

(10) International Publication Number
WO 2016/100542 A1(43) International Publication Date
23 June 2016 (23.06.2016)

(51) International Patent Classification:

C07D 207/14 (2006.01) A61K 31/166 (2006.01)
 C07D 213/24 (2006.01) A61K 31/443 (2006.01)
 C07D 235/30 (2006.01) A61K 31/506 (2006.01)
 C07D 307/38 (2006.01) A61K 31/341 (2006.01)
 C07D 307/52 (2006.01) A61K 31/44 (2006.01)
 C07D 405/12 (2006.01) A61K 31/505 (2006.01)
 C07C 43/205 (2006.01) A61K 31/40 (2006.01)
 C07C 233/58 (2006.01) A61P 35/00 (2006.01)
 A61K 31/075 (2006.01)

(21) International Application Number:

PCT/US2015/066146

(22) International Filing Date:

16 December 2015 (16.12.2015)

(25) Filing Language:

English

(26) Publication Language:

English

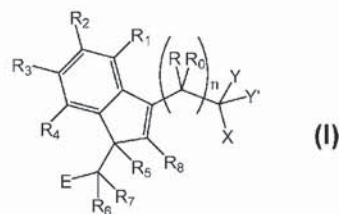
(30) Priority Data:

14/571,647 16 December 2014 (16.12.2014) US

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(US).(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY,
BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM,
DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR,
KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG,
MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM,

[Continued on next page]

(54) Title: INDENYL COMPOUNDS, PHARMACEUTICAL COMPOSITIONS, AND MEDICAL USES THEREOF





PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE,

Published:

— with international search report (Art. 21(3))

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 722083	FOR FURTHER ACTION		See Form PCT/IPEA/416
International application No. PCTUS2015/066146	International filing date (<i>day/month/year</i>) 16.12.2015	Priority date (<i>day/month/year</i>) 16.12.2014	
International Patent Classification (IPC) or national classification and IPC INV. C07D207/14			
Applicant ADT Pharmaceuticals, Inc.			
1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of <u>4</u> sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. ☒ (<i>sent to the applicant and to the International Bureau</i>) a total of <u>14</u> sheets, as follows: ☒ sheets of the description, claims and/or drawings which have been amended and/or sheets containing rectifications authorized by this Authority, unless those sheets were superseded or cancelled, and any accompanying letters (see Rules 46.5, 66.8, 70.16, 91.2, and Section 607 of the Administrative Instructions). ☐ sheets containing rectifications, where the decision was made by this Authority not to take them into account because they were not authorized by or notified to this Authority at the time when this Authority began to draw up this report, and any accompanying letters (Rules 66.4bis, 70.2(e), 70.16 and 91.2). ☐ superseded sheets and any accompanying letters, where this Authority either considers that the superseding sheets contain an amendment that goes beyond the disclosure in the international application as filed, or the superseding sheets were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in item 4 of Box No. I and the Supplemental Box (see Rule 70.16(b)). b. ☐ (<i>sent to the International Bureau only</i>) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing, in the form of an Annex C/ST.25 text file, as indicated in the Supplemental Box Relating to Sequence Listing (see paragraph 3ter of Annex C of the Administrative Instructions).			
4. This report contains indications relating to the following items: ☒ Box No. I Basis of the report ☐ Box No. II Priority ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability ☐ Box No. IV Lack of unity of invention ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement ☐ Box No. VI Certain documents cited ☐ Box No. VII Certain defects in the international application ☐ Box No. VIII Certain observations on the international application			
Date of submission of the demand 27.07.2016		Date of completion of this report 06.04.2017	
Name and mailing address of the international preliminary examining authority:  European Patent Office Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840		Authorized officer Hoepfner, Wolfgang Telephone No. +49 30 25901-337	



**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/US2015/066146

Box No. I Basis of the report

1. With regard to the **language**, this report is based on
- ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
 - ☐ international search (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a) and (b))
2. With regard to the **elements*** of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

Description, Pages

1-142 as originally filed

Claims, Numbers

1-17 filed in electronic form on

09-12-2016

Drawings, Sheets

1/18-18/18 as originally filed

- ☐ a sequence listing - see Supplemental Box Relating to Sequence Listing.
3. ☒ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☒ the claims, Nos. 18-37
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since either they are considered to go beyond the disclosure as filed, or they were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in the Supplemental Box (Rules 70.2(c) and (c-bis)):
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
5. ☐ This report has been established:
- ☐ taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rules 66.1(d-bis) and 70.2(e)).
 - ☐ without taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91(Rules 66.4bis and 70.2(e)).

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/US2015/066146

6. ☒ With regard to top-up searches (Rules 66.1 *ter* and 70.2(f)):
- ☒ A top-up search was carried out by this Authority on 10.03.2017 (all discovered documents are listed in the Supplemental Box Relating to Top-up Search).
 - ☐ Additional relevant documents have been discovered during the top-up search.
 - ☐ No top-up search was carried out by this Authority because it would serve no useful purpose.
7. ☐ Supplementary international search report(s) from Authority(ies) has/have been received and taken into account in establishing this report (Rule 45bis.8(b) and (c)).

* If item 4 applies, some or all of those sheets may be marked "superseded".

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-17</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-17</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-17</u>
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Reference is made to the following document:

D1 WO 97/47303 A1 (CELL PATHWAYS INC [US]; UNIV ARIZONA [US])
 18 December 1997 (1997-12-18) cited in the application

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Novelty

The document D1 generically discloses N-heterocyclyl(alkyl) derivatives of benzylidene indenyl formamides which are useful for the treatment of cancer, and from which the compounds of claim 1 *inter alia* structurally differ in the particular novel selection of variable R' (see page 1, lines 2, 3; page 5, lines 5-19; page 6, Formula I; page 8, line 20 - page 9, line 2; page 9, line 8 - page 10, line 15; Examples; pages 47-54; claims 27, 38).

Consequently, the subject-matter of independent claims 1, 10, 12 and 16 and dependent claims 2-9, 11, 13-15 and 17 is deemed novel by this Authority.

Inventive step

The *subjective* problem underlying the said novel subject-matter may be regarded as the provision of compounds which are useful for prevention or treatment of cancer (see description, page 6).

One primary distinguishing feature between such novel subject-matter and document D1 which addresses the same technical problem (see D1, page 1) may be seen as the particular novel selection of variable R'.

Since it is not possible to decide by direct comparison of the available experimental data (see description, pages 131-140; D1, pages 47-45), if this feature gives rise to technical advantages compared to D1, the *objective* problem underlying the novel subject-matter can merely be regarded as the provision of *further* compounds which are useful for prevention or treatment of cancer.

The claimed solution to this very general problem was the particular novel selection of variable R' from the generic disclosure of D1.

However, since this selection was not derivable from the prior art; and since it may be deemed surprising that of all things the novel compounds of claim 1 would likewise give rise to anti-cancer medicaments; the presence of inventive step for the novel subject-matter can be acknowledged by this Authority, even in the absence of comprehensible technical progress.

IN THE IPEA/EP

International application No. PCT/US2015/066146	International filing date (day/month/year) 16 December 2015	(Earliest) Priority date (day/month/year) 16 December 2014
Title of invention INDENYL COMPOUNDS, PHARMACEUTICAL COMPOSITIONS, AND MEDICAL USES THEREOF		
Applicant ADT PHARMACEUTICALS, INC.		

RESPONSE TO THE SECOND WRITTEN OPINION

ISA
European Patent Office
Gitschiner Str. 103
D-10958
Berlin, Germany

Dear Examiner Hoepfner,

In response to the Written Opinion dated November 9, 2016 ("the second Written Opinion"), please replace pages 143-171 of the application as originally filed with substitute sheet(s) numbered 143-154 provided herewith. Please also consider the following remarks.

Examiner's Telephone Call and Request for Consultation

Applicant wishes to thank Examiner Dr. Hoepfner for the voicemail he left for the undersigned on October 27, 2016. The voicemail indicated that Applicant will have opportunity to submit further response and that the Examiner would be willing to discuss any proposed amendment on the telephone.

To expedite the issuance of a positive IPRP, Applicant hereby requests a telephone consultation with the Examiner. In particular, Applicant invites the Examiner to contact the undersigned attorney to discuss possible interview dates and times, noting that the undersigned is located in the United States Central Standard Time zone.

Substitute Sheet(s)

The substitute sheets incorporate changes to the claims. The abstract has been resubmitted merely to indicate the new page number.

Also provided herewith are substitute sheets showing changes to the claims. Deletions are indicated by strikethrough text, whereas insertions are indicated by underlined text.

In the original claims, the following changes have been made. Original claims 1-37 are being replaced with amended claims 1-17. Thus, original claims 1-8, 10-14, and 25-31 have been cancelled without prejudice. Original claim 9 has been rewritten as an independent claim including the description of X from original claim 14 which depended ultimately upon original claim 9. The inadvertent duplicate entry of "alkylcarbonyloxy" in the description of R₁, R₂, R₃, R₄, R₁₂, R₁₃, R₁₄, R₁₅ and R₁₆ has been deleted from claim 9. Original claim 9 also has been amended to include the proviso that "when R and R₀ are hydrogens, at least one of R₁, R₂, R₃, and R₄ is halogen, Y and Y' together is double-bonded oxygen, and R' is furanylalkyl, then R₁₃-R₁₅ are not each methoxy" as supported by the original disclosure, e.g., at paragraphs [0200] and [0210]-[0211]. Original claim 9 also has been amended to delete the reference to prodrug. Amended claims 5-7 are supported by the original disclosure, e.g. at [0215]-[0217]. Original dependent claims 15-24 and 33-37 (amended claims 2-11 and 13-17) have been amended consistent with the amendments made to original claim 9. No new matter has been added by way of these amendments.

The Written Opinion

The second Written Opinion indicated that claims 1 and 6 as filed on July 27, 2016 extended beyond the disclosure as filed and therefore did not address these claims for novelty and inventive step. The second Written Opinion indicated that claims 1 and 6 as filed on July 27, 2016 included formula I' which allegedly constituted new matter.

In view of the foregoing, the second Written Opinion addressed claims 1 and 6 as originally filed and claims 2-5 and 7-17 as filed on July 27, 2016. The second Written Opinion raises the following concern: D1 (i.e., WO 97/47303 A1) allegedly discloses, or renders obvious, the subject matter of addressed claims 1-5 and 7-17.

Discussion of Objections

The second Written Opinion states that the subject matter of independent claims 1 and 6 overlaps with the subject matter of D1 in case variable R' has the meaning "piperidinyl", "piperazinyl", and "pyrrolidinyl," thereby defeating the novelty of these claims.

The second Written Opinion also states that a primary distinguishing feature between what is novel in the present application and the disclosure of D1 may be a possible selection of heterocyclic residues R' from the generic disclosure of D1. The second Written Opinion further states that an objective problem underlying the novel subject matter of the present application is the provision of further compounds which as useful for the prevention or treatment of cancer. The second Written Opinion also states that inventive step could be acknowledged for a set of claims including novel subject matter where R' is "furylmethyl," inasmuch as clear preference is given to "benzyl" in D1.

Applicant has now amended the claims to recite only novel subject matter. Applicant also submits that the claims have been amended such that the subject matter of the amended claims is inventive over D1. As acknowledged by the second Written Opinion, the subject matter where R' is "furylmethyl" is inventive. Please note that the terms "furfuryl" and "furan-2-ylmethyl" used in the present claims mean the same group as "furylmethyl" mentioned in the second Written Opinion. Applicant submits that the subject matter of the present claims where R' is (1H-pyrrol-2-yl)methyl or (1-methyl-1H-pyrrol-2-yl)methyl is also inventive inasmuch as there is no suggestion to employ such groups as R' in D1.

In view of the foregoing, it is submitted that the novelty and inventive step objections set forth in the second Written Opinion have been addressed.

Conclusion

In view of the above amendments and remarks, the application is considered to be in good and proper form, and the Examiner is respectfully requested to indicate the acceptability of the present application in the International Preliminary Report on Patentability.

Respectfully submitted,

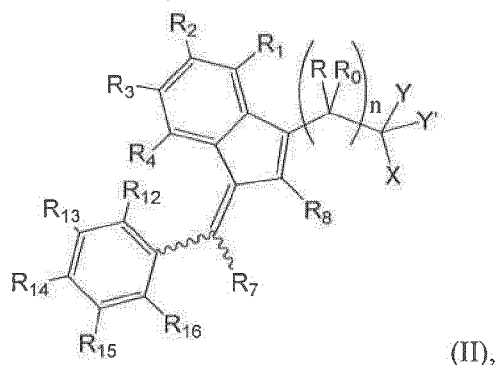
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Date: December 9, 2016

CLAIMS:

1. A compound of formula (II):



wherein:

R and R₀ are independently selected from hydrogen, hydroxyl, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, alkenyl, alkenylalkyl, alkynyl, alkynylalkyl, cyano, cyanoalkyl, halogen, azido, alkoxy, haloalkyl and a substituted or unsubstituted group selected from aminocarbonyl, aminocarbonylalkyl, aminosulfonyl, aminosulfonylalkyl, alkylcarbonyl, alkylcarbonylalkyl, amino, alkylamino, dialkylamino, aminocarbonylalkylamino, and carbocyclylamino, carbocyclylalkylamino, heterocyclylamino and heterocyclylalkylamino wherein the ring structures are saturated or unsaturated; or R and R₀ together is double-bonded oxygen or double-bonded sulfur, or R and R₀ together is a double-bonded nitrogen bonded to one of hydrogen, hydroxyl, alkyl, or haloalkyl, or R and R₀ together is a double-bonded carbon bonded to two substituents independently selected from hydrogen, hydroxyl, alkyl and haloalkyl, or R₀ is nitrogen which is part of a substituted or unsubstituted, saturated or unsaturated, 3-, 4-, 5-, 6- or 7- membered heterocyclic ring; or R and R₀ together is a substituted or unsubstituted, saturated or unsaturated 3-, 4-, 5-, 6- or 7- membered heterocyclic ring;

n is 0, 1 or 2;

Y is hydrogen, alkyl, or haloalkyl, and Y' is hydrogen, alkyl, haloalkyl, amino, alkylamino, or alkoxy, or Y and Y' together is double-bonded oxygen or double-bonded

sulfur, or Y and Y' together is a double-bonded nitrogen bonded to hydrogen, hydroxyl, alkyl, or haloalkyl;

R₁, R₂, R₃, R₄, R₁₂, R₁₃, R₁₄, R₁₅ and R₁₆ are independently selected from hydrogen, halogen, alkyl, cycloalkyl, haloalkyl, hydroxyl, carboxyl, alkoxy, formyloxy, alkylcarbonyloxy, hydroxyalkyl, aldehydo, amino, aminoalkyl, alkylaminoalkyl, dialkylamino, mercapto, alkylmercapto, cyano, cyanoalkyl, nitro, azido, and substituted or unsubstituted groups selected from alkylsulfinyloxy, alkylsulfonyloxy, carbamate, carbamido, alkoxycarbonyl, alkylaminocarbonyl, aminocarbonyl, alkylcarbonyloxyalkyloxy, aminocarbonyloxyalkyloxy, arylcarbonyloxy, arylalkylcarbonyloxy, aryloxycarbonyloxy, heterocyclylcarbonyloxy, heterocyclylalkylcarbonyloxy, phosphonooxy, phosphonoalkyloxy, and sulfonamido, or any two of R₁₂, R₁₃, R₁₄, R₁₅ and R₁₆ form an alkylenedioxy group;

R₇ and R₈ are independently selected from hydrogen, alkyl, haloalkyl, and alkoxy;

X is NR'R'' where R' is selected from 2-furfuryl, (1H-pyrrol-2-yl)methyl, and (1-methyl-1H-pyrrol-2-yl)methyl; and R'' is hydrogen;

a pharmaceutically acceptable salt thereof;

with the proviso that when R and R₀ are hydrogens, at least one of R₁, R₂, R₃, and R₄ is halogen, Y and Y' together is double-bonded oxygen, and R' is furanylalkyl, then R₁₃-R₁₅ are not each methoxy.

2. The compound or salt of claim 1, wherein R and R₀ are independently selected from hydrogen and hydroxyl, and R₁, R₂, R₃ and R₄ are independently selected from halogen, alkoxy, alkyl and haloalkyl; n is 1; R₁₂, R₁₃, R₁₄, R₁₅ and R₁₆ are independently selected from hydrogen, halogen, alkyl, haloalkyl, hydroxyl, alkoxy, formyloxy, alkylcarbonyloxy, hydroxyalkyl, aldehydo, amino, alkylamino, aminoalkyl, alkylaminoalkyl, dialkylamino, mercapto, azido, and substituted or unsubstituted groups selected from alkylsulfinyloxy, alkylsulfonyloxy, carbamate, carbamido, and sulfonamido, or any two of R₁₂, R₁₃, R₁₄, R₁₅ and R₁₆ form an alkylenedioxy group.

3. The compound or salt of claim 2, wherein R₁, R₂, R₃ and R₄ are independently selected from halogen, alkoxy, alkyl and haloalkyl; three of R₁₂, R₁₃, R₁₄, R₁₅ and R₁₆ are independently selected from hydrogen, halogen, alkyl, haloalkyl, hydroxyl, alkoxy, formyloxy, alkylcarbonyloxy, hydroxyalkyl, aldehydo, amino, alkylamino, aminoalkyl, alkylaminoalkyl, dialkylamino, mercapto, azido, and substituted or unsubstituted groups

selected from alkylsulfinyloxy, alkylsulfonyloxy, carbamate, carbamido, and sulfonamido, and one of R₁₂, R₁₃, R₁₄, R₁₅ and R₁₆ is independently selected from hydroxyl, hydroxyalkyl, amino, alkylamino, dialkylamino, and mercapto.

4. The compound or salt of claim 3, wherein three of R₁₂, R₁₃, R₁₄, R₁₅ and R₁₆ are independently selected from halogen, alkyl, haloalkyl, alkoxy, amino, alkylamino, aminoalkyl, alkylaminoalkyl, dialkylamino, and mercapto, and one of R₁₂, R₁₃, R₁₄, R₁₅ and R₁₆ is independently selected from hydroxyl, hydroxyalkyl, aldehyde, amino, alkylamino, dialkylamino, and mercapto; and R₈ is methyl.

5. The compound or salt of claim 4, wherein R₂ is selected from halogen, alkoxy and alkylmercapto, R₁ and R₃ are hydrogen; and three of R₁₂, R₁₃, R₁₄, R₁₅ and R₁₆ are independently selected from hydrogen, halogen, alkyl, haloalkyl, alkoxy, alkylamino, alkylaminoalkyl, and dialkylamino, and one of R₁₂, R₁₃, R₁₄, R₁₅ and R₁₆ is independently selected from hydroxyl, hydroxyalkyl, amino, alkylamino, dialkylamino, and mercapto.

6. The compound or salt of claim 5, wherein R₂ is selected from halogen and alkoxy, and R₁ and R₃ are hydrogen.

7. The compound or salt of claim 6, wherein R₂ is selected from fluoro and methoxy.

8. The compound of claim 1, which is selected from:

(Z)-N-(furan-2-ylmethyl)-2-(1-(4-hydroxy-3,5-dimethylbenzylidene)-5-methoxy-2-methyl-1H-inden-3-yl)acetamide (001),

(Z)-2-(5-fluoro-1-(4-formoxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)acetamide (002),

(Z)-N-(furan-2-ylmethyl)-2-(1-(4-hydroxy-3,5-dimethoxybenzylidene)-5-methoxy-2-methyl-1H-inden-3-yl)acetamide (006),

(Z)-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)acetamide (007),

(Z)-N-(furan-2-ylmethyl)-2-(1-(4-hydroxy-3,5-dimethoxybenzylidene)-5,6-dimethoxy-2-methyl-1H-inden-3-yl)acetamide (**008**),

(Z)-N-(furan-2-ylmethyl)-2-(1-(4-hydroxy-3-methoxybenzylidene)-5-methoxy-2-methyl-1H-inden-3-yl)acetamide (**012**),

(Z)-2-(1-(3-bromo-4-hydroxy-5-methoxybenzylidene)-5-methoxy-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)acetamide (**013**),

(Z)-2-(1-(3-chloro-4-hydroxy-5-methoxybenzylidene)-5-methoxy-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)acetamide (**014**),

(Z)-2-(1-(3-fluoro-4-hydroxy-5-methoxybenzylidene)-5-methoxy-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)acetamide (**016**),

(Z)-2-(5-fluoro-1-((7-hydroxybenzo[d][1,3]dioxol-5-yl)methylene)-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)acetamide (**017**),

(Z)-N-((1H-pyrrol-2-yl)methyl)-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)acetamide (**018**),

(Z)-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-((1-methyl-1H-pyrrol-2-yl)methyl)acetamide (**019**),

(Z)-N-(furan-2-ylmethyl)-2-(1-(3-hydroxy-4-methoxybenzylidene)-5-methoxy-2-methyl-1H-inden-3-yl)acetamide (**020**),

(Z)-2-(5-fluoro-1-(4-(hydroxymethyl)-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)acetamide (**021**),

(Z)-N-((1H-pyrrol-2-yl)methyl)-2-(1-(4-hydroxy-3,5-dimethoxybenzylidene)-5-methoxy-2-methyl-1H-inden-3-yl)acetamide (**022**),

(Z)-2-(5-fluoro-1-(4-mesyloxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)acetamide (**029**),

(Z)-2-(5-methoxy-2-methyl-1-(3,4,5-trimethoxybenzylidene)-1H-inden-3-yl)-N-(1-methylpyrrolidin-3-yl)acetamide (**030**), (Z)-2-(5-fluoro-2-methyl-1-(3,4,5-trimethoxybenzylidene)-1H-inden-3-yl)-N-(1-methylpyrrolidin-3-yl)acetamide (**031**),

(Z)-2-(1-(4-aminocarbonyl-3,5-dimethoxybenzylidene)-5-fluoro-2-methyl-1H-inden-3-yl)-N-((1-methyl-1H-pyrrol-2-yl)methyl)acetamide (**065**),

(Z)-4-((5-fluoro-3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl (2-(dimethylamino)ethyl)carbamate (**099**),

(Z)-2-(5-fluoro-1-(4-mercapto-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-((1-methyl-1H-pyrrol-2-yl)methyl)acetamide (**100**),

(Z)-2-(1-((6-(dimethylamino)pyridin-3-yl)methylene)-5-methoxy-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)acetamide (**130**),

(Z)-2-(1-((2-(dimethylamino)pyrimidin-5-yl)methylene)-5-methoxy-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)acetamide (**131**),

(Z)-N-(furan-2-ylmethyl)-2-(5-methoxy-2-methyl-1-(3,4,5-trimethoxybenzylidene)-1H-inden-3-yl)-N-methylacetamide (**135**),

(Z)-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)-N-(trifluoromethyl)acetamide (**152**),

(Z)-2-(5-cyano-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)acetamide (**154**),

(Z)-N-(furan-2-ylmethyl)-2-(1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-5-(trifluoromethyl)-1H-inden-3-yl)acetamide (**155**),

(Z)-4-((5-fluoro-3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl benzoate (**214**),

(Z)-4-((3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-5-methoxy-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl (4-nitrophenyl) carbonate (**300**),

(Z)-4-((3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-5-methoxy-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl benzoate (301),

(Z)-4-((3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-5-methoxy-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl nicotinate (302),

(Z)-4-((3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-5-methoxy-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl (2-(dimethylamino)ethyl)carbamate (303),

(Z)-4-((3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-5-methoxy-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl morpholine-4-carboxylate (304),

(Z)-4-((3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-5-methoxy-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl (1-methylpiperidin-4-yl)carbamate (305),

(Z)-4-((3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-5-methoxy-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl 4-methylpiperazine-1-carboxylate (306),

(Z)-4-((3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-5-methoxy-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl 4-(1-methylpiperidin-4-yl)piperazine-1-carboxylate (307),

(Z)-4-((3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-5-methoxy-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl dihydrogen phosphate (308),

(Z)-4-((3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-5-methoxy-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenoxy)methyl dihydrogen phosphate (309),

(Z)-4-((5-fluoro-3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl nicotinate (311),

(Z)-4-((5-fluoro-3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl (4-nitrophenyl) carbonate (312),

(Z)-4-((5-fluoro-3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl (2-(dimethylamino)ethyl)carbamate (313),

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(Z)-4-((5-fluoro-3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl morpholine-4-carboxylate (314),

(Z)-4-((5-fluoro-3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl (1-methylpiperidin-4-yl)carbamate (315),

(Z)-4-((5-fluoro-3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl 4-methylpiperazine-1-carboxylate (316),

(Z)-4-((5-fluoro-3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl 4-(1-methylpiperidin-4-yl)piperazine-1-carboxylate (317),

(Z)-4-((5-fluoro-3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl dihydrogen phosphate (318),

(Z)-4-((5-fluoro-3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenoxy)methyl dihydrogen phosphate (319),

(Z)-4-((5-fluoro-2-methyl-3-(2-(((1-methyl-1H-pyrrol-2-yl)methyl)amino)-2-oxoethyl)-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl benzoate (340),

(Z)-4-((5-fluoro-2-methyl-3-(2-(((1-methyl-1H-pyrrol-2-yl)methyl)amino)-2-oxoethyl)-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl nicotinate (341),

(Z)-4-((5-fluoro-2-methyl-3-(2-(((1-methyl-1H-pyrrol-2-yl)methyl)amino)-2-oxoethyl)-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl (4-nitrophenyl) carbonate (342),

(Z)-4-((5-fluoro-2-methyl-3-(2-(((1-methyl-1H-pyrrol-2-yl)methyl)amino)-2-oxoethyl)-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl (2-(dimethylamino)ethyl)carbamate (343),

(Z)-4-((5-fluoro-2-methyl-3-(2-(((1-methyl-1H-pyrrol-2-yl)methyl)amino)-2-oxoethyl)-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl morpholine-4-carboxylate (344),

(Z)-4-((5-fluoro-2-methyl-3-(2-(((1-methyl-1H-pyrrol-2-yl)methyl)amino)-2-oxoethyl)-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl (1-methylpiperidin-4-yl)carbamate **(345)**,

(Z)-4-((5-fluoro-2-methyl-3-(2-(((1-methyl-1H-pyrrol-2-yl)methyl)amino)-2-oxoethyl)-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl 4-methylpiperazine-1-carboxylate **(346)**,

(Z)-4-((5-fluoro-2-methyl-3-(2-(((1-methyl-1H-pyrrol-2-yl)methyl)amino)-2-oxoethyl)-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl 4-(1-methylpiperidin-4-yl)piperazine-1-carboxylate **(347)**,

(Z)-4-((5-fluoro-2-methyl-3-(2-(((1-methyl-1H-pyrrol-2-yl)methyl)amino)-2-oxoethyl)-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl dihydrogen phosphate **(348)**,

(Z)-4-((5-fluoro-2-methyl-3-(2-(((1-methyl-1H-pyrrol-2-yl)methyl)amino)-2-oxoethyl)-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenoxy)methyl dihydrogen phosphate **(349)**,

(Z)-2-(benzylamino)-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)acetamide **(202)**,

(Z)-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)-2-((pyridin-4-ylmethyl)amino)acetamide **(203)**,

(Z)-N-(furan-2-ylmethyl)-2-(1-(4-hydroxy-3,5-dimethoxybenzylidene)-5-methoxy-2-methyl-1H-inden-3-yl)-2-(1H-imidazol-1-yl)acetamide **(401)**,

(Z)-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-2-((furan-2-ylmethyl)amino)acetamide **(404)**,

(Z)-2-(cyclopropylamino)-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)acetamide **(410)**,

(Z)-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-((1-methyl-1H-pyrrol-2-yl)methyl)-2-(pyrrolidin-1-yl)acetamide **(412)**,

(Z)-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-((1-methyl-1H-pyrrol-2-yl)methyl)-2-((pyridin-3-ylmethyl)amino)acetamide (**413**),

(Z)-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)-2-((1-methylpyrrolidin-3-yl)amino)acetamide (**430**),

(Z)-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)-2-((oxazol-2-ylmethyl)amino)acetamide (**431**),

(Z)-2-cyano-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-((1-methyl-1H-pyrrol-2-yl)methyl)acetamide (**436**),

or the corresponding Z- or E-isomer or salt thereof.

9. The compound, Z- or E-isomer, or salt of claim 8, wherein the compound is selected from:

(Z)-2-(5-fluoro-1-(4-formoxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)acetamide (**002**),

(Z)-N-(furan-2-ylmethyl)-2-(1-(4-hydroxy-3,5-dimethoxybenzylidene)-5-methoxy-2-methyl-1H-inden-3-yl)acetamide (**006**),

(Z)-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)acetamide (**007**),

(Z)-N-((1H-pyrrol-2-yl)methyl)-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)acetamide (**018**),

(Z)-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-((1-methyl-1H-pyrrol-2-yl)methyl)acetamide (**019**),

(Z)-N-((1H-pyrrol-2-yl)methyl)-2-(1-(4-hydroxy-3,5-dimethoxybenzylidene)-5-methoxy-2-methyl-1H-inden-3-yl)acetamide (**022**),

(Z)-2-(5-fluoro-1-(4-mesyloxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)acetamide (**029**),

(Z)-4-((3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-5-methoxy-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl benzoate (**301**),

(Z)-4-((5-fluoro-3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl nicotinate (**311**),

(Z)-4-((5-fluoro-3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl dihydrogen phosphate (**318**), and

(Z)-4-((5-fluoro-2-methyl-3-(2-(((1-methyl-1H-pyrrol-2-yl)methyl)amino)-2-oxoethyl)-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl (2-(dimethylamino)ethyl)carbamate (**343**).

10. A pharmaceutical composition comprising a compound or salt of any one of claims 1-9 and a pharmaceutically acceptable carrier.

11. The pharmaceutical composition of claim 10, further including at least one therapeutic agent which is not a compound of formula II, or a pharmaceutically acceptable salt thereof.

12. A compound or salt of any one of claims 1-9, or the pharmaceutical composition of claim 10 or 11, for use in the treatment or prophylaxis of a human or nonhuman mammalian patient with cancer.

13. The compound or salt thereof or the pharmaceutical composition for use according to claim 12, wherein the cancer is selected from pancreatic cancer, lung cancer, colorectal cancer, melanoma, ovarian cancer, renal cancer, prostate cancer, head and neck cancer, endocrine cancer, uterine cancer, breast cancer, sarcoma cancer, gastric cancer, hepatic cancer, esophageal cancer, central nervous system cancer, brain cancer, hepatic cancer, germline cancer, lymphoma, and leukemia.

14. The compound or salt for use according to claim 13, wherein the cancer is selected from pancreatic cancer, colorectal cancer, and lung cancer.

15. The compound or salt for use according to any one of claims 12-14, wherein the cancer is drug-resistant or radiation-resistant.

16. A compound of any one of claims 1-9 or a compound selected from (001), (002), (006)-(008), (012)-(014), (016)-(022), (029), (065), (095), (099), (100), (130), (131), (135), (152), (154), (155), (214), (300)-(309), (311)-(319), (340)-(349), (202), (203), (401), (410), (412), (413), (430), (431), and (436), or a pharmaceutically acceptable salt thereof, for use in the treatment or prophylaxis of a disease or condition treatable by the inhibition of one or more neoplastic or cancerous process in a human or nonhuman mammalian patient, either alone or in combination with at least one therapeutic agent which is not a compound of any one of claims 1-9 or a compound selected from (001), (002), (006)-(008), (012)-(014), (016)-(022), (029), (065), (095), (099), (100), (130), (131), (135), (152), (154), (155), (214), (300)-(309), (311)-(319), (340)-(349), (202), (203), (401), (410), (412), (413), (430), (431), and (436), or a pharmaceutically acceptable salt thereof.

17. The compound or salt for use according to claim 16, wherein the neoplastic or cancerous process is selected from growth, proliferation, survival, metastasis, drug resistance and radiation resistance of a tumor cell.