Title: INDOLE DERIVATIVES, PHARMACEUTICAL COMPOSITIONS CONTAINING SUCH INDOLES AND THEIR USE AS DNA METHYLATION MODULATORS

Abstract: The present invention refers to compounds of formula (I): as well as to a method for their preparation, pharmaceutical compositions comprising the same, and use thereof for the treatment and/or chemoprevention of cancer hematological malignancy, proliferative diseases, genetic diseases, neurological disorders and immunologic disorders.


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INDOLE DERIVATIVES, PHARMACEUTICAL COMPOSITIONS CONTAINING SUCH INDOLES AND THEIR USE AS DNA METHYLATION MODULATORS.

FIELD OF THE INVENTION

The present invention is related to new compounds derived from polysubstituted indole rings, processes for their preparation, pharmaceutical compositions containing such compounds and use thereof as inhibitors of DNA methylation and therapeutic agents for preventing or treating diseases associated with aberrant DNA methylation such as cancer, hematological malignancy, proliferative diseases, genetic diseases, neurological disorders and immunological disorders.

BACKGROUND OF THE INVENTION

DNA methyltransferase (DNMT) enzymes promote the covalent addition of a methyl group to a specific nucleotide base in DNA, using S-adenosyl methionine (SAM) as the methyl donor. Three DNMT enzymes are involved in the control of the methylation state of the C-5 position of cytosine residues located at CpG dinucleotides in genome: DNMT1, DNMT3A and DNMT3B. By specifically inhibiting DNMTs, the aberrant methylation of the DNA gene promoter regions can be prevented. Thus, DNMT enzymes constitute a therapeutic target for preventing or treating diseases associated with aberrant DNA methylation.


Dysregulation of epigenetic marks or epigenetic mechanisms related to DNMT function have been recognized to occur also in other diseases and syndromes (cf. "Epigenetics in Biology and Medicine", edited by M. Esteller, 1st Edition (2008), CRC Press Inc), which include genetic syndromes such as ATR-X, Rett, Fragile X, Prader-Willi, Angelman, CHARGE, CSB, SIOD (Schimke Immuno-Osseous Dysplasia), ICF, Rubinstein-Taybi syndrome and FSHD (Facioscapulo-humeral Dystrophy). Also, immune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis or progressive systemic sclerosis (PSS), as well as neurologic disorders such as schizophrenia and Alzheimer (cf. J. Graff, I.M. Mansuy Behav. Brain Res. 2008, 192, 70; J. Graff, I.M. Mansuy Eur J Neurosci 2009, 30, 1) show disregulation of DNMT function.

On the other hand, 1H-indoles have been included in the category of "privileged structures" (cf. D. A. Horton, G. T. Bourne and M. L. Smythe Chem. Rev. 2003, 103, 893; D. Miiller Drug Discovery Today 2003, 8, 681) defined as "single molecular

Although a large number of drugs containing indole framework can be found within the field of oncology, such as vincristine (cf. H. Ishikawa et al. J. Am. Chem. Soc. 2009, 131, 4904), ellipticine (cf. M. G. Ferkin et al. ChemMedChem 2009, 4, 363; J. B. Le Pecq et al. Proc. Natl. Acad. Sci. USA 1974, 71, 5078) and many other compounds (see for example A. Ahmad, W. A. Sakr, K. M. Rahman Curr Drug Targets 2010, 11, 652; A.-R. Farghaly ARKIVOC 2010, 11, 177-187; Y.K. Chiang et al. J Med Chem 2009, 52, 4221; A. Stolle et al. (2002) PCT No. WO 2002030895), the interaction between DNMTs and non-covalent inhibitors based on 1H-indole scaffolds and polyalkoxy and/or polyhydroxyphenyl groups is unknown.


Several other small-molecule inhibitors of DNA methylation have been described, whose general structures can be found in different reviews (cf. T. E. Fandy Curr. Med. Chem. 2009, 16, 2075; N. Yu, M. Wang Curr. Med. Chem. 2008, 15, 1350), including the psammaplin sponge metabolites (cf. Pina et al. J. Org. Chem. 2003, 68, 3866), which are potent direct inhibitors of DNA methyltransferases but are less effective in cellular assays (cf. A.M. Godert et al. Bioorg. Med. Chem. Lett. 2006, 16, 3330). Other non-nucleoside demethylating agents such as (-)-epigallocatechin-3-gallate (EGCG), hydralazine and procainamide were also shown to be far less effective in reactivating genes than decitabine (cf. J. C. Chuang et al Mol Cancer Ther 2005, 4, 1515). Non covalent small molecule inhibitors of DNMT are rarely found in the literature, and the ones that are reported sometimes suffer from weak potency and/or lack of selectivity. In addition, no structure-activity relationship can be envisaged, since the number of crystal structures of human DNMT and non covalent inhibitors is very scarce.

Thus, there still exists a need to develop effective non covalent DNMT inhibitors which can be used in the prevention or treatment of diseases associated with aberrant DNA methylation such as cancer, hematological malignancy, proliferative diseases, genetic diseases, neurological disorders and immunological disorders.

**OBJECT OF THE INVENTION**

A first aspect of the invention refers to compounds of general formula (I),
wherein:

- $X$ is a $-(CH_2)_n$ group, or a H group which is bonded to the N atom through the -CH; 
- $Z$ is a C=Y group; 
- $Y$ is a O atom or a N-OH group; 
- $n$ is selected from 1, 2, 3, 4, 5 and 6; 
- $m$ is 0 or 1; 

- $R'-R^9$ represent, independently of each other, hydrogen, halogen, hydroxyl, alkoxy or -OC(0)-alkyl,

with the proviso that:

- when $X$ is a $-(CH_2)_n$ group, $m=1$ and the dashed line does not represent a bond; and 
- when $X$ is a H group, $m=0$ and the dashed line represents a carbon-carbon single bond, forming together with the benzyl group an indole ring; 

or a solvate or a salt or prodrug thereof for its use as a medicament.

Another aspect of the invention refers to a compound of formula (I) as defined above for its use in the treatment of cancer, hematological malignancy, proliferative diseases, genetic diseases, neurological disorders and immunological disorders.

Another aspect of the present invention relates to the use of a compound of general formula (I) as defined above, or a salt, solvate or prodrug thereof, in the preparation of a medicament for the treatment of cancer, hematological malignancy and proliferative diseases, proliferative diseases, genetic diseases, neurological disorders and immunological disorders.

According to another aspect, the present invention is directed to a method of treating cancer, hematological malignancy proliferative diseases, genetic diseases, neurological
disorders and immunological disorders, which comprises the administration to a patient
needing such treatment, of a therapeutically effective amount of at least one compound
of general formula (I) as defined above or a salt, solvate or prodrug thereof.
Another aspect of the invention refers to a compound of formula (I) as defined above or
a solvate or a salt or prodrug thereof;

the following compounds being excluded when X is a —\( \text{c=c—} \) group:
\[ \begin{align*}
R^1 & =R^9=H, \, Y=0 \text{ and } n=1; \\
R^2 & =R^4=R^8=H, \, R^6=OMe, \, Y=0 \text{ and } n=1; \\
R^2 & =R^4=R^5=R^6=R^8=H, \, R^7=Br, \, Y=0 \text{ and } n=1; \\
R^2 & =R^4=R^5=R^6=R^8=H, \, R^1=R^3=OMe, \, R^7=C1, \, Y=0 \text{ and } n=1; \\
R^2 & =R^4=R^5=R^6=R^8=H, \, R^1=R^3=OMe, \, R^7=OH, \, Y=0 \text{ and } n=1;
\end{align*} \]
and the following compounds being excluded when X is a -(CH\(_2\))\(_n\) group:
\[ \begin{align*}
R^1 & =R^9=H, \, Y=N-OH \text{ and } n=1; \\
R^1 & =R^9=H, \, Y=O \text{ and } n=1; \\
R^2 & =OMe; \, R^1, \, R^3=R^9=H, \, Y=N-OH \text{ and } n=1; \\
R^2 & =OMe; \, R^1, \, R^3-R^6, \, R^8-R^9=H, \, Y=N-OH \text{ and } n=1; \\
R^2 & =OMe; \, R^7=C1; \, R^1, \, R^3-R^6, \, R^8-R^9=H, \, Y=N-OH \text{ and } n=1; \\
R^2 & =OMe; \, R^1-R^6, \, R^8-R^9=H, \, Y=0 \text{ and } n=1; \\
R^7 & =C1; \, R^1-R^6, \, R^8-R^9=H, \, Y=0 \text{ and } n=1; \\
R^1 & =R^3=OMe, \, R^2=R^4-R^9=H, \, Y=0 \text{ and } n=1 \\
R^1 & =R^3=OMe, \, R^7=Br, \, R^2=R^4=R^5=R^6=R^8=R^9=H, \, Y=0 \text{ and } n=1; \\
R^2 & =OMe; \, R^1, \, R^3-R^9=H, \, Y=0 \text{ and } n=1; \\
R^4 & =OH; \, R^1-R^3, \, R^5-R^9=H, \, Y=0 \text{ and } n=1; \\
R^2 & =R^7=OH, \, R^1, \, R^3-R^6, \, R^8-R^9=H, \, Y=0 \text{ and } n=1.
\end{align*} \]
This compound can also be defined as a compound of formula (I):

\[ R^2 = \text{Br} ; R^1, R^3 - R^9 = \text{H} , Y=0 \text{ and } n=2 ; \]
\[ R^2 = \text{Br} ; R^2 = \text{Cl} , R^1, R^3 - R^6, R^8 - R^9 = \text{H} , Y=0 \text{ and } n=2 ; \]
\[ R^2 = \text{Br} ; R^2 = \text{OMe} , R^1, R^3 - R^6, R^8 - R^9 = \text{H} , Y=0 \text{ and } n=2 ; \]
\[ R^2 = R^7 = \text{Br} , R^1, R^3 - R^6, R^8 - R^9 = \text{H} , Y=0 \text{ and } n=2 . \]

wherein:

- \( c=c \) when \( X \) is a \(-(\text{CH}_2)_n\)- group, or a \( \text{H} \) group which is bonded to the \text{N} \ atom through the \(-\text{CH};\)

- \( Z \) is a \( \text{C}=\text{Y} \) group;

- \( Y \) is a \( \text{O} \) atom or a \( \text{N-OH} \) group;

- \( n \) is selected from 1, 2, 3, 4, 5 and 6;

- \( m \) is 0 or 1;

- \( R^1 - R^9 \) represent, independently of each other, hydrogen, halogen, hydroxyl, alkoxy or \(-\text{OC}(0)\)-alkyl,

with the proviso that:

- when \( X \) is a \(-(\text{CH}_2)_n\)- group, \( m=1 \) and the dashed line does not represent a bond; and

- when \( X \) is a \( \text{H} \) group, \( m=0 \) and the dashed line represents a carbon-carbon single bond, forming together with the benzyl group an indole ring;

and wherein:

- when \( X \) is a \( \text{H} \) group, \( Y=0 \) and \( n=1 \), then:
at least one of R'-R⁹ is not H;
at least one of R₁ and R³ is not OMe when R², R⁴-R⁹ are H; and
R⁷ is not Br, Cl or OH, when R², R⁴, R⁵, R⁶, R⁸-R⁹ are H and R₁ and R³ are OMe;

- when X is a -(CH₂)ₙ group and n=1 ; then:
at least one of R¹-R⁹ is not H;
- when X is a -(CH₂)ₙ group, Y=N-OH and n=1 ; then
  R² is not OMe when R¹, R³-R⁹ are H; and
  R⁷ is not OMe or Cl, when R¹, R³-R⁶, R⁸-R⁹ is H and R² is OMe;
- when X is a -(CH₂)ₙ group, Y=0 and n=1 ; then:
  R⁷ is not OMe or Cl, when R¹-R⁶, R⁸-R⁹ are H;
  at least one of R¹ and R³ is not OMe, when R², R⁴-R⁹ are H;
  R⁷ is not Br, when R², R⁴-R⁶, R⁸-R⁹ are H and R¹ and R³ are OMe;
  R² is not OMe, when R¹, R³-R⁹ are H;
R⁴ is not OH, when of R¹-R³, R⁵-R⁹ are H; and
  at least one of R² and R⁷ is not OH, when R¹, R³-R⁶, R⁸-R⁹ are H;
- when X is a -(CH₂)ₙ group, Y=0 and n=2; then:
at least one of R¹-R⁹ is not H;
  R² is not OMe, Cl or Br, when R¹, R³-R⁹ are H;
  R⁷ is not Cl, Br or OMe, when R¹, R³-R⁶, R⁸-R⁹ are H, and R² is OMe;
  R⁷ is not Cl, Br or OMe, when R¹, R³-R⁶, R⁸-R⁹ are H and R² is Cl; and
  R⁷ is not Cl, Br or OMe, when R¹, R³-R⁶, R⁸-R⁹ are H and R² is Br;
or a solvate or a salt or prodrug thereof

Likewise, another aspect of the invention refers to the process for the preparation of compounds of general formula (I), or a solvate or a salt or prodrug thereof as those defined above.

A further object of the invention is a pharmaceutical composition comprising at least one compound of general formula (I) as those defined above, or a salt, solvate or prodrug thereof, and at least one pharmaceutically acceptable excipient.

**DETAILED DESCRIPTION OF THE INVENTION**

First, the present invention provides compounds of general formula (I),
wherein:

- $c=c$ is a $-(\text{CH}_2)_n$ group, or a H group which is bonded to the N atom through the -CH;
- $Z$ is a C=Y group;
- $Y$ is a O atom or a N-OH group;
- $n=1-6$
- $m=0$ or 1;
- $R'-R^9$ represent, independently of each other, hydrogen, halogen, hydroxyl, alkoxy or -OC(0)-alkyl,

with the proviso that:

- when $X$ is a $-(\text{CH}_2)_n$ group, $m=1$ and the dashed line does not represent a bond; and
- when $X$ is a H group, $m=0$ and the dashed line represents a carbon-carbon single bond, forming together with the benzyl group an indole ring;

or a solvate or a salt or prodrug thereof, for its use as a medicament.

The term "halogen" refers to -F, -Cl, -Br or -I.

The term "alkyl" refers to a linear or branched hydrocarbon chain radical consisting of carbon and hydrogen atoms, containing no unsaturation, having 1 to 6 carbon atoms, which is attached to the rest of the molecule by a single bond. Exemplary alkyl groups can be methyl, ethyl, n-propyl, or i-propyl.

The term "alkoxy" refers to a radical of the formula -O-alkyl, wherein "alkyl" is as defined above. In an embodiment of the invention, alkoxy refers to a radical of formula -O-C$_1$C$_3$ alkyl. Exemplary alkoxy radicals are methoxyl, ethoxyl, n-propoxyl or i-propoxyl.
According to a particular embodiment, at least one of $R^1$, $R^2$, $R^3$ and $R^4$ is not hydrogen.

In another particular embodiment, at least one of $R^5$, $R^6$, $R^7$, $R^8$ or $R^9$ is not hydrogen.

In another particular embodiment, at least one of $R^1$, $R^2$, $R^3$ and $R^4$ is selected from halogen, preferably fluor, hydroxyl and alkoxyl.

According to a further embodiment, at least one of $R^5$, $R^6$, $R^7$, $R^8$ and $R^9$ is selected from halogen, preferably fluor, hydroxyl, alcoxy and $-OC(0)$-alkyl, more preferably at least one of $R^5$, $R^6$, $R^7$, $R^8$ and $R^9$ is selected from halogen, preferably fluor, hydroxyl and $-OC(0)$-alkyl.

According to a particular embodiment, at least one of $R^1$, $R^2$, $R^3$ and $R^4$ is an alkoxyl group, and at least one of $R^5$, $R^6$, $R^7$, $R^8$ and $R^9$ is a hydroxyl group. According to a particular embodiment, $R^3$ is an alkoxyl group, and at least one of $R^5$, $R^6$, $R^7$, $R^8$ and $R^9$ is a hydroxyl group. According to a particular embodiment, $R^1$ and $R^3$ are alkoxyl groups, and at least one of $R^5$, $R^6$, $R^7$, $R^8$ and $R^9$ is a hydroxyl group.

According to a particular embodiment, at least one of $R^1$, $R^2$, $R^3$ and $R^4$ is an alkoxyl group, and at least one of $R^5$, $R^6$, $R^7$, $R^8$ and $R^9$ is $-OC(0)$-alkyl. According to a particular embodiment, $R^3$ is an alkoxyl group, and at least one of $R^5$, $R^6$, $R^7$, $R^8$ and $R^9$ is $-OC(0)$-alkyl. According to a particular embodiment, $R^1$ and $R^3$ are alkoxyl groups, and at least one of $R^5$, $R^6$, $R^7$, $R^8$ and $R^9$ is $-OC(0)$-alkyl.

According to another particular embodiment, each alkoxyl group is independently $-O-C_{1-3}$ alkyl, preferably methoxyl.

In a preferred embodiment, the compounds of general formula (I) used in the present invention are selected from:

1. 1-(4-Hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-6-methoxy-1H-indol-1-yl] ethanone, with the following structural formula:

![Structural formula of compound 1](image1)

2. 1-(3-Hydroxyphenyl)-2-[3-(3-hydroxyphenyl)-6-methoxy-1H-indol-1-yl] ethanone, with the following structural formula:

![Structural formula of compound 2](image2)
[3] 1-(2-Hydroxyphenyl)-2-[3-(2-hydroxyphenyl)-6-methoxy-1H-indol-1-yl]ethanone, with the following structural formula:

![Structural formula 1](image1)

[4] 1-(3,4-Dihydroxyphenyl)-2-[3-(3,4-dihydroxyphenyl)-6-methoxy-1H-indol-1-yl]ethanone, with the following structural formula:

![Structural formula 2](image2)

[5] 2-[6-Methoxy-3-(2,3,4-trihydroxyphenyl)-1H-indol-1-yl]-1-(2,3,4-trihydroxyphenyl)ethanone, with the following structural formula:

![Structural formula 3](image3)

[6] 1-(4-Hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-4,6-dimethoxy-1H-indol-1-yl]ethanone, with the following structural formula:

![Structural formula 4](image4)
[7] 1-(2-Hydroxyphenyl)-2-[3-(2-hydroxyphenyl)-4,6-dimethoxy-1\(H\)-indol-1-yl]ethanone, with the following structural formula:

![Structural formula of 1-(2-Hydroxyphenyl)-2-[3-(2-hydroxyphenyl)-4,6-dimethoxy-1\(H\)-indol-1-yl]ethanone](image1)

[8] 1-(3,4-Dihydroxyphenyl)-2-[3-(3,4-dihydroxyphenyl)-4,6-dimethoxy-1\(H\)-indol-1-yl]ethanone, with the following structural formula:

![Structural formula of 1-(3,4-Dihydroxyphenyl)-2-[3-(3,4-dihydroxyphenyl)-4,6-dimethoxy-1\(H\)-indol-1-yl]ethanone](image2)

[9] 1-(2,4-Dihydroxyphenyl)-2-[3-(2,4-dihydroxyphenyl)-4,6-dimethoxy-1\(H\)-indol-1-yl]ethanone, with the following structural formula:

![Structural formula of 1-(2,4-Dihydroxyphenyl)-2-[3-(2,4-dihydroxyphenyl)-4,6-dimethoxy-1\(H\)-indol-1-yl]ethanone](image3)

[10] 1-(3,5-Dihydroxyphenyl)-2-(3-(3,5-dihydroxyphenyl)-4,6-dimethoxy-1\(H\)-indol-1-yl)ethanone, with the following structural formula:

![Structural formula of 1-(3,5-Dihydroxyphenyl)-2-(3-(3,5-dihydroxyphenyl)-4,6-dimethoxy-1\(H\)-indol-1-yl)ethanone](image4)
2-[4,6-Dimethoxy-3-(2,3,4-trihydroxyphenyl)-1H-indol-1-yl]-1-(2,3,4-trihydroxyphenyl)ethanone, with the following structural formula:

[12] 1-(4-Fluorophenyl)-2-[3-(4-fluorophenyl)-4,6-dimethoxy-1H-indol-1-yl]ethanone, with the following structural formula:

[13] 1-(4-Hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-4,7-dimethoxy-1H-indol-1-yl]ethanone, with the following structural formula:

[14] 1-(4-Hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-5,6-dimethoxy-1H-indol-1-yl]ethanone, with the following structural formula:
[15] 2-[5-Hydroxy-3-(4-hydroxyphenyl)-6-methoxy-1H-indol-1-yl]-1-(4-hydroxyphenyl)ethanone, with the following structural formula:

[16] 2-[4,6-Difluoro-3-(4-hydroxyphenyl)-1H-indol-1-yl]-1-(4-hydroxyphenyl)ethanone, with the following structural formula:

[17] 2-[6-Hydroxy-3-(4-hydroxyphenyl)-1H-indol-1-yl]-1-(4-hydroxyphenyl)ethanone, with the following structural formula:
[18] 2-[5-Hydroxy-3-(4-hydroxyphenyl)-1H-indol-1-yl]-1-(4-hydroxyphenyl)ethanone, with the following structural formula:

![Structural formula for 2-[5-Hydroxy-3-(4-hydroxyphenyl)-1H-indol-1-yl]-1-(4-hydroxyphenyl)ethanone]

[19] 2-[5-Fluoro-3-(4-hydroxyphenyl)-1H-indol-1-yl]-1-(4-hydroxyphenyl)ethanone, with the following structural formula:

![Structural formula for 2-[5-Fluoro-3-(4-hydroxyphenyl)-1H-indol-1-yl]-1-(4-hydroxyphenyl)ethanone]

[20] 1-(4-Hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-1H-indol-1-yl]ethanone, with the following structural formula:

![Structural formula for 1-(4-Hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-1H-indol-1-yl]ethanone]

[21] (E)-1-(4-Hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-4,6-dimethoxy-1H-indol-1-yl]ethanone oxime, with the following structural formula:

![Structural formula for (E)-1-(4-Hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-4,6-dimethoxy-1H-indol-1-yl]ethanone oxime]
[22] (Z)- l-(4-Hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-4,6-dimethoxy-1H-indol-1-yl]ethanone oxime, with the following structural formula:

[23] 2,2'-(3-Methoxyphenyl)azanediyl]-bis[l-(2,3,4-trihydroxyphenyl) ethanone], with the following structural formula:

[24] 2,2'-(3,5-dimethoxyphenyl)azanediyl]-bis[l-(2,3,4-trihydroxyphenyl) ethanone], with the following structural formula:

[25] Potassium salt of l-(4-hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-6-methoxy-1H-indol-1-yl] ethanone

[26] Potassium salt of l-(4-hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-4,6-dimethoxy-1H-indol-1-yl] ethanone
[27] Calcium salt of 1-(4-hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-4,6-dimethoxy-1H-indol-1-yl] ethanone

[28] 4-{1-[2-(4-Acetoxyphenyl)-2-oxoethyl]-6-methoxy-1H-indol-3-yl}phenyl acetate, with the following structural formula:

[29] 4-{1-[2-(4-Acetoxyphenyl)-2-oxoethyl]-4,6-dimethoxy-1H-indol-3-yl}phenyl acetate, with the following structural formula:

[30] 4-{1-[2-(3,4-Diacetoxyphenyl)-2-oxoethyl]-4,6-dimethoxy-1H-indol-3-yl} - 1,2-phenylene diacetate, with the following structural formula:

[31] 4-{1-[2-(3,4-Diacetoxyphenyl)-2-oxoethyl]-6-methoxy-1H-indol-3-yl} - 1,2-phenylene diacetate, with the following structural formula:
or a solvate or a salt or prodrug thereof.

In a more preferred embodiment, the compound of formula (I) used in the present invention is 1-(4-Hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-4,6-dimethoxy-1H-indol-1-yljethanone [compound 6].

The compounds of formula (I) defined above may be in the form of solvates or salts or prodrugs, preferably as a pharmaceutically acceptable species.

The term "pharmaceutically acceptable species" refers to compositions and molecular entities that are physiologically tolerable and do not typically produce an allergic reaction or a similar unfavorable reaction as gastric disorders, dizziness and suchlike, when administered to a human or animal. Preferably, the term "pharmaceutically acceptable" means it is approved by a regulatory agency of a state or federal government or is included in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals, and more particularly in humans.

The term "prodrug" is used in its broadest sense and encompasses those derivatives that are converted in vivo into the compounds of the invention. Experts in the art would readily produce such derivatives, and include, depending on the functional groups present in the molecule and without limitation, the following derivatives of the present compounds: disulfides, thioesters, esters, amino acid esters, phosphate esters, esters of metallic salt sulfonates, carbamates and amides.

The term "solvate" means any form of the active compound of the invention which has another molecule (for example a polar solvent such as water or ethanol, a cyclodextrin or a dendrimer) attached to it through noncovalent bonds. Methods of solvation are known within the art.

Compounds of formula (I) may also be in the form of salts. Non-limiting examples are sulphates; hydrohalide salts; phosphates; lower alkane sulphonates; arylsulphonates; salts of C1-C20 aliphatic mono-, di- or tribasic acids which may contain one or more double bonds, an aryl nucleus or other functional groups such as hydroxy, amino, or keto; salts of aromatic acids in which the aromatic nuclei may or may not be substituted with groups such as hydroxyl, lower alkoxy, amino, mono- or di- lower alkylamino sulphonamido. Also included within the scope of the invention are quaternary salts of the tertiary nitrogen atom with lower alkyl halides or sulphates, and oxygenated derivatives of the tertiary nitrogen atom, such as the N-oxides. In preparing dosage formulations, those skilled in the art will select the pharmaceutically acceptable salts.

Solvates, salts and prodrugs can be prepared by methods known in the state of the art. Note that the non-pharmaceutically acceptable solvates and prodrugs also fall within the
scope of the invention because they can be useful in preparing pharmaceutically acceptable salts, solvates or prodrugs.

The compounds of formula (I) defined above also seek to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by a carbon enriched in $^{11}$C, $^{13}$C or $^{14}$C or a $^{15}$N enriched nitrogen are within the scope of this invention.

Another aspect of the invention refers to the compounds of formula (I) as defined above for its use in a variety of therapeutic applications. According to a particular embodiment, the compounds of general formula (I) are useful for the treatment of various types of cancer, hematological malignancy, proliferative diseases, genetic diseases, neurological disorders and immunological disorders, by changing the methylation pattern of DNA regions involved in the mentioned diseases.

Methylation changes in gene promoter regions can modify the gene expression of many classic tumor-suppressor genes, androgen and estrogen receptor genes, cell adhesion genes, cell-cycle control genes or apoptotic genes. These modifications may restrict tumor growth and metastasis or may activate mechanisms of apoptosis induction or other processes that stop the development of primary or metastatic tumors.

According to a particular embodiment, the cancer is selected from breast cancer, chronic myelogenous (or myeloid) leukemia (CML), colorectal cancer, fibrosarcoma, gastric cancer, glioblastoma, kidney cancer, liver cancer, lung cancer, melanoma, nasopharyngeal cancer, oral cancer, orthotopic multiple myeloma, osteosarcoma, ovarian cancer, pancreatic cancer, and prostate cancer.

According to an embodiment of the invention, the neurological disorder is schizophrenia, fragile X syndrome or Alzheimer.

According to an embodiment of the invention, the genetic disease is ATR-X, Rett, Fragile X, Prader-Willi, Angelman, CHARGE, CSB, SIOD (Schimke Immuno-Osseous Dysplasia), ICF, Rubinstein-Taybi syndrome or FSHD (Facioscapulo-humeral Dystrophy).

According to an embodiment of the invention, the immunological disorder is lupus erythematosus (SLE), rheumatoid arthritis or progressive systemic sclerosis (PSS).

Another aspect of the present invention refers to a compound of formula (I):
wherein:

- \( c=c \) is a -\((CH_2)_n\) group, or a H group which is bonded to the N atom through the \(-CH_2\);
- \( Z \) is a C=Y group;
- \( Y \) is an O atom or a N-OH group;
- \( n \) is selected from 1, 2, 3, 4, 5 and 6;
- \( m \) is 0 or 1;
- \( R'-R^9 \) represent, independently of each other, hydrogen, halogen, hydroxyl, alkoxy or \(-OC(0)-alkyl\),

with the proviso that:

- when \( X \) is a -\((CH_2)_n\) group, \( m=1 \) and the dashed line does not represent a bond; and

- when \( X \) is a \( H \) group, \( m=0 \) and the dashed line represents a carbon-carbon single bond, forming together with the benzyl group an indole ring;

or a solvate or a salt or prodrug thereof,

the following compounds being excluded when \( X \) is a \( H \) group:

- \( R'-R^H, Y=0 \) and \( n=1 \);
- \( R^2=R^4=R^5=R^8=R^9=H, R^R^OMe, Y=0 \) and \( n=1 \);
- \( R^2=R^4=R^5=R^6=R^8=R^9=H, R^R^OMe, Y=0 \) and \( n=1 \);
- \( R^2=R^4=R^5=R^6=R^8=R^9=H, R^R^OMe, Y=0 \) and \( n=1 \);

and the following compounds being excluded when \( X \) is a -\((CH_2)_n\) group:

- \( R'-R^H, Y=N-OH \) and \( n=1 \);
- \( R^1=R^9=H, Y=0 \) and \( n=1 \);
- \( R^2=OMe; R^1, R^3-R^9=H, Y=N-OH \) and \( n=1 \);
- \( R^2=OMe; R^7=C1; R^1, R^3-R^6, R^8-R^9=H, Y=N-OH \) and \( n=1 \);
- \( R^7=OMe; R^1-R^6, R^3-R^9=H, Y=0 \) and \( n=1 \);
- \( R^7=C1; R^1-R^6, R^8-R^9=H, Y=0 \) and \( n=1 \);
- \( R^1=R^3=OMe, R^2=R^4-R^9=H, Y=0 \) and \( n=1 \);
R^R^OMe, R^2=Br, R^3=R^4=R^5=R^6=R^8=H, Y=0 and n=l;
R^2=OMe; R^3=R^8=H, Y=0 and n=l;
R^4=OH; R^1-R^3, R^5-R^9=H, Y=0 and n=l;
R^2=R^7=OH, R^1, R^3-R^6, R^8-R^9=H, Y=0 and n=l.

5 R^1-R^9=H, Y=0 and n=2;
R^2=OMe; R^1, R^3-R^9=H, Y=0 and n=2;
R^2=OMe, R^7=C1, R^1, R^3-R^6, R^8-R^9=H, Y=0 and n=2;
R^2=OMe, R^7=Br, R^1, R^3-R^6, R^8-R^9=H, Y=0 and n=2;
R^2=R^7=OMe, R^1, R^3-R^6, R^8-R^9=H, Y=0 and n=2;
R^2=R^2=C1; R^1, R^3-R^9=H, Y=0 and n=2;
R^2=R^7=C1, R^1, R^3-R^6, R^8-R^9=H, Y=0 and n=2;
R^2=C1, R^7=OMe, R^1, R^3-R^6, R^8-R^9=H, Y=0 and n=2;
R^2=C1, R^7=Br, R^1, R^3-R^6, R^8-R^9=H, Y=0 and n=2;
R^2=Br; R^1, R^3-R^9=H, Y=0 and n=2;
10 R^2=Br, R^7=C1, R^1, R^3-R^6, R^8-R^9=H, Y=0 and n=2;
R^2=Br, R^7=OMe, R^1, R^3-R^6, R^8-R^9=H, Y=0 and n=2;
R^2=Br, R^7=OMe, R^1, R^3-R^6, R^8-R^9=H, Y=0 and n=2;
R^2=R^7=Br, R^1, R^3-R^6, R^8-R^9=H, Y=0 and n=2.

This compound can also be defined as a compound of formula (I):

![](image)

wherein:

- X is a -(CH\_2)_n- group, or a group which is bonded to the N atom through the -CH;
- Z is a C=Y group;
- Y is a O atom or a N-OH group;
n is selected from 1, 2, 3, 4, 5 and 6;
m is 0 or 1;
R'-R^9 represent, independently of each other, hydrogen, halogen, hydroxyl, alkoxyl or \( \text{-OC(0)-alkyl} \),

with the proviso that:

when X is a -(CH₂)ₙ- group, m=1 and the dashed line does not represent a bond; and

\[ \text{H} \quad | \quad \text{c=c-c} \]

when X is a \( \text{H} \)- group, m=0 and the dashed line represents a carbon-carbon single bond, forming together with the benzyl group an indole ring;

and wherein:

\[ \text{H} \quad | \quad \text{c=c-c} \]

- when X is a \( \text{H} \)- group, Y=0 and n=1, then:
  
  at least one of R'-R^9 is not H;
  
  at least one of R^1 and R^3 is not OMe when R^2, R^4-R^9 are H; and
  
  R^7 is not Br, Cl or OH, when R^2, R^4, R^5, R^6, R^8-R^9 are H and R^1 and R^3 are OMe;

- when X is a -(CH₂)ₙ- group and n=1; then:
  
  at least one of R^1-R^9 is not H;

- when X is a -(CH₂)ₙ- group, Y=N-OH and n=1; then
  
  R^2 is not OMe when R^1, R^3-R^9 are H; and
  
  R^7 is not OMe or Cl, when R^1, R^3-R^6, R^8-R^9 is H and R^2 is OMe;

- when X is a -(CH₂)ₙ- group, Y=0 and n=1; then:
  
  R^7 is not OMe or Cl, when R^1-R^6, R^8-R^9 are H;
  
  at least one of R^1 and R^3 is not OMe, when R^2, R^4-R^9 are H;
  
  R^7 is not Br, when R^2, R^4-R^6, R^8-R^9 are H and R^1 and R^3 are OMe;

- R^2 is not OMe, when R^1, R^3-R^9 are H;

- R^4 is not OH, when of R^1-R^3, R^5-R^9 are H; and
  
  at least one of R^2 and R^7 is not OH, when R^1, R^3-R^6, R^8-R^9 are H;

- when X is a -(CH₂)ₙ- group, Y=0 and n=2; then:
  
  at least one of R^1-R^9 is not H;

- R^2 is not OMe, Cl or Br, when R^1, R^3-R^9 are H;

- R^7 is not Cl, Br or OMe, when R^1, R^3-R^6, R^8-R^9 are H, and R^2 is OMe;

- R^7 is not Cl, Br or OMe, when R^1, R^3-R^6, R^8-R^9 are H and R^2 is Cl; and
R\(^7\) is not Cl, Br or OMe, when R\(^1\), R\(^3\)-R\(^6\), R\(^8\)-R\(^9\) are H and R\(^2\) is Br; or a solvate or a salt or prodrug thereof.

According to a particular embodiment, at least one of R\(^1\), R\(^2\), R\(^3\) and R\(^4\) is not hydrogen. In another particular embodiment, at least one of R\(^5\), R\(^6\), R\(^7\), R\(^8\) and R\(^9\) is not hydrogen.

According to a further embodiment, at least one of R\(^1\), R\(^2\), R\(^3\) and R\(^4\) is selected from halogen, preferably fluor, hydroxyl and alkoxyl.

According to a particular embodiment, at least one of R\(^1\), R\(^2\), R\(^3\) and R\(^4\) is an alkoxyl group, and at least one of R\(^5\), R\(^6\), R\(^7\), R\(^8\) and R\(^9\) is a hydroxyl group. According to a particular embodiment, R\(^3\) is an alkoxyl group, and at least one of R\(^5\), R\(^6\), R\(^7\), R\(^8\) and R\(^9\) is a hydroxyl group. According to a particular embodiment, R\(^1\) and R\(^3\) are alkoxyl groups, and at least one of R\(^5\), R\(^6\), R\(^7\), R\(^8\) and R\(^9\) is a hydroxyl group.

According to a particular embodiment, at least one of R\(^1\), R\(^2\), R\(^3\) and R\(^4\) is an alkoxyl group, and at least one of R\(^5\), R\(^6\), R\(^7\), R\(^8\) and R\(^9\) is -OC(0)-alkyl. According to a particular embodiment, R\(^3\) is an alkoxyl group, and at least one of R\(^5\), R\(^6\), R\(^7\), R\(^8\) and R\(^9\) is -OC(0)-alkyl. According to a particular embodiment, R\(^1\) and R\(^3\) are alkoxyl groups, and at least one of R\(^5\), R\(^6\), R\(^7\), R\(^8\) and R\(^9\) is -OC(0)-alkyl.

According to another particular embodiment, each alkoxyl group is independently -O-C\(^1\)-C\(^3\) alkyl, preferably methoxy.

In a preferred embodiment, the compounds of general formula (I) of the invention are selected from:

\[
\begin{align*}
1\text{-}(4\text{-Hydroxyphenyl})\text{-}2\text{-}[3\text{-}(4\text{-hydroxyphenyl})\text{-}6\text{-methoxy}\text{-}1H\text{-indol\text{-}1-yl}]\text{ethanone,} \\
1\text{-}(3\text{-Hydroxyphenyl})\text{-}2\text{-}[3\text{-}(3\text{-hydroxyphenyl})\text{-}6\text{-methoxy}\text{-}1H\text{-indol\text{-}1-yl}]\text{ethanone,} \\
1\text{-}(2\text{-Hydroxyphenyl})\text{-}2\text{-}[3\text{-}(2\text{-hydroxyphenyl})\text{-}6\text{-methoxy}\text{-}1H\text{-indol\text{-}1-yl}]\text{ethanone,} \\
1\text{-}(3\text{-4-Dihydroxyphenyl})\text{-}2\text{-}[3\text{-}(3\text{-4-dihydroxyphenyl})\text{-}6\text{-methoxy}\text{-}1H\text{-indol\text{-}1-yl}]\text{ethanone,} \\
2\text{-}[6\text{-Methoxy\text{-}3\text{-}(2\text{-3\text{-4-trihydroxyphenyl})\text{-}1H\text{-indol\text{-}1-yl}]\text{-}1\text{-}(2\text{-3\text{-4-trihydroxyphenyl})\text{ethanone,} } \\
1\text{-}(2\text{-Hydroxyphenyl})\text{-}2\text{-}[3\text{-}(2\text{-hydroxyphenyl})\text{-}4\text{-6-dimethoxy\text{-}1H\text{-indol\text{-}1-yl}]\text{ethanone,} \\
1\text{-}(3\text{-4-Dihydroxyphenyl})\text{-}2\text{-}[3\text{-}(3\text{-4-dihydroxyphenyl})\text{-}4\text{-6-dimethoxy\text{-}1H\text{-indol\text{-}1-yl}]\text{ethanone,} \\
1\text{-}(2\text{-4-Dihydroxyphenyl})\text{-}2\text{-}[3\text{-}(2\text{-4-dihydroxyphenyl})\text{-}4\text{-6-dimethoxy\text{-}1H\text{-indol\text{-}1-yl}]\text{ethanone,} \\
1\text{-}(3\text{-5-dihydroxyphenyl})\text{-}2\text{-}[3\text{-}(3\text{-5-dihydroxyphenyl})\text{-}4\text{-6-dimethoxy\text{-}1H\text{-indol\text{-}1-yl}]\text{ethanone,} \\
\end{align*}
\]
2-[4,6-Dimethoxy-3-(2,3,4-trihydroxyphenyl)-1H-indol-1-yl]-1-(2,3,4-trihydroxyphenyl)ethanone,
1-(4-Fluorophenyl)-2-[3-(4-fluorophenyl)-4,6-dimethoxy-1H-indol-1-yl] ethanone,
1-(4-Hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-4,7-dimethoxy-1H-indol-1-yl]ethanone,
1-(4-Hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-5,6-dimethoxy-1H-indol-1-yl]ethanone,
2-[5-Hydroxy-3-(4-hydroxyphenyl)-6-methoxy-1H-indol-1-yl]-1-(4-hydroxyphenyl)ethanone,
1-(4-Hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-1H-indol-1-yl]ethanone,
(E)-1-(4-Hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-4,6-dimethoxy-1H-indol-1-yl]ethanone oxime,
(X)-1-(4-Hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-4,6-dimethoxy-1H-indol-1-yl]ethanone oxime,
2,2'-(3-Methoxyphenyl)azanediyl]-bis[l-(2,3,4-trihydroxyphenyl) ethanone],
2,2'-(3,5-dimethoxyphenyl)azanediyl]-bis[l-(2,3,4-trihydroxyphenyl) ethanone],
Potassium salt of l-(4-hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-6-methoxy-1H-indol-1-yl] ethanone
Potassium salt of l-(4-hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-4,6-dimethoxy-1H-indol-1-yl] ethanone
Calcium salt of l-(4-hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-4,6-dimethoxy-1H-indol-1-yl] ethanone
4- {1-[2-(4-Acetoxyphenyl)-2-oxoethyl]-6-methoxy-1H-indol-3-yl} phenyl acetate,
4- {1-[2-(4-Acetoxyphenyl)-2-oxoethyl]-4,6-dimethoxy-1H-indol-3-yl} phenyl acetate,
4- {1-[2-(3,4-Diacetoxyphenyl)-2-oxoethyl]-4,6-dimethoxy-1H-indol-3-yl} - 1,2-phenylene diacetate,
4- {1-[2-(3,4-Diacetoxyphenyl)-2-oxoethyl]-6-methoxy-1H-indol-3-yl} - 1,2-phenylene diacetate,
or a solvate or a salt or prodrug thereof.

**Synthesis of compounds of formula (I)**

2-[4,6-Dimethoxy-3-(2,3,4-trihydroxyphenyl)-1H-indol-1-yl]-1-(2,3,4-trihydroxyphenyl)ethanone,
Another aspect of the invention refers to procedures to obtain compounds of general formula (I) of the invention. The following methods A, B, C and D describe the procedures for obtaining compounds of general formula (I), among which include compounds of formula (la), (lb), (lc) and (ld), or solvates or salts or prodrugs thereof.

Compounds of formula (la) correspond to compounds of formula (I), wherein R'-R^9 and n have the meaning given above, X is -CH=C-, Y=0 and m=0.

Compounds of formula (lb) correspond to compounds of formula (I), wherein R'^1-R^9 and n have the meaning given above, X is -(CH_2)_n, Y=0 and m=1.

Compounds of formula (lc) correspond to compounds of formula (I), wherein R'^1-R^9 and n have the meaning given above, X is -CH=C-, Y=-N-OH and m=0.

Compounds of formula (ld) correspond to compounds of formula (I), wherein R'^1-R^9 and n have the meaning given above, X is -(CH_2)_n, Y=-N-OH and m=1.

Method A

Method A represents a procedure for the preparation of compounds of general formula (la):

\[
\text{(la)}
\]

wherein R'^1-R^9 and n have the meaning given above, which comprises reacting:

a) a compound of general formula (II),

\[
\text{(II)}
\]

wherein R', R^2, R^3 and R^4 have the meaning given above;

with

b) a compound of general formula (III),
wherein Q is a chlorine, bromine or iodine atom, or a leaving group, such as mesylate or tosylate, and R5, R6, R7, R8, R9 have the meaning given above; in the presence of

c) a base, either organic or inorganic; and
d) an appropriate solvent

leaving the reaction to react for at least 16 hours.

Method B
Method B represents a procedure for the preparation of compounds of general formula (lb):

wherein R1-R9 and n have the meaning given above, which comprises reacting:

a) a compound of general formula (II),

wherein R1, R2, R3 and R4 have the meaning given above;

b) a compound of general formula (III),
wherein Q is a chlorine, bromine or iodine atom, or a leaving group, such as mesylate or tosylate, and R⁵, R⁶, R⁷, R⁸, R⁹ have the meaning given above;

in the presence of

c) a base, either organic or inorganic; and
d) an appropriate solvent.

leaving the reaction to react for three hours at the most.

The reaction defined in Method A and Method B usually takes place at temperatures ranging from 25°C to +170°C until completion of the reaction.

For the aims of the invention, the reaction mixture defined in Method A and Method B made up of the four compounds of phases a) to d) can be made by adding one of the components to the mixture formed by the three other components at a temperature ranging from +25°C to +170°C. After completion of the addition, the resulting mixture is stirred until completion of the reaction.

The base used in Methods A and B can be selected among inorganic or organic bases. The inorganic base may be selected from the group consisting of carbonates of alkaline metals or alkaline earth metals (e.g. sodium, lithium, potassium, calcium, or magnesium carbonate), bicarbonates of alkaline metals (e.g. sodium, lithium or potassium bicarbonate), sulfates of alkaline metals or alkaline earth metals (e.g. sodium, lithium, potassium, calcium, or magnesium sulfate), acetates of alkaline metals or alkaline earth metals (e.g. sodium, lithium, potassium, calcium, or magnesium acetate), hydroxides of alkaline metals or alkaline earth metals (e.g. sodium, lithium, potassium, calcium, or magnesium hydroxide) or phosphates, monohydrogen phosphates or dihydrogen phosphates of alkaline metals or alkaline earth metals (e.g. sodium, lithium, potassium, calcium, or magnesium phosphate, or potassium dihydrogen phosphate). The organic base may be a primary, secondary or tertiary amine, preferably a tertiary amine selected from among the cyclic or acyclic aliphatic amines with C₃-C₁₀ carbon atoms and the alkanoylamic amines with C₉-C₁₅ carbon atoms, more preferably N,N-dimethylaniline, triethylamine, N,N-diisopropyl ethylamine (DIPEA), N-methyl morpholine, N-methylpyrrolidine, 1,8-diazabicyclo[5.4.0]Undec-7-ene (DBU), pyridine

The solvent used in Methods A and B can be a polar protic solvent such an alcohol, for example ethanol or other liquid alcohol at room temperature, a polar nonprotic solvent such a cyclic or acyclic ether, N,N-dimethylformamide or 1,2-dimethoxyethane, or a nonpolar solvent such as a linear or branched aliphatic hydrocarbon of C₅-C₁₀ carbons or an aromatic hydrocarbon such as toluene, xylene or similar.

Method C
Method C represents a procedure for the preparation of compounds of general formula (Ic):

(Ic)

wherein R'-R⁹ have the meaning given in the description of Method A, which comprises:

a) preparing a compound of general formula (Ia) as described in Method A; and

b) reacting the mentioned compound of formula (la) with a mixture of hydroxylamine hydrochloride and phenolphthalein in the presence of an excess of sodium methoxide in methanol.

Method D

Method D represents a procedure for the preparation of compounds of general formula (Id):

(Id)

wherein R'-R⁹ have the meaning given in the description of Method B, which comprises:

a) preparing a compound of general formula (lb) as described in Method B; and
b) reacting the mentioned compound of formula (lb) with a mixture of hydroxylamine hydrochloride and phenolphthalein in the presence of an excess of sodium methoxide in methanol.

For the aims of the invention, and regarding Methods C and D, the ketone of general formula (la) or (lb) is added to a mixture of hydroxylamine hydrochloride and phenolphthalein in the presence of an excess of sodium methoxide in methanol. Upon completion of the reaction, after the corresponding treatment, compounds of formula (lc) and (ld) are obtained.

In a particular embodiment, when any of R⁵-R⁹ is -OC(0)-alkyl, said radical can be obtained from the hydroxyl group. In particular, hydroxyl groups can be protected by known procedures, for example, by treatment with the corresponding anhydride. In an embodiment of the invention the reaction takes place using acetic anhydride and a aromatic organic base, preferably pyridine (see for example T.G. Bonner and P. McNamara J. Chem. Soc. B 1968, 7, 795; H. Chung and N.R. Washburn ACS Appl. Mater. Interfaces 2012, 4, 2840) at a temperature ranging from 0°C to +40°C.

A further embodiment of the invention is a salt of a compound of formula (I) of the invention. According to a particular embodiment, the salt is a phenoxy salt of alkaline metals or alkaline earth metals. To obtain the salts corresponding to compounds of formula (I) wherein at least one of the R⁵-R⁹ is a hydroxyl group, hydroxyl groups can be treated with hydroxides of alkaline metals or alkaline earth metals (e.g. sodium, lithium, potassium, calcium, or magnesium hydroxide) at a temperature ranging from 0°C to +40°C. In an embodiment of the invention the reaction takes place at room temperature using water as solvent.

The initial compounds and starting materials, e.g. the compounds of formula (II) and (III), are either commercially available or can be obtained following procedures described in the literature. For example, see Chen L., Ding Q., Gillespie P., Kim K., Lovey A. J., McComas W. W., Mullin J. G. and Perrota A., (2002) PCT No. WO 2002057261 (e.g. Examples 7-13, pages 46-50; or Examples 14H-140, pages 57-60); King L. C., Ostrum G. K. J. Org. Chem. 1964, 29, 3459-3461; Diwu Z., Beachdel C., Klaubert D.H. Tetrahedron Lett. 1998, 39, 4987-4990; Bakke B. A., McIntosh M. C., Turnbull K.D. J. Org. Chem. 2005, 70(1), 4338-4345).

**Pharmaceutical compositions**

Another aspect of the present invention refers to a pharmaceutical composition which comprises the compounds of formula (I) of the invention, or a pharmaceutically acceptable solvate or salt or prodrug thereof, and at least a pharmaceutically acceptable excipient.

The term "excipient" refers to a vehicle, diluent or adjuvant that is administered with the active ingredient. Such pharmaceutical excipients can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and similars. Water or saline aqueous solutions and aqueous dextrose and glycerol solutions, particularly for injectable solutions, are preferably used as vehicles. Suitable pharmaceutical vehicles are described in "Remington's Pharmaceutical Sciences" by E.W. Martin, 21st Edition,

Examples of pharmaceutical compositions include any solid composition (tablets, pills, capsules, granules, etc.) or liquid composition (solutions, suspensions or emulsions) for oral, topical or parenteral administration.

In a preferred embodiment the pharmaceutical compositions are in oral delivery form. Pharmaceutical forms suitable for oral administration may be tablets and capsules and may contain conventional excipients known in the art such as binders, for example syrup, gum arabic, gelatin, tragacanth or polyvinylpyrrolidone; fillers, for example lactose, sugar, cornstarch, calcium phosphate, sorbitol or glycine; lubricants for the preparation of tablets, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycolate or microcrystalline cellulose; or pharmaceutically acceptable wetting agents such as sodium lauryl sulphate.

Solid oral compositions can be prepared by conventional methods of blending, filling or preparation of tablets. Repeated blending operations can be used to distribute the active ingredient in all the compositions that use large amounts of fillers. Such operations are conventional in the art. The tablets can be prepared, for example, by dry or wet granulation and optionally can be coated by well known methods in normal pharmaceutical practice, in particular using an enteric coating.

Pharmaceutical compositions can also be adapted for parenteral administration, such as sterile solutions, suspensions or lyophilized products in the appropriate unit dosage form. Suitable excipients such as fillers, buffering agents or surfactants can be used.

The mentioned formulations will be prepared using standard methods such as those described or referred to in the Spanish and U.S. Pharmacopoeias and similar reference texts.

In general, the effective amount of a compound of the invention to be administered will depend on the relative efficacy of the compound chosen, the severity of the disorder being treated and the patient's weight. However, the active compounds will normally be administered one or more times a day, for example 1, 2, 3 or 4 times daily, with typical total daily doses in the range from 0.01 up to 1000 mg/kg/day.

The compounds of the present invention can be used with at least another drug to provide a combination therapy. This other drug or drugs may be part of the same pharmaceutical composition, or may be provided as a separate composition and can be administered at the same time or at different times.

The term "treatment" or "treating" in the context of this document means administration of a compound or a formulation according to this invention to prevent, improve or eliminate the disease or one or more symptoms associated with the disease. "Treatment" also encompasses preventing, improving or eliminating the physiological sequelae of the disease.

In order to facilitate the understanding of the preceding ideas, some examples of experimental procedures and embodiments of the present invention are described below. These examples are merely illustrative.
EXAMPLES

General Synthesis Methods

Method A: Synthesis of indoles

A.l) Synthesis of 1,3-disubstituted indoles

A mixture of the aniline 1 (7.0 mmol), the α-haloketone 2 (21.0 mmol) and the corresponding base (17.5 mmol) was refluxed in an appropriate solvent (70 ml) for 16-48 h. Examples of bases, solvents and reaction times employed are detailed in the examples below. The resulting mixture was cooled down and evaporated. The residue was solved in AcOEt (350 ml) and washed with HCl IN (3 x 100 ml). The organic fraction was dried over Na₂S₀₄ and evaporated under reduced pressure. The crude product was purified by column chromatography on silicagel and/or reverse phase.

A.2) Formation of salts

The corresponding indole (1.0 mmol) obtained following procedure A.l was suspended in water (3.5 ml). The hydroxide of the corresponding alkaline or alkaline earth metal (1.0 mmol) was added, and the mixture was stirred for 1 h. The crude reaction solution was evaporated to dryness.

A3) Formation of acetylated derivatives

The corresponding indole (5.0 mmol) obtained following procedure A.l was placed under argon atmosphere and cooled down to 0°C, and pyridine (25 ml) was added
dropwise. When a homogeneous solution was formed, acetic anhydride (2.5 equivalents per hydroxyl group to be protected) was added dropwise while keeping temperature at 0°C. The mixture was stirred for 16 hours at room temperature and then evaporated. The residue was solved in AcOEt (100 ml) and washed with H$_2$O (5 x 15 ml). The organic fraction was dried over Na$_2$SO$_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography on silicagel and/or reverse phase.

**Method B: Synthesis of oxime derivatives**

![Chemical structure](image)

To a solution of hydroxylamine hydrochloride (0.36 g, 5.6 mmol) and phenolphtalein (1 mg) in methanol (1 ml) under inert atmosphere, an aliquot of sodium methoxide in methanol (taken from a solution of 2.70 g, 50 mmol of sodium methoxide in 10 ml of methanol) was added dropwise until a permanent pink color was observed. The corresponding indole (1 mmol) obtained following procedure A1 and sodium methoxide in methanol (7.5 mmol, 0.75 ml of the previously prepared solution) were subsequently added, and the reaction mixture was stirred for 26h. Water (3 ml) was added, and this solution was acidified with glacial acetic acid and extracted with CH$_2$Cl$_2$ (3 x 10 ml). The combined organic fractions were dried over Na$_2$SO$_4$ and evaporated under reduced pressure.

**Method C: Synthesis of 2,2’-(arylimino)bis(l-aryl) ethanones**

![Chemical structure](image)

A mixture of the aniline 1 (3.0 mmol), the α-haloketone 2 (9.0 mmol) and the corresponding base (7.5 mmol) was refluxed in an appropriate solvent (30 ml) for 3 hours. Examples of bases, solvents and reaction times employed are detailed in the examples below. The resulting mixture was cooled down and evaporated. The residue was solved in AcOEt (150 ml) and washed with HCl IN (3 x 45 ml). The organic fraction was dried over Na$_2$SO$_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography on silicagel and/or reverse phase.
Synthesis of Compounds of the invention

Example 1: Preparation of l-(4-hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-6-methoxy-1H-indol-l-yl]ethanone, with the following structural formula:

This compound was prepared following procedure A.1 from 3-methoxy aniline and 2-bromo-l-(4-hydroxyphenyl)ethanone, using N,N-dimethylaniline as base and xylene as solvent at reflux for 24 h. m.p. 198-199°C; IR 3378, 1674, 1605, 1445, 1228, 989, 829, 782 cm⁻¹; 1H-NMR (500 MHz, δ ppm, CDCl₃) 9.29 (s, 1H), 7.99 (d, J = 8.5 Hz, 2H), 7.66 (d, J = 8.7 Hz, 1H), 7.42 (d, J = 8.3 Hz, 2H), 7.32 (s, 1H), 6.96 (s, 1H), 6.93 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.3 Hz, 2H), 6.76 - 6.71 (m, 1H), 5.76 (s, 2H), 3.74 (s, 3H); 13C-NMR (75 MHz, δ ppm, DMSO-d₆) 192.2, 162.5, 155.7, 130.0, 127.5, 126.4, 126.3, 125.2, 124.9, 119.9, 119.7, 115.6, 115.3, 114.4, 109.3, 93.8, 55.3, 51.7. C₂₃H₁₉N₀₄; MS (ESI, m/z): 372.04 [M-H].

Example 2: Preparation of l-(3-hydroxyphenyl)-2-[3-(3-hydroxyphenyl)-6-methoxy-1H-indol-l-yl]ethanone, with the following structural formula:

This compound was prepared following procedure A.1 from 3-methoxy aniline and 2-bromo-l-(3-hydroxyphenyl)ethanone, using N,N-dimethylaniline as base and xylene as solvent at reflux for 24 h. IR 3326, 1686, 1447, 1264, 1163, 776 cm⁻¹; 1H-NMR (500 MHz, δ ppm, DMSO-d₆) 9.91 (s, 1H), 9.38 (s, 1H), 7.72 (d, J = 8.7 Hz, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.46 - 7.39 (m, 1H), 7.21 (t, J = 7.8 Hz, 1H), 7.08 - 7.02 (m, 3H), 6.96 (d, J = 8.3 Hz, 1H), 6.77 (dd, J = 8.7 Hz, J' = 2.1 Hz, 1H), 5.86 (s, 2H), 3.75 (s, 3H). C₂₃H₁₉N₀₄; MS (ESI, m/z): 372.20 [M-H].

Example 3: Preparation of l-(2-hydroxyphenyl)-2-[3-(2-hydroxyphenyl)-6-methoxy-1H-indol-l-yl]ethanone, with the following structural formula:
This compound was prepared following procedure A.1 from 3-methoxy aniline and 2-bromo-l-(2-hydroxyphenyl)ethanone, using N,N-dimethylaniline as base and xylene as solvent at reflux for 24 h. m.p. 144-146°C; IR 3440, 1654, 1450, 1258, 1158, 744 cm⁻¹; 1H-NMR (300 MHz, δ ppm, CDCl₃) 11.31 (s, 1H), 9.37 (s, 1H), 7.97 (dd, J = 7.9 Hz, 1H), 7.58 - 7.48 (m, 3H), 7.10 - 6.91 (m, 5H), 6.88 (dt, J = 7.4 Hz, J’ = 1.1 Hz, 1H), 6.73 (dd, J = 8.7 Hz, J’ = 2.2 Hz, 1H), 5.85 (s, 2H), 3.75 (s, 3H); ¹³C-NMR (126 MHz, δ ppm, DMSO-d₆) 198.2, 159.8, 155.6, 154.1, 137.7, 135.8, 130.3, 129.1, 128.5, 126.3, 122.2, 120.8, 120.6, 120.3, 119.3, 119.1, 117.6, 115.7, 111.6, 109.1, 93.6, 55.3, 53.7. C₂₃H₂₁NO₅; MS (ESI, m/z): 372.08 [M-H]⁻.

**Example 4:** Preparation of l-(3,4-dihydroxyphenyl)-2-{3-(3,4-dihydroxyphenyl)-6-methoxy-lH-indol-l-yl}ethanone, with the following structural formula:

This compound was prepared following procedure A.1 from 3-methoxy aniline and 2-bromo-l-(3,4-dihydroxyphenyl)ethanone, using sodium bicarbonate as base and ethanol as solvent at reflux for 48 h. m.p. 140-141°C; IR 3275, 1671, 1594, 1438, 1272, 1166, 778 cm⁻¹; 1H-NMR (500 MHz, δ ppm, DMSO-d₆) 7.65 (d, J = 8.7 Hz, 1H), 7.55 (dd, J = 8.2 Hz, J’ = 2.1 Hz, 1H), 7.44 (d, J = 1.9 Hz, 1H), 7.26 (s, 1H), 7.03 (d, J = 1.9 Hz, 1H), 6.93 - 6.85 (m, 4H), 6.78 (d, J = 8.1 Hz, 1H), 5.70 (s, 2H), 3.73 (s, 3H); ¹³C-NMR (126 MHz, δ ppm, DMSO-d₆) 192.5, 155.8, 151.3, 145.5, 143.5, 138.5, 126.9, 126.8, 125.4, 121.6, 120.0, 119.9, 117.6, 116.2, 115.8, 115.3, 114.9, 114.1, 109.3, 93.9, 55.4, 51.7. C₂₃H₂₁NO₅; MS (ESI, m/z): 404.15 [M-H]⁻.

**Example 5:** Preparation of 2-{6-methoxy-3-(2,3,4-trihydroxyphenyl)-lH-indol-l-yl}-l-(2,3,4-trihydroxyphenyl)ethanone, with the following structural formula:
This compound was prepared following procedure A.1 from 3-methoxy aniline and 2-bromo-l-(2,3,4-trihydroxyphenyl)ethanone, using sodium bicarbonate as base and ethanol as solvent at reflux for 48 h. m.p. 132-133°C; IR 3352, 1622, 1466, 1255, 1167, 1005, 789 cm⁻¹; 1H-NMR (500 MHz, δ ppm, DMSO-d₆) 11.83 (s, 1H), 10.19 (s, 1H), 8.97 (s, 1H), 8.71 (s, 1H), 8.30 (s, 1H), 8.08 (s, 1H), 7.53 (d, J = 8.8 Hz, 2H), 7.33 (s, 1H), 6.94 (d, J = 1.8 Hz, 1H), 6.79 (d, J = 8.3 Hz, 1H), 6.68 (dd, J = 8.7 Hz, J' = 1.9 Hz, 1H), 6.51 (d, J = 8.6 Hz, 1H), 6.39 (d, J = 8.3 Hz, 1H), 5.78 (s, 2H), 3.74 (s, 3H); ¹³C-NMR (126 MHz, δ ppm, DMSO-d₆) 198.5, 155.7, 153.0, 152.9, 151.9, 144.4, 143.8, 137.9, 132.7, 127.5, 122.2, 121.3, 120.9, 119.3, 114.5, 112.5, 111.9, 108.2, 106.9, 100.4, 93.6, 55.5, 51.6. C₂₃H₁₉NO₅; MS (ESI, m/z): 436.10 [M-H]

Example 6: Preparation of l-(4-hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-4,6-dimethoxy-lH-indol-l-yl]ethanone, with the following structural formula:

This compound was prepared following procedure A.1 from 3,5-dimethoxyaniline and 2-bromo-l-(4-hydroxyphenyl)ethanone, using N,N-dimethylaniline as base and xylene as solvent at reflux for 24 h. m.p. 226°C (dec); IR 3368, 1680, 1605, 1502, 1449, 1224, 991, 837, 625 cm⁻¹; 1H-NMR (500 MHz, δ ppm, DMSO-d₆) 10.47 (s, 1H), 9.17 (s, 1H), 7.98 (d, J = 8.6 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H), 7.00 (s, 1H), 6.92 (d, J = 8.6 Hz, 2H), 6.73 (d, J = 8.5 Hz, 2H), 6.53 (s, 1H), 6.20 (s, 1H), 5.70 (s, 2H), 3.73 (s, 3H), 3.72 (s, 3H); ¹³C-NMR (75 MHz, δ ppm, DMSO-d₆) 192.1, 162.5, 156.6, 155.2, 154.2, 139.2, 130.6, 129.9, 126.8, 126.4, 125.2, 116.5, 115.3, 114.4, 109.9, 91.5, 86.2, 55.5, 54.9, 51.8. C₂₂H₁₉NO₅; MS (ESI, m/z): 402.02 [M-H]

Example 7: Preparation of l-(2-hydroxyphenyl)-2-[3-(2-hydroxyphenyl)-4,6-dimethoxy-lH-indol-l-yl]ethanone, with the following structural formula:
This compound was prepared following procedure A.1 from 3,5-dimethoxyaniline and 2-bromo-l-(2-hydroxyphenyl)ethanone, using N,N-dimethylaniline as base and xylene as solvent at reflux for 24 h. m.p. 150-151°C; IR 3422, 1647, 1617, 1497, 1452, 1253, 1198, 753 cm⁻¹; 1H-NMR (500 MHz, δ ppm, CDCl₃) 11.66 (s, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 7.4 Hz, 1H), 7.26 - 7.20 (m, 2H), 7.05 (d, J = 8.4 Hz, 1H), 7.02-6.96 (m, 2H), 6.94 (t, J = 7.4 Hz, 1H), 6.26 (d, J = 10.5 Hz, 2H), 5.47 (s, 2H), 3.80 (s, 3H), 3.74 (s, 3H); 13C-NMR (126 MHz, δ ppm, DMSO-d₆) 198.1, 159.8, 156.6, 154.2, 138.6, 135.8, 132.3, 130.3, 127.0, 126.5, 122.9, 120.3, 119.3, 117.9, 117.6, 114.9, 111.5, 111.3, 91.7, 86.2, 55.4, 55.1, 53.8. C₂₄H₂₄N₅O₅ MS (ESI, m/z): 402.21 [M-H]⁻

Example 8: Preparation of l-(3,4-dihydroxyphenyl)-2-[3-(3,4-dihydroxyphenyl)-4,6-dimethoxy-lH-indol-l-yl]ethanone, with the following structural formula:

![Chemical Structure](image)

This compound was prepared following procedure A.1 from 3,5-dimethoxyaniline and 2-bromo-l-(3,4-dihydroxyphenyl)ethanone, using sodium bicarbonate as base and ethanol as solvent at reflux for 16 h. m.p. 101-103°C; IR 3346, 1668, 1595, 1448, 1269, 1164, 806 cm⁻¹; 1H-NMR (500 MHz, δ ppm, DMSO-d₆) 9.96 (s, 1H), 9.41 (s, 1H), 8.58 (s, 1H), 7.54 (d, J = 8.1 Hz, 1H), 7.44 (s, 1H), 6.96 (s, 2H), 6.89 (d, J = 8.1 Hz, 1H), 6.76 (d, J = 8.3 Hz, 1H), 6.68 (d, J = 8.0 Hz, 1H), 6.50 (s, 1H), 6.19 (s, 1H), 5.65 (s, 2H), 3.74 (s, 3H), 3.71 (s, 3H); 13C-NMR (126 MHz, δ ppm, DMSO-d₆) 192.2, 156.6, 154.2, 151.2, 145.4, 144.3, 143.2, 139.2, 127.4, 126.8, 125.3, 121.5, 119.9, 116.9, 116.8, 115.2, 114.9, 114.9, 109.9, 91.5, 86.2, 59.8, 55.3, 55.0, 51.7. C₂₄H₂₄N₅O₇ MS (ESI, m/z): 434.20 [M-H]⁻

Example 9: Preparation of l-(2,4-dihydroxyphenyl)-2-[3-(2,4-dihydroxyphenyl)-4,6-dimethoxy-lH-indol-l-yl]ethanone, with the following structural formula:
This compound was prepared following procedure A.1 from 3,5-dimethoxyaniline and 2-bromo-l-(2,4-dihydroxyphenyl)ethanone, using sodium bicarbonate as base and ethanol as solvent at reflux for 16 h. m.p. 231-232°C; IR 3392, 1698, 1631, 1501, 1456, 1224, 1146, 805 cm⁻¹; 1H-NMR (500 MHz, δ ppm, DMSO-d₆) 11.85 (s, 1H), 10.67 (s, 1H), 9.00 (s, 1H), 8.74 (s, 1H), 7.92 (d, J = 8.7 Hz, 1H), 7.02 - 6.93 (m, 2H), 6.51 (s, 1H), 6.46 (d, J = 8.4 Hz, 1H), 6.32 (d, J = 8.0 Hz, 2H), 6.19 (d, J = 8.0 Hz, 1H), 6.15 (s, 1H), 5.67 (s, 2H), 3.71 (s, 3H), 3.65 (s, 3H); 13C-NMR (126 MHz, δ ppm, DMSO-d₆) 196.9, 164.8, 163.5, 156.4, 156.2, 155.6, 154.3, 138.5, 132.6, 132.5, 126.4, 113.9, 111.8, 111.7, 111.5, 108.3, 105.4, 102.5, 102.2, 91.5, 86.1, 55.3, 55.0, 51.9. C₂₄H₂₁NO₇. MS (ESI, m/z): 434.00 [M-H].

Example 10: Preparation of l-(3,5-dihydroxyphenyl)-2-[3-(3,5-dihydroxyphenyl)-4,6-dimethoxy-1H-indol-l-yl]ethanone, with the following structural formula:

```
    OH
   /   \OH
  /     \   \OCH₃
 CH₃  N  \N
   \     \    
   OH    OH
```

This compound was prepared following procedure A.1 from 3,5-dimethoxyaniline and 2-bromo-l-(3,5-dihydroxyphenyl)ethanone, using sodium bicarbonate as base and ethanol as solvent at reflux for 16 h. m.p. 234-235°C; IR 3408, 1698, 1598, 1456, 1360, 1205, 1161, 994, 852, 803, 688 cm⁻¹; 1H-NMR (500 MHz, δ ppm, DMSO-d₆) 9.66 (s, 1H), 8.94 (s, 1H), 7.04 (s, 1H), 6.93 (s, 2H), 6.54 (s, 2H), 6.43 (s, 2H), 6.22 (s, 1H), 6.07 (s, 1H), 5.69 (s, 2H), 3.75 (s, 3H), 3.72 (s, 3H); 13C-NMR (126 MHz, δ ppm, DMSO-de) 193.9, 158.7, 157.5, 156.1, 154.1, 139.2, 137.5, 136.6, 126.0, 117.0, 109.7, 107.3, 106.1, 99.8, 91.8, 86.3, 68.5, 55.8, 55.3, 55.1, 52.3. C₂₄H₂₁NO₇. MS (ESI, m/z): 434.13 [M-H]⁺.

Example 11: Preparation of 2-[4,6-dimethoxy-3-(2,3,4-trihydroxyphenyl)-1H-indol-l-yl]-l-(2,3,4-trihydroxyphenyl)ethanone, with the following structural formula:
This compound was prepared following procedure A.1 from 3,5-dimethoxyaniline and 2-bromo-l-(2,3,4-trihydroxyphenyl)ethanone, using sodium bicarbonate as base and ethanol as solvent at reflux for 16 h. m.p. 166-167°C; IR 3187, 1618, 1451, 1264, 1201, 1033, 793 cm⁻¹; 1H-NMR (500 MHz, δ ppm, DMSO-d₆) 7.51 (d, J = 8.8 Hz, 1H), 6.97 (s, 1H), 6.55 (d, J = 8.4 Hz, 1H), 6.52 (d, J = 1.4 Hz, 1H), 6.50 (d, J = 8.8 Hz, 1H), 6.27 (d, J = 8.3 Hz, 1H), 6.16 (d, J = 1.4 Hz, 1H), 5.69 (s, 2H), 3.71 (s, 3H), 3.64 (s, 3H); ¹³C-NMR (126 MHz, δ ppm, DMSO-d₆) 198.2, 156.5, 154.3, 152.7, 151.8, 145.5, 144.2, 144.1, 138.6, 132.5, 132.4, 126.5, 121.9, 115.0, 111.9, 111.8, 111.6, 107.9, 105.8, 91.6, 86.2, 55.4, 55.1, 51.5. C₂₄H₂₁NO₉. MS (ESI, m/z): 466.16 [M-H]

Example 12: Preparation of l-(4-fluorophenyl)-2-[3-(4-fluorophenyl)-4,6-dimethoxy-lH-indol-l-yl] ethanone, with the following structural formula:

This compound was prepared following procedure A.1 from 3,5-dimethoxyaniline and 2-bromo-l-(4-fluorophenyl)ethanone, using potassium carbonate as base and ethanol as solvent at reflux for 16 h. m.p. 98-100°C; IR 3445, 1699, 1592, 1504, 1220, 1157, 1071, 833, 811 cm⁻¹; 1H-NMR (300 MHz, δ ppm, CDCl₃) 8.03 - 7.94 (m, 2H), 7.57 - 7.48 (m, 2H), 7.15 (t, J = 8.6 Hz, 2H), 7.02 (t, J = 8.9 Hz, 2H), 6.81 (s, 1H), 6.52 (s, 1H), 6.26 (d, J = 1.9 Hz, 1H), 6.22 (d, J = 1.9 Hz, 1H), 5.32 (s, 2H), 3.78 (s, 3H), 3.77 (s, 3H); ¹³C-NMR (126 MHz, δ ppm, DMSO-de) 192.8, 166.4, 164.3, 161.5, 159.6, 156.9, 154.1, 139.4, 132.3, 131.2, 131.1, 130.5, 130.4, 129.9, 127.7, 126.1, 115.9, 115.8, 114.3, 114.2, 109.7, 91.9, 86.4, 55.4, 55.0, 52.4. C₂₄H₁₉F₂NO₃. MS (ESI, m/z): 406.03 [M-H]

Example 13: Preparation of l-(4-hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-4,7-dimethoxy-lH-indol-l-yl] ethanone, with the following structural formula:
This compound was prepared following procedure A.1 from 2,5-dimethoxyaniline and 2-bromo-l-(4-hydroxyphenyl)ethanone, using N, N-dimethylaniline as base and xylene as solvent at reflux for 24 h. m.p. 240-241°C; IR 3362, 1673, 1602, 1516, 1437, 1254, 1237, 1086, 1059, 837 cm⁻¹; 1H-NMR (500 MHz, δ ppm, DMSO-d₆) 10.42 (s, 1H), 9.17 (s, 1H), 7.93 (d, J = 8.7 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H), 6.74 (d, J = 8.5 Hz, 2H), 6.50 (d, J = 8.5 Hz, 1H), 5.79 (s, 2H), 3.67 (s, 3H), 3.53 (s, 3H); 13C-NMR (126 MHz, δ ppm, DMSO-d₆) 192.3, 162.3, 155.3, 148.3, 141.9, 130.3, 130.2, 128.2, 127.7, 126.5, 126.4, 117.7, 116.4, 115.4, 114.3, 102.8, 99.6, 55.8, 55.3, 54.5. C₂₄H₂₁N₀₅. MS (ESI, m/z): 404.02 [M+H]+.

**Example 14:** Preparation of l-(4-hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-5,6-dimethoxy-lH-indol-1-yl]ethanone, with the following structural formula:

This compound was prepared following procedure A.1 from 3,4-dimethoxyaniline and 2-bromo-l-(4-hydroxyphenyl)ethanone, using N, N-dimethylaniline as base and xylene as solvent at reflux for 24 h. m.p. 142-143°C; IR 3416, 3371, 1673, 1579, 1488, 1208, 1165, 1071, 986, 832 cm⁻¹; 1H-NMR (500 MHz, δ ppm, DMSO-d₆) 7.97 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.2 Hz, 2H), 7.25 (d, J = 13.0 Hz, 2H), 7.03 (s, 1H), 6.90 (d, J = 8.1 Hz, 2H), 6.83 (d, J = 8.2 Hz, 2H), 5.73 (s, 2H), 3.78 (s, 3H), 3.74 (s, 3H); 13C-NMR (126 MHz, δ ppm, DMSO-d₆) 192.4, 162.5, 155.3, 146.7, 144.8, 132.3, 130.7, 127.5, 126.6, 126.5, 124.9, 118.2, 115.7, 115.5, 115.4, 102.0, 94.5, 56.2, 55.9, 51.9. C₂₄H₂₁N₀₅. MS (ESI, m/z): 402.06 [M-H]-.

**Example 15:** Preparation of 2-[5-hydroxy-3-(4-hydroxyphenyl)-6-methoxy-lH-indol-1-yl]-l-(4-hydroxyphenyl)ethanone, with the following structural formula:
This compound was prepared following procedure A.1 from 4-amino-2-methoxyphenol and 2-bromo-1-(4-hydroxyphenyl)ethanone, using N,N-dimethylaniline as base and xylene as solvent at reflux for 24 h. m.p. 275-277 °C; IR 3471, 3362, 1668, 1594, 1483, 1439, 1340, 1215, 1165, 1065, 991, 832 cm⁻¹; 1H-NMR (300 MHz, δ ppm, DMSO-d₆) 10.44 (s, 1H), 9.22 (s, 1H), 8.28 (s, 1H), 7.98 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.6 Hz, 2H), 7.23 (s, 1H), 7.16 (s, 1H), 6.99 - 6.88 (m, 3H), 6.82 (d, J = 8.6 Hz, 2H), 5.70 (s, 2H), 3.75 (s, 3H); 13C-NMR (126 MHz, δ ppm, DMSO-d₆) 192.5, 162.5, 155.1, 145.6, 141.8, 131.8, 130.7, 127.2, 126.8, 126.5, 124.8, 118.8, 115.8, 115.4, 114.7, 104.0, 94.3, 55.9, 51.8. C₁₂H₁₂N₂O₅. MS (ESI, m/z): 388.15 [M-H]

**Example 16:** Preparation of 2-[4,6-difluoro-3-(4-hydroxyphenyl)-1H-indol-1-yl]-1-(4-hydroxyphenyl) ethanone, with the following structural formula:

This compound was prepared following procedure A.1 from 3,5-difluoroaniline and 2-bromo-1-(4-hydroxyphenyl)ethanone, using N,N-dimethylaniline as base and xylene as solvent at reflux for 24 h. m.p. 234-235 °C; IR 3385, 1673, 1601, 1549, 1508, 1463, 1237, 1164, 1100, 981, 837 cm⁻¹; 1H-NMR (500 MHz, δ ppm, DMSO-d₆) 10.48 (s, 1H), 9.33 (s, 1H), 7.97 (d, J = 8.7 Hz, 2H), 7.37 (s, 1H), 7.33 (dd, J = 9.9 Hz, J' = 1.8 Hz, 1H), 6.93 (d, J = 8.7 Hz, 2H), 6.87 - 6.82 (m, 1H), 6.80 (d, J = 8.5 Hz, 2H), 5.81 (s, 2H); 13C-NMR (126 MHz, δ ppm, DMSO-d₆) 191.6, 162.6, 155.9, 130.7, 129.3, 129.3, 128.3, 127.7, 126.2, 124.9, 115.7, 115.4, 115.1, 114.9, 94.8, 93.4, 52.2. C₁₂H₁₂F₂N₂O₃. MS (ESI, m/z): 378.05 [M-H]

**Example 17:** Preparation of 2-[6-hydroxy-3-(4-hydroxyphenyl)-1H-indol-1-yl]-1-(4-hydroxyphenyl) ethanone, with the following structural formula:
This compound was prepared following procedure A.1 from 3-hydroxy aniline and 2-bromo-l-(4-hydroxyphenyl)ethanone, using N,N-dimethylaniline as base and xylene as solvent at reflux for 24 h. m.p. 268°C (dec); IR 3360, 1670, 1603, 1552, 1458, 1336, 1235, 1166, 829, 785, 589 cm⁻¹; 1H-NMR (500 MHz, δ ppm, DMSO-d₆) 10.49 (s, 1H), 9.27 (s, 1H), 8.97 (s, 1H), 8.00 (d, J = 8.5 Hz, 2H), 7.59 (d, J = 8.5 Hz, 1H), 7.42 (d, J = 8.3 Hz, 2H), 7.26 (s, 1H), 6.93 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 6.63 (d, J = 9.4 Hz, 1H), 6.61 (s, 1H), 5.65 (s, 2H); ¹³C-NMR (126 MHz, δ ppm, DMSO-d₆) 192.4, 162.6, 155.3, 153.3, 138.6, 130.7, 127.4, 126.5, 126.4, 124.7, 119.8, 119.2, 115.6, 115.5, 115.4, 109.9, 95.5, 51.7. C₂₂H₁₇NO₄. MS (ESI, m/z): 358.17 [M-H].

Example 18: Preparation of 2-[5-hydroxy-3-(4-hydroxyphenyl)-lH-indol-1-yl]-l-(4-hydroxyphenyl) ethanone, with the following structural formula:

This compound was prepared following procedure A.1 from 4-hydroxyaniline and 2-bromo-l-(4-hydroxyphenyl)ethanone, using N,N-dimethylaniline as base and xylene as solvent at reflux for 24 h. m.p. 188-189°C; IR 3355, 1647, 1601, 1572, 1456, 1351, 1217, 1161, 839, 792 cm⁻¹; 1H-NMR (500 MHz, δ ppm, DMSO-d₆) 10.58 (s, 1H), 9.36 (s, 1H), 7.97 (d, J = 8.7 Hz, 2H), 7.38 (d, J = 8.5 Hz, 2H), 7.14 (d, J = 1.9 Hz, 1H), 7.11 (d, J = 8.8 Hz, 1H), 6.91 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 8.5 Hz, 2H), 6.63 (dd, J = 8.7 Hz, J' = 2.0 Hz, 1H), 5.68 (s, 2H); ¹³C-NMR (126 MHz, δ ppm, DMSO-de) 192.7, 162.7, 155.3, 151.4, 132.2, 130.8, 127.6, 127.3, 126.8, 126.5, 126.4, 115.8, 115.6, 114.8, 111.6, 110.8, 103.4, 55.9. C₂₂H₁₇NO₄. MS (ESI, m/z): 358.17 [M-H].

Example 19: Preparation of 2-[5-fluoro-3-(4-hydroxyphenyl)-lH-indol-1-yl]-l-(4-hydroxyphenyl) ethanone, with the following structural formula:
This compound was prepared following procedure A.1 from 4-fluoroaniline and 2-
(bromo-l-(4-hydroxyphenyl)ethanone, using N,N-dimethylaniline as base and xylene as
solvent at reflux for 24 h. m.p. 236-237°C; IR 3580, 3437, 3257, 1654, 1591, 1478,
1456, 1237, 1172, 992, 878, 835, 799 cm⁻¹; 1H-NMR (500 MHz, δ ppm, DMSO-d₆) 10.49 (s, 1H), 9.33 (s, 1H), 7.99 (d, J = 8.6 Hz, 2H), 7.56 (s, 1H), 7.50 (dd, J = 10.3 Hz,
J ’ = 2.4 Hz, 1H), 7.43 (d, J = 8.4 Hz, 2H), 7.39 (dd, J = 4.5 Hz, 1H), 6.97 (td, J = 9.1 Hz, J ’ = 2.4 Hz, 1H), 6.85 (d, J = 8.6 Hz, 2H), 5.82 (s, 2H); ¹³C-NMR (126 MHz, δ ppm, DMSO-d₆) 192.1, 162.6, 158.4, 156.5, 155.6,

**Example 20:** Preparation of l-(4-hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-lH-indol-1-
yl]ethanone, with the following structural formula:

This compound was prepared following procedure A.1 from aniline and 2-
(bromo-l-(4-hydroxyphenyl)ethanone, using N,N-dimethylaniline as base and xylene as solvent at reflux for 24 h. m.p. 236-237°C; IR 3400, 3302, 1669, 1601, 1549, 1467, 1344, 1291,
1224, 1157, 987, 829, 664, 569 cm⁻¹; 1H-NMR (300 MHz, δ ppm, DMSO-d₆) 10.48 (s, 1H), 9.30 (s, 1H), 7.99 (d, J = 8.7 Hz, 2H), 7.80 (dd, J = 6.7, 1.8 Hz, 1H), 7.46 (d, J = 9.9 Hz, 3H), 7.34 (dd, J = 6.9, 1.6 Hz, 1H), 7.16 - 7.05 (m, 2H), 6.93 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 5.80 (s, 2H); ¹³C-NMR (126 MHz, δ ppm, CD₃OD) 194.0, 164.3, 156.8, 139.1, 131.9, 129.4, 128.3, 128.1, 127.6, 127.5, 122.9, 120.8,
120.7, 118.0, 116.7, 116.6, 110.9, 52.8. C₃₂H₂₈FNO₃. MS (ESI, m/z): 344.05 [M+H]⁺.

**Example 21:** Preparation of (E)-l-(4-hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-4,6-
dimethoxy-lH-indol-l-yl]ethanone oxime, with the following structural formula:
This compound was prepared following procedures A.1 and B from 3,5-dimethoxyaniline and 2-bromo-l-(4-hydroxyphenyl)ethanone, using N, N-dimethylaniline as base and xylene as solvent at reflux for 24 h. m.p. 189-190°C; IR 3381, 3237, 1605, 1550, 1507, 1450, 1335, 1290, 1165, 1040, 839 cm\(^{-1}\); 1H-NMR (500 MHz, δ ppm, DMSO-d\(\text{g}\)) 7.46 (d, \(J = 8.3\) Hz, 2H), 7.20 (d, \(J = 8.1\) Hz, 2H), 7.01 (s, 1H), 6.74 - 6.61 (m, 5H), 6.16 (s, 1H), 5.36 (s, 2H), 3.75 (s, 3H), 3.67 (s, 3H); \(^{13}\)C-NMR (126 MHz, δ ppm, DMSO-d\(\text{g}\)) 158.3, 156.8, 155.4, 154.3, 152.4, 138.2, 129.9, 127.9, 126.6, 125.3, 124.5, 116.6, 115.1, 114.5, 109.8, 91.6, 86.3, 55.3, 54.9. C\(_{24}\)H\(_{22}\)N\(_2\)O\(_5\). MS (ESI, m/z): 417.15 [M-H].

Example 22: Preparation of (Z)-l-(4-hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-4,6-dimethoxy-lH-indol-l-yl]ethanone oxime, with the following structural formula:

This compound was prepared following procedures A.1 and B from 3,5-dimethoxyaniline and 2-bromo-l-(4-hydroxyphenyl)ethanone, using N, N-dimethylaniline as base and xylene as solvent at reflux for 24 h. m.p. 189-190°C; IR 3381, 3237, 1605, 1550, 1507, 1450, 1335, 1290, 1165, 1040, 839 cm\(^{-1}\); 1H-NMR (500 MHz, δ ppm, DMSO-d\(\text{g}\)) 7.46 (d, \(J = 8.3\) Hz, 2H), 7.20 (d, \(J = 8.1\) Hz, 2H), 7.01 (s, 1H), 6.74 - 6.61 (m, 5H), 6.16 (s, 1H), 5.36 (s, 2H), 3.75 (s, 3H), 3.67 (s, 3H); \(^{13}\)C-NMR (126 MHz, δ ppm, DMSO-d\(\text{g}\)) 158.3, 156.8, 155.4, 154.3, 152.4, 138.2, 129.9, 127.9, 126.6, 125.3, 124.5, 116.6, 115.1, 114.5, 109.8, 91.6, 86.3, 55.3, 54.9. C\(_{24}\)H\(_{22}\)N\(_2\)O\(_5\). MS (ESI, m/z): 417.15 [M-H].

Example 23: Preparation of 2,2'-(3-methoxyphenyl)azanediyl]-bis[l-(2,3,4-trihydroxyphenyl) ethanone], with the following structural formula:
This compound was prepared following procedure C from 3-methoxy aniline and 2-bromo-l-(2,3,4-trihydroxyphenyl)ethanone, using sodium bicarbonate as base and ethanol as solvent at reflux for 3 h. m.p. 119-120°C; IR 3379, 1611, 1500, 1442, 1249, 1201, 1166, 1004, 790 cm⁻¹; 1H-NMR (500 MHz, δ ppm, DMSO-d₆) 12.04 (s, 2H), 10.15 (s, 2H), 8.66 (s, 2H), 7.44 (d, J = 8.9 Hz, 2H), 6.98 (t, J = 8.2 Hz, 1H), 6.43 (d, J = 8.8 Hz, 2H), 6.21 (dd, J = 8.1 Hz, J' = 1.8 Hz, 1H), 6.06 (dd, J = 8.3 Hz, J' = 2.0 Hz, 1H), 5.96 (s, 1H), 4.92 (s, 4H), 3.60 (s, 3H); ¹³C-NMR (126 MHz, δ ppm, DMSO-d₆) 201.1, 160.2, 152.5, 151.8, 149.9, 132.5, 129.7, 121.5, 112.1, 107.9, 104.8, 101.2, 98.3, 57.1, 54.7. C₂₃H₂₁NO₉. MS (ESI, m/z): 454.22 [M-H]⁻.

Example 24: Preparation of 2,2'-[3,5-dimethoxyphenyl]azanediyl]-bis[l-(2,3,4-trihydroxyphenyl)ethanone], with the following structural formula:

![Structural formula]

This compound was prepared following procedure C from 3,5-dimethoxyaniline and 2-bromo-l-(2,3,4-trihydroxyphenyl)ethanone, using sodium bicarbonate as base and ethanol as solvent at reflux for 3 h. IR 3422, 1620, 1452, 1295, 1250, 1201, 1168, 992, 805, 792 cm⁻¹; 1H-NMR (500 MHz, δ ppm, DMSO-d₆) 7.43 (d, J = 8.8 Hz, 2H), 6.43 (d, J = 8.8 Hz, 2H), 5.84 (s, 1H), 5.62 (s, 2H), 4.90 (s, 4H), 3.59 (s, 6H); ¹³C-NMR (126 MHz, δ ppm, DMSO-de) 201.1, 161.1, 152.5, 151.7, 150.3, 132.4, 121.5, 112.1, 107.8, 91.3, 88.3, 57.1, 54.8. C₂₄H₂₃NO₁₀. MS (ESI, m/z): 484.10 [M-H]⁻.

Example 25: Preparation of a potassium phenoxide salt of l-(4-hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-6-methoxy-IH-indol-1-yl]ethanone:

This compound was prepared following procedures A.1 and A.2 from 3-methoxy aniline and 2-bromo-l-(4-hydroxyphenyl)ethanone, using N, N-dimethylaniline as base and xylene as solvent at reflux for 24 h. m.p. 250°C (dec); IR 3247, 1596, 1503, 1371, 1228, 1160, 1007, 830 cm⁻¹; 1H-NMR (500 MHz, δ ppm, DMSO-d₆) 8.56 (s, 1H), 7.87 (d, J = 8.3 Hz, 2H), 7.66 (d, J = 8.7 Hz, 1H), 7.42 (d, J = 8.1 Hz, 2H), 7.31 (s, 1H), 6.94 (s, 1H), 6.84 (d, J = 8.1 Hz, 2H), 6.74 (d, J = 8.4 Hz, 2H), 6.65 (d, J = 8.2 Hz, 1H), 5.67 (s, 2H), 3.74 (s, 3H); ¹³C-NMR (126 MHz, δ ppm, DMSO-d₆) 191.1, 165.6, 155.7, 155.6, 138.4, 130.7, 127.4, 126.8, 126.2, 125.4, 119.8, 119.7, 116.5, 115.7, 114.4, 109.2, 93.8, 55.3, 51.3. C₃H₈KNO₄.
Example 26: Preparation of a potassium phenoxide salt of l-(4-hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-4,6-dimethoxy-lH-indol-1-yl] ethanone:

This compound was prepared following procedures A.1 and A.2 from 3,5-dimethoxyaniline and 2-bromo-l-(4-hydroxyphenyl)ethanone, using \( N, N \)-dimethylaniline as base and xylene as solvent at reflux for 24 h. m.p. 214-216°C; IR 3049, 1574, 1503, 1217, 1199, 1159, 1043, 832 cm⁻¹; 1H-NMR (500 MHz, δ ppm, DMSO-d₆) 7.79 (d, \( J = 8.5 \) Hz, 2H), 7.30 (d, \( J = 8.1 \) Hz, 2H), 6.99 (s, 1H), 6.73 (d, \( J = 8.1 \) Hz, 2H), 6.56 (d, \( J = 8.5 \) Hz, 2H), 6.49 (s, 1H), 6.19 (s, 1H), 5.55 (s, 2H), 3.73 (s, 3H), 3.72 (s, 3H); \(^{13}\)C-NMR (126 MHz, δ ppm, DMSO-d₆) 190.1, 171.2, 156.5, 155.6, 154.2, 139.2, 130.8, 129.8, 126.6, 125.4, 120.6, 117.2, 116.3, 114.5, 113.8, 109.9, 91.4, 86.2, 55.3, 54.9, 51.2. C₁₄H₂₀KNO₅.

Example 27: Preparation of a calcium phenoxide salt of l-(4-hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-4,6-dimethoxy-lH-indol-1-yl] ethanone:

This compound was prepared following procedures A.1 and A.2 from 3,5-dimethoxyaniline and 2-bromo-l-(4-hydroxyphenyl)ethanone, using \( N, N \)-dimethylaniline as base and xylene as solvent at reflux for 24 h. m.p. 182°C (dec); IR 3309, 1578, 1502, 1443, 1217, 1164, 1045, 835 cm⁻¹; 1H-NMR (500 MHz, δ ppm, DMSO-d₆) 7.92 (d, \( J = 8.4 \) Hz, 2H), 7.30 (d, \( J = 8.3 \) Hz, 2H), 7.00 (s, 1H), 6.82 (d, \( J = 7.9 \) Hz, 2H), 6.73 (d, \( J = 8.4 \) Hz, 2H), 6.52 (s, 1H), 6.20 (s, 1H), 5.65 (s, 2H), 3.73 (s, 3H), 3.71 (s, 3H); \(^{13}\)C-NMR (126 MHz, δ ppm, DMSO-d₆) 191.6, 169.9, 156.6, 155.2, 154.2, 139.2, 130.7, 129.9, 126.8, 125.3, 116.5, 115.9, 115.4, 114.4, 109.9, 91.5, 86.2, 55.3, 54.9, 51.6. C₁₄H₂₀CaNO₅.

Example 28: Preparation of 4-{l-[2-(4-acetoxyphenyl)-2-oxoethyl]-6-methoxy-lH-indol-3-yl}phenyl acetate, with the following structural formula:

![Structural formula](image)

This compound was prepared following procedures A.1 and A.3 from 3-methoxy aniline and 2-bromo-l-(4-hydroxyphenyl)ethanone, using \( N, N \)-dimethylaniline as base and xylene as solvent at reflux for 24 h. m.p. 67-68°C; IR 1754, 1694, 1599, 1504, 1462, 1368, 1189, 1160, 1013, 909, 848 cm⁻¹; 1H-NMR (500 MHz, δ ppm, DMSO-d₆) 8.18 (d, \( J = 8.6 \) Hz, 2H), 7.75 (d, \( J = 8.7 \) Hz, 1H), 7.66 (d, \( J = 8.5 \) Hz, 2H), 7.52 (s, 1H), 7.39 (d, \( J = 8.6 \) Hz, 2H), 7.18 (d, \( J = 8.6 \) Hz, 2H), 7.07 (d, \( J = 2.0 \) Hz, 1H), 6.78 (dd, \( J = 8.7, 2.1 \) Hz, 1H), 5.92 (s, 2H), 3.75 (s, 3H), 2.33 (s, 3H), 2.29 (s, 3H); \(^{13}\)C-NMR (126 MHz, δ ppm, DMSO-d₆) 193.2, 169.3, 168.8, 156.0, 154.6, 148.2, 138.6, 133.1, 132.4, 129.9, 127.0, 126.5, 122.3, 122.2, 119.7, 119.5, 114.7, 109.9, 94.0, 55.8, 55.4, 52.3, 20.9. C₁₇H₂₃NO₆. MS (ESI, m/z): 458.29 [M+H]+.
Example 29: Preparation of 4-{1-[2-(4-acetoxyphenyl)-2-oxoethyl]-4,6-dimethoxy-1H-indol-3-yl} phenyl acetate, with the following structural formula:

This compound was prepared following procedures A.1 and A.3 from 3,5-dimethoxyaniline and 2-bromo-1-(4-hydroxyphenyl)ethanone, using N, N-dimethylaniline as base and xylene as solvent at reflux for 24 h. m.p. 180-181°C; IR 1755, 1695, 1552, 1501, 1366, 1217, 1197, 1160, 910, 851, 810 cm⁻¹; 1H-NMR (500 MHz, δ ppm, DMSO-d₅) 8.17 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.3 Hz, 2H), 7.38 (d, J = 8.3 Hz, 2H), 7.19 (s, 1H), 7.09 (d, J = 8.3 Hz, 2H), 6.64 (s, 1H), 6.26 (s, 1H), 5.86 (s, 2H), 3.77 (s, 3H), 3.73 (s, 3H), 2.33 (s, 3H), 2.28 (s, 3H); 13C-NMR (126 MHz, δ ppm, DMSO-de) 193.1, 166.9, 164.5, 154.5, 154.0, 150.9, 148.3, 139.4, 133.5, 132.4, 129.8, 129.5, 126.2, 127.3, 120.8, 115.8, 109.6, 91.9, 86.4, 55.4, 55.0, 52.4, 20.9; C₂₅H₂₅NO₇. MS (ESI, m/z): 486.25 [M-H].

Example 30: Preparation of 4-{1-[2-(3,4-diacetoxyphenyl)-2-oxoethyl]-4,6-dimethoxy-1H-indol-3-yl}-1,2-phenylene diacetate, with the following structural formula:

This compound was prepared following procedures A.1 and A.3 from 3,5-dimethoxyaniline and 2-bromo-1-(3,4-dihydroxyphenyl)ethanone, using sodium bicarbonate as base and ethanol as solvent at reflux for 16 h. m.p. 72-73°C; IR 1766, 1698, 1605, 1503, 1369, 1257, 1196, 1154, 1008, 899, 819 cm⁻¹; 1H-NMR (500 MHz, δ ppm, DMSO-d₅) 8.08 (dd, J = 8.4 Hz, J ′ = 1.9 Hz, 1H), 7.98 (d, J = 1.9 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.42 (dd, J = 8.4 Hz, J ′ = 2.0 Hz, 1H), 7.38 (d, J = 1.9 Hz, 1H), 7.24 (s, 1H), 7.20 (d, J = 8.4 Hz, 1H), 6.67 (d, J = 1.6 Hz, 1H), 6.26 (d, J = 1.6 Hz, 1H), 5.86 (s, 2H), 3.77 (s, 3H), 3.73 (s, 3H), 2.33 (s, 6H), 2.29 (s, 6H); 13C-NMR (126 MHz, δ ppm, DMSO-de) 192.5, 168.4, 168.3, 168.2, 167.9, 157.0, 153.9, 146.3, 142.3, 141.2, 139.6, 139.5, 134.6, 133.3, 126.9, 126.6, 126.4, 124.2, 123.6, 123.5, 122.5, 115.1, 109.3, 92.0, 86.5, 55.4, 54.9, 52.5, 20.4; C₃₂H₂₉NO₁. MS (ESI, m/z): 602.17 [M-H].
Example 31: Preparation of 4-{1-[2-(3,4-diacetoxyphenyl)-2-oxoethyl]-6-methoxy-1H-indol-3-yl}-1,2-phenylene diacetate, with the following structural formula:

This compound was prepared following procedures A.1 and A.3 from 3-methoxyaniline and 2-bromo-1-(3,4-dihydroxyphenyl)ethanone, using sodium bicarbonate as base and ethanol as solvent at reflux for 48 h. m.p. 62-63°C; IR 1764, 1702, 1608, 1499, 1368, 1193, 1105, 1007, 890 cm⁻¹; 1H-NMR (500 MHz, δ ppm, DMSO-dg) 8.10 (dd, J = 8.3 Hz, J’ = 1.9 Hz, 1H), 8.00 (d, J = 1.8 Hz, 1H), 7.74 (d, J = 8.8 Hz, 1H), 7.58 - 7.52 (m, 3H), 7.50 (d, J = 1.8 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.1 (d, J = 1.9 Hz, 1H), 6.80 (dd, J = 8.7 Hz, J’ = 2.0 Hz, 1H), 5.92 (s, 2H), 3.76 (s, 3H), 2.34 (s, 6H), 2.30 (s, 6H); 13C-NMR (126 MHz, δ ppm, DMSO-dg) 192.6, 168.4, 168.3, 168.2, 167.9, 156.1, 146.4, 142.3, 139.5, 138.7, 134.2, 133.3, 126.9, 124.2, 124.0, 123.9, 123.5, 120.9, 119.6, 119.3, 114.0, 110.2, 94.1, 64.9, 55.4, 52.4, 20.5, 20.4, 20.3. C31H27NO10. MS (ESI, m/z): 572.1 [M-H].

Biological Assays

Example 32: In vitro biological activity

The inhibition of the enzymatic activity of DNMT1 was tested using low volume radioisotope-based assay which uses tritium-labeled AdoMet (3H-SAM) as a methyl donor. Inhibitors diluted in DMSO were added by using acoustic technology (Echo550, Labcyte Inc. Sunnyvale, CA) into enzyme/substrate mixture in nano-liter range. The reaction was initiated by the addition of 3H-SAM, and incubated at 30°C for 1 hour. Total final methylations on the substrate poly(dL-dC) were detected by a filter binding approach. Data analysis was performed using GraphPad Prism software (La Jolla, CA) for IC50 curve fits. Reactions were carried out at 1 µM of S-adenosyl-L-methionine (SAM), 25 nM DNMT1 (Human DNMT1 GenBank Accession No. NM_001 130823, a- a 2-1632, with N-terminal GST tag, Mw=211 kDa, expressed in baculo virus expression system), 0.005 mg/ml Poly(dL-dC) (Sigma, Cat. # P4929). S-adenosyl-L-homocysteine (SAH) was used as standard positive control. Inhibitors were tested in 10-dose IC50 (effective concentration to inhibit DNMT1 activity by 50%) with three-fold serial dilution.

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC50 (µM)</th>
<th>Compound</th>
<th>IC50 (µM)</th>
</tr>
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<tr>
<td>SAH</td>
<td>0.25</td>
<td>Example 14</td>
<td>43.35</td>
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</table>
**Example 33: Biological Activity in Cancer Cell lines**

Cell culture-based assays were used to evaluate the ability of compounds of the invention to inhibit cancer cell growth inhibition.

Cells were obtained from the American Type Culture Collection (ATCC) and European Collection of Cell Cultures (ECACC).

Cells were thawed in their appropriate media plus supplements (see table below). Cells were passaged at confluence by washing once in HBSS cation-free followed by a 3 minutes incubation with trypsin ((0.5 µg/ml/EDTA [0.2 µg/ml]) (Gibco-BRL, 15400054) solution in HBSS at 37°C (except non-adherent cell lines), and transferred to their appropriate media plus supplements. Prior to seeding at defined cell concentration, cells were recovered in medium, centrifuged and taken up in medium, and counted.

Cells were plated at 3000/5000/10000 cells/well in 100 µl media in tissue culture 96 well plates (Cultek). After 24h, media was supplemented by 100 µl/well of diluted IPDNs at 100 µM.

The Hexosaminidase assay was used for the adherent cell lines, whereas the AlamarBlue® assay was used for the non-adherent cell lines.

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Cell Lines</th>
<th>Culture Media</th>
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<tbody>
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<td>Breast</td>
<td>BT474</td>
<td>DEMEM High Glucose (4500 mg/l)+10FCS</td>
</tr>
<tr>
<td></td>
<td>MDA-MB-231</td>
<td>DEMEM High Glucose (4500 mg/l)+10FCS</td>
</tr>
<tr>
<td></td>
<td>MDA-MB-468</td>
<td>DEMEM High Glucose (4500 mg/l)+10FCS</td>
</tr>
<tr>
<td></td>
<td>MCF-7</td>
<td>EMEM + 2mM Glutamine+1% Non-essential Aminoacids + 10FCS</td>
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<tr>
<td>Tissue</td>
<td>Cell Line</td>
<td>Culture Medium</td>
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<tr>
<td>Prostate</td>
<td>SK-BR-3</td>
<td>DEMEM High Glucose (4500 mg/l)+10FCS</td>
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<td>DEMEM High Glucose (4500 mg/l)+10FCS</td>
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<td>LNCaP</td>
<td>RPMI + 2 mM Glutamine + 10% FCS</td>
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Dose-response curves were generated by serial dilutions (1:1) of the compounds. Negative control did not contain compounds. Reagent blanks, containing media plus colorimetric reagent without cells were run on each plate. Blank values were subtracted from test values and were routinely 5-10% of uninhibited control values. Plates were incubated 72h, and living cell number was determined by AlamarBlue® and Hexosaminidase test. The advantages of using those assays are that both can be done in the same microwell plate. AlamarBlue® assay: plates were incubated 72h and living cell number was determined by AlamarBlue® (Biosource DALI 100). After 4h incubation at 37°C, relative fluorescent intensity, which correlates with the number of living cells, was read in a Cytofluor plate reader (Millipore) at 535/590 nm (Excitation/emission). The hexosaminidase activity was measured according to the following protocol: the media was removed and cells were washed once with PBS. 60 µl of substrate solution (p-nitrophenol-N-acetyl-beta-D-glucosamide 7.5 mM [Sigma N-9376], sodium citrate 0.1 M, pH 5.0, 0.25% Triton X-100) was added to each well and incubated at 37°C for 1-2 hours; after this incubation time, a bright yellow appears; then, plates could be developed by adding 90 µl of developer solution (Glycine 50 mM, pH 10.4; EDTA 5 mM), and absorbance was recorded at 405 nM.

Data analysis was done by calculating the percentage of cell viability normalized in front of negative control values, which were considered as a 100%. The curve was adjusted using a sigmoidal dose-response (variable slope) equation and EC50 values were obtained from the equation

\[ Y = Bottom + \frac{(Top - Bottom)}{1 + 10^{(LogEC50 - X)\cdot HillSlope}} \]

where,

- X is the logarithm of concentration. Y is the response.
- Bottom is the Y value at the bottom plateau
- Top is the Y value at the top plateau
- LogEC50 is the X value when the response is halfway between Bottom and Top. With different kinds of variables, this variable is sometimes called ED50 (effective dose, 50%), or IC50 (inhibitory concentration, 50%> used when the curve goes downhill).

### EXAMPLE 6 EC50 (µM)

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**EXAMPLE 8 EC50 (µM)**

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**EXAMPLE 4 EC50 (µM)**

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**EXAMPLE 30 EC50 (µM)**

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</table>
CLAIMS

1. A compound of general formula (I),

(1)

wherein:

\[ -\text{c=c} - \]

X is a \(-(\text{CH}_2)_n\) group, or a \(\text{H}\) group which is bonded to the N atom through the \(-\text{CH}\);

Y is a O atom or a N-OH group;

Z is a C=Y group;

n is selected from 1, 2, 3, 4, 5 and 6;

m is 0 or 1;

R'-R⁹ represent, independently of each other, hydrogen, halogen, hydroxyl, alkoxy or \(-\text{OC(0)-alkyl}\)

with the proviso that:

when X is a \(-(\text{CH}_2)_n\) group, m=1 and the dashed line does not represent a bond; and

\[ -\text{c=c} - \]

when X is a \(\text{H}\) group, m=0 and the dashed line represents a carbon-carbon single bond, forming together with the benzyl group an indole ring;

or a solvate or a salt or prodrug thereof;

for its use as a medicament.

2. Compound of formula (I) as defined in claim 1 for its use in the treatment of a disease or condition selected from the group consisting of cancer, hematological
malignancy, proliferative diseases, genetic diseases, neurological disorders and immunological disorders.

3. A compound of formula (I):

\[
\begin{array}{c}
\text{R}_2 \quad \text{R}_1 \\
\text{R}_3 \quad \text{R}_4 \\
\text{R}_5 \quad \text{R}_6 \\
\text{R}_7 \quad \text{R}_8 \\
\end{array}
\]

wherein:

- \( X \) is a \(-(\text{CH}_2)_n\) group, or a \( \text{H} \) group which is bonded to the \( \text{N} \) atom through the \(-\text{CH};\)
- \( Z \) is a \( \text{C}=\text{Y} \) group;
- \( Y \) is a \( \text{O} \) atom or a \( \text{N-OH} \) group;
- \( n \) is selected from 1, 2, 3, 4, 5 and 6;
- \( m \) is 0 or 1;
- \( \text{R}'-\text{R}^9 \) represent, independently of each other, hydrogen, halogen, hydroxyl, alkoxy or \(-\text{OC}(0))-\text{alkyl},

with the proviso that:

- when \( X \) is a \(-(\text{CH}_2)_n\) group, \( m=1 \) and the dashed line does not represent a bond; and
- when \( X \) is a \( \text{H} \) group, \( m=0 \) and the dashed line represents a carbon-carbon single bond, forming together with the benzyl group an indole ring;

and wherein:

- when \( X \) is a \( \text{H} \) group, \( Y=0 \) and \( n=1 \), then:
  - at least one of \( \text{R}'-\text{R}^9 \) is not \( \text{H} \);
  - at least one of \( \text{R}^1 \) and \( \text{R}^3 \) is not \( \text{OMe} \) when \( \text{R}^2, \text{R}^4-\text{R}^9 \) are \( \text{H} \); and
R7 is not Br, Cl or OH, when R2, R4, R5, R6, R8-R9 are H and R1 and R3 are OMe;
- when X is a -(CH2)n- group and n=1 ; then:
  at least one of R1-R9 is not H;
  - when X is a -(CH2)n- group, Y=N-OH and n=1 ; then
    R2 is not OMe when R1, R3-R9 are H; and
    R7 is not OMe or Cl, when R1, R3-R6, R8-R9 is H and R2 is OMe;
  - when X is a -(CH2)n- group, Y=0 and n=1 ; then:
    R7 is not OMe or Cl, when R1-R6, R8-R9 are H;
  at least one of R1 and R3 is not OMe, when R2, R4-R9 are H;
    R7 is not Br, when R2, R4-R6, R8-R9 are H and R1 and R3 are OMe;
    R2 is not OMe, when R1, R3-R9 are H;
    R4 is not OH, when of R1-R3, R5-R9 are H; and
    at least one of R2 and R7 is not OH, when R1, R3-R6, R8-R9 are H;
- when X is a -(CH2)n- group, Y=0 and n=2; then:
  at least one of R1-R9 is not H;
    R2 is not OMe, Cl or Br, when R1, R3-R9 are H;
    R7 is not Cl, Br or OMe, when R1, R3-R6, R8-R9 are H, and R2 is OMe;
    R7 is not Cl, Br or OMe, when R1, R3-R6, R8-R9 are H and R2 is Cl; and
    R7 is not Cl, Br or OMe, when R1, R3-R6, R8-R9 are H and R2 is Br;
or a solvate or a salt or prodrug thereof.

4. Compound according to claim 3, wherein at least one of R1, R2, R3 and R4 is not hydrogen, and at least one of R5, R6, R7, R8 and R9 is not hydrogen.

5. Compound according to anyone of claims 3 and 4, wherein at least one of R1, R2, R3 or R4 is an alkoxyl and wherein at least one of R5, R6, R7, R8 and R9 is a hydroxyl group.

6. Compound according to anyone of claims 3 to 5, wherein at least one of R1, R2, R3 and R4 is an alkoxyl and wherein at least one of R5, R6, R7, R8 and R9 is -OC(O)-alkyl.

7. Compound according to anyone of claims 3 to 5, wherein at least one of R1, R2, R3 and R4 is an alkoxyl and wherein at least one of R5, R6, R7, R8 and R9 is a halogen.

8. Compound according to anyone of claims 3 to 7, wherein each alkoxyl group is independently selected from -0-Ci-C alkyl.

9. Compound according to claim 5, wherein Y is a N-OH group.

10. Compound of general formula (I) according to anyone of claims 3 to 4 selected from the group consisting of:
1-(4-Hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-6-methoxy-1H-indol-1-yl] ethanone, with the following structural formula:

1-(3-Hydroxyphenyl)-2-[3-(3-hydroxyphenyl)-6-methoxy-1H-indol-1-yl] ethanone, with the following structural formula:

1-(2-Hydroxyphenyl)-2-[3-(2-hydroxyphenyl)-6-methoxy-1H-indol-1-yl] ethanone, with the following structural formula:

1-(3,4-Dihydroxyphenyl)-2-[3-(3,4-dihydroxyphenyl)-6-methoxy-1H-indol-1-yl]ethanone, with the following structural formula:

2-[6-Methoxy-3-(2,3,4-trihydroxyphenyl)-1H-indol-1-yl]-1-(2,3,4-trihydroxyphenyl)ethanone, with the following structural formula:
1-(2-Hydroxyphenyl)-2-[3-(2-hydroxyphenyl)-4,6-dimethoxy-1H-indol-1-yl]ethanone, with the following structural formula:

\[
\text{Structure Image}
\]

1-(3,4-Dihydroxyphenyl)-2-[3-(3,4-dihydroxyphenyl)-4,6-dimethoxy-1H-indol-1-yl]ethanone, with the following structural formula:

\[
\text{Structure Image}
\]

1-(2,4-Dihydroxyphenyl)-2-[3-(2,4-dihydroxyphenyl)-4,6-dimethoxy-1H-indol-1-yl]ethanone, with the following structural formula:

\[
\text{Structure Image}
\]
1-(3,5-dihydroxyphenyl)-2-(3-(3,5-dihydroxyphenyl)-4,6-dimethoxy-1H-indol-1-yl)ethanone, with the following structural formula:

![Structural formula 1](image1)

2-[4,6-Dimethoxy-3-(2,3,4-trihydroxyphenyl)-1H-indol-1-yl]-1-(2,3,4-trihydroxyphenyl)ethanone, with the following structural formula:

![Structural formula 2](image2)

1-(4-Fluorophenyl)-2-[3-(4-fluorophenyl)-4,6-dimethoxy-1H-indol-1-yl]ethanone, with the following structural formula:

![Structural formula 3](image3)

1-(4-Hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-4,7-dimethoxy-1H-indol-1-yl]ethanone, with the following structural formula:

![Structural formula 4](image4)
1-(4-Hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-5,6-dimethoxy-1H-indol-1-yl]ethanone, with the following structural formula:

2-[5-Hydroxy-3-(4-hydroxyphenyl)-6-methoxy-1H-indol-1-yl]-1-(4-hydroxyphenyl)ethanone, with the following structural formula:

2-[4,6-Difluoro-3-(4-hydroxyphenyl)-1H-indol-1-yl]-1-(4-hydroxyphenyl)ethanone, with the following structural formula:
2-[6-Hydroxy-3-(4-hydroxyphenyl)-1H-indol-1-yl]-1-(4-hydroxyphenyl) ethanone, with the following structural formula:

![Chemical Structure 1](image1)

2-[5-Hydroxy-3-(4-hydroxyphenyl)-1H-indol-1-yl]-1-(4-hydroxyphenyl) ethanone, with the following structural formula:

![Chemical Structure 2](image2)

2-[5-Fluoro-3-(4-hydroxyphenyl)-1H-indol-1-yl]-1-(4-hydroxyphenyl) ethanone, with the following structural formula:

![Chemical Structure 3](image3)

1-(4-Hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-1H-indol-1-yl]ethanone, with the following structural formula:
(E)-1-(4-Hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-4,6-dimethoxy-1H-indol-1-yl]ethanone oxime, with the following structural formula:

(X)-1-(4-Hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-4,6-dimethoxy-1H-indol-1-yl]ethanone oxime, with the following structural formula:

2,2'-(3-Methoxyphenyl)azanediyl]-bis[l-(2,3,4-trihydroxyphenyl) ethanone], with the following structural formula:

2,2'-(3,5-Dimethoxyphenyl)azanediyl]-bis[l-(2,3,4-trihydroxyphenyl) ethanone], with the following structural formula:
Potassium salt of l-(4-hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-6-methoxy-1H-indol-1-yl] ethanone

Potassium salt of l-(4-hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-4,6-dimethoxy-1H-indol-1-yl] ethanone

Calcium salt of l-(4-hydroxyphenyl)-2-[3-(4-hydroxyphenyl)-4,6-dimethoxy-1H-indol-1-yl] ethanone

4- {1-[2-(4-Acetoxyphenyl)-2-oxoethyl]-6-methoxy-1H-indol-3-yl} phenyl acetate, with the following structural formula:

4- {1-[2-(3,4-Diacetoxyphenyl)-2-oxoethyl]-4,6-dimethoxy-1H-indol-3-yl} phenyl acetate, with the following structural formula:

4- {1-[2-(3,4-Diacetoxyphenyl)-2-oxoethyl]-4,6-dimethoxy-1H-indol-3-yl} -1,2-phenylene diacetate, with the following structural formula:
4-\{1-[2-(3,4-Diacetoxyphenyl)-2-oxoethyl]-6-methoxy-1H-indol-3-yl\} - 1,2-phenylene diacetate, with the following structural formula:

or a solvate or a salt or prodrug thereof.

11. Process for the preparation of a compound of general formula (I) as defined in claim 3, wherein R'-R and n have the meaning given in claim 3, X is -CH=C-, Y=0 and m=0, which comprises reacting:

a) a compound of general formula (II):

wherein R¹, R², R³ and R⁴ have the meaning given above;

b) a compound of general formula (III),
wherein Q can be a chlorine, bromine or iodine atom, or a leaving group, and R^5, R^6, R^7, R^8, R^9 and n have the meaning given above;

in the presence of

c) a base, either organic or inorganic; and

d) a solvent

leaving the reaction to react for at least 16 hours,

and, optionally, performing one or more of the reactions selected from the group consisting of: (i) treating the compound of formula (I) with a hydroxide of an alkaline metal or an alkaline earth metal to obtain the corresponding salt; and (ii) protecting any hydroxyl group to obtain the corresponding -OC(=O)-alkyl group.

12. Process for the preparation of a compound of general formula (I) as defined in claim 3, wherein R^5-R^9 and n have the meaning given in claim 3, X is -(CH_2)_m, Y=0 and m=1, which comprises reacting:

a) a compound of formula (II)

\[
\begin{align*}
R^1 & \\
R^2 & \\
R^3 & \\
R^4 & \\
\text{NH}_2 & \\
\end{align*}
\]

(II)

wherein R^1, R^2, R^3 and R^4 have the meaning given above; with

b) a compound of general formula (III),

\[
\begin{align*}
Q & \text{-(CH}_2)_n \\
\text{R}_9 & \\
\text{R}_8 & \\
\text{R}_7 & \\
\text{R}_6 & \\
\text{R}_5 & \\
\end{align*}
\]

(III)

wherein Q can be a chlorine, bromine or iodine atom, or a leaving group, and R^5, R^6, R^7, R^8, R^9 and n have the meaning given above;

in the presence of

 c) a base, either organic or inorganic; and

d) a solvent

leaving the reaction to react for 3 hours at the most,

and, optionally, performing one or more of the reactions selected from the group consisting of: (i) treating the compound of formula (I) with a hydroxide of an
alkaline metal or an alkaline earth metal to obtain the corresponding salt; and (ii)
protecting any hydroxyl group to obtain the corresponding -OC(O)-alkyl group.

13. Process for the preparation of a compound of general formula (I) as defined in
claim 3, wherein R'-R \(^9\) and n have the meaning given in claim 3, X is -CH=C-, Y=N-OH and m=0, which comprises:

(a) preparing a compound of general formula (I) as described in claim 11; and

(b) further reacting the obtained product of formula (I) with a mixture of
hydroxylamine hydrochloride and phenolphthalein in the presence of an
excess of sodium methoxide in methanol.

14. Process for the preparation of a compound of general formula (I) as defined in
claim 3, wherein R'-R \(^9\) and n have the meaning given in claim 3, X is -(CH\(_2\))\(_n\),
Y=N-OH and m=0, which comprises:

(c) preparing a compound of general formula (I) as described in claim 12; and

(d) further reacting the obtained product of formula (I) with a mixture of
hydroxylamine hydrochloride and phenolphthalein in the presence of an
excess of sodium methoxide in methanol.

15. A pharmaceutical composition that comprises at least a compound of formula (I) as
defined in any of claims 3 to 10, or a pharmaceutically acceptable solvate or a salt
or prodrug thereof, and at least a pharmaceutically acceptable excipient.
**INTERNATIONAL SEARCH REPORT**

*International application No*

PCT/EP2013/073209

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. C07C225/22 C07D209/04 C07D209/12 A61K31/404 A61P35/00

**ADD.**

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:
  - "A" document defining the general state of the art which is not considered to be of particular relevance
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**Date of the actual completion of the international search**

20 January 2014

**Date of mailing of the international search report**

29/01/2014

**Name and mailing address of the ISA/Authorized officer**

European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016

de Nooy, Arjan
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<td>G. RAVINDRAN, N.G. RENGANATHAN: &quot;Condensation of 3-aza-1,5-di ketones with N-nucleophiles&quot;, ORG. COMMUN., vol. 3, no. 4, 2010, pages 76-83, XP002694087, the whole document</td>
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