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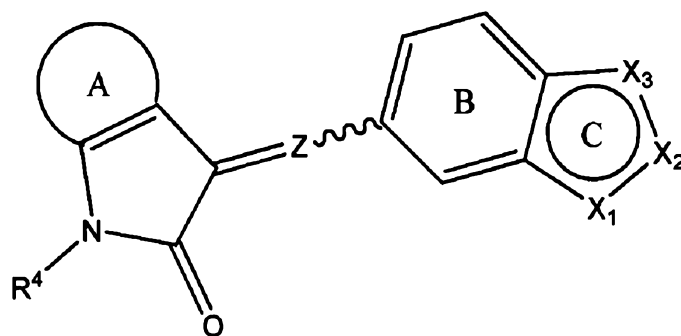
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(54) **Title:** INDAZOLYL, BENZIMIDAZOLYL, BENZOTRIAZOLYL SUBSTITUTED INDOLINONE DERIVATIVES AS KINASE INHIBITORS USEFUL IN THE TREATMENT OF CANCER



(A),

(57) **Abstract:** The present invention is directed to a compound is represented by Structural Formula (A): or a pharmaceutically acceptable salt thereof. The present invention is also directed to a pharmaceutical composition comprising a compound represented by Structural Formula (A) described above or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent. Also disclosed is a method of treating a subject having cancer, wherein the method comprises administering a therapeutically effective amount of a compound represented by Structural Formula (A) described above or a pharmaceutically acceptable salt thereof.

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KINASE INHIBITORS AND METHOD OF TREATING CANCER WITH SAME

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Serial
5 No. 61/131,717, filed June 11, 2008 and U.S. Provisional Application No.
61/008,865, filed December 21, 2007. The entire teachings of these two applications
are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Protein kinases have been the subject of extensive study in the search for
10 new therapeutic agents in various diseases, for example, cancer. Protein kinases are
known to mediate intracellular signal transduction by effecting a phosphoryl transfer
from a nucleoside triphosphate to a protein acceptor that is involved in a signaling
pathway. There are a number of kinases and pathways through which extracellular
and other stimuli cause a variety of cellular responses to occur inside the cell.

15 The polo-like kinase (PLK) family of serine/threonine kinases comprises at
least four known members: PLK1, PLK2 (also known as Snk), PLK3 (also known as
Fnk or Prk) and PLK4 (also known as Sak). PLK4 is the least understood and most
divergent member of the PLK family. The N-terminal catalytic domain of PLK4 has
a different substrate specificity from that of PLK1-3. PLK4 also has a divergent C-
20 terminus comprising only a single polo-box sequence, not the tandem PB sequences
in PLK1-3, that appears to act as a homodimerization domain rather than a
localization domain (Lowery *et al.*, (2005) *Oncogene* 24: 248-259).

PLK4 is known to be involved in the control of mitotic entry and exit, and a
regulator of centrosome duplication (Habedanck *et al.* *Nature Cell Biology* 7: 1140-
25 1146, 2005). PLK4 transcripts increase from S through M phase, and the protein is
ubiquitylated and destroyed by the anaphase promoting complex (APC) (Hudson *et al.* *Curr. Biol.* 11: 441-446, 2001; Fode *et al.* *Mol. Cell. Biol.* 16: 4665-4672,
1996). PLK4 is required for late mitotic progression (Fode *et al.* *PNAS.* 91: 6388-
6392, 1994; Hudson *et al.* *Curr. Biol.* 11: 441-446, 2001), cell survival and
30 postgastrulation embryonic development (Hudson *et al.* *Curr. Biol.* 11: 441-446,
2001). PLK4 knockout mice are embryonic lethal (E7.5), with a marked increase in
mitotic and apoptotic cells (Hudson *et al.* *Curr. Biol.* 11: 441-446, 2001). PLK4 is

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transcriptionally repressed by p53 (Li *et al.* Neoplasia 7: 312-323, 2005). This repression is likely mediated through the recruitment of histone deacetylase (HDAC) repressors and repression appears to contribute to p53-induced apoptosis (Li *et al.* Neoplasia 7: 312-323, 2005).

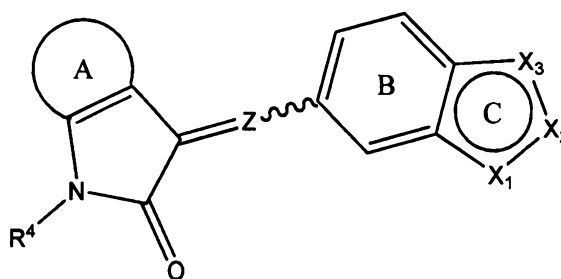
5 PLK4 has been reported to be overexpressed in colorectal tumors with expression reported as low in adjacent normal intestinal mucosa (Macmillian *et al.* Ann. Surg. Oncol. 8: 729-740, 2001). In addition, PLK4 mRNA has been reported to be overexpressed in some tumor cell lines (Hitoshi, *et al.*, U.S. Patent Application No. US 2003/0027756). In addition, Applicants described overexpression of PLK4
10 in basal-like tumors in a co-pending U.S. Provisional Application No. 61,003,825, filed on November 20, 2007 (the entire teachings of which are incorporated herein by reference).

Therefore, agents which inhibit a protein kinase, in particular PLK4, have the potential to treat cancer. There is a need for additional agents which can act as
15 protein kinase inhibitors, in particular PLK4 inhibitors.

SUMMARY OF THE INVENTION

Applicants have now discovered that certain indolinone compounds are potent kinase inhibitors, such as polo-like kinases (PLK) (*see* Example B). Applicants have also now discovered that these indolinone compounds have potent
20 anticancer activity (*see* Example C). Based on these discoveries, indolinone compounds, pharmaceutical compositions thereof, and methods of treating cancer with the indolinone compounds are disclosed herein.

In one embodiment, the present invention is directed to a compound represented by Structural Formula (A):



25

(A),

or a pharmaceutically acceptable salt thereof.

Ring A is an optionally substituted 5- or 6-membered aromatic ring.

Ring B is an optionally substituted phenyl ring.

Ring C is a 5-membered heteroaromatic ring wherein one of X1-X3 is N, one of X1-X3 is NR⁵, and one of X1-X3 is N or CR⁶.

Z is =N- or =CR³-.

5 R³ is -H, halogen, C1-C6 alkyl or C1-C6 haloalkyl.

each of R⁴ and R⁵ independently is -H, C1-C6 alkyl, phenyl, -C(O)(C1-C6 alkyl), -C(O)(phenyl), -C(O)O(C1-C6 alkyl), -C(O)O(phenyl), -S(O)₂(C1-C6 alkyl) or -S(O)₂(phenyl), wherein each said alkyl in the groups represented by R⁴ and R⁵ independently is optionally substituted with one or more substituents selected from
10 the group consisting of halogen, hydroxy, nitro, cyano, amino, phenyl, 5-6 membered heteroaryl, C1-C6 alkoxy and C1-C6 haloalkoxy, and wherein each said phenyl in the groups represented by R⁴ and R⁵ independently is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 alkoxy
15 and C1-C6 haloalkoxy.

R⁶ is hydrogen, halogen, nitro, cyano, R', -OR, -SR, -N(R)₂, -C(O)R, -C(O)OR, -OC(O)R, -C(O)N(R)₂, -OC(O)N(R)₂, -NRC(O)R, -NRC(O)OR, -SOR', -SO₂R', -SO₃R', -SO₂N(R)₂, -NRS(O)R', -NRSO₂R', -NRC(O)N(R)₂, -NRC(O)ON(R)₂, or -NRSO₂N(R)₂.

20 each R independently is hydrogen, C₁₋₁₀ aliphatic, phenyl or 5-6 membered heteroaryl, wherein said aliphatic is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, phenyl, 5-6 membered heteroaryl, C1-C6 alkoxy, C1-C6 haloalkoxy, and wherein each of the phenyl and heteroaryl groups represented by R, and the phenyl
25 and heteroaryl groups in the substituents for the aliphatic group represented by R independently is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 alkoxy, C1-C6 haloalkoxy, or

N(R)₂ forms a non-aromatic heterocyclic group optionally substituted with
30 one or more substituents selected from the group consisting of =O, =S, halogen, nitro, cyano, hydroxy, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, amino, C₁₋₆ alkylamino, C₁₋₆ dialkylamino, C₁₋₆ aminoalkyl, (C₁₋₆ alkylamino)C₁₋₆ alkyl, (C₁₋₆

dialkylamino)C₁₋₆ alkyl, (phenyl)C₁₋₆ alkyl, (5-6 membered heteroaryl)C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₆ alkylcarbonyloxy, C₁₋₆ alkoxycarbonyl, C₁₋₆ alkylcarbonyl, phenyl and 5-6 membered heteroaryl.

each R' independently is C₁₋₁₀ aliphatic, phenyl or 5-14 membered heteroaryl,
5 wherein said aliphatic is optionally substituted with one or more substituents
selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, phenyl,
5-6 membered heteroaryl, C1-C6 alkoxy, C1-C6 haloalkoxy, C₁₋₆ dialkylamino, C₁₋₆
dialkylamino, -C(O)(C1-C6 alkyl), -C(O)(C1-C6 haloalkyl), -C(O)(phenyl),
-C(O)(non-aromatic heterocyclic group), -C(O)O(C1-C6 alkyl), -C(O)O(C1-C6
10 haloalkyl), -C(O)O(phenyl), -OC(O)(C1-C6 alkyl), -OC(O)(C1-C6 haloalkyl),
-OC(O)(phenyl), -S(O)₂(C1-C6 alkyl), -S(O)₂(C1-C6 haloalkyl) and -S(O)₂(phenyl),
and wherein each of the phenyl and heteroaryl groups represented by R', and the
phenyl and heteroaryl groups in the substituents for the aliphatic group represented
by R' independently is optionally substituted with one or more substituents selected
15 from the group consisting of halogen, hydroxy, nitro, cyano, amino, C1-C6 alkyl,
C1-C6 haloalkyl, C1-C6 alkoxy, C1-C6 haloalkoxy, non-aromatic heterocyclic
group, C₁₋₆ dialkylamino, C₁₋₆ dialkylamino, -C(O)(C1-C6 alkyl), -C(O)(C1-C6
haloalkyl), -C(O)(phenyl), -C(O)(non-aromatic heterocyclic group), -C(O)O(C1-C6
alkyl), -C(O)O(C1-C6 haloalkyl), -C(O)O(phenyl), -OC(O)(C1-C6 alkyl),
20 -OC(O)(C1-C6 haloalkyl), -OC(O)(phenyl), -S(O)₂(C1-C6 alkyl), -S(O)₂(C1-C6
haloalkyl), and -S(O)₂(phenyl).

In another embodiment, the present invention is directed to a pharmaceutical
composition comprising a compound represented by Structural Formula (A)
described above or a pharmaceutically acceptable salt thereof, and a
25 pharmaceutically acceptable carrier or diluent.

The present invention also includes a method of treating a subject having
cancer comprising administering a therapeutically effective amount of a compound
of the invention disclosed herein or a pharmaceutically acceptable salt thereof.

The present invention also includes a method of inhibiting Aurora B and/or
30 PLK-4 in a subject in need of inhibition of Aurora B and/or PLK-4, comprising
administering a therapeutically effective amount of a compound of the invention
disclosed herein or a pharmaceutically acceptable salt thereof.

Also, use of a compound of the invention disclosed herein or a pharmaceutically acceptable salt thereof in therapy is included in the present invention. In one embodiment, the therapy is for treating a subject with cancer. In another embodiment, the therapy is for inhibiting Aurora B and/or PLK-4 in a
5 subject in need of inhibition of Aurora B and/or PLK-4.

Also included in the present invention is the use of a compound of the invention disclosed herein or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating a subject with cancer.

Also included in the present invention is the use of a compound of the
10 invention disclosed herein or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for inhibiting Aurora B and/or PLK-4 in a subject in need of inhibition of Aurora B and/or PLK-4.

BRIEF DESCRIPTION OF THE DRAWINGS

The figure is a bar graph showing the inhibition of HUV-EC-C Cell Tube
15 Formation by compound Example A57.

DETAILED DESCRIPTION OF THE INVENTION

In one aspect, the present invention is directed to an indolinone compound represented by Structural Formula (A). A first set of values and specific values for the variables in Structural Formula (A) are provided in the following paragraphs:

20 Ring A is an optionally substituted 5- or 6-membered aromatic ring. In one embodiment, ring A is optionally substituted benzene ring. In another embodiment, ring A is optionally substituted pyridine ring. In another embodiment, ring A is optionally substituted pyrrole ring. In another embodiment, ring A is optionally substituted thiophene ring. In another embodiment, ring A is optionally substituted
25 thiozole ring.

In one embodiment, ring A is optionally substituted with one or more substituents Q^a , and phenyl ring B is optionally substituted with one or more substituents Q^b . Typically, each of Q^a and Q^b independently is selected from the group consisting of halogen, $-X-R^1$, $-\text{NO}_2$, $-\text{CN}$, $-\text{NCS}$, Ak^1 , Ar^1 , $(\text{C}_{1-10}$
30 $\text{alkylene})-\text{Ar}^1$, $(\text{C}_{2-10} \text{ alkenylene})-\text{Ar}^1$, $-\text{O}-[\text{CH}_2]_p-\text{O}-$, $-\text{S}-[\text{CH}_2]_p-\text{S}-$ and $-\text{[CH}_2\text{]}_q-$. In one embodiment, one of Q^a and Q^b is halogen, $-\text{NO}_2$, $-\text{CN}$, Ak^1 , Ar^1 , $(\text{C}_{1-10}$

alkylene)-Ar¹, (C₂₋₁₀ alkenylene)-Ar¹ or -X-R¹; and the other of Q^a and Q^b is halogen, hydroxy, nitro, cyano, amino, methyl, methoxy, halomethyl or halomethoxy. In another embodiment, one of Q^a and Q^b is halogen, hydroxy, cyano, nitro, C1-C6 alkyl, C1-C6 haloalkyl, -C(O)(C1-C6 alkyl), -C(O)NH₂, -C(O)NH(C1-C6 alkyl), -C(O)N(C1-C6 alkyl)₂, -SO₂NH₂, -SO₂NH(C1-C6 alkyl), -SO₂N(C1-C6 alkyl)₂, -OH, -O(C1-C6 alkyl), -O(C1-C6 haloalkyl), -SH, -S(C1-C6 alkyl), -S(C1-C6 haloalkyl), -NH₂, -NH(C1-C6 alkyl), -N(C1-C6 alkyl)₂, -NHC(O)(C1-C6 alkyl), -NHC(O)O(C1-C6 alkyl), -NHC(O)NH₂, -NHC(O)NH(C1-C6 alkyl), -NHC(O)N(C1-C6 alkyl)₂, -NHC(O)ONH₂, -NHC(O)ONH(C1-C6 alkyl), -NHC(O)ON(C1-C6 alkyl)₂, -NHSO₂NH₂, -NHSO₂NH(C1-C6 alkyl), -NHSO₂N(C1-C6 alkyl)₂ or -NHSO₂(C1-C6 alkyl); and the other Q^a and Q^b is halogen, hydroxy, nitro, cyano, amino, methyl, methoxy, halomethyl or halomethoxy. In yet another embodiment, one of Q^a and Q^b is halogen, hydroxy, cyano, nitro, Ph, -CH₂Ph, -C(O)Ph, -C(O)NH(Ph), -C(O)N(C1-C6 alkyl)(Ph), -SO₂NH(Ph), -SO₂N(C1-C6 alkyl)(Ph), -O(Ph), -S(Ph), -NH(Ph), -N(C1-C6 alkyl)(Ph), -NHC(O)(Ph), -NHC(O)O(Ph), -NHC(O)NH(Ph), -NHC(O)N(C1-C6 alkyl)(Ph), -NHC(O)ONH(Ph), -NHC(O)ON(C1-C6 alkyl)(Ph), -NHSO₂NH(Ph), -NHSO₂N(C1-C6 alkyl)(Ph) or -NHSO₂(Ph), wherein each Ph is a phenyl group independently and optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy and C1-C3 haloalkoxy; and the other Q^a and Q^b is halogen, hydroxy, nitro, cyano, amino, methyl, methoxy, halomethyl or halomethoxy. In yet another example, both of Q^a and Q^b are independently halogen, hydroxy, nitro, cyano, amino, methyl, methoxy, halomethyl or halomethoxy. In another embodiment, Q^a is halogen, cyano, -NR¹R², -NR²C(O)R¹, -C(O)OR¹, -OC(O)R¹, -N(R²)C(O)NR¹R², -OR¹, C₁₋₆ alkyl, wherein the C₁₋₆ alkyl is optionally substituted with one or more substituents selected from the group consisting of halogen, -OH, -SH, -O(C₁₋₆ alkyl), -S(C₁₋₆ alkyl) and C₁₋₆ haloalkoxy; and Q^b is halogen, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₁₋₃ alkoxy, or C₁₋₃ haloalkoxy. In another embodiment, Q^a is -OH, C₁₋₆ alkoxy or C₁₋₆ haloalkoxy; and Q^b is halogen, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₁₋₃ alkoxy, or C₁₋₃ haloalkoxy.

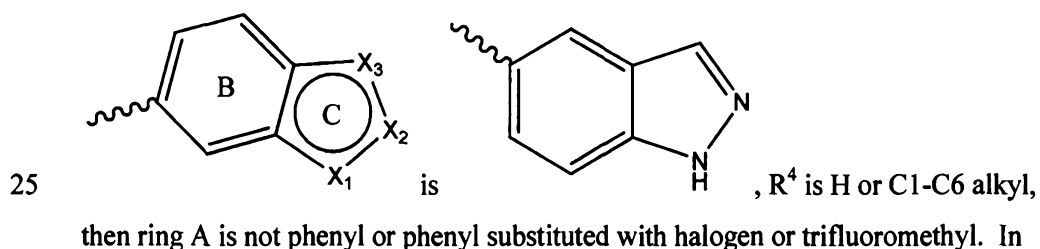
X is -C(O)O-, -C(O)-, -C(S)-, -OC(O)-, -C(O)N(R²)-, -C(S)N(R²)-, -OC(O)N(R²)-, -S(O)-, -S(O)₂-, -SO₃-, -SO₂NR²-, -O-, -S-, -NR²-, -NR²C(O)-, -NR²S(O)-, -NR²C(O)O-, -NR²C(O)ONR²-, -N(R²)C(O)NR²-, -NR²SO₂NR²- or -NR²SO₂-. Alternatively, X is -C(O)-, -C(S)-, -C(O)N(R²)-, -OC(O)N(R²)-, -SO₂NR²-, -O-, -S-, -NR²-, -NR²C(O)-, -NR²C(O)O-, -NR²C(O)ONR²-, -N(R²)C(O)NR²-, -NR²SO₂NR²- or -NR²SO₂-.
5

Each R¹ independently is: i) hydrogen; ii) an optionally substituted C₆₋₁₄ aryl group or an optionally substituted 5-14 membered heteroaryl group; or iii) an optionally substituted C₁₋₁₀ aliphatic group, provided that R¹ is other than hydrogen when X is -S(O)-, -S(O)₂-, -SO₃-, -NR²S(O)- or -NR²SO₂-. In one embodiment, each R¹ independently is i) hydrogen; ii) an optionally substituted phenyl group or an optionally substituted 5-6 membered heteroaryl group; or iii) an optionally substituted C₁₋₁₀ alkyl, provided that R¹ is other than hydrogen when X is -S(O)-, -S(O)₂-, -SO₃-, -NR²S(O)- or -NR²SO₂-. Typically, each of the aryl and heteroaryl groups represented by R¹ is independently and optionally substituted with one or more substituents selected from the group consisting of halogen, -NO₂, -CN, -NCS, Ak¹⁰, (C₁₋₁₀ alkylene)-Ar¹⁰, (C₂₋₁₀ alkenylene)-Ar¹⁰, -C(O)OR¹⁰, -C(O)R¹⁰, -C(S)R¹⁰, -OC(O)R¹⁰, -C(O)N(R¹¹)₂, -C(S)N(R¹¹)₂, -OC(O)N(R¹¹)₂, -S(O)R¹², -S(O)₂R¹², -SO₃R¹², -SO₂N(R¹¹)₂, -OR¹⁰, -SR¹⁰, -N(R¹¹)₂, -NR¹¹C(O)R¹⁰, -NR¹¹S(O)R¹², -NR¹¹C(O)OR¹², -N(R¹¹)C(O)N(R¹¹)₂, -NR¹¹SO₂N(R¹¹)₂ and -NR¹¹SO₂R¹². In one embodiment, each of the aryl and heteroaryl groups represented by R¹ is independently and optionally substituted with one or more substituents selected from the group consisting of halogen, nitro, cyano, Ak¹⁰, (C₁₋₁₀ alkylene)-Ar¹⁰, (C₂₋₁₀ alkenylene)-Ar¹⁰, -OR¹⁰, -SR¹⁰, -OC(O)N(R¹¹)₂, -N(R¹¹)₂, -C(O)NR¹¹, -NR¹¹C(O)R¹⁰, -N(R¹¹)C(O)N(R¹¹)₂, -NR¹¹SO₂N(R¹¹)₂, -NR¹¹SO₂R¹², -SO₂N(R¹¹)₂, -OC(O)R¹⁰, -C(O)OR¹⁰ and -C(O)R¹⁰. Typically, the aliphatic group, including alkyl group, represented by R¹ is optionally substituted with one or more substituents selected from the group consisting of halogen, -NO₂, -CN, -NCS, Ar¹⁰, -C(O)OR¹⁰, -C(O)R¹⁰, -C(S)R¹⁰, -OC(O)R¹⁰, -C(O)N(R¹¹)₂, -C(S)N(R¹¹)₂, -OC(O)N(R¹¹)₂, -S(O)R¹², -S(O)₂R¹², -SO₃R¹², -SO₂N(R¹¹)₂, -OR¹⁰, -SR¹⁰, -N(R¹¹)₂, -NR¹¹C(O)R¹⁰, -NR¹¹S(O)R¹², -NR¹¹C(O)OR¹², -N(R¹¹)C(O)N(R¹¹)₂, -NR¹¹SO₂N(R¹¹)₂ and -NR¹¹SO₂R¹². In one embodiment, the aliphatic group, including alkyl group,

represented by R^1 is optionally substituted with one or more substituents selected from the group consisting of halogen, nitro, cyano, Ar^{10} , $-OR^{10}$, $-SR^{10}$, $-N(R^{11})_2$, $-OC(O)R^{10}$, $-C(O)OR^{10}$ and $-C(O)R^{10}$. In another embodiment, R^1 is -H- or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with one or more substituents
 5 independently selected from the group consisting of halogen, -OH, -SH, $-O(C_{1-3}$ alkyl), $-S(C_{1-3}$ alkyl) and C_{1-6} haloalkoxy.

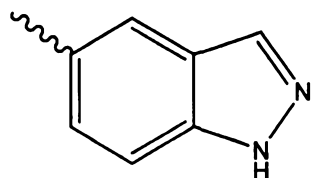
Each R^2 independently is R^1 , $-CO_2R^1$, $-SO_2R^1$ or $-C(O)R^1$, or, taken together with NR^1 , forms an optionally substituted non-aromatic heterocyclic group represented by NR^1R^2 . In one embodiment, each R^2 is -H or C_{1-6} alkyl.
 10 Typically, the non-aromatic heterocyclic group represented by NR^1R^2 is optionally substituted with one or more substituents selected from the group consisting of =O, =S, halogen, nitro, cyano, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, C_{1-6} aminoalkyl, $(C_{1-6}$ alkylamino) C_{1-6} alkyl, $(C_{1-6}$ dialkylamino) C_{1-6} alkyl, (phenyl) C_{1-6} alkyl, (5-6 membered heteroaryl) C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkylcarbonyloxy, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonyl, phenyl and 5-6 membered heteroaryl. In one embodiment, the non-aromatic heterocyclic group represented by NR^1R^2 is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, =O, C_{1-3} alky, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy and
 15 amino. In another embodiment, R^2 is -H- or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -SH, $-O(C_{1-3}$ alkyl), $-S(C_{1-3}$ alkyl) and C_{1-6} haloalkoxy.

Z is =N- or = CR^3 -. In one embodiment, when Z is =N-,

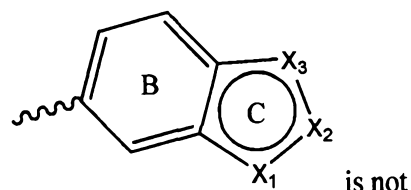


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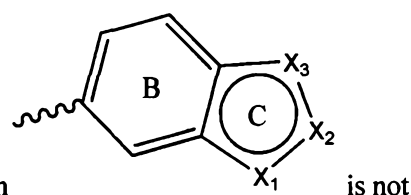
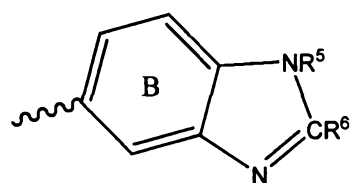
another embodiment, when Z is =N-, then



R^3 is -H, halogen, C1-C6 alkyl or C1-C6 haloalkyl. In one embodiment, R^3 is -H or C1-C6 alkyl. In another embodiment, R^3 is -H, halogen, C1-C6 alkyl or C1-



5 C6 haloalkyl, wherein when R^3 is halogen, then



Each of R^4 and R^5 independently is -H, C1-C6 alkyl, phenyl, -C(O)(C1-C6 alkyl), -C(O)(phenyl), -C(O)O(C1-C6 alkyl), -C(O)O(phenyl), -S(O)₂(C1-C6 alkyl) or -S(O)₂(phenyl). Typically, each alkyl in the groups represented by R^4 and R^5 is independently and optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, phenyl, 5-6 membered heteroaryl, C1-C6 alkoxy and C1-C6 haloalkoxy. Typically, each phenyl in the groups represented by R^4 and R^5 independently is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 alkoxy and C1-C6 haloalkoxy. In one embodiment, R^4 and R^5 are both -H.

R^6 is hydrogen, halogen, nitro, cyano, R' , -OR, -SR, -N(R)₂, -C(O)R, -C(O)OR, -OC(O)R, -C(O)N(R)₂, -OC(O)N(R)₂, -NRC(O)R, -NRC(O)OR, -SOR', -SO₂R', -SO₃R', -SO₂N(R)₂, -NRS(O)R', -NRSO₂R', -NRC(O)N(R)₂, -NRC(O)ON(R)₂ or -NRSO₂N(R)₂. In one embodiment, R^6 is hydrogen, halogen,

nitro, cyano, R', -OR, -SR or -N(R)₂. In another embodiment, R⁶ is hydrogen, halogen, nitro, cyano, hydroxy, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 alkoxy, C1-C6 haloalkoxy, -S(C1-C6 alkyl), -S(C1-C6 haloalkyl), amino, C1-C6 alkylamino, C1-C6 dialkylamino, phenoxy or phenyl, wherein each of said alkyl and said alkoxy

5 in the groups represented by R⁶ is independently and optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, phenyl, C1-C3 alkoxy and C1-C3 haloalkoxy, and wherein each said phenyl in the groups represented by R⁶ is independently and optionally substituted with one or more substituents selected from the group consisting of

10 halogen, hydroxy, nitro, cyano, amino, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy and C1-C3 haloalkoxy. In another embodiment, R⁶ is hydrogen, halogen, C1-C6 alkyl or C1-C6 haloalkyl. In another embodiment, R⁶ is optionally substituted phenyl, optionally substituted 5-12 membered heteroaryl, -CH₂-(optionally substituted phenyl), -CH₂-(optionally substituted 5-12 membered heteroaryl), -CH₂-

15 CH₂-(optionally substituted phenyl), -CH₂-CH₂-(optionally substituted 5-12 membered heteroaryl), -CH=CH-(optionally substituted phenyl), -CH=CH-(optionally substituted 5-12 membered heteroaryl), -CH=CH-C(O)O(optionally substituted C₁₋₆ alkyl), or -CH=CH-OC(O)(optionally substituted C₁₋₆ alkyl). In another embodiment, R⁶ is an optionally substituted phenyl or an optionally

20 substituted 5-6 membered heteroaryl. In another embodiment, the phenyl and 5-6 membered heteroaryl represented by R⁶ are independently and optionally substituted with one or more substituents selected from the group consisting of: halogen, hydroxy, nitro, cyano, amino, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 alkoxy and C1-C6 haloalkoxy. In yet another embodiment, R⁶ is an optionally substituted phenyl

25 group, an optionally substituted pyridyl group, an optionally substituted pyrrolyl group, an optionally substituted pyrazolyl, an optionally substituted thiazolyl, an optionally substituted pyrimidyl, or an optionally substituted thienyl. In yet another embodiment, R⁶ is an -CH=CH-(optionally substituted phenyl) -CH=CH-(optionally substituted 5-12 membered heteroaryl), -C≡C-(optionally substituted phenyl) or

30 -C≡C-(optionally substituted 5-12 membered heteroaryl), wherein the heteroaryl is an optionally substituted pyridyl group, an optionally substituted pyrrolyl group, an

optionally substituted pyrazolyl, an optionally substituted thiazolyl, an optionally substituted pyrimidyl, or an optionally substituted thienyl.

- Each R¹⁰ independently is: i) hydrogen; ii) an optionally substituted C₆₋₁₄ aryl group or an optionally substituted 5-14 membered heteroaryl group; or iii) an optionally substituted C₁₋₁₀ alkyl group. In one embodiment, each R¹⁰ independently is i) hydrogen; ii) an optionally substituted phenyl group or an optionally substituted 5-6 membered heteroaryl group; or iii) an optionally substituted C₁₋₆ alkyl group. Typically, each of the aryl, including phenyl, and heteroaryl groups represented by R¹⁰ is independently and optionally substituted with one or more substituents selected from the group consisting of halogen, nitro, cyano, hydroxy, C₁₋₁₀ alkyl, C₁₋₁₀ haloalkyl, (C₁₋₁₀ haloalkoxy)C₁₋₁₀ alkyl, (C₁₋₁₀ alkoxy)C₁₋₁₀ alkyl, C₁₋₁₀ hydroxyalkyl, C₁₋₁₀ aminoalkyl, (C₁₋₁₀ alkylamino)C₁₋₁₀ alkyl, (C₁₋₁₀ dialkylamino)C₁₋₁₀ alkyl, (phenyl)C₁₋₁₀ alkyl, (5-6 membered heteroaryl)C₁₋₁₀ alkyl, amino, C₁₋₁₀ alkylamino, C₁₋₁₀ dialkylamino, C₁₋₁₀ alkoxy, C₁₋₁₀ haloalkoxy, C₁₋₁₀ alkylcarbonyloxy, C₁₋₁₀ alkoxycarbonyl and C₁₋₁₀ alkylcarbonyl. In one embodiment, each of the aryl, including phenyl, and heteroaryl groups represented by R¹⁰ is independently and optionally substituted with one or more substituents selected from the group consisting of halogen, nitro, cyano, hydroxy, C₁₋₆ alkyl, C₁₋₆ haloalkyl, (C₁₋₆ haloalkoxy)C₁₋₆ alkyl, (C₁₋₆ alkoxy)C₁₋₆ alkyl, C₁₋₆ hydroxyalkyl, (C₁₋₆ aminoalkyl, (C₁₋₆ alkylamino)C₁₋₆ alkyl, (C₁₋₆ dialkylamino)C₁₋₆ alkyl, amino, C₁₋₆ alkylamino, C₁₋₆ dialkylamino, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₆ alkylcarbonyloxy, C₁₋₆ alkoxycarbonyl and C₁₋₆ alkylcarbonyl. In another embodiment, each of the aryl, including phenyl, and heteroaryl groups represented by R¹⁰ is independently and optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, amino, cyano, nitro, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy and C1-C3 haloalkoxy. Typically, the alkyl group represented by R¹⁰ is optionally substituted with one or more substituents selected from the group consisting of halogen, nitro, cyano, hydroxy, C₁₋₁₀ haloalkyl, C₁₋₁₀ alkoxy, C₁₋₁₀ haloalkoxy, amino, C₁₋₁₀ alkylamino, C₁₋₁₀ dialkylamino, C₁₋₁₀ alkylcarbonyloxy, C₁₋₁₀ alkoxycarbonyl, C₁₋₁₀ alkylcarbonyl and phenyl, said phenyl being optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy

and C1-C3 haloalkoxy. In one embodiment, the alkyl group represented by R^{10} is optionally substituted with one or more substituents selected from the group consisting halogen, nitro, cyano, hydroxy, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, amino, C₁₋₆ alkylamino, C₁₋₆ dialkylamino, C₁₋₆ alkylcarbonyloxy, C₁₋₆ alkoxycarbonyl, C₁₋₆ alkylcarbonyl and phenyl. In another embodiment, the alkyl group represented by R^{10} is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, amino, cyano, nitro, C1-C3 alkoxy, C1-C3 haloalkoxy and phenyl.

Each R^{11} independently is R^{10} , $-\text{CO}_2R^{10}$, $-\text{SO}_2R^{10}$ or $-\text{C}(\text{O})R^{10}$, or $-\text{N}(\text{R}^{11})_2$ taken together is an optionally substituted non-aromatic heterocyclic group. Typically, the non-aromatic heterocyclic group represented by $\text{N}(\text{R}^{11})_2$ is optionally substituted with one or more substituents selected from the group consisting of $=\text{O}$, $=\text{S}$, halogen, nitro, cyano, hydroxy, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, amino, C₁₋₆ alkylamino, C₁₋₆ dialkylamino, C₁₋₆ aminoalkyl, (C₁₋₆ alkylamino)C₁₋₆ alkyl, (C₁₋₆ dialkylamino)C₁₋₆ alkyl, (phenyl)C₁₋₆ alkyl, (5-6 membered heteroaryl)C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₆ alkylcarbonyloxy, C₁₋₆ alkoxycarbonyl, C₁₋₆ alkylcarbonyl, phenyl and 5-6 membered heteroaryl. In one example, the non-aromatic heterocyclic group represented by $\text{N}(\text{R}^{11})_2$ is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, $=\text{O}$, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy, C1-C3 haloalkoxy and amino.

Each R^{12} independently is: i) an optionally substituted C₆₋₁₄ aryl group or an optionally substituted 5-14 membered heteroaryl group; or ii) an optionally substituted C₁₋₁₀ alkyl group. Alternatively, each R^{12} independently is i) an optionally substituted phenyl group or an optionally substituted 5-6 membered heteroaryl group; or ii) an optionally substituted C₁₋₆ alkyl group. Typically, each of the aryl, including phenyl, and heteroaryl groups represented by R^{12} is independently and optionally substituted with one or more substituents selected from the group consisting of halogen, nitro, cyano, hydroxy, C₁₋₁₀ alkyl, C₁₋₁₀ haloalkyl, (C₁₋₁₀ haloalkoxy)C₁₋₁₀ alkyl, (C₁₋₁₀ alkoxy)C₁₋₁₀ alkyl, C₁₋₁₀ hydroxyalkyl, C₁₋₁₀ aminoalkyl, (C₁₋₁₀ alkylamino)C₁₋₁₀ alkyl, (C₁₋₁₀ dialkylamino)C₁₋₁₀ alkyl, (phenyl)C₁₋₁₀ alkyl, (5-6 membered heteroaryl)C₁₋₁₀ alkyl, amino, C₁₋₁₀ alkylamino,

C₁₋₁₀ dialkylamino, C₁₋₁₀ alkoxy, C₁₋₁₀ haloalkoxy, C₁₋₁₀ alkylcarbonyloxy, C₁₋₁₀ alkoxy carbonyl and C₁₋₁₀ alkylcarbonyl. In one example, each of the aryl, including phenyl, and heteroaryl groups represented by R¹² is independently and optionally substituted with one or more substituents selected from the group consisting of

5 halogen, nitro, cyano, hydroxy, C₁₋₆ alkyl, C₁₋₆ haloalkyl, (C₁₋₆ haloalkoxy)C₁₋₆ alkyl, (C₁₋₆ alkoxy)C₁₋₆ alkyl, C₁₋₆ hydroxyalkyl, (C₁₋₆ aminoalkyl, (C₁₋₆ alkylamino)C₁₋₆ alkyl, (C₁₋₆ dialkylamino)C₁₋₆ alkyl, amino, C₁₋₆ alkylamino, C₁₋₆ dialkylamino, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₆ alkylcarbonyloxy, C₁₋₆ alkoxy carbonyl and C₁₋₆ alkylcarbonyl. In another example, each of the aryl, including phenyl, and

10 heteroaryl groups represented by R¹² is independently and optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, amino, cyano, nitro, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy and C1-C3 haloalkoxy. Typically, the alkyl group represented by R¹² is optionally substituted with one or more substituents selected from the group consisting of halogen, nitro,

15 cyano, hydroxy, C₁₋₁₀ haloalkyl, C₁₋₁₀ alkoxy, C₁₋₁₀ haloalkoxy, amino, C₁₋₁₀ alkylamino, C₁₋₁₀ dialkylamino, C₁₋₁₀ alkylcarbonyloxy, C₁₋₁₀ alkoxy carbonyl, C₁₋₁₀ alkylcarbonyl and phenyl, said phenyl being optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy and C1-C3 haloalkoxy. In one

20 example, the alkyl group represented by R¹² is optionally substituted with one or more substituents selected from the group consisting halogen, nitro, cyano, hydroxy, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, amino, C₁₋₆ alkylamino, C₁₋₆ dialkylamino, C₁₋₆ alkylcarbonyloxy, C₁₋₆ alkoxy carbonyl, C₁₋₆ alkylcarbonyl and phenyl. In another example, the alkyl group represented by R¹² is optionally

25 substituted with one or more substituents selected from the group consisting of halogen, hydroxy, amino, cyano, nitro, C1-C3 alkoxy, C1-C3 haloalkoxy and phenyl.

Each R²¹ independently is hydrogen, optionally substituted C₁₋₆ alkyl, optionally substituted phenyl or optionally substituted 5-6 membered heteroaryl, or N(R²¹)₂ forms an optionally substituted non-aromatic heterocyclic group.

30 Alternatively, each R²¹ independently is hydrogen, optionally substituted C₁₋₆ alkyl or optionally substituted phenyl. Typically, each of the phenyl and heteroaryl groups represented by R²¹ is independently and optionally substituted with one or

- more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy and C1-C3 haloalkoxy. Typically, the alkyl group represented by R^{21} is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C1-C3 alkoxy, C1-C3 haloalkoxy and phenyl. Typically, the non-aromatic heterocyclic represented by $N(R^{21})_2$ is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, =O, C1-C3 alky, C1-C3 haloalkyl, C1-C3 alkoxy, C1-C3 haloalkoxy and amino.
- 10 Each R^{22} independently is optionally substituted C_{1-6} alkyl, optionally substituted phenyl or optionally substituted 5-6 membered heteroaryl. Alternatively, each R^{22} independently is optionally substituted C_{1-6} alkyl or optionally substituted phenyl. Typically, each of the phenyl and heteroaryl groups represented by R^{22} is independently and optionally substituted with one or more substituents selected from
- 15 the group consisting of halogen, hydroxy, nitro, cyano, amino, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy and C1-C3 haloalkoxy. Typically, the alkyl group represented by R^{22} is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C1-C3 alkoxy, C1-C3 haloalkoxy and phenyl.
- 20 Each R independently is hydrogen, optionally substituted C_{1-10} aliphatic, optionally substituted phenyl or optionally substituted 5-6 membered heteroaryl. Alternatively, $N(R)_2$ forms an optionally substituted non-aromatic heterocyclic group. Typically, the aliphatic group represented by R is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy,
- 25 nitro, cyano, amino, phenyl, 5-6 membered heteroaryl, C1-C6 alkoxy and C1-C6 haloalkoxy, wherein each of the phenyl and the 5-6 membered heteroaryl groups are independently and optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 alkoxy and C1-C6 haloalkoxy. Typically, each of the phenyl and
- 30 the heteroaryl groups represented by R is independently and optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 alkoxy and C1-

C6 haloalkoxy. Typically, the non-aromatic heterocyclic group represented by N(R)₂ is optionally substituted with one or more substituents selected from the group consisting of =O, =S, halogen, nitro, cyano, hydroxy, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, amino, C₁₋₆ alkylamino, C₁₋₆ dialkylamino, C₁₋₆ aminoalkyl, (C₁₋₆ alkylamino)C₁₋₆ alkyl, (C₁₋₆ dialkylamino)C₁₋₆ alkyl, (phenyl)C₁₋₆ alkyl, (5-6 membered heteroaryl)C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₆ alkylcarbonyloxy, C₁₋₆ alkoxy carbonyl, C₁₋₆ alkylcarbonyl, phenyl and 5-6 membered heteroaryl. In one example, the non-aromatic heterocyclic group represented by N(R)₂ is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, =O, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy, C1-C3 haloalkoxy and amino.

Each R' independently is optionally substituted C₁₋₁₀ aliphatic, optionally substituted phenyl or optionally substituted 5-14 membered heteroaryl. Alternatively, each R' independently is -CH₂-(optionally-substituted phenyl), -CH₂-(optionally-substituted 5-6 membered heteroaryl), -CH₂-CH₂-(optionally-substituted phenyl), -CH₂-CH₂-(optionally-substituted 5-6 membered heteroaryl), CH=CH-(optionally-substituted phenyl) or -CH=CH₂-(optionally-substituted 5-6 membered heteroaryl). Alternatively, each R' independently is -CH₂-(optionally-substituted phenyl), -CH₂-(optionally-substituted pyridyl), -CH₂-CH₂-(optionally-substituted phenyl), -CH₂-CH₂-(optionally-substituted pyridyl), CH=CH-(optionally-substituted phenyl) or -CH=CH₂-(optionally-substituted pyridyl). Typically, the aliphatic group represented by R' is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, phenyl, 5-6 membered heteroaryl, C1-C6 alkoxy and C1-C6 haloalkoxy, C₁₋₆ alkylamino, C₁₋₆ dialkylamino, -C(O)(C1-C6 alkyl), -C(O)(C1-C6 haloalkyl), -C(O)(phenyl), -C(O)(non-aromatic heterocyclic group), -C(O)O(C1-C6 alkyl), -C(O)O(C1-C6 haloalkyl), -C(O)O(phenyl), -OC(O)(C1-C6 alkyl), -OC(O)(C1-C6 haloalkyl), -OC(O)(phenyl), -S(O)₂(C1-C6 alkyl), -S(O)₂(C1-C6 haloalkyl) and -S(O)₂(phenyl), wherein each of the phenyl and the 5-6 membered heteroaryl groups are independently and optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 alkoxy and C1-C6 haloalkoxy. Typically, each of the

- phenyl and the heteroaryl groups represented by R' is independently and optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 alkoxy and C1-C6 haloalkoxy, non-aromatic heterocyclic group, C₁₋₆ alkylamino, C₁₋₆ dialkylamino, -C(O)(C1-C6 alkyl), -C(O)(C1-C6 haloalkyl), -C(O)(phenyl), -C(O)(non-aromatic heterocyclic group), -C(O)O(C1-C6 alkyl), -C(O)O(C1-C6 haloalkyl), -C(O)O(phenyl), -OC(O)(C1-C6 alkyl), -OC(O)(C1-C6 haloalkyl), -OC(O)(phenyl), -S(O)₂(C1-C6 alkyl), -S(O)₂(C1-C6 haloalkyl), and -S(O)₂(phenyl).
- Each Ak¹ independently is an optionally substituted C₁₋₁₀ aliphatic group. Alternatively, each Ak¹ independently is an optionally substituted C₁₋₁₀ alkyl group. Alternatively, each Ak¹ independently is an optionally substituted C₁₋₆ alkyl group. Typically, each of the aliphatic and alkyl groups represented by Ak¹ is independently and optionally substituted with one or more substituents selected from the group consisting of halogen, nitro, cyano, -N(R²¹)₂, -C(O)N(R²¹)₂, -C(O)N(R²¹)₂, -NR²¹C(O)R²¹, -SO₂R²², -SO₂N(R²¹)₂, -NR²¹SO₂R²², -NR²¹C(O)OR²¹, -OC(O)N(R²¹)₂, -NR²¹C(O)N(R²¹)₂, -NRC(O)ON(R)₂, -NR²¹SO₂N(R²¹)₂, -OR²¹, -SR²¹, C₁₋₁₀ haloalkoxy, -C(O)R²¹, -C(O)OR²¹ and -OC(O)R²¹. In one example, each of the aliphatic and alkyl groups represented by Ak¹ is independently and optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, amino, cyano, nitro, C1-C3 alkoxy, C1-C3 haloalkoxy and phenyl.
- Each Ak¹⁰ independently is an optionally substituted C₁₋₁₀ alkyl group. Alternatively, each Ak¹ independently is an optionally substituted C₁₋₆ alkyl group. Typically, the alkyl group represented by Ak¹⁰ is optionally substituted with one or more substituents selected from the group consisting of halogen, nitro, cyano, -OH, -SH, -O(C₁₋₆ alkyl), -S(C₁₋₆ alkyl), C₁₋₆ haloalkoxy, amino, C₁₋₆ alkylamino, C₁₋₆ dialkylamino, C₁₋₆ alkylcarbonyloxy, C₁₋₆ alkoxy carbonyl and C₁₋₆ alkylcarbonyl. In one example, the alkyl group represented by Ak¹⁰ is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, amino, cyano, nitro, C1-C3 alkoxy, C1-C3 haloalkoxy and phenyl.

Each Ar¹ independently is an optionally substituted C₆₋₁₄ aryl group or an optionally substituted 5-14 membered heteroaryl group. Alternatively, each Ar¹ independently is an optionally substituted phenyl group or an optionally substituted 5-6 membered heteroaryl group. Typically, suitable substituents for each of the aryl and heteroaryl groups represented by Ar¹ independently include halogen, nitro, cyano, hydroxy, C₁₋₆ alkyl, C₁₋₆ haloalkyl, (C₁₋₆ haloalkoxy)C₁₋₆ alkyl, (C₁₋₆ alkoxy)C₁₋₆ alkyl, C₁₋₆ hydroxyalkyl, (C₁₋₆ aminoalkyl, (C₁₋₆ alkylamino)C₁₋₆ alkyl, (C₁₋₆ dialkylamino)C₁₋₆ alkyl, -NR²¹₂, -C(O)NR²¹₂, -C(O)NR²¹₂, -NR²¹C(O)R²¹, -S(O)₂R²², -SO₂NR²¹₂, -NR²¹SO₂R²², -NR²¹C(O)NR²²₂, -NR²¹SO₂NR²¹₂, -OR²¹, -SR²¹, C₁₋₆ haloalkoxy, -C(O)R²¹, -C(O)OR²¹, -OC(O)R²¹ and benzyl. Additional suitable substituents include a phenyl group and a 5-6 membered heteroaryl group, each of which is independently and optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy and C1-C3 haloalkoxy. In one example, each of the phenyl and heteroaryl groups represented by Ar¹ is independently and optionally substituted with one or more substituents selected from the group consisting of halogen, nitro, cyano, hydroxy, C₁₋₆ alkyl, C₁₋₆ haloalkyl, (C₁₋₆ haloalkoxy)C₁₋₆ alkyl, (C₁₋₆ alkoxy)C₁₋₆ alkyl, C₁₋₆ hydroxyalkyl, (C₁₋₆ aminoalkyl, (C₁₋₆ alkylamino)C₁₋₆ alkyl, (C₁₋₆ dialkylamino)C₁₋₆ alkyl, -NR²¹₂, -C(O)NR²¹₂, -C(O)NR²¹₂, -NR²¹C(O)R²¹, -S(O)₂R²², -SO₂NR²¹₂, -NR²¹SO₂R²², -NR²¹C(O)NR²²₂, -NR²¹SO₂NR²¹₂, -OR²¹, -SR²¹, C₁₋₆ haloalkoxy, -C(O)R²¹, -C(O)OR²¹, -OC(O)R²¹, phenyl, benzyl and 5-6 membered heteroaryl. In another example, each of the phenyl and heteroaryl groups represented by Ar¹ is independently and optionally substituted with one or more substituents selected from the group consisting of halogen, nitro, cyano, -OH, -SH, -O(C₁₋₆ alkyl), -S(C₁₋₆ alkyl), C₁₋₆ alkyl, C₁₋₆ haloalkyl, (C₁₋₆ haloalkoxy)C₁₋₆ alkyl, (C₁₋₆ alkoxy)C₁₋₆ alkyl, C₁₋₆ hydroxyalkyl, (C₁₋₆ aminoalkyl, (C₁₋₆ alkylamino)C₁₋₆ alkyl, (C₁₋₆ dialkylamino)C₁₋₆ alkyl, (phenyl)C₁₋₆ alkyl, (5-6 membered heteroaryl)C₁₋₆ alkyl, amino, C₁₋₆ alkylamino, C₁₋₆ dialkylamino, C₁₋₆ haloalkoxy, C₁₋₆ alkylcarbonyloxy, C₁₋₆ alkoxycarbonyl and C₁₋₆ alkylcarbonyl. In yet another example, each of the phenyl and heteroaryl groups represented by Ar¹ is independently and optionally substituted with one or more substituents selected from the group consisting of

halogen, hydroxy, amino, cyano, nitro, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy and C1-C3 haloalkoxy.

Each Ar¹⁰ independently is an optionally substituted C₆₋₁₄ aryl group or an optionally substituted 5-14 membered heteroaryl group. Alternatively, each Ar¹⁰ independently is an optionally substituted phenyl group or an optionally substituted 5-6 membered heteroaryl group. Typically, suitable substituents for each of the aryl and heteroaryl groups represented by Ar¹⁰ include halogen, nitro, cyano, -OH, -SH, -O(C₁₋₁₀ alkyl), -S(C₁₋₁₀ alkyl), C₁₋₁₀ alkyl, C₁₋₁₀ haloalkyl, (C₁₋₁₀ haloalkoxy)C₁₋₁₀ alkyl, (C₁₋₁₀ alkoxy)C₁₋₁₀ alkyl, C₁₋₁₀ hydroxyalkyl, (C₁₋₁₀ aminoalkyl), (C₁₋₁₀ alkylamino)C₁₋₁₀ alkyl, (C₁₋₁₀ dialkylamino)C₁₋₁₀ alkyl, (phenyl)C₁₋₁₀ alkyl, (5-6 membered heteroaryl)C₁₋₁₀ alkyl, amino, C₁₋₁₀ alkylamino, C₁₋₁₀ dialkylamino, C₁₋₁₀ haloalkoxy, C₁₋₁₀ alkylcarbonyloxy, C₁₋₁₀ alkoxycarbonyl and C₁₋₁₀ alkylcarbonyl. In one example, each of the phenyl and heteroaryl groups represented by Ar¹⁰ is independently and optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, amino, cyano, nitro, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy and C1-C3 haloalkoxy.

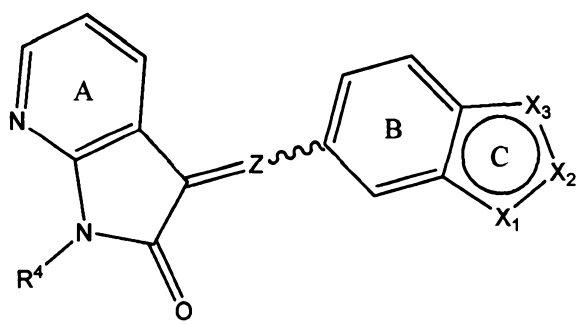
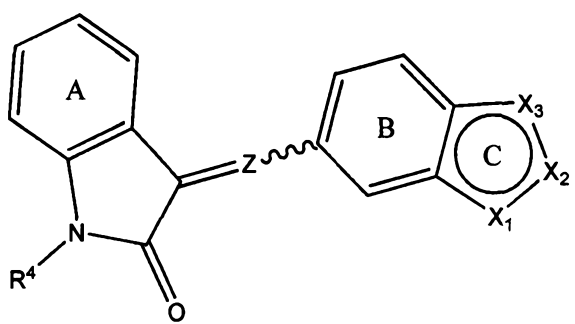
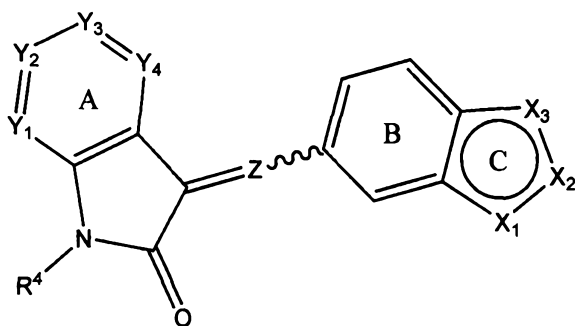
Each p independently is 1, 2 or 3.

Each q independently is 2, 3, 4 or 5.

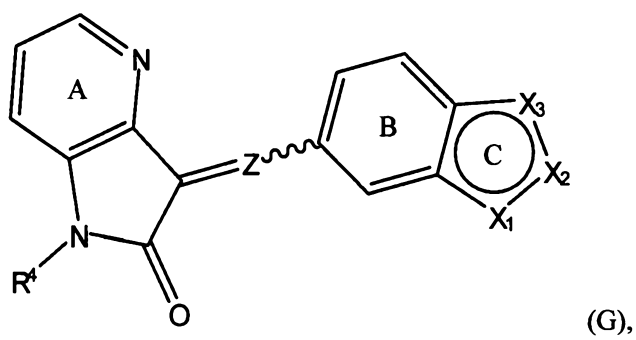
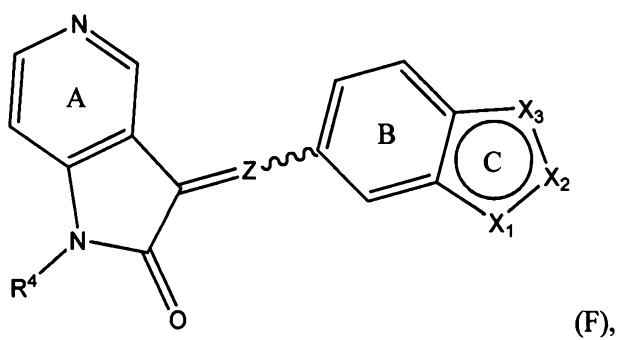
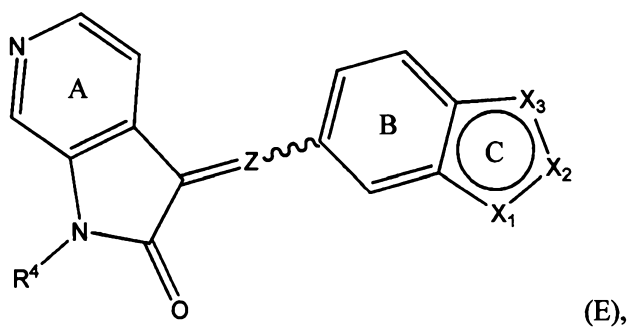
Examples of the heteroaryl groups, including 5-14 membered heteroaryl groups or 5-6 membered heteroaryl groups, referred to in the definitions of the variables for Structural Formula (A) are as described later. Typical examples of the 5-6 membered heteroaryl groups referred to in the definitions of variables for Structural Formula (A) include a furanyl group, an imidazolyl group, an isoxazolyl group, an oxadiazolyl group, an oxazolyl, a pyrazolyl group, a pyrrolyl group, a pyridyl group, a pyrimidinyl group, a pyridazinyl group, a thiazolyl group, a triazolyl group, a tetrazolyl group, a thienyl group, a pyrimidinyl group, a pyridinyl group or a pyridazinyl group. Typical 5-14 membered heteroaryl groups referred to in the definitions of variables for Structural Formula (A) include an indolyl group, a quinolinyl group, a furanyl group, an imidazolyl group, an isoxazolyl group, an oxadiazolyl group, an oxazolyl, a pyrazolyl group, a pyrrolyl group, a pyridyl group, a pyrimidinyl group, a pyridazinyl group, a thiazolyl group, a triazolyl group, a

tetrazolyl group, a thienyl group, a pyrimidinyl group, a pyridinyl group or a pyridazinyl group.

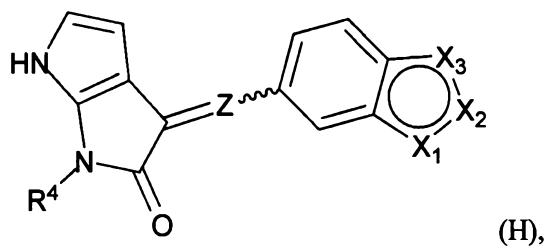
In one embodiment, the compound of the present invention is represented by Structural Formula (B), (C), (D), (E), (F), (G), (H), (I'), (J) or (K):

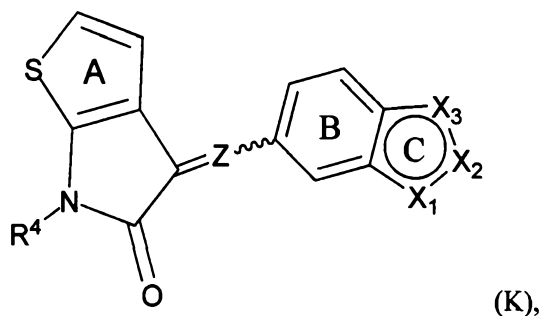
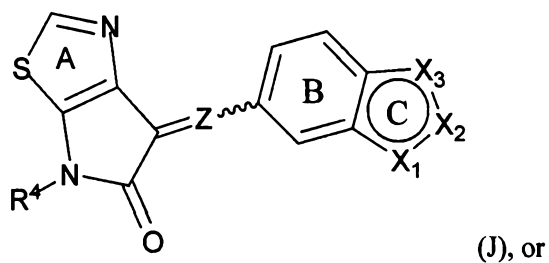
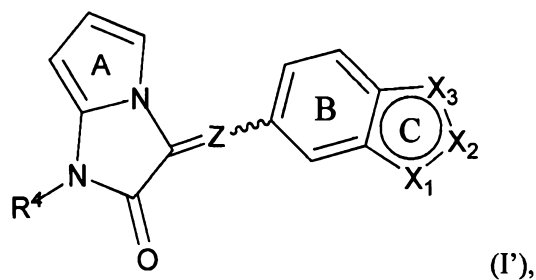


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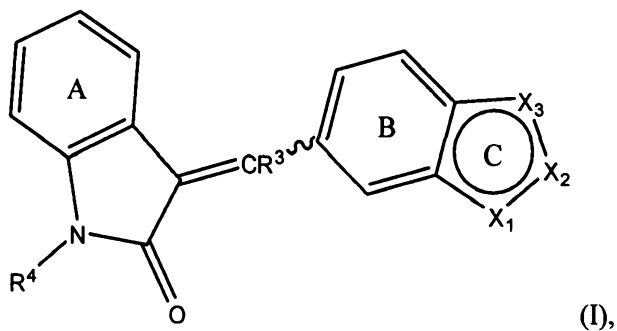


or a pharmaceutically acceptable salt thereof.

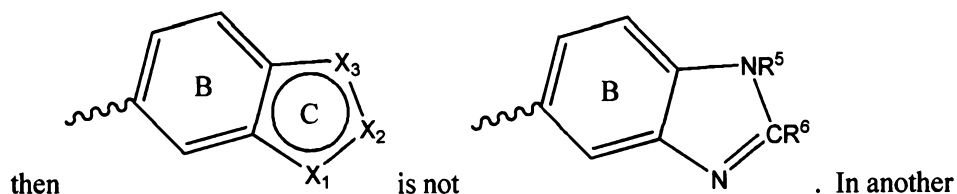
5 Each of Y_1 , Y_2 , Y_3 and Y_4 in Structural Formula (B) is independently -N or -CH.

Ring A and ring B of Structural Formulas (B)-(K) are optionally substituted. Values and specific values for the remainder of the variables are as described above for Structural Formula (A).

10 In a first embodiment, the compound of the present invention is represented by Structural Formula (I):



or a pharmaceutically acceptable salt thereof. Value and specific values are as described above for Structural Formula (A). In a more specific embodiment, R^3 is -H, halogen, C1-C6 alkyl or C1-C6 haloalkyl, provided when R^3 is halogen, then



5 more specific embodiment, R^3 is H, C1-C6 alkyl or C1-C6 haloalkyl.

In a second embodiment, the compound of the present invention is represented by Structural Formula (I), wherein a first set of values for the variables of Structural Formula (I) is provided in the following paragraphs:

R^3 is -H, C1-C6 alkyl or C1-C6 haloalkyl.

10 each R^1 independently is C_{1-10} aliphatic, phenyl or 5-6 membered heteroaryl, wherein said aliphatic is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, phenyl, 5-6 membered heteroaryl, C1-C6 alkoxy, C1-C6 haloalkoxy, and wherein each of the phenyl and heteroaryl groups represented by R^1 , and the phenyl and heteroaryl

15 groups in the substituents for the aliphatic group represented by R^1 independently is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 alkoxy, C1-C6 haloalkoxy.

20 Values and specific values for the remainder of the variables are as described above for Structural Formula (A).

A second set of values for the variables in Structural Formula (I) is provided in the following paragraphs:

25 X is -C(O)-, -C(S)-, -C(O)N(R^2)-, -OC(O)N(R^2)-, -SO₂N(R^2)-, -O-, -S-, -NR²-, -NR²C(O)-, -NR²C(O)O-, -NR²C(O)ONR²-, -N(R^2)C(O)NR²-, -NR²SO₂N(R^2)- or -NR²SO₂-.

Each R^1 independently is i) hydrogen; ii) an optionally substituted phenyl group or an optionally substituted 5-6 membered heteroaryl group; or iii) an optionally substituted C_{1-10} alkyl group. Suitable substituents for each of the alkyl,

phenyl and heteroaryl groups represented by R^1 independently are as described above for the first set of values.

Each Ak^1 independently is an optionally substituted C_{1-10} alkyl group. Suitable substituents for the alkyl group represented by Ak^1 are as described above
 5 for the first set of values.

Each Ar^1 independently is a phenyl group or a 5-6 membered heteroaryl group, each optionally and independently substituted with one or more substituents selected from the group consisting of halogen, nitro, cyano, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, (C_{1-6} haloalkoxy) C_{1-6} alkyl, (C_{1-6} alkoxy) C_{1-6} alkyl, C_{1-6} hydroxyalkyl, (C_{1-6} aminoalkyl, (C_{1-6} alkylamino) C_{1-6} alkyl, (C_{1-6} dialkylamino) C_{1-6} alkyl, $-NR^{21}_2$,
 10 $-C(O)NR^{21}_2$, $-C(O)NR^{21}_2$, $-NR^{21}C(O)R^{21}$, $-S(O)_2R^{22}$, $-SO_2NR^{21}_2$, $-NR^{21}SO_2R^{22}$, $-NR^{21}C(O)NR^{22}_2$, $-NR^{21}SO_2NR^{21}_2$, $-OR^{21}$, $-SR^{21}$, C_{1-6} haloalkoxy, $-C(O)R^{21}$, $-C(O)OR^{21}$, $-OC(O)R^{21}$, phenyl, benzyl and 5-6 membered heteroaryl.

Values and specific values for the remainder of the variables of Structural
 15 Formula (I) are each independently as described above in first set of values of the second embodiment.

A third set of values for the variables in Structural Formula (I) is provided in the following paragraphs

Each Ak^{10} independently is an optionally substituted C_{1-6} alkyl group.
 20 Suitable substituents for the alkyl group represented by Ak^{10} are as described above for the first set of values.

Each Ar^{10} independently is a phenyl group or a 5-6 membered heteroaryl group, each optionally and independently substituted with one or more substituents selected from the group consisting of halogen, nitro, cyano, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, (C_{1-6} haloalkoxy) C_{1-6} alkyl, (C_{1-6} alkoxy) C_{1-6} alkyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, (C_{1-6} alkylamino) C_{1-6} alkyl, (C_{1-6} dialkylamino) C_{1-6} alkyl, benzyl,
 25 phenyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, C_{1-6} alkylcarbonyloxy, C_{1-6} alkoxy carbonyl and C_{1-6} alkylcarbonyl.

Each R^{10} independently is: i) hydrogen; ii) an optionally substituted phenyl
 30 group or an optionally substituted 5-6 membered heteroaryl group; or iii) an optionally substituted C_{1-6} alkyl group. Each of the phenyl and heteroaryl groups represented by R^{10} is optionally and independently substituted with one or more

substituents selected from the group consisting of halogen, nitro, cyano, hydroxy, C₁₋₆ alkyl, C₁₋₆ haloalkyl, (C₁₋₆ haloalkoxy)C₁₋₆ alkyl, (C₁₋₆ alkoxy)C₁₋₆ alkyl, C₁₋₆ hydroxyalkyl, (C₁₋₆ aminoalkyl, (C₁₋₆ alkylamino)C₁₋₆ alkyl, (C₁₋₆ dialkylamino)C₁₋₆ alkyl, amino, C₁₋₆ alkylamino, C₁₋₆ dialkylamino, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₆ alkylcarbonyloxy, C₁₋₆ alkoxycarbonyl and C₁₋₆ alkylcarbonyl. The alkyl group represented by R¹⁰ is optionally substituted with one or more substituents selected from the group consisting halogen, nitro, cyano, hydroxy, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, amino, C₁₋₆ alkylamino, C₁₋₆ dialkylamino, C₁₋₆ alkylcarbonyloxy, C₁₋₆ alkoxycarbonyl, C₁₋₆ alkylcarbonyl and phenyl.

Each R¹¹ independently is R¹⁰, -CO₂R¹⁰, -SO₂R¹⁰ or -C(O)R¹⁰, or -N(R¹¹)₂ taken together is a 5-6 membered non-aromatic heterocyclic group optionally substituted with halogen, hydroxy, nitro, cyano, =O, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy, C1-C3 haloalkoxy and amino.

Each R¹² independently is: i) an optionally substituted phenyl group or an optionally substituted 5-6 membered heteroaryl group; or ii) an optionally substituted C₁₋₆ alkyl group. Each of the phenyl and heteroaryl groups represented by R¹² is optionally and independently substituted with one or more substituents selected from the group consisting of halogen, nitro, cyano, hydroxy, C₁₋₆ alkyl, C₁₋₆ haloalkyl, (C₁₋₆ haloalkoxy)C₁₋₆ alkyl, (C₁₋₆ alkoxy)C₁₋₆ alkyl, C₁₋₆ hydroxyalkyl, (C₁₋₆ aminoalkyl, (C₁₋₆ alkylamino)C₁₋₆ alkyl, (C₁₋₆ dialkylamino)C₁₋₆ alkyl, amino, C₁₋₆ alkylamino, C₁₋₆ dialkylamino, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₆ alkylcarbonyloxy, C₁₋₆ alkoxycarbonyl and C₁₋₆ alkylcarbonyl. The alkyl group represented by R¹² is optionally substituted with one or more substituents selected from the group consisting halogen, nitro, cyano, hydroxy, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, amino, C₁₋₆ alkylamino, C₁₋₆ dialkylamino, C₁₋₆ alkylcarbonyloxy, C₁₋₆ alkoxycarbonyl, C₁₋₆ alkylcarbonyl and phenyl.

Each R²¹ independently is hydrogen, C₁₋₆ alkyl or optionally substituted phenyl. Suitable substituents for the phenyl group represented by R²¹ are as described above for the first set of values.

Each R²² independently is C₁₋₆ alkyl or optionally substituted phenyl. Suitable substituents for the phenyl group represented by R²² are as described above for the first set of values.

Values and specific values for X, R¹, Ak¹ and Ar¹ are each independently as described above in the second set of values of the second embodiment.

Values and specific values for the remainder of the variables of Structural Formula (I) are each independently as described above in the first set of values of
5 the second embodiment.

A fourth set of values for the variables in Structural Formula (I) is provided in the following paragraphs:

Each R¹ independently is i) hydrogen; ii) an optionally substituted phenyl group or an optionally substituted 5-6 membered heteroaryl group; or iii) an
10 optionally substituted C₁₋₁₀ alkyl group. Each of the phenyl and heteroaryl groups represented by R¹ is optionally and independently substituted with one or more substituents selected from the group consisting of halogen, nitro, cyano, Ak¹⁰, (C₁₋₁₀ alkylene)-Ar¹⁰, (C₂₋₁₀ alkenylene)-Ar¹⁰, -OR¹⁰, -SR¹⁰, -OC(O)N(R¹¹)₂, -N(R¹¹)₂, -C(O)NR¹¹, -NR¹¹C(O)R¹⁰, -N(R¹¹)C(O)N(R¹¹)₂, -NR¹¹SO₂N(R¹¹)₂, -NR¹¹SO₂R¹²,
15 -SO₂N(R¹¹)₂, -OC(O)R¹⁰, -C(O)OR¹⁰ and -C(O)R¹⁰. The alkyl group represented by R¹ is optionally substituted with one or more substituents selected from the group consisting of halogen, nitro, cyano, Ar¹⁰, -OR¹⁰, -SR¹⁰, -N(R¹¹)₂, -OC(O)R¹⁰, -C(O)OR¹⁰ and -C(O)R¹⁰.

Each Ak¹ independently is a C₁₋₁₀ alkyl group optionally substituted with one
20 or more substituents selected from the group consisting of halogen, nitro, cyano, -OH, -SH, -O(C₁₋₆ alkyl), -S(C₁₋₆ alkyl), C₁₋₆ haloalkoxy, amino, C₁₋₆ alkylamino, C₁₋₆ dialkylamino, C₁₋₆ alkylcarbonyloxy, C₁₋₆ alkoxycarbonyl and C₁₋₆ alkylcarbonyl.

Each Ar¹ independently is a phenyl group or a 5-6 membered heteroaryl
25 group, each optionally and independently substituted with one or more substituents selected from the group consisting of halogen, nitro, cyano, -OH, -SH, -O(C₁₋₆ alkyl), -S(C₁₋₆ alkyl), C₁₋₆ alkyl, C₁₋₆ haloalkyl, (C₁₋₆ haloalkoxy)C₁₋₆ alkyl, (C₁₋₆ alkoxy)C₁₋₆ alkyl, C₁₋₆ hydroxyalkyl, (C₁₋₆ aminoalkyl, (C₁₋₆ alkylamino)C₁₋₆ alkyl, (C₁₋₆ dialkylamino)C₁₋₆ alkyl, (phenyl)C₁₋₆ alkyl, (5-6 membered heteroaryl)C₁₋₆
30 alkyl, amino, C₁₋₆ alkylamino, C₁₋₆ dialkylamino, C₁₋₆ haloalkoxy, C₁₋₆ alkylcarbonyloxy, C₁₋₆ alkoxycarbonyl and C₁₋₆ alkylcarbonyl.

Values and specific values for X, R¹⁰, R¹¹, R¹², R²¹, R²², Ak¹⁰ and Ar¹⁰ are each independently as described above in the third set of values of the second embodiment.

5 Values and specific values for the remainder of the variables of Structural Formula (I) are each independently as described above in the first set of values of the second embodiment.

A fifth set of values for the variables in Structural Formula (I) is provided in the following paragraphs:

Each R¹⁰ independently is i) hydrogen, ii) a phenyl group or a 5-6
10 membered heteroaryl group, each of which is independently and optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, amino, cyano, nitro, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy and C1-C3 haloalkoxy, or iii) a C₁₋₁₀ alkyl group optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, amino,
15 cyano, nitro, C1-C3 alkoxy, C1-C3 haloalkoxy and phenyl.

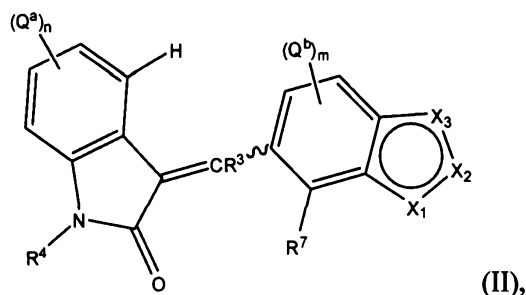
Each R¹² independently i) a phenyl group or a 5-6 membered heteroaryl group, each of which is independently and optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, amino, cyano, nitro, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy and C1-C3 haloalkoxy, or ii) a
20 C₁₋₁₀ alkyl group optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, amino, cyano, nitro, C1-C3 alkoxy, C1-C3 haloalkoxy and phenyl.

Each Ar¹⁰ independently is a phenyl group or a 5-6 membered heteroaryl group, each of which is independently and optionally substituted with one or more
25 substituents selected from the group consisting of halogen, hydroxy, amino, cyano, nitro, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy and C1-C3 haloalkoxy.

Values and specific values for X, R¹, R¹¹, R²¹, R²², Ak¹, Ak¹⁰ and Ar¹ are each independently as described above in the fourth set of values of the second embodiment.

30 Values and specific values for the remainder of the variables of Structural Formula (I) are each independently as described above in the first set of values of the second embodiment.

In a third embodiment, the compound of the invention is represented by Structural Formula (II) or a pharmaceutically acceptable salt thereof:



5 wherein values and specific values for the variables of Structural Formula (II) are provided in the following paragraphs:

Each of n and m is independently 0, 1 or 2.

Each R^2 is $-H$ or C1-C6 alkyl.

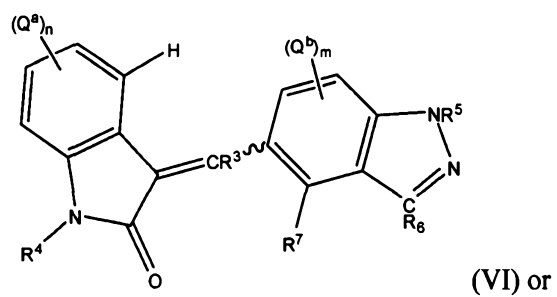
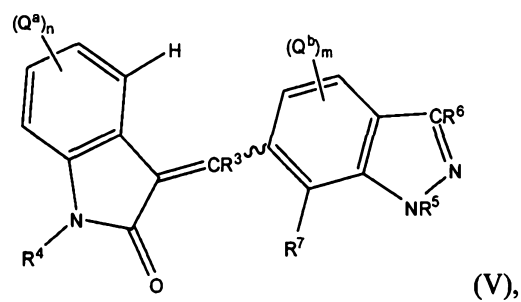
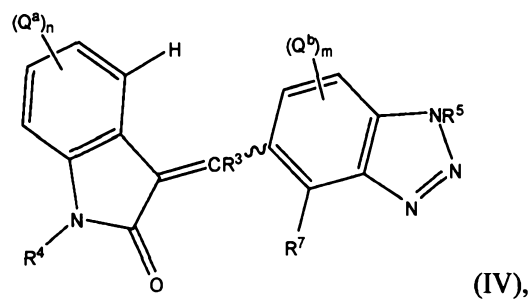
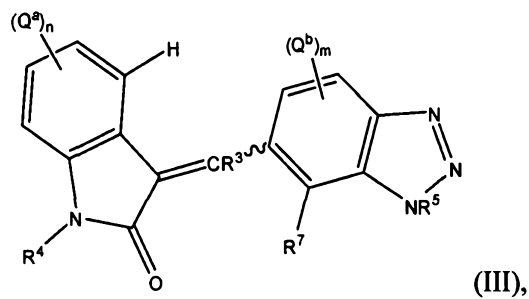
Each of R^4 and R^5 is independently $-H$, C1-C6 alkyl, phenyl, $-C(O)(C1-C6$
 10 alkyl), $-C(O)(phenyl)$, $-C(O)O(C1-C6 alkyl)$, $-C(O)O(phenyl)$, $-S(O)_2(C1-C6 alkyl)$
 or $-S(O)_2(phenyl)$, wherein each said phenyl in the groups represented by R^4 and R^5
 independently is optionally substituted with one or more substituents selected from
 the group consisting of halogen, hydroxy, nitro, cyano, amino, C1-C6 alkyl, C1-C6
 haloalkyl, C1-C6 alkoxy and C1-C6 haloalkoxy, and wherein each said alkyl in the
 15 groups represented by R^4 and R^5 independently is optionally substituted with one
 or more substituents selected from the group consisting of halogen, hydroxy, nitro,
 cyano, amino, C1-C6 alkoxy, C1-C6 haloalkoxy and phenyl.

R^7 is $-H$, F, Cl or methyl.

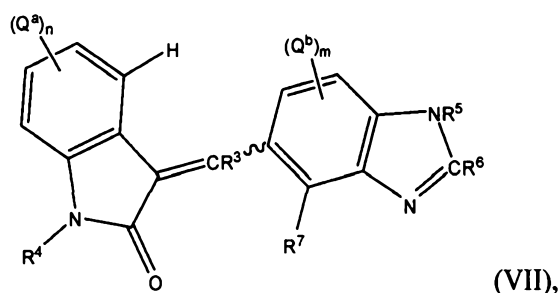
20 Values and specific values for the remainder of the variables of Structural
 Formula (II) are each independently as described above in the second embodiment
 for the variables of Structural Formula (I).

Alternatively, each of n and m is independently 0, 1 or 2; and values and
 specific values for the remaining variables of Structural Formula (II) are each
 independently as described in the first set, the second set, the third set, the fourth set
 25 or the fifth set of values for the variables of Structural Formula (I) in the second
 specific embodiment.

In a fourth embodiment, the compound of the invention is represented by Structural Formula (III), (IV), (V), (VI) or (VII), or a pharmaceutically acceptable salt thereof:



- 29 -



wherein a first set of values and specific values for the variables of Structural Formulas (III) – (VII) is provided in the following paragraphs:

One of Q^a and Q^b is halogen, $-\text{NO}_2$, $-\text{CN}$, Ak^1 , Ar^1 , $(\text{C}_{1-10} \text{ alkylene})-\text{Ar}^1$, $(\text{C}_{2-10} \text{ alkenylene})-\text{Ar}^1$ or $-\text{X}-\text{R}^1$; and the other of Q^a and Q^b is halogen, hydroxy, nitro, cyano, amino, methyl, methoxy, halomethyl or halomethoxy.

Each of n and m independently is 0, 1 or 2.

Each R^2 is $-\text{H}$ or C1-C6 alkyl.

R^3 is $-\text{H}$, halogen, C1-C6 alkyl or C1-C6 haloalkyl.

Each of R^4 and R^5 independently is $-\text{H}$, C1-C6 alkyl, phenyl, $-\text{C}(\text{O})(\text{C1-C6 alkyl})$, $-\text{C}(\text{O})(\text{phenyl})$, $-\text{C}(\text{O})\text{O}(\text{C1-C6 alkyl})$, $-\text{C}(\text{O})\text{O}(\text{phenyl})$, $-\text{S}(\text{O})_2(\text{C1-C6 alkyl})$ or $-\text{S}(\text{O})_2(\text{phenyl})$, wherein each said phenyl in the groups represented by R^4 and R^5 independently is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 alkoxy and C1-C6 haloalkoxy, and wherein each said alkyl in the groups represented by R^4 and R^5 independently is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C1-C6 alkoxy, C1-C6 haloalkoxy and phenyl.

R^6 is hydrogen, halogen, nitro, cyano, R' , $-\text{OR}$, $-\text{SR}$, $-\text{N}(\text{R})_2$, $-\text{C}(\text{O})\text{R}$, $-\text{C}(\text{O})\text{OR}$, $-\text{OC}(\text{O})\text{R}$, $-\text{C}(\text{O})\text{N}(\text{R})_2$, $-\text{OC}(\text{O})\text{N}(\text{R})_2$, $-\text{NRC}(\text{O})\text{R}$, $-\text{NRC}(\text{O})\text{OR}$, $-\text{SOR}'$, $-\text{SO}_2\text{R}'$, $-\text{SO}_3\text{R}'$, $-\text{SO}_2\text{N}(\text{R})_2$, $-\text{NRS}(\text{O})\text{R}'$, $-\text{NRSO}_2\text{R}'$, $-\text{NRC}(\text{O})\text{N}(\text{R})_2$, $-\text{NRC}(\text{O})\text{ON}(\text{R})_2$ or $-\text{NRSO}_2\text{N}(\text{R})_2$. Alternatively, each R^6 is hydrogen, halogen, nitro, cyano, R' , $-\text{OR}$, $-\text{SR}$ or $-\text{N}(\text{R})_2$; and each R independently is hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted phenyl or optionally substituted 5-6 membered heteroaryl, or $\text{N}(\text{R})_2$ taken together is a non-aromatic heterocyclic group optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro,

cyano, =O, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy, C1-C3 haloalkoxy and amino; and each R¹ independently is optionally substituted C₁₋₆ alkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted phenyl or optionally substituted 5-6 membered heteroaryl.

5 Each R⁷ independently is -H, F, Cl or methyl.

Values and specific values for the remainder of the variables of Structural Formulas (III) – (VII) are each independently as described above in the first set of values for the variables of Structural Formula (I).

10 A second set of values and specific values for the variables of Structural Formulas (III) – (VII) is provided in the following paragraphs:

Each of R⁴ and R⁵ independently is -H, C1-C6 alkyl, phenyl, -C(O)(C1-C6 alkyl), -C(O)(phenyl), -C(O)O(C1-C6 alkyl), -C(O)O(phenyl), -S(O)₂(C1-C6 alkyl) or -S(O)₂(phenyl).

15 Values and specific values for n, m, Q^a and Q^b, R², R⁶ and R⁷ are each independently as described above in the first set of values for Structural Formulas (III) – (VII).

Values and specific values for the remainder of the variables of Structural Formulas (III) – (VII) are each independently as described above in the first set of values for the variables of Structural Formula (I).

20 A third set of values and specific values for the variables of Structural Formulas (III) – (VII) is provided in the following paragraphs:

Both of Q^a and Q^b are independently halogen, hydroxy, nitro, cyano, amino, methyl, methoxy, halomethyl or halomethoxy.

25 Values and specific values for n, m, R², R³, R⁴, R⁵, R⁶ and R⁷ are each independently as described above in the second set of values for Structural Formulas (III) – (VII).

Values and specific values for the remainder of the variables of Structural Formulas (III) – (VII) are each independently as described above in the first set of values for the variables of Structural Formula (I).

30 A fourth set of values and specific values for the variables of Structural Formulas (III) – (VII) is provided in the following paragraphs:

One of Q^a and Q^b is halogen, hydroxy, cyano, nitro, C1-C6 alkyl, C1-C6 haloalkyl, -C(O)(C1-C6 alkyl), -C(O)NH₂, -C(O)NH(C1-C6 alkyl), -C(O)N(C1-C6 alkyl)₂, -SO₂NH₂, -SO₂NH(C1-C6 alkyl), -SO₂N(C1-C6 alkyl)₂, -OH, -O(C1-C6 alkyl), -O(C1-C6 haloalkyl), -SH, -S(C1-C6 alkyl), -S(C1-C6 haloalkyl), -NH₂,
 5 -NH(C1-C6 alkyl), -N(C1-C6 alkyl)₂, -NHC(O)(C1-C6 alkyl), -NHC(O)O(C1-C6 alkyl), -NHC(O)NH₂, -NHC(O)NH(C1-C6 alkyl), -NHC(O)N(C1-C6 alkyl)₂, -NHC(O)ONH₂, -NHC(O)ONH(C1-C6 alkyl), -NHC(O)ON(C1-C6 alkyl)₂, -NHSO₂NH₂, -NHSO₂NH(C1-C6 alkyl), -NHSO₂N(C1-C6 alkyl)₂ or -NHSO₂(C1-C6 alkyl); and the other of Q^a and Q^b is halogen, hydroxy, nitro, cyano, amino,
 10 methyl, methoxy, halomethyl or halomethoxy.

Alternatively, one of Q^a and Q^b is halogen, hydroxy, cyano, nitro, Ph, -CH₂Ph, -C(O)Ph, -C(O)NH(Ph), -C(O)N(C1-C6 alkyl)(Ph), -SO₂NH(Ph), -SO₂N(C1-C6 alkyl)(Ph), -O(Ph), -S(Ph), -NH(Ph), -N(C1-C6 alkyl)(Ph), -NHC(O)(Ph), -NHC(O)O(Ph), -NHC(O)NH(Ph), -NHC(O)N(C1-C6 alkyl)(Ph),
 15 -NHC(O)ONH(Ph), -NHC(O)ON(C1-C6 alkyl)(Ph), -NHSO₂NH(Ph), -NHSO₂N(C1-C6 alkyl)(Ph) or -NHSO₂(Ph), wherein each Ph independently and optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy and C1-C3 haloalkoxy; and the other of Q^a and Q^b is halogen,
 20 hydroxy, nitro, cyano, amino, methyl, methoxy, halomethyl or halomethoxy.

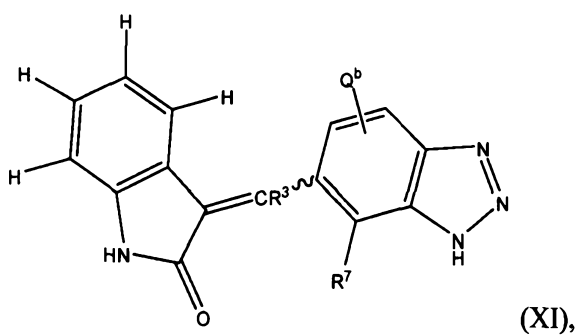
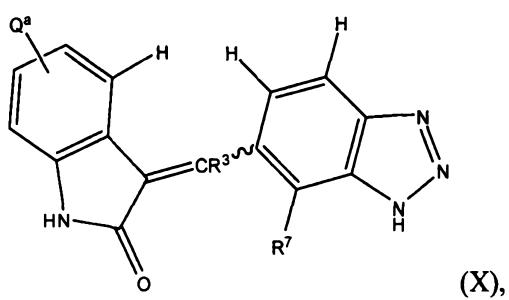
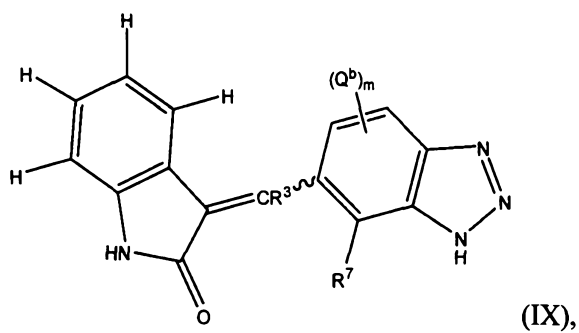
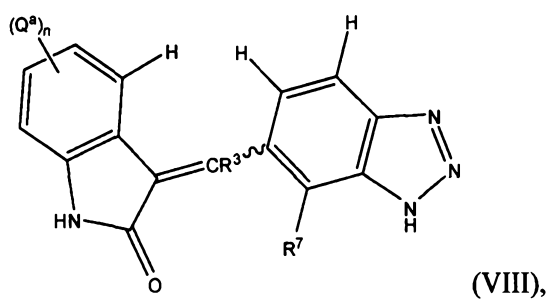
Values and specific values for the remainder of the variables of Structural Formulas (III) – (VII) are each independently as described above in the first set of values for the variables of Structural Formula (I) in second embodiment.

In a fifth set, each of n and m independently is 0, 1 or 2; and values and
 25 specific values for the remaining variables of each Structural Formula (III) – (VII) are independently as described in the first set, the second set, the third set, the fourth set or the fifth set of values for the variables of Structural Formula (I) in the second embodiment.

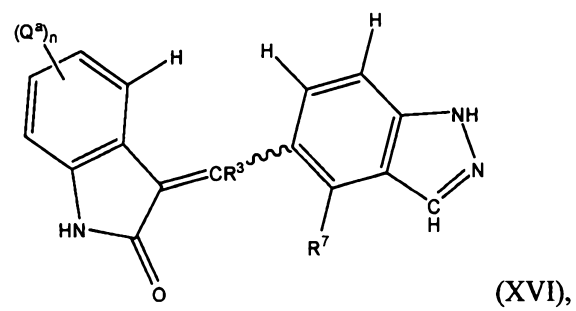
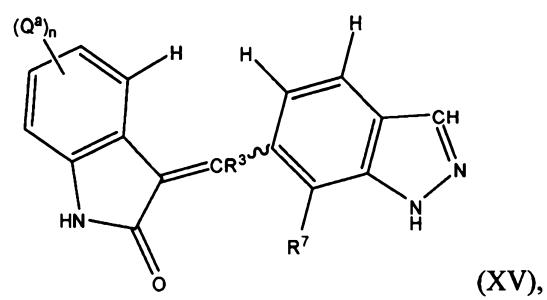
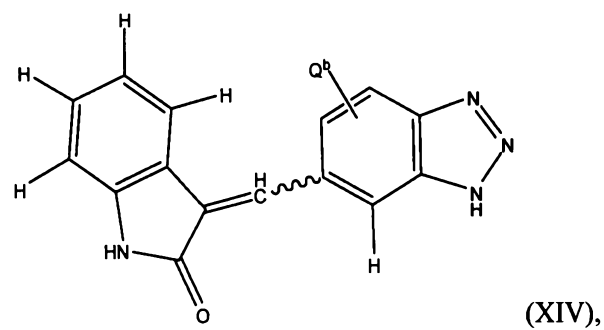
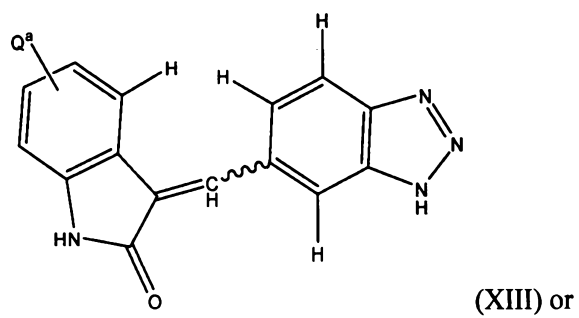
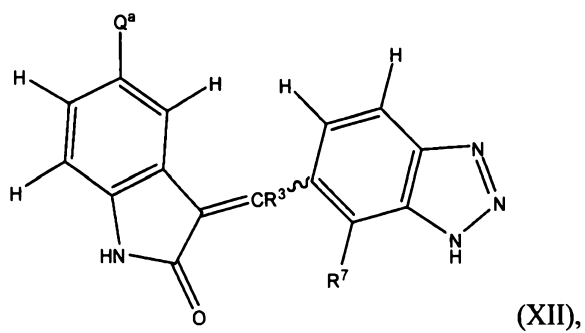
In a sixth set, values and specific values for the remaining variables of each
 30 Structural Formula (III) – (VII) are independently as described in the first set of values for the variables of Structural Formula (II) in the third embodiment.

In a fifth embodiment, the compound of the invention is represented by a structural formula selected from Structural Formulas (VIII) – (XXXV) or a pharmaceutically acceptable salt thereof:

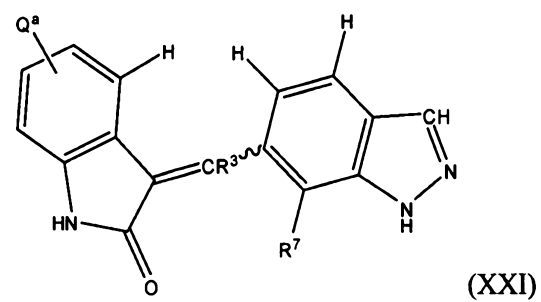
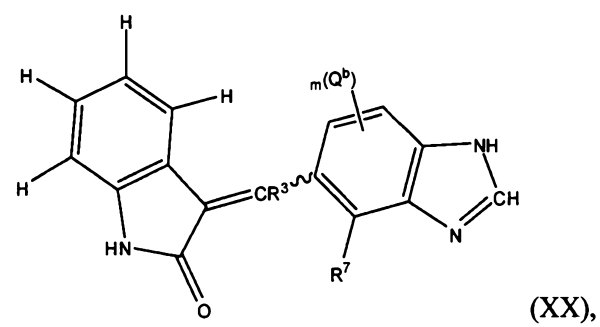
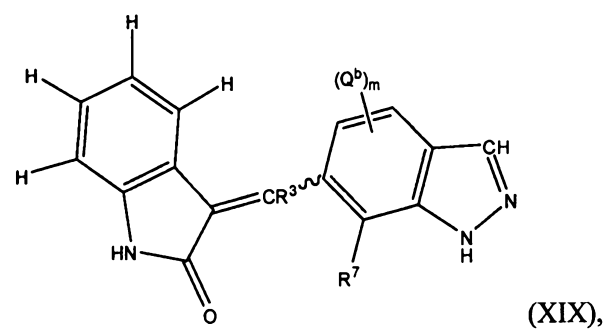
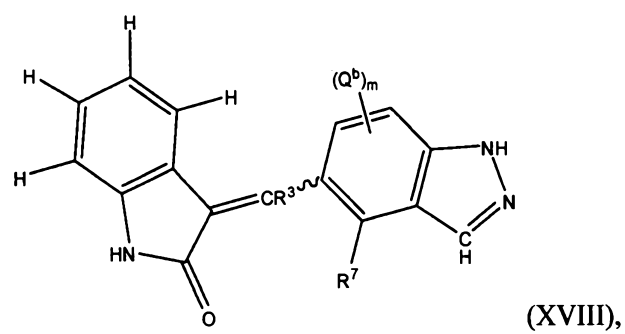
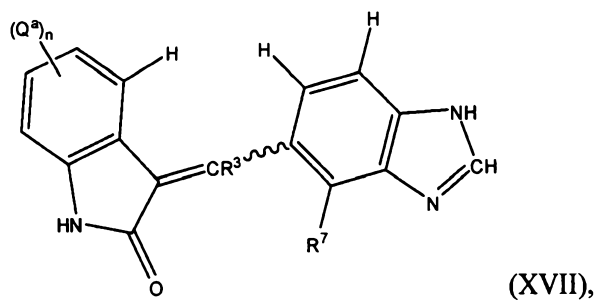
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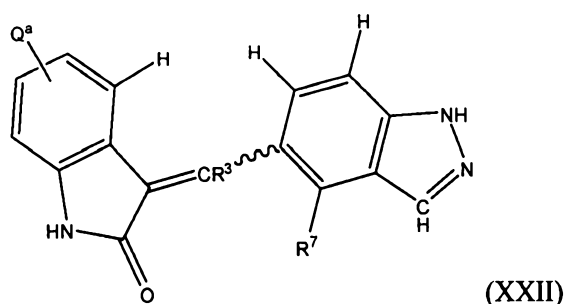
- 33 -



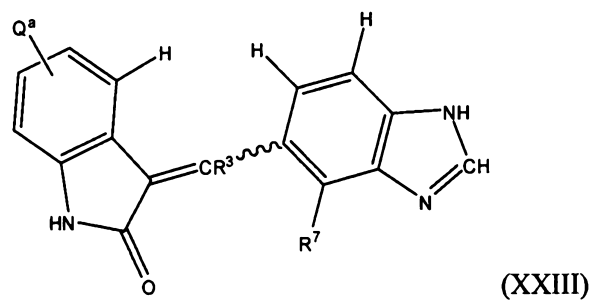
- 34 -



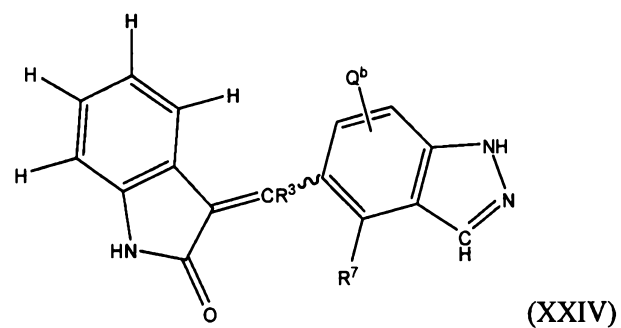
- 35 -



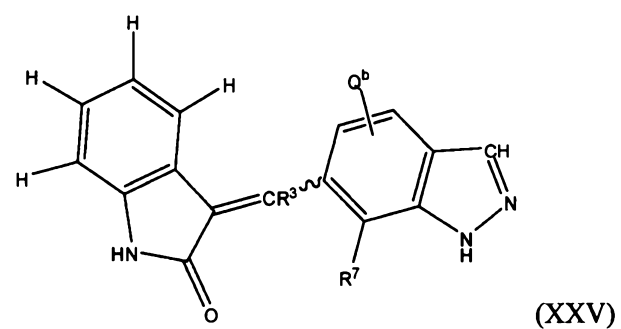
(XXII)



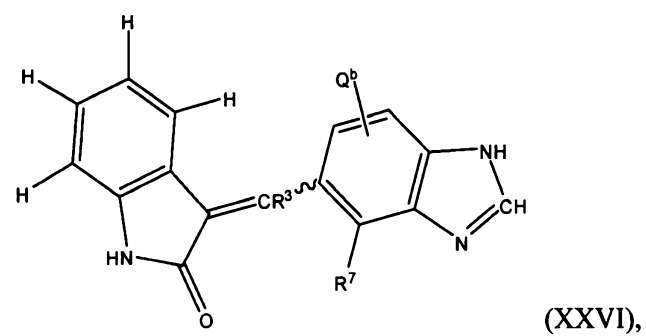
(XXIII)



(XXIV)

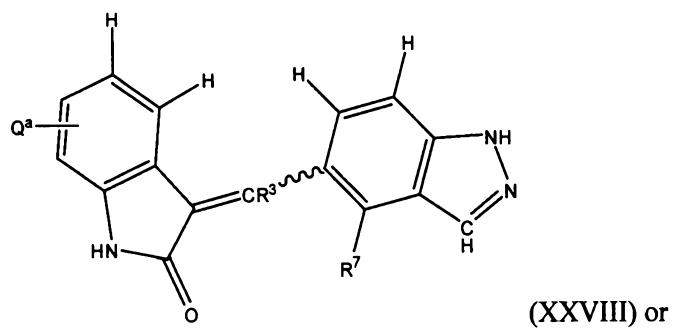


(XXV)

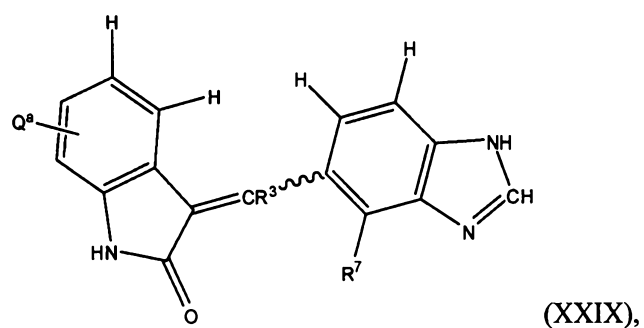


(XXVI),

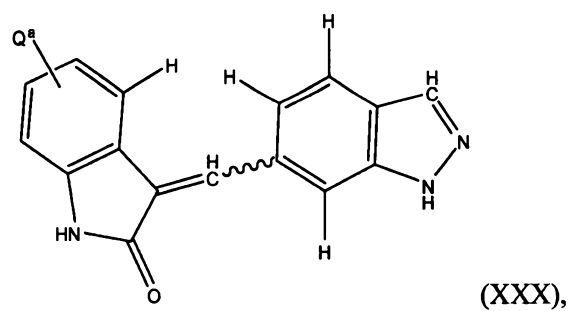
(XXVII),



(XXVIII) or

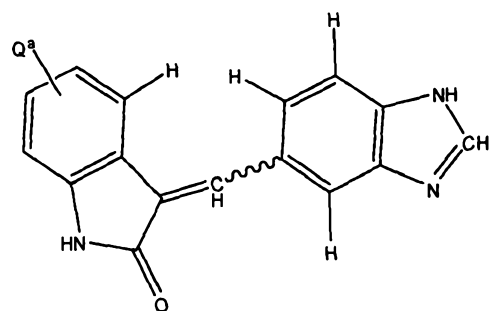


(XXIX),

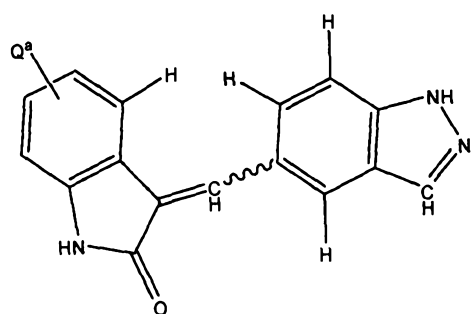


(XXX),

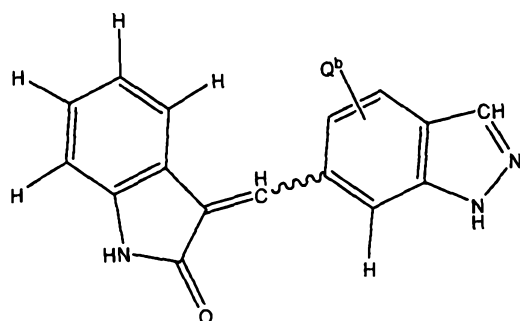
- 37 -



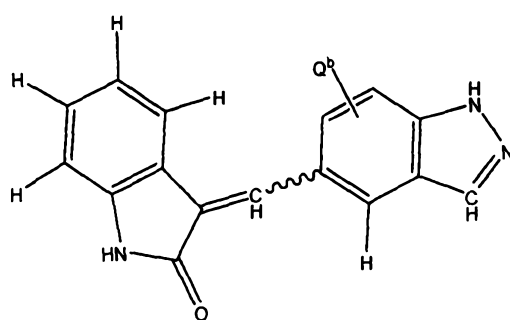
(XXXI),



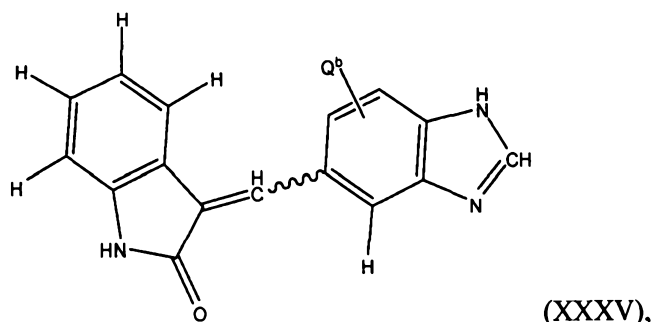
(XXXII),



(XXXIII),



(XXXIV) or



wherein a first set of values and preferred values for the variables of Structural Formulas (VIII) – (XXXV) is provided in the following paragraphs:

- 5 Each Q^a in Structural Formulas (VIII), (X), (XII), (XIII), (XV), (XVI), (XVII), (XXI), (XXII), (XXIII), (XXVII), (XXVIII), (XXIX), (XXX), (XXXI) and (XXXII) independently is halogen, $-\text{NO}_2$, $-\text{CN}$, Ak^1 , Ar^1 , $(\text{C}_{1-10} \text{ alkylene})-\text{Ar}^1$, $(\text{C}_{2-10} \text{ alkenylene})-\text{Ar}^1$ or $-\text{X}-\text{R}^1$. Each Q^b in Structural Formulas (IX), (XI), (XIV), (XVIII), (XIX), (XX), (XXIV), (XXV), (XXVI), (XXXIII), (XXXIV) and (XXXV)
- 10 independently is halogen, $-\text{NO}_2$, $-\text{CN}$, Ak^1 , Ar^1 , $(\text{C}_{1-10} \text{ alkylene})-\text{Ar}^1$, $(\text{C}_{2-10} \text{ alkenylene})-\text{Ar}^1$ or $-\text{X}-\text{R}^1$.

Each of n and m in Structural Formulas (VIII), (IX), (XV), (XVI), (XVII), (XVIII), (XIX) and (XX) independently is 0, 1 or 2.

Each R^2 is $-\text{H}$ or C1-C6 alkyl.

- 15 R^3 is $-\text{H}$, halogen, C1-C6 alkyl or C1-C6 haloalkyl.

Each R^7 in Structural Formulas (VIII) - (XII) and (XV) - (XXIX) independently is $-\text{H}$, F, Cl or methyl.

- Values and specific values for the remainder of the variables of Structural Formulas (VIII) – (XXXV) are each independently as described above in the first set
- 20 of values for the variables of Structural Formula (I).

A second set of values and specific values for the variables of Structural Formulas (VIII) – (XXXV) is provided in the following paragraphs:

- Each Q^a in Structural Formulas (VIII), (X), (XII), (XIII), (XV), (XVI), (XVII), (XXI), (XXII), (XXIII), (XXVII), (XXVIII), (XXIX), (XXX), (XXXI) and
- 25 (XXXII) independently is halogen, hydroxy, cyano, nitro, C1-C6 alkyl, C1-C6 haloalkyl, $-\text{C}(\text{O})(\text{C1-C6 alkyl})$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NH}(\text{C1-C6 alkyl})$, $-\text{C}(\text{O})\text{N}(\text{C1-C6 alkyl})_2$, $-\text{SO}_2\text{NH}_2$, $-\text{SO}_2\text{NH}(\text{C1-C6 alkyl})$, $-\text{SO}_2\text{N}(\text{C1-C6 alkyl})_2$, $-\text{OH}$, $-\text{O}(\text{C1-C6 alkyl})$.

alkyl), -O(C1-C6 haloalkyl), -SH, -S(C1-C6 alkyl), -S(C1-C6 haloalkyl), -NH₂,
 -NH(C1-C6 alkyl), -N(C1-C6 alkyl)₂, , -NHC(O)(C1-C6 alkyl), -NHC(O)O(C1-C6
 alkyl), -NHC(O)NH₂, -NHC(O)NH(C1-C6 alkyl), -NHC(O)N(C1-C6 alkyl)₂,
 -NHC(O)ONH₂, -NHC(O)ONH(C1-C6 alkyl), -NHC(O)ON(C1-C6 alkyl)₂,
 5 -NHSO₂NH₂, -NHSO₂NH(C1-C6 alkyl), -NHSO₂N(C1-C6 alkyl)₂ or -NHSO₂(C1-
 C6 alkyl). Alternatively, each Q^a in Structural Formulas (VIII), (X), (XII), (XIII),
 (XV), (XVI), (XVII), (XXI), (XXII), (XXIII), (XXVII), (XXVIII), (XXIX), (XXX),
 (XXXI) and (XXXII) independently is halogen, hydroxy, cyano, nitro, Ph, -CH₂Ph,
 -C(O)Ph, -C(O)NH(Ph), -C(O)N(C1-C6 alkyl)(Ph), -SO₂NH(Ph), -SO₂N(C1-C6
 10 alkyl)(Ph), -O(Ph), -S(Ph), -NH(Ph), -N(C1-C6 alkyl)(Ph), -NHC(O)(Ph),
 -NHC(O)O(Ph), -NHC(O)NH(Ph), -NHC(O)N(C1-C6 alkyl)(Ph),
 -NHC(O)ONH(Ph), -NHC(O)ON(C1-C6 alkyl)(Ph), -NHSO₂NH(Ph),
 -NHSO₂N(C1-C6 alkyl)(Ph) or -NHSO₂(Ph), wherein each Ph is a phenyl group
 independently and optionally substituted with one or more substituents selected from
 15 the group consisting of halogen, hydroxy, nitro, cyano, amino, C1-C3 alkyl, C1-C3
 haloalkyl, C1-C3 alkoxy and C1-C3 haloalkoxy.

Each Q^b in Structural Formulas (IX), (XI), (XIV), (XVIII), (XIX), (XX),
 (XXIV), (XXV), (XXVI), (XXXIII), (XXXIV) and (XXXV) independently is
 halogen, hydroxy, cyano, nitro, C1-C6 alkyl, C1-C6 haloalkyl, -C(O)(C1-C6 alkyl),
 20 -C(O)NH₂, -C(O)NH(C1-C6 alkyl), -C(O)N(C1-C6 alkyl)₂, -SO₂NH₂, -SO₂NH(C1-
 C6 alkyl), -SO₂N(C1-C6 alkyl)₂, -OH, -O(C1-C6 alkyl), -O(C1-C6 haloalkyl), -SH,
 -S(C1-C6 alkyl), -S(C1-C6 haloalkyl), -NH₂, -NH(C1-C6 alkyl), -N(C1-C6 alkyl)₂, ,
 -NHC(O)(C1-C6 alkyl), -NHC(O)O(C1-C6 alkyl), -NHC(O)NH₂, -NHC(O)NH(C1-
 C6 alkyl), -NHC(O)N(C1-C6 alkyl)₂, -NHC(O)ONH₂, -NHC(O)ONH(C1-C6 alkyl),
 25 -NHC(O)ON(C1-C6 alkyl)₂, -NHSO₂NH₂, -NHSO₂NH(C1-C6 alkyl),
 -NHSO₂N(C1-C6 alkyl)₂ or -NHSO₂(C1-C6 alkyl). Alternatively, each Q^b in
 Structural Formulas (IX), (XI), (XIV), (XVIII), (XIX), (XX), (XXIV), (XXV),
 (XXVI), (XXXIII), (XXXIV) and (XXXV) independently is halogen, hydroxy,
 cyano, nitro, Ph, -CH₂Ph, -C(O)Ph, -C(O)NH(Ph), -C(O)N(C1-C6 alkyl)(Ph),
 30 -SO₂NH(Ph), -SO₂N(C1-C6 alkyl)(Ph), -O(Ph), -S(Ph), -NH(Ph), -N(C1-C6
 alkyl)(Ph), -NHC(O)(Ph), -NHC(O)O(Ph), -NHC(O)NH(Ph), -NHC(O)N(C1-C6
 alkyl)(Ph), -NHC(O)ONH(Ph), -NHC(O)ON(C1-C6 alkyl)(Ph), -NHSO₂NH(Ph),

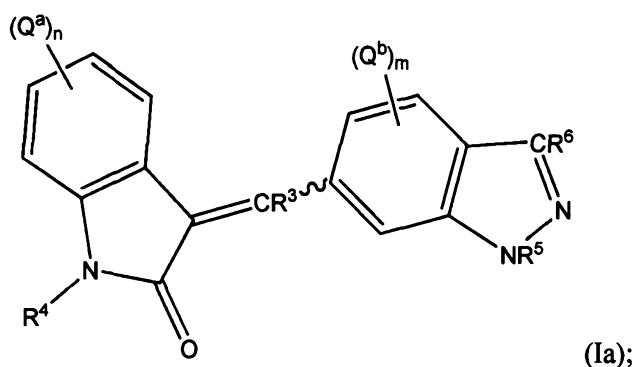
-NHSO₂N(C1-C6 alkyl)(Ph) or -NHSO₂(Ph), wherein each Ph is a phenyl group independently and optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy and C1-C3 haloalkoxy.

- 5 Values and specific values for R³, R⁷, n and m are each independently as described above in the first set of values for the variables of Structural Formulas (VIII) – (XXXV).

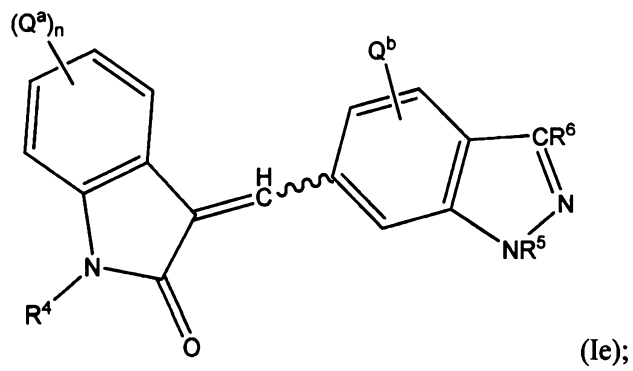
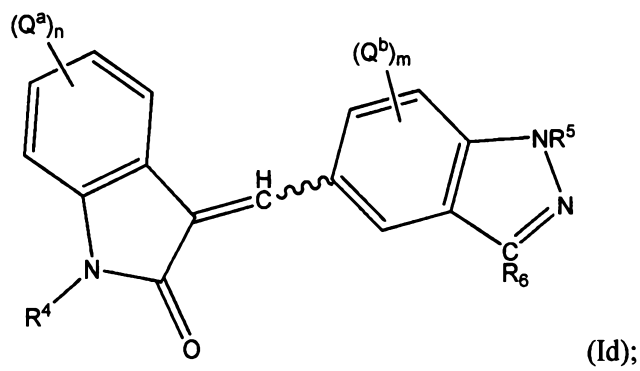
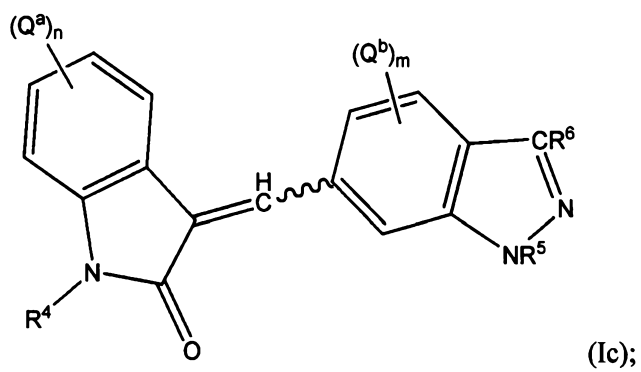
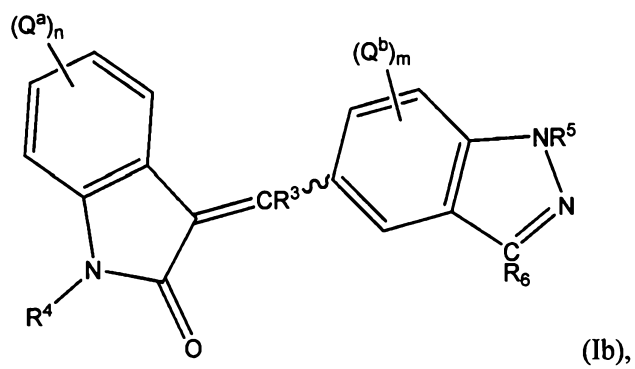
- In a third set, each of n and m independently is 0, 1 or 2; and values and preferred values of the remaining variables of Structural Formulas (VIII) – (XXXV) are each independently as described above for the first set, second set, third set,
10 fourth set or the fifth set of values for the variables of Structural Formula (I) of the second embodiment.

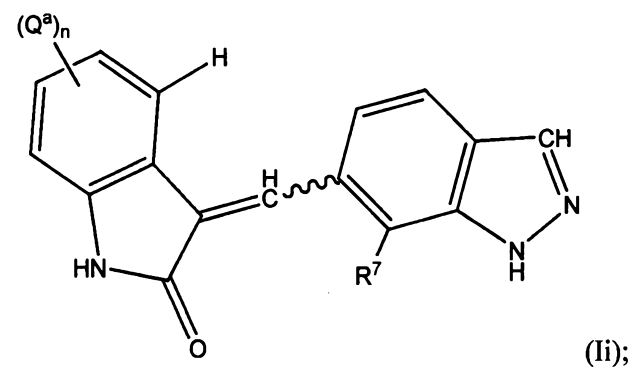
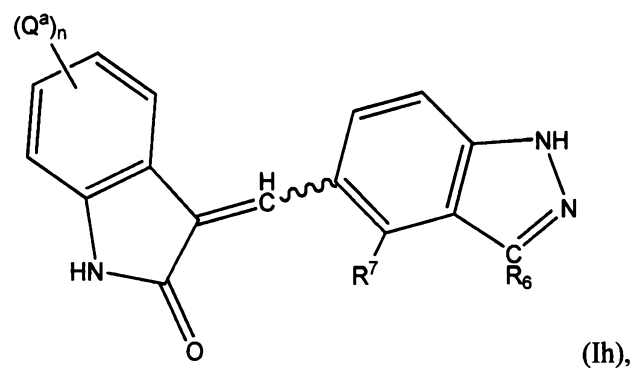
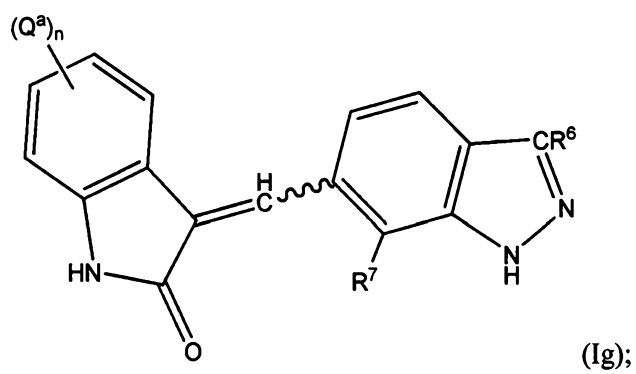
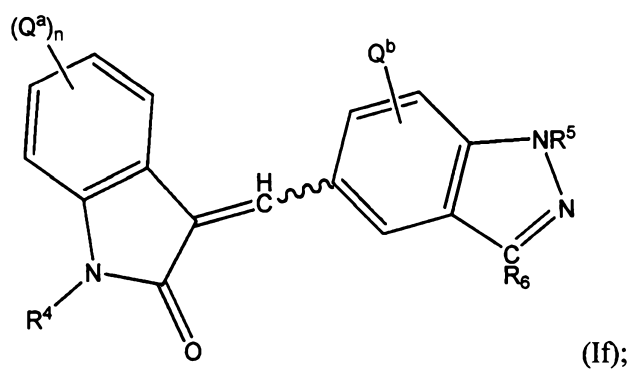
- In a fourth set, values and specific values for the remaining variables of each Structural Formulas (VIII) – (XXXV) are each independently as described in the
15 first set of values for the variables of Structural Formula (II).

In a sixth embodiment, the compound of the present invention is represented by Structural Formula (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (Ik), (Il), (C1)-(C4), (D1)-(D8), (E1)-(E8), (F1)-(F8), (G1)-(G8), (H1)-(H8), (I'1)-(I'8), (J1)-(J8), (K1)-(K8):

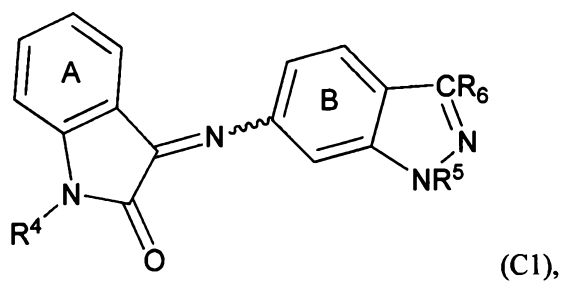
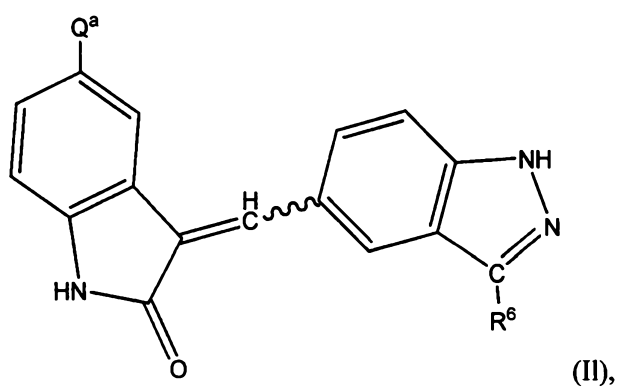
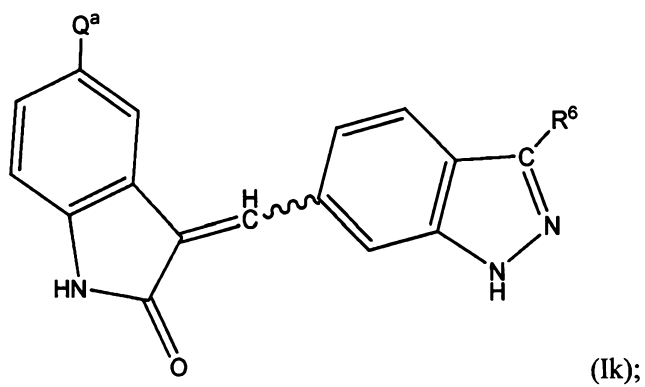
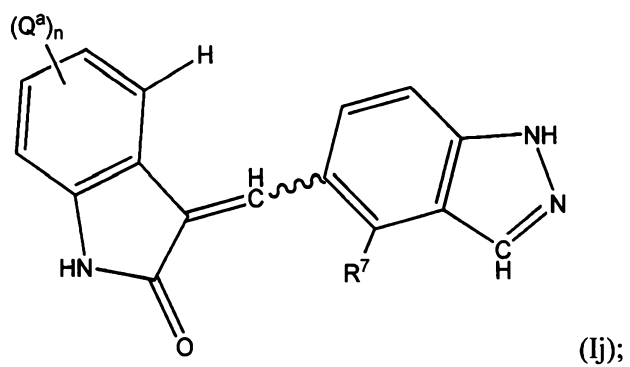


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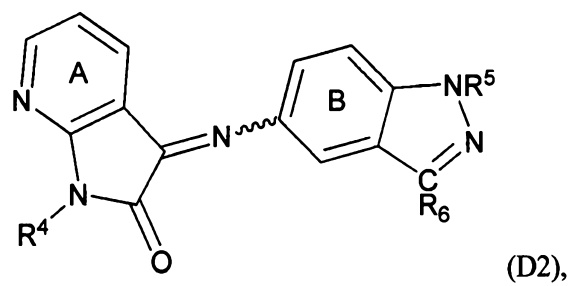
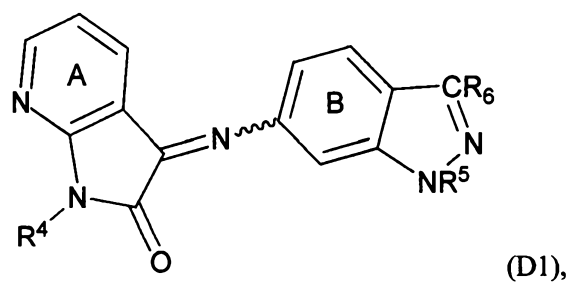
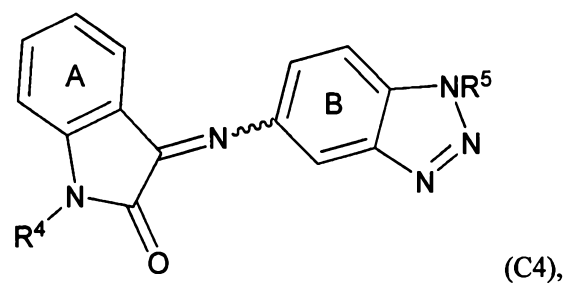
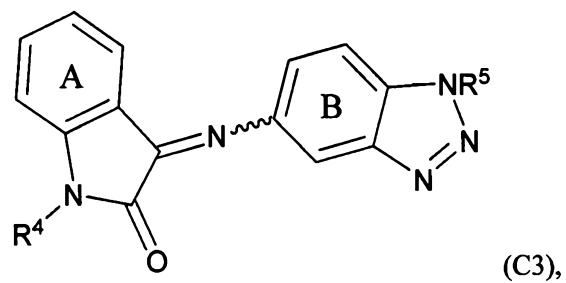
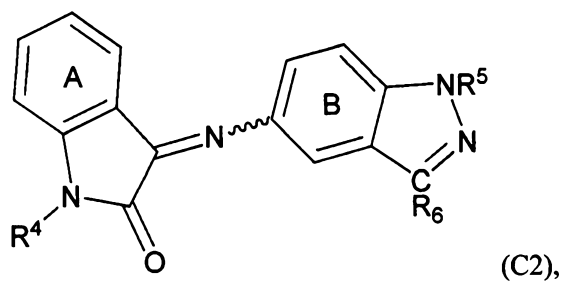




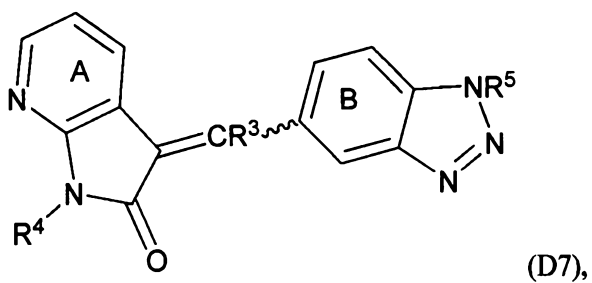
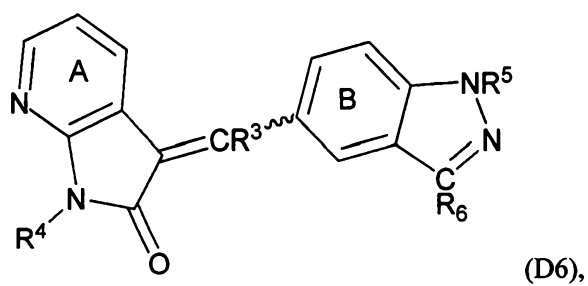
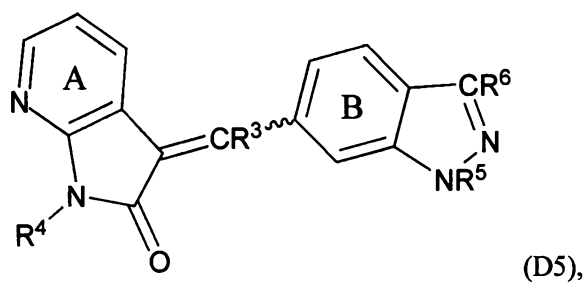
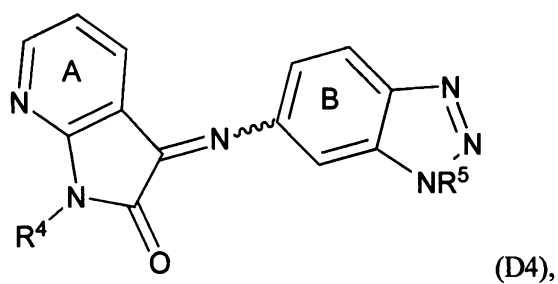
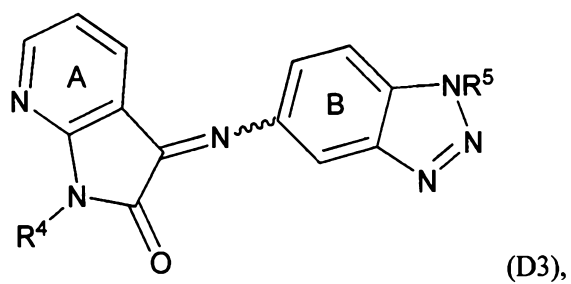
- 43 -



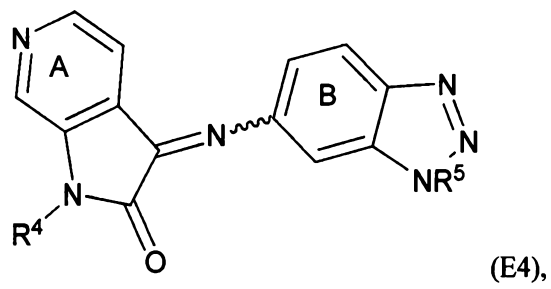
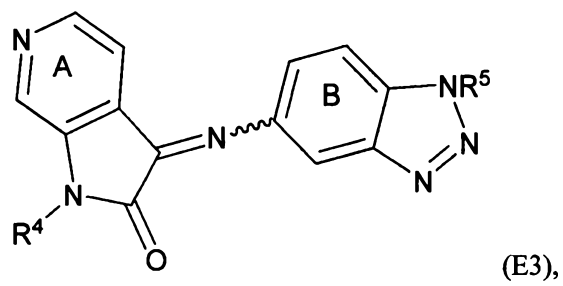
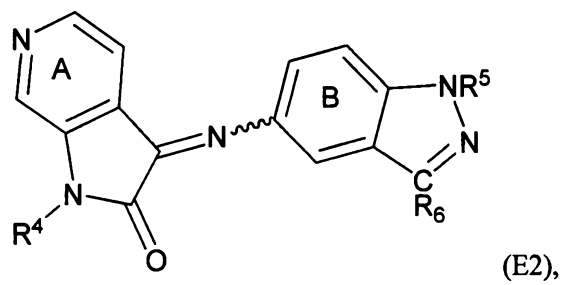
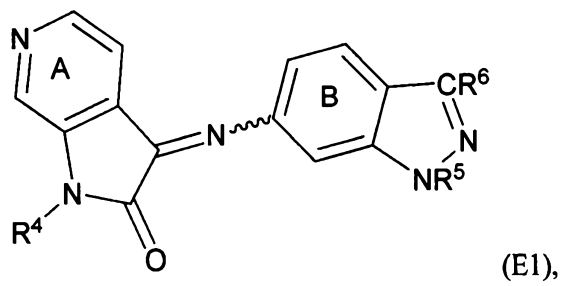
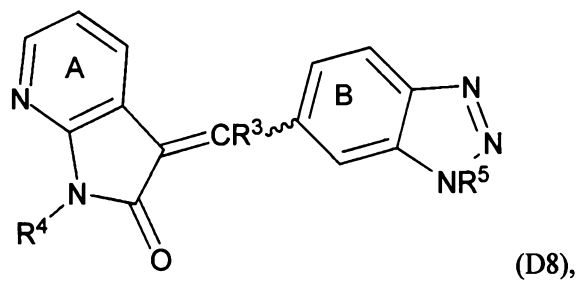
- 44 -



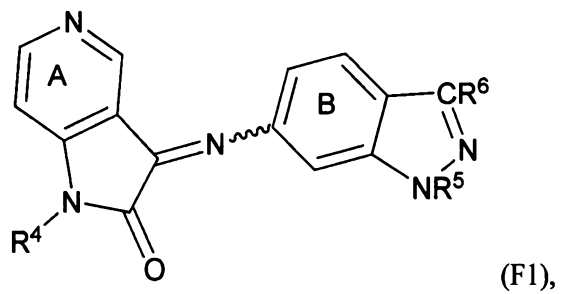
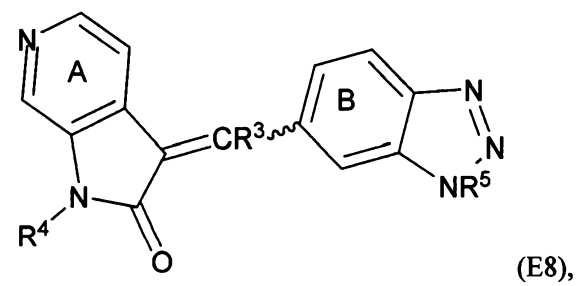
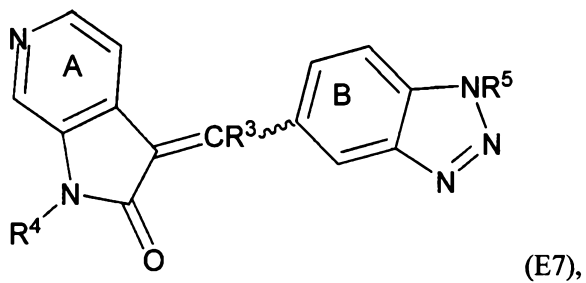
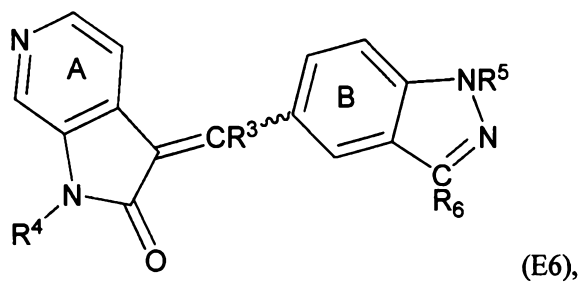
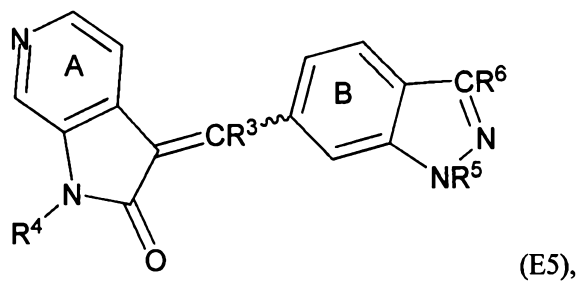
- 45 -



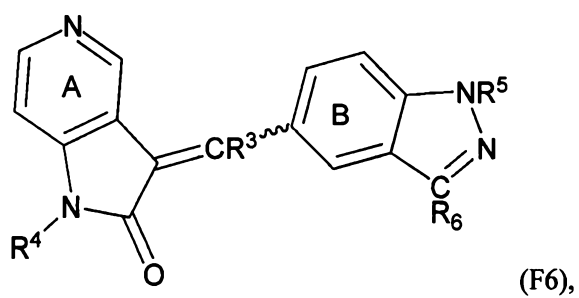
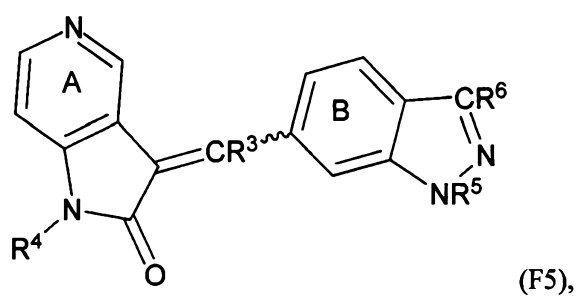
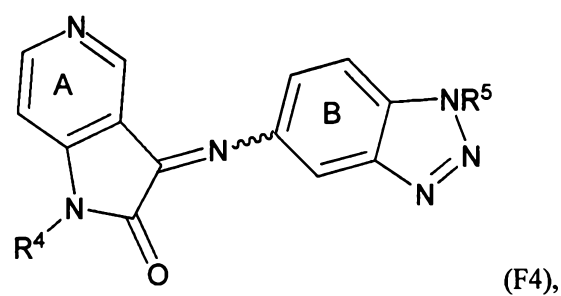
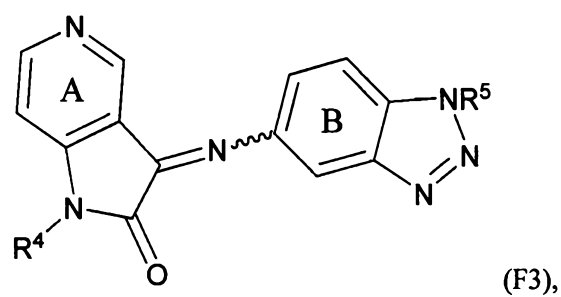
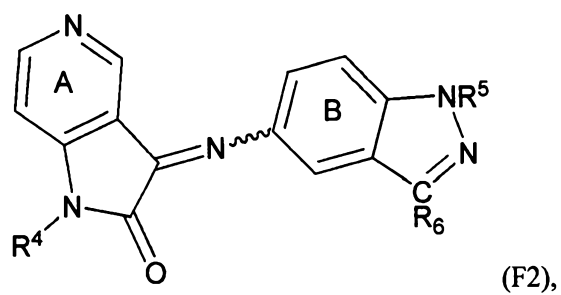
- 46 -

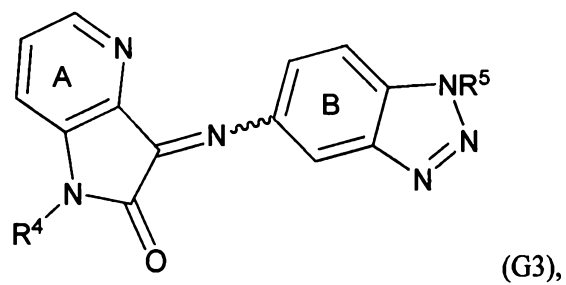
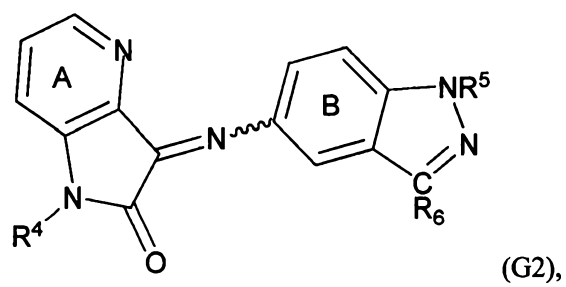
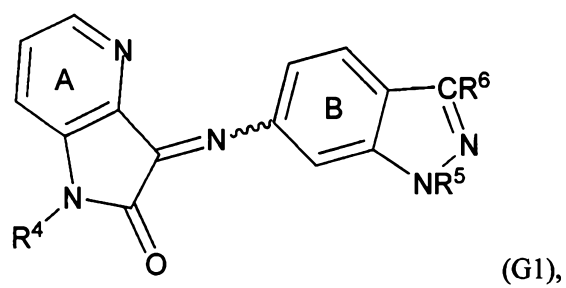
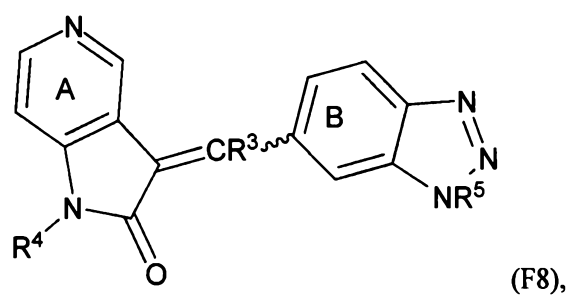
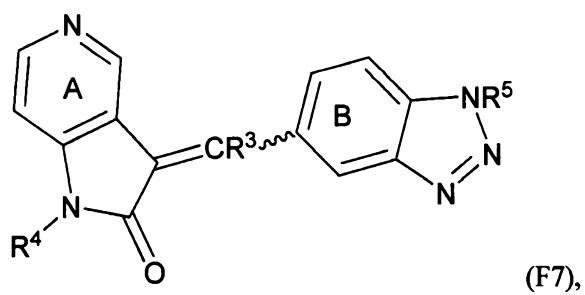


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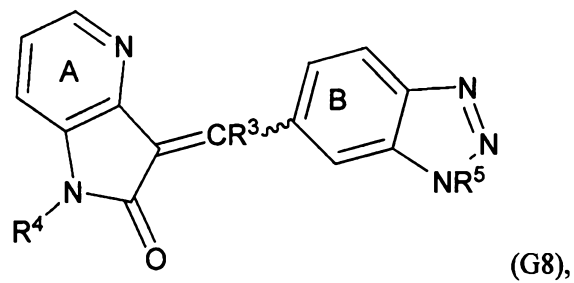
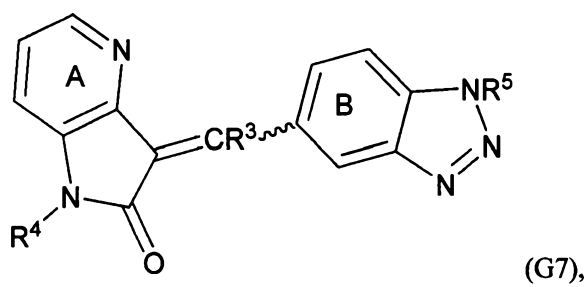
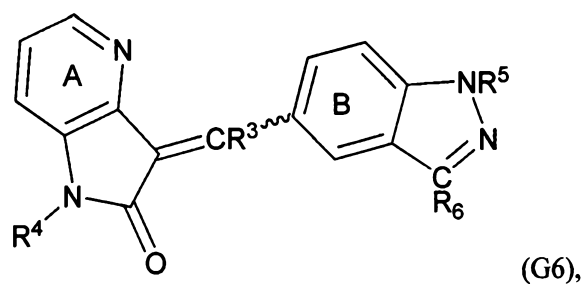
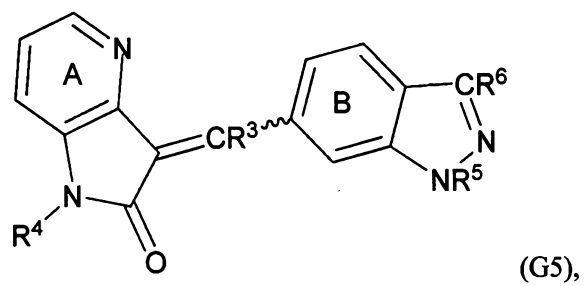
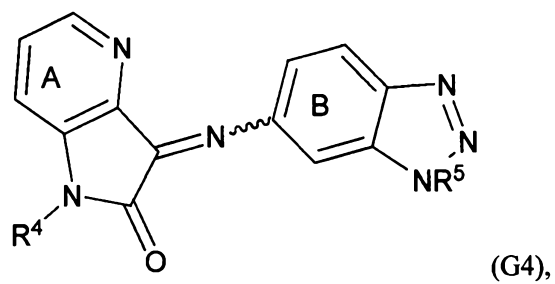


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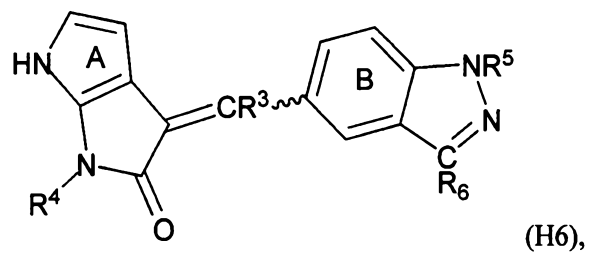
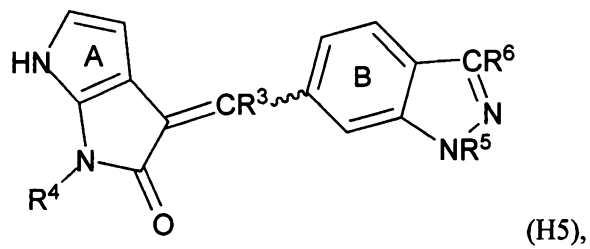
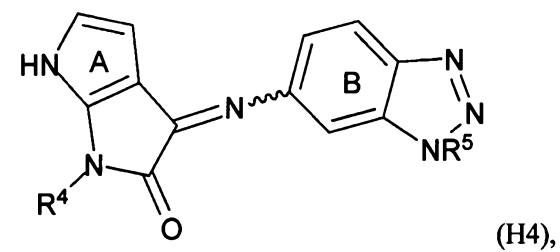
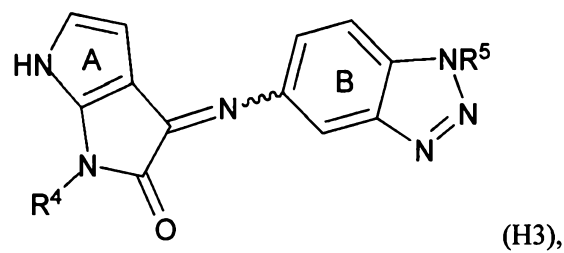
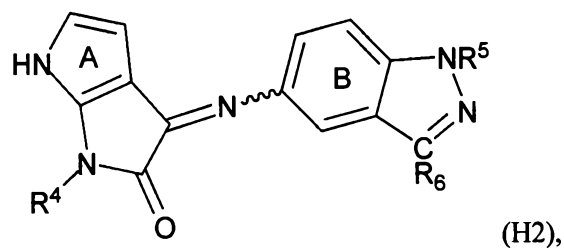
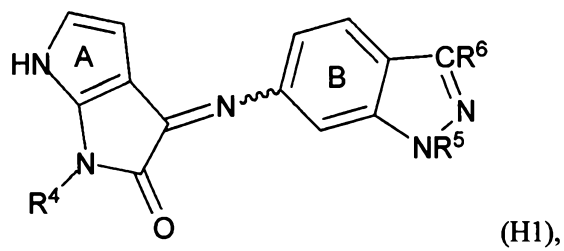




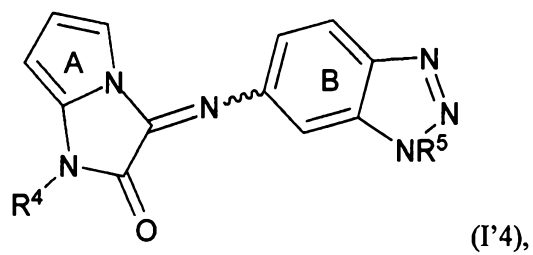
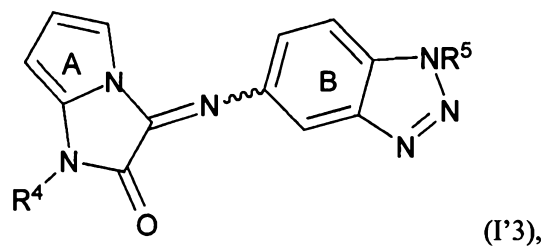
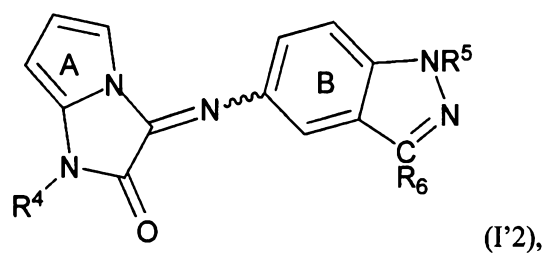
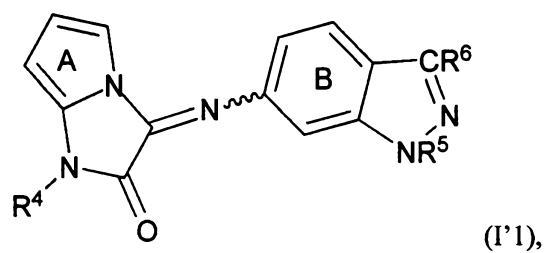
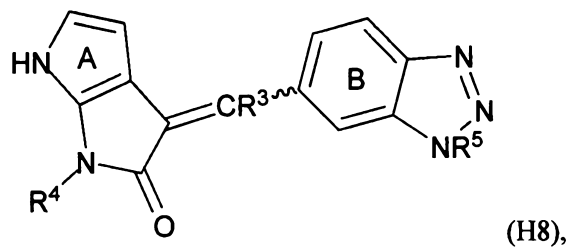
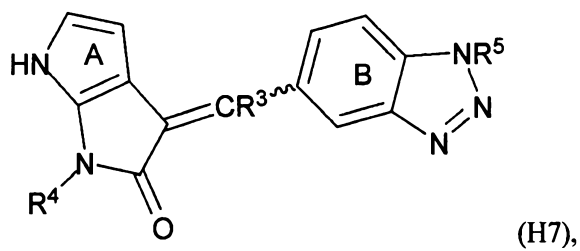
- 50 -



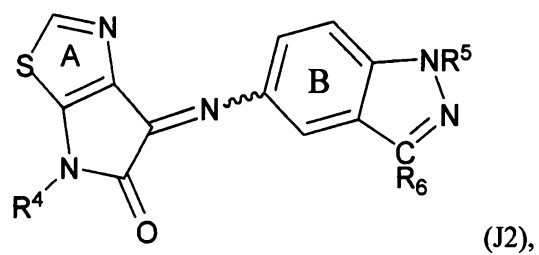
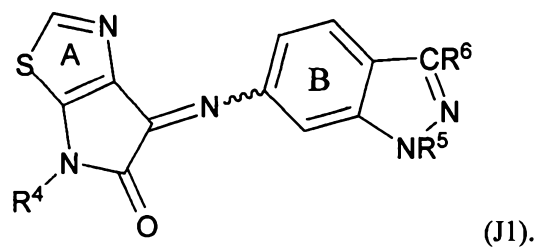
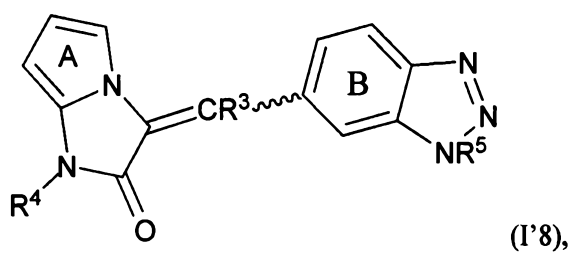
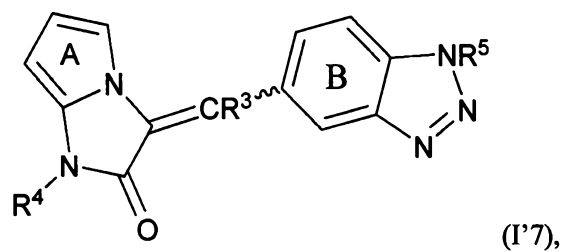
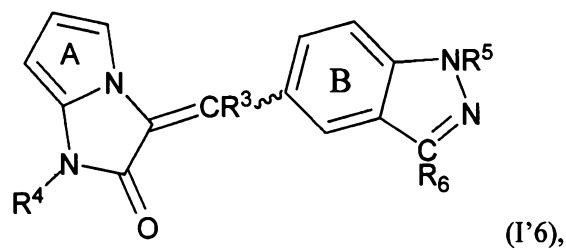
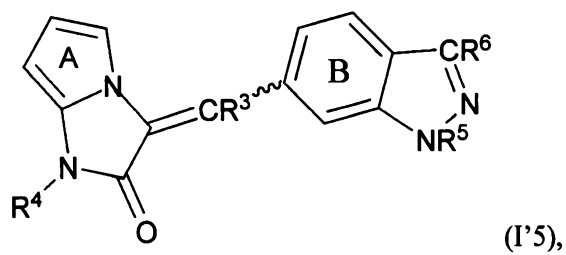
- 51 -

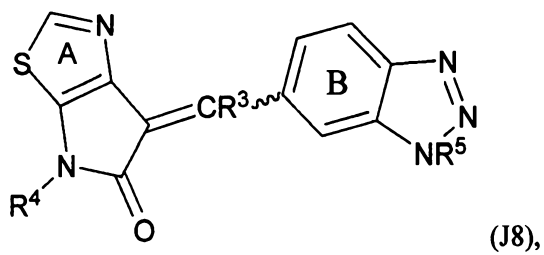
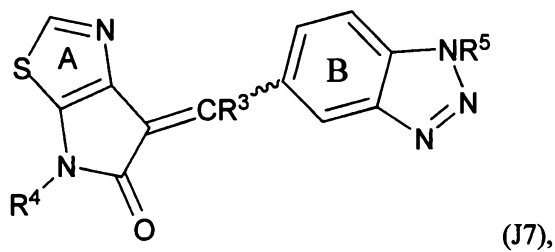
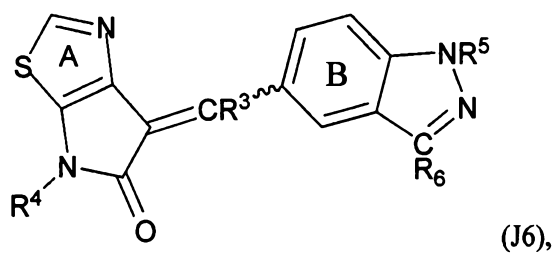
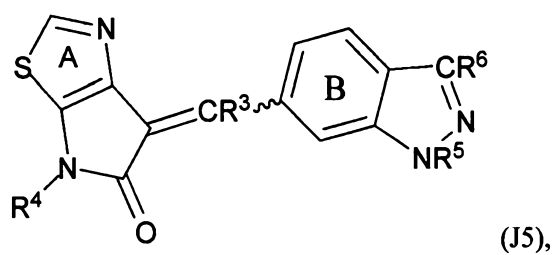
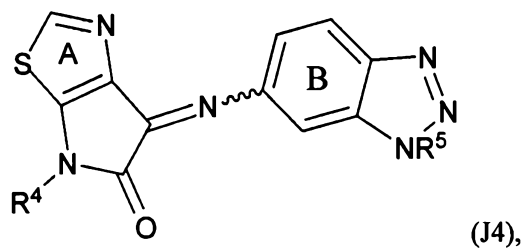
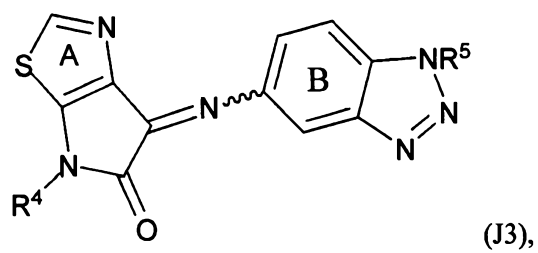


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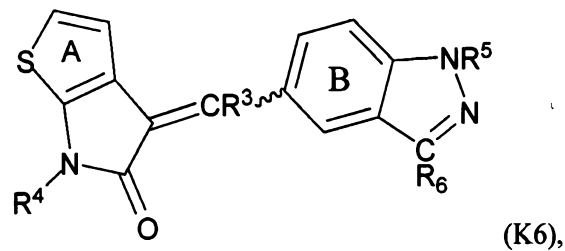
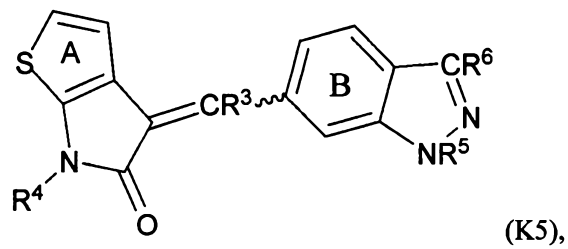
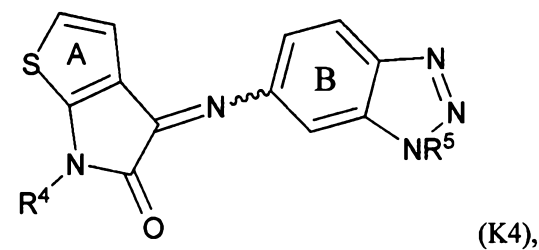
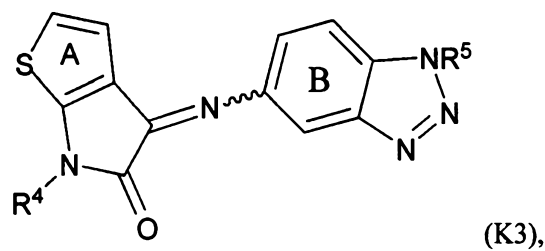
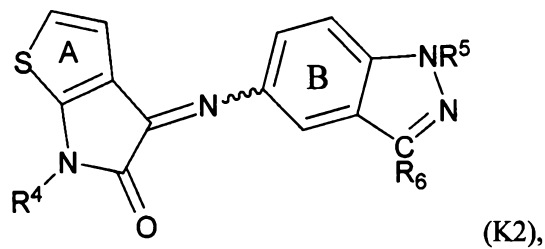
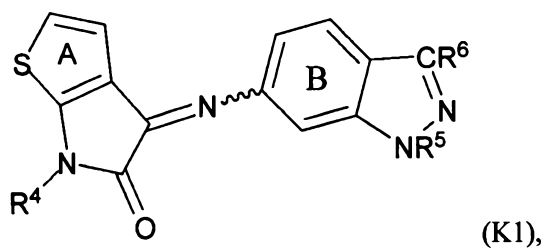


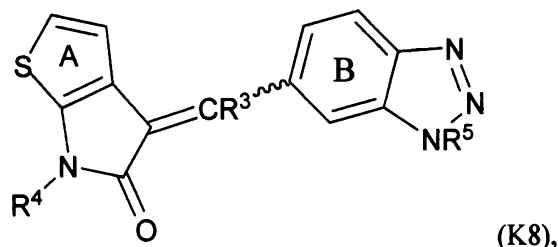
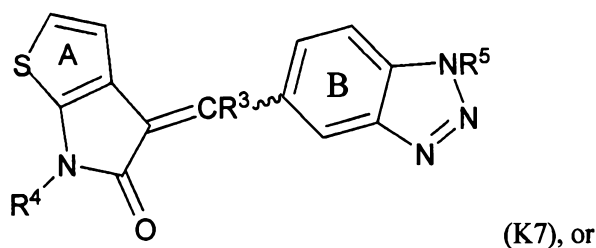
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or a pharmaceutically acceptable salt thereof, wherein:

R^6 for Structural Formulas (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ik), (Il),
 5 (C1), (C2), (D1), (D2), (D5), (D6), (E1), (E2), (E5), (E6), (F1), (F2), (F5), (F6),
 (G1), (G2), (G5), (G6), (H1), (H2), (H5), (H6), (I'1), (I'2), (I'5), (I'6), (J1), (J2),
 (J5), (J6), (K1), (K2), (K5) and (K6) is optionally substituted phenyl, optionally
 substituted 5-12 membered heteroaryl, $-\text{CH}_2$ -(optionally substituted phenyl), $-\text{CH}_2$ -
 (optionally substituted 5-12 membered heteroaryl), $-\text{CH}_2\text{CH}_2$ -(optionally
 10 substituted phenyl), $-\text{CH}_2\text{CH}_2$ -(optionally substituted 5-12 membered heteroaryl),
 $-\text{CH}=\text{CH}$ -(optionally substituted phenyl), $-\text{CH}=\text{CH}$ -(optionally substituted 5-12
 membered heteroaryl), $-\text{CH}=\text{CH}-\text{C}(\text{O})\text{O}$ (optionally substituted C_{1-6} alkyl), or
 $-\text{CH}=\text{CH}-\text{OC}(\text{O})$ (optionally substituted C_{1-6} alkyl). R^6 can also be $-\text{C}\equiv\text{C}$ -(optionally
 15 substituted phenyl), $-\text{C}\equiv\text{C}$ -(optionally substituted 5-12 membered heteroaryl), $-\text{C}\equiv\text{C}-$
 $\text{C}(\text{O})\text{O}$ (optionally substituted C_{1-6} alkyl), or $-\text{C}\equiv\text{C}-\text{OC}(\text{O})$ (optionally substituted
 C_{1-6} alkyl);

R^7 of Structural Formulas (Ig), (Ih), (Ii) and (Ij) is -H, -F, -Cl or methyl and n
 in Structural Formulas (Ii), (Ij), (Ik) and (Il) is 0 or 1.

Values and specific values for the remainder of the variables of Structural
 20 Formulas (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (Ik), and (Il) are as
 describe above for Structural Formula (I) in the first embodiment. Values and
 specific values for the remainder of the variables of Structural Formulas (C1)-(C4),
 (D1)-(D8), (E1)-(E8), (F1)-(F8), (G1)-(G8), (H1)-(H8), (I'1)-(I'8), (J1)-(J8) and
 (K1)-(K8) are as described above for Structural Formula (A).

In one embodiment, for Structural Formula (C1), when R⁶ is -H, R⁵ is H and R⁴ is H or C1-C6 alkyl, then ring A is not phenyl or phenyl substituted with halogen or trifluoromethyl. In another embodiment, for Structural Formula (C1), R⁵ and R⁶ are not both -H. In one embodiment for Structural Formulas (Ia) and (Ib), R³ is -H,
 5 C1-C6 alkyl or C1-C6 haloalkyl.

In a seventh embodiment, R⁴ and R⁵ of Structural Formulas (Ia), (Ib), (Ic), (Id), (Ie), (If), (C1)-(C4), (D1)-(D8), (E1)-(E8), (F1)-(F8), (G1)-(G8), (H1)-(H8), (I'1)-(I'8), (J1)-(J8), and (K1)-(K8) are each independently -H, C1-C6 alkyl, phenyl, -C(O)(C1-C6 alkyl), -C(O)(phenyl), -C(O)O(C1-C6 alkyl), -C(O)O(phenyl),
 10 -S(O)₂(C1-C6 alkyl) or -S(O)₂(phenyl), wherein each phenyl in the group represented by R⁴ and R⁵ is optionally substituted with one or more substituents independently selected from the group consisting of halogen, C₁₋₆ alkyl, -O(C₁₋₆ alkyl), C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, cyano and nitro. Values and specific values for the remainder of the variables are as described above in the sixth embodiment.

In an eighth embodiment, R⁴ and R⁵ of Structural Formulas (Ia), (Ib), (Ic), (Id), (Ie) (If), (C1)-(C4), (D1)-(D8), (E1)-(E8), (F1)-(F8), (G1)-(G8), (H1)-(H8), (I'1)-(I'8), (J1)-(J8) and (K1)-(K8) are as described above in the seventh embodiment and R⁶ for Structural Formulas (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (Ik), (Il), (C1), (C2), (D1), (D2), (D5), (D6), (E1), (E2), (E5), (E6), (F1),
 20 (F2), (F5), (F6), (G1), (G2), (G5), (G6), (H1), (H2), (H5), (H6), (I'1), (I'2), (I'5), (I'6), (J1), (J2), (J5), (J6), (K1), (K2), (K5) and (K6) is optionally substituted phenyl, optionally substituted 5-12 membered heteroaryl, -CH₂-(optionally substituted phenyl), -CH₂-(optionally substituted 5-12 membered heteroaryl), -CH₂-CH₂-(optionally substituted phenyl), -CH₂-CH₂-(optionally substituted 5-12 membered heteroaryl), -CH=CH-(optionally substituted phenyl), -CH=CH-
 25 (optionally substituted 5-12 membered heteroaryl), -CH=CH-C(O)O(optionally substituted C₁₋₆ alkyl), or -CH=CH-OC(O)(optionally substituted C₁₋₆ alkyl). Alternatively, R⁶ can also be -C≡C-(optionally substituted phenyl), -C≡C-(optionally substituted 5-12 membered heteroaryl), -C≡C-C(O)O(optionally substituted C₁₋₆ alkyl), or -C≡C-OC(O)(optionally substituted C₁₋₆ alkyl). The 5-12 membered heteroaryl in the group represented by R⁶ is selected from the group consisting of pyridyl, thiazolyl, pyrazinyl, thiophenyl, indolyl, quinolinyl, pyrrolyl, pyrazolyl, and
 30

pyrimidyl, each of which is optionally substituted. Values and specific values for the remainder of the variables are as described above in the sixth embodiment.

In a ninth embodiment, values for the variables in Structural Formulas (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (Ik), (Il), (C1)-(C4), (D1)-(D8), (E1)-(E8), (F1)-(F8), (G1)-(G8), (H1)-(H8), (I'1)-(I'8), (J1)-(J8) and (K1)-(K8) are
5 provided in the following paragraphs:

Ring A in Structural Formulas (C1)-(C4), (D1)-(D8), (E1)-(E8), (F1)-(F8), (G1)-(G8), (H1)-(H8), (I'1)-(I'8), (J1)-(J8) and (K1)-(K8) are optionally substituted with one or more Q^a and ring B in Structural Formulas (C1)-(C4), (D1)-(D8), (E1)-
10 (E8), (F1)-(F8), (G1)-(G8), (H1)-(H8), (I'1)-(I'8), (J1)-(J8) and (K1)-(K8) are optionally substituted with one or more Q^b .

Q^a and Q^b are each independently halogen, cyano, $-NR^1R^2$, $-NR^2C(O)R^1$, $-C(O)OR^1$, $-OC(O)R^1$, $-C(O)NR^1R^2$, $-NR^2C(O)OR^1$, $-N(R^2)C(O)NR^1R^2$, $-OR^1$, $-SO_2NR^1R^2$, $-NR^2SO_2R^1$, C_{1-6} alkyl, phenyl or 5-12 membered heteroaryl, wherein
15 the C_{1-6} alkyl represented by Q_a and Q_b is optionally substituted with one or more substituents selected from the group consisting of halogen, nitro, cyano, -OH, -SH, $-O(C_{1-6}$ alkyl), $-S(C_{1-6}$ alkyl), C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, C_{1-6} alkylcarbonyloxy, C_{1-6} alkoxycarbonyl and C_{1-6} alkylcarbonyl; and the phenyl or the 5-12 membered heteroaryl represented by Q_a and Q_b is
20 optionally substituted with one or more substituents selected from the group consisting of halogen, nitro, cyano, -OH, -SH, $-O(C_{1-6}$ alkyl), $-S(C_{1-6}$ alkyl), C_{1-6} alkyl, C_{1-6} haloalkyl, $(C_{1-6}$ haloalkoxy) C_{1-6} alkyl, $(C_{1-6}$ alkoxy) C_{1-6} alkyl, C_{1-6} hydroxyalkyl, $(C_{1-6}$ aminoalkyl), $(C_{1-6}$ alkylamino) C_{1-6} alkyl, $(C_{1-6}$ dialkylamino) C_{1-6} alkyl, (phenyl) C_{1-6} alkyl, (5-6 membered heteroaryl) C_{1-6} alkyl, amino, C_{1-6}
25 alkylamino, C_{1-6} dialkylamino, C_{1-6} haloalkoxy, C_{1-6} alkylcarbonyloxy, C_{1-6} alkoxycarbonyl and C_{1-6} alkylcarbonyl;

R^1 and R^2 are each independently -H- or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -SH, $-O(C_{1-3}$ alkyl), $-S(C_{1-3}$ alkyl) and C_{1-6}
30 haloalkoxy;

the phenyl or the 5-12 membered heteroaryl in the group represented by R^6 for Structural Formulas (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (Ik), (Il),

(C1), (C2), (D1), (D2), (D5), (D6), (E1), (E2), (E5), (E6), (F1), (F2), (F5), (F6), (G1), (G2), (G5), (G6), (H1), (H2), (H5), (H6), (I'1), (I'2), (I'5), (I'6), (J1), (J2), (J5), (J6), (K1), (K2), (K5) and (K6) is optionally substituted with one or more substituents selected from the group consisting of halogen, nitro, cyano, -OH, -SH, -O(C₁₋₆ alkyl), -S(C₁₋₆ alkyl), C₁₋₆ alkyl, C₁₋₆ haloalkyl, (C₁₋₆ haloalkoxy)C₁₋₆ alkyl, (C₁₋₆ alkoxy)C₁₋₆ alkyl, C₁₋₆ hydroxyalkyl, (C₁₋₆ aminoalkyl, (C₁₋₆ alkylamino)C₁₋₆ alkyl, (C₁₋₆ dialkylamino)C₁₋₆ alkyl, (phenyl)C₁₋₆ alkyl, (5-6 membered heteroaryl)C₁₋₆ alkyl, amino, C₁₋₆ alkylamino, C₁₋₆ dialkylamino, C₁₋₆ haloalkoxy, C₁₋₆ alkylcarbonyloxy, C₁₋₆ alkoxycarbonyl and C₁₋₆ alkylcarbonyl. In another embodiment, -(CH₂)₀₋₃-*N*-piperidinyl, -(CH₂)₀₋₃-*N*-morpholinyl, -(CH₂)₀₋₃-*N*-pyrrolidinyl and -(CH₂)₀₋₃-*N*-piperazinyl, wherein the *N*-piperaziinyl is optionally *N*'-substituted with C₁₋₆ alkyl or C₁₋₆ acyl are additional permissible substituents for the phenyl or the 5-12 membered heteroaryl in the group represented by R⁶; and the C₁₋₆ alkyl in the group represented by R⁶ for Structural Formulas (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (Ik), (Il), (C1), (C2), (D1), (D2), (D5), (D6), (E1), (E2), (E5), (E6), (F1), (F2), (F5), (F6), (G1), (G2), (G5), (G6), (H1), (H2), (H5), (H6), (I'1), (I'2), (I'5), (I'6), (J1), (J2), (J5), (J6), (K1), (K2), (K5) and (K6) is optionally substituted one or more substituents selected from the group consisting of halogen, nitro, cyano, -OH, -SH, -O(C₁₋₆ alkyl), -S(C₁₋₆ alkyl), C₁₋₆ haloalkoxy, amino, C₁₋₆ alkylamino, C₁₋₆ dialkylamino, C₁₋₆ alkylcarbonyloxy, C₁₋₆ alkoxycarbonyl and C₁₋₆ alkylcarbonyl.

Values and specific values for the remainder of the variables are as described above in the sixth, seventh or eighth embodiments.

In a tenth embodiment, values for the variables in Structural Formulas (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (Ik), (Il), (C1)-(C4), (D1)-(D8), (E1)-(E8), (F1)-(F8), (G1)-(G8), (H1)-(H8), (I'1)-(I'8), (J1)-(J8) and (K1)-(K8) are provided in the following paragraphs:

Ring A in Structural Formulas (C1)-(C4), (D1)-(D8), (E1)-(E8), (F1)-(F8), (G1)-(G8), (H1)-(H8), (I'1)-(I'8), (J1)-(J8) and (K1)-(K8) are optionally substituted with one or more Q^a and ring B in Structural Formulas (C1)-(C4), (D1)-(D8), (E1)-(E8), (F1)-(F8), (G1)-(G8), (H1)-(H8), (I'1)-(I'8), (J1)-(J8) and (K1)-(K8) are optionally substituted with one or more Q^b.

- 60 -

Q^a is halogen, cyano, $-NR^1R^2$, $-NR^2C(O)R^1$, $-C(O)OR^1$, $-OC(O)R^1$, $-N(R^2)C(O)NR^1R^2$, $-OR^1$, C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with one or more substituents selected from the group consisting of halogen, $-OH$, $-SH$, $-O(C_{1-6}$ alkyl), $-S(C_{1-6}$ alkyl) and C_{1-6} haloalkoxy;

5 Q^b is halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, or C_{1-3} haloalkoxy; and the phenyl, the 5-12 membered heteroaryl and the C_{1-6} alkyl in the group represented by R^6 is optionally substituted with one or more substituents selected from the group consisting of halogen, nitro, cyano, $-O(C_{1-6}$ alkyl), C_{1-6} alkyl, C_{1-6} haloalkyl and C_{1-6} haloalkoxy.

10 Values and specific values for the remainder of the variables are as described above in the sixth, seventh, eighth or ninth embodiments.

In a eleventh embodiment, values for the variables in Structural Formulas (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (Ik), (Il), (C1)-(C4), (D1)-(D8), (E1)-(E8), (F1)-(F8), (G1)-(G8), (H1)-(H8), (I'1)-(I'8), (J1)-(J8) and (K1)-(K8) are
15 provided in the following paragraphs:

Ring A in Structural Formulas (C1)-(C4), (D1)-(D8), (E1)-(E8), (F1)-(F8), (G1)-(G8), (H1)-(H8), (I'1)-(I'8), (J1)-(J8) and (K1)-(K8) are optionally substituted with one or more Q^a and ring B in Structural Formulas (C1)-(C4), (D1)-(D8), (E1)-(E8), (F1)-(F8), (G1)-(G8), (H1)-(H8), (I'1)-(I'8), (J1)-(J8) and (K1)-(K8) are
20 optionally substituted with one or more Q^b .

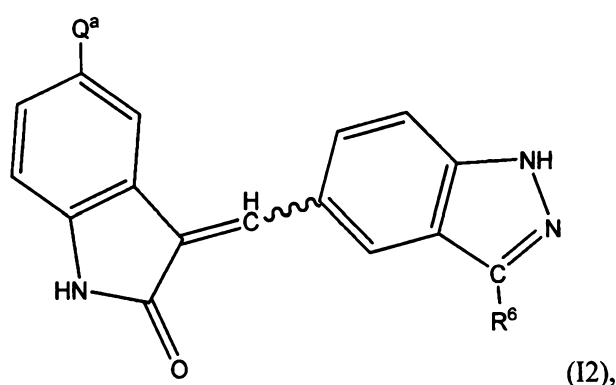
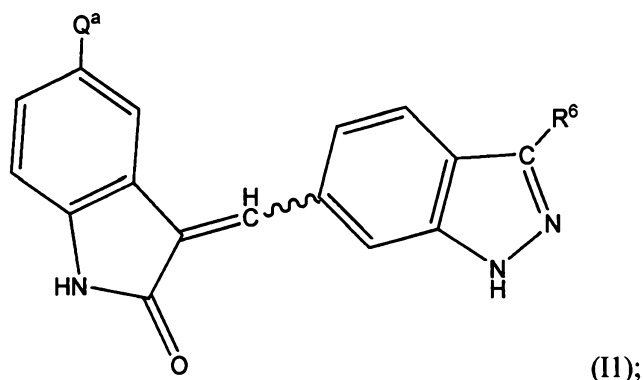
Q^a is $-OH$, C_{1-6} alkoxy or C_{1-6} haloalkoxy;

Q^b is halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, or C_{1-3} haloalkoxy and the phenyl, the 5-12 membered heteroaryl and the C_{1-6} alkyl in the group represented by R^6 are each optionally substituted with one or more substituents
25 independently selected from the group consisting of halogen, methyl, methoxy and trifluoromethyl.

In a twelfth embodiment, the compound of the present invention is represented

by a structural formula selected from (I1) and (I2):

30



or a pharmaceutically acceptable salt thereof, wherein:

Q^a is -H, halogen, -NH₂, (C₁₋₆alkyl)amine or C₁₋₆ alkoxy;

- 5 R^6 is phenyl, 5-6 membered heteroaryl, -CH=CH-(phenyl), -CH=CH-(5-6 membered heteroaryl), -C≡C-(phenyl), -C≡C-(5-6 membered heteroaryl) wherein each phenyl and heteroaryl in the group represented by R^6 is optionally substituted with halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, (C₁₋₆ aminoalkyl), (C₁₋₆ alkylamino)C₁₋₆ alkyl, (C₁₋₆ dialkylamino)C₁₋₆ alkyl, (phenyl)C₁₋₆ alkyl, amino, C₁₋₆ alkylamino, C₁₋₆ dialkylamino, -(CH₂)₀₋₃-*N*-piperidinyl, -(CH₂)₀₋₃-*N*-morpholinyl, -(CH₂)₀₋₃-*N*-pyrrolidinyl and -(CH₂)₀₋₃-*N*-piperazinyl, wherein the *N*-piperazinyl is optionally *N'*-substituted with C₁₋₆ alkyl or C₁₋₆ acyl. Alternatively for Structural Formulas (I1) and (I2), each heteroaryl in the group represented by R^6 is pyridinyl, pyrimidinyl or pyrazinyl and each is optionally substituted halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, (C₁₋₆ aminoalkyl), (C₁₋₆ alkylamino)C₁₋₆ alkyl, (C₁₋₆ dialkylamino)C₁₋₆ alkyl, (phenyl)C₁₋₆ alkyl, amino, C₁₋₆ alkylamino, C₁₋₆ dialkylamino, -(CH₂)₀₋₃-*N*-piperidinyl, -(CH₂)₀₋₃-*N*-morpholinyl, -(CH₂)₀₋₃-*N*-pyrrolidinyl and -(CH₂)₀₋₃-*N*-piperazinyl, wherein the *N*-piperazinyl is optionally *N'*-substituted with C₁₋₆ alkyl or C₁₋₆ acyl.
- 10
- 15

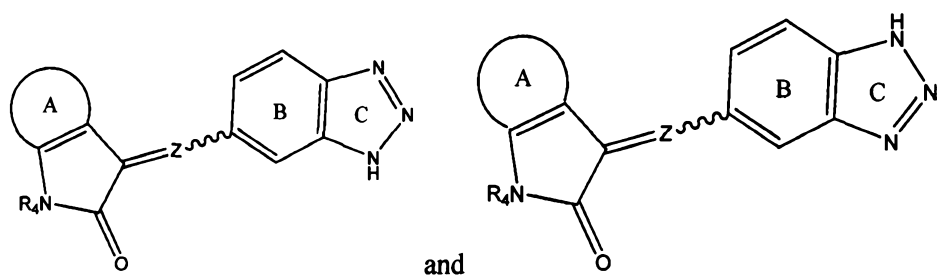
Values and specific values for the remainder of the variables are as described above in the sixth, seventh, eighth, ninth or tenth embodiments.

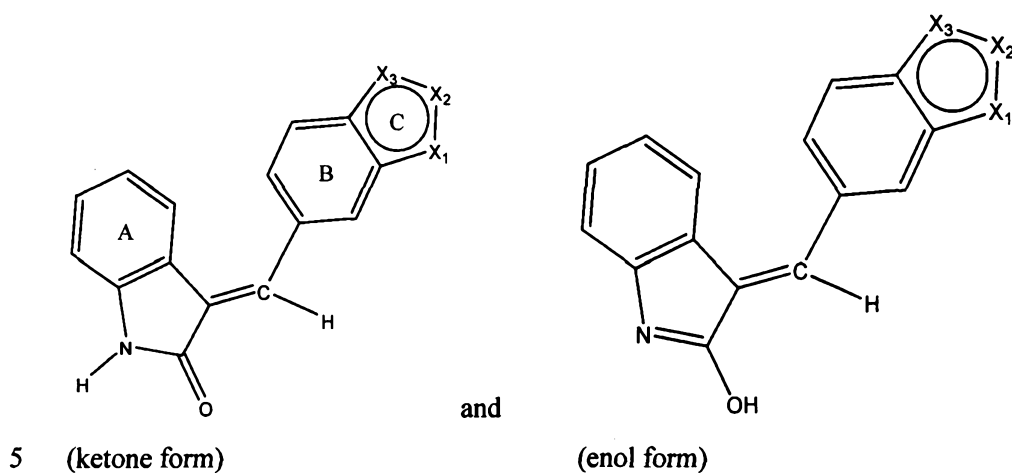
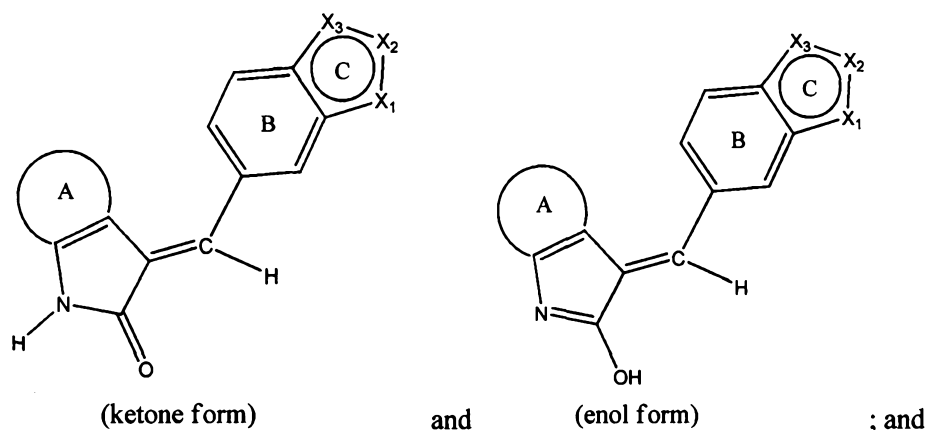
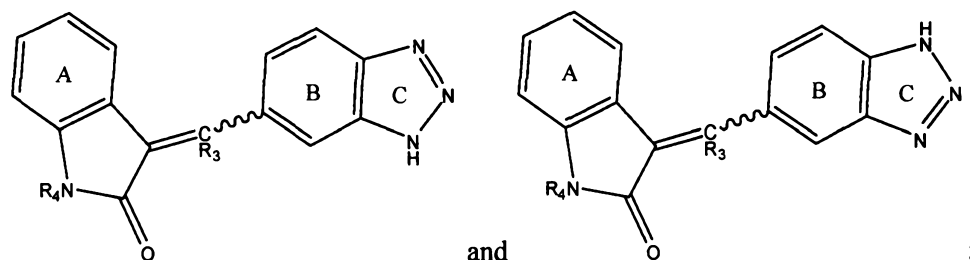
As used herein, the phenyl, the 5-12 membered heteroaryl and the C₁₋₆ alkyl in the group represented by R⁶ refers to the phenyl, the 5-12 membered heteroaryl and the C₁₋₆ alkyl represented by R⁶ as well as the phenyl, the 5-12 membered heteroaryl and the C₁₋₆ alkyl in the groups represented by R⁶, for example, -CH₂-(optionally substituted phenyl), -CH₂-(optionally substituted 5-12 membered heteroaryl), -CH₂-CH₂-(optionally substituted phenyl), -CH₂-CH₂-(optionally substituted 5-12 membered heteroaryl), -CH=CH-(optionally substituted phenyl), -CH=CH-(optionally substituted 5-12 membered heteroaryl), -CH=CH-C(O)O(optionally substituted C₁₋₆ alkyl), and -CH=CH-OC(O)(optionally substituted C₁₋₆ alkyl) represented by R⁶. Similarly, the language “a specific moiety in the group represented by a variable” refers to the moiety represented by the variable or the moiety in a group represented by the variable.

Specific examples of the compounds of the invention include compounds exemplified in the examples below, stereoisomers thereof, and pharmaceutically acceptable salts thereof.

In Structural Formulas described herein, when a hydrogen atom(s) is depicted at a particular position(s) of the aromatic ring(s) of the structural formula(s), no substitution is permitted at that (those) particular position(s).

Tautomeric forms exist when a compound is a mixture of two or more structurally distinct compounds that are in rapid equilibrium. Certain compounds of the invention exist as tautomeric forms. For example, the following compound represented by Structural Formula (A), wherein two of X1-X3 are N, one of X1-X3 is NH or compound represented by Structural Formula (I), wherein two of X1-X3 are N, one of X1-X3 is NH, include at least the following tautomers forms:

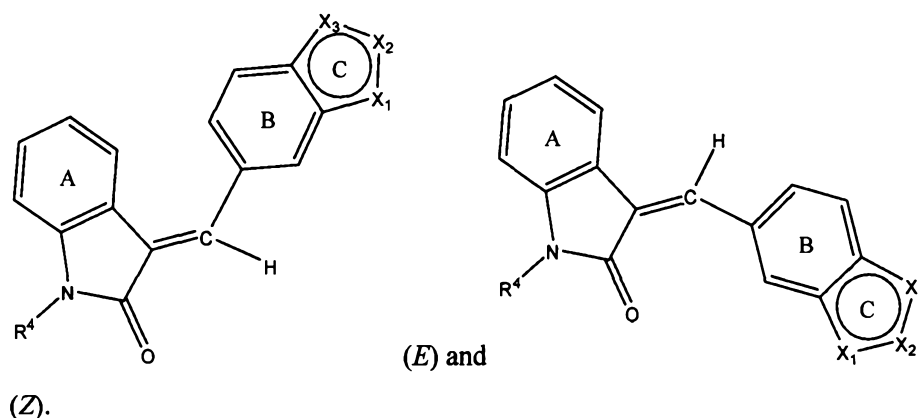
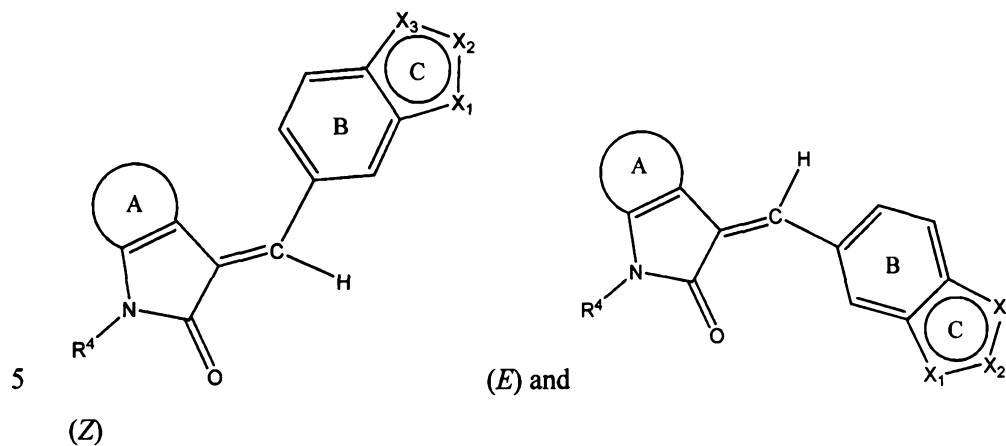




It is to be understood that when one tautomeric form of a compound is depicted by name or structure, all tautomeric forms of the compound are included.

The compounds of the invention may contain one or more chiral center and/or double bond and, therefore, exist as stereoisomers, such as double-bond isomers (*i.e.*, geometric isomers), enantiomers, and/or diastereomers. When compounds of the invention are depicted or named without indicating the

stereochemistry, it is to be understood that both stereomerically pure forms (*e.g.*, geometrically pure, enantiomerically pure, or diastereomerically pure) and stereoisomeric mixtures are encompassed. For example, compounds represented by Structural Formulas (A) or (I) have *E* and *Z* geometric isomers shown below:



10

Accordingly, the compounds of the invention depicted by Structural Formula (A) or (I) include the pure *E* geometric isomer isomer, the pure *Z* geometric isomer, and mixtures thereof.

15 The invention encompasses all geometrically-pure forms and geometrically-enriched (*i.e.* greater than 50% of either *E* or *Z* isomer) mixtures, of the compounds disclosed herein. Mixtures include 1:20, 1:10, 20:80, 30:70, 40:60 and 50:50 *E*:*Z* and *Z*:*E* ratios by mole.

As used herein, a racemic mixture means 50% of one enantiomer and 50% of is corresponding enantiomer relative to all chiral centers in the molecule. The

invention encompasses all enantiomerically-pure, enantiomerically-enriched, diastereomerically pure, diastereomerically enriched, and racemic mixtures, and diastereomeric mixtures of the compounds of the invention which have chiral center(s).

5 Enantiomeric and diastereomeric mixtures can be resolved into their component enantiomers or stereoisomers by well known methods, such as chiral-phase gas chromatography, chiral-phase high performance liquid chromatography, crystallizing the compound as a chiral salt complex, or crystallizing the compound in a chiral solvent. Enantiomers and diastereomers can also be obtained from
10 diastereomerically- or enantiomerically-pure intermediates, reagents, and catalysts by well known asymmetric synthetic methods.

 When the stereochemistry of the disclosed compounds is named or depicted by structure, the named or depicted stereoisomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by weight pure relative to the other stereoisomers. When a single
15 stereoisomer is named or depicted by structure, the depicted or named stereoisomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% pure. Percent purity by weight is the ratio of the weight of the named stereoisomer over the weight of the named stereoisomer plus the weight of its stereoisomers.

 Included in the invention are pharmaceutically acceptable salts of the
20 compounds disclosed herein. The disclosed compounds have basic amine groups and therefore can form pharmaceutically acceptable salts with pharmaceutically acceptable acid(s). Suitable pharmaceutically acceptable acid addition salts of the compounds of the invention include salts of inorganic acids (such as hydrochloric acid, hydrobromic, phosphoric, metaphosphoric, nitric, and sulfuric acids) and of
25 organic acids (such as, acetic acid, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isethionic, lactic, lactobionic, maleic, malic, methanesulfonic, succinic, p- toluenesulfonic, and tartaric acids). Compounds of the invention with acidic groups such as carboxylic acids can form pharmaceutically acceptable salts with pharmaceutically acceptable base(s). Suitable
30 pharmaceutically acceptable basic salts include ammonium salts, alkali metal salts (such as sodium and potassium salts) and alkaline earth metal salts (such as magnesium and calcium salts). Compounds with a quaternary ammonium group

also contain a counteranion such as chloride, bromide, iodide, acetate, perchlorate and the like. Other examples of such salts include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, tartrates [e.g. (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures],

5 succinates, benzoates and salts with amino acids such as glutamic acid.

The term "halo" as used herein means halogen and includes chloro, fluoro, bromo and iodo.

An "aliphatic group" is non-aromatic, consists solely of carbon and hydrogen and may optionally contain one or more units of unsaturation, e.g., double and/or
10 triple bonds. An aliphatic group may be straight chained, branched or cyclic. When straight chained or branched, an aliphatic group typically contains between about one and about twenty carbon atoms, typically between about one and about ten carbon atoms, more typically between about one and about six carbon atoms. When cyclic, an aliphatic group typically contains between about three and about ten
15 carbon atoms, more typically between about three and about seven carbon atoms. A "substituted aliphatic group" is substituted at any one or more "substitutable carbon atom". A "substitutable carbon atom" in an aliphatic group is a carbon in an aliphatic group that is bonded to one or more hydrogen atoms. One or more hydrogen atoms can be optionally replaced with a suitable substituent group. A
20 "haloaliphatic group" is an aliphatic group, as defined above, substituted with one or more halogen atoms. Suitable substituents on a substitutable carbon atom of an aliphatic group are the same as those for an alkyl group.

The term "alkyl" used alone or as part of a larger moiety, such as "alkoxy", "haloalkyl", "arylalkyl", "alkylamine", "cycloalkyl", "dialkylamine", "alkylamino",
25 "dialkylamino" "alkylcarbonyl", "alkoxycarbonyl" and the like, includes as used herein means saturated straight-chain, cyclic or branched aliphatic group. As used herein, a C1-C6 alkyl group is referred to "lower alkyl." Similarly, the terms "lower alkoxy", "lower haloalkyl", "lower arylalkyl", "lower alkylamine", "lower cycloalkylalkyl", "lower dialkylamine", "lower alkylamino", "lower dialkylamino"
30 "lower alkylcarbonyl", "lower alkoxycarbonyl" include straight and branched, saturated chains containing one to six carbon atoms, and cyclic saturated chains containing three to six carbon atoms.

The term "alkoxy" means -O-alkyl; "hydroxyalkyl" means alkyl substituted with hydroxy; "aralkyl" means alkyl substituted with an aryl group; "alkoxyalkyl" mean alkyl substituted with an alkoxy group; "alkylamine" means amine substituted with an alkyl group; "cycloalkylalkyl" means alkyl substituted with cycloalkyl;
5 "dialkylamine" means amine substituted with two alkyl groups; "alkylcarbonyl" means -C(O)-R, wherein R is alkyl; "alkoxycarbonyl" means -C(O)-OR, wherein R is alkyl; and where alkyl is as defined above.

The terms "haloalkyl" and "haloalkoxy" means alkyl or alkoxy, as the case may be, substituted with one or more halogen atoms. The term "halogen" means F,
10 Cl, Br or I. Preferably the halogen in a haloalkyl or haloalkoxy is F.

The term "acyl group" means -C(O)R, wherein R is an optionally substituted alkyl group or aryl group (e.g., optionally substituted phenyl). R is preferably an unsubstituted alkyl group or phenyl.

An "alkylene group" is represented by $-\text{[CH}_2\text{]}_z-$, wherein z is a positive
15 integer, preferably from one to eight, more preferably from one to four.

An "alkenylene group" is an alkylene in which at least a pair of adjacent methylenes are replaced with $-\text{CH}=\text{CH}-$.

An "alkynylene group" is an alkylene in which at least a pair of adjacent methylenes are replaced with $-\text{C}\equiv\text{C}-$.

20 The term "aryl group" used alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl", means carbocyclic aromatic rings. The term "carbocyclic aromatic group" may be used interchangeably with the terms "aryl", "aryl ring" "carbocyclic aromatic ring", "aryl group" and "carbocyclic aromatic group". An aryl group typically has six – fourteen ring atoms. A
25 "substituted aryl group" is substituted at any one or more substitutable ring atom. The term "C₆₋₁₄aryl" as used herein means a monocyclic, bicyclic or tricyclic carbocyclic ring system containing from 6 to 14 carbon atoms and includes phenyl, naphthyl, anthracenyl, 1,2-dihydronaphthyl, 1,2,3,4-tetrahydronaphthyl, fluorenyl, indanyl, indenyl and the like.

30 The term "heteroaryl", "heteroaromatic", "heteroaryl ring", "heteroaryl group" and "heteroaromatic group", used alone or as part of a larger moiety as in "heteroaralkyl" or "heteroarylalkoxy", refers to aromatic ring groups having five to

fourteen ring atoms selected from carbon and at least one (typically 1 -4, more typically 1 or 2) heteroatom (e.g., oxygen, nitrogen or sulfur). They include monocyclic rings and polycyclic rings in which a monocyclic heteroaromatic ring is fused to one or more other carbocyclic aromatic or heteroaromatic rings. The term

5 “5-14 membered heteroaryl” as used herein means a monocyclic, bicyclic or tricyclic ring system containing one or two aromatic rings and from 5 to 14 atoms of which, unless otherwise specified, one, two, three, four or five are heteroatoms independently selected from N, NH, N(C₁₋₆alkyl), O and S and includes thienyl, furyl, pyrrolyl, pyrididyl, indolyl, quinolyl, isoquinolyl, tetrahydroquinolyl,

10 benzofuryl, benzothienyl and the like.

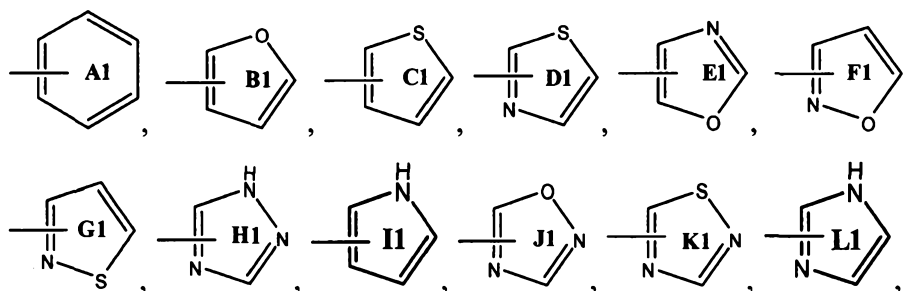
Examples of monocyclic 5-6 membered heteroaryl groups include furanyl (e.g., 2-furanyl, 3-furanyl), imidazolyl (e.g., *N*-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), isoxazolyl (e.g., 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl), oxadiazolyl (e.g., 2-oxadiazolyl, 5-oxadiazolyl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl, 5-

15 oxazolyl), pyrazolyl (e.g., 3-pyrazolyl, 4-pyrazolyl), pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl), pyridazinyl (e.g., 3-pyridazinyl), thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), triazolyl (e.g., 2-triazolyl, 5-triazolyl), tetrazolyl (e.g., tetrazolyl), thienyl (e.g., 2-thienyl, 3-thienyl), pyrimidinyl,

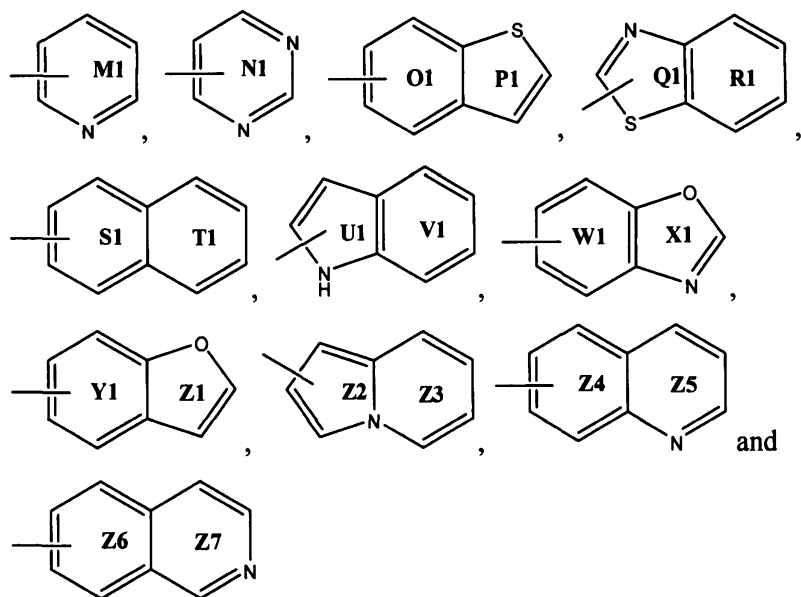
20 pyridinyl and pyridazinyl. Examples of polycyclic aromatic heteroaryl groups include carbazolyl, benzimidazolyl, benzothienyl, benzofuranyl, indolyl, quinolinyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, isoquinolinyl, indolyl, isoindolyl, acridinyl, or benzisoxazolyl.

Other examples for the aryl and heteroaryl groups include:

25

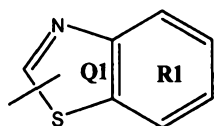


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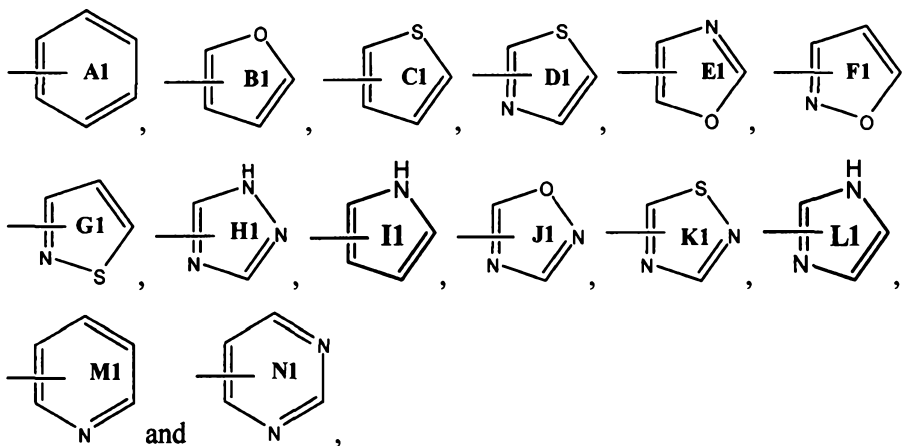
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wherein each of rings A1-Z7 is optionally substituted. It is noted that, as shown above, rings O1-Z7 can be attached to their designated atom through any ring carbon of the rings which is not at a position bridging two aryl groups. For example,



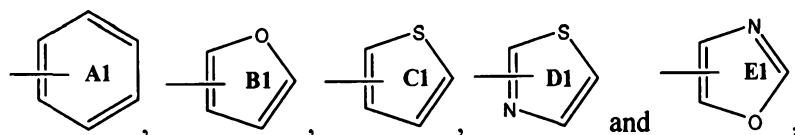
means that the group is attached to its designated atom through

10 either ring Q1 or ring R1. Yet other examples for the aryl and heteroaryl groups include:



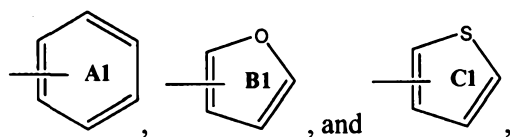
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wherein each of rings A1-N1 is optionally substituted. More specific values for the aryl and heteroaryl groups include:



5

wherein each of rings A1-E1 is optionally substituted. Even more specific values for the aryl and heteroaryl groups include:



10

wherein each of rings A1-C1 is optionally substituted. An optionally substituted ring A1 is the most common specific value for each of the aryl group, including the C₆₋₁₄ aryl group.

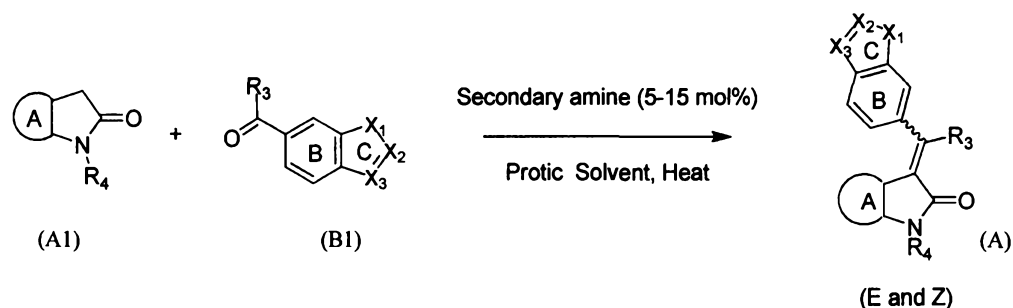
As used herein, the term "non-aromatic heterocyclic group" means a
 15 monocyclic (typically having 3- to 10-members) or a polycyclic (typically having 7- to 20-members) heterocyclic ring system which is an unsaturated non-aromatic ring. A 3- to 10-membered heterocycle can contain up to 5 heteroatoms; and a 7- to 20-membered heterocycle can contain up to 7 heteroatoms. Typically, a heterocycle has at least one carbon atom ring member. Each heteroatom is independently
 20 selected from nitrogen, which can be oxidized (e.g., N(O)) or quaternized; oxygen; and sulfur, including sulfoxide and sulfone. The heterocycle may be attached via any heteroatom or carbon atom. Representative heterocycles include morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl,
 25 tetrahydropyrindinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

The aryl group, and the aromatic and non-aromatic heteroaryl groups, unless otherwise indicated, can be optionally substituted with one or more substituents

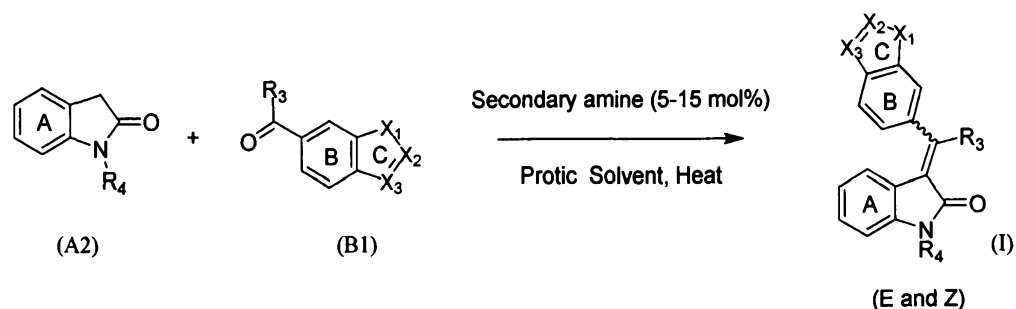
selected from the group consisting of halogen, nitro, cyano, hydroxy, C₁₋₂₀ alkyl, C₂₋₂₀ alkenyl, C₂₋₂₀ alkynyl, amino, C₁₋₂₀ alkylamino, C₁₋₂₀ dialkylamino, C₁₋₂₀ alkoxy, (C₁₋₁₀ alkoxy)C₁₋₂₀ alkyl, C₁₋₂₀ haloalkoxy, (C₁₋₁₀ haloalkoxy)C₁₋₂₀ alkyl and C₁₋₂₀ haloalkyl. Typical substituents include halogen, nitro, cyano, hydroxy, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, amino, C₁₋₁₀ alkylamino, C₁₋₁₀ dialkylamino, C₁₋₁₀ alkoxy, (C₁₋₆ alkoxy)C₁₋₁₀ alkyl, C₁₋₁₀ haloalkoxy, (C₁₋₆ haloalkoxy)C₁₋₁₀ alkyl and C₁₋₁₀ haloalkyl. More typical substituents include C₁₋₁₀ alkyl, -OH, C₁₋₁₀ alkoxy, C₁₋₁₀ haloalkyl, halogen, C₁₋₁₀ haloalkoxy, amino, nitro and cyano.

In accordance with another aspect of the present invention, the compounds of the invention can be prepared by processes analogous to those established in the art. By way of illustration, compounds of Structural Formula (A) (wherein Z is =CR³-) or (I), wherein Rings A, B and C are as defined herein may be prepared by the methods outlined in Scheme 1. Reaction of an appropriately substituted A1 or indolin-2-one A2 wherein ring A is as defined herein is reacted with a suitable aldehyde (R³ = H) or a ketone (R³ is not H) in the presence of a secondary amine (such as piperidine) in a protic solvent (such as ethanol) at the reflux temperature of the solvent (generally about 60 °C to 120 °C). In addition this reaction can be carried out under a variety of alternative conditions including secondary amines in aprotic solvents such as DMSO or DMF; solventless with KF/Al₂O₃; acidic conditions (p-TsOH) in toluene or a strong base (e.g. LDA) in THF.

Scheme 1



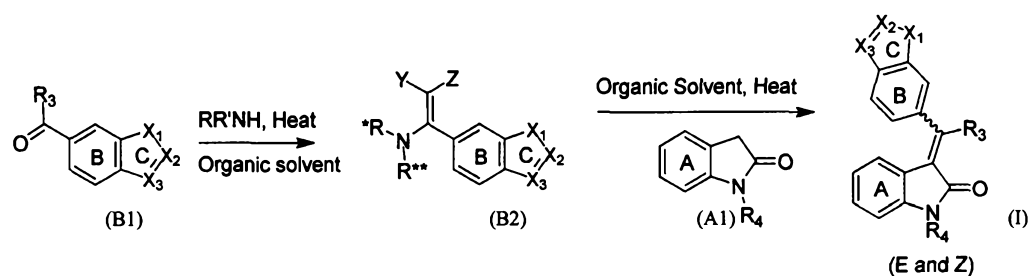
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In another aspect of the invention (Scheme 2) in which R³ of compound **B1** is not H, the ketone **B1** is first converted to an enamine **B2** (wherein Y and Z are proton or small alkyl) by reaction with a secondary amine (wherein R* and R** are small alkyl or together form five or six membered ring such as pyrrolidine or piperidine). Subsequent reaction of the enamine **B2** with the indolin-2-one **A2** in a refluxing organic solvent (such as toluene) yields compounds of Structural Formula (I) (wherein Z is =CR³-).

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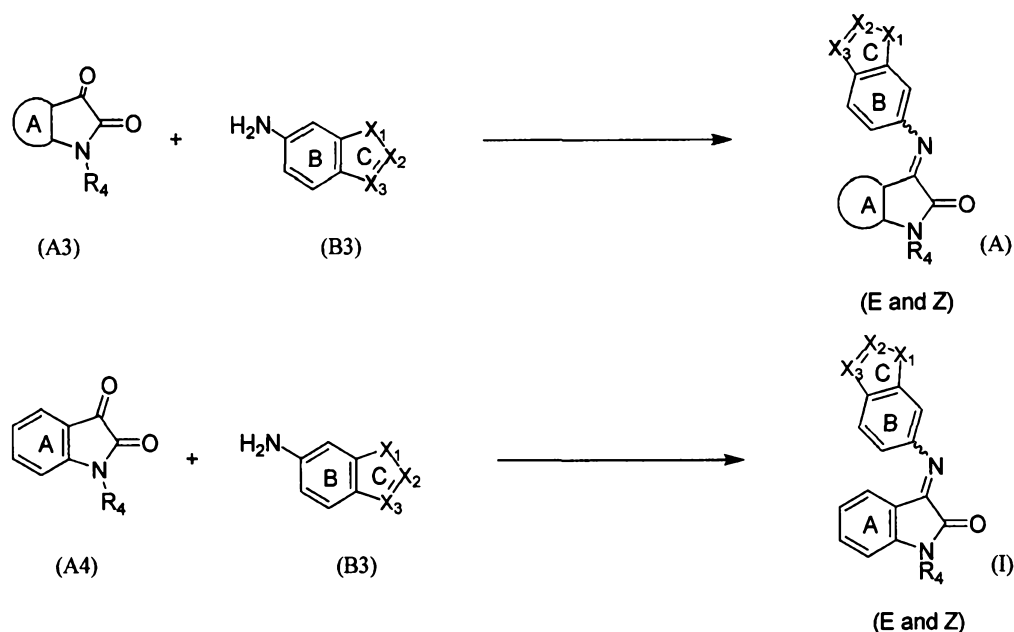
Scheme 2.



Compounds of Structural Formula (A) (wherein Z is =N-) or compounds of Structural Formula (C) (wherein Z is =N-), wherein Rings A, B and C are as defined herein may be prepared by the methods outlined in Scheme 3.

15

Scheme 3



- The present invention includes radiolabeled forms of the compounds of the invention, for example, compounds of the invention labeled by incorporation within the structure of ³H, ¹¹C or ¹⁴C or a radioactive halogen such as ¹²⁵I and ¹⁸F. A radiolabeled compound of the invention may be prepared using standard methods known in the art. For example, tritium may be incorporated into a compound of the invention using standard techniques, for example by hydrogenation of a suitable precursor to a compound of the invention using tritium gas and a catalyst.
- Alternatively, a compound of the invention containing radioactive iodine may be prepared from the corresponding trialkyltin (suitably trimethyltin) derivative using standard iodination conditions, such as [¹²⁵I] sodium iodide in the presence of chloramine-T in a suitable solvent, such as dimethylformamide. The trialkyltin compound may be prepared from the corresponding non-radioactive halo-, suitably iodo-, compound using standard palladium-catalyzed stannylation conditions, for example hexamethylditin in the presence of tetrakis(triphenylphosphine) palladium (0) in an inert solvent, such as dioxane, and at elevated temperatures, suitably 50-100°C. Further, a compound of the invention containing a radioactive fluorine may be prepared, for example, by reaction of K[¹⁸F]/K222 with a suitable precursor compound, such as a compound of Formula I comprising a suitable leaving group, for example a tosyl group, that may be displaced with the ¹⁸F anion.

In some cases the chemistries outlined above may have to be modified, for instance by use of protective groups, to prevent side reactions due to reactive groups, such as reactive groups attached as substituents. This may be achieved by means of conventional protecting groups, for example as described in "Protective Groups in Organic Chemistry" McOmie, J.F.W. Ed., Plenum Press, 1973 and in Greene, T.W. and Wuts, P.G.M., "Protective Groups in Organic Synthesis", John Wiley & Sons, 3rd Edition, 1999.

Indolinone compounds of the invention can inhibit various kinases, including the PLK4, PLK1, PLK2, Aurora A, Aurora B and FLT-3 (*see* Examples B, C, D, E, F, and H). Thus, generally, the indolinone compounds of the invention are useful in the treatment of diseases or conditions associated with such kinases. For example, PLK4, PLK1, Aurora A and Aurora B are believed to be involved in cellular mitotic progression. Thus, small molecule inhibitors of these enzymes can be potential anti-tumor agents.

In a specific embodiment, the compounds of the invention are PLK, Aurora A, Aurora B and/or FLT-3 inhibitors, and are useful for treating diseases, such as cancer, associated with such a kinase(s). In another specific embodiment, the compounds of the invention are PLK inhibitors and are useful for treating diseases associated with PLK, such as cancer. Typically, the PLK is PLK4, PLK2 and PLK1. In one example, the PLK is PLK1 and PLK4. In another example, the PLK is PLK4. In another specific embodiment, the compounds of the invention are Aurora A and/or B inhibitors and are useful in inhibiting Aurora A and/or B activity for the treatment of various conditions such as cancers. In yet another specific embodiment, the compounds of the invention are FLT-3 inhibitors and are useful in inhibiting FLT-3 activity for the treatment of various conditions such as cancers.

Another aspect of the invention relates to a method of treating cancer comprising administering an effective amount of a compound of the invention disclosed herein. In one embodiment, the compounds of the invention inhibit the growth of a tumor. Specifically, the compounds of the invention inhibit the growth of a tumor that overexpresses at least one of PLK, Aurora A, Aurora B, and FLT-3. More specifically, the compounds of the invention inhibit the growth of a tumor that overexpresses PLK, for example, PLK1, PLK2 and/or PLK4. Even more

specifically, the compounds of the invention inhibit the growth of a tumor that overexpresses PLK4. In another embodiment, the compounds of the invention inhibit the growth of the tumor by inducing apoptosis of the tumor cells or by inhibiting proliferation of the tumor cells.

- 5 Cancers that can be treated or prevented by the methods of the present invention include lung cancer, breast cancer, colon cancer, brain cancer, neuroblastoma, prostate cancer, melanoma, glioblastoma multiform, ovarian cancer, lymphoma, leukemia, melanoma, sarcoma, paraneoplasia, osteosarcoma, germinoma, glioma and mesothelioma. In one specific embodiment, the cancer is
- 10 lung cancer, colon cancer, brain cancer, neuroblastoma, prostate cancer, melanoma, glioblastoma multiform or ovarian cancer. In another specific embodiment, the cancer is lung cancer, breast cancer, colon cancer, brain cancer, neuroblastoma, prostate cancer, melanoma, glioblastoma multiform or ovarian cancer. In yet another specific embodiment, the cancer is a breast cancer. In yet another specific
- 15 embodiment, the cancer is a basal sub-type breast cancer or a luminal B sub-type breast cancer. In yet another specific embodiment, the cancer is a soft tissue cancer. A "soft tissue cancer" is an art-recognized term that encompasses tumors derived from any soft tissue of the body. Such soft tissue connects, supports, or surrounds various structures and organs of the body, including, but not limited to, smooth
- 20 muscle, skeletal muscle, tendons, fibrous tissues, fatty tissue, blood and lymph vessels, perivascular tissue, nerves, mesenchymal cells and synovial tissues. Thus, soft tissue cancers can be of fat tissue, muscle tissue, nerve tissue, joint tissue, blood vessels, lymph vessels, and fibrous tissues. Soft tissue cancers can be benign or malignant. Generally, malignant soft tissue cancers are referred to as sarcomas, or
- 25 soft tissue sarcomas. There are many types of soft tissue tumors, including lipoma, lipoblastoma, hibernoma, liposarcoma, leiomyoma, leiomyosarcoma, rhabdomyoma, rhabdomyosarcoma, neurofibroma, schwannoma (neurilemoma), neuroma, malignant schwannoma, neurofibrosarcoma, neurogenic sarcoma, nodular tenosynovitis, synovial sarcoma, hemangioma, glomus tumor, hemangiopericytoma,
- 30 hemangioendothelioma, angiosarcoma, Kaposi sarcoma, lymphangioma, fibroma, elastofibroma, superficial fibromatosis, fibrous histiocytoma, fibrosarcoma, fibromatosis, dermatofibrosarcoma protuberans (DFSP), malignant fibrous

histiocytoma (MFH), myxoma, granular cell tumor, malignant mesenchymomas, alveolar soft-part sarcoma, epithelioid sarcoma, clear cell sarcoma, and desmoplastic small cell tumor. In a particular embodiment, the soft tissue cancer is a sarcoma selected from the group consisting of a fibrosarcoma, a gastrointestinal sarcoma, a
5 leiomyosarcoma, a dedifferentiated liposarcoma, a pleomorphic liposarcoma, a malignant fibrous histiocytoma, a round cell sarcoma, and a synovial sarcoma.

The invention further relates to a method of treating a subject with tumor cells, comprising administering to the subject, an amount of a compound disclosed herein that is effective to reduce effectively PLK activity, such as PLK 2 or PLK4
10 activity, in the subject. In a specific embodiment, the PLK is PLK4.

The invention further relates to a method of inhibiting Aurora B and/or PLK-4 in a subject in need of inhibition of Aurora B and/or PLK-4. As used herein, a "subject in need of inhibition of Aurora B and/or PLK-4" means the subject has a disease(s) or condition(s) associated with overexpression of Aurora B and/or PLK-4,
15 or a disease(s) or condition(s) on which inhibition of Aurora B and/or PLK-4 have a beneficial effect(s).

The term a "therapeutically effective amount", "effective amount" or a "sufficient amount" of a compound of the present invention is a quantity sufficient to, when administered to the subject, including a mammal, for example a human,
20 effect beneficial or desired results, including clinical results. A "therapeutically effective amount" of a compound of the invention is an amount which prevents, inhibits, suppresses or reduces the cancer (e.g., as determined by clinical symptoms or the amount of cancer cells) in a subject as compared to a control. Specifically, "treating a subject with a cancer" includes achieving, partially or substantially, one
25 or more of the following: arresting the growth or spread of a cancer, reducing the extent of a cancer (e.g., reducing size of a tumor or reducing the number of affected sites), inhibiting the growth rate of a cancer, and ameliorating or improving a clinical symptom or indicator associated with a cancer (such as tissue or serum components).

30 Generally, a therapeutically effective amount amount of a compound of the invention varies depending upon various factors, such as the given drug or compound, the pharmaceutical formulation, the route of administration, the type of

disease or disorder, the identity of the subject or host being treated, and the like, but can nevertheless be routinely determined by one skilled in the art. As defined herein, a therapeutically effective amount of a compound of the present invention may be readily determined by one of ordinary skill by routine methods known in the art.

In an embodiment, a therapeutically effective amount of a compound of the invention ranges from about 0.1 to about 15 mg/kg body weight, suitably about 1 to about 5 mg/kg body weight, and more suitably, from about 2 to about 3 mg/kg body weight. The skilled artisan will appreciate that certain factors may influence the dosage required to effectively treat a subject suffering from cancer and these factors include, but are not limited to, the severity of the disease or disorder, previous treatments, the general health and/or age of the subject and other diseases present.

Moreover, a "treatment" regime of a subject with a therapeutically effective amount of the compound of the present invention may consist of a single administration, or alternatively comprise a series of applications. For example, the compound of the present invention may be administered at least once a week. However, in another embodiment, the compound may be administered to the subject from about one time per week to once daily for a given treatment. The length of the treatment period depends on a variety of factors, such as the severity of the disease, the age of the patient, the concentration and the activity of the compounds of the present invention, or a combination thereof. It will also be appreciated that the effective dosage of the compound used for the treatment or prophylaxis may increase or decrease over the course of a particular treatment or prophylaxis regime. Changes in dosage may result and become apparent by standard diagnostic assays known in the art. In some instances, chronic administration may be required.

As used herein, "treatment" is an approach for obtaining beneficial or desired results, including clinical results. Beneficial or desired clinical results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of extent of disease, stabilized (i.e. not worsening) state of disease, preventing spread of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or

total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment.

The term "subject" or "patient" or synonym thereto, as used herein includes all members of the animal kingdom, especially mammals, including human. The
5 subject or patient is suitably a human.

In one embodiment, the method of the present invention is a mono-therapy where the pharmaceutical compositions of the invention are administered alone. Accordingly, in this embodiment, the compound of the invention is the only pharmaceutically active ingredient in the pharmaceutical compositions or the only
10 pharmaceutically active ingredient administered to the subject.

In another embodiment, the method of the invention is a co-therapy with one or more of other therapeutically active drugs or therapies known in the art for treating the desired diseases or indications. In one example, one or more other anti-proliferative or anticancer therapies are combined with the compounds of the
15 invention. In another example, the compounds disclosed herein are co-administered with one or more of other anticancer drugs known in the art. Anticancer therapies that may be used in combination with the compound of the invention include surgery, radiotherapy (including, but not limited to, gamma-radiation, neutron beam radiotherapy, electron beam radiotherapy, proton therapy, brachytherapy, and
20 systemic radioactive isotopes) and endocrine therapy. Anticancer agents that may be used in combination with the the compounds of the invention include biologic response modifiers (including, but not limited to, interferons, interleukins, and tumor necrosis factor (TNF)), hyperthermia and cryotherapy, agents to attenuate any adverse effects (e.g., antiemetics), and other approved chemotherapeutic drugs (e.g.
25 taxol and analogs thereof).

When the compounds of the invention are combined with other anticancer drugs, they can be administered contemporaneously. As used herein, "administered contemporaneously" means that two substances are administered to a subject such that they are both biologically active in the subject at the same time. The exact
30 details of the administration will depend on the pharmacokinetics of the two substances in the presence of each other, and can include administering one substance within a period of time of one another, *e.g.*, 24 hours of administration of

the other, if the pharmacokinetics are suitable. Designs of suitable dosing regimens are routine for one skilled in the art. In particular embodiments, two substances will be administered substantially simultaneously, *i.e.* within minutes of each other, or in a single composition that comprises both substances. Alternatively, the two agents
5 can be administered separately, such that only one is biologically active in the subject at the same time.

The compounds of the invention can be administered to a patient in a variety of forms depending on the selected route of administration, as will be understood by those skilled in the art. The compounds of the invention may be administered, for
10 example, by oral, parenteral, buccal, sublingual, nasal, rectal, patch, pump or transdermal administration and the pharmaceutical compositions formulated accordingly. Parenteral administration includes intravenous, intraperitoneal, subcutaneous, intramuscular, transepithelial, nasal, intrapulmonary, intrathecal, rectal and topical modes of administration. Parenteral administration can be by
15 continuous infusion over a selected period of time.

The compounds of the invention can be suitably formulated into pharmaceutical compositions for administration to a subject. The pharmaceutical compositions of the invention optionally include one or more pharmaceutically acceptable carriers and/or diluents therefor, such as lactose, starch, cellulose and
20 dextrose. Other excipients, such as flavoring agents; sweeteners; and preservatives, such as methyl, ethyl, propyl and butyl parabens, can also be included. More complete listings of suitable excipients can be found in the Handbook of Pharmaceutical Excipients (5th Ed., Pharmaceutical Press (2005)). A person skilled in the art would know how to prepare formulations suitable for various types of
25 administration routes. Conventional procedures and ingredients for the selection and preparation of suitable formulations are described, for example, in Remington's Pharmaceutical Sciences (2003 - 20th edition) and in The United States Pharmacopeia: The National Formulary (USP 24 NF19) published in 1999. The carriers, diluents and/or excipients are "acceptable" in the sense of being compatible
30 with the other ingredients of the pharmaceutical composition and not deleterious to the recipient thereof.

Typically, for oral therapeutic administration, a compound of the invention may be incorporated with excipient and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like.

Typically for parenteral administration, solutions of a compound of the invention can generally be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, DMSO and mixtures thereof with or without alcohol, and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

Typically, for injectable use, sterile aqueous solutions or dispersion of, and sterile powders of, a compound of the invention for the extemporaneous preparation of sterile injectable solutions or dispersions.

For nasal administration, the compounds of the invention can be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomizing device. Alternatively, the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal after use. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas such as compressed air or an organic propellant such as fluorochlorohydrocarbon. The aerosol dosage forms can also take the form of a pump-atomizer.

For buccal or sublingual administration, the compounds of the invention can be formulated with with a carrier such as sugar, acacia, tragacanth, or gelatin and glycerine, as tablets, lozenges or pastilles.

For rectal administration, the compounds of the invention can be formulated in the form of suppositories containing a conventional suppository base such as cocoa butter.

The compounds of the invention, can be formulated alone or for contemporaneous administration with other agents for treating cancer. Therefore, in

another aspect, a pharmaceutical composition of the invention comprises a pharmaceutically acceptable carrier or diluent, a compound disclosed herein or a pharmaceutically acceptable salt thereof and another anti-cancer agent, for example, but not limited to a glucose metabolism inhibitor or taxol.

5 Meanings for the abbreviations used herein are provided below:

Chemicals :

| | | |
|----|-------------------------------------------|-----------------------------------------|
| | THF | tetrahydrofuran |
| | EtOAc | ethyl acetate |
| 10 | Et ₂ O | diethyl ether |
| | PDC | pyridinium dichromate |
| | MeOH | methanol |
| | DMSO | dimethylsulfoxide |
| | DMF | N,N-dimethylformamide |
| 15 | H ₂ NMe | methyl amine |
| | AcOH, HOAc | acetic acid |
| | DMAP | dimethylaminopyridine |
| | dba | dibenzylideneacetone |
| | <i>n</i> -BuOH | <i>n</i> -butanol |
| 20 | DCM | dichloromethane |
| | DI-H ₂ O | distilled or deionized water |
| | ^t BuOK | potassium tert-butoxide |
| | Et ₃ N | triethylamine |
| | EtOH | ethanol |
| 25 | TBTU | ... uranium** |
| | HOBt | 1-hydroxy-benzotriazole |
| | DIPEA | diisopropylethylamine (Hunig's base) |
| | TFA | trifluoroacetic acid |
| | MeCN | acetonitrile |
| 30 | OAc | acetate (e.g. Pd(OAc) ₂) |
| | <i>o</i> -Tol | ortho-toluenyl** |
| | <i>o</i> -tolyl | ortho-toluenyl** |
| | <i>o</i> -MeC ₆ H ₄ | ortho-toluenyl** |
| | EDC | ** |
| 35 | Hex | hexane |
| | TBAB | tetrabutylammonium bromide |
| | SEMCl | (2-(Chloromethoxy)ethyl)trimethylsilane |
| | mCPBA | meta-chloroperoxybenzoic acid |
| | DME | dimethoxyethane |
| 40 | TBAF | tetrabutylammonium fluoride |
| | PPh ₃ | triphenylphosphine |
| | PhMe | toluene |
| | <i>n</i> -BuLi | <i>n</i> -butyllithium |

| | | |
|----|----------------------|--------------------------------------------------------------|
| | Other: | |
| | NMR | nuclear magnetic resonance |
| | s, d, t, q, br. s, m | singlet, doublet, triplet, quartet, broad singlet, multiplet |
| | MS ESI | mass spectroscopy, electrospray ionization |
| 5 | LC-MS | liquid chromatography coupled to mass spectroscopy |
| | HPLC | high pressure liquid chromatography |
| | prep-HPLC | preparative scale high pressure liquid chromatography |
| | prepTLC | preparative scale thin layer chromatography |
| | calcd | calculated |
| 10 | mL, L, uL | milliliters, liters, microliters |
| | mmol, mol | millimoles, moles |
| | mg, g | milligrams, grams |
| | MHz | megaHertz |
| | M | molar |
| 15 | N | normal |
| | rt | room temperature |
| | °C | degrees Celsius |
| | min | minutes |
| | hrs, h | hour(s) |
| 20 | d | day(s) |
| | sep. | separatory |
| | wt. % | percent by weight |
| | atm | atmospheres of pressure |
| | temp. | temperature |
| 25 | sat., sat | saturated |
| | O/N | overnight |
| | quant | quantitative |
| | xs. | excess |
| | anh, anh. | anhydrous |
| 30 | aq | aqueous |
| | SPE | solid phase extraction |

The invention is illustrated by the following examples which are not intended to be limiting in any way.

EXEMPLIFICATION

35 **A. Syntheses of Compounds of the Invention**

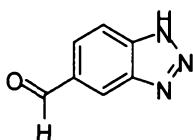
General Experimental Methods

All starting materials, reagents, and solvents were used as received from commercial sources. In general, anhydrous reactions were performed under an inert atmosphere
 40 such as nitrogen or argon. Microwave reactions were performed with a Biotage Initiator microwave reactor. Reaction progress was generally monitored by TLC

using Merck silica gel plates with visualization by UV at 254 nm, by analytical HPLC or by LCMS (Bruker Exquire 4000). Work-up means drying over sodium or magnesium sulfate, filtering, and concentrating *in vacuo*. Flash column chromatographic purification of intermediates or final products was performed using 5 230-400 mesh silica gel 60 from EMD chemicals. Final products were sometimes purified by preparative reverse-phase HPLC. Purification was performed on a Varian PrepStar model SD-1 HPLC system with a Varian Monochrom 10u C-18 reverse-phase column using a gradient of about 5-30% acetonitrile/ 0.05% TFA water to 70-100% acetonitrile/0.05% TFA water over a 20-40-min period at a flow rate of 30-50 mL/min. Fractions containing the desired material were concentrated and lyophilized to obtain the final products. Proton NMRs were recorded on a 10 Bruker Avance III 400 MHz spectrometer, and mass spectra were obtained using a Bruker Esquire 4000 spectrometer.

15 Preparation of Starting Materials

Synthesis of 1H-benzo[d][1,2,3]triazole-5-carbaldehyde



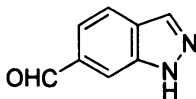
A. Synthesis of (1H-benzo[d][1,2,3]triazol-5-yl)methanol

20 Under a nitrogen atmosphere a dry round-bottom flask was charged with LiAlH_4 (0.316 g, 7.90 mmol) and THF (15 mL). Methyl 1H-benzo[d][1,2,3]triazole-5-carboxylate (1.0 g, 5.64 mmol) was then added portion-wise over 10min at room temperature and reaction allowed to stir for 4 hours at which time the reaction was quenched with EtOAc (5 mL), and the mixture poured into ice-water. The mixture 25 was acidified to pH = 3 with 10% H_2SO_4 and extracted 4X with EtOAc. The combined organics were washed with brine, dried (MgSO_4) and the solvent removed. The resulting brown solid was boiled in Et_2O and the solids filtered and dried to give the title compound as a light brown solid (678 mg, 81 %). ^1H NMR (400 MHz, CD_3OD) δ 7.85 (m, 2H), 7.47 (d, J = 8.4 Hz, 1H), 4.79 (s, 2H); MS ESI 30 150.0 $[\text{M} + \text{H}]^+$, calcd for $[\text{C}_7\text{H}_7\text{N}_3\text{O} + \text{H}]^+$ 150.16.

B. 1H-benzo[d][1,2,3]triazole-5-carbaldehyde

A suspension of (1H-benzo[d][1,2,3]triazol-5-yl)methanol (0.860 g, 5.77 mmol) in acetone (25 mL) was purged with Ar, by bubbling through solution, then
5 PDC (2.60 g, 6.92 mmol) was added portion-wise over 20 min. The reaction was stirred overnight (18 hrs). The acetone was removed *in vacuo*, the solids dissolved in MeOH and silica gel was added. The MeOH was then removed and the silica dry-loaded onto a silica gel column, and the product eluted with 1:1 Hexanes/EtOAc to give 444 mg, 52 % of a white solid. ¹H NMR (400 MHz, CD₃OD) δ 10.14 (s,
10 1H), 8.55 (s, 1H), 8.04 (d, J = 8.8 Hz, 1H), 7.96 (d, J = 8.4 Hz, 1H); MS ESI 148.0 [M + H]⁺, calcd for [C₇H₅N₃O + H]⁺ 148.14.

Synthesis of 1H-indazole-6-carbaldehyde



15 *A. 6-bromo-1H-indazole*

To a vigorously stirred solution of 5-bromo-2-fluorobenzaldehyde (40.6 g, 0.2 mol) in DMSO (80 mL) was added N₂H₄·xH₂O (40 mL, 0.8 mol) dropwise over 15 min (slow addition to keep the reaction not too hot). The resulting yellow slurry was heated at 120 °C (oil temp.) for 21 h. The whole mixture was transferred to a 1
20 L flask and cooled for 10 min in air before quenching with ice (300 mL) and ice-cold H₂O (100 mL). The resulting mixture was stirred for 30 min at rt. Precipitated formed was collected by suction filtration, rinsed thoroughly with H₂O (100 mL x 2), 2 M HCl (100 mL x 2), H₂O (100 mL x 2), 0.5 M Na₂CO₃ (100 mL x 2), H₂O (100 mL x 2), dried in air for 1 h and under high vacuum for 2 days to give 6-bromo-1H-indazole (30.05 g, 76%) as a light yellow solid. MS ESI 196.9 [M + H]⁺,
25 calcd for [C₇H₅BrN₂ + H]⁺ 197.0.

B. 1H-indazole-6-carbaldehyde

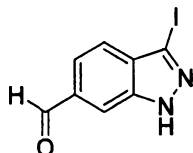
To a suspension of 60 % NaH (10.0 g, 0.24 mol) in THF (240 mL) was added a suspension of 6-bromo-1H-indazole (39.4 g, 0.2 mol) in THF (280 mL)
30 dropwise over 45 min. After addition, the resulting mixture was stirred for 1 h at rt to give a dark red clear solution which was cooled to -78 °C. *s*-BuLi (1.4 M in

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hexane, 300 mL, 0.42 mol) was added dropwise over 1 h. During this addition, additional THF (130 mL) was added to keep the mixture stirring. After the addition, the resulting mixture was stirred for 75 min at -78 °C; DMF (90 mL) was added dropwise (note: reaction solidified upon addition of DMF, occasional warming was
 5 needed to keep the mixture stirring). The resulting mixture was stirred at rt overnight and cooled to 0 °C. Solid NH₄Cl and saturated NH₄Cl were added to quench the reaction and bring the pH to about 7. The product was extracted with EtOAc (800 mL + 200 mL + 300 mL, 1.3 L in total) and the combined extracts were washed with H₂O (300 mL x 3) and dried (Na₂SO₄). Evaporation of the solvent gave a dark red
 10 solid which was triturated by EtOAc (4 times, the last filtrate was purified by flash chromatography) to give the title compound (16.96 g in total, 58%) as yellow brown solid. ¹H NMR (400 MHz, DMSO-d₆) δ 13.62 (s, 1H, NH), 10.12 (s, 1H, CHO), 8.23 (s, 1H), 8.17 (s, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H); MS ESI 147.0 [M + H]⁺, calcd for [C₈H₆N₂O + H]⁺ 147.0.

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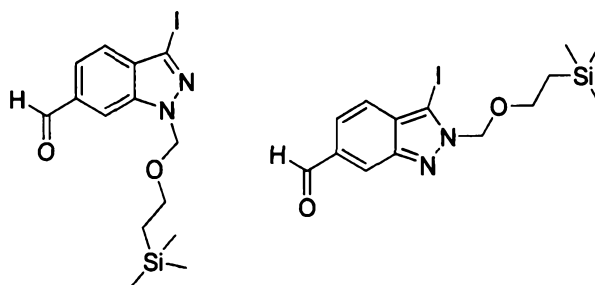
Synthesis of 3-iodo-1H-indazole-6-carbaldehyde



To a solution of 1H-Indazole-6-carbaldehyde (2.00 g, 13.7 mmol), K₂CO₃ (3.79 g, 27.4 mmol) in DMF (15 mL) was added dropwise a solution of I₂ (5.91 g, 23.3
 20 mmol) in DMF (15 mL) and the reaction allowed to stir for two hours. An aqueous solution consisting of Na₂S₂O₄ (3.30 g) / K₂CO₃ (0.20 g) / H₂O (30 mL) was then added and the solution stirred for one hour. The product was then precipitated by pouring the solution over ice-water (300 mL) and collected by vacuum filtration to give after drying 3.02 g, 81 % of a beige powder. ¹H NMR (400 MHz, CD₃OD) δ
 25 10.11 (s, 1H), 8.11 (s, 1H), 7.74 (d, J = 8.34 Hz, 1H), 7.62 (d, J = 8.34 Hz, 1H); MS ESI 272.9 [M + H]⁺, calcd for [C₈H₅IN₂O + H]⁺ 272.95.

Synthesis of 3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-
carbaldehyde and 3-iodo-2-((2-(trimethylsilyl)ethoxy)methyl)-2H-indazole-6-
 30 carbaldehyde

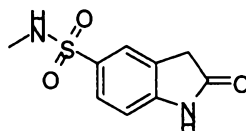
- 86 -



To a suspension of 3-iodo-1H-indazole-6-carbaldehyde (3.01 g, 11.1 mmol) in CH_2Cl_2 (70 mL) and 50 % aq. KOH (20 mL) was added tetrabutylammonium bromide (36 mg, 0.111 mmol) and the solution cooled to 0 °C. (2-(Chloromethoxy)ethyl)trimethylsilane (2.3 mL, 13.3 mmol) was then added dropwise and the reaction stirred at 0 °C for 3 hours. The solution was then transferred to a sep. funnel containing CH_2Cl_2 (200 mL) and the organic layer was washed with brine (2 X 100 mL), dried (MgSO_4) and the solvent removed *in vacuo*. The resulting residue was purified by column chromatography (100 % CH_2Cl_2) to give 2.88 g, 65 % of the N-1 isomer (higher eluting spot) and 757 mg, 17 % of the N-2 isomer (lower eluting spot). N-1 isomer: ^1H NMR (400 MHz, CDCl_3) δ 10.18 (s, 1H), 8.11 (s, 1H), 7.81 (d, $J = 8.4$ Hz, 1H), 7.65 (d, $J = 8.4$ Hz, 1H), 5.82 (s, 2H), 3.60 (m, 2H), 0.91 (m, 2H), -0.042 (s, 9H); MS ESI 425.0 $[\text{M} + \text{Na}]^+$, calcd for $[\text{C}_{14}\text{H}_{19}\text{IN}_2\text{O}_2\text{Si} + \text{Na}]^+$ 425.02.

N-2 isomer: ^1H NMR (400 MHz, CD_3OD) 10.09 (s, 1H), 8.31 (s, 1H), 7.62 (m, 2H), 5.91 (s, 2H), 3.71 (m, 2H), 0.92 (m, 2H), -0.039 (s, 9H); MS ESI 425.0 $[\text{M} + \text{Na}]^+$, calcd for $[\text{C}_{14}\text{H}_{19}\text{IN}_2\text{O}_2\text{Si} + \text{Na}]^+$ 425.02

Synthesis of N-methyl-2-oxoindoline-5-sulfonamide



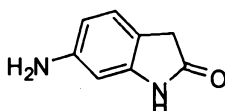
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A dry round-bottom flask was charged with 1 mL of a 2.0 M solution of H_2NMe in THF. 2-oxoindoline-5-sulfonyl chloride (100 mg, 0.432 mmol) was then added and the reaction stirred overnight. The solvents were removed and the residue purified by column chromatography (silica gel, 93:7 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to give 73 mg, 74 % of a brown solid. ^1H NMR (400 MHz, CD_3OD) δ 7.73 (d, $J = 8.8$ Hz, 1H), 7.72 (s, 1H),

25

7.03 (d, J = 8.0 Hz, 1H), 3.35 (s, 2H), 2.52 (s, 3H); MS ESI 226.9 [M + H]⁺, calcd for [C₉H₁₀N₂O₃S + H]⁺ 227.05.

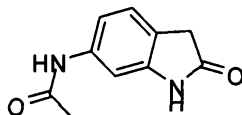
Synthesis of 6-aminoindolin-2-one



5

A solution of 2-(2,4-dinitrophenyl)acetic acid (1.0 g, 4.42 mmol), AcOH (10 mL), and MeOH (5 mL) was purged with Ar for 15 minutes at which time 10wt. % Pd/C (100mg) was added. The mixture was then purged briefly with H₂ and then stirred under 1atm of H₂ overnight. The mixture was filtered through a pad of celite, the solvent removed *in vacuo*, and the residue purified by column chromatography (silica gel, 90:10 CH₂Cl₂/MeOH) to give 462 mg, 71 % of a brown solid. ¹H NMR (400 MHz, CD₃OD) δ 6.95 (d, J = 7.7 Hz, 1H), 6.37 (d, J = 7.8 Hz, 1H), 6.34 (s, 1H), 3.38 (s, 2H); MS ESI 149.0 [M + H]⁺, calcd for [C₈H₈N₂O + H]⁺ 149.07.

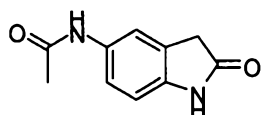
Synthesis of N-(2-oxoindolin-6-yl)acetamide



To 6-aminoindolin-2-one (30 mg, 0.202 mmol) in THF (1 mL) was added acetic anhydride (19 uL, 0.202 mmol). After 2 hrs the product was precipitated with ether, filtered and dried to give 25 mg, 66% of a white solid. ¹H NMR (400 MHz, CD₃OD) δ 7.41 (s, 1H), 7.16 (d, J = 7.0 Hz, 1H), 7.00 (d, J = 8.0 Hz, 1H), 3.49 (s, 2H), 2.12 (s, 3H); MS ESI 191.0 [M + H]⁺, calcd for [C₁₀H₁₀N₂O₂ + H]⁺ 191.08.

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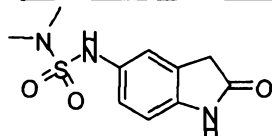
Synthesis of N-(2-oxoindolin-5-yl)acetamide



25 According to procedure for the synthesis of N-(2-oxoindolin-6-yl)acetamide, except substituting 5-aminoindolin-2-one (50 mg, 0.34 mmol), the title compound was

prepared as a beige solid (46 mg, 71%). ^1H NMR (400 MHz, CDCl_3) δ 7.49 (s, 1H), 7.31 (d, $J = 7.0$ Hz, 1H), 6.83 (d, $J = 8.0$ Hz, 1H), 3.52 (s, 2H), 2.10 (s, 3H).

Synthesis of *N,N*-dimethyl-*N'*-(2-oxo-2,3-dihydro-1*H*-indol-5-yl)sulfamide

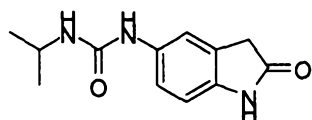


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To 5-aminoindolin-2-one (100 mg, 0.68 mmol) in ethyl acetate/DMF 1:1 (2 mL) was added dimethylsulfamoyl chloride (290 mg, 2.04 mmol) and DMAP (1 mg). After 72 h the product was precipitated with ether, filtered and dried to give 56 mg, 32% of a white solid. ^1H NMR (400 MHz, CD_3OD) δ 7.21 (s, 1H), 7.16 (d, $J = 7.0$ Hz, 1H), 7.00 (d, $J = 8.0$ Hz, 1H), 3.53 (s, 2H), 2.77 (s, 6H).

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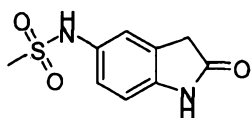
Synthesis of 1-isopropyl-3-(2-oxoindolin-5-yl)urea



To 5-aminoindolin-2-one (50 mg, 0.34 mmol) in ethyl acetate (1 mL) was added isopropylisocyanate (0.04 mL, 0.4 mmol). The solution was stirred at rt for 16h and the product was precipitated with ether, filtered and dried to give 46 mg, 58% of a yellow solid. ^1H NMR (400 MHz, CD_3OD) δ 7.31 (s, 1H), 7.13 (d, $J = 8.3$ Hz, 1H), 6.80 (d, $J = 8.3$ Hz, 1H), 3.90-3.83 (m, 1H), 3.51 (s, 2H), 1.77 (d, $J = 7.3$ Hz, 6H).

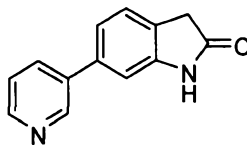
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20 Synthesis of *N*-(2-oxoindolin-5-yl)methanesulfonamide

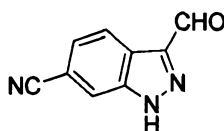


To 5-aminoindolin-2-one (50 mg, 0.34 mmol) in DMF (1 mL) was added methanesulfonyl chloride (51 mg, 0.51 mmol) and DMAP (1 mg). The solution was stirred at rt for 16h and the product was precipitated with ether, filtered and dried to give 10 mg, 13% of a yellow solid. ^1H NMR (400 MHz, CD_3OD) δ 7.22 (s, 1H), 7.13 (d, $J = 8.3$ Hz, 1H), 6.87 (d, $J = 7.6$ Hz, 1H), 3.55 (s, 2H), 2.91 (s, 3H).

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Synthesis of 6-(Pyridin-3-yl)indolin-2-one

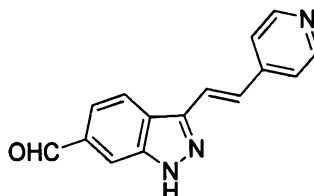
A mixture 6-chloroindolin-2-one (100 mg, 0.60 mmol), 3-(3,3,4,4-tetramethylborolan-1-yl)pyridine (184 mg, 0.90 mmol), Pd₂dba₃ (5.4 mg, 0.0060 mmol) and powdered K₃PO₄ (252 mg, 1.2 mmol) in *n*-BuOH (2 mL) was degassed by evacuation and refilling with Ar. Dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (11.4 mg, 0.024 mmol) was added under the atmosphere of Ar. The reaction mixture was sealed and heated with stirring under microwave irradiation at 100 °C for 99 min. Later the reaction was cooled to rt and treated with degassed H₂O (0.25 mL). The mixture was reheated under microwave irradiation at 110 °C for 1 h. The crude reaction mixture was concentrated under reduced pressure and purified by flash chromatography on silica gel using MeOH (0 to 6 %) in DCM as the eluent to provide the title compound as a pale yellow solid (100 mg, 80 %). %).
¹H NMR (400 MHz, CD₃OD) δ ppm 8.77 (d, *J*=1.52 Hz, 1 H), 8.52 (dd, *J*=4.80, 1.52 Hz, 1 H), 8.05 - 8.10 (m, 1 H), 7.52 (dd, *J*=7.33, 4.80 Hz, 1 H), 7.39 (d, *J*= 7.6 Hz, 1 H), 7.30 (dd, *J*=7.71, 1.39 Hz, 1 H), 7.17 (s, 1 H), 3.59 (s, 2 H); MS ESI 211.0 (100) [M + H]⁺, calcd for [C₁₃H₁₀N₂O + H]⁺ 211.2.

Synthesis of 3-formyl-1H-indazole-6-carbonitrile

To a solution of NaNO₂ (11.04g, 160 mmol) in DI-H₂O (200 mL) was added 6-cyanoindole (5.68 g, 40 mmol) in one portion slowly. The resulting suspension was stirred for 5 min at rt. 6N HCl (32 mL, 192 mmol) was added dropwise via a dropping funnel over 30 min and the pH was about 1. The resulting suspension was stirred for 4.5 h at rt before 400 mL of EtOAc was added. After stirring for additional 10 min to dissolve the precipitate, the two layers were separated and the aqueous layer was extracted with EtOAc (150 mL). Combined extracts were dried over Na₂SO₄. Removal of solvents afforded 6.864 g (100%) of title compound as

brown (coffee color) solid. ^1H NMR (400 MHz, DMSO- d_6) δ 14.70 (s, 1H, NH), 10.22 (s, 1H, CHO), 8.38 (s, 1H), 8.28 (d, $J = 8.4$ Hz, 1H), 7.69 (d, $J = 8.4$ Hz, 1H). MS ESI 172.0 $[\text{M} + \text{H}]^+$, calcd for $[\text{C}_9\text{H}_5\text{N}_3\text{O} + \text{H}]^+$ 172.0.

5 Synthesis of (E)-3-(2-(pyridin-4-yl)vinyl)-1H-indazole-6-carbaldehyde



a) *(E)-3-(2-(pyridin-4-yl)vinyl)-1H-indazole-6-carbonitrile*

To a suspension of 4-chloropyridine hydrochloride (3.28 g, 20 mmol) in benzene (50 mL) was added 40% NaOH (1.35 mL). The resulting mixture was
10 sonicated for 10 min and filtered. The residue was treated with additional benzene (15 mL), sonicated and filtered. The combined benzene layers were dried (Na_2SO_4) to give a solution of 4-chloropyridine which was used without further characterization (*vide infra*). A solution of diethyl phosphate (3.03 g, 22 mmol) in benzene (35 mL) was treated with freshly cut Na (510 mg, 22 mmol). The resulting
15 mixture was refluxed for 30 min (oil temp. 90°C), cooled to 0°C , then treated added dropwise over 10 min. with the solution of 4-chloropyridine in benzene (prepared as described above). After addition, the resulting mixture was refluxed for 3 h (oil temp. 100°C) under argon then cooled to rt. The insoluble white precipitate was removed by filtration and rinsed with benzene (20 mL). The combined filtrate was
20 concentrated and dried under high vacuum to give 3.5 g of diethyl pyridin-4-ylmethylphosphonate as a colorless liquid.

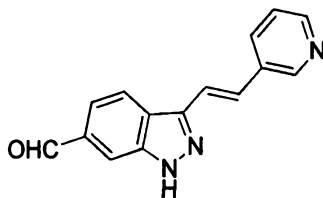
Diethyl pyridin-4-ylmethylphosphonate was redissolved in DMF (25 mL) and cooled to 0°C . $t\text{BuOK}$ (3.36 g, 30 mmol) was added portion wise over 2 min and the reaction mixture turned dark brown red. After stirring for 2 min at 0°C , a
25 solution of 3-formyl-1H-indazole-6-carbonitrile (1.71 g, 10 mmol) in DMF (15 mL) was added dropwise by pipette over 5 min. The resulting mixture was stirred for 40 min at 0°C before quenching with ice, 2N HCl (20 mL) and H_2O (20 mL). After stirring for 10 min at rt, the reaction mixture was carefully basified with sat. NaHCO_3 to pH about 8 and copious amounts of yellow precipitate formed. The solid

was collected by suction filtration and rinsed with H₂O. After drying under high vacuum, 2.016 g (82%) of title compound was obtained as beige solid. ¹H NMR (400 MHz, DMSO-d₆) δ 13.90 (s, 1H, NH), 8.60-8.54 (m, 2H), 8.43 (d, J = 8.0 Hz, 1H), 8.20 (s, 1H), 7.93 (d, J = 16.0 Hz, 1H), 7.70 (d, J = 4.0 Hz, 2H), 7.58 (d, J = 8.0 Hz, 1H, partially overlapping with the doublet at 7.55 ppm), 7.55 (d, J = 16.0 Hz, 1H, partially overlapping with the doublet at 7.58 ppm); MS ESI 250.0 [M + H]⁺, calcd for [C₁₅H₁₁N₃O + H]⁺ 250.1.

b) (E)-3-(2-(pyridin-4-yl)vinyl)-1H-indazole-6-carbaldehyde

To a solution of (E)-3-(2-(pyridin-4-yl)vinyl)-1H-indazole-6-carbonitrile (246 mg, 1 mmol) in HOAc/pyridine (3 mL/6 mL) was added a solution of sodium hypophosphite (352 mg, 4 mmol) in H₂O (3 mL), followed by Raney-Nickel 2400 (slurry in H₂O, 0.2 mL). The resulting mixture was heated at 55 °C (oil temp.) for 1 h then cooled to rt. Water (30 mL) was added and the mixture was extracted with EtOAc (30 mL x 3). The combined extracts were washed with H₂O (20 mL x 3), brine (10 mL) and dried (Na₂SO₄). Removal of solvent gave a yellow solution containing pyridine. H₂O (60 mL) was added with swirling and large amounts of yellow precipitate formed which was collected by suction filtration and rinsed with H₂O. After drying under high vacuum, the title compound (75 mg, 30 %) was obtained as a beige solid. ¹H NMR (400 MHz, DMSO-d₆) δ 13.90 (s, 1H, NH), 10.14 (s, 1H, CHO), 8.57 (d, J = 5.6 Hz, 2H), 8.40 (d, J = 8.4 Hz, 1H), 8.20 (s, 1H), 7.89 (d, J = 16.8 Hz, 1H), 7.73-7.69 (m, 3H), 7.55 (d, J = 16.4 Hz, 1H). MS ESI 247.0 [M + H]⁺, calcd for [C₁₅H₁₁N₃O + H]⁺ 247.1.

Synthesis of ((E)-3-(2-(pyridin-3-yl)vinyl)-1H-indazole-6-carbaldehyde



a) (E)-3-(2-(pyridin-3-yl)vinyl)-1H-indazole-6-carbonitrile

To a suspension of 3-chloropyridine hydrochloride (6.54 g, 40 mmol) in benzene (75 mL) was added 40% NaOH (2.7 mL). The resulting mixture was sonicated for 10 min and filtered. The residue was treated with additional benzene

(25 ml), sonicated and filtered. The combined benzene layers were dried (Na_2SO_4) to give a solution of 4-chloropyridine in benzene.

To a solution of diethyl phosphate (6.06 g, 44 mmol) in benzene (50 mL) was added freshly cut Na (1.02 g, 44 mmol). The resulting mixture was refluxed (oil temp. 95 °C) for 30 min then cooled to 0 °C. The solution of 4-chloropyridine in benzene obtained above was added dropwise to this solution via dropping funnel over 15 min. After addition, the resulting mixture was refluxed for 2 h (oil temp. 100 °C) and LC-MS indicated the completion of reaction. After cooling to rt, the insoluble white precipitate (NaCl) was filtered off and rinsed with benzene (50 mL). The filtrate was concentrated and dried under high vacuum to give 6.30 g of diethyl pyridin-3-ylmethylphosphonate as a light yellow liquid.

Diethyl pyridin-3-ylmethylphosphonate was redissolved in DMF (50 mL), cooled to 0 °C and treated with $t\text{BuOK}$ (6.72 g, 60 mmol) portion wise over 3 min; the reaction turned a dark reddish brown. After stirring for 3 min at 0 °C, a solution of 3-formyl-1H-indazole-6-carbonitrile (3.42 g, 20 mmol) in DMF (25 mL) was added dropwise by pipette over 5 min. After addition, the resulting mixture was stirred for 1 h at 0 °C before quenching with ice (100 mL). The reaction mixture was cooled to 0 °C and slowly acidified with 2M HCl until pH 5. During this addition, a copious amount of precipitate was formed. After stirring for 2 min at this temperature, sat NaHCO_3 was added slowly until pH 8 and the mixture was stirred for an additional 2 min. Water was added until the total volume reached 600 mL. After stirring for 10 min, the resulting precipitate was collected by suction filtration and rinsed thoroughly with water, then dried under high vacuum to give the title compound (3.30 g, 67%) as a beige solid. ^1H NMR (400 MHz, DMSO-d_6) δ 13.80 (s, 1H, NH), 8.89 (s, 1H), 8.48 (d, J = 4.4 Hz, 1H), 4.42 (d, J = 8.4 Hz, 1H), 8.22-8.17 (m, 2H), 7.74 (d, J = 16.8 Hz, 1H), 7.59 (d, J = 18.0 Hz, 1H, partially overlapping with the doublet at 7.55 ppm), 7.55 (d, J = 10.0 Hz, 1H, partially overlapping with the doublet at 7.59 ppm), 7.43 (dd, J = 8.0 Hz, 5.6 Hz, 1H); MS ESI 247.0 $[\text{M} + \text{H}]^+$, calcd for $[\text{C}_{15}\text{H}_{10}\text{N}_4 + \text{H}]^+$ 247.1.

b) *(E)*-3-(2-(pyridin-3-yl)vinyl)-1H-indazole-6-carbaldehyde

To a suspension of *(E)*-3-(2-(pyridin-4-yl)vinyl)-1H-indazole-6-carbonitrile (984 mg, 3 mmol) in pyridine (30 mL) was added HOAc (8 mL), followed by DMF

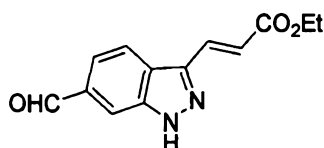
(30 mL). The resulting mixture was heated and sonicated to make a clear solution. After cooling to 0 °C, a solution of sodium hypophosphite (1.408 g, 16 mmol) in H₂O (8 mL) was added, followed by Raney-Nickel 2400 (slurry in H₂O, 0.8 mL). The resulting mixture was heated at 60 °C (oil temp.) for 1 h before cooling to rt.

5 H₂O (50 mL) was added and the mixture was extracted with EtOAc (100 mL + 50 mL x 2). The combined extracts were dried (Na₂SO₄). Removal of low boiling point solvents gave a yellow solution in DMF (about 30 mL); H₂O (500 mL) was added with swirling and a yellow precipitate formed. After standing 10 min, the resulting precipitate was collected by suction filtration, rinsed with H₂O and dried under high

10 vacuum to give the title compound (500 mg, 50 %) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ 13.79 (s, 1H, NH), 10.14 (s, 1H, CHO), 8.90 (s, 1H), 8.48 (d, J = 4.8 Hz, 1H), 8.39 (d, J = 8.0 Hz, 1H), 8.19 (d, J = 9.2 Hz, 1H, partially overlapping with the singlet at 8.18 ppm), 8.18 (s, 1H, partially overlapping with the doublet at 8.19 ppm), 7.75 (d, J = 16.4 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 16.8 Hz,

15 1H), 7.43 (dd, J = 8.0 Hz, 5.2 Hz, 1H); MS ESI 250.0 [M + H]⁺, calcd for [C₁₅H₁₁N₃O + H]⁺ 250.1.

Synthesis of (E)-ethyl 3-(6-formyl-1H-indazol-3-yl)acrylate



20 *A) (E)-ethyl 3-(6-cyano-1H-indazol-3-yl)acrylate*

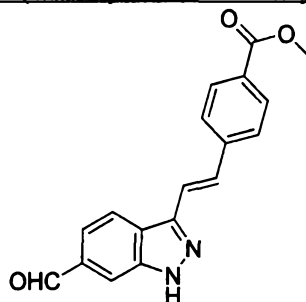
To a mixture of triethyl phosphonoacetate (125 mg, 0.55 mmol) and LiOH (26.4 mg, 1.1 mmol) in DMF (3 mL) at rt was added 3-formyl-1H-indazole-6-carbonitrile (85.5 mg, 0.5 mmol) in one portion. The resulting mixture was stirred at rt O/N. It was quenched with ice, followed by 2 M HCl (6 mL). After stirring for 5

25 min, the resulting precipitate was collected by suction filtration, washed with H₂O, hexane, dried to give the title compound (75 mg, 62%) as a beige solid. ¹H NMR (400 MHz, DMSO-d₆) δ 14.18 (s, 1H, NH), 8.35 (d, J = 8.8 Hz, 1H), 8.25 (s, 1H), 7.92 (d, J = 16.0 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 6.82 (d, J = 16.4 Hz, 1H), 4.22 (q, J = 7.2 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H); MS ESI 242.0 [M + H]⁺, calcd for

30 [C₁₃H₁₁N₂O₃ + H]⁺ 242.1.

B) ((E)-ethyl 3-(6-formyl-1H-indazol-3-yl)acrylate

To a solution of (E)-ethyl 3-(6-cyano-1H-indazol-3-yl)acrylate (723 mg, 3 mmol) in pyridine (10 mL) was added acetic acid (3 mL), followed by a solution of NaH₂PO₂ (1.056 g, 12 mmol) in H₂O (3 mL). The resulting mixture was stirred for 5 0.5 min at rt before Raney-Nickel 2400 (slurry in H₂O, 0.6 mL) was added in one portion. The resulting mixture was heated at 55 °C (oil temp.) for 1 h before cooling to rt. H₂O (30 mL) was added and the mixture was extracted with EtOAc (50 mL x 2). Combined extracts were washed with H₂O (20 mL), 2 M HCl (20 mL), H₂O (20 mL x 2), brine (15 mL) and dried (Na₂SO₄). Removal of solvent gave an orange red 10 oil which solidified upon standing O/N under high vacuum. It was then triturated with H₂O (30 mL) and suction filtered, rinsed with H₂O, dried to give the title compound (476 mg, 65%) as an orange red solid. ¹H NMR (400 MHz, DMSO-d₆) δ 14.16 (s, 1H, NH), 10.14 (s, 1H, CHO), 8.30 (d, J = 8.8 Hz, 1H), 8.22 (s, 1H), 7.92 (d, J = 16.4 Hz, 1H), 7.71 (d, J = 7.6 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 4.22 (q, J = 6.8 Hz, 2H), 1.28 (t, J = 6.8 Hz, 3H); MS ESI 245.0 [M + H]⁺, calcd for [C₁₃H₁₂N₂O₃ + H]⁺ 245.1.

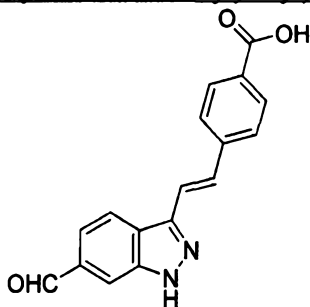
Synthesis of (E)-methyl 4-(2-(6-formyl-1H-indazol-3-yl)vinyl)benzoate

20 A mixture of methyl 4-(bromomethyl)benzoate (4.58 g, 20 mmol) and trimethyl phosphite (3.54 mL, 30 mmol) was refluxed (oil temp. 125 °C) for 1 h under argon. After cooling to rt, the reaction mixture was diluted with DMF (50 mL) and cooled to 0 °C using ice bath. ^tBuOK (3.92 g, 35 mmol) was added slowly. After addition, the resulting dark brown solution was stirred for 5 min at 0 °C before a 25 solution of 3-formyl-1H-indazole-6-carbonitrile (2.0 g, 11.7 mmol) in DMF (15 mL) was added dropwise via a pasteur pipette over 5 min. The reaction mixture was then stirred for 90 min at 0 °C; 2N HCl (25 mL) was added slowly over 2 min, followed by H₂O (100 mL). The resulting suspension was stirred for 5 min at 0 °C.

The precipitates collected by suction filtration were rinsed well with H₂O and dried to give crude (E)-methyl 4-(2-(6-cyano-1H-indazol-3-yl)vinyl)benzoate (3.70 g) as an orange solid. Trituration with 50 mL of ether, followed by sonication and suction filtration gave pure (E)-methyl 4-(2-(6-cyano-1H-indazol-3-yl)vinyl)benzoate (2.56 g, 72 %) as an orange solid. ¹H NMR (400 MHz, DMSO-d₆) δ 13.83 (s, 1H), 8.43 (d, J = 8.8 Hz, 1H), 8.18 (s, 1H), 7.97 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 16.4 Hz, 1H), 7.63 (d, J = 16.8 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 3.86 (s, 3H); MS ESI 304.1 [M + H]⁺, calcd for [C₁₈H₁₃N₃O₂ + H]⁺ 304.1.

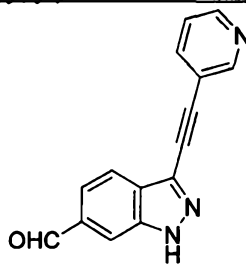
To a mixture of (E)-methyl 4-(2-(6-cyano-1H-indazol-3-yl)vinyl)benzoate (606 mg, 2 mmol) in HOAc/pyridine/DMF (4 mL/8 mL/6 mL) was added a solution of NaH₂PO₂ (704 mg, 8 mmol) in H₂O (4 mL), followed by Raney-Nickel 2400 (slurry in H₂O, 0.4 mL). The resulting mixture was heated for 1 h at 55 °C (oil temp.). After cooling to rt, it was diluted with EtOAc (80 mL) and washed with H₂O (30 mL). Aqueous layer was extracted with EtOAc (50 mL). Combined organic layers were washed with 2 N HCl (20 mL), H₂O (20 mL) and dried (Na₂SO₄). Evaporation of solvent gave crude title compound as an orange solid which was triturated with EtOAc (10 mL), followed by suction filtration to give the title compound (240 mg, 39 %) as light beige solid. The filtrate was concentrated, triturated with H₂O, sonicated and the resulting precipitates were collected by suction filtration and rinsed with H₂O, dried to give additional title compound (151 mg, 25%) as orange solid. ¹H NMR (400 MHz, DMSO-d₆) δ 13.82 (s, 1H), 10.14 (s, 1H), 8.40 (d, J = 8.8 Hz, 1H), 8.18 (s, 1H), 7.97 (d, J = 8.0 Hz, 2H), 7.88 (d, J = 7.6 Hz, 2H), 7.77 (d, J = 16.8 Hz, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.64 (d, J = 15.6 Hz, 1H), 3.86 (s, 3H); MS ESI 307.0 [M + H]⁺, calcd for [C₁₈H₁₄N₂O₃ + H]⁺ 307.1.

Synthesis of (E)-4-(2-(6-formyl-1H-indazol-3-yl)vinyl)benzoic acid



To a round bottom flash containing (E)-methyl 4-(2-(6-cyano-1H-indazol-3-yl)vinyl)benzoate (606 mg, 2 mmol) was added 2 M NaOH (20 mL, 40 mmol), followed by THF (10 mL) and MeOH (10 mL). The resulting mixture was stirred O/N at rt. After removal of THF and MeOH via rotavap, the residue was cooled to 0 °C and treated with 2 M HCl (25 mL) and stirred for 2 min at that temp. The precipitates collected by suction filtration were rinsed with H₂O to give crude (E)-4-(2-(6-cyano-1H-indazol-3-yl)vinyl)benzoic acid as a brown red solid. It was redissolved in HOAc/pyridine/DMF (4 mL/8 mL/6 mL) and a solution of NaH₂PO₂ (704 mg, 8 mmol) in H₂O (4 mL) was added, followed by Raney-Nickel 2400 (slurry in H₂O, 0.4 mL). The resulting mixture was heated for 1 h at 55 °C (oil temp.). Usual aqueous workup, followed by trituration with H₂O gave the title compound (332 mg, 54%) as a beige solid. ¹H NMR (400 MHz, DMSO-d₆) δ 13.81 (s, 1H), 12.90 (s, br, 1H), 10.14 (s, 1H), 8.39 (d, J = 8.0 Hz, 1H), 8.19 (s, 1H), 7.96 (d, J = 8.0 Hz, 2H), 7.86 (d, J = 8.0 Hz, 2H), 7.76 (d, J = 16.8 Hz, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.64 (d, J = 16.4 Hz, 1H); MS ESI 293.0 [M + H]⁺, calcd for [C₁₇H₁₂N₂O₃ + H]⁺ 293.1.

Synthesis of 3-(pyridin-3-ylethynyl)-1H-indazole-6-carbaldehyde



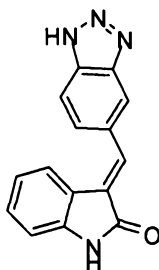
To a solution of 3-iodo-1H-indazole-6-carbaldehyde (136 mg, 0.5 mmol), Pd(PPh₃)₂Cl₂ (14 mg, 0.02 mmol) and CuI (7.6 mg, 0.04 mmol) in DMF (3 mL) was added Et₃N (5 mL), followed by 3-ethynylpyridine (77 mg, 0.75 mmol). The resulting mixture was heated at 100 °C (oil temp.) for 45 min. After removal of Et₃N, the residue was loaded directly onto a silical gel column. Flash chromatography (eluent: hex to ethyl acetate), followed by trituration with water and suction filtration gave the title compound (112 mg, 91%) as a light yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ 14.16 (s, 1H), 10.16 (s, 1H), 8.90 (s, 1H), 6.64 (d, J = 4.0 Hz, 1H), 8.26 (s, 1H), 8.12 (d, J = 8.0 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.74

(d, $J = 8.4$ Hz, 1H), 7.52 (dd, $J = 8.0$ Hz, $J = 5.2$ Hz, 1H); MS ESI 248.0 $[M + H]^+$, calcd for $[C_{15}H_9N_3O + H]^+$ 248.1.

Preparation of Compounds of the Invention

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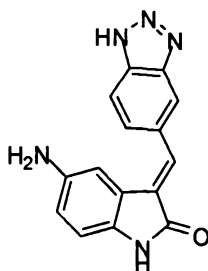
Example A1. (E)-3-((1H-benzo[d][1,2,3]triazol-5-yl)methylene)indolin-2-one



A scintillation vial was charged with indolin-2-one (101 mg, 0.760 mmol), 1H-benzo[d][1,2,3]triazole-5-carbaldehyde (123 mg, 0.836 mmol), piperidine (7.5
10 μ L, 0.076 mmol) and EtOH (4 mL). The reaction was then heated to 90°C for 2 hrs. A yellow precipitate formed which was further precipitated by cooling to room temperature and adding more EtOH (5 mL). The yellow solid was then filtered and washed with EtOH (20 mL) giving 149 mg, 75 % of the title compound. 1H NMR (400 MHz, d_6 -DMSO) δ 15.94 (s, 1H), 10.65 (s, 1H), 8.27 (bs, 1H), 8.05 (bs, 1H),
15 7.80 (s, 1H), 7.77 (bs, 1H), 7.51 (d, $J = 7.6$ Hz, 1H), 7.24 (t, $J = 7.6$ Hz, 1H), 6.88 (d, $J = 7.6$ Hz, 1H), 6.84 (d, $J = 7.6$ Hz, 1H); MS ESI 263.0 $[M + H]^+$, calcd for $[C_{15}H_{10}N_4O + H]^+$ 263.09.

Example A2. (E)-3-((1H-benzo[d][1,2,3]triazol-5-yl)methylene)-5-aminoindolin-2-one

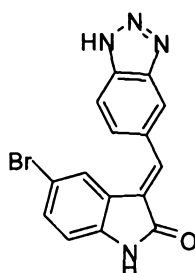
20 one



A scintillation vial was charged with 5-aminoindolin-2-one (37 mg, 0.247 mmol), 1H-benzo[d][1,2,3]triazole-5-carbaldehyde (40 mg, 0.272 mmol), piperidine

(2.5 uL, 0.025 mmol) and EtOH (2 mL). The reaction was then heated to 90°C for 2 hrs. The EtOH was removed *in vacuo* and the residue loaded onto a silica gel column eluting with 92:8 CH₂Cl₂/MeOH to give 14 mg, 20 % of a red solid. ¹H NMR (400 MHz, d₆-DMSO) δ 15.96 (bs, 1H), 10.15 (s, 1H), 8.21 (bs, 1H), 8.02 (bs, 1H), 7.73 (bs, 1H), 7.67 (s, 1H), 6.87 (s, 1H), 6.59-6.47 (m, 2H), 4.65 (bs, 2H); MS ESI 278.0 [M + H]⁺, calcd for [C₁₅H₁₁N₅O + H]⁺ 278.10.

Example A3. (E)-3-((1H-benzo[d][1,2,3]triazol-5-yl)methylene)-5-bromoindolin-2-one

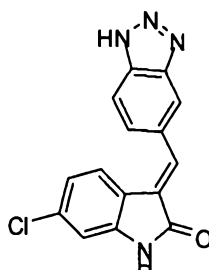


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The title compound was synthesized according to the method described for Example A1, except reacting 5-bromooxindole (39 mg, 0.185 mmol) with 1H-benzo[d][1,2,3]triazole-5-carbaldehyde (30 mg, 0.204 mmol) to obtain 32 mg, 51 %. ¹H NMR (400 MHz, d₆-DMSO) δ 15.97 (s, 1H), 10.85 (s, 1H), 9.27 (s, 1H), 8.37 (d, J = 9.2 Hz, 1H), 8.16 (s, 1H), 8.02 (s, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.39 (d, J = 8.2 Hz, 1H), 6.80 (d, J = 8.3 Hz, 1H); MS ESI 341.0 [M + H]⁺, calcd for [C₁₅H₉BrN₄O + H]⁺ 341.00.

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Example A4. (E)-3-((1H-benzo[d][1,2,3]triazol-5-yl)methylene)-6-chloroindolin-2-one



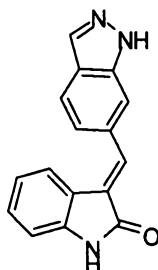
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The title compound was synthesized according to the method described for Example A1 except reacting 6-chlorooxindole (36 mg, 0.216 mmol) with 1H-

benzo[d][1,2,3]triazole-5-carbaldehyde (35 mg, 0.238 mmol) to obtain 32 mg, 51 %. ^1H NMR (400 MHz, d_6 -DMSO) δ 15.95 (s, 1H), 10.81 (s, 1H), 8.27 (bs, 1H), 8.04 (bs, 1H), 7.85 (s, 1H), 7.76 (bs, 1H), 7.49 (d, J = 8.8 Hz, 1H), 6.91 (bs, 2H); MS ESI 297.0 $[\text{M} + \text{H}]^+$, calcd for $[\text{C}_{15}\text{H}_9\text{ClN}_4\text{O} + \text{H}]^+$ 297.05.

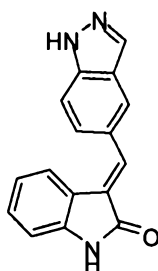
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Example A5. (E)-3-((1H-indazol-6-yl)methylene)indolin-2-one



The title compound was synthesized according to the method described for Example A1 except reacting oxindole (67 mg, 0.216 mmol) with 1H-indazole-6-carbaldehyde (73 mg, 0.238 mmol) to obtain 32 mg, 51 %. ^1H NMR (400 MHz, CD_3OD) δ 8.14 (s, 1H), 7.91 (d, J = 8.5 Hz, 1H), 7.89 (s, 2H), 7.65 (d, J = 7.6 Hz, 1H), 7.47 (d, J = 8.4 Hz, 1H), 7.25 (t, J = 7.7 Hz, 1H), 6.93 (d, J = 7.8 Hz, 1H), 6.87 (t, J = 7.6 Hz, 1H); MS ESI 262.0 $[\text{M} + \text{H}]^+$, calcd for $[\text{C}_{16}\text{H}_{11}\text{N}_3\text{O} + \text{H}]^+$ 262.10.

15 Example A6. (E)-3-((1H-indazol-5-yl)methylene)indolin-2-one



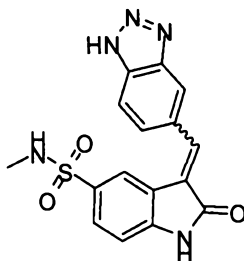
A scintillation vial was charged with indolin-2-one (67 mg, 0.500 mmol), 1H-indazole-5-carbaldehyde (73 mg, 0.550 mmol), piperidine (5.0 μL , 0.076 mmol) and EtOH (2 mL). The reaction was then heated to 90°C for 2 hrs. The EtOH was removed and the product purified by preparatory reverse-phase HPLC to give 10 mg, 7.6 % of the title compound. ^1H NMR (400 MHz, CD_3OD) δ 8.20-8.18 (m, 2H), 7.89 (s, 1H), 7.76 (d, J = 7.9 Hz, 1H), 7.71-7.67 (m, 2H), 7.24 (t, J = 7.4 Hz, 1H),

20

- 100 -

6.93 (d, $J = 7.7$ Hz, 1H), 6.90 (t, $J = 7.5$ Hz, 1H); MS ESI 262.0 $[M + H]^+$, calcd for $[C_{16}H_{11}N_3O + H]^+$ 262.10.

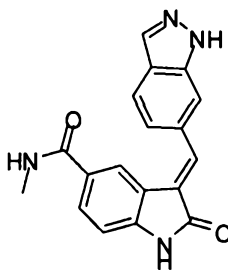
Example A7. 3-((1H-benzo[d][1,2,3]triazol-5-yl)methylene)-N-methyl-2-oxoindoline-5-sulfonamide



The compound was synthesized according to the method described for Example A6 except reacting N-methyl-2-oxoindoline-5-sulfonamide (14 mg, 0.0618 mmol) with 1H-benzo[d][1,2,3]triazole-5-carbaldehyde (10 mg, 0.0680 mmol) to obtain 5.6 mg, 12 % of the title compound as a mixture of (E) and (Z) isomers (69:21 by NMR). 1H NMR (400 MHz, d_6 -DMSO) δ 16.02, 16.00 (bs, 1H), 11.10, 11.15 (s, 1H), 8.55-8.10 (m, 2H), 7.95-7.80 (m, 3H), 7.77-7.60 (m, 1H), 7.27, 7.21 (q, $J = 5.2$ Hz, 1H), 7.07, 7.03 (d, $J = 8.3$ Hz, 1H), 2.44, 2.36 (s, 3H); MS ESI 356.1 $[M + H]^+$, calcd for $[C_{16}H_{13}N_5O_3S + H]^+$ 356.08.

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Example A8. (E)-3-((1H-indazol-6-yl)methylene)-N-methyl-2-oxoindoline-5-carboxamide



A. N-methyl-2-oxoindoline-5-carboxamide

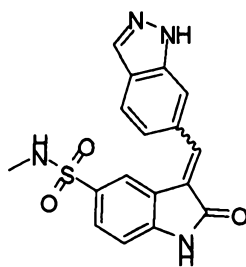
20 An oven-dried round-bottom flask was charged with 2-oxoindoline-5-carboxylic acid (89 mg, 0.500 mmol), TBTU (193 mg, 0.600 mmol), HOBT hydrate (81 mg, 0.600 mmol), DIPEA (0.13 mL, 0.750 mmol) and DMF (3.0 mL) and stirred for 5 minutes. Methyl amine (0.75 mL of a 2.0 M solution in THF) was then

added and reaction was stirred for 4 hours at which time $\text{NaHCO}_3(\text{sat.})$ (2mL) was added. Solvents were removed *in vacuo* and the residue was purified by column chromatography (silica gel, 92:8 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to give the title compound (11 mg, 12 %). ^1H NMR (400 MHz, CD_3OD) δ ppm 7.69 - 7.75 (m, 2 H), 6.94 (d, $J=8.1$ Hz, 1 H), 3.58 (s, 2 H), 2.97 (s, 3 H); MS ESI 191.0 $[\text{M} + \text{H}]^+$, calcd for $[\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_2 + \text{H}]^+$ 191.08.

B. (E)-3-((1H-indazol-6-yl)methylene)-N-methyl-2-oxoindoline-5-carboxamide

The title compound was synthesized from N-methyl-2-oxoindoline-5-carboxamide (11 mg, 0.0578 mmol) and 1H-indazole-6-carbaldehyde (10 mg, 0.0636 mmol) according to the method described for Example A1 to obtain 3.0 mg, 17 %. ^1H NMR (400 MHz, d_6 -DMSO) δ 13.33 (s, 1H), 10.88 (s, 1H), 8.24-8.22 (m, 1H), 8.18 (s, 2H), 7.93-7.88 (m, 2H), 7.84 (s, 1H), 7.72 (d, $J = 7.9$ Hz, 1H), 7.46 (d, $J = 8.0$ Hz, 1H), 6.91 (d, $J = 8.0$ Hz, 1H), 2.68 (d, $J = 4.0$ Hz, 3H); MS ESI 319.1 $[\text{M} + \text{H}]^+$, calcd for $[\text{C}_{18}\text{H}_{14}\text{N}_4\text{O}_2 + \text{H}]^+$ 319.12.

Example A9. (E and Z)-3-((1H-indazol-6-yl)methylene)-N-methyl-2-oxoindoline-5-sulfonamide

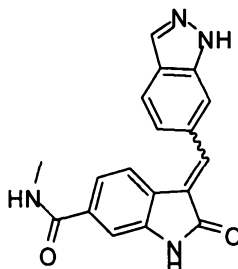


20

According to the method described for Example A1 the title compound was prepared from N-methyl-2-oxoindoline-5-sulfonamide (41 mg, 0.181 mmol) and 1H-indazole-6-carbaldehyde (29 mg, 0.199 mmol) as a mixture of geometric isomers (24 mg, 38 %). (E) and (Z) isomers: 55:45 by NMR. ^1H NMR (400 MHz, d_6 -DMSO) δ 13.43, 13.38 (s, 1H), 11.13, 11.11 (s, 1H), 9.03, 8.23 (s, 1H), 8.20-7.82 (m, 5H), 7.65, 7.47 (d, $J = 8.4$ Hz, 1H), 7.25, 7.20 (m, 1H), 7.06, 7.01 (d, $J = 8.4$ Hz, 1H), 2.45, 2.32 (s, 3H); MS ESI 355.1 $[\text{M} + \text{H}]^+$, calcd for $[\text{C}_{17}\text{H}_{14}\text{N}_4\text{O}_3\text{S} + \text{H}]^+$ 355.09.

25

Example A10. (E and Z)-3-((1H-indazol-6-yl)methylene)-N-methyl-2-oxoindoline-6-carboxamide



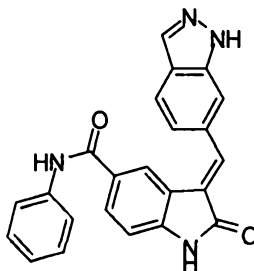
5 *A. N-methyl-2-oxoindoline-6-carboxamide*

The compound was synthesized according to the method described for N-methyl-2-oxoindoline-5-carboxamide except substituting 2-oxoindoline-6-carboxylic acid (89 mg, 0.500 mmol), to obtain the title compound (18 mg, 19 %). ¹H NMR (400 MHz, CD₃OD) δ 7.52 (d, J = 7.6 Hz, 1H), 7.15 (d, J = 8.0 Hz, 1H),
 10 6.40 (d, J = 7.6 Hz, 1H), 3.33 (s, 2H), 2.87 (s, 3H); MS ESI 191.0 [M + H]⁺, calcd for [C₁₀H₁₀N₂O₂ + H]⁺ 191.08.

B. (3-((1H-indazol-6-yl)methylene)-N-methyl-2-oxoindoline-6-carboxamide

According to the method described for Example A6, the title compound (2.8 mg, 9.3 %) was obtained from N-methyl-2-oxoindoline-6-carboxamide (18 mg, 0.0950 mmol) as a mixture of (E) and (Z) isomers (70:30 by NMR). ¹H NMR (400 MHz, CD₃OD) δ 8.99, 8.16 (s, 1H), 8.10-7.69 (m, 4H), 7.52-7.36 (m, 1H), 7.37-7.28 (m, 2H), 2.94, 2.91 (s, 3H); MS ESI 319.1 [M + H]⁺, calcd for [C₁₈H₁₄N₄O₂ + H]⁺ 319.12.

20 Example A11. (E)-3-((1H-indazol-6-yl)methylene)-2-oxo-N-phenylindoline-5-carboxamide



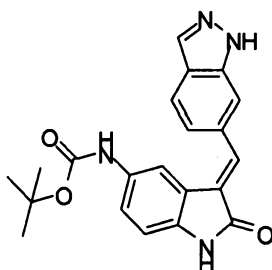
A. 2-oxo-N-phenylindoline-5-carboxamide

The title compound was synthesized according to the method described for N-methyl-2-oxoindoline-5-carboxamide from 2-oxoindoline-6-carboxylic acid (89 mg, 0.500 mmol) and aniline (0.14 mL, 1.50 mmol) to obtain 45 mg, 36 %. ¹H NMR (400 MHz, CD₃OD) δ 7.88 (d, J = 8.4 Hz, 1H), 7.87 (s, 1H), 7.67 (d, J = 7.9 Hz, 2H), 7.36 (t, J = 7.9 Hz, 2H), 7.15 (t, J = 7.4 Hz, 1H), 7.00 (d, J = 8.0 Hz, 1H), 3.34 (s, 2H); MS ESI 253.0 [M + H]⁺, calcd for [C₁₅H₁₂N₂O₂ + H]⁺ 253.10.

B. (E)-3-((1H-indazol-6-yl)methylene)-2-oxo-N-phenylindoline-5-carboxamide

A scintillation vial was charged with 2-oxo-N-phenylindoline-5-carboxamide (22 mg, 0.087 mmol), 1H-indazole-6-carbaldehyde (14 mg, 0.096 mmol), piperidine (1 μL, 0.008 mmol) and MeOH (2 mL). The reaction was then heated to 60°C for 2 hrs. A yellow precipitate formed which was further precipitated by cooling to room temperature and adding more MeOH (2 mL). The yellow solid was then filtered and washed with MeOH (10 mL) to give 8.0 mg, 24 % of the title compound. ¹H NMR (400 MHz, d₆-DMSO) δ 13.42 (s, 1H), 11.02 (s, 1H), 10.16 (s, 1H), 9.01 (s, 1H), 8.39 (s, 1H), 8.14 (s, 2H), 8.03 (d, J = 7.3 Hz, 1H), 7.89-7.82 (m, 2H), 7.79 (d, J = 6.5 Hz, 2H), 7.36 (t, J = 6.6 Hz, 2H), 7.11-7.09 (m, 1H), 6.96 (d, J = 6.9 Hz, 1H); MS ESI 381.1 [M + H]⁺, calcd for [C₂₃H₁₆N₄O₂ + H]⁺ 381.14.

Example A12. (E)-tert-butyl 3-((1H-indazol-6-yl)methylene)-2-oxoindolin-5-ylcarbamate

*A. tert-butyl 2-oxoindolin-5-ylcarbamate*

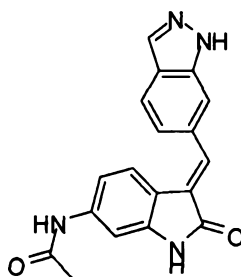
A THF (20 mL) solution of 5-aminoindolin-2-one (200 mg, 1.3 mmol) and di-*t*-butyl dicarbonate (300 mg, 1.4 mmol) at rt under N₂, was treated with Et₃N

(0.37 mL, 2.7 mmol). The stirring was continued at rt overnight; the reaction mixture was concentrated under reduced pressure, taken into DCM and washed (H₂O 2x, brine). The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure. Trituration with hexanes provided the title compound as a white solid (260 mg, 77 %). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.43 (br. s., 2 H), 7.07 (dd, *J*=8.84, 1.26 Hz, 1 H), 6.77 (d, *J*=8.59 Hz, 1 H), 6.39 (br. s., 1 H), 3.52 (s, 2 H), 1.52 (s, 9 H); MS ESI 249.0 (80) [M + H]⁺, calcd for [C₁₃H₁₆N₂O₃ + H]⁺ 249.3.

B. (E)-tert-butyl 3-((1H-indazol-6-yl)methylene)-2-oxoindolin-5-ylcarbamate

The title compound was synthesized according to the method described for Example A11B from tert-butyl 2-oxoindolin-5-ylcarbamate (100 mg, 0.403 mmol) and precipitation with CH₂Cl₂ to obtain the title compound (70 mg, 46 %). ¹H NMR (400 MHz, CD₃OD) δ 8.92 (s, 1H), 8.09 (s, 1H), 7.89-7.80 (m, 4H), 7.18 (d, *J* = 7.0 Hz, 1H), 6.80 (d, *J* = 8.3 Hz, 1H), 1.56 (s, 9H); MS ESI 377.3 [M + H]⁺, calcd for [C₂₁H₂₀N₄O₃ + H]⁺ 377.16.

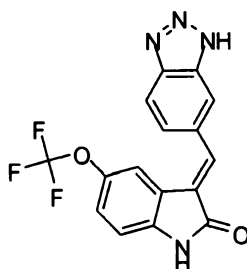
Example A13. (E)-N-(3-((1H-indazol-6-yl)methylene)-2-oxoindolin-6-yl)acetamide



The title compound was synthesized according to the method described for Example A11B except substituting N-(2-oxoindolin-6-yl)acetamide (25 mg, 0.131 mmol), to obtain 12 mg, 29 %. ¹H NMR (400 MHz, d₆-DMSO) δ 13.25 (s, 1H), 10.59 (s, 1H), 10.08 (s, 1H), 8.15 (s, 1H), 7.88 (s, 2H), 7.62 (s, 1H), 7.54 (d, *J* = 6.9 Hz, 1H), 7.50 (s, 1H), 7.41 (d, *J* = 7.9 Hz, 1H), 6.87 (d, *J* = 7.0 Hz, 1H), 2.04 (s, 3H); MS ESI 319.1 [M + H]⁺, calcd for [C₁₈H₁₄N₄O₂ + H]⁺ 319.12.

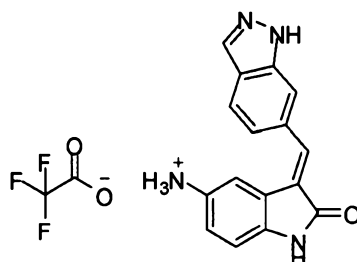
Example A14. (E)-3-((1H-benzo[d][1,2,3]triazol-5-yl)methylene)-5-(trifluoromethoxy)indolin-2-one

- 105 -

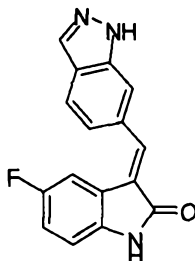


A scintillation vial was charged with 5-(trifluoromethoxy)indolin-2-one (27 mg, 0.124 mmol), 1H-benzo[d][1,2,3]triazole-5-carbaldehyde (20 mg, 0.136 mmol), piperidine (2 μ L, 0.012 mmol) and MeOH (2 mL). The reaction was then heated to 60°C for 2 hrs. The MeOH was removed in vacuo and the residue purified by column chromatography (silica gel, 95:4:1, CH₂Cl₂/MeOH/AcOH) to give the title compound as a yellow solid (10 mg, 23 %). ¹H NMR (400 MHz, CD₃OD) δ 8.23 (s, 1H), 8.04 (d, J = 4.5 Hz, 1H), 8.02 (s, 1H), 7.77 (d, J = 9.3 Hz, 1H), 7.42 (s, 1H), 7.21-7.18 (m, 1H), 6.99 (s, 1H); MS ESI 347.0 [M + H]⁺, calcd for [C₁₆H₉F₃N₄O₂ + H]⁺ 347.08.

Example A15. (E)-3-((1H-indazol-6-yl)methylene)-2-oxoindolin-5-aminium 2,2,2-trifluoroacetate

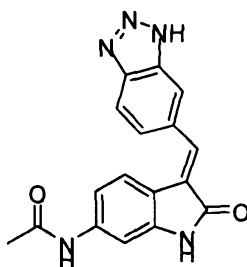


To (E)-tert-butyl 3-((1H-indazol-6-yl)methylene)-2-oxoindolin-5-ylcarbamate (15 mg, 0.040 mmol) in CH₂Cl₂ (2 mL) was added TFA (0.1 mL). After 1.5 hrs the solvent was removed and the product precipitated with ether and filtered washing with ether to give 9 mg, 56 % of the title compound as a brown solid. ¹H NMR (400 MHz, d₆-DMSO) δ 13.41 (s, 1H), 10.79 (s, 1H), 9.25-8.90 (bs, 3H), 9.01 (s, 1H), 8.14 (s, 1H), 8.00-7.96 (m, 2H), 7.82 (d, J = 8.5 Hz, 1H), 7.56 (s, 1H), 7.09-7.07 (m, 1H), 6.86 (d, J = 8.1 Hz, 1H); MS ESI 277.0 [M]⁺, calcd for [C₁₆H₁₃N₄O]⁺ 277.11.

Example A16. (E)-3-((1H-indazol-6-yl)methylene)-5-fluoroindolin-2-one

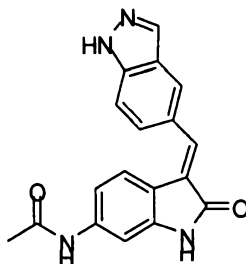
A scintillation vial was charged with 5-fluoroindolin-2-one (40 mg, 0.265 mmol), 1H-indazole-6-carbaldehyde (43 mg, 0.292 mmol), piperidine (3 μ L, 0.027 mmol) and MeOH (2 mL). The reaction was then heated to 60°C for 2 hrs. LC-MS analysis of the filtered yellow solid indicated a 9:1 mixture of geometric isomers. The mixture was resolved through prep-HPLC purification to give 11 mg, 15 % of the major isomer (E) as the title compound. The minor fraction was also isolated; see Example A32. ¹H NMR (400 MHz, *d*₆-DMSO) δ 13.31 (s, 1H), 10.66 (s, 1H), 8.18 (s, 1H), 7.92 (d, *J* = 8.7 Hz, 1H), 7.91 (s, 1H), 7.86 (s, 1H), 7.42 (d, *J* = 8.5 Hz, 1H), 7.29 (d, *J* = 9.5 Hz, 1H), 7.10 (t, *J* = 6.8 Hz, 1H), 6.88 (dd, *J*₁ = 8.8 Hz, *J*₂ = 4.7, 1H); MS ESI 280.0 [M + H]⁺, calcd for [C₁₆H₁₀FN₃O + H]⁺ 280.09.

Example A17. (E)-N-(3-((1H-benzo[d][1,2,3]triazol-5-yl)methylene)-2-oxoindolin-6-yl)acetamide



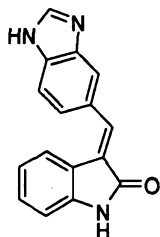
The title compound was synthesized according to the method described for Example A11B except substituting N-(2-oxoindolin-6-yl)acetamide (30 mg, 0.158 mmol) and 1H-benzo[d][1,2,3]triazole-6-carbaldehyde (26 mg, 0.174 mmol) to obtain 22 mg, 44 %. ¹H NMR (400 MHz, *d*₆-DMSO) δ ~16 (s, 1H), 10.60 (s, 1H), 10.10 (s, 1H), 8.23 (s, 1H), 8.01 (s, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.64 (s, 1H), 7.51 (s, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 6.86 (d, *J* = 7.4 Hz, 1H), 2.02 (s, 3H); MS ESI 320.1 [M + H]⁺, calcd for [C₁₇H₁₃N₅O₂ + H]⁺ 320.11.

Example A18. ((E)-N-(3-((1H-indazol-5-yl)methylene)-2-oxoindolin-6-yl)acetamide



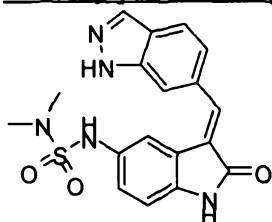
The title compound was synthesized according to the method described for
5 Example A11B except substituting N-(2-oxoindolin-6-yl)acetamide (40mg, 0.210
mmol) and 1H-indazole-5-carbaldehyde (34 mg, 0.231 mmol) to obtain 41 mg, 61
%. ¹H NMR (400 MHz, d₆-DMSO) δ 13.31 (s, 1H), 10.55 (s, 1H), 10.07 (s, 1H),
8.19 (s, 1H), 8.15 (s, 1H), 7.71-7.64 (m, 2H), 7.61 (s, 1H), 7.57 (d, J = 8.4 Hz, 1H),
7.48 (s, 1H), 6.89 (d, J = 8.3 Hz, 1H), 2.04 (s, 3H); MS ESI 319.1 [M + H]⁺, calcd
10 for [C₁₈H₁₄N₄O₂ + H]⁺ 319.12.

Example A19 (E)-3-((1H-benzo[d]imidazol-5-yl)methylene)indolin-2-one



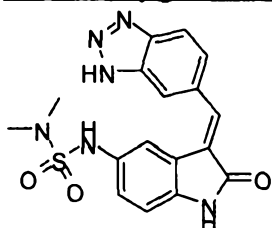
Indolin-2-one (80 mg, 0.60 mmol), 1H-benzo[d]imidazole-5-carbaldehyde
15 (97 mg, 0.66 mmol) and piperidine (2 drops) in EtOH (2 mL) were heated with
stirring in a sealed tube under microwave irradiation at 90 °C for 15 min. A yellow
precipitate was filtered and rinsed with EtOH. Recrystallization from EtOH
afforded the title compound as a yellow powder (15.5 mg, 10 %). ¹H NMR (400
MHz, DMSO-d₆) δ ppm 12.71 (br. s., 1 H), 10.59 (s, 1 H), 8.35 (s, 1 H), 7.99 (s, 1
20 H), 7.78 (s, 1 H), 7.65-7.75 (m, 2 H), 7.59 (d, J=8.34 Hz, 1 H), 7.22 (t, J=7.58 Hz, 1
H), 6.82 - 6.91 (m, 2 H); MS ESI [M + H]⁺ 262.0, calcd for [C₁₆H₁₁N₃O + H]⁺
262.3.

Example A20. *N'*-[(3*E*)-3-(1*H*-indazol-6-ylmethylidene)-2-oxo-2,3-dihydro-1*H*-indol-5-yl]-*N,N*-dimethylsulfamide



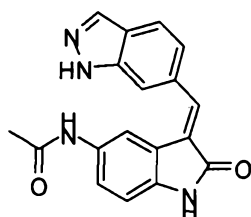
To a solution of *N,N*-dimethyl-*N'*-(2-oxo-2,3-dihydro-1*H*-indol-5-yl)sulfamide (28 mg, 0.11 mmol) was added 1*H*-indazole-6-carbaldehyde (18 mg, 0.12 mmol), piperidine (2 μ L, 0.012 mmol) and MeOH (2 mL). The reaction was then heated to 85°C for 30 min. The MeOH was removed in vacuo and the residue purified by column chromatography (silica gel, 95:5, CH₂Cl₂/MeOH) to give 14 mg, 33 % of the title compound as an orange solid. ¹H NMR (400 MHz, CDCl₃) δ 8.13 (s, 1H), 7.91 (s, 1H), 7.84 (s, 1H), 7.64 (s, 1H), 7.45 (d, *J* = 8.3 Hz, 1H), 7.07 (d, *J* = 8.1 Hz, 1H), 6.86 (d, *J* = 8.3 Hz, 1H), 2.59 (s, 6H); MS ESI 384.1 [M + H]⁺, calcd for [C₁₈H₁₇N₅O₃S + H]⁺ 384.1.

Example A21. *N'*-[(3*E*)-3-(1*H*-benzotriazol-5-ylmethylidene)-2-oxo-2,3-dihydro-1*H*-indol-5-yl]-*N,N*-dimethylsulfamide



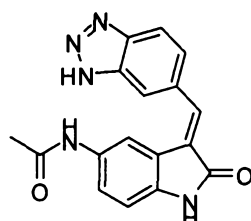
According to the method described in example A20, except substituting 1*H*-benzo[d][1,2,3]triazole-5-carbaldehyde (18 mg, 0.12 mmol), the title compound was obtained as an orange solid (16 mg, 38%). ¹H NMR (400 MHz, CDCl₃) δ 8.20 (s, 1H), 8.02 (d, *J* = 8.3 Hz, 1H), 7.92 (s, 1H), 7.78 (d, *J* = 8.3 Hz, 1H), 7.59 (s, 1H), 7.09 (d, *J* = 8.1 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 1H), 2.61 (s, 6H); MS ESI 385.1 [M + H]⁺, calcd for [C₁₇H₁₆N₆O₃S + H]⁺ 385.1.

Example A22. (E)-*N*-(3-((1*H*-indazol-6-yl)methylene)-2-oxoindolin-5-yl)acetamide



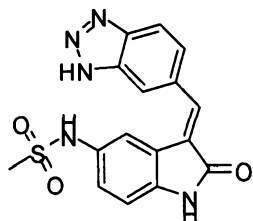
To a solution of N-(2-oxoindolin-5-yl)acetamide (19 mg, 0.1 mmol) was added 1H-indazole-6-carbaldehyde (16 mg, 0.12 mmol), piperidine (2 uL, 0.011 mmol) and MeOH (2 mL). The reaction was then heated to 85°C for 30 min. The MeOH was removed in vacuo and the solid triturated with ether to give 11 mg, 34 % of the title compound as an orange solid. ¹H NMR (400 MHz, CD₃OD) δ 8.13 (s, 1H), 8.06 (s, 1H), 7.92-7.88 (m, 2H), 7.84 (s, 1H), 7.49 (d, J = 8.6 Hz, 1H), 7.35 (d, 1H), 6.88 (d, J = 8.3 Hz, 1H), 2.04 (s, 3H); MS ESI 319.1 [M + H]⁺, calcd for [C₁₈H₁₇N₅O₃S + H]⁺ 319.11.

Example A23. (E)-N-(3-((1H-benzo[d][1,2,3]triazol-5-yl)methylene)-2-oxoindolin-5-yl)acetamide



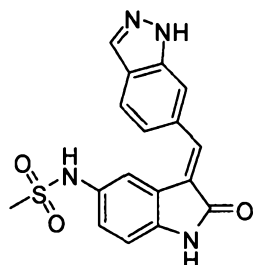
According to the method of Example A22, except substituting substituting 1H-benzo[d][1,2,3]triazole-5-carbaldehyde (16 mg, 0.12 mmol), the title compound was obtained as an orange solid (7 mg, 22%). ¹H NMR (400 MHz, DMSO-d₆) δ 10.54 (s, 1H), 9.73 (s, 1H), 8.32-8.22 (m, 1H), 8.05-7.75 (m, 2H), 7.92 (s, 1H), 7.80-7.7 (m, 2H), 7.47 (d, 1H), 6.82 (d, J = 8.3 Hz, 1H), 1.92 (s, 3H); MS ESI 320.0 [M + H]⁺, calcd for [C₁₇H₁₃N₅O₂ + H]⁺ 320.1.

Example A24. (E)-N-(3-((1H-benzo[d][1,2,3]triazol-5-yl)methylene)-2-oxoindolin-5-yl)methanesulfonamide



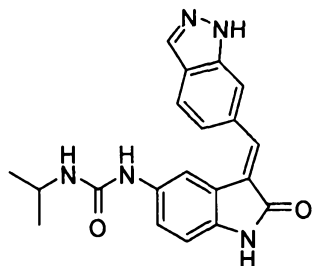
According to the method of Example A20, except substituting N-(2-oxoindolin-5-yl)methanesulfonamide (12 mg, 0.053 mmol) and 1H-benzo[d][1,2,3]triazole-5-carbaldehyde (9 mg, 0.058 mmol), the title compound was
 5 obtained as an orange solid (8 mg, 42%). ¹H NMR (400 MHz, CDCl₃) δ 8.22 (s, 1H), 8.00 (d, J = 8.6 Hz, 1H), 7.93 (s, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.61 (s, 1H), 7.14 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 8.3 Hz, 1H), 2.86 (s, 3H); MS ESI 356.0 [M + H]⁺, calcd for [C₁₆H₁₃N₅O₃S + H]⁺ 356.1.

10 Example A25. (E)-N-(3-((1H-indazol-6-yl)methylene)-2-oxoindolin-5-yl)methanesulfonamide



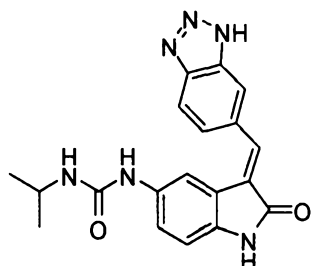
According to the method of Example A20, except substituting N-(2-oxoindolin-5-yl)methanesulfonamide (10 mg, 0.044 mmol), the title compound was
 15 obtained as an orange solid (2 mg, 13%). ¹H NMR (400 MHz, DMSO-d₆) δ 13.29 (s, 1H), 10.61 (s, 1H), 8.17 (s, 1H), 7.86-7.87 (m, 2H), 7.79 (s, 1H), 7.61 (s, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.11 (d, J = 7.8 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 2.86 (s, 3H); MS ESI 355.1 [M + H]⁺, calcd for [C₁₆H₁₃N₅O₃S + H]⁺ 355.1.

20 Example A26. (E)-1-(3-((1H-indazol-6-yl)methylene)-2-oxoindolin-5-yl)-3-isopropylurea



According to the method of Example A20, except substituting 1-isopropyl-3-(2-oxoindolin-5-yl)urea (23 mg, 0.099 mmol), the title compound was obtained as an orange solid (8 mg, 22%). ¹H NMR (400 MHz, DMSO-d₆) δ 13.29 (s, 1H), 10.41 (s, 1H), 8.16 (s, 1H), 8.00 (s, 1H), 7.87 (m, 2H), 7.72 (s, 1H), 7.60 (s, 1H), 7.45 (d, J = 9.4 Hz, 1H), 7.37 (d, J = 7.8 Hz, 1H), 6.74 (d, J = 8.1 Hz, 1H), 5.76 (d, J = 8.6 Hz, 1H), 3.75-3.70 (m, 1H), 1.03-1.00 (m, 6H); MS ESI 362.1 [M + H]⁺, calcd for [C₂₀H₁₉N₅O₂ + H]⁺ 362.2.

10 Example A27. (E)-1-(3-((1H-benzo[d][1,2,3]triazol-5-yl)methylene)-2-oxoindolin-5-yl)-3-isopropylurea

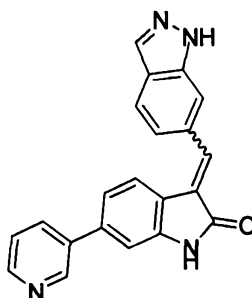


According to the method of Example A20, except substituting 1-isopropyl-3-(2-oxoindolin-5-yl)urea (23 mg, 0.099 mmol) and 1H-benzo[d][1,2,3]triazole-5-carbaldehyde (15 mg, 0.11 mmol), the title compound was obtained as an orange solid (6 mg, 16%). ¹H NMR (400 MHz, DMSO-d₆) δ 10.44 (s, 1H), 8.01 (s, 1H), 7.75 (s, 1H), 7.57-7.59 (m, 2H), 7.31 (d, J = 7.6 Hz, 1H), 6.74 (d, J = 8.4 Hz, 1H), 5.76 (d, J = 7.6 Hz, 1H), 3.75-3.70 (m, 1H), 1.03-1.00 (d, 6H); MS ESI 363.1 [M + H]⁺, calcd for [C₂₀H₁₉N₅O₂ + H]⁺ 363.2.

20

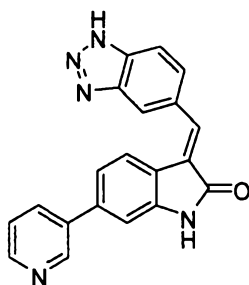
Example A28. (E and Z)-3-(3-((1H-indazol-6-yl)methylene)-2-oxoindolin-6-yl)pyridinium 2,2,2-trifluoroacetate

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6-(Pyridin-3-yl)indolin-2-one (25 mg, 0.12 mmol) and 1H-indazole-6-carbaldehyde (17.4 mg, 0.12 mmol) were heated with stirring in a sealed tube under microwave irradiation at 90 °C for 15 min. The crude mixture was concentrated and purified by prepTLC (SiO₂ 20 % MeOH/DCM) followed by HPLC. Subsequent recrystallization from MeCN provided the title compound as a dark orange solid (6.2 mg, 12 %) in a (2:1) mixture of E and Z isomers. E-isomer: ¹H NMR (400 MHz, CD₃OD) 8.97 (br. s., 1 H), 8.67 (br. s., 1 H), 8.45 (d, *J*=7.83 Hz, 1 H), 8.15 (s, 1 H), 7.76 - 8.01 (m, 5 H), 7.50 (d, *J*=8.34 Hz, 1 H), 7.22 - 7.29 (m, 2 H); Z-isomer: ¹H NMR (400 MHz, CD₃OD) δ ppm 9.01 (br. s., 1 H), 8.67 (br. s., 1 H), 8.54 (d, *J*=7.33 Hz, 1 H), 8.09 (s, 1 H), 7.76 - 8.01 (m, 6 H), 7.43 (d, *J*=7.58 Hz, 1 H), 7.22 - 7.29 (m, 1 H); MS ESI 339.1 (100) [M + H]⁺, calcd for [C₂₁H₁₄N₄O + H]⁺ 339.4.

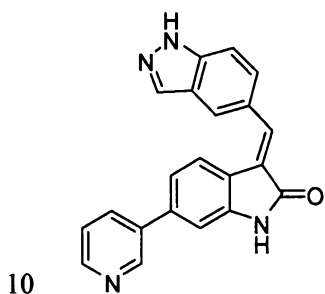
Example A29. (E)-3-((1H-benzo[d][1,2,3]triazol-5-yl)methylene)-6-(pyridin-3-yl)indolin-2-one



According to the method of Example A19, utilizing 6-(pyridin-3-yl)indolin-2-one (37.1 mg, 0.18 mmol) and 1H-benzo[d][1,2,3]triazole-5-carbaldehyde (25.8 mg, 0.18 mmol), the title compound was obtained as an orange solid (20 mg, 34 %). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 15.96 (br.s. 1H), 10.83 (s, 1 H), 8.86 (br. s., 1

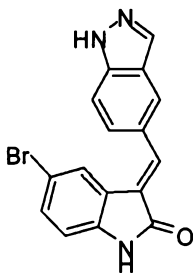
H), 8.57 - 8.61 (m, 1 H), 8.45 (br. s., 0.5 H), 8.18 (br. s., 1 H), 8.05 (d, $J=7.83$ Hz, 1 H), 7.95 (br. s., 1 H), 7.86 (s, 0.5 H), 7.75 (br. s., 1 H), 7.64 (d, $J=7.33$ Hz, 1 H), 7.49 (dd, $J=7.71, 4.93$ Hz, 1 H), 7.22 (d, $J=7.58$ Hz, 1 H), 7.17 (s, 1 H); ^1H NMR (400 MHz, $\text{DMF}-d_7$) δ ppm 10.77 (br. s., 1 H), 8.94 (br. s., 1 H), 8.61 - 8.65 (m, 1 H), 8.42 (s, 1 H), 8.13 (t, $J=7.96$ Hz, 1 H), 7.93 (s, 1 H), 7.90 (d, $J=8.84$ Hz, 1 H), 7.78 (d, $J=7.83$ Hz, 1 H), 7.52 (dd, $J=7.71, 4.67$ Hz, 1 H), 7.33 (s, 1 H), 7.30 (d, $J=7.83$ Hz, 1 H); MS ESI 340.1 (100) $[\text{M} + \text{H}]^+$, calcd for $[\text{C}_{20}\text{H}_{13}\text{N}_5\text{O} + \text{H}]^+$ 340.4.

Example A30. (E)-3-((1H-indazol-5-yl)methylene)-6-(pyridin-3-yl)indolin-2-one



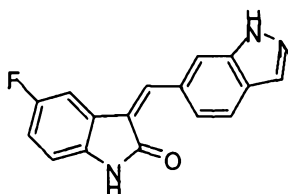
According to the method of Example A19, utilizing 6-(pyridin-3-yl)indolin-2-one (25 mg, 0.12 mmol) and 1H-indazole-5-carbaldehyde (17.4 mg, 0.12 mmol), the title compound was obtained as an orange solid (7 mg, 17 %). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 13.32 (br. s., 1 H), 10.81 (s, 1H), 9.04 (s, 1 H), 8.89 (d, $J=1.26$ Hz, 1 H), 8.57 (dd, $J=4.55, 1.26$ Hz, 1 H), 8.52 (d, $J=7.83$ Hz, 1 H), 8.25 (s, 1 H), 8.06 - 8.11 (m, 1 H), 8.04 (s, 1 H), 7.87 (d, $J=7.83$ Hz, 1 H), 7.62 (d, $J=8.84$ Hz, 1 H), 7.49 (dd, $J=7.33, 4.55$ Hz, 1 H), 7.38 (dd, $J=7.83, 1.26$ Hz, 1 H), 7.11 (d, $J=1.01$ Hz, 1 H); MS ESI 339.1 (100) $[\text{M} + \text{H}]^+$, calcd for $[\text{C}_{21}\text{H}_{14}\text{N}_4\text{O} + \text{H}]^+$ 339.4.

20 **Example A31. (E)-3-((1H-indazol-5-yl)methylene)-5-bromoindolin-2-one**



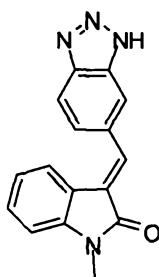
The title compound was synthesized according to the method described for Example A11B except substituting 5-bromooxindole (40 mg, 0.189 mmol) and 1H-indazole-5-carbaldehyde (30 mg, 0.208 mmol) to obtain the title compound (6.8 mg, 4.0 %) as a yellow solid. ¹H NMR (400 MHz, CD₃OD) δ 8.19 (s, 1H), 8.17 (s, 1H), 7.95 (s, 1H), 7.77 (s, 1H), 7.76-7.68 (m, 2H), 7.38 (d, J = 8.59 Hz, 1H), 6.87 (d, J = 8.59 Hz, 1H); MS ESI 340.1 [M + H]⁺, calcd for [C₁₆H₁₀BrN₃O + H]⁺ 340.01.

Example A32. (Z)-3-((1H-indazol-6-yl)methylene)-5-fluoroindolin-2-one



The title compound was isolated through resolution of mixed fractions of (E) and (Z) isomers from Example A16 by preparatory-HPLC to obtain 6.1 mg (8.0 %) of a yellow solid. ¹H NMR (400 MHz, CD₃OD) δ 8.94 (s, 1H), 8.07 (s, 1H), 7.94-7.85 (m, 2H), 7.80 (d, J = 8.59 Hz, 1H), 7.49 (d, J = 8.84 Hz, 1H), 6.97 (t, J = 9.20 Hz, 1H), 6.87-6.81 (m, 1H); MS ESI 280.0 [M + H]⁺, calcd for [C₁₆H₁₀FN₃O + H]⁺ 280.09.

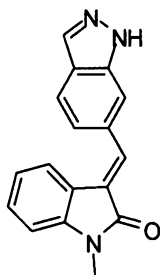
Example A33. (E)-3-((1H-benzo[d][1,2,3]triazol-5-yl)methylene)-1-methylindolin-2-one



The title compound was synthesized according to the method described for Example A11B, except substituting 1-methylindolin-2-one (18 mg, 0.124 mmol) and 1H-benzo[d][1,2,3]triazole-6-carbaldehyde (20 mg, 0.136 mmol) and then purified by preparatory HPLC to obtain 3.4 mg, 10 % of a yellow solid. ¹H NMR (400 MHz, CD₃OD) δ 8.23 (bs, 1H), 8.00 (bs, 1H), 7.95 (s, 1H), 7.84-7.75 (m, 1H), 7.59 (d, J =

7.58 Hz, 1H), 7.34 (t, J = 8.00 Hz, 1H), 7.04 (d, J = 7.83 Hz, 1H), 6.92 (d, J = 7.58 Hz, 1H), 3.35 (s, 3H); MS ESI 277.0 [M + H]⁺, calcd for [C₁₆H₁₂N₄O + H]⁺ 277.11.

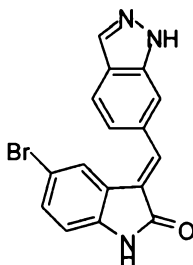
Example A34. (E)-3-((1H-indazol-6-yl)methylene)-1-methylindolin-2-one



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The desired product was synthesized according to the method described for Example A11B, except substituting 1-methylindolin-2-one (37 mg, 0.249 mmol) and 1H-indazole-6-carbaldehyde (40 mg, 0.274 mmol) and then purified by preparatory HPLC to obtain the title compound (12 mg, 17 %) as a yellow solid. ¹H NMR (400 MHz, CD₃OD) δ 8.13 (s, 1H), 7.96-7.86 (m, 3H), 7.67 (d, J = 7.83 Hz, 1H), 7.46 (d, J = 8.08 Hz, 1H), 7.33 (t, J = 7.71 Hz, 1H), 7.02 (d, J = 7.83 Hz, 1H), 6.93 (t, J = 7.71 Hz, 1H), 3.31 (s, 3H); MS ESI 276.1 [M + H]⁺, calcd for [C₁₇H₁₃N₃O + H]⁺ 276.11.

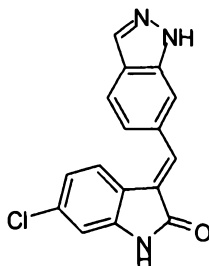
15 Example A35. (E)-3-((1H-indazol-6-yl)methylene)-5-bromoindolin-2-one



The title compound was synthesized according to the method described for Example A11B except substituting 5-bromooxindole (40 mg, 0.189 mmol) and 1H-indazole-6-carbaldehyde (30 mg, 0.208 mmol) to obtain 1.0 mg (1.6 %) of a yellow solid. ¹H NMR (400 MHz, CD₃OD) δ 8.16 (s, 1H), 7.98-7.92 (m, 2H), 7.87 (s, 1H), 7.73 (s, 1H), 7.44 (d, J = 8.34 Hz, 1H), 7.39 (d, J = 8.59 Hz, 1H), 6.87 (d, J = 8.34 Hz, 1H); MS ESI 340.1 [M + H]⁺, calcd for [C₁₆H₁₀BrN₃O + H]⁺ 340.01.

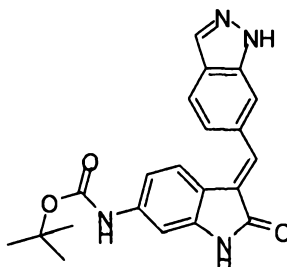
20

Example A36. (E)-3-((1H-indazol-6-yl)methylene)-6-chloroindolin-2-one



The title compound was synthesized according to the method described for Example A11B except substituting 6-chloroindolin-2-one (30 mg, 0.179 mmol) and 1H-indazole-6-carbaldehyde (29 mg, 0.197 mmol) to obtain 22 mg (42 %) of a yellow solid. ¹H NMR (400 MHz, d₆-DMSO) δ 13.30 (s, 1H), 10.79 (s, 1H), 8.16 (s, 1H), 7.90-7.87 (m, 2H), 7.83 (s, 1H), 7.56 (d, J = 8.00 Hz, 1H), 7.41 (d, J = 8.80 Hz, 1H), 6.93-6.88 (m, 2H); MS ESI 296.0 [M + H]⁺, calcd for [C₁₆H₁₀ClN₃O + H]⁺ 296.06.

10 Example A37. (E)-tert-butyl 3-((1H-indazol-6-yl)methylene)-2-oxoindolin-6-ylcarbamate



A. tert-butyl 2-oxoindolin-6-ylcarbamate

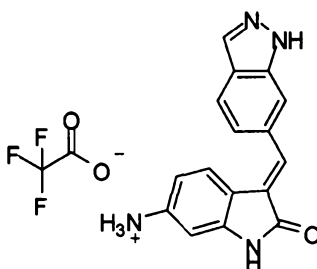
A THF (2.5 mL) solution of 6-aminoindolin-2-one (100 mg, 0.675 mmol) and di-tert-butyl dicarbonate (155 mg, 0.709 mmol) at rt under N₂, was treated with Et₃N (0.28 mL, 2.03 mmol). The solvent was removed *in vacuo* and the residue purified by column chromatography (silica gel, CH₂Cl₂/MeOH, 98:2 to 95:5) to give 76 mg, 45% of a tan solid. ¹H NMR (400 MHz, CDCl₃) δ 7.21 (s, 1H), 7.10 (d, J = 8.08 Hz, 1H), 6.88 (d, J = 7.58 Hz, 1H), 3.45 (s, 2H), 1.51 (s, 9H); MS ESI 249.0 [M + H]⁺, calcd for [C₁₃H₁₆N₂O₃ + H]⁺ 249.12.

B. (E)-tert-butyl 3-((1H-indazol-6-yl)methylene)-2-oxoindolin-6-ylcarbamate

The synthetic method followed that described in Example A11B, with a modified purification procedure. The MeOH was removed *in vacuo* and the residue was

treated with 95:5 CH₂Cl₂/MeOH. The resulting precipitate was filtered and washed with 95:5 CH₂Cl₂/MeOH to obtain the title compound as a yellow-brown solid (40 mg, 35 %). ¹H NMR (400 MHz, CD₃OD) δ 8.11 (s, 1H), 7.89-7.83 (m, 2H), 7.71 (s, 1H), 7.52 (d, J = 8.40 Hz, 1H), 7.44 (d, J = 9.60 Hz, 1H), 7.29 (s, 1H), 6.73 (d, J = 8.40 Hz, 1H), 1.51 (s, 9H); MS ESI 377.2 [M + H]⁺, calcd for [C₂₁H₂₀N₄O₃ + H]⁺ 377.16.

Example A38. (E)-3-((1H-indazol-6-yl)methylene)-2-oxoindolin-6-aminium 2,2,2-trifluoroacetate

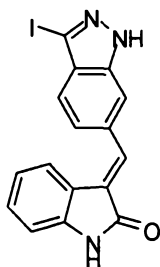


10

The title compound was synthesized according to the method described for Example A15 except substituting (E)-tert-butyl 3-((1H-indazol-6-yl)methylene)-2-oxoindolin-6-ylcarbamate (31 mg, 0.0823 mmol) to obtain 14 mg (44 %) of a brown solid. ¹H NMR (400 MHz, CD₃OD) δ 8.09 (s, 1H), 7.85 (d, J = 8.59 Hz, 1H), 7.82 (s, 1H), 7.55 (s, 1H), 7.49-7.37 (m, 2H), 6.34 (d, J = 1.77 Hz, 1H), 6.23 (dd, J = 8.46, 1.89 Hz, 1H); MS ESI 277.0 [M + H]⁺, calcd for [C₁₆H₁₂N₄O + H]⁺ 277.11.

15

Example A39. (E)-3-((3-iodo-1H-indazol-6-yl)methylene)indolin-2-one

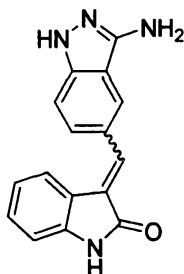


20

The title compound was synthesized from 3-iodo-1H-indazole-6-carbaldehyde (15 mg, 0.0551 mmol) and oxindole (8 mg, 0.0616 mmol) according to the method described for Example A11B and purified by column chromatography (silica gel, CH₂Cl₂/MeOH, 98:2 to 96:4) to obtain 6.9 mg, 33 % of a yellow solid.

^1H NMR (400 MHz, CD_3OD) δ 7.89-7.82 (m, 2H), 7.63-7.49 (m, 3H), 7.23 (t, J = 8.21 Hz, 1H), 6.91 (d, J = 7.07 Hz, 1H), 6.89-6.83 (m, 1H); MS ESI 388.0 $[\text{M} + \text{H}]^+$, calcd for $[\text{C}_{16}\text{H}_{10}\text{N}_3\text{O} + \text{H}]^+$ 387.99.

5 Example A40: (E & Z)-3-((3-amino-1H-indazol-5-yl)methylene)indolin-2-one



A. 5-(1,3-dioxolan-2-yl)-2-fluorobenzonitrile

To a solution of 2-fluoro-5-formylbenzonitrile (450 mg, 3 mmol) in toluene (10 mL) was added ethylene glycol (2 mL) and p-toluene sulfonic acid (25 mg). The solution was heated to 70 °C overnight. The solution was cooled to room temperature. Ethyl acetate (100 mL) was added and the solution was washed with sat. sodium bicarbonated (10 mL), water (10 mL) and brine (10 mL), dried over MgSO_4 and concentrated to a clear oil (567 mg, 98%). ^1H NMR (400 MHz, CDCl_3) δ 7.78 (dd 1H, J = 6.3, 2.3 Hz), 7.74-7.70 (m, 1H), 7.27-7.24 (m, 1H), 5.80 (s, 1H), 4.14-4.08 (m, 4H).

B. 5-(1,3-dioxolan-2-yl)-1H-indazol-3-amine

To a solution of 5-(1,3-dioxolan-2-yl)-2-fluorobenzonitrile (567 mg, 3 mmol) in n-butanol (5 mL) was added hydrazine hydrate (1.47 mL, 30 mmol). The solution was heated to 110 °C for 2 h and cooled to room temperature. The solution was stirred overnight and the resulting precipitate was collected to give the title compound as a white solid (220 mg, 36%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.44 (s, 1H), 7.78 (s, 1H), 7.28-7.26 (m, 1H), 7.21-7.19 (m, 1H), 5.72 (s, 1H), 5.37 (bs), 4.08-4.02 (m, 2H), 3.98-3.92 (m, 2H); MS ESI 206.0 $[\text{M} + \text{H}]^+$, calcd for $[\text{C}_{10}\text{H}_{11}\text{N}_3\text{O}_2 + \text{H}]^+$ 206.1.

C. 3-amino-1H-indazole-5-carbaldehyde

To a solution of 5-(1,3-dioxolan-2-yl)-1H-indazol-3-amine (75 mg, 0.36 mmol) in THF (5 mL) and H_2O (0.5 mL) was added p-toluene sulfonic acid (25 mg) and the

reaction was stirred overnight at room temperature. Ethyl acetate (75 mL) was added and the solution was washed with sat. sodium bicarbonate (5 mL), brine (2 x 5 mL), dried over MgSO₄ and concentrated to give the title compound as an orange solid (52 mg, 89%). ¹H NMR (400 MHz, CD₃OD) δ 9.68 (s, 1H), 8.94 (s, 1H), 8.18 (d, 1H, J = 7.6 Hz), 7.68 (d, 1H, J = 8.4 Hz).

D. tert-butyl 5-formyl-1H-indazol-3-ylcarbamate

To a solution of 3-amino-1H-indazole-5-carbaldehyde (50 mg, 0.31 mmol) in DMF (3 mL) was added di-tert-butyl dicarbonate (135 mg, 0.62 mmol) and triethylamine (0.17 mL, 1.2 mmol). The mixture was stirred overnight and concentrated. The residue was dissolved into ethyl acetate (50 mL), washed with H₂O and dried over MgSO₄. The title compound was purified by silica gel chromatography (EtOAc/Hex 1:1) as a red solid (25 mg, 30%). ¹H NMR (400 MHz, CD₃OD) δ 10.07 (s, 1H), 8.26-8.02 (m, 3H), 1.73-1.71 (m, 9H).

E. (E)-tert-butyl 5-((2-oxoindolin-3-ylidene)methyl)-1H-indazol-3-ylcarbamate

To a solution of oxindole (13 mg, 0.01 mmol) and tert-butyl 5-formyl-1H-indazol-3-ylcarbamate (25 mg, 0.01 mmol) in ethanol (1 mL) was added piperidine (1 drop). The mixture was heated to 80 °C for 2 h and cooled to rt. The solution was loaded onto a silica gel column and the title compound was eluted with EtOAc/Hex 4:1 as a red solid (14 mg, 37%). ¹H NMR (400 MHz, CD₃OD) δ 8.14-8.02 (m, 2H), 7.90-7.83 (m, 2H), 7.63 (s, 1H), 7.24 (bs, 1H), 7.00-6.91 (m, 2H), 1.71 (s, 9H).

F. (E and Z)-3-((3-amino-1H-indazol-5-yl)methylene)indolin-2-one

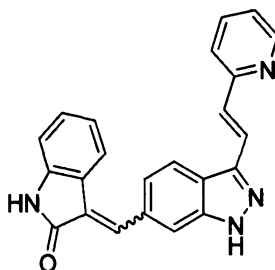
To a solution of (E)-tert-butyl 5-((2-oxoindolin-3-ylidene)methyl)-1H-indazol-3-ylcarbamate (14 mg, 0.04 mmol) in CH₂Cl₂ (1 mL) was added TFA (0.25 mL) and the reaction was stirred for 3 h. The solution was concentrated to dryness and purified by preparatory HPLC to give the title compound as a 3:2 mixture of E/Z isomers. ESI 277.0 [M + H]⁺, calcd for [C₁₆H₁₂N₄O + H]⁺ 277.1.

E-isomer: Short Retention Time by reverse phase HPLC; ¹H NMR (400 MHz, CD₃OD) δ 8.93 (s, 1H), 8.50 (d, 1H, J = 8.6 Hz), 7.82 (s, 1H), 7.64 (d, 1H, J = 7.7 Hz), 7.41 (d, 1H, J = 8.6 Hz), 7.26-7.21 (m 1H), 6.94-6.88 (m, 2H).

Z-isomer: Long Retention Time by reverse phase HPLC; ^1H NMR (400 MHz, CD_3OD) δ 8.22 (s, 1H), 7.87 (d, 1H, $J = 8.9$ Hz), 7.82 (s, 1H), 7.70 (d, 1H, $J = 7.0$ Hz), 7.50 (d, 1H, $J = 8.8$ Hz), 7.26-7.21 (m 1H), 7.05 (t, 1H, $J = 7.6$ Hz) 6.94-6.88 (m, 1H).

5

Example A41: (E and Z)-3-((3-((E)-2-(pyridin-2-yl)vinyl)-1H-indazol-6-yl)methylene)indolin-2-one



A. 3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-6-carbaldehyde

10 An oven-dried round bottom flask under Ar was charged with 3-iodo-1H-indazole-6-carbaldehyde (50 mg, 0.184 mmol), THF (1.5 mL) and CH_2Cl_2 (1.0 mL). Methanesulfonic acid (1.4 μL , 0.0221 mmol) was added and the solution cooled with an ice-water bath. A solution of 3,4-dihydro-2H-pyran (41 μL , 0.460 mmol) in CH_2Cl_2 (0.5 mL) was then added dropwise over 15 minutes and the reaction stirred
15 overnight. The solvents were removed *in vacuo* and the residue purified by column chromatography (silica gel, 99:1 to 98:2 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to give the title compound as a white powder (16 mg, 25 %). ^1H NMR (400 MHz, CDCl_3) δ 10.18 (s, 1H), 8.13 (s, 1H), 7.77 (d, $J = 8.4$ Hz, 1H), 7.62 (d, $J = 8.4$ Hz, 1H), 5.84-5.77 (m, 1H), 4.07-4.02 (m, 1H), 3.83-3.75 (m, 1H), 2.62-2.51 (m, 1H), 2.20-2.10 (m, 2H), 1.86-1.70
20 (m, 3H); MS ESI 378.9 $[\text{M} + \text{Na}]^+$, calcd for $[\text{C}_{13}\text{H}_{13}\text{IN}_2\text{O}_2 + \text{Na}]^+$ 378.99.

B. Synthesis of (E)-3-(2-(pyridin-2-yl)vinyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-6-carbaldehyde

In a scintillation vial a solution of 3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-6-carbaldehyde (24 mg, 0.0673 mmol), 2-vinylpyridine (9.4 μL , 0.0875
25 mmol), DIPEA (24 μL , 0.135 mmol) and DMF (1.0 mL) was purged with Ar for 20 min. $\text{Pd}(\text{OAc})_2$ (1.5 mg, 0.0067 mmol) and $\text{P}(o\text{-tolyl})_3$ (6.1 mg, 0.0202 mmol) were then added and the vial was capped and heated to 100°C overnight. The solution was cooled to room temperature and extracted with EtOAc, washing with NH_4Cl

(sat.), H₂O, and brine. The organic layer was dried over MgSO₄, the solvent removed *in vacuo*, and the residue purified by column chromatography (silica gel, 96:4 CH₂Cl₂/MeOH) to give 17 mg, 77% of a yellow oil which was 70 % pure by NMR. This crude material was used for the subsequent synthetic step. ¹H NMR (400 MHz, CD₃OD) δ 10.16 (s, 1H), 8.59 (s, 1H), 8.34 (s, 1H), 8.27 (d, *J* = 8.4 Hz, 1H), 7.95-7.83 (m, 4H), 7.75 (m, 1H), 7.68 (d, *J* = 16.0 Hz, 1H), 6.00 (d, *J* = 9.6 Hz, 1H), 4.05-4.01 (m, 1H), 3.93-3.86 (m, 1H), 2.65-2.56 (m, 1H), 2.27-2.10 (m, 2H), 1.92-1.66 (m, 3H); MS ESI 334.1 [M + H]⁺, calcd for [C₂₀H₁₉N₃O₂ + H]⁺ 334.16.

C. (E)-3-((3-((E)-2-(pyridin-2-yl)vinyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)methylene)indolin-2-one

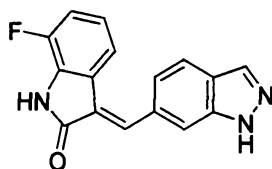
To a solution of (E)-3-(2-(pyridin-2-yl)vinyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-6-carbaldehyde (25 mg, 0.0749 mmol), oxindole (10 mg, 0.0749 mmol), and MeOH (1 mL) was added piperidine (1 uL) and the reaction heated to 60 °C for 3 hours. The reaction was cooled to room temperature and the product yellow solid was precipitated with MeOH (1 mL) and then filtered to give 11mg. The filtrate was purified by column chromatography (silica gel, 99:1 to 98:2 CH₂Cl₂/MeOH) to give an additional 6 mg of product (17 mg total, 50 %). ¹H NMR (400 MHz, CDCl₃) δ 8.69-8.62 (m, 1H), 8.14 (d, *J* = 8.3 Hz, 1H), 8.00-7.91 (m, 3H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.72 (t, *J* = 8.3 Hz, 1H), 7.63 (d, *J* = 16.9 Hz, 1H), 7.53 (m, 2H), 7.44 (b.s., 1H), 7.25-7.17 (m, 2H), 6.92-6.86 (m, 2H), 5.77 (d, *J* = 10.6 Hz, 1H), 4.09 (d, *J* = 9.6 Hz, 1H), 3.84-3.74 (m, 1H), 2.67-2.53 (m, 1H), 2.24-2.13 (m, 2H), 1.85-1.66 (m, 3H); MS ESI 449.2 [M + H]⁺, calcd for [C₂₈H₂₄N₄O₂ + H]⁺ 449.20.

D. (E and Z)-3-((3-((E)-2-(pyridin-2-yl)vinyl)-1H-indazol-6-yl)methylene)-indolin-2-one

To a solution of (E)-3-((3-((E)-2-(pyridin-2-yl)vinyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)methylene)indolin-2-one (17 mg, 0.0379 mmol) in MeOH (3 mL) was added *p*-TsOH.H₂O (30 mg). The reaction was heated to reflux for 5 hours at which time LC-MS indicated complete consumption of starting material. The MeOH was removed *in vacuo* and the product extracted into EtOAc washing with NaHCO₃ (sat.), H₂O, and brine. The organic layer was dried over MgSO₄ and the solvent removed to give an orange solid. The solid was titrated 2X

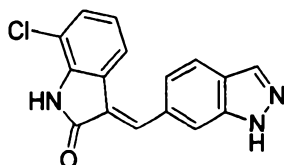
with 5:1 hexanes/Et₂O while decanting off the solvent to give the orange solid (10 mg, 71 %). The compound was a 3:1 mixture of (*E*)/(*Z*) isomers by analysis of the proton NMR. ¹H NMR (400 MHz, d₆-DMSO) δ 13.60, 13.50 (s, 1H), 10.71, 10.65 (s, 1H), 9.01, 7.92 (s, 1H), 8.61 (m, 1H), 8.33, 8.25 (d, *J* = 8.5 Hz, 1H), 8.08-7.53 (m, 7H), 7.34-7.17 (m, 2H), 6.93-6.82 (m, 2H); MS ESI 365.2 [M + H]⁺, calcd for [C₂₃H₁₆N₄O + H]⁺ 365.14.

Example A42. (*E*)-3-((1*H*-indazol-6-yl)methylene)-7-fluoroindolin-2-one



10 According to the method described in example A6, except substituting 7-fluorooxindole (15 mg, 0.1 mmol) the title compound was prepared as a brown solid (20 mg, 71%). ¹H NMR (400 MHz, CD₃OD) δ 8.14 (s, 1H), 7.69 (s, 1H), 7.25 (d, 1H, *J* = 8 Hz), 7.90 (s, 1H), 7.48 (dd, 2H, *J* = 8 Hz, 4 Hz), 7.08 (t, 1H, *J* = 8 Hz), 6.89-6.84 (m, 1H); MS ESI [M + H]⁺, calcd for [C₁₆H₁₀FN₃O + H]⁺ 280.09; found *m/z* 280.1.

Example A43. (*E*)-3-((1*H*-indazol-6-yl)methylene)-7-chloroindolin-2-one

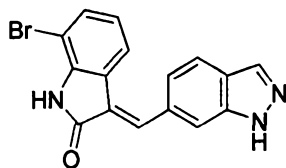


20 According to the method described in example A6, except substituting 7-chlorooxindole (17 mg, 0.1 mmol), the title compound was prepared as a dark yellow solid (29 mg, 97%). ¹H NMR (400 MHz, DMSO) δ 13.33 (s, 1H), 11.07 (s, 1H), 8.16 (s, 1H), 7.90 (m, 3H), 7.55 (d, 1H, *J* = 8 Hz), 7.42 (d, 1H, *J* = 8 Hz), 7.32 (d, 1H, *J* = 8 Hz), 6.88 (t, 1H, *J* = 8 Hz); MS ESI [M + H]⁺, calcd for [C₁₆H₁₀ClN₃O + H]⁺ 296.06; found *m/z* 296.1.

25

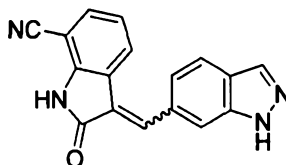
Example A44. (*E*)-3-((1*H*-indazol-6-yl)methylene)-7-bromoindolin-2-one

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According to the method described in example A6, except substituting 7-bromooxindole (21mg, 0.1 mmol), the title compound was prepared as a yellow solid (6.8 mg, 20%). ¹H NMR (400 MHz, CD₃OD) δ 8.15 (s, 1H), 7.96 (s, 1H), 7.93 (d, 1H, *J* = 8Hz), 7.89 (s, 1H), 7.62 (d, 1H, *J* = 8 Hz), 7.46 (d, 1H, *J* = 8 Hz), 7.41 (d, 1H, *J* = 8 Hz), 6.81 (t, 1H, *J* = 8 Hz); MS ESI [M + H]⁺, calcd for [C₁₆H₁₀BrN₃O + H]⁺ 340.01; found *m/z* 340.0.

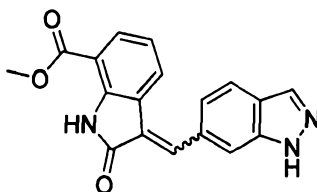
10 Example A45. (E and Z)-3-((1H-indazol-6-yl)methylene)-2-oxoindoline-7-carbonitrile



According to the method described in example A6, except substituting 7-cyanooxindole (32 mg, 0.2 mmol), the title compound was prepared as a mixture of isomers (*Z:E* = 41:59) and red solid (40 mg, 70%). *Z* isomer: ¹H NMR (400 MHz, DMSO) δ 8.95 (s, 1H), 8.17 (m, 1H), 8.14 (m, 1H), 8.08 (d, 1H, *J* = 7.6 Hz), 7.99 (d, 1H, *J* = 7.6 Hz), 7.85-7.83 (m, 1H), 7.62-7.58 (m, 1H), 7.16 (t, 1H, *J* = 7.6 Hz). *E* isomer: ¹H NMR (400 MHz, DMSO) δ 8.17 (m, 1H), 7.94-7.90 (m, 3H), 7.85-7.83 (m, 1H), 7.62-7.58 (m, 1H), 7.43 (d, 1H, *J* = 8 Hz), 6.99 (t, 1H, *J* = 8 Hz); MS ESI [M + H]⁺, calcd for [C₁₇H₁₀N₄O + H]⁺ 287.09; found *m/z* 287.1.

20

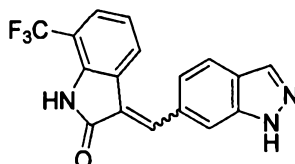
Example A46. (E and Z)-methyl 3-((1H-indazol-6-yl)methylene)-2-oxoindoline-7-carboxylate



According to the method described in example A6, except substituting methyl
oxindole-7-carboxylate (23 mg, 0.12 mmol), the title compound was prepared as a
mixture of isomers (*Z*:*E* = 62:38) and yellow solid (36 mg, 91%). *Z* isomer: ¹H
NMR (400 MHz, DMSO) δ 13.45 (s, 1H), 10.47 (s, 1H), 8.95 (s, 1H), 8.14 (m, 2H),
5 8.14 (d, 1H, *J* = 7.6 Hz), 8.06 (d, 1H, *J* = 7.6 Hz), 7.84 (d, 1H, *J* = 8.8 Hz), 7.76 (d,
1H, *J* = 8 Hz), 7.15 (t, 1H, *J* = 8 Hz), 3.89 (s, 3H). *E* isomer: ¹H NMR (400 MHz,
CD₃OD) δ 8.20 (s, 1H), 8.16 (s, 1H), 8.00-7.95 (m, 2H), 7.92-7.89 (m, 2H), 7.50 (d,
1H, *J* = 8.8 Hz), 7.01 (t, 1H, *J* = 8 Hz), 3.99 (s, 3H); MS ESI [*M* + *H*]⁺, calcd for
[C₁₈H₁₃N₃O₃ + *H*]⁺ 320.10; found *m/z* 320.1.

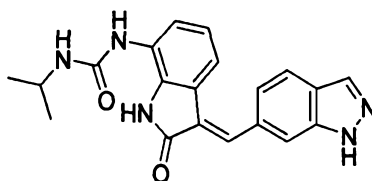
10

Example A47. (E and Z)-3-((1H-indazol-6-yl)methylene)-7-
(trifluoromethyl)indolin-2-one



According to the method described in example A6, except substituting 7-
15 (trifluoromethyl)indolin-2-one (40 mg, 0.2 mmol), the title compound was prepared
as a mixture of isomers (*Z*:*E* = 1:5) and yellow solid (4.6 mg, 7%). *Z* isomer: ¹H
NMR (400 MHz, CD₃OD) δ 9.00 (s, 1H), 8.10 (s, 1H), 7.93 (d, 1H, *J* = 8 Hz), 7.89
(s, 1H), 7.85 (d, 1H, *J* = 8 Hz), 7.50-7.45 (m, 2H), 7.19 (t, 1H, *J* = 8 Hz). *E* isomer:
¹H NMR (400 MHz, CD₃OD) δ 8.15 (s, 1H), 8.02 (s, 1H), 7.93 (d, 1H, *J* = 8 Hz),
20 7.89 (s, 1H), 7.85 (d, 1H, *J* = 8 Hz), 7.50-7.45 (m, 2H), 7.00 (t, 1H, *J* = 8 Hz); MS
ESI [*M* + *H*]⁺, calcd for [C₁₇H₁₀F₃N₃O + *H*]⁺ 330.08; found *m/z* 330.1.

Example A48. (E)-1-(3-((1H-indazol-6-yl)methylene)-2-oxoindolin-7-yl)-3-
isopropyl-urea



25

A. 1-isopropyl-3-(2-oxoindolin-7-yl)urea

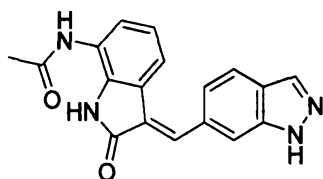
To a suspension of 7-aminoindolin-2-one (60 mg, 0.41 mmol) in THF (3 mL) was added DIPEA (0.28 mL, 1.62 mmol), and 2-isocyanatopropane (0.05 mL, 0.49 mmol). The mixture was stirred at rt overnight then filtered. The filter cake was washed with diethyl ether to give the title compound as a pale solid (57.3 mg, 61%).

5 ^1H NMR (400 MHz, CD_3OD) δ 7.09-7.04 (m, 2H), 6.99-6.95 (m, 1H), 3.57 (s, 2H), 2.64 (m, 1H), 1.20 (d, 6H, $J = 6.4\text{Hz}$). MS ESI $[\text{M} + \text{H}]^+$, calcd for $[\text{C}_{12}\text{H}_{15}\text{N}_3\text{O}_2 + \text{H}]^+$ 234.12; found m/z 234.0.

B. *(E)-1-(3-((1H-indazol-6-yl)methylene)-2-oxoindolin-7-yl)-3-isopropyl-urea*

10 According to the method described in example A6, except substituting 1-isopropyl-3-(2-oxoindolin-7-yl)urea (57 mg, 0.24 mmol), the title compound was prepared as a yellow solid (61.4 mg, 70%). ^1H NMR (400 MHz, DMSO) δ 13.29 (s, 1H), 10.16 (s, 1H), 8.15 (s, 1H), 8.00 (s, 1H), 7.89 (s, 2H), 7.78 (s, 1H), 7.41 (d, 1H, $J = 8\text{Hz}$), 7.35 (d, 1H, $J = 8\text{Hz}$), 7.28 (d, 1H, $J = 8\text{Hz}$), 6.77 (t, 1H, $J = 8\text{Hz}$), 6.09 (d, 1H, $J = 7.6\text{Hz}$), 3.77 (m, 1H), 1.12 (s, 3H), 1.10 (s, 3H); MS ESI $[\text{M} + \text{H}]^+$, calcd for $[\text{C}_{20}\text{H}_{19}\text{N}_5\text{O}_2 + \text{H}]^+$ 362.16; found m/z 362.2.

Example A49. *(E)-N-(3-((1H-indazol-6-yl)methylene)-2-oxoindolin-7-yl)acetamide*



20 A. *N-(2-oxoindolin-7-yl)acetamide*

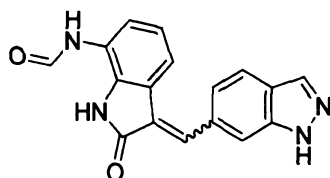
According to the method described in example A48a, 7-aminoindolin-2-one (80 mg, 0.54) was reacted with acetic anhydride (66 mg, 0.65 mmol) to give the title compound as a white solid (82 mg, 80%). ^1H NMR (400 MHz, CD_3OD) δ 7.13 (d, 2H, $J = 8\text{Hz}$), 6.99 (t, 1H, $J = 8\text{Hz}$), 3.57 (s, 2H), 2.16 (s, 3H). MS ESI $[\text{M} + \text{H}]^+$, calcd for $[\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_2 + \text{H}]^+$ 191.08; found m/z 191.0.

B. *(E)-N-(3-((1H-indazol-6-yl)methylene)-2-oxoindolin-7-yl)acetamide*

According to the method described in example A6, except substituting N-(2-oxoindolin-7-yl)acetamide (18 mg, 0.095 mmol), the title compound was prepared as a yellow solid (6.8 mg, 20%). ^1H NMR (400 MHz, CD_3OD) δ 8.16 (s, 1H), 7.94

(m, 3H), 7.54 (d, 1H, $J = 8\text{Hz}$), 7.48 (d, 1H, $J = 8\text{Hz}$), 7.26 (d, 1H, $J = 8\text{Hz}$), 6.89(t, 1H, $J = 8\text{Hz}$), 2.19 (s, 3H). MS ESI $[M + H]^+$, calcd for $[C_{18}H_{14}N_4O_2 + H]^+$ 319.12; found m/z 391.1.

5 Example A50. (E and Z)-N-(3-((1H-indazol-6-yl)methylene)-2-oxoindolin-7-yl)formamide



A) *N*-(2-oxoindolin-7-yl)formamide

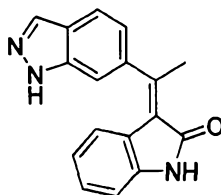
To a suspension of 7-aminoindole (32 mg, 0.22 mmol) in CH_2Cl_2 (1 mL) was
 10 added EDC (83 mg, 0.43 mmol) and formic acid (12 mg, 0.26 mmol). The reaction mixture was stirred at rt for 2 h and then filtered. The filter cake was washed with diethyl ether to give the title compound as a grey solid (27 mg, 71%). 1H NMR (400 MHz, CD_3OD) δ 8.23 (s, 1H), 7.20 (d, 1H, $J = 8\text{ Hz}$), 7.15 (d, 1H, $J = 8\text{ Hz}$), 7.02 (t, 1H, $J = 8\text{ Hz}$), 3.59 (s, 2H); MS ESI $[M + H]^+$, calcd for $[C_9H_8N_2O_2 + H]^+$ 177.07;
 15 found m/z 177.0.

B. *N*-(3-((1H-indazol-6-yl)methylene)-2-oxoindolin-7-yl)formamide

According to the method described in example A1, except substituting *N*-(2-oxoindolin-7-yl)formamide (20 mg, 0.11 mmol), the title compound was prepared as a mixture of isomers ($Z:E = 35:65$) and dark brown solid (12 mg, 35%). *Z* isomer:
 20 1H NMR (400 MHz, DMSO) δ 9.88 (s, 1H), 8.98 (s, 1H), 8.61 (m, 1H), 8.12 (s, 1H), 8.02 (s, 1H), 7.97 (d, 1H, $J = 8\text{ Hz}$), 7.82 (s, 1H), 7.61 (d, 1H, $J = 7.2\text{ Hz}$), 7.25 (m, 1H), 7.01 (t, 1H, $J = 8\text{ Hz}$). *E* isomer: 1H NMR (400 MHz, DMSO) δ 9.88 (s, 1H), 8.26 (s, 1H), 8.12 (s, 1H), 7.90 (m, 2H), 7.82 (s, 1H), 7.53 (m, 1H), 7.42 (m, 2H), 6.84 (t, 1H, $J = 8\text{ Hz}$); MS ESI $[M + H]^+$, calcd for $[C_{17}H_{12}N_4O_2 + H]^+$ 305.10;
 25 found m/z 305.1.

Example A51: (E)-3-(1-(1H-indazol-6-yl)ethylidene)indolin-2-one

- 127 -



A. 1-(1H-indazol-6-yl)ethanol

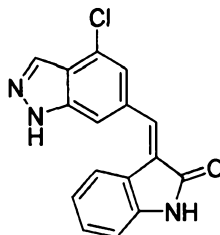
To a solution of 1H-indazole-6-carbaldehyde (200 mg, 1.37 mmol) in THF (7 mL) at -78°C was added methyl magnesium bromide (1.4 mL, 4.11 mmol) dropwise under argon. The solution was warmed to rt and quenched with saturated ammonium chloride (2 mL). The mixture was extracted into ethyl acetate (3 x 10 mL), dried over MgSO₄ and concentrated. The yellow oil was purified by silica gel chromatography (EtOAc/Hex 4:1) to yield the title compound as a clear oil (135 mg, 60%). ¹H NMR (400 MHz, CDCl₃) δ 8.07 (s, 1H), 7.76 (s, 1H), 7.50-7.47 (m, 2H), 5.05 (q, 1H, J = 7.4 Hz), 1.57 (d, 3H, J = 7.2 Hz); MS ESI [M + H]⁺, calcd for [C₉H₁₀N₂O + H]⁺ 163.1; found *m/z* 163.0.

B. 1-(1H-indazol-6-yl)ethanone

To a solution of 1-(1H-indazol-6-yl)ethanol (100 mg, 0.6 mmol) in acetone (50 mL) was added PDC (1.11 g, 3 mmol). The mixture was stirred overnight at rt. The mixture was filtered through silica gel and purified by silica gel chromatography (4:1 EtOAc/Hex) to give the title compound as a brown solid (70 mg, 72%). ¹H NMR (400 MHz, CDCl₃) δ 8.45 (s, 1H), 8.23 (s, 1H), 8.09-8.08 (m, 1H), 7.56-7.54 (m, 1H), 2.72 (s, 3H).

C. (E)-3-(1-(1H-indazol-6-yl)ethylidene)indolin-2-one

A solution of oxindole (16 mg, 0.12 mmol), pyrrolidine (10 μL, 0.12 mmol) and 1-(1H-indazol-6-yl)ethanone (20 mg, 0.12 mmol) in toluene was refluxed in a Dean-Stark trap for 2 h. The solution was then stirred at 50 °C for 72 h. Two equivalents of pyrrolidine were added and the solution was heated to reflux for 48 h. The solution was concentrated and the red residue was purified by preparatory HPLC to give the title compound as an orange solid (5 mg, 16%). ¹H NMR (400 MHz, CDCl₃) δ 8.13 (s, 1H), 7.78 (s, 1H), 7.70 (d, 1H, J = 8.5 Hz), 7.34 (d, 1H, J = 8.5 Hz), 7.03 (t, 1H, J = 7.6 Hz), 6.81 (d, 1H, J = 7.7 Hz), 6.50 (t, 1H, J = 7.6 Hz), 6.05 (d, 1H, J = 7.7 Hz), 2.82 (s, 3H); MS ESI [M + H]⁺, calcd for [C₁₇H₁₃N₃O + H]⁺ 276.1; found *m/z* 276.0.

Example A52: (E)-3-((4-chloro-1H-indazol-6-yl)methylene)indolin-2-one*A. (4-chloro-1H-indazol-6-yl)methanol*

5 A solution of 4-chloro-1H-indazole-6-carboxylic acid (100 mg, 0.5 mmol) in THF (1 mL) was cooled to 0°C under argon. Borane (1.4 mL, 1.4 mmol) was added dropwise and the solution was stirred overnight at rt. The reaction was quenched with ice cold sat. sodium bicarbonate, extracted with ethyl acetate (3 x 10 mL), dried over MgSO₄ and concentrated to give the title compound as a white solid (60 mg, 66%). MS ESI [M + H]⁺, calcd for [C₈H₇ClN₂O + H]⁺ 183.0; found *m/z* 183.0.

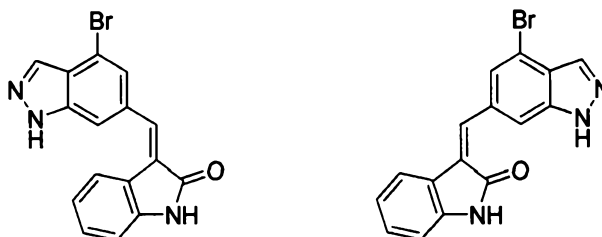
B. 4-chloro-1H-indazole-6-carbaldehyde

To a solution of (4-chloro-1H-indazol-6-yl)methanol (30 mg, 0.18 mmol) in acetone (5 mL) was added PDC (100 mg, 0.27 mmol). The mixture was stirred overnight at rt. The mixture was filtered through celite, the filter cake was washed with ethyl acetate. The solution was washed with water (2 x 10 mL), brine (10 mL), dried over MgSO₄ and concentrated to a brown solid (30 mg, 100%). ¹H NMR (400 MHz, CD₃OD) δ 10.1 (s, 1H), 8.21 (s, 1H), 8.08 (s, 1H), 7.62 (s, 1H).

C. (E)-3-((4-chloro-1H-indazol-6-yl)methylene)indolin-2-one

The compound was synthesized according to the method described for
20 Example A1. Oxindole (8 mg, 0.06 mmol) was reacted with 4-chloro-1H-indazole-6-carbaldehyde (11 mg, 0.06 mmol) to give the title compound as an orange solid (3 mg, 13%). ¹H NMR (400 MHz, CD₃OD) δ 8.21 (s, 1H), 7.87 (s, 1H), 7.82 (s, 1H), 7.59 (d, 1H, J = 7.8 Hz), 7.48 (s, 1H), 7.28 (t, 1H, J = 7.9 Hz), 6.95 (d, 1H, J = 7.7 Hz), 6.90 (t, 1H, J = 8.2 Hz); MS ESI [M + H]⁺, calcd for [C₁₆H₁₀ClN₃O + H]⁺
25 296.1; found *m/z* 296.1.

Example A53a: (E)-3-((4-bromo-1H-indazol-6-yl)methylene)indolin-2-one and
A53b: (Z)-3-((4-bromo-1H-indazol-6-yl)methylene)indolin-2-one



A. (4-bromo-1H-indazol-6-yl)methanol

According to the method of A52A, 4-bromo-1H-indazole-6-carboxylic acid (1 g, 4 mmol) was reacted with borane (6 ml, 6 mmol) to give the title compound as a pale yellow solid (800 mg, 88%). MS ESI $[M + H]^+$, calcd for $[C_8H_7BrN_2O + H]^+$ 227.0, 229.0; found m/z 226.9, 228.9.

B. 4-bromo-1H-indazole-6-carbaldehyde

According to the method of A52B, (4-bromo-1H-indazol-6-yl)methanol was oxidized with PDC to give the title compound as a beige solid (413 mg, 53%). MS ESI $[M + H]^+$, calcd for $[C_8H_5BrN_2O + H]^+$ 225.0, 227.0; found m/z 224.9, 226.9.

C. 3-((4-bromo-1H-indazol-6-yl)methylene)indolin-2-one

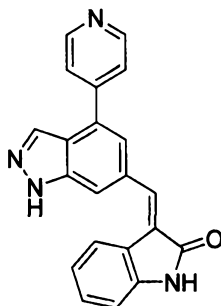
According to the method described for Example A1, oxindole (15 mg, 0.11 mmol) was reacted with 4-bromo-1H-indazole-6-carbaldehyde (25 mg, 0.11 mmol) to give the title compound as an orange solid. The E and Z stereoisomers were separated by HPLC.

(E-isomer 7 mg, 19%, HPLC retention time, 11 min). 1H NMR (400 MHz, CD_3OD) δ 8.11 (s, 1H), 7.87 (s, 1H), 7.80 (s, 1H), 7.63 (s, 1H), 7.56 (d, 1H, $J = 7.7$ Hz), 7.28 (t, 1H, $J = 7.8$ Hz), 6.93 (d, 1H, $J = 7.7$ Hz), 6.89 (t, 1H, $J = 7.7$ Hz); MS ESI $[M + H]^+$, calcd for $[C_{16}H_{10}BrN_3O + H]^+$ 339.0, 341.0; found m/z 340.0, 342.0.

(Z-isomer, 3 mg, 8%, HPLC retention time, 11.8 min) 1H NMR (400 MHz, $DMSO-d_6$) δ 13.75 (s, 1H), 10.72 (s, 1H), 8.85 (s, 1H), 8.41 (s, 1H), 8.07 (s, 1H), 7.96 (s, 1H), 7.73 (d, 1H, $J = 7.5$ Hz), 7.22 (t, 1H, $J = 7.5$ Hz), 7.02 (t, 1H, $J = 7.4$ Hz), 6.85 (d, 1H, $J = 7.8$ Hz); MS ESI $[M + H]^+$, calcd for $[C_{16}H_{10}BrN_3O + H]^+$ 339.0, 341.0; found m/z 340.0, 342.0.

Example A54a: (E)-3-((4-(pyridin-4-yl)-1H-indazol-6-yl)methylene)indolin-2-one
and A54b: (E)-3-((4-(pyridin-4-yl)-1H-indazol-6-yl)methylene)indolin-2-one

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A. 4-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde

To a solution of 4-bromo-1H-indazole-6-carbaldehyde (225 mg, 1 mmol) in CH_2Cl_2 (10 mL) and aqueous KOH (2 mL, 50% wt) at 0°C was added TBAB (3 mg, 0.01 mmol) and SEMCl (200 mg, 1.2 mmol). The mixture was stirred at 0°C for 4 h, warmed to rt and extracted with ethyl acetate (100 mL). The organic phase was washed with water (2 x 10 mL) and brine (10 mL), dried over MgSO_4 and concentrated. The residue was purified by silica gel chromatography (1:1 EtOAc/Hex) to give the title compound as a pale yellow solid (280 mg, 82%). ^1H NMR (400 MHz, CD_3OD) δ 10.02 (s, 1H), 8.21-8.19 (m, 2H), 7.80 (s, 1H), 5.78 (s, 2H), 3.70-3.65 (m, 2H), 0.95-0.92 (m, 2H), -0.05 (s, 9H).

B. 4-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde

To a solution of 4-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (50 mg, 0.14 mmol) and pyridine boronic acid (20 mg, 0.16 mmol) in 10:1 DMF/water (1 mL) was added K_2CO_3 (36 mg, 0.26 mmol) and tetrakis(triphenylphosphine) palladium (7.5 mg, 0.007 mmol). The mixture was heated to 120°C under microwave irradiation for 20 min. Ethyl acetate (20 mL) was added and the solution was washed with water (2 x 5 mL) and brine (5 mL), dried over MgSO_4 and concentrated. The residue was purified by silica gel chromatography (3:1 EtOAc/Hex) to give the title compound as a pale yellow solid (31 mg, 62%). MS ESI $[\text{M} + \text{H}]^+$, calcd for $[\text{C}_{19}\text{H}_{23}\text{N}_3\text{O}_2\text{Si} + \text{H}]^+$ 354.2; found m/z 354.2.

C. 3-((4-(pyridin-4-yl)-1H-indazol-6-yl)methylene)indolin-2-one

To a solution of oxindole (12 mg, 0.08 mmol) and 4-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (31 mg, 0.087 mmol) in ethanol (2 mL) was added pyrrolidine (20 μL). The mixture was heated to 70°C for

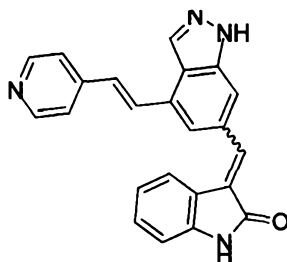
3 h. The solution was concentrated to dryness and treated with 4M HCl (1 mL) in ethanol (3 mL) at 70°C for 4 h. The solution was cooled to rt and extracted with ethyl acetate (50 mL), dried over MgSO₄ and concentrated to give the title compound as a mixture of E/Z isomers which were separated by preparatory HPLC.

5 (E-isomer 5.4 mg, 18%, HPLC retention time, 6.6 min). ¹H NMR (400 MHz, CD₃OD) δ 8.94-8.91(m, 2H), 8.44 (s, 1H), 8.39 (d, 2H, J = 6.4 Hz), 8.16 (s, 1H), 7.93 (s, 1H), 7.86 (s, 1H), 7.59 (d, 1H, J = 7.9 Hz), 7.26 (t, 1H, J = 7.8 Hz), 6.95 (d, 1H, 7.7 Hz), 6.86 (t, 1H, J = 7.8 Hz); MS ESI [M + H]⁺, calcd for [C₂₁H₁₄N₄O + H]⁺ 339.1; found *m/z* 339.1.

10 (Z-isomer, 3.3 mg, 12%, HPLC retention time, 7.2 min) ¹H NMR (400 MHz, CD₃OD) δ 8.92 (d, 2H, J = 5.6 Hz), 8.76 (s, 1H), 8.73 (s, 1H), 8.48 (d, 2H, J = 6.7 Hz), 8.43 (s, 1H), 7.99 (s, 1H), 7.71 (d, 1H, J = 7.8 Hz), 7.28 (t, 1H, J = 7.5 Hz), 7.08 (t, 1H, J = 7.9 Hz), 6.90 (d, 1H, J = 7.9 Hz); MS ESI [M + H]⁺, calcd for [C₂₁H₁₄N₄O + H]⁺ 339.1; found *m/z* 339.1.

15

Example A55. (E and Z)-3-((4-((E)-2-(pyridin-4-yl)vinyl)-1H-indazol-6-yl)methylene)indolin-2-one



20 *A. (E)-4-(2-(pyridin-4-yl)vinyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde*

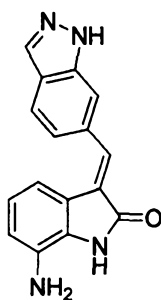
A solution of 4-(pyridine-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (50 mg, 0.14 mmol) and 4-pyridylethylene (20 μL, 0.19 mmol) in acetonitrile (1.5 mL) was purged with argon. Palladium acetate (2 mg, 0.007 mmol), tri-*o*-tolylphosphine (4 mg, 0.014 mmol) and DIPEA (50 μL) was added and the mixture was heated to 70°C for 16 h. Ethyl acetate (50 mL) was added and the mixture was washed with water (2 x 5 mL), brine (5 mL), dried over MgSO₄ and concentrated. The residue was purified by silica gel chromatography

(98:2 EtOAc/MeOH) to give the title compound as a yellow solid (28 mg, 53%). MS ESI $[M + H]^+$, calcd for $[C_{21}H_{25}N_3O_2Si + H]^+$ 380.2; found m/z 380.2.

B. (E and Z)-3-((4-((E)-2-(pyridin-4-yl)vinyl)-1H-indazol-6-yl)methylene)-indolin-2-one

- 5 According to the method of A54C, oxindole (10 mg, 0.07 mmol) was reacted with (E)-4-(2-(pyridin-4-yl)vinyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carb-aldehyde (27 mg, 0.06 mmol) and then treated with HCl to give the title compound as a 3:1 mixture of E/Z isomers (4 mg, 28%). MS ESI $[M + H]^+$, calcd for $[C_{23}H_{16}N_4O + H]^+$ 365.1; found m/z 365.2. E-isomer 1H NMR (400 MHz, DMSO- d_6) δ 8.82-8.79 (m, 2H), 8.20-8.12 (m, 3H), 7.96 (s, 1H), 7.81-7.74 (m, 3H), 7.64 (s, 1H), 7.52 (d, 1H, $J = 8.1$ Hz), 7.23 (t, 1H, $J = 7.8$ Hz), 6.89 (d, 1H, $J = 8.0$ Hz), 6.88-6.86 (m, 1H); Z-isomer 1H NMR (400 MHz, DMSO- d_6) δ 8.97 (s, 1H), 8.67 (s, 1H), 8.60-8.58 (m, 2H), 8.27 (s, 1H), 8.01 (s, 1H), 7.91 (d, 1H, $J = 16.8$ Hz), 7.77 (d, 1H, $J = 7.5$ Hz), 7.74 (d, 2H, $J = 5.5$ Hz), 7.49 (d, 1H, $J = 16$ Hz), 7.23 (t, 1H, $J = 7.8$ Hz), 7.02 (t, 1H, $J = 7.6$ Hz), 6.86 (d, 1H, $J = 7.6$ Hz).

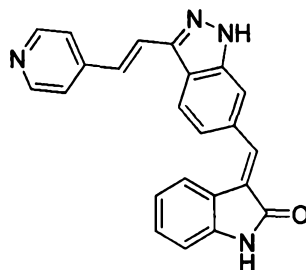
Example A56. (E)-3-((1H-indazol-6-yl)methylene)-7-aminoindolin-2-one



- A 13 mg (0.0877 mmol) solution of 7-aminooxindole (T. Nakashima & I. Suzuki, Chem. Pharm. Bull. (1969) 11, 2293) and 1H-indazole-6-carbaldehyde (14 mg, 0.0965 mmol) in MeOH (1.0 mL) was treated with piperidine (~1 μ L, 0.00877 mmol) and the reaction was heated to 60 $^{\circ}$ C for 4 hours. The MeOH was then removed *in vacuo* and the residue treated with 95:5 CH_2Cl_2 /MeOH. The resulting precipitate was filtered and washed with 95:5 CH_2Cl_2 /MeOH to obtain the title compound as a orange powder (6.7 mg, 28 %). 1H NMR (400 MHz, CD_3OD) δ 8.14 (s, 1H), 7.94-7.87 (m, 3H), 7.46 (d, $J = 8.19$ Hz, 1H), 7.31 (d, $J = 7.63$ Hz, 1H), 6.90

(d, J = 7.89 Hz, 1H), 6.81 (t, J = 7.79 Hz, 1H); MS ESI 277.0 [M + H]⁺, calcd for [C₁₆H₁₂N₄O + H]⁺ 277.11.

5 Example A57. (E)-3-((3-((E)-2-(pyridin-4-yl)vinyl)-1H-indazol-6-yl)methylene)-indolin-2-one



A. *(E)-3-(2-(pyridin-4-yl)vinyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde*

A solution of 3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-
10 carbaldehyde (2.0 g, 4.98 mmol), 4-vinylpyridine (0.69 mL, 6.47 mmol),
diisopropylethylamine (1.74 mL, 9.96 mmol) and DMF (50 mL) was purged with Ar
gas for 20 min at which time Pd(OAc)₂ (112 mg, 0.500 mmol) and P(o-tol)₃ (457
mg, 1.50 mmol) were added and the reaction heated to 100 °C for 20 hours. The
reaction was cooled to room temperature and partitioned between EtOAc and
15 NH₄Cl. The aqueous layer was extracted with EtOAc (3X) and the combined
organics washed with water (2X) and brine (2X). The organic layer was dried over
MgSO₄ and the EtOAc removed *in vacuo*. The residue was purified by column
chromatography (silica gel, 97:3 CH₂Cl₂ / MeOH) to give 927 mg, 49 % of the title
compound which was used without further purification. MS ESI 380.2 [M + H]⁺,
20 calcd for [C₂₁H₂₅N₃O₂Si + H]⁺ 380.18.

B. *(E)-3-((3-((E)-2-(pyridin-4-yl)vinyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)methylene)indolin-2-one*

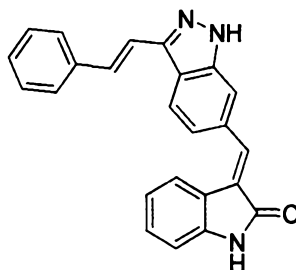
To a solution of (E)-3-(2-(pyridin-4-yl)vinyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-
1H-indazole-6-carbaldehyde (927 mg, 2.44 mmol), oxindole (325 mg, 2.44 mmol)
25 and MeOH (20 mL) was added piperidine (24 uL, 0.244 mmol) and the reaction
heated to 60 °C for 4 hours. A yellow precipitate crashed out of the reaction medium
which was filtered and washed with MeOH to give the title compound (960 mg, 79

%) as a yellow solid. MS ESI 495.3 $[M + H]^+$, calcd for $[C_{29}H_{30}N_4O_2Si + H]^+$ 495.22.

C. *(E)*-3-((3-((*E*)-2-(pyridin-4-yl)vinyl)-1*H*-indazol-6-yl)methylene)-indolin-2-one

- 5 A dry-round bottom was charged with (*E*)-3-((3-((*E*)-2-(pyridin-4-yl)vinyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazol-6-yl)methylene)indolin-2-one (906 mg, 1.83 mmol), and CH_2Cl_2 (100 mL) under an atmosphere of N_2 . Boron trifluoride etherate (2.3 mL, 18.3 mmol) was added dropwise and the reaction was stirred for 4 hours at which time LC-MS indicated complete conversion to the partially de-
- 10 protected material (*E*)-3-((1-(hydroxymethyl)-3-((*E*)-2-(pyridin-4-yl)vinyl)-1*H*-indazol-6-yl)methylene)-indolin-2-one. The CH_2Cl_2 was removed *in vacuo*, and then 150 mL of a 2:1 mixture of EtOH / 2M HCl was added and the reaction heated to 50 °C for 3 hours at which time LC-MS indicated complete conversion to the title compound. The reaction was cooled with an ice-bath and neutralized with NH_4OH
- 15 to pH~8, the EtOH was removed and the suspension filtered washing with water. The dried solid was collected and then titrated and filtered several times with 90:10 CH_2Cl_2 / MeOH which gave, after drying, the title compound (353 mg, 53 %) as an orange solid. 1H NMR (400 MHz, d^6 -DMSO) δ 13.57 (s, 1H), 10.64 (s, 1H), 8.57 (d, $J = 5.16$ Hz, 2H), 8.38 (d, $J = 8.13$ Hz, 1H), 7.92 (s, 1H), 7.87 (d, $J = 16.7$ Hz, 1H), 7.80 (s, 1H), 7.71 (d, $J = 5.16$ Hz, 2H), 7.62-7.53 (m, 3H), 7.23 (t, $J = 8.29$ Hz, 1H), 6.91-6.82 (m, 2H); MS ESI 365.1 $[M + H]^+$, calcd for $[C_{23}H_{16}N_4O + H]^+$ 365.14.
- 20

Example A58. (*E*)-3-((*E*)-(3-styryl)-1*H*-indazol-6-yl)methylene)indolin-2-one



- 25 A. *(E)*-3-styryl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole-6-carbaldehyde
- A solution of 3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole-6-carbaldehyde (100 mg, 0.249 mmol), styrene (37 μ L, 0.324 mmol),

diisopropylethylamine (87 μ L, 0.324 mmol) and DMF (2.5 mL) was purged with Ar gas for 20 min at which time Pd(OAc)₂ (2.8 mg, 0.0125 mmol) and P(o-tol)₃ (11 mg, 0.0374 mmol) were added and the reaction heated to 100 °C for 20 hours. The reaction was cooled to room temperature and partitioned between EtOAc and
5 NH₄Cl. The aqueous layer was extracted 3X with EtOAc and the combined organics washed with water (2X) and brine (2X). The organic layer was dried over MgSO₄ and the EtOAc removed in vacuo. The residue was purified by column chromatography (silica gel, 5:1 hexanes / EtOAc) to give the title compound (63 mg, 67 %) which was used without further purification. MS ESI 379.2 [M + H]⁺, calcd
10 for [C₂₂H₂₆N₂O₂Si + H]⁺ 379.18.

B. (E)-3-styryl-1H-indazole-6-carbaldehyde

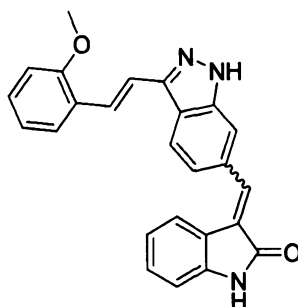
A solution of (E)-3-styryl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (63 mg, 0.166 mmol) in THF (2.0 mL) was treated with TBAF (0.83 mL of a 1M solution in THF) and refluxed overnight. The solvent was removed and
15 the residue re-dissolved into EtOAc. The organics were washed with water (2X), brine (2X) and then dried (MgSO₄). The solvent was removed and the residue purified by column chromatography (silica gel, 98:2 CH₂Cl₂/MeOH) to give the title compound (27 mg, 66 %) which was used without further purification. MS ESI 249.0 [M + H]⁺, calcd for [C₁₆H₁₂N₂O + H]⁺ 249.10.

20 *C. (E)-3-((E)-(3-styryl-1H-indazol-6-yl)methylene)indolin-2-one*

A solution of (E)-3-styryl-1H-indazole-6-carbaldehyde (27 mg, 0.109 mmol) and oxindole (15 mg, 0.109 mmol) in MeOH (1.0 mL) was treated with piperidine (1 μ L, 0.011 mmol) and the reaction stirred at 60 °C for 4 hours. The MeOH was removed and the residue purified by prep-HPLC to give 4.7 mg, 12 % of a yellow powder.
25 ¹H NMR (400 MHz, CD₃OD) δ 8.26 (d, J = 8.38 Hz, 2H), 7.91-7.86 (m, 2H), 7.71-7.64 (m, 3H), 7.60-7.49 (m, 2H), 7.42 (t, J = 7.41 Hz, 2H), 7.31 (t, J = 7.49 Hz, 1H), 7.26 (t, J = 7.89 Hz, 1H), 6.94 (d, J = 7.75 Hz, 1H), 6.89 (t, J = 6.86 Hz, 1H); MS ESI 364.2 [M + H]⁺, calcd for [C₂₄H₁₇N₃O + H]⁺ 364.14.

30 Example A59. (E and Z)-3-((3-((E)-2-methoxystyryl)-1H-indazol-6-yl)methylene)-indolin-2-one

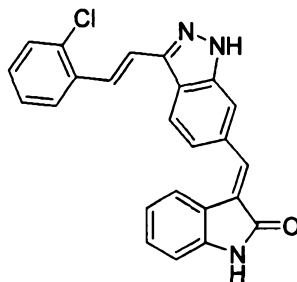
- 136 -



The synthetic method followed of that described in Example A58 starting from 2-methoxystyrene (43 uL, 0.324 mmol) and 3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (100 mg, 0.249 mmol).

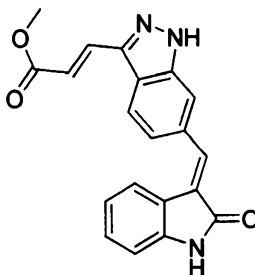
- 5 Obtained 4.6 mg (4.7 % yield over 3 steps) of a yellow powder after prep-HPLC purification. Was isolated as a 75:25 mixture of (E)/(Z) isomers. ¹H NMR (400 MHz, CD₃OD) δ 8.91, 7.89 (s, 1H), 8.19, 8.09 (d, J = 7.43 Hz, 1H), 7.95-7.85 (m, 2H), 7.71-7.67 (m, 2H), 7.58-7.46 (m, 2H), 7.33-7.23 (m, 2H), 7.09-6.98 (m, 2H), 6.96-6.87 (m, 2H), 3.97 (s, 3H); MS ESI 394.2 [M + H]⁺, calcd for [C₂₅H₁₉N₃O₂ + H]⁺ 394.16.
- 10

Example A60. (E)-3-((3-((E)-2-chlorostyryl)-1H-indazol-6-yl)methylene)indolin-2-one



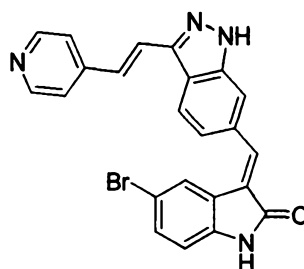
- 15 According to the method described in Example A58 2-chlorostyrene (42 uL, 0.324 mmol) and 3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (100 mg, 0.249 mmol) were reacted to obtain, after prep-HPLC purification, the title compound (2.0 mg, 2.0 %) as a yellow powder. ¹H NMR (400 MHz, CD₃OD) δ 8.20 (d, J = 8.51, 1H), 7.99-7.88 (m, 4H), 7.68 (d, J = 7.32 Hz, 1H), 7.60-7.46 (m, 3H), 7.39 (t, J = 7.68 Hz, 1H), 7.33-7.23 (m, 2H), 6.94 (d, J = 8.02 Hz, 1H), 6.90 (t, J = 7.77 Hz, 1H); MS ESI 398.2 [M + H]⁺, calcd for [C₂₄H₁₆ClN₃O + H]⁺ 398.11.
- 20

Example A61. (E)-methyl 3-(6-((E)-(2-oxoindolin-3-ylidene)methyl)-1H-indazol-3-yl)acrylate



The synthetic method followed that described in Example A58, starting from methylacrylate (41 μ L, 0.457 mmol) and 3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (153 mg, 0.381 mmol). In the final step a yellow solid precipitated from the reaction medium which was filtered and washed with MeOH to give the title compound (3.8 mg, 2.9 %). ^1H NMR (400 MHz, d^6 -DMSO) δ 13.87 (s, 1H), 10.65 (s, 1H), 8.25 (d, J = 8.74 Hz, 1H), 7.95 (s, 1H), 7.93 (d, J = 16.7 Hz, 1H), 7.78 (s, 1H), 7.57-7.54 (m, 2H), 7.24 (t, J = 7.28 Hz, 1H), 6.90-6.80 (m, 3H), 3.77 (s, 3H); MS ESI 346.2 $[\text{M} + \text{H}]^+$, calcd for $[\text{C}_{20}\text{H}_{15}\text{N}_3\text{O}_3 + \text{H}]^+$ 346.12.

Example A62 (E)-5-bromo-3-((3-((E)-2-(pyridin-4-yl)vinyl)-1H-indazol-6-yl)-methylene)indolin-2-one



A. *(E)-5-bromo-3-((3-((E)-2-(pyridin-4-yl)vinyl)-1-((2-(trimethylsilyl)ethoxy)-methyl)-1H-indazol-6-yl)methylene)indolin-2-one*

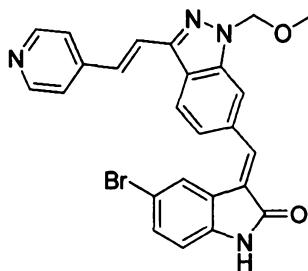
The title compound was prepared from 5-bromooxindole (36 mg, 0.171 mmol) and (E)-3-(2-(pyridin-4-yl)vinyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (65 mg, 0.171 mmol) as described in Example A57 part B to give, after silica gel column chromatography (Eluent: 98:2 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) the title

compound as a yellow oil (75 mg, 77 %). MS ESI 573.4 $[M + H]^+$, calcd for $[C_{29}H_{29}BrN_4O_2Si + H]^+$ 573.13.

B. (E)-5-bromo-3-((3-((E)-2-(pyridin-4-yl)vinyl)-1H-indazol-6-yl)methylene)-indolin-2-one

- 5 A solution of (E)-5-bromo-3-((3-((E)-2-(pyridin-4-yl)vinyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)methylene)indolin-2-one (75 mg, 0.131 mmol) in 12 mL of a 2:1:1 mixture of MeOH / EtOH / 4M HCl was heated to 80 °C for 24 hours. LC-MS indicated a mixture of the title compound plus a partially deprotected methoxymethyl indazole compound (see Example A63). The solvents were removed
10 and the mixture was purified by prep-HPLC to give 7.3 mg (13 %) of the title compound as a yellow solid. 1H NMR (400 MHz, d^6 -DMSO) δ 13.87 (s, 1H), 10.82 (s, 1H), 8.76 (d, J = 5.78 Hz, 2H), 8.45 (d, J = 8.00 Hz, 1H), 8.23-8.13 (m, 3H), 8.04 (s, 1H), 7.96 (s, 1H), 7.73 (d, J = 16.6 Hz, 1H), 7.64 (s, 1H), 7.60 (d, J = 7.81 Hz, 1H), 7.43 (d, J = 7.31 Hz, 1H), 6.87 (d, J = 8.11 Hz, 1H); MS ESI 443.3 $[M + H]^+$,
15 calcd for $[C_{23}H_{15}BrN_4O + H]^+$ 443.05.

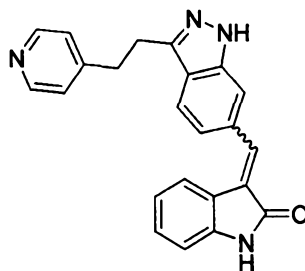
Example A63. (E)-5-bromo-3-((1-(methoxymethyl)-3-((E)-2-(pyridin-4-yl)vinyl)-1H-indazol-6-yl)methylene)indolin-2-one



- 20 The title compound (4.0 mg, 7.0 % of a yellow powder) was isolated by prep-HPLC as a bi-product from the final deprotection step in Example A62. 1H NMR (400 MHz, d^6 -DMSO) δ 10.84 (s, 1H), 8.75 (d, J = 4.81 Hz, 2H), 8.48 (d, J = 8.54 Hz, 1H), 8.24 (s, 1H), 8.18-8.10 (m, 3H), 7.88 (s, 1H), 7.75 (d, J = 16.8 Hz, 1H), 7.67-7.61 (m, 2H), 7.43 (d, J = 7.53 Hz, 1H), 6.87 (d, J = 8.28 Hz, 1H), 5.83 (s, 2H), 3.33
25 (s, 3H); MS ESI 487.3 $[M + H]^+$, calcd for $[C_{25}H_{19}BrN_4O_2 + H]^+$ 487.08.

Example A64. (E and Z)-3-((3-(2-(pyridin-4-yl)ethyl)-1H-indazol-6-yl)methylene)-indolin-2-one

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A. 4-(2-(pyridin-4-yl)ethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde

A solution of (E)-3-(2-(pyridin-4-yl)vinyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (see Example A2 for preparation) (58 mg, 0.153 mmol) in EtOAc (5.0 mL) was purged with Ar gas for 10 min at which time 6 mg of 10 % Pd/C (Degussa type) was added. The reaction was then purged briefly with H₂ (g) and then stirred under an atmosphere of H₂ (g) for 5 hours. The reaction was then filtered through a pad of celite, washed with EtOAc, and the solvent removed to give the title compound (54 mg, 93 %) as a yellow oil. MS ESI 382.2 [M + H]⁺, calcd for [C₂₁H₂₇N₃O₂Si + H]⁺ 382.20.

B. 3-((3-(2-(pyridin-4-yl)ethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)-methylene)indolin-2-one

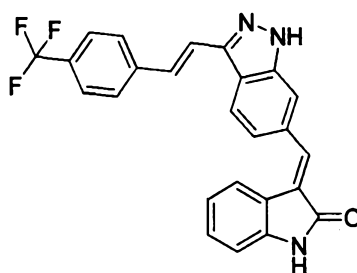
A solution of 3-(2-(pyridin-4-yl)ethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (54 mg, 0.142 mmol), oxindole (19 mg, 0.142 mmol) in MeOH (2.0 mL) was treated with piperidine (1.5 uL, 0.0142 mmol) and the reaction heated to 60 °C and stirred for 4 hours at which time the solvent was removed and the residue purified by column chromatography (silica gel, 96:4 CH₂Cl₂/MeOH) to give the title compound (57 mg, 80 %) as a yellow film. MS ESI 497.2 [M + H]⁺, calcd for [C₂₉H₃₂N₄O₂Si + H]⁺ 497.24.

C. (E and Z)-3-((3-(2-(pyridin-4-yl)ethyl)-1H-indazol-6-yl)methylene)indolin-2-one

A solution of 3-((3-(2-(pyridin-4-yl)ethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)methylene)indolin-2-one (57 mg, 0.115 mmol) in THF (3 mL) was treated with TBAF (0.58 mL of a 1.0 M solution in THF) and the reaction heated at reflux for 20 hours. The solvent was removed and the residue re-dissolved into EtOAc. The organics were washed with water (2X), brine (2X) and then dried (MgSO₄). The solvent was removed and the residue purified by column

chromatography (silica gel, 93:7 CH₂Cl₂/MeOH) to give a yellow solid which was impure by LC-MS. The mixture was further purified by prep-HPLC to give 11.3 mg, 27 % of the title compound as a 76:24 mixture of (E)/(Z) geometric isomers. ¹H NMR (400 MHz, CD₃OD) δ 8.79, 7.87 (s, 1H), 8.69, 8.66 (d, J = 6.52 Hz, 2H), 7.98-7.73 (m, 4H), 7.74, 7.62 (d, J = 8.36 Hz, 1H), 7.66, 7.44 (d, J = 8.44 Hz, 1H), 7.25, 7.05 (t, J = 7.79 Hz, 1H), 6.95-6.84 (m, 2H), 3.53, 3.51 (s, 4H); MS ESI 367.2 [M + H]⁺, calcd for [C₂₃H₁₈N₄O + H]⁺ 367.16.

10 Example A65. (E & Z)-3-((3-((E)-4-(trifluoromethyl)styryl)-1H-indazol-6-yl)-methylene)-indolin-2-one



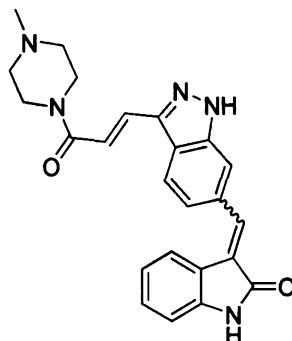
A. (E)-3-((3-(4-(trifluoromethyl)styryl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)methylene)indolin-2-one

The synthetic method followed that described in Example A57, parts A and B starting from 4-trifluoromethylstyrene (48 uL, 0.324 mmol) and 3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (100 mg, 0.249 mmol) to obtain the title compound (49 mg, 35 %). MS ESI 562.2 [M + H]⁺, calcd for [C₃₁H₃₀F₃N₃O₂Si + H]⁺ 562.21.

20 *B. (E and Z)-3-((3-((E)-4-(trifluoromethyl)styryl)-1H-indazol-6-yl)-methylene)-indolin-2-one*

The synthetic method followed that described in Example A64, part C starting from (E)-3-((3-(4-(trifluoromethyl)styryl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)methylene)indolin-2-one (49 mg, 0.087 mmol). Following prep-HPLC purification, the title compound was obtained of a yellow powder (4.5 mg, 12 %) which consisted of a 72:28 mixture of (E)/(Z) isomers. ¹H NMR (400 MHz, CD₃OD) δ 8.92, 7.89 (two s, 1H), 8.27, 8.16 (two d, J = 8.45 Hz, 1H), 7.98-7.83 (m, 3H), 7.70-7.56 (m, 5H), 7.26, 7.06 (two t, J = 8.24 Hz, 1H), 7.64 (s, 1H), 6.95-6.86 (m, 2H); MS ESI 432.2 [M + H]⁺, calcd for [C₂₅H₁₆F₃N₃O + H]⁺ 432.13.

Example A66. (E and Z)-3-((3-((E)-3-(4-methylpiperazin-1-yl)-3-oxoprop-1-enyl)-1H-indazol-6-yl)methylene)indolin-2-one



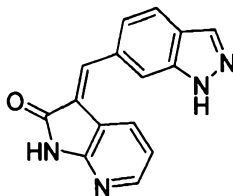
5 *A. 1-(4-methylpiperazin-1-yl)prop-2-en-1-one*

A dry round-bottom flask was charged with 1-methylpiperazine (0.15 mL, 1.36 mmol), diisopropylethylamine (0.65 mL, 3.72 mmol) and CH₂Cl₂ (6 mL) and then the solution was cooled with an ice-water bath. Acryloyl chloride (0.10 mL, 1.24 mmol) was then added dropwise and the reaction was allowed to warm to room temperature. After 3 hours TLC indicated reaction completion. The CH₂Cl₂ was removed and the residue taken up in EtOAc, washed with NaHCO₃ (sat.) (1X), brine (2X) and then dried over MgSO₄. The EtOAc was removed *in vacuo* which yielded after drying, the title compound as an orange-brown oil. (400 MHz, CDCl₃) 6.57 (dd, J₁ = 16.8 Hz, J₂ = 10.5 Hz, 1H), 6.29 (d, J = 16.8 Hz, 1H), 5.70 (d, J = 10.5 Hz, 1H), 3.73 (bs, 2H), 3.60 (bs, 2H), 2.46-2.41 (m, 4H), 2.34 (s, 3H); MS ESI 155.0 [M + H]⁺, calcd for [C₈H₁₄N₂O + H]⁺

B. (E and Z)-3-((3-((E)-3-(4-methylpiperazin-1-yl)-3-oxoprop-1-enyl)-1H-indazol-6-yl)methylene)indolin-2-one

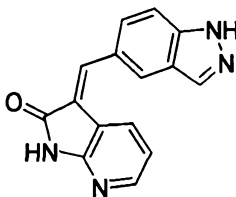
The synthetic method followed of that described in Example A2 with a modified purification. A yellow oil was obtained which was titrated and sonicated with 1:5 Et₂O/hexanes which after decanting off the solvent gave 4.7 mg (8.5 % yield over 3 steps) of an orange-yellow powder as a 73:27 mixture of (E)/(Z) isomers. ¹H NMR (400 MHz, CD₃OD) δ 8.93, 7.97 (s, 1H), 8.17, 8.06 (d, J = 8.33 Hz, 1H), 7.98-7.87 (m, 2H), 7.69-7.58 (m, 2H), 7.46, 7.42 (d, J = 15.5 Hz, 1H), 7.25 (t, J = 7.77 Hz, 1H), 7.07-6.85 (m, 2H), 3.95-3.78 (m, 4H), 2.68-2.55 (bs, 4H), 2.41 (s, 3H); MS ESI 414.2 [M + H]⁺, calcd for [C₂₄H₂₃N₅O₂ + H]⁺ 414.19.

Example A67: (E)-3-((1H-indazol-6-yl)methylene)-1H-pyrrolo[2,3-b]pyridin-2(3H)-one



5 To a mixture of 1H-pyrrolo[2,3-b]pyridin-2(3H)-one (26.8 mg, 0.2 mmol) and 1H-indazole-6-carbaldehyde (29.2 mg, 0.2 mmol) in MeOH (2 mL) was added 1 drop of piperidine via syringe needle. The resulting mixture was refluxed for 2 h (oil temp. 70 °C) and then cooled to rt. The resulting precipitate was collected by suction filtration to give the title compound as a yellow solid (37 mg, 71%). ¹H NMR (400
10 MHz, DMSO-d₆) δ 13.31 (s, 1H, NH), 11.25 (s, 1H, NH), 8.16 (s, 1H), 8.10 (d, J = 5.2 Hz, 1H), 7.93-7.87 (m, 4H), 7.44 (d, J = 8.8 Hz, 1H), 6.90 (dd, J = 7.6 Hz, 5.6 Hz, 1H); MS ESI 263.0 [M + H]⁺, calcd for [C₁₅H₁₀N₄O + H]⁺ 263.1.

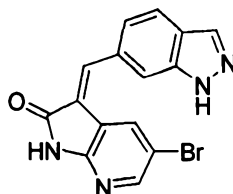
15 Example A68: (E)-3-((1H-indazol-5-yl)methylene)-1H-pyrrolo[2,3-b]pyridin-2(3H)-one



The title compound (50mg, 95 %) was synthesized as an orange solid according to the method described for Example A67 using 1H-pyrrolo[2,3-b]pyridin-2(3H)-one (26.8 mg, 0.2 mmol) and 1H-indazole-5-carbaldehyde (29.2
20 mg, 0.2 mmol). ¹H NMR (400 MHz, DMSO-d₆) δ 13.36 (s, 1H, NH), 11.20 (s, 1H, NH), 8.21 (s, 2H), 8.09 (d, J = 5.2 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.89 (s, 1H), 7.72 (d, J = 8.8 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 6.91 (dd, J = 8.0 Hz, 5.6 Hz, 1H); MS ESI 263.0 [M + H]⁺, calcd for [C₁₅H₁₀N₄O + H]⁺ 263.1.

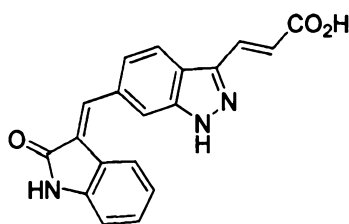
25 Example A69: (E and Z)-3-((1H-indazol-6-yl)methylene)-5-bromo-1H-pyrrolo[2,3-b]pyridin-2(3H)-one

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The title compound (50mg, 95 %) was synthesized as a green solid according to the method described for Example A67 using 5-bromo-1H-pyrrolo[2,3-b]pyridin-2(3H)-one (21.3 mg, 0.1 mmol) and 1H-indazole-6-carbaldehyde (14.6 mg, 0.1 mmol). ¹H NMR indicated 56:44 mixture of E/Z isomers. E isomer: ¹H NMR (400 MHz, DMSO-d₆) δ 13.38 (s, 1H, NH), 11.45 (s, 1H, NH), 8.38 (d, J = 2.0 Hz, 1H), 8.25 (d, J = 2.0 Hz, 1H), 8.19 (s, 1H), 8.01 (s, 1H), 7.93 (s, 1H), 7.90 (d, J = 2.0 Hz, 1H), 7.45 (dd, J = 8.4 Hz, 2.0 Hz, 1H); Z isomer: δ 13.46 (s, 1H, NH), 11.45 (s, 1H, NH), 8.94 (s, 1H), 8.21 (d, J = 2.0 Hz, 1H), 8.19 (s, 1H), 8.15 (s, 1H), 7.99 (dd, J = 8.8 Hz, 1.6 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H); MS ESI 341.0 [M + H]⁺, calcd for [C₁₅H₉BrN₄O + H]⁺ 341.1.

Example A70: (E)-3-(6-((E)-(2-oxoindolin-3-ylidene)methyl)-1H-indazol-3-yl)acrylic acid



a) (E)-3-(6-cyano-1H-indazol-3-yl)acrylic acid

To a mixture of 3-formyl-1H-indazole-6-carbonitrile (34 mg, 0.2 mmol) and malic acid (104 mg, 1 mmol) in pyridine (3 mL) was added 2 drops of piperidine. The resulting mixture was refluxed for 1 h (oil temp. 130 °C) before cooling to 0 °C. the reaction was quenched with ice, followed by 2M HCl (30 mL). The resulting mixture was extracted with EtOAc (30 mL + 15 mL). The combined extracts were washed with 2 M HCl and dried (Na₂SO₄). Evaporation of the solvents gave the title compound (29 mg, 68%) as an orange solid. ¹H NMR (400 MHz, DMSO-d₆) δ 14.13 (s, 1H, NH), 12.55 (brs, 1H, CO₂H), 8.31 (d, J = 8.0 Hz, 1H), 8.24 (s, 1H),

7.86 (d, $J = 16.4$ Hz, 1H), 7.56 (d, $J = 8.0$ Hz, 1H), 6.75 (d, $J = 16.4$ Hz, 1H); MS ESI 214.0 $[M + H]^+$, calcd for $[C_{11}H_8N_2O_3 + H]^+$ 214.1.

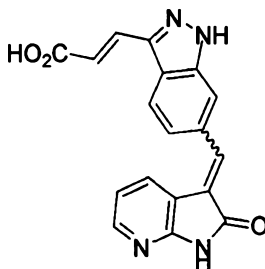
b) (E)-3-(6-formyl-1H-indazol-3-yl)acrylic acid

To a solution of (E)-3-(6-cyano-1H-indazol-3-yl)acrylic acid (25 mg, 0.12 mmol) in acetic acid/pyridine (2 mL/4 mL) was added a solution of sodium hypophosphite (42 mg, 0.48 mmol) in H₂O (2 mL), followed by Raney-Nickel 2400 (slurry in H₂O, 0.1 mL). The resulting mixture was heated at 55 °C (oil temp.) for 1 h before cooling to rt. H₂O (20 mL) was added and the mixture was extracted with EtOAc (30 mL x 2). The combined extracts were washed with 2M HCl (10 mL x 2), H₂O (10 mL x 2), brine (10 mL) and dried (Na₂SO₄). Removal of the solvent gave the title compound (18 mg, 72%) as a beige solid. ¹H NMR (400 MHz, DMSO-d₆) δ 14.12 (s, 1H, NH), 12.24 (brs, 1H, CO₂H), 10.01 (s, 1H, CHO), 8.26 (d, $J = 8.8$ Hz, 1H), 8.22 (s, 1H), 7.87 (d, $J = 16.0$ Hz, 1H), 7.71 (d, $J = 8.8$ Hz, 1H), 6.76 (d, $J = 16.4$ Hz, 1H); MS ESI 217.0 $[M + H]^+$, calcd for $[C_{11}H_8N_2O_3 + H]^+$ 217.1.

c) (E)-3-(6-((E)-(2-oxoindolin-3-ylidene)methyl)-1H-indazol-3-yl)acrylic acid

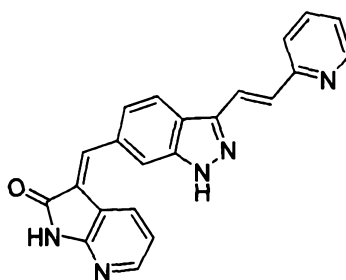
The title compound (7 mg, 21 %) was synthesized as an orange solid according to the method described for Example A67 using oxindole (13.3 mg, 0.1 mmol) and (E)-3-(6-formyl-1H-indazol-3-yl)acrylic acid (21.6 mg, 0.1 mmol). ¹H NMR (400 MHz, DMSO-d₆) δ 13.80 (br. s, 1H, NH), 10.64 (s, 1H, CO₂H), 8.20 (d, $J = 8.4$ Hz, 1H), 7.94 (s, 1H), 7.85 (d, $J = 16.4$ Hz, 1H), 7.78 (s, 1H), 7.58-7.53 (m, 2H), 7.24 (t, $J = 7.6$ Hz, 1H), 6.88 (d, $J = 8.0$ Hz, 1H), 6.84 (t, $J = 7.8$ Hz, 1H), 6.75 (d, $J = 16.0$ Hz, 1H); MS ESI 332.1 $[M + H]^+$, calcd for $[C_{19}H_{13}N_3O_3 + H]^+$ 332.1.

Example A71: (E)-3-(6-((E & Z)-(2-oxo-1H-pyrrolo[2,3-b]pyridin-3(2H)-ylidene)-methyl)-1H-indazol-3-yl)acrylic acid



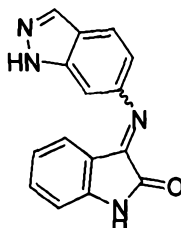
The title compound (13 mg, 39 %) was synthesized as an orange solid according to the method described for Example A67 using 1H-pyrrolo[2,3-b]pyridin-2(3H)-one (13.4 mg, 0.1 mmol) and (E)-3-(6-formyl-1H-indazol-3-yl)acrylic acid (21.6 mg, 0.1 mmol). The ¹H NMR indicated a 5:2 mixture of E/Z isomers. ¹H NMR (400 MHz, DMSO-d₆) δ 11.25 (br. s, 1H), 8.21 (d, J = 8.4 Hz, 1H), 8.12-8.07 (m, 2H), 7.6 (s, 1H), 7.93 (s, 1H), 7.82 (d, J = 16.0 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 6.90 (dd, J = 8.4 Hz, 3.2 Hz, 1H), 6.75 (d, J = 16.0 Hz, 1H); MS ESI 332.1 [M + H]⁺, calcd for [C₁₈H₁₂N₄O₃ + H]⁺ 332.1.

10 Example A72: (E)-3-((3-((E)-2-(pyridin-2-yl)vinyl)-1H-indazol-6-yl)methylene)-1H-pyrrolo[2,3-b]pyridin-2(3H)-one



The title compound (7 mg, 21 %) was synthesized as yellow solid according to the method described for Example A67 using 1H-pyrrolo[2,3-b]pyridin-2(3H)-one (9.3 mg, 0.07 mmol) and (E)-3-(2-(pyridin-2-yl)vinyl)-1H-indazole-6-carbaldehyde (17 mg, 0.068 mmol). ¹H NMR (400 MHz, DMSO-d₆) δ 13.53 (s, 1H, NH), 11.27 (s, 1H, NH), 8.62 (d, J = 4.0 Hz, 1H), 8.35 (d, J = 8.4 Hz, 1H), 8.12 (d, J = 5.2 Hz, 1H), 8.02-7.89 (m, 4H), 7.82 (t, J = 8.0 Hz, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.63 (d, J = 16.8 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.28 (t, J = 6.0 Hz, 1H), 6.91 (dd, J = 7.6 Hz, 5.6 Hz, 1H); MS ESI 366.1 [M + H]⁺, calcd for [C₂₂H₁₅N₅O + H]⁺ 366.1.

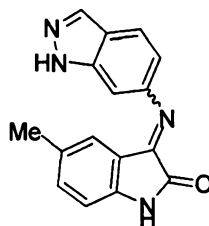
Example A73: (E and Z)-3-(1H-indazol-6-ylimino)indolin-2-one



To a mixture of isatin (147 mg, 1 mmol) and 6-aminoindazole (133 mg, 1 mmol) in EtOH (5 mL) was added 2 drops of acetic acid. The resulting mixture was capped and microwaved 60 min at 120 °C. After cooling to rt, the precipitate was collected by suction filtration to give 135 mg (48%) of title compound as yellow solid. ¹H NMR indicated a 85:15 mixture of E/Z isomers. ¹H NMR (400 MHz, DMSO-d₆) δ 13.04 (s, 1H, NH), 11.00 (s, 1H, NH), 8.09 (s, 1H), 8.36 (d, J = 8.4 Hz, 1H), 7.32 (t, J = 8.0 Hz, 1H), 7.07 (s, 1H), 6.89 (t, J = 8.0 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 6.66 (t, J = 7.6 Hz, 1H), 6.32 (d, J = 7.6 Hz, 1H); MS ESI 263.0 [M + H]⁺, calcd for [C₁₅H₁₀N₄O + H]⁺ 263.1.

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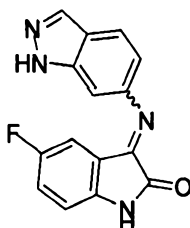
Example A74: (E and Z)-3-(1H-indazol-6-ylimino)-5-methylindolin-2-one



To a mixture of 5-methylisatin (80.5 mg, 0.5 mmol) and 6-aminoindazole (66.5 mg, 0.5 mmol) in EtOH (2 mL) was added 1 drops of acetic acid. The resulting mixture was capped and microwaved 30 min at 120 °C. After cooling to rt, it was stirred for 5 min at rt and the resulting precipitate was collected by suction filtration to give the title compound (35 mg, 28 %) as an orange red solid. ¹H NMR indicated a 80:20 mixture of E/Z isomers. ¹H NMR (400 MHz, DMSO-d₆) δ 13.03 (s, 1H, NH), 10.89 (s, 1H, NH), 8.10 (s, 1H), 7.84 (d, J = 8.8 Hz, 1H), 7.15 (d, J = 7.2 Hz, 1H), 7.07 (s, 1H), 6.81-6.74 (m, 2H), 6.17 (s, 1H), 2.49 (s, 3H, CH₃); MS ESI 277.0 [M + H]⁺, calcd for [C₁₆H₁₂N₄O + H]⁺ 277.1.

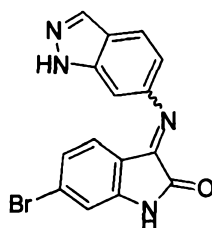
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Example A75: (E and Z)-3-(1H-indazol-6-ylimino)-5-fluoroindolin-2-one



The title compound (76mg, 54 %) was synthesized as a dark red solid according to the method described for Example A74 using 5-fluoroisatin (82.5 mg, 0.5 mmol) and 6-aminoindazole (66.5 mg, 0.5 mmol). ¹H NMR analysis indicated a 79:21 mixture of E/Z isomers. ¹H NMR (400 MHz, DMSO-d₆) δ 13.08 (s, 1H, NH), 11.03 (s, 1H, NH), 8.11 (s, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.22 (dt, J = 9.2 Hz, 2.8 Hz, 1H), 6.90 (dd, J = 8.4 Hz, 4.4 Hz, 1H), 6.82-6.77 (m, 1H), 5.98 (dd, J = 8.0 Hz, 2.0 Hz, 1H); MS ESI 281.0 [M + H]⁺, calcd for [C₁₅H₉FN₄O + H]⁺ 281.1.

Example A76: (E and Z)-3-(1H-indazol-6-ylimino)-6-bromoindolin-2-one

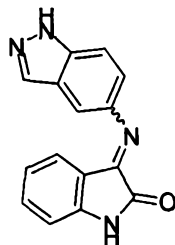


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The title compound (82 mg, 48 %) was synthesized as an orange red solid according to the method described for Example A74 using 6-bromoisatin (113 mg, 0.5 mmol), 6-aminoindazole (73 mg, 0.55 mmol). ¹H NMR indicated a 83:17 mixture of E/Z isomers. ¹H NMR (400 MHz, DMSO-d₆) δ 13.07 (s, 1H, NH), 10.93 (brs, 1H, NH), 8.09 (s, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.08 (s, 1H), 7.05 (d, J = 1.6 Hz, 1H), 6.92 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 6.77 (dd, J = 8.4 Hz, 1.2 Hz, 1H), 6.27 (d, J = 8.0 Hz, 1H); MS ESI 341.1 [M + H]⁺, calcd for [C₁₅H₉BrN₄O + H]⁺ 341.1.

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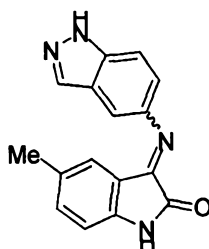
20 Example A77: (E and Z)-3-(1H-indazol-5-ylimino)indolin-2-one



The title compound (165 mg, 63 %) was synthesized as a yellow solid according to the method described for Example A74 using isatin (147 mg, 1 mmol), 5-aminoindazole (133 mg, 1 mmol) and 2 drops of HOAc. ¹H NMR indicated a 5:1

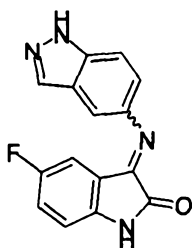
mixture of E/Z isomers. ^1H NMR (400 MHz, DMSO- d_6) δ 13.17 (s, 1H, NH), 11.00 (s, 1H, NH), 8.07 (s, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.35 (s, 1H), 7.31 (t, J = 7.6 Hz, 1H), 7.07 (dd, J = 9.2 Hz, 1.6 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 6.67 (t, J = 8.0 Hz, 1H), 6.45 (d, J = 7.6 Hz, 1H); MS ESI 263.0 $[\text{M} + \text{H}]^+$, calcd for $[\text{C}_{15}\text{H}_{10}\text{N}_4\text{O} + \text{H}]^+$ 263.1.

Example A78: (E and Z)-3-(1H-indazol-5-ylimino)-5-methylindolin-2-one



The title compound (83 mg, 60 %) was synthesized as a brown solid according to the method described for Example A74 using 5-methylisatin (80.5 mg, 0.5 mmol), 5-aminoindazole (66.5 mg, 0.5 mmol). ^1H NMR indicated a 78:22 mixture of E/Z isomers. ^1H NMR (400 MHz, DMSO- d_6) δ 13.15 (s, 1H, NH), 10.86 (s, 1H, NH), 8.08 (s, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.36 (s, 1H), 7.14 (d, J = 8.4 Hz, 1H), 7.07 (dd, J = 8.8 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H) 6.33 (s, 1H), 1.89 (s, 3H); MS ESI 277.0 $[\text{M} + \text{H}]^+$, calcd for $[\text{C}_{16}\text{H}_{12}\text{N}_4\text{O} + \text{H}]^+$ 277.1.

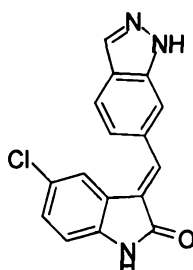
Example A79: (E and Z)-3-(1H-indazol-5-ylimino)-5-fluoroindolin-2-one



The title compound (62 mg, 43 %) was synthesized as a brick red solid (instead of stirring at rt, 1 mL of H_2O was added to crash out the product) according to the method described for Example A74 using 5-fluoroisatin (82.5 mg, 0.5 mmol), 5-aminoindazole (66.5 mg, 0.5 mmol). ^1H NMR indicated a 3:1 mixture of E/Z isomers. ^1H NMR (400 MHz, DMSO- d_6) δ 13.22 (s, 1H), 11.00 (s, 1H), 8.10 (s, 1H), 6.67 (d, J = 8.8 Hz, 1H), 7.39 (s, 1H), 7.22 (dt, J = 9.2 Hz, 2.4 Hz, 1H), 7.10

(dd, $J = 8.8$ Hz, 1.6 Hz, 1H), 6.90 (dd, $J = 8.8$ Hz, 4.4 Hz, 1H), 6.14 (dd, $J = 8.8$ Hz, 2.8 Hz, 1H); MS ESI 281.0 $[M + H]^+$, calcd for $[C_{15}H_9FN_4O + H]^+$ 281.1.

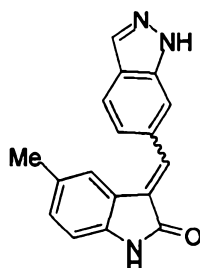
Example A80 (E)-3-((1*H*-indazol-6-yl)methylene)-5-chloroindolin-2-one



5

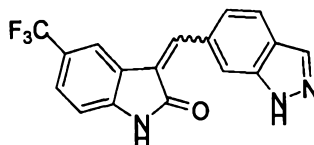
The title compound was prepared according to the procedure described in Example A1, except substituting 5-chlorooxindole (21 mg, 0.13 mmol) to give 6.3 mg of a yellow solid (29 %). 1H NMR (400 MHz, CD_3OD) δ 8.17 (s, 1H), 7.96 (s, 1H), 7.94 (d, $J = 8.0$ Hz, 1H), 7.88 (s, 1H), 7.59 (d, $J = 4.0$ Hz, 1H), 7.45 (d, $J = 8.0$ Hz, 1H),
10 7.25 (dd, $J = 8.0, 4.0$ Hz, 1H), 6.92 (d, $J = 4.0$ Hz, 1H); MS ESI 296.0 $[M + H]^+$, calcd for $[C_{16}H_{10}ClN_3O + H]^+$ 296.06.

Example A81. (E and Z)-3-((1*H*-indazol-6-yl)methylene)-5-methylindolin-2-one



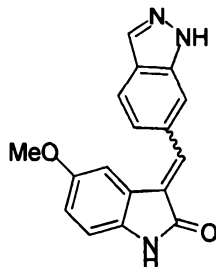
15 The title compound was prepared according to the procedure described in Example A1, except substituting 5-methyloxindole (18 mg, 0.12 mmol) to give 15 mg of a yellow solid (43 %). A mixture of (E)- and (Z)- isomers (89:11 by NMR) was obtained. 1H NMR (400 MHz, CD_3OD) δ 8.14 (s, 1H), 7.91 (d, $J = 8.0$ Hz, 1H), 7.89 (s, 1H), 7.84 (s, 1H), 7.48 (s, 1H), 7.45 (d, $J = 8.0$ Hz, 1H), 7.07 (d, $J = 8.0$ Hz, 1H),
20 6.82 (d, $J = 8.0$ Hz, 1H), 2.18 (s, 3H); MS ESI 276.1 $[M + H]^+$, calcd for $[C_{17}H_{13}N_3O + H]^+$ 276.11.

Example A82. (E and Z)-3-((1H-indazol-6-yl)methylene)-5-(trifluoromethyl)-indolin-2-one



The title compound was prepared according to the procedure described in Example
 5 A1, except substituting 5-trifluoromethyl-oxindole (28 mg, 0.14 mmol) to give 2.2
 mg of a yellow solid (7 %). A mixture of (E and Z)- isomers (40:60 by NMR) was
 obtained. ¹H NMR (400 MHz, d₆-DMSO) δ 13.43 (br s, 1H), 11.07 (br s, 1H), 8.98
 (s, 1H), 8.21 (s, 1H), 8.14(s, 1H), 8.05 (d, J = 8.5 Hz, 1H), 7.93 (d, J = 12.4 Hz, 1H),
 7.84 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.00 (d, J = 8.0 Hz, 1H); MS ESI
 10 330.1 [M + H]⁺, calcd for [C₁₇H₁₀F₃N₃O + H]⁺ 330.08.

Example A83. (E and Z)-3-((1H-indazol-6-yl)methylene)-5-methoxyindolin-2-one

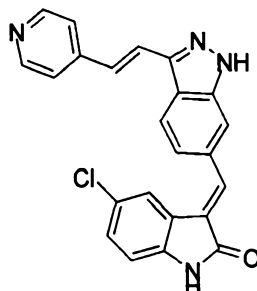


The title compound was prepared according to the procedure described in Example
 15 A1, except substituting 5-methoxyoxindole (22 mg, 0.14 mmol) to give 12.3 mg as a
 yellow solid (31 %). A mixture of (E)- and (Z)- isomers (84:16 by NMR) was
 obtained. ¹H NMR (400 MHz, CD₃OD) δ 8.14 (s, 1H), 7.95-7.87 (m, 3H), 7.46 (d, J
 = 8.8 Hz, 1H), 7.23 (s, 1H), 6.84 (s, 2H), 3.62 (s, 3H); MS ESI 292.1 [M + H]⁺,
 calcd for [C₁₇H₁₃N₃O₂ + H]⁺ 292.10.

20

Example A84. (E)-5-chloro-3-((3-((E)-2-(pyridin-4-yl)vinyl)-1H-indazol-6-yl)methylene)indolin-2-one

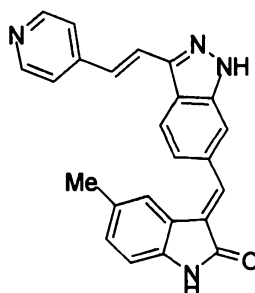
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According to the procedure for the synthesis of (E)-3-((3-((E)-2-(pyridin-4-yl)vinyl)-1H-indazol-6-yl)methylene)indolin-2-one (Example A57), except substituting 5-chlorooxindole (14 mg, 0.08 mmol), the title compound was prepared
 5 as an orange solid (13.5 mg, 42 %). ¹H NMR (400 MHz, d₆-DMSO) δ 13.63 (br s, 1H), 10.78 (br. s, 1H), 8.56 (d, J = 4.0 Hz, 2H), 8.40 (d, J = 10.0 Hz, 1H), 7.91 (s, 1H), 7.89 (d, J = 13.2 Hz, 2H), 7.72 (d, J = 3.5 Hz, 2H), 7.57 (d, J = 12.0 Hz, 1H), 7.52 (d, J = 12.0 Hz, 2H), 7.30 (d, J = 10.0 Hz, 1H), 6.90 (d, J = 11.5 Hz, 1H); MS ESI 399.2 [M + H]⁺, calcd for [C₂₃H₁₅ClN₄O + H]⁺ 399.09.

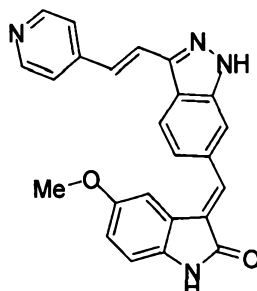
10

Example A85. (E)-5-methyl-3-((3-((E)-2-(pyridin-4-yl)vinyl)-1H-indazol-6-yl)methylene)indolin-2-one



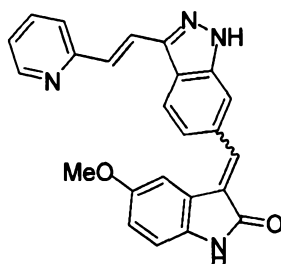
According to procedure for the synthesis of (E)-3-((3-((E)-2-(pyridin-4-yl)vinyl)-1H-indazol-6-yl)methylene)indolin-2-one, except substituting 5-methyloxindole (9
 15 mg, 0.06 mmol) to give the title compound as an orange solid (5.9 mg, 26 %). ¹H NMR (400 MHz, d₆-DMSO) δ 13.58 (br s, 1H), 10.53 (br s, 1H), 8.57 (br s, 2H), 8.36 (d, J = 8.0 Hz, 1H), 7.93-7.46 (m, 8H), 7.06 (d, J = 8.0 Hz, 1H), 6.79 (d, J = 5.8 Hz, 1H), 2.16 (s, 3H); MS ESI 379.2 [M + H]⁺, calcd for [C₂₄H₁₈N₄O + H]⁺
 20 379.15.

Example A86. (E)-5-methoxy-3-((3-((E)-2-(pyridin-4-yl)vinyl)-1H-indazol-6-yl)methylene)indolin-2-one



According to procedure for the synthesis of (E)-3-((3-((E)-2-(pyridin-4-yl)vinyl)-1H-indazol-6-yl)methylene)indolin-2-one, except substituting 5-methoxyoxindole (11 mg, 0.068 mmol) to give the title compound as an orange solid (13.6 mg, 51 %). ¹H NMR (400 MHz, d₆-DMSO) δ 13.58 (br s, 1H), 10.45 (br s, 1H), 8.57 (d, J = 6.0 Hz, 2H), 8.37 (d, J = 8.5 Hz, 1H), 7.93 (s, 1H), 7.87 (d, J = 16.6 Hz, 1H), 7.79 (s, 1H), 7.71 (d, J = 6.0 Hz, 2H), 7.57 (d, J = 2.3 Hz, 1H), 7.54 (d, J = 6.3 Hz, 1H), 7.18 (d, J = 10.0 Hz, 1H), 6.86 (dd, J = 8.8, 2.5 Hz, 1H), 6.80 (d, J = 8.3 Hz, 1H), 3.6 (s, 3H); MS ESI 395.2 [M + H]⁺, calcd for [C₂₄H₁₈N₄O₂ + H]⁺ 395.14.

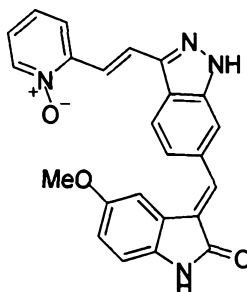
Example A87. (E and Z)-5-methoxy-3-((3-((E)-2-(pyridin-2-yl)vinyl)-1H-indazol-6-yl)methylene)indolin-2-one



According to procedure for the synthesis of (E)-3-((3-((E)-2-(pyridin-2-yl)vinyl)-1H-indazol-6-yl)methylene)indolin-2-one (Example A41), except substituting 5-methoxyoxindole (14 mg, 0.086 mmol), the title compound was prepared as an orange solid (8.8 mg, 26 %). A mixture of (E)- and (Z)- isomers (80:20 by NMR) was obtained. ¹H NMR (400 MHz, CD₃OD) δ 8.59-57 (m, 1H), 8.28 (d, J = 8.5 Hz, 1H), 7.95 (d, J = 16.6 Hz, 1H), 7.92-7.89 (m, 2H), 7.86 (dd, J = 7.5, 1.8 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 16.6 Hz, 1H), 7.59 (dd, J = 8.8, 1.3 Hz, 1H),

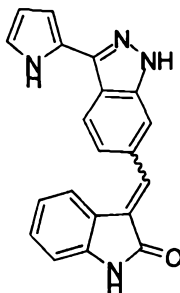
7.33 (ddd, $J = 7.5, 5.0, 1.3$ Hz, 1H), 7.27 (t, $J = 1.3$ Hz, 1H), 6.86-6.85 (m, 2H), 3.85 (s, 3H); MS ESI 395.2 $[M + H]^+$, calcd for $[C_{24}H_{18}N_4O_2 + H]^+$ 395.14.

5 Example A88. 2-((E)-2-(6-((E)-5-methoxy-2-oxoindolin-3-ylidene)methyl)-1H-indazol-3-yl)vinyl)pyridine 1-oxide



A round bottom flask was charged with (E)-5-methoxy-3-((3-((E)-2-(pyridin-2-yl)vinyl)-1H-indazol-6-yl)methylene)indolin-2-one (25 mg, 0.063 mmol), *m*CPBA (13 mg, 0.076 mmol), and dichloromethane (4 mL). The reaction was stirred at rt for 10 24 hrs. Solvent was removed *in vacuo* and the residue was loaded onto a silica gel column. Elution with 90:10 $CH_2Cl_2/MeOH$ gave 9 mg (35 %) of the title compound as an orange solid. 1H NMR (400 MHz, CD_3OD) δ 8.41 (d, $J = 6.0$ Hz, 1H), 8.31 (d, $J = 8.5$ Hz, 1H), 8.19 (d, $J = 16.3$ Hz, 1H), 8.14 (d, $J = 8.0$ Hz, 1H), 8.04 (d, $J = 17.1$ Hz, 1H), 7.91 (d, $J = 16.1$ Hz, 2H), 7.67-7.60 (m, 2H), 7.47-7.43 (m, 1H), 7.25 (s, 15 1H), 6.85 (s, 2H), 3.64 (s, 3H); MS ESI 411.2 $[M + H]^+$, calcd for $[C_{24}H_{18}N_4O_3 + H]^+$ 411.14.

Example A89. (E and Z)-3-((3-(1H-pyrrol-2-yl)-1H-indazol-6-yl)methylene)indolin-2-one



20

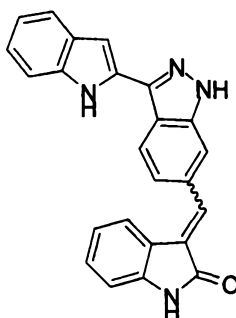
A. 3-(1H-pyrrol-2-yl)-1H-indazole-6-carbaldehyde

A mixture of 3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (50 mg, 0.12 mmol), 1-(tert-butoxycarbonyl)-1H-pyrrol-2-ylboronic acid (40 mg, 0.19 mmol), Pd(PPh₃)₄ (15 mg, 0.012 mmol) and 2M Na₂CO₃ (0.19 mL, 0.37 mmol) in DME/H₂O (2 mL/1 mL) was degassed by evacuation and
5 blanketed with Ar. The reaction mixture was sealed and heated with stirring under microwave irradiation at 125 °C for 60 min. The crude reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using EtOAc (2 %) in DCM as the eluent to provide a pale yellow solid (39 mg, 71 %). The solid was dissolved in THF (8 mL) and treated
10 with 1M TBAF (0.44 mL, 0.44 mmol); the resulting reaction mixture was heated under reflux for 16 h. The crude reaction mixture was concentrated under reduced pressure. Ethyl acetate (5 mL) was added and the solution was washed with brine (2 x 10 mL), dried over MgSO₄, filtered and concentrated. The crude product was purified by flash chromatography on silica gel using EtOAc (20 %) in DCM as the
15 eluent to provide the title compound a pale yellow solid (4.3 mg, 24%). ¹H NMR (400 MHz, CDCl₃) δ ppm 10.11 (s, 1 H), 8.16 (d, *J* = 8.0 Hz, 1 H), 8.09 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 1 H), 6.92 (s, 1 H), 6.79 (d, *J* = 2.2 Hz, 1 H), 6.28 (s, 1H); MS ESI 212.0 (100) [M + H]⁺, calcd for [C₁₂H₉N₃O + H]⁺ 212.07.

20 *B. (E and Z)-3-((3-(1H-pyrrol-2-yl)-1H-indazol-6-yl)methylene)indolin-2-one*

According to the procedure described in A1, except substituting 3-(1H-pyrrol-2-yl)-1H-indazole-6-carbaldehyde (6.9 mg, 0.033 mmol), the title compound was prepared as a yellow solid (6.8 mg, 64 %). A mixture of (E)- and (Z)- isomers (83:17 by NMR) was obtained. ¹H NMR (400 MHz, CD₃OD) δ 8.13 (d, *J* = 8.5 Hz, 1H), 7.96
25 (d, *J* = 19.1 Hz, 2H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 8.3 Hz, 1H), 7.24 (t, *J* = 7.5, 1.0 Hz, 1H), 6.94-6.91 (m, 2H), 6.88 (t, *J* = 7.8 Hz, 1H), 6.80 (d, *J* = 2.5 Hz, 1H), 6.29 (t, *J* = 3.5 Hz, 1H); MS ESI 327.1 [M + H]⁺, calcd for [C₂₀H₁₄N₄O + H]⁺ 327.12.

30 Example A90. (E and Z)-3-((3-(1H-indol-2-yl)-1H-indazol-6-yl)methylene)indolin-2-one



A. 3-(1H-indol-2-yl)-1H-indazole-6-carbaldehyde

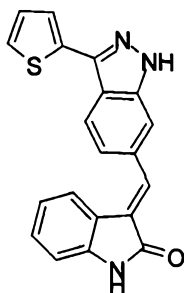
According to the procedure for the synthesis of 3-(1H-pyrrol-2-yl)-1H-indazole-6-carbaldehyde, except substituting 1-(tert-butoxycarbonyl)-1H-indol-2-ylboronic acid
 5 (39 mg, 0.15 mmol), the title compound was prepared as a beige solid (4.4 mg, 14%). ¹H NMR (400 MHz, CDCl₃) δ ppm 10.18 (s, 1 H), 9.09 (s, 1H), 8.29 (d, J = 8.8 Hz, 1 H), 8.06 (s, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.0520-7.15 (m, 2H); MS ESI 262.1 (100) [M + H]⁺, calcd for [C₁₆H₁₁N₃O + H]⁺ 262.09.

10 *B. (E and Z)-3-((3-(1H-indol-2-yl)-1H-indazol-6-yl)methylene)indolin-2-one*
 According to the procedure for the synthesis of (E)-3-((1H-indazol-6-yl)methylene)indolin-2-one, except substituting 3-((3-(1H-indol-2-yl)-1H-indazol-6-yl)methylene)indolin-2-one (4.6 mg, 0.018 mmol), the title compound was prepared
 as a yellow solid (2.2 mg, 33 %). A mixture of (E)- and (Z)- isomers (66:34 by
 15 NMR) was obtained. ¹H NMR (400 MHz, CD₃OD) δ 8.30 (d, J = 8.5 Hz, 1H), 7.93 (d, J = 4.3 Hz, 1H), 7.92 (s, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 7.8 Hz, 1H), 7.59 (dd, J = 7.5, 1.0 Hz, 1H), 7.48 (dd, J = 8.0, 0.8 Hz, 1H), 7.26 (t, J = 7.3 Hz, 1H), 7.19-7.14 (m, 2H), 7.09-7.03 (m, 1H), 6.95 (d, J = 7.5 Hz, 1H), 6.90 (td, J = 7.5, 1.0 Hz, 1H); MS ESI 377.2 [M + H]⁺, calcd for [C₂₄H₁₆N₄O + H]⁺ 377.13.

20

Example A91. (E)-3-((3-(thiophen-2-yl)-1H-indazol-6-yl)methylene)indolin-2-one

- 156 -



A. 3-(thiophen-2-yl)-1H-indazole-6-carbaldehyde

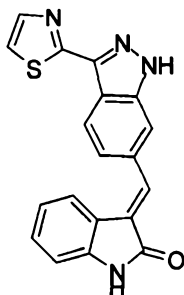
A mixture of 1H-indazole-6-carbaldehyde (50 mg, 0.18 mmol), thiophen-2-ylboronic acid (47 mg, 0.37 mmol), Pd(PPh₃)₄ (21 mg, 0.018 mmol) and 2M Na₂CO₃ (0.28 mL, 0.55 mmol) in DME/H₂O (2 mL/1 mL) was heated under reflux for 16 hours. The crude reaction mixture was concentrated under reduced pressure and purified by flash chromatography on silica gel using EtOAc (10 to 20 %) in DCM as the eluent to provide the title compound as a pale yellow solid (29 mg, 70 %). ¹H NMR (400 MHz, CD₃OD) δ ppm 10.09 (s, 1 H), 8.15 (d, *J* = 8.5 Hz, 1 H), 8.09 (s, 1 H), 7.72 (d, *J* = 8.5 Hz, 1 H), 7.69 (d, *J* = 3.8 Hz, 1 H), 7.48 (d, *J* = 5.0 Hz, 1 H), 7.19 (dd, *J* = 4.8, 3.8 Hz, 1 H); MS ESI 229.0 (100) [M + H]⁺, calcd for [C₁₂H₈N₂OS + H]⁺ 229.04.

B. (E)-3-((3-(thiophen-2-yl)-1H-indazol-6-yl)methylene)indolin-2-one

According to the procedure for the synthesis of (E)-3-((1H-indazol-6-yl)methylene)indolin-2-one, except substituting 3-(thiophen-2-yl)-1H-indazole-6-carbaldehyde (29 mg, 0.13 mmol), the title compound was prepared as a yellow solid (19.7 mg, 45 %). ¹H NMR (400 MHz, d₆-DMSO) δ 10.64 (br s, 1H), 8.22 (d, *J* = 8.5 Hz, 1H), 7.92 (s, 1H), 7.79 (s, 2H), 7.61 (d, *J* = 7.5 Hz, 1 H), 7.59 (d, *J* = 5.0 Hz, 1 H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.26-7.20 (m, 2H), 6.89 (d, *J* = 7.5 Hz, 1H), 6.85 (t, *J* = 7.5 Hz, 1H); MS ESI 344.1 [M + H]⁺, calcd for [C₂₀H₁₃N₃OS + H]⁺ 344.08.

Example A92. (E)-3-((3-(thiazol-2-yl)-1H-indazol-6-yl)methylene)indolin-2-one

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A. 3-(thiazol-2-yl)-1H-indazole-6-carbaldehyde

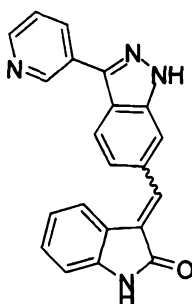
A mixture of 3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (100 mg, 0.25 mmol), 2-(tributylstannyl)thiazole (85 mg, 0.23 mmol),
 5 Pd₂(dba)₃ (23 mg, 0.025 mmol), P(*o*-Tol)₃ (15 mg, 0.05 mmol), and Et₃N (0.05 mL, 0.30 mmol) in DMF (2 mL) was degassed by evacuation and refilling with Ar. The reaction mixture was sealed and heated with stirring under microwave irradiation at 125 °C for 2 h. Ethyl acetate (5 mL) was added and the solution was washed with brine (2 x 20 mL), dried over MgSO₄, filtered and concentrated. The crude product
 10 was purified by flash chromatography on silica gel using EtOAc (10 %) in hexanes as the eluent to provide a pale yellow solid (33 mg, 37 %). The solid was dissolved in THF (10 mL) and 1M TBAF (0.47 mL, 0.47 mmol) was added. The resulting reaction mixture was heated under reflux for 16 h. The crude reaction mixture was concentrated under reduced pressure. Ethyl acetate (5 mL) was added and the
 15 solution was washed with brine (2 x 10 mL), dried over MgSO₄, filtered and concentrated. The crude product was purified by flash chromatography on silica gel using EtOAc (40 %) in hexanes as the eluent to provide the title compound a pale yellow solid (4.6 mg, 8%). ¹H NMR (400 MHz, CDCl₃) δ ppm 10.18 (s, 1 H), 8.70 (d, *J* = 8.5 Hz, 1 H), 8.08 (s, 1H), 8.01 (d, *J* = 3.0 Hz, 1 H), 8.86 (d, *J* = 8.5 Hz, 1H),
 20 7.43 (d, *J* = 3.3 Hz, 1 H); MS ESI 230.0 (100) [M + H]⁺, calcd for [C₁₁H₇N₃OS + H]⁺ 230.03.

B. (E)-3-((3-(thiazol-2-yl)-1H-indazol-6-yl)methylene)indolin-2-one

According to the procedure for the synthesis of (E)-3-((1H-indazol-6-yl)methylene)indolin-2-one, except substituting 3-(thiazol-2-yl)-1H-indazole-6-carbaldehyde (4.6 mg, 0.02 mmol), the title compound was prepared as a yellow
 25 solid (2.3 mg, 36%). ¹H NMR (400 MHz, d₆-DMSO) δ 13.75 (br. s, 1H), 10.64 (br. s, 1H), 8.44 (d, *J* = 8.5 Hz, 1H), 8.03 (d, *J* = 3.3 Hz, 1H), 7.96 (s, 1H), 7.80-7.78 (m ,

2H), 7.60 (d, 7.3 Hz, 1H), 7.58 (d, $J = 7.5$ Hz, 1 H), 7.25 (td, $J = 7.5, 1.0$ Hz, 1 H), 6.88 (d, $J = 7.8$ Hz, 1H), 6.85 (td, $J = 7.5, 1.0$ Hz, 1H); MS ESI 345.1 $[M + H]^+$, calcd for $[C_{19}H_{12}N_4OS + H]^+$ 345.07.

5 Example A93. (E and Z)-3-((3-(pyridin-3-yl)-1H-indazol-6-yl)methylene)indolin-2-one



A. 3-(pyridin-3-yl)-1H-indazole-6-carbaldehyde

A mixture of 3-iodo-1H-indazole-6-carbaldehyde (50 mg, 0.18 mmol), pyridin-3-ylboronic acid (27 mg, 0.22 mmol), $PdCl_2(PPh_3)_2$ (13 mg, 0.018 mmol) and 2M Na_2CO_3 (0.10 mL, 0.18 mmol) in DME/ H_2O /EtOH (1.4 mL/0.4 mL/0.2 mL) was degassed by evacuation and refilling with Ar. The reaction mixture was sealed and heated with stirring under microwave irradiation at 125 °C for 60 min. The crude reaction mixture was concentrated under reduced pressure. Ethyl acetate (5 mL) was added and the solution was washed with brine (2 x 20 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography on silica gel using MeOH (5 %) in DCM as the eluent to provide the title compound a pale yellow solid (24 mg, 59%). 1H NMR (400 MHz, $CDCl_3$) δ ppm 10.17 (s, 1 H), 8.88 (d, $J = 2.3$ Hz, 1 H), 8.69 (d, $J = 4.8$ Hz, 1H), 8.16 (d, $J = 8.5$ Hz, 1 H), 8.10 (s, 1 H), 7.92 (d, $J = 8.0$ Hz, 1 H), 7.82 (d, $J = 8.5$ Hz, 1 H), 7.45 (dd, $J = 8.0, 5.0$ Hz, 1 H); MS ESI 224.0 (100) $[M + H]^+$, calcd for $[C_{13}H_9N_3O + H]^+$ 224.07.

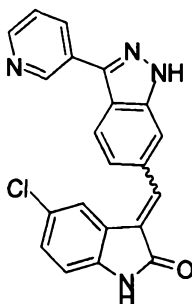
B. (E and Z)-3-((3-(pyridin-3-yl)-1H-indazol-6-yl)methylene)indolin-2-one

According to the procedure for the synthesis of (E)-3-((1H-indazol-6-yl)methylene)indolin-2-one, except substituting 3-(pyridin-3-yl)-1H-indazole-6-carbaldehyde (24 mg, 0.11 mol), the title compound was prepared as a yellow solid (9.2 mg, 25 %). A mixture of (E)- and (Z)- isomers (83:17 by NMR) was obtained. 1H NMR (400 MHz, d_6 -DMSO) δ 10.65 (br s, 1H), 9.23 (s, 1H), 8.62 (d, $J = 5.0$ Hz,

1H), 8.41 (d, J = 7.5 Hz, 1H), 8.21 (d, J = 8.5 Hz, 1H), 7.97 (s, 1H), 7.80 (s, 1H), 7.62 (d, J = 7.5, 1H), 7.58-7.53 (m, 2H), 7.24 (t, J = 7.8 Hz, 1H), 6.89 (d, J = 7.8 Hz, 1H), 6.85 (t, J = 7.3 Hz, 1H); MS ESI 339.1 [M + H]⁺, calcd for [C₂₁H₁₄N₄O + H]⁺ 339.12.

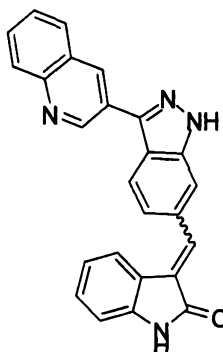
5

Example A94. (E and Z)-5-chloro-3-((3-(pyridin-3-yl)-1H-indazol-6-yl)methylene)-indolin-2-one



According to the procedure for the synthesis of 3-((3-(pyridin-3-yl)-1H-indazol-6-yl)methylene)indolin-2-one, except substituting 5-chlorooxindole (5.3 mg, 0.031 mmol) the title compound was prepared as a yellow solid (6.5 mg, 54 %). A mixture of (E)- and (Z)- isomers (68:32 by NMR) was obtained. ¹H NMR (400 MHz, d₆-DMSO) δ 13.77 (br s, 1H), 10.80 (br s, 1H), 9.24 (d, J = 1.5 Hz, 1H), 8.63 (dd, J = 4.8, 1.8 Hz, 1H), 8.41 (dt, J = 7.8, 1.8 Hz, 1H), 8.28 (d, J = 8.5 Hz, 1H), 8.21-8.16 (m, 1H), 7.98 (s, 1H), 7.89 (s, 1H), 7.57 (t, J = 4.5, 1H), 7.55-7.52 (m, 1H), 7.31 (dd, J = 8.3, 2.3 Hz, 1H), 6.91 (d, J = 8.3 Hz, 1H); MS ESI 373.1 [M + H]⁺, calcd for [C₂₁H₁₃ClN₄O + H]⁺ 373.08.

20 Example A95. (E and Z)-3-((3-(quinolin-3-yl)-1H-indazol-6-yl)methylene)indolin-2-one



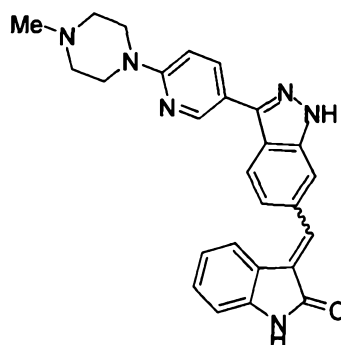
A. 3-(quinolin-3-yl)-1H-indazole-6-carbaldehyde

According to the procedure for the synthesis of 3-(pyridin-3-yl)-1H-indazole-6-carbaldehyde, except substituting quinolin-3-ylboronic acid (38 mg, 0.22 mmol), the title compound was obtained as a beige solid (15 mg, 30%). ¹H NMR (400 MHz, CDCl₃) δ ppm 10.19 (s, 1 H), 9.61 (d, J = 2.0 Hz, 1 H), 8.73 (d, J = 2.0 Hz, 1H), 8.27 (d, J = 8.3 Hz, 1H), 8.21 (d, J = 8.3 Hz, 1H), 8.13 (s, 1H), 7.98 (d, J = 8.3 Hz, 1H), 7.87 (dd, J = 8.5, 1.3 Hz, 1 H), 7.80 (ddd, J = 8.3, 7.0, 1.5 Hz, 1H), 7.66 (ddd, J = 8.3, 7.0, 1.3 Hz, 1H); MS ESI 274.0 (100) [M + H]⁺, calcd for [C₁₇H₁₁N₃O + H]⁺ 274.09.

B. (E and Z)-3-((3-(quinolin-3-yl)-1H-indazol-6-yl)methylene)indolin-2-one

According to the procedure for the synthesis of (E)-3-((1H-indazol-6-yl)methylene)indolin-2-one, except substituting 3-(quinolin-3-yl)-1H-indazole-6-carbaldehyde (8 mg, 0.03 mol), the title compound was obtained as a yellow solid (4.3 mg, 38 %). A mixture of (E)- and (Z)- isomers (94:6 by NMR) was obtained. ¹H NMR (400 MHz, d₆-DMSO) δ 13.75 (br s, 1H), 10.66 (br. s, 1H), 9.61 (d, J = 2.0 Hz, 1H), 9.04 (d, J = 2.3 Hz, 1H), 8.47 (d, J = 8.8 Hz, 1H), 8.22 (d, J = 7.8 Hz, 1H), 8.08 (d, J = 8.0 Hz, 1H), 8.01 (s, 1H), 7.83 (s, 1H), 7.80 (td, J = 6.8, 1.3 Hz, 1H), 7.68 (t, J = 7.8, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.25 (t, J = 7.8 Hz, 1H), 6.90 (d, J = 8.3 Hz, 1H), 6.86 (t, J = 7.8 Hz, 1H); MS ESI 389.1 [M + H]⁺, calcd for [C₂₅H₁₆N₄O + H]⁺ 389.13.

Example A96. (E and Z)-3-((3-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1H-indazol-6-yl)methylene)indolin-2-one



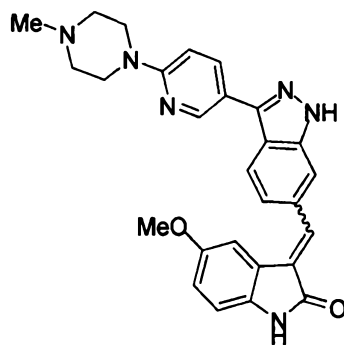
A. 3-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1H-indazole-6-carbaldehyde

According to the procedure for the synthesis of 3-(pyridin-3-yl)-1H-indazole-6-carbaldehyde, except substituting 1-methyl-4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine (67 mg, 0.22 mmol), the title compound was obtained as a beige solid (57 mg, 99%). ¹H NMR (400 MHz, CD₃OD) δ ppm 10.11 (s, 1 H), 8.73 (d, J = 2.3 Hz, 1 H), 8.16 (dd, J = 8.8, 2.3 Hz, 1H), 8.14 (s, 1H), 8.09 (d, J = 8.3 Hz, 1H), 7.72 (d, J = 8.5 Hz, 1H), 7.05 (d, J = 8.8 Hz, 1 H), 3.83-3.78 (m, 4H), 3.01 (t, J = 5.0 Hz, 4H), 2.67 (s, 3H); MS ESI 322.1 (100) [M + H]⁺, calcd for [C₁₈H₁₉N₅O + H]⁺ 322.16.

B. (E and Z)-3-((3-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1H-indazol-6-yl)methylene)-indolin-2-one

According to the procedure for the synthesis of (E)-3-((1H-indazol-6-yl)methylene)indolin-2-one, except substituting 3-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1H-indazole-6-carbaldehyde (40 mg, 0.12 mol), the title compound was prepared as a yellow solid (4.9 mg, 9 %). A mixture of (E)- and (Z)- isomers (79:21 by NMR) was obtained. ¹H NMR (400 MHz, d₆-DMSO) δ 13.34 (br. s, 1H), 10.64 (br. s, 1H), 8.76 (d, J = 2.3 Hz, 1H), 8.14 (dd, J = 8.8, 2.5 Hz, 2H), 7.91 (s, 1H), 7.79 (s, 1H), 7.62 (d, J = 7.8, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.24 (t, J = 7.5 Hz, 1H), 6.99 (d, J = 9.0 Hz, 1H), 6.89 (d, J = 7.8 Hz, 1H), 6.85 (t, J = 7.3 Hz, 1H), 3.57 (t, J = 4.5 Hz, 4H), 2.42 (t, J = 5.0 Hz, 4H), 2.23 (s, 3H); MS ESI 437.2 [M + H]⁺, calcd for [C₂₆H₂₄N₆O + H]⁺ 437.20.

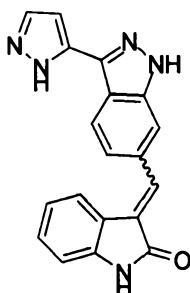
Example A97. (E and Z)-5-methoxy-3-((3-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1H-indazol-6-yl)methylene)indolin-2-one



According to the procedure for the synthesis of 3-((3-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1H-indazol-6-yl)methylene)indolin-2-one (Example A97), except

substituting 5-methoxyoxindole (28 mg, 0.087 mol), the title compound was prepared as a yellow solid (14.4 mg, 35 %). A mixture of (E)- and (Z)- isomers (83:17 by NMR) was obtained. ¹H NMR (400 MHz, CD₃OD) 8.74 (d, J = 2.3 Hz, 1H), 8.14 (dd, J = 8.8, 2.3 Hz, 1H), 8.07 (d, J = 8.5 Hz, 1H), 7.87 (d, J = 10.0 Hz, 2H), 7.49 (d, J = 8.3 Hz, 1H), 7.26 (s, 1H), 7.01 (d, J = 8.8, 1H), 6.83 (s, 2H), 3.75-3.69 (br. m, 4H), 3.62 (s, 3H), 2.82-2.76 (br. m, 4H), 2.51 (s, 3H); MS ESI 467.2 [M + H]⁺, calcd for [C₂₇H₂₆N₆O₂ + H]⁺ 467.21.

10 Example A98. (E and Z)-3-((3-(1H-pyrazol-5-yl)-1H-indazol-6-yl)methylene)-indolin-2-one



A. 3-(1H-pyrazol-5-yl)-1H-indazole-6-carbaldehyde

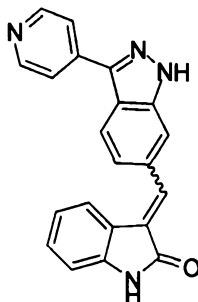
According to the procedure for the synthesis of 3-(pyridin-3-yl)-1H-indazole-6-carbaldehyde, except substituting 1H-pyrazole-5-boronic acid (25 mg, 0.22 mmol), the title compound was prepared as a beige solid (5.3 mg, 13%). ¹H NMR (400 MHz, CD₃OD) δ ppm 10.13 (s, 1 H), 8.44-8.32 (br. m, 1 H), 8.14 (s, 1H), 7.78 (d, J = 1.8 Hz, 1 H), 7.75 (d, J = 8.3 Hz, 1 H), 6.90 (d, J = 2.0 Hz, 1 H); MS ESI 213.0 (100) [M + H]⁺, calcd for [C₁₁H₈N₄O + H]⁺ 213.07.

20 *B. (E and Z)-3-((3-(1H-pyrazol-5-yl)-1H-indazol-6-yl)methylene)indolin-2-one*

According to the procedure for the synthesis of (E)-3-((1H-indazol-6-yl)methylene)indolin-2-one, except substituting 3-(1H-pyrazol-5-yl)-1H-indazole-6-carbaldehyde (5.3 mg, 0.025 mmol), the title compound was prepared as a yellow solid (4.4 mg, 54 %). A mixture of (E)- and (Z)- isomers (78:22 by NMR) was obtained. ¹H NMR (400 MHz, CD₃OD) δ 8.35 (br. s, 1H), 7.92-7.89 (m, 2H), 7.79-7.77 (m, 1H), 7.68 (d, J = 7.8 Hz, 1H), 7.53 (d, J = 8.5 Hz, 1H), 7.25 (t, J = 7.5 Hz,

1H), 6.94-6.86 (m, 3H); MS ESI 328.1 $[M + H]^+$, calcd for $[C_{19}H_{13}N_5O + H]^+$ 328.11.

Example A99. (E and Z)-3-((4-(pyridin-3-yl)-1H-indazol-6-yl)methylene)indolin-2-one



A. 3-(pyridin-4-yl)-1H-indazole-6-carbaldehyde

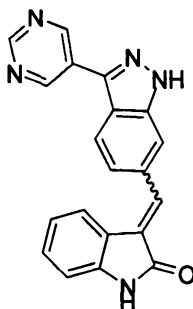
According to the procedure for the synthesis of 3-(pyridin-3-yl)-1H-indazole-6-carbaldehyde, except substituting pyridin-4-ylboronic acid (27 mg, 0.22 mmol), the title compound was obtained as a beige solid (3.7 mg, 9%). 1H NMR (400 MHz, CD_3OD) δ ppm 10.15 (s, 1 H), 8.69 (d, $J = 6.3$ Hz, 2 H), 8.32 (d, $J = 8.8$ Hz, 1 H), 8.22 (s, 1H), 8.10 (d, $J = 6.3$ Hz, 2 H), 7.84 (d, $J = 6.3$ Hz, 1 H); MS ESI 224.0 (100) $[M + H]^+$, calcd for $[C_{13}H_9N_3O + H]^+$ 224.07.

B. (E and Z)-3-((4-(pyridin-3-yl)-1H-indazol-6-yl)methylene)indolin-2-one

According to the procedure for the synthesis of (E)-3-((1H-indazol-6-yl)methylene)-indolin-2-one, except substituting 3-(pyridin-4-yl)-1H-indazole-6-carbaldehyde (3.9 mg, 0.017 mol), the title compound was prepared as a yellow solid (4.8 mg, 81 %). A mixture of (E)- and (Z)- isomers (64:36 by NMR) was obtained. 1H NMR (400 MHz, CD_3OD) δ 8.69 (d, $J = 6.0$ Hz, 2H), 8.30 (d, $J = 8.5$ Hz, 1H), 8.13 (d, $J = 6.0$ Hz, 2H), 7.97 (s, 1H), 7.90 (s, 1H), 7.67 (d, $J = 8.0$ Hz, 1H), 7.63 (d, $J = 8.9$ Hz, 1H), 7.26 (t, $J = 8.0$ Hz, 1H), 6.94 (d, $J = 8.0$ Hz, 1H), 6.89 (t, $J = 7.8$ Hz, 1H); MS ESI 339.1 $[M + H]^+$, calcd for $[C_{21}H_{14}N_4O + H]^+$ 339.12.

Example A100. (E and Z)-3-((3-(pyrimidin-5-yl)-1H-indazol-6-yl)methylene)-indolin-2-one

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A. 3-(pyrimidin-5-yl)-1H-indazole-6-carbaldehyde

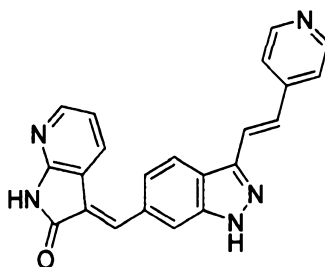
According to the procedure for the synthesis of 3-(1H-pyrrol-2-yl)-1H-indazole-6-carbaldehyde, except substituting pyrimidin-5-ylboronic acid (34 mg, 0.15 mmol),
 5 the title compound was obtained as a beige solid (8.1 mg, 30%). ¹H NMR (400 MHz, CD₃OD) δ ppm 10.15 (s, 1 H), 9.44 (s, 2H), 9.21 (s, 1H), 8.26 (d, J = 8.5 Hz, 1 H), 8.23 (t, J = 1.3 Hz, 1H), 7.84 (dd, J = 8.5, 1.3 Hz, 1H); MS ESI 225.0 (100) [M + H]⁺, calcd for [C₁₂H₈N₄O + H]⁺ 225.07.

B. (E and Z)-3-((3-(pyrimidin-5-yl)-1H-indazol-6-yl)methylene)indolin-2-one

10 According to the procedure for the synthesis of (E)-3-((1H-indazol-6-yl)methylene)indolin-2-one, except substituting 3-(pyrimidin-5-yl)-1H-indazole-6-carbaldehyde (8.5 mg, 0.038 mol), the title compound was prepared as a yellow solid (1.2 mg, 9 %). A mixture of (E)- and (Z)- isomers (63:37 by NMR) was obtained. ¹H NMR (400 MHz, CD₃OD) δ 9.47 (s, 2H), 9.22 (s, 1H), 8.24 (d, J = 8.5
 15 Hz, 1H), 7.97 (s, 1H), 7.90 (s, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 8.5 Hz, 1H), 7.26 (t, J = 8.0 Hz, 1H), 6.49 (d, J = 8.0 Hz, 1H), 6.88 (t, J = 7.8 Hz, 1H); MS ESI 340.1 [M + H]⁺, calcd for [C₂₀H₁₃N₅O + H]⁺ 340.11.

Example A101: (E)-3-((3-((E)-2-(pyridin-4-yl)vinyl)-1H-indazol-6-yl)methylene)-

20 1H-pyrrolo[2,3-b]pyridin-2(3H)-one

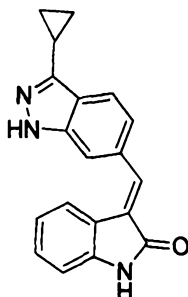


The title compound (64 mg, 64 %) was synthesized as orange red solid according to the method described for Example A11B from 1H-pyrrolo[2,3-b]pyridin-2(3H)-one (26.8 mg, 0.2 mmol) and E-3-(2-(pyridin-4-yl)vinyl)-1H-indazole-6-carbaldehyde (49.8 mg, 0.2 mmol). ¹H NMR (400 MHz, DMSO-d₆) δ

5 13.60 (s, 1H, NH), 11.28 (s, 1H, NH), 8.57 (d, J = 5.6 Hz, 2H), 8.39 (d, J = 8.4 Hz, 1H), 8.12 (d, J = 4.8 Hz, 1H), 7.95 (s, 2H), 7.90 (d, J = 6.4 Hz, 1H, partially overlapping with the peak at 7.87 ppm), 7.87 (d, J = 16.4 Hz, 1H, partially overlapping with the peak at 7.90 ppm), 7.71 (d, J = 5.6 Hz, 2H), 7.57 (d, J = 8.0 Hz, 1H, partially overlapping with the peak at 7.56 ppm), 7.56 (d, J = 16.4 Hz, 1H, partially overlapping with the peak at 7.57 ppm), 6.91 (dd, J = 7.6 Hz, 5.2 Hz, 1H);

10 MS ESI 366.1 [M + H]⁺, calcd for [C₂₂H₁₅N₅O + H]⁺ 366.1.

Example A102 (E)-3-((3-cyclopropyl-1H-indazol-6-yl)methylene)indolin-2-one



15 A. 3-cyclopropyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde

A degassed mixture of 3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (51 mg, 0.12 mmol), cyclopropylboronic acid (21 mg, 0.24 mmol), powdered K₃PO₄ (103 mg, 0.48 mmol) and Pd(PPh₃)₄ (10 mg, 0.009 mmol) in

20 PhMe (2 mL) and H₂O (0.1 mL) was heated with stirring in a sealed tube under Ar at 95 -100 °C for 1 d. The crude mixture was concentrated and purified by prepTLC (SiO₂ 5:1 hexanes/EtOAc) to provide the title compound as a clear oil (40 mg, quant): ¹H NMR (400 MHz, CDCl₃) δ ppm 10.13 (s, 1 H), 8.02 (s, 1 H), 7.87 (d, J=8.28 Hz, 1 H), 7.70 (d, J=8.28 Hz, 1 H), 5.71 (s, 2 H), 3.54 (d, J=8.53 Hz, 2 H),

25 2.19 - 2.28 (m, 1 H), 1.06 - 1.12 (m, 4 H), 0.89 (d, J=8.28 Hz, 2 H), -0.07 (s, 9 H); MS ESI 317.1 [M + H]⁺, calcd for [C₁₇H₂₄N₂O₂Si + H]⁺ 317.5.

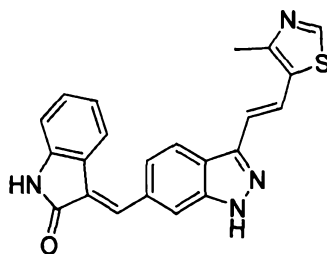
B. (E)-3-((3-cyclopropyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)methyl-ene)indolin-2-one

According to the method of Example A19, indolin-2-one (17 mg, 0.13 mmol) and 3-cyclopropyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (40 mg, 0.13 mmol) were reacted to obtain crude product. The crude mixture was purified by prepTLC (SiO₂ 2 % MeOH in DCM) to provide the title compound as a yellow solid (48 mg, 88 %). MS ESI 432.2 [M + H]⁺, calcd for [C₂₅H₂₉N₃O₂Si + H]⁺ 432.6.

C. (E)-3-((3-cyclopropyl-1H-indazol-6-yl)methylene)indolin-2-one

A mixture of (E)-3-((3-cyclopropyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)methylene)indolin-2-one (47 mg, 0.11 mmol) and tetrabutylammonium fluoride (1.0 M in THF, 10 mL, 10 mmol) in anh. THF (30 mL) was refluxed under Ar for 18 h. The reaction mixture was then concentrated to a brown oil, which was diluted with H₂O, extracted (2 % MeOH in DCM), washed (H₂O (2x), brine), dried (Na₂SO₄ and MgSO₄) and concentrated under reduced pressure. The material was suspended in DCM, collected by filtration and washed with xs. DCM to afford the title compound as a yellow solid (7.0 mg, 21 %). ¹H NMR (400 MHz, CD₃OD) δ ppm 7.90 (d, *J*=8.53 Hz, 1 H), 7.86 (s, 1 H), 7.78 (s, 1 H), 7.65 (d, *J*=8.03 Hz, 1 H), 7.42 (d, *J*=8.78 Hz, 1 H), 7.23 (t, *J*=8.03 Hz, 1 H), 6.92 (d, *J*=7.78 Hz, 1 H), 6.87 (t, *J*=7.65 Hz, 1 H), 2.26 - 2.36 (m, 1 H), 1.04 - 1.11 (m, 4 H); MS ESI 302.1 [M + H]⁺, calcd for [C₁₉H₁₅N₃O + H]⁺ 302.3.

Example A103 (E)-3-((3-((E)-2-(4-methylthiazol-5-yl)vinyl)-1H-indazol-6-yl)methyl-ene)indolin-2-one



A. (E)-3-(2-(4-methylthiazol-5-yl)vinyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde

A degassed mixture of 3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (70 mg, 0.17 mmol), 4-methyl-5-vinylthiazole (44 mg, 0.35 mmol), N-ethyl-N-isopropylpropan-2-amine (DIPEA, 45 mg, 0.35 mmol), Pd(OAc)₂ (3.9 mg, 0.017 mmol) and P(*o*-MeC₆H₄)₃ (16 mg, 0.052 mmol) in anhydrous MeCN (2 mL) were heated with stirring in a sealed tube under Ar at 90 °C for 1 d. The crude mixture was later concentrated under reduced pressure and purified by prepTLC (SiO₂ 5:1 hexanes/EtOAc) to provide the title compound (30 mg, 43 %): ¹H NMR (400 MHz, CDCl₃) δ ppm 10.17 (s, 1 H), 8.64 (s, 1 H), 8.12 (s, 1 H), 8.06 (d, *J*=8.28 Hz, 1 H), 7.83 (d, 1 H), 7.64 (d, *J*=16.06 Hz, 1 H), 7.12 (d, *J*=16.31 Hz, 1 H), 5.82 (s, 2 H), 3.62 (t, *J*=8.28 Hz, 2 H), 2.62 (s, 3 H), 0.92 (t, *J*=8.28 Hz, 2 H), -0.05 (s, 9 H); MS ESI 400.2 [M + H]⁺, calcd for [C₂₀H₂₅N₃O₂SSi + H]⁺ 400.6.

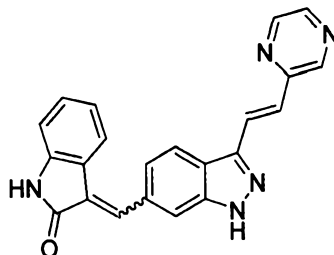
B. (E)-3-(2-(4-methylthiazol-5-yl)vinyl)-1H-indazole-6-carbaldehyde

A mixture of (E)-3-(2-(4-methylthiazol-5-yl)vinyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (30 mg, 0.075 mmol) and tetrabutylammonium fluoride (1.0 M in THF, 0.37 mL, 0.37 mmol) in anh. THF (10 mL) was refluxed under Ar for 1 d. The reaction mixture was then concentrated under reduced pressure and purified by prepTLC (SiO₂ 10 % MeOH/DCM) to provide the title compound (15 mg, 74 %) as a tan solid (7.0 mg, 21 %). MS ESI 270.0 [M + H]⁺, calcd for [C₁₄H₁₁N₃OS + H]⁺ 270.3.

C. (E)-3-((3-((E)-2-(4-methylthiazol-5-yl)vinyl)-1H-indazol-6-yl)methylene)-indolin-2-one

According to the method of Example A19, indolin-2-one (7.5 mg, 0.056 mmol) and 3(E)-3-(2-(4-methylthiazol-5-yl)vinyl)-1H-indazole-6-carbaldehyde (15 mg, 0.059 mmol) were reacted to obtain crude product. The crude mixture was concentrated under reduced pressure and triturated with DCM, followed by MeCN to provide the title compound as a yellow solid (3.0 mg, 13 %). ¹H NMR (400 MHz, DMF-*d*₇) δ ppm 13.67 (br. s., 1 H), 10.66 (br. s., 1 H), 9.01 (s, 1 H), 8.41 (d, *J*=8.03 Hz, 1 H), 7.86 (s, 1 H), 7.78 (d, *J* = 16.1 Hz, 1 H), 7.73 (d, *J*=8.03 Hz, 1 H), 7.61 (d, *J*=8.28 Hz, 1 H), 7.26 - 7.35 (m, 2 H), 7.02 (d, *J*=7.78 Hz, 1 H), 6.90 (t, *J*=7.28 Hz, 1 H), 2.62 (s, 3 H); MS ESI 385.1 [M + H]⁺, calcd for [C₂₂H₁₆N₄OS + H]⁺ 385.4.

Example A104 (E and Z)-3-((3-((E)-2-(pyrazin-2-yl)vinyl)-1H-indazol-6-yl)methylene)-indolin-2-one



A. *(E)-3-(2-(pyrazin-2-yl)vinyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde*

A degassed mixture of 3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (70 mg, 0.17 mmol), 2-vinylpyrazine (27 mg, 0.25 mmol), N-ethyl-N-isopropylpropan-2-amine (DIPEA, 45 mg, 0.35 mmol), Pd(OAc)₂ (3.9 mg, 0.017 mmol) and P(*o*-MeC₆H₄)₃ (16 mg, 0.052 mmol) in anhyd MeCN (2.5 mL) was heated with stirring in a sealed tube under microwave irradiation at 120 °C for 40 min. The crude mixture was later concentrated under reduced pressure and purified by prepTLC (SiO₂ 2:1 hexanes/EtOAc) to provide the title compound as a colorless solid (28 mg, 43 %): ¹H NMR (400 MHz, CDCl₃) δ ppm 10.18 (s, 1 H), 8.73 (s, 1 H), 8.60 (br. s., 1 H), 8.47 (d, *J*=2.26 Hz, 1 H), 8.14 - 8.18 (m, 2 H), 8.07 (d, *J*=16.06 Hz, 1 H), 7.84 (d, *J*=8.53 Hz, 1 H), 7.61 (d, *J*=16.31 Hz, 1 H), 5.85 (s, 2 H), 3.61 (t, *J*=8.28 Hz, 2 H), 0.94 (t, *J*=8.53 Hz, 2 H), -0.05 (s, 9 H); MS ESI 381.2 [M + H]⁺, calcd for [C₂₀H₂₄N₄O₂Si + H]⁺ 381.5.

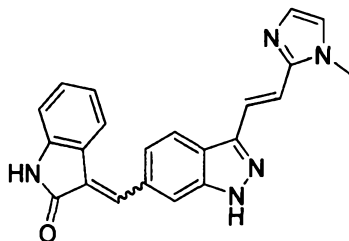
B. *(E)-3-((3-((E)-2-(pyrazin-2-yl)vinyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)methylene)indolin-2-one*

The title compound was synthesized according to the method of Example A19, utilizing indolin-2-one (10.0 mg, 0.075 mmol) and (E)-3-(2-(pyrazin-2-yl)vinyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (28 mg, 0.074 mmol). The crude mixture was concentrated under reduced pressure and purified by prepTLC (SiO₂ 2 % MeOH/DCM) to provide the title compound as a yellow material (20 mg, 55 %); MS ESI 496.3 [M + H]⁺, calcd for [C₂₈H₂₉N₅O₂Si + H]⁺ 496.6.

C. *(E & Z)-3-((3-((E)-2-(pyrazin-2-yl)vinyl)-1H-indazol-6-yl)methylene)indolin-2-one*

A degassed mixture of (E)-3-((3-((E)-2-(pyrazin-2-yl)vinyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)methylene)indolin-2-one (20 mg, 0.040 mmol) and tetrabutylammonium fluoride (1.0 M in THF, 0.6 mL, 0.6 mmol) in anh. THF (10 mL) was refluxed under Ar for 1 d. The reaction mixture was then concentrated under reduced pressure and purified by prepTLC (SiO₂ 12 % MeOH/DCM) and trituration with DCM to provide the title compound as a 1.5:1.0 (E:Z) mixture of isomers: a yellow solid (1.7 mg, 12 %). ¹H NMR (400 MHz, DMF-*d*₇) δ ppm 9.33 (s, 0.35 H), 9.16 (d, *J*=1.51 Hz, 1.0 H), 8.84 - 8.87 (m, 1.1 H), 8.70 (t, *J*=2.26 Hz, 1.0 H), 8.60 (d, *J*=8.78 Hz, 0.6 H), 8.51 (d, *J*=8.28 Hz, 0.45 H), 8.37 - 8.46 (m, 1.6 H), 8.26 (d, *J*=5.52 Hz, 1.0 H), 8.04 (s, 0.6 H), 8.02 (d, *J*=7.53 Hz, 0.39 H), 7.92 - 7.98 (m, 1.7 H), 7.79 (d, *J*=8.03 Hz, 0.60 H), 7.41 - 7.49 (m, 1.1 H), 7.05 - 7.25 (m, 2.1 H); MS ESI 366.2 [M + H]⁺, calcd for [C₂₂H₁₅N₅O + H]⁺ 366.4.

Example A105 (E and Z)-3-((3-((E)-2-(1-methyl-1H-imidazol-2-yl)vinyl)-1H-indazol-6-yl)methylene)indolin-2-one



A. (E)-3-(2-(1-methyl-1H-imidazol-2-yl)vinyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde

The title compound was synthesized according to the method of Example A103, utilizing 1-methyl-2-vinyl-1H-imidazole (35 mg, 0.32 mmol) and 3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (100 mg, 0.23 mmol). Purified by prepTLC (SiO₂ 10 % MeOH/DCM) to provide the title compound (15 mg, 74 %) as a tan oil (41.6 mg, 47 %). ¹H NMR (400 MHz, CD₃OD) δ ppm 10.09 (s, 1 H), 8.22 (t, *J*=1.00 Hz, 1 H), 8.13 (d, *J*= 8.53 Hz, 1 H), 7.78 (dd, *J*=8.53, 1.25 Hz, 1 H), 7.68 (d, *J*=16.06 Hz, 1 H), 7.43 (d, *J*=16.06 Hz, 1 H), 7.13 (d, *J*=1.25 Hz, 1 H), 7.05 (d, *J*=1.00 Hz, 1 H), 5.84 (s, 2 H), 4.89 (s, 3H), 3.63 (t, *J*=8.03 Hz, 1 H), 0.87 (t, *J*=8.03 Hz, 2 H), -0.10 (s, 9 H); MS ESI 383.2 [M + H]⁺, calcd for [C₂₀H₂₆N₄O₂Si + H]⁺ 383.5.

B. (E)-3-((3-((E)-2-(1-methyl-1H-imidazol-2-yl)vinyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)methylene)indolin-2-one

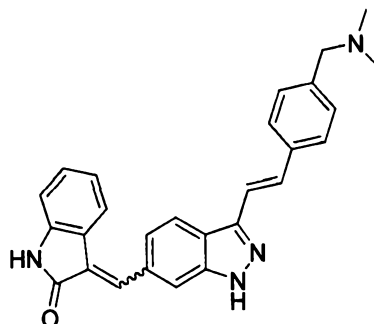
Synthesized according to the method of Example A19, utilizing indolin-2-one (14.5 mg, 0.11 mmol) and (E)-3-(2-(1-methyl-1H-imidazol-2-yl)vinyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (41.6 mg, 0.11 mmol).
 5 The crude mixture was concentrated under reduced pressure and purified by prepTLC (SiO₂ 10 % MeOH/DCM) to provide the title compound to as a yellow material (35.4 mg, 65%); MS ESI 498.4 [M + H]⁺, calcd for [C₂₈H₃₁N₅O₂Si + H]⁺ 498.7.

10 *C. (E and Z)-3-((3-((E)-2-(1-methyl-1H-imidazol-2-yl)vinyl)-1H-indazol-6-yl)methylene)-indolin-2-one hydrochloride*

A sealed, degassed mixture of (E)-3-((3-((E)-2-(1-methyl-1H-imidazol-2-yl)vinyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)methylene)indolin-2-one (35.4 mg, 0.071 mmol) in EtOH (4 mL) and aq HCl (4 M, 1 mL) was heated at 75-80 °C
 15 under Ar for 1 d. The reaction mixture was cooled to rt, diluted with MeCN (10 mL) and Et₂O (5 mL) and stored at -20 °C overnight. The precipitate was collected by filtration, washed with MeCN to provide the title compound as a 1.5:1.0 (E:Z) mixture of isomers: a yellow solid (14.5 mg, 51 %). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.93 (s, 0.44 H), 8.25 (d, J=8.28 Hz, 1.00 H), 8.13 (d, J=8.53 Hz, 0.65 H), 8.02
 20 - 8.06 (m, 0.45 H), 8.02 (s, 1.78 H), 7.92 - 8.00 (m, 1.78 H), 7.86 - 7.91 (m, 1.47 H), 7.58 - 7.71 (m, 5.0 H), 7.53 (d, J=16.81 Hz, 1.29 H), 7.25 (t, J=7.65 Hz, 1.52 H), 7.05 (t, J=7.78 Hz, 0.66 H), 6.94 (d, J=7.78 Hz, 1.01 H), 6.83 - 6.91 (m, 1.73 H), 4.04 (s, 2.46 H), 4.03 (s, 1.41 H); MS ESI 368.1 [M + H]⁺, calcd for [C₂₂H₁₇N₅O + H]⁺ 368.4.

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Example A106 (E and Z)-3-[(3-{(E)-2-[4-((dimethylamino)methyl)-phenyl]-ethenyl}-1H-indazol-6-yl)methylidene]-1,3-dihydro-2H-indol-2-one 2,2,2-trifluoroacetate



A. *(E)*-3-(4-((dimethylamino)methyl)styryl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde

The title compound was synthesized according to the method of Example A103, utilizing *N,N*-dimethyl-1-(4-vinylphenyl)methanamine (42 mg, 0.26 mmol) and 3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (70 mg, 0.17 mmol). Purified by prepTLC (SiO₂ 10 % MeOH/DCM) to provide the title compound to as a pale orange gum (33.4 mg, 44 %). ¹H NMR (400 MHz, CD₃OD) δ ppm 10.13 (s, 1 H), 8.27 (m, 2 H), 7.81 (d, *J*=9.29 Hz, 1 H), 7.69 (d, *J*=8.28 Hz, 2 H), 7.61 (d, *J*=16.6 Hz, 1 H), 7.50 (d, *J*=16.6 Hz, 1 H), 7.43 (d, *J*=8.28 Hz, 2 H), 5.86 (s, 2 H), 3.82 (s, 2 H), 3.62 (t, *J*=8.03 Hz, 1 H), 2.50 (s, 6 H), 0.87 (t, *J*=8.03 Hz, 2 H), -0.09 (s, 9 H); MS ESI 436.3 [M + H]⁺, calcd for [C₂₅H₃₃N₃O₂Si + H]⁺ 436.6.

B. *(E)*-3-((3-(4-((dimethylamino)methyl)styryl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)methylene)indolin-2-one

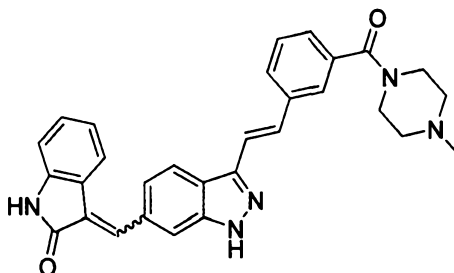
Synthesized according to the method of Example A19, utilizing indolin-2-one (10.4 mg, 0.078 mmol) and *(E)*-3-(4-((dimethylamino)methyl)styryl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (33.4 mg, 0.077 mmol). The crude mixture was concentrated under reduced pressure and purified by prepTLC (SiO₂ 10 % MeOH/DCM) to provide the title compound to as as a 1.5-2.0: 1.0 (E:Z) mixture of isomers: a yellow solid (29.1 mg, 67 %): ¹H NMR (400 MHz, CD₃OD) δ ppm 9.09 - 9.14 (s, 0.31 H), 8.22 (d, *J*=8.28 Hz, 0.84 H), 8.09 (d, *J*=8.53 Hz, 0.34 H), 7.83 - 7.87 (m, 1.25 H), 7.61 - 7.69 (m, 4.02 H), 7.56 - 7.60 (m, 1.69 H), 7.50 (s, 0.61 H), 7.36 - 7.48 (m, 3.85 H), 7.24 (t, *J*=7.78 Hz, 1.48 H), 7.03 (t, *J*=7.28 Hz, 0.48 H), 6.92 (d, *J*=7.53 Hz, 1.01 H), 6.81 - 6.89 (m, 1.49 H), 5.80 (s, 0.60 H), 5.78 (s, 1.52 H), 3.59 - 3.65 (m, 2.20 H), 2.37 - 2.42 (m, 7.40 H), 0.89 (t,

$J=8.28$ Hz, 3.05 H), -0.09 (s, 9 H); MS ESI 551.4 $[M + H]^+$, calcd for $[C_{33}H_{38}N_4O_2Si + H]^+$ 551.8.

C. (E and Z)-3-[(3-{(E)-2-[4-((dimethylamino)methyl)phenyl]-ethenyl}-1H-indazol-6-yl)methylidene]-1,3-dihydro-2H-indol-2-one 2,2,2-trifluoroacetate

- 5 The title compound was synthesized according to the method of Example A105-C utilizing (E)-3-((3-(4-((dimethylamino)methyl)styryl)-1-((2-(trimethylsilyl)ethoxy)-methyl)-1H-indazol-6-yl)methylene)indolin-2-one (29.1 mg, 0.052 mmol). The crude reaction mixture was concentrated under reduced pressure to dryness, triturated with Et₂O and DCM. Later the material was purified by prepTLC (SiO₂ 30 % MeOH/DCM) followed by prep HPLC to provide the title compound as a 1.7: 1.0 (E:Z) mixture of isomers: a yellow solid (1.8 mg, 6 %); ¹H NMR (400 MHz, D₂O) δ ppm 7.93 - 8.36 and 5.96 - 7.33 (m, 13 H), 3.82 (br. s., 2 H), 2.62 (br. s., 6 H); MS ESI 421.2 $[M + H]^+$, calcd for $[C_{27}H_{24}N_4O + H]^+$ 421.5.
- 10

- 15 Example A107 (E and Z)-3-((3-((E)-3-(4-methylpiperazine-1-carbonyl)styryl)-1H-indazol-6-yl)methylene)indolin-2-one 2,2,2-trifluoroacetate



A. (E)-3-((3-(4-methylpiperazine-1-carbonyl)styryl)-1-((2-(trimethylsilyl)ethoxy)-methyl)-1H-indazole-6-carbaldehyde

- 20 The title compound was synthesized according to the method of Example A103, utilizing 1-[(3-ethenylphenyl)carbonyl]-4-methylpiperazine (76 mg, 0.33 mmol) and 3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (100 mg, 0.25 mmol). Purified by prepTLC (SiO₂ 10 % MeOH/DCM) to provide the title compound to as a colorless material (30.1 mg, 24 %). ¹H NMR (400 MHz, CD₃OD) δ ppm 10.14 (s, 1 H), 8.27 (s, 1 H), 7.80 (m, 1 H), 7.71 (s, 1 H), 7.65 (d, $J=16.6$ Hz, 1 H), 7.56 - 7.60 (m, 1 H), 7.57 (s, 1 H), 7.48 - 7.55 (m, 2 H), 7.35 (d, $J=7.28$ Hz, 1 H), 5.86 (s, 2 H), 3.69 - 3.90 (m, 2 H), 3.63 (t, $J=7.91$ Hz, 2 H), 3.43 -
- 25

3.56 (m, 2 H), 2.40 - 2.64 (m, 4 H), 2.35 (s, 3 H), 0.88 (t, $J=7.91$ Hz, 2 H), -0.09 (m, 9 H); MS ESI 505.4 $[M + H]^+$, calcd for $[C_{28}H_{36}N_4O_3Si + H]^+$ 505.7.

B. (3E & 3Z)-3-((3-((E)-3-(4-methylpiperazine-1-carbonyl)styryl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-5-yl)methylene)indolin-2-one

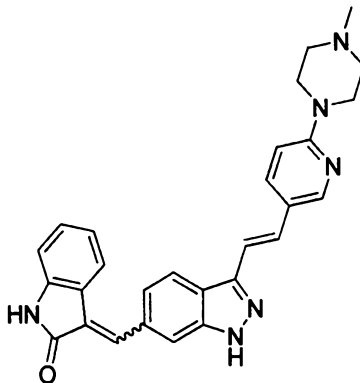
5 The title compound was synthesized according to the method of Example A19, utilizing indolin-2-one (7.9 mg, 0.059 mmol) and (E)-3-(3-(4-methylpiperazine-1-carbonyl)-styryl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (30.1 mg, 0.060 mmol). The crude mixture was concentrated under reduced pressure and purified by prepTLC (SiO₂ 10 % MeOH/DCM) to provide the title compound as
 10 a ~2.5:1 (E:Z) mixture of isomers: a yellow solid (21.6 mg, 59 %): ¹H NMR (400 MHz, CD₃OD) δ ppm 9.06 (s, 0.22 H), 8.20 (d, $J=8.28$ Hz, 0.72 H), 8.07 (d, $J=8.53$ Hz, 0.27 H), 7.94 - 7.96 (m, 0.98 H), 7.92 (d, $J=9.0$ Hz, 0.82 H), 7.84 (s, 0.82 H), 7.72 - 7.79 (m, 2.53 H), 7.45-7.66 H), 7.31 - 7.36 (m, 1.29 H), 7.18 - 7.25 (m, 1.30 H), 7.01 (t, $J=7.40$ Hz, 0.42 H), 6.90 (d, $J=7.78$ Hz, 0.83 H), 5.78 (s., 0.57 H), 5.77
 15 (s, 1.24 H), 3.75-3.90 (m, 2.28 H), 3.58-3.68 (m, 2.63 H), 3.45-3.57 (m, 2.43 H), 2.39 - 2.62 (m, 4.67 H), 2.36 (s, 3.53 H), 0.84-0.93 (t, $J=7.91$ Hz, 2.63 H), -0.09 (s, 9.81 H); MS ESI 505.4 $[M - CH_2CH_2SiMe_3 - Me + H]^+$, calcd for $[C_{30}H_{26}N_5O_3 + H]^+$ 505.6.

C. (E and Z)-3-((3-((E)-3-(4-methylpiperazine-1-carbonyl)styryl)-1H-indazol-6-yl)methylene)indolin-2-one 2,2,2-trifluoroacetate

20 A degassed mixture of (3E)-3-((3-((E)-3-(4-methylpiperazine-1-carbonyl)styryl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-5-yl)methylene)indolin-2-one (21.6 mg, 0.035 mmol), tetrabutylammonium fluoride (1.0 M in THF, 0.05 mL, 0.05 mmol) and activated molecular sieves (4 Å) in anh. THF (5 mL) was refluxed under
 25 Ar for 1 d. The reaction mixture diluted with MeOH, filtered, concentrated under reduced pressure and purified by prepHPLC to provide the title compound as a ~4:1 (E:Z) mixture of isomers: a yellow solid (2.8 mg, 14 %). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.88 (s, 0.28 H), 8.26 (d, $J=8.28$ Hz, 1.00 H), 8.15 (d, $J=8.28$ Hz, 0.29 H), 7.98 (d, $J=8.28$ Hz, 0.37 H), 7.88 - 7.91 (m, 1.65 H), 7.82 - 7.87 (m, 1.51
 30 H), 7.79 (s, 1.14 H), 7.52 - 7.71 (m, 5.35 H), 7.42 (d, $J=7.53$ Hz, 1.13 H), 7.25 (t, $J=7.78$ Hz, 1.19 H), 7.05 (d, $J=7.53$ Hz, 0.28 H), 6.94 (d, $J=8.03$ Hz, 1.01 H), 6.84 -

6.91 (m, 1.15 H), 3.36 - 3.81 (m, 4.22 H), 3.06 - 3.28 (m, ~4 H), 2.98 (s, 3.42 H);
MS ESI 490.3 $[M + H]^+$, calcd for $[C_{30}H_{27}N_5O_2 + H]^+$ 490.6.

A108 (E and Z)-3-((3-((E)-2-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)vinyl)-1H-indazol-6-yl)methylene)indolin-2-one



A. 1-Methyl-4-(5-vinylpyridin-2-yl)piperazine

A sealed, degassed mixture of powdered KOH (123 mg, 2.2 mmol) and 1,2-dibromoethane (0.05 mL, 0.6 mmol) in anhyd THF (2 mL) under Ar was heated under microwave irradiation at 95 °C for 70 min. The reaction mixture was then cooled to rt and treated with $Pd(OAc)_2$ (5.0 mg, 0.022 mmol), PPh_3 (11.5 mg, 0.044 mmol), 1-methyl-4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine (120 mg, 0.39 mmol) and degassed MeOH (2 mL). The sealed reaction mixture was heated again under microwave irradiation at 95 °C for 60 min. The crude mixture was concentrated under reduced pressure and purified by prepTLC (SiO_2 10 % MeOH/DCM) to provide the title compound a colorless gum (0.18 g, quant): 1H NMR (400 MHz, CD_3OD) δ ppm 8.07 (d, $J=2.26$ Hz, 1 H), 7.73 (dd, $J=8.91, 2.38$ Hz, 1 H), 6.82 (d, $J=9.03$ Hz, 1 H), 6.62 (dd, $J=17.82, 11.04$ Hz, 1 H), 5.63 (d, 1 H), 5.12 (d, $J=10.79$ Hz, 4 H), 3.52 - 3.66 (m, 4 H), 2.50 - 2.61 (m, 4 H), 2.35 (s, 3 H); MS ESI 204.0 $[M + H]^+$, calcd for $[C_{12}H_{17}N_3 + H]^+$ 204.3.

B. (E)-3-(2-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)vinyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde

The title compound was synthesized according to the method of Example A103, utilizing 1-methyl-4-(5-vinylpyridin-2-yl)piperazine (65 mg, 0.32 mmol) and 3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (100 mg,

0.25 mmol). Purified by prepTLC (SiO₂ 10 % MeOH/DCM) to provide the title compound as a pale orange material (46 mg, 39 %). ¹H NMR (400 MHz, CD₃OD) δ ppm 10.14 (s, 1 H), 8.34 (d, *J*=2.26 Hz, 1.0 H), 8.24 - 8.28 (m, 2 H), 8.00 (dd, *J*=8.91, 2.38 Hz, 1 H), 7.80 (d, *J*=8.78 Hz, 1 H), 7.51 (d, *J*=16.56 Hz, 1 H), 7.36 (d, *J*=16.56 Hz, 1 H), 6.97 (d, *J*=9.29 Hz, 1 H), 5.85 (s, 2 H), 3.77 - 3.87 (m, 4 H), 3.63 (t, *J*=7.91 Hz, 2 H), 3.06 - 3.15 (m, 4 H), 2.75 (s, 3 H), 0.88 (t, *J*=8.03 Hz, 2 H), -0.09 (s, 9 H); MS ESI 478.3 [M + H]⁺, calcd for [C₂₆H₃₅N₅O₂Si + H]⁺ 478.7.

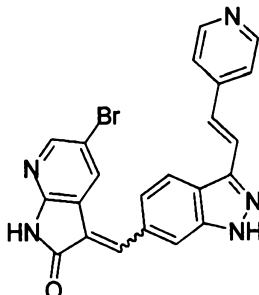
C. (E & Z)-3-((3-((E)-2-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)vinyl)-1H-indazol-6-yl)methylene)-1-((2-(trimethylsilyl)ethoxy)methyl)indolin-2-one

The title compound was synthesized according to the method of Example A19, utilizing indolin-2-one (8.3 mg, 0.062 mmol) and (E)-3-(2-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)vinyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (46 mg, 0.096 mmol). The crude mixture was concentrated under reduced pressure and purified by prepTLC (SiO₂ 10 % MeOH/DCM) to provide the title compound as a (E:Z) mixture of isomers: a yellow solid (22.5 mg, 40 %); MS ESI 593.4 [M + H]⁺, calcd for [C₃₄H₄₀N₆O₂Si + H]⁺ 593.8.

D. (E & Z)-3-((3-((E)-2-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)vinyl)-1H-indazol-6-yl)methylene)indolin-2-one dihydrochloride

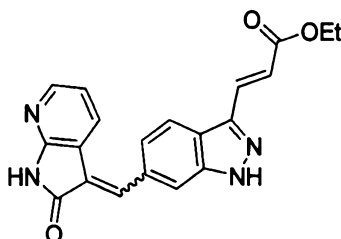
The title compound was prepared according to the method of Example A105-C utilizing (E & Z)-3-((3-((E)-2-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)vinyl)-1H-indazol-6-yl)-methylene)-1-((2-(trimethylsilyl)ethoxy)methyl)indolin-2-one (22.5 mg, 0.038 mmol). The crude reaction mixture was stored at -20 °C overnight. The precipitate was collected by filtration, washed with MeCN to provide the title compound as a ~4:1 (E:Z) mixture of isomers: a yellow solid (6.9 mg, 34 %). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.87 (s, 0.16 H), 8.56 (d, *J*=9.54 Hz, 1.0 H), 8.33 (s, 0.95 H), 8.26 (d, *J*=8.28 Hz, 0.72 H), 8.14 (d, *J*=9.54 Hz, 0.23 H), 7.98 (d, *J*=8.53 Hz, 0.20 H), 7.85 - 7.91 (m, 1.56 H), 7.68 (d, *J*=7.03 Hz, 0.25 H), 7.65 (d, *J*=7.78 Hz, 0.86 H), 7.50 - 7.61 (m, 3.31 H), 7.25 (t, *J*=7.53 Hz, 1.03 H), 7.05 (t, *J*=8.03 Hz, 0.24 H), 6.94 (d, *J*=7.53 Hz, 0.73 H), 6.84 - 6.91 (m, 0.93 H), 4.49 (br. s., 1.66 H), 3.73 (br. s., 3.84 H), 3.34 - 3.52 (m, 1.47 H), 3.03 (s, 2.78 H); MS ESI 463.2 [M + H]⁺, calcd for [C₂₈H₂₆N₆O + H]⁺ 462.5.

Example A109: (E and Z)-5-bromo-3-((3-((E)-2-(pyridin-4-yl)vinyl)-1H-indazol-6-yl)methyl-ene)-1H-pyrrolo[2,3-b]pyridin-2(3H)-one



The title compound (64 mg, 64 %) was synthesized as a greenish yellow solid according to the method described for Example A67 (oil temp 75 °C, reflux 2 h) using 5-bromo-1H-pyrrolo[2,3-b]pyridin-2(3H)-one (42.6 mg, 0.2 mmol) and (E)-3-(2-(pyridin-4-yl)vinyl)-1H-indazole-6-carbaldehyde (49.8 mg, 0.2 mmol). ¹H NMR indicated 7:6 mixture of E/Z isomers. ¹H NMR (400 MHz, DMSO-d₆) δ 8.57 (d, J = 5.2 Hz, 2H), 8.34 (d, J = 8.4 Hz, 1H), 8.26 (d, 1H), 8.22 (s, 1H), 8.12 (d, J = 8.8 Hz, 1H), 8.03 (s, 1H), 7.93 (d, 1H), 7.89 (d, J = 16.8 Hz, 1H), 7.72 (t, J = 4.8 Hz, 2H), 7.55 (d, J = 16.0 Hz, 1H); MS ESI 444.3 [M + H]⁺, calcd for [C₂₂H₁₄BrN₅O + H]⁺ 444.0.

Example A110: (E and Z)-ethyl 3-(6-((E)-2-oxo-1H-pyrrolo[2,3-b]pyridin-3(2H)-ylidene)methyl)-1H-indazol-3-yl)acrylate

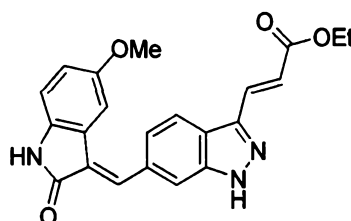


The title compound (46 mg, 64 %) was synthesized as a brown solid according to the method described for Example A67 (oil temp 75 °C, reflux 2 h) using 1H-pyrrolo[2,3-b]pyridin-2(3H)-one (26.8 mg, 0.2 mmol) and (E)-ethyl 3-(6-formyl-1H-indazol-3-yl)acrylate (48.8 mg, 0.2 mmol). ¹H NMR indicated 7:3 mixture of E/Z isomers. ¹H NMR (400 MHz, DMSO-d₆) δ 13.30 (br. s, 1H, NH), 11.20 (br. s, 1H, NH), 8.26 (d, J = 8.8 Hz, 1H), 8.11 (d, J = 5.5 Hz, 1H, partially overlapping with the peak at 8.09 ppm), 8.09 (d, J = 6.4 Hz, 1H, partially

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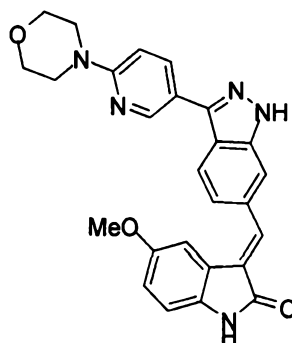
overlapping with the peak at 8.11 ppm), 7.95 (d, $J = 17.2$ Hz, 1H, partially overlapping with the peak at 7.93 ppm), 7.93 (s, 1H, partially overlapping with the peak at 7.95 ppm), 7.87 (d, $J = 7.6$ Hz, 1H), 7.56 (d, $J = 8.0$ Hz, 1H), 6.90 (dd, $J = 7.6$ Hz, 4.8 Hz, 1H), 6.81 (d, $J = 16.4$ Hz, 1H), 4.23 (q, $J = 6.8$ Hz, 2H), 1.29 (t, $J = 6.8$ Hz, 3H); MS ESI 361.1 $[M + H]^+$, calcd for $[C_{20}H_{16}N_4O_3 + H]^+$ 361.1.

Example A111: (E)-ethyl 3-(6-((E)-(5-methoxy-2-oxoindolin-3-ylidene)methyl)-1H-indazol-3-yl)acrylate



The title compound (60 mg, 77 %) was synthesized as an orange red solid according to the method described for Example A67 (oil temp 75 °C, reflux 2 h) using 5-methoxyoxindole (26.8 mg, 0.2 mmol) and (E)-ethyl 3-(6-formyl-1H-indazol-3-yl)acrylate (48.8 mg, 0.2 mmol). 1H NMR (400 MHz, DMSO- d_6) δ 13.80 (brs, 1H, NH), 10.44 (s, 1H, NH), 8.26 (d, $J = 8.4$ Hz, 1H), 7.96 (s, 1H), 7.92 (d, $J = 16.4$ Hz, 1H), 7.77 (s, 1H), 7.56 (d, $J = 8.4$ Hz, 1H), 7.14 (d, 1H), 6.90-6.80 (m, 3H), 4.23 (q, $J = 7.2$ Hz, 2H), 3.58 (s, 3H), 2.29 (t, $J = 7.2$ Hz, 3H); MS ESI 390.3 $[M + H]^+$, calcd for $[C_{22}H_{19}N_3O_4 + H]^+$ 390.1.

Example A112. (E)-5-methoxy-3-((3-(6-morpholinopyridin-3-yl)-1H-indazol-6-yl)-methylene)indolin-2-one



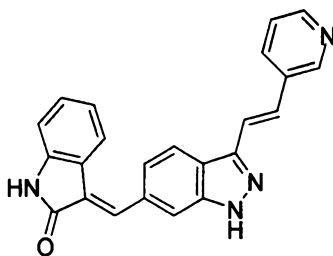
A. 3-(6-morpholinopyridin-3-yl)-1H-indazole-6-carbaldehyde

According to procedure for the synthesis of 3-(pyridin-3-yl)-1H-indazole-6-carbaldehyde, except substituting 2-(4-morpholino)pyridine-5-boronic acid pinacol ester (64 mg, 0.22 mmol), the title compound was prepared as a yellow powder (35 mg, 62%). ¹H NMR (400 MHz, d₆-DMSO) δ ppm 13.71 (br s, 1H), 10.14 (s, 1 H), 8.77 (d, J = 1.9 Hz, 1 H), 8.02-8.18 (m, 2H), 8.15 (dd, J = 8.9 Hz, 2.5, 1H), 7.64 (d, J = 8.6 Hz, 1H), 7.00 (d, J = 8.8 Hz, 1H), 3.73 (t, J = 4.5 Hz, 4H), 3.53 (t, J = 5.1 Hz, 4H); MS ESI 309.1 (100) [M + H]⁺, calcd for [C₁₇H₁₆N₄O₂ + H]⁺ 309.13.

B. (E)-5-methoxy-3-((3-(6-morpholinopyridin-3-yl)-1H-indazol-6-yl)methylene)-indolin-2-one

- 10 According to procedure for the synthesis of (E)-3-((1H-indazol-6-yl)methylene)indolin-2-one, except substituting 3-(6-morpholinopyridin-3-yl)-1H-indazole-6-carbaldehyde (35 mg, 0.11 mmol), the title compound was prepared as an orange powder (22 mg, 42 %). ¹H NMR (400 MHz, d₆-DMSO) δ 13.37 (br s, 1H), 10.43 (br s, 1H), 8.79 (d, J = 2.2 Hz, 1H), 8.17 (d, J = 8.6 Hz, 2H), 7.93 (s, 1H), 7.79 (s, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.21 (d, J = 1.8 Hz, 1H), 7.00 (d, J = 9.0 Hz, 1H), 6.85 (dd, J = 8.5, 2.0 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 3.73 (t, J = 4.6 Hz, 4H), 5.59 (s, 3H), 3.53 (t, J = 4.8 Hz, 4H); MS ESI 454.3 [M + H]⁺, calcd for [C₂₆H₂₃N₅O₂ + H]⁺ 454.18.
- 15

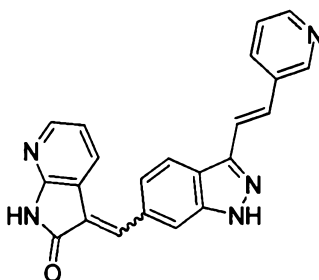
- 20 Example A113: (E)-3-((3-((E)-2-(pyridin-3-yl)vinyl)-1H-indazol-6-yl)methylene)-indolin-2-one



- The title compound (61 mg, 84 %) was synthesized as a yellow solid according to the method described for Example A67 (oil temp 75 °C, reflux 90 min) using oxindole (26.6 mg, 0.2 mmol) and (E)-3-(2-(pyridin-3-yl)vinyl)-1H-indazole-6-carbaldehyde (49.8 mg, 0.2 mmol). ¹H NMR (400 MHz, DMSO-d₆) δ 13.46 (s, 1H, NH), 10.64 (s, 1H, NH), 8.91 (s, 1H), 8.48 (d, J = 4.4 Hz, 1H), 8.36 (d, J = 8.4 Hz, 1H), 8.20 (d, J = 8.4 Hz, 1H), 7.90 (s, 1H), 7.80 (s, 1H), 7.73 (d, J = 16.8 Hz,
- 25

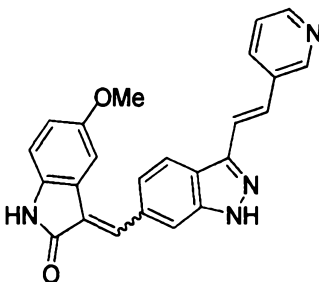
1H), 7.61 (d, J = 7.2 Hz, 1H, partially overlapping with the peak at 7.60 ppm), 7.60 (d, J = 17.2 Hz, 1H, partially overlapping with the peak at 7.61 ppm), 7.54 (d, J = 8.4 Hz, 1H), 7.43 (dd, J = 7.8 Hz, 4.8 Hz, 1H), 7.24 (t, J = 7.8 Hz, 1H), 6.89 (d, J = 7.6 Hz, 1H), 6.85 (t, J = 7.8 Hz, 1H); MS ESI 365.1 [M + H]⁺, calcd for [C₂₃H₁₆N₄O + H]⁺ 365.1.

Example A114: (E and Z)-3-((3-((E)-2-(pyridin-3-yl)vinyl)-1H-indazol-6-yl)methylene)-1H-pyrrolo[2,3-b]pyridin-2(3H)-one



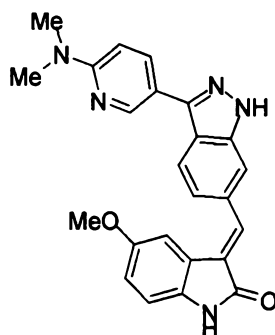
The title compound (59 mg, 81 %) was synthesized as an orange solid according to the method described for Example A67 (oil temp 75 °C, reflux 90 min) using 1H-pyrrolo[2,3-b]pyridin-2(3H)-one (26.8 mg, 0.2 mmol) and (E)-3-(2-(pyridin-3-yl)vinyl)-1H-indazole-6-carbaldehyde (49.8 mg, 0.2 mmol). ¹H NMR indicated 5:2 mixture of Z/E isomers. ¹H NMR (400 MHz, DMSO-d₆) δ 13.60 (s, 1H, NH), 11.30 (s, 1H, NH), 8.95 (s, 1H), 8.91 (d, 1H), 8.47 (d, J = 4.4 Hz, 1H), 8.31 (d, J = 8.4 Hz, 1H), 8.19 (d, J = 7.2 Hz, 1H), 8.13-8.07 (m, 4H), 7.72 (d, J = 16.8 Hz, 1H), 7.59 (d, J = 17.2 Hz, 1H), 7.42 (dd, J = 8.0 Hz, 4.4 Hz, 1H), 7.50 (dd, J = 7.2 Hz, 5.6 Hz, 1H); MS ESI 444.3 [M + H]⁺, calcd for [C₂₂H₁₅N₅O + H]⁺ 366.1.

Example A115: (E and Z)-5-methoxy-3-((3-((E)-2-(pyridin-3-yl)vinyl)-1H-indazol-6-yl)methylene)indolin-2-one



The title compound (53 mg, 67 %) was synthesized as an orange red solid according to the method described for Example A67 (oil temp 75 °C, reflux 90 min) using 5-methoxyoxindole (32.6 mg, 0.2 mmol) and (E)-3-(2-(pyridin-3-yl)vinyl)-1H-indazole-6-carbaldehyde (49.8 mg, 0.2 mmol). ¹H NMR indicated 4:1 mixture of E/Z isomers. ¹H NMR (400 MHz, DMSO-d₆) δ 13.50 (br. s, 1H, NH), 10.44 (s, 1H, NH), 8.91 (d, 1H), 8.48 (d, J = 4.8 Hz, 1H), 8.36 (d, J = 8.4 Hz, 1H), 8.20 (d, J = 7.6 Hz, 1H), 7.92 (s, 1H), 7.79 (s, 1H), 7.73 (d, J = 16.8 Hz, 1H), 7.59 (d, J = 16.4 Hz, 1H), 7.54 (d, J = 8.8 Hz, 1H), 7.43 (dd, J = 8.0 Hz, 5.2 Hz, 1H), 7.19 (d, 1H), 6.86 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 3.78 (s, 3H); MS ESI 395.2 [M + H]⁺, calcd for [C₂₄H₁₈N₄O₂ + H]⁺ 395.1.

Example A116. (E)-3-((3-(6-(dimethylamino)pyridin-3-yl)-1H-indazol-6-yl)methylene)-5-methoxyindolin-2-one



A. 3-(6-(dimethylamino)pyridin-3-yl)-1H-indazole-6-carbaldehyde

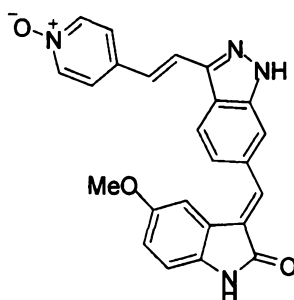
According to the procedure for the synthesis of 3-(pyridin-3-yl)-1H-indazole-6-carbaldehyde, except substituting 2-(dimethylamino)pyridine-5-boronic acid hydrate (41 mg, 0.22 mmol), the title compound was prepared as a yellow powder (14 mg, 29%). ¹H NMR (400 MHz, d₆-DMSO) δ ppm 10.13 (s, 1 H), 8.72 (d, J = 2.4 Hz, 1 H), 8.17-8.16 (m, 2H), 8.09 (dd, J = 8.4, 2.1 Hz, 1H), 7.62 (d, J = 8.9 Hz, 1H), 6.79 (d, J = 8.8 Hz, 1H), 3.09 (s, 6H); MS ESI 267.0 (100) [M + H]⁺, calcd for [C₁₅H₁₄N₄O + H]⁺ 267.12.

B. (E)-3-((3-(6-(dimethylamino)pyridin-3-yl)-1H-indazol-6-yl)methylene)-5-methoxyindolin-2-one

According to the procedure for the synthesis of (E)-3-((1H-indazol-6-yl)methylene)-indolin-2-one, except substituting 3-(6-(dimethylamino)pyridin-3-yl)-

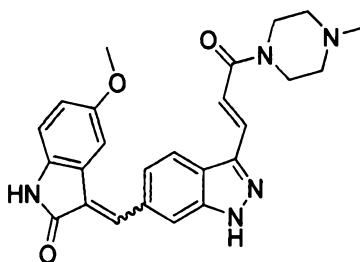
1H-indazole-6-carbaldehyde (14 mg, 0.053 mol), the title compound was prepared as a red solid (2.9 mg, 13 %). ¹H NMR (400 MHz, d₆-DMSO) δ 13.30 (br. s, 1H), 10.43 (br s, 1H), 8.75 (s, 1H), 8.15 (d, J = 8.7 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.92 (s, 1H), 7.78 (s, 1H), 7.47 (d, J = 7.7 Hz, 1H), 7.22 (s, 1H), 6.86-6.79 (m, 3H), 3.60 (s, 3H), 3.10 (s, 6H); MS ESI 412.2 [M + H]⁺, calcd for [C₂₄H₂₁N₅O₂ + H]⁺

Example A117. 4-((E)-2-(6-((E)-(5-methoxy-2-oxoindolin-3-ylidene)methyl)-1H-indazol-3-yl)vinyl)pyridine 1-oxide



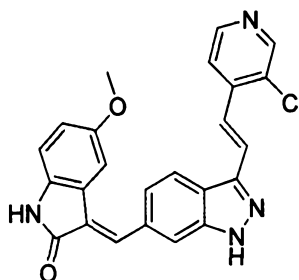
According to the procedure for the synthesis of 2-((E)-2-(6-((E)-(5-methoxy-2-oxoindolin-3-ylidene)methyl)-1H-indazol-3-yl)vinyl)pyridine 1-oxide (Example A88), except substituting (E)-5-methoxy-3-((3-((E)-2-(pyridin-4-yl)vinyl)-1H-indazol-6-yl)methyl-ene)indolin-2-one (8.1 mg, 0.021 mmol), the title compound was prepared as an orange solid (1.3 mg, 15 %). ¹H NMR (400 MHz, DMSO-d₆) δ 13.55 (br. s, 1H), 10.45 (s, 1H), 8.35 (d, J = 8.6 Hz, 1H), 8.20 (d, J = 6.8 Hz, 2H), 7.93 (s, 1H), 7.79-7.72 (m, 4H), 7.55 (d, J = 14.3 Hz, 1H), 7.54 (d, J = 8.9 Hz, 1H), 7.17 (d, J = 2.7 Hz, 1H), 6.86 (dd, J = 8.5, 2.7 Hz, 1H), 6.80 (d, J = 8.5 Hz, 1H), 3.60 (s, 3H); MS ESI 411.2 [M + H]⁺, calcd for [C₂₄H₁₈N₄O₃ + H]⁺ 411.14.

Example A118. (E and Z)-5-methoxy-3-((3-((E)-3-(4-methylpiperazin-1-yl)-3-oxoprop-1-enyl)-1H-indazol-6-yl)methylene)indolin-2-one



The synthetic method followed that described in Example A66 starting from 5-methoxyoxindole (10 mg, 0.0583 mmol) and (E)-3-(3-(4-methylpiperazin-1-yl)-3-oxoprop-1-enyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (25 mg, 0.0583 mmol) to give 2.5 mg of the title compound as an 85:15 mixture of (E)/(Z) isomers. ¹H NMR (400 MHz, CD₃OD) 8.95, 7.80 (s, 1H), 8.21-8.16 (m, 1H), 7.97-7.87 (m, 2H), 7.59 (d, J = 7.52 Hz, 1H), 7.45 (d, J = 15.7 Hz, 1H), 7.32, 7.22 (s, 1H), 6.85 (s, 2H), 3.84, 3.63 (s, 3H), 3.90-3.75 (m, 4H), 2.62-2.48 (br. s, 4H), 2.34 (s, 3H); MS ESI 444.2 [M + H]⁺, calcd for [C₂₅H₂₅N₅O₃ + H]⁺ 444.20.

10 Example A119. (E)-3-((3-((E)-2-(3-chloropyridin-4-yl)vinyl)-1H-indazol-6-yl)methyl-ene)-5-methoxyindolin-2-one



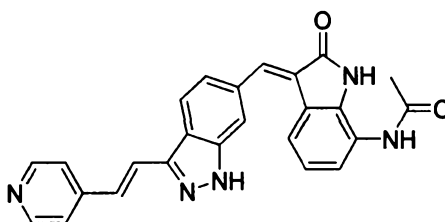
A. 3-chloro-4-vinylpyridine

A dry round-bottom flask containing with methyltriphenylphosphonium iodide (632 mg, 1.77 mmol) and THF (25 mL) was cooled with an ice-water bath and the suspension treated with *n*-BuLi (1.0 mL of a 1.6M solution in hexanes) and the reaction stirred for 0.5 hours. The solution was cooled to -78 °C and 3-chloroisonicotinaldehyde (250 mg, 1.77 mmol) was added portion-wise and then the reaction was allowed to warm to room temperature over 4 hours. The reaction was quenched with AcOH (0.10 mL) and the THF removed *in vacuo*. The residue was dissolved in EtOAc and then washed with water (2X), and brine (2X), the organic layer dried (MgSO₄) and the EtOAc was removed. The residue was purified by column chromatography, silica gel (99:1 to 98:2 CH₂Cl₂ / MeOH) to give the title compound (135 mg, 55 %) as a yellow oil. MS ESI 140.0 [M + H]⁺, calcd for [C₇H₆ClN + H]⁺ 140.03.

B. (E)-3-((3-((E)-2-(3-chloropyridin-4-yl)vinyl)-1H-indazol-6-yl)methylene)-5-methoxyindolin-2-one

The synthetic method followed that described in Example A57 starting from 3-chloro-4-vinylpyridine (42 mg, 0.299 mmol) and 3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (100 mg, 0.249 mmol) with a modified purification procedure. The title compound was purified by prep-HPLC to give 4.0 mg of an orange-red powder. ¹H NMR (400 MHz, CD₃OD) δ 8.97 (s, 1H), 8.67 (s, 1H), 8.50 (d, J = 5.20 Hz, 1H), 8.11-7.84 (m, 6H), 7.33 (s, 1H), 6.86-6.78 (m, 2H), 3.85 (s, 3H); MS ESI 429.2 [M + H]⁺, calcd for [C₂₄H₁₇ClN₄O₂ + H]⁺ 429.11.

10 Example A120: N-((E)-2-oxo-3-((3-((E)-2-(pyridin-4-yl)vinyl)-1H-indazol-6-yl)methylene)indolin-7-yl)acetamide



A.

N-((E)-2-oxo-3-((3-((E)-2-(pyridin-4-yl)vinyl)-1-((2-(trimethylsilyl)ethoxy)-methyl)-1H-indazol-6-yl)methylene)indolin-7-yl)acetamide

15 According to the method of A57B, N-(2-oxoindolin-7-yl)acetamide (30 mg, 0.16 mmol) was reacted with (E)-3-(2-(pyridin-4-yl)vinyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (60 mg, 0.16 mmol) to give the title compound as an orange solid (64 mg, 72%). MS ESI 552.3 [M + H]⁺, calcd for [C₃₁H₃₃N₅O₃Si + H]⁺ 552.2.

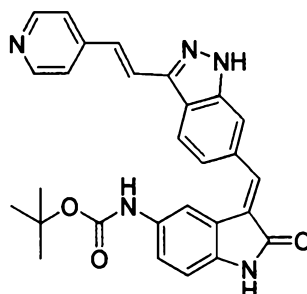
20

B.

N-((E)-2-oxo-3-((3-((E)-2-(pyridin-4-yl)vinyl)-1H-indazol-6-yl)methylene)-indolin-7-yl)acetamide

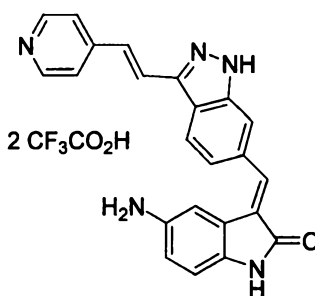
According to the method of A57C, N-((E)-2-oxo-3-((3-((E)-2-(pyridin-4-yl)vinyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)methylene)indolin-7-yl)acetamide (64 mg, 0.11 mmol) was treated with boron trifluoride etherate, followed by 2 N HCl to give the title compound as an orange solid (33 mg, 71%). ¹H NMR (400 MHz, d⁶-DMSO) δ 10.33 (s, 1H), 9.42 (s, 1H), 8.85 (d, J = 6.2 Hz, 2H), 8.46-8.30 (m, 4H), 7.98 (s, 1H), 7.87-7.78 (m, 2H), 7.80 (s, 1H), 7.63 (d, J = 8.2 Hz, 1H), 7.42-7.35 (m, 2H), 6.81 (t, J = 8.1 Hz, 1H), 2.05 (s, 3H); MS ESI 422.1 [M + H]⁺, calcd for [C₂₅H₁₉N₅O₂ + H]⁺ 422.2.

Example A121: *tert*-butyl (E)-2-oxo-3-((3-((E)-2-(pyridin-4-yl)vinyl)-1H-indazol-6-yl)methylene)indolin-5-ylcarbamate



5 The title compound (102 mg, 76 %) was synthesized as orange-yellow solid according to the method described for Example A11B from *tert*-butyl 2-oxoindolin-5-ylcarbamate (70 mg, 0.282 mmol) and (E)-3-(2-(pyridin-4-yl)vinyl)-1H-indazole-6-carbaldehyde (70 mg, 0.282 mmol). ¹H NMR (400 MHz, d₆-DMSO) δ 13.53 (s, 1H), 10.47 (s, 1H), 9.14 (s, 1H), 8.55 (d, J = 6.5 Hz, 2H), 8.33 (d, J = 8.8 Hz, 1H), 7.88-7.83 (m, 3H), 7.74 (s, 2H), 7.69 (d, J = 6.5 Hz, 2H), 7.56-7.50 (m, 2H), 6.75 (d, J = 8.2 Hz, 1H), 1.34 (s, 9H); MS ESI 480.3 [M + H]⁺, calcd for [C₂₈H₂₅N₅O₃ + H]⁺ 480.20.

15 Example A122: (E)-5-amino-3-((3-((E)-2-(pyridin-4-yl)vinyl)-1H-indazol-6-yl)methylene)indolin-2-one bis(2,2,2-trifluoroacetate)

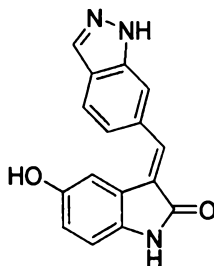


tert-Butyl (E)-2-oxo-3-((3-((E)-2-(pyridin-4-yl)vinyl)-1H-indazol-6-yl)methylene)indolin-5-ylcarbamate (13 mg, 0.027 mmol) was dissolved into CH₂Cl₂ (1.0 mL) and then trifluoroacetic acid (0.1 mL) was added and the reaction stirred for 1 hour. The solvent was removed and the residue titrated with ether/EtOAc to give after drying 4.6 mg, 29 % of the title compound as an orange powder. ¹H NMR (400 MHz, CD₃OD) δ 8.68 (d, J = 5.8 Hz, 2H), 8.31 (d, J = 8.7 Hz, 1H), 8.21-8.12

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(m, 3H), 7.97 (s, 1H), 7.88 (s, 1H), 7.70 (d, J = 16.8 Hz, 1H), 7.62-7.57 (m, 2H), 7.18 (d, J = 8.8 Hz, 1H), 6.99 (d, J = 8.6 Hz, 1H); MS ESI 380.1 [M + H]⁺, calcd for [C₂₃H₁₇N₅O + H]⁺ 380.15.

5 Example A123: (E)-3-((1H-indazol-6-yl)methylene)-5-hydroxyindolin-2-one



A. *5-Hydroxyindolin-2-one*

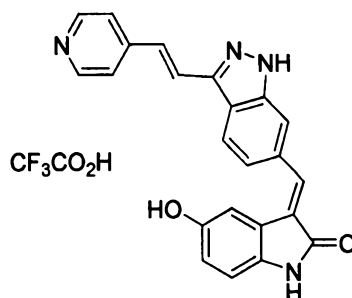
An oven-dried flask was charged with BBr₃.SMe₂ (2.80 g, 9.20 mmol) and 1,2-dichloroethane (15 mL). 5-Methoxyindolin-2-one (0.30g, 1.84 mmol) was then added and the mixture was heated to reflux for 18 hours. The reaction was then cooled to room temperature and quenched with MeOH (1.0 mL). The mixture was then extracted into EtOAc washing with brine (3X). The organic layer was dried over MgSO₄, filtered and the solvent removed *in vacuo*; the resulting residue was then purified by column chromatography (silica gel, 94:6 to 92:8, CH₂Cl₂/MeOH) to give 144 mg, 53 % of a beige powder. MS ESI 149.9 [M + H]⁺, calcd for [C₈H₇NO₂ + H]⁺ 150.06

B. *(E)-3-((1H-indazol-6-yl)methylene)-5-hydroxyindolin-2-one*

The title compound was synthesized according to the method described for Example A11B from 5-Hydroxyindolin-2-one (16 mg, 0.107 mmol) and precipitation with 98:2 CH₂Cl₂/MeOH to obtain the title compound (18 mg, 60 %). ¹H NMR (400 MHz, CD₃OD) δ 8.14 (s, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.87 (s, 1H), 7.85 (s, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.15 (s, 1H), 6.75 (d, J = 8.2 Hz, 1H), 6.69 (d, J = 8.2 Hz, 1H); MS ESI 278.0 [M + H]⁺, calcd for [C₁₆H₁₁N₃O₂ + H]⁺ 278.09.

25 Example A124: (E)-5-hydroxy-3-((3-((E)-2-(pyridin-4-yl)vinyl)-1H-indazol-6-yl)methylene)indolin-2-one 2,2,2-trifluoroacetate

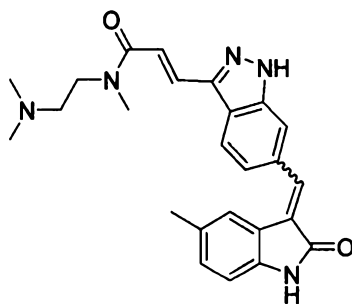
- 186 -



The title compound was synthesized according to the method described in Example A57 from 5-Hydroxyindolin-2-one (10 mg, 0.107 mmol) with a modified purification procedure. The title compound was purified by preparatory HPLC to give 10 mg, 30 % of a yellow solid. ¹H NMR (400 MHz, CD₃OD) δ 8.73 (d, J = 6.5 Hz, 2H), 8.35 (d, J = 8.8 Hz, 1H), 8.27 (d, J = 6.5 Hz, 2H), 8.24 (d, J = 16.4 Hz, 1H), 7.94 (s, 1H), 7.88 (s, 1H), 7.83 (d, J = 16.4 Hz, 1H), 7.61 (d, J = 8.1 Hz, 1H), 7.13 (s, 1H), 6.77 (d, J = 8.2 Hz, 1H), 6.71 (d, J = 8.2 Hz, 1H); MS ESI 381.1 [M + H]⁺, calcd for [C₂₃H₁₆N₄O₂ + H]⁺ 381.13.

10

Example A125: (E and Z)-N-(2-(dimethylamino)ethyl)-N-methyl-3-(6-((E)-(5-methyl-2-oxoindolin-3-ylidene)methyl)-1H-indazol-3-yl)acrylamide



A. (E)-N-(2-(dimethylamino)ethyl)-3-(6-formyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-3-yl)-N-methylacrylamide

A dry round-bottom flask was charged with N1,N1,N2-trimethylethane-1,2-diamine (0.32 mL, 2.50 mmol), diisopropylethylamine (0.87 mL, 5.00 mmol) and CH₂Cl₂ (12 mL) and the solution cooled with an ice-water bath. Acryloyl chloride (0.20 mL, 2.50 mmol) was added dropwise and the reaction allowed to warm to room temperature. After 3 hours the solvent was removed and the residue purified by column chromatography (silica gel, 88:10:2, CH₂Cl₂/MeOH/7M NH₃ in MeOH) to give 50 mg of a crude oil to which was added 3-iodo-1-((2-

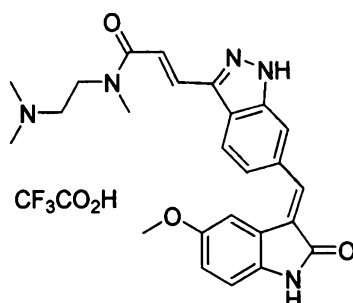
(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (105 mg, 0.262 mmol), DMF (5 mL) and diisopropylethylamine (0.091 mL, 0.524 mmol). The mixture was degassed by bubbling Argon through the solution for 15 min. Pd(OAc)₂ (3.0 mg, 0.013 mmol) and P(o-tolyl)₃ (12 mg, 0.039 mmol) were then added and the reaction
 5 heated to 110 °C for 18 hours. The mixture was cooled to room temperature, NaHCO_{3(sat.)} (5 mL) was added, and the product extracted (3X) with EtOAc. The organic layer was washed with water (2X) and brine (2X), and then dried over MgSO₄. After removal of solvent the residue was purified by column chromatography (silica gel, 93:6:1, CH₂Cl₂/MeOH/7M NH₃ in MeOH) to give 41
 10 mg, 41 % of a red-orange oil. MS ESI 431.2 [M + H]⁺, calcd for [C₂₂H₃₄N₄O₃Si + H]⁺ 431.25.

B. (E and Z)-N-(2-(dimethylamino)ethyl)-N-methyl-3-(6-((E)-(5-methyl-2-oxoindolin-3-ylidene)methyl)-1H-indazol-3-yl)acrylamide

15 The title compound was synthesized according to the method described in Example A57 from 5-methylindolin-2-one (8.0 mg, 0.0535 mmol) and (E)-N-(2-(dimethylamino)ethyl)-3-(6-formyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-3-yl)-N-methylacrylamide (23 mg, 0.0535 mmol) with a modified purification procedure. The product was extracted into EtOAc after the final
 20 deprotection step and washed with NaHCO_{3(sat.)} (2X), brine (2X) and the organic layer dried over MgSO₄. After removal of solvent the resulting film was titrated with Et₂O/hexanes to give after drying 9.4 mg, 41% yield of a yellow solid which was a 77:23 mixture of (E)/(Z) isomers. ¹H NMR (400 MHz, CD₃OD) δ 8.94, 7.91 (s, 1H), 8.20, 8.16 (d, J = 8.7 Hz, 1H), 7.98-7.93 (m, 1H), 7.84 (s, 1H), 7.59, 7.43 (d, J = 8.2 Hz, 1H), 7.52-7.42 (m, 2H), 7.08 (d, J = 7.2 Hz, 1H), 6.82, 6.78 (d, J = 7.6
 25 Hz, 1H), 3.77-3.68 (m, 2H), 3.60, 3.13 (s, 3H), 2.68-2.61 (m, 2H), 2.37 (s, 6H), 2.19 (s, 3H); MS ESI 430.3 [M + H]⁺, calcd for [C₂₅H₂₇N₅O₂ + H]⁺ 430.22.

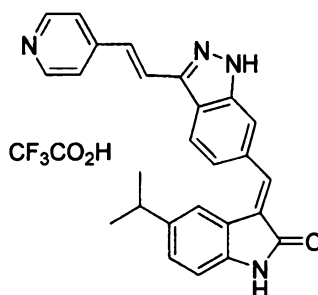
Example A126: (E)-N-(2-(dimethylamino)ethyl)-3-(6-((E)-(5-methoxy-2-oxoindolin-3-ylidene)methyl)-1H-indazol-3-yl)-N-methylacrylamide 2,2,2-trifluoroacetate
 30

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The title compound was synthesized according to the method described in Example A57 from 5-methoxyindolin-2-one (8.0 mg, 0.0535 mmol) and (E)-N-(2-(dimethylamino)ethyl)-3-(6-formyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-3-yl)-N-methylacrylamide (23 mg, 0.0535 mmol) with a modified purification procedure. The final compound was purified by preparatory-HPLC to give 4.0 mg, 17% of a yellow powder. ¹H NMR (400 MHz, CD₃OD) δ 8.17 (d, J = 8.6 Hz, 1H), 8.02 (d, J = 15.7 Hz, 1H), 7.94 (s, 1H), 7.88 (s, 1H), 7.59 (d, J = 8.1 Hz, 1H), 7.44 (d, J = 15.5 Hz, 1H), 7.21 (s, 1H), 6.86 (s, 2H), 3.95-3.90 (m, 2H), 3.63 (s, 3H), 3.46-3.42 (m, 2H), 3.36 (s, 3H), 3.03 (s, 6H); MS ESI 446.3 [M + H]⁺, calcd for [C₂₅H₂₇N₃O₃ + H]⁺ 446.22.

Example A127: (E)-5-isopropyl-3-((3-((E)-2-(pyridin-4-yl)vinyl)-1H-indazol-6-yl)methylene)indolin-2-one 2,2,2-trifluoroacetate



A. 5-isopropylindolin-2-one

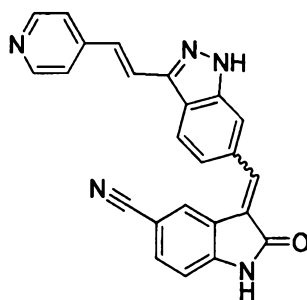
A mixture of 5-bromoindolin-2-one (106 mg, 0.500 mmol), isopropenylboronic acid pinacol ester (0.14 mL, 0.750 mmol), K₃PO₄ (212mg, 1.00 mmol), water (1mL) and *n*-BuOH (4mL) was briefly sonicated in a microwave vial and then purged with argon for 15 min. Tris(dibenzylideneacetone)dipalladium (9.2 mg, 0.010 mmol) and dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (19 mg, 0.040 mmol) were added, the vial sealed and heated in microwave reactor at 110

°C for 1 hour. The solvent was removed and the residue purified by column chromatography (silica gel, 2:1, hexanes/EtOAc) to give 40 mg, 46% of 5-isopropenylindolin-2-one as a beige solid; 5-isopropenylindolin-2-one (15 mg, 0.0866 mmol) was then dissolved into MeOH and the solution purged with N₂ (g). 2 mg of 10 % Pd/C (Degussa type) was then added and the mixture purged briefly with H₂ (g). The mixture was stirred under 1 atm of H₂ (g) for 3 hours and then filtered through a pad of celite. The solvent was removed to give 15 mg, 99 % of the product as an off-white solid. MS ESI 176.0 [M + H]⁺, calcd for [C₁₁H₁₃NO + H]⁺ 176.11.

10 *B. (E)-5-isopropyl-3-((3-((E)-2-(pyridin-4-yl)vinyl)-1H-indazol-6-yl)methylene)indolin-2-one 2,2,2-trifluoroacetate*

The title compound was synthesized according to the method described in Example A57 from 5-isopropylindolin-2-one (7.0 mg, 0.040 mmol) and (E)-3-(2-(pyridin-4-yl)vinyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (15 mg, 0.040 mmol) with a modified purification procedure. The final compound was purified by preparatory-HPLC to give 3.1 mg, 19 % yield of a yellow powder. ¹H NMR (400 MHz, CD₃OD) δ 8.72 (d, J = 6.7 Hz, 2H), 8.36 (d, J = 8.1 Hz, 1H), 8.26 (d, J = 6.7 Hz, 2H), 8.24 (d, J = 16.3 Hz, 1H), 7.96 (s, 1H), 7.87 (s, 1H), 7.78 (d, J = 16.3 Hz, 1H), 7.64 (d, J = 6.7 Hz, 1H), 7.53 (s, 1H), 7.15 (d, J = 6.5 Hz, 1H), 6.86 (d, J = 7.9 Hz, 1H), 2.77-2.72 (m, 1H), 1.12 (d, J = 6.9 Hz, 6H); MS ESI 407.2 [M + H]⁺, calcd for [C₂₆H₂₂N₄O + H]⁺ 407.19.

Example A128: (E and Z)-2-oxo-3-((3-((E)-2-(pyridin-4-yl)vinyl)-1H-indazol-6-yl)methylene)indoline-5-carbonitrile

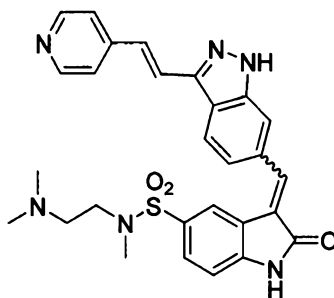


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The title compound was synthesized according to the method described in Example A57 from 2-oxoindoline-5-carbonitrile (10 mg, 0.063 mmol) and (E)-3-(2-

(pyridin-4-yl)vinyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (25 mg, 0.063 mmol) with a modified purification procedure. The product was precipitated with EtOAc and filtered washing with EtOAc to give 4.5 mg, 30% of a yellow powder which was a 65:35 mixture of (E)/(Z) isomers. ¹H NMR (400 MHz, d₆-DMSO) δ 14.04, 13.94 (s, 1H), 11.24, 11.22 (s, 1H), 9.01, 8.42 (s, 1H), 8.83 (d, J = 5.5 Hz, 2H), 8.50-8.17 (m, 3H), 8.03 (s, 1H), 7.99 (s, 1H), 7.86 (s, 1H), 7.81-7.65 (m, 3H), 7.07, 7.01 (d, J = 8.4 Hz, 1H); MS ESI 390.1 [M + H]⁺, calcd for [C₂₄H₁₅N₅O + H]⁺ 390.14.

10 Example A129: (E and Z)-N-(2-(dimethylamino)ethyl)-N-methyl-2-oxo-3-((3-((E)-2-(pyridin-4-yl)vinyl)-1H-indazol-6-yl)methylene)indoline-5-sulfonamide



A. *N*-(2-(dimethylamino)ethyl)-*N*-methyl-2-oxoindoline-5-sulfonamide

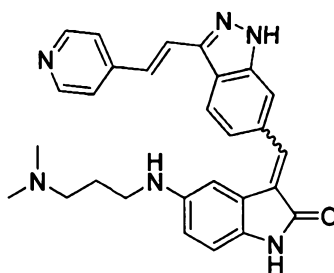
To a solution of N1,N1,N2-trimethylethane-1,2-diamine (26 uL, 0.20 mmol) in THF (2 mL) was added 2-oxoindoline-5-sulfonyl chloride (30 mg, 0.130 mmol) and the reaction stirred for 3 hours. The solvent was removed and the crude material used for the next step. MS ESI 298.0 [M + H]⁺, calcd for [C₁₃H₁₉N₃O₃S + H]⁺ 298.12.

20 B. *(E and Z)-N*-(2-(dimethylamino)ethyl)-*N*-methyl-2-oxo-3-((3-((*E*)-2-(pyridin-4-yl)vinyl)-1H-indazol-6-yl)methylene)indoline-5-sulfonamide

The title compound was synthesized according to the method described in Example A57 from *N*-(2-(dimethylamino)ethyl)-*N*-methyl-2-oxoindoline-5-sulfonamide and (E)-3-(2-(pyridin-4-yl)vinyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (25 mg, 0.065 mmol) with a modified purification procedure. The product was extracted into EtOAc, and washed with NaHCO₃(sat) (2X), brine (2X) and the organic layer dried over MgSO₄. After removal of solvent

the resulting yellow solid was titrated with Et₂O/hexanes to give after drying 1.5 mg, 4.1 % yield of a yellow solid which was a 77:23 mixture of (E)/(Z) isomers. ¹H NMR (400 MHz, CD₃OD) δ 9.01, 8.03 (s, 1H), 8.55-8.45 (m, 2H), 8.30-8.05 (m, 3H), 7.96-7.76 (m, 2H), 7.75-7.65 (m, 3H), 7.58-7.51 (m, 1H), 7.10, 7.07 (d, J = 8.6 Hz, 1H), 3.05-2.99 (m, 2H), 2.90, 2.72 (m, 2H), 2.80, 2.63 (s, 3H), 2.57, 2.34 (s, 6H); MS ESI 529.2 [M + H]⁺, calcd for [C₂₈H₂₈N₆O₃S + H]⁺ 529.20.

Example A130: (E and Z)-5-(3-(dimethylamino)propylamino)-3-((3-((E)-2-(pyridin-4-yl)-vinyl)-1H-indazol-6-yl)methylene)indolin-2-one

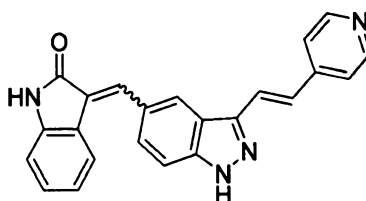


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A mixture of mono(4-((E)-2-(6-((E)-5-ammonio-2-oxoindolin-3-ylidene)methyl)-1H-indazol-3-yl)vinyl)pyridinium) di(2,2,2-trifluoroacetate) (10 mg, 0.016 mmol), K₂CO₃ (11 mg, 0.082 mmol) and DMF (1.0 mL) was cooled to 0 °C and then 3-bromo-N,N-dimethylpropan-1-amine hydrobromide (4.0 mg, 0.0164 mmol) was added. The reaction was allowed to warm to room temperature and stirred for 18 hours. EtOAc (10mL) was added and the mixture washed with brine (3X). The organic layer was dried over MgSO₄ and the solvent removed to give a red gum which was titrated with ether/EtOAc (~10:1) three times while decanting the mother liquor to give after drying 2.4 mg, 32 % of a red powder which was a 85:15 mixture of (E)/(Z) isomers. ¹H NMR (400 MHz, CD₃OD) δ 9.03, 7.93 (s, 1H), 8.55-8.49 (m, 2H), 8.23 (d, J = 8.3 Hz, 1H), 7.82-7.73 (m, 2H), 7.68-7.64 (m, 2H), 7.59-7.50 (m, 2H), 7.11, 7.10 (s, 1H), 6.71-6.64 (m, 2H), 4.54-4.50 (m, 2H), 2.40-2.34 (m, 2H), 2.25, 2.22 (s, 6H), 2.18-2.10 (m, 2H); MS ESI 465.2 [M + H]⁺, calcd for [C₂₈H₂₈N₆O + H]⁺ 465.24.

25

Example A131: (E and Z)-3-((3-((E)-2-(pyridin-4-yl)vinyl)-1H-indazol-5-yl)-methylene)indolin-2-one hydrochloride



A. 3-iodo-1H-indazole-5-carbaldehyde

To a solution of 1H-indazole-5-carbaldehyde (315.2 mg, 2.16 mmol), K₂CO₃ (598.8 mg, 4.33 mmol) in DMF (2.5 mL) was added dropwise a solution of I₂ (938 mg, 3.7 mmol) in DMF (2.5 mL) and the reaction allowed to stir for three hours. An aqueous solution consisting of Na₂S₂O₄ (511 mg) / K₂CO₃ (35 mg) / H₂O (3.5 mL) was then added and the solution stirred for two hours. Water (30mL) and aqueous sodium hydrogen sulfate (1M, 10mL) was added and the product was extracted with ethyl acetate (350 mL); this organic layer was washed with brine (3x25mL). The aqueous layer was then extracted with dichloromethane (3x75mL), this second organic layer was also washed with brine (25mL). TLC indicated product present in both, so the residues were combined and purified by chromatography (10g silica SPE tube, Silicycle, 5% ethyl acetate in dichloromethane) to yield a beige solid (203mg, 35%). A precipitate that formed in the original aqueous layer was collected by vacuum filtration to give after drying a beige solid (first crop 135.6 mg, 23 %; second crop 147 mg, 25%). ¹H NMR (400 MHz, CDCl₃ plus a drop of CD₃OD) δ 10.03 (s, 1H), 8.00 (s, 1H), 7.95 (d, *J* = 8.8 Hz, 1H), 7.54 (d, *J* = 8.8 Hz, 1H).

B. 3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-5-carbaldehyde

To a suspension of 3-iodo-1H-indazole-6-carbaldehyde (126.6 mg, 0.46 mmol) in CH₂Cl₂ (5 mL) and 50 % aq. KOH (1.0 mL) was added tetrabutylammonium bromide (3.4 mg, 0.01 mmol) and the solution cooled to 0 °C. (2-(Chloromethoxy)ethyl)trimethylsilane (0.10 mL, 0.56 mmol) was then added dropwise and the reaction stirred at 0 °C for 1.5 hours. The solution was then transferred to a sep. funnel containing ethyl acetate (200 mL) and the organic layer was washed with water (2 x 20 mL) and brine (20 mL), dried (Na₂SO₄) and the solvent removed *in vacuo*. The resulting residue was adsorbed onto silica using dichloromethane – methanol to dissolve, and evaporated to dryness. Chromatography (10g silica SPE tube, Silicycle, 50-100 % dichloromethane in

hexane, 10% ethyl acetate in dichloromethane) to give 88 mg, 47 %. ¹H NMR: (400 MHz, CDCl₃) δ 10.12 (s, 1H), 8.05 (m, 2H), 7.67 (d, *J* = 9.2 Hz, 1H), 5.77 (s, 2H), 3.60 (m, 2H), 0.90 (m, 2H), -0.048 (s, 9H).

5 C. *(E)*-3-(2-(pyridin-4-yl)vinyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-5-carbaldehyde

To a suspension of 3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-5-carbaldehyde (87mg, 0.22 mmol), NaOAc (36 mg, 0.44mmol), ⁿBu₄NCl (61 mg, 0.44 mmol), and Pd(OAc)₂ (8.0 mg, 0.036 mmol) in DMF (2 mL) under argon was added 4-vinylpyridine (0.05 mL, 0.46 mmol). The resulting mixture was heated in a sealed vial at 100 °C for 14 hours. Ethyl acetate (200 mL) was added and the solution was washed with water (20 mL) and brine (3 x 20 mL), dried over Na₂SO₄ and concentrated. The residue was chromatographed (5g silica SPE tube, Silicycle, 1-2% MeOH in CH₂Cl₂, repeated for mixed fractions) gave the title compound as a yellow solid (43 mg, 52%). ¹H NMR (400 MHz, CDCl₃ plus a drop of CD₃OD) δ 10.07 (s, 1H), 8.52 (m, 3H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 8.8 Hz, 1H); 7.60 (d, *J* = 16.4 Hz, 1H); 7.48 (m, 3H); 5.73 (s, 2H), 3.56 (m, 2H), 0.86 (m, 2H), -0.12 (s, 9H).

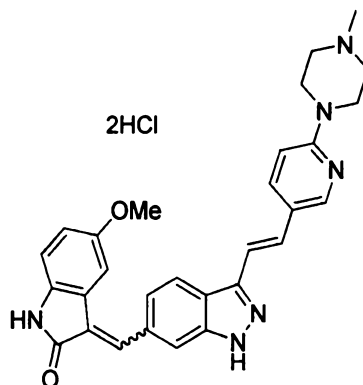
20 D. *(E and Z)*-3-((3-((*E*)-2-(pyridin-4-yl)vinyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-5-yl)methylene)indolin-2-one

A solution of piperidine (0.2M in EtOH, 0.10 mL, 0.02 mmol) was added to a suspension of oxindole (16.5 mg, 0.12 mmol) and (*E*)-3-(2-(pyridin-4-yl)vinyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-5-carbaldehyde (42.5 mg, 0.11 mmol) in EtOH (4 mL). The reaction was then heated to 75°C for 15 hrs. The solvent was evaporated *in vacuo*. MeOH was added and the resulting suspension was sonicated, but the solution was still cloudy even after EtOAc was added. The solid was removed by filtration and the solvent evaporated *in vacuo*. Chromatography (5g silica SPE tube, Silicycle, 2% MeOH in CH₂Cl₂) gave a yellow solid (35 mg, 64%, 55:45 mixture of *E/Z* isomers). ¹H NMR (400 MHz, CDCl₃ plus a drop of CD₃OD) δ 9.77 (s, 0.45H), 8.63 (m, 1.9H), 8.42 (s, 0.55H), 8.18 (s, 0.45H), 8.14 (dd, *J* = 8.8, 1.2 Hz, 0.45H), 8.00 (s, 1H), 7.83-7.42 (m, 7H), 7.26 (t, *J* = 7.6 Hz, 1H), 7.09 (t, *J* = 7.6 Hz, 0.45H), 6.94-6.88 (m, 1.6H), 5.80 (s, 0.55H), 5.77 (s, 0.45H), 3.64 (m, 2H), 0.95 (m, 2H), -0.02 (s, 5H), -0.03 (s, 4H).

E. (E and Z)-3-((3-((E)-2-(pyridin-4-yl)vinyl)-1H-indazol-5-yl)methylene)-indolin-2-one hydrochloride

According to the method of A57C and D, 3-((3-((E)-2-(pyridin-4-yl)vinyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-5-yl)methylene)indolin-2-one (13.1 mg, 0.026 mmol) was treated with boron trifluoride etherate, followed by 2 N HCl (water / EtOH) treatment. Suction filtration gave a solid which was rinsed with 1:1 EtOH : water (2 x 1 mL). Pumping under high vacuum gave an orange solid (7.3 mg, 69%, 55:45 mixture of E/Z isomers, HCl salt). ¹H NMR (400 MHz, CD₃OD) δ 9.83 (s, 0.4H), 8.73 (m, 2H), 8.59 (s, 0.6H), 8.33-8.20 (m, 3.5H), 7.95 (m, 1H), 7.91-7.87 (m, 1H), 7.80-7.63 (m, 3H), 7.25 (t, *J* = 8.4 Hz, 1H), 7.07 (t, *J* = 7.6 Hz, 0.4H), 6.96-6.87 (m, 1.6H); MS ESI 365.2 [M + H]⁺, calcd for [C₂₃H₁₆N₄O + H]⁺ 365.14.

Example A132: (E and Z)-5-methoxy-3-((3-((E)-2-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)vinyl)-1H-indazol-6-yl)methylene)indolin-2-one dihydrochloride



A. 5-methoxy-3-(E & Z)-((3-((E)-2-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)vinyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)methylene)indolin-2-one

The title compound was synthesized according to the method of Example A19, utilizing 5-methoxyindolin-2-one (14.7 mg, 0.090 mmol) and (E)-3-(2-(6-(4-methylpiperazin-1-yl)pyridine-3-yl)vinyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (Example A108-B: 41 mg, 0.086 mmol). The crude mixture was concentrated under reduced pressure and purified by prepTLC (SiO₂ 5 % MeOH/DCM) to provide the title compound as a (E:Z) mixture of isomers: a

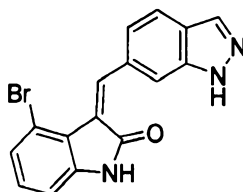
yellow solid (11.5 mg, 21 %); ^1H NMR (400 MHz, CD_3OD) δ ppm 8.29 (d, $J=2.26$ Hz, 1 H), 8.22 (d, $J=8.03$ Hz, 1 H), 7.92 – 7.97 (m, 2 H), 7.86 (s, 1 H), 7.57 (d, $J=8.53$ Hz, 1 H), 7.50 (d, $J=16.6$ Hz, 1 H), 7.30 (d, $J=16.6$ Hz, 1 H), 7.20 (br. s, 1 H), 6.89 (d, $J=9.03$ Hz, 1 H), 6.84 (s, 2 H), 5.77 (s, 2 H), 3.58 – 3.67 (m, 9 H), 2.55 – 2.62 (m, 4 H), 2.37 (s, 3 H), 0.88 (t, $J=8.16$ Hz, 2 H), -0.09 (s, 9 H); MS ESI $[\text{M} + 2\text{H} - \text{CH}_2\text{CH}_2\text{SiMe}_3]^+$ 523.4, calcd for $[\text{C}_{35}\text{H}_{42}\text{N}_6\text{O}_3\text{Si} + \text{H}]^+$ 623.8.

B. (E and Z)-5-methoxy-3-((3-((E)-2-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)vinyl)-1H-indazol-6-yl)methylene)indolin-2-one dihydrochloride

To a DCM (50 mL) solution of 5-methoxy-3-(E & Z)-((3-((E)-2-(6-(4-methylpiperazin-1-yl)-pyridin-3-yl)vinyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)methyl-ene)indolin-2-one (0.85 g, 1.36 mmol) was added $\text{BF}_3 \cdot \text{OEt}_2$ (1.7 mL, 13.6 mmol) at 0°C . The cooling bath was removed and the reaction mixture was stirred for 4 h. After removal of the solvent under reduced pressure, the residue was heated in EtOH (40 mL) and 2 M aq HCl (20 mL) at 60°C overnight. The reaction was then stored at 5°C overnight. A red precipitate was collected and washed separately with EtOAc, MeCN and Et_2O to provide the title compound as a 3.3:1 (E:Z) mixture of isomers: an orange-red powder (0.32 g, 42 %). ^1H NMR (400 MHz, CD_3OD) δ ppm 8.87 (s, 0.3 H), 8.53 – 8.61 (m, 1.0 H), 8.28 – 8.32 (m, 1 H), 8.26 (d, $J=8.53$ Hz, 0.7 H), 8.13 (d, $J=8.28$ Hz, 0.3 H), 8.00 (t, $J=7.99$ Hz, 0.3 H), 7.95 – 8.02 (m, 1.5 H), 7.83 – 7.90 (m, 3.3 H), 7.30 (d, $J=2.3$ Hz, 0.3 H), 7.24 (s, 0.7 H), 6.84 (s, 1.4 H), 6.76 – 6.84 (m, 0.4 H), 4.39 – 4.59 (br.s, 2 H), 3.64 – 3.85 (br.s., 4 H), 3.63 (s, 3 H), 3.32 – 3.60 (br.s., 2 H), 3.03 (s, 3 H); MS ESI $[\text{M} + \text{H}]^+$ 493.3, calcd for $[\text{C}_{29}\text{H}_{28}\text{N}_6\text{O}_2 + \text{H}]^+$ 493.6.

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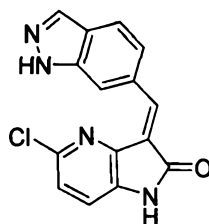
Example A133: (Z)-3-((1H-indazol-6-yl)methylene)-4-bromoindolin-2-one



The title compound was synthesized according to the method of Example A19, utilizing 4-bromoindolin-2-one (50 mg, 0.23 mmol) and 1H-indazole-6-carbaldehyde (34.5 mg, 0.23 mmol). On completion the reaction mixture was stored at rt overnight. Filtration and rinsing with xs EtOH provided the title compound as an orange solid (30 mg, 38 %). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 13.36 (br. s., 1 H), 10.91 (br. s., 1 H), 8.78 (s, 1 H), 8.73 (s, 1 H), 8.13 (s, 1 H), 7.80 (d, *J*=8.28 Hz, 1 H), 7.65 (d, *J*=8.28 Hz, 1 H), 7.22 (d, *J*=8.28 Hz, 1 H), 7.16 (t, *J*=7.78 Hz, 1 H), 6.88 (d, *J*=7.78 Hz, 1 H); MS ESI [M+ H]⁺ 340.1/341.9, calcd for [C₁₆H₁₀BrN₃O+ H]⁺ 340.0/342.0.

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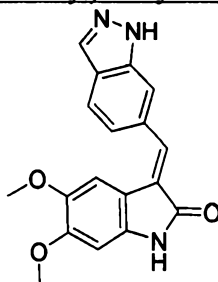
Example A134: (E)-3-((1H-indazol-6-yl)methylene)-5-chloro-1H-pyrrolo[3,2-b]pyridin-2(3H)-one



15 The title compound (40 mg, 67 %) was synthesized as an orange solid according to the method described for Example A67 (oil temp 75 °C, reflux 30 min) using 5-chloro-1H-pyrrolo[3,2-b]pyridin-2(3H)-one (33.7 mg, 0.2 mmol) and 1H-indazole-6-carbaldehyde (29.2 mg, 0.2 mmol). ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.56 (s, 1H), 10.90 (s, 1H), 8.93 (s, 1H), 8.37 (d, *J* = 8.4 Hz, 1H), 8.17 (s, 1H), 7.93 (s, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H); MS ESI 297.0 [M + H]⁺, calcd for [C₁₅H₉ClN₄O + H]⁺ 297.1.

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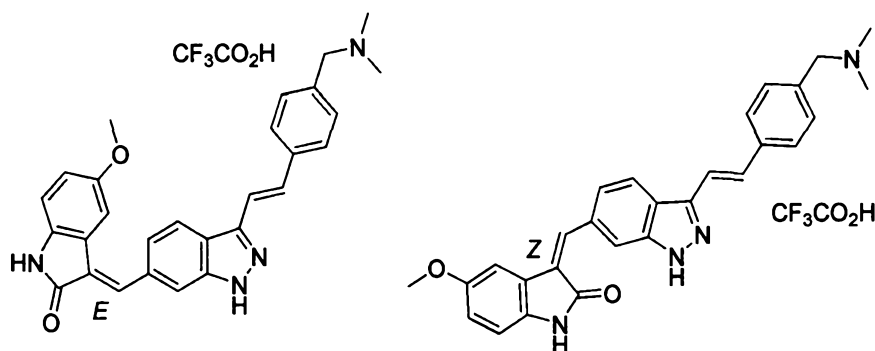
Example A135: (E)-3-((1H-indazol-6-yl)methylene)-5,6-dimethoxyindolin-2-one



25 The title compound (43 mg, 67 %) was synthesized as an orange yellow solid according to the method described for Example A67 (oil temp 75 °C, reflux 90 min)

using 5,6-dimethoxyindolin-2-one (38.6 mg, 0.2 mmol) and 1H-indazole-6-carbaldehyde (29.2 mg, 0.2 mmol). ¹H NMR (400 MHz, DMSO-d₆) δ 13.26 (s, 1H), 10.36 (s, 1H), 8.14 (s, 1H), 7.95-7.85 (m, 2H), 7.57 (s, 1H), 7.46-7.37 (m, 1H), 7.24 (s, 1H), 6.52 (s, 1H), 3.78 (s, 3H), 3.53 (s, 3H); MS ESI 322.1 [M + H]⁺, calcd for [C₁₈H₁₅N₃O₃ + H]⁺ 322.1.

Examples A136(a): (E)-3-((3-(4-((dimethylamino)methyl)styryl)-1H-indazol-6-yl)-methylene)-5-methoxyindolin-2-one 2,2,2-trifluoroacetate and A136(b): (Z)-3-((3-(4-((dimethylamino)methyl)styryl)-1H-indazol-6-yl)-methylene)-5-methoxyindolin-2-one 2,2,2-trifluoroacetate



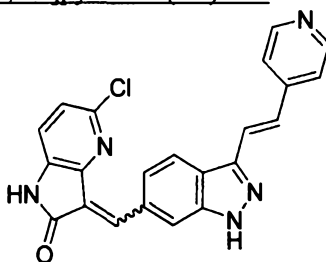
Piperidine (0.01 mL, 0.1 mmol) was added to a solution of 5-methoxyoxindole (52 mg, 0.32 mmol) and (E)-3-(4-((dimethylamino)methyl)styryl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (contaminated with TBAF from previous deprotection attempt, 95.5 mg, 0.22 mmol) in EtOH (5 mL). The reaction was then heated to 75°C for 25 hrs. The solvent was evaporated *in vacuo*. Chromatography (5g silica SPE tube, Silicycle, 5-10% MeOH in CH₂Cl₂) gave a brown oil (105 mg, contained product and TBAF by NMR). The residue was dissolved in EtOAc (100 mL) and washed with brine (3 x 15 mL), dried over Na₂SO₄ and the solvent was evaporated *in vacuo* to give 3-((3-(4-((dimethylamino)methyl)styryl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)methylene)-5-methoxyindolin-2-one as a brown oil (110mg, used without further purification).

According to the method of A57C, 3-((3-(4-((dimethylamino)methyl)styryl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)methylene)-5-methoxyindolin-2-one (19 mg, 0.033 mmol) was treated with boron trifluoride etherate, followed by

2 N HCl (water / EtOH) treatment. The solvents were removed in vacuo using additional EtOH to azeotropically remove water. The residue was dissolved in MeOH / EtOAc and filtered to remove solid, then the solvent was evaporated *in vacuo*. Purification by prep-HPLC gave the title compound (*E* isomer, first eluting fraction, 94% by HPLC) as an orange solid (11 mg, 60% yeild.). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.26 (d, *J*=8.5 Hz, 1 H), 7.88 (d, *J*=9.3 Hz, 2 H), 7.80 (d, *J*=8.3 Hz, 2 H), 7.61 (s, 2 H), 7.51 - 7.58 (m, 3 H), 7.26 (s, 1 H), 6.84 (s, 2 H), 4.34 (s, 2 H), 3.63 (s, 3 H), 2.89 (s, 6 H); MS ESI 451.2 [M + H]⁺, calcd for [C₂₈H₂₆N₄O₂ + H]⁺ 451.22. The second eluting fraction was the *Z*-isomer (5 mg, 30%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.89 (s, 1 H), 8.15 (d, *J*=9.0 Hz, 1 H), 7.99 (dd, *J*=9.0, 1.3 Hz, 1 H), 7.90 (s, 1 H), 7.81 (d, *J*=8.3 Hz, 2 H), 7.57 - 7.61 (m, 2 H), 7.53 (d, *J*=8.3 Hz, 2 H), 7.33 (d, *J*=2.0 Hz, 1 H), 6.85 (dd, *J*=8.4, 2.4 Hz, 1 H), 6.80 (d, *J*=8.4 Hz, 1 H), 4.34 (s, 2 H), 3.84 (s, 3 H), 2.89 (s, 6 H); MS ESI 451.2 [M + H]⁺, calcd for [C₂₈H₂₆N₄O₂ + H]⁺ 451.22.

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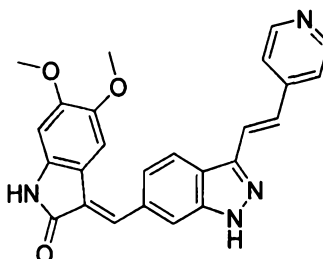
Example A137: (E and Z)-5-chloro-3-((3-((E)-2-(pyridin-4-yl)vinyl)-1H-indazol-6-yl)methylene)-1H-pyrrolo[3,2-b]pyridin-2(3H)-one



The title compound (*E/Z*=3:1, 63 mg, 84 %) was synthesized as an orange solid according to the method described for Example A67 (oil temp 70 °C, reflux 60 min) using 5-chloro-1H-pyrrolo[3,2-b]pyridin-2(3H)-one (33.7 mg, 0.2 mmol) and (E)-3-(2-(pyridin-4-yl)vinyl)-1H-indazole-6-carbaldehyde (49.8 mg, 0.2 mmol). ¹H NMR (400 MHz, DMSO-d₆) *E* isomer: δ 13.83 (s, 1H), 10.92 (s, 1H), 8.91 (s, 1H), 8.57 (d, *J* = 6.0 Hz, 3H), 8.37 (d, *J* = 8.8 Hz, 1H), 7.95 (s, 1H), 7.90 (d, *J* = 16.4 Hz, 1H), 7.75-7.70 (m, 2H), 7.57 (d, *J* = 16.8 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 1H); *Z* isomer: δ 13.80 (s, 1H), 11.03 (s, 1H), 9.15 (s, 1H), 8.57 (d, *J* = 6.0 Hz, 2H, buried under the doublet at 8.57), 8.34 (d, *J* = 8.4 Hz, 1H, partially overlapping with the doublet at 8.37), 8.25 (d, *J* = 9.2 Hz, 1H), 8.20 (s, 1H), 7.86 (d, *J* = 14.4 Hz, 1H, partially overlapping with the doublet at 7.90), 7.75-7.70 (m, buried

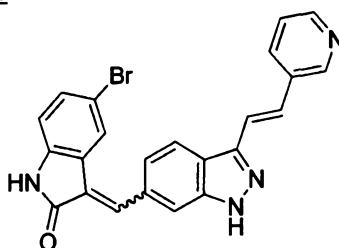
under the multiplet 7.75-7.70), 7.56 (d, J = 16.8 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H); MS ESI 400.0 [M + H]⁺, calcd for [C₂₂H₁₄ClN₅O + H]⁺ 400.1.

5 Example A138: (E)-5,6-dimethoxy-3-((3-((E)-2-(pyridin-4-yl)vinyl)-1H-indazol-6-yl)methylene)indolin-2-one



The title compound (36 mg, 42 %) was synthesized as an orange red solid according to the method described for Example A67 (oil temp 75 °C, reflux 90 min) using 5,6-dimethoxyindolin-2-one (38.6 mg, 0.2 mmol) and (E)-3-(2-(pyridin-4-yl)vinyl)-1H-indazole-6-carbaldehyde (49.8 mg, 0.2 mmol). ¹H NMR (400 MHz, DMSO-d₆) δ 13.54 (s, 1H), 10.39 (s, 1H), 8.60-8.53 (m, 2H), 8.35 (d, J = 7.2 Hz, 1H), 7.94 (s, 1H), 7.87 (d, J = 16.4 Hz, 1H), 7.75-7.67 (m, 2H), 7.63-7.50 (m, 3H), 7.25 (s, 1H), 6.53 (s, 1H), 3.80 (s, 3H), 3.55 (s, 3H); MS ESI 425.2 [M + H]⁺, calcd for [C₂₅H₂₀N₄O₃ + H]⁺ 425.1.

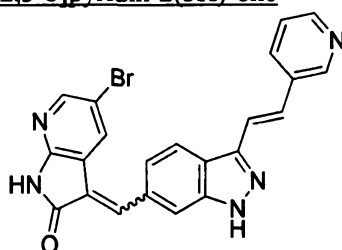
Example A139: (E and Z)-5-bromo-3-((3-((E)-2-(pyridin-3-yl)vinyl)-1H-indazol-6-yl)methylene)indolin-2-one



20 The title compound (E:Z=1:4, 73 mg, 83 %) was synthesized as a dark yellow solid according to the method described for Example A67 (oil temp 75 °C, reflux 2 h) using 5-bromoindolin-2-one (44.5 mg, 0.21 mmol) and (E)-3-(2-(pyridin-3-yl)vinyl)-1H-indazole-6-carbaldehyde (49.8 mg, 0.2 mmol). ¹H NMR (400 MHz, DMSO-d₆): δ 13.60 (s, 1H), 10.84 (s, 1H), 8.99 (s, 1H), 8.91 (s, 1H), 8.48 (d, J = 4.4 Hz, 1H), 8.30 (d, J = 8.4 Hz, 1H), 8.19 (d, J = 8.0 Hz, 1H), 8.16-8.10 (m, 3H), 8.04 (s, 1H), 7.71 (d, J = 16.8 Hz, 1H), 7.59 (d, J = 17.2 Hz, 1H), 7.43 (dd, J = 7.6 Hz, J =

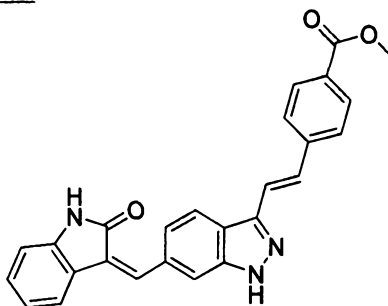
4.8 Hz, 1H), 7.39 (dd, $J = 8.0$ Hz, $J = 1.2$ Hz, 1H); MS ESI 443.3 $[M + H]^+$, calcd for $[C_{23}H_{15}BrN_4O + H]^+$ 443.1.

5 Example A140: (E and Z)-5-bromo-3-((3-((E)-2-(pyridin-3-yl)vinyl)-1H-indazol-6-yl)methylene)-1H-pyrrolo[2,3-b]pyridin-2(3H)-one



The title compound (E/Z=5:4, 75 mg, 84 %) was synthesized as a yellow solid according to the method described for Example A67 (oil temp 75 °C, reflux 2 h) using 5-bromo-1H-pyrrolo[2,3-b]pyridin-2(3H)-one (44.5 mg, 0.21 mmol) and (E)-3-(2-(pyridin-3-yl)vinyl)-1H-indazole-6-carbaldehyde (49.8 mg, 0.2 mmol). ¹H NMR (400 MHz, DMSO-d₆) δ 13.64 (s, 0.45 H), 13.56 (s, 0.48 H), 11.50 (s, 0.91 H), 8.94 (s, 0.43H), 8.91 (s, 0.97H), 8.48 (d, $J = 3.6$ Hz, 0.99H), 8.43-8.37 (m, 0.98 H), 8.33 (d, $J = 8.0$ Hz, 0.52 H), 8.28-8.17 (m, 2.36H), 8.11 (d, $J = 8.8$ Hz, 0.50H), 8.03 (s, 0.56H), 7.94 (s, 1.02H), 7.77-7.69 (2 doublets partially overlapping, $J = 17.2$ Hz, 1.07H, vinylic proton), 7.64-7.54 (m, 1.54H), 7.45-7.41 (2 doublets overlapping, $J = 8.8$ Hz, 1.00H); MS ESI 444.3 $[M + H]^+$, calcd for $[C_{22}H_{14}BrN_5O + H]^+$ 444.1.

20 Example A141: methyl 4-((E)-2-(6-((Z)-2-oxoindolin-3-ylidene)methyl)-1H-indazol-3-yl)vinyl)benzoate

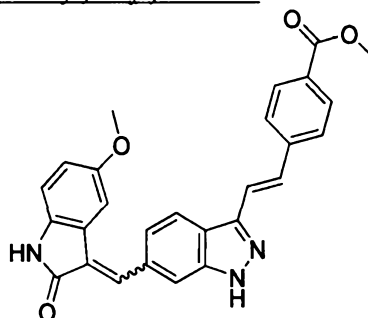


The title compound (40 mg, 83 %) was synthesized as an orange solid according to the method described for Example A67 (oil temp 75 °C, reflux 150 min) using indolin-2-one (26.6 mg, 0.2 mmol) and (E)-methyl 4-(2-(6-formyl-1H-indazol-3-yl)vinyl)benzoate (61.2 mg, 0.2 mmol). ¹H NMR (400 MHz, DMSO-d₆) δ 13.60 (s, 1H), 10.70 (s, 1H), 9.00 (s, 1H), 8.29 (d, $J = 8.0$ Hz, 1H), 8.08 (d, $J = 8.4$

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Hz, 1H), 8.00 (s, 1H), 7.98 (d, J = 8.0 Hz, 2H), 7.88 (d, J = 8.0 Hz, 2H), 7.77 (d, J = 8.4 Hz, 1H, partially overlapping with the doublet at 7.74), 7.74 (d, J = 17.2 Hz, 1H, partially overlapping with the doublet at 7.77), 7.63 (d, J = 17.2 Hz, 1H), 7.23 (t, J = 7.6 Hz, 1H), 7.01 (t, J = 7.6 Hz, 1H), 6.84 (d, J = 7.6 Hz, 1H), 3.86 (s, 3H); MS ESI
 5 422.3 [M + H]⁺, calcd for [C₂₆H₁₉N₃O₃ + H]⁺ 422.1.

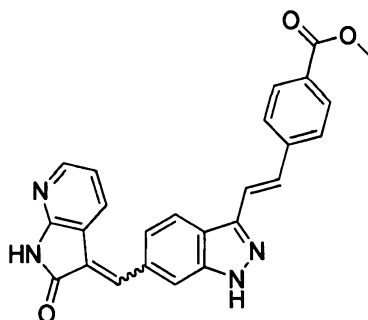
Example A142: methyl 4-((E)-2-(6-((E and Z)-(5-methoxy-2-oxoindolin-3-ylidene)methyl)-1H-indazol-3-yl)vinyl)benzoate



10 The title compound (E/Z = 2:1, 60 mg, 67 %) was synthesized as an orange red solid according to the method described for Example A67 (oil temp 75 °C, reflux 150 min) using 5-methoxyindolin-2-one (32.6 mg, 0.2 mmol) and (E)-methyl 4-(2-(6-formyl-1H-indazol-3-yl)vinyl)benzoate (61.2 mg, 0.2 mmol). ¹H NMR (400 MHz, DMSO-d₆) E isomer: δ 13.25 (s, br, 1H), 10.45 (s, 1H), 8.37 (d, J = 8.0 Hz, 1H), 7.98 (d, J = 8.4 Hz, 2H), 7.93 (s, 1H), 7.89 (d, J = 8.0 Hz, 2H), 7.79 (s, 1H),
 15 7.76 (d, J = 16.8 Hz, 1H), 7.64 (d, J = 16.8 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.19 (d, J = 2.0 Hz, 1H), 6.86 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 3.86 (s, 3H), 3.6 (s, 3H); Z isomer: δ 13.25 (s, br, 1H), 10.50 (s, 1H), 9.02 (s, 1H), 8.29 (d, J = 8.4 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.99 (s, 1H), 7.98 (d, J = 8.4 Hz, 2H,
 20 buried by doublet at 7.98), 7.89 (d, J = 8.0 Hz, 2H, buried by doublet at 7.89), 7.74 (d, J = 16.8 Hz, 1H), 7.63 (d, J = 16.4 Hz, 1H), 7.47 (d, J = 2.0 Hz, 1H), 6.80 (d, 1H, buried by doublet at 6.80), 6.74 (d, 8J = 8.4 Hz, 1H), 3.86 (s, 3H), 3.78 (s, 3H); MS ESI 452.3 [M + H]⁺, calcd for [C₂₇H₂₁N₃O₄ + H]⁺ 452.2.

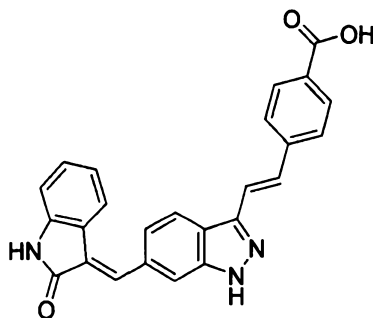
25 Example A143: methyl 4-((E)-2-(6-((E and Z)-(2-oxo-1H-pyrrolo[2,3-b]pyridin-3(2H)-ylidene)methyl)-1H-indazol-3-yl)vinyl)benzoate

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The title compound (E/Z = 9:1, 62 mg, 73 %) was synthesized as a yellow solid according to the method described for Example A67 (oil temp 75 °C, reflux 120 min) using 1H-pyrrolo[2,3-b]pyridin-2(3H)-one (26.8 mg, 0.2 mmol) and (E)-methyl 4-(2-(6-formyl-1H-indazol-3-yl)vinyl)benzoate (61.2 mg, 0.2 mmol). ¹H NMR (400 MHz, DMSO-d₆) δ 15.53 (s, 1H), 11.27 (s, 1H), 8.38 (d, J = 8.0 Hz, 1H), 8.11 (d, J = 4.4 Hz, 1H), 7.98 (d, J = 8.4 Hz, 2H), 7.95-7.87 (m, 5H), 7.76 (d, J = 16.8 Hz, 1H), 7.64 (d, J = 17.2 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 6.91 (dd, J = 7.2 Hz, J = 5.6 Hz, 1H), 3.86 (s, 3H); MS ESI 423.2 [M + H]⁺, calcd for [C₂₅H₁₈N₄O₃ + H]⁺ 423.1.

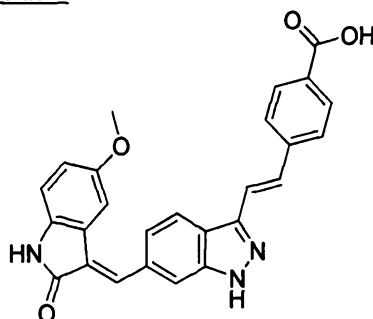
Example A144: 4-((E)-2-(6-((E)-2-oxoindolin-3-ylidene)methyl)-1H-indazol-3-yl)vinyl)benzoic acid



The title compound (17 mg, 21 %) was synthesized as an orange solid according to the method described for Example A67 (oil temp 75 °C, reflux 90 min) using indolin-2-one (26.6 mg, 0.2 mmol) and (E)-4-(2-(6-formyl-1H-indazol-3-yl)vinyl)benzoic acid (58.4 mg, 0.2 mmol). ¹H NMR (400 MHz, DMSO-d₆) δ 13.49 (s, 1H), 12.90 (s, br, 1H), 10.64 (s, 1H), 8.37 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 8.4 Hz, 2H), 7.91 (s, 1H), 7.86 (d, J = 8.0 Hz, 2H), 7.80 (s, 1H), 7.74 (d, J = 16.8 Hz, 1H), 7.63 (d, J = 15.6 Hz, 1H partially overlapping with the singlet at 7.62), 7.62 (s, 1H)

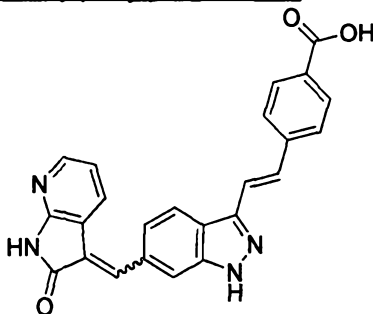
partially overlapping with the doublet at 7.63), 7.24 (t, $J = 7.4$ Hz, 1H), 6.91-6.82 (m, 2H); MS ESI 408.2 $[M + H]^+$, calcd for $[C_{25}H_{17}N_3O_3 + H]^+$ 408.1.

5 Example A145: 4-((E)-2-(6-((E)-(5-methoxy-2-oxoindolin-3-ylidene)methyl)-1H-indazol-3-yl)vinyl)benzoic acid



The title compound (20 mg, 23 %) was synthesized as an orange red solid according to the method described for Example A67 (oil temp 75 °C, reflux 90 min) using 5-methoxyindolin-2-one (32.6 mg, 0.2 mmol) and (E)-4-(2-(6-formyl-1H-indazol-3-yl)vinyl)benzoic acid (58.4 mg, 0.2 mmol). 1H NMR (400 MHz, DMSO-
10 d_6) δ 13.50 (s, 1H), 12.90 (s, br, 1H), 10.45 (s, 1H), 8.37 (d, $J = 8.4$ Hz, 1H), 7.96 (d, $J = 8.0$ Hz, 2H), 7.92 (s, 1H), 7.86 (d, $J = 8.0$ Hz, 2H), 7.79 (s, 1H), 7.74 (d, $J = 16.8$ Hz, 1H), 7.63 (d, $J = 16.4$ Hz, 1H), 7.54 (d, $J = 8.4$ Hz, 1H), 7.19 (s, 1H), 6.86 (dd, $J = 8.8$ Hz, $J = 2.4$ Hz, 1H), 6.80 (d, $J = 8.4$ Hz, 1H), 3.60 (s, 3H); MS ESI
15 438.2 $[M + H]^+$, calcd for $[C_{26}H_{19}N_3O_4 + H]^+$ 438.1.

Example A146: 4-((E)-2-(6-((E/Z)-(2-oxo-1H-pyrrolo[2,3-b]pyridin-3(2H)-ylidene)methyl)-1H-indazol-3-yl)vinyl)benzoic acid

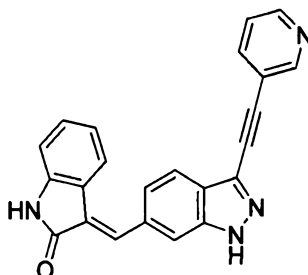


20 The title compound (E/Z = 10:3, 54 mg, 66 %) was synthesized as a yellow solid according to the method described for Example A67 (oil temp 75 °C, reflux 450 min) using 1H-pyrrolo[2,3-b]pyridin-2(3H)-one (26.8 mg, 0.2 mmol) and (E)-4-(2-(6-formyl-1H-indazol-3-yl)vinyl)benzoic acid (58.4 mg, 0.2 mmol). 1H NMR (400 MHz, DMSO- d_6) δ 13.52 (s, 1H), 11.27 (s, 1H), 8.32 (d, $J = 8.8$ Hz, 1H), 8.11

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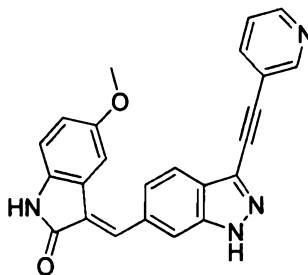
(t, $J = 5.2$ Hz, 2H), 7.97-7.89 (m, 4H), 7.84 (d, $J = 8.4$ Hz, 2H), 7.73 (d, $J = 16.8$ Hz, 1H), 7.63 (d, $J = 16.4$ Hz, 1H), 7.53 (d, $J = 8.4$ Hz, 1H), 6.91 (dd, $J = 7.2$ Hz, $J = 5.2$ Hz, 1H); MS ESI 409.2 $[M + H]^+$, calcd for $[C_{24}H_{16}N_4O_3 + H]^+$ 409.1.

5 Example A147: (E)-3-((3-(pyridin-3-ylethynyl)-1H-indazol-6-yl)methylene)indolin-2-one



The title compound (30 mg, 83 %) was synthesized as a yellow solid according to the method described for Example A67 (oil temp 75 °C, reflux 2 h) using indolin-2-one (13.3 mg, 0.1 mmol) and 3-(pyridin-3-ylethynyl)-1H-indazole-6-carbaldehyde (24.7 mg, 0.1 mmol). ¹H NMR (400 MHz, DMSO-d₆) δ 13.80 (s, 1H), 10.64 (s, 1H), 8.90 (s, 1H), 9.64 (d, $J = 4.4$ Hz, 1H), 8.12 (d, $J = 8.0$ Hz, 1H), 8.03 (d, $J = 8.0$ Hz, 1H), 7.96 (s, 1H), 7.80 (s, 1H), 7.60-7.50 (m, 3H), 7.24 (t, $J = 7.8$ Hz, 1H), 6.89 (d, $J = 7.6$ Hz, 1H) 6.84 (t, $J = 7.8$ Hz, 1H); MS ESI 363.1 $[M + H]^+$, calcd for $[C_{23}H_{14}N_4O + H]^+$ 363.1.

15 Example A148: (E)-5-methoxy-3-((3-(pyridin-3-ylethynyl)-1H-indazol-6-yl)methylene)indolin-2-one



20 The title compound (34 mg, 53 %) was synthesized as a orange red solid according to the method described for Example A67 (oil temp 75 °C, reflux 2 h) using 5-methoxyindolin-2-one (29 mg, 0.18 mmol) and 3-(pyridin-3-ylethynyl)-1H-indazole-6-carbaldehyde (40 mg, 0.163 mmol), followed by additional 90 min with additional 5-methoxyindolin-2-one (5.8 mg, 0.036 mmol). ¹H NMR (400 MHz, DMSO-d₆) δ 13.80 (s, br, 1H, NH), 10.46 (s, 1H, NH), 8.90 (s, 1H), 8.63 (d, $J = 4.4$

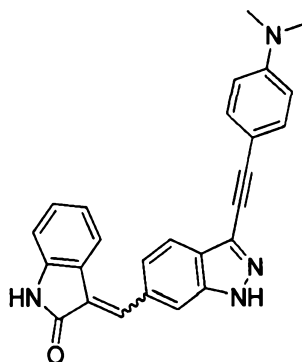
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Hz, 1H), 8.12 (dt, $J = 8.0$ Hz, 1H), 8.04 (d, $J = 8.4$ Hz, 1H), 7.98 (s, 1H), 7.79 (s, 1H), 7.58 (d, $J = 8.4$ Hz, 1H), 7.52 (dd, $J = 8.0$ Hz, $J = 4.8$ Hz, 1H), 7.13 (d, $J = 1.6$ Hz, 1H), 6.86 (dd, $J = 8.0$ Hz, $J = 2.4$ Hz, 1H), 6.80 (d, $J = 8.4$ Hz, 1H), 3.59 (s, 3H); MS ESI 393.2 $[M + H]^+$, calcd for $[C_{24}H_{16}N_4O_2 + H]^+$ 393.1.

5

Example A149: (E and Z)-3-((3-((4-(dimethylamino)phenyl)ethynyl)-1H-indazol-6-yl)methylene)indolin-2-one



10 To a solution of 3-iodo-1H-indazole-6-carbaldehyde (136 mg, 0.5 mmol), $Pd(PPh_3)_2Cl_2$ (14 mg, 0.02 mmol) and CuI (7.6 mg, 0.04 mmol) in DMF (3 mL) was added Et_3N (5 mL), followed by 4-ethynyl-N,N-dimethylaniline (109 mg, 0.75 mmol). The resulting mixture was heated at 100 °C (oil temp.) for 45 min. After removal of Et_3N , the residue was loaded directly onto a silical gel column. Flash chromatography (eluent: hex to hex/ethyl acetate = 5:1 to 1:1, to ethyl acetate) gave the crude 3-((4-(dimethylamino)phenyl)ethynyl)-1H-indole-6-carbaldehyde as greenish brown solid, which was redissolved in MeOH (20 mL). 2-Oxindole (53.2 mg, 0.4 mmol) and piperidine (10 drops) were added and the resulting mixture was refluxed (oil temp 75 °C) for 2 h. Additional 2-oxindole (13.3 mg) was added and the mixture was refluxed for another hour. After cooling to rt, the reaction mixture was suction filtered and the filter cake was rinsed with MeOH (10 mL). The filtrate was concentrated to about 0.5 mL and diluted with EtOAc (8 mL). Hexane (15 mL) was added and the resulting precipitate was collected by suction filtration to give the title compound (63mg, 31 % over 2 steps) as a golden solid (E:Z = 9:1). 1H NMR (400 MHz, DMSO- d_6) δ 13.40 (s, br, 1H), 10.64 (s, 1H), 7.93 (d, $J = 8.4$ Hz, 1H), 7.91 (s, 1H), 7.79 (s, 1H), 7.57 (d, $J = 7.2$ Hz, 1H), 7.53 (d, $J = 8.8$ Hz, 1H), 7.47 (d, $J = 8.8$ Hz, 2H), 7.24 (t, $J = 7.6$ Hz, 1H), 6.89 (d, $J = 7.6$ Hz, 1H), 6.84 (t, $J = 7.4$ Hz,

15

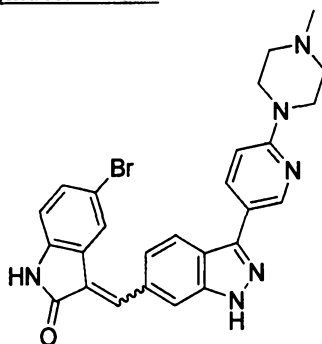
20

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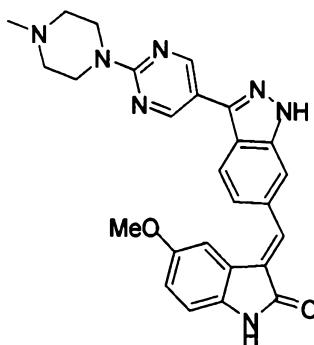
1H), 6.75 (d, J = 8.8 Hz, 2H), 2.97 (s, 6H); MS ESI 405.2 [M + H]⁺, calcd for [C₂₆H₂₀N₄O + H]⁺ 405.2.

5 Example A150: (E and Z)-5-bromo-3-((3-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1H-indazol-6-yl)methylene)indolin-2-one



The title compound (E/Z=3:4, 65 mg, 88 %) was synthesized as an orange solid according to the method described for Example A67 (oil temp 75 °C, reflux 3 h) using 5-bromoindolin-2-one (32 mg, 0.15 mmol) and 3-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1H-indazole-6-carbaldehyde (46 mg, 0.143 mmol). ¹H NMR (400 MHz, DMSO-d₆) E isomer: δ 13.41 (s, 1H), 10.80 (s, 1H), 8.76 (s, 1H), 8.20-8.03 (m, 2H), 7.91 (s, 1H), 7.87 (s, 1H), 7.67 (d, 1H), 7.48-7.40 (m, 2H), 7.99 (d, J = 8.8 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 3.57 (t, 4H), 2.41 (t, 4H), 2.23 (s, 3H); Z isomer: δ 13.48 (s, 1H), 10.84 (s, 1H), 9.02 (s, 1H), 8.76 (s, 1H), 8.20-8.03 (m, 5H), 7.38 (d, J = 8.0 Hz, 1H), 6.98 (d, J = 9.6 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 3.57 (t, 4H), 2.41 (t, 4H), 2.23 (s, 3H); MS ESI 515.4 [M + H]⁺, calcd for [C₂₆H₂₃BrN₆O + H]⁺ 515.1.

20 Example A151. (E)-5-methoxy-3-((3-(2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)-1H-indazol-6-yl)methylene)indolin-2-one



A. 3-(2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)-1H-indazole-6-carbaldehyde

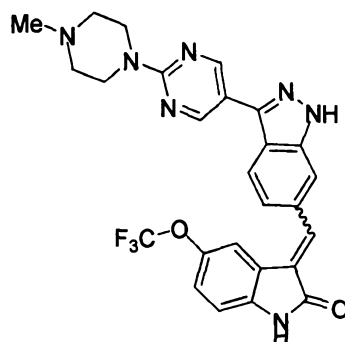
A mixture of 1H-indazole-6-carbaldehyde (50 mg, 0.18 mmol), 2-(4-Methylpiperazin-1-yl)pyrimidine-5-boronic acid pinacol ester (70 mg, 0.22 mmol), Pd(PPh₃)₄ (13 mg, 0.018 mmol) and 2M Na₂CO₃ (0.10 mL, 0.22 mmol) in DME/H₂O/EtOH (1.4 mL/0.4 mL/0.2 mL) was sealed and heated with stirring under
5 microwave irradiation at 125 °C for 120 min. The crude reaction mixture was concentrated under reduced pressure and purified by flash chromatography on silica gel using MeOH (5% to 10 %) in DCM as the eluent to provide the title compound as a pale yellow solid (47 mg, 80 %). ¹H NMR (400 MHz, CD₃OD) δ ppm 10.12 (s, 1 H), 8.91 (s, 2 H), 8.14 (s, 1 H), 8.09 (d, J = 8.6 Hz, 1 H), 7.74 (d, J = 8.4 Hz, 1 H),
10 3.94 (t, J = 4.5 Hz, 4 H), 2.56 (t, J = 4.9 Hz, 4 H), 2.37 (s, 3 H); MS ESI 323.1 (100) [M + H]⁺, calcd for [C₁₇H₁₈N₆O + H]⁺ 323.2.

B. (E)-5-methoxy-3-((3-(2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)-1H-indazol-6-yl)methylene)indolin-2-one

A round bottom flask was charged with 3-(2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)-1H-indazole-6-carbaldehyde (26 mg, 0.80 mmol), 5-methoxyoxindole (13 mg, 0.80 mmol), piperidine (0.8 uL, 0.008 mmol) and MeOH (2 mL). The reaction was
15 then heated to 60°C for 4 hrs. An orange precipitate formed which was further precipitated by cooling to room temperature. The orange solid was then filtered and washed with MeOH (5 mL) giving 9.8 mg, 26 % of the title compound. ¹H NMR (400 MHz, d₆-DMSO) δ 13.46 (s, 1H), 10.44 (s, 1H), 8.97 (s, 2H), 8.18 (d, J = 8.5 Hz, 1H), 7.94 (s, 1H), 7.78 (s, 1H), 7.48 (d, J = 8.8 Hz, 1H), 7.20 (s, 1H), 6.85 (d, J = 10.6 Hz, 1H), 6.80 (d, J = 9.0 Hz, 1H), 3.82 (br t, 4H), 3.59 (s, 3H), 2.39 (br t, 4H), 2.23 (s, 3H); MS ESI 468.3 [M + H]⁺, calcd for [C₂₆H₂₅N₇O₂ + H]⁺ 468.2.

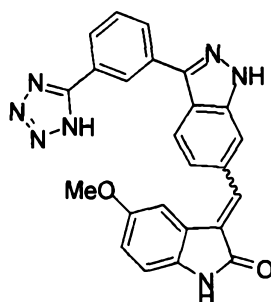
25 Example A152. (E & Z)-3-((3-(2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)-1H-indazol-6-yl)methylene)-5-(trifluoromethoxy)indolin-2-one

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According to the procedure for the synthesis of (E)-5-methoxy-3-((3-(2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)-1H-indazol-6-yl)methylene)indolin-2-one, except substituting 5-trifluoromethoxyindole (14 mg, 0.065 mmol), the title compound was prepared as a yellow solid (17.6 mg, 52 %). A mixture of (E)- and (Z)- isomers (83:17 by NMR) was obtained. ¹H NMR (400 MHz, d₆-DMSO) 13.51 (s, 1H), 10.85 (s, 1H), 8.97 (s, 2H), 8.18 (d, J = 8.2 Hz, 1H), 7.92 (s, 1H), 7.94 (s, 1H), 7.48-7.46 (m, 2H), 7.27 (d, J = 9.2 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 3.82 (br t, 4H), 2.39 (br t, 4H), 2.23 (s, 3H); MS ESI 522.3 [M + H]⁺, calcd for [C₂₆H₂₂F₃N₇O₂ + H]⁺ 522.2.

Example A153. (E and Z)-3-((3-(3-(1H-tetrazol-5-yl)phenyl)-1H-indazol-6-yl)methylene)-5-methoxyindolin-2-one



A. 3-(3-(1H-tetrazol-5-yl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde

A mixture of 3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (100 mg, 0.25 mmol), 3-(tetrazol-5-yl)phenylboronic acid (57 mg, 0.30 mmol), Pd(PPh₃)₄ (18 mg, 0.025 mmol) and 2M Na₂CO₃ (0.13 mL, 0.25 mmol) in DME/H₂O/EtOH (2.8 mL/0.8 mL/0.4 mL) was degassed by evacuation and blanketed with Ar. The reaction mixture was sealed and heated with stirring

under microwave irradiation at 125 °C for 4 hours. The crude reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using MeOH (5% to 10 %) in DCM as the eluent to provide a white solid (40 mg, 38 %). ¹H NMR (400 MHz, CD₃OD) δ ppm 10.10 (s, 1 H), 8.59 (s, 1 H), 8.25 (s, 1 H), 8.21 (d, *J* = 8.5 Hz, 1 H), 8.11 (d, *J* = 7.9 Hz, 1 H), 8.04 (d, *J* = 8.3 Hz, 1 H), 7.77 (d, *J* = 8.4 Hz, 1 H), 7.67 (t, *J* = 7.8 Hz, 1 H), 5.88 (s, 2 H), 3.66 (t, *J* = 8.1 Hz, 2 H), 0.89 (t, *J* = 8.0 Hz, 2 H), -0.10 (s, 9 H); MS ESI 421.1 (100) [M + H]⁺, calcd for [C₂₁H₂₄N₆O₂Si + H]⁺ 421.2.

5 *B. (E and Z)-3-((3-(3-(1H-tetrazol-5-yl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)methylene)-5-methoxyindolin-2-one*

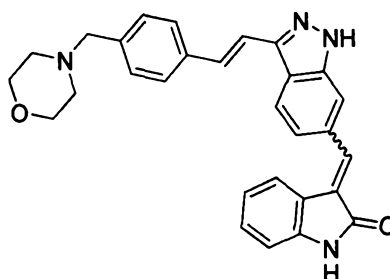
According to the procedure for the synthesis of (E)-5-methoxy-3-((3-(2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)-1H-indazol-6-yl)methylene)indolin-2-one, except substituting 3-(4-(1H-tetrazol-5-yl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (40 mg, 0.094 mmol), the title compound was prepared as an orange solid (39 mg, 73 %). A mixture of (E)- and (Z)- isomers (77:23 by NMR) was obtained. ¹H NMR (400 MHz, d₆-DMSO) δ 10.48 (s, 1H), 8.69 (s, 1H), 8.36 (d, *J* = 8.7 Hz, 1H), 8.25 (d, *J* = 7.8 Hz, 1H), 8.21 (s, 1H), 8.13 (d, *J* = 8.2 Hz, 1H), 7.81-7.77 (m, 2H), 7.66 (d, *J* = 8.6 Hz, 1H), 7.13 (d, *J* = 2.5 Hz, 1H), 6.88-6.80 (m, 2H), 5.90 (s, 2H), 3.66 (t, *J* = 8.3 Hz, 2H), 3.58 (s, 3H), 0.84 (t, *J* = 8.1 Hz, 2H), -0.11 (s, 9H); MS ESI 566.3 [M + H]⁺, calcd for [C₃₀H₃₁N₇O₃Si + H]⁺ 566.2.

15 *C. (E and Z)-3-((3-(3-(1H-tetrazol-5-yl)phenyl)-1H-indazol-6-yl)methylene)-5-methoxyindolin-2-one*

A round bottom flask was charged with (E and Z)-3-((3-(4-(1H-tetrazol-5-yl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)methylene)-5-methoxyindolin-2-one (35 mg, 0.062 mmol), concentrated HCl (1 mL), and EtOH (2 mL). The reaction was then heated to 72 °C for 4 hrs. A red precipitate formed which was further precipitated by cooling to room temperature. The red solid was then filtered and washed with MeOH (2 mL) giving 15 mg, 56 % of the title compound. A mixture of (E)- and (Z)- isomers (78:22 by NMR) was obtained. ¹H NMR (400 MHz, d₆-DMSO) 13.71 (br. s, 1H), 10.47 (s, 1H), 8.70 (s, 1H), 8.34 (d, *J* = 8.5 Hz, 1H), 8.27 (d, *J* = 7.8 Hz, 1H), 8.11 (d, *J* = 7.0 Hz, 1H), 8.01 (s, 1H), 7.81-

7.76 (m, 2H), 7.59 (d, $J = 8.6$ Hz, 1H), 7.21 (d, $J = 2.2$ Hz, 1H), 6.87 (dd, $J = 8.5, 2.4$ Hz, 1H), 6.81 (d, $J = 8.4$ Hz, 1H), 3.60 (s, 3H); MS ESI 436.3 $[M + H]^+$, calcd for $[C_{24}H_{17}N_7O_2 + H]^+$ 436.1.

5 Example A154. (E and Z)-3-((3-(4-(morpholinomethyl)styryl)-1H-indazol-6-yl)-methylene)indolin-2-one



A. (E)-3-(4-(morpholinomethyl)styryl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde

10 According to the method of example A57A, 3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (402 mg, 1 mmol) was reacted with 4-(4-vinylbenzyl)morpholine (304 mg, 1.5 mmol) to give the title compound upon silica gel purification (1:1 hexane/ethyl acetate) as a yellow solid (120 mg, 25 %). MS ESI 478.3 $[M + H]^+$, calcd for $[C_{27}H_{35}N_3O_3Si + H]^+$ 478.2.

15 B. (E)-3-((3-(4-(morpholinomethyl)styryl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)methylene)indolin-2-one

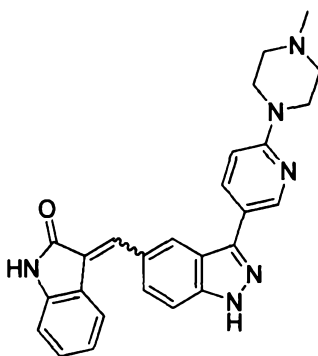
According to the method of A57B, oxindole (39 mg, 0.29 mmol) was reacted (E)-3-(4-(morpholinomethyl)styryl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (116 mg, 0.25 mmol) to give the title compound as a yellow solid
20 upon silica gel purification (95:5 $CH_2Cl_2/MeOH$) (95 mg, 64%). MS ESI 593.5 $[M + H]^+$, calcd for $[C_{35}H_{40}N_4O_3Si + H]^+$ 593.3

C. (E)-3-((3-(4-(morpholinomethyl)styryl)-1H-indazol-6-yl)methylene)indolin-2-one

According to the method of A57C, (E)-3-((3-(4-(morpholinomethyl)styryl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)methylene)indolin-2-one (95 mg, 0.16 mmol) was treated with boron trifluoride etherate, followed by 2 N HCl to give the title compound as an orange solid (33 mg, 42%). 1H NMR (400 MHz, CD_3OD)

δ 8.21 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 6.0 Hz), 7.78(d, J = 8.2 Hz, 2H), 7.66 (d, J = 7.6 Hz, 1H), 7.53-7.58 (m, 5H), 7.24 (t, J = 7.7 Hz, 1H), 6.93 (d, J = 7.6 Hz, 1H), 6.87 (td, J = 6.7 Hz, 0.9 Hz, 1H), 4.39 (s, 2H), 4.05-4.09 (m, 2H), 3.72-3.78 (m, 2H), 3.40-3.43 (m, 2H), 3.21-3.26 (m, 2H); MS ESI 463.3 $[M + H]^+$, calcd for $[C_{29}H_{26}N_4O_2 + H]^+$ 463.2.

Example A155. (*E* and *Z*)-3-((3-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1H-indazol-5-yl)methylene)indolin-2-one



10 *A. (E)-3-((3-iodo-1H-indazol-5-yl)methylene)indolin-2-one*

Piperidine (0.01 mL, 0.1 mmol) was added to a suspension of oxindole (72 mg, 0.54 mmol) and 3-iodo-1H-indazole-5-carbaldehyde (146 mg, 0.54 mmol) in EtOH (10 mL). On heating to 75°C, the suspended solid dissolved, and a new precipitate formed. Heating was continued at 75°C for 14 hrs. After the mixture was cooled to room temperature, suction filtration and rinsing with EtOH (4x2mL) gave 3-((3-iodo-1H-indazol-5-yl)methylene)indolin-2-one (yellow solid, 131.9mg, 63%). ¹H NMR (400 MHz, d⁶-DMSO) δ 13.75 (br. s, 1H), 10.61 (br. s, 1H), 7.84 (s, 1H), 7.77 (m, 2H), 7.69 (d, J = 8.8 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.23 (m, 1H), 6.88 (d, J = 8.0 Hz, 1H), 6.84 (m, 1H); MS ESI 388.0 $[M + H]^+$, calcd for $[C_{16}H_{10}IN_3O + H]^+$ 388.0.

20 *B. (E and Z)-3-((3-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1H-indazol-5-yl)methylene)-indolin-2-one*

The reaction was carried out according to the method of example A93-A, except substituting 3-((3-iodo-1H-indazol-5-yl)methylene)indolin-2-one (29.9 mg, 0.077 mmol) and 1-methyl-4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine (26.9 mg, 0.089 mmol). Purification using chromatography (10g silica

SPE tube, Silicycle, 5-15% MeOH in dichloromethane) yielded a dark yellow product (14.7 mg) contaminated with a compound identified as 3-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1H-indazole-5-carbaldehyde by LC-MS. Piperidine (0.2M in EtOH, 0.02 mL, 4 μ mol) was added to a solution of this crude material (10 mg) and oxindole (2.5 mg, 19 μ mol) in EtOH (1 mL) and the resulting mixture was heated at 80°C for 14h. After the solvent was evaporated, chromatography (5g silica SPE tube, Silicycle, 5-15% MeOH in dichloromethane) yielded the title compound as a yellow solid (60:40 mixture of E:Z isomers, 3.6 mg, 15%). ¹H NMR (400 MHz, CD₃OD) δ ppm 9.47 (s, 0.4 H), 8.87 (m, 0.4 H), 8.75 (s, 0.6 H), 8.38 (s, 0.6 H), 8.29 (m, 0.8 H), 8.17 (m, 0.6 H), 7.92 (m, 1 H), 7.80 (m, 0.6 H), 7.76-7.67 (m, 2 H), 7.59 (m, 0.4 H), 7.23 (m, 1.2 H), 7.09-7.01 (m, 1.6 H), 6.96-6.87 (m, 1.8 H), 3.80-3.72 (br m, 4 H), 2.90-2.82 (br m, 4 H), 2.58 (s, 1.2 H), 2.55 (s, 1.8 H); MS ESI 437.2 [M + H]⁺, calcd for [C₂₆H₂₄N₆O + H]⁺ 437.2.

15 **Example B: PLK4 Inhibition Assay**

Active PLK4 was purified from an *E. coli* expression system as an amino terminal GST fusion of residues 1-391 of human PLK4. The protein was purified from clarified cell extracts after induction at 15°C overnight using glutathione sepharose, gel permeation chromatography, and ion exchange (Resource Q). The resulting protein was dephosphorylated with lambda phosphatase (NEB cat# P0753), and resolved from the phosphatase using glutathione sepharose. The dephosphorylated GST-PLK4 was stored in aliquots at -80°C until use.

PLK4 activity was measured using an indirect ELISA detection system. Dephosphorylated GST-PLK4 (4 nM) was incubated in the presence of 15 μ M ATP (Sigma cat# A7699), 50 mM HEPES-Na²⁺ pH 7.4, 10 mM MgCl₂, 0.01% Brij 35 (Sigma cat# 03-3170), in a 96 well microtitre plate pre-coated with MBP (Millipore cat# 30-011). The reaction was allowed to proceed for 30 minutes, followed by 5 washes of the plate with Wash Buffer (50 mM TRIS-Cl pH 7.4 and 0.2% Tween 20), and incubation for 30 minutes with a 1:3000 dilution of primary antibody (Cell Signaling cat# 9381). The plate was washed 5 times with Wash Buffer, incubated for 30 minutes in the presence of secondary antibody coupled to horse radish peroxidase (BioRad cat# 1721019, 1:3000 concentration), washed an additional 5

times with Wash Buffer, and incubated in the presence of TMB substrate (Sigma cat# T0440). The colourimetric reaction was allowed to continue for 5 minutes, followed by addition of stop solution (0.5 N sulphuric acid), and quantified by detection at 450 nm with either a monochromatic or filter based plate reader

5 (Molecular Devices M5 or Beckman DTX880, respectively).

Compound inhibition was determined at either a fixed concentration (10 μ M) or at a variable inhibitor concentration (typically 50 μ M to 0.1 μ M in a 10 point dose response titration). Compounds were pre-incubated in the presence of enzyme for 15 minutes prior to addition of ATP and the activity remaining quantified using the
10 above described activity assay. The % Inhibition of a compound was determined using the following formula; % Inhibition = $100 \times (1 - (\text{experimental value} - \text{background value}) / (\text{high activity control} - \text{background value}))$. The IC_{50} value was determined using a non-linear 4 point logistic curve fit (XLfit4, IDBS) with the formula; $(A + (B / (1 + ((x/C)^D))))$, where A = background value, B = range, C =
15 inflection point, D = curve fit parameter.

Example C: PLK1 Inhibition Assay

PLK1 inhibition was determined using the Z-Lyte assay kit from Invitrogen (cat# PV3802). The assay was performed using the recommended manufacturer's
20 instructions with 25 μ M ATP and 8 nM PLK1 (Invitrogen cat # PV3501). The % inhibition values were determined according to the manufacturer's directions and IC_{50} values were obtained using a non-linear 4 point logistic curve fit (XLfit4, IDBS)

25 Example D: PLK2 Inhibition Assay

PLK2 inhibition was determined using the Z-Lyte assay kit from Invitrogen (cat# PV3802). The assay was performed using the recommended manufacturer's instructions with 60 μ M ATP and 133 nM PLK2 (Invitrogen cat # PV4204). The %
30 inhibition values were determined according to the manufacturer's directions and IC_{50} values were obtained using a non-linear 4 point logistic curve fit (XLfit4, IDBS)

Example E: Aurora A Inhibition Assay

Aurora A inhibition was determined using the Z-Lyte assay kit from Invitrogen. The assay was performed using the recommended manufacturer's instructions with 20 μ M ATP and 12 nM Aurora A (Invitrogen cat # PV3612). The % inhibition values were determined according to the manufacturer's directions and IC_{50} values were obtained using a non-linear 4 point logistic curve fit (XLfit4, IDBS)

Example F: Aurora B Inhibition Assay

Aurora B inhibition was determined using the Z-Lyte assay kit from Invitrogen. The assay was performed using the recommended manufacturer's instructions with 128 μ M ATP and 28 nM Aurora B (Invitrogen cat # PV3970). The % inhibition values were determined according to the manufacturer's directions and IC_{50} values were obtained using a non-linear 4 point logistic curve fit (XLfit4, IDBS)

In Tables 1 to 5 below, IC_{50} values for PLK4, PLK1, PLK2, Aurora A and Aurora B Kinases are indicated as "A," "B," and "C," for those less than or equal to 5 μ M; those greater than 5 μ M and less than or equal to 50 μ M; and those greater than 50 μ M, respectively. The relative inhibition percentages at a dose of 10 μ M are indicated as "X" and "Y" for those equal to or greater than 50% inhibition and those less than 50% inhibition, respectively. The relative inhibition percentages at a dose of 1 μ M are indicated as "W" and "Z" for those equal to or greater than 50% inhibition and those less than 50% inhibition, respectively. As shown in Tables 1 and 2, numerous compounds of the invention are effective PLK inhibitors, in particular PLK4 inhibitors. In addition, a number of compounds of the invention, as shown in Tables 1-5, inhibit Aurora kinases, in particular Aurora B kinase, in addition to PLK4.

Table 1: Inhibition Data of PLK4, PLK1, PLK2, Aurora A and Aurora B Kinases

| Compound # | IC ₅₀ Ranges | | | | |
|-------------|-------------------------|------|------|----------|----------|
| | PLK4 | PLK1 | PLK2 | Aurora A | Aurora B |
| Example A1 | A | B | B | Y | A |
| Example A33 | B | C | -- | -- | -- |

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| | | | | | |
|-------------|---|----|----|----|----|
| Example A4 | B | B | -- | -- | -- |
| Example A2 | A | B | Y | A | A |
| Example A3 | A | B | X | Y | B |
| Example A7 | A | B | -- | -- | -- |
| Example A23 | A | B | -- | -- | -- |
| Example A27 | B | B | -- | -- | -- |
| Example A21 | A | B | -- | -- | -- |
| Example A24 | A | B | -- | -- | -- |
| Example A14 | A | C | -- | -- | -- |
| Example A17 | B | B | -- | -- | -- |
| Example A29 | A | C | -- | -- | -- |
| Example A39 | A | -- | -- | -- | -- |
| Example A19 | B | B | -- | -- | -- |
| Example A28 | B | -- | -- | -- | -- |
| Example A40 | B | -- | -- | -- | -- |
| Example A5 | A | B | B | A | A |
| Example A34 | B | B | -- | -- | -- |
| Example A9 | A | A | -- | -- | -- |

Table 2: Inhibition Data of PLK4, PLK1, PLK2, Aurora A and Aurora B Kinases

| Compound # | PLK4 | PLK1 | PLK2 | Aurora A | Aurora B |
|-------------|------|------|------|----------|----------|
| Example A11 | A | C | Y | X | X |
| Example A8 | B | B | | -- | -- |
| Example A10 | A | A | | -- | -- |
| Example A15 | A | B | | -- | -- |
| Example A38 | A | B | Y | B | A |
| Example A25 | A | A | | -- | -- |
| Example A20 | A | A | -- | -- | -- |
| Example A26 | A | B | Y | A | Y |
| Example A12 | A | B | -- | -- | -- |
| Example A37 | B | C | C | Y | A |
| Example A22 | A | B | X | X | B |
| Example A13 | A | B | Y | X | Y |
| Example A16 | A | B | A | A | A |
| Example A32 | A | B | Y | X | A |
| Example A35 | A | C | Y | Y | A |

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| | | | | | |
|-------------|---|---|----|----|----|
| Example A36 | A | B | Y | C | A |
| Example A6 | A | B | A | A | A |
| Example A31 | A | C | B | Y | X |
| Example A18 | A | B | -- | -- | -- |
| Example A30 | B | C | -- | -- | -- |
| Example A41 | A | C | C | A | A |

Table 3: Inhibition Data of PLK4, PLK1, PLK2, Aurora A and Aurora B Kinases

| Compound # | PLK4 | PLK1 | PLK2 | Aurora A | Aurora B |
|-------------------|-------------|-------------|-------------|-----------------|-----------------|
| Example A42 | A | C | X | A | A |
| Example A43 | A | C | X | B | A |
| Example A44 | A | -- | -- | -- | -- |
| Example A45 | B | -- | -- | -- | -- |
| Example A46 | A | -- | -- | -- | -- |
| Example A47 | C | C | C | C | B |
| Example A48 | A | -- | -- | -- | -- |
| Example A49 | A | C | X | -- | -- |
| Example A50 | A | -- | -- | -- | -- |
| Example A51 | A | -- | -- | -- | B |
| Example A52 | A | -- | -- | -- | -- |
| Example A53a | A | Y | X | -- | A |
| Example A53b | A | -- | -- | -- | -- |
| Example A54a | A | C | X | X | A |
| Example A54b | A | -- | -- | -- | -- |
| Example A55 | A | -- | -- | -- | A |
| Example A56 | A | C | A | A | A |
| Example A57 | A | Y | X | A | A |
| Example A58 | A | Y | Y | A | A |
| Example A59 | A | Y | Y | A | A |
| Example A60 | A | Y | Y | A | A |
| Example A61 | A | Y | Y | A | A |
| Example A62 | A | Y | Y | A | A |
| Example A63 | A | Y | Y | -- | -- |

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| | | | | | |
|-------------|---|----|----|----|----|
| Example A64 | A | Y | Y | X | A |
| Example A65 | A | -- | -- | -- | -- |
| Example A66 | A | -- | -- | -- | -- |
| Example A67 | A | X | X | X | X |
| Example A68 | A | -- | -- | -- | -- |
| Example A69 | A | X | X | X | X |

Table 3: Inhibition Data of PLK4, PLK1, PLK2, Aurora A and Aurora B Kinases

| Compound # | PLK4 | PLK1 | PLK2 | Aurora A | Aurora B |
|-------------------|-------------|-------------|-------------|-----------------|-----------------|
| Example A70 | A | -- | -- | -- | -- |
| Example A71 | A | -- | -- | X | A |
| Example A72 | A | Y | Y | X | A |
| Example A73 | A | -- | -- | -- | -- |
| Example A74 | A | -- | -- | -- | -- |
| Example A75 | B | -- | -- | -- | -- |
| Example A76 | B | -- | -- | -- | -- |
| Example A77 | B | -- | -- | -- | -- |
| Example A78 | A | -- | -- | -- | -- |
| Example A79 | B | -- | -- | -- | -- |
| Example A80 | A | Y | Y | A | A |
| Example A81 | A | Y | Y | A | A |
| Example A82 | A | -- | -- | -- | -- |
| Example A83 | A | X | X | X | A |
| Example A84 | A | Y | Y | A | A |
| Example A85 | A | Y | Y | A | A |
| Example A86 | A | Y | Y | X | A |
| Example A87 | A | Y | Y | X | A |
| Example A88 | A | -- | -- | -- | A |
| Example A89 | A | Y | Y | A | A |
| Example A90 | A | -- | -- | -- | -- |
| Example A91 | A | Y | Y | B | A |
| Example A92 | A | -- | -- | -- | -- |

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| | | | | | |
|-------------|---|----|----|----|----|
| Example A93 | A | Y | Y | A | A |
| Example A94 | A | Y | Y | C | A |
| Example A95 | A | -- | -- | -- | -- |
| Example A96 | A | Y | -- | X | A |
| Example A97 | A | -- | -- | -- | A |
| Example A98 | A | -- | -- | -- | -- |
| Example A99 | A | -- | -- | -- | -- |

Table 4: Inhibition Data of PLK4, PLK1, PLK2, Aurora A and Aurora B Kinases

| Compound # | IC50 Ranges | | | | |
|--------------|-------------|------|------|----------|----------|
| | PLK4 | PLK1 | PLK2 | Aurora A | Aurora B |
| Example A100 | A | Y | Y | X | A |
| Example A101 | A | Y | Y | X | A |
| Example A102 | A | -- | -- | -- | -- |
| Example A103 | A | Y | Y | X | A |
| Example A104 | A | Y | Y | A | A |
| Example A105 | A | -- | -- | -- | -- |
| Example A106 | A | Y | -- | X | A |
| Example A107 | A | X | Y | A | A |
| Example A108 | A | Y | Y | A | A |
| Example A109 | A | Y | Y | A | A |
| Example A110 | A | Y | Y | A | A |
| Example A111 | A | Y | Y | A | -- |
| Example A112 | A | Y | Y | A | A |
| Example A113 | A | Y | Y | A | A |
| Example A114 | A | Y | Y | A | A |
| Example A115 | A | Y | Y | A | A |
| Example A116 | A | Y | Y | A | A |
| Example A117 | A | Y | Y | A | A |
| Example A118 | A | Y | Y | A | A |
| Example A119 | A | Y | Y | A | A |
| Example A120 | A | Y | Y | A | A |
| Example A121 | A | -- | -- | -- | A |

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| | | | | | |
|--------------|---|----|----|----|---|
| Example A122 | A | -- | -- | -- | A |
| Example A123 | A | -- | -- | A | A |
| Example A124 | A | -- | -- | A | A |
| Example A125 | A | -- | -- | X | A |
| Example A126 | A | -- | -- | X | A |
| Example A127 | A | -- | -- | A | A |
| Example A128 | A | -- | -- | A | A |
| Example A129 | A | -- | -- | -- | A |

Table 5: Inhibition Data of PLK4, Aurora A and Aurora B Kinases

| Compound # | PLK4 | Aurora A | Aurora B |
|---------------|------|----------|----------|
| Example A130 | A | -- | A |
| Example A131 | A | -- | -- |
| Example A132 | A | A | A |
| Example A133 | A | -- | -- |
| Example A134 | A | -- | -- |
| Example A135 | A | -- | -- |
| Example A136a | A | -- | A |
| Example A136b | A | A | A |
| Example A137 | A | A | A |
| Example A138 | A | A | A |
| Example A139 | A | A | A |
| Example A140 | A | A | A |
| Example A141 | A | W | A |
| Example A142 | A | W | A |
| Example A143 | A | W | A |
| Example A144 | A | A | A |
| Example A145 | A | A | A |
| Example A146 | A | A | A |
| Example A147 | A | -- | -- |
| Example A148 | A | -- | A |

| | | | |
|--------------|---|----|----|
| Example A149 | A | B | A |
| Example A150 | A | -- | -- |
| Example A151 | A | B | A |
| Example A152 | A | -- | B |
| Example A153 | A | A | A |
| Example A154 | A | -- | -- |
| Example A155 | A | -- | -- |

Example G: Kinase Selectivity Assays

The inhibitory activity of selected compounds of the invention was evaluated against a panel of 45 different kinase enzymes by CEREP, France. The assays were

- 5 performed using standard HTRF assay methods as documented by CEREP against the human orthologues of Abl kinase, Akt1/PKBa, AMPKa, BMX kinase (Etk), Brk, CaMK2a, CaMK4, CDC2/CDK1 (cycB), CDK2 (cycE), CHK1, CHK2, c-Met kinase, CSK, EphB4 kinase, ERK1, ERK2 (P42mapk), FGFR2 kinase, FGFR4 kinase, FLT-1 kinase (VEGFR1), FLT-3 kinase, Fyn kinase, IGF1R kinase, IRK
 10 (InsR), JNK 2, KDR kinase (VEGFR2), Lck kinase, Lyn kinase, MAPKAPK2, MEK1/MAP2K1, p38a kinase, p38d kinase, p38g kinase, PDGFRb kinase, PDK1, PKA, PKCa, PKCb1, PKCb2, PKCg, Ret kinase, ROCK2, RSK2, Src kinase, Syk, and TRKA. The % Inhibition was determined
 15 by the formula; % Inhibition = 100 x (1 – (experimental value – background value)/(high activity control – background value)), and tabulated below.

Table 6: Percent Inhibition Values For Examples A1, A5, A41, A60, A97 and A132 at 10 μ M Concentration

| Kinase | % Inhibition at 10 μ M Concentration | | | | | |
|---------------|------------------------------------------|------------|-------------|-------------|-------------|--------------|
| | Example A1 | Example A5 | Example A41 | Example A60 | Example A97 | Example A132 |
| Abl | 34 | 24 | 100 | 40 | 99 | 23 |
| Akt1/PKBalpha | -3 | -4 | -3 | -14 | -4 | -5 |
| AMPKalpha | 15 | 54 | 81 | 8 | 76 | 34 |
| BMX (Etk) | 15 | -3 | 53 | 18 | 9 | 0 |
| Brk | 5 | -6 | 40 | 4 | 7 | -2 |
| CaMK2alpha | 4 | -3 | 31 | -2 | 14 | 2 |

| | | | | | | |
|----------------|-----|----|-----|-----|-----|-----|
| CaMK4 | 3 | 26 | 27 | -15 | 2 | 6 |
| CDC2/CDK1 | 2 | 9 | 62 | 18 | 15 | 11 |
| CDK2 (cycE) | 10 | 16 | 8 | 5 | 3 | -- |
| CHK1 | -6 | -2 | 7 | -1 | 3 | 0 |
| CHK2 | 14 | 2 | 22 | 6 | 4 | -4 |
| c-Met | -20 | 2 | 35 | 0 | 28 | 2 |
| CSK | 8 | 5 | 86 | 17 | 51 | 6 |
| EphB4 | 5 | -5 | 85 | -14 | 6 | -1 |
| ERK1 | 6 | 6 | 13 | 1 | 10 | 2 |
| ERK (P42mapk) | 3 | 0 | 14 | 2 | -9 | 15 |
| FGFR2 | 68 | 31 | 97 | 10 | 35 | 4 |
| FGFR4 | 18 | -4 | 38 | 6 | 30 | -30 |
| FLT-1 (VEGFR1) | 0 | 16 | 99 | 42 | 73 | 30 |
| FLT-3 | 93 | 76 | 100 | 10 | 100 | 32 |
| Fyn | 24 | 5 | 91 | 70 | 13 | 4 |
| IGF1R | 7 | -4 | 43 | 81 | 4 | 5 |
| IRK (InsR) | 13 | 12 | 34 | 6 | 9 | 2 |
| JNK 2 | 13 | 14 | 52 | 3 | 14 | 15 |
| KDR (VEGFR2) | 59 | 29 | 100 | 8 | 93 | 32 |
| Lck | 15 | 0 | 88 | 30 | 89 | 13 |
| Lyn | 14 | -5 | 98 | 88 | 85 | -2 |
| MAPKAPK2 | 6 | 0 | 0 | 19 | 4 | 6 |
| MEK1/MAP2K1 | 20 | 3 | 46 | 16 | 9 | -3 |
| p38alpha | -8 | 18 | 16 | 1 | 11 | 22 |
| p38delta | 0 | -8 | -5 | 3 | 13 | -2 |
| p38gamma | 14 | 5 | 2 | 10 | 1 | 12 |
| PDGFRbeta | 46 | 19 | 100 | 2 | 0 | 14 |
| PDK1 | -3 | 2 | 4 | 1 | 73 | 5 |
| PKA | 9 | -1 | -4 | 7 | 0 | -5 |
| PKCalpha | 9 | 0 | 2 | -1 | 9 | 7 |
| PKCbeta 1 | 1 | -5 | -2 | 0 | 2 | 1 |
| PKCbeta 2 | 0 | 2 | 12 | 4 | 37 | 4 |
| PKCgamma | 9 | -6 | 0 | 3 | 0 | 3 |
| Ret | 67 | 41 | 98 | 33 | 93 | 33 |
| ROCK2 | 1 | 3 | -3 | -1 | 22 | -20 |
| RSK2 | 4 | 1 | 38 | 0 | 37 | -4 |
| Src | 10 | -9 | 59 | 0 | 24 | 26 |
| Syk | -2 | -3 | 70 | -- | 21 | -1 |
| TRKA | -13 | 60 | 99 | 75 | 93 | 43 |

Table 6 shows the percent inhibition values obtained for Examples A1, A5, A41, A60, A97 and A132 at 10 μ M concentration. From this inhibition data it is apparent that certain kinases, e.g. Abl, FGFR2, FLT-1, FLT-3, KDR, Lyn, PDGFRbeta Ret and TRKA kinases are strongly inhibited (i.e. >95%) by compounds of the invention at 10 μ M. For a number of compounds, IC50 values were estimated against kinases of interest based on Millipore protocols. Kinase assays at Millipore were performed using a radiolabelled phosphopeptide filter binding detection

system, in duplicate, at each compound concentration. The ATP substrate concentration in the reactions was at the K_m for each enzyme.

- To allow for a more direct comparison of compound inhibition, an IC_{50} value was estimated from the inhibition determined at three compound concentrations. Several assumptions were made to allow this calculation using a 4 parameter non linear curve fit model, including full inhibition set at 100%, no inhibition set to 0%, and a curve fit parameter set at 1. The inflection point was reported as the estimated IC_{50} .

- In Table 7, IC_{50} value estimates against the Receptor Tyrosine Kinase family (e.g. Abl, FGFR2, FLT-1, KDR, Lyn, and PDGFR β) are indicated as "A," "B," and "C," for those less than or equal to 5 μM ; those greater than 5 μM and less than or equal to 50 μM ; and those greater than 50 μM , respectively. These activities may impart additional therapeutic benefit to these compounds.

Table 7. IC_{50} value estimates against Abl, FGFR2, FLT-1, KDR, Lyn, and PDGFR β

| Compound # | Abl | FGFR1 | FLT-1 | KDR | Lyn | PDGFR β | Ret | TrkA |
|-------------|-----|-------|-------|-----|-----|---------------|-----|------|
| Example A41 | A | A | A | A | A | A | A | A |
| Example A57 | A | A | A | A | A | A | A | A |
| Example A97 | A | A | A | A | B | B | A | A |
| Example 106 | A | A | A | A | A | A | A | A |

Example H: PLK3 Inhibition Assay

- PLK3 inhibition was determined using the Z-Lyte assay kit from Invitrogen (cat# PV3802). The assay was performed using the recommended manufacturer's instructions with 100 μM ATP and 21 nM PLK3 (Invitrogen cat # PV3812). The % inhibition values were determined according to the manufacturer's directions and IC_{50} values were obtained using a non-linear 4 point logistic curve fit (XLfit4, IDBS). The majority of the compounds of the invention tested in this assay inhibited PLK3 with IC_{50} values of less than or equal to 0.5 μM ; certain compound examples including A2, A6, A26, A45, A49, A125, A127, A148, A149, A152 and A153 exhibited PLK3 IC_{50} values of greater than 0.5 μM .

Example I: Cancer Cell Line Data of Compounds of the Invention

Breast cancer cells (MCF-7, MDA-MB-468, HCC1954), colon cancer cells (SW620) and lung cancer cells (A549), together with human mammary epithelial primary cells (HMEC), were seeded (1000 to 4000 per 80µl per well depending on the cell growth rate) into 96 well plates, 24 hours before compound overlay. Compounds were prepared as 10mM stock solutions in 100% DMSO which were diluted with DMEM (Dulbecco's Modified Eagle's Medium) cell growth Medium (Invitrogen, Burlington, ON, Canada) containing 10% FBS (Fetal Bovine Serum) to concentrations ranging from 50nM to 250µM. Aliquots (20µl) from each concentration were overlaid to 80µl of the pre-seeded cells in the 96 well plates to make final concentrations of 10nM to 50µM. The cells were cultured for 5 days before the Sulforhodamine B assay (SRB) was performed to determine the compound's cell growth inhibition activity.

Sulforhodamine B (purchased from Sigma, Oakville, ON, Canada) is a water-soluble dye that binds to the basic amino acids of the cellular proteins. Thus, colorimetric measurement of the bound dye provides an estimate of the total protein mass that is related to the cell number. the cells are fixed in situ by gently aspirating off the culture media and adding 50µl ice cold 10% Tri-chloroacetic Acid (TCA) per well and incubate at 4°C for 30-60 min, The plates are washed with water five times and allowed to air dry for 5min. Addition of 50µl 0.4%(w/v) SRB solution in 1% (v/v) acetic acid to each well and incubation for 30min at RT completes the staining reaction. Following staining, plates are washed four times with 1% acetic acid to remove unbound dye and then allowed to air dry for 5min. The stain is solubilized with 100µl of 10mM Tris pH10.5 per well. Absorbance is read at 570nm.

The percentage (%) of relative growth inhibition was calculated by comparing to DMSO treated only cells (100%). GI₅₀'s were determined for compounds with cytotoxic activity. The GI₅₀ was calculated using GraphPad PRISM software (GraphPad Software, Inc., San Diego, CA, USA). GI₅₀ (growth inhibition) is the compound concentration that causes 50% inhibition of cell growth.

In Table 8 below, GI₅₀ value ranges for several compound examples against a luminal breast cancer cell line (MCF-7), two basal breast cancer cell line (MDA-MB-468, HCC1954), a lung cancer cell line (A549), a colon cancer cell line (SW-

620) and primary breast cells (HMEC) are given. The example compounds demonstrated varying growth inhibition/cell killing activity against cancer cells of luminal breast cancer and basal breast cancer cell, lung cancer and colon cancer. In general, these compounds showed less activity against normal cells as exemplified by HMEC. The GI₅₀ ranges are indicated as "A," "B," "C," and "D," for values less than or equal to 5 μ M; those greater than 5 μ M and less than or equal to 20 μ M; those greater than 20 μ M and less than or equal to 50 μ M; and those greater than 50 μ M, respectively.

Table 8: Cell Growth Inhibition Data

| Example # | Cell Line GI ₅₀ Range | | | | | |
|-----------|----------------------------------|------------|----------|--------|-------|------|
| | MCF-7 | MDA-MB-468 | HCC-1954 | SW-620 | A-549 | HMEC |
| A2 | D | B | -- | -- | -- | -- |
| A4 | B | B | -- | -- | -- | -- |
| A6 | B | B | -- | -- | -- | -- |
| A10 | C | C | -- | -- | -- | -- |
| A19 | B | A | -- | -- | -- | -- |
| A32 | B | B | -- | -- | -- | -- |
| A31 | A | A | -- | -- | -- | -- |
| A41 | A | A | C | B | B | D |
| A59 | A | A | B | A | B | -- |
| A84 | A | A | B | A | D | D |
| A91 | A | A | A | A | -- | B |
| A96 | A | A | A | A | A | -- |
| A97 | A | A | A | A | A | C |
| A103 | A | A | B | A | B | D |
| A106 | A | A | A | A | A | B |
| A108 | A | A | A | A | A | A |
| A109 | A | A | D | A | A | D |
| A127 | A | A | A | A | B | -- |
| A147 | C | B | D | C | D | -- |
| A150 | A | A | A | A | A | -- |

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In addition to the cell lines tested as described above, selected compounds have been assayed against an extended panel. These include: breast cancer cell lines (T47 D, MDA-MB-231, HS578T, BT474, SKBR3, HCC1954), a lung cancer cell line (H358), brain cancer cell lines (A172, Hs683, SK-N-SH), Colon cancer cell lines (Colo 205, CT-15, HCT116+/-, HCT116+/+), ovarian cancer cell lines (OVCAR-3, SK-OV-3, SW 626), a melanoma cell line (518A2), a prostate cancer

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cell line (PC-3) and an immortalized breast cell line (184A1). The sulforhodamine B assay (SRB) described above was used to assay test compounds against the extended panel (Table 9). The GI₅₀ ranges are indicated as "A," "B," "C," and "D," for values less than or equal to 5 μ M; those greater than 5 μ M and less than or equal to 20 μ M; those greater than 20 μ M and less than or equal to 50 μ M; and those greater than 50 μ M, respectively.

Table 9: Cell Growth Inhibition Data

| Example # Cell line | GI ₅₀ Range | | | | |
|------------------------|------------------------|-----|------|------|------|
| | A41 | A97 | A109 | A108 | A132 |
| T47 D | A | A | A | A | A |
| MDA-MB-231 | B | A | A | A | A |
| HS578T | B | A | A | A | A |
| BT474 | D | A | B | A | A |
| SKBR3 | A | A | D | A | A |
| HCC1954 | A | A | D | A | A |
| H358 | A | -- | A | A | A |
| A172 | A | -- | A | A | A |
| Hs683 | A | -- | A | A | A |
| SK-N-SH | A | -- | A | A | A |
| Colo 205 | A | A | A | A | A |
| HCT-15 | A | -- | A | A | A |
| HCT116+/- | D | A | A | A | A |
| HCT116+/+ | D | A | A | A | A |
| OVCAR-3 | D | -- | A | A | A |
| SK-OV-3 | D | -- | B | A | A |
| SW 626 | D | -- | B | A | A |
| 518A2 | A | -- | A | A | A |
| PC-3 | C | -- | A | A | A |
| 184A1 | C | A | A | A | A |

Some compounds of the invention, although inhibiting the isolated PLK-4 enzyme activity, generally failed to inhibit the growth of Breast Cancer cell lines, i.e.,. Compound examples A7, A9, A70 and A111 had GI₅₀ values > 50 µM on the MCF-7, MDA-MB-468 and T47D Breast cancer cell lines.

5 Example J: In vitro Angiogenesis Assay.

Compounds of the invention had micromolar and submicromolar activity against Receptor Tyrosine Kinases (RTKs) such as FGFR2, VEGFR1, VEGFR2 and PDGFRbeta. Activity against these RTKs can result in antiangiogenic activity which is associated with slowed tumor growth and/or tumor regression. To measure the effects of these compounds they were tested in an angiogenesis assay as described below. Note that compound Example A57 showed anti-angiogenic effects at micromolar concentrations (Figure 1).

HUV-EC-C cells were obtained from the American Type Culture Collection (ATCC, CRL-1730), and were used at early passage for the assay. The *in vitro* Angiogenesis Assay Kit (Chemicon) was used according to the manufacturer's recommendation. An ice-cold mixture of ECMatrix was transferred into a precooled 96-well plate. After the matrix solution had solidified (>1 hr incubation at 37 °C), 8,000 cells were mixed with the appropriate inhibitor concentration (in 100 microlitres EGM-2) and plated into each well. After incubation at 37 °C for 4 hr, tube formation was inspected. Two methods, pattern recognition and branch point counting, were used to quantify the progression of angiogenesis and expressed as a percentage of the control tube count (Figure 1).

While this invention has been particularly shown and described with references to example embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

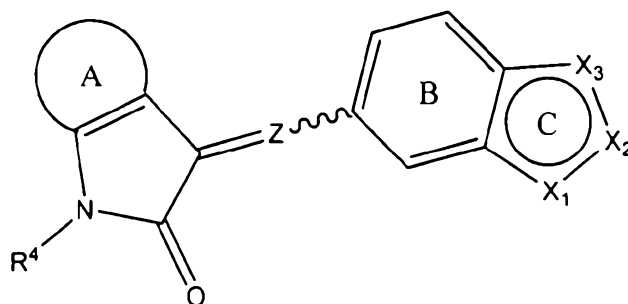
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Throughout this specification, unless the context requires otherwise, the word "comprise" or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element or integer or method step or group of elements or integers or method steps but not the exclusion of any element or integer or method step or group of elements or integers or method steps.

Reference to any prior art in this specification is not, and should not be taken as, an acknowledgment or any form of suggestion that this prior art forms part of the common general knowledge in any country.

CLAIMS:

1. A compound represented by the following structural formula:



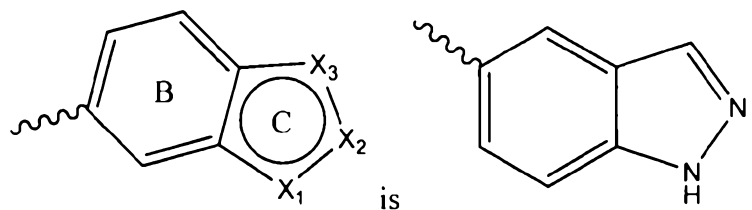
or a pharmaceutically acceptable salt thereof, wherein:

ring A is an optionally substituted 5- or 6-membered carbocyclic aromatic or heteroaromatic ring;

ring B is an optionally substituted phenyl ring; and

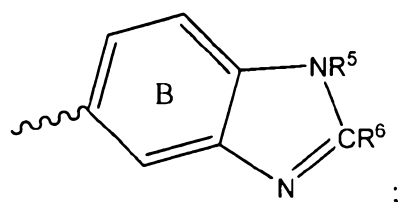
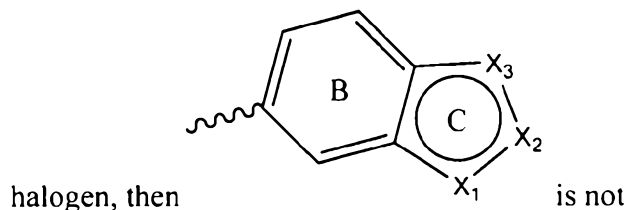
ring C is a 5-membered heteroaromatic ring wherein one of X1-X3 is N, one of X1-X3 is NR⁵, and one of X1-X3 is N or CR⁶;

Z is =N- or =CR³-, provided that when Z is =N-,



R⁴ is H or C1-C6 alkyl, then ring A is not phenyl or phenyl substituted with halogen or trifluoromethyl;

R³ is -H, halogen, C1-C6 alkyl or C1-C6 haloalkyl, provided when R³ is



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R^4 is -H, C1-C6 alkyl, -C(O)(C1-C6 alkyl), -C(O)(phenyl), -C(O)O(C1-C6 alkyl), -C(O)O(phenyl), -S(O)₂(C1-C6 alkyl) or -S(O)₂(phenyl);

R^5 is -H, C1-C6 alkyl, phenyl, -C(O)(C1-C6 alkyl), -C(O)(phenyl), -C(O)O(C1-C6 alkyl), -C(O)O(phenyl), -S(O)₂(C1-C6 alkyl) or -S(O)₂(phenyl), wherein each said alkyl in the groups represented by R^4 and R^5 independently is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, phenyl, 5-6 membered heteroaryl, C1-C6 alkoxy and C1-C6 haloalkoxy, and wherein each said phenyl in the groups represented by R^4 and R^5 independently is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 alkoxy and C1-C6 haloalkoxy;

R^6 is hydrogen, halogen, nitro, cyano, R' , -OR, -SR, -N(R)₂, -C(O)R, -C(O)OR, -OC(O)R, -C(O)N(R)₂, -OC(O)N(R)₂, -NRC(O)R, -NRC(O)OR, -SOR', -SO₂R', -SO₃R', -SO₂N(R)₂, -NRS(O)R', -NRSO₂R', -NRC(O)N(R)₂, -NRC(O)ON(R)₂, or -NRSO₂N(R)₂; and each R independently is hydrogen, C₁₋₁₀ aliphatic, phenyl or 5-6 membered heteroaryl, wherein said aliphatic is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, phenyl, 5-6 membered heteroaryl, C1-C6 alkoxy, C1-C6 haloalkoxy, and wherein each of the phenyl and heteroaryl groups represented by R, and the phenyl and heteroaryl groups in the substituents for the aliphatic group represented by R independently is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 alkoxy, C1-C6 haloalkoxy, or

N(R)₂ forms a non-aromatic heterocyclic group optionally substituted with one or more substituents selected from the group consisting of =O, =S, halogen, nitro, cyano, hydroxy, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆

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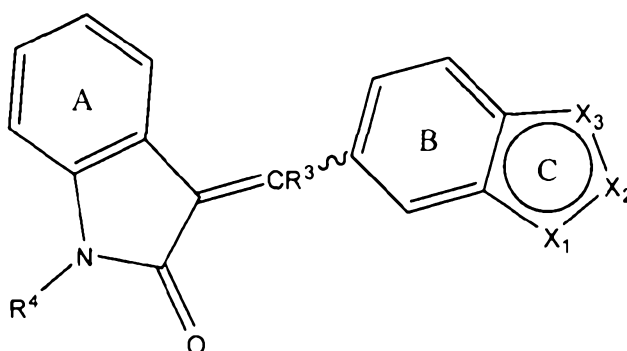
hydroxyalkyl, amino, C₁₋₆ alkylamino, C₁₋₆ dialkylamino, C₁₋₆ aminoalkyl, (C₁₋₆ alkylamino)C₁₋₆ alkyl, (C₁₋₆ dialkylamino)C₁₋₆ alkyl, (phenyl)C₁₋₆ alkyl, (5-6 membered heteroaryl)C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₆ alkylcarbonyloxy, C₁₋₆ alkoxycarbonyl, C₁₋₆ alkylcarbonyl, phenyl and 5-6 membered heteroaryl; and

each R' independently is C₁₋₁₀ aliphatic, phenyl or 5-14 membered heteroaryl, wherein said aliphatic is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, phenyl, 5-6 membered heteroaryl, C1-C6 alkoxy, C1-C6 haloalkoxy, C₁₋₆ alkylamino, C₁₋₆ dialkylamino, -C(O)(C1-C6 alkyl), -C(O)(C1-C6 haloalkyl), -C(O)(phenyl), -C(O)(non-aromatic heterocyclic group), -C(O)O(optionally substituted C1-C6 alkyl), -C(O)O(C1-C6 haloalkyl), -C(O)O(phenyl), -OC(O)(optionally substituted C1-C6 alkyl), -OC(O)(C1-C6 haloalkyl), -OC(O)(phenyl), -S(O)₂(C1-C6 alkyl), -S(O)₂(C1-C6 haloalkyl) and -S(O)₂(phenyl), and wherein each of the phenyl and heteroaryl groups represented by R', and the phenyl and heteroaryl groups in the substituents for the aliphatic group represented by R' independently is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C1-C6 alkyl, C1-C6 haloalkyl, C₁₋₆ aminoalkyl, (C₁₋₆ alkylamino)C₁₋₆ alkyl, (C₁₋₆ dialkylamino)C₁₋₆ alkyl, (phenyl)C₁₋₆ alkyl, C1-C6 alkoxy, C1-C6 haloalkoxy, non-aromatic heterocyclic group, C₁₋₆ alkylamino, C₁₋₆ dialkylamino, -C(O)(C1-C6 alkyl), -C(O)(C1-C6 haloalkyl), -C(O)(phenyl), -C(O)(non-aromatic heterocyclic group), -C(O)O(C1-C6 alkyl), -C(O)O(C1-C6 haloalkyl), -C(O)O(phenyl), -OC(O)(C1-C6 alkyl), -OC(O)(C1-C6 haloalkyl), -OC(O)(phenyl), -S(O)₂(C1-C6 alkyl), -S(O)₂(C1-C6 haloalkyl), -S(O)₂(phenyl), -(CH₂)_{0.3}-N-piperidiny, -(CH₂)_{0.3}-N-morpholinyl, -(CH₂)_{0.3}-N-

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pyrrolidinyl and $-(CH_2)_{0-3}$ -*N*-piperazinyl, wherein the *N*-piperazinyl is optionally *N'*-substituted with C_{1-6} alkyl or C_{1-6} acyl.

2. The compound of Claim 1, wherein the compound is represented by the following structural formula:



or a pharmaceutically acceptable salt thereof, wherein ring A and ring B are optionally substituted.

3. The compound of Claim 2, wherein:

R^3 is -H, C1-C6 alkyl or C1-C6 haloalkyl;

each R' independently is C_{1-10} aliphatic, phenyl or 5-6 membered heteroaryl, wherein said aliphatic is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, phenyl, 5-6 membered heteroaryl, C1-C6 alkoxy, C1-C6 haloalkoxy, and wherein each of the phenyl and heteroaryl groups represented by R' , and the phenyl and heteroaryl groups in the substituents for the aliphatic group represented by R' independently is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 alkoxy, C1-C6 haloalkoxy;

phenyl ring A is optionally substituted with one or more substituents Q^a , and phenyl ring B is optionally substituted with one or more substituents Q^b , each of Q^a and Q^b independently is selected from the group consisting of halogen,

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$-X-R^1$, $-NO_2$, $-CN$, $-NCS$, Ar^1 , $(C_{1-10} \text{ alkylene})-Ar^1$, $(C_{2-10} \text{ alkenylene})-Ar^1$, $-O-[CH_2]_p-O-$, $-S-[CH_2]_p-S-$ and $-[CH_2]_q-$,

wherein X is $-C(O)O-$, $-C(O)-$, $-C(S)-$, $-OC(O)-$, $-C(O)N(R^2)-$, $-C(S)N(R^2)-$,
 $-OC(O)N(R^2)-$, $-S(O)-$, $-S(O)_2-$, $-SO_3-$, $-SO_2NR^2-$, $-O-$, $-S-$, $-NR^2-$,
 $-NR^2C(O)-$, $-NR^2S(O)-$, $-NR^2C(O)O-$, $-NR^2C(O)ONR^2-$,
 $-N(R^2)C(O)NR^2-$, $-NR^2SO_2NR^2-$ or $-NR^2SO_2-$;

each R^1 independently is:

- i) hydrogen;
- ii) a C_{6-14} aryl group or a 5-14 membered heteroaryl group, each optionally and independently substituted with one or more substituents selected from the group consisting of halogen, $-NO_2$, $-CN$, $-NCS$, Ar^{10} , $(C_{1-10} \text{ alkylene})-Ar^{10}$, $(C_{2-10} \text{ alkenylene})-Ar^{10}$, $-C(O)OR^{10}$, $-C(O)R^{10}$, $-C(S)R^{10}$, $-OC(O)R^{10}$, $-C(O)N(R^{11})_2$, $-C(S)N(R^{11})_2$, $-OC(O)N(R^{11})_2$, $-S(O)R^{12}$, $-S(O)_2R^{12}$, $-SO_3R^{12}$, $-SO_2N(R^{11})_2$, $-OR^{10}$, $-SR^{10}$, $-N(R^{11})_2$, $-NR^{11}C(O)R^{10}$, $-NR^{11}S(O)R^{12}$, $-NR^{11}C(O)OR^{12}$, $-N(R^{11})C(O)N(R^{11})_2$, $-NR^{11}SO_2N(R^{11})_2$ and $-NR^{11}SO_2R^{12}$; or
- iii) a C_{1-10} aliphatic group optionally substituted with one or more substituents selected from the group consisting of halogen, $-NO_2$, $-CN$, $-NCS$, Ar^{10} , $-C(O)OR^{10}$, $-C(O)R^{10}$, $-C(S)R^{10}$, $-OC(O)R^{10}$, $-C(O)N(R^{11})_2$, $-C(S)N(R^{11})_2$, $-OC(O)N(R^{11})_2$, $-S(O)R^{12}$, $-S(O)_2R^{12}$, $-SO_3R^{12}$, $-SO_2N(R^{11})_2$, $-OR^{10}$, $-SR^{10}$, $-N(R^{11})_2$, $-NR^{11}C(O)R^{10}$, $-NR^{11}S(O)R^{12}$, $-NR^{11}C(O)OR^{12}$, $-N(R^{11})C(O)N(R^{11})_2$, $-NR^{11}SO_2N(R^{11})_2$ and $-NR^{11}SO_2R^{12}$,

provided that R^1 is other than hydrogen when X is $-S(O)-$, $-S(O)_2-$, $-SO_3-$, $-NR^2S(O)-$ or $-NR^2SO_2-$; and

each R^2 independently is R^1 , $-CO_2R^1$, $-SO_2R^1$ or $-C(O)R^1$, or, taken together with NR^1 , forms a non-aromatic heterocyclic group optionally substituted with one or more substituents selected from the group consisting of $=O$, $=S$, halogen, nitro, cyano, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, C_{1-6} aminoalkyl, $(C_{1-6}$

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alkylamino)C₁₋₆ alkyl, (C₁₋₆ dialkylamino)C₁₋₆ alkyl, (phenyl)C₁₋₆ alkyl, (5-6 membered heteroaryl)C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₆ alkylcarbonyloxy, C₁₋₆ alkoxycarbonyl, C₁₋₆ alkylcarbonyl, phenyl and 5-6 membered heteroaryl;

each R¹⁰ independently is:

- i) hydrogen;
- ii) a C₆₋₁₄ aryl group or a 5-14 membered heteroaryl group, each optionally and independently substituted with one or more substituents selected from the group consisting of halogen, nitro, cyano, hydroxy, C₁₋₁₀ alkyl, C₁₋₁₀ haloalkyl, (C₁₋₁₀ haloalkoxy)C₁₋₁₀ alkyl, (C₁₋₁₀ alkoxy)C₁₋₁₀ alkyl, C₁₋₁₀ hydroxyalkyl, C₁₋₁₀ aminoalkyl, (C₁₋₁₀ alkylamino)C₁₋₁₀ alkyl, (C₁₋₁₀ dialkylamino)C₁₋₁₀ alkyl, (phenyl)C₁₋₁₀ alkyl, (5-6 membered heteroaryl)C₁₋₁₀ alkyl, amino, C₁₋₁₀ alkylamino, C₁₋₁₀ dialkylamino, C₁₋₁₀ alkoxy, C₁₋₁₀ haloalkoxy, C₁₋₁₀ alkylcarbonyloxy, C₁₋₁₀ alkoxycarbonyl and C₁₋₁₀ alkylcarbonyl; or
- iii) a C₁₋₁₀ alkyl group optionally substituted with one or more substituents selected from the group consisting of halogen, nitro, cyano, hydroxy, C₁₋₁₀ haloalkyl, C₁₋₁₀ alkoxy, C₁₋₁₀ haloalkoxy, amino, C₁₋₁₀ alkylamino, C₁₋₁₀ dialkylamino, C₁₋₁₀ alkylcarbonyloxy, C₁₋₁₀ alkoxycarbonyl, C₁₋₁₀ alkylcarbonyl and phenyl, said phenyl being optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy and C1-C3 haloalkoxy;

each R¹¹ independently is R¹⁰, -CO₂R¹⁰, -SO₂R¹⁰ or -C(O)R¹⁰, or

-N(R¹¹)₂ taken together is a non-aromatic heterocyclic group optionally substituted with one or more substituents selected from the group consisting of =O, =S, halogen, nitro, cyano, hydroxy, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, amino, C₁₋₆ alkylamino, C₁₋₆ dialkylamino, C₁₋₆ aminoalkyl, (C₁₋₆ alkylamino)C₁₋₆ alkyl, (C₁₋₆ dialkylamino)C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆

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haloalkoxy, C₁₋₆ alkylcarbonyloxy, C₁₋₆ alkoxy carbonyl and C₁₋₆ alkylcarbonyl; and

each R¹² independently is:

- i) a C₆₋₁₄ aryl group or a 5-14 membered heteroaryl group, each optionally and independently substituted with one or more substituents selected from the group consisting of halogen, nitro, cyano, hydroxy, C₁₋₁₀ alkyl, C₁₋₁₀ haloalkyl, (C₁₋₁₀ haloalkoxy)C₁₋₁₀ alkyl, (C₁₋₁₀ alkoxy)C₁₋₁₀ alkyl, C₁₋₁₀ hydroxyalkyl, C₁₋₁₀ aminoalkyl, (C₁₋₁₀ alkylamino)C₁₋₁₀ alkyl, (C₁₋₁₀ dialkylamino)C₁₋₁₀ alkyl, amino, C₁₋₁₀ alkylamino, C₁₋₁₀ dialkylamino, C₁₋₁₀ alkoxy, C₁₋₁₀ haloalkoxy, C₁₋₁₀ alkylcarbonyloxy, C₁₋₁₀ alkoxy carbonyl and C₁₋₁₀ alkylcarbonyl; or
- ii) a C₁₋₁₀ alkyl group optionally substituted with one or more substituents selected from the group consisting halogen, nitro, cyano, hydroxy, C₁₋₁₀ haloalkyl, C₁₋₁₀ alkoxy, C₁₋₁₀ haloalkoxy, amino, C₁₋₁₀ alkylamino, C₁₋₁₀ dialkylamino, C₁₋₁₀ alkylcarbonyloxy, C₁₋₁₀ alkoxy carbonyl, C₁₋₁₀ alkylcarbonyl and phenyl, said phenyl being optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy and C1-C3 haloalkoxy;

each Ak¹ independently is a C₁₋₁₀ aliphatic group optionally substituted with one or more substituents selected from the group consisting halogen, nitro, cyano, -N(R²¹)₂, -C(O)N(R²¹)₂, -NR²¹C(O)R²¹, -SO₂R²², -SO₂N(R²¹)₂, -NR²¹SO₂R²², -NR²¹C(O)OR²¹, -OC(O)N(R²¹)₂, -NR²¹C(O)N(R²¹)₂, -NRC(O)ON(R)₂, -NR²¹SO₂N(R²¹)₂, -OR²¹, -SR²¹, C₁₋₁₀ haloalkoxy, -C(O)R²¹, -C(O)OR²¹ and -OC(O)R²¹;

each Ak¹⁰ independently is a C₁₋₁₀ alkyl group optionally substituted with one or more substituents selected from the group consisting halogen, nitro, cyano, -OH, -SH, -O(C₁₋₆ alkyl), -S(C₁₋₆ alkyl), C₁₋₆ haloalkoxy, amino, C₁₋₆

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alkylamino, C₁₋₆ dialkylamino, C₁₋₆ alkylcarbonyloxy, C₁₋₆ alkoxycarbonyl and C₁₋₆ alkylcarbonyl;

each Ar¹ independently is a C₆₋₁₄ aryl group or a 5-14 membered heteroaryl group, each optionally and independently substituted with one or more substituents selected from the group consisting of halogen, nitro, cyano, C₁₋₁₀ alkyl, C₁₋₁₀ haloalkyl, (C₁₋₁₀ haloalkoxy)C₁₋₁₀ alkyl, (C₁₋₁₀ alkoxy)C₁₋₁₀ alkyl, C₁₋₁₀ hydroxyalkyl, C₁₋₁₀ aminoalkyl, (C₁₋₁₀ alkylamino)C₁₋₁₀ alkyl, (C₁₋₁₀ dialkylamino)C₁₋₁₀ alkyl, -N(R²¹)₂, -C(O)N(R²¹)₂, -NR²¹C(O)R²¹, -SO₂R²², -SO₂N(R²¹)₂, -NR²¹SO₂R²², -NR²¹C(O)N(R²¹)₂, -NRC(O)ON(R)₂, -NR²¹SO₂N(R²¹)₂, -OR²¹, -SR²¹, C₁₋₁₀ haloalkoxy, -C(O)R²¹, -C(O)OR²¹, -OC(O)R²¹, phenyl and 5-6 membered heteroaryl, wherein said phenyl and said 5-6 membered heteroaryl 5 are each independently and optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy and C1-C3 haloalkoxy;

each Ar¹⁰ independently is a C₆₋₁₄ aryl group or a 5-14 membered heteroaryl group, each optionally and independently substituted with one or more substituents selected from the group consisting of halogen, nitro, cyano, -OH, -SH, -O(C₁₋₁₀ alkyl), -S(C₁₋₁₀ alkyl), C₁₋₁₀ alkyl, C₁₋₁₀ haloalkyl, (C₁₋₁₀ haloalkoxy)C₁₋₁₀ alkyl, (C₁₋₁₀ alkoxy)C₁₋₁₀ alkyl, C₁₋₁₀ hydroxyalkyl, (C₁₋₁₀ aminoalkyl), (C₁₋₁₀ alkylamino)C₁₋₁₀ alkyl, (C₁₋₁₀ dialkylamino)C₁₋₁₀ alkyl, (phenyl)C₁₋₁₀ alkyl, (5-6 membered heteroaryl)C₁₋₁₀ alkyl, amino, C₁₋₁₀ alkylamino, C₁₋₁₀ dialkylamino, C₁₋₁₀ haloalkoxy, C₁₋₁₀ alkylcarbonyloxy, C₁₋₁₀ alkoxycarbonyl and C₁₋₁₀ alkylcarbonyl; and

each R²¹ independently is hydrogen, C₁₋₆ alkyl, phenyl or 5-6 membered heteroaryl, wherein each of the phenyl and heteroaryl groups represented by R²¹ is independently and optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy and C1-C3 haloalkoxy, and wherein the alkyl group represented by R²¹ is optionally substituted with one or more substituents selected from the group consisting

of halogen, hydroxy, nitro, cyano, amino, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy and C1-C3 haloalkoxy; or

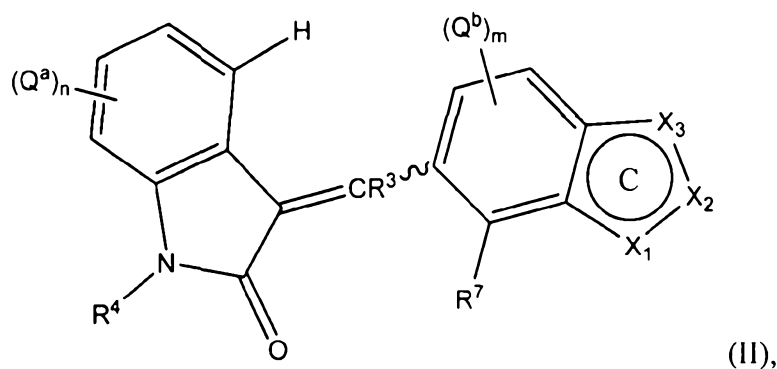
$N(R^{21})_2$ forms a non-aromatic heterocyclic group optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, =O, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy, C1-C3 haloalkoxy and amino;

each R^{22} independently C₁₋₆ alkyl, phenyl or 5-6 membered heteroaryl, wherein each of the phenyl and heteroaryl groups represented by R^{22} is independently and optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy and C1-C3 haloalkoxy, and wherein the alkyl group represented by R^{22} is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy and C1-C3 haloalkoxy;

each p is 1, 2 or 3; and

each q is 2, 3, 4 or 5.

4. The compound of Claim 3, wherein the compound is represented by the following structural formula:



or a pharmaceutically acceptable salt thereof, wherein

each of n and m independently is 0, 1 or 2;

R^4 is -H, C1-C6 alkyl, -C(O)(C1-C6 alkyl), -C(O)(phenyl), -C(O)O(C1-C6 alkyl), -C(O)O(phenyl), -S(O)₂(C1-C6 alkyl) or -S(O)₂(phenyl);

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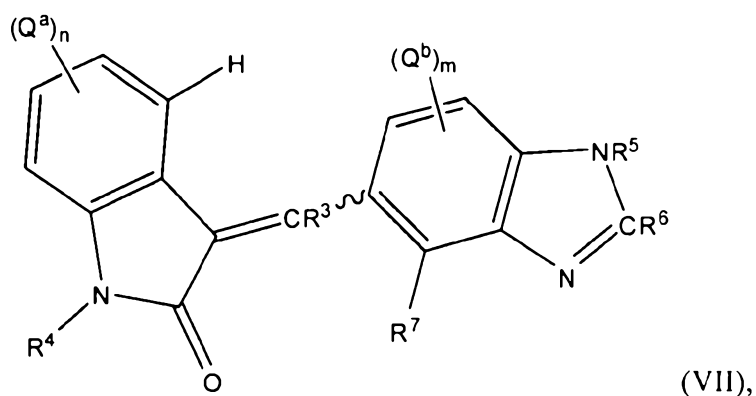
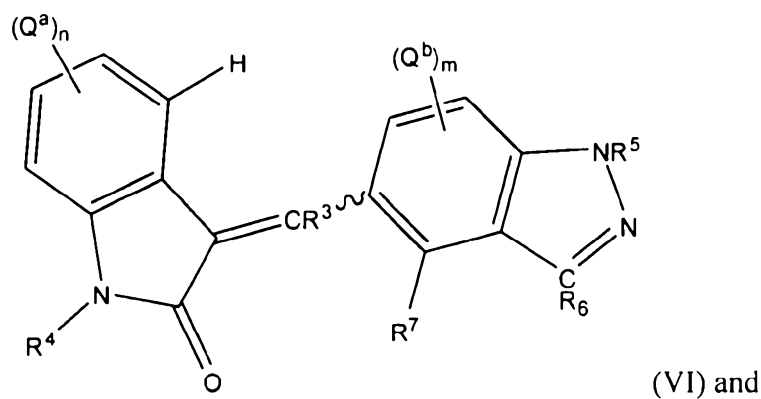
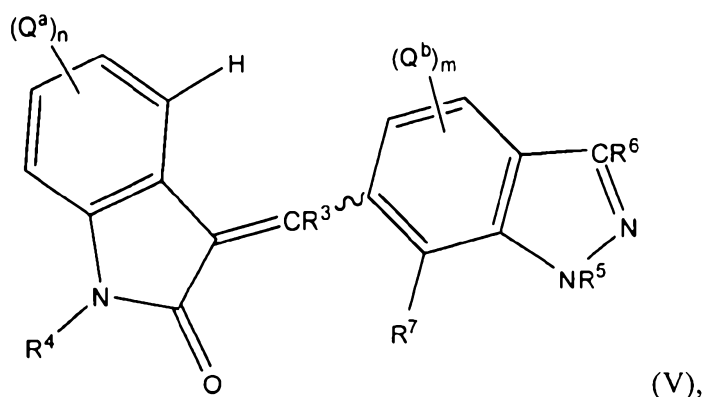
R^5 is -H, C1-C6 alkyl, phenyl, -C(O)(C1-C6 alkyl), -C(O)(phenyl), -C(O)O(C1-C6 alkyl), -C(O)O(phenyl), -S(O)₂(C1-C6 alkyl) or -S(O)₂(phenyl), wherein each said phenyl in the groups represented by R^4 and R^5 independently is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 alkoxy and C1-C6 haloalkoxy, and wherein each said alkyl in the groups represented by R^4 and R^5 independently is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C1-C6 alkoxy, C1-C6 haloalkoxy and phenyl;

R^7 is -H, F, Cl or methyl;

the optionally substituted 5-6 membered heteroaryl group represented by each of R and R' independently is an optionally substituted furanyl group, an optionally substituted imidazolyl group, an optionally substituted isoxazolyl group, an optionally substituted oxadiazolyl group, an optionally substituted oxazolyl, an optionally substituted pyrazolyl group, an optionally substituted pyrrolyl group, an optionally substituted pyridyl group, an optionally substituted pyrimidinyl group, an optionally substituted pyridazinyl group, an optionally substituted thiazolyl group, an optionally substituted triazolyl group, an optionally substituted tetrazolyl group or an optionally substituted thienyl group; and

the 5-6 membered heteroaryl group in the substituents for the groups represented by each of R and R' independently is a furanyl group, an imidazolyl group, an isoxazolyl group, an oxadiazolyl group, an oxazolyl, a pyrazolyl group, a pyrrolyl group, a pyridyl group, a pyrimidinyl group, a pyridazinyl group, a thiazolyl group, a triazolyl group, a tetrazolyl group or a thienyl group.

5. The compound of Claim 4, wherein the compound is represented by a structural formula selected from:



or a pharmaceutically acceptable salt thereof, wherein:

one of Q^a and Q^b is halogen, $-\text{NO}_2$, $-\text{CN}$, Ak^1 , Ar^1 , $(\text{C}_{1-10} \text{ alkylene})-\text{Ar}^1$, $(\text{C}_{1-10} \text{ alkenylene})-\text{Ar}^1$ or $-\text{X}-\text{R}^1$; and the other of Q^a and Q^b is halogen, hydroxy, nitro, cyano, amino, methyl, methoxy, halomethyl or halomethoxy;

each R^6 independently is hydrogen, halogen, nitro, cyano, R^1 , $-\text{OR}$, $-\text{SR}$ or $-\text{N}(\text{R})_2$; and

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each R independently is hydrogen, optionally substituted C₁₋₆ alkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted phenyl or optionally substituted 5-6 membered heteroaryl; or

N(R)₂ taken together is a non-aromatic heterocyclic group optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, =O, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy, C1-C3 haloalkoxy and amino; and

each R' independently is optionally substituted C₁₋₆ alkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted phenyl or optionally substituted 5-6 membered heteroaryl.

6. The compound of Claim 5, wherein R' is -CH₂-(optionally-substituted phenyl), -CH₂-(optionally-substituted 5-6 membered heteroaryl), -CH₂-CH₂-(optionally-substituted phenyl), -CH₂-CH₂-(optionally-substituted 5-6 membered heteroaryl), CH=CH-(optionally-substituted phenyl) or -CH=CH₂-(optionally-substituted 5-6 membered heteroaryl).
7. The compound of Claim 6, wherein R' is -CH₂-(optionally-substituted phenyl), -CH₂-(optionally-substituted pyridyl), -CH₂-CH₂-(optionally-substituted phenyl), -CH₂-CH₂-(optionally-substituted pyridyl), CH=CH-(optionally-substituted phenyl) or -CH=CH₂-(optionally-substituted pyridyl); R⁴ is -H, C1-C6 alkyl, -C(O)(C1-C6 alkyl), -C(O)(phenyl), -C(O)O(C1-C6 alkyl), -C(O)O(phenyl), -S(O)₂(C1-C6 alkyl) or -S(O)₂(phenyl), and R⁵ is -H, C1-C6 alkyl, phenyl, -C(O)(C1-C6 alkyl), -C(O)(phenyl), -C(O)O(C1-C6 alkyl), -C(O)O(phenyl), -S(O)₂(C1-C6 alkyl) or -S(O)₂(phenyl).
8. The compound of Claim 7, wherein R⁶ is an optionally substituted phenyl group, an optionally substituted pyridyl group, an optionally substituted pyrrolyl group, an optionally substituted pyrazolyl, an optionally substituted thiazolyl, an optionally substituted pyrimidinyl, or an optionally substituted thienyl; and the group represented by R⁶ is optionally substituted with one or more substituents selected

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from the group consisting of: halogen, hydroxy, nitro, cyano, amino, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 alkoxy and C1-C6 haloalkoxy.

9. The compound of Claim 8, wherein:

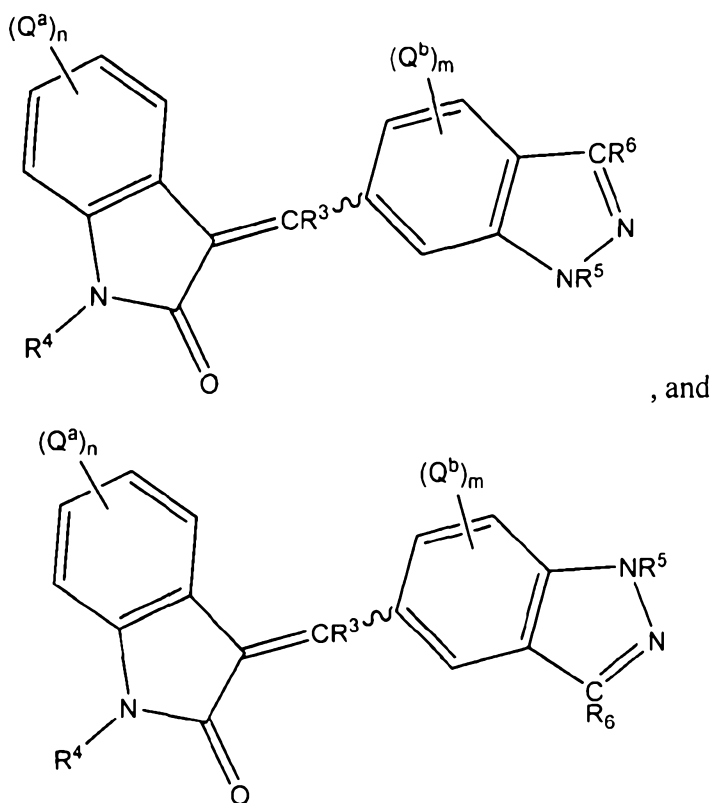
one of Q^a and Q^b of each of Structural Formulas (V) – (VII) independently is halogen, hydroxy, cyano, nitro, C1-C6 alkyl, C1-C6 haloalkyl, -C(O)(C1-C6 alkyl), -C(O)NH₂, -C(O)NH(C1-C6 alkyl), -C(O)N(C1-C6 alkyl)₂, -SO₂NH₂, -SO₂NH(C1-C6 alkyl), -SO₂N(C1-C6 alkyl)₂, -OH, -O(C1-C6 alkyl), -O(C1-C6 haloalkyl), -SH, -S(C1-C6 alkyl), -S(C1-C6 haloalkyl), -NH₂, -NH(C1-C6 alkyl), -N(C1-C6 alkyl)₂, -NHC(O)(C1-C6 alkyl), -NHC(O)O(C1-C6 alkyl), -NHC(O)NH₂, -NHC(O)NH(C1-C6 alkyl), -NHC(O)N(C1-C6 alkyl)₂, -NHC(O)ONH₂, -NHC(O)ONH(C1-C6 alkyl), -NHC(O)ON(C1-C6 alkyl)₂, -NHSO₂NH₂, -NHSO₂NH(C1-C6 alkyl), -NHSO₂N(C1-C6 alkyl)₂ or -NHSO₂(C1-C6 alkyl), and the other Q^a and Q^b of each of Structural Formulas (V) – (VII) independently is halogen, hydroxy, nitro, cyano, amino, methyl, methoxy, halomethyl or halomethoxy.

10. The compound of Claim 9, wherein:

one of Q^a and Q^b of each of Structural Formulas (V) – (VII) independently is halogen, hydroxy, cyano, nitro, Ph, -CH₂Ph, -C(O)Ph, -C(O)NH(Ph), -C(O)N(C1-C6 alkyl)(Ph), -SO₂NH(Ph), -SO₂N(C1-C6 alkyl)(Ph), -O(Ph), -S(Ph), -NH(Ph), -N(C1-C6 alkyl)(Ph), -NHC(O)(Ph), -NHC(O)O(Ph), -NHC(O)NH(Ph), -NHC(O)N(C1-C6 alkyl)(Ph), -NHC(O)ONH(Ph), -NHC(O)ON(C1-C6 alkyl)(Ph), -NHSO₂NH(Ph), -NHSO₂N(C1-C6 alkyl)(Ph) or -NHSO₂(Ph), wherein each Ph is a phenyl group independently and optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy and C1-C3 haloalkoxy, and the other Q^a and Q^b of each of Structural Formulas (V) – (VII)

independently is halogen, hydroxy, nitro, cyano, amino, methyl, methoxy, halomethyl or halomethoxy.

11. The compound of Claim 4, wherein the compound is represented by a structural formula selected from:



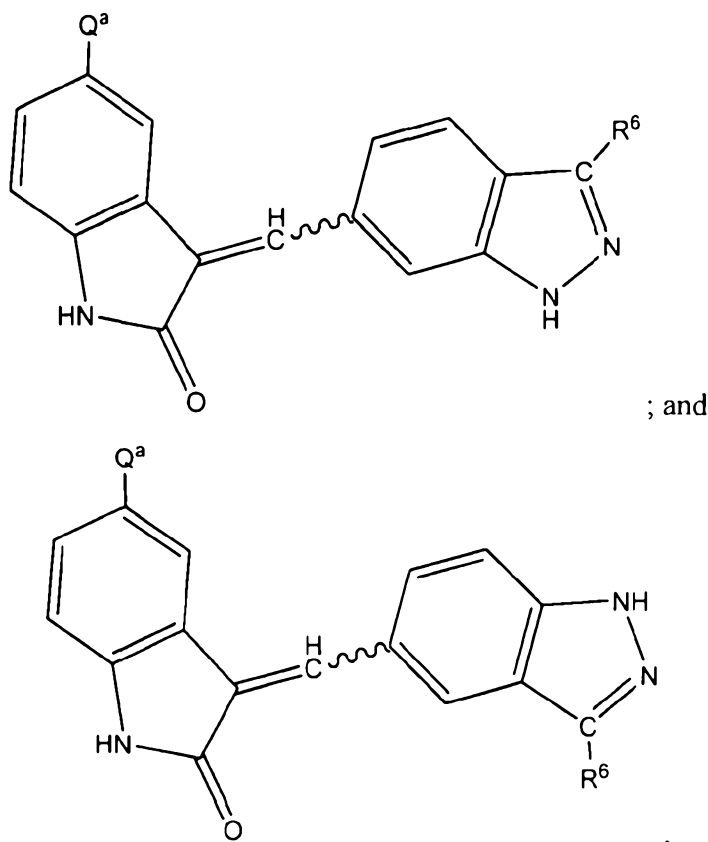
or a pharmaceutically acceptable salt thereof, wherein:

R^6 is optionally substituted phenyl, optionally substituted 5-12 membered heteroaryl, $-\text{CH}_2$ -(optionally substituted phenyl), $-\text{CH}_2$ -(optionally substituted 5-12 membered heteroaryl), $-\text{CH}_2\text{CH}_2$ -(optionally substituted phenyl), $-\text{CH}_2\text{CH}_2$ -(optionally substituted 5-12 membered heteroaryl), $-\text{CH}=\text{CH}$ -(optionally substituted phenyl), $-\text{CH}=\text{CH}$ -(optionally substituted 5-12 membered heteroaryl), $-\text{CH}=\text{CH}-\text{C}(\text{O})\text{O}$ (optionally substituted C_{1-6} alkyl), or $-\text{CH}=\text{CH}-\text{OC}(\text{O})$ (optionally substituted C_{1-6} alkyl).

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12. The compound of Claim 11, wherein the compound is represented by a structural formula selected from:



or a pharmaceutically acceptable salt thereof.

13. The compound of Claim 12, wherein

the 5-12 membered heteroaryl in the group represented by R^6 is selected from the group consisting of pyridyl, thiazolyl, pyrazinyl, thiophenyl, indolyl, quinoliny, pyrrolyl, pyrazolyl, and pyrimidinyl, each of which is optionally substituted;

Q^a and Q^b are each independently halogen, cyano, $-NR^1R^2$, $-NR^2C(O)R^1$, $-C(O)OR^1$, $-OC(O)R^1$, $-C(O)NR^1R^2$, $-NR^2C(O)OR^1$, $-N(R^2)C(O)NR^1R^2$, $-OR^1$, $-SO_2NR^1R^2$, $-NR^2SO_2R^1$, C_{1-6} alkyl, phenyl or 5-12 membered heteroaryl, wherein the C_{1-6} alkyl represented by Q_a and Q_b is optionally substituted with one or more substituents selected from the group consisting of halogen, nitro, cyano, $-OH$, $-SH$, $-O(C_{1-6} \text{ alkyl})$, $-S(C_{1-6} \text{ alkyl})$, C_{1-6} haloalkoxy,

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amino, C₁₋₆ alkylamino, C₁₋₆ dialkylamino, C₁₋₆ alkylcarbonyloxy, C₁₋₆ alkoxy carbonyl and C₁₋₆ alkylcarbonyl; and the phenyl or the 5-12 membered heteroaryl represented by Q_a and Q_b is optionally substituted with one or more substituents selected from the group consisting of halogen, nitro, cyano, -OH, -SH, -O(C₁₋₆ alkyl), -S(C₁₋₆ alkyl), C₁₋₆ alkyl, C₁₋₆ haloalkyl, (C₁₋₆ haloalkoxy)C₁₋₆ alkyl, (C₁₋₆ alkoxy)C₁₋₆ alkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ aminoalkyl, (C₁₋₆ alkylamino)C₁₋₆ alkyl, (C₁₋₆ dialkylamino)C₁₋₆ alkyl, (phenyl)C₁₋₆ alkyl, (5-6 membered heteroaryl)C₁₋₆ alkyl, amino, C₁₋₆ alkylamino, C₁₋₆ dialkylamino, C₁₋₆ haloalkoxy, C₁₋₆ alkylcarbonyloxy, C₁₋₆ alkoxy carbonyl and C₁₋₆ alkylcarbonyl;

R¹ and R² are each independently -H- or C₁₋₆ alkyl, wherein the C₁₋₆ alkyl is optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -SH, -O(C₁₋₃ alkyl), -S(C₁₋₃ alkyl) and C₁₋₆ haloalkoxy;

the phenyl or the 5-12 membered heteroaryl in the group represented by R⁶ is optionally substituted with one or more substituents selected from the group consisting of halogen, nitro, cyano, -OH, -SH, -O(C₁₋₆ alkyl), -S(C₁₋₆ alkyl), C₁₋₆ alkyl, C₁₋₆ haloalkyl, (C₁₋₆ haloalkoxy)C₁₋₆ alkyl, (C₁₋₆ alkoxy)C₁₋₆ alkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ aminoalkyl, (C₁₋₆ alkylamino)C₁₋₆ alkyl, (C₁₋₆ dialkylamino)C₁₋₆ alkyl, (phenyl)C₁₋₆ alkyl, (5-6 membered heteroaryl)C₁₋₆ alkyl, amino, C₁₋₆ alkylamino, C₁₋₆ dialkylamino, C₁₋₆ haloalkoxy, C₁₋₆ alkylcarbonyloxy, C₁₋₆ alkoxy carbonyl, C₁₋₆ alkylcarbonyl, -(CH₂)₀₋₃-*N*-piperidinyl, -(CH₂)₀₋₃-*N*-morpholinyl, -(CH₂)₀₋₃-*N*-pyrrolidinyl and -(CH₂)₀₋₃-*N*-(CH₂)₀₋₃-piperazinyl, wherein the *N*-piperazinyl is optionally *N*'-substituted with C₁₋₆ alkyl or C₁₋₆ acyl; and

the C₁₋₆ alkyl in the group represented by R⁶ is optionally substituted one or more substituents selected from the group consisting of halogen, nitro, cyano, -OH, -SH, -O(C₁₋₆ alkyl), -S(C₁₋₆ alkyl), C₁₋₆

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haloalkoxy, amino, C₁₋₆ alkylamino, C₁₋₆ dialkylamino, C₁₋₆ alkylcarbonyloxy, C₁₋₆ alkoxycarbonyl and C₁₋₆ alkylcarbonyl.

14. The compound of Claim 13 wherein the phenyl or the 5-12 membered heteroaryl in the group represented by R⁶ is optionally substituted with one or more substituents selected from the group consisting of halogen, nitro, cyano, -OH, -SH, -O(C₁₋₆ alkyl), -S(C₁₋₆ alkyl), C₁₋₆ alkyl, C₁₋₆ haloalkyl, (C₁₋₆ haloalkoxy)C₁₋₆ alkyl, (C₁₋₆ alkoxy)C₁₋₆ alkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ aminoalkyl, (C₁₋₆ alkylamino)C₁₋₆ alkyl, (C₁₋₆ dialkylamino)C₁₋₆ alkyl, (phenyl)C₁₋₆ alkyl, (5-6 membered heteroaryl)C₁₋₆ alkyl, amino, C₁₋₆ alkylamino, C₁₋₆ dialkylamino, C₁₋₆ haloalkoxy, C₁₋₆ alkylcarbonyloxy, C₁₋₆ alkoxycarbonyl and C₁₋₆ alkylcarbonyl.
15. The compound of Claim 14, wherein:

Q^a is halogen, cyano, -NR¹R², -NR²C(O)R¹, -C(O)OR¹, -OC(O)R¹, -N(R²)C(O)NR¹R², -OR¹, C₁₋₆ alkyl, wherein the C₁₋₆ alkyl is optionally substituted with one or more substituents selected from the group consisting of halogen, -OH, -SH, -O(C₁₋₆ alkyl), -S(C₁₋₆ alkyl) and C₁₋₆ haloalkoxy;

Q^b is halogen, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₁₋₃ alkoxy, or C₁₋₃ haloalkoxy; and

the phenyl, the 5-12 membered heteroaryl and the C₁₋₆ alkyl in the group represented by R⁶ is optionally substituted with one or more substituents selected from the group consisting of halogen, nitro, cyano, -O(C₁₋₆ alkyl), C₁₋₆ alkyl, C₁₋₆ haloalkyl and C₁₋₆ haloalkoxy.
16. The compound of Claim 15, wherein:

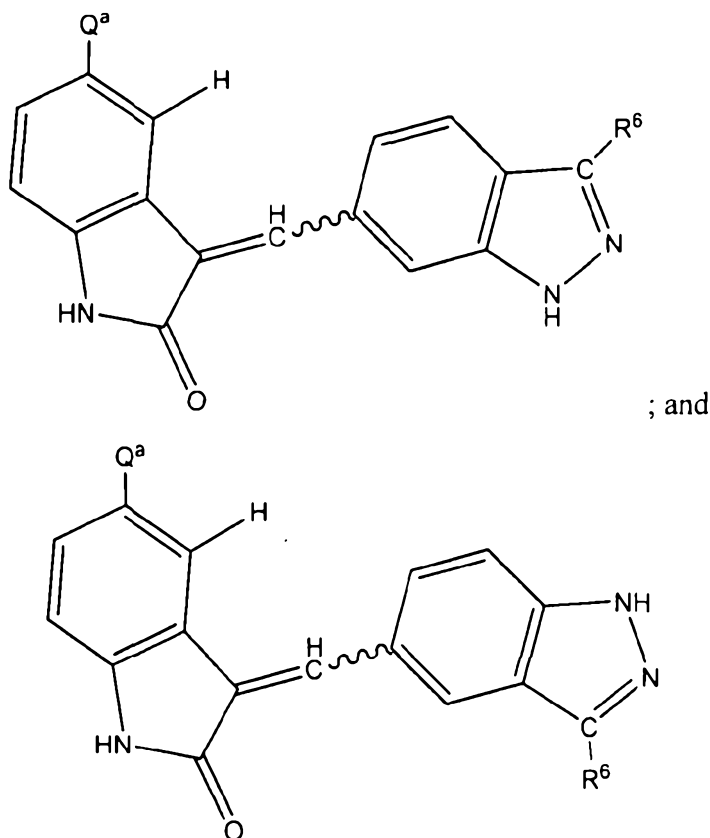
Q^a is -OH, C₁₋₆ alkoxy or C₁₋₆ haloalkoxy; and

the phenyl, the 5-12 membered heteroaryl and the C₁₋₆ alkyl in the group represented by R⁶ are each optionally substituted with one or more substituents independently selected from the group consisting of halogen, methyl, methoxy and trifluoromethyl.

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17. The compound of Claim 1 wherein the compound is represented by a structural formula selected from



or a pharmaceutically acceptable salt thereof, wherein:

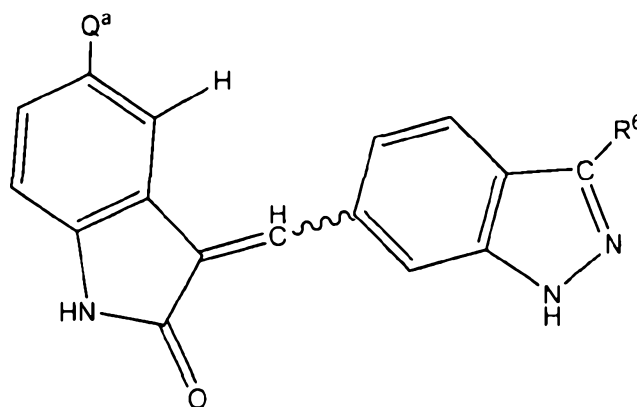
Q^a is -H, halogen, -NH₂, (C₁₋₆alkyl)amine or C₁₋₆ alkoxy;

R^6 is phenyl, 5-6 membered heteroaryl, -CH=CH-(phenyl), -CH=CH-(5-6 membered heteroaryl), -C≡C-(phenyl), -C≡C-(5-6 membered heteroaryl) wherein each phenyl and heteroaryl in the group represented by R^6 is optionally substituted with halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ aminoalkyl, (C₁₋₆ alkylamino)C₁₋₆ alkyl, (C₁₋₆ dialkylamino)C₁₋₆ alkyl, (phenyl)C₁₋₆ alkyl, amino, C₁₋₆ alkylamino, C₁₋₆ dialkylamino, -(CH₂)₀₋₃-N-piperidinyl, -(CH₂)₀₋₃-N-morpholinyl, -(CH₂)₀₋₃-N-pyrrolidinyl and -(CH₂)₀₋₃-N-piperazinyl, wherein the N-piperazinyl is optionally N'-substituted with C₁₋₆ alkyl or C₁₋₆ acyl.

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18. The compound of Claim 17 wherein each heteroaryl in the group represented by R^6 is pyridinyl, pyrimidinyl or pyrazinyl and each is optionally substituted halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} aminoalkyl, $(C_{1-6}$ alkylamino) C_{1-6} alkyl, $(C_{1-6}$ dialkylamino) C_{1-6} alkyl, (phenyl) C_{1-6} alkyl, amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, *N*-piperidinyl, *N*-morpholinyl, *N*-pyrrolidinyl and *N*-piperazinyl, wherein the *N*-piperazinyl is optionally *N'*-substituted with C_{1-6} alkyl or C_{1-6} acyl.
19. The compound of Claim 1 that is the *E*-isomer.
20. The compound of Claim 17 wherein the compound is represented by the structural formula



21. A pharmaceutical composition comprising a pharmaceutically acceptable carrier, and a compound in any of Claims 1 to 20 or a pharmaceutically acceptable salt thereof.
22. Use of a compound in any of Claims 1 to 20 for the treatment of cancer in a subject in need thereof.
23. Use of a compound in any of Claims 1 to 20 for the treatment of cancer in a subject in need thereof, wherein the cancer is selected from a group consisting of lung cancer, breast cancer, colon cancer, brain cancer, prostate cancer, melanoma, glioblastoma multiform, ovarian cancer, germinoma, glioma and mesothelioma.

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24. A compound according to any one of Claims 1-20 or a pharmaceutical composition of Claim 21 or a use according to Claim 22 or 23 substantially as herein described with reference to the Figures and/or Examples.

1/1

Fig. 1

