

PHYSIOLOGICAL FUNCTION AND HOMEOSTASIS MODULATING COMPOUNDS

CROSS REFERENCE TO RELATED APPLICATION

- 5 **[0001]** This application claims the benefit of and priority to U.S. Provisional Patent Application Nos. US 63/546372 and US 63/546365, both filed on October 30th, 2023. The content of the above-noted patent applications is hereby expressly incorporated by reference into the detailed description hereof.

10 **FIELD**

- [0002]** The specification relates to compounds useful for modulating cellular physiological function and homeostasis and methods of use thereof.

BACKGROUND

- 15 **[0003]** Regulation of physiological function and cellular homeostasis are essential for the normal development and activity of a number of human cells lines.
- [0004]** Originally studied for its involvement in mediating detoxification of xenobiotic compounds, the aryl hydrocarbon receptor (AhR) is now known to play an important function in normal cellular development and homeostasis. Regulation of
- 20 AhR is central to major signaling systems and transcriptional programs critical to a variety of physiological functions (Kou Z, Dai W. Aryl hydrocarbon receptor: Its roles in physiology. Biochemical pharmacology. 2021 Mar 1;185:114428, incorporated herein by reference).
- [0005]** Activation of the aryl hydrocarbon receptor (AhR), and its downstream
- 25 signal transduction, is known to occur with a wide number of exogenous and endogenous ligands via canonical and non-canonical pathways (Kou Z, Dai W. Aryl hydrocarbon receptor: Its roles in physiology. Biochemical pharmacology. 2021 Mar 1; 185:114428; Denison MS, Nagy SR. Activation of the aryl hydrocarbon receptor by structurally diverse exogenous and endogenous chemicals. Annual review of

pharmacology and toxicology. 2003 Apr 1;43(1):309-34, incorporated herein by reference).

[0006] Retention of inactive AhR complexes with molecular chaperons, such as heat shock protein 90 (Hsp90), in the cytosol are typical of canonical pathways.

- 5 Where upon activation, AhR undergoes a conformational change, releasing the receptor from the chaperone proteins and subsequent translation to the nucleus. Within the nucleus AhR heterodimerizes with aryl hydrocarbon receptor nuclear translocator protein (ARNT) then binds to xenobiotic responsive elements (XREs) of target genes, including cytochrome P450 superfamily enzyme Cyp1a1, Cyp1a3, and
- 10 Cyp1b1; regulating their expression. The induction of CYP1A1 has therefore been used as a model system by which to define the mechanism by which AhR regulates gene expression (Denison MS, Nagy SR. Activation of the aryl hydrocarbon receptor by structurally diverse exogenous and endogenous chemicals. Annual review of pharmacology and toxicology. 2003 Apr 1;43(1):309-34, incorporated herein by
- 15 reference). Where binding of AhR to different intranuclear transcription factors may lead to non-canonical signaling pathways through binding of non-XRE deoxyribonucleic acid (DNA) elements.

[0007] Activation of the AhR pathway has been known to occur through a variety of ligands which are both synthetic in nature and those that are naturally

20 occurring. The majority of compounds which activate AhR include planar, hydrophobic halogenated aromatic hydrocarbons (HAHs) and polycyclic aromatic hydrocarbons (PAHs) or related compounds thereof (Denison MS, Nagy SR. Activation of the aryl hydrocarbon receptor by structurally diverse exogenous and endogenous chemicals. Annual review of pharmacology and toxicology. 2003 Apr

25 1;43(1):309-34, incorporated herein by reference). Exogenous ligands are known to be inclusive of tea flavonoids (epigallocatechin gallate), bacterial metabolic by-products including indirubin, and coal tar high molecular weight aromatic hydrocarbons (Palermo CM, Westlake CA, Gasiewicz TA. Epigallocatechin gallate inhibits aryl hydrocarbon receptor gene transcription through an indirect mechanism

30 involving binding to a 90 kDa heat shock protein. Biochemistry. 2005 Apr 5;44(13):5041-52; Adachi J, Mori Y, Matsui S, Takigami H, Fujino J, Kitagawa H, Miller CA, Kato T, Saeki K, Matsuda T. Indirubin and indigo are potent aryl hydrocarbon receptor ligands present in human urine. Journal of Biological

- Chemistry. 2001 Aug 24;276(34):31475-8; Furue M, Tsuji G, Mitoma C, Nakahara T, Chiba T, Morino-Koga S, Uchi H. Gene regulation of filaggrin and other skin barrier proteins via aryl hydrocarbon receptor. *Journal of dermatological science*. 2015 Nov 1;80(2):83-8; Hahn ME. The aryl hydrocarbon receptor: a comparative perspective. *Comparative Biochemistry and Physiology Part C: Pharmacology, Toxicology and Endocrinology*. 1998 Nov 1;121(1-3):23-53, all incorporated herein by reference). Endogenous ligands are known to be inclusive of kynurine, lumichrome, lipoxin A4, bilirubin, kynurenic acid, and 6-formylindolo[3,2-b] carbazole (FICZ) (Mezrich JD, Fechner JH, Zhang X, Johnson BP, Burlingham WJ, Bradfield CA. An interaction between kynurenine and the aryl hydrocarbon receptor can generate regulatory T cells. *The Journal of Immunology*. 2010 Sep 15;185(6):3190-8; Kou Z, Dai W. Aryl hydrocarbon receptor: Its roles in physiology. *Biochemical pharmacology*. 2021 Mar 1; 185:114428; Sinal CJ, Bend JR. Aryl hydrocarbon receptor-dependent induction of cyp1a1 by bilirubin in mouse hepatoma hepa 1c1c7 cells. *Molecular pharmacology*. 1997 Oct 1;52(4):590-9; DiNatale BC, Murray IA, Schroeder JC, Flaveny CA, Lahoti TS, Laurenzana EM, Omiecinski CJ, Perdew GH. Kynurenic acid is a potent endogenous aryl hydrocarbon receptor ligand that synergistically induces interleukin-6 in the presence of inflammatory signaling. *Toxicological sciences*. 2010 May 1;115(1):89-97; Rannug A, Rannug U. The tryptophan derivative 6-formylindolo [3, 2-b] carbazole, FICZ, a dynamic mediator of endogenous aryl hydrocarbon receptor signaling, balances cell growth and differentiation. *Critical reviews in toxicology*. 2018 Aug 9;48(7):555-74, all incorporated herein by reference).

[0008] As a promiscuous receptor, a diverse population of ligands are able to activate the AhR pathway. The range of AhR ligands is known to elicit differentiated downstream pathways through activation of the AhR. This variable activation along with co-activation of other AhR independent pathways can lead to the detrimental effects seen in ligands like 2,3,7,8-tetrachlorodibenzodioxin TCDD or the beneficial effects of ligands found in naturally occurring and pharmaceutically derived ligands (Larigot L, Juricek L, Dairou J, Coumoul X. AhR signaling pathways and regulatory functions. *Biochimie open*. 2018 Dec 1;7:1-9, incorporated herein by reference). The inherent role of AhR as a regulator of physiological function and homeostasis is impacted by a wide array of ligands where pathway interactors results in a complex system with downstream impacts that are dependent upon the ligand structure

(Rothhammer V, Quintana FJ. The aryl hydrocarbon receptor: an environmental sensor integrating immune responses in health and disease. Nature Reviews Immunology. 2019 Mar;19(3):184-97, incorporated herein by reference).

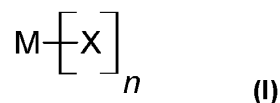
[0009] Although modulation of the AhR pathway has shown to have great potential in many therapeutic applications, exploration of novel AhR-activating compounds has been historically limited. This is in-part due to the observation that many exogenous ligands are known to elicit detrimental or undesired effects (Harmon AC, Hebert VY, Cormier SA, Subramanian B, Reed JR, Backes WL, Dugas TR. Particulate matter containing environmentally persistent free radicals induces AhR-dependent cytokine and reactive oxygen species production in human bronchial epithelial cells. PloS one. 2018 Oct 11;13(10):e0205412, incorporated herein by reference) through undesired production of reactive oxygen species. In these cases, AhR ligands activate CYP1A1 pathways without activation of the nuclear factor erythroid 2-related factor 2 (NRF2) pathway and subsequent upregulation of the downstream heme oxygenase 1 gene (HMOX-1), glutamate-cysteine ligase modifier subunit (GCLM), and NAD(P)H dehydrogenase [quinone] 1 (NQO1) to attenuate ROS production. Constructive therapeutic pathways invoking AhR are also known to upregulate FLG and LOR through OVOL-1 pathways.

[0010] There is a need in the art for one or more compounds that activate AhR. In addition, there is a need in the art for one or more compounds that activate AhR, which discretely modulate desired pathways to elicit favorable therapeutic outcomes. Further, there is a need in the art for a process of preparation of one or more compounds that activate AhR. Moreover, there is a need in the art for compositions containing one or more compounds that activate AhR.

[0011] The background herein is included solely to explain the context of the disclosure. This is not to be taken as an admission that any of the material referred to was published, known, or part of the common general knowledge as of the priority date.

SUMMARY

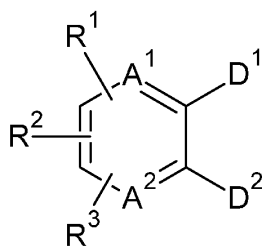
[0012] In one aspect, the specification relates to a compound of formula (I):



[0013] its hydrate, anhydrous or salt form thereof;

[0014] wherein M is Zn, and n is 1, 2 or 3;

[0015] X is a bidentate ligand, and each X independently is:



5 (i)

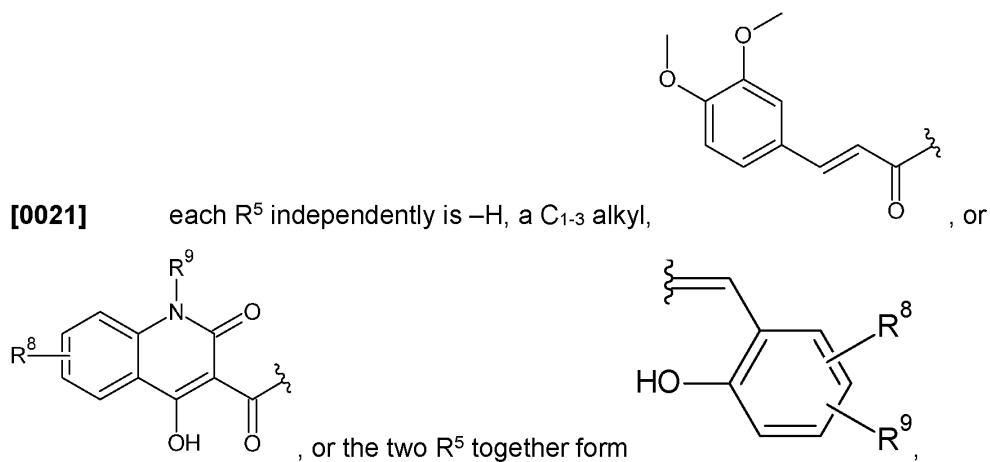
[0016] wherein

[0017] A¹ and A² each independently is CH, N, or SH;

[0018] each R¹, R² or R³ independently is –H, a C₁₋₉ substituent optionally having one or more heteroatoms, –OR⁴, –SR⁴, –N(R⁴)₂, –C(=O)NR⁴, –NC(=O)R⁴, –C(=O)R⁴, –C(=O)OR⁴, or a halogen, or R¹ and R² together form a C₅- or C₆-membered ring optionally having one or more heteroatoms, the C₅- or C₆-membered ring optionally being mono or di-substituted with C₁₋₃-alkyl, C₁₋₃-alkoxy, phenyl, –N(R⁴)₂, –C(O)R⁴, –COOR⁴, or a halogen; and wherein when both A¹ and A² are other than CH, R³ is absent;

15 **[0019]** each R⁴ independently is –H, or a C₁₋₃ substituent optionally having one or more heteroatoms;

[0020] D¹ and D² are each independently –H, –OH, –N(R⁵)₂, –SH, –CO₂R⁶ or –C(=O)R⁷, wherein if one of D¹ or D² is –H, the other D¹ or D² is other than –H,

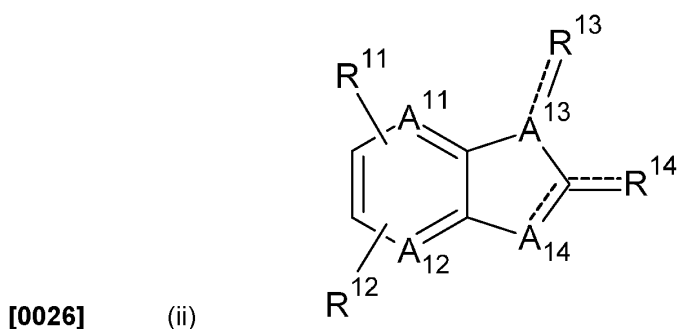


[0022] R⁶ is ⁽⁻⁾ (absent and is a negative charge), –H, or a C₁₋₃ alkyl;

[0023] R⁷ is –H, –C₁–C₅–substituent or aryl, wherein the –C₁–C₅–substituent or
5 aryl optionally has one or more heteroatoms;

[0024] R⁸ is –H, –OH, a C₁₋₃-alkyl substituent optionally having one or more heteroatoms, a –OC₁₋₃-alkyl substituent optionally having one or more heteroatoms, or a halogen; and

[0025] R⁹ is –H, or a C₁₋₃ alkyl substituent optionally having one or more
10 heteroatoms;



[0027] wherein

[0028] A¹¹ and A¹² each independently is –CH or N;

[0029] R¹¹ and R¹² each independently is –H, a C₁₋₃-substituent optionally
15 having one or more heteroatoms, a –O–C₁₋₃-substituent, or a halogen;

[0030] ----- is a single or a double bond, and only one of ----- in -----A¹⁴ and -----R¹⁴ is a double bond;

[0031] when ----- between A¹³ and R¹³ is a single bond, A¹³ is C–H or N, and R¹³ is –H,

- 5 **[0032]** when ----- between A¹³ and R¹³ is a double bond, A¹³ is C, and R¹³ is CH_y, wherein y is 1 or 2; and when y is 1, the CH is coupled to a substituted or unsubstituted aryl or heteroaryl;

[0033] when ----- of -----A¹⁴ is a single bond, A¹⁴ is NH or CH₂,

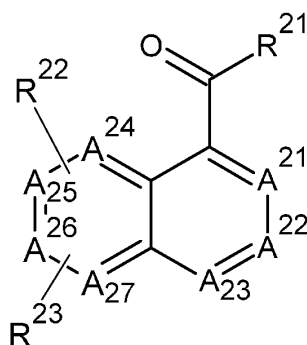
[0034] when ----- of -----A¹⁴ is a double bond, A¹⁴ is N or CR¹⁵, wherein R¹⁵ is

- 10 –C(=O)– coupled to a substituted or unsubstituted heteroaryl;

[0035] when ----- of -----R¹⁴ is a single bond, R¹⁴ is –H, –COO⁽⁻⁾, or –S(=O)R¹⁶, wherein R¹⁶ is CH_z optionally coupled to a substituted or unsubstituted aryl or heteroaryl, where z is 1, 2 or 3;

[0036] when ----- of -----R¹⁴ is a double bond, R¹⁴ is O or S;

- 15 **[0037]** or



[0038] (iii)

[0039] wherein

[0040] A²¹ is N, and each of A²² to A²⁷ independently is –CH or N;

[0041] R²¹ is –OR²⁴ or –SR²⁵, wherein R²⁴ or R²⁵ is absent, –H, –C₁–C₃–alkyl or aryl; and

[0042] R²² and R²³ each independently is –H, a C₁₋₃-substituent optionally having one or more heteroatoms, a halogen, or R²² and R²³ together form a C₅- or
5 C₆-membered aromatic ring, the C₅- or C₆-membered aromatic ring being optionally mono or di-substituted with C₁–C₃–alkyl, C₁–C₃–alkoxy, –NR²⁶₂, –C(O)R²⁷, –COOR²⁸, –CHO or halogen;

[0043] wherein each of R²⁶ to R²⁸ is independently –H, –C₁–C₃–alkyl or aryl.

[0044] In a second aspect, the specification relates to a pharmaceutical
10 composition comprising the compound of formula (I), its hydrate form, anhydrous form, solvated form or salt thereof, disclosed herein, and a pharmaceutically acceptable excipient.

[0045] In a third aspect, the specification relates to a use of the compound of formula (I), its hydrate form, anhydrous form, solvated form or salt thereof, as
15 disclosed herein, for treatment of a disease associated with activation of aryl hydrocarbon receptor (AhR).

[0046] In a fourth aspect, the specification relates to a use of the compound of formula (I), its hydrate form, anhydrous form, solvated form or salt thereof, as disclosed herein, for modulating aryl hydrocarbon receptor (AhR) activity.

20 **[0047]** In a fifth aspect, the specification relates to a method of medical treatment of a disease associated with activation of aryl hydrocarbon receptor (AhR) activity comprising administering to a subject in thereof, a pharmaceutically effective amount of the compound of formula (I), its hydrate form, anhydrous form, solvated form or salt thereof, as disclosed herein.

25 **[0048]** In a sixth aspect, the specification relates to a method of modulating aryl hydrocarbon receptor (AhR) activity comprising providing the compound of formula (I), its hydrate form, anhydrous form, solvated form or salt thereof, as disclosed herein.

[0049] In a seventh aspect, the specification relates to a process for
30 preparation of the compound of formula (I), its hydrate form, anhydrous form, solvated form or salt thereof, the process comprising:

[0050] reacting a zinc salt or zinc compound having a chelated ligand and one or more ligands in a solvent.

BRIEF DESCRIPTION OF DRAWINGS

5 **[0051]** Reference will now be made, by way of example, to the accompanying drawings which show example embodiments of the present application, and by which the present application can be further understood from the following description with reference to the Figures. The present application includes drawings, wherein:

10 **[0052]** Figure 1 is a bar graph showing the fold change in AhR activation of stably transfected Human HT29 colon adenocarcinoma - AhR reporter cells (HT29-Lucia™ AhR Cells; InvivoGen; ht2l-ahr), following a 24-hour exposure of compound 1-5 at 6.25uM. Adherent cells were plated at 56,000 cells/well into a 96 well plate. Fold change calculated at 24 hours, versus untreated media control.

15

DESCRIPTION OF EXAMPLE EMBODIMENTS

[0053] Unless otherwise explained, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Although any methods and materials similar
20 or equivalent to those described herein can be used in the practice for testing of the present invention, the typical materials and methods are described herein. In describing and claiming the present invention, the common terminology generally used is described herein below. It is also to be understood that the terminology used herein is for the purpose of describing particular aspects only and is not intended to
25 be limiting.

[0054] Many patent applications, patents, and publications are referred to herein to assist in understanding the aspects described. Each of these references are incorporated herein by reference in their entirety.

[0055] When introducing elements disclosed herein, the articles “a”, “an”,
30 “the”, and “said” are intended to mean that there may be one or more of the elements.

[0056] The term "comprising" and its derivatives, as used herein, are intended to be open ended terms that specify the presence of the stated features, elements, components, groups, integers, and/or steps, but do not exclude the presence of other unstated features, elements, components, groups, integers and/or steps. The foregoing also applies to words having similar meanings such as the terms, "including", "having" and their derivatives. It will be understood that any embodiments described as "comprising" certain components may also "consist of" or "consist essentially of," these components, wherein "consisting of" has a closed-ended or restrictive meaning and "consisting essentially of" means including the components specified but excluding other components except for materials present as impurities, unavoidable materials present as a result of processes used to provide the components, and components added for a purpose other than achieving the technical effects described herein. For example, a composition defined using the phrase "consisting essentially of" encompasses any known acceptable additive, excipient, diluent, carrier, and the like, suitable for the composition described herein. Typically, a composition consisting essentially of a set of components will comprise less than 5% by weight, typically less than 3% by weight, more typically less than 1% by weight of non-specified components.

[0057] It will be understood that any component defined herein as being included may be explicitly excluded from the claimed invention by way of proviso or negative limitation, such as any specific compounds or method steps, whether implicitly or explicitly defined herein.

[0058] In addition, all ranges given herein include the end of the ranges and also any intermediate range points, whether explicitly stated or not.

[0059] Finally, terms of degree such as "substantially", "about" and "approximately" as used herein mean a reasonable amount of deviation of the modified term such that the end result is not significantly changed. These terms of degree should be construed as including a deviation of at least $\pm 5\%$ of the modified term if this deviation would not negate the meaning of the word it modifies.

[0060] The abbreviation, "e.g." is derived from the Latin *exempli gratia*, and is used herein to indicate a non-limiting example. Thus, the abbreviation "e.g." is

synonymous with the term “for example.” The word “or” is intended to include “and” unless the context clearly indicates otherwise.

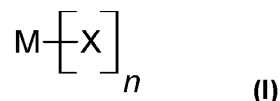
[0061] The phrase “at least one of” is understood to be one or more. The phrase “at least one of...and...” is understood to mean at least one of the elements listed or a combination thereof, if not explicitly listed. For example, “at least one of A, B, and C” is understood to mean A alone or B alone or C alone or a combination of A and B or a combination of A and C or a combination of B and C or a combination of A, B, and C.

[0062] The specification relates to a compound, its salt form, hydrate form or anhydrous form, which elicit activation of AhR pathways useful in treatment of a disease which may benefit from modulation of AhR pathways.

[0063] The specification includes sub-heading to assist the reader with understanding the specification. The disclosure under one sub-heading is not exclusive nor limited to the sub-heading, rather it should be taken and understood taking into consideration the entire disclosure of the specification.

[0064] The compound

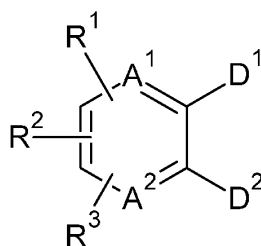
[0065] In one aspect, the specification relates to compound of Formula (I):



[0066] its hydrate, anhydrous or salt form thereof;

20 **[0067]** wherein M is Zn, and n is 1, 2 or 3;

[0068] X is a bidentate ligand, and each X independently is:



[0069] (i)

[0070] wherein

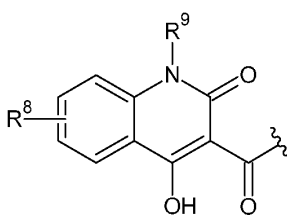
[0071] A¹ and A² each independently is CH, N, or SH;

- [0072]** each R^1 , R^2 or R^3 independently is $-H$, a C_{1-9} substituent optionally having one or more heteroatoms, $-OR^4$, $-SR^4$, $-N(R^4)_2$, $-C(=O)NR^4$, $-NC(=O)R^4$, $-C(=O)R^4$, $-C(=O)OR^4$, or a halogen, or R^1 and R^2 together form a C_5 - or C_6 -membered ring optionally having one or more heteroatoms, the C_5 - or C_6 -membered ring optionally being mono or di-substituted with C_{1-3} -alkyl, C_{1-3} -alkoxy, phenyl, $-N(R^4)_2$, $-C(O)R^4$, $-COOR^4$, or a halogen; and wherein when both A^1 and A^2 are other than CH , R^3 is absent;

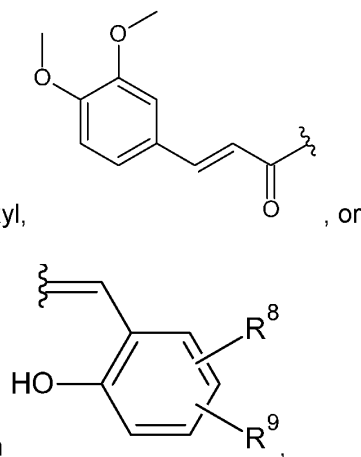
[0073] each R^4 independently is $-H$, or a C_{1-3} substituent optionally having one or more heteroatoms;

- 10 **[0074]** D^1 and D^2 are each independently $-H$, $-OH$, $-N(R^5)_2$, $-SH$, $-CO_2R^6$ or $-C(=O)R^7$, wherein if one of D^1 or D^2 is $-H$, the other D^1 or D^2 is other than $-H$,

[0075] each R^5 independently is $-H$, a C_{1-3} alkyl,



, or the two R^5 together form

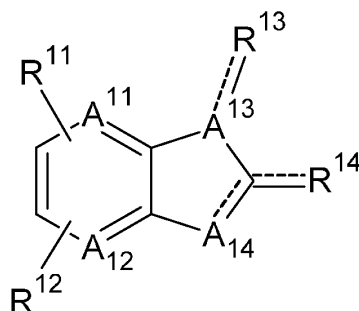


[0076] R^6 is $(^-)$ (absent and is a negative charge), $-H$, or a C_{1-3} alkyl;

- 15 **[0077]** R^7 is $-H$, $-C_{1-5}$ -substituent or aryl, wherein the $-C_{1-5}$ -substituent or aryl optionally has one or more heteroatoms;

[0078] R^8 is $-H$, $-OH$, a C_{1-3} -alkyl substituent optionally having one or more heteroatoms, a $-OC_{1-3}$ -alkyl substituent optionally having one or more heteroatoms, or a halogen; and

- 20 **[0079]** R^9 is $-H$, or a C_{1-3} alkyl substituent optionally having one or more heteroatoms;



[0080] (ii)

[0081] wherein

[0082] A¹¹ and A¹² each independently is –CH or N;

[0083] R¹¹ and R¹² each independently is –H, a C₁₋₃-substituent optionally
 5 having one or more heteroatoms, a –O–C₁₋₃-substituent, or a halogen;

[0084] _____ is a single or a double bond, and only one of _____ in _____A¹⁴ and _____R¹⁴ is a double bond;

[0085] when _____ between A¹³ and R¹³ is a single bond, A¹³ is C–H or N, and R¹³ is –H,

10 [0086] when _____ between A¹³ and R¹³ is a double bond, A¹³ is C, and R¹³ is CH_y, wherein y is 1 or 2; and when y is 1, the CH is coupled to a substituted or unsubstituted aryl or heteroaryl;

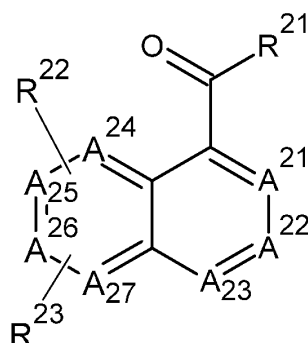
[0087] when _____ of _____A¹⁴ is a single bond, A¹⁴ is NH or CH₂,

[0088] when _____ of _____A¹⁴ is a double bond, A¹⁴ is N or CR¹⁵, wherein R¹⁵ is
 15 –C(=O)– coupled to a substituted or unsubstituted heteroaryl;

[0089] when _____ of _____R¹⁴ is a single bond, R¹⁴ is –H, –COO⁽⁻⁾, or –S(=O)R¹⁶, wherein R¹⁶ is CH_z optionally coupled to a substituted or unsubstituted aryl or heteroaryl, where z is 1, 2 or 3;

[0090] when _____ of _____R¹⁴ is a double bond, R¹⁴ is O or S;

20 [0091] or



[0092] (iii)

[0093] wherein

[0094] A²¹ is N, and each of A²² to A²⁷ independently is –CH or N;

[0095] R²¹ is –OR²⁴ or –SR²⁵, wherein R²⁴ or R²⁵ is absent, –H, –C₁–C₃–alkyl or aryl; and

[0096] R²² and R²³ each independently is –H, a C₁₋₃–substituent optionally having one or more heteroatoms, a halogen, or R²² and R²³ together form a C₅- or C₆-membered aromatic ring, the C₅- or C₆-membered aromatic ring being optionally mono or di-substituted with C₁–C₃–alkyl, C₁–C₃–alkoxy, –NR²⁶₂, –C(O)R²⁷, –COOR²⁸, –CHO or halogen;

[0097] wherein each of R²⁶ to R²⁸ is independently –H, –C₁–C₃–alkyl or aryl.

[0098] The term, ‘hydrate’ as used herein is not particularly limited and should be known or understood to a person of skill in the art. A hydrate is a substance that contains water or its constituent elements. Hydrates can be considered as inorganic salts containing water molecules combined in a definite ratio as an integral part of the crystal that are either bound to a metal center or that have crystallized with the metal complex. Such hydrates are also said to contain water of crystallization or water of hydration.

[0099] The term, ‘anhydrous’ form as disclosed herein is not particularly limited and should be known or understood by a person of skill in the art. An anhydrous form of a substance refers to a compound that contains no water or substantially no water. In practice, it is very difficult to achieve perfect dryness as anhydrous compounds gradually absorb water from the atmosphere, requiring

Careful storage. In one embodiment, an anhydrous compound is where water is generally absent from the crystal lattice of the compound.

[00100] The term, 'salt' as disclosed herein is not particularly limited and should be known or understood by a person of skill in the art. The term includes acid or base addition salts, where an acid or a base is present or added to the compound to form its acid or base addition salt. In one embodiment, for example and without limitation, the compound of formula **(I)** is formed as a pharmaceutically acceptable salt.

[00101] A pharmaceutically acceptable salt form of the compound of formula **(I)** may also initially confer a desirable pharmacokinetic property on the active ingredient which were absent in the non-salt form and may even positively affect the pharmacodynamics of the active ingredient with respect to its therapeutic activity in the body.

[00102] Pharmaceutically acceptable salt of the compound of formula **(I)** refer to a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Non-limiting examples of such salts can include, without limitation, acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as glycolic acid, pyruvic acid, lactic acid, malonic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, salicylic acid, muconic acid, and the like; or basic addition salts formed with the conjugate bases of any of the inorganic acids listed above, wherein the conjugate bases comprise a cationic component selected from among Na^+ , K^+ , Mg^{+2} , Ca^{+2} , and quaternary ammonium. In one embodiment, for example and without limitation, where the compound of formula **(I)** has a positive charge, the counter-ion can be, for example and without limitation, HCO_3^- , BF_4^- , CO_3^{2-} , NO_3^- , ClO_4^- , SO_4^{2-} , F^- , Br^- , $\text{C}_3\text{H}_3\text{O}_2^-$, NH_3 , MnO_4^- , NO_2^- , BrO_3^- , IO_3^- , $\text{Cr}_2\text{O}_7^{2-}$, OH^- , ClO_3^- , HCO_2^- , and the like.

[00103] The metal (M) present in the compound of formula (I) is zinc (Zn). Zinc has an electron configuration of $[\text{Ar}]3d^{10}4s^2$ and is a member of the group 12 of the periodic table. In the context of the specification, in the compound of formula (I), the oxidation state of zinc is +2, and is present as Zn^{+2} , having an electronic configuration of $[\text{Ar}]3d^{10}$. In the context of the specification, the geometry of the complexes can exist as square planar, distorted square planar, octahedral or distorted octahedra.

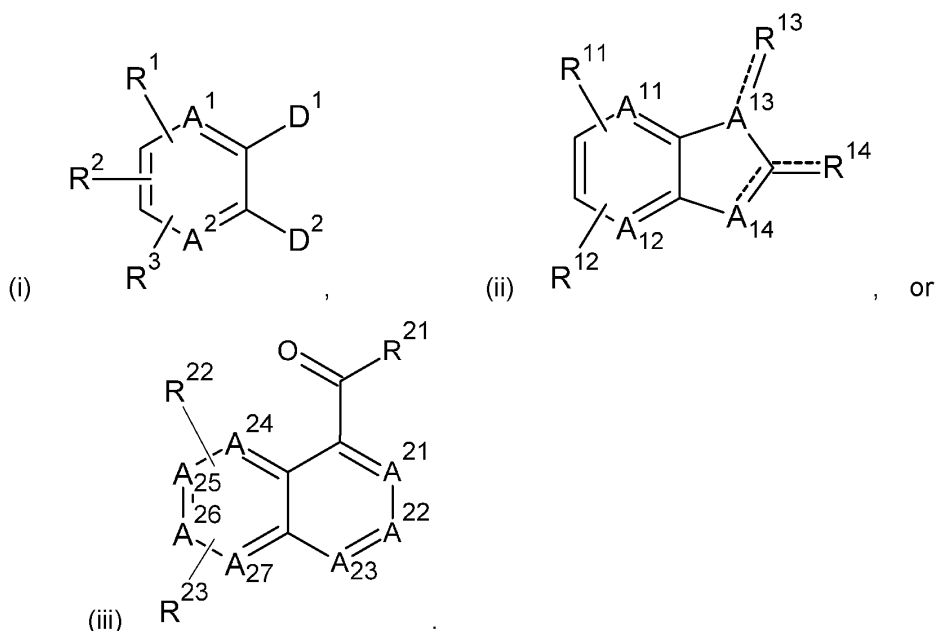
[00104] The term, "ligand" as used herein is not particularly limited and should be known or understood by a person of skill in the art. In coordination chemistry, a ligand is an ion or molecule (having a functional group) that binds to a central metal atom to form a coordination complex. This is typically achieved by the ligand donating a pair of electron (forming a dative bond) to the electronegative central M element. In other words, the bonding with the metal generally involves formal donation of one or more of the ligand's electron pairs, often through Lewis bases. The nature of metal–ligand bonding can range from covalent to ionic. Furthermore, the metal–ligand bond order typically can range from one to three, with higher bond orders also known to exist. Ligands are viewed as Lewis bases, although some cases are known to involve Lewis acidic "ligands".

[00105] The ligands as disclosed herein chelate with zinc to form a zinc complex. The zinc complex can have 1, 2 or 3 ligands that bind to zinc. In addition, where 2 or 3 ligands bind to zinc, the ligands can be the same or different. The zinc complex formed can be present as a salt form. Furthermore, the zinc complex can be in an anhydrous form or hydrate form. Moreover, when the zinc complex is present in an anhydrous form or a hydrate form, it can also be present in a salt form of the hydrate or anhydrous form. In the hydrate form of the zinc complex, water can bind to the zinc metal in forming the complex.

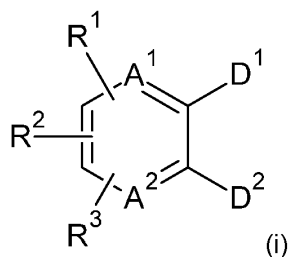
[00106] In the one or more ligands present in the compound of formula (I), each of the one or more ligand is a bidentate ligand. The term, bidentate ligand, is not particularly limited and should be known or understood by a person of skill in the art. A bidentate ligand is a Lewis base that can donate two pairs ("bi") of electrons to a metal atom. Bidentate ligands are often referred to as chelating ligands ("chelate" is derived from the Greek word for "claw") because they can "grab" a metal atom in two places. It should be noted that the ligands disclosed herein can bind to zinc from

more than two sites. For instance, the ligand can bind from three (tridentate ligand) or four (tetradentate) sites. In the context of the current specification, the ligands disclosed herein are at least a bidentate ligand. As such, the ligands contemplated herein can also be tridentate or tetradentate, and thereby have three or four atoms that bond to zinc.

[00107] The position of the atom donating the lone pair of electrons to bind to the zinc is not particularly limited. The binding can take place from a pair of electrons being donated from an atom present on the aromatic ring of the ligand, or from a moiety that is coupled to the aromatic ring, as disclosed herein. The bidentate ligands, as disclosed herein, can have the core structure of:



[00108] In one embodiment, for example and without limitation, one or more of the ligands present in the compound of formula (1) is ligand (i) (or ligand type (i)), as shown below:



[00109] wherein

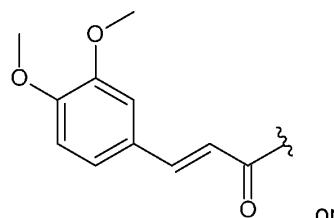
[00110] A¹ and A² each independently is CH, N, or SH;

[00111] each R¹, R² or R³ independently is -H, a C₁₋₉ substituent optionally having one or more heteroatoms, -OR⁴, -SR⁴, -N(R⁴)₂, -C(=O)NR⁴, -NC(=O)R⁴, -C(=O)R⁴, -C(=O)OR⁴, or a halogen, or R¹ and R² together form a C₅- or C₆-membered ring optionally having one or more heteroatoms, the C₅- or C₆-membered ring optionally being mono or di-substituted with C₁₋₃-alkyl, C₁₋₃-alkoxy, phenyl, -N(R⁴)₂, -C(O)R⁴, -COOR⁴, or a halogen; and wherein when both A¹ and A² are other than CH, R³ is absent;

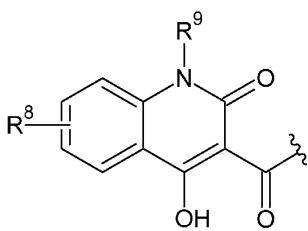
[00112] each R⁴ independently is -H, or a C₁₋₃ substituent optionally having one or more heteroatoms;

[00113] D¹ and D² are each independently -H, -OH, -N(R⁵)₂, -SH, -CO₂R⁶ or -C(=O)R⁷, wherein if one of D¹ or D² is -H, the other D¹ or D² is other than -H,

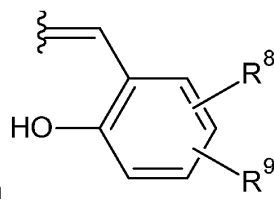
[00114] each R⁵ independently is -H, a C₁₋₃ alkyl,



, or



, or the two R⁵ together form



[00115] R⁶ is ⁻ (absent and is a negative charge), -H, or a C₁₋₃ alkyl;

[00116] R⁷ is –H, –C₁–C₅–substituent or aryl, wherein the –C₁–C₅–substituent or aryl optionally has one or more heteroatoms;

[00117] R⁸ is –H, –OH, a C₁₋₃-alkyl substituent optionally having one or more heteroatoms, a –OC₁₋₃-alkyl substituent optionally having one or more heteroatoms,
5 or a halogen; and

[00118] R⁹ is –H, or a C₁₋₃ alkyl substituent optionally having one or more heteroatoms.

[00119] The binding of the bidentate ligands to the zinc metal can take place from a number of different atoms on the ligand. For instance, when ligand (i) is
10 present in the zinc complex, the lone pair of electrons from the ligand can be donated by A¹, A², D¹, D², R¹, R² or R³, or the structure represented by A¹, A², D¹, D², R¹, R² or R³. As the ligand is a bidentate ligand, the two pairs of electrons donated to zinc can come from any one or a combination of any two of A¹, A², D¹, D², R¹, R² or R³. Alternatively, the two pairs of electrons can be donated by a single
15 functional group, such as –COO⁽⁻⁾, that can represent any one of A¹, A², D¹, D², R¹, R² or R³. The position of the atoms donating the lone pairs of electrons in the ligand is also not particularly limited, so long as the ligand can chelate to zinc. Similarly, when ligand (ii) is present in the zinc complex of formula (I), the two lone pairs of electrons from the bidentate ligand can be donated by any one or two A¹¹, A¹², A¹³,
20 A¹⁴, R¹¹, R¹², R¹³, or R¹⁴. Similarly, when ligand (iii) is present in the zinc complex of formula (I), the two lone pairs of electrons from the bidentate ligand can be donated by any one or two A²¹, A²², A²³, A²⁴, A²⁵, A²⁶, A²⁷, R²¹, R²², or R²³.

[00120] The bidentate ligand present in the zinc complex of formula (I) can be any one or combination of ligand (i), (ii) or (iii). As such, the zinc complex of formula
25 (I) can have only type of ligand, such ligand (i), (ii) or (iii). Alternatively, the zinc complex of formula (I) can have any two types of the bidentate ligands, such as, ligands (i) and (ii), ligands (i) and (iii), or ligands (ii) and (iii). Moreover, the zinc complex of formula (I) can have all types of ligands (i), (ii) and (iii), depending on the compound of formula (I) being formed.

[00121] The term, C₁₋₉ substituent, and the like, as used herein is not particularly limited and should be known or understood by a person of skill in the art. The term relates to an organic substituent having from one to nine carbon atoms.

The number of carbon atoms present in the substituent are noted in the subscript with C (denoting the carbon atom). As such, a C₁₋₃ substituent refers to an organic substituent having from one to three carbon atoms, or a C₁₋₅ substituent refers to an organic substituent having from one to five carbon atoms. An organic substituent, as used herein, is any chemical moiety containing carbon. As such, the C₁₋₉ substituent can be, for example and without limitation, an alkyl, an alkenyl, an alkynyl, a cyclic structure, such as, for example and without limitation, a carbocyclic moiety, an aromatic moiety, a polycyclic moiety, or a combination thereof. Non-limiting examples of a C₁₋₉ substituent can include methyl, ethyl, ethylenyl, ethynyl, propyl, propylenyl, propynyl, isopropyl, butyl, butenyl, butynyl, phenyl, benzyl, cyclohexanyl, ethyl-cyclohexyl, coumarin moiety, and others.

[00122] As disclosed herein, the C₁₋₉ substituent can be optionally substituted having one or more heteroatoms, -OR⁴, -SR⁴, -N(R⁴)₂, or a halogen. The presence of the non-carbon atom changes the class of organic compounds, but are considered to be included in the specification, so long as the total number of carbon atoms range from one to nine. As such, other organic classes, such as alcohols and ethers (represented by -OR⁴), thiols or thioethers (represented by -SR⁴), amines (represented by -NR⁴), amides (represented by -C(=O)NR⁴ and -NC(=O)R⁴), aldehydes and ketones (represented by -C(=O)R⁴), carboxylic acid (or its anionic form) and esters (represented by -C(=O)OR⁴) are contemplated within the scope of the specification, so long as the substituent has a total of from one to nine carbon atoms, and do not prevent binding of the ligand with zinc. Non-limiting examples of a C₁₋₉ substituent optionally having one or more heteroatoms contemplated within the specification include trifluoromethyl (-CF₃), ethoxy (-OCH₂CH₃), propanol (-CH₂CH₂OH), propanthiol (HSCH₂CH₂-), ethyl methylene sulfide (CH₃CH₂SCH₂-), pyridine, aniline, an acetic acid moiety (-CH₂C(=O)OH), or bromine, to name a few.

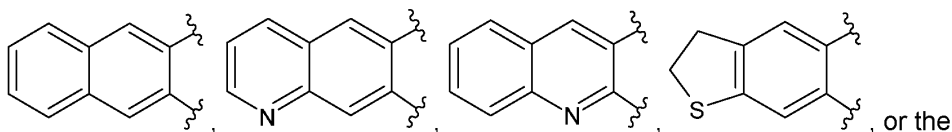
[00123] The term, heteroatom, as used herein is not particularly limited and should be known or understood by a person of skill in the art. Heteroatoms refer to any atom other than carbon and hydrogen. In one embodiment, for example and without limitation, the heteroatom is one or more of nitrogen, oxygen, sulphur or a halogen.

[00124] The term, halogen, as used herein is not particularly limited and should be known or understood by a person of skill in the art. The halogens are elements

that form group 17 of the periodic table. Halogen include fluorine, chlorine, bromine, or iodine.

[00125] In the type (i) ligand disclosed in the specification, the R^1 and R^2 can together form a C_5 - or C_6 -membered ring, optionally substituted, as disclosed herein.

- 5 The C_5 - or C_6 -membered ring are bonded to the aromatic core structure of ligand (i), and form a polycyclic ring structure. In addition, the C_5 - or C_6 -membered ring can be an aromatic ring, or saturated or unsaturated ring. As such, structures, such as



like, are contemplated to be within the scope of the specification. Furthermore, the

- 10 C_5 - or C_6 -membered ring optionally being mono or di-substituted with C_{1-3} -alkyl, C_{1-3} -alkoxy, phenyl, $-N(R^4)_2$, $-C(O)R^4$, $-COOR^4$, or a halogen.

[00126] In the ligand (i), when both A^1 and A^2 are other than CH, R^3 is absent. As such, R^1 , R^2 and R^3 can only be present when one or both A^1 and A^2 are CH.

When both, A^1 and A^2 are, for example, N and/or SH, then R^3 is not present in the

- 15 ligand (i).

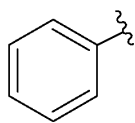
[00127] In the ligand (i), when one of D^1 or D^2 is $-H$, the other D^1 or D^2 is other than $-H$. As such, both D^1 and D^2 cannot be $-H$ in ligand (i). If one of D^1 is $-H$, then the other D^2 is a substituent other than $-H$. Furthermore, both D^1 and D^2 can be other than $-H$ in ligand (i) disclosed herein.

- 20 **[00128]** The term, alkyl, as used herein is not particularly limited and should be known or understood by a person of skill in the art. In organic chemistry, an alkyl group is an alkane missing one hydrogen. The term alkyl is intentionally unspecific to include many possible substitutions. An acyclic alkyl has the general formula of $-C_nH_{2n+1}$. A cycloalkyl group is derived from a cycloalkane by removal of a hydrogen
- 25 atom from a ring and has the general formula $-C_nH_{2n-1}$. Typically an alkyl is a part of a larger molecule. The smallest alkyl group is methyl, with the formula $-CH_3$. The term, C_{1-3} -alkyl as used herein refers to an alkyl group having from one to three carbon atoms. Examples of a C_{1-3} -alkyl include, methyl, ethyl, propyl or isopropyl.

- [00129]** The term, alkoxy, as used herein is not particularly limited and should
- 30 be known or understood by a person of skill in the art. Describe C_{1-3} -alkoxy

- [00130]** An alkoxy group is an alkyl group which is singularly bonded to oxygen, and can be denoted by the structure R-O, where R is an organic substituent. A C₁₋₃-alkoxy refers to an alkoxy group having from one to three carbon atoms. Examples of a C₁₋₃-alkoxy include methoxy (CH₃O-), ethoxy (CH₃CH₂O-), propyloxy (CH₃CH₂CH₂O-), or iso-propyloxy ((CH₃)₂CHO-).

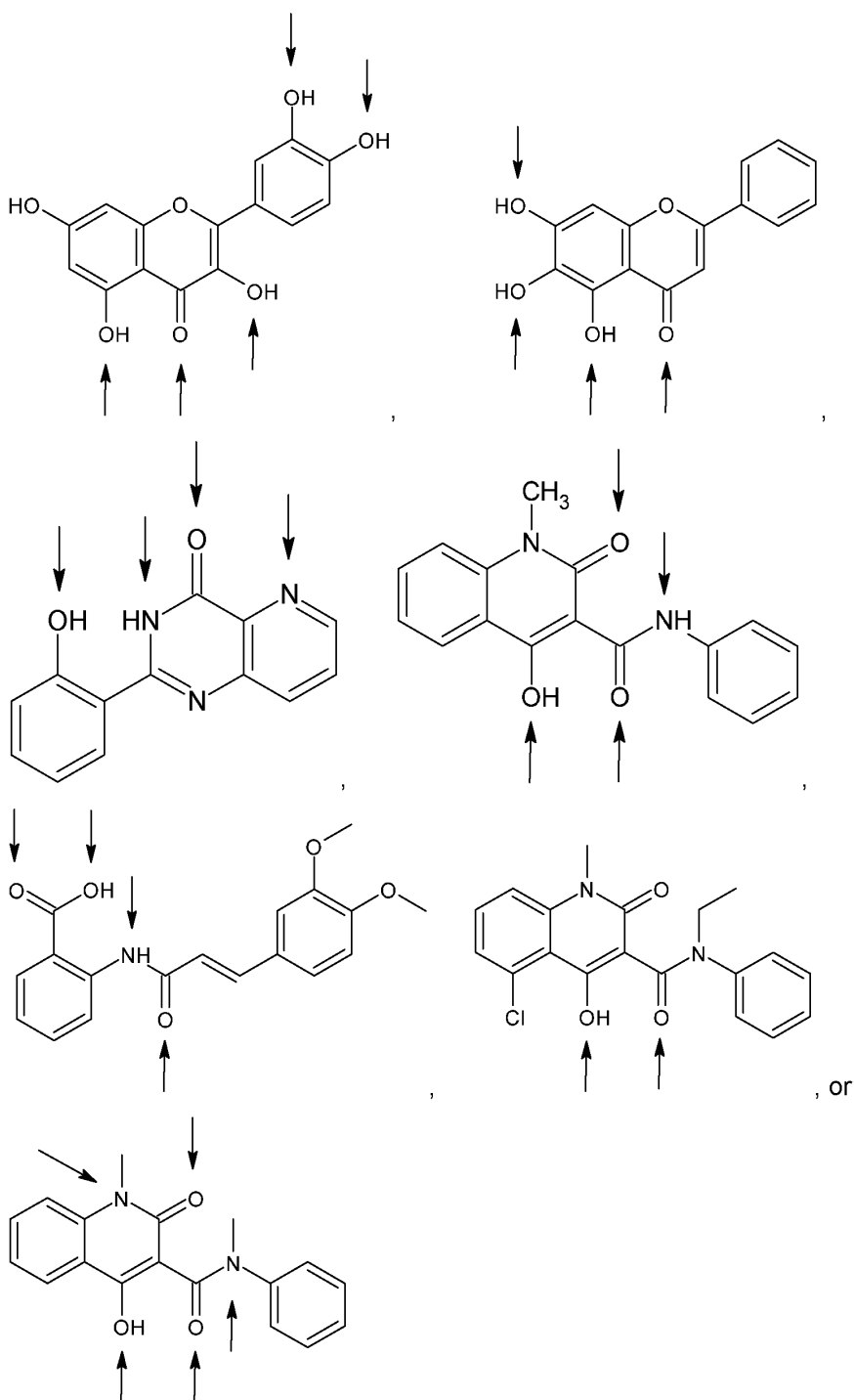
[00131] The term, aryl, as used herein is not particularly limited and should be known or understood by a person of skill in the art. An aryl is any compound, functional group or substituent derived from an aromatic ring, usually an aromatic hydrocarbon. An example of an aryl group is phenyl (C₆H₅-), having the structure



- 10 , where  denotes the point of bonding of the phenyl group to the remaining chemical structure.

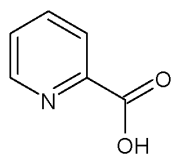
[00132] The term, heteroaryl, as used herein is not particularly limited and should be known or understood by a person of skill in the art. A heteroaryl is an aryl having one or more heteroatoms.

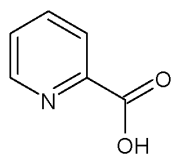
- 15 **[00133]** In the ligands disclosed herein, when a carboxylic acid or a phenolic group is present on the ligand, the carboxylic acid or phenolic group can be in the protonated form (-COOH or -OH) or it can be in the deprotonated form (-COO⁽⁻⁾ or -O⁽⁻⁾). When the term carboxylic acid or a phenolic structure is noted, both the protonated and deprotonated forms are contemplated within the context of the
- 20 specification. Further, where a protonated form of carboxylic acid or phenolic group is denoted, the deprotonated form is also considered to be encompassed within it. As should be recognized by a person of skill in the art, the form the carboxylic acid or phenol group is present in depends upon the pH of the solution, and the protonated form can convert to the deprotonated form at lower pH's, and vice versa. Further,
- 25 depending on the conditions used, the amine group present on the chelate can be in a protonated form (-N⁽⁺⁾H) or the deprotonated form (-N:). Similar to the carboxylic acid and phenol group noted herein, in the context of the specification, when form of the amine (primary, secondary or tertiary amine) is disclosed, both the protonated form and deprotonated form are contemplated and considered encompassed within
- 30 the scope of the specification.

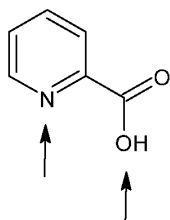


[00135] And where $\leftarrow$ (the arrow) represent a potential point of chelation of the bidentate ligand to Zn. As should be recognized by a person of skill in the art, there are multiple points of chelation of the ligand to the metal, as noted herein. The particular complex formed can depend on the reaction conditions. The particular point of chelation of the ligand to the zinc can also be affected by kinetic, thermodynamic and steric factors. As such, where a ligand binds to the zinc and forms a five or six membered ring, with an absence of adjacent bulky or sterically hindered moieties, is more likely to occur than when the chelation atoms are further apart in the ligand or adjacent to bulky or sterically hindered structures.

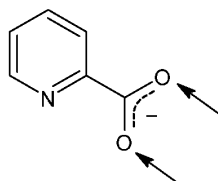
- 10 **[00136]** In some instances, a particular ligand can chelate with the zinc from more than two locations, as noted herein. For example and without limitation, the



ligand, , can chelate with zinc from two different positions, as shown below, with chelation from the N and the O of the carboxylic acid moiety being more likely to occur. While the other possible chelation of the ligand is from the two oxygen atoms of the carboxylic acid group, and which is less likely to occur. Complexes formed from types of chelation are contemplated and considered encompassed within the specification.



(chelation through N and O is more likely than)



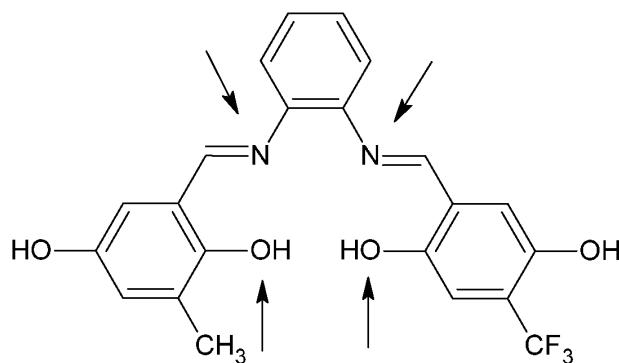
(chelation through the two oxygen atoms of carboxylic acid is

- 20 possible, however, less likely to occur).

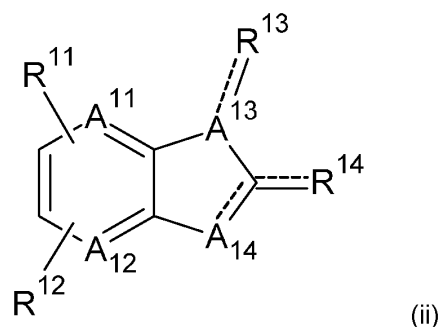
[00137] As noted herein, the chelation of the ligand can also occur from more than two atoms, thereby being, for example and without limitation, a tridentate ligand

or a tetradentate ligand. In one embodiment, for example and without limitation, the ligand is a tetradentate ligand, with binding of the ligand taking place from four different atoms in the ligand, as shown below, with the $\leftarrow$ (the arrow) representing the point of chelation of the ligand to the metal.

5



[00138] In an embodiment, for example and without limitation, one or more of the ligands present in the compound of formula (1) is ligand (ii) (or ligand type (ii)), as shown below:



10 **[00139]** wherein

[00140] A^{11} and A^{12} each independently is $-\text{CH}$ or N ;

[00141] R^{11} and R^{12} each independently is $-\text{H}$, a C_{1-3} -substituent optionally having one or more heteroatoms, a $-\text{O}-\text{C}_{1-3}$ -substituent, or a halogen;

15 **[00142]** ----- is a single or a double bond, and only one of ----- in $\text{-----}A^{14}$ and $\text{-----}R^{14}$ is a double bond;

[00143] when ----- between A^{13} and R^{13} is a single bond, A^{13} is $\text{C}-\text{H}$ or N , and R^{13} is $-\text{H}$,

[00144] when _____ between A^{13} and R^{13} is a double bond, A^{13} is C, and R^{13} is CH_y , wherein y is 1 or 2; and when y is 1, the CH is coupled to a substituted or unsubstituted aryl or heteroaryl;

[00145] when _____ of _____ A^{14} is a single bond, A^{14} is NH or CH_2 ,

- 5 **[00146]** when _____ of _____ A^{14} is a double bond, A^{14} is N or CR^{15} , wherein R^{15} is $-C(=O)-$ coupled to a substituted or unsubstituted heteroaryl;

[00147] when _____ of _____ R^{14} is a single bond, R^{14} is $-H$, $-COO^{(-)}$, or $-S(=O)R^{16}$, wherein R^{16} is CH_z optionally coupled to a substituted or unsubstituted aryl or heteroaryl, where z is 1, 2 or 3;

- 10 **[00148]** when _____ of _____ R^{14} is a double bond, R^{14} is O or S;

[00149] As disclosed herein, the feature "_____" in the structure of ligand (ii) can be a single or a double bond. There are three different positions in ligand (ii), where the feature "_____" is present, one between A^{13} and R^{13} (denoted as $A^{13}-----R^{13}$), a second instance can occur where ligand (ii) has the structural feature $A^{14}-----C$

- 15 (where the C is the carbon of the five membered ring of ligand (ii)), and the third instance can occur where ligand (iii) has the structural feature $C-----R^{14}$ (where the C is the carbon of the five membered ring of ligand (ii)). It should be recognized by a person of skill in the art that the C bonded to A^{13} , A^{14} and R^{14} can only form a double bond between one of A^{14} and R^{14} , and not both, as it would result in a carbon atom
- 20 having five bonds. Consequently, in ligand (ii), only one of "_____" in _____ A^{14} and _____ R^{14} in ligand (ii) is a double bond, and the other has to be a single bond. Hence, in ligand (ii), when "_____" between _____ A^{14} is a double bond, the "_____" in _____ R^{14} is a single bond. Further, in ligand (ii), when "_____" between _____ R^{14} is a double bond, the "_____" in _____ A^{14} is a single bond.

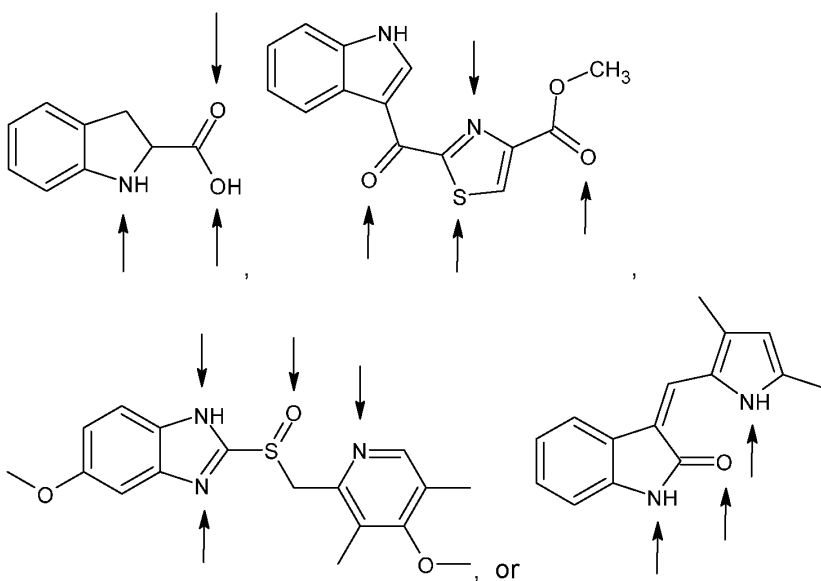
- 25 **[00150]** In ligand (ii), as disclosed herein, when _____ between A^{13} and R^{13} is a single bond, A^{13} is C-H or N, and R^{13} is $-H$. Further, in ligand (ii), when _____ between A^{13} and R^{13} is a double bond, A^{13} is C, and R^{13} is CH_y , wherein y is 1 or 2. As such, CH_y can be $-CH_2$ or $-CH-$, which is bonded to substituted or unsubstituted heteroaryl. Consequently, when y is 1, the CH is coupled to a substituted or
- 30 unsubstituted aryl or heteroaryl. In one embodiment, for example and without limitation, the heteroaryl is not particularly limited and can have from four to nine carbon atoms (i.e. C_{4-9} -heteroaryl). In another embodiment, for example and without

limitation, the heteroaryl can be substituted with one or more C₁₋₃-substituent having one or more heteroatoms.

- [00151]** In an embodiment in accordance with the specification, when ----- of -----R¹⁴ is a single bond, R¹⁴ is -H, -COO⁽⁻⁾, or -S(=O)R¹⁶, wherein R¹⁶ is CH₂ optionally coupled to a substituted or unsubstituted aryl or heteroaryl, where z is 1, 2 or 3. As such, CH_z can be -CH₃, -CH₂-, or -CH<, where the CH₂ is bonded to another moiety and the CH is bonded to two other chemical moieties. Hence, when CH_z is CH₂ or CH, it is coupled to a substituted or unsubstituted aryl or heteroaryl. In one embodiment, for example and without limitation, the heteroaryl is not particularly limited and can have from four to nine carbon atoms (i.e. C₄₋₉-heteroaryl). In another embodiment, for example and without limitation, the heteroaryl can be substituted with one or more C₁₋₃-substituents having one or more heteroatoms.

- [00152]** Further, as disclosed herein, in an embodiment, for example and without limitation, in ligand (ii) when ----- of -----R¹⁴ is a double bond, R¹⁴ is O (oxygen) or S (sulphur).

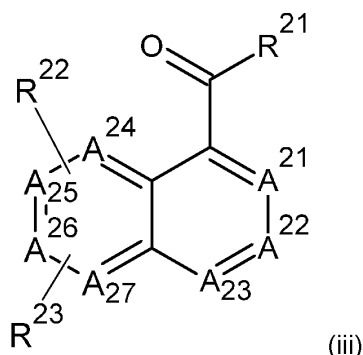
[00153] Non-limiting examples of ligand (ii) include



- [00154]** And where ← (the arrow) represent a potential point of chelation of the bidentate ligand to Zn. As should be recognized by a person of skill in the art, and as described herein with respect to the ligand (i), there are multiple points of

chelation of the ligand to the metal, as noted herein, and the description with respect to ligand (i) is also applicable to ligand (ii), disclosed herein.

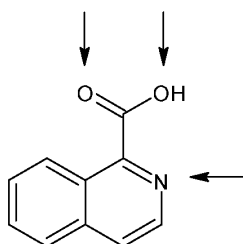
[00155] In an embodiment, for example and without limitation, one or more of the ligands present in the compound of formula (1) is ligand (iii) (or ligand type (iii)),
 5 as shown below:



[00156] wherein A^{21} is N, and each of A^{22} to A^{27} independently is $-CH$ or N. Further, in ligand (iii), R^{21} is $-OR^{24}$ or $-SR^{25}$, wherein R^{24} or R^{25} is absent, $-H$, $-C_1$ - C_3 -alkyl or aryl. When R^{24} or R^{25} is absent, there is a negative charge (anion
 10 formed) on O or S (represented as, $O^{(-)}$ or $S^{(-)}$).

[00157] In ligand (iii), R^{22} and R^{23} each independently is $-H$, a C_{1-3} -substituent optionally having one or more heteroatoms, a halogen, or R^{22} and R^{23} together form a C_5 - or C_6 -membered aromatic ring, the C_5 - or C_6 -membered aromatic ring being optionally mono or di-substituted with C_1 - C_3 -alkyl, C_1 - C_3 -alkoxy, $-NR^{26}_2$, $-C(O)R^{27}$,
 15 $-COOR^{28}$, $-CHO$ or halogen, wherein each of R^{26} to R^{28} is independently $-H$, $-C_1$ - C_3 -alkyl or aryl.

[00158] A non-limiting example of ligand (iii) includes



[00159] And where $\leftarrow$ (the arrow) represent a potential point of chelation of the bidentate ligand to Zn. As should be recognized by a person of skill in the art,
 20

and as described herein with respect to the ligands (i) and (ii), there are multiple points of chelation of the ligand to the metal, as noted herein, and the description with respect to ligand (i) and (ii) is also applicable to ligand (iii), disclosed herein.

[00160] With respect to the zinc complexes disclosed herein, their hydrate form, anhydrous form, or salt thereof, in a first embodiment, for example and without limitation, the compounds, their hydrate form, anhydrous form, or salt thereof, can have a minimum solubility in aqueous media of 0.1 nM at 25 °C and 1 bar at neutral pH. In a second embodiment, for example and without limitation, the compounds, their hydrate form, anhydrous form, or salt thereof, can have a minimum solubility in aqueous media of 0.1 μM at 25 °C.

[00161] With respect to the zinc complexes, disclosed herein, their hydrate form, anhydrous form, or salt thereof, in a first embodiment, for example and without limitation, the compounds, their hydrate form, anhydrous form, or salt thereof, can have a minimum solubility in non-aqueous media, including, for example and without limitation, in DMSO, of 0.1 μM at 25 °C and 1 bar at neutral pH. In a second embodiment, for example and without limitation, the compounds, their hydrate form, anhydrous form, or salt thereof, can have a minimum solubility in non-aqueous media, including, for example and without limitation, in DMSO, of 1.0 μM at 25 °C.

[00162] With respect to the zinc complex compounds, disclosed herein, their hydrate form, anhydrous form, or salt thereof, in a first embodiment, for example and without limitation, the formation constant (K_f) or stability constant, defined as the formation of a complex ion from its central ion (M) and attached ligands (L) via $K_f = [M_xL_y]/[M]^x[L]^y$ determined at 25 °C and 1 bar at neutral pH, of the compound of Formula 1, its hydrate form, anhydrous form, or salt thereof, can range from $K_f = 1.0 \times 10^5$ to $K_f = 1.0 \times 10^{35}$. In a second embodiment, for example and without limitation, the formation constant (K_f) of the compounds, disclosed herein, their hydrate form, anhydrous form, or salt thereof, can range from $K_f = 1.0 \times 10^5$ to $K_f = 1.0 \times 10^{25}$. In a third embodiment, for example and without limitation, the formation constant (K_f) of the compounds, disclosed herein, their hydrate form, anhydrous form, or salt thereof, can range from $K_f = 1.0 \times 10^{10}$ to $K_f = 1.0 \times 10^{25}$.

[00163] The structures disclosed herein above, permit secondary interactions encountered by the compounds, their hydrate form, anhydrous form, solvated form

or salt thereof, with atoms derived from solvents encountered by the compounds, their hydrate form, anhydrous form, solvated form or salt thereof, during synthetic procedures, isolation procedures, formulation, and or therapeutic uses. These interactions may afford structures that include atoms and ligands derived
5 encountered by the compounds, their hydrate form, anhydrous form, solvated form or salt thereof, during synthesis, isolation, formulation and therapeutic uses. Such secondary interactions may result in a ligand displacement, thereby affording an opening or exchange, wherein the atoms and ligands encountered in the secondary interaction may insinuate themselves into the compounds, its hydrate form,
10 anhydrous form, solvated form or salt thereof. Such structures are expressly contemplated in the present specification.

[00164] Compositions

[00165] The specification also provides embodiments of the compounds, their hydrate form, anhydrous form, solvated form or salt thereof, disclosed herein as
15 pharmaceutical formulations.

[00166] Pharmaceutical formulations of the compounds, their hydrate form, anhydrous form, solvated form or salt thereof, described herein may be manufactured in a manner that is known including, but not limited to dissolution, granulation, emulsification, mixing, encapsulation, lyophilizing or combinations
20 thereof.

[00167] The specification also provides embodiments of the compounds, their hydrate form, anhydrous form, solvated form or salt thereof, that may be formulated into appropriate aqueous solutions for the purpose of injection, either subcutaneous or intravenous. Such compositions may include appropriate solutions including but
25 not limited to physiologically compatible buffers. Such compositions may be formulated with the intention of delivery as a bolus injection or continuous infusion and may include excipients known in the art to enable suspension, stabilization, delivery, or dispersion.

[00168] The specification also provides embodiments of the compounds, their
30 hydrate form, anhydrous form, solvated form or salt thereof, that may be formulated with appropriate penetrants, known in the art, to afford transmucosal or transcutaneous administration. Such formulations may be inclusive of carriers

including, but not limited to, liquids, gels, hydrogels, solids, slurries and may include suitable excipients known in the art to afford control over rheological and release properties.

[00169] The specification also provides embodiments of the compounds, their hydrate form, anhydrous form, solvated form or salt thereof, that may be formulated into an aerosolized, spray, or nebulized format, with or without the use of a suitable propellant known in the art. Such formulations may be prepared in a solid, liquid or gel format through the inclusion of appropriate excipients known in the art. Such formulations may be utilized for delivery of the compounds, their hydrate form, anhydrous form, solvated form or salt thereof, and formulations described herein to dermal, hair, mucosal membranes, or inhaled.

[00170] The specification also provides embodiments of the compounds, their hydrate form, anhydrous form, solvated form or salt thereof, that may be formulated into a reservoir such that the release or delivery of the compounds, their hydrate form, anhydrous form, solvated form or salt thereof, may proceed over the course of an extended period for long-acting formulations.

[00171] The specification also provides embodiments of the compounds, their hydrate form, anhydrous form, solvated form or salt thereof, that may be formulated in combination with excipients or pharmaceutical compounds which may direct or target delivery to a discrete location within a biological system. Such formulations may employ use of liposomes, emulsions, self-assembled structures, polymeric compounds, sustained release materials, or combinations thereof.

[00172] The specification also provides embodiments of the compounds, their hydrate form, anhydrous form, solvated form or salt thereof, that may be formulated in combination with non-aqueous formulations. Such formulations may employ use of silica, silicones, cross-linked silicones and suitable excipients known in the art to contribute to rheological and delivery properties.

[00173] The compounds of the specification can be provided as salts with pharmaceutically compatible counterions such as sodium, potassium, calcium, ammonium or other non-toxic pharmaceutically acceptable salts known to those skilled in the art, or combinations thereof.

[00174] Pharmaceutical compositions of the compounds, their hydrate form, anhydrous form, solvated form or salt thereof, described in the present specification may be formulated and administered through a variety of means. Such administration may include systemic, localized, or topical including but not limited to
5 oral, rectal, transmucosal, transcutaneous, intestinal, parenteral, intramuscular, subcutaneous, intramedullary, intrathecal, intravenous, intraventricular, intraperitoneal, intranasal, and intraocular. Therein the mode of administration may be tailored to the desired site and delivery scheme.

[00175] Pharmaceutical compositions of the compounds, their hydrate form,
10 anhydrous form, solvated form or salt thereof, described in the present specification may be suitable wherein the active ingredients are contained and delivered in an effective amount to achieve a desired outcome and intended purpose. Such a therapeutically effective quantity can include an amount of the compounds, their hydrate form, anhydrous form, solvated form or salt thereof, described in the present
15 specification which may treat, prevent, or ameliorate a disease or disorder in a subject. As used herein, the terms “treating,” “preventing,” and “ameliorating” refer to interventions performed with the intention of alleviating the symptoms associated with, preventing the development of, or altering the pathology of a disease, disorder or condition. Thus, in various embodiments, the terms may include the prevention
20 (prophylaxis), moderation, reduction, or curing of a disease, disorder or condition at various stages. In various embodiments, therefore, those in need of therapy/treatment may include those already having the disease, disorder or condition and/or those prone to, or at risk of developing, the disease, disorder or condition and/or those in whom the disease, disorder or condition is to be prevented.

[00176] Pharmaceutical compositions of the compounds, their hydrate form, anhydrous form, solvated form or salt thereof, described in the present specification may be suitable for medical, dental, pharmaceutical, cosmeceutical, personal care, veterinary, agricultural, materials engineering, and over-the-counter fields. Such compositions may be used in the treatment and or therapy of subject inclusive of
25 humans or other vertebrate wherein the composition provides either subjective relief of symptoms or an objectively identifiable improvement as noted by the clinician or other qualified observer.

[00177] The therapeutically effective does for any of the compounds, , their hydrate form, anhydrous form, solvated form or salt thereof, described in the present specification may initially be estimated by *in-vitro* cell culture assays as disclosed herein. However, it is understood to those skilled in the art, that the specific dose
5 required for higher organisms including animals and humans, may be determined more accurately through *in-vivo* studies including determination of lethal dose (LD₅₀) concentrations and effective dose concentrations (ED₅₀) and the effective ratios thereof. It is also understood to those skilled in the art that the dosing regimen can more accurately through dose-finding studies in a clinical setting. It is also
10 understood that the specific dose for any particular patient may be dependent upon a variety of factors including but not limited to age, sex, weight, height, health, time of administration, route of administration, drug pharmacokinetics and pharmacodynamics, drug interactions, the severity of the disease, and the recommendations and judgement of the prescribing physician.

15 **[00178]** In a one embodiment, compounds, their hydrate form, anhydrous form, solvated form or salt thereof, disclosed herein can have certain pharmacological properties including low toxicity, low carcinogenicity, desirable *in-vitro* and *in-vivo* half lives and reasonable efficacy.

[00179] Process for preparation

20 **[00180]** As disclosed herein, in a seventh aspect, the specification relates to a process for preparation of the compound of formula (I), its hydrate form, anhydrous form, solvated form or salt thereof, the process comprising:

[00181] reacting a zinc salt or zinc compound having a chelated ligand and one or more ligands in a solvent.

25 **[00182]** In one embodiment, for example and without limitation, the compound is prepared via an initial dissolution of the central M metal into an aqueous media following by the addition of a suitable oxidizing or reducing agent and acid or base to affect the desired orbital geometry prior to addition of the desired chelate to form the compound of formula (I), its hydrate form, anhydrous form, solvated form or salt
30 thereof .

[00183] Conjugate acid and base or desired salts of the compounds may be prepared through appropriate adjudgment of the pH of the complex or ion exchange to obtain the desired salt.

[00184] In an embodiment, for example and without limitation, in accordance with the specification, the process involves reaction of a salt or chelate form of the central metal with a secondary chelate or mixed chelate system to form a desired chelate complex exhibiting various physiochemical properties, particularly stability and yield, rendering them suitable for industrial and commercial applications.

[00185] In another embodiment, for example and without limitation, the process involves dissolution of the central metal into a suitable solvent, pH, and temperature to support dissolution. The solvent may be selected from aqueous or organic media; inclusive but not limited to water, methanol, ethanol, dimethylformamide, dimethyl sulfoxide, toluene, or hexanes. The pH of the media may be adjusted by appropriate strong or weak acid or base to a pH of 2 to 14. In a more preferred embodiment, the pH of the media may be adjusted by a strong acid or base to a pH of 4 to 10. In some embodiments, the dissolution of the metal is conducted at a temperature ranging from about 0° C to about 100° C for about 0 minutes to about 90 minutes. In another embodiment, for example and without limitation, the dissolution of the metal is conducted at a temperature ranging from about 20° C to about 50° C for about 0 minutes to 10 minutes. In another further embodiment, for example and without limitation, the concentration of the metal ranges from about 0.01 mM to about 2.0 M.

[00186] In a still embodiment, for example and without limitation, the process can involve dissolution of the ligand chelate or ligand chelates into a suitable solvent, pH, and temperature to support dissolution. The solvent may be selected from aqueous or organic media; inclusive but not limited to water, methanol, ethanol, dimethylformamide, dimethyl sulfoxide, toluene, or hexanes. The pH of the media may be adjusted by appropriate strong or weak acid or base to a pH of 2 to 14. In a more preferred embodiment, the pH of the media may be adjusted by a strong acid or base to a pH of 4 to 10. In another embodiment, for example and without limitation, the dissolution of the metal is conducted at a temperature ranging from about 0° C to about 100° C for about 0 minutes to about 90 minutes. In another further embodiment, for example and without limitation, the dissolution of the metal is

conducted at a temperature ranging from about 20° C to about 50° C for about 0 minutes to 10 minutes. In a still embodiment, for example and without limitation, the concentration of the ligand chelate or ligand chelates ranges from about 0.01 mM to about 4.0 M.

- 5 **[00187]** In an embodiment, for example and without limitation, the ligand chelate solutions are added in series to the metal solution. In another embodiment, for example and without limitation, the mixed ligand chelate solution is added simultaneously to the metal solution. In a further embodiment, for example and without limitation, the ligand chelate, or ligand chelate systems are added directly to
- 10 the metal solution. In a still embodiment, for example and without limitation, the metal is added directly to the ligand chelate solution or mixed ligand chelate solution.

- [00188]** In an embodiment, for example and without limitation, the pH of the reaction solution forming the metal chelate complex may be adjusted by appropriate strong or weak acid or base to a pH of 2 to 14. In another embodiment, for example
- 15 and without limitation, the pH of the media may be adjusted by a strong acid or base to a pH of 4 to 10. In a further embodiment, for example and without limitation, the formation of the metal chelate complex may be conducted at a temperature ranging from about 0° C to about 100° C for about 0 minutes to about 48 hours. In another further embodiment, for example and without limitation, the formation of the metal
- 20 chelate complex is conducted at a temperature ranging from about 20° C to about 90° C for about 0 minutes to 90 minutes.

- [00189]** In an embodiment, for example and without limitation, of the specification, the metal chelate complex may be isolated by filtration and optionally further purified. In another embodiment, for example and without limitation, of the
- 25 specification, the metal chelate complex may be isolated by the reaction solution by formation of a conjugate acid or base and filtration and optionally further purified. In a further embodiment, for example and without limitation, of the specification, the metal chelate complex may be isolated from the reaction solution by the addition of a pharmaceutically suitable counterion to form a desired salt complex and isolated by
- 30 filtration and optionally further purified.

[00190] In a still further embodiment, for example and without limitation, of the specification, further purification may proceed via recrystallization, sublimation,

extraction, adsorption chromatography, column chromatography, high pressure liquid chromatography, or other methods known in the art.

[00191] Biological assay

[00192] Historical agonists of AhR have been quantified via nuclear
5 translocation of AhR following ligand binding, resulting in the induction of cytochrome P450 and genetic expression of *cyp1a1*; exclusively and definitively downstream of AhR. However, more recent findings have identified that inducers of low *cyp1a1* expression are therapeutically advantageous and aligned with non-canonical pathways of AhR modulation.

10 **[00193]** The present specification describes compounds which induce the genetic expression of *cyp1a1* via Human HT29 colon adenocarcinoma or AhR reporter cells. As exemplified in the present specification (Figure 1), the chelates described herein have demonstrated significant induction of the expression of *cyp1a1*, a gene which is exclusively downstream of AhR promoter region and
15 transcribed upon activation of AhR, within Human HT29 colon cells.

EXAMPLES

[00194] The above disclosure generally describes the present invention. A more complete understanding can be obtained by reference to the following specific
20 Examples. These Examples are described solely for purposes of illustration and are not intended to limit the scope of the invention. Changes in form and substitution of equivalents are contemplated as circumstances may suggest or render expedient. Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the following illustrative examples, make and utilize
25 the constructs of the present invention and practice the claimed methods. The following working examples therefore, specifically point out the typical aspects of the present invention and are not to be construed as limiting in any way in the remainder of the disclosure. Although specific terms have been employed herein, such terms are intended in a descriptive sense and not for purposes of limitation.

30 **[00195]** Example 1: 2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-4H-1-benzopyran-4-one (0.5mmol, 10ml milli-Q water) was solubilized at room temperature with stirring following the addition of KOH (0.5mmol, 100ul). In a separate flask, 2-aminophenol

(1mmol, 10ml milli-Q water) was solubilized by heating between 40-50 °C with KOH (1mmol, 200ul). A solution of ZnCl₂ (0.5mmol, 0.5ml milli-Q water) was dissolved with stirring at room temperature, then added to 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-1-benzopyran-4-one in a solution stirring at room temperature. This was followed quickly by the addition of 2-aminophenol. The mixture was stirred at room temperature for 1hr resulting in a dark reddish-brown solution with brown precipitate. The product, Compound 1 [Zn(2-aminophenol)₂(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-4H-1-benzopyran-4-one)] was isolated by vacuum filtration and washed twice with milli-Q water (68mg, 12% yield). Elemental Analysis: Theoretical C, 54.9; H, 3.4, N, 4.9; O, 25.3; Zn, 11.5; Actual C, 55.8; H, 3.3, N, 4.8; O, 24.8; Zn, 11.3; UV-Vis; λ_{max} = 380 nm.

[00196] Example 2: ZnCl₂ (1mmol, 1mL H₂O) was added slowly to 5-bromo-3-methyl picolinic acid (1mmol, 4ml 50% EtOH) while stirring at room temperature. 2-aminophenol (0.227g, 2mmol, 5mL H₂O) was solubilized with KOH (2mmol, 100ul), stirring between 40-50 °C, and then titrated slowly into the previous solution. The reaction mixture was quickly transferred to a round bottom and was set to reflux under stirring (70-80 °C) for 3 hours resulting in the formation of a brown precipitate and dark brown solution. The product, Compound 2 [Zn(2-aminophenol)₂(5-bromo-3-methyl picolinate)] was isolated via vacuum filtration and washed twice with milli-Q water (yield 383mg, 77%). Elemental Analysis: Theoretical C, 46.3; H, 2.7, N, 8.5; O, 13.0; Br, 8.5; Zn, 13.3; Actual C, 46.1; H, 3.1, N, 8.5; O, 12.9; Zn, 13.2; UV-Vis; λ_{max} = 440 nm.

[00197] Example 3: 2-Aminophenol (0.114g, 2mmol) was solubilized in 5mL H₂O with KOH (2mmol, 100uL) by stirring at 40-50 °C. A reaction mixture was made by first adding previously solubilized ZnCl₂ (0.146g, 1mmol, 1ml H₂O) at room temperature, to indoline-2-carboxylic acid (0.169g, 1mmol, 6.7ml EtOH) stirring at 50 °C resulting in a colourless turbid solution. The heated 2-aminophenol was added to the reaction mixture stirred at 50 °C for 30min. A pale green byproduct was separated from a red-brown solution by centrifugation (1000xg, 5min). The product, Compound 3 [Zn(2-aminophenol)₂(indoline-2-carboxylate)] was isolated by adding 5mL of milli-Q water with stirring at room temperature (85mg, 19%). Elemental Analysis: Theoretical C, 57.4; H, 3.7, N, 9.6; O, 14.5; Zn, 14.9; Actual C, 57.1; H, 4.1, N, 9.5; O, 14.5; Zn, 14.8; UV-Vis; λ_{max} = 430 nm.

[00198] Example 4: Indoline-2-carboxylic acid (0.162g, 1mmol, 12mL EtOH) was dissolved at 45 °C, before room temperature dissolved Picolinic acid (0.097g, 0.76mmol, 2.3ml H₂O) was added and the reaction mixture continued to stir at 45 °C. Room temperature dissolved ZnCl₂ (0.136g, 0.5mmol, 0.5mL H₂O) was added slowly and then refluxed while stirring for 2 hours between 50-72 °C. The red-brown reaction solution was cooled to room temperature and left overnight wherein a fine white precipitate formed. This by-product precipitate was isolated using vacuum filtration and 5mL of milli-Q water was added to the solution to crash out the product, Compound 4: [Zn(indoline-2-carboxylate)₂(picolinate)], a brown solid was isolated (49mg, 12% yield). Elemental Analysis: C, 53.7; H, 3.0, N, 8.9; O, 20.4; Zn, 13.9; UV-Vis; λ_{max} = 320 nm.

[00199] Example 5: Separately, indoline-2-carboxylic acid (0.836g, 0.5mmol, 3mL H₂O) and isoquinoline-1-carboxylic acid (0.085g, 0.5mmol, 2.5mL H₂O) were dissolved in H₂O and solubilized with 1M equivalent of KOH (100uL, 5M). Both reactants were warmed to 40-50 °C to solubilize and was kept warm to maintain solubility. A solution of Zinc acetate (0.111g, 0.5mmol, 0.5mL H₂O) was dissolved at room temperature and then added to warm (40-50 °C) Isoquinoline-1-carboxylic acid resulting in the formation of a white precipitate. Immediately, warm (40-50 °C) Indoline-2-carboxylic acid was added while stirring, a peach-coloured precipitate was observed. After 10-20 min the peach-coloured product, Compound 5 [Zn(indoline-2-carboxylate) (isoquinoline-1-carboxylate)] was isolated as the monohydrate via vacuum filtration and washed twice with milli-Q H₂O (185mg, 93% yield). Elemental Analysis: Theoretical C, 54.8; H, 3.6, N, 6.7; O, 19.2; Zn, 15.7; Actual C, 54.4; H, 4.3, N, 6.7; O, 19.1; Zn, 15.6; UV-Vis; λ_{max} = 330nm.

[00200] Example 7: Luciferase Assay

[00201] Human HT29 colon adenocarcinoma - AhR reporter cells (HT29-LuciaTM AhR Cells; InvivoGen; ht2l-ahr) were used to determine the EC₅₀ of the described compounds. HT29-LuciaTM AhR Cells are engineering to express Lucia luciferase reporter gene with human Cyp1a1 gene transcription upon AhR activation. Briefly, cells were expanded using DMEM supplemented with 5% heat inactivated FBS, 1% Penicillin-Streptomycin, 2mM L-Glutamine, and 100µg/mL Normocin. After 2 passages, selective antibiotic, Zeocin, was added to media at 100µg/mL to select for stably transfected cells. Dose response and EC₅₀ was evaluated by plating

56,000 cells/well into a 96 well plate in test media containing only DMEM + 5% heat inactivated FBS, 2mM L-Glutamine, and 1% Penicillin-Streptomycin. Compounds were solubilized in DMSO, and 1uL was added to each well for a final DMSO concentration of 0.5%. Cells were incubated with compounds at 37°C and 5% CO₂ for 24 hours. Following 24hr incubation, 20µL of cell supernatant was transferred to a 96-well white opaque plate. A working stock of QUANTI-LucTM 4 Reagent was prepared by adding 23.75mL of sterile H₂O to the concentrated stock. 45µL of QUANTI-LucTM 4 Reagent was added to each well containing cell supernatant. The luminescence of each compound evaluated at 6.25 uM was immediately and reported fold change was determined where statistically significant from baseline induction as shown in Figure 1.

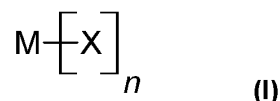
Compound Number	<i>cyp1a1</i> Fold Change
Compound 1	1.384
Compound 2	2.006
Compound 3	2.283
Compound 4	1.220
Compound 5	3.707

[00202] All publications, patents and patent applications cited above are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety.

[00203] Although preferred embodiments of the invention have been described herein in detail, it will be understood by those skilled in the art that variations may be made thereto without departing from the spirit of the invention or the scope of the appended claims.

WE CLAIM:

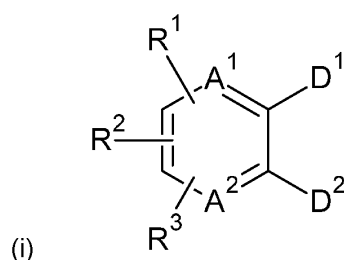
1. A compound of formula (I):



its hydrate, anhydrous or salt form thereof;

- 5 wherein M is Zn, and n is 1, 2 or 3;

X is a bidentate ligand, and each X independently is:



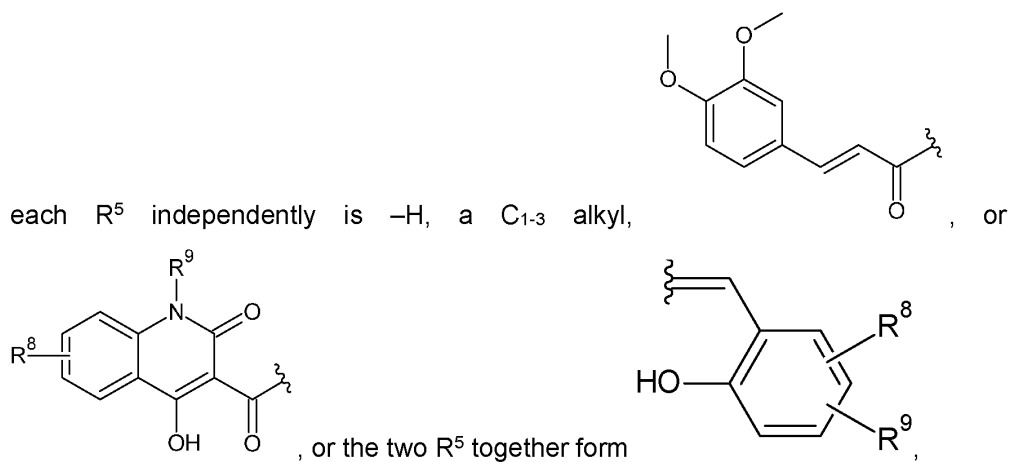
wherein

A¹ and A² each independently is CH, N, or SH;

- 10 each R¹, R² or R³ independently is -H, a C₁₋₉ substituent optionally having one or more heteroatoms, -OR⁴, -SR⁴, -N(R⁴)₂, -C(=O)NR⁴, -NC(=O)R⁴, -C(=O)R⁴, -C(=O)OR⁴, or a halogen, or R¹ and R² together form a C₅- or C₆-membered ring optionally having one or more heteroatoms, the C₅- or C₆-membered ring optionally being mono or di-substituted with C₁₋₃-alkyl, C₁₋₃-alkoxy, phenyl, -N(R⁴)₂, -C(O)R⁴, -COOR⁴, or a
- 15 halogen; and wherein when both A¹ and A² are other than CH, R³ is absent;

each R⁴ independently is -H, or a C₁₋₃ substituent optionally having one or more heteroatoms;

D¹ and D² are each independently -H, -OH, -N(R⁵)₂, -SH, -CO₂R⁶ or -C(=O)R⁷, wherein if one of D¹ or D² is -H, the other D¹ or D² is other than -H,

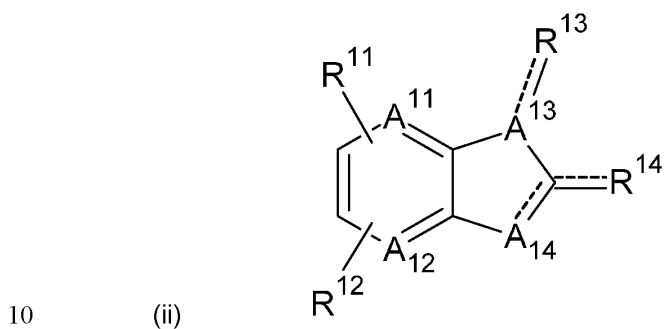


R^6 is $(^-)$ (absent and is a negative charge), $-H$, or a C_{1-3} alkyl;

R^7 is $-H$, $-C_{1-5}$ -substituent or aryl, wherein the $-C_{1-5}$ -substituent or aryl optionally has one or more heteroatoms;

R^8 is $-H$, $-OH$, a C_{1-3} -alkyl substituent optionally having one or more heteroatoms, a $-OC_{1-3}$ -alkyl substituent optionally having one or more heteroatoms, or a halogen; and

R^9 is $-H$, or a C_{1-3} alkyl substituent optionally having one or more heteroatoms;



wherein

A^{11} and A^{12} each independently is $-CH$ or N ;

R^{11} and R^{12} each independently is $-H$, a C_{1-3} -substituent optionally having one or more heteroatoms, a $-O-C_{1-3}$ -substituent, or a halogen;

_____ is a single or a double bond, and only one of _____ in _____ A^{14} and _____ R^{14} is a double bond;

when ----- between A^{13} and R^{13} is a single bond, A^{13} is C-H or N, and R^{13} is -H,

when ----- between A^{13} and R^{13} is a double bond, A^{13} is C, and R^{13} is CH_y , wherein y is 1 or 2; and when y is 1, the CH is coupled to a substituted or unsubstituted aryl or heteroaryl;

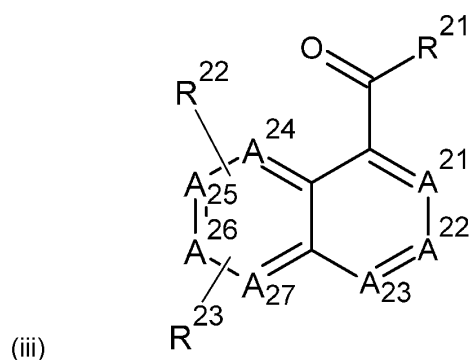
5 when ----- of ----- A^{14} is a single bond, A^{14} is NH or CH_2 ,

when ----- of ----- A^{14} is a double bond, A^{14} is N or CR^{15} , wherein R^{15} is $-C(=O)-$ coupled to a substituted or unsubstituted heteroaryl;

when ----- of ----- R^{14} is a single bond, R^{14} is -H, $-COO^{(-)}$, or $-S(=O)R^{16}$, wherein R^{16} is CH_z optionally coupled to a substituted or unsubstituted aryl or heteroaryl, where z
10 is 1, 2 or 3;

when ----- of ----- R^{14} is a double bond, R^{14} is O or S;

or



wherein

15 A^{21} is N, and each of A^{22} to A^{27} independently is -CH or N;

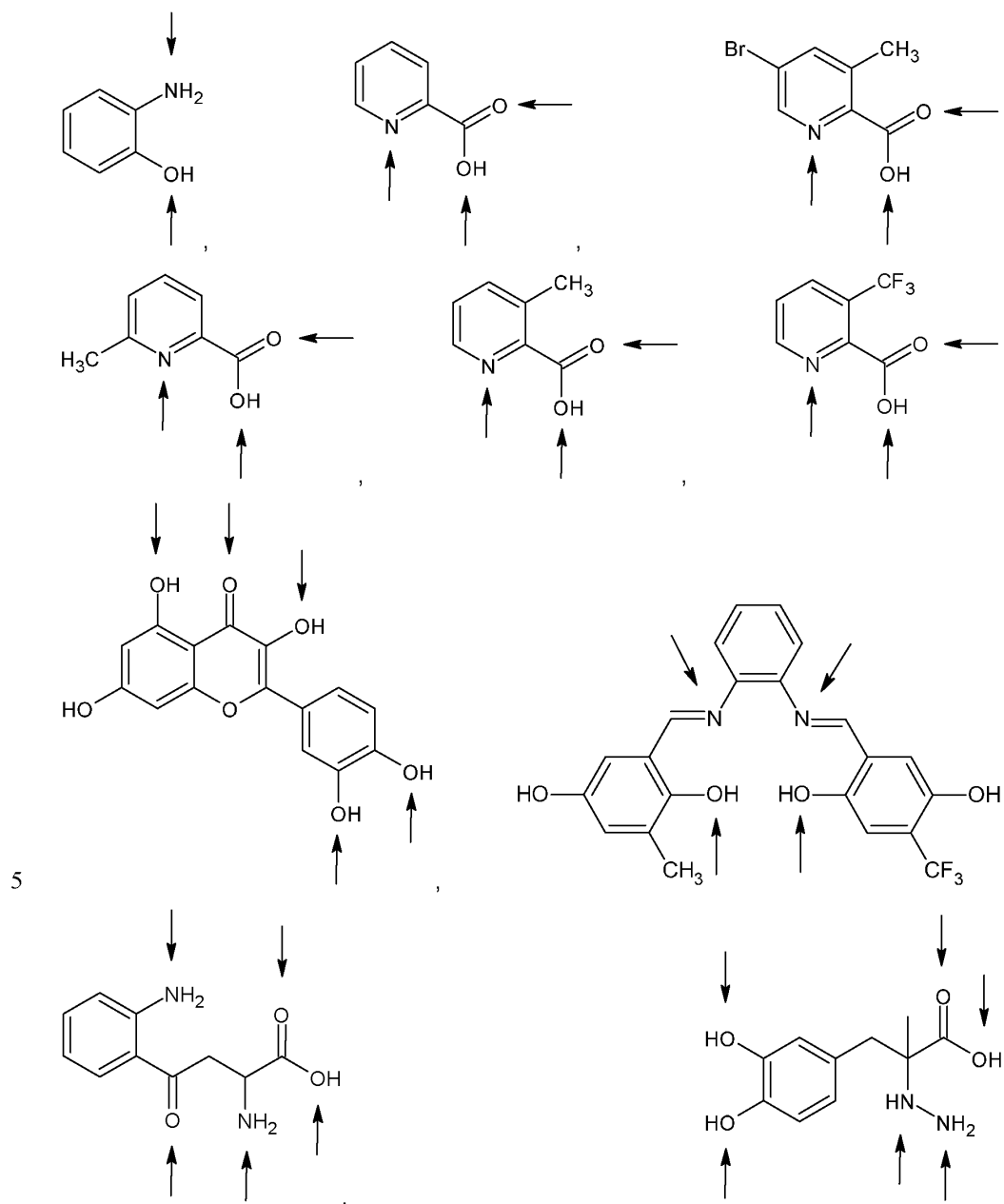
R^{21} is $-OR^{24}$ or $-SR^{25}$, wherein R^{24} or R^{25} is absent, -H, $-C_1-C_3$ -alkyl or aryl; and

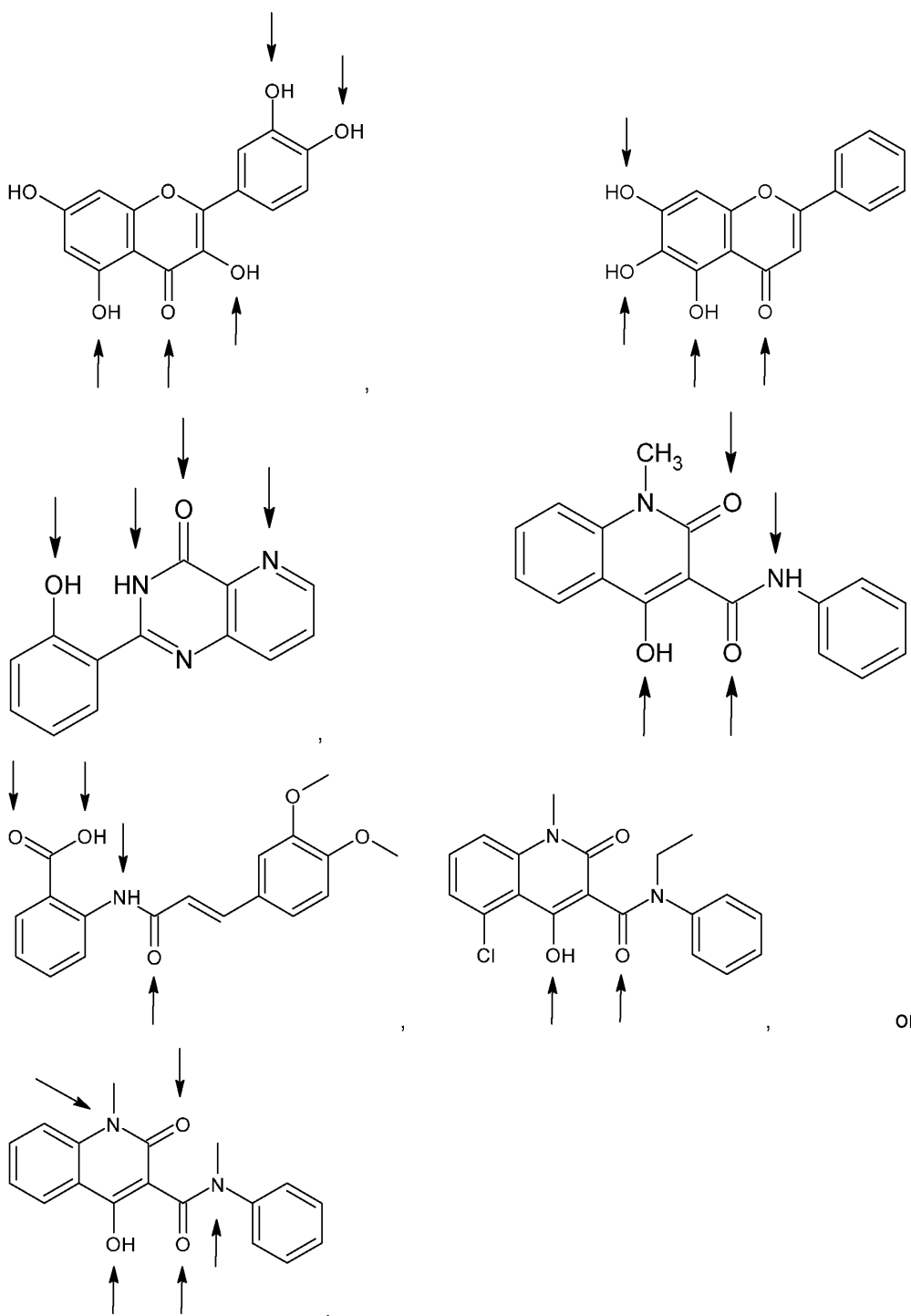
R^{22} and R^{23} each independently is -H, a C_1 - C_3 -substituent optionally having one or more heteroatoms, a halogen, or R^{22} and R^{23} together form a C_5 - or C_6 -membered aromatic ring, the C_5 - or C_6 -membered aromatic ring being optionally mono or di-substituted

20 with C_1 - C_3 -alkyl, C_1 - C_3 -alkoxy, $-NR^{26}_2$, $-C(O)R^{27}$, $-COOR^{28}$, -CHO or halogen;

wherein each of R^{26} to R^{28} is independently -H, $-C_1-C_3$ -alkyl or aryl.

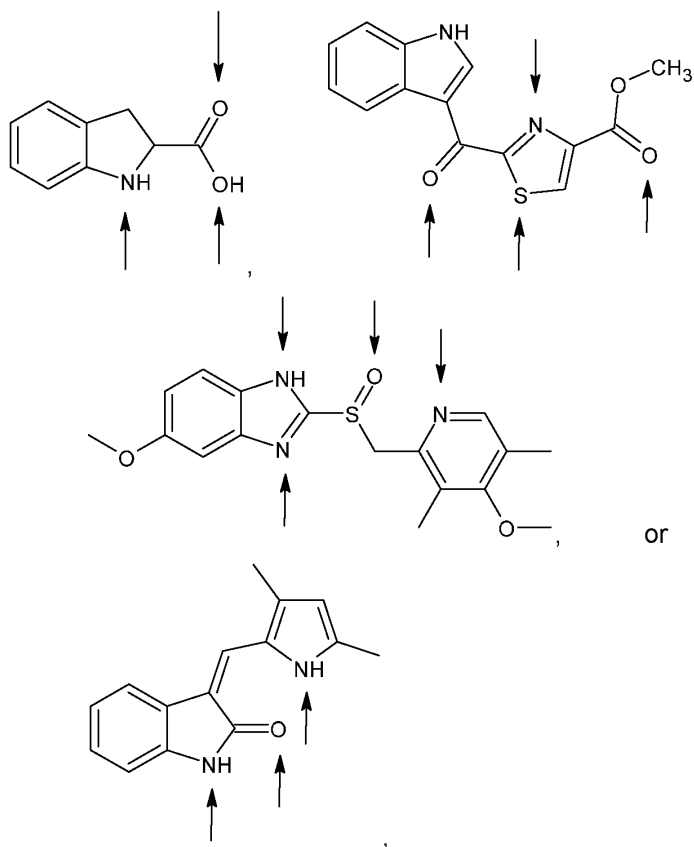
2. The compound, its hydrate, anhydrous or salt form thereof, as defined in claim 1, wherein at least one X is:





5 wherein  represent a potential point of chelation of the bidentate ligand to Zn.

3. The compound, its hydrate, anhydrous or salt form thereof, as defined in claim 1 or 2, wherein at least one X is:



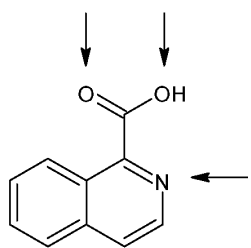
5

or

wherein  represent a potential point of chelation of the bidentate ligand to Zn.

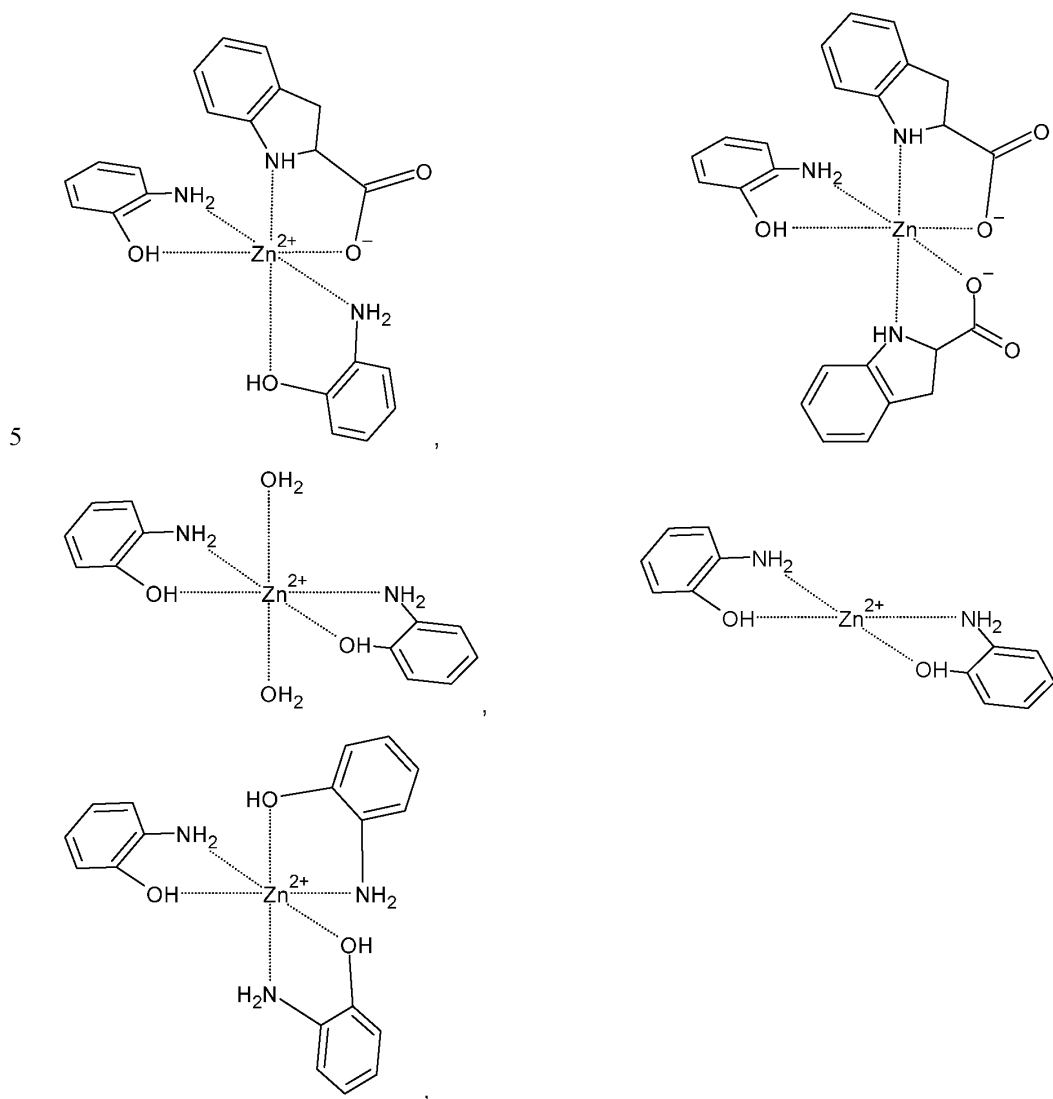
4. The compound, its hydrate, anhydrous or salt form thereof, as defined in any one of claims 1 to 3, wherein at least one X is:

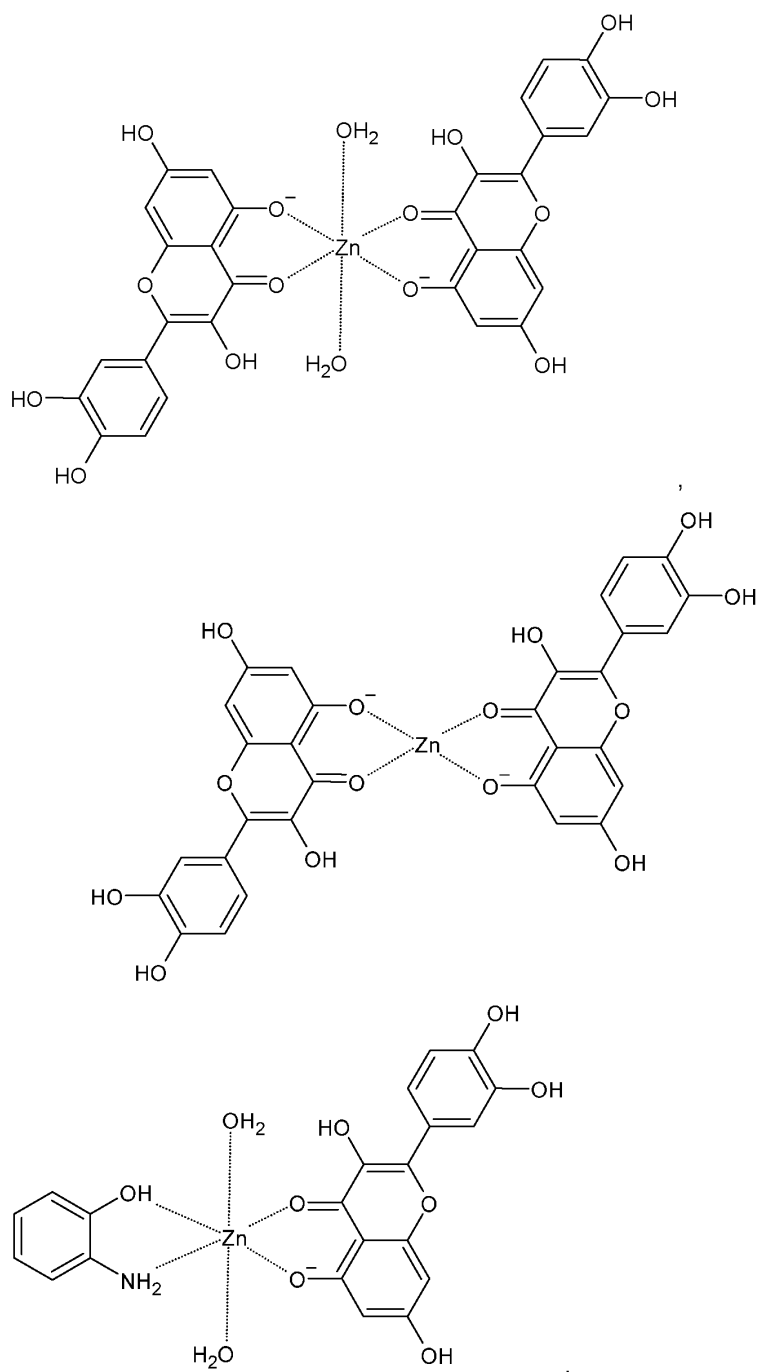
10

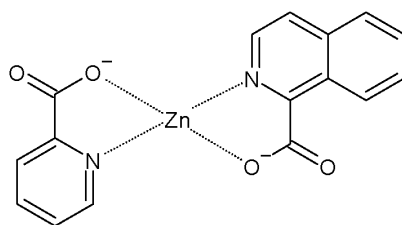
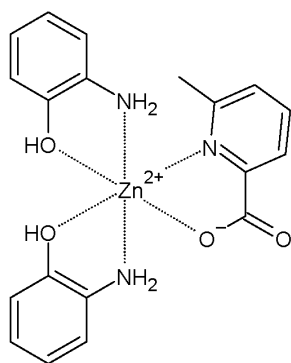
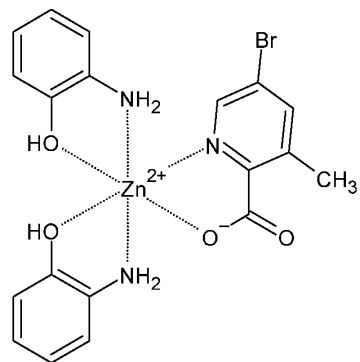
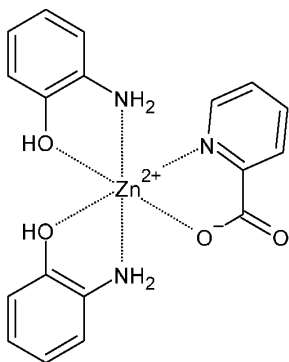
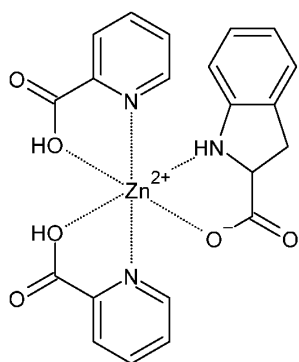
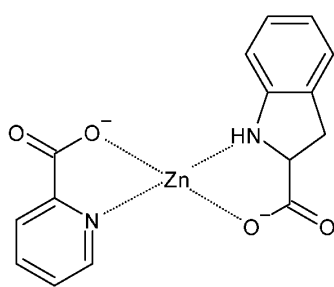
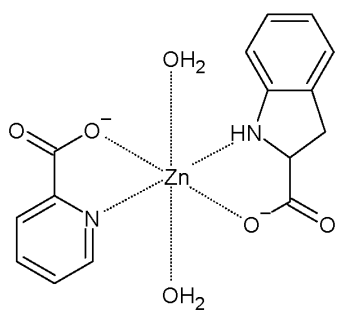
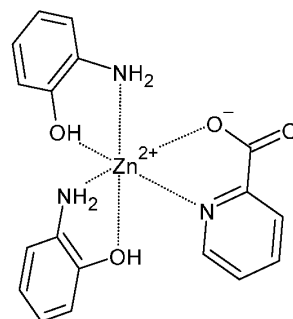


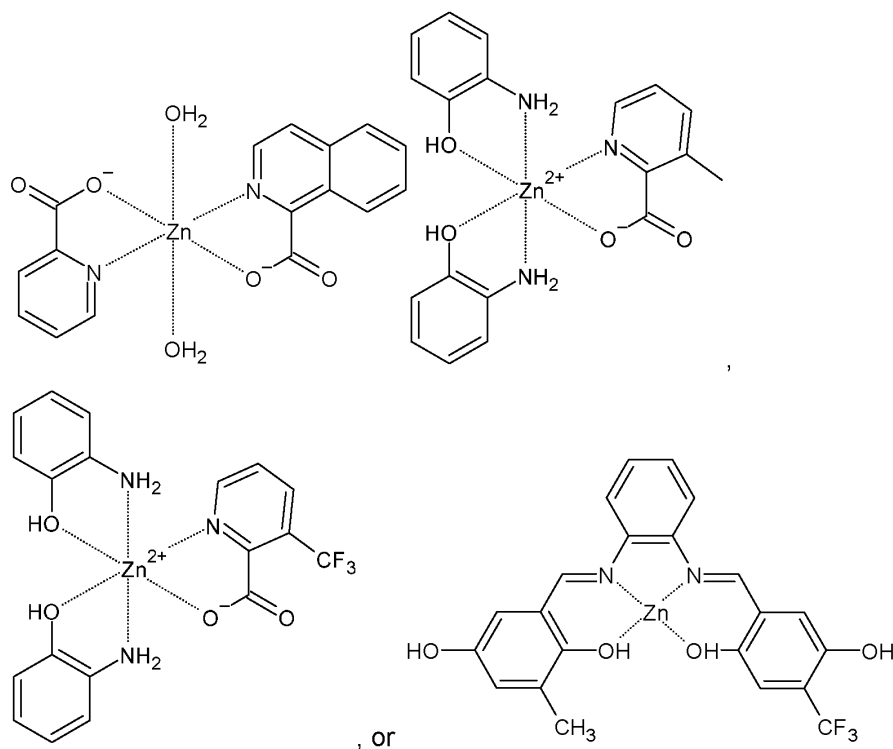
wherein  represent a potential point of chelation of the bidentate ligand to Zn.

5. The compound, its hydrate, anhydrous or salt form thereof, as defined in any one of claims 1 to 4, wherein the compound of formula (I) is:









5 6. The compound of formula (I), its hydrate form, anhydrous form, or salt thereof, as defined in any one of claims 1 to 5 having a minimum solubility in aqueous media of 0.1 nM at 25 °C and 1 bar at neutral pH.

7. The compound of formula (I), its hydrate form, anhydrous form, or salt thereof, as defined in any one of claims 1 to 5 having a minimum solubility in aqueous media of 0.1 μM at 25 °C.

8. The compound of formula (I), its hydrate form, anhydrous form, or salt thereof, as defined in any one of claims 1 to 5 having a minimum solubility in non-aqueous media of 0.1 μM at 25 °C and 1 bar at neutral pH.

9. The compound of formula (I), its hydrate form, anhydrous form, or salt thereof, as defined in any one of claims 1 to 5 having a minimum solubility in non-aqueous media of 1.0 μM at 25 °C.

5 10. The compound of formula (I), its hydrate form, anhydrous form, or salt thereof, as defined in claim 8 or 9, wherein the non-aqueous media is dimethyl sulfoxide (DMSO).

10 11. The compound of formula (I), its hydrate form, anhydrous form, or salt thereof, as defined in any one of claims 1 to 10 having a formation constant (K_f) ranging from 1.0×10^5 to 1.0×10^{35} determined at 25 °C and 1 bar at neutral pH.

15 12. The compound of formula (I), its hydrate form, anhydrous form, or salt thereof, as defined in any one of claims 1 to 10 having a formation constant (K_f) ranging from 1.0×10^5 to 1.0×10^{25} determined at 25 °C and 1 bar at neutral pH.

20 13. The compound of formula (I), its hydrate form, anhydrous form, or salt thereof, as defined in any one of claims 1 to 10 having a formation constant (K_f) ranging from 1.0×10^{10} to 1.0×10^{25} determined at 25 °C and 1 bar at neutral pH.

14. A pharmaceutical composition comprising the compound of formula (I), its hydrate form, anhydrous form, solvated form or salt thereof, as defined in any one of claims 1 to 13, and a pharmaceutically acceptable excipient.

25 15. Use of the compound of formula (I), its hydrate form, anhydrous form, solvated form or salt thereof, as defined in any one of claims 1 to 13, for treatment of a disease associated with activation of aryl hydrocarbon receptor (AhR).

16. Use of the compound of formula (I), its hydrate form, anhydrous form, solvated form or salt thereof, as defined in any one of claims 1 to 13, for modulating aryl hydrocarbon receptor (AhR) activity.

5 17. A method of medical treatment of a disease associated with activation of aryl hydrocarbon receptor (AhR) activity comprising administering to a subject in thereof, a pharmaceutically effective amount of the compound of formula (I), its hydrate form, anhydrous form, solvated form or salt thereof, as defined in any one of claims 1 to 13.

10

18. A method of modulating aryl hydrocarbon receptor (AhR) activity comprising providing the compound of formula (I), its hydrate form, anhydrous form, solvated form or salt thereof, as defined in any one of claims 1 to 13.

15 19. A process for preparation of the compound of formula (I), its hydrate form, anhydrous form, solvated form or salt thereof, the process comprising:
reacting a zinc salt or zinc compound having a chelated ligand and one or more ligands in a solvent.