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Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. _____ S. _____

D SUPERINDUSTRIA Y COMERCIO

Radicacion : 00049777 00000001

Folios: 128

Fecha (AHD): 2000-09-29 17:17:28

Tramite : 002 PATENTES D 1 REGISTRO/ 444 REPUESTA

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Re: **Expediente No. 00.049.777.**

Solicitud de Patente de Invención titulada:

“COMPUESTOS DE INDAZOL Y COMPOSICIONES
FARMACEUTICAS PARA LA INHIBICION DE
PROTEINA KINASA, Y METODOS PARA SU USO”.

Solicitante: **AGOURON PHARMACEUTICALS, INC.**

RESPUESTA AL AUTO NOTIFICADO POR ESTADO No. 121
DE FECHA 17 DE AGOSTO DE 2000, CONCEPTO TECNICO No. 1289

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá D.C., identificado tal como aparece al pie de mi firma en mi carácter de apoderado de la sociedad en referencia, me permito manifestar lo siguiente ante el auto emanado por ese Despacho, dentro del término legal:

1. En atención a la primera observación del Examinador Técnico, adjunto el arte final en tamaños 12 x 12 cm (duplicado) y 6 x 6 cm en papel mantequilla.

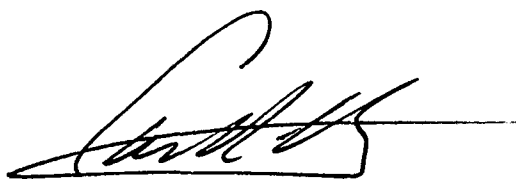
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2. En respuesta a las observaciones del Examinador Jurídico, presento la Copia Certificada, de la cual se reclama prioridad, de la Solicitud de Patente No. 60/142,130 presentada el 2 de julio de 1999 ante la Oficina de Patentes y Marcas Estadounidense, así como la traducción de su Capítulo Reivindicatorio. Igualmente, adjunto el Documento de Poder, debidamente legalizado y oficialmente traducido.

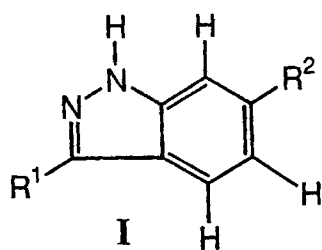
Atentamente,



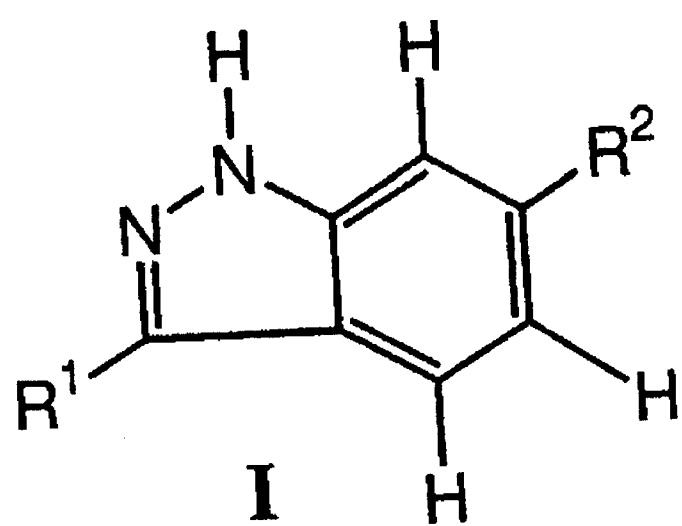
CARLOS R. OLARTE
C.C. No. 79.782.747 de Bogotá
T.P. 74.295

Anexos: Arte.
 Copia Certificada del Documento de Prioridad.
 Traducción del Capítulo Reivindicatorio del Documento de Prioridad.
 Poder.

Nota:
Se retira arte final de
6x6cm para anexar a la
torjeta de archivo temático.
202040.



Nota:
Se retiró arte final de
12 x 12 cm para anexar al
Extracto para publicación.
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Esta es una traducción parcial al idioma español de un documento escrito originalmente en el idioma inglés.

TRADUCCION DOCUMENTO
DE PRIORIDAD

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LOS ESTADOS UNIDOS DE AMERICA

A TODOS AQUELLOS A QUIEN ESTE DOCUMENTO SE LES PRESENTE:

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS

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Oficina de Patentes y Marcas de los Estados Unidos

Agosto 8, 2000

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ESTO ES PARA CERTIFICAR QUE LO ANEXADO A LA PRESENTE ES UNA FIEL COPIA DE LOS EXPEDIENTES DE LA OFICINA DE PATENTES Y MARCAS DE LOS ESTADOS UNIDOS DE AQUELLOS DOCUMENTOS DE LA SOLICITUD DE PATENTE IDENTIFICADA A CONTINUACION QUE REUNIERON LOS REQUERIMIENTOS PARA QUE SE LE CONCEDA UNA FECHA DE PRESENTACION BAJO 35 USC (Código de los Estados Unidos)

20

NO. DE SOLICITUD: 60/142,130

FECHA DE PRESENTACION: 2 de Julio de 1999

25

SELLO DE LA
OFICINA DE MARCAS Y PATENTES
DE LOS ESTADOS UNIDOS DE

Por la Autoridad del
COMISIONADO DE PATENTES Y MARCAS

[firma ilegible]

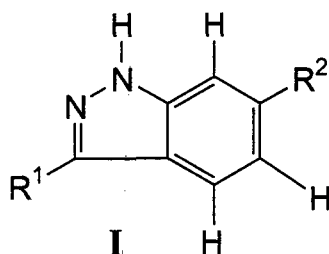
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P.R. GRANT
Oficial de Certificación

REIVINDICACIONES

Lo que se reivindica es:

1. Un compuesto de la fórmula I



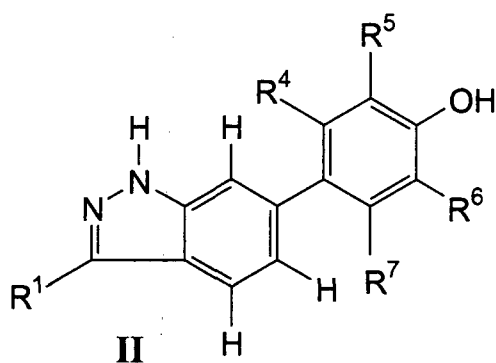
- 5 en el que:

R^1 es un arilo, heteroarilo sustituido o no sustituido, o un grupo de la fórmula $\text{CH}=\text{CH}-R^3$ o $\text{CH}=\text{N}-R^3$, donde R^3 es un alkilo, alkenilo, cicloalkilo, heterocicloalkilo, arilo o heteroarilo sustituido o no sustituido; y

R^2 es un arilo sustituido o no sustituido o $\text{Y}-\text{Ar}$, donde Y es O, S, $\text{C}=\text{CH}_2$, $\text{C}=\text{O}$, $\text{S}=\text{O}$, SO_2 , CH_2 , CHCH_3 , NH, o $\text{N}-(\text{C}_1-\text{C}_8 \text{ alkilo})$, y Ar es un arilo sustituido o no sustituido;

o una prodroga farmacéuticamente aceptable, un metabolito farmacéuticamente activo o una sal de la misma farmacéuticamente aceptable.

2. Un compuesto de fórmula II:



- 15 en la que:

R^1 es un arilo, heteroarilo sustituido o no sustituido, o un grupo de la fórmula $\text{CH}=\text{CH}-R^3$ o $\text{CH}=\text{N}-R^3$, donde R^3 es un alkilo, cicloalkilo, heterocicloalkilo, arilo o heteroarilo sustituido o no sustituido;

R^2 es un arilo, heteroarilo sustituido o no sustituido, o un grupo de la fórmula $\text{CH}=\text{CH}-R^3$ o $\text{CH}=\text{N}-R^3$, donde R^3 es un alkilo, alkenilo, cicloalkilo, heterocicloalkilo, arilo o heteroarilo sustituido o no sustituido;

R^5 y R^6 son cada uno independientemente hidrógeno, OH, halo, Z-alkilo, Z-arilo, o $Z-CH_2CH=CH_2$, donde Z es O, S, NH, o CH_2 , y la porción de alkilo y arilo del Z-alkilo y Z-arilo están cada una opcionalmente sustituidas;

5 o una prodroga farmacéuticamente aceptable, un metabolito farmacéuticamente activo o una sal de la misma farmacéuticamente aceptable.

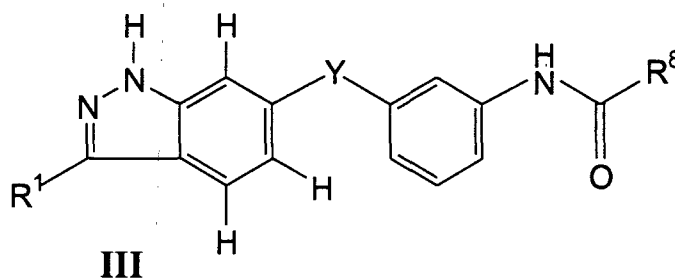
3. Un compuesto de acuerdo a la reivindicación 2, en la que:

R^1 es un hetroarilo bicíclico sustituido o no sustituido o un grupo de fórmula $CH=CH-R^3$, donde R^3 es un alkilo, cicloalkilo, heterocicloalkilo, arilo o heteroarilo sustituido o no sustituido;

10 R^4 y R^7 son cada uno independientemente hidrógeno, OH, halo, C_1-C_8 alkilo, o $CH_2-O-(C_1-C_8$ alkilo); y

R^5 y R^6 son cada uno independientemente hidrógeno, OH, halo, Z-alkilo, Z-arilo, o $Z-CH_2CH=CH_2$, donde Z es O, S, NH, o CH_2 , y la porción de alkilo y arilo está opcionalmente sustituida.

4. Un compuesto de fórmula III:



en la que:

R^1 es un arilo, heteroarilo sustituido o no sustituido, o un grupo de la fórmula $CH=CH-R^3$ o $CH=N-R^3$, donde R^3 es un alkilo, cicloalkilo, heterocicloalkilo, arilo o heteroarilo sustituido o no sustituido;

Y es O, S, $C=CH_2$, $C=O$, $S=O$, SO_2 , CH_2 , $CHCH_3$, NH, o $N-(C_1-C_8$ alkilo);

R^8 es un alkilo, heteroalkilo, cicloalkilo, heterocicloalkilo, arilo, heteroarilo, alcoxilo o ariloxilo sustituido o no sustituido;

o una prodroga farmacéuticamente aceptable, un metabolito farmacéuticamente activo o una sal de la misma farmacéuticamente aceptable.

25 5. Un compuesto de acuerdo con la reivindicación 4, en la que:

R¹ es un hetroarilo bicíclico sustituido o no sustituido o un grupo de fórmula CH=CH—R³, donde R³ es un alkilo, cicloalkilo, heterocicloalkilo, arilo o heteroarilo sustituido o no sustituido.

- 5 6. Un compuesto de acuerdo con la reivindicación 5, en la que: R¹ es
CH=CH—R³, donde R³ es un grupo arilo sustituido o no sustituido;
Y es O o S; y
R⁸ es un arilo o heteroarilo sustituido o no sustituido.

- 10 7. Una composición farmacéutica que consta de:
(a) Una cantidad terapéuticamente eficaz de un compuesto, prodroga
farmacéuticamente aceptable, metabolito farmacéuticamente activo, o una
sal farmacéuticamente aceptable de la reivindicación 1; y
(b) Un transporte, diluyente o vehículo farmacéuticamente aceptable.

8. Un método de tratar una condición de enfermedad en un mamífero
mediada por la actividad de la kinasa proteínica, que comprende la administración, a un
mamífero en necesidad de la misma, de una cantidad terapéuticamente eficaz de un
compuesto, una prodroga farmacéuticamente aceptable, un metabolito
farmacéuticamente activo, o una sal farmacéuticamente aceptable tal y como se define
en la reivindicación 1.

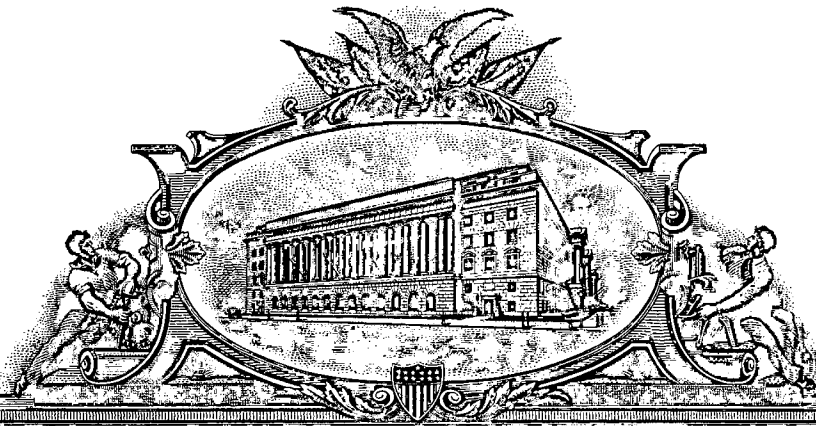
- 20 9. Un método de acuerdo con la reivindicación 8, en el que la condición de
enfermedad del mamífero está asociada aun crecimiento de tumor, proliferación de
células o angiogénesis.

- 25 10. Un método de modular o inhibir la actividad de un receptor de kinasa
proteínica, que comprende el poner en contacto el receptor de la kinasa con una cantidad
eficaz de un compuesto, una prodroga farmacéuticamente aceptable, un metabolito
farmacéuticamente activo, o una sal farmacéuticamente aceptable tal y como se define
en la reivindicación 1.

11. Un método de acuerdo a la reivindicación 10, en el que el receptor de
kinasa proteínica es un receptor VEGF.

RESUMEN

Se describen los compuestos de indazol que modulan y/o inhiben la actividad de ciertas kinasas proteínicas. Estos compuestos y composiciones farmacéuticas que los contienen son capaces de mediar la transducción de señal de la tirosina kinasa y por tanto modular y/o inhibir la proliferación celular no deseada. El invento está también dirigido al uso terapéutico o profiláctico de composiciones farmacéuticas que contienen tales compuestos, y a métodos de tratamiento del cáncer y otros estados de enfermedad asociados con una angiogénesis indeseada y/o proliferación celular, tal como retinopatía diabética, glaucoma neovascular, artritis reumática, y soriasis, administrando cantidades eficaces de tales compuestos.



THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

August 08, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 60/142,130

FILING DATE: July 02, 1999



By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

P. R. Grant

P. R. GRANT

Certifying Officer

00-49777

Box Provisional Patent Application
Assistant Commissioner For Patents
Washington, DC 20231

Attorney Docket No.

0072-60-US

Substitute Form PTO/SB/16

PROVISIONAL APPLICATION FOR U.S. PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 C.F.R. § 1.53(b)

INVENTOR(S)					
Given Name (first and middle (if any))		Family Name or Surname		Residence (City and either State or Foreign Country)	
Robert Steven		Kania		San Diego, CA	
☒ Additional inventors are being named on the <u>1</u> separately numbered sheet(s) attached hereto.					
TITLE OF THE INVENTION (280 characters max)					
Compounds And Pharmaceutical Compositions For Inhibiting Protein Kinases, And Methods For Their Use					
CORRESPONDENCE ADDRESS					
Direct all correspondence to:					
☐ Customer Number OR		Type Customer Name Here		Place Customer Number Bar Code Label Here	
☒ Individual Name		Linda S. Evans			
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Address		10350 North Torrey Pines Road			
City		La Jolla	State	California	Zip 92037
County		San Diego	Telephone	858-622-8864	Fax 858-622-3297
ENCLOSED APPLICATION PARTS (check all that apply)					
☒ Specification Number of Pages		101		☐ Small Entity Statement	
☐ Drawing(s) Number of Sheets				☐ Other (specify)	
METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT (check one)					
☐ A check or money order is enclosed to cover the filing fees. The Commissioner is authorized to charge any deficiencies in the enclosed or credit any overpayment to Deposit Account Number:					
☒ The Commissioner is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number:					
				FILING FEE AMOUNT (\$)	
500329				\$150.00	
The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.					
☒ No.					
☐ Yes, the name of the U.S. Government agency and the Government contract number are:					

Respectfully submitted,

SIGNATURE Linda S. Evans
TYPED OR PRINTED NAME Linda S. Evans

REGISTRATION NO.: 33,873
DATE July 2, 1999

PROVISIONAL APPLICATION FOR U.S. PATENT COVER SHEET

INVENTOR(S) - continued from page 1		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
John F.	Braganza	San Diego, CA
Cynthia Louise	Palmer	La Mesa, CA
Steven Lee	Bender	Oceanside, CA
Siegfried Heinz	Reich	Solana Beach, CA
Michael David	Varney	Solana Beach, CA

Express Mail mailing label number EM594812145US

Date of Deposit: July 2, 1999

I hereby certify that this paper and any other papers or fees identified herein as being transmitted herewith are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above, addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Linda S. Evans

Linda S. Evans

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UNITED STATES PROVISIONAL APPLICATION FOR PATENT

For

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**COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS
FOR INHIBITING PROTEIN KINASES, AND METHODS FOR THEIR USE**

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Inventors: Robert Steven Kania
John F. Braganza
Cynthia Louise Palmer
Steven Lee Bender
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Agouron Pharmaceuticals, Inc.
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FIELD OF THE INVENTION

This invention is directed to indazole compounds that mediate and/or inhibit the activity of certain protein kinases, and to pharmaceutical compositions containing such compounds. The invention is also directed to the therapeutic or prophylactic use of such compounds and compositions, and to methods of treating cancer as well as other disease states associated with unwanted angiogenesis and/or cellular proliferation, by administering effective amounts of such compounds.

BACKGROUND OF THE INVENTION

Protein kinases are a family of enzymes that catalyze phosphorylation of the hydroxyl group of specific tyrosine, serine, or threonine residues in proteins. Typically, such phosphorylation dramatically perturbs the function of the protein, and thus protein kinases are pivotal in the regulation of a wide variety of cellular processes, including metabolism, cell proliferation, cell differentiation, and cell survival. Of the many different cellular functions in which the activity of protein kinases is known to be required, some processes represent attractive targets for therapeutic intervention for certain disease states. Two examples are angiogenesis and cell-cycle control, in which protein kinases play a pivotal role; these processes are essential for the growth of solid tumors as well as for other diseases.

Angiogenesis is the mechanism by which new capillaries are formed from existing vessels. When required, the vascular system has the potential to generate new capillary networks in order to maintain the proper functioning of tissues and organs. In the adult, however, angiogenesis is fairly limited, occurring only in the process of wound healing and neovascularization of the endometrium during menstruation. See Merenmies et al., *Cell Growth & Differentiation*, 8, 3-10 (1997). On the other hand, unwanted angiogenesis is a hallmark of several diseases, such as retinopathies, psoriasis, rheumatoid arthritis, age-related macular degeneration (AMD), and cancer (solid tumors). Folkman, *Nature Med.*, 1, 27-31 (1995). Protein kinases which have been shown to be involved in the angiogenic process include three members of the growth factor receptor tyrosine kinase family: VEGF-R2 (vascular endothelial growth factor receptor 2, also known as KDR (kinase insert domain receptor) and as FLK-1); FGF-R (fibroblast growth factor receptor); and TEK (also known as Tie-2).

VEGF-R2, which is expressed only on endothelial cells, binds the potent angiogenic growth factor VEGF and mediates the subsequent signal transduction through

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activation of its intracellular kinase activity. Thus, it is expected that direct inhibition of the kinase activity of VEGF-R2 will result in the reduction of angiogenesis even in the presence of exogenous VEGF (see Strawn et al., *Cancer Research*, 56, 3540-3545 (1996)), as has been shown with mutants of VEGF-R2 which fail to mediate signal
5 transduction. Millauer et al., *Cancer Research*, 56, 1615-1620 (1996). Furthermore, VEGF-R2 appears to have no function in the adult beyond that of mediating the angiogenic activity of VEGF. Therefore, a selective inhibitor of the kinase activity of VEGF-R2 would be expected to exhibit little toxicity.

Similarly, FGF-R binds the angiogenic growth factors aFGF and bFGF and
10 mediates subsequent intracellular signal transduction. Recently, it has been suggested that growth factors such as bFGF may play a critical role in inducing angiogenesis in solid tumors that have reached a certain size. Yoshiji et al., *Cancer Research*, 57, 3924-3928 (1997). Unlike VEGF-R2, however, FGF-R is expressed in a number of different cell types throughout the body and may or may not play important roles in other normal
15 physiological processes in the adult. Nonetheless, systemic administration of a small-molecule inhibitor of the kinase activity of FGF-R has been reported to block bFGF-induced angiogenesis in mice without apparent toxicity. Mohammad et al., *EMBO Journal*, 17, 5996-5904 (1998).

TEK (also known as Tie-2) is another receptor tyrosine kinase expressed only on
20 endothelial cells which has been shown to play a role in angiogenesis. The binding of the factor angiopoietin-1 results in autophosphorylation of the kinase domain of TEK and results in a signal transduction process which appears to mediate the interaction of endothelial cells with peri-endothelial support cells, thereby facilitating the maturation of newly formed blood vessels. The factor angiopoietin-2, on the other hand, appears to
25 antagonize the action of angiopoietin-1 on TEK and disrupts angiogenesis. Maisonpierre et al., *Science*, 277, 55-60 (1997).

As a result of the above-described developments, it has been proposed to treat angiogenesis by the use of compounds inhibiting the kinase activity of VEGF-R2, FGF-R, and/or TEK. For example, WIPO International Publication No. WO 97/34876 discloses
30 certain cinnoline derivatives that are inhibitors of VEGF-R2, which may be used for the treatment of disease states associated with abnormal angiogenesis and/or increased vascular permeability such as cancer, diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, arterial restinosis,

autoimmune diseases, acute inflammation, and ocular diseases with retinal vessel proliferation.

In addition to its role in angiogenesis, protein kinases also play a crucial role in cell-cycle control. Uncontrolled cell proliferation is the insignia of cancer. Cell proliferation in response to various stimuli is manifested by a de-regulation of the cell division cycle, the process by which cells multiply and divide. Tumor cells typically have damage to the genes that directly or indirectly regulate progression through the cell division cycle.

Cyclin-dependent kinases (CDKs) are serine-threonine protein kinases that play critical roles in regulating the transitions between different phases of the cell cycle. See, e.g., the articles compiled in *Science*, 274, 1643-1677 (1996). CDK complexes are formed through association of a regulatory cyclin subunit (e.g., cyclin A, B1, B2, D1, D2, D3, and E) and a catalytic kinase subunit (e.g., cdc2 (CDK1), CDK2, CDK4, CDK5, and CDK6). As the name implies, the CDKs display an absolute dependence on the cyclin subunit in order to phosphorylate their target substrates, and different kinase/cyclin pairs function to regulate progression through specific phases of the cell cycle.

It is CDK4 complexed to the D cyclins that plays a critical part in initiating the cell-division cycle from a resting or quiescent stage to one in which cells become committed to cell division. This progression is subject to a variety of growth regulatory mechanisms, both negative and positive. Aberrations in this control system, particularly those that affect the function of CDK4, have been implicated in the advancement of cells to the highly proliferative state characteristic of malignancies, particularly familial melanomas, esophageal carcinomas, and pancreatic cancers. See, e.g., Kamb, *Trends in Genetics*, 11, 136-140 (1995); Kamb et al., *Science*, 264, 436-440 (1994).

Myriad publications describe a variety of chemical compounds useful against a variety of therapeutic targets. For example, WIPO International Publication Nos. WO 99/23077 and WO 99/23076 describe indazole-containing compounds having phosphodiesterase type IV inhibitory activity produced by an indazole-for-catechol bioisostere replacement. U.S. Patent No. 5,760,028 discloses heterocycles including 3-[1-[3-(imidazolin-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2-(benzyloxycarbonylamino)propionic acid, which are useful as antagonists of the $\alpha\beta_3$ integrin and related cell surface adhesive protein receptors. WIPO International Publication No. WO 98/09961 discloses certain indazole derivatives and their use as

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inhibitors of phosphodiesterase (PDE) type IV or the production of tumor necrosis factor (TNF) in a mammal. Recent additions to the virtual library of known compounds include those described as being anti-proliferative therapeutic agents that inhibit CDKs. For example, U.S. Patent No. 5,621,082 to Xiong et al. discloses nucleic acid encoding an inhibitor of CDK6, and European Patent Publication No. 0 666 270 A2 describes peptides and peptide mimetics that act as inhibitors of CDK1 and CDK2. WIPO International Publication No. WO 97/16447 discloses certain analogs of chromones that are inhibitors of cyclin-dependent kinases, in particular of CDK/cyclin complexes such as CDK4/cyclin D1, which may be used for inhibiting excessive or abnormal cell proliferation, and therefore for treating cancer. WIPO International Publication No. WO 99/21845 describes 4-aminothiazole derivatives that are useful as CDK inhibitors.

There is still a need, however, for small-molecule compounds that may be readily synthesized and are effective in inhibiting one or more CDKs or CDK/cyclin complexes. Because CDK4 may serve as a general activator of cell division in most cells, and complexes of CDK4 and D-type cyclins govern the early G₁ phase of the cell cycle, there is a need for effective inhibitors of CDK4, and D-type cyclin complexes thereof, for treating one or more types of tumors. Also, the pivotal roles of cyclin E/CDK2 and cyclin B/CDK1 kinases in the G₁/S phase and G₂/M transitions, respectively, offer additional targets for therapeutic intervention in suppressing deregulated cell-cycle progression in cancer.

Another protein kinase, CHK-1, plays an important role as a checkpoint in cell-cycle progression. Checkpoints are control systems that coordinate cell-cycle progression by influencing the formation, activation and subsequent inactivation of the cyclin-dependent kinases. Checkpoints prevent cell-cycle progression at inappropriate times, maintain the metabolic balance of cells while the cell is arrested, and in some instances can induce apoptosis (programmed cell death) when the requirements of the checkpoint have not been met. See, e.g., O'Connor, *Cancer Surveys*, 29, 151-182 (1997); Nurse, *Cell*, 91, 865-867 (1997); Hartwell et al., *Science*, 266, 1821-1828 (1994); Hartwell et al., *Science*, 246, 629-634 (1989).

One series of checkpoints monitors the integrity of the genome and, upon sensing DNA damage, these "DNA damage checkpoints" block cell-cycle progression in G₁ and G₂ phases, and slow progression through S phase. O'Connor, *Cancer Surveys*, 29, 151-182 (1997); Hartwell et al., *Science*, 266, 1821-1828 (1994). This action enables DNA

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repair processes to complete their tasks before replication of the genome and subsequent separation of this genetic material into new daughter cells takes place. Importantly, the most commonly mutated gene in human cancer, the p53 tumor suppressor gene, produces a DNA damage checkpoint protein that blocks cell-cycle progression in G₁ phase and/or induces apoptosis (programmed cell death) following DNA damage. Hartwell et al., *Science*, 266, 1821-1828 (1994). The p53 tumor suppressor has also been shown to strengthen the action of a DNA damage checkpoint in G₂ phase of the cell cycle. See, e.g., Bunz et al., *Science*, 28, 1497-1501 (1998); Winters et al., *Oncogene*, 17, 673-684 (1998); Thompson, *Oncogene*, 15, 3025-3035 (1997).

Given the pivotal nature of the p53 tumor suppressor pathway in human cancer, therapeutic interventions that exploit vulnerabilities in p53-defective cancer have been actively sought. One emerging vulnerability lies in the operation of the G₂ checkpoint in p53 defective cancer cells. Cancer cells, because they lack G₁ checkpoint control, are particularly vulnerable to abrogation of the last remaining barrier protecting them from the cancer-killing effects of DNA-damaging agents: the G₂ checkpoint. The G₂ checkpoint is regulated by a control system that has been conserved from yeast to humans. Important in this conserved system is a kinase, CHK-1, which transduces signals from the DNA-damage sensory complex to inhibit activation of the cyclin B/Cdc2 kinase, which promotes mitotic entry. See, e.g., Peng et al., *Science*, 277, 1501-1505 (1997); Sanchez et al., *Science*, 277, 1497-1501 (1997). Inactivation of CHK1 has been shown to both abrogate G₂ arrest induced by DNA damage inflicted by either anticancer agents or endogenous DNA damage, as well as result in preferential killing of the resulting checkpoint defective cells. See, e.g., Nurse, *Cell*, 91, 865-867 (1997); Weinert, *Science*, 277, 1450-1451 (1997); Walworth et al., *Nature*, 363, 368-371 (1993); and Al-Khodairy et al., *Molec. Biol. Cell*, 5, 147-160 (1994).

Selective manipulation of checkpoint control in cancer cells could afford broad utilization in cancer chemotherapeutic and radiotherapy regimens and may, in addition, offer a common hallmark of human cancer "genomic instability" to be exploited as the selective basis for the destruction of cancer cells. A number of factors place CHK1 as a pivotal target in DNA-damage checkpoint control. The elucidation of inhibitors of this and functionally related kinases such as Cds1/CHK2, a kinase recently discovered to cooperate with CHK1 in regulating S phase progression (see Zeng et al., *Nature*, 395,

507-510 (1998); Matsuoka, *Science*, 282, 1893-1897 (1998)), could provide valuable new therapeutic entities for the treatment of cancer.

Tyrosine kinases can be of the receptor type (having extracellular, transmembrane and intracellular domains) or the non-receptor type (being wholly intracellular). At least one of the non-receptor protein tyrosine kinases, namely, LCK, is believed to mediate the transduction in T-cells of a signal from the interaction of a cell-surface protein (Cd4) with a cross-linked anti-Cd4 antibody. A more detailed discussion of non-receptor tyrosine kinases is provided in Bolen, *Oncogene*, 8, 2025-2031 (1993), which is incorporated herein by reference.

In addition to the protein kinases identified above, many other protein kinases have been considered to be therapeutic targets, and numerous publications disclose inhibitors of kinase activity, as reviewed in the following: McMahon et al., *Current Opinion in Drug Discovery & Development*, 1, 131-146 (1998); Strawn et al., *Exp. Opin. Invest. Drugs*, 7, 553-573 (1998).

There is still a need, however, for effective inhibitors of protein kinases. Moreover, as is understood by those skilled in the art, it is desirable for kinase inhibitors to possess both high affinity for the target kinase as well as high selectivity versus other protein kinases.

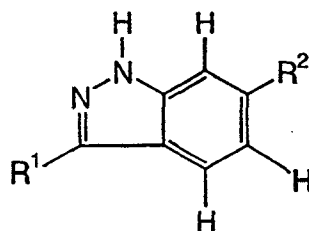
SUMMARY OF THE INVENTION

Thus, an objective of the invention is to discover potent inhibitors of protein kinases. Another objective of the invention is to discover effective kinase inhibitors having a strong and selective affinity for a particular kinase.

These and other objectives of the invention, which will become apparent from the following description, have been achieved by the discovery of the indazole compounds, pharmaceutically acceptable prodrugs, pharmaceutically active metabolites, and pharmaceutically acceptable salts thereof (such compounds, prodrugs, metabolites and salts are collectively referred to as "agents") described below, which modulate and/or inhibit the activity of protein kinases. Pharmaceutical compositions containing such agents are useful in treating diseases mediated by kinase activity, such as cancer, as well as other disease states associated with unwanted angiogenesis and/or cellular proliferation, such as diabetic retinopathy, neovascular glaucoma, rheumatoid arthritis, and psoriasis. Further, the agents have advantageous properties relating to the modulation

and/or inhibition of the kinase activity associated with VEGF-R, FGF-R, CDK complexes, CHK1, and/or LCK.

In a general aspect, the invention relates to compounds of the Formula I:



I

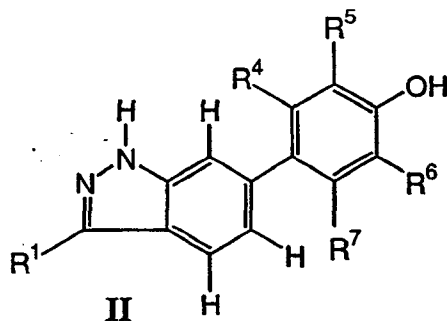
wherein:

- 5 R^1 is a substituted or unsubstituted aryl or heteroaryl, or a group of the formula $CH=CH-R^3$ or $CH=N-R^3$ where R^3 is a substituted or unsubstituted alkyl, alkenyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; and

- R^2 is a substituted or unsubstituted aryl or $Y-Ar$, where Y is O, S, $C=CH_2$, $\bar{C}=O$, $S=O$, SO_2 , CH_2 , $CHCH_3$, NH, or $N-(C_1-C_8 \text{ alkyl})$, and Ar is a substituted or unsubstituted
10 aryl.

The invention is also directed to pharmaceutically acceptable prodrugs, pharmaceutically active metabolites, and pharmaceutically acceptable salts of the compounds of Formula I. Advantageous methods of making the compounds of the Formula I are also described.

- 15 In one preferred general embodiment, the invention relates to compounds having the Formula II:



II

wherein:

- R^1 is a substituted or unsubstituted aryl or heteroaryl, or a group of the formula
20 $CH=CH-R^3$ or $CH=N-R^3$, where R^3 is a substituted or unsubstituted alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

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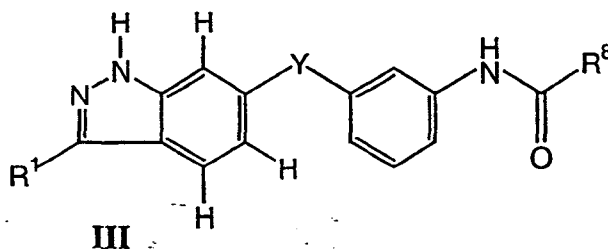
R^4 and R^7 are each independently hydrogen, OH, halo, C_1-C_8 alkyl, C_1-C_8 alkoxy, C_1-C_8 alkenyl, aryloxy, thioaryl, CH_2-OH , $CH_2-O-(C_1-C_8 \text{ alkyl})$, $CH_2-O\text{-aryl}$, $CH_2-S-(C_1-C_8 \text{ alkyl})$, or $CH_2-S\text{-aryl}$;

- R^5 and R^6 are each independently hydrogen, OH, halo, Z-alkyl, Z-aryl, or Z-
5 $CH_2CH=CH_2$, where Z is O, S, NH, or CH_2 , and the alkyl and aryl moieties of Z-alkyl and Z-aryl are each optionally substituted;

and pharmaceutically acceptable prodrugs, pharmaceutically active metabolites, and pharmaceutically acceptable salts thereof.

- In preferred embodiments of Formula II: R^1 is a substituted or unsubstituted
10 bicyclic heteroaryl, or a group of the formula $CH=CH-R^3$ where R^3 is a substituted or unsubstituted aryl; R^4 and R^7 are each independently hydrogen or C_1-C_8 alkyl; and R^5 and R^6 are each independently halo, Z-alkyl, or Z- $CH_2CH=CH_2$, where Z is O or S.

In another preferred general embodiment, compounds of the invention are of Formula III:



- 15 wherein:

R^1 is a substituted or unsubstituted aryl or heteroaryl, or a group of the formula $CH=CH-R^3$ or $CH=N-R^3$, where R^3 is a substituted or unsubstituted alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

Y is O, S, $C=CH_2$, $C=O$, $S=O$, SO_2 , CH_2 , $CHCH_3$, NH, or $N-(C_1-C_8 \text{ alkyl})$;

- 20 R^8 is a substituted or unsubstituted alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxyl, or aryloxy;
and pharmaceutically acceptable prodrugs, pharmaceutically acceptable metabolites, and pharmaceutically acceptable salts thereof.

- More preferably, in Formula III: R^1 is a substituted or unsubstituted bicyclic
25 heteroaryl, or a group of the formula $CH=CH-R^3$ where R^3 is a substituted or unsubstituted aryl or heteroaryl; Y is O, S, $C=CH_2$, $C=O$, NH, or $N-(C_1-C_8 \text{ alkyl})$; and R^8 is a substituted or unsubstituted aryl or heteroaryl.

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The invention also relates to a method of modulating and/or inhibiting the kinase activity of VEGF-R, FGF-R, a CDK complex, CHK1, and/or LCK by administering a compound of the Formula I, II, or III, or a pharmaceutically acceptable prodrug, pharmaceutically active metabolite, or pharmaceutically acceptable salt thereof. Preferred compounds of the present invention that have selective kinase activity—i.e., they possess significant activity against one specific kinase while possessing less or minimal activity against a different kinase. In one preferred embodiment of the invention, compounds of the present invention are those of Formula I possessing substantially higher potency against VEGF receptor tyrosine kinase than against FGF-R1 receptor tyrosine kinase.

10 The invention is also directed to methods of modulating VEGF receptor tyrosine kinase activity without significantly modulating FGF receptor tyrosine kinase activity.

The invention also relates pharmaceutical compositions, each comprising an effective amount of an agent selected from compounds of Formula I and pharmaceutically acceptable salts, pharmaceutically active metabolites, and pharmaceutically acceptable prodrugs thereof; and a pharmaceutically acceptable carrier or vehicle for such agent. The invention further provides methods of treating cancer as well as other disease states associated with unwanted angiogenesis and/or cellular proliferation, comprising administering effective amounts of such an agent to a patient in need of such treatment.

DETAILED DESCRIPTION OF INVENTION AND PREFERRED EMBODIMENTS

20 The inventive compounds of the Formula I, II, and III are useful for mediating the activity of protein kinases. More particularly, the compounds are useful as anti-angiogenesis agents and as agents for modulating and/or inhibiting the activity of protein kinases, thus providing treatments for cancer or other diseases associated with cellular proliferation mediated by protein kinases.

25 The term "alkyl" as used herein refers to straight- and branched-chain alkyl groups having one to twelve carbon atoms. Exemplary alkyl groups include methyl (Me), ethyl (Et), n-propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl (t-Bu), pentyl, isopentyl, tert-pentyl, hexyl, isohexyl, and the like. The term "lower alkyl" designates an alkyl having from 1 to 8 carbon atoms (a C₁₋₈-alkyl). Suitable substituted alkyls include fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 3-fluoropropyl, hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl, and the like.

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The term "alkenyl" refers to straight- and branched-chain alkenyl groups having from two to twelve carbon atoms. Illustrative alkenyl groups include prop-2-enyl, but-2-enyl, but-3-enyl, 2-methylprop-2-enyl, hex-2-enyl, and the like.

5 The term "cycloalkyl" refers to saturated carbocycles having from three to twelve carbon atoms, including bicyclic and tricyclic cycloalkyl structures. Suitable cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like.

A "heterocycloalkyl" group is intended to mean a monocyclic radical containing carbon atoms, preferably 4 or 5 ring carbon atoms, and at least one heteroatom selected from nitrogen, oxygen and sulfur, and having no unsaturation.

10 The terms "aryl" and "heteroaryl" refer to monocyclic and polycyclic unsaturated or aromatic ring structures, with "aryl" referring to those that are carbocycles and "heteroaryl" referring to those that are heterocycles. Examples of aromatic ring structures include phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, furyl, thienyl, pyrrolyl, pyridyl, pyridinyl, pyrazolyl, imidazolyl, pyrazinyl, pyridazinyl, 1,2,3-triazinyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1-H-
15 tetrazol-5-yl, indolyl, quinolinyl, benzofuranyl, benzothiophenyl (thianaphthenyl), and the like. Such moieties may be optionally substituted by a fused-ring structure or bridge, for example $\text{OCH}_2\text{-O}$.

The term "alkoxy" is intended to mean the radical -O-alkyl . Illustrative examples include methoxy, ethoxy, propoxy, and the like.

20 The term "aryloxy" represents -O-aryl , wherein aryl is defined above.

The term "halogen" represents chlorine, fluorine, bromine or iodine. The term "halo" represents chloro, fluoro, bromo or iodo.

In general, the various moieties or functional groups for variables in the formulae may be optionally substituted by one or more suitable substituents. Exemplary substituents
25 include a halogen (F, Cl, Br, or I), lower alkyl, -OH , -NO_2 , -CN , $\text{-CO}_2\text{H}$, -O-lower alkyl , -aryl , -aryl-lower alkyl , $\text{-CO}_2\text{CH}_3$, -CONH_2 , $\text{-OCH}_2\text{CONH}_2$, -NH_2 , $\text{-SO}_2\text{NH}_2$, haloalkyl (e.g., -CF_3 , $\text{-CH}_2\text{CF}_3$), -O-haloalkyl (e.g., -OCF_3 , -OCHF_3), and the like.

The terms "comprising" and "including" are used in an open, non-limiting sense.

It is understood that a compound of Formula I may exhibit the phenomenon of
30 tautomerism and that the structural formulas within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which modulates and/or inhibits kinase activity and is not to be limited merely to any one tautomeric form shown in a given formula.

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Some of the inventive compounds may exist as single stereoisomers (i.e., essentially free of other stereoisomers), racemates, and/or mixtures of enantiomers and/or diastereomers. All such single stereoisomers, racemates and mixtures thereof are intended to be within the scope of the present invention. Preferably, the inventive

5 compounds that are optically active are used in optically pure form.

As generally understood by those skilled in the art, an optically pure compound having one chiral center is one that consists essentially of one of the two possible enantiomers (i.e., is enantiomerically pure), and an optically pure compound having more than one chiral center is one that is both diastereomerically pure and enantiomerically pure. Preferably, the

10 compounds of the present invention are used in a form that is at least 90% optically pure, that is, a form that contains at least 90% of a single isomer (80% enantiomeric excess ("e.e.") or diastereomeric excess ("d.e.")), more preferably at least 95% (90% e.e. or d.e.), even more preferably at least 97.5% (95% e.e. or d.e.), and most preferably at least 99% (98% e.e. or d.e.).

15 Additionally, the formulas are intended to cover solvated as well as unsolvated forms of the identified structures. For example, Formula I includes compounds of the indicated structure in both hydrated and non-hydrated forms. Other examples of solvates include the structures in combination with isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid, or ethanolamine.

20 In addition to compounds of the Formula I, II, and III, the invention includes pharmaceutically acceptable prodrugs, pharmaceutically active metabolites, and pharmaceutically acceptable salts of such compounds.

"A pharmaceutically acceptable prodrug" is a compound that may be converted under physiological conditions or by solvolysis to the specified compound or to a pharmaceutically

25 acceptable salt of such compound.

"A pharmaceutically active metabolite" is intended to mean a pharmacologically active product produced through metabolism in the body of a specified compound or salt thereof. Metabolites of a compound may be identified using routine techniques known in the art and their activities determined using tests such as those described herein.

30 "A pharmaceutically acceptable salt" is intended to mean a salt that retains the biological effectiveness of the free acids and bases of the specified compound and that is not biologically or otherwise undesirable. A compound of the invention may possess a sufficiently acidic, a sufficiently basic, or both functional groups, and accordingly react with

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any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. Exemplary pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a mineral or organic acid or an inorganic base, such as salts including sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrate, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, xylenesulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, γ -hydroxybutyrates, glycollates, tartrates, methane-sulfonates, propanesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, and mandelates.

If the inventive compound is a base, the desired pharmaceutically acceptable salt may be prepared by any suitable method available in the art, for example, treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, or with an organic acid, such as acetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an α -hydroxy acid, such as citric acid or tartaric acid, an amino acid, such as aspartic acid or glutamic acid, an aromatic acid, such as benzoic acid or cinnamic acid, a sulfonic acid, such as p-toluenesulfonic acid or ethanesulfonic acid, or the like.

If the inventive compound is an acid, the desired pharmaceutically acceptable salt may be prepared by any suitable method, for example, treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary or tertiary), an alkali metal hydroxide or alkaline earth metal hydroxide, or the like. Illustrative examples of suitable salts include organic salts derived from amino acids, such as glycine and arginine, ammonia, primary, secondary, and tertiary amines, and cyclic amines, such as piperidine, morpholine and piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum and lithium.

In the case of agents that are solids, it is understood by those skilled in the art that the inventive compounds and salts may exist in different crystal or polymorphic forms, all of

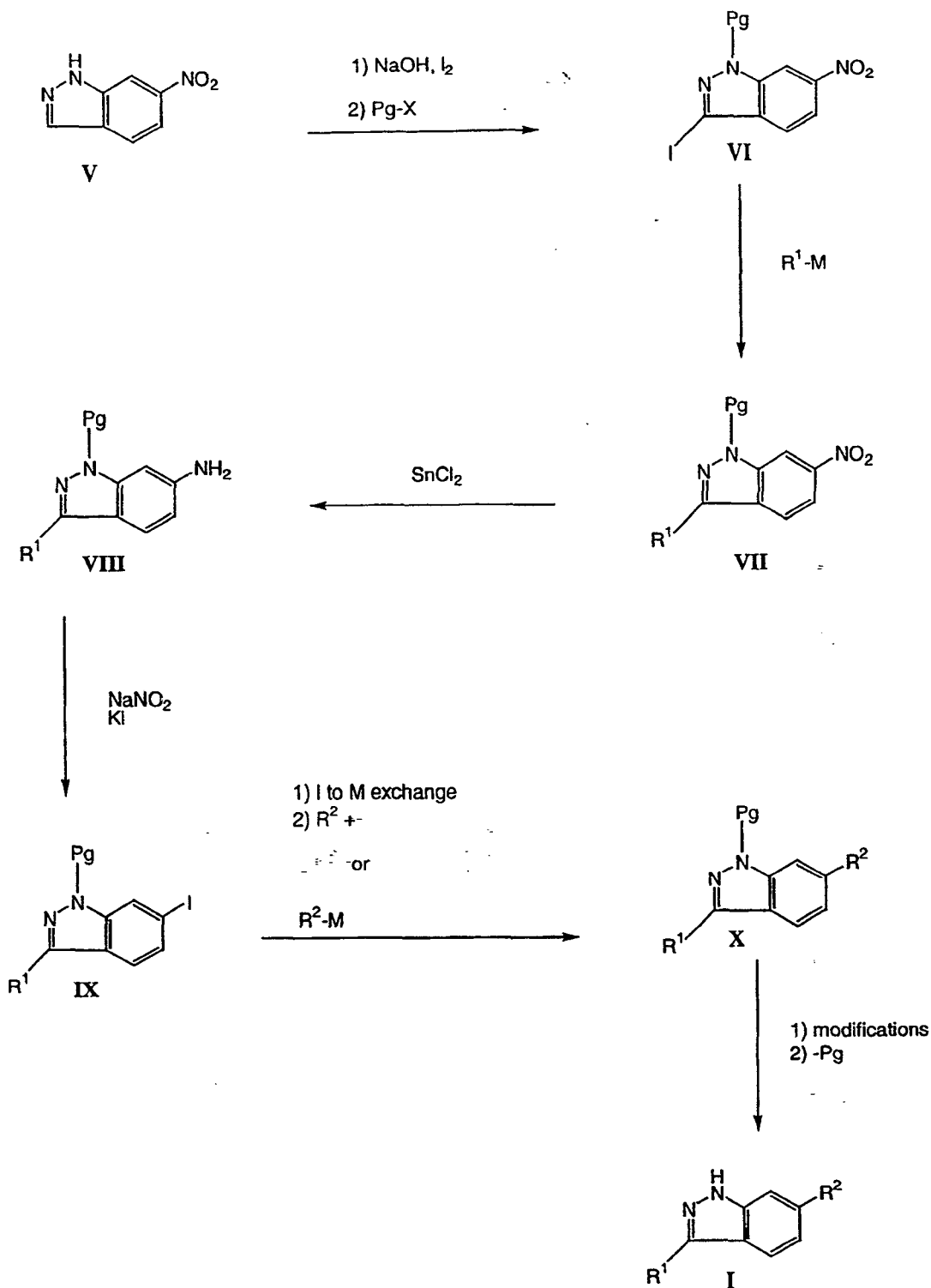
which are intended to be within the scope of the present invention and specified formulas.

Therapeutically effective amounts of the agents of the invention may be used to treat diseases mediated by modulation or regulation of protein kinases. An "effective amount" is intended to mean that amount of an agent that, when administered to a mammal in need of such treatment, is sufficient to effect treatment for a disease mediated by the activity of one or more protein kinases, such as tyrosine kinases. Thus, e.g., a therapeutically effective amount of a compound of the Formula I, salt, active metabolite or prodrug thereof is a quantity sufficient to modulate, regulate, or inhibit the activity of one or more protein kinases such that a disease condition which is mediated by that activity is reduced or alleviated.

The amount of a given agent that will correspond to such an amount will vary depending upon factors such as the particular compound, disease condition and its severity, the identity (e.g., weight) of the mammal in need of treatment, but can nevertheless be routinely determined by one skilled in the art. "Treating" is intended to mean at least the mitigation of a disease condition in a mammal, such as a human, that is affected, at least in part, by the activity of one or more protein kinases, such as tyrosine kinases, and includes: preventing the disease condition from occurring in a mammal, particularly when the mammal is found to be predisposed to having the disease condition but has not yet been diagnosed as having it; modulating and/or inhibiting the disease condition; and/or alleviating the disease condition.

The inventive agents may be prepared using the reaction routes and synthesis schemes as described below, employing the techniques available in the art using starting materials that are readily available.

In one general synthetic process, compounds of Formula I are prepared according to the following reaction scheme:



6-Nitroindazole (compound V) is treated with iodine and base, e.g., NaOH, in an aqueous/organic mixture, preferably with dioxane. The mixture is acidified and the product isolated by filtration. To the resulting 3-iodo-6-nitroindazole in dichloromethane-

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50% aqueous KOH at 0 °C is added a protecting group ("Pg") reagent (wherein X = halo), preferably trimethylsilylethoxymethyl chloride (SEM-Cl), and a phase transfer catalyst, e.g., tetrabutylammonium bromide (TBABr). After 1-4 hours, the two phases are diluted, the organics are separated, dried with sodium sulfate, filtered and concentrated. The

5 crude product is purified by silica gel chromatography to give compound VI.

Treatment of compound VI in a suitable organic solvent with a suitable R¹-organometallic reagent, preferably an R¹-boronic acid, in the presence of aqueous base, e.g., sodium carbonate, and a suitable catalyst, preferably Pd(PPh₃)₄, gives, after extractive work-up and silica gel chromatography, compound VII. Treatment of compound VII with a reducing

10 agent, preferably SnCl₂, provides, after conventional aqueous work up and purification, compound VIII. For the series of derivatives where Y = NH or N-lower alkyl, compounds of formula VIII may be treated with aryl or heteroaryl chlorides, bromides, iodides or triflates in the presence of a base, preferably Cs₂CO₃, and catalyst, preferably Pd-BINAP, (and where Y = N-lower alkyl, with a subsequent alkylation step) to provide compounds of formula X. To

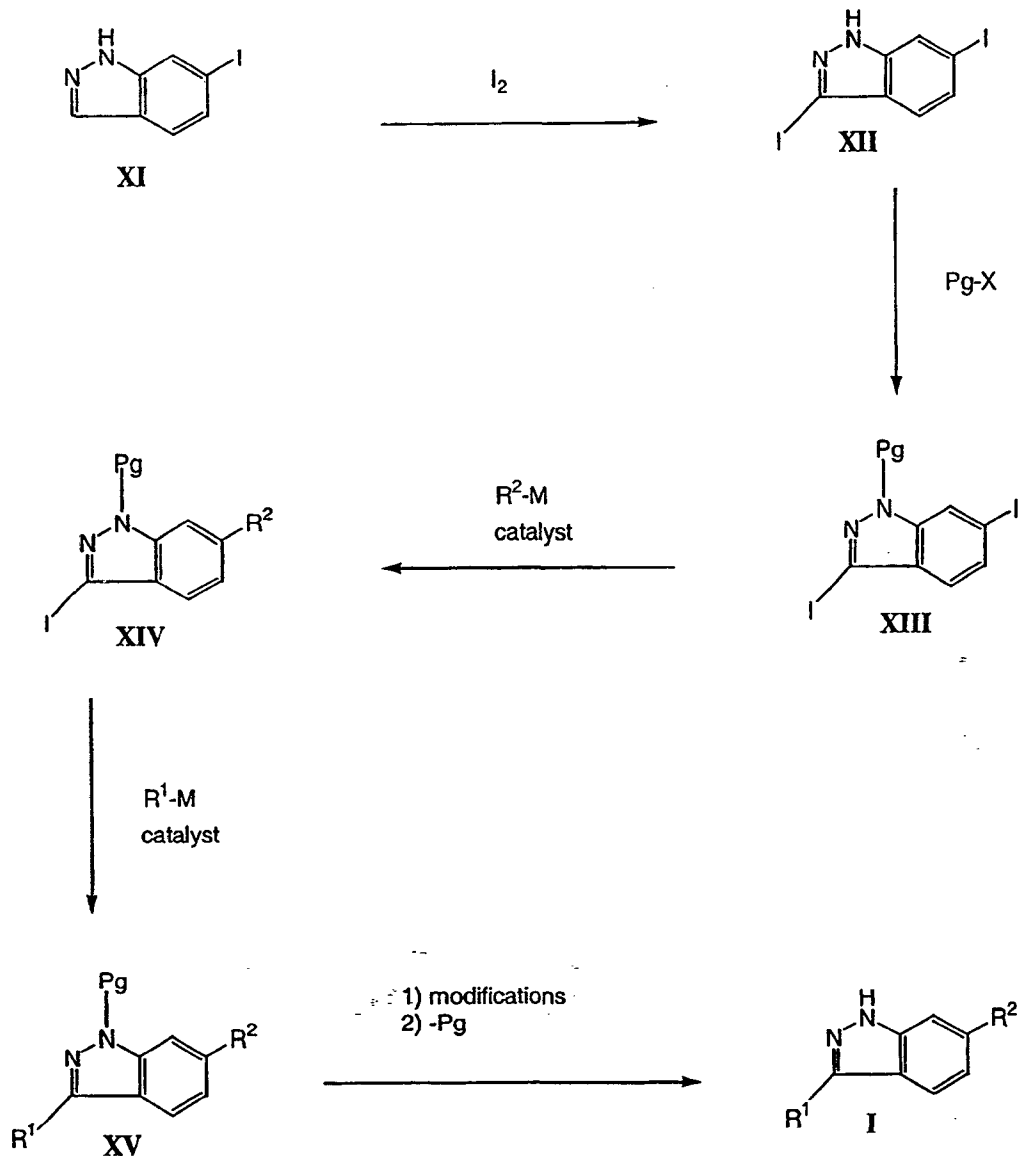
15 produce other Y linkages, sodium nitrite is added to compound VIII under chilled standard aqueous acidic conditions followed by the addition of potassium iodide and gentle warming. Standard work-up and purification produces iodide compound IX.

Treatment of compound IX with an organometallic reagent, e.g., butyllithium, promotes lithium halogen exchange. This intermediate is then reacted with an R²

20 electrophile, e.g., a carbonyl or triflate, through the possible mediation of additional metals and catalysts, preferably zinc chloride and Pd(PPh₃)₄, to provide compounds of formula X. Alternatively, compound IX may be treated with an organometallic reagent such as an organoboronic acid in the presence of a catalyst, e.g., Pd(PPh₃)₄, under a carbon monoxide atmosphere to give compounds of formula X. Conventional functional group interchanges,

25 such as oxidations, reductions, alkylations, condensations, and deprotections may then be employed to further derivatize this series giving final compounds of Formula I.

The inventive compounds of Formula I may also be prepared according general procedure shown in the following scheme:



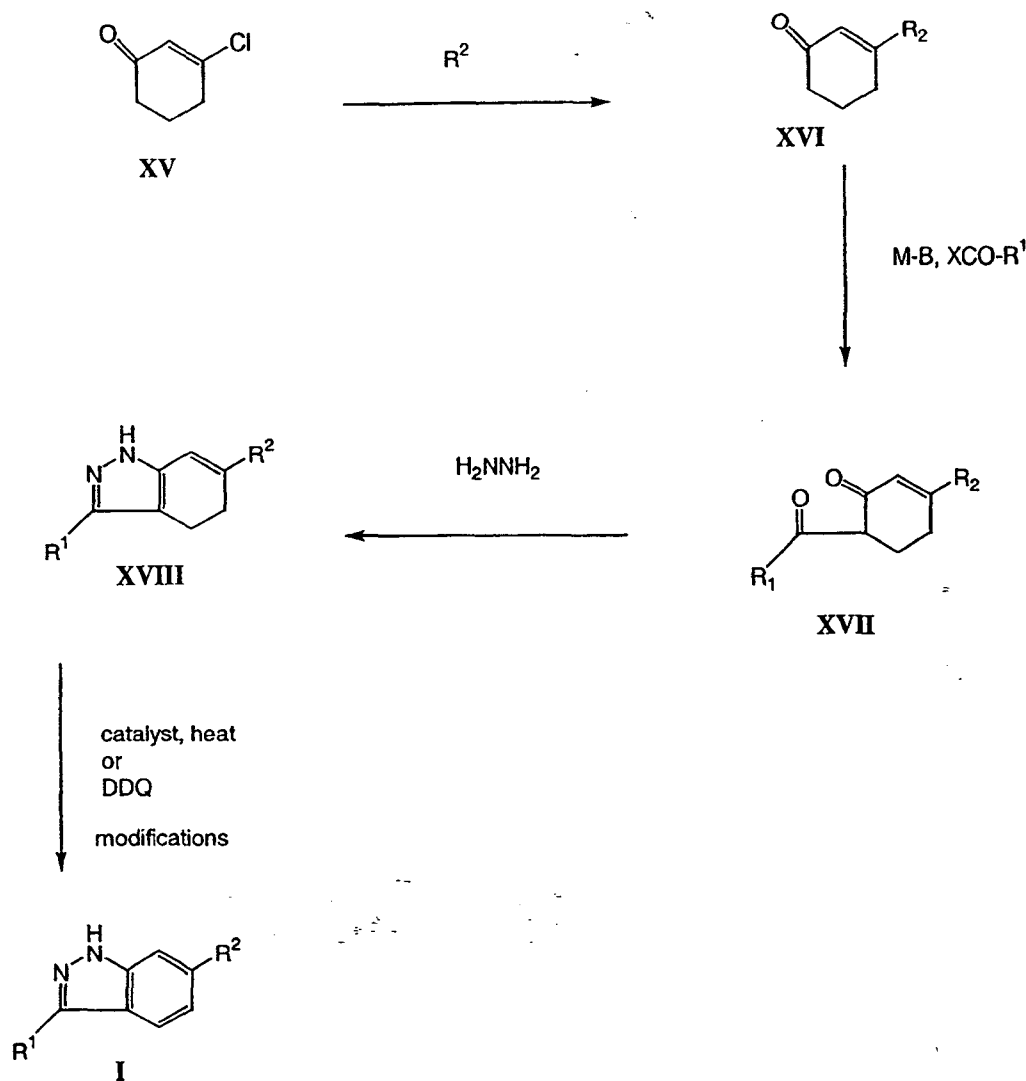
- 6-Iodoindazole (XI) is treated with iodine and base, e.g., NaOH, in an aqueous/organic mixture, preferably with dioxane. The mixture is acidified and the product XII is isolated by filtration. To the resulting 3,6-iodoindazole in dichloromethane-50% aqueous KOH at 0 °C is added a protecting group reagent, preferably SEM-Cl, and a phase transfer catalyst, e.g., TBABr. The two phases are diluted, the organics separated, dried with sodium sulfate, filtered and concentrated. The crude product is purified by silica gel chromatography to give compounds of the formula XIII. Treatment of compound XIII in a suitable organic solvent with a suitable R^2 -organometallic reagent, e.g., R^2-ZnCl or boron R^2 -boron reagent and a suitable catalyst, preferably $Pd(PPh_3)_4$, gives, after extractive work-up and

silica gel chromatography, compounds of formula XIV. Treatment of compound XIV in a suitable organic solvent with a suitable R^1 -organometallic reagent (e.g., boron R^1 -boron reagent or R^1 -ZnCl), in the presence of aqueous base, sodium carbonate, and a suitable catalyst, preferably $Pd(PPh_3)_4$, gives, after extractive work-up and silica gel chromatography, compound XV. Conventional functional group interchanges, such as oxidations, reductions, alkylations, condensations and deprotections may then be employed to further derivatize this series giving final compounds of Formula I.

Alternatively, compounds of Formula I where R^2 is a substituted or unsubstituted Y-Ar, where Y is O or S may be prepared according to the following general scheme:

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A stirred acetone solution of 3-chloro-cyclohex-2-enone (XV), $H-R^2$, and anhydrous potassium carbonate is refluxed for 15-24 hours, cooled, and filtered.

- 5 Concentrating and chromatographing the filtrate on silica gel gives 3- R^2 -cyclohex-2-enone (XVI).

The ketone XVI may be reacted with a suitable base (M-B), preferably lithium bis(trimethylsilyl)amide, and reacted with R^1-CO-X (where X = halogen), which after standard acid work up and purification provides compounds of the formula XVII. This

- 10 product, in HOAc/EtOH, combined with hydrazine monohydrate, is heated at a suitable temperature for an appropriate time period, preferably at 60-80 °C for 2-4 hours. After cooling, the mixture is poured into saturated sodium bicarbonate solution, extracted with

an organic solvent, concentrated, and purified on silica gel to give compound XVIII. Compound XVIII may be oxidized using a variety of known methods to give compounds of the Formula I.

Other compounds of Formula I may be prepared in manners analogous to the general procedures described above or the detailed procedures described in the examples herein. The affinity of the compounds of the invention for a receptor may be enhanced by providing multiple copies of the ligand in close proximity, preferably using a scaffolding provided by a carrier moiety. It has been shown that provision of such multiple valence compounds with optimal spacing between the moieties dramatically improves binding to a receptor. See, e.g., Lee et al., *Biochem*, 23, 4255 (1984). The multivalency and spacing can be controlled by selection of a suitable carrier moiety or linker units. Such moieties include molecular supports which contain a multiplicity of functional groups that can be reacted with functional groups associated with the compounds of the invention. Of course, a variety of carriers can be used, including proteins such as BSA or HAS, a multiplicity of peptides including, for example, pentapeptides, decapeptides, pentadecapeptides, and the like. The peptides or proteins can contain the desired number of amino acid residues having free amino groups in their side chains; however, other functional groups, such as sulfhydryl groups or hydroxyl groups, can also be used to obtain stable linkages.

Compounds that potently regulate, modulate, or inhibit the protein kinase activity associated with receptors VEGF, FGF, CDK complexes, TEK, CHK-1, and LCK, among others, and which inhibit angiogenesis and/or cellular proliferation is desirable and is one preferred embodiment of the present invention. The present invention is further directed to methods of modulating or inhibiting protein kinase activity, for example in mammalian tissue, by administering an inventive agent. The activity of the inventive compounds as modulators of protein kinase activity, such as the activity of kinases, may be measured by any of the methods available to those skilled in the art, including *in vivo* and/or *in vitro* assays. Examples of suitable assays for activity measurements include those described in Parast C. et al., *BioChemistry*, 37, 16788-16801 (1998); Jeffrey et al., *Nature*, 376, 313-320 (1995); WIPO International Publication No. WO 97/34876; and WIPO International Publication No. WO 96/14843. These properties may be assessed, for example, by using one or more of the biological testing procedures set out in the examples below.

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The active agents of the invention may be formulated into pharmaceutical compositions as described below. Pharmaceutical compositions of this invention comprise an effective modulating, regulating, or inhibiting amount of a compound of Formula I, II, or III and an inert, pharmaceutically acceptable carrier or diluent. In one embodiment of the pharmaceutical compositions, efficacious levels of the inventive agents are provided so as to provide therapeutic benefits involving modulation of protein kinases. By "efficacious levels" is meant levels in which the effects of protein kinases are, at a minimum, regulated. These compositions are prepared in unit-dosage form appropriate for the mode of administration, e.g., parenteral or oral administration.

10 An inventive agent is administered in conventional dosage form prepared by combining a therapeutically effective amount of an agent (e.g., a compound of Formula I) as an active ingredient with appropriate pharmaceutical carriers or diluents according to conventional procedures. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

15 The pharmaceutical carrier employed may be either a solid or liquid. Exemplary of solid carriers are lactose, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time-delay or time-release material known in the art, such as glyceryl monostearate or glyceryl distearate alone or with a wax, ethylcellulose, hydroxypropylmethylcellulose, methylmethacrylate and the like.

20 A variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier may vary, but generally will be from about 25 mg to about 1 g. If a liquid carrier is used, the preparation will be in the form of syrup, emulsion, soft gelatin capsule, sterile injectable solution or suspension in an ampoule or vial or non-aqueous liquid suspension.

25 To obtain a stable water-soluble dose form, a pharmaceutically acceptable salt of an inventive agent is dissolved in an aqueous solution of an organic or inorganic acid, such as 0.3M solution of succinic acid or citric acid. If a soluble salt form is not available, the agent may be dissolved in a suitable cosolvent or combinations of cosolvents. Examples of suitable cosolvents include, but are not limited to, alcohol, propylene glycol, polyethylene glycol 300, polysorbate 80, glycerin and the like in concentrations ranging from 0-60% of the total volume. In an exemplary embodiment, a compound of Formula I is dissolved in DMSO and

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diluted with water. The composition may also be in the form of a solution of a salt form of the active ingredient in an appropriate aqueous vehicle such as water or isotonic saline or dextrose solution.

5 It will be appreciated that the actual dosages of the agents used in the compositions of this invention will vary according to the particular complex being used, the particular composition formulated, the mode of administration and the particular site, host and disease being treated. Optimal dosages for a given set of conditions can be ascertained by those skilled in the art using conventional dosage-determination tests in view of the experimental data for an agent. For oral administration, an exemplary daily dose generally employed is 10 from about 0.001 to about 1000 mg/kg of body weight, more preferably from about 0.001 to about 50 mg/kg body weight, with courses of treatment repeated at appropriate intervals. Administration of prodrugs are typically dosed at weight levels which are chemically equivalent to the weight levels of the fully active form.

15 The compositions of the invention may be manufactured in manners generally known for preparing pharmaceutical compositions, e.g., using conventional techniques such as mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing. Pharmaceutical compositions may be formulated in a conventional manner using one or more physiologically acceptable carriers, which may be selected from excipients and auxiliaries that facilitate processing of the active compounds 20 into preparations which can be used pharmaceutically.

25 Proper formulation is dependent upon the route of administration chosen. For injection, the agents of the invention may be formulated into aqueous solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

30 For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained using a solid excipient in admixture with the active ingredient (agent), optionally grinding the resulting mixture, and processing the mixture of granules after adding suitable auxiliaries, if desired, to obtain

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tablets or dragee cores. Suitable excipients include: fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; and cellulose preparations, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as crosslinked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, polyvinyl pyrrolidone, Carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active agents.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the active agents may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration. For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For administration intranasally or by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of gelatin for use in an inhaler or insufflator and the like may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit-dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous

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vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active agents may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use. The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, e.g, containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described above, the compounds may also be formulated as a depot preparation. Such long-acting formulations may be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion-exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

A pharmaceutical carrier for hydrophobic compounds is a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. The cosolvent system may be a VPD co-solvent system. VPD is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant polysorbate 80, and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. The VPD co-solvent system (VPD:5W) contains VPD diluted 1:1 with a 5% dextrose in water solution. This co-solvent system dissolves hydrophobic compounds well, and itself produces low toxicity upon systemic administration. Naturally, the proportions of a co-solvent system may be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of polysorbate 80; the fraction size of polyethylene

glycol may be varied; other biocompatible polymers may replace polyethylene glycol, e.g. polyvinyl pyrrolidone; and other sugars or polysaccharides may be substituted for dextrose.

Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are known examples of delivery vehicles or carriers
5 for hydrophobic drugs. Certain organic solvents such as dimethylsulfoxide also may be employed, although usually at the cost of greater toxicity. Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials have been established and are known by those skilled in the art. Sustained-release capsules
10 may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization may be employed.

The pharmaceutical compositions also may comprise suitable solid- or gel-phase carriers or excipients. Examples of such carriers or excipients include calcium carbonate,
15 calcium phosphate, sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

Some of the compounds of the invention may be provided as salts with pharmaceutically compatible counter ions. Pharmaceutically compatible salts may be formed with many acids, including hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, etc.
20 Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free-base forms.

The preparation of preferred compounds of the present invention is described in detail in the following examples, but the artisan will recognize that the chemical reactions described may be readily adapted to prepare a number of other protein kinase inhibitors of the
25 invention. For example, the synthesis of non-exemplified compounds according to the invention may be successfully performed by modifications apparent to those skilled in the art, e.g., by appropriately protecting interfering groups, by changing to other suitable reagents known in the art, or by making routine modifications of reaction conditions. Alternatively, other reactions disclosed herein or known in the art will be recognized as having applicability
30 for preparing other compounds of the invention.

EXAMPLES

In the examples described below, unless otherwise indicated all temperatures are set forth in degrees Celsius and all parts and percentages are by weight. Reagents were

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purchased from commercial suppliers such as Aldrich Chemical Company or Lancaster Synthesis Ltd. and were used without further purification unless otherwise indicated. Tetrahydrofuran (THF), N,N-dimethylformamide (DMF), dichloromethane, toluene, and dioxane were purchased from Aldrich in Sure seal bottles and used as received. All solvents
5 were purified using standard methods readily known to those skilled in the art, unless otherwise indicated.

The reactions set forth below were done generally under a positive pressure of argon or nitrogen or with a drying tube, at ambient temperature (unless otherwise stated), in anhydrous solvents, and the reaction flasks were fitted with rubber septa for the introduction
10 of substrates and reagents via syringe. Glassware was oven dried and/or heat dried.

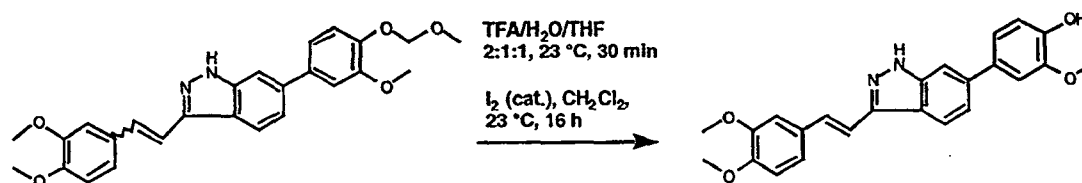
Analytical thin layer chromatography (TLC) was performed on glass-backed silica gel 60 F 254 plates Analtech (0.25 mm) and eluted with the appropriate solvent ratios (v/v), and are denoted where appropriate. The reactions were assayed by TLC and terminated as judged by the consumption of starting material.

15 Visualization of the TLC plates was done with a *p*-anisaldehyde spray reagent or phosphomolybdic acid reagent (Aldrich Chemical 20 wt % in ethanol) and activated with heat. Work-ups were typically done by doubling the reaction volume with the reaction solvent or extraction solvent and then washing with the indicated aqueous solutions using 25% by volume of the extraction volume unless otherwise indicated. Product solutions were
20 dried over anhydrous Na₂SO₄ prior to filtration and evaporation of the solvents under reduced pressure on a rotary evaporator and noted as solvents removed *in vacuo*. Flash column chromatography (Still et al., *J. Org. Chem.*, 43, 2923 (1978)) was done using Baker grade flash silica gel (47-61 μm) and a silica gel: crude material ratio of about 20:1 to 50:1 unless otherwise stated. Hydrogenolysis was done at the pressure indicated in the examples or at
25 ambient pressure.

¹H-NMR spectra were recorded on a Bruker instrument operating at 300 MHz and ¹³C-NMR spectra were recorded operating at 75 MHz. NMR spectra were obtained as CDCl₃ solutions (reported in ppm), using chloroform as the reference standard (7.25 ppm and 77.00 ppm) or CD₃OD (3.4 and 4.8 ppm and 49.3 ppm), or internally tetramethylsilane (0.00 ppm)
30 when appropriate. Other NMR solvents were used as needed. When peak multiplicities are reported, the following abbreviations are used: s (singlet), d (doublet), t (triplet), m (multiplet), br (broadened), dd (doublet of doublets), dt (doublet of triplets). Coupling constants, when given, are reported in Hertz (Hz).

Infrared (IR) spectra were recorded on a Perkin-Elmer FT-IR Spectrometer as neat oils, as KBr pellets, or as CDCl₃ solutions, and when given are reported in wave numbers (cm⁻¹). The mass spectra were obtained using LSIMS or electrospray. All melting points (mp) are uncorrected.

5 **Example 1(a_{LEI})**: 3-[E-2-(3,4-Dimethoxy-phenyl)vinyl]-6-(3-methoxy-4-hydroxy-phenyl)-1*H*-indazole

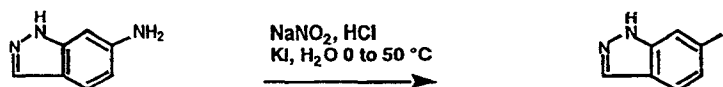


10 The 3-[E/Z-2-(3,4-dimethoxy-phenyl)vinyl]-6-[3-methoxy-4-(methoxymethoxy)phenyl]-1*H*-indazole (~205 mg, 0.461 mmol (theoretical)) was dissolved in tetrahydrofuran (THF, 10 mL) and was treated with water (10 mL) and trifluoroacetic acid (TFA, 20 mL). The reaction mixture was allowed to stir at 23 °C for 30 minutes (min.). The mixture was diluted with toluene (100 mL) and the volatile materials were removed under
15 reduced pressure (30 mm Hg, 35 °C) to give a concentrated volume of ~ 5 mL. Again, toluene (100 mL) was added and the mixture was concentrated under reduced pressure to give crude material which still contained some acid. The material was partitioned between ethyl acetate and saturated sodium bicarbonate, the organic material was separated, dried over sodium sulfate, decanted, and concentrated under reduced pressure. The residue, a mixture of
20 olefin isomers, (~185 mg, 0.461 mmol (theoretical)) was taken up in dichloromethane (50 mL) at 23 °C and was treated with iodine (80 mg). The mixture was allowed to stir at 23 °C for 12 hours (h). The mixture was treated with saturated sodium bicarbonate (10 mL) and 5% aqueous sodium bisulfite (10 mL). The mixture was diluted with ethyl acetate (200 mL) and the organic material was washed with saturated sodium bicarbonate (100 mL), dried over
25 sodium sulfate, decanted, and concentrated under reduced pressure to give crude product. The crude was purified on silica (40 mL, 6:4 -> 7:3 ethyl acetate/hexane) and all fractions containing desired were combined, concentrated and precipitated from a dichloromethane/hexane bilayer (1:3) to give 3-[E-2-(3,4-Dimethoxy-phenyl)vinyl]-6-(3-methoxy-4-hydroxy-phenyl)-1*H*-indazole as a white solid (93 mg combined crops): R_f sm
30 0.42, p 0.35 (ethyl acetate-hexane 7:3); FTIR (thin film) 3324, 1600, 1514, 1463, 1422,

1264, 1137, 1024, 959, 852 cm^{-1} ; ^1H NMR (CDCl_3) δ 10.0 (bs, 1H), 8.08 (d, 1H, $J = 8.4$ Hz), 7.59 (s, 1H), 7.49 (d, 1H, $J = 16.6$ Hz), 7.45 (dd, 1H, $J = 1.4, 8.4$ Hz), 7.34 (d, 1H, $J = 16.6$ Hz), 7.20-7.12 (m, 4H), 7.03 (d, 1H, $J = 8.0$ Hz), 6.91 (d, 1H, $J = 8.2$ Hz), 5.68 (bs, 1H), 3.99 (s, 3H), 3.97 (s, 3H), 3.93 (s, 3H); ^{13}C NMR (CDCl_3) δ 149.6, 149.5, 146.0, 144.0, 142.6, 140.8, 133.9, 131.4, 130.7, 121.7, 121.4, 120.9, 120.4, 120.2, 118.6, 115.4, 111.7, 110.8, 109.1, 108.2, 56.4, 56.3, 56.2; HRMS (ES) $[m+H]^+/z$ Calc'd 403.1658, Found 403.1658; $[m-H]^+/z$ Calc'd 401, Found 401.

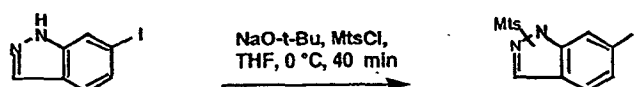
The starting material was prepared as follows:

(i)



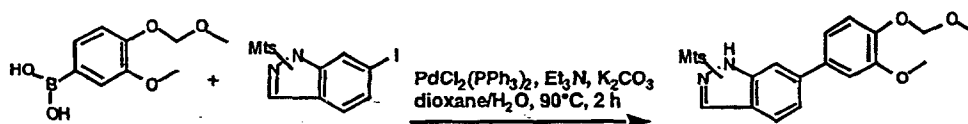
To 6-aminoindazole (40.8 g, 0.3065 mol, 1 equiv) in a 2-liter (2-L) round-bottom flask containing a large magnetic stir bar was added ice (256 g), followed by water (128 mL) and the reaction vessel was lowered into an ice bath. To this stirring slurry at 0 °C was added concentrated aqueous HCl (128 mL, 1.53 mol, 5 equiv). Immediately after, a solution of NaNO_2 (23.3 g, 0.338 mol, 1.1 equiv) in water (96 mL) was added. After 10 min of stirring at 0 °C, KI (61 g, 0.368 mol, 1.2 equiv) was added very slowly at first (~100 mg at a time because the first small bits of KI cause an abrupt evolution of gas) then more rapidly (5 min total time). The cold bath was removed and the reaction mixture was warmed to 40 °C (gas evolved). When the rate of gas evolution decreased (~30 min) the reaction mixture was warmed to 50 °C for 30 min. The mix was then cooled to 23 °C, and 3N NaOH (320 mL) was added to neutralize followed by 50% saturated NaHCO_3 (320 mL). The slurry was then filtered through a Buchner funnel to give a dark reddish-brown solid. The solid was taken up in warm THF (800 mL) and silica (600 mL dry) was added with stirring. To this slurry was added hexane (1.2 L) and the mix was vacuum filtered through a pad of silica (300 mL) in a large fritted filter. The silica was further washed with 2 L of 40% THF in hexane. The filtrates were combined and concentrated under reduced pressure to give a solid. The solid was further triturated with ethyl acetate (~100 mL), filtered and dried under reduced pressure to give 6-iodo-1H-indazole as a light brown solid (36.1 g, 48% yield): R_f sm 0.12, p 0.48 (Hex-EtOAc 1:1); ^1H NMR (300 MHz, CDCl_3) 7.9 (s, 1H), 7.8 (s, 1H), 7.42 (d, 1H), 7.33 (d, 1H); MS (ES) $[m+H]^+/z$ Calc'd 245, Found 245, $[m-H]^+/z$ Calc'd 243, Found 243.

(ii)



To a solution of 6-iodo-1H-indazole (7.35 g, 30.1 mmol, 1 equiv) in THF (100 mL) cooled to 0 °C under argon, was added sodium *t*-butoxide (2.89 g, 30.1 mmol, 1 equiv). A color change from orange to red was observed. Mesitylenesulfonyl chloride (6.60 g, 30.1 mmol, 1 equiv) was added in one portion and the ice bath was removed allowing the reaction mixture to warm to 23 °C. After 40 min the mixture was quenched with saturated ammonium chloride and partitioned between water and ethyl acetate. The aqueous was extracted a total of 3 times with ethyl acetate. The combined organic material was washed with brine, dried over sodium sulfate and concentrated under reduced pressure to give 6-iodo-1-(2,4,6-trimethyl-benzenesulfonyl)-1H-indazole as an orange solid (12.8 g, 100% yield, 2:1 mixture): ¹H NMR (CDCl₃) 8.51 (s, 1H), 7.95 (s, 0.66H, major isomer), 7.91 (s, 0.33H, minor isomer), 7.47 (d, 0.33H, J = 8.4 Hz), 7.29 (d, 0.33H, J = 8.4 Hz), 7.26 (d, 0.66H, J = 8.9 Hz), 7.18 (d, 0.66H, 8.9 Hz), 6.84 (s, 2H), 2.51 (s, 6H), 2.15 (s, 3H).

(iii)



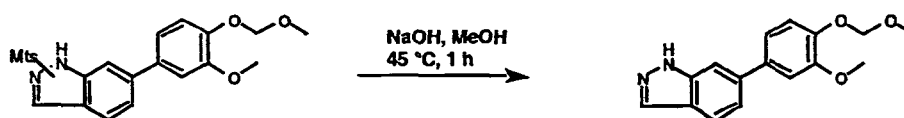
A mixture of 6-iodo-1-(2,4,6-trimethyl-benzenesulfonyl)-1H-indazole (5.78 g, 13.56 mmol, 1.00 equiv) and 3-methoxy-4-(methoxymethoxy)benzeneboronic acid (3.45 g, 16.27 mmol, 1.20 equiv) under argon was dissolved in dioxane (15 mL) and water (2.0 mL). To this solution was added triethylamine (2.83 mL, 20.3 mmol, 1.5 equiv), potassium carbonate (2.8 g, 20.3 mmol, 1.5 equiv) and dichlorobis(triphenylphosphine)palladium (476 mg, 0.678 mmol, 0.05 equiv). The reaction mixture was heated to 90 °C for 2 h and then was cooled to 23 °C. The mixture was separated between ethyl acetate (250 mL) and saturated sodium bicarbonate (150 mL). The organic material was dried over sodium sulfate, decanted and concentrated under reduced pressure to give crude 6-(3-methoxy-4-methoxymethoxy-phenyl)-1-(2,4,6-trimethyl-benzenesulfonyl)-1H-indazole that was dried under high vacuum for 15 h and was used without further purification.

3-Methoxy-4-(methoxymethoxy)benzeneboronic acid was prepared as follows: In a 100 mL flask a mixture of 50% KOH in water (20 g KOH, 7 equiv, 20 g ice) was prepared under argon. To this rapidly stirring mixture at 0 °C (maintained with an ice bath) was added

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dichloromethane (50 mL) followed by 4-bromo-2-methoxyphenol (10.1g, 50 mmol, 1.00 equiv), methoxymethylchloride (MOMCl) (4.00 mL, 42.5 mmol, 1.05 equiv) and tetrabutylammonium bromide (322 mg, 1 mmol, 0.02 equiv). The bath was removed and the mixture was slowly allowed to warm to 23 °C with rapid stirring for 2 h. The mixture is transferred to a separatory funnel and diluted with dichloromethane (350 mL) and water (300 mL) which are used to aid the transfer. The organic material (now the bottom layer) are separated, dried over sodium sulfate, decanted and concentrated under reduced pressure to give 4-bromo-2-methoxy-1-(methoxymethoxy)benzene as a yellow liquid which is pure by ¹H NMR (11.9 g, 97%): ¹H NMR (CDCl₃) δ 7.0 (s, 3H), 5.13 (s, 2H), 3.84 (s, 3H), 3.47 (s, 3H); MS (EI) [m+H]⁺/z Calc'd 235, Found 235. In a 50 mL round-bottom flask, 4-bromo-2-methoxy-1-(methoxymethoxy)benzene (4.80 g, 19.4 mmol, 1.00 equiv) was taken up in THF (35 mL) and was cooled to -78 °C (20 min for this volume). To this was added *n*-BuLi (12.75 mL, 1.6 M in hexane, 20.4 mmol, 1.05 equiv) and the mixture was allowed to stir at -78 °C for 40 min. This was then added via cannula to a second flask containing B(OMe)₃ (22 mL, 194 mmol, 10 equiv) in THF (50 mL) at -78 °C. After 20 min, the cold bath was removed. After 15 min of warming (~0 °C, ice on the side of the flask begins to melt) water (50 mL) was added to the reaction mixture which was stirred for 45 min. The mixture was concentrated under reduced pressure to remove most THF and was then partitioned between ethyl acetate (300 mL) and water (150 mL) which was made acidic by addition of a small amount of 20% citric acid (~10 mL). The organic material was dried over sodium sulfate and concentrated under reduced pressure to give a solid. Trituration with ethyl acetate (10 mL) and hexane (5 mL) followed by filtering gave 3-methoxy-4-(methoxymethoxy)benzene-boronic acid as a white solid (3.15 g, 77%): R_f sm 0.59, p 0.18 (ethyl acetate-hexane 1:1); ¹H NMR (CDCl₃) δ 7.85 (d, 1H, J = 8 Hz), 7.72 (s, 1H), 7.22 (d, 1H, J = 8 Hz), 5.30 (s, 2H), 4.00 (s, 3H), 3.55 (s, 3H).

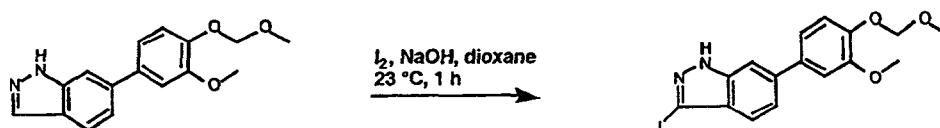
(iv)



Unpurified 6-(3-methoxy-4-methoxymethoxy-phenyl)-1-(2,4,6-trimethyl-benzenesulfonyl)-1H-indazole (under argon) was dissolved in THF (20 mL) and was treated with 1N NaOH in MeOH (70 mL degassed by bubbling through argon for 3 to 5 min). The mixture was heated to 45 °C for 1 h and allowed to cool. The mixture was neutralized by

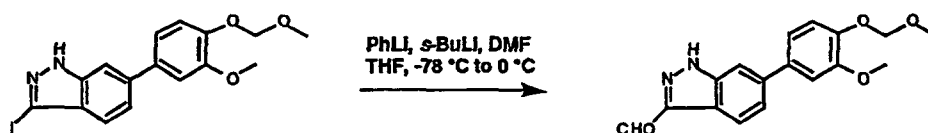
addition of 1N HCl (50 mL) followed by saturated sodium bicarbonate (200 mL). The product was extracted into ethyl acetate (350 mL), dried over sodium sulfate and concentrated under reduced pressure to give crude 6-(3-methoxy-4-methoxymethoxy-phenyl)-1*H*-indazole. Purification by silica gel chromatography (500 mL silica, 20% ethyl acetate in benzene (1.8 L), 30% ethyl acetate in benzene (1.8 L)) gave 6-(3-methoxy-4-methoxymethoxy-phenyl)-1*H*-indazole (1.19 g, 31%): ¹H NMR (CDCl₃) δ 7.80 (s, 1H), 7.69 (d, 1H, *J* = 8.5 Hz), 7.52 (s, 1H), 7.29 (d, 1H, *J* = 8.5 Hz), 7.16 (s, 1H), 7.13 (s, 1H), 7.08 (s, 1H). MS (ES) [*m*+Na]/*z* Calc'd 337, Found 337; [*m*+Cl]/*z* Calc'd 349, Found 349.

(v)



In a 100-mL round-bottom flask under argon, 6-(3-methoxy-4-methoxymethoxy-phenyl)-1*H*-indazole (1.19 g, 4.18 mmol, 1 equiv) was dissolved in dioxane (25 mL) and 3N NaOH (14 mL). This mixture was treated with iodine (1.17 g, 14.60 mmol, 1.10 equiv) added in ~5 portions (~10 min). Several (~4) additional portions of iodine (50 mg each) were added until the reaction was complete as visualized by TLC (3:7 ethyl acetate/hexane). The mixture was acidified with 20% citric acid (25 mL) and 5% NaHSO₃ (20 mL) was added. The mixture was partitioned between ethyl acetate (150 mL) and water (100 mL). The organic material was washed with saturated sodium bicarbonate (80 mL) and brine (50 mL) and were dried over sodium sulfate and concentrated under reduced pressure. Purification by crystallization from ethyl acetate (3 mL) then hexane (7 mL) gave pure 3-iodo-6-(3-methoxy-4-methoxymethoxy-phenyl)-1*H*-indazole as a solid (1.33 g, 78 %): ¹H NMR (CDCl₃) δ 10.48 (bs, 1H), 7.62 (s, 1H), 7.57 (d, 1H, *J* = 8.5 Hz), 7.47 (dd, 1H, *J* = 1.3, 8.5 Hz), 7.18 (m, 3H), 5.29 (s, 2H), 3.99 (s, 3H), 3.55 (s, 3H).

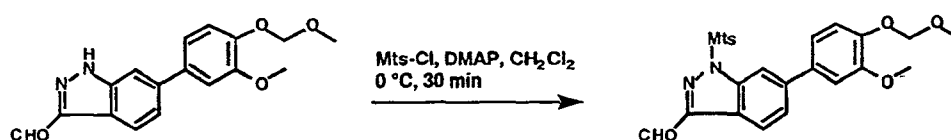
(vi)



In a 100-mL round-bottom flask, 3-iodo-6-(3-methoxy-4-methoxymethoxy-phenyl)-1*H*-indazole (921 mg, 2.245 mmol, 1.00 equiv) was dissolved in THF (36 mL) and cooled to -78 °C (allow 8 min at this scale). A solution of PhLi (2.5 mL, 1.8 M, 4.49 mmol, 2.00 equiv) was added and the mixture was allowed to stir for 30 min. A solution of *s*-BuLi (3.63

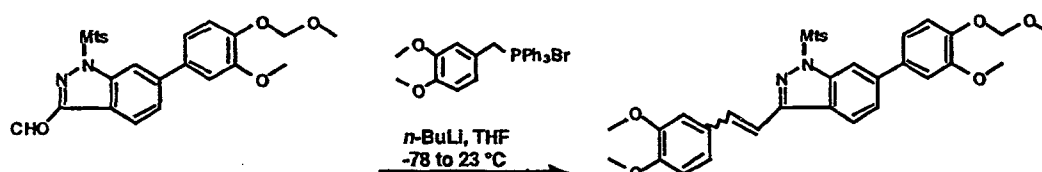
mL, 4.71 mmol, 2.1 equiv) was added and the reaction mixture was allowed to stir for 1 h at -78 °C. Neat DMF (1.4 mL, 18 mmol, 8.0 equiv) was added. The cold bath was removed and the reaction was allowed to slowly warm to 0 °C in the air. As the ice melted saturated sodium bicarbonate (20 mL) was added. The product was extracted into ethyl acetate (200 mL) from saturated sodium bicarbonate (75 mL more), dried over sodium sulfate, decanted and concentrated under reduced pressure. Purification by silica gel chromatography (450 mL silica, 4:6 ethyl acetate/hexane) gave 6-(3-methoxy-4-methoxymethoxy-phenyl)-1*H*-indazole-3-carbaldehyde (498 mg, 71%): *R*_f sm 0.30, p 0.14 (ethyl acetate-hexane 4:6); ¹H NMR (CDCl₃) δ 10.85 (bs, 1H), 10.25 (s, 1H), 8.37 (d, 1H, *J* = 8.4 Hz), 7.67 (s, 1H), 7.60 (d, 1H, *J* = 8.4 Hz), 6.26 (d, 1H, *J* = 8.7 Hz), 7.19 (m, 2H), 5.30 (s, 2H), 3.99 (s, 3H), 3.55 (s, 3H).

(vii)



6-(3-methoxy-4-methoxymethoxy-phenyl)-1*H*-indazole-3-carbaldehyde (441 mg, 1.41 mmol, 1.0 equiv) was taken up as a suspension in dichloromethane (15 mL) and was cooled to 0 °C. This mixture was treated with mesitylene sulfonyl chloride (324 mg, 1.48 mmol, 1.05 equiv) and dimethylamino pyridine (DMAP) (181 mg, 1.48 mmol, 1.05 equiv). The mixture was allowed to stir for 1 h at 0 °C and was quenched with the addition of water. The mixture was partitioned between water and a 1:1 ethyl acetate/hexane organic layer. The organic material was dried over sodium sulfate, decanted and concentrated under reduced pressure to give crude material which was purified by silica gel chromatography (50 mL silica, 3:7 ethyl acetate/hexane) to give 6-(3-methoxy-4-methoxymethoxy-phenyl)-1-(2,4,6-trimethyl-benzenesulfonyl)-1*H*-indazole-3-carbaldehyde (374 mg, 54%): *R*_f sm 0.17, p 0.53 (ethyl acetate-hexane 4:6); ¹H NMR (CDCl₃) δ 10.20 (s, 1H), 8.41 (s, 1H), 8.37 (d, 1H, *J* = 8.5 Hz), 7.73 (dd, 1H, *J* = 1.4, 8.4 Hz), 7.3 (m, 3H), 7.08 (s, 2H), 5.36 (s, 2H), 4.08 (s, 3H), 3.71 (s, 3H), 2.74 (s, 6H), 2.40 (s, 3H).

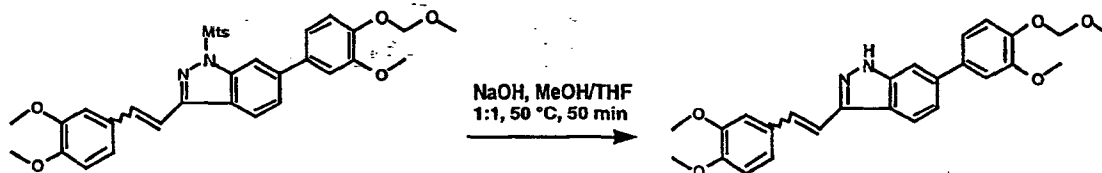
(viii)



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Finely ground triphenyl(3,4-dimethoxybenzyl)phosphonium bromide (1.09 g, 2.22 mmol, 4.0 equiv) was taken up as a slurry in THF (15 mL) and was cooled to -78 °C. To this mixture was added *n*-BuLi (1.04 mL, 1.6 M, 1.66 mmol, 3.0 equiv) which gave a red/orange solution. The mixture was allowed to warm to 23 °C for 1 h. This mixture was then added to a 0 °C solution of 6-(3-methoxy-4-methoxymethoxy-phenyl)-1-(2,4,6-trimethyl-benzenesulfonyl)-1*H*-indazole-3-carbaldehyde (274 mg, 0.554 mmol, 1.0 equiv) in THF (5 mL) via cannula. The resulting mixture was allowed to stir at 0 °C for 10 min and was quenched with saturated sodium bicarbonate. The resulting mixture was partitioned between saturated sodium bicarbonate and ethyl acetate. The organic material was concentrated under reduced pressure and the residue was purified by silica gel chromatography (50 mL silica, 3:7 -> 4:6 ethyl acetate/hexane) to give a 2.5:1 mixture of *cis/trans* 3-[2-(3,4-dimethoxy-phenyl)-vinyl]-6-(3-methoxy-4-methoxymethoxy-phenyl)-1-(2,4,6-trimethyl-benzenesulfonyl)-1*H*-indazole (289 mg, 83%); *R_f* sm 0.53, p 0.32 (ethyl acetate-hexane 4:6); ¹H NMR (CDCl₃) δ 8.35 (s, 0.3H), 8.32 (s, 0.7H), 8.03 (d, 0.3H, *J* = 8.4 Hz), 7.60-6.85 (m, H), 6.65 (d, 0.7H, *J* = 8.4 Hz), 6.60 (d, 0.7H, *J* = 12.5 Hz), 5.30 (s, 0.6H), 5.29 (s, 1.4H), 4.00-3.50 (8 singlets, 12H), 2.72 (s, 1.8H), 2.67 (s, 4.2H), 2.34 (s, 3H); MS (ES) [*m*+*H*]/*z* Calc'd 629, Found 629, [*m*-*H*]/*z* Calc'd 627, Found 627.

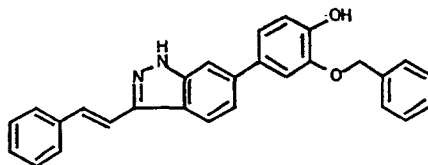
(ix)



20 A 1M solution of KOH (1.0 g, 17.8 mmol) in 1:1 water/MeOH (18 mL total) was prepared under argon and was degassed by vacuum/purge cycles with argon (5 times). In a separate flask, 3-[2-(3,4-dimethoxy-phenyl)-vinyl]-6-(3-methoxy-4-methoxymethoxy-phenyl)-1-(2,4,6-trimethyl-benzenesulfonyl)-1*H*-indazole (289 mg, 0.461 mmol, 1.0 equiv) was dissolved in THF (8 mL) under argon. To this solution was added the above 1M KOH solution (10 mL, 1:1 water/MeOH). The reaction was warmed to 30 °C and was allowed to stir for 7 h. The reaction mix was neutralized by the addition of 20% citric acid (7 mL). The resulting mix was partitioned between ethyl acetate (150 mL) and water (100 mL). The organic material was separated, dried over sodium sulfate, decanted, and concentrated under reduced pressure to give *cis* and *trans* 3-[2-(3,4-dimethoxy-phenyl)-vinyl]-6-(3-methoxy-4-methoxymethoxy-phenyl)-1*H*-indazole (used crude): *R_f* sm 0.46, p1 0.17, p2 0.23 (ethyl

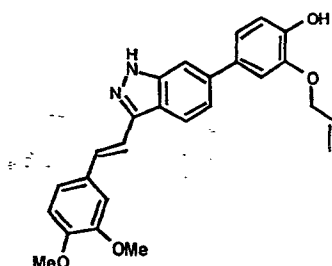
acetate-hexane 1:1); ^1H NMR *cis* isomer (CDCl_3) δ 7.55 (s, 1H), 7.3-7.1 (m, 6H), 7.02 (dd, 1H, $J = 1.9, 8.3$ Hz), 6.85 (d, 1H, $J = 12.5$ Hz), 6.78 (d, 1H, $J = 12.5$ Hz), 6.74 (d, 1H, $J = 8.3$ Hz), 5.21 (s, 2H), 3.88 (s, 3H), 3.70 (s, 3H), 3.43 (s, 3H), 3.42 (s, 3H); MS (ES) $[\text{m}+\text{H}]/z$ Calc'd 447, Found 447, $[\text{m}-\text{H}]/z$ Calc'd 445, Found 445.

5 **Example 1(b)_(LE2): 3-(E-styryl)-6-(3-benzyloxy-4-hydroxy-phenyl)-1H-indazole**



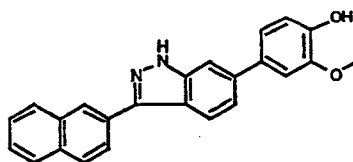
Example 1(b) was prepared in a similar manner to that described for Example 1(a), except that 4-bromo-2-benzyloxy-phenol was used in step(iii) in place of 4-bromo-2-methoxy-phenol. R_f sm 0.35, p 0.30 (ethyl acetate-hexane 4:6); ^1H NMR (CDCl_3) δ 8.06 (d, 1H, $J = 8.6$ Hz), 7.63- 7.18 (m, 17H), 7.05 (d, 1H, $J = 8.2$ Hz), 5.19 (s, 2H); MS (CI) $[\text{m}+\text{H}]/z$ Calc'd 419, Found 419, $[\text{m}-\text{H}]/z$ Calc'd 417, Found 417.

10 **Example 1(c)_(LE3): 3-[E-2-(3,4-Dimethoxy-phenyl)vinyl]-6-(3-allyloxy-4-hydroxy-phenyl)-1H-indazole**



15 Example 1(c) was prepared in a similar manner to that described for Example 1(a), except that 3-allyloxy-4-(methoxymethoxy)benzene-boronic acid was used instead of 3-methoxy-4-(methoxymethoxy)benzene-boronic acid in step (iii). MS (ESI) $[\text{M}+\text{H}]/z$ Calc'd 429, Found 429; MS (ESI) $[\text{M}-\text{H}]/z$ Calc'd 427, Found 427.

Example 2(a)_(LE4): 3-(Naphthalen-2-yl)-6-(3-methoxy-4-hydroxy-phenyl)-1H-indazole



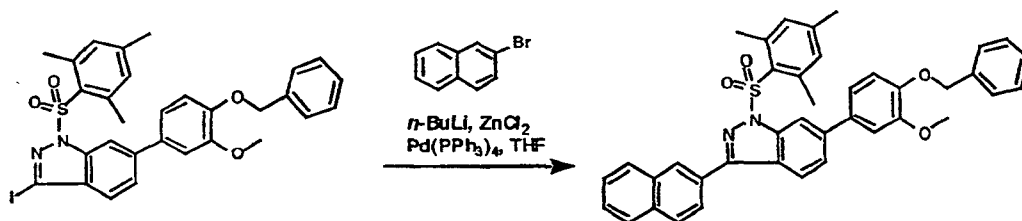
20 6-(4-Benzyloxy-3-methoxy-phenyl)-3-naphthalen-2-yl-1H-indazole (25 mg, 0.055 mmol) was dissolved in a mixture of ethyl acetate (2 mL), benzene (2 mL) and methanol (2 mL). To this solution was added palladium on carbon (25 mg, 10% wt) and the reaction

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1/9
vessel was vacuum/purged with hydrogen gas for five cycles. The reaction mixture was allowed to stir for 3 days (d) at 23 °C and was filtered through a plug of Celite.

Concentration and purification by silica gel chromatography afforded 3-(Naphthalen-2-yl)-6-(3-methoxy-4-hydroxy-phenyl)-1H-indazole (8 mg, 40%): ¹H NMR (CDCl₃) δ 10.3 (bs, 1H), 8.50 (s, 1H), 8.20 (d, 1H, J = 8 Hz), 7.98 (d, 1H, J = 8 Hz), 7.90 (m, 1H), 7.7-6.8 (m, 9H), 3.98 (s, 3H); MS (ES) [m+H]⁺/z Calc'd 367, Found 367, [m-H]⁻/z Calc'd 365, Found 365.

The starting material was prepared as follows:

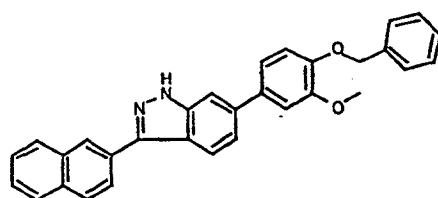
(i)



2-Bromonaphthalene (117 mg, 0.564 mmol, 6.0 equiv) was dissolved in THF (0.75 mL) and cooled to -78 °C. The mixture was treated with *n*-BuLi (226 μL, 2.5 M, 6.0 equiv) and was allowed to stir at -78 °C for 30 min. The mixture was then added to freshly dried ZnCl₂ solid (139 mg, 0.80 mmol, 8.5 equiv) via cannula and the resulting mix was allowed to warm to 23 °C (during the addition the yellow color disappears). After 30 min at 23 °C the mixture is added to a mixture of 6-(4-benzyloxy-3-methoxy-phenyl)-3-iodo-1-(2,4,6-trimethyl-benzenesulfonyl)-1H-indazole (60 mg, 0.094 mmol, 1 equiv) and Pd(PPh₃)₄ (6 mg, 0.005 mmol, 0.05 equiv) via cannula. The resulting solution was allowed to stir for 16 h. Saturated sodium bicarbonate was added and the mixture was partitioned between saturated sodium bicarbonate (15 mL) and ethyl acetate (15 mL). The organic material was dried over sodium sulfate, decanted and concentrated. Purification by silica gel chromatography (1:9 - 2:8 ethyl acetate-hexane) gave 6-(4-benzyloxy-3-methoxy-phenyl)-3-naphthalen-2-yl-1-(2,4,6-trimethyl-benzenesulfonyl)-1H-indazole as a solid (42 mg, 70%): R_f sm 0.4, p 0.4 (ethyl acetate-hexane 3:7); ¹H NMR (CDCl₃) δ 8.44 (s, 1H), 8.41 (s, 1H), 8.12 (d, 1H, J = 8 Hz), 8.05-7.00 (m, 17H), 5.30 (s, 2H), 4.02 (s, 3H), 2.80 (s, 3H), 2.34 (s, 3H).

6-(4-benzyloxy-3-methoxy-phenyl)-3-iodo-1-(2,4,6-trimethyl-benzenesulfonyl)-1H-indazole was prepared in a similar manner as described in Example 1(a), steps (i) to (v).

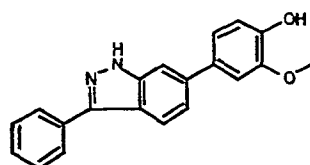
(ii)



6-(4-Benzyloxy-3-methoxy-phenyl)-3-naphthalen-2-yl-1-(2,4,6-trimethyl-benzenesulfonyl)-1*H*-indazole was converted to 6-(4-benzyloxy-3-methoxy-phenyl)-3-naphthalen-2-yl-1*H*-indazole as described in Example 1(a), step (ix). R_f sm 0.40, p 0.17

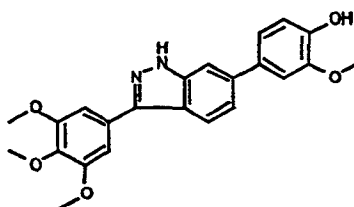
5 (ethyl acetate-hexane 3:7); ^1H NMR (CDCl_3) δ 8.40 (s, 1H), 8.12 (d, 1H, $J = 8.5$ Hz), 8.10 (dd, 1H, $J = 1.6, 8.4$ Hz), 7.93 (d, 1H, $J = 8.3$ Hz), 7.88 (m, 2H), 7.61 (m, 1H) 7.56 (s, 1H), 7.43 (m, 5H), 7.30 (m 3H), 7.15 (d, 1H, $J = 2.0$ Hz), 7.08 (dd, 1H, $J = 2.1, 8.3$ Hz), 6.91 (d, 1H, $J = 8.3$ Hz), 5.16 (s, 2H), 3.91 (s, 3H).

Example 2(b_[LES]): 3-phenyl-6-(3-methoxy-4-hydroxy-phenyl)-1*H*-indazole



Example 2(b) was prepared in a similar manner to that described for Example 2(a), except that phenyllithium was used in place of 2-naphthyllithium generated from 2-bromonaphthylene in step (i). ¹H NMR (300 MHz, CDCl₃) δ 7.87 (d, 1H), 7.83 (d, 2H), 7.55-7.27 (m, 5H), 7.01 (m, 2H), 6.80 (d, 1H), 3.83 (s, 3H). MS (ES) [m+H]⁺/z Calc'd 317, Found 317, [m-H]⁻/z Calc'd 315, Found 315.

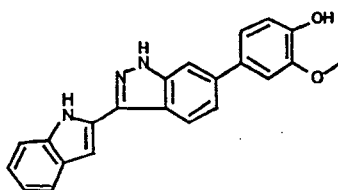
Example 2(C₁LE6): 3-(3,4,5-trimethoxyphenyl)-6-(3-methoxy-4-hydroxy-phenyl)-1*H*-indazole



20 Example 2(c) was prepared in a similar manner to that described for Example 2(a), except that 3,4,5-trimethoxyphenyl bromide was used in step (i) in place of 2-bromonaphthylene. R_f sm 0.67, p 0.38 (ethyl acetate-hexane 8:2); ^1H NMR (CDCl_3) δ 7.93 (d, 1H, $J = 8$ Hz), 7.58 (s, 1H), 7.39 (d, 1H, $J = 8$ Hz), 7.10 (m, 4H), 6.92 (d, 1H, $J = 8$ Hz),

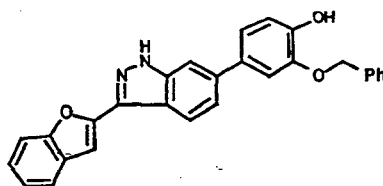
3.90 (s, 9H), 3.85 (s, 3H); MS (ES) [m+H]/z Calc'd 407, Found 407, [m-H]/z Calc'd 405, Found 405.

Example 2(d_[LE7]): 3-(1*H*-Indol-2-yl)-6-(3-methoxy-4-hydroxy-phenyl)-1*H*-indazole



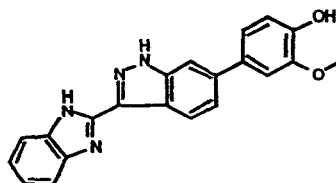
- 5 Example 2(d) was prepared in a similar manner to that described for Example 2(a) above, except that 1-phenylsulfonyl-indazole was used in place of 2-bromonaphthylene in step (i). *R_f* sm 0.20, p 0.15 (ethyl acetate-hexane 4:6); ¹H NMR (CDCl₃) δ 10.0 (bs, 1H), 9.05 (bs, 1H), 8.01 (d, 1H, *J* = 8.0 Hz), 7.55 (d, 1H, *J* = 8.0 Hz), 7.49 (s, 1H), 7.37 (d, 1H, *J* = 8 Hz), 7.29 (d, 1H, *J* = 8 Hz), 7.2-7.1 (m, 5H), 6.92 (d, 1H, *J* = 8 Hz), 5.63 (bs, 1H); MS (ES) [m+H]/z Calc'd 356, Found 356; [m-H]/z Calc'd 354, Found 354.

Example 2(e_[LE8]): 3-(Benzofuran-2-yl)-6-(3-benzyloxy-4-hydroxy-phenyl)-1*H*-indazole



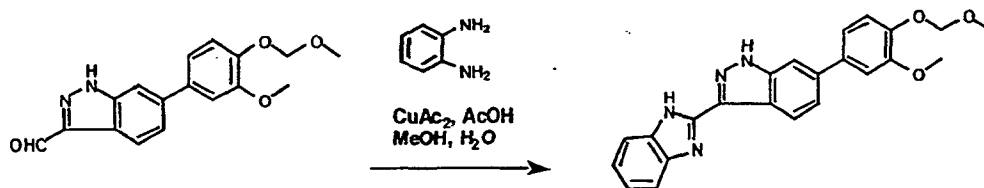
- 15 Example 2(e) was prepared in a similar manner to that described for Example 2(a) above, except that benzofuran was used in place of 2-bromonaphthylene in step (i). ¹H NMR (CDCl₃) δ 8.21 (d, 1H, *J* = 8.0 Hz), 7.60 (m, 3H), 7.30-7.10 (m, 12H), 7.01 (d, 1H, *J* = 8 Hz), 5.82 (bs, 1H), 5.15 (s, 3H).

Example 3_[LE9]: 3-(1*H*-Indol-2-yl)-6-(3-methoxy-4-methoxymethoxy-phenyl)-1*H*-indazole



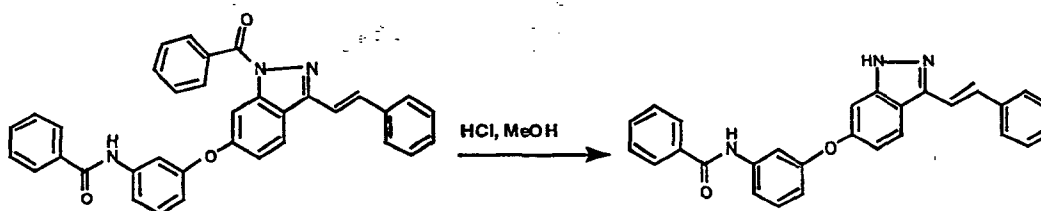
- 20 3-(1*H*-Benzoimidazol-2-yl)-6-(3-methoxy-4-methoxymethoxy-phenyl)-1*H*-indazole was converted to 4-[3-(1*H*-benzoimidazol-2-yl)-1*H*-indazol-6-yl]-2-methoxy-phenol according to the procedure described in Example 1(a) (3.5 mg, 28%). HRMS (FAB) [m+H]/z Calc'd 357.1351, Found 357.1349.

The starting material was prepared as follows:



6-(3-Methoxy-4-methoxymethoxy-phenyl)-1H-indazole-3-carbaldehyde (from Example 1(a), step (vi)) (20 mg, 0.064 mmol, 1 equiv) was dissolved in degassed 1:1 MeOH-water (0.7 mL) and was treated with acetic acid (19 μ L, 5 equiv), 1,2-diaminobenzene (8.3 mg, 1.2 equiv) and copper(II) acetate (18 mg, 1.4 equiv) at 23 $^{\circ}$ C. The mixture stirred for 30 min, was diluted with ethanol (3 mL) and water (2 mL) and was treated with a bubbling stream of SH_2 for 3 min which gave a black precipitate. The mixture was allowed to stir for 12 h. The mixture was filtered and concentrated. Purification by silica gel chromatography (6:4 ethyl acetate-hexane) gave 3-(1H-benzimidazol-2-yl)-6-(3-methoxy-4-methoxymethoxy-phenyl)-1H-indazole as a solid (14 mg, 54%); R_f sm 0.39, p 0.24 (ethyl acetate-hexane 6:4); ^1H NMR (CDCl_3) δ 8.69 (d, 1H, $J = 8\text{ Hz}$), 7.70 (bs, 2H), 7.58 (s, 1H), 7.53 (d, 1H, $J = 8\text{ Hz}$), 7.30-7.15 (m, 7H), 5.30 (s, 2H), 3.97 (s, 3H), 3.58 (s, 3H); MS (ES) $[m+H]^+/z$ Calc'd 401, Found 401, $[m-H]^+/z$ Calc'd 399, Found 399.

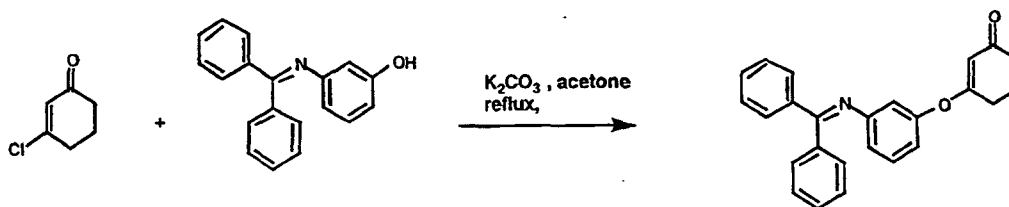
Example 4(a_{LE10}): N-[3-(3-Styryl-1H-indazol-6-yloxy)-phenyl]-benzamide



A solution of N-[3-(2-benzoyl-3-styryl-1H-indazol-6-yloxy)-phenyl]-benzamide (0.09 g, 0.17 mmol) in 2 mL of 6N HCl (aqueous) and 3 mL of MeOH was heated at 65 $^{\circ}$ C for about 4 h. The cooled solution was poured cautiously into saturated sodium bicarbonate solution. The precipitate was filtered, collected and chromatographed on silica gel eluting hexanes/EtOAc (1:1). N-[3-(3-Styryl-1H-indazol-6-yloxy)-phenyl]-benzamide was obtained as a beige solid (32 mg, 50%); ^1H NMR ($\text{DMSO}-d_6$) δ 13.50 (s, 1H), 10.32 (s, 1H), 8.23 (d, 1H, $J = 8.7\text{ Hz}$), 7.92 (d, 2H, $J = 6.8\text{ Hz}$), 7.72 (d, 2H, $J = 7.3\text{ Hz}$), 7.71-7.51 (m, 7H), 7.51 - 7.47 (m, 3H), 7.30 (t, 1H, $J = 7.2\text{ Hz}$), 7.05 (s, 1H), 7.01 (d, 1H, $J = 8.7\text{ Hz}$), 6.86 (dd, 1H, $J = 8.2, 2.3\text{ Hz}$). Anal. Calc. for $\text{C}_{24}\text{H}_{21}\text{N}_3\text{O}_2 \cdot 0.3\text{H}_2\text{O}$: C, 76.97; H, 4.98; N, 9.62. Found: C, 76.94; H, 5.13; N, 9.40.

The starting material was prepared as follows:

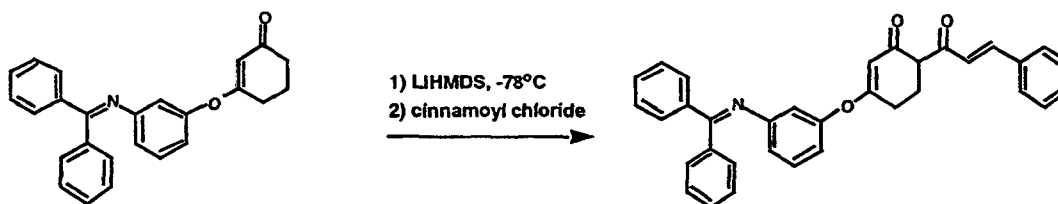
(i)



A suspension of the 3-(benzhydrylidene-amino)-phenol (10.47 g, 38.3 mmol), 3-chloro-cyclohex-2-enone (5.00 g, 38.3 mmol) and potassium carbonate (5.82, 42.1 mmol) in 150 mL of acetone was heated at reflux overnight. The cooled reaction mixture was filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel eluting hexanes/EtOAc (2:1). In this manner, 3-[3-(benzhydrylidene-amino)-phenoxy]-cyclohex-2-enone was obtained as a yellow solid, (8.82 g, 63%): ^1H NMR ($CDCl_3$) δ 7.78 (d, 2H, $J = 7.0$ Hz), 7.50 (d, 1H, $J = 7.1$ Hz), 7.45 (d, 2H, $J = 7.7$ Hz), 7.34-7.10 (m, 6H), 6.69 (d, 1H, $J = 8.0$ Hz), 6.61 (d, 1H, $J = 8.0$ Hz), 6.38 (s, 1H), 4.89 (s, 1H), 2.55 (t, 2H, $J = 6.2$ Hz), 2.34 (t, 2H, $J = 6.2$ Hz), 2.06 (m, 2H). Anal. Calc. for $C_{25}H_{21}NO_2 \cdot 0.2H_2O$: C, 80.92; H, 5.81; N, 3.78. Found: C, 81.12; H, 5.81; N, 3.72.

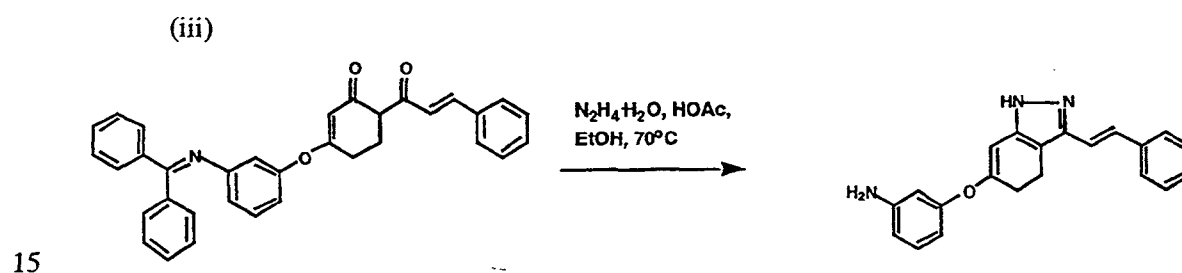
3-(Benzhydrylidene-amino)-phenol was prepared as follows: A stirred solution of benzophenone imine (15.0 g, 82.8 mmol) and 3-aminophenol (9.03 g, 82.8 mmol) in 25 mL toluene was heated at reflux with removal of H_2O with a Dean-Stark trap for 3.5 h. The crystals that formed from the cooled reaction mixture were collected by vacuum filtration, washed with hexanes and air dried. In this manner, 3-(benzhydrylidene-amino)-phenol was obtained as a light yellow solid (17.3 g, 76%): ^1H NMR ($CDCl_3$) δ 7.64 (d, 2H, $J = 7.1$ Hz), 7.38 (d, 1H, $J = 7.1$ Hz), 7.34 - 7.15 (m, 7H), 7.04 (d, 2H, $J = 7.2$ Hz), 6.88 (t, 1H, $J = 8.1$ Hz), 6.82 (d, 1H, $J = 8.2$ Hz), 6.23 (s, 1H), 6.21 (d, 1H, $J = 7.8$ Hz). Anal. Calc. for $C_{19}H_{15}NO$: C, 83.49; H, 5.53; N, 5.12. Found: C, 83.51; H, 5.65; N, 5.03.

(ii)



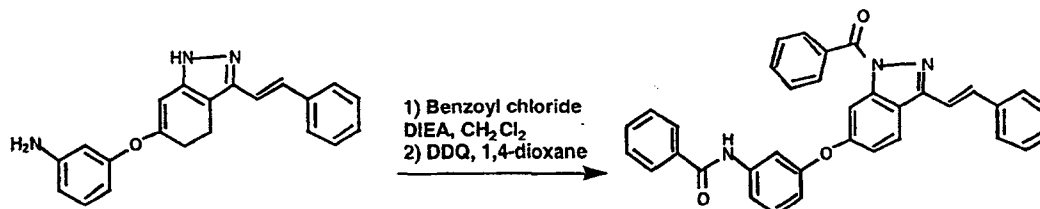
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A solution of 3-[3-(benzhydrylidene-amino)-phenoxy]-cyclohex-2-enone (4.37g, 11.89 mmol) in 20 mL of THF was added slowly to a solution of LiHMDS (25.0 mL of 1.0 M solution in THF) in 10 mL of THF at -78°C . Five minutes after the addition was complete trans-cinnamoyl chloride (1.98 g, 11.89 mmol) was added all at once, and stirring was continued at -78°C for 30 min. The reaction was quenched with saturated NH_4Cl solution. And extracted with EtOAc (2x). The combined organic layers were washed with saturated NaCl solution, dried (MgSO_4) and concentrated under reduced pressure. The residue was chromatographed on silica gel eluting hexanes/EtOAc (5:1). In this manner, 3-[3-(benzhydrylidene-amino)-phenol]-6-(3-phenyl-acryloyl)-cyclohex-2-enone was obtained as a yellow-orange solid (3.34 g, 56%). ^1H NMR(CDCl_3) δ : 15.69 (s, 1H), 7.80 (d, 2H, $J = 7.1$ Hz), 7.63-7.01 (m, 15H), 6.93 (d, 1H, $J = 15.6$ Hz), 6.75 (d, 1H, $J = 7.6$ Hz), 6.66 (d, 1H, $J = 8.0$ Hz), 6.46 (s, 1H), 4.92 (s, 1H), 2.85 (t, 2H, $J = 7.2$ Hz), 2.62 (t, 2H, $J = 7.2$ Hz). Anal. Calc. for $\text{C}_{34}\text{H}_{27}\text{NO}_3$: C, 82.07; H, 5.47; N, 2.82. Found: C, 81.88; H, 5.53; N, 2.81.



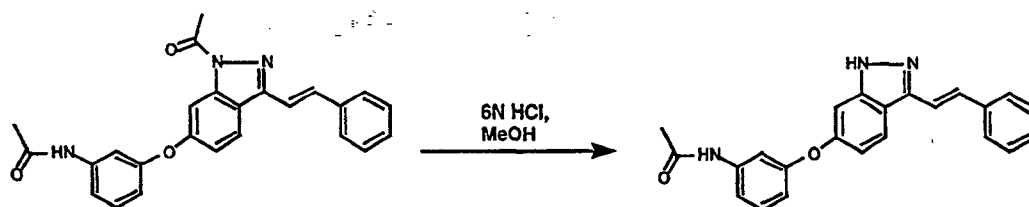
To a stirred solution of 3-[3-(benzhydrylidene-amino)-phenol]-6-(3-phenyl-acryloyl)-cyclohex-2-enone (1.81 g, 3.64 mmol) dissolved in 10 mL of HOAc/EtOH(1:1) was added hydrazine hydrate (2.0 mL, 41.23 mmol). The solution was heated at 75°C for 25 min. After cooling, the reaction mixture was cautiously poured into saturated sodium bicarbonate solution and extracted with EtOAc (2x). The combined organic layer was washed with saturated NaCl solution, dried (MgSO_4) and concentrated under reduced pressure. The residue was chromatographed on silica gel eluting hexanes/EtOAc (1:1). 3-(3-Styryl-4, 5-dihydro-1H-indazol-6-yloxy)-phenylamine was obtained as a yellow solid (539 mg, 45%). ^1H NMR ($\text{DMSO}-d_6$) δ : 7.55 (d, 2H, $J = 7.2\text{Hz}$), 7.38 (t, 2 H, $J = 7.2$ Hz), 7.27 (t, 1H, $J = 7.2$ Hz), 7.05 (m, 3H), 6.38 (d, 1H, $J = 8.0$ Hz), 6.31 (s, 1H), 6.23 (d, 1H, $J = 7.9$ Hz), 5.52 (s, 1H), 5.26 (s, 2H), 2.92 (t, 2H, $J = 8.0$ Hz), 2.58 (t, 2H, $J = 8.1$ Hz). Anal. Calc. for $\text{C}_{21}\text{H}_{19}\text{N}_3\text{O} \cdot 0.3\text{H}_2\text{O}$: C, 75.33; H, 5.90; N, 12.55. Found: C, 75.46; H, 5.96; N, 12.35.

(iv)



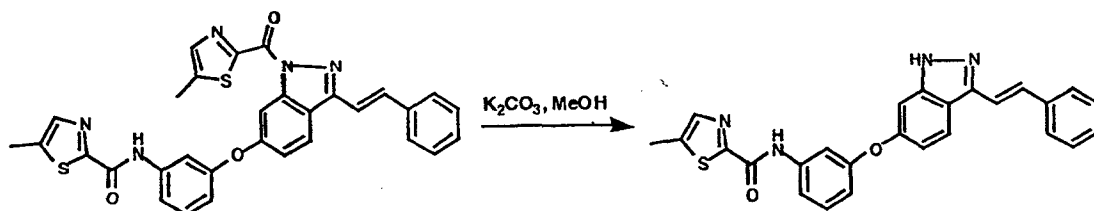
To a stirred solution of 3-(3-styryl-4,5-dihydro-1H-indazol-6-yloxy)-phenylamine (50 mg, 0.15 mmol) and *N,N*-diisopropylethylamine (54 μ l, 0.31 mmol) in 5 mL of CH₂Cl₂, was added benzoyl chloride (36 μ l, 0.31 mmol). After 15 min, the reaction mixture was diluted with CH₂Cl₂ and washed sequentially with 0.5N HCl, saturated sodium bicarbonate solution and brine, dried (MgSO₄) and concentrated under reduced pressure. To a stirred solution of the residue in 1,4-dioxane was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (35 mg, 0.15 mmol). After 1 h, the reaction mixture was concentrated under reduced pressure and the residue was chromatographed on silica gel eluting hexanes/EtOAc (2:1). In this manner, *N*-[3-(2-benzoyl-3-styryl-1H-indazol-6-yloxy)-phenyl]-benzamide was prepared as a rust colored solid (90 mg, ~quantitative): ¹H NMR (CDCl₃) δ 8.13 (s, 1H), 8.02 (d, 2H, *J* = 7.0 Hz), 7.94 (d, 1H, *J* = 8.7 Hz), 7.74 (d, 2H, *J* = 6.8 Hz), 7.57-7.19 (m, 17H), 6.84 (d, 1H, *J* = 8.3 Hz).

Example 4(b_(LE11)): *N*-[3-(3-Styryl-1H-indazol-6-yloxy)-phenyl]-acetamide



Example 4(b) was prepared in a similar manner to that described for Example 4(a) above, except that acetic anhydride was used instead of benzoyl chloride in step (iv). ¹H NMR(DMSO-*d*₆) δ 13.08 (bs, 1H), 10.03 (s, 1H), 8.22 (d, 1H, *J* = 8.7 Hz), 7.72(d, 2H, *J* = 7.3 Hz), 7.52 (s, 2H), 7.44-7.27 (m, 6H), 7.01 (s, 1H), 6.96 (dd, 1H, *J* = 8.7, 2.1 Hz), 6.78 (d, 1H, *J* = 6.9 Hz), 2.01 (s, 3H). Anal. Calc. for C₂₃H₁₇N₃O₂ · 0.25 H₂O: C, 73.88; H, 5.26; N, 11.24. Found: C, 74.20; H, 5.57; N, 10.82.

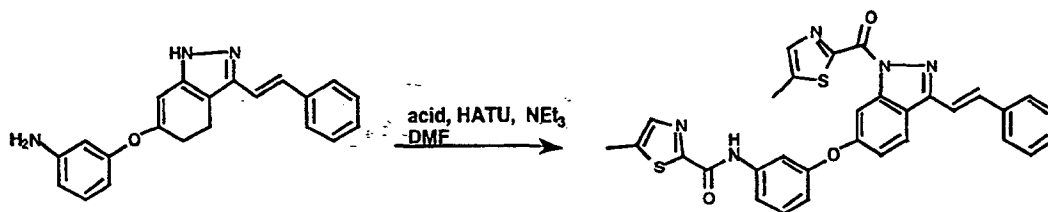
Example 5(a_(LE12)): 5-Methyl-thiazole-2-carboxylic acid {3-(3-styryl-1H-indazol-6-yloxy)-phenyl}-amide



A suspension of 5-methyl-thiazole-2-carboxylic acid {3-[1-(5-methyl-thiazole-2-carboxyl)-3-styryl-1H-indazol-6-yloxy]-phenyl} amide (57 mg, 0.10 mmol) and potassium carbonate (50 mg, 0.36 mmol) in MeOH was stirred at 23 °C for 20 min. The solution was filtered, diluted with EtOAc and washed with brine (2x). The organic layer was dried (MgSO₄) and concentrated under reduced pressure. In this manner, 5-methyl-thiazole-2-carboxylic acid {3-(3-styryl-1H-indazol-6-yloxy)-phenyl}-amide was prepared as a tan solid in 47% yield. ¹H NMR (DMSO-d₆) δ 13.00 (s, 1H), 10.80 (s, 1H), 8.23 (d, 1H, J = 8.8 Hz), 7.79 (s, 2H), 7.71 (t, 2H, J = 8.6 Hz), 7.53 (s, 2H), 7.41-7.27 (m, 5H), 7.04 (s, 1H), 7.00 (d, 1H, J = 8.7 Hz), 6.89 (d, 1H, J = 8.5 Hz), 2.54 (s, 3H); Anal. Calc. for C₂₆H₂₀N₄O₂S · 1.15H₂O: C, 65.98; H, 4.75; N, 11.84; S, 6.78; Found: C, 65.99; H, 4.71; N, 11.58; S, 6.76.

The starting material was prepared as follows:

(i)

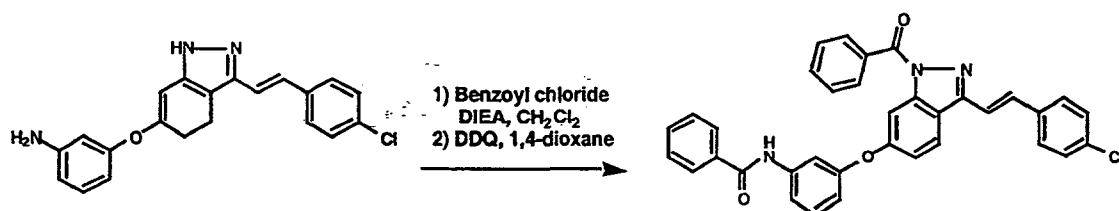


3-(3-Styryl-4,5-dihydro-1H-indazol-6-yloxy)-phenylamine was converted to 5-methyl-thiazole-2-carboxylic acid {3-[1-(5-methyl-thiazole-2-carboxyl)-3-styryl-1H-indazol-6-yloxy]-phenyl} amide by treatment with 5-methyl-thiazole-2-carboxylic acid and HATU (o-(2-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate) in DMF and analogous work-up, DDQ treatment and isolation to Example 4(a), step (iv) (50% yield): ¹H NMR(DMSO-d₆) δ 10.85 (s, 1H), 8.45 (d, 1H, J = 9.8 Hz), 8.24 (m, 3H), 7.99-7.62 (m, 6H), 7.54-7.34 (m, 5H), 6.96 (d, 1H, J = 8.5 Hz), 2.64 (s, 3H), 2.54 (s, 3H).

Starting with 3-[3-(benzhydrylidene-amino)-phenoxy]-cyclohex-2-enone and 3-(4-chloro-phenyl)-acryloyl chloride (prepared as described below), the general procedure for Example 4(a), step (ii) was employed. The product was used without purification in the hydrazine cyclization procedure, Example 4(a) step (iii), to give 3-{3-[2-(4-chloro-phenyl)-vinyl]-4,5-dihydro-1H-indazol-6-yloxy}-phenylamine as a yellow solid in 30% yield. ¹H NMR (DMSO-d₆) δ 12.45 (s, 1H), 7.58 (d, 2H, J = 8.5 Hz), 7.43 (d, 2H, J = 8.5 Hz), 5.52 (s, 1H), 5.26 (s, 2H), 2.92 (t, 2H, J = 8.0 Hz), 2.58 (t, 2H, J = 8.0 Hz). Anal. Calc. for C₂₁H₁₈ClN₃O · 0.75H₂O: C, 66.84; H, 5.21; N, 11.14. Found: C, 66.73; H, 4.89; N, 11.01.

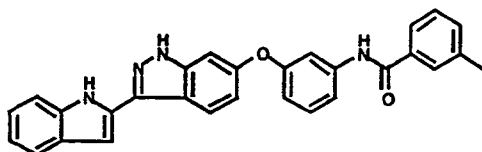
3-(4-chloro-phenyl)-acryloyl chloride was prepared as follows: To a stirred suspension of 4-chloro-trans-cinnamic acid (2.51 g, 13.77 mmol) in benzene was added thionyl chloride (1.1 mL, 15.14 mmol) and a catalytic amount of DMAP. The reaction mixture was heated at reflux for 1.5 h. The volatile materials were removed under reduced pressure. The white residue was dissolved in Et₂O and concentrated again under reduced pressure, to give 3-(4-chloro-phenyl)-acryloyl chloride (2.78 g, quantitative) as a white solid: ¹H NMR (CDCl₃) δ 7.81 (d, 1H, J = 15.6 Hz), 7.54 (d, 2H, J = 8.6 Hz), 7.44 (d, 2H, J = 8.6 Hz), 6.65 (d, 1H, J = 15.6 Hz).

(ii)



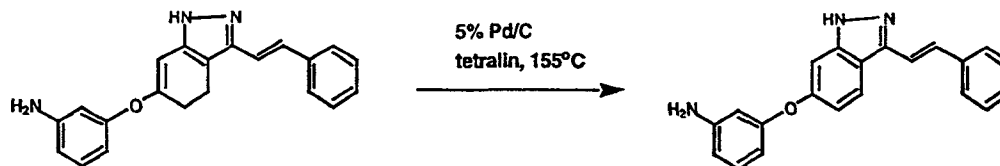
3-{3-[2-(4-Chloro-phenyl)-vinyl]-4,5-dihydro-1H-indazol-6-yloxy}-phenylamine was converted into N-(3-{1-benzoyl-3-[2-(4-chloro-phenyl)-vinyl]-1H-indazol-6-yloxy}-phenyl)-benzamide by the procedure described in Example 4(a), step (iv) (85% yield). ¹H NMR (DMSO-d₆) δ 10.37 (s, 1H), 8.43 (d, 1H, J = 8.8 Hz), 8.00-7.39 (m, 21H), 7.34 (d, 1H, J = 8.8 Hz), 6.93 (d, 1H, J = 8.8 Hz).

Example 6(b_[LE15]): N-{3-[3-(2-Indolyl)-1H-indazol-6-yloxy]-phenyl}-3-methylbenzamide



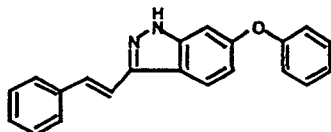
Example 6(b) was prepared in a similar manner to that described for Example 6(a) above, except that 1-SEM-indazole-2-carboxylic acid was used in step (i) in place of 4-chloro-*trans*-cinnamic acid. ¹H NMR (DMSO-*d*₆) δ 13.19 (s, 1H), 11.59 (s, 1H), 10.29 (s, 1H), 8.23 (d, 1H, J = 8.7 Hz), 7.73-7.38 (m, 9H), 7.12 (s, 1H), 7.03 (d, 2H, J = 7.3 Hz), 6.88 (d, 1H, J = 7.8 Hz), 2.38 (s, 1H). HRMS [m+H]⁺/z Calc'd: 459.1821. Found: 459.1836.

Example 7_[LE16]: 3-(Styryl-1H-indazol-6-yloxy)-phenylamine



A suspension of 3-(3-styryl-4,5-dihydro-1H-indazol-6-yloxy)-phenylamine (75 mg, 0.23 mmol) and 90 mg of 5% palladium on carbon (Pd/C) was heated at 155°C. After 4 h, more 5% Pd/C (39 mg) was added. After 22 h, more 5% Pd/C (30 mg) was added. The reaction mixture was filtered while hot after 26 h. The catalyst was washed and the filtrate concentrated under reduced pressure. The residue was chromatographed on silica eluting hexanes/EtOAc (1:1). The appropriate fractions were concentrated and triturated with CH₂Cl₂/hexanes to give the title compound as an off-white solid (20 mg, 27%): ¹H NMR (DMSO-*d*₆) δ 8.16 (d, 1H, J = 8.5 Hz), 7.71 (d, 2H, J = 6.7 Hz), 7.50 (s, 2H), 7.40 (t, 2H, J = 7.0 Hz), 7.30 (d, 1H, J = 6.5 Hz), 7.06-6.92 (m, 3H), 6.35 (d, 1H, J = 8.3 Hz), 6.23 (s, 2H), 5.26 (s, 2H). Anal. Calc. for C₂₁H₁₇N₃O · 0.15CH₂Cl₂: C, 74.69; H, 5.13; N, 12.36. Found: C, 74.64; H, 5.23; N, 12.25.

Example 8_[LE17]: 3-(E-styryl)-6-phenoxy-1H-indazole



A suspension of 3-(E-styryl)-6-phenoxy-4,5-dihydro-1H-indazole (200 mg, 0.64 mmol) and 5% Pd/C (200 mg) in 10 mL of tetralin was heated at 155 °C for 18 h. The catalyst was removed by filtering the hot solution and washed with THF, EtOAc and MeOH. The filtrate was concentrated under reduced pressure and the residue was chromatographed on silica gel eluting hexanes/EtOAc (2:1) to provide 3-(E-styryl)-6-phenoxy-1H-indazole as an off-white solid (110 mg, 55%). ¹H NMR (DMSO-*d*₆) δ 6.96 (s, 2H), 7.10 (d, 2H, J = 7.7 Hz), 7.20 (t, 1H, J = 7.1 Hz), 7.30 (t, 1H, J = 7.1 Hz), 7.44 (m, 6H), 7.71 (d, 2H, J = 7.5 Hz),

515
07
8.20 (d, 1H, J = 9.2 Hz), 12.90 (s, 1H). Anal. Calc. for $C_{21}H_{16}N_2O \cdot 0.1H_2O$: C, 80.28; H, 5.20; N, 8.92. Found: C, 80.20; H, 5.21; N, 8.93.

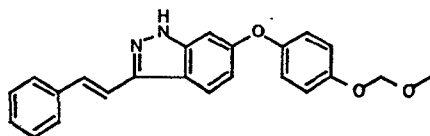
The starting material was prepared as follows:

(i) To a stirred solution of 3-chloro-cyclohex-2-enone (3.00g, 23.0 mmol) and phenol (2.16 g, 23.0 mmol) in 25 mL of acetone was added powdered, anhydrous K_2CO_3 (3.81 g, 27.6 mmol). After refluxing for 18 h, the mixture was cooled and filtered. The filtrate was concentrated under reduced pressure and chromatographed on silica gel eluting with hexanes/EtOAc (4:1) to give 3-phenoxy-cyclohex-2-enone as a white solid: ^1H NMR ($CDCl_3$) δ 2.10 (quint, 2H, J = 6.3 Hz), 2.40 (t, 2H, J = 6.2 Hz), 2.68 (t, 2H, J = 6.3 Hz), 5.14 (s, 1H), 7.05 (d, 2H, J = 7.5 Hz), 7.26 (t, 1H, J = 7.3 Hz), 7.41 (t, 2H, J = 7.6 Hz).

(ii) A solution of 3-phenoxy-cyclohex-2-enone (301 mg, 1.6 mmol) in 1 mL of THF was added to a stirred solution of 1.0 M solution of lithium bis(trimethylsilyl)amide in THF (3.2 mL) at $-78^\circ C$. After 15 min, cinnamoyl chloride (266 mg, 1.6 mmol) was added all at once. After 15 min, the reaction mixture was poured into 0.5 N HCl and extracted with EtOAc (2x). The combined organic layers were washed with saturated NaCl solution, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Chromatography of the residue with 4:1 hexanes/ethyl acetate as eluant provided 220 mg (43%) of 3-phenoxy-6-(3-phenyl-acryloyl)-cyclohex-2-enone as a yellow solid (220 mg, 43%): ^1H NMR ($CDCl_3$) (enol form) δ 2.66 (t, 2H, J = 7.2 Hz), 2.84 (t, 2H, J = 7.1 Hz), 5.11 (s, 1H), 6.86 (d, 1H, J = 15.6 Hz), 7.02 (d, 2H, J = 8.1 Hz), 7.20 (m, 2H), 7.28-7.38 (m, 3H). HRMS $M+H^+$ calc: 319.1334. Found: 319.1340.

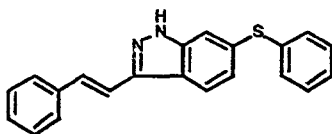
(iii) To a stirred solution of 3-phenoxy-6-(3-phenyl-acryloyl)-cyclohex-2-enone (1.13 g, 3.55 mmol) in 20 mL of HOAc/EtOH(1:1) was added hydrazine monohydrate (.21 mL, 4.3 mmol). The reaction was heated at $70^\circ C$ for 3 h, cooled and poured cautiously into saturated Na HCO_3 solution and extracted with EtOAc (2x). The combined organic layers were washed with saturated NaCl solution, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on silica gel eluting hexanes/EtOAc (2:1) to give 6-phenoxy-3-styryl-4,5-dihydro-1H-indazole (3) as an off-white solid (406 mg, 36%): ^1H NMR ($DMSO-d_6$) δ 2.64 (t, 2H, J = 8.0 Hz), 2.95 (t, 2H, J = 8.0 Hz), 5.46 (s, 1H), 7.04 (AB, 2H, J = 16.8 Hz), 7.15 (d, 2H, J = 8.1 Hz), 7.25 (m, 2H), 7.42 (m, 4H), 7.55 (d, 2H, J = 7.7 Hz), 12.44 (s, 1H). Anal. Calc. for $C_{21}H_{18}N_2O \cdot 0.2H_2O$: C, 79.32; H, 5.83; N, 8.81. Found: C, 79.36; H, 5.85; N, 8.84.

Example 8(b_(LE18)): 3-(E-styryl)-6-[4-(methoxymethoxy)phenoxy]-1H-indazole



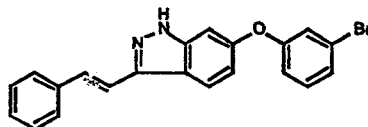
Example 8(b) was prepared in a similar manner to that described for Example 8(a) above, except that 4-(methoxymethoxy)phenol was used in place of phenol in step (i). ¹H NMR (DMSO-d₆) δ 12.90 (s, 1H), 8.17 (d, 1H, J = 8.8 Hz), 7.71 (d, 2H, J = 7.6 Hz), 7.50 (s, 3H), 7.41 (t, 2H, J = 7.6 Hz), 7.31 (d, 1H, J = 7.4 Hz), 7.10 (s, 3H), 6.95 (dd, 1H, J = 8.8, 1.9 Hz), 6.84 (s, 1H), 5.20 (s, 2H), 3.42 (s, 3H). Anal. Calc. for C₂₃H₂₀N₂O₃: C, 74.17; H, 5.41, N, 7.52. Found: C, 74.21; H, 5.59; N, 7.46.

10 Example 8(c_(LE19)): 3-(E-styryl)-6-phenylsulfanyl-1H-indazole



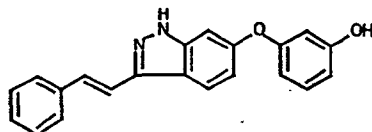
Example 8(c) was prepared in a similar manner to that described for Example 8(a) above, except that thiophenol was used in step (i) in place of phenol. ¹H NMR (DMSO-d₆) δ 7.29 (d, 1H, J = 8.5 Hz), 7.45-7.59 (m, 9H), 7.67 (s, 2H), 7.86 (d, 2H, J = 7.2 Hz), 8.35 (d, 1H, J = 8.5 Hz), 13.30 (s, 1H). Anal. Calc. For C₂₁H₁₆N₂S 0.25H₂O: C, 75.76; H, 5.00; N, 8.41; S, 9.63. Found: C, 75.79; H, 4.99; N, 8.16; S, 9.63.

Example 8(d_(LE20)): 6-(3-Bromo-phenoxy)-3-styryl-1H-indazole



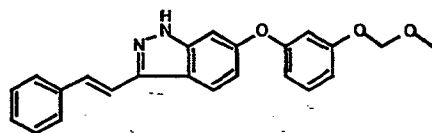
Example 8(d) was prepared in an analogous manner to that described for Example 8(a) above, except that 3-bromophenol was used in step (i) in place of phenol. ¹H NMR (DMSO-d₆) δ 13.08 (s, 1H), 8.23 (d, 1H, J = 8.8 Hz), 7.72 (d, 2H, J = 7.3 Hz), 7.53 (s, 2H), 7.43 - 7.35 (m, 4H), 7.30 (t, 2H, J = 7.2 Hz), 7.11 (d, 1H, J = 7.2 Hz), 7.09 (s, 1H), 6.98 (d, 1H, J = 8.8 Hz). Anal. Calc. for C₂₁H₁₅BrN₂O: C, 64.46; H, 3.86; Br, 20.42; N, 7.16. Found: C, 64.31; H, 3.99; Br, 20.52; N, 7.11.

25 Example 9 (a_(LE21)): 3-(E-styryl)-6-[3-hydroxyphenoxy]-1H-indazole



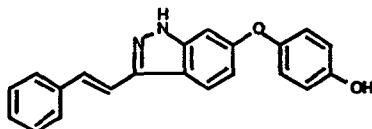
To a stirred solution of 3-(E-styryl)-6-[3-(methoxymethoxy)phenoxy]-1H-indazole (50 mg, 0.13 mmol) in 5 mL CH_2Cl_2 at -25°C was added trimethylsilylbromide (75 μL , 0.57 mmol). After 1.5 h, saturated NaHCO_3 solution was added and the product was extracted with EtOAc (2x). The combined organic layers were washed with saturated NaCl solution, dried (MgSO_4) and concentrated under reduced pressure. The residue was chromatographed on silica gel eluting hexanes/EtOAc (1:1) to give, after trituration with CH_2Cl_2 /hexanes, 3-(E-styryl)-6-[3-hydroxyphenoxy]-1H-indazole as an off-white solid (22 mg, 50%): ^1H NMR ($\text{DMSO}-d_6$) δ 6.37 (s, 1H), 6.43 (d, 1H, $J = 8.1$ Hz), 6.50 (d, 1H, $J = 8.1$ Hz), 6.88 (d, 1H, $J = 8.8$ Hz), 6.92 (s, 1H), 7.12 (t, 1H, $J = 8.1$ Hz), 7.24 (t, 1H, $J = 7.3$ Hz), 7.31 (t, 2H, $J = 7.6$ Hz), 7.44 (s, 2H), 7.64 (d, 2H, $J = 7.5$ Hz), 8.12 (d, 1H, $J = 8.7$ Hz), 9.54 (s, 1H), 12.92 (s, 1H). Anal. Calc. For $\text{C}_{21}\text{H}_{16}\text{N}_2\text{O}_2 \cdot 0.3\text{H}_2\text{O}$: C, 75.57; H, 5.01; N, 8.39. Found: C, 75.74; H, 5.11; N, 8.25.

The starting material, 3-(E-styryl)-6-[3-(methoxymethoxy)phenoxy]-1H-indazole, was prepared as described in Example 8(b).



^1H NMR (CDCl_3) δ 3.42 (s, 3H), 5.10 (s, 2H), 6.64 (d, 1H, $J = 8.2$ Hz), 6.72 (s, 1H), 6.80 (d, 1H, $J = 8.3$ Hz), 6.98 (s, 1H), 7.00 (d, 1H, $J = 8.8$ Hz), 7.19-7.38 (m, 5H), 7.53 (m, 3H), 7.92 (d, 1H, $J = 8.9$ Hz). Anal. Calc. For $\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_3$: $\text{M}+\text{H}^+$: 373.1552. Found: 373.1546

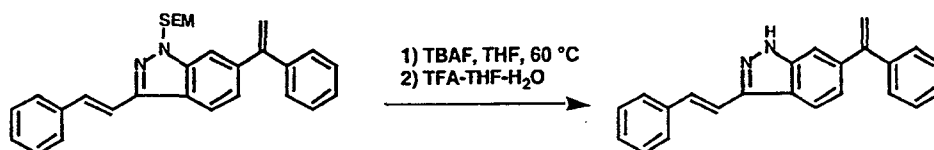
Example 9(b_{LE22}): 3-(E-styryl)-6-[4-hydroxyphenoxy]-1H-indazole



Example 9(b) was prepared like Example 9(a) above, except that 3-(E-styryl)-6-[4-(methoxymethoxy)phenoxy]-1H-indazole was used in place of 3-(E-styryl)-6-[3-(methoxymethoxy)phenoxy]-1H-indazole. ^1H NMR ($\text{DMSO}-d_6$) δ 12.95 (s, 1H), 9.58 (s, 1H), 8.33 (d, 1H, $J = 9.0$ Hz), 7.89 (d, 2H, $J = 7.1$ Hz), 7.68 (s, 1H), 7.58 (t, 1H, $J = 7.3$ Hz), 7.48 (d, 1H, $J = 7.3$ Hz), 7.24 (s, 1H), 7.13 (m, 3H), 6.99 (d, 2H, J

518
= 8.8 Hz). HRMS [m+H]/z Calc'd: 329.1290. Found: 329.1293. Anal. Calc. for C₂₁H₁₆N₂O₂ · 0.35H₂O: C, 75.36; H, 5.03; N, 8.37. Found: C, 75.35; H, 5.22; N, 8.24.

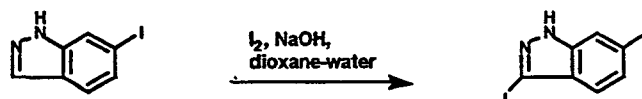
Example 10_(LE23): 6-(1-Phenyl-vinyl)-3-styryl-1*H*-indazole



- 5 6-(1-Phenyl-vinyl)-3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1*H*-indazole (16.2 mg, 0.0358 mmol) was dissolved in THF (0.6 mL) and was treated with tetrabutylammonium fluoride (TBAF, 1M in THF, 0.6 mL). The mixture was heated to 60 °C under argon for 4 h. The mix was cooled, neutralized with excess saturated sodium bicarbonate and the organic material was extracted into ethyl acetate and concentrated. This mix of 3 compounds (by
- 10 TLC visualization) was treated with THF-water-TFA (1:1:2, 4 mL) for 30 min. The mix was diluted with toluene (20 mL), concentrated, neutralized with excess saturated sodium bicarbonate, and the organic material was extracted into ethyl acetate. The organic material was dried over sodium sulfate, decanted and concentrated. Purification by silica gel chromatography (2:8 ethyl acetate-hexane) gave 6-(1-Phenyl-vinyl)-3-styryl-1*H*-indazole (4.6
- 15 mg, 40%): R_f sm 0.62, p 0.24 (ethyl acetate-hexane 3:7); ¹H NMR (300 MHz, CDCl₃) δ 7.99 (d, 1H, J = 8.5 Hz), 7.60-7.25 (m, 14H), 5.58 (d, 1H, J = 1.1 Hz), 5.56 (d, 1H, J = 1.1 Hz); HRMS (FAB) [m+H]/z Calc'd 323.1548, Found 323.1545.

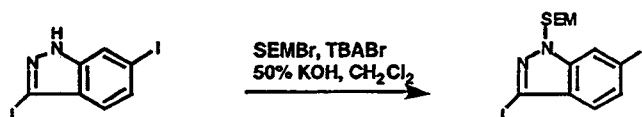
The starting material was prepared as follows:

(i)

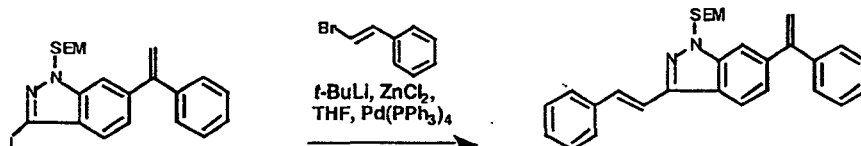


20 6-Iodoindazole was converted to 3,6-diiodoindazole (82%) as described in Example 1(a), step (v): ¹H NMR (300 MHz, CDCl₃) δ 10.3 (bs, 1H), 7.90 (s, 1H), 7.52 (dd, 1H, J = 1.2, 8.5 Hz), 7.24 (d, 1H, J = 8.5 Hz).

(ii)

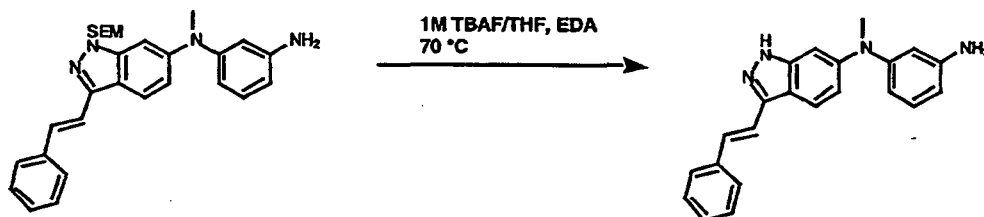


25 3,6-Diiodoindazole (755 mg, 2.04 mmol) was added to 50% KOH (2.5 g in 2.5 mL water) at 0 °C and dichloromethane (4 mL) was added. To this mixture was added



Preparation of 6-(1-Phenyl-vinyl)-3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1H-indazole: E-2-Bromostyrene (23 μ L, 0.174 mmol, 2.5 equiv) was dissolved in THF (1.0 mL) and was cooled to -78 $^{\circ}$ C. *t*-BuLi (205 μ L, 0.348 mmol, 5.00 equiv) was added and the mixture was warmed to -42 $^{\circ}$ C for 7 min to give a deep red mixture. The solution was added to freshly dried zinc chloride (29 mg, 0.209 mmol, 3.00 equiv) via cannula and the mix was allowed to warm to 23 $^{\circ}$ C with stirring for 20 min. This solution was added to a neat mixture of 3-Iodo-6-(1-phenyl-vinyl)-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1H-indazole (33.1 mg, 0.0696 mmol, 1.0 equiv) and Pd(PPh₃)₄ (4 mg, 0.0035 mmol, 0.05 equiv) at 23 $^{\circ}$ C via cannula. This solution was allowed to stir for 15 min and was treated with saturated sodium bicarbonate and extracted with ethyl acetate. The organic material was dried over sodium sulfate, decanted and concentrated. Purification by silica gel chromatography using two columns (5:95 ethyl acetate-hexane; 12 mL silica: and 1:99 ethyl acetate-benzene; 12 mL silica) gave 6-(1-Phenyl-vinyl)-3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1H-indazole (16.2 mg, 51%): *R*_f sm 0.38, *p* 0.29 (ethyl acetate-hexane 1:9); ¹H NMR (300 MHz, CDCl₃) δ 7.98 (d, 1H, *J* = 8.4 Hz), 7.62-7.22 (m, 14H), 5.71 (s, 2H), 5.57 (s, 2H), 3.60 (t, 2H, *J* = 8.2 Hz), 0.90 (t, 2H, *J* = 8.2 Hz), -0.08 (s, 9H); HRMS (FAB) [*m*+*H*]/*z* Calc'd 453.2362, Found 453.2354.

Example 11_(LE24): *N*-Methyl-*N*-(3-styryl-1H-indazol-6-yl)-benzene-1,3-diamine



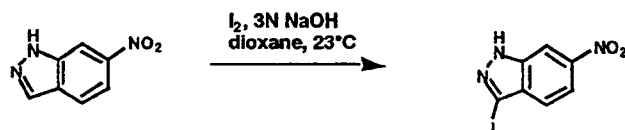
To *N*-methyl-*N*-(3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1H-indazol-6-yl)-benzene-1,3-diamine (237 mg, 0.5 mmol) was added 1M TBAF in THF (10.1 mL, 10.1 mmol), followed by ethylenediamine (0.34 mL, 5.04 mmol, 10 equiv). The resulting mixture was heated to 70 $^{\circ}$ C for 5 h. The reaction was then quenched with saturated NaHCO₃ (10 mL) and extracted 3x35 mL EtOAc. The pooled EtOAc phase was washed 5 x 20 mL H₂O, then brine (20 mL), dried with Na₂SO₄, decanted and concentrated under reduced pressure to

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a foam. The crude material was purified by silica gel chromatography (9:1 dichloromethane/ethyl acetate) to give *N*-methyl-*N*-(3-styryl-1*H*-indazol-6-yl)-benzene-1,3-diamine as a foam (120 mg, 70% yield). *R*_f sm 0.73, *R*_f p 0.27 (dichloromethane:ethylacetate 7:3); ¹³C NMR (75 MHz, CDCl₃) δ 150.3, 148.8, 147.5, 147.5, 143.9, 143.4, 137.5, 131.1, 130.3, 129.3, 128.9, 128.2, 127.9, 126.7, 121.0, 120.5, 117.0, 116.0, 112.6, 109.8, 109.0, 98.3, 40.7; LCMS (ESI) [M+H]⁺/*z* Calc'd 341, Found 341. Anal. Calc'd: C, 77.62; H, 5.92; N, 16.46. Found: C, 76.16; H, 5.88; N, 15.95.

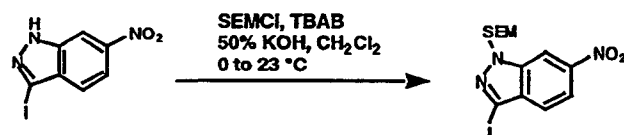
Starting material prepared as follows:

(i)



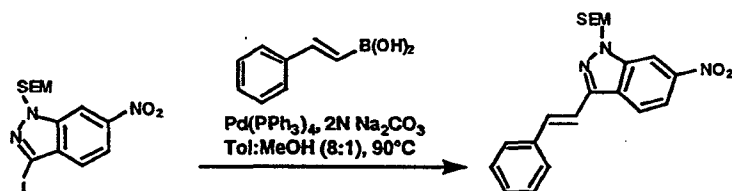
6-nitro-1*H*-indazole was converted to 3-Iodo-6-nitro-1*H*-indazole as described in Example 1(a), step (v) (50.6 g, 87%): FTIR (KBr) 3376, 3076, 2964, 2120, 1739, 1626, 1526, 1439, 1294, 1128, 954 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.28 (s, 1H), 8.05 (s, 1H), 7.66 (d, 1H, *J* = 8.13 Hz), 7.45 (dd, 1H, *J* = 8.33, 1.38 Hz), 7.17 (d, 1H, *J* = 1.01 Hz), 7.14 (s, 1H), 7.03 (d, 1H, *J* = 8.04 Hz), 6.89 (s, 2H), 3.82 (s, 3H), 2.55 (s, 6H), 2.21 (s, 3H), 1.32 (s, 9H). MS (FAB) [M+H]⁺/*z* Calc'd 311, Found 311. Anal. Calc'd: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.41; H, 5.98; N, 8.79.

(ii)



3-Iodo-6-nitro-1*H*-indazole was converted to 6-Nitro-3-iodo-[2-(trimethyl-silanyl)-ethoxymethyl]-1*H*-indazole as described in Example 10, step (ii) (10.2 g, 81% yield): mp 58 °C. Anal. Calc'd: C, 37.24; H, 4.33; N, 10.02. Found: C, 37.21; H, 4.38; N, 10.00.

(iii)

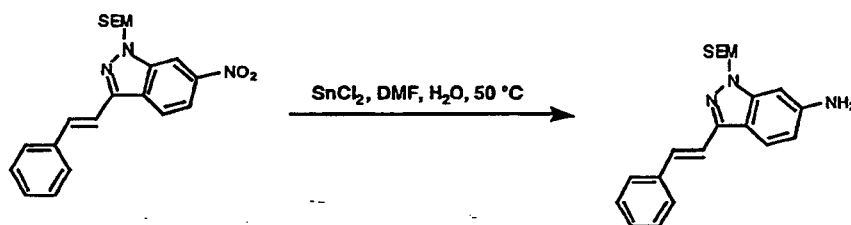


522

67

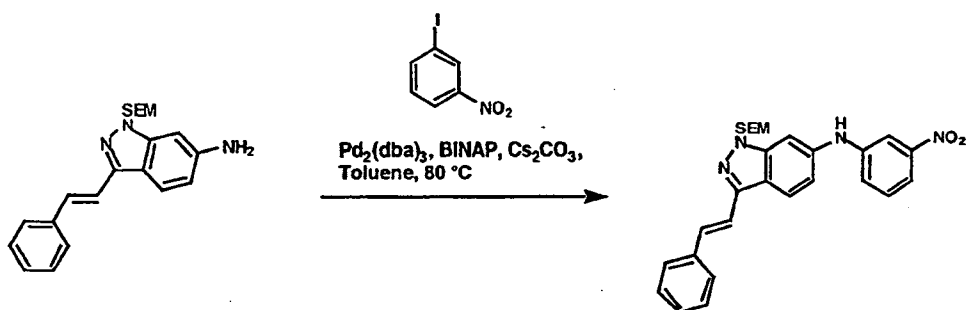
To 6-nitro-3-iodo-[2-(trimethyl-silanyl)-ethoxymethyl]-1*H*-indazole (11.0 g, 26.1 mmol), styryl boronic acid (4.64, 31.4 mmol), and Pd(PPh₃)₄ (1.25 g, 1.08 mmol) under an atmosphere of argon was added toluene (192 mL), MeOH (4 mL) and 2*N* NaOH (aq) (32.6 mL, 65.3 mmol). The resulting heterogeneous mixture was heated to 90 °C. After 8 h the reaction was diluted with EtOAc (150 mL) and water (50 mL), the phases were separated and the organic was extracted 2x 50 mL EtOAc. The pooled organic phase was washed with brine (50 mL), then dried with Na₂SO₄, filtered and concentrated under reduced pressure. The crude reaction was purified by silica gel chromatography (1:9 EtOAc:hexane) to give 6-nitro-3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1*H*-indazole as a yellow solid (7.65 g, 74%):
¹³C NMR (75 MHz, CDCl₃) δ 148.3, 145.0, 141.3, 138.1, 134.2, 130.5, 129.9, 129.8, 129.5, 128.1, 127.4, 123.2, 119.8, 117.8, 108.2, 79.7, 68.5, 19.2, 0.0; MS (FAB) [M+Na]⁺/z Calc'd 418, Found 418. Anal. Calc'd: C, 63.77; H, 6.37; N, 10.62. Found: C, 64.04; H, 6.29; N, 10.56.

(iv)

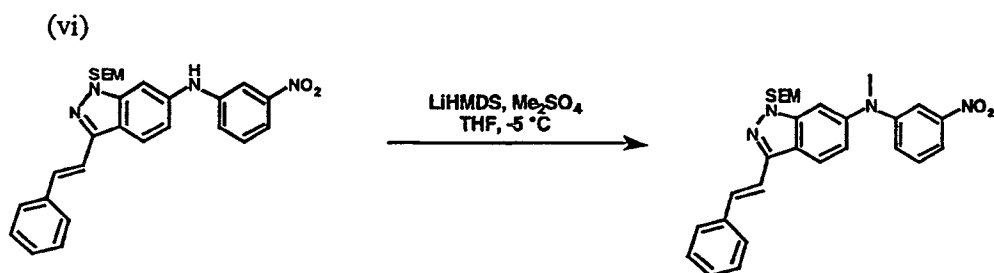


6-Nitro-3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1*H*-indazole (8.1 g, 20.5 mmol) was dissolved in DMF (75 mL) at 23 °C under an atmosphere of argon. SnCl₂ (12.9 g, 67.7 mmol) was added followed by water (1.7 mL, 92.2 mmol) and the resulting mixture was heated to 50 °C. After 4 h, 3*N* NaOH (45 mL, 135 mmol) was added followed by EtOAc (100 mL). The resulting emulsion was filtered hot through Celite and the bed of Celite was washed with hot EtOAc (3 x 100 mL). The filtrate was concentrated under reduced pressure, the residue was dissolved in EtOAc, washed with brine, dried with Na₂SO₄, filtered and concentrated under reduced pressure to give a solid. The crude material was purified by silica gel chromatography (2:8 • 7: 3 ethyl acetate:hexane), to give 3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1*H*-indazol-6-ylamine as a yellow solid (5.1 g, 68% yield). MS (FAB) [M+H]⁺/z Calc'd 366, Found 366.

(v)



To 3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1H-indazol-6-ylamine (1.1 g, 3 mmol, m-nitro-iodobenzene (0.9 g, 3.6 mmol), BINAP (0.07 g, 0.133 mmol), Pd₂(dba)₃ (34 mg, 0.0375 mmol) and Cs₂CO₃ (1.37 g, 4.2 mmol) under an atmosphere of argon was added toluene (6 mL). The resulting heterogeneous mixture was heated to 80 °C. After 46 h the reaction was cooled to 23 °C diluted with ethyl acetate (EtOAc) (20 mL) and filtered. Water (5 mL) was added, the phases were separated, and the organic was extracted 2 x 50 mL EtOAc. The pooled organic material was washed with brine, then dried with Na₂SO₄, filtered and concentrated under reduced pressure. The crude reaction was purified by silica gel chromatography (eluting with 9:1 hexane:EtOAc) to give (3-nitro-phenyl)-{(3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1H-indazol-6-yl)}-amine as a yellow solid (7.65 g, 74%): TLC (Hexane:EtOAc 7:3) R_f sm 0.16, R_f p 0.30 (ethyl acetate:hexane 3:7); FTIR (KBr) 3391, 3059, 2952, 2894, 1614, 1530, 1483, 1346, 1248, 1076, 836, 734 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.86 (s, 1H), 7.83 (s, 1H), 7.65 (dt, 1H, J = 2.21, 5.13 Hz), 7.15 - 7.41 (m, 5H), 6.93 (dd, 1H, J = 1.87, 8.67 Hz), 5.56 (s, 2H), 3.51 (t, 2H, J = 8.17 Hz), 0.81 (t, 2H, J = 7.96 Hz), -0.15 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 149.6, 144.8, 143.5, 142.4, 140.9, 137.3, 131.8, 130.3, 129.0, 128.2, 126.7, 122.8, 122.6, 120.1, 119.3, 116.1, 115.6, 111.4, 98.5, 77.9, 66.7, 18.0, -1.2; MS (ESI) [M+H]⁺/z Calc'd 487, Found 487. Anal. Calc'd: C, 66.64; H, 6.21; N, 11.51. Found: C, 66.91; H, 6.21; N, 11.44.

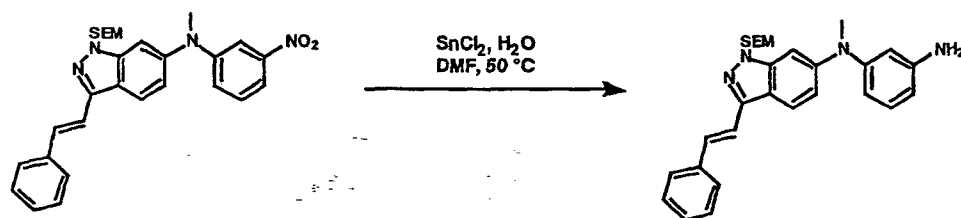


To (3-nitro-phenyl)-{(3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1H-indazol-6-yl)}-amine (434 mg, 0.89 mmol) in THF (5 mL) cooled to -5 °C under an atmosphere of

argon, was added dimethylsulfate (0.42 mL, 4.5 mmol) followed by LiHMDS (1M in THF) (1.8 mL, 1.8 mmol). After 20 min the reaction was quenched with saturated NH₄Cl(aq) (2 mL), then extracted 3x20 mL EtOAc. The pooled organic material was washed with brine (10 mL), dried with Na₂SO₄, decanted and concentrated under reduced pressure. Purification by silica gel chromatography (eluting with hexane:EtOAc 9:1) gave methyl-(3-nitro-phenyl)-{3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1H-indazol-6-yl}-amine, as an oil (367 mg, 82%); TLC (Hexane:EtOAc 7:3) R_f sm 0.29, R_f p 0.39 (ethyl acetate: hexane 3:7); FTIR (KBr) 2951, 2894, 1611, 1528, 1485, 1348, 1248, 1077 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.99 (d, 1H, J = 8.67 Hz) 7.77 (t, 1H, J = 2.25 Hz), 7.72 (dd, 1H, J = 0.79, 2.09 Hz), 7.60, (d, 2H, J = 7.22 Hz), 7.26 - 7.54 (m, 7H), 7.19 (dd, 1H, J = 0.78, 2.41 Hz) 7.07 (dd, 1H, J = 1.85, 8.69 Hz), 5.70 (s, 2H), 3.63 (t, 2H, J = 8.10 Hz), 3.48 (s, 3H), 0.92 (t, 2H, J = 8.10 Hz), -0.04 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 150.2, 149.6, 147.1, 143.5, 142.5, 137.3, 131.9, 129.8, 129.0, 128.2, 126.8, 123.1, 122.6, 120.2, 120.0, 119.7, 114.4, 111.4, 104.5, 78.0, 66.8, 41.1, 18.0, -1.2; LCMS (ESI) [M+H]⁺/z Calc'd 501, Found 510.

15

(vii)



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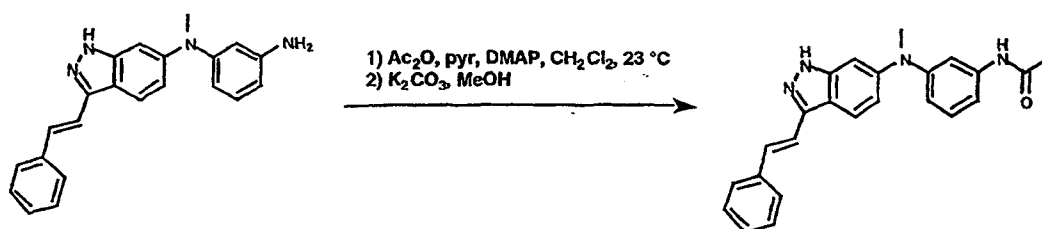
Methyl-(3-nitro-phenyl)-{3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1H-indazol-6-yl}-amine was converted to N-methyl-N-{3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1H-indazol-6-yl}-benzene-1,3-diamine as described in Example 11, step (iv). R_f sm 0.55, R_f p 0.31 (ethyl acetate:hexane 3:7); FTIR (thin film) 3455, 3360, 2951, 2893, 1621, 1601, 1494, 1449, 1249, 1074 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.81 (d, 1H, J = 8.8 Hz) 7.58 (d, 2H, J = 7.21 Hz), 7.26 - 7.50 (m 5H), 7.12 (t, 1H, J = 7.93 Hz), 7.01 (d, 1H, J = 1.73 Hz), 6.95 (dd, 1H, J = 1.99, 8.85 Hz), 5.67 (s, 2H), 3.63 (t, 2H, J = 8.12 Hz), 3.38 (s, 3H), 0.93 (t, 2H, J = 8.13 Hz), -0.04 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 150.3, 149.0, 147.7, 143.4, 143.0, 137.6, 131.3, 130.4, 128.9, 128.0, 126.7, 121.2, 120.6, 117.3, 117.0, 113.1, 110.1, 109.3, 97.5, 77.8, 66.6, 41.0, 18.0, -1.2; LCMS (ESI) [M+H]⁺/z Calc'd 471, Found 471.

25

Example 12(a)(LE25): N-{3-[Methyl-(3-styryl-1H-indazol-6-yl)-amino]-phenyl}-acetamide

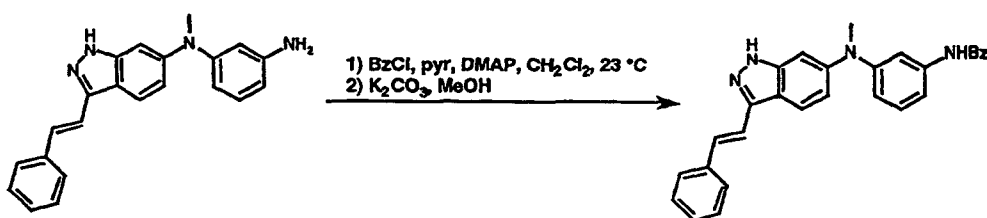
525

70



N-Methyl-*N*-{3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1*H*-indazol-6-yl}-benzene-1,3-diamine, prepared in Example 11 (34 mg, 0.041 mmol) was suspended in CH₂Cl₂ (0.5 mL) at 23 °C under an atmosphere of argon. Pyridine (81 µL, 1.0 mmol), Ac₂O (94 µL, 1.0 mmol) and DMAP (cat.) were added. The reaction became homogeneous immediately. After 1 h, TLC analysis (CH₂Cl₂:EtOAc 4:1) indicated no starting material. The reaction was quenched with saturated NaHCO₃(aq) (2 mL) then diluted with EtOAc (15 mL) and the organic phase was washed with brine (3 mL), decanted and concentrated under reduced pressure to an oil. The oil was suspended in MeOH (2 mL) and K₂CO₃ (83 mg, 0.6 mmol) was added. The resulting mixture was stirred at 23 °C under an atmosphere of argon. After 1 h, the reaction was diluted with EtOAc (15 mL) and the organic phase was washed with brine (3 mL), decanted and concentrated under reduced pressure. The crude material was purified by semi-prep HPLC to give *N*-{3-[methyl-(3-styryl-1*H*-indazol-6-yl)-amino]-phenyl}-acetamide (8.4 mg, 22%). ¹H NMR (300 MHz, CDCl₃) δ 7.86 (d, 1H, *J* = 8.68 Hz), 7.58 (d, 1H, *J* = 7.17 Hz), 7.16 - 7.45 (m, 7H), 7.15 (d, 1H, *J* = 8.29 Hz), 6.98 (m, 1H), 6.95 (d, 1H, *J* = 1.92 Hz), 6.8 (dd, 1H, *J* = 1.16, 8.05 Hz), 3.37 (s, 3H), 2.14 (s, 3H). LCMS (ESI) [M+H]⁺/*z* Calc'd 383, Found 383. Anal. Calc'd: C, 75.37; H, 5.80; N, 14.65. Found: C, 73.53; H, 6.01; N, 13.73.

Example 12(b)_[LE26]: *N*-{3-[Methyl-(3-styryl-1*H*-indazol-6-yl)-amino]-phenyl}-benzamide



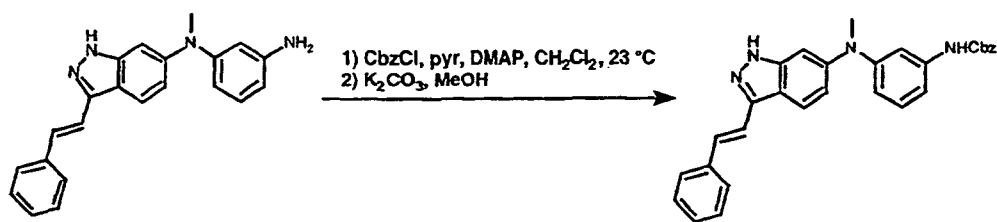
Example 12(b) was prepared in a similar manner to that described for Example 12(a) above, except that benzoyl chloride was used instead of acetic anhydride. LCMS (ESI)

526

[M+H]⁺/z Calc'd 475, Found 475; Anal. Calc'd C (78.36), H (5.44), N (12.60) Found, C (76.57), H (5.50), N (12.12).

Example 12(c)_[LE27]: {3-[Methyl-(3-styryl-1H-indazol-6-yl)-amino]-phenyl}-carbamic acid benzyl ester

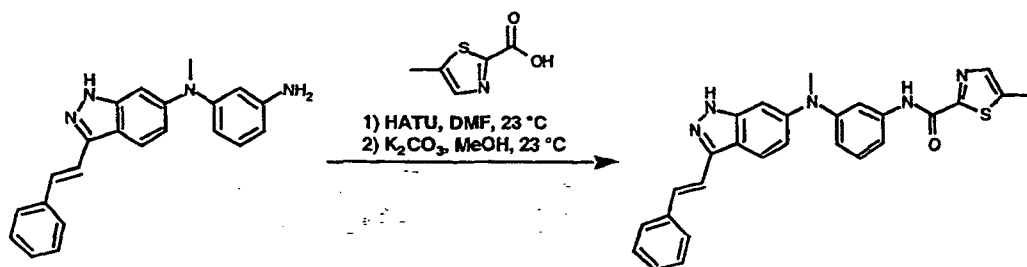
5



Example 12(c) was prepared in a similar manner to that described for Example 12(a) above, except that carbobenzyloxy chloride was used instead of acetic anhydride. R_f sm 0.30, R_f p 0.57 (CH₂Cl₂:EtOAc 8:2); LCMS (ESI⁺) [M+H]⁺/z Calc'd 475 Found 475; Anal. Calc'd C (75.93), H (5.52), N (11.81) Found, C (75.60), H (5.96), N (10.75).

Example 12(d)_[LE28]: 5-Methyl-thiazole-2-carboxylic acid {3-[methyl-(3-styryl-1H-indazol-6-yl)-amino]-phenyl}-amide

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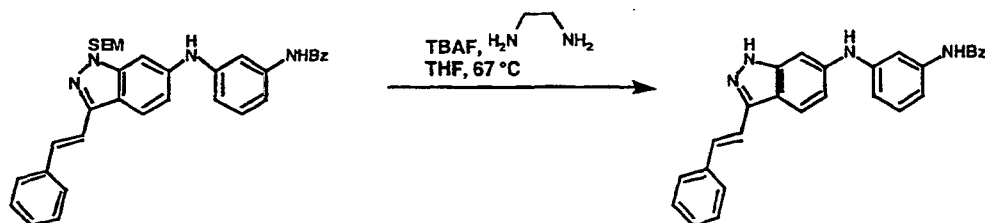
To a solution of *N*-methyl-*N*-(3-styryl-1H-indazol-6-yl)-benzene-1,3-diamine, prepared in Example 11, (26 mg, 0.075 mmol) and 5-methylthiazole-2-carboxylic acid (64 mg, 0.45 mmol) in DMF (0.375 mL) at 23 °C under an atmosphere of argon was added HATU (171 mg, 0.45 mmol). After 1 h, TLC analysis (CH₂Cl₂:EtOAc 8:2) indicated no starting material. The reaction was quenched with saturated NaHCO₃(aq) (2 mL) then diluted with EtOAc (15 mL) and the organic phase was washed with brine (3 mL), decanted and concentrated under reduced pressure. The oil was suspended in MeOH (2 mL) and K₂CO₃ (62 mg, 0.45 mmol) was added. The resulting mixture was stirred at 23 °C under an atmosphere of argon. After 1 h TLC analysis (CH₂Cl₂:EtOAc 8:2) indicated no starting material. The reaction was diluted with EtOAc (15 mL) and the organic phase was washed with brine (3 mL), decanted and concentrated under reduced pressure to a solid. The crude

15

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material was purified by silica gel chromatography (eluting with CH₂Cl₂:EtOAc 85:15) to give the title compound after purification by semi-prep. HPLC (9.9 mg, 28 %). *R_f* sm 0.25, *R_f* p 0.39 (hexane:EtOAc 8:2) ; LCMS (ESI+) [M+H]⁺/z Calc'd 466, Found 466. Anal. Calc'd C (69.65), H (4.98), N (15.04) S (6.89). Found, C (69.24), H (5.35), N (13.97) S (5.95).

5 **Example 13_(LE29): *N*-[3-(3-Styryl-1*H*-indazol-6-ylamino)-phenyl]-benzamide**

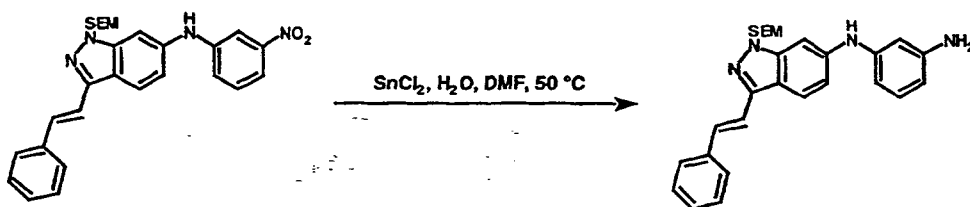


N-[3-(3-Styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1*H*-indazol-6-ylamino)-phenyl]-benzamide was converted to *N*-[3-(3-styryl-1*H*-indazol-6-ylamino)-phenyl]-benzamide as described in Example 11. LCMS (ESI) [M+H]⁺/z Calc'd 431, Found 431.

10 Anal. Calc'd: C, 78.12; H, 5.15; N, 13.01. Found: C, 77.06; H, 6.91; N, 9.88.

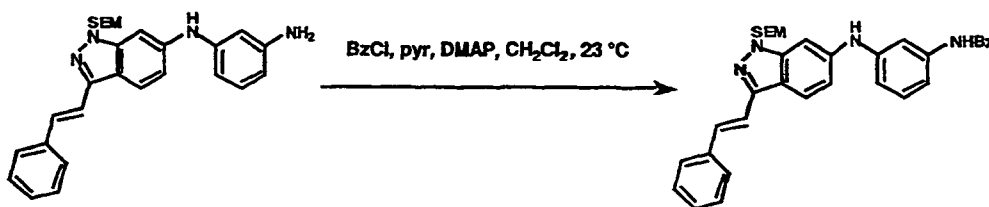
The starting material was prepared as follows:

(i)



15 (3-Nitro-phenyl)-[3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1*H*-indazol-6-yl]-amine, prepared in Example 11, step (vi), was converted to *N*-[3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1*H*-indazol-6-yl]-benzene-1,3-diamine as described in Example 11, step (iv). LCMS (ESI) [M+H]⁺/z Calc'd 457, Found 457.

(ii)

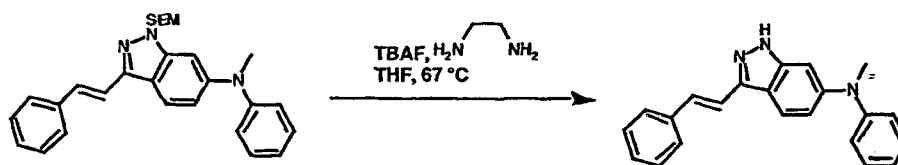


20 To a solution of *N*-[3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1*H*-indazol-6-yl]-benzene-1,3-diamine (91 mg, 0.2 mmol) and pyridine (0.081 mL, 1.0 mmol) in CH₂Cl₂ (0.5

528
73

mL) cooled to -5 °C under an atmosphere of argon was added benzoyl chloride (0.028 mL, 0.24 mmol). After 0.5 h the reaction was quenched with saturated NaHCO₃(aq) then extracted 2 x 5 mL CH₂Cl₂. The pooled organic material was washed with brine (5 mL), dried with Na₂SO₄, decanted and concentrated under reduced pressure to give an oil. The crude material was purified by silica gel chromatography (eluting with hexane:EtOAc 3:2) to give *N*-(3-(3-Styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1*H*-indazol-6-ylamino)-phenyl)-benzamide (108 mg, 96% yield). *R*_f sm 0.35, *R*_f p 0.44 (ethyl acetate:hexane 1:1); FTIR (thin film) 3320, 2951, 2893, 1657, 1604, 1537, 1493, 1409, 1303, 1248, 1074 cm⁻¹; LCMS (ESI) [M+H]⁺/*z* Calc'd 561, Found 561. Anal. Calc'd: C, 72.82; H, 6.47; N, 9.99. Found: C, 72.33; H, 6.39; N, 9.81.

Example 14_[LE30]: Methyl-phenyl-(3-styryl-1*H*-indazol-6-yl)-amine

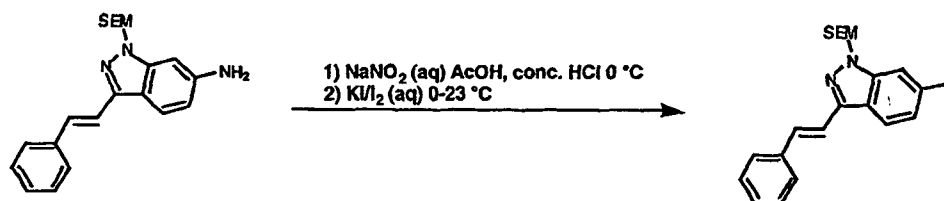


Methyl-phenyl-{3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1*H*-indazol-6-yl)-amine was converted to methyl-phenyl-(3-styryl-1*H*-indazol-6-yl)-amine as described in

Example 11. MS (ESI) [M+H]⁺/*z* Calc'd 326, Found 326.

The starting material was made as follows:

(i)



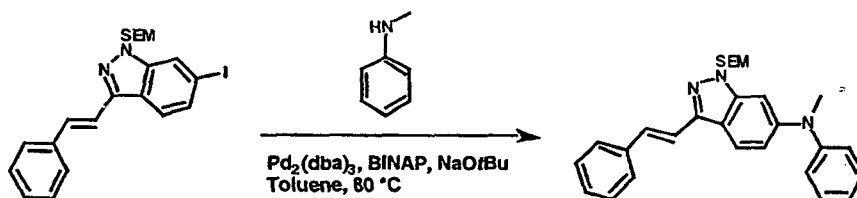
To a solution of 3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1*H*-indazol-6-ylamine (1.58 g, 4 mmol) in AcOH (14 mL), water (3 mL) and concentrated HCl (1.67 mL) cooled to 2 °C was added a solution of NaNO₂ (304 mg, 4.4 mmol) in water (0.5 mL) over 5 min. The resulting dark red solution was stirred at 2 °C for 0.5 h, then a solution of KI (797 mg, 4.8 mmol) and I₂ (610 mg, 2.4 mmol) in water (1 mL) was added drop-wise so as to keep the internal temperature below 5 °C. After 2 h at 2 °C the reaction was allowed to stir at 23 °C for 17 h. The reaction was quenched with 3 N NaOH (aq), diluted with EtOAc (50 mL) and H₂O (15 mL), the phases were separated and the aqueous was extracted 2 x 15 mL

529
74

EtOAc. The pooled organic phase was washed 3 x 20 mL 5% NaHSO₃, brine (15 mL), dried with Na₂SO₄, decanted and concentrated under reduced pressure. The crude reaction was purified by silica gel chromatography (eluting with 1:1 hexane:EtOAc) to give 6-iodo-3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1H-indazole as a white solid (1.3 g, 68% yield).

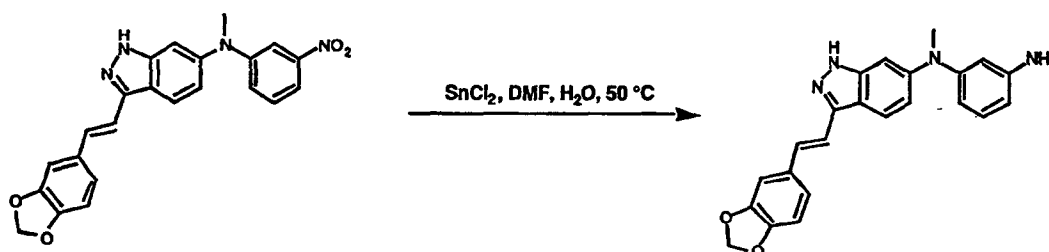
¹H NMR (300 MHz, CDCl₃) δ 8.03 (s, 1H), 7.79 (d, 1H, J = 9.0 Hz), 7.30 - 7.60 (m, 8H), 5.73 (s, 2H), 3.63 (t, 2H, J = 6.0 Hz), 0.96 (t, 2H, J = 6.0 Hz), 0.0 (s, 9); ¹³C NMR (75 MHz, CDCl₃) δ 143.6, 142.4, 137.2, 132.1, 130.8, 129.0, 128.3, 126.8, 122.5, 122.4, 119.6, 119.5, 92.9, 78.1, 66.9, 18.0, -1.2. Anal. Calc'd: C, 52.94; H, 5.29; N, 5.88. Found: C, 52.66; H, 5.29; N, 5.74.

10 (ii)



6-Iodo-3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1H-indazole was converted to methyl-phenyl-{3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1H-indazol-6-yl}-amine as described in Example 11, step (v). R_f sm 0.35 R_f p 0.13 (EtOAc:hexane 1:9); IR (KBr) 3031, 2951, 1625, 1595, 1498, 1449, 1326, 1303, 1248, 1212, 1076, 835, 694 cm⁻¹; MS (ESI) [M+H]⁺/z Calc'd 456, Found 456.

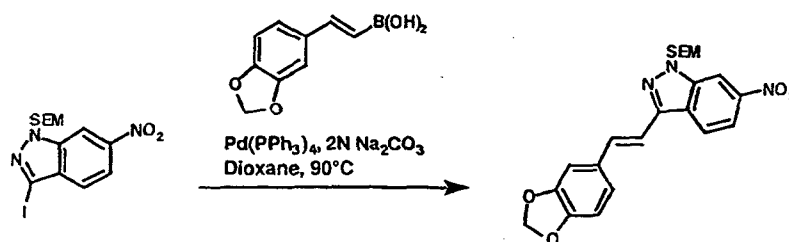
Example 15_(LE31): *N*-[3-(2-Benzo[1,3]dioxol-5-yl-vinyl)-1H-indazol-6-yl]-*N*-methyl-benzene-1,3-diamine



[3-(2-Benzo[1,3]dioxol-5-yl-vinyl)-1H-indazol-6-yl]-methyl-(3-nitro-phenyl)-amine was converted to *N*-[3-(2-benzo[1,3]dioxol-5-yl-vinyl)-1H-indazol-6-yl]-*N*-methyl-benzene-1,3-diamine as described in Example 11, step (iv). LCMS (ESI) [M+H]⁺/z Calc'd 385, Found 385. Anal. Calc'd: C, 71.86; H, 5.24; N, 14.57. Found: C, 70.99; H, 5.60; N, 13.80.

The starting material was prepared as follows:

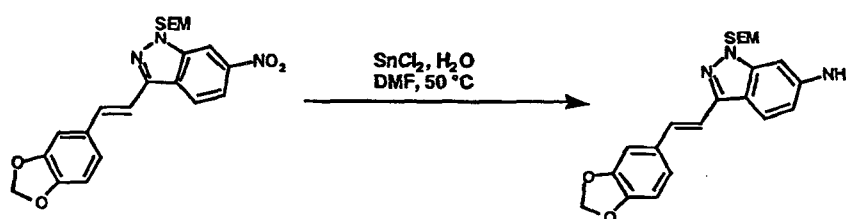
(i)



To a mixture of 6-nitro-3-iodo-[2-(trimethyl-silanyl)-ethoxymethyl]-1H-indazole (4.2 g, 10 mmol), boronic acid (3.46 g, 15 mmol), and Pd(PPh₃)₄ (0.58 g, 0.5 mmol) at 23 °C under an atmosphere of argon was added 1,4-dioxane (38 mL) and 2N NaOH (aq) (12.5 mL, 25 mmol). The resulting mixture was heated to 90 °C. After 2 h the reaction was diluted with EtOAc (100 mL) and water (70 mL), the phases were separated and the organic was extracted 2 X 100 mL EtOAc. The pooled organic phase was washed with brine (20 mL) then dried with Na₂SO₄, filtered and concentrated under reduced pressure. The crude mixture was purified by silica gel chromatography (eluting with 9:1 hexane:EtOAc) to give 3-(2-benzo[1,3]dioxol-5-yl-vinyl)-6-nitro-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1H-indazole as a yellow solid (4.15 g, 94% yield). FTIR (thin film) 2950, 2898, 1523, 1501, 1483, 1446, 1344, 1249, 1080, 1043, 927 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.56 (dd, 1H, J = 0.68, 1.75 Hz), 8.14 (d, 1H, J = 1.78 Hz), 8.13 (d, 1H, J = 0.67 Hz), 7.50 (d, 1H, 16.53 Hz), 7.25 (d, 1H, 16.52 Hz), 7.18 (d, 1H, J = 1.67 Hz), 7.07 (dd, 1H, J = 1.65, 8.13 Hz), 6.88 (d, 1H, J = 8.0 Hz), 6.05 (s, 2H), 5.84 (s, 2H), 3.66 (t, 2H, J = 7.33 Hz), 0.97 (t, 2H, J = 7.24 Hz), 0.0 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 148.5, 148.2, 147.0, 143.9, 140.1, 132.7, 131.3, 126.1, 122.3, 121.9, 116.7, 116.5, 108.7, 106.9, 105.7, 101.5, 78.4, 67.2, 17.9, -1.3; LCMS (ESI) [M+H]⁺/z Calc'd 531, Found 531.

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(ii)

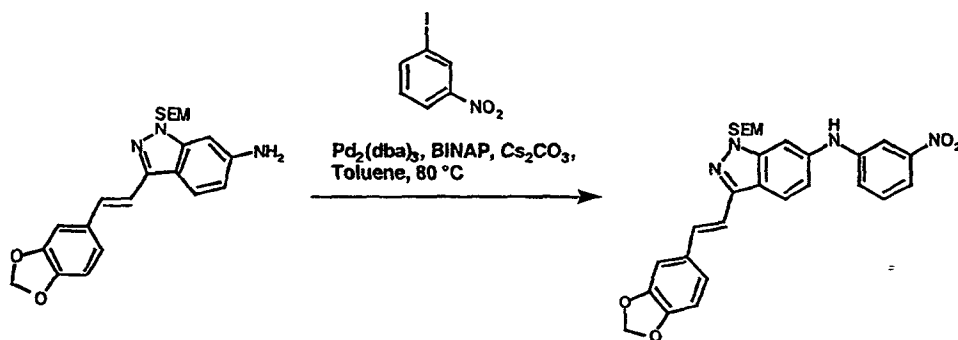


3-(2-Benzo[1,3]dioxol-5-yl-vinyl)-6-nitro-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1H-indazole was converted to 3-(2-Benzo[1,3]dioxol-5-yl-vinyl)-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1H-indazol-6-ylamine as described in Example 11, step (iv). ¹H NMR (300

53, 76

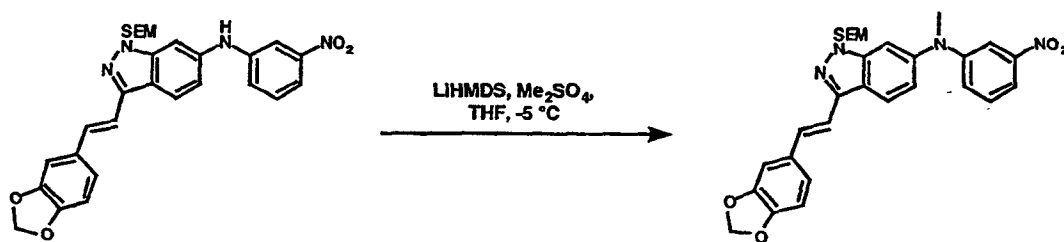
MHz, CDCl₃) δ 7.73 (d, 1H, J = 8.56 Hz), 7.52 (d, 1H, J = 16.57 Hz), 7.18 (d, 1H, J = 16.56 Hz), 7.10 (d, 1H, J = 1.49 Hz), 6.98 (dd, 1H, J = 1.52, 8.06 Hz), 6.80 (d, 1H, J = 8.01 Hz), 6.68 (d, 1H, J = 1.44 Hz), 6.63 (dd, 1H, J = 1.86, 8.57 Hz), 5.95 (s, 2H), 5.59 (s, 2H), 3.59 (t, 2H, J = 8.17 Hz), 0.91 (t, 2H, J = 8.33 Hz), 0.04 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 148.3, 147.6, 146.4, 143.4, 143.0, 132.0, 130.8, 122.0, 121.7, 118.8, 116.5, 113.1, 108.5, 105.5, 101.3, 92.9, 77.6, 66.3, 17.9, -1.3; LCMS (ESI) [M+H]⁺/z Calc'd 410, Found 410.

(iii)



3-(2-Benzo[1,3]dioxol-5-yl-vinyl)-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1H-indazol-6-ylamine was converted to 3-(2-Benzo[1,3]dioxol-5-yl-vinyl)-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1H-indazol-6-yl-(3-nitro-phenyl)-amine as described in Example 11, step (v). ¹³C NMR (75 MHz, CDCl₃) δ 150.8, 149.7, 149.1, 146.0, 144.8, 143.6, 142.1, 133.1, 132.7, 131.6, 124.0, 123.8, 123.1, 120.4, 119.5, 117.2, 116.8, 112.6, 109.9, 106.9, 102.6, 99.7, 79.1, 67.9, 19.2, 0.0; MS (FAB) [M+H]⁺/z Calc'd 531, Found 531. Anal. Calc'd: C, 63.38; H, 5.70; N, 10.56. Found: C, 63.49; H, 5.76; N, 10.42.

(iv)

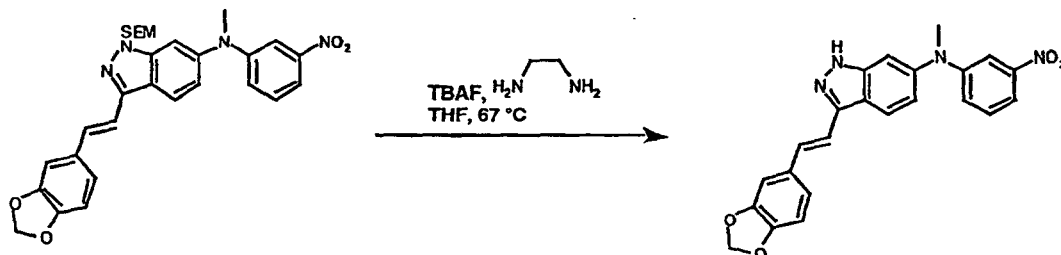


3-(2-Benzo[1,3]dioxol-5-yl-vinyl)-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1H-indazol-6-yl-(3-nitro-phenyl)-amine was converted to 3-(2-Benzo[1,3]dioxol-5-yl-vinyl)-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1H-indazol-6-yl-methyl-(3-nitro-phenyl)-amine as described in Example 11, step (vi). FTIR (KBr) 2952, 2894, 1612, 1529, 1503, 1489, 1446, 1407, 1348, 1306, 1251, 1077, 1039 cm⁻¹; ¹³C NMR (75 MHz, CDCl₃) δ 150.1, 149.5,

148.4, 147.8, 147.0, 143.5, 142.4, 131.8, 131.5, 129.8, 123.0, 122.49, 121.9, 120.1, 119.5, 118.2, 114.3, 111.3, 108.7, 105.7, 104.5, 101.4, 78.0, 66.8, 41.0, 17.9, -1.2; MS (FAB) [M+H]⁺/z Calc'd 545, Found 545. Anal. Calc'd: C, 63.95; H, 5.92; N, 10.29. Found: C, 62.63; H, 5.72; N, 9.62.

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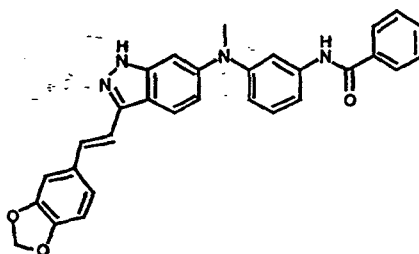
(v)



{3-(2-Benzo[1,3]dioxol-5-yl-vinyl)-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1H-indazol-6-yl]-methyl-(3-nitro-phenyl)-amine was converted to [3-(2-Benzo[1,3]dioxol-5-yl-vinyl)-1H-indazol-6-yl]-methyl-(3-nitro-phenyl)-amine as described in Example 11. LCMS (ESI) [M+H]⁺/z Calc'd 415, Found 415. Anal. Calc'd: C, 66.66; H, 4.38; N, 13.52. Found: C, 66.56; H, 4.48; N, 13.35.

10

Example 16(a)(LE32): *N*-(3-([3-(2-Benzo[1,3]dioxol-5-yl-vinyl)-1H-indazol-6-yl]-methyl-amino)-phenyl)-benzamide

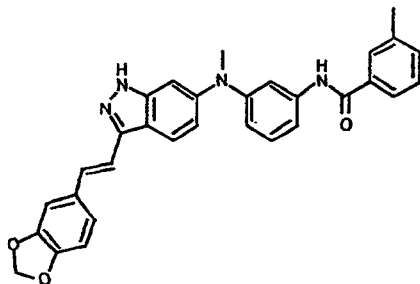


15

N-[3-(2-Benzo[1,3]dioxol-5-yl-vinyl)-1H-indazol-6-yl]-*N*-methyl-benzene-1,3-diamine (prepared as described in Example 15) was converted to *N*-(3-([3-(2-benzo[1,3]dioxol-5-yl-vinyl)-1H-indazol-6-yl]-methyl-amino)-phenyl)-benzamide in the manner described in Example 12(a). LCMS (ESI) [M+H]⁺/z Calc'd 489, Found 489. Anal. Calc'd: C, 73.76; H, 4.95; N, 11.47. Found: C, 73.19; H, 5.09; N, 11.20.

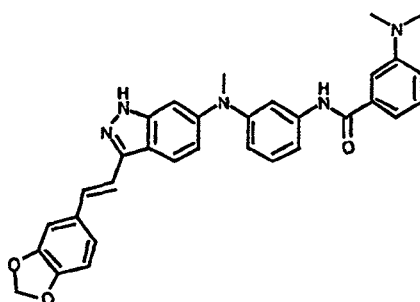
20

Example 16(b)(LE33): *N*-(3-([3-(2-Benzo[1,3]dioxol-5-yl-vinyl)-1H-indazol-6-yl]-methyl-amino)-phenyl)-3-methyl-benzamide



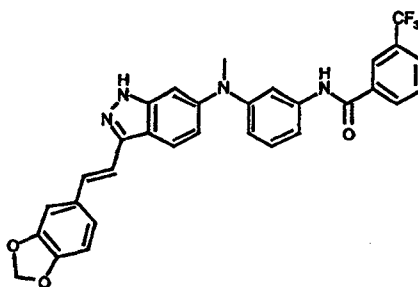
Example 16(b) was prepared in a similar manner to that described for Example 16(a) above, except that *m*-toluyl chloride was used instead of benzoyl chloride. LCMS (ESI) [M+H]⁺/z Calc'd 504, Found 504. Anal. Calc'd: C, 74.09; H, 5.21; N, 11.15. Found: C, 73.04; H, 5.84; N, 10.29.

Example 16(c)_(LE34): *N*-(3-([3-(2-Benzo[1,3]dioxol-5-yl)-vinyl]-1*H*-indazol-6-yl)-methyl-amino)-phenyl)-3-dimethylamino-benzamide



Example 16(c) was prepared in a similar manner to that described for Example 16(a), except that *m*-dimethylaminobenzoyl chloride was used instead of benzoyl chloride. LCMS (ESI) [M+H]⁺/z Calc'd 532, Found 532. Anal. Calc'd: C, 72.30; H, 5.50; N, 13.17. Found: C, 71.61; H, 5.80; N, 12.75.

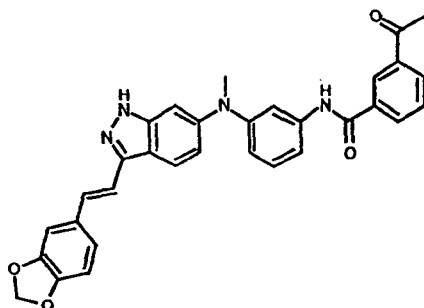
Example 16(d)_(LE35): *N*-(3-([3-(2-Benzo[1,3]dioxol-5-yl)-vinyl]-1*H*-indazol-6-yl)-methyl-amino)-phenyl)-3-trifluoromethyl-benzamide



Example 16(d) was prepared in a similar manner to that described for Example 16(a), except that *m*-trifluoromethylbenzoyl chloride was used instead of benzoyl chloride. LCMS

(ESI) [M+H]⁺/z Calc'd 557, Found 557. Anal. Calc'd: C, 66.90; H, 4.17; N, 10.07. Found: C, 66.64; H, 4.34; N, 9.82.

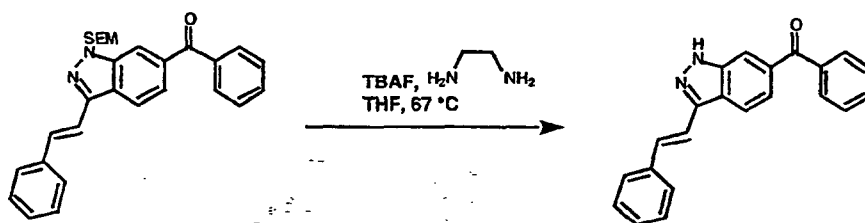
Example 16(e)_(LE36): 3-Acetyl-N-(3-{[3-(2-benzo[1,3]dioxol-5-yl-vinyl)-1H-indazol-6-yl]-methyl-amino}-phenyl)-benzamide



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Example 16(e) was prepared in a similar manner to that described for Example 16(a), except that m-acetylbenzoyl chloride was used instead of benzoyl chloride. LCMS (ESI) [M+H]⁺/z Calc'd 531, Found 531. Anal. Calc'd: C, 72.44; H, 4.94; N, 10.56. Found: C, 55.51; H, 4.21; N, 7.58.

10 Example 17_(LE37): Phenyl-(3-styryl-1H-indazol-6-yl)-methanone

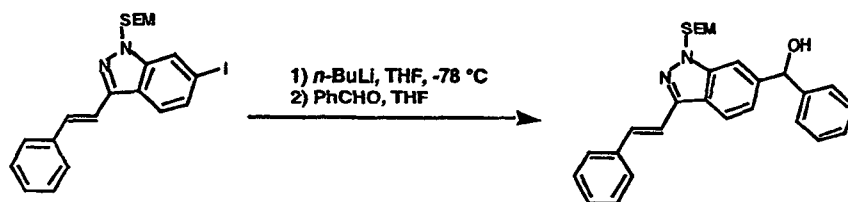


Phenyl-{3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1H-indazol-6-yl}-methanone was converted to phenyl-(3-styryl-1H-indazol-6-yl)-methanone as described in Example 11 (30 mg, 78%).; MS (ESI) [M+H]⁺/z Calc'd 325, Found 325. Anal. Calc'd: C, 81.46; H, 4.97; N, 8.46. Found: C, 80.36; H, 5.16; N, 8.51.

15

The starting material was prepared as follows:

(i)

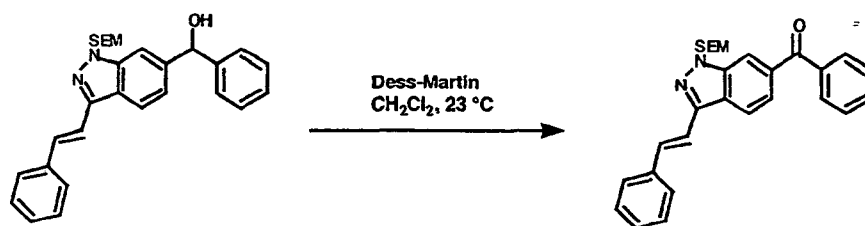


To a solution of 6-iodo-3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1H-indazole, prepared in Example 14, step (i), (143 mg, 0.3 mmol) in THF (1 mL) cooled to -78 °C under

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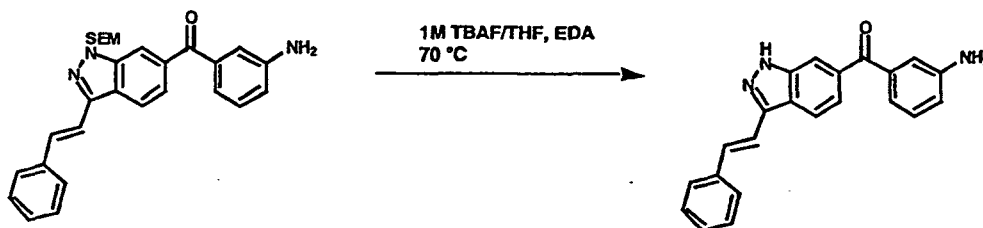
an atmosphere of argon was added *n*-BuLi (0.2 mL, 0.315 mmol) dropwise. The resulting mixture was stirred at -78 °C for 30 min, then a solution of benzaldehyde (0.035 mL, 0.33 mmol) in THF (0.5 mL) was added rapidly via a cannula. After 0.5 h the reaction was quenched with saturated NH₄Cl (aq) and diluted with EtOAc (10 mL) and H₂O (3 mL). The phases were separated and the aqueous was extracted 2x10 mL EtOAc. The pooled EtOAc was washed with brine (5 mL), dried with Na₂SO₄, decanted and concentrated under reduced pressure. The crude mixture was purified by silica gel chromatography (eluting with hexane:EtOAc 4:1) to give phenyl-{3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1*H*-indazol-6-yl}-methanol (68 mg, 50% yield). *R*_f sm = 0.72; *R*_f p = 0.39 (7:3 hexane:EtOAc); FTIR (thin film): 3368, 2952, 2893, 1621, 1478, 1449, 1374, 1307, 1249, 1216, 1078, 960, 859, 835 cm⁻¹; MS (ESI) [M+H]⁺/z Calc'd 457, Found 457.

(ii)



To a solution of phenyl-{3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1*H*-indazol-6-yl}-methanol (68 mg, 0.15 mmol) in dichloromethane (3 mL) at 23 °C under an atmosphere of argon was added periodinane (Dess-Martin reagent) (190 mg, 0.45 mmol). The resulting mixture was stirred at 23 °C for 1 hour. The solution was then diluted with hexane (3 mL) then filtered through Celite and concentrated under reduced pressure to a solid. The crude mixture was purified by silica gel chromatography (eluting with hexane:EtOAc 9:1) to give phenyl-{3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1*H*-indazol-6-yl}-methanone (54 mg, 79% yield). *R*_f sm = 0.41, *R*_f p = 0.63 (7:3 hexane:EtOAc); FTIR (thin film) 3059, 2952, 2894, 1659, 1474, 1448, 1307, 1249, 1078, 836, 649 cm⁻¹. MS (ESI) [M+H]⁺/z Calc'd 455, Found 455.

Example 18_[LE38]: (3-Amino-phenyl)-(3-styryl-1*H*-indazol-6-yl)-methanone

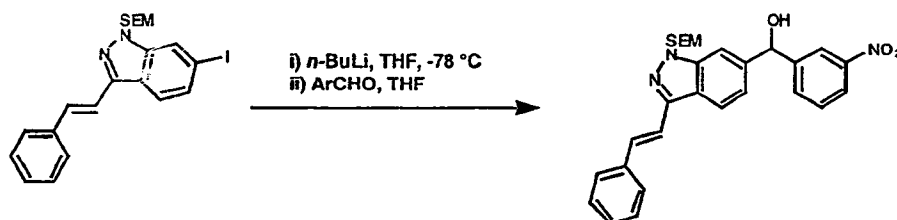


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(3-Amino-phenyl)-{3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1*H*-indazol-6-yl}-methanone was converted to (3-amino-phenyl)-(3-styryl-1*H*-indazol-6-yl)-methanone as described in Example 11. ¹H NMR (300 MHz, CDCl₃) δ 8.07 (dd, 1H, J = 0.71, 8.50 Hz), 7.91 (s, 1H), 7.64 (dd, 1H, J = 1.35, 8.48 Hz), 7.54 - 7.60 (m, 2H), 7.46 (d, 2H, J = 12.84 Hz), 7.35 - 7.40 (m, 2H), 7.22 - 7.31 (m, 2H), 7.16 - 7.13 (m, 2H), 6.91 (ddd, 1H, J = 1.08, 7.89 Hz); LCMS (ESI) [M+H]⁺/z Calc'd 340, Found 340.

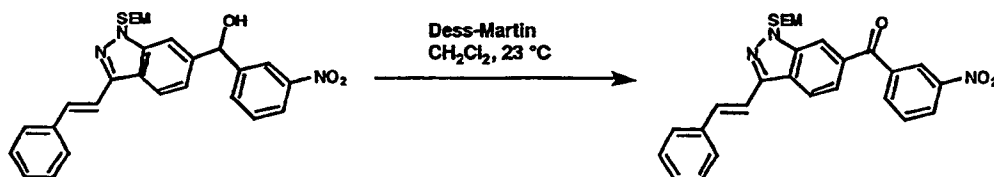
The starting material was prepared as follows:

(i)



6-Iodo-3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1*H*-indazole was converted to (3-nitro-phenyl)-{3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1*H*-indazol-6-yl}-methanol as described in Example 17, step (i). R_f sm = 0.71, R_f p = 0.25 (7:3 hexane:EtOAc); FTIR (thin film) 3369, 3061, 2952, 2894, 2361, 1620, 1578, 1530, 1478, 1449, 1350, 1308, 1249, 1215, 1080, 961, 859 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.35 (s, 1H), 8.14 (dd, 1H, J = 1.34, 8.14 Hz), 7.99 (d, 1H, J = 8.38 Hz), 7.76 (d, 1H, J = 7.72 Hz), 7.68 (s, 1H), 7.59 - 7.30 (m, 8H), 7.21 (d, 1H, J = 8.33 Hz), 6.09 (s, 1H), 5.73 (s, 2H), 3.61 (t, 2H, J = 8.30 Hz), 0.90 (t, 2H, J = 8.30 Hz), -0.06 (s, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 148.5, 145.9, 143.4, 142.4, 141.3, 137.1, 132.7, 132.0, 129.5, 128.9, 128.2, 126.7, 122.6, 122.6, 121.8, 121.5, 120.8, 119.6, 107.8, 77.7, 75.4, 66.8, 17.8, -1.3. Anal. Calc'd: C, 67.04; H, 6.23; N, 8.38. Found: C, 66.93; H, 6.20; N, 8.41.

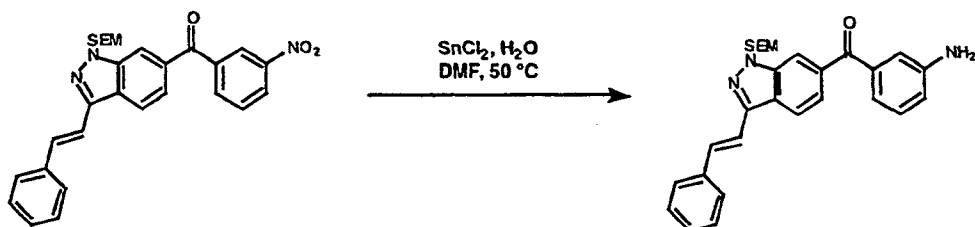
(ii)



(3-Nitro-phenyl)-{3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1*H*-indazol-6-yl}-methanol was converted to (3-nitro-phenyl)-{3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1*H*-indazol-6-yl}-methanone as described in Example 17, step (ii) (129 mg, 91%). R_f sm = 0.46, R_f p = 0.23 (7:3 hexane:EtOAc); FTIR (thin film) 3082, 2952, 2894, 1665, 1613, 1532,

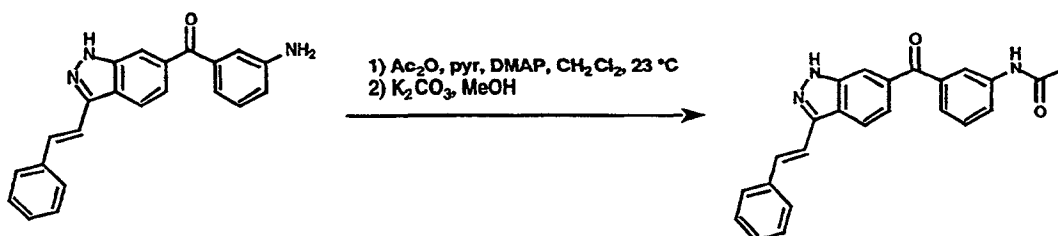
1476, 1349, 1298, 1250, 1080, 836, 718 cm^{-1} ; LCMS (ESI) $[M+H]^+/z$ Calc'd. 500, Found 500.

(iii)



- 5 (3-Nitro-phenyl)-{3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1H-indazol-6-yl}-methanone was converted to (3-amino-phenyl)-{3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1H-indazol-6-yl}-methanone as described in Example 11, step (iv) (102 mg, 84%). LCMS (ESI) $[M+H]^+/z$ Calc'd 340, Found 340.

Example 19(a)_(LE39): *N*-[3-(3-Styryl-1H-indazole-6-carbonyl)-phenyl]-acetamide

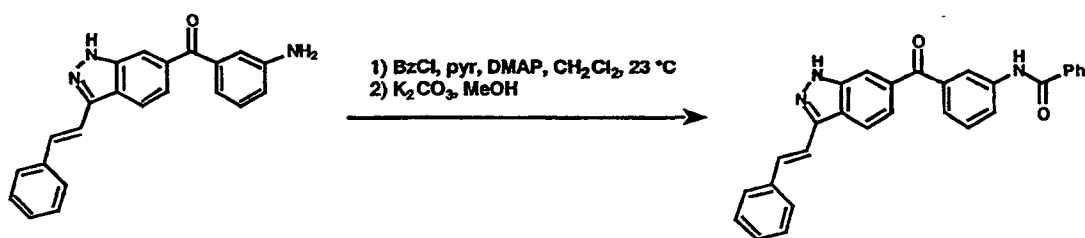


10

(3-Amino-phenyl)-(3-styryl-1H-indazol-6-yl)-methanone, prepared in Example 18, was converted to *N*-[3-(3-styryl-1H-indazole-6-carbonyl)-phenyl]-acetamide as described in Example 12(a) (12.2 mg, 78%). R_f sm = 0.16, R_f p = 0.35 (8:2 CH_2Cl_2 :EtOAc); LCMS (ESI) $[M+H]^+/z$ Calc'd 382, Found 382. Anal. Calc'd: C, 75.57; H, 5.02; N, 11.02. Found:

15 C, 74.32; H, 5.41; N, 10.54.

Example 19(b)_(LE40): *N*-[3-(3-Styryl-1H-indazole-6-carbonyl)-phenyl]-benzamide

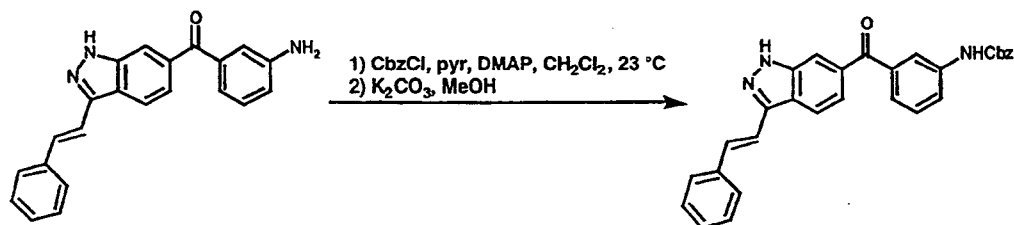


Example 19(b) was prepared in a similar manner to that described for Example 19(a), except that benzoyl chloride was used instead of acetic anhydride. ^1H NMR (300 MHz, CDCl_3) δ 8.40 (s, 1H), 8.02 (d, 1H, $J = 8.49$ Hz), 7.98 (d, 1H, $J = 1.01$ Hz), 7.95 (s, 1H), 7.95

20

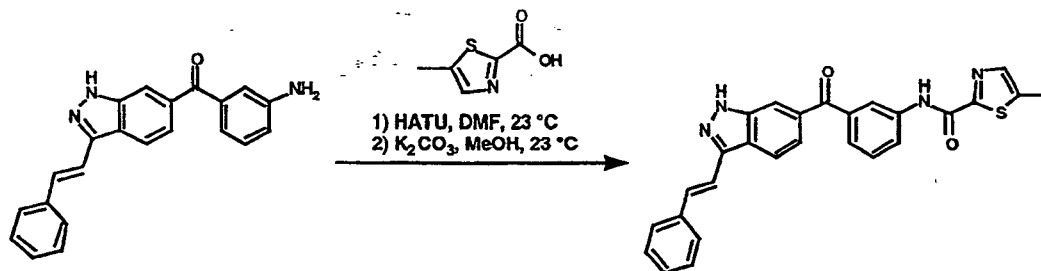
(s, 1H), 7.83 - 7.88 (m, 3H), 7.65 (dd, 1H, J = 1.04, 8.48 Hz), 7.29 - 7.56 (m, 11H); MS (ESI) [M+H]⁺/z Calc'd 444, Found 444. Anal. Calc'd: C, 78.54; H, 4.77; N, 9.47. Found: C, 78.01; H, 4.87; N, 9.32.

Example 19(c_[LE41]): [3-(3-Styryl-1H-indazole-6-carbonyl)-phenyl]-carbamic acid benzyl ester



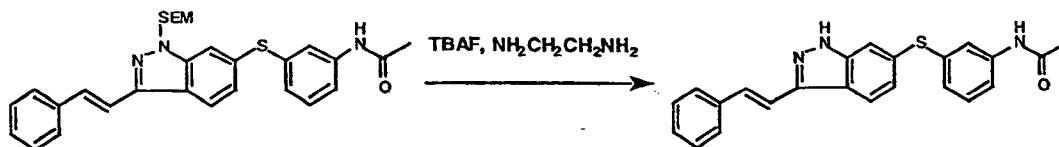
The title compound was prepared in a similar manner to that described for Example 19(a), except that carboxybenzyloxy chloride was used instead of acetic anhydride. ¹H NMR (300 MHz, DMSO-d₆) δ 8.37 (d, 1H, J = 8.48 Hz), 7.98 (s, 1H), 7.88 (s, 1H), 7.79 (s, 1H), 7.75 (d, 2H, J = 7.44 Hz), 7.61 (d, 2H, J = 1.81 Hz), 7.58 (s, 1H), 7.51 (t, 1H, J = 7.79 Hz), 7.42 (t, 5H, J = 6.56 Hz), 7.31 - 7.37 (m, 4H), 5.16 (s, 2H); LCMS (ESI) [M+H]⁺/z Calc'd 474, Found 474. Anal. Calc'd: C, 76.09; H, 4.90; N, 8.87. Found: C, 73.82; H, 4.93; N, 8.27.

Example 19(d_[LE42]): 5-Methyl-thiazole-2-carboxylic acid [3-(3-styryl-1H-indazole-6-carbonyl)-phenyl]-amide



(3-Amino-phenyl)-(3-styryl-1H-indazol-6-yl)-methanone was converted to 5-methylthiazole-2-carboxylic acid [3-(3-styryl-1H-indazole-6-carbonyl)-phenyl]-amide as described in Example 12(d) (9.9 mg, 28 %). ¹H NMR (300 MHz, CDCl₃) δ 8.15 (d, 1H, J = 8.49 Hz), 8.09 (t, 1H, J = 1.86 Hz), 8.04 (dd, 1H, J = 1.0, 7.98 Hz), 7.99 (s, 1H), 7.75 (dd, 1H, J = 1.31, 8.47 Hz), 7.67 (s, 1H), 7.63 (d, 2H, J = 7.30 Hz), 7.54 - 7.58 (m, 3H), 7.50 (s, 1H), 7.42 (t, 3H, J = 8.09 Hz); LCMS (ESI) [M+H]⁺/z Calc'd 465, Found 465.

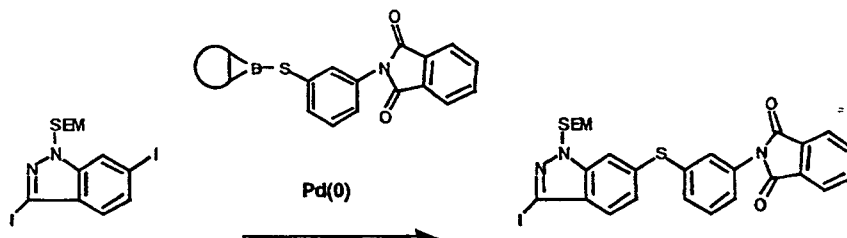
Example 20(a_[LE43]): 6-(3-Acetamido-phenylsulfanyl)-3-styryl-1H-indazole



6-(3-Acetamido-phenylsulfanyl)-3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1H-indazole was converted to 6-(3-acetamido-phenylsulfanyl)-3-styryl-1H-indazole as described in Example 11 (30 mg, 81%): R_f sm 0.65, p 0.35 (10% methanol in dichloromethane); ^1H NMR (300 MHz, CDCl_3) δ 7.81 (d, 1H, $J = 8.5$ Hz), 7.59 (bs, 1H), 7.48-7.0 (m, 13H), 1.98 (s, 3H); HRMS (FAB) $[\text{M}+\text{Na}]/z$ Calc'd 408.1147, Found 408.1156.

The starting material was prepared as follows:

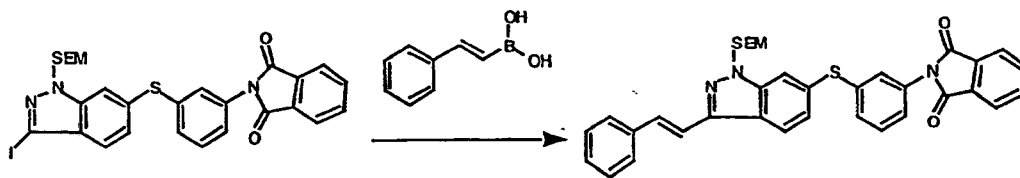
(i)



To the 9-BBN adduct of 3-phthalamido-thiophenol (1.4 equiv), which was prepared *in situ* as described below, was added 3,6-Diiodo-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1H-indazole (250 mg, 0.5 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (87 mg, 0.2 equiv) and potassium phosphate (339 mg, 1.6 mmol, 3.00 equiv) in DMF (3.0 mL). The reaction mixture was heated to 90 °C for 9 h. The mixture was cooled and partitioned between ethyl acetate and saturated sodium bicarbonate. The organic material was dried over sodium sulfate, decanted and concentrated. Purification by silica gel chromatography (2:8 ethyl acetate-hexane) gave 6-(3-phthalamido-phenylsulfanyl)-3-iodo-1H-indazole as an oil (159 mg, 50%): ^1H NMR (300 MHz, CDCl_3) δ 7.93 (m, 2H), 7.79 (m, 2H), 7.62 (s, 1H), 7.5-7.3 (m, 5H), 7.22 (d, 1H), 5.68 (s, 2H), 3.55 (t, 2H, $J = 8.2$ Hz), 0.87 (t, 2H, $J = 8.2$ Hz), -.06 (s, 9H); HRMS (FAB) $[\text{M}+\text{Cs}]/z$ Calc'd 759.9563, Found 759.9571.

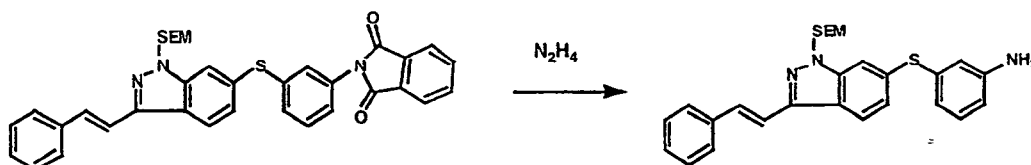
The boron reagent was prepared as follows: In a 10 mL Schlenk flask 3-phthalamido-thiophenol was dried under high vacuum. To this was added a solution of 9-BBN (0.5 M in THF, 1.6 mL, 1.0 equiv). The mixture was heated to 55 °C for 2 h. The volatile material was removed under a stream of argon at 70 °C for 1.5 h. The residue was used without further manipulation.

(ii)



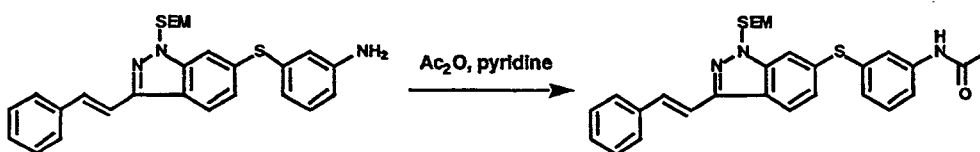
6-(3-Phthalamido-phenylsulfanyl)-3-iodo-1*H*-indazole was converted to 6-(3-phthalamido-phenylsulfanyl)-3-styryl-1*H*-indazole as described in Example 11, step (iii). ¹H NMR (300 MHz, CDCl₃) δ 7.93 (m, 3H), 7.78 (m 2H), 7.7 (s, 1H), 7.58 (m, 2H), 7.47-7.26 (m, 10H), 5.71 (s, 2H), 3.59 (t, 2H, J = 8.2 Hz), 0.89 (t, 2H, J = 8.2 Hz), -0.06 (s, 9H); HRMS (FAB) [M+Cs]⁺/z Calc'd 736.1066, Found 736.1058.

(iii)



To a solution of 6-(3-phthalamidophenylsulfanyl)-3-styryl-1*H*-indazole (121 mg, 0.2 mmol) in ethanol (3.5 mL) was added hydrazine (63 μL, 2.0 mmol, 10 equiv). The reaction mixture was allowed to stir at 23 °C for 45 min and was diluted with saturated sodium bicarbonate and ethyl acetate. The organic material was dried over sodium sulfate, decanted and concentrated. Purification by silica gel chromatography (3:7 ethyl acetate-hexane) gave 6-(3-aminophenylsulfanyl)-3-styryl-1*H*-indazole as an oil (79 mg, 90%): ¹H NMR (300 MHz, CDCl₃) δ 7.92 (d, 1H, J = 8.5 Hz), 7.57 (m, 3H), 7.49 (d, 1H, J = 16.8 Hz), 7.4-7.25 (m, 4H), 7.23 (dd, 1H, J = 1.5, 8.5 Hz), 7.11 (t, 1H, J = 7.9 Hz), 6.79 (m, 1H), 6.70 (t, 1H, J = 1.9 Hz), 6.59 (m, 1H), 5.66 (s, 2H), 3.60 (bs, 2H), 3.59 (t, 2H, J = 8.2 Hz), 0.90 (t, 2H, J = 8.2 Hz), -0.05 (s, 9H); HRMS (FAB) [M+H]⁺/z Calc'd 474.2035, Found 474.2019.

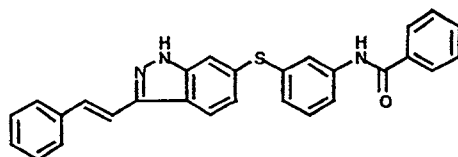
(iv)



To a solution of 6-(3-aminophenylsulfanyl)-3-styryl-1*H*-indazole (43.7 mg, 0.10 mmol) in dichloromethane (0.5 mL) was added pyridine (81 μL, 1.0 mmol, 10 equiv), and acetic anhydride (47 μL, 0.5 mmol, 5 equiv). The mixture was allowed to stir for 10 min at 23 °C. The mixture was diluted with water and the product was extracted with 30% hexane in ethyl acetate. The organic material was washed with 5% citric acid and saturated sodium

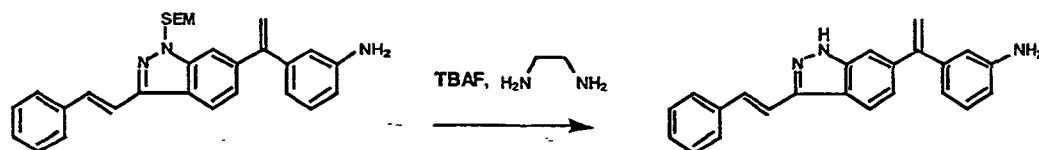
bicarbonate. The organic material was dried over sodium sulfate, decanted and concentrated. Purification by silica gel chromatography (3:7 ethyl acetate-hexane) gave 6-(3-acetamidophenylsulfanyl)-3-styryl-1H-indazole as an oil (50-mg, 97%): R_f sm 0.33, R_f p 0.18 (ethyl acetate-hexane 3:7); ^1H NMR (300 MHz, CDCl_3) δ 7.94 (d, 1H), 7.65-7.1 (m, 13H), 5.70 (s, 2H), 3.62 (t, 2H, $J = 8.2$ Hz), 2.18 (s, 3H), 0.93 (t, 2H, $J = 8.2$ Hz), -0.05 (s, 9H); HRMS (FAB) $[\text{M}+\text{Cs}]/z$ Calc'd 648.1117, Found 648.1098.

Example 20(b)_(LE44): 6-(3-(Benzoylamido)-phenylsulfanyl)-3-styryl-1H-indazole



The title compound was prepared like Example 20(a), except that benzoyl chloride was used instead of acetic anhydride in step (iv). ^1H NMR (300 MHz, CDCl_3) δ 8.03 (s, 1H), 7.73 (d, 1H, $J = 8.5$ Hz), 7.63 (m, 2H), 7.47 (m, 1H), 7.42 (t, 1H, $J = 1.9$ Hz), 7.37 (m, 3H), 7.31 (m, 1H), 7.28-6.98 (m, 9H); HRMS (FAB) $[\text{M}+\text{H}]/z$ Calc'd 448.1484, Found 448.1490.

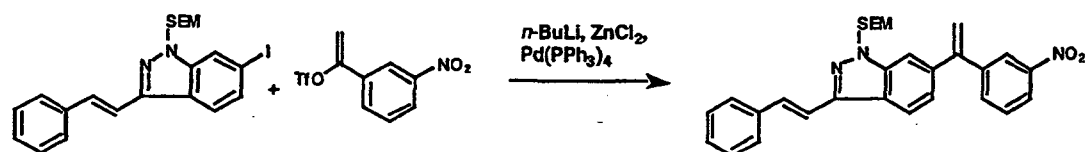
Example 21_(LE45): 6-(1-(3-Aminophenyl)-vinyl)-3-styryl-1H-indazole



6-(1-(3-Aminophenyl)-vinyl)-3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1H-indazole was converted to the title compound as described for Example 11 (85 mg, 85%): R_f sm 0.72, p 0.37 (ethyl acetate-hexane 1:1); FTIR (thin film) 3385, 3169, 2953, 1621, 1581, 1489, 1447, 1349, 1251, 1165, 1071, 959, 906, 870, 817 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.98 (d, 1H, $J = 8.5$ Hz), 7.60 (m, 2H), 7.51 (s, 1H), 7.48 (s, 1H), 7.40 (m, 3H), 7.29 (m, 2H), 7.15 (m, 1H), 6.78 (m, 1H), 6.68 (m, 2H), 5.50 (s, 2H), 3.65 (bs, 2H); MS (ES) $[\text{M}+\text{H}]/z$ Calc'd 338, Found 338; MS (ES) $[\text{M}-\text{H}]/z$ Calc'd 336, Found 336.

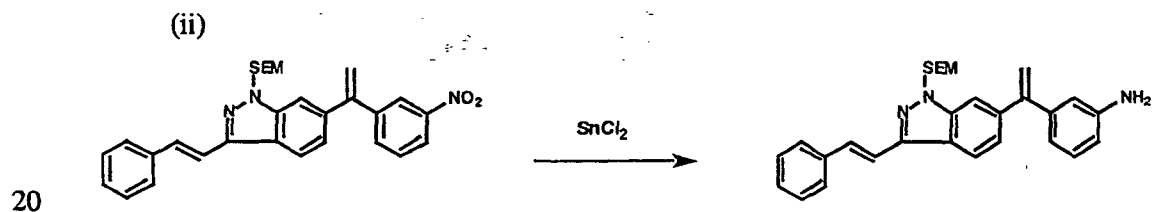
The starting material was prepared as follows:

(i)



542
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To a solution of 6-iodo-3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1*H*-indazole, prepared in Example 14, step (i), (330 mg, 0.693 mmol) in THF (3.0 mL) at -78 °C was added *n*-butyllithium (0.56 mL, 1.5 M, 1.2 equiv). After 20 min, this solution was then added to anhydrous zinc chloride (170 mg) and the mixture was warmed to 23 °C and stirred for 15 min. To this mixture was added 1-(3-nitro-phenyl)vinyltriflate (146 μL, 1.05 equiv) and Pd(PPh₃)₄ (40 mg, 0.05 equiv). This mixture was stirred for 30 min, was partitioned between ethyl acetate and saturated sodium bicarbonate and the organic layer was separated. The organic material was dried over sodium sulfate, decanted and concentrated under reduced pressure. Purification by silica gel chromatography (1:9 ethyl acetate-hexane) then a second column (1% ethyl acetate/benzene) gave 6-(1-(3-nitrophenyl)-vinyl)-3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1*H*-indazole as an oil (180 mg, 52%): FTIR (thin film) 2951, 1616, 1530, 1477, 1448, 1348, 1305, 1248, 1217, 1077, 961, 913, 859 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.26 (t, 1H, J = 1.9 Hz), 8.21 (m, 1H), 8.00 (d, 1H, J = 8.5 Hz), 7.69 (dt, 1H, J = 1.4, 7.8), 7.62-7.28 (m, 9H), 7.19 (dd, 1H, J = 1.4, 8.4 Hz), 5.72 (s, 3H), 5.69 (s, 1H), 3.60 (t, 2H, J = 8.2 Hz), 0.89 (t, 2H, J = 8.2 Hz), -0.05 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 149.9, 149.6, 144.7, 144.5, 142.8, 140.7, 138.6, 135.6, 133.1, 130.7, 130.2, 129.4, 128.0, 124.4, 124.2, 124.1, 123.8, 122.6, 121.2, 118.9, 111.0, 79.2, 68.0, 19.2, 0.0; HRMS (FAB) [M+Na]⁺/z Calc'd 520.2031, Found 520.2046.

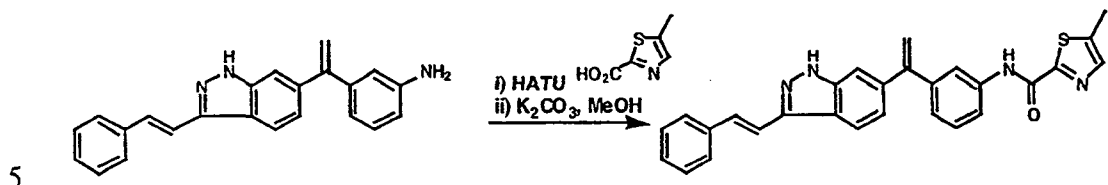


6-(1-(3-Nitrophenyl)-vinyl)-3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1*H*-indazole was converted to 6-(1-(3-aminophenyl)-vinyl)-3-styryl-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1*H*-indazole as described in Example 11, step (iv) (140 mg, 95%): R_f sm 0.59, p 0.46 (ethyl acetate-hexane 4:6); FTIR (thin film) 3460, 3366, 3223, 3084, 3028, 2952, 2894, 2246, 1616, 1601, 1581, 1489, 1474, 1448, 1359, 1303, 1249, 1217, 1076, 961, 909, 860, 836, 733, 692 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.96 (d, 1H, J = 8.5 Hz), 7.59 (m, 3H), 7.50 (s, 1H), 7.46 (s, 1H), 7.40 (m, 2H), 7.30 (m, 1H), 7.25 (m, 1H), 7.14 (m, 1H), 6.77 (m, 1H), 6.68 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 151.6, 147.7, 144.6, 143.9, 142.8, 142.4, 138.6, 132.8, 130.6, 130.2, 129.3, 128.0, 124.4, 123.6, 121.9, 121.5, 120.2, 116.4,

543
88

116.1, 110.8, 79.0, 67.9, 19.2, 0.0; HRMS (FAB) [M+Na]/z Calc'd 490.2291, Found 490.2302.

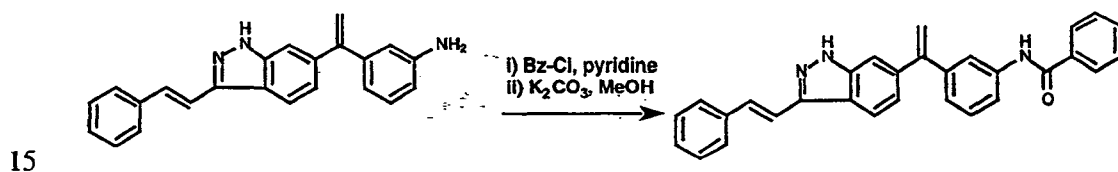
Example 22(a)_[LE46]: 6-(1-(3-(5-Methyl-thiazole-2-carboxoylamido)phenyl)-vinyl)-3-styryl-1H-indazole



6-(1-(3-Aminophenyl)-vinyl)-3-styryl-1H-indazole was converted to the title compound as described in Example 12(d) (20 mg, 72%): FTIR (thin film) 3271, 1673, 1605, 1585, 1538, 1486, 1428, 1349, 1304, 1090, 960, 907, 871 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 10.7 (bs, 1H), 9.09 (s, 1H), 8.0 (d, 1H), 7.79 (m, 1H), 7.60 (m, 3H), 7.51 (m, 3H), 7.44-7.15 (m, 7H), 5.59 (s, 2H), 2.54 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 162.2, 157.9, 149.8, 144.4, 142.8, 142.2, 141.9, 141.5, 140.6, 137.63, 137.56, 131.6, 129.5, 129.1, 128.3, 126.9, 125.1, 122.6, 121.2, 120.9, 120.5, 120.2, 119.8, 116.1, 110.2, 12.8; HRMS (FAB) [M+H]/z Calc'd 463.1593, Found 463,1582.

10

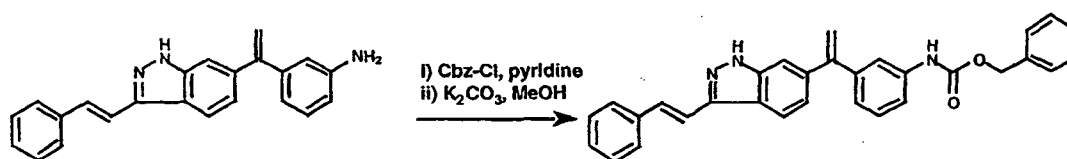
Example 22(b)_[LE47]: 6-(1-(3-(Benzoylamido)phenyl)-vinyl)-3-styryl-1H-indazole



Example 22(b) was prepared in a similar manner to that described for Example 22(a), except that benzoyl chloride was used instead of 5-methylthiazole-2-carboxylic acid and HATU. FTIR (thin film) 3243, 1651, 1606, 1580, 1538, 1485, 1447, 1428, 1349, 1307, 1258, 1073, 959, 907 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 9.09 (s, 1H), 7.99 (d, 1H, $J = 8.5$ Hz), 7.78 (m, 1H), 7.60 (m, 3H), 7.51 (m, 3H), 7.43-7.15 (m, 10H), 5.56 (d, 2H, $J = 3.2$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 166.5, 149.7, 144.3, 142.7, 142.1, 140.6, 138.1, 137.6, 135.0, 132.3, 131.6, 129.4, 129.1, 128.3, 127.4, 126.9, 125.0, 122.5, 120.9, 120.8, 120.6, 120.5, 115.9, 110.2; HRMS (FAB) [M+H]/z Calc'd 442.1919, Found 442.1919.

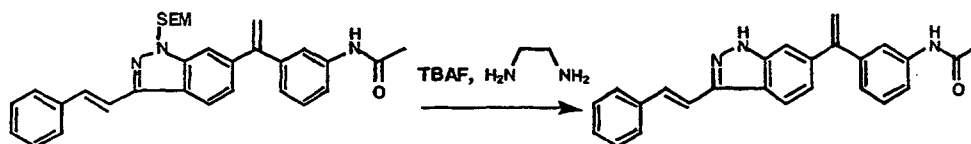
20

Example 22(c)_[LE48]: 6-(1-(3-(Benzoylamido)phenyl)-vinyl)-3-styryl-1H-indazole



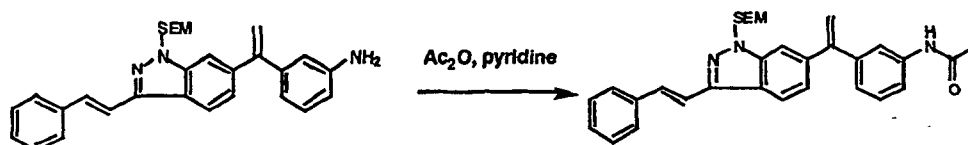
The title compound was prepared in a similar manner to that described for Example 22(a), except that carbobenzyloxy chloride was used instead of 5-methyl-thiazole-2-carboxylic acid and HATU. FTIR (thin film) 3305, 1712, 1606, 1586, 1537, 1487, 1445, 1348, 1216, 1059, 959, 908 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.99 (d, 1H, $J = 8.5$ Hz), 7.6-7.0 (m, 18H), 5.55 (s, 2H), 5.19 (s, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 153.9, 149.8, 144.3, 142.7, 142.1, 140.7, 138.2, 137.6, 136.3, 131.7, 129.4, 129.1, 129.0, 128.7, 128.7, 128.3, 126.9, 124.0, 122.6, 121.1, 120.8, 120.4, 115.9, 110.1, 67.4; HRMS (FAB) $[\text{M}+\text{H}]^+/z$ Calc'd 472.025, Found 472.026.

10 **Example 23_[LE49]: 6-(1-(3-Acetamido-phenyl)-vinyl)-3-styryl-1H-indazole**



6-(1-(3-Acetamido-phenyl)-vinyl)-3-styryl-1-[2-trimethylsilyl-ethoxymethyl]-1H-indazole was converted to 6-(1-(3-acetamido-phenyl)-vinyl)-3-styryl-1H-indazole as described for Example 11: FTIR (thin film) 3252, 1667, 1606, 1557, 1486 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 10.4 (bs, 1H), 7.91 (d, 1H, $J = 8.5$ Hz), 7.5-7.0 (m, 13H), 5.47 (s, 2H), 2.10 (s, 3H); MS (ES) $[\text{M}+\text{H}]^+/z$ Calc'd 380, Found 380; $[\text{M}-\text{H}]^+/z$ Calc'd 378, Found 378.

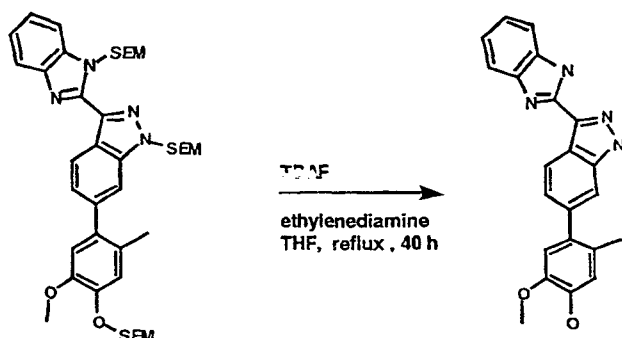
The starting material was prepared as follows:



6-(1-(3-Aminophenyl)-vinyl)-3-styryl-1-[2-trimethylsilyl-ethoxymethyl]-1H-indazole was converted to 6-(1-(3-acetamido-phenyl)-vinyl)-3-styryl-1-[2-trimethylsilyl-ethoxymethyl]-1H-indazole as described for Example 12(a): R_f sm 0.42, p 0.26 (ethyl acetate-hexane 4:6); FTIR (thin film) 3305, 3059, 2952, 1667, 1608, 1585, 1555, 1486, 1448, 1433, 1369, 1306, 1249, 1076, 912, 859, 836, 748, 693 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.98 (d, 1H, $J = 8.5$ Hz), 7.7-7.4 (m, 9H), 7.35 (m, 2H), 7.26 (dd, 1H, $J = 1.3, 8.4$ Hz), 7.16 (bd, 1H, $J = 7.8$ Hz), 5.75 (s, 2H), 5.62 (s, 1H), 5.61 (s, 1H), 3.66 (t, 2H, $J = 8.2$ Hz), 2.16 (s,

3H), 0.98 (t, 2H, J = 8.2 Hz), -0.02 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 169.8, 150.9, 144.6, 143.5, 142.8, 142.0, 139.4, 138.6, 132.9, 130.3, 129.3, 127.9, 125.6, 124.2, 123.7, 122.0, 121.3, 121.0, 117.1, 110.8, 68.0, 25.8, 19.1, 0.0; HRMS (FAB) $[\text{M}+\text{Na}]/z$ Calc'd 532.2396, Found 532.2410.

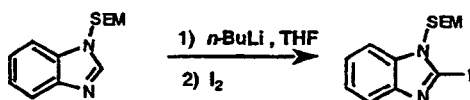
5 **Example 24(a_[LE50]): 4-[3-(1-*H*-Benzoimidazol-2-yl)-1-*H*-indazol-6-yl]-2-methoxy-5-methyl-phenol**



- 6-[5-Methoxy-2-methyl-4-[2-(trimethyl-silanyl)-ethoxymethoxy]-phenyl]-1-[2-(trimethyl-silanyl)-ethoxymethyl]-3-{1-[2-(trimethyl-silanyl)-ethoxymethyl]-1-*H*-benzamidazol-2-yl}-1-*H*-indazole (326 mg, 0.43 mmol) was stirred in a solution of TBAF (4.5 mL of 1 M in THF, which was concentrated *in vacuo* to 2.5 mL) and ethylenediamine (0.6 mL, 8.9 mmol) at reflux for 40 h. The reaction was diluted with ethyl acetate/THF (40 mL/5 mL) and washed with H_2O (20 mL) and brine (20 mL). Organics were dried (MgSO_4) and concentrated *in vacuo*. Purification by silica gel chromatography (60% THF/hexanes) and then precipitation from chloroform gave 108 mg (68%) of 4-[3-(1-*H*-benzoimidazol-2-yl)-1-*H*-indazol-6-yl]-2-methoxy-5-methyl-phenol as a white solid. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 13.62 (s, 1 H), 13.05 (br s, 1 H), 9.01 (s, 1 H), 8.50 (d, 1 H, J = 8.4 Hz), 7.62 (br s, 2 H), 7.49 (s, 1 H), 7.28-7.20 (m, 3 H), 6.85 (s, 1 H), 6.74 (s, 1 H), 3.77 (s, 3 H), 2.15 (s, 3 H). Anal. ($\text{C}_{22}\text{H}_{14}\text{N}_4\text{O}_2 \cdot 1.3 \text{H}_2\text{O}$) C, H, N. Calculated: C, 67.10; H, 5.27; N, 14.23. Found: C, 67.30; H, 5.27; N, 14.11.

The starting materials were prepared as follows:

(i)



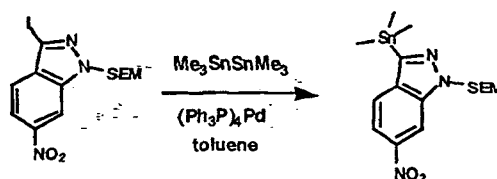
Preparation of 2-iodo-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1*H*-benzoimidazole.

- 25 A solution of 1-[2-(trimethyl-silanyl)-ethoxymethyl]-1*H*-benzoimidazole (5.029 g, 20.25

546

mmol) (see Witten et al., *J. Org. Chem.*, 51, 1891-1894 (1986)) in THF (50 mL) was cooled to -78 °C and added dropwise over 12 min via cannula to a flask containing n-butyllithium (2.5 M in hexanes, 12.2 mL) in THF (30 mL) at -78 °C under argon. After stirring for 25 min at -78 °C, the flask was warmed to 0 °C for 10 min, then cooled again to -78 °C. This solution was then added via cannula to a second flask containing iodine (25.7 g, 101 mmol) in THF (50 mL) at -78 °C. Once the addition was complete (~5 min), the cooling bath was removed, and stirring was continued for 30 min. The reaction mixture was partitioned between ethyl acetate (500 mL) and water (100 mL). The organic layer was washed with saturated aqueous sodium metabisulfite (2 x 100 mL) to remove the dark iodine color, dried (MgSO₄), and concentrated *in vacuo*. Purification by flash chromatography (10% to 50% ethyl acetate/hexanes) yielded 4.79 g (63%) of pure 2-iodo-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1H-benzimidazole as a yellow solid. ¹H NMR (300 MHz, CDCl₃) δ 7.76-7.72 (m, 1 H), 7.54-7.51 (m, 1 H), 7.29-7.25 (m, 2 H), 5.54 (s, 2 H), 3.59 (t, 2 H, J = 8.1 Hz), 0.92 (t, 2 H, J = 8.1 Hz), -0.03 (s, 9 H). Anal. (C₁₃H₁₉IN₂OS) C, H. Calculated: C, 41.71; H, 5.12; I, 33.90; N, 7.48. Found: C, 41.90; H, 5.09; I, 34.00; N, 7.37.

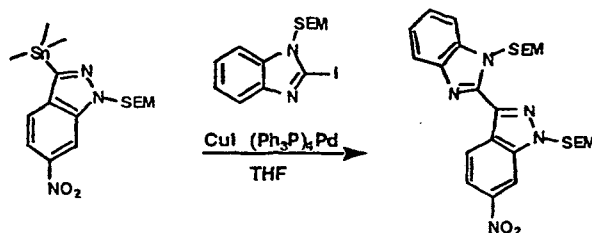
(ii)



Preparation of 6-nitro-1-[2-(trimethyl-silanyl)-ethoxymethyl]-3-(trimethyl-stannanyl)-1H-indazole: 3-Iodo-6-nitro-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1H-indazole (10.0 g, 23.9 mmol) and hexamethylditin (10.0 g, 30.5 mmol) were combined with dry toluene (45 mL) in a flask purged with argon. Tetrakis(triphenylphosphine)-palladium(0) (300 mg, 0.26 mmol) was added, and the reaction stirred at reflux under argon for 2.5 h. The reaction was cooled to 23 °C and diluted with ether (60 mL). Organics were washed with 0.1N HCl (20 mL) and brine (20 mL), dried (MgSO₄), and concentrated. Purification by silica gel chromatography (3% to 8% ether/hexanes) gave 7.70 g (71%) of 6-nitro-1-[2-(trimethyl-silanyl)-ethoxymethyl]-3-(trimethyl-stannanyl)-1H-indazole as a faintly yellow solid. ¹H NMR (300 MHz, CDCl₃) δ 8.53 (d, 1 H, J = 1.8 Hz), 8.03 (dd, 1 H, J = 8.7, 1.8 Hz), 7.81 (d, 1 H, J = 8.7 Hz), 5.84 (s, 2 H), 3.58 (t, 2 H, J = 8.1 Hz), 0.90 (t, 2 H, J = 8.1 Hz), 0.50 (t, 9 H, J = 28.2 Hz), -0.05 (s, 9 H). Anal.

(C₁₆H₂₇N₃O₃SiSn) C, H, N. Calculated: C, 42.13; H, 5.97; N, 9.21. Found: C, 42.39; H, 6.01; N, 9.26.

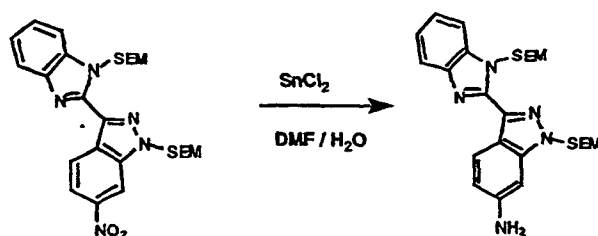
(iii)



- 5 Preparation of 6-nitro-1-[2-(trimethyl-silanyl)-ethoxymethyl]-3-{1-[2-(trimethyl-silanyl)-ethoxymethyl]-1-*H*-benzimidazol-2-yl}-1-*H*-indazole: 6-Nitro-1-[2-(trimethyl-silanyl)-ethoxymethyl]-3-(trimethyl-stannanyl)-1-*H*-indazole (7.50 g, 16.4 mmol), 3-iodo-1-[2-(trimethyl-silanyl)-ethoxymethyl]-1-*H*-benzimidazole (6.50 g, 17.4 mmol), and copper(I) iodide (313 mg, 1.64 mmol) were combined with dry THF (150 mL) in a flask
- 10 purged with argon. Tetrakis(triphenylphosphine)palladium(0) was added, and the reaction stirred at reflux under argon for 23 h. The reaction was cooled and adsorbed directly onto silica gel (~16 g). Purification by silica gel chromatography (4% to 15% ethyl acetate/hexanes) gave 7.28 g (82%) of 6-nitro-1-[2-(trimethyl-silanyl)-ethoxymethyl]-3-{1-[2-(trimethyl-silanyl)-ethoxymethyl]-1-*H*-benzimidazol-2-yl}-1-*H*-indazole as a light yellow solid. ¹H NMR (300 MHz, CDCl₃) δ 8.91 (d, 1 H, *J* = 9.0 Hz), 8.59 (d, 1 H, *J* = 1.8 Hz), 8.22 (dd, 1 H, *J* = 8.7, 1.8 Hz), 7.92-7.89 (m, 1 H), 7.66-7.62 (m, 1 H), 7.40-7.36 (m, 2 H), 6.24 (s, 2 H), 5.90 (s, 2 H), 3.68-3.59 (m, 4 H), 0.94 (t, 2 H, *J* = 8.1 Hz), 0.86 (t, 2 H, *J* = 8.1 Hz), -0.04 (s, 9 H), -0.15 (s, 9 H). Anal. (C₂₆H₃₇N₅O₄Si₂) C, H, N. Calculated: C, 57.85; H, 6.91; N, 12.97. Found: C, 57.60; H, 6.81; N, 12.82.

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(iv)

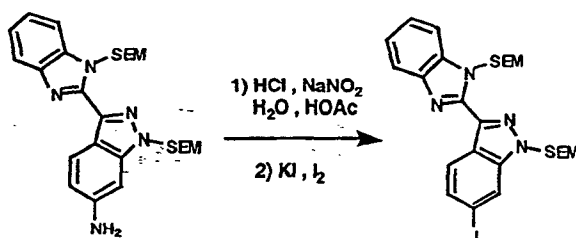


Preparation of 6-Amino-1-[2-(trimethyl-silanyl)-ethoxymethyl]-3-{1-[2-(trimethyl-silanyl)-ethoxymethyl]-1-*H*-benzimidazol-2-yl}-1-*H*-indazole: Tin(II) chloride (12.0 g, 63.3 mmol) was added to a solution of 6-nitro-1-[2-(trimethyl-silanyl)-ethoxymethyl]-3-{1-[2-(trimethyl-silanyl)-ethoxymethyl]-1-*H*-benzimidazol-2-yl}-1-*H*-indazole (7.28 g, 16.4 mmol) in DMF (100 mL) and H₂O (10 mL) at room temperature. The mixture was stirred for 24 h, then poured into water and extracted with ethyl acetate. The combined organic layers were washed with water, dried with Na₂SO₄, and concentrated under reduced pressure to give a crude product. Purification by silica gel chromatography (4% to 15% ethyl acetate/hexanes) gave 6.50 g (89%) of 6-amino-1-[2-(trimethyl-silanyl)-ethoxymethyl]-3-{1-[2-(trimethyl-silanyl)-ethoxymethyl]-1-*H*-benzimidazol-2-yl}-1-*H*-indazole as a light yellow solid. ¹H NMR (300 MHz, CDCl₃) δ 8.91 (d, 1 H, *J* = 9.0 Hz), 8.59 (d, 1 H, *J* = 1.8 Hz), 8.22 (dd, 1 H, *J* = 8.7, 1.8 Hz), 7.92-7.89 (m, 1 H), 7.66-7.62 (m, 1 H), 7.40-7.36 (m, 2 H), 6.24 (s, 2 H), 5.90 (s, 2 H), 3.68-3.59 (m, 4 H), 0.94 (t, 2 H, *J* = 8.1 Hz), 0.86 (t, 2 H, *J* = 8.1 Hz), -0.04 (s, 9 H), -0.15 (s, 9 H). Anal. (C₂₆H₃₇N₅O₄Si₂) C, H, N. Calculated: C, 57.85; H, 6.91; N, 12.97. Found: C, 57.60; H, 6.81; N, 12.82.

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ethoxymethyl]-3-{1-[2-(trimethyl-silanyl)-ethoxymethyl]-1-*H*-benzoimidazol-2-yl]-1-*H*-indazole (7.18 g, 13.3 mmol) in DMF/H₂O (160 mL/10 mL), and the reaction stirred at 50 °C for 2.5 h. The reaction was cooled to 0 °C, and saturated sodium bicarbonate was added slowly, with mixing, until all frothing from quenching had subsided. The material was concentrated *in vacuo* and taken up in ether (100 mL). Insoluble material was removed by filtration and rinsed with ether (50 mL). The filtrate was washed with brine (50 mL), dried (Na₂SO₄), and concentrated *in vacuo*. Purification by silica gel chromatography (25% ethyl acetate/hexane) gave 6.05 g (89%) of 6-amino-1-[2-(trimethyl-silanyl)-ethoxymethyl]-3-{1-[2-(trimethyl-silanyl)-ethoxymethyl]-1-*H*-benzoimidazol-2-yl]-1-*H*-indazole as a faintly yellow waxy solid. ¹H NMR (300 MHz, CDCl₃) δ 8.40 (d, 1 H, J = 9.0 Hz), 7.89-7.86 (m, 1 H), 7.63-7.60 (m, 1 H), 7.35-7.31 (m, 2 H), 6.78 (dd, 1 H, J = 8.7, 1.8 Hz), 6.75 (s, 1 H), 6.25 (s, 2 H), 5.69 (s, 2 H), 3.93 (br s, 2 H), 3.65-3.55 (m, 4 H), 0.93 (t, 2 H, J = 8.1 Hz), 0.85 (t, 2 H, J = 8.1 Hz), -0.04 (s, 9 H), -0.15 (s, 9 H). Anal. (C₂₆H₃₉N₅O₂Si₂) C, H, N. Calculated: C, 61.26; H, 7.71; N, 13.74. Found: C, 61.18; H, 7.65; N, 13.82.

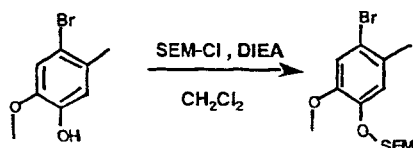
(v)



Preparation of 6-iodo-1-[2-(trimethyl-silanyl)-ethoxymethyl]-3-{1-[2-(trimethyl-silanyl)-ethoxymethyl]-1-*H*-benzoimidazol-2-yl]-1-*H*-indazole: A solution of 6-amino-1-[2-(trimethyl-silanyl)-ethoxymethyl]-3-{1-[2-(trimethyl-silanyl)-ethoxymethyl]-1-*H*-benzoimidazol-2-yl]-1-*H*-indazole (500 mg, 0.98 mmol) in acetic acid (1.5 mL) was diluted with H₂O (1.0 mL) and stirred at 0 °C. Concentrated HCl (250 µL, ~ 3 mmol) in H₂O (250 µL) was added. Sodium nitrate (90 mg, 1.3 mmol) in H₂O (300 µL) was added, and the reaction stirred for 8 min. Iodine (10 mg) and a solution of potassium iodide (250 mg, 1.3 mmol) in H₂O (250 µL) were added, and the frothing reaction stirred for 30 min at 23 °C. The reaction was diluted with H₂O (25 mL) and extracted with ethyl acetate (2 x 20 mL). Organics were washed with saturated sodium metabisulfite solution (10 mL) and brine (10 mL), dried (Na₂SO₄), and concentrated *in vacuo*. Purification by silica gel

chromatography (8% ethyl acetate/hexanes) gave 316 mg (52%) of 6-iodo-1-[2-(trimethyl-silanyl)-ethoxymethyl]-3-{1-[2-(trimethyl-silanyl)-ethoxymethyl]-1-*H*-benzoimidazol-2-yl}-1-*H*-indazole as a faintly yellow oil, which slowly crystallized to a white solid. ¹H NMR (300 MHz, CDCl₃) δ 8.45 (d, 1 H, J = 9.0 Hz), 8.05 (s, 1 H), 7.91-7.88 (m, 1 H), 7.67-7.62 (m, 2 H), 7.38-7.34 (m, 2 H), 6.24 (s, 2 H), 5.77 (s, 2 H), 3.65-3.57 (m, 4 H), 0.93 (t, 2 H, J = 8.1 Hz), 0.85 (t, 2 H, J = 8.1 Hz), -0.04 (s, 9 H), -0.15 (s, 9 H). Anal. (C₂₆H₃₇IN₂O₂Si₂) C, H, N. Calculated: C, 50.31; H, 6.01; N, 9.03. Found: C, 50.55; H, 6.08; N, 9.00.

(vi)



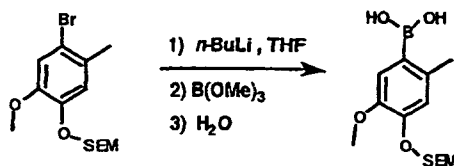
10

Preparation of [2-(4-bromo-2-methoxy-5-methyl-phenoxy-methoxy)-ethyl]-trimethyl-silane: 4-Bromo-2-methoxy-5-methyl-phenol (see Chien-Hsun et al., *Syn. Lett.*, 12, 1351-1352 (1997)) was stirred in dry CH₂Cl₂ (100 mL) at 23 °C. DIEA (6.05 mL, 34.6 mmol), and then 2-(trimethylsilyl)ethoxymethyl chloride (5.6 mL, 31.7 mmol) were added. After stirring for 1 h, the solution was washed with H₂O, 0.1 N HCl, H₂O, saturated NaHCO₃, and brine (25 mL each). Organics were dried (Na₂SO₄) and concentrated *in vacuo*. Purification by silica gel chromatography (6% ethyl acetate/hexanes) gave 9.06 g (91%) of [2-(4-bromo-2-methoxy-5-methyl-phenoxy-methoxy)-ethyl]-trimethyl-silane as a clear oil. ¹H NMR (300 MHz, CDCl₃) δ 7.06 (s, 1 H), 7.02 (s, 1 H), 5.24 (s, 2 H), 3.84 (s, 3 H), 3.79 (t, 2 H, J = 8.4 Hz), 2.31 (s, 3 H), 0.96 (t, 2 H, J = 8.4 Hz), 0.01 (s, 9 H).

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(vii)



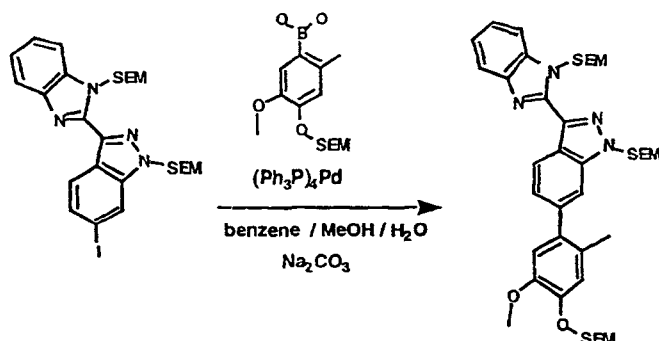
25

Preparation of 5-methoxy-2-methyl-4-[2-(trimethyl-silanyl)-ethoxymethoxy]-phenyl-boronic acid: [2-(4-Bromo-2-methoxy-5-methyl-phenoxy-methoxy)-ethyl]-trimethyl-silane (2.6 g, 7.5 mmol) was stirred in dry THF (10 mL) at -78 °C under argon. *n*-Butyllithium (3.75 mL, 2.5 M in hexanes, 9.36 mmol) was added dropwise, and the reaction stirred for 30 min before it was transferred via cannula to a flask of trimethyl

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borate (8.4 mL, 75 mmol) in THF (15 mL), which was also stirring at -78 °C under argon. After addition was complete, the reaction stirred 30 min at -78 °C and then 30 min while warming to 0 °C. It was then quenched with H₂O (20 mL), acidified with 0.1 N HCl, and extracted with ethyl acetate (2 x 25 mL). Organics were washed with brine (20 mL), dried (Na₂SO₄), and concentrated *in vacuo*. Purification by silica gel chromatography (20% to 50% ethyl acetate/hexanes) gave 1.11 g (47%) of 5-methoxy-2-methyl-4-[2-(trimethyl-silanyl)-ethoxymethoxy]-phenyl-boronic acid as a white solid. ¹H NMR (300 MHz, CDCl₃) δ 7.78 (s, 1 H), 7.10 (s, 1 H), 5.36 (s, 2 H), 3.93 (s, 3 H), 3.83 (t, 2 H, J = 8.4 Hz), 2.79 (s, 3 H), 0.98 (t, 2 H, J = 8.4 Hz), 0.01 (s, 9 H). Anal. (C₁₄H₂₅BO₃Si - H₂O) C, H. Calculated: C, 57.15; H, 7.88. Found: C, 56.89; H, 7.87.

(viii)

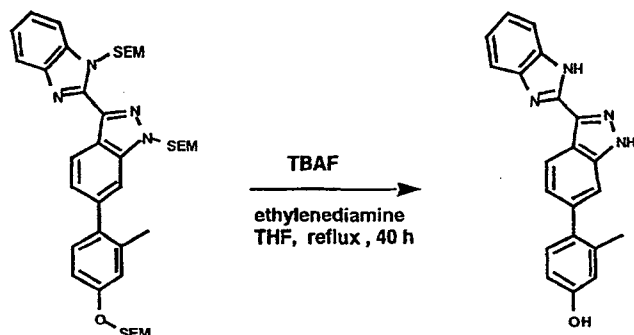


Preparation of 6-{5-methoxy-2-methyl-4-[2-(trimethyl-silanyl)-ethoxymethoxy]-phenyl}-1-[2-(trimethyl-silanyl)-ethoxymethyl]-3-{1-[2-(trimethyl-silanyl)-ethoxymethyl]-1-*H*-benzamidazol-2-yl}-1-*H*-indazole. 6-Iodo-1-[2-(trimethyl-silanyl)-ethoxymethyl]-3-{1-[2-(trimethyl-silanyl)-ethoxymethyl]-1-*H*-benzamidazol-2-yl}-1-*H*-indazole (350 mg, 0.56 mmol), 5-methoxy-2-methyl-4-[2-(trimethyl-silanyl)-ethoxymethoxy]-phenyl-boronic acid (211 mg, 0.68 mmol), and sodium carbonate (72 mg, 0.68 mmol) were stirred in a mixture of benzene (5 mL), H₂O (330 µL), and methanol (1 mL) in a flask purged with argon. Tetrakis(triphenylphosphine)palladium(0) was added, and the reaction stirred at reflux under argon for 16 h. After cooling to 23 °C, the reaction was diluted with ether (20 mL), washed with H₂O (10 mL) and brine (10 mL), dried (Na₂SO₄), and concentrated *in vacuo*. Purification by silica gel chromatography (15% ethyl acetate/hexanes) gave 382 mg (89%) of 6-{5-methoxy-2-methyl-4-[2-(trimethyl-silanyl)-ethoxymethoxy]-phenyl}-1-[2-(trimethyl-silanyl)-ethoxymethyl]-3-{1-[2-(trimethyl-silanyl)-ethoxymethyl]-1-*H*-benzamidazol-2-yl}-1-*H*-indazole as a white solid. ¹H NMR (300 MHz, CDCl₃) δ 8.68 (d, 1 H, J = 8.4 Hz), 7.93-7.90 (m, 1 H), 7.67-

7.63 (m, 1 H), 7.54 (s, 1 H), 7.38-7.32 (m, 3 H), 7.13 (s, 1 H), 6.86 (s, 1 H), 6.29 (s, 2 H), 5.83 (s, 2 H), 5.34 (s, 2 H), 3.89 (s, 3 H), 3.86 (t, 2 H, $J = 8.4$ Hz), 3.69-3.58 (m, 4 H), 2.22 (s, 3 H), 1.01 (t, 2 H, $J = 8.4$ Hz), 0.95-0.83 (m, 4 H), 0.03 (s, 9 H), -0.05 (s, 9 H), -0.15 (s, 9 H). Anal. ($C_{40}H_{60}N_4O_5Si_3$) C, H, N. Calculated: C, 63.12; H, 7.95; N, 7.36.

5 Found: C, 63.22; H, 7.93; N, 7.46.

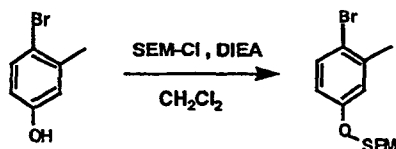
Example 24(b_[LE51]): 4-[3-(1-*H*-Benzoimidazol-2-yl)-1-*H*-indazol-6-yl]-3-methyl-phenol



To prepare the title compound, the procedure described for Example 24(a) was followed, with 2-methyl-4-[2-(trimethyl-silanyl)-ethoxymethoxy]-phenyl-boronic acid (prepared as described below) substituted for 5-methoxy-2-methyl-4-[2-(trimethyl-silanyl)-ethoxymethoxy]-phenyl-boronic acid in step (viii). ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.60 (s, 1 H), 12.99 (br s, 1 H), 9.41 (s, 1 H), 8.49 (d, 1 H, $J = 8.4$ Hz), 7.72 (br s, 1 H), 7.52 (br s, 1 H), 7.45 (s, 1 H), 7.25-7.21 (m, 3 H), 7.12 (d, 1 H, $J = 8.1$ Hz), 6.73-6.67 (m, 2 H), 2.20 (s, 3 H). Anal. ($C_{21}H_{16}N_4O \cdot 0.7 H_2O$) C, H, N. Calculated: C, 71.45; H, 4.97; N, 15.87. Found: C, 71.44; H, 4.96; N, 15.77.

2-Methyl-4-[2-(trimethyl-silanyl)-ethoxymethoxy]-phenyl-boronic acid was prepared as follows:

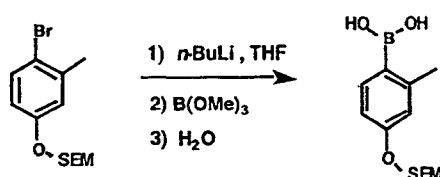
(i)



[2-(4-Bromo-3-methyl-phenoxy-methoxy)-ethyl]-trimethyl-silane was prepared in 86% yield from 4-bromo-3-methyl-phenol according to the procedure for [2-(4-bromo-2-methoxy-5-methyl-phenoxy-methoxy)-ethyl]-trimethyl-silane. ¹H NMR (300 MHz, CDCl₃) δ 7.39 (d, 1 H, $J = 8.7$ Hz), 6.93 (d, 1 H, $J = 2.7$ Hz), 6.75 (dd, 1 H, $J = 8.7, 2.7$

Hz), 5.16 (s, 2 H), 3.74 (t, 2 H, $J = 8.4$ Hz), 2.36 (s, 3 H), 0.95 (t, 2 H, $J = 8.4$ Hz), 0.01 (s, 9 H). Anal. ($C_{13}H_{21}BrO_2Si$) C, H. Calculated: C, 49.21; H, 6.67. Found: C, 49.33; H, 6.67.

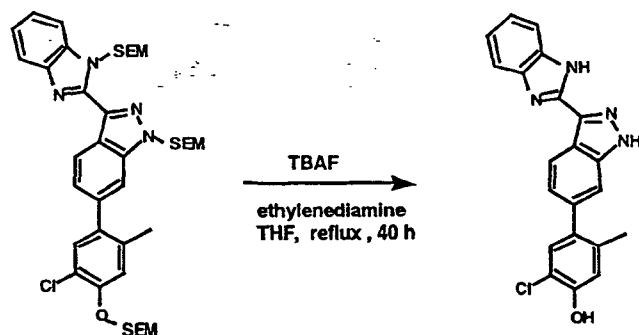
(ii)



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2-Methyl-4-[2-(trimethyl-silanyl)-ethoxymethoxy]-phenyl-boronic acid was prepared in 52% yield from [2-(4-bromo-3-methyl-phenoxy-methoxy)-ethyl]-trimethyl-silane according to the procedure for 5-methoxy-2-methyl-4-[2-(trimethyl-silanyl)-ethoxymethoxy]-phenyl-boronic acid above. ^1H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, 1 H, $J = 8.1$ Hz), 6.98-6.92 (m, 2 H), 5.29 (s, 2 H), 3.78 (t, 2 H, $J = 8.4$ Hz), 2.78 (s, 3 H), 0.98 (t, 2 H, $J = 8.4$ Hz), 0.01 (s, 9 H). Anal. ($C_{13}H_{23}BO_4Si - H_2O$) C, H. Calculated: C, 59.10; H, 8.01. Found: C, 59.07; H, 8.08.

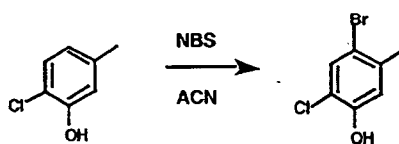
Example 24(c)_{LES21}): 4-[3-(1-*H*-Benzoimidazol-2-yl)-1-*H*-indazol-6-yl]-2-chloro-5-methyl-phenol



To prepare the title compound, 5-chloro-2-methyl-4-[2-(trimethyl-silanyl)-ethoxymethoxy]-phenyl-boronic acid, prepared as described below, was substituted for 5-methoxy-2-methyl-4-[2-(trimethyl-silanyl)-ethoxymethoxy]-phenyl-boronic acid in the procedure described in Example 24(a), step (viii). ^1H NMR (300 MHz, $DMSO-d_6$) δ 13.61 (s, 1 H), 13.00 (br s, 1 H), 10.22 (s, 1 H), 8.51 (d, 1 H, $J = 8.4$ Hz), 7.64 (br s, 2 H), 7.50 (s, 1 H), 7.26-7.21 (m, 4 H), 6.95 (s, 1 H), 2.19 (s, 3 H).

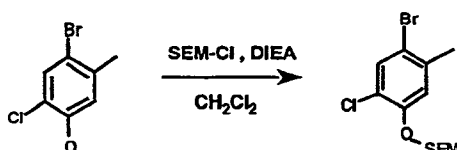
5-Chloro-2-methyl-4-[2-(trimethyl-silanyl)-ethoxymethoxy]-phenyl-boronic acid was prepared as follows:

(i)



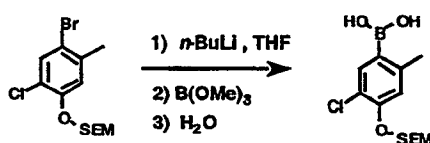
2-Chloro-5-methyl-phenol (6.68 g, 46.9 mmol) was stirred in acetonitrile (200 mL). *N*-Bromosuccinimide (8.5 g, 47.8 mmol) was added, and the reaction stirred for 45 min. The solution was concentrated *in vacuo* and re-dissolved in chloroform (100 mL). Organics were washed with saturated NaHCO_3 (50 mL) and brine (50 mL), dried (MgSO_4), and concentrated *in vacuo*. Purification by silica gel chromatography (8% ethyl acetate/hexanes) gave 7.98 g (77%) of 4-bromo-3-chloro-5-methyl-phenol as a clear oil. ^1H NMR (300 MHz, CDCl_3) δ 7.47 (s, 1 H), 6.91 (s, 1 H), 5.52 (br s, 1 H), 2.32 (s, 3 H). Anal. ($\text{C}_7\text{H}_6\text{ClBrO} \cdot 0.1 \text{ H}_2\text{O}$) C, H. Calculated: C, 37.66; H, 2.80. Found: C, 37.57; H, 2.82.

(ii)



[2-(4-Bromo-2-chloro-5-methyl-phenoxymethoxy)-ethyl]-trimethyl-silane was prepared in 83% yield from 4-bromo-3-chloro-5-methyl-phenol according to the procedure for [2-(4-bromo-2-methoxy-5-methyl-phenoxymethoxy)-ethyl]-trimethyl-silane. ^1H NMR (300 MHz, CDCl_3) δ 7.51 (s, 1 H), 7.09 (s, 1 H), 5.26 (s, 2 H), 3.79 (t, 2 H, $J = 8.4$ Hz), 2.35 (s, 3 H), 0.95 (t, 2 H, $J = 8.4$ Hz), 0.02 (s, 9 H). Anal. ($\text{C}_{13}\text{H}_{20}\text{ClBrO}_2\text{Si}$) C, H. Calculated: C, 44.39; H, 5.73. Found: C, 45.08; H, 5.91.

(iii)



5-Chloro-2-methyl-4-[2-(trimethyl-silanyl)-ethoxymethoxy]-phenyl-boronic acid was prepared in 54% yield from [2-(4-bromo-2-chloro-5-methyl-phenoxymethoxy)-ethyl]-trimethyl-silane according to the procedure for 5-methoxy-2-methyl-4-[2-(trimethyl-silanyl)-ethoxymethoxy]-phenyl-boronic acid. ^1H NMR (300 MHz, CDCl_3) δ 8.11 (s, 1 H), 7.09 (s, 1 H), 5.37 (s, 2 H), 3.84 (t, 2 H, $J = 8.4$ Hz), 2.76 (s, 3 H), 0.98 (t, 2

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H, J = 8.4 Hz), 0.01 (s, 9 H). Anal. (C₁₃H₂₂BClO₄Si - H₂O) C, H. Calculated: C, 52.28; H, 6.75. Found: C, 51.98; H, 6.84.

The exemplary compounds described above may be tested for their activity using the tests described below.

5 BIOLOGICAL TESTING; ENZYME ASSAYS

The stimulation of cell proliferation by growth factors such as VEGF, FGF, and others is dependent upon their induction of autophosphorylation of each of their respective receptor's tyrosine kinases. Therefore, the ability of a protein kinase inhibitor to block cellular proliferation induced by these growth factors is directly correlated with its ability to block receptor autophosphorylation. To measure the protein kinase inhibition activity of the compounds, the following constructs were devised.

VEGF-R2 Construct for Assay: This construct determines the ability of a test compound to inhibit tyrosine kinase activity. A construct (VEGF-R2Δ50) of the cytosolic domain of human vascular endothelial growth factor receptor 2 (VEGF-R2) lacking the 50 central residues of the 68 residues of the kinase insert domain was expressed in a baculovirus/insect cell system. Of the 1356 residues of full-length VEGF-R2, VEGF-R2Δ50 contains residues 806-939 and 990-1171, and also one point mutation (E990V) within the kinase insert domain relative to wild-type VEGF-R2. Autophosphorylation of the purified construct was performed by incubation of the enzyme at a concentration of 4 μM in the presence of 3 mM ATP and 40 mM MgCl₂ in 100 mM HEPES, pH 7.5, containing 5% glycerol and 5 mM DTT, at 4 °C for 2 h. After autophosphorylation, this construct has been shown to possess catalytic activity essentially equivalent to the wild-type autophosphorylated kinase domain construct. See Parast et al., *Biochemistry*, 37, 16788-16801 (1998).

FGF-R1 Construct for Assay: The intracellular kinase domain of human FGF-R1 was expressed using the baculovirus vector expression system starting from the endogenous methionine residue 456 to glutamate 766, according to the residue numbering system of Mohammadi et al., *Mol. Cell. Biol.*, 16, 977-989 (1996). In addition, the construct also has the following 3 amino acid substitutions: L457V, C488A, and C584S.

LCK Construct for Assay: The LCK tyrosine kinase was expressed in insect cells as an N-terminal deletion starting from amino acid residue 223 to the end of the protein at residue 509, with the following two amino acid substitutions at the N-terminus: P233M and C224D.

CHK-1 Construct for Assay: C-terminally His-tagged full-length human CHK-1 (FL-CHK-1) was expressed using the baculovirus/insect cell system. It contains 6 histidine residues (6 x His-tag) at the C-terminus of the 476 amino acid human CHK-1. The protein was purified by conventional chromatographic techniques.

5 CDK2/Cyclin A Construct for Assay: CDK2 was purified using published methodology (Rosenblatt et al., *J. Mol. Biol.*, 230, 1317-1319 (1993)) from insect cells that had been infected with a baculovirus expression vector. Cyclin A was purified from *E. coli* cells expressing full-length recombinant cyclin A, and a truncated cyclin A construct was generated by limited proteolysis and purified as described previously (Jeffrey et al., *Nature*,
10 376, 313-320 (1995)).

CDK4/Cyclin D Construct for Assay: A complex of human CDK4 and cyclin D3, or a complex of cyclin D1 and a fusion protein of human CDK4 and glutathione-S-transferase (GST-CDK4), was purified using traditional biochemical chromatographic techniques from insect cells that had been co-infected with the corresponding baculovirus expression vectors.

15 VEGF-R2 Assay

Coupled Spectrophotometric (FLVK-P) Assay

The production of ADP from ATP that accompanies phosphoryl transfer was coupled to oxidation of NADH using phosphoenolpyruvate (PEP) and a system having pyruvate kinase (PK) and lactic dehydrogenase (LDH). The oxidation of NADH was monitored by
20 following the decrease of absorbance at 340 nm ($\epsilon_{340} = 6.22 \text{ cm}^{-1} \text{ mM}^{-1}$) using a Beckman DU 650 spectrophotometer. Assay conditions for phosphorylated VEGF-R2 Δ 50 (indicated as FLVK-P in the tables below) were the following: 1 mM PEP; 250 μ M NADH; 50 units of LDH/mL; 20 units of PK/mL; 5 mM DTT; 5.1 mM poly(E_4Y_1); 1 mM ATP; and 25 mM $MgCl_2$ in 200 mM HEPES, pH 7.5. Assay conditions for unphosphorylated VEGF-R2 Δ 50
25 (indicated as FLVK in the tables) were the following: 1 mM PEP; 250 μ M NADH; 50 units of LDH/mL; 20 units of PK/mL; 5 mM DTT; 20 mM poly(E_4Y_1); 3 mM ATP; and 60 mM $MgCl_2$ and 2 mM $MnCl_2$ in 200 mM HEPES, pH 7.5. Assays were initiated with 5 to 40 nM of enzyme. K_i values were determined by measuring enzyme activity in the presence of varying concentrations of test compounds. The data were analyzed using Enzyme Kinetic and
30 Kaleidagraph software.

ELISA Assay

Formation of phosphogastrin was monitored using biotinylated gastrin peptide (1-17) as substrate. Biotinylated phosphogastrin was immobilized using streptavidin coated 96-well microtiter plates followed by detection using anti-phosphotyrosine-antibody conjugated to horseradish peroxidase. The activity of horseradish peroxidase was monitored using 2,2'-azino-di-[3-ethylbenzthiazoline sulfonate(6)] diammonium salt (ABTS). Typical assay solutions contained: 2 μ M biotinylated gastrin peptide; 5 mM DTT; 20 μ M ATP; 26 mM $MgCl_2$; and 2 mM $MnCl_2$ in 200 mM HEPES, pH 7.5. The assay was initiated with 0.8 nM of phosphorylated VEGF-R2 Δ 50. Horseradish peroxidase activity was assayed using ABTS, 10 mM. The horseradish peroxidase reaction was quenched by addition of acid (H_2SO_4), followed by absorbance reading at 405 nm. K_i values were determined by measuring enzyme activity in the presence of varying concentrations of test compounds. The data were analyzed using Enzyme Kinetic and Kaleidagraph software.

FGF-R Assay

The spectrophotometric assay was carried out as described above for VEGF-R2, except for the following changes in concentration: FGF-R = 50 nM, ATP = 2 mM, and poly(E4Y1) = 15 mM.

LCK Assay

The spectrophotometric assay was carried out as described above for VEGF-R2, except for the following changes in concentration: LCK = 60 nM, $MgCl_2$ = 0 mM, poly(E4Y1) = 20 mM.

CHK-1 Assay

The production of ADP from ATP that accompanies phosphoryl transfer to the synthetic substrate peptide Syntide-2 (PLARTLSVAGLPGKK) was coupled to oxidation of NADH using phosphoenolpyruvate (PEP) through the actions of pyruvate kinase (PK) and lactic dehydrogenase (LDH). The oxidation of NADH was monitored by following the decrease of absorbance at 340 nm ($\epsilon_{340} = 6.22 \text{ cm}^{-1} \text{ mM}^{-1}$) using a HP8452 spectrophotometer. Typical reaction solutions contained: 4 mM PEP; 0.15 mM NADH; 28 units of LDH/mL; 16 units of PK/mL; 3 mM DTT; 0.125 mM Syntide-2; 0.15 mM ATP; 25 mM $MgCl_2$ in 50 mM TRIS, pH 7.5; and 400 mM NaCl. Assays were initiated with 10 nM of FL-CHK-1. K_i values were determined by measuring initial enzyme activity in the presence of varying concentrations of test compounds. The data were analyzed using Enzyme Kinetic and Kaleidagraph software.

CDK2/Cyclin A and CDK4/Cyclin D Assays

Cyclin-dependent kinase activity was measured by quantifying the enzyme-catalyzed, time-dependent incorporation of radioactive phosphate from [^{32} P]ATP into a recombinant fragment of the retinoblastoma protein. Unless noted otherwise, assays were performed in 96-well plates in a total volume of 50 μ L, in the presence of 10 mM HEPES (N-[2-hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid]) (pH 7.4), 10 mM MgCl₂, 25 μ M adenosine triphosphate (ATP), 1 mg/mL ovalbumin, 5 μ g/mL leupeptin, 1 mM dithiothreitol, 10 mM β -glycerophosphate, 0.1 mM sodium vanadate, 1 mM sodium fluoride, 2.5 mM ethylene glycol-bis(β -aminoethyl ether)-N,N,N',N'-tetraacetic acid (EGTA), 2% (v/v) dimethylsulfoxide, and 0.03 - 0.2 μ Ci [^{32} P]ATP. The substrate (0.3-0.5 μ g) was purified recombinant retinoblastoma protein fragment (Rb) (residues 386-928 of the native retinoblastoma protein; 62.3 kDa, containing the majority of the phosphorylation sites found in the native 106-kDa protein, as well as a tag of six histidine residues for ease of purification). Reactions were initiated with CDK2 (150 nM CDK2/Cyclin A complex) or CDK4 (50 nM CDK4/Cyclin D3 complex), incubated at 30°C, and terminated after 20 minutes (min.) by the addition of ethylenediaminetetraacetic acid (EDTA) to 250 mM. The phosphorylated substrate was then captured on a nitrocellulose membrane using a 96-well filtration manifold, and unincorporated radioactivity was removed by repeated washing with 0.85% phosphoric acid. Radioactivity was quantified by exposing the dried nitrocellulose membranes to a phosphorimager. Apparent K_i values were measured by assaying enzyme activity in the presence of different compound concentrations and subtracting the background radioactivity measured in the absence of enzyme. The kinetic parameters (k_{cat} , K_m for ATP) were measured for each enzyme under the usual assay conditions by determining the dependence of initial rates on ATP concentration. The data were fit to an equation for competitive inhibition using Kaleidagraph (Synergy Software), or were fit to an equation for competitive tight-binding inhibition using the software KineTic (BioKin, Ltd.). Measured K_i values for known inhibitors against CDK4 and CDK2 agreed with published IC_{50} values. The specific activity of CDK4 was the same whether complexed to full-length cyclin D3 or the truncated Cyclin D3 construct; both complexes also yielded very similar K_i values for selected inhibitors.

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To determine the whether a protein kinases inhibitor should have therapeutic usefulness in treating cancer, it is important to demonstrate the inhibitor's ability to block cellular proliferation in response to a growth factor that is involved in mediating a proliferative disorder. The protocol for assessing cellular proliferation in cancer cells is similar to that used for assessments in HUVEC cells. Two thousand lung cancer cells (line MV522, acquired from American Tissue Cultural Collection) were seeded in growth media (RPMI1640 medium supplemented with 2 mM glutamine and 10% FBS). Cells are allowed to attach for 1 day prior to addition of test agents and /or vehicles. Cells are treated simultaneously with the same test agents used in the HUVEC assay. Cellular proliferation is quantified by MTT dye reduction assay 72 hours after exposure to test

agents. The total length of the assay is 4 days vs. 5 for HUVEC cells because MV522 cells are not exposed to starvation medium.

Mouse PK Assay

The pharmacokinetics (e.g., absorption and elimination) of drugs in mice were analyzed using the following experiment. Test compounds were formulated as a suspension in a 30:70 (PEG 400: acidified H₂O) vehicle. This solution was administered orally (p.o.) and intraperitoneally (i.p.) at 50 mg/kg to two distinct groups (n=4) of B6 female mice. Blood samples were collected via an orbital bleed at time points: 0 hour (pre-dose), 0.5 hr, 1.0 hr, 2.0 hr, and 4.0 hr post dose. Plasma was obtained from each sample by centrifugation at 2500 rpm for 5 min. Test compound was extracted from the plasma by an organic protein precipitation method. For each time bleed 50 μ L of plasma was combined with 1.0 mL of acetonitrile, vortexed for 2 min. and then spun at 4000 rpm for 15 min. to precipitate the protein and extract out the test compound. Next, the acetonitrile supernatant (the extract containing test compound) was poured into new test tubes and evaporated on a hot plate (25 $^{\circ}$ C) under a stream of N₂ gas. To each tube containing the dried test compound extract 125 μ L of mobile phase (60:40, 0.025 M NH₄H₂PO₄ +2.5 mL/L TEA:acetonitrile) was added. The test compound was resuspended in the mobile phase by vortexing and more protein was removed by centrifugation at 4000 rpm for 5 min. Each sample was poured into an HPLC vial for test compound analysis on an Hewlett Packard 1100 series HPLC with UV detection. From each sample, 95 μ L was injected onto a Phenomenex-Prodigy reverse phase C-18, 150 x 3.2 mm column and eluted with a 45-50% acetonitrile gradient run over 10 min. Test-compound plasma concentrations (μ g/mL) were determined by a comparison to standard curve (peak area vs. conc. μ g/mL) using known concentrations of test compound extracted from plasma samples in the manner described above. Along with the standards and unknowns, three groups (n=4) of quality controls (0.25 μ g/mL, 1.5 μ g/mL, and 7.5 μ g/mL) were run to insure the consistency of the analysis. The standard curve had an R²> 0.99 and the quality controls were all within 10 % of their expected values. The quantitated test samples were plotted for visual display using Kalidagraph software and their pharmacokinetic parameters were determined using WIN NONLIN software.

Human Liver Microsome (HLM) Assay

Compound metabolism in human liver microsomes was measured by LC-MS analytical assay procedures as follows. First, human liver microsomes (HLM) were thawed and diluted to 5 mg/mL with cold 100 mM potassium phosphate (KPO₄) buffer. Appropriate amounts of

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KPO4 buffer, NADPH-regenerating solution (containing B-NADP, glucose-6-phosphate, glucose-6-phosphate dehydrogenase, and MgCl₂), and HLM were preincubated in 13 x 100 mm glass tubes at 37 C for 10 min. (3 tubes per test compound--triplicate). Test compound (5 μM final) was added to each tube to initiate reaction and was mixed by gentle vortexing, followed by incubation at 37 C. At t=0, 2 h, a 250-μL sample was removed from each incubation tube to separate 12 x 75 mm glass tubes containing 1 mL ice-cold acetonitrile with 0.05 μM reserpine. Samples were centrifuged at 4000 rpm for 20 min. to precipitate proteins and salt (Beckman Allegra 6KR, S/N ALK98D06, #634). Supernatant was transferred to new 12 x 75 mm glass tubes and evaporated by Speed-Vac centrifugal vacuum evaporator. Samples were reconstituted in 200 μL 0.1% formic acid/acetonitrile (90/10) and vortexed vigorously to dissolve. The samples were then transferred to separate polypropylene microcentrifuge tubes and centrifuged at 14000 x g for 10 min. (Fisher Micro 14, S/N M0017580). For each replicate (#1-3) at each timepoint (0 and 2 h), an aliquot sample of each test compound was combined into a single HPLC vial insert (6 total samples) for LC-MS analysis, which is described below.

The combined compound samples were injected into the LC-MS system, composed of a Hewlett-Packard HP1100 diode array HPLC and a Micromass Quattro II triple quadrupole mass spectrometer operating in positive electrospray SIR mode (programmed to scan specifically for the molecular ion of each test compound. Each test compound peak was integrated at each timepoint. For each compound, peak area at each timepoint (n=3) was averaged, and this mean peak area at 2 h was divided by the average peak area at time 0 hour to obtain the percent test compound remaining at 2 h.

The results of the testing of the compounds using various assays are summarized in the table below, where a notation of "% @" indicates the percent inhibition at the stated concentration and "*" indicates the determination was made with ELISA assay rather than the spectrophotometric assay.

Ex. #	FLVK-P K _i (nM)	FLVK K _i (nM)	LCK K _i (nM)	CHK-1 K _i (nM)	FGF-P K _i (nM)	CDK2 K _i (nM)	CDK4 K _i (nM)	HUVEC IC ₅₀ (nM)	MV52 IC ₅₀ (μM)	Mouse 2 PKAUC ip μg- h/mL	Mouse PK Auc, po μg- h/mL	clog P (Log P)	%Rem aining (HLM, 2 h)
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Cell Lines

Ex. #	FLVK-P K _i (nM)	FLVK K _i (nM)	LCK K _i (nM)	CHK-1 K _i (nM)	FGF-P K _i (nM)	CDK2 K _i (nM)	CDK4 K _i (nM)	HUVEC IC ₅₀ (nM)	MV52 IC ₅₀ (μM)	Mouse 2 PKAUC ip μg- h/mL	Mouse PK AUC, po μg- h/mL	clog P (Log P)	%Rem aining (HLM, 2 h)
1(a)	0.3	2	88	5.2	27	19	13	54	0.35	0.69	0.33	4.65	
1(b)	2.2			1400		4000	1300	>1000	>10			6.76	
1(c)	1.4		46% at 1 μM	78		560	670	>1000	>10			5.42	
2(a)	40					610	1600	>1000	0.58			5.97	
2(b)	300*	425			228,000	2,200	8,000						
2(c)	2600*					>50,000	26,000						
2(d)	3.7		43% @ 1 μM		68	53	53	450	0.18			5.13	
2(e)	40											7.33	
3	6.6		37% at 1 μM	4.8	112	16	23	930	2.2			4.63	
4(a)	1.4	0.65			15.4			3				7.03	35
4(b)	2.7	1.9	13% @ 1 μM		4.9			25	3.2			5.54	63

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Ex. #	FLVK-P K _i (nM)	FLVK K _i (nM)	LCK K _i (nM)	CHK-1 K _i (nM)	FGF-P K _i (nM)	CDK2 K _i (nM)	CDK4 K _i (nM)	HUVEC IC ₅₀ (nM)	MV52 IC ₅₀ (μM)	Mouse 2 PKAUC ip μg- h/mL	Mouse PK Auc, po μg- h/mL	clog P (Log P)	%Rem aining (HLM, 2 h)
5(a)		0.03	28% @ 1 μM		10.4			16				6.83	
5(b)		0.9						5	8.5			7.53	
6(a)		0.74						13				7.74	
6(b)		0.15											
7	18											5.31	
8(a)	3.2	34	43% at 1 μM	530	42	> 100,000	> 100,000	>1000	>10			6.44	
8(b)	72			12% @ 50 μM								5.77	
8(c)	2.6	16	34% at 1 μM	>10,000		> 100,000	> 100,000	280	>10			6.25	
8(d)	10.5												
9(a)	2.4	16	162	400			1700	870	>10			5.88	
9(b)	24			448								5.88	

Ex. #	FLVK-P K _i (nM)	FLVK K _i (nM)	LCK K _i (nM)	CHK-1 K _i (nM)	FGF-P K _i (nM)	CDK2 K _i (nM)	CDK4 K _i (nM)	HUVEC IC ₅₀ (nM)	MV52 IC ₅₀ (μM)	Mouse PKAUC ip μg- h/mL	Mouse PK AUC, po μg- h/mL	clog P (Log P)	%Rem aining (HLM, 2 h)
10	9			9100				>700	>10			6.08	
11	12											5.01	
12(a)	6.9	1.8						10	2.1			5.26	
12(b)	1.8	0.48			31			12				6.75	29
12(c)	1.6											7.28	
12(d)		0.39						10				6.69	
13		1.3						5				6.59	
14	15											6.24	
15		15										4.58	
16(a)		0.08						6				6.31	
16(b)		0.34						8	>10			6.81	

Ex. #	FLVK-P K _i (nM)	FLVK K _i (nM)	LCK K _i (nM)	CHK-1 K _i (nM)	FGF-P K _i (nM)	CDK2 K _i (nM)	CDK4 K _i (nM)	HUVEC IC ₅₀ (nM)	MV52 IC ₅₀ (μM)	Mouse 2 PKAUC ip μg- h/mL	Mouse PK Auc, po μg- h/mL	clog P (Log P)	%Rem aining (HLM, 2 h)
16(c)		1.1						100 - 1000	>10			6.67	
16(d)		4.3						16	>10			7.55	
16(e)		1.3						6	>10			6.21	
17	11											5.43	
18	12.5											4.5	
19(a)	13.8	6.8						51				4.71	
19(b)	6.6	0.49						3.4				6.2	137
19(c)	5.9							30 - 300				6.64	
19(d)		0.72						5.7				5.78	
20(a)	29	12.7						200	9.4			5.27	52
20(b)	8	1.6						12				6.76	

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Ex. #	FLVK-P K _i (nM)	FLVK K _i (nM)	LCK K _i (nM)	CHK-1 K _i (nM)	FGF-P K _i (nM)	CDK2 K _i (nM)	CDK4 K _i (nM)	HUVEC IC ₅₀ (nM)	MV52 IC ₅₀ (μM)	Mouse 2 PKAUC ip μg- h/mL	Mouse PK AUC, po μg- h/mL	clog p (Log p)	%Rem aining (HLM, 2 h)
21	4.7							>700				4.85	
22(a)	0.2	0.22										6.53	
22(b)	1.2	0.63			21.5							6.59	
22(c)	0.64											7.12	
23	2.1	1.6	12% @ 1 μM		14% @ 50 μM			9.5	5.5			5.1	74
24(a)		98.3				20	5.1						
24(b)		33.1				25	3.2						
24(c)						4.8	1.5						

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The exemplary compounds described above may be formulated into pharmaceutical compositions according to the following general examples.

Example 1: Parenteral Composition

To prepare a parenteral pharmaceutical composition suitable for administration by
5 injection, 100 mg of a water-soluble salt of a compound of Formula I is dissolved in DMSO
and then mixed with 10 mL of 0.9% sterile saline. The mixture is incorporated into a dosage
unit form suitable for administration by injection.

Example 2: Oral Composition

To prepare a pharmaceutical composition for oral delivery, 100 mg of a compound of
10 Formula I is mixed with 750 mg of lactose. The mixture is incorporated into an oral dosage
unit for, such as a hard gelatin capsule, which is suitable for oral administration.

It is to be understood that the foregoing description is exemplary and explanatory
in nature, and is intended to illustrate the invention and its preferred embodiments.

15 Through routine experimentation, the artisan will recognize apparent modifications and
variations that may be made without departing from the spirit of the invention. Thus, the
invention is intended to be defined not by the above description, but by the following
claims and their equivalents.

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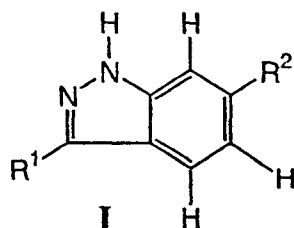
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CLAIMS

What is claimed is:

1. A compound of the Formula I



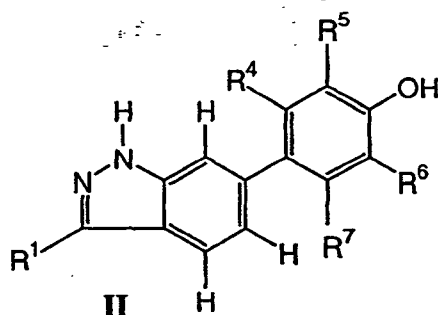
- 5 wherein:

R^1 is a substituted or unsubstituted aryl or heteroaryl, or a group of the formula $CH=CH-R^3$ or $CH=N-R^3$, where R^3 is a substituted or unsubstituted alkyl, alkenyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; and

- 10 R^2 is a substituted or unsubstituted aryl or $Y-Ar$, where Y is O, S, $C=CH_2$, $C=O$, $S=O$, SO_2 , CH_2 , $CHCH_3$, NH , or $N-(C_1-C_8 \text{ alkyl})$, and Ar is a substituted or unsubstituted aryl;

or a pharmaceutically acceptable prodrug, pharmaceutically active metabolite, or pharmaceutically acceptable salt thereof.

2. A compound of the Formula II:



- 15 wherein:

R^1 is a substituted or unsubstituted aryl or heteroaryl, or a group of the formula $CH=CH-R^3$ or $CH=N-R^3$, where R^3 is a substituted or unsubstituted alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

- 20 R^4 and R^7 are each independently hydrogen, OH, halo, C_1-C_8 alkyl, C_1-C_8 alkoxy, C_1-C_8 alkenyl, aryloxy, thioaryl, CH_2-OH , $CH_2-O-(C_1-C_8 \text{ alkyl})$, $CH_2-O-aryl$, $CH_2-S-(C_1-C_8 \text{ alkyl})$, or $CH_2-S-aryl$;

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R^5 and R^6 are each independently hydrogen, OH, halo, Z-alkyl, Z-aryl, or Z- $\text{CH}_2\text{CH}=\text{CH}_2$, where Z is O, S, NH, or CH_2 , and the alkyl and aryl moiety of Z-alkyl and Z-aryl are each optionally substituted;

or a pharmaceutically acceptable prodrug, pharmaceutically active metabolite, or

5 pharmaceutically acceptable salt thereof.

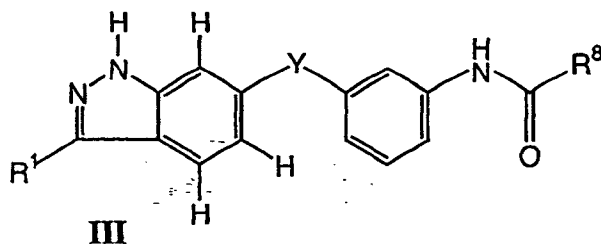
3. A compound according to claim 2, wherein:

R^1 is a substituted or unsubstituted bicyclic heteroaryl or a group of the formula $\text{CH}=\text{CH}-R^3$, where R^3 is a substituted or unsubstituted alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

10 R^4 and R^7 are each independently hydrogen, OH, halo, C_1-C_8 alkyl, or $\text{CH}_2-\text{O}-(\text{C}_1-\text{C}_8 \text{ alkyl})$; and

R^5 and R^6 are each independently hydrogen, OH, halo, Z-alkyl, Z-aryl, or Z- $\text{CH}_2\text{CH}=\text{CH}_2$, where Z is O, S, NH, or CH_2 , and each alkyl or aryl moiety is optionally substituted.

15 4. A compound of the Formula III:



wherein:

R^1 is a substituted or unsubstituted aryl or heteroaryl, or a group of the formula $\text{CH}=\text{CH}-R^3$ or $\text{CH}=\text{N}-R^3$, where R^3 is a substituted or unsubstituted alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

20 Y is O, S, $\text{C}=\text{CH}_2$, $\text{C}=\text{O}$, $\text{S}=\text{O}$, SO_2 , CH_2 , CHCH_3 , NH, or $\text{N}-(\text{C}_1-\text{C}_8 \text{ alkyl})$;

R^8 is a substituted or unsubstituted alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, or aryloxy;

or a pharmaceutically acceptable prodrug, pharmaceutically active metabolite, or pharmaceutically acceptable salt thereof.

25 5. A compound according to claim 4, wherein:

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ABSTRACT

Indazole compounds that modulate and/or inhibit the activity of certain protein kinases are described. These compounds and pharmaceutical compositions containing them are capable of mediating tyrosine kinase signal transduction and thereby modulate
5 and/or inhibit unwanted cell proliferation. The invention is also directed to the therapeutic or prophylactic use of pharmaceutical compositions containing such compounds, and to methods of treating cancer and other disease states associated with unwanted angiogenesis and/or cellular proliferation, such as diabetic retinopathy, neovascular glaucoma, rheumatoid arthritis, and psoriasis, by administering effective
10 amounts of such compounds.

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MARIA TERESA LARA R.
TRADUCTORA OFICIAL
RESOLUCION NO. 01016
DE MINJUSTICIA

NOTARIO PUBLICO DEL ESTADO DE CALIFORNIA
CIRCULO O HAGO CONSTAR QUE ESTA
FOTOCOPIA COINCIDE CON EL ORIGI-
NAL
24 AGO. 2000
BONNIE ACOSTA
NOTARIO PUBLICO DEL ESTADO DE CALIFORNIA

Dado y firmado en La Jolla, California, E.U.A., a los 19 días del mes de julio de 2000.

Gary E. Friedman, Vicepresidente,
Secretario y Asesor General Corporativo

ANITA TERESA LARA R.
TRADUCTORA OFICIAL
RESOLUCION NO. 01018
DE MINJUSTICIA

EN CONSTANCIA firmo y coloco mi sello oficial.

[Sello]

**COMO TARIO ONCE DE ESTE
CIRCULO HAGO CONSTAR QUE ESTA
FOTO COINCIDE CON EL ORIGI-
NAL QUE HE TENIDO A LA VISTA**

24 AGO 2000

ANTONIO DE JESUS D.C. COLOMBIA
FELIX ALVARO DE BAUTISTA
MQ PARTITION CE(II)

OPCIONAL

574
119

Aunque la siguiente información no se requiere por ley, puede resultar valiosa para las personas que confíen en el documento y podría impedir la remoción fraudulenta y la reutilización de este formulario en otro documento.

Descripción del Documento Adjunto

Título o Tipo de Documento: Poder 0072-01-CO (Colombia)

Fecha del Documento: 7/19/00

Número de Páginas: una

Signatario(s) Distinto(s) del Anterior: ninguno

Calidad(es) Reclamada(s) por el(los) Signatario(s)

Nombre del Signatario: Friedman

☐ Individuo

☒ Funcionario Social

Cargo(s): Vicepresidente, Secretario y Asesor General Corporativo

☐ Socio ☐ Comanditario ☐ General

☐ Apoderado

☐ Fideicomisario

☐ Tutor o Curador

☐ Otro: _____

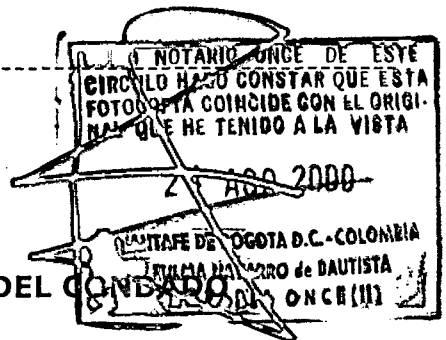
PULGAR DERECHO
DEL SIGNATARIO

El Signatario representa a:

Agouron Pharmaceuticals, Inc.

CONDADO DE SAN DIEGO

GREGORY J. SMITH
TASADOR/REGISTRADOR/SECRETARIO DEL CONDADO



El suscrito, GREGORY J. SMITH, Tasador/Registrador/Secretario del Condado de San Diego, Estado de California, legalmente provisto de Sello, CERTIFICO POR EL PRESENTE que:

575
120

BONNIE ACOSTA, cuyo nombre suscribe el juramento o Certificado de Prueba o Reconocimiento del instrumento adjunto y aparece allí escrito, era en el momento de recibir dicho juramento, o Prueba o Reconocimiento, una Notario Público, en y para dicho Condado, debidamente comisionada y juramentada y debidamente autorizada por las leyes de dicho Estado para recibir el mismo y para recibir juramentos y tomar los Reconocimientos y Pruebas de Escrituras y otros instrumentos escritos que deban registrarse en este Estado. Conozco la letra manuscrita de dicha Notario Público y considero que la firma en dicho juramento o Certificado de Prueba o Reconocimiento es auténtica. Y CERTIFICO ADEMÁS que bajo las leyes del Estado de California el citado juramento o Certificado de Prueba o Reconocimiento requiere darse bajo sello, pero la impresión de dicho sello no requiere según las leyes del Estado de California estar registrada en mi oficina o en cualquier otro lugar.

AT

ALDA TERESA LARA R.
TRADUCTORA OFICIAL
RESOLUCION No. 0
DE MINISTERIO DE JUSTICIA

FECHADO: 07-26-00 Firmado en constancia

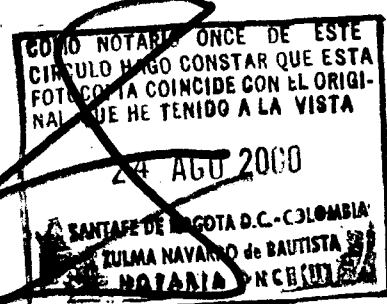
GREGORY J. SMITH, Tasador/Registrador/Secretario
del Condado

Por:

(Fdo.) Karen J. Miller, Secretaria Principal

Estado de California

SECRETARÍA DE ESTADO



Yo, BILL JONES, Secretario de Estado del Estado de California, certifico por el presente:

576
121

Que GREGORY J. SMITH, cuyo nombre aparece en el certificado adjunto, era, el 26 DE JULIO DE 2000, el TASADOR/REGISTRADOR/SECRETARIO debidamente elegido, calificado y en funciones del Condado de SAN DIEGO, en el antedicho Estado.

Que el sello allí estampado es el sello de dicho Condado; que la firma allí colocada aparenta ser la firma de GREGORY J. SMITH y que el certificado adjunto ha sido expedido en la debida forma y por el funcionario apropiado.

EN FE DE LO CUAL, firmo este certificado y estampo el Gran Sello del Estado de California a los 26 días del mes de julio de 2000.

(Fdo.) Bill Jones

BILL JONES
Secretario de Estado

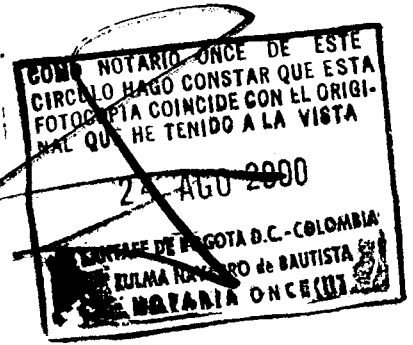
por: (Fdo.) Connie R. Christensen
Delegada

ANITA TERESA LARA R.
TRADUCTORA OFICIAL
RESOLUCION NO. 01013
DE MINISTERIO

No. 00043249-1

Estados Unidos de América

DEPARTAMENTO DE ESTADO



A todo aquel que viere el presente, un Saludo:

Certifico Que el documento adjunto lleva el Sello del Estado de California y que a dicho sello se debe dar plena fe y crédito.*

577

122

En testimonio de lo cual, yo, Madeleine K. Albright, Secretaria de Estado, he hecho estampar aquí el sello del Departamento de Estado y he hecho suscribir mi nombre por la Oficial de Autenticaciones Asistente del citado Departamento, en la ciudad de Washington, en el Distrito de Columbia, a los siete días del mes de agosto de 2000.

(Firmado) Madeleine K. Albright
Secretaria de Estado

(Firmado) Jacqueline Pridgen
Oficial de Autenticaciones Asistente,
Departamento de Estado

* Por el contenido del documento adjunto, el Departamento no asume responsabilidad

Este Certificado carece de validez si aparece borrado o alterado en cualquier forma.

EN ESPAÑOL: Autenticación de la firma de la Oficial de Autenticaciones del Departamento de Estado de los Estados Unidos por el Consulado de Colombia en Washington, D.C., bajo el No. 2034 de fecha 9 de agosto de 2000. Legalización de la firma de la Vicecónsul por el Ministerio de Relaciones Exteriores de Colombia, bajo el No. 515559 de fecha 17 de agosto de 2000.

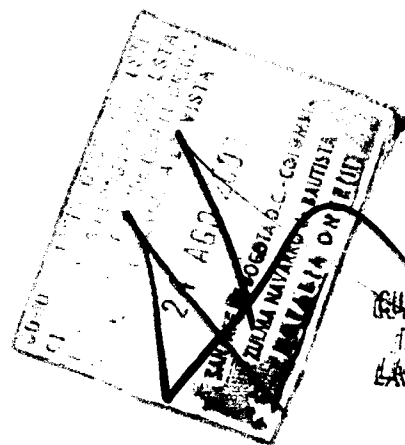
=====

La anterior es traducción fiel y completa del documento en referencia, de la cual se deja copia en este archivo para su confrontación.



Maria Teresa Lara R.
María Teresa Lara R.
c.c. 41.568.055 de Bogotá
Traductora Oficial según
Resolución No. 01016 del
2 de octubre de 1998, del
Ministerio de Justicia

MINISTERIO DE JUSTICIA
TRADUCTORA OFICIAL
RESOLUCION NO. 01016
DE 1998



MINISTERIO DE RELACIONES
EXTERIORES

516507

QUE FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

NO SE ASUME
RESPONSABILIDAD DEL
CONTENIDO

2000 AUG 18 A P 35

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

RAISBECK, LARA, RODRIGUEZ & RURDA

Members of the Firm -

BAKER & McKENZIE

ATTORNEYS AT LAW

APARTADO AEREO 3748

TELEFONO: 288-1400

SANTAFE DE BOGOTA, D.C.

COLOMBIA

POWER OF ATTORNEY

The undersigned.

Agouron Pharmaceuticals, Inc.

located in

10350 North Torrey Pines Road,

La Jolla, California 92037-1020, U.S.

declares that it hereby grants to

ALVARO CORREA ORDOÑEZ and/or
LUZ HELENA VILLAMIL and/or
CARLOS REINALDO OLARTE

a full and sufficient power of attorney to apply to the
proper national officers and authorities for the issue of:

Letters Patent, mergers, changes of name,
assignments, filing and prosecution of oppositions,
changes of address

to which end it empowers them to take all steps
necessary before said authorities for the objects stated,
to file petitions, prepare descriptions, make protests,
declarations, appeals and objections, pay imposts,
apply for certifications, receive documents and
securities, abandon applications and collect refunds.
To the said mandatories sufficient power is granted
hereby to receive notifications for and on behalf of the
Company, to confer powers on those who are to
represent the company judicially and extrajudicially, to
answer in court in the matter of all claims and demands
that may be presented in connection with the patents,
and to do everything that may be required, before
administrative or judicial officers of any class giving
them likewise power to substitute these presents and
revoke such substitutions if necessary.

Done and subscribed in La Jolla, California USA

On the 19th day of July 2000

XIX

Gary E. Friedman, Corporate Vice President,
Secretary and General Counsel

PODER

La abajo firmada.

domiciliada en

declara por el presente otorgar a

ALVARO CORREA ORDOÑEZ y/o
LUZ HELENA VILLAMIL y/o
CARLOS REINALDO OLARTE

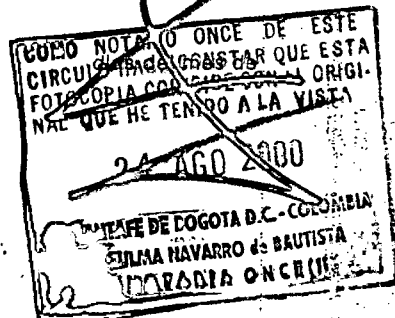
poder especial amplio y bastante para recabar de las
oficinas y autoridades nacionales que correspondan, la
obtención de:

a cuyo efecto los faculta para dar ante dichas
autoridades, todos los pasos necesarios al objeto
indicado, elevar solicitudes, formular descripciones,
protestas, declaraciones, apelaciones y reclamos,
oblar impuestos, solicitar testimonios, recibir
documentos y valores, deslitar y por el. Se concede a
los expresados mandatarios poder bastante para
recibir notificaciones a nombre de la compañía, otorgar
poderes a quienes vayan a representar a la compañía
judicial y extrajudicialmente, responder en juicio a
todas las reclamaciones o demandas que por motivo
de las patentes se presentaren y hacer cuanto fuere
necesario, ante las autoridades administrativas o
judiciales de cualquier orden, dándoles asimismo
facultad para sustituir el presente y en caso necesario
revocar dichas sustituciones.

Dado y firmado en

A los

19



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124
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CONSULADO DE COLOMBIA
WASHINGTON, D.C.



No. 2034

EL CONSULADO DE COLOMBIA

CERTIFICA:

Que es auténtica la firma de JACQUELINE PRIDGEN.
quien el día 7 DE AGOSTO DEL 2000
desempeñaba las funciones de OFICIAL DE AUTENTICACIONES DEPARTAMENTO DE ESTADO.
la cual aparece al pie de los documentos anexos relacionados con PODER.

Dado en Washington, D.C. a los NUEVE (9)
AGOSTO. del año dos mil (2000)

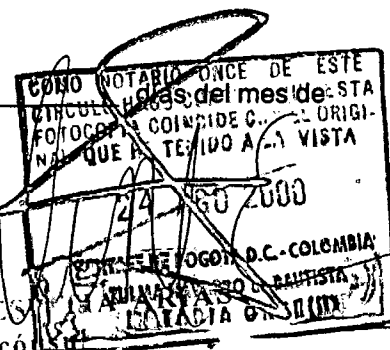
Pagado Impuesto de Timbre 7=

Pagado Derecho Consular 75=

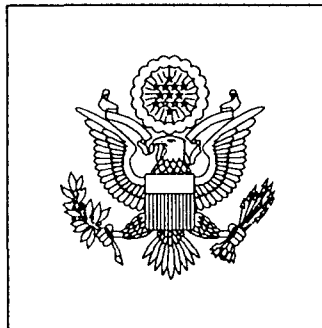
Total 22=

(El Consulado no asume ninguna
responsabilidad por el contenido de los
documentos anexos)

JAQUELINE PRIDGEN
Vicecónsul



United States of America



DEPARTMENT OF STATE

To all to whom these presents shall come, Greetings:

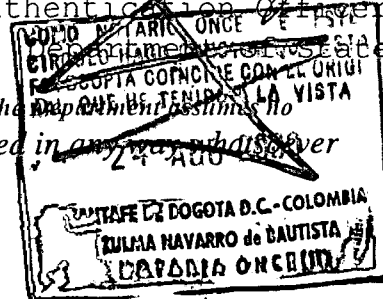
I Certify That the document hereunto annexed is under the Seal of the State(s) of California, and that such Seal(s) is/are entitled to full faith and credit.*

In testimony whereof, I, Madeleine K. Albright, Secretary of State, have hereunto caused the seal of the Department of State to be affixed and my name subscribed by the Assistant Authentication Officer, of the said Department, at the city of Washington, in the District of Columbia, this seventh day of August, 2000.

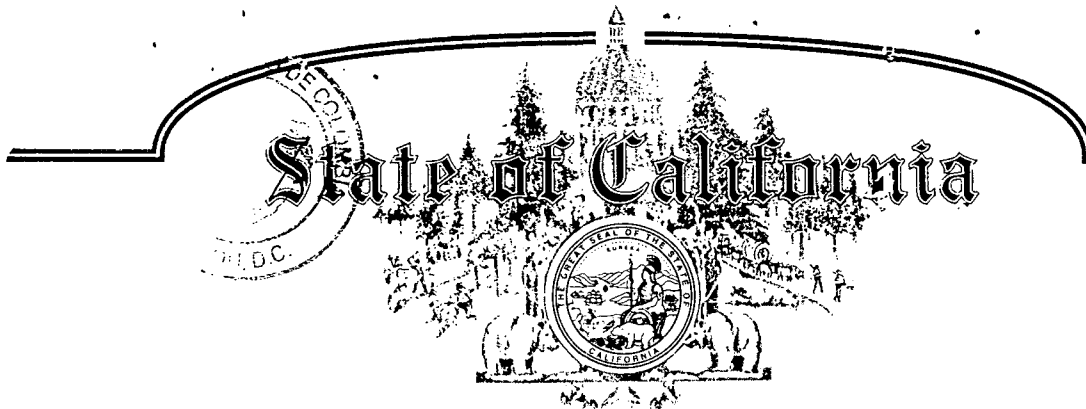
Madeleine K. Albright
Secretary of State
By *Jacqueline R. Parker*
Assistant Authentication Officer

Issued pursuant to CHXIV, State of
Sept. 15, 1789, 1 Stat. 68-69; 22
USC 2657; 22 USC 2651a; 5 USC
301; 28 USE 1733 et. seq.; 8 USC
1443(f); RULE 44 Federal Rules of
Civil Procedure.

*For the contents of the annexed document, the Department assumes no responsibility.
This certificate is not valid if it is removed or altered in any way whatsoever



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126



State of California

SECRETARY OF STATE

I, BILL JONES, Secretary of State of the State of California, hereby certify:

That GREGORY J. SMITH , whose name appears on the annexed certificate, was on JULY 26,2000, the duly elected, qualified and acting ASSESSOR/RECORDER/CLERK of the County of SAN DIEGO , in said State.

That the seal affixed thereto is the seal of said County; that the signature thereon appears to be the signature of GREGORY J. SMITH and that the annexed certificate is in due form and by proper officer.

IN WITNESS WHEREOF, I execute this certificate and affix the Great Seal of the State of California this 26TH day of JULY, 2000.



Bill Jones
BILL JONES
Secretary of State
27 JUL 2000
COLOMBIA
NATURAL

Gregory J. Smith

COUNTY OF SAN DIEGO

ASSESSOR / RECORDER / COUNTY CLERK

ASSESSOR'S OFFICE

1600 Pacific Highway, Room 103
San Diego, CA 92101-2480
Tel. (619) 236-3771 • Fax (619) 557-4056

www.sdarcc.com

RECORDER/COUNTY CLERK'S OFFICE

1600 Pacific Highway, Room 260
P.O. Box 121750 • San Diego, CA 92112-1750
Tel. (619) 237-0502 • Fax (619) 557-4155

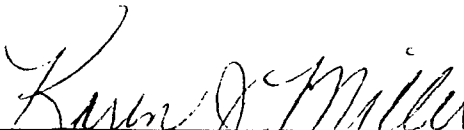
I, GREGORY J. SMITH, Assessor/Recorder/County Clerk of the County of San Diego, State of California, having by law a Seal, DO HEREBY CERTIFY that:

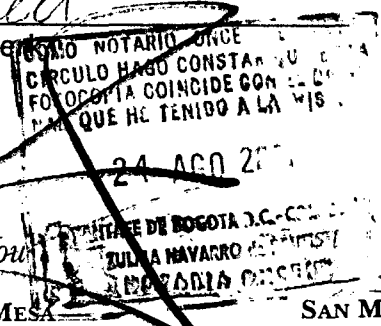
BONNIE ACCSTA whose name is subscribed to the oath or Certificate of Proof or Acknowledgment of the annexed instrument and thereon written, was at the time of taking such oath, or Proof or Acknowledgment, a Notary Public, in and for said County, duly commissioned and sworn and duly authorized by the laws of said State to take the same and administer oaths and to take the Acknowledgments and Proofs of Deeds and other instruments in writing to be recorded in this State. I am acquainted with the handwriting of such Notary Public and believe that the signature to said oath or Certificate of Proof Acknowledgment is genuine. I further certify that under the laws of the State of California the said oath or Certificate of Proof or Acknowledgment is required to be under seal, but the impression of said seal is not required by the laws of the State of California to be filed in my office or in any other place.

DATED: 07-26-00 Witness by hand

GREGORY J. SMITH, County Assessor/Recorder/Clerk

By:


Karen J. Miller, Principal Clerk



Branch Offices Available To Serve You

CHULA VISTA

344 "F" Street, Suite 200
Chula Vista, CA 91910-2646
(619) 498-2200

EL CAJON

198 West Main Street, Suite 101
El Cajon, CA 92020-3316
(619) 401-5700

KEARNY MESA

5473 Kearny Villa Road, 3rd Floor
San Diego, CA 92123-1142
(858) 505-6262

SAN MARCOS

334 Via Vera Cruz, Suite 150
San Marcos, CA 92069-2638
(760) 940-6868

ALIFORNIA ALL-PURPOSE ACKNOWLEDGMENT

State of California

County of San Diego

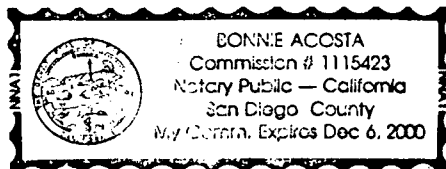
SS.

On 19 July 2000, before me, Bonnie Acosta, Notary Public,
Date Name and Title of Officer (e.g., "Jane Doe, Notary Public")

personally appeared Gary E. Friedman,
Name(s) of Signer(s)

- ☒ personally known to me
☐ proved to me on the basis of satisfactory evidence

to be the person(s) whose name(s) is/are subscribed to the within instrument and acknowledged to me that he/she/they executed the same in his/her/their authorized capacity(ies), and that by his/her/their signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.



Place Notary Seal Above

WITNESS my hand and official seal.

Bonnie Acosta
Signature of Notary Public

OPTIONAL

Though the information below is not required by law, it may prove valuable to persons relying on the document and could prevent fraudulent removal and reattachment of this form to another document.

Description of Attached Document

Title or Type of Document: Power of Attorney 0072-01-CO (Columbia)

Document Date: 7/19/00 Number of Pages: one

Signer(s) Other Than Named Above: none

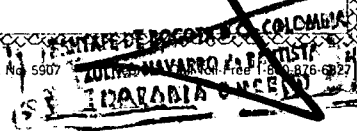
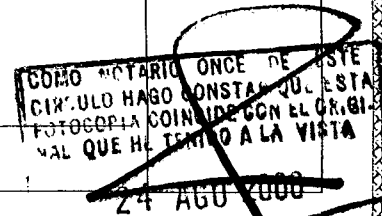
Capacity(ies) Claimed by Signer

Signer's Name: Friedman

- ☐ Individual
☒ Corporate Officer — Title(s): Corporate Vice President, Secretary
☐ Partner — ☐ Limited ☐ General and General Counsel
☐ Attorney in Fact
☐ Trustee
☐ Guardian or Conservator
☐ Other: _____

Signer Is Representing: Agouron Pharmaceuticals, Inc.

RIGHT THUMBPRINT
OF SIGNER
Top of thumb here



2do. EXAMEN DE FORMA PATENTE DE INVENCION

Folio 584

Radicación no 00-49777

Concepto Técnico no 627

Clasificación Internacional de Patentes A 61 K 31 / 415

Practicado el examen de acuerdo a lo establecido en el Art. 38 de la Decisión 486 se determinó que esta solicitud de **Patente de Invención**:

- SI ☒ NO ☐ Contiene un resumen de la invención (Art.26-e).
- SI ☒ NO ☐ Contiene el título o nombre de la invención (Art.27-d).
- SI ☒ NO ☐ Contiene la descripción de la invención (Art.26-b).
- SI ☒ NO ☐ NO ES APLICABLE ☐ Contiene los dibujos necesarios para comprender la invención (Art.26-d)
- SI ☒ NO ☐ Contiene una o más reivindicaciones. (Art.26-c).
- SI ☐ NO ☐ NO ES APLICABLE ☒ Han sido desarrollados los productos y/o procedimientos a partir de recursos genéticos o de sus productos derivados de los que cualquiera de los Países Miembros es país de origen. (Art. 26- h).
- SI ☐ NO ☐ NO ES APLICABLE ☒ Los productos y/o procedimientos han sido obtenidos o desarrollados a partir de los conocimientos tradicionales de las comunidades indígenas, afroamericanas, o locales de los países miembros, de acuerdo a lo establecido en la Decisión 391 y sus modificaciones y reglamentaciones vigentes.(Art.26-i).
- SI ☐ NO ☒ La invención se refiere a un producto relativo a un material biológico. (Art.26-J).
- SI ☐ NO ☒ La prioridad coincide con la materia reivindicada.
- SI ☒ NO ☐ **CUMPLE LOS REQUISITOS TÉCNICOS**

OBSERVACIONES Y OTROS: SI ☐ NO ☐ ver hoja(s) anexa(s)

1. La prioridad no coincide con la materia reivindicada puesto que los grupos que aparecen como R₂ en el compuesto de fórmula I de la prioridad no corresponden con los sustituyentes del compuesto de fórmula I del capítulo reivindicatorio. Así mismo, los R₁₀ del compuesto de fórmula III del capítulo reivindicatorio, no están contemplados en la prioridad.
2. Se adjuntan los artefactos finales de la fórmula química característica según lo requerido.

EXAMINADOR TÉCNICO

202040

Bogotá D. C., Abril 04, 2002.

2020
Bogotá D.C.,

416
2002-08-29

Doctor:
Carlos R. Olarte
Apoderado

REFERENCIA:	Radicación N°	00-49777
	Trámite	002
	Evento	001
	Actuación	416
	Oficio N°	1160
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente de invención que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en los artículos 26 y 27 de la Decisión 486 de la Comisión del Acuerdo de Cartagena, y en las demás disposiciones vigentes sobre la materia, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial, conforme lo establece el artículo 40 de la misma Decisión.

Cúmplase

Dado en Bogotá D.C., a los 29 de Agosto de 2002


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

Bogotá, DC, 04-05-05 El extracto de esta solicitud fue publicado en el número 519 de la Gaceta de Propiedad Industrial, de fecha 29-08-02 El término hábil señalado por la ley expiró el 26-11-02 y SI ☐ NO ☒ se presentaron oposiciones por parte de terceros.

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. **00-49777**

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION** FUE
PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **519**, DE FECHA **29 DE**
AGOSTO DE 2002, EL TERMINO HABIL SEÑALADO POR LA LEY EXPIRA EL **26 DE**
NOVIEMBRE DE 2002.

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO _____