



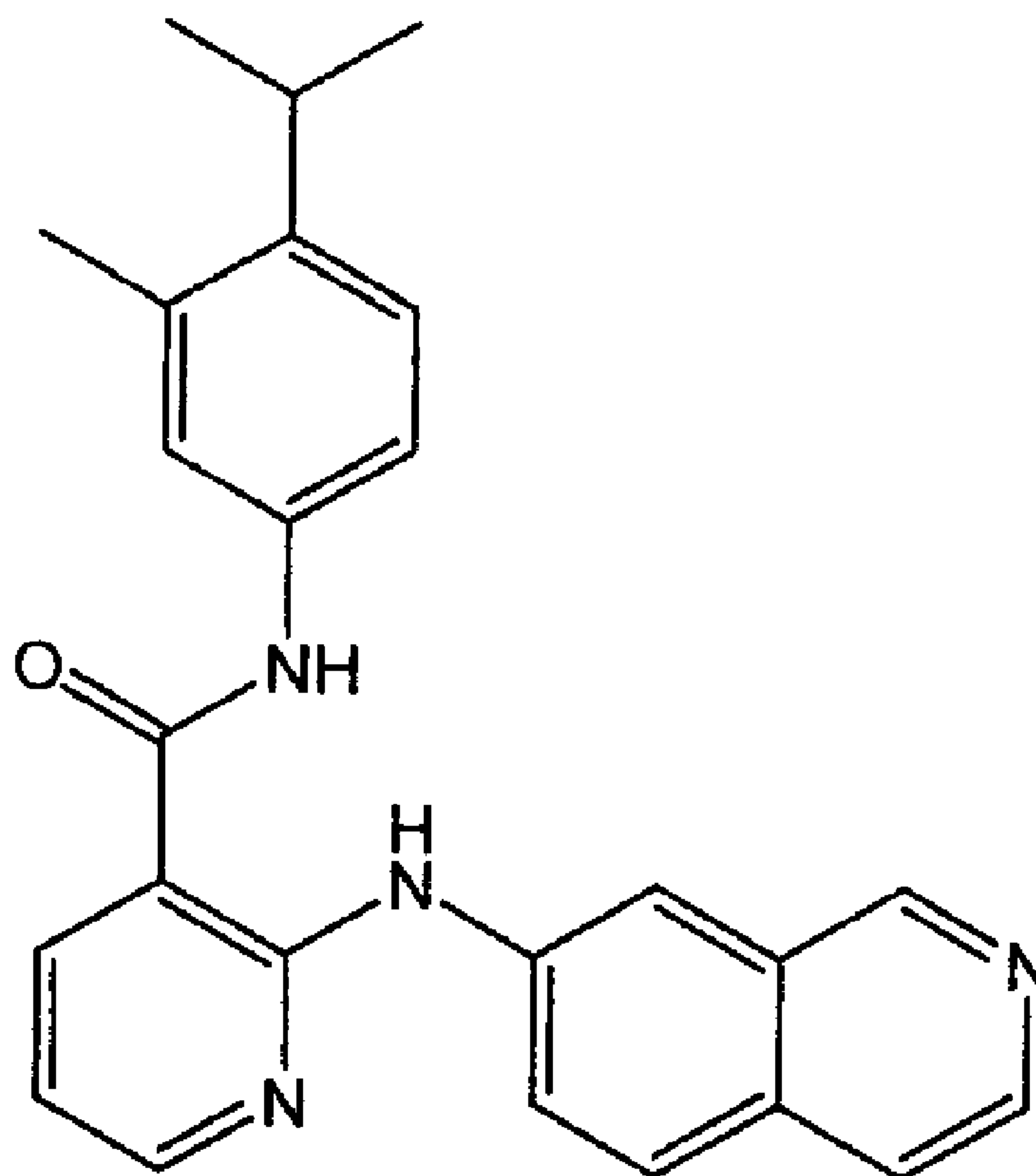
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(54) Titre : DERIVES AMINES A SUBSTITUTION ARYLE ET PROCEDES D'UTILISATION

(54) Title: SUBSTITUTED ARYL-AMINE DERIVATIVES AND METHODS OF USE



(57) Abrégé/Abstract:

The present invention provides 2-(7-isoquinolinylamino)-N-(3-methyl-4-(1-methylethyl)phenyl)-3-pyridinecarboxamide or pharmaceutically acceptable salt form thereof which is useful for treating angiogenesis and related diseases such as cancer.



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ABSTRACT

The present invention provides 2-(7-isoquinolinylamino)-N-(3-methyl-4-(1-methylethyl)phenyl)-3-pyridinecarboxamide or pharmaceutically acceptable salt form thereof which is useful for treating angiogenesis and related diseases such as cancer.

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JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

THIS IS VOLUME __1__ OF __2__

NOTE: For additional volumes please contact the Canadian Patent Office.

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SUBSTITUTED ARYL-AMINE DERIVATIVES AND METHODS OF USE

5

FIELD OF THE INVENTION

10 This invention is in the field of pharmaceutical agents and specifically relates to compounds, compositions, uses and methods for treating cancer and angiogenesis-related disorders.

BACKGROUND OF THE INVENTION

15

Protein kinases represent a large family of proteins which play a central role in the regulation of a wide variety of cellular processes, maintaining control over cellular function. A partial list of such kinases includes
20 ab1, Akt, bcr-ab1, Blk, Brk, Btk, c-kit, c-met, c-src, CDK1, CDK2, CDK3, CDK4, CDK5, CDK6, CDK7, CDK8, CDK9, CDK10, cRaf1, CSF1R, CSK, EGFR, ErbB2, ErbB3, ErbB4, Erk, Fak, fes, FGFR1, FGFR2, FGFR3, FGFR4, FGFR5, Fgr, flt-1, Fps, Frk, Fyn, Hck, IGF-1R, INS-R, Jak, KDR, Lck, Lyn, MEK,
25 p38, PDGFR, PIK, PKC, PYK2, ros, tie, tie2, TRK, Yes, and Zap70. Inhibition of such kinases has become an important therapeutic target.

Certain diseases are known to be associated with deregulated angiogenesis, for example ocular
30 neovascularisation, such as retinopathies (including diabetic retinopathy), age-related macular degeneration, psoriasis, hemangioblastoma, hemangioma, arteriosclerosis, inflammatory disease, such as a rheumatoid or rheumatic inflammatory disease, especially arthritis (including
35 rheumatoid arthritis), or other chronic inflammatory disorders, such as chronic asthma, arterial or post-transplantational atherosclerosis, endometriosis, and

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neoplastic diseases, for example so-called solid tumors and liquid tumors (such as leukemias).

At the center of the network regulating the growth and differentiation of the vascular system and its components, both during embryonic development and normal growth, and in a wide number of pathological anomalies and diseases, lies the angiogenic factor known as Vascular Endothelial Growth Factor" (VEGF; originally termed 'Vascular Permeability Factor", VPF), along with its cellular receptors (see G. Breier et al., Trends in Cell Biology, 6, 454-6 (1996)).

VEGF is a dimeric, disulfide-linked 46-kDa glycoprotein related to "Platelet-Derived Growth Factor" (PDGF); it is produced by normal cell lines and tumor cell lines; is an endothelial cell-specific mitogen; shows angiogenic activity in *in vivo* test systems (e.g. rabbit cornea); is chemotactic for endothelial cells and monocytes; and induces plasminogen activators in endothelial cells, which are involved in the proteolytic degradation of extracellular matrix during the formation of capillaries. A number of isoforms of VEGF are known, which show comparable biological activity, but differ in the type of cells that secrete them and in their heparin-binding capacity. In addition, there are other members of the VEGF family, such as "Placenta Growth Factor" (PlGF) and VEGF-C.

VEGF receptors (VEGFR) are transmembranous receptor tyrosine kinases. They are characterized by an extracellular domain with seven immunoglobulin-like domains and an intracellular tyrosine kinase domain. Various types of VEGF receptor are known, e.g. VEGFR-1 (also known as flt-1), VEGFR-2 (also known as KDR), and VEGFR-3.

A large number of human tumors, especially gliomas and carcinomas, express high levels of VEGF and its receptors. This has led to the hypothesis that the VEGF released by tumor cells stimulates the growth of blood capillaries and

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the proliferation of tumor endothelium in a paracrine manner and through the improved blood supply, accelerate tumor growth. Increased VEGF expression could explain the occurrence of cerebral edema in patients with glioma. Direct evidence of the role of VEGF as a tumor angiogenesis factor *in vivo* is shown in studies in which VEGF expression or VEGF activity was inhibited. This was achieved with anti-VEGF antibodies, with dominant-negative VEGFR-2 mutants which inhibited signal transduction, and with antisense-VEGF RNA techniques. All approaches led to a reduction in the growth of glioma cell lines or other tumor cell lines *in vivo* as a result of inhibited tumor angiogenesis.

Angiogenesis is regarded as an absolute prerequisite for tumors which grow beyond a diameter of about 1-2 mm; up to this limit, oxygen and nutrients may be supplied to the tumor cells by diffusion. Every tumor, regardless of its origin and its cause, is thus dependent on angiogenesis for its growth after it has reached a certain size.

Three principal mechanisms play an important part in the activity of angiogenesis inhibitors against tumors: 1) Inhibition of the growth of vessels, especially capillaries, into avascular resting tumors, with the result that there is no net tumor growth owing to the balance that is achieved between cell death and proliferation; 2) Prevention of the migration of tumor cells owing to the absence of blood flow to and from tumors; and 3) Inhibition of endothelial cell proliferation, thus avoiding the paracrine growth-stimulating effect exerted on the surrounding tissue by the endothelial cells which normally line the vessels. See R. Connell and J. Beebe, *Exp. Opin. Ther. Patents*, 11, 77-114 (2001).

VEGF's are unique in that they are the only angiogenic growth factors known to contribute to vascular hyperpermeability and the formation of edema. Indeed,

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vascular hyperpermeability and edema that is associated with the expression or administration of many other growth factors appears to be mediated via VEGF production.

Inflammatory cytokines stimulate VEGF production.

5 Hypoxia results in a marked upregulation of VEGF in numerous tissues, hence situations involving infarct, occlusion, ischemia, anemia, or circulatory impairment typically invoke VEGF/VPF-mediated responses. Vascular hyperpermeability, associated edema, altered transendothelial exchange and
10 macromolecular extravasation, which is often accompanied by diapedesis, can result in excessive matrix deposition, aberrant stromal proliferation, fibrosis, etc. Hence, VEGF-mediated hyperpermeability can significantly contribute to disorders with these etiologic features. As such, regulators
15 of angiogenesis have become an important therapeutic target.

Schipper US patent 3,226,394, issued Dec. 28, 1965, describes anthranilamides as CNS depressants. Japanese patent JP2000256358 describes pyrazole derivatives that block the calcium release-activated calcium channel. EP
20 947500, published 6 October 1999, describes compounds as PGE₂ antagonists. PCT publication WO96/41795, published 27 December 1996, describes benzamides as vasopressin antagonists. WO01/29009 describes aminopyridines as KDR inhibitors. WO01/30745 describes
25 anthranilic acids as cGMP phosphodiesterase inhibitors. WO00/02851, published 20 Jan 2000 describes arylsulfonylaminoaryl amides as guanylate cyclase activators. WO98/45268 describes nicotinamide derivatives as PDE4 inhibitors. WO98/24771 describes benzamides as vasopressin
30 antagonists.

US Patent No. 5,532,358, issued July 2, 1996, describes the preparation of 2-(cyclopropylamino)-N-(2-methoxy-4-methyl-3-pyridinyl)-3-pyridinecarboxamide as an intermediate for HIV inhibitors. Triazine-substituted

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amines are described for their aggregating ability (J. Amer. Chem. Soc., 115, 905-16 (1993). Substituted imidazolines were tested for their antidepressant activity in Ind. J. Het. Chem., 2, 129-32 (1992). N-(4-Pyridyl)anthranilic amides were described in Chem Abstr. 97:109837 (1981). PCT publication W099/32477, published 1 July 1999, describes anthranilamides as anti-coagulants. US patent 6,140,351 describes anthranilamides as anti-coagulants. PCT publication W099/62885, published 9 December 1999, describes 1-(4-aminophenyl)pyrazoles as antiinflammatories. PCT publication W000/39111, published 6 July 2000, describes amides as factor Xa inhibitors. PCT publication W000/39117, published 6 July 2000, describes heteroaromatic amides as factor Xa inhibitors. PCT publication W000/27819, published 18 May 2000, describes anthranilic acid amides as VEGF inhibitors. PCT publication W000/27820 published 18 May 2000, describes N-aryl anthranilic acid amides as VEGF inhibitors. 7-Chloroquinolinylamines are described in FR2168227 as antiinflammatories. W001/55114, published 2 Aug. 2001, describes nicotinamides for the treatment of cancer. W001/55115, published 2 Aug. 2001, describes nicotinamides for the treatment of apoptosis. W001/85715, published 15 November 2001, describes substituted pyridines and pyrimidines as anti-angiogenesis agents. PCT publication W001/85691 published 15 November 2001, describes anthranilic amides as VEGF inhibitors. PCT publication W001/85671 published 15 November 2001, describes anthranil amides as VEGF inhibitors. PCT publication W001/81311 published 1 November 2001, describes anthranilic amides as VEGF inhibitors. U.S. Patent No. 6,462,075, issued October 8, 2002, describes chalcone and its analogs as agents for the inhibition of angiogenesis and related disease states. U.S. Patent No. 6,608,058, issued August 19, 2003, describes the preparation of 6-methyl nicotinamides as anti-

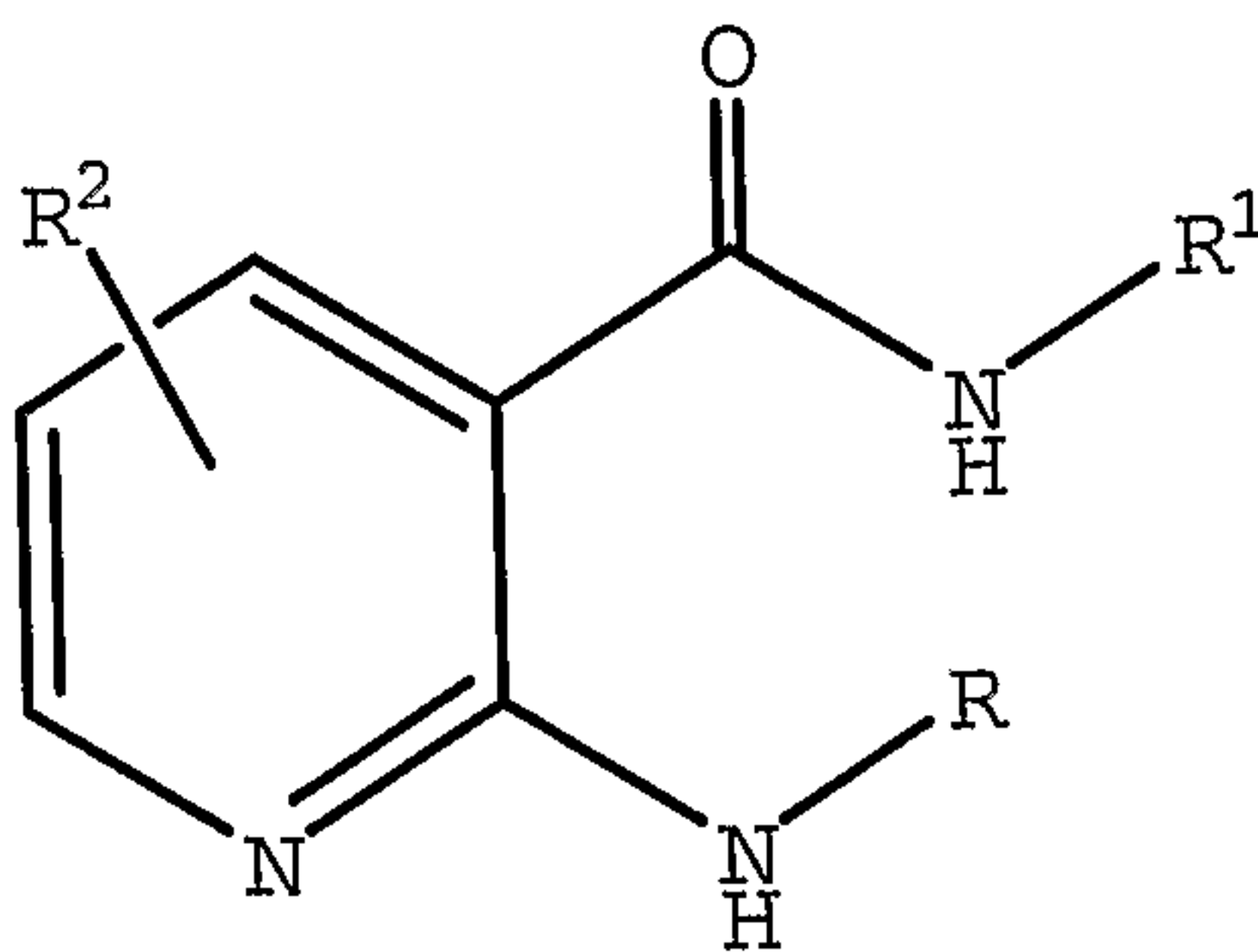
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viral agents. U.S. Patent Publication No. 2002111495,
published August 15, 2002, describes the preparation of
nicotinamides as PDE4 D isozyme inhibitors. U.S. Patent
Publication No. 2003073836, published April 17, 2003,
5 describes the preparation of biphenylcarboxylic acid amides
as inhibitors of microsomal triglyceride transfer protein
(MPT). U.S. Patent Publication No. 20040053908, published
March 18, 2004, describes nitrogen containing aromatic
derivatives as VEGF inhibitors. U.S. Patent Publication No.
10 20040067985, published April 8, 2004, describes
nicotinamides as inhibitors of angiogenesis, and useful for
treating cancer. However, the compounds of the present
invention have not been previously described as inhibitors
of angiogenesis, and useful for treating angiogenesis-
15 related diseases such as cancer.

DESCRIPTION OF THE INVENTION

The present invention provides classes of compounds,
20 including their pharmaceutically acceptable derivatives,
useful for treating angiogenesis and related diseases such
as cancer. One class of compounds are defined by general
Formula I



25

I

wherein R is a 9- or 10-membered heterocyclyl ring
containing at least one nitrogen or oxygen atom, the

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ring selected from 7-isoquinolinyl, 2-methyl-3-oxo-2,3-dihydroindazol-6-yl, [1,6]-naphthydrin-3-yl, [1,7]-naphthydrin-2-yl, 1-oxo-2,3-dihydrobenzofuran-4-yl, 3-oxo-2,3-dihydrobenzofuran-5-yl, dihydro-
5 benzodioxinyl, 6-quinazolinyl, 2-amino-6-quinazolinyl, 4-methylamino-6-quinazolinyl, 2,4-diamino-6-quinazolinyl, 3-oxo-3,4-dihydro-1,4-benzoxazin-6-yl, 2,2-difluoro-1,3-benzodioxol-5-yl and 2,2,3,3-tetrafluoro-2,3-dihydro-1,4-benzodioxin-6-yl, each of
10 which is optionally substituted with one or more substituents selected from halo, haloalkyl, C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, N-dimethylamino-C₁₋₆-alkyl, N-dimethylamino-C₁₋₆-alkoxy, amino, alkyl-carbonylamino, morpholino-sulfonyl, amino-sulfonyl, oxazolyl,
15 pyrrolyl, morpholinyl, carboxyl, cyano, and acetyl;
wherein R¹ is selected from unsubstituted or substituted phenyl,
5-6 membered heteroaryl,
9-10 membered bicyclic heterocyclyl and
20 11-14 membered tricyclic heterocyclyl,
advantageously, R¹ is selected from phenyl, 3-isoxazolyl, 3-pyrazolyl, 2-thiazolyl, 1,3,4-thiadiazol-2-yl, thienyl, 3-pyridyl, pyrimidinyl, pyridazinyl, 1,2-dihydroquinolyl, 1,2,3,4-tetrahydroquinolyl, 1,2,3,4-tetrahydro-isoquinolyl,
25 2-oxo-1,2,3,4-tetrahydroquinolyl, 2-oxo-1,2,3,4-tetrahydroquinolyl, 1-oxo-1,2,3,4-tetrahydro-isoquinolyl, 1',2'-dihydro-spiro[cyclopropane-1,3'-[3H]indol]-6'-yl, isoquinolyl, quinolyl, indol-6-yl, 6-isoindolyl, 3,4-dihydro-2H-benzo[1,4]oxazin-6-yl, 3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl, 2,3-dihydro-1H-indol-6-yl,
30 naphthyridinyl, 2-oxo-3,4-dihydro-1H-[1,8]naphthyridin-7-yl, 3,4-dihydro-[1,8]naphthyridinyl, 1,2,3,4-tetrahydro-[1,8]naphthyridinyl, quinoxalinyl, 2-oxo-chromen-7-yl, benzo[d]isothiazolyl, 3,4-dihydro-quinazolinyl,

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2,3,4,4a,9,9a-hexahydro-1H-3-aza-fluorenyl, 5,6,7-trihydro-
 1,2,4-triazolo[3,4-a]isoquinolyl, 5,6-dihydro-
 [1,2,4]triazolo[3,4-a]isoquinolin-9-yl, indazol-6-yl, 2,1,3-
 benzothiadiazolyl, benzodioxanyl, benzothienyl, 2,3-dihydro-
 5 benzofuran-6-yl, benzofuranyl, benzimidazolyl, dihydro-
 benzimidazolyl, benzoxazolyl and 5-benzthiazol-5-yl,

more advantageously, R¹ is selected from phenyl,

1,2,3,4-tetrahydroisoquinol-7-yl, 2,3-dihydro-1H-
 indol-6-yl, 1,2,3,4-tetrahydro-[1,8]naphthyridinyl,
 10 1',2'-dihydro-spiro[cyclopropane-1,3'-[3H]indol-6'-
 yl, tetrahydroquinolin-7-yl, 3-isoxazolyl, 3-
 pyrazolyl, 1,3,4-thiadiazol-2-yl, 3-pyridyl, 2-oxo-
 1,2,3,4-tetrahydroquinol-7-yl, 2-oxo-
 tetrahydroquinolin-7-yl, 1-oxo-1,2,3,4-tetrahydro-
 15 isoquinol-7-yl, indol-6-yl, 3,4-dihydro-2H-
 benzo[1,4]oxazin-6-yl, 3-oxo-3,4-dihydro-2H-
 benzo[1,4]oxazin-6-yl, 2-oxo-3,4-dihydro-1H-
 [1,8]naphthyridin-7-yl, 2-oxo-chromen-7-yl, 5,6-
 dihydro-[1,2,4]triazolo[3,4-a]isoquinolin-9-yl,
 20 indazol-6-yl, 2,1,3-benzothiadiazolyl, 2,3-dihydro-
 benzofur-6-yl, and 5-benzthiazol-5-yl, and

even more advantageously, R¹ is phenyl substituted

with one or more substituents selected from
 methyl, propyl, isopropyl, n-butyl, isobutyl,
 25 tert-butyl, methoxy, hydroxyl, phenyl, chloro,
 ethyl-2-propanoyl, 2-methyl-2-(1-methylpiperidin-
 4-yl)ethyl, methylsulfonylamino,
 dimethylaminomethylcarbonylamino, piperazine-
 methyl, 4-methylsulfonyl-1-piperazine-methyl, 1-
 30 pyrrolidinyl-CH₂-C(=O)-NH-, 1-methyl-
 pyrrolidinyl-CH₂-O-, 1-isopropyl-pyrrolidinyl-
 CH₂-O-, 1-acetyl-pyrrolidinyl-CH₂-O-, 2-hydroxy-3-
 pyrrolidinyl-propoxy, 4-morpholinyl-CH₂-C(=O)-NH-
 , 1-pyrrolidinyl-CH₂CH₂O-, pyrrolidinyl-propyl,

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5 piperidinyl-propyl, 1-methyl-1,2,3,6-tetrahydro-4-pyridinyl, 1-pyrrolidinyl-1-butenyl, 3,3-dimethylamino-1-propynyl, 4-methyl-1-piperazinyl, piperazinyl, 4-methyl-1-piperazinyl-methyl, morpholino-propyl, 1-N-methyl-piperidinyl-CH₂-, 1-piperidinyl-propyl, hydroxyethylamino, 3-tetrahydrofuryl-O-C(=O)-NH-, 3-tetrahydrofuryl-CH₂O-, trifluoromethyl, pentafluoroethyl, tetrafluoroethoxyl, 1,1-di(trifluoromethyl)-1-hydroxymethyl, 1,1-di(trifluoromethyl)-1-(pyrrolidin-2-ylmethoxy)methyl, 3-tetrahydrofuryloxy, 1-methylcarbonyl-pyrrolidin-2-ylmethoxy, 1-methyl-pyrrolidin-2-ylmethoxy, piperidinyl-amino, N,N-dimethyl-glycyl-amino, 15 isopropyl-piperidinyl-methoxyl, isopropyl-piperazinyl, benzoxyl, 4-N-methyl-piperazinyl-propyl, 4-N-propyl-piperazinyl, methylsulfonyl, and methylsulfonylaminoethoxy, yet even more advantageously, R¹ is selected from 20 4,4-dimethyl-3,4-dihydro-2-oxo-1H-quinolinyl, 4,4-dimethyl-1,2,3,4-tetrahydro-1H-quinolinyl, 4,4-dimethyl-3,4-dihydro-2-oxo-1H-[1,8]naphthyridinyl, 3,3-dimethyl-2,3-dihydro-1H-indol-6-yl optionally substituted with one or more substituents 25 selected from pyrrolidin-1-yl-carbonyl, pyrrolidin-1-yl-methyl, 1-methyl-4-piperidinyl, 1-methyl-4-piperidinyl-methyl, 1-4-piperidinyl, tetrahydro-2-furanylcarbonyl, acetyl, N,N-dimethylglycyl, methylcarbonyl, and 30 methylsulfonyl, 4,4-dimethyl-1,2,3,4-tetrahydro-1H-isoquinolin-7-yl, and

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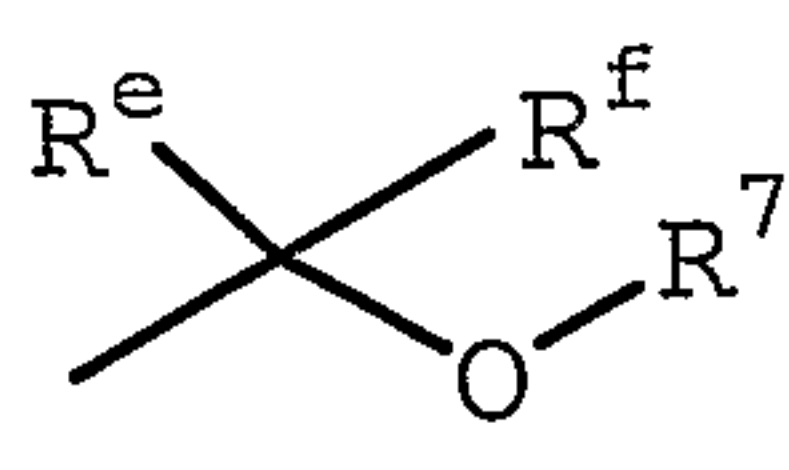
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4,4-dimethyl-1,2,3,4-tetrahydro-2-oxo-1H-
isoquinolin-7-yl;

where R¹ is substituted with one or more substituents, the
substituents are selected from halo, optionally
5 substituted C₁₋₆-alkyl, optionally substituted C₃₋₆-
cycloalkyl, optionally substituted phenyl, optionally
substituted phenyl-C₁₋₄-alkylenyl, C₁₋₂-haloalkoxy,
optionally substituted phenyloxy, optionally substituted
10 4-6 membered heterocyclyl-C₁₋₆-alkyl, optionally
substituted 4-6 membered heterocyclyl-C₂₋₄-alkenyl,
optionally substituted 4-6 membered heterocyclyl,
optionally substituted 4-6 membered heterocycliloxy,
optionally substituted 4-6 membered heterocyclyl-C₁₋₄-
alkoxy, optionally substituted 4-6 membered
15 heterocyclylsulfonyl, optionally substituted 4-6
membered heterocyclylamino, optionally substituted 4-6
membered heterocyclylcarbonyl, optionally substituted 4-
6 membered heterocyclyl-C₁₋₄-alkylcarbonyl, optionally
substituted 4-6 membered heterocyclylcarbonyl-C₁₋₄-alkyl,
20 optionally substituted 4-6 membered heterocyclyl-C₁₋₄-
alkylcarbonylamino, optionally substituted 4-6 membered
heterocyclyl-oxycarbonylamino, C₁₋₂-haloalkyl, C₁₋₄-
aminoalkyl, optionally substituted C₁₋₄-
aminoalkylcarbonyl, nitro, amino, C₁₋₃-
25 alkylsulfonylamino, hydroxy, cyano, alkylthio,
haloalkylthio, arylthio, aralkylthio, aminosulfonyl, C₁-
2-alkylsulfonyl, C₁₋₂-alkylsulfonylamino, C₁₋₂-
alkylsulfonylamino-C₁₋₄-alkoxy, halosulfonyl, C₁₋₄-
alkylcarbonyl, amino-C₁₋₄-alkylcarbonyl, C₁₋₃-alkylamino-
30 C₁₋₄-alkylcarbonyl, C₁₋₃-alkylamino-C₁₋₄-
alkylcarbonylamino, C₁₋₄-alkoxycarbonyl-C₁₋₄-alkyl, C₁₋₃-
alkylamino-C₁₋₃-alkyl, C₁₋₃-alkylamino-C₁₋₃-alkoxy, C₁₋₃-
alkylamino-C₁₋₃-alkoxy-C₁₋₃-alkoxy, C₁₋₄-alkoxycarbonyl, C₁-
4-alkoxycarbonylamino-C₁₋₄-alkyl, C₁₋₃-alkylsulfonylamino-

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C₁₋₃-alkoxy, C₁₋₄-hydroxyalkyl,  and C₁₋₄-alkoxy;

advantageously, the R¹ substituents are selected from
 bromo, chloro, fluoro, iodo, nitro, amino, cyano,
 5 Boc-aminoethyl, hydroxy, fluorosulfonyl,
 methylsulfonyl, aminosulfonyl, 4-
 methylpiperazinylsulfonyl, cyclohexyl, phenyl,
 phenylmethyl, 4-pyridylmethyl, 4-morpholinylmethyl,
 1-methylpiperazin-4-ylmethyl, 1-methylpiperazin-4-
 10 ylpropyl, morpholinylpropyl, piperidin-1-ylmethyl, 1-
 methylpiperidin-4-ylmethyl, 2-methyl-2-(1-
 methylpiperidin-4-yl)ethyl, 2-methyl-2-(4-
 pyrimidinyl)ethyl, 2-methyl-2-(5-methyloxadiazol-2-
 yl)ethyl, 2-methyl-2-(pyrazol-5-yl)ethyl, 2-methyl-2-
 15 (1-ethoxycarbonyl-1,2,3,6-tetrahydropyridin-4-
 yl)ethyl, morpholinylethyl, 1-(4-morpholinyl)-2,2-
 dimethylpropyl, 1-(4-morpholinyl)-2,2-dimethylethyl,
 piperidin-4-ylethyl, 1-Boc-piperidin-4-ylethyl,
 piperidin-1-ylethyl, 1-Boc-piperidin-4-ylethyl,
 20 piperidin-4-ylmethyl, 1-Boc-piperidin-4-ylmethyl,
 piperidin-4-ylpropyl, 1-Boc-piperidin-4-ylpropyl,
 piperidin-1-ylpropyl, pyrrolidin-1-ylpropyl,
 pyrrolidin-2-ylpropyl, 1-Boc-pyrrolidin-2-ylpropyl,
 1-(pyrrolidin-1-yl)-2-methylpropyl, pyrrolidin-1-
 25 ylmethyl, pyrrolidin-2-ylmethyl, 1-Boc-pyrrolidin-2-
 ylmethyl, pyrrolidinylpropenyl, pyrrolidinylbutenyl,
 methylcarbonyl, Boc, piperidin-1-ylmethylcarbonyl,
 pyrrolidin-1-yl-carbonyl, 4-pyridylcarbonyl, 4-
 methylpiperazin-1-ylcarbonylethyl, CH₃O-C(=O)-CH₂-,
 30 methoxycarbonyl, aminomethylcarbonyl,
 dimethylaminomethylcarbonyl, methylsulfonylamino,
 dimethylaminomethylcarbonylamino, 1-pyrrolidinyl-CH₂-
 C(=O)-NH-, 4-morpholinyl-CH₂-C(=O)-NH-, 3-

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tetrahydrofuryl-O-C(=O)-NH-, cyclohexyl-N(CH₃)-, (4-pyrimidinyl)amino, (2-methylthio-4-pyrimidinyl)amino, 3-ethoxycarbonyl-2-methyl-fur-5-yl, 4-methylpiperazin-1-yl, 4-methyl-1-piperidyl, 1-Boc-4-piperidyl, piperidin-4-yl, 1-methylpiperidin-4-yl, 1-methyl-(1,2,3,6-tetrahydropyridyl), imidazolyl, morpholinyl, 4-trifluoromethyl-1-piperidinyl, hydroxybutyl, methyl, gem-dimethyl, ethyl, propyl, isopropyl, butyl, tert-butyl, sec-butyl, trifluoromethyl, pentafluoroethyl, nonafluorobutyl, dimethylaminopropyl, 1,1-di(trifluoromethyl)-1-hydroxymethyl, 1,1-di(trifluoromethyl)-1-(piperidinylethoxy)methyl, 1,1-di(trifluoromethyl)-1-(pyrrolidin-2-ylmethoxy)methyl, 1,1-di(trifluoromethyl)-1-(methoxyethoxyethoxy)methyl, 1-hydroxyethyl, 2-hydroxyethyl, trifluoromethoxy, 1-aminoethyl, 2-aminoethyl, 1-(N-isopropylamino)ethyl, 2-(N-isopropylamino)ethyl, 3-tetrahydrofuryloxy, dimethylaminoethoxy, 4-chlorophenoxy, phenyloxy, azetidin-3-ylmethoxy, 1-Boc-azetidin-3-ylmethoxy, 3-tetrahydrofurylmethoxy, pyrrolidin-2-ylmethoxy, 1-methylcarbonyl-pyrrolidin-2-ylmethoxy, 1-Boc-pyrrolidin-2-ylmethoxy, pyrrolidin-1-ylmethoxy, 1-methyl-pyrrolidin-2-ylmethoxy, 1-isopropyl-pyrrolidin-2-ylmethoxy, 1-Boc-piperdin-4-ylmethoxy, (1-pyrrolidinyl)ethoxy, piperdin-4-ylmethoxy, piperdin-3-ylmethoxy, 1-methylpiperdin-4-yloxy, methylsulfonylaminoethoxy, isopropoxy, methoxy and ethoxy;

even more advantageously, the R¹ substituents are selected from chloro, fluoro, acetyl, oxo, methylsulfonyl, 2-methyl-2-(1-methylpiperidin-4-yl)ethyl, piperidine-ethoxy-ditrifluoromethyl-methyl-, 1-methylpiperidin-4-yl, 1-

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methylpiperidin-4-yl-methyl, 1-methylpiperidin-4-yl-propyl, pyrrolidin-1-yl-carbonyl, methylsulfonylamino, dimethylaminomethylcarbonylamino, 1-pyrrolidinyl-CH₂-C(=O)-NH-, N-methyl-pyrrolidinyl-CH₂-O-, N-isopropyl-pyrrolidinyl-CH₂-O-, N-pyrrolidinyl-CH₂CH₂O-, pyrrolidinyl-propyl, morpholine-propyl, N-methyl-piperazine, piperazine-methyl, 4N-methylsulfonyl-piperazine-methyl, tetrafluoroethyl-O-, 4-morpholinyl-CH₂-C(=O)-NH-, N-Boc-methyl C(O)-, amino-CH₂-C(O)-, 3-tetrahydrofuryl-C(=O)-, 3-tetrahydrofuryl-O-C(=O)-NH-, 3-tetrahydrofuryl-CH₂-O-, N,N-dimethylamino-CH₂-C(O)-, N,N-dimethylamino-CH₂-C(O)NH-, N,N-dimethylamino-CH₂CH₂CH₂-, hydroxyethylamino, methylcyclopropyl, methyl, gem-dimethyl, ethyl, tert-butyl, t-butoxycarbonyl, propyl, isopropyl, methoxy, piperidinemethyl, 1,1-dimethyl-propyl, azetidiny, trifluoromethyl, pentafluoroethyl, 1,1-di(trifluoromethyl)-1-hydroxymethyl, 1-hydroxy-1,1-di(trifluoromethyl) methyl, 1,1-di(trifluoromethyl)-1-(pyrrolidin-2-ylmethoxy)methyl, 3-tetrahydrofuryloxy, 1-methylcarbonyl-pyrrolidin-2-ylmethoxy, 1-methylpyrrolidin-2-ylmethoxy, 2-hydroxy-3-pyrrolidin-propoxy, 1,1-dimethylethylacetyl, 1,1-dimethylacetic acid, and methylsulfonylaminoethoxy, and yet even more advantageously, the R¹ substituents are selected from methyl, ethyl, isopropyl, t-butyl, 2-methyl-2-(1-ethoxycarbonyl-1,2,3,6-tetrahydropyridin-4-yl)ethyl, 1-(4-morpholinyl)-2,2-dimethylethyl, pyrrolidin-1-yl-carbonyl, CH₃O-C(=O)-CH₂-,

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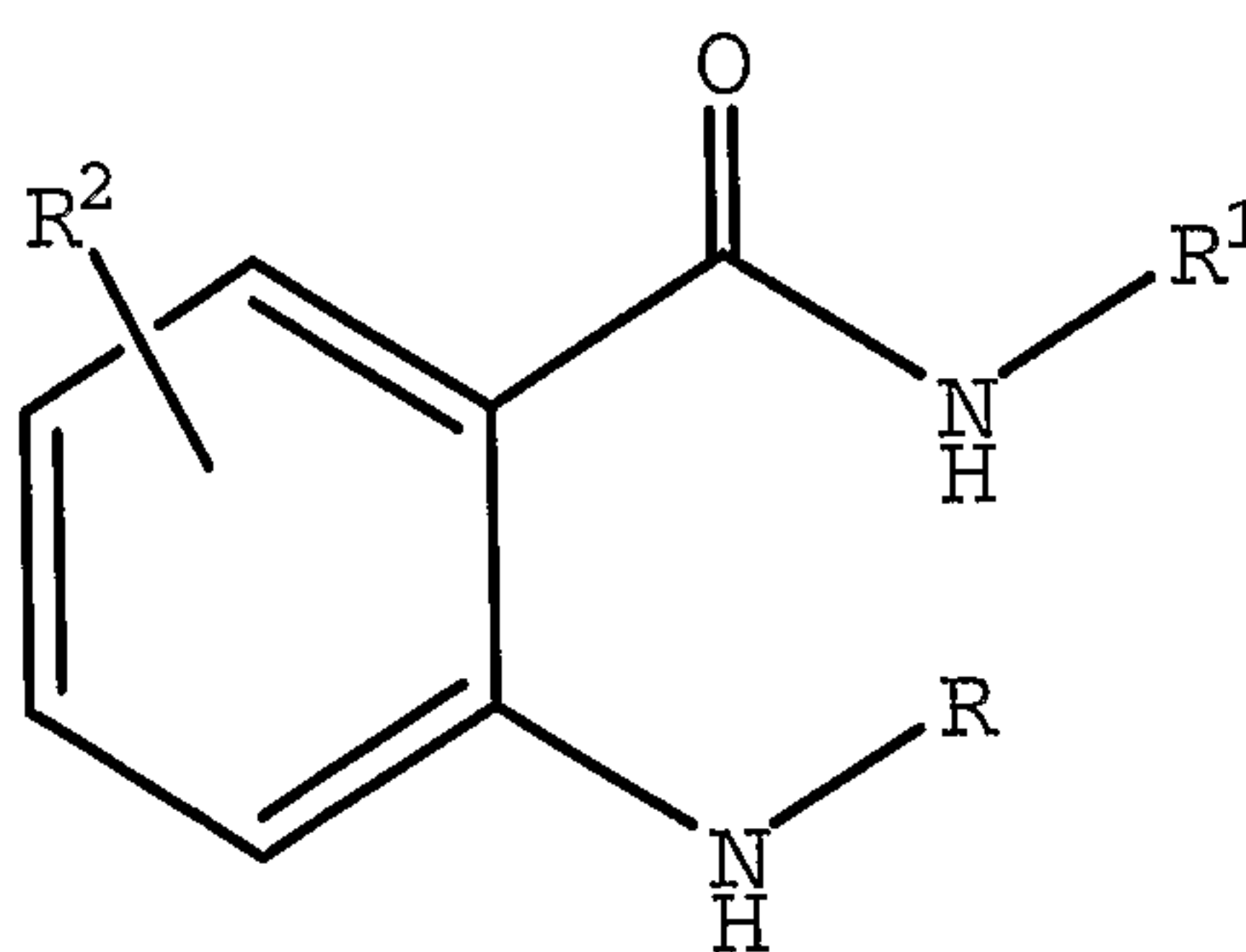
5 methylsulfonylamino,
 dimethylaminomethylcarbonylamino, 1-
 pyrrolidinyl-CH₂-C(=O)-NH-, 4-morpholinyl-CH₂-
 C(=O)-NH-, 3-tetrahydrofuryl-O-C(=O)-NH-, 1,1-
 di(trifluoromethyl)-1-(pyrrolidin-2-
 ylmethoxy)methyl, 3-tetrahydrofuryloxy, 1-
 methylcarbonyl-pyrrolidin-2-ylmethoxy, and
 methylsulfonylaminoethoxy;

10 wherein R^e and R^f are independently selected from H and C₁₋₂-
 haloalkyl; advantageously -CF₃;

wherein R⁷ is selected from H, C₁₋₃-alkyl, optionally
 substituted phenyl, optionally substituted phenyl-C₁₋₃-
 alkyl, 4-6 membered heterocyclyl, optionally
 substituted 4-6 membered heterocyclyl-C₁₋₃-alkyl, C₁₋₃-
 15 alkoxy-C₁₋₂-alkyl and C₁₋₃-alkoxy-C₁₋₃-alkoxy-C₁₋₃-alkyl;
 and

wherein R² is selected from H, halo, haloalkyl and C₁₋₆
 alkyl, and advantageously, H, fluoro, chloro, bromo,
 trifluoromethyl, methyl, ethyl, isopropyl and t-butyl.

20 In another embodiment, the invention provides a second class
 of compounds as defined below by Formula II:



II

25 wherein R is selected from 7-isoquinolinyl, 2-methyl-3-oxo-
 2,3-dihydroindazol-6-yl, [1,6]-naphthydrin-3-yl,
 [1,7]-naphthydrin-2-yl, oxo-2,3-dihydrobenzofuranyl,
 dihydro-benzodioxinyl, 6-quinazolinyl, 2-amino-6-

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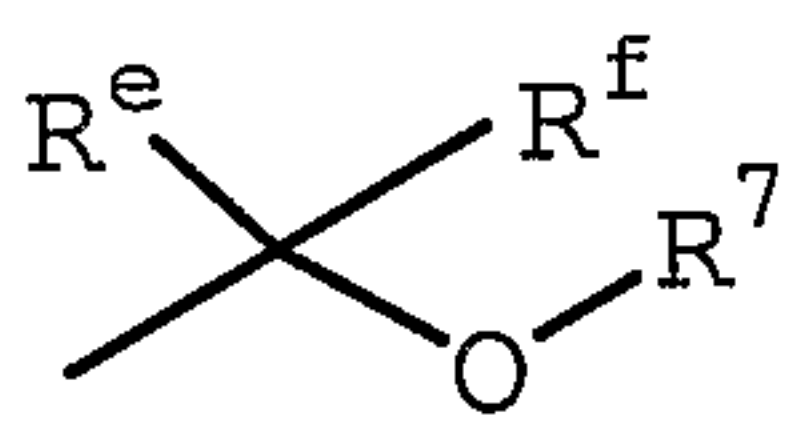
quinazolinyl, 4-methylamino-6-quinazolinyl, 2,4-diamino-6-quinazolinyl, 3-oxo-3,4-dihydro-1,4-benzoxazin-6-yl, 2,2-difluoro-1,3-benzodioxol-5-yl and 2,2,3,3-tetrafluoro-2,3-dihydro-1,4-benzodioxin-6-yl, each of which is optionally substituted with one or more substitutions selected from halo, haloalkyl, C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, N-dimethylamino-C₁₋₆-alkyl, N-dimethylamino-C₁₋₆-alkoxy, amino, carbonylamino, morpholino-sulfonyl, amino-sulfonyl, oxazolyl, pyrrolyl, morpholinyl, carboxyl, cyano, and acetyl;

wherein R¹ is selected from unsubstituted or substituted 1,2-dihydroquinolyl, 1,2,3,4-tetrahydroquinolyl, 1,2,3,4-tetrahydro-isoquinolyl, 2-oxo-1,2,3,4-tetrahydroquinolyl, 2-oxo-1,2,3,4-tetrahydro-isoquinolyl, 1-oxo-1,2,3,4-tetrahydro-isoquinolyl, isoquinolyl, quinolyl, indol-6-yl, 6-isoindolyl, 3,4-dihydro-2H-benzo[1,4]oxazin-6-yl, 3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl, 2,3-dihydro-1H-indol-6-yl, naphthyridinyl, 2-oxo-3,4-dihydro-1H-[1,8]naphthyridin-7-yl, 3,4-dihydro-[1,8]naphthyridinyl, 1,2,3,4-tetrahydro-[1,8]naphthyridinyl, quinoxalinyl, wherein substituted R¹ is substituted with one or more substituents selected from halo, optionally substituted C₁₋₆-alkyl, optionally substituted C₃₋₆-cycloalkyl, optionally substituted phenyl, optionally substituted phenyl-C₁-C₄-alkylenyl, C₁₋₂-haloalkoxy, optionally substituted phenyloxy, optionally substituted 4-6 membered heterocyclyl-C₁-C₆-alkyl, optionally substituted 4-6 membered heterocyclyl-C₂-C₄-alkenyl, optionally substituted 4-6 membered heterocyclyl, optionally substituted 4-6 membered heterocyclyloxy, optionally substituted 4-6 membered heterocyclyl-C₁₋₄-alkoxy, optionally substituted 4-6 membered heterocyclylsulfonyl, optionally substituted

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4-6 membered heterocyclylamino, optionally substituted
 4-6 membered heterocyclylcarbonyl, optionally
 substituted 4-6 membered heterocyclyl-C₁₋₄-
 alkylcarbonyl, optionally substituted 4-6 membered
 5 heterocyclylcarbonyl-C₁₋₄-alkyl, optionally substituted
 4-6 membered heterocyclyl-C₁₋₄-alkylcarbonylamino,
 optionally substituted 4-6 membered heterocyclyl-
 oxycarbonylamino, C₁₋₂-haloalkyl, C₁₋₄-aminoalkyl,
 10 optionally substituted C₁₋₄-aminoalkylcarbonyl, nitro,
 amino, C₁₋₃-alkylsulfonylamino, hydroxy, cyano,
 aminosulfonyl, C₁₋₂-alkylsulfonyl, C₁₋₂-
 alkylsulfonylamino, C₁₋₂-alkylsulfonylamino-C₁₋₄-alkoxy,
 halosulfonyl, C₁₋₄-alkylcarbonyl, amino-C₁₋₄-
 alkylcarbonyl, C₁₋₃-alkylamino-C₁₋₄-alkylcarbonyl, C₁₋₃-
 15 alkylamino-C₁₋₄-alkylcarbonylamino, C₁₋₄-alkoxycarbonyl-
 C₁₋₄-alkyl, C₁₋₃-alkylamino-C₁₋₃-alkyl, C₁₋₃-alkylamino-C₁₋₃-
 alkoxy, C₁₋₃-alkylamino-C₁₋₃-alkoxy-C₁₋₃-alkoxy, C₁₋₄-
 alkoxycarbonyl, C₁₋₄-alkoxycarbonylamino-C₁₋₄-alkyl, C₁₋₃-
 alkylsulfonylamino-C₁₋₃-alkoxy, C₁₋₄-hydroxyalkyl,

20  and C₁₋₄-alkoxy; and

wherein R^e and R^f are independently selected from H and C₁₋₂-
 haloalkyl;

wherein R⁷ is selected from H, C₁₋₃-alkyl, optionally
 substituted phenyl, optionally substituted phenyl-C₁₋₃-
 25 alkyl, 4-6 membered heterocyclyl, optionally
 substituted 4-6 membered heterocyclyl-C₁₋₃-alkyl, C₁₋₃-
 alkoxy-C₁₋₂-alkyl and C₁₋₃-alkoxy-C₁₋₃-alkoxy-C₁₋₃-alkyl;
 and

wherein R² is selected from H, halo, haloalkyl and C₁₋₆
 30 alkyl.

The compounds of the present invention further include
 pharmaceutically acceptable derivatives, including salts,
 of the compounds defined by Formulas I and II.

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An exemplary grouping of compounds of interest encompassed within Formulas I and II consist of compounds and pharmaceutically-acceptable derivatives thereof as follows:

- 5 2-((2-amino-6-quinazolinyl)amino)-N-(3-methyl-4-(1-methylethyl)phenyl)-3-pyridinecarboxamide;
- N-(4,4-dimethyl-1,2,3,4-tetrahydro-7-quinolinyl)-2-(6-quinazolinylamino)-3-pyridinecarboxamide;
- N-(4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-7-quinolinyl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;
- 10 N-(5-(1,1-dimethylethyl)-3-isoxazolyl)-2-((1-oxo-2,3-dihydro-1H-isoindol-4-yl)amino)-3-pyridinecarboxamide;
- N-(5-(1,1-dimethylethyl)-3-isoxazolyl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;
- 15 N-(1-(N,N-dimethylglycyl)-4,4-dimethyl-1,2,3,4-tetrahydro-7-quinolinyl)-2-(1H-indazol-6-ylamino)-3-pyridinecarboxamide;
- N-(1-acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;
- 20 N-(4,4-dimethyl-1,2,3,4-tetrahydro-7-isoquinolinyl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;
- 5-fluoro-2-(7-isoquinolinylamino)-N-(3-methyl-4-(1-methylethyl)phenyl)-3-pyridinecarboxamide;
- N-(4,4-dimethyl-1,2,3,4-tetrahydro-7-quinolinyl)-2-(1H-indazol-6-ylamino)-3-pyridinecarboxamide;
- 25 N-(4,4-dimethyl-1,2,3,4-tetrahydro-7-quinolinyl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;
- N-(3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;
- 30 N-(6-(1,1-dimethylethyl)-3-pyridinyl)-2-((1-oxo-2,3-dihydro-1H-isoindol-4-yl)amino)-3-pyridinecarboxamide;
- N-(2-glycyl-4,4-dimethyl-1,2,3,4-tetrahydro-7-isoquinolinyl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;

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- 2-(7-isoquinolinylamino)-N-(3-methyl-4-(1-methylethyl)phenyl)-3-pyridinecarboxamide;
 N-(3-(((2S)-1-methyl-2-pyrrolidinyl)methyl)oxy)-5-(trifluoromethyl)phenyl)-2-((1-oxo-2,3-dihydro-1H-isoindol-4-yl)amino)-3-pyridinecarboxamide;
 5 N-(3,3-dimethyl-1-((2S)-tetrahydro-2-furanylcarbonyl)-2,3-dihydro-1H-indol-6-yl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;
 N-(4-(1,1-dimethylethyl)phenyl)-2-(6-quinazolinylamino)-3-pyridinecarboxamide;
 10 N-(4,4-dimethyl-1,2,3,4-tetrahydro-7-isoquinolinyl)-2-(6-quinazolinylamino)-3-pyridinecarboxamide;
 N-(5,5-dimethyl-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;
 15 N-(1-acetyl-4,4-dimethyl-1,2,3,4-tetrahydro-7-quinolinyl)-2-(1H-indazol-6-ylamino)-3-pyridinecarboxamide;
 2-(7-isoquinolinylamino)-N-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-3-pyridinecarboxamide;
 N-(1-acetyl-4,4-dimethyl-1,2,3,4-tetrahydro-7-quinolinyl)-2-((1-oxo-2,3-dihydro-1H-isoindol-4-yl)amino)-3-pyridinecarboxamide;
 20 N-(4,4-dimethyl-2-((2R)-tetrahydro-2-furanylcarbonyl)-1,2,3,4-tetrahydro-7-isoquinolinyl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;
 25 N-(5-(1,1-dimethylethyl)-3-isoxazolyl)-2-(6-quinazolinylamino)-3-pyridinecarboxamide;
 N-(5,5-dimethyl-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)-2-(6-quinazolinylamino)-3-pyridinecarboxamide;
 N-(4-(1,1-dimethylethyl)phenyl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;
 30 N-(4,4-dimethyl-1,2,3,4-tetrahydro-7-isoquinolinyl)-2-(5-isoquinolinylamino)-3-pyridinecarboxamide;
 N-(2-acetyl-4,4-dimethyl-1,2,3,4-tetrahydro-7-isoquinolinyl)-2-(7-isoquinolinylamino)-3-

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- pyridinecarboxamide;
 2-(7-isoquinolinylamino)-N-(3-methyl-4-(pentafluoroethyl)phenyl)-3-pyridinecarboxamide;
 N-(5-(1,1-dimethylethyl)-3-isoxazolyl)-2-(5-isoquinolinylamino)-3-pyridinecarboxamide;
 5 N-(4-(1,1-dimethylpropyl)phenyl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;
 2-(7-isoquinolinylamino)-N-(3-(methyloxy)-5-(trifluoromethyl)phenyl)-3-pyridinecarboxamide;
 10 N-(4,4-dimethyl-1,2,3,4-tetrahydro-7-isoquinolinyl)-2-(1,6-naphthyridin-3-ylamino)-3-pyridinecarboxamide;
 N-(6-(1,1-dimethylethyl)-3-pyridinyl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;
 N-(1-(N,N-dimethylglycyl)-4,4-dimethyl-1,2,3,4-tetrahydro-7-quinolinyl)-2-((1-oxo-2,3-dihydro-1H-isoindol-4-yl)amino)-3-pyridinecarboxamide;
 15 N-(4-(1,1-dimethylethyl)phenyl)-2-(5-isoquinolinylamino)-3-pyridinecarboxamide;
 2-(1-oxo-2,3-dihydro-1H-isoindol-4-yl)amino)-N-(4-(2,2,2-trifluoro-1-(methyloxy)-1-(trifluoromethyl)ethyl)phenyl)-3-pyridinecarboxamide;
 20 N-(6-(1-methylcyclopropyl)-3-pyridinyl)-2-((1-oxo-2,3-dihydro-1H-isoindol-4-yl)amino)-3-pyridinecarboxamide;
 2-(1H-1,2,3-benzotriazol-5-ylamino)-N-(5-(1,1-dimethylethyl)-3-isoxazolyl)-3-pyridinecarboxamide;
 25 2-((1-oxo-2,3-dihydro-1H-isoindol-4-yl)amino)-N-(4-(pentafluoroethyl)-3-(1-piperazinylmethyl)phenyl)-3-pyridinecarboxamide;
 2-(7-isoquinolinylamino)-N-(4-(pentafluoroethyl)phenyl)-3-pyridinecarboxamide;
 30 2-(7-isoquinolinylamino)-N-(4-(2,2,2-trifluoro-1-(methyloxy)-1-(trifluoromethyl)ethyl)phenyl)-3-pyridinecarboxamide;
 2-(1H-indazol-6-ylamino)-N-(6-(1-methylcyclopropyl)-3-

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- pyridinyl)-3-pyridinecarboxamide;
 N-(4-(1,1-dimethylethyl)phenyl)-2-(1,6-naphthyridin-3-ylamino)-3-pyridinecarboxamide;
 2-(7-isoquinolinylamino)-N-(2-methyl-1,3-benzothiazol-5-yl)-
 5 3-pyridinecarboxamide;
 N-(4-chloro-3-(trifluoromethyl)phenyl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;
 2-(7-isoquinolinylamino)-N-(4-(trifluoromethyl)phenyl)-3-pyridinecarboxamide;
 10 2-(1,6-naphthyridin-3-ylamino)-N-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-3-pyridinecarboxamide;
 1,1-dimethylethyl 4,4-dimethyl-7-(((2-(1,6-naphthyridin-3-ylamino)-3-pyridinyl) carbonyl) amino)-3,4-dihydro-
 15 2(1H)-isoquinolinecarboxylate;
 N-(3-((4-(methylsulfonyl)-1-piperazinyl)methyl)-4-(pentafluoroethyl)phenyl)-2-((1-oxo-2,3-dihydro-1H-isoindol-4-yl) amino)-3-pyridinecarboxamide;
 N-(4,4-dimethyl-1,2,3,4-tetrahydro-7-isoquinolinyl)-2-((1-oxo-1,3-dihydro-2-benzofuran-4-yl) amino)-3-pyridinecarboxamide;
 20 2-((1-oxo-2,3-dihydro-1H-isoindol-4-yl) amino)-3-pyridinecarboxamide;
 N-(7-isoquinolinyl)-2-((1-oxo-2,3-dihydro-1H-isoindol-4-yl) amino)-3-pyridinecarboxamide;
 25 N-(4-(1,1-dimethylethyl)phenyl)-2-((2-methyl-3-oxo-2,3-dihydro-1H-indazol-6-yl) amino)-3-pyridinecarboxamide
 2-((2,2-difluoro-1,3-benzodioxol-5-yl) amino)-N-(4,4-dimethyl-1,2,3,4-tetrahydro-7-isoquinolinyl)-3-pyridinecarboxamide;
 30 2-((2,4-diamino-6-quinazolinyl) amino)-N-(4-(1,1-dimethylethyl)phenyl)-3-pyridinecarboxamide;
 2-((1-oxo-2,3-dihydro-1H-isoindol-4-yl) amino)-N-(6-(trifluoromethyl)-3-pyridinyl)-3-pyridinecarboxamide

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N-(6-chloro-3-pyridinyl)-2-((1-oxo-2,3-dihydro-1H-isoindol-4-yl)amino)-3-pyridinecarboxamide;

N-(2-acetyl-4,4-dimethyl-1,2,3,4-tetrahydro-7-isoquinolinyl)-2-((4-(methylamino)-6-

5 quinazolinyl)amino)-3-pyridinecarboxamide;

2-(4-(1,1-dimethylethyl)phenyl)-4-(1H-indazol-6-ylamino)-1,2-dihydro-3H-pyrrolo[3,4-c]pyridin-3-one;

2-(5-isoquinolinylamino)-N-(3-(((2S)-1-methyl-2-pyrrolidinyl)methyl)oxy)-5-(trifluoromethyl)phenyl)-3-
10 pyridinecarboxamide;

N-(1-acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-((1-oxo-1,3-dihydro-2-benzofuran-4-yl)amino)-3-pyridinecarboxamide;

N-(4-(phenyloxy)phenyl)-2-((4-(trifluoromethyl)phenyl)amino)-3-pyridinecarboxamide;
15

N-(3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-((1-oxo-1,3-dihydro-2-benzofuran-4-yl)amino)-3-pyridinecarboxamide;

2-((1-oxo-1,3-dihydro-2-benzofuran-5-yl)amino)-N-(4-(pentafluoroethyl)phenyl)-3-pyridinecarboxamide;
20

N-(4-(1,1-dimethylethyl)phenyl)-2-((1-oxo-1,3-dihydro-2-benzofuran-4-yl)amino)-3-pyridinecarboxamide;

2-((1-oxo-1,3-dihydro-2-benzofuran-4-yl)amino)-N-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-
25 3-pyridinecarboxamide;

N-(3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-(5-isoquinolinylamino)-3-pyridinecarboxamide;

2-((3-oxo-1,3-dihydro-2-benzofuran-5-yl)amino)-N-(4-(pentafluoroethyl)phenyl)-3-pyridinecarboxamide;

30 N-(6-(1-azetidiny)-3-pyridinyl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;

N-(5-(1-azetidiny)-2-pyridinyl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;

N-(5-(1,1-dimethylethyl)-3-isoxazolyl)-2-((2,2,3,3-

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- tetrafluoro-2,3-dihydro-1,4-benzodioxin-6-yl) amino)-3-pyridinecarboxamide;
- N-(4-(1,1-dimethylethyl)phenyl)-2-((2,2,3,3-tetrafluoro-2,3-dihydro-1,4-benzodioxin-6-yl) amino)-3-pyridinecarboxamide;
- 5 N-(4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-7-quinolinyl)-2-((2,2,3,3-tetrafluoro-2,3-dihydro-1,4-benzodioxin-6-yl) amino)-3-pyridinecarboxamide;
- 2-(1H-1,2,3-benzotriazol-5-ylamino)-N-(2-methyl-1,3-benzothiazol-5-yl)-3-pyridinecarboxamide;
- 10 2-(1H-1,2,3-benzotriazol-5-ylamino)-N-(4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-7-quinolinyl)-3-pyridinecarboxamide;
- 2-(7-isoquinolinylamino)-N-(3-((2R)-tetrahydro-2-furanylmethyl)oxy)-5-(trifluoromethyl)phenyl)-3-pyridinecarboxamide;
- 15 N-(5,5-dimethyl-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)-2-((3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-yl) amino)-3-pyridinecarboxamide;
- 20 N-(5-(1,1-dimethylethyl)-3-isoxazolyl)-2-((3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-yl) amino)-3-pyridinecarboxamide;
- 2-(1H-indazol-6-ylamino)-N-(2-methyl-1,3-benzothiazol-5-yl)-3-pyridinecarboxamide;
- 25 ethyl (2S)-2-(4-((2-(7-isoquinolinylamino)-3-pyridinyl) carbonyl) amino)phenyl)propanoate;
- (2S)-2-(4-((2-(7-isoquinolinylamino)-3-pyridinyl) carbonyl) amino)phenyl)propanoic acid;
- 2-(7-isoquinolinylamino)-N-(3-oxo-3,4-dihydro-2H-1,4-benzothiazin-6-yl)-3-pyridinecarboxamide; and
- 30 N-(4-(1,1-dimethylethyl)phenyl)-2-(5-quinolinylamino)-3-pyridinecarboxamide.

A second exemplary grouping of compounds of interest within Formulas I and II consist of compounds as follows:

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- N-(4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-7-quinolinyl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;
- N-(4,4-dimethyl-1,2,3,4-tetrahydro-7-quinolinyl)-2-(7-isoquinolinylamino)benzamide;
- 5 N-(5-(1,1-dimethylethyl)-3-isoxazolyl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;
- 2-(7-isoquinolinylamino)-N-(3-methyl-4-(1-pyrrolidinyl)phenyl)-3-pyridinecarboxamide;
- N-(1-acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;
- 10 N-(4,4-dimethyl-1,2,3,4-tetrahydro-7-isoquinolinyl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;
- 5-fluoro-2-(7-isoquinolinylamino)-N-(3-methyl-4-(1-methylethyl)phenyl)-3-pyridinecarboxamide;
- 15 N-(4,4-dimethyl-1,2,3,4-tetrahydro-7-quinolinyl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;
- N-(3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;
- N-(2-glycyl-4,4-dimethyl-1,2,3,4-tetrahydro-7-isoquinolinyl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;
- 20 N-(3,3-dimethyl-1-((2S)-tetrahydro-2-furanylcarbonyl)-2,3-dihydro-1H-indol-6-yl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;
- 25 N-(5,5-dimethyl-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;
- N-(4-(1,1-dimethylethyl)phenyl)-2-(7-isoquinolinylamino)benzamide;
- 2-(7-isoquinolinylamino)-N-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-3-pyridinecarboxamide;
- 30 N-(4,4-dimethyl-2-((2R)-tetrahydro-2-furanylcarbonyl)-1,2,3,4-tetrahydro-7-isoquinolinyl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;

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- N-(4-(1,1-dimethylethyl)phenyl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;
- N-(2-acetyl-4,4-dimethyl-1,2,3,4-tetrahydro-7-isoquinolinyl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;
- 5 2-(7-isoquinolinylamino)-N-(3-methyl-4-(pentafluoroethyl)phenyl)-3-pyridinecarboxamide;
- N-(4-(1,1-dimethylethyl)phenyl)-3-fluoro-2-(7-isoquinolinylamino)benzamide;
- 10 2-(7-isoquinolinylamino)-N-(4-(1-methylethyl)phenyl)-3-pyridinecarboxamide;
- N-(4-(1,1-dimethylpropyl)phenyl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;
- 2-(7-isoquinolinylamino)-N-(3-(methyloxy)-5-(trifluoromethyl)phenyl)-3-pyridinecarboxamide;
- 15 N-(3-chloro-4-methylphenyl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;
- N-(6-(1,1-dimethylethyl)-3-pyridinyl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;
- 20 2-(7-isoquinolinylamino)-N-(4-(pentafluoroethyl)phenyl)-3-pyridinecarboxamide;
- 2-(7-isoquinolinylamino)-N-(4-(2,2,2-trifluoro-1-(methyloxy)-1-(trifluoromethyl)ethyl)phenyl)-3-pyridinecarboxamide;
- 25 2-(7-isoquinolinylamino)-N-(2-methyl-1,3-benzothiazol-5-yl)-3-pyridinecarboxamide;
- N-(4-chloro-3-(trifluoromethyl)phenyl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;
- 2-(7-isoquinolinylamino)-N-(4-(trifluoromethyl)phenyl)-3-pyridinecarboxamide;
- 30 N-(6-(1-azetidiny)-3-pyridinyl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;
- N-(5-(1-azetidiny)-2-pyridinyl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;

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- 2-(7-isoquinolinylamino)-N-(3-(((2R)-tetrahydro-2-furanylmethyl)oxy)-5-(trifluoromethyl)phenyl)-3-pyridinecarboxamide;
- ethyl (2S)-2-(4-(((2-(7-isoquinolinylamino)-3-pyridinyl)carbonyl)amino)phenyl)propanoate;
- (2S)-2-(4-(((2-(7-isoquinolinylamino)-3-pyridinyl)carbonyl)amino)phenyl)propanoic acid;
- (2R)-2-(4-(((2-(7-isoquinolinylamino)-3-pyridinyl)carbonyl)amino)phenyl)propanoic acid;
- 2-(7-isoquinolinylamino)-N-(3-oxo-3,4-dihydro-2H-1,4-benzothiazin-6-yl)-3-pyridinecarboxamide;
- 2-(7-isoquinolinylamino)-N-(4-((trifluoromethyl)oxy)phenyl)-3-pyridinecarboxamide; and
- N-(3-chloro-4-(trifluoromethyl)phenyl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide.

A third exemplary grouping of compounds of interest within Formulas I and II consist of pharmaceutically-acceptable hydrochloride, sulfate, sulfonate or phosphate salts of the follow compounds:

- N-(4,4-dimethyl-2-oxo-1,2,3,4-tetrahydro-7-quinolinyl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;
- N-(4,4-dimethyl-1,2,3,4-tetrahydro-7-quinolinyl)-2-(7-isoquinolinylamino)benzamide;
- N-(5-(1,1-dimethylethyl)-3-isoxazolyl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;
- 2-(7-isoquinolinylamino)-N-(3-methyl-4-(1-pyrrolidinyl)phenyl)-3-pyridinecarboxamide;
- N-(1-acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;
- N-(4,4-dimethyl-1,2,3,4-tetrahydro-7-isoquinolinyl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;
- 5-fluoro-2-(7-isoquinolinylamino)-N-(3-methyl-4-(1-methylethyl)phenyl)-3-pyridinecarboxamide;
- N-(4,4-dimethyl-1,2,3,4-tetrahydro-7-quinolinyl)-2-(7-

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- isoquinolinylamino)-3-pyridinecarboxamide;
N-(3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-(7-
isoquinolinylamino)-3-pyridinecarboxamide;
N-(2-glycyl-4,4-dimethyl-1,2,3,4-tetrahydro-7-
5 isoquinolinyl)-2-(7-isoquinolinylamino)-3-
pyridinecarboxamide;
N-(3,3-dimethyl-1-((2S)-tetrahydro-2-furanylcarbonyl)-2,3-
dihydro-1H-indol-6-yl)-2-(7-isoquinolinylamino)-3-
pyridinecarboxamide;
10 N-(5,5-dimethyl-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-2-
yl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;
N-(4-(1,1-dimethylethyl)phenyl)-2-(7-
isoquinolinylamino)benzamide;
2-(7-isoquinolinylamino)-N-(4-(2,2,2-trifluoro-1-hydroxy-1-
15 (trifluoromethyl)ethyl)phenyl)-3-
pyridinecarboxamide;
N-(4,4-dimethyl-2-((2R)-tetrahydro-2-furanylcarbonyl)-
1,2,3,4-tetrahydro-7-isoquinolinyl)-2-(7-
isoquinolinylamino)-3-pyridinecarboxamide;
20 N-(4-(1,1-dimethylethyl)phenyl)-2-(7-isoquinolinylamino)-3-
pyridinecarboxamide;
N-(2-acetyl-4,4-dimethyl-1,2,3,4-tetrahydro-7-
isoquinolinyl)-2-(7-isoquinolinylamino)-3-
pyridinecarboxamide;
25 2-(7-isoquinolinylamino)-N-(3-methyl-4-
(pentafluoroethyl)phenyl)-3-pyridinecarboxamide;
N-(4-(1,1-dimethylethyl)phenyl)-3-fluoro-2-(7-
isoquinolinylamino)benzamide;
2-(7-isoquinolinylamino)-N-(4-(1-methylethyl)phenyl)-3-
30 pyridinecarboxamide;
N-(4-(1,1-dimethylpropyl)phenyl)-2-(7-isoquinolinylamino)-3-
pyridinecarboxamide;
2-(7-isoquinolinylamino)-N-(3-(methyloxy)-5-
(trifluoromethyl)phenyl)-3-pyridinecarboxamide;

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- N-(3-chloro-4-methylphenyl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;
- N-(6-(1,1-dimethylethyl)-3-pyridinyl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;
- 5 2-(7-isoquinolinylamino)-N-(4-(pentafluoroethyl)phenyl)-3-pyridinecarboxamide;
- 2-(7-isoquinolinylamino)-N-(4-(2,2,2-trifluoro-1-(methyloxy)-1-(trifluoromethyl)ethyl)phenyl)-3-pyridinecarboxamide;
- 10 2-(7-isoquinolinylamino)-N-(2-methyl-1,3-benzothiazol-5-yl)-3-pyridinecarboxamide;
- N-(4-chloro-3-(trifluoromethyl)phenyl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;
- 2-(7-isoquinolinylamino)-N-(4-(trifluoromethyl)phenyl)-3-pyridinecarboxamide;
- 15 N-(6-(1-azetidiny)-3-pyridinyl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;
- N-(5-(1-azetidiny)-2-pyridinyl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide;
- 20 2-(7-isoquinolinylamino)-N-(3-(((2R)-tetrahydro-2-furanylmethyl)oxy)-5-(trifluoromethyl)phenyl)-3-pyridinecarboxamide;
- ethyl (2S)-2-(4-(((2-(7-isoquinolinylamino)-3-pyridinyl)carbonyl)amino)phenyl)propanoate;
- 25 (2S)-2-(4-(((2-(7-isoquinolinylamino)-3-pyridinyl)carbonyl)amino)phenyl)propanoic acid;
- (2R)-2-(4-(((2-(7-isoquinolinylamino)-3-pyridinyl)carbonyl)amino)phenyl)propanoic acid;
- 2-(7-isoquinolinylamino)-N-(3-oxo-3,4-dihydro-2H-1,4-benzothiazin-6-yl)-3-pyridinecarboxamide;
- 30 2-(7-isoquinolinylamino)-N-(4-((trifluoromethyl)oxy)phenyl)-3-pyridinecarboxamide; and
- N-(3-chloro-4-(trifluoromethyl)phenyl)-2-(7-isoquinolinylamino)-3-pyridinecarboxamide.

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INDICATIONS

Compounds of the present invention would be useful
5 for, but not limited to, the prevention or treatment of
angiogenesis related diseases and physiological conditions.
Particularly, the compounds of the invention would inhibit
the growth of blood vessels thereby reducing the blood flow
to and from a given tumor site, resulting in no net growth
10 to the tumor at that site and reduced or no migration of
tumor cells to and from that site. Accordingly, these
compounds are useful for an overall reduction in the size of
the tumor.

The compounds of the present invention have kinase
15 inhibitory activity, such as VEGFR/KDR inhibitory activity,
and are useful in therapy to minimize deleterious effects of
VEGF. Accordingly, the compounds of the present invention
would be useful, as antineoplasia agents, for the treatment
of neoplasia including cancer and metastasis, including, but
20 not limited to: carcinoma such as cancer of the bladder,
breast, colon, kidney, liver, lung (including small cell
lung cancer), esophagus, gall-bladder, ovary, pancreas,
stomach, cervix, thyroid, prostate, and skin (including
squamous cell carcinoma); hematopoietic tumors of lymphoid
25 lineage (including leukemia, acute lymphocytic leukemia,
acute lymphoblastic leukemia, B-cell lymphoma, T-cell-
lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy
cell lymphoma and Burkett's lymphoma); hematopoietic tumors
of myeloid lineage (including acute and chronic myelogenous
30 leukemias, myelodysplastic syndrome and promyelocytic
leukemia); tumors of mesenchymal origin (including
fibrosarcoma and rhabdomyosarcoma, and other sarcomas, e.g.
soft tissue and bone); tumors of the central and peripheral
nervous system (including astrocytoma, neuroblastoma, glioma
35 and schwannomas); and other tumors (including melanoma,
seminoma, teratocarcinoma, osteosarcoma, xenoderoma
pigmentosum, keratocanthoma, thyroid follicular cancer and

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Kaposi's sarcoma). Preferably, the compounds are useful for the treatment of neoplasia selected from lung cancer, colon cancer and breast cancer.

The compounds of the present invention also would be useful for treatment of ophthalmological conditions such as corneal graft rejection, ocular neovascularization, retinal neovascularization including neovascularization following injury or infection, diabetic retinopathy, retrolental fibroplasia and neovascular glaucoma; retinal ischemia; vitreous hemorrhage; ulcerative diseases such as gastric ulcer; pathological, but non-malignant, conditions such as hemangiomas, including infantile hemangiomas, angiofibroma of the nasopharynx and avascular necrosis of bone; and disorders of the female reproductive system such as endometriosis. The compounds are also useful for the treatment of edema, and conditions of vascular hyperpermeability.

The compounds of the present invention are useful in therapy of proliferative diseases. These compounds can be used for the treatment of an inflammatory rheumatoid or rheumatic disease, especially of manifestations at the locomotor apparatus, such as various inflammatory rheumatoid diseases, especially chronic polyarthritis including rheumatoid arthritis, juvenile arthritis or psoriasis arthropathy; paraneoplastic syndrome or tumor-induced inflammatory diseases, turbid effusions, collagenosis, such as systemic Lupus erythematosus, poly-myositis, dermatomyositis, systemic scleroderma or mixed collagenosis; postinfectious arthritis (where no living pathogenic organism can be found at or in the affected part of the body), seronegative spondylarthritis, such as spondylitis ankylosans; vasculitis, sarcoidosis, or arthrosis; or further any combinations thereof. An example of an inflammation related disorder is (a) synovial inflammation,

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for example, synovitis, including any of the particular forms of synovitis, in particular bursal synovitis and purulent synovitis, as far as it is not crystal-induced. Such synovial inflammation may for example, be consequential to or associated with disease, e.g. arthritis, e.g. osteoarthritis, rheumatoid arthritis or arthritis deformans. The present invention is further applicable to the systemic treatment of inflammation, e.g. inflammatory diseases or conditions, of the joints or locomotor apparatus in the region of the tendon insertions and tendon sheaths. Such inflammation may be, for example, consequential to or associated with disease or further (in a broader sense of the invention) with surgical intervention, including, in particular conditions such as insertion endopathy, myofasciale syndrome and tendomyosis. The present invention is further especially applicable to the treatment of inflammation, e.g. inflammatory disease or condition, of connective tissues including dermatomyositis and myositis.

The compounds of the present invention can be used as active agents against such disease states as arthritis, atherosclerosis, psoriasis, hemangiomas, myocardial angiogenesis, coronary and cerebral collaterals, ischemic limb angiogenesis, wound healing, peptic ulcer Helicobacter related diseases, fractures, cat scratch fever, rubeosis, neovascular glaucoma and retinopathies such as those associated with diabetic retinopathy or macular degeneration. In addition, some of these compounds can be used as active agents against solid tumors, malignant ascites, hematopoietic cancers and hyperproliferative disorders such as thyroid hyperplasia (especially Grave's disease), and cysts (such as hypervascularity of ovarian stroma, characteristic of polycystic ovarian syndrome (Stein- Leventhal syndrome)) since such diseases require a

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proliferation of blood vessel cells for growth and/or metastasis.

Further, some of these compounds can be used as active agents against burns, chronic lung disease, stroke, polyps, anaphylaxis, chronic and allergic inflammation, ovarian hyperstimulation syndrome, brain tumor-associated cerebral edema, high-altitude, trauma or hypoxia induced cerebral or pulmonary edema, ocular and macular edema, ascites, and other diseases where vascular hyperpermeability, effusions, exudates, protein extravasation, or edema is a manifestation of the disease. The compounds will also be useful in treating disorders in which protein extravasation leads to the deposition of fibrin and extracellular matrix, promoting stromal proliferation (e.g. fibrosis, cirrhosis and carpal tunnel syndrome).

The compounds of the present invention are also useful in the treatment of ulcers including bacterial, fungal, Mooren ulcers and ulcerative colitis.

The compounds of the present invention are also useful in the treatment of conditions wherein undesired angiogenesis, edema, or stromal deposition occurs in viral infections such as Herpes simplex, Herpes Zoster, AIDS, Kaposi's sarcoma, protozoan infections and toxoplasmosis, following trauma, radiation, stroke, endometriosis, ovarian hyperstimulation syndrome, systemic lupus, sarcoidosis, synovitis, Crohn's disease, sickle cell anaemia, Lyme disease, pemphigoid, Paget's disease, hyperviscosity syndrome, Osler-Weber-Rendu disease, chronic inflammation, chronic occlusive pulmonary disease, asthma, and inflammatory rheumatoid or rheumatic disease. The compounds are also useful in the reduction of sub-cutaneous fat and for the treatment of obesity.

The compounds of the present invention are also useful in the treatment of ocular conditions such as ocular and

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macular edema, ocular neovascular disease, scleritis, radial keratotomy, uveitis, vitritis, myopia, optic pits, chronic retinal detachment, post-laser complications, glaucoma, conjunctivitis, Stargardt's disease and Eales disease in addition to retinopathy and macular degeneration.

The compounds of the present invention are also useful in the treatment of cardiovascular conditions such as atherosclerosis, restenosis, arteriosclerosis, vascular occlusion and carotid obstructive disease.

The compounds of the present invention are also useful in the treatment of cancer related indications such as solid tumors, sarcomas (especially Ewing's sarcoma and osteosarcoma), retinoblastoma, rhabdomyosarcomas, neuroblastoma, hematopoietic malignancies, including leukemia and lymphoma, tumor-induced pleural or pericardial effusions, and malignant ascites.

The compounds of the present invention are also useful in the treatment of diabetic conditions such as diabetic retinopathy and microangiopathy.

The compounds of the present invention may also act as inhibitors of other protein kinases, e.g. Src, Lck, Abl, GSK, Kit, p38, EGFR, CDK-2, CDK-5, IKK, JNK3, bFGFR, PDGFR, RAF and ZAP70. Thus, these compounds may be effective in the treatment of diseases and conditions associated with the function and activity of various other protein kinases, such as those listed above.

Besides being useful for human treatment, these compounds are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. By way of example, these compounds may be used to treat horses, dogs, and cats.

DEFINITIONS

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The term "treatment" includes therapeutic treatment as well as prophylactic treatment (either preventing the onset of disorders altogether or delaying the onset of a preclinically evident stage of disorders in individuals).

5 The term "derivative" is broadly construed herein, and intended to encompass any salt of a compound of this invention, any ester of a compound of this invention, or any other compound, such as a prodrug, which upon administration to a patient is capable of providing
10 (directly or indirectly) a compound of this invention, or a metabolite or residue thereof, characterized by the ability to inhibit angiogenesis.

The term and "pharmaceutically-acceptable derivative" as used herein, denotes a derivative which is
15 pharmaceutically acceptable.

The phrase "therapeutically-effective" is intended to qualify the amount of each agent, which will achieve the goal of improvement in disorder severity and the frequency of incidence over treatment of each agent by itself, while
20 avoiding adverse side effects typically associated with alternative therapies. For example, effective neoplastic therapeutic agents prolong the survivability of the patient, inhibit the rapidly-proliferating cell growth associated with the neoplasm, or effect a regression of the neoplasm.

25 The term "carrier", as used herein, denotes any pharmaceutically acceptable additive, excipient, adjuvant, or other suitable ingredient, other than the active pharmaceutical ingredient (API), which is typically included for formulation and/or administration purposes.

30 The term "H" denotes a single hydrogen atom. This radical may be attached, for example, to an oxygen atom to form a hydroxyl radical.

Where the term "alkyl" is used, either alone or within other terms such as "haloalkyl" and "alkylamino", it

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embraces linear or branched radicals having one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, hexyl and the like. The phrase "one or more alkyl substitutions" embraces, beyond its normal meaning, the instance where a single atom, such as carbon, has two of the same or different substituents attached to it. For example, a "gem-dimethyl" group, which the phrase above embraces, refers to a single carbon atom in a structural moiety having two methyl radicals attached to it. The term "alkylenyl" embraces bridging divalent alkyl radicals such as methylenyl and ethylenyl.

15 The term "alkenyl" embraces linear or branched radicals having at least one carbon-carbon double bond of two to about twelve carbon atoms. More preferred alkenyl radicals are "lower alkenyl" radicals having two to about six carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, allyl, propenyl, butenyl and 4-methylbutenyl. The terms "alkenyl" and "lower alkenyl", embrace radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations.

25 The term "alkynyl" denotes linear or branched radicals having at least one carbon-carbon triple bond and having two to about twelve carbon atoms. More preferred alkynyl radicals are "lower alkynyl" radicals having two to about six carbon atoms. Most preferred are lower alkynyl radicals having two to about four carbon atoms. Examples of such radicals include propargyl, butynyl, and the like.

30 The term "halo" means halogens such as fluorine, chlorine, bromine or iodine atoms.

 The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo

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as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals including perhaloalkyl. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" embraces radicals having 1-6 carbon atoms. Even more preferred are lower haloalkyl radicals having one to three carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl.

"Perfluoroalkyl" means alkyl radicals having all hydrogen atoms replaced with fluoro atoms. Examples include trifluoromethyl and pentafluoroethyl.

The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl. Even more preferred are lower hydroxyalkyl radicals having one to three carbon atoms.

The term "alkoxy" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and *tert*-butoxy. Even more preferred are lower alkoxy radicals having one to three carbon atoms. Alkoxy radicals may be further substituted with one or more halo atoms, such

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as fluoro, chloro or bromo, to provide "haloalkoxy" radicals. Even more preferred are lower haloalkoxy radicals having one to three carbon atoms. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy.

The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one or two rings wherein such rings may be attached together in a fused manner. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, indenyl, tetrahydronaphthyl, and indanyl. More preferred aryl is phenyl. Said "aryl" group may have 1 to 5 substituents such as lower alkyl, hydroxyl, halo, haloalkyl, nitro, cyano, alkoxy and lower alkylamino. Phenyl substituted with -O-CH₂-O- forms the aryl benzodioxolyl substituent.

The term "heterocyclyl" embraces saturated, partially saturated and unsaturated heteroatom-containing ring radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. It does not include rings containing -O-O-, -O-S- or -S-S- portions. Said "heterocyclyl" group may have 1 to 3 substituents such as oxo (also known as "carbonyl"), hydroxyl, Boc, halo, haloalkyl, cyano, lower alkyl, lower aralkyl, lower alkoxy, amino and lower alkylamino.

Examples of saturated heterocyclic radicals include saturated 3 to 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atoms [e.g. pyrrolidinyl, imidazolidinyl, piperidinyl, pyrrolinyl, piperazinyl]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. morpholinyl]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl]. Examples of partially saturated heterocyclyl

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radicals include dihydrothienyl, dihydropyranyl, dihydrofuryl and dihydrothiazolyl.

Examples of unsaturated heterocyclic radicals, also termed "heteroaryl" radicals, include unsaturated 5 to 6 membered heteromonocyclyl group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl]; unsaturated 5- to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, 2-furyl, 3-furyl, etc.; unsaturated 5 to 6-membered heteromonocyclic group containing a sulfur atom, for example, 2-thienyl, 3-thienyl, etc.; unsaturated 5- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl]; unsaturated 5 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl].

The term also embraces radicals where heterocyclic radicals are fused/condensed with aryl radicals: unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyll, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo [1,5-b]pyridazinyl]; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl]; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl]; and saturated, partially unsaturated and unsaturated condensed heterocyclic group

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containing 1 to 2 oxygen or sulfur atoms [e.g. benzofuryl, benzothienyl, 2,3-dihydro-benzo[1,4]dioxinyl, benxo[1,3]dioxyly, dihydrobenzofuryl and dihydroisobenzofuryl]. Preferred heterocyclic radicals include five to ten membered fused or unfused radicals. More preferred examples of heteroaryl radicals include quinolyl, isoquinolyl, imidazolyl, pyridyl, thienyl, thiazolyl, oxazolyl, furyl, and pyrazinyl. Other preferred heteroaryl radicals are 5- or 6-membered heteroaryl, containing one or two heteroatoms selected from sulfur, nitrogen and oxygen, selected from thienyl, furyl, pyrrolyl, indazolyl, pyrazolyl, oxazolyl, triazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridyl, piperidinyl and pyrazinyl.

Particular examples of non-nitrogen containing heteroaryl include pyranyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, benzofuryl, benzothienyl, and the like.

Particular examples of partially saturated and saturated heterocyclyl include pyrrolidinyl, imidazolidinyl, piperidinyl, pyrrolinyl, pyrazolidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, thiazolidinyl, dihydrothienyl, 2,3-dihydro-benzo[1,4]dioxanyl, indolinyl, isoindolinyl, dihydrobenzothienyl, dihydrobenzofuryl, isochromanyl, chromanyl, 1,2-dihydroquinolyl, 1,2,3,4-tetrahydro-isoquinolyl, 1,2,3,4-tetrahydro-quinolyl, 2,3,4,4a,9,9a-hexahydro-1H-3-aza-fluorenyl, 5,6,7-trihydro-1,2,4-triazolo[3,4-a]isoquinolyl, 3,4-dihydro-2H-benzo[1,4]oxazinyl, benzo[1,4]dioxanyl, 2,3-dihydro-1H-1λ'-benzo[d]isothiazol-6-yl, dihydropyranyl, dihydrofuryl and dihydrothiazolyl, and the like.

The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals -SO₂-.

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The term "aminosulfonyl" denotes a sulfonyl radical substituted with an amine radical, forming a sulfonamide ($-\text{SO}_2\text{NH}_2$).

The term "alkylaminosulfonyl" includes "N-alkylaminosulfonyl" where sulfamyl radicals are independently substituted with one or two alkyl radical(s). More preferred alkylaminosulfonyl radicals are "lower alkylaminosulfonyl" radicals having one to six carbon atoms. Even more preferred are lower alkylaminosulfonyl radicals having one to three carbon atoms. Examples of such lower alkylaminosulfonyl radicals include N-methylaminosulfonyl, and N-ethylaminosulfonyl.

The term "carboxy", whether used alone or with other terms, such as "carboxyalkyl", denotes $-\text{CO}_2\text{H}$.

The term "carbonyl", whether used alone or with other terms, such as "aminocarbonyl", denotes $-(\text{C}=\text{O})-$.

The term "aminocarbonyl" denotes an amide group of the formula $-\text{C}(=\text{O})\text{NH}_2$.

The terms "N-alkylaminocarbonyl" and "N,N-dialkylaminocarbonyl" denote aminocarbonyl radicals independently substituted with one or two alkyl radicals, respectively. More preferred are "lower alkylaminocarbonyl" having lower alkyl radicals as described above attached to an aminocarbonyl radical.

The terms "N-arylaminocarbonyl" and "N-alkyl-N-arylaminocarbonyl" denote aminocarbonyl radicals substituted, respectively, with one aryl radical, or one alkyl and one aryl radical.

The terms "heterocyclalkyl" and "heterocyclalkylenyl" embrace heterocyclic-substituted alkyl and alkylene radicals. More preferred heterocyclalkylenyl radicals are "5- or 6-membered heteroarylalkylenyl" radicals having alkyl portions of one to six carbon atoms and a 5- or 6-membered heteroaryl

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radical. Even more preferred are lower heteroarylalkylenyl radicals having alkyl portions of one to three carbon atoms. Examples include such radicals as pyridylmethyl and thienylmethyl.

5 The terms "aralkyl" and "aryl alkylenyl" embrace aryl-substituted alkyl and alkylenyl radicals. Preferable aralkyl radicals are "lower aralkyl" radicals having aryl radicals attached to alkyl radicals having one to six carbon atoms. Even more preferred are "phenylalkylenyl" attached to alkyl
10 portions having one to three carbon atoms. Examples of such radicals include benzyl, diphenylmethyl and phenylethyl. The aryl in said aralkyl may be additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy.

15 The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. Even more preferred are lower alkylthio radicals having one to three carbon atoms. An example of "alkylthio" is methylthio, (CH₃S-).

20 The term "haloalkylthio" embraces radicals containing a haloalkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. Even more preferred are lower haloalkylthio radicals having one to three carbon atoms. An example of "haloalkylthio" is trifluoromethylthio.

25 The term "alkylamino" embraces "N-alkylamino" and "N,N-dialkylamino" where amino groups are independently substituted with one alkyl radical and with two alkyl radicals, respectively. More preferred alkylamino radicals are "lower alkylamino" radicals having one or two alkyl
30 radicals of one to six carbon atoms, attached to a nitrogen atom. Even more preferred are lower alkylamino radicals having one to three carbon atoms. Suitable alkylamino radicals may be mono or dialkylamino such as N-methylamino,

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N-ethylamino, N,N-dimethylamino, N,N-diethylamino and the like.

The term "arylamino" denotes amino groups, which have been substituted with one or two aryl radicals, such as N-phenylamino. The arylamino radicals may be further substituted on the aryl ring portion of the radical.

The term "heteroarylamino" denotes amino groups, which have been substituted with one or two heteroaryl radicals, such as N-thienylamino. The "heteroarylamino" radicals may be further substituted on the heteroaryl ring portion of the radical.

The term "aralkylamino" denotes amino groups, which have been substituted with one or two aralkyl radicals. More preferred are phenyl-C₁-C₃-alkylamino radicals, such as N-benzylamino. The aralkylamino radicals may be further substituted on the aryl ring portion.

The terms "N-alkyl-N-arylamino" and "N-aralkyl-N-alkylamino" denote amino groups, which have been independently substituted with one aralkyl and one alkyl radical, or one aryl and one alkyl radical, respectively, to an amino group.

The term "aminoalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more amino radicals. More preferred aminoalkyl radicals are "lower aminoalkyl" radicals having one to six carbon atoms and one or more amino radicals. Examples of such radicals include aminomethyl, aminoethyl, aminopropyl, aminobutyl and aminohexyl. Even more preferred are lower aminoalkyl radicals having one to three carbon atoms.

The term "alkylaminoalkyl" embraces alkyl radicals substituted with alkylamino radicals. More preferred alkylaminoalkyl radicals are "lower alkylaminoalkyl" radicals having alkyl radicals of one to six carbon atoms.

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Even more preferred are lower alkylaminoalkyl radicals having alkyl radicals of one to three carbon atoms. Suitable alkylaminoalkyl radicals may be mono or dialkyl substituted, such as N-methylaminomethyl, N,N-dimethyl-aminoethyl, N,N-diethylaminomethyl and the like.

The term "alkylaminoalkoxy" embraces alkoxy radicals substituted with alkylamino radicals. More preferred alkylaminoalkoxy radicals are "lower alkylaminoalkoxy" radicals having alkoxy radicals of one to six carbon atoms. Even more preferred are lower alkylaminoalkoxy radicals having alkyl radicals of one to three carbon atoms. Suitable alkylaminoalkoxy radicals may be mono or dialkyl substituted, such as N-methylaminoethoxy, N,N-dimethylaminoethoxy, N,N-diethylaminoethoxy and the like.

The term "alkylaminoalkoxyalkoxy" embraces alkoxy radicals substituted with alkylaminoalkoxy radicals. More preferred alkylaminoalkoxyalkoxy radicals are "lower alkylaminoalkoxyalkoxy" radicals having alkoxy radicals of one to six carbon atoms. Even more preferred are lower alkylaminoalkoxyalkoxy radicals having alkyl radicals of one to three carbon atoms. Suitable alkylaminoalkoxyalkoxy radicals may be mono or dialkyl substituted, such as N-methylaminomethoxyethoxy, N-methylaminoethoxyethoxy, N,N-dimethylaminoethoxyethoxy, N,N-diethylaminomethoxymethoxy and the like.

The term "halosulfonyl" embraces sulfonyl radicals substituted with a halogen radical. Examples of such halosulfonyl radicals include chlorosulfonyl and fluorosulfonyl.

The term "arylthio" embraces aryl radicals of six to ten carbon atoms, attached to a divalent sulfur atom. An example of "arylthio" is phenylthio.

The term "aralkylthio" embraces aralkyl radicals as described above, attached to a divalent sulfur atom. More

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preferred are phenyl-C₁-C₃-alkylthio radicals. An example of "aralkylthio" is benzylthio.

The term "aryloxy" embraces optionally substituted aryl radicals, as defined above, attached to an oxygen atom.

5 Examples of such radicals include phenoxy.

The term "aralkoxy" embraces oxy-containing aralkyl radicals attached through an oxygen atom to other radicals. More preferred aralkoxy radicals are "lower aralkoxy" radicals having optionally substituted phenyl radicals attached to lower alkoxy radical as described above.

The term "heterocyclyloxy" embraces optionally substituted heteroaryl radicals, as defined above, attached to an oxygen atom.

The term "heterocyclylalkoxy" embraces oxy-containing heteroarylalkyl radicals attached through an oxygen atom to other radicals. More preferred heteroarylalkoxy radicals are "lower heteroarylalkoxy" radicals having optionally substituted heteroaryl radicals attached to lower alkoxy radical as described above.

20 The term "cycloalkyl" includes saturated carbocyclic groups. Preferred cycloalkyl groups include C₃-C₆ rings. More preferred compounds include, cyclopentyl, cyclopropyl, and cyclohexyl.

The term "comprising" or "comprises" is meant to be open ended, i.e., including the indicated component but not excluding other elements.

The terms "Formula I and Formula II" include any sub formulas.

30 The present invention also comprises the use of a compound of the invention, or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment either acutely or chronically of an angiogenesis mediated disease state, including those described previously. The compounds of the present invention are

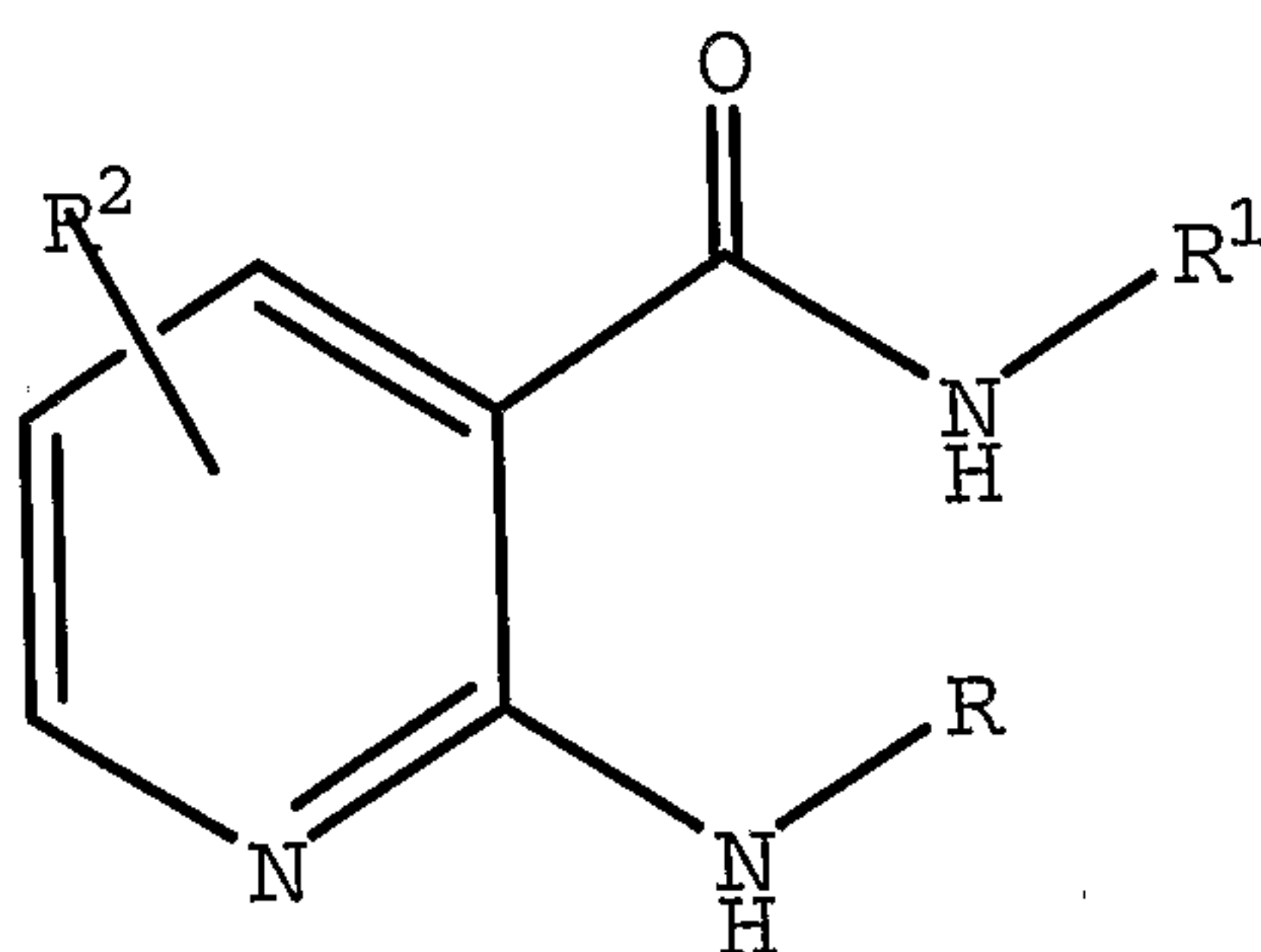
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useful in the manufacture of an anti-cancer medicament. The compounds of the present invention are also useful in the manufacture of a medicament to attenuate or prevent disorders through inhibition of KDR.

5 The present invention comprises a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I or Formula II in association with a least one pharmaceutically acceptable carrier, adjuvant or diluent.

10 The present invention also comprises a method of treating angiogenesis related disorders in a subject having or susceptible to such disorder, the method comprising treating the subject with a therapeutically effective amount of a compound of Formula I



15

I

or a pharmaceutically acceptable derivative thereof, wherein R is a 9- or 10-membered heterocyclcyl ring containing at least one nitrogen or oxygen atom, said ring
 20 selected from 7-isoquinolinyl, 2-methyl-3-oxo-2,3-dihydroindazol-6-yl, [1,6]-naphthydrin-3-yl, [1,7]-naphthydrin-2-yl, 1-oxo-2,3-dihydrobenzofuran-4-yl, 3-oxo-2,3-dihydrobenzofuran-5-yl, dihydro-benzodioxinyl, 6-quinazolinyl, 2-amino-6-quinazolinyl, 4-methylamino-6-quinazolinyl, 2,4-diamino-6-quinazolinyl, 3-oxo-3,4-dihydro-
 25 1,4-benzoxazin-6-yl, 2,2-difluoro-1,3-benzodioxol-5-yl and 2,2,3,3-tetrafluoro-2,3-dihydro-1,4-benzodioxin-6-yl, each

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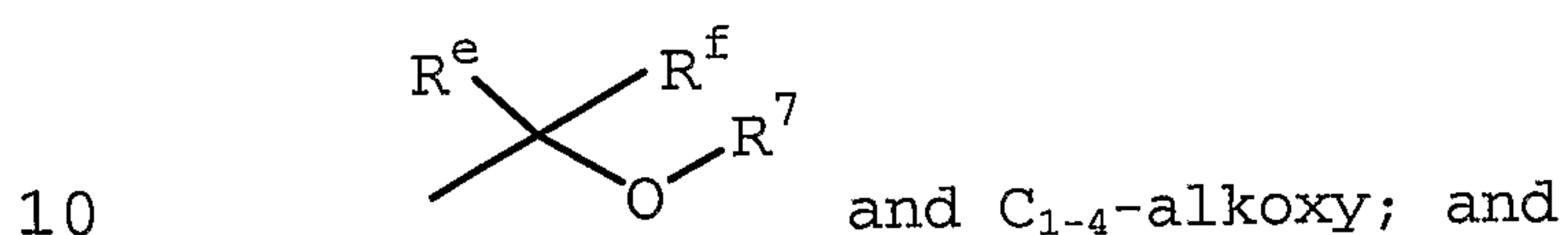
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of which is optionally substituted with one or more
substitutions selected from halo, haloalkyl, C₁₋₆ alkyl, C₂₋₈
alkenyl, C₂₋₈ alkynyl, N-dimethylamino-C₁₋₆-alkyl, N-
dimethylamino-C₁₋₆-alkoxy, amino, alkyl-carbonylamino,
5 morpholino-sulfonyl, amino-sulfonyl, oxazolyl, pyrrolyl,
morpholinyl, carboxyl, cyano, and acetyl;
wherein R¹ is selected from unsubstituted or substituted
phenyl,
5-6 membered heteroaryl,
10 9-10 membered bicyclic heterocyclyl and
11-14 membered tricyclic heterocyclyl,
wherein substituted R¹ is substituted with one or more
substituents selected from halo, optionally
substituted C₁₋₆-alkyl, optionally substituted C₃₋₆-
15 cycloalkyl, optionally substituted phenyl, optionally
substituted phenyl-C₁₋₄-alkylenyl, C₁₋₂-haloalkoxy,
optionally substituted phenyloxy, optionally
substituted 4-6 membered heterocyclyl-C₁₋₆-alkyl,
optionally substituted 4-6 membered heterocyclyl-C₂₋₄-
20 alkenyl, optionally substituted 4-6 membered
heterocyclyl, optionally substituted 4-6 membered
heterocycloxy, optionally substituted 4-6 membered
heterocyclyl-C₁₋₄-alkoxy, optionally substituted 4-6
membered heterocyclylsulfonyl, optionally substituted
25 4-6 membered heterocyclylamino, optionally substituted
4-6 membered heterocyclylcarbonyl, optionally
substituted 4-6 membered heterocyclyl-C₁₋₄-
alkylcarbonyl, optionally substituted 4-6 membered
heterocyclylcarbonyl-C₁₋₄-alkyl, optionally substituted
30 4-6 membered heterocyclyl-C₁₋₄-alkylcarbonylamino,
optionally substituted 4-6 membered heterocyclyl-
oxycarbonylamino, C₁₋₂-haloalkyl, C₁₋₄-aminoalkyl,
optionally substituted C₁₋₄-aminoalkylcarbonyl, nitro,
amino, C₁₋₃-alkylsulfonylamino, hydroxy, cyano,

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aminosulfonyl, C₁₋₂-alkylsulfonyl, C₁₋₂-
 alkylsulfonylamino, C₁₋₂-alkylsulfonylamino-C₁₋₄-alkoxy,
 halosulfonyl, C₁₋₄-alkylcarbonyl, amino-C₁₋₄-
 alkylcarbonyl, C₁₋₃-alkylamino-C₁₋₄-alkylcarbonyl, C₁₋₃-
 5 alkylamino-C₁₋₄-alkylcarbonylamino, C₁₋₄-alkoxycarbonyl-
 C₁₋₄-alkyl, C₁₋₃-alkylamino-C₁₋₃-alkyl, C₁₋₃-alkylamino-C₁₋₃-
 alkoxy, C₁₋₃-alkylamino-C₁₋₃-alkoxy-C₁₋₃-alkoxy, C₁₋₄-
 alkoxycarbonyl, C₁₋₄-alkoxycarbonylamino-C₁₋₄-alkyl, C₁₋₃-
 alkylsulfonylamino-C₁₋₃-alkoxy, C₁₋₄-hydroxyalkyl,



wherein R^e and R^f are independently selected from H and C₁₋₂-
 haloalkyl; and

wherein R⁷ is selected from H, C₁₋₃-alkyl, optionally
 substituted phenyl, optionally substituted phenyl-C₁₋₃-
 15 alkyl, 4-6 membered heterocyclyl, optionally
 substituted 4-6 membered heterocyclyl-C₁₋₃-alkyl, C₁₋₃-
 alkoxy-C₁₋₂-alkyl and C₁₋₃-alkoxy-C₁₋₃-alkoxy-C₁₋₃-alkyl;
 and

wherein R² is selected from H, halo, haloalkyl and C₁₋₆
 20 alkyl.

Similarly, the present invention further comprises a
 method of treating angiogenesis related disorders in a
 subject having or susceptible to such disorder, the method
 comprising treating the subject with a therapeutically
 25 effective amount of a compound of Formula II, as described
 herein.

COMBINATIONS

30 While the compounds of the present invention can be
 administered as the sole active pharmaceutical agent, they
 can also be used in combination with one or more compounds
 of the invention or other agents. When administered as a

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combination, the therapeutic agents can be formulated as separate compositions that are administered at the same time or sequentially at different times, or the therapeutic agents can be formulated and administered as a single
5 composition.

The phrase "co-therapy" (or "combination-therapy"), in defining use of a compound of the present invention and another pharmaceutical agent, is intended to embrace administration of each agent in a sequential manner in a
10 regimen that will provide beneficial effects of the drug combination, and is intended as well to embrace co-administration of these agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of these active agents or in multiple, separate
15 capsules or other formulations for each agent.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the accepted dosage ranges. Compounds of Formulas I and II may also be administered sequentially with known anticancer or
20 cytotoxic agents when a combination formulation is inappropriate. The invention is not limited in the sequence of administration; compounds of the invention may be administered either prior to, simultaneous with or after administration of the known anticancer or cytotoxic agent.

The administration of compounds, or compositions, of the present invention may be in conjunction with additional therapies known to those skilled in the art in the prevention or treatment of neoplasia, such as with radiation therapy or with cytostatic or cytotoxic agents. In some
25 embodiments, the combination therapy can include a compound, or composition, of the present invention with at least one anti-tumor agent or other conventional therapeutic agent. In some embodiments, the combination comprises a compound, or composition, of the present invention (e.g., an antibody
30 or antigen binding region) in combination with at least one
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anti-angiogenic agent. Agents are inclusive of, but not limited to, *in vitro* synthetically prepared chemical compositions, antibodies, antigen binding regions, radionuclides, and combinations and conjugates thereof. An agent can be an agonist, antagonist, allosteric modulator, toxin or, more generally, may act to inhibit or stimulate its target (e.g., receptor or enzyme activation or inhibition), and thereby promote cell death or arrest cell growth.

10 Currently, standard treatment of primary tumors consists of surgical excision followed by either radiation or IV administered chemotherapy. The typical chemotherapy regime consists of either DNA alkylating agents, DNA intercalating agents, CDK inhibitors, or microtubule poisons. The chemotherapy doses used are just below the maximal tolerated dose and therefore dose limiting toxicities typically include, nausea, vomiting, diarrhea, hair loss, neutropenia and the like.

20 There are large numbers of antineoplastic agents available in commercial use, in clinical evaluation and in pre-clinical development, which would be selected for treatment of neoplasia by combination drug chemotherapy. Such antineoplastic agents fall into several major categories, namely, antibiotic-type agents, alkylating-type agents, antimetabolite-type agents, hormonal agents, immunological agents, interferon-type agents and a category of miscellaneous antineoplastic agents.

30 A first family of antineoplastic agents, which may be used in combination with compounds of the present invention, consists of antimetabolite-type/thymidilate synthase inhibitor antineoplastic agents. Suitable antimetabolite-type antineoplastic agents may be selected from, but not limited to, the group consisting of 5-FU-fibrinogen, acanthifolic acid, aminothiadiaazole, brequinar sodium, carmofur, Ciba-Geigy CGP-30694, cyclopentyl cytosine,

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cytarabine phosphate stearate, cytarabine conjugates, Lilly DATHF, Merrel Dow DDFC, dezaguanine, dideoxycytidine, dideoxyguanosine, didox, Yoshitomi DMDC, doxifluridine, Wellcome EHNA, Merck & Co. EX-015, fazarabine, Daiichi

5 Seiyaku FO-152, isopropyl pyrrolizine, Lilly LY-188011, Lilly LY-264618, methobenzaprim, Wellcome MZPES, norspermidine, NCI NSC-127716, NCI NSC-264880, NCI NSC-39661, NCI NSC-612567, Warner-Lambert PALA, pentostatin, piritrexim, plicamycin, Asahi Chemical PL-AC, Takeda TAC-

10 788, thioguanine, tiazofurin, Erbamont TIF, tyrosine kinase inhibitors, Taiho UFT, uricytin, folic acid analogs such as methotrexate and trimetrexate, pyrimidine analogs such as 5-fluorouracil, N-(2'-furanidyl)-5-fluorouracil, floxuridine, fluorodeoxyuridine, gemcitabine, cytosine arabinoside (AraC,

15 cytarabine), 5-azacytidine, 2,2'-difluorodeoxycytidine and purine analogs such as 6-mercaptopurine, 6-thioguanine, azathioprine, 2'-deoxycoformycin (pentostatin), erythrohydroxynonyladenine (EHNA), fludarabine phosphate, and 2-chlorodeoxyadenosine (cladribine, 2-CdA).

20 A second family of antineoplastic agents, which may be used in combination with compounds of the present invention, consists of alkylating-type antineoplastic agents. Suitable alkylating-type antineoplastic agents may be selected from, but not limited to, the group consisting of Shionogi 254-S,

25 aldo-phosphamide analogues, alkyl sulfonates such as busulfan, altretamine, anaxirone, Boehringer Mannheim BBR-2207, bestrabucil, budotitane, Wakunaga CA-102, carboplatin, carmustine (BCNU), Chinoin-139, Chinoin-153, chlorambucil, cisplatin, cyclophosphamide, American Cyanamid CL-286558,

30 Sanofi CY-233, cyplatate, Degussa D-19-384, Sumimoto DACHP(Myrr)2, diphenylspiromustine, diplatinum cytostatic, Erba distamycin derivatives, Chugai DWA-2114R, ITI E09, elmustine, Erbamont FCE-24517, estramustine, estramustine phosphate, estramustine phosphate sodium, fotemustine,

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Unimed G-6-M, Chinoin GYKI-17230, hepsul-fam, ifosfamide, iproplatin, lomustine (CCNU), mafosfamide, mechlorethamine, melphalan, mitolactol, Nippon Kayaku NK-121, nitrogen mustards, NCI NSC-264395, NCI NSC-342215, oxaliplatin, Upjohn PCNU, prednimustine, Proter PTT-119, ranimustine, semustine (methyl-CCNU), SmithKline SK&F-101772, Yakult Honsha SN-22, spiromustine, Tanabe Seiyaku TA-077, tauromustine, temozolomide, teroxirone, tetraplatin and trimelamol, ethylenimines/methylmelamine such as thriethylenemelamine (TEM), triethylene, thiophosphoramidate (thiotepa), hexamethylmelamine (HMM, altretamine) and triazines such as dacarbazine (DTIC).

A third family of antineoplastic agents which may be used in combination with compounds of the present invention consists of antibiotic-type antineoplastic agents. Suitable antibiotic-type antineoplastic agents may be selected from, but not limited to, the group consisting of Taiho 4181-A, aclarubicin, actinomycin, actinomycin D, actinoplanone, Erbamont ADR-456, aeroplysinin derivative, Ajinomoto AN-201-II, Ajinomoto AN-3, Nippon Soda anisomycins, anthracycline, azino-mycin-A, bisucaberin, Bristol-Myers BL-6859, Bristol-Myers BMY-25067, Bristol-Myers BMY-25551, Bristol-Myers BMY-26605, Bristol-Myers BMY-27557, Bristol-Myers BMY-28438, bleomycins such as bleomycin sulfate, bryostatin-1, Taiho C-1027, calicheomycin, chromoximycin, dactinomycin, daunorubicin, daunomycin (rubidomycin), mitoxantrone Kyowa Hakko DC-102, Kyowa Hakko DC-79, Kyowa Hakko DC-88A, Kyowa Hakko DC89-A1, Kyowa Hakko DC92-B, ditrisarubicin B, Shionogi DOB-41, doxorubicin, doxorubicin-fibrinogen, elsamicin-A, epirubicin, erbstatin, esorubicin, esperamicin-A1, esperamicin-Alb, Erbamont FCE-21954, Fujisawa FK-973, fostriecin, Fujisawa FR-900482, glidobactin, gregatin-A, grincamycin, herbimycin, idarubicin, illudins, kazusamycin, kesarirhodins, Kyowa Hakko KM-5539, Kirin Brewery KRN-8602,

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Kyowa Hakko KT-5432, Kyowa Hakko KT-5594, Kyowa Hakko KT-6149, American Cyanamid LL-D49194, Meiji Seika ME 2303, menogaril, mitomycin, mitomycinC, mitoxantrone, SmithKline M-TAG, neoenactin, Nippon Kayaku NK-313, Nippon Kayaku NKT-5 01, SRI International NSC-357704, oxalysine, oxaunomycin, peplomycin, pilatin, pirarubicin, plicamycin (mithramycin), porothramycin, pyrindanycin A, Tobishi RA-I, rapamycin, rhizoxin, rodorubicin, sibanomicin, siwenmycin, Sumitomo SM-5887, Snow Brand SN-706, Snow Brand SN-07, sorangicin-A, 10 sparsomycin, SS Pharmaceutical SS-21020, SS Pharmaceutical SS-7313B, SS Pharmaceutical SS-9816B, steffimycin B, Taiho 4181-2, talisomycin, Takeda TAN-868A, terpentecin, thrazine, tricrozarin A, Upjohn U-73975, Kyowa Hakko UCN-10028A, Fujisawa WF-3405, Yoshitomi Y-25024 and zorubicin.

15 A fourth family of antineoplastic agents which may be used in combination with compounds of the present invention consists of a miscellaneous families of antineoplastic agents, including tubulin interacting agents, topoisomerase II inhibitors, topoisomerase I inhibitors and hormonal

20 agents, selected from, but not limited to, the group consisting of α -carotene, α -difluoromethyl-arginine, acitretin, Biotec AD-5, Kyorin AHC-52, alstonine, amonafide, amphethinile, amsacrine, Angiostat, ankinomycin, anti-neoplaston A10, antineoplaston A2, antineoplaston A3,

25 antineoplaston A5, antineoplaston AS2-1, Henkel APD, aphidicolin glycinate, asparaginase, Avarol, baccharin, batracylin, benfluron, benzotript, Ipsen-Beaufour BIM-23015, bisantrene, Bristol-Myers BMY-40481, Vestar boron-10, bromofosfamide, Wellcome BW-502, Wellcome BW-773,

30 caracemide, carmethizole hydrochloride, Ajinomoto CDAF, chlorsulfaquinoxalone, Chemes CHX-2053, Chemex CHX-100, Warner-Lambert CI-921, Warner-Lambert CI-937, Warner-Lambert CI-941, Warner-Lambert CI-958, clanfenur, claviridenone, ICN compound 1259, ICN compound 4711, Contracan, Yakult Honsha

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CPT-11, crisnatol, curaderm, cytochalasin B, cytarabine,
 cytocytin, Merz D-609, DABIS maleate, dacarbazine,
 datelliptinium, didemnin-B, dihaematoporphyrin ether,
 dihydrolenperone, dinaline, distamycin, Toyo Pharmar DM-341,
 5 Toyo Pharmar DM-75, Daiichi Seiyaku DN-9693, docetaxel
 elliprabin, elliptinium acetate, Tsumura EPMTc, the
 epothilones, ergotamine, etoposide, etretinate, fenretinide,
 Fujisawa FR-57704, gallium nitrate, genkwadaphnin, Chugai
 GLA-43, Glaxo GR-63178, grifolan NMF-5N,
 10 hexadecylphosphocholine, Green Cross HO-221,
 homoharringtonine, hydroxyurea, BTG ICRF-187, ilmofosine,
 isoglutamine, isotretinoin, Otsuka JI-36, Ramot K-477,
 Otsuka K-76COONa, Kureha Chemical K-AM, MECT Corp KI-8110,
 American Cyanamid L-623, leukoregulin, lonidamine, Lundbeck
 15 LU-23-112, Lilly LY-186641, NCI (US) MAP, marycin, Merrel
 Dow MDL-27048, Medco MEDR-340, merbarone, merocyanine
 derivatives, methylanilinoacridine, Molecular Genetics MGI-
 136, minactivin, mitonafide, mitoquidone mopidamol,
 motretinide, Zenyaku Kogyo MST-16, N-(retinoyl)amino acids,
 20 Nisshin Flour Milling N-021, N-acylated-dehydroalanines,
 nafazatrom, Taisho NCU-190, nocodazole derivative,
 Normosang, NCI NSC-145813, NCI NSC-361456, NCI NSC-604782,
 NCI NSC-95580, ocreotide, Ono ONO-112, oquizanocine, Akzo
 Org-10172, natural antimitotic drugs such as paclitaxel,
 25 pancratistatin, pazelliptine, Warner-Lambert PD-111707,
 Warner-Lambert PD-115934, Warner-Lambert PD-131141, Pierre
 Fabre PE-1001, ICRT peptide D, piroxantrone,
 polyhaematoporphyrin, polypreic acid, Efamol porphyrin,
 ppipodophylotoxins such as etoposide and teniposide,
 30 probimane, procarbazine, proglumide, Invitron protease nexin
 I, Tobishi RA-700, razoxane, Sapporo Breweries RBS,
 restrictin-P, retelliptine, retinoic acid, Rhone-Poulenc RP-
 49532, Rhone-Poulenc RP-56976, SmithKline SK&F-104864,
 Sumitomo SM-108, Kuraray SMANCS, SeaPharm SP-10094, spatol,

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spirocyclopropane derivatives, spirogermanium, Unimed, SS Pharmaceutical SS-554, strypoldinone, Stypoldione, Suntory SUN 0237, Suntory SUN 2071, superoxide dismutase, taxotere, Toyama T-506, Toyama T-680, taxol, Teijin TEI-0303, 5 teniposide, thaliblastine, Eastman Kodak TJB-29, tocotrienol, topotecan, Topostin, Teijin TT-82, Kyowa Hakko UCN-01, Kyowa Hakko UCN-1028, ukrain, Eastman Kodak USB-006, vinca alkaloids including vinblastine (VLB), vinblastine sulfate, vincristine, vindesine, vinestramide, vinorelbine, 10 vintriptol and vinzolidine, withanolides, Yamanouchi YM-534, enzymes such as L-asparaginase, biological response modifiers such as G-CSF and GM-CSF, miscellaneous agents including platinum coordination complexes such as cisplatin and carboplatin, anthracenediones such as mitoxantrone, 15 substituted urea such as hydroxyurea, methylhydrazine derivatives including N-methylhydrazine (MIH) and procarbazine, adrenocortical suppressants such as mitotane (o,p'-DDD) and aminogluthethimide, hormones and antagonists including adrenocorticosteroid antagonists such as 20 prednisone and equivalents, dexamethasone and aminogluthethimide, progestin such as hydroxyprogesterone caproate, medroxyprogesterone acetate and megestrol acetate, estrogen such as diethylstilbestrol and ethinyl estradiol equivalents, antiestrogen such as tamoxifen, androgens 25 including testosterone propionate and fluoxymesterone/equivalents, antiandrogens such as flutamide, gonadotropin-releasing hormone analogs and leuprolide, and non-steroidal antiandrogens such as flutamide.

30 Alternatively, the compounds of the present invention may also be used in co-therapies with other miscellaneous anti-neoplastic agents, such as acemannan, aclarubicin, aldesleukin, alemtuzumab, alitretinoin, altretamine, amifostine, aminolevulinic acid, amrubicin, amsacrine,

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anagrelide, anastrozole, ANCER, aneastim, ARGLABIN, arsenic
 trioxide, BAM 002 (Novelos), bexarotene, bicalutamide,
 broxuridine, capecitabine, celmoleukin, cetorelix,
 cladribine, clotrimazole, cytarabine ocfosfate, DA 3030
 5 (Dong-A), daclizumab, denileukin diftitox, deslorelin,
 dexrazoxane, dilazep, docetaxel, docosanol,
 doxercalciferol, doxifluridine, doxorubicin, bromocriptine,
 carmustine, cytarabine, fluorouracil, HIT diclofenac,
 interferon alfa, daunorubicin, tretinoin, edelfosine,
 10 edrecolomab, eflornithine, emitefur, epirubicin, epoetin
 beta, etoposide phosphate, exemestane, exisulind,
 fadrozole, filgrastim, finasteride, fludarabine phosphate,
 formestane, fotemustine, gallium nitrate, gemcitabine,
 gentuzumab zogamicin, gimeracil/oteracil/tegafur
 15 combination, glycopine, goserelin, heptaplatin, human
 chorionic gonadotropin, human fetal alpha fetoprotein,
 ibandronic acid, idarubicin, (imiquimod, interferon alfa,
 interferon alfa, natural, interferon alfa-2, interferon
 alfa-2a, interferon alfa-2b, interferon alfa-N1, interferon
 20 alfa-n3, interferon alfacon-1, interferon alpha, natural,
 interferon beta, interferon beta-1a, interferon beta-1b,
 interferon gamma, natural interferon gamma-1a, interferon
 gamma-1b, interleukin-1 beta, iobenguane, irinotecan,
 irsogladine, lanreotide, LC 9018 (Yakult), leflunomide,
 25 lenograstim, lentinan sulfate, letrozole, leukocyte alpha
 interferon, leuprorelin, levamisole + fluorouracil,
 liarozole, lobaplatin, lonidamine, lovastatin, masoprocol,
 melarsoprol, metoclopramide, mifepristone, miltefosine,
 mirimostim, mismatched double stranded RNA, mitoguazone,
 30 mitolactol, mitoxantrone, molgramostim, nafarelin, naloxone
 + pentazocine, nartograstim, nedaplatin, nilutamide,
 noscapine, novel erythropoiesis stimulating protein, NSC
 631570 octreotide, oprelvekin, osaterone, oxaliplatin,
 paclitaxel, pamidronic acid, pegaspargase, peginterferon

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alfa-2b, pentosan polysulfate sodium, pentostatin,
 picibanil, pirarubicin, rabbit antithymocyte polyclonal
 antibody, polyethylene glycol interferon alfa-2a, porfimer
 sodium, raloxifene, raltitrexed, rasburicase, rhenium Re
 5 186 etidronate, RII retinamide, rituximab, ritromurtide,
 samarium (153 Sm) lexidronam, sargramostim, sizofiran,
 sobuzoxane, sonermin, strontium-89 chloride, suramin,
 tasonermin, tazarotene, tegafur, temoporfin, temozolomide,
 teniposide, tetrachlorodecaoxide, thalidomide, thymalfasin,
 10 thyrotropin alfa, topotecan, toremifene, tositumomab-iodine
 131, altreptin, trastuzumab, treosulfan, tretinoin,
 trilostane, trimetrexate, triptorelin, tumor necrosis
 factor alpha, natural, ubenimex, bladder cancer vaccine,
 Maruyama vaccine, melanoma lysate vaccine, valrubicin,
 15 verteporfin, vinorelbine, VIRULIZIN™, zinostatin stimalamer,
 or zoledronic acid; abarelix; AE 941 (Aeterna),
 ambamustine, antisense oligonucleotide, bcl-2 (Genta), APC
 8015 (Dendreon), cetuximab, decitabine,
 dexamino-glutethimide, diaziquone, EL 532 (Elan), EM 800
 20 (Endorecherche), eniluracil, etanidazole, fenretinide,
 filgrastim SD01 (Amgen), fulvestrant, galocitabine, gastrin
 17 immunogen, HLA-B7 gene therapy (Vical), granulocyte
 macrophage colony stimulating factor, histamine
 dihydrochloride, ibritumomab tiuxetan, ilomastat, IM 862
 25 (Cytran), interleukin-2, iproxifene, LDI 200 (Milkhaus),
 leridistim, lintuzumab, CA 125 MAb (Biomira), cancer MAb
 (Japan Pharmaceutical Development), HER-2 and Fc MAb
 (Medarex), idiotypic 105AD7 MAb (CRC Technology), idiotypic
 CEA MAb (Trilex), LYM-1-iodine 131 MAb (Techniclone),
 30 polymorphic epithelial mucin-yttrium 90 MAb (Antisoma),
 marimastat, menogaril, mitumomab, motexafin gadolinium, MX
 6 (Galderma), nelarabine, nolatrexed, P 30 protein,
 pegvisomant, pemetrexed, porfiromycin, prinomastat, RL 0903
 (Shire), rubitecan, satraplatin, sodium phenylacetate,

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sparfosic acid, SRL 172 (SR Pharma), SU 5416 (SUGEN), TA 077 (Tanabe), tetrathiomolybdate, thaliblastine, thrombopoietin, tin ethyl etiopurpurin, tirapazamine, cancer vaccine (Biomira), melanoma vaccine (New York University), melanoma vaccine (Sloan Kettering Institute), melanoma oncolysate vaccine (New York Medical College), viral melanoma cell lysates vaccine (Royal Newcastle Hospital), or valspodar.

Alternatively, the compounds of the present invention may also be used in co-therapy with anti-tumor and anti-angiogenic agents (both administered as cancer therapy agents). Exemplary anti-tumor agents include HERCEPTIN™ (trastuzumab), which may be used to treat breast cancer and other forms of cancer, and RITUXAN™ (rituximab), ZEVALIN™ (ibritumomab tiuxetan), and LYMPHOCIDE™ (epratuzumab), which may be used to treat non-Hodgkin's lymphoma and other forms of cancer, GLEEVAC™ which may be used to treat chronic myeloid leukemia and gastrointestinal stromal tumors, and BEXXAR™ (iodine 131 tositumomab) which may be used for treatment of non-Hodgkins's lymphoma.

Exemplary anti-angiogenic agents that may be used in combination with compounds of the present invention include ERBITUX™ (IMC-C225), KDR (kinase domain receptor) inhibitory agents (e.g., antibodies and antigen binding regions that specifically bind to the kinase domain receptor), anti-VEGF agents (e.g., antibodies or antigen binding regions that specifically bind VEGF, or soluble VEGF receptors or a ligand binding region thereof) such as AVASTIN™ or VEGF-TRAP™, and anti-VEGF receptor agents (e.g., antibodies or antigen binding regions that specifically bind thereto), EGFR inhibitory agents (e.g., antibodies or antigen binding regions that specifically bind thereto) such as ABX-EGF (panitumumab), IRESSA™ (gefitinib), TARCEVA™ (erlotinib), anti-Ang1 and anti-Ang2 agents (e.g., antibodies or antigen binding regions specifically binding thereto or to their receptors, e.g., Tie2/Tek), and anti-Tie-2 kinase inhibitory agents (e.g., antibodies or antigen binding regions that

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specifically bind thereto). The pharmaceutical compositions of the present invention can also include one or more agents (e.g., antibodies, antigen binding regions, or soluble receptors) that specifically bind and inhibit the activity of growth factors, such as antagonists of hepatocyte growth factor (HGF, also known as Scatter Factor), and antibodies or antigen binding regions that specifically bind its receptor "c-met".

Other anti-angiogenic agents that may be used in combination with compounds of the present invention include Campath, IL-8, B-FGF, Tek antagonists (Ceretti et al., U.S. Publication No. 2003/0162712; U.S. Pat. No. 6,413,932), anti-TWEAK agents (e.g., specifically binding antibodies or antigen binding regions, or soluble TWEAK receptor antagonists; see, Wiley, U.S. Pat. No. 6,727,225), ADAM distintegrin domain to antagonize the binding of integrin to its ligands (Fanslow et al., U.S. Publication No. 2002/0042368), specifically binding anti-eph receptor and/or anti-ephrin antibodies or antigen binding regions (U.S. Pat. Nos. 5,981,245; 5,728,813; 5,969,110; 6,596,852; 6,232,447; 6,057,124 and patent family members thereof), and anti-PDGF-BB antagonists (e.g., specifically binding antibodies or antigen binding regions) as well as antibodies or antigen binding regions specifically binding to PDGF-BB ligands, and PDGFR kinase inhibitory agents (e.g., antibodies or antigen binding regions that specifically bind thereto).

Additional anti-angiogenic/anti-tumor agents that may be used in combination with compounds of the present invention include: SD-7784 (Pfizer, USA); cilengitide (Merck KGaA, Germany, EPO 770622); pegaptanib octasodium, (Gilead Sciences, USA); Alphastatin, (BioActa, UK); M-PGA, (Celgene, USA, US 5712291); ilomastat, (Arriva, USA, US 5892112); emaxanib, (Pfizer, USA, US 5792783); vatalanib, (Novartis, Switzerland); 2-methoxyestradiol, (EntreMed, USA); TLC ELL-12, (Elan, Ireland); anecortave acetate, (Alcon, USA); alpha-D148 Mab, (Amgen, USA); CEP-7055, (Cephalon, USA); anti-Vn Mab, (Crucell, Netherlands) DAC:antiangiogenic, (ConjuChem, Canada); Angiocidin, (InKine Pharmaceutical,

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USA); KM-2550, (Kyowa Hakko, Japan); SU-0879, (Pfizer, USA);
 CGP-79787, (Novartis, Switzerland, EP 970070); ARGENT
 technology, (Ariad, USA); YIGSR-Stealth, (Johnson & Johnson,
 USA); fibrinogen-E fragment, (BioActa, UK); angiogenesis
 5 inhibitor, (Trigen, UK); TBC-1635, (Encysive
 Pharmaceuticals, USA); SC-236, (Pfizer, USA); ABT-567,
 (Abbott, USA); Metastatin, (EntreMed, USA); angiogenesis
 inhibitor, (Tripep, Sweden); maspin, (Sosei, Japan); 2-
 methoxyestradiol, (Oncology Sciences Corporation, USA); ER-
 10 68203-00, (IVAX, USA); Benefin, (Lane Labs, USA); Tz-93,
 (Tsumura, Japan); TAN-1120, (Takeda, Japan); FR-111142,
 (Fujisawa, Japan, JP 02233610); platelet factor 4,
 (RepliGen, USA, EP 407122); vascular endothelial growth
 factor antagonist, (Boreau, Denmark); cancer therapy,
 15 (University of South Carolina, USA); bevacizumab (pINN),
 (Genentech, USA); angiogenesis inhibitors, (SUGEN, USA); XL
 784, (Exelixis, USA); XL 647, (Exelixis, USA); MAb,
 alpha5beta3 integrin, second generation, (Applied Molecular
 Evolution, USA and MedImmune, USA); gene therapy,
 20 retinopathy, (Oxford BioMedica, UK); enzastaurin
 hydrochloride (USAN), (Lilly, USA); CEP 7055, (Cephalon, USA
 and Sanofi-Synthelabo, France); BC 1, (Genoa Institute of
 Cancer Research, Italy); angiogenesis inhibitor, (Alchemia,
 Australia); VEGF antagonist, (Regeneron, USA); rBPI 21 and
 25 BPI-derived antiangiogenic, (XOMA, USA); PI 88, (Progen,
 Australia); cilengitide (pINN), (Merck KGaA, German; Munich
 Technical University, Germany, Scripps Clinic and Research
 Foundation, USA); cetuximab (INN), (Aventis, France); AVE
 8062, (Ajinomoto, Japan); AS 1404, (Cancer Research
 30 Laboratory, New Zealand); SG 292, (Telios, USA); Endostatin,
 (Boston Childrens Hospital, USA); ATN 161, (Attenuon, USA);
 ANGIOSTATIN™, (Boston Childrens Hospital, USA); 2-
 methoxyestradiol, (Boston Childrens Hospital, USA); ZD 6474,
 (AstraZeneca, UK); ZD 6126, (Angiogene Pharmaceuticals, UK);
 35 PPI 2458, (Praecis, USA); AZD 9935, (AstraZeneca, UK); AZD
 2171, (AstraZeneca, UK); vatalanib (pINN), (Novartis,
 Switzerland and Schering AG, Germany); tissue factor pathway
 inhibitors, (EntreMed, USA); pegaptanib (Pinn), (Gilead
 Sciences, USA); xanthorrhizol, (Yonsei University, South

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Korea); vaccine, gene-based, VEGF-2, (Scripps Clinic and Research Foundation, USA); SPV5.2, (Supratek, Canada); SDX 103, (University of California at San Diego, USA); PX 478, (ProlX, USA); METASTATIN™, (EntreMed, USA); troponin I, 5 (Harvard University, USA); SU 6668, (SUGEN, USA); OXI 4503, (OXiGENE, USA); o-guanidines, (Dimensional Pharmaceuticals, USA); motuporamine C, (British Columbia University, Canada); CDP 791, (Celltech Group, UK); atiprimod (pINN), (GlaxoSmithKline, UK); E 7820, (Eisai, Japan); CYC 381, 10 (Harvard University, USA); AE 941, (Aeterna, Canada); vaccine, angiogenesis, (EntreMed, USA); urokinase plasminogen activator inhibitor, (Dendreon, USA); oglufanide (pINN), (Melmotte, USA); HIF-1alfa inhibitors, (Xenova, UK); CEP 5214, (Cephalon, USA); BAY RES 2622, (Bayer, Germany); 15 Angiocidin, (InKine, USA); A6, (Angstrom, USA); KR 31372, (Korea Research Institute of Chemical Technology, South Korea); GW 2286, (GlaxoSmithKline, UK); EHT 0101, (ExonHit, France); CP 868596, (Pfizer, USA); CP 564959, (OSI, USA); CP 547632, (Pfizer, USA); 786034, (GlaxoSmithKline, UK); KRN 20 633, (Kirin Brewery, Japan); drug delivery system, intraocular, 2-methoxyestradiol, (EntreMed, USA); anginex, (Maastricht University, Netherlands, and Minnesota University, USA); ABT 510, (Abbott, USA); AAL 993, (Novartis, Switzerland); VEGI, (ProteomTech, USA); tumor 25 necrosis factor-alpha inhibitors, (National Institute on Aging, USA); SU 11248, (Pfizer, USA and SUGEN USA); ABT 518, (Abbott, USA); YH16, (Yantai Rongchang, China); S-3APG , (Boston Childrens Hospital, USA and EntreMed, USA); MAb, KDR, (ImClone Systems, USA); MAb, alpha5 beta1, (Protein 30 Design, USA); KDR kinase inhibitor, (Celltech Group, UK, and Johnson & Johnson, USA); GFB 116, (South Florida University, USA and Yale University, USA); CS 706, (Sankyo, Japan); combretastatin A4 prodrug, (Arizona State University, USA); chondroitinase AC, (IBEX, Canada); BAY RES 2690, (Bayer, 35 Germany); AGM 1470, (Harvard University, USA, Takeda, Japan, and TAP, USA); AG 13925, (Agouron, USA); Tetrathiomolybdate, (University of Michigan, USA); GCS 100, (Wayne State University, USA) CV 247, (Ivy Medical, UK); CKD 732, (Chong Kun Dang, South Korea); MAb, vascular endothelium growth

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factor, (Xenova, UK); irsogladine (INN), (Nippon Shinyaku, Japan); RG 13577, (Aventis, France); WX 360, (Wilex, Germany); squalamine (pINN), (Genaera, USA); RPI 4610, (Sirna, USA); cancer therapy, (Marinova, Australia);

5 heparanase inhibitors, (InSight, Israel); KL 3106, (Kolon, South Korea); Honokiol, (Emory University, USA); ZK CDK, (Schering AG, Germany); ZK Angio, (Schering AG, Germany); ZK 229561, (Novartis, Switzerland, and Schering AG, Germany); XMP 300, (XOMA, USA); VGA 1102, (Taisho, Japan); VEGF

10 receptor modulators, (Pharmacopeia, USA); VE-cadherin-2 antagonists, (ImClone Systems, USA); Vasostatin, (National Institutes of Health, USA); vaccine, Flk-1, (ImClone Systems, USA); TZ 93, (Tsumura, Japan); TumStatins, (Beth Israel Hospital, USA); truncated soluble FLT 1 (vascular

15 endothelial growth factor receptor 1), (Merck & Co, USA); Tie-2 ligands, (Regeneron, USA); and, thrombospondin 1 inhibitor, (Allegheny Health, Education and Research Foundation, USA).

Cancer therapy agents that may be used in combination

20 with compounds of the present invention also include polypeptides (peptidal or peptide-like cancer therapy agents), which selectively induce apoptosis in tumor cells, including, but not limited to, the TNF-related polypeptide TRAIL. Certain cancer therapy agents include, but are not

25 limited to: thalidomide and thalidomide analogues (N-(2,6-dioxo-3-piperidyl)phthalimide); tecogalan sodium (sulfated polysaccharide peptidoglycan); TAN 1120 (8-acetyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-10-[[octahydro-5-hydroxy-2-(2-hydroxypropyl)-4,10-dimethylpyrano[3,4-d]-

30 1,3,6-dioxazocin-8-yl]oxy]-5,12-naphthacenedione); suradista (7,7'-[carbonylbis[imino(1-methyl-1H-pyrrole-4,2-diyl)carbonylimino(1-methyl-1H-pyrrole-4,2-diyl)carbonylimino]]bis-1,3-naphthalenedisulfonic acid tetrasodium salt); SU 302; SU 301; SU 1498 ((E)-2-cyano-3-

35 [4-hydroxy-3,5-bis(1-methylethyl)phenyl]-N-(3-phenylpropyl)-2-pro penamide); SU 1433 (4-(6,7-dimethyl-2-quinoxaliny)-

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1,2-benzenediol); ST 1514; SR 25989; soluble Tie-2; SERM derivatives, Pharmos; semaxanib (pINN) (3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1,3-dihydro-2H-indol-2-one); S 836; RG 8803; RESTIN; R 440 (3-(1-methyl-1H-indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)-1H-pyrrole-2,5-dione); R 123942 (1-[6-(1,2,4-thiadiazol-5-yl)-3-pyridazinyl]-N-[3-(trifluoromethyl)phenyl]-4-piperidinamine); prolyl hydroxylase inhibitor; progression elevated genes; prinomastat (INN) ((S)-2,2-dimethyl-4-[[p-(4-pyridyloxy)phenyl]sulphonyl]-3-thiomorpholinecarboxylic acid); NV 1030; NM 3 (8-hydroxy-6-methoxy-alpha-methyl-1-oxo-1H-2-benzopyran-3-acetic acid); NF 681; NF 050; MIG; METH 2; METH 1; manassantin B (alpha-[1-[4-[5-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1-methylethoxy]-3-methoxyphenyl]tetrahydro-3,4-dimethyl-2-furanyl]-2-methoxyphenoxy]ethyl]-1,3-benzodioxole-5-methanol); KDR monoclonal antibody; alpha5beta3 integrin monoclonal antibody; LY 290293 (2-amino-4-(3-pyridinyl)-4H-naphtho[1,2-b]pyran-3-carbonitrile); KP 0201448; KM 2550; integrin-specific peptides; INGN 401; GYKI 66475; GYKI 66462; greenstatin (101-354-plasminogen (human)); gene therapy for rheumatoid arthritis, prostate cancer, ovarian cancer, glioma, endostatin, colorectal cancer, ATF BTPI, antiangiogenesis genes, angiogenesis inhibitor, or angiogenesis; gelatinase inhibitor, FR 111142 (4,5-dihydroxy-2-hexenoic acid 5-methoxy-4-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-1-oxaspiro[2.5]oct-6-yl ester); forfenimex (pINN) (S)-alpha-amino-3-hydroxy-4-(hydroxymethyl)benzeneacetic acid); fibronectin antagonist (1-acetyl-L-prolyl-L-histidyl-L-seryl-L-cysteinyl-L-aspartamide); fibroblast growth factor receptor inhibitor; fibroblast growth factor antagonist; FCE 27164 (7,7'-[carbonylbis[imino(1-methyl-1H-pyrrole-4,2-diyl)carbonylimino(1-methyl-1H-pyrrole-4,2-

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diyl)carbonylimino]]bis-1,3,5-naphthalenetrisulfonic acid
 hexasodium salt); FCE 26752 (8,8'-[carbonylbis[imino(1-
 methyl-1H-pyrrole-4,2-diyl)carbonylimino(1-methyl-1H-
 pyrrole-4,2-diyl)carbonylimino]]bis-1,3,6-
 5 naphthalenetrisulfonic acid); endothelial monocyte
 activating polypeptide II; VEGFR antisense oligonucleotide;
 anti-angiogenic and trophic factors; ANCHOR angiostatic
 agent; endostatin; Del-1 angiogenic protein; CT 3577;
 contortrostatin; CM 101; chondroitinase AC; CDP 845;
 10 CanStatin; BST 2002; BST 2001; BLS 0597; BIBF 1000;
 ARRESTIN; apomigren (1304-1388-type XV collagen (human gene
 COL15A1 alpha1-chain precursor)); angiopoietin 2;
 angiainhibin; aaATIII; A 36; 9alpha-
 fluoromedroxyprogesterone acetate ((6-alpha)-17-(acetyloxy)-
 15 9-fluoro-6-methyl-pregn-4-ene-3,20-dione); 2-methyl-2-
 phthalimidino-glutaric acid (2-(1,3-dihydro-1-oxo-2H-
 isoindol-2-yl)-2-methylpentanedioic acid); Yttrium 90
 labelled monoclonal antibody BC-1; Semaxanib (3-(4,5-
 Dimethylpyrrol-2-ylmethylene)indolin-2-one) (C15 H14 N2 O);
 20 PI 88 (phosphomannopentaose sulfate); Alvocidib (4H-1-
 Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-(3-
 hydroxy-1-methyl-4-piperidinyl)-cis-(-)-) (C21 H20 Cl N
 O5); E 7820; SU 11248 (5-[3-Fluoro-2-oxo-1,2-dihydroindol-
 (3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic
 25 acid (2-diethylaminoethyl)amide) (C22 H27 F N4 O2);
 Squalamine (Cholestane-7,24-diol, 3-[[3-[(4-
 aminobutyl)aminopropyl]amino]-, 24-(hydrogen sulfate),
 (3.beta.,5.alpha.,7.alpha.)-) (C34 H65 N3 O5 S); Eriochrome
 Black T; AGM 1470 (Carbamic acid, (chloroacetyl)-, 5-
 30 methoxy-4-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-1-
 oxaspiro[2,5] oct-6-yl ester, [3R-[3alpha, 4alpha(2R, 3R),
 5beta, 6beta]]) (C19 H28 Cl N O6); AZD 9935; BIBF 1000; AZD
 2171; ABT 828; KS-interleukin-2; TEK/Fc; Uteroglobulin; A 6;
 NSC 639366 (1-[3-(Diethylamino)-2-hydroxypropylamino]-4-

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(oxyran-2-ylmethylamino)anthraquinone fumerate) (C24 H29 N3 O4 . C4 H4 O4); ISV 616; anti-ED-B fusion proteins; HUI 77; Troponin I; BC-1 monoclonal antibody; SPV 5.2; ER 68203; CKD 731 (3-(3,4,5-Trimethoxyphenyl)-2(E)-propenoic acid
 5 (3R,4S,5S,6R)-4-[2(R)-methyl-3(R)-3(R)-(3-methyl-2-butenyl)oxiran-2-yl]-5-methoxy-1-oxaspiro[2.5]oct-6-yl ester) (C28 H38 O8); IMC-1C11; aaATIII; SC 7; CM 101; Angiocol; Kringle 5; CKD 732 (3-[4-[2-(Dimethylamino)ethoxy]phenyl]-2(E)-propenoic acid) (C29 H41 N
 10 O6); U 995; Canstatin; SQ 885; CT 2584 (1-[11-(Dodecylamino)-10-hydroxyundecyl]-3,7-dimethylxanthine) (C30 H55 N5 O3); Salmosin; EMAP II; TX 1920 (1-(4-Methylpiperazino)-2-(2-nitro-1H-1-imidazolyl)-1-ethanone) (C10 H15 N5 O3); Alpha-v Beta-x inhibitor; CHIR 11509 (N-(1-
 15 Propynyl)glycyl-[N-(2-naphthyl)]glycyl-[N-(carbamoylmethyl)]glycine bis(4-methoxyphenyl)methylamide) (C36 H37 N5 O6); BST 2002; BST 2001; B 0829; FR 111142; and 4,5-Dihydroxy-2(E)-hexenoic acid (3R,4S, 5S, 6R)-4-[1(R),2(R)-epoxy-1,5-dimethyl-4-
 20 hexenyl]-5-methoxy-1-oxaspiro[2.5]octan-6-yl ester (C22 H34 O7).

Exemplary cancers include, but are not limited to, breast cancer, colorectal cancer, gastric carcinoma, glioma, head and neck squamous cell carcinoma, hereditary and
 25 sporadic papillary renal carcinoma, leukemia, lymphoma, Li-Fraumeni syndrome, malignant pleural mesothelioma, melanoma, multiple myeloma, non-small cell lung carcinoma, osteosarcoma, ovarian cancer, pancreatic cancer, prostate cancer, small cell lung cancer, synovial sarcoma, thyroid
 30 carcinoma, and transitional cell carcinoma of urinary bladder.

Alternatively, the compounds of the present invention may also be used in co-therapies with other anti-neoplastic agents, such as other kinase inhibitors including p38

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inhibitors and CDK inhibitors, TNF inhibitors, matrix metalloproteinase inhibitors (MMP), COX-2 inhibitors including celecoxib, rofecoxib, parecoxib, valdecoxib, and etoricoxib, NSAID's, SOD mimics, C-met inhibitors or $\alpha_v\beta_3$ inhibitors.

In some embodiments, the invention includes administration of, in addition to a Tek antagonist, one or more chemotherapeutic agents in combination with the compound(s) or compositions of the invention. Suitable chemotherapeutic agents, including various soluble forms thereof, include, without limitation, Flt3 ligand, CD40 ligand, interleukin-2, interleukin-12, 4-1BB ligand, anti-4-1BB antibodies, TNF antagonists and TNF receptor antagonists including TNFR/Fc, TWEAK antagonists and TWEAK-R antagonists including TWEAK-R/Fc, TRAIL, VEGF antagonists including anti-VEGF antibodies, VEGF receptor (including VEGF-R1 and VEGF-R2, also known as Flt1 and Flk1 or KDR) antagonists, and CD148 (also referred to as DEP-1, ECRTF, and PTPRJ, see Takahashi et al., J. Am. Soc. Nephrol. 10:2135-45, 1999) agonists.

In other embodiments, compounds or compositions of the invention may be combined with agents disclosed in the following patents and publications: U.S. Patent Nos. 5521184, 5747498, 5770599, 5990141, 6235764, 6258812, 6515004, 6630500, 6713485; U.S. Patent Publication No. US20030105091; and PCT application Nos: WO01/37820, WO01/32651, WO0268406, WO0266470, WO0255501, WO0405279, WO0407481, WO0407458, WO0409784, WO0259110, WO9945009, WO9835958, WO0059509, WO9961422, WO0012089 and WO0002871; as well as the following specific compounds: N-(4-chlorophenyl)-4-(4-pyridinylmethyl)-1-phthalazinamine;

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4-[4-[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl-2-pyridinecarboxamide;

5 N-[2-(diethylamino)ethyl]-5-[(5-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide;

3-[(4-bromo-2,6-difluorophenyl)methoxy]-5-[[[4-(1-pyrrolidinyl)butyl]amino]carbonyl]amino]-4-isothiazolecarboxamide;

10 N-(4-bromo-2-fluorophenyl)-6-methoxy-7-[(1-methyl-4-piperidinyl)methoxy]-4-quinazolinamine;

3-[5,6,7,13-tetrahydro-9-[(1-methylethoxy)methyl]-5-oxo-12H-indeno[2,1-a]pyrrolo[3,4-c]carbazol-12-yl]propyl ester N,N-dimethyl-glycine;

15 N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide;

N-[3-chloro-4-[(3-fluorophenyl)methoxy]phenyl]-6-[5-[[[2-(methylsulfonyl)ethyl]amino]methyl]-2-furanyl]-4-quinazolinamine;

20 4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-phenyl]benzamide;

N-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-(4-morpholinyl)propoxy]-4-quinazolinamine;

25 N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine;

N-(3-(((2R)-1-methyl-2-pyrrolidinyl)methyl)oxy)-5-(trifluoromethyl)phenyl)-2-((3-(1,3-oxazol-5-yl)phenyl)amino)-3-pyridinecarboxamide;

2-(((4-fluorophenyl)methyl)amino)-N-(3-(((2R)-1-methyl-2-pyrrolidinyl)methyl)oxy)-5-(trifluoromethyl)phenyl)-3-pyridinecarboxamide;

30 N-[3-(Azetidin-3-ylmethoxy)-5-trifluoromethyl-phenyl]-2-(4-fluoro-benzylamino)-nicotinamide;

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- 6-fluoro-N-(4-(1-methylethyl)phenyl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide;
 2-((4-pyridinylmethyl)amino)-N-(3-((2S)-2-pyrrolidinylmethyl)oxy)-5-(trifluoromethyl)phenyl)-3-pyridinecarboxamide;
 5 N-(3-(1,1-dimethylethyl)-1H-pyrazol-5-yl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide;
 N-(3,3-dimethyl-2,3-dihydro-1-benzofuran-6-yl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide;
 10 N-(3-(((2S)-1-methyl-2-pyrrolidinyl)methyl)oxy)-5-(trifluoromethyl)phenyl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide;
 2-((4-pyridinylmethyl)amino)-N-(3-(2-(1-pyrrolidinyl)ethyl)oxy)-4-(trifluoromethyl)phenyl)-3-pyridinecarboxamide;
 15 N-(3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide;
 N-(4-(pentafluoroethyl)-3-((2S)-2-pyrrolidinylmethyl)oxy)phenyl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide;
 20 N-(3-((3-azetidinylmethyl)oxy)-5-(trifluoromethyl)phenyl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide;
 N-(3-(4-piperidinyloxy)-5-(trifluoromethyl)phenyl)-2-((2-(3-pyridinyl)ethyl)amino)-3-pyridinecarboxamide;
 25 N-(4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-(1H-indazol-6-ylamino)-nicotinamide;
 2-(1H-indazol-6-ylamino)-N-[3-(1-methylpyrrolidin-2-ylmethoxy)-5-trifluoromethyl-phenyl]-nicotinamide;
 N-[1-(2-dimethylamino-acetyl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl]-2-(1H-indazol-6-ylamino)-nicotinamide;
 30 2-(1H-indazol-6-ylamino)-N-[3-(pyrrolidin-2-ylmethoxy)-5-trifluoromethyl-phenyl]-nicotinamide;
 N-(1-acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-(1H-indazol-6-ylamino)-nicotinamide;

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N-(4,4-dimethyl-1-oxo-1,2,3,4-tetrahydro-isoquinolin-7-yl)-
2-(1H-indazol-6-ylamino)-nicotinamide;

N-[4-(tert-butyl)-3-(3-piperidylpropyl)phenyl][2-(1H-
indazol-6-ylamino)(3-pyridyl)]carboxamide;

5 N-[5-(tert-butyl)isoxazol-3-yl][2-(1H-indazol-6-ylamino)(3-
pyridyl)]carboxamide; and

N-[4-(tert-butyl)phenyl][2-(1H-indazol-6-ylamino)(3-
pyridyl)]carboxamide.

Specific binding agents to a cancer therapy agent(s)
10 may be administered with the cancer therapy agent, in
conjunction with the compound, or composition, of the
present invention. Binding agents may be administered
prophylactically or therapeutically to prevent or mitigate
the disease or condition in question.

15 Included in the compounds of Formulas I and II are the
pharmaceutically acceptable salts of the free-base
compounds. The term "pharmaceutically-acceptable salts"
embraces salts commonly used to form alkali metal salts and
to form addition salts of free acids or free bases. As
20 appreciated by those of ordinary skill in the art, salts may
be formed from ionic associations, charge-charge
interactions, covalent bonding, complexation, coordination,
etc. The nature of the salt is not critical, provided that
it is pharmaceutically acceptable. The term
25 pharmaceutically-acceptable" when used with reference to a
compound, including a salt or derivative, a carrier,
excipient, adjuvant, and other ingredients used for
formulation, is intended to refer to a form of the
ingredient that is safe for administration. For example, a
30 salt form of a compound of Formula I or of Formula II, which
has been approved for mammalian use, via ingestion or by
other administrative routes, by a governing body or
regulatory agency, such as the Food and Drug Administration
(FDA) of the United States, is pharmaceutically acceptable.

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Suitable pharmaceutically acceptable acid addition salts of compounds of Formulas I and II may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, hydrofluoric, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, arylaliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which include, without limitation, formic, acetic, adipic, butyric, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, ethanedisulfonic, benzenesulfonic, pantothenic, 2-hydroxyethanesulfonic, toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, camphoric, camphorsulfonic, digluconic, cyclopentanepropionic, dodecylsulfonic, glucoheptanoic, glycerophosphonic, heptanoic, hexanoic, 2-hydroxy-ethanesulfonic, nicotinic, 2-naphthalenesulfonic, oxalic, palmoic, pectinic, persulfuric, 2-phenylpropionic, picric, pivalic propionic, succinic, thiocyanic, undecanoic, stearic, algenic, β -hydroxybutyric, salicylic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formulas I and II include metallic salts, such as salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc, or salts made from organic bases including, without limitation, primary, secondary and tertiary amines, substituted amines including cyclic amines, such as caffeine, arginine, diethylamine, N-ethyl piperidine, histidine, glucamine, isopropylamine, lysine, morpholine, N-ethyl morpholine, piperazine, piperidine, triethylamine, diisopropylethylamine and trimethylamine. All of these salts

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may be prepared by conventional means from the corresponding compound of the invention by reacting, for example, the appropriate acid or base with the compound of Formulas I or II.

5 Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl,
10 lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

Examples of acids that may be employed to form
15 pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, hydrobromic acid, citric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, stearic and, salicylic acid, pamoic acid, gluconic acid, ethanesulfonic acid,
20 methanesulfonic acid, toluenesulfonic acid, tartaric acid, fumaric acid, medronic acid, napsylic acid, maleic acid, succinic acid and citric acid. Other examples include salts with alkali metals or alkaline earth metals such as sodium, potassium, calcium or magnesium, or with organic bases.
25 Preferred salts include hydrochloride, phosphate and edisylate.

In one embodiment of the invention, the compound of Formulas I or II is in the form of a salt, such as a hemi-, mono-, or di-salt complex, wherein the salt is selected from
30 a benzenesulfonate salt, an ethanesulfonate salt, an ethanedisulfonate salt, a methanesulfonate salt, a p-toluenesulfonate salt, a phosphate salt, a hydrobromide salt, a nitrate salt, a hydrochloride salt, a citrate salt, a medronate salt, a tosylate salt, a maleate salt, a

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fumarate salt, a napsylate salt, a pamoate salt, a salicylate salt and a stearate salt.

Additional examples of such salts can be found in Berge et al., J. Pharm. Sci., 66, 1 (1977). Conventional
5 methods may be used to form the salts. For example, a phosphate salt of a compound of the invention may be made by combining the desired compound free base in a desired solvent, or combination of solvents, with phosphoric acid in a desired stoichiometric amount, at a desired temperature,
10 typically under mild heat between 40-80 °C (depending upon the boiling point of the solvent). Generally, polar solvents such as alcohols (like EtOH), DMF, DMSO, and the like are used to form salts, as is readily appreciated by those of ordinary skill in the art. The salt can be precipitated upon
15 cooling (slow or fast) and may crystallize (i.e., if crystalline in nature), as appreciated by those of ordinary skill in the art. (See Example 75 for instance) Further, hemi-, mono-, di, tri- and poly-salt forms of the compounds of the present invention are also contemplated herein.
20 Similarly, hemi-, mono-, di, tri- and poly-hydrated forms of the compounds, salts and derivatives thereof, are also contemplated herein.

The present invention further comprises procedures for the preparation of a compound of Formulas I and II.

25

GENERAL SYNTHETIC PROCEDURES

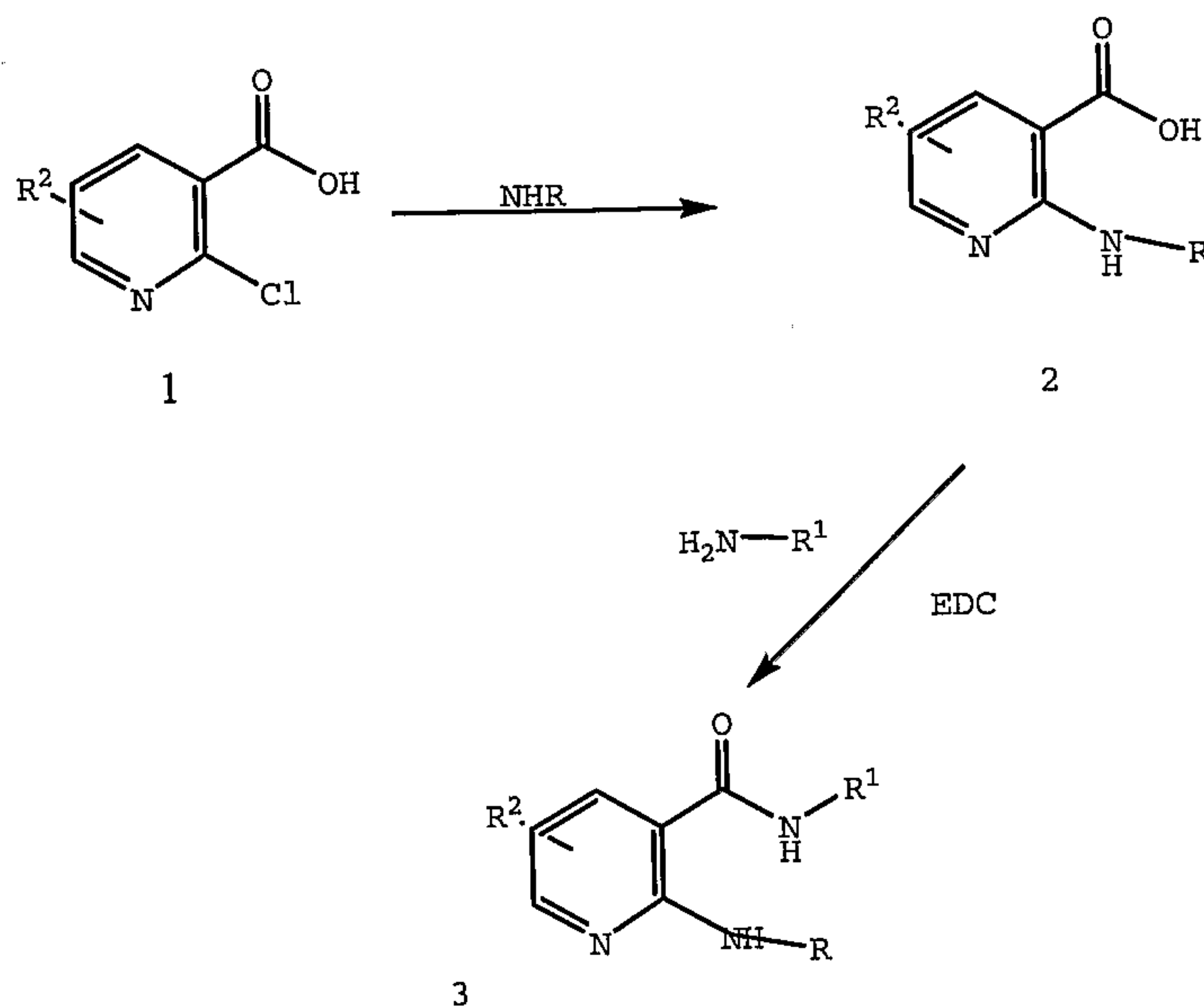
The compounds of the invention can be synthesized according to the following procedures of Schemes 1-33,
30 wherein the substituents are as defined for Formulas I and II, above, except where further noted. Although schemes 1-33 illustrate procedures for preparing compounds of Formula I (amino-nicotinamides), these schemes are also applicable as exemplary methods for the preparation of corresponding
35 amino-benzamides of Formula II, which are described in more

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detail in the "Preparations" immediately following the General Synthetic Procedures.

Scheme 1



5

Substituted nicotinamides **3** can be prepared from the corresponding halo analogs **1** by the process outlined in Scheme 1. Substituted amino acids **2** are prepared from the corresponding chloro compounds **1** such as by reacting with an amine at a suitable temperature, such as about $80^\circ C$. The acid **2** is coupled with an amine, preferably in the presence of a coupling agent such as EDC, to form the corresponding amide **3**.

The amination process can be carried out as an Ullmann type reaction using a copper catalyst, such as copper[0] or a copper[I] compound such as copper[I]oxide, copper[I]bromide or copper[I]iodide in the presence of a suitable base (such as a metal carbonate, for example K_2CO_3 to neutralize the acid generated in the reaction.

20

This reaction is reviewed in Houben-Weyl "Methoden der Organischen Chemie", Band 11/1, page 32 -33, 1958, in Organic Reactions, 14, page 19-24, 1965 and by J. Lindley (1984) in Tetrahedron, 40, page 1433-1456.

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The amount of catalyst is typically in the range of 1 to 20 mole percent. The reaction is carried out in an inert, aprotic solvent such as an ether solvent (for example dimethoxyethane or dioxane) or an amide solvent (for example
5 dimethylformamide or *N*-methylpyrrolidone), under an inert atmosphere in the temperature range of 60-180 °C.

An alternative amination process involves using a Group VIII element, where the metal core of the catalyst should be a zero-valent transition metal, such as palladium
10 or nickel, which has the ability to undergo oxidative addition to the aryl-halogen bond. The zero valent state of the metal may be generated in situ from the M[II] state. The catalyst complexes may include chelating ligands, such as alkyl, aryl or heteroaryl derivatives of phosphines or
15 biphosphines, imines or arsines. Preferred catalysts contain palladium or nickel.

Examples of such catalysts include palladium[II] chloride, palladium[II]acetate, tetrakis(triphenylphosphine)palladium[0] and nickel[II]acetylacetonate. The
20 metal catalyst is typically in the range of 0.1 to 10 mole percent. The chelating ligands may be either monodentate, as in the case for example of trialkylphosphines, such as tributylphosphine, triarylphosphines, such as tri-(*ortho*-tolyl)phosphine, and triheteroaryl phosphines, such as tri-
25 2-furylphosphine; or they may be bidentate such as in the case of 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, 1,2-bis(diphenylphosphino)ethane, 1,1'-bis(diphenylphosphino)ferrocene and 1-(*N,N*-dimethyl-amino)-1'-
(dicyclohexylphosphino)biphenyl. The supporting ligand may
30 be complexed to the metal center in the form of a metal complex prior to being added to the reaction mixture or may be added to the reaction mixture as a separate compound. The supporting ligand is typically present in the range 0.01 to 20 mole percent. It is often necessary to add a suitable

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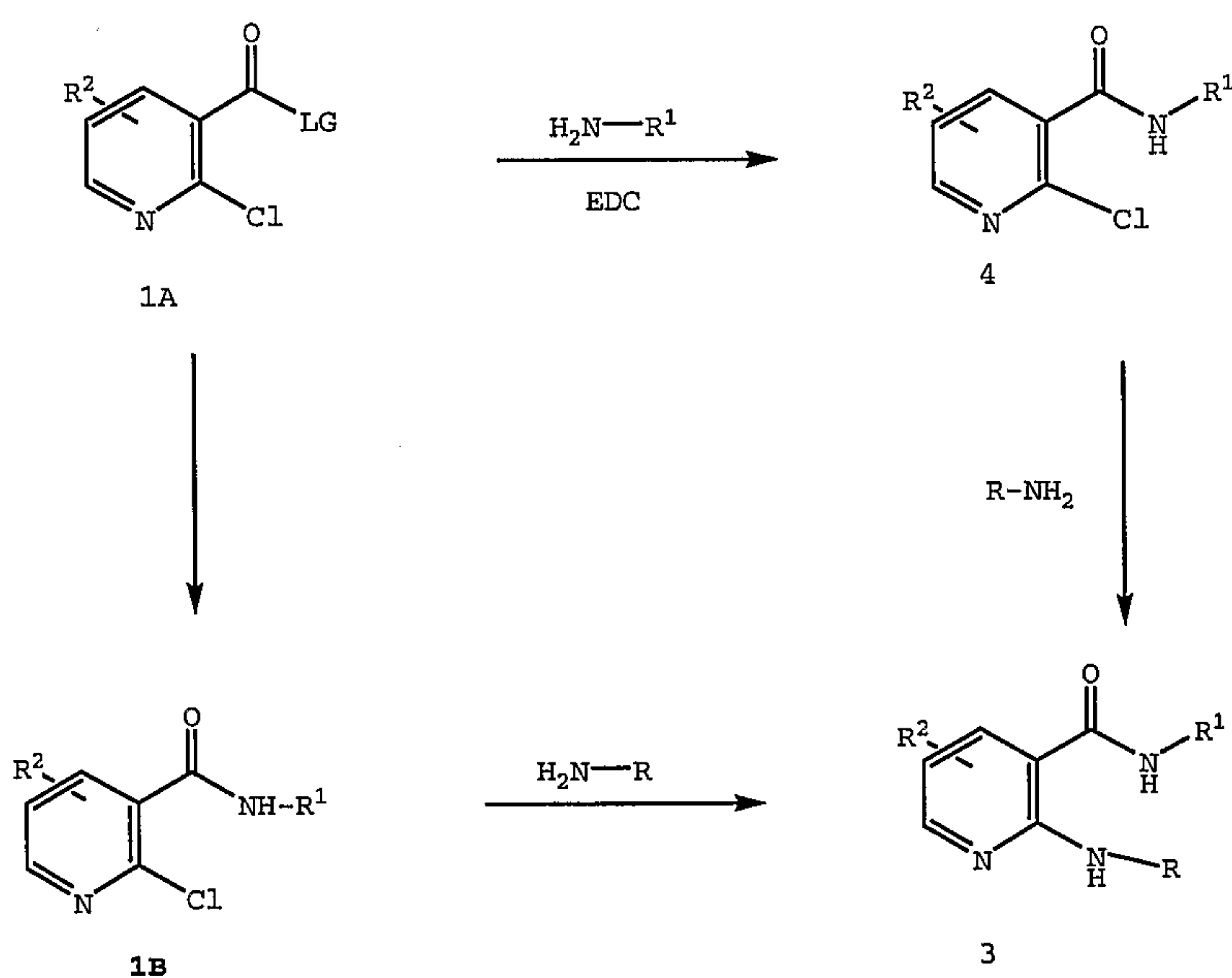
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base to the reaction mixture, such as a trialkylamine (for example, DIEA or 1,5-diazabicyclo[5,4,0]undec-5-ene), a Group I alkali metal alkoxide (for example potassium *tert*-butoxide) or carbonate (for example cesium carbonate) or potassium phosphate. The reaction is typically carried out in an inert aprotic solvent such as an ether solvent (for example dimethoxyethane or dioxane) or an amide solvent (for example, DMF or *N*-methylpyrrolidone), under an inert atmosphere in the temperature range of 60-180 °C.

The amination is preferably carried out in an inert, aprotic, preferably anhydrous, solvent or solvent mixture, for example in a carboxylic acid amide, for example DMF or dimethylacetamide, a cyclic ether, for example THF or dioxane, or a nitrile, for example CH₃CN, or in a mixture thereof, at an appropriate temperature, for example in a temperature range of from about 40 °C to about 180 °C, and if necessary under an inert gas atmosphere, for example a nitrogen or argon atmosphere.

20

Scheme 2



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Substituted nicotinamides **3** can also be prepared from the corresponding halo analogs **1A** by the process outlined in Scheme 2. The chloro acid **1** (LG is OH) is coupled with an amine, preferably in the presence of a coupling agent such as EDC, to form the corresponding chloro amide **4**.
Substituted amino-nicotinamides **3** are prepared from the corresponding chloro compounds **4** such as by reacting with an amine at a suitable temperature, such as about 80 °C. The amination reaction can be run in the presence of an appropriate catalyst such as a palladium catalyst, in the presence of an aprotic base such as sodium *t*-butoxide or cesium carbonate, or a nickel catalyst, or a copper catalyst.

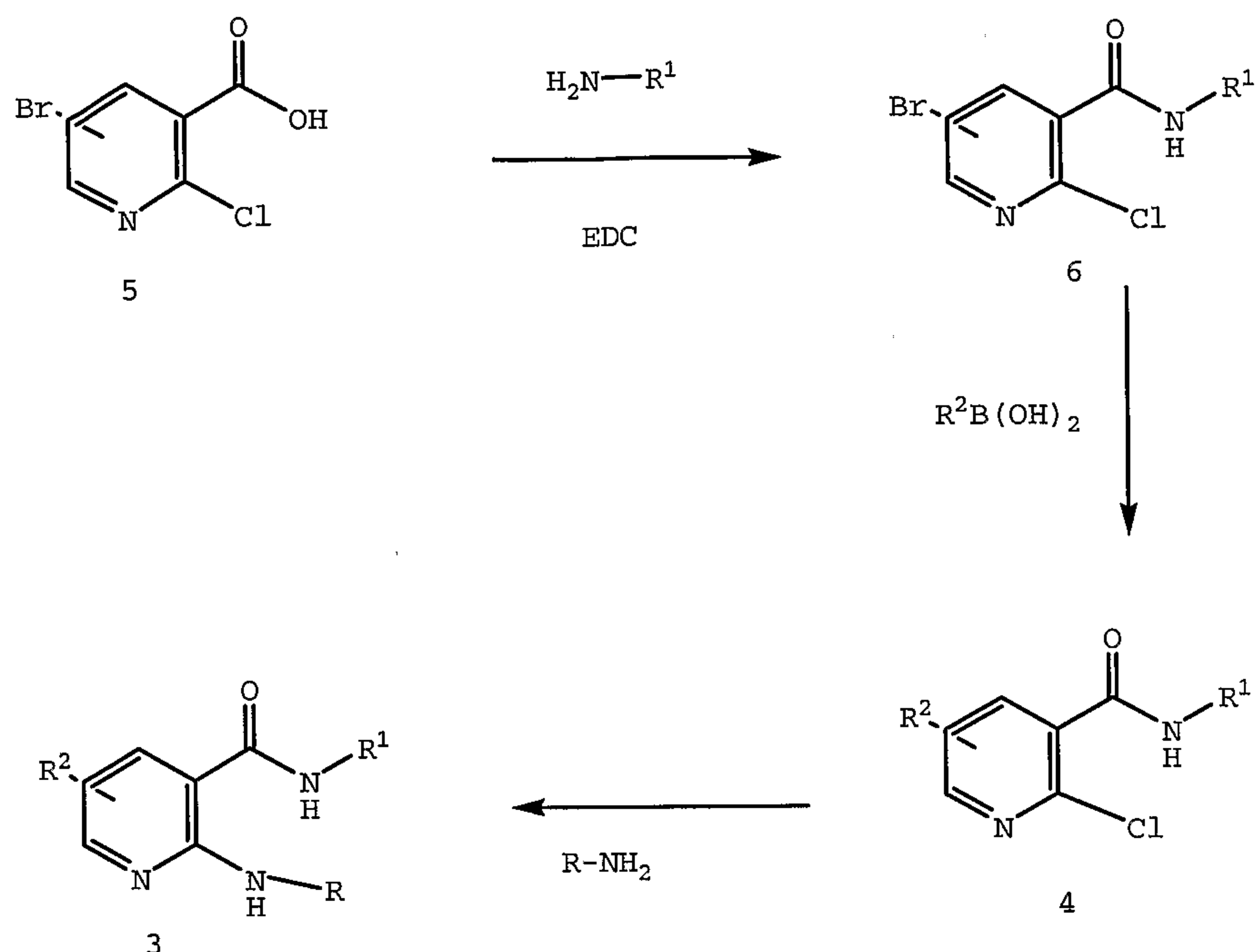
Alternatively, nicotinamides **3** can be prepared from 2-chloro-heterocyclyl acid chloride **1A** (LG is Cl) by coupling first with R¹-NH₂ such as in the presence of base, e.g., NaHCO₃, triethylamine (TEA) or other weak base, in a suitable solvent, such as CH₂Cl₂, to form the amide **1B**, then coupling with a primary or secondary amine in the presence of a base, such as LiHMDS or other strong base, to yield the substituted nicotinamide **3**.

Additionally, where A is a pi-electron rich heterocycle, the addition of KF, such as 40% KF on alumina in IpOH, at a temperature over about 100 °C, preferably about 160 °C, can be used in the formation of **3** from **1B**.

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Scheme 3



5

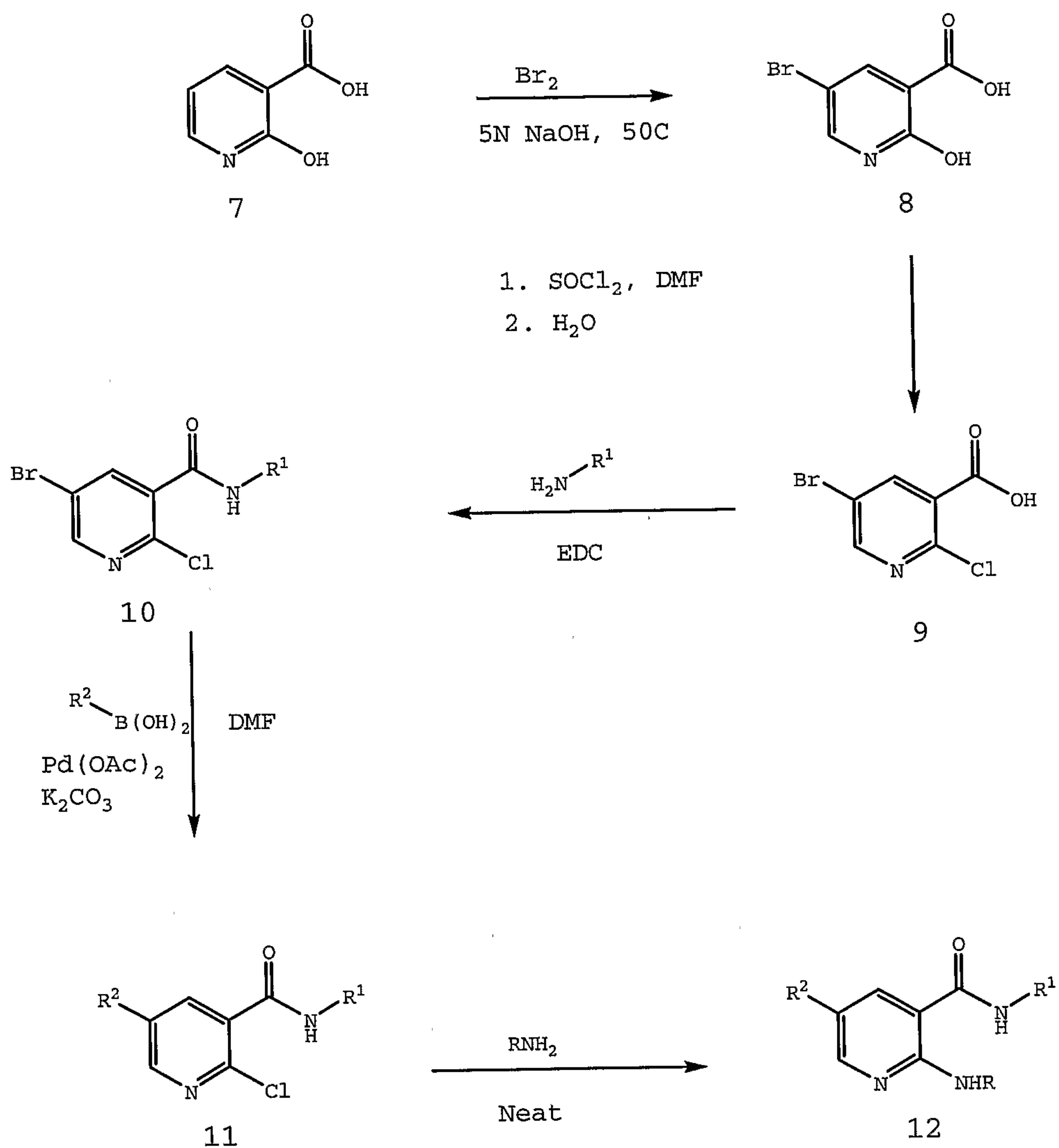
Substituted carboxamides **3** can also be prepared from the corresponding bromo/chloro analogs **5** by the process outlined in Scheme 3. The bromo/chloro acid **5** is coupled with an amine, preferably in the presence of a coupling agent such as EDC, to form the corresponding bromo substituted amide **6**. Suzuki coupling with the bromo amide **6** and suitable boronic acids provides the substituted amide **4**. Substituted amino-amides **3** are prepared from the corresponding chloro compounds **4** as described in Scheme 2.

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Scheme 4



5

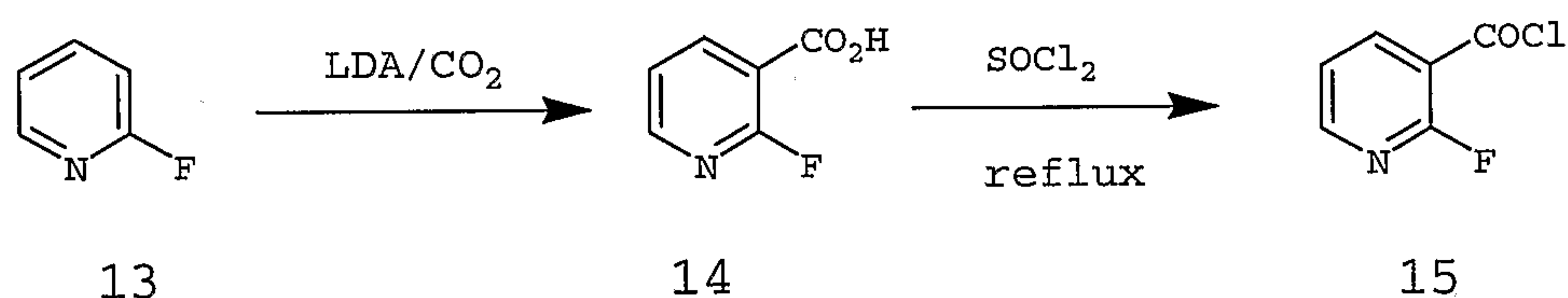
Substituted pyridines 12 can be prepared by the procedure described in Scheme 4. A solution of sodium hypobromite is freshly prepared and added to a 2-hydroxynicotinic acid 7 and heated, such as at a temperature of about 50 °C. Additional sodium hypobromide may be added to form the bromo compound 8 as needed. The 5-bromo-2-hydroxynicotinic acid 8 is reacted with thionyl chloride, at suitable temperature, such as at a temperature >RT, and

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preferably at about 80 °C, to form the 2-chloro-nicotinic acid analog **9**. The acid is coupled with an amine, preferably in the presence of a suitable coupling agent(s), such as EDC, HOBT, and DIEA, to form the corresponding substituted amide **10**. Suzuki coupling with the bromo nicotinamide **10** and suitable boronic acids, provides the substituted nicotinamide **11**. 2-Amino-nicotinamides **12** are prepared from the corresponding chloro compounds **11** such as by reacting with substituted amines at a suitable temperature, such as about 80 °C.

Scheme 5



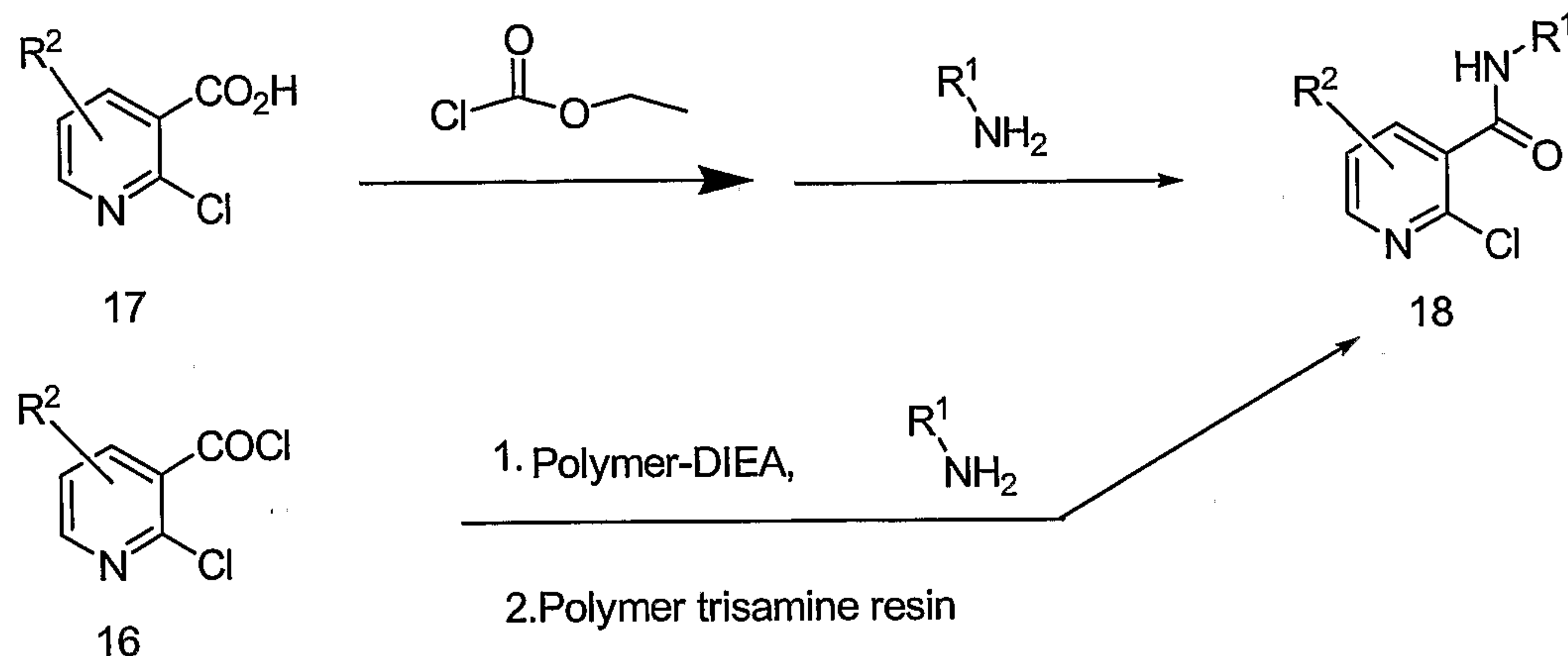
15

2-Amino-nicotinamides can also be prepared by first functionalizing pyridine compounds, as shown by the procedure described in Scheme 5. 2-Fluoropyridine **13** is lithiated by treatment with a lithium base, such as LDA or butyl lithium, at a temperature below about 0 °C, and preferably at about -78 °C, and quenched with a stream of dry CO₂ to form the nicotinic acid **14**. Solid CO₂ (dry ice) can be used, preferably dried with N₂, instead of gaseous CO₂. The acid **14** is converted to the acid halide **15**, such as by treatment with thionyl chloride and heating at a temperature above about 50 °C, and preferably at about reflux.

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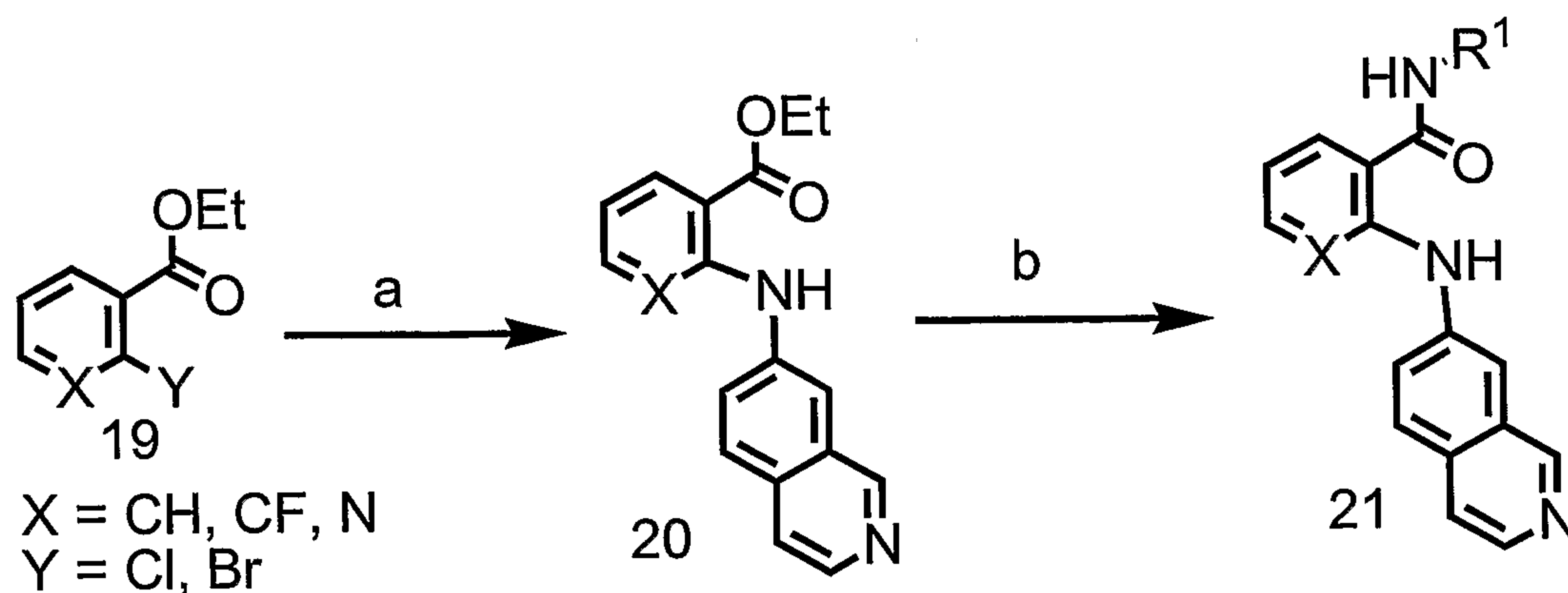
Scheme 6



Chloro-substituted pyridines **18** are prepared such as by the
 5 procedure described in Scheme 6. 2-Chloronicotinic acid **17**
 is activated with ethyl chloroformate, in the presence of
 base, such as TEA, at a temperature of about RT, to form the
 mixed anhydride (not shown). Reaction of the mixed
 anhydride with an amine produces amide **18**. Alternatively,
 10 the amine can be coupled with the acid chloride **16**, such as
 with polymer-supported DIEA. Excess acid chloride is
 removed by treating the reaction mixture with polymer-
 supported trisamine resin, to form amide **18**.

15

Scheme 7



a: 7-Aminoisoquinoline, $\text{Pd}(\text{OAc})_2$, BINAP, Toluene, K_2CO_3

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b: (i) LiOH, MeOH, H₂O, THF. (ii) R¹-NH₂, TBTU, N,N-diisopropylethylamine, Methylene chloride.

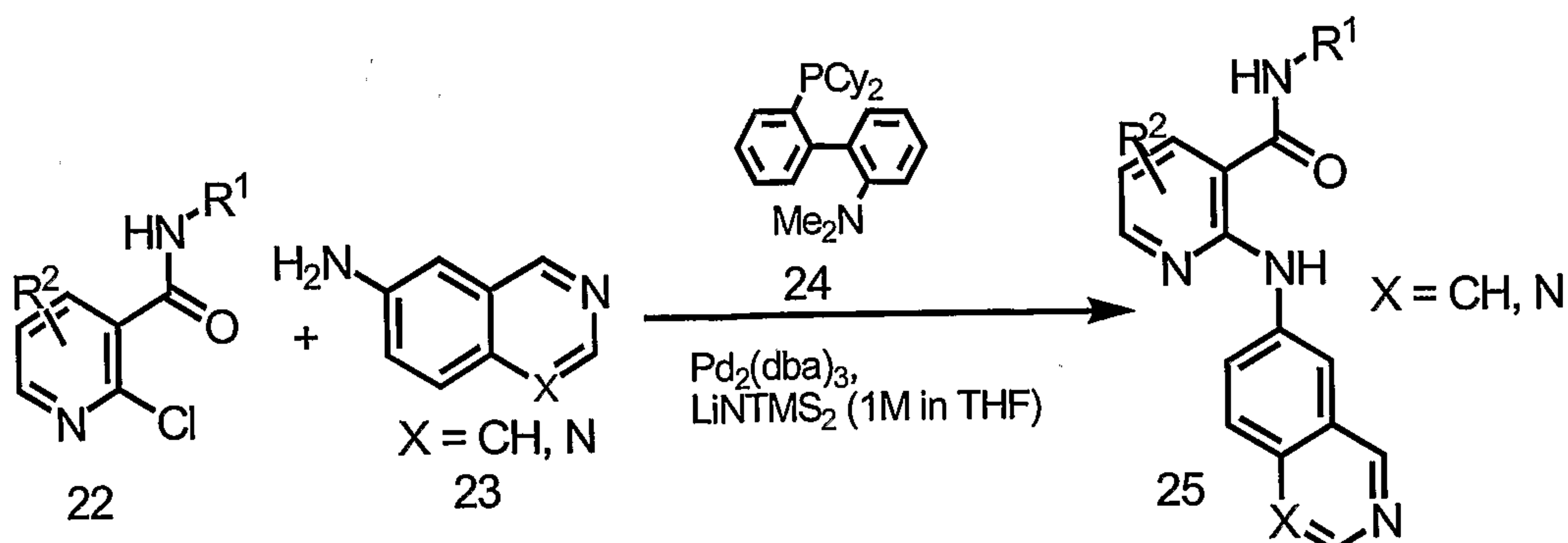
Amino-isoquinoline-aryl-amides **21** can be prepared such as by the procedure described in Scheme 7. As shown, a halo-benzoic acid ester or nicotinic acid ester **19** can be coupled to an amino-isoquinoline under Buchwald-type palladium coupling conditions, such as with the use of Pd(OAc)₂ and BINAP in toluene with a mild base such as a carbonate base (see conditions a). The resulting isoquinolin-7-ylamino-acid ester **20** can be saponified to the corresponding acid using a hydroxide base, such as LiOH, in a suitable solvent, such as in a mixed solvent of MeOH, water and THF, at mild temperature. The acid intermediate (not shown) can then be treated with known, conventional acid activating/coupling reagents, such as TBTU, HBTU, DCC, and the like, in the presence of a mild base, such as a tertiary amine base like DIEA (N,N-diisopropylethyl amine), and reacted with a desired amine such as an amino-tetrahydroisoquinoline **22** (below), or suitable other nucleophile (not shown in scheme 7), to afford the amino-isoquinolines **21** as the product. This method is useful for installing the desired isoquinolines prior to modifying the amide moieties of compound **21**.

25

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Scheme 8



Alternatively, amino-isoquinoline (or quinazoline)-

5 aryl-nicotinamides **25** (where R^1 is aryl) can be prepared by the procedure described in Scheme 8, as follows: Amino-isoquinolines **23** can be coupled to benzoic esters or nicotinic esters **19** (scheme 7) after it has been converted to the desired amide **22** (see scheme 7 above), under N_2 , by

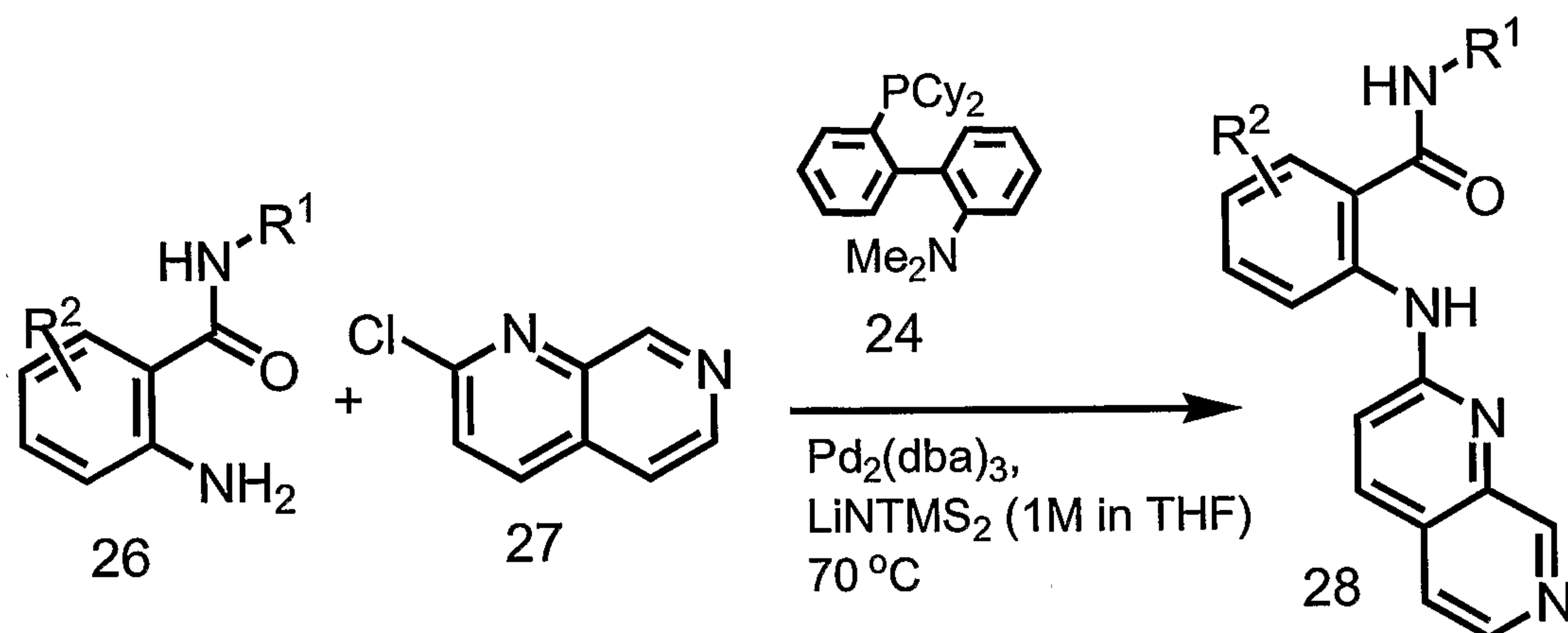
10 reacting compounds **22** and **23** in the presence of $\text{Pd}_2(\text{dba})_3$, a catalytic amount of 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl **24** (Cas# 213697-53-1, Strem Chemicals 15-1145,) and 1.0 M LiNTMS_2 THF solution, in a pressure-sealed reaction vessel. The reaction vessel is generally

15 stirred at elevated temperatures, as at about 70°C for a prolonged period of time, such as about 17 hours. After cooling, the product **25** can be recovered by conventional extraction and/or purification methods.

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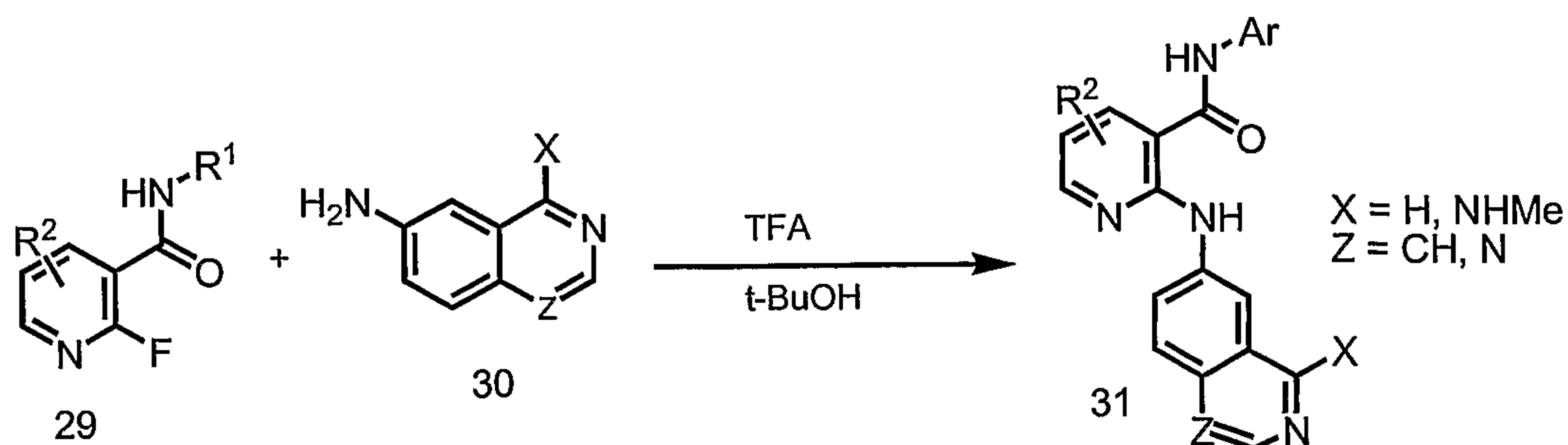
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Scheme 9



As an alternative to Scheme 8, amino-naphthydrin-aryl-nicotinamides **28** (see also similar compounds **22**, **25**) can be prepared by the procedure described in Scheme 9, as follows: 2-amino-N-(4-tert-butyl-phenyl)-benzamide **26** (where R¹ is 4-tert-butyl-phenyl) and 2-chloro-[1,7]naphthyridine **27** can be coupled to form compound **28** using the reagents shown in scheme 8, i.e., Pd₂(dba)₃, (2'-dicyclohexylphosphanyl-biphenyl-2-yl)-dimethyl-amine, and 1M solution of LiN(TMS)₂ in THF, in a sealed reaction vessel at 70 °C for about 24h. Such a method is useful especially where desired amino-naphthydrins, for use in the procedure described in Scheme 8, are not commercially available and/or are difficult to synthesize.

Scheme 10



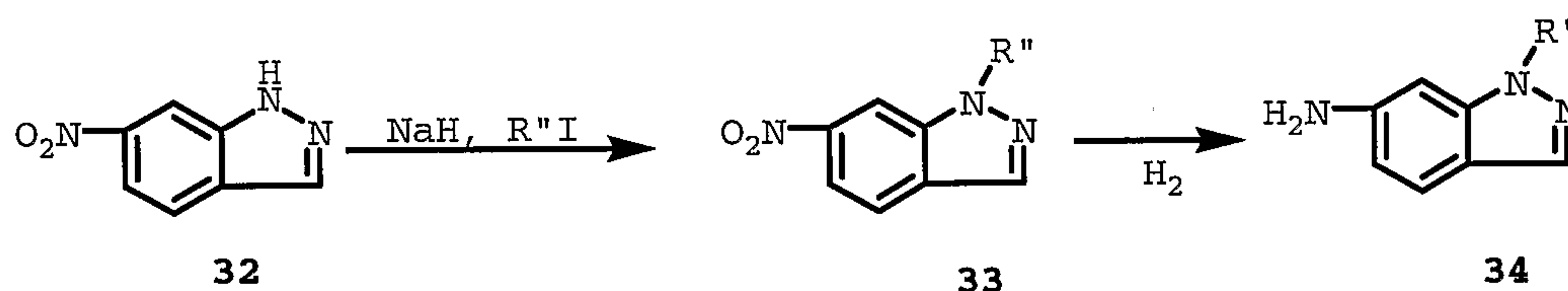
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Nicotinamides **31** can be made under various coupling conditions. For example, and as shown in Scheme 10, nicotinamides **31** can be made by treating a desired fluoro-nicotinamide **29** and a desired 7-aminoisoquinoline (or quinazoline where Z=N) **30** with TFA in a suitable solvent, such as t-BuOH, and stirring the resulting mixture for 24 hours at elevated temperature, such as at 90 °C.

Various aryl R and R¹ groups of the compounds of the present invention can be prepared as described in the following Schemes 11-25, 27-30 and 32-33.

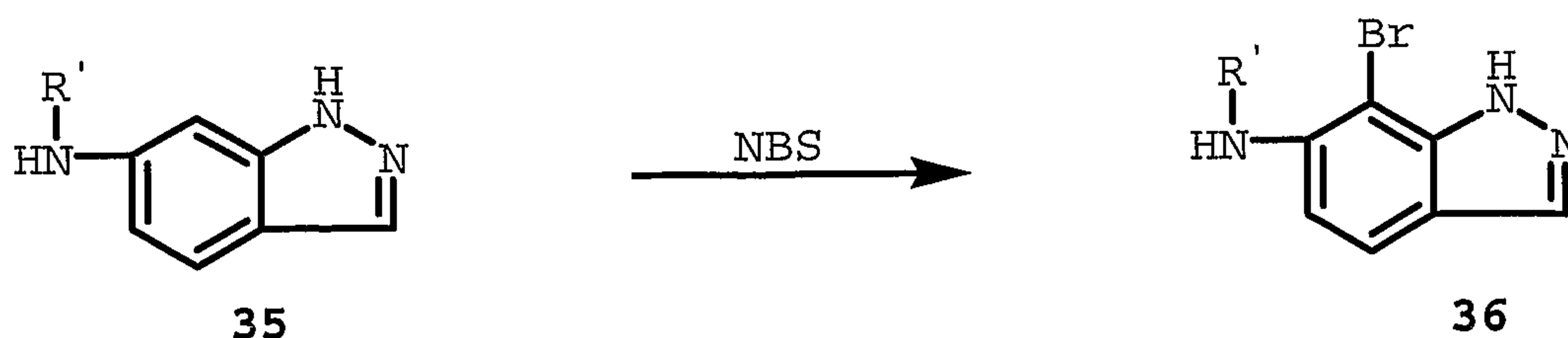
Scheme 11

15

Alkylated indazoles can be prepared by the procedure described in Scheme 11. To a solution of 6-nitroindazole **32** in a solvent such as THF is added strong base, such as NaH at a temperature below RT, preferably at about 0 °C.

Alkylhalides, such as where R'' is methyl, are added and reacted at a temperature about RT to give 1-alkyl-6-nitro-1H-indazole **33**. The nitro indazole **33** is hydrogenated, such as with an H₂ atmosphere in the presence of a catalyst, such as Pd/C to give the 1-substituted-6-amino-1H-indazole **34**.

25

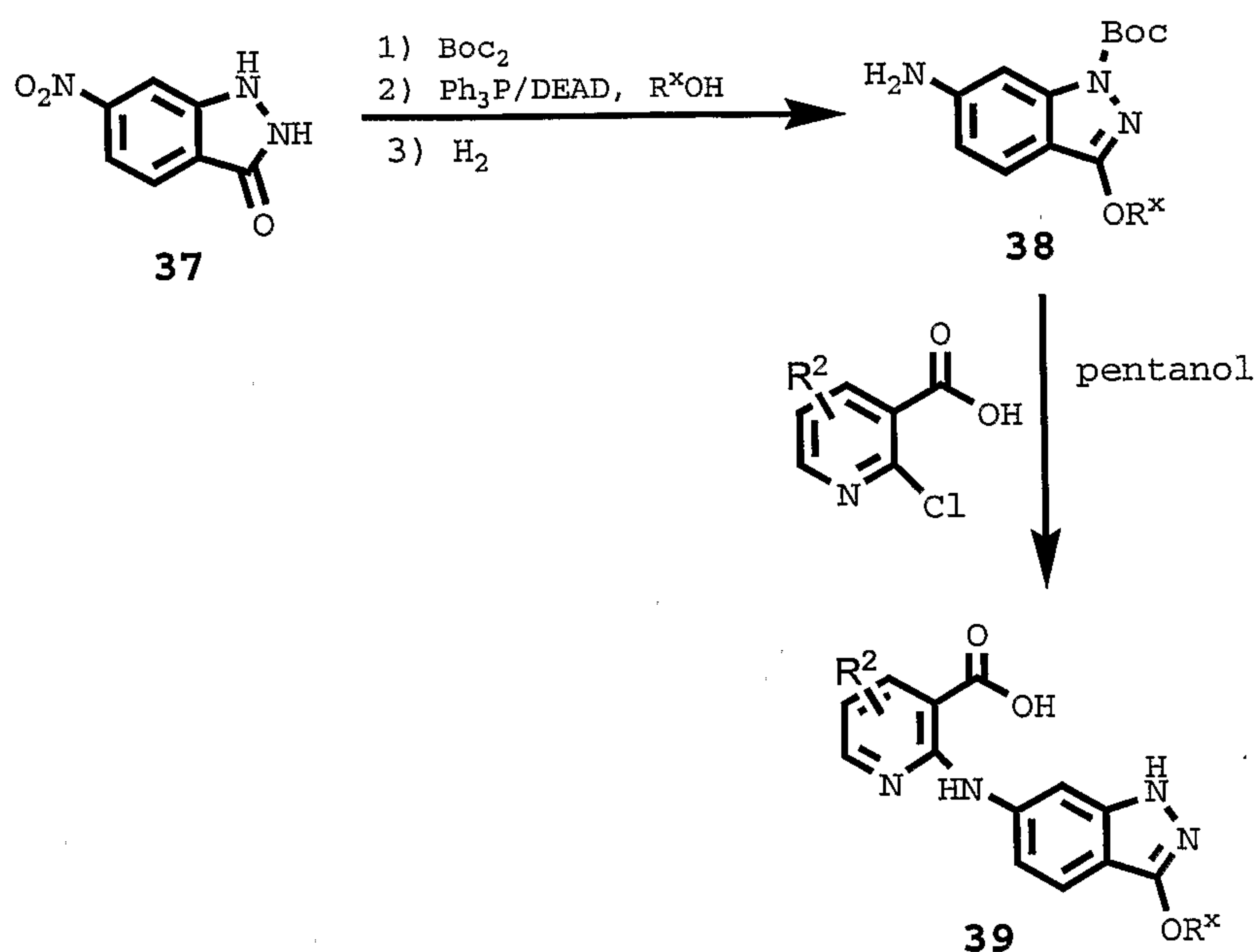
Scheme 12

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Brominated indazoles can be prepared by the procedure described in Scheme 12. NBS is slowly added to an acidic solution, such as a mixture of TFA:H₂SO₄ (5:1) and *tert*-butyl-4-nitrobenzene **35** at a temperature of about RT to yield the brominated compound **36**.

Scheme 13



10

Indazolyl ethers **38** can be prepared by the procedure described in Scheme 13. 6-Nitro-1H-2-hydroindazol-3-one **37** is protected such as with Boc₂O and DMAP in CH₂Cl₂ at a temperature of about RT, to give the protected 6-nitro-2-hydroindazol-3-one. The protected 6-nitro-2-hydroindazol-3-one is reacted with an alcohol (where R^x is an appropriate substituent selected from the possible substituents on R¹) and Ph₃P in a solvent, such as THF, and DEAD, at a temperature of about RT, to give the protected 6-nitro(indazol-3-yl) ether. The nitro intermediate is hydrogenated, such as with an H₂ atmosphere in the presence

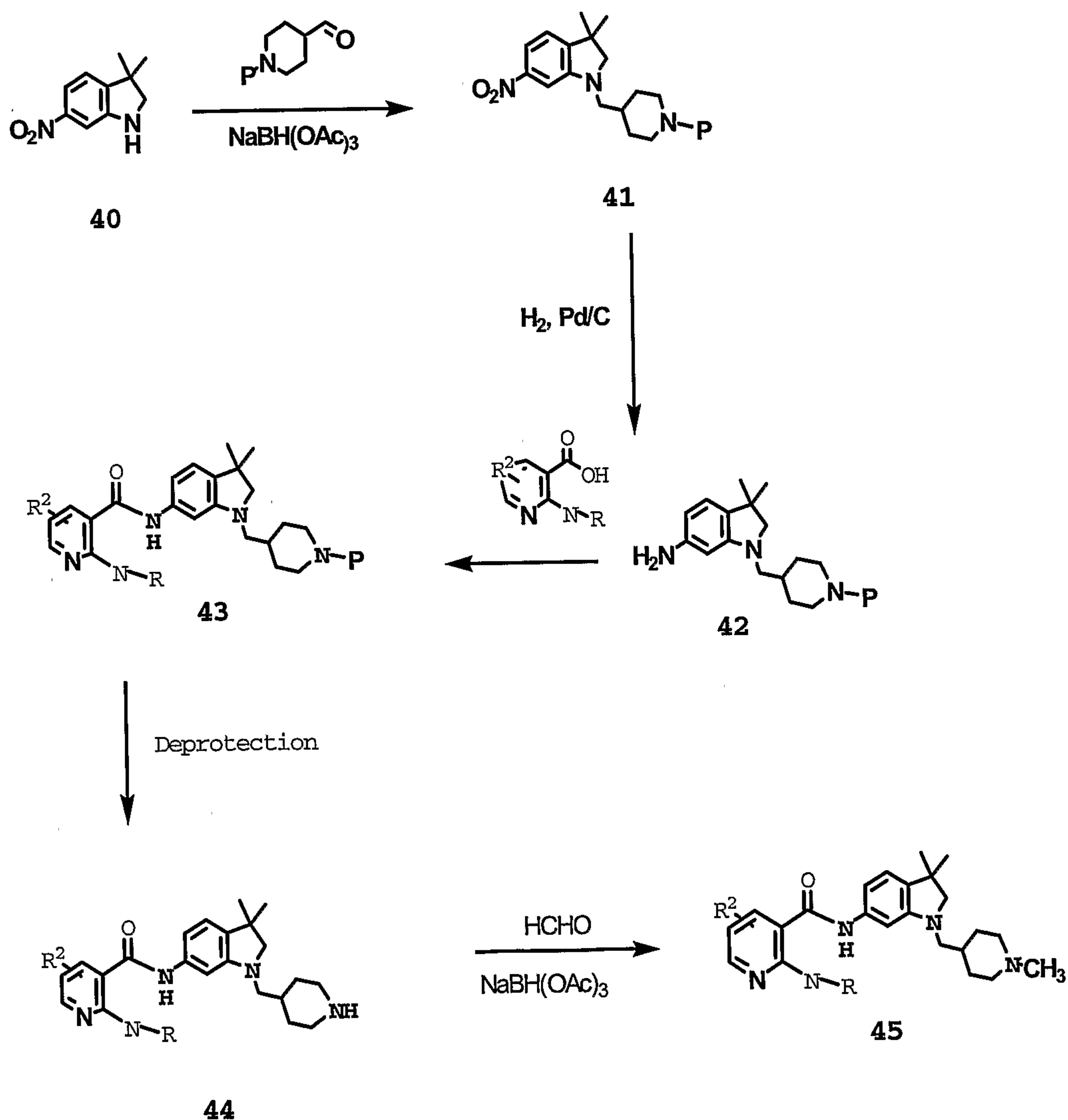
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of a catalyst, such as Pd/C, to give the protected 6-amino(indazol-3-yl) ether **38**. The amine **38** is coupled with 2-chloronicotinic acid in a solvent, such as an alcohol, preferably pentanol, at a temperature above RT, preferably at a temperature above about 75 °C, and more preferably at a temperature at about 130 °C to give the coupled and deprotected compound **39**.

Scheme 14

10



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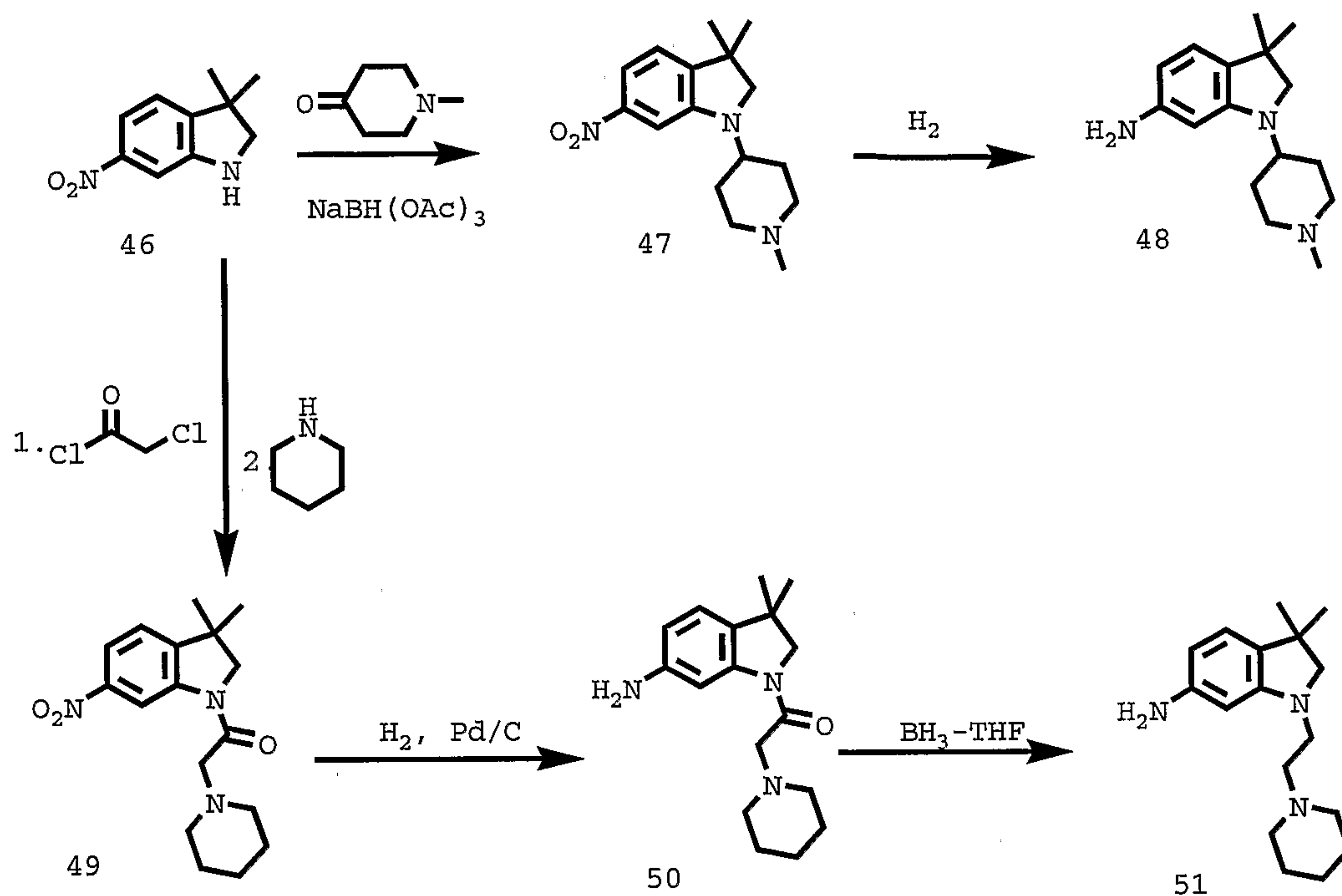
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Indolinyl substituted carboxamides **45** can be prepared from the corresponding nitro indoline **40** by the procedure described in Scheme 14. For example, 3,3-dimethyl-6-nitroindoline **40** is alkylated, such as with N-protected-4-formylpiperidine in the presence of NaHB(OAc)₃ and acid, such as glacial AcOH, and solvent, such as dichloromethane, at a temperature of about RT, to afford the alkylated indane **41**. Hydrogenation of the alkylated indane **41**, such as with an H₂ atmosphere in the presence of a catalyst, such as Pd/C, in the presence of a solvent, such as an alcohol, preferably MeOH, to give the amino intermediate **42**. Alternatively, other hydrogenation methods can be used, such as Fe powder with NH₄Cl. Coupling of the amine **42**, such as with 2-chloronicotinic acid and DIEA, HOBt and EDC, in a solvent such as CH₂Cl₂ at a temperature of about RT provides the protected carboxamide **43**, which upon deprotection and alkylation yields other compounds of the invention, **44** and **45**, respectively. Alternatively, amine **42** is reacted with 2-fluoronicotinoyl chloride to form a 2-fluoronicotinamide, which can be alkylated such as in Scheme 14.

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Scheme 15



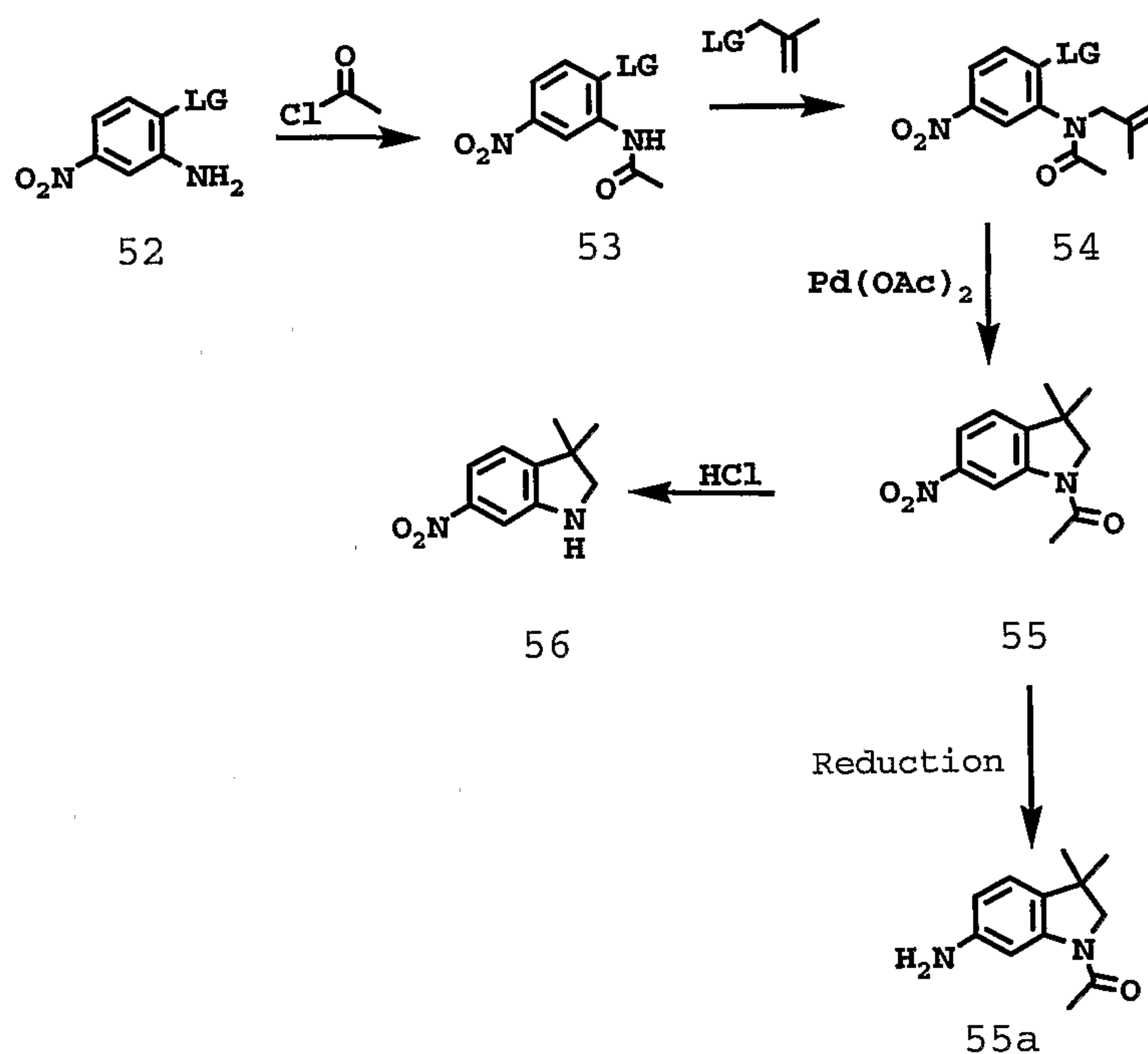
Substituted indolines **51** are prepared such as by the procedures described in Scheme 15. Substituted amino-indolines **48** are prepared from the nitroindoline **46** and a ketone in the presence of $\text{NaHB}(\text{OAc})_3$ to form the 1-substituted indoline **47**. The nitroindoline **47** is hydrogenated, such as with H_2 in the presence of a catalyst, such as Pd/C , to yield the amino-indoline **48**.

Alternatively, substituted amino-indolines **51** are prepared from the nitroindoline **46**. Nitroindoline **46**, is reacted with an acid chloride to form an amide. Further treatment with a primary or secondary amine, preferably a secondary amine, such as in the presence of NaI , at a temperature above about 50°C , and preferably at about 70°C yields the nitroindoline **49**. The nitro compound **49** is hydrogenated, such as with H_2 in the presence of a catalyst, such as Pd/C , to yield the amino-indoline **50**. The carbonyl is reduced, such as with $\text{BH}_3\text{-THF}$ yields 1-aminoalkyl-indolines **51**.

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Scheme 16



- 5 Substituted indolines (**55**, **55a**, and **56**) are prepared such as by the procedures described in Scheme 16. Substituted acetamides **53** are prepared from the coupling of halo-5-nitroanilines **52** (where LG is bromo or chloro, preferably chloro) and an acylating agent, such as acetyl chloride or acetic anhydride, under standard coupling chemistry, such as with DIEA, and DMAP, at a temperature of about RT, in a suitable solvent, such as CH_2Cl_2 , DMF and/or DMAC. The N-(2-methylprop-2-enyl)acetamide **54** is prepared from the acetamide **53**, such as by the treatment of base, such as NaH in a suitable solvent such as NMP or anhydrous DMF and a 3-halo-2-methylpropene such as 3-bromo-2-methylpropene or 3-chloro-2-methylpropene, at a temperature between about 0 °C and RT, and preferably at about RT; or with CsCO_3 at a temperature above RT, preferably above about 50 °C and more preferably above about 60 °C. Cyclization of the N-(2-methylprop-2-enyl)acetamide **54**, such as by the Heck-type reaction (treatment with Pd(OAc)_2 in the presence

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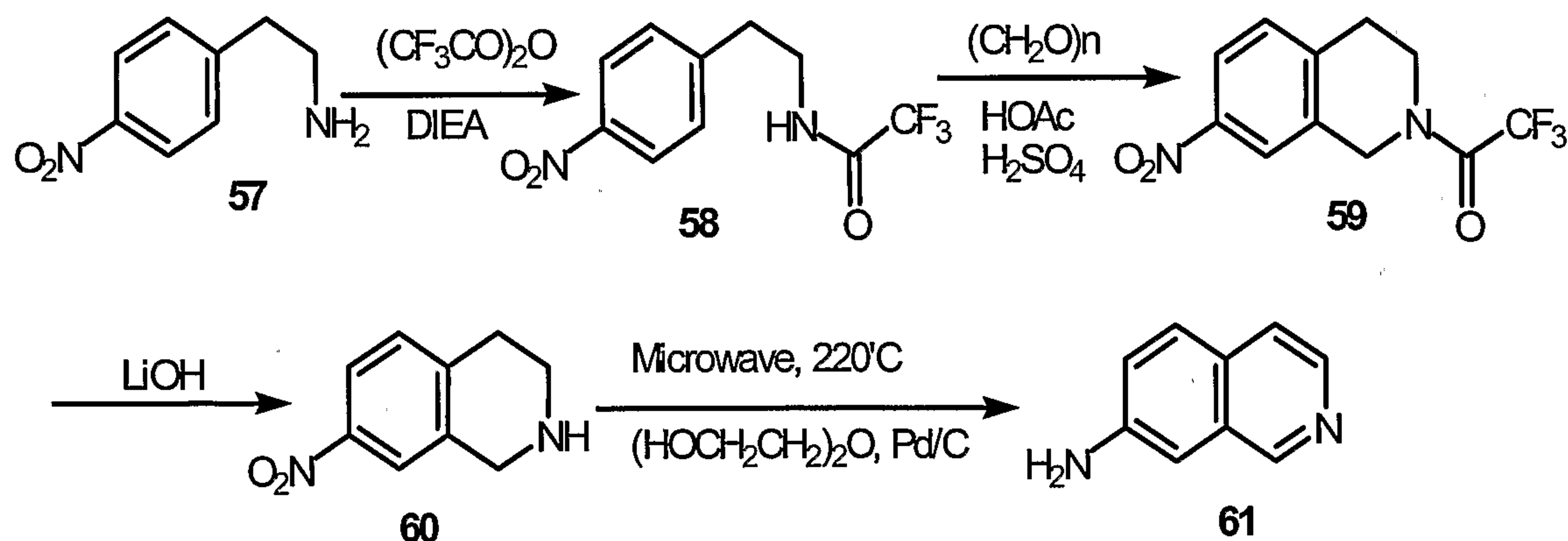
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of base, for example tetraethyl-ammonium chloride, sodium formate, and NaOAc) at a temperature above about 50 °C, and preferably at about 80 °C, yields the protected (3,3-dimethyl-6-nitro-2,3-dihydro-indol-1-yl)ethanone **55**.

- 5 Deprotection, such as with strong acid such as HCl or AcOH at a temperature above about 50 °C, and preferably at about 70-80 °C, yields the 3,3-dimethyl-6-nitro-2,3-dihydro-indol-1-yl **56**. Alternatively, the protected dihydro-6-nitro indoline **55** can be reduced, such as with Fe, or with 10% Pd/C in the presence of an excess of $\text{NH}_4\text{CO}_2\text{H}$, or with H_2 in the presence of a catalyst to form the protected dihydro-6-amino indoline **55a**.

Scheme 17

15



- 7-Amino-isoquinolines **61** can be prepared by the procedure described in Scheme 17. 4-Nitrophenethylamine hydrochloride **57** can be treated with triflic anhydride in the presence of base, such as DIEA, in a suitable solvent, such as CH_2Cl_2 , at reduced temperature and stirred at about RT to form the protected amino compound **58**. Treatment of the resulting yellow 2,2,2-trifluoro-N-[2-(4-nitro-phenyl)-ethyl]-acetamide **58** with paraformaldehyde and acid, such as HOAc or a mixture of HOAc with H_2SO_4 , slowly under

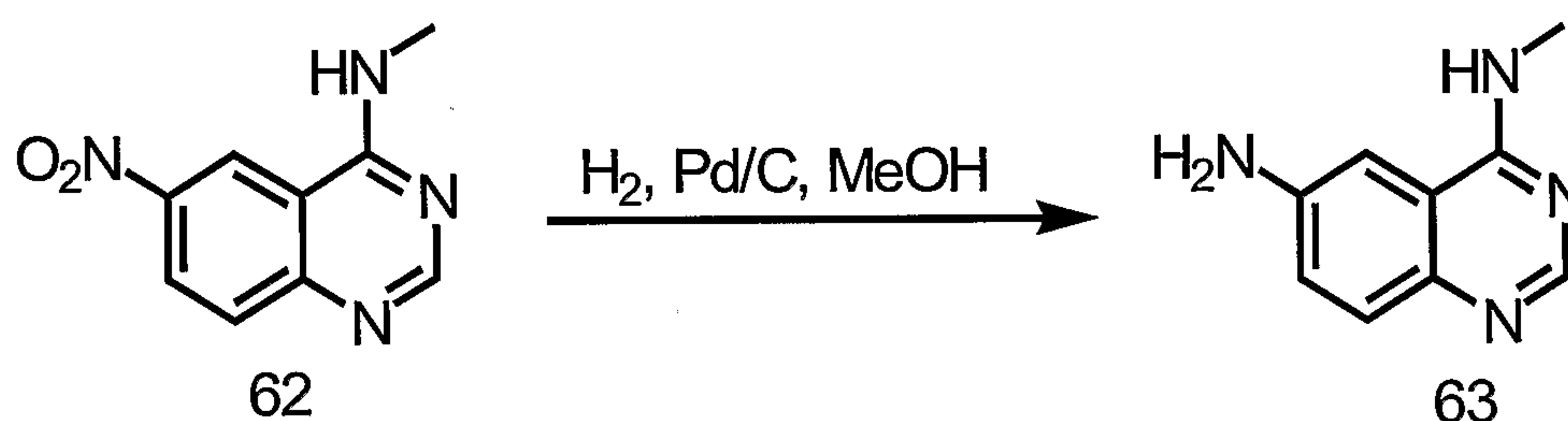
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controlled reaction conditions affords the N-acetyl protected 7-nitro-1,2,3,4-tetrahydroisoquinoline **59**.

Isoquinoline-acetamide **59** can then be reduced to 7-nitro-1,2,3,4-tetrahydro-isoquinoline **60** with a hydroxide base, such as LiOH, for example, in solvent such as MeOH, CH₂Cl₂ and H₂O, to cleave the acetamide. The nitro group resulting nitro-tetrahydroisoquinoline **60** can then be reduced to the corresponding 7-amino-isoquinoline **61** with 10%Pd on carbon in diethylene glycol under radiation, such as in a Smith Synthesizer microwave at 220 °C.

Scheme 18



62 **63**

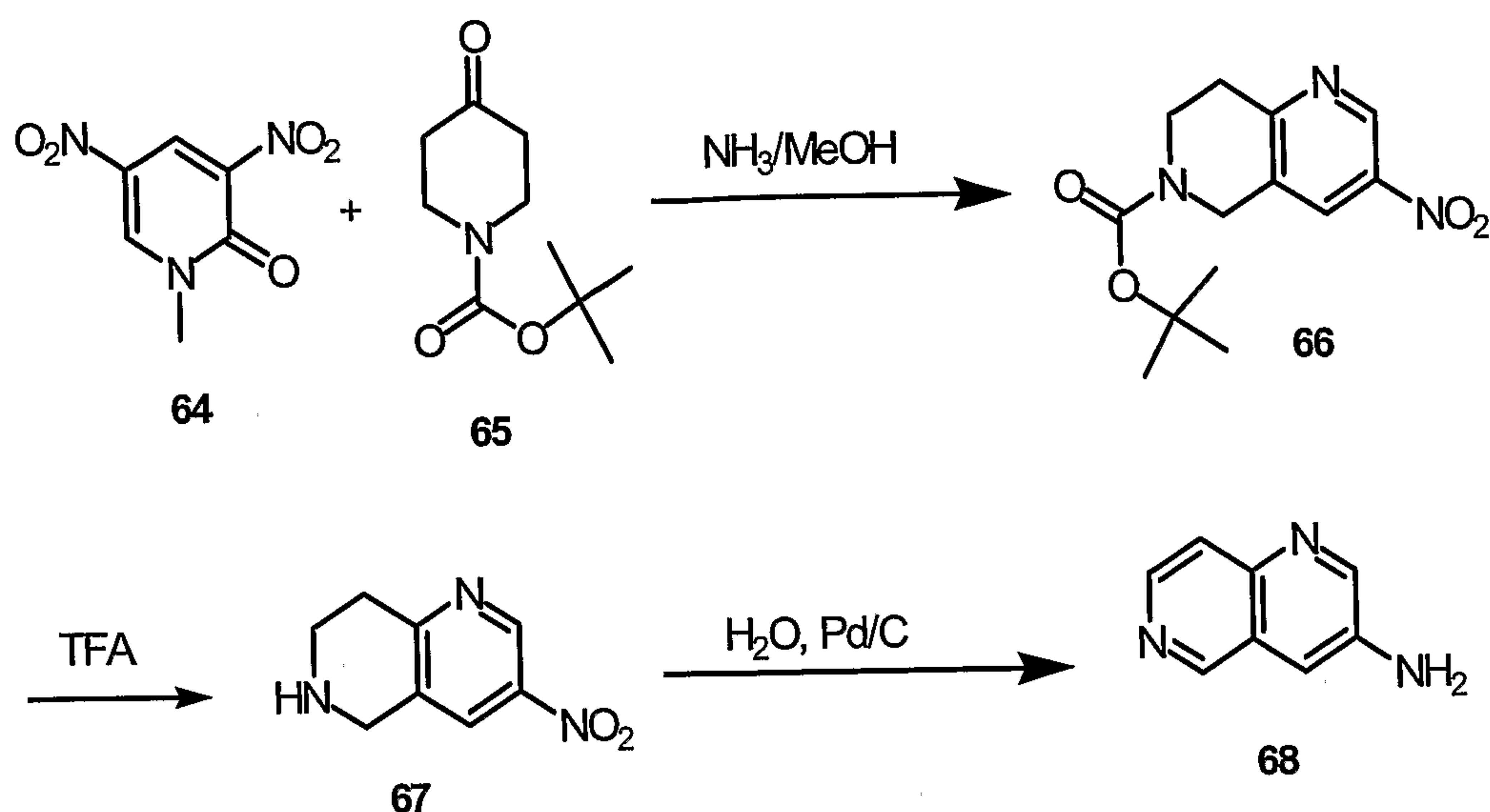
62 **63**

15 N⁴-Substituted-quinazoline-4,6-diamines **63** can be prepared by the procedure described in Scheme 18. The nitro group of substituted-(6-nitro-quinazolin-4-yl)-amines **62** can be reduced by conventional hydrogenation methods, such as with palladium on carbon (10 wt%) in suitable solubilizing solvent, such as methanol, under a suitable pressure of hydrogen gas.

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Scheme 19

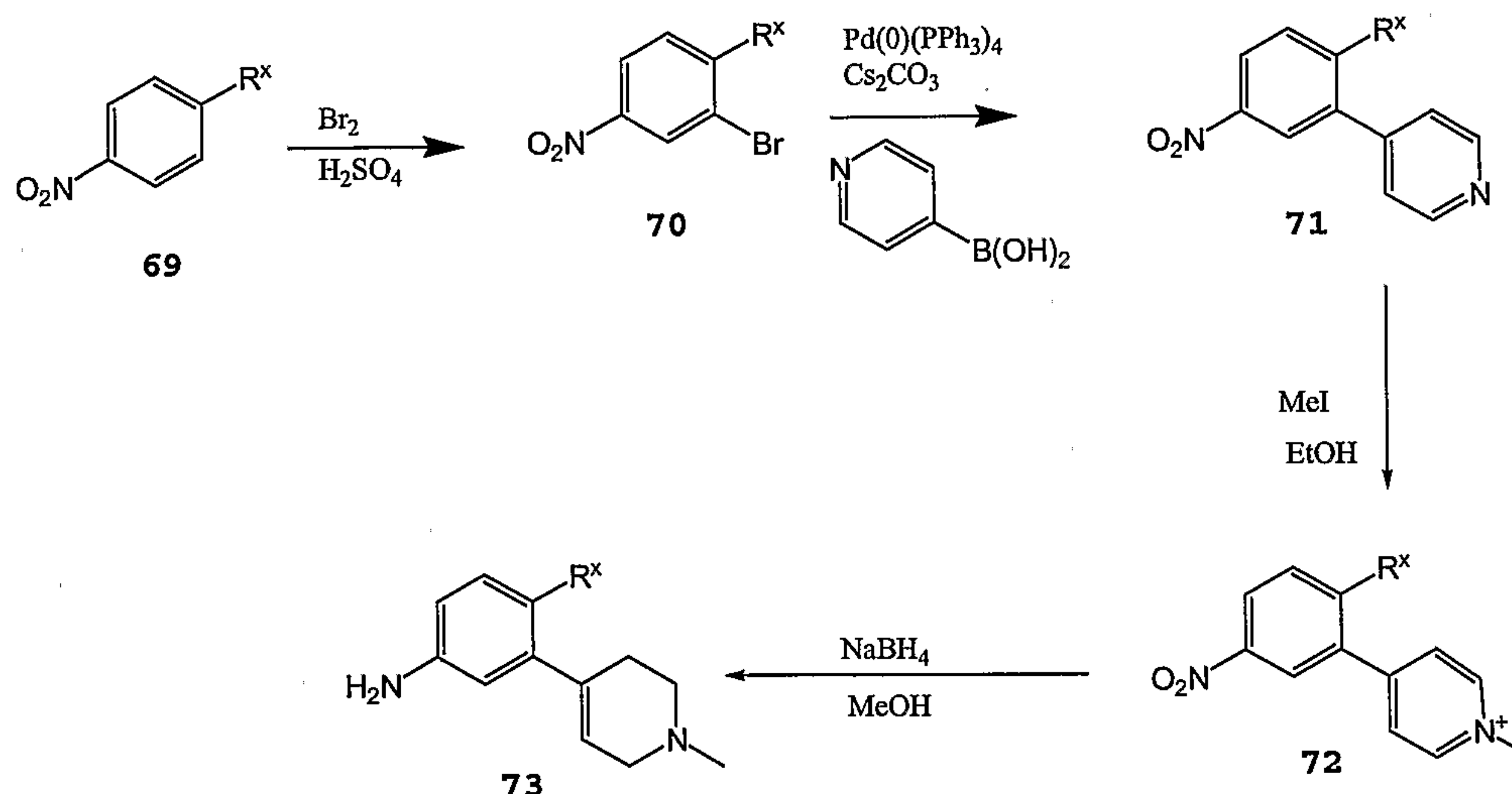


[1,6]Naphthyridin-3-ylamines **68** can be prepared by the
 5 procedure described in Scheme 19. 3-Nitro-7,8-dihydro-5H-
 [1,6]naphthyridine-6-carboxylic acid tert-butyl ester **66** can
 be prepared by reacting 1-methyl-3,5-dinitro-1H-pyridin-2-
 one **64** and 4-oxo-piperidine-1-carboxylic acid tert-butyl
 ester **65** with 2M solution of NH_3 in MeOH in a sealed vessel
 10 for 24h at 70 °C. Cooling and concentration of the reaction
 affords the crude compound **66**, which may be recrystallized
 from one or more suitable solvents, such as from MeOH. The
 Boc protecting group of 3-nitro-7,8-dihydro-5H-
 [1,6]naphthyridine-6-carboxylic acid tert-butyl ester **66** can
 15 be removed using standard deprotection chemistry, such as
 with TFA in solvent, to yield 3-nitro-5,6,7,8-tetrahydro-
 [1,6]naphthyridine **67**. Compound **67** may be recrystallized
 from suitable solvents, such as CH_3CN . Hydrogenation of 3-
 nitro-5,6,7,8-tetrahydro-[1,6]naphthyridine **67** with Pd/C,
 20 with simultaneous oxidation under known conditions, such as
 in a microwave reaction vessel, affords the corresponding
 amino-naphthydrins **68**.

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Scheme 20

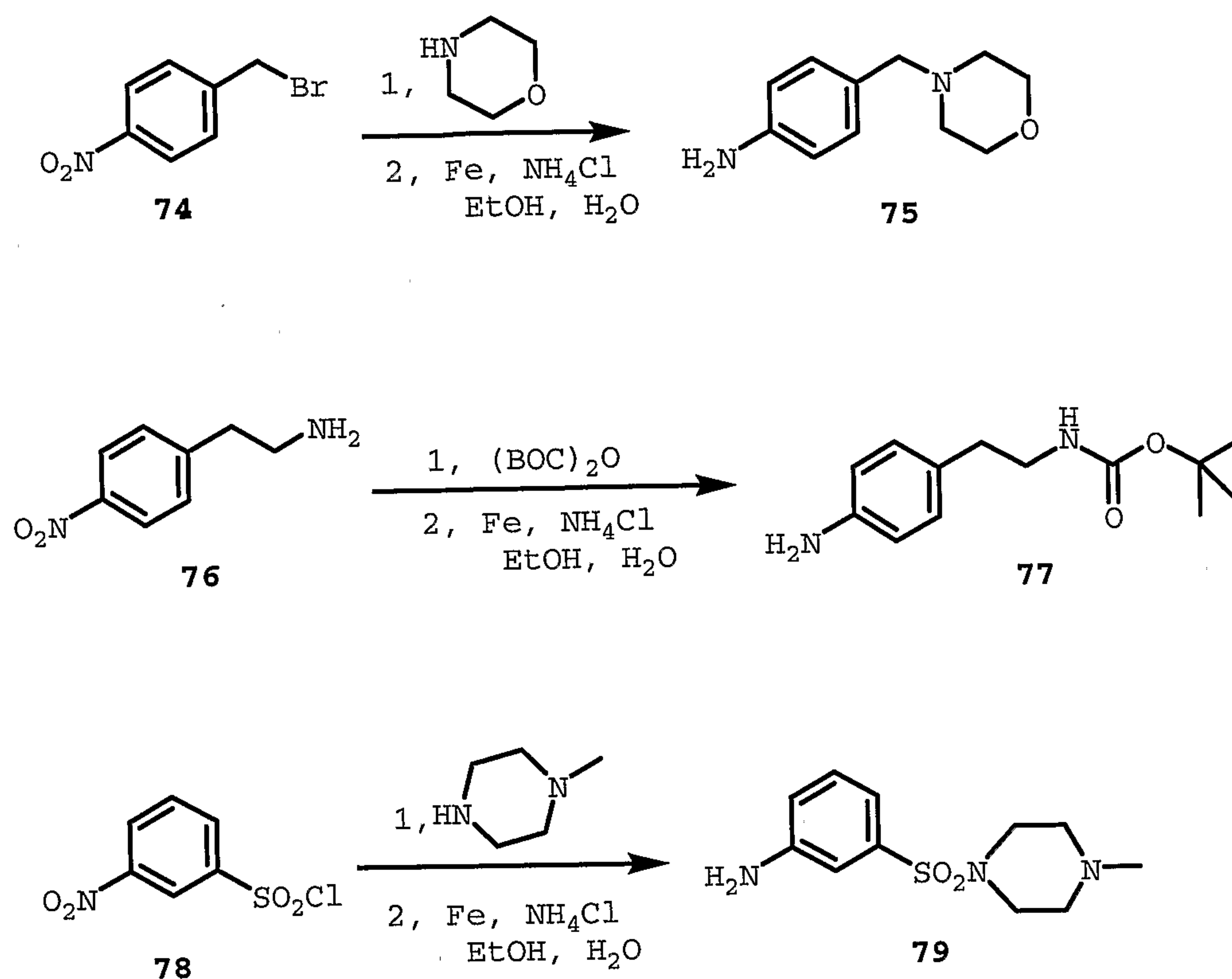


- 5 1,2,3,6-Tetrahydro-pyridyl substituted anilines **73** are prepared such as by the procedure described in Scheme 20. Nitrobenzenes **69** are brominated, such as with bromine in the presence of acid, H_2SO_4 for example, or with NBS to yield the 3-bromo derivative **70**. Suzuki coupling of the bromo-
- 10 derivative **70** and a substituted pyridylboronic acid, such as at a temperature above RT, preferably above about $50\text{ }^\circ\text{C}$, and more preferably at about $80\text{ }^\circ\text{C}$, yields the pyridyl derivative **71**. Alkylation of the nitrophenyl-pyridine **71**, such as by treatment with iodomethane, preferably above
- 15 about $50\text{ }^\circ\text{C}$, and more preferably at about $80\text{ }^\circ\text{C}$, yields the pyridinium compound **72**, which upon reduction, such as by NaBH_4 , yields the tetrahydro-pyridine substituted aniline **73**.

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Scheme 21



A series of substituted anilines are prepared such as
 5 by the procedure described in Scheme 21. A nitrobenzyl
 bromide **74** is coupled with morpholine, such as at a
 temperature at about RT, to yield the heterocyclylmethyl
 nitrobenzene derivative (not shown). Reduction of the nitro
 compound (step 2), such as with iron powder, preferably
 10 above about 50 °C, and more preferably at about 80 °C,
 yields the heterocyclylmethyl substituted aniline **75**.

Protected alkylamine substituted anilines can be
 prepared from the nitro free amines **76**, such as with
 standard protecting agents and chemistry known in the art,
 15 such as BOC chemistry. Reduction of the protected nitro
 compound, such as with iron powder, preferably above about
 50 °C, and more preferably at about 80 °C, yields the
 aniline **77**.

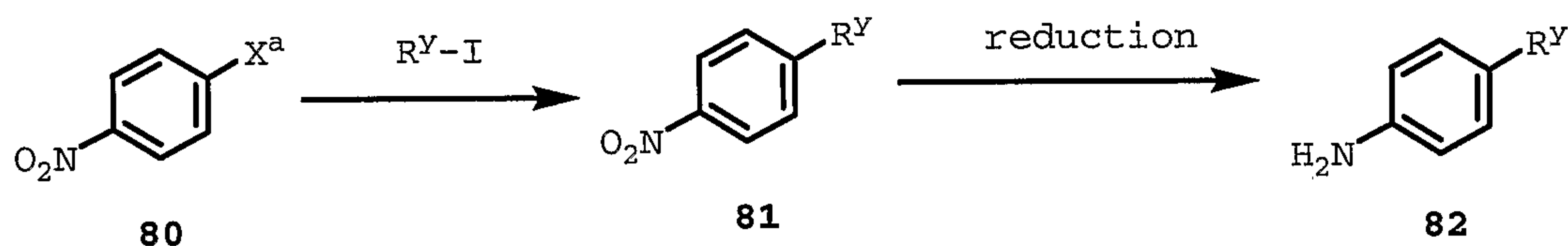
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Sulfonamide substituted anilines can be prepared from nitrobenzenesulfonyl chlorides **78**. Coupling of nitrobenzenesulfonyl chlorides **78** with reactive heterocyclic compounds, such as substituted piperazines, piperidines, and the like, in a protic solvent such as EtOH, such as at a temperature about RT, yields the nitrobenzenesulfonamides **78**. Reduction of the nitro benzenesulfonamide, such as with iron powder, preferably above about 50 °C, and more preferably at about 80 °C, yields the aniline **79**.

10

Scheme 22



A series of perhaloalkyl-substituted anilines **82**, where R^Y represents perhaloalkyl radicals, are prepared such as by the procedure described in Scheme 22. 1-Nitro-4-(perfluoroethyl)benzene can be synthesized by the method described in the reference [John N. Freskos, Synthetic Communications, 18(9), 965-972 (1988)]. Alternatively, 1-Nitro-4-(perfluoroalkyl)benzene can be synthesized from the nitro compound, where X^a is a leaving group, such as bromo or iodo, by the method described by W. A. Gregory, et al. [J. Med. Chem., 1990, 33, 2569-2578].

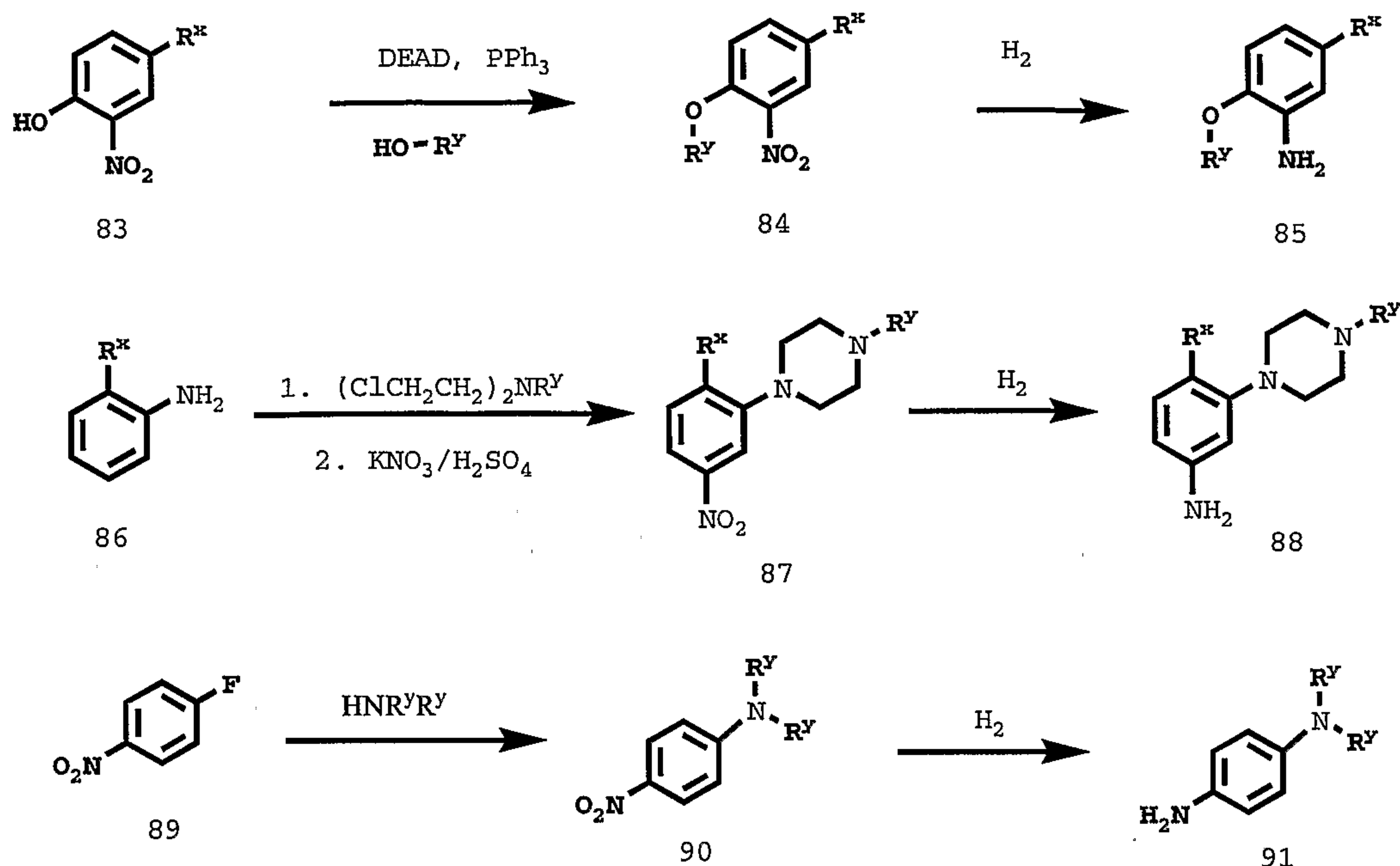
Reduction of the nitrobenzenes **81**, with a metal such as iron powder, at a temperature above about 50 °C, and preferably at about 80 °C, yields the aniline **82**. Hydrogenation, such as with H_2 atmosphere in the presence of a catalyst, such as 10% Pd/C, is also possible.

30

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Scheme 23



- 5 Additional series of substituted anilines (**85**, **88** and **91**) are prepared such as by the procedures described in Scheme 23 (where R^x is a substituent selected those available for substituted R^1 , preferably haloalkyl and alkyl). 2-Alkoxy substituted anilines **85** are prepared from
- 10 the corresponding phenol compounds **83** such as by the Mitsunobu reaction, including treatment with a N,N-dialkylethanolamine and PPh_3 and DEAD to give the corresponding nitro compound **84**, followed by hydrogenation, such as with H_2 to give the aniline **85**.
- 15 Alternatively, piperazinyl substituted anilines **88** can be prepared by the treatment of an aniline **86** with an N-substituted-bis(2-chloroethyl)amine, base, such as K_2CO_3 and NaI , at a temperature above about 50°C , preferably above about 100°C , and more preferably at about 170°C , to give
- 20 the piperazinylbenzene compound **87**. Nitration, such as with H_2SO_4 and HNO_3 , at a temperature above 0°C , and preferably

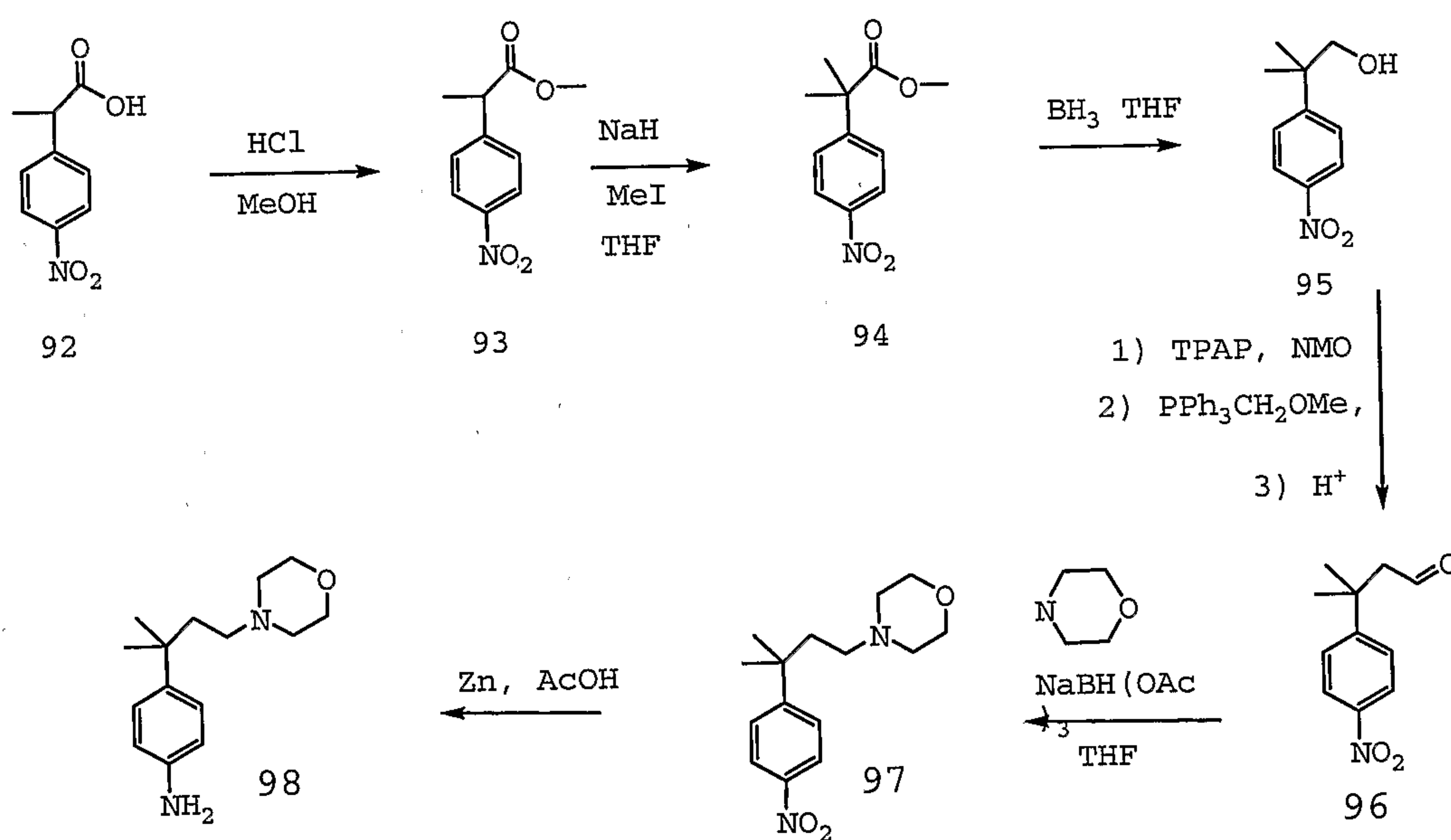
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at about RT, followed by hydrogenation, such as with H₂ atmosphere gives the substituted aniline **88**.

Alternatively, piperazinyl substituted anilines **91** can be prepared by the treatment of a fluoro-nitro-substituted aryl compounds **89**. The fluoro-nitro-substituted aryl compounds **89** and 1-substituted piperazines are heated, preferably neat, at a temperature above about 50 °C, and preferably at about 90 °C, to yield the piperazinyl-nitroaryl compounds **90**. Hydrogenation, such as with H₂ atmosphere in the presence of a catalyst, such as 10% Pd/C, gives the substituted aniline **91**.

Scheme 24



15

Substituted anilines **98** are prepared such as by the procedures described in Scheme 24. Nitrophenyl esters **93** are formed from the acid **92**, such as by treatment with MeOH and acid. Alkylation of the ester **93**, such as by treatment with base, followed by alkyl halide, yields the branched alkyl compounds **94**. Reduction of the ester **94**, such as with BH₃, yields the alcohol **95**. The aldehyde **96** is

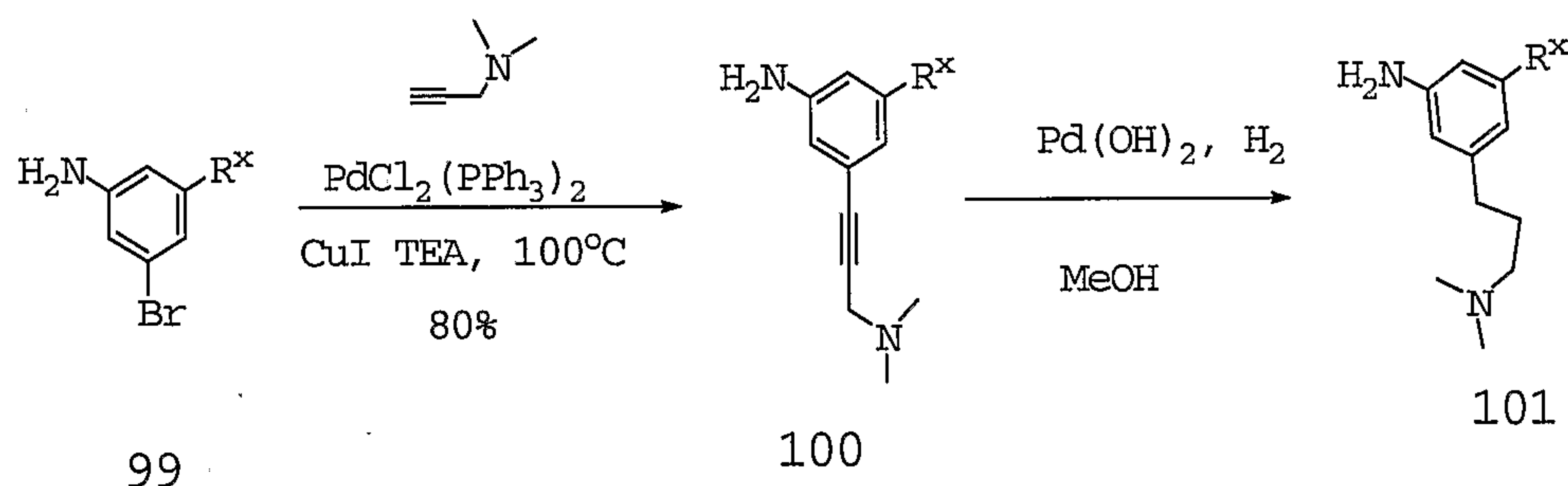
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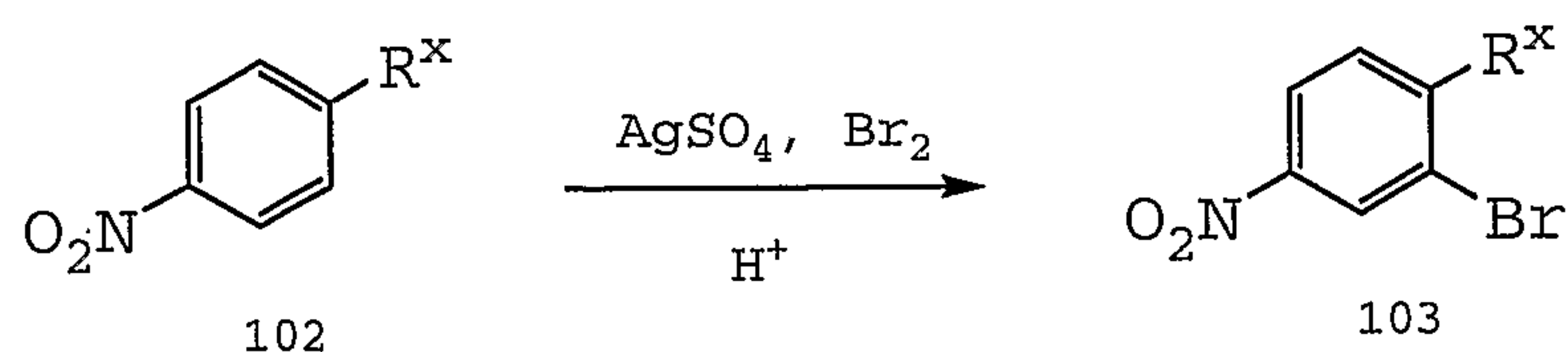
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prepared from the alcohol **95**, such as by treatment with TPAP in the presence of N-methylmorpholine-N-oxide. Subsequent treatment with methoxymethyltriphenylphosphonium chloride and KHMDS yields **96**. Coupling of the aldehyde **96** and
 5 morpholine, such as with $\text{NaBH}(\text{OAc})_3$ yields the tertiary amine **97**. Reduction of the nitro group on compound **97**, such as with acid, for example AcOH, and zinc yields the aniline **98**.

10

Scheme 25

Substituted aniline compounds **101** are prepared such as
 15 by the procedure described in Scheme 25 (where R^x is a substituent selected those available for substituted R^1 , preferably haloalkyl and alkyl). Alkynyl-aniline **100**, prepared similar to that described in Scheme 26 (below), is hydrogenated such as with H_2 in the presence of a catalyst,
 20 such as $\text{Pd}(\text{OH})_2$, to yield the substituted alkyl **101**.

Scheme 26

25

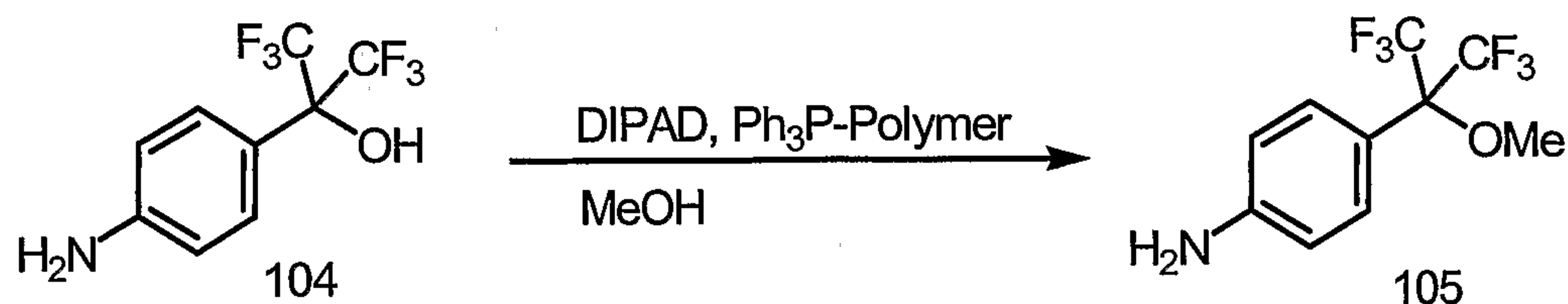
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Substituted bromophenyl compounds **103** are prepared such as by the procedure described in Scheme 26. Bromine is added to a optionally substituted nitrobenzene **102**, silver(II)sulfate and acid, such as H_2SO_4 , to provide the

5 bromo derivative **103**.

Scheme 27



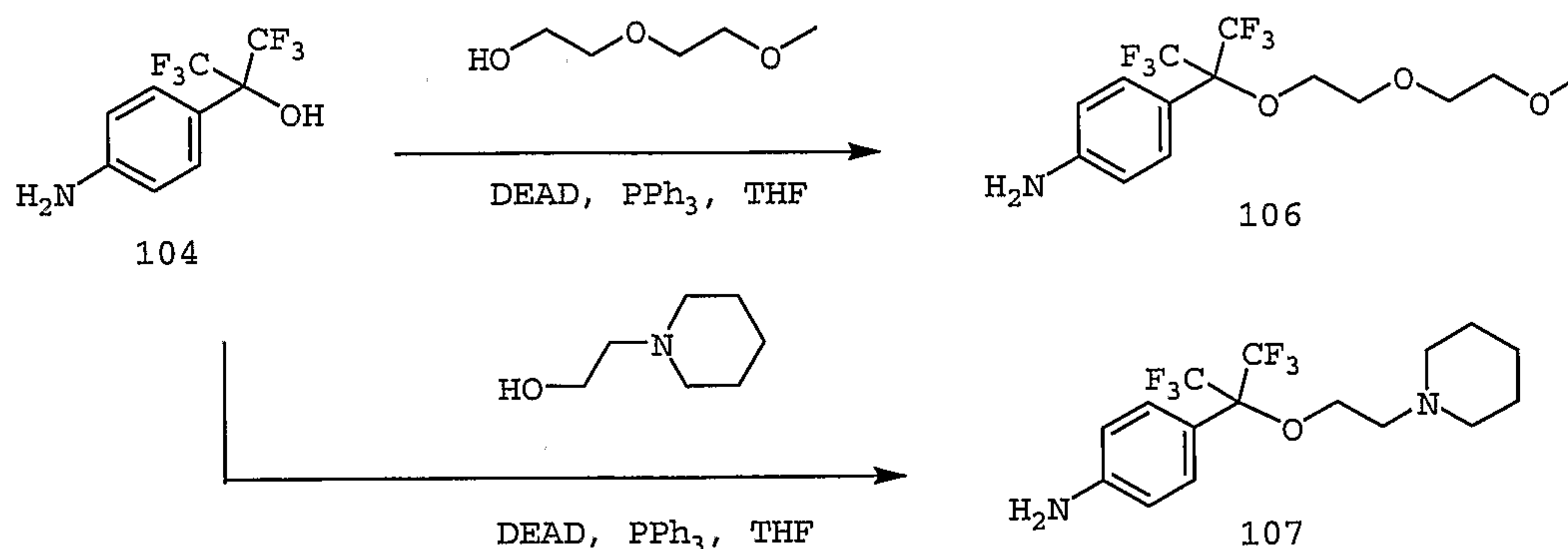
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4-(2,2,2-Trifluoro-1-methoxy-1-trifluoromethyl-ethyl)-phenylamine **105** can be prepared by the procedure described in scheme 27, as follows: the hydroxyl group of 2-(4-amino-phenyl)-1,1,1,3,3,3-hexafluoro-propan-2-ol **104** can be

15 activated for displacement by conventional methods, such as by treating **104** with diisopropyl azodicarboxylate in the presence of triphenylphosphine (polymer-bound, excess equivalents) then treated with MeOH and stirred at about reflux.

20

Scheme 28

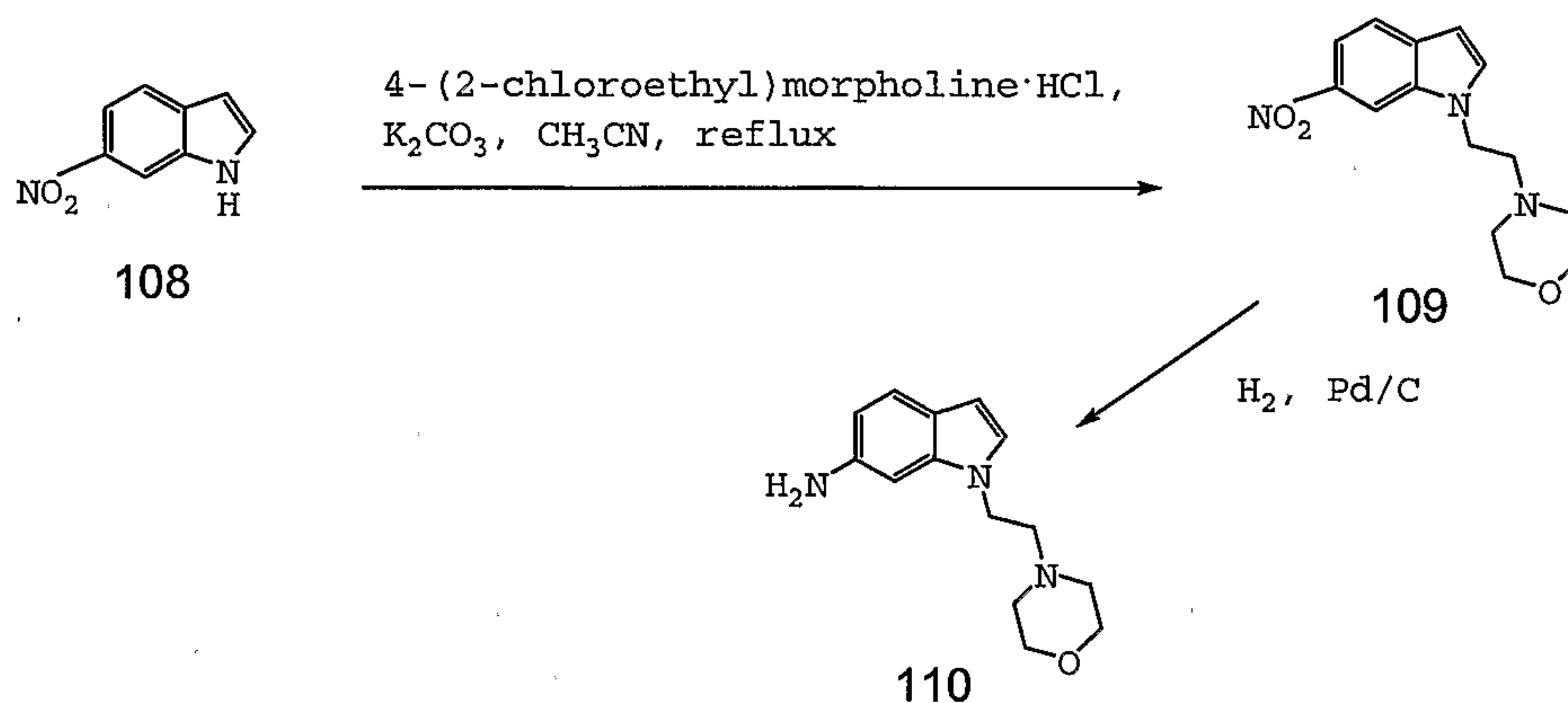


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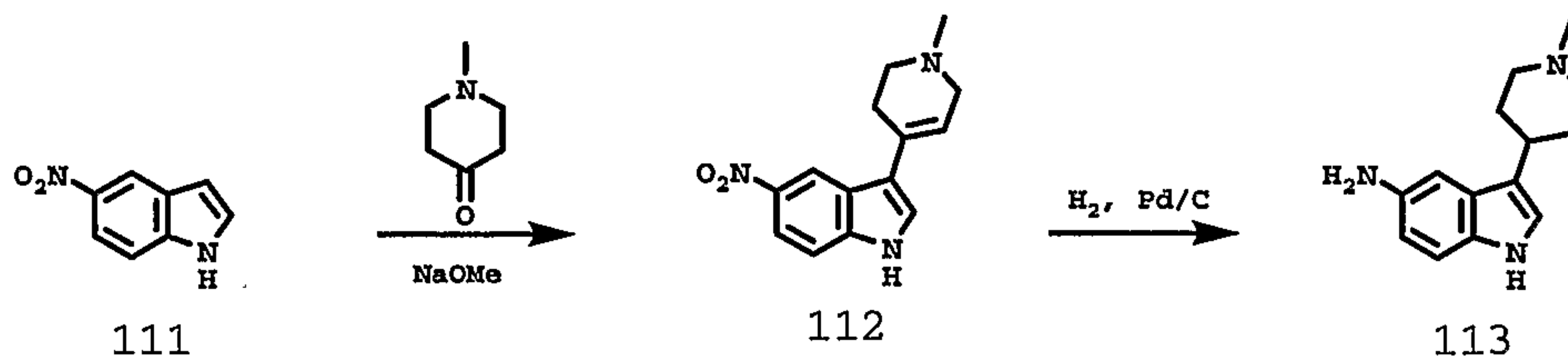
Substituted anilines (**106** and **107**) are prepared such as by the procedure described in Scheme 28. Treatment with the haloalkyl alcohol **104** with an alcohol, under Mitsunobu conditions such as in the presence of DEAD and PPh₃ yields the corresponding ether adducts **106** or **107**.

Scheme 29



Substituted indoles **110** are prepared such as by the procedure described in Scheme 29. A nitroindole **108** is coupled with a halo compound, in the presence of base, for example K₂CO₃. Heating at a temperature above about 50 °C, and preferably at about reflux yields the substituted-nitro-1H-indole **109**. Hydrogenation similar to conditions described above yield the amino derivative **110**.

Scheme 30



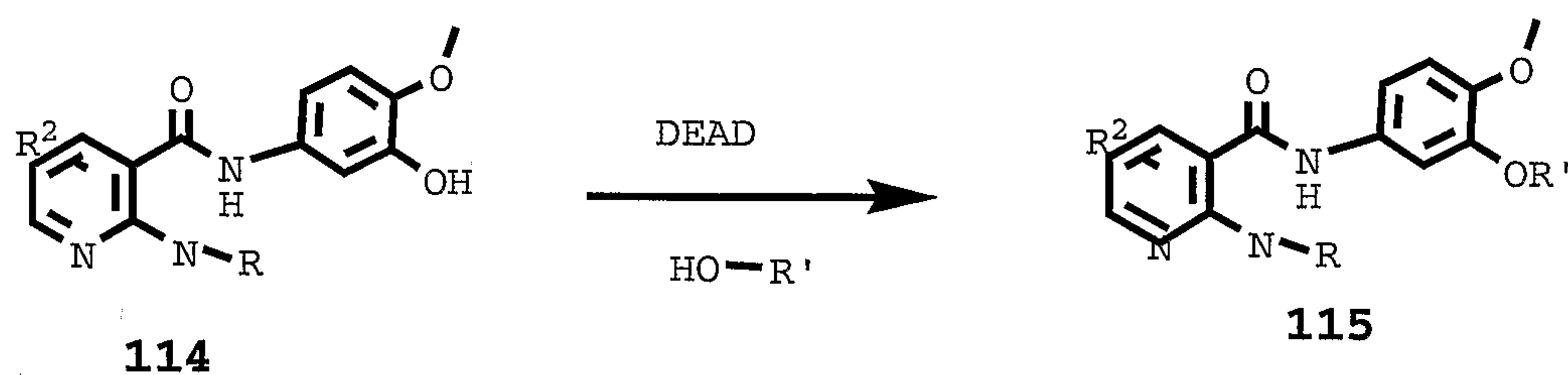
Amino-substituted indoles **113** are prepared such as by the procedure described in Scheme 30. Nitroindoline **111** is

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reacted with N-methyl-4-piperidone in the presence of NaOMe at a temperature above about 50 °C, and preferably at about reflux, to form the 3-substituted indole **112**. Hydrogenation as previously discussed yields the amino indole **113**.

5

Scheme 31

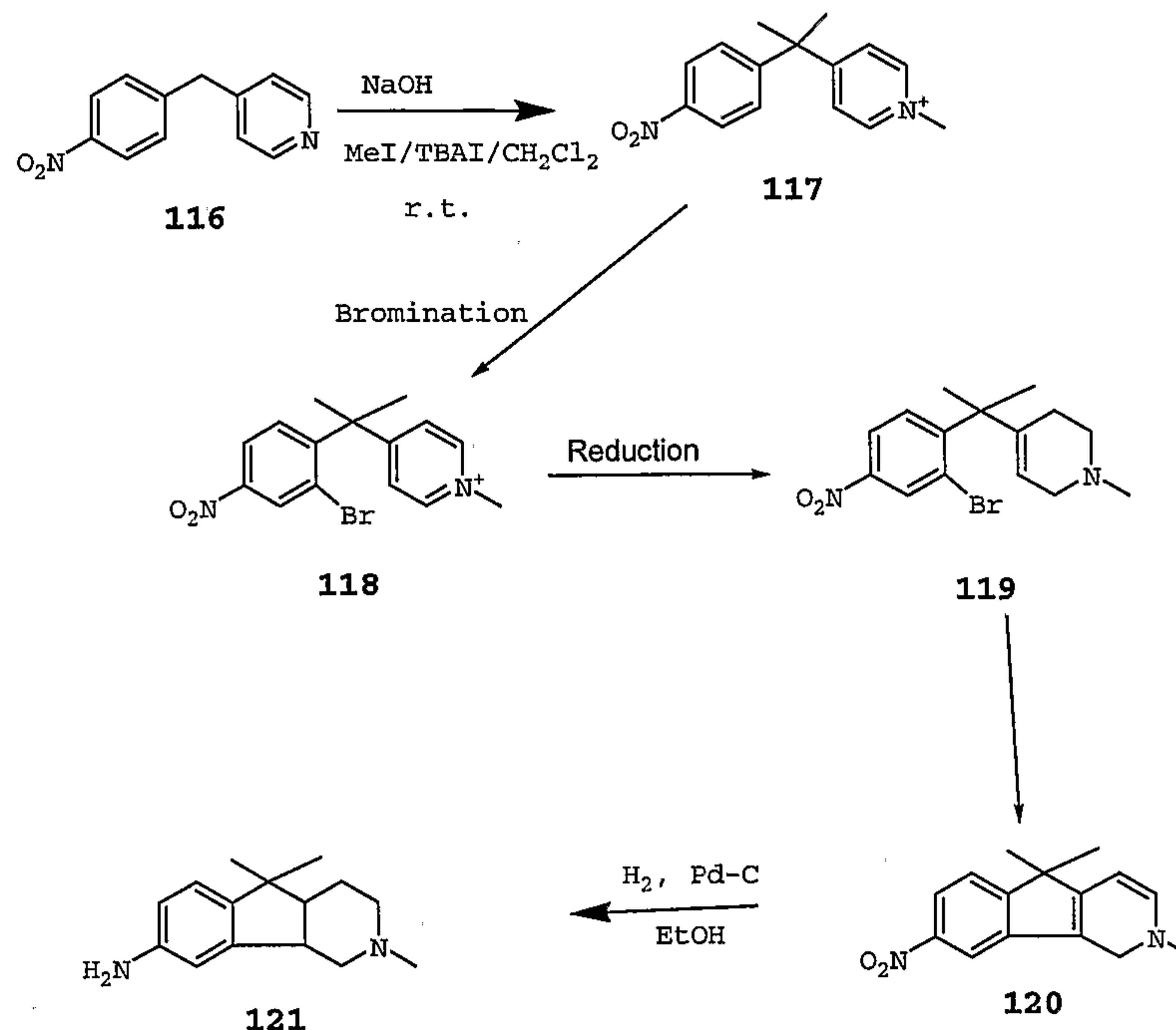
10 Substituted carboxamides **115** can be prepared from the corresponding phenols **114** of the invention, by the procedure described in Scheme 31. A carboxamide **114** is coupled with an alcohol, such as 4-hydroxy-N-methylpiperidine, in the presence of DEAD and triphenylphosphine, in a solvent such as THF, at a temperature of about RT, provides the ether **115**.

15

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Scheme 32

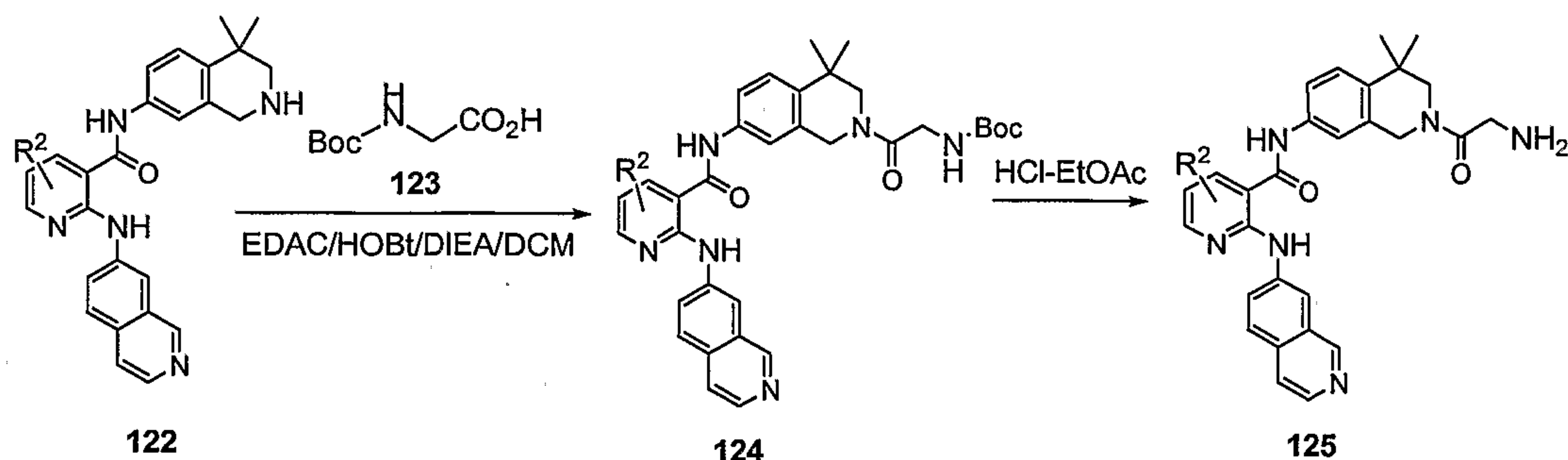


- 5 2,3,4,4a,9,9a-Hexahydro-1H-3-aza-fluoren-6-ylamine **121** can be prepared by the procedure described in Scheme 32. Nitrobenzylpyridines **116** are alkylated, such as with MeI, in the presence of TBAI and base to form the pyridinium compound **117**. The pyridinium compounds **117** are halogenated, such as brominated with NBS, to form the brominated pyridinium compounds **118** which are reduced such as with NaBH₄, dehalogenated and reduced to form the hexahydro-fluorenes **121**.
- 10

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Scheme 33



5 Acylated amino-isoquinoline-tetrahydroisoquinoline-nicotinamides **124** can be prepared by the procedure described in scheme 33. Tetrahydroisoquinoline-quinoline nicotinamides **122** can be treated with Boc-protected glycine **123** in the presence of known acid-activating coupling reagents and combinations of same reagents, such as EDAC and HOBt, with a mild base, such as DIEA, to effect the acylation of compound **122** and provide compound **124**. The glycyl amine can be deprotected or cleaved using dilute HCl to afford the free glycine amine **125**, for subsequent coupling to desired chemical structures. Amides (not shown) of compound **125** can be made by coupling compound **125** with activated carboxylic acid compounds (not shown) such as acid chlorides, or by displacing other suitable leaving groups of desired compounds.

20 The starting compounds defined in Schemes 1-33 may also be present with functional groups in protected form if necessary, such as BOC-protected glycine, and/or in the form of salts, provided a salt-forming group is present and the reaction in salt form is possible. If so desired, one compound of Formula I or II can be converted into another compound of Formula I or II, or a N-oxide thereof; a compound of Formula I or II can be converted into a salt; a salt of a compound of Formula I or II can be converted into the free compound or another salt; and/or a mixture of

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isomeric compounds of Formula I or II can be separated into the individual isomers.

N-Oxides are also contemplated to be included in the present invention. N-oxides can be obtained in a known matter by reacting a compound of Formula I or II with hydrogen peroxide or a peracid, e.g. 3-chloroperoxy-benzoic acid, in an inert solvent, e.g. dichloromethane, at a temperature between about -10-35 °C, such as about 0 °C - RT.

10 If one or more other functional groups, for example carboxy, hydroxy, amino, or mercapto, are or need to be protected in a compound of Formula I or II or in the preparation of compounds of Formula I or II, because they should not take part in the reaction, these are such groups as are usually used in the synthesis of peptide compounds, and also of cephalosporins and penicillins, as well as nucleic acid derivatives and sugars.

20 The protecting groups may already be present in precursors and should protect the functional groups concerned against unwanted secondary reactions, such as acylations, etherifications, esterifications, oxidations, solvolysis, and similar reactions. It is a characteristic of protecting groups that they lend themselves readily, i.e. without undesired secondary reactions, to removal, typically by solvolysis, reduction, photolysis or also by enzyme activity, for example under conditions analogous to physiological conditions, and that they are not present in the end-products. The specialist knows, or can easily establish, which protecting groups are suitable with the reactions mentioned above and hereinafter.

30 The protection of such functional groups by such protecting groups, the protecting groups themselves, and their removal reactions are described for example in standard reference works, such as J. F. W. McOmie,

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"Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in T. W. Greene, "Protective Groups in Organic Synthesis", Wiley, New York 1981, in "The Peptides"; Volume 3 (editors: E. Gross and J. Meienhofer), Academic Press, London and New York 1981, in "Methoden der organischen Chemie" (Methods of organic chemistry), Houben Weyl, 4th edition, Volume 15/1, Georg Thieme Verlag, Stuttgart 1974, in H.-D. Jakubke and H. Jescheit, "Aminosäuren, Peptide, Proteine" (Amino acids, peptides, proteins), Verlag Chemie, Weinheim, Deerfield Beach, and Basel 1982, and in Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide und Derivate" (Chemistry of carbohydrates: monosaccharides and derivatives), Georg Thieme Verlag, Stuttgart 1974.

15 In the additional process steps, carried out as desired, functional groups of the starting compounds which should not take part in the reaction may be present in unprotected form or may be protected for example by one or more of the protecting groups mentioned above under

20 "protecting groups". The protecting groups are then wholly or partly removed according to one of the methods described there.

Salts of a compound of Formula I or II with a salt-forming group may be prepared in a manner known per se. Acid

25 addition salts of compounds of Formula I or II may thus be obtained by treatment with an acid or with a suitable anion exchange reagent. A salt with two acid molecules (for example a dihalogenide of a compound of formula I) may also be converted into a salt with one acid molecule per compound

30 (for example a monohalogenide); this may be done by heating to a melt, or for example by heating as a solid under a high vacuum at elevated temperature, for example from 130 °C to 170 °C, one molecule of the acid being expelled per molecule of a compound of Formula I or II.

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Acid salts can usually be converted to free-base compounds, e.g. by treating with suitable basic agents, for example with alkali metal carbonates, alkali metal hydrogen carbonates, or alkali metal hydroxides, typically potassium carbonate or sodium hydroxide. Similarly, basic salts of
5 compounds may be converted to the corresponding free-base compound by treatment with the desired number of equivalents of a suitable acidic agent, such as HCl, acetic acid, and the like.

10 A carbonyl group in a compound of Formula I or II may be converted into the respective thiocarbonyl, for example, by using an appropriate sulfur compound, e. g. using reaction with Lawesson's reagent (2,4-bis-(4-methoxyphenyl)2,4-dithioxo-1,2,3,4-dithiaphosphetan) in a
15 halogenated hydrocarbon, such as CH₂Cl₂, or an aprotic solvent, such as toluene or xylene, at temperatures from about 30 °C to reflux.

All process steps described here can be carried out under known reaction conditions, preferably under those
20 specifically mentioned, in the absence of or usually in the presence of solvents or diluents, preferably such as are inert to the reagents used and able to dissolve these, in the absence or presence of catalysts, condensing agents or neutralizing agents, for example ion exchangers, typically
25 cation exchangers, for example in the H⁺ form, depending on the type of reaction and/or reactants at reduced, normal, or elevated temperature, for example in the range from about -100 °C to about 190 °C, preferably from about -80 °C to about 150°C, for example at about -80°C to about 60°C, at
30 room temperature, at about -20 °C to about 40 °C or at the boiling point of the solvent used, under atmospheric pressure or in a closed vessel, where appropriate under pressure, and/or in an inert atmosphere, for example under argon or nitrogen.

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Salts may be present in all starting compounds and transients, if these contain salt-forming groups. Salts may also be present during the reaction of such compounds, provided the reaction is not thereby disturbed.

5 In certain cases, typically in hydrogenation processes, it is possible to achieve stereoselective reactions, allowing for example easier recovery of individual isomers.

Suitable solvents, which may be selected to carry out
10 the reactions in question, as appreciated by those of ordinary skill in the art. Suitable aqueous, organic and inorganic solvents include, without limitation, water; esters, typically lower alkyl-lower alkanates, e.g., ethyl acetate; ethers, typically aliphatic ethers, e.g.,
15 diethylether, or cyclic ethers, e.g., THF; liquid aromatic hydrocarbons, typically benzene or toluene; alcohols, typically MeOH, EtOH or 1-propanol, IPOH, BuOH, t-BuOH; nitriles, typically CH₃CN; halogenated hydrocarbons, typically CH₂Cl₂, CHCl₃; acid amides, typically DMF; bases,
20 typically heterocyclic nitrogen bases, e.g. pyridine; carboxylic acids, typically lower alkanecarboxylic acids, e.g., AcOH; carboxylic acid anhydrides, typically lower alkane acid anhydrides, e.g., acetic anhydride; cyclic, linear, or branched hydrocarbons, typically cyclohexane,
25 hexane, pentane, cyclopentane, or isopentane; and mixtures of such solvents, e.g., aqueous solutions and solvent combinations, unless otherwise stated in the description of the process. Such solvent mixtures may also be used in
30 recrystallization.

The invention relates also to those methods of the process in which one starts from a compound obtainable at any stage as a transient and carries out the missing steps, or breaks off the process at any stage, or forms a starting

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material under the reaction conditions, or uses said starting material in the form of a reactive derivative or salt, or produces a compound obtainable by means of the process according to the invention and processes the said
5 compound *in situ*. In the preferred embodiment, one starts from those starting materials, which lead to the compounds described above as preferred.

The compounds of Formula I or II, including their derivatives, are also obtainable in the form of salts,
10 hydrates or crystals. A crystalline form, for example, can include the solvent, or solvents, used for crystallization (generally present as solvates).

New starting materials and/or intermediates, as well as processes for the preparation thereof, are likewise the
15 subject of this invention. In the preferred embodiment, such starting materials are used and reaction conditions so selected as to enable the preferred compounds to be obtained.

Starting materials of the invention, are known, are
20 commercially available, or can be synthesized in analogy to or according to methods that are known in the art.

For example, amine compounds, represented in Schemes 11, 18, 20 and 22, can be prepared by reduction of the corresponding nitro precursor. The reduction preferably
25 takes place in the presence of a suitable reducing agent, such as tin(II) chloride or hydrogen in the presence of an appropriate catalyst, such as Raney nickel (then preferably the hydrogen is used under pressure, e.g. between 2 and 20 bar), Pd or PtO₂, in an appropriate solvent, e.g. an
30 alcohol, such as MeOH. The reaction temperature is preferably between about 0 °C and about 80 °C, especially about 15 °C to about 30 °C.

It would also be possible to reduce the nitro compound after forming the other amide linkages, under reaction

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conditions analogous to those for the reduction of nitro compounds described above. This would eliminate the need to protect the free amino group as described in various of the schemes above.

5 In the preparation of starting materials, existing functional groups, which do not participate in the reaction should, if necessary, be protected. Preferred protecting groups, their introduction and their removal are described above or in the examples.

10 All remaining starting materials are known, capable of being prepared according to known processes, or commercially obtainable; in particular, they can be prepared using processes as described in the examples.

Compounds of the present invention can possess, in
15 general, one or more asymmetric carbon atoms and, therefore, are capable of existing in the form of optical isomers as well as in the form of racemic or non-racemic mixtures thereof. The optical isomers can be obtained by resolution of the racemic mixtures according to
20 conventional processes, e.g., by formation of diastereoisomeric salts, by treatment with an optically active acid or base. Examples of appropriate acids are tartaric, diacetyltartaric, dibenzoyltartaric, ditoluoyltartaric, and camphorsulfonic acid and then
25 separation of the mixture of diastereoisomers by crystallization followed by liberation of the optically active bases from these salts. A different process for separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize the
30 separation of the enantiomers. Still another available method involves synthesis of covalent diastereoisomeric molecules by reacting compounds of the invention with an optically pure acid in an activated form or an optically pure isocyanate. The synthesized diastereoisomers can be

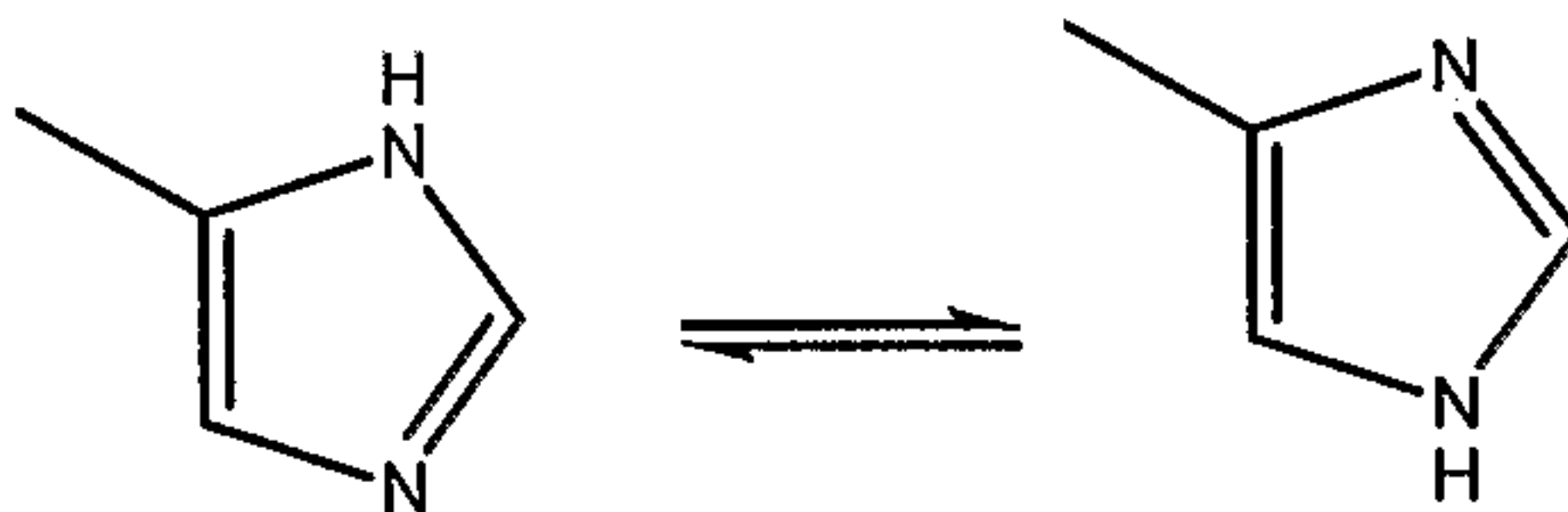
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separated by conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure compound. The optically active compounds of the invention can
5 likewise be obtained by using optically active starting materials. These isomers may be in the form of a free acid, a free base, an ester or a salt.

The compounds of the present invention may contain one or more asymmetric centers and, therefore, occur as
10 racemates and racemic mixtures, scalemic mixtures, single enantiomers, individual diastereomers and diastereomeric mixtures. All such isomeric forms of these compounds are expressly included in the present invention.

The compounds of this invention may also be
15 represented in multiple tautomeric forms, for example, as illustrated below:



20 The invention expressly includes all tautomeric forms of the compounds described herein.

The compounds of this invention may also occur in cis- or trans- or E- or Z- double bond isomeric forms. All such isomeric forms of such compounds are expressly included in
25 the invention. All crystal forms of the compounds described herein are expressly included in the invention.

Substituents on ring moieties (e.g., phenyl, thienyl, etc.) may be attached to specific atoms, whereby they are intended to be fixed to that atom, or they may be drawn
30 unattached to a specific atom, whereby they are intended to be attached at any available atom that is not already substituted by an atom other than H (hydrogen).

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The compounds of this invention may contain heterocyclic ring systems attached to another ring system. Such heterocyclic ring systems may be attached through a carbon atom or a heteroatom in the ring system.

5 Alternatively, a compound of Formula I or II herein may be synthesized according to any of the procedures described herein. In the procedures described herein, the steps may be performed in an alternate order and may be preceded, or followed, by additional protection/deprotection
10 steps as necessary. The procedures may further comprise use of appropriate reaction conditions, including inert solvents, additional reagents, such as bases (e.g., LDA, DIEA, pyridine, K_2CO_3 , and the like), catalysts, and salt forms of the above. The intermediates may be isolated or
15 carried on *in situ*, with or without purification. Purification methods are known in the art and include, for example, crystallization, chromatography (liquid and gas phase, simulated moving bed ("SMB")), extraction, distillation, trituration, reverse phase HPLC and the like.
20 Reactions conditions such as temperature, duration, pressure, and atmosphere (inert gas, ambient) are known in the art and may be adjusted as appropriate for the reaction.

As can be appreciated by the skilled artisan, the above synthetic schemes are not intended to comprise a
25 comprehensive list of all means by which the compounds described and claimed in this application may be synthesized. Further methods will be evident to those of ordinary skill in the art. Additionally, the various synthetic steps described above may be performed in an
30 alternate sequence or order to give the desired compounds. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the inhibitor compounds described herein are known in the art and include, for example, those such as

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described in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 3rd. Ed., John Wiley and Sons (1999); L. Fieser and M. Fieser, 5 *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); A. Katritzky and A. Pozharski, Handbook of Heterocyclic Chemistry, 2nd Ed. (2001); M. Bodanszky, A. Bodanszky: *The practice of Peptide Synthesis* Springer-Verlag, Berlin Heidelberg 1984; J. Seyden-Penne: 10 *Reductions by the Alumino- and Borohydrides in Organic Synthesis*, 2nd Ed., Wiley-VCH, 1997; and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995).

The compounds of the present invention may be modified 15 by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological compartment (e.g., blood, lymphatic system, central nervous system), increase 20 oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

The following examples contain detailed descriptions of the methods for the preparation of exemplary compounds of 25 Formula I or II. These detailed descriptions fall within the scope, and serve to exemplify, the above-described General Synthetic Procedures, which form part of the invention. These detailed descriptions are presented for illustrative purposes only and are not intended as a 30 restriction on the scope of the invention.

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Anhydrous solvents such as DMF, THF, CH₂Cl₂ and toluene were obtained from the Aldrich Chemical Company,

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typically available as nitrogen blanketed, sure-sealed bottles. All reactions involving air- or moisture-sensitive compounds were performed under a nitrogen atmosphere. Flash chromatography was performed using Aldrich Chemical Company silica gel (200-400 mesh, 60A) or Biotage pre-packed column. Thin-layer chromatography (TLC) was performed with Analtech gel TLC plates (250 μ). Preparative TLC was performed with Analtech silica gel plates (1000-2000 μ). Preparative HPLC was conducted on a Beckman or Waters HPLC system with 0.1% TFA/H₂O and 0.1% TFA/CH₃CN as mobile phase. The flow rate was at 20 ml/min. and gradient method was used. ¹H NMR spectra were determined with super conducting FT NMR spectrometers operating at 400 MHz or a Varian 300 MHz instrument. Chemical shifts are expressed in ppm downfield from internal standard tetramethylsilane. All compounds showed NMR spectra consistent with their assigned structures. Mass spectra (MS) were determined on a Perkin Elmer - SCIEX API 165 electrospray mass spectrometer (positive and, or negative) or an HP 1100 MSD LC-MS with electrospray ionization and quadrupole detection. All parts are by weight and temperatures are in Degrees centigrade unless otherwise indicated.

The following abbreviations, which are used in the description of the invention, mean the following:

25	AcOH -	acetic acid
	Ac ₂ O -	acetic anhydride
	AIBN -	2,2'-azobisisobutyronitrile
	Ar -	argon
	AgSO ₄ -	silver sulfate
30	AlCl ₃ -	aluminum trichloride
	ATP -	adenosine triphosphate
	BH ₃ -	borane
	Boc -	tert-butyloxycarbonyl
	Boc ₂ O -	Boc anhydride

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	BOP-Cl -	bis(2-oxo-3-oxazolidinyl)phosphinic chloride
	Br ₂ -	bromine
	BSA -	bovine serum albumin
5	t-BuOH -	tert-butanol
	CAN -	ammonium cerium(IV) nitrate
	CH ₃ CN, AcCN -	acetonitrile
	CH ₂ Cl ₂ -	dichloromethane
	CH ₃ I, MeI -	iodomethane, methyl iodide
10	CCl ₄ -	carbon tetrachloride
	CCl ₃ -	chloroform
	CO ₂ -	carbon dioxide
	Cs ₂ CO ₃ -	cesium carbonate
	DIEA -	diisopropylethylamine
15	CuI -	copper iodide
	CuCN -	copper cyanide
	DCE -	1,2-dichloroethane
	DEAD -	diethyl azodicarboxylate
	DIEA -	diisopropylethylamine
20	DIPAD -	disopropyl azodicarboxylate
	dppf -	1,1-diphenylphosphinoferrocene
	DMAP -	4-(dimethylamino)pyridine
	DMAC -	N,N-dimethylacetamide
	DMF -	dimethylformamide
25	DMSO -	dimethylsulfoxide
	DTT -	dithiothreitol
	EDC, EDAC-	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
	EGTA -	ethylene glycol-bis(β-aminoethyl ether)-
30		N,N,N',N'-tetraacetic acid
	EtOAc -	ethyl acetate
	EtOH -	ethanol
	Et ₂ O -	diethyl ether
	Fe -	iron

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	g -	gram
	h -	hour
	HATU -	O-(7-azabenzotriazol-1-yl)-N,N,N',N'- tetramethyluronium hexafluorophosphate
5	H ₂ -	hydrogen
	H ₂ O -	water
	HCl -	hydrochloric acid
	H ₂ SO ₄ -	sulfuric acid
	H ₂ NNH ₂ -	hydrazine
10	HC(OEt) ₃ -	triethylorthoformate
	HCHO, H ₂ CO -	formaldehyde
	HCO ₂ Na -	sodium formate
	HOAc, AcOH -	acetic acid
	HOAt -	1-hydroxy-7-azabenzotriazole
15	HOBt -	hydroxybenzotriazole
	IpOH -	isopropanol
	KF -	potassium fluoride
	K ₂ CO ₃ -	potassium carbonate
	KHMDS -	potassium hexamethylsilazane
20	KNO ₃ -	potassium nitrate
	KOAc -	potassium acetate
	KOH -	potassium hydroxide
	LAH, LiAlH ₄ -	lithium aluminum hydride
	LDA -	lithium diisopropylamide
25	LiCl -	lithium chloride
	LiHMDS -	lithium hexamethyldisilazide
	MeOH -	methanol
	MgCl ₂ -	magnesium chloride
	MgSO ₄ -	magnesium sulfate
30	mg -	milligram
	ml -	milliliter
	MnCl ₂ -	manganese chloride
	NBS -	N-bromosuccinimide
	NMO -	4-methylmorpholine, N-oxide

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	NMP -	N-methylpyrrolidone
	Na ₂ SO ₄ -	sodium sulfate
	Na ₂ S ₂ O ₅ -	sodium metabisulfite
	NaHSO ₃ -	sodium bisulfite
5	NaHCO ₃ -	sodium bicarbonate
	Na ₂ CO ₃ -	sodium carbonate
	NaCl -	sodium chloride
	NaH -	sodium hydride
	NaI -	sodium iodide
10	NaOH -	sodium hydroxide
	NaOMe -	sodium methoxide
	NaOEt -	sodium ethoxide
	NaCNBH ₃ -	sodium cyanoborohydride
	NaBH ₄ -	sodium borohydride
15	NaNO ₂ -	sodium nitrate
	NaBH(OAc) ₃ -	sodium triacetoxyborohydride
	NH ₄ Cl -	ammonium chloride
	N ₂ -	nitrogen
	Pd/C -	palladium on carbon
20	PdCl ₂ (PPh ₃) ₂ -	palladium chloride bis(triphenylphosphine)
	PdCl ₂ (dppf) -	1,1-bis(diphenylphosphino)ferrocene
		palladium chloride
	Pd(PPh ₃) ₄ -	palladium tetrakis triphenylphosphine
	Pd(OH) ₂ -	palladium hydroxide
25	Pd(OAc) ₂ -	palladium acetate
	PMB -	para methoxybenzyl
	POCl ₃ -	phosphorus oxychloride
	PPh ₃ -	triphenylphosphine
	PtO ₂ -	platinum oxide
30	RT -	room temperature
	SiO ₂ -	silica
	SOCl ₂ -	thionyl chloride
	TBAI -	tetrabutylammonium iodide

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TBTU -	O-(1H-benzotriazol-1-yl)-N,N,N',N'- tetramethyluronium tetrafluoroborate
TEA -	triethylamine
Tf ₂ NPh -	N-phenyltrifluoromethanesulfonimide
5 TFA -	trifluoroacetic acid
THF -	tetrahydrofuran
TPAP -	tetrapropylammoniumperruthenate
Tris-HCl -	Tris(hydroxymethyl)aminomethane hydrochloride salt
10 Zn -	zinc

PREPARATIONS

The preparation of the following exemplary compounds,
15 intermediates and starting materials should assist in the
understanding and appreciation of the invention.

Preparation I - 3-nitro-5-trifluoromethyl-phenol:

1-Methoxy-3-nitro-5-trifluoromethyl-benzene (10g, Aldrich)
20 and pyridine-HCl (41.8g, Aldrich) were mixed together and
heated neat at 210 °C in an open flask. After 2.5 h the
mixture was cooled to RT and partitioned between 1N HCl and
EtOAc. The EtOAc fraction was washed with 1N HCl (4x), brine
(1x), dried with Na₂SO₄, filtered and concentrated in vacuo
25 to form 3-nitro-5-trifluoromethyl-phenol as an off-white
solid.

Preparation II - 1-Boc-4-(3-nitro-5-trifluoromethyl- phenoxy)-piperidine:

30 3-Nitro-5-trifluoromethyl-phenol (8.81g) was dissolved in
THF (76 ml). 1-Boc-4-hydroxy-piperidine (8.81 g, Aldrich)
and Ph₃P (11.15 g) were added and the solution was cooled to
-20 °C. A solution of DEAD (6.8 ml, Aldrich) in THF (36 ml)
was added dropwise, maintaining the temperature between -20
35 and -10 °C. The reaction was warmed to RT and stirred

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overnight. The reaction was concentrated in vacuo and trituated with hexane. The yellow solid was removed by filtration and washed with Et₂O (25 ml), and hexane. The white filtrate was washed with 1N NaOH (2x), brine (1x) and
5 the hexane layer was dried over Na₂SO₄, filtered and concentrated in vacuo. The crude material was purified with flash chromatography (SiO₂, 5-10% EtOAc/hexane) to obtain 1-Boc-4-(3-nitro-5-trifluoromethyl-phenoxy)-piperidine.

10 The following compounds were prepared similarly to the procedure outlined above:

- a) (S)-1-Boc-[2-(5-nitro-2-trifluoromethylphenoxy)methyl]-pyrrolidine
- 15 b) (R)-1-Boc-[2-(5-nitro-2-trifluoromethylphenoxy)methyl]-pyrrolidine.
- c) (R) 1-Boc-2-(3-Nitro-5-trifluoromethyl-phenoxy)methyl)-pyrrolidine
- d) 4-(2-tert-Butyl-5-nitro-phenoxy)methyl)-1-methyl-
20 piperidine.
- e) (S) 1-Boc-2-(3-Nitro-5-trifluoromethyl-phenoxy)methyl)-pyrrolidine
- f) 1-Boc-3-(5-nitro-2-pentafluoroethyl-phenoxy)methyl)-azetidine.
- 25 g) N-Boc-[2-(5-nitro-2-pentafluoroethyl-phenoxy)-ethyl]amine.
- h) (R) 3-(2-tert-Butyl-5-nitro-phenoxy)methyl)-1-Boc-pyrrolidine.
- i) 3-(2-tert-Butyl-5-nitro-phenoxy)methyl)-1-Boc-azetidine.
- 30 j) (S)-1-Boc-[2-(5-nitro-2-tert-butylphenoxy)methyl]-pyrrolidine
- k) (S) 3-(2-tert-Butyl-5-nitro-phenoxy)methyl)-1-Boc-pyrrolidine.

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- 1) (R)-1-Boc-[2-(5-nitro-2-tert-butylphenoxy)methyl]-pyrrolidine

Preparation III - 1-Boc-4-(3-amino-5-trifluoromethyl-phenoxy)-piperidine:

1-Boc-4-(3-nitro-5-trifluoromethyl-phenoxy)-piperidine (470 mg) was dissolved in MeOH (12 ml) and Pd/C (10 mg) was added. After sparging briefly with H₂, the mixture was stirred under H₂ for 6 H. The catalyst was removed by filtration and the MeOH solution was concentrated in vacuo to yield 1-Boc-4-(3-amino-5-trifluoromethyl-phenoxy)-piperidine as an off-white foam.

The following compounds were prepared similarly to the procedure outlined above:

- a) 1-Boc-2-(3-Amino-5-trifluoromethyl-phenoxy)methyl-pyrrolidine.
- b) 2-(3-Amino-5-trifluoromethyl-phenoxy)methyl-1-methyl-pyrrolidine.
- c) [2-(1-Methylpiperidin-4-yl)oxy]-pyridin-4-yl)methylamine. ESI (M+H)=222.
- d) [2-(2-Morpholin-4-yl-ethoxy)-pyridin-4-yl)methylamine.
- e) [2-(2-Morpholin-4-yl-propoxy)-pyridin-4-yl)methylamine.
- f) [2-(1-Methyl-pyrrolidin-2-ylmethoxy)-pyridin-4-yl)methylamine. ESI MS: (M+H)=222.
- g) (4-Aminomethyl-pyridin-2-yl)-(3-morpholin-4-yl-propyl)-amine. ESI MS: (M+H)=251.
- h) 4-tert-Butyl-3-(1-methyl-piperidin-4-ylmethoxy)-phenylamine.
- i) 4-tert-Butyl-3-(2-piperidin-1-yl-ethoxy)-phenylamine.
- j) 3-(1-Methyl-piperidin-4-ylmethoxy)-4-pentafluoroethyl-phenylamine.

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- k) 3-(1-Isopropyl-piperidin-4-ylmethoxy)-4-pentafluoroethyl-phenylamine.
- l) (S) 3-Oxiranylmethoxy-4-pentafluoroethyl-phenylamine.
- m) 3-(2-Pyrrolidin-1-yl-ethoxy)-4-trifluoromethyl-phenylamine.
- 5 n) 3-(2-Piperidin-1-yl-ethoxy)-4-trifluoromethyl-phenylamine.
- o) (S) 3-(1-Boc-pyrrolidin-2-ylmethoxy)-4-pentafluoroethyl-phenylamine.
- 10 p) (R) 3-(1-Boc-pyrrolidin-2-ylmethoxy)-4-pentafluoroethyl-phenylamine.
- q) (R) 3-(1-Methyl-pyrrolidin-2-ylmethoxy)-5-trifluoromethyl-phenylamine.
- r) (S) 3-(1-Methyl-pyrrolidin-2-ylmethoxy)-5-trifluoromethyl-phenylamine
- 15 s) (R) 3-Oxiranylmethoxy-4-pentafluoroethyl-phenylamine.
- t) (R) 2-(5-Amino-2-pentafluoroethyl-phenoxy)-1-pyrrolidin-1-yl-ethanol.
- u) 3-(1-Boc-azetidin-3-ylmethoxy)-4-pentafluoroethyl-phenylamine.
- 20 v) 3-(2-(Boc-amino)ethoxy)-4-pentafluoroethyl-phenylamine.
- w) 6-Amino-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one. M+H 193.2. Calc'd 192.1.
- x) 2,2,4-Trimethyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylamine.
- 25 y) 1-(6-Amino-2,2-dimethyl-2,3-dihydro-benzo[1,4]oxazin-4-yl)-ethanone. M+H 221.4. Calc'd 220.3.
- z) [2-(1-Benzhydryl-azetidin-3-yloxy)-pyridin-4-yl]-methylamine.
- 30 aa) [2-(1-Methyl-piperidin-4-ylmethoxy)-pyridin-4-yl]-methylamine. M+H 236.3. Calc'd 235.2.
- ab) 3-(4-Boc-piperazin-1-ylmethyl)-5-trifluoromethyl-phenylamine. M+H 360.3.

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- ac) 2-Boc-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-ylamine.
- ad) 3-Morpholin-4-ylmethyl-4-pentafluoroethyl-phenylamine.
- ae) 3-(4-Methyl-piperazin-1-ylmethyl)-4-pentafluoroethyl-phenylamine. M+H 410.3. Calc'd 409.4.
- 5 af) 7-Amino-2-(4-methoxy-benzyl)-4,4-dimethyl-3,4-dihydro-2H-isoquinolin-1-one. M+H 311.1.
- ag) 7-Amino-4,4-dimethyl-3,4-dihydro-2H-isoquinolin-1-one.
- ah) (3-Amino-5-trifluoromethyl-phenyl)-(4-Boc-piperazin-1-yl)-methanone. M+H 374.3; Calc'd 373.
- 10 ai) 3-(4-Boc-Piperazin-1-ylmethyl)-5-trifluoromethyl-phenylamine.
- aj) 1-(7-Amino-4,4-dimethyl-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone. M+H 219.2.
- 15 ak) {2-[2-(1-Methylpiperidin-4-yl)ethoxy]-pyridin-4-yl}-methylamine.
- al) {2-[2-(1-Pyrrolidinyl)ethoxy]-pyridin-4-yl}-methylamine.
- am) {2-[2-(1-Methylpyrrolin-2-yl)ethoxy]-pyridin-4-yl}-methylamine.
- 20 an) (2-Chloro-pyrimidin-4-yl)-methylamine.
- ao) 3-(1-Boc-azetidin-3-ylmethoxy)-5-trifluoromethyl-phenylamine.
- ap) 4-tert-Butyl-3-(1-Boc-pyrrolidin-3-ylmethoxy)-phenylamine. M+H 385.
- 25 aq) 4-tert-Butyl-3-(1-Boc-azetidin-3-ylmethoxy)-phenylamine. M+Na 357.
- ar) (S) 4-tert-Butyl-3-(1-Boc-pyrrolidin-2-ylmethoxy)-phenylamine. M+Na 371.
- as) 3-tert-Butyl-4-(4-Boc-piperazin-1-yl)-phenylamine
- 30 at) 3-(1-Methyl-piperidin-4-yl)-5-trifluoromethyl-phenylamine.
- au) 3,3-Dimethyl-2,3-dihydro-benzofuran-6-ylamine.
- av) 3,9,9-Trimethyl-2,3,4,4a,9,9a-hexahydro-1H-3-aza-fluoren-6-ylamine.

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- aw) 4-[1-Methyl-1-(1-methyl-piperidin-4-yl)-ethyl]-phenylamine was prepared using EtOH as the solvent.
- ax) 4-tert-Butyl-3-(4-pyrrolidin-1-yl-but-1-enyl)-phenylamine.
- 5 ay) (R) 3-(1-Boc-pyrrolidin-2-ylmethoxy)-5-trifluoromethyl-phenylamine.
- az) (S) 3-(1-Boc-pyrrolidin-2-ylmethoxy)-5-trifluoromethyl-phenylamine.
- 10 **Preparation IV - 1-Boc-4-{3-[(2-fluoro-pyridine-3-carbonyl)-amino]-5-trifluoromethyl-phenoxy}-piperidine:**
- 1-Boc-4-(3-amino-5-trifluoromethyl-phenoxy)-piperidine (4.37 g) was dissolved in CH₂Cl₂ (100 ml) and NaHCO₃ (2.4 g, Baker) was added. 2-Fluoropyridine-3-carbonyl chloride (2.12 g)
- 15 was added and the reaction was stirred at RT for 2.5 h. The reaction was filtered and concentrated *in vacuo* to yield a yellow foam. (30%) EtOAc/Hexane was added and 1-Boc-4-{3-[(2-fluoro-pyridine-3-carbonyl)-amino]-5-trifluoromethyl-phenoxy}-piperidine precipitated as an off white solid.
- 20 The following compounds were prepared similarly to the procedure outlined above:
- a) 2-Fluoro-N-[3-(3-piperidin-1-yl-propyl)-5-trifluoromethyl-phenyl]-nicotinamide.
- 25 b) N-[4-tert-Butyl-3-(2-piperidin-1-yl-ethoxy)-phenyl]-2-fluoro-nicotinamide.
- c) N-[3,3-Dimethyl-1-(1-methyl-piperidin-4-ylmethyl)-2,3-dihydro-1H-indol-6-yl]-2-fluoro-nicotinamide.
- 30 d) N-[1-(2-Dimethylamino-acetyl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl]-2-fluoro-nicotinamide
- e) N-[3,3-Dimethyl-1-(2-(Boc-amino)acetyl)-2,3-dihydro-1H-indol-6-yl]-2-fluoro-nicotinamide.

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- f) N-(4-Acetyl-2,2-dimethyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-2-fluoro-nicotinamide. M+H 344.5. Calc'd 343.4.
- g) 2-Fluoro-N-(2,2,4-trimethyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-nicotinamide. M+H 316.2. Calc'd 315.1.
- 5 h) N-(2,2-Dimethyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-2-fluoro-nicotinamide. M+H 316.1. Calc'd 315.10.
- i) 2-Fluoro-N-[3-(4-methyl-piperazin-1-ylmethyl)-5-trifluoromethyl-phenyl]-nicotinamide. M+H 481. Calc'd 480.
- 10 j) 2-Fluoro-N-(2-Boc-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-nicotinamide. M+H 400.
- k) 2-Fluoro-N-[3-(4-methyl-piperazin-1-ylmethyl)-4-pentafluoroethyl-phenyl]-nicotinamide. M+H 447.0. Calc'd 446.
- 15 l) 2-Fluoro-N-(3-morpholin-4-ylmethyl-4-pentafluoroethyl-phenyl)-nicotinamide.
- m) 2-Fluoro-N-[4-iodophenyl]-nicotinamide.
- n) 2-Fluoro-N-(4,4-dimethyl-1-oxo-1,2,3,4-tetrahydro-isoquinolin-7-yl)-nicotinamide. M+H 314.0, Calc'd 311.
- 20 o) 2-Fluoro-N-[3-(4-Boc-piperazine-1-carbonyl)-5-trifluoromethyl-phenyl]-nicotinamide. M+H 495.
- p) 2-Fluoro-N-[3-(4-Boc-piperazin-1-ylmethyl)-5-trifluoromethyl-phenyl]-nicotinamide. M+H 483.3; Calc'd 482.
- 25 q) N-(2-Acetyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-fluoro-nicotinamide. M+H 430.0.
- r) N-[3,3-Dimethyl-1-(1-methyl-piperidin-4-yl)-2,3-dihydro-1H-indol-6-yl]-2-fluoro-nicotinamide. M+H 383.2; Calc'd 382.5.
- 30 s) N-(4-tert-Butylphenyl)-2-fluoronicotinamide.
- t) N-(4-Trifluoromethylphenyl)-2-fluoronicotinamide.

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- u) 2-Fluoro-N-[3-(1-Boc-azetidin-3-ylmethoxy)-5-trifluoromethyl-phenyl]-nicotinamide. M-H 468.2; Calc'd 469.16.
- v) 2-Fluoro-N-[3-(1-Boc-azetidin-3-ylmethoxy)-4-tert-butyl-phenyl]-nicotinamide.
- 5 w) (S) N-[4-tert-Butyl-3-(1-Boc-pyrrolidin-2-ylmethoxy)-phenyl]-2-fluoro-nicotinamide. M+Na = 494.
- x) N-[3-(1-Methyl-piperidin-4-yl)-5-trifluoromethyl-phenyl]-2-fluoro-nicotinamide was prepared with K₂CO₃ instead of
- 10 NaHCO₃.
- y) N-(3-Bromo-5-trifluoromethyl-phenyl)-2-fluoro-nicotinamide.
- z) 2-Fluoro-N-(3,9,9-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-3-aza-fluoren-6-yl)-nicotinamide.
- 15 aa) 2-Fluoro-N-{4-[1-methyl-1-(1-methyl-piperidin-4-yl)-ethyl]-phenyl}-nicotinamide
- ab) N-[3,3-Dimethyl-1-(1-Boc-piperidin-4-ylmethyl)-2,3-dihydro-1H-indol-6-yl]-2-fluoro-nicotinamide.
- 20 **Preparation V - 1-Boc-4-{3-[(2-chloro-pyridine-3-carbonyl)-amino]-5-trifluoromethyl-phenoxy}-piperidine:**
- 1-Boc-4-{3-[(2-chloro-pyridine-3-carbonyl)-amino]-5-trifluoromethyl-phenoxy}-piperidine was prepared from 1-Boc-4-(3-amino-5-trifluoromethyl-phenoxy)-piperidine and 2-
- 25 chloropyridine-3-carbonyl chloride by a procedure similar to that described in the preparation of 1-Boc-4-{3-[(2-fluoro-pyridine-3-carbonyl)-amino]-5-trifluoromethyl-phenoxy}-piperidine.
- 30 The following compounds were prepared similarly to the procedure outlined above:
- a) N-(4-tert-Butyl-3-nitro-phenyl)-2-chloro-nicotinamide.

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- b) 2-Chloro-N-[3-(3-piperidin-1-yl-propyl)-5-trifluoromethyl-phenyl]-nicotinamide.
- c) 2-Chloro-N-[3-(3-morpholin-4-yl-propyl)-5-trifluoromethyl-phenyl]-nicotinamide.
- 5 d) 2-Chloro-N-[3-(1-methylpiperidin-4-yl)-5-trifluoromethyl-phenyl]-nicotinamide.
- e) 2-Chloro-N-[3-(1-methyl-piperidin-4-ylmethoxy)-4-pentafluoroethyl-phenyl]-nicotinamide.
- f) 2-Chloro-N-[3-(1-isopropyl-piperidin-4-ylmethoxy)-4-pentafluoroethyl-phenyl]-nicotinamide.
- 10 g) (S) 2-Chloro-N-[4-(oxiranylmethoxy)-3-pentafluoroethyl-phenyl]-nicotinamide.
- h) 2-Chloro-N-[3-(2-pyrrolidin-1-yl-ethoxy)-4-trifluoromethyl-phenyl]-nicotinamide.
- 15 i) 2-Chloro-N-[3-(2-piperidin-1-yl-ethoxy)-4-pentafluoroethyl-phenyl]-nicotinamide.
- j) (R) 2-Chloro-N-[3-(1-Boc-pyrrolidin-2-ylmethoxy)-4-pentafluoroethyl-phenyl]-nicotinamide.
- k) (S) 2-Chloro-N-[3-(1-Boc-pyrrolidin-2-ylmethoxy)-4-pentafluoroethyl-phenyl]-nicotinamide.
- 20 l) (R) 2-Chloro-N-[3-(1-methyl-pyrrolidin-2-ylmethoxy)-5-trifluoromethyl-phenyl]-nicotinamide.
- m) (S) 2-Chloro-N-[3-(1-methyl-pyrrolidin-2-ylmethoxy)-5-trifluoromethyl-phenyl]-nicotinamide.
- 25 n) (R) 2-Chloro-N-[4-(oxiranylmethoxy)-3-pentafluoroethyl-phenyl]-nicotinamide.
- o) (R) Acetic acid 2-{5-[(2-chloro-pyridine-3-carbonyl)-amino]-2-pentafluoroethyl-phenoxy}-1-pyrrolidin-1-yl-ethyl ester.
- 30 p) 2-Chloro-N-[3-(4-methyl-piperazin-1-ylmethyl)-5-trifluoromethyl-phenyl]-nicotinamide.
- q) 2-Chloro-N-[2-(4-methoxy-benzyl)-4,4-dimethyl-1-oxo-1,2,3,4-tetrahydro-isoquinolin-7-yl]-nicotinamide. M+H 450.2. Calc'd 449.

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- r) 2-Chloro-N-(4,4-dimethyl-1-oxo-1,2,3,4-tetrahydro-isoquinolin-7-yl)-nicotinamide. M+H 330.1, Calc'd 329.
- s) 2-Chloro-N-[3-(4-Boc-piperazin-1-ylmethyl)-5-trifluoromethyl-phenyl]-nicotinamide.
- 5 t) 2-{3-[(2-Chloro-pyridine-3-carbonyl)-amino]-phenyl}-2-methyl-propionic acid methyl ester. M+H 405
- u) N-{4-tert-Butyl-3-[2-(1-Boc-piperidin-4-yl)-ethyl]-phenyl}-2-chloro-nicotinamide. M+Na 524. Calc'd 501.1.
- v) N-[3,3-Dimethyl-1,1-dioxo-2,3-dihydro-1H-benzo[d]isothiazol-6-yl]-2-chloro-nicotinamide.
- 10 w) N-[1,1,4,4-Tetramethyl-1,2,3,4-tetrahydro-naphth-6-yl]-2-chloro-nicotinamide.
- x) 2-Chloro-N-[3,3-dimethyl-2,3-dihydro-benzofuran-6-yl]-2-chloro-nicotinamide.
- 15 y) 2-Chloro-N-[3-(1-Boc-piperidin-4-yloxy)-5-trifluoromethyl-phenyl]-nicotinamide.
- z) 2-Chloro-N-[3-(1-methyl-piperidin-4-ylmethyl)-5-trifluoromethyl-phenyl]-nicotinamide.
- aa) 2-Chloro-N-[3-(3-piperidin-1-yl-propyl)-5-trifluoromethyl-phenyl]-nicotinamide.
- 20 ab) N-[4-tert-Butyl-3-(4-pyrrolidin-1-yl-but-1-enyl)-phenyl]-2-chloro-nicotinamide.
- ac) (R) 2-Chloro-N-[3-(1-Boc-pyrrolidin-2-ylmethoxy)-5-trifluoromethyl-phenyl]-nicotinamide.
- 25 ad) (S) 2-Chloro-N-[3-(1-Boc-pyrrolidin-2-ylmethoxy)-5-trifluoromethyl-phenyl]-nicotinamide.

Preparation VI - 1-Boc-2-{3-[(2-fluoro-pyridine-3-carbonyl)-amino]-5-trifluoromethyl-phenoxyethyl}-pyrrolidine:

- 30 1-Boc-2-{3-[(2-Fluoro-pyridine-3-carbonyl)-amino]-5-trifluoromethyl-phenoxyethyl}-pyrrolidine was prepared from 1-Boc-2-(3-amino-5-trifluoromethyl-phenoxyethyl)-pyrrolidine by a procedure similar to that described in the

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preparation of 1-Boc-4-{3-[(2-fluoro-pyridine-3-carbonyl)-amino]-5-trifluoromethyl-phenoxy}-piperidine.

Preparation VII - 2-(3-nitro-5-trifluoromethyl-phenoxymethyl)-pyrrolidine:

1-Boc-2-(3-nitro-5-trifluoromethyl-phenoxymethyl)-pyrrolidine (2.35 g) was dissolved in CH₂Cl₂ (60 ml) and TFA (20 ml) was added. After stirring for 1 h at RT, the mixture was concentrated in vacuo to yield 2-(3-nitro-5-trifluoromethyl-phenoxymethyl)-pyrrolidine as an oil that solidified upon standing. The material was used as is without further purification.

The following compounds were prepared similarly to the procedure outlined above:

- a) (4-Aminomethyl-pyrimidin-2-yl)-(3-morpholin-4-yl-propyl)-amine.
- b) (4-Aminomethyl-pyrimidin-2-yl)-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-amine.

Preparation VIII - 1-methyl-2-(3-nitro-5-trifluoromethyl-phenoxymethyl)-pyrrolidine:

2-(3-Nitro-5-trifluoromethyl-phenoxymethyl)-pyrrolidine (6 mmol) was dissolved in CH₃CN (20 ml) and formaldehyde (2.4 ml, 37% aqueous) was added. NaBH₃CN (607 mg) was added, an exotherm was observed. The pH is monitored every 15 min and adjusted to ~7 with AcOH. After 45 min, the mixture was concentrated in vacuo and the residue is dissolved in EtOAc, washed with 6N NaOH, 1N NaOH, and 2N HCl (3x). The acid washings were combined, adjusted to ~pH 10 with solid Na₂CO₃ and extracted with EtOAc (2x). The EtOAc fractions were combined, dried with Na₂SO₄, and purified with flash chromatography (SiO₂, 95:5:0.5 CH₂Cl₂:MeOH:NH₄OH) to afford

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1-methyl-2-(3-nitro-5-trifluoromethyl-phenoxyethyl)-pyrrolidine.

5 The following compounds were prepared similarly to the procedure outlined above:

- a) 2-(1-Methylpiperidin-4-yl)-ethanol.
- b) 2-{3-[(2-Fluoro-pyridine-3-carbonyl)-amino]-5-trifluoromethyl-phenoxyethyl}-1-methylpyrrolidine.

10

Preparation IX - 4-tert-butyl-3-nitro-phenylamine:

A mixture of 1,3-dinitro-4-tert-butylbenzene (10.0 g) in H₂O (56 ml) was heated to reflux. A mixture of Na₂S (21.42 g) and sulfur (2.85 g) in H₂O (34 ml) was added over 1 h via an addition funnel. The reaction maintained at reflux for 1.5 h then cooled to RT and extracted with EtOAc. The organic extracts were combined and washed with H₂O, brine, dried over MgSO₄ and concentrated in vacuo to afford 4-tert-butyl-3-nitro-phenylamine, which was used as is without further purification.

20

Preparation X - N-(3-bromo-5-trifluoromethyl-phenyl)-acetamide:

3-Bromo-5-(trifluoromethyl)phenylamine (5 g, Alfa-Aesar) was dissolved in AcOH (140 ml) and Ac₂O (5.9 ml, Aldrich) was added. The reaction was stirred at RT overnight. The mixture was added slowly to H₂O (~700 ml) forming a white precipitate. The solid was isolated by filtration, washed with H₂O and dried under vacuum to yield N-(3-bromo-5-trifluoromethyl-phenyl)-acetamide.

30

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Preparation XI - N-[3-(3-piperidin-1-yl-propyl)-5-trifluoromethyl-phenyl]-acetamide:

Allylpiperidine (1.96 g, Lancaster) was degassed under vacuum, dissolved in 0.5 M 9-BBN in THF (31.2 ml, Aldrich),
5 and heated to reflux for 1 h, then cooled to RT.
PD(dppf)Cl₂/CH₂Cl₂ was added to a degassed mixture of N-(3-bromo-5-trifluoromethyl-phenyl)-acetamide, K₂CO₃ (9.8 g) DMF (32.1 ml and H₂O (3 ml). The allyl piperidine solution was added heated to 60 °C for 3 h. After cooling to RT and
10 reheating at 60 °C for 6 h, the mixture was cooled to RT and poured into H₂O. The mixture was extracted with EtOAc (2x), and the EtOAc portion was washed with 2 N HCl (2x) and brine. The aqueous phases were combined and the pH was adjusted to ~11 with NaOH (15%) forming a cloudy suspension.
15 The cloudy suspension was extracted with EtOAc (2x) and the EtOAc portion was dried with Na₂SO₄, filtered and concentrated in vacuo. The crude material was purified by flash chromatography (SiO₂, 95:5:0.5 CH₂Cl₂:MeOH:NH₄OH) to afford N-[3-(3-piperidin-1-yl-propyl)-5-trifluoromethyl-
20 phenyl]-acetamide as a brown oil that solidified under vacuum.

The following compounds were prepared similarly to the procedure outlined above:

25

- a) N-(3-Morpholin-4-ylpropyl-5-trifluoromethyl-phenyl)-acetamide from 4-allyl-morpholine.
- b) N-(3-(1-methylpiperidin-4-ylmethyl-5-trifluoromethyl-phenyl)-acetamide from 1-Methyl-4-methylene-piperidine.

30

Preparation XII - 3-(3-piperidin-1-yl-propyl)-5-trifluoromethyl-phenylamine:

N-[3-(3-Piperidin-1-yl-propyl)-5-trifluoromethyl-phenyl]-acetamide (1.33 g) was dissolved in EtOH (40 ml) and 12 N

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HCl (40 ml) was added. After stirring overnight at 70 °C and RT, the mixture was concentrated *in vacuo*, affording 3-(3-piperidin-1-yl-propyl)-5-trifluoromethyl-phenylamine as a brown oil.

5

The following compounds were prepared similarly to the procedure outlined above:

- a) 3,3-Dimethyl-6-nitro-2,3-dihydro-1H-indole. M+H 193.1;
10 Calc'd 192.2.
- b) 3-(1-Methyl-piperidin-4-ylmethyl)-5-trifluoromethyl-phenylamine.
- c) 3-Morpholin-4-ylmethyl-5-trifluoromethyl-phenylamine.

15 **Preparation XIII - 3,3-Dimethyl-6-nitro-1-piperidin-4-ylmethyl-2,3-dihydro-1H-indole:**

3,3-Dimethyl-1-(1-Boc-piperidin-4-ylmethyl)-6-nitro-2,3-dihydro-1H-indole was dissolved in HCl/EtOAc and stirred for 2 h. The mixture was concentrated *in vacuo* and partitioned
20 between 1,2-dichloroethane and 1N NaOH. The organic layer was removed, washed with brine, dried (Na₂SO₄) and filtered. The material was used without further purification.

25 **Preparation XIV - N-[3-(3-morpholin-4-yl-propyl)-5-trifluoromethyl-phenyl]-acetamide:**

N-[3-(3-Morpholin-4-yl-propyl)-5-trifluoromethyl-phenyl]-acetamide was prepared from allyl morpholine and N-(3-bromo-5-trifluoromethyl-phenyl)-acetamide similar to that described in the preparation of N-[3-(3-piperidin-1-yl-propyl)-5-trifluoromethyl-phenyl]-acetamide.
30

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Preparation XV - 3-(3-morpholin-4-yl-propyl)-5-trifluoromethyl-phenylamine:

3-(3-Morpholin-4-yl-propyl)-5-trifluoromethyl-phenylamine was prepared from N-[3-(3-morpholin-4-yl-propyl)-5-trifluoromethyl-phenyl]-acetamide similar to that described in the preparation of 3-(3-piperidin-1-yl-propyl)-5-trifluoromethyl-phenylamine.

Preparation XVI - 1-methyl-4-methylene-piperidine:

Ph₃PCH₃I (50 g, Aldrich) was suspended in Et₂O (20 ml) and butyllithium (77.3 ml, 1.6 M in hexanes, Aldrich) was added dropwise. The reaction was stirred for 2 h at RT then 1-methylpiperidone (12.3 ml, Aldrich) was added slowly. The mixture was stirred at RT overnight. The solid was removed by filtration, the volume was reduced to ~400 ml and additional solid was removed by filtration. The Et₂O was washed with H₂O (2x) and 2N HCl (4x). The pH of the acid washings was adjusted to ~11 with 6 N NaOH, then they were extracted with CH₂Cl₂ (4x). The CH₂Cl₂ washings were dried over Na₂SO₄ and concentrated cold in vacuo to provide 1-methyl-4-methylene-piperidine, which was used as is.

Preparation XVII - N-[3-(1-methylpiperidin-4-yl)-5-trifluoromethyl-phenyl]-acetamide:

N-[3-(1-Methylpiperidin-4-yl)-5-trifluoromethyl-phenyl]-acetamide was prepared from 1-methyl-4-methylene-piperidine and N-(3-bromo-5-trifluoromethyl-phenyl)-acetamide similar to that described in the preparation of N-[3-(3-piperidin-1-yl-propyl)-5-trifluoromethyl-phenyl]-acetamide.

30

Preparation XVIII - 3-(1-methylpiperidin-4-yl)-5-trifluoromethyl-phenylamine:

3-(1-Methylpiperidin-4-yl)-5-trifluoromethyl-phenylamine was prepared from N-[3-(1-methylpiperidin-4-yl)-5-

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trifluoromethyl-phenyl]-acetamide similar to the procedure described in the preparation of 3-(3-piperidin-1-yl-propyl)-5-trifluoromethyl-phenylamine.

5 **Preparation XIX - 2-(1-methylpiperidin-4-yloxy)-4-pyridylcarbonitrile:**

4-Hydroxy-1-methylpiperidine (25.4 g) was dissolved in THF (50 ml) in a 100 mL r.b. flask. NaH/mineral oil mixture (9.58 g) was slowly added to the flask and stirred for 20
10 min. 2-Chloro-4-cyanopyridine was added to the mixture and stirred at RT until completion. Diluted mixture with EtOAc and added H₂O to quench mixture, then transferred contents to a sep. funnel. The organic phase was collected while the aqueous phase was washed two times with EtOAc. The combined
15 organics were dried over Na₂SO₄, filtered, then concentrated *in vacuo*. Then redissolved mixture in CH₂Cl₂, 10% HCl (300 ml) was added and the mixture was transferred to sep. funnel. The org. was extracted, while EtOAc along with 300 mL 5N NaOH was added to the sep. funnel. The organic phases
20 were collected, dried over Na₂SO₄, filtered and concentrated *in vacuo* affording 2-(1-methylpiperidin-4-yloxy)-4-pyridylcarbonitrile as a brown solid. ESI (M+H) = 218.

The following compounds were prepared similarly to the
25 procedure outlined above:

- a) 2-(1-methylpiperidin-4-ylmethoxy)-4-pyridylcarbonitrile.
M+H 232.1. Calc'd 231.1.
- b) 2-(1-Benzhydryl-azetidin-3-yloxy)-4-pyridylcarbonitrile.
30 M+H 342.2. Calc'd 341.2.
- c) 2-(1-methylpiperidin-4-ylethoxy)-4-pyridylcarbonitrile.
- d) 2-(1-pyrrolidinylethoxy)-4-pyridylcarbonitrile.
- e) 2-(1-methylpyrrolin-2-ylethoxy)-4-pyridylcarbonitrile.
- f) 2-[2-(1-Boc-azetidin-3-yl)-ethoxy]-4-pyridylcarbonitrile.

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Preparation XX - [2-(1-methylpiperidin-4-yloxy)-pyridin-4-yl]methanamine bis hydrochloride:

[2-(1-Methylpiperidin-4-yloxy)-pyridin-4-yl]methanamine was
5 diluted with Et₂O (50 ml) and 1M HCl/Et₂O (47 ml) was added.
The vessel was swirled until precipitate formed.

Preparation XXI - 2-(2-morpholin-4-yl-ethoxy)-4-pyridylcarbonitrile:

10 2-(2-Morpholin-4-yl-ethoxy)-4-pyridylcarbonitrile was
prepared from 2-chloro-4-cyanopyridine and 2-morpholin-4-yl-
ethanol by a procedure similar to that described in the
preparation of 2-(1-methylpiperidin-4-yloxy)-4-
pyridylcarbonitrile. The HCl salt was prepared similar to
15 that described for [2-(1-methylpiperidin-4-yloxy)-pyridin-4-
yl]methanamine bis hydrochloride.

Preparation XXII - 2-morpholin-4-yl-propanol:

LAH powder (1.6 g) was added to a flask while under N₂
20 atmosphere, immediately followed by THF (50 ml). The
mixture was chilled to 0°C, methyl 2-morpholin-4-yl-
propionate (5 g) was added dropwise to the reaction mixture
and stirred at 0°C. After 1 h, the mixture was worked up by
adding H₂O (44 mL), 2N NaOH (44 mL), then H₂O (44 mL, 3x).
25 After 30 min of stirring, the mixture was filtered through
Celite® and the organic portion was concentrated *in vacuo*
providing 2-morpholin-4-yl-propanol as a colorless oil.

The following compounds were prepared similarly to the
30 procedure outlined above:

a) (1-Methyl-piperidin-4-yl)-methanol. M+H 130.2. Calc'd
129.1.

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Preparation XXIII - 2-(2-morpholin-4-yl-propoxy)-4-pyridylcarbonitrile:

2-(2-Morpholin-4-yl-propoxy)-4-pyridylcarbonitrile was prepared from 2-chloro-4-cyanopyridine and 2-morpholin-4-yl-propanol by a procedure similar to that described in the preparation of 2-(1-methylpiperidin-4-yloxy)-4-pyridylcarbonitrile.

Preparation XXIV - 2-(1-Methyl-pyrrolidin-2-ylmethoxy)-4-pyridylcarbonitrile:

2-(1-Methyl-pyrrolidin-2-ylmethoxy)-4-pyridylcarbonitrile was prepared from 2-chloro-4-cyanopyridine and 1-methyl-pyrrolidin-2-ylmethanol by a procedure similar to that described in the preparation of 2-(1-methylpiperidin-4-yloxy)-4-pyridylcarbonitrile. ESI MS: (M+H)=218.

Preparation XXV - 2-(3-morpholin-4-yl-propylamino)-4-pyridylcarbonitrile:

To a flask charged with 2-chloro-4-cyanopyridine (2.0 g), was added the aminopropyl morpholine (2.11 ml). The mixture was heated to 79 °C for 5 h and stirred. After 5 h the reaction was incomplete. The mixture was then heated at 60 °C overnight. The crude compound was purified on silica gel (1-5% MeOH/CH₂Cl₂ gradient). ESI MS: (M+H)=247, (M-H)=245.

25

Preparation XXVI - 5-Nitro-2-pentafluoroethylphenol:

Combined 2-methoxy-4-nitro-1-pentafluoroethylbenzene (9.35 g) and pyridine HCl in a round bottom flask and heated at 210 °C for 1 h then cooled to RT. The mixture was diluted with EtOAc and 2N HCl (>500 ml) until all residue dissolved. The organic layer was removed, washed with 2N HCl (2x) and concentrated *in vacuo*. The residue was dissolved in hexanes and Et₂O, washed with 2N HCl, then brine. Dried organic layer over Na₂SO₄, filtered, concentrated *in vacuo* and dried

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under high vacuum to provide 5-nitro-2-pentafluoromethylphenol.

Preparation XXVII - 2-tert-Butyl-5-nitro-aniline:

5 To H₂SO₄ (98%, 389 mL) in a 500 mL 3-neck flask was added 2-tert-butyl aniline (40.6 mL). The reaction was cooled to -10 °C and KNO₃ in 3.89 g aliquots was added every 6 min for a total of 10 aliquots. Tried to maintain temperature at -5 °C to -10 °C. After final addition of KNO₃, stirred the
10 reaction for five min then it was poured onto ice (50 g). The black mix was diluted with H₂O and extracted with EtOAc. The aqueous layer was basified with solid NaOH slowly then extracted with EtOAc (2x). The combined organic layers were washed with 6N NaOH and then with a mix of 6N NaOH and
15 brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to obtain crude 2-tert-butyl-5-nitro-aniline as a dark red-black oil which solidified when standing at RT. The crude material was triturated with about 130 mL hexanes. After decanting the hexanes, the material was dried to obtain a
20 dark-red black solid.

Preparation XXVIII - 2-tert-Butyl-5-nitrophenol:

In a 250 ml round bottom flask, 20 mL concentrated H₂SO₄ was added to 2-tert-butyl-5-nitro-aniline (7.15 g) by adding 5
25 mL aliquots of acid and sonicating with occasional heating until all of the starting aniline went into solution. H₂O (84 ml) was added with stirring, then the reaction was cooled to 0 °C forming a yellow-orange suspension. A solution of NaNO₂ (2.792 g) in H₂O (11.2 mL) was added
30 dropwise to the suspension and stirred for 5 min. Excess NaNO₂ was neutralized with urea, then the cloudy solution was transferred to 500 ml 3-necked round bottom flask then added 17 mL of 1:2 H₂SO₄:H₂O solution, and heated at reflux. Two additional 5 mL aliquots of 1:2 H₂SO₄:H₂O solution, a 7

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mL aliquot of 1:2 H₂SO₄:H₂O solution and another 10 mL of 1:2 H₂SO₄: H₂O were added while heating at reflux. The mixture was cooled to RT forming a black layer floating on top of the aqueous layer. The black layer was diluted with EtOAc (300 mL) and separated. The organic layer was washed with H₂O then brine, dried over Na₂SO₄ and concentrated *in vacuo*. Crude oil was purified on silica gel column with 8% EtOAc/Hexanes. Upon drying under vacuum, the 2-tert-butyl-5-nitrophenol was isolated as a brown solid.

10

Preparation XXIX - 1-methylpiperidine-4-carboxylic acid ethyl ester:

Piperidine-4-carboxylic acid ethyl ester (78 g) was dissolved in MeOH (1.2 L) at RT then formaldehyde (37%, 90 ml) and acetic acid (42 ml) were added and stirred for 2 h. The mixture was cooled to 0 °C, NaCNBH₃ (70 g) was added, and the mix was stirred for 20 min at 0 °C, then overnight at RT. The mixture was cooled to 0 °C then quenched with 6N NaOH. The mixture was concentrated *in vacuo* to an aqueous layer, which was extracted with EtOAc (4x), brine-washed, dried over Na₂SO₄, and concentrated *in vacuo* to provide 1-methylpiperidine-4-carboxylic acid ethyl ester.

The following compounds were prepared similarly to the procedure outlined above:

a) (1-Methyl-piperidin-4-yl)-methanol. M+H 130.2. Calc'd 129.1.

Preparation XXX - N-[4-tert-Butyl-3-(1-methyl-piperidin-4-ylmethoxy)-phenyl]-2-chloro-nicotinamide:

N-[4-tert-Butyl-3-(1-methyl-piperidin-4-ylmethoxy)-phenyl]-2-chloro-nicotinamide was prepared from 4-tert-butyl-3-(1-methyl-piperidin-4-ylmethoxy)-phenylamine by a procedure

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similar to that described in the preparation of 1-Boc-4-{3-[(2-chloro-pyridine-3-carbonyl)-amino]-5-trifluoromethyl-phenoxy}-piperidine.

5 **Preparation XXXI - 1-[2-(2-tert-Butyl-5-nitro-phenoxy)-ethyl]-piperidine:**

To 2-tert-butyl-5-nitrophenol (1.01 g) and K_2CO_3 (1.72 g) was added acetone (35 ml) and H_2O (10.5 mL), then 1-(2-chloroethyl)piperidine HCl (1.909 g) and TBAI (153 mg). The
10 mixture was stirred at reflux overnight. Additional K_2CO_3 (850 mg) and 1-(2-chloroethyl)-piperidine HCl (950 mg) were added and the mixture was heated at reflux for 6 h. The mixture was concentrated *in vacuo* to an aqueous layer which was acidified with 2N HCl and extracted with EtOAc. The
15 aqueous layer was basified with 6N NaOH and washed with CH_2Cl_2 (3x). The combined organic layers were washed with brine/1N NaOH and dried over Na_2SO_4 . Washed the EtOAc layer with 2N NaOH/brine and dried over Na_2SO_4 . The crude material was purified by silica gel column chromatography
20 with 15% EtOAc/Hexanes to yield 1-[2-(2-tert-butyl-5-nitro-phenoxy)-ethyl]-piperidine as a light tan solid.
(M+1)=307.3.

25 **Preparation XXXII - 1-Boc-Piperidine-4-carboxylic acid ethyl ester:**

To a stirred solution of piperidine-4-carboxylic acid ethyl ester (23.5 g) in EtOAc (118 ml) at 0°C was added dropwise Boc_2O in EtOAc (60 ml). The reaction was warmed to RT and stirred overnight. The reaction was washed with H_2O , 0.1N
30 HCl, H_2O , $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The liquid was dried under vacuum to provide 1-Boc-piperidine-4-carboxylic acid ethyl ester.

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The following compounds were prepared similarly to the procedure outlined above:

- a) N-Boc-(2-chloropyrimidin-4-yl)-methylanine.
- 5 b) 1-(2-tert-Butyl-4-nitrophenyl)-4-Boc-piperazine.
- c) 1-Boc-azetidine-3-carboxylic acid
- d) 1-Boc-4-Hydroxymethyl-piperidine using TEA.

Preparation XXXIII - 1-Boc-4-hydroxymethyl-piperidine:

- 10 1-Boc-4-Hydroxymethyl-piperidine was prepared from 1-Boc-piperidine-4-carboxylic acid ethyl ester by a procedure similar to that described in the preparation of 2-morpholin-4-yl-propanol.

15 **Preparation XXXIV - 1-Boc-4-Methylsulfonyloxymethyl-piperidine:**

- Dissolved 1-Boc-4-hydroxymethyl-piperidine in anhydrous CH_2Cl_2 (50 ml) and TEA (4.5 ml) and cooled to 0 °C. Mesyl chloride (840 μl) was added and the mixture was stirred for
20 15 min then at RT for 45 min. The mixture was washed with brine/1N HCl and then brine, dried over Na_2SO_4 , concentrated in vacuo and dried under high vacuum to provide 1-Boc-4-methylsulfonyloxymethyl-piperidine as a yellow orange thick oil.

25

The following compounds were prepared similarly to the procedure outlined above:

- a) 1-Boc-3-methylsulfonyloxymethyl-azetidine.

30

Preparation XXXV - 1-Boc-4-(3-nitro-6-pentafluoroethyl-phenoxy-methyl)-piperidine:

To a slurry of 60% NaH suspension in DMF (30 mL) at RT added a solution of 5-nitro-2-pentafluoroethyl-phenol (3.6 g) in 5

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mL DMF. The dark red mixture was stirred at RT for 10 min then added a solution of 1-Boc-4-methylsulfonyloxymethyl-piperidine (3.1 g) in 5 mL DMF. The reaction was stirred at 60 °C and 95 °C. After 1 h, added 2.94 g K₂CO₃ and stirred overnight at 105 °C. After cooling to RT, the reaction was diluted with hexanes and 1N NaOH. Separated layers, and washed organic layer with 1N NaOH and with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification with silica gel column chromatography with 8% EtOAc/Hexanes yielded 1-Boc-4-(3-nitro-6-pentafluoroethyl-phenoxyethyl)-piperidine as a light yellow thick oil.

Preparation XXXVI - 4-(3-nitro-6-pentafluoroethyl-phenoxyethyl)-piperidine:

4-(3-Nitro-6-pentafluoroethyl-phenoxyethyl)-piperidine was prepared from 1-Boc-4-(3-nitro-6-pentafluoroethyl-phenoxyethyl)-piperidine by a procedure similar to that described in the preparation of 2-(3-nitro-5-trifluoromethyl-phenoxyethyl)-pyrrolidine.

Preparation XXXVII - 1-methyl-4-(3-nitro-6-pentafluoroethyl-phenoxyethyl)-piperidine:

4-(3-Nitro-6-pentafluoroethyl-phenoxyethyl)-piperidine (316.5 mg) was dissolved in 2.7 mL CH₃CN, then added 37% formaldehyde/H₂O (360 ul) and then NaBH₃CN (90 mg). Upon addition of NaCNBH₃ the reaction was found to be slightly exothermic. The reaction was stirred at RT and pH was maintained at ~7 by addition of drops of glacial AcOH. After about 1 h, the mixture was concentrated *in vacuo*, treated with 8 mL 2N KOH and extracted two times with 10 mL Et₂O. The organic layers were washed with 0.5N KOH and then the combined organic layers were extracted two times with 1N HCl. The aqueous layer was basified with solid KOH and extracted two times with Et₂O. This organic layer was then

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washed with brine/1N NaOH, dried over Na₂SO₄, filtered, concentrated *in vacuo* and dried under high vacuum to give pure compound.

5 **Preparation XXXVIII - 1-Isopropyl-4-(5-nitro-2-pentafluoroethyl-phenoxyethyl)-piperidine:**

Dissolved 4-(5-nitro-2-pentafluoroethyl-phenoxyethyl)-piperidine (646 mg) in 1,2-dichloroethane (6.4 ml), then added acetone (136 ul), NaBH(OAc)₃ (541 mg) and finally AcOH (105 ul). Stirred the cloudy yellow solution under N₂ at RT overnight. Added another 130 uL acetone and stirred at RT over weekend. Quenched the reaction with 30 mL N NaOH/H₂O and stirred 10 min. Extracted with Et₂O and the organic layer was brine-washed, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Dried under high vacuum for several h to obtain 1-isopropyl-4-(5-nitro-2-pentafluoroethyl-phenoxyethyl)-piperidine as a yellow orange solid.

The following compounds were prepared similarly to the procedure outlined above:

- a) 3,3-Dimethyl-1-(1-methyl-piperidin-4-yl)-6-nitro-2,3-dihydro-1H-indole was prepared using 1-methyl-piperidin-4-one. M+H 290; Calc'd 289.4.
- 25 b) 3,3-Dimethyl-1-(1-Boc-piperidin-4-ylmethyl)-6-nitro-2,3-dihydro-1H-indole using 1-Boc-4-formyl-piperidine.

Preparation XXXIX - 3,3-Dimethyl-1-(1-methyl-piperidin-4-ylmethyl)-6-nitro-2,3-dihydro-1H-indole:

30 3,3-Dimethyl-1-piperidin-4-ylmethyl-6-nitro-2,3-dihydro-1H-indole was treated with an excess of formaldehyde and NaBH(OAc)₃ and stirred overnight at RT. The reaction was quenched with MeOH and concentrated *in vacuo*. The residue was partitioned between EtOAc and 1N NaOH. The organic layer

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was removed, washed with brine, dried (Na_2SO_4), filtered and concentrated to provide the compound.

Preparation XL - (S) 2-(5-Nitro-2-pentafluoroethyl-phenoxymethyl)-oxirane:

Combined 5-nitro-2-pentafluoromethylphenol (2.69 g), DMF (25 ml) K_2CO_3 (3.03 g) and (S) toluene-4-sulfonic acid oxiranylmethyl ester (2.27 g) and stirred the mixture at 90°C .

After about 4 h, the mix was cooled, diluted with EtOAc, washed with H_2O , 1N NaOH (2x), 1N HCl and then with brine. Dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purified the crude on silica gel column with 5% EtOAc/hexane and drying under high vacuum provided the (S)-2-(5-nitro-2-pentafluoroethyl-phenoxymethyl)-oxirane.

The following compounds were prepared similarly to the procedure outlined above:

a) (R)-2-(5-Nitro-2-pentafluoroethyl-phenoxymethyl)-oxirane.

Preparation XLI - (S) 2-Chloro-N-[3-(2-hydroxy-3-pyrrolidin-1-yl-propoxy)-4-pentafluoroethyl-phenyl]-nicotinamide:

(S) 2-Chloro-N-[4-(2-oxiranylmethoxy)-3-pentafluoroethyl-phenyl]-nicotinamide (1.11 g) in a sealed tube and added pyrrolidine (285 μl). Stirred after sealing tube at 60°C . After 12 h, the mixture was concentrated *in vacuo* and purified on a silica gel column (5:95:0.5 MeOH: CH_2Cl_2 : NH_4OH - 8:92:1, MeOH: CH_2Cl_2 : NH_4OH). The product fractions were concentrated *in vacuo* and dried under high vacuum to obtain pure compound.

The following compounds were prepared similarly to the procedure outlined above:

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a) (R) 1-(5-Nitro-2-pentafluoroethyl-phenoxy)-3-pyrrolidin-1-yl-propan-2-ol.

Preparation XLII - 5-nitro-2-trifluoromethylanisole:

5 Cooled 140 mL pyridine in a large sealable vessel to -40 °C. Bubbled in trifluoromethyl iodide from a gas cylinder, which had been kept in freezer overnight. After adding ICF₃ for 20 min, added 2-iodo-5-nitroanisole (24.63 g) and copper powder (67.25 g). Sealed vessel and stirred vigorously for
10 22 h at 140 °C After cooling to -50 °C, carefully unsealed reaction vessel and poured onto ice and Et₂O. Repeatedly washed with Et₂O and H₂O. Allowed the ice - Et₂O mixture to warm to RT. Separated layers, washed organic layer with 1N HCl (3x), then brine, dried over Na₂SO₄, filtered and
15 concentrated in vacuo. Eluted material through silica gel plug (4.5:1 Hex:CH₂Cl₂) to provide 5-nitro-2-trifluoromethylanisole.

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Preparation XLIII - 1-[2-(5-nitro-2-trifluoromethylphenoxy)ethyl]pyrrolidine:

1-[2-(5-Nitro-2-trifluoromethylphenoxy)ethyl]-pyrrolidine was prepared from 5-nitro-2-trifluoromethyl-phenol and 1-(2-chloroethyl)pyrrolidine by a procedure similar to that described for 1-[2-(2-tert-butyl-5-nitro-phenoxy)-ethyl]-piperidine.

Preparation XLIV - 1-[2-(5-Nitro-2-pentafluoroethylphenoxy)-ethyl]-piperidine:

1-[2-(5-Nitro-2-pentafluoroethylphenoxy)-ethyl]-piperidine was prepared from 5-nitro-2-pentafluoroethylphenol and 1-(2-chloroethyl)piperidine by a procedure similar to that described in the preparation of 1-[2-(2-tert-butyl-5-nitro-phenoxy)-ethyl]-piperidine.

Preparation XLV - 3-(1-Boc-pyrrolidin-2-ylmethoxy)-4-pentafluoroethyl-phenylamine:

3-(2-Pyrrolidin-1-yl-methoxy)-4-trifluoromethyl-phenylamine was prepared from 1-[2-(5-nitro-2-trifluoromethylphenoxy)methyl]-pyrrolidine by a procedure similar to that described in the preparation of 1-Boc-4-(3-amino-5-trifluoromethyl-phenoxy)-piperidine.

Preparation XLVI - 2-Chloro-N-[3-(2-pyrrolidin-1-yl-ethoxy)-4-trifluoromethyl-phenyl]-nicotinamide:

2-Chloro-N-[3-(2-pyrrolidin-1-yl-ethoxy)-4-trifluoromethyl-phenyl]-nicotinamide was prepared from 3-(2-pyrrolidin-1-yl-ethoxy)-4-trifluoromethyl-phenylamine and 2-chloropyridine-3-carbonyl chloride by a procedure similar to that described in the preparation of 1-Boc-4-{3-[(2-chloro-pyridine-3-carbonyl)-amino]-5-trifluoromethyl-phenoxy}-piperidine.

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Preparation XLVII - (R) Acetic acid 2-(5-nitro-2-pentafluoroethyl-phenoxy)-1-pyrrolidin-1-ylmethyl-ethyl ester:

Dissolved 1-(5-nitro-2-pentafluoroethyl-phenoxy)-3-
5 pyrrolidin-1-yl-propan-2-ol (3.5 g) in CH₂Cl₂ (15 ml) ,
added TEA (2.55 ml) and cooled to 0 °C. Acetyl chloride
(781.3 µl) was added dropwise, forming a suspension. The
mixture was warmed to RT and stirred for 1.5 h. Additional
acetyl chloride (200 µl) was added and the mix was stirred
10 for another h. The mixture was diluted with CH₂Cl₂ and
washed with sat. NaHCO₃. The organic layer was removed,
washed with brine and back extracted with CH₂Cl₂. Dried the
combined organic layers over Na₂SO₄, filtered and
concentrated in vacuo. The residue was purified over silica
15 gel column (5:94.5:0.5 MeOH: CH₂Cl₂:NH₄OH) to provide acetic
acid 2-(5-nitro-2-pentafluoroethyl-phenoxy)-1-pyrrolidin-1-
ylmethyl-ethyl ester as a yellow brown oil.

The following compounds were prepared similarly to the
20 procedure outlined above:

- a) (R) Acetic acid 2-(5-amino-2-pentafluoroethyl-phenoxy)-1-pyrrolidin-1-yl-methyl-ethyl ester.
- b) 1-(2,2-Dimethyl-6-nitro-2,3-dihydro-benzo[1,4]oxazin-4-
25 yl)-ethanone. M-NO₂ 206.4; Calc'd 250.1.

Preparation XLVIII - (R) 2-Chloro-N-[3-(2-hydroxy-2-pyrrolidin-1-yl-propoxy)-4-pentafluoroethyl-phenyl]-nicotinamide:

30 (R) Acetic acid 2-{5-[(2-chloro-pyridine-3-carbonyl)-amino]-2-pentafluoroethyl-phenoxy}-1-pyrrolidin-1-yl-ethyl ester
(408 mg) was dissolved in MeOH (15 ml) and NH₄OH (6 ml) was
added and the mixture was stirred at RT for 6 h. The
reaction was concentrated in vacuo and dried under high

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vacuum. The residue was purified over silica gel column (8:92:0.6 MeOH: CH₂Cl₂:NH₄OH). The purified fractions were concentrated in vacuo and dried again to provide (R)-2-chloro-N-[3-(2-hydroxy-2-pyrrolidin-1-yl-ethoxy)-4-pentafluoroethyl-phenyl]-nicotinamide as a white foam.

Preparation XLIX - 2-Dimethylamino-1-(3,3-dimethyl-6-nitro-2,3-dihydro-indol-1-yl)-ethanone

3,3-Dimethyl-6-nitro-2,3-dihydro-1H-indole (5 g) was dissolved in DMF (100 ml) and HOAt (3.89 g) dimethylamino-acetic acid (5.83 g) and EDC (3.89 g) were added. The reaction was stirred overnight. The mixture was diluted with CH₂Cl₂ (1L) and washed with sat'd NaHCO₃ (3x200 ml). The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash chromatography (SiO₂, EtOAc to 5%MeOH/EtOAc) to afford the title compound.

The following compounds were prepared similarly to the procedure outlined above:

a) 1-(3,3-Dimethyl-6-nitro-2,3-dihydro-indol-1-yl)-2-(N-Boc-amino)-ethanone.

Preparation L - 1-(6-Amino-3,3-dimethyl-2,3-dihydro-indol-1-yl)-2-(N-Boc-amino)-ethanone:

1-(3,3-Dimethyl-6-nitro-2,3-dihydro-indol-1-yl)-2-(N-Boc-amino)-ethanone (3.9 g) was dissolved in EtOH (30 ml) and Fe powder (3.1 g) NH₄Cl (299 mg) and H₂O (5 ml) were added. The reaction was stirred at 80 °C overnight. The reaction was filtered through Celite® and evaporated off the MeOH. The residue was partitioned between CH₂Cl₂ and sat'd NaHCO₃. The organic layer was removed, washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was

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purified by flash chromatography (SiO₂, 25% EtOAc/hexane). The purified fractions were concentrated *in vacuo* to afford the compound as a white powder.

5 The following compounds were prepared similarly to the procedure outlined above:

- a) 1-(6-Amino-3,3-dimethyl-2,3-dihydro-indol-1-yl)-2-dimethylamino-ethanone.
- 10 b) 3,3-Dimethyl-1-(1-methyl-piperidin-4-ylmethyl)-2,3-dihydro-1H-indol-6-ylamine.
- c) 3-(4-Methyl-piperazin-1-ylmethyl)-4-pentafluoroethyl-phenylamine. M+H 324.2. Calc'd 323.
- d) 3,3-Dimethyl-1-(1-methyl-piperidin-4-yl)-2,3-dihydro-1H-15 indol-6-ylamine. M+H 259.6; Calc'd 259.3.
- e) 3,3-Dimethyl-1,1-dioxo-2,3-dihydro-1H-116-benzo[d]isothiazol-6-ylamine
- f) 1,1,4,4-Tetramethyl-1,2,3,4-tetrahydro-naphth-6-ylamine.
- g) 3,3-Dimethyl-1-(1-Boc-piperidin-4-ylmethyl)-2,3-dihydro-20 1H-indol-6-ylamine.

Preparation LI - 2-Boc-4,4-dimethyl-7-nitro-1,2,3,4-tetrahydro-isoquinoline:

4,4-Dimethyl-7-nitro-1,2,3,4-tetrahydro-isoquinoline (150
25 mg) was dissolved with CH₂Cl₂ (3 ml) DIEA (100 ul) DMAP (208 mg and Boc₂O (204 mg) and the mixture was stirred for 6 h at RT. The reaction was diluted with CH₂Cl₂, washed with sat'd NaHCO₃ and dried over MgSO₄, filtered and concentrated to provide the compound which was used without further
30 purification.

The following compounds were prepared similarly to the procedure outlined above substituting Ac₂O:

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a) 1-(4,4-Dimethyl-7-nitro-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone. M+H 249.3.

**Preparation LII - 2-Bromo-N-(4-methoxy-benzyl)-5-nitro-
5 benzamide:**

PMB-amine (5.35 ml) in CH₂Cl₂ (130 ml) was slowly added to 2-bromo-5-nitro-benzoyl chloride (10.55 g) and NaHCO₃ (9.6 g) and the mixture was stirred at RT for 1 h. The mixture was diluted with CH₂Cl₂ (1 L), filtered, washed with diluted
10 HCl, dried, filtered again, concentrated and dried under vacuum to provide the compound as a white solid. M+H 367. Calc'd 366.

**Preparation LIII - 2-Bromo-N-(4-methoxy-benzyl)-N-(2-methyl-
15 allyl)-5-nitro-benzamide:**

To a suspension of NaH (1.22 g) in DMF (130 ml) was added 2-bromo-N-(4-methoxy-benzyl)-5-nitro-benzamide (6.2 g) in DMF (60 ml) at -78 °C. The mixture was warmed to 0 °C, 3-bromo-2-methyl-propene (4.57 g) was added and the mixture was
20 stirred for 2 h at 0 °C. The reaction was poured into ice H₂O, extracted with EtOAc (2x400 ml), dried over MgSO₄, filtered and concentrated to a DMF solution which was used without further purification.

**Preparation LIV - of 2-(4-Methoxy-benzyl)-4,4-dimethyl-7-
25 nitro-3,4-dihydro-2H-isoquinolin-1-one:**

2-Bromo-N-(4-methoxy-benzyl)-N-(2-methyl-allyl)-5-nitro-benzamide (23.4 mmol) was dissolved in DMF (150 ml) and Et₄NCl (4.25 g), HCO₂Na (1.75 g) and NaOAc (4.99 g) were
30 added. N₂ was bubbled through the solution for 10 min, then Pd(OAc)₂ (490 mg) was added and the mixture was stirred overnight at 70 °C. The mixture was extracted with EtOAc, washed with sat'd NH₄Cl, dried over MgSO₄, filtered and

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concentrated until the compound precipitated as a white solid.

The following compounds were prepared similarly to the procedure outlined above:

- a) 3,3-Dimethyl-6-nitro-2,3-dihydro-benzofuran was prepared from 1-bromo-2-(2-methyl-allyloxy)-4-nitro-benzene.
- b) 3,9,9-Trimethyl-6-nitro-4,9-dihydro-3H-3-aza-fluorene was prepared from 4-[1-(2-bromo-4-nitro-phenyl)-1-methyl-ethyl]-1-methyl-1,2,3,6-tetrahydro-pyridine.

Preparation LV - 4,4-Dimethyl-7-nitro-3,4-dihydro-2H-isoquinolin-1-one:

2-(4-Methoxy-benzyl)-4,4-dimethyl-7-nitro-3,4-dihydro-2H-isoquinolin-1-one (2.0 g) was dissolved in CH₃CN (100 ml) and H₂O (50 ml) and cooled to 0 °C. CAN (9.64 g) was added and the reaction was stirred at 0 °C for 30 min, then warmed to RT and stirred for 6 h. The mixture was extracted with CH₂Cl₂ (2x300 ml) washed with sat'd NH₄Cl, dried over MgSO₄, filtered and concentrated. The crude material was recrystallized in CH₂Cl₂/EtOAc (1:1) to give 4,4-dimethyl-7-nitro-3,4-dihydro-2H-isoquinolin-1-one as a white solid.

Preparation LVI - 4,4-Dimethyl-7-nitro-1,2,3,4-tetrahydro-isoquinoline:

4,4-Dimethyl-7-nitro-3,4-dihydro-2H-isoquinolin-1-one (230 mg) was dissolved in THF (10 ml) and BH₃Me₂S (400 ul) was added and the reaction was stirred overnight at RT. The reaction was quenched with MeOH (10 ml) and NaOH (200 mg) and heating at reflux for 20 min. The mixture was extracted with EtOAc, washed with sat'd NH₄Cl, extracted with 10% HCl (20 ml). The acidic solution was treated with 5N NaOH (15 ml), extracted with EtOAc (30 ml) dried, filtered and

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evaporated to give the compound as a yellow solid. M+H
207.2, Calc'd 206.

The following compounds were prepared similarly to the
5 procedure outlined above:

a) 4-Boc-2,2-dimethyl-6-nitro-3,4-dihydro-2H-
benzo[1,4]oxazine.

10 **Preparation LVII - 2-Bromomethyl-4-nitro-1-pentafluoroethyl-
benzene:**

2-Methyl-4-nitro-1-pentafluoroethyl-benzene (2.55 g) was
dissolved in CCl₄ (30 ml) and AIBN (164 mg) and NBS (1.96 g)
were added. The reaction was heated to reflux and stirred
15 for 24 h. The mix was diluted with CH₂Cl₂, washed with sat'd
NaHCO₃, dried over MgSO₄ and concentrated to give the
compound as an oil which was used without further
purification.

20 **Preparation LVIII - 1-Methyl-4-(5-nitro-2-pentafluoroethyl-
benzyl)-piperazine:**

2-Bromomethyl-4-nitro-1-pentafluoroethyl-benzene (2.6 g) was
added to N-methylpiperazine (5 ml) and stirred at RT for 3
h. The mixture was filtered and the filtrate was treated
25 with 1-chlorobutane, extracted with 2N HCl (100 ml). The
acidic solution was treated with 5N NaOH (6 ml) then
extracted with EtOAc. The organic layer was removed, dried
over MgSO₄ and concentrated to give the compound as an oil.

30 The following compounds were prepared similarly to the
procedure outlined above:

a) 4-(5-Nitro-2-pentafluoroethyl-benzyl)-morpholine.

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Preparation LIX - 1-Boc-4-(5-nitro-2-pentafluoroethyl-benzyl)-piperazine.

2-Bromomethyl-4-nitro-1-pentafluoroethyl-benzene (2.5 g) was dissolved in CH₂Cl₂ and added to N-Boc-piperazine (2.5 g) and NaHCO₃ (1 g) and stirred at RT overnight. The mixture was diluted with CH₂Cl₂ (100 ml), washed with sat'd NH₄Cl, dried over MgSO₄, filtered and concentrated. The residue was purified by silica gel chromatography (hexane, CH₂Cl₂:hexane 2:8) to give the compound as a yellow solid.

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Preparation LX - (4-Boc-piperazin-1-yl)-(3-nitro-5-trifluoromethyl-phenyl)-methanone:

A mixture of 3-nitro-5-trifluoromethyl-benzoic acid (4.13 g), 4-Boc-piperazine (2.97 g), EDC (3.88 g), HOBt (2.74 g) and DIEA (3.33 ml) in CH₂Cl₂ (120 ml) was stirred at RT for 3 h. The mixture was diluted with CH₂Cl₂ (100 ml), washed with sat'd NH₄Cl, dried over MgSO₄, filtered and concentrated. The residue was purified by silica gel chromatography (hexane, CH₂Cl₂:hexane 1:2) to give the compound as a white solid.

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Preparation LXI - 1-Boc-4-(3-nitro-5-trifluoromethyl-benzyl)-piperazine:

(4-Boc-piperazin-1-yl)-(3-nitro-5-trifluoromethyl-phenyl)-methanone (403 mg) was dissolved in THF (6 ml) and BH₃Me₂S (300 µl) was added and the reaction was stirred for 3 h at 60 °C and 2 h at RT. The reaction was quenched with MeOH (5 ml) and NaOH (100 mg) and stirred at RT for 1 h. The mixture was concentrated and dissolved in CH₂Cl₂, washed with sat'd NH₄Cl/NaHCO₃, dried (MgSO₄), filtered and evaporated to give the compound as an oil. M+H 390.3.

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Preparation LXII - 2-Ethyl-4-aminomethyl pyridine:

To a solution of 2-ethyl-4-thiopyridylamide (10 g) in MeOH (250 ml) was added Raney 2800 Nickel (5 g, Aldrich) in one portion. The mixture was stirred at RT for 2 days then at 60 °C for 16 h. The mixture was filtered, concentrated to provide the desired compound.

Preparation LXIII - N-Boc-[2-(4-morpholin-4-yl-butyl)-pyrimidin-4-ylmethyl]-amine:

10 N-Boc-(2-chloropyrimidine)-methylamine (663 mg) and 4-(aminopropyl)morpholine (786 mg) were dissolved in MeOH and concentrated *in vacuo*. The residue was heated at 100 °C for 15 min, forming a solid, which was dissolved in CH₂Cl₂/MeOH then concentrated again and heated 15 min more. The solution was concentrated *in vacuo* and dried under high vacuum, and the resulting solid was triturated with a small amount of IpOH and allowed to settle over a weekend. The solid was filtered, rinsing with a small amount of IpOH, to provide the compound as a white solid.

20

The following compounds were prepared similarly to the procedure outlined above:

a) (4-Bocaminomethyl-pyrimidin-2-yl)-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-amine. M+H 336.5; Calc'd 335.45.

25

Preparation LXIV - 2-fluoronicotinic acid:

In a flame dried 3-necked round bottom flask equipped with a dropping funnel and thermometer, under N₂, THF (250 ml) was added via cannula. LDA (2M in cyclohexane, 54 ml) was added via cannula as the flask was cooled to -78 °C. At -78 °C, 2-fluoropyridine (8.87 ml) was added dropwise over 10 min. The reaction was stirred for 3 h. Condensation was blown off (with N₂) a few cubes of solid CO₂ and they were added to

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the mixture. The mixture was warmed to RT once the solution turned yellow, and it was stirred overnight. The reaction was cooled to 0 °C and the pH was adjusted to ~2.5 with 5N HCl. The mixture was concentrated in vacuo and extracted with EtOAc. The EtOAc layer was washed with brine, dried over MgSO₄, filtered and concentrated to dryness. The resulting solid was taken into a slurry with EtOAc (100 ml), filtered, washed with cold EtOAc and dried at 50 °C for 1 h to afford 2-fluoronictinic acid. M+H 142.1; Calc'd 141.0.

10

Preparation LXV - 4-cyano-2-methoxypyridine:

Under a stream of N₂ and with cooling, Na metal (2.7 g) was added to MeOH (36 ml) with a considerable exotherm. After the Na is dissolved, a solution of 2-chloro-4-cyanopyridine (15 g) in dioxane:MeOH (1:1, 110 ml) was added via dropping funnel over a 10 min period. The reaction was heated to reflux for 3.5 h then cooled at ~10 °C overnight. Solid was filtered off and the solid was washed with MeOH. The filtrate was concentrated to ~60 ml and H₂O (60 ml) was added to redissolve a precipitate. Upon further concentration, a precipitate formed which was washed with H₂O. Further concentration produced additional solids. The solids were combined and dried in vacuo overnight at 35 °C to provide 4-cyano-2-methoxypyridine which was used as is.

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Preparation LXVI - (2-methoxypyridin-4-yl)methylamine:

4-Cyano-2-methoxypyridine (1.7 g) was dissolved in MeOH (50 ml) and conc. HCl (4.96 ml) was added. Pd/C (10%) was added and H₂ was added and let stand overnight. The solids were filtered through Celite® and the cake was washed with MeOH (~250 ml). Concentration in vacuo produced an oil which was dissolved in MeOH (~20 ml). Et₂O (200 ml) was added and stirred for 1 h. The resulting precipitate was filtered and

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washed with Et₂O to afford (2-methoxypyridin-4-yl)methylamine (HCl salt) as an off-white solid.

Preparation LXVII - 2-(4-Amino-phenyl)-2-methyl-propionic acid methyl ester:

2-Methyl-2-(4-nitro-phenyl)-propionic acid methyl ester (2.1 g) was dissolved in THF (70 ml) and AcOH (5 ml) and Zn (10 g) were added. The mixture was stirred for 1 h and filtered through Celite®. The filtrate was rinsed with EtOAc and the organics were evaporated to a residue which was purified on silica gel chromatography (40%EtOAc/hexanes) to provide the desired compound as a yellow oil. M+H 194.

Preparation LXVIII - 1-(2-tert-Butyl-phenyl)-4-methyl-piperazine:

2-tert-Butyl-phenylamine and bis-(2-chloro-ethyl)-methylamine were mixed together with K₂CO₃ (25 g), NaI (10 g) and diglyme (250 mL) and heated at 170 °C for 8 h. The reaction mixture was cooled, the solid filtered and solvent evaporated. The residue was diluted with EtOAc, washed with NaHCO₃ solution, extracted twice more with EtOAc, washed with brine, dried over Na₂SO₄ and evaporated to give the compound as a dark solid.

The following compounds were prepared similarly to the procedure outlined above:

a) 1-Bromo-2-(2-methyl-allyloxy)-4-nitro-benzene was prepared from methallyl bromide.

Preparation LXIX - 3-(1-Methyl-1,2,3,6-tetrahydro-pyridin-4-yl)-5-trifluoromethyl-phenylamine:

3-(5,5-Dimethyl-[1,3,2]dioxaborinan-2-yl)-5-trifluoromethyl-phenylamine (8.8 g, 0.032 mol) was added to trifluoro-

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methanesulfonic acid 1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl ester (7.91 g, 0.032 mol) and 2N Na₂CO₃ aqueous solution (25 mL) was bubbled through N₂ for 5 min. Pd(PPh₃)₄ (3.7 g, 3.2 mmol) was added and the reaction was heated to 80 °C for 16 h. The reaction was cooled to RT and diluted with Et₂O (100 mL). The mixture was filtered through Celite® and the filtrate was washed with NaHCO₃ aqueous solution (25 mL) followed by brine (25 mL). The organic phase was dried over Na₂SO₄ and concentrated *in vacuo*. The desired compound was isolated by passing through silica gel column chromatography (EtOAc, then (2M NH₃) in MeOH/EtOAc) to provide a yellow oil.

Preparation LXX - 3,3-Dimethyl-6-nitro-2,3-dihydro-benzo[d]isothiazole 1,1-dioxide:

3,3-Dimethyl-2,3-dihydro-benzo[d]isothiazole 1,1-dioxide was added to KNO₃ in H₂SO₄ cooled to 0 °C and stirred for 15 min. The reaction was warmed to RT and stirred overnight. The mix was poured into ice and extracted with EtOAc (3x), washed with H₂O and brine, dried and evaporated to give the compound which was used without further purification.

The following compounds were prepared similarly to the procedure outlined above:

a) 1,1,4,4-Tetramethyl-6-nitro-1,2,3,4-tetrahydro-naphthalene

Preparation LXXI - 3-(1-Methyl-1,2,3,4-tetrahydro-pyridin-4-yl)-5-trifluoromethyl-phenylamine:

3-(5,5-Dimethyl-[1,3,2]dioxaborinan-2-yl)-5-trifluoromethyl-phenylamine (1.2 g) was added to trifluoro-methanesulfonic acid 1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl ester (1.0 g), LiCl (500 mg, Aldrich), PPh₃ (300 mg, Aldrich) and 2M Na₂CO₃

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aqueous solution (6 ml) and was bubbled with N₂ for 5 min. Pd(PPh₃)₄ (300 mg, Aldrich) was added and the reaction was heated to 80 °C for 16 h. The reaction was cooled to RT and diluted with Et₂O (100 mL). The mixture was filtered
5 through Celite® and the filtrate was washed with NaHCO₃ aqueous solution (25 ml) followed by brine (25 mL). The organic phase was dried over Na₂SO₄ and concentrated *in vacuo*. The desired compound was isolated by silica gel column chromatography (EtOAc 10% (2M NH₃) in MeOH/EtOAc) to
10 provide yellow oil. M+H 257.2; Calc'd 256.1.

Preparation LXXII - Trifluoromethylsulfonic acid 1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl ester:

In a three-necked round bottom flask equipped with a
15 thermometer and an additional funnel was placed anhydrous THF (200 mL) and 2M LDA (82.8 mL). The solution was cooled to -78 °C and a solution of 1-methyl-piperidin-4-one (20 mL) in anhydrous THF (70 mL) was added drop-wise. The reaction was warmed to -10 °C over 30 min and cooled down again to -
20 78 °C. Tf₂NPh (54.32 g) in 200 mL of anhydrous THF was added through the additional funnel over 30 min and anhydrous THF (30 mL) was added to rinse the funnel. The reaction was warmed to RT and the reaction solution was concentrated *in vacuo*. The residue was dissolved in Et₂O
25 purified on neutral Al₂O₃ column chromatography (Et₂O as elutant). The compound was obtained as orange oil. (20 g)

Preparation LXXIII - 3-(5,5-Dimethyl-[1,3,2]dioxaborinan-2-yl)-5-trifluoromethyl-phenylamine:

30 N₂ was bubbled through a solution of 3-bromo-5-trifluoromethyl-phenylamine (2.38 g), 5,5,5',5'-tetramethyl-[2,2']bi[[1,3,2]dioxaborinanyl] (2.24 g, Frontier Scientific) and KOAc (2.92 g), dppf (165 mg, Aldrich) in anhydrous dioxane (50 ml) for 2 min. PdCl₂ (dppf) (243 mg,

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Aldrich) was added and the reaction was heated to 80°C for 4 h. After cooling to RT, the mix was diluted with 50 mL of Et₂O, filtered through Celite®, and the filtrate was concentrated *in vacuo*. The residue was dissolved in Et₂O (100 mL), washed with sat. NaHCO₃ aqueous solution (50 mL) followed by brine (50 mL). The organic phase was dried over Na₂SO₄ and concentrated *in vacuo*. The residue was dissolved in 3:2 Et₂O/Hex (100 mL), filtered through Celite® and the filtrate was concentrated *in vacuo* to afford a dark brown semi-solid.

Preparation LXXIV - 1-Boc-3-Hydroxymethyl-azetidine:

A solution of 1-Boc-azetidine-3-carboxylic acid (1.6 g) and Et₃N (2 ml) in anhydrous THF (60 ml) was cooled to 0°C. Isopropyl chloroformate (1.3 g) was added via a syringe slowly; forming a white precipitate almost immediately. The reaction was stirred for 1 h at 0 °C and the precipitate was filtered out. The filtrate was cooled to 0 °C again and aqueous NaBH₄ solution (900 mg, 5 ml) was added via pipette and stirred for 1 h. The reaction was quenched with NaHCO₃ solution (50 mL) and the compound was extracted with EtOAc (200 mL). The organic phase was washed with brine (50 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The residue was dissolved in EtOAc and passed through a short silica gel pad. Concentrating the filtrate *in vacuo* provided the compound as a light yellow oil.

Preparation LXXV - 1-Boc-3-(3-nitro-5-trifluoromethyl-phenoxy)methyl-azetidine:

A mixture of 1-Boc-3-methylsulfonyloxymethyl-azetidine (1.47 g), 3-nitro-5-trifluoromethyl-phenol (1.15 g) and K₂CO₃ (1.15 g) in DMF (20 ml) at 80 °C was stirred overnight. The reaction was cooled to RT and diluted with 25 mL of sat. NaHCO₃ and 50 mL of EtOAc. The organic phase was separated

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and washed with brine (25 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The crude compound was purified by column chromatography (50% EtOAc/hex).

5 **Preparation LXXVI - 2,2-Dimethyl-6-nitro-3,4-dihydro-2H-benzo[1,4]oxazine:**

2,2-Dimethyl-6-nitro-4H-benzo[1,4]oxazin-3-one was added to BH₃-THF complex (Aldrich) in THF with ice cooling. The mixture was heated to reflux for 2 h then carefully diluted
10 with 12 mL of MeOH and heated to reflux for an additional 1 h. Concentrated HCl (12 mL) was added and heated to reflux for 1 h. The mixture was concentrated and the resulting solid was suspended in a dilute aqueous solution of NaOH (1 M) and extracted with EtOAc (100 mL x 4). The organic
15 layers were washed with H₂O and dried over MgSO₄. Evaporation of solvent gave a yellow solid.

Preparation LXXVII - 2,2,4-Trimethyl-6-nitro-4H-benzo[1,4]oxazin-3-one:

20 2,2-Dimethyl-6-nitro-4H-benzo[1,4]oxazin-3-one (1.1 g) was mixed with MeI (850 mg, Aldrich), K₂CO₃ (1.38 g, Aldrich) and DMF (30 mL, Aldrich) at 40°C for 48 h. The DMF was removed *in vacuo* and the residue was diluted with EtOAc (80 mL). The organic phase was washed with H₂O (50 mL), aqueous
25 Na₂SO₃ (50 mL) and brine (50 mL). The resulting solution was dried (MgSO₄) and concentrated to provide the compound which was used as is for the next reaction step.

30 **Preparation LXXVIII - 2-Bromo-N-(2-hydroxy-5-nitro-phenyl)-2-methyl-propionamide:**

2-Amino-4-nitro-phenol (3.08 g, Aldrich) was stirred with THF (30 mL, Aldrich) in an ice bath. 2-Bromo-2-methyl-propionyl bromide (2.47 mL, Aldrich) and Et₃N (2.0 g, Aldrich) was slowly added via syringe. The mixture was

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stirred for 45 min then poured into ice. The aqueous phase was extracted by EtOAc (50 mL x 4). The organic layer was dried and concentrated. The desired compound was crystallized from EtOAc (*Chem. Pharm. Bull* 1996, 44(1) 103-114).

Preparation LXXIX - 2,2-Dimethyl-6-nitro-4H-benzo[1,4]oxazin-3-one:

2-Bromo-N-(2-hydroxy-5-nitro-phenyl)-2-methyl-propionamide was mixed with K_2CO_3 in 20 mL of DMF and stirred overnight at 50°C. The reaction mixture was poured into ice H₂O. The precipitate was collected by filtration and washed with H₂O. The crude compound was recrystallized from EtOH.

Preparation LXXX -4-[1-(2-Bromo-4-nitro-phenyl)-1-methyl-ethyl]-1-methyl-pyridinium iodide:

1-Methyl-4-[1-methyl-1-(4-nitro-phenyl)-ethyl]-pyridinium (8 g) was dissolved in glacial HOAc (10 ml) then diluted with H₂SO₄ (50 ml), then NBS (3.8 g) was added. After 1 h, additional NBS (1.2 g) was added, 30 min later another 0.5 g of NBS, then 15 min later 200 mg more NBS. After 1 h, the mixture was neutralized with NH₄OH (conc.) with ice bath cooling. The neutralized mixture was then concentrated and used as is.

Preparation LXXXI - 4-[1-(2-Bromo-4-nitro-phenyl)-1-methyl-ethyl]-1-methyl-1,2,3,6-tetrahydro-pyridine:

4-[1-(2-Bromo-4-nitro-phenyl)-1-methyl-ethyl]-1-methyl-pyridiniumiodide was mixed with MeOH (400 ml) and CH₂Cl₂ (200 ml), then treated with NaBH₄ (2.5 g) in portions. After stirring at RT for 2 h, the mixture was extracted with CH₂Cl₂ (300 mL x 3). The CH₂Cl₂ layer was washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*, to provide the desired compound.

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Preparation LXXXII - 1-Methyl-4-[1-methyl-1-(4-nitro-phenyl)-ethyl]-pyridinium iodide:

4-(4-Nitro-benzyl)-pyridine (4.3 g) was mixed with MeI (4
5 ml, 9.12 g)/NaOH (5N, 30 ml), Bu₄NI (150 mg) and CH₂Cl₂ (50
ml) and stirred at RT overnight. Additional MeI (2 mL) was
added along with 50 mL of NaOH (5N). 6 h later, more MeI (2
mL) was added. The mixture was stirred at RT over the
weekend. The mixture was cooled on ice bath and the base
10 was neutralized by conc. HCl (aq) addition dropwise to pH 7.
The compound was used as is.

Preparation LXXXIII - 1-Methyl-4-(4-nitro-benzyl)-1,2,3,6-tetrahydro-pyridine:

15 4-(4-Nitrobenzyl)pyridine (64 g) and TBAI (6 g) were
dissolved in CH₂Cl₂ (500 mL) and the solution was suspended
with NaOH (aq. 5N, 450 mL) in a 3L 3-necked round bottom
flask. With vigorous stirring, CH₃I (213 g) was added and
stirred vigorously at RT for 60 h (or until blue color
20 disappears). The reaction was quenched with dimethylamine
(100 mL) and MeOH (300 mL) and stirred for 2 h. NaBH₄ (19
g) was added to the mixture in small portions. The reaction
mixture was stirred for 30 min at RT, then partitioned
between CH₂Cl₂/H₂O (500 mL/500 mL). The organic layer was
25 collected and the aqueous layer was washed with CH₂Cl₂ (300
mL x 3). The combined organic layers was washed with brine
then concentrated in vacuo. The residue was purified on a
silica wash-column (7% TEA in EtOAc). The desired fractions
were combined and concentrated under vacuum to give the
30 desired compound as a dark gray solid. (MS: M+1=261).

Preparation LXXXIV - 1-Boc-4-formylpiperidine:

4A Molecular sieves were heated to 100 °C and a vacuum was
applied. They were cooled to RT and purged with N₂. CH₂Cl₂

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(420 ml) and CH₃CN (40 ml), NMO (40 g) and 1-Boc-4-hydroxymethylpiperidine (50 g) were added and the mix was stirred for 5 min then cooled to 15 °C. TPAP (4.1 g) is added and an exotherm was observed. The reaction was maintained at RT with external cooling. The reaction was stirred at RT for 3 h, filtered, concentrated, diluted with 50% EtOAc/hexanes and purified on a silica gel plug (50%EtOAc/hexanes). The eluant fractions were concentrated to afford a yellow oil.

10

Preparation LXXXV 2-Chloro-4-cyanopyridine:

2-Chloro-4-cyanopyridine was prepared similar to the method described by Daves et al., J. Het. Chem., 1, 130-32 (1964).

15 **Preparation LXXXVI 4-(2-tert-Butyl-5-nitro-phenyl)-but-3-en-1-ol:**

A mix of 1-(tert-butyl)-2-bromo-4-nitrobenzene (3.652 g), TEA (5.92 ml), 3-buten-1-ol (5.48 ml), Pd(OAc)₂ (32 mg), Pd(PPh₃)₄ (327 mg) and toluene (40 ml) was degassed with nitrogen and heated in a sealed vessel for 16 h at 120 °C. The next day, the reaction mixture was cooled to RT, filtered, and concentrated in vacuo. The crude was eluted on a silica gel column with 15% to 22% EtOAc/hexanes gradient system to yield a yellow-brown oil.

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Preparation LXXXVII 4-(2-tert-Butyl-5-nitro-phenyl)-but-3-enal:

4-(2-tert-Butyl-5-nitro-phenyl)-but-3-en-1-ol (1.024 g) was dissolved in 10 ml of CH₂Cl₂ and added dropwise over 5 min to a -78 °C mix of oxalyl chloride (0.645 ml), DMSO (0.583 ml), and 10 ml CH₂Cl₂. The reaction was stirred at -78 °C for 1 h, then treated with a solution of TEA (1.52 ml) in 7 ml CH₂Cl₂ and stirred at -78 °C for an additional 25 min, then warmed to -30 °C for 35 min. The reaction was treated

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with 50 ml of saturated aqueous NH_4Cl , diluted with H_2O and extracted with EtOAc. The organic layer was brine-washed, dried over Na_2SO_4 , filtered, and concentrated in vacuo to yield a yellow oil which was used as is in Preparation LXXXVIII.

Preparation LXXXVIII 1-[4-(2-tert-Butyl-5-nitro-phenyl)-but-3-enyl]-pyrrolidine:

4-(2-tert-Butyl-5-nitro-phenyl)-but-3-enal (895 mg) was dissolved in 40 ml THF, and to the solution was added pyrrolidine (0.317 ml). To the deep orange solution was added $\text{NaBH}(\text{OAc})_3$ (1.151 g) and glacial AcOH (0.207 ml). The reaction was stirred at RT overnight, then treated with saturated aqueous NaHCO_3 and diluted with Et_2O and some 1N NaOH. The layers were separated, and the organic layer was extracted with aqueous 2N HCl. The acidic aqueous layer was basified to $\text{pH} > 12$ with 6 N NaOH, extracted with Et_2O , brine-washed, dried over Na_2SO_4 , filtered, and concentrated in vacuo to provide 1-[4-(2-tert-butyl-5-nitro-phenyl)-but-3-enyl]-pyrrolidine as a orange-brown oil.

Preparation LXXXVIX - N-Boc-(2-chloropyrimidin-4-yl)-methylamine:

To 2-chloropyrimidine-4-carbonitrile [2.5 g, prepared by the procedure of Daves et. al. [*J. Het. Chem.* 1964, 1, 130-132)] in EtOH (250 ml) under N_2 was added Boc_2O (7.3 g). After the mixture was briefly placed under high vacuum and flushed with N_2 , 10% Pd/C (219 mg) was added. H_2 was bubbled through the mixture (using balloon pressure with a needle outlet) as it stirred 4.2 h at RT. After filtration through Celite®, addition of 1.0 g additional Boc_2O , and concentration, the residue was purified by silica gel chromatography (5:1 → 4:1 hexanes/EtOAc) to obtain N-Boc-(2-chloropyrimidin-4-yl)-methylamine.

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Preparation XC - Methanesulfonic acid 1-Boc-azetidin-3-ylmethyl ester:

To a solution of (1-Boc-azetidin-3-yl)-methanol (1.06 g, 5.7 mmol), TEA (1.18 mL, 8.52 mmol) in CH₂Cl₂ at 0 °C was added MeSO₂Cl (0.53 mL, 6.82 mmol) via a syringe. The reaction was warmed to RT over 2 h and stirring was continued at RT for 2 h. The white solid formed was removed by filtration and the filtrate was washed with 25 mL of H₂O. The organic phase was dried over Na₂SO₄, and concentrated *in vacuo* to afford yellow oil.

Preparation XCI - N-(2-bromo-5-nitrophenyl)acetamide:

2-Bromo-5-nitroaniline (10 g) was dissolved in 500 mL of CH₂Cl₂, DIEA (6.6 g) was added to the mixture, followed by DMAP (100 mg). The mixture was cooled to 0 °C in ice bath. Acetyl chloride (4 g in 50 mL CH₂Cl₂) was added dropwise to the reaction mixture. After the mixture was stirred at RT over 3 h, extracted once with saturated NaHCO₃ solution and once with brine, the resulting organic layer was dried over MgSO₄, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel with 1:1 EtOAc:Hexane to 100% EtOAc to afford N-(2-bromo-5-nitrophenyl)acetamide as a white solid. MS: 258 (M-1). Calc'd. for C₈H₇BrN₂O₃-259.06.

Preparation XCII - N-(2-bromo-5-nitrophenyl)-N-(2-methylprop-2-enyl)acetamide:

A suspension of 2 g NaH (95% powder) in anhydrous DMF (100 mL) was cooled to -78 °C, N-(2-bromo-5-nitrophenyl)acetamide (7 g) in dry DMF (50 mL) was added to the mixture under N₂ atmosphere. After the mixture was warmed to 0 °C, 3-bromo-2-methylpropene (7.3 g in 20 dry DMF) was added to the mixture. The mixture was stirred at RT overnight. The

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mixture was poured into a container of ice and extracted between saturated NaHCO_3 solution and EtOAc. The resulting organic layer was dried over MgSO_4 , filtered and concentrated in vacuo. The crude material was purified by
5 flash chromatography on silica gel with 7:2 hexane:EtOAc to afford the title compound as a yellow gum. MS: 314 (M+1). Calc'd. for $\text{C}_{12}\text{H}_{13}\text{BrN}_2\text{O}_3$ -313.15.

10 **Preparation XCIII - 1-(3,3-dimethyl-6-nitro-2,3-dihydro-indol-1-yl)ethanone:**

N-(2-Bromo-5-nitrophenyl)-N-(2-methylprop-2-enyl)acetamide (4.5 g) was dissolved in anhydrous DMF (50 mL), tetraethylammonium chloride (2.5 g), sodium formate (1.2 g), NaOAc (3 g) were added, and the resulting mixture was bubbled with N_2
15 gas for 10 min. $\text{Pd}(\text{OAc})_2$ (350 mg) was added and the mixture was heated at 80 °C under N_2 atmosphere overnight. After the mixture was concentrated in vacuo, it was partitioned between saturated NaHCO_3 solution and EtOAc, the resulting organic layer was dried over MgSO_4 , filtered and
20 concentrated in vacuo. The crude material was purified by flash chromatography on silica gel with 2:1 Hexane:EtOAc to afford the title compound as a yellow gum. MS: 235 (M+1). Calc'd. for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_3$ -234.25.

25 **Preparation XCIV - 3,3-dimethyl-6-nitroindoline:**

1-(3,3-Dimethyl-6-nitro-2,3-dihydro-indol-1-yl)ethanone (1.8 g) was dissolved in EtOH (50 mL), 12N HCl (50 mL) was added and the resulting mixture was heated at 70 °C overnight. After the mixture was concentrated in vacuo, it was
30 partitioned between saturated NaHCO_3 solution and EtOAc, the resulting organic layer was dried over MgSO_4 , filtered and concentrated in vacuo to afford a yellow solid. MS: 193 (M+1). Calc'd. for $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_2$ -192.21.

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Preparation XCV - 1-Acetyl-6-amino-3,3-dimethylindoline

1-(3,3-Dimethyl-6-nitro-2,3-dihydro-indol-1-yl)ethanone (250 mg) was dissolved in MeOH (20 mL), the mixture was bubbled with H₂ for 10 min. 10% Pd/C (50 mg) was added and the mixture was stirred under H₂ overnight. The mixture was filtered through Celite® and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel with 1:1 EtOAc:CH₂Cl₂ to afford the title compound as a white crystalline material. MS: 205 (M+1).
Calc'd. for C₁₂H₁₆N₂O-204.27.

Preparation XCVI - 4-(1,1,2,2,3,3,4,4,4-nonafluorobutyl)phenylamine:

4-Nitro-(1,1,2,2,3,3,4,4,4-nonafluorobutyl)benzene was synthesized by a method analogous to that described by Gregory, W. A. et al. (J. Med. Chem, 1990, 33(9) 2569 - 2578). The mixture of the above nitro intermediate (1.0 mmol), iron powder (5.0 mmol) and NH₄Cl (0.7 mmol) in EtOH (3 mL) and H₂O (3 mL) was stirred for 4 h at 80°C. Filtration and concentration gave the crude title compound, which was used without further purification.

Preparation XCVII - 2-bromo-1-tert-butyl-4-nitrobenzene:

NBS (125.0 g, 697.5 mmol, 1.5 eq) was slowly added to a solution of TFA:H₂SO₄ (5:1, 750 mL) and tert-butyl-4-nitrobenzene (100.0 g, 558.0 mmol) at RT. The solution was stirred for 24 h and poured over 5 kg of ice. The resulting suspension was filtered and washed with a 1:1 MeOH:H₂O solution (200 mL) and dried in a vacuum oven. MS (ES+): 258.1, 260.1 (M+H)⁺. Calc'd for C₁₀H₁₂BrNO₂: 257.0.

Preparation XCVIII - 4-(2-tert-butyl-5-nitrophenyl)pyridine:

To a solution of 2-bromo-1-tert-butyl-4-nitrobenzene (8.6 g, 33.3 mmol) and toluene (70 mL) in a 150 mL round bottom

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flask, 4-pyridylboronic acid (4.5 g, 36.6 mmol, 1.1 eq), Pd(PPh₃)₄ (3.8 g, 3.3 mmol, 0.1 eq) and K₂CO₃ (13.8 g, 99.9 mmol, 3 eq) were added. The solution was stirred for 24 h at 80°C before cooling to RT. The solution was filtered
5 through a pad of Celite® and purified by silica flash chromatography (30% EtOAc/Hexanes). This afforded the desired compound as a yellow solid. MS (ES⁺): 257.2 (M+H)⁺; (ES⁻): 255.2 (M-H)⁻. Calc'd for C₁₅H₁₆N₂O₂: 256.1.

10 **Preparation XCIX - 4-(2-tert-butyl-5-nitrophenyl)-1-methylpyridinium:**

4-(2-tert-Butyl-5-nitrophenyl)pyridine (2.0 g, 7.8 mmol) was added to a round-bottom flask and dissolved in EtOH (10 mL). CH₃I (30 mL) was added to the flask which was placed in a
15 80°C sand bath and heated to reflux. After 6 h, the solution was cooled to RT and the excess CH₃I and EtOH were stripped-off under reduced pressure resulting in the desired compound as a light brown solid. MS (ES⁺): 271.2 (M+H)⁺; (ES⁻): 269.2 (M-H)⁻. Calc'd for C₁₆H₁₉N₂O₂⁺: 271.1.

20

Preparation C - 4-tert-butyl-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)aniline:

4-(2-tert-Butyl-5-nitrophenyl)-1-methylpyridinium (2.1 g, 7.8 mmol, Step C) was added to a 100 mL round-bottom flask and dissolved in a 10% H₂O/EtOH mixture. To the flask iron
25 dust (1.31 g, 23.4 mmol, 3 eq) and NH₄Cl (460 mg, 8.6 mmol, 1.1 eq) were added. The flask was placed in a 100°C sand bath and heated to reflux. After 2 h, the solution was cooled to RT and filtered through a pad of Celite®. The
30 resulting solution was stripped down to a yellow solid and redissolved in MeOH (20 mL, anhydrous). The solution was cooled to 0°C by placing it in an ice bath and slowly adding NaBH₄ (450 mg, 11.7 mmol, 1.5 eq). After addition of the NaBH₄, the solution was cooled to RT and stirred for 30 min.

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The solvent was stripped-off under vacuum and the solid was redissolved in CH_2Cl_2 and filtered. The solution was concentrated *in vacuo* to afford an amorphous clear yellow solid. MS (ES⁺): 245.2 (M+H)⁺. Calc'd for $\text{C}_{16}\text{H}_{24}\text{N}_2$: 244.2.

5

Preparation CI - [1-(4-amino-phenyl)-ethyl]carbamic acid tert-butyl ester:

A mixture of 1-(S)-1-(4-nitrophenyl)ethylamine hydrochloride (2 g), Boc_2O (2.6 g) and NaHCO_3 (3 g) in $\text{MeOH}/\text{H}_2\text{O}$ (1:1, 200 ml) was stirred at RT overnight. The reaction was extracted with EtOAc twice then washed with H_2O followed by brine. The organic layer was dried with Na_2SO_4 and evaporated under reduced pressure to give the protected nitrophenyl ethylamine. Boc-1-(S)-1-(4 nitrophenyl)ethylamine (1 g) was hydrogenated by H_2 atmosphere in the presence of Pd/C (200 mg) to give Boc protected aniline (0.8 g). The intermediate was deprotected with 4N HCl/dioxane to give the title compound as the HCl salt.

20 **Preparation CII - 1-[2-(tert-butyl)-5-aminophenyl]-4-methylpiperazine:**

A mixture of 2-t-butylaniline (5.4 g) and methylchlorethylamine hydrochloride (7 g) and K_2CO_3 (5 g) in NaI (2 g) in diglyme (150 m) was heated at 170 °C for 8 h. The reaction was filtered and the filtrate was evaporated under high vacuum. The residue was mixed with EtOAc (200 ml) and H_2O (200 ml) and extracted with EtOAc twice. The combined organic layer was washed with brine and dried over Na_2SO_4 and evaporated to give crude 1-[2-(tert-butylphenyl)]-4-methylpiperazine. The crude 1-[2-(tert-butylphenyl)]-4-methylpiperazine (260 mg) was stirred with H_2SO_4 (3 ml) at 0°C and HNO_3 (1.2 ml, 70%) was slowly added to the reaction. The reaction was warmed to RT, stirred for 30 min, poured on ice and basified with K_2CO_3 slowly. The solution was

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extracted with EtOAc three times, washed with H₂O, followed by brine, dried over Na₂SO₄ and evaporated under reduced pressure. The residue was purified by column chromatography to give 1-[2-(tert-butyl)-5-nitrophenyl]-4-methylpiperazine (260 mg), which was hydrogenated under H₂ atmosphere to give 1-[2-(tert-butyl)-5-aminophenyl]-4-methylpiperazine.

The following compounds were prepared similarly to the procedure outlined above:

10

a) 1-(5-aminophenyl)-4-methylpiperazine

Preparation CIII - 4-(tert-butyl)-2-(4-methylpiperazinyl)phenylamine:

15 A mixture of 1-(tert-butyl)-2-bromo-4-nitrobenzene (3 g) and N-methylpiperazine (8 g) was heated neat at 130 °C for 4 h. The residue was purified by column chromatography to give 1-[4-bromo-5-(tert-butyl)-2-nitrophenyl]-4-methylpiperazine, which was hydrogenated to furnish 4-(tert-butyl)-2-(4-methylpiperazinyl)-phenylamine.

20

Preparation CIV - {2-[4-(tert-butyl)-2-aminophenoxy]ethyl}dimethylamine:

DEAD (2.6 ml) was added to a mixture of 2-nitro-4-tert-butylphenol (2 g) and N,N-dimethylethanolamine (1.3 g) and Ph₃P (4 g) in THF (50 ml). The reaction was stirred at RT for 1 h, diluted with EtOAc (50 ml) and washed with 1 N HCl twice. The aqueous layer was basified with NaHCO₃, extracted with EtOAc twice and washed with H₂O and brine. The organic layer was dried over Na₂SO₄ and evaporated to give {2-[4-(tert-butyl)-2-nitrophenoxy]ethyl}-dimethylamine. It was hydrogenated under H₂ atmosphere to give {2-[4-(tert-butyl)-2-aminophenoxy]ethyl}-dimethylamine.

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The following compounds were prepared similarly to the procedure outlined above:

a) [2-(2-aminophenoxy)ethyl]-dimethylamine.

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Preparation CV - 2-amino-5,6,7-trihydro-1,2,4-triazolo[3,4-a]isoquinoline:

7-Nitro-2,3,4-trihydroisoquinolin-1-one (500 mg) was heated in POCl₃ (10 ml) to reflux for 8 h. The mixture was
10 evaporated, mixed with toluene and evaporated again. The residue was dissolved in THF, H₂NNH₂ (1 ml) was slowly added to the reaction and stirred for 2 h. The reaction was evaporated, heated with HC(OEt)₃ (15 ml) at 115°C for 2 h, extracted with EtOAc and hydrogenated to give 2-amino-5,6,7-
15 trihydro-1,2,4-triazolo[3,4-a]isoquinoline.

Preparation CVI - tert-butyl 4-[(6-nitro-3,3-dimethylindolinyl)methyl]piperidinecarboxylate:

3,3-Dimethyl-6-nitroindoline (450 mg) was dissolved in 20 mL
20 of dichloroethane, N-boc-4-formylpiperidine (750 mg) was added to the mixture, followed by 2 g NaHB(OAc)₃ and 1 mL of glacial AcOH. The mixture was stirred at RT overnight. Saturated NaHCO₃ solution (20 mL) was added to the reaction mixture and stirred for 1 h. The resulting mixture was
25 separated by separation funnel, the organic layer was extracted once with saturated NaHCO₃ solution and once with brine. The resulting organic layer was dried over MgSO₄, filtered and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel with 9:1
30 Hexane:EtOAc to afford an orange oil. MS: 290 (M-99).
Calc'd. for C₂₁H₃₁N₃O₄ - 389.5.

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Preparation CVII - 3,3-dimethyl-1-piperidin-4-ylmethyl-2,3-dihydro-1H-indol-6-ylamine:

tert-Butyl 4-[(6-nitro-3,3-dimethylindolinyl)-methyl]piperidinecarboxylate (900 mg) was dissolved in 10 mL MeOH, the mixture was bubbled with H₂ for 10 min. 10% Pd/C (30 mg) was added and the mixture was stirred under H₂ overnight. The mixture was filtered through Celite® and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel with 1:1 Hexane:EtOAc to afford a colorless oil. MS: 360 (M+1). Calc'd. for C₂₁H₃₃N₃O₂ - 359.5.

Preparation CVIII - (2-chloro-(3-pyridyl))-N-(4-phenoxyphenyl)carboxamide:

2-Chloronicotinoyl chloride (9.15 g, 0.052 mol) was added to a stirred solution of 4-phenoxyaniline (10 g, 0.054 mol) and DIEA (10 mL, 0.057 mol) in CH₂Cl₂ (100 mL) at RT. The mixture was stirred for 48 h before removal of solvent under reduced pressure. The resulting residue was dissolved in EtOAc and washed several times with saturated NaHCO₃ aqueous solution and brine, respectively. The organic layer was dried over Na₂SO₄ and evaporated to leave a solid. This material was re-crystallized from EtOAc/Hexane mixture, followed by filtration and rinsing with Et₂O to give the desired compound as a white solid. MS m/z: 325 (M+1); 323 (M-1).

Preparation CIX - 1-(1-methyl(4-piperidyl))-6-nitroindoline:

6-Nitroindoline (5 g) was dissolved in 200 mL of dichloroethane. N-Methyl-4-piperidone (5 g) was added to the mixture, followed by NaHB(OAc)₃ (12 g) and 1 mL of glacial AcOH. The mixture was stirred at RT overnight. A saturated NaHCO₃ (200 mL) solution was added to the reaction mixture and stirred for 1 h. The resulting mixture was separated by

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separation funnel. The organic layer was extracted once with saturated NaHCO_3 solution and once with brine. The resulting organic layer was dried over MgSO_4 , filtered and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel with 2:1 EtOAc:MeOH to afford orange oil. MS: 262 (M+1). Calc'd. for $\text{C}_{14}\text{H}_{19}\text{N}_3\text{O}_2$ - 261.3.

Preparation CX - 1-(1-methyl-4-piperidyl)indoline-6-ylamine:

1- (1-Methyl(4-piperidyl))-6-nitroindoline (3 g) was dissolved in 100 mL MeOH and the mixture was bubbled with H_2 for 10 min. 10% Pd/C (200 mg) was added and the mixture was stirred under H_2 overnight. The mixture was filtered through Celite® and concentrated in vacuo to afford light yellow oil. MS: 232 (M+1). Calc'd. for $\text{C}_{14}\text{H}_{21}\text{N}_3$ - 231.3.

Preparation CXI - N-(2-bromo-5-nitrophenyl)acetamide:

2-Bromo-5-nitroaniline (10 g) was dissolved in CH_2Cl_2 (500 mL), DIEA (6.6 g) was added to the mixture, followed by 100 mg of DMAP. The mixture was cooled to 0 °C in ice bath. Acetyl chloride (4 g in 50 mL CH_2Cl_2) was added dropwise to the reaction mixture, which was then stirred at RT over 3 h, and extracted once with saturated NaHCO_3 solution and once with brine. The separated organic layer was dried over MgSO_4 , filtered and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel with 1:1 EtOAc:Hexane to 100% EtOAc to afford a white solid. MS: 258 (M-1). Calc'd. for $\text{C}_8\text{H}_7\text{BrN}_2\text{O}_3$ - 259.1.

Preparation CXII - N-(2-bromo-5-nitrophenyl)-N-(2-methylprop-2-enyl)acetamide:

A suspension of NaH (2 g) (95% powder) in 100 mL anhydrous DMF was cooled to -78 °C, and N-(2-bromo-5-nitrophenyl)acetamide (7 g) in 50 mL dry DMF was added to

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the mixture under N₂. After the mixture was warmed to 0°C, 3-bromo-2-methylpropene (7.3 g in 20 dry DMF) was added to the mixture. The mixture was stirred at RT overnight. The mixture was poured into a container of ice and extracted
5 between saturated NaHCO₃ solution and EtOAc. The resulting organic layer was dried over MgSO₄, filtered and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel with 7:2 Hexane:EtOAc to afford a yellow gum. MS: 314 (M+1). Calc'd. for C₁₂H₁₃BrN₂O₃
10 - 313.1.

Preparation CXIII - 1-(3,3-dimethyl-6-nitro-2,3-dihydro-indol-1-yl)ethanone:

N-(2-Bromo-5-nitrophenyl)-N-(2-methylprop-2-enyl)acetamide
15 (4.5 g) was dissolved in 50 mL anhydrous DMF, 2.5 g tetraethyl-ammonium chloride, 1.2 g sodium formate, 3 g sodium acetate were added, the resulting mixture was bubbled with N₂ gas for 10 min. Pd(OAc)₂ (350 mg) was added and the mixture was heated at 80 °C under N₂ overnight. After the
20 mixture was concentrated in vacuo, it was extracted between saturated NaHCO₃ solution and EtOAc, the resulting organic layer was dried over MgSO₄, filtered and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel with 2:1 Hexane:EtOAc to afford
25 a yellow gum. MS: 235 (M+1). Calc'd. for C₁₂H₁₄N₂O₃ - 234.2.

Preparation CXIV - 3,3-dimethyl-6-nitroindoline:

1-(3,3-Dimethyl-6-nitro-2,3-dihydro-indol-1-yl)ethanone (1.8 g) was dissolved in 50 mL EtOH, 50 mL 12N HCl was added and
30 the resulting mixture was heated at 70 °C overnight. After the mixture was concentrated in vacuo, it was extracted between saturated NaHCO₃ solution and EtOAc. The resulting organic layer was dried over MgSO₄, filtered and

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concentrated in vacuo to afford a yellow solid. MS: 193 (M+1). Calc'd. for $C_{10}H_{12}N_2O_2$ - 192.2.

**Preparation CXV - 3,3-dimethyl-1-(4-methyl-piperazin-1-yl)-
5 6-nitro-2,3-dihydro-1H-indole:**

3,3-Dimethyl-6-nitroindoline (0.8 g) was dissolved in 50 mL of dichloroethane, N-methyl-4-piperidone (1 g) was added to the mixture, followed by 2.5 g $NaHB(OAc)_3$ and 1 mL of glacial AcOH. The mixture was stirred at RT overnight.
10 Saturated $NaHCO_3$ solution (50 mL) was added to the mixture and stirred for 1 h. The resulting mixture was separated by separation funnel, the organic layer was extracted once with saturated $NaHCO_3$ solution and once with brine, the resulting organic layer was dried over $MgSO_4$, filtered and
15 concentrated in vacuo. The crude material was purified by flash chromatography on silica gel with 9:1 EtOAc:MeOH to afford an orange oil. MS: 290 (M+1). Calc'd. for $C_{16}H_{23}N_3O_2$ - 289.4.

**Preparation CXVI - 3,3-dimethyl-1-(1-methyl(4-
20 piperidyl))indoline-6-ylamine:**

3,3-Dimethyl-1-(4-methyl-piperazin-1-yl)-6-nitro-2,3-dihydro-1H-indole (600 mg) was dissolved in 20 mL MeOH, the mixture was bubbled with H_2 for 10 min. 10% Pd/C (100 mg)
25 was added and the mixture was stirred under H_2 . The mixture was filtered through Celite® and concentrated in vacuo to afford an oil. MS: 260 (M+1). Calc'd. for $C_{16}H_{25}N_3$ - 259.4.

**Preparation CXVII - 3-(1-methyl-1,2,3,6-tetrahydro-pyridin-
30 4-yl)-5-nitro-1H-indole:**

5-Nitroindole (2.6 g) was dissolved in 100 mL anhydrous MeOH, followed by 5 g N-methyl-4-piperidone and NaOMe (5 g) powder. The mixture was heated to reflux under N_2 overnight. The mixture was concentrated in vacuo, and was extracted

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between saturated NaHCO_3 solution and EtOAc. The resulting organic layer was dried over MgSO_4 , filtered and concentrated in vacuo to afford a yellow solid. This solid was washed with 5 mL EtOAc and 2 mL MeOH to afford a bright yellow solid. MS: 258 (M+1). Calc'd. for $\text{C}_{14}\text{H}_{15}\text{N}_3\text{O}_2$ - 257.29.

Preparation CXVIII - 3-(1-methyl-4-piperidyl)indole-5-ylamine:

3-(1-Methyl-1,2,3,6-tetrahydro-pyridin-4-yl)-5-nitro-1H-indole (2.7 g) was dissolved in 50 mL MeOH, the mixture was bubbled with H_2 for 10 min. 10% Pd/C (150 mg) was added and the mixture and stirred under H_2 overnight. The mixture was filtered through Celite® and concentrated in vacuo to afford a yellow oil. MS: 230 (M+1). Calc'd. for $\text{C}_{14}\text{H}_{19}\text{N}_3$ - 229.3.

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Preparation CXIX - {3-[3-amino-5-(trifluoromethyl)phenyl]propynyl}dimethylamine:

A mixture of 3-bromo-5-trifluoromethylaniline (1.4 g, 5.9 mmol), 1-dimethylamino-2-propyne (1.3 mL, 0.76 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (0.26 g, 0.29 mmol) and CuI (114 mg, 0.60 mmol) in 10 mL of TEA was heated at 100 °C in a sealed tube for 3 h. The resulting mixture was filtered over Celite®. The filtrate was concentrated, and the residue was purified by prep-HPLC (reverse phase) to give the aniline. MS (ES+): 243 (M+H)⁺; (ES-): 241 (M-H)⁻. Calc'd $\text{C}_{12}\text{H}_{13}\text{F}_3\text{N}_2$ - 242.24.

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Preparation CXX - {3-[3-amino-5-(trifluoromethyl)phenyl]propyl}dimethylamine:

A mixture of {3-[3-amino-5-(trifluoromethyl)phenyl]propyl}dimethylamine (7 g, 29 mmol) and $\text{Pd}(\text{OH})_2$ (0.5 g) in 250 mL of MeOH was stirred under 50 psi H_2 . After 2 h, the resulting mixture was filtered over Celite®. The filtrate was concentrated, and the residue was diluted with aq. 1N HCl. The aq. layer was washed with Et_2O , made basic

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with aq. 5N NaOH, and extracted with CH₂Cl₂. The organic solution was dried over Na₂SO₄ and concentrated to give the titled compound. MS (ES⁺): 386 (M+H)⁺; (ES⁻): 384 (M-H)⁻. Calc'd C₁₈H₁₉ClF₃N₃O - 385.8.

5

Preparation CXXI - 4,4,5,5-tetramethyl-2-(1-methyl(4-1,2,5,6-tetrahydropyridyl))-1,3,2-dioxaborolane:

To a solution of LiHMDS (25 mL, 25 mmol, 1.0 M in THF) in 35 mL of THF was added 1-methyl-4-piperidinone (3.0 mL, 25 mmol) at -78 °C. The resulting solution was stirred for 2 h, then Tf₂NPh (8.9 g, 25 mmol) was added. The resulting solution was warmed to RT and stirred for 2 h. The mixture was concentrated, and the residue was purified by alumina (neutral) chromatography to give 1-methyl-4-(1,2,5,6-tetrahydro)pyridyl-(trifluoromethyl) sulfonate. A mixture of above triflate (5.0 g, 20 mmol), bis(pinacolato)diboron (5.6 g, 22 mmol), potassium acetate (6.5 g, 66 mmol), PdCl₂dppf (0.44g, 0.6mmol), and (dppf)₂ (0.33g, 0.6 mmol) in 60 mL of dioxane was heated at 80 °C for 4 h. The resulting mixture was cooled to RT, diluted with Et₂O (150 mL). The ethereal solution was washed with H₂O followed by brine. The organic layer dried over Na₂SO₄, concentrated, and recrystallized in hexane-Et₂O to give the title intermediate.

Preparation CXXII - 5-(1-methyl(4-1,2,5,6-tetrahydropyridyl))-3-(trifluoro-methyl)phenylamine:

To a mixture of 4,4,5,5-tetramethyl-2-(1-methyl(4-1,2,5,6-tetrahydropyridyl))-1,3,2-dioxaborolane (1.0 g, 4.4 mmol), PdCl₂pddf (0.16 g, 0.2 mmol) and K₂CO₃ (1.8g, 13.2 mmol) and 3-amino-5-bromobenzotrifluoride (0.8g, 3.3 mmol) in DMF (25 mL) was heated at 80°C for 16 h. The resulting mixture was diluted with EtOAc, washed with H₂O, dried over Na₂SO₄, and concentrated. The residue was purified by SiO₂

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chromatography to give the title intermediate. MS (ES⁺): 257 (M+H)⁺. Calc'd C₁₃H₁₅F₃N₂ - 256.3.

Preparation CXXIII - 4-phenylpiperidine:

5 4-Cyano-4-phenylpiperidine HCl (10.0 g, 45.0 mmol) was combined with KOH pellets and stirred vigorously under Ar at 160°C for 4 h. The reaction mix was cooled to RT and dissolved into toluene (100 ml) and H₂O (100 ml). After separation of the layers, the aqueous layer was back-
10 extracted two times with toluene. The combined organic layer was dried over Na₂SO₄, concentrated *in vacuo*, and dried under high vacuum, yielding a white solid.

Preparation CXXIV - 1-methyl-4-phenylpiperidine:

15 To a stirring mixture at RT of 4-phenylpiperidine (5.24 g, 32.48 mmol) in CH₃CN (95 ml) was added a 37% solution of HCHO in H₂O (13 ml). To this mixture was added NaCNBH₃ (3.27 g, 51.97 mmol). AcOH was added dropwise every 10 min over the next h to maintain the reaction pH near 7. The
20 reaction volume was then reduced *in vacuo*. The reaction mix was diluted with CH₂Cl₂ and washed with 2N NaOH and then brine. The crude was concentrated *in vacuo* and eluted through a silica gel column with 10% MeOH/CH₂Cl₂. The 1-methyl-4-phenylpiperidine was concentrated *in vacuo*,
25 yielding a clear oil.

Preparation CXXV - 4-(1-methyl-4-piperidyl)phenylamine:

To 1-methyl-4-phenylpiperidine (2.663 g, 15.19 mmol) was added carefully H₂SO₄ (15.2 ml). The reaction was cooled in
30 an ice bath and a solution of H₂SO₄ (1.66 ml) and fuming HNO₃ (0.67 ml, 15.95 mmol) was added dropwise over 45 min. The mix was stirred at 0°C for 3 h then at RT for 1.5 h before being poured over about 90 g ice and basified with 24 g solid NaOH. The mix was extracted with CH₂Cl₂. The organic

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layer was washed with H₂O, dried over Na₂SO₄, and concentrated *in vacuo*. The crude was eluted on a silica gel column with a MeOH/CH₂Cl₂ gradient to yield 1-methyl-4-(4-nitrophenyl)piperidine which was hydrogenated under H₂ to furnish the title compound.

Preparation CXXVI - 1-piperidylprop-2-en-1-one:

To a 0°C solution of acryloyl chloride (4.576 g, 50.558 mmol) in CH₂Cl₂ (50 ml) was added dropwise and very carefully piperidine (4.305 g, 50.558 mmol). The reaction flask was vented during the exothermic addition. After the addition was completed, the white slurry was stirred at 0°C for 40 min and at RT for 1 h. The reaction was diluted with 70 ml CH₂Cl₂ and washed first with about 60 ml 2N HCl and then with about 60 ml of a mix of 2N NaOH and brine. The organic layer was dried over Na₂SO₄. The solution was evaporated by heating in a H₂O bath at 60°C without vacuum. Once most solvent had been evaporated off, dried the clear oil under high vacuum at RT for 30 min.

Preparation CXXVII - 1-(tert-butyl)-2-bromo-4-nitrobenzene:

Bromine (17.4 ml) was added dropwise over 40 min to a stirred mixture of 4-tert-butylnitrobenzene (59.5 g, 332 mmol), silver(II)sulfate (56.5 g, 181 mmol), H₂SO₄ (300 ml), and H₂O (33 ml) at RT. The mixture was stirred for a further 3 h and then poured into 0.1 M Na₂S₂O₅/H₂O (1L). The solid was filtered, washed with H₂O, Et₂O, and CH₂Cl₂. The filtrate layers were separated. The aqueous fraction was extracted with Et₂O. The combined organic layers were combined, dried over Na₂SO₄, and concentrated *in vacuo*. The yellow solid was triturated with hexanes to give a pale yellow crystalline solid.

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Preparation CXXVIII - (2E)-3-[2-(tert-butyl)-5-nitrophenyl]-1-piperidylprop-2-en-1-one:

1-(tert-Butyl)-2-bromo-4-nitrobenzene (6.885 g, 26.674 mmol), 1-piperidylprop-2-en-1-one (4.827 g, 34.677 mmol),
5 and TEA (7.44 ml, 53.35 mmol) were dissolved in toluene (70 ml). To this solution was added Pd(OAc)₂ (60 mg, 0.267 mmol) and Pd(PPh₃)₄ (617 mg, 0.5335 mmol). The mix was degassed with N₂ and heated in a sealed vessel at 120 °C for 15 h. The reaction mixture was cooled to RT, filtered, and
10 concentrated *in vacuo*. The dark crude oil was eluted through a silica gel column with 15% to 22% EtOAc/hexanes gradient system to yield a viscous, amber-colored oil as the title compound.

15 **Preparation CXXIX - 3-(5-amino-2-tert-butylphenyl)-1-piperidin-1-yl-propenone:**

(2E)-3-[2-(tert-Butyl)-5-nitrophenyl]-1-piperidylprop-2-en-1-one (3.22 g, 10.177 mmol) was dissolved in dioxane (20 ml) and IpOH (40 ml). To the N₂-degassed solution was added
20 Pd/C 10% by weight catalyst (2 g). The mix was placed in a Parr hydrogenator and stirred for 18 h under 60 psi H₂. The reaction was not complete the next day, so the reaction was continued for an additional 20 h with fresh catalyst. The mix was filtered through Celite® and concentrated *in vacuo*
25 to give a foamy oil.

Preparation CXXX - 4-(tert-butyl)-3-(3-piperidylpropyl)phenylamine:

3-(5-Amino-2-tert-butylphenyl)-1-piperidin-1-yl-propenone
30 (2.312 g, 7.619 mmol) was dissolved in THF (100 ml) at RT. To this solution was added LiAlH₄ (434 mg, 11.43 mmol). After the exothermic reaction stopped, the reaction mixture was heated at reflux at about 80°C for 4 h. The reaction mixture was cooled to 0°C and treated by dropwise addition

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of 0.458 ml H₂O, 0.730 ml 10% aqueous NaOH, and 1.19 ml H₂O, respectively. The mixture was stirred at RT for 1 h. After 40 min about 3 g of Na₂SO₄ was added. The mixture was filtered through Celite® and concentrated *in vacuo*. The crude was eluted through silica gel column with a gradient system of 95:5 to 90:10 CH₂Cl₂/MeOH, to yield a thick, amber-colored oil as the title compound.

The following compounds were prepared similarly to the procedure outlined above:

- a) 3-((1E)-4-Pyrrolidinylbut-1-enyl)-4-(tert-butyl)phenylamine.
- b) 4-(tert-Butyl)-3-(3-pyrrolidinylpropyl)phenylamine.
- 15 c) 4-(tert-Butyl)-3-(3-morpholin-4-ylpropyl)phenylamine.
- d) 3-[3-(4-methylpiperazinyl)propyl]phenylamine.
- e) 4-[3-(4-methylpiperazinyl)propyl]phenylamine.

20 **Preparation CXXXI - 3-(3-nitrophenyl)-1-(4-methylpiperazinyl)propan-1-one:**

A slurry consisting of CH₂Cl₂ (15 ml), 3-nitrocinnamic acid (3.154 g, 16.329 mmol), 1-methylpiperazine (1.487 g, 14.845 mmol) and EDC (3.557 g, 18.556 mmol) were stirred at RT for 60 h. The reaction was diluted with H₂O and EtOAc. The aqueous layer was back-extracted with EtOAc. The combined organic layers were washed with 2N NaOH and then brine, dried over Na₂SO₄, and concentrated *in vacuo*. The crude was eluted through a silica gel column with 5% MeOH/CH₂Cl₂, to yield an off-white solid, mostly trans-olefin compound.

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Preparation CXXXII - 3-(3-aminophenyl)-1-(4-methylpiperazinyl)propan-1-one:

To a nitrogen-degassed solution of 3-(3-nitrophenyl)-1-(4-methylpiperazinyl)propan-1-one (3.67 g, 13.330 mmol, Step A) in MeOH (50 ml) was added 10% by weight Pd/C (500 mg). The mix was stirred under H₂ atmosphere for 18 h then filtered through Celite® and concentrated *in vacuo*, yielding a thick amber oil which eventually solidified into a dark pink solid.

10

The following compounds were prepared similarly to the procedure outlined above:

a) 4-[3-(4-methylpiperazinyl)-3-oxopropyl]phenylamine.

15 Preparation CXXXIII - 1-(2-morpholin-4-ylethyl)indol-6-ylamine:

K₂CO₃ (5.08 g, 36.726 mmol) was added to a slurry of 6-nitroindole (1.985 g, 12.242 mmol), 4-(2-chloroethyl)morpholine.HCl (2.278 g, 12.242 mmol), and CH₃CN (100 ml). The mix was heated to reflux for 18 h, then cooled to RT, filtered, and concentrated *in vacuo*. The crude was eluted through a silica gel column with a gradient of 3:97 to 5:95 and finally 8:92 MeOH/CH₂Cl₂, to yield upon drying the desired intermediate which was hydrogenated under conditions previously described.

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Preparation CXXXIV - methyl 2-methyl-2-(4-nitrophenyl)propanoate:

To a stirred solution of 2-(4-nitrophenyl)propionic acid (9 g, 46 mmol, 1 eq) in MeOH (300 mL) was added HCl (4M in Dioxane, 11.5 mL, 46 mmol, 1 eq). The mixture was stirred at RT overnight and was quenched with aqueous NaHCO₃. The mixture was extracted with EtOAc. The organic layer was dried over MgSO₄ and evaporated under reduced pressure and

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the partial residue (4.34 g, 20.7 mmol, 1eq) at 0°C in THF (100 mL) was added NaH (1.66 g, 41.5 mmol, 2 eq). Mixture was stirred at RT for 1h and CH₃I (2.58 g, 41.5 mmol, 2 eq) was added. Reaction was stirred at RT overnight and was quenched with H₂O. Mixture was extracted with EtOAc. The organic layer was dried over MgSO₄ and evaporated under reduced pressure and used for the next step without further purification to give title compound.

10

Preparation CXXXV - 3-methyl-3-(4-nitrophenyl)butan-1-one:

To a stirred solution of methyl 2-methyl-2-(4-nitrophenyl)propionate (5.32 g, 23.8 mmol) in THF (200 mL) at 0°C was added a solution of 1M BH₃ in THF (25.8 mL, 45.8 mmol). The reaction was stirred at RT overnight and was quenched with MeOH. THF was evaporated under reduced pressure and the residue was diluted in EtOAc and aqueous HCl (1M) was added. The mixture was extracted with EtOAc, the organic layer was dried over MgSO₄ and evaporated under reduced pressure. Purification by flash chromatography using 40% EtOAc-hexane gave a yellow solid. To the yellow solid (2.08 g, 10.8 mmol) at 0°C in CH₂Cl₂ was added NMO (1.9 g, 16.1 mmol), molecular sieves 4Å and TPAP (76 mg, 0.2 mmol). The reaction was stirred for 1h and filtered on a silica pad. Solvent was evaporated under reduced pressure, forming the crude aldehyde which was used as is. To a suspension of methoxymethyltriphenylphosphonium chloride (6.4 g, 18.6 mmol) in THF (150 mL) was added a solution of KHMDS 0.5 M in toluene (37 mL, 18.5 mmol). The mixture was stirred for 30 min and crude aldehyde was added. The reaction was stirred at RT for 1h and quenched with H₂O. The mixture was extracted with EtOAc, dried and evaporated under reduced pressure. Et₂O was added and a precipitate formed, which was filtered on a silica pad and rinsed with

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40% EtOAc-hexane. The solvent was removed and crude material was dissolved in CH₂Cl₂. A solution of TFA-H₂O (1:1, 10 mL) was added and the reaction was stirred for 2 h at RT. Aqueous NaHCO₃ was added until pH 7 and the mixture
5 was extracted with CH₂Cl₂. The organic layer was dried, filtered and evaporated. Crude compound was purified by flash chromatography (40% EtOAc-hexane) to give the title compound as a yellow oil.

10 **Preparation CXXXVI - 4-(1,1-dimethyl-3-morpholin-4-ylpropyl)phenylamine:** To a stirred solution of 3-methyl-3-(4-nitrophenyl)butan-1-one (509 mg, 2.4 mmol) and morpholine (0.21 mL, 2.4 mmol) in THF (30 mL) was added NaBH(OAc)₃ (0.73 g, 3.4 mmol). The mixture was stirred at RT overnight
15 and washed with HCl (1M). CH₂Cl₂ was added and the layers were separated. The aqueous layer was basified to pH 9 using NaOH 1M and extracted with CH₂Cl₂. The organic layer was dried and evaporated the nitro compound. To a solution of the nitro compound (0.50 g, 1.8 mmol) in THF (40 mL) was
20 added AcOH (1.97 mmol, 34.5 mmol) followed by zinc (9.1 g, 137 mmol). The mixture was stirred for 1 h, filtered on Celite®, diluted with H₂O and aqueous NaHCO₃, and the THF layer was evaporated. The residue was extracted with EtOAc, dried and evaporated to give the title compound.

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Preparation CXXXVII - 4-{2,2,2-trifluoro-1-[2-(2-methoxy)ethoxy]-1-(trifluoromethyl)ethyl}phenylamine:
Diethyl azodicarboxylate (366 mg, 2.1 mmol) was added drop-
wise to a solution of 2-(4-aminophenyl)-1,1,1,3,3,3-
30 hexafluoropropan-2-ol (520 mg, 2 mmol), 2-(2-methoxyethoxy)ethan-1-ol (240 mg, 2 mmol) and PPh₃ (550 mg, 2.1 mmol) in THF (10 mL). The mixture was stirred for 2 h, then partitioned between EtOAc and aqueous NaHCO₃ solution. The organic phase was washed with brine. After

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concentration in vacuo, the organic residue was purified by flash chromatography on silica to give the compound. MS: 362 (M+1). Calc'd. for $C_{14}H_{17}F_6NO_3$ - 361.29.

5 **Preparation CXXXVIII - 2-fluoropyridine-3-carbonyl chloride:**

To a solution of 2-fluoropyridine (10 g, 100 mmol) in THF (150 mL) under $-78^{\circ}C$ was added an LDA solution (2M in heptane/THF/ethylbenzene, 60 mL) dropwise. The mixture was stirred at $-78^{\circ}C$ for 3 h, then was quenched with a stream of
10 dry CO_2 . After warming to RT, the mixture was partitioned between EtOAc (100 mL) and H_2O (200 mL). The aqueous layer was acidified to pH between 3-4, and extracted with EtOAc. The organic solution was collected and washed with brine and dried over Na_2SO_4 . After removing the solvent in vacuum, 2-
15 fluoropyridine-3-carboxylic acid was obtained as a brown oil. MS: 140 (M-H). Calc'd. for $C_6H_4FNO_2$ - 141.10. 2-Fluoropyridine-3-carboxylic acid (7 g) was suspended in $SOCl_2$ (100 mL). After heating under reflux for 2 h, the mixture became homogeneous. Access $SOCl_2$ was removed in
20 vacuo to afford a brown solid as desired compound.

Preparation CXXXIX - N-(3-Amino-5-chloro-phenyl)-2-dimethylamino-acetamide:

To a solution of 5-chloro-benzene-1,3-diamine (3 g, 21 mmol) and dimethylamino-acetic acid (2.2 g, 21 mmol) in CH_2Cl_2
25 (300 mL) was added EDC (5 g, 25 mmol), HOBt (2.9 g, 21 mmol), and DIEA (5 mL). The reaction mixture was stirred at RT for overnight. Solvent was removed in vacuum and the residue was purified through flash chromatography on silica
30 gel (0-8% MeOH in EtOAc) to give the desired compound.

Preparation CXL - 2-amino-4-nitro-benzamide:

To a solution of 2-amino-4-nitro-benzoic acid (9.1 g, 50 mmol) in CH_2Cl_2 (500 mL) was added EDC (12 gram, 60 mmol),

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HOBt (6.8 g, 50 mmol), DIEA (12 mL), and NH_3 in MeOH (2M, 40 mL). The reaction was stirred at RT for overnight, and a precipitation formed. The solid was isolated via vacuum filtration.

5

Preparation CXLI - 6-nitro-3H-quinazolin-4-one:

2-Amino-4-nitro-benzamide was suspended in triethyl orthoformate (50 mL) and the mixture was heated to 140°C for 5 h. Excess reagent was removed in vacuum. The residue was washed in hexanes to give the compound as a yellow solid.

10

Preparation CXLII - 6-amino-3H-quinazolin-4-one:

Hydrogenation of 6-nitro-3H-quinazolin-4-one (2 g) in EtOH (200 mL) was catalyzed by Pd/c (10%, 200 mg) under a H_2 balloon for 1 h. MeOH (200 mL) was added to the mixture. The suspension was filtered through a layer of Celite® and the filtrate was concentrated in vacuum to give the desired compound.

15

20 Preparation CXLIII - (2,4-dinitro-phenyl)-acetic acid methyl ester:

To a solution of (2,4-dinitro-phenyl)-acetic acid (5 g) in MeOH (100 mL) was added concentrated H_2SO_4 (1 mL) and the resulting solution was heated at reflux for overnight.

25

After removing solvent in vacuum, the residue was partitioned between EtOAc and aqueous NaHCO_3 (sat.). The organic solution was concentrated in vacuum to give the desired compound which was used without further purification.

30

Preparation CXLIV - 6-amino-1,3-dihydro-indol-2-one:

An EtOH solution of (2,4-dinitro-phenyl)-acetic acid methyl ester was treated with H_2 balloon and catalyzed with Pd/c (10%, 500 mg) at RT. The resulting mixture was filtered

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through a layer of Celite® and concentrated in vacuum to afford the desired compound.

5 Preparation CXLVI - 3-Methyl-but-2-enoic acid (6-bromo-pyridin-2-yl)-amide:

To a solution of 2-amino-6-bromopyridine (3.015 g, 0.017 mol) and Et₃N (2.40 mL, 0.017 mol) in CH₂Cl₂ (20.0 mL), was added 3,3-dimethylacryloylchloride (1.96 mL, 0.017 mol) under N₂ at 0 °C. The mixture was slowly warmed to RT and stirred for 12 h. The reaction was quenched by the addition of H₂O (20.0 mL), the organic layer was separated, dried over Na₂SO₄ and evaporated to dryness to yield crude compound which was used without purification.

15 Preparation CXLVI - 3-Methyl-but-2-enoic acid (6-amino-pyridin-2-yl)-amide:

To a solution of 3-methyl-but-2-enoic acid (6-bromo-pyridin-2-yl)-amide (4.30 g, 0.017 mol) and copper (0.214 g, 3.372 mmol) in IpOH (20.0 mL), was added NH₄OH (20.0 mL) in a sealed vessel under N₂. The reaction was sealed and heated to 90 °C for 12 h. The reaction mixture was cooled to RT and EtOAc (50.0 mL) was added. The organic layer was separated, and then the aq layer was washed with EtOAc (50.0 mL). Combined organic layers were evaporated to dryness, the resulting residue was dissolved in CH₂Cl₂ (50.0 mL) and washed with H₂O (4 x 30 mL). The organic layer was dried over Na₂SO₄ and evaporated to dryness to yield crude aminopyridine, which was used without purification.

30 Preparation CXLVII - 7-Amino-4,4-dimethyl-3,4-dihydro-1H-[1,8]naphthyridin-2-one:

To a mixture of aminopyridine (1.12 g, 5.833 mmol) and AlCl₃ (3.11 g, 0.023 mol) was added chlorobenzene (10.0 mL) in a sealed vessel under Ar. The reaction was sealed and heated

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to 120 °C for 12 h. The reaction mixture was cooled to RT and the mixture was poured over ice/HCl mixture and extracted with EtOAc (3 x 50.0 mL). The aqueous layer was neutralized via addition of solid NaHCO₃ and extracted with
5 EtOAc (5 x 50 mL). Combined organic layers were dried over Na₂SO₄ and evaporated to dryness to yield crude compound. Chromatography (Silica gel, CH₂Cl₂:MeOH, 99:1) yielded pure naphthyridin.

10 **Preparation CXLVIII - 2-[1-(3-Amino-phenyl)-2,2,2-trifluoro-1-trifluoromethyl-ethoxymethyl]-pyrrolidine-1-carboxylic acid tert-butyl ester:**

To a mixture of 2-(3-amino-phenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (1.30 g), 2-hydroxymethyl-pyrrolidine-1-
15 carboxylic acid tert-butyl ester (1.04 g), PPh₃ (2.64 g) and molecular sieves 4 Å in THF (100 mL) was added diethyl diazocarboxylate (1.55 mL) slowly. The reaction was stirred at RT for 4h and at reflux for overnight. After filtration to remove solids, the filtrate was concentrated and the
20 residue was taken into Et₂O. The organic phase was washed with saturated NaHCO₃ and brine. The organic layer was dried over MgSO₄ and evaporated to give a crude compound as very viscous brown oil, which was purified by chromatography through silica gel (500 g, 30% to 50% EtOAc in hexanes) to
25 afford 2-[1-(3-amino-phenyl)-2,2,2-trifluoro-1-trifluoromethyl-ethoxymethyl]-pyrrolidine-1-carboxylic acid tert-butyl ester as a light brown oil.

Preparation CXLIX - Pyrimidine-4-carbaldehyde oxime:

30 9.14 g (97.11 mmol) of 4-methylpyrimidine was slowly added to a 0°C solution of 8.75 g HCl in 40 ml EtOH. To this white suspension was added, over 5 min, 61 ml of a 10-20% by weight solution of ethyl nitrite in EtOH. The reaction was stirred at 0 °C for 10 min and then at RT for 2.5 h. The

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white salt was filtered and dried under vacuum. The salt was dissolved into 20 ml H₂O and very slowly treated with about 200 ml saturated aqueous KHCO₃. A white solid precipitated out of the purple solution. The solid was
5 filtered and dried under vacuum to yield the titled compound.

Preparation CL - C-Pyrimidin-4-yl-methylamine dihydrogen chloride:

10 To a solution of 3.549 g (28.82 mmol) pyrimidine-4-carbaldehyde oxime in 200 ml MeOH was added after degassing with Ar, 800 mg of 10% by weight Pd/C. The mix was stirred under H₂ for 4 h, then filtered through a Celite® plug. The solution was concentrated under vacuum to a volume of about
15 50 ml and then treated carefully with 30 ml of 4N HCl in dioxane. The mix was concentrated and dried under vacuum to yield the titled compound as a pink solid.

Preparation CLI - 2-(2,4-Dinitro-phenyl)-3,3,3-trifluoro-2-trifluoromethyl-propionic acid methyl ester:

20 A mixture of 7.08 g (38.07 mmol) 2,4-dinitrofluorobenzene, 2.43 g (41.88 mmol) KF, and 0.58 g (2.21 mmol) 18-crown-6-ether in 37 ml sulfolane was added 4.00 g (19.04 mmol) methyl 2-(trifluoromethyl)-3,3,3-trifluoropropionate
25 dropwise over about 7 h via syringe pump. After the addition was complete, another 2.43 g KF, 0.58 g 18-Crown-6-ether were added and then 4.00 g Methyl 2-(trifluoromethyl)-3,3,3-trifluoropropionate were added dropwise over 12 h. The next day, repeated additions using same amounts and
30 setting syringe pump addition over 14 h. The following day, the additions were again repeated, this time using half the amounts as above additions and setting syringe pump addition at 12 h. After addition was completed, the reaction mix was cooled to RT and diluted into Et₂O and 0.5N

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aqueous HCl. The layers were separated, and the organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated under vacuum. The crude was eluted on a silica gel column with EtOAc/hexanes gradient, to yield the titled compound, as a yellow solid.

[See Vlasov et al.; J.Org. Chemistry USSR (Engl. Trans.); 15; 1979; 1953-1964).]

Preparation CLII - 6-Amino-1-hydroxy-3,3-bis-trifluoromethyl-1,3-dihydro-indol-2-one:

To an argon-degassed solution of 5.13 g (13.64 mmol) 2-(2,4-dinitro-phenyl)-3,3,3-trifluoro-2-trifluoromethyl-propionic acid methyl ester in 300 ml EtOH was added 0.5 g of 10% by weight Pd/C. The reaction was stirred under H₂ overnight and filtered through Celite®, concentrated down, and dried under vacuum, yielding the titled compound.

Preparation CLIII - 6-Amino-3,3-bis-trifluoromethyl-1,3-dihydro-indol-2-one:

To a solution of 1.245 g (4.151 mmol) 6-amino-1-hydroxy-3,3-bis-trifluoromethyl-1,3-dihydro-indol-2-one in 80 ml THF was added 3.565 ml (62.27 mmol) glacial AcOH and 19 g (290.6 mmol) Zinc dust (100 mesh). The reaction was stirred 40 min at RT and then 5 h at reflux. The reaction was cooled to RT. The solvent was decanted and concentrated, then dissolved in EtOAc and filtered through Celite®. The EtOAc solution was then washed with saturated aqueous NaHCO₃ and brine, dried over Na₂SO₄, filtered, and concentrated and dried under vacuum, to yield the titled compound, as a yellow solid.

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Preparation CLIV - N-[3-(2-Amino-ethoxy)-4-pentafluoroethyl-phenyl]-2-chloro-nicotinamide:

To a solution of 500 mg (0.98 mmol) Boc-N-[3-(2-Amino-ethoxy)-4-pentafluoroethyl-phenyl]-2-chloro-nicotinamide in
5 10 ml CH₂Cl₂ was added 10 ml TFA and stirred for 2 h. The reaction was concentrated down, treated with 6N aqueous NaOH, and extracted 3 times with CH₂Cl₂. The combined organic extracts were dried over Na₂SO₄, filtered, concentrated down, and dried under vacuum, yielding the
10 titled compound.

Preparation CLV - 2-Chloro-N-[3-(2-methanesulfonylamino-ethoxy)-4-pentafluoroethyl-phenyl]-nicotinamide:

To a solution of 381 mg (0.93 mmol) N-[3-(2-amino-ethoxy)-4-pentafluoroethyl-phenyl]-2-chloro-nicotinamide in 10 ml
15 CH₂Cl₂ at 0 °C was added 0.389 ml Et₃N and 0.072 ml (0.93 mmol) methanesulfonylchloride. After 5 min, the reaction was stirred at RT for 30 min. The reaction was diluted with CH₂Cl₂, washed with brine, dried over Na₂SO₄, filtered,
20 concentrated, and dried under vacuum, yielding the titled compound as a white foamy solid.

Preparation CLVI - 2-Methyl-2-(4-nitro-phenyl)-propionic acid:

25 To a solution of 2-(4-nitro-phenyl)-propionic acid (50 g, 0.26 mole) in 250 mL of MeOH was added 6 mL of concentrated HCl. The resulting solution was heated at reflux for 16 h. Then the resultant mixture was diluted with 200 mL of aq. NaHCO₃ and 500 mL of EtOAc. The organic layer was
30 separated, dried over Na₂SO₄, and concentrated. The residue was diluted with 100 mL of THF and added to a suspension of NaH (11.2 g, 0.28 mole, 60% in mineral oil) in 600 mL of THF. To the resulting mixture was added CH₃I (18.3 mL, 0.29 mole) in one portion. The resulting mixture was stirred for

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48 h at 40 °C, then was diluted with aq. NH_4Cl solution and EtOAc. The organic layer was separated, dried over Na_2SO_4 , and concentrated. The residue was used without further purification.

- 5 To a solution of the residue (54 g, 0.24 mole) in 500 ml of MeOH was added 5N aq. NaOH (144 mL, 0.72 mole). The mixture was stirred for 16 h at 40 °C. The resulting mixture was concentrated, the residue was diluted with H_2O (500 mL), and acidified with 2N HCl to give a precipitate. The
10 precipitate was filtered and dried to give the titled compound as a yellowish solid. MS: 210 (M+1), Calc'd for $\text{C}_{10}\text{H}_{12}\text{NO}_4$ - 210.20.

Preparation CLVII - 2-Methyl-5-[1-methyl-1-(4-nitro-phenyl)-ethyl]-[1,3,4]oxadiazole:

15 A mixture of 2-methyl-2-(4-nitro-phenyl)-propionic acid (5 g, 24 mmol.) and a few drops of DMF in SOCl_2 was stirred at reflux for 16 h. The resulting solution was concentrated to give corresponding acid chloride as a brown solid.

- 20 To a mixture of the acid chloride (2.33 g, 10.2 mmol), acetic acid hydrazide (0.91 g, 12.2 mmol.), Et_3N (2.86 mL, 20.2 mmol.) in CH_2Cl_2 (50 mL) was added 2 crystals of DMAP at RT. The mixture was stirred for 16 h and concentrated. A solution of the residue in 50 mL of phosphorous oxychloride
25 was heated at 95°C for 16 h. The mixture was concentrated and diluted with ice-water and EtOAc. The organic layer was washed with saturated aq. NaHCO_3 solution twice, dried over Na_2SO_4 , and concentrated. The residue was purified by SiO_2 chromatography (hexane: EtOAc=1:1) to give the titled
30 compound as a pale yellow crystal. MS: 248 (M+1), Calc'd for $\text{C}_{12}\text{H}_{14}\text{N}_3\text{O}_3$ -248.10.

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Preparation CLVIII - 2-Methyl-5-[1-methyl-1-(4-amino-phenyl)-ethyl]-[1,3,4]oxadiazole:

A mixture of 2-methyl-5-[1-methyl-1-(4-nitro-phenyl)-ethyl]-[1,3,4]oxadiazole (1.36 g, 5.5 mmol.) and Pd/C (68 mg) in EtOAc (50 mL), was stirred under 1 atm of H₂ for 16 h. The resultant was filtered over Celite®, and the filtrate was concentrated to give the titled compound as a pale yellow crystalline. MS: 218 (M+1) calc'd for C₁₂H₁₆N₃O-218.12.

Preparation CLIX - 4-[1-Methyl-1-(4-nitro-phenyl)-ethyl]-pyrimidine:

To a mixture of 1-(4-nitro-phenyl)-propan-2-one (5.32 g, 29.7 mmol.), triethylbenzylammonium chloride (0.34g, 1.5 mmol.), and 13 mL of aq. 5N KOH solution (65.3 mmol.) in CH₂Cl₂ was added CH₃I (4.06 mL, 65.3 mmol.). The resulting mixture was stirred at 40 °C, and then diluted with EtOAc and H₂O. The organic layer was dried and concentrated. To the residue (1.0 g, 4.8 mmol.) in toluene (30 mL) was added dimethylformamide dimethylacetal (1.27 mL, 9.6 mmol.). The resulting mixture was heated at reflux for 6 h then concentrated to give 1-dimethylamino-4-methyl-4-(4-nitro-phenyl)-pent-1-en-3-one as a yellow solid (MS 263 (M+1) Calc'd for C¹⁴H₁₉N₂O₃-263.13).

A mixture of 1-dimethylamino-4-methyl-4-(4-nitro-phenyl)-pent-1-en-3-one (0.5 g, 1.9 mmol.), formamidine HCl (0.305 g, 3.8 mmol.), and NaOEt (1.29 g, 4.0 mmol) was heated in Smith synthesizer under microwave for 10 min at 150 °C. The resultant mixture was diluted with H₂O and EtOAc. The organic layer was dried, and the residue was used without further purification. MS: 244 (M+1) Calc'd for C₁₃H₁₄N₃O₂-244.10.

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Preparation CLX - 5-[1-Methyl-1-(4-nitro-phenyl)-ethyl]-1H-pyrazole:

A mixture of 1-dimethylamino-4-methyl-4-(4-nitro-phenyl)-pent-1-en-3-one (0.36 g, 1.4 mmol.) and hydrazine hydrate (1.0 g, 6.25 mmol.) in EtOH was heated at 50°C for 3h. The mixture was concentrated, and the residue was diluted with H₂O and EtOAc. The organic layer was dried over Na₂SO₄ and concentrated to give the titled compound as a yellow solid. MS: 232 (M+1) Calc'd for C₁₂H₁₄N₃O₂ -232.10.

10

Preparation CLXI - 2-tert-Butyl-5-nitro-phenylamine:

Concentrated H₂SO₄ (1 L) was cooled to -10°C with a dry ice IpOH bath in a 2 L 3-neck round bottom flask fitted with a mechanical stirrer and temperature probe. 2-*t*-Butylaniline (109 g, 730 mmol) was added, giving a clumpy solid. Once the temperature of the mixture was stabilized at -10°C, KNO₃ (101 g, 1001 mmol) was added portion-wise, as the solid, over 4 h, maintaining the temperature between -20 and -5°C. Once all of the KNO₃ was added, the reaction was stirred overnight with gradual warming to RT. The reaction was quenched by diluting it with H₂O and extracting it 3x with EtOAc. The EtOAc extracts were washed multiple times with saturated NaHCO₃(aq), until gas evolution ceased, then with brine. The EtOAc extracts were combined, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure giving a black oil. The oil was eluted through a 36 x 7 cm column of silica gel with a 5%; 10%; 15%; 25%; and 50% EtOAc:Hexanes step gradient (2 L each step) giving 2-tert-butyl-5-nitro-phenylamine as a red solid.

30

Preparation CLXII - 2-Bromo-N-(2-tert-butyl-5-nitro-phenyl)-acetamide:

2-tert-Butyl-5-nitro-phenylamine (70 g, 359 mmol) and a catalytic amount of DMAP were dissolved in THF (1.5 L) under

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N₂. TEA (109 g, 1077 mmol) was added and the solution was cooled to 0 °C. Bromoacetyl bromide (207 g, 1023 mmol) was added and the reaction was gradually warmed to RT with stirring overnight. The reaction was partially concentrated under reduced pressure, treated with H₂O and extracted with EtOAc (3x). The EtOAc extracts were washed with brine, combined, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure giving a black oil. This oil was eluted through a 38 x 7 cm column of silica gel with 95:5:0.5 CH₂Cl₂:MeOH:NH₄OH_(aq) eluant giving 2-bromo-N-(2-tert-butyl-5-nitro-phenyl)-acetamide as a brown solid.

Preparation CLXIII - N-(2-tert-Butyl-5-nitro-phenyl)-2-dimethylamino-acetamide:

2-Bromo-N-(2-tert-butyl-5-nitro-phenyl)-acetamide (80 g, 253 mmol) and K₂CO₃ (70 g, 506 mmol) were combined in a 3-L 3-neck round bottom flask fitted with a mechanical stirrer, N₂ inlet, and pressure equalizing addition funnel. THF (1.75 L) was added and the mixture was cooled to 0 °C under N₂. DMA (400 mL of a 2 M solution in THF, 800 mmol) was added to the mixture through the pressure equalizing addition funnel over 30 min. The mixture was gradually warmed to RT with stirring overnight. The reaction was quenched by filtering it under vacuum and then concentrating the filtrate under reduced pressure. The recovered material was eluted through a 36 x 7 cm column of silica gel with 50% EtOAc:Hexanes giving N-(2-tert-butyl-5-nitro-phenyl)-2-dimethylamino-acetamide as a brown solid.

The pyrrolidino and morpholino analogs are prepared by substituting the dimethylamine with respectively pyrrolidine or morpholine and using the same chemistry as described.

a) N-(2-tert-Butyl-5-nitro-phenyl)-2-pyrrolidin-1-yl-acetamide.

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b) N-(2-tert-Butyl-5-nitro-phenyl)-2-morpholin-4-yl-acetamide.

Preparation CLXIV - N-(5-Amino-2-tert-butyl-phenyl)-2-dimethylamino-acetamide:

5 N-(2-tert-Butyl-5-nitro-phenyl)-2-dimethylamino-acetamide (25.8 g, 92 mmol) was dissolved in EtOH (1.4 L) and 1,4-dioxane (200 mL). The solution was degassed under vacuum with stirring. 10% Pd/C (2.5 g) was added (as a slurry in
10 EtOH). The mixture was degassed again, then the reaction vessel was charged with H₂ gas (balloon) and stirred overnight at RT. The reaction was filtered through Celite[®] with MeOH and the filtrate was concentrated under reduced pressure. The recovered material was eluted through a 36 x
15 7 cm column of silica gel with a 97.5:2.5:0.25 and 95:5:0.5 CH₂Cl₂:MeOH:NH₄OH_(aq) step gradient giving N-(5-amino-2-tert-butyl-phenyl)-2-dimethylamino-acetamide as a brown solid.

Preparation CLXV - 5-Chloro-1-methyl-1H-pyrazole-4-carboxylic acid (4-tert-butyl-phenyl)-amide:

20 5-Chloro-1-methyl-1H-pyrazole-4-carbonyl chloride (1.0 g, 5.6 mmol) was dissolved in CH₂Cl₂ (100 mL) under N₂ and cooled to 0 °C. 4-*t*-Butylaniline was added and the reaction was stirred with gradual warming to RT overnight. The
25 reaction was quenched with saturated NaHCO₃(aq) and extracted 3 x with fresh CH₂Cl₂. The CH₂Cl₂ extracts were washed with brine, combined, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure giving 5-chloro-1-methyl-1H-pyrazole-4-carboxylic acid (4-tert-butyl-
30 phenyl)-amide as a foamy pink solid.

Preparation CLXVI - 1,2-dihydro-3-spiro-1'-cyclopropyl-1H-indole:

A solution of 3-(2-bromo-ethyl)-1H-indole (5 g) in anhydrous
35 CH₃CN (100 mL) was suspended with oven dried K₂CO₃ (20 g) and

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heated to reflux for 10 h. After cooling to RT, the mixture was filtered and the filter cake was washed with EtOH (50 mL). The combined filtrate was treated with NaBH₄ (300 mg) and stirred for 3 h at RT. Solvents were removed *in vacuo* and the residue was partitioned between H₂O (160 mL) and EtOAc (60 mL). The organic layer was extracted with aqueous HCl (0.5N, 30 mL X 2). The acid layer was basified with NH₄OH (aq. Conc.) and extracted with EtOAc. The organic phase was washed with brine and dried over Na₂SO₄ and concentrated to give the desired compound as a colorless thin oil.

Preparation CLXVII- 6-nitro-1,2-dihydro-3-spiro-1'-cyclopropyl-1H-indole:

1',2'-Dihydrospiro(cyclopropane-1,3'-[3H]indole) (1.8 g 12.4 mmol) was added in dropwise over a period of 20 min to a cooled (-5 to -10°C) solution of NaNO₃ (1.3 g) in H₂SO₄ (conc., 30 mL). After the addition, the reaction was stirred for another 40 min., then the mixture was poured onto crushed ice (200 g) and the resulting mixture was basified with NH₄OH (aq., conc.) with cooling. The basified mixture was extracted with EtOAc twice and the organic layer was washed with brine then dried over Na₂SO₄. After concentration *in vacuo*, the compound was isolated as a dark gray solid.

Preparation CLXVIII - Ethyl 6-nitro-1,2-dihydro-3-spiro-1'-cyclopropyl-1H-indole-1-carbamate:

A solution of 6-nitro-1,2-dihydro-3-spiro-1'-cyclopropyl-1H-indole (2.7 g) in CH₂Cl₂ (100 mL) was suspended with NaHCO₃ (5 g), and ethyl chloroformate was added dropwise with vigorous stirring. After the addition, the reaction was stirred overnight. The mixture was washed with H₂O (100 mL), then dried over Na₂SO₄ and concentrated in *vacuo*. The

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residue was recrystallized in MeOH to give the title compound as a dark gray crystalline.

Preparation CLXIX - Ethyl 6-amino-1,2-dihydro-3-spiro-1'-cyclopropyl-1H-indole-1-carbamate:

Ethyl 6-nitro-1,2-dihydro-3-spiro-1'-cyclopropyl-1H-indole-1-carbamate (2.1 g) was dissolved in EtOH (200 mL), suspended with Pd/C (10%, 560mg) and equipped with a balloon filled with H₂. The hydrogenation was finished in 3 h. The reaction mixture was filtered through a layer of Celite®. The filtrate was concentrated *in vacuo* to give the desired product as a white solid.

Preparation CLXX - 4-[1-Methyl-1-(4-nitro-phenyl)-ethyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid ethyl ester:

1-Methyl-4-[1-methyl-1-(4-nitro-phenyl)-ethyl]-1,2,3,6-tetrahydro-pyridine (5.2 g) was dissolved in toluene (100 mL) and ethyl chloroformate (2.4 g). The mixture was heated at reflux for overnight and cooled to RT. The toluene solution was washed with NaHCO₃ (aq., sat., 100 mL) then brine (100 mL) and dried over Na₂SO₄. The organic phase was concentrated *in vacuo* to give the desired compound which was used without purification.

Preparation CLXXI - 4-[1-Methyl-1-(4-amino-phenyl)-ethyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid ethyl ester:

4-[1-Methyl-1-(4-nitro-phenyl)-ethyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid ethyl ester was dissolved in EtOH (150 mL) and suspended with Pd/C (10%, 1g). The reaction flask was equipped with a balloon filled with H₂. The hydrogenation was continued for 3 days. The mixture was filtered through a layer of Celite® and concentrated *in vacuo* to provide the desired compound as a light brown oil.

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Preparation CLXXII: 3,3-dimethyl-6-nitroindoline 3-Methyl-but-2-enoic acid (3-acetylamino-phenyl)-amide:

3,3-Dimethylacryloyl chloride (3.3 ml, 29.3 mmol) was added to a mixture of 3'-aminoacetanilide (4.40 g, 29.3 mmol) and Et₃N (4.5 ml, 32.2 mmol) in 50 ml of CH₂Cl₂ and 25 ml of THF at 0 °C under N₂. The mixture was stirred at RT overnight, diluted with 100 ml of CH₂Cl₂, washed with aqueous Na₂CO₃, then brine, condensed, and purified by flash column chromatography (15 to 30% of EtOAc in CH₂Cl₂). The titled compound was obtained as an off-white solid. MS (ES⁺): 233.1 (M+H)⁺. Calc'd for C₁₃H₁₆N₂O₂ - 232.28.

The following compounds were prepared similarly to the procedure outlined above:

15

a) 3-Methyl-but-2-enoic acid phenylamide. MS(ES⁺): 176.1 (M+H)⁺. Calc'd for C₁₁H₁₃NO - 175.23.

Preparation CLXXIII - N-(4,4-Dimethyl-2-oxo-1,2,3,4-tetrahydro-quinolin-7-yl)-acetamide:

The mixture of 3,3-dimethyl-6-nitroindoline 3-Methyl-but-2-enoic acid (3-acetylamino-phenyl)-amide (1.05 g, 4.52 mmol) and AlCl₃ (5.0 g, 37.5 mmol, Aldrich, 99.99%) in 50 ml of anhydrous chlorobenzene was stirred at 120 °C (oil bath temperature) under N₂ overnight, cooled to RT, poured into 10 ml of ice cold HCl, stirred for 30 min, and extracted with EtOAc. The organic portions were combined, washed with brine, dried with Na₂SO₄, filtered, condensed, and purified by flash column chromatography (1% of MeOH in CH₂Cl₂). The titled compound was obtained as an off-white solid. MS (ES⁺): 233.2 (M+H)⁺. Calc'd for C₁₃H₁₆N₂O₂ - 232.28.

The following compounds were prepared similarly to the procedure outlined above:

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a) 4,4-Dimethyl-3,4-dihydro-1*H*-quinolin-2-one MS(ES⁺): 175.6 (M+H)⁺. Calc'd for C₁₁H₁₃NO - 175.23.

5 **Preparation CLXXIV: 7-Amino-4,4-dimethyl-3,4-dihydro-1*H*-quinolin-2-one:**

N-(4,4-Dimethyl-2-oxo-1,2,3,4-tetrahydro-quinolin-7-yl)-acetamide (1.50 g, 6.46 mmol) in 10 ml of HCl (concentrated, 37%) and 30 ml of EtOH was stirred at 75 °C
10 for 4 h. The solvents were removed under reduced pressure. The residue was dissolved in EtOAc/H₂O, neutralized with NaHCO₃, washed with brine, dried with Na₂SO₄, filtered, and condensed to give the titled compound as an off-white solid. MS (ES⁺): 191.2 (M+H)⁺. Calc'd for C₁₁H₁₄N₂O - 190.24.

15

Preparation CLXXV - 4,4-Dimethyl-1,2,3,4-tetrahydro-quinolin-7-ylamine:

The mixture of 7-amino-4,4-dimethyl-3,4-dihydro-1*H*-quinolin-2-one (1.07 g, 5.62 mmol) and borane dimethylsulfide complex
20 (1.60 ml, 16.9 mmol) in 40 ml of anhydrous THF was heated at reflux under N₂ for 15 h. The solvents were removed under reduced pressure. The residue was heated at reflux in 20 ml of MeOH for 2 h, then 0.80 g of NaHCO₃ was added, and the mixture was heated at reflux for 2 h. The mixture was
25 filtered, condensed, and the residue was purified by flash column chromatography (5 to 10% of EtOAc in CH₂Cl₂). The titled compound was obtained as a viscous oil. MS(ES⁺): 176.9 (M+H)⁺. Calc'd for C₁₁H₁₆N - 176.26.

30 The following compounds were prepared similarly to the procedure outlined above:

a) 4,4-Dimethyl-1,2,3,4-tetrahydroquinoline MS(ES⁺): 162.5 (M+H)⁺. Calc'd for C₁₁H₁₅N - 161.24.

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Preparation CLXXVI - N-(4,4-Dimethyl-1,2,3,4-tetrahydro-quinolin-7-yl)-2-fluoronicotinamide:

The mixture of 4,4-dimethyl-1,2,3,4-tetrahydro-quinolin-7-ylamine (0.20g, 1.13 mmol), 2-fluoronicotinic acid (0.16g, 1.13 mmol), TBTU (0.36 g, 1.13 mmol), and DIEA (0.24 ml, 1.36 mmol) in 5 ml of DMF was stirred at RT for 3 h, then partitioned between EtOAc and Na₂CO₃ (aq). The organic layer was washed with H₂O, brine, dried with MgSO₄, filtered, condensed, and the residue was purified by flash column chromatography (20 to 30% of EtOAc in CH₂Cl₂). The titled compound was obtained as an off-white solid. MS (ES⁺): 300.1 (M+H)⁺. Calc'd for C₁₇H₁₈FN₃O- 299.34.

The following compounds were prepared similarly to the procedure outlined above:

- a) N-(4,4-Dimethyl-2-oxo-1,2,3,4-tetrahydro-quinolin-7-yl)-2-fluoronicotinamide, as an off-white solid. MS (ES⁺): 314.2 (M+H)⁺. Calc'd for C₁₇H₁₆FN₃O₂- 313.33.
- b) N-(1-Ethyl-4,4-dimethyl-1,2,3,4-tetrahydro-quinolin-7-yl)-2-fluoronicotinamide, MS(ES⁺): 328.3 (M+H)⁺. Calc'd for C₁₉H₂₂FN₃O - 327.40.

Preparation CLXXVII - 4,4-Dimethyl-7-nitro-1,2,3,4-tetrahydro-quinoline:

To 13 ml of H₂SO₄ (96%) cooled in a salt ice bath was added dropwise 4,4-dimethyl-1,2,3,4-tetrahydro-quinoline (5.80 g, 36.0 mmol). The resulting slurry was stirred for 30 min, upon when concomitant addition of HNO₃ (90%, 1.70 ml, 36.0 mmol) and H₂SO₄ (96%, 7 ml) was started, the addition was finished in 20 min, the mixture was stirred at 0 °C to 15 °C for 2 h, poured into ice, and extracted with EtOAc. The organic portion was washed with brine, condensed, and

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purified by flash column chromatography (0 to 10% of EtOAc in hexanes). The titled compound was obtained as a yellow oil. MS (ES⁺): 206.9 (M+H)⁺. Calc'd for C₁₁H₁₄N₂O₂ - 206.24.

5 **Preparation CLXXVIII - 1-Ethyl-4,4-dimethyl-7-nitro-1,2,3,4-tetrahydroquinoline:**

The mixture of 4,4-dimethyl-7-nitro-1,2,3,4-tetrahydroquinoline (0.48g, 2.33 mmol), iodoethane (0.21 ml, 2.56 mmol), and NaH (60%, 0.10g, 2.5 mmol) in 10 ml of DMF was
10 stirred at RT overnight, and partitioned between EtOAc and H₂O. The combined organic portions were washed with brine, dried with MgSO₄, filtered, and condensed. The crude compound was purified by flash column chromatography (5 to 10% of CH₂Cl₂ in hexanes). The titled compound was obtained
15 as a yellow oil. MS (ES⁺): 235.3 (M+H)⁺. Calc'd for C₁₃H₁₈N₂O₂ - 234.29.

Preparation CLXXIX: 1-Ethyl-4,4-dimethyl-1,2,3,4-tetrahydroquinolin-7-ylamine:

20 The mixture of 1-ethyl-4,4-dimethyl-7-nitro-1,2,3,4-tetrahydroquinoline (0.28 g) and Pd/C (0.060 g, 10% wt) in 10 ml of EtOAc was placed under H₂ which was provided by a balloon and stirred at RT overnight. Then the mixture was filtered through Celite®, condensed, and the residue was
25 purified by flash column chromatography (2% of EtOAc in CH₂Cl₂). The titled compound was obtained as a pink oil. MS(ES⁺): 204.8 (M+H)⁺. Calc'd for C₁₁H₁₆N - 204.31.

30 **Preparation CLXXX - 1-(4-Nitro-phenyl)-cyclopropanecarbonitrile:**

NaOH (5.0 N, 80ml) was added to a mixture of 4-nitrophenylacetonitrile (10.0 g, 61.7 mmol), 1,2-dibromoethane (8.0 ml, 92.5 mmol), and tetraethylammonium chloride hydrate (10.2 g, 61.7 mmol) in 200 ml of CH₂Cl₂ at

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RT. The resulting mixture was stirred at RT for 24 h, diluted with CH₂Cl₂, and acidified with HCl (10%, aq). The organic layer was separated, washed with brine, condensed, and the crude was purified by flash column chromatography. The titled compound was obtained as a light yellowish solid.

Preparation CLXXXI - C-[1-(4-Nitro-phenyl)-cyclopropyl]-methylaniline:

The mixture of 1-(4-nitro-phenyl)-cyclopropanecarbonitrile (3.0 g, 15.9 mmol) and borane THF complex (1.0 M solution in THF, 32 ml, 32 mmol) in 50 ml of anhydrous THF was heated at reflux overnight. The mixture was cooled to RT, quenched with 2.5 ml of 50% AcOH aqueous solution, then partitioned between EtOAc and NaHCO₃ (aq). The combined organic portions were washed with brine, dried with MgSO₄, filtered, and condensed. The crude was purified by flash column chromatography (1 to 2% of MeOH in CH₂Cl₂). The titled compound was obtained as a light brownish solid. MS (ES⁺): 192.9. Calc'd for C₁₀H₁₂N₂O₂- 192.2.

Preparation CLXXXII - 2,2,2-Trifluoro-N-[1-(4-nitro-phenyl)-cyclopropylmethyl]-acetamide:

Trifluoroacetic anhydride (5.26 ml, 36.9 mmol) was added to a mixture of C-[1-(4-nitro-phenyl)-cyclopropyl]-methylaniline (2.37 g, 12.3 mmol) and triethyl amine (8.6 ml, 61.5 mmol) in 50 ml of CH₂Cl₂ at RT. The resulting mixture was stirred for 2 h. The volatiles were removed under reduced pressure and the residue was partitioned between EtOAc and aqueous NaHCO₃. The organic layer was washed with brine, dried with MgSO₄, filtered, and condensed. The crude compound was purified by flash column chromatography (10 to 20% of EtOAc in hexanes), and the titled compound was obtained as an off-white solid.

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Preparation CLXXXIII - 1-(7-Nitro-4-spiro-1'-cyclopropane-3,4-dihydro-1H-isoquinolin-2-yl)-2,2,2-trifluoroethanone:

A mixture of 2,2,2-trifluoro-N-1-(4-nitro-phenyl)-cyclopropylmethyl]-acetamide (3.10 g, 10.7 mmol) and
5 paraformaldehyde (0.54 g, 17.2 mmol) was added to a mixture of 12 ml of glacial AcOH and 20 ml of H₂SO₄ at RT. The resulting mixture was stirred at 40 °C for 12 h, poured into ice-water and extracted with EtOAc. The combined organic
10 portion was washed with NaHCO₃ (aq), H₂O, brine, then dried with MgSO₄, and condensed. The crude compound was purified by flash column chromatography (10 to 20% of EtOAc in hexanes), and the titled compound was obtained as a white solid.

15 **Preparation CLXXXIV - 7-Nitro-4-spiro-1'-cyclopropane-1,2,3,4-tetrahydroisoquinoline:**

A mixture of 1-(7-nitro-4-spiro-1'-cyclopropane-3,4-dihydro-1H-isoquinolin-2-yl)-2,2,2-trifluoroethanone (0.32 g, 1.07 mmol) and K₂CO₃ (1.50 g, 14.2 mmol) in 7 ml of MeOH and 2 ml
20 of H₂O was stirred at RT overnight. The mixture was filtered, and the filtrate was concentrated. The residue was dissolved in EtOAc, washed with NH₄Cl (aq), brine, dried with MgSO₄, filtered, and condensed to give the titled compound as a light yellowish solid. MS (ES⁺): 204.9
25 (M+H)⁺. Calc'd for C₁₁H₁₂N₂O₂ - 204.23.

Preparation CLXXXV - tert-Butyl N-[7-nitro-4-spiro-1'-cyclopropane-3,4-dihydro-1H-isoquinoline-2-carbamate:

The mixture of 7-nitro-4-spiro-1'-cyclopropane-1,2,3,4-tetrahydroisoquinoline (0.20g, 0.98 mmol), BOC₂O (0.24 g, 1.08 mmol), DMAP(0.025g, 0.20 mmol), DIEA (0.51 ml, 2.94 mmol) in 10 ml of CH₂Cl₂ was stirred at RT for 2 h. The
30 solvent was removed, the residue was purified by flash

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column chromatography (5 to 10% of EtOAc in hexanes), and the titled compound was obtained as a white solid.

Preparation CLXXXVI: *tert*-Butyl N-[7-amino-4-spiro-1'-cyclopropane-3,4-dihydro-1*H*-isoquinoline]carbamate

A mixture of *tert*-butyl N-[7-nitro-4-spiro-1'-cyclopropane-3,4-dihydro-2*H*-isoquinoline-2-carbamate (0.27 g, 0.89 mmol) and Pd/C (0.05 g, 10% wt) in 15 ml of MeOH was placed under H₂ which was provided by a balloon and stirred at RT for 1.5 h. The mixture was filtered through Celite®, and condensed to give the titled compound as a white solid. MS (ES⁺): 274.8 (M+H)⁺. Calc'd for C₁₆H₂₂N₂O₂ - 274.36.

Preparation CLXXXVII - 4-methyl-6-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-pyrimidin-2-ylamine:

To a solution of (S)-(-)-1-methyl-2-pyrrolidine (320 mg, 2.78 mmol) in dry THF (10 mL) at 0 °C was added NaH (167 mg, 4.16 mmol). After stirred at RT for 1 h, 2-amino-4-chloro-6-methylpyrimidine (600 mg, 4.16 mmol) in dry THF (10 mL) was added dropwise via the addition funnel. The resulting mixture was heated to reflux under Ar gas for 20 h. The reaction was cooled to RT and quenched with sat. NH₄Cl. Solvent was removed. The residue was partitioned between H₂O and CHCl₃. The organic layer was washed with H₂O, brine, dried over MgSO₄, and evaporated to dryness. This crude compound was purified in column eluted with CH₂Cl₂:MeOH = 95%:5% to yield the title compound. MS *m/z*: 223.2 (M+H). Calc'd. for C₁₂H₂₀N₄ - 222.2.

Preparation CLXXXVIII - (6-bromo-pyridin-2-yl)3-Methyl-but-2-enoic -amide:

To a solution of 2-amino-6-bromopyridine (4, 3.015 g, 0.017 mol) and Et₃N (2.40 mL, 0.017 mol) in CH₂Cl₂ (20.0 mL), was added 3,3-dimethylacryloylchloride (1.96 mL, 0.017 mol)

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under N₂ at 0 °C. The reaction mixture was slowly warmed to RT and stirred for 12 h. The reaction was quenched by the addition of H₂O (20.0 mL). The organic layer was separated, dried over Na₂SO₄ and evaporated to dryness to yield crude compound which was used without purification.

Preparation CLXXXIX - (6-amino-pyridin-2-yl) 3-Methyl-but-2-enoic -amide:

To a solution of 2-amino-6-bromopyridine (4.30 g, 0.017 mol) and copper (0.214 g, 3.372 mmol) in IPOH (20.0 mL), was added NH₄OH (20.0 mL) in a sealed vessel under N₂. The reaction was sealed and heated to 90 °C for 12 h. The mixture was cooled to RT and EtOAc (50.0 mL) was added. The organic layer was separated, and the aq layer was washed with EtOAc (50.0 mL). The combined organic layers were evaporated to dryness, the resulting residue was dissolved in CH₂Cl₂ (50.0 mL) and washed with H₂O (4 x 30 mL). The organic layer was dried over Na₂SO₄ and evaporated to dryness to yield crude compound which was used without purification.

Preparation CXC - 7-Amino-4,4-dimethyl-3,4-dihydro-1H-[1,8]naphthyridin-2-one:

To a mixture of aminopyridine 6 (1.12 g, 5.833 mmol) and AlCl₃ (3.11 g, 0.023 mol) was added chlorobenzene (10.0 mL) in a sealed vessel under Ar. The reaction was sealed and heated to 120 °C for 12 h. The reaction mixture was cooled to RT and the mixture was poured over ice/HCl mixture and extracted with EtOAc (3 x 50.0 mL). The Aq layer was neutralized with solid NaHCO₃ and extracted with EtOAc (5 x 50 mL). The combined organic layers were dried over Na₂SO₄ and evaporated to dryness to yield crude compound which was purified by chromatography (Silica gel, CH₂Cl₂:MeOH, 99:1) yielding the title compound.

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Preparation CXCI - 2-[1-(3-Amino-phenyl)-2,2,2-trifluoro-1-trifluoromethyl-ethoxymethyl]-pyrrolidine-1-carboxylic acid tert-butyl ester:

To a mixture of 2-(3-amino-phenyl)-1,1,1,3,3,3-hexafluoro-
5 propan-2-ol (1.30 g), 2-hydroxymethyl-pyrrolidine-1-
carboxylic acid tert-butyl ester (1.04 g), PPh₃ (2.64 g) and
molecular sieves 4 Å in THF (100 mL) was added DEAD (1.55
mL) slowly. The reaction was stirred at RT for 4 h and at
10 reflux overnight. After filtration to remove solids, the
filtrate was concentrated and the residue was taken up into
Et₂O. The organic phase was washed with saturated NaHCO₃ and
brine. The organic layer was dried over MgSO₄ and
evaporated to give a viscous brown oil, which was purified
by chromatography through silica gel (500 g, 30% to 50%
15 EtOAc in hexanes) to afford 2-[1-(3-amino-phenyl)-2,2,2-
trifluoro-1-trifluoromethyl-ethoxymethyl]-pyrrolidine-1-
carboxylic acid tert-butyl ester as a light brown oil.

**Preparation CXCII - N-(3-Amino-5-chloro-phenyl)-2-
20 dimethylamino-acetamide:**

To a solution of 5-chloro-benzene-1,3-diamine (3 g, 21 mmol)
and dimethylamino-AcOH (2.2 g, 21 mmol) in CH₂Cl₂ (300 mL)
was added EDC (5 g, 25 mmol), HOBt (2.9 g, 21 mmol), and
DIEA (5 mL). The reaction mixture was stirred at RT
25 overnight. Solvent was removed in vacuo and the residue was
purified through flash chromatography on silica gel (0-8%
MeOH in EtOAc) to give the desired compound.

**General Procedure for the preparation of 2,6-
30 diaminopyridines:**

To a solution of 2-amino-6-bromopyridine (1.070 g, 6.061
mmol) in 2,4-dimethylphenol (2.0 mL) was added amine (6.667
mmol) and the reaction mixture was heated to 150 °C for 12
h. The mixture was cooled to RT and aq. HCl (2.0 M, 30 mL)

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was added. EtOAc (50 mL) was added and the organic layer was separated. The Aq layer was washed with EtOAc (2 x 40 mL) and the combined organic layers were washed with H₂O (50 mL), dried over Na₂SO₄, concentrated under vacuo to yield
5 crude compound which was used without purification.

The following compounds were prepared similarly to the procedure outlined above:

- 10 a) 3,4,5,6-Tetrahydro-2H-[1,2']bipyridinyl-6'-ylamine:
b) 6-(4-Methyl-piperazin-1-yl)-pyridin-2-ylamine:

Preparation CXCI - 2-Methyl-2-(4-nitrophenyl)propionic acid:

- 15 To a solution of 2-(4-nitrophenyl)propionic acid (50 g, 0.26 mol) in 250 mL of MeOH was added 6 mL of concentrated HCl. The resulting solution was heated at reflux for 16 h. The reaction was diluted with 200 mL of aq. NaHCO₃ and 500 mL of EtOAc. The organic layer was separated, dried over Na₂SO₄,
20 and concentrated. The residue was diluted with 100 mL of THF and added to a suspension of NaH (11.2 g, 0.28 mol, 60 % in mineral oil) in 600 mL of THF. To the resulting mixture was added CH₃I (18.3 mL, 0.29 mol) in one portion. The resulting mixture was stirred for 48 h at 40 °C and diluted with aq.
25 NH₄Cl solution and EtOAc. The organic layer was separated, dried over Na₂SO₄, and concentrated. The residue was used without further purification.

- To a solution of the residue (54 g, 0.24 mol) in 500 mL of MeOH was added 5N aq. NaOH solution (144 mL, 0.72
30 mol). The mixture was stirred for 16 h at 40°C, then, concentrated, and the residue was diluted with H₂O (500 mL). The aq. solution was acidified with 2N HCl to give a precipitate which was filtered and dried to give the titled

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compound as a yellowish solid. MS: (ES+) 210 (M+H). Calc'd for $C_{10}H_{12}NO_4$ - 210.20.

Preparation CXCI - 2-Methyl-5-[1-methyl-1-(4-nitro-phenyl)-ethyl]-[1,3,4]oxadiazole:

A mixture of 2-methyl-2-(4-nitro-phenyl)-propionic acid (5 g, 24 mmol) and a few drops DMF in $SOCl_2$ was stirred at reflux for 16 h. The resulting solution was concentrated to give corresponding acid chloride as a brown solid.

To a mixture of the acid chloride (2.33 g, 10.2 mmol), acetic acid hydrazide (0.91 g, 12.2 mmol), Et_3N (2.86 mL, 20.2 mmol) in CH_2Cl_2 (50 mL) was added 2 crystals of DMAP at RT. The resulting mixture was stirred for 16 h and concentrated. A solution of the residue in 50 mL of $POCl_3$ was heated at 95 °C for 16 h. The resulting mixture was concentrated and diluted with ice- H_2O and EtOAc. The organic layer was washed with saturated aq. $NaHCO_3$ solution twice, dried over Na_2SO_4 , and concentrated. The residue was purified by SiO_2 chromatography (hexane: EtOAc=1:1) to give the titled compound as a pale yellow crystalline solid. MS: (ES+) 248 (M+H). Calc'd for $C_{12}H_{14}N_3O_3$ - 248.10.

Preparation CXCV - 2-Methyl-5-[1-methyl-1-(4-amino-phenyl)-ethyl]-[1,3,4]oxadiazole:

A mixture of 2-methyl-5-[1-methyl-1-(4-nitro-phenyl)-ethyl]-[1,3,4]oxadiazole (1.36 g, 5.5 mmol) and Pd/C (68 mg) in EtOAc (50 mL) was stirred under 1 atm of H_2 for 16 h. The resulting slurry was filtered over Celite®, and the filtrate was concentrated to give the titled compound as a pale yellow crystalline solid. MS: (ES+) 218 (M+H). Calc'd for $C_{12}H_{16}N_3O$ - 218.12.

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Preparation CXCVI - 4-[1-Methyl-1-(4-nitro-phenyl)-ethyl]-pyrimidine:

To a mixture of 1-(4-nitro-phenyl)-propan-2-one (5.32 g, 29.7 mmol), triethylbenzylammonium chloride (0.34 g, 1.5 mmol), and 13 mL of aq. 5N KOH solution (65.3 mmol) in CH₂Cl₂ was added CH₃I (4.06 mL, 65.3 mmol). The resulting mixture was stirred at 40 °C then diluted with EtOAc and H₂O. The organic layer was dried and concentrated.

To the residue (1.0 g, 4.8 mmol) in toluene (30 mL) was added dimethylformamide dimethylacetal (1.27 mL, 9.6 mmol). The resulting mixture was heated at reflux for 6 h, then concentrated to give 1-dimethylamino-4-methyl-4-(4-nitro-phenyl)-pent-1-en-3-one as a yellow solid. MS: (ES+) 263 (M+H). Calc'd for C₁₄H₁₉N₂O₃-263.13.

A mixture of 1-dimethylamino-4-methyl-4-(4-nitro-phenyl)-pent-1-en-3-one (0.5 g, 1.9 mmol), formamidine hydrochloride (0.305 g, 3.8 mmol), and NaOEt (1.29 g, 4.0 mmol) was heated in Smith synthesizer under microwave for 10 min at 150 °C. The resultant was diluted with H₂O and EtOAc. The organic layer was dried, and the residue was used without further purification. MS: (ES+) 244 (M+H). Calc'd for C₁₃H₁₄N₃O₂ - 244.10.

Preparation CXCVII - 5-[1-Methyl-1-(4-nitro-phenyl)-ethyl]-1H-pyrazole:

A mixture of 1-dimethylamino-4-methyl-4-(4-nitro-phenyl)-pent-1-en-3-one (0.36 g, 1.4 mmol) and hydrazine hydrate (1.0 g, 6.25 mmol) in EtOH was heated at 50 °C for 3h. The mixture was concentrated, and the residue was diluted with H₂O and EtOAc. The organic layer was dried over Na₂SO₄ and concentrated to give the titled compound as a yellow solid. MS: (ES+) 232 (M+H.) Calc'd for C₁₂H₁₄N₃O₂ -232.10.

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Preparation CXCVIII - 2-Methyl-2-(4-nitro-phenyl)-1-pyrrolidin-yl-propan-1-one:

To a round bottom flask charged with 2-methyl-2-(4-nitro-phenyl)-propionic acid, was added 6.5 ml of SOCl_2 . The mixture was heated to 80°C , with stirring under inert atmosphere for 3.5 h. The mixture was cooled to RT, and then dried in-vacuo. The residue was placed under high vac. After completely dry, the residue was used without further purification.

To the residue was added 10 ml of CH_2Cl_2 , along with Et_3N and the mixture was cooled to 0°C on an ice/ H_2O bath. Pyrrolidine .46 mL (1.25 eq.) was added into the mixture, then stirred to RT under inert atmosphere. After 3 h of stirring, the mixture was quenched with H_2O , diluted with CH_2Cl_2 , and transferred to a separatory funnel. The organics were collected, combined, dried over Na_2SO_4 and filtered. The crude was concentrated in vacuo. After drying, the title compound was produced as an amorphous solid. MS: 263 (M+1); calc'd for $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_3$ - 262

Preparation CXCIX - 4-(1,1-Dimethyl-2-pyrrolidin-1-yl-ethyl)-phenylamine:

To a 3-neck round bottom flask, charged with 2-Methyl-2-(4-nitro-phenyl)-1-pyrrolidin-yl-propan-1-one was added 66 ml of 1M BH_3/THF soln, while the mixture was maintained at 0°C on an ice/ H_2O bath. The mixture was stirred under inert atmosphere overnight. A couple drops of 5N NaOH was added slowly to the reaction mixture for quenching. After stirring an additional 5 min, 22 ml of 5N NaOH was added into the reaction mixture, then stirred vigorously for 3 h. The mixture was diluted with 50 ml of 1N NaOH and 100 ml of EtOAc, then transferred into a sep. funnel. The organics were collected and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 , then NaHCO_3 soln. was added into the

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mixture the organic extracts were dried over Na_2SO_4 , filtered, then concentrated *in vacuo*.

To a round bottom flask charged with Pd/C in MeOH under inert atmosphere, was added 1-[2-methyl-2-(4-nitro-phenyl)-propyl]-pyrrolidine in MeOH and H_2 was added while stirring vigorously overnight. The mixture was filtered through Celite® and concentrated *in vacuo* to yield a light yellow oil. MS: 219 (M+1); calc'd for $\text{C}_{14}\text{H}_{22}\text{N}_2$.

10 **Preparation CC - 1-methyl-1-(4-nitro-phenyl)-ethylamine:**

To a round bottom flask charged with 2-methyl-2-(4-nitro-phenyl)-propionic acid (10 g; 0.0440 mole), was added SOCl_2 (32 ml). The mixture was heated to reflux, until completion of the reaction. After heating, the residual SOCl_2 was removed by *in vacuo*, then placed the residue on high vac. The crude was used without further purification.

To the residue, was added 20 ml toluene and stirred. Then slowly NaN_3 (7.14 g; 0.1099 mole) was added into the mixture, and stirred vigorously under inert atmosphere for 1.5 h. The mixture was poured into 50 ml H_2O and transferred into a sep. funnel, with 50 ml EtOAc. The organics were collected, dried, filtered, and concentrated *in-vacuo*. The residue was dissolved in toluene and heated to 100°C while stirring vigorously under inert atmosphere for 1 h. The solvent was removed *in-vacuo*, 20% HCl aq was added and the mixture stirred vigorously under reflux conditions at 100°C for 9 h. The mixture was evaporated *in-vacuo* and to the residue was added 50 ml of 5N NaOH and 80 ml EtOAc, then transferred the mixture to a sep. funnel.

30 The organic layer was collected, dried, filtered, and conc. *in-vacuo*. The residue was purified on silica-gel column in a solvent gradient of 80% EtOAc/Hexanes to 10% MeOH/ CH_2Cl_2 yielding a brown solid resulted. MS: 181 (M+1); calc'd for $\text{C}_9\text{H}_{12}\text{N}_2\text{O}_2$ -180.

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Preparation CCI - [1-(4-Amino-phenyl)-1-methyl-ethyl]-(2-methylsulfanyl-pyrimidin-4-yl)-amine:

To a Personal Chemistry reaction tube, was added 1-methyl-1-(4-nitro-phenyl)-ethylamine, along with 4-chloro-2-methylsulfanyl-pyrimidine, DIEA (2.0 eq) and t-BuOH (0.6 ml). The tube was heated by microwave to 150°C for 10 min. After heating, the crude was diluted with CH₂CL₂ and H₂O, then transferred into a sep. funnel. The organics were collected, dried over Na₂SO₄, then concentrated *in vacuo*. The crude was used without further purification.

To a round bottom flask charged with PtO₂ (12% wt.) in MeOH (5 ml), was added crude nitro-intermediate (.170 g.; 0.0006 mole). The mixture was stirred vigorously under H₂ for 2.5 h. The mixture was filtered through Celite® and concentrated *in-vacuo*. The desired material was purified by silica-gel chromatography in a solvent gradient of 80% EtOAc/Hexanes to 5% MeOH/CH₂CL₂. After drying in high vac, the title compound resulted as a light yellow amorphous solid.

Preparation CCII - 2-(2,2,2-Trifluoro-ethoxy)-isonicotinonitrile:

To the suspension of NaH (2.78 g, 0.11 mole) in THF 100 mL) 2,2,2-trifluoroethanol (10 g, 0.1 mol) was added slowly. The mixture was stirred at RT till it turned clear. A solution of 2-chloro-isonicotinonitrile (13.8 g, 0.1 mol) in THF (100 mL) was slowly added and stirred at reflux for 3 h. After filtration and concentration, the crude oily compound was purified through column chromatography providing pure compound as an oil.

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Preparation CCIII - [2-(2,2,2-Trifluoro-ethoxy)-pyridin-4-yl]-methylamine hydrogen chloride:

A mixture of 2-(2,2,2-trifluoro-ethoxy)-isonicotinonitrile (3.90 g, 19.40 mmol), 12N HCl (8.0 mL) and 10% Pd/C (800 mg) in MeOH (100 ml) was stirred under a balloon of H₂ for 7 h. After filtration, the filtrate was concentrated to give compound as a white solid. MS (ES⁺): 206.9 (M+H)⁺. Calc'd. for C₈H₉F₃N₂O - 206.07.

Preparation CCIV - 2-Bromomethyl-3-nitro-benzoic acid methyl ester:

The mixture of methyl 2-methyl-3-nitro benzoate (5.06 g, 25.9 mmol), NBS (5.54 g, 31.1 mmol), and AIBN (0.43 g, 2.59 mmol) in 100 ml of anhydrous CCl₄ was heated at reflux under N₂ for 22 h, cooled to RT, diluted with EtOAc, and washed with Na₂CO₃ (aq). The organic portion was separated, washed with brine, dried with Na₂SO₄, filtered, and condensed. The crude material was purified by flash column chromatography to yield pure product, which was used without further purification.

Preparation CCV - 4-Nitro-2, 3-dihydro-isoindol-1-one:

NH₃ (2.0 M in MeOH, 50 ml) was slowly added to the solution of 2-bromomethyl-3-nitro-benzoic acid methyl ester (4.46 g, contaminated with a small amount of assumed starting material, 16.3 mmol) in 30 ml of MeOH at RT. The resulting mixture was stirred at RT overnight, to provide the title compound as a white solid. MS (ES⁺): 179.2 (M+H)⁺. Calc'd for C₈H₆N₂O₃ - 178.14.

Preparation CCVI - 4-Amino-2, 3-dihydro-isoindol-1-one:

To the suspension of 4-nitro-2,3-dihydro-isoindol-1-one (2.40 g, 13.5 mmol) in 100 ml of MeOH was added Pd/C (10 wt%, 0.36 g). The mixture was then placed under H₂ from a

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balloon, stirred at RT for 24 h, filtered through Celite®, and condensed to give the titled compound as a light greenish solid. MS (ES⁺): 149.1 (M+H)⁺. Calc'd for C₈H₈N₂O - 148.16.

5

Preparation CCVII - Pyridin-4-ylmethyl-carbamic acid tert-butyl ester:

Boc anhydride (23 g, 105 mmol) was carefully added to a solution of pyridin-4-yl-methylamine (11 g, 102 mmol) and DMAP (0.5 g, 4 mmole) in CH₂Cl₂ (150 mL). The reaction was extended for 1 hr after the addition. The reaction mixture was concentrated *in vacuo* and the residue was recrystallized in EtOAc to afford an off white crystal as the desired compound.

15

Preparation CCVIII - (1-Oxy-pyridin-4-ylmethyl)-carbamic acid tert-butyl ester:

Pyridin-4-ylmethyl-carbamic acid tert-butyl ester (2.1 g, 10 mmol) was dissolved in a one to one mixture of aqueous MeOH (200 mL) with NaHCO₃ (5 g, 60 mmol) and Oxone® (12.3 g, 20 mmol). The mixture was stirred overnight then concentrated *in vacuo* to remove MeOH. The resulted aqueous mixture was diluted with H₂O (150 mL) and filtered. The filter cake was washed with H₂O and dried to afford a white solid as the desired compound.

25

Preparation CCIX - C-(1-Oxy-pyridin-4-yl)-methylamine:

Oxy-pyridin-4-ylmethyl)-carbamic acid tert-butyl ester (2.1 g, 9.4 mmol) was dissolved in a 4N HCl in dioxane solution (50 mL) and heated to 50 C for 2 h. After removing solvent *in vacuo*, a white solid was received as an HCl salt of the desired compound.

30

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Preparation CCX - 2-(4-Methoxy-benzylamino)-isonicotinonitrile:

To pyridine (500 mL) were added 2-chloroisonicotinonitrile (22.0 g, 159 mmole), para-methoxybenzylamine (25 g, 114% Meq.), and NaHCO₃ (30 g). The mixture was heated under reflux overnight. After cooling to RT, the mixture was filtered and the filter cake was rinsed with CH₂Cl₂. The combined filtrate was concentrated to dryness in vacuum to form a yellow solid. This solid is then recrystallized in EtOAc to give a light yellow crystalline compound and the mother liquor was concentrated and subjected to EtOAc again (repeating three times) to yield the desired compound.

Preparation CCXI - (4-Aminomethyl-pyridin-2-yl)-(4-methoxy-benzyl)-amine:

2-(4-Methoxy-benzylamino)-isonicotinonitrile (12 g, 50 mmole) was dissolved in a mixed solvent of EtOH (800 mL) Et₃N (200 mL) and suspended with 2 g of Pd/C (10%). After removing air with vacuum, the flask was charged with H₂ with a balloon. The H₂ balloon was refilled every morning and evening. Pd/C was recharged twice (1.3 g each) on days 2 and 3. Reaction was completed on the 4th day and the reaction mixture was filtered through a pad of Celite®. The filter cake was rinsed with MeOH and the combined filtrate was concentrated in vacuo to give the desired compound as a light brown solid.

Preparation CCXII - 4-Aminomethyl-pyridin-2-ylamine:

(4-Aminomethyl-pyridin-2-yl)-(4-methoxy-benzyl)-amine (12 g, 50 mmole) was dissolved in TFA (150 mL) and heated to reflux for 1 h. After cooling, the reaction mixture was concentrated in vacuum and the residue was partitioned between HCl (1N, aq.) and EtOAc. The aqueous layer was washed with EtOAc then hexanes and concentrated to dryness

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in vacuum to give an off white solid as a dihydrochloric salt.

Preparation CCXIII - 2-Methylamino-isonicotinonitrile:

5 To a solution of 2-chloroisonicotinonitrile (22.0 g, 159 mmole) in pyridine (500 mL) was added methylamine in THF (2N, 160 mL), and NaHCO₃ (54 g). The mixture was heated to 120 °C in a sealed vessel for 40 h. After cooled to RT, the mixture was filtered and the filter cake was washed with
10 CH₂Cl₂. The combined filtrate was concentrated *in vacuo* to give a yellow solid (21 g) as the desired compound.

Preparation CCXIV - (4-Aminomethyl-pyridin-2-yl)-methylamine:

15 A suspension of 2-Methylamino-isonicotinonitrile (5.6 g) and Pd/C (10%, 4 g) in EtOH (150 mL) and TEA (40 mL) was placed in a 500 mL Parr Hydrogenation bottle and hydrogenated at or below 60 psi H₂ pressure over night. After filtering through a pad of Celite®, the reaction mixture was
20 concentrated *in vacuo* to give a yellow oil as the desired compound.

Preparation CCXV - 3-Fluoro-pyridine 1-oxide:

3-Chloroperoxybenzoic acid (70%, 35.0 g, 142 mmol) was added
25 to the solution of 3-fluoropyridine (6.90 g, 71.1 mmol) in 200 ml of CH₂Cl₂, the mixture was stirred at RT overnight, washed with a small amount of saturated NaHCO₃ solution, dried with Na₂SO₄, filtered, condensed, the crude compound was purified by flash column chromatography (1 to 2% of MeOH
30 in CH₂Cl₂), the titled compound was obtained as a light yellowish solid. MS (ES⁺): 114.1 (M+H)⁺. Calc'd for C₅H₄FNO - 113.09.

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Preparation CCXVI - 3-Fluoro-pyridine-2-carbonitrile:

The mixture of 3-fluoro-pyridine 1-oxide (0.99 g, 8.75 mmol), trimethylsilyl cyanide (4.80 ml, 35.0 mmol), and triethyl amine (1.84 ml, 13.2 mmol) in 100 ml of CH₃CN was heated at reflux overnight. The solvents were removed, under reduced pressure and the residue was partitioned between EtOAc and saturated NaHCO₃. The organic portion was separated, dried with Na₂SO₄, filtered, condensed, the crude compound as purified by flash column chromatography (10 to 20% of EtOAc in hexanes). The titled compound was obtained as a light yellowish solid. MS (ES⁺): 123.1 (M+H)⁺. Calc'd for C₆H₃FN₂ - 122.10.

Preparation CCXVII - C-(3-Fluoro-pyridin-2-yl)-methylanine:

The mixture of 3-fluoro-pyridine-2-carbonitrile (0.81 g, 6.63 mmol) and Pd/C (0.20 g, 10% wt) in 10 ml of MeOH and 2.7 ml of concentrated HCl was placed under H₂ which was provided by a balloon and stirred at RT for 4 h, filtered through Celite®, condensed, the residue was purified by flash column chromatography, 0.13 g of the titled compound was obtained as a light yellowish oil. MS(ES⁺): 127.1 (M+H)⁺. Calc'd for C₆H₇FN₂ - 126.13.

Preparation CCXVIII: 5-Bromo-pyridine-2-carbonitrile:

The mixture of 2,5-dibromopyridine (4.74 g, 20.0 mmol), zinc cyanide (1.40 g, 12.0 mmol), zinc dust (0.059 g, 0.90 mmol), and Pd(dppf)Cl₂.CH₂Cl₂ (0.36 g, 0.44 mmol) in 25 ml of DMF was heated at reflux for 5 h, cooled to RT, diluted with H₂O, extracted with EtOAc, the organic portion was washed with brine, the solvents were removed, the crude compound was purified by flash column chromatography (5 to 15% of EtOAc in hexanes), the titled compound was obtained as an off-white solid.

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Preparation CCXIX - 5-Fluoro-pyridine-2-carbonitrile:

The mixture of 5-bromo-pyridine-2-carbonitrile (0.50 g, 2.73 mmol), and KF (0.48 g, 8.20 mmol) in 10 ml of 1-methyl-2-pyrrolidinone was stirred at 175 °C for 18 h, cooled to RT, diluted with H₂O, extracted with EtOAc, the combined organic portions were washed with H₂O, brine, dried with Na₂SO₄, filtered, condensed, the crude compound was purified by flash column chromatography (5 to 20% of EtOAc in hexanes). The titled compound was obtained as an off-white solid.

10

Preparation CCXX - C-(5-Fluoro-pyridin-2-yl)-methylamine:

The mixture of 5-fluoro-pyridine-2-carbonitrile (0.16 g, 1.27mmol) and Pd/C (0.030 g, 10% wt) in 15 ml of MeOH and 0.50 ml of concentrated HCl was placed under H₂ which was provided by a balloon and stirred at RT for 4 h, filtered through Celite®, condensed, the residue was purified by flash column chromatography. The titled compound was obtained as a light yellowish solid. MS(ES⁺): 127.2 (free base) (M+H)⁺. Calc'd for C₆H₇FN₂ (free base)- 126.13.

20

Preparation CCXXI - 1H-Pyrrolo[2,3-b]pyridine 7-oxide:

To a suspension of 1H-pyrrolo[2,3-b]pyridine (10.0 g) and NaHCO₃ (45.2 g) in 1:1 MeOH/H₂O (1000 mL) was added Oxone® (106 g) in portions during 40 min period. The mixture was stirred at RT for 5 h. The solid was removed by filtration and the filtrate was concentrated to 200 mL in volume. This aqueous phase was extracted with CH₂Cl₂ (200 mL X 7) to afford 1H-pyrrolo[2,3-b]pyridine 7-oxide.

Preparation CCXXII - 4-chloro-1H-pyrrolo[2,3-b]pyridine:

To a cooled POCl₃ (50 mL) in a dried round bottom flask, 1H-pyrrolo[2,3-b]pyridine 7-oxide (5.73 g, step A) was added in portions. The mixture was heated to reflux for 5 h. After cooled down to RT, POCl₃ was evaporated under high vacuum

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under gentle heating (40-50 °C) to obtain black residue. 50 mL of H₂O was added slowly and pH was adjusted to 8-9 with Na₂CO₃ (first with solid, then saturated aqueous solution). The resulting precipitate was collected by filtration, washed with cold H₂O and dried in a vacuum oven (50 °C) to give 4-chloro-1H-pyrrolo[2,3-b]pyridine as tan powder.

Preparation CCXXIII - 1-(4-iodo-pyrrolo[2,3-b]pyridin-1-yl)-ethanone:

10 To a suspension of 4-chloro-1H-pyrrolo[2,3-b]pyridine (3.80 g, step B) and NaI (19.15 g) in CH₃CN (40 mL) was added acetyl chloride (5.0 mL) slowly. The mixture was heated to reflux for overnight. After cooled to RT, 40 mL of 10% Na₂CO₃ and 40 mL of 10% NaHSO₃ were added. After stirring for 15 min, the mixture was extracted with EtOAc 4 times. The combined organic phases were washed with brine, dried over MgSO₄ and concentrated to give a brown residue as the crude compound, which was purified by chromatography through silica gel (220 g, 5 to 15% EtOAc/hexanes to afford 1-(4-iodo-pyrrolo[2,3-b]pyridin-1-yl)-ethanone as white solid.

Preparation CCXXIV - 1-acetyl-1H-pyrrolo[2,3-b]pyridine-4-carbonitrile:

A mixture of 1-(4-iodo-pyrrolo[2,3-b]pyridin-1-yl)-ethanone (4.30 g, step C), CuCN (6.841 g), Pd₂dba₃ (0.729 g), and dppf (1.636 g) in 85 mL of dioxane was heated to reflux for 2 h. Solid was removed by filtration through a pad of Celite®. The filtrate was concentrated to give a yellow solid as crude compound, which was purified by chromatography through silica gel (250 g, 5-30% EtOAc/hexanes, stepwise gradient) to afford 1-acetyl-1H-pyrrolo[2,3-b]pyridine-4-carbonitrile as a white fluffy solid.

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Preparation CCXXV - 1-(4-aminomethyl-pyrrolo[2,3-b]pyridin-1-yl)-ethanone:

A mixture of 1-acetyl-1H-pyrrolo[2,3-b]pyridine-4-carbonitrile (0.872 g, step D), 10% Pd/C (0.882 g), 20 mL of Et₃N, and 80 mL of EtOH was stirred at RT under balloon pressure of H₂ for overnight. Solid was removed by filtration through a pad of Celite® and the filtrate was concentrated to yield a cream color residue, which was purified by chromatography through silica gel (70 g, 2 to 5% MeOH/CHCl₃ with 1% NH₄OH) to afford 1-(4-aminomethyl-pyrrolo[2,3-b]pyridin-1-yl)-ethanone as a white solid.

Preparation CCXXVI - N-(1-acetyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-4-ylmethyl)-acetamide:

To a mixture of 1-acetyl-1H-pyrrolo[2,3-b]pyridine-4-carbonitrile (0.691 g, example 15, step D), 10% Pd/C (0.702 g), 5 mL of Et₃N, and 20 mL of EtOAc was added acetic anhydride (1.0 mL). The mixture was stirred at RT under balloon pressure of H₂ for overnight. Solid was removed by filtration through a pad of Celite® and the filtrate was concentrated to yield a white residue, which was purified by chromatography through silica gel (150 g, 1 to 5% MeOH/CHCl₃ with 1% NH₄OH, stepwise gradient) to afford N-(1-acetyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-4-ylmethyl)-acetamide (0.50 g) as white solid.

Preparation CCXXVII - C-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-4-yl)-methylamine hydrogen chloride salt:

A mixture of N-(1-acetyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-4-ylmethyl)-acetamide (0.50 g, step A), HCl (conc., 3 mL) and EtOH (12 mL) was heated to 70 °C for overnight. Additional 3 mL of conc. HCl was added to the reaction and the heating was continued for 3 more days. Solvent was evaporated to give a white residue as crude C-

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(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-4-yl)-methylanine HCl salt, which was used without further purification.

General Procedure for the Preparation of 2-amino-4-
5 **methylaminopyridines**

Preparation CCXXVIII - 2-aminoisonicotinonitrile:

To a slurry of 2-chloro-4-cyanopyridine (10.00 g, 0.079 mol) and sodiumbicarbonate (19.92 g, 0.237 mol) in amine (0.174
10 mol) was added pyridine (35.0 mL) and the reaction was heated to 90 °C for 3 h. The reaction was then cooled to RT, diluted with the addition of CH₂Cl₂ (100 mL) and filtered. The solid was washed with EtOAc. Combined washes were concentrated in vacuo. A mixture of MeOH/hexanes was added
15 and kept in the fridge for 12 h. The crystals that formed were filtered and washed with hexanes.

Preparation CCXXIX - 2-amino-4-methylaminopyridine:

To a mixture of 2-aminoisonicotinonitrile (0.043 mol) and
20 Pd/C (10%, 6.00 g) was added Et₃N (40.0 mL) and EtOH (160.0 mL) in a parr bottle and hydrogenated at 50 psi for 12 h. Crude mixture was filtered through Celite®, concentrated under vacuo and dried under high vacuum to yield compound.

25 **Preparation CCXXX - (2-Pyrrolidin-1-yl-pyridin-4-yl)-
methylanine:**

Prepared according to the general procedure with pyrrolidine as the amine.

30 **Preparation CCXXXI - (2-Morpholin-4-yl-pyridin-4-yl)-
methylanine:**

Prepared according to the general procedure with morpholine as the amine.

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Preparation CCXXXII - 3,9,9-Trimethyl-6-nitro-4,9-dihydro-3H-3-aza-fluorene:

4-[1-(2-Bromo-4-nitro-phenyl)-1-methyl-ethyl]-1-methyl-1,2,3,6-tetrahydro-pyridine (9 g), Pd(OAc)₂ (900 mg), and
5 DIEA (15 mL) was dissolved in DMF (300 mL), and heated to 80°C overnight. Solvents were removed *in vacuo*. The residue was partitioned between CH₂Cl₂/NaHCO₃(sat, aq.). The CH₂Cl₂ layer was washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified via flash
10 chromatography on silica to give the desired compound. (MS: M+H=257).

Preparation CCXXXIII - 3,9,9-Trimethyl-2,3,4,4a,9,9a-hexahydro-1H-3-aza-fluoren-6-ylamine(156):

15 3,9,9-Trimethyl-6-nitro-4,9-dihydro-3H-3-aza-fluorene (700 mg) was dissolved in EtOH (20 mL) with aqueous HCl (1N, 5 mL) and suspended with Pd/C (10%, 100 mg). The flask was capped with a balloon filled with H₂. The reaction was completed in 6 h at RT. The reaction mixture was filtered
20 through a layer of Celite® with MeOH. The combined filtrate was concentrated to give desired compound. (MS: M+H=231).

Preparation CCXXXIV - 2-Chloro-5-nitro-phenol:

A mixture of 2-chloro-4-nitroanisole (10 g, 53.3 mmol) and
25 pyridinium chloride (50 g, 426 mmol) was heated at 200 °C for 3 h. After cooling to RT, the mixture was dissolved in 150 mL of aqueous 2N HCl and 150 mL of EtOAc. The organic phase was separated and was washed with aqueous 2N HCl (2 x 100 mL). The resulting organic phase was dried over MgSO₄
30 and concentrated *in vacuo*. The title compound was obtained via chromatography (silica gel, 10:1 hexane/EtOAc) as a yellow solid.

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Preparation CCXXXV - 3-(5-Amino-2-chloro-phenoxyethyl)-azetidine-1-carboxylic acid tert-butyl ester:

To a solution of 3-(2-chloro-5-nitro-phenoxyethyl)-azetidine-1-carboxylic acid tert-butyl ester (2.5 g, 7.29 mmol) in 60 mL of MeOH/H₂O (1:1) and 3 mL of acetic acid (J.T. Baker) was added Zn powder (2.3 g, 36.47 mmol, Aldrich) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h then stirred at 10 °C for 2 h. The resulting mixture was filtered through a Celite® pad and the filtrate was concentrated *in vacuo*. The residue was treated with 60 mL of saturated aqueous NaHCO₃ and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine and dried with MgSO₄. The resulting solution was concentrated *in vacuo* and the title compound was obtained by column chromatography (silica gel, EtOAc) as a yellow solid.

Preparation CCXXXVI: 3-(Benzotriazol-1-yloxy)-6-chloro-pyridazine-4-carboxylic acid (4-tert-butyl-phenyl)-amide:

A mixture of 3,6-dichloropyridazine-4-carboxylic acid (1.00 g, 5.18 mmol), 4-tert-butylaniline (0.92 mL, 5.60 mmol), TBTU (1.75 g, 5.44 mmol), and DIEA (1.80 mL, 10.4 mmol) in 7.5 mL of anhydrous DMF was stirred at RT under N₂ overnight. The mixture was diluted with H₂O, extracted with EtOAc, and the combined organic portions were washed with brine, dried with Na₂SO₄, filtered, and condensed. The crude compound was purified by flash column chromatography (hexanes/EtOAc/CH₂Cl₂, 9:0:1 to 7:2:1), to provide the desired compound as a light yellowish solid. MS (ES⁺): 423.0 (M+H)⁺. Calc'd for C₂₁H₁₉ClN₅O₂ - 422.87.

30

Preparation CCXXXVII - 3-Hydroxyethyl-azetidine-1-carboxylic acid benzyl ester:

To a mixture of azetidine-1,3-dicarboxylic acid monobenzyl ester (6.4 g) in THF (200 mL) was added BH₃•THF (6 eq, 163

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mL, 1M solution) dropwise via an addition funnel at -40 C under an N₂ atmosphere. The solution was warmed to RT and stirred overnight. To the reaction, 5N NaOH (50 mL) was added and then concentrated under vacuum. The resulting aqueous solution was extracted with Et₂O (3 x 100 mL). The organic layer was dried over Na₂SO₄ and evaporated to give the title compound which was used without further purification.

10 **Preparation CCXXXVIII - 3-Methanesulfonyloxymethyl-azetidine-1-carboxylic acid benzyl ester:**

3-Hydroxymethyl-azetidine-1,3-dicarboxylic acid monobenzyl ester (6.6 g) was dissolved in CH₂Cl₂ (100 mL) and brought to -15 C. While stirring, TEA was added (3 eq, 9.43 g) followed by methanesulphonic chloride (2.0 eq, 7.69 g) and allowed to come to RT and stirred for 1 h. The resulting organic solution was extracted with water (3 x 100 mL). The organic layer was dried over Na₂SO₄ and evaporated to give the desired product as a clear oil which was used without further purification.

Preparation CCXXXIX - 3-Nitro-5-trifluoromethyl-phenol:

A flask containing 1-Methoxy-3-nitro-5-trifluoromethyl-benzene (10g) and hydrochloride pyridine (10 eq, 52.0 g) was heated to 210 C and stirred for 12 h. Once complete, the reaction was cooled and the residue was dissolved in CH₂Cl₂ and washed twice with water (100 mL). The organic layer was concentrated under vacuum and then set in the freezer overnight. The resulting crystalline product was filtered off and washed with ether and used as is.

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Preparation CCXL - 3-(3-Nitro-5-trifluoromethyl-phenoxy-methyl)-azetidine-1-carboxylic acid benzyl ester:

A mixture of 3-nitro-5-trifluoromethyl-phenol (750 mg, Step C), K_2CO_3 (3 eq., 1.5 g) and 3-hydroxymethyl-azetidine-1-carboxylic acid benzyl ester (1.1 eq., 1.2 g) in DMF was heated to 80 C for 1 h. The solution was cooled to RT then filtered and concentrated under vacuum. The residue was dissolved in CH_2Cl_2 and washed with H_2O twice, followed by brine. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography using 5% MeOH/ CH_2Cl_2 to provide the desired compound as a colorless solid.

Preparation CCXLI - 3-(3-amino-5-trifluoromethyl-phenoxy-methyl)-azetidine-1-carboxylic acid benzyl ester:

To a solution of 3-(3-nitro-5-trifluoromethyl-mg) and NH_4Cl (1.1 eq., 80mg) was added iron dust (3 eq., 220 mg) in a 10% water/EtOH solution. The solution was heated to reflux for 6 h. The solution was cooled, then filtered through a pad of Celite®. The resulting solution was concentrated under vacuum to provide the desired compound as a dark yellow solid and used as is.

Preparation CCXLII - 3-nitro-5-(trifluoromethyl)phenylamine

To a solution of 3,5-dinitrobenzotrifluoride (10 g, 42 mmols, 1 eq.) in 150 mL of EtOH was added 17.6 mL (258.3 mmols, 6.15 eq.) of ammonium sulfide in water (50% by weight, Aldrich). The reaction was heated to reflux for 16 h during which time it became orange and a yellow precipitate formed. After cooling the volume was reduced to approximately 50 mL. The solid was removed by filtration and the filtrate evaporated to dryness *in vacuo*. The resulting orange solid was purified by column chromatography

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eluting with a step gradient of 20-30% EtOAc:hexane to provide the compound as a yellow/orange solid.

Preparation CCXLIII - N-(3-nitro-5-

(trifluoromethyl)phenyl)methanesulfonamide

- 5 3-Nitro-5-(trifluoromethyl)phenylamine (2 g, 9.7 mmols, 1 eq) was dissolved in 100 mL of CH₂Cl₂. The yellow solution was cooled to 0 °C. Et₃N (2 mL, 14.55 mmols, 1.5 eq) was added followed by mesyl chloride (0.75 mL, 9.7 mmols, 1 eq).
- 10 The reaction was stirred for 2 h at 0 °C and warmed to RT. Pyridine (0.785 mL, 9.7 mmols, 1 eq) and a catalytic amount of dimethylamine pyridine were added. The reaction was stirred at RT for 16 h. An additional equivalent of mesyl chloride was added and the reaction was heated to reflux for
- 15 24 h. After cooling, the solvent was removed *in vacuo*, and the residue redissolved in CH₂Cl₂. The solution was washed twice with 2 N HCl and once with brine. After drying over Na₂SO₄, the solution was filtered and the solvent removed. The resulting solid was triturated briefly with 10%
- 20 EtOAc:hexane to provide a white solid that was a mixture of sulfonimide and sulfonimide.

- The above mixture was dissolve in 20 mL of MeOH that had been saturated with K₂CO₃. After 30 min the reaction was stripped and the resulting solid portioned between 2 N
- 25 HCl and CH₂Cl₂. The CH₂Cl₂ was dried over Na₂SO₄ and stripped to provide and off-white solid.

Preparation CCXLIV - (3S)-tetrahydro-3-furanyl 3-nitro-5-(trifluoromethyl)phenylcarbamate

- 30 3-(S)-Hydroxytetrahydrofuran (4.8 mL, 60.7 mmols, 5 eq) was dissolved in 60 mL of toluene. The solution was cooled to 0 °C and Et₃N (5.1 mL, 36.4 mmols, 3 eq) was added. Trichloromethyl chloroformate (3.65 mL, 30.33 mmols, 2.5 eq) was added slowly. The solurion was stirred at 0 °C for 45

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min. 3-Amino-5-nitrobenzotrifluoride (2.5 g, 12.13 mmols, 1 eq) was added dropwise in 20 mL of toluene. The reaction was stirred at 0 °C for 1 h. An additional 5 eq of 3-(S)-hydroxytetrahydrofuran was converted to the chloroformate as described above, and added to the reaction mixture. After an additional h at 0 °C, the reaction was heated to 60 °C for 1 h. The reaction was cooled to RT and concentrated. The residue was dissolved in EtOAc, washed twice with saturated NH₄Cl and once with brine. After being dried over Na₂SO₄ the solution was filtered and the solvent removed *in vacuo*. The crude product was purified using a Biotage chromatography system eluting with a gradient of 5% to 35% EtOAc:hexane to yield the desired compound.

15 **Preparation CCXLV - N-(2-((3-nitro-5-**

(trifluoromethyl)phenyl)oxy)ethyl)-methanesulfonamide

2-((3-Nitro-5-(trifluoromethyl)phenyl)oxy)ethylamine (4.05 g, 16.2 mmols, 1 eq) was dissolved in 100 mL of CH₂Cl₂. The solution was cooled to 0 °C. Pyridine (2.6 mL, 32.4 mmols, 2 eq) was added followed by mesyl chloride (1.25 mL, 16.2 mmols, 1 eq). The reaction was stirred for 18 h during which time it was warmed slowly to RT. The solvent was removed *in vacuo*, and the residue dissolved in EtOAc. The resulting solution was washed twice with 2 N HCl, once with water, and 3x with brine. After being dried over Na₂SO₄ the solution was filtered and concentrated. The crude was purified by silica gel chromatography eluting with 50% to 60% EtOAc:hexane to yield the desired compound.

30 **Preparation CCXLVI - N-(2-((3-amino-5-**

(trifluoromethyl)phenyl)oxy)ethyl)methanesulfonamide

N-(2-((3-Nitro-5-(trifluoromethyl)phenyl)oxy)ethyl)-methanesulfonamide (1.7 g, 5.2 mmols, 1 eq) was dissolved in 50 L of MeOH. 10% Pd/C (170 mg, 10 weight %) was added and

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the reaction sparged with H₂. The suspension was stirred for 5 h, then filtered through Celite. The filtrate was stripped to yield the title compound.

5 The following compounds were prepared similarly to the procedure outlined above:

a) 3-((((2R)-1-acetyl-2-pyrrolidinyl)methyl)oxy)-5-(trifluoromethyl)phenylamine.

10 b) (3S)-tetrahydro-3-furanyl 3-amino-5-(trifluoromethyl)phenylcarbamate.

c) N-(3-amino-5-(trifluoromethyl)phenyl)-methanesulfonamide

Preparation CCXLVII - (2R)-1-acetyl-2-(((3-nitro-5-
15 **(trifluoromethyl)phenyl)oxy)methyl)pyrrolidine**
(2R)-2-(((3-nitro-5-(trifluoromethyl)phenyl)oxy)methyl)pyrrolidine (3.46 g, 11.9 mmols, 1 eq) was dissolved in 100 mL of CH₂Cl₂. Et₃N (5 mL, 35.7 mmols, 3 eq) was added followed by Ac₂O (1.2 mL, 13.1 mmols, 1.1 eq). The reaction
20 was stirred at RT for 1.5 h. The solvent was removed *in vacuo* and the residue dissolved in EtOAc. The solution was washed once each with saturated NH₄Cl, 1 N HCl, and twice with brine. The organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude material was
25 purified on a Biotage chromatography system eluting with a gradient of 10% to 75% EtOAc:hexane to yield the title compound.

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Preparation CCXLVIII - 3-(2-Chloro-5-nitro-phenoxyethyl)-azetidine-1-carboxylic acid tert-butyl ester:

To the mixture of 2-chloro-5-nitro-phenol (1.31 g, 7.54 mmol) and K_2CO_3 (1.57 g, 11.31 mmol) in 20 mL of DMF was added 3-methanesulfonyloxyethyl-azetidine-1-carboxylic acid tert-butyl ester (2.0 g, 7.54 mol). The reaction mixture was stirred at 50 °C for 1 h. After cooling to RT, the reaction mixture was diluted in 100 mL of EtOAc and quenched with 50 mL of water. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuum. The title compound was obtained via column chromatography (silica gel, 1;1 hexane/EtOAc) as yellow oil with 93% yield.

The following additional preparations for exemplary compounds, intermediates, and starting materials should further assist in the understanding and appreciation of various embodiments, and additional examples (Tables 1-5), of compounds of the present invention.

Example 1

Preparation of 2,2,2-trifluoro-N-[2-(4-nitro-phenyl)-ethyl]-acetamide:

To a solution of 4-nitrophenethylamine hydrochloride (50 g, 0.247 mole), DIEA (128 mL, 0.74 mole, 3 eq.) and CH_2Cl_2 (500 mL) in a 1L round bottom flask equipped with a magnetic stirrer was added $(CF_3CO)_2O$ (52.5 mL, 0.37 mole, 1.5 eq) dropwise at 5-10 °C (with ice/water bath). After stirring for another 1 h after the addition at RT, the reaction was quenched with water (200 mL) and transferred into a separatory funnel. The organic layer was separated,

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washed with water and sat. NH_4Cl , dried over Na_2SO_4 , filtered, concentrated to give a brown oil. The crude was triturated with water (300 mL), filtered and dried on vacuum overnight to give the desired 2,2,2-trifluoro-N-[2-(4-nitro-phenyl)-ethyl]-acetamide as a yellow solid. This can be used for next step without further purification. An analytical sample was obtained through recrystallization from $\text{CH}_3\text{OH}/\text{H}_2\text{O}$ as a yellow solid.

10

Example 2

Preparation of 2,2,2-trifluoro-1-(7-nitro-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone:

To the mixture of 2,2,2-trifluoro-N-[2-(4-nitro-phenyl)-ethyl]-acetamide (65 g, 0.25 mole), paraformaldehyde (42.4 g, 0.375 mole, 1.5 eq.) and HOAc (200 mL) in a 1L round bottom flask equipped with a magnetic stirrer and a ice/water bath was added H_2SO_4 (300 mL) slowly while maintaining reaction temperature under 40°C . The resulting mixture was stirred for 2 h at 40°C , poured into ice, extracted with EtOAc, washed with water, sat. Na_2CO_3 and sat. NH_4Cl , dried over Na_2SO_4 , filtered and concentrated to give the title ethanone compound. This can be used in the next step without further purification. An analytical sample was obtained through silica gel column chromatography with eluant of $\text{CH}_2\text{Cl}_2:\text{MeOH}$ (9:1).

Example 3

Preparation of 7-nitro-1,2,3,4-tetrahydro-isoquinoline:

To a mixture of 2,2,2-trifluoro-1-(7-nitro-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone (24 g, 0.087 mole), MeOH (300 mL), CH_2Cl_2 (50 mL) and H_2O (100mL) in a 1L round bottom flask equipped with a magnetic stirrer was added LiOH

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(24 g). The reaction was completed after stirring for 10 min at RT. The mixture was concentrated, extracted with CH_2Cl_2 , washed with water, dried over Na_2SO_4 , filtered, concentrated to give the title isoquinoline compound as an off-white solid. MS: (ES+) 179(M+H). Calc'd. for $\text{C}_9\text{H}_{10}\text{N}_2\text{O}_2$ - 178.07.

Example 4

Preparation of 7-amino-isoquinoline:

10 A mixture of 7-nitro-1,2,3,4-tetrahydro-isoquinoline (1.5g, 8.38 mmole) and 10% Pd/C (300 mg) in diethylene glycol (5 mL) was reacted in a Smith Synthesizer under microwave radiation at 220 °C for 25 min. The resulting mixture was diluted with MeOH and filtered. The filtrate was
15 concentrated and diluted with CH_2Cl_2 , washed with sat. aq. NH_4Cl and dried over Na_2SO_4 . After filtration and concentration, the title compound was isolated through flash chromatography (eluted with CH_2Cl_2 :MeOH 9:1) as an orange solid. MS: (ES+) 145(M+H). Calc'd. for $\text{C}_9\text{H}_8\text{N}_2$ - 144.07.

20

Example 5

Preparation of N⁴-methyl-quinazoline-4,6-diamine:

A mixture of methyl-(6-nitro-quinazolin-4-yl)-amine
25 (0.16 g; see Synthesis of Certain Nitroquinazoline Derivatives Structurally Related to some Chemotherapeutic Agents, Botros, S., et. al., *Egyptian Journal of Pharmaceutical Sciences*, 13(1), 11-21, (1972) for a description of preparing the nitro-quinazoline) and Pd/C (10
30 wt%, 0.032 g) in 10 ml of MeOH was placed under H_2 from a balloon and stirred at RT for 3 h, filtered through a pad of Celite[®]. Removal of the solvents afforded the title compound as an off-white solid. MS (MH+) = 175.3; Calc'd for $\text{C}_9\text{H}_{10}\text{N}_4$ - 174.20.

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Example 6

Preparation of 3-nitro-7,8-dihydro-5H-[1,6]naphthyridine-6-carboxylic acid tert-butyl ester:

2M solution of NH_3 in MeOH (225 mL, 452.25 mmol) was added to a reaction vessel containing 1-methyl-3,5-dinitro-1H-pyridin-2-one (6 g, 30.15 mmol) and 4-oxo-piperidine-1-carboxylic acid tert-butyl ester (6.6 g, 33.15 mmol). The vessel was then sealed and the reaction was stirred for 24 h at 70 °C. After the resulting mixture was cooled to RT, the solvent was removed to give crude product as yellow solid. After recrystallization in MeOH, the desired title compound was obtained as tan solid. MS (ES^+): 280.1 ($\text{M}+\text{H}^+$). Calc'd for $\text{C}_{13}\text{H}_{17}\text{N}_3\text{O}_4$ - 279.12.

Example 7

Preparation of 3-nitro-5,6,7,8-tetrahydro-[1,6]naphthyridine:

To the solution of 3-nitro-7,8-dihydro-5H-[1,6]naphthyridine-6-carboxylic acid tert-butyl ester (6.14 g, 22 mmol) in CH_2Cl_2 (60 mL) was added TFA (7 mL). The reaction was stirred for 18h at RT. After evaporation of the solvent, the residue was taken into water and neutralized with saturated NaHCO_3 aqueous solution. The solid was filtered and washed with cold water and dried. The solid was recrystallized from CH_3CN to give desired title compound as pale white solid. MS (ES^+): 180.1 ($\text{M}+\text{H}^+$). Calc'd for $\text{C}_8\text{H}_9\text{N}_3\text{O}_2$ - 179.07.

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Example 8

Preparation of [1,6]naphthyridin-3-ylamine:

3-Nitro-5,6,7,8-tetrahydro-[1,6]naphthyridine (1 g,
5 5.6 mmol), pentanol (2 mL) and Pd/C (300mg) were placed in a
microwave reaction vessel and stirred under microwave
irradiation at 180 °C for 1 h. After cooling, the mixture
was diluted with MeOH and filtered through a pad of Celite.
The solvent was removed and the crude was purified by flash
10 column chromatography to give the desired title compound as
a yellow solid. MS (ES⁺): 146.2 (M+H)⁺. Calc'd for C₈H₇N₃ -
145.06.

Example 9

15

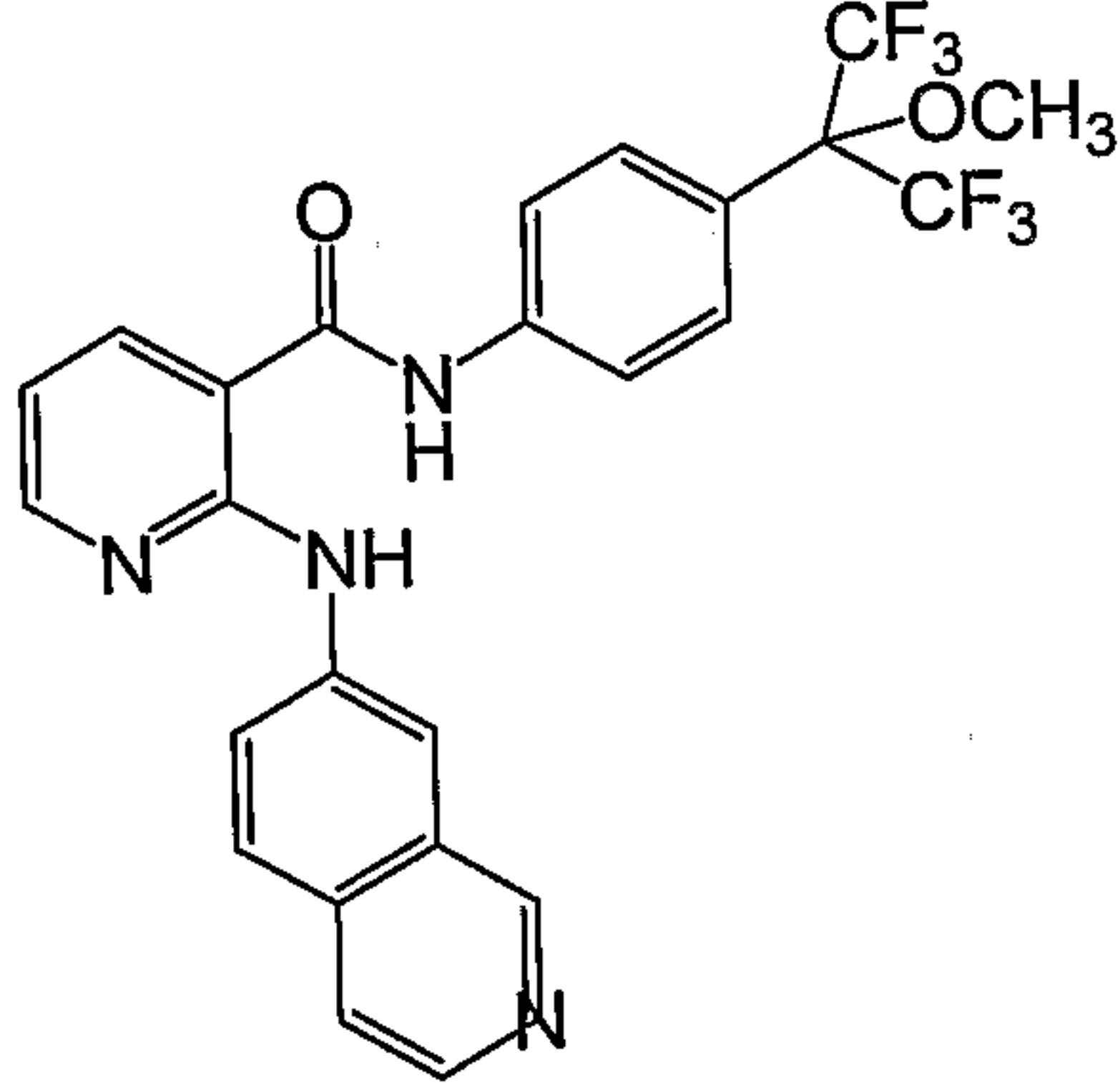
4-(2,2,2-Trifluoro-1-methoxy-1-trifluoromethyl-ethyl)-
phenylamine:

A mixture of 2-(4-amino-phenyl)-1,1,1,3,3,3-
hexafluoro-propan-2-ol (1 eq.), DIAD(1.96 eq.), PPh₃
20 (polymer-bound, 2.36 eq) and MeOH (1.1 eq) in THF (100 mL)
was stirred at reflux for 16 h. After filtration and
concentration, the crude was purified by flash
chromatography (20% EtOAc/CH₂Cl₂) to give the title compound
as a white solid. MS (ES⁺): 274 (M+H)⁺. Calc'd for
25 C₁₀H₉F₆NO- 273.06.

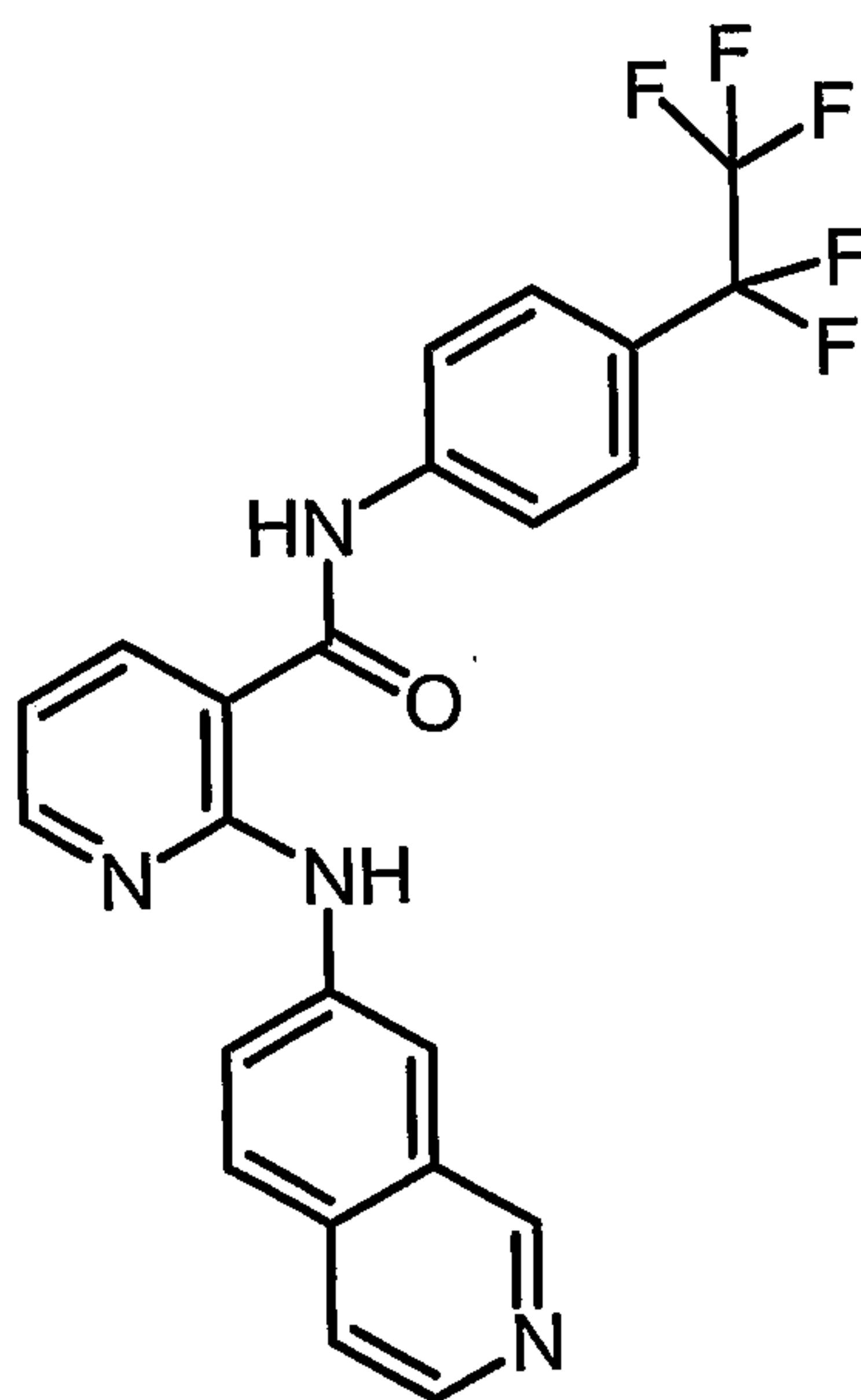
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The following Example 10 was prepared utilizing a starting material made by the method described in Example 9.

Ex. #	Structure	Mol. formula	Calc'd Mass	M+H
10	 2-(Isoquinolin-7-ylamino)-N-[4-(2,2,2-trifluoro-1-methoxy-1-trifluoromethyl-ethyl)-phenyl]-nicotinamide	$C_{23}H_{18}F_6N_4O_2$	520.13	521

5

Example 11

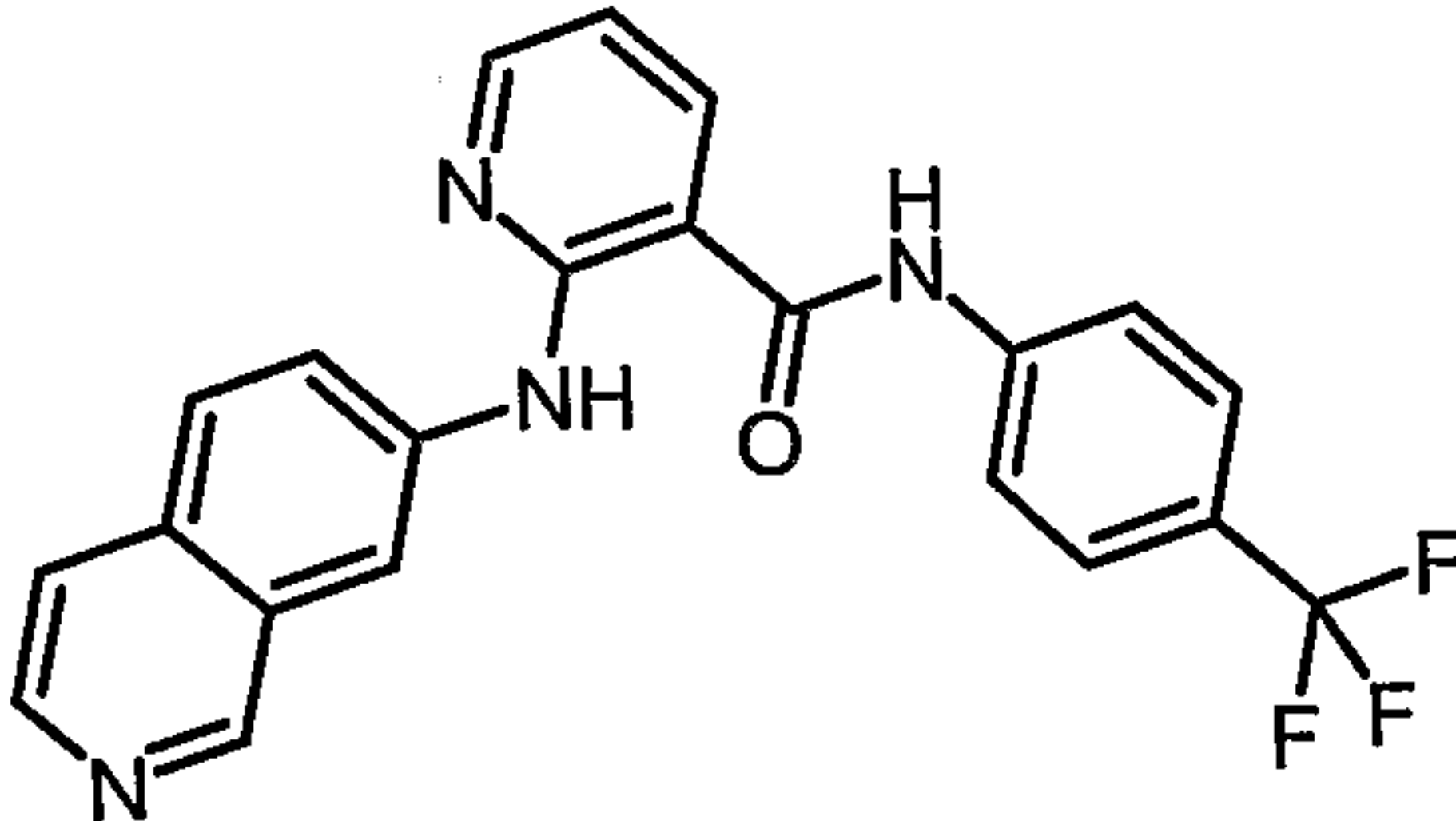
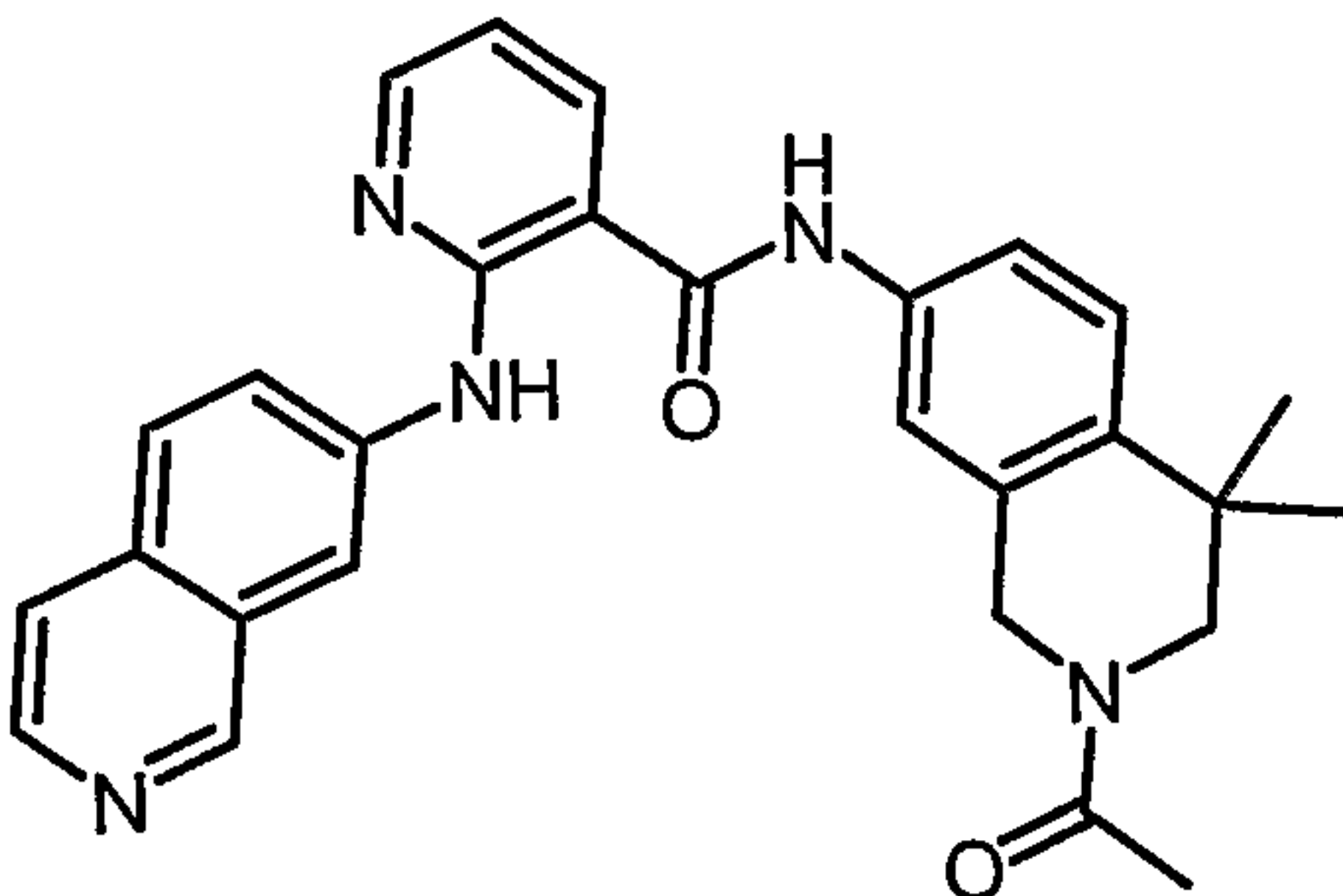
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2-(Isoquinolin-7-ylamino)-N-(4-pentafluoroethyl-phenyl)-
nicotinamide

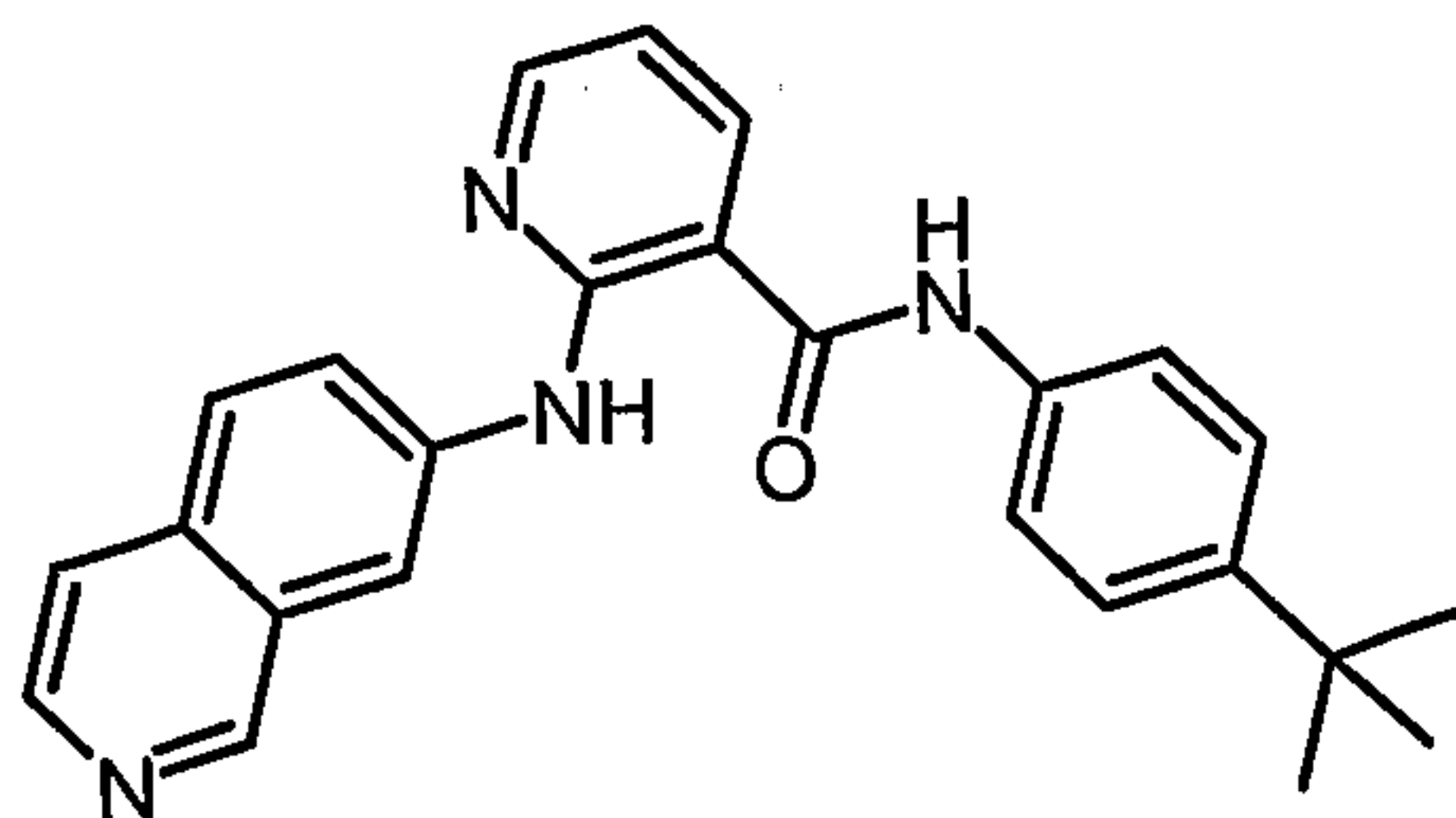
To a mixture of 2-fluoro-N-(4-pentafluoroethyl-
5 phenyl)-nicotinamide (112 mg) and 7-aminoisoquinoline (40
mg) in t-BuOH (0.5 mL) was added TFA (94 μ L). The resulting
mixture was stirred for 24 h at 90 °C, cooled to RT and
purified by flash chromatography (4:1:0.1; MeOH/CH₂Cl₂/MeOH)
to give the title compound as a yellow solid. MS (ES⁺): 459
10 (M+H)⁺. Calc'd for C₂₃H₁₅F₅N₄O- 458.12.

The following Examples 12-25 were prepared utilizing a
method similar to that described in Example 11.

Ex. #	Structure	Mol. formula	Calc'd Mass	M+H
12	 2-(Isoquinolin-7-ylamino)- N-(4-trifluoromethyl- phenyl)-nicotinamide	C ₂₂ H ₁₅ F ₃ N ₄ O	408.12	409
13	 N-(2-Acetyl-4,4-dimethyl- 1,2,3,4-tetrahydro- isoquinolin-7-yl)-2- (isoquinolin-7-ylamino)- nicotinamide	C ₂₈ H ₂₇ N ₅ O ₂	465.22	466

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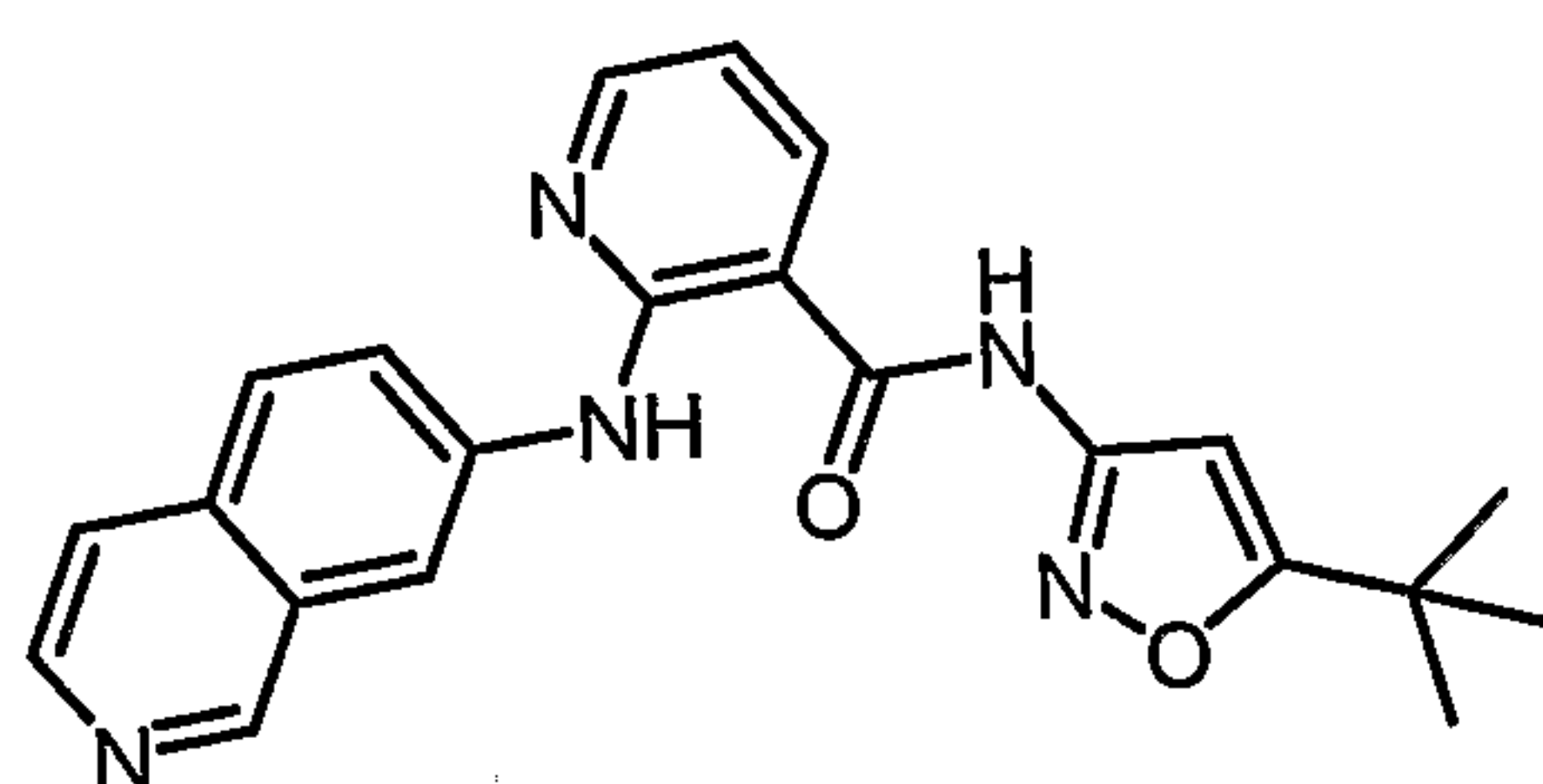
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14 N-(4-tert-Butyl-phenyl)-
2-(isoquinolin-7-ylamino)-nicotinamide

 $C_{25}H_{24}N_4O$

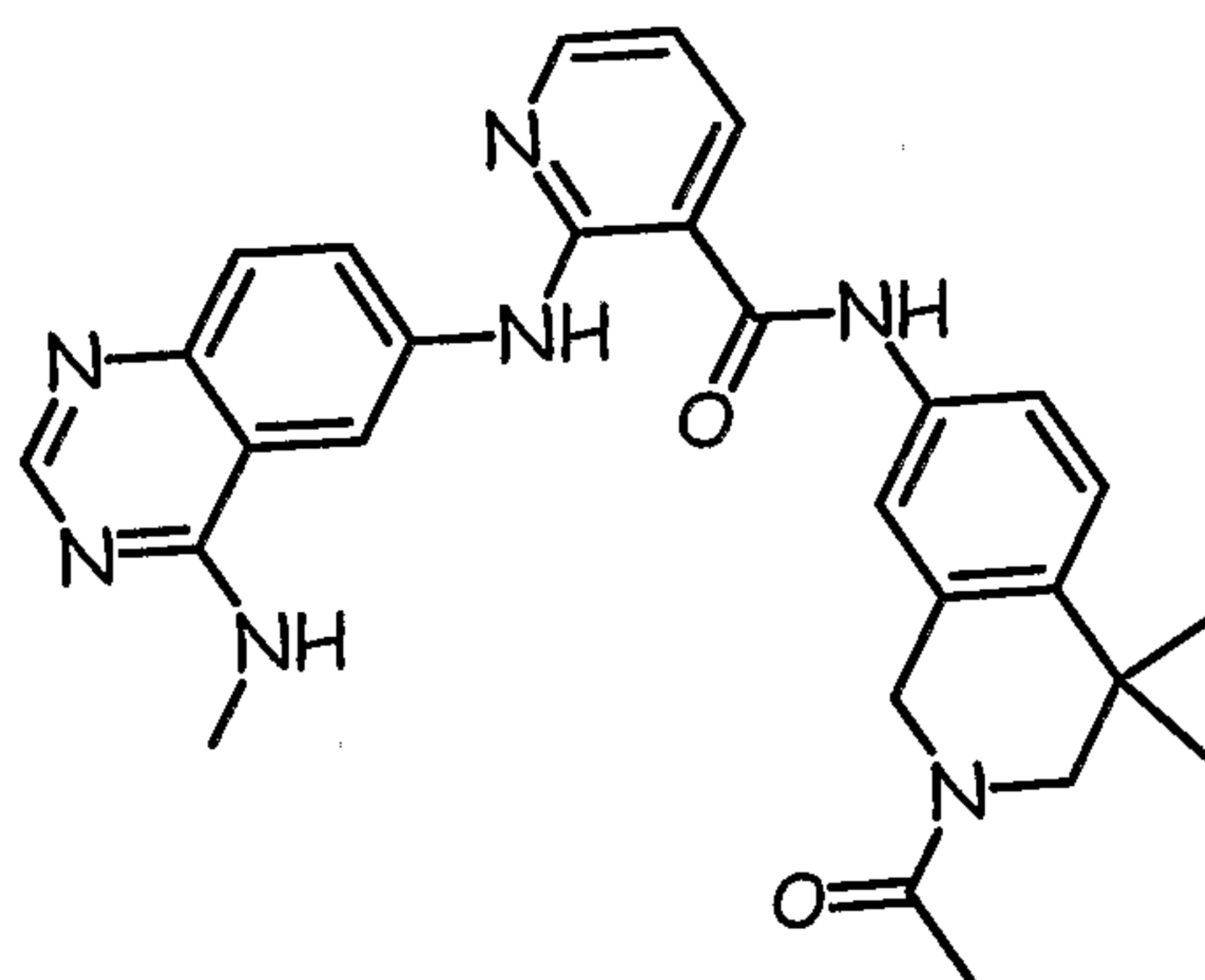
396.20 397



15 N-(5-tert-Butyl-
isoxazol-3-yl)-2-
(isoquinolin-7-ylamino)-
nicotinamide

 $C_{22}H_{21}N_5O_2$

387.17 388



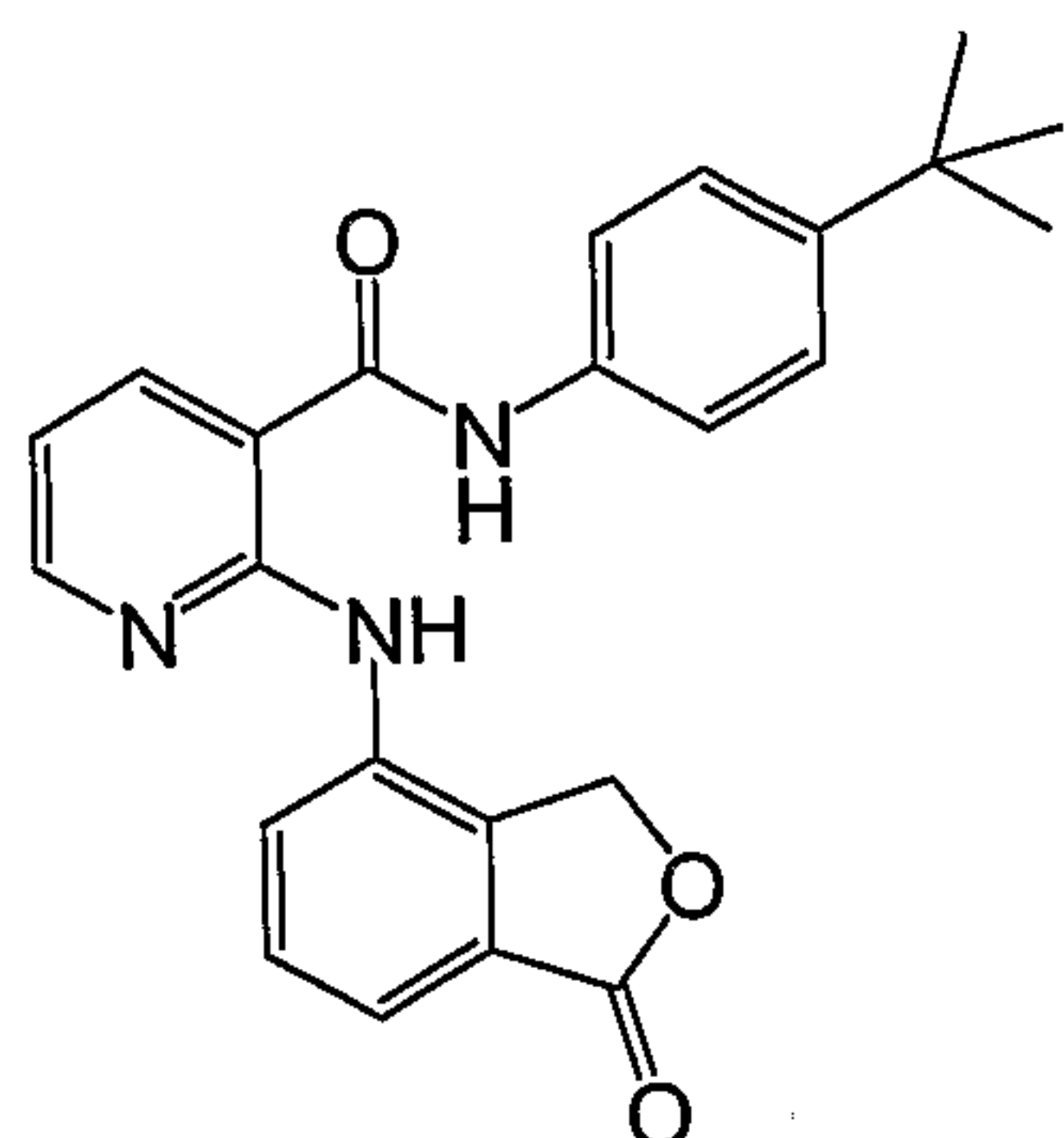
16 N-(2-Acetyl-4,4-
dimethyl-1,2,3,4-
tetrahydro-isoquinolin-
7-yl)-2-(4-methylamino-
quinazolin-6-ylamino)-
nicotinamide

 $C_{28}H_{29}N_7O_2$

495.58 496

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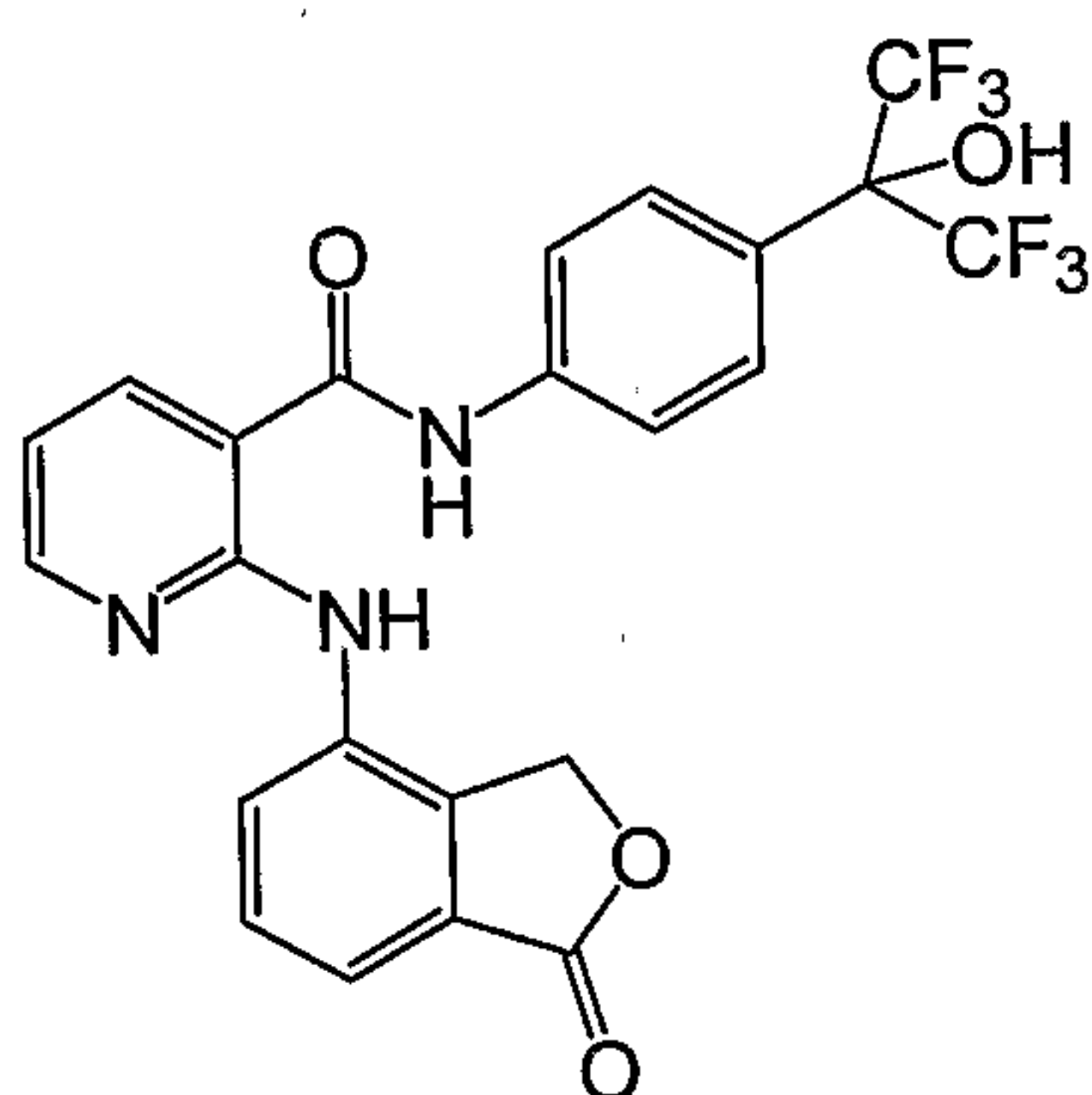


17 N-(4-tert-Butyl-phenyl)-
2-(1-oxo-1,3-dihydro-
isobenzofuran-4-
ylamino)-nicotinamide

 $C_{24}H_{23}N_3O_3$

401.17

402.1

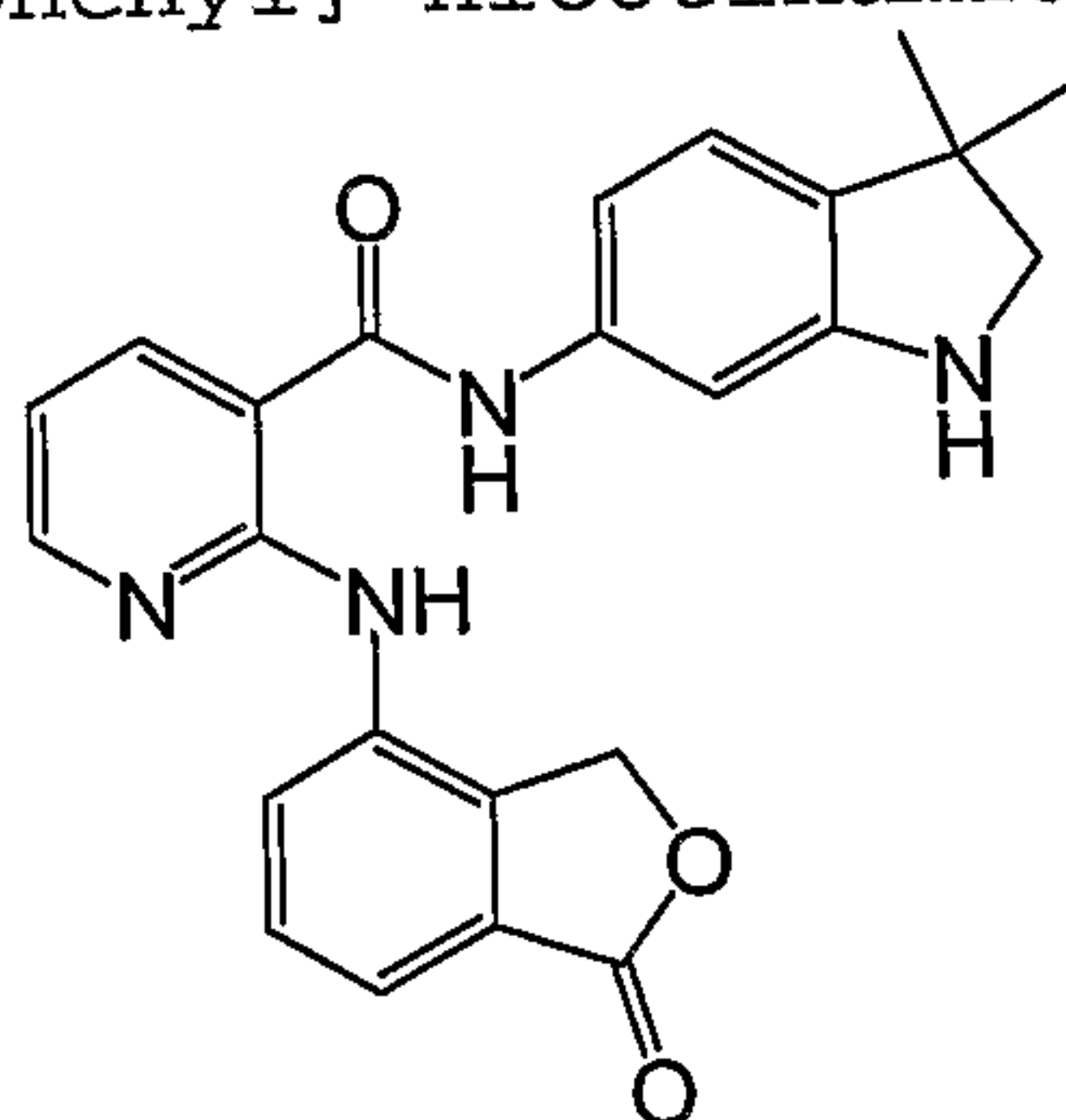


18 2-(1-Oxo-1,3-dihydro-
isobenzofuran-4-
ylamino)-N-[4-(2,2,2-
trifluoro-1-hydroxy-1-
trifluoromethyl-ethyl)-
phenyl]-nicotinamide

 $C_{23}H_{15}F_6N_3O_4$

511.10

512.1



19 N-(3,3-Dimethyl-2,3-
dihydro-1H-indol-6-yl)-
2-(1-oxo-1,3-dihydro-
isobenzofuran-4-
ylamino)-nicotinamide

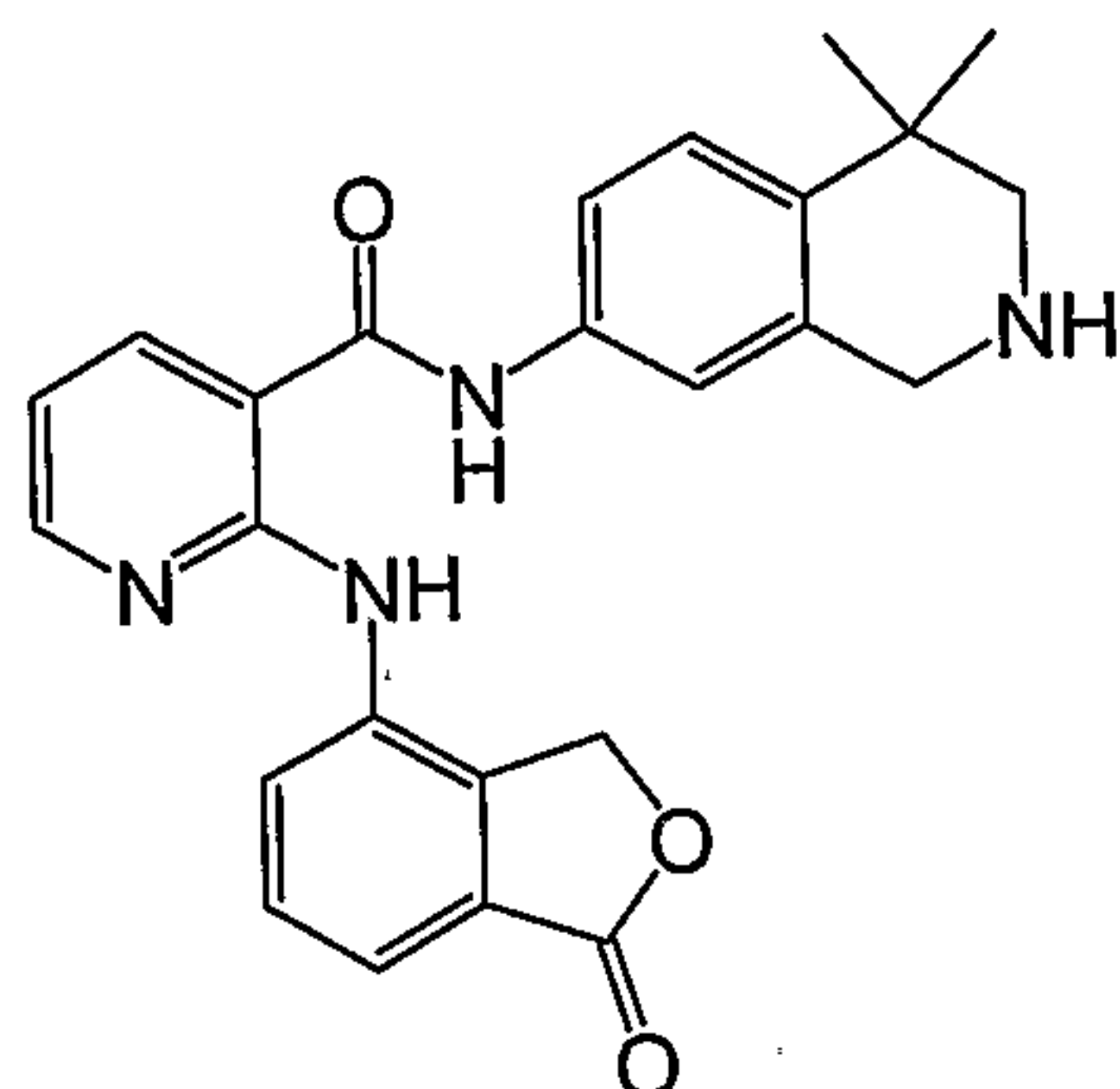
 $C_{24}H_{22}N_4O_3$

414.17

415.1

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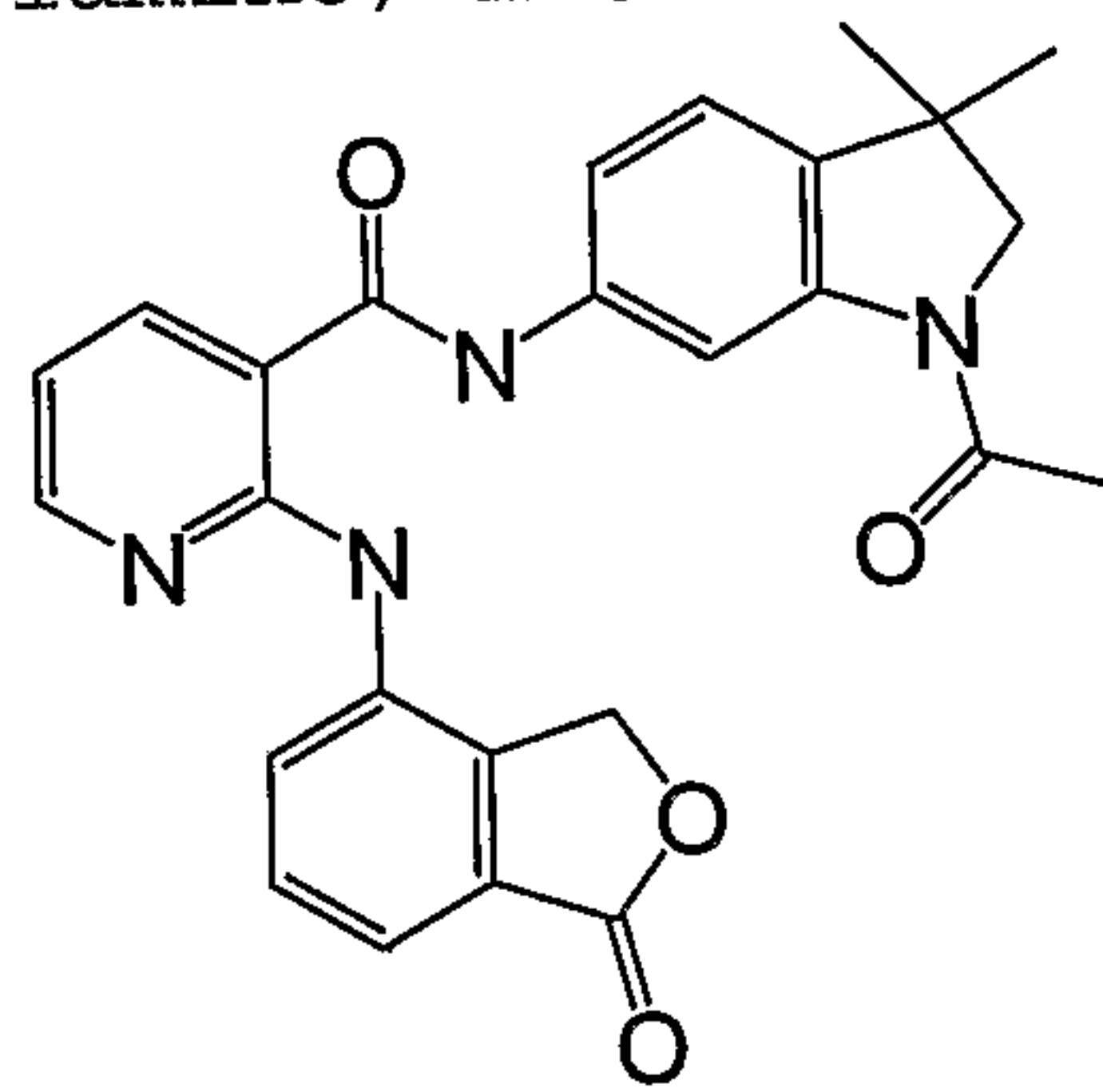


20 N-(4,4-Dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-(1-oxo-1,3-dihydro-isobenzofuran-4-ylamino)-nicotinamide

C₂₅H₂₄N₄O₃

428.18

429.1

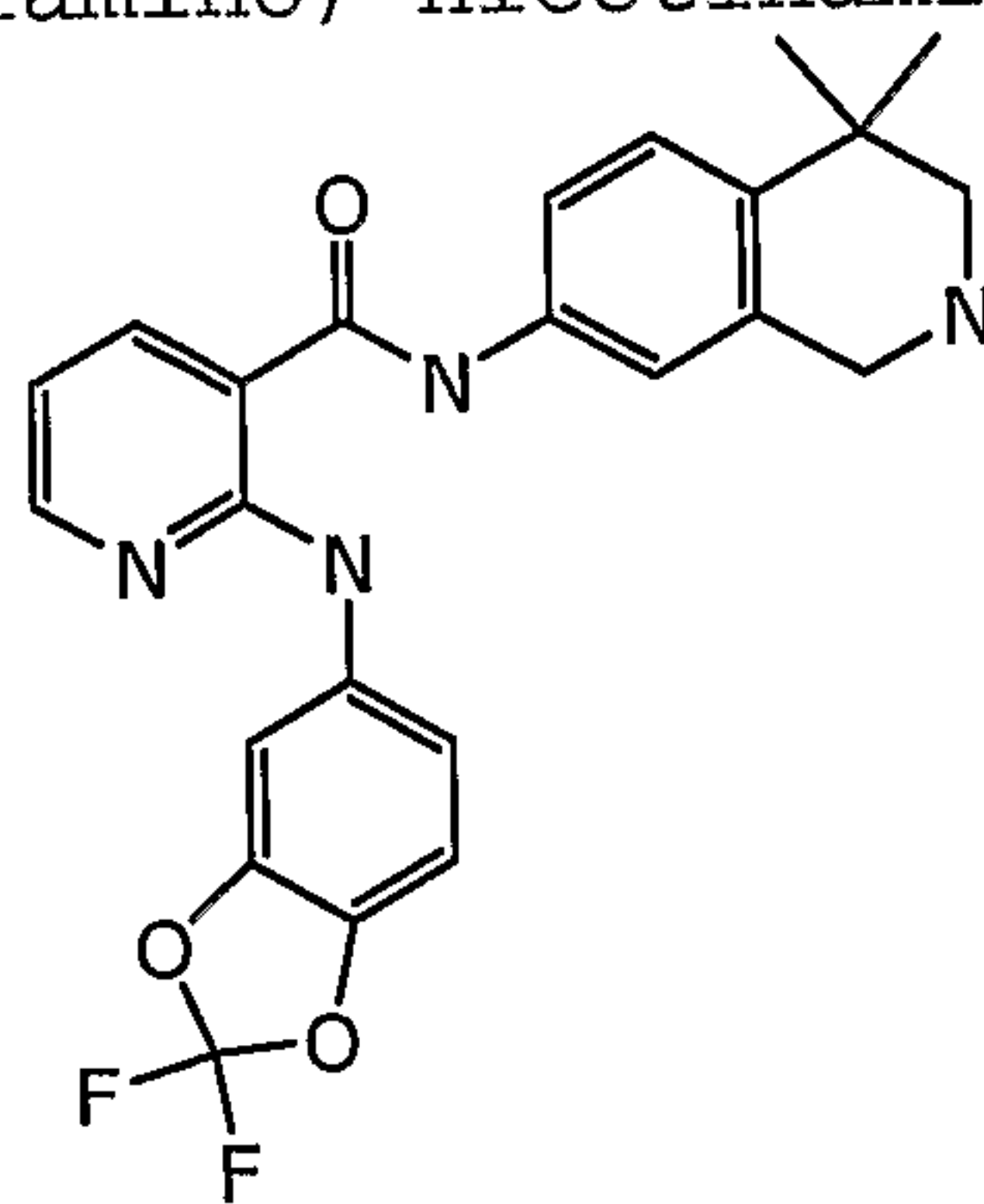


21 N-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-(1-oxo-1,3-dihydro-isobenzofuran-4-ylamino)-nicotinamide

C₂₆H₂₄N₄O₄

456.18

457.1



22 2-(2,2-Difluoro-benzo[1,3]dioxol-5-ylamino)-N-(4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-nicotinamide

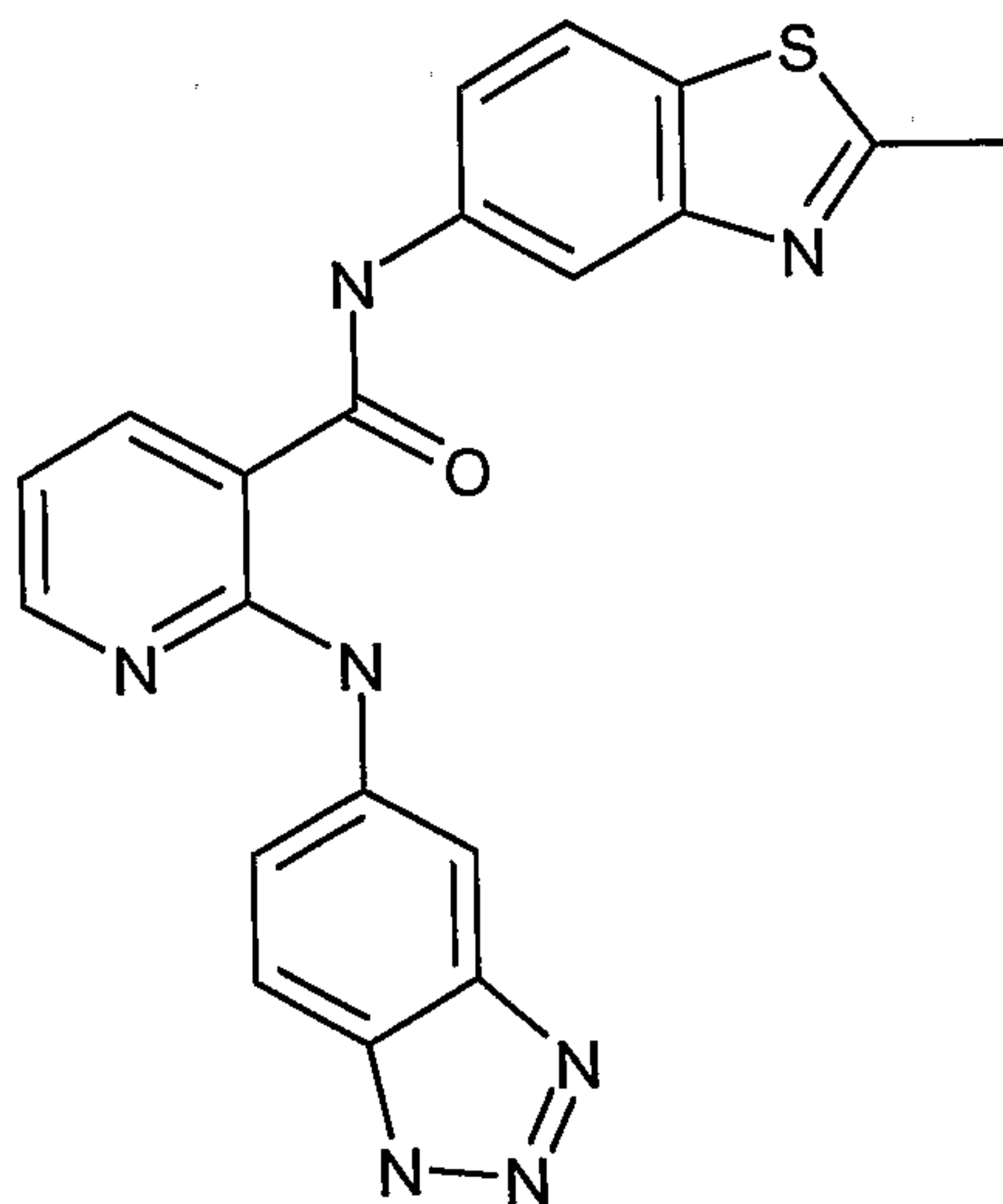
C₂₄H₂₂F₂N₄O₃

452.17

453.1

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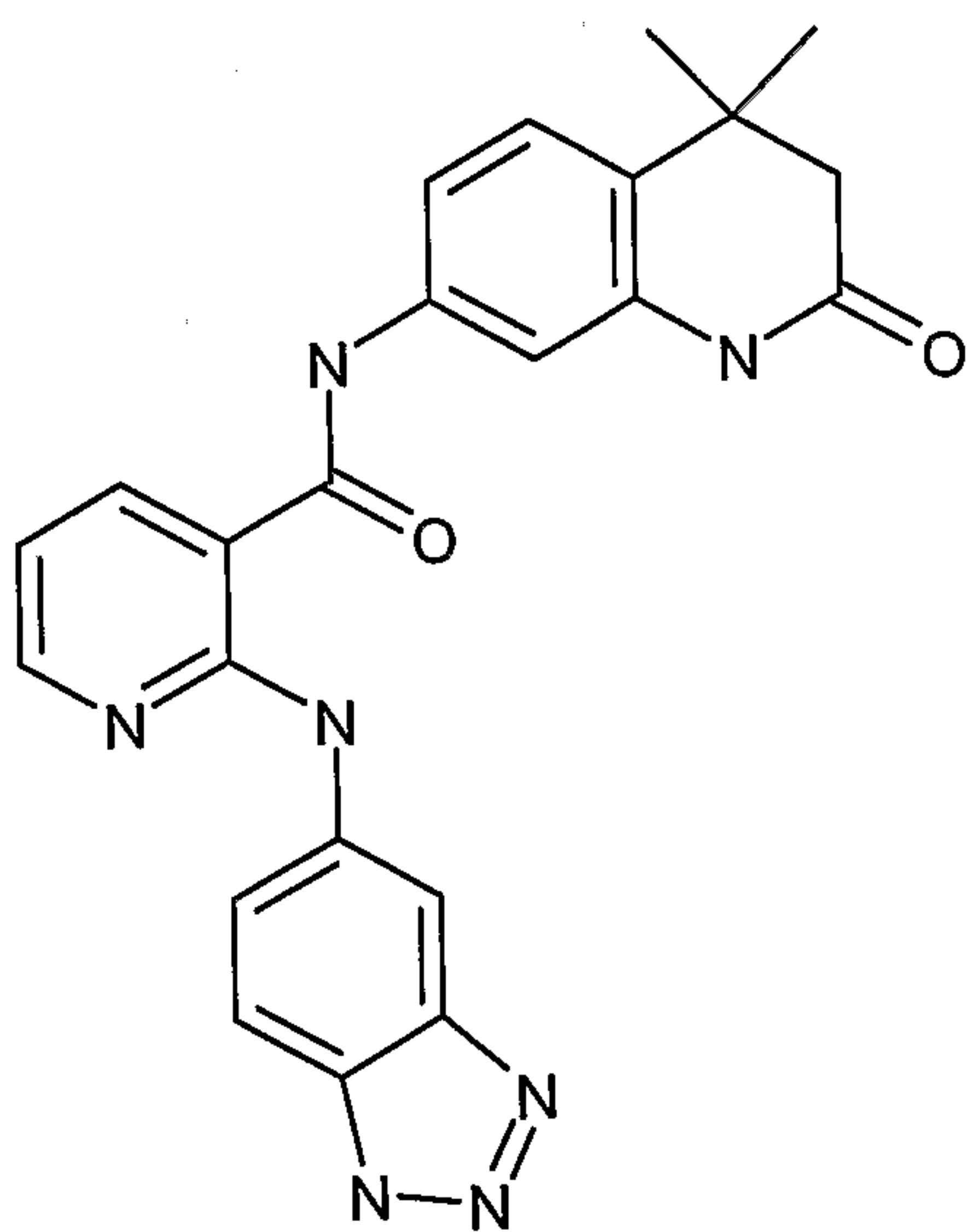


23 2-(1H-Benzotriazol-5-ylamino)-N-(2-methylbenzothiazol-5-yl)-nicotinamide

C₂₀H₁₅N₇OS

401.44

402.7



24 2-(1H-1,2,3-benzotriazol-5-ylamino)-N-(4,4-dimethyl-2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)nicotinamide

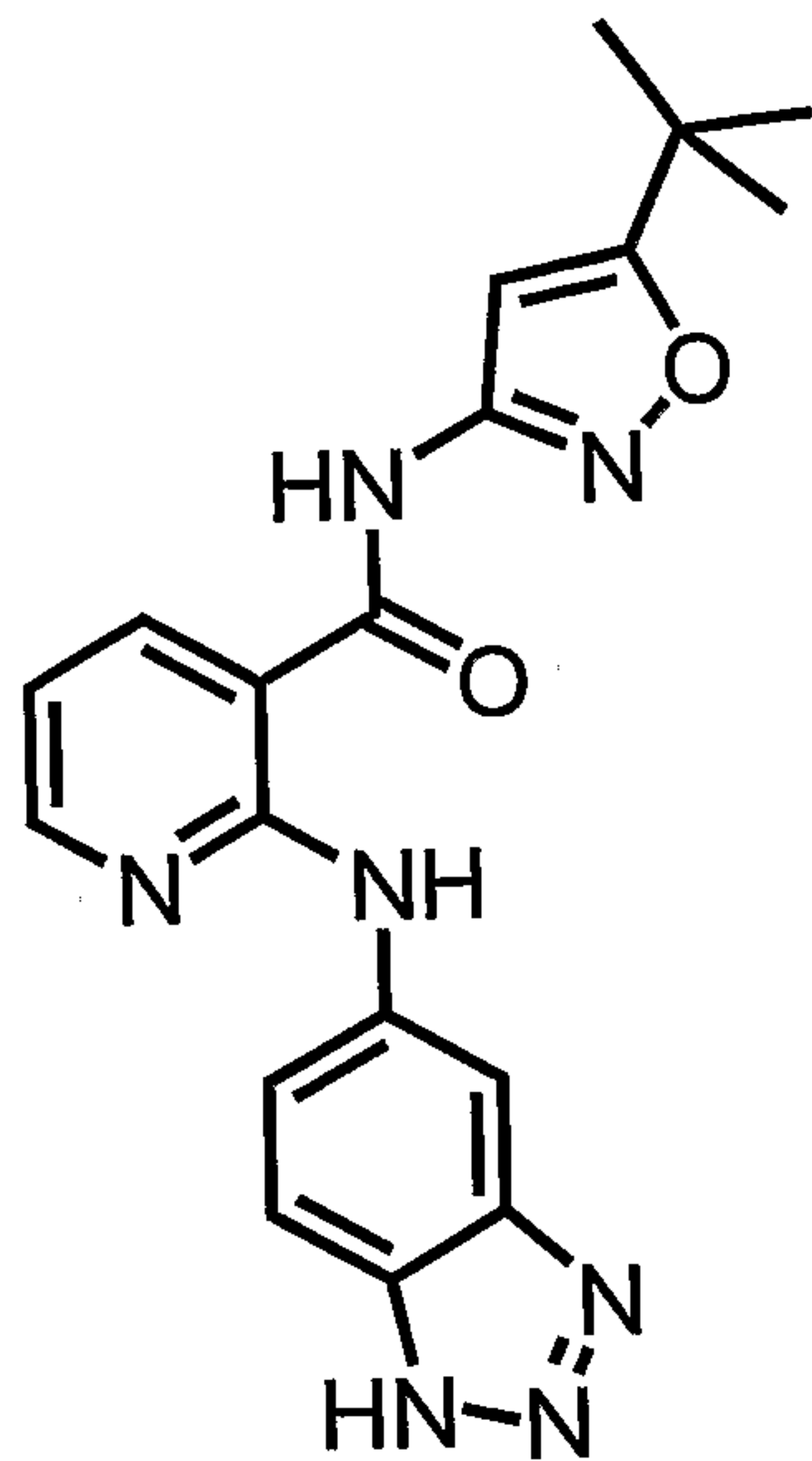
C₂₃H₂₁N₇O₂

427.46

428.

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2-(1H-
benzo[d][1,2,3]triazol-
5-ylamino)-N-(5-tert-
butylisoxazol-3-
yl)nicotinamide

C₁₉H₁₉N₇O₂

377.16 378

25

Example 26

2-(isoquinolin-7-ylamino)-benzoic acid ethyl ester:

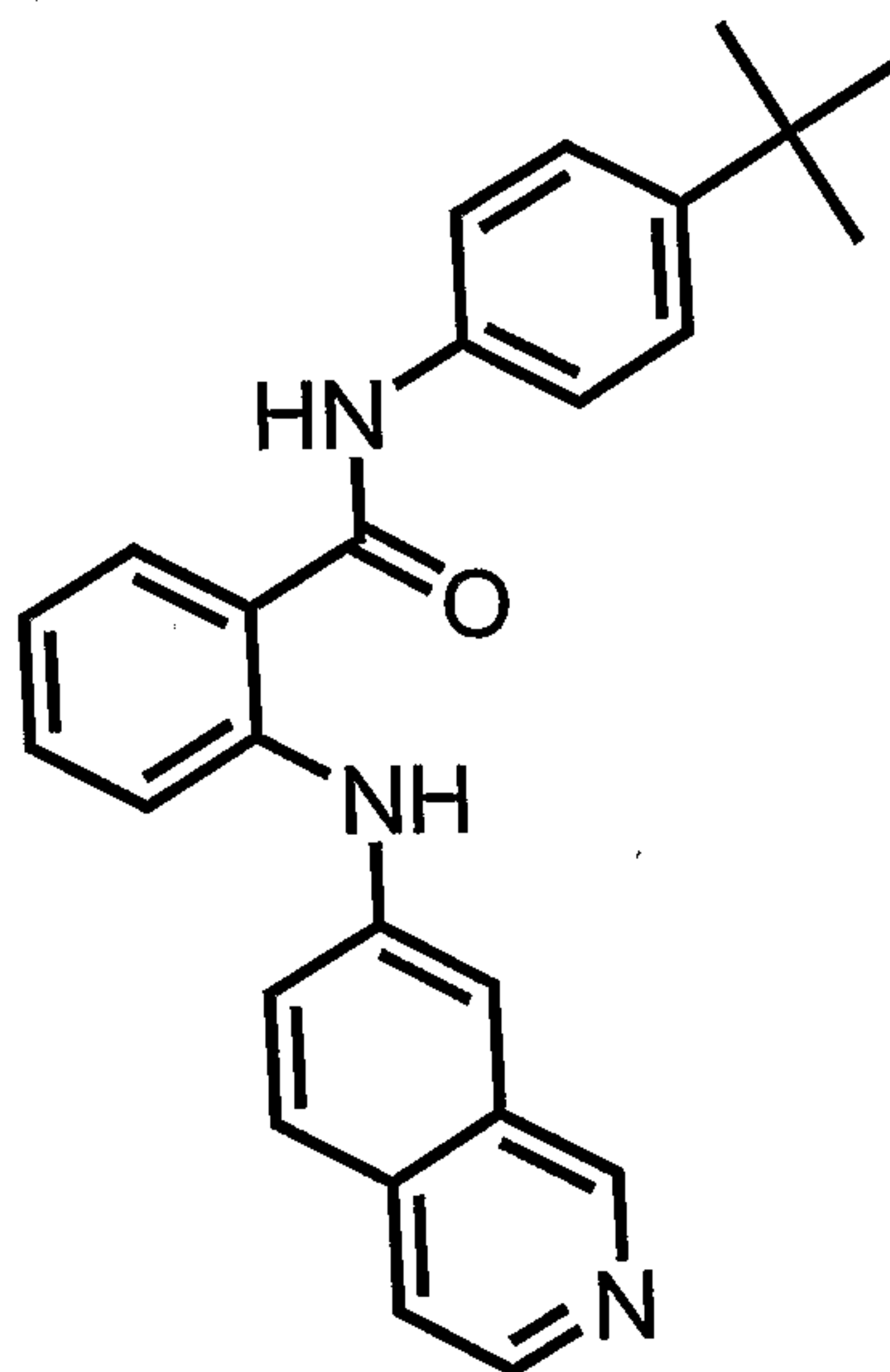
5 A mixture of 2-bromo-benzoic acid ethyl ester (458 mg, 2.0 mmol), 7-aminoisoquinoline (144 mg, 1.0 mmol), Pd(OAc)₂ (11 mg), BINAP (30 mg) and K₂CO₃ (414 mg) in 1 mL of toluene in a sealed tube was stirred for 16 h at 105 °C. The reaction mixture was then allowed to cool to RT, diluted

10 with 20 mL of CH₂Cl₂, filtered through a Celite[®] packed funnel and concentrated under reduced pressure. The concentrate was purified by flash column chromatography. The titled compound was obtained as oil. MS (ES⁺): 293.3 (M+H)⁺. Calc'd for C₁₈H₁₆N₂O₂- 292.

15

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Example 27

5 N-(4-tert-Butyl-phenyl)-2-(isoquinolin-7-ylamino)-benzamide

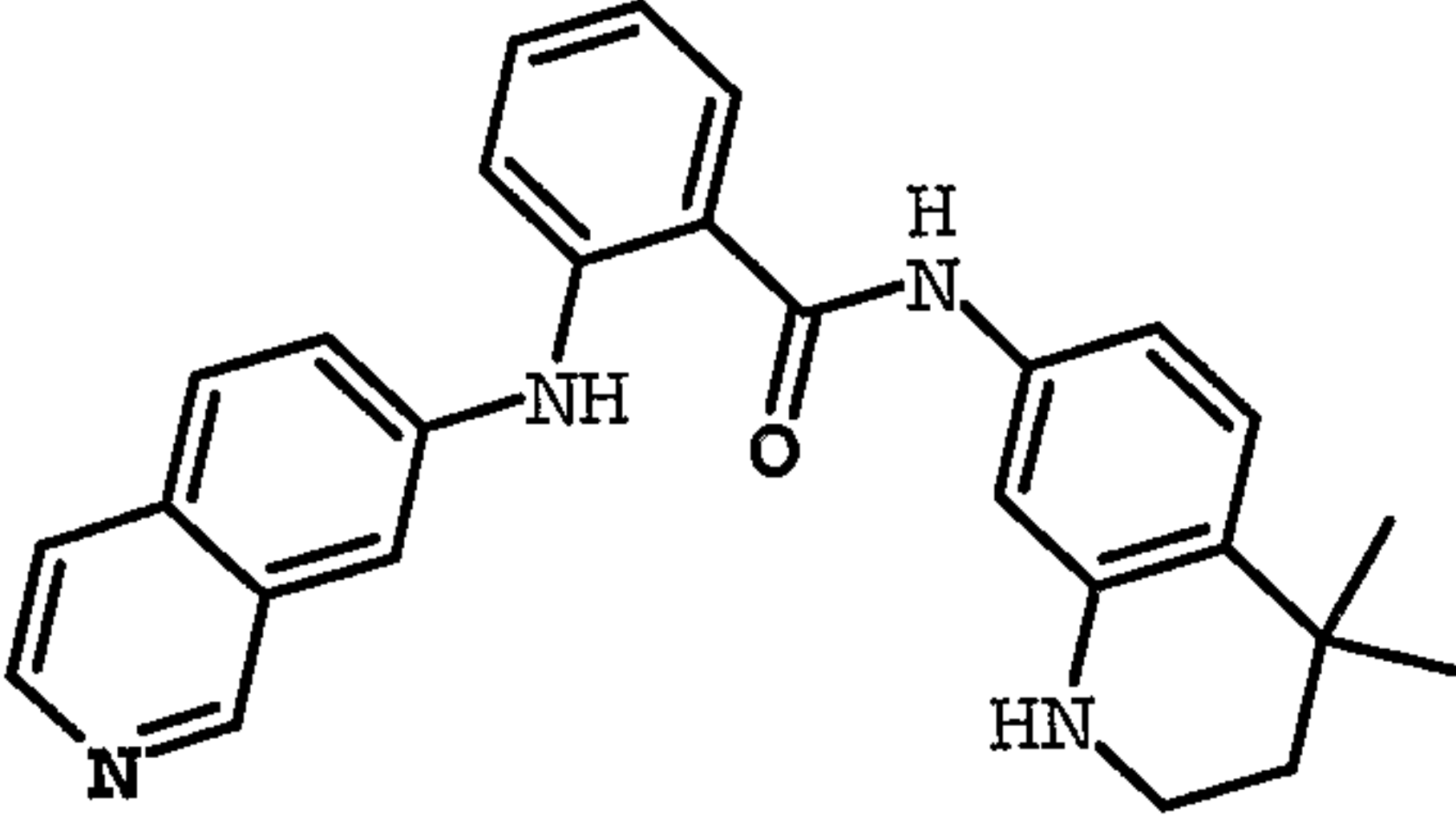
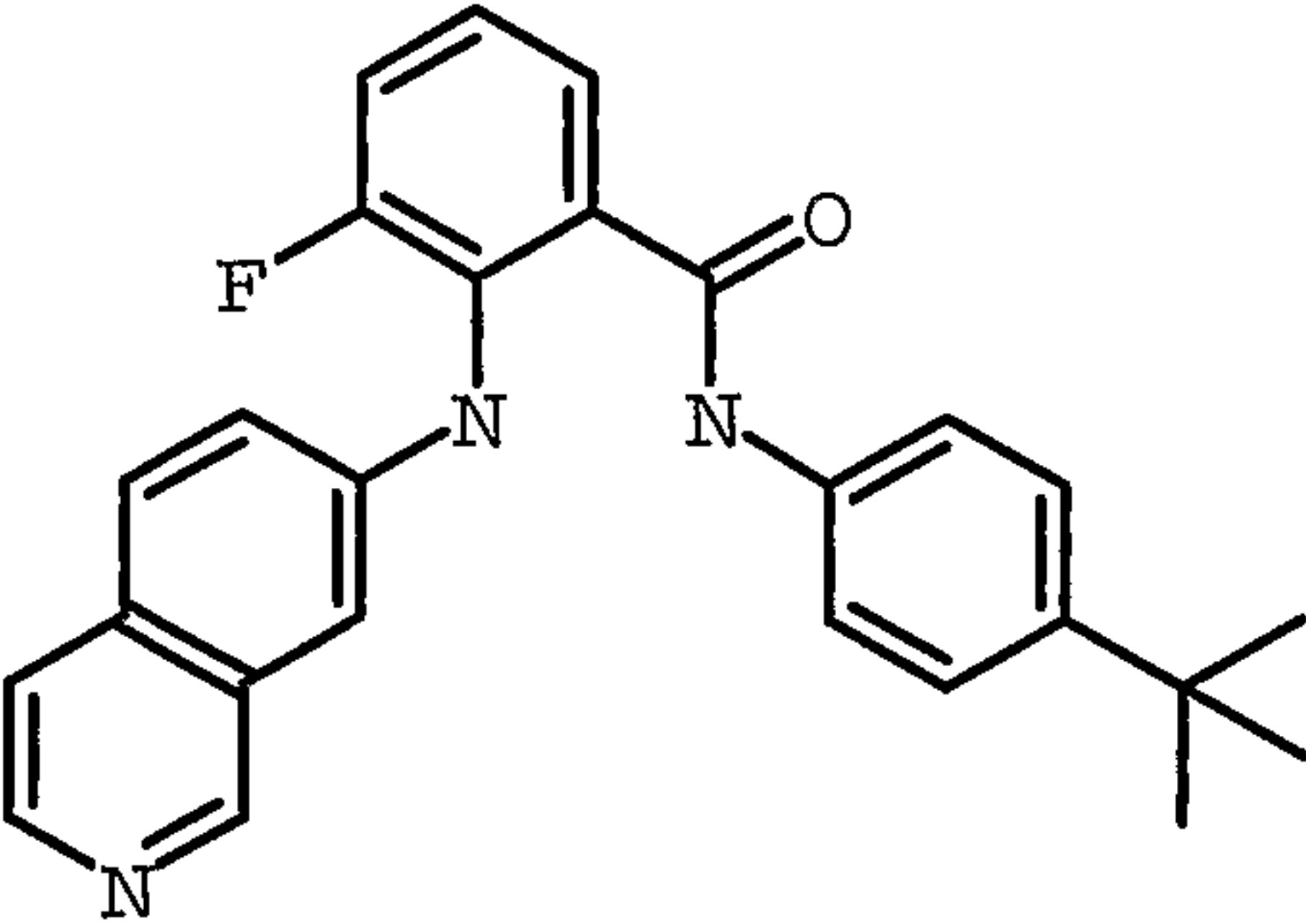
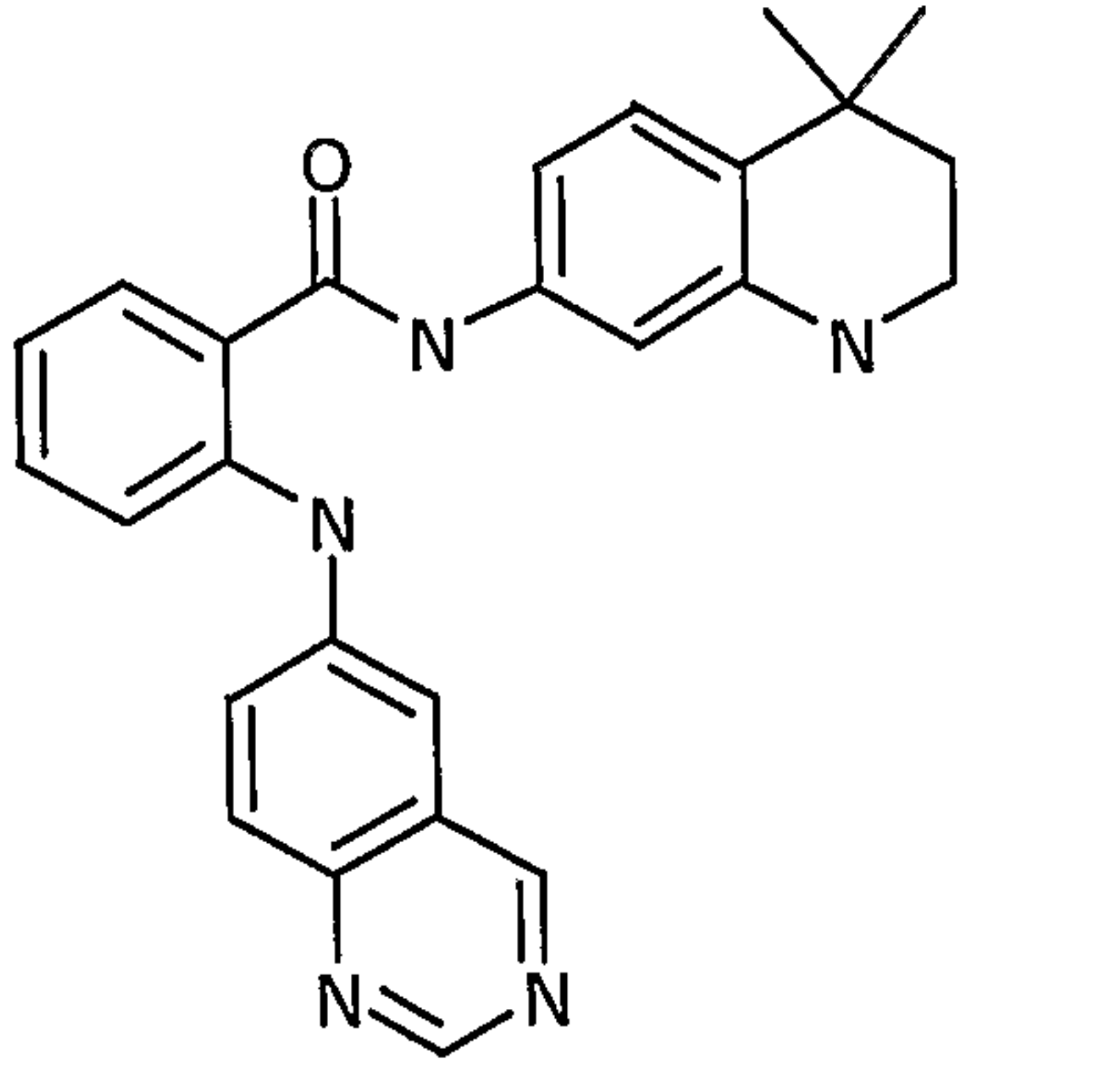
A mixture of 2-(isoquinolin-7-ylamino)-benzoic acid ethyl ester (155 mg, 0.53 mmole) and LiOH monohydrate (67 mg, 1.6 mmol) in a mix solvent of MeOH (1 mL), water (1 mL) and THF (1 mL) was stirred for 14 h at RT. The resulting mixture was concentrated to dryness to the corresponding acid lithium salt as a white solid. The lithium salt obtained was mixed with 4-t-butylaniline (149 mg, 1.0 mmol), TBTU (176 mg, 0.55 mmol) and DIEA (0.04 ml) in 1 ml of DMF and the mixture was stirred at RT for 16 h, then diluted with more CH₂Cl₂. The organic layer was washed with water, brine, dried with MgSO₄, filtered, concentrated and the residue was purified by flash column chromatography (0 to 30% of EtOAc in CH₂Cl₂). Upon concentration of the desired fractions, the title compound was obtained as a white solid.

20 MS (ES⁺): 396.1 (M+H)⁺. Calc'd for C₂₆H₂₅N₃O- 395.20.

The following Examples 28-41 were prepared utilizing a method similar to that described in Examples 11 and 27.

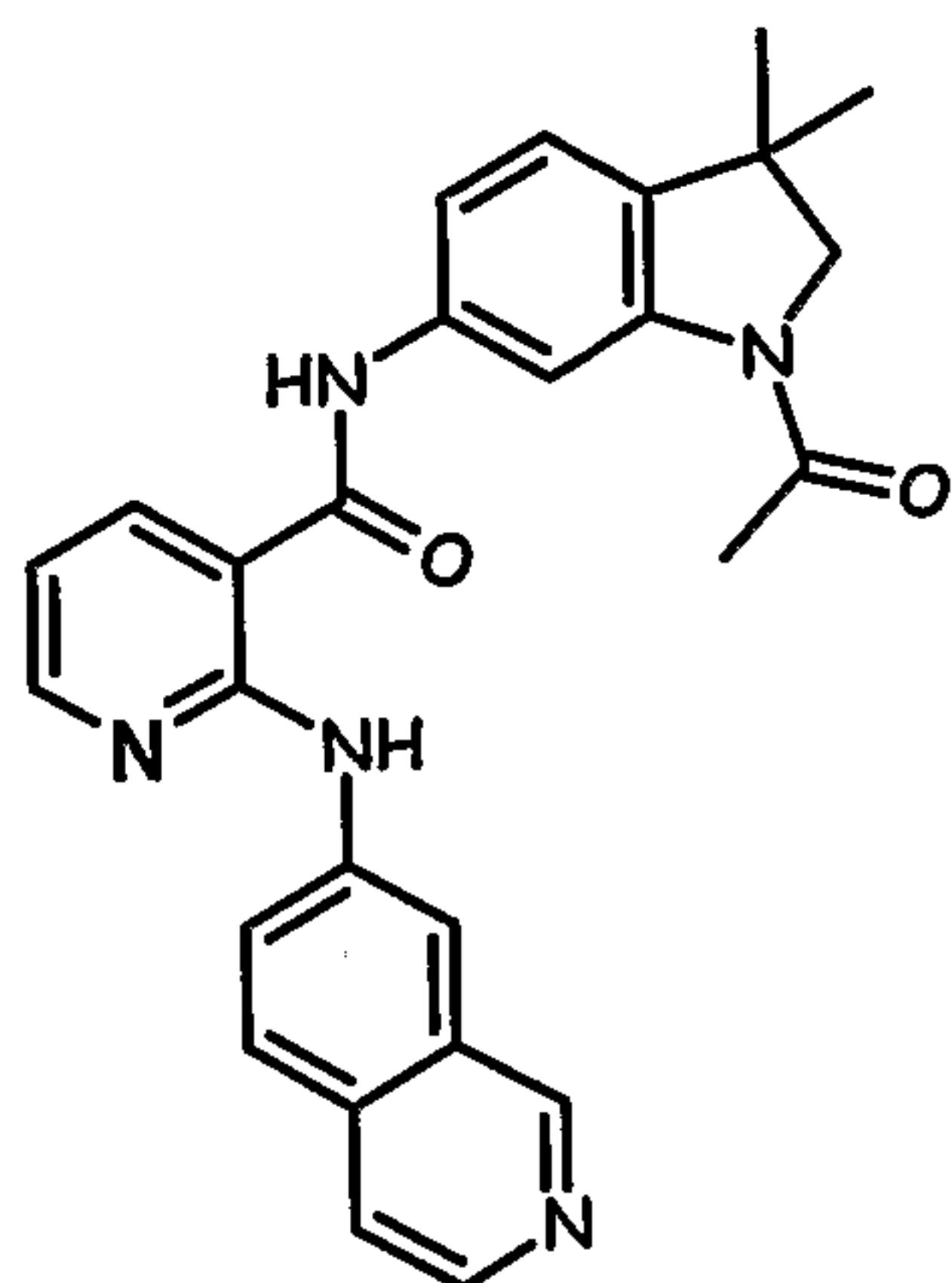
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Ex. #	Structure	Mol. formula	Calc'd Mass	M+H
28	 N-(4,4-Dimethyl-1,2,3,4-tetrahydro-quinolin-7-yl)-2-(isoquinolin-7-ylamino)-benzamide	$C_{27}H_{26}N_4O$	422.52	423
29	 N-(4-tert-Butyl-phenyl)-3-fluoro-2-(isoquinolin-7-ylamino)-benzamide	$C_{26}H_{24}FN_3O$	413.19	414.4
30	 N-(4,4-Dimethyl-1,2,3,4-tetrahydro-quinolin-7-yl)-2-(quinazolin-6-ylamino)-benzamide	$C_{26}H_{25}N_5O$	423.21	424.

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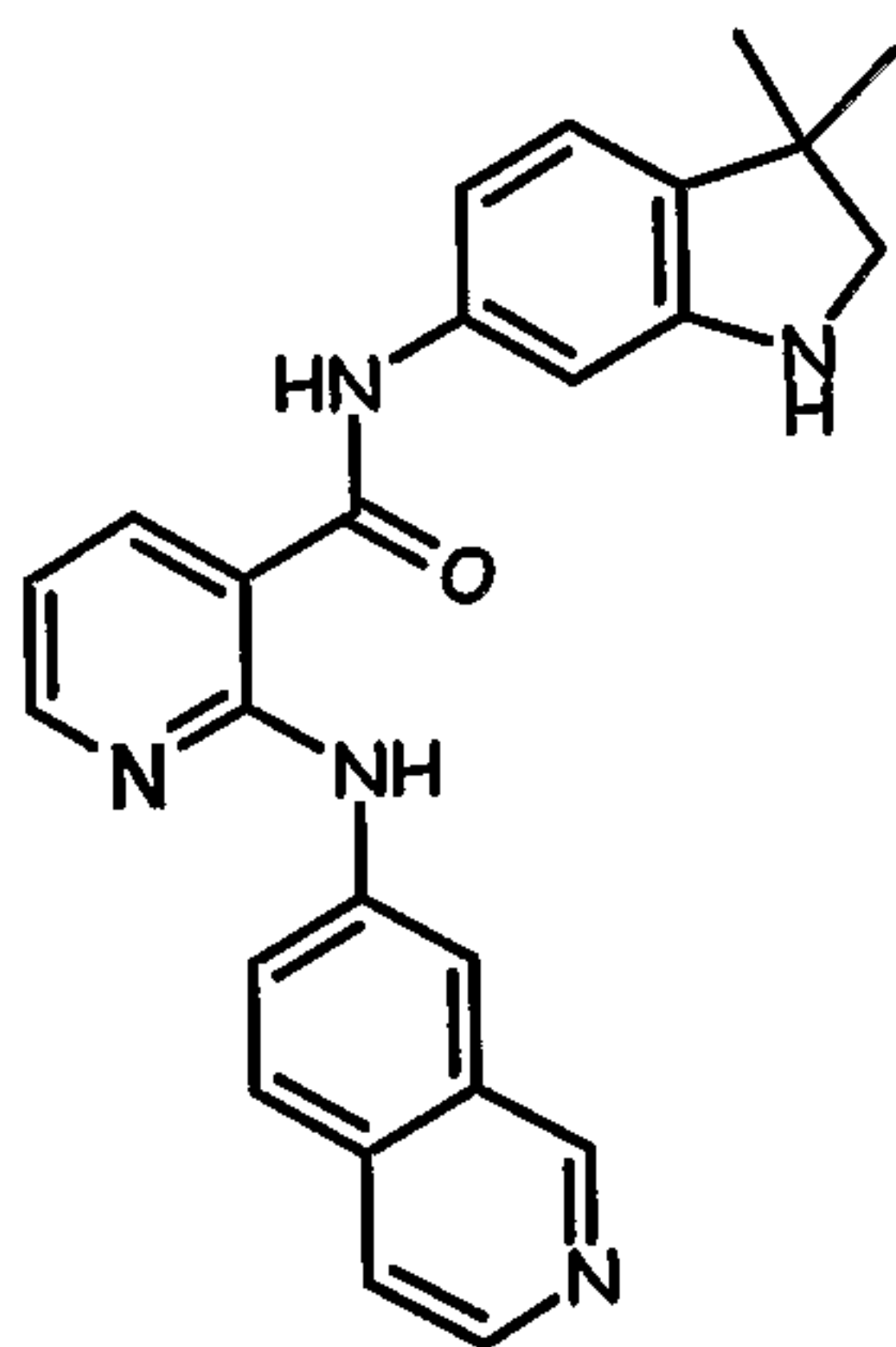
N-(1-Acetyl-3,3-
dimethyl-2,3-dihydro-1H-
indol-6-yl)-2-
(isoquinolin-7-ylamino)-
nicotinamide

31

 $C_{27}H_{25}N_5O_2$

451.52

452.3



N-(3,3-Dimethyl-2,3-
dihydro-1H-indol-6-yl)-
2-(isoquinolin-7-
ylamino)-nicotinamide

32

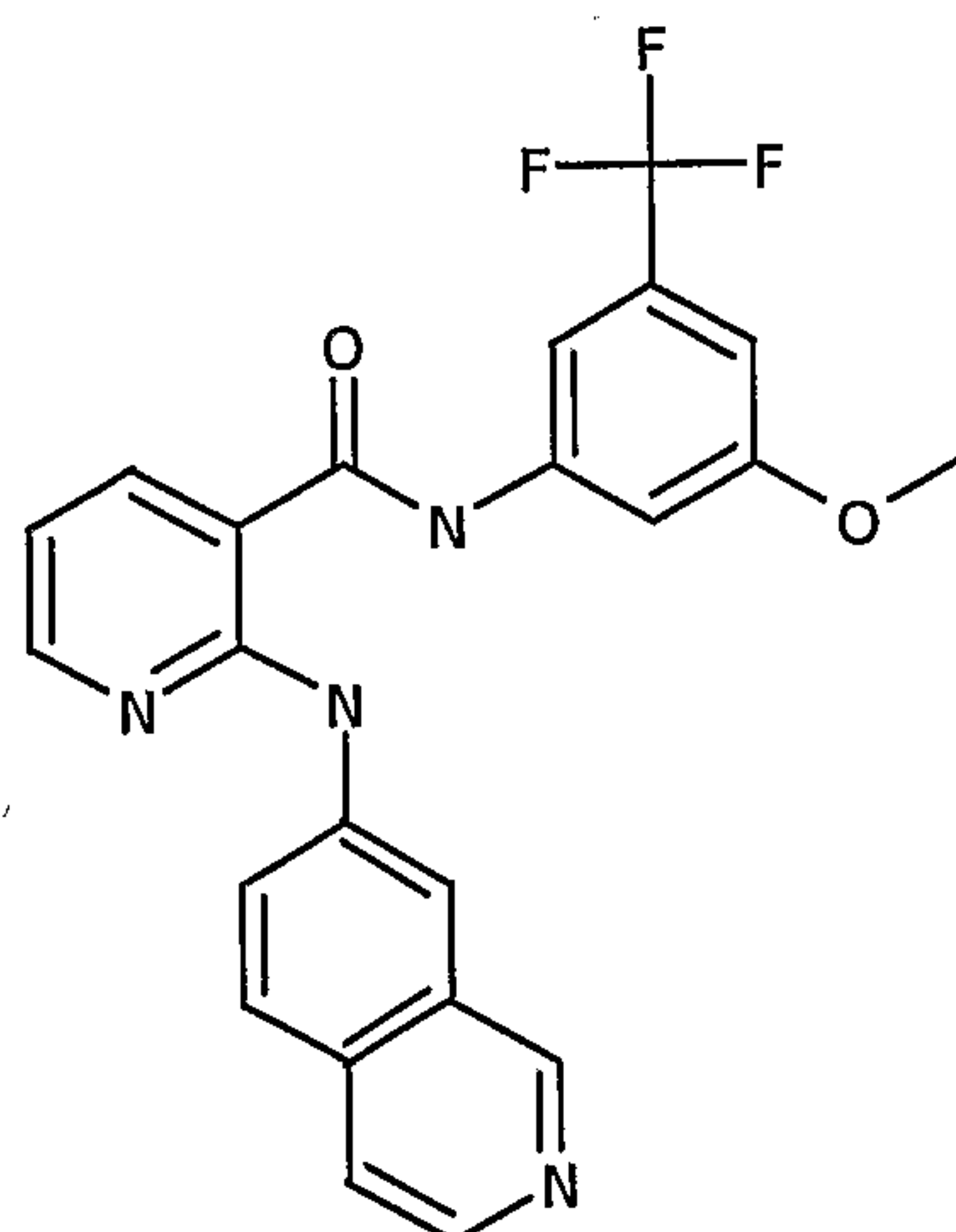
 $C_{25}H_{23}N_5O$

409.48

410.6

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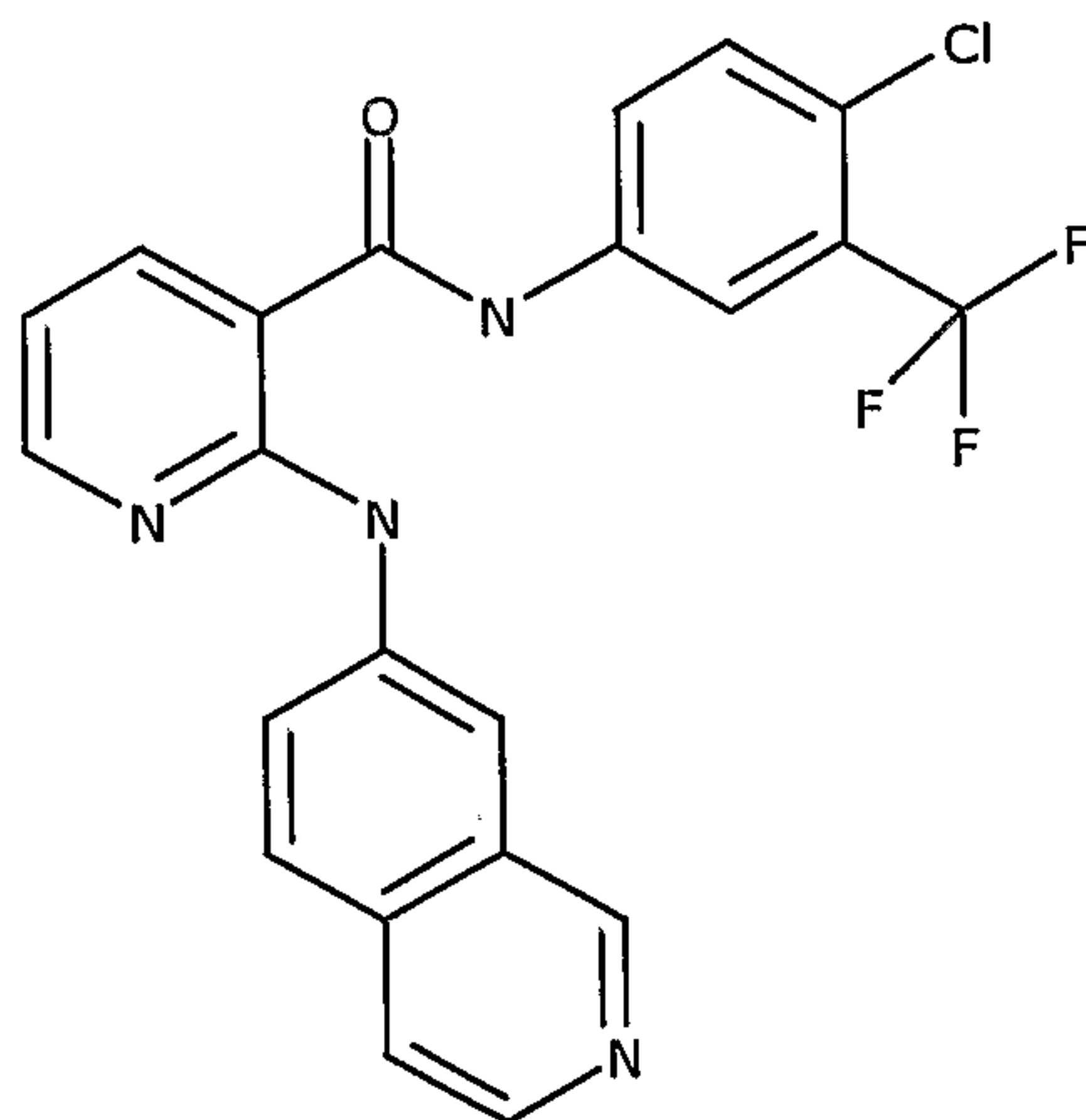


33 2-(Isoquinolin-7-ylamino)-N-(3-methoxy-5-trifluoromethyl-phenyl)-nicotinamide

C₂₃H₁₇F₃N₄O₂

438.13

439.1



34 N-(4-Chloro-3-(trifluoromethyl)-phenyl)-2-(isoquinolin-7-ylamino)-nicotinamide

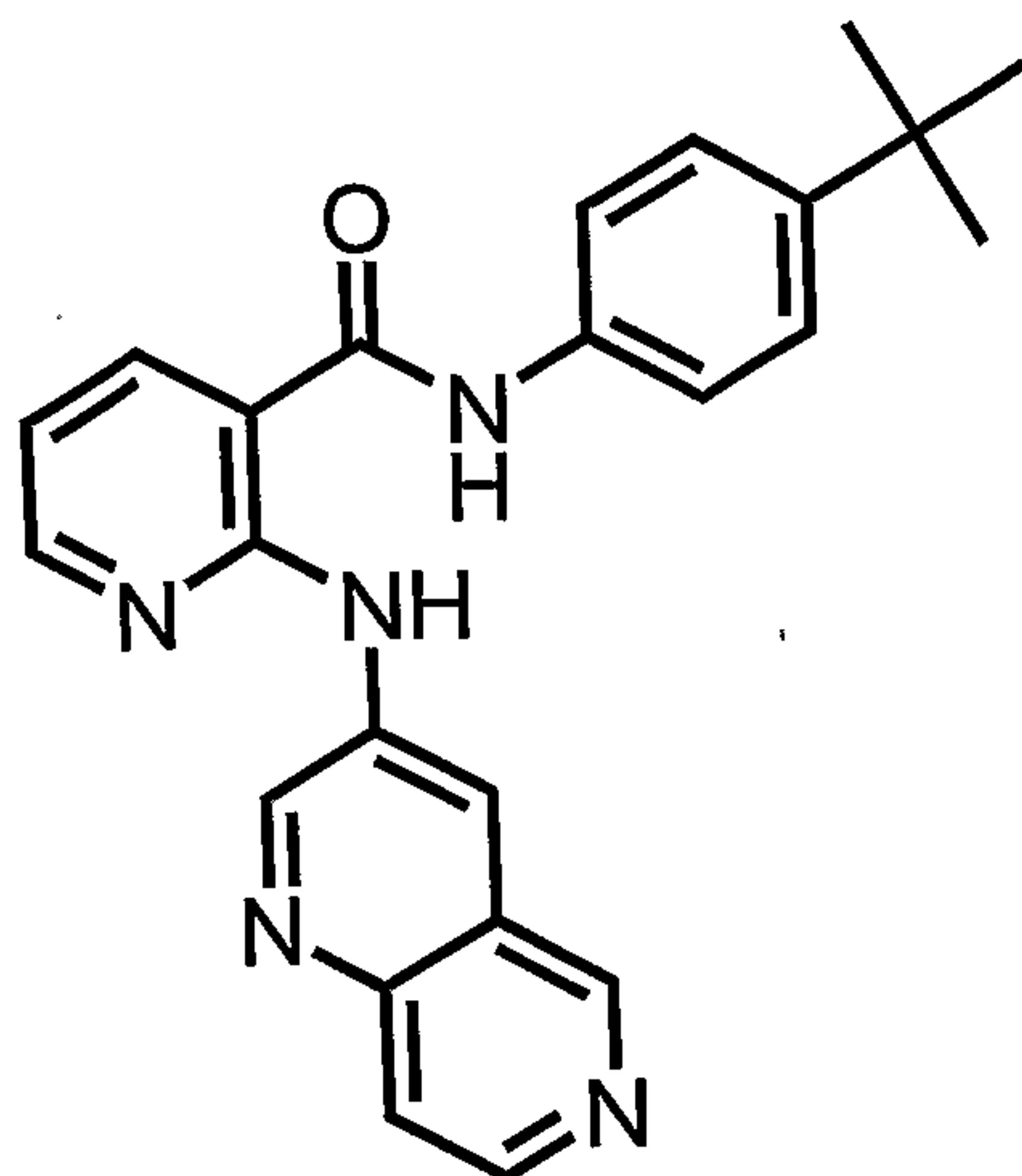
C₂₂H₁₄ClF₃N₄O

442.08

443.1

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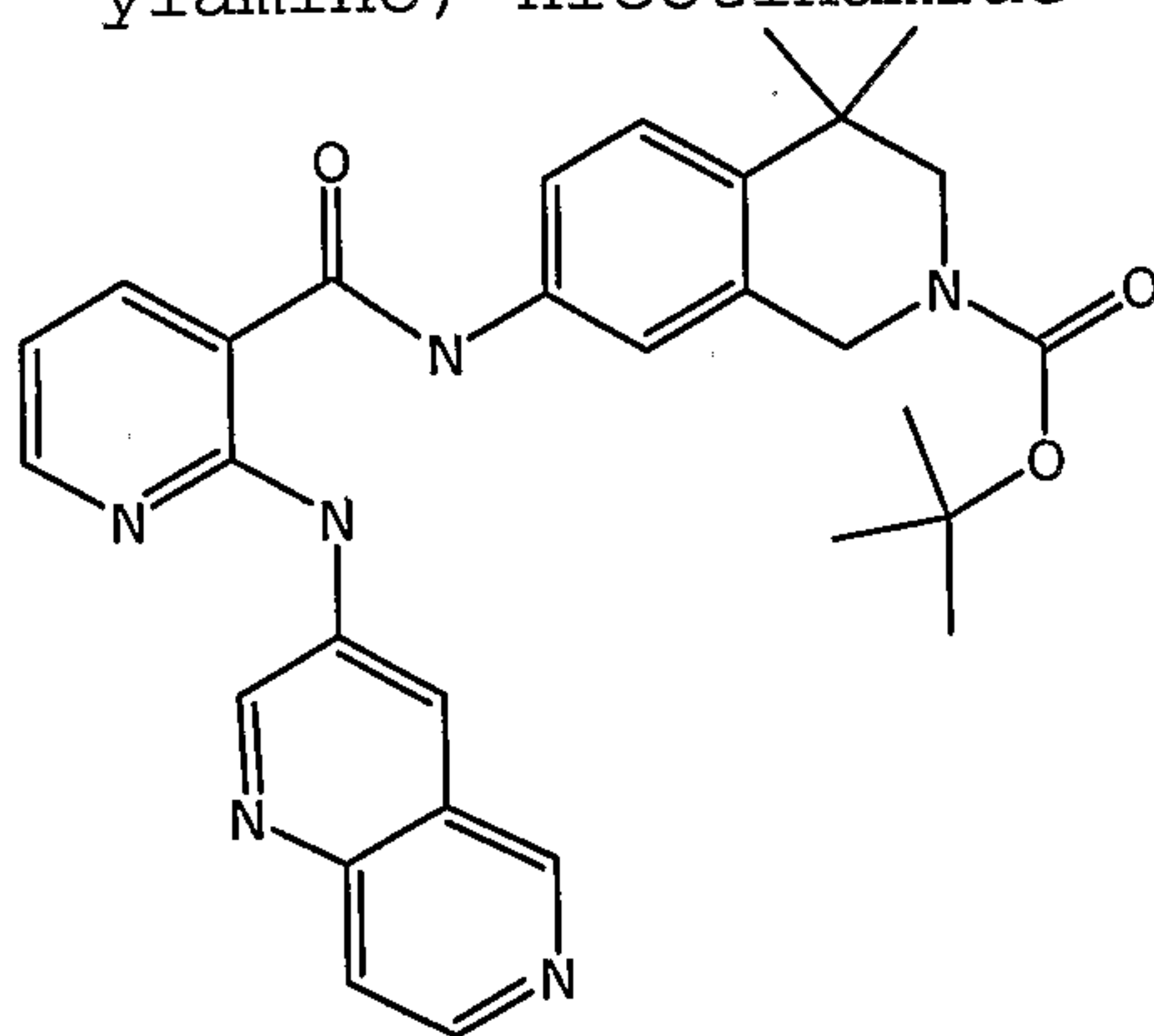


35 N-(4-tert-Butyl-phenyl)-
2-([1,6]naphthyridin-3-
ylamino)-nicotinamide

 $C_{24}H_{23}N_5O$

397.19

398.3



36 4,4-Dimethyl-7-{[2-
([1,6]naphthyridin-3-
ylamino)-pyridine-3-
carbonyl]-amino}-3,4-
dihydro-1H-isoquinoline-
2-carboxylic acid tert-
butyl ester

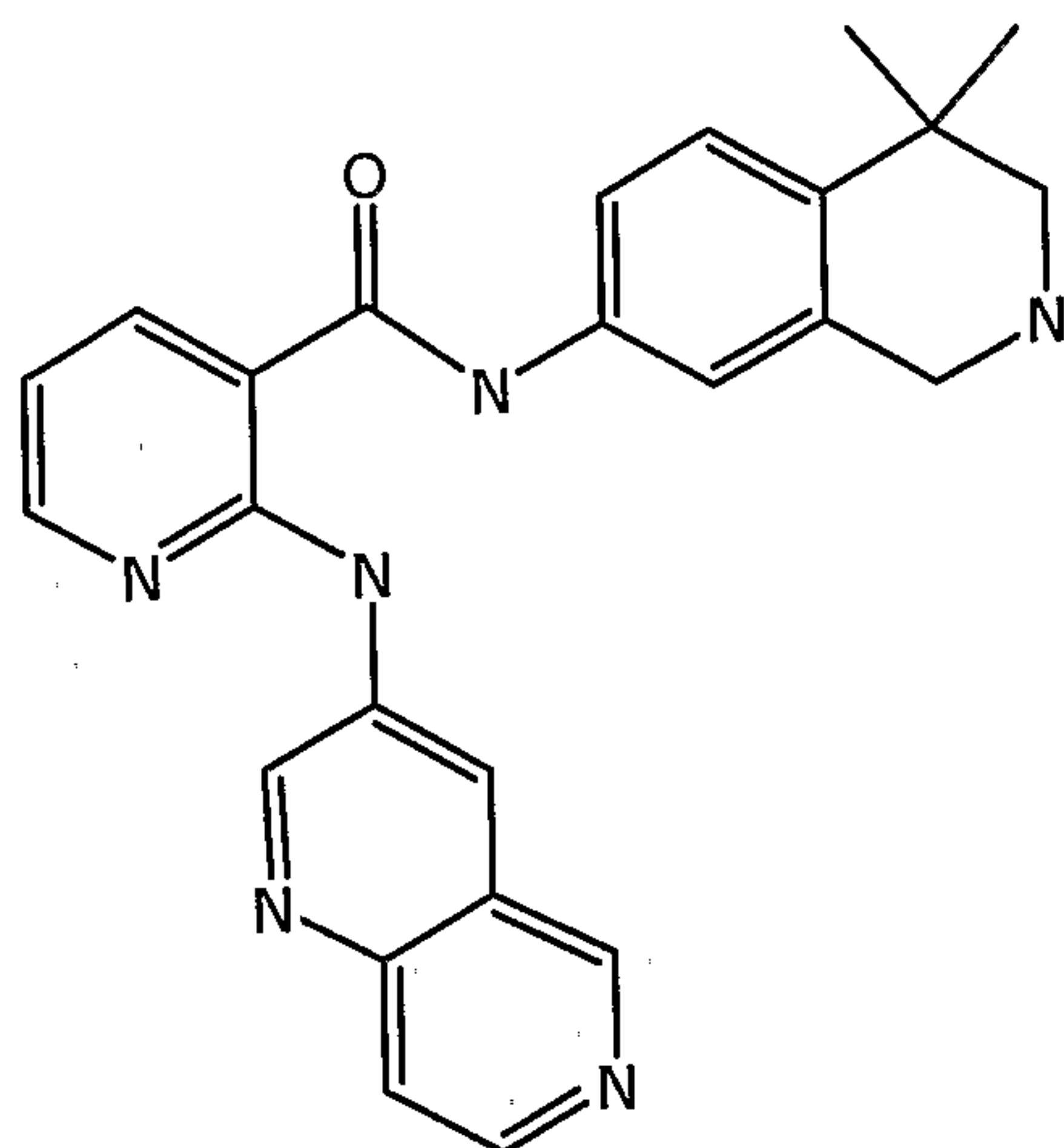
 $C_{30}H_{22}N_6O_3$

524.25

525.3

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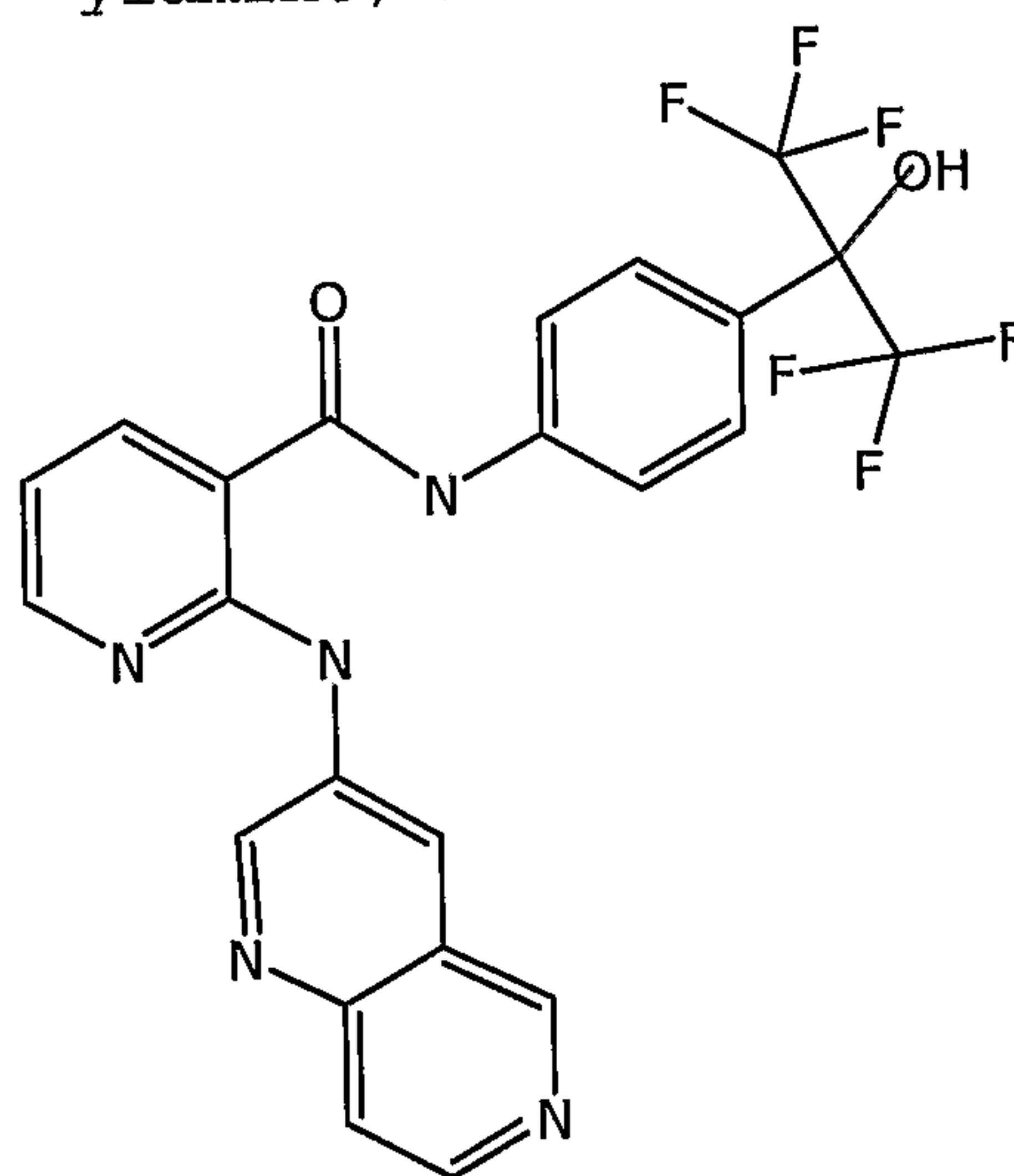


37 N-(4,4-Dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-([1,6]naphthyridin-3-ylamino)-nicotinamide

 $C_{25}H_{24}N_6O$

424.2

425.4



38 2-([1,6]Naphthyridin-3-ylamino)-N-[4-(2,2,2-trifluoro-1-hydroxy-1-trifluoromethyl-ethyl)-phenyl]-nicotinamide

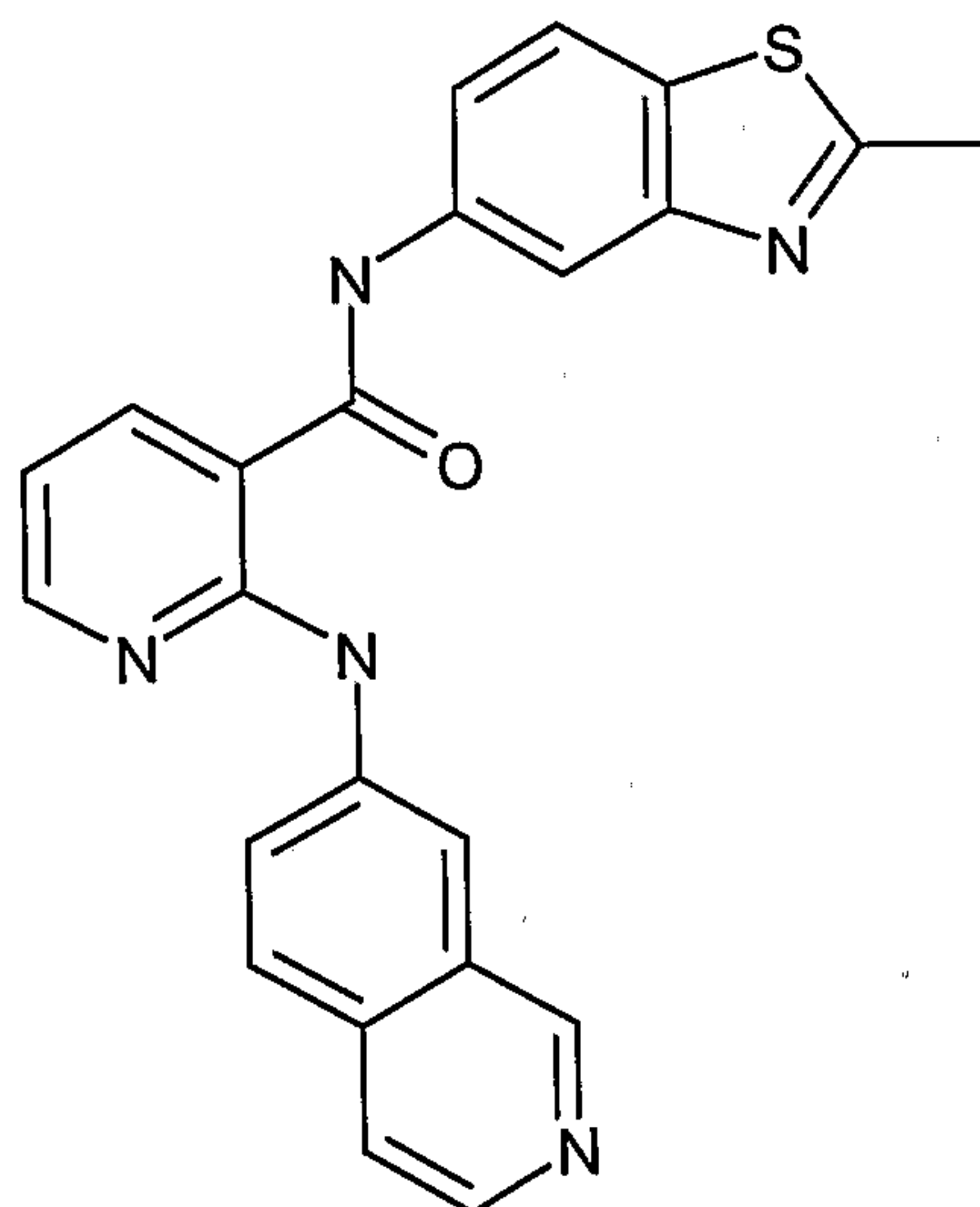
 $C_{23}H_{15}F_6N_5O_2$

507.11

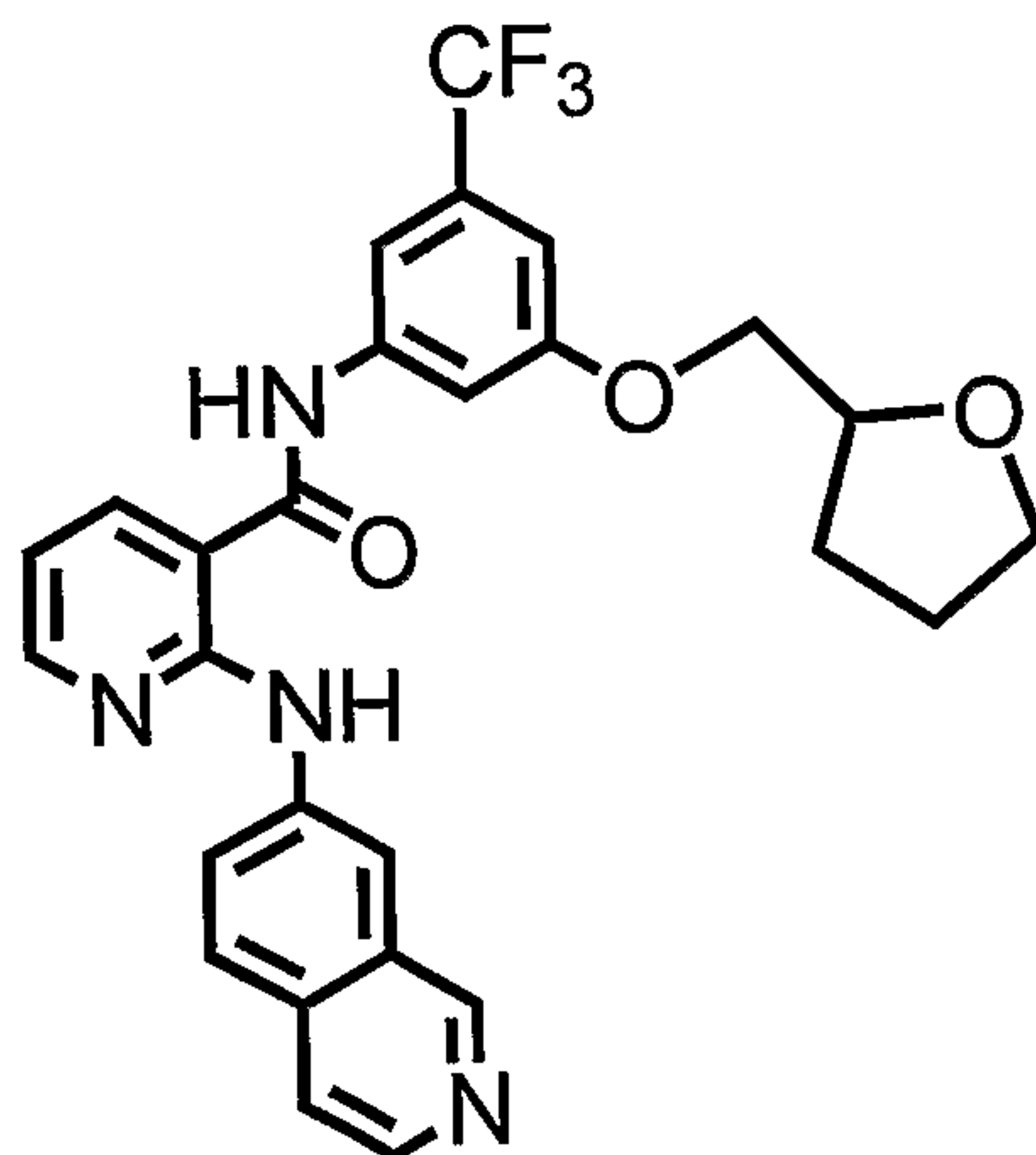
508.1

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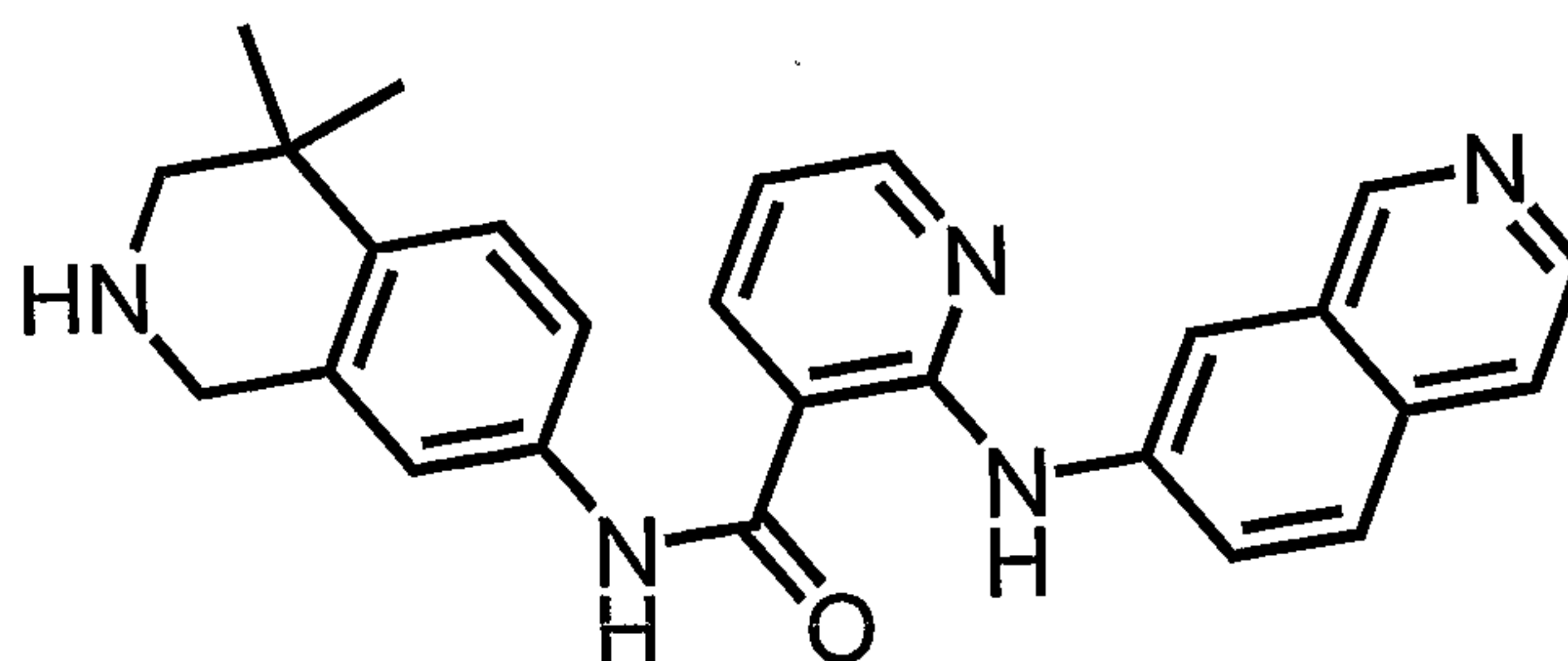


39 2-(isoquinolin-7-ylamino)-N-(2-methyl-1,3-benzothiazol-5-yl)nicotinamide $C_{23}H_{17}N_5O_2S$ 411.48 412.3



40 N-(4-chloro-3-methylphenyl)-2-(isoquinolin-7-ylamino)nicotinamide $C_{27}H_{23}F_5N_4O_3$ 508.50 509

Example 41



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N-(4,4-Dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-(isoquinolin-7-ylamino)-nicotinamide

Preparation of 7-[(2-chloro-pyridine-3-carbonyl)-amino]-4,4-dimethyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester

To a solution of 2-chloronicotinoyl chloride (3.52 g, 20 mmol, 1.0 eq.) and 7-amino-4,4-dimethyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (5.52 g, 20 mmol, 1.0 eq.) in CH₂Cl₂ (100 mL) was added NaHCO₃ (6.4 g, 80 mmol, 4.0 eq.). The mixture was stirred for 1 h at RT, then filtered and concentrated, followed by drying on a vacuum pump for 3 hours. 7-[(2-Chloro-pyridine-3-carbonyl)-amino]-4,4-dimethyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester was obtained as a white foamy solid. This title compound was used for next step without further purification.

Preparation of 7-{[2-(isoquinolin-7-ylamino)-pyridine-3-carbonyl]-amino}-4,4-dimethyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester:

To a mixture of 7-[(2-chloro-pyridine-3-carbonyl)-amino]-4,4-dimethyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (20.8 g, 50 mmol, 1.0 eq.), 7-aminoisoquinoline (7.2 g, 50 mmol, 1.0 eq.), Pd₂(dba)₃ (915 mg, 1 mmol, 0.02 eq), 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (CAS# 213697-53-1, Strem Chemicals cat no. 15-1145; 785 mg, 2 mmol, 0.04 eq) under N₂ in a 250 mL pressure reaction vessel was added 1.0 M LiNTMS₂ THF solution (120 mL, 120 mmol, 2.4 eq.). The reaction vessel was sealed with a Teflon screwcap and the mixture was stirred at 70 °C for 17 h. The mixture was then cooled to RT. 100 mL of water was added to the mixture and the mixture was extracted with 500 mL of EtOAc. The organic layer was

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washed with sat. NH_4Cl solution, 1M NaHPO_4 solution (4x200 mL) then dried over MgSO_4 . After filtration and concentration, the crude was purified through a silica gel column chromatography, eluting with $\text{CH}_2\text{Cl}_2/\text{EtOAc}$. The
5 desired title compound was obtained as a yellow solid. MS (ES^+): 524 ($\text{M}+\text{H}$) $^+$. Calc'd for $\text{C}_{31}\text{H}_{33}\text{N}_5\text{O}_3$ - 523.26

**Preparation of N-(4,4-Dimethyl-1,2,3,4-tetrahydro-
isoquinolin-7-yl)-2-(isoquinolin-7-ylamino)-nicotinamide:**

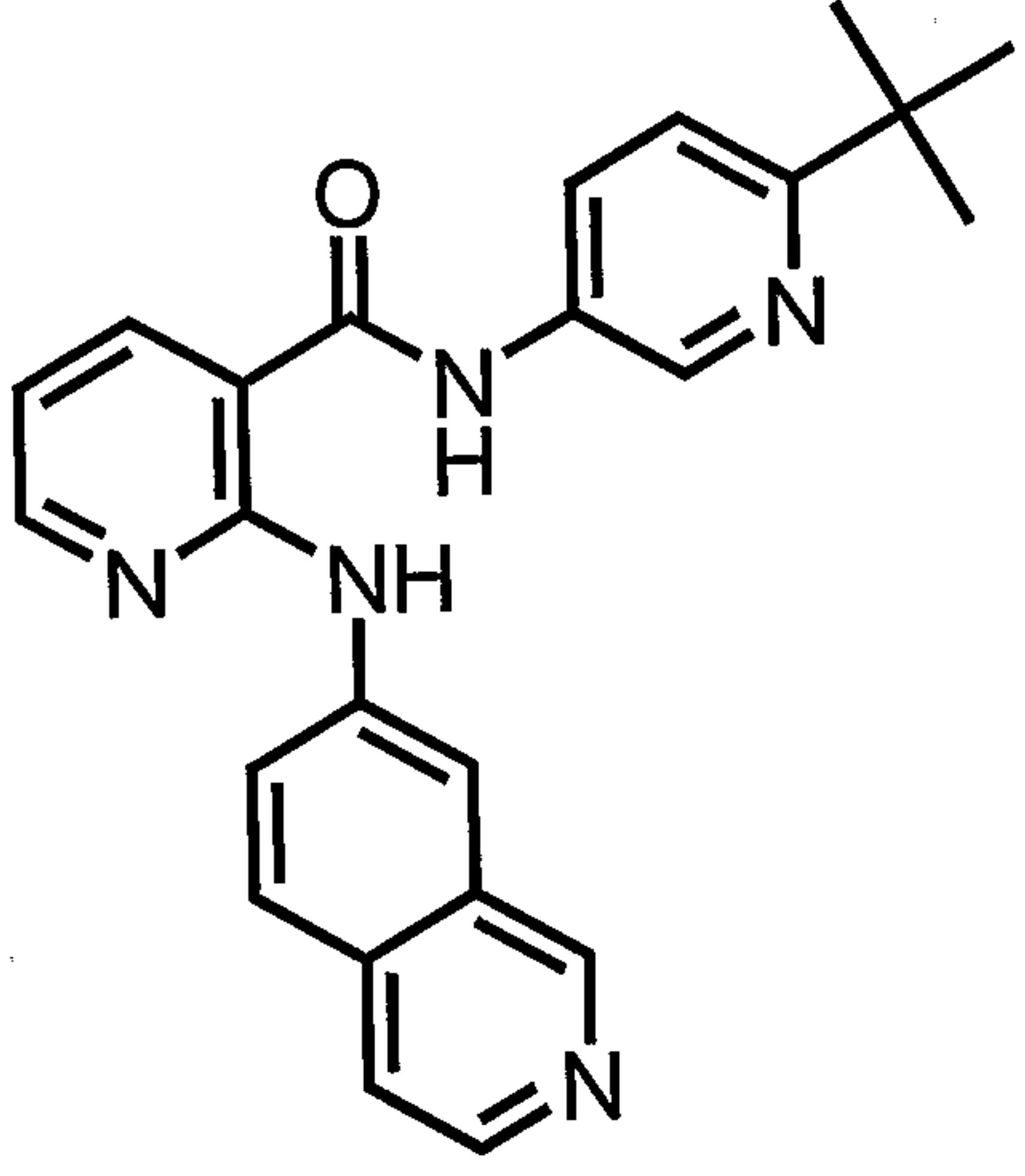
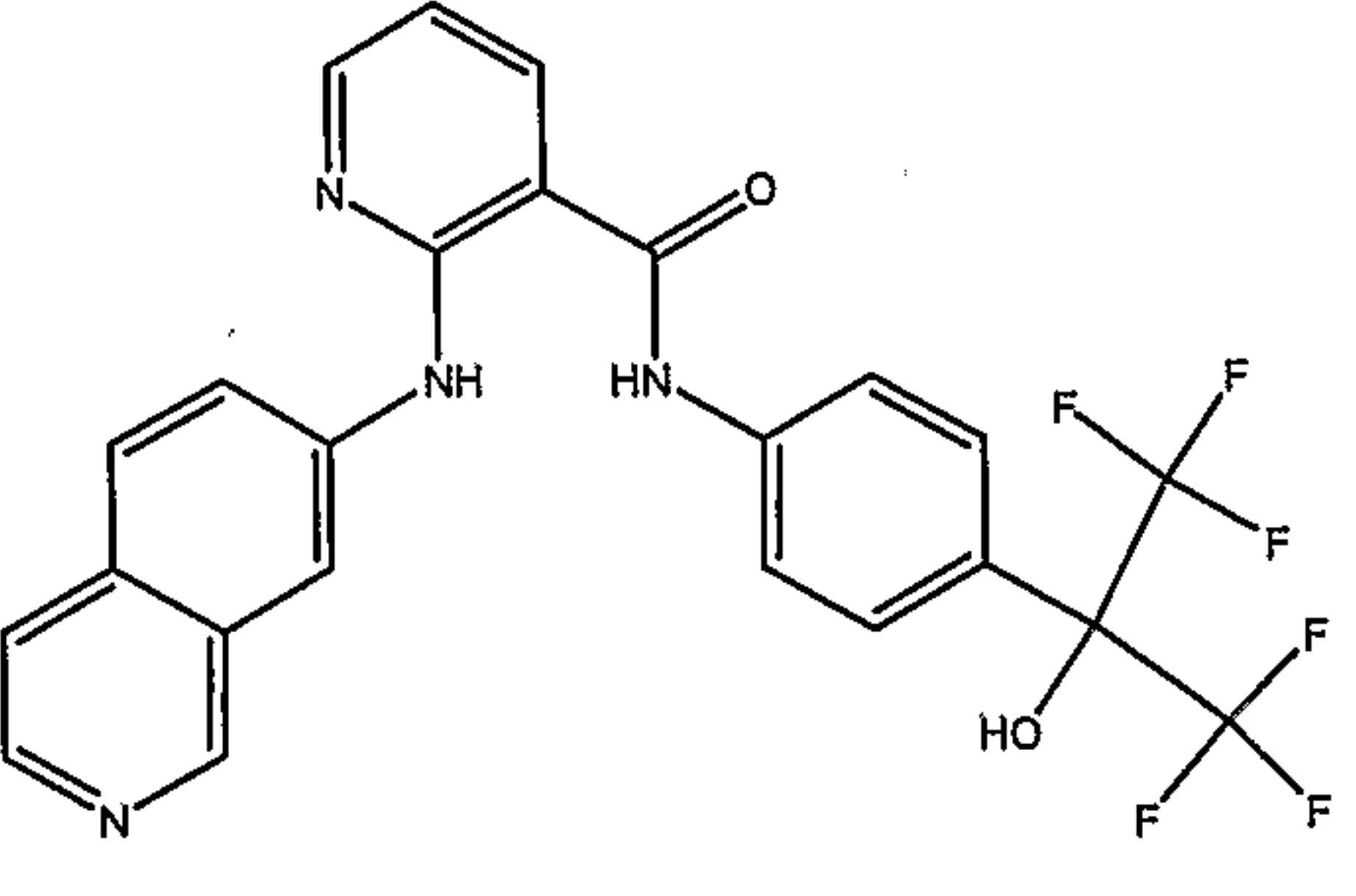
10 To 14.62 g of the compound in the step above (27.95 mmole) in a 2 L RBF was added 4N HCl in EtOAc (500 mL). The mixture was stirred for 20 h at RT and filtered to collect the product as multi-HCl salt. This solid was dissolved in
15 EtOAc. The aqueous layer was acidified to about pH 5 with 2 N NaOH solution. The title compound (as monohydrate and mono HCl salt) was obtained after filtration and drying on vacuum pump for 24 h as a light yellow solid. MS (ES^+): 424 ($\text{M}+\text{H}$) $^+$. Calc'd for $\text{C}_{26}\text{H}_{25}\text{N}_5\text{O}$ - 423.21.

20

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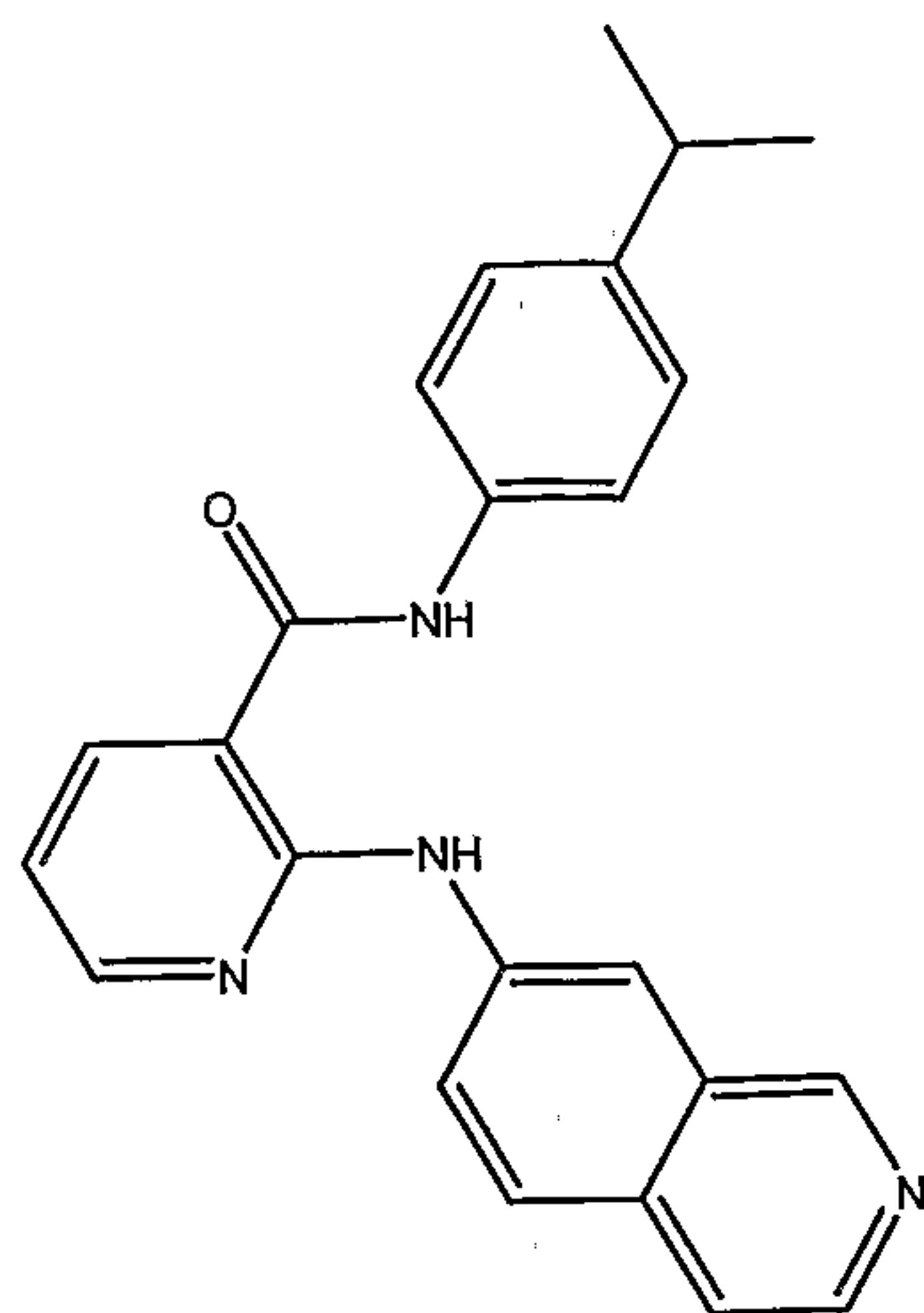
- 246 -

The following examples 42-66 were prepared according to a method similar to that described in Example 41:

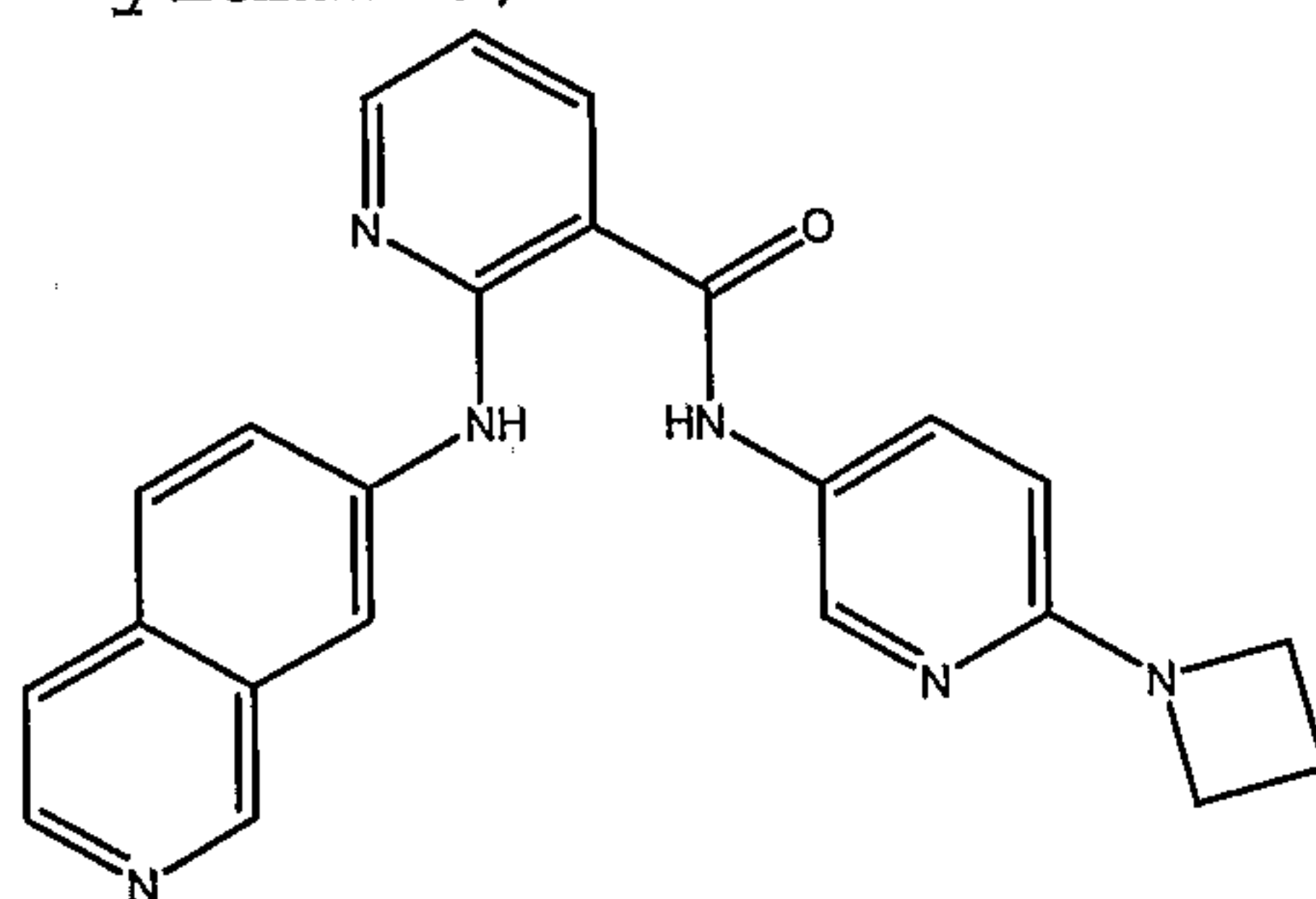
Ex. #	Structure	Mol. formula	Calc'd Mass	M+H
				
42	N-(6-tert-Butyl-pyridin-3-yl)-2-(isoquinolin-7-ylamino)-nicotinamide	$C_{24}H_{23}N_5O$	397.19	398
				
43	2-(Isoquinolin-7-ylamino)-N-[4-(2,2,2-trifluoro-1-hydroxy-1-trifluoromethyl-ethyl)-phenyl]-nicotinamide	$C_{24}H_{16}F_6N_4O_2$	506.12	507

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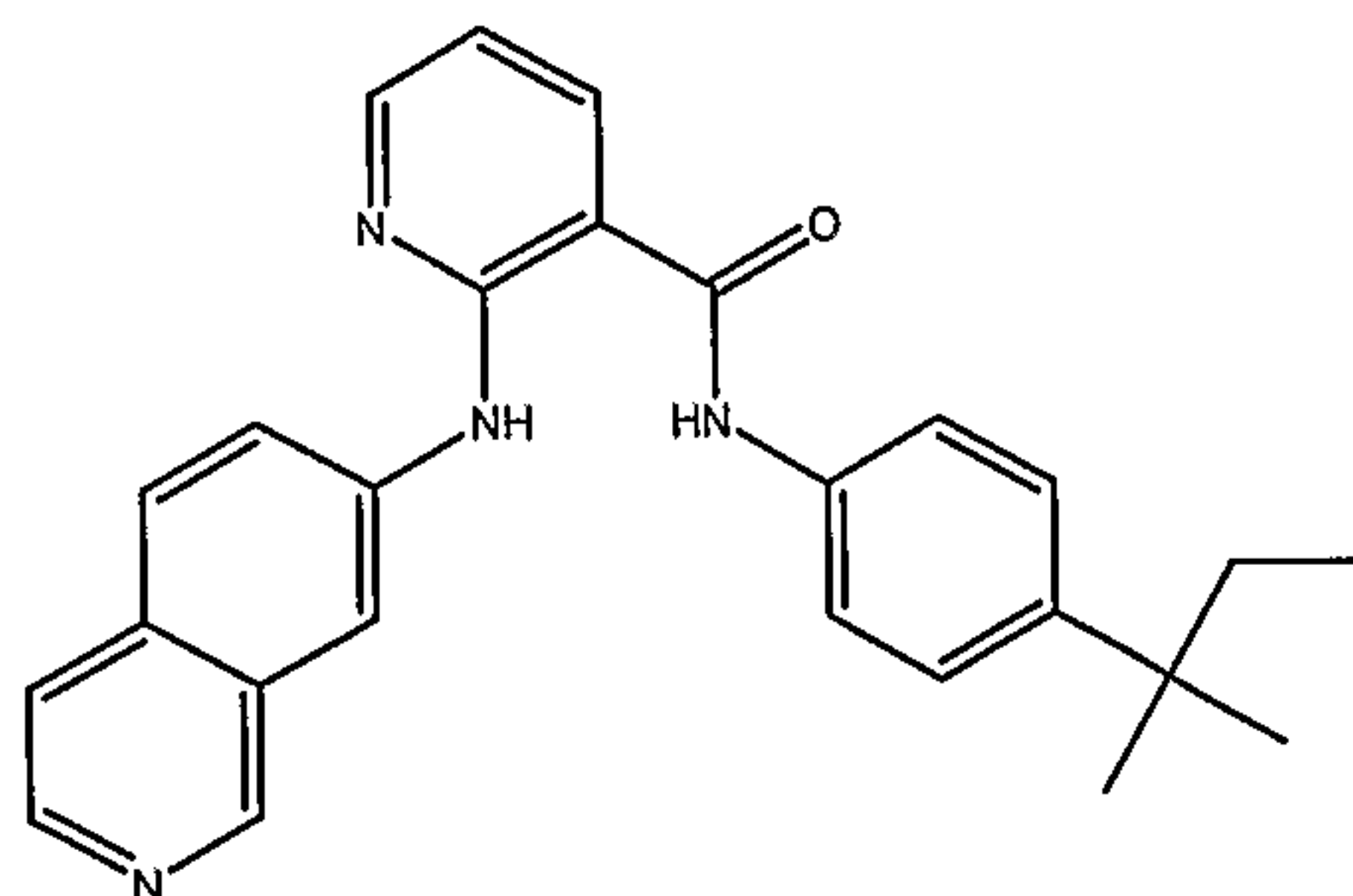
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44	N-(4-Isopropyl-phenyl)- 2-(isoquinolin-7-ylamino)-nicotinamide	$C_{24}H_{22}N_4O$	382.18	383
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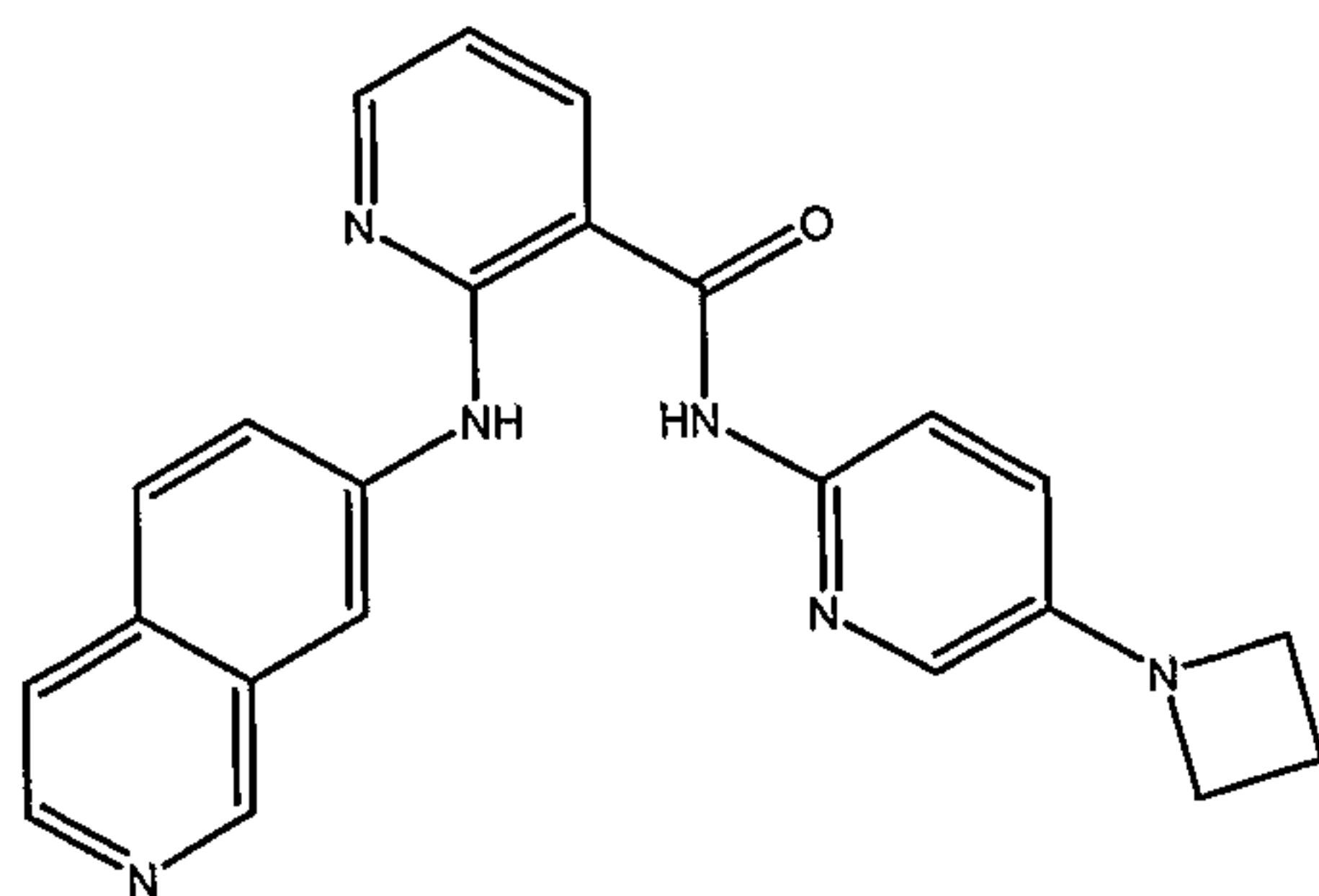
45	N-(6-Azetidin-1-yl- pyridin-3-yl)-2- (isoquinolin-7-ylamino)- nicotinamide	$C_{23}H_{20}N_6O$	396.17	397
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46	N-[4-(1,1-Dimethyl- propyl)-phenyl]-2- (isoquinolin-7-ylamino)- nicotinamide	$C_{26}H_{26}N_4O$	410.21	411
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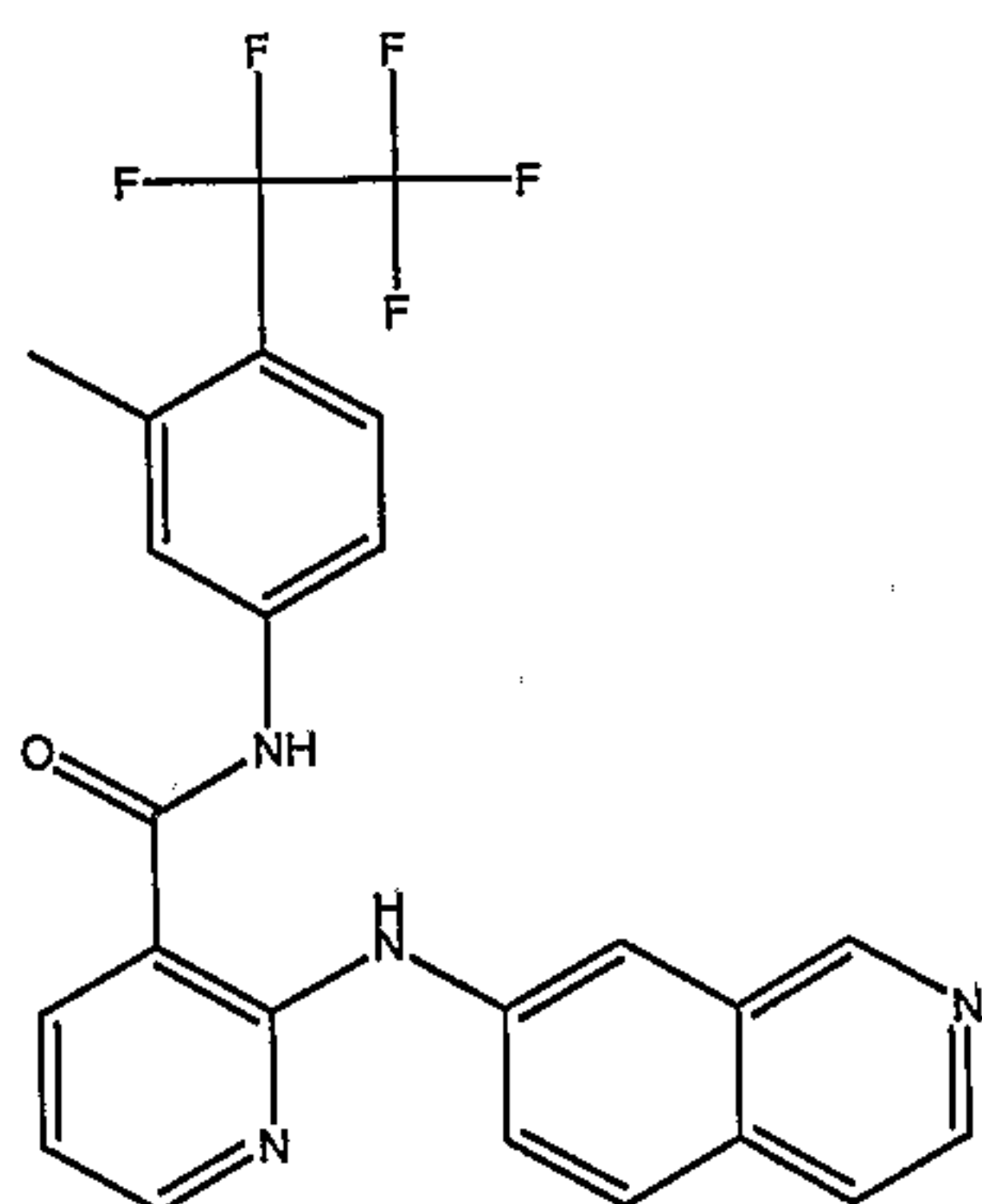


N-(5-Azetidin-1-yl-
pyridin-2-yl)-2-
(isoquinolin-7-ylamino)-
nicotinamide

47

 $C_{23}H_{20}N_6O$

396.17 397

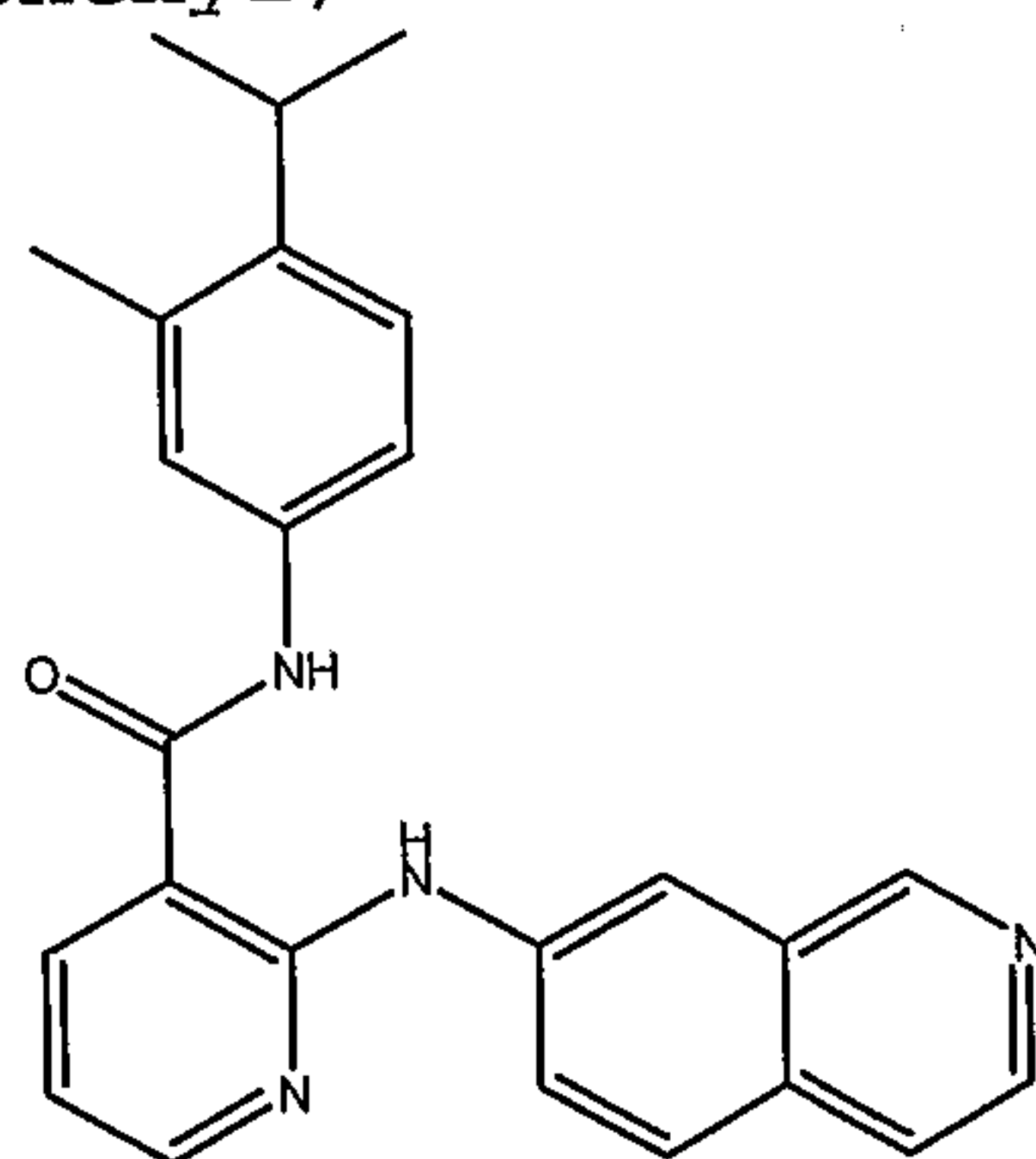


2-(Isoquinolin-7-
ylamino)-N-(3-methyl-4-
pentafluoroethyl-
phenyl)-nicotinamide

48

 $C_{24}H_{17}F_5N_4O$

472.13 473



N-(4-Isopropyl-3-methyl-
phenyl)-2-(isoquinolin-
7-ylamino)-nicotinamide

49

 $C_{25}H_{24}N_4O$

396.20 397

DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS
COMPREND PLUS D'UN TOME.**

CECI EST LE TOME __1__ DE __2__

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

THIS IS VOLUME __1__ OF __2__

NOTE: For additional volumes please contact the Canadian Patent Office.

WHAT IS CLAIMED IS:

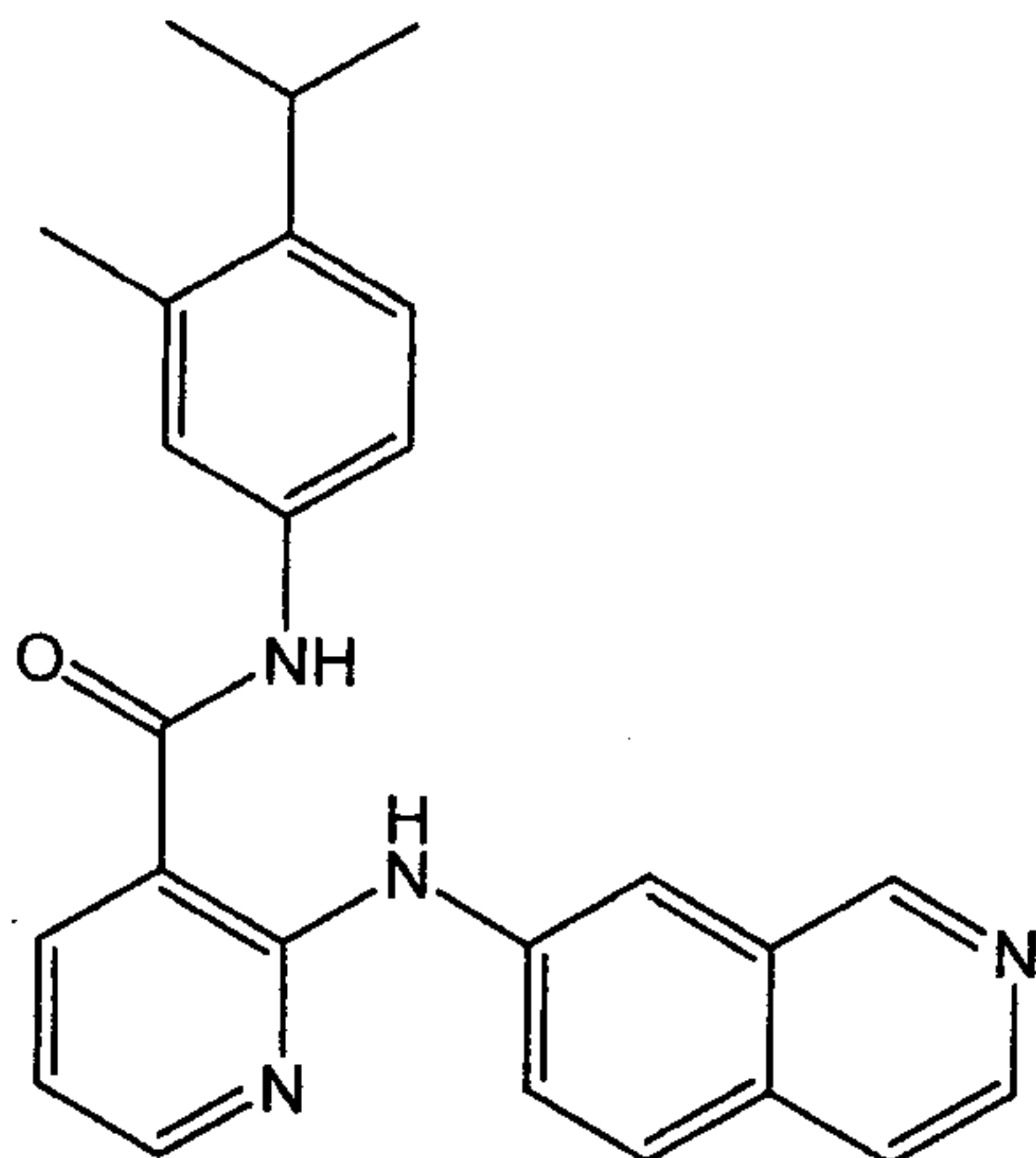
1. A compound or a pharmaceutically acceptable salt form thereof, wherein the compound is 2-(7-isoquinolinylamino)-N-(3-methyl-4-(1-methylethyl)phenyl)-3-pyridinecarboxamide.

2. The compound of claim 1.

3. The pharmaceutically acceptable salt form of the compound of claim 1.

4. The pharmaceutically acceptable salt form of the compound of claim 1, wherein the salt is selected from a benzenesulfonate salt, an ethanesulfonate salt, an ethanedisulfonate salt, a methanesulfonate salt, a p-toluenesulfonate salt, a phosphate salt, a hydrobromide salt, a nitrate salt, a hydrochloride salt, a citrate salt, a medronate salt, a tosylate salt, a maleate salt, a fumarate salt, a napsylate salt, a pamoate salt, a salicylate salt or a stearate salt.

5. A compound or one of a hydrochloride, a sulfate, a sulfonate or a phosphate salt thereof, wherein the compound has the formula



6. A pharmaceutical composition comprising a pharmaceutically-acceptable carrier and the compound of claim 1 or the pharmaceutically acceptable salt form thereof.

5 7. A pharmaceutical composition comprising a pharmaceutically-acceptable carrier and the pharmaceutically acceptable salt form of claim 4.

10 8. A use of an effective amount of the compound or the pharmaceutically acceptable salt of claim 1 for treating cancer in a subject.

15 9. A use of an effective amount of the compound or the pharmaceutically acceptable salt of claim 1 for the preparation of a medicament for treating cancer in a subject.

20 10. A use of an effective amount of the compound or the pharmaceutically acceptable salt of claim 1 in combination with one or more compounds selected from antineoplastic agents, anti-angiogenic agents, chemotherapeutic agents and peptidal cancer therapy agents, for treating cancer in a subject.

25 11. A use of an effective amount of the compound or the pharmaceutically acceptable salt of claim 1 in combination with one or more compounds selected from antineoplastic agents, anti-angiogenic agents, chemotherapeutic agents and peptidal cancer therapy agents, for the preparation of one or more medicaments for treating cancer in a subject.

30 12. A use of an effective amount of the compound or the pharmaceutically acceptable salt of claim 1 for reducing blood flow in a tumor in a subject.

13. A use of an effective amount of the compound or the pharmaceutically acceptable salt of claim 1 for the preparation of a medicament for reducing blood flow in a tumor in a subject.

5

14. A use of an effective amount of the compound or the pharmaceutically acceptable salt of claim 1 for reducing tumor size in a subject.

10

15. A use of an effective amount of the compound or the pharmaceutically acceptable salt of claim 1 for the preparation of a medicament for reducing tumor size in a subject.

15

16. A use of an effective amount of the compound or the pharmaceutically acceptable salt of claim 1 for treating diabetic retinopathy in a subject.

20

17. A use of an effective amount of the compound or the pharmaceutically acceptable salt of claim 1 for the preparation of a medicament for treating diabetic retinopathy in a subject.

25

18. A use of an effective amount of the compound or the pharmaceutically acceptable salt of claim 1 for inhibiting angiogenesis in a subject.

30

19. A use of an effective amount of the compound or the pharmaceutically acceptable salt of claim 1 for the preparation of a medicament for inhibiting angiogenesis in a subject.

