# SUBSTITUTED HETEROCYCLIC COMPOUNDS AND THEIR DERIVATIVES AS CBP AND/OR p300 DEGRADERS

The present application claims priority to and the benefit of Indian Patent Application No. IN202441025578, filed on 28th March 2024, which application is incorporated herein by reference in its entirety.

## TECHNICAL FIELD

The present application is directed to compounds of formula (I), a pharmaceutically acceptable salt thereof, a solvate thereof or an isomer thereof as degraders of target proteins. Particularly, the present invention provides a compound of formula (I) useful for treating or preventing a disease or disorder responsive to the degradation of target proteins, preferably cancer, viral infection, autoimmune disease or disorder, inflammatory disease or disorder, neurodegenerative disease and metabolic disorder.

## BACKGROUND

Gene expression is regulated via genetic and epigenetic modifications in cellular DNA. Altered genetic and epigenetic modifications such as histone modifications, DNA methylation, micro RNAs and nucleosome remodelling has been identified as one of the hallmarks of cancer (Kanwal R, Gupta S, Clin Genet. 2012, Apr; 81(4):303-11).

The E1A binding protein (p300) and its counterpart CREB binding protein (CBP or CREBBP) are widely expressed histone acetyl transferases (HATs) and recognized for their oncogenic roles in various cancer types. CBP and p300 regulate the gene transcription via acetylation of histone and non-histone proteins (Delvecchio M. et al., Nat Struct Mol Biol. 2013, 20, 1040–1046). In addition to HAT function, CBP/p300 have crotonyl-transferase activities, and CBP/p300-catalyzed histone crotonylation directly stimulates transcription to a greater degree (Liu X., et al., Cell Discov 2017, 3, 17016). They also serve as scaffolds or co-activators, enhancing the activity of various transcription factors, including HIF1a, BRCA-1, p53, c-Myc, programmed death-ligand 1 (PD-L1), estrogen receptor (ER), and androgen receptor (AR) (Pao GM. et al., Proc Natl Acad Sci U S A. 2000 Feb 1; 97(3):1020-5).

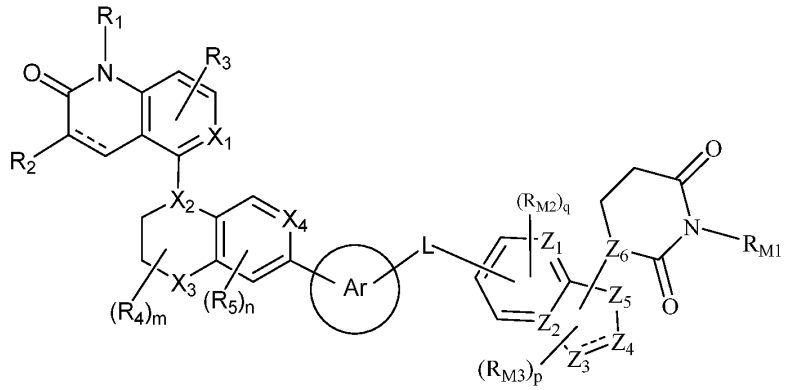
CBP/p300 are important for T regulatory cell development and function, and antitumor immunity can be achieved by targeting CBP/p300 in $Foxp3^+$ Treg cells (Liu Y et al., Nat Med. 2013 Sep; 19(9):1173-7). As CBP and p300 proteins are reported to be highly expressed in various cancers, conventional approaches have been used in the past to prevent tumorigenesis.

Therefore, degradation of CBP/p300 provides a promising route to the treatment of certain cancers; however, as there are no dual degraders of CBP/p300 available in the literature having proven benefits, compounds that can degrade CBP/p300 are of interest in cancer therapy.

## SUMMARY

Provided herein are compounds of formula (I) and pharmaceutical compositions thereof, which are capable of degrading CBP and/or p300 proteins.

In one aspect of the present disclosure, it comprises compounds of formula (I):



(I)

or a pharmaceutically acceptable salt thereof or a stereoisomer thereof;

wherein,

------ represents a single bond or a double bond;

$R_1$ is hydrogen, ($C_1$-$C_6$)alkyl, halo($C_1$-$C_6$)alkyl or ($C_3$-$C_6$)cycloalkyl;

$R_2$ is hydrogen, halo, ($C_1$-$C_6$)alkyl, halo($C_1$-$C_6$)alkyl or ($C_3$-$C_6$)cycloalkyl;

$R_3$ is hydrogen, halo, ($C_1$-$C_6$)alkyl, halo($C_1$-$C_6$)alkyl, cyano, ($C_3$-$C_6$)cycloalkyl, 3 to 12 membered heterocycloalkyl or -$OR_{3a}$;

$R_4$ at each occurrence is independently hydrogen, halo, ($C_1$-$C_6$)alkyl, cyano or halo($C_1$-$C_6$)alkyl;

$R_5$ at each occurrence is independently hydrogen, halo, ($C_1$-$C_6$)alkyl, cyano, halo($C_1$-$C_6$)alkyl or -$OR_{5a}$;

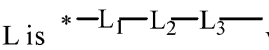
$R_{3a}$ and $R_{5a}$ are independently hydrogen, ($C_1$-$C_6$)alkyl or halo($C_1$-$C_6$)alkyl;

$X_1$ is CH or N;

each $X_2$ and $X_4$ are independently C or N;

$X_3$ is C, N, S or O;

ring Ar is an unsubstituted or substituted ($C_3$-$C_6$)cycloalkylenyl, unsubstituted or substituted 3 to 12 membered heterocycloalkylenyl, unsubstituted or substituted 6 to 10 membered arylenyl or unsubstituted or substituted 5 to 12 membered heteroarylenyl; wherein the substituent is independently selected from one or more($C_1$-$C_6$)alkyl, halo, cyano, hydroxy or ($C_1$-$C_6$)alkoxy;

L is  wherein the asterisk mark [*] represents the point of attachment with the ring Ar;

each $L_1$ and $L_2$ is independently a bond, ($C_1$-$C_6$)alkylenyl, unsubstituted or substituted 6 to 10 membered arylenyl, unsubstituted or substituted 6 to 10 membered heteroarylenyl, unsubstituted or substituted ($C_3$-$C_6$)cycloalkylenyl or unsubstituted or substituted 3 to 12 membered heterocycloalkylenyl; wherein the substituent is independently selected from one or more ($C_1$-$C_6$)alkyl, halo, cyano, hydroxy or ($C_1$-$C_6$)alkoxy;

$L_3$ is a bond, ($C_1$-$C_6$)alkylenyl, unsubstituted or substituted 6 to 10 membered arylenyl, unsubstituted or substituted 6 to 10 membered heteroarylenyl, unsubstituted or substituted 3 to 12 membered heterocycloalkylenyl or unsubstituted or substituted ($C_3$-$C_6$)cycloalkylenyl; wherein the substituent is independently selected from one or more ($C_1$-$C_6$)alkyl, halo, cyano, hydroxy or ($C_1$-$C_6$)alkoxy;

each $Z_1$, $Z_3$ $Z_4$ and $Z_5$ is independently C or N; wherein at least one of $Z_3$, $Z_4$, and $Z_5$ is C;

$Z_2$ is C;

$Z_6$ is CH or N;

$R_{M1}$ is hydrogen or ($C_1$-$C_6$)alkyl;

$R_{M2}$ at each occurrence independently is hydrogen, halo, cyano, ($C_1$-$C_6$)alkyl or ($C_1$-$C_6$)alkoxy;

$R_{M3}$ at each occurrence is independently hydrogen or ($C_1$-$C_6$)alkyl; or two $R_{M3}$ on the same carbon atom together represent an oxo group;

one of $R_{M2}$ and one of $R_{M3}$ together get cyclized to form a 5 to 6 membered fused ring system;

subscript 'm' is 0, 1, 2 or 3;

subscript 'n' is 0, 1, 2 or 3;

subscript 'p' is 1, 2 or 3; and

subscript 'q' is 1, 2 or 3.

In yet another aspect, the present application provides pharmaceutical compositions comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof or a stereoisomer thereof, and at least one pharmaceutically acceptable excipient (such as a pharmaceutically acceptable carrier or diluent).

In yet another aspect, the present application relates to the preparation of compounds of formula (I).

In yet another aspect of the present application, provided herein are compounds of formula (I), which are capable of degrading CBP and/or p300 proteins and therapeutic use thereof.

**DETAILED DESCRIPTION**

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in art to which the subject matter herein belongs. As used in the specification and the appended claims, unless specified to the contrary, the following terms have the meaning indicated to facilitate the understanding of the present disclosure.

As used herein, unless otherwise defined the term "alkyl" alone or in combination with other term(s) means saturated aliphatic hydrocarbon chains, including $C_1$-$C_{14}$ straight or $C_1$-$C_{14}$ branched alkyl groups, where "$C_1$-$C_{14}$" means one to fourteen carbons. Alkyl may also include, for example, a $C_1$-$C_6$ alkyl group, where "$C_1$-$C_6$" means one to six carbons, a $C_1$-$C_5$ alkyl group, where "$C_1$-$C_5$" means one to five carbons, a $C_1$-$C_4$ alkyl group, where "$C_1$-$C_4$" means one to four carbons, a $C_1$-$C_3$ alkyl group, where "$C_1$-$C_3$" means one to three carbons, or a $C_1$-$C_2$ alkyl group, where "$C_1$-$C_2$" means one to two carbons. Examples of "alkyl" include but are not limited to methyl, ethyl, 1-propyl, 2-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, 1-pentyl, 2-pentyl, 3-pentyl, neo-pentyl, 1-hexyl, 2-hexyl, 3-hexyl, 1-heptyl, 2-heptyl, 3-

heptyl, 4-heptyl, 1-octyl, 2-octyl, 3-octyl and 4-octyl and the like. As used herein, the term "alkylenyl" refers to a divalent alkyl group, wherein the "alkyl" group is as defined above. Examples of "alkylenyl" include, but are not limited to, $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH(CH_3)CH_2CH_2CH_2-$, $-CH_2CH(CH_3)CH_2CH_2-$ and $-(CH_2)_{1-14}-$ .

As used herein, the term "halo" or "halogen" alone or in combination with other term(s) means fluorine, chlorine, bromine or iodine.

As used herein, the term "oxo" refers to =O group.

As used herein, the term "haloalkyl" means alkyl substituted with one or more halogen atoms, wherein the alkyl groups are as defined above. The term "halo" is used herein interchangeably with the term "halogen" means F, Cl, Br or I. Examples of "haloalkyl" include but are not limited to fluoromethyl, difluoromethyl, chloromethyl, trifluoromethyl, 2,2,2-trifluoroethyl and the like.

As used herein, the term "hydroxy" or "hydroxyl" alone or in combination with other term(s) means –OH.

As used herein, the term "alkoxy" alone or in combination with other term(s) refers to the group alkyl-O- or –O-alkyl, where alkyl groups are as defined above. Exemplary $C_1$-$C_{10}$ alkoxy includes but are not limited to methoxy, ethoxy, n-propoxy, n-butoxy, t-butoxy and the like. An alkoxy group can be unsubstituted or substituted with one or more suitable groups.

As used herein, the term "cyano" refers to –CN.

As used herein the term "cycloalkyl" alone or in combination with other term(s) means -$C_3$-$C_{10}$ saturated cyclic hydrocarbon ring. A cycloalkyl may be a single ring, which typically contains from 3 to 7 carbon ring atoms. Examples of single-ring cycloalkyls include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. A cycloalkyl may alternatively be polycyclic or contain more than one ring. Examples of polycyclic cycloalkyls include bridged, fused and spirocyclic carbocyclyls and the like.

As used herein, the term "aryl" is unsubstituted or substituted monocyclic, bicyclic or polycyclic aromatic hydrocarbon ring system of about 6 to 14 carbon atoms. Examples of a $C_6$-$C_{14}$ aryl group include, but are not limited to phenyl, naphthyl, anthryl, tetrahydronaphthyl, fluorenyl, indanyl, biphenylenyl and acenaphthyl. An aryl group may typically contain 6 to 10 carbon atoms. An aryl group may be unsubstituted or substituted with one or more suitable groups. As used herein, the term "arylenyl" refers to a divalent aryl group, wherein the aryl group is as defined above.

The term "heterocycloalkyl" refers to a non-aromatic, saturated or partially saturated monocyclic or polycyclic, fused, bridged or spiro ring system of 3 to 15 members having at least one heteroatom or hetero group selected from O, N, S, S(O), $S(O)_2$ or NH with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen and sulfur. A heterocycloalkyl may typically contain 3 to 12 ring atoms. A monocyclic heterocycloalkyl may typically contain 4 to 7 ring atoms. Examples of “heterocycloalkyl” include, but are not limited to azetidinyl, oxetanyl, imidazolidinyl, pyrrolidinyl, oxazolidinyl, thiazolidinyl, pyrazolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, tetrahydropyranyl, morpholinyl, oxapiperazinyl, oxapiperidinyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiophenyl, dihydropyranyl, indolinyl, azepanyl and N-oxides thereof. Attachment of a heterocycloalkyl substituent can occur via either a carbon atom or a heteroatom. A heterocycloalkyl group can be unsubstituted or substituted with one or more suitable groups by one or more aforesaid groups. Preferably “heterocycloalkyl” refers to 5- to 10-membered ring. In one embodiment, “heterocycloalkyl” refers to 5- to 6-membered ring selected from the group consisting of imidazolidinyl, pyrrolidinyl, oxazolidinyl, thiazolidinyl, pyrazolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, 1,4-dioxanyl and N-oxides thereof. More preferably, “heterocycloalkyl” includes azetidinyl, pyrrolidinyl, morpholinyl and piperidinyl.

As used herein, the term “heterocycloalkylenyl” refers to a divalent heterocycloalkyl group as defined herein. All “heterocycloalkyl” / “heterocycloalkylenyl” are optionally substituted by one or more aforesaid groups.

As used herein, the term "cycloalkylenyl" refers to a divalent form of an optionally substituted cycloalkyl group. Examples of ‘cycloalkylenyl include, but not limited to, cyclopropylenyl, cyclobutylenyl, cyclopentylenyl, cyclohexylenyl and cycloheptylenyl.

As used herein, the term "heteroaryl" alone or in combination with other term(s) means a completely unsaturated ring system containing a total of 5 to 14 ring atoms. At least one of the ring atoms is a heteroatom (i.e., oxygen, nitrogen, or sulfur), with the remaining ring atoms/groups being independently selected from the group consisting of carbon, oxygen, nitrogen or sulfur. A heteroaryl may typically contain 5 to 10 ring atoms. A heteroaryl may be a single-ring (monocyclic) or polycyclic ring system. Examples of "heteroaryl" include but are not limited to pyridyl, indolyl, benzimidazolyl, benzothiazolyl and the like.

The term "heteroatom" as used herein designates a sulfur, nitrogen or oxygen atom.

As used in the above definitions, the term "optionally substituted" or “substituted” or “optionally substituted with suitable groups” refers to replacement of one or more hydrogen radicals in a given structure with a radical of a specified substituent including, but not limited to: halo, alkyl, alkenyl, alkynyl, aryl, heterocyclyl, thiol, alkylthio, arylthio, alkylthioalkyl, arylthioalkyl, alkylsulfonyl, alkylsulfonylalkyl, arylsulfonylalkyl, alkoxy, aryloxy, aralkoxy, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkoxycarbonyl, aryloxycarbonyl, haloalkyl, amino, trifluoromethyl, cyano, nitro, alkylamino, arylamino, alkylaminoalkyl, arylaminoalkyl, aminoalkylamino, hydroxy, alkoxyalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, acyl, aralkoxycarbonyl, carboxylic acid, sulfonic acid, sulfonyl, phosphonic acid, aryl, heteroaryl, heterocyclic and aliphatic. It is understood that any substituent may be further substituted.

As used herein, the term ‘compound(s)’ comprises the compounds disclosed in the present disclosure.

As used herein, the term "comprise" or "comprising" is generally used in the sense of include, that is to say permitting the presence of one or more features or components.

As used herein the term “and/or” should be understood to mean “either or both” of the elements so conjoined, i.e., elements that are conjunctively present in some cases and disjunctively present in other cases. Multiple elements listed with “and/or” should be construed in the same fashion, i.e., “one or more” of the elements so conjoined.

As used herein, the term "or" means "and/or" unless stated otherwise.

As used herein, the term "including" as well as other forms, such as "include", "includes" and "included" is not limiting.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

As used herein, the term "treat", "treating" and "treatment" refer to a method of alleviating or abrogating a disease and/or its attendant symptoms.

As used herein, the term "prevent", "preventing" and "prevention" refer to a method of preventing the onset of a disease and/or its attendant symptoms or barring a subject from

acquiring a disease. As used herein, "prevent", "preventing" and "prevention" also include delaying the onset of a disease and/or its attendant symptoms and reducing a subject's risk of acquiring a disease.

As used herein, the term "therapeutically effective amount" refers to that amount of the compound being administered sufficient to prevent development of or alleviate to some extent one or more of the symptoms of the condition or disorder being treated.

"Pharmaceutically acceptable" means that, which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary as well as human pharmaceutical use.

As used herein, the phrase "pharmaceutically acceptable excipient" refers to a pharmaceutically acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, solvent, or encapsulating material. Excipients or carriers are generally safe, non-toxic and neither biologically nor otherwise undesirable and include excipients or carriers that are acceptable for veterinary use as well as human pharmaceutical use. In one embodiment, each component is "pharmaceutically acceptable" as defined herein. See, e.g., Remington: The Science and Practice of Pharmacy, 21st ed.; Lippincott Williams & Wilkins: Philadelphia, Pa., 2005; Handbook of Pharmaceutical Excipients, 6th ed.; Rowe et al, Eds.; The Pharmaceutical Press and the American Pharmaceutical Association: 2009; Handbook of Pharmaceutical Additives, 3rd ed.; Ash and Ash Eds. ; Gower Publishing Company: 2007; Pharmaceutical Pre-formulation and Formulation, 2nd ed. ; Gibson Ed.; CRC Press LLC: Boca Raton, Fla., 2009.

As used herein, “pharmaceutically acceptable salt(s)” refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the present disclosure include the conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present disclosure can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the

two; generally, non-aqueous media like ether, ethyl acetate, alcohols or acetonitrile (ACN) are preferred.

The term "stereoisomers" refers to any enantiomers, diastereoisomers, or geometrical isomers of the compounds of Formula (I), (IA), (IB) and (IC) wherever they are chiral or when they bear one or more double bonds. When the compounds of the formula (I), (IA), (IB) and (IC) are chiral, they can exist in racemic or in optically active form. It should be understood that the disclosure encompasses all stereochemical isomeric forms, including diastereomeric, enantiomeric and epimeric forms, as well as *d*-isomers and *l*-isomers and mixtures thereof. Individual stereoisomers of compounds can be prepared synthetically from commercially available starting materials which contain chiral centers or by preparation of mixtures of enantiomeric products followed by separation such as conversion to a mixture of diastereomers followed by separation or recrystallization, chromatographic techniques, direct separation of enantiomers on chiral chromatographic columns, or any other appropriate method known in the art. Starting compounds of particular stereochemistry are either commercially available or can be made and resolved by techniques known in the art. Additionally, the compounds of the present disclosure may exist as geometric isomers. The present disclosure includes all cis, trans, syn, anti, *R* and *S*, entgegen (*E*) and zusammen (*Z*) isomers as well as the appropriate mixtures thereof.

The CBP degraders as used herein is alternatively referred to as “CBP protein degraders” or ‘‘CBP modulators”.

The p300 degraders as used herein is alternatively referred to as “p300 protein degraders” or “p300 modulators”.

The CBP and/or p300 degraders as used herein is alternatively referred to as “degraders of one or both of CBP and p300”. “CBP and/or p300 degrader” refers to a compound that binds to the CBP bromodomain and/or p300 bromodomain and degrades and/or reduces a biological activity of CBP and/or p300.

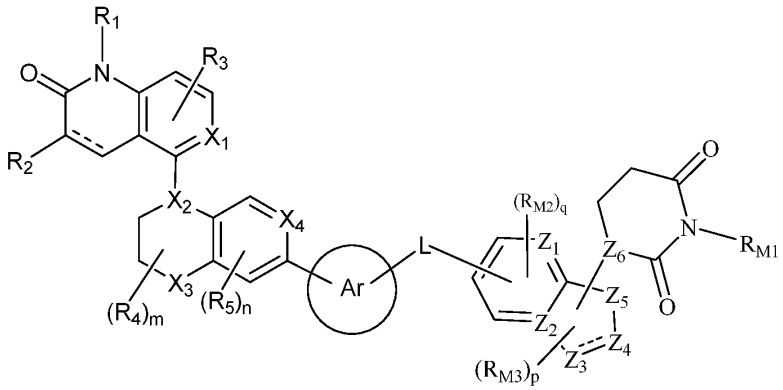
The present disclosure provides compounds of formula (I), which are useful as CBP and/or p300 degraders.

The present disclosure further provides pharmaceutical compositions comprising the said compounds of formula (I), and their derivatives as therapeutic agents.

It will be apparent to those skilled in the art that various modifications and variations can be made to the compounds, compositions, and methods described herein without departing from the scope or spirit of various embodiments disclosed herein. For instance, features illustrated or described as part of one embodiment can be applied to another embodiment to yield a still further embodiment. Thus, it is intended that the present application includes such modifications and variations and their equivalents. Other objects, features, and aspects of the present application are disclosed in, or are obvious from, the following detailed description. It is to be understood by one of ordinary skill in the art that the present discussion is a description of exemplary embodiments and is not to be construed as limiting the broader aspects of the present disclosure.

The embodiments below are illustrative of the present disclosure and are not intended to limit the claims to the specific embodiments exemplified.

In a first embodiment, the present application provides compounds of formula (I),



(I)

or a pharmaceutically acceptable salt thereof or a stereoisomer thereof;

wherein,

$\overline{\text{------}}$ represents a single bond or a double bond;

$R_1$ is hydrogen, $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl or $(C_3\text{-}C_6)$cycloalkyl;

$R_2$ is hydrogen, halo, $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl or $(C_3\text{-}C_6)$cycloalkyl;

$R_3$ is hydrogen, halo, $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, cyano, $(C_3\text{-}C_6)$cycloalkyl, 3 to 12 membered heterocycloalkyl or $-OR_{3a}$;

$R_4$ at each occurrence is independently hydrogen, halo, ($C_1$-$C_6$)alkyl, cyano or halo($C_1$-$C_6$)alkyl;

$R_5$ at each occurrence is independently hydrogen, halo, ($C_1$-$C_6$)alkyl, cyano, halo($C_1$-$C_6$)alkyl or -$OR_{5a}$;

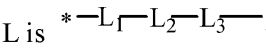
$R_{3a}$ and $R_{5a}$ are independently hydrogen, ($C_1$-$C_6$)alkyl or halo($C_1$-$C_6$)alkyl;

$X_1$ is CH or N;

each $X_2$ and $X_4$ are independently C or N;

$X_3$ is C, N, S or O;

ring Ar is an unsubstituted or substituted ($C_3$-$C_6$)cycloalkylenyl, unsubstituted or substituted 3 to 12 membered heterocycloalkylenyl, unsubstituted or substituted 6 to 10 membered arylenyl or unsubstituted or substituted 5 to 12 membered heteroarylenyl; wherein the substituent is independently selected from one or more($C_1$-$C_6$)alkyl, halo, cyano, hydroxy or ($C_1$-$C_6$)alkoxy;

L is  wherein the asterisk mark [*] represents the point of attachment with the ring Ar;

each $L_1$ and $L_2$ is independently a bond, ($C_1$-$C_6$)alkylenyl, unsubstituted or substituted 6 to 10 membered arylenyl, unsubstituted or substituted 6 to 10 membered heteroarylenyl, unsubstituted or substituted ($C_3$-$C_6$)cycloalkylenyl or unsubstituted or substituted 3 to 12 membered heterocycloalkylenyl; wherein the substituent is independently selected from one or more ($C_1$-$C_6$)alkyl, halo, cyano, hydroxy or ($C_1$-$C_6$)alkoxy;

$L_3$ is a bond, ($C_1$-$C_6$)alkylenyl, unsubstituted or substituted 6 to 10 membered arylenyl, unsubstituted or substituted 6 to 10 membered heteroarylenyl, unsubstituted or substituted 3 to 12 membered heterocycloalkylenyl or unsubstituted or substituted ($C_3$-$C_6$)cycloalkylenyl; wherein the substituent is independently selected from one or more ($C_1$-$C_6$)alkyl, halo, cyano, hydroxy or ($C_1$-$C_6$)alkoxy;

each $Z_1$, $Z_3$ $Z_4$ and $Z_5$ is independently C or N; wherein at least one of $Z_3$, $Z_4$, and $Z_5$ is C;

$Z_2$ is C;

$Z_6$ is CH or N;

$R_{M1}$ is hydrogen or ($C_1$-$C_6$)alkyl;

$R_{M2}$ at each occurrence independently is hydrogen, halo, cyano, ($C_1$-$C_6$)alkyl or ($C_1$-$C_6$)alkoxy;

$R_{M3}$ at each occurrence is independently hydrogen or ($C_1$-$C_6$)alkyl; or two $R_{M3}$ on the same carbon atom together represent an oxo group;

one of $R_{M2}$ and one of $R_{M3}$ together get cyclized to form a 5 to 6 membered fused ring system;

subscript 'm' is 0, 1, 2 or 3;

subscript 'n' is 0, 1, 2 or 3;

subscript 'p' is 1, 2 or 3; and

subscript 'q' is 1, 2 or 3.

In another embodiment of the present application, it provides compounds of formula (I), or a pharmaceutically acceptable salt thereof or a stereoisomer thereof,

wherein,

------ represents a single bond or a double bond;

$R_1$ is hydrogen or ($C_1$-$C_6$)alkyl;

$R_2$ is hydrogen or ($C_1$-$C_6$)alkyl;

$R_3$ is hydrogen or 3 to 12 membered heterocycloalkyl;

$R_4$ at each occurrence is hydrogen;

$R_5$ at each occurrence is independently hydrogen, halo($C_1$-$C_6$)alkyl;

$X_1$ is CH or N;

each $X_2$ and $X_4$ are independently C or N;

$X_3$ is C;

ring Ar is an unsubstituted or substituted 3 to 12 membered heterocycloalkylenyl or unsubstituted or substituted 5 to 12 membered heteroarylenyl; wherein the substituent is independently selected from one or more($C_1$-$C_6$)alkyl, halo, cyano or hydroxy;

L is $^{*}-L_1-L_2-L_3-$ wherein the asterisk mark [*] represents the point of attachment with the ring Ar;

each $L_1$ and $L_2$ is independently a bond, or unsubstituted or substituted 3 to 12 membered heterocycloalkylenyl; wherein the substituent is independently selected from one or more $(C_1\text{-}C_6)$alkyl, halo, cyano or hydroxy;

$L_3$ is a bond or unsubstituted or substituted 3 to 12 membered heterocycloalkylenyl; wherein the substituent is independently selected from one or more $(C_1\text{-}C_6)$alkyl, halo, cyano or hydroxy;

each $Z_1$, $Z_3$ $Z_4$ and $Z_5$ is independently C or N; wherein at least one of $Z_3$, $Z_4$, and $Z_5$ is C;

$Z_2$ is C;

$Z_6$ is CH;

$R_{M1}$ is $(C_1\text{-}C_6)$alkyl;

$R_{M2}$ at each occurrence independently is hydrogen or $(C_1\text{-}C_6)$alkyl;

$R_{M3}$ at each occurrence is independently hydrogen or $(C_1\text{-}C_6)$alkyl; or two $R_{M3}$ on the same carbon atom together represent an oxo group;

one of $R_{M2}$ and one of $R_{M3}$ together get cyclized to form a 5 to 6 membered fused ring system;

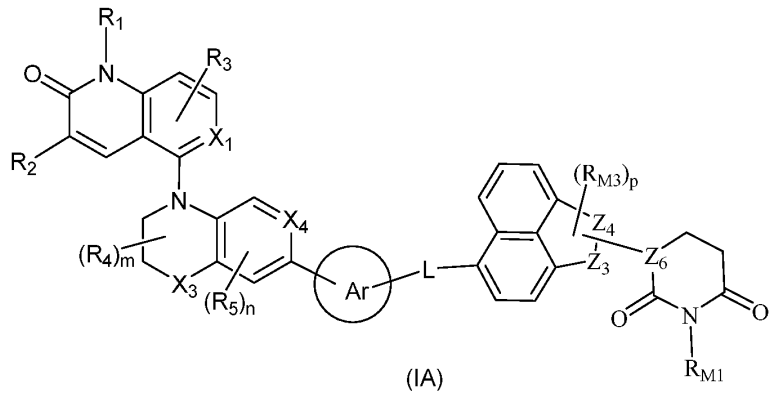
subscript 'm' is 0, 1, 2 or 3;

subscript 'n' is 0, 1, 2 or 3;

subscript 'p' is 1, 2 or 3; and

subscript 'q' is 1, 2 or 3.

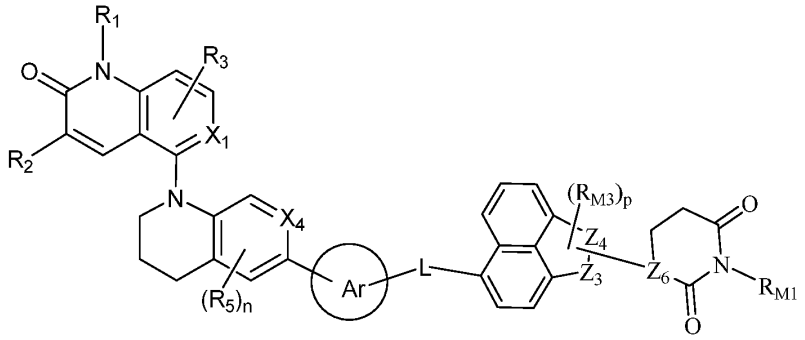
In another embodiment of the present application, it provides compounds of formula (IA),



(IA)

or a pharmaceutically acceptable salt thereof or a stereoisomer thereof; wherein subscript 'p' is 1 or 2.

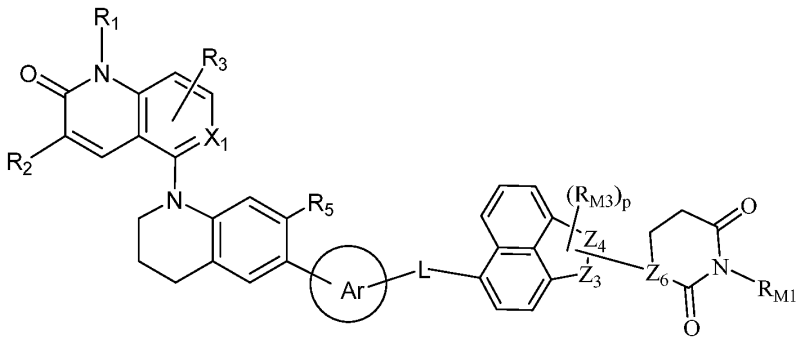
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(IB)

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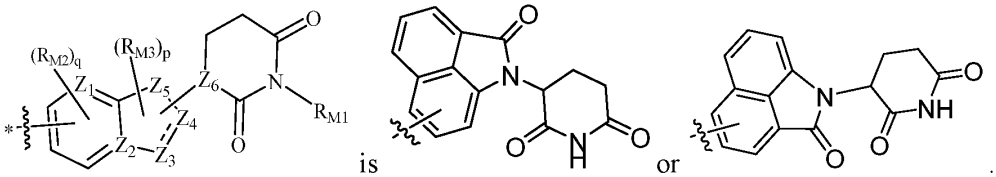
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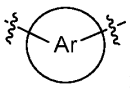
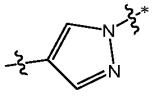
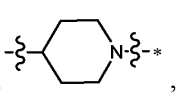
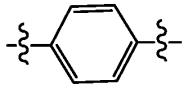
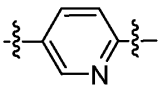


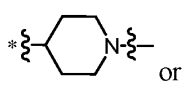
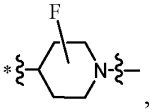
(IC)

or a pharmaceutically acceptable salt thereof or a stereoisomer thereof; wherein subscript 'p' is 1 or 2.

In one embodiment of the present application, it provides compounds of formula (I), wherein,



In one embodiment of the present application, it provides compounds of formula (I) to (IC), wherein the ring  is , ,  or , wherein the asterisk mark [*] represents the point of attachment with linker L.

In one embodiment of the present application, it provides compounds of formula (I) to (IC), wherein L represented by  is a bond,  or , wherein the asterisk mark [*] represents the point of attachment with the ring Ar.

In one embodiment of the present application, it provides compounds of formula (I) to (IC), wherein $R_1$ is hydrogen, ($C_1$-$C_6$)alkyl or halo($C_1$-$C_6$)alkyl.

In one embodiment, $R_1$ is hydrogen or ($C_1$-$C_6$)alkyl.

In one embodiment, $R_1$ is ($C_1$-$C_6$)alkyl.

In one embodiment, $R_2$ is hydrogen, $(C_1$-$C_6)$alkyl or halo$(C_1$-$C_6)$alkyl.

In one embodiment, $R_2$ is hydrogen or $(C_1$-$C_6)$alkyl.

In one embodiment, $R_2$ is $(C_1$-$C_6)$alkyl.

In one embodiment, $R_3$ is hydrogen, halo, $(C_1$-$C_6)$alkyl, 3 to 12 membered heterocycloalkyl, $(C_3$-$C_6)$cycloalkyl or -$OR_{3a}$.

In one embodiment, $R_3$ is hydrogen, halo, $(C_1$-$C_6)$alkyl, 3 to 12 membered heterocycloalkyl or $(C_3$-$C_6)$cycloalkyl.

In one embodiment, $R_3$ is hydrogen, halo, 3 to 12 membered heterocycloalkyl or $(C_3$-$C_6)$cycloalkyl.

In one embodiment, $R_3$ is hydrogen, 3 to 12 membered heterocycloalkyl or $(C_3$-$C_6)$cycloalkyl.

In one embodiment, $R_3$ is hydrogen or 3 to 12 membered heterocycloalkyl.

In one embodiment, $R_{3a}$ is $(C_1$-$C_6)$alkyl.

In one embodiment, $R_4$ is halo or $(C_1$-$C_6)$alkyl.

In one embodiment, $R_4$ is $(C_1$-$C_6)$alkyl.

In one embodiment, $R_5$ is hydrogen, halo, $(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl or -$OR_{5a}$.

In one embodiment, $R_5$ is hydrogen, halo, $(C_1$-$C_6)$alkyl or halo$(C_1$-$C_6)$alkyl.

In one embodiment, $R_5$ is halo$(C_1$-$C_6)$alkyl.

In one embodiment, $R_{5a}$ is $(C_1$-$C_6)$alkyl.

In one embodiment of the present application, it provides compounds of formula (I), wherein,

$R_1$ is $(C_1$-$C_6)$alkyl;

$R_2$ is $(C_1$-$C_6)$alkyl;

$R_3$ is hydrogen or 3 to 12 membered heterocycloalkyl;

$R_4$ at each occurrence is hydrogen;

$R_5$ at each occurrence is independently hydrogen, halo$(C_1$-$C_6)$alkyl;

$X_1$ is CH or N;

each $X_2$ and $X_4$ are independently C or N;

$X_3$ is C;

ring Ar is an unsubstituted or substituted 3 to 12 membered heterocycloalkylenyl or unsubstituted or substituted 5 to 12 membered heteroarylenyl; wherein the substituent is independently selected from one or more($C_1$-$C_6$)alkyl, halo, cyano or hydroxy;

L is $*-L_1-L_2-L_3-$ wherein the asterisk mark [*] represents the point of attachment with the ring Ar;

each $L_1$ and $L_2$ is independently a bond, or unsubstituted or substituted 3 to 12 membered heterocycloalkylenyl; wherein the substituent is independently selected from one or more ($C_1$-$C_6$)alkyl, halo, cyano or hydroxy;

$L_3$ is a bond or unsubstituted or substituted 3 to 12 membered heterocycloalkylenyl; wherein the substituent is independently selected from one or more ($C_1$-$C_6$)alkyl, halo, cyano or hydroxy;

each $Z_1$, $Z_3$ $Z_4$ and $Z_5$ is independently C or N; wherein at least one of $Z_3$, $Z_4$, and $Z_5$ is C;

$Z_2$ is C;

$Z_6$ is CH;

$R_{M1}$ is hydrogen;

$R_{M2}$ at each occurrence independently is hydrogen or ($C_1$-$C_6$)alkyl;

$R_{M3}$ at each occurrence is independently hydrogen or ($C_1$-$C_6$)alkyl; or two $R_{M3}$ on the same carbon atom together represent an oxo group;

one of $R_{M2}$ and one of $R_{M3}$ together get cyclized to form a 5 to 6 membered fused ring system;

subscript ‘m’ is 0, 1, 2 or 3;

subscript ‘n’ is 0, 1, 2 or 3;

subscript ‘p’ is 1, 2 or 3; and

subscript ‘q’ is 1, 2 or 3.

In certain embodiments, the present application provides a compound selected from:

| Comp. No. | IUPAC Name |
|---|---|
| 1 | 3-(6-(4-(4-(7-(difluoromethyl)-1',3'-dimethyl-2'-oxo-1',2',3,4-tetrahydro-2H-[1,5'-biquinolin]-6-yl)-1H-pyrazol-1-yl)piperidin-1-yl)-2-oxobenzo[cd]indol-1(2H)-yl)piperidine-2,6-dione; |
| 2 | 3-(6-(4-(4-(7-(difluoromethyl)-1',3'-dimethyl-2'-oxo-7'-(tetrahydro-2H-pyran-4-yl)-1',2',3,4-tetrahydro-2H-[1,5'-biquinolin]-6-yl)-1H-pyrazol-1-yl)piperidin-1-yl)-2-oxobenzo[cd]indol-1(2H)-yl)piperidine-2,6-dione |
| 3 | 3-(5-(4-(4-(7-(difluoromethyl)-1',3'-dimethyl-2'-oxo-1',2',3,4-tetrahydro-2H-[1,5'-biquinolin]-6-yl)-1H-pyrazol-1-yl)piperidin-1-yl)-2-oxobenzo[cd]indol-1(2H)-yl)piperidine-2,6-dione; |
| 4 | 3-(6-(4-(7-(difluoromethyl)-1',3'-dimethyl-2'-oxo-1',2',3,4-tetrahydro-2H-[1,5'-biquinolin]-6-yl)piperidin-1-yl)-2-oxobenzo[cd]indol-1(2H)-yl)piperidine-2,6-dione; |
| 5 | 3-(6-(4-(5-(7-(difluoromethyl)-1-(1,3-dimethyl-2-oxo-1,2-dihydro-1,6-naphthyridin-5-yl)-1,2,3,4-tetrahydroquinolin-6-yl)pyridin-2-yl)piperidin-1-yl)-2-oxobenzo[cd]indol-1(2H)-yl)piperidine-2,6-dione; |
| 6 | 3-(6-(4-(4-(7-(difluoromethyl)-1-(1,3-dimethyl-2-oxo-1,2-dihydro-1,6-naphthyridin-5-yl)-1,2,3,4-tetrahydroquinolin-6-yl)-1H-pyrazol-1-yl)-3-fluoropiperidin-1-yl)-2-oxobenzo[cd]indol-1(2H)-yl)piperidine-2,6-dione; |
| 7 | 3-(6-(4-(4-(1-(7-cyclopropyl-1,3-dimethyl-2-oxo-1,2-dihydro-1,6-naphthyridin-5-yl)-7-(difluoromethyl)-1,2,3,4-tetrahydroquinolin-6-yl)-1H-pyrazol-1-yl)piperidin-1-yl)-2-oxobenzo[cd]indol-1(2H)-yl)piperidine-2,6-dione; |
| 8 | 3-(6-(4-(4-(7-(difluoromethyl)-1-(1,3-dimethyl-2-oxo-7-(tetrahydro-2H-pyran-4-yl)-1,2-dihydro-1,6-naphthyridin-5-yl)-1,2,3,4-tetrahydroquinolin-6-yl)-1H-pyrazol-1-yl)piperidin-1-yl)-2-oxobenzo[cd]indol-1(2H)-yl)piperidine-2,6-dione; |
| 9 | 3-(6-(4-(5-(7-(difluoromethyl)-1',3'-dimethyl-2'-oxo-7'-(tetrahydro-2H-pyran-4-yl)-1',2',3,4-tetrahydro-2H-[1,5'-biquinolin]-6-yl)pyridin-2-yl)piperidin-1-yl)-2-oxobenzo[cd]indol-1(2H)-yl)piperidine-2,6-dione; and |

| | |
|---|---|
| 10 | 3-(5-(4-(4-(7-(difluoromethyl)-1',3'-dimethyl-2'-oxo-7'-(tetrahydro-2H-pyran-4-yl)-1',2',3,4-tetrahydro-2H-[1,5'-biquinolin]-6-yl)-1H-pyrazol-1-yl)piperidin-1-yl)-2-oxobenzo[cd]indol-1(2H)-yl)piperidine-2,6-dione |

or a pharmaceutically acceptable salt thereof or a stereoisomer thereof.

In certain embodiments, the present disclosure provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof or a stereoisomer thereof as described herein and at least one pharmaceutically acceptable excipient (such as a pharmaceutically acceptable carrier or diluent). Preferably, the pharmaceutical composition comprises a therapeutically effective amount of at least one compound described herein. The compounds described in the present disclosure 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.

In yet another embodiment, the compounds of the present disclosure are CBP and/or p300 degraders.

In yet another embodiment, the compound of formula (I), or a pharmaceutically acceptable salt thereof or a stereoisomer thereof is a CBP and p300 degrader.

In yet another embodiment, the compound of formula (I), or a pharmaceutically acceptable salt thereof or a stereoisomer thereof is a CBP degrader.

In yet another embodiment, the compound of formula (I), or a pharmaceutically acceptable salt thereof or a stereoisomer thereof is a p300 degrader.

In another embodiment, the present disclosure provides pharmaceutical composition for use in treating and/or preventing a disease and/or disorder responsive to the modulation of CBP and/ or p300 activity.

In another embodiment, the present disclosure provides pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof or a stereoisomer thereof, for use in the manufacture of a medicament for treating and/or preventing a disease and/or disorder responsive to the modulation of CBP and/or p300 activity.

In another embodiment, the present disclosure provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof or a stereoisomer thereof and at least one pharmaceutically acceptable carrier or excipient.

In an embodiment, the present disclosure provides pharmaceutical composition comprising the compound of formula (I), or a pharmaceutically acceptable salt thereof or a stereoisomer thereof for use in treating a subject suffering from a disease or condition associated with CBP and/or p300.

In an embodiment, the present disclosure provides pharmaceutical composition comprising the compound of formula (I), or a pharmaceutically acceptable salt thereof or a stereoisomer thereof for use as a medicament.

In an embodiment, the present disclosure provides pharmaceutical composition comprising the compound of formula (I), or a pharmaceutically acceptable salt thereof or a stereoisomer thereof for use in the manufacture of a medicament for the treatment of cancer.

The compounds of the disclosure are typically administered in the form of a pharmaceutical composition. Such compositions can be prepared using procedures well known in the pharmaceutical art and comprise at least one compound of the present disclosure. The pharmaceutical composition of the present disclosure comprises one or more compounds described herein and one or more pharmaceutically acceptable excipients. Typically, the pharmaceutically acceptable excipients are approved by regulatory authorities or are generally regarded as safe for human or animal use. The pharmaceutically acceptable excipients include, but are not limited to, carriers, diluents, glidants and lubricants, preservatives, buffering agents, chelating agents, polymers, gelling agents, viscosifying agents, solvents and the like.

The pharmaceutical composition can be administered by oral, parenteral or inhalation routes. Examples of the parenteral administration include administration by injection, percutaneous, transmucosal, transnasal and transpulmonary administrations.

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

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

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

Administration of the compounds of the disclosure, in pure form or in an appropriate pharmaceutical composition, can be carried out using any of the accepted routes of administration of pharmaceutical compositions. The route of administration may be any route which effectively transports the active compound of the present disclosure to the appropriate or desired site of action. Suitable routes of administration include, but are not limited to, oral, nasal, buccal, dermal, intradermal, transdermal, parenteral, rectal, subcutaneous, intravenous, intraurethral, intramuscular or topical.

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.

Liquid formulations include, but are not limited to, syrups, emulsions and sterile injectable liquids, such as suspensions or solutions.

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

The pharmaceutical compositions of the present disclosure may be prepared by conventional techniques known in literature.

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

In one embodiment, the compounds as disclosed in the present disclosure are formulated for pharmaceutical administration. Yet another embodiment of the present disclosure provides use of the compounds as disclosed in the present application in the treatment and prevention of diseases and/or disorder responsive to the CBP and/ or p300 degraders activity.

Yet another embodiment of the present disclosure provides use of the compound or a pharmaceutically acceptable salt thereof, in treating and/or preventing a disease for which the symptoms thereof are treated, improved, diminished and/or prevented by CBP and/or p300 degraders.

According to yet another embodiment, the disease and/or disorder responsive to CBP and/or p300 degraders or condition is cancer, viral infection and autoimmune disease or disorder, inflammatory disease or disorder, neurodegenerative disease and metabolic disorder.

According to yet another embodiment, the disease and/or disorder responsive to CBP and/or p300 degraders or condition is cancer.

In yet another aspect of an embodiment, the cancer is cancer is prostate cancer, neuroendocrine prostate cancer, breast cancer, colorectal cancer, colon cancer, pancreatic cancer, intestinal cancer, stomach cancer, hematological cancer, multiple myeloma, chronic lymphocytic leukemia, lymphoma, glioblastoma, myeloid leukemia, acute myeloid leukemia, acute T-cell lymphoma, T-cell lymphoma, leukemia, lympho-plasmacytoid B-cell lymphoma, glioma, small cell lung cancer, neuroblastoma, angiosarcoma, chondrosarcoma, Ewing's sarcoma, fibroblastic sarcoma, gynaecological sarcoma, liposarcoma, osteosarcoma, rhabdomyosarcoma, soft tissue sarcoma, synovial sarcoma, cancer of prostate adenocarcinoma, breast invasive carcinoma, bladder urothelial carcinoma, lung adenocarcinoma, liver hepatocellular carcinoma, cervical squamous cell carcinoma and endocervical adenocarcinoma, cholangiocarcinoma, lung squamous cell carcinoma, colon adenocarcinoma, rectum adenocarcinoma, pancreatic adenocarcinoma, uterine corpus endometrial carcinoma, uterine carcinosarcoma, head and neck squamous cell carcinoma, mesothelioma, testicular germ cell tumors, ovarian serous cystadenocarcinoma, thyroid carcinoma, sarcoma, skin cutaneous melanoma, adrenocortical carcinoma, kidney renal clear cell carcinoma, pheochromocytoma and paraganglioma, kidney renal papillary cell carcinoma, lymphoid neoplasm diffuse large B-cell lymphoma, thymoma, brain lower grade glioma, kidney

chromophobe, glioblastoma multiforme, uveal melanoma, lymphoma or lymphoid malignancy or metastatic cancer.

In yet another aspect of an embodiment, the cancer is colon cancer, colorectal cancer or intestinal cancer.

According to yet another embodiment, the autoimmune or inflammatory disease or disorder is selected from diabetes, multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, fatty liver disease, HIV/AIDS, systemic lupus erythematosus, psoriasis, dermatitis, prurigo nodularis, Addison's disease, acute gout, ankylosing spondylitis, asthma, atherosclerosis, Behcet's disease, bullous skin diseases, chronic obstructive pulmonary disease, Crohn's disease, eczema, giant cell arteritis, fibrosis, glomerulonephritis, hepatic vascular occlusion, hepatitis, hypophysitis, immunodeficiency syndrome, Kawasaki disease, lupus nephritis, myocarditis, myositis, nephritis, organ transplant rejection, osteoarthritis, pancreatitis, pericarditis, Polyarteritis nodosa, pneumonitis, primary biliary cirrhosis, psoriatic arthritis, scleritis, sclerosing cholangitis, sepsis, systemic lupus erythematosus, Takayasu's Arteritis, toxic shock, thyroiditis, ulcerative colitis, uveitis, vitiligo, vasculitis, and Wegener's granulomatosis.

According to yet another embodiment, the neurodegenerative disease is selected from Alzheimer’s disease, Parkinson’s disease, dementia, Huntington’s disease or amyotrophic lateral sclerosis.

According to yet another embodiment, present disclosure provides a method further comprising administering to the subject a therapeutically effective amount of a compounds of the present disclosure along with one or more chemotherapeutic agents, anti-viral agents, anti-inflammatory agent, immunosuppressant agents or pain-relieving agents.

According to yet another embodiment, present disclosure provides a method further comprising administering to the subject a therapeutically effective amount of the compounds of the present disclosure or a pharmaceutically acceptable salt thereof.

According to yet another embodiment, the present disclosure provides compound of formula (I), or a pharmaceutically acceptable salt thereof or a stereoisomer thereof for use in the treatment of cancer.

According to yet another embodiment, the subject is a mammal including human.

According to yet another embodiment, the present disclosure provides compounds or pharmaceutically acceptable salts thereof or stereoisomers thereof, for use as a medicament.

According to yet another embodiment, the disclosure provides the use of the compounds of the present disclosure in the manufacture of a medicament.

According to yet another embodiment, the disclosure provides a compound of formula (I) or a pharmaceutically acceptable salt thereof or a stereoisomer thereof, for use in the manufacture of a medicament for the treatment cancer.

According to yet another embodiment, the disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof or a stereoisomer thereof, for use in degrading the target protein in a subject, wherein the target protein is CBP and/or p300.

According to yet another embodiment, the disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof or a stereoisomer thereof, for use in degrading the target protein in a subject, wherein the target protein is p300.

According to yet another embodiment, the disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof or a stereoisomer thereof, for use in degrading the target protein in a subject, wherein the target protein is CBP.

According to yet another embodiment, the disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof or a stereoisomer thereof, for use in the treatment of CBP and/or p300 mediated disorder.

According to yet another embodiment, the CBP and/or p300-mediated disorder is cancer, viral infection and autoimmune disease or disorder, inflammatory disease or disorder, or neurodegenerative disease and metabolic disorder.

According to yet another embodiment, the disclosure provides the use of the compounds of formula (I) or a pharmaceutically acceptable salt or a stereoisomer thereof, in the manufacture of a medicament for the treatment of disease or disorder responsive to the CBP and/or p300 degradation.

According to yet another embodiment, the disclosure provides a compound or a pharmaceutically acceptable salt or a stereoisomer thereof, in the manufacture of a medicament for the treatment of cancer, an inflammatory disease or disorder, autoimmune disease or disorder, neurodegenerative disease or metabolic disorder.

In yet another embodiment, the disclosure provides the use of the compounds of the present disclosure in the manufacture of a medicament for the treatment of cancer.

In yet another embodiment, the disclosure provides the use of the compounds of the present disclosure in the manufacture of a medicament for the treatment of cancer wherein the cancer is prostate cancer, neuroendocrine prostate cancer, breast cancer, colorectal cancer, colon cancer, pancreatic cancer, intestinal cancer, stomach cancer, hematological cancer, multiple myeloma, chronic lymphocytic leukemia, lymphoma, glioblastoma, myeloid leukemia, acute myeloid leukemia, acute T-cell lymphoma, T-cell lymphoma, leukemia, lympho-plasmacytoid B-cell lymphoma, glioma, small cell lung cancer, neuroblastoma, angiosarcoma, chondrosarcoma, Ewing's sarcoma, fibroblastic sarcoma, gynaecological sarcoma, liposarcoma, osteosarcoma, rhabdomyosarcoma, soft tissue sarcoma, synovial sarcoma, cancer of prostate adenocarcinoma, breast invasive carcinoma, bladder urothelial carcinoma, lung adenocarcinoma, liver hepatocellular carcinoma, cervical squamous cell carcinoma and endocervical adenocarcinoma, cholangiocarcinoma, lung squamous cell carcinoma, colon adenocarcinoma, rectum adenocarcinoma, pancreatic adenocarcinoma, uterine corpus endometrial carcinoma, uterine carcinosarcoma, head and neck squamous cell carcinoma, mesothelioma, testicular germ cell tumors, ovarian serous cystadenocarcinoma, thyroid carcinoma, sarcoma, skin cutaneous melanoma, adrenocortical carcinoma, kidney renal clear cell carcinoma, pheochromocytoma and paraganglioma, kidney renal papillary cell carcinoma, lymphoid neoplasm diffuse large B-cell lymphoma, thymoma, brain lower grade glioma, kidney chromophobe, glioblastoma multiforme, uveal melanoma, lymphoma or lymphoid malignancy or metastatic cancer.

In yet another embodiment, the present application provides compounds for use as a medicament for treating a subject suffering from diseases and/or disorder responsive to the CBP and/or p300 degradation activity.

In yet another embodiment, the present disclosure comprises administering to the subject in need thereof a therapeutically effective amount of a compound of the present disclosure along with one or more additional chemotherapeutic agents independently selected from anti-proliferative agents, anti-cancer agents, immunosuppressant agents and pain-relieving agents.

In yet another embodiment, the present disclosure comprises administering to the subject in need thereof a therapeutically effective amount of a compound of the present

disclosure along with one or more additional anti-viral agents and drugs used in the treatment of autoimmune disease or disorder.

The method(s) of treatment of the present disclosure comprises administering a safe and therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof or a stereoisomer thereof to a patient (particularly a human) in need thereof.

In certain embodiments, the present disclosure provides a method of treating or preventing a disease and/or disorder responsive to CBP and/or p300 degraders in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of formula (I) , or a pharmaceutically acceptable salt thereof or a stereoisomer thereof.

According to the preceding embodiment, the disease or disorder is cancer, viral infection and autoimmune disease or disorder, inflammatory disease or disorder, neurodegenerative disease and metabolic disorder.

According to yet another embodiment, the disease or disorder is cancer.

In certain embodiments, the present disclosure provides a method of modulating p300 in a subject, comprising contacting CBP and/or p300 proteins with a compound of formula (I), or a pharmaceutically acceptable salt thereof or a stereoisomer thereof.

In certain embodiments, the present disclosure provides a method of treating or preventing a disease or disorder mediated by CBP and/or p300 proteins, the disease or disorder is cancer, viral infection, autoimmune disease or disorder, inflammatory disease or disorder, neurodegenerative disease and metabolic disorder.

According to certain foregoing embodiments, the present disclosure provides a method wherein the disease or disorder is cancer.

According to certain foregoing embodiments, the present disclosure provides a method wherein the cancer is prostate cancer, neuroendocrine prostate cancer, breast cancer, colorectal cancer, colon cancer, pancreatic cancer, intestinal cancer, stomach cancer, hematological cancer, multiple myeloma, chronic lymphocytic leukemia, lymphoma, glioblastoma, myeloid leukemia, acute myeloid leukemia, acute T-cell lymphoma, T-cell lymphoma, leukemia, lympho-plasmacytoid B-cell lymphoma, glioma, small cell lung cancer, neuroblastoma,

angiosarcoma, chondrosarcoma, Ewing's sarcoma, fibroblastic sarcoma, gynaecological sarcoma, liposarcoma, osteosarcoma, rhabdomyosarcoma, soft tissue sarcoma, synovial sarcoma, cancer of prostate adenocarcinoma, breast invasive carcinoma, bladder urothelial carcinoma, lung adenocarcinoma, liver hepatocellular carcinoma, cervical squamous cell carcinoma and endocervical adenocarcinoma, cholangiocarcinoma, lung squamous cell carcinoma, colon adenocarcinoma, rectum adenocarcinoma, pancreatic adenocarcinoma, uterine corpus endometrial carcinoma, uterine carcinosarcoma, head and neck squamous cell carcinoma, mesothelioma, testicular germ cell tumors, ovarian serous cystadenocarcinoma, thyroid carcinoma, sarcoma, skin cutaneous melanoma, adrenocortical carcinoma, kidney renal clear cell carcinoma, pheochromocytoma and paraganglioma, kidney renal papillary cell carcinoma, lymphoid neoplasm diffuse large B-cell lymphoma, thymoma, brain lower grade glioma, kidney chromophobe, glioblastoma multiforme, uveal melanoma, lymphoma or lymphoid malignancy or metastatic cancer.

In certain embodiments, the present disclosure provides a method of treating or preventing viral infection in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the compound of formula (I), or a pharmaceutically acceptable salt thereof or a stereoisomer thereof.

In certain embodiments, the present disclosure provides a method of treating or preventing autoimmune or inflammatory disease in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the compound of formula (I), or a pharmaceutically acceptable salt thereof or a stereoisomer thereof.

According to certain foregoing embodiments, the present disclosure provides a method wherein the autoimmune or inflammatory disease or disorder is selected from diabetes, multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, fatty liver disease, HIV/AIDS, systemic lupus erythematosus, psoriasis, dermatitis, prurigo nodularis, Addison's disease, acute gout, ankylosing spondylitis, asthma, atherosclerosis, Behcet's disease, bullous skin diseases, chronic obstructive pulmonary disease, Crohn's disease, eczema, giant cell arteritis, fibrosis, glomerulonephritis, hepatic vascular occlusion, hepatitis, hypophysitis, immunodeficiency syndrome, Kawasaki disease, lupus nephritis, myocarditis, myositis, nephritis, organ transplant rejection, osteoarthritis, pancreatitis, pericarditis, Polyarteritis nodosa, pneumonitis, primary biliary cirrhosis, psoriatic arthritis, scleritis, sclerosing

cholangitis, sepsis, systemic lupus erythematosus, Takayasu's Arteritis, toxic shock, thyroiditis, ulcerative colitis, uveitis, vitiligo, vasculitis, and Wegener's granulomatosis.

In certain embodiments, the present disclosure provides a method of treating or preventing neurodegenerative disease in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the compound of formula (I), or a pharmaceutically acceptable salt thereof or a stereoisomer thereof.

According to certain foregoing embodiments, the present disclosure provides a method wherein the neurodegenerative disease is selected from Alzheimer's disease, Parkinson's disease, dementia, Huntington's disease or amyotrophic lateral sclerosis.

According to certain foregoing embodiments, the present disclosure provides a method comprising administering to the subject in need thereof a therapeutically effective amount of a compound of the present disclosure along with one or more chemotherapeutic agents, anti-viral agents, anti-inflammatory agent, immunosuppressant agents or pain-relieving agents.

In certain embodiments, the present disclosure provides a method of treating or preventing viral infection in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the compound of formula (I), or a pharmaceutically acceptable salt thereof or a stereoisomer thereof.

In certain embodiments, the present disclosure provides a method of treating or preventing autoimmune disease or disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the compound of formula (I), or a pharmaceutically acceptable salt thereof or a stereoisomer thereof.

In certain embodiments, the present disclosure provides a method of treating or preventing cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the compound of formula (I), or a pharmaceutically acceptable salt thereof or a stereoisomer thereof.

Compounds of the disclosure are indicated both in the therapeutic and/or prophylactic treatment of the above-mentioned conditions. For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder or disease indicated.

The compounds of the present disclosure may be used as single drug or as a pharmaceutical composition in which the compound is mixed with various pharmacologically acceptable materials.

According to one embodiment, the present disclosure provides compounds for use in combination with other compounds or biologic entities for treatment of cancer. Suitable combinations and doses of compounds for combination therapy used in treating the diseases or disorders described herein can be determined by those skilled in the relevant art. Combination therapies for compounds of the present disclosure can be used for treatment of cancer.

According to one embodiment, the compounds of the present disclosure can also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the present disclosure also embraces isotopically-labeled variants of the present disclosure which are identical to those recited herein, but for the fact that one or more atoms of the compound are replaced by an atom having the atomic mass or mass number different from the predominant atomic mass or mass number usually found in nature for the atom. All isotopes of any particular atom or element as specified are contemplated within the scope of the compounds of the disclosure and their uses. Exemplary isotopes that can be incorporated in to compounds of the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, chlorine and iodine, such as $^{2}H$ ("D"), $^{3}H$, $^{11}C$, $^{13}C$, $^{14}C$, $^{13}N$, $^{15}N$, $^{15}O$, $^{17}O$, $^{18}O$, $^{32}P$, $^{33}P$, $^{35}S$, $^{18}F$, $^{36}Cl$, $^{123}I$ and $^{125}I$. Isotopically labeled compounds of the present disclosure can generally be prepared by following procedures analogous to those disclosed in the schemes and/or in the examples herein below, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

**EXPERIMENTAL**

The present application provides methods for the preparation of compound of formula (I), according to the description provided herein using appropriate methods and/or materials. It is to be understood by those skilled in the art that known variations of the conditions and processes of the following procedures can be used to prepare these intermediates and compounds. Moreover, by utilizing the procedures described in detail, one of ordinary skill in the art can prepare additional compounds of the present disclosure.

Following general guidelines apply to all experimental procedures described here. Until otherwise stated, experiments are performed under positive pressure of nitrogen, temperature described are the external temperature (i.e. oil bath temperature). Reagents and solvents

received from vendors are used as such without any further drying or purification. Molarities mentioned here for reagents in solutions are approximate as it was not verified by a prior titration with a standard. All reactions are stirred under magnetic stir bar. Cooling to minus temperature was done by acetone / dry ice or wet ice / salts. Magnesium sulfate and sodium sulfate were used as solvent drying agent after reaction work up and are interchangeable. Removing of solvents under reduced pressure or *under vacuum* means distilling of solvents in rotary evaporator.

Compounds of this disclosure may be made by synthetic chemical processes, examples of which are shown herein. It is meant to be understood that the order of the steps in the processes may be varied, that reagents, solvents and reaction conditions may be substituted for those specifically mentioned and that vulnerable moieties may be protected and deprotected, as necessary.

The specifics of the process for preparing compounds of the present disclosure are detailed in the experimental section.

The present disclosure shall be illustrated by means of some examples, which are not construed to be viewed as limiting the scope of the disclosure.

Unless otherwise stated, work-up includes distribution of the reaction mixture between the organic and aqueous phases, separation of layers and drying the organic layer over anhydrous sodium sulphate, filtration and evaporation of the solvent. Purification, unless otherwise mentioned, includes purification by silica gel chromatographic techniques, generally using ethyl acetate/petroleum ether mixture of a suitable polarity as the mobile phase.

Analysis for the compounds of the present disclosure unless mentioned, was conducted in general methods well known to a person skilled in the art. Having described the disclosure with reference to certain preferred embodiments, other embodiments will become apparent to one skilled in the art from consideration of the specification. The disclosure is further defined by reference to the following examples, describing in detail the analysis of the compounds of the disclosure.

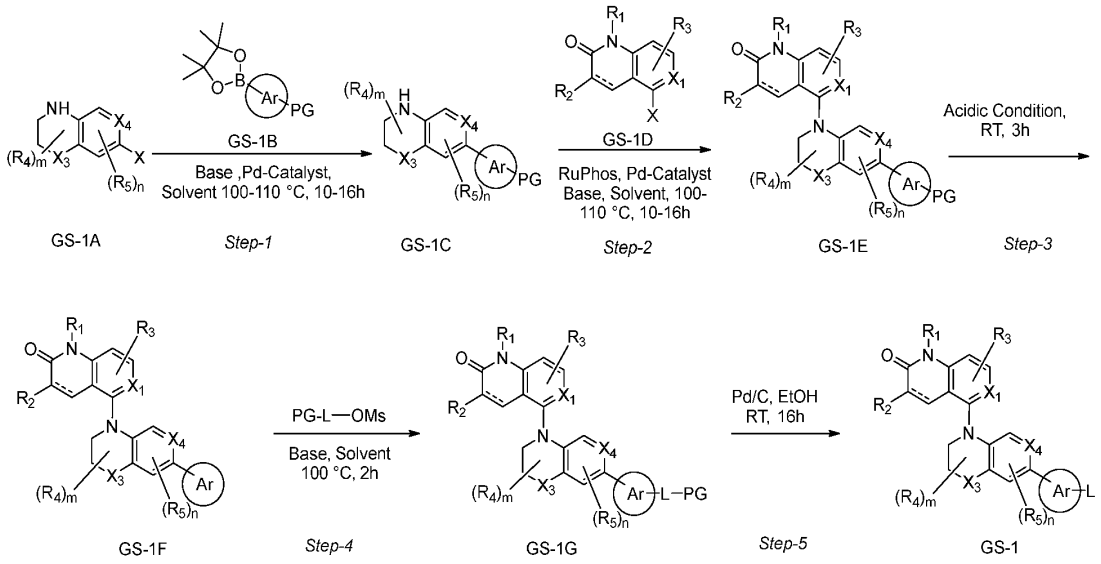
It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the scope of the disclosure. Some of the intermediates were taken to next step based on TLC results, without further characterization, unless otherwise specified.

## ABBREVATIONS

DCM - Dichloromethane; RM - Reaction mixture; EtOAc/EA - Ethyl acetate; Pd(dppf)$Cl_2$.DCM - 1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II); RuPhos Pd G2 - Chloro(2-dicyclohexylphosphino-2′,6′-diisopropoxy-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II); RuPhos - 2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl; TLC - This layer chromatography; RT - Room temperature; THF - tetrahydrofuran; SM - Starting material; LC-MS - Liquid chromatography-mass spectrometry; NMP - N-Methyl-2-pyrrolidone; MTBE - Methyl tert-butyl ether; DMF - N,N-Dimethylformamide; HCl – Hydrochloric acid; Ar - Argon; TFA - Trifluoroacetic acid; EtOH - Ethyl alcohol; Pd/C - Palladium on carbon; NaOH - Sodium hydroxide; $K_2CO3$- Potassium carbonate; $Tf_2O$ - Trifluoromethanesulfonic anhydride; [Pd-PEPPSI-I Hept-Cl] – [3-chloropyridine;4,5-dichloro-1,3-bis[2,6-di(heptan-4-yl)phenyl]-2*H*-imidazol-2-ide;dichloropalladium complex]; $PtO_2$ - platinum oxide; TEA - Triethylamine; DMSO - Dimethyl sulfoxide; NaOtBu - sodium tert-butoxide; $Pd(OAc)_2$ - Palladium acetate; HPLC - High-performance liquid chromatography; NMR - Nuclear Magnetic Resonance; s - Singlet; d - Doublet; t - Triplet; q - Quartet; dd - doublet of doublets; td - Triplet of doublets; h – Hour; MHz – Megahertz; and Comp. - Compound.

## GENERAL SCHEMES:

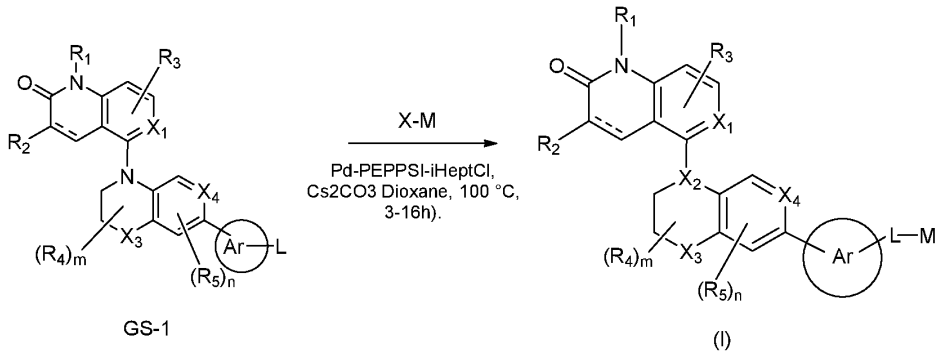
## GENERAL SCHEME-1




X= halogen
PG= Nitrogen-Protecting Group
X1, X3, X4, R1, R2, R3, R4, R5, Ar, L, and M is as defined as in the specification.

Some compounds of the present invention may be generally synthesized utilizing the process outlined in General Scheme-1. The intermediate GS-1B was reacted with GS-1A with suitable reaction conditions (Base: $K_2CO3$, $Pd(dppf)Cl_2.DCM$, Solvents : Dioxane, Water, under 100-110 °C, 10-16h), to afford GS-1C, which further undergoes coupling reaction with GS-1D under suitable conditions (Base: NaOtBu, RuPhos, Ruphos-Pd-Catalyst, Solvents : Dioxane, Water, under 100-110 °C, 10-16h) to afford GS-1E. GS-1E Further underwent deprotection with suitable conditions (Acidic conditions like HCl, THF, RT, 3h) to afford GS-1F. GS-1F forms GS-1G in the presence of suitable reagents and conditions (Base : $Cs_2CO_3$, Solvent: DMF, 100-110 °C, 2h). GS-1G further gets deprotected to form GS-1 under suitable reaction conditions like (Pd/C, EtOH, RT, 16h).

**GENERAL SCHEME-2**

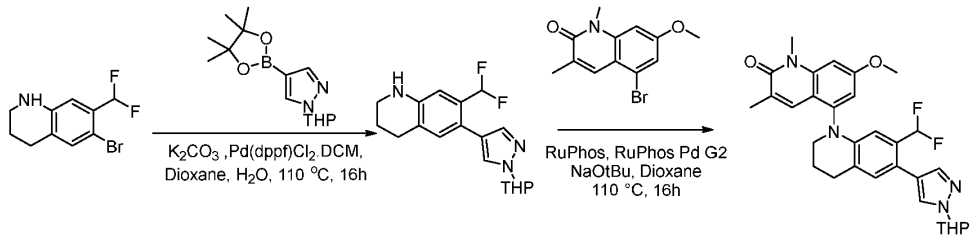



X= halogen
X1, X3, X4, R1, R2, R3, R4, R5, Ar, L, and M is as defined as in the specification.

Some compounds of the present invention may be generally synthesized utilizing the process outlined in General Scheme-2. The intermediate GS-1 reacts with X-M to afford formula (I) under suitable conditions like (Pd-PEPPSI-iHeptCl, $Cs_2CO_3$ Dioxane, 100 °C, 3-16h).

**SYNTHESIS OF INTERMEDIATES:**

**Intermediate-1: 7-(difluoromethyl)-7'-methoxy-1',3'-dimethyl-6-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-3,4-dihydro-2H-[1,5'-biquinolin]-2'(1'H)-one**




*Step-1* 1-A *Step-2* **Intermediate-1**

**Step-1: 7-(difluoromethyl)-6-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroquinoline**

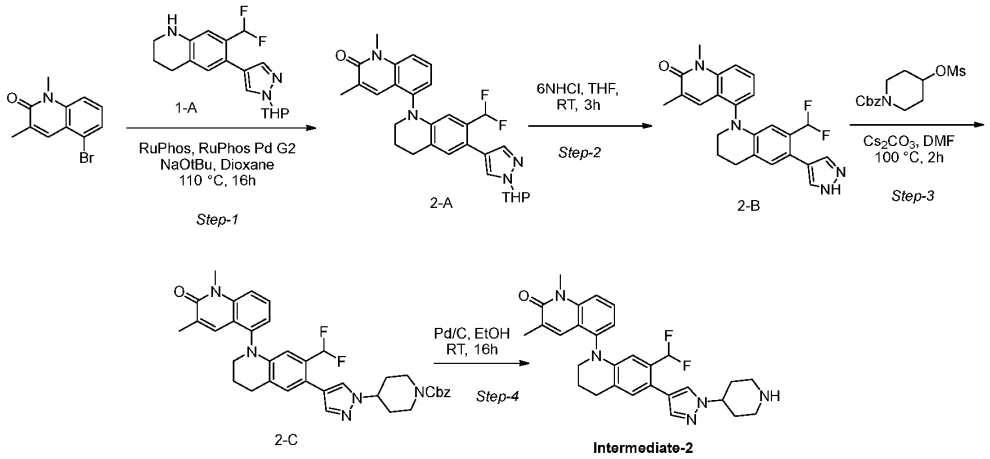
To a mixture of 6-bromo-7-(difluoromethyl)-1,2,3,4-tetrahydroquinoline (29 g, 110.64 mmol) and 1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (33.8 g, 278.16 mmol) in water (110 ml) and dioxane (430 ml), was added $K_2CO_3$ (30.5 g, 221.29 mmol) and purged with argon for 5 mins. To this Pd(dppf)$Cl_2$.DCM (8.09 g, 11.06 mmol) was added and purged argon again for 5 mins. The reaction mixture was heated at 110°C for 16 h. Reaction mixture was dissolved in ethyl acetate and filtered through celite bed. Water was added to the filtrate and the organic layer was separated and concentrated under reduced pressure to afford crude product. Purification was done using combi flash in EtOAc-Hexane system. Crude product was eluted at 15-20% EtOAc-Hexane to afford the pure title intermediate 1-A (29 g, 78.62%).

**Step-2: 7-(difluoromethyl)-7'-methoxy-1',3'-dimethyl-6-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-3,4-dihydro-2H-[1,5'-biquinolin]-2'(1'H)-one**

5-bromo-7-methoxy-1,3-dimethylquinolin-2(1H)-one (5 g, 17.72 mmol) and intermediate 1-A (7.6 g, 23.03 mmol) were taken in 1,4-dioxane (50 ml) and sodium tert-butoxide (4.25 g, 44.3 mmol) was added under argon gas atmosphere in a seal tube. Then RuPhos (0.99 g, 2.12 mmol) and RuPhos Pd G2 (0.2 g, 0.26 mmol) were added and once again purging was continued for another 5 min. Then the seal tube was closed and heated at 110 °C for 16h. The progress was monitored by TLC. TLC showed completion of the starting materials. Then RM was cooled to RT and filtered through celite using ethyl acetate. Ethyl acetate layer was washed with water and brine solution. Organic layer was concentrated under

reduced pressure to afford crude. Crude was purified by using combi flash in Ethyl acetate-Hexane system. Desired product eluted at 40-70% ethyl acetate-hexane to afford the pure intermediate-1 (4 g, 42.2%).

**Intermediate-2: 7-(difluoromethyl)-1',3'-dimethyl-6-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-3,4-dihydro-2H-[1,5'-biquinolin]-2'(1'H)-one**




**Step-1: Synthesis of 7-(difluoromethyl)-1',3'-dimethyl-6-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-3,4-dihydro-2H-[1,5'-biquinolin]-2'(1'H)-one**

5-bromo-1,3-dimethylquinolin-2(1H)-one (10 g, 39.66 mmol) and intermediate 1-A (14.54 g, 43.63 mmol) were taken in 1,4-dioxane (200 ml) and sodium tert-butoxide (9.53 g, 99.16 mmol) was added under argon gas atmosphere in a seal tube. Then RuPhos (2.22 g, 4.76 mmol) and RuPhos Pd G2 (1.8 g, 2.38 mmol) were added and once again purging was continued for another 5 min. Then the seal tube was closed and heated at 110 °C for 16h. The progress was monitored by TLC. TLC showed completion of the starting materials. Then RM was cooled to RT and filtered through celite using ethyl acetate. Ethyl acetate layer was washed with water and brine solution. Organic layer was concentrated under reduced pressure to afford crude. Crude was purified by using combi flash in Ethyl acetate-Hexane system. Desired product eluted at 40-70% ethyl acetate-hexane to afford the pure intermediate 2-A (16 g, crude). LC-MS: 505.23 $[M+H]^+$.

**Step-2: Synthesis of 7-(difluoromethyl)-1',3'-dimethyl-6-(1H-pyrazol-4-yl)-3,4-dihydro-2H-[1,5'-biquinolin]-2'(1'H)-one**

Intermediate 2-A (16 g, 31.71 mmol) was taken in THF (160 ml) and added 6N HCl (160 ml) then the reaction mixture was stirred at RT for 3h The reaction mixture was evaporated and basified with saturated sodium bicarbonate in ice cold conditions. The resultant solid was vacuum filtered and washed with hexane to get the title intermediate 2-B (12 g). LC-MS: 421.41 $[M+H]^+$.

**Step-3: Synthesis of benzyl 4-(4-(7-(difluoromethyl)-1',3'-dimethyl-2'-oxo-1',2',3,4-tetrahydro-2H-[1,5'-biquinolin]-6-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate**

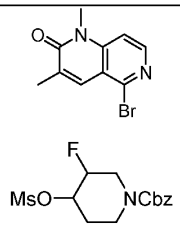
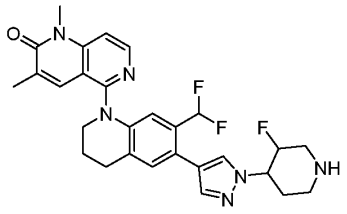
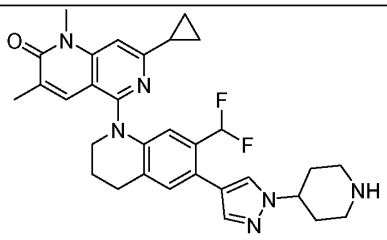
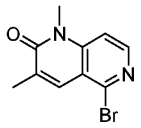
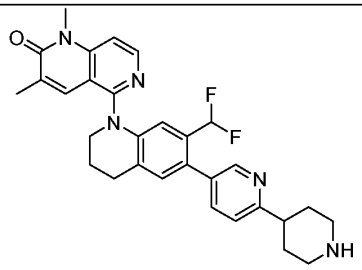
To intermediate 2-B (12g, 28.53mmol) in DMF (250ml) was added $Cs_2CO_3$ (23.24g, 71.35mmol). Stir for 15min and add benzyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate ( 17.88g, 57.07mmol). RM was heated to 100 °C for 2h. Progress of the reaction was monitored by TLC till SM was consumed. RM was extracted with ethyl acetate and water organic layers were concentrated and washed with pentane to get the title intermediate 2-C (15g, crude). LC-MS: 638.3 $[M+H]^+$.

**Step-4: Synthesis of 7-(difluoromethyl)-1',3'-dimethyl-6-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-3,4-dihydro-2H-[1,5'-biquinolin]-2'(1'H)-one**

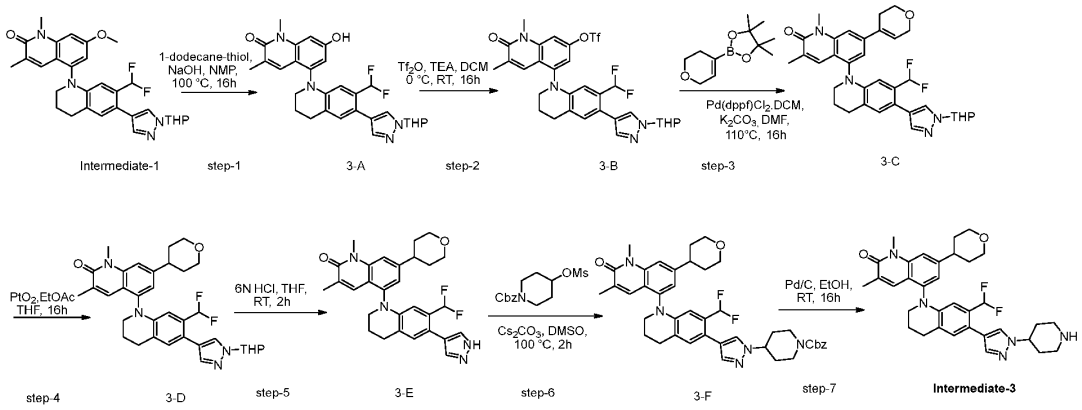
To intermediate 2-C (4.5g, 7.05mmol) in EtOH (100 ml) was added Pd/C (0.6g, 5.64mmol) at inert atmosphere then RM was stirred at RT for 16h under $H_2$ atmosphere. Progress of the reaction was monitored by TLC. SM was consumed, RM was filtered through cellite and washed with methanol. Filtrate was concentrated to afford a crude. Crude was washed with diethyl ether to get the title intermediate-2 (4g, crude). LC-MS: 504.41 $[M+H]^+$.

The intermediates listed in below **Table-1** were prepared by reacting the corresponding starting material and using a procedure similar to the one described in step 1 to 4 of synthesis of intermediate-2 with appropriate variations in quantities of reagents, solvents and reaction conditions. The characterization data of the compounds are summarized herein the below table-1.

**Table-1:**

| Intermediate No. | Raw material used | Intermediate structure | Characterization data |
|---|---|---|---|
| A-1 |  |  | LC-MS: 523.21 $[M+H]^+$. |
| A-2 | Intermediate-5 |  | LC-MS: 545.1 $[M+H]^+$. |
| A-3 |  & Intermediate-6 |  | LC-MS: 516.3 $[M+H]^+$. |

**Intermediate-3: 7-(difluoromethyl)-1',3'-dimethyl-6-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-7'-(tetrahydro-2H-pyran-4-yl)-3,4-dihydro-2H-[1,5'-biquinolin]-2'(1'H)-one**




**Step-1: Synthesis of 7-(difluoromethyl)-7'-hydroxy-1',3'-dimethyl-6-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-3,4-dihydro-2H-[1,5'-biquinolin]-2'(1'H)-one**

To 7-(difluoromethyl)-7'-methoxy-1',3'-dimethyl-6-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-3,4-dihydro-2H-[1,5'-biquinolin]-2'(1'H)-one (3.7g, 6.92mmol) in NMP (15 ml) was added NaOH (0.83g, 20.76mmol) and 1-dodecane-thiol (2.1g, 10.38mmol). The reaction mixture was heated at 100 °C for 16h. RM was acidified with 1N HCl, precipitated solid was filtered and dried. Solid was washed with MTBE and dried to afford the title intermediate 3-A (3.4g, crude). LC-MS: 521.41 $[M+H]^+$.

**Step-2: Synthesis of 7-(difluoromethyl)-1',3'-dimethyl-2'-oxo-6-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-1',2',3,4-tetrahydro-2H-[1,5'-biquinolin]-7'-yl trifluoromethanesulfonate**

To intermediate 3-A (0.5g, 0.93mmol) in DCM (20 ml) was added triethylamine (0.47g, 4.67mmol) and triflic anhydride (0.79g, 2.80mmol). The reaction mixture was stirred at RT for 16h. Water was added and extracted with dichloromethane and evaporated to afford the title intermediate 3-B (0.8g, crude). LC-MS: 653.12 $[M+H]^+$.

**Step-3: Synthesis of 7-(difluoromethyl)-7'-(3,6-dihydro-2H-pyran-4-yl)-1',3'-dimethyl-6-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-3,4-dihydro-2H-[1,5'-biquinolin]-2'(1'H)-one**

Intermediate 3-B (1.4g, 2.14mmol) and 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.6g, 3.21mmol) were taken in DMF (30 ml) and added $K_2CO_3$ (0.88g, 6.43mmol). Reaction mixture was purged with argon gas for 5 min and $Pd(dppf)Cl_2$.DCM was added (0.26g, 0.32mmol). The reaction mixture was heated at 110 °C for 16h. Progress of the reaction was monitored by analysis then reaction mixture was extracted with ethyl acetate and water. The organic layer was dried and concentrated under reduced pressure. Crude material was purified by combi flash column chromatography using 24g column and elutes at 50-60% EA and hexane and evaporated to afford the title intermediate 3-C (1g, 79.47%). LC-MS: 587.4 $[M+H]^+$.

**Step-4: Synthesis of 7-(difluoromethyl)-1',3'-dimethyl-6-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-7'-(tetrahydro-2H-pyran-4-yl)-3,4-dihydro-2H-[1,5'-biquinolin]-2'(1'H)-one**

Intermediate 3-C (1g, 1.70mmol) in THF (8 ml) and ethyl acetate (4 ml) was added platinum oxide (0.19g, 0.85mmol). Reaction mixture was stirred under hydrogen for 16h. The

progress of the reaction was monitored by analysis then reaction mixture was filtered through celite and evaporated to afford the title intermediate 3-D (0.8g, crude). LC-MS: 589.3 $[M+H]^+$.

**Step-5: Synthesis of 7-(difluoromethyl)-1',3'-dimethyl-6-(1H-pyrazol-4-yl)-7'-(tetrahydro-2H-pyran-4-yl)-3,4-dihydro-2H-[1,5'-biquinolin]-2'(1'H)-one**

Intermediate 3-D (0.8g, 1.35mmol) was taken in THF (20 ml) and added 6N HCl (7 ml) then the reaction mixture was stirred at RT for 2h. Reaction mixture was evaporated and basified with saturated sodium bicarbonate in ice cold conditions. The resultant solid was vacuum filtered and washed with hexane to afford the title intermediate 3-E (4g). LC-MS: 505.24 $[M+H]^+$.

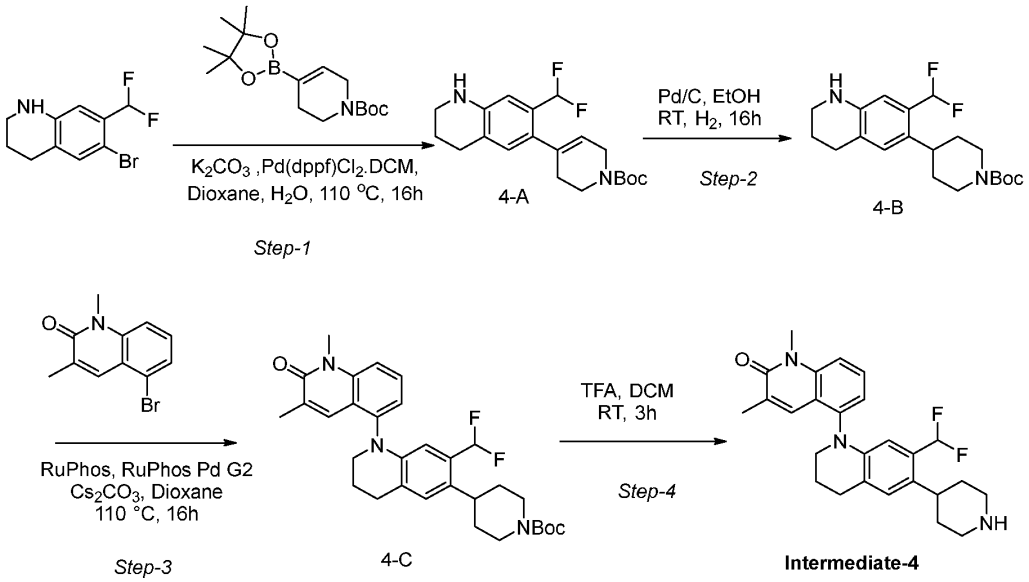
**Step-6: Synthesis of benzyl 4-(4-(7-(difluoromethyl)-1',3'-dimethyl-2'-oxo-7'-(tetrahydro-2H-pyran-4-yl)-1',2',3,4-tetrahydro-2H-[1,5'-biquinolin]-6-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate**

To intermediate 3-E (4g, 8.87mmol) in DMSO (40ml) was added $Cs_2CO_3$ (11.5g, 35.51mmol). Stir for 15min and add benzyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate ( 5.54g, 17.75mmol). RM was heated to 100 °C for 2h. Progress of the reaction was monitored by TLC till SM was consumed. RM was extracted with ethyl acetate and water organic layers were concentrated and washed with pentane to get the title intermediate 3-F (6g, crude). LC-MS: 722.43 $[M+H]^+$.

**Step-7: Synthesis of 7-(difluoromethyl)-1',3'-dimethyl-6-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-7'-(tetrahydro-2H-pyran-4-yl)-3,4-dihydro-2H-[1,5'-biquinolin]-2'(1'H)-one**

To intermediate 3-F (5g, 7.48mmol) in EtOH (50 ml) was added Pd/C (0.5g, 4.69mmol) at inert atmosphere then RM was stirred at RT for 16h under $H_2$ atmosphere. Progress of the reaction was monitored by TLC. SM was consumed, RM was filtered through celite and washed with methanol. Filtrate was concentrated to afford a crude. Crude was washed with diethyl ether to get the title intermediate-3 (2.7g, crude). LC-MS: 588.3 $[M+H]^+$.

**Intermediate-4:**




**Step-1: tert-butyl 4-(7-(difluoromethyl)-1,2,3,4-tetrahydroquinolin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate**

To a mixture of 6-bromo-7-(difluoromethyl)-1,2,3,4-tetrahydroquinoline (1 g, 3.81 mmol) and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (1.76 g, 5.72 mmol) in water (2 ml) and 1,4-dioxane (18 ml), was added $K_2CO_3$ (1.58 g, 11.44 mmol) and purged with argon for 5 mins. To this $Pd(dppf)Cl_2.DCM$ (0.31 g, 0.38 mmol) was added and purged argon again for 5 mins. The reaction mixture was heated at 110°C for 16 h. Reaction mixture was dissolved in ethyl acetate and filtered through celite bed. Water was added to the filtrate and the organic layer was separated and concentrated under reduced pressure to afford crude product. Purification was done using combi flash in EtOAc-Hexane system. Crude product was eluted at 15-20% EtOAc-Hexane to afford the pure title intermediate 4-A (1.3 g, 93.5%).

**Step-2: tert-butyl 4-(7-(difluoromethyl)-1,2,3,4-tetrahydroquinolin-6-yl)piperidine-1-carboxylate**

Intermediate 4-A (1.0 g, 2.74 mmol) in Ethanol (20ml) was added Pd/C (0.14 g, 1.37 mmol) and the reaction mixture was stirred under hydrogen atmosphere for 16h at RT. TLC showed completion of SM. Filtered through celite and evaporated to afford desired intermediate 4-B (0.8 g, 79.56%).

**Step-3: tert-butyl 4-(7-(difluoromethyl)-1',3'-dimethyl-2'-oxo-1',2',3,4-tetrahydro-2H-[1,5'-biquinolin]-6-yl)piperidine-1-carboxylate**

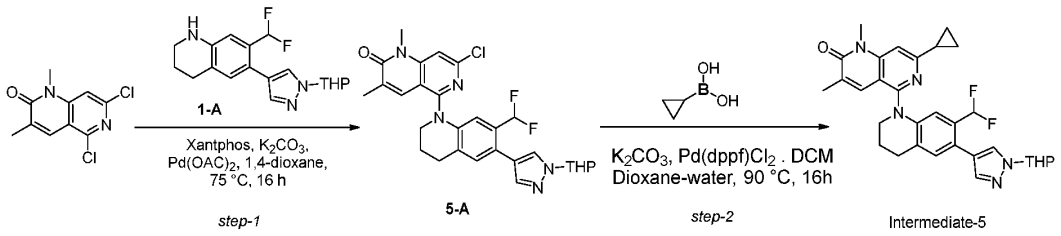
5-bromo-7-methoxy-1,3-dimethylquinolin-2(1H)-one (0.2 g, 0.79 mmol) and intermediate 4-B (0.34 g, 0.95 mmol) were taken in 1,4-dioxane (5 ml) and cesium carbonate (0.77 g, 2.37 mmol) was added under argon gas atmosphere in a seal tube. Then RuPhos (37 mg, 0.079 mmol) and RuPhos Pd G2 (62 mg, 0.079 mmol) were added and once again purging was continued for another 5 min. Then the seal tube was closed and heated at 110 °C for 16h. The progress was monitored by TLC. TLC showed completion of the starting materials. Then RM was cooled to RT and filtered through celite using ethyl acetate. Ethyl acetate layer was washed with water and brine solution. Organic layer was concentrated under reduced pressure to afford crude. Crude was purified by using combi flash in Ethyl acetate-Hexane system. Desired product eluted at 40-70% ethyl acetate-hexane to afford the pure intermediate 4-C (0.25 g, 58.64%).

**Step-4: 7-(difluoromethyl)-1',3'-dimethyl-6-(piperidin-4-yl)-3,4-dihydro-2H-[1,5'-biquinolin]-2'(1'H)-one**

Intermediate 4-C (0.18 g, 0.33 mmol) was taken in DCM (4 ml) and added TFA (0.19 g, 1.67 mmol) then the reaction mixture was stirred at RT for 3h. The reaction mixture was evaporated and basified with saturated sodium bicarbonate in ice cold conditions. The resultant solid was vacuum filtered and washed with hexane to get the title Intermediate-4 (0.13 g).

**Intermediate-5:**

**Synthesis of 5-(7-(difluoromethyl)-6-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-7-methoxy-1,3-dimethyl-1,6-naphthyridin-2(1H)-one**




**Step-1: 7-chloro-5-(7-(difluoromethyl)-6-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-1,3-dimethyl-1,6-naphthyridin-2(1H)-one**

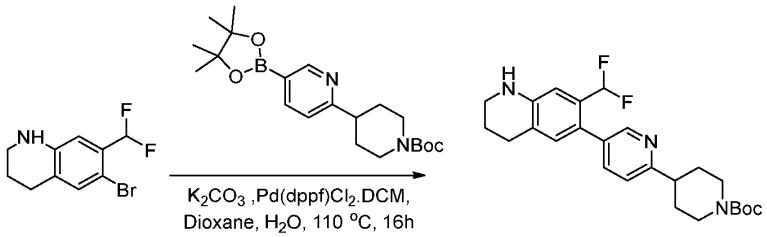
A solution of 5,7-dichloro-1,3-dimethyl-1,6-naphthyridin-2(1H)-one (1g, 4.11mmol) and intermediate 1-A (1.5g, 4.52mmol) in 1,4-dioxane (25ml) were taken in a biotage vial and added potassium carbonate (1.7g, 12.34mmol) and palladium acetate (92mg, 0.41mmol)

followed by xantphos (0.47g, 0.82mmol). The reaction mixture was stirred for 16 hours at 75° C. The progress of the reaction was monitored by checking TLC. After 16 hours, the reaction mixture was cooled to RT. Water was added to the reaction mixture and extracted with ethyl acetate. The organic layer was passed through sodium sulphate, concentrated on rota and purification was done by combi flash column chromatography to afford intermediate 5-A. (0.5g, 22.5%). LC-MS: 540.05 $[M+H]^+$.

**Step-2: 7'-cyclopropyl-7-(difluoromethyl)-1',3'-dimethyl-6-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-3,4-dihydro-2H-[1,5'-biquinolin]-2'(1'H)-one**

Intermediate 5-A (0.5g, 0.92mmol) and cyclopropylboronic acid (0.16g, 1.85mmol) were taken in dioxane (12ml) and added $K_2CO_3$ (0.32g, 2.31mmol) in water (3ml) this was purged with Ar gas for 5 min and added $Pd(dppf)_2Cl_2$.DCM (75mg, 0.092mmol) and again purged for 5min. This RM was heated at 90°C for 16h. Progress of the reaction was monitored by TLC analysis then reaction mixture was extracted with ethyl acetate and water. Organic layers were dried and concentrated under reduced pressure and purification was done by combi flash column chromatography to afford intermediate-5. (0.34g, 68%). LC-MS: 546.12 $[M+H]^+$.

**Intermediate-6:**




*Step-1*

**Intermediate 6**

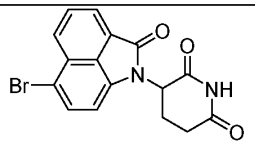
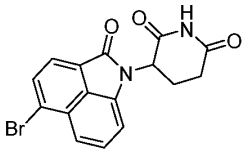
**Step-1: tert-butyl 4-(5-(7-(difluoromethyl)-1,2,3,4-tetrahydroquinolin-6-yl)pyridin-2-yl)piperidine-1-carboxylate**

To a mixture of 6-bromo-7-(difluoromethyl)-1,2,3,4-tetrahydroquinoline (2 g, 7.63 mmol) and tert-butyl 4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperidine-1-carboxylate (2.7 g, 11.44 mmol) in water (10 ml) and dioxane (80 ml), was added $K_2CO_3$ (2.63 g, 19.07 mmol) and purged with argon for 5 mins. To this $Pd(dppf)Cl_2$.DCM (0.55 g, 0.76 mmol) was added and purged argon again for 5 mins. The reaction mixture was heated at 110°C for 16 h. Reaction mixture was dissolved in ethyl acetate and filtered through celite bed. Water was added to the filtrate and the organic layer was

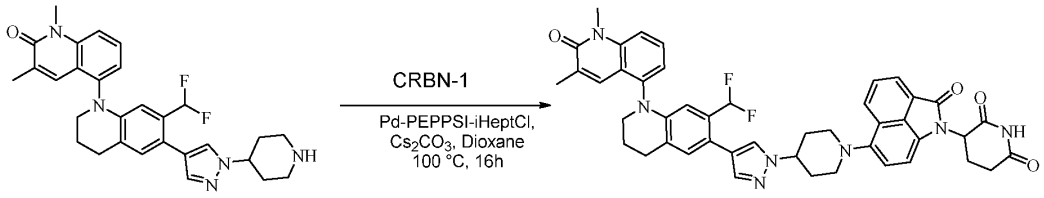
separated and concentrated under reduced pressure to afford crude product. Purification was done using combi flash in EtOAc-Hexane system. Crude product was eluted at 15-20% EtOAc-Hexane to afford the pure title intermediate-6 (0.9 g, 40%).

List of CRBN analogues, commercially available or synthesized using literature, were used with appropriate variations and summarized herein the below table-2.

**Table-2:**

| CRBN analogue No. | Structure |
|---|---|
| CRBN-1 |  |
| CRBN-2 |  |

**Example-1: Synthesis of 3-(6-(4-(4-(7-(difluoromethyl)-1',3'-dimethyl-2'-oxo-1',2',3,4-tetrahydro-2H-[1,5'-biquinolin]-6-yl)-1H-pyrazol-1-yl)piperidin-1-yl)-2-oxobenzo[cd]indol-1(2H)-yl)piperidine-2,6-dione.**




Intermediate-2 *step-1* **Compound-1**

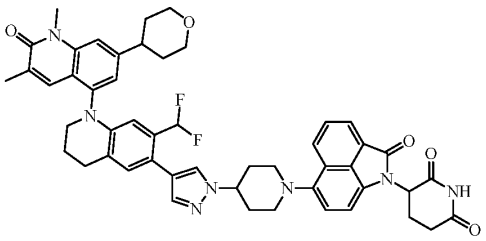
To 7-(difluoromethyl)-1',3'-dimethyl-6-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-3,4-dihydro-2H-[1,5'-biquinolin]-2'(1'H)-one (0.15g, 0.29mmol), 3-(6-bromo-1-oxoisoindolin-2-yl)piperidine-2,6-dione (0.16g, 0.44mmol) in Dioxane (3ml) was added, cesium carbonate (0.19g, 0.59mmol). Purged with argan for 5 min. Pd-PEPPSI-IHept-Cl (14mg, 0.015mmol) was added. Purging continued for another 5min. The reaction mixture was heated at 100 °C for 16h. Filtered through celite bed, washed with ethyl acetate. The organic part was washed with water, brine, dried over $Na_2SO_4$, filtered, and evaporated to afford crude. Purification was done

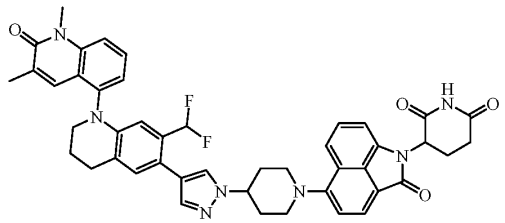
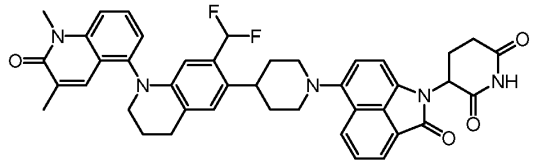
by combi flash column chromatography; Crude was eluted with 2-3% methanol-dichloromethane to afford pure compound-1. (0.18g, 77.26%).

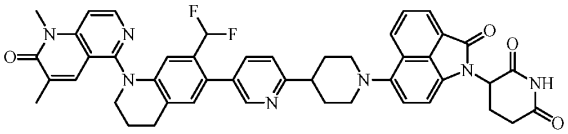
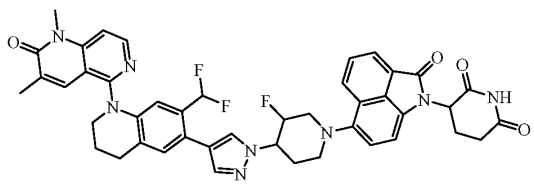
LC-MS: 782.1 $[M+H]^+$; HPLC: 98.32%; 1H-NMR (400 MHz, DMSO-d6) δ 11.15 (s, 1H), 8.34-8.29 (d, 1H), 8.14-8.08 (d, 1H), 7.94 (s, 1H), 7.87-7.82 (t, 1H), 7.74-7.66 (q, 2H), 7.58 (s, 1H), 7.56-7.50 (d, 1H), 7.25-7.21 (d, 2H), 7.03 (t, 2H), 6.88-6.60 (t, 1H), 4.46-4.39 (m, 1H), 3.53 (s, 3H), 3.62-3.50 (m, 4H), 3.31-2.31 (m, 5H), 2.78-2.69 (dd, 1H), 2.64-2.59 (m, 1H), 2.42-2.30 (m, 3H), 2.28-2.18 (m, 3H), 2.16-2.00 (m, 6H).

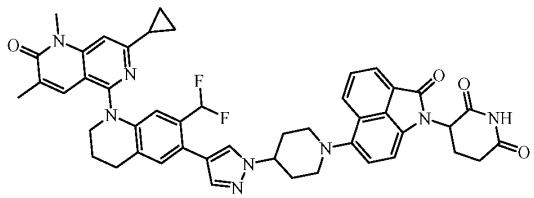
The compounds listed in below **Table-3** were prepared by reacting appropriate intermediates using a procedure similar to the one described in Example-1 with appropriate variations. The characterization data of the compounds are summarized herein the below table-3.

**Table-3:**

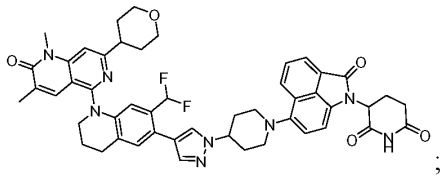
| Comp. No. | Compound structure / Intermediates used | Characterization data |
|---|---|---|
| 2 |  **Intermediates used** Intermediate-3 & CRBN-1 | LC-MS: 866.4 $[M+H]^+$; HPLC: 98.25%; 1H-NMR (400 MHz, DMSO-d6) δ 11.1 (s, 1H), 8.32-8.30 (d, 1H), 8.10-8.09 (d, 1H), 7.94 (s, 1H), 7.86-7.82 (m, 1H), 7.65 (s, 1H), 7.58 (s, 1H), 7.37 (s, 1H), 7.21 (s, 1H), 7.17 (s, 1H), 7.02 (s, 2H), 6.88-6.61 (t, 1H), 6.21 (s, 1H), 5.40-5.33 (dd, 1H), 4.53-4.49 (m, 1H), 4.24-4.16 (m, 1H), 3.98-3.97 (d, 2H), 3.62-3.59 (m, 4H), 3.45-3.42 (m, 2H), 2.99-2.90 (m, 4H), 2.62-2.59 (m, 1H), 2.57-2.52 (m, 2H), 2.49-2.26 (m, 2H), 2.23-2.21 (m, 3H), 2.16-2.10 (m, 3H), 2.08 |

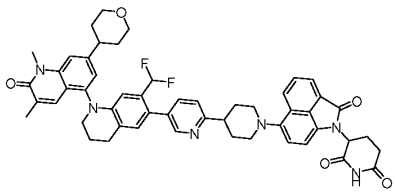
| | | |
|---|---|---|
| | | (s, 3H), 2.06-1.95 (m, 3H), 1.78-1.72 (m, 4H), 1.76-1.24 (m, 4H). |
| 3 |  **Intermediates used** Intermediate-2 & CRBN-2 | LC-MS: 782.00 $[M+H]^+$; HPLC: 98.59%; 1H-NMR (400 MHz, DMSO-d6) δ 11.1 (s, 1H), 7.99-7.97 (d, 1H), 7.94 (s,1H), 7.73 (s, 1H), 7.71-7.66 (m, 2H), 7.58 (s, 1H), 7.54-7.52 (d, 1H), 7.49-7.45 (t, 1H), 7.25-7.21 (m, 3H), 7.11-7.09 (d, 1H), 6.88-6.61 (m, 1H), 6.17 (s, 1H), 5.44-5.39 (m, 1H), 4.48-4.79 (m, 1H), 3.92 (s, 3H), 3.86-3.79 (d, 2H), 3.7 (s, 3H), 3.67-3.58 (m, 1H), 3.54-3.46 (m, 1H), 3.36-3.28 (m, 2H), 3.15-3.07 (m, 2H), 2.93-2.86 (m, 2H), 2.70 (s, 3H), 2.23-2.14 (t, 3H), 1.96-1.87 (m, 2H). |
| 4 |  **Intermediates used** Intermediate-4 & CRBN-1 | LC-MS: 716.25 $[M+H]^+$; HPLC: 99.88%; 1H-NMR (400 MHz, DMSO-d6) δ 11.1 (s, 1H), 8.35-8.33 (d,1H), 8.11-8.09 (d, 1H), 7.87-7.85 (t, 1H), 7.77 (s, 1H), 7.68-7.64 (m, 1H), 7.51-7.49 (d, 1H), 7.31 (s, 1H), 7.21-7.19 (d, 1H), 7.10-6.82 (m, 3H), 6.08 (s, 1H), 5.44-5.39 (m, |

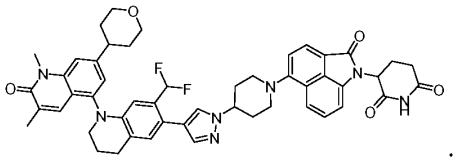
| | | |
|---|---|---|
| | | 1H), 4.48-4.79 (m, 1H), 3.92 (s, 3H), 3.86-3.79 (d, 2H), 3.7 (s, 3H), 3.67-3.58 (m, 1H), 3.54-3.46 (m, 1H), 3.36-3.28 (m, 2H), 3.15-3.07 (m, 2H), 2.93-2.86 (m, 2H), 2.70 (s, 3H), 2.23-2.14 (t, 3H), 1.96-1.87 (m, 2H). |
| 5 |  **Intermediates used** A-3 & CRBN-1 | LC-MS: 794.2 $[M+H]^+$; HPLC: 88.5%; 1H-NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.47-8.44 (m, 1H), 8.16-8.15 (d, 1H), 8.10-8.09 (d, 1H), 7.87 (s, 1H), 7.71-7.66 (m, 1H), 7.55-7.53 (m, 2H), 7.43-7.40 (d, 1H), 7.20 (s, 1H), 7.17-7.11 (m, 3H), 6.47-6.44 (m, 1H), 6.43 (s, 1H), 5.08-5.03 (m, 1H), 4.52-4.46 (m, 1H), 4.36-4.32 (m, 1H), 4.24-4.20 (m, 1H), 4.04-4.01 (d, 2H), 3.71 (s, 3H), 3.62-3.53 (m, 2H), 2.95-2.90 (m, 4H), 2.61-2.60 (m, 1H), 2.39-2.34 (m, 1H), 2.15-2.14 (m, 2H), 2.12 (s, 3H), 2.08-1.96 (m, 4H). |
| 6 |  **Intermediates used** A-1 & CRBN-1 | LC-MS: 801.2 $[M+H]^+$; HPLC: 99.8%; 1H-NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.48-8.46 (d, 1H), 8.38-8.36 (d, 1H), 8.12-8.11 (d, 1H), 8.05 (s, 1H), |

| | | |
|---|---|---|
| | | 7.88-7.84 (t, 1H), 7.74 (s, 1H), 7.70 (s, 1H), 7.42-7.41 (d, 1H), 7.29 (s, 1H), 7.12-7.05 (m, 2H), 6.92-6.65 (m, 1H), 6.41 (s, 1H), 5.08-5.03 (m, 1H), 4.52-4.46 (m, 1H), 4.36-4.32 (m, 1H), 4.24-4.20 (m, 1H), 4.04-4.01 (d, 2H), 3.71 (s, 3H), 3.62-3.53 (m, 2H), 2.95-2.90 (m, 4H), 2.61-2.60 (m, 1H), 2.39-2.34 (m, 1H), 2.15-2.14 (m, 2H), 2.12 (s, 3H), 2.08-1.96 (m, 3H). |
| 7 | <br>**Intermediates used**<br>A-2 & CRBN-1 | LC-MS: 823.35 $[M+H]^+$; HPLC: 98.27%; 1H-NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.38-8.36 (d, 1H), 8.12-8.11 (d, 1H), 8.05 (s, 1H), 7.88-7.84 (t, 1H), 7.74 (s, 1H), 7.70 (s, 1H), 7.42-7.41 (d, 1H), 7.29 (s, 1H), 7.12-7.05 (m, 2H), 6.92-6.65 (m, 1H), 6.41 (s, 1H), 5.08-5.03 (m, 1H), 4.52-4.46 (m, 1H), 4.04-4.01 (d, 2H), 3.71 (s, 3H), 3.62-3.53 (m, 2H), 2.95-2.90 (m, 4H), 2.61-2.60 (m, 1H), 2.39-2.34 (m, 1H), 2.20-2.18 (m, 1H), 2.15-2.14 (m, 4H), 2.12 (s, 3H), 2.08-1.96 (m, 4H), 0.96-0.84 (m, 4H). |

Although the present application has been illustrated by certain of the preceding examples, it is not to be construed as being limited thereby; but rather, the present application encompasses the generic area as hereinbefore disclosed. For example, the compounds below which can be prepared by following similar procedure as described in above Schemes/Examples with suitable modifications known to the one ordinary skilled in the art are also included in the scope of the present application:

8. ;

9. ; and

10. .

**BIOLOGICAL ASSAY**

Targeted protein degradation controls the amount of a harmful cellular protein rather than modulation or inhibition of its function. This novel therapeutic approach also offers many opportunities to differentiate from inhibitor-based therapies. First, by catalysing the destruction of their target protein, degrader molecules may also disrupt scaffolding functions of proteins otherwise not addressed by small1molecule inhibitors, allowing for drug properties that are unlike other classes of drugs. Second, degraders may offer higher potency and differentiated cellular pharmacology. Unlike inhibitors, which must remain bound to a single target protein, degrader molecules can catalyse the ubiquitination and destruction of multiple copies of the same protein since the degraders themselves are not degraded in the proteasome.

There are various technologies now currently available to directly measure the degradation of target proteins induced by PROTACs, for example Western Blot and Capillary Electrophoresis Immunoassays, High-Throughput Flow Cytometry and In-Cell Western, AlphaLISA SureFire Technology, Time-Resolved Fluorescence Energy Transfer-Based Assays or Nano-Glo HiBiT Technology.

**Determination of Degradation of Protein in HiBiT Assay:**

**U2OS-HiBiT Assay Protocol:**

U2OS-CBP and U2OS-p300 HiBiT cells were seeded and incubated overnight at 37°C in a $CO_2$ incubator for adherence. Next day, both the cells were pretreated with various concentrations of degrader for 24 hrs in the incubator. Working HiBiT-lytic reagent was added to the cells and incubated on orbital shaker at room temperature for 20 mins. Post incubation, the chemiluminescent signal was read using a luminometer. Selected compounds of the present invention were screened in the above-mentioned assay procedure and the percentage of CBP and p300 degradation in HiBiT assay were determined. $DC_{50}$ was generated for the selected compounds.

Exemplary compounds of the present application were screened by the above-mentioned assay.

**Table-4: % p300 degradation @0.2µM of exemplary compounds**

| Comp. No. | % p300 degradation @0.2µM |
|---|---|
| 1 | 73 |
| 2 | 93 |
| 3 | 88 |
| 4 | 91 |
| 5 | 92 |
| 6 | 77 |
| 7 | 43 |

**Table-5: % CBP degradation @0.2µM of exemplary compounds**

| Comp. No. | % CBP degradation @0.2µM |
|---|---|
| 1 | 89 |
| 2 | 85 |
| 3 | 90 |
| 4 | 84 |
| 5 | 86 |
| 6 | 87 |
| 7 | 28 |

**Incorporation by Reference**

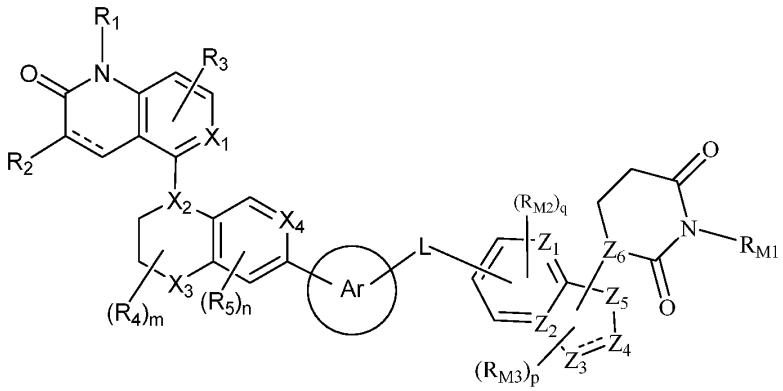
All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent were specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

**Equivalents**

While specific embodiments of the subject disclosure have been discussed, the above specification is illustrative and not restrictive. Many variations of the disclosure will become apparent to those skilled in the art upon review of this specification and the claims below. The full scope of the disclosure should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

**We claim:**

1. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof or a stereoisomer thereof;

wherein,

------ represents a single bond or a double bond;

$R_1$ is hydrogen, $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl or $(C_3\text{-}C_6)$cycloalkyl;

$R_2$ is hydrogen, halo, $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl or $(C_3\text{-}C_6)$cycloalkyl;

$R_3$ is hydrogen, halo, $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, cyano, $(C_3\text{-}C_6)$cycloalkyl, 3 to 12 membered heterocycloalkyl or $-OR_{3a}$;

$R_4$ at each occurrence is independently hydrogen, halo, $(C_1\text{-}C_6)$alkyl, cyano or halo$(C_1\text{-}C_6)$alkyl;

$R_5$ at each occurrence is independently hydrogen, halo, $(C_1\text{-}C_6)$alkyl, cyano, halo$(C_1\text{-}C_6)$alkyl or $-OR_{5a}$;

$R_{3a}$ and $R_{5a}$ are independently hydrogen, $(C_1\text{-}C_6)$alkyl or halo$(C_1\text{-}C_6)$alkyl;

$X_1$ is CH or N;

each $X_2$ and $X_4$ are independently C or N;

$X_3$ is C, N, S or O;

ring Ar is an unsubstituted or substituted $(C_3\text{-}C_6)$cycloalkylenyl, unsubstituted or substituted 3 to 12 membered heterocycloalkylenyl, unsubstituted or substituted 6 to 10

membered arylenyl or unsubstituted or substituted 5 to 12 membered heteroarylenyl; wherein the substituent is independently selected from one or more($C_1$-$C_6$)alkyl, halo, cyano, hydroxy or ($C_1$-$C_6$)alkoxy;

L is $*-L_1-L_2-L_3-$ wherein the asterisk mark [*] represents the point of attachment with the ring Ar;

each $L_1$ and $L_2$ is independently a bond, ($C_1$-$C_6$)alkylenyl, unsubstituted or substituted 6 to 10 membered arylenyl, unsubstituted or substituted 6 to 10 membered heteroarylenyl, unsubstituted or substituted ($C_3$-$C_6$)cycloalkylenyl or unsubstituted or substituted 3 to 12 membered heterocycloalkylenyl; wherein the substituent is independently selected from one or more ($C_1$-$C_6$)alkyl, halo, cyano, hydroxy and ($C_1$-$C_6$)alkoxy;

$L_3$ is a bond, ($C_1$-$C_6$)alkylenyl, unsubstituted or substituted 6 to 10 membered arylenyl, unsubstituted or substituted 6 to 10 membered heteroarylenyl, unsubstituted or substituted 3 to 12 membered heterocycloalkylenyl or unsubstituted or substituted ($C_3$-$C_6$)cycloalkylenyl; wherein the substituent is independently selected from one or more ($C_1$-$C_6$)alkyl, halo, cyano, hydroxy or ($C_1$-$C_6$)alkoxy;

each $Z_1$, $Z_3$ $Z_4$ and $Z_5$ is independently C or N; wherein at least one of $Z_3$, $Z_4$, and $Z_5$ is C;

$Z_2$ is C;

$Z_6$ is CH or N;

$R_{M1}$ is hydrogen or ($C_1$-$C_6$)alkyl;

$R_{M2}$ at each occurrence independently is hydrogen, halo, cyano, ($C_1$-$C_6$)alkyl or ($C_1$-$C_6$)alkoxy;

$R_{M3}$ at each occurrence is independently hydrogen or ($C_1$-$C_6$)alkyl; or two $R_{M3}$ on the same carbon atom together represent an oxo group;

one of $R_{M2}$ and one of $R_{M3}$ together get cyclized to form a 5 to 6 membered fused ring system;

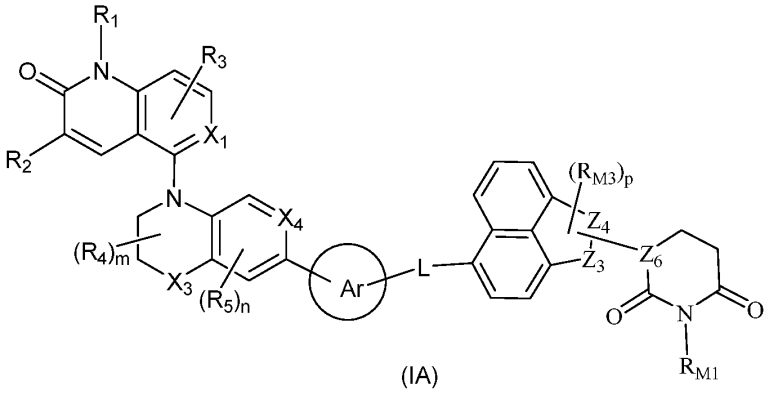
subscript ‘m’ is 0, 1, 2 or 3;

subscript ‘n’ is 0, 1, 2 or 3;

subscript ‘p’ is 1, 2 or 3; and

subscript 'q' is 1, 2 or 3.

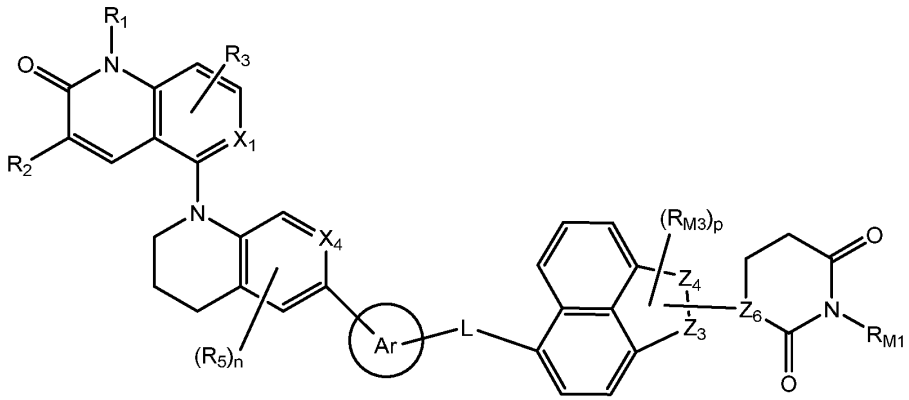
2. The compound as claimed in claim 1, having formula (IA):



(IA)

or a pharmaceutically acceptable salt thereof or a stereoisomer thereof; wherein subscript 'p' is 1 or 2.

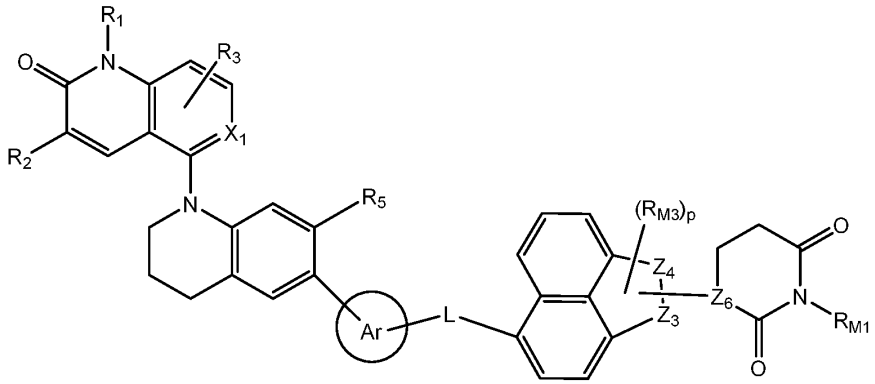
3. The compound as claimed in claim 1, having formula (IB):



(IB)

or a pharmaceutically acceptable salt thereof or a stereoisomer thereof; wherein subscript 'p' is 1 or 2.

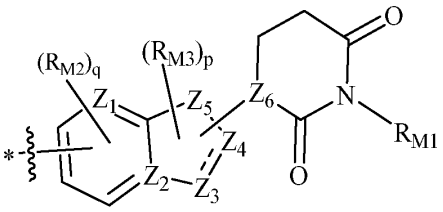
4. The compound as claimed in claim 1, having formula (IC):

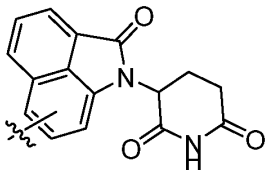
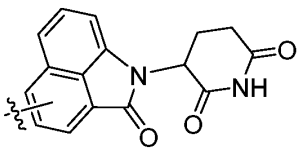


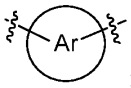
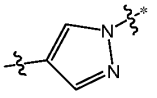
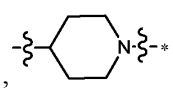
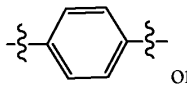
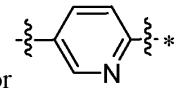
(IC)

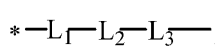
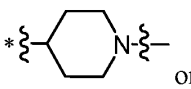
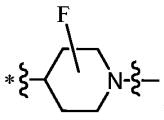
or a pharmaceutically acceptable salt thereof or a stereoisomer thereof; wherein subscript 'p' is 1 or 2.

5. The compound as claimed in any one of claims 1 to 4, wherein,



is  or .

6. The compound as claimed in any one of claims 1 to 4, wherein the ring  is , ,  or , wherein the asterisk mark [*] represents the point of attachment with linker L.

7. The compound as claimed in any one of claims 1 to 4, wherein L represented by  is a bond,  or  wherein the asterisk mark [*] represents the point of attachment with the ring Ar.

8. The compound as claimed in any one of claims 1 to 4, wherein $R_1$ is hydrogen, ($C_1$-$C_6$)alkyl or halo($C_1$-$C_6$)alkyl.

9. The compound as claimed in any one of claims 1 to 4, wherein $R_1$ is hydrogen or ($C_1$-$C_6$)alkyl.

10. The compound as claimed in any one of claims 1 to 4, wherein $R_2$ is hydrogen, ($C_1$-$C_6$)alkyl or halo($C_1$-$C_6$)alkyl.

11. The compound as claimed in any one of claims 1 to 4, wherein $R_2$ is hydrogen or ($C_1$-$C_6$)alkyl.

12. The compound as claimed in any one of claims 1 to 4, wherein $R_3$ is hydrogen, halo, ($C_1$-$C_6$)alkyl, 3 to 12 membered heterocycloalkyl or ($C_3$-$C_6$)cycloalkyl.

13. The compound as claimed in any one of claims 1 to 4, wherein $R_3$ is hydrogen, 3 to 12 membered heterocycloalkyl or ($C_3$-$C_6$)cycloalkyl.

14. The compound as claimed in any one of claims 1 to 4, wherein $R_5$ is hydrogen, halo, ($C_1$-$C_6$)alkyl or halo($C_1$-$C_6$)alkyl.

15. The compound as claimed in any one of claims 1 to 4, wherein $R_5$ is halo($C_1$-$C_6$)alkyl.

16. The compound as claimed in claim 1, wherein,

$R_1$ is ($C_1$-$C_6$)alkyl;

$R_2$ is ($C_1$-$C_6$)alkyl;

$R_3$ is hydrogen or 3 to 12 membered heterocycloalkyl;

$R_4$ at each occurrence is hydrogen;

$R_5$ at each occurrence is independently hydrogen or halo($C_1$-$C_6$)alkyl;

$X_1$ is CH or N;

each $X_2$ and $X_4$ are independently C or N;

$X_3$ is C;

ring Ar is an unsubstituted or substituted 3 to 12 membered heterocycloalkylenyl or unsubstituted or substituted 5 to 12 membered heteroarylenyl; wherein the substituent is independently selected from one or more($C_1$-$C_6$)alkyl, halo, cyano or hydroxy;

L is $*-L_1-L_2-L_3-$ wherein the asterisk mark [*] represents the point of attachment with the ring Ar;

each $L_1$ and $L_2$ is independently a bond, or unsubstituted or substituted 3 to 12 membered heterocycloalkylenyl; wherein the substituent is independently selected from one or more $(C_1\text{-}C_6)$alkyl, halo, cyano or hydroxy;

$L_3$ is a bond or unsubstituted or substituted 3 to 12 membered heterocycloalkylenyl; wherein the substituent is independently selected from one or more $(C_1\text{-}C_6)$alkyl, halo, cyano or hydroxy;

each $Z_1$, $Z_3$ $Z_4$ and $Z_5$ is independently C or N; wherein at least one of $Z_3$, $Z_4$, and $Z_5$ is C;

$Z_2$ is C;

$Z_6$ is CH;

$R_{M1}$ is hydrogen;

$R_{M2}$ at each occurrence independently is hydrogen or $(C_1\text{-}C_6)$alkyl;

$R_{M3}$ at each occurrence is independently hydrogen or $(C_1\text{-}C_6)$alkyl; or two $R_{M3}$ on the same carbon atom together represent an oxo group;

one of $R_{M2}$ and one of $R_{M3}$ together get cyclized to form a 5 to 6 membered fused ring system;

subscript 'm' is 0, 1, 2 or 3;

subscript 'n' is 0, 1, 2 or 3;

subscript 'p' is 1, 2 or 3; and

subscript 'q' is 1, 2 or 3.

17. A compound selected from:

| Comp. No. | IUPAC Name |
|---|---|
| 1 | 3-(6-(4-(4-(7-(difluoromethyl)-1',3'-dimethyl-2'-oxo-1',2',3,4-tetrahydro-2H-[1,5'-biquinolin]-6-yl)-1H-pyrazol-1-yl)piperidin-1-yl)-2-oxobenzo[cd]indol-1(2H)-yl)piperidine-2,6-dione; |

| | |
|---|---|
| 2 | 3-(6-(4-(4-(7-(difluoromethyl)-1',3'-dimethyl-2'-oxo-7'-(tetrahydro-2H-pyran-4-yl)-1',2',3,4-tetrahydro-2H-[1,5'-biquinolin]-6-yl)-1H-pyrazol-1-yl)piperidin-1-yl)-2-oxobenzo[cd]indol-1(2H)-yl)piperidine-2,6-dione; |
| 3 | 3-(5-(4-(4-(7-(difluoromethyl)-1',3'-dimethyl-2'-oxo-1',2',3,4-tetrahydro-2H-[1,5'-biquinolin]-6-yl)-1H-pyrazol-1-yl)piperidin-1-yl)-2-oxobenzo[cd]indol-1(2H)-yl)piperidine-2,6-dione; |
| 4 | 3-(6-(4-(7-(difluoromethyl)-1',3'-dimethyl-2'-oxo-1',2',3,4-tetrahydro-2H-[1,5'-biquinolin]-6-yl)piperidin-1-yl)-2-oxobenzo[cd]indol-1(2H)-yl)piperidine-2,6-dione; |
| 5 | 3-(6-(4-(5-(7-(difluoromethyl)-1-(1,3-dimethyl-2-oxo-1,2-dihydro-1,6-naphthyridin-5-yl)-1,2,3,4-tetrahydroquinolin-6-yl)pyridin-2-yl)piperidin-1-yl)-2-oxobenzo[cd]indol-1(2H)-yl)piperidine-2,6-dione; |
| 6 | 3-(6-(4-(4-(7-(difluoromethyl)-1-(1,3-dimethyl-2-oxo-1,2-dihydro-1,6-naphthyridin-5-yl)-1,2,3,4-tetrahydroquinolin-6-yl)-1H-pyrazol-1-yl)-3-fluoropiperidin-1-yl)-2-oxobenzo[cd]indol-1(2H)-yl)piperidine-2,6-dione; |
| 7 | 3-(6-(4-(4-(1-(7-cyclopropyl-1,3-dimethyl-2-oxo-1,2-dihydro-1,6-naphthyridin-5-yl)-7-(difluoromethyl)-1,2,3,4-tetrahydroquinolin-6-yl)-1H-pyrazol-1-yl)piperidin-1-yl)-2-oxobenzo[cd]indol-1(2H)-yl)piperidine-2,6-dione; |
| 8 | 3-(6-(4-(4-(7-(difluoromethyl)-1-(1,3-dimethyl-2-oxo-7-(tetrahydro-2H-pyran-4-yl)-1,2-dihydro-1,6-naphthyridin-5-yl)-1,2,3,4-tetrahydroquinolin-6-yl)-1H-pyrazol-1-yl)piperidin-1-yl)-2-oxobenzo[cd]indol-1(2H)-yl)piperidine-2,6-dione; |
| 9 | 3-(6-(4-(5-(7-(difluoromethyl)-1',3'-dimethyl-2'-oxo-7'-(tetrahydro-2H-pyran-4-yl)-1',2',3,4-tetrahydro-2H-[1,5'-biquinolin]-6-yl)pyridin-2-yl)piperidin-1-yl)-2-oxobenzo[cd]indol-1(2H)-yl)piperidine-2,6-dione; and |
| 10 | 3-(5-(4-(4-(7-(difluoromethyl)-1',3'-dimethyl-2'-oxo-7'-(tetrahydro-2H-pyran-4-yl)-1',2',3,4-tetrahydro-2H-[1,5'-biquinolin]-6-yl)-1H-pyrazol-1-yl)piperidin-1-yl)-2-oxobenzo[cd]indol-1(2H)-yl)piperidine-2,6-dione; |

or a pharmaceutically acceptable salt thereof or a stereoisomer thereof.

18. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof or a stereoisomer thereof and at least one pharmaceutically acceptable carrier or excipient.

19. The compound as claimed in any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof or a stereoisomer thereof, for use as a medicament.

20. The compound as claimed in any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof or a stereoisomer thereof, for use in the manufacture of a medicament for the treatment of cancer.

21. The compound as claimed in any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof or a stereoisomer thereof, for use in degrading the target protein in a subject, wherein the target protein is CBP and/or p300.

22. The compound as claimed in any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof or a stereoisomer thereof, for use in degrading the target protein in a subject, wherein the target protein is p300.

23. The compound as claimed in any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof or a stereoisomer thereof, for use in degrading the target protein in a subject, wherein the target protein is CBP.

24. The compound as claimed in any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof or a stereoisomer thereof, for use in the treatment of CBP and/or p300-mediated disorder.

25. The compound as claimed in claim 24, wherein the CBP and/or p300-mediated disorder is cancer, viral infection and autoimmune disease or disorder, inflammatory disease or disorder, or neurodegenerative disease and metabolic disorder.

26. A method of treating or preventing a disease and/or disorder responsive to CBP and/or p300 degraders in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound as claimed in any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof or a stereoisomer thereof.

27. The method as claimed in claim 26, wherein the disease or disorder is cancer, viral infection and autoimmune disease or disorder, inflammatory disease or disorder, neurodegenerative disease and metabolic disorder.

28. The method as claimed in claim 27, wherein the disease or disorder is cancer.

29. The method as claimed in claim 28, wherein the cancer is prostate cancer, neuroendocrine prostate cancer, breast cancer, colorectal cancer, colon cancer, pancreatic cancer, intestinal cancer, stomach cancer, hematological cancer, multiple myeloma, chronic lymphocytic leukemia, lymphoma, glioblastoma, myeloid leukemia, acute myeloid leukemia,

acute T-cell lymphoma, T-cell lymphoma, leukemia, lympho-plasmacytoid B-cell lymphoma, glioma, small cell lung cancer, neuroblastoma, angiosarcoma, chondrosarcoma, Ewing's sarcoma, fibroblastic sarcoma, gynaecological sarcoma, liposarcoma, osteosarcoma, rhabdomyosarcoma, soft tissue sarcoma, synovial sarcoma, cancer of prostate adenocarcinoma, breast invasive carcinoma, bladder urothelial carcinoma, lung adenocarcinoma, liver hepatocellular carcinoma, cervical squamous cell carcinoma and endocervical adenocarcinoma, cholangiocarcinoma, lung squamous cell carcinoma, colon adenocarcinoma, rectum adenocarcinoma, pancreatic adenocarcinoma, uterine corpus endometrial carcinoma, uterine carcinosarcoma, head and neck squamous cell carcinoma, mesothelioma, testicular germ cell tumors, ovarian serous cystadenocarcinoma, thyroid carcinoma, sarcoma, skin cutaneous melanoma, adrenocortical carcinoma, kidney renal clear cell carcinoma, pheochromocytoma and paraganglioma, kidney renal papillary cell carcinoma, lymphoid neoplasm diffuse large B-cell lymphoma, thymoma, brain lower grade glioma, kidney chromophobe, glioblastoma multiforme, uveal melanoma, lymphoma or lymphoid malignancy or metastatic cancer.

30. The method as claimed in claim 27, wherein autoimmune or inflammatory disease or disorder is selected from diabetes, multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, fatty liver disease, HIV/AIDS, systemic lupus erythematosus, psoriasis, dermatitis, prurigo nodularis, Addison's disease, acute gout, ankylosing spondylitis, asthma, atherosclerosis, Behcet's disease, bullous skin diseases, chronic obstructive pulmonary disease, Crohn's disease, eczema, giant cell arteritis, fibrosis, glomerulonephritis, hepatic vascular occlusion, hepatitis, hypophysitis, immunodeficiency syndrome, Kawasaki disease, lupus nephritis, myocarditis, myositis, nephritis, organ transplant rejection, osteoarthritis, pancreatitis, pericarditis, polyarteritis nodosa, pneumonitis, primary biliary cirrhosis, psoriatic arthritis, scleritis, sclerosing cholangitis, sepsis, systemic lupus erythematosus, Takayasu's Arteritis, toxic shock, thyroiditis, ulcerative colitis, uveitis, vitiligo, vasculitis, and Wegener's granulomatosis.

31. The method as claimed in claim 27, wherein neurodegenerative disease is selected from Alzheimer's disease, Parkinson's disease, dementia, Huntington's disease or amyotrophic lateral sclerosis.

32. The method as claimed in any one of claims 26 to 31, further comprising administering to the subject a therapeutically effective amount of a compound as claimed in claim 1 to 17,

along with one or more chemotherapeutic agents, anti-viral agents, anti-inflammatory agent, immunosuppressant agents or pain-relieving agents.

33. A method of treating or preventing viral infection in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the compound as claimed in any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof or a stereoisomer thereof.

34. A method of treating or preventing autoimmune disease or disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the compound as claimed in any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof or a stereoisomer thereof.

35. A method of treating or preventing cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the compound as claimed in any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof or a stereoisomer thereof.

36. The method as claimed in claim 35, wherein the cancer is prostate cancer, neuroendocrine prostate cancer, breast cancer, colorectal cancer, colon cancer, pancreatic cancer, intestinal cancer, stomach cancer, hematological cancer, multiple myeloma, chronic lymphocytic leukemia, lymphoma, glioblastoma, myeloid leukemia, acute myeloid leukemia, acute T-cell lymphoma, T-cell lymphoma, leukemia, lympho-plasmacytoid B-cell lymphoma, glioma, small cell lung cancer, neuroblastoma, angiosarcoma, chondrosarcoma, Ewing's sarcoma, fibroblastic sarcoma, gynaecological sarcoma, liposarcoma, osteosarcoma, rhabdomyosarcoma, soft tissue sarcoma, synovial sarcoma, cancer of prostate adenocarcinoma, breast invasive carcinoma, bladder urothelial carcinoma, lung adenocarcinoma, liver hepatocellular carcinoma, cervical squamous cell carcinoma and endocervical adenocarcinoma, cholangiocarcinoma, lung squamous cell carcinoma, colon adenocarcinoma, rectum adenocarcinoma, pancreatic adenocarcinoma, uterine corpus endometrial carcinoma, uterine carcinosarcoma, head and neck squamous cell carcinoma, mesothelioma, testicular germ cell tumors, ovarian serous cystadenocarcinoma, thyroid carcinoma, sarcoma, skin cutaneous melanoma, adrenocortical carcinoma, kidney renal clear cell carcinoma, pheochromocytoma and paraganglioma, kidney renal papillary cell carcinoma, lymphoid neoplasm diffuse large B-cell lymphoma, thymoma, brain lower grade glioma, kidney

chromophobe, glioblastoma multiforme, uveal melanoma, lymphoma or lymphoid malignancy or metastatic cancer.

37. Use of a compound as claimed in any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof or a stereoisomer thereof, in the manufacture of a medicament for the treatment of disease or disorder responsive to the CBP and/or p300 degradation.

38. Use of a compound as claimed in any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof or a stereoisomer thereof, in the manufacture of a medicament for the treatment of cancer, an inflammatory disease or disorder, autoimmune disease or disorder, neurodegenerative disease or metabolic disorder.

39. The use as claimed in claim 38, wherein the cancer is prostate cancer, neuroendocrine prostate cancer, breast cancer, colorectal cancer, colon cancer, pancreatic cancer, intestinal cancer, stomach cancer, hematological cancer, multiple myeloma, chronic lymphocytic leukemia, lymphoma, glioblastoma, myeloid leukemia, acute myeloid leukemia, acute T-cell lymphoma, T-cell lymphoma, leukemia, lympho-plasmacytoid B-cell lymphoma, glioma, small cell lung cancer, neuroblastoma, angiosarcoma, chondrosarcoma, Ewing's sarcoma, fibroblastic sarcoma, gynaecological sarcoma, liposarcoma, osteosarcoma, rhabdomyosarcoma, soft tissue sarcoma, synovial sarcoma, cancer of prostate adenocarcinoma, breast invasive carcinoma, bladder urothelial carcinoma, lung adenocarcinoma, liver hepatocellular carcinoma, cervical squamous cell carcinoma and endocervical adenocarcinoma, cholangiocarcinoma, lung squamous cell carcinoma, colon adenocarcinoma, rectum adenocarcinoma, pancreatic adenocarcinoma, uterine corpus endometrial carcinoma, uterine carcinosarcoma, head and neck squamous cell carcinoma, mesothelioma, testicular germ cell tumors, ovarian serous cystadenocarcinoma, thyroid carcinoma, sarcoma, skin cutaneous melanoma, adrenocortical carcinoma, kidney renal clear cell carcinoma, pheochromocytoma and paraganglioma, kidney renal papillary cell carcinoma, lymphoid neoplasm diffuse large B-cell lymphoma, thymoma, brain lower grade glioma, kidney chromophobe, glioblastoma multiforme, uveal melanoma, lymphoma or lymphoid malignancy or metastatic cancer.