquinolin-5-yl)carbamate.

IR (KBr) 3369, 3270, 1667, 1643, 1578, 1523, 1465, 1423, 1321, 1267, 1221, 1189, 1132, 1078, 967, 823 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 1.82(s, 2H), 2.63(s, IH), 3.27(d, 2H, J = 9.0 Hz), 3.27(d, 2H, J = 9.0 Hz), 6.76-7.25(m, 5H), 7.60(t, IH), 7.74(d, IH), 7.90(d, IH), 8.24(d, IH), 8.53(d, IH), 8.60(s, IH), 9.27(s, IH); m.p. is 170-172 °C.

Example 17: Preparation of 1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(3,4-difluorophenyl)-3-azabicyclo[3.1.0]hexane (Compound No. 17)

Step 1: Preparation of 1-(3,4-difluorophenyl)-2,5-dihydro-l H-pyrrole

This compound was prepared by the same method as described in step 1 of the example 7 from intermediate 5 and 3,4-difluoro aniline.

IR (KBr) 3035, 2949, 2855, 2849, 1607, 1555, 1523, 1470, 1316, 1355, 1279, 1155, 1036, 1019, 9066; δ 2776cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.10(s, 4H), 5.98(s, 2H), 6.80(m, IH), 7.1(s, IH), 7.32(m, IH).

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

This compound was prepared by the same method as described in step 2 of the example 7 from 1-(3,4-difluoro)phenyl-2,5-dihydro-1 H-pyrrole and N,N-dibenzyl formamide.

IR (KBr) 3067, 2887, 2867, 1578, 1516, 1489, 1345, 1336, 1290, 1189, 1156, 1098, 1010, 967, 819 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 1.43(s, 2H), 1.74(s, IH), 3.05(d, 2H, J = 9.0 Hz), 62
3.39(d, 2H, J = 9.0 Hz), 3.63 (s, 4H), 6.66(m, IH), 6.87 (m, IH), 7.07(m, IH), 7.24-7.35(m, 10H).

**Step 3**: Preparation of Ia, 5a, 6a-tert-butyl [3-(3,4-difluoro)phenyl]-3-azabicyclo [3.1.0] hex-6-yl carbamate

This compound was prepared by the same method as described in step 3 of the example 7 from 1α, 5α, 6α-tert-butyl [3-(3,4-difluoro)phenyl]-3-azabicyclo [3.1.0] hex-6-yl carbamate and phenyl isoquinolin-5-yl carbamate.

**Step 4**: Preparation of Ia, 5a, 6a-[6-(5-isoquinolylaminocarboxamido)-3-(3,4-difluoro)phenyl]-3-azabicyclo [3.1.0]hexane

This compound was prepared by the same method as described in step 4 of example 7 from 1α, 5α, 6α-tert-butyl [3-(3,4-difluoro)phenyl]-3-azabicyclo [3.1.0] hex-6-yl carbamate and phenyl isoquinolin-5-yl carbamate.

**Example 18**: Preparation of 1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2-fluoro-5-methylphenyl)]-3-azabicyclo [3.1.0]hexane (Compound No. 18)

**Step 1**: Preparation of I-(2-fluoro-5-methylphenyl)-2,5-dihydro-lH-pyrrole

This compound was prepared by the same method as described in step 1 of the example 7 from intermediate 5 and 2-fluoro-5-methyl aniline.

**Step 2**: Preparation of Ia, 5a, 6a- N,N-dibenzyl-3-(2-fluoro-5-methylphenyl)-3-azabicyclo[3.1.0] hexan-6-amine

This compound was prepared by the same method as described in step 2 of the example 7 from l-(2-fluoro-5-methylphenyl)-2,5-dihydro-l H-pyrrole and N,N-dibenzyl formamide.
IR (KBr) 3055, 2890, 2850, 1589, 1527, 1460, 1344, 1336, 1269, 1 154, 1 114, 1092, 1000, 905, 815 cm⁻¹. ¹H-NMR (300 MHz, DMSO-d₆) δ 1.48(s, 2H), 1.67 (s, IH), 2.50 (s, 3H), 3.22 (d, 2H, J = 9.0 Hz), 3.51(d, 2H, J = 9.0 Hz), 3.64 (s, 4H), 6.82(d, 1H), 7.29-7.35(m, 12H).

Step 3: Preparation of 1a, 5a, 6a-tert-buty 1[3-(2-fluoro-5-methylphenyl)]-3-azabicyclo [3.1.0] hex-6-yl] carbamate

This compound was prepared by the same method as described in step 3 of the example 7 from α, 5α, 6α-N,N-dibenzyl-3-(2-fluoro-5-methylphenyl)-3-azabicyclo[3.1.0] hexan-6-amine.

IR (KBr) 3345, 3167, 2843, 2823, 1665, 1565, 1520, 1414, 1375, 1332, 1254, 1145, 1012, 1098, 912, 856 cm⁻¹. ¹H NMR (300 MHz, DMSO-d₆) δ 1.32(s, 3H), 2.10(s, 2H), 2.68(s, 3H), 2.78 (s, 3H). 7.33 (d, 2H, J = 9.0 Hz), 3.70 (d, 2H, J = 9.0 Hz), 2.25(s, 2H), 3.52(s, 2H), 3.78(s, 2H), 7.83 (m, 2H), 8.33 (s, 1H), 8.51 (d, 1H, J = 9.0 Hz) 9.30 (s, 1H); m.p. is 218-219 °C

Example 19: Preparation of 1α, 5α, 6α-6-(5-isooquinolylaminocarboxamido)-3-(2-fluoro-5-methylphenyl)-3-azabicyclo [3.1.0]hexane

Step 1: Preparation of 1-(3-fluorophenyl)-1H, 5-dihydro-1H-pyrrole

This compound was prepared by the same method as described in step 1 of the example 7 from intermediate 5 and 3-fluoro aniline.

IR (KBr) 3032, 2945, 2858, 2878, 1612, 1573, 1522, 1410, 1314, 1333, 1274, 1208, 1160, 1028, 9612, 9655, 8199 cm⁻¹. ¹H-NMR (300 MHz, CDCl₃): δ 4.26(s, 4H), 6.01 (s, 2H), 6.98(m, 2H), 7.25(s, IH), 7.30(d, IH).

Step 2: Preparation of 1a, 5a, 6a-N,N-dibenzyl-3-(3-fluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine

This compound was prepared by the same method as described in step 2 of the example 7 from 1-(3-fluorophenyl)-2,5-dihydro-1H-pyrrole and N,N-dibenzylformamide.

IR (KBr) 3032, 2945, 2858, 2878, 1612, 1573, 1522, 1410, 1314, 1333, 1274, 1208, 1160, 1028, 9612, 9655, 8199 cm⁻¹. ¹H-NMR (300 MHz, CDCl₃): δ 4.26(s, 4H), 6.01 (s, 2H), 6.98(m, 2H), 7.25(s, IH), 7.30(d, IH).
**Step 3: Preparation of Ia, 5a, 6a-tert-butyl[3-(3-fluoro)phenyl]-3-azabicyclo[3.1.0]hex-6-yl carbamate**

This compound was prepared by the same method as described in step 3 of the example 7 from α, 5α, 6α-N,N-dibenzy1-3-(3-fluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine.

IR (KBr) 3332, 3121, 2843, 2854, 1621, 1565, 1521, 1416, 1356, 1332, 1298, 1178, 1043, 1021, 916, 887 cm⁻¹. ¹H-NMR (300 MHz, DMSO-d₆) δ 1.24(s, 9H), 1.74(s, 2H), 2.22(s, 1H), 3.35(d, 2H, J = 9.0 Hz), 3.65(d, 2H, J = 9.0 Hz), 6.35(d, 2H, J = 9.0 Hz), 6.95(s, 1H), 7.12(m, 1H), 7.42-7.56(m, 2H).

**Step 4: Preparation of Ia, 5a, 6a-[6-(5-isoquinolylaminocarbamido)-3-(3-fluoro)phenyl]-3-azabicyclo[3.1.0]hexane**

This compound was prepared by the same method as described in step 4 of example 7 from 1α, 5α, 6α-tert-butyl[3-(3-fluoro)phenyl]-3-azabicyclo[3.1.0]hex-6-yl carbamate and phenyl isoquinolin-5-yl carbamate.

IR (KBr) 3355, 3039, 2923, 2844, 1679, 1556, 1544, 1513, 1509, 1345, 1278, 1023, 1016, 829 cm⁻¹. ¹H-NMR (300 MHz, DMSO-d₆) δ 2.26(s, 2H), 2.75(s, 1H), 2.95(d, 2H, J = 9.0 Hz), 3.73(d, 2H, J = 9.0 Hz), 6.31(m, 3H), 7.14(m, 1H), 7.28(d, 1H), 7.64(d, 1H), 7.79-7.98(m, 3H), 8.42(s, 1H), 8.54(d, 1H) J = 9.0 Hz) 9.31(s, 1H); m.p. isl26-127 °C

**Example 20: Preparation of 1α, 5α, 6α-[6-(5-isoquinolylaminocarbamido)-3-(3-fluoro)phenyl]-3-azabicyclo[3.1.0]hexane (Compound No. 20)**

**Step 1: Preparation of 1-[2-(cyclopropylmethoxy)phenyl]-2,5-dihydro-1H-pyrrole**

This compound was prepared by the same method as described in step 1 of the example 7 from intermediate 5 and 2-(cyclopropylmethoxy) aniline.

IR (KBr): 3021, 2940, 2845, 2898, 1605, 1521, 1509, 1465, 1332, 1398, 1243, 1209, 1145, 1026, 1011, 969, 813 cm⁻¹. ¹H-NMR (300 MHz, CDCl₃): 6 0.35(d, 2H), 0.51(d, 2H), 1.29(m, 1H), 1.79(s, 2H), 4.17(s, 4H), 5.90(s, 2H), 6.98(m, 2H), 7.25-7.30(m, 2H).

**Step 2: Preparation of Ia, 5a, 6a-N,N-dibenzyl-3-[2-(cyclopropylmethoxy)phenyl]-3-azabicyclo[3.1.0]hexan-6-amine**

This compound was prepared by the same method as described in step 2 of the example 7 from 1-[2-(cyclopropylmethoxy)phenyl]-2,5-dihydro-1H-pyrrole and N,N-dibenzyl formamide.

IR (KBr) 3078, 2899, 2833, 1650, 1578, 1489, 1378, 1344, 1278, 1145, 1113, 1021, 1009, 935, 823 cm⁻¹. ¹H-NMR(300 MHz, DMSO-d₆) δ 0.36(d, 2H), 0.50(d, 2H), 1.28(m, 1H), 1.40(s, 2H), 1.64(s, 1H), 1.81(s, 2H), 3.09(d, 2H, J = 9.0 Hz), 3.40(d, 2H, J = 9.0 Hz), 3.64(s, 4H), 6.49(m, 2H), 6.59(m, 2H), 7.30-7.41(m, 10H).
Step 3: Preparation of Ia, 5a, 6a-tert-butyl-3-[2-(cyclopropylmethoxy)phenyl]-3-azabicyclo[3.1.0]hex-6-yl carbamate

This compound was prepared by the same method as described in step 3 of the example 7 from 1α, 5α, 6α,N,N-dibenzyl-3-[2-(cyclopropylmethoxy)phenyl]-3-azabicyclo[3.1.0]hexane-6-amine

IR (KBr) 3378, 3199, 2832, 2843, 1678, 1589, 1509, 1443, 1387, 1332, 1221, 1167, 1054, 1021, 967, 832 cm⁻¹. ¹H-NMR (300 MHz, DMSO-d₆) δ 0.36(d, 2H), 0.50(d, 2H), 1.24(s, 9H), 1.28(m, 1H), 1.74(s, 2H), 1.91 (s, 2H), 2.26(s, IH), 3.23 (d, 2H, J = 9.0 Hz), 3.45 (d, 2H, J = 9.0 Hz), 7.1 1 (m, 2H), 7.23 (m, 2H).

Step 4: Preparation of Ia, 5a, 6a-[6-(5-isooquinolylaminocarboxamido)-3-(3-fluorophenyl)-3-azabicyclo[3.1.0]hexane

This compound was prepared by the same method as described in step 4 of example 7 from 1α, 5α, 6α-tert-butyl-3-[2-(cyclopropylmethoxy)phenyl]-3-azabicyclo[3.1.0]hex-6-yl carbamate and phenyl isoquinolin-5-yl carbamate.

IR (KBr) 3346, 3046, 2900, 2856, 1639, 1589, 1561, 1514, 1505, 1328, 1231, 1007, 1020, 825 cm⁻¹. ¹H-NMR (300 MHz, DMSO-d₆) δ 1.24(s, 2H), 1.25 (m, IH), 1.77(s, 2H), 2.70 (s, IH), 3.12 (d, 2H, J = 9.0 Hz), 3.77 (d, 2H, J = 9.0 Hz), 3.87(d, 2H, J = 9.0 Hz) 6.66-6.85 (m, 5H), 7.60 (t, IH), 7.74 (d, IH), 7.89 (d, IH), 8.24 (d, IH), 8.53 (d, IH), 8.58 (s, IH), 9.27 (s, IH). m.p. is 152-154 0°C

Example 21: Preparation of 1α, 5α, 6α-[6-(5-isooquinolylaminocarboxamido)-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl carbamate (Compound No. 21)

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

This compound was prepared by the same method as described in step 1 of the example 7 from intermediate 1 and 2,4-difluoro aniline.

IR (KBr): 3028, 2987, 2894, 2856, 1600, 1525, 1548, 1463, 1330, 1394, 1243, 1219, 1156, 1045, 1019, 934, 810 cm⁻¹. ¹H-NMR (300 MHz, CDCl₃): δ 4.17(s, 4H), 5.98(s, 2H), 6.64(m, IH), 6.89(m, IH), 7.1 1(s, IH).

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

This compound was prepared by the same method as described in step 2 of the example 7 from 1-(2,4-difluorophenyl)-2,5-dihydro-1 H-pyrrole and N,N-dibenzyl formamide.

IR (KBr) 3056, 2866, 2832, 1698, 1555, 1478, 1378, 1332, 1256, 1189, 1122, 1067, 101 1, 937, 829 cm⁻¹. ¹H-NMR (300 MHz, DMSO-d₆) δ 1.43(s, 2H), 1.74 (s, IH), 3.04 (d, 2H, J = 9.0 Hz),
3.43(d, 2H, J = 9.0 Hz), 3.63 (s, 4H), 6.67(m, IH), 6.87(m, IH), 7.08(m, IH), 7.26-7.35(m, 10H).

Step 3: Preparation of 1a, 5a, 6a-tert-butyl-3-[2,4-difluorophenyl]-3-azabicyclo[3.1.0]hex-6-yl carbamate

This compound was prepared by the same method as described in step 3 of the example 7 from 1α, 5α, 6α-iso-N-dibenzyl-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine. IR (KBr) 3356, 3132, 2854, 2832 1625, 1521, 1502, 1467, 1343, 1356, 1232, 1167, 1099, 1021, 909, 843 cm⁻¹, ¹H-NMR (300 MHz, DMSO-d₆) δ 1.32(s, 9H), 1.68(s, 2H), 2.42(s, IH), 3.18(d, 2H, J = 9.0 Hz), 3.52 (d, 2H, J = 9.0 Hz), 6.92 (m, IH), 7.24 (s, IH), 7.44 (s, IH).

Step 4: Preparation of 1a, 5a, 6a-[6-(5-isoquinolylaminocarboxamido)-3-(2,4-difluoro)phenyl]-3-azabicyclo[3.1.0]hexane

This compound was prepared by the same method as described in step 4 of example 7 from 1α, 5α, 6α-tert-butyl-3-[2,4-difluorophenyl]-3-azabicyclo[3.1.0]hex-6-yl carbamate and phenyl isoquinolin-5-yl carbamate.

IR (KBr) 3292, 3103, 2978, 2852, 1651, 1579, 1516, 1483, 1459, 1387, 1327, 1360, 1269, 1252, 1135, 1100, 948, 845 cm⁻¹. ¹H-NMR (300 MHz, DMSO-d₆) δ 1.83 (s, 2H), 2.63 (s, IH), 3.22 (d, 2H, J = 9.0 Hz), 3.67 (d, 2H, J = 9.0 Hz), 6.79-6.92 (m, 3H), 7.08 (t, IH), 7.58 (t, IH), 7.74 (d, IH), 7.90 (d, IH), 8.22 (d, IH), 8.53 (d, IH), 8.60 (s, IH), 9.27 (s, IH).

m.p. is 207-209 °C

Example 22: Preparation of 1α, 5α, 6α-tert-butyl-3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl carbamate (Compound No. 22).

Step 1: Preparation of 1-(2,6-difluorophenyl)-2,5-dihydro-1H-pyrrole

This compound was prepared by the same method as described in step 1 of the example 7 from intermediate 5 and 2,6-difluoroaniline.

IR (KBr): 3078, 2970, 2890, 2834, 1615, 1527, 1545, 1460, 1323, 1378, 1223, 1210, 1178, 1044, 1023, 987, 817 cm⁻¹, ¹H-NMR (300 MHz, CDCl₃): δ 4.42(s, 4H), 5.98(s, 2H), 6.93-7.10(m, 3H).

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

This compound was prepared by the same method as described in step 2 of the example 7 from 1-(2,6-difluorophenyl)-2,5-dihydro-1H-pyrrole and N,N-dibenzyl formamide.
IR (KBr) 3012, 3008, 2876, 2850, 1588, 1555, 1498, 1364, 1336, 1243, 1161, 1114, 1071, 1027, 906, 815 cm⁻¹. ¹H-NMR (300 MHz, DMSO-d₆) δ 1.37(s, 2H), 1.79 (s, IH), 3.20-3.34 (m, 8H), 3.62(s, 2H), 3.61 (s, 4H), 6.90-6.95(m, IH), 7.30-7.34 (m, 12H).

Step 3: Preparation of Ia, 5a, 6a-tert-butyl-3-[2,6-difluorophenyl]-3-azabicyclo[3.1.0]hex-6-ylj carbamate

This compound was prepared by the same method as described in step 3 of the example 7 from 1α, 5α, 6α-α,N-dibenzyl-3-(2,6-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine.

IR (KBr) 3334, 3178, 2854, 2832, 1665, 1554, 1521, 1414, 1387, 1343, 1276, 1178, 1098, 1045, 909, 857 cm⁻¹. ¹H NMR (300 MHz, DMSOD-δ) δ1.38(s, 9H), 1.68(s, 2H), 2.50(s, IH), 3.18(d, 2H, J = 9.0 Hz), 3.55 (d, 2H, J = 9.0 Hz), 6.74 (m, IH), 6.90(s, IH), 7.09 (m, IH).

Step 4: Preparation of Ia, 5a, 6a-6-(5-isoquinolylaminocarboxamido)-3-(2,6-difluoro)phenyl]-3-azabicyclo[3.1.0]hexane

This compound was prepared by the same method as described in step 4 of example 7 from 1α, 5α, 6α-tert-butyl-3-[2,6-difluorophenyl]-3-azabicyclo[3.1.0]hexan-6-amine and phenyl isoquinolin-5-yl carbamate.

IR (KBr) 3291, 3106, 3063, 2856, 1645, 1542, 1484, 1470, 1359, 1254, 1158, 1138, 1033, 973, 828 cm⁻¹. ¹H-NMR (300 MHz, DMSO-d₆) δ 1.76 (s, 2H), 2.70 (s, IH), 3.51 (d, 2H, J = 9.0 Hz), 3.60 (d, 2H, J = 9.0 Hz), 6.82-7.00 (m, 4H), 7.60 (t, IH), 7.74 (d, IH), 7.88 (d, IH), 8.24 (d, IH), 8.53 (d, IH), 8.55 (s, IH), 9.27 (s, IH); m.p. is 201-203 °C

Example 23: Preparation of 1α, 5α, 6α-6-(5-isoquinolylaminocarboxamido)-3-(2-fluoro-3-trifluoro methyl) phenyl]-3-azabicyclo r3.1.0]hexane (Compound No. 23)

Step 1: Preparation of 1-(2-fluoro-3-trifluoromethylphenyl)-2,5-dihydro-IH-pyrrole

This compound was prepared by the same method as described in step 1 of the example 7 from intermediate 5 and 2-fluoro-3-(trifluoromethyl) aniline.

IR (KBr): cm⁻¹ 3034, 2974, 2843, 2890, 1610, 1512, 1523, 1445, 1387, 1323, 1290, 1210, 1155, 1078, 1045, 998, 815 cm⁻¹. ¹H-NMR (300 MHz, CDCl₃): δ 4.28(s, 4H), 6.00(s, 2H), 6.93-7.01(m, 3H).

Step 2: Preparation of Ia, 5a, 6a-N,N-dibenzyl-3-(2-fluoro-3-trifluoromethylphenyl)-3-azabicyclo[3.1.0]hexan-6-amine

This compound was prepared by the same method as described in step 2 of the example 7 from 1-(2-fluoro-3-trifluoromethylphenyl)-2,5-dihydro-IH-pyrrole and N,N-dibenzy1formamide.

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IR (KBr) 3076, 2843, 2821, 1576, 1511, 1490, 1356, 1322, 1265, 1143, 1115, 1092, 1056, 905, 844; 1H NMR (300 MHz, DMSO-d$_6$) $\delta$ 1.48(s, 2H), 1.66 (s, IH), 3.21(d, 2H, J = 9.0 Hz), 3.50(d, 2H, $J = 9.0$ Hz), 3.63(s, 4H), 6.73(d, 1H), 6.91(d, IH), 7.24-7.33(m, 12H).

Step 3: Preparation of 1a, 5a, 6a-tert-butyl-3-[2-fluoro-3-trifluoromethyl phenyl]-3-azabicyclo[3.1.0]hex-6-yl carbamate

This compound was prepared by the same method as described in step 3 of the example 7 from 1\(\alpha\), 5\(\alpha\), 6\(\alpha\)-N,N-dibenzyl-3-(2-fluoro-3-trifluoromethylphenyl)-3-azabicyclo[3.1.0]hexan-6-amine.

IR (KBr) 3344, 3134, 2854, 2821, 1602, 1566, 1544, 1498, 1376, 1332, 1235, 1101, 1043, 1026, 910, 885 cm$^{-1}$; 1H-NMR (300 MHz, DMSOd$_6$) $\delta$ 1.34(s, 9H), 1.65(s, 2H), 2.52(s, 9H), 3.16(d, 2H, $J = 9.0$ Hz), 3.54 (d, 2H, $J = 9.0$ Hz), 6.78 (m, IH), 6.92(s, IH), 7.19 (m, IH).

Step 4: Preparation of 1a, 5a, 6a-[6-(5-isoquinolylaminocarboxamido)-3-(2-fluoro-3-trifluoromethyl phenyl]-3-azabicyclo[3.1.0]hexane

This compound was prepared by the same method as described in step 4 of example 7 from 1\(\alpha\), 5\(\alpha\), 6\(\alpha\)-tert-butyl-3-[2-fluoro-3-trifluoromethyl phenyl]-3-azabicyclo[3.1.0]hex-6-yl carbamate and phenyl isoquinolin-5-yl carbamate.

IR (KBr) 3430, 3299, 3059, 2948, 2838, 1644, 1586, 1494, 1478, 1362, 1320, 1250, 1226, 1169, 119, 995, 827 cm$^{-1}$; 1H-NMR (300 MHz, DMSOd$_6$) $\delta$ 1.89 (s, 2H), 2.50 (s, IH), 3.54 (d, 2H, $J = 9.0$ Hz), 3.77 (d, 2H, $J = 9.0$ Hz), 6.88 (s, IH), 7.01(m, 2H), 7.20 (d, IH), 7.61 (t, IH), 7.75 (d, IH), 7.90 (d, IH), 8.22 (d, IH), 8.53 (d, IH), 8.62(s, IH), 9.27 (s, IH). m.p. is 224-226 °C

Example 24: Preparation of 1\(\alpha\), 5\(\alpha\), 6\(\alpha\)-t[6-(5-isoquinolylaminocarboxamido)]-3-(2-trifluoromethoxy) phenyl]-3-azabicyclo[3.1.0]hexane (Compound No. 24)

Step 1: Preparation of 1-(2-trifluoromethoxyphenyl)-2,5-dihydro-l H-pyrrole

This compound was prepared by the same method as described in step 1 of the example 7 from intermediate 5 and 2-(trifluoromethoxy)aniline.

IR (KBr): 3034, 2974, 2843, 2890, 1610, 1512, 1523, 1445, 1387, 1323, 1290, 1210, 1155, 1078, 1044, 9988, 8155 cm$^{-1}$; 1H NMR (3000 MHz, CDCl$_3$): $\delta$ 4.2 l(s, 4H), 6.00(s, 2H), 6.70(t, IH, $J = 6.0$ Hz), 6.79(d, IH), 7.19-7.21(m, 2H).

Step 2: Preparation of 1a, 5a, 6a-N,N-dibenzyl-3-(2-trifluoromethoxyphenyl)-3-azabicyclo[3.1.0]hexan-6-amine

This compound was prepared by the same method as described in step 2 of the example 7 from 1-(2-trifluoromethoxyphenyl)-2,5-dihydro-l H-pyrrole and N,N-dibenzyl formamide.
IR (KBr) 3044, 2898, 2832, 1566, 1503, 1478, 1354, 1321, 1292, 1148, 1101, 1055, 1021, 965, 822 cm⁻¹. ¹H NMR (300 MHz, DMSO) δ 1.45 (s, 2H), 1.67 (s, 2H), 3.08 (d, 2H, J = 9.0 Hz), 3.46 (d, 2H, J = 9.0 Hz), 3.63 (s, 4H), 6.79 (d, 2H), 7.15-7.30 (m, 13H).

Step 3: Preparation of 1a, 5a, 6a-tert-butyl-3-[2-trifluoromethoxyphenyl]-3-azabicyclo [3.1.0] hex-6-yl carbamate

This compound was prepared by the same method as described in step 3 of the example 7 from 1α, 5α, 6α, N,N-dibenzyl-3-(2-trifluoromethoxyphenyl)-3-azabicyclo[3.1.0]hexan-6-amine.

IR (KBr) 3313, 3066, 2905, 2845, 1650, 1567, 1501, 1479, 1359, 1260, 1205, 1156, 1107, 1056, 1020, 921,826 cm⁻¹; ¹H-NMR (300 MHz, DMSO) δ 1.36 (s, 9H), 1.73 (s, 2H), 2.23 (d, 2H), 2.88 (d, 2H, J = 9.0 Hz), 3.05 (d, 2H, J = 9.0 Hz), 3.52 (d, 2H), 6.68 (2H), 6.98 (m, 2H).

Step 4: Preparation of 1a, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2-trifluoromethoxyphenyl)]-3-azabicyclo [3.1.0]hexane

This compound was prepared by the same method as described in step 4 of example 7 from 1α, 5α, 6α-tert-butyl-3-[2-trifluoromethoxyphenyl]-3-azabicyclo [3.1.0]hex-6-yl carbamate and phenyl isoquinolin-5-yl carbamate.

Example 25: Preparation of 1α, 5α, 6α-tert-butyl-3-[2-trifluoromethoxyphenyl]-3-azabicyclo [3.1.0]hexan-6-amine (Compound No. 25)

Step 1: Preparation of l-(2-trifluoromethylphenyl)-2,5-dihydro-1H-pyrrole

This compound was prepared by the same method as described in step 1 of the example 7 from intermediate 5 and 2-(trifluoromethyl) aniline.

IR (KBr) 3067, 2998, 2847, 2832, 1667, 1532, 1587, 1432, 1343, 1398, 1221, 1287, 1143, 1089, 1054, 997, 821 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃): δ 4.16 (s, 4H), 5.98 (s, 2H), 6.93 (t, 2H), 7.09 (d, 2H), 7.47 (t, 2H), 7.58 (d, 2H).

Step 2: Preparation of 1α, 5a, 6a-N,N-dibenzyl-3-(2-trifluoromethylphenyl)-3-azabicyclo [3.1.0] hexan-6-amine

This compound was prepared by the same method as described in step 2 of the example 7 from l-(2-trifluoromethylphenyl)-2,5-dihydro-1H-pyrrole and N,N-dibenzyl formamide.
IR (KBr) 3078, 2865, 2834 1598, 1532, 1456, 1378, 1320, 1232, 1189, 1132, 1079, 1021, 906, 803 cm⁻¹. ¹H-NMR (300 MHz, DMSO-d₆) δ 1.41(s, 2H), 1.96 (s, IH), 3.05 (d, 2H, J = 9.0 Hz), 3.17(d, 2H, J = 9.0 Hz), 3.61 (s, 4H), 7.12 (m, IH), 7.27-7.34(m, HH), 7.52 (m, 2H).

Step 3: Preparation of Ia, 5a, 6a-tert-butyl-3-[2-trifluoromethylphenyl]-3-azabicyclo[3.1.0]hex-6-yl carbamate

This compound was prepared by the same method as described in step 3 of the example 7 from Ia, 5α, 6α-Ν,Ν-dibenzyl-3-(2-trifluoromethylphenyl)-3-azabicyclo[3.1.0]hexan-6-amine.

IR (KBr) 3335, 3198, 2833, 2866, 1654, 1577, 1522, 1455, 1373, 1332, 1212, 1193, 1016, 1021, 916, 821 cm⁻¹. ¹H NMR (300 MHz, DMSO-d₆) δ 1.38 (s, 9H), 1.75(s, 2 H), 2.25( s, IH), 2.90 (d, 2H, J = 9.0 Hz), 3.54 (d, 2H, J = 9.0 Hz), 6.70 (d, 2H), 6.99 (m, 2H)

Step 4: Preparation of Ia, 5a, 6a-[6-(5-isoquinolylaminocarboxamido)-3-(2-trifluoromethyl)phenyl]-3-azabicyclo[3.1.0]hexane

This compound was prepared by the same method as described in step 4 of example 7 from 1α, 5α, 6α-tert-butyl-3-[2-trifluoromethylphenyl]-3-azabicyclo[3.1.0]hexan-6-y1 carbamate and phenyl isoquinolin-5-yl carbamate.

IR (KBr) 3358, 3264, 1650, 1604, 1556, 1496, 1476, 1496, 1357, 1257, 1239, 1210, 1138, 1097, 1033, 962,826 cm⁻¹. ¹H NMR (300 MHz, DMSO-d₆) δ 1.77 (s, 2H), 2.81 (s, IH), 3.26 (d, 2H, J = 9.0 Hz), 3.35 (d, 2H, J = 9.0 Hz), 6.80 (m, IH), 7.21 (t, 2H), 7.41 (d, IH), 7.60 (m, 3H), 7.74 (d, IH), 7.89 (d, IH), 8.25 (d, IH), 8.53 (d, IH), 8.59 (s, IH) 9.27(s, IH); m.p. is 165-167 °C Example 26: Preparation of 1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-[2-fluoro-(5-trifluoro methyl) phenyl] ]-3-azabicyclo [3.1.0]hexane (Compound No. 26)

Step 1: Preparation of 1-[2-fluoro-(5-trifluoromethyl) phenyl]-2,5-dihydro-1H-pyrrole

This compound was prepared by the same method as described in step 1 of the example 7 from intermediate 5 and 2-fluoro-5-(trifluoromethyl) aniline.

IR (KBr) 3021, 2987, 2898, 2843, 1632, 1576, 1545, 1436, 1333, 1345, 1230, 1257, 1167, 1060, 1053, 996, 820 cm⁻¹. ¹H-NMR (300 MHz, CDCl₃): δ 4.28(s, 4H), 6.33(s, 2H), 6.84(d, 1H, J = 9.0 Hz), 6.97(d, 1H, J = 9.0 Hz) 7.68(s, IH).

Step 2: Preparation of Ia, 5a, 6a-Ν,Ν-dibenzyl-3-[2-fluoro-(5-trifluoromethyl)phenyl]-3-azabicyclo[3.1.0]hexan-6-amine

This compound was prepared by the same method as described in step 2 of the example 7 from 1-[2-fluoro-(5-trifluoromethyl) phenyl]-2,5-dihydro-1 H-pyrrole and Ν,Ν-dibenzyl formamide.

IR (KBr) 3098, 2834, 2878, 1545, 1520, 1460, 1319, 1302, 1205, 1145, 1191, 1058, 1048, 929, 840 cm⁻¹. ¹H-NMR 1.44(s, 2H), 1.65(s, 1H), 3.07(d, 2H, J = 9.0 Hz), 3.41(d, 2H, J = 9.0 Hz), 3.62 (s, 4H), 6.45(m, 2H), 6.88 (m, IH), 7.26-7.35(m, 10H).
Step 3: Preparation of Ia, 5α, 6α-tert-butyl-3-[2-fluoro-(5-trifluoromethyl)phenyl]-3-azabicyclo[3.1.0]hex-6-yl carbamate

This compound was prepared by the same method as described in step 3 of the example 7 from 1α, 5α, 6α-N,N-dibenzyl-3-[2-fluoro-(5-trifluoromethyl)phenyl]-3-azabicyclo [3.1.0]hex-6-yl aniline.

IR (KBr) 3334, 3178, 2843, 2856, 1639, 1565, 1520, 1416, 1354, 1332, 1296,1186, 1043, 1021, 916, 842 cm⁻¹, ¹H NMR (300 MHz, DMSO-d⁶) δ 1.23(s, 9H), 2.27(s, 2H), 2.58(s, 1H), 3.36 (d, 2H, J = 9.0 Hz), 3.77 (d, 2H, J = 9.0 Hz), 6.95 (s, 1H), 7.44-7.58(m, 2H).

Step 4: Preparation of Ia, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-[2-fluoro-(5-trifluoromethyl)phenyl]-3-azabicyclo[3.1.0]hexane

This compound was prepared by the same method as described in step 4 of example 7 from 1α, 5α, 6α-tert-butyl-3-[2-fluoro-(5-trifluoromethyl)phenyl]-3-azabicyclo [3.1.0]hex-6-yl carbamate and phenyl isooquinolin-5-yl carbamate.

IR (KBr) 3365, 3291, 1650, 1579, 1523, 1483, 1437, 1360, 1292, 1253, 1211, 1112, 1082, 992, 816 cm⁻¹, ¹H NMR (300 MHz, DMSO-d⁶) δ 1.88 (s, 2H), 2.56 (s, 1H), 3.40 (d, 2H, J = 9.0 Hz), 3.78 (d, 2H, J = 9.0 Hz), 6.87-6.95 (m, 2H), 7.05 (d, 1H), 7.24 (m, 1H), 7.60 (t, 1H), 7.75 (d, 1H), 7.88 (d, 1H), 8.22 (d, 1H), 8.53 (d, 1H), 8.60 (s, 1H), 9.27(s, 1H); m.p. is 230-232°C

Example 27: Preparation of 1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-[2-fluoro-(4-difluoromethoxy) phenyl]-3-azabicyclo[3.1.0]hexane (Compound No. 27)

Step 1: Preparation of l-(2-fluoro-4-difluoromethoxyphenyl)-2,5-dihydro-lH-pyrrole

This compound was prepared by the same method as described in step 1 of the example 7 from intermediate 5 and 2-fluoro-(4-difluoromethoxy) aniline.

IR (KBr) 3034, 2955, 2878, 2889, 1634, 1567, 1523, 1467, 1334, 1398, 1254, 1267, 1109, 1007, 1045, 997, 818 cm⁻¹ ¹H NMR (300 MHz, CDCl₃): 4.26(s, 4H), 6.29(s, 2H), 6.84(m, 1H), 6.97(m, 1H), 7.1(t, 1H, J = 7.2 Hz), 7.68(s, 1H).

Step 2: Preparation of Ia, 5α, 6α-N,N-dibenzyl-3-[2-fluoro-(4-difluoromethoxy)phenyl]-3-azabicyclo[3.1.0]hex-an-6-amine

This compound was prepared by the same method as described in step 2 of the example 7 from l-(2-fluoro-4-difluoromethoxyphenyl)-2,5-dihydro-lH-pyrrole and N,N-dibenzyl formamide.

IR (KBr) 3058, 2821, 2865, 1543, 1510, 1443, 1313, 1204, 1121, 1104, 1078, 1021, 909, 850 cm⁻¹ ¹H NMR 1.44(s, 2H), 1.65(s, 1H), 3.05(d, 2H, J = 9.0 Hz), 3.44(d, 2H, J = 9.0 Hz), 3.63 (s, 2H), 6.48(m, 2H), 6.59 (m, 1H), 7.11(t, 1H, J = 7.2 Hz), 7.28-7.37(m, 10H).
**Step 3: Preparation of Ia, 5a, 6a-tert-butyl-3-[2-fluoro-4-(difluoromethoxy)phenyl]-3-azabicyclo [3.1.0] hex-6-yl] carbamate**

This compound was prepared by the same method as described in step 3 of the example 7 from 1α, 5α, 6α-N7V-dibenzyl-3-[2-fluoro-4-(difluoromethoxy)phenyl]-3-azabicyclo[3.1.0] hexan-6-amine.

IR (KBr) 3334, 3125, 2843, 2855, 1623, 1566, 1522, 1417, 1358, 1333, 1296, 1172, 1047, 10232, 917, 889 cm⁻¹. ¹H-NMR (300 MHz, DMSOd_6) δ 1.25(s, 9H), 2.28(s, 2H), 2.54(s, IH), 3.37 (d, 2H, J = 9.0 Hz), 3.78 (d, 2H, J = 9.0 Hz), 6.88 (s, IH), 7.10 (t, IH, J = 72.0 Hz), 7.45-7.59(m, 2H).

**Step 4: Preparation of Ia, 5a, 6a-[6-(5-isoquinolylaminocarboxamido)-3-[2-fluoro-(4-difluoromethoxy)phenyl]-3-azabicyclo [3.1.0]hexane**

This compound was prepared by the same method as described in step 4 of example 7 from 1α, 5α, 6α-tert-butyl-3-[2-fluoro-4-(difluoromethoxy)phenyl]-3-azabicyclo [3.1.0] hex-6-yl carbamate and phenyl isoquinolin-5-yl carbamate.

IR (KBr) 3364, 3292, 310-8, 2978, 2958, 2910, 2856, 1650, 1579, 1518, 1483, 1387, 1360, 1327, 1252, 1224, 1135, 1100, 1062, 976, 948, 828cm⁻¹. ¹H-NMR (300 MHz, DMSOd_6) δ 1.84 (s, 2H), 2.60 (s, IH), 3.53 (d, 2H, J = 9.0 Hz), 3.69 (d, 2H, J = 9.0 Hz), 6.75-6.87 (m, 3H), 7.02 (t, IH, J = 72.0 Hz), 7.08 (s, IH), 7.60 (t, IH), 7.75 (d, IH), 7.90 (d, IH), 8.23 (d, IH), 8.55 (d, IH), 8.61 (s, IH), 9.27(s, IH); m.p. is 201-203°C

**Example 28: Preparation of 1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2,3,4-trifluoro)phenyl]-3-azabicyclo [3.1.0]hexane (Compound No. 28)**

**Step 1: Preparation of 1-(2,3,4-trifluorophenyl)-2,5-dihydro-1H-pyrrole**

This compound was prepared by the same method as described in step 1 of the example 7 from intermediate 5 and 2,3,4-trifluoroaniline.

IR (KBr) 3045, 2978, 2899, 2886, 1675, 1532, 1578, 1445, 1399, 1223, 1267, 1123, 1045, 1078, 999, 823 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): 4.24(s, 4H), 5.91(s, 2H), 6.17(m, IH), 6.75(m, IH).

**Step 2: Preparation of Ia, 5a, 6a-N,N-dibenzyl-3-(2,3,4-trifluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine**

This compound was prepared by the same method as described in step 2 of the example 7 from 1-(2,3,4-trifluorophenyl)-2,5-dihydro-1H-pyrrole and N,N-dibenzyl formamide.

IR (KBr) 3089, 2876, 2843, 1592, 1518, 1445, 1319, 1204, 1178, 1144, 1010, 1008, 949, 812 cm⁻¹. ¹H-NMR (300 MHz, DMSOd_6) δ 1.46(s, 2H), 1.69 (s, IH), 3.12(d, 2H, J = 9.0 Hz), 3.42(d, 2H, J = 9.0 Hz), 3.63(s, 4H), 6.45(m, IH), 7.05 (m, IH), 7.27-7.38(m, 10H).
Step 3: Preparation of \( \text{Ia}, 5 \alpha, 6 \alpha\text{-tert-butyl-3-(2,3,4-trifluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl}} \) carbamate

This compound was prepared by the same method as described in step 3 of the example 7 from \( \text{Ia}, 5 \alpha, 6 \alpha\text{-N,N-dibenyl-3-(2,3,4-trifluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine} \).

IR (KBr) 3334, 3187, 2840, 2833, 1671, 1546, 1589, 1435, 1389, 1332, 1227, 1178, 1043, 1021, 967, 832 cm\(^{-1}\); \(^{1}\)H-NMR (300 MHz, DMSO\(\text{d}_6\)) \( \delta \) 61.38 (s, 9H), 1.62 (s, 2H), 2.50 (s, IH), 3.37 (d, 2H, \( J = 9.0 \text{ Hz} \)), 3.45 (d, 2H, \( J = 9.0 \text{ Hz} \)), 6.95-7.06(m, 2H).

Step 4: Preparation of \( \text{Ia, 5 \alpha, 6 \alpha\text{-[6-(5-isoquinolylaminocarboxamido)-3-(2,3,4-trifluoro)phenyl J-3-azabicyclo[3.1.0]hexane}} \)

This compound was prepared by the same method as described in step 4 of example 7 from \( \text{Ia}, 5 \alpha, 6 \alpha\text{-tert-butyl-3-(2,3,4-trifluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine} \) and phenyl isoquinolin-5-yl carbamate.

IR (KBr) 3292, 2869, 1650, 1519, 1581, 1496, 1363, 1284, 1253, 1187, 1154, 1048, 1008, 827 cm\(^{-1}\); \(^{1}\)H-NMR (300 MHz, DMSO\(\text{d}_6\)) \( \delta \) 1.86 (s, 2H), 2.57 (s, IH), 3.34 (d, 2H, \( J = 9.0 \text{ Hz} \)), 3.70 (d, 2H, \( J = 9.0 \text{ Hz} \)), 6.56 (m, IH), 6.86 (s, IH), 7.11 (m, IH), 7.58 (t, IH), 7.75 (d, IH), 7.88 (d, IH), 8.22 (d, IH), 8.53 (d, IH), 8.61 (s, IH), 9.27 (s, IH); m.p. is 207 °C.

Example 29: Preparation of \( \text{Ia, 5 \alpha, 6 \alpha\text{-[6-(5-isoquinolylaminocarboxamido)-3-(2A6-trifluoro)phenyl J-3-azabicyclo[3.1.0]hexane}} \) (Compound No. 29)

Step 1: Preparation of \( \text{l-(2,4,6-trifluorophenyl)-2,5-dihydro-IH-pyrrole} \)

This compound was prepared by the same method as described in step 1 of the example 7 from intermediate 5 and 2,4,6-trifluoro aniline.

IR (KBr) 3056, 2977, 2856, 2870, 1634, 1544, 1590, 1434, 1356, 1278, 1234, 1120, 1078, 1034, 990, 825 cm\(^{-1}\); \(^{1}\)H-NMR (300 MHz, CDCl\text{3})\(\delta\) 4.28(s, 4H), 5.87(s, 2H), 6.59-6.65(m, 2H).

Step 2: Preparation of \( \text{Ia, 5 \alpha, 6 \alpha\text{-N,N-dibenyl-3-(2,4,6-trifluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine}} \)

This compound was prepared by the same method as described in step 2 of the example 7 from 1-(2,4,6-trifluorophenyl)-2,5-dihydro-I H-pyrrole and N,N-dibenzy formamide.

IR (KBr) 3055, 2893, 2821, 1554, 1518, 1458, 1389, 1278, 1121, 1146, 1099, 1034, 956, 810 cm\(^{-1}\); \(^{1}\)H-NMR (300 MHz, DMSO\(\text{d}_6\)) \( \delta \) 61.45(s, 2H), 1.68(s, IH), 3.1 l(d, 2H, \( J = 9.0 \text{ Hz} \)), 3.42(d, 2H, \( J = 9.0 \text{ Hz} \)), 3.62(s, 4H), 6.48(m, IH), 7.07 (m, IH), 7.28-7.39(m, 10H).

Step 3: Preparation of \( \text{Ja, 5 \alpha, 6 \alpha\text{-tert-butyl-3-(2,4,6-trifluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine}} \)

This compound was prepared by the same method as described in step 3 of the example 7 from \( \text{Ia, 5 \alpha, 6 \alpha\text{-A,N-dibenyl-3-(2,3,4-trifluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine}} \)

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IR (KBr) 3332, 3121, 2856, 2824, 1679, 1565, 1523, 1416, 1357, 1333, 1298, 1177, 1042, 1026, 919, 883 cm⁻¹. ¹H-NMR (300 MHz, DMSO-d₆) δ 8.39 (s, 9H), 1.65 (s, 2H), 2.53 (s, 1H), 3.39 (d, 2H, J = 9.0 Hz), 3.46 (d, 2H, J = 9.0 Hz), 6.97-7.05 (m, 2H).

**Step 4: Preparation of 1a, 5a, 6a-[6-(5-isoquinolylaminocarboxamido)-3-(2,4,6-trifluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl] carbamate**

This compound was prepared by the same method as described in step 4 of example 7 from 1α, 5α, 6α-fer/-butyl-3-(2,3-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl carbamate and phenyl isoquinolin-5-yl carbamate.

IR (KBr) 3364, 3297, 3122, 3067, 2914, 2855, 1650, 1586, 1517, 1484, 1387, 1346, 1329, 1358, 1254, 1211, 1176, 1025, 916, 828 cm⁻¹. ¹H-NMR (300 MHz, DMSO-d₆) δ 1.76 (s, 2H), 2.72 (s, 1H), 3.16 (d, 2H, J = 9.0 Hz), 3.44 (d, 2H, J = 9.0 Hz), 6.81 (m, 2H), 7.13 (t, 2H), 7.60 (t, 1H), 7.74 (d, 1H), 7.88 (d, 1H), 8.23 (d, 1H), 8.53 (d, 1H), 8.60 (s, 1H), 9.27 (s, 1H); m.p. is 179 °C

**Example 30: Preparation of 1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2,3-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl] carbamate (Compound No. 30)**

**Step 1: Preparation of 1-(2,3-difluorophenyl)-2,5-dihydro-1H-pyrrole**

This compound was prepared by the same method as described in step 1 of the example 7 from intermediate 5 and 2,3-difluoroaniline.

IR (KBr): 3066, 2978, 2889, 2856, 1689, 1544, 1590, 1434, 1329, 1249, 1269, 1127, 1044, 1078, 995, 827 cm⁻¹.

¹H-NMR (300 MHz, CDC1₃): 4.21 (s, 4H), 5.90 (s, 2H), 6.72 (m, 1H), 6.78-6.92 (m, 2H).

**Step 2: Preparation of 1a, 5a, 6a-N,N-dibenzyl-3-(2,3-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine**

This compound was prepared by the same method as described in step 2 of the example 7 from 1-(2,3-difluorophenyl)-2,5-dihydro-1H-pyrrole and N,N-dibenzylformamide.

IR (KBr) 3077, 2889, 2832, 1678, 1555, 1467, 1373, 1331, 1256, 1183, 1125, 1060, 1011, 945, 822 cm⁻¹. ¹H NMR (300 MHz, DMSO-d₆) δ 1.42 (s, 2H), 1.75 (s, 1H), 3.07 (d, 2H, J = 9.0 Hz), 3.44 (d, 2H, J = 9.0 Hz), 3.63 (s, 4H), 6.68 (m, 1H), 6.89 (m, 1H), 7.09 (m, 1H), 7.28-7.36 (m, 10H).

**Step 3: Preparation of 1a, 5a, 6a-tert-butyl-3-(2,3-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-yl] carbamate**

This compound was prepared by the same method as described in step 3 of the example 7 from 1α, 5α, 6α-N,7V-dibenzyl-3-(2,3-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine.
IR (KBr) 3356, 3134, 2867, 2823, 1698, 1545, 1534, 1478, 1335, 1367, 1265, 1134, 1056, 1067, 989, 808 cm⁻¹. ¹H NMR (300 MHz, DMSO-d₆) δ 1.34 (s, 9H), 1.66 (s, 2H), 2.43 (s, 1H), 3.16 (d, 2H, J = 9.0 Hz), 3.53 (d, 2H, J = 9.0 Hz), 6.96 (m, IH), 7.27 (s, IH), 7.47 (s, IH).

Step 4: Preparation of Ia, 5a, 6a-{6-(5-isoquinolylaminocarboxamido)-3-(2,3-difluoro)phenyl}-3-azabicyclo[3.1.0]hex-6-yl carbamate

This compound was prepared by the same method as described in step 4 of example 7 from 1α, 5α, 6α-tert-butyl-3-(2,3-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-yl carbamate and phenyl isoquinolin-5-yl carbamate.

IR (KBr) 3296, 3066, 2965, 2870, 1640, 1582, 1512, 1475, 1463, 1363, 1327, 1259, 1187, 1073, 910, 822 cm⁻¹. ¹H-NMR (300 MHz, DMSO-d₆) δ 1.87 (s, 2H), 2.27 (s, 1H), 3.29 (d, 2H, J = 9.0 Hz), 3.74 (d, 2H, J = 9.0 Hz), 6.56 (t, IH), 6.68 (t, IH), 6.87 (s, IH), 6.97 (m, IH), 7.58 (t, IH), 7.75 (d, IH), 7.88 (d, IH), 8.22 (d, IH), 8.53 (d, IH), 8.62 (s, IH), 9.28 (s, IH). m.p. is 212 °C

Example 31: Preparation of Ia, 5α, 6α-{6-(5-isoquinolylaminocarboxamido)-3-(2-fluoro-4-methylphenyl)}-3-azabicyclo[3.1.0]hexane (Compound No. 31)

Step 1: Preparation of 1-(2-fluoro-4-methylphenyl)-2,5-dihydro-IH-pyrrole

This compound was prepared by the same method as described in step 1 of example 7 from intermediate 5 and 2-fluoro-4-methyl aniline.

IR (KBr) cm⁻¹ 3034, 2999, 2845, 2878, 1645, 1578, 1532, 1412, 1334, 1255, 1236, 1123, 1067, 1035, 992, 816 cm⁻¹. ¹H-NMR (300 MHz, CDCl₃): 2.20 (s, 3H), 4.20 (s, 4H), 5.95 (s, 2H), 6.70 (m, IH), 6.78 (s, IH), 6.98 (m, IH).

Step 2: Preparation of Ia, 5a, 6a- N,N-dibenzyl-3-(2-fluoro-4-methylphenyl)-3-azabicyclo[3.1.0]hexan-6-amine

This compound was prepared by the same method as described in step 2 of the example 7 from 1-(2-fluoro-4-methylphenyl)-2,5-dihydro-I H-pyrrole and N,N-dibenzyl formamide.

IR (KBr) 3076, 2883, 2812, 1677, 1532, 1456, 1378, 1323, 1265, 1134, 1165, 1069, 1056, 944, 826 cm⁻¹. ¹H-NMR (300 MHz, DMSO-d₆) δ 1.42 (s, 2H), 1.72 (s, 3H), 2.17 (s, 3H), 3.10 (d, 2H, J = 9.0 Hz), 3.52 (d, 2H, J = 9.0 Hz), 3.63 (s, 4H), 6.46 (d, IH), 7.27-7.38 (m, 12H).

Step 3: Preparation of Ia, 5a, 6a-tert-butyl-3-(2-fluoro-4-methylphenyl)-3-azabicyclo[3.1.0] hexan-6-yl] carbamate

This compound was prepared by the same method as described in step 3 of the example 7 from 1α, 5α, 6α- N,N-dibenzyl-3-(2-fluoro-4-methylphenyl)-3-azabicyclo[3.1.0]hexan-6-amine.
IR (KBr) 3378, 3156, 2889, 2867, 1645, 1578, 1534, 1478, 1334, 1378, 1278, 1145, 1067, 1067, 934, 832 cm⁻¹; ¹H-NMR (300 MHz, DMSO-d₆) δ 1.24(s, 9H), 2.27(s, 2H), 2.58(s, 1H), 2.67(s, 3H), 3.34(d, 2H, J = 9.0 Hz), 3.69(d, 2H, J = 9.0 Hz), 6.95(s, 1H), 7.44-7.58(m, 2H).

Step 4: Preparation of 1a, 5a, 6a-[6-(5-isoquinolylaminocarboxamido)-3-(2-fluoro-4-methylphenyl) phenyl]-3-azabicyclo[3.1.0]hexane

This compound was prepared by the same method as described in step 4 of example 7 from 1α, 5α, 6α-[6-tert-butyl-3-(2-fluoro-4-methylphenyl)-3-azabicyclo[3.1.0]hexane-6-yl] carbamate and phenyl isoquinolinin-5-yl carbamate.

IR (KBr) 3291, 3351, 3177, 2916, 2899, 2850, 1649, 1581, 1519, 1483, 1459, 1359, 1327, 1253, 1140, 1170, 1117, 1033, 1061, 967, 854 cm⁻¹; ¹H-NMR (300 MHz, DMSO-d₆) δ 1.81(s, 2H), 2.19(s, 3H), 2.63(s, 1H), 3.20(d, 2H, J = 9.0 Hz), 3.67(d, 2H, J = 9.0 Hz), 6.65(t, 1H), 6.84-6.91(m, 3H), 7.60(t, 1H), 7.74(d, 1H), 7.88(d, 1H), 8.22(d, 1H), 8.53(d, 1H), 8.59(s, 1H), 9.27(s, 1H); m.p. is 218°C

Example 32: Preparation of 1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2-isopropylphenyl)-3-azabicyclo[3.1.0]hexane-3-yl] hexane (Compound No. 32)

Step 1: Preparation of l-(2-isopropyl)-2,5-dihydro-lH-pyrrole

This compound was prepared by the same method as described in step 1 of the example 7 from intermediate 5 and 2-isopropylaniline.

IR (KBr) 3025, 2899, 2854, 1598, 1535, 1477, 1374, 1338, 1269, 1163, 1125, 1075, 1027, 919, 817 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 1.21(s, 6H), 2.83(m, 4H), 4.09(s, 4H), 5.94(s, 4H), 6.48(d, 2H, J = 9.0 Hz), 7.04(d, 2H, J = 8.7 Hz).

Step 2: Preparation of 1a, 5a, 6α-N,N-dibenzyl-3-(2-isopropylphenyl)-3-azabicyclo[3.1.0]hexan-6-amine

This compound was prepared by the same method as described in step 2 of the example 7 from l-(2-isopropyl)-2,5-dihydro-l H-pyrrole and N,N-dibenzylformamide.

IR (KBr) 3055, 2890, 2850, 1589, 1527, 1460, 1344, 1336, 1269, 1154, 1114, 1092, 1000, 905, 815 cm⁻¹; ¹H-NMR (300 MHz, DMSO-d₆) δ 1.29(s, 6H), 1.42(s, 1H), 1.50(s, 2H), 1.70(s, 1H), 3.08(d, 2H, J = 9.0 Hz), 3.34(d, 2H, J = 9.0 Hz), 3.66(s, 4H), 6.43(d, 2H), 7.21-7.36(m, 12H).

Step 3: Preparation of 1a, 5a, 6α-tert-butyl-3-(2-isopropylphenyl)-3-azabicyclo[3.1.0]hexane-6-yl carbamate

This compound was prepared by the same method as described in step 3 of the example 7 from 1α, 5α, 6α-N,N-dibenzyl-3-(2-isopropylphenyl)-3-azabicyclo[3.1.0]hexan-6-amine.

IR (KBr) 3377, 3177, 2887, 2843, 1665, 1578, 1523, 1454, 1321, 1311, 1256, 1198, 1132, 1054, 1021, 902, 809 cm⁻¹; ¹H-NMR (300 MHz, DMSO-d₆) δ 1.29 (s, 6H), 1.37 (s, 9H), 1.42(s, 1H),

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2.24(s, 2H), 2.54(s, IH), 3.25 (d, 2H, J = 9.0 Hz), 3.69 (d, 2H, J = 9.0 Hz), 6.66 (m, 2H), 7.24 (m, 2H).

**Step 4: Preparation of Ia, 5a, 6a-[6-(5-isoquinolylaminocarboxamido)-3-(2-isopropylphenyl)-3-azabicyclo [3.1.0]hexane**

This compound was prepared by the same method as described in step 4 of example 7 from 1α, 5α, 6α-tert-butyl-3-(2-isopropylphenyl)-3-azabicyclo [3.1.0] hex-6-yl carbamates and phenyl isoquinolin-5-yl carbamate

IR (KBr) 3345, 3265, 1689, 1634, 1580, 1534, 1478, 1456, 1345, 1290, 1227, 1134, 1167, 1045, 966, 827 cm⁻¹; ¹H-NMR (300 MHz, DMSO-d₆) δ 1.09 (m, IH), 1.15 (d, 6H, J = 6.6 Hz); 1.73 (s, 2H), 2.97 (s, IH); 3.10 (d, 2H, J = 9.0 Hz); 3.24 (d, 2H, J = 9.0 Hz); 6.08 (s, IH); 7.04-7.13 (m, 3H); 7.22 (d, IH, J = 8.1 Hz); 7.57 (m, IH, J = 9.0 Hz); 7.74 (d, IH, J = 9.0 Hz); 7.89 (d, IH, J = 9.0 Hz); 8.25 (d, IH, J = 9.0 Hz); 8.53 (d, IH, J = 9.0 Hz); 8.60 (s, IH); 9.27 (s, 1H); m.p. is 195°C

**Example 33: 1α, 5α, 6α-r6-(5-isoquinolylaminocarboxamido)-3-(3,5-difluorophenyl)-3-azabicyclo [3.1.0] hexan-6-yl carbamate (Compound No. 33)**

**Step 1: Preparation of 1a-(3,5-difluorophenyl)-2,5-dihydro-lH-pyrrole**

This compound was prepared by the same method as described in step 2 of the example 7 from intermediate 5 and 3,5-difluoro aniline.

IR (KBr) (cm⁻¹): 3361, 1673, 1525, 1166, 948, 843; ¹H NMR (CDCl₃): δ 4.06 (4H, s); 5.94 (2H, s); 5.92-6.20 (2H, m); 6.96-7.20 (IH, m).

**Step 2: Preparation of 1a, 5a, 6a-N,N-dibenzyl-3-(3,5-difluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine**

This compound was prepared by the same method as described in step 2 of the example 7 from 1-(3,5-difluorophenyl)-2,5-dihydro-lH-pyrrole and N,N-dibenzyl formamide.

¹H NMR (CDCl₃): δ 1.40-1.44 (2H, m); 1.88-1.92 (1H, m); 3.08 (2H, d, J = 9.3 Hz); 3.48 (2H, d, J = 9.0 Hz); 3.67 (4H, s); 5.92-6.20 (2H, m); 6.96-7.20 (IH, m); 7.20-7.30 (10H, m).

**Step 3: Preparation of 1a, 5a, 6a-tert-butyl 3-(3,5-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl carbamate**

This compound was prepared by the same method as described in step 3 of the example 7 from 1α, 5α, 6α-tert-benzyl-3-(3,5-difluorophenyl)-3-azabicyclo[3.1.0] hexan-6-amine.

IR (KBr) (cm⁻¹): 3361, 1673, 1525, 1166, 948, 843; ¹H NMR (CDCl₃): δ 1.46 (9H, s); 1.84-1.90 (2H, m); 2.38-2.41 (1H, m); 3.30 (2H, d, J = 8.1 Hz); 3.54 (2H, d, J = 9.1 Hz); 4.70-4.80 (IH, m); 6.08-6.20 (IH, m); 7.24-7.44 (2H, m).
Step 4: Preparation of Ia, 5a, 6a-[6-(5-isoquinolylamino)carboxamido]-3-(3,5-difluorophenyl)-3-azabicyclo[3.1.0]hexane

This compound was prepared by the same method as described in step 4 of example 7 from 1α, 5α, 6α-tert-butyl 3-(3,5-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-ylcarbamate and phenyl isoquinolin-5-yl carbamate.

IR (KBr) (cm⁻¹): 3308, 1638, 1578, 1567, 1211, 811; ¹H NMR (DMSO- d₆): δ 1.90-1.98 (2H, m); 2.40-2.48 (IH, m); 3.28-3.40 (2H, m); 3.58 (2H, d, J = 9.0 Hz); 6.18-6.40 (3H, m); 6.90 (IH, s); 7.61 (IH, t, J = 7.5 Hz); 7.77 (IH, d, J = 7.8 Hz); 7.90 (IH, d, J = 5.7 Hz); 8.23 (IH, d, J = 7.8 Hz); 8.54 (IH, d, J = 6.0 Hz); 8.63 (IH, s); 9.28 (IH, s); m/z (M+1): 381.36; m.p. 206-208 °C.

Example 34: Preparation of 1α, 5α, 6α-tert-(5-isoquinolylaminocarboxamido)-3-(2,4,5-trifluorophenyl)-3-azabicyclo[3.1.0]hexane (Compound No. 34)

Step 1: Preparation of 1-(2,4,5-trifluorophenyl)-2,5-dihydro-lH-pyrrole

This compound was prepared by the same method as described in step 1 of the example 7 from intermediate 5 and 2,4,5-trifluoro aniline.

IR (KBr) (cm⁻¹): 3361, 1673, 1525, 1166, 948, 843; ¹H NMR (CDCl₃): δ 4.23 (4H, s); 5.90 (2H, s); 6.30-6.42 (IH, m); 6.80-6.92 (IH, m).

Step 2: Preparation of Ia, 5a, 6a-N,N-dibenzyl-3-(2,4,5-trifluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine

This compound was prepared by the same method as described in step 2 of the example 7 from 1-(2,4,5-trifluorophenyl)-2,5-dihydro-lH-pyrrole and N,N-dibenzy1 formamide.

¹H NMR (CDCl₃): δ 1.40-1.44 (2H, m); 1.88-1.92 (1IH, m); 3.08 (2H, d, J = 9.3 Hz); 3.48 (2H, d, J = 9.0 Hz); 3.67 (4H, s); 6.30-6.42 (IH, m); 6.80-6.92 (IH, m); 7.20-7.30 (10H, m).

Step 3: Preparation of Ia, 5a, 6α-tert-butyl 3-(2,4,5-trifluorophenyl)-3-azabicyclo[3.1.0]hex-6-ylcarbamate

This compound was prepared by the same method as described in step 3 of the example 7 from 1α, 5α, 6α- N,N-dibenzy1-3-(2,4,5-trifluorophenyl)-3-azabicyclo[3.1.0]hexan-6-amine.

IR (KBr) (cm⁻¹): 3364, 1672, 1528, 1245, 1181, 1163, 870; ¹H NMR (CDCl₃): δ 1.46 (9H, s); 1.72-1.82 (2H, m); 2.52-2.61 (1IH, m); 3.25 (2H, d, J = 9.0 Hz); 3.73 (2H, d, J = 8.7 Hz); 4.72 (IH, s); 6.32-6.48 (IH, m); 6.78-6.92 (IH, m).

Step 4: Preparation of Ia, 5a, 6a-[6-(5-isoquinolylaminocarboxamido)-3-(2,4,5-trifluorophenyl) ]-3-azabicyclo [3.1.O]hexane
This compound was prepared by the same method as described in step 4 of example 7 from 1α, 5α, 6α-tert-butyl 3-(2,4,5-trifluorophenyl)-3-azabicyclo[3.1.0]hex-6-ylcarbamate and phenyl isoquinolin-5-yl carbamate

1H NMR (DMSO- d6): δ 1.82-1.90 (2H, m); 2.55-2.61 (1H, m); 3.30 (2H, d, J = 8.4 Hz); 3.70 (2H, d, J = 7.8 Hz); 6.78-6.90 (IH, m); 6.86 (IH, s); 7.34-7.48 (IH, m); 7.61 (IH, d, J = 7.5 Hz); 7.76 (IH, d, J = 7.8 Hz); 7.90 (IH, d, J = 6.0 Hz); 8.24 (IH, d, J = 7.5 Hz); 8.54 (IH, d, J = 6.3 Hz); 8.62 (IH, s); 9.28 (IH, s); IR (KBr) (cm⁻¹): 3306, 1635, 1589, 1528, 1178, 822; m/z (M+1): 399.31; m.p. 227-229 °C

Example 35: Preparation of 1α, 5α, 6α-t6-(5-isoquinolylaminocarboxamido)-3-(2,4-difluorophenyl)l-3-azabicyclo [3.1.0]hexane trifluoro acetate salt (Compound No. 35)

To a well stirred solution of 1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2,4-difluorophenyl)-3-azabicyclo [3.1.0]hexane (1 mmol) (Example 21) in dichloromethane (10 mL) was added trifluoro acetic acid (1 mmol) at OoC and stirred at room temperature for 10-12 hours. The residue obtained after removal of solvent was triturated with diethyl ether and dried to get the product.

IR (KBr) 3380, 1646, 1579, 1515, 1202, 1181, 1122, 796 cm⁻¹; 1H-NMR (300 MHz, DMSO-d6) δ 1.83-1.89 (m, 2H), 2.63-2.68 (m, IH), 3.25 (d, 2H, J = 9.0 Hz), 3.69 (d, 2H, J = 9.0 Hz), 6.74-6.86 (m, IH), 6.88-6.98 (m, 2H), 7.09-7.20 (t, IH, J = 7.8 Hz), 7.92 (d, IH, J = 8.4 Hz), 8.09 (d, IH, J = 6.3 Hz), 8.35 (d, IH, J = 7.5 Hz), 8.61 (d, IH, J = 6.3 Hz), 8.77 (s, IH), 9.49 (s, IH); m.p. is 147-149 °C

Example 36: Preparation of 1α, 5α, 6α-t6-(5-isoquinolylaminocarboxamido)-3-(2,4-difluorophenyl)l-3-azabicyclo [3.1.0]hexane triflate salt (Compound No. 36)

To a well stirred solution of 1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2,4-difluorophenyl)-3-azabicyclo [3.1.0]hexane (1 mmol) (Example 21) in dichloromethane (10 mL) was added trifluoromethane sulphonic acid (1 mmol) at OoC and stirred at room temperature for 10-12 hours. The residue obtained after removal of solvent was triturated with diethyl ether and dried to get the product.

IR (KBr) 3357, 3293, 3071, 3055, 1694, 1558, 1274, 1226, 1026 cm⁻¹; 1H-NMR (300 MHz, DMSOD δ) δ 1.84-1.90 (m, 2H), 2.62-2.70 (m, IH), 3.25 (d, 2H, J = 8.4 Hz), 3.70 (d, 2H, J = 8.7 Hz), 6.74-6.86 (m, IH), 6.88-6.98 (m, 2H), 7.08-7.20 (m, IH), 7.94-8.04 (m, IH), 8.17-8.24 (m, IH), 8.42-8.50 (m, IH), 8.50-8.60 (m, IH), 8.72-8.78 (m, IH), 8.98 (s, IH), 9.89 (s, IH); m.p. is 216-218 °C

Example 37: Preparation of 1α, 5α, 6α-t6-(5-isoquinolylaminocarboxamido)-3-(2,4-difluorophenyl)-3-azabicyclo [3.1.0]hexane hydrochloride salt (Compound No. 37)
To a well stirred solution of 1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2,4-difluoro)phenyl]-3-azabicyclo[3.1.0]hexane (1 mmol) (Example 21) in ethyl acetate (10 mL) was added 10% HCl in ethyl acetate at 0°C and stirred at room temperature for 10-12 hours. The residue obtained after removal of solvent was trituted with diethyl ether and dried to get the product.

IR (KBr): 3420, 3290, 2618, 1706, 1552, 1246, 820 cm⁻¹. ¹H-NMR (300 MHz, DMSO-δd) δ 1.78-1.86 (m, 2H), 2.60-2.68 (m, 1H), 3.25 (d, 2H, J = 9.0 Hz), 3.68 (d, 2H, J = 8.7 Hz), 6.74-6.84 (m, 2H), 6.88-6.98 (m, 2H), 7.06-7.20 (m, 1H), 7.70-7.78 (m, 1H), 7.96 (t, IH, J = 7.5 Hz), 8.15 (d, IH, J = 8.4 Hz), 8.64-8.74 (m, 2H), 8.91-8.98 (m, 1H), 9.73 (s, IH), 9.88 (s, IH); m.p. is >250 °C

Example 38: Preparation of 1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2,4-difluoro)phenyl]-3-azabicyclo[3.1.0]hexane mesylate salt (Compound No. 38)

To a well stirred solution of 1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2,4-difluoro)phenyl]-3-azabicyclo[3.1.0]hexane (1 mmol) (Example 21) in dichloromethane (10 mL) was added methane sulphonic acid (1 mmol) at 0°C and stirred at room temperature for 10-12 hours. The residue obtained after removal of solvent was trituated with diethyl ether and dried to get the product.

IR (KBr) 3421, 3282, 3052, 1695, 1557, 1274, 1208, 1192, 1044 cm⁻¹. ¹H-NMR (300 MHz, DMSO-dδ) δ 1.83-1.89 (m, 2H), 2.33 (s, IH), 2.62-2.68 (m, 1H), 3.24 (d, 2H, J = 9.3 Hz), 3.30-3.80 (m, 2H), 6.74-6.84 (m, 1H), 6.88-7.0 (m, 2H), 7.10-7.20 (m, 1H), 7.92-8.0 (m, 1H), 8.16 (d, IH, J = 6.0 Hz), 8.40-8.46 (m, 1H), 8.50-8.57 (m, 1H), 8.72 (d, IH, J = 6.0 Hz), 8.99 (s, IH), 9.83 (s, IH); m.p. is 176-178 °C

Example 39: Preparation of 1α, 5α, 6α-6-(5-isoquinolylaminocarboxamido)-3-(4-chlorophenyl)sulfonyl1-3-azabicyclo[3.1.0]hexane (Compound No. 39)

To a solution of N-3-azabicyclo[3.1.0]hex-6-yl-N'-isoquinolin-5-ylurea (1 mmol) in dry THF at 0°C was added triethylamine (8mmol). A solution of 4-chloro benzene sulfonyl chloride(1mmol) in dry THF was added slowly to the reaction mixture at 0°C. Reaction mixture was stirred at RT for 15 hours. Excess solvent was evaporated under vacuum. Reaction mixture was diluted with ethylacetate. Ethyl acetate layer was washed with water, dried over anhydrous sodium sulphate and evaporated under vacuum. Crude product was column purified to afford the desired compound as a white solid.

¹H NMR (DMSO-δd): 51.71-1.79 (2H, m); 2.39-2.46 (IH, m); 3.11 (2H, d, J = 9.0 Hz); 3.53 (2H, d, J = 9.0 Hz); 6.81 (IH, s); 7.60 (IH, t, J = 8.4 Hz); 7.70-7.90 (6H, m); 8.19 (IH, d, J =
Example 40: Preparation of 1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-T4- (trifluoromethyl)phenyl]sulfonyl]-3-azabicyclo[3.1.0]hexane (Compound No. 40)

This compound was prepared by the same method as described in example 39 from N-3-azabicyclo[3.1.0]hex-6-yl-N'-isoquinolin-5-ylurea and 4-(trifluoromethyl)benzene sulfonyl chloride.

1H NMR (DMSO- d6):  δ 1.71-1.79 (2H, m); 2.39-2.45 (IH, m); 3.14 (2H, d, J = 9.3 Hz); 3.56 (2H, d, J = 9.6 Hz); 6.98 (IH, s); 7.59 (IH, t, J = 7.8 Hz); 7.75 (IH, d, J = 8.1 Hz); 7.88-7.98 (IH, m); 8.00-8.10 (4H, m); 8.20 (IH, d, J = 7.5 Hz); 8.51 (IH, d, J = 6.0 Hz); 8.68-8.78 (IH, m); 9.26 (IH, s); IR (KBr) (cm⁻¹): 3346, 1651, 1556, 1529, 1346, 1261, 1160, 1089, 630; MS (M+h⁺): 475.33; m.p. 209°C.

Example 41: Preparation of lα, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(4-fluorophenyl)sulfonyl]-3-azabicyclo[3.1.0]hexane (Compound No. 41)

This compound was prepared by the same method as described in example 39 from N-3-azabicyclo[3.1.0]hex-6-yl-N'-isoquinolin-5-ylurea and 4-fluoro benzenesulfonyl chloride.

1H NMR (DMSO- d6):  δ 1.71-1.78 (2H, m); 2.37-2.43 (IH, m); 3.09 (2H, d, J = 8.4 Hz); 3.52 (2H, d, J = 9.6 Hz); 6.79 (IH, s); 7.46-7.56 (2H, m); 7.57-7.63 (IH, m); 7.76 (IH, d, J = 7.8 Hz); 7.72-7.93 (3H, m); 8.19 (IH, d, J = 6.6 Hz); 8.52 (IH, d, J = 5.7 Hz); 8.59 (IH, s); 9.27 (IH, s); IR (KBr) (cm⁻¹): 3296, 1645, 1579, 1569, 1345, 1157, 621; MS (M+h⁺): 427.45; m.p. 197°C.

Example 42: Preparation of 1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2,6-dichlorophenyl)sulfonyl]-3-azabicyclo[3.1.0]hexane (Compound No. 42)

This compound was prepared by the same method as described in example 39 from N-3-azabicyclo[3.1.0]hex-6-yl-N'-isoquinolin-5-ylurea and 2,6-dichlorobenzene sulfonyl chloride.

1H NMR (DMSO- d6):  δ 1.71-1.77 (2H, m); 2.42-2.47 (IH, m); 3.48 (2H, m, J = 9.0 Hz); 3.64 (2H, m, J = 9.3 Hz); 6.83 (IH, s); 7.56-7.78 (5H, m); 7.86 (IH, d, J = 5.4 Hz); 8.20 (IH, d, J = 6.6 Hz); 8.53 (IH, d, J = 5.4 Hz); 8.62 (IH, s); 9.27 (IH, s); IR (KBr) (cm⁻¹): 3370, 1657, 1556, 1426, 1346, 1176, 617; MS (M+h⁺): 477.46; m.p. 190°C.

Example 43: Preparation of lα, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2,6-difluorophenyl)sulfonyl]-3-azabicyclo[3.1.0]hexane (Compound No. 43)

This compound was prepared by the same method as described in example 39 from N-3-azabicyclo[3.1.0]hex-6-yl-N'-isoquinolin-5-ylurea and 2,6-difluoro benzenesulfonyl chloride.
$^1$H NMR (DMSO- $d_6$): $\delta$ 1.74-1.82 (2H, m); 2.34-2.40 (IH, m); 3.30-3.68 (4H, m); 7.32-7.41 (2H, m); 7.52-7.62 (IH, m); 7.66-7.74 (IH, m); 7.75-7.84 (IH, m); 7.94-8.00 (IH, m); 8.28-8.39 (2H, m); 8.44 (IH, s); 9.23 (IH, s); 9.40 (IH, s); IR (KBr) (cm$^{-1}$): 3321, 1644, 1611, 1579, 1465, 1167, 793,536; MS (M$^+$+): 443.33; m.p. 233 0°C.

Example 44: Preparation of 1$\alpha$, 5$\alpha$-[(6-(5-isoquinolylaminocarboxamido)-3-(2,4-dichlorophenyl)sulfonyl]3-azabicyclo[3.1.0]hexane (Compound No. 44)

This compound was prepared by the same method as described in example 39 from N-3-azabicyclo[3.1.0]hex-6-yl-N'-isoquinolin-5-ylurea and 2,4-dibromo benzenesulfonyl chloride.

$^1$H NMR (DMSO- $d_6$): $\delta$ 1.80-1.86 (2H, m); 2.44-2.56 (IH, m); 3.43 (2H, d, $J = 10.5$ Hz); 3.56 (2H, d, $J = 9.6$ Hz); 6.84 (IH, s); 7.59 (IH, t, $J = 8.1$ Hz); 7.76 (IH, d, $J = 8.7$ Hz); 7.81-7.95 (3H, m); 8.18-8.24 (2H, m); 8.53 (IH, d, $J = 6.0$ Hz); 8.61 (IH, s); 9.27 (IH, s).

IR (KBr) (cm$^{-1}$): 3315, 1644, 1563, 1365, 1164, 624; MS (M$^+$+): 565.35; m.p. 229 0°C.

Example 45: Preparation of 1$\alpha$, 5$\alpha$-[(6-(5-isoquinolylaminocarboxamido)-3-(2,4-dichlorophenyl)sulfonyl)3-azabicyclo[3.1.0]hexane (Compound No. 45)

This compound was prepared by the same method as described in example 39 from N-3-azabicyclo[3.1.0]hex-6-yl-N'-isoquinolin-5-ylurea and 2,4-dichloro benzene sulfonyl chloride.

$^1$H NMR (DMSO- $d_6$): $\delta$ 1.71-1.79 (2H, m); 2.39-2.46 (IH, m); 3.11 (2H, m, $J = 9.0$ Hz); 3.53 (2H, m, $J = 9.0$ Hz); 6.82 (IH, s); 7.60 (IH, t, $J = 7.5$ Hz); 7.68 (IH, d, $J = 8.1$ Hz); 7.76 (IH, d, $J = 7.5$ Hz); 7.87 (IH, d, $J = 6.0$ Hz); 7.92-8.02 (2H, m); 8.20 (IH, d, $J = 7.8$ Hz); 8.53 (IH, d, $J = 5.7$ Hz); 8.62 (IH, s); 9.27 (IH, s).

IR (KBr) (cm$^{-1}$): 3315, 1643, 1572, 1552, 1164,822,631; MS (M$^+$+): 477.17; m.p. 214 0°C.

Example 46: Preparation of 1$\alpha$, 5$\alpha$, 6$\alpha$-[(6-(5-isoquinolylaminocarboxamido)-3-(2-trifluoromethyl phenyl) sulfonyl]3-azabicyclo[3.1.0]hexane (Compound No. 46)

This compound was prepared by the same method as described in example 39 from N-3-azabicyclo[3.1.0]hex-6-yl-N'-isoquinolin-5-ylurea and 2-trifluoromethyl benzene sulfonyl chloride.

$^1$H NMR (DMSO- $d_6$): $\delta$ 1.80-1.87 (2H, m); 2.46-2.60 (IH, m); 3.30-3.46 (2H, m); 3.61 (2H, m, $J = 9.6$ Hz); 6.83 (IH, s); 7.60 (IH, t, $J = 7.8$ Hz); 7.76 (IH, d, $J = 7.8$ Hz); 7.85-7.98 (3H, m); 8.02-8.12 (2H, m); 8.20 (IH, d, $J = 7.5$ Hz); 8.53 (IH, d, $J = 5.7$ Hz); 8.62 (IH, s); 9.27 (IH, s);

IR (KBr) (cm$^{-1}$): 3374, 1651, 1552, 1308, 1170, 1118, 616; MS (M$^+$+): 477.25; m.p. 193 0°C.

Example 47: Preparation of 1$\alpha$, 5$\alpha$, 6$\alpha$-[(6-(5-isoquinolylaminocarboxamido)-3-(2-fluorophenyl)sulfonyl]3-azabicyclo[3.1.0]hexane (Compound No. 47)
This compound was prepared by the same method as described in example 39 from N-3-azabicyclo[3.1.0]hex-6-yl-N'-isoquinolin-5-ylurea and 2-fluoro benzene sulfonyl chloride.

$^1$H NMR (DMSO- $d_6$): $\delta$ 1.74-1.83 (2H, m); 2.33-2.40 (IH, m); 3.24-3.38 (2H, m); 3.56 (2H, m, $J = 9.6$ Hz); 6.80 (IH, s); 7.42-7.64 (3H, m); 7.72-7.90 (4H, m); 8.19 (IH, d, $J = 8.1$ Hz); 8.53 (IH, m); 10.37 (IH, f); 6.64 (IH, f); 9.23 (IH, f); 9.25 (IH, f); 9.26 (IH, f); 9.27 (IH, f); 15.85 (IH, f); 3318, 1686, 1644, 1474, 1338, 1163, 614; M S (M$^+$): 427.47; m. p. 193-195 °C.

Example 48: Preparation of $\alpha$, $\alpha'$, $\alpha''$, $\alpha'''$, $\alpha''''$-[6-(5-isoquinolylaminocarboxamido)-3-(2-chlorophenyl)sulfonyl]-3-azabicyclo[3.1.0]hexane (Compound No. 48)

This compound was prepared by the same method as described in example 39 from N-3-azabicyclo[3.1.0]hex-6-yl-N'-isoquinolin-5-ylurea and 2-chloro benzene sulfonyl chloride.

$^1$H NMR (DMSO- $d_6$): $\delta$ 1.78-1.86 (2H, m); 2.42-2.49 (IH, m); 3.35-3.46 (2H, m); 3.57 (2H, d, $J = 9.1$ Hz); 6.83 (IH, s); 7.55-7.65 (2H, m); 7.66-7.80 (3H, m); 7.87 (IH, d, $J = 6.3$ Hz); 8.00 (IH, d, $J = 8.1$ Hz); 8.21 (IH, d, $J = 7.2$ Hz); 8.53 (IH, d, $J = 5.7$ Hz); 8.62 (IH, s); 9.28 (IH, s); IR (KBr) (cm$^{-1}$): 3295, 1645, 1580, 1569, 1345, 1157, 1109, 731, 621; M S (M$^+$): 443.38; m. p. 206-208 °C.

Example 49: Preparation of $\alpha$, $\alpha'$, $\alpha''$, $\alpha'''$, $\alpha''''$-[6-(5-isoquinolylaminocarboxamido)-3-(2-bromophenyl)sulfonyl]-3-azabicyclo[3.1.0]hexane (Compound No. 49)

This compound was prepared by the same method as described in example 39 from N-3-azabicyclo[3.1.0]hex-6-yl-N'-isoquinolin-5-ylurea and 2-bromo benzene sulfonyl chloride.

$^1$H NMR (DMSO- $d_6$): $\delta$ 1.70-1.78 (2H, m); 2.36-2.44 (IH, m); 3.09 (2H, m, $J = 6.6$ Hz); 3.53 (2H, d, $J = 9.3$ Hz); 6.78 (IH, s); 7.54-7.90 (8H, m); 8.15-8.24 (IH, m); 8.50-8.56 (IH, m); 8.58 (IH, s); 9.27 (IH, s); IR (KBr) (cm$^{-1}$): 3367, 1655, 1552, 1330, 1308, 1168, 615; M S (M$^+$): 509.42; m. p. 184-186 °C.

Example 50: Preparation of $\alpha$, $\alpha'$, $\alpha''$, $\alpha'''$, $\alpha''''$-[(5-isoquinolyaminocarboxamido)-3-(4-bromophenyl)sulfonyl]-3-azabicyclo[3.1.0]hexane (Compound No. 50)

This compound was prepared by the same method as described in example 39 from N-3-azabicyclo[3.1.0]hex-6-yl-N'-isoquinolin-5-ylurea and benzene sulfonyl chloride.

$^1$H NMR (DMSO- $d_6$): $\delta$ 1.70-1.78 (2H, m); 2.36-2.44 (IH, m); 3.09 (2H, m, $J = 6.6$ Hz); 3.53 (2H, d, $J = 9.3$ Hz); 6.78 (IH, s); 7.54-7.90 (8H, m); 8.15-8.24 (IH, m); 8.50-8.56 (IH, m); 8.58 (IH, s); 9.27 (IH, s); IR (KBr) (cm$^{-1}$): 3367, 1655, 1552, 1330, 1308, 1168, 615; M S (M$^+$): 495.42; m. p. 184-186 °C.
This compound was prepared by the same method as described in example 39 from N-3-azabicyclo[3.1.0]hex-6-yl-N'-isoquinolin-5-ylurea and 4-bromo benzene sulfonyl chloride,

\[ 1^1 \text{H NMR (DMSO-} d_6\text{): } \delta 1.71-1.79 (2H, m); 2.39-2.46 (IH, m); 3.11 (2H, d, J = 9.0 Hz); 3.53 (2H, d, J = 9.0 Hz); 6.81 (IH, s); 7.60 (IH, t, J = 8.4 Hz); 7.70-7.90 (6H, m); 8.19 (IH, d, J = 7.5 Hz); 8.54 (IH, s); 8.61 (IH, s); 7.92 (IH, s); IR (KBr) (cm\(^{-1}\)): 3309, 1642, 1577, 1346, 1162, 741, 623; MS (M+1): 487.43; m.p. 227-229 0°C.

**Example 52:** Preparation of 1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(4-iodophenyl)sulfonyl]-3-azabicyclo [3.1.0]hexane (Compound No. 52)

This compound was prepared by the same method as described in example 39 from N-3-azabicyclo[3.1.0]hex-6-yl-N'-isoquinolin-5-ylurea and 4-iodo benzene sulfonyl chloride,

\[ 1^1 \text{H NMR (DMSO-} d_6\text{): } \delta 1.70-1.78 (2H, m); 2.39-2.46 (IH, m); 3.04-3.16 (2H, m); 3.46-3.58 (2H, m); 6.80 (IH, s); 7.55 (2H, d, J = 7.2 Hz); 7.50-7.64 (IH, m); 7.74-7.81 (IH, m); 7.82-7.89 (IH, m); 8.05 (IH, d, J = 6.6 Hz); 8.14-8.24 (IH, m); 8.50-8.57 (IH, m); 8.59 (IH, s); 9.27 (IH, s); IR (KBr) (cm\(^{-1}\)): 32996, 1645, 1569, 1580, 1345, 1109, 731, 621; MS (M+1): 535.30; m.p. 222-224 0°C.

**Example 53:** Preparation of 1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(4-methylphenyl)sulfonyl]-3-azabicyclo [3.1.0]hexane (Compound No. 53)

This compound was prepared by the same method as described in example 39 from N-3-azabicyclo[3.1.0]hex-6-yl-N'-isoquinolin-5-ylurea and 4-methyl benzene sulfonyl chloride,

\[ 1^1 \text{H NMR (DMSO-} d_6\text{): } \delta 1.64-1.76 (2H, m); 2.32-2.46 (IH, m); 2.42 (3H, s) 3.00-3.10 (2H, m); 3.42-3.54 (2H, m); 5.70-5.80 (IH, m); 6.79 (IH, s); 7.40-7.90 (6H, m); 8.14-8.24 (IH, m); 8.53 (IH, d, J = 5.7 Hz); 8.59 (IH, s); 9.27 (IH, s); IR (KBr) (cm\(^{-1}\)): 3308, 1642, 1577, 1346, 1163, 1104, 741, 623; MS (M+1): 423.44; m.p. 203-205 0°C.

**Example 54:** Preparation of 1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(4-bromobenzoyl)]-3-azabicyclo [3.1.0]hexane (Compound No. 54)

This compound was prepared by the same method as described in example 39 from N-3-azabicyclo[3.1.0]hex-6-yl-N'-isoquinolin-5-ylurea and 4-bromo benzoyl chloride,

\[ 1^1 \text{H NMR (CDCl}_3\text{): } \delta 1.712-1.84 (2H, m); 2.32-2.41 (IH, m); 3.64-3.75 (2H, m); 3.98-4.08 (2H, m); 6.85 (IH, s); 7.39-7.48 (2H, m); 7.56-7.69 (3H, m); 7.64-7.80 (IH, m); 7.84-7.91 (IH, m); 8.16-8.24 (IH, m); 8.50-8.55 (IH, m); 8.60 (IH, s); 9.28 (IH, s); MS (M+1): 453.52; IR (KBr) (cm\(^{-1}\)): 3436, 3330, 3291, 1644, 1584, 1255, 830; m.p. 230-233 0°C.

**Example 55:** Preparation of 1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(4-chlorobenzoyl)]-3-azabicyclo [3.1.0]hexane (Compound No. 55)
This compound was prepared by the same method as described in example 39 from N-3-
azabicyclo[3.1.0]hex-6-yl-N'-isoquinolin-5-ylurea and 4-chloro benzoyl chloride as off-white
solid.

1H NMR (DMSO- d6): δ 1.79 (2H, m); 2.36 (IH, m); 3.43-3.50 (2H, t); 3.69 (IH, m);
3.99-4.04 (IH, d, J = 12 Hz); 6.94 (IH, m); 7.51 (4H, s); 7.56-7.62 (IH, t, J = 8.1Hz); 7.74-7.76
(2H, m); 7.89-7.91 (IH, d, J = 5.1 Hz); 8.19-8.21 (IH, d, J = 8.1Hz); 8.51-8.52 (IH, d,
J = 5.4Hz); 8.66 (IH, bs); 9.26 (IH, bs); IR (KBr) (cm⁻¹): 3435, 3292, 1627, 1255, 651; MS

Example 56: Preparation of 1α, 5α, 6α-r6-(5-isoquinolylaminocarboxamido)-3-(3-
fluorobenzoyl)-3-azabicyclo [3.1.0]hexane (Compound No. 56)

This compound was prepared by the same method as described in example 39 from N-3-
azabicyclo[3.1.0]hex-6-yl-N'-isoquinolin-5-ylurea and 3-fluoro benzoyl chloride as off-white
solid.

1H NMR (DMSO- d6): δ 1.80 (2H, m); 2.38 (IH, m); 3.41-3.51 (2H, t); 3.70 (IH,m); 3.99-
4.03 (IH, d, J = 11.7 Hz); 7.01(1H, bs); 7.31 (3H, m); 7.49 (IH, t); 1.51-1.62 (IH, t, J = 7.8
Hz); 7.74-7.76 (2H, m); 7.90-7.91(1H, d, J = 5.1 Hz); 8.19(1H, d); 8.51-8.53 (IH, d,J =
5.1 Hz); 8.72 (IH, bs); 9.26 (IH, bs); IR (KBr) (cm⁻¹): 3434, 3291, 1644, 1255, 652;
MS (M⁺+I): 391.33.

Example 57: Preparation of 1α, 5α, 6α-6-(5-isoquinolylaminocarboxamido)-3-(2-
bromobenzoyl)-3-azabicyclo [3.1.0]hexane (Compound No. 57)

This compound was prepared by the same method as described in example 39 from N-3-
azabicyclo[3.1.0]hex-6-yl-N'-isoquinolin-5-ylurea and 2-bromo benzoyl chloride as a pale
yellow solid.

1H NMR (DMSO- d6): δ 1.78-1.84 (2H, m); 3.1 1-3.15 (IH, m); 3.44-3.52 (3H, m); 3.91-3.95(1H,
d, J = 12Hz); 6.86 (IH, bs); 7.38 (2H, t); 7.45-7.49 (IH, t, J = 6.8 Hz); 7.57-7.62(1H, t, J = 7.7
Hz); 7.67-7.70 (IH, d, J = 7.5 Hz); 7.74-7.77 (IH, d, J = 8.1 Hz); 7.86-7.88(1H, d,J = 6 Hz);
8.2O-8.23(1H, d, J = 7.5Hz); 8.52-8.54 (IH, d, J = 6Hz); 8.60 (IH, s); 9.27 (IH, brs); IR (KBr)
(cm⁻¹): 3366, 1619, 1547, 1236, 764; MS (M⁺+I): 451.35.

Example 58: Preparation of 1α, 5α, 6α-6-(5-isoquinolylaminocarboxamido)-3-(2-
fluorobenzoyl)-3-azabicyclo [3.1.0]hexane (Compound No. 58)

This compound was prepared by the same method as described in example 39 from N-3-
azabicyclo[3.1.0]hex-6-yl-N'-isoquinolin-5-ylurea and 2-fluorobenzoyl chloride as an off-white
solid.

1H NMR (DMSO- d6): δ 1.78-1.83 (2H, m); 2.37 (IH, m); 3.22 (IH, m); 3.49-3.53 (2H, m);
3.95-3.99 (IH, d, J = 12Hz); 6.85 (IH, bs); 7.28-7.3 1(2H, m); 7.40-7.42 (IH, t); 7.50-7.52 (IH,
Example 59: Preparation of 1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2-chlorobenzoyl)]-3-azabicyclo[3.1.0]hex-6-yl-N′-isoquinolin-5-ylurea (Compound No. 59)

This compound was prepared by the same method as described in example 39 from N-3-azabicyclo[3.1.0]hex-6-yl-N′-isoquinolin-5-ylurea and 2-chloro benzoyl chloride as a pale yellow solid.

1H NMR (DMSO- d6): δ 1.77-1.84 (2H, m); 2.25-2.38 (IH, m); 3.16(1H, m); 3.51-3.68(2H, m); 3.93 (IH, d); 6.87(1H, brs); 7.42-7.53 (5H, m); 7.75-7.87 (2H, m); 8.21 (IH, brs); 8.53-8.62 (2H, m); 9.27 (IH, brs); IR (KBr) (cm⁻¹): 3355, 1621, 1549, 1316, 754; MS (M+): 441.24

Example 60: Preparation of 1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(4-methylbenzoyl)]-3-azabicyclo[3.1.0]hexane (Compound No. 60)

This compound was prepared by the same method as described in example 39 from N-3-azabicyclo[3.1.0]hex-6-yl-N′-isoquinolin-5-ylurea and 4-methyl benzoyl chloride as a pale yellow solid.

1H NMR (DMSO- d6): δ 1.78 (2H, m); 2.33 (4H, s); 3.48 (2H, m); 3.68 (IH, m); 4.01-4.06 (IH, d, J=12 Hz); 6.84 (IH, s); 7.23-7.25 (2H, d, J = 6.6Hz); 7.35-7.38 (2H, d, J = 7.8 Hz); 7.57-7.62 (IH, t, J = 7.8Hz); 7.74-7.77 (IH, d, J = 7.5Hz); 7.85-7.87 (IH, d, J = 5.7Hz); 8.18(1H, d); 8.51-8.53(1H, d,J = 5.1Hz); 8.59(1H, s); 9.27(1H, bs). IR (KBr) (cm⁻¹): 3292, 1643, 1255, 829, 641; MS (M+): 387.21.

Example 61: Preparation of 1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2-trifluoromethyl) benzoyl]-3-azabicyclo[3.1.0]hexane (Compound No. 61)

This compound was prepared by the same method as described in example 39 from N-3-azabicyclo[3.1.0]hex-6-yl-N′-isoquinolin-5-ylurea and 2-(trifluoromethyl) benzoyl chloride a white solid.

1H NMR (DMSO- d6): δ 1.76-1.82 (2H, m); 2.35-2.40 (IH, m); 3.15-3.28 (2H, m); 3.94 (2H,m); 6.89 (IH, bs); 7.65-7.76 (7H, m); 8.21(1H, m); 8.53-8.63(2H, m); 9.29 (IH, bs). IR (KBr) (cm⁻¹): 3336,1621,1549,1316,754; MS (M+): 441.24
Example 62: Preparation of 1α, 5α, 6α-[6-(5-isoquinolyaminocarboxamido)-3-(4-trifluoromethylbenzoyl)-3-azabicyclo[3.1.0]hex-6-yl-N′-isoquinolin-5-ylurea] and 4-(trifluoromethyl) benzoyl chloride.

This compound was prepared by the same method as described in example 39 from N-3-azabicyclo[3.1.0]hex-6-yl-N′-isoquinolin-5-ylurea and 4-(trifluoromethyl) benzoyl chloride.

1H NMR (DMSO-d6, δ = 1.80 (2H, m); 2.40 (IH, m); 3.43 (IH, m); 3.51-3.54 (IH, d, J = 10.2 Hz); 3.68 (1H, m); 4.00-4.04 (1H, d, J = 12.3 Hz); 6.87 (1H, s); 7.57-7.61 (1H, t, J = 7.2 Hz); 7.68-7.67 (6H, m); 8.19 (1H, m); 8.51-8.53 (IH, d, J = 5.7 Hz); 8.60 (1H, s); 9.27 (1H, bs); IR (KBr) (cm⁻¹): 3292, 1643, 1582, 1337, 1243, 1044, 828, 748, 727, 748, 727 cm⁻¹.

Example 63: Preparation of 1α, 5α, 6α-f6-(5-isoquinolyaminocarboxamido)-3-(4-bromobenzoyl)-3-azabicyclo[3.1.0]hexane (Compound No. 63)

This compound was prepared by the same method as described in example 39 from N-3-azabicyclo[3.1.0]hex-6-yl-N′-isoquinolin-5-ylurea and 4-bromo benzoyl chloride.

1H NMR (CDCl₃, δ = 1.712-1.84 (2H, m); 2.32-2.41 (IH, m); 3.64-3.75 (2H, m); 3.98-4.08 (2H, m); 6.85 (1H, s); 7.39-7.48 (2H, m); 7.56-7.69 (3H, m); 7.64-7.80 (IH, m); 7.84-7.91 (IH, m); 8.16-8.24 (IH, m); 8.50-8.55 (IH, m); 8.60 (1H, s); 9.28 (1H, s); MS (M⁺+H): 453.52; IR (KBr) (cm⁻¹): 3436, 3330, 3291, 1644, 1584, 1255, 830 m.p. 230-233 °C.

Example 64: Preparation of 1α, 5α, 6α-r6-(5-isoquinolyaminocarboxamido)-3-(4-benzylbenzoyl)-3-azabicyclo[3.1.0]hexane (Compound No. 64)

This compound was prepared by the same method as described in example 39 from N-3-azabicyclo[3.1.0]hex-6-yl-N′-isoquinolin-5-ylurea and benzyl bromide.

IR (KBr): 3440, 2887, 1647, 1565, 1365, 1243, 1136, 1078, 995, 827, 748, 727 cm⁻¹.

1H-NMR (300 MHz, DMSO-d6, δ = 1.54 (s, 2H), 2.37 (d, 2H, J = 7.8 Hz), 2.89(s,1H,2.98 (d, 2H, J = 8.7 Hz), 3.55 (s, 2H), 6.69 (s, 1H), 7.27-7.32 (m, 5H), 7.60t, (IH, J = 7.5 Hz), 7.73 (d, IH, J = 7.5 Hz), 7.86 (d, IH, J = 5.4 Hz), 8.23(d, IH, J = 7.5 Hz), 8.52s (2H), 9.25 (s, IH); m.p.184-186°C.

Example 65: Preparation of 1α, 5α, 6α-[6-(5-isoquinolyaminocarboxamido)-3-(4-chlorobenzyl)-3-azabicyclo[3.1.0]hexane (Compound No. 65)

This compound was prepared by the same method as described in example 39 from N-3-azabicyclo[3.1.0]hex-6-yl-N′-isoquinolin-5-ylurea and 4-chloro benzyl bromide.

IR (KBr): 3355, 3302, 2907, 2795, 1651, 1570, 1347, 1265, 1090, 828, 640 cm⁻¹.

1H-NMR (300 MHz, DMSO-d6, δ = 1.55 (s, 2H), 2.38 (d, 2H, J = 8.1 Hz), 2.88(s,1H,2.98 (d, 2H, J = 8.7 Hz), 3.55 (s, 2H), 6.70 (s, 1H), 7.29 (d, 2H, J = 8.4 Hz), 7.32 (d, 2H, J = 8.1 Hz), 7.59(t, IH, J = 7.8 Hz), 7.74 (d, IH, J = 8.1 Hz), 7.87 (d, IH, J = 6.0 Hz), 8.24(d, IH, J = 6.9 Hz), 8.52(d, 2H, J = 6.0 Hz), 9.27 (s, IH); m.p.184-186°C.
Example 66: Preparation of 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(4-trifluoromethylbenzyl)]-3-azabicyclo[3.1.0]hexane (Compound No. 66)

This compound was prepared by the same method as described in example 39 from N-3-azabicyclo[3.1.0]hex-6-yl-N\\-isoquinolin-5-ylurea and 4-(trifluoromethyl) benzyl bromide.

IR (KBr): 3385, 3348, 1648, 1495, 1365, 1249, 1080, 995, 827, 748, 525 cm⁻¹.

¹H-NMR (300 MHz, DMSO-D₆): δ 1.56 (s, 2H), 2.41 (d, 2H, J = 8.4 Hz), 2.90 (s, 1H), 3.00 (d, 2H, J = 8.7 Hz), 6.07 (s, 1H), 7.49-7.73 (m, 6H), 7.87 (s, 1H), 8.23 (s, 1H), 8.53 (s, 2H), 9.26 (s, 1H); m.p-175-177°C

Example 67: Preparation of 1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-phenyl-3-azabicyclo[3.1.0]hexane (Compound No. 67)

Step 1: Preparation of 1-phenyl-1H-pyrrole-2,5-dione

To the solution of maleic anhydride (5.2 g, 53.76 mmol) in benzene (100 ml), aniline was added drop wise at room temperature and stirred for 2-3hrs. The solid precipitated was filtered and taken in acetic anhydride (70 ml). To that solution sodium acetate (6.6 g, 80.64 mmol) was added and heated for 1-2hrs at 80-90°C. The reaction mixture was cooled to room temperature and poured in ice water (700 ml). The solid precipitated was filtered, washed with water & dried to afford 5.4 g of product as white solid.; ¹H-NMR (300 MHz, DMSO-D₆): δ 7.19 (s, 2H), 7.27-7.51 (m, 5H).

Step 2: Preparation of(1R,5S,6s)-6-nitro-3-phenyl-3-azabicyclo[3.1.0]hexane-2,4-dione

To the mixture of 1-phenyl-1H-pyrrole-2,5-dione (5.0g, 28.99 mmol), celite (5.0g), and molecular sieves (2.5g) in N,N-dimethyl formamide (50 ml), bromonitromethane (8.1g, 57.8 mmol) was added at -20°C. Thereafter potassium carbonate (8.0g, 57.8 mmol) was added portion wise at -20°C. The reaction mixture was filtered through celite bed. The filtrate was diluted with water (500ml) and extracted by ethyl acetate (3x100ml).the organic volume was concentrated and purified by silica gel column chromatography using 10% ethyl acetate in petroleum ether to afford the product (700mg); ¹H-NMR (300 MHz, CDCl₃): δ 3.53 (s, 2H); 4.82 (s, 1H); 7.19-7.49 (m, 5H).

Step 3: Preparation of (1a, 5a, 6a)-6-nitro-3-phenyl-3-azabicyclo[3.1.0]hexane-2,4-dione

To the solution of (1α, 5α, 6α)-6-nitro-3-phenyl-3-azabicyclo[3.1.0]hexane-2,4-dione (700mg, 3.01 mmol) in tetrahydrofuran (30 ml), sodium borohydride (343mg, 9.05 mmol) was
added at -20°C. Then after boron trifluoride-ether complex (1.28g, 9.05mmol) was added slowly at -30°C. The reaction mixture was stirred at room temperature for 24 hrs. The reaction mixture was quenched by adding water (100ml) at 0-5°C. The organic mass was extracted by ethyl acetate (3x50ml). The organic volume was extracted over anhydrous sodium sulfate and concentrated under reduced pressure to afford the product as off-white solid (300mg).

$^1$H-NMR (300 MHz, DMSO-$d_6$): δ 2.90 (s, 2H); 3.28 (d, 2H, J = 9.9); 3.74 (s, 2H); 4.45 (s, IH); 6.54 (d, 2H, J = 8.1 Hz); 6.67 (t, IH, J = 6.9 Hz); 7.16 (t, 2H, J = 7.8 Hz).

**Step 4: Preparation of Ia, 5a, 6a-f-tertJ-butyloxy carbamoylJ5-phenylS-azabicyclo [3.1.0] hexane**

The suspension of 1α, 5α, 6α (1-6-nitro-3-phenyl-3-azabicyclo[3.1.0]hexane (300mg, 1.47mmol) and Raney nickel (60 mg) in methanol was hydrogenated in an aparr apparatus at 20-30 psi of H$_2$ for 1 hr. The reaction mixture was filtered through celite. To the filtrate boc anhydride (385mg, 1.76 mmol) and triethyl amine (0.5ml) was added and stirred at room temperature for 2 hrs. The crude product obtained after usual work up was purified through silica gel column using 10% ethyl acetate in petroleum ether. Yield=100mg

$^1$H-NMR (300 MHz, DMSO-$d_6$): δ 1.45 (s, 9H); 1.83 (s, 2H); 2.43 (s, IH); 3.26 (d, 2H, J = 8.4); 3.64 (d, 2H, J = 9.0 Hz); 4.72 (s, IH); 6.54 (d, 2H, J = 7.2 Hz); 6.67(brs, IH), 7.20 (m, 2H).

**Step 5: Preparation of Ia, 5a, 6a-[6-(5-isoquinolylaminocarboxamido)-3-phenyl]-3-azabicyclo [3.1.0] hexane**

To the solution of 1α, 5α, 6α-[6-(tert)-butyloxy carbamoyl]-3-phenyl-3-azabicyclo [3.1.0] hexane (100mg, 0.5747mmol) in ethyl acetate was added a solution of 15% HCl in ethyl acetate and stirred for 3-4 hours. The residue obtained after removal of solvent was taken in dimethyl sulfoxide (1ml) followed by addition of TEA (0.5ml) and 5-amino isoquinoline phenyl carbamate (150mg, 0.5747mmole) was added and stirred at room temperature for 2 hrs. Reaction mixture was poured on ice cold water. Solid precipitate out was filtered and leached in methanol to get pure product (30 mg) white solid.

IR (KBr) 3435, 3352, 2837, 1637, 1565, 1365, 1243, 1080, 995, 827, 748 cm$^{-1}$.

$^1$H-NMR (300 MHz, DMSO-d$_6$): δ 1.90 (s, 2H); 3.22 (d, 3H, J = 8.1Hz); 3.60 (d, 2H, J = 9.3 Hz); 6.55-6.63 (m, 3H); 6.88 (s, IH); 7.15(t, 2H, J = 7.5 Hz); 7.60 (t, IH, J = 8.1 Hz); 7.76 (d, IH, J = 8.1 Hz); 7.89 (d, IH, J = 5.4 Hz); 8.23(d, IH, J = 7.5 Hz); 8.54 (d,lIH, J = 6.0 Hz); 8.60(s, IH); 9.27 (s, IH); m.p is 225-227°C

Example 68: Preparation of N-P-O-trifluoromethylpyridin^vQl-S-azabicyclo1.0 1-hex-6-y1- N-isoquinolin-5-yl urea (Compound No. 68)

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To a stirred solution of 1-isoquinolin-7-yl-3-[3-(3-(trifluoromethyl)pyridin-2-yl)-3-
anazabicyclo[3.1.0]hex-6-yl]thiourea (1.0 equi), triethylamine in dry THF at 0°C was added 1.1-
thiocarbonyl diimidazole and stirred for 30-40 minutes. Then after a solution of isoquinolin-5-
amine (1.0 equi) in dry THF was added and stirred for 8-10 hrs. The solid residue obtained after
removal of solvent was subjected to column chromatography using mixture methanol and
chlorem as an eluent to afford the product as off white solid.

\(^{1}\)H-NMR (300 MHz, DMSO-d_6) \( \delta \) 1.92-2.13 (m, 2H), 2.64 (s, 1H), 3.59 (d, 2H, \( J = 10.5 \) Hz),
3.91-4.25 (m, 2H, \( J = 9.0 \) Hz), 6.85 (s, 1H), 7.70 (m, 3H), 7.95 (d, 1H, \( J = 9.3 \) Hz), 8.09 (d, 1H, \( J =
9.3 \) Hz), 8.33 (s, 1H), 8.52 (d, 1H, \( J = 5.7 \) Hz), 9.34 (s, 1H), 9.55 (s, 1H), 9.72 (s, 1H). IR (KBr)
3160, 2868, 1581, 1462, 3086
\( \delta \) 3330, 2968, 1581, 1462, 1384, 1260, 1167, 1111, 1092, 1018, 815, 759 cm\(^{-1}\). MS: [M+H]^+ = 430.23; m.p. is 191-192 °C

Example 69: Preparation of \( \sigma \), \( \alpha \)-[6-(5-isoquinolynylamino)carboxamido]-3-(3-chloropyrid-2-
yl)\]-3-azabicyclo [3.1.0] hexane (Compound No. 69).

A solution of \( \sigma \), \( \alpha \)-[6-amino-3-(3-chloropyrid-2-yl)]-3-azabicyclo [3.1.0] hexane (intermediate 7) (100mg, 0.465 mmol) and phenyl-N-(5-amino isoquinolin-5-yl) carbamate (127 mg, 0.51 mmol) in dimethyl sulfoxide (5.0 mL) was stirred at room temperature for 12-13 hrs. The reaction mixture was diluted with water (50 mL), extracted with ethyl acetate (3x25mL). The combined organic layers were washed with water and dried over anhydrous sodium sulfate. The residue obtained after removal of solvent was purified through silica gel column 2.0 \% methanol in chloroform as an eluent to obtain 38 mg of product as off white solid. IR (KBr):
3330, 2968, 1581, 1462, 1384, 1260, 1167, 1111, 1092, 1018, 815, 759 cm\(^{-1}\). \(^{1}\)H-NMR (300 MHz, CDCl_3): 1.90 (s, 2H), 2.62 (s, 1H), 3.62 (d, 2H, \( J = 9.6 \) Hz), 4.29 (d, 2H, \( J = 10.8 \) Hz), 6.73 (m, 1H), 7.65 (m, 2H), 7.90 (m, 1H), 8.08 (m, 2H), 8.47 (d, 1H, \( J = 6.0 \) Hz), 9.23 (bs, 1H). m.p. 245-247 °C (decomposed)

Example 70: Preparation of \( \sigma \), \( \alpha \)-[6-(5-isoquinolynylamino)carboxamido]-3-(5-
trifluororornethylpyrid-2-yl)1-3-azabicyclo [3.1.0] hexane (Compound No. 70).

A solution of \( \sigma \), \( \alpha \)-[6-amino-3-(5-trifluoromethyl pyrid-2-yl)]-3-azabicyclo [3.1.0] hexane (intermediate 8) (100 mg, 0.401 mmol) and phenyl-N-(5-amino isoquinolin-5-yl) carbamate (127 mg, 0.51 mmol) in dimethyl sulfoxide (5.0 mL) was stirred at room temperature for 12-13 hrs. The reaction mixture was diluted with water (50 mL), extracted with ethyl acetate (3 x 25mL). The combined organic layers were washed with water and dried over
anhydrous sodium sulfate. The residue obtained after removal of solvent was purified through silica gel column 2.0 % methanol in chloroform as an eluent to obtain 50 mg of product as an off-white solid. IR (KBr): 3334, 2971, 1671, 1586, 1432, 1321, 1245, 1041, 793 cm⁻¹. H-NMR (300 MHz, CDCl₃): 1.95 (s, 2H), 2.40 (s, IH), 3.55 (d, 2H, J = 9.6 Hz), 3.82 (d, 2H, J = 10.8 Hz), 6.42 (bs, IH), 6.62 (d, IH, J = 8.7 Hz), 6.90 (s, IH), 7.60 (m, IH), 7.77 (m, 2H), 7.90 (s, IH), 8.23 (m, IH), 8.39 (bs, IH), 8.55 (d, HH, J = 6.0 Hz), 8.62 (s, IH), 9.27 (s, IH). m.p. 195-197 °C (decomposed)

Example 71: Preparation of 1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(3-trifluoromethylpyrid-2-yl)]-3-azabicyclo[3.1.0] hexane (Compound No. 71)

A solution of 1α, 5α, 6α-[6-amino-3-(3-trifluoromethyl pyrid-2-yl)]-3-azabicyclo[3.1.0] hexane (intermediate 9) (100 mg, 0.401 mmol), phenyl-N-(5-amino isoquinolin-5-yl) carbamate (127 mg, 0.51 16 mmol) in dimethyl sulfoxide (5.0 mL) was stirred at room temperature for 12-13 hrs. The reaction mixture was diluted with water (50 mL), extracted with ethyl acetate (3 x 25mL). The combined organic layers were washed with water and dried over anhydrous sodium sulfate. The residue obtained after removal of solvent was purified through silica gel column 2.0 % methanol in chloroform as an eluent to get 50 mg of product as off white solid. IR (KBr): 2971, 1669, 1578, 1428, 1321, 1245, 1041, 793 cm⁻¹. H-NMR (300 MHz, CDCl₃): 1.87 (s, 2H), 2.38 (s, IH), 3.61 (d, 2H, J = 9.6 Hz), 3.96 (d, 2H, J = 10.8 Hz), 6.86 (bs, 2H), 7.60 (t, IH, J = 8.7 Hz), 7.70 (d, IH, J = 7.8 Hz), 7.89 (d, IH, J = 5.7 Hz), 7.96 (d, 2H, J = 7.8 Hz), 8.24 (d, IH, J = 6.3 Hz), 8.37 (bs, IH), 8.54 (d, IH, J = 6.0 Hz), 8.61 (bs, IH), 9.27 (s, IH). m.p. 201-203 °C.

Example 72: Preparation of 1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(3-chloro-5-trifluoromethylpyrid-2-yl)]-3-azabicyclo[3.1.0] hexane (Compound No. 72)

A solution of 1α, 5α, 6α-[6-amino-3-(2-chloro-5-trifluoromethyl pyrid-2-yl)]-3-azabicyclo[3.1.0] hexane (intermediate 10) (100 mg, 0.40 mmol), phenyl-N-(5-amino isoquinolin-5-yl) carbamate (127 mg, 0.51 16 mmol) in dimethyl sulfoxide (5.0 mL) was stirred at room temperature for 12-13 hrs. The reaction mixture was diluted with water (50 mL), extracted with ethyl acetate (3 x 25mL). The combined organic layers were washed with water and dried over anhydrous sodium sulfate. The residue obtained after removal of solvent was purified through silica gel column 2.0 % methanol in chloroform as an eluent to get 50 mg of product as off white solid. m.p. 191-196 °C. IR (KBr): 2971, 1669, 1578, 1428, 1325, 1249,
1033, 795 cm⁻¹. ¹H-NMR (300 MHz, CDCl₃): 1.91 (s, 2H), 2.42 (s, 1H), 3.80 (d, 2H, J = 9.6 Hz), 4.25 (d, 2H, J = 10.8 Hz), 6.88 (t, 1H), 7.60 (s, 2H), 7.99 (bs, 1H), 8.23 (d, 1H, J = 6.3 Hz), 8.41 (bs, 1H), 8.54 (d, 1H, J = 6.0 Hz), 8.61 (bs, 1H), 9.27 (s, 1H). [M-1] + 446

Example 73: Preparation of 1α, 5α, 6α-[6-(5-isoquinolylaminocarboxylamido)-3-(3-nitro pyrid-2-yl)]-3-azabicyclo[3.1.0]hexane (Compound No. 73)

A solution of 1α, 5α, 6α-[6-amino-3-(3-nitro pyrid-2-yl)]-3-azabicyclo[3.1.0]hexane (intermediate 11) (100 mg, 0.45 mmol), phenyl-N-(5-amino isoquinolin-5-yl) carbamate (127 mg, 0.51 mmol) in dimethyl sulfoxide (5.0 mL) was stirred at room temperature for 12-13 hrs. The reaction mixture was diluted with water (50 mL), extracted with ethyl acetate (3 x 25 mL). The combined organic layers were washed with water and dried over anhydrous sodium sulfate. The residue obtained after removal of solvent was purified through silica gel column 2.0 % methanol in chloroform as an eluent to get 50 mg of product as off white solid. IR (KBr): 2981, 1672, 1532, 1433, 1352, 1249, 1033, 795 cm⁻¹. ¹H-NMR (300 MHz, CDCl₃): 1.95 (s, 2H), 2.73 (s, 1H), 3.66 (d, 2H, J = 9.6 Hz), 4.31 (d, 2H, J = 10.8 Hz), 5.50 (brs, 1H), 6.68 (m, 1H), 7.53 (d, 1H, J = 7.80), 7.64 (t, 1H, J = 7.2 Hz), 7.79 (d, 1H, J = 7.8 Hz), 7.96 (brs, 1H), 8.08 (d, 1H, J = 3.3 Hz), 8.25 (d, 1H, J = 7.5 Hz), 8.47 (d, 1H, J = 6.0 Hz), 9.23 (s, 1H). [M-1] + 389 m.p. 162-164 °C.

Example 74: Preparation of 1α, 5α, 6α-[6-(5-isoquinolylaminocarboxylamido)-3-(4-t-butylbenzoyl)]-3-azabicyclo[3.1.0]hexane (Compound No. 74)

Step 1: Preparation of 1α, 5α, 6α-[6-(t-butylxy carbonyl)]-3-(4-t-butylbenzoyl)]-3-azabicyclo[3.1.0]hexane

To a well stirred solution of intermediate 12 (100 mg, 0.50 mmol) in benzene was added triethyl amine followed by addition of 4-t-butyl benzoic chloride (98 mg, 0.50 mmol). Reaction mixture was then heated to reflux for 7-8 hours. Reaction mixture was then cooled to room temperature, diluted with water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water and dried over anhydrous sodium sulfate, the residue obtained after removal of solvent was purified through silica gel column using 1% methanol in chloroform as an eluent to get 100 mg of product as yellow oil. ¹H-NMR (300 MHz, DMSOd₆): δ 1.32 (s, 9H), 1.44 (s, 9H), 1.60 (s, 2H), 2.61 (s, 1H), 3.42 (m, 2H), 3.78 (m, 2H) 6.19 (s, 1H), 7.45 (d, 2H, J = 8.1 Hz), 7.67 (d, 2H, J = 8.4 Hz).
Step 2: Preparation of Ia, 5a, 6a-[6-(5-isoquinolylaminocarboxamido)-3-(4-t-butylbenzoyl)l-3-azabicyclo [3.1.0] hexane

To a well stirred solution of lot, 5α, 6α-[6-(t-butyloxy carbonyl)-3-(4-t-butyl benzoyl)] -3-azabicyclo [3.1.0] hexane (100mg, 0.27 mmol) in ethyl acetate was added ethyl acetate saturated with HCl (5.0 mL) and stirred for 5-6 hours. The residue obtained treated with triethyl amine (1.0 mL) in dimethyl sulfoxide (5.0 mL) followed by addition of phenyl-N-(5-amino isoquinolin-5-yl) carbamate (73 mg, 0.2789 mmol). Reaction mixture was then stirred at room temperature for 5-6 hours, diluted with water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water and dried over anhydrous sodium sulfate, the residue obtained after removal of solvent was purified through silica gel column using 1% methanol in chloroform as an eluent to get 100 mg of product as off-white solid.

IR (KBr): 2972, 1679, 1549, 1439, 1359, 1252, 1009, 835, 795 cm⁻¹. ¹H-NMR (300 MHz, DMSO-d₆): δ 1.32 (s, 9H), δ 1.44 (s, 9H) 1.60 (s, 2H), 2.61 (s, 1H), 3.42 (m, 2H), 3.78 (m, 2H), 7.45 (d, 2H, J = 8.1 Hz), 7.67 (d, 2H, J = 8.4 Hz), 7.89 (d, 1H, J = 5.7 Hz), 7.99 (brs, 1H) 8.11 (d, 1H, J = 8.4 Hz), 8.23 (d, 1H, J = 6.3 Hz), 8.41 (bs, 1H), 8.54 (d, 1H, J = 6.0 Hz), 8.61 (s, 1H), 9.27 (s, 1H).[M-1]⁺: 427

Example 75: Preparation of 1-[3-(2,4-Difluorophenyl)-3-azabicvclo[3.1.0]hex-6-yl]-3-(2-methyl-1-oxo-1,2-dihydro isoquinolin-5-yl]urea (Compound No. 75)

Step 1: Preparation of 5-Nitro isochromen-1-one

A solution of 2-Methyl-3-nitro benzoic acid (5.08 g) in Dry DMF (40 mL) and DMF-dimethylacetal (10.01 g, 3 eq.) was refluxed for 22 h with stirring. After removal of the solvent, the residue was column chromatographed to obtain 1.62 g of the title compound in 30% yield. ¹H NMR (CDCl₃, 300 MHz): δ 7.38-7.45 (AB q, J = 6.0 Hz and 9.9 Hz, 2H); 7.68 (t, J = 7.5 Hz and 8.7 Hz, 1H); 8.50 (d, J = 7.8 Hz, 1H); 8.65 (d, J = 8.4 Hz, 1H).

Step 2: Preparation of 2-Methyl-5-nitro-2H-isooquinolin-1-one

A solution of 5-Nitro isochromen-1-one (0.6 g) and methylamine (40%, ImL) in methanol (15 mL) was refluxed for 1 h. After removal of the solvent, the residue was extracted with CH₂Cl₂-MeOH (95:5). The extract was washed with water, dried over Na₂SO₄ and evaporated to dryness to give 0.5 g of the title compound.
Step 3: Preparation of 2-Methyl-5-amino-2H-isouquinolin-1-one

A solution of 2-Methyl-5-nitro-2H-isouquinolin-1-one (0.5 g) in methanol (20 mL) containing Palladium on carbon (0.25 g, 50% moisture) was subjected to hydrogenation at 60 psi hydrogen pressure in a Parr apparatus. After completion of the reaction, the solution was filtered through celite and the filtrate was evaporated to dryness to give 0.25 g of the title compound. ¹H NMR (DMSO-d₆, 300 MHz): δ 3.46 (s, 3H); 5.65 (br s, 2H); 6.73 (d, J = 7.8 Hz, IH); 6.84 (d, J = 7.8 Hz, IH); 7.16 (t, J = 8.1 Hz, IH); 7.33 (d, J = 7.2 Hz, IH); 7.42 (d, J = 7.8 Hz, IH).

Step 4: Preparation of 1-[3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-methyl-1-oxo-1,2-dihydro isouquinolin-5-yl)-urea

To a solution of 2-Methyl-5-amino-2H-isouquinolin-1-one (0.25 g) in CH₂Cl₂ (30 mL) was added phenyl chloroformate (1 eq.) and stirred the reaction mixture at rt for 1 h. The solution was then adsorbed on silica gel and purified by column chromatography to give 0.1 g of (2-Methyl-1-oxo-1, 2-dihydro isouquinolin-5-yl)-carbamic acid phenyl ester. The above was then added to a solution of 3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-ylamine (0.067 g) and triethylamine (0.5 mL) in DMSO (5 mL) and stirred the reaction mixture at rt for 12 h. The reaction mixture was then quenched with water; the precipitate was filtered and washed with ethyl acetate (15 mL) to get 25 mg of the title compound as a white solid.

mp: 205-210°C; IR (KBr, cm⁻¹): 3382, 3295, 1714, 1639, 1626, 1607, 1591, 1517, 1360, 1242, 1209, 1135, 1071, 948, 850, 708; ¹H NMR (DMSO-d₆, 300 MHz): δ 1.80 (s, 2H); 2.59 (s, IH); 3.22 (d, J = 8.7 Hz, 2H); 3.49 (s, 3H); 3.66 (d, J = 8.1 Hz, 2H); 6.63 (d, J = 7.5 Hz, IH); 6.74 (br s, 2H); 6.90 (br t, IH); 7.10 (br t, IH); 7.38 (br t, IH); 7.51 (d, J = 7.2 Hz, IH); 7.87 (d, J = 7.8 Hz, IH); 8.08 (br d, IH); 8.28 (br s, IH).

Example 76: Screening for TRPV1 antagonist using ⁴⁵Ca 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 were diluted to appropriate final concentrations in assay buffer keeping
the final DMSO concentration between 0.1% and 0.55%. \( ^{45}\text{Ca} \) was used at a final concentration of 2.5 \( \mu \text{Ci/ml} \) (\( ^{45}\text{Ca} \), ICN). Assay buffer was composed of F-12 DMEM medium supplemented with 1.8 mM \( \text{CaCl}_2 \) (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, pH 7.5, 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 et.al. (See Toth A et. al, Life Sciences 73 p 487-498, 2003). Human TRPV1 expressing CHO cells were 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\(^\circ\)C in the presence of 5% \( \text{CO}_2 \). Cells were then washed twice with 200 \( \mu \text{l} \) of assay buffer and re-suspended in 144 \( \mu \text{l} \) of the same. Assay was carried out at 30\(^\circ\)C in total volume of 200 \( \mu \text{l} \). 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 \( \mu \text{l} \) of ice cold wash buffer 3X. The cells were lysed in 50 \( \mu \text{l} \) lysis buffer for 20 min. 40 \( \mu \text{l} \) of cell lysate was mixed with 150 \( \mu \text{l} \) 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 \( ^{45}\text{Ca} \) uptake values were normalized over basal \( ^{45}\text{Ca} \) value. Data was expressed as % inhibition of \( ^{45}\text{Ca} \) uptake by test compound with respect to maximum \( ^{45}\text{Ca} \) uptake induced by capsaicin alone. \( \text{IC}_{50} \) value was calculated from dose response curve by nonlinear regression analysis using GraphPadPRISM software.

The results summarized in the Table 2 and 3 below.

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Table 3

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We Claim:

1. A compound of general formula (I)

\[ \text{(I)} \]

or a prodrug thereof, a pharmaceutically acceptable salt thereof, an N-oxide thereof, an ester thereof, a solvate thereof, a tautomer thereof, a stereoisomer thereof or a polymorph thereof, wherein:

- \( X \) is O or S;
- \( R^1 \) is selected from

\[ \text{A}, \text{B}, \text{C}, \text{D} \]

wherein \( R^1 \) is linked to the main structure through any carbon atom in the ring and is optionally substituted with one or more \( R \) groups;

- each occurrence of \( R \) and \( R^6 \) is independently selected from hydrogen, nitro, cyano, formyl, acetyl, halogen, \(-\text{OR}^7\), \(-\text{SR}^7\), oxo, thio, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, a substituted or unsubstituted heterocyclic group, substituted or
unsubstituted heterocyclylalkyl, -C(O)R⁷, -C(O)O-R⁷, -C(O)NR⁷R⁸, -NR⁷R⁸, -S(O)₃⁻R⁷, -S(O)ₕ⁻NR⁷R⁸, and a protecting group;

each occurrence of R⁷ and R⁸ is independently selected from hydrogen, nitro, halo, cyano, -OR₃, -SR₃, oxo, thio, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, a substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, -C(O)R₃, -C(O)O-R₃, -C(O)NR₃R₄, -S(O)₃⁻R₃, -S(O)ₕ⁻NR₃R₄, -NR₃R₄, and a protecting group, or R⁷ and R⁸, when both are directly bound to the same nitrogen atom, are joined together with the nitrogen atom to which they are attached to form an optionally substituted 3 to 7 membered saturated or unsaturated cyclic ring, which optionally includes one or more heteroatoms selected from O, NR₃ and S;

each occurrence of R³ and R⁴ is independently selected from hydrogen, halogen, nitro, cyano, formyl, acetyl, oxo, thio, -C(O)-R⁵, -C(O)NR⁵R⁶, -S(O)₃⁻R⁵, -S(O)ₕ⁻NR⁵R⁶, -NR⁵R⁶, -OR⁵, -SR⁵, a protecting group, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, and a substituted or unsubstituted heteroarylalkyl;

each occurrence of R⁵ and R⁶ is independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, or a substituted or unsubstituted heteroarylalkyl and a protecting group, or R⁵ and R⁶, when both are directly bound to the same nitrogen atom, are joined together with the nitrogen atom to which
they are attached to form an optionally substituted 3 to 7 membered saturated or unsaturated cyclic ring, which optionally includes one or more heteroatoms selected from O, NR\text{e} or S;

- each occurrence of R\text{e} is independently selected from hydrogen or substituted and unsubstituted alkyl,
  
- each occurrence of m is 0, 1, or 2;

- R\text{2} and R\text{3} are independently selected from hydrogen, hydroxy and C\text{1-6} alkyl; and

- each occurrence of R\text{4} and R\text{5} is independently selected from hydrogen, halogen, and alkyl, or when R\text{4} and R\text{5} are bound to the same carbon atom R\text{4} and R\text{5} together form an oxo or a thio group.

2. The compound according to claim 1, wherein R\text{6} is not a substituted or unsubstituted pyrimidine.

3. The compound according to claim 1 or 2, wherein R\text{6} is not a substituted or unsubstituted pyrrolidinealkyl.

4. The compound according to any one of claims 1-3, wherein R\text{1} is not a substituted or unsubstituted amino group.

5. The compound according to any one of claims 1-4, wherein R\text{1} is a substituted or unsubstituted quinoline, a substituted or unsubstituted quinolone, a substituted or unsubstituted isoquinoline or a substituted or unsubstituted isoquolinone.

6. The compound according to any one of claims 1-5, wherein R\text{1} is a substituted or unsubstituted quinoline or isoquinoline attached to the nitrogen at position 5, 6, 7, or 8.

7. The compound according to any one of claims 1-6, wherein R\text{1} is a substituted or unsubstituted isoquinoline attached to the nitrogen at position 5.

8. The compound according to any one of claims 1-7, wherein R\text{2}, R\text{3}, R\text{4} and R\text{5} are hydrogen.
9. The compound according to any one of claims 1-8, wherein X is O.

10. The compound according to any one of claims 1-9, wherein R^6 is substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, a substituted or unsubstituted heterocyclic group or substituted or unsubstituted heterocyclylalkyl, C(O)R^7, C(O)OR^7 or S(O)_nNR^7R^8.

11. The compound according to claim 10, wherein R^6 is substituted or unsubstituted heteroaryl, C(O)R^7, C(O)OR^7 or S(O)_nNR^7R^8.

12. A compound of general formula (Ia)

![Chemical structure](image)

(Ia)

a prodrug thereof, a pharmaceutically acceptable salt thereof, an N-oxide thereof, an ester thereof, a solvate thereof, a tautomer thereof, a stereoisomer thereof or a polymorph thereof wherein

- X is O or S;
- R^2, R^3, R^4 and R^5 are hydrogen;
- R^6 is substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, C(O)R^7, S(O)_2R^7 or COOR^7; and
- R^7 is substituted or unsubstituted aryl.

13. The compound according to claim 12, wherein substituent is selected from methyl, isopropyl, t-butyl, trifluoromethyl, bromo, chloro, fluoro, iodo, nitro, methoxy,
cyclopropylmethoxy, difluoromethoxy, trifluoromethoxy, acetylamino, trifluoroacetylamino and methanesulfonylamino.

14. The compound according to claim 12 or 13, wherein R^6 is substituted or unsubstituted aryl.

15. The compound according to any one of claims 14, wherein R^6 is selected from phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 2,6-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2,3,4-trifluorophenyl, 2,4,5-trifluorophenyl, 2,4,6-trifluorophenyl, 3,4,5-trifluorophenyl, 2-methoxyphenyl, 4-methoxyphenyl, 2-isopropylphenyl, 4-isopropylphenyl, 4-t-butyl phenyl, 2,4-dimethylphenyl, 2-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2,4-difluoromethoxyphenyl, 2-trifluoromethoxyphenyl, 2-fluoro-5-methylphenyl, 2-cyclopropylmethoxyphenyl, 2-fluoro-3-trifluoromethylphenyl, 2-trifluoromethylphenyl, 2-fluoro-5-trifluoromethylphenyl, 2-fluoro-4-difluoromethoxyphenyl, and 2-fluoro-4-methylphenyl.

16. The compound according to claim 12 or 13, wherein R^6 is arylalkyl.

17. The compound according to claim 16, wherein R^6 is selected from benzyl, 4-chlorobenzyl and 4-trifluoromethylbenzyl.

18. The compound according to claim 12 or 13, wherein R^6 is heteroaryl.

19. The compound according to any one of claims 18, wherein R^6 is selected from 3-(acetyl amino)pyridin-2-yl, 3-(trifluoroacetyl amino)pyridin-2-yl, 3-(methanesulphonylamino) pyrid-2-yl, 3, 5-dichloropyridin-2-yl, 3-bromopyridin-2-yl, 5-trifluoromethylpyrid-2-yl, 3-chloropyridyl-3-yl, 3-chloro,5-trifluoropyridyl-2-yl, 3-nitropyridyl-2-yl, 3-trifluoromethylpyrid-2-yl and 5-nitro-pyridin-2-yl.

20. The compound according to claim 12 or 13, wherein R^6 is -SO_2Ar.
21. The compound according to claim 20, wherein R₆ is selected from 4-chlorophenylsulfonyl, 4-trifluoromethylphenylsulfonyl, 4-fluorophenylsulfonyl, 2,6-dichlorophenylsulfonyl, 2,6-difluorophenylsulfonyl, 2,4-dibromophenylsulfonyl, 2,4-dichlorophenylsulfonyl, 2-trifluoromethyl phenylsulfonyl, 2-fluorophenylsulfonyl, 2-chlorophenylsulfonyl, 2-bromophenylsulfonyl, phenylsulfonyl, 4-bromophenylsulfonyl, 4-iodophenylsulfonyl and 4-methylphenylsulfonyl.

22. The compound according to claim 12 or 13, wherein R₆ is -COAr.

23. The compound according to claim 22, wherein R₆ is selected from 4-bromobenzoyl, 4-chlorobenzoyl, 3-fluorobenzoyl, 2-bromobenzoyl, 2-fluorobenzoyl, 2-chlorobenzoyl, 4-methyl benzoyl, 2-trifluoromethylbenzoyl, 4-trifluoromethyl benzoyl, 4-bromo benzoyl, 4-t-butylbenzoyl and 4-benzyl benzoyl.

24. A compound selected from:

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1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(3-trifluoroacetylaminopyrid-2-yl)]-3-azabicyclo [3.1.0]hexane,

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(3-methanesulphonylaminopyridyl -2-yl)]-3-azabicyclo [3.1.0]hexane,

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(3-(3,5-dichloro) pyrid -2-yl)]-3-azabicyclo [3.1.0]hexane,

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(3-bromopyrid -2-yl)]-3-azabicyclo [3.1.0]hexane,

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(5-nitropyrid -2-yl)]-3-azabicyclo [3.1.0]hexane,
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1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(4-isopropylphenyl)]-3-azabicyclo[3.1.0]hexane,
1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2-methoxyphenyl)]-3-azabicyclo[3.1.0]hexane,
1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(4-t-butylphenyl)]-3-azabicyclo[3.1.0]hexane,
1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2,4-dimethylphenyl)]-3-azabicyclo[3.1.0]hexane,
1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(4-trifluoromethyl)phenyl]-3-azabicyclo[3.1.0]hexane,
1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-((4-methoxy)phenyl)-3-azabicyclo[3.1.0]hexane,
1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2,4-difluoromethoxy)phenyl]-3-azabicyclo[3.1.0]hexane,
1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2,6-difluoro)phenyl]-3-azabicyclo[3.1.0]hexane,
1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2-fluoro-3-trifluoromethyl)phenyl]-3-azabicyclo [3.1.0]hexane,

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2-trifluoromethoxy)phenyl]-3-azabicyclo [3.1.0]hexane,

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2-trifluoromethyl)phenyl]-3-azabicyclo [3.1.0]hexane,

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-[2-fluoro-(5-trifluoromethyl)phenyl]]-3-azabicyclo [3.1.0]hexane,

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-[2-fluoro-(4-difluoromethoxy)phenyl]]-3-azabicyclo [3.1.0]hexane,

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2,3,4-trifluoro)phenyl]-3-azabicyclo [3.1.0]hexane,

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2,4,6-trifluorophenyl)phenyl]-3-azabicyclo [3.1.0]hexane,

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2,3-difluorophenyl)phenyl]-3-azabicyclo [3.1.0]hexane,

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2-fluoro-4-methylphenyl)phenyl]-3-azabicyclo [3.1.0]hexane,

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2-isopropyl)phenyl]-3-azabicyclo [3.1.0]hexane,

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2,4,6-trifluorophenyl)phenyl]-3-azabicyclo [3.1.0]hexane,

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2,4-difluorophenyl)phenyl]-3-azabicyclo [3.1.0]hexane trifluoroacetate salt,

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2,4-difluorophenyl)phenyl]-3-azabicyclo [3.1.0]hexane triflate salt,

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2,4-difluorophenyl)phenyl]-3-azabicyclo [3.1.0]hexane hydrochloride salt,

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2,4-difluorophenyl)phenyl]-3-azabicyclo [3.1.0]hexane mesylate salt,
1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(4-chlorophenyl)sulfonyl]-3-azabicyclo [3.1.0]hexane,

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-[4-(trifluoromethyl)phenyl)sulfonyl]-3-azabicyclo [3.1.0]hexane,

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(4-fluorophenyl)sulfonyl]-3-azabicyclo [3.1.0]hexane,

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2,6-dichlorophenyl)sulfonyl]-3-azabicyclo [3.1.0]hexane,

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2,6-difluorophenyl)sulfonyl]-3-azabicyclo [3.1.0]hexane,

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2-trifluoromethyl phenyl)sulfonyl]-3-azabicyclo [3.1.0]hexane,

1α, 5α, 6α-[6-(5-isoquinolylaminocarboxamido)-3-(2-chlorophenyl)sulfonyl]-3-azabicyclo [3.1.0]hexane,
$\alpha$, $5\alpha$, $6\alpha$-[6-(5-isoquinolylaminocarboxamido)-3-(4-chlorobenzoyl)]-3-azabicyclo[3.1.0]hexane,

$\alpha$, $5\alpha$, $6\alpha$-[6-(5-isoquinolylaminocarboxamido)-3-(3-fluorobenzoyl)]-3-azabicyclo[3.1.0]hexane,

$\alpha$, $5\alpha$, $6\alpha$-[6-(5-isoquinolylaminocarboxamido)-3-(2-bromobenzoyl)]-3-azabicyclo[3.1.0]hexane,

$\alpha$, $5\alpha$, $6\alpha$-[6-(5-isoquinolylaminocarboxamido)-3-(2-fluorobenzoyl)]-3-azabicyclo[3.1.0]hexane,

$\alpha$, $5\alpha$, $6\alpha$-[6-(5-isoquinolylaminocarboxamido)-3-(2-chlorobenzoyl)]-3-azabicyclo[3.1.0]hexane,

$\alpha$, $5\alpha$, $6\alpha$-[6-(5-isoquinolylaminocarboxamido)-3-(4-methylbenzoyl)]-3-azabicyclo[3.1.0]hexane,

$\alpha$, $5\alpha$, $6\alpha$-[6-(5-isoquinolylaminocarboxamido)-3-(4-trifluoromethyl)benzoyl]-3-azabicyclo[3.1.0]hexane,

$\alpha$, $5\alpha$, $6\alpha$-[6-(5-isoquinolylaminocarboxamido)-3-(2-trifluoromethyl)phenyl]-3-azabicyclo[3.1.0]hexane,

$\alpha$, $5\alpha$, $6\alpha$-[6-(5-isoquinolylaminocarboxamido)-3-(4-trifluoromethylbenzoyl)]-3-azabicyclo[3.1.0]hexane,

$\alpha$, $5\alpha$, $6\alpha$-[6-(5-isoquinolylaminocarboxamido)-3-(4-bromobenzoyl)]-3-azabicyclo[3.1.0]hexane,

$\alpha$, $5\alpha$, $6\alpha$-[6-(5-isoquinolylaminocarboxamido)-3-(4-benzylbenzoyl)]-3-azabicyclo[3.1.0]hexane,

$\alpha$, $5\alpha$, $6\alpha$-[6-(5-isoquinolylaminocarboxamido)-3-(4-chlorobenzyl)]-3-azabicyclo[3.1.0]hexane,
1α,5α,6α-[6-(5-isooquinolylaminocarboxamido)-3-(3-chloro-5-trifluoromethylpyrid-2-yl)]-3-azabicyclo [3.1.0] hexane,

1α, 5α, 6α-[6-(5-isooquinolylaminocarboxamido)-3-(3-chloro-5-trifluoromethyl pyrid-2-yl)]-3-azabicyclo [3.1.0] hexane,

1α, 5α, 6α-[6-(5-isooquinolylaminocarboxamido)-3-(3-nitro pyrid-2-yl)]-3-azabicyclo [3.1.0] hexane,

1α, 5α, 6α-[6-(5-isooquinolylaminocarboxamido)-3-(4-t-butylbenzoyl)]-3-azabicyclo [3.1.0] hexane, and

1-[3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-3-(2-methyl-1-oxo-1,2-dihydro isoquinolin-5-yl)-urea, or

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

25. The pharmaceutically acceptable salts according to any one of claims 1-24, wherein the salt is selected from inorganic acid addition salt selected from hydrochloride, sulphate, phosphate or nitrate; organic acid addition salts selected as acetate, trifluoroacetate, oxalate, maleate, triflate, tartarate, citrate, mesylate, succinate and cinnamate.

26. A pharmaceutical composition comprising a compound according to any one of claims 1-25 and one or more pharmaceutically acceptable carriers, diluents or excipients.

27. 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 1-26.

28. The method according to claim 27, wherein the vanilloid receptor mediated disease, disorder or syndrome is a pain or inflammatory disease, disorder or syndrome mediated by VR1.

29. The method according to claim 27 or 28, 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, arthalgia, 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, keratoacanthoma, alopecia, Meniere's disease, tinnitus, hyperacusis,
angery disorders and benign prostate hyperplasia.

30. A method of treating 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 1-26.

31. The method according to claim 30, wherein the pain is acute pain.

32. The method according to claim 30, wherein the pain is chronic pain.

33. The method according to claim 30, wherein the pain is post-operative pain.

34. 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 1-26.

35. 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 1-26.
36. 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 1-26.

37. 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 1-26.

38. 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 1-26.

39. 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 1-26.

40. A compound of formula 26,

\[
\text{\begin{figure}
\includegraphics[width=0.2\textwidth]{formula26.png}
\end{figure}}
\]

wherein

- R^4 and R^5 are hydrogen; and
- R^6 is selected from phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 2,6-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2,3,4-trifluorophenyl, 2,4,5-trifluorophenyl, 2,4,6-trifluorophenyl, 3,4,5-trifluorophenyl, 2-methoxyphenyl, 4-methoxyphenyl, 2-isopropylphenyl, 4-isopropylphenyl, 4^-butyl phenyl, 2,4-dimethylphenyl, 2-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-difluoromethoxyphenyl, 2-trifluoromethoxyphenyl, 2-fluoro-5-methylphenyl, 2-cyclopropylmethoxyphenyl, 2-fluoro-3-trifluoromethylphenyl, 2-trifluoromethoxyphenyl, 2-fluoro-5-trifluoromethylphenyl, 2-fluoro-4-trifluoromethoxyphenyl.
difluoromethoxyphenyl, 2-fluoro-4-methylphenyl, benzyl, 4-chlorobenzyl, A-
trifluoromethylbenzyl, 4-chlorophenylsulfonyl, 4-trifluoromethylphenylsulfonyl, A-
fluorophenylsulfonyl, 2,6-dichlorophenylsulfonyl, 2,6-difluorophenylsulfonyl, 2,4-
dibromophenylsulfonyl, 2,4-dichlorophenylsulfonyl, 2-trifluoromethyl phenylsulfonyl, 2-
fluorophenylsulfonyl, 2-chlorophenylsulfonyl, 2-bromophenylsulfonyl, phenylsulfonyl, A-
bromophenylsulfonyl, 4-iodophenylsulfonyl, 4-methylphenylsulfonyl, 4-bromobenzoyl, A-
chlorobenzoyl, 3-fluorobenzoyl, 2-bromobenzoyl, 2-fluorobenzoyl, 2-chlorobenzoyl, 4-methyl
benzoyl, 2-trifluoromethylbenzoyl, 4-trifluoromethyl benzoyl, 4-bromo benzoyl, 4-benzyl
benzoyl, 3-(acetyl amino)pyridin-2-yl, 3-(trifluoroacetyl amino)pyridin-2-yl, 3-
(methanesulphonylamino) pyrid-2-yl, 3, 5-dichloropyridin-2-yl, 3-bromopyridin-2-yl or 5-nitro-
pyridin-2-yl.

41. A compound of formula 6a,

\[
\begin{array}{c}
\text{PGHN} \\
\text{H} \\
\text{R}^4 \\
\text{R}^5 \\
\text{R}^6 \\
\text{R}^7 \\
\text{N} \\
\text{R}^8 \\
\text{6a}
\end{array}
\]

wherein

- \( R^4 \) and \( R^5 \) are hydrogen;
- \( R^6 \) is selected from phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,3-
difluorophenyl, 2,4-difluorophenyl, 2,6-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl,
2,3,4-trifluorophenyl, 2,4,5-trifluorophenyl, 2,4,6-trifluorophenyl, 3,4,5-trifluorophenyl, 2-
methoxyphenyl, 4-methoxyphenyl, 2-isopropylphenyl, 4-isopropylphenyl, 4-t-butyl phenyl, 2,4-
dimethylphenyl, 2-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-difluoromethoxyphenyl, 2-
trifluoromethoxyphenyl, 2-fluoro-5-methylphenyl, 2-cyclopropylmethoxyphenyl, 2-fluoro-3-
trifluoromethylphenyl, 2-trifluoromethoxyphenyl, 2-fluoro-5-trifluoromethylphenyl, 2-fluoro-4-
difluoromethoxyphenyl, 2-fluoro-4-methylphenyl, benzyl, 4-chlorobenzyl, A-
trifluoromethylbenzyl, 4-chlorophenylsulfonyl, 4-trifluoromethylphenylsulfonyl, A-
fluorophenylsulfonyl, 2,6-dichlorophenylsulfonyl, 2,6-difluorophenylsulfonyl, 2,4-
dibromophenylsulfonyl, 2,4-dichlorophenylsulfonyl, 2-trifluoromethyl phenylsulfonyl, 2-

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fluorophenylsulfonyl, 2-chlorophenylsulfonyl, 2-bromophenylsulfonyl, phenylsulfonyl, 4-bromophenylsulfonyl, 4-iodophenylsulfonyl, 4-methylphenylsulfonyl, 4-bromobenzoyl, 4-chlorobenzoyl, 3-fluorobenzoyl, 2-bromobenzoyl, 2-fluorobenzoyl, 2-chlorobenzoyl, 4-methylbenzoyl, 2-trifluoromethylbenzoyl, 4-trifluoromethyl benzoyl, 4-bromo benzoyl, 4-benzyl benzoyl, 3-(acetyl amino)pyridin-2-yl, 3-(trifluoroacetyl amino)pyridin-2-yl, 3-(methanesulphonylamino) pyrid-2-yl, 3, 5-dichloropyridin-2-yl, 3-bromopyridin-2-yl or 5-nitropyridin-2-yl; and

PG is an N-protecting group.

42. A compound of formula 7,

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{R}^4 \\
\text{H}_2 & \quad \text{H} \\
\text{R}^{4} & \quad \text{N} \\
\text{R}^{5} & \quad \text{R}^{5} \\
7 & \quad \text{R}^{6} \\
\end{align*}
\]

wherein

R^4 and R^5 are hydrogen; and

R^6 is selected from phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 2,6-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2,3,4-trifluorophenyl, 2,4,5-trifluorophenyl, 2,4,6-trifluorophenyl, 3,4,5-trifluorophenyl, 2-methoxyphenyl, 4-methoxyphenyl, 2-isopropylphenyl, 4-isopropylphenyl, 4-t-butyl phenyl, 2,4-dimethylphenyl, 2-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-difluoromethoxyphenyl, 2-trifluoromethoxyphenyl, 2-fluoro-5-methylphenyl, 2-cyclopropylmethoxyphenyl, 2-fluoro-3-trifluoromethylphenyl, 2-trifluoromethoxyphenyl, 2-fluoro-5-trifluoromethylphenyl, 2-fluoro-4-difluoromethoxyphenyl, 2-fluoro-4-methylphenyl, benzyl, 4-chlorobenzyl, 4-trifluoromethylbenzyl, 4-chlorophenylsulfonyl, 4-trifluoromethylphenylsulfonyl, 4-fluorophenylsulfonyl, 2,6-dichlorophenylsulfonyl, 2,6-difluorophenylsulfonyl, 2,4-dibromophenylsulfonyl, 2,4-dichlorophenylsulfonyl, 2-trifluoromethyl phenylsulfonyl, 2-fluorophenylsulfonyl, 2-chlorophenylsulfonyl, 2-bromophenylsulfonyl, phenylsulfonyl, 4-bromophenylsulfonyl, 4-iodophenylsulfonyl, 4-methylphenylsulfonyl, 4-bromobenzoyl, 4-chlorobenzoyl, 3-fluorobenzoyl, 2-bromobenzoyl, 2-fluorobenzoyl, 2-chlorobenzoyl, 4-methyl
benzoyl, 2-trifluoromethylbenzoyl, 4-trifluoromethyl benzoyl, 4-bromo benzoyl, 4-benzyl benzoyl, 3-(acetyl amino)pyridin-2-yl, 3-(trifluoroacetyl amino)pyridin-2-yl, 3-(methanesulphonylamino) pyrid-2-yl, 3, 5-dichloropyridin-2-yl, 3-bromopyridin-2-yl or 5-nitropyridin-2-yl.

43. A process for the preparation of a compound of claim 1, wherein R³ is H and X is O, comprising reacting a compound of formula 7 with a compound of formula 8a

\[
\begin{align*}
\text{NHR}^3 & \\
\text{R}^4 & \\
\text{R}^5 & \\
\text{R}^6 & \\
\end{align*}
\]
\[
\begin{align*}
\text{R}^1 & \\
\text{R}^2 & \\
\end{align*}
\]

wherein L is a leaving group selected from halogen, aryloxy, alkoxy, imidazolyl, imidazolyl, benzimidazolyl, tetrazolyl, benzotetrazolyl and succinimidylxoy, to form a compound of formula (I).

44. The process according to claim 43, wherein the reaction is carried out in the presence of a base.

45. The process according to claim 43 or 44, wherein the base is selected from triethylamine or pyridine.

46. A process for the preparation of a compound of claim 1, wherein R² and R³ are hydrogen, comprising reacting a compound of formula 7 with a compound of formula 8b

\[
\begin{align*}
\text{NHR}^3 & \\
\text{R}^4 & \\
\text{R}^5 & \\
\text{R}^6 & \\
\end{align*}
\]
\[
\begin{align*}
\text{X=C=N-R}^1 & \\
\end{align*}
\]
to form a compound of formula (I).

47. The process according to claim 46, wherein the reaction is carried out in the presence of a base.

48. The process according to claim 46 or 47, wherein the base is selected from triethylamine and pyridine.