



(86) Date de dépôt PCT/PCT Filing Date: 2008/12/12
(87) Date publication PCT/PCT Publication Date: 2009/06/18
(85) Entrée phase nationale/National Entry: 2010/06/11
(86) N° demande PCT/PCT Application No.: US 2008/086594
(87) N° publication PCT/PCT Publication No.: 2009/076602
(30) Priorité/Priority: 2007/12/13 (US61/013,457)

(51) Cl.Int./Int.Cl. *C07D 401/12* (2006.01),
A61K 31/465 (2006.01), *A61P 11/06* (2006.01),
A61P 17/06 (2006.01), *A61P 29/00* (2006.01),
A61P 37/00 (2006.01), *C07D 401/14* (2006.01)

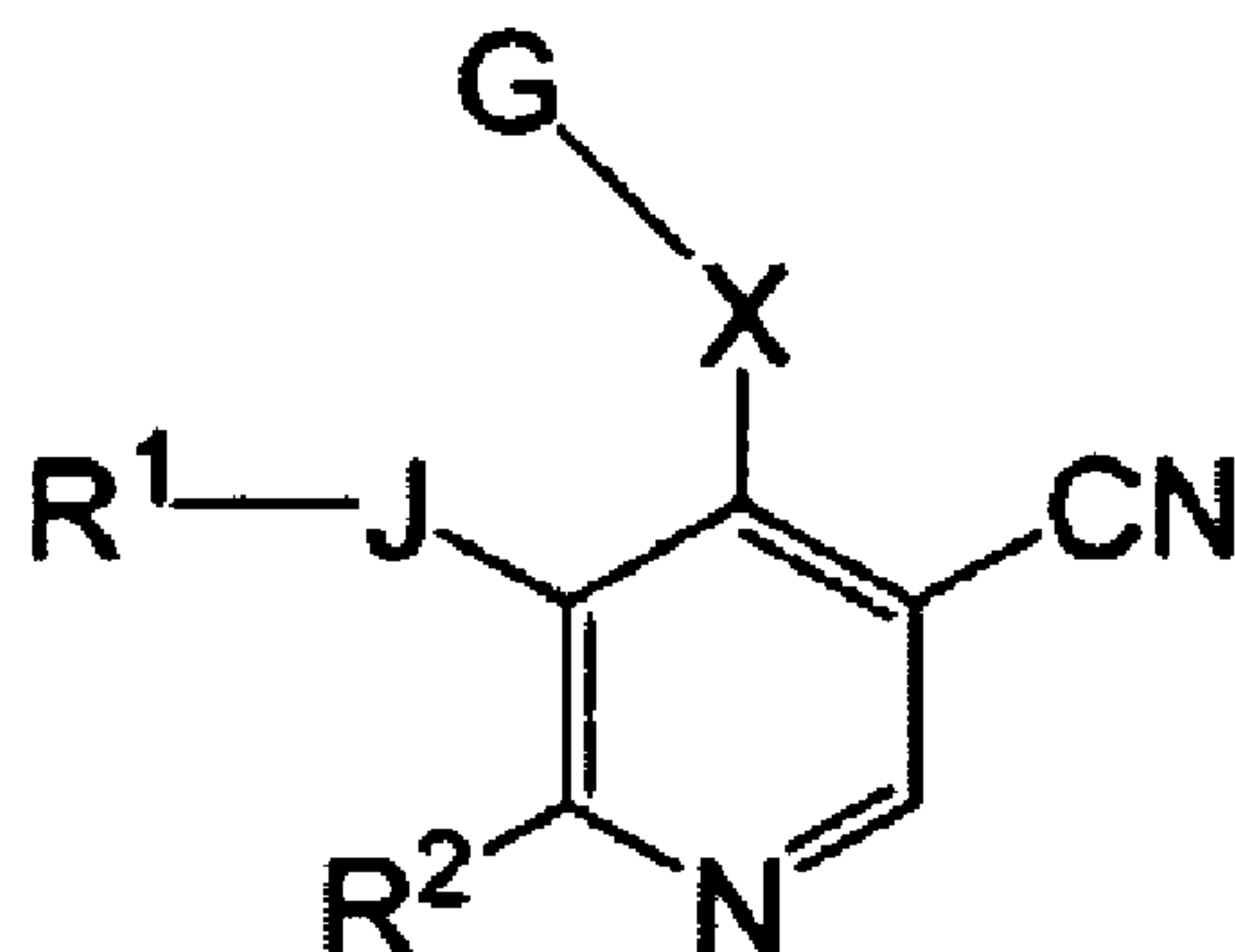
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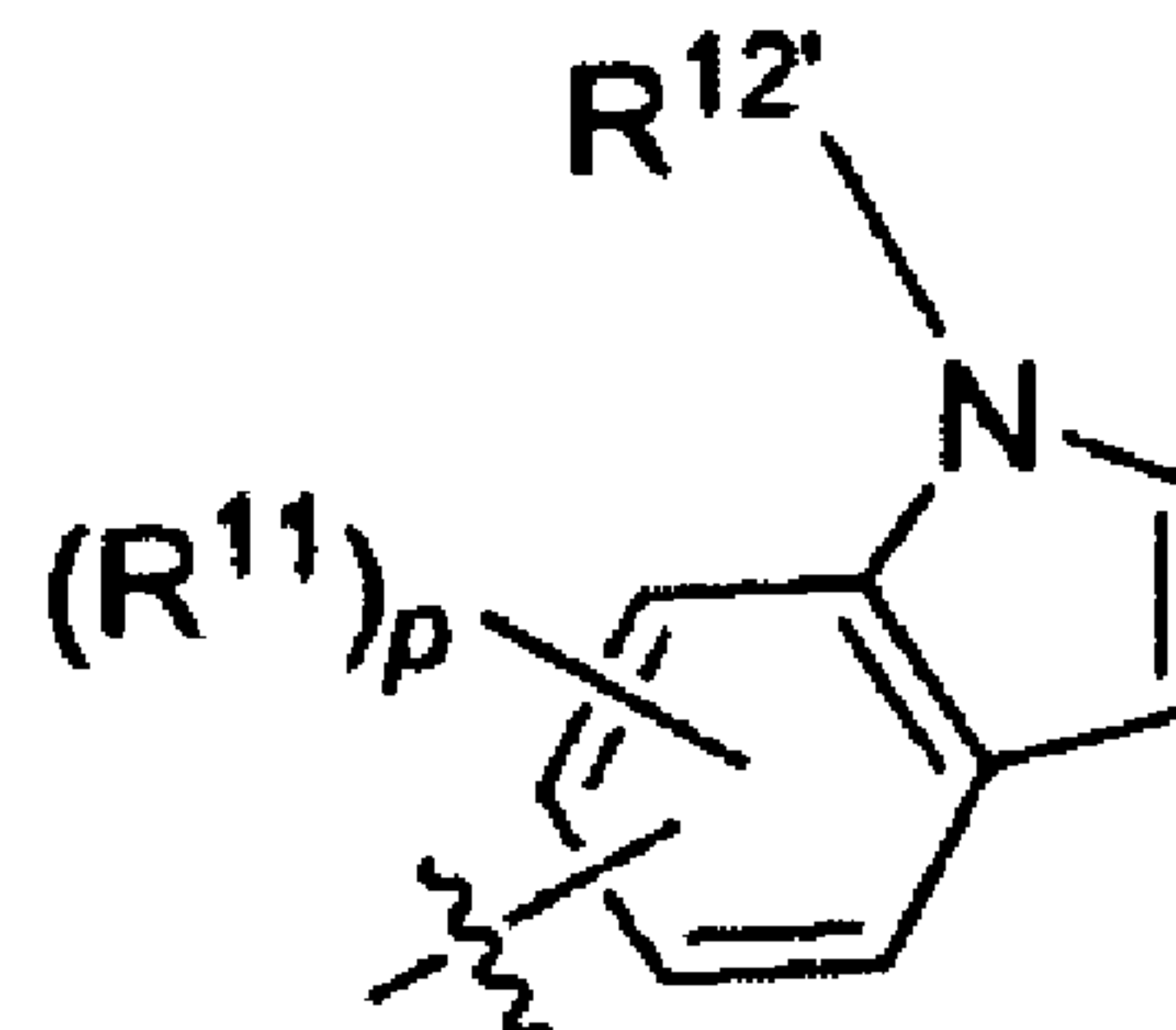
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(54) Titre : 5-ALKYL/ALCENYL-3-CYANOPYRIDINES EN TANT QU'INHIBITEURS DE KINASE

(54) Title: 5-ALKYL/ALKENYL-3-CYANOPYRIDINES AS KINASE INHIBITORS



(I)



(57) Abrégé/Abstract:

Described herein are compounds of formula I: wherein G is and pharmaceutically acceptable salts thereof, wherein J, X, R¹, R², R¹¹, R^{12'} and p are as defined herein. Also provided herein are methods of making the compounds of formula I, and methods of using these compounds for inhibiting or treating a pathological condition or disorder linked to or mediated by a protein kinase in a mammal.



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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
18 June 2009 (18.06.2009)

PCT

(10) International Publication Number
WO 2009/076602 A1

(51) International Patent Classification:

C07D 401/12 (2006.01) *A61P 17/06* (2006.01)
C07D 401/14 (2006.01) *A61P 29/00* (2006.01)
A61K 31/465 (2006.01) *A61P 37/00* (2006.01)
A61P 11/06 (2006.01)

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(21) International Application Number:

PCT/US2008/086594

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(22) International Filing Date:

12 December 2008 (12.12.2008)

(81) **Designated States** (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/013,457 13 December 2007 (13.12.2007) US

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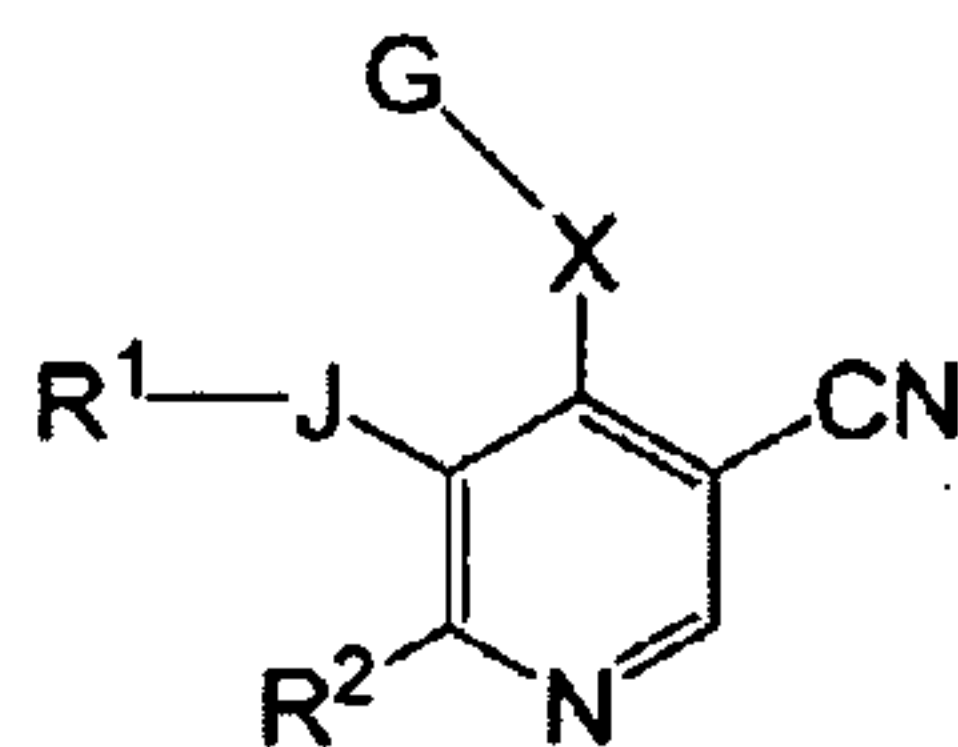
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(84) **Designated States** (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

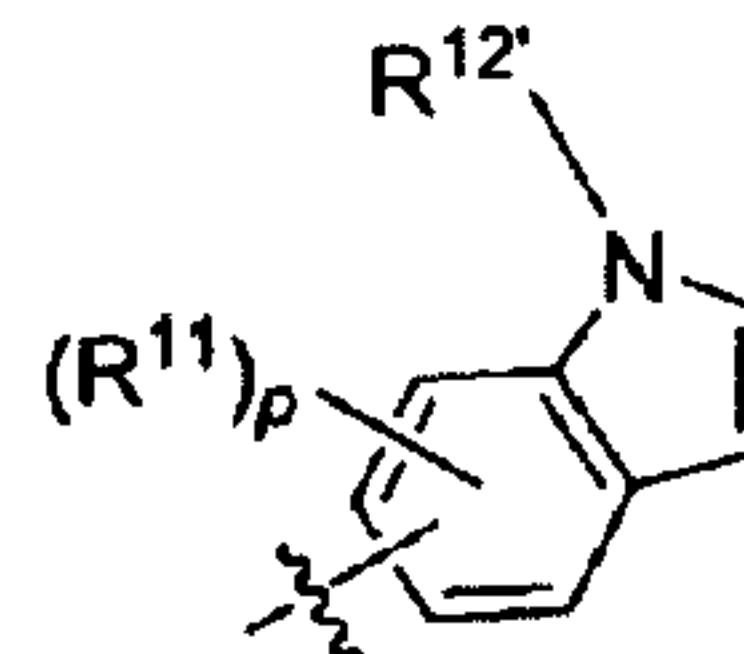
Published:

- *with international search report*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(54) **Title:** 5-ALKYL/ALKENYL-3-CYANOPYRIDINES AS KINASE INHIBITORS



(I)



(57) **Abstract:** Described herein are compounds of formula I: wherein G is and pharmaceutically acceptable salts thereof, wherein J, X, R¹, R², R¹¹, R¹² and p are as defined herein. Also provided herein are methods of making the compounds of formula I, and methods of using these compounds for inhibiting or treating a pathological condition or disorder linked to or mediated by a protein kinase in a mammal.

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5-ALKYL/ALKENYL-3-CYANOPYRIDINES AS KINASE INHIBITORS

TECHNICAL FIELD

[0001] This invention relates to 3-cyanopyridine compounds which are useful as kinase inhibitors.

BACKGROUND

[0002] Protein kinases are enzymes that catalyze the transfer of a phosphate group from adenosine triphosphate (ATP) to an amino acid residue, such as tyrosine, serine, threonine or histidine, on a protein. Regulation of these protein kinases is essential for the control of a wide variety of cellular events including proliferation and migration. A large number of diseases are associated with abnormal cellular events that are mediated by these kinases, for example, various inflammatory diseases and autoimmune diseases such as asthma, psoriasis, rheumatoid arthritis, inflammatory bowel disease, and joint inflammation. See, e.g., Salek-Ardakami, S., *et al.*, *J. Immunology*, (2004), 173(10), 6440-47; Marsland, B., *et al.*, *J. Exp. Med.*, (2004), 200(2), 181-89; Tan, S., *et al.*, *J. Immunology*, (2006), 176, 2872-79; Salek-Ardakami, S., *et al.*, *J. Immunology*, (2005), 175(11), 7635-41; Anderson, K., *et al.*, *Autoimmunity*, (2006), 39(6), 469-78; Healy, A., *et al.*, *J. Immunology*, (2006), 177(3), 1886-93; Sun, Z., *et al.*, *Nature*, (2000), 404, 402-7; and Pfeifhofer, C., *et al.*, *J. Exp. Med.*, (2003), 197(11), 1525-35.

[0003] One class of serine/threonine kinases is the protein kinase C (PKC) family. This group of kinases consists of 10 members that share sequence and structural homology. The PKCs are divided into 3 groups and include the classic, the novel, and the atypical isoforms. The theta isoform (PKC θ) is a member of the novel calcium-independent class of PKCs (Baier, G. *et al.*, *J. Biol. Chem.*, (1993), 268: 4997-5004). PKC θ is highly expressed in T cells (Mischak, H. *et al.*, *FEBS Lett.*, (1993), 326: 51-5), with some expression reported in mast cells (Liu, Y. *et al.* (2001), *J. Leukoc. Biol.*, 69: 831-40), endothelial cells (Mattila, P. *et al.*, *Life Sci.*, (1994), 55:

1253-60), and skeletal muscles (Baier, G. *et al.*, *Eur. J. Biochem.*, (1994), 225: 195-203). It has been shown that PKC θ plays an essential role in T cell receptor (TCR)-mediated signaling (Tan, S.L. *et al.*, *Biochem. J.*, (2003), 376: 545-52). Specifically, it has been observed that inhibiting PKC θ signal transduction, as demonstrated with two independent PKC θ knockout mouse lines, will result in defects in T cell activation and interleukin-2 (IL-2) production (Sun, Z. *et al.*, *Nature*, (2000), 404: 402-7; Pfeifhofer, C. *et al.*, *J. Exp. Med.*, (2003), 197: 1525-35). It also has been shown that PKC θ -deficient mice show impaired pulmonary inflammation and airway hyperresponsiveness (AHR) in a Th2-dependent murine asthma model, with no defects in viral clearance and Th1-dependent cytotoxic T cell function (Berg-Brown, N.N. *et al.*, *J. Exp. Med.*, (2004), 199: 743-52; Marsland, B.J. *et al.*, *J. Exp. Med.*, (2004), 200: 181-9). The impaired Th2 cell responses result in reduced levels of interleukin-4 (IL-4) and immunoglobulin E (IgE), contributing to the AHR and inflammatory pathophysiology.

[0004] Evidence also exists that PKC θ participates in the IgE receptor (Fc ϵ RI)-mediated response of mast cells (Liu, Y. *et al.*, *J. Leukoc. Biol.*, (2001), 69: 831-840). In human-cultured mast cells (HCMC), it has been demonstrated that PKC θ kinase activity rapidly localizes (in less than five minutes) to the membrane following Fc ϵ RI cross-linking (Kimata, M. *et al.*, *Biochem. Biophys. Res. Commun.*, (1999), 257(3): 895-900). A recent study examining *in vitro* activation of bone marrow mast cells (BMMCs) derived from wild-type and PKC θ -deficient mice shows that upon Fc ϵ RI cross-linking, BMMCs from PKC θ -deficient mice produced reduced levels of interleukin-6 (IL-6), tumor necrosis factor- α (TNF α), and interleukin-13 (IL-13) in comparison with BMMCs from wild-type mice, suggesting a potential role for PKC θ in mast cell cytokine production in addition to T cell activation (Ciarletta, A.B. *et al.*, poster presentation at the 2005 American Thoracic Society International Conference, (2005)).

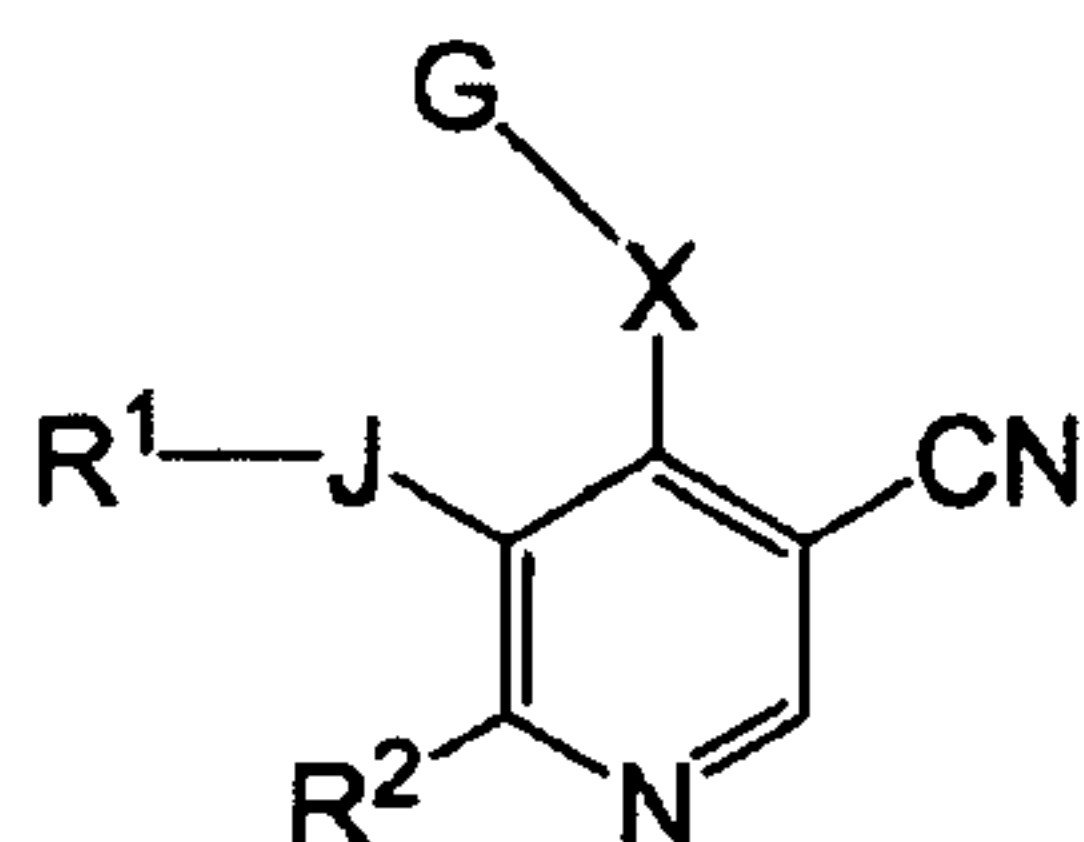
[0005] Other serine/threonine kinases include those of the mitogen-activated protein kinase (MAPK) pathway which consists of the MAP kinases (MAPK) (e.g., erk) and the MAPK kinases (MAPKK) (e.g., mek and their substrates). Members of the raf family of kinases phosphorylate residues on mek. The cyclin-dependent kinases (cdks), including cdc2/cyclin B, cdk2/cyclin A, cdk2/cyclin E and cdk4/cyclin D, and others,

are serine/threonine kinases that regulate mammalian cell division. Additional serine/threonine kinases include the protein kinases A and B. These kinases, known as PKA or cyclic AMP-dependent protein kinase and PKB (Akt), play key roles in signal transduction pathways.

[0006] Tyrosine kinases (TKs) are divided into two classes: the non-transmembrane TKs and transmembrane growth factor receptor TKs (RTKs). Growth factors, such as epidermal growth factor (EGF), bind to the extracellular domain of their partner RTK on the cell surface which activates the RTK, initiating a signal transduction cascade that controls a wide variety of cellular responses. In addition to EGF, there are several other RTKs including FGFR (the receptor for fibroblast growth factor (FGF)); flk-1 (also known as KDR), and flt-1 (the receptors for vascular endothelial growth factor (VEGF)); and PDGFR (the receptor for platelet derived growth factor (PDGF)). Other RTKs include tie-1 and tie-2, colony stimulating factor receptor, the nerve growth factor receptor, and the insulin-like growth factor receptor. In addition to the RTKs there is another family of TKs termed the cytoplasmic protein or non-receptor TKs. The cytoplasmic protein TKs have intrinsic kinase activity, are present in the cytoplasm and nucleus, and participate in diverse signaling pathways. There are a large number of non-receptor TKs including Abl, Jak, Fak, Syk, Zap-70 and Csk, and the Src family of kinases (SFks) which include Src, Lck, Lyn, Fyn and others.

SUMMARY

[0007] One aspect of the present invention is directed to compounds of formula I:



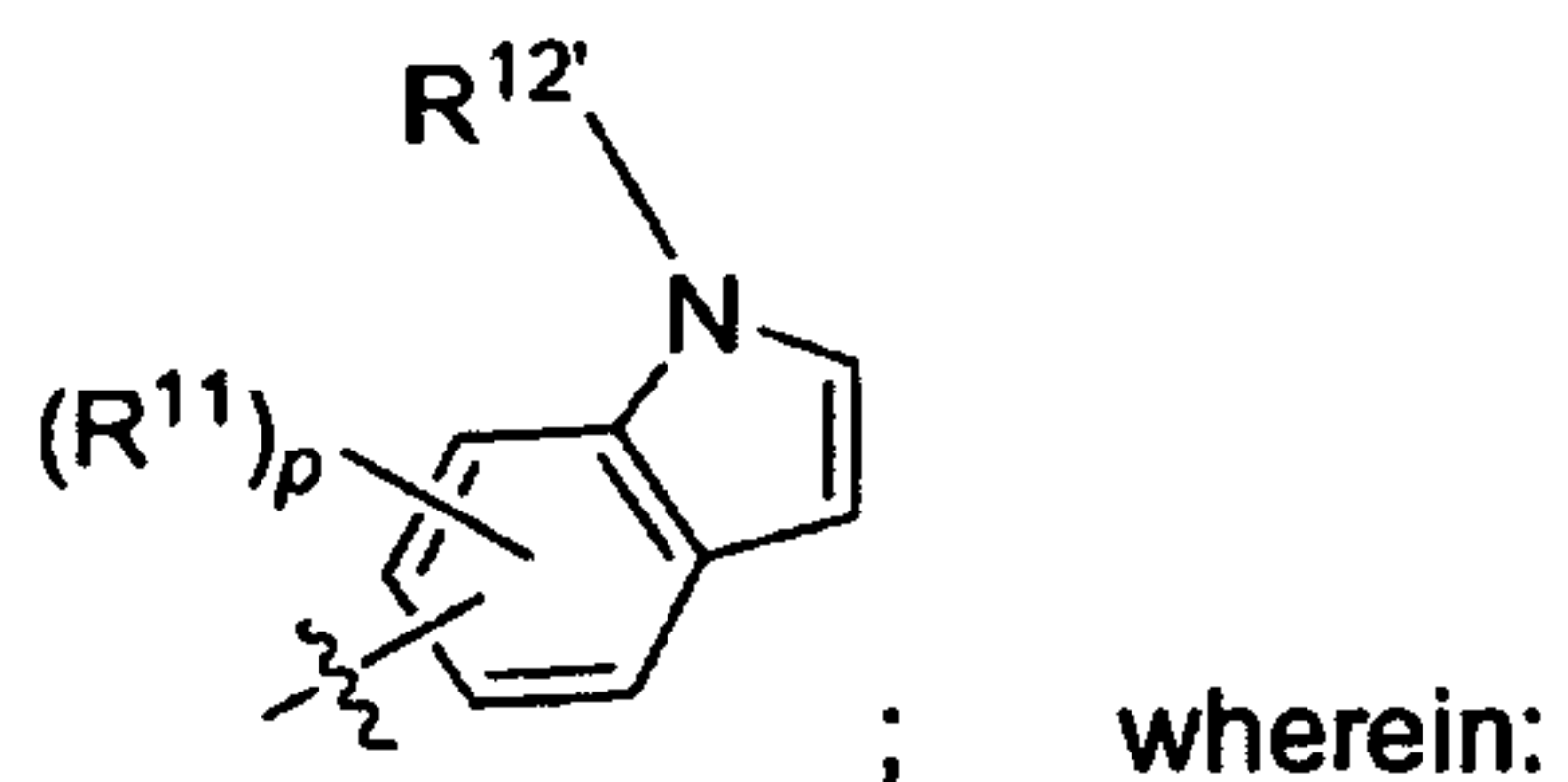
(I)

or a pharmaceutically acceptable salt thereof, wherein:

X is -O- or -N(R¹⁰)-; wherein

R¹⁰ is H or CH₃;

G is



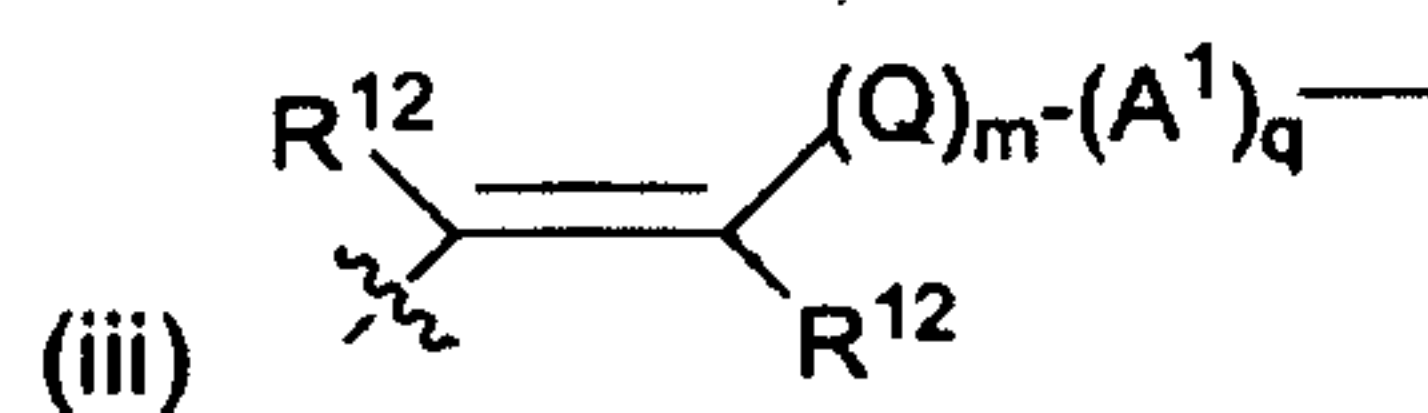
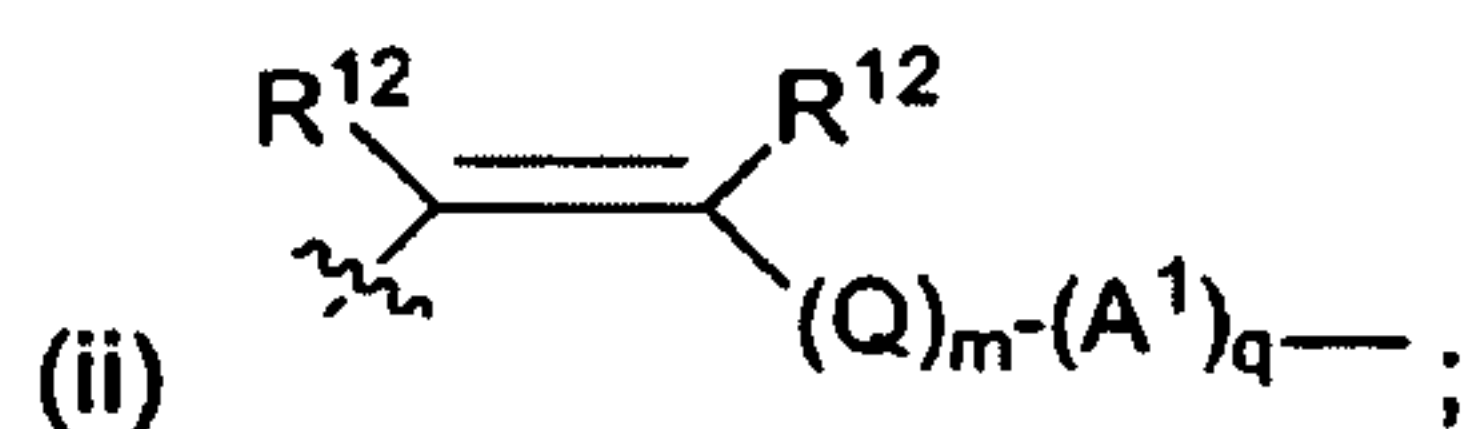
R¹¹ is, independently at each occurrence, selected from halo, -O-R^{12''}, C₁₋₄ alkyl, -CF₃ and -N(R^{12''})-R^{12''};

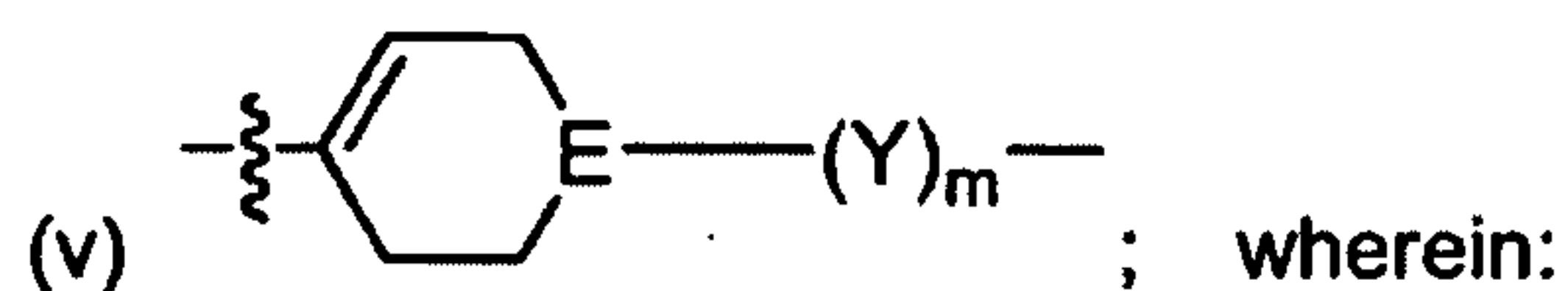
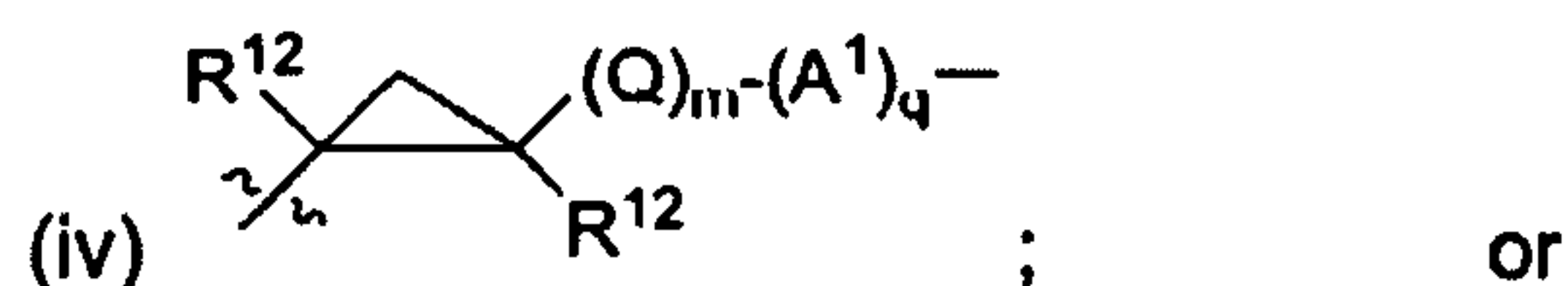
R^{12'} is, independently at each occurrence, H or CH₃;

R^{12''} is, independently at each occurrence, H or CH₃; and

p is 0, 1 or 2;

J is (i) -Q-(A¹)_q-;





Q is, independently at each occurrence, C₁₋₄ alkylene;

A¹ is (i) a C₆₋₁₀ aryl, (ii) a 5- to 10-membered hetero₁₋₃aryl, (iii) 3- to 10-membered hetero₁₋₃cyclyl or (iv) a 5- to 8-membered cycloalkyl, wherein each of (i)-(iv) is optionally substituted with 1 or 2 substituents independently selected from halo, -O-R¹³, C₁₋₄ alkyl, C₁₋₄ haloalkyl, formyl, -S-R¹³, -Q-O-R¹³, -Q-N(R¹³)-R¹³, -C(O)-O-R¹³, -C(O)-R¹³, -O-C(O)-R¹³, -C(O)-N(R¹³)-R¹³, -N(R¹³)-C(O)-R¹³, -S(O)₂-N(R¹³)-R¹³, -N(R¹³)-S(O)₂-R¹³, -O-Q-O-R¹³, -O-Q-N(R¹³)-R¹³, -N(R¹³)-Q-O-R¹³, -N(R¹³)-Q-N(R¹³)-R¹³, -O-C(O)-N(R¹³)-R¹³, -N(R¹³)-C(O)-O-R¹³, -S(O)₂-R¹³, -SO₂NH(NH)NH₂, -SO₂NH(NH)NR¹³R¹³ or wherein 2 substituents together on the same carbon atom form an oxo group;

R¹² is, independently at each occurrence, H or CH₃;

m and q are independently 0 or 1;

E is N or C(R^{12'}); wherein:

when E is N, Y is absent, -C(O)-, -C(O)-O-, -C(O)-N(R¹³)- or -S(O)₂-; and

when E is C(R^{12'}), Y is -O-, -C(O)-, -C(O)-O-, -O-C(O)-, -C(O)-N(R¹³)-, -O-C(O)-N(R¹³)-, -N(R¹³)-C(O)-, -N(R¹³)-C(O)-O-, -N(R¹³)-C(O)-N(R¹³)-, -S-, -S(O)-, -S(O)₂-, -S(O)₂-N(R¹³)- or -N(R¹³)-S(O)₂-;

R¹³ is, independently at each occurrence, selected from (i) an electron pair, (ii) H, (iii) C₁₋₆ alkyl, (iv) C₆₋₁₀ aryl, (v) 5- to 10-membered heteroaryl, (vi) 3- to 10-membered hetero₁₋₃cyclyl or (vii) two R¹³ together on the same carbon atom form a 4- to 8-membered ring containing 1-3 heteroatoms, wherein each of (iii)-(vi) is optionally substituted with 1-2 R¹⁴; and

R^{14} is, independently at each occurrence, (i) H, (ii) oxo when two R^{14} together on the same carbon atom are bound to an oxygen atom, (iii) C_{1-6} alkyl, (iv) C_{3-8} cycloalkyl, (v) C_{6-10} aryl, (vi) 5- to 10-membered heteroaryl, (vii) 3- to 10-membered hetero₁₋₃cyclyl, wherein each of (iii)-(vii) is optionally substituted with 1-2 C_{1-6} alkyl;

R^1 is C_{1-4} alkyl, C_{2-4} alkenyl or $-(L)_r(A^2-A^3)$, wherein:

L is $-(T)_r(Q)_u$, $-(Q)_u(T)_t$, or $-(T)_r(Q)_u(T)_t$, wherein:

T is, independently at each occurrence, -O-, -C(O)-, -C(O)-O-, -O-C(O)-, -C(O)-N(R^{13})-, -O-C(O)-N(R^{13})-, -N(R^{13})-, -N(R^{13})-C(O)-, -N[C(O) R^{13}]-, -N(R^{13})-C(O)-O-, -N(R^{13})-C(O)-N(R^{13})-, -S-, -S(O)-, -S(O)₂-, -S(O)₂-N(R^{13})- or -N(R^{13})-S(O)₂-;

t is, independently at each occurrence, 0 or 1;

u is, independently at each occurrence, 0 or 1;

r is, independently at each occurrence, 0 or 1;

A^2 is (i) absent, (ii) C_{1-6} alkylene, (iii) a C_{6-10} arylene, (iv) 5- to 10-membered heteroarylene, (v) 3- to 10-membered hetero₁₋₃cyclylene or (vi) C_{3-8} cycloalkylene, wherein each of (ii)-(vi) is optionally substituted with 1 or 2 substituents independently selected from halo, -O- R^{13} , C_{1-4} alkyl, C_{1-4} haloalkyl, -S- R^{13} , -N(R^{13}) R^{13} , -Q-O- R^{13} , -Q-N(R^{13})- R^{13} , -C(O)-O- R^{13} , -O-C(O)- R^{13} , -C(O)-N(R^{13})- R^{13} , -N(R^{13})-C(O)- R^{13} , -S(O)₂-N(R^{13})- R^{13} , -N(R^{13})-S(O)₂- R^{13} , -O-Q-O- R^{13} , -O-Q-N(R^{13})- R^{13} , -N(R^{13})-Q-O- R^{13} , -N(R^{13})-Q-N(R^{13})- R^{13} , -O-C(O)-N(R^{13})- R^{13} , -N(R^{13})-C(O)-O- R^{13} , -S(O)₂- R^{13} , -OS(O)₂-OR¹³, -C(O)- R^{13} and oxo when 2 substituents together on the same carbon atom are bound to an oxygen atom; and

A^3 is (i) H, (ii) halo, (iii) -O- R^{14} , (iv) R^{13} , (v) -CHO, (vi) -S(O)-O- R^{13} , (vii) -N(R^{13}) R^{13} (viii) C_6 - C_{10} aryl, (ix) 5- or 6-membered heteroaryl, (x) 3- to 10-membered hetero₁₋₃cyclyl or (xi) C_{3-8} cycloalkyl, wherein each of (viii)-(xi) is optionally substituted with 1 or 2 substituents independently selected from halo, -O- R^{13} , C_{1-4} alkyl, C_{1-4} haloalkyl, -S- R^{13} , -N(R^{13}) R^{13} , -Q-O- R^{13} , -Q-N(R^{13})- R^{13} ,

-C(O)-O-R¹³, -O-C(O)-R¹³, -C(O)-N(R¹³)-R¹³, -N(R¹³)-C(O)-R¹³,
 -S(O)₂-N(R¹³)-R¹³, -N(R¹³)-S(O)₂-R¹³, -O-Q-O-R¹³, -O-Q-N(R¹³)-R¹³,
 -N(R¹³)-Q-O-R¹³, -N(R¹³)-Q-N(R¹³)-R¹³, -O-C(O)-N(R¹³)-R¹³,
 -N(R¹³)-C(O)-O-R¹³, -S(O)₂-R¹³, -C(O)-R¹³ and oxo when 2 substituents
 together on the same carbon atom are bound to an oxygen atom;

and R² is H, C₁₋₄ alkyl or -CF₃.

- [0008]** Another aspect of the present invention is directed to compositions comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.
- [0009]** Another aspect of the present invention is directed to a method of using compounds of the present invention for inhibiting or treating a pathological condition or disorder linked to or mediated by a protein kinase, for example protein kinase C, in a mammal. The method comprises administering to the mammal (e.g., a human), a therapeutically effective amount of the compound of formula I or a pharmaceutically acceptable salt thereof. One embodiment of the invention is wherein the method is used to reduce symptoms of a pathological condition or disorder, for example in the treatment of inflammation in a mammal.
- [0010]** Another aspect of the present invention is directed to methods of making the compounds of formula I and pharmaceutically acceptable salts thereof.
- [0011]** Another aspect of the present invention is directed to intermediate compounds useful for making the compounds of formula I.

DETAILED DESCRIPTION

Definitions

- [0012]** Except where otherwise indicated, the terms below have the following meanings everywhere in this specification and in the appended claims:
- [0013]** As used herein, the terms "include", "includes", "including" and the like are intended to be open-ended unless otherwise specified, i.e., e.g., "including" means "including but not limited to" in the absence of an express limitation.
- [0014]** As used herein, alone or as part of another group, "halo" or "halogen" refers to fluoro, chloro, bromo and/or iodo.
- [0015]** As used herein, alone or as part of another group, "alkyl" refers to a straight-chain or branched saturated hydrocarbyl group having from 1 to 8 carbon atoms. In some embodiments, an alkyl group can have from 1 to 6 carbon atoms. In some embodiments, an alkyl group can have from 1 to 4 carbon atoms. Examples of C₁₋₄ alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and *tert*-butyl. Examples of C₁₋₆ alkyl groups include the aforementioned C₁₋₄ alkyl groups as well as pentyl, isopentyl, neopentyl, hexyl and the like. Additional examples of alkyl groups include heptyl, octyl and the like.
- [0016]** As used herein, alone or as part of another group, "alkylene" refers to a diradical of a straight-chain or branched saturated hydrocarbon group having from 1 to 6 carbon atoms. In some embodiments, an alkylene group can have from 1 to 4 carbon atoms. In some embodiments, an alkylene group can have from 1 to 2 carbon atoms. Examples of C₁₋₂ alkylene groups include methylene and ethylene. Examples of C₁₋₄ alkylene groups include the aforementioned C₁₋₂ alkylene groups as well as trimethylene (1,3-propanediyl), propylene (1,2-propanediyl), tetramethylene (1,4-butanediyl), butylene (1,2-butanediyl), 1,3-butanediyl, 2-methyl-1,3-propanediyl and the like. Examples of C₁₋₆ alkylene groups include the aforementioned C₁₋₄ alkylene groups as well as pentamethylene (1,5-pentanediyl), pentylene (1,2-pentanediyl), hexamethylene (1,6-hexanediyl), hexylene (1,2-hexanediyl), 2,3-dimethyl-1,4-butanediyl and the like. In some embodiments, an alkylene group is

an α,ω -diradical. Examples of α,ω -diradical alkylene groups include methylene, ethylene, trimethylene, tetramethylene, pentamethylene and hexamethylene.

[0017] As used herein, alone or as part of another group, "alkoxy" or "alkyloxy" refers to an -O-alkyl group having from 1 to 8 carbon atoms. In some embodiments, an alkoxy group can have from 1 to 6 carbon atoms. In some embodiments, an alkoxy group can have from 1 to 4 carbon atoms. Examples of C_{1-4} alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, butoxy, *tert*-butoxy and the like. Examples of C_{1-6} alkoxy groups include the aforementioned C_{1-4} alkoxy groups as well as pentyloxy, isopentyloxy, neopentyloxy, hexyloxy and the like. Additional examples of alkoxy groups include heptyloxy, octyloxy and the like.

[0018] As used herein, alone or as part of another group, "cycloalkyl" refers to a monocyclic, saturated cyclic hydrocarbonyl group having from 3 to 8 ring carbon atoms. In some embodiments (" C_{3-6} cycloalkyl"), a cycloalkyl group can have from 3 to 6 ring carbon atoms. In some embodiments (" C_{5-6} cycloalkyl"), a cycloalkyl group can have from 5 to 6 ring carbon atoms. Examples of C_{5-6} cycloalkyl groups include cyclopentyl and cyclohexyl. Examples of C_{3-6} cycloalkyl groups include the aforementioned C_{5-6} cycloalkyl groups as well as cyclopropyl and cyclobutyl. Examples of C_{3-8} cycloalkyl groups include the aforementioned C_{3-6} cycloalkyl groups as well as cycloheptyl and cyclooctyl.

[0019] As used herein, alone or as part of another group, "haloalkyl" refers to a C_{1-4} alkyl group as defined above wherein one or more of the alkyl group's hydrogen atoms has been replaced with a halogen atom. For each replacement, the halogen atom is independently selected from -F, -Cl, -Br and -I. In some embodiments, a haloalkyl group can be an alkyl group in which one of the alkyl group's hydrogen atoms has been replaced with a halogen atom. Examples of such haloalkyl groups include -CH₂F, -CH₂Cl, -CH₂CH₂Br, -CH₂CH₂I, -CH₂CH₂CH₂F, -CH₂CH₂CH₂Cl, -CH₂CH₂CH₂CH₂Br, -CH₂CH₂CH₂CH₂I, -CH₂CH₂CH₂CH₂CH₂Br, -CH₂CH₂CH₂CH₂CH₂I, -CH₂CH(Br)CH₃, -CH₂CH(Cl)CH₂CH₃ and -CH(F)(CH₂)₃CH₃. In some embodiments, a haloalkyl group can be an alkyl group in which one to three of the alkyl group's hydrogen atoms has been replaced with a halogen atom. Examples of such haloalkyl groups include the aforementioned haloalkyl groups as

well as -CCl_3 , -CF_3 and $\text{-CH}_2\text{CF}_3$. Other examples of haloalkyl groups include $\text{-CF}_2(\text{CH}_2)_8\text{CHCl}_2$.

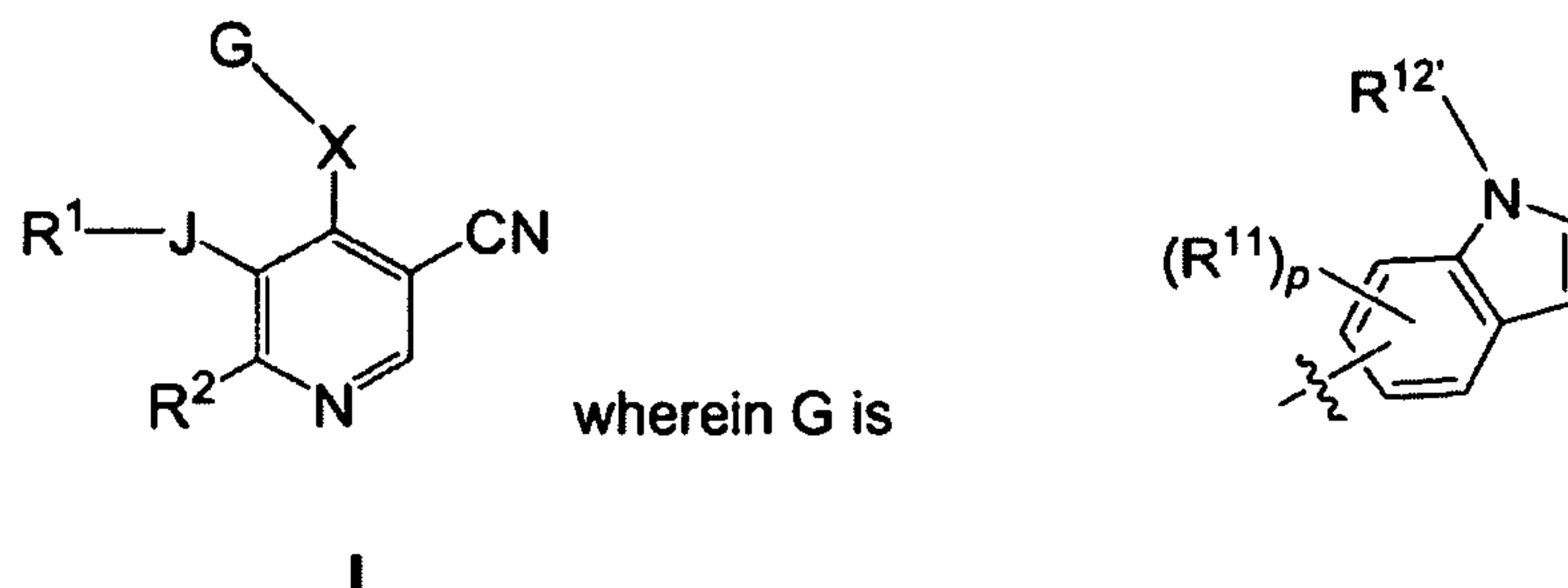
- [0020]** In some embodiments ("perhaloalkyl"), "haloalkyl" can refer to a C_{1-3} alkyl group wherein all of the hydrogen atoms are each independently replaced with fluoro or chloro. In some embodiments, all of the hydrogen atoms are each replaced with fluoro. In some embodiments, all of the hydrogen atoms are each replaced with chloro. Examples of perhaloalkyl groups include -CF_3 , $\text{-CF}_2\text{CF}_3$, $\text{-CF}_2\text{CF}_2\text{CF}_3$, -CCl_3 , -CFCl_2 , $\text{-CF}_2\text{Cl}$ and the like.
- [0021]** As used herein, alone or as part of another group, "aryl" refers to a radical of an aromatic monocyclic or bicyclic ring system having from 6 to 10 ring carbon atoms. Examples of such aryl groups include phenyl, 1-naphthyl and 2-naphthyl.
- [0022]** As used herein, alone or as part of another group, "heteroaryl" refers to a radical or diradical of a 5- to 10-membered aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, each heteroatom independently selected from N, O and S. Examples of such heteroaryl groups include pyrrolyl, furanyl (furyl), thiophenyl (thienyl), pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl (pyridyl), pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, indolyl, benzofuranyl, benzothiophenyl (benzothienyl), indazolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthyridinyl and the like. As the foregoing examples illustrate, in some embodiments a heteroaryl group can be monocyclic ("monocyclic heteroaryl"), and in some embodiments a heteroaryl group can be bicyclic ("bicyclic heteroaryl"). In some embodiments ("hetero₁₋₂aryl"), heteroaryl can refer to a heteroaryl group having 1 or 2 ring heteroatoms and otherwise as defined above. In some embodiments ("monocyclic hetero₁₋₂aryl"), heteroaryl can refer to a monocyclic heteroaryl group having 1 or 2 ring heteroatoms and otherwise as defined above. In some embodiments ("bicyclic hetero₁₋₂aryl"), heteroaryl can refer to a bicyclic heteroaryl group having 1 or 2 ring heteroatoms and otherwise as defined above.
- [0023]** As used herein, alone or as part of another group, "heterocyclyl" refers to a radical or diradical of a 3- to 10-membered non-aromatic ring system having ring carbon atoms

and 1 to 4 ring heteroatoms, each heteroatom independently selected from N, O and S. In some embodiments ("hetero₁₋₃cyclyl"), a heterocyclyl group can have ring atoms selected from carbon atoms and 1 to 3 heteroatoms, and otherwise defined as above. In some embodiments ("hetero₁₋₂cyclyl"), a heterocyclyl group can have ring atoms selected from carbon atoms and 1 or 2 heteroatoms, and otherwise defined as above. Examples of hetero₁₋₂cyclyl groups include pyrrolidinyl, dihydropyrrolyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, piperidinyl, tetrahydropyridinyl, dihydropyridinyl, piperazinyl, tetrahydropyranyl, dioxanyl, morpholinyl, azepanyl, diazepanyl, diazepinyl, oxepanyl, dioxepanyl, oxazepanyl, oxazepinyl and the like. Examples of hetero₁₋₃cyclyl groups include the aforementioned hetero₁₋₂cyclyl groups as well as oxiranyl, aziridinyl, oxetanyl, azetidiny, triazolidinyl, oxadiazolidinyl, triazinanyl and the like. Additional examples of heterocyclyl groups include decahydroisoquinolinyl, decahydroisoquinolinyl, octahydrochromenyl, octahydroisochromenyl, decahydronaphthyridinyl; and bridged heterocyclyl groups such as 2,5-diazabicyclohexane and 2-oxa-5-azabicyclo [2.2.1]heptane, and the like. Hetero₁₋₃cyclyl groups or hetero₁₋₂cyclyl groups may also include groups where the heterocyclyl moiety is fused to another ring which may be saturated, unsaturated or an aromatic ring. Examples of such fused rings include, but are not limited to, phthalimide and tetrahydroisoquinoline.

[0024] As used herein, alone or as part of another term, "pharmaceutically acceptable" refers to a substance that is acceptable for use in pharmaceutical applications from a toxicological perspective.

[0025] Abbreviations, as used herein, are generally known in the art. Examples of such abbreviations include, but are not limited to: t-butyl (tertiary butyl), LG (leaving group), PG (protecting group), CDI (1,1'-carbonyldiimidazole), DCE (1,2-dichloroethane), DCM (dichloromethane), DMF (dimethylformamide), DMF-DMA (dimethylformamide dimethyl acetal), DMSO (dimethylsulfoxide), EDCI (ethyl (dimethylaminopropyl)carbodiimide), EtOAc (ethyl acetate), HOAc (acetic acid), HPLC (high performance Liquid Chromatography), rt (retention time), TBAF (tetrabutylammonium fluoride), TEA (triethylamine), TFA (trifluoroacetic acid), THF (tetrahydrofuran) and TMS (trimethylsilyl).

[0026] Compounds of formula I include:

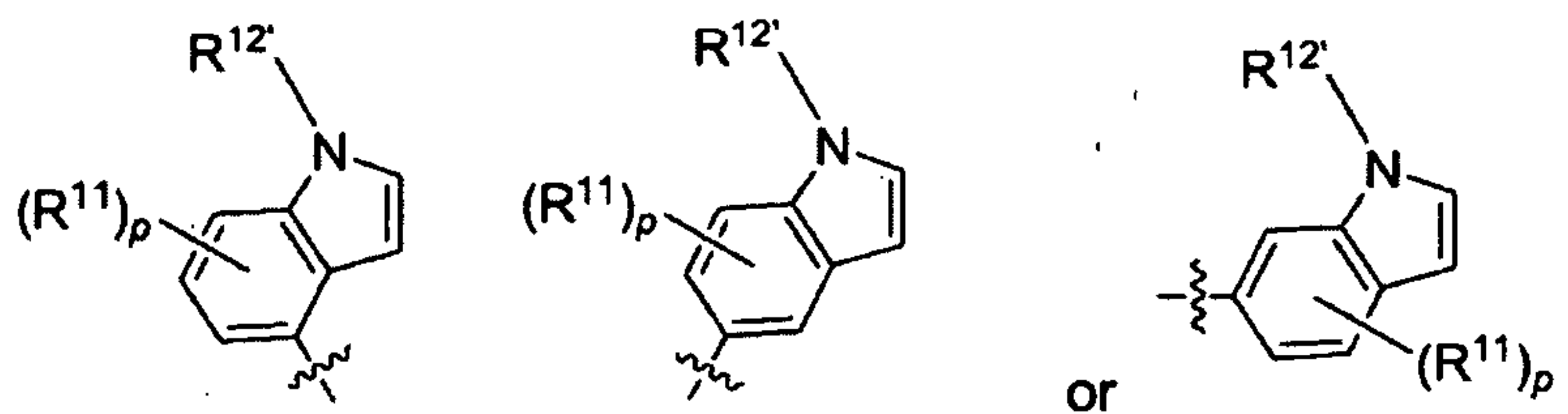


or a pharmaceutically acceptable salt thereof.

[0027] In some embodiments of the compound of formula I, or pharmaceutically acceptable salt thereof, X is -O- or -N(R¹⁰)-. In some embodiments, X is -N(R¹⁰)-. In further embodiments, R¹⁰ is H or CH₃. In some embodiments, X is -NH-.

[0028] In some embodiments of the compound of formula I, or pharmaceutically acceptable salt thereof, R² is H, C₁₋₄ alkyl or -CF₃. In some embodiments, R² is H. In some embodiments, R² is methyl, ethyl, propyl or isopropyl. In some embodiments, R² is methyl.

[0029] In some embodiments of the compound of formula I, or pharmaceutically acceptable salt thereof, G is



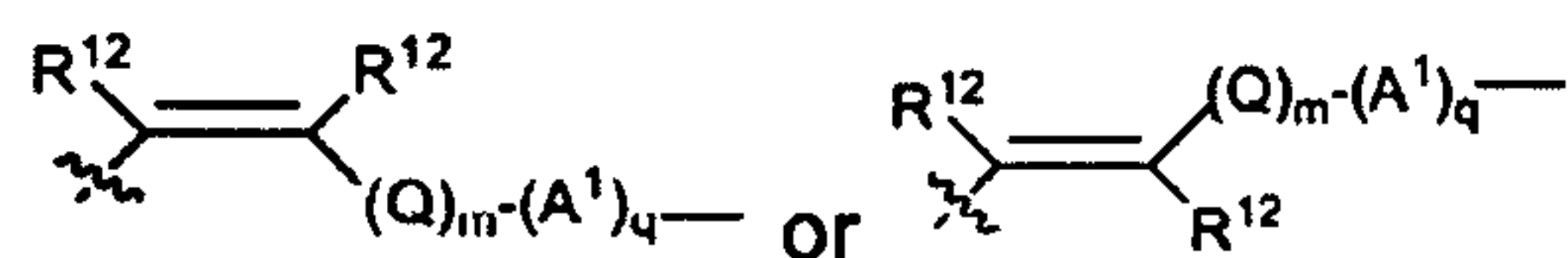
[0030] R¹¹ is an optional substituent at any indolyl ring carbon position. In some embodiments of the compound of formula I, or pharmaceutically acceptable salt thereof, R¹¹ is, independently at each occurrence, selected from halo, -O-R^{12''}, C₁₋₄ alkyl, -CF₃ and -N(R^{12''})-R^{12''}. In some embodiments, R¹¹ is, independently at each occurrence, halo or C₁₋₄ alkyl. In further embodiments, R¹¹ is, independently at each occurrence, chloro or methyl.

[0031] In some embodiments of the compound of formula I, or pharmaceutically acceptable salt thereof, G is indol-4-yl, indol-5-yl, 2-methylindol-5-yl, 4-methylindol-5-yl, 2,4-dimethylindol-5-yl, 4,7-dimethylindol-5-yl, 4-methyl-7-chloroindol-5-yl or indol-6-yl. In further embodiments, G is indol-5-yl or 4-methylindol-5-yl.

[0032] In some embodiments of the compound of formula I, or pharmaceutically acceptable salt thereof, $R^{12'}$ and $R^{12''}$ is, each independently, H or CH_3 .

[0033] In some embodiments of the compound of formula I, or pharmaceutically acceptable salt thereof, J is $-Q-(A^1)_q-$. In some embodiments of J, q is 0. In some embodiments of J, q is 1.

[0034] In some embodiments of the compound of formula I, or pharmaceutically acceptable salt thereof, J may be a cis or trans alkene. In some embodiments, J is



In some embodiments of the compound of formula I, or pharmaceutically acceptable salt thereof, J is a trans alkene. In some

embodiments, J is $\begin{array}{c} R^{12} \quad (Q)_m-(A^1)_q- \\ \diagdown \quad / \\ C=C \\ / \quad \backslash \\ R^{12} \end{array}$. In some embodiments of J, R^{12} is H. In some embodiments of J, m is 0. In some embodiments of J, q is 0 or 1.

[0035] In some embodiments of the compound of formula I, or pharmaceutically acceptable

salt thereof, J is $\begin{array}{c} R^{12} \quad (Q)_m-(A^1)_q- \\ \diagdown \quad / \\ \text{Cyclohexane ring} \\ / \quad \backslash \\ R^{12} \end{array}$. In some embodiments of J, R^{12} is H. In some embodiments of J, m is 0. In some embodiments of J, q is 0 or 1.

[0036] In some embodiments of the compound of formula I, or pharmaceutically acceptable

salt thereof, J is $\begin{array}{c} \text{Cyclohexene ring} \\ | \\ E-(Y)_m- \end{array}$. In some embodiments of J, E is N. In some embodiments of J, m is 0 or 1.

[0037] In some embodiments of the compound of formula I, or pharmaceutically acceptable salt thereof, A^1 is optionally substituted C_{6-10} arylene. In further embodiments, A^1 is optionally substituted phenylene. In some embodiments, A^1 is optionally substituted

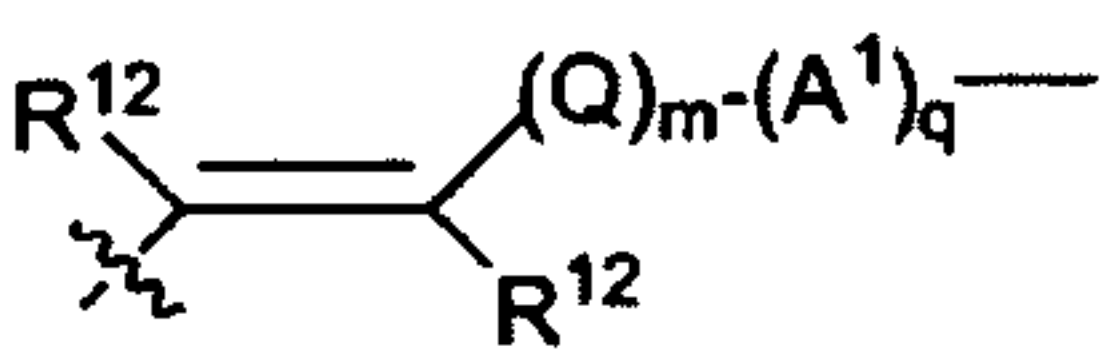
5- to 10-membered hetero_{1,3}arylene. In further embodiments, A¹ is optionally substituted pyridinyl, thiazolyl furanyl or thienyl.

[0038] In some embodiments of the compound of formula I, or pharmaceutically acceptable salt thereof, Q is methylene, ethylene, trimethylene or tetramethylene. In some embodiments, Q is methylene, ethylene or propylene.

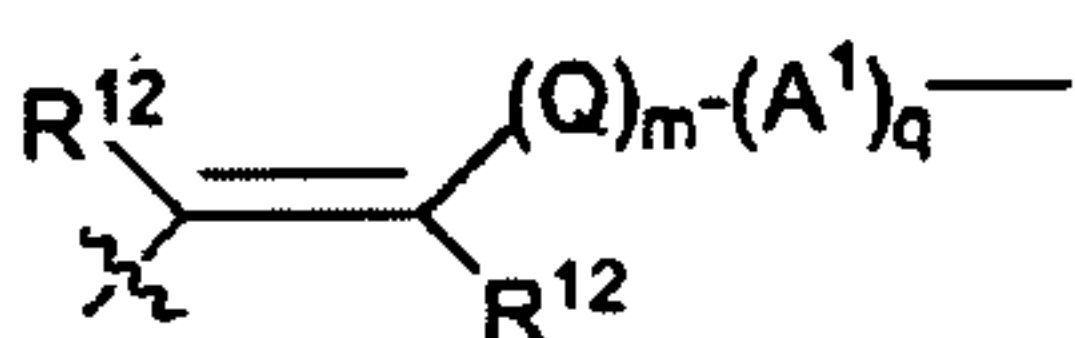
[0039] In some embodiments of the compound of formula I, or pharmaceutically acceptable salt thereof, R¹ is -(L)_r-(A²-A³). In further embodiments of R¹, r is 0 and R¹ is -(A²-A³).

[0040] In some embodiments of the compound of formula I, or pharmaceutically acceptable salt thereof, L is -(T)_t(Q)_u- or -(Q)_u(T)_t-. In some embodiments, t is 0. In further embodiments, t is 0 and u is 0 or 1. In some embodiments, t is 1. In further embodiments, t is 1 and u is 0 or 1. In some embodiments, u is 0, t is 0 and L is a covalent bond. In some embodiments, T is -O- or -N(R¹³)-. In some embodiments, Q is methylene, ethylene or propylene. In further embodiments, Q is methylene.

[0041] In some embodiments of the compound of formula I, or pharmaceutically acceptable

salt thereof, J is , R¹² is H; m is 0; R² is H; X is -(NR¹⁰)- and A¹ is optionally substituted C₆₋₁₀ arylene or optionally substituted 5- to 10-membered hetero_{1,3}arylene.

[0042] In some embodiments of the compound of formula I, or pharmaceutically acceptable

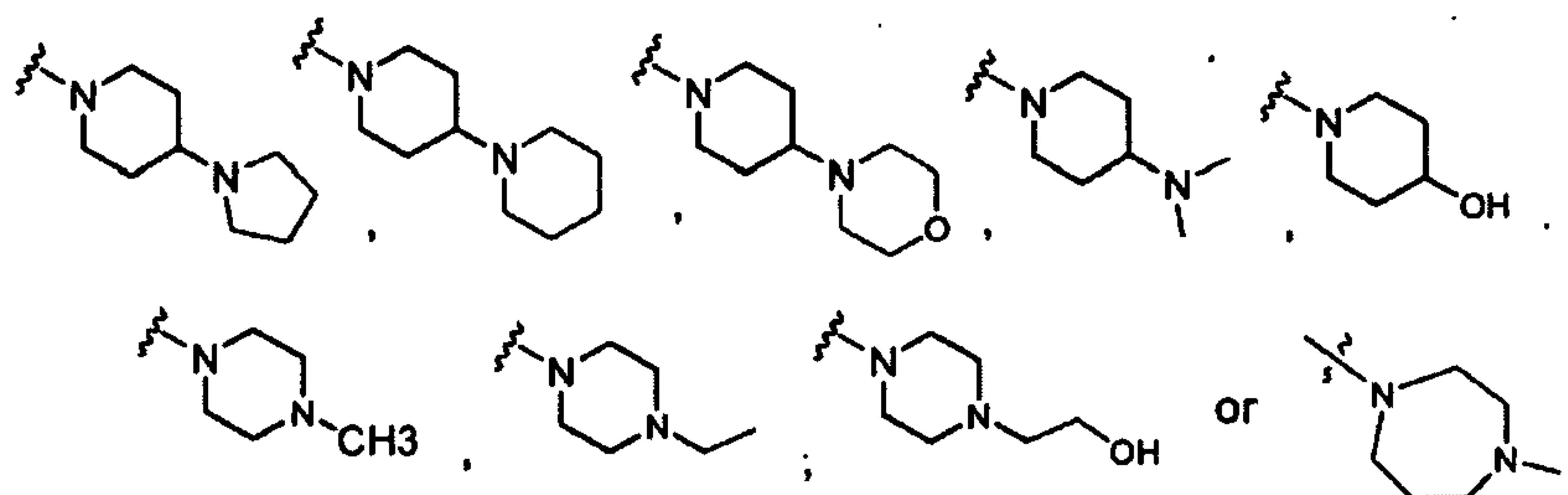
salt thereof, J may be a trans alkene, wherein J is ; R¹² is H, m is 0, R² is H; X is -(NR¹⁰)-, A¹ is phenylene, pyridinyl, thiazolyl, or furanyl, each of which is optionally substituted. In some embodiments, A¹ is optionally substituted phenylene. In other embodiments, A¹ is optionally substituted 5- to 10-membered hetero_{1,3}arylene. In further embodiments, A¹ is optionally substituted pyridinyl, thiazolyl furanyl or thienyl. In further embodiments, A¹ is optionally substituted phenylene, T is -O-, u is 1 and A₃ is 3- to 7-membered hetero_{1,3}cycyl. In further embodiments of the compound of formula I, or pharmaceutically acceptable salt thereof, R¹ is -(L)_r-(A²-A³), wherein L is -(T)_t(Q)_u- or -(Q)_u(T)_t-. In further embodiments, t is 0, u is 1, L is -Q- and Q is methylene.

[0043] In some embodiments of the compound of formula I, or pharmaceutically acceptable salt thereof, J is J(ii) or J(iii) and $-(Q)_m-(A^1)_q-R_1$ is:

- (B1) $-A^3$, wherein m, q and r are 0 and A^2 is absent and A^3 is as defined in claim 1; or
- (B2) $-A^1-A^2-A^3$, wherein m is 0, q is 1, and r is 0 and wherein A^1 and A^3 are as defined in claim 1 and A^2 is C_{1-6} alkylene; or
- (B3) $-A^2-A^3$, wherein m, q and r are 0 and A^2 and A^3 are as defined in claim 1; or
- (B4) $-A^1-T-A^3$, wherein m is 0, q is 1, A^2 is absent, r is 1 and L is $-T-$ and A^1 , T and A^3 are as defined in claim 1; or
- (B5) $-A^1-T-A^2-A^3$, wherein m is 0, q and r are 1 and L is $-T-$ and A^1 , T, A^2 and A^3 are as defined in claim 1; or
- (B6) $-A^1-Q-T-A^2-A^3$, wherein m is 0, q and r are 1 and L is $-Q-T-$ and A^1 , T, A^2 and A^3 are as defined in claim 1; or
- (B7) $A^1-Q-A^2-A^3$, wherein m is 0, q and r are 1 and L is $-Q-$ and A^1 , Q, A^2 and A^3 are as defined in claim 1.

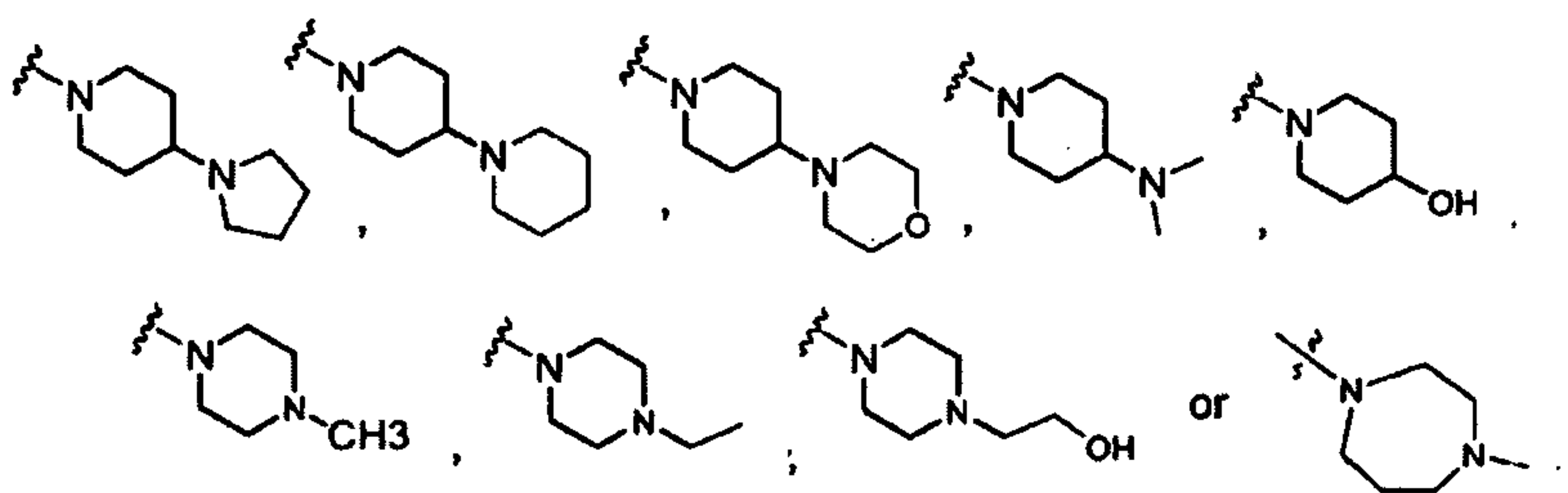
[0044] In further embodiments of the compound of formula I, or pharmaceutically acceptable salt thereof, wherein J is J(ii) or J(iii) and:

- (C1) $(Q)_m-(A^1)_q-R_1$ is B1 and A^3 is optionally substituted C_6-C_{10} aryl, 5- or 6-membered heteroaryl, 3- to 10-membered hetero_{1,3}cyclyl or C_{3-8} cycloalkyl; or
- (C2) $-(Q)_m-(A^1)_q-R_1$ is B2 and A^1 is optionally substituted C_6-C_{10} aryl or optionally substituted 5- to 10- membered hetero_{1,3}aryl, and A^3 is $-N(R^{13})R^{13}$ or optionally substituted 3- to 10-membered hetero_{1,3}cyclyl wherein at least one heteroatom is a nitrogen atom and A^3 is joined via the nitrogen atom to A^2 .
- (C3) $-(Q)_m-(A^1)_q-R_1$ is B3 and $-(A^2-A^3)$ is:



or

- (C4) $-(Q)_m-(A^1)_q-R_1$ is B4 and A^1 is optionally substituted C_{6-10} aryl or optionally substituted 5- to 10-membered hetero₁₋₃aryl and A^3 is optionally substituted 3- to 10-membered hetero₁₋₃cyclyl and T is $-O-$, $-NH-$, $-C(O)-$, or $-C(O)-NH-$ or $-S(O)_2-$; or
- (C5) $-(Q)_m-(A^1)_q-R_1$ is B5 and A^2 is alkylene and A^1 is optionally substituted C_{6-10} aryl or optionally substituted 5- to 10-membered hetero₁₋₃aryl and A^3 is optionally substituted 3- to 10-membered hetero₁₋₃cyclyl and T is $-O-$, $-C(O)-$, or $-C(O)-NH-$ or $-S(O)_2-$; or
- (C6) $-(Q)_m-(A^1)_q-R_1$ is B6 and A^1 is optionally substituted C_{6-10} aryl or optionally substituted 5- to 10-membered hetero₁₋₃aryl and A^2 is alkylene or is absent, T is $-O-$, $-NH-$, $-C(O)-$, $-C(O)-NH-$ or $-S(O)_2-$ and A^3 is $-N(R^{13})R^{13}$ or optionally substituted 3- to 10-membered hetero₁₋₃cyclyl; or
- (C7) $-(Q)_m-(A^1)_q-R_1$ is B7 and A^1 is optionally substituted C_{6-10} aryl or optionally substituted 5- to 10-membered hetero₁₋₃aryl and wherein $-(A^2-A^3)$ or $-A^3$ when A^2 is absent is:



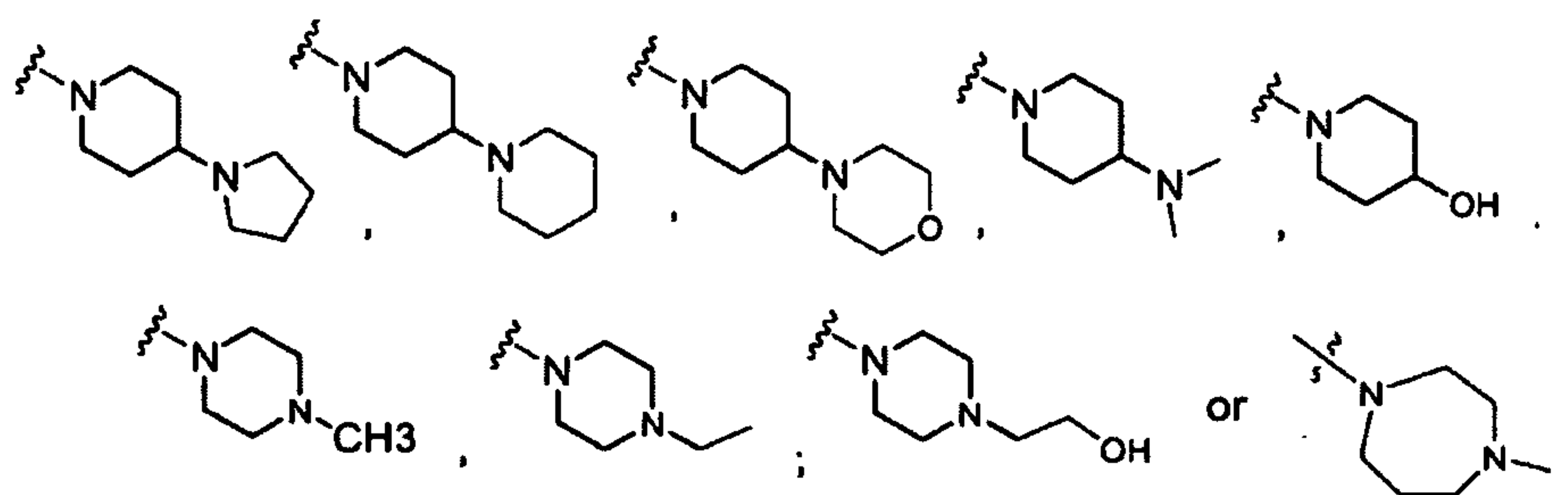
[0045] In some embodiments of the compound of formula I, or pharmaceutically acceptable salt thereof, A^2 is optionally substituted phenylene. In some embodiments, A^2 is morpholinyl, piperidinyl, piperazinyl, pyrrolidinyl, azetidiny, thiomorpholinyl, thiomorpholinyl-1,1-dioxide, 1,3-dioxoisindolyl, oxopiperazinyl, 1,4-diazepanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,2,3,4-tetrahydroisoquinolinyl and indolinyl, wherein A^2 is optionally substituted. In some embodiments, A^2 is optionally substituted 3- to 10-membered hetero₁₋₂cyclyl. In some embodiments, A^2 is optionally substituted piperidinyl, piperazinyl or pyrrolidinyl. In some embodiments, A^2 is optionally substituted C_{3-8} cycloalkyl. In some embodiments, A^2 is optionally substituted cyclohexyl.

[0046] In some embodiments of the compound of formula I, or pharmaceutically acceptable salt thereof, A^2 is absent.

[0047] In some embodiments of the compound of formula I, or pharmaceutically acceptable salt thereof, A^3 is H.

[0048] In some embodiments of the compound of formula I, or pharmaceutically acceptable salt thereof, A^3 , when present, is $-NR^{13}R^{13}$, 5- to 10-membered heteroarylene or 3- to 10-membered hetero_{1,3}cyclylene, and wherein each A^3 contains a nitrogen atom, joined via the nitrogen atom to A^2 , when present, or when A^2 is absent, joined via the nitrogen atom to an adjacent atom.

[0049] In some embodiments of the compound of formula I, or pharmaceutically acceptable salt thereof, $-(A^2-A^3)$ is



[0050] Examples of compounds of formula I, or a pharmaceutically acceptable salt thereof, are as described herein throughout the specification, some of which are:

5-[(*E*)-2-[2-methoxy-4-(piperazin-1-ylmethyl)phenyl]vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[3-({[2-(1-methylpyrrolidin-2-yl)ethyl]amino}methyl)phenyl]ethenyl]pyridine-3-carbonitrile;

5-[(1*E*)-4-(4-aminopiperidin-1-yl)but-1-en-1-yl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[2-(2-piperazin-1-ylethoxy)phenyl]vinyl]nicotinonitrile;

5-[(*E*)-2-(6-bromopyridin-2-yl)vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

5-[(*E*)-2-(6-chloropyridin-2-yl)vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[6-(piperazin-1-ylmethyl)pyridin-2-yl]vinyl]nicotinonitrile;
- 5-[(*E*)-2-(5-bromopyridin-3-yl)ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[6-(thiomorpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile;
- 5-[(*E*)-2-{6-[(4-cyclopentylpiperazin-1-yl)methyl]pyridin-2-yl}ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;
- 5-[(*E*)-2-(6-{[4-(1-methylethyl)piperazin-1-yl]methyl}pyridin-2-yl)ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;
- 5-[(*E*)-2-{6-[(4-methyl-1,4-diazepan-1-yl)methyl]pyridin-2-yl}ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[6-({[3-(2-oxopyrrolidin-1-yl)propyl]amino}methyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile;
- 5-[(*E*)-2-[6-({[2-(dimethylamino)ethyl]amino}methyl)pyridin-2-yl]ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[6-({[2-(1-methylpyrrolidin-2-yl)ethyl]amino}methyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile;
- 5-[(*E*)-2-(6-{[(2-azepan-1-ylethyl)amino]methyl}pyridin-2-yl)ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;
- 5-[(*E*)-2-{3-[(4-cyclopentylpiperazin-1-yl)methyl]phenyl}ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{3-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}vinyl]nicotinonitrile;
- 6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{3-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}ethenyl]pyridine-3-carbonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]nicotinonitrile;
- 5-[(*E*)-2-(3-{[4-(dimethylamino)piperidin-1-yl]methyl}phenyl)ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;
- 5-[(*E*)-2-[3-({[2-(dimethylamino)ethyl]amino}methyl)phenyl]ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}vinyl]nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{2-[(4-methylpiperazin-1-yl)methyl]-1,3-thiazol-4-yl}vinyl]nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{6-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}vinyl]nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[4-(2-pyrrolidin-1-ylethoxy)phenyl]vinyl]nicotinonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}vinyl]nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{3-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}vinyl]nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{3-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{5-[(4-methylpiperazin-1-yl)methyl]-3-furyl}vinyl]nicotinonitrile;

5-[(*E*)-2-{2-methoxy-5-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{4-[(4-pyrrolidin-1-yl)piperidin-1-yl)methyl]phenyl}vinyl]nicotinonitrile;

5-[(*E*)-2-[4-(1,4'-bipiperidin-1'-ylmethyl)phenyl]ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}ethenyl]pyridine-3-carbonitrile;

5-[(*E*)-2-[5-(1,4'-bipiperidin-1'-ylmethyl)pyridin-2-yl]ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

5-[(*E*)-2-(5-{4-(dimethylamino)piperidin-1-yl}methyl)pyridin-2-yl]ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

5-[(*E*)-2-{5-[(4-methyl-1,4-diazepan-1-yl)methyl]pyridin-2-yl}ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

5-[(*E*)-2-(6-{4-(2-hydroxyethyl)piperazin-1-yl}methyl)pyridin-2-yl]ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

5-[(*E*)-2-[6-(1,4'-bipiperidin-1'-ylmethyl)pyridin-2-yl]ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{6-[(4-pyrrolidin-1-yl)piperidin-1-yl)methyl]pyridin-2-yl}ethenyl]pyridine-3-carbonitrile;

5-[(*E*)-2-(6-{[4-(dimethylamino)piperidin-1-yl]methyl}pyridin-2-yl)ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{4-[(4-pyrrolidin-1-yl)piperidin-1-yl]methyl}phenyl]ethenyl]pyridine-3-carbonitrile;

5-[(*E*)-2-[4-({[2-(dimethylamino)ethyl]amino}methyl)phenyl]ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{3-[(4-pyrrolidin-1-yl)piperidin-1-yl]methyl}phenyl]ethenyl]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(4-{[(2-pyrrolidin-1-ylethyl)amino]methyl}phenyl)ethenyl]pyridine-3-carbonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{5-[(4-morpholin-4-yl)piperidin-1-yl]methyl}pyridin-2-yl]ethenyl]pyridine-3-carbonitrile;

5-[(*E*)-2-[5-(1,4'-bipiperidin-1'-ylmethyl)pyridin-2-yl]ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

5-[(*E*)-2-(3-{[4-(dimethylamino)piperidin-1-yl]methyl}phenyl)vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile; or

5-[(*E*)-2-[3-(1,4'-bipiperidin-1'-ylmethyl)phenyl]vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile.

[0051] Pharmaceutically acceptable salts of the compounds of formula I having an acidic moiety can be formed using organic and/or inorganic bases. Both mono and polyanionic salts are contemplated, depending on the number of acidic hydrogens available for deprotonation. Suitable salts formed with bases include metal salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium and magnesium salts; ammonia salts and organic amine salts, such as those formed with morpholine, thiomorpholine, piperidine, pyrrolidine, a mono-, di- or tri-(C₁₋₆ alkyl)amine (e.g., ethyl-tert-butyl-, diethyl-, diisopropyl-, triethyl-, tributyl- or dimethylpropyl-amine), or a mono-, di-, or tri-hydroxy (C₁₋₆ alkyl)amine (e.g., mono-, di- or tri-ethanolamine). Examples of inorganic bases useful for forming such pharmaceutically acceptable salts include NaHCO₃, Na₂CO₃, KHCO₃, K₂CO₃, Cs₂CO₃, LiOH, NaOH, KOH, NaH₂PO₄, Na₂HPO₄ and Na₃PO₄. Similarly, pharmaceutically acceptable salts of the compounds of formula I having a basic moiety can be formed using organic and/or inorganic acids. Both mono and polycationic salts are contemplated, depending on the number of lone-pair electrons

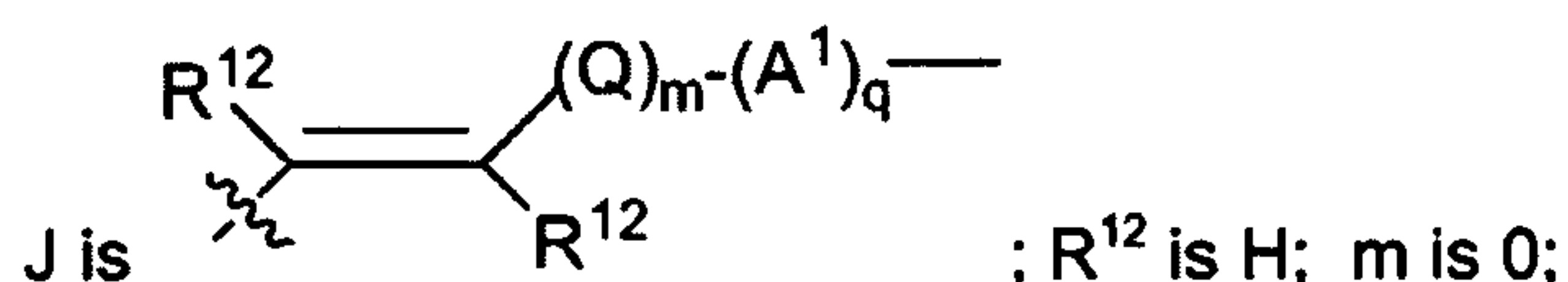
available for donation. For example, suitable salts can be formed from the following acids: acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, dichloroacetic, ethenesulfonic, formic, fumaric, gluconic, glutamic, hippuric, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, malonic, mandelic, methanesulfonic, mucic, naphthalenesulfonic, nitric, oxalic, palmitic, pantothenic, phosphoric, phthalic, propionic, succinic, sulfuric, tartaric, and toluenesulfonic.

[0052] Esters of the compounds of formula I can include various pharmaceutically acceptable esters known in the art that can be metabolized into the free acid form (e.g., a free carboxylic acid form) in a mammal. Examples of such esters include alkyl esters (e.g., of 1 to 10 carbon atoms), cycloalkyl esters (e.g., of 3-10 carbon atoms), aryl esters (e.g., of 6-14 carbon atoms, including of 6-10 carbon atoms), and heterocyclic analogues thereof (e.g., of 3-14 ring atoms, 1-3 of which can be selected from oxygen, nitrogen, and sulfur heteroatoms), wherein the alcohol residue can include further substituents. In some embodiments, esters of the compounds disclosed herein can be C₁₋₁₀ alkyl esters, such as methyl esters, ethyl esters, propyl esters, isopropyl esters, butyl esters, isobutyl esters, t-butyl esters, pentyl esters, isopentyl esters, neopentyl esters, and hexyl esters; C₃₋₁₀ cycloalkyl esters, such as cyclopropyl esters, cyclopropylmethyl esters, cyclobutyl esters, cyclopentyl esters, and cyclohexyl esters; or aryl esters, such as phenyl esters, benzyl esters, and tolyl esters.

[0053] The compounds of this invention may contain one or more asymmetric centers. They may occur as racemates and racemic mixtures, single enantiomers, individual diastereomers and diastereomeric mixtures. Enantiomers may occur in enantiomeric excess of more than 50%, for example, an enantiomeric excess of at least 60%, 70%, 80%, 85%, 90%, 95%, or 98%. Some compounds may have an enantiomeric excess of at least 99%. All such isomeric forms of these compounds are expressly included in the present invention. The syntheses described herein may also employ racemates, enantiomers or diastereomers as starting materials or intermediates. Single enantiomers can be obtained by asymmetric synthesis, synthesis from optically pure precursors or by resolution of the racemates. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for

example a chiral HPLC column. Similarly, diastereomeric products resulting from such syntheses may be separated by chromatographic or crystallization methods, or by other methods known in the art. Each of the asymmetric carbon atoms, when present in the compounds of this invention, may be in one of two configurations (R or S), both of which are within the scope of the present invention. The compounds may also occur in cis- or trans- or E- or Z-double bond isomeric forms. The compounds may also be represented in multiple tautomeric forms. All such isomeric and tautomeric forms of such compounds are expressly included in the present invention. Crystalline forms of the compounds described herein are expressly included in the present invention.

[0054] Another aspect of the present invention relates to compositions comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. A further embodiment of the invention relates to compositions comprising a compound of formula I, wherein:



R^2 is H; X is $\text{---}(\text{NR}^{10})\text{---}$, A^1 is phenylene, pyridinyl, thiazolyl, or furanyl, each of which is optionally substituted and R^1 is $\text{---}(\text{L})\text{---}(\text{A}^2\text{---}\text{A}^3)$, wherein L is $\text{---}(\text{T})_t(\text{Q})_u\text{---}$ or $\text{---}(\text{Q})_u(\text{T})_t\text{---}$.

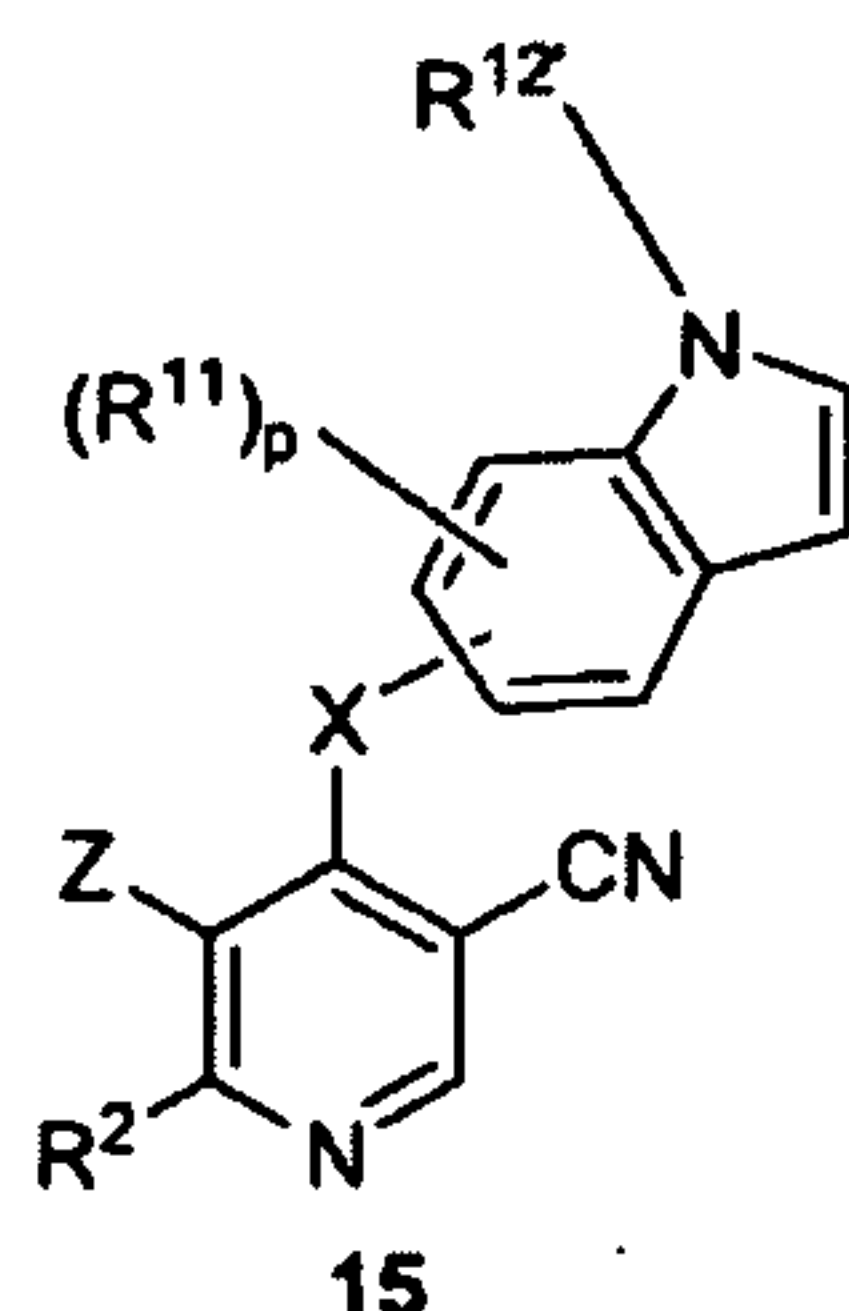
[0055] Compositions can include at least one compound of formula I, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients, or diluents. Suitable excipients are those that do not adversely interact with the active ingredient are compatible with the other ingredients in the formulation and are biologically acceptable. Examples of such excipients are well known to those skilled in the art, e.g., as described in *Handbook of Pharmaceutical Excipients*, 5th edition, eds. R.C. Rowe, P.J. Sheskey and S.C. Owen, Pharmaceutical Press: London, UK (2003), the entire disclosure of which is incorporated by reference herein. Examples of such compositions are well known to those skilled in the art and can be prepared in accordance with acceptable pharmaceutical procedures, such as, e.g., those described in *Remington: The Science and Practice of Pharmacy*, 20th edition, ed. A.R. Gennaro, Lippincott Williams & Wilkins: Baltimore, MD (2000), the

entire disclosure of which is incorporated by reference herein. Supplementary active ingredients can also be incorporated into the pharmaceutical compositions.

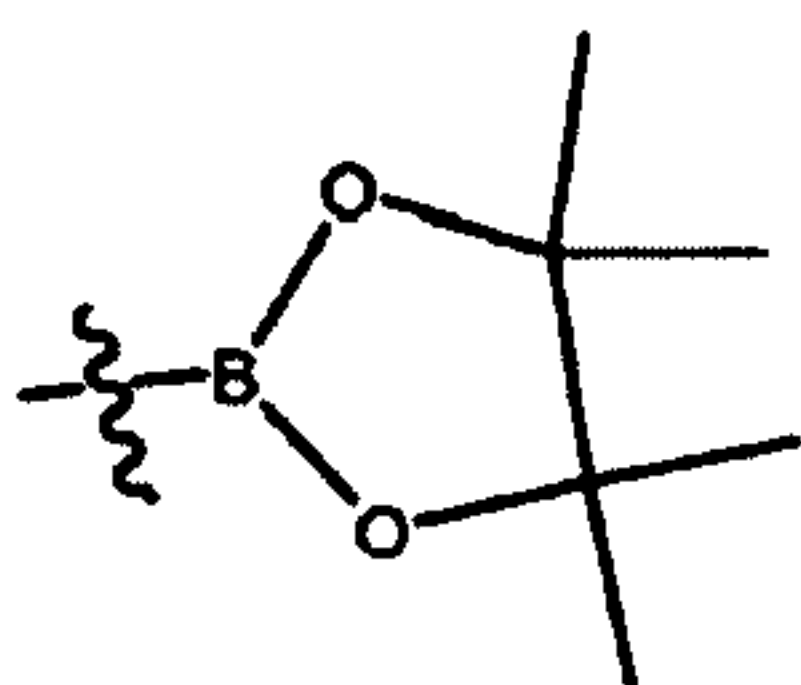
[0056] Throughout the description, where compositions are described as having, including, or comprising specific components, or where processes are described as having, including, or comprising specific process steps, it is contemplated that compositions of the present teachings also consist essentially of, or consist of, the recited components, and that the processes of the present teachings also consist essentially of, or consist of, the recited processing steps.

[0057] It should be understood that the order of steps or order for performing certain actions is immaterial so long as the present teachings remain operable. Moreover, two or more steps or actions may be conducted simultaneously.

Processes are provided for preparing a compound of formula I, wherein J is J(ii) or J(iii) as defined herein, the process comprising reacting a compound of formula 15

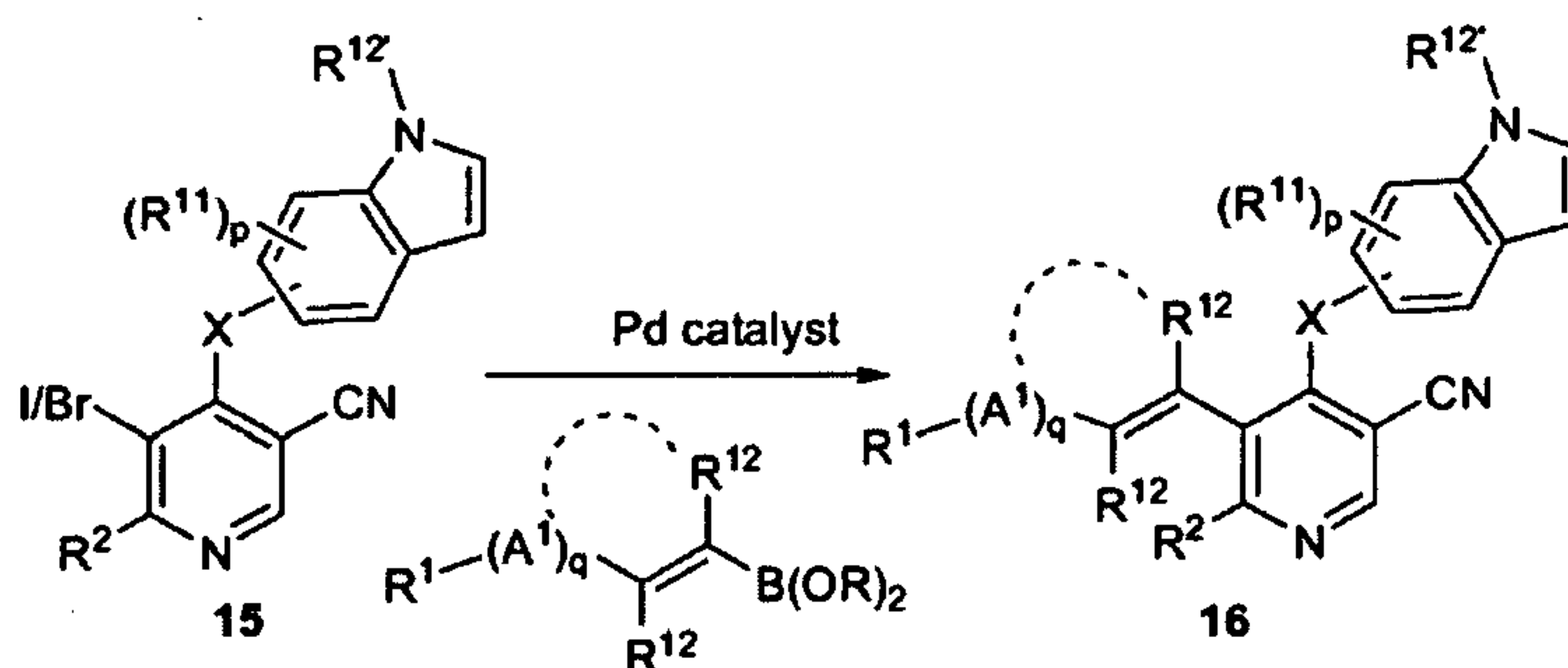


[0058] wherein R^2 , R^{11} , R^{12} and p are as defined herein and Z is I or Br; in the presence of a Pd catalyst; with a compound of formula $R^1-J-B(OR)_2$, wherein J and R^1 are as defined herein, and each R is, independently at each occurrence, H or C_1-C_6 alkyl; or two R groups together in $-B(OR)_2$, with R comprising C_1-C_6 alkylene, form a ring comprising boron, oxygen and carbon atoms. In some embodiments, the $-B(OR)_2$

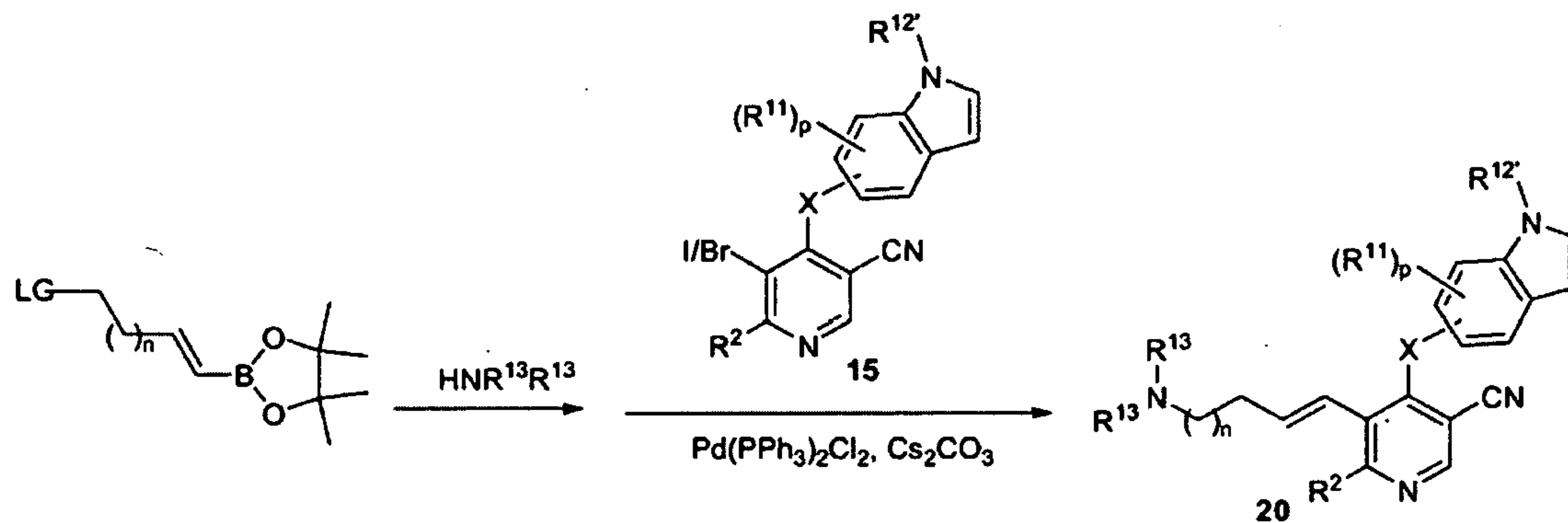


moiety may be

[0059] An example of such a reaction is shown below:

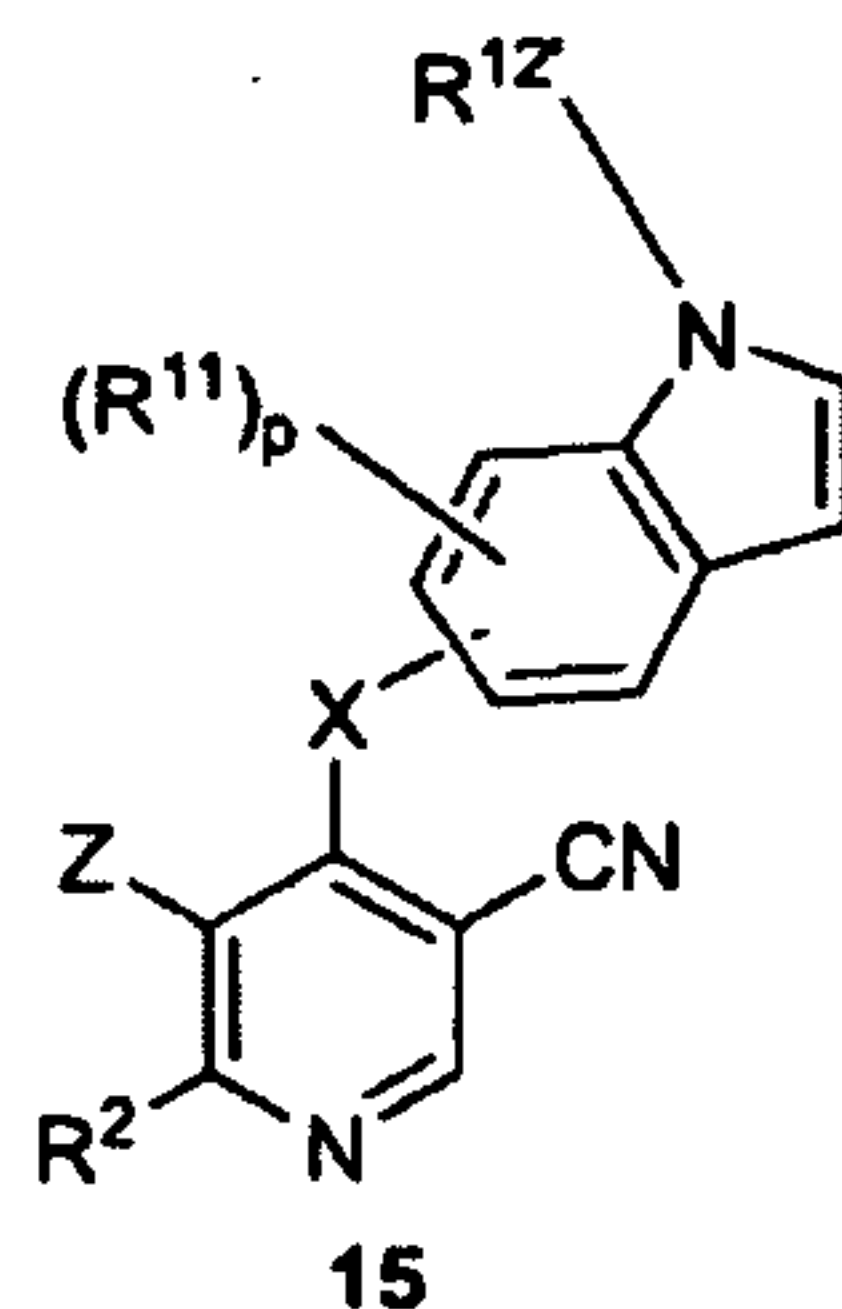


[0060] Another example of such a reaction is shown below:



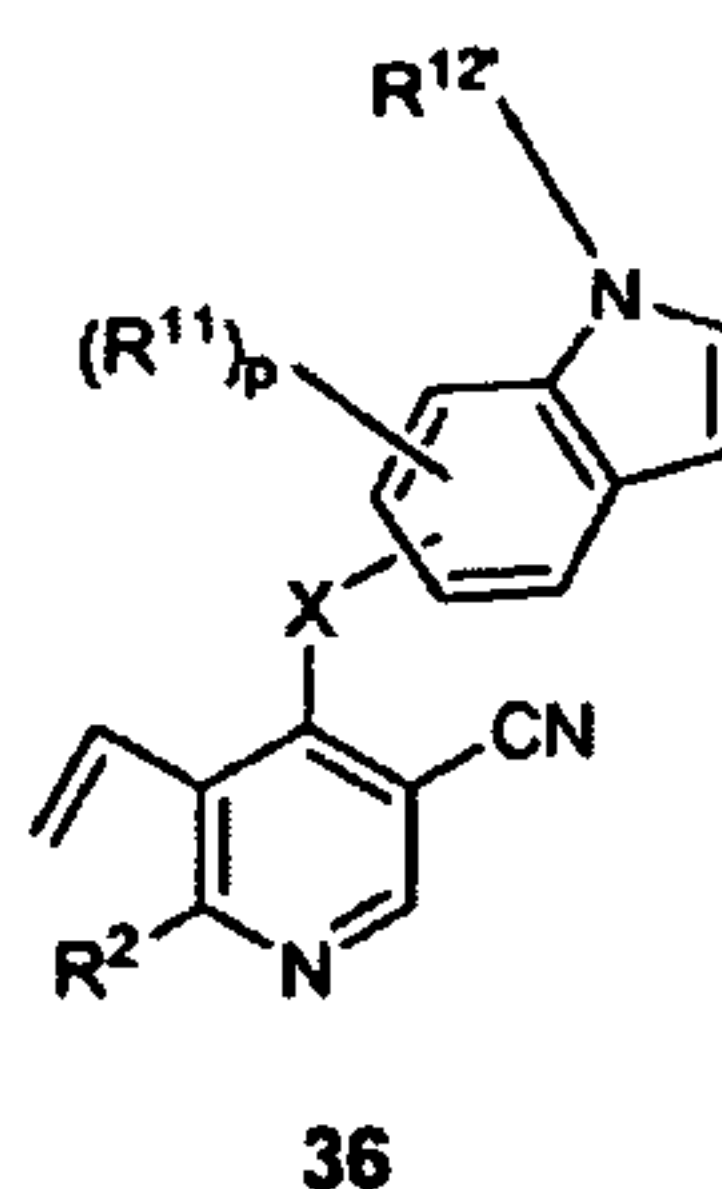
where -NR¹³R¹³ is equivalent to (A²-A³) as defined for Formula I.

[0061] Processes are also provided for preparing a compound of formula I, wherein J is J(iii), the process comprising reacting a compound of formula 15

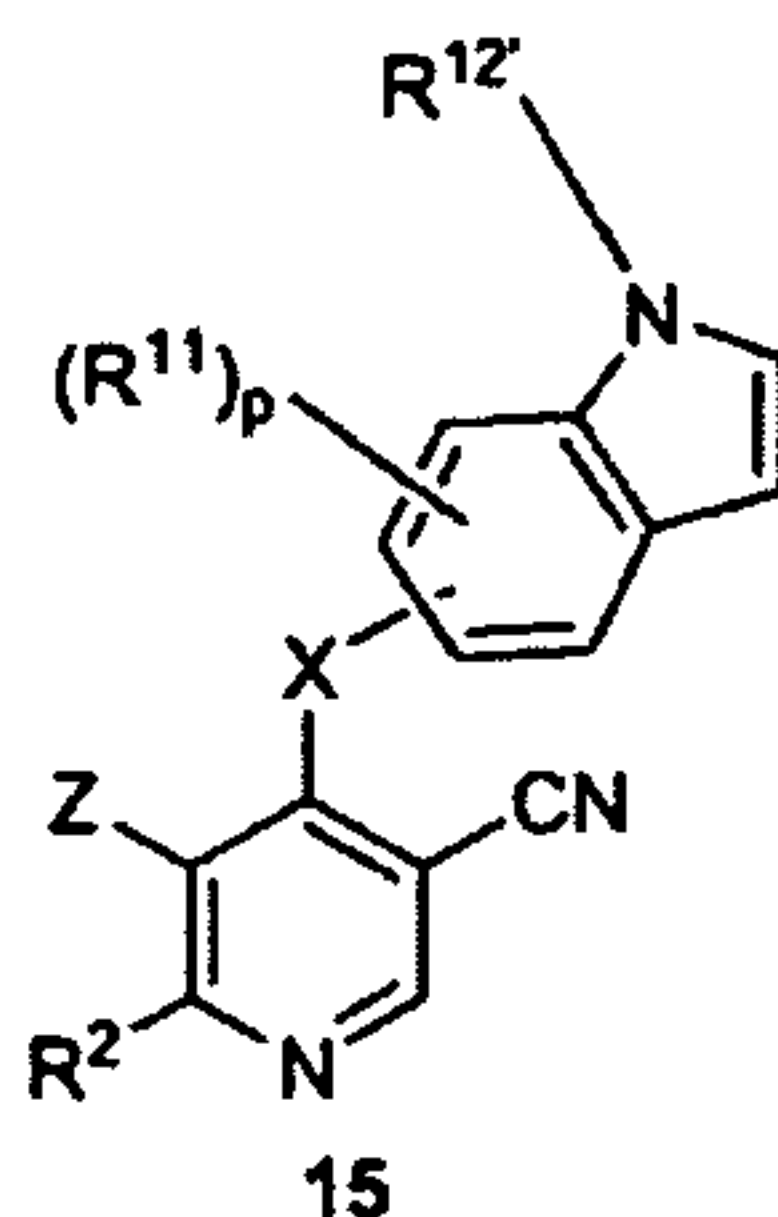


wherein R^2 , R^{11} , R^{12} and p are as defined herein and Z is I or Br; in the presence of a Pd catalyst; with a compound of formula $R^1-(A^1)_q(Q)_m$, wherein q is 1, m is 0 and R^1 is as defined herein.

[0062] Processes are also provided for preparing a compound of formula I, wherein J is J(iii) as defined herein, comprising reacting a compound of formula 36

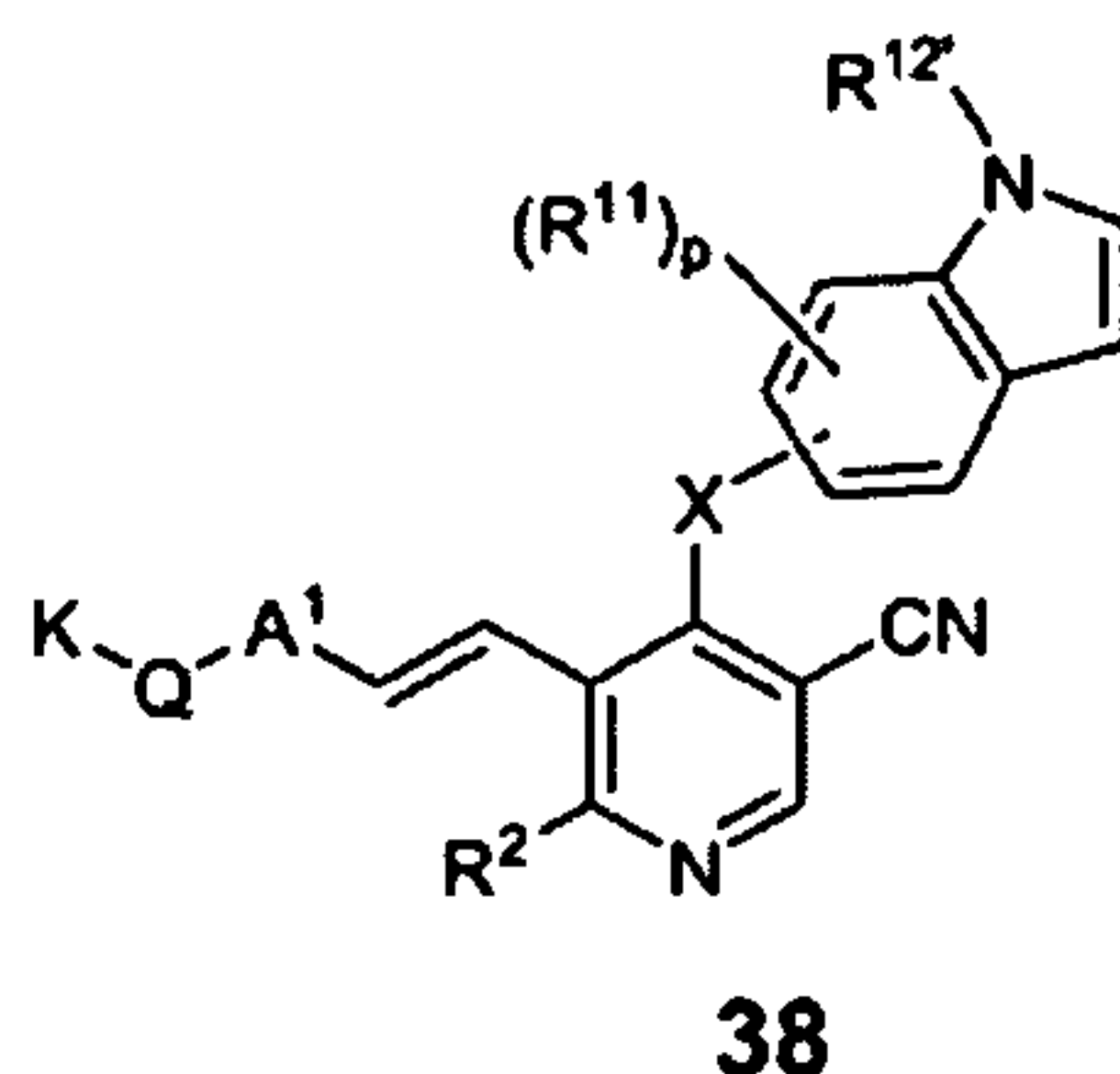


wherein R^2 , R^{11} , R^{12} and p are as defined herein; in the presence of a palladium catalyst; with a compound of formula R^1A^1Br or R^1A^1I , wherein R^1 and A^1 is as defined herein. A further embodiment of the process comprises reacting a compound of formula 15



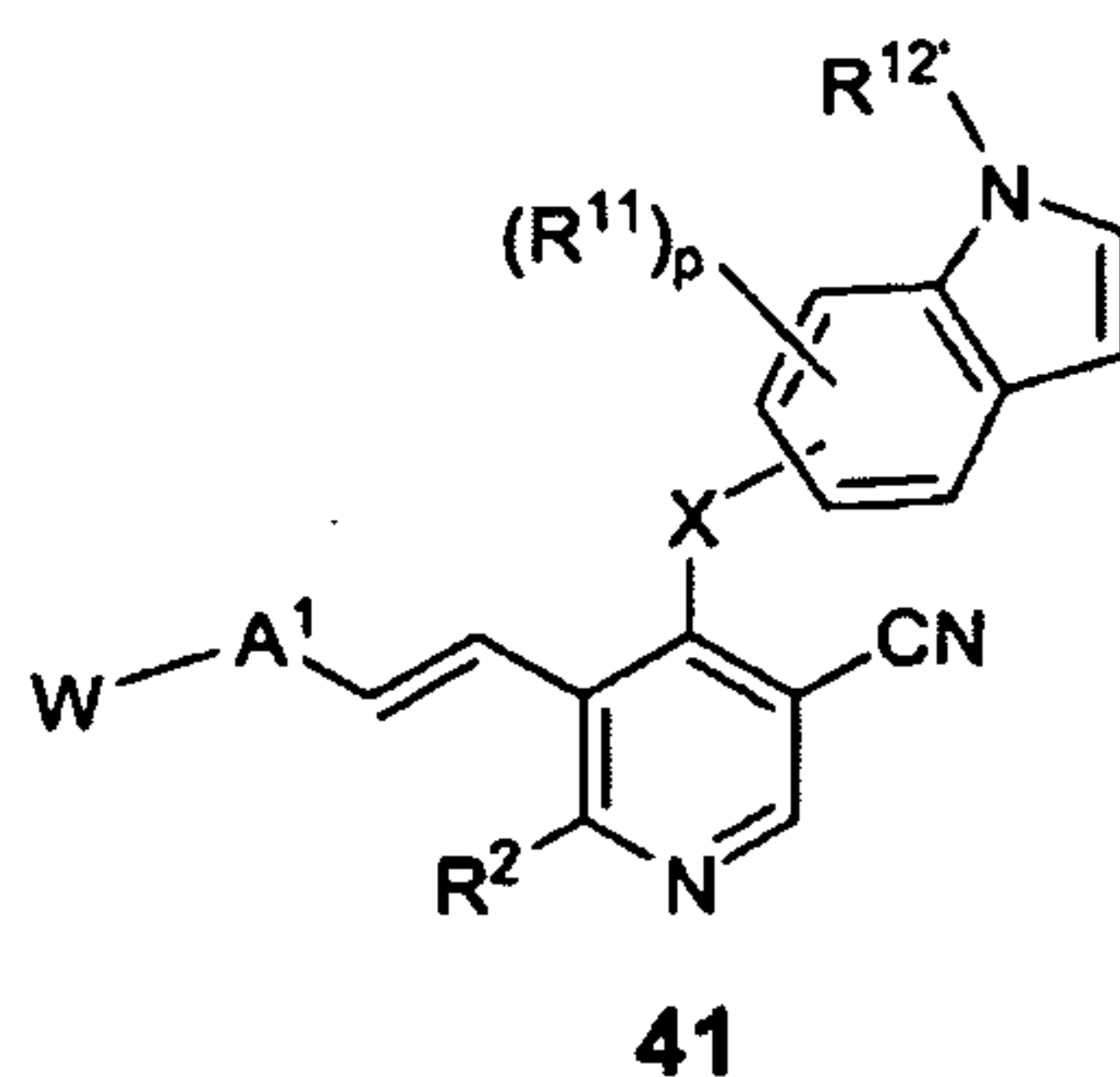
in the presence of a palladium catalyst, with a vinyl reagent, to give a compound of formula 36. The vinyl reagent may be any reagent that transfers a vinyl moiety to an aryl or heteroaryl ring. In some embodiments, the vinyl reagent may be tributyl(vinyl)tin, vinyl boronic acid pinacol ester, vinyl boronic acid dibutyl ester or potassium vinyl trifluoroborate.

[0063] Processes are also provided for processes for preparing a compound of formula I wherein J is J(iii), the process comprising first reacting a compound of formula 38



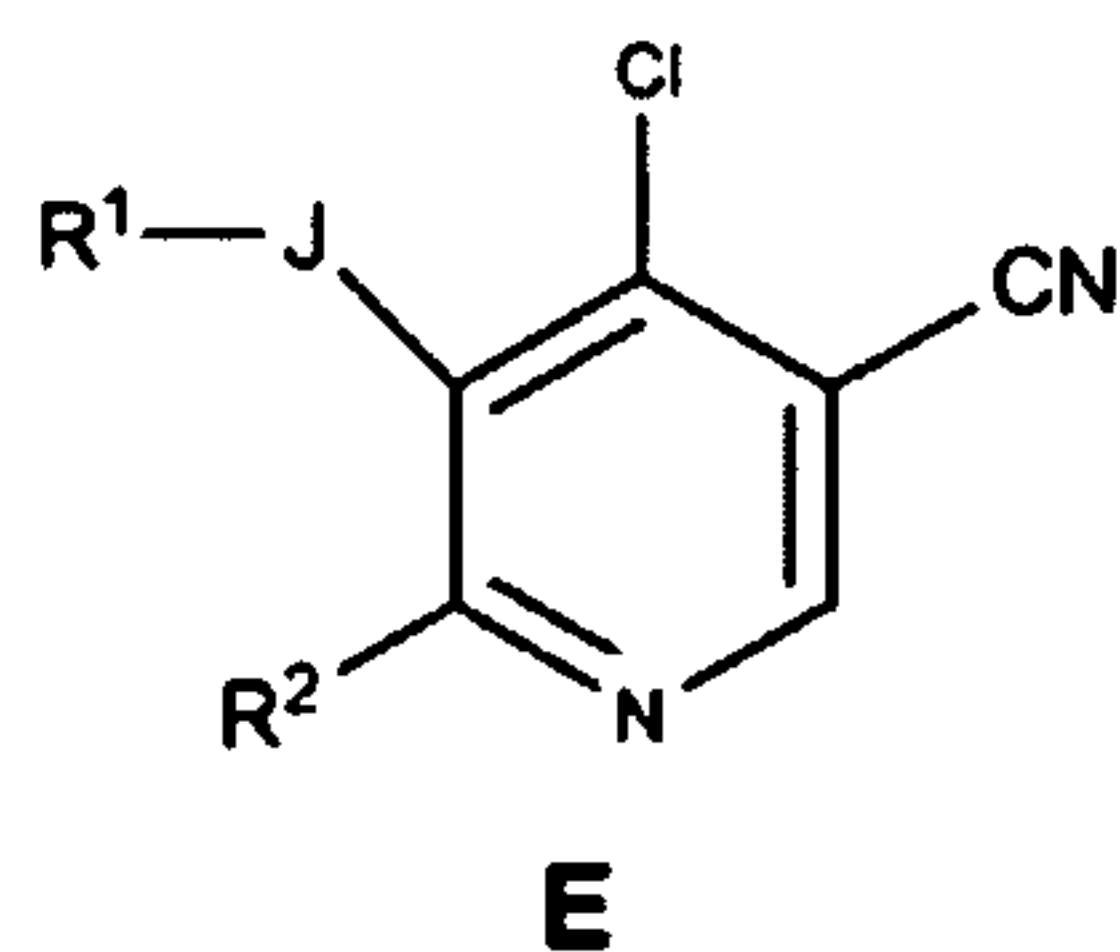
wherein K is OH; Q is methylene and A¹, R¹¹, R^{12'}, p, X and R² are as defined herein; with an alcohol-activating agent to form an electrophile; followed by reacting the electrophile with an amine R¹³R¹³NH. In one embodiment of the invention, the alcohol activating agent may comprise a base and an alkyl or aryl sulfonyl chloride. In one embodiment of the invention, the base may be a tertiary amine. In a further embodiment, the tertiary amine may be triethylamine or diisopropylethylamine. In one embodiment of the invention, the alkyl or aryl sulfonyl chloride may be *p*-toluenesulfonyl chloride or methanesulfonyl chloride.

[0064] Processes are also provided for preparing a compound of formula I wherein J is J(iii), the process comprising reacting a compound of formula 41

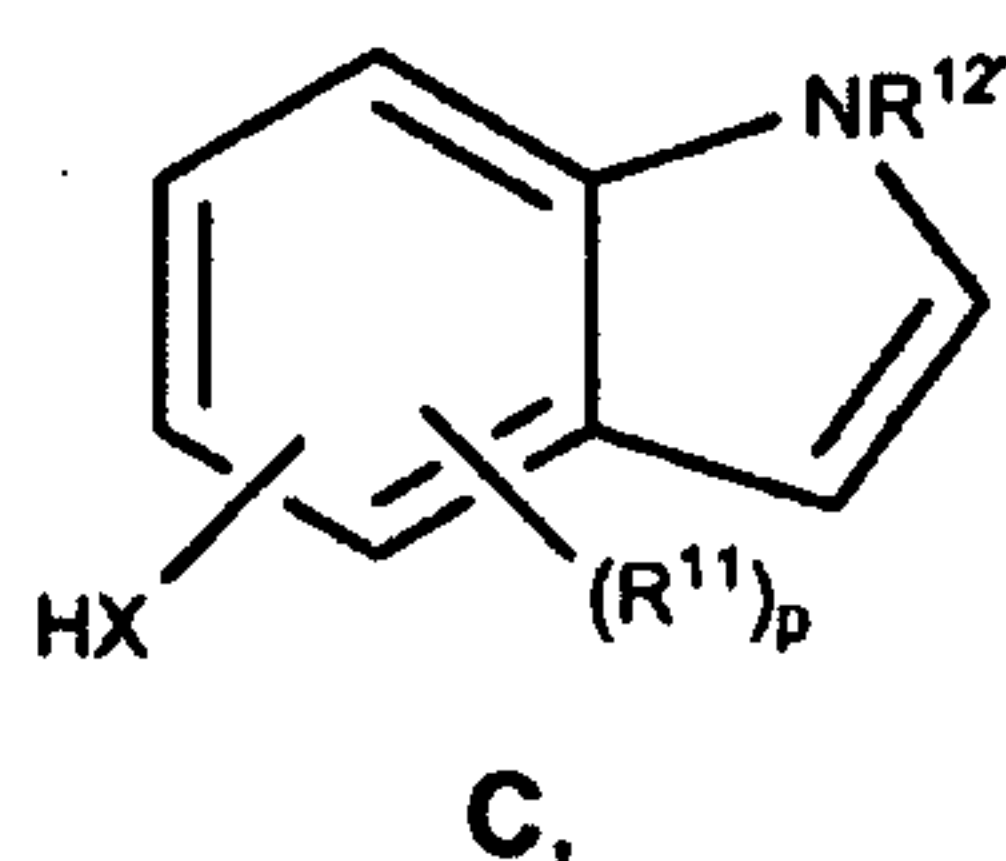


wherein W is CHO; A¹, R¹¹, R^{12'}, p, X and R² are as defined herein; with an amine R¹³R¹³NH, in the presence of a reducing agent. Various reducing agents known in the art may be used. In some embodiments, the reducing agent may be sodium cyanoborohydride or sodium triacetoxyborohydride.

[0065] The teachings of the present invention also provide for processes for preparing compounds herein, comprising reacting a compound of formula E

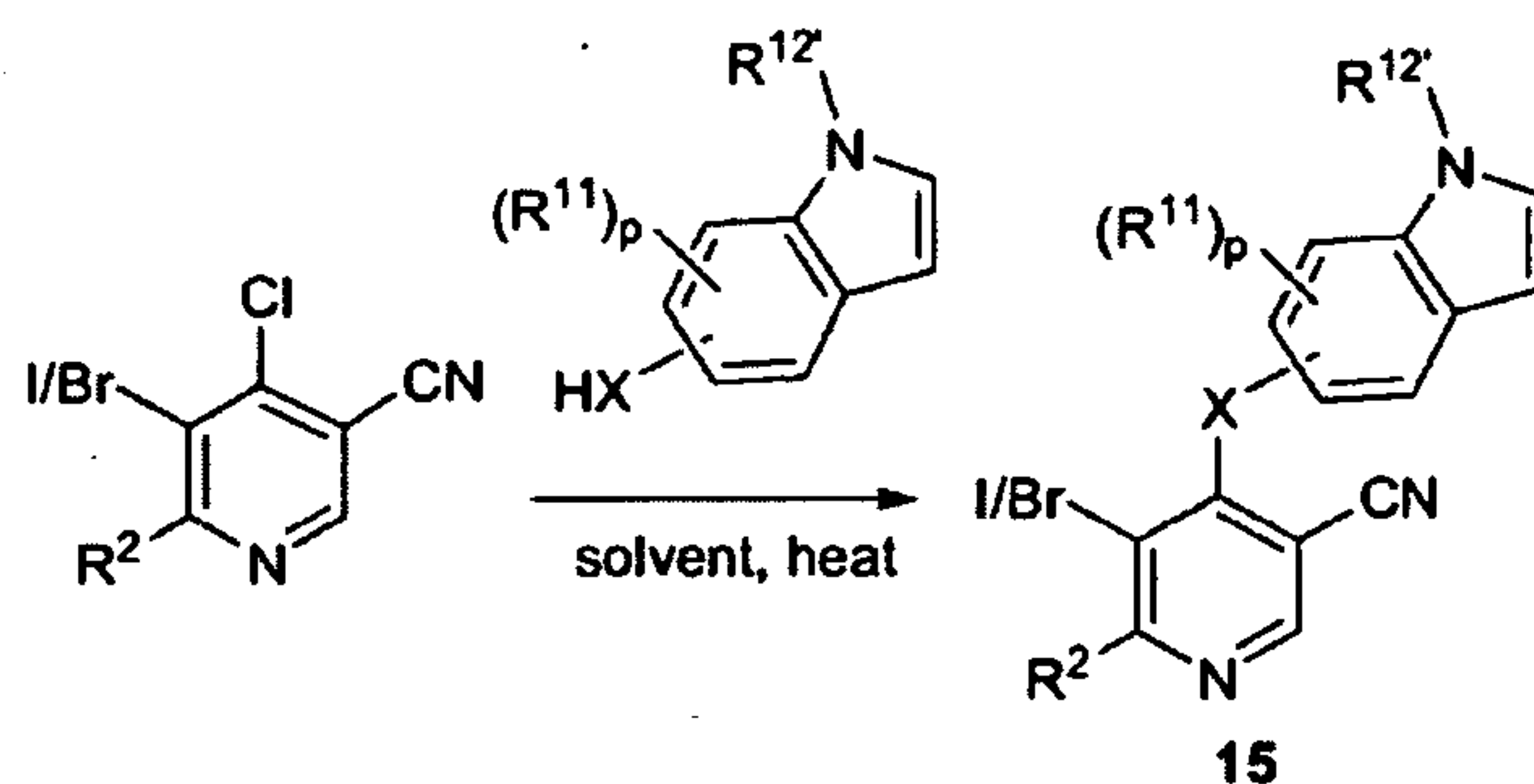


with a compound of formula **C**



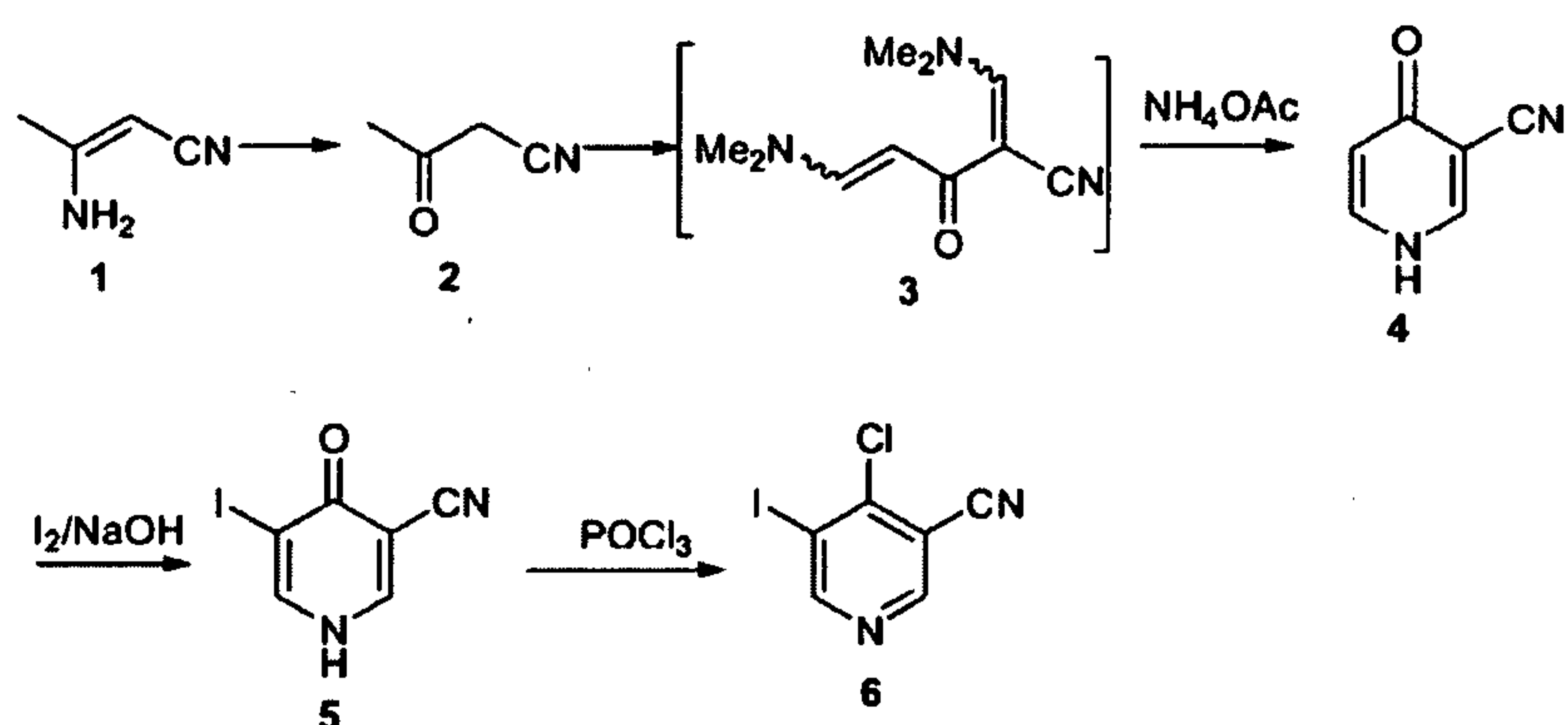
wherein R^1 , J , R^2 , X , R^{11} , R^{12} and p are as defined herein.

[0066] The compound of Formula **15** is made by utilizing the reaction:

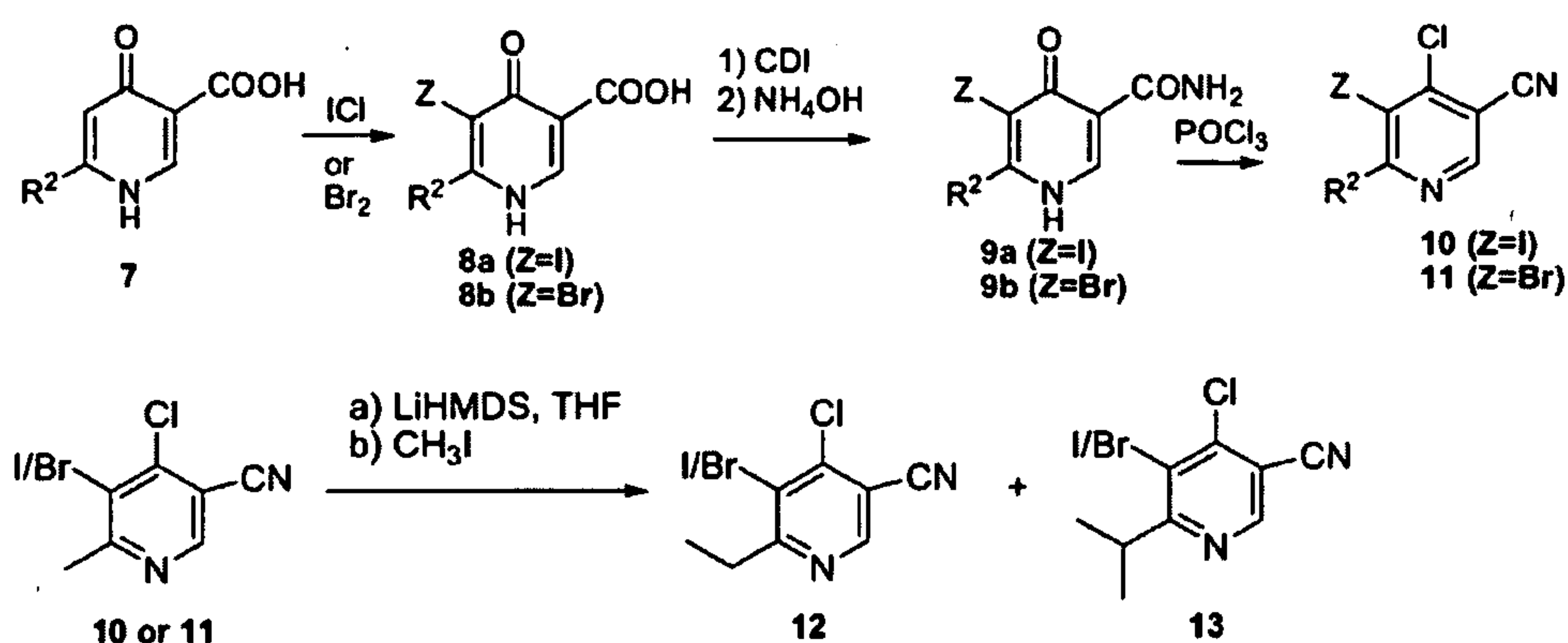


[0067] The following Schemes and description provide further illustrative examples.

[0068] Several intermediates serve important roles in the syntheses of compounds of Formula I. One example of such an intermediate is compound **6**, the synthesis of which is outlined in Scheme 1.

[0069] Scheme 1:

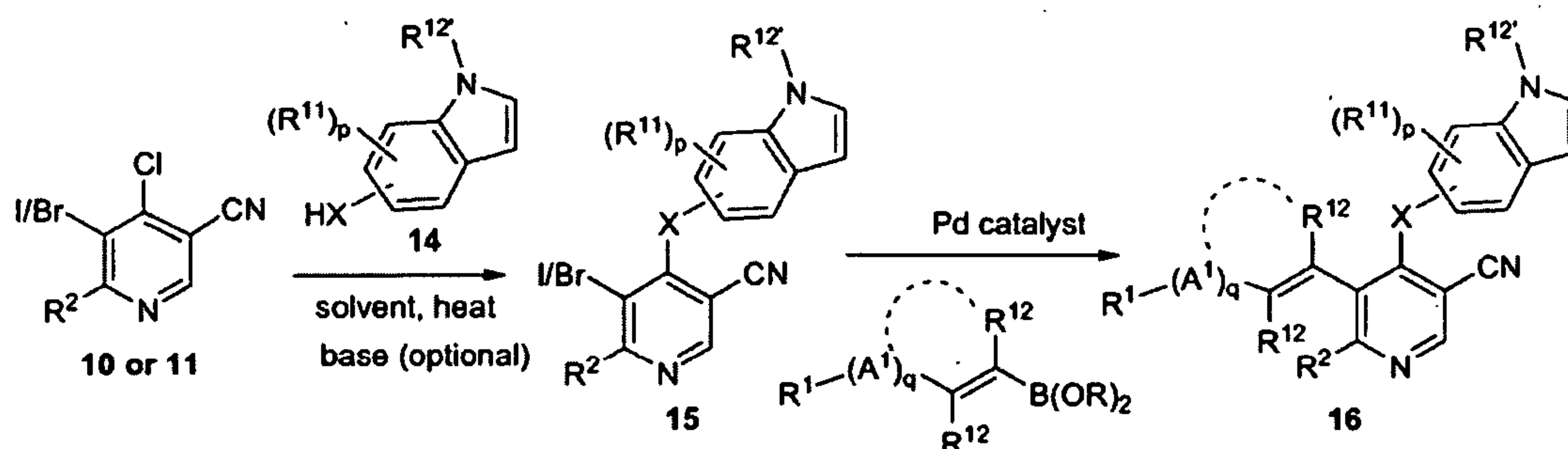
[0070] The synthesis of compound 6 begins with 3-aminobut-2-enenitrile 1 which is heated in acid (e.g., aqueous HCl) to yield acetoacetonitrile 2. Acetoacetonitrile 2 is treated with t-butoxybis(dimethylamino)methane and DMF-DMA at an elevated temperature to yield 5-(dimethylamino)-2-[(dimethylamino)methylene]-3-oxopent-4-enenitrile 3, which is then treated with ammonium acetate in EtOH at reflux to produce 4-hydroxynicotinonitrile 4. (An alternate synthesis of 4-hydroxynicotinonitrile is reported in the literature: Broekman, F. W. et al., *Recueil des Travaux Chimiques des Pays-Bas*, 81: 792-796 (1962)). A mixture of 4-hydroxynicotinonitrile 4, iodine and NaOH in water is heated overnight to yield 4-hydroxy-5-iodonicotinonitrile 5, which is then treated with POCl₃ at an elevated temperature to yield 4-chloro-5-iodonicotinonitrile 6. The analogous 4-bromo-5-iodonicotinonitrile may be prepared in two steps from compound 4 using bromine in acetic acid followed by treatment with POCl₃.

[0071] Scheme 2:

[0072] Another intermediate in the syntheses of compounds of Formula I is **10/11**. A useful synthesis of **10/11** is illustrated in scheme 2. The 6-alkyl-4(1H)-pyridone-3-carboxylic acids **7** can be iodinated at C-5 using the method reported in WO9948892 to prepare 5-iodo-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (**8a** where R^2 is Me). The carboxylic acid group is converted to the primary amide **9a** by reaction with N,N-carbonyldiimidazole followed by treatment with aqueous ammonium hydroxide. Heating of the amide **9a** in phosphorus oxychloride, optionally in the presence of a catalytic amount of DMF, results in dehydration of the amide with concomitant chlorination at C-4 to give the key 4-chloro-5-iodo intermediate **10**. The analogous 5-bromo-4-chloro intermediates can be prepared by bromination of **7** at C-5 with bromine in acetic acid containing an optional amount of pyridine to give **8b**. The subsequent steps to generate the C-5 bromo analogs **9b** and **11** are the same as described above.

[0073] In certain circumstances, one C-6 alkyl group can be transformed into another group. Specifically, as illustrated in scheme 2, the C-6 methyl group of **10/11** can be deprotonated with a strong base such as LHMDs and be quenched with a carbon electrophile such as MeI to give **12** or **13**. The ratio of **12:13** can be controlled by adjusting the equivalents of base and electrophile used. Those skilled in the art can envision various related transformations to yield larger and more diverse alkyl groups.

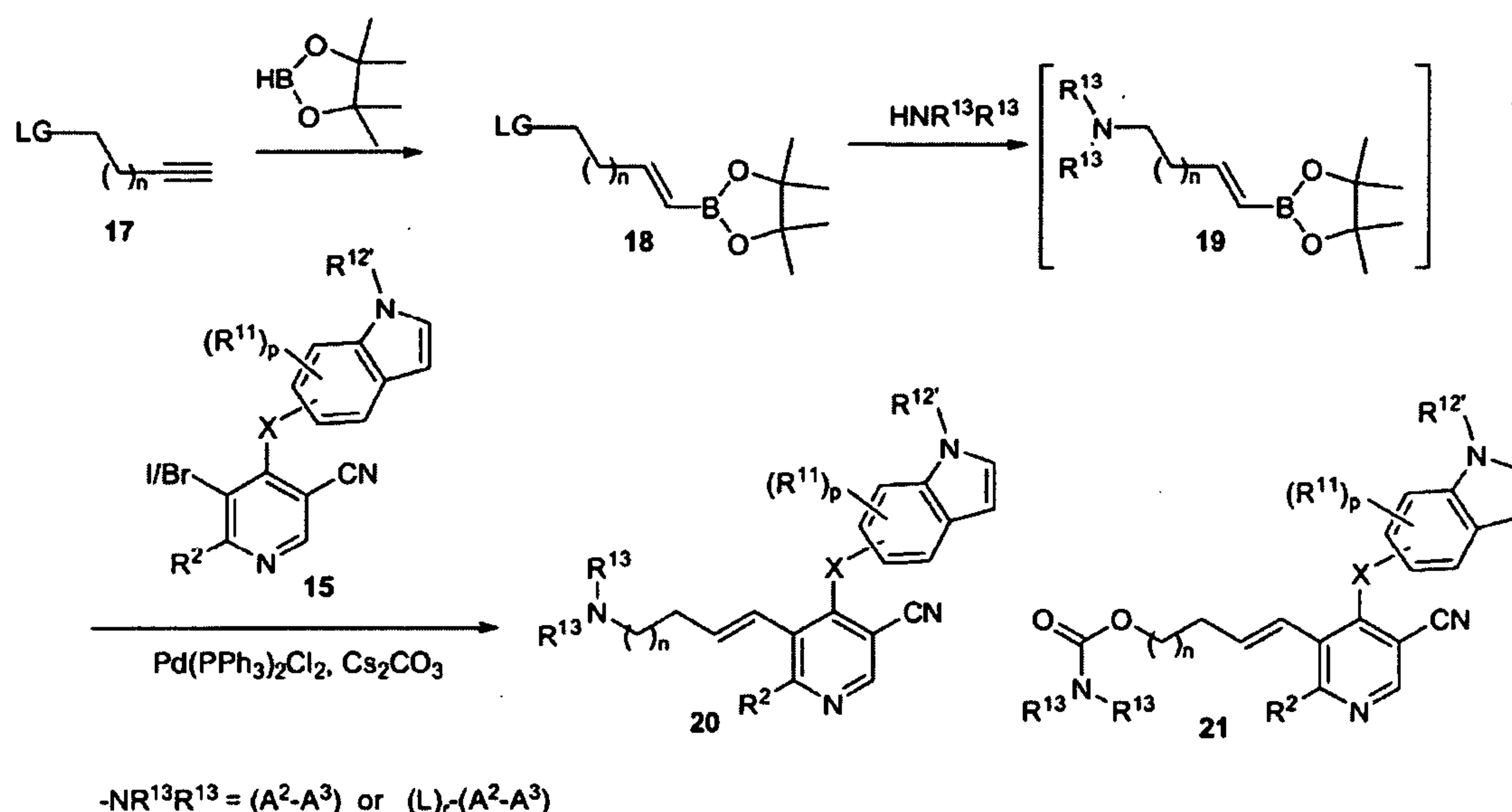
[0074] **Scheme 3:**



[0075] Treatment of compound **10** or **11** with various aryl compounds of formula **14** in a suitable solvent such as ethanol or ethoxyethanol at an elevated temperature leads to compound **15**. When appropriate, this reaction may be performed in the presence

of a base such as potassium carbonate, sodium bicarbonate, or triethylamine. Compound 15 may be further elaborated by well documented procedures such as Suzuki or Stille couplings as shown to ultimately give compounds of the invention, such as 16.

[0076] Scheme 4:

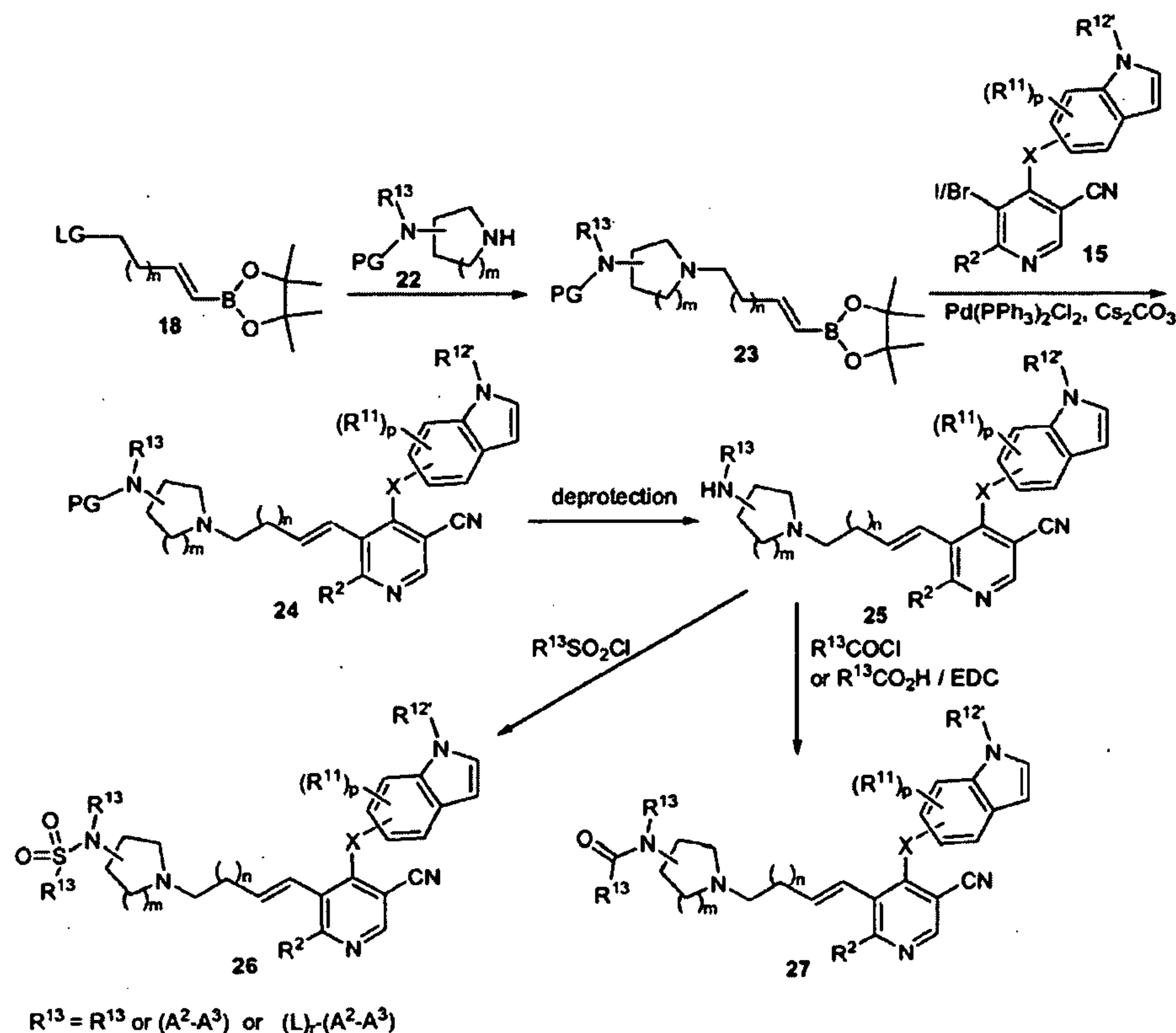


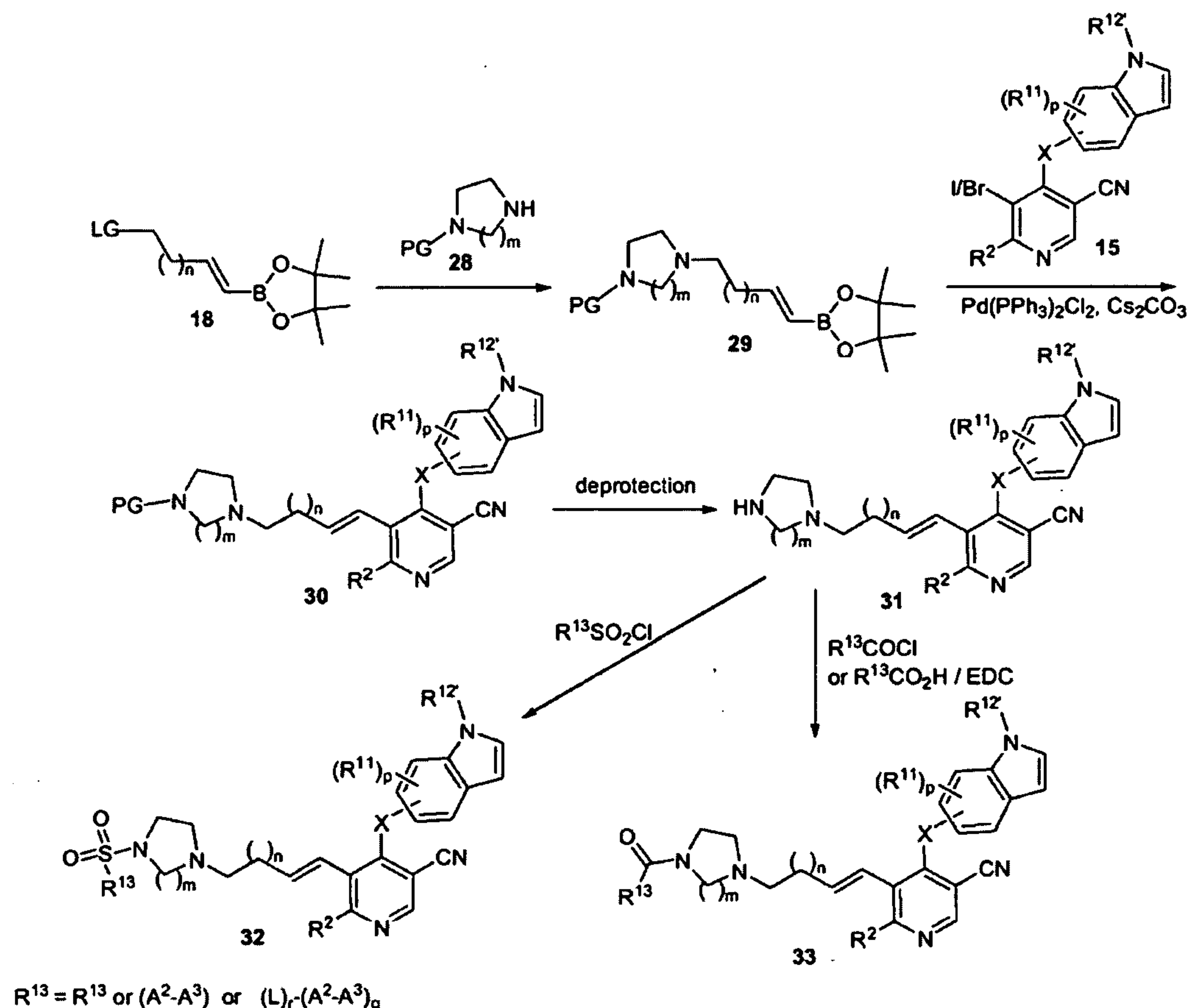
[0077] An example of a procedure for the synthesis of compound 20 is illustrated in Scheme 4. An alkyne of formula 17 is hydroborated under conditions well known to those skilled in the art (Tetrahedron Letters, 46(50), 8777-8780; 2005) to provide boronic esters of formula 18. This reaction can be performed neat or in a solvent such as dichloroethane and related solvents at temperatures ranging from 0° C to 100° C, preferably approximately 20° C. The leaving group (LG) is displaced by nucleophiles such as primary and secondary amines in a suitable solvent such as DMF or DMSO. Leaving groups are selected from Cl, Br, o-tosyl, and the like. The displacement generally occurs at room temperature, but elevated temperatures and reduced temperatures are necessary and beneficial under particular circumstances. Intermediate 19 is treated with intermediate 15 and an appropriate catalyst such as $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ or $\text{Pd}(\text{PPh}_3)_4$ under basic conditions at an elevated temperature to provide compounds of formula 20. It should be understood that analogous

procedures utilizing the related tin reagents (Stille coupling) may also be employed to obtain compound **20**. Moreover, it is not necessary to isolate each intermediate illustrated in scheme 4. In specific circumstances intermediate **18** is subjected to the Suzuki conditions in the presence of an amine nucleophile to obtain compound **20** without the isolation of intermediate **19**.

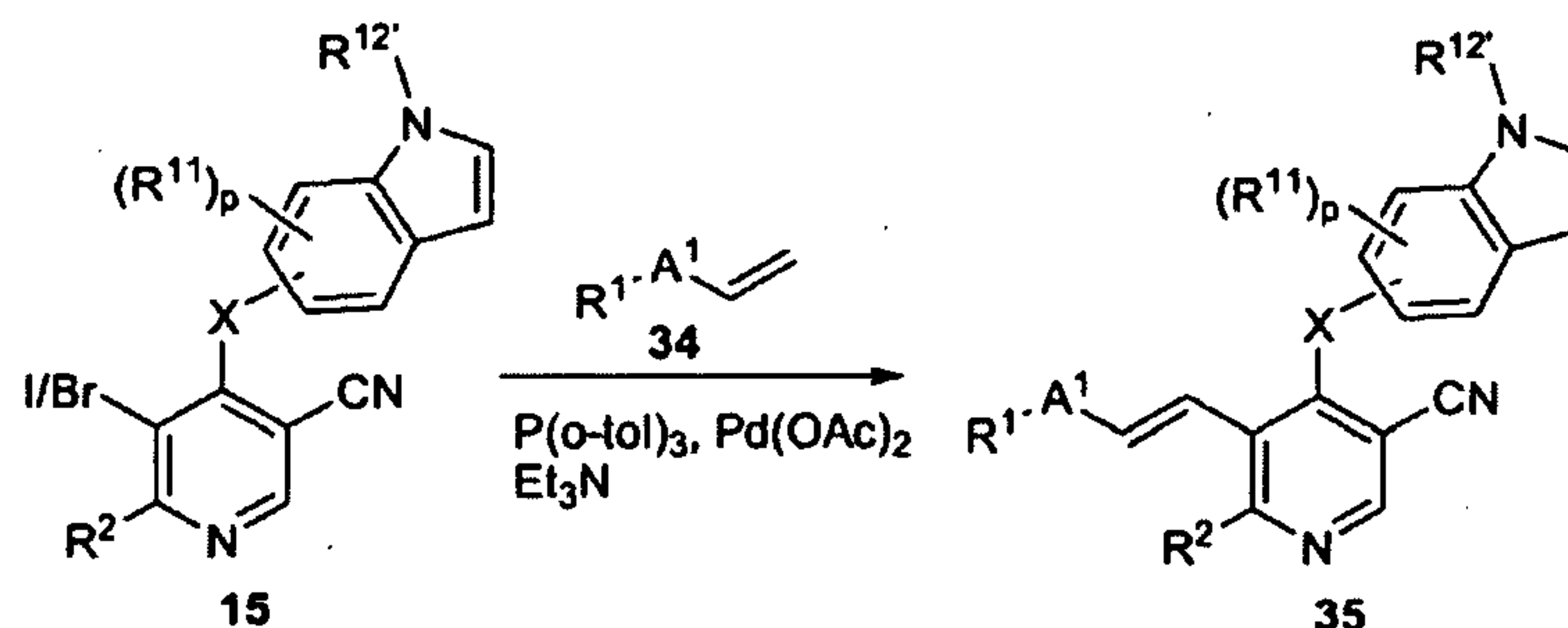
[0078] In cases where compound **18** is treated under Suzuki conditions in the presence of both a secondary amine and a carbonate base, compound **21** may be formed as a mixture with compound **20**. The ratio of **20:21** can be influenced by the choice of solvent, temperature, and base. In some circumstances, compound **21** may be obtained as the major product of the reaction. The formation of compound **21** may be minimized by treatment of compound **18** with excess secondary amine at room temperature prior to treatment with the carbonate base and palladium catalyst necessary for the subsequent Suzuki coupling. This will be made more clear in the specific examples that follow this general description.

[0079] Scheme 5:

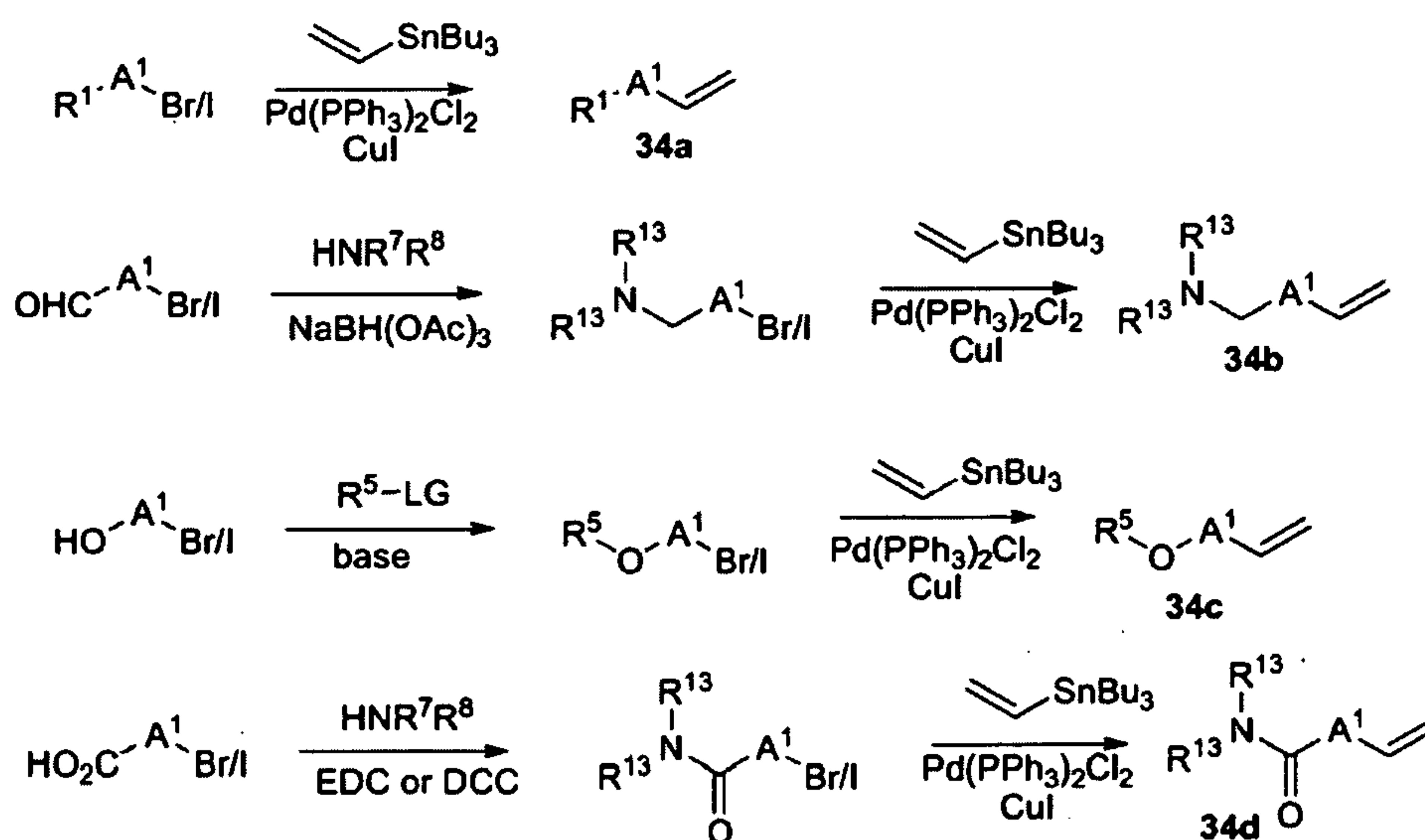


Scheme 6:

[0080] In particular circumstances, compounds can be prepared by the routes illustrated in Schemes 5 and 6. Similar to the previously shown route, compound 18 is treated with an appropriately protected diamine to give boronic ester 23 / 29. Preferred protecting groups include, but are not limited to, Boc and Cbz. The boronic ester 23 / 29 is coupled under the previously discussed conditions to give compound 24 / 30. Deprotection, frequently utilizing TFA and dichloromethane at room temperature, gives compound 25 / 31. Compound 25 / 31 may be further derivatized to compounds 26 / 27 / 32 / 33 via sulfonylation and amidation chemistry that is well known in the art.

[0081] Scheme 7:

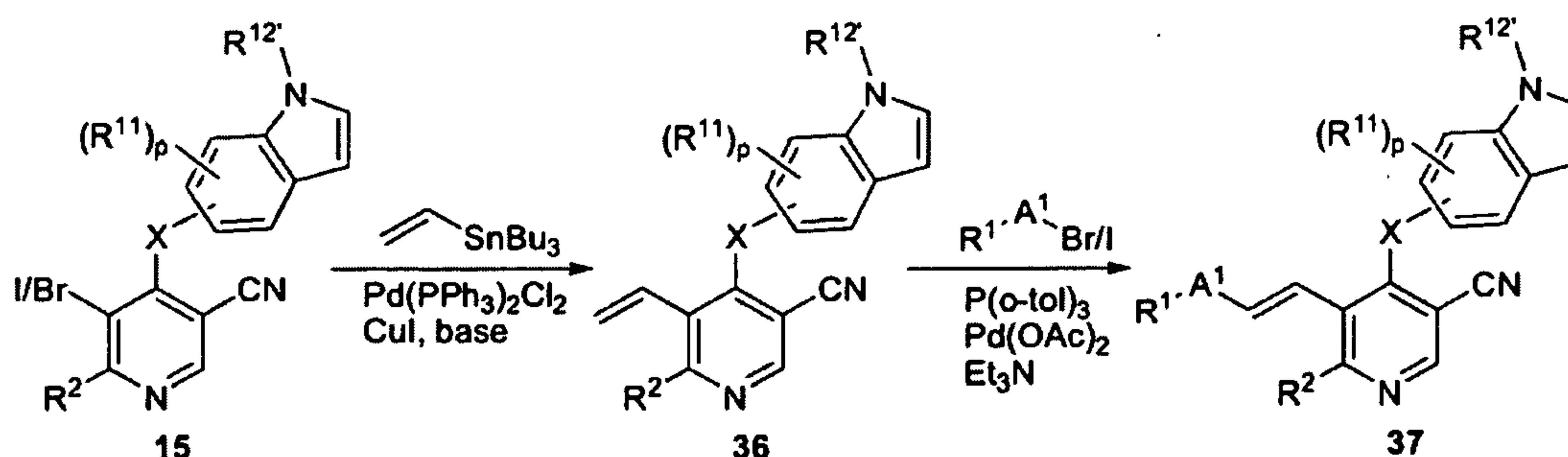
[0082] In addition to the routes described above, a Heck reaction (Scheme 7) may be utilized to synthesize various compounds. As such, compounds of formula 35 may be prepared by a Heck reaction with an appropriate alkene coupling partner such as 34 (where A¹ is aryl or heteroaryl). The reaction may be conducted under conditions well known to those skilled in the art. An especially useful set of conditions is the treatment of an aryl halide 15 with an alkene of formula 34 in the presence of Pd(OAc)₂ and tri(ortho-tolyl)phosphine in a solvent such as DMF at an elevated temperature, preferably 70-120 °C. Generally, excess base such as triethyl amine (preferably 3 equivalents) is utilized for this transformation.

[0083] Scheme 8:

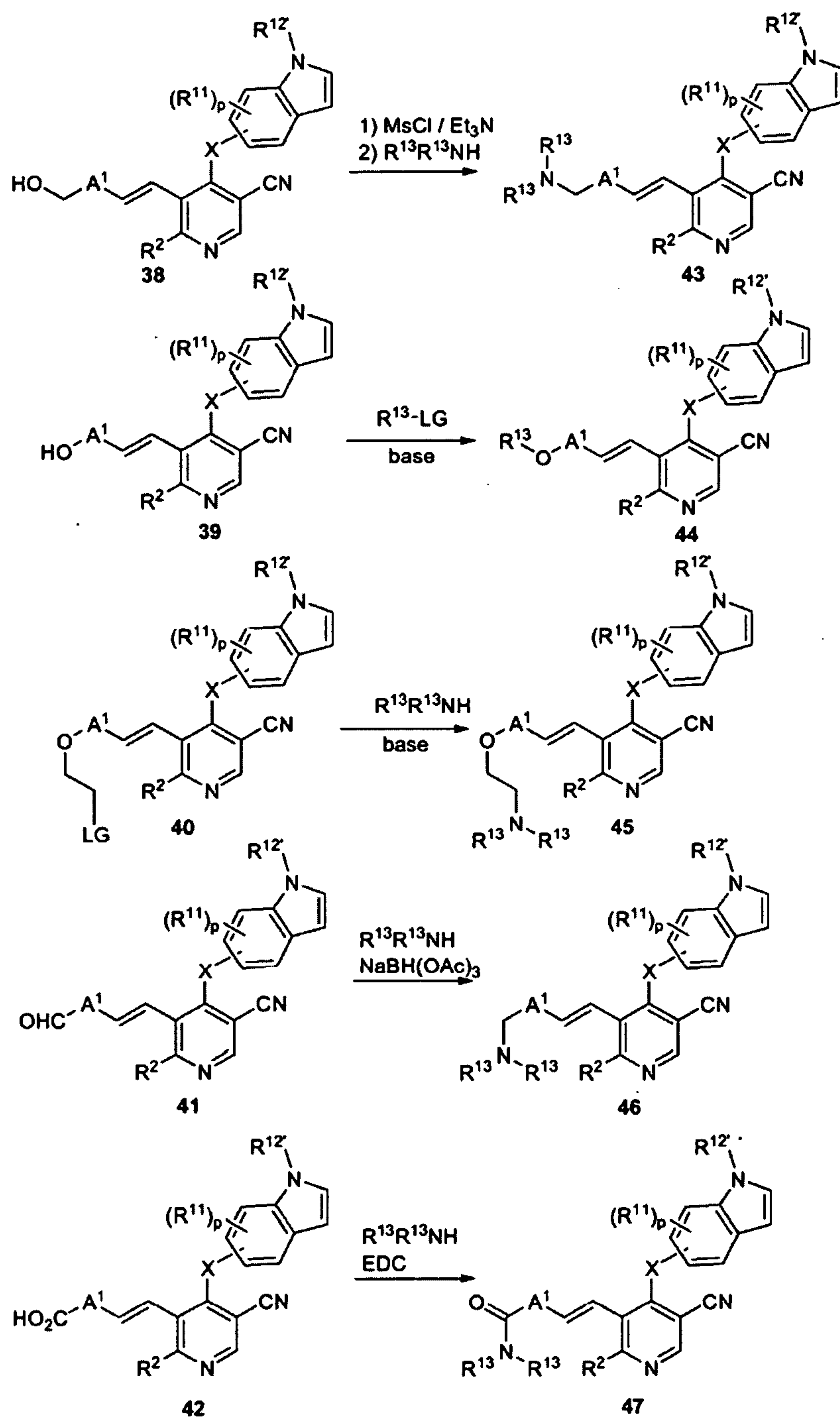
-NR¹³R¹³ = -NR¹³R¹³ or (A²-A³) or (L)_r-(A²-A³)

[0084] The appropriate alkene coupling partner, **34**, may be obtained commercially or may be readily synthesized via Stille couplings of an aryl or heteroaryl halide with a vinyl tin reagent. The synthesis of several especially useful compounds of formula **34a-d** are illustrated in Scheme 8. The synthesis of additional coupling partners can be easily envisioned by those skilled in the art.

[0085] **Scheme 9:**



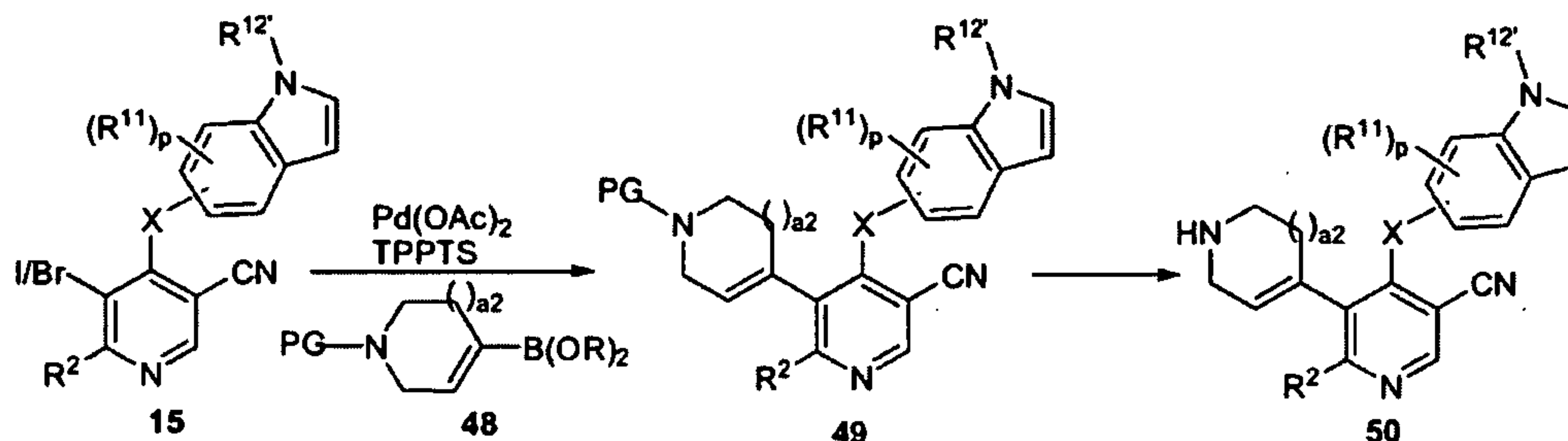
[0086] The alkene and the aryl halide coupling partners may be transposed as illustrated in Scheme 9. As such, compound **15** is subjected to Stille coupling conditions with a vinyl tin to give compound **36**. This reaction generally requires the use of a palladium catalyst such as $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, an additive such as CuI , and a base such as NaHCO_3 or K_2CO_3 . The reaction is conducted at an elevated temperature in a suitable solvent such as DMF. The unsubstituted vinyl derivative thus obtained (**36**) is treated under standard Heck coupling conditions with an aryl or heteroaryl halide to give compounds of formula **37**. Generally the Heck reaction is conducted in the presence of a catalytic amount of $\text{Pd}(\text{OAc})_2$ and tri(ortho-tolyl)phosphine in a solvent such as DMF or DMSO. An excess of base, usually a tertiary amine such as Et_3N or Hunig's base is generally required for the reaction to proceed. The reaction is generally conducted at an elevated temperature, preferably 80°C to 120°C .

[0087] **Scheme 10:**

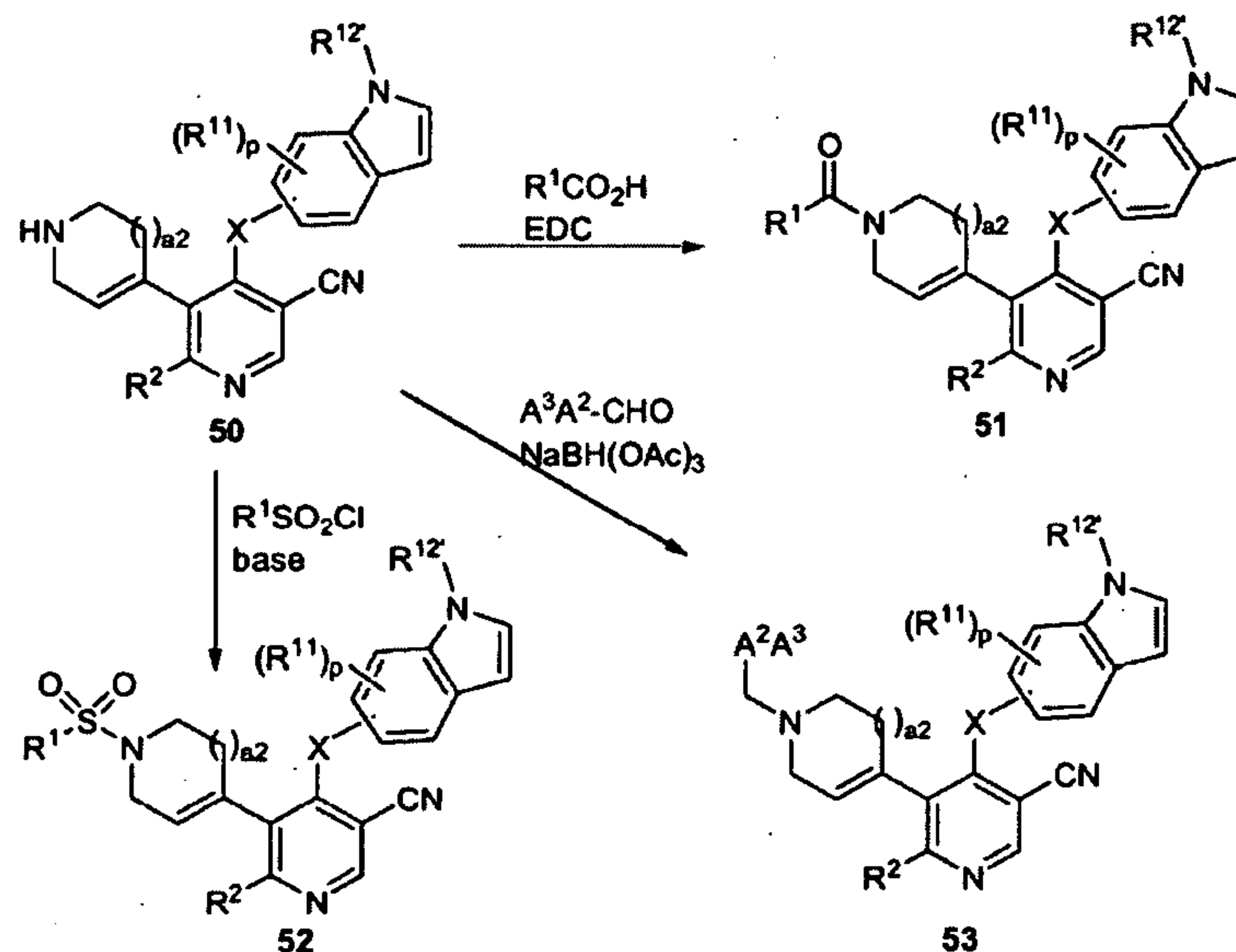
$-NR^{13}R^{13} = -NR^{13}R^{13}$ or (A^2-A^3) or $(L)_r(A^2-A^3)$
 $-OR^{13} = (A^2-A^3)$ or $(L)_r(A^2-A^3)$

[0088] The various intermediates (38-42) illustrated in Scheme 10 can be prepared by routes illustrated in schemes 1-9. These intermediates can be subjected as shown to conditions well known in the art to form compounds 43-47. These conditions include such standard transformations as nucleophilic displacements, reductive aminations, amidations, sulfonylations, alkylations, acylations and the like.

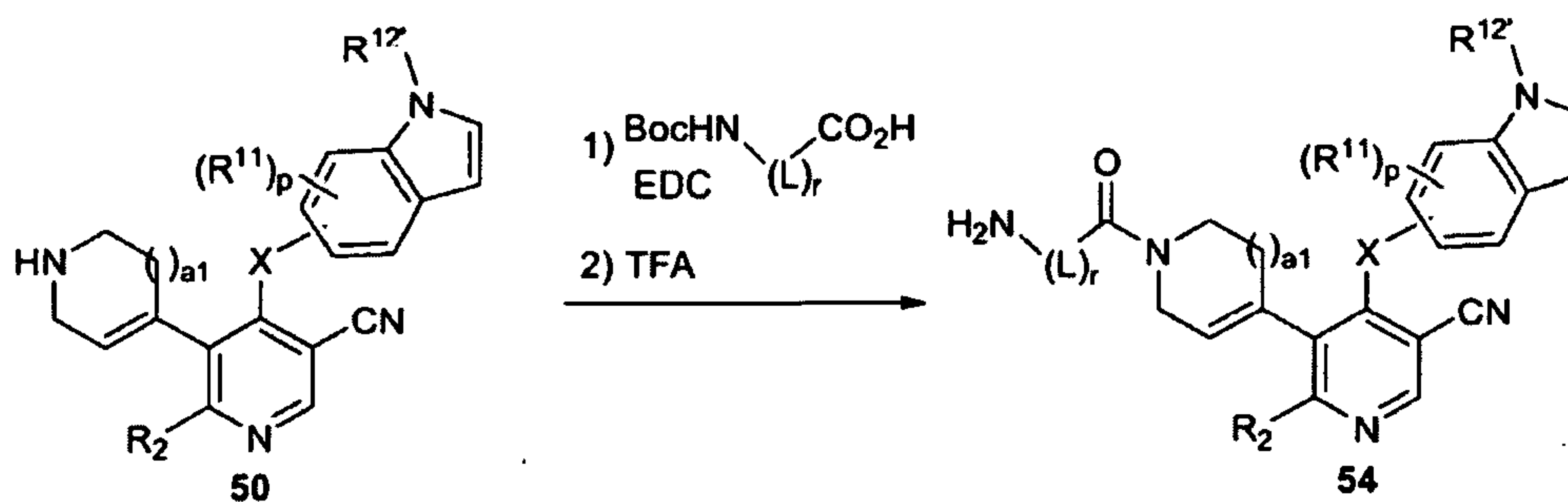
[0089] **Scheme 11:**

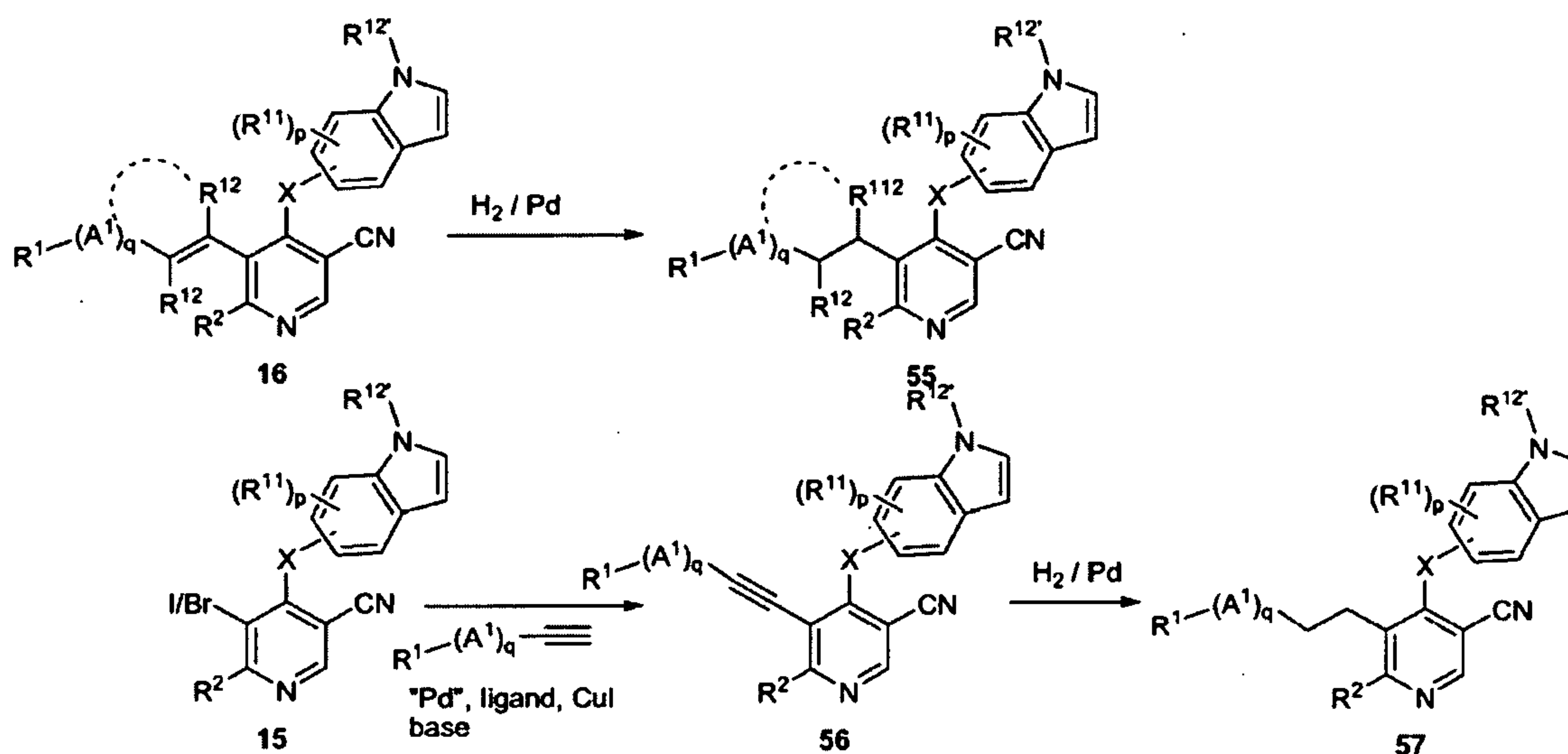


[0090] As shown in Scheme 11, cyclic alkenyl boronic acids (48) can also be coupled to core 15 giving structure 49. This coupling can be conducted under standard Suzuki conditions or, preferably, utilizing a less well-known ligand, triphenylphosphine trisulfonic acid trisodium salt (TPPTS) in conjunction with Pd(OAc)₂. Generally the reaction is performed in a solvent such as DME, DMF, or dioxane containing a base such as sodium bicarbonate. Reactions are typically heated to 70-90° C for 2-24h. The requisite cyclic boronic acids are commercially available or can be synthesized according to methods known in the art (Tetrahedron Letters, 41(19), 3705-3708; 2000). Deprotection of the cyclic amine (typically with TFA/DCM when PG = Boc) results in secondary amine 50.

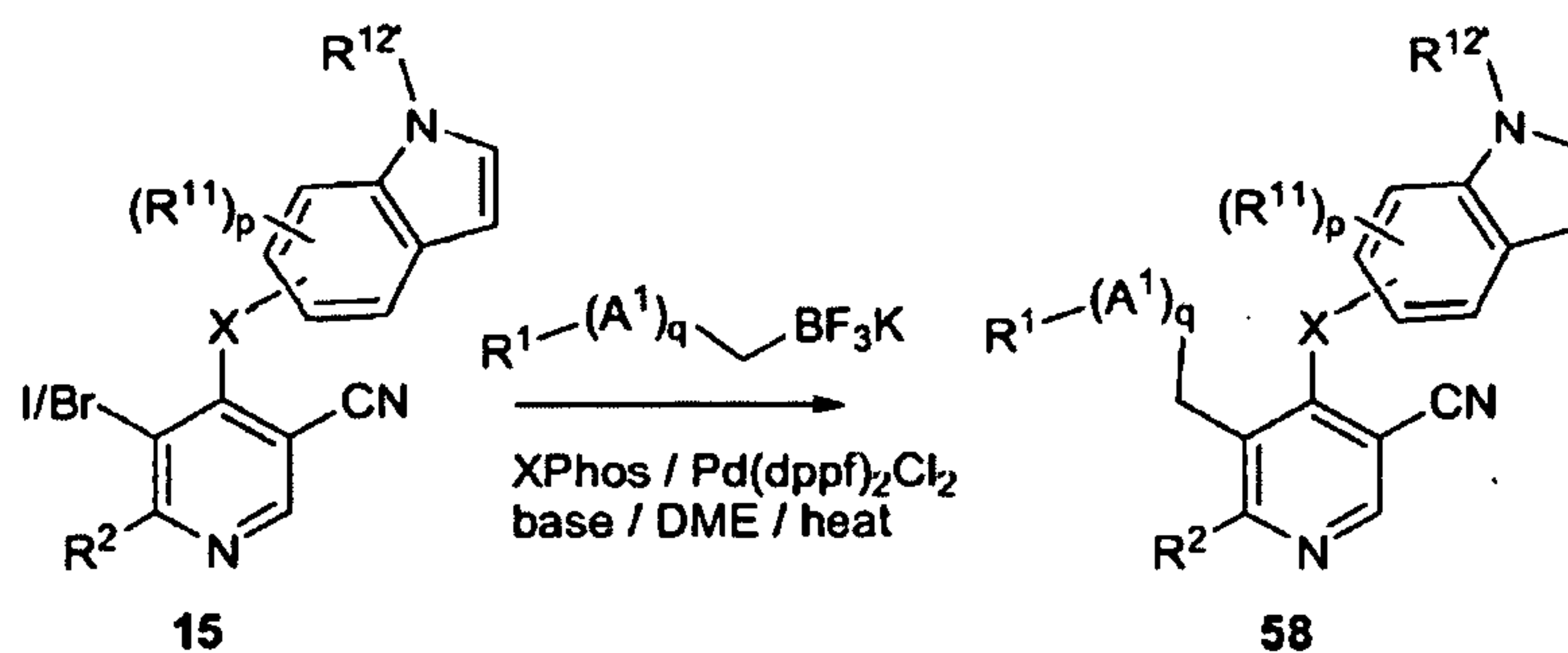
[0091] Scheme 12:

[0092] Compound **50** may be further manipulated as shown via acylations, sulfonylations, reductive aminations and the like as illustrated in Scheme 12. In particular examples, compound **50** can be acylated with a Boc-protected amino acid followed by deprotection to give compound **54** as illustrated in Scheme 13.

[0093] Scheme 13:

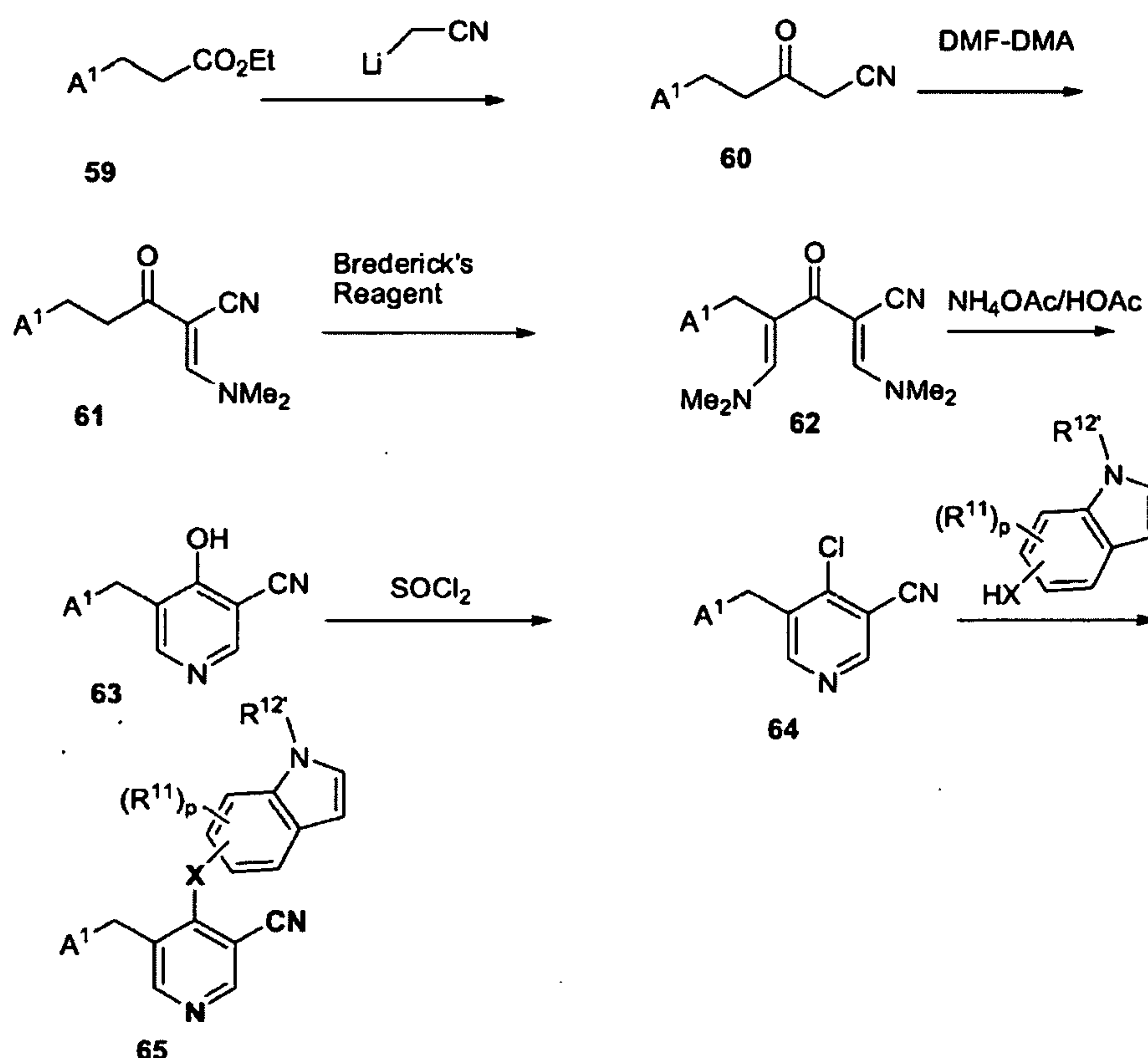
[0094] Scheme 14:

[0095] Shown in Scheme 14 are two methods for the synthesis of compounds of the invention substituted with alkanes at the C5-position. Such alkane derivatives may be synthesized by palladium catalyzed reduction of compound 16 (prepared by any of the aforementioned routes) to give alkane 55. Any of the various methods of reduction known in the art may be utilized to affect this transformation. Of particular utility is the use of 10% palladium on activated carbon under a 10-30 psi atmosphere of hydrogen performed in a mixture of ethanol and toluene at 10-20° C. In a similar manner, alkynes such as 56 may be catalytically reduced to the corresponding alkanes utilizing methods well known in the art. The requisite alkynes are made by palladium catalyzed couplings of terminal acetylenes and compound 15.

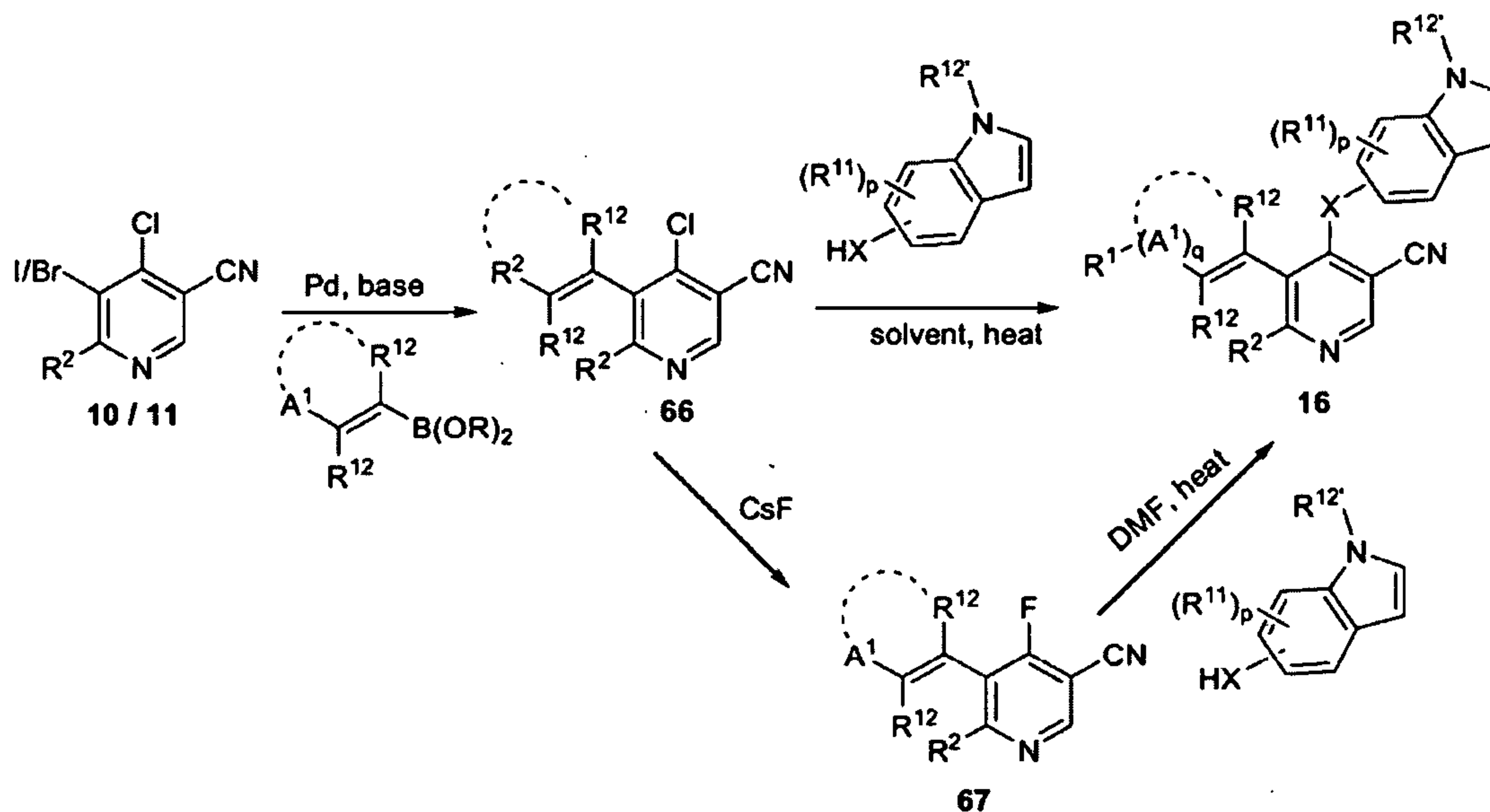
[0096] Scheme 15:

[0097] An alternative preparation of alkane derivatives involves the use of transition metal catalyzed carbon-carbon bond formation. One particularly useful reaction has been reported by Molander (Organic Letters (2007), 9(8), 1597-1600). As such, compound **15** may be heated with an alkyl tetrafluoroborate salt and a suitable catalyst / ligand system such as XPhos and Pd(dppf)₂Cl₂ in the presence of a suitable base such as sodium bicarbonate to give compounds of formula **58**.

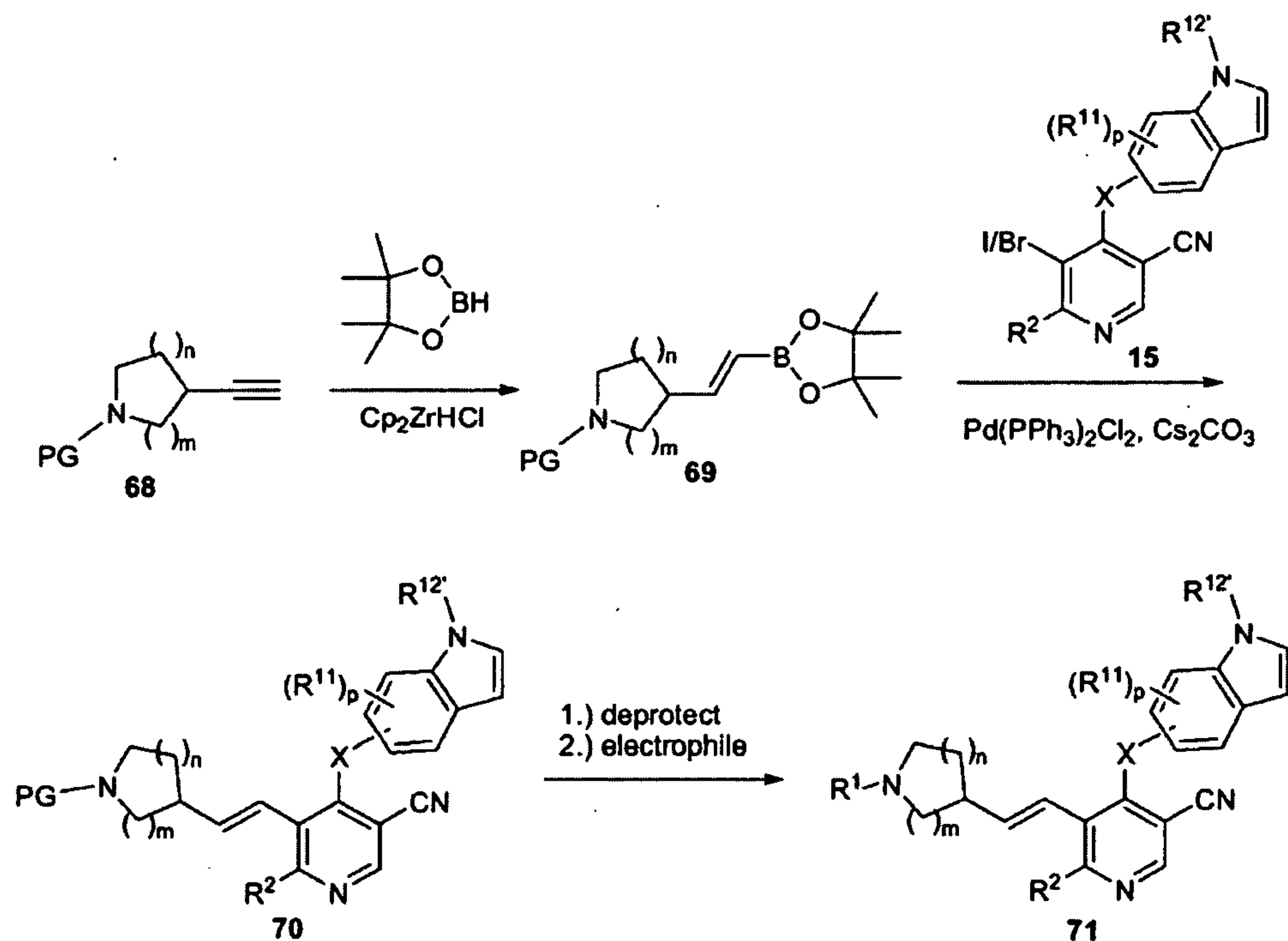
[0098] **Scheme 16:**



[0099] Scheme 16 illustrates an alternative synthesis of 5-alkyl cyanopyridines. A 3-aryl-propanoic ester **59** is treated with the anion of acetonitrile in a solvent such as THF to give ketone **60**. The ketone is treated sequentially with DMF-DMA followed by Brederick's reagent to give bis-vinylous amide **62**. **62** can be treated with ammonia in acetic acid to give the 4-hydroxypyridine **63**. This compound can be chlorinated with $POCl_3$ and transformed to **65** by the aforementioned routes.

[00100] Scheme 17:

[00101] An alternative preparation of compound 16 is illustrated in scheme 17. The 4-chloro,5-iodo/bromo core (10 or 11) is first treated under Suzuki conditions or Heck conditions as previously described to give compounds of formula 66. Treatment of 66 with an indolyl nucleophile in an appropriate solvent such as DMF, DMSO, ethanol, or ethoxyethanol at elevated temperatures (60° to 150° C) leads to compounds of formula 16. In certain cases, the indolyl nucleophile proves to be unreactive in the displacement of the 4-Cl in compound 66. In these cases, compound 66 may be treated with an anhydrous fluoride source such as CsF in DMF to give the more reactive 4-F pyridine 67. Subsequent treatment of 67 with an indolyl nucleophile in an appropriate solvent such as DMF, DMSO, ethanol, or ethoxyethanol at elevated temperatures (60° to 150° C) leads to compounds of formula 16.

[00102] Scheme 18:

[00103] Scheme 18 illustrates a further synthesis of compounds of the present invention. Alkynes such as 68 may be hydroborated by conditions well known in the art to give the alkenyl boronic ester 69. This boronic ester undergoes a Pd catalyzed coupling reaction as previously described to give compound 70. Useful protecting groups include Boc, Cbz, and the like. Deprotection of the amine gives the corresponding secondary amine. The addition of various electrophiles utilizing conditions well known by those skilled in the art may give compounds of the invention such as compound 71.

[00104] Another aspect relates to methods of reducing an increased activity of an enzyme in a mammal, wherein the enzyme is a protein kinase, and wherein the method comprises administering to the mammal an effective amount of the compound of formula I, or a pharmaceutically acceptable salt thereof. In some embodiments, the protein kinase is protein kinase C. In further embodiments, the protein kinase C is a theta isoform.

[00105] Compounds of Formula I can be useful for treating a pathological condition or disorder in a mammal, for example, a human. As used herein, "treating" refers to partially or completely alleviating and/or ameliorating the condition and/or symptoms thereof. One embodiment of the present invention relates to the use of the compounds disclosed herein for treating a pathological condition or disorder mediated by a protein kinase such as protein kinase C (PKC) and protein kinase C theta isoform (PKC θ). One aspect relates to the use of the compounds disclosed herein for treating or preventing inflammation, in a mammal. Another aspect relates to the use of the compounds disclosed herein for treating asthma, colitis, multiple sclerosis, psoriasis, rheumatoid arthritis, inflammatory bowel disease, joint inflammation, organ transplant and graft rejection in a mammal, for example, in a human. The present teachings further include use of the compounds disclosed herein as active therapeutic substances for the prevention and/or inhibition of the pathological condition or disorder listed above.

[00106] In some embodiments, the methods include identifying a mammal having a pathological condition or disorder linked to a protein kinase such as PKC and PKC θ , and providing to the mammal an effective amount of a compound as described herein. The present teachings accordingly include a method of providing to a mammal a pharmaceutical composition that includes a compound of the present teachings in combination or association with a pharmaceutically acceptable carrier. Compounds of the present teachings can be administered alone or in combination with other therapeutically effective compounds or therapies for the treatment of a pathological condition or disorder. As used herein, "therapeutically effective" refers to a substance or an amount that elicits a desirable biological activity or effect.

[00107] Compounds of the present teachings can be administered orally or parenterally, neat or in combination with conventional pharmaceutical carriers. Applicable solid carriers can include one or more substances which can also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents, or encapsulating materials. The compounds can be formulated in conventional manner, for example, in a manner similar to that used for known antiinflammatory agents. Oral formulations containing an active compound disclosed herein can include any conventionally used oral form, including tablets,

capsules, buccal forms, troches, lozenges and oral liquids, suspensions or solutions. In powders, the carrier can be a finely divided solid, which is an admixture with a finely divided active compound. In tablets, an active compound can be mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets may contain up to 99% of the active compound.

[00108] Capsules can contain mixtures of active compound(s) with inert filler(s) and/or diluent(s) such as the pharmaceutically acceptable starches (e.g., corn, potato or tapioca starch), sugars, artificial sweetening agents, powdered celluloses (e.g., crystalline and microcrystalline celluloses), flours, gelatins, gums, and the like.

[00109] Useful tablet formulations can be made by conventional compression, wet granulation or dry granulation methods and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, surface modifying agents (including surfactants), suspending or stabilizing agents, including magnesium stearate, stearic acid, sodium lauryl sulfate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, microcrystalline cellulose, sodium carboxymethyl cellulose, carboxymethylcellulose calcium, polyvinylpyrrolidone, alginic acid, acacia gum, xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, sucrose, sorbitol, dicalcium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, low melting waxes, and ion exchange resins. Preferred surface modifying agents include nonionic and anionic surface modifying agents. Representative examples of surface modifying agents include poloxamer 188, benzalkonium chloride, calcium stearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, magnesium aluminum silicate, and triethanolamine. Oral formulations herein can utilize standard delay or time-release formulations to alter the absorption of the active compound(s). The oral formulation can also comprise a compound as described herein in water or fruit juice, containing appropriate solubilizers or emulsifiers as needed.

[00110] Liquid carriers can be used in preparing solutions, suspensions, emulsions, syrups, elixirs, and for inhaled delivery. A compound described herein can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic

solvent, or a mixture of both, or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers, and osmo-regulators. Examples of liquid carriers for oral and parenteral administration include water (particularly containing additives as described above, e.g., cellulose derivatives such as a sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g., glycols) and their derivatives, and oils (e.g., fractionated coconut oil and arachis oil). For parenteral administration, the carrier can be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellants.

[00111] Liquid pharmaceutical compositions, which are sterile solutions or suspensions, can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. Compositions for oral administration can be in either liquid or solid form.

[00112] Preferably the pharmaceutical composition is in unit dosage form, for example, as tablets, capsules, powders, solutions, suspensions, emulsions, granules, or suppositories. In such form, the pharmaceutical composition can be sub-divided in unit dose(s) containing appropriate quantities of the active compound. The unit dosage forms can be packaged compositions, for example, packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. Alternatively, the unit dosage form can be a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form. Such unit dosage form may contain from about 1 mg/kg of active compound to about 500 mg/kg of active compound, and can be given in a single dose or in two or more doses. Such doses can be administered in any manner useful in directing the active compound(s) to the recipient's bloodstream, including orally, via implants, parenterally (including intravenous, intraperitoneal and subcutaneous injections), rectally, vaginally, and transdermally. Such administrations can be carried out using the compounds of the present

teachings including pharmaceutically acceptable salts thereof, in lotions, creams, foams, patches, suspensions, solutions, and suppositories (rectal and vaginal).

[00113] When administered for the treatment or inhibition of a particular disease state or disorder, it is understood that an effective dosage can vary depending upon many factors such as the particular compound utilized, the mode of administration, and severity of the condition being treated, as well as the various physical factors related to the individual being treated. In therapeutic applications, a compound of the present teachings can be provided to a patient already suffering from a disease in an amount sufficient to cure or at least partially ameliorate the symptoms of the disease and its complications. The dosage to be used in the treatment of a specific individual typically must be subjectively determined by the attending physician. The variables involved include the specific condition and its state as well as the size, age and response pattern of the patient.

[00114] In some cases, for example those in which the lung is the targeted organ, it may be desirable to administer a compound directly to the airways of the patient, using devices such as metered dose inhalers, breath-operated inhalers, multidose dry-powder inhalers, pumps, squeeze-actuated nebulized spray dispensers, aerosol dispensers, and aerosol nebulizers. For administration by intranasal or intrabronchial inhalation, the compounds of the present teachings can be formulated into a liquid composition, a solid composition, or an aerosol composition. The liquid composition can include, by way of illustration, one or more compounds of the present teachings dissolved, partially dissolved, or suspended in one or more pharmaceutically acceptable solvents and can be administered by, for example, a pump or a squeeze-actuated nebulized spray dispenser. The solvents can be, for example, isotonic saline or bacteriostatic water. The solid composition can be, by way of illustration, a powder preparation including one or more compounds of the present teachings intermixed with lactose or other inert powders that are acceptable for intrabronchial use, and can be administered by, for example, an aerosol dispenser or a device that breaks or punctures a capsule encasing the solid composition and delivers the solid composition for inhalation. The aerosol composition can include, by way of illustration, one or more compounds of the present teachings, propellants, surfactants, and co-solvents, and can be administered by, for example, a metered

device. The propellants can be a chlorofluorocarbon (CFC), a hydrofluoroalkane (HFA), or other propellants that are physiologically and environmentally acceptable.

[00115] Compounds described herein can be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds or pharmaceutically acceptable salts, hydrates, or esters thereof can be prepared in water suitably mixed with a surfactant such as hydroxyl-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations typically contain a preservative to inhibit the growth of microorganisms.

[00116] The pharmaceutical forms suitable for injection can include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In preferred embodiments, the form is sterile and its viscosity permits it to flow through a syringe. The form preferably is stable under the conditions of manufacture and storage and can be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

[00117] Compounds described herein can be administered transdermally, i.e., administered across the surface of the body and the inner linings of bodily passages including epithelial and mucosal tissues. Such administration can be carried out using the compounds of the present teachings including pharmaceutically acceptable salts, hydrates, and esters thereof, in lotions, creams, foams, patches, suspensions, solutions, and suppositories (rectal and vaginal). Topical formulations that deliver active compound(s) through the epidermis can be useful for localized treatment of inflammation and arthritis.

[00118] Transdermal administration can be accomplished through the use of a transdermal patch containing an active compound and a carrier that can be inert to the active compound, can be non-toxic to the skin, and can allow delivery of the active compound for systemic absorption into the blood stream via the skin. The carrier can take any number of forms such as creams and ointments, pastes, gels, and occlusive

devices. The creams and ointments can be viscous liquid or semisolid emulsions of either the oil-in-water or water-in-oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active compound can also be suitable. A variety of occlusive devices can be used to release the active compound into the blood stream, such as a semi-permeable membrane covering a reservoir containing the active compound with or without a carrier, or a matrix containing the active compound. Other occlusive devices are known in the literature.

[00119] Compounds described herein can be administered rectally or vaginally in the form of a conventional suppository. Suppository formulations can be made from traditional materials, including cocoa butter, with or without the addition of waxes to alter the suppository's melting point, and glycerin. Water-soluble suppository bases, such as polyethylene glycols of various molecular weights, can also be used.

[00120] Lipid formulations or nanocapsules can be used to introduce compounds of the present teachings into host cells either *in vitro* or *in vivo*. Lipid formulations and nanocapsules can be prepared by methods known in the art.

[00121] To increase the effectiveness of compounds of the present teachings, it can be desirable to combine a compound with other agents effective in the treatment of the target disease. For inflammatory diseases, other active compounds (i.e., other active ingredients or agents) effective in their treatment, and particularly in the treatment of asthma and arthritis, can be administered with active compounds of the present teachings. The other agents can be administered at the same time or at different times than the compounds disclosed herein.

[00122] General experimental conditions:

[00123] Method A (abbreviated as [a] in experimental section): Prodigy ODS3, 0.46 x 15 cm column, 1.0 mL/min, 20min gradient of acetonitrile in water/trifluoroacetic acid.

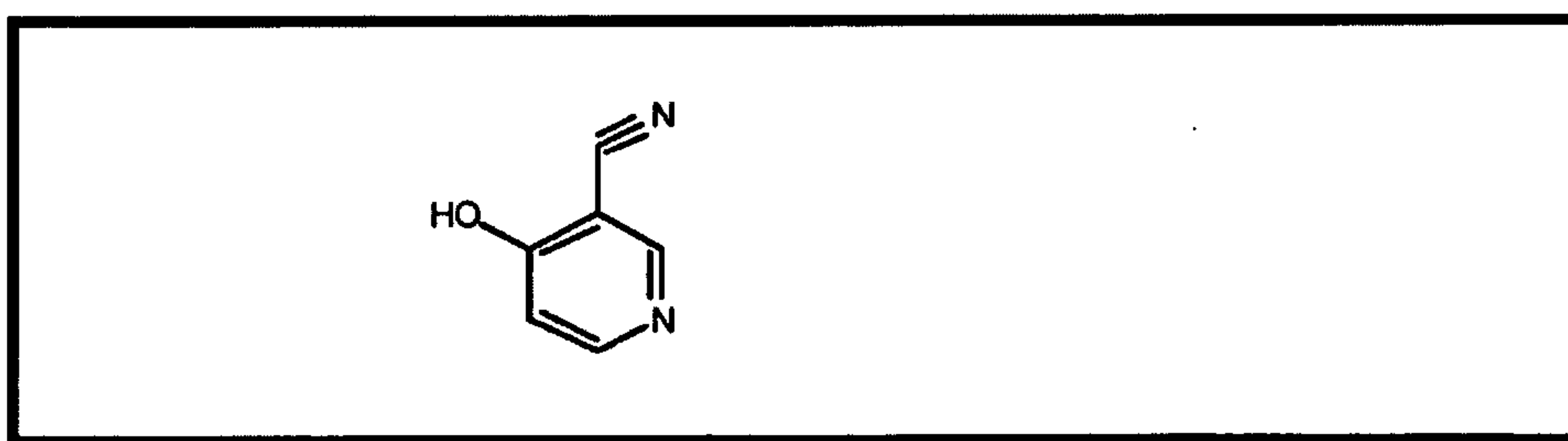
[00124] Method B (abbreviated as [b] in experimental section): Prodigy ODS3, 0.46 x 15 cm column, 1.0 mL/min, 20 min Gradient MeOH in H₂O/TFA.

[00125] Method C (abbreviated as [c] in experimental section): Prodigy ODS3, 0.46 x 15 cm column, 1.0 mL/min, 20 min Gradient ACN in ammonium hydroxide.

[00126] Method D (abbreviated as [d] in experimental section): Thermo Aquasil C18 50 X 2.1mm, 0.8 mL/min, 2.5 min gradient of acetonitrile in water/formic acid.

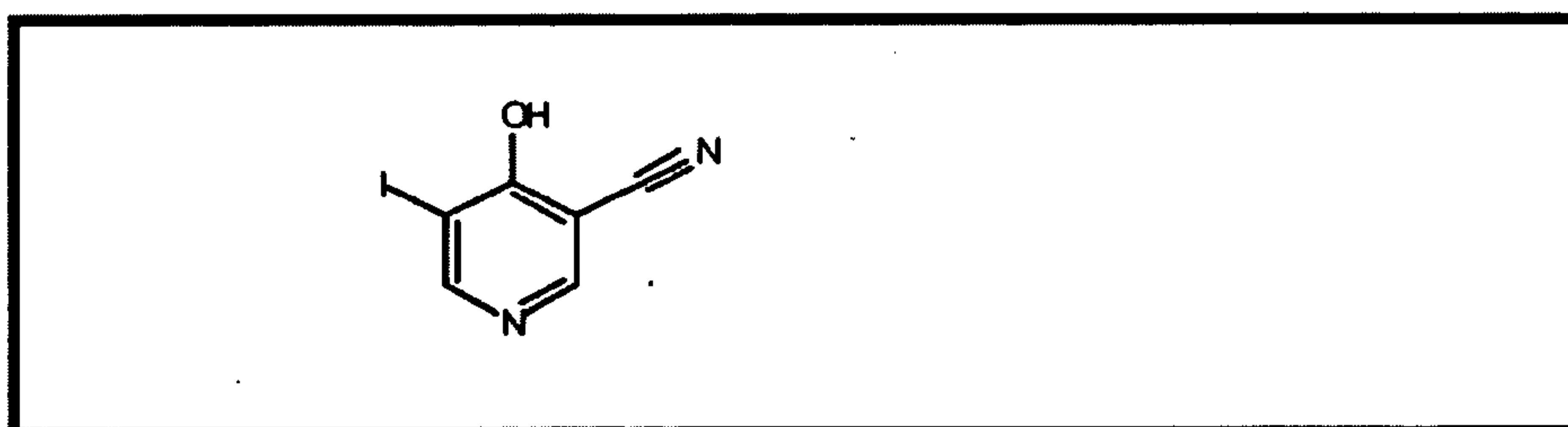
[00127] Method E (abbreviated as [e] in experimental section): Prodigy ODS3, 0.46 x 15 cm column, 1.0 mL/min, 10 min gradient of acetonitrile in water/trifluoroacetic acid.

[00128] The following examples are presented to illustrate certain embodiments of the present invention, but should not be construed as limiting the scope of this invention.

**[00129] Preparation of 4-hydroxynicotinonitrile:**

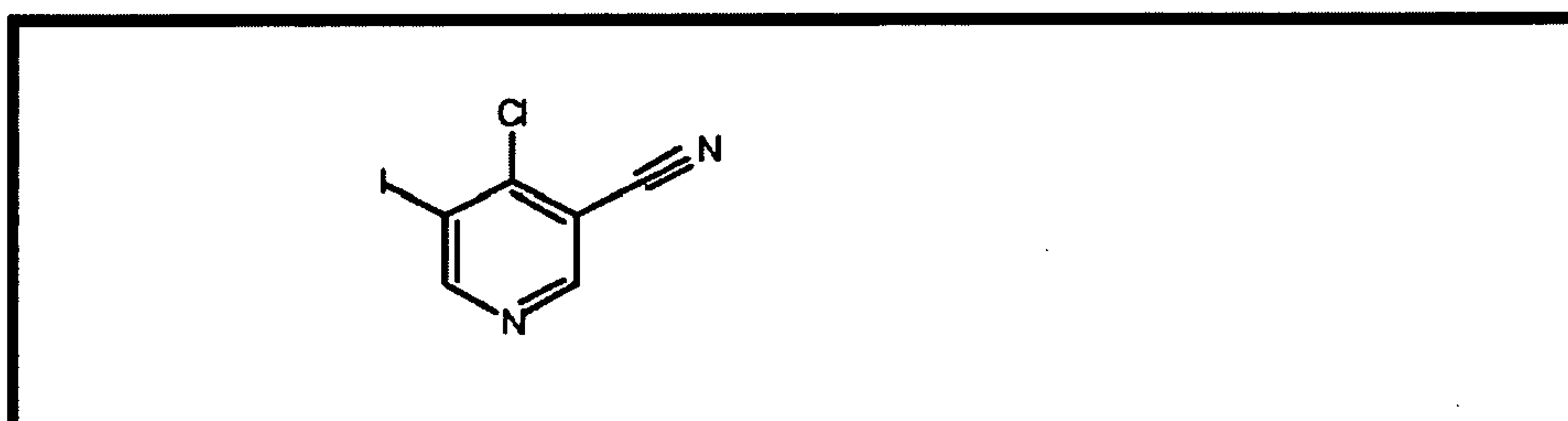
A mixture of acetoacetonitrile (41 g, 493 mmol), t-butoxybis(dimethyl amino)methane (86 g, 493 mmol) and DMF-DMA (263 mL, 1.97 mol) was heated at 100°C overnight and evaporated to remove the volatiles. The residue was triturated with hexanes/ether (1:1) and the solids were collected by filtration and washed with hexanes/ether (1:1) and a minimum amount of EtOAc to give 64.3 g (67%) of 5-(dimethylamino)-2-[(dimethylamino)methylene]-3-oxopent-4-enenitrile as a light yellow solid, which was used for the next step without further purification.

[00130] A mixture of 5-(dimethylamino)-2-[(dimethylamino)methylene]-3-oxopent-4-enenitrile (64.3 g, 333 mmol) and ammonium acetate (126 g, 1.66 mol) in EtOH (1.8 L) was heated at reflux for 60 h and concentrated to remove solvent. The resultant semi-solid residue was diluted with EtOAc, filtered and washed with EtOAc followed by CH₂Cl₂. The filtrate was evaporated to a reduced volume. The precipitated solids were collected by filtration, washed with EtOAc and a minimum amount of EtOH. The process of evaporation and crystallization was repeated to obtain more solid product from the mother liquor. The combined off-white solids provided 20.9 g of 4-hydroxynicotinonitrile (53%), m.p. 234-236°C.



[00131] Preparation of 4-hydroxy-5-iodonicotinonitrile:

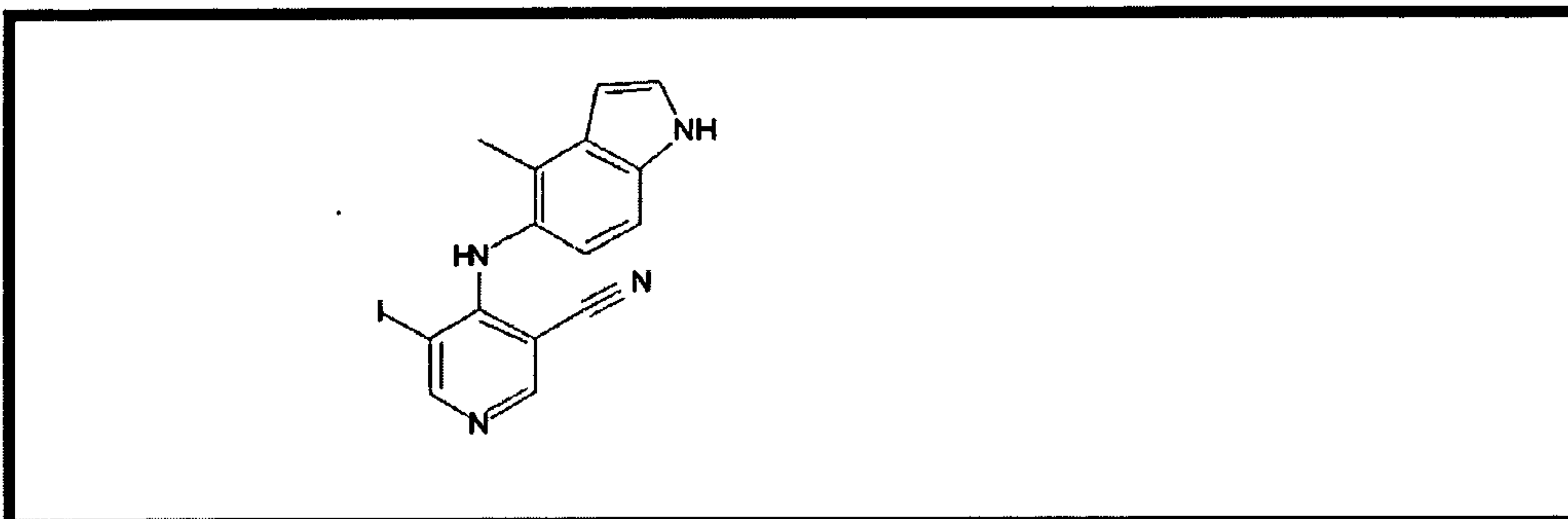
A mixture of 4-hydroxynicotinonitrile (45.7 g, 381 mmol), iodine (96.6 g, 381 mmol) and NaOH (19.8 g, 825 mmol) in water (600 mL) was heated at 85°C overnight, cooled to r.t. and diluted with water. The precipitate was collected by filtration and washed with water to give 57.5 g (61%) of 4-hydroxy-5-iodonicotinonitrile as a tan solid, mp >245°C.



[00132] Preparation of 4-chloro-5-iodonicotinonitrile:

A mixture of 4-hydroxy-5-iodonicotinonitrile (57.5 g, 234 mmol) and POCl₃ (200 mL) was heated at 100°C for 2 hours, cooled to room temperature and evaporated to remove excess POCl₃. The residue was cooled in an ice-water bath, adjusted to pH 8-9 with aqueous 10 N NaOH and extracted with ethyl acetate. The combined organics were washed with water and brine, dried over magnesium sulfate and concentrated. The resulting solid residue was

washed with a minimum amount of methanol and methylene chloride to give 46.5 g (75%) of 4-chloro-5-iodonicotinonitrile as a tan solid, mp 120-122°C.

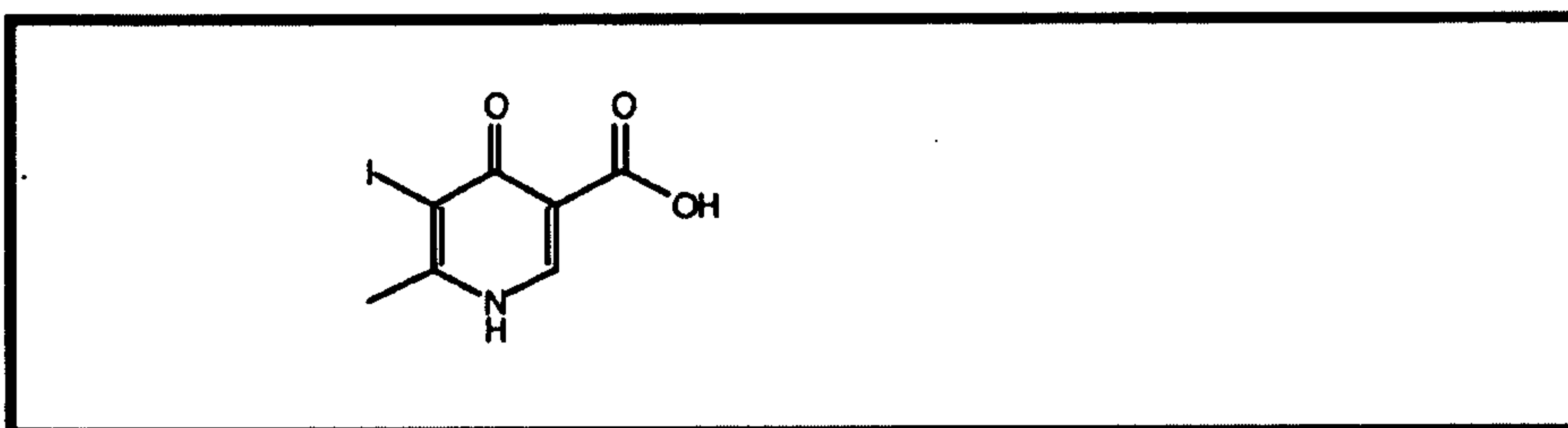


[00133] Preparation of 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

A mixture of 4-chloro-5-iodonicotinonitrile (5.0 g, 18.9 mmol) and 5-amino-4-methylindole (3.0 g, 20.8 mmol) in EtOH (100 mL) was heated at reflux for 3 days, cooled to r.t. and diluted with saturated aq. Na₂SO₄ (300 mL). The precipitated solids were collected by filtration, washed with water and dried to give 5.3 g (75%) of 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile as a grey solid. mp 192-194°C; MS (M+H⁺): 375.1.

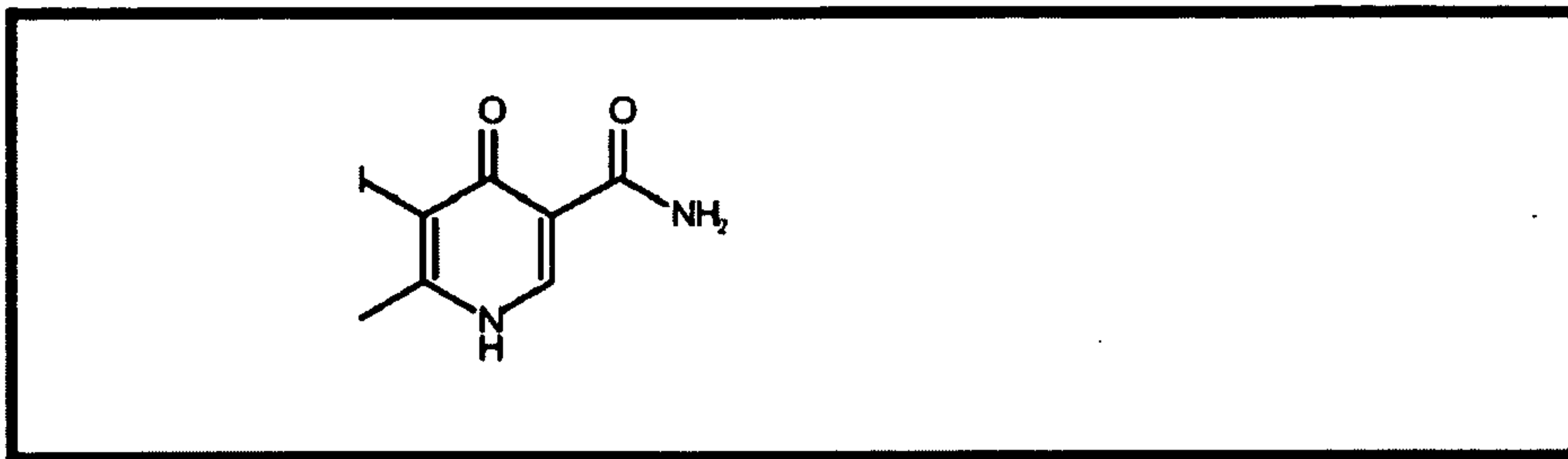
[00134] Preparation of 6-methyl-4(1H)-pyridone-3-carboxylic acid:

6-Methyl-4(1H)-pyridone-3-carboxylic acid was prepared from 4-hydroxy-6-methyl-2-pyrone according to the route in J. Org. Chem., (1972), 37, 1145.



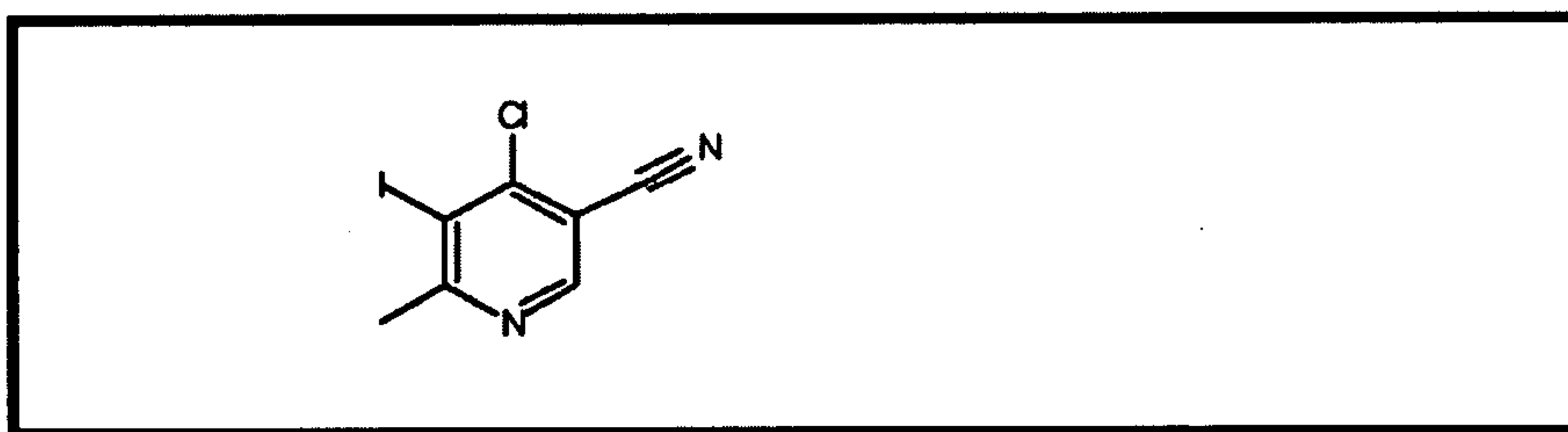
[00135] Preparation of 5-iodo-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid:

6-Methyl-4(1H)-pyridone-3-carboxylic acid was converted to 5-iodo-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid by the published route: see WO9948892 step a of Example 82.



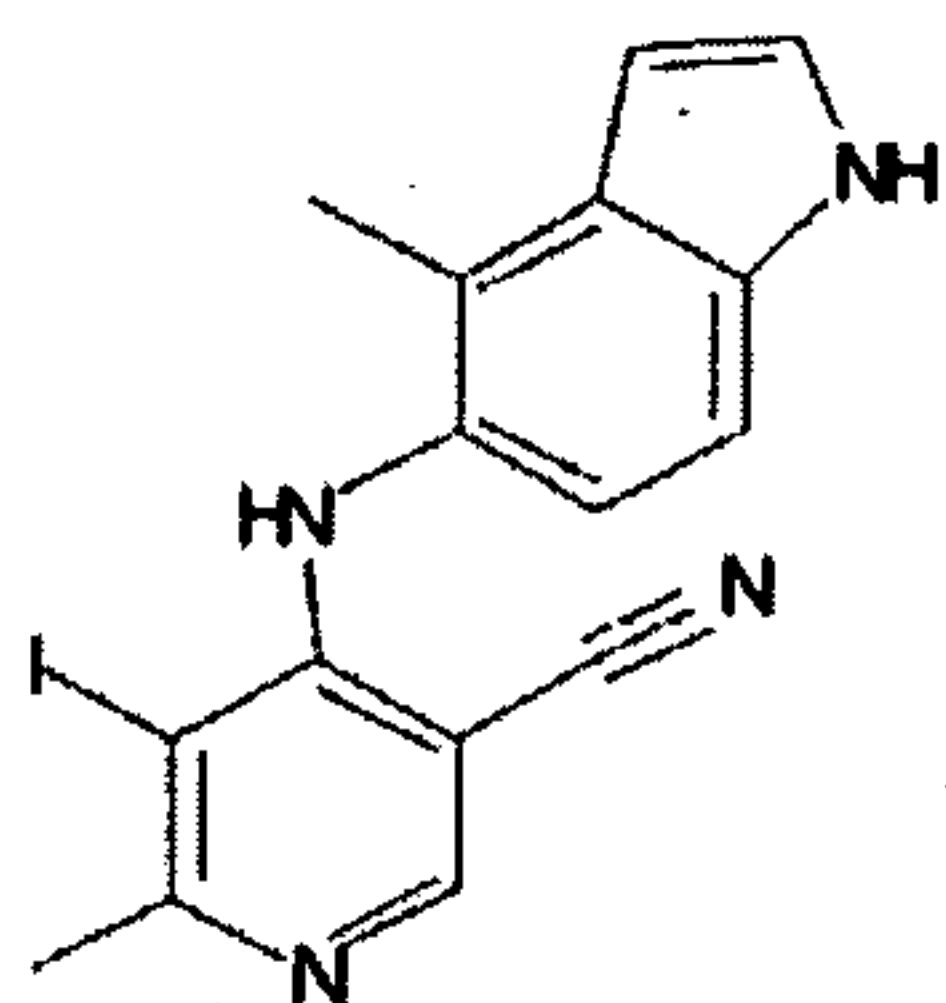
[00136] Preparation of 5-iodo-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxamide:

A mixture of 5-iodo-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (5.0 g, 17.9 mmol) and 1,1'-carbonyldiimidazole (CDI) (6.39 g, 39.4 mmol) in 60 mL of DMF was heated at 60-70°C for 3 h. The reaction mixture was cooled on an ice-bath and poured into cooled 29% aqueous ammonium hydroxide (84 mL). After stirring at 0-5°C for 3 h, the mixture was poured onto ice and the pH was adjusted to 5-6. The solids were collected by filtration, then washed with water followed by diethyl ether to provide 3.30 g (66%) of 5-iodo-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxamide as a white solid, mp 296-298°C; MS 277.1 (M-H)⁻.



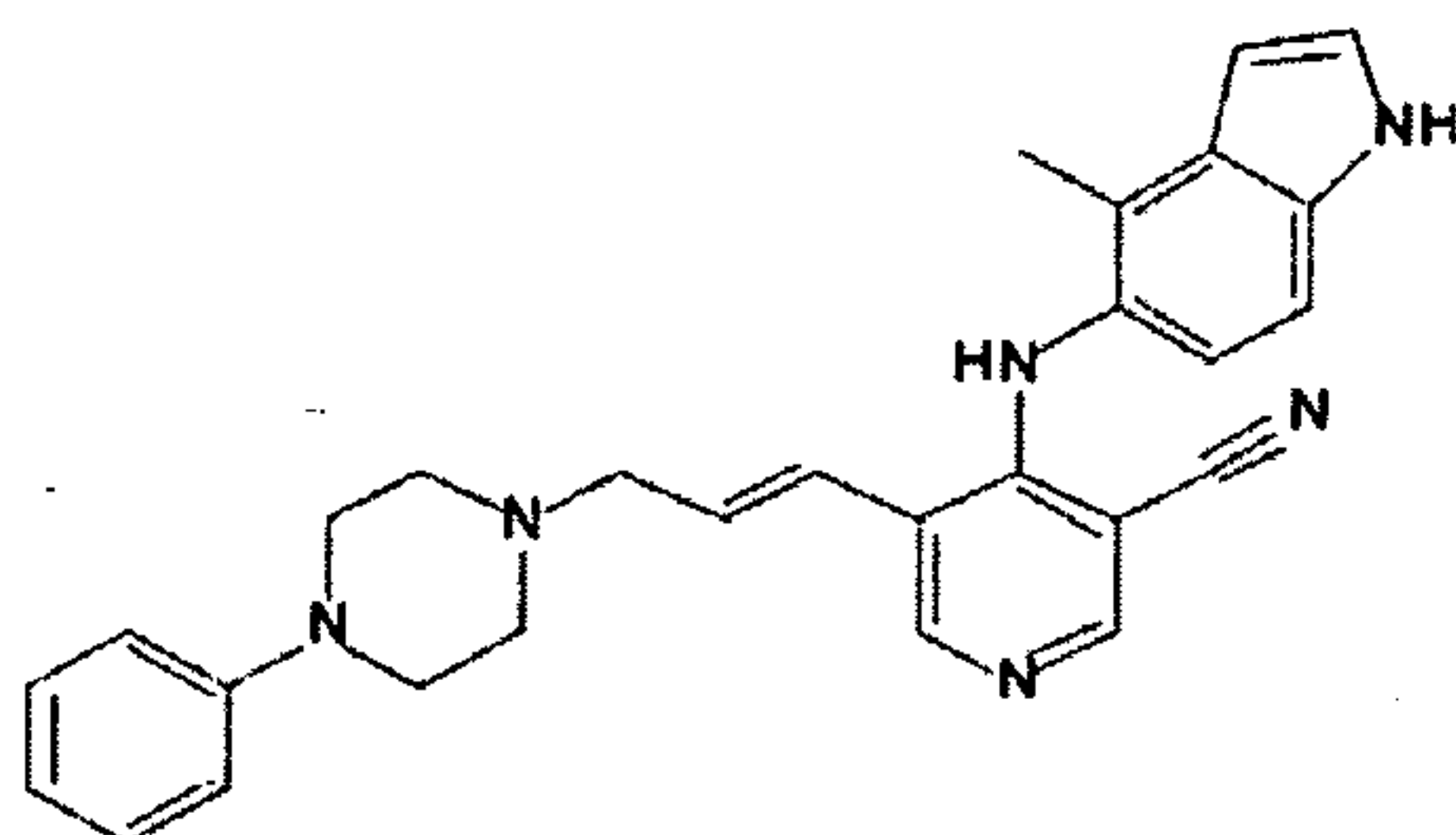
[00137] Preparation of 4-chloro-5-iodo-6-methylnicotinonitrile:

A mixture of 5-iodo-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxamide (3.0 g, 10.8 mmol) and phosphorus oxychloride (16.6 g, 108 mmol) was heated at 60-70°C for 30 min. The temperature was slowly increased to 90°C and a drop of DMF was added. Heating was continued for 2 h resulting in a dark brown solution. The volatiles were removed *in vacuo* and the residue was slurried with ice. Aqueous sodium bicarbonate was slowly added. The solids were collected by filtration, washing with aqueous sodium bicarbonate and water to provide 2.85 g (95%) of 4-chloro-5-iodo-6-methylnicotinonitrile as a light yellow solid, mp 120-122°C; MS 279.1 (M+H).



[00138] Preparation of 5-iodo-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

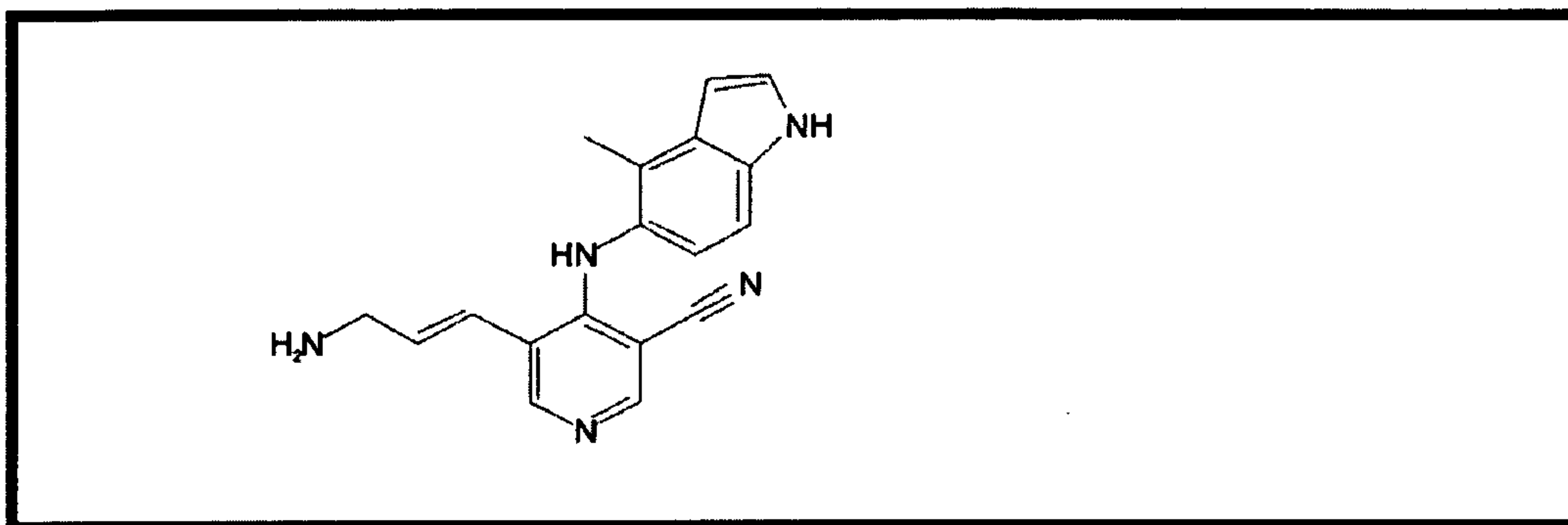
5-iodo-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxamide (4.0 g, 14.4 mmol) and 5-amino-4-methylindole (2.7 g, 18.7 mmol) were heated to a vigorous reflux in 100 mL EtOH. After heating for 4 days, the reaction was cooled and the grey solid was filtered to give 3.4 g of 5-iodo-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile, mp 222-223°C; MS 389.2 (M+H).



[00139] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-3-(4-phenylpiperazin-1-yl)prop-1-en-1-yl]nicotinonitrile:

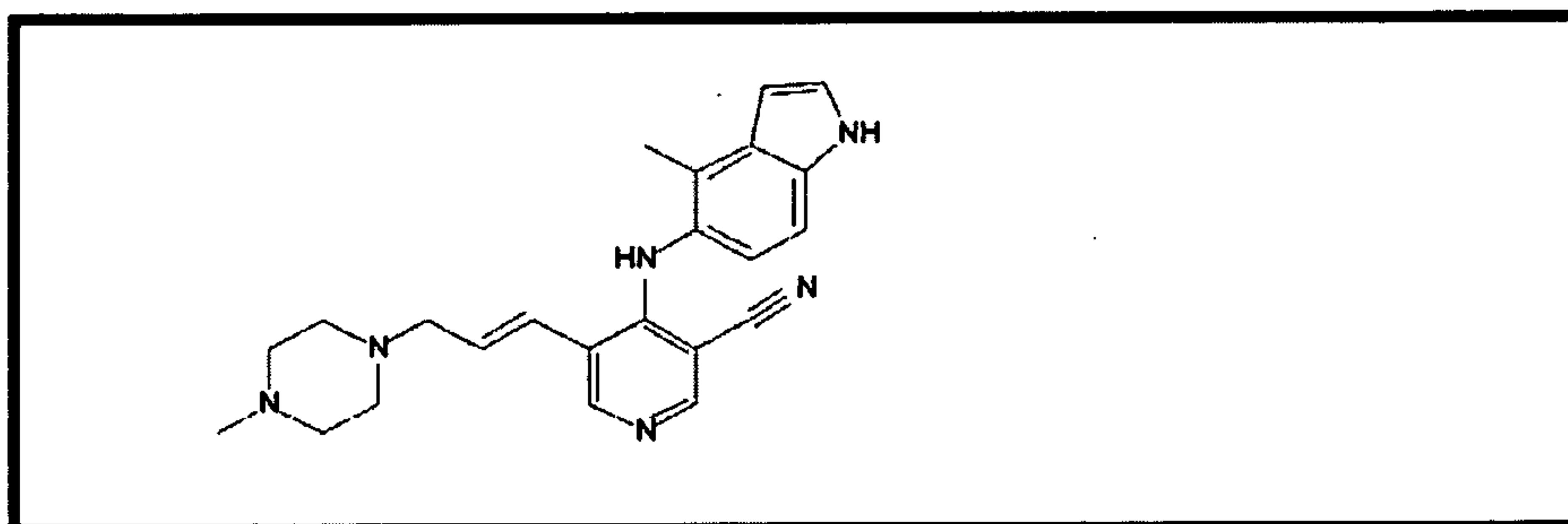
A mixture of 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (90 mg, 0.24 mmol), 1-phenylpiperazine (117 mg, 0.72 mmol), trans-2-chloromethylvinylboronic acid (58 mg, 0.48 mmol), cesium carbonate (157 mg, 0.48 mmol) and Pd(PPh₃)₂Cl₂ (8.4 mg, 0.012 mmol) in 3 mL of DMSO was heated at 90°C for 16 h, cooled to room temperature, diluted with water and extracted into EtOAc. The organic layer was washed with water and the crude material was purified by silica gel chromatography, eluting with MeOH/ DCM to give 4-[(4-methyl-1H-indol-

5-yl)amino]-5-[(1E)-3-(4-phenylpiperazin-1-yl)prop-1-en-1-yl]nicotinonitrile as a solid; MS 449.4 (M+H); HPLC: rt = 6.4 min [a].



[00140] Preparation of 5-[(1E)-3-aminoprop-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

A mixture of 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (100 mg, 0.27 mmol), 7N ammonia in MeOH (2.7 mmol), trans-2-chloromethylvinylboronic acid (62 mg, 0.53 mmol), cesium carbonate (173 mg, 0.53 mmol) and Pd(PPh₃)₂Cl₂ (9.4 mg, 0.014 mmol) in 2 mL of DMSO was heated at 75° for 16 h, cooled to room temperature, diluted with EtOAc and washed with water. The organic extracts were concentrated and the crude product was purified by silica gel chromatography with a MeOH / DCM / EtOAc gradient to give 5-[(1E)-3-aminoprop-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile. The HCl salt of 5-[(1E)-3-aminoprop-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile was made by treatment with HCl/dioxane; MS 304.2 (M+H); HPLC: rt = 2.8 min [c].



[00141] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-3-(4-methylpiperazin-1-yl)prop-1-en-1-yl]nicotinonitrile:

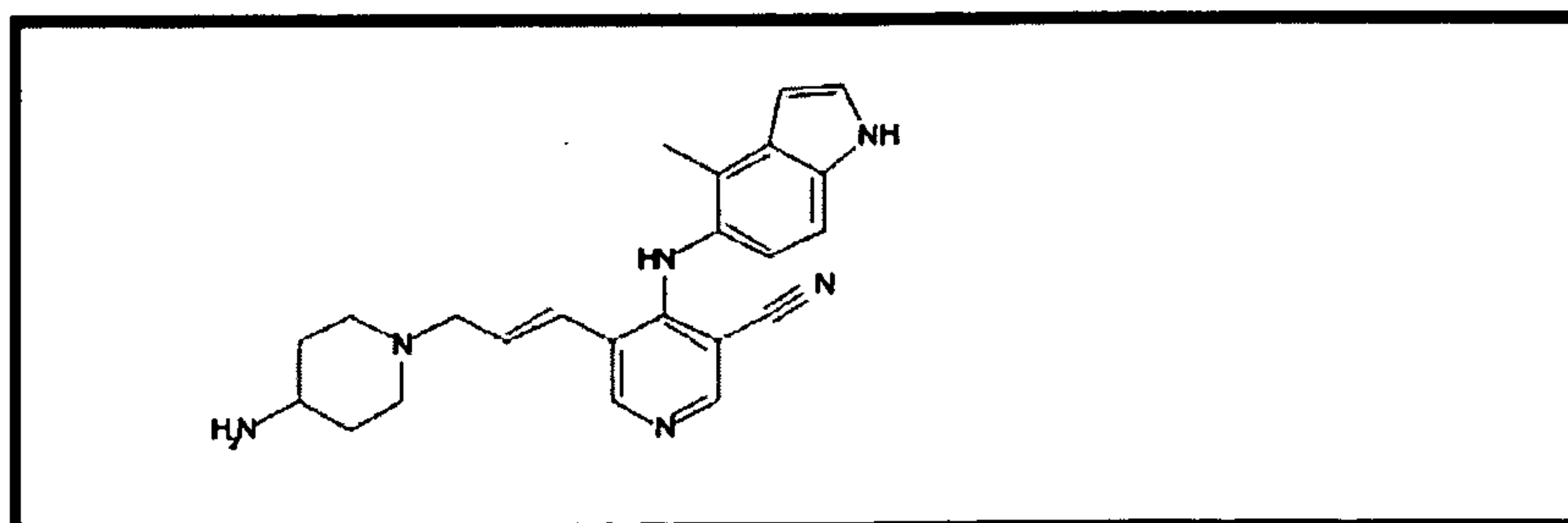
A mixture of 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (100 mg, 0.27 mmol), 1-methylpiperazine (80 mg, 0.80 mmol), trans-2-chloromethylvinylboronic acid (64 mg, 0.53 mmol), cesium carbonate (173 mg, 0.53 mmol) and Pd(PPh₃)₂Cl₂ (9.5 mg, 0.014 mmol) in 3 mL of DMSO was heated at 90°C for 16 h, cooled to room temperature, and filtered. The filtrate was concentrated and purified by HPLC to give 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-3-(4-methylpiperazin-1-yl)prop-1-en-1-yl]nicotinonitrile. The HCl salt of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-3-(4-methylpiperazin-1-yl)prop-1-en-1-yl]nicotinonitrile was made by treatment with HCl/ dioxane; MS 387.3 (M+H); HPLC: rt = 7.4 min [b].

[00142] Preparation of compounds in Table 1:

Compounds were prepared from 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile, the corresponding amine and trans-2-chloromethylvinylboronic acid via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-3-(4-methylpiperazin-1-yl)prop-1-en-1-yl]nicotinonitrile.

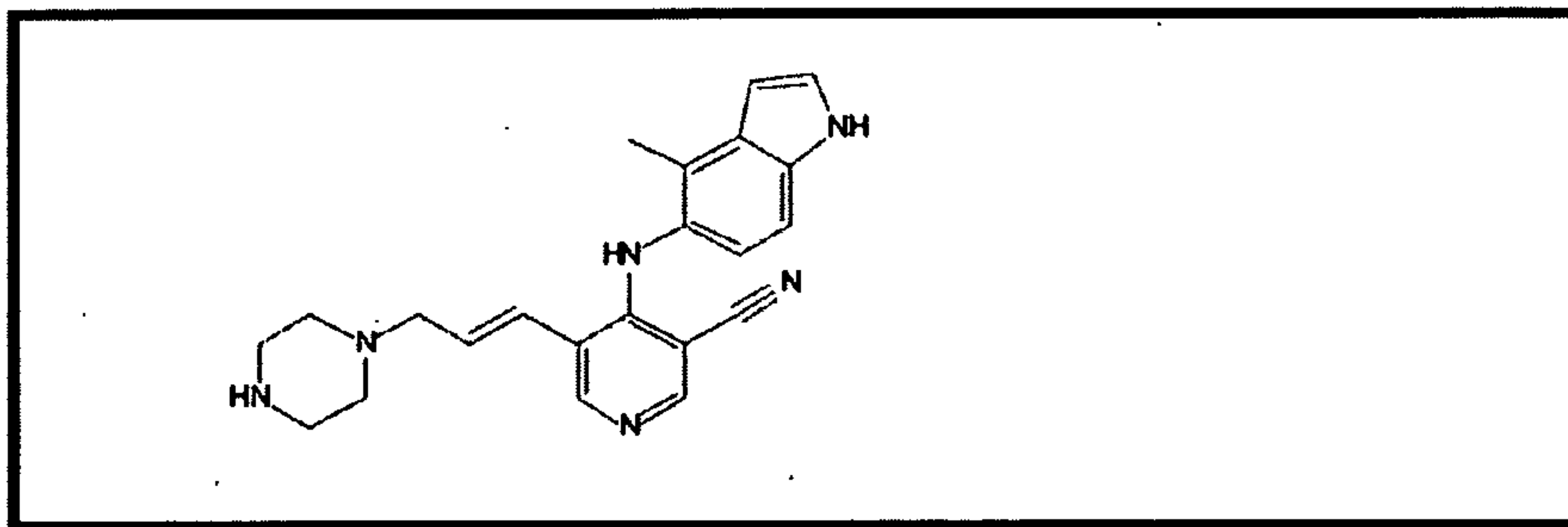
Table 1

Name	MS (M+H)	HPLC rt
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-3-morpholin-4-ylprop-1-en-1-yl]nicotinonitrile	374.3	4.1 min[a]
5-[(1E)-3-(3,4-dihydroisoquinolin-2(1H)-yl)prop-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	420.4	6.1 min[a]
tert-butyl {1-[(2E)-3-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-yl}prop-2-en-1-yl]piperidin-4-yl}carbamate	487.5	6.6 min[a]
tert-butyl 4-[(2E)-3-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-yl}prop-2-en-1-yl]piperazine-1-carboxylate	473.4	6.6 min[a]
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-3-piperidin-1-ylprop-1-en-1-yl]nicotinonitrile	372.4	4.8 min[a]



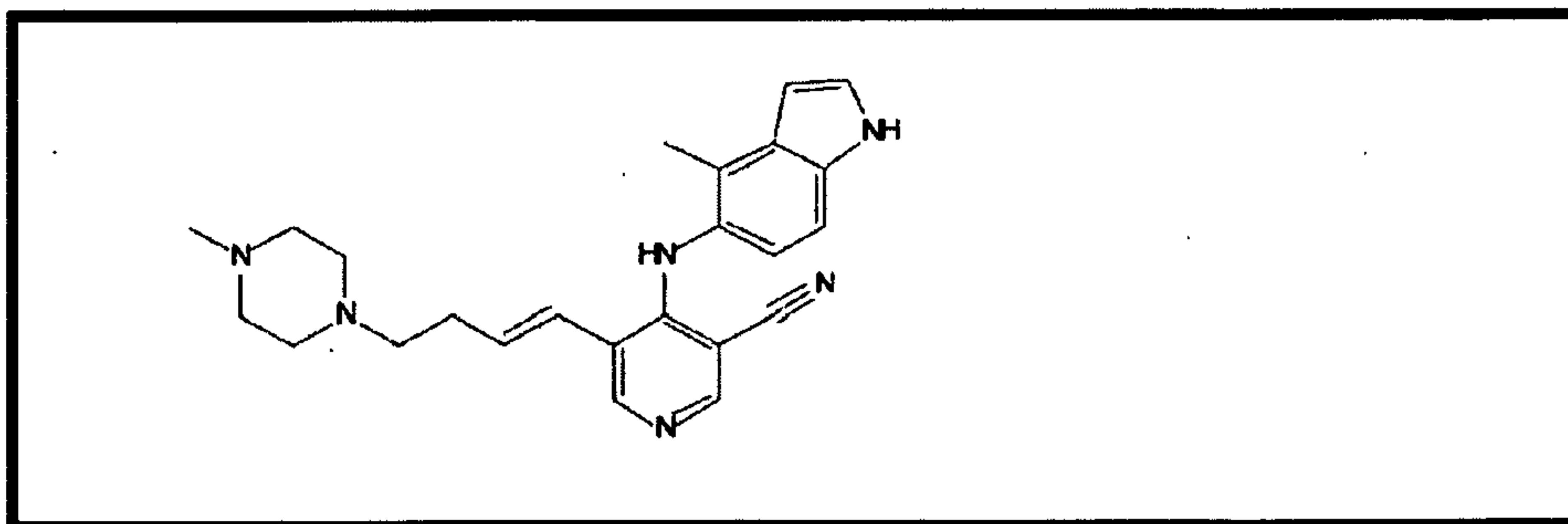
[00143] Preparation of 5-[(1E)-3-(4-aminopiperidin-1-yl)prop-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

A solution of tert-butyl{1-[(2E)-3-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-yl}prop-2-en-1-yl]piperidin-4-yl}carbamate (64 mg, 0.13 mmol) in 10% trifluoroacetic acid/ DCM was stirred for 1 h at room temperature. The reaction was quenched with NaOH until the reaction solution was neutral pH. The product was extracted into DCM/ MeOH. The extracts were concentrated and the crude product was purified by silica gel chromatography using a DCM/ MeOH gradient to give 5-[(1E)-3-(4-aminopiperidin-1-yl)prop-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)aminol]nicotinonitrile; MS 387.3 (M+H); HPLC: rt = 2.9 min[a].



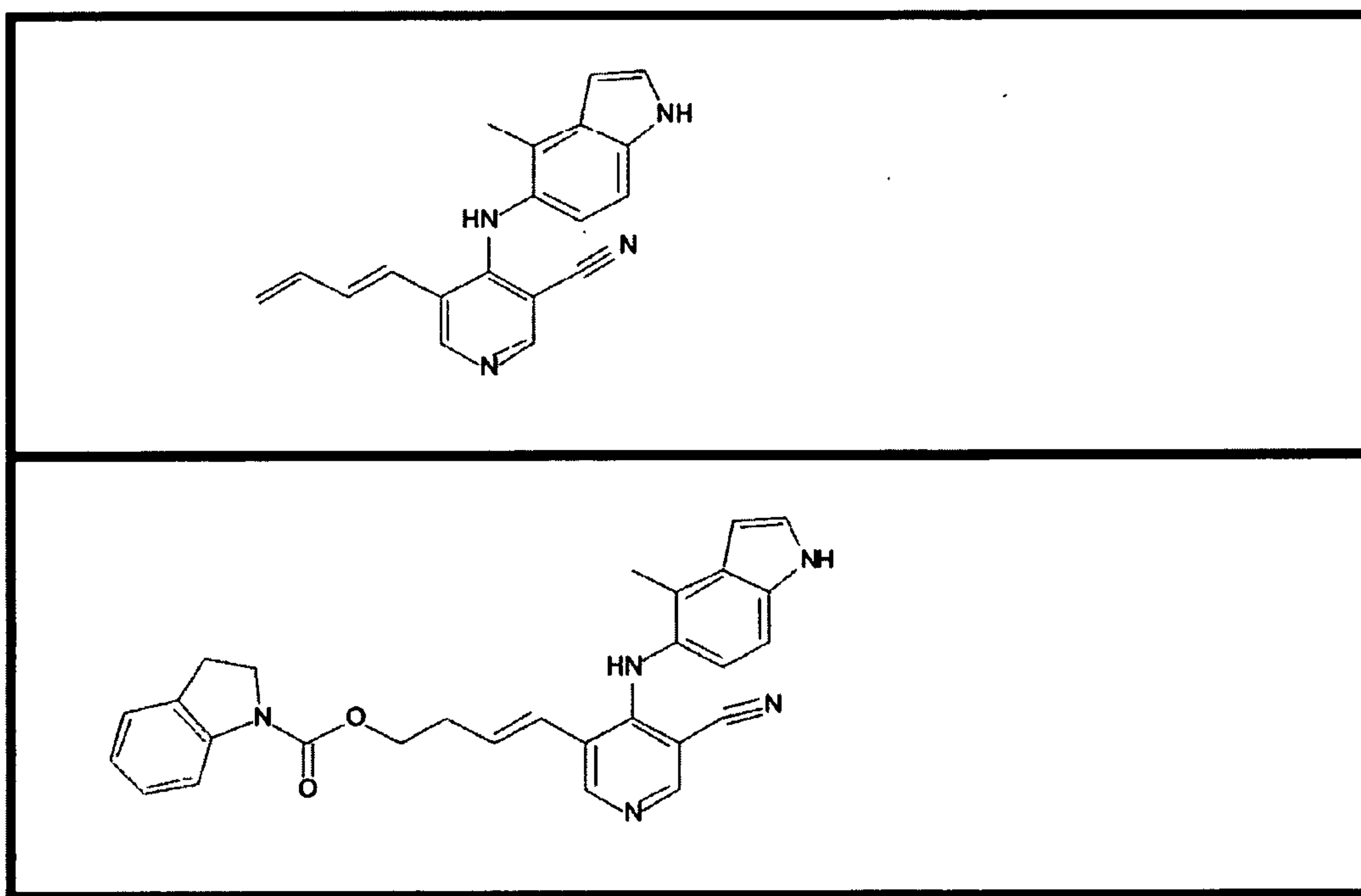
[00144] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-3-piperazin-1-ylprop-1-en-1-yl]nicotinonitrile:

4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-3-piperazin-1-ylprop-1-en-1-yl]nicotinonitrile was prepared from tert-butyl 4-[(2E)-3-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-yl}prop-2-en-1-yl]piperazine-1-carboxylate via the route used to prepare 5-[(1E)-3-(4-aminopiperidin-1-yl)prop-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)aminol]nicotinonitrile; MS 373.3 (M+H); HPLC: rt = 3.7 min[a].



[00145] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-3-(4-methylpiperazin-1-yl)but-1-en-1-yl]nicotinonitrile:

A mixture of 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (100 mg, 0.27 mmol), 1-methylpiperazine (80 mg, 0.80 mmol), (E)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-enyl 4-methylbenzenesulfonate (187 mg, 0.53 mmol), cesium carbonate (173 mg, 0.53 mmol) and Pd(PPh₃)₄ (16 mg, 0.014 mmol) in 3 mL of DMSO was heated at 70° for 16 h, cooled to room temperature, and filtered. The filtrate was concentrated and purified by HPLC to give 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-3-(4-methylpiperazin-1-yl)but-1-en-1-yl]nicotinonitrile. The HCl salt of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-3-(4-methylpiperazin-1-yl)but-1-en-1-yl]nicotinonitrile was generated by addition of HCl/ dioxane; MS 401.4 (M+H); HPLC: rt = 5.1 min[b].



[00146] Preparation of 5-[(1E)-buta-1,3-dien-yl]-4-[(4-methyl-1H-indol-5-yl)amino] nicotinonitrile and (3E)-4-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino] pyridine-3-yl}but-3-en-1-yl indoline-1-carboxylate:

A mixture of 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (100 mg, 0.27 mmol), indoline (95 mg, 0.80 mmol), (E)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-enyl 4-

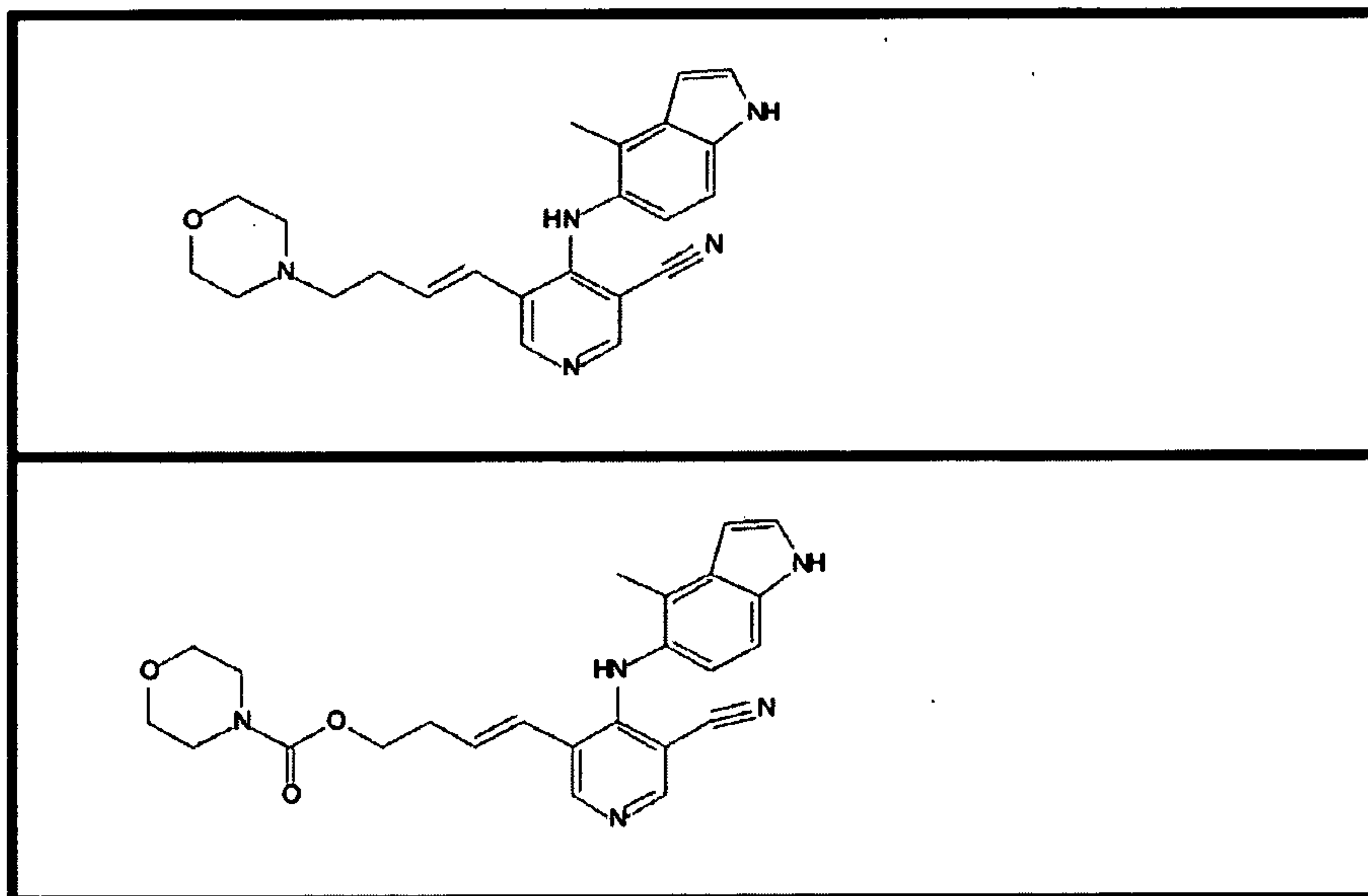
methylbenzenesulfonate (187 mg, 0.53 mmol), cesium carbonate (173 mg, 0.53 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (16 mg, 0.014 mmol) in 3 mL of DMSO was heated at 70° for 16 h, cooled to room temperature, diluted with EtOAc and washed with water. The crude material was purified by silica gel chromatography with an EtOAc/ hexane gradient to give 5-[(1E)-buta-1,3-dienyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and (3E)-4-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl indoline-1-carboxylate. The HCl salt of (3E)-4-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl indoline-1-carboxylate was generated by addition of HCl/ dioxane.

[00147] 5-[(1E)-buta-1,3-dienyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

MS 301.2 (M+H); HPLC: t_r = 7.9 min[a]

[00148] (3E)-4-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl indoline-1-carboxylate (HCl salt):

MS 464.3 (M+H); HPLC: t_r = 10.4 min.[a].



[00149] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-4-morpholin-4-ylbut-1-en-1-yl]nicotinonitrile and (3E)-4-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-yl}but-3-en-1-yl morpholine-4-carboxylate:

A mixture of 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (150 mg, 0.40 mmol), morpholine (104 mg, 1.2 mmol), (E)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-enyl 4-methylbenzenesulfonate (281 mg, 0.80 mmol), cesium carbonate (261 mg, 0.80 mmol) and Pd(PPh₃)₄ (23 mg, 0.02 mmol) in 4 mL of DMSO was heated at 70° for 16 h, cooled to room temperature, diluted with EtOAc and washed with water. The crude extracts were purified by silica gel chromatography with a MeOH/ DCM gradient to give (3E)-4-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl morpholine-4-carboxylate and 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-4-morpholin-4-ylbut-1-en-1-yl]nicotinonitrile. The HCl salt of both products were generated using HCl/ dioxane:

[00150] 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-4-morpholin-4-ylbut-1-en-1-yl]nicotinonitrile:

MS 386.2 (M-H); HPLC: rt = 5.4 min [b]

[00151] (3E)-4-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl morpholine-4-carboxylate:

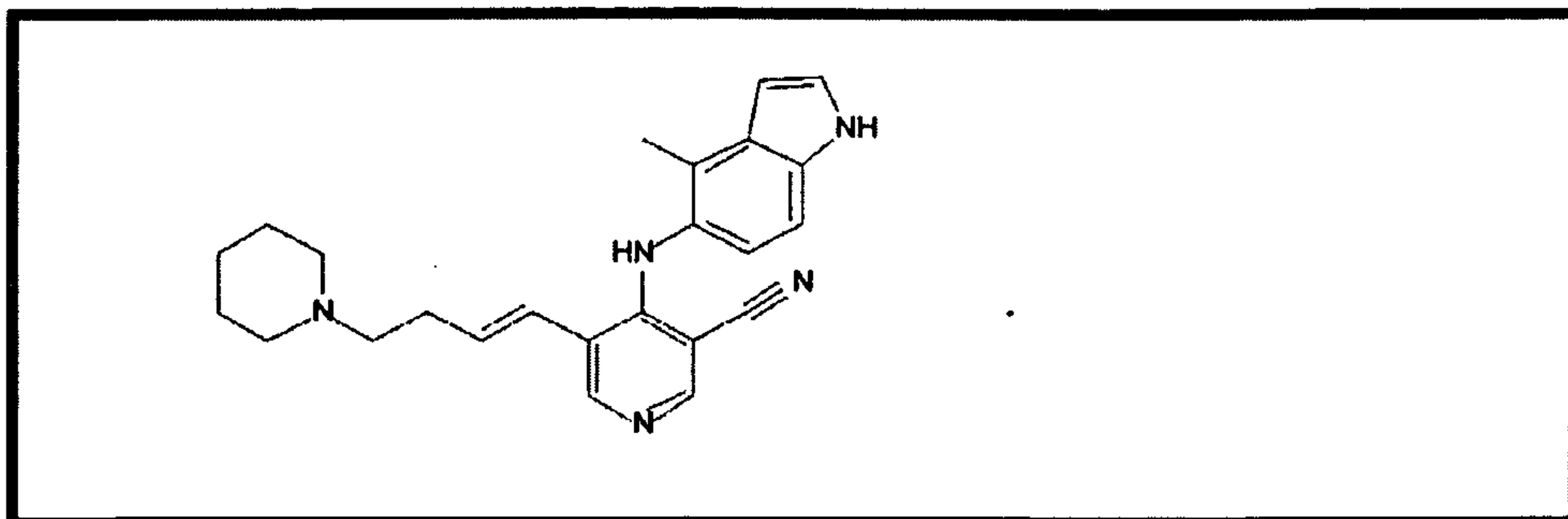
MS 432.2 (M+H); HPLC: rt = 7.8 min [a]

[00152] Preparation of compounds in Table 2:

These compounds were prepared from 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile, the corresponding amine and (E)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-enyl 4-methylbenzenesulfonate via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-4-morpholin-4-ylbut-1-en-1-yl]nicotinonitrile.

[00153] Table 2:

Name	MS (M+H)	HPLC rt
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-4-(4-phenyl piperazine-1-yl)but-1-en-1-yl]nicotinonitrile	463.4	6.9 min[a]
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-4-pyrrolidin-1-yl]but-1-en-1-yl]nicotinonitrile	372.3	4.8 min[a]
(3E)-4-{5cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl]thiomorpholine-4-carboxylate 1,1-dioxide	480.3	7.6 min[a]



[00154] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-4-piperidin-1-ylbut-1-en-1-yl]nicotinonitrile:

A mixture of piperidine (104 mg, 1.2 mmol) and (E)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-enyl 4-methylbenzenesulfonate (200 mg, 0.57 mmol) in 2 mL of DMSO was stirred for 16 h at room temperature. 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (108 mg, 0.29 mmol), cesium carbonate (186 mg, 0.57 mmol) and Pd(PPh₃)₄ (17 mg, 0.015 mmol) were added to the same pot. After heating the reaction to 70° for 16 h, the reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated and purified by HPLC to give 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-4-piperidin-1-ylbut-1-en-1-yl]nicotinonitrile as its TFA salt; MS 386.4 (M+H); HPLC rt = 4.8 min[a].

[00155] Preparation of compounds in Table 3:

The compounds in Table 3 were prepared from 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile, the corresponding amine and (E)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-enyl 4-methylbenzenesulfonate via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-4-piperidin-1-ylbut-1-en-1-yl]nicotinonitrile.

[00156] Table 3:

Name	MS (M+H)	HPLC rt
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-4-thiomorpholin-4-ylbut-1-en-1-yl]nicotinonitrile	404.2	4.8 min[a]
5-[(1E)-4-(4-acetylpiperazin-1-yl)but-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	429.4	4.2 min[a]
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-4-[4-(methylsulfonyl)piperazin-1-yl]but-1-en-1-yl]nicotinonitrile	465.4	4.8 min[a]

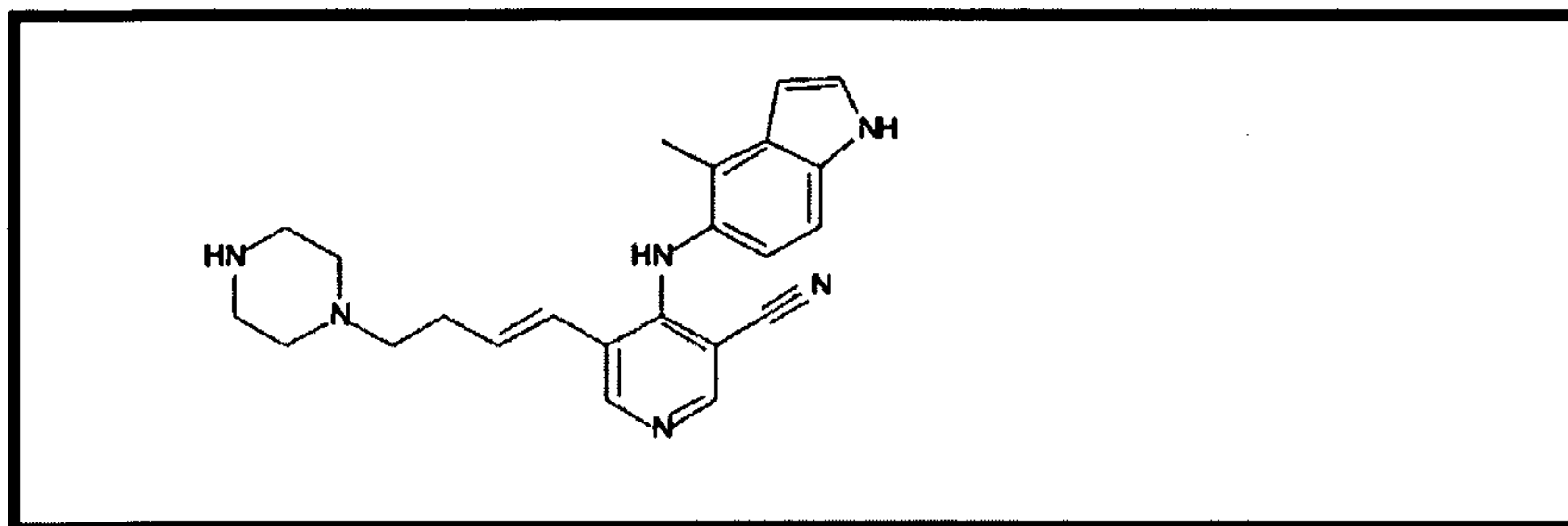
Name	MS (M+H)	HPLC rt
tert-butyl-4-[(3E)-4-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl]piperazine-1-carboxylate	487.4	6.6 min[a]
tert-butyl-{1-[(3E)-4-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl]piperidin-4-yl}carbamate	501.4	6.6 min[a]
5-[(1E)-4-aminobut-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	318.3	5.2 min[b]
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-4-[(2-morpholin-4-ylethyl)amino]but-1-en-1-yl]nicotinonitrile	431.4	3.9 min[a]
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-3-[(2-morpholin-4-ylethyl)amino]prop-1-en-1-yl]nicotinonitrile	417.2	1.22 min[d]
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-4-(4-phenylpiperidin-1-yl)but-1-en-1-yl]nicotinonitrile	462.3	1.56 min[d]
5-[(1E)-4-[4-(dimethylamino)piperidin-1-yl]but-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	429.3	1.09 min[d]
5-[(1E)-4-(4-hydroxypiperidin-1-yl)but-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	402.2	1.25 min[d]
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-4-(4-morpholin-4-ylpiperidin-1-yl)but-1-en-1-yl]nicotinonitrile	471.3	1.12 min[d]
5-[(1E)-4-(isopropylamino)but-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	360.4	4.9 min[a]
5-[(1E)-4-(cyclohexylamino)but-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	400.4	6.0 min[a]
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-4-(piperidin-4-ylamino)but-1-en-1-yl]nicotinonitrile	401.4	2.3 min[a]
5-[(1E)-4-(2,5-diazabicyclo[2.2.1]hept-2-yl)but-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	399.2	2.24 min[d]
5-[(1E)-4-(dimethylamino)but-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	346.4	7.4 min[b]
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-4-[(1-methylpiperidin-4-yl)amino]but-1-en-1-yl]nicotinonitrile	415.5	3.3 min[a]
5-[(1E)-4-(4-hydroxy-4-phenylpiperidin-1-yl)but-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	478.5	8.3 min[a]
5-[(1E)-4-[(trans-4-hydroxycyclohexyl)amino]but-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	416.4	6.0 min[a]
5-[(1E)-4-[4-(hydroxymethyl)piperidin-1-yl]but-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	416.3	4.1 min[a]
5-[(1E)-4-[(3R)-3-hydroxypyrrolidin-1-yl]but-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	388.3	3.8 min[a]
5-[(1E)-4-[(3S)-3-hydroxypyrrolidin-1-yl]but-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	388.3	3.8 min[a]
5-[(1E)-4-(4-methoxypiperidin-1-yl)but-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	416.3	4.8 min[a]
5-[(1E)-4-[(3R)-3-hydroxypiperidin-1-yl]but-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	402.2	1.33 min[d]
5-[(1E)-4-[(3S)-3-hydroxypiperidin-1-yl]but-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	402.2	1.33 min[d]
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-4-(3-oxopiperazin-1-yl)but-1-en-1-yl]nicotinonitrile	401.2	7.7 min[b]
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-4-[4-(pyrrolidin-1-ylcarbonyl)piperidin-1-yl]but-1-en-1-yl]nicotinonitrile	483.5	5.5 min [a]

[00157] Preparation of compounds in Table 4:

The appropriate boc-protected amine (0.53 mmol) and (E)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-enyl 4-methylbenzenesulfonate (186 mg, 0.53 mmol) were stirred in 1 mL of DMSO for 16 h at room temperature. 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (100 mg, 0.27 mmol), cesium carbonate (173 mg, 0.53 mmol) and Pd(PPh₃)₄ (16 mg, 0.014 mmol) were added to the same pot and heated at 70°C for 16 h. The reaction mixture was cooled to room temperature, diluted with EtOAc and washed with water to give the corresponding Boc protected intermediate. The crude organic extracts were concentrated and treated with 10% trifluoroacetic acid/ DCM for 2 hr at room temperature. Concentration and purification by HPLC gave the desired product as its TFA salt.

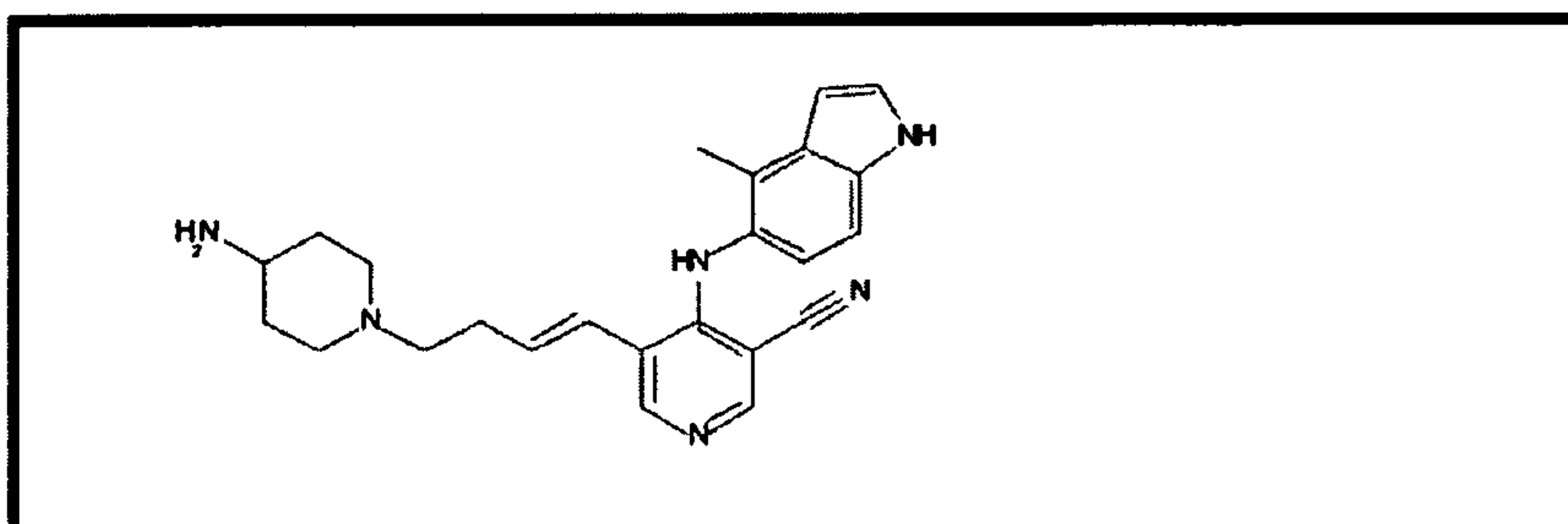
[00158] Table 4:

Amine	Name	MS (M+H)	HPLC rt
(R)-tert-butyl pyrrolidin-3-ylcarbamate	5-[(1E)-4-[(3R)-3-aminopyrrolidin-1-yl]but-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	387.2	1.04 min[d]
(R)-tert-butyl pyrrolidin-3-ylcarbamate	(3E)-4-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl (3R)-3-aminopyrrolidine-1-carboxylate	431.2	1.37 min[d]
(S)-tert-butyl pyrrolidin-3-ylcarbamate	5-[(1E)-4-[(3S)-3-aminopyrrolidin-1-yl]but-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	387.2	1.05 min[d]
tert-butyl azetidin-3-yl carbamate	5-[(1E)-4-(3-aminoazetidin-1-yl)but-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	373.3	1.25 min[d]
tert-butyl 1,4-diazepane-1-carboxylate	5-[(1E)-4-(1,4-diazepan-1-yl)but-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	401.2	1.06 min[d]
tert-butyl methyl(piperidin-4-yl)carbamate	5-[(1E)-4-[4-(methylamino)piperidin-1-yl]but-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	415.3	1.08 min[d]
(R) tert-butyl piperidin-3-ylcarbamate	5-[(1E)-4-[(3R)-3-aminopiperidin-1-yl]but-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	401.2	1.26 min[d]
(S) tert-butyl piperidin-3-ylcarbamate	5-[(1E)-4-[(3S)-3-aminopiperidin-1-yl]but-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	401.2	2.24 min[d]
tert-butyl piperidin-4-ylmethylcarbamate	5-[(1E)-4-[4-(aminomethyl)piperidin-1-yl]but-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	415.3	1.09 min[d]



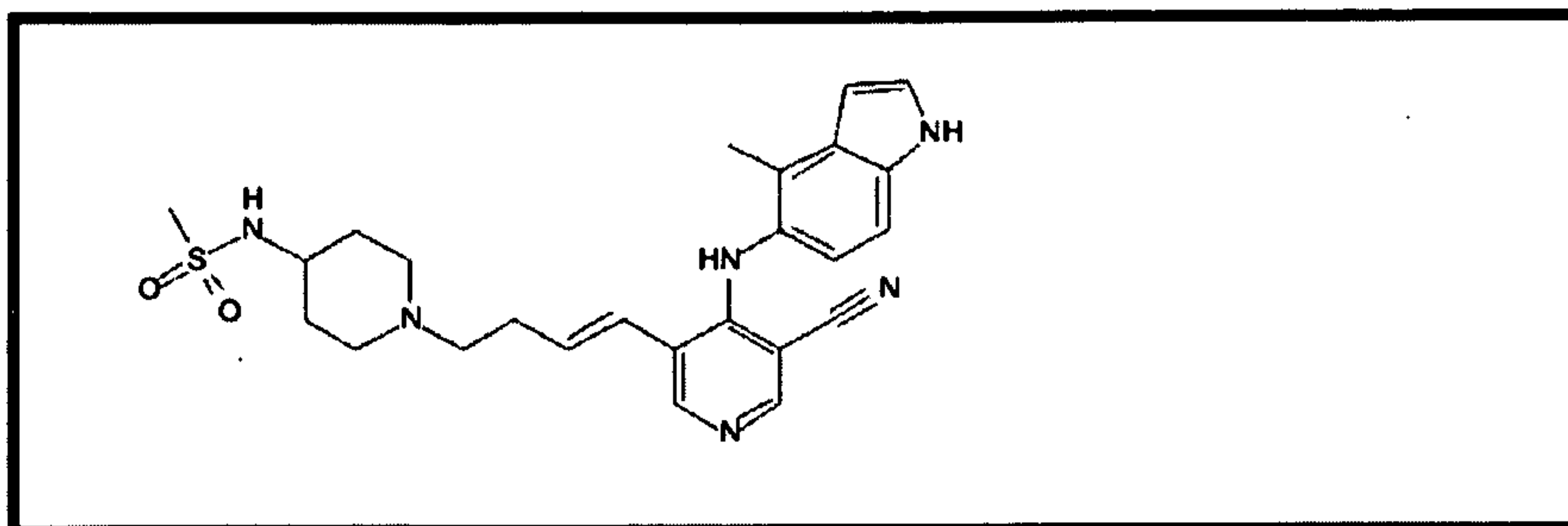
[00159] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-4-piperazin-1-ylbut-1-en-1-yl]nicotinonitrile:

A solution of tert-butyl 4-[(3E)-4-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]-pyridin-3-yl}-but-3-en-1-yl]piperazine-1-carboxylate (54 mg, 0.11 mmol) in 10% trifluoroacetic acid/ DCM was stirred for 1 h at room temperature. The reaction mixture was concentrated and purified by HPLC to give 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-4-piperazin-1-ylbut-1-en-1-yl]nicotinonitrile as its TFA salt; HRMS 387.2 (M+H); HPLC rt = 2.8 min[a].



[00160] Preparation of 5-[(1E)-4-(4-aminopiperidin-1-yl)but-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

Tert-butyl-{1-[(3E)-4-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]-pyridin-3-yl}-but-3-en-1-yl]piperidin-4-yl}carbamate was used to prepare 5-[(1E)-4-(4-aminopiperidin-1-yl)but-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile via the route used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-4-piperazin-1-ylbut-1-en-1-yl]nicotinonitrile; HRMS 401.2 (M+H); HPLC rt = 2.3 min[a].



[00161] Preparation of N-{1-[(3E)-4-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl]piperidin-4-yl}methanesulfonamide:

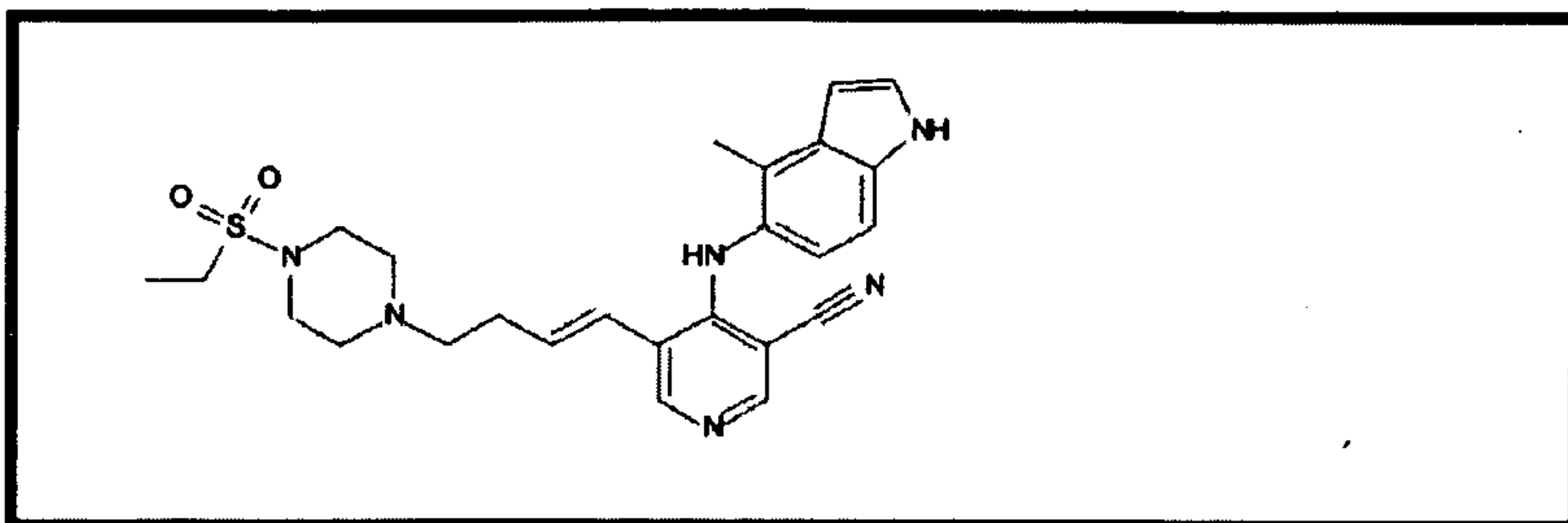
5-[(1E)-4-(4-amino piperidin-1-yl)but-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (75 mg, 0.10 mmol), methanesulfonyl chloride (15 mg, 0.13 mmol) and triethylamine (41 mg, 0.40 mmol) in 1 mL of DMF were stirred at room temperature for 1 h. The reaction mixture was filtered and the filtrate was purified by HPLC to give N-{1-[(3E)-4-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl]piperidin-4-yl}methanesulfonamide as its TFA salt; HRMS 479.2 (M+H); HPLC rt = 4.6 min[a].

[00162] Preparation of compounds in Table 5:

These analogs were prepared using 5-[(1E)-4-(4-aminopiperidin-1-yl)but-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and the appropriate sulfonyl chloride or acid chloride via the procedure used for N-{1-[(3E)-4-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl]piperidin-4-yl}methanesulfonamide.

[00163] Table 5:

Name	MS (M+H)	HPLC rt
N-{1-[(3E)-4-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl]piperidin-4-yl}propane-2-sulfonamide	507.2	1.45 min[d]
N-{1-[(3E)-4-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl]piperidin-4-yl}ethanesulfonamide	493.4	4.9 min[a]
N-{1-[(3E)-4-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl]piperidin-4-yl}benzenesulfonamide	541.4	6.3 min[a]
N-{1-[(3E)-4-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl]piperidin-4-yl}acetamide	443.5	4.1 min[a]



[00164] Preparation of 5-((1E)-4-[4-(ethylsulfonyl)piperazin-1-yl]but-1-en-1-yl)-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

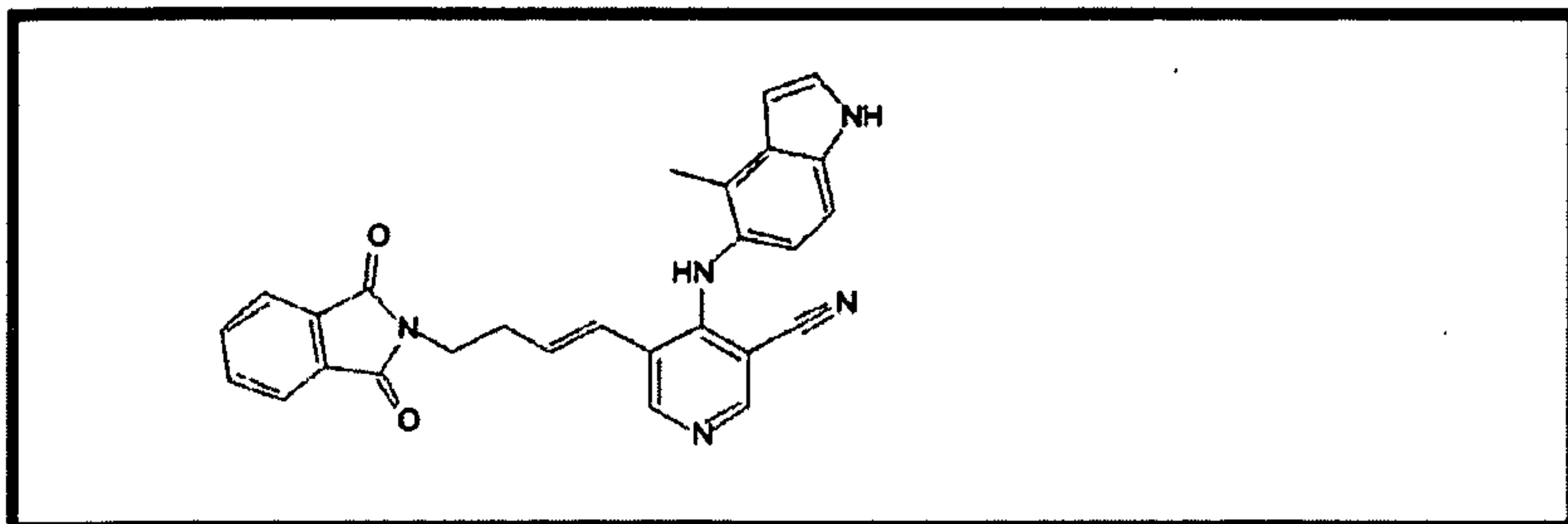
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-4-piperazin-1-ylbut-1-en-1-yl]nicotinonitrile (75 mg, 0.12 mmol), ethanesulfonyl chloride (21 mg, 0.16 mmol) and triethylamine (36 mg, 0.36 mmol) in 1 mL of DMF was stirred at room temperature for 1 h. The reaction mixture was filtered and the filtrate was purified by HPLC to give 5-((1E)-4-[4-(ethylsulfonyl)piperazin-1-yl]but-1-en-1-yl)-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile, as its TFA salt; HRMS 479.2227 (M+H); HPLC: rt = 4.8 min[a].

[00165] Preparation of compounds in Table 6:

The analogs in Table 6 were prepared using 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-4-piperazin-1-ylbut-1-en-1-yl]nicotinonitrile and the appropriate electrophile via the procedure used for 5-((1E)-4-[4-(ethylsulfonyl)piperazin-1-yl]but-1-en-1-yl)-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile.

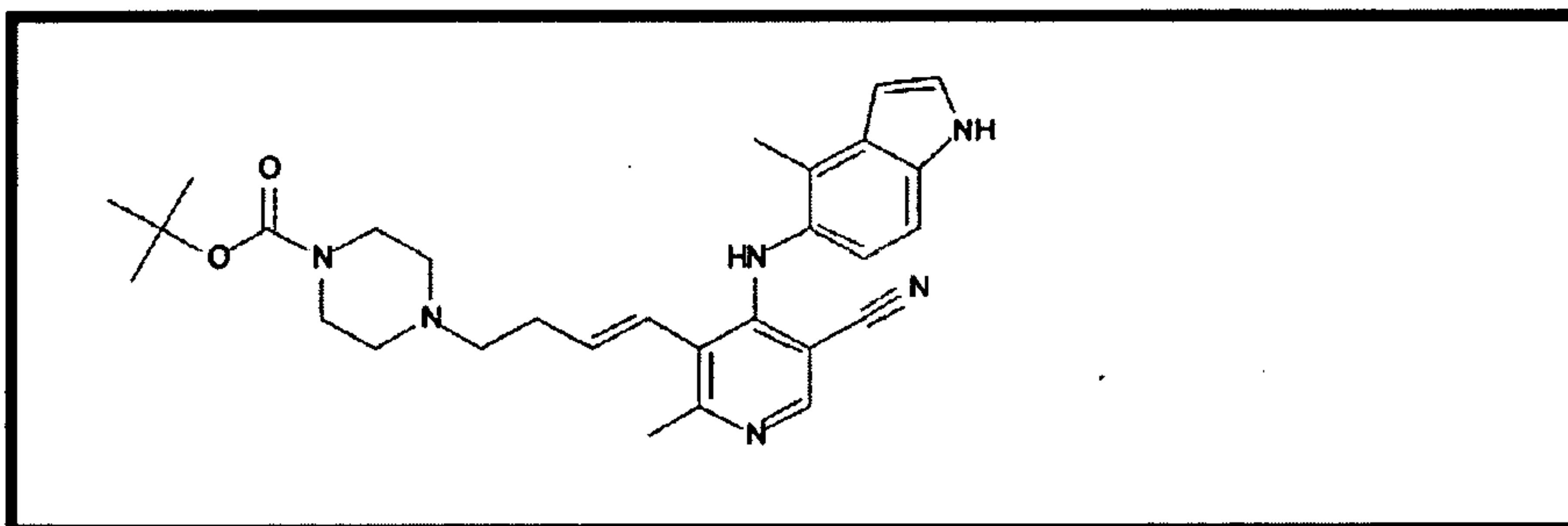
[00166] Table 6:

Name	MS (M+H)	HPLC rt
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-4-[4-(phenylsulfonyl)piperazin-1-yl]but-1-en-1-yl]nicotinonitrile	527.2	6.2 min.[a]
5-[(1E)-4-[4-(2,2-dimethylpropanoyl)piperazin-1-yl]but-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	471.2	5.4 min[a]
5-[(1E)-4-[4-(isopropylsulfonyl)piperazin-1-yl]but-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	493.2	1.42 min[d]



[00167] Preparation of 5-[(1E)-4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)but-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

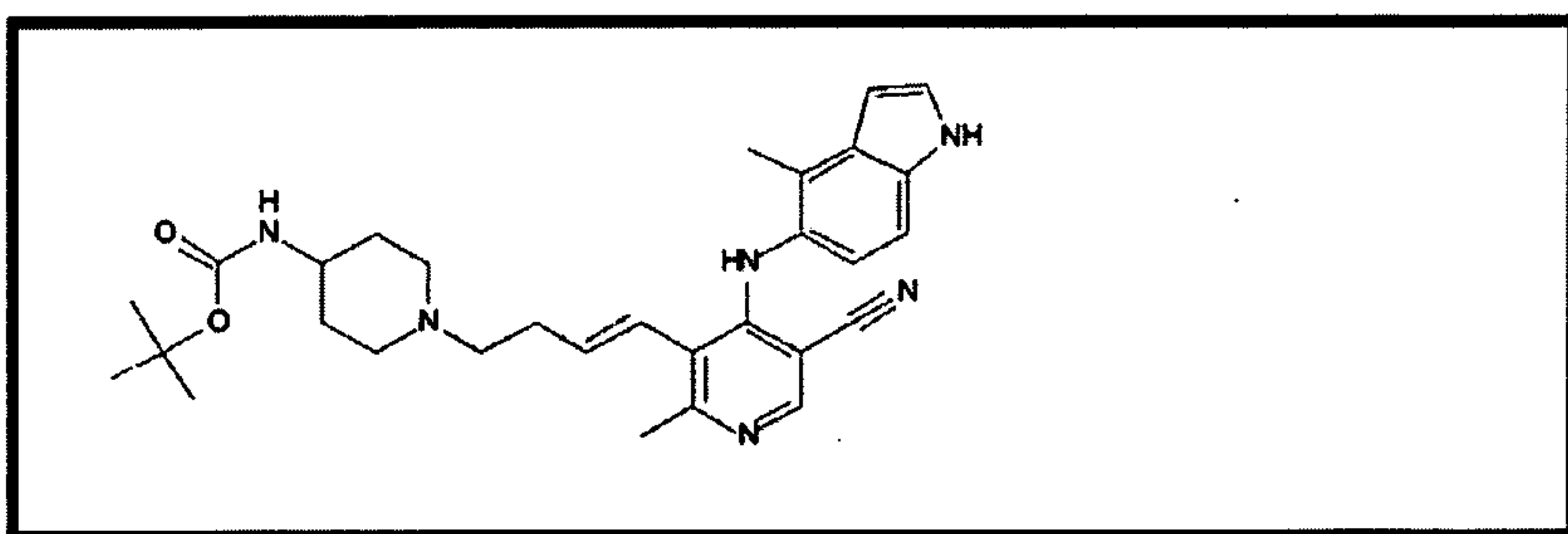
A mixture of 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (153 mg, 0.41 mmol), (E)-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-enyl)isoindoline-1,3-dione (200 mg, 0.61 mmol), sodium bicarbonate (0.40 mL, sat.) and Pd(PPh₃)₄ (23.5 mg, 0.02 mmol) in 2 mL of DME was heated at 80° for 16 h. The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated and purified by HPLC to give 5-[(1E)-4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)but-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile as a solid; HRMS 448.1768 (M+H); HPLC rt = 9.2 min [a].



[00168] Preparation of tert-butyl 4-[(3E)-4-{5-cyano-2-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl]piperazine-1-carboxylate:

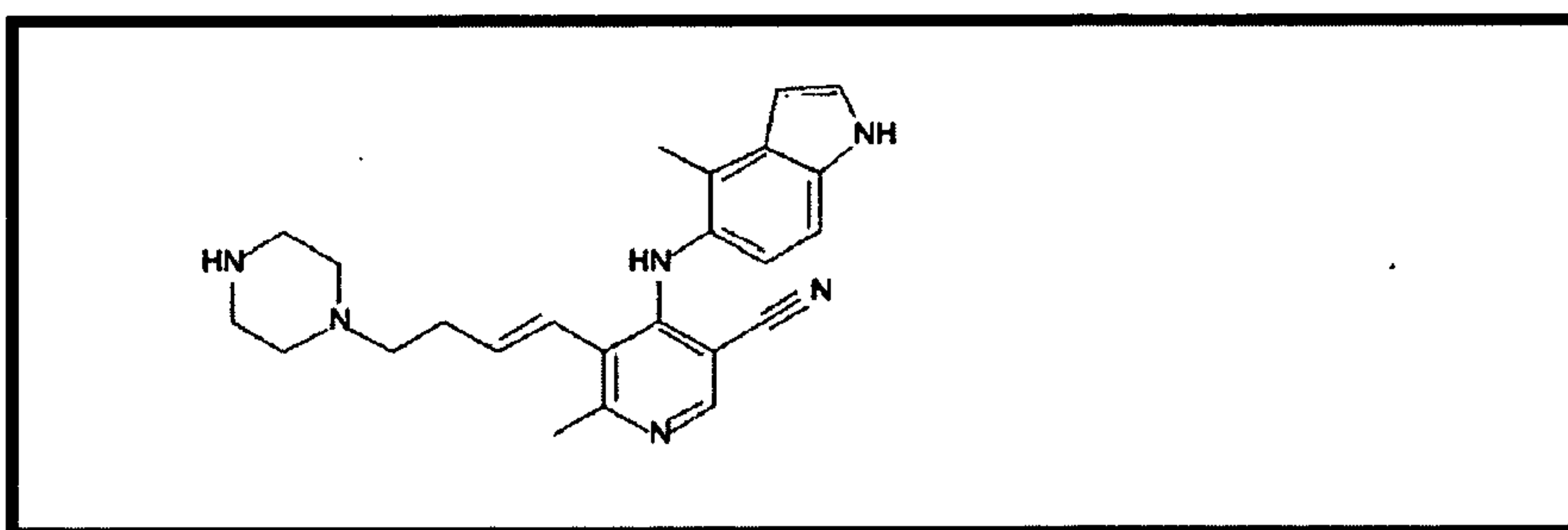
A mixture of tert-butyl piperazine-1-carboxylate (193 mg, 1.04 mmol) and (E)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-enyl 4-methylbenzenesulfonate (183 mg, 0.52 mmol) in 1 mL of DMSO was stirred for 16 h at room temperature. 5-iodo-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (100 mg, 0.26 mmol), cesium carbonate (170 mg, 0.52 mmol) and Pd(PPh₃)₄ (15 mg, 0.013 mmol) were added to the same pot and the resulting suspension was heated at 70° for 16 h. After cooling to room temperature, the reaction was diluted with EtOAc and washed with water. The organic extracts were concentrated and purified by silica

gel chromatography with a MeOH/ DCM gradient to give tert-butyl 4-[(3E)-4-{5-cyano-2-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl]piperazine-1-carboxylate as a solid; MS 501.5 (M+H); HPLC: rt = 6.5 min[a].



[00169] Preparation of tert-butyl{1-[(3E)-4-{5-cyano-2-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl]piperidin-4-yl}carbamate:

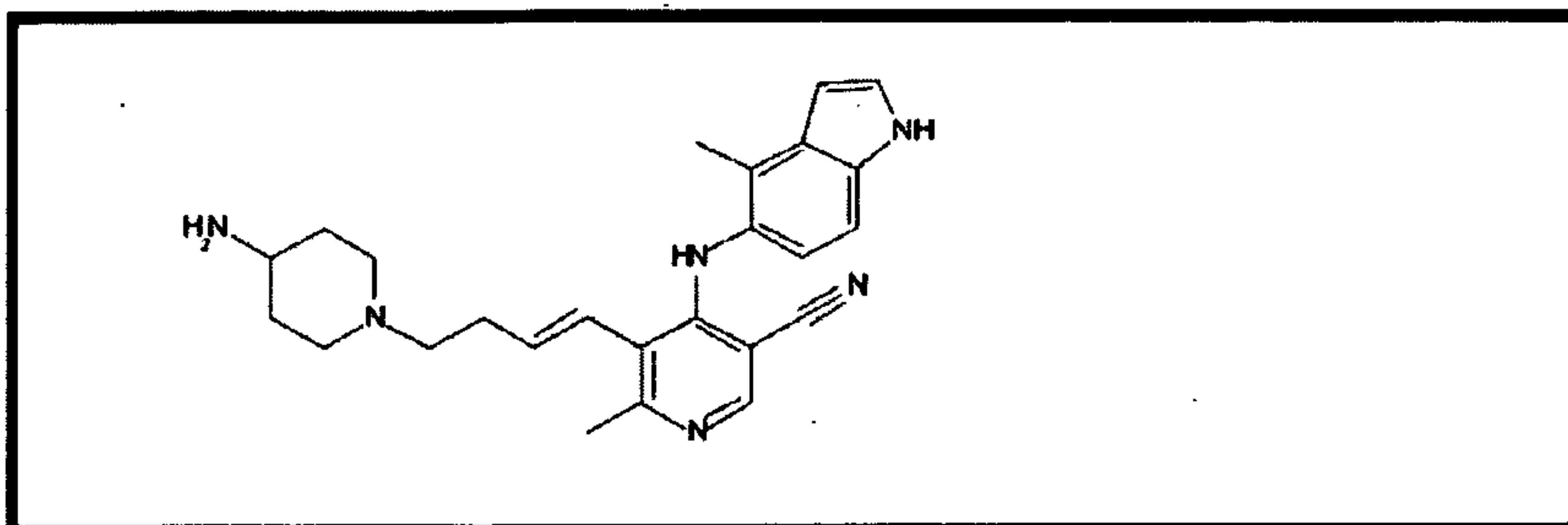
5-iodo-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile, tert-butylpiperidin-4-yl carbamate and (E)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-enyl-4-methyl benzenesulfonate were used to prepare tert-butyl {1-[(3E)-4-{5-cyano-2-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl]piperidin-4-yl}carbamate via the same method used for preparing tert-butyl 4-[(3E)-4-{5-cyano-2-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl]piperazine-1-carboxylate, above; MS 515.5 (M+H); HPLC: rt = 6.4 min [a].



[00170] Preparation of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-4-piperazin-1-ylbut-1-en-1-yl]nicotinonitrile:

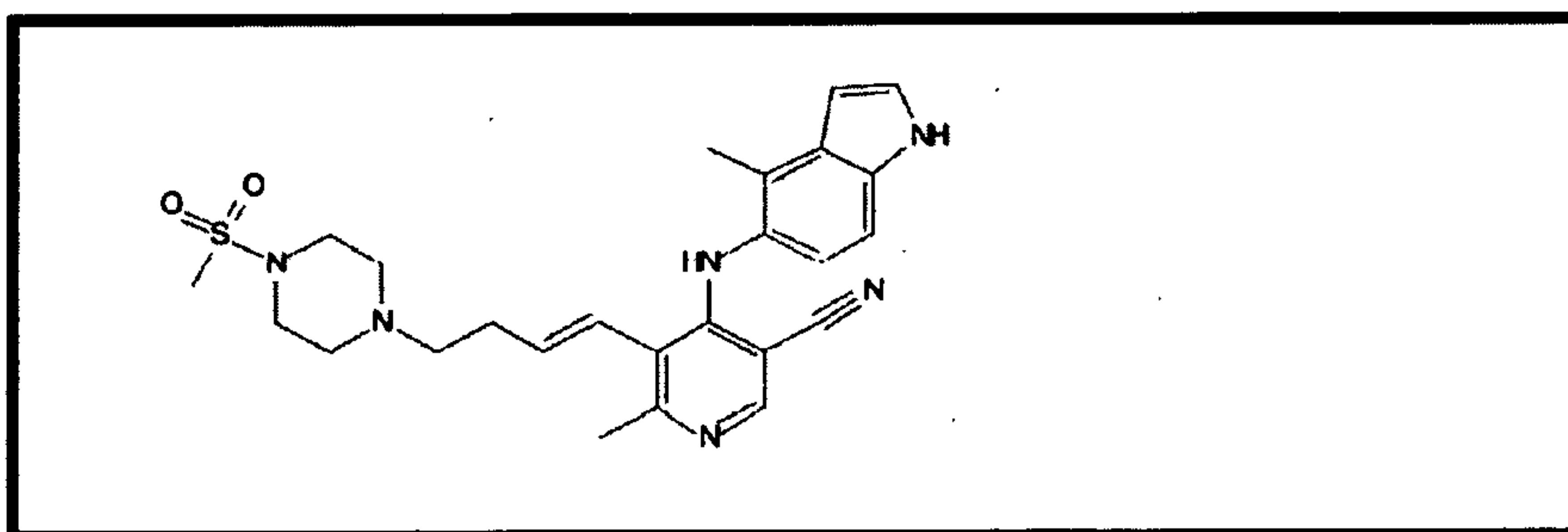
A solution of tert-butyl 4-[(3E)-4-{5-cyano-2-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl]piperazine-1-carboxylate (402 mg, 0.80 mmol) in 10% trifluoroacetic acid/ DCM was stirred for 1 h at room temperature. The reaction was concentrated and the residue

was purified by HPLC to give 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-4-piperazin-1-ylbut-1-en-1-yl]nicotinonitrile as its TFA salt; MS 401.4 (M+H); HPLC: rt = 4.8 min [b].



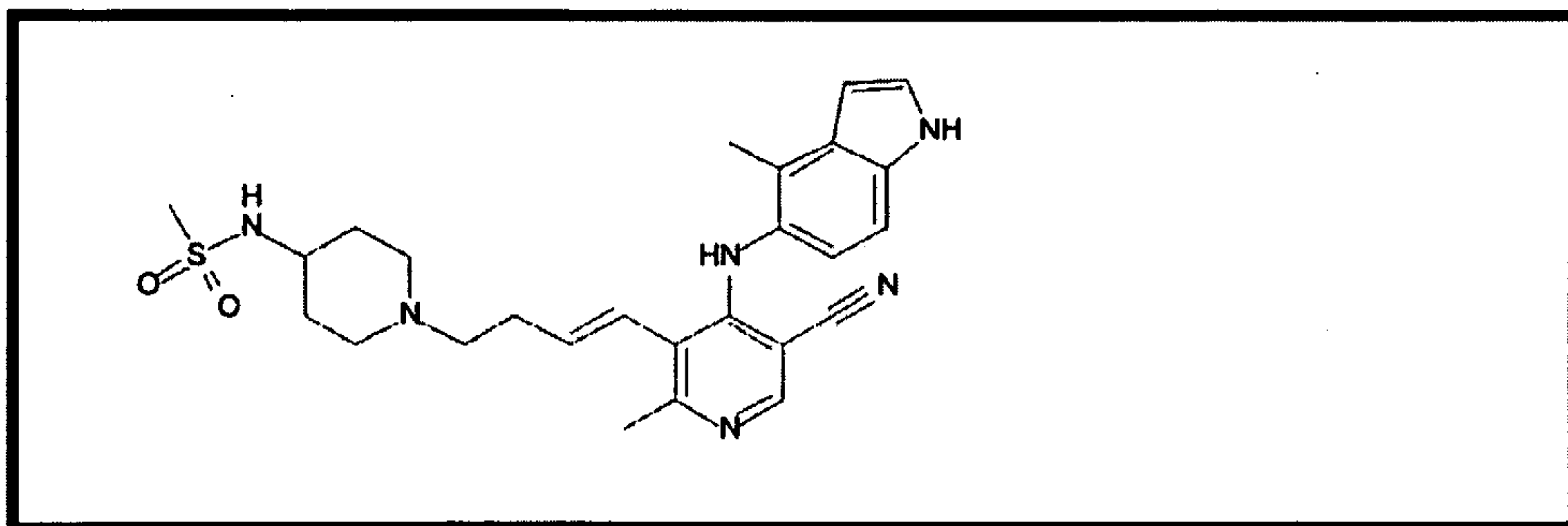
[00171] Preparation of 5-[(1E)-4-(4-aminopiperidin-1-yl)but-1-en-1-yl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

Tert-butyl {1-[(3E)-4-{5-cyano-2-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl]piperidin-4-yl}carbamate was used to prepare 5-[(1E)-4-(4-aminopiperidin-1-yl)but-1-en-1-yl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile via the route used to prepare 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-4-piperazin-1-ylbut-1-en-1-yl]nicotinonitrile, above. The title compound was isolated as its TFA salt; HRMS 415.2610 (M+H); HPLC: rt = 5.6 min [b].



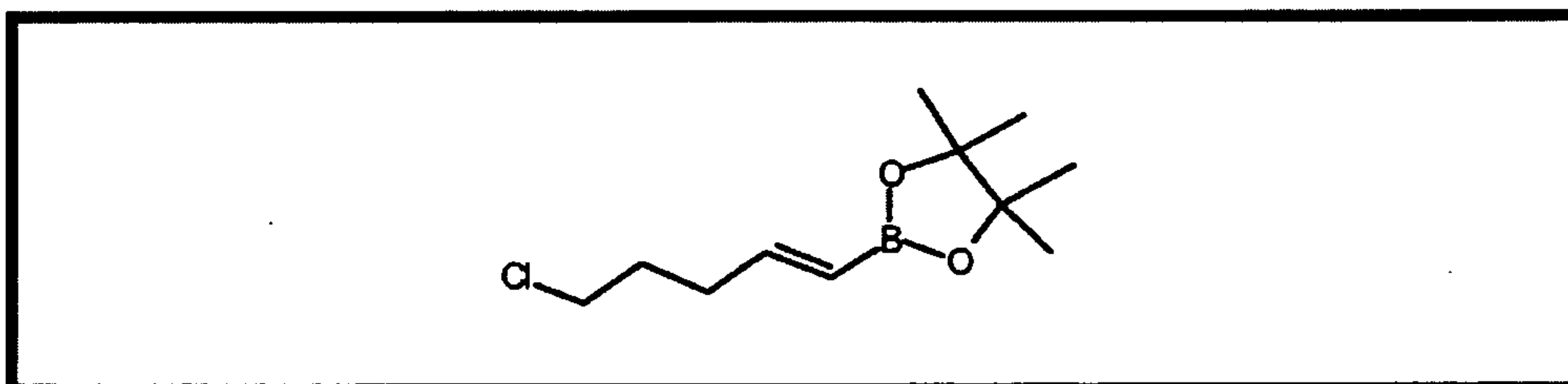
[00172] Preparation of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-4-[4-(methylsulfonyl)piperazin-1-yl]but-1-en-1-yl]nicotinonitrile:

A solution of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-4-piperazin-1-ylbut-1-en-1-yl]nicotinonitrile (106 mg, 0.27 mmol), methane sulfonyl chloride (42 mg, 0.37 mmol) and triethylamine (109 mg, 1.08 mmol) in 1 mL DMF was stirred for 1 h at room temperature. The reaction was filtered and the filtrate was purified by HPLC to give 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-4-[4-(methylsulfonyl)piperazin-1-yl]but-1-en-1-yl]nicotinonitrile as its TFA salt; MS 479.4 (M+H); HPLC: rt = 5.1 min [a].



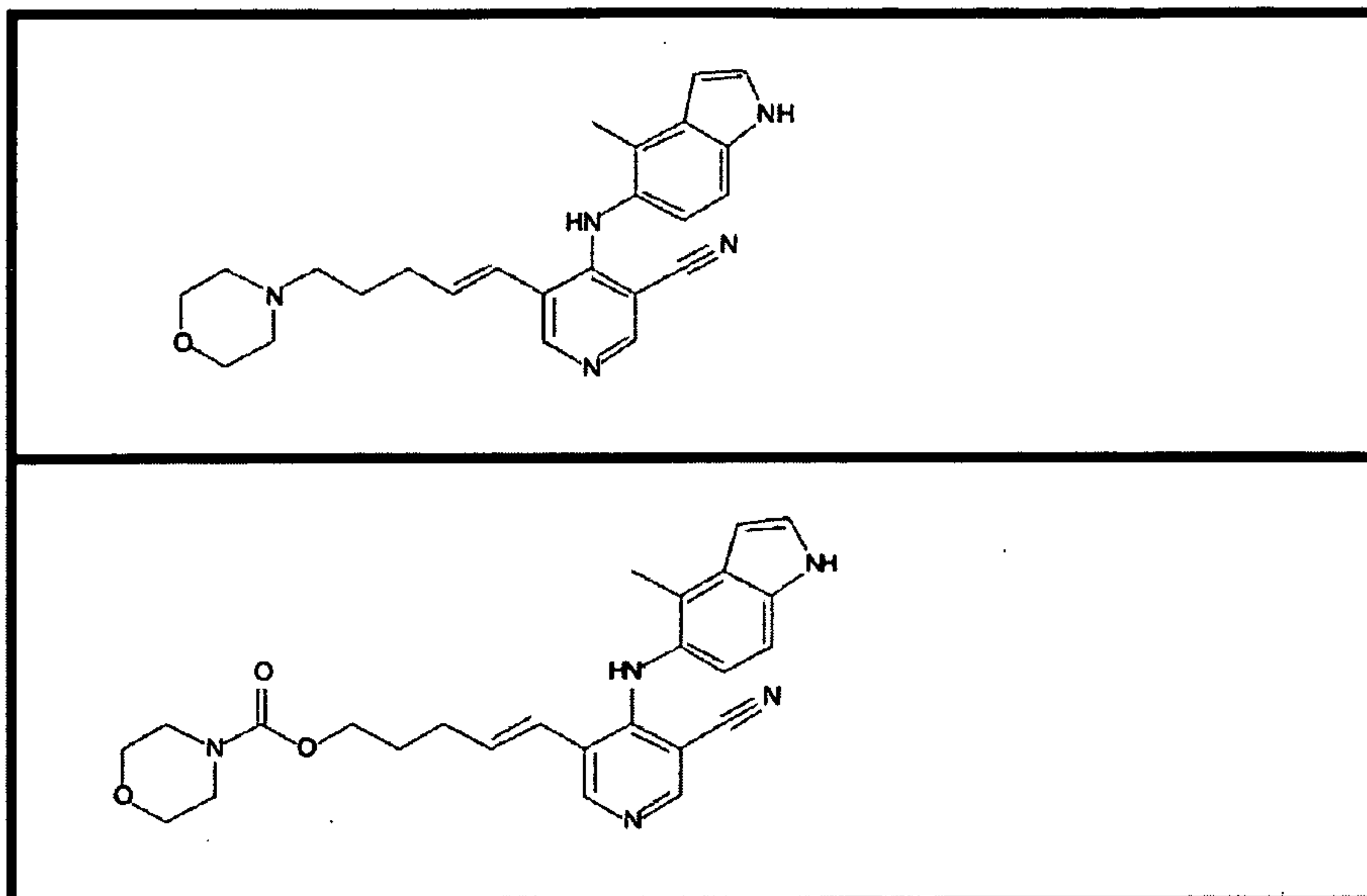
[00173] Preparation of N-{1-[(3E)-4-{5-cyano-2-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl]piperidin-4-yl}methanesulfonamide:

A solution of 5-[(1E)-4-(4-aminopiperidin-1-yl)but-1-en-1-yl]-6-methyl-4-[(4-methyl-1H-indol-5-yl) amino]nicotinonitrile (92 mg, 0.22 mmol), methane sulfonyl chloride (36 mg, 0.31 mmol) and triethylamine (89 mg, 0.88 mmol) in 1 mL DMF was stirred for 1 h at room temperature. The reaction was filtered and the filtrate was purified by HPLC to give N-{1-[(3E)-4-{5-cyano-2-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl]piperidin-4-yl}methane sulfonamide as its TFA salt; MS 493.5 (M+H); HPLC: rt = 4.8 min [a].



[00174] Preparation of (E)-2-(5-chloropent-1-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane:

A mixture of 5-chloro-1-pentyne (500 mg, 4.9 mmol), 4,4,5-tetramethyl-1,3,2-dioxaborolane (947 mg, 7.4 mmol), bis(cyclopentadienyl)-zirconium(IV) chloride hydride (191 mg, 0.74 mmol) and triethylamine (49.5 mg, 0.49 mmol) were stirred neat at room temperature for 24 hr. The reaction was dissolved in DCM, filtered through a pad of silica gel and washed with DCM. The eluent was removed to give 824 mg of (E)-2-(5-chloropent-1-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as a clear yellow liquid; MS 231.2 (M+H); HPLC: rt = 18.2 min [a].



[00175] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-5-morpholin-4-ylpent-1-en-1-yl]nicotinonitrile and (4E)-5-{5-cyano-(4-methyl-1H-indol-5-yl) amino}pyridin-3-yl}pent-4-en-1-yl morpholine-4-carboxylate:

A mixture of morpholine (148 mg, 1.7 mmol) and (E)-2-(5-chloropent-1-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (131 mg, 0.61 mmol) in 1 mL of DMSO was stirred for 16 hr at room temperature. 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (108 mg, 0.29 mmol), cesium carbonate (186 mg, 0.57 mmol) and Pd(PPh₃)₄ (16 mg, 0.014 mmol) were added and the reaction mixture was heated at 70° for 16 h. The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated and purified by HPLC to give 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-5-morpholin-4-ylpent-1-en-1-yl]nicotinonitrile and (4E)-5-{5-cyano-(4-methyl-1H-indol-5-yl)amino}pyridin-3-yl}pent-4-en-1-ylmorpholine-4-carboxylate.

[00176] 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-5-morpholin-4-ylpent-1-en-1-yl]nicotinonitrile: (TFA salt):

HRMS 402.2288 (M+H); HPLC: rt = 6.1 min [b]

[00177] (4E)-5-{5-cyano-(4-methyl-1H-indol-5-yl)amino}pyridin-3-yl}pent-4-en-1-yl morpholine-4-carboxylate:

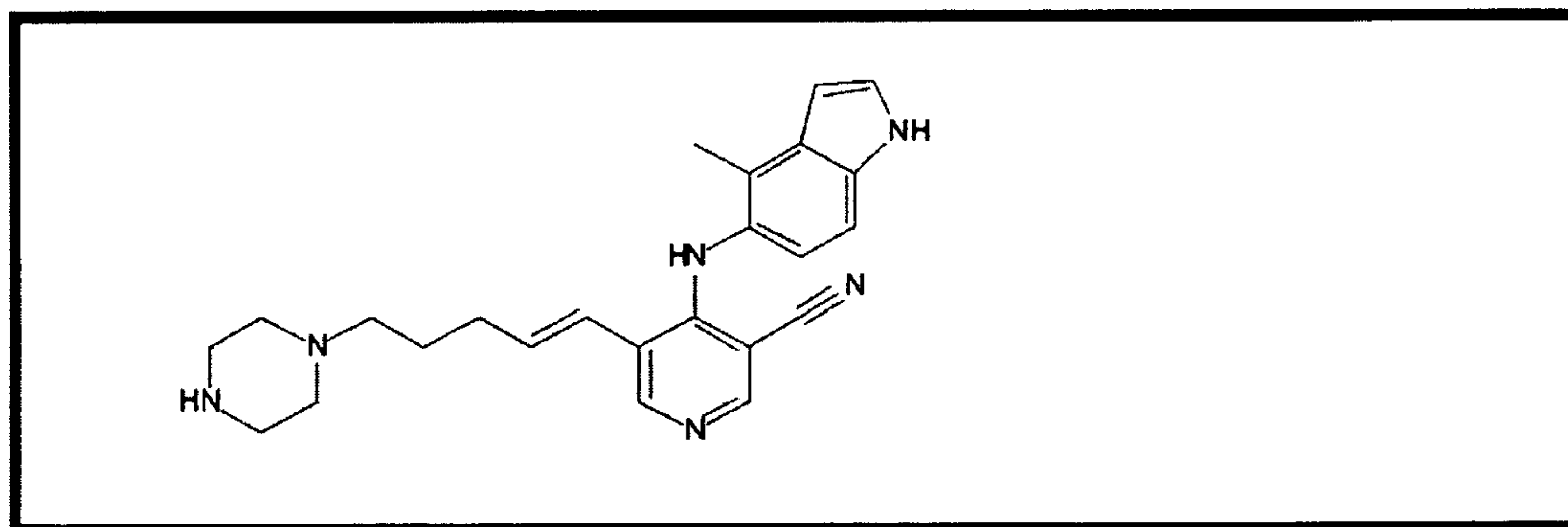
HRMS 446.2187 (M+H); HPLC rt = 11.9 min[b].

[00178] Preparation of compounds in Table 7A:

These analogs were prepared using 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile, (E)-2-(5-chloropent-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, and the appropriate amine via the procedure used for 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-5-morpholin-4-ylpent-1-en-1-yl]nicotinonitrile.

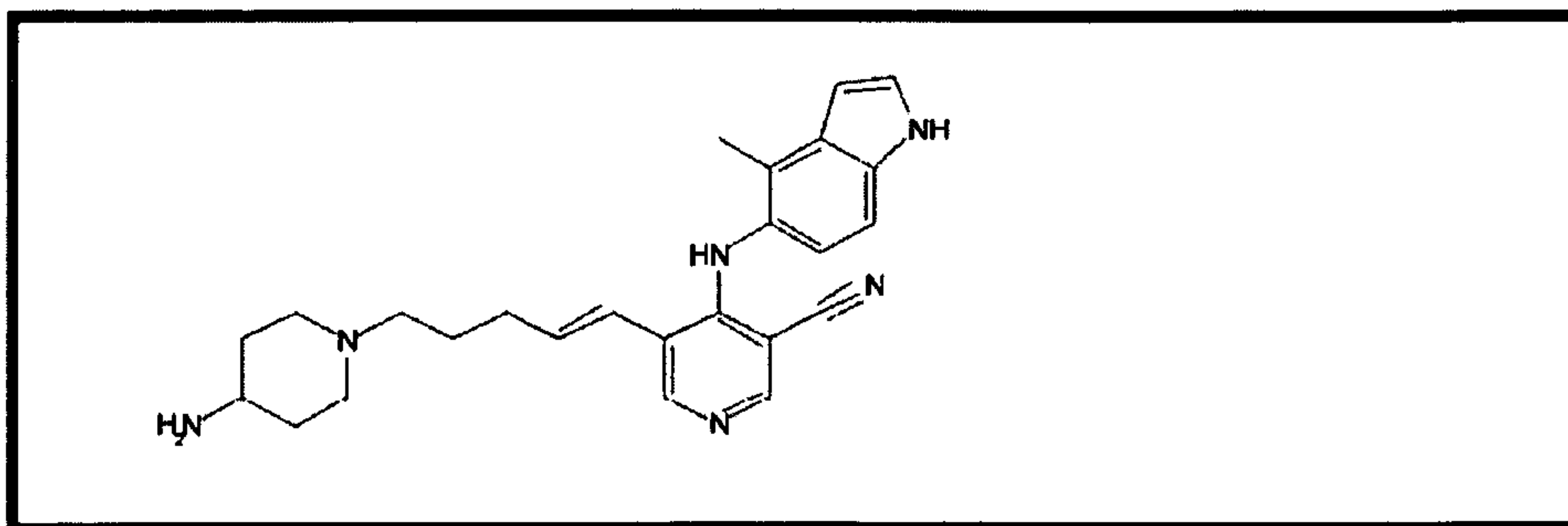
Table 7A

Name	MS (M+H)	HPLC rt
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-5-(4-methylpiperazin-1-yl)pent-1-en-1-yl]nicotinonitrile	415.2608	5.9 min[b]
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-5-pyrrolidin-1-ylpent-1-en-1-yl]nicotinonitrile	386.2344	6.5 min[b]
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-5-piperidin-1-ylpent-1-en-1-yl]nicotinonitrile	400.4	5.1 min[a]
tert-butyl 4-[(4E)-5-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}pent-4-en-1-yl]piperazine-1-carboxylate	501.5	6.7 min[a]
tert-butyl {1-[(4E)-5-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}pent-4-en-1-yl]piperidin-4-yl}carbamate	515.5	6.7 min[a]
5-[(1E)-5-(4-hydroxypiperidin-1-yl)pent-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	416.4	6.4 min[a]

**[00179] Preparation 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-5-piperazin-1-ylpent-1-en-1-yl]nicotinonitrile:**

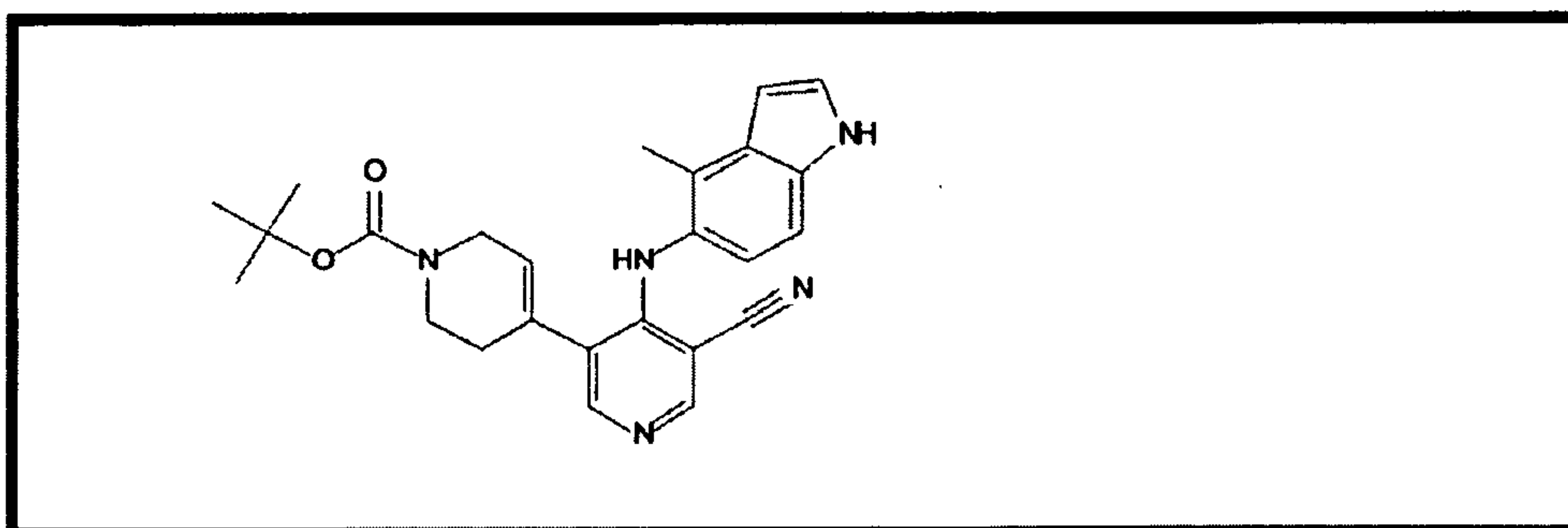
A solution of tert-butyl 4-[(4E)-5-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}pent-4-en-1-yl]piperazine-1-carboxylate (91 mg, 0.18 mmol) in 10% trifluoroacetic acid/ DCM was stirred for 1 h at room temperature. The reaction was filtered and the filtrate was concentrated

and purified by HPLC to give the title compound as its TFA salt; HRMS 401.2456 (M+H); HPLC: rt = 7.3 min [b].



[00180] Preparation of 5-[(1E)-5-(4-aminopiperidin-1-yl)pent-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

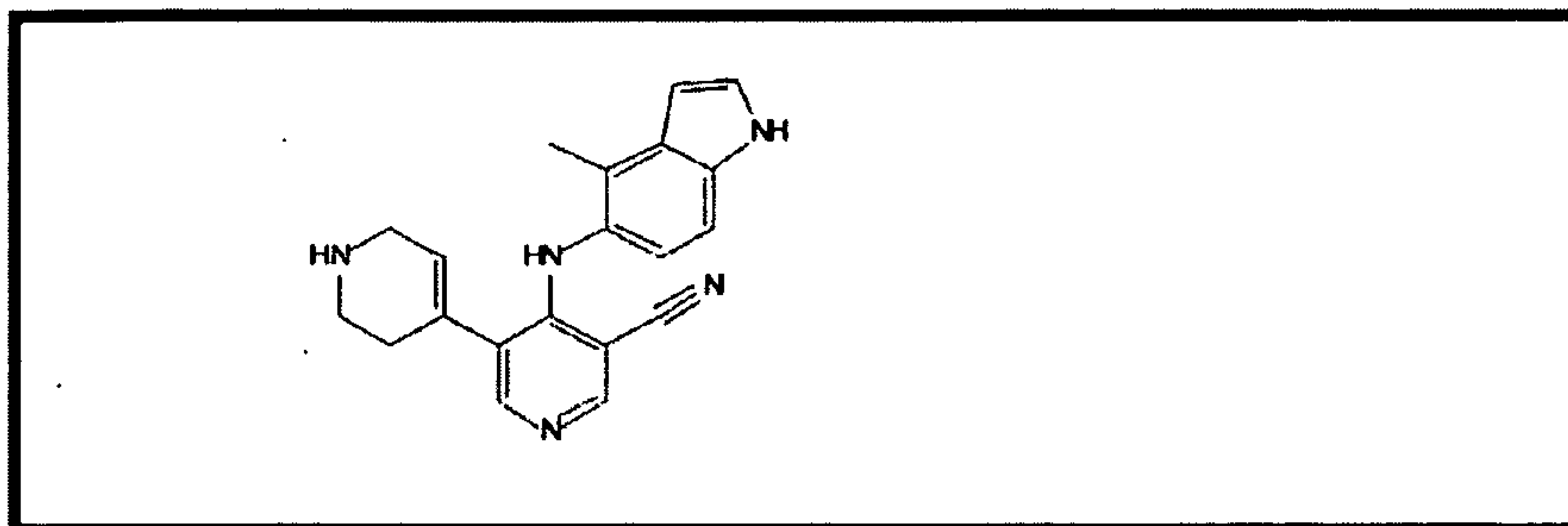
Tert-butyl{1-[(4E)-5-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}pent-4-en-1-yl]piperidin-4-yl}carbamate was used to prepare 5-[(1E)-5-(4-aminopiperidin-1-yl)pent-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl) amino]nicotinonitrile via the route used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-5-piperazin-1-ylpent-1-en-1-yl]nicotinonitrile: HRMS 415.2605 (M+H); HPLC: rt = 6.9 min [b].



[00181] Preparation of tert-butyl 5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]-3',6'-dihydro-3,4'-bipyridine-1'(2'H)-carboxylate:

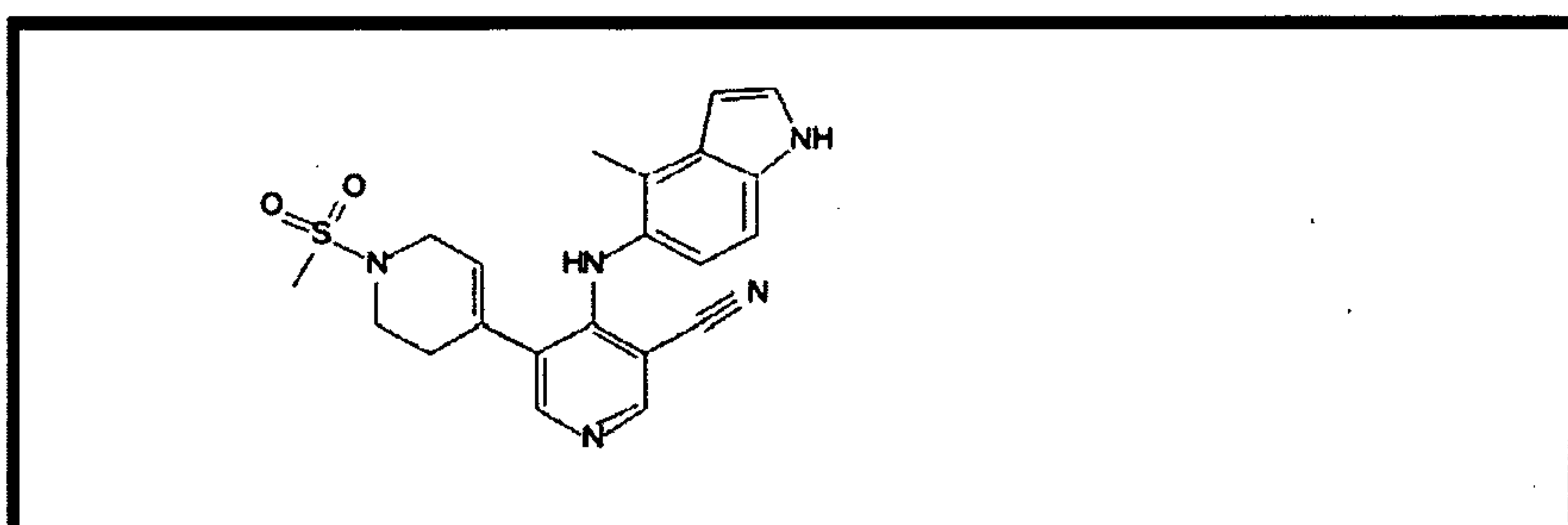
A mixture of 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (1.5 g, 4.0 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (1.85 g, 6 mmol), Pd(OAc)₂ (62.7 mg; 0.28 mmol), triphenylphosphine trisulfonic acid (340 mg; 0.6 mmol) and sodium bicarbonate (saturated aq., 4 mL) in 50 mL of dimethoxyethane was heated at 90°C for 16 h, cooled to room temperature, diluted with EtOAc and washed with water. The

crude organic extract was concentrated and the residue was purified by silica gel chromatography with a hexane/ EtOAc gradient to give 640 mg of tert-butyl 5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]-3',6'-dihydro-3,4'-bipyridine-1'(2'H)-carboxylate as a solid; MS 430.3 (M+H); HPLC: rt = 9.8 min [a].



[00182] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile:

Tert-butyl-5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]-3',6'-dihydro-3,4'-bipyridine-1'(2'H)-carboxylate (100 mg, 0.23 mmol) was treated with 10% trifluoroacetic acid/ DCM to give 96 mg of 4-[(4-methyl-1H-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile as its TFA salt upon concentration; MS 330.2 (M+H); HPLC: rt = 3.7 min [a].



[00183] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-1'-(methylsulfonyl)-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile:

A mixture of 4-[(4-methyl-1H-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile (100 mg, 0.23 mmol), methane sulfonyl chloride (28.7 mg, 0.25 mmol), and triethylamine (68.7 mg, 0.68 mmol) in 1 mL of DMF was stirred at room temperature for 10 min. The reaction was filtered and the filtrate was purified by HPLC to give 4-[(4-methyl-1H-

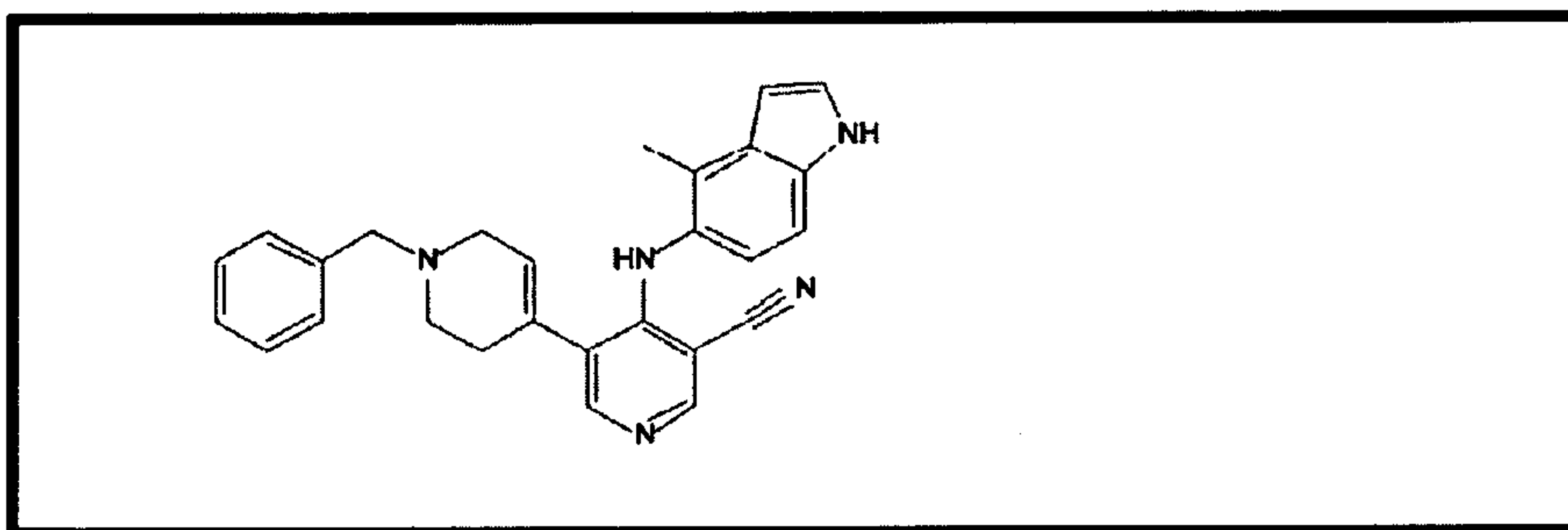
indol-5-yl)amino]-1'-(methylsulfonyl)-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile as a solid; MS 408.3 (M+H); HPLC: rt = 6.7 min [a].

[00184] Preparation of compounds in Table 7B:

These compounds were prepared from 4-[(4-methyl-1H-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile, the corresponding electrophile and triethylamine in DMF via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-1'-(methylsulfonyl)-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile.

[00185] Table 7B:

Electrophile	Name	MS (M+H)	HPLC rt
Benzenesulfonyl chloride	4-[(4-methyl-1H-indol-5-yl)amino]-1'-(phenyl sulfonyl)-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	470.2	9.3 min[a]
Acetyl chloride	1'-acetyl-4-[(4-methyl-1H-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	372.1	5.8 min[a]
Ethyl isocyanate	5-cyano-N-ethyl-4-[(4-methyl-1H-indol-5-yl)amino]-3',6'-dihydro-3,4'-bipyridine-1'(2'H)-carboxamide	401.2	6.2 min[a]
Ethyl chloroformate	ethyl 5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]-3',6'-dihydro-3,4'-bipyridine-1'(2'H)-carboxylate	402.2	7.6 min[a]



[00186] Preparation of 1'-benzyl-4-[(4-methyl-1H-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile:

A mixture of 4-[(4-methyl-1H-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile (100mg, 0.23 mmol), benzaldehyde (31.8 mg, 0.30 mmol), and sodium triacetoxyborohydride (195 mg, 0.92 mmol) in 1 mL of DCE was stirred at room temperature for 1 h. The reaction was filtered and the filtrate was purified by HPLC to give 1'-benzyl-4-[(4-

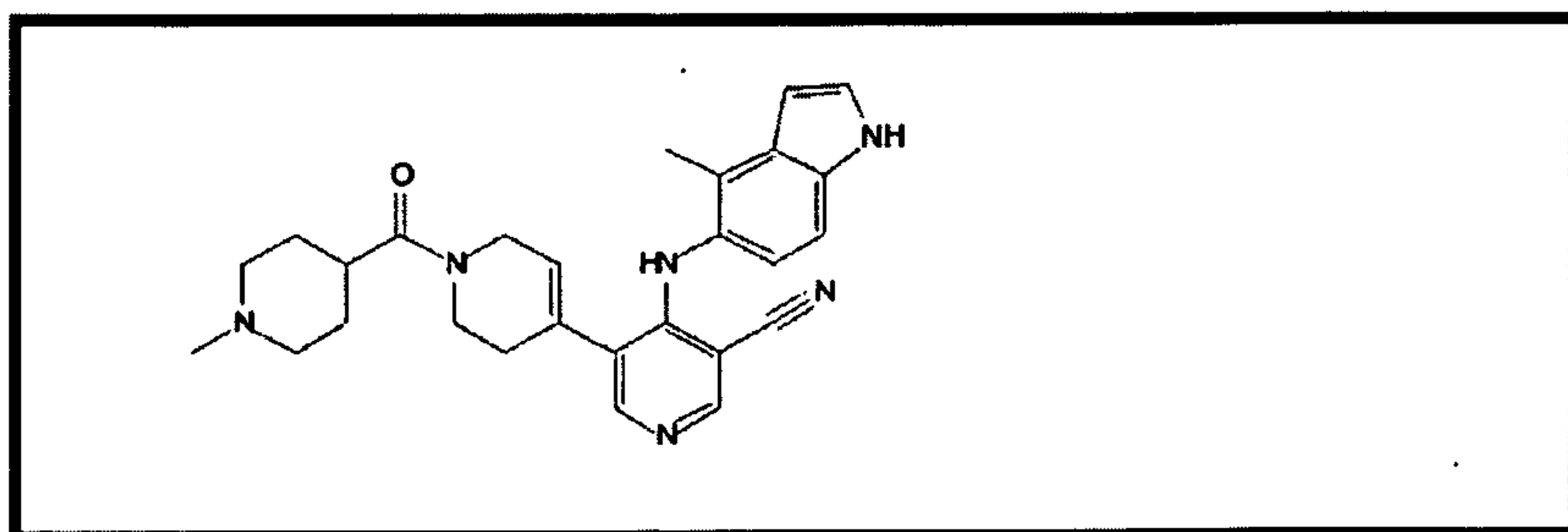
methyl-1H-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile as its TFA salt; MS 420.3 (M+H); HPLC: rt = 5.7 min [a].

[00187] Preparation of compounds in Table 8:

4-[(4-methyl-1H-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile was used to prepare these analogs via the same route used to prepare 1'-benzyl-4-[(4-methyl-1H-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile.

[00188] Table 8:

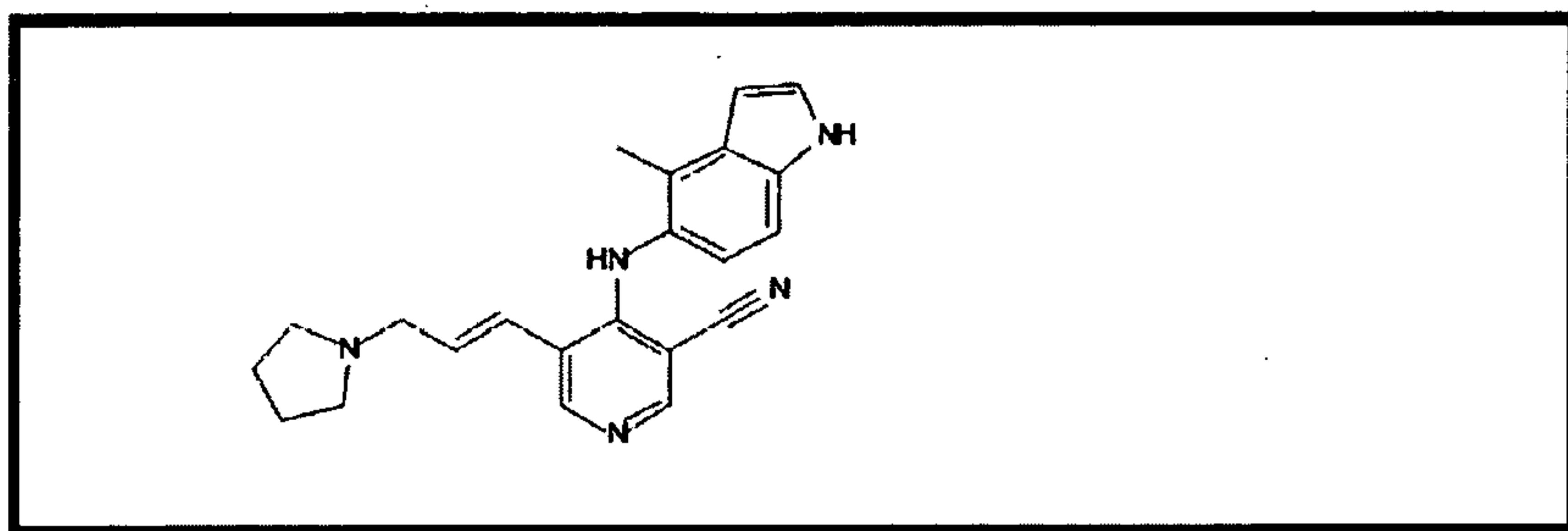
Name	MS (M+H)	HPLC rt
1'-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	344.3	3.8 min[a]
4-[(4-methyl-1H-indol-5-yl)amino]-1'-(2-phenylethyl)-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	434.5	6.2 min[a]
1'-(2-fluorobenzyl)-4-[(4-methyl-1H-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	438.3	5.6 min[a]
1'-(3-fluorobenzyl)-4-[(4-methyl-1H-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	438.3	5.9 min[a]
1'-(4-fluorobenzyl)-4-[(4-methyl-1H-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	438.3	5.9 min[a]
4-[(4-methyl-1H-indol-5-yl)amino]-1'-(piperidin-4-ylmethyl)-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	427.4	3.8 min[b]



[00189] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-1'-[(1-methylpiperidin-4-yl)carbonyl]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile:

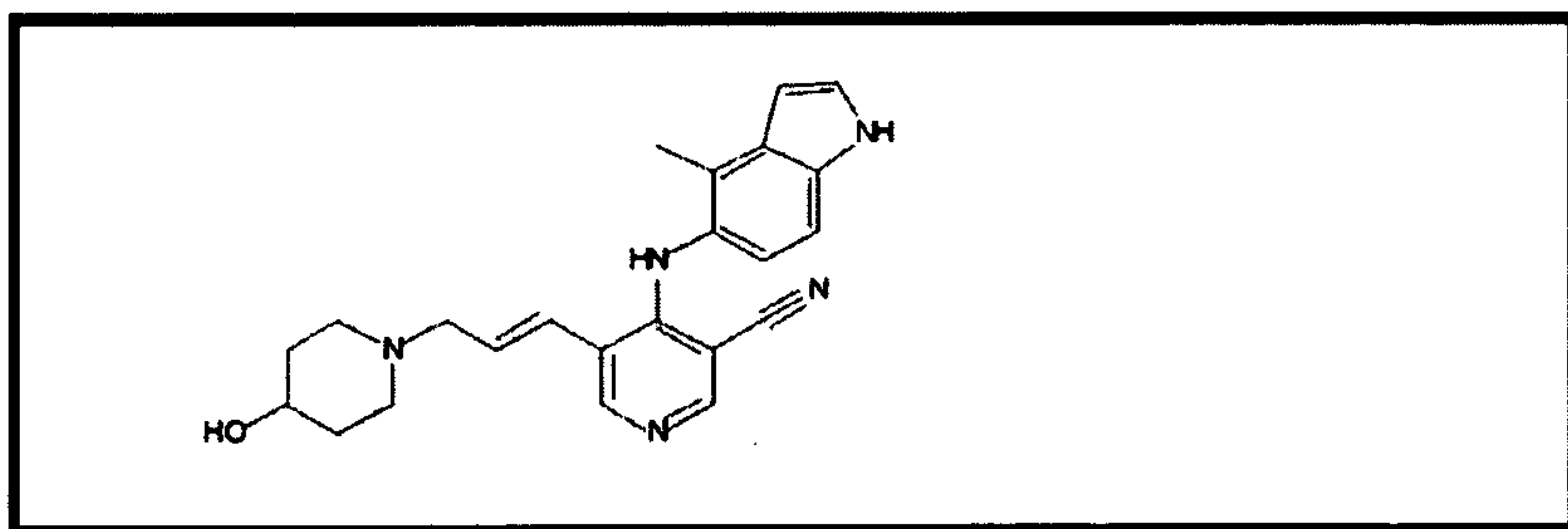
A mixture of 4-[(4-methyl-1H-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile (100mg, 0.23 mmol), 1-methylpiperidine-4-carboxylic acid (54 mg, 0.30 mmol), 1-

ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (88 mg, 0.46 mmol), and triethylamine (69.7 mg; 0.69 mmol) in 2 mL of DMF was stirred at room temperature for 1 h. The reaction was filtered and the filtrate was purified by HPLC to give 4-[(4-methyl-1H-indol-5-yl)amino]-1'-[(1-methylpiperidin-4-yl)carbonyl]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile as its TFA salt; MS 455.4 (M+H); HPLC: rt = 4.2 min [a].



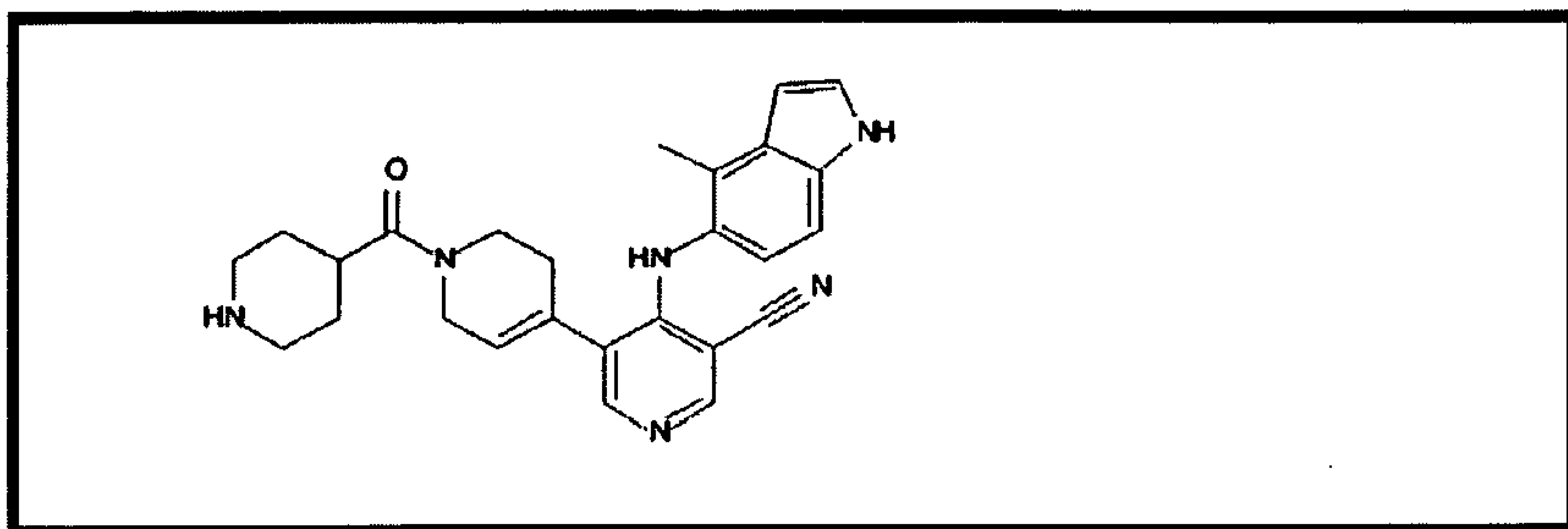
[00190] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-3-pyrrolidin-1-ylprop-1-en-1-yl]nicotinonitrile:

(E)-3-Chloroprop-1-enylboronic acid (67 mg, 0.53 mmol), 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (0.27 mmol, 100 mg), pyrrolidine (57 mg, 0.80 mmol), palladium bis(triphenylphosphine) dichloride (9.0 mg, 0.013 mmol) and cesium carbonate (172 mg, 0.53 mmol) were heated in 3 mL DME at 90° C overnight. The reaction mixture was partitioned between DCM/MeOH and water. The organic layer was washed twice with water and concentrated onto silica gel. Elution with 10% MeOH/DCM (ammonia modifier) gave 28 mg of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-3-pyrrolidin-1-ylprop-1-en-1-yl]nicotinonitrile; MS 358.3 (M+H); HPLC: rt = 5.8 min [b].



[00191] Preparation of 5-[(1E)-3-(4-hydroxypiperidin-1-yl)prop-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

The title compound was synthesized from 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 4-hydroxypiperidine according to the procedure described for 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-3-pyrrolidin-1-ylprop-1-en-1-yl]nicotinonitrile; MS 388.4 (M+H); HPLC: rt = 3.9 min [a].



[00192] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-1'-(piperidin-4-ylcarbonyl)-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile:

4-[(4-methyl-1H-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile (70 mg, 0.12 mmol), 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (37 mg, 0.16 mmol), triethyl amine (36 mg, 0.36 mmol), and EDC (46 mg, 0.24 mmol) were stirred in 5 mL of DCM. After 30 minutes, the reaction was treated with TFA (2 mL) and stirred for 1h. The reaction mixture was concentrated and the residue was purified by HPLC to give 4-[(4-methyl-1H-indol-5-yl)amino]-1'-(piperidin-4-ylcarbonyl)-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile; MS 387.1 (M+H); HPLC: rt = 1.2 min [a].

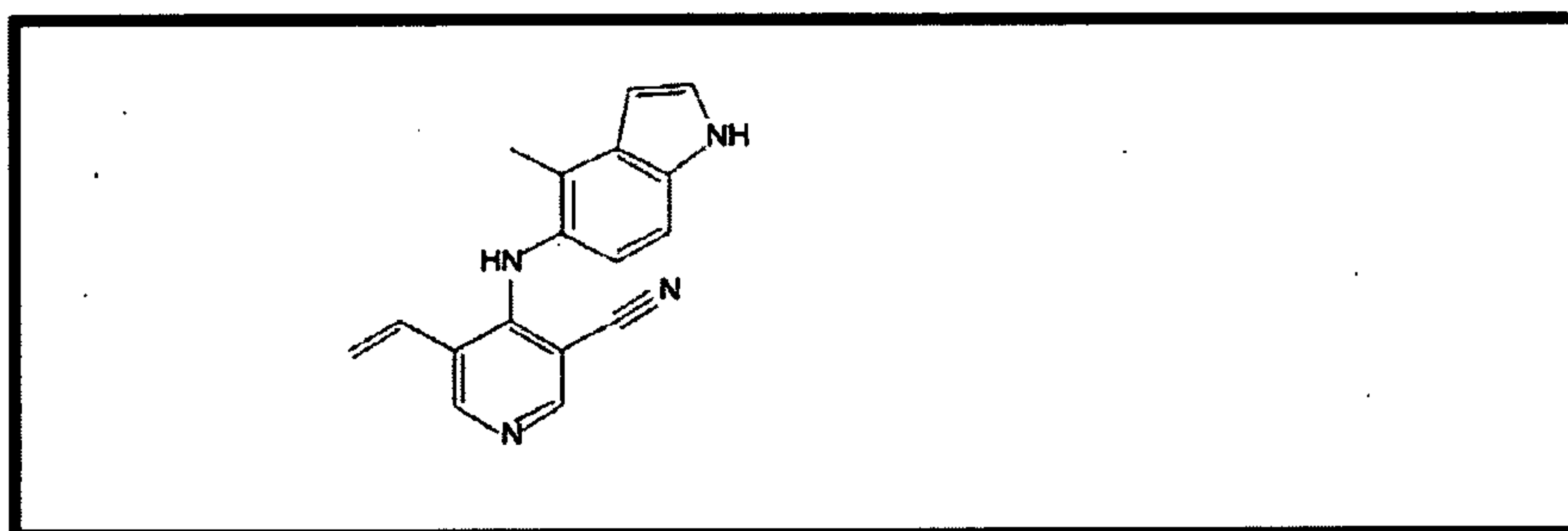
[00193] Preparation of compounds in Table 9:

The compounds in Table 9 were prepared from 4-[(4-methyl-1H-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile and the appropriate Boc-protected amino acid by the method described for 4-[(4-methyl-1H-indol-5-yl)amino]-1'-(piperidin-4-ylcarbonyl)-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile:

[00194] Table 9:

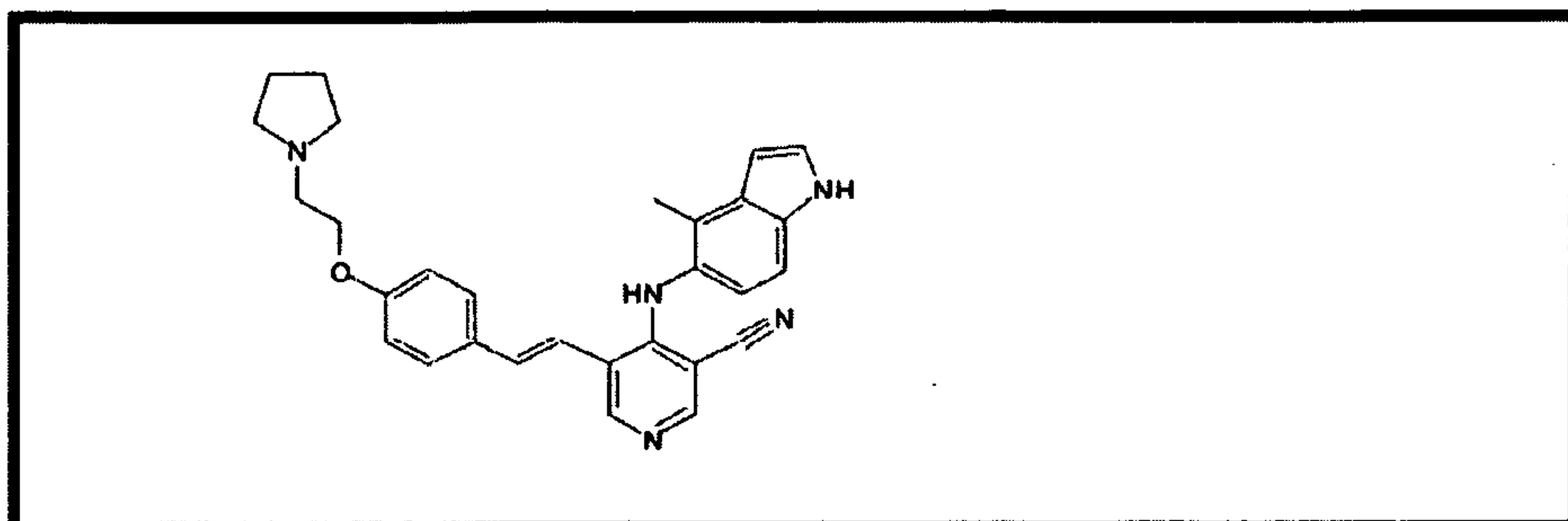
Compound name	MS (M+H)	HPLCrt [method]
1'-glycyl-4-[(4-methyl-1H-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	387.1	1.2 min [d]

Compound name	MS (M+H)	HPLCrt [method]
1'-(2-methylalanyl)-4-[(4-methyl-1H-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	415.1	1.3 min [d]
1'-b-alanyl-4-[(4-methyl-1H-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	401.2	1.2 min [d]
4-[(4-methyl-1H-indol-5-yl)amino]-1'-D-valyl-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	429.3	1.4 min [d]
4-[(4-methyl-1H-indol-5-yl)amino]-1'-L-valyl-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	429.1	1.4 min [d]
4-[(4-methyl-1H-indol-5-yl)amino]-1'-D-prolyl-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	427.1	1.3 min [d]
4-[(4-methyl-1H-indol-5-yl)amino]-1'-L-prolyl-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	427.1	1.3 min [d]
4-[(4-methyl-1H-indol-5-yl)amino]-1'-(pyrrolidin-3-ylcarbonyl)-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	427.1	1.3 min [d]



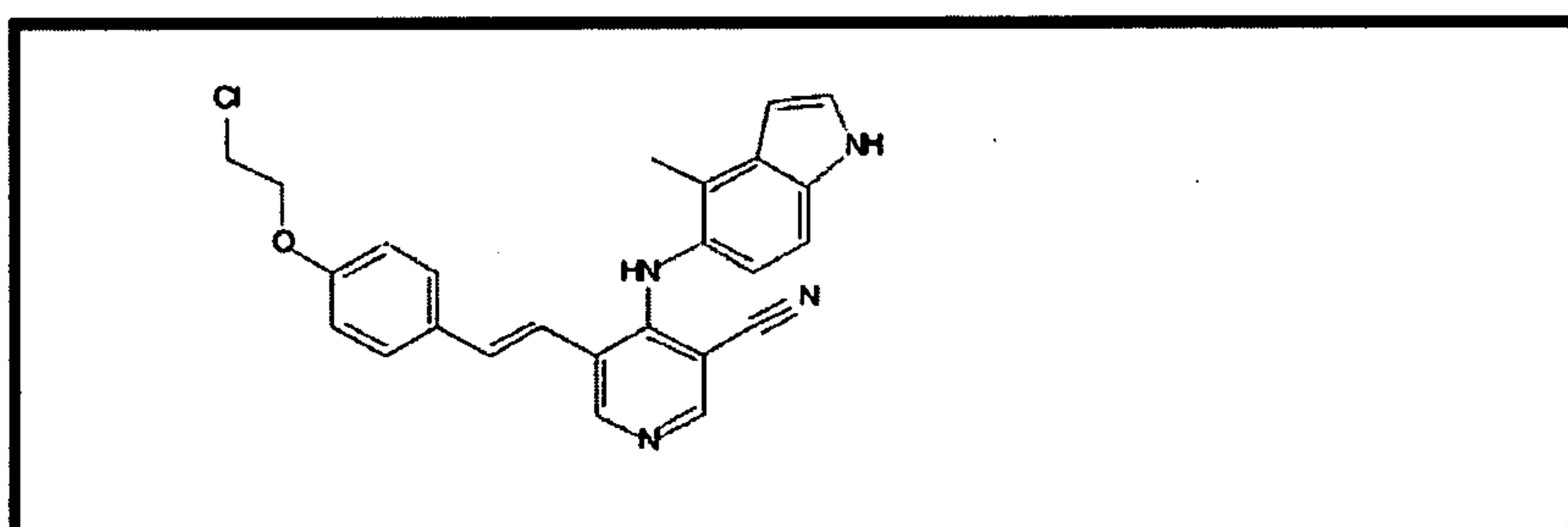
[00195] Preparation of 4-[(4-methyl-1H-indol-5-ylamino)]-5-vinylnicotinonitrile:

A mixture of 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (300 mg, 0.80 mmol), tributyl(vinyl)tin (350 μ L, 1.20 mmol), CuI (5 mg) and (Ph₃P)₂PdCl₂ (15 mg) in 8 mL of DMF was heated at 80°C for 30 min. After cooling to room temperature the reaction mixture was partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was triturated with ethyl acetate to give 128 mg (58%) of 4-[(4-methyl-1H-indol-5-ylamino)]-5-vinylnicotinonitrile as a light tan solid; MS 275.2 (M+H); HPLC: 95.5% at 215 nm, 6.2 min [a].



[00196] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(2-pyrrolidin-1-ylethoxy)phenyl]vinyl]nicotinonitrile:

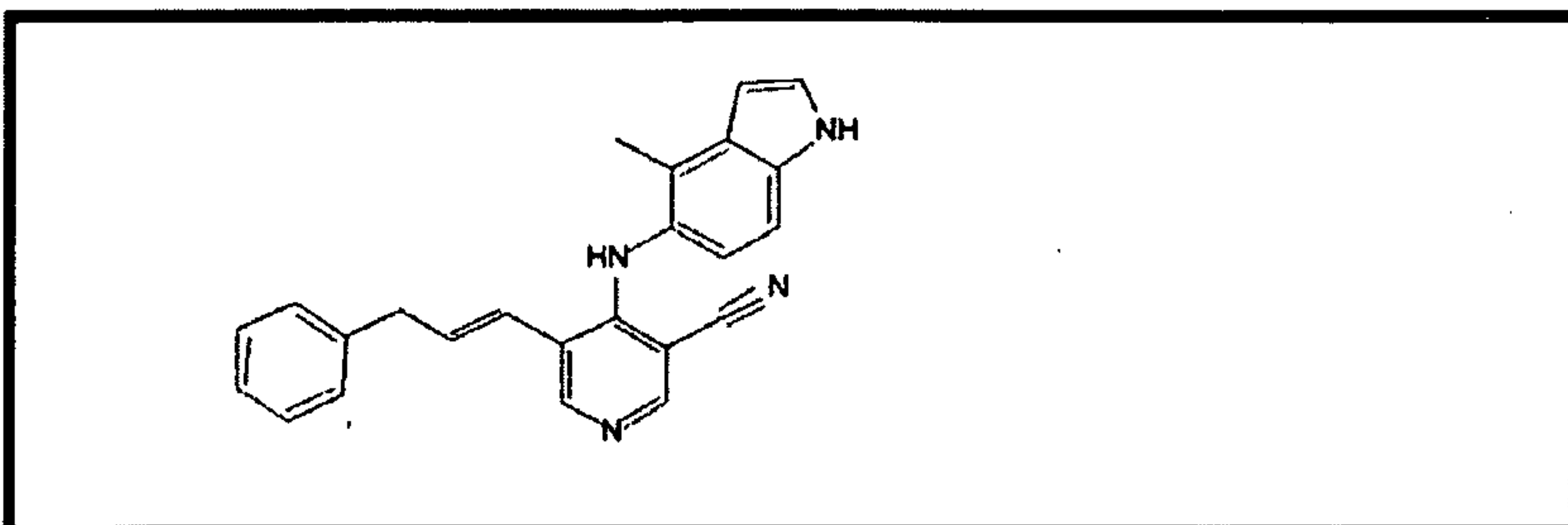
4-[(4-methyl-1H-indol-5-ylamino)]-5-vinylnicotinonitrile (60 mg, 0.22 mmol), 1-(2-(4-bromophenoxy)ethyl)pyrrolidine (70 mg, 0.26 mmol), tri(ortho-tolyl)phosphine (10 mg, 0.033 mmol), and palladium acetate (4 mg, 0.016 mmol) were heated to 120° C in a mixture of 2 mL DMF and 92 μ L (0.66 mmol) of triethyl amine. After heating for 1h, the reaction was cooled and filtered. The filtrate was concentrated and the product was purified by preparative HPLC (ACN/water) to give 50 mg of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(2-pyrrolidin-1-ylethoxy)phenyl]vinyl]nicotinonitrile as its TFA salt; MS 464.4 (M+H); HPLC: rt = 6.0 min [a].



[00197] Preparation of 5-[(E)-2-[4-(2-chloroethoxy)phenyl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

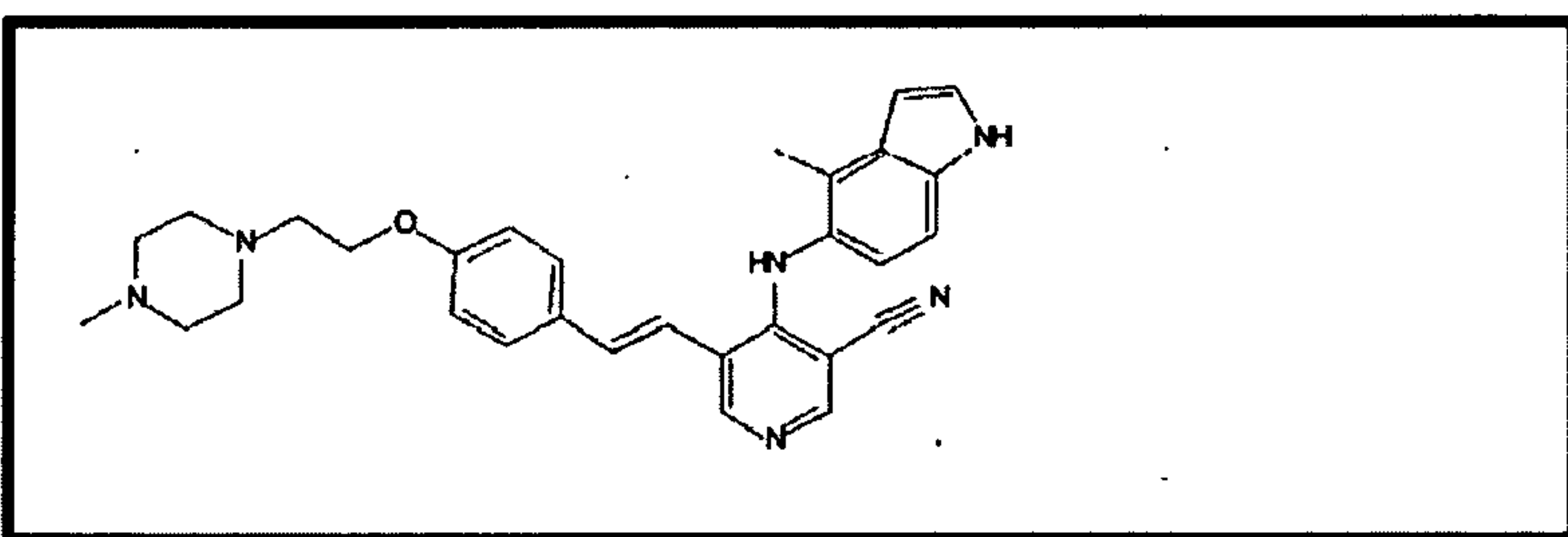
4-[(4-methyl-1H-indol-5-ylamino)]-5-vinylnicotinonitrile (100 mg, 0.36 mmol), 1-bromo-4-(2-chloroethoxy)benzene (103 mg, 0.44 mmol), tri(ortho-tolyl)phosphine (16 mg, 0.054 mmol), and palladium acetate (6 mg, 0.027 mmol) were heated to 120° C in a mixture of 2 mL DMF and 100 μ L (0.72 mmol) of triethyl amine. After heating for 1h, the reaction was cooled and diluted with EtOAc/methanol and washed twice with water. The organic layer was

concentrated onto silica gel and purified by chromatography (EtOAc/hex) to give 66 mg of 5-[(E)-2-[4-(2-chloroethoxy)phenyl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile; MS 429.3 (M+H); HPLC rt = 10.7 min [a].



[00198] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-3-phenylprop-1-en-1-yl]nicotinonitrile:

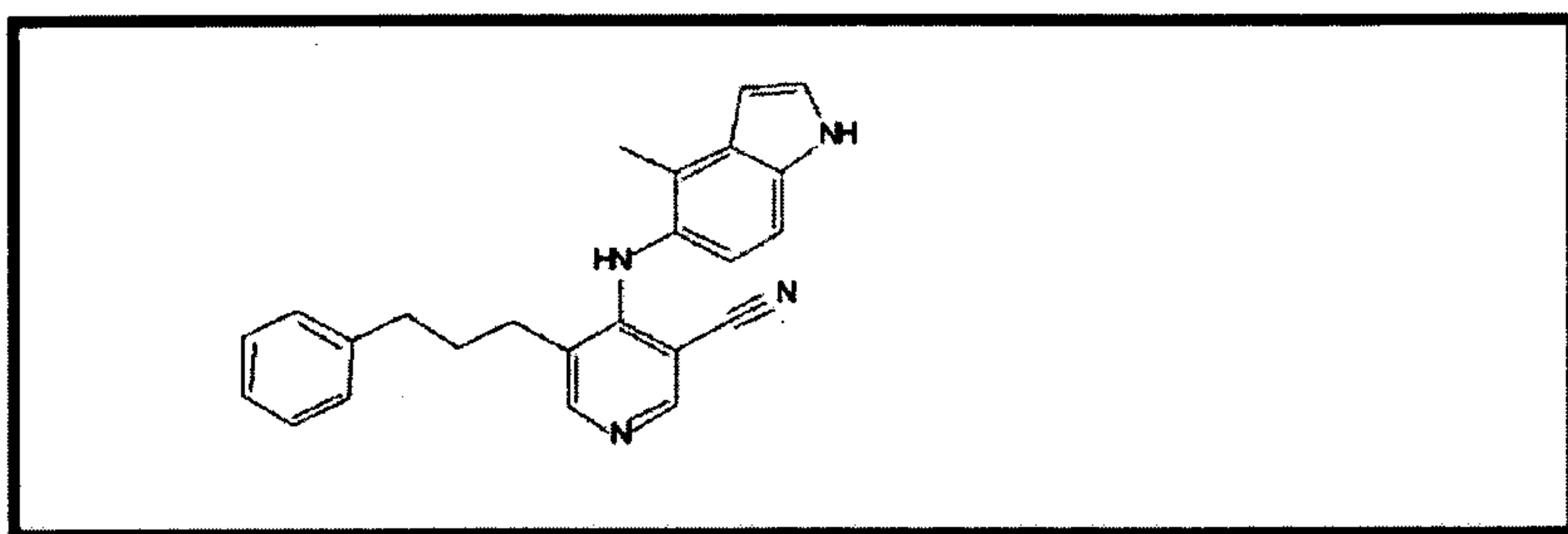
5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (200 mg, 0.53 mmol), (E)-3-phenylprop-1-enylboronic acid (121 mg, 0.75 mmol), and tetrakis(triphenylphosphine) palladium (50 mg) was heated to 80° C in 5 mL of DMF and 0.5 mL of saturated aqueous sodium bicarbonate. After heating overnight, the reaction was filtered and the filtrate was purified by preparative HPLC (acetonitrile/water) to give 100 mg of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-3-phenylprop-1-en-1-yl]nicotinonitrile; MS 365.3 (M+H); HPLC: rt = 10.0 min [a].



[00199] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]vinyl]nicotinonitrile:

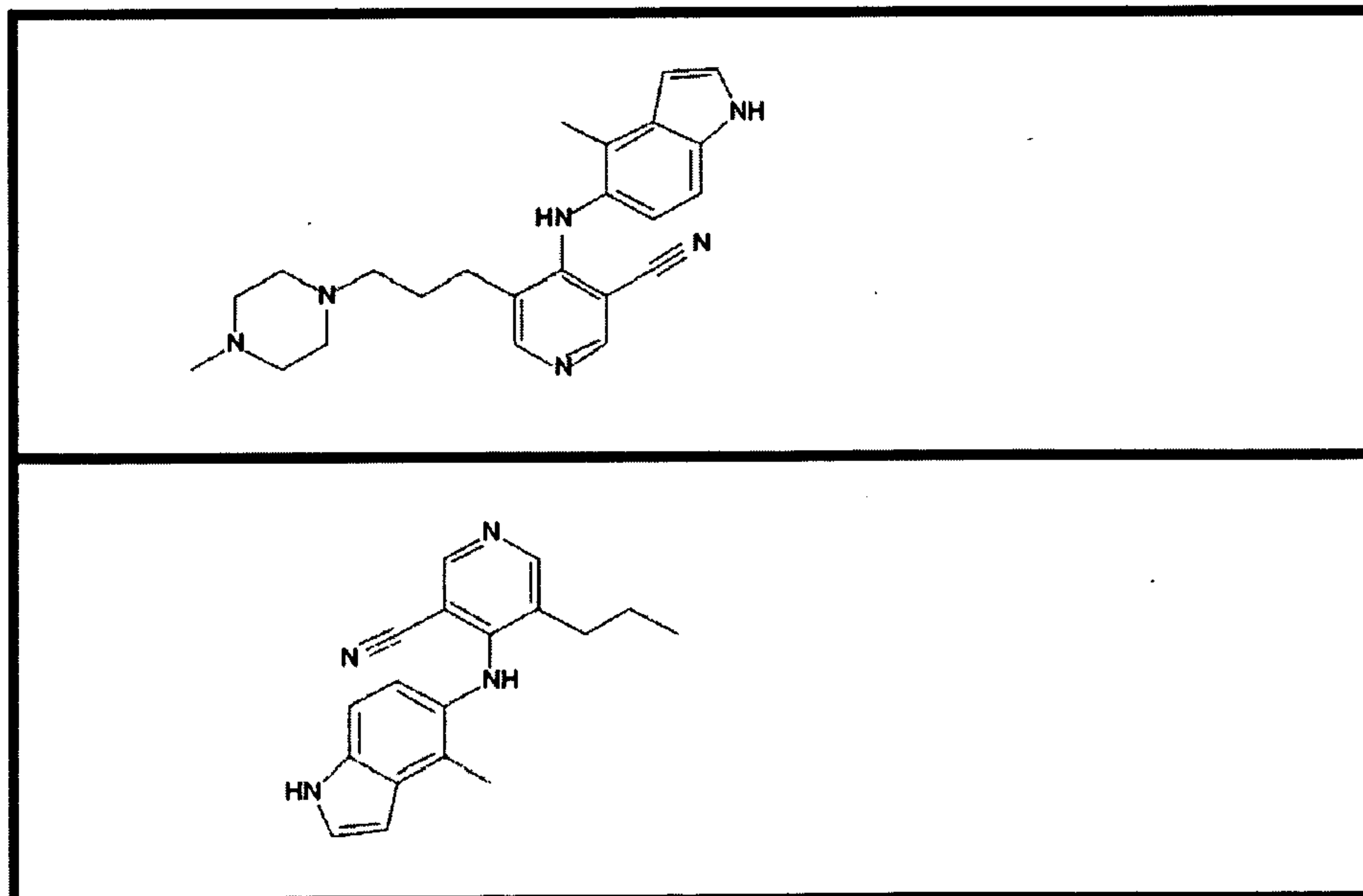
5-[(E)-2-[4-(2-chloroethoxy)phenyl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (75 mg, 0.18 mmol), N-methyl piperazine (54 mg, 0.54 mmol), and NaI (8 mg, 0.05 mmol) were heated in 3 mL DME at 100° C for 48h. The reaction was concentrated, dissolved in DMF, and purified by preparative HPLC (acetonitrile/water) to give 4-[(4-methyl-1H-indol-5-yl)amino]-

5-[(E)-2-{4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}vinyl]nicotinonitrile as its bis-TFA salt. The free base was generated by addition of excess polymer-bound ammonium carbonate to a solution of the title compound in DCM/methanol: MS 493.4 (M+H); HPLC: rt = 5.8 min [a].



[00200] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-(3-phenylpropyl)nicotinonitrile:

4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-3-phenylprop-1-en-1-yl]nicotinonitrile (80 mg) was treated with 15 mg of 10% Pd on activated carbon and shaken in 10 mL EtOH under 30 PSI of hydrogen. After 2h the reaction mixture was filtered and the filtrate was concentrated and purified by HPLC to give 35 mg of 4-[(4-methyl-1H-indol-5-yl)amino]-5-(3-phenylpropyl)nicotinonitrile; MS 367.3 (M+H); HPLC: rt = 9.8 min [a].



[00201] Preparation 4-[(4-methyl-1H-indol-5-yl)amino]-5-[3-(4-methylpiperazin-1-yl)propyl]nicotinonitrile and 4-[(4-methyl-1H-indol-5-yl)amino]-5-propyl nicotinonitrile:

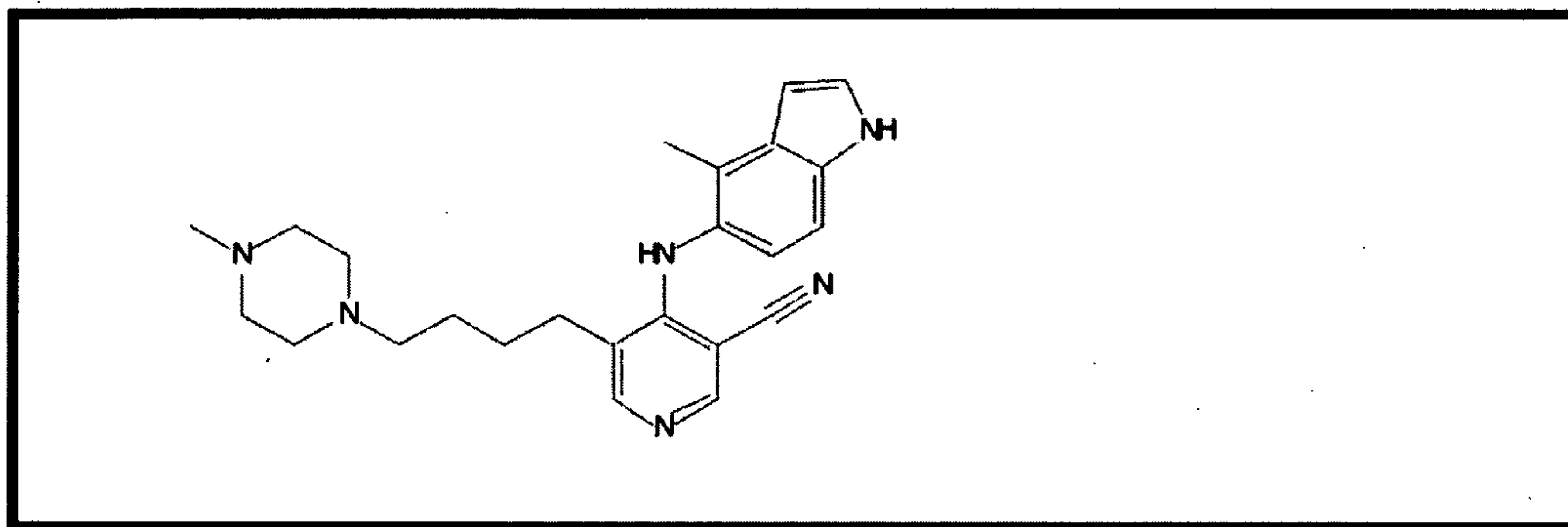
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-3-(4-methylpiperazin-1-yl) prop-1-en-1-yl] nicotinonitrile (154 mg, 0.40 mmol) and palladium (15 mg, 10% on C; wet) in 30 mL of EtOH was stirred rapidly under H₂ at 1 atm for 1 hr at room temperature. The reaction was filtered and the two products were isolated from the filtrate via HPLC purification.

[00202] 4-[(4-methyl-1H-indol-5-yl)amino]-5-[3-(4-methylpiperazin-1-yl)propyl] nicotinonitrile:

MS 389.4 (M+H); HPLC: rt = 2.7 min [a]

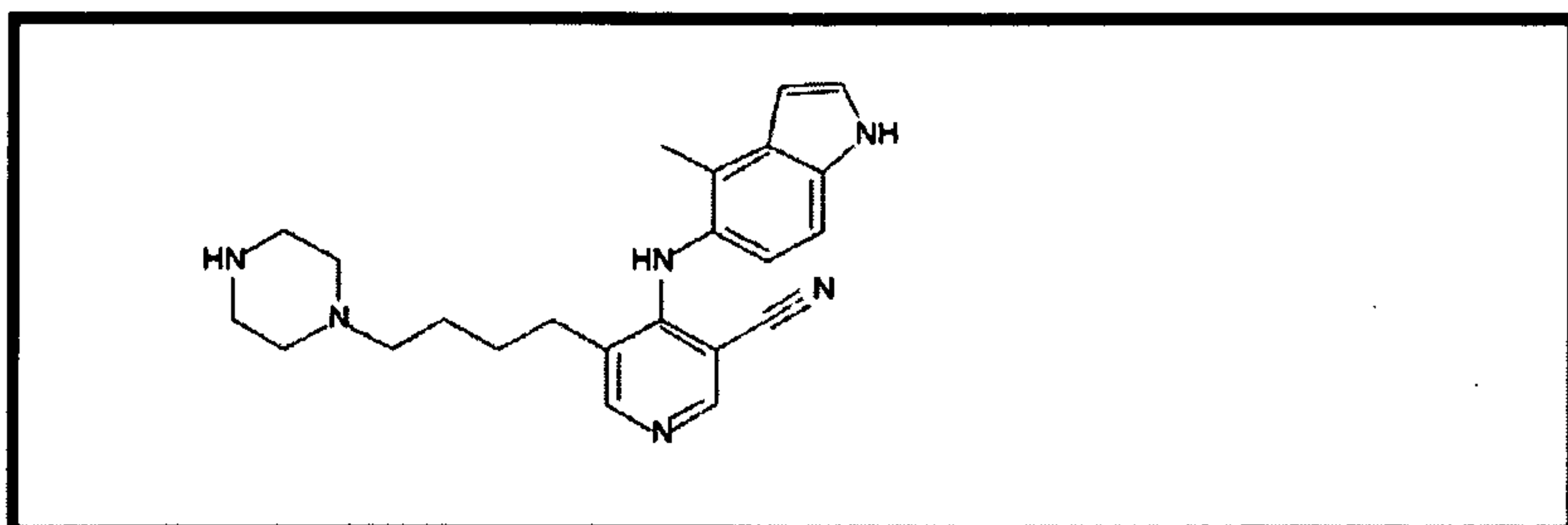
[00203] 4-[(4-methyl-1H-indol-5-yl)amino]-5-propylnicotinonitrile:

MS 291.2 (M+H); HPLC: rt = 1.59 min[c].



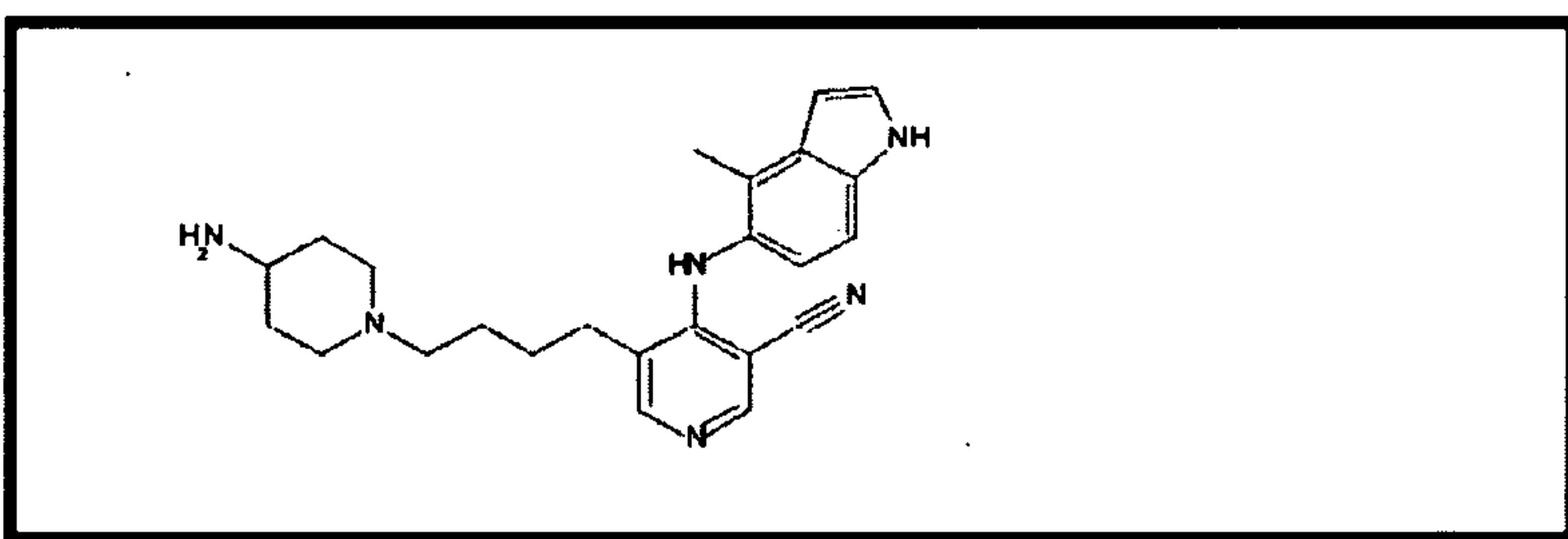
[00204] Preparation 4-[(4-methyl-1H-indol-5-yl)amino]-5-[4-(4-methylpiperazin-1-yl)butyl]nicotinonitrile:

4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-3-(4-methylpiperazin-1-yl)but-1-en-1-yl]nicotinonitrile (92 mg, 0.23 mmol) and palladium (9 mg, 10%; wet) in 20 mL of EtOH was stirred rapidly under H₂ at 1 atm for 1 hr at room temperature. The palladium was filtered and the filtrate was purified by HPLC to give 4-[(4-methyl-1H-indol-5-yl)amino]-5-[4-(4-methylpiperazin-1-yl)butyl]nicotinonitrile as a solid; MS 403.4 (M+H); HPLC rt = 4.6 min [b].



[00205] Preparation 4-[(4-methyl-1H-indol-5-yl)amino]-5-(4-piperazin-1-ylbutyl)nicotinonitrile:

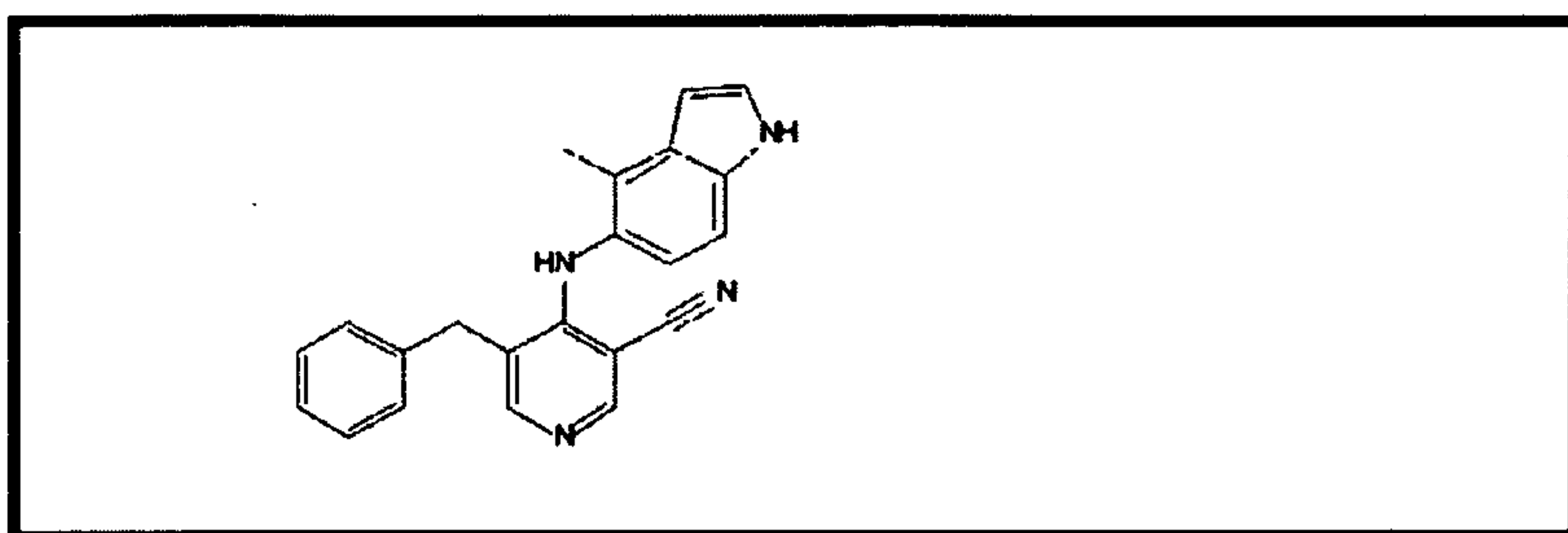
Tert-Butyl-4-[(3E)-4-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]-pyridin-3-yl}-but-3-en-1-yl]piperazine-1-carboxylate (194 mg, 0.40 mmol) and palladium (20 mg, 10%; wet) in 20 mL of EtOH was stirred rapidly under H₂ at 1 atm for 16 hr at room temperature. Additional palladium (20 mg, 10%; wet) was added and the reaction was shaken under 30 psi H₂ for 6 hr. The palladium and solvent were removed to give tert-butyl 4-(4-(5-cyano-4-(4-methyl-1H-indol-5-ylamino)pyridin-3-yl)butyl) piperazine-1-carboxylate. 10% Trifluoroacetic acid/ DCM (5.5 mL) was added to the crude tert-butyl 4-(4-(5-cyano-4-(4-methyl-1H-indol-5-ylamino)pyridin-3-yl)butyl)piperazine-1-carboxylate. After stirring for 3 hr at room temperature, the reaction was concentrated and the residue was purified by HPLC to give 4-[(4-methyl-1H-indol-5-yl)amino]-5-(4-piperazin-1-ylbutyl)nicotinonitrile as its TFA salt; HRMS 389.2454 (M+H); HPLC: rt = 4.2 min [b].



[00206] Preparation 5-[4-(4-aminopiperidin-1-yl)butyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

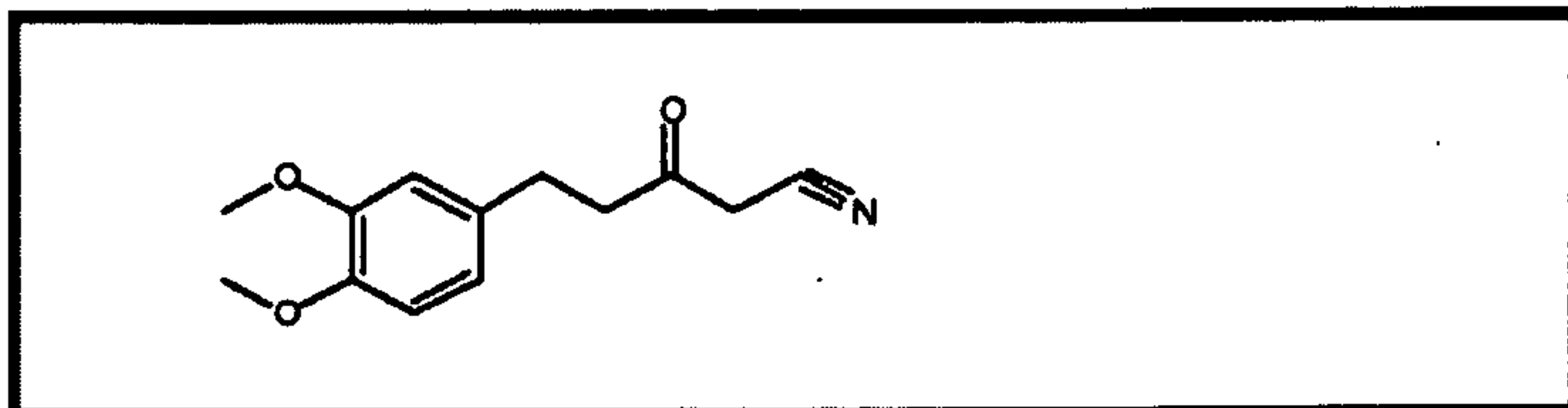
Tert-butyl-{1-[(3E)-4-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]-pyridin-3-yl}-but-3-en-1-yl]piperidin-4-yl}carbamate (200 mg, 0.40 mmol) and palladium (20 mg, 10%; wet) in 20 mL of EtOH was stirred rapidly under H₂ at 1 atm for 16 hr at room temperature. The solvent and

palladium were removed to give tert-butyl 1-(4-(5-cyano-4-(4-methyl-1H-indol-5-ylamino)pyridin-3-yl)butyl)piperidin-4-ylcarbamate. 10% Trifluoroacetic acid/ DCM (5.5 mL) was added to the crude tert-butyl 1-(4-(5-cyano-4-(4-methyl-1H-indol-5-ylamino)pyridin-3-yl)butyl)piperidin-4-ylcarbamate. After stirring for 2 hr at room temperature the reaction was concentrated and the residue was purified by HPLC to give 5-[4-(4-aminopiperidin-1-yl)butyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile as its TFA salt; HRMS 403.2612 (M+H); HPLC: rt = 5.3 min [b].



[00207] Preparation 5-benzyl-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

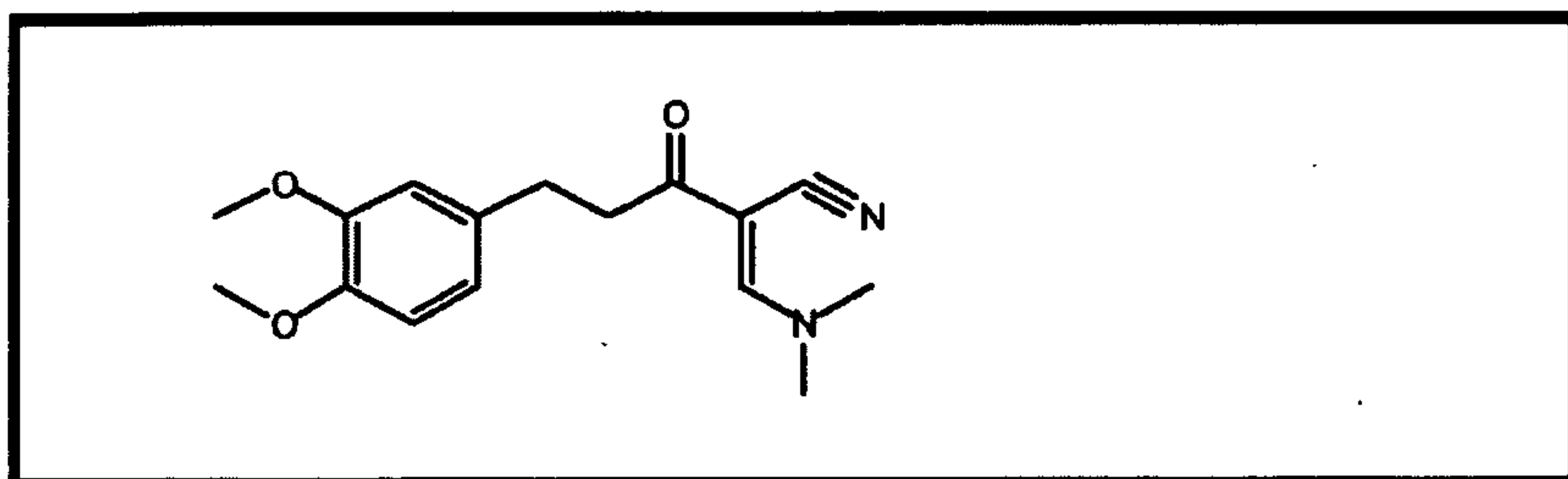
5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (150 mg, 0.40 mmol), potassium benzyltrifluoroborate (158 mg, 0.80 mmol), 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (38 mg, 0.08 mmol), cesium carbonate (391 mg, 1.2 mmol) and palladium acetate (18 mg, 0.08 mmol) in 2.2 mL of 10: 1 THF/ water was heated at 80°C for 32 hr, cooled to room temperature, diluted with DCM and washed with water. The crude material was purified by silica gel chromatography with a MeOH/ DCM gradient to give 5-benzyl-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile as a solid; MS 339.2 (M+H); HPLC: rt = 1.88 min [c]. 4-methyl-1,5-dihydropyrido[4,3-b]pyrrolo[2,3-f]indole-6-carbonitrile was isolated as a by product of this reaction; MS 245.2 (M-H).



[00208] Preparation of 5-(3,4-dimethoxyphenyl)-3-oxopentanitrile:

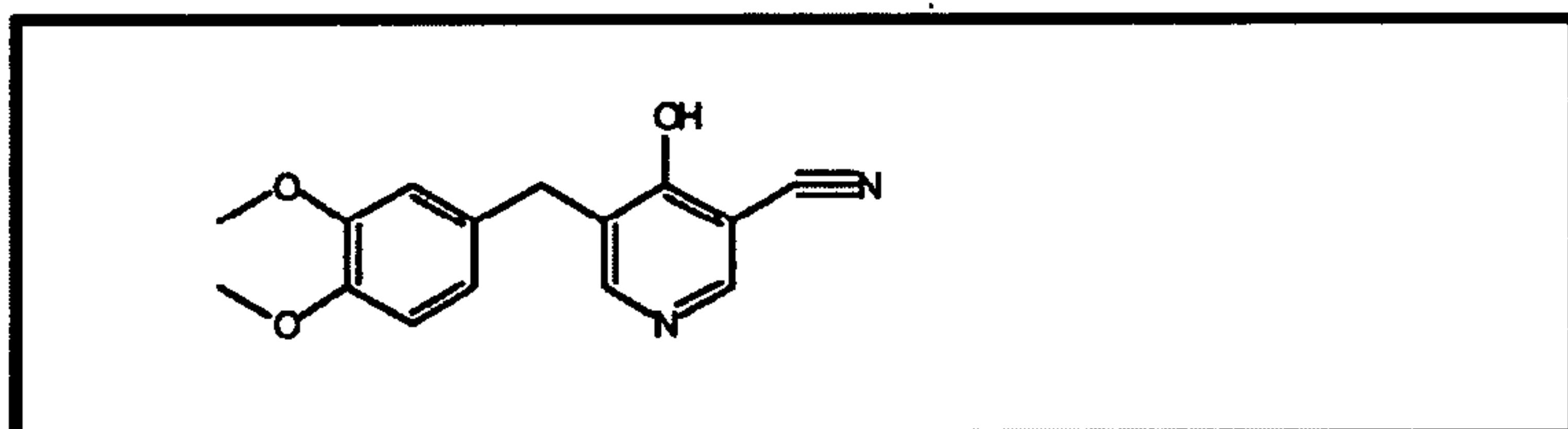
To 65 mL of THF at -78°C was added 2.5 M *n*-butyllithium in hexane (44 mL, 110 mmol). To this solution was added a solution of acetonitrile (4.92 g, 120 mmol) in 120 mL of THF during

10 min. After stirring for 15 min at -78°C the solution was treated with a solution of ethyl 3-(3,4-dimethoxyphenyl)propanoate (11.9 g, 50 mmol) in 15 mL of THF over 5 min. The solution was stirred at -78°C for 30 min, quenched with HOAc (7.2 mL, 125 mmol), and partitioned between Et_2O and water. The organic layer was washed with brine, dried and concentrated to give 5-(3,4-dimethoxyphenyl)-3-oxopentanitrile as a white solid (11.4 g, 97%).



[00209] Preparation of 2-(dimethylaminomethylene)- 5-(3,4-dimethoxyphenyl)-3-oxopentanitrile:

A solution of 5-(3,4-dimethoxyphenyl)-3-oxopentanitrile (4.67 g, 20 mmol) and dimethyl formamide dimethyl acetal (3.1 mL, 22 mmol) was stirred at 25°C for 20 min and concentrated under high vacuum to give 2-(dimethylaminomethylene)-5-(3,4-dimethoxyphenyl)-3-oxopentanitrile as an oil.

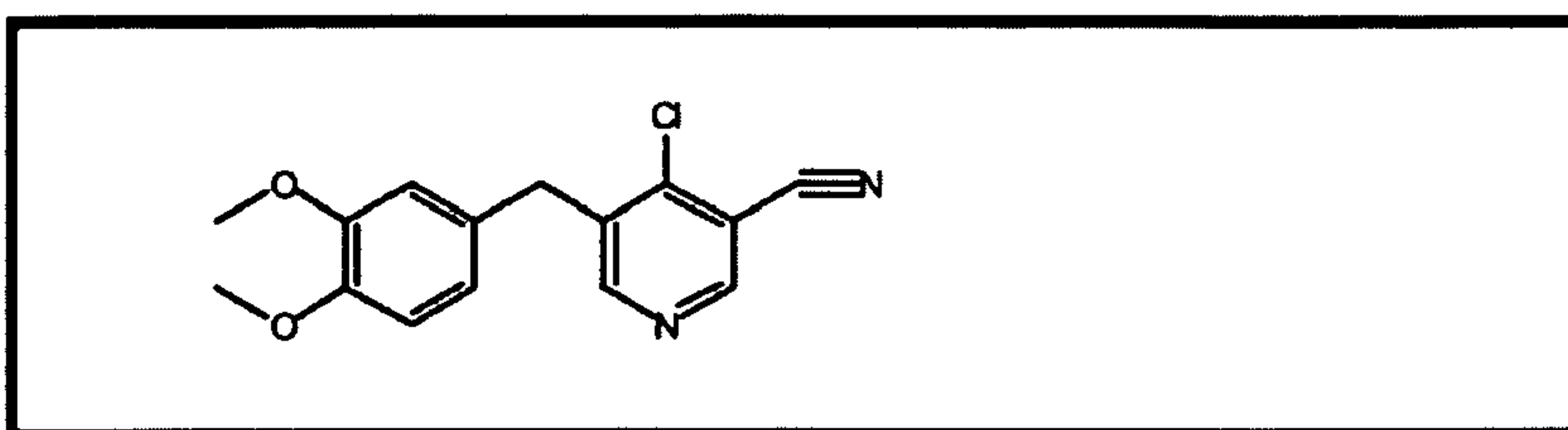


[00210] Preparation of 5-(3,4-dimethoxybenzyl)-4-hydroxynicotinonitrile:

A solution of 2-(dimethylaminomethylene)- 5-(3,4-dimethoxyphenyl)-3-oxopentanitrile (3.46 g, 12.0 mmol), *t*-butoxybis(dimethylamino)methane (3.72 mL, 18 mmol), and 6.0 mL of toluene was heated at reflux for 30 min and concentrated under high vacuum to give 2,4-bis(dimethylaminomethylene)- 5-(3,4-dimethoxyphenyl)-3-oxopentanitrile as a syrup.

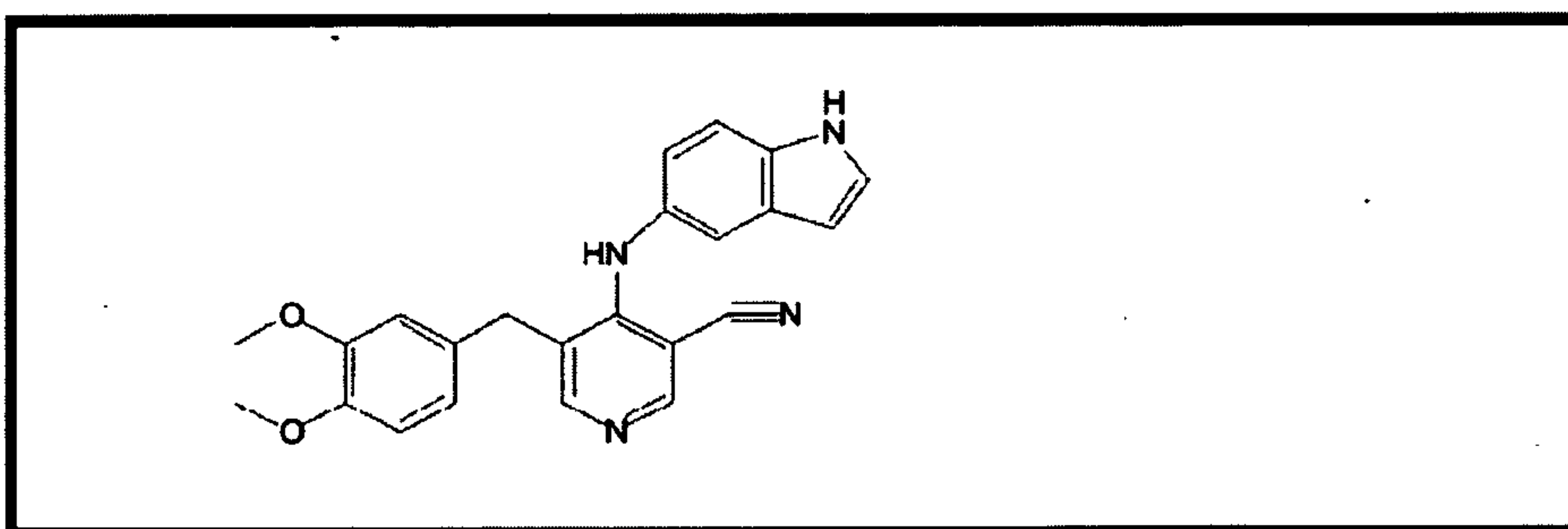
A solution of 2,4-bis(dimethylaminomethylene)- 5-(3,4-dimethoxyphenyl)-3-oxopentanitrile (4.6 g, 12 mmol) in 36 mL of HOAc at 0°C was gassed with ammonia. The resulting suspension was heated at 65°C for 30 min and concentrated to dryness. The residue was

partitioned between EtOAc and water. The EtOAc layer was washed with water, dried and concentrated to give a sticky solid. Recrystallization from EtOH gave 1.96 g of 5-(3,4-dimethoxybenzyl)-4-hydroxynicotinonitrile as a tan solid, mp 228-235°C; MS 269.1 (M-H).



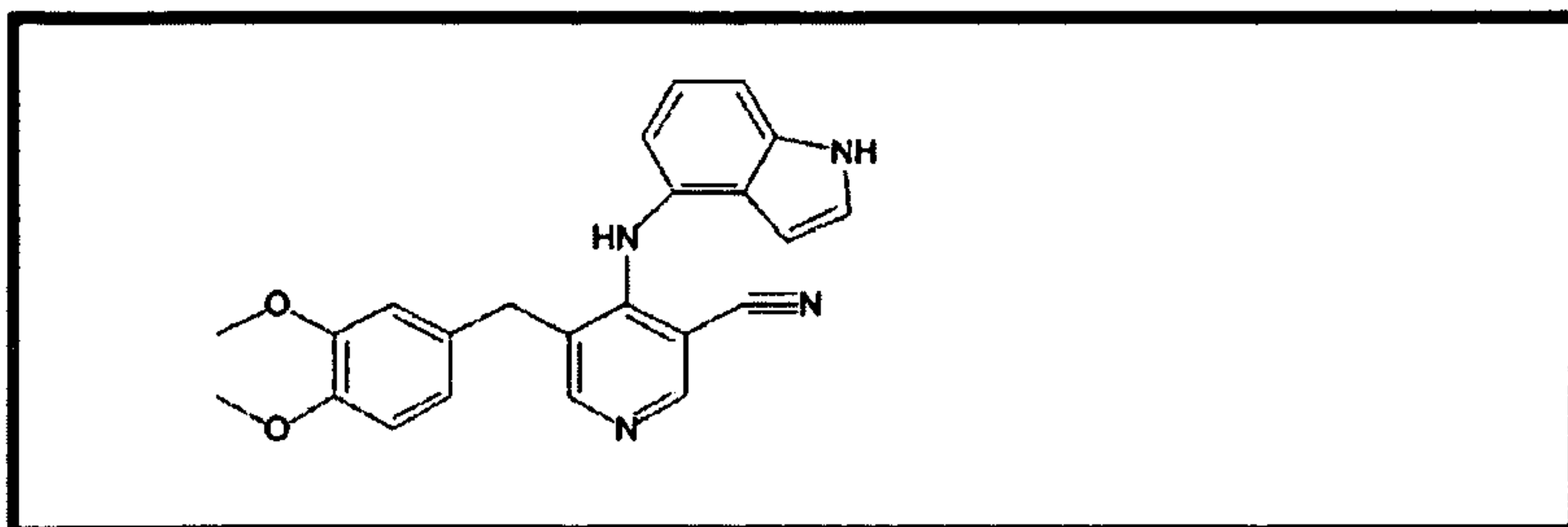
[00211] Preparation of 4-chloro-5-(3,4-dimethoxybenzyl)nicotinonitrile:

To a stirred suspension of 5-(3,4-dimethoxybenzyl)-4-hydroxynicotinonitrile (1.24 g, 4.6 mmol) and 46 mL of thionyl chloride at 25 °C was added 0.07 mL of DMF. The resulting solution was stirred for 3 h and concentrated to dryness under high vacuum. A solution of the residue in 5:1 DCM-toluene was passed through a pad of Magnesol. The filtrate was concentrated to give 4-chloro-5-(3,4-dimethoxybenzyl)nicotinonitrile as a light amber solid (1.14 g, 86%).



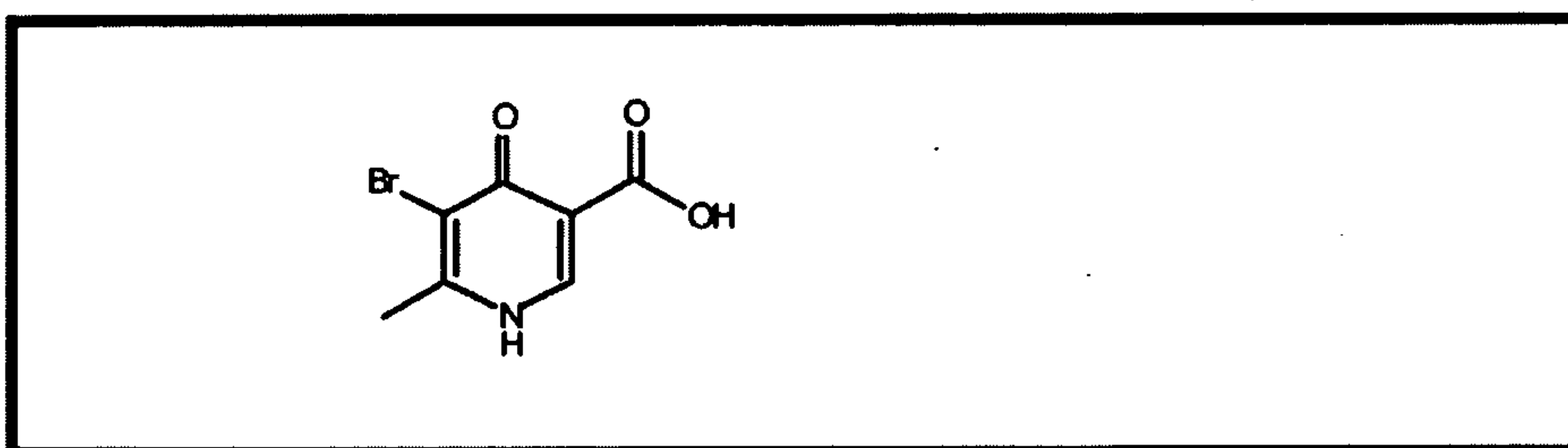
[00212] Preparation of 5-(3,4-dimethoxybenzyl)-4-(1H-indol-5-ylamino)nicotinonitrile:

A stirred solution of 4-chloro-5-(3,4-dimethoxybenzyl)nicotinonitrile (144 mg, 0.50 mmol), 5-aminoindole (99 mg, 0.75 mmol), pyridine hydrochloride (58 mg, 0.50 mmol), and 1.5 mL of i-PrOH was heated at reflux for 1.5 h and concentrated to dryness. The residue was stirred in dilute aq NaHCO₃, and the resulting solid was filtered, washed with water, and dried. Crystallization from EtOAc-hexane gave 5-(3,4-dimethoxybenzyl)-4-(1H-indol-5-ylamino)nicotinonitrile as a tan solid (50 mg, 26%), mp 108-115°C; MS 385.2 (M+H).



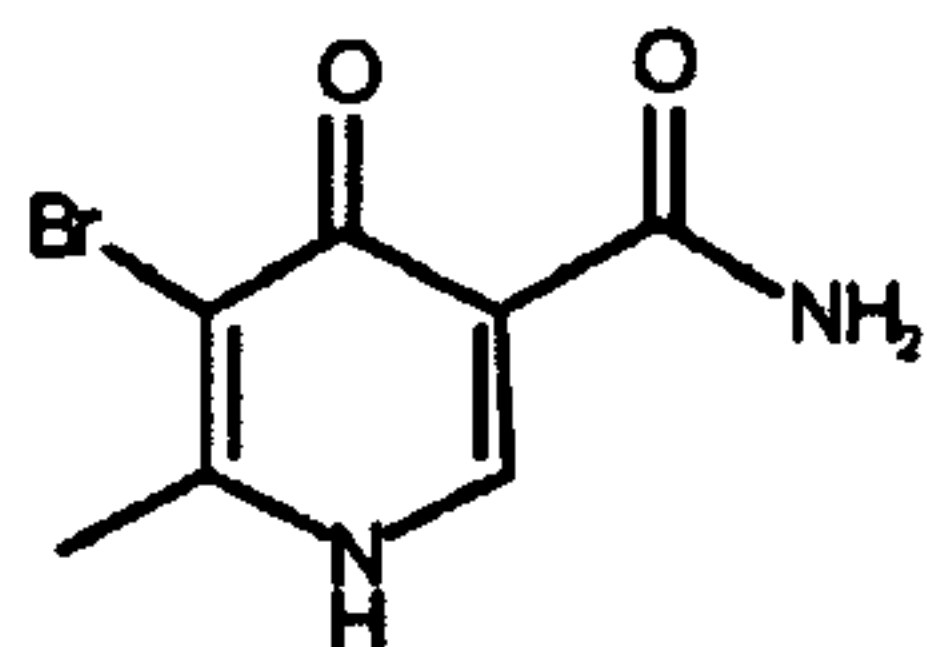
[00213] Preparation of 5-(3,4-dimethoxybenzyl)-4-(1H-indol-4-ylamino)nicotinonitrile:

A stirred solution of 4-chloro-5-(3,4-dimethoxybenzyl)nicotinonitrile (144 mg, 0.50 mmol), 4-aminoindole (99 mg, 0.75 mmol), pyridine hydrochloride (58 mg, 0.50 mmol), and 1.5 mL of *t*-amyl alcohol was heated at reflux for 24 h. The cooled mixture was stirred in dilute NaHCO₃ and hexane, and the resulting solid was filtered, washed with water, and dried. Chromatography of the residue on silica gel with DCM-EtOAc-MeOH gave 5-(3,4-dimethoxybenzyl)-4-(1H-indol-4-ylamino)nicotinonitrile as an amber solid (82 mg, 43%); *R*_f (25:25:1 DCM-EtOAc-MeOH) 0.50; MS 385.1 (M+H).



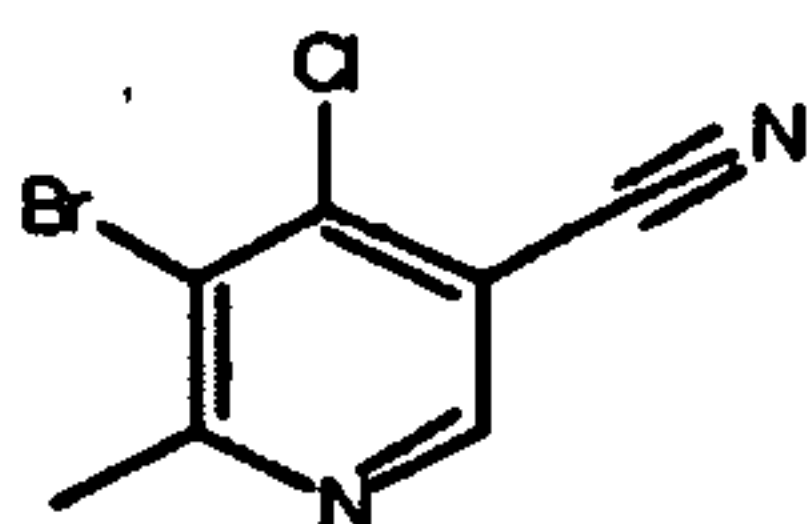
[00214] Preparation of 5-bromo-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid:

To 6-methyl-4(1H)-pyridone-3-carboxylic acid (1.54 g, 10.06 mmol) and 800 µL of pyridine in 30 mL of acetic acid at 100°C was slowly added 720 µL of bromine in 5 mL of acetic acid. The reaction mixture was kept at 100°C for 2 h then cooled to room temperature. The solids were collected by filtration and washed with methanol to provide 850 mg (36%) of 5-bromo-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid as a white solid; MS 232.0 (M+H).



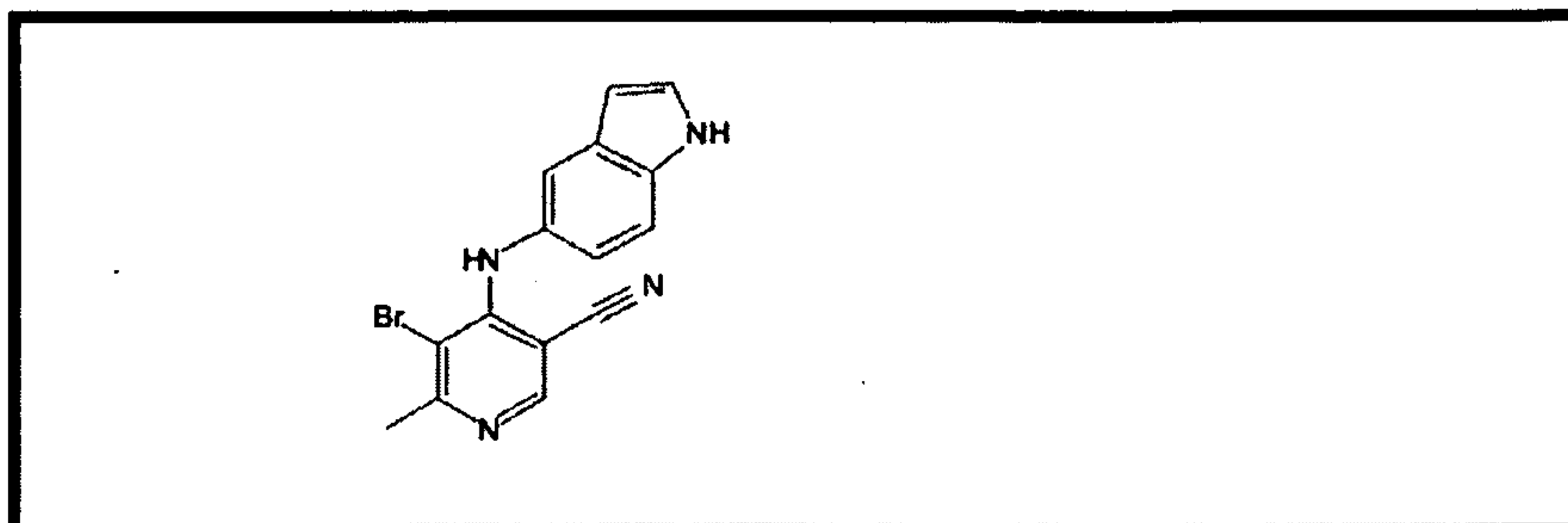
[00215] Preparation of 5-bromo-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxamide:

A mixture of 5-bromo-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (8.0 g, 34.5 mmol) and 1,1'-carbonyldiimidazole (12.2 g, 75.3 mmol) in 120 mL of DMF was heated at 65-75°C for 3 h. The reaction mixture was cooled on an ice-bath and poured into cooled 29% aqueous ammonium hydroxide (84 mL). After stirring at 0-5°C for 1.5 h, the mixture was poured onto ice and the pH was adjusted to 5-6 with 1 N hydrochloric acid. The solids were collected by filtration, then washed with water followed by diethyl ether to provide 7.25 g (91%) of 5-bromo-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxamide as a white solid; MS 228.9(M-H).



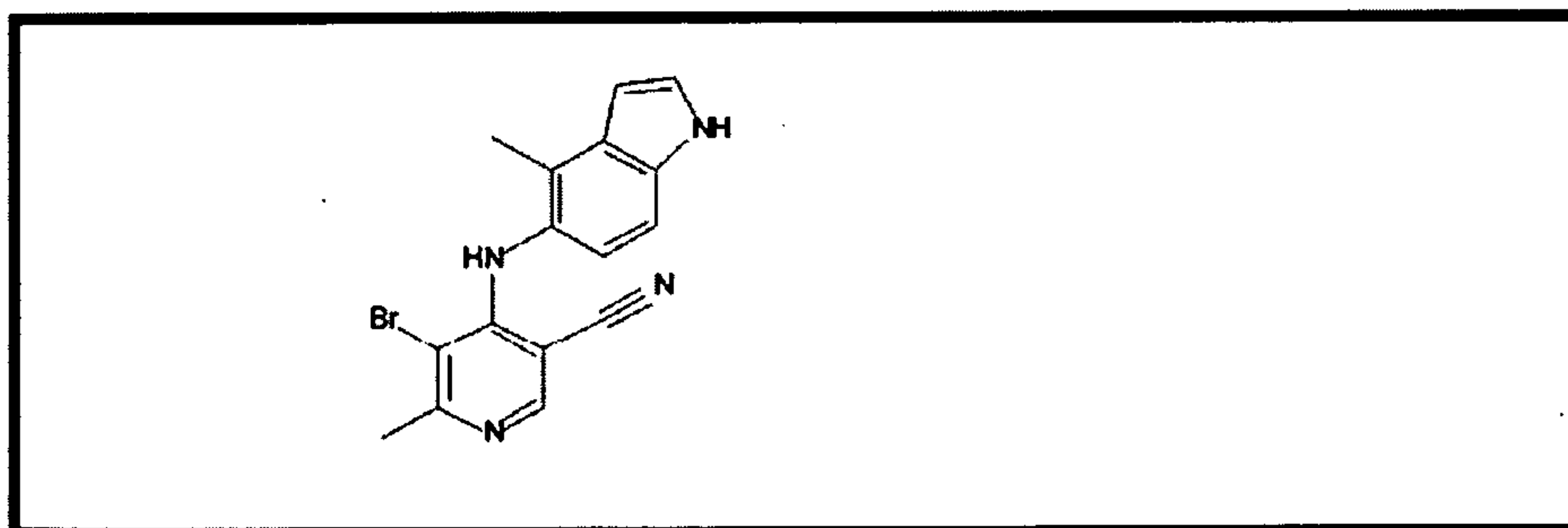
[00216] Preparation of 5-bromo-4-chloro-6-methylnicotinonitrile:

A mixture of 5-bromo-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxamide (7.12 g, 30.8 mmol) and 1 drop of DMF in 30 mL of phosphorus oxychloride was heated at reflux for 2 h. The volatiles were removed *in vacuo* and the residue was slurried with ice. Saturated aqueous sodium bicarbonate was slowly added until the mixture had a basic pH. The solids were collected by filtration, washing with aqueous sodium bicarbonate and water to provide 5.50 g (77%) of 5-bromo-4-chloro-6-methylnicotinonitrile as a tan solid; MS 231.0 (M+H).



[00217] Preparation of 5-bromo-4-(1H-indol-5-ylamino)-6-methylnicotinonitrile:

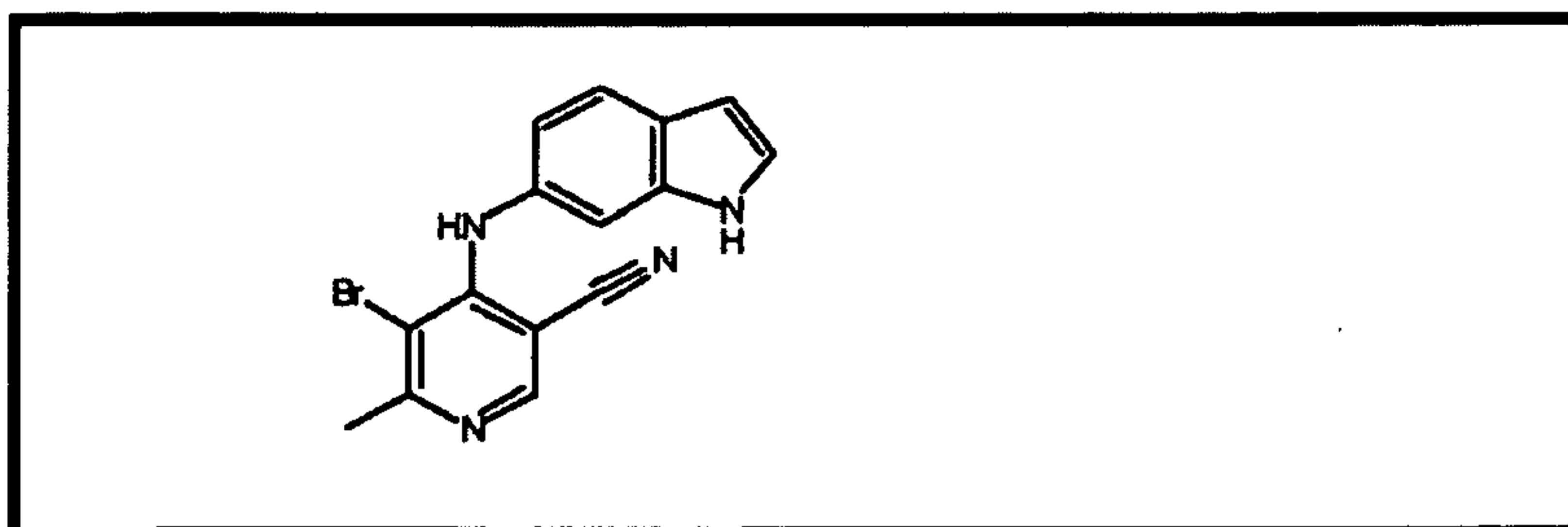
A mixture of 5-bromo-4-chloro-6-methylnicotinonitrile (1.0 g, 4.31mmol) and 5-aminoindole (830 mg, 6.29 mmol) in 10 mL of ethanol was heated at reflux for 2 h. The resulting mixture was cooled slightly and filtered, washing with ethanol and diethyl ether. The solid was stirred with saturated aqueous sodium bicarbonate for 30 min then the aqueous mixture was extracted with ethyl acetate. The layers were separated and the organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was triturated with diethyl ether to give 852 mg (60%) of 5-bromo-4-(1H-indol-5-ylamino)-6-methylnicotinonitrile as a light tan solid; MS 327.2 (M+H); HPLC: 99.9% at 215 nm, 8.6 min [a].



[00218] Preparation of 5-bromo-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

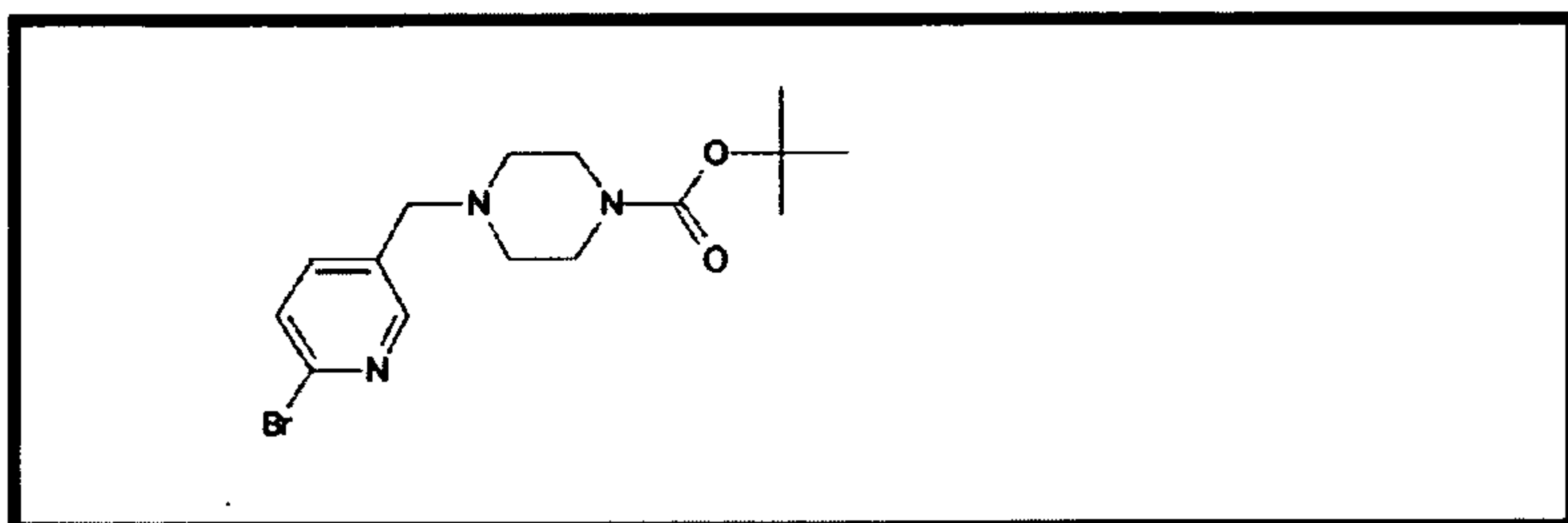
Mixture of 5-bromo-4-chloro-6-methylnicotinonitrile (2.00 g, 8.63 mmol) and 5-amino-4-methylindole (1.82 mg, 12.47 mmol) in 20 mL of ethanol was heated at reflux overnight. The resulting mixture was cooled slightly and filtered washing with ethanol. The solid was stirred with saturated aqueous sodium bicarbonate then the aqueous mixture was extracted with ethyl acetate. The layers were separated and the organic layer was washed with saturated aqueous sodium bicarbonate dried over magnesium sulfate, filtered and concentrated *in vacuo*. The

residue was triturated with diethyl ether to give 1.21 g (41%) of 5-bromo-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile as an off-white solid; MS 341.2 (M+H); HPLC: 99.2% at 215 nm, 9.5 min [a].



[00219] Preparation of 5-bromo-4-(1H-indol-6-ylamino)-6-methylnicotinonitrile:

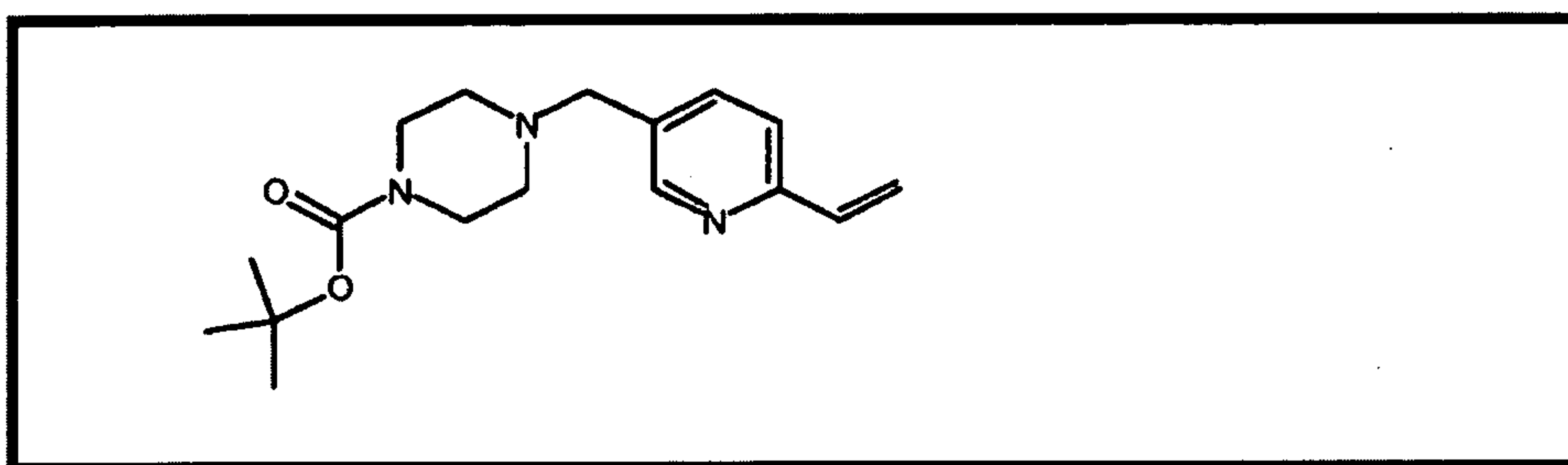
A mixture of 5-bromo-4-chloro-6-methylnicotinonitrile (500 mg, 2.15 mmol) and 6-aminoindole (415 mg, 3.14 mmol) in 5 mL of ethanol was heated at reflux for 2 h. The resulting mixture was cooled slightly and filtered washing with ethanol. The residue was poured into saturated aqueous sodium bicarbonate and the aqueous mixture was extracted with ethyl acetate. The layers were separated and the organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was triturated with diethyl ether to give 253 g (36%) of 5-bromo-4-(1H-indol-6-ylamino)-6-methylnicotinonitrile as an off-white solid; MS 327.1 (M+H); HPLC: 99.7% at 215 nm, *rt* = 9.1 min [a].



[00220] Preparation of tert-butyl 4-[(6-bromopyridin-3-yl)methyl]piperazine-1-carboxylate:

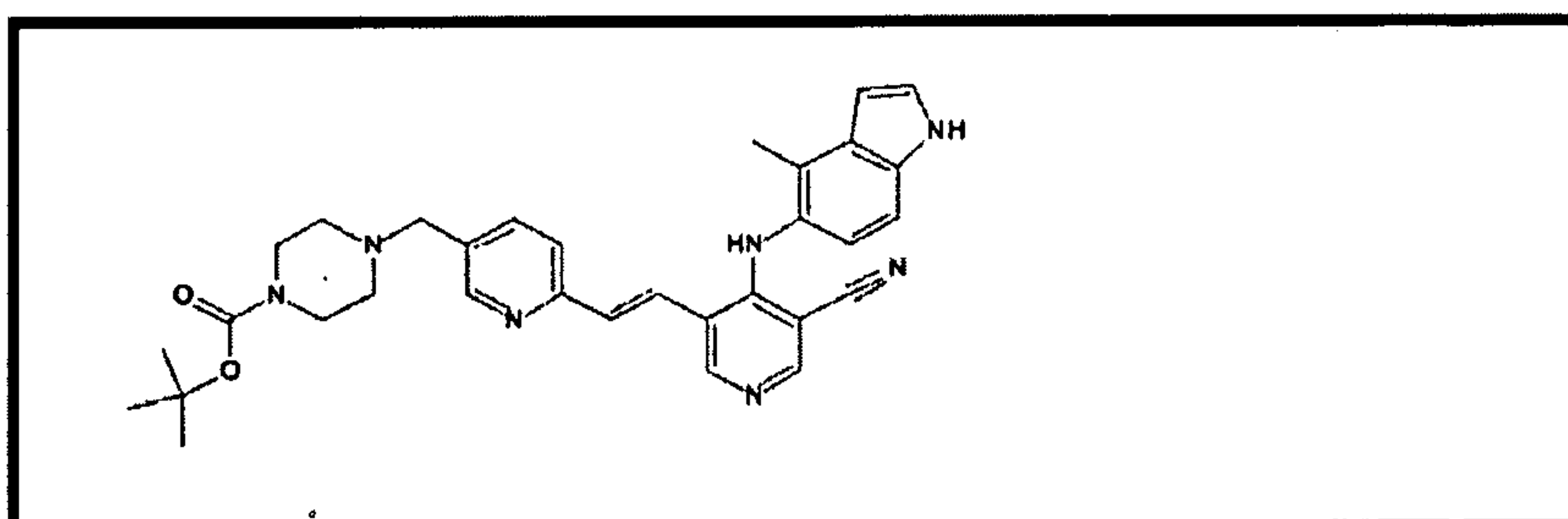
To a 0°C solution of 6-bromopyridine-3-carbaldehyde (2.06 g, 11.08 mmol) and tert-butyl piperazine-1-carboxylate (2.94g, 15.81 mmol) in 40 mL of dichloromethane and 2 mL of 1-methyl-2-pyrrolidinone was added sodium triacetoxyborohydride (3.12 g, 14.72 mmol). After 10 min, 400 µL of acetic acid was added and the reaction mixture was allowed to stir at room

temperature overnight. Additional amounts of both tert-butyl piperazine-1-carboxylate (1.0 g) and sodium triacetoxyborohydride (0.98 g) were added and the reaction mixture was stirred at room temperature for 3 h then partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The layers were separated and the organic layer was washed with saturated aqueous sodium bicarbonate, dried over magnesium sulfate, filtered and concentrated *in vacuo*. Trituration of the residue with hexane gave 1.80 g (46%) of tert-butyl 4-[(6-bromopyridin-3-yl)methyl]piperazine-1-carboxylate as off-white crystals; MS 356.2 (M+H).



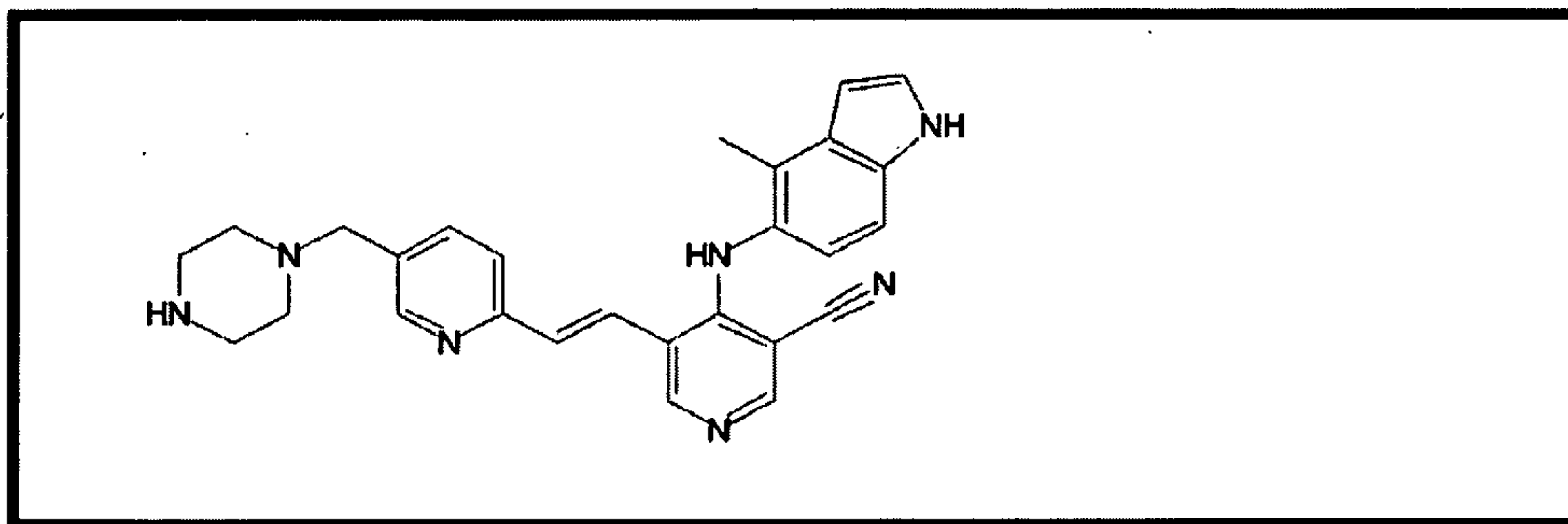
[00221] Preparation of tert-butyl 4-[(6-vinylpyridin-3-yl)methyl]piperazine-1-carboxylate:

A mixture of tert-butyl 4-[(6-bromopyridin-3-yl)methyl]piperazine-1-carboxylate (1.52 g, 4.25 mmol), tributyl(vinyl)tin (1.84 mL, 6.30 mmol), CuI (50 mg) and (Ph₃P)₂PdCl₂ (150 mg) in 20 mL of toluene was heated at reflux overnight. After cooling to room temperature the reaction mixture was partitioned between saturated aqueous potassium carbonate and dichloromethane. The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography eluting with a gradient of 3:1 hexane:ethyl acetate to 100% ethyl acetate to give 1.04 g (81%) of tert-butyl 4-[(6-vinylpyridin-3-yl)methyl]piperazine-1-carboxylate as a light yellow oil; MS 304.3 (M+H).



[00222] Preparation of tert-butyl 4-((6-((E)-2-(5-cyano-4-((4-methyl-1H-indol-5-yl)amino)pyridin-3-yl)vinyl)pyridin-3-yl)methyl)piperazine-1-carboxylate:

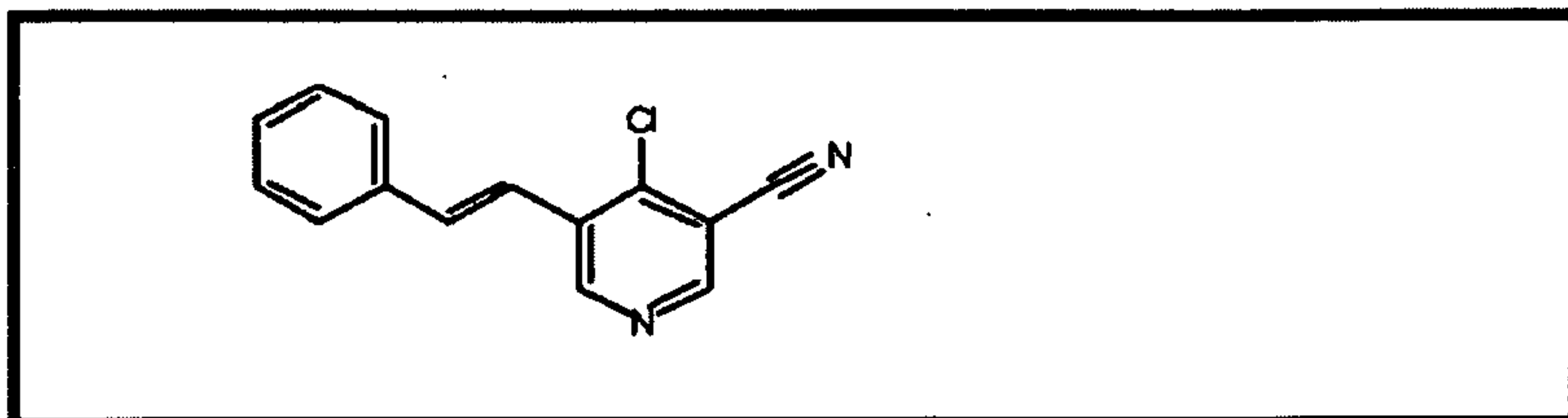
A mixture of 5-iodo-4-((4-methyl-1H-indol-5-yl)amino)nicotinonitrile (240 mg, 0.64 mmol), tert-butyl 4-((6-vinylpyridin-3-yl)methyl)piperazine-1-carboxylate (318 mg, 1.05 mmol), palladium(II)acetate (25 mg), tri(ortho-tolyl)phosphine (12 mg) and 600 μ L of triethylamine in 6 mL of DMF was heated at 90-105°C for 3 h. After cooling to room temperature the reaction mixture was partitioned between saturated aqueous sodium bicarbonate and dichloromethane. The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography eluting with a gradient of 1:1 hexane:ethyl acetate to all ethyl acetate to 20% methanol in ethyl acetate to give 149 mg (42%) of tert butyl 4-((6-((E)-2-(5-cyano-4-((4-methyl-1H-indol-5-yl)amino)pyridin-3-yl)vinyl)pyridin-3-yl)methyl)piperazine-1-carboxylate as a yellow solid; MS 550.5 (M+H) HPLC 97.2% at 215 nm, rt = 7.1 min [a].



[00223] Preparation of 4-((4-methyl-1H-indol-5-yl)amino)-5-((E)-2-[5-(piperazin-1-yl)methyl]pyridin-2-yl)vinyl)nicotinonitrile:

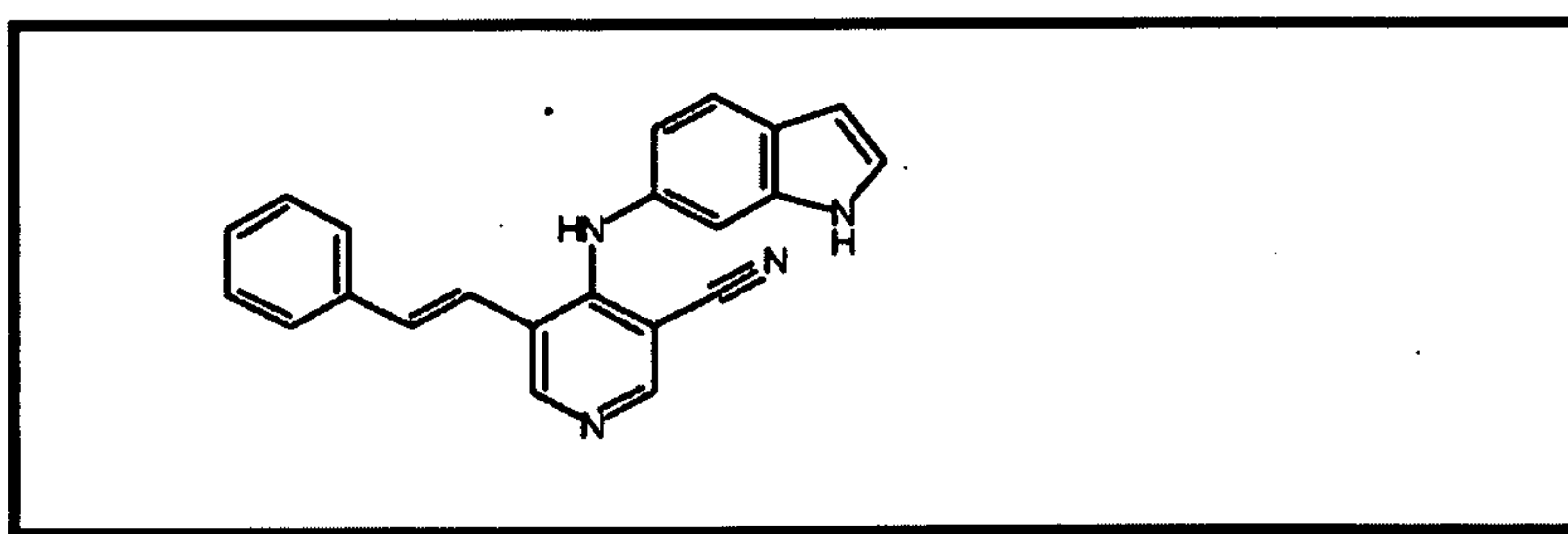
To a solution of tert-butyl 4-((6-((E)-2-(5-cyano-4-((4-methyl-1H-indol-5-yl)amino)pyridin-3-yl)vinyl)pyridin-3-yl)methyl)piperazine-1-carboxylate (143 mg, 0.26 mmol) in 4 mL of dichloromethane was added 400 μ L of TFA. Black solids formed and the mixture was stirred at room temperature for 3.5 h. The solvent was decanted off and the residue was stirred with saturated aqueous sodium bicarbonate. The solids were collected by filtration, washing with water, ethyl acetate and diethyl ether, then heated with dichloromethane and the resulting precipitate was filtered. The filtrate was concentrated and purified by flash column chromatography eluting with a gradient of 10% methanol in dichloromethane to 2% ammonium hydroxide in 30% methanol in dichloromethane to give 12 mg (9%) of 4-((4-methyl-1H-indol-5-

yl)amino]-5-[(E)-2-[5-(piperazin-1-ylmethyl)pyridin-2-yl]vinyl]nicotinonitrile as a tan solid; MS 450.3 (M+H); ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.33 (s, 3H), 2.56 (m, 4H), 3.09 (m, 4H), 3.60 (s, 2H), 6.51 (s, 1H), 6.92 (d, J = 8 Hz, 1H), 7.23-7.36 (m, 3H), 7.68-7.74 (m, 2H), 7.83 (d, J = 16 Hz, 1H), 8.30 (s, 1H), 8.45-8.55 (m, 2H), 8.61 (s, 1H), 8.93 (s, 1H), 11.14 (s, 1H).



[00224] Preparation of 4-chloro-5-[(E)-2-phenylvinyl]nicotinonitrile:

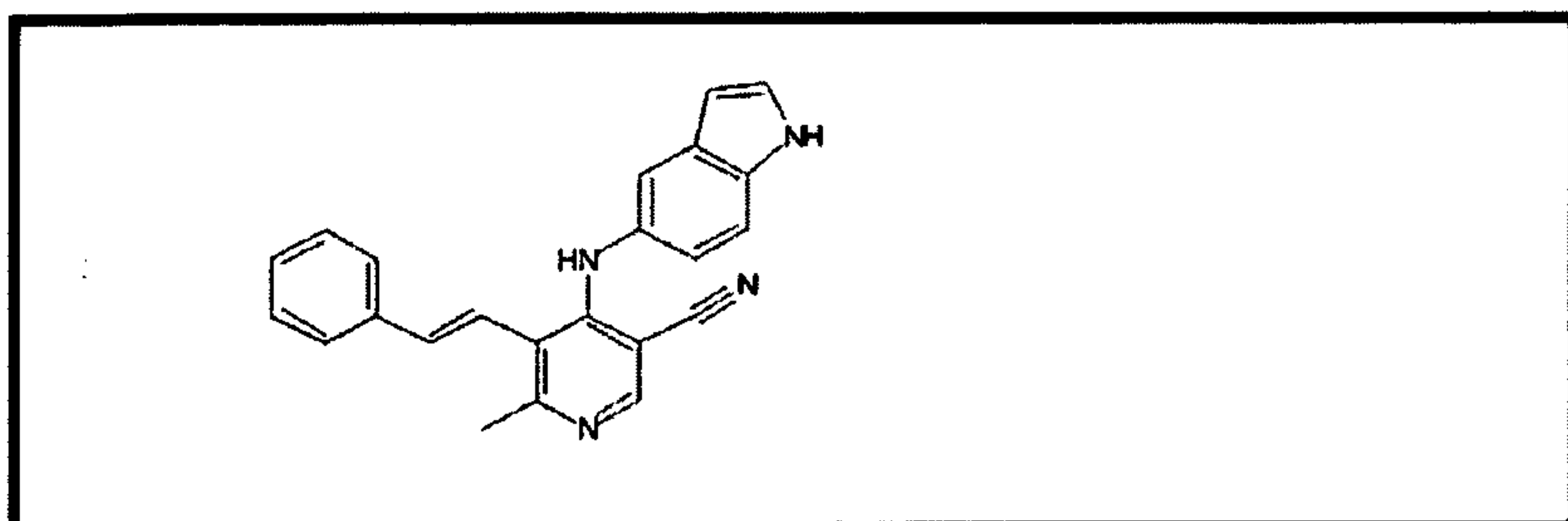
A mixture of 4-chloro-5-iodonicotinonitrile (2.00 g, 7.56 mmol), *trans* 2-phenylvinylboronic acid (1.27 g, 8.57 mmol) and (Ph₃P)₄Pd (90 mg) in 30 mL of 1,2-dimethoxyethane and 15 mL of saturated aqueous sodium bicarbonate was heated at 90-100°C for 1 h. After cooling to room temperature the reaction mixture was partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue triturated with ethyl acetate to give 225 mg (12%) of 4-chloro-5-[(E)-2-phenylvinyl]nicotinonitrile as a white solid; MS 241.1 (M+H); HPLC 97.0% at 215 nm, 16.5 min [a]. Concentration of the filtrate and trituration with ethyl acetate provided an additional 996 mg (55%) of 4-chloro-5-[(E)-2-phenylvinyl]nicotinonitrile.



[00225] Preparation of 4-(1H-indol-6-ylamino)-5-[(E)-2-phenylvinyl]nicotinonitrile:

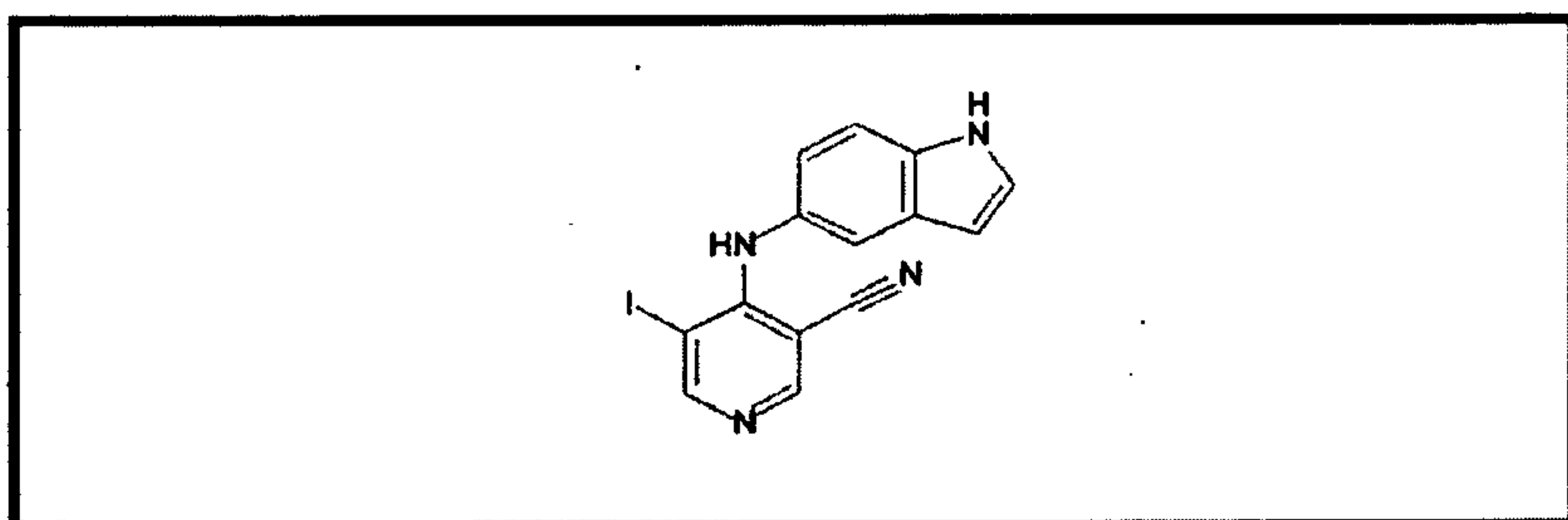
A mixture of 4-chloro-5-[(E)-2-phenylvinyl]nicotinonitrile (134 mg, 0.56 mmol) and 6-aminoindole (100 mg, 0.76 mmol) in 3 mL of ethanol was heated at reflux overnight. The resulting mixture was cooled to room temperature and partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. The layers were separated and the organic layer was

dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was triturated with ethyl acetate and the solid was collected by filtration washing with diethyl ether to give 110 mg (59%) of 4-(1H-indol-6-ylamino)-5-[(E)-2-phenylvinyl]nicotinonitrile as a pale yellow solid; MS 337.2 (M+H); HPLC: 97.3% at 215 nm, *rt* = 10.0 min [a].



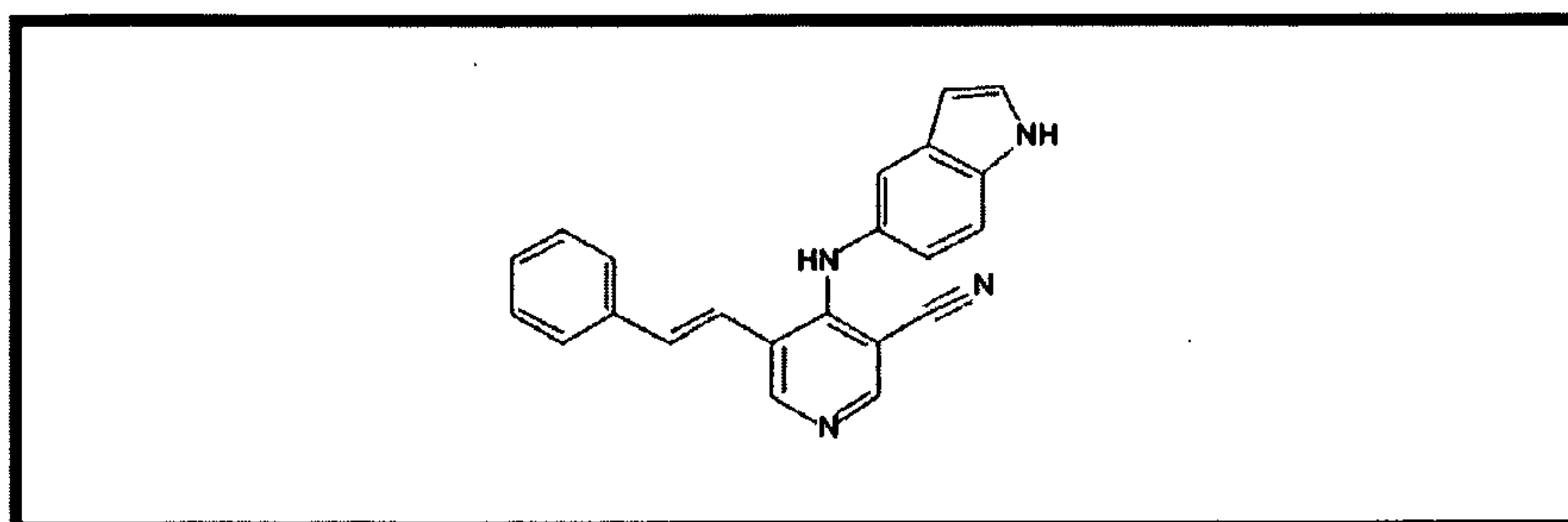
[00226] Preparation of 4-(1H-indol-5-ylamino)-6-methyl-5-[(E)-2-phenylvinyl]nicotinonitrile:

A mixture of 5-bromo-4-(1H-indol-5-ylamino)-6-methylnicotinonitrile (130 mg, 0.40 mmol), *trans* 2-phenylvinylboronic acid (110 mg, 0.74 mmol) and (Ph₃P)₄Pd (50 mg) in 10 mL of 1,2-dimethoxyethane and 5 mL of saturated aqueous sodium bicarbonate was heated at 90-100°C for 2 h. After cooling to room temperature the reaction mixture was partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography eluting with a gradient of 4:1 hexane:ethyl acetate to 1:1 hexane:ethyl acetate to give 49 mg (35%) of 4-(1H-indol-5-ylamino)-6-methyl-5-[(E)-2-phenylvinyl]nicotinonitrile as a light yellow solid; MS 351.3 (M+H); HPLC: 94.7% at 215 nm, *rt* = 9.5 min [a].



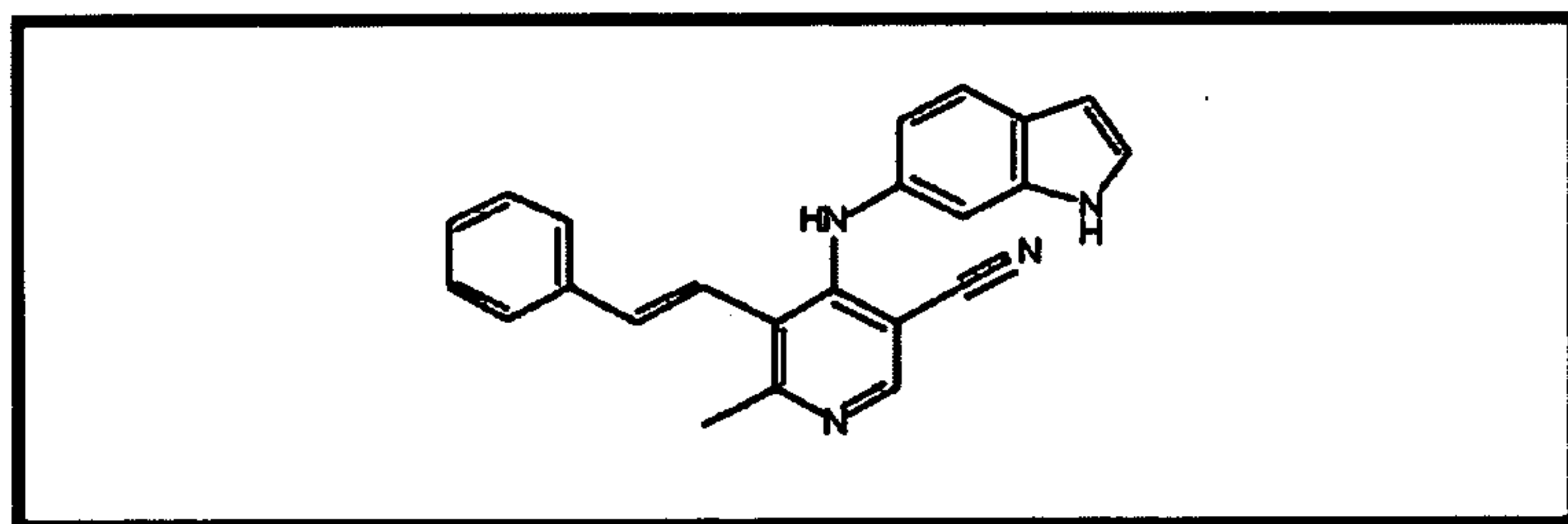
[00227] Preparation of 4-(1H-indol-5-ylamino)-5-iodonicotinonitrile:

The title compound was prepared from 5-aminoindole and 4-chloro-5-iodonicotinonitrile by the procedure described for 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile: MS 377 (M+H); HPLC: *rt* = 9.3 min [a].



[00228] Preparation of 4-(1H-indol-5-ylamino)-5-[(E)-2-phenylvinyl]nicotinonitrile:

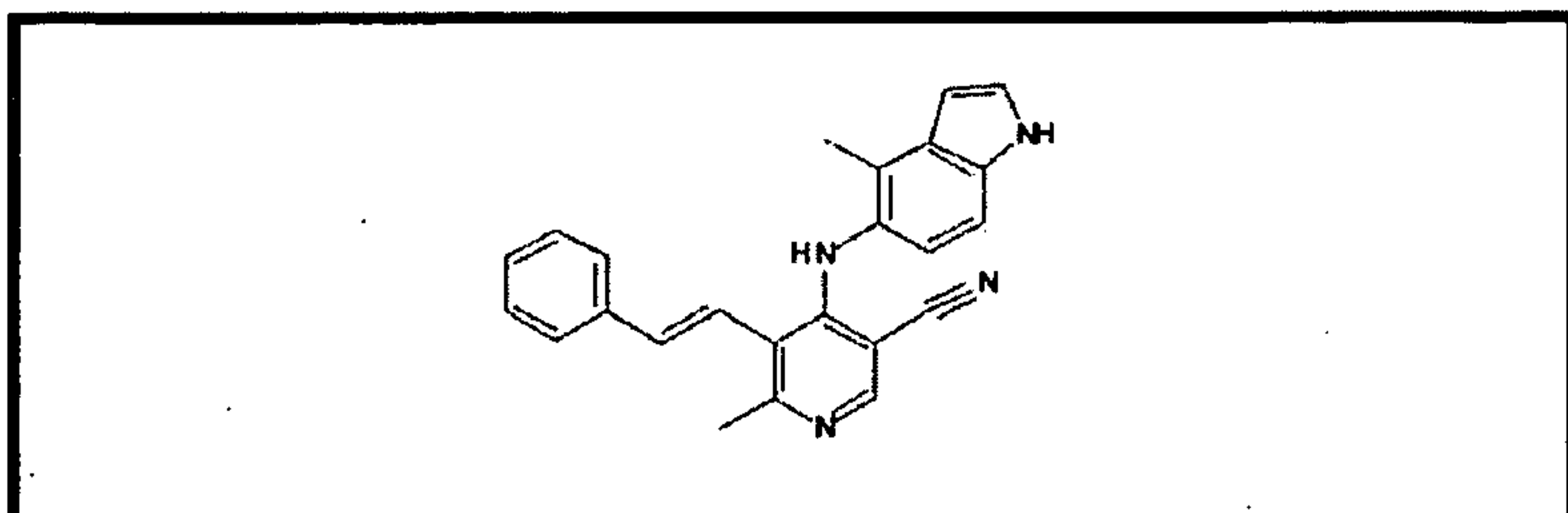
The title compound was prepared from 4-(1H-indol-5-ylamino)-5-iodonicotinonitrile and *trans* 2-phenylvinylboronic acid via the procedure used to prepare 4-(1H-indol-5-ylamino)-6-methyl-5-[(E)-2-phenylvinyl]nicotinonitrile; MS 337.3 (M+H); HPLC: 99.8% at 215 nm, *rt* = 9.3 min [a].



[00229] Preparation of 4-(1H-indol-6-ylamino)-6-methyl-5-[(E)-2-phenylvinyl]nicotinonitrile:

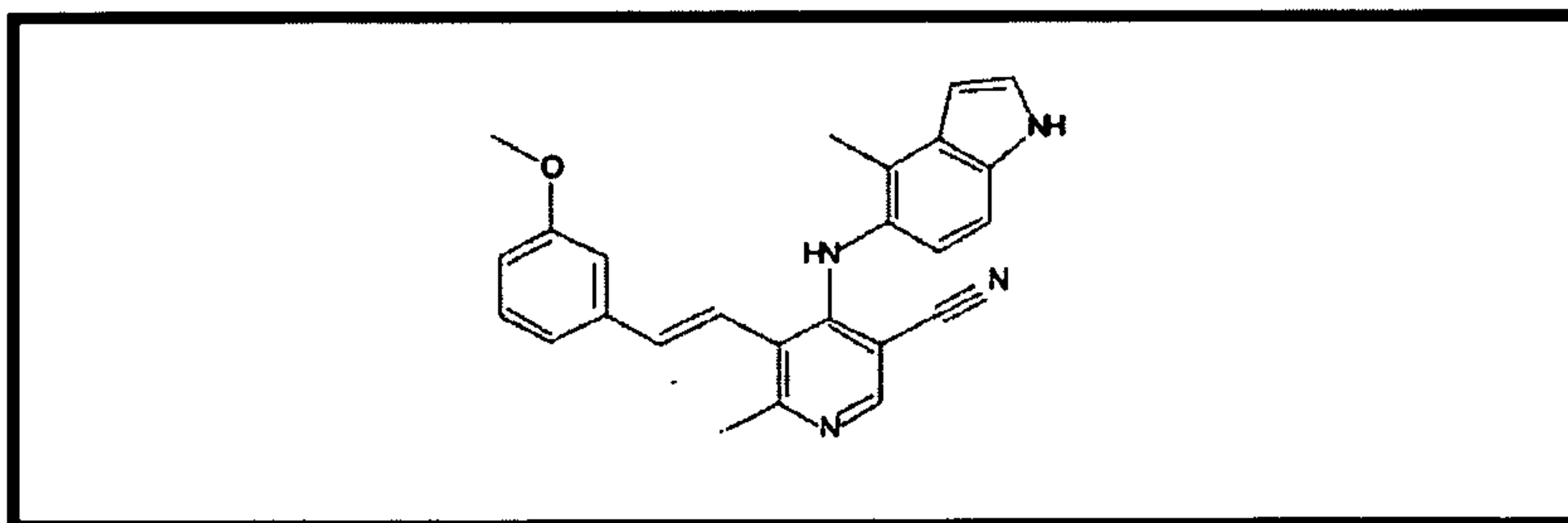
A mixture of 5-bromo-4-(1H-indol-6-ylamino)-6-methylnicotinonitrile (190 mg, 0.58 mmol), *trans* 2-phenylvinylboronic acid (130 mg, 0.88 mmol) and (Ph₃P)₄Pd (50 mg) in 10 mL of 1,2-dimethoxyethane and 5 mL of saturated aqueous sodium bicarbonate was heated at 90-100°C for 2 h. After cooling to room temperature the reaction mixture was partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography eluting with a gradient of 4:1 hexane:ethyl acetate to 1:1 hexane:ethyl acetate to give 146 mg (72%) of 4-(1H-indol-6-ylamino)-6-methyl-5-[(E)-2-

phenylvinyl]nicotinonitrile as a pale yellow solid; MS 351.3 (M+H); HPLC: 95.2% at 215 nm, rt = 9.7 min [a].



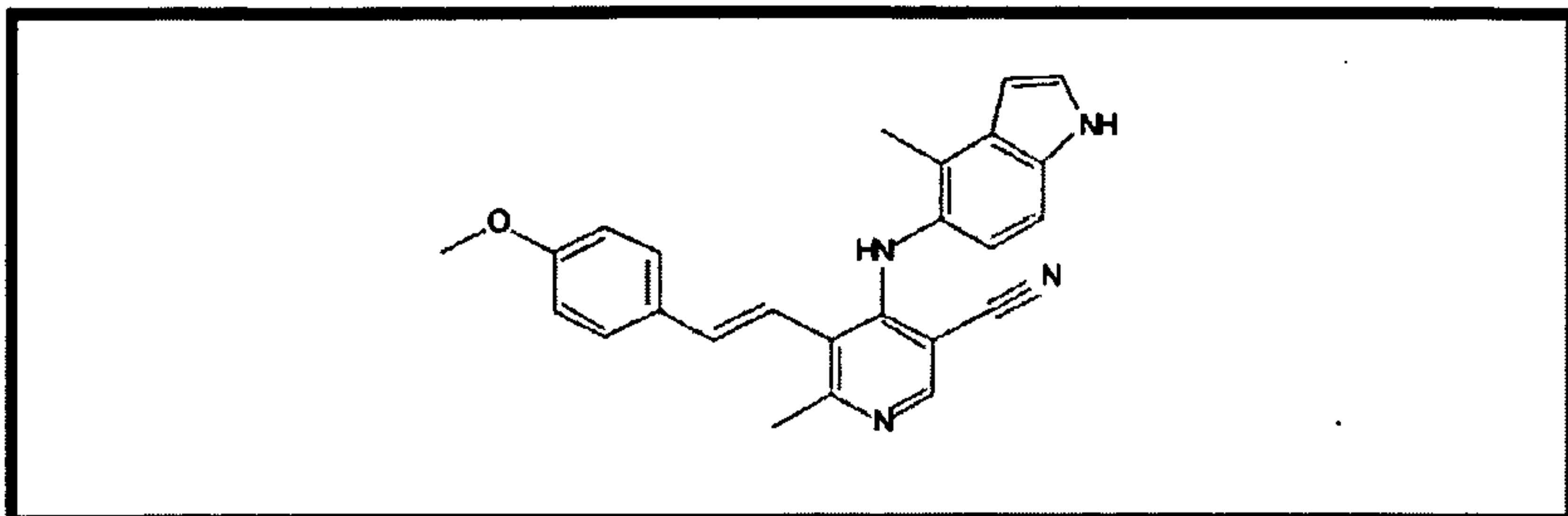
[00230] Preparation of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-phenylvinyl]nicotinonitrile:

The title compound was prepared from 5-bromo-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and *trans* 2-phenylvinylboronic acid via the procedure used to prepare 4-(1H-indol-6-ylamino)-6-methyl-5-[(E)-2-phenylvinyl]nicotinonitrile; MS 365.3 (M+H); HPLC: 94.8% at 215 nm, rt = 9.6 min [a].



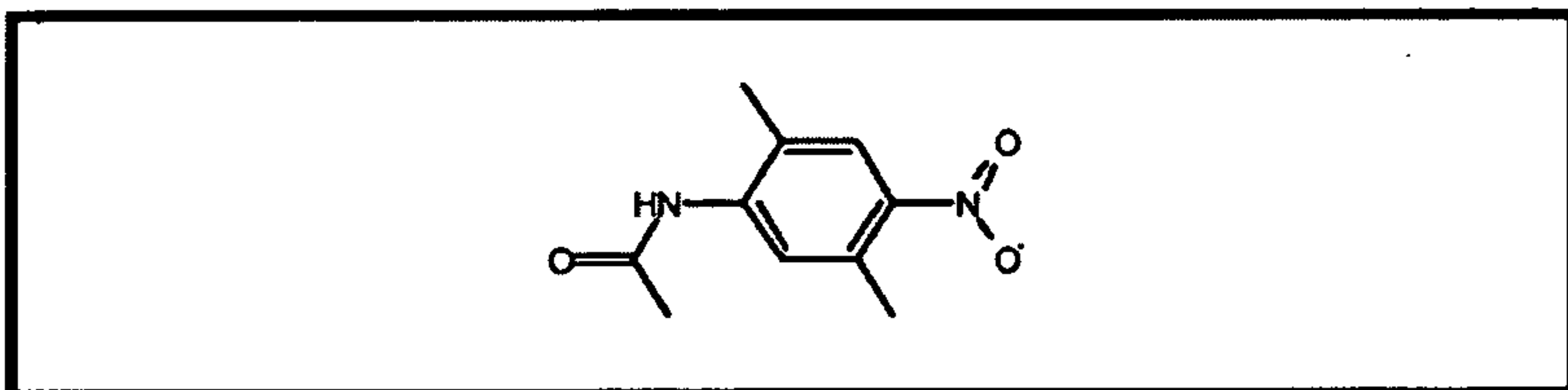
[00231] Preparation of 5-[(E)-2-(3-methoxyphenyl)vinyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

The title compound was prepared from 5-bromo-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and *trans* 2-(3-methoxyphenyl) vinylboronic acid via the procedure used to prepare 4-(1H-indol-6-ylamino)-6-methyl-5-[(E)-2-phenylvinyl]nicotinonitrile; MS 395.2 (M+H); HPLC: 98.1% at 215 nm, rt = 9.8 min [a].



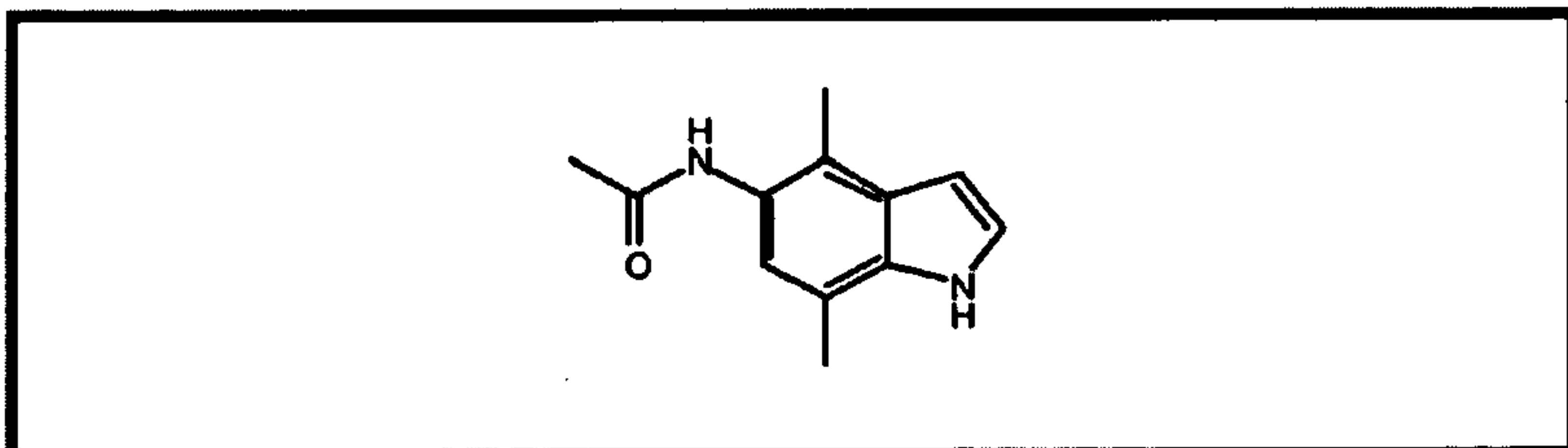
[00232] Preparation of 5-[(E)-2-(4-methoxyphenyl)vinyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

The title compound was prepared from 5-bromo-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and *trans* 2-(4-methoxyphenyl) vinylboronic acid via the procedure used to prepare 4-(1H-indol-6-ylamino)-6-methyl-5-[(E)-2-phenylvinyl]nicotinonitrile; MS 395.2 (M+H); HPLC: 98.0% at 215 nm, *rt* = 9.5 min [a].



[00233] Preparation of 2,5-dimethyl-4-nitroacetanilide:

2,5-Dimethylaniline in dichloromethane was treated with acetyl chloride. The reaction mixture was evaporated to a solid residue. The residue was dissolved in a mixture of acetic acid and sulfuric acid. To the cooled mixture (-10 °C) was added a mixture of nitric acid and sulfuric acid. The resulting acidic solution was poured on to ice. The precipitate was filtered and washed with water. The solid was recrystallized twice from ethanol. The crystalline 2,5-dimethyl-4-nitroacetanilide was dried under high vacuum.

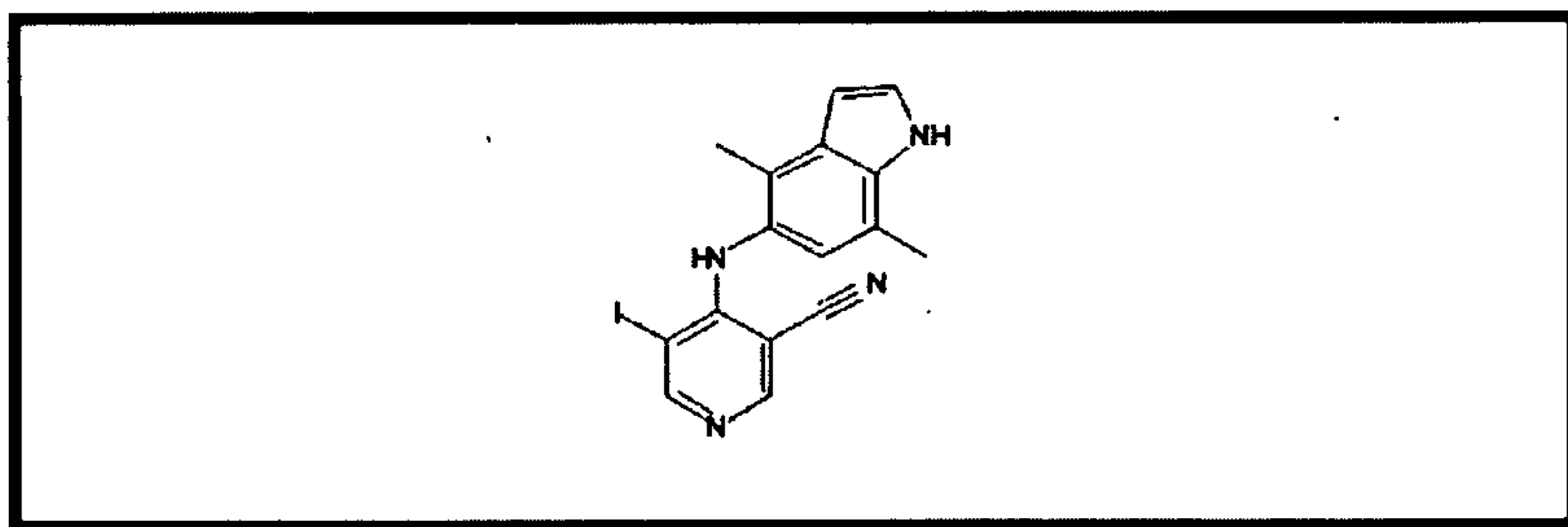


[00234] Preparation of N-acetyl-5-amino-4,7-dimethylindole:

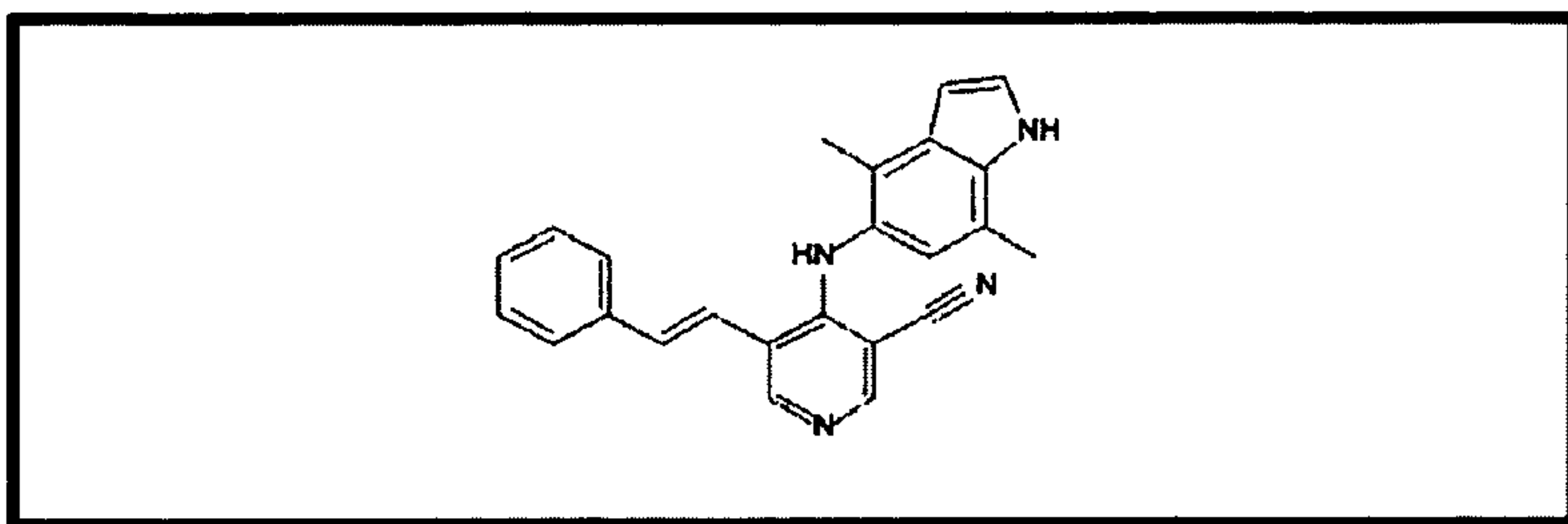
A solution of 2,5-dimethyl-4-nitroacetanilide in THF was added to vinyl magnesium bromide in THF at -30°C and the resulting mixture was allowed to warm to room temperature. The reaction mixture was poured into a saturated solution of ammonium chloride. The aqueous phase was extracted with ethyl acetate. An analytical sample of N-acetyl-5-amino-4,7-dimethylindole was prepared by silica gel chromatography (chloroform).

[00235] Preparation of 5-amino-4,7-dimethylindole:

A solution of N-acetyl-5-amino-4,7-dimethylindole in THF was mixed with 1N HCl. The resulting solution was heated at reflux for 72 h. The reaction mixture was allowed to cool to room temperature and then basified with ammonia solution. The aqueous phase was extracted with dichloromethane. The combined extracts were dried (magnesium sulfate) and concentrated. The concentrated residue was purified by silica gel chromatography (hexanes-ethyl acetate, 4:1) to afford 5-amino-4,7-dimethylindole.

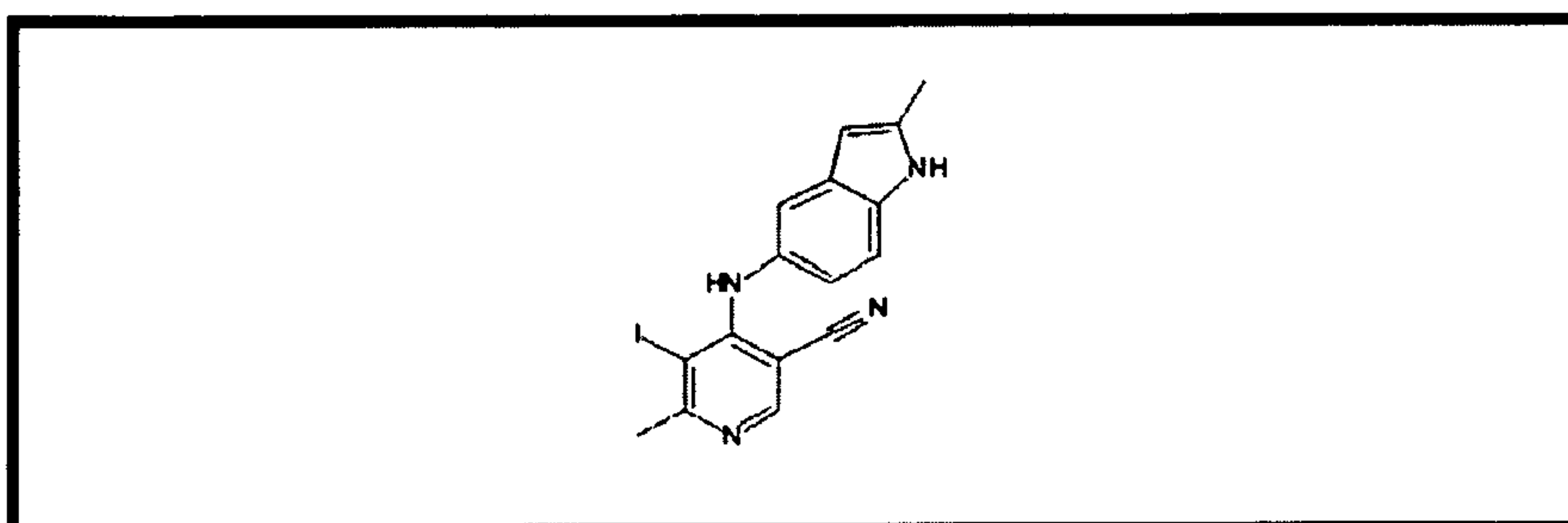
**[00236] Preparation of 4-[(4,7-dimethyl-1H-indol-5-yl)amino]-5-iodonicotinonitrile:**

A mixture of 4-chloro-5-iodonicotinonitrile (630 mg, 2.39 mmol) and 5-amino-4,7-dimethylindole (350 mg, 2.18 mmol) in 10 mL of ethanol was heated in a sealed tube at 95°C for 16 h. The resulting mixture was cooled to room temperature. The precipitate was filtered and dried *in vacuo* (450 mg, 53 %). An analytical sample was obtained by prep HPLC purification (column: Phenomenex Gemini 5 m C18 100 x 30 mm; eluent: aq acetonitrile containing 0.02 % trifluoroacetic acid) followed by basification with ammonia solution to give 4.5 mg of 4-[(4,7-dimethyl-1H-indol-5-yl)amino]-5-iodonicotinonitrile as a grey solid; MS 389.1 (M+H).



[00237] Preparation of 4-[(4,7-dimethyl-1H-indol-5-yl)amino]-5-[(E)-2-phenylvinyl]nicotinonitrile:

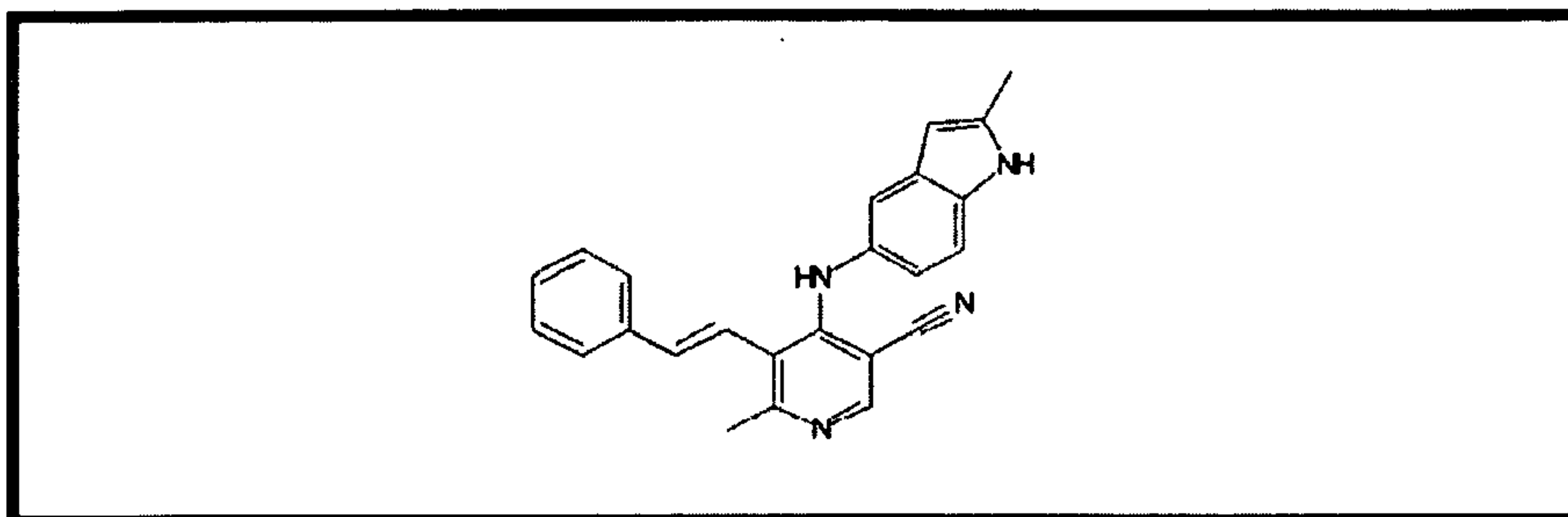
A mixture of 4-[(4,7-dimethyl-1H-indol-5-yl)amino]-5-iodonicotinonitrile (96 mg, 0.24 mmol), (*E*)-2-phenylvinylboronic acid (90 mg, 0.61 mmol), tetrakis(triphenylphosphine)palladium (10.7 mg), and saturated sodium bicarbonate (5 mL) in DME (5 mL) was heated at reflux 14 h. The reaction mixture was allowed to cool to room temperature. The reaction mixture was extracted (ethyl acetate, 3 x 20 mL) and the organic extracts were combined, dried (magnesium sulfate), and concentrated. The residue, weighing 60 mg, was purified by prep HPLC (column: Phenomenex Gemini 5 C₁₈ 100 x 30 mm; eluent: aq acetonitrile containing 0.02 % trifluoroacetic acid) followed by basification with ammonia solution giving 10.0 mg (11%) of 4-[(4,7-dimethyl-1H-indol-5-yl)amino]-5-[(*E*)-2-phenylvinyl]nicotinonitrile as a yellow solid; MS 365.2 (M+H), HPLC: rt = 10.2 min [a].



[00238] Preparation of 5-iodo-4-(2-methyl-1H-indol-5-ylamino)-6-methylnicotinonitrile:

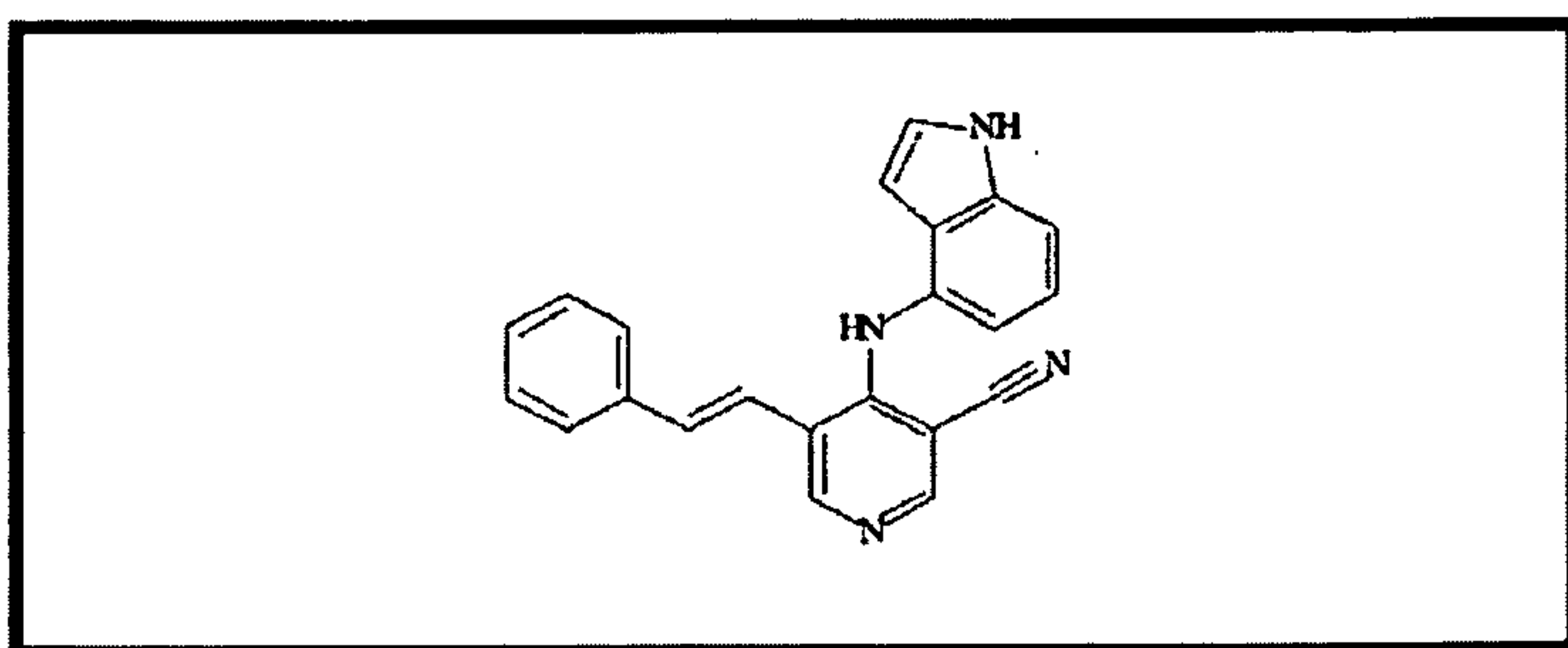
A mixture of 4-chloro-5-iodo-6-methylnicotinonitrile (1.0 g, 3.6 mmol) and 5-amino-2-methylindole (735 mg, 5.0 mmol) in 8 mL of ethanol was heated at reflux 3 h. The resulting mixture was cooled to room temperature, diluted with saturated aqueous sodium bicarbonate, filtered and washed with ethanol, water to give 781 mg (56%) of 5-iodo-4-(2-methyl-1H-indol-

5-ylamino)-6-methylnicotinonitrile as a light yellow solid; MS 389.1 (M+H); HPLC: rt = 9.5 min [a].



[00239]. Preparation of 6-methyl-4-[(2-methyl-1H-indol-5-yl)amino]-5-[(E)-2-phenylvinyl] nicotinonitrile:

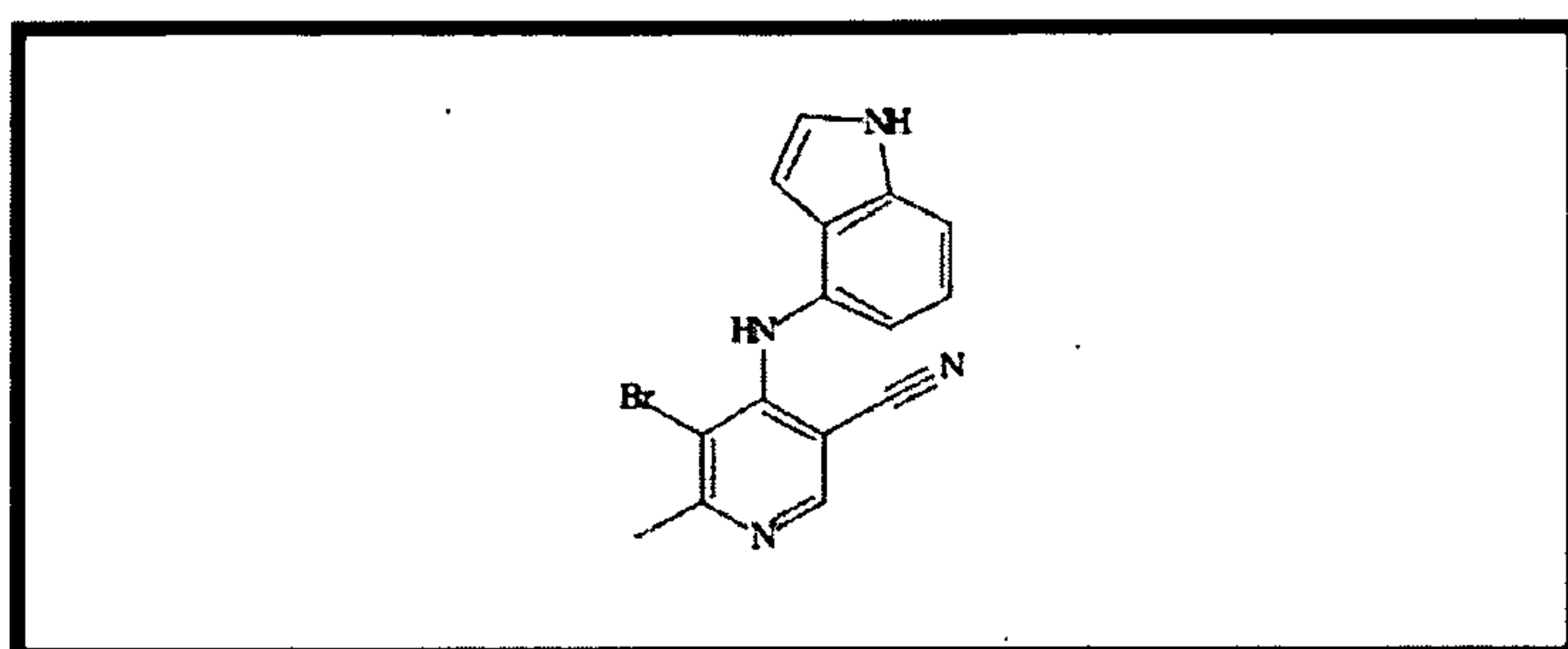
A mixture of 5-iodo-4-(2-methyl-1H-indol-5-ylamino)-6-methylnicotinonitrile (194 mg, 0.5 mmol), *trans*-2-phenylvinylboronic acid (110 mg, 0.75 mmol) and (Ph₃P)₄Pd (57mg) in 5 mL of 1,2-dimethoxyethane and 1 mL of 2 M aqueous sodium bicarbonate was heated at reflux for 5 h. After cooling to room temperature the reaction mixture was partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography eluting with a gradient of 4:1 hexane:ethyl acetate to 3:1 hexane:ethyl acetate to give 170 mg (93%) of 6-methyl-4-[(2-methyl-1H-indol-5-yl)amino]-5-[(E)-2-phenyl vinyl]nicotinonitrile as a light yellow solid; MS 365.4 (M+H); HPLC: rt = 9.9 min [a].



[00240] Preparation of 4-(1H-indol-4-ylamino)-5-[(E)-2-phenylvinyl]nicotinonitrile:

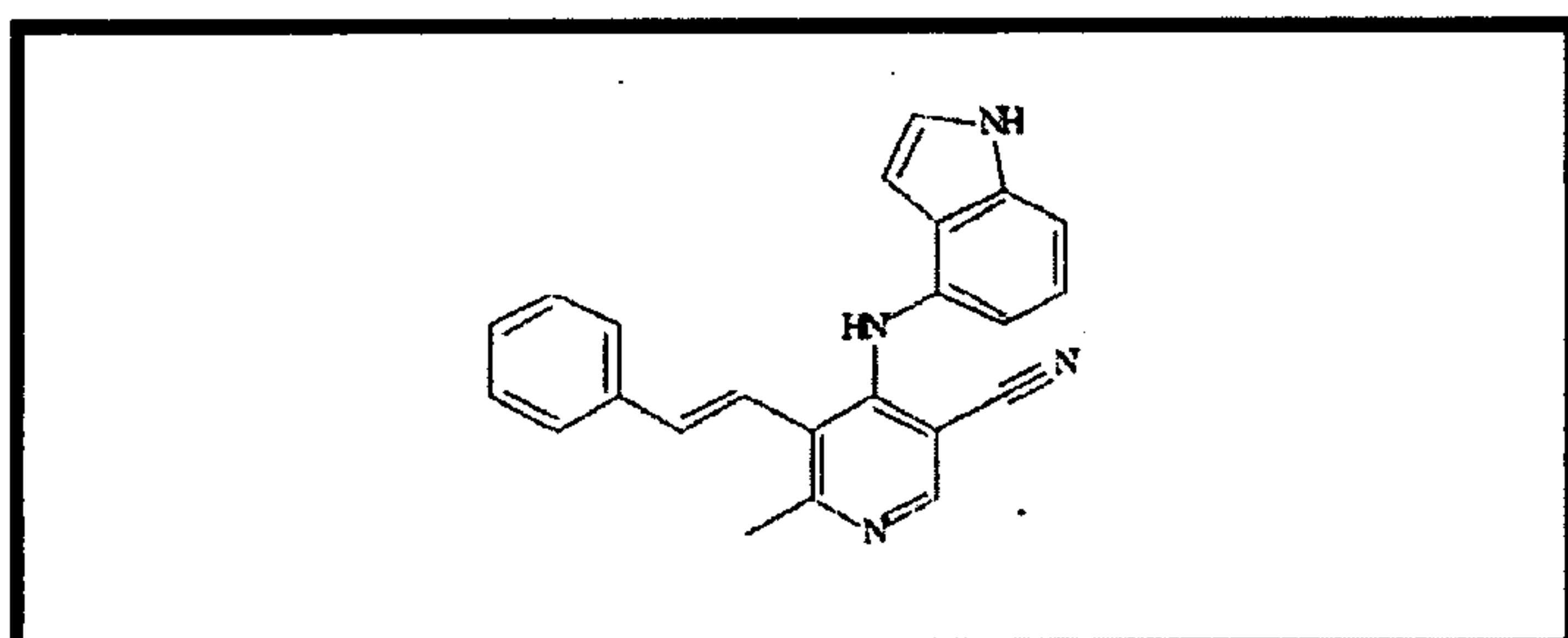
A mixture of 4-chloro-5-[(E)-2-phenylvinyl]nicotinonitrile (135 mg, 0.56 mmol) and 4-aminoindole (105 mg, 0.79 mmol) in 4 mL of ethanol was heated at reflux overnight. The

resulting mixture was cooled slightly and filtered, washing with diethyl ether. The solid was stirred with saturated aqueous sodium bicarbonate for 20 min, then the suspension was extracted with ethyl acetate. The layers were separated and the organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was triturated with diethyl ether and the solid was collected by filtration washing with diethyl ether to give 45 mg (23%) of 4-(1H-indol-4-ylamino)-5-[(E)-2-phenylvinyl]nicotinonitrile as a yellow solid; MS 337.2 (M+H); HPLC: 98.8% at 215 nm, *rt* = 9.7 min [a].



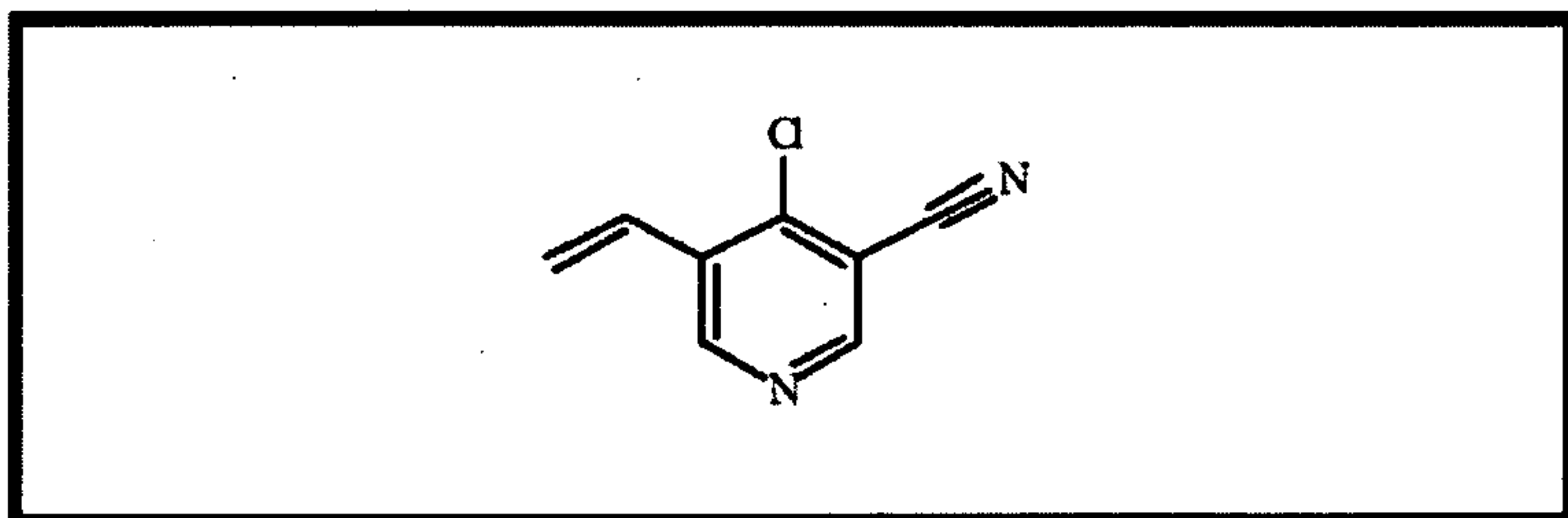
[00241] Preparation of 5-bromo-4-(1H-indol-4-ylamino)-6-methylnicotinonitrile:

A mixture of 5-bromo-4-chloro-6-methylnicotinonitrile (530 mg, 2.29 mmol) and 4-aminoindole (440 mg, 3.33 mmol) in 5 mL of ethanol was heated at reflux for 6.5 h. The resulting mixture was cooled slightly and filtered washing with diethyl ether. The solid was partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. The layers were separated and the organic layer was washed with saturated aqueous sodium bicarbonate, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was triturated with diethyl ether to give 448 mg (60%) of 5-bromo-4-(1H-indol-4-ylamino)-6-methylnicotinonitrile as a light tan solid; MS 327.1 (M+H); HPLC: 98.3% at 215 nm, *rt* = 9.3 min [a].



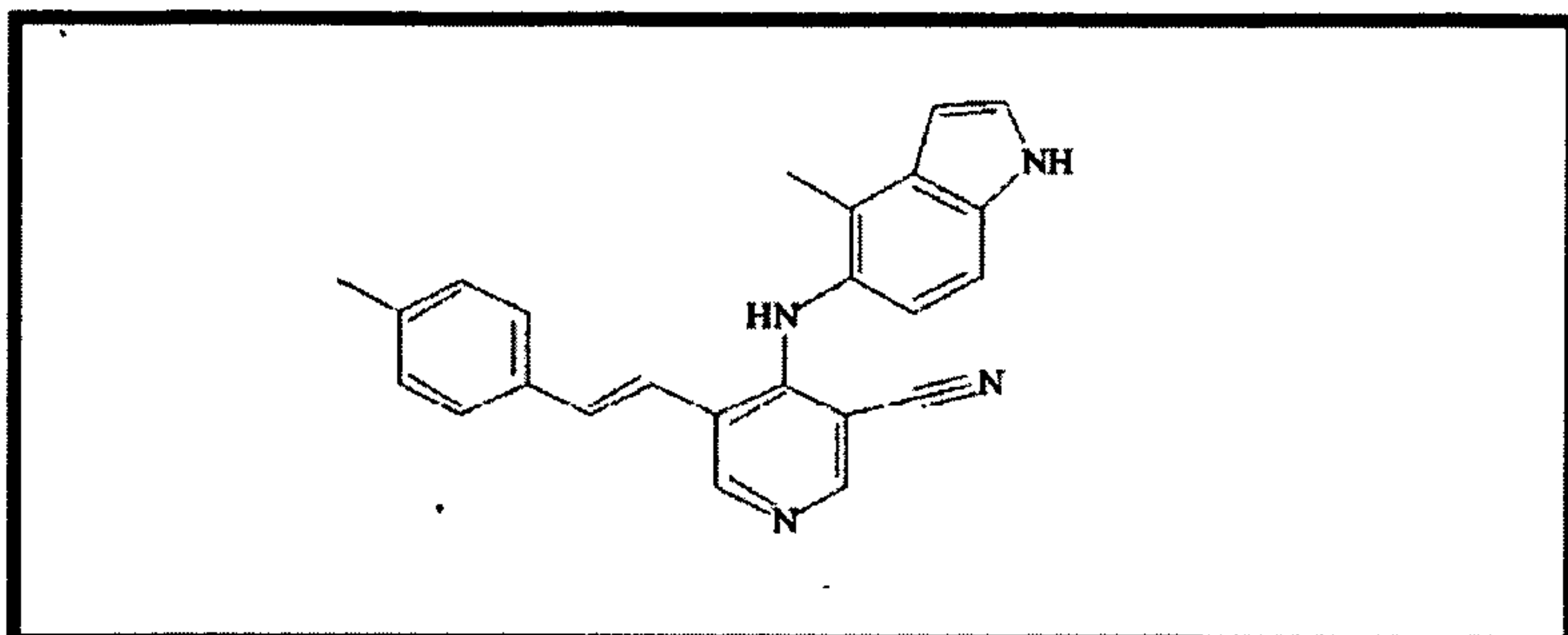
[00242] Preparation of 4-(1H-indol-4-ylamino)-6-methyl-5-[(E)-2-phenylvinyl]nicotinonitrile:

A mixture of 5-bromo-4-(1H-indol-4-ylamino)-6-methylnicotinonitrile (190 mg, 0.58 mmol), *trans* 2-phenylvinylboronic acid (130 mg, 0.88 mmol) and $(\text{Ph}_3\text{P})_4\text{Pd}$ (50 mg) in 10 mL of 1,2-dimethoxyethane and 5 mL of saturated aqueous sodium bicarbonate was heated at 90-100°C for 1.25 h. After cooling to room temperature the reaction mixture was partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. The organic layer was washed with saturated aqueous sodium bicarbonate, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography eluting with a gradient of 4:1 hexane:ethyl acetate to 1:1 hexane:ethyl acetate to give 155 mg (76%) of 4-(1H-indol-4-ylamino)-6-methyl-5-[(E)-2-phenylvinyl]nicotinonitrile as a yellow solid; MS 351.2 (M+H); HPLC: 99.2% at 215 nm, *rt* = 9.4 min [a].



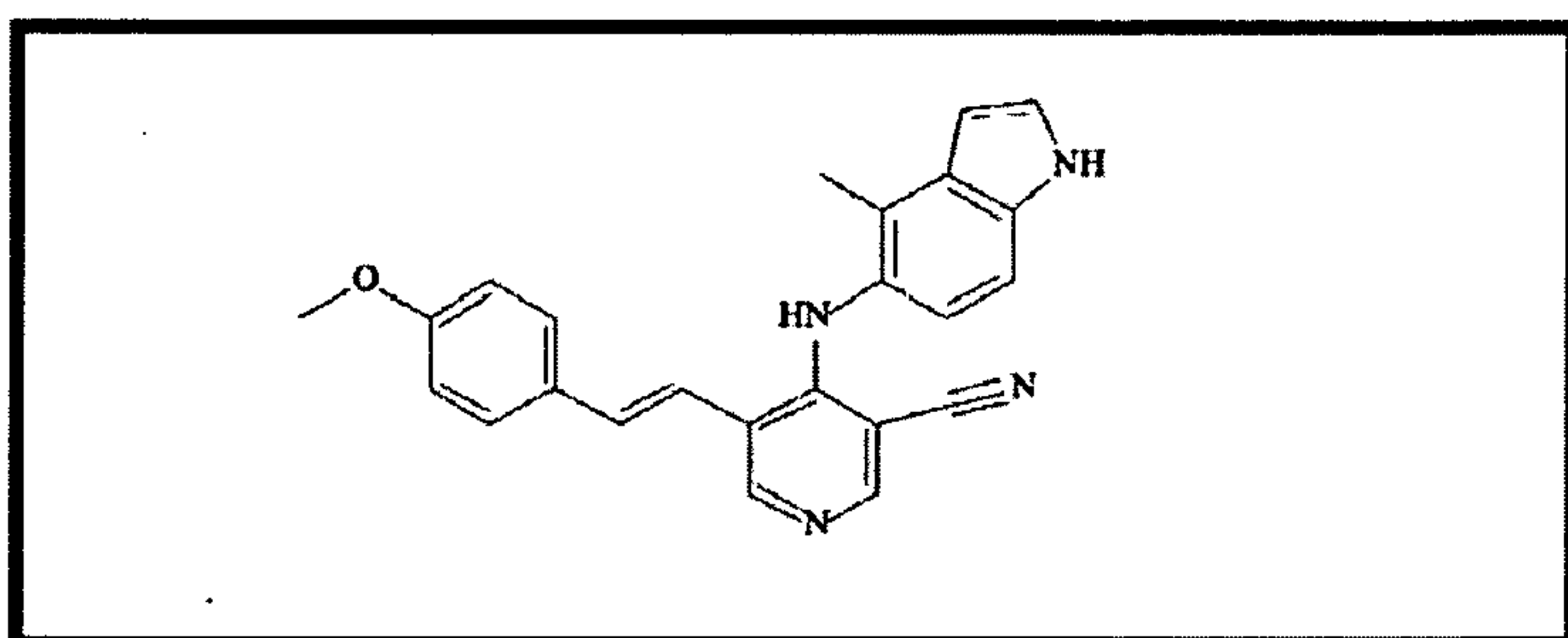
[00243] Preparation of 4-chloro-5-vinylnicotinonitrile:

A mixture of 4-chloro-5-iodonicotinonitrile (1.42 g, 5.37 mmol), tributyl(vinyl)tin (1.8 mL, 6.17 mmol), CuI (25 mg) and $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ (70 mg) in 10 mL of toluene and 2 mL of DMF was heated at 80°C for 2.5 h. After cooling to room temperature the reaction mixture was partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was triturated with diethyl ether and hexane to give 390 mg (44%) of 4-chloro-5-vinylnicotinonitrile as a pale yellow solid. The filtrate was concentrated and purified by flash column chromatography eluting with a gradient of 6:1 hexane:ethyl acetate to 2:1 hexane:ethyl acetate to give 233 mg (26%) of 4-chloro-5-vinylnicotinonitrile as a pale yellow solid; MS 165.0 (M+H); HPLC: 98.5% at 215 nm, *rt* = 11.4 min [a].



[00244] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4-methylphenyl)vinyl]nicotinonitrile:

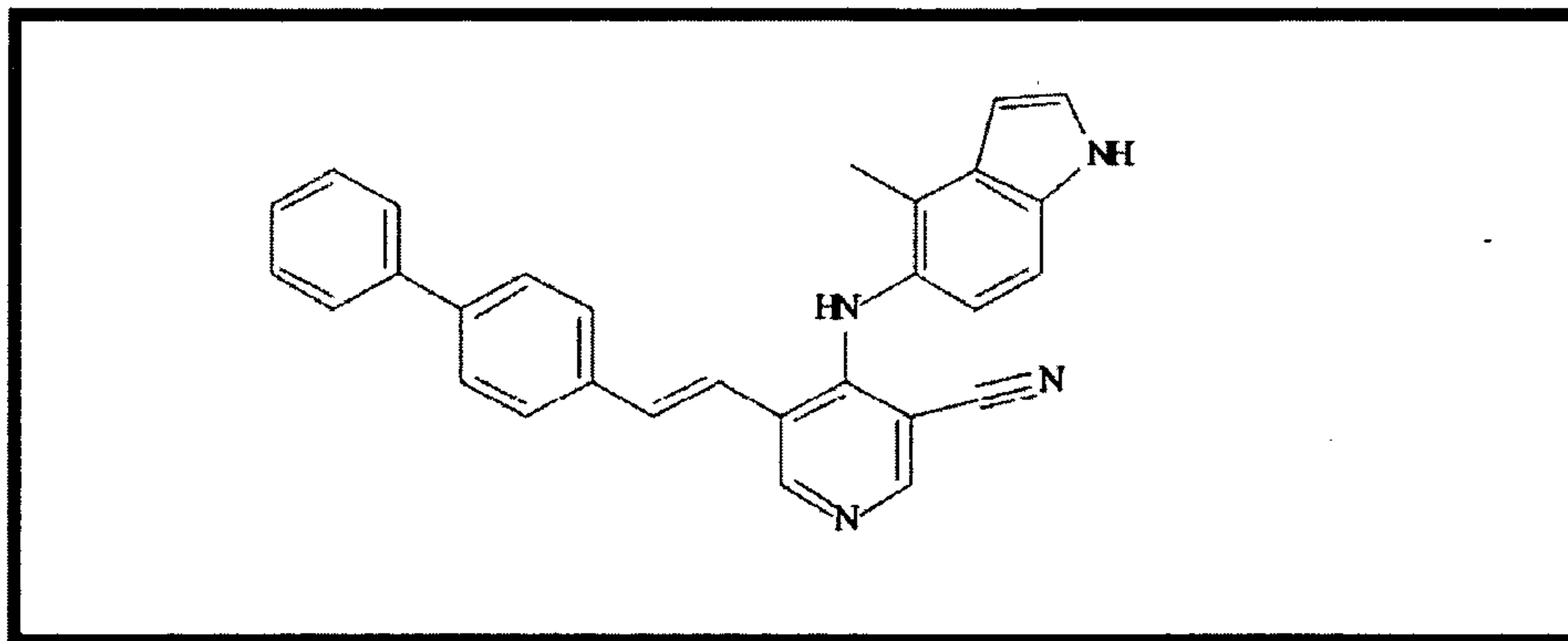
To a reaction mixture of 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (75 mg, 0.2 mmol), *trans*-2-(4-methylphenyl) vinylboronic acid (65 mg, 0.4 mmol) and Pd(PPh₃)₄ (23 mg, 0.02 mmol) in 1.0 mL of 1,2-dimethoxyethane was added 0.5 mL of saturated aq NaHCO₃ solution. The reaction mixture was heated at reflux for 3 h then diluted with ethyl acetate. The organic layer was washed with H₂O, brine and dried over Na₂SO₄. After filtration and concentration, the residue was purified by silica gel chromatography eluting with hexane-ethyl acetate (1:1 to 100% ethyl acetate), providing 70 mg (96%) of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4-methylphenyl)vinyl]nicotinonitrile as a yellow solid; MS 365.4 (M+H); HPLC: 92% at 215 nm, rt = 10.4 min [a].



[00245] Preparation of 5-[(E)-2-(4-methoxyphenyl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

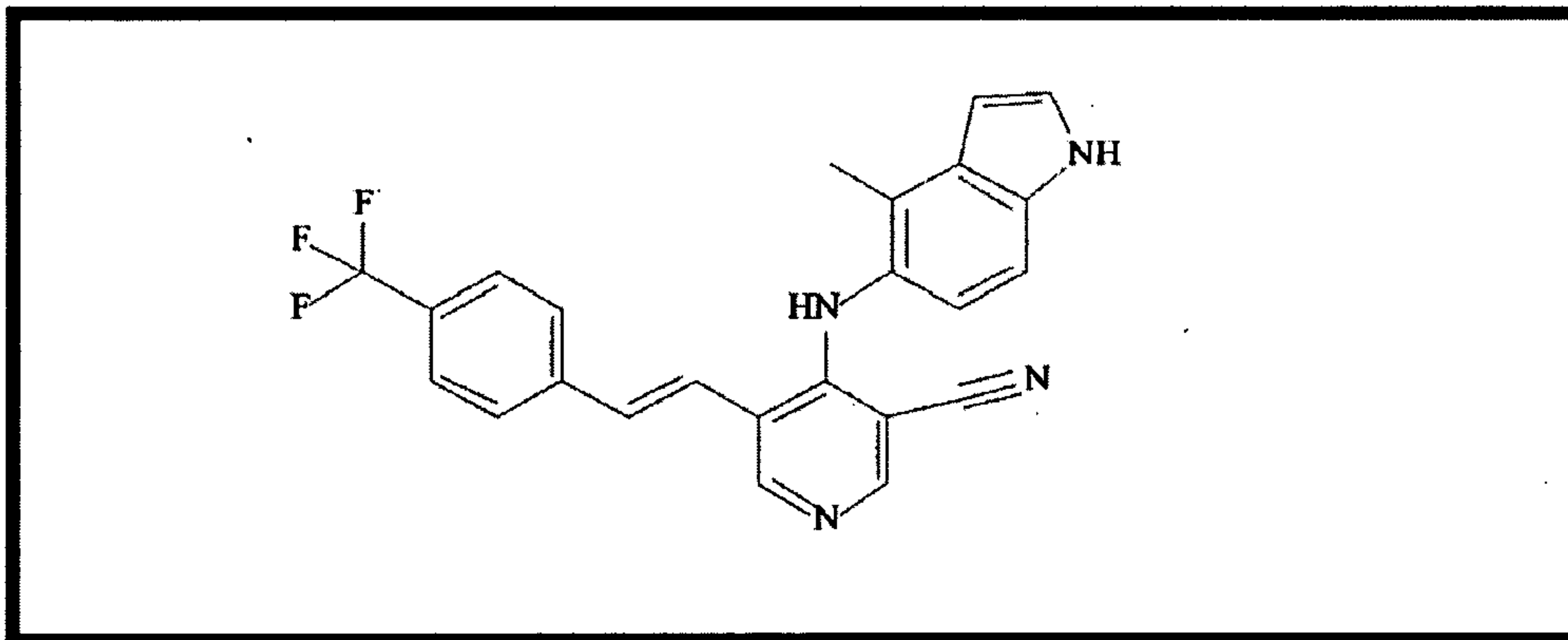
The title compound was prepared from 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and *trans*-2-(4-methoxyphenyl)vinylboronic acid via the procedure used to prepare 4-[(4-

methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4-methylphenyl)vinyl]-nicotinonitrile; MS 381.4 (M+H); HPLC: rt = 9.6 min [a].



[00246] Preparation of 5-[(E)-2-biphenyl-4-ylvinyl]-4-[(4-methyl-1H-indol-5-yl)amino]-nicotinonitrile:

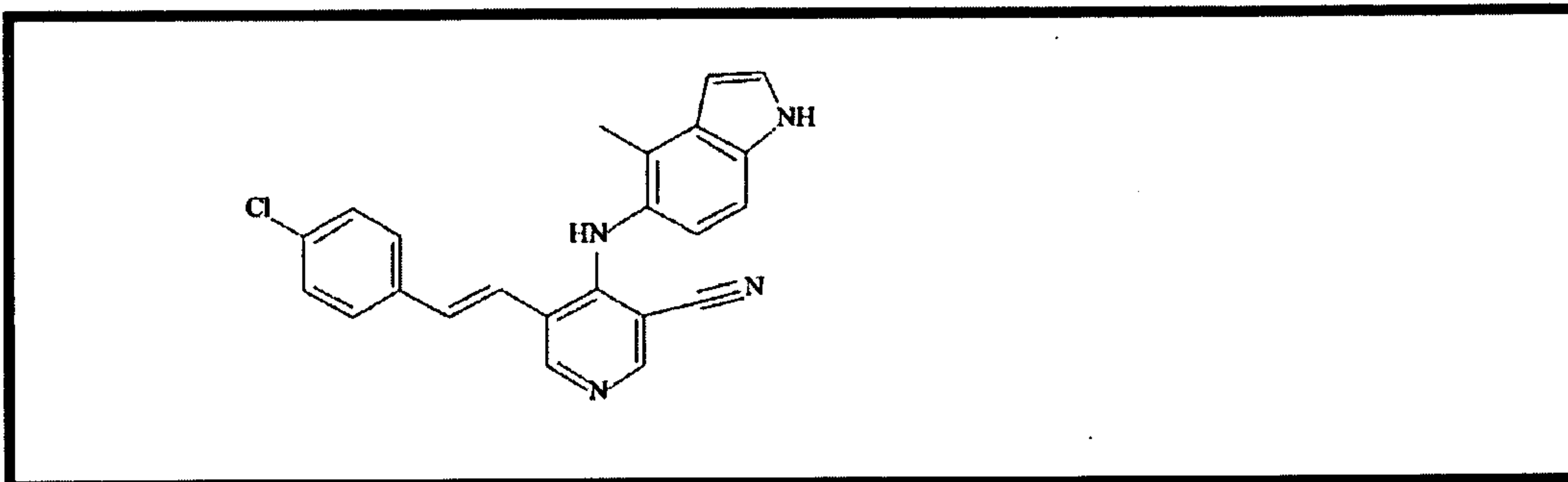
The title compound was prepared from 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and *trans*-2-(4-biphenyl)vinylboronic acid via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4-methylphenyl)vinyl]-nicotinonitrile; MS 427.4 (M+H); HPLC: 99% at 215 nm, rt = 9.6 min [a].



[00247] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(trifluoromethyl)phenyl]vinyl]nicotinonitrile:

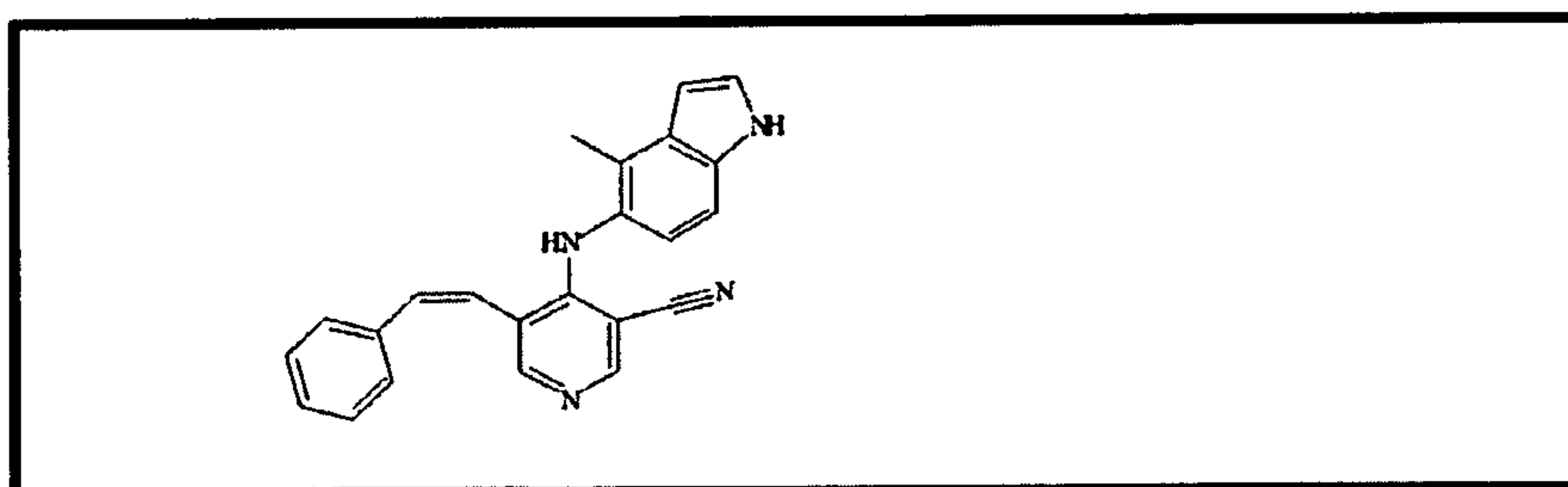
The title compound was prepared from 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and *trans*-2-(4-trifluoromethylphenyl)vinylboronic acid via the procedure used to prepare 4-[(4-

methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4-methylphenyl)vinyl]nicotinonitrile; MS 419.2 (M+H); HPLC: 98% at 215 nm, rt = 11.5 min [a].



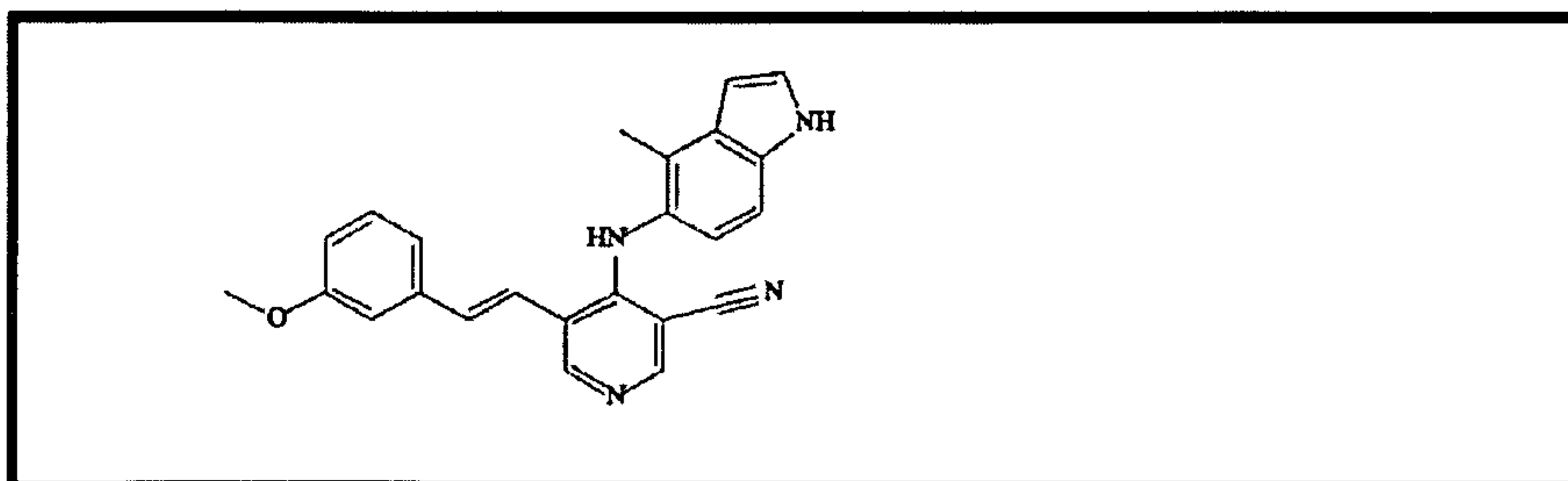
[00248] Preparation of 5-[(E)-2-(4-chlorophenyl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

The title compound was prepared from 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and *trans*-2-(4-chlorophenyl)vinylboronic acid via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4-methyl phenyl)vinyl]-nicotinonitrile; MS 385.2 (M+H); HPLC: rt = 10.8 min [a].



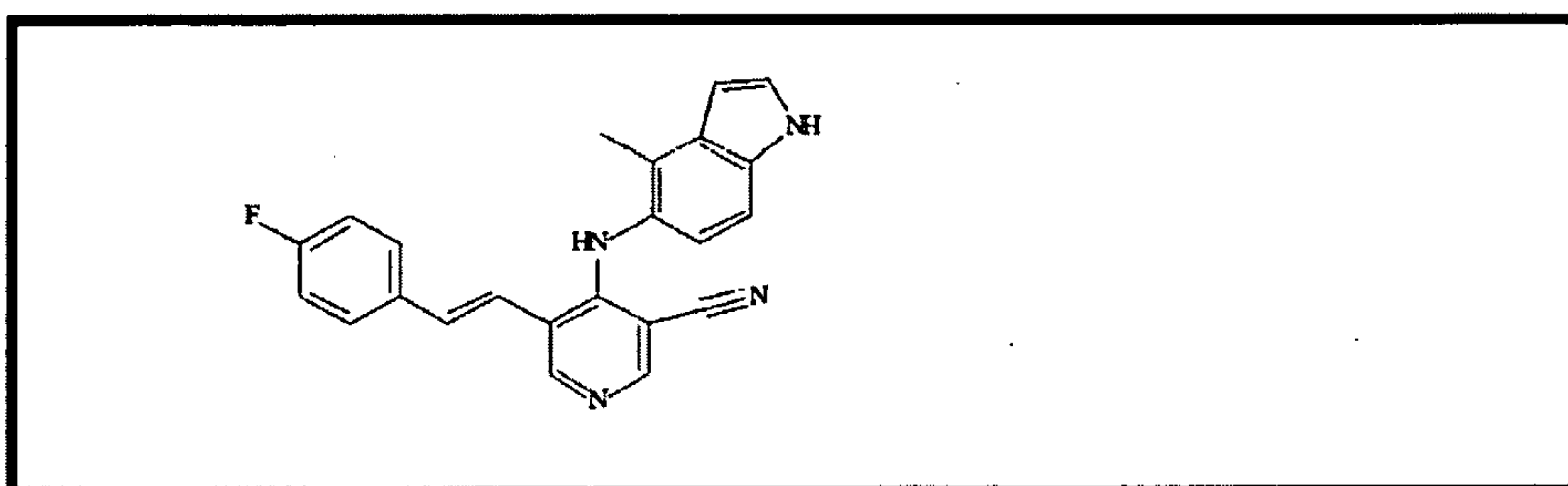
[00249] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(Z)-2-phenylvinyl]nicotinonitrile:

The title compound was prepared from 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and *cis*-2-phenylvinylboronic acid via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4-methylphenyl)vinyl]nicotinonitrile; MS 351.3 (M+H); HPLC: 94% at 215 nm, rt = 8.9 min [a].



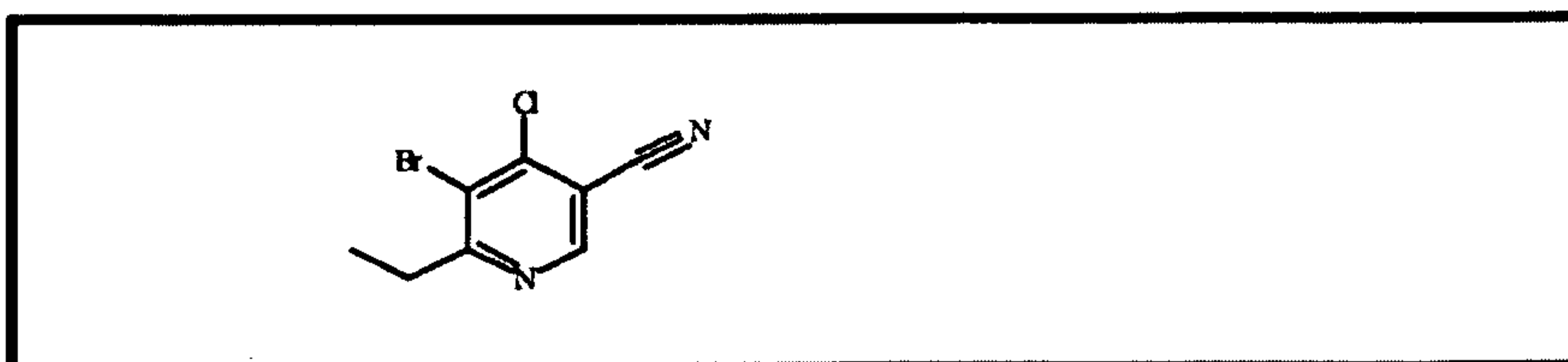
[00250] Preparation of 5-[(E)-2-(3-methoxyphenyl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

The title compound was prepared from 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and *trans*-2-(3-methoxyphenyl)vinylboronic acid via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4-methylphenyl)vinyl]-nicotinonitrile; MS 381.2 (M+H); HPLC 94% at 215 nm, rt = 10.6 min [a].



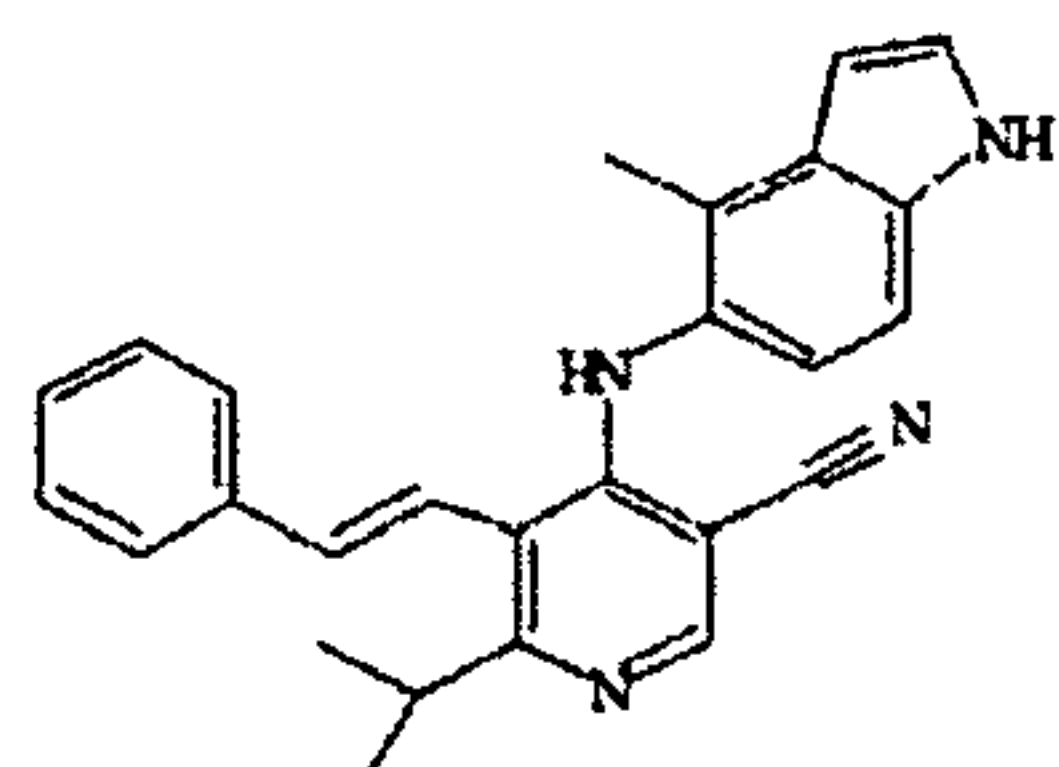
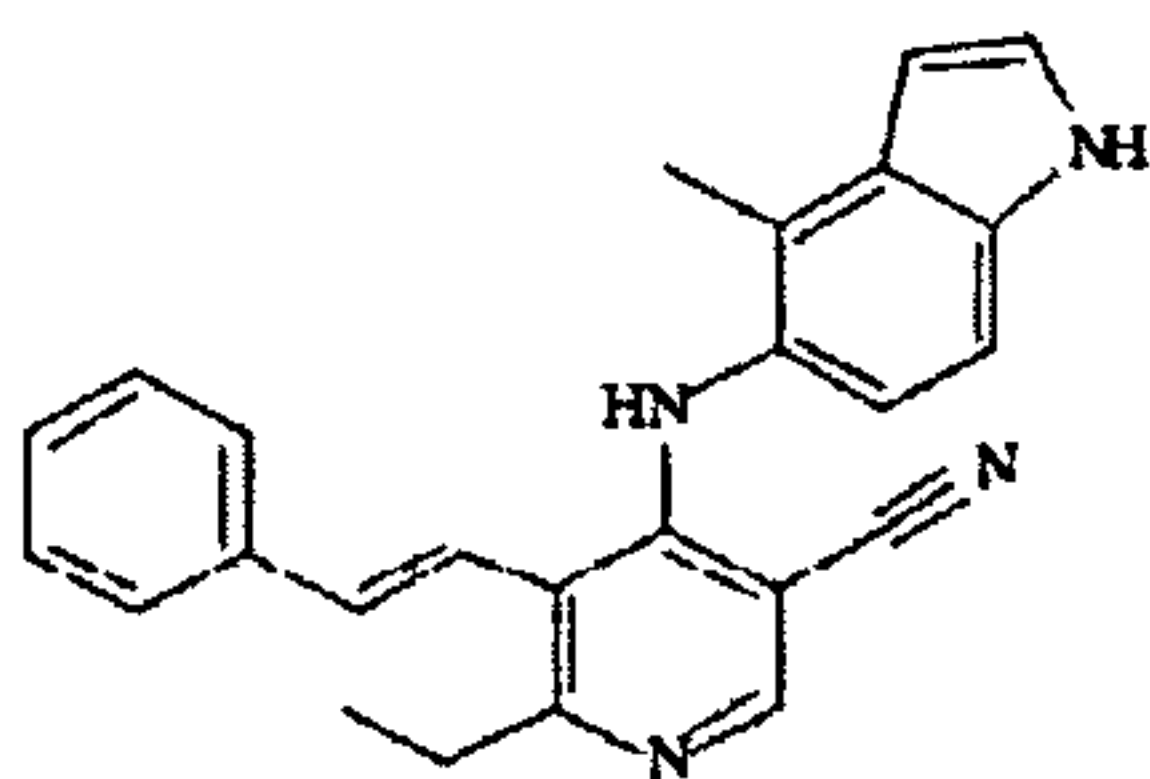
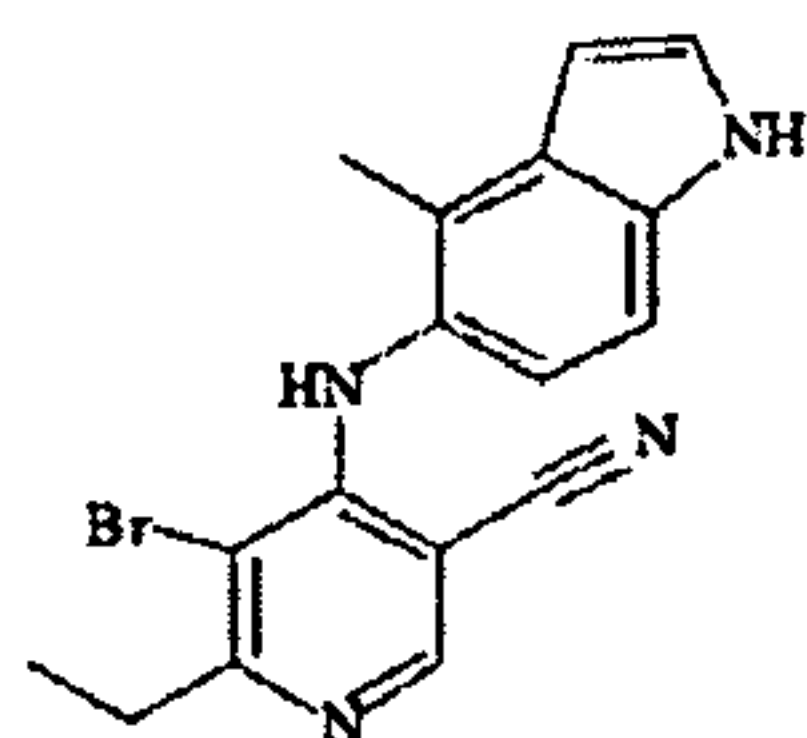
[00251] Preparation of 5-[(E)-2-(4-fluorophenyl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

The title compound was prepared from 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and *trans*-2-(4-fluorophenyl)vinylboronic acid via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4-methylphenyl)vinyl]-nicotinonitrile; MS 369.3 (M+H); HPLC: rt = 10.1 min [a].



[00252] Preparation of 5-bromo-4-chloro-6-ethylnicotinonitrile:

To a -78°C solution of 5-bromo-4-chloro-6-methylnicotinonitrile (392 mg, 1.7 mmol) in anhydrous tetrahydrofuran (8.0 mL) was slowly added lithium bis(trimethylsilyl)amide (3.8 mL, 3.8 mmol). The resulting slurry was stirred at -78°C for 1 h under N_2 . Iodomethane (483 mg, 3.4 mmol) was added and the reaction mixture was stirred at -78°C then gradually warmed to room temperature overnight. The reaction was quenched with 1.0 M citric acid solution and H_2O , then extracted with ethyl acetate three times. The combined organic layers were washed with H_2O and brine then dried over Na_2SO_4 . After filtration and concentration, the residue was purified by silica gel column chromatography, eluting with dichloromethane, providing 74 mg (18%) of 5-bromo-4-chloro-6-ethylnicotinonitrile as a yellow solid containing a small amount of 5-bromo-4-chloro-6-isopropylnicotinonitrile (<10%); MS 245 (M+H).



[00253] Preparation of 5-bromo-6-ethyl-4-(4-methyl-1H-indol-5-ylamino)nicotinonitrile, 6-ethyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-phenylvinyl]-nicotinonitrile,

and of 6-isopropyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-phenylvinyl]-nicotinonitrile:

5-Bromo-4-chloro-6-ethylnicotinonitrile (71 mg, 0.29 mmol) contaminated with a small amount of the corresponding isopropyl derivative was combined with 5-amino-4-methyl indole (42 mg, 0.29 mmol) in anhydrous ethanol (1.0 mL) and heated at reflux for 48 h. After cooling to room temperature, the reaction mixture was added to 10 mL of H₂O and filtered. The solid residue was washed with H₂O and diethyl ether then dried *in vacuo* to provide a quantitative amount of crude 5-bromo-6-ethyl-4-(4-methyl-1H-indol-5-ylamino)nicotinonitrile as a dark solid which was used directly without further purification; MS 355 (M+H). The product was contaminated with small amounts of the corresponding isopropyl derivative.

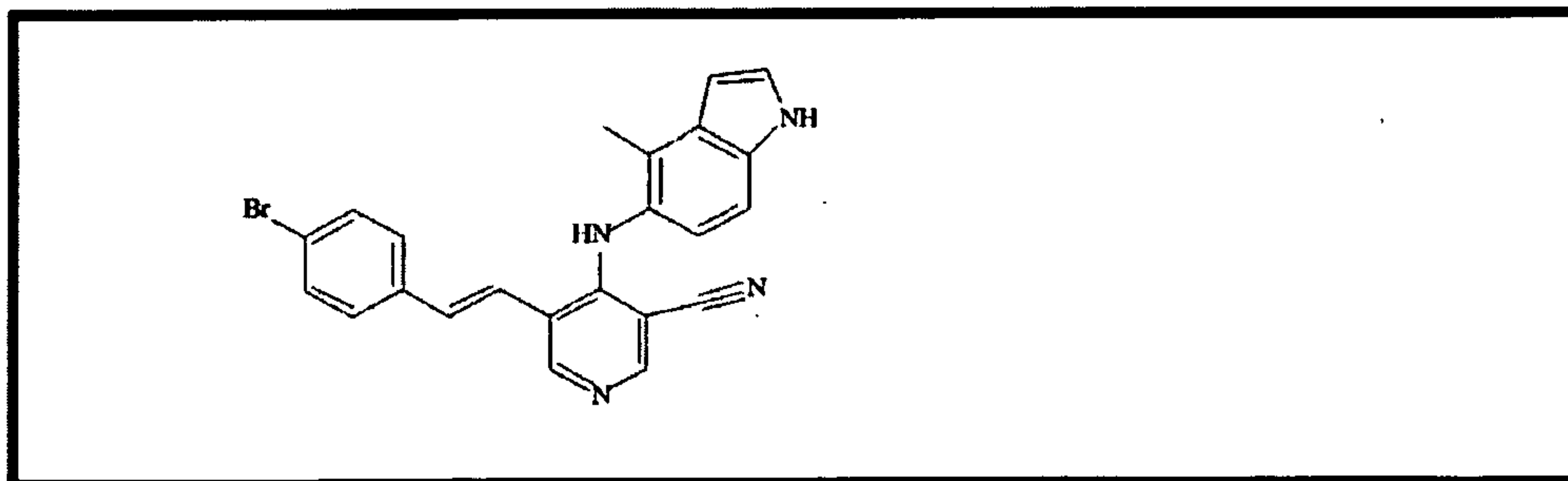
[00254] The mixture thus obtained was treated with *trans*-2-phenylvinylboronic acid via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4-methylphenyl)vinyl]-nicotinonitrile. Two products were isolated, 6-ethyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-phenylvinyl]-nicotinonitrile and 6-isopropyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-phenylvinyl]-nicotinonitrile.

[00255] 6-ethyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-phenylvinyl]-nicotinonitrile:

MS 379.3 (M+H); HPLC: *rt* = 10.4 min [a].

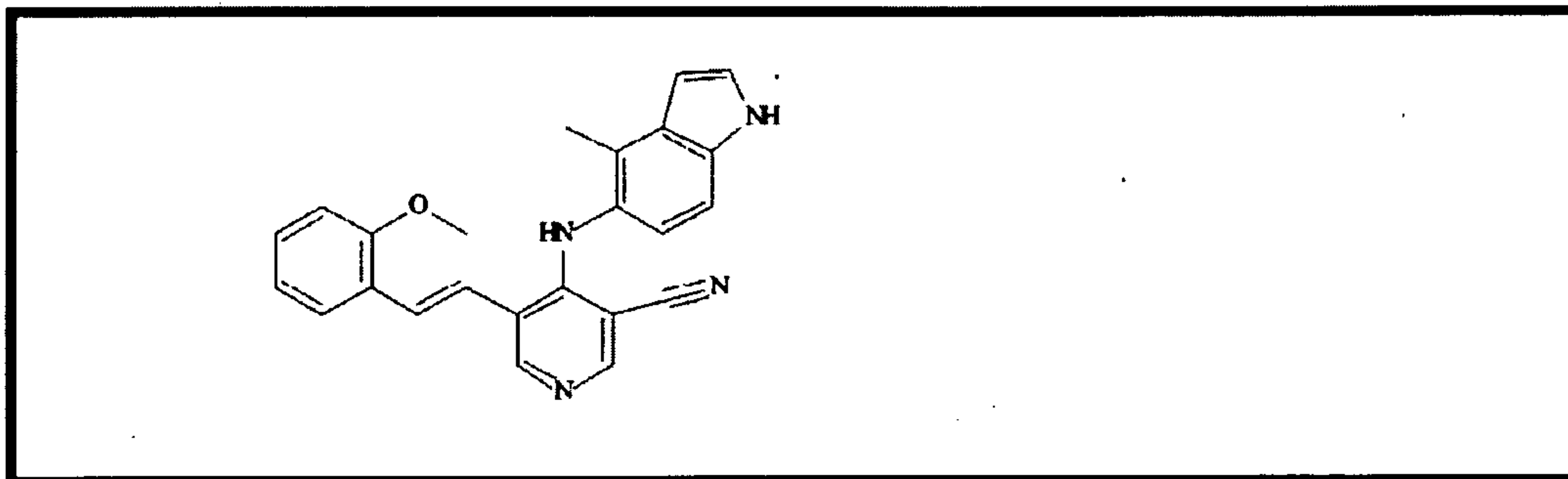
[00256] 6-isopropyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-phenylvinyl]-nicotinonitrile:

MS 393.3 (M+H); HPLC: *rt* = 11.1 min [a].



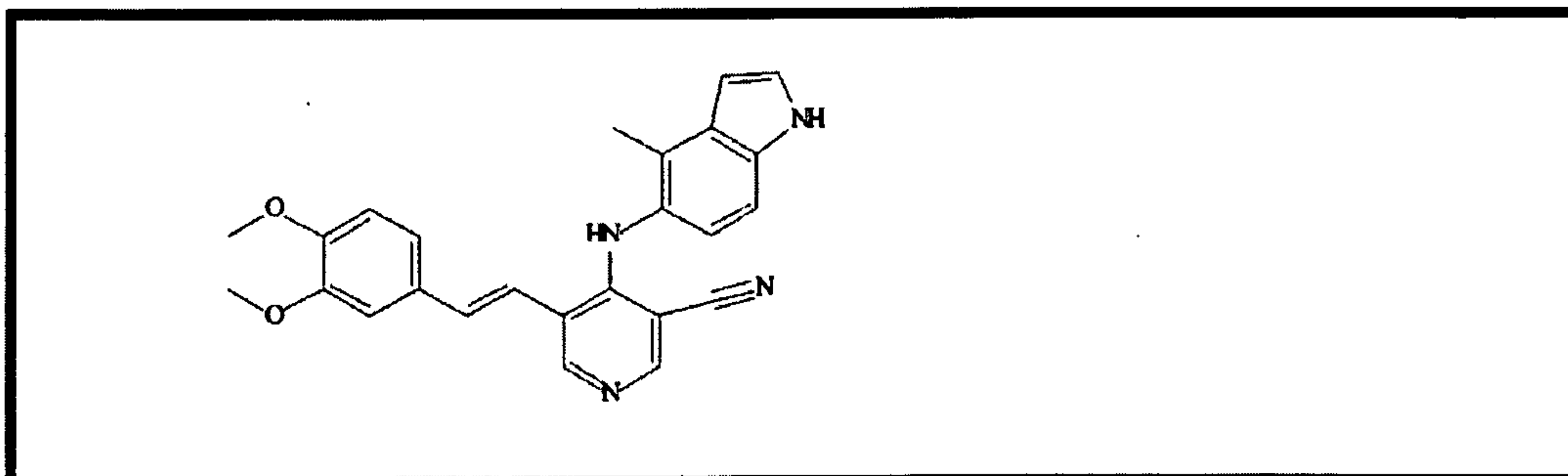
[00257] Preparation of 5-[(E)-2-(4-bromophenyl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]-nicotinonitrile:

To a reaction mixture of 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (75 mg, 0.2 mmol), 4-bromostyrene (48 mg, 0.26 mmol), Pd(AcO)₂ (14 mg, 0.06 mmol) and tri(ortho-tolyl)phosphine (3 mg, 0.01 mmol) in 1.0 mL of DMF was added triethylamine (42 μ L, 0.3 mmol). The reaction mixture was heated to 100°C for 2.5 h, then concentrated. The residue was purified by silica gel chromatography eluting with CH₂Cl₂-THF (9:1), providing 52 mg (61%) of 5-[(E)-2-(4-bromophenyl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]-nicotinonitrile as a yellow solid; MS 429.2 (M+H); HPLC: rt = 11.7 min [a].



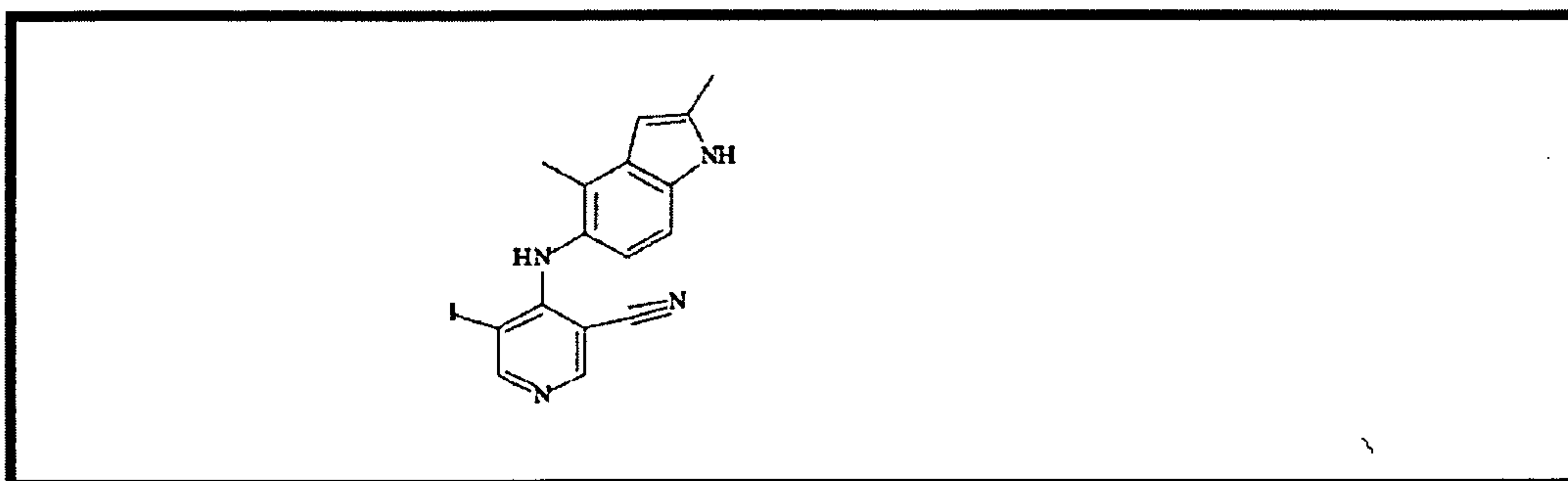
[00258] Preparation of 5-[(E)-2-(2-methoxyphenyl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

The title compound was prepared from 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 2-methoxystyrene via the procedure used to prepare 5-[(E)-2-(4-bromophenyl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]-nicotinonitrile; MS 381.2 (M+H); HPLC: rt = 10.6 min [a].



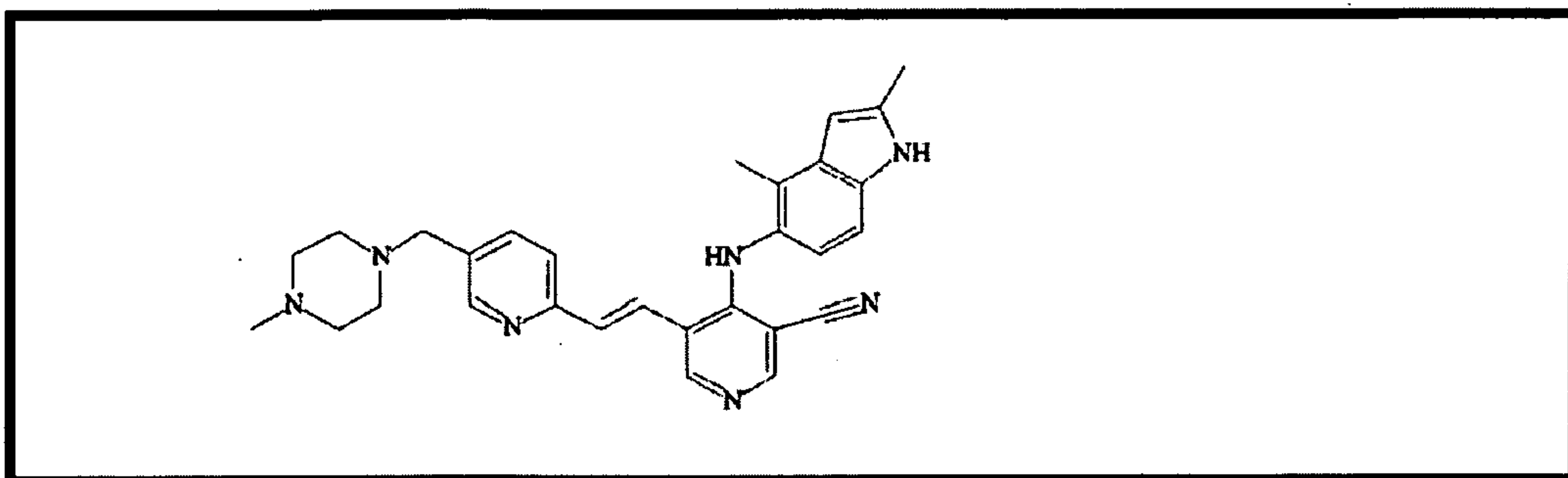
[00259] Preparation of 5-[(E)-2-(3,4-dimethoxyphenyl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

The title compound was prepared from 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 3,4-dimethoxystyrene via the procedure used to prepare 5-[(E)-2-(4-bromophenyl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]-nicotinonitrile; MS 411.3 (M+H); HPLC: *rt* = 9.7 min[a].



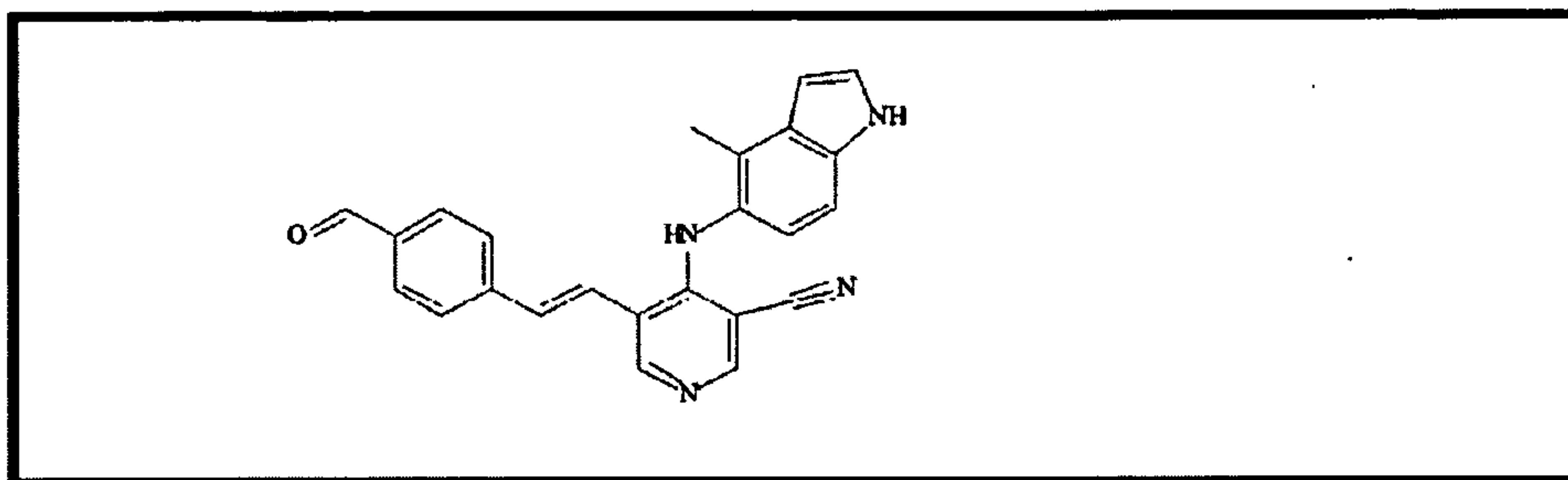
[00260] Preparation of 4-[(2,4-dimethyl-1H-indol-5-yl)amino]-5-iodonicotinonitrile:

To a reaction mixture of 5-amino-2,4-dimethylindole (800 mg, 5.0 mmol) and 4-chloro-5-iodonicotinonitrile (1.056 g, 4.0 mmol) in 15 mL of anhydrous ethanol was added triethylamine (0.78 mL, 5.6 mmol). The reaction mixture was heated at reflux for 40 h and subsequently concentrated to remove half of the solvent. To the residue was added saturated NaHCO₃ solution and H₂O. The suspension was filtered and the solid was washed with H₂O several times and dried *in vacuo* to give 1.45 g of crude 4-[(2,4-dimethyl-1H-indol-5-yl)amino]-5-iodonicotinonitrile. The product was further purified by preparative HPLC, providing 1.28 g (66%) of 4-[(2,4-dimethyl-1H-indol-5-yl)amino]-5-iodonicotinonitrile as a dark solid; MS 389.1 (M+H).



[00261] Preparation of 4-[(2,4-dimethyl-1H-indol-5-yl)amino]-5-[(E)-2-{5-[(4-methyl-piperazin-1-yl)methyl]pyridin-2-yl}vinyl]nicotinonitrile:

The title compound was prepared from 4-[(2,4-dimethyl-1H-indol-5-yl)amino]-5-iodonicotinonitrile and 1-methyl-4-[(6-vinylpyridin-3-yl)methyl]piperazine via the procedure used to prepare 5-[(E)-2-(4-bromophenyl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]-nicotinonitrile; MS 478.5 (M+H); HPLC: *rt* = 5.5 min [a].

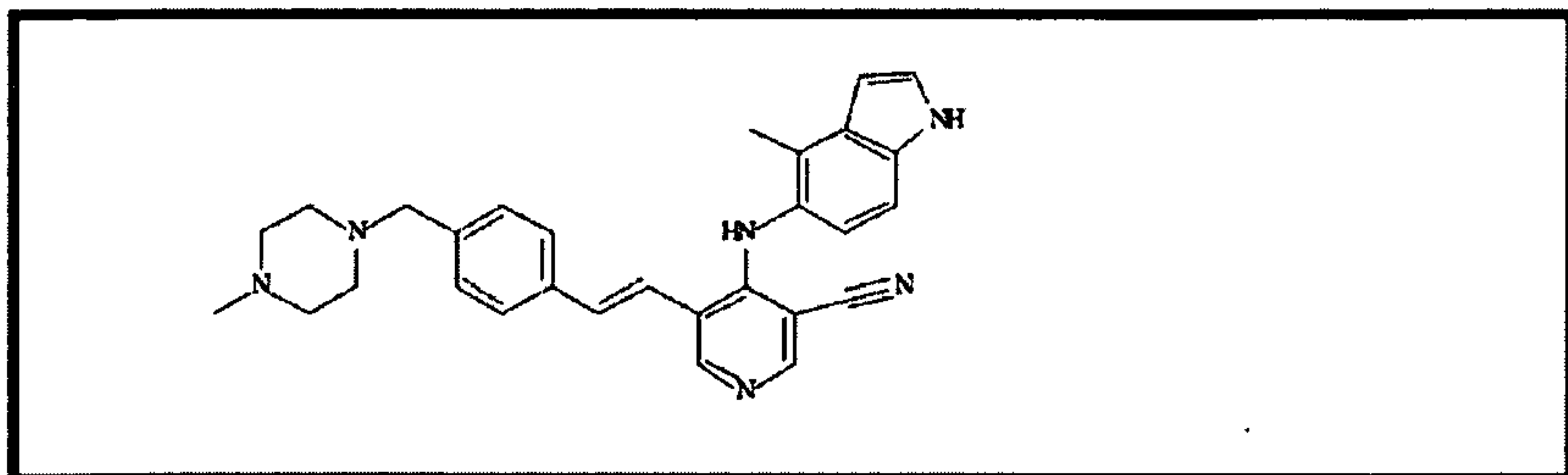


[00262] Preparation of 5-[(E)-2-(4-formylphenyl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

5-[(E)-2-(4-formylphenyl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile was prepared from 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 4-vinylbenzaldehyde via the procedure used to prepare 5-[(E)-2-(4-bromophenyl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]-nicotinonitrile; MS 379.0 (M+H).

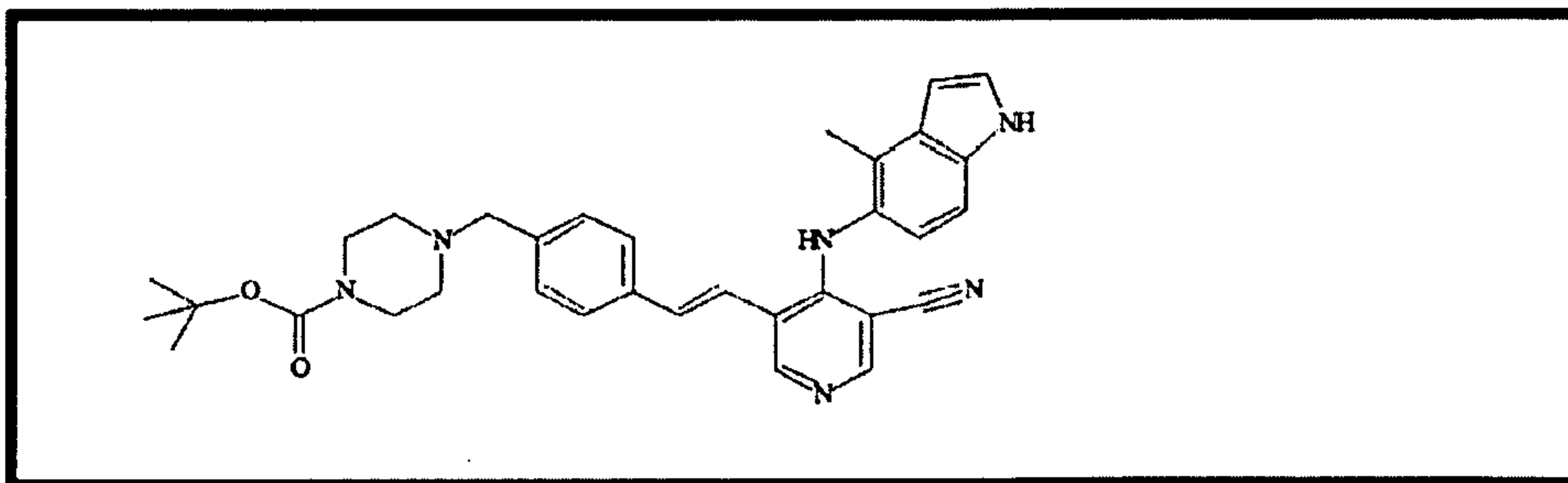
5-[(E)-2-(4-formylphenyl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile was also prepared by an alternative method as follows. To a reaction mixture of 4-[(E)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethenyl] benzaldehyde (1.0 g, 3.9 mmol), 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (1.73 g, 4.8 mmol) and Pd(PPh₃)₄ (266 mg, 0.23 mmol) in 1,2-dimethoxyethane (50 mL) at room temperature was added saturated NaHCO₃ solution (26 mL). The reaction mixture was heated to 100°C for 3.5 h, then stirred at room temperature overnight, quenched with H₂O, extracted with a mixture of THF-EtOAc (1:2) three times. The extracts were combined and washed with H₂O and brine. Drying, filtration and evaporation gave a brown solid, which was purified by silica gel chromatography (hexane-EtOAc, 10:1 to 2:1), providing 2.6 g (72%) the title compound as a yellow solid. ¹HNMR(300 MHz, DMSO) 2.34 (s, 3H), 6.53 (s, 1H), 6.95 (d, 1H, *J* = 8.0 Hz), 7.26 (d, 1H, *J* = 8.0 Hz),

7.36(m, 2H), 7.61 (m, 2H), 7.84 (m, 1H), 7.96 (d, 1H, J = 8.0 Hz), 8.16 (s, 1H), 8.29 (s, 1H), 8.62 (s, 1H), 8.93 (s, 1H), 9.98 (s, 1H), 11.16 (s, 1H); MS 379.2 (M+H).



[00263] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]nicotinonitrile:

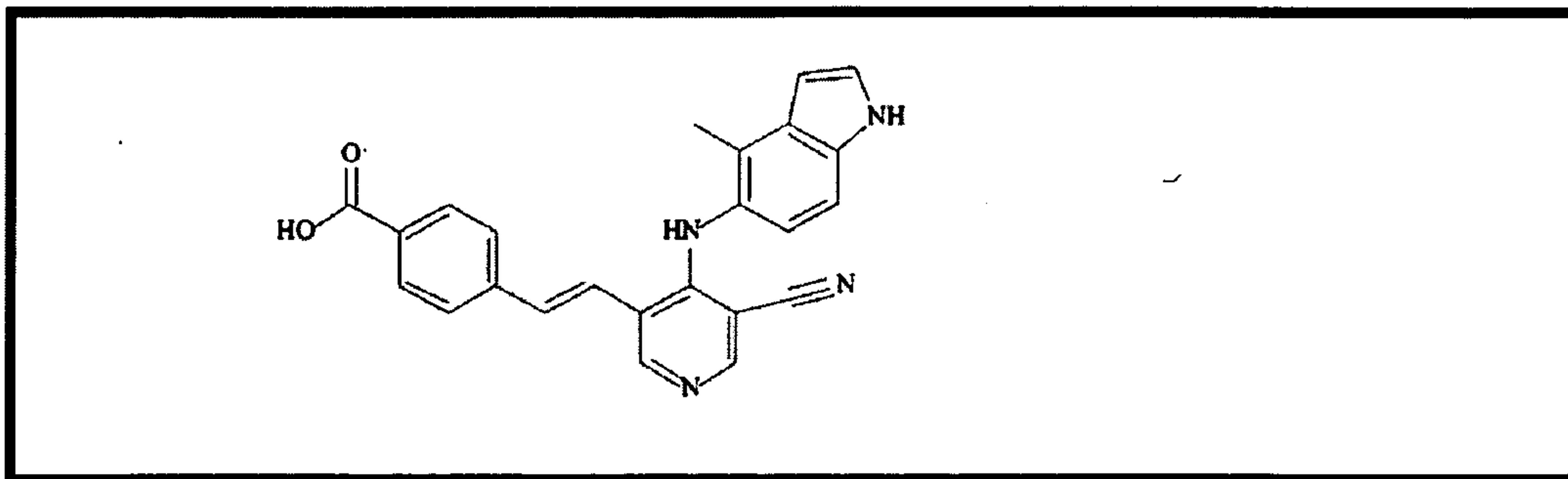
To a reaction mixture of 5-[(E)-2-(4-formylphenyl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (75 mg, 0.2 mmol) and 1-methylpiperazine (100 mg, 1.0 mmol) in 3 mL of CH₂Cl₂ was added 0.5 mL of 1-methyl-2-pyrrolidinone plus two drops of glacial HOAc. The resulting mixture was stirred at room temperature for 40 min. To this was added NaBH(OAc)₃ (212 mg, 1.0 mmol) in portions over a period of 20 min. The reaction mixture was stirred at room temperature for 16 h and then concentrated. The residue was purified by preparative HPLC, providing 10 mg (11%) of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]nicotinonitrile as a yellow solid; MS 369.3 (M+H); HPLC 98% at 215 nm, rt = 12.4 min[b].



[00264] Preparation of tert-butyl 4-{4-[(E)-2-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}vinyl]benzyl}piperazine-1-carboxylate:

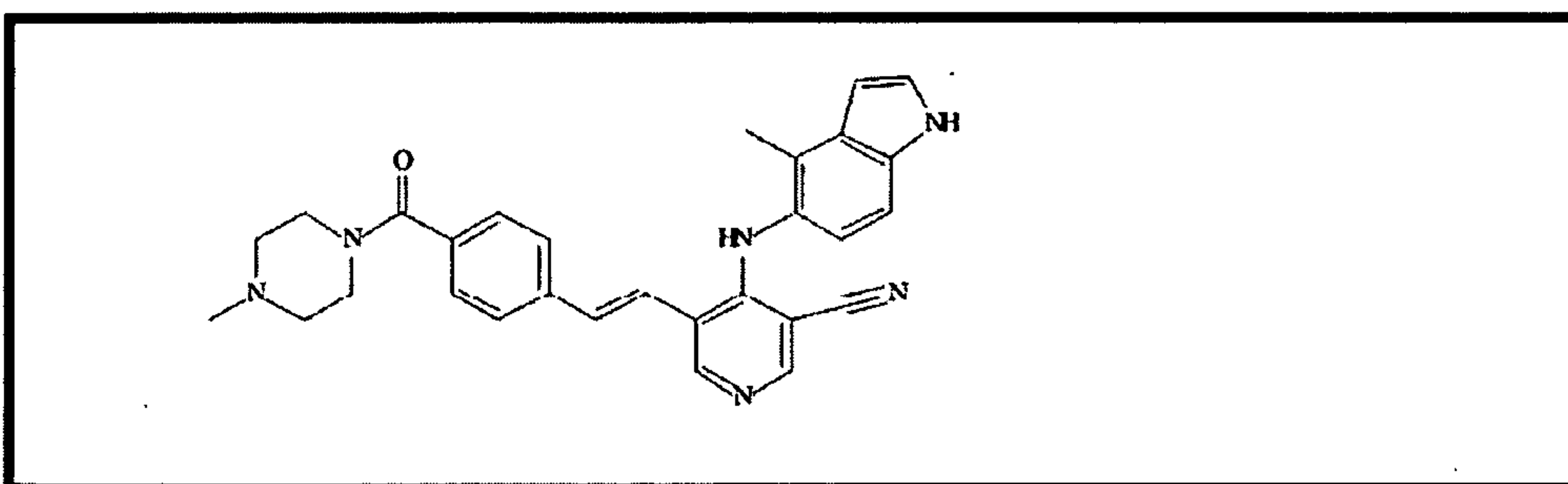
The title compound was prepared from 5-[(E)-2-(4-formylphenyl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 1-Boc-piperazine via the procedure used to prepare 4-[(4-methyl-

1H-indol-5-yl)amino]-5-[(E)-2-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]nicotinonitrile; MS 549.5 (M+H); HPLC: rt = 7.8 min [a].



[00265] Preparation of 4-[(E)-2-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}vinyl]benzoic acid:

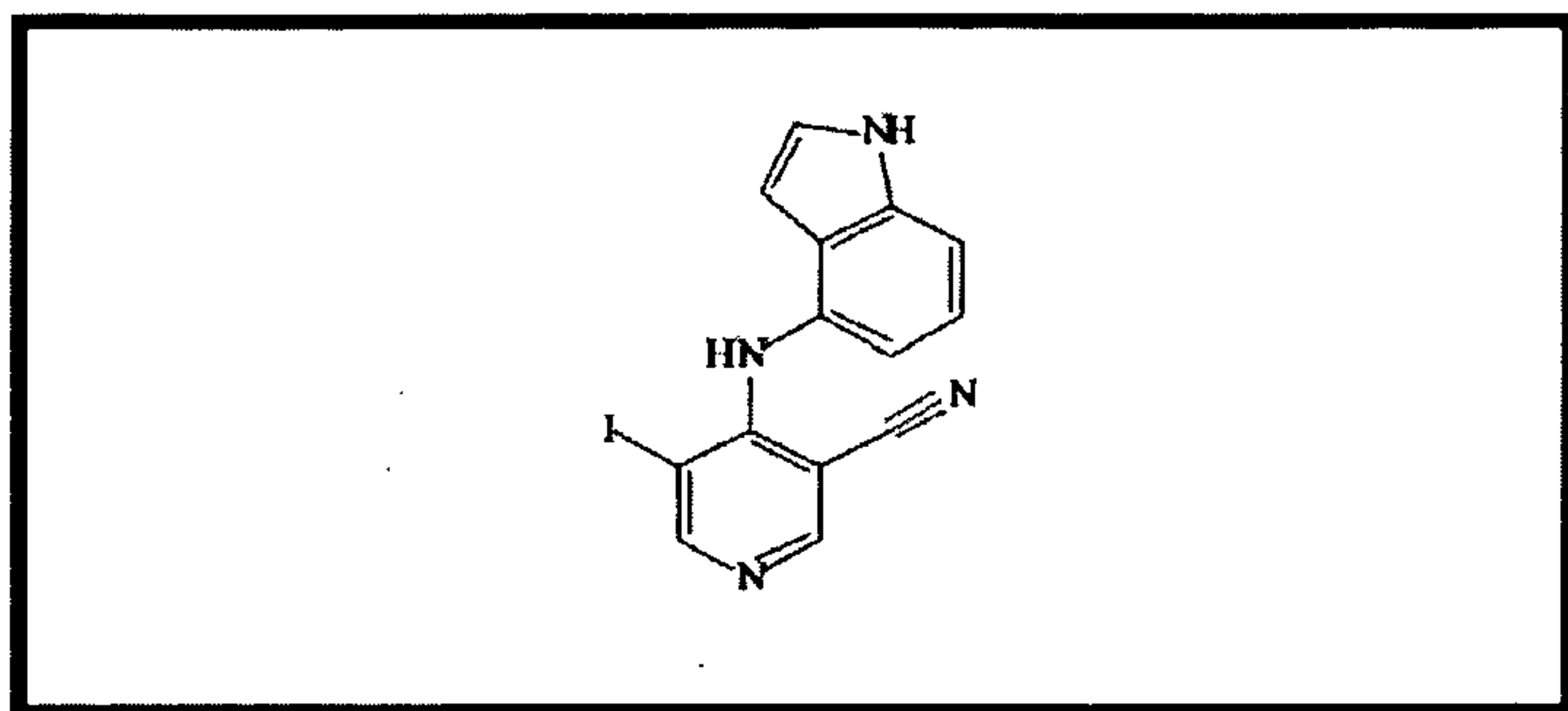
The title compound was prepared from 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 4-vinylbenzoic acid via the procedure used to prepare 5-[(E)-2-(4-bromophenyl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]-nicotinonitrile; MS 395.3 (M+H); HPLC: 97% at 215 nm, rt = 8.0 min [a].



[00266] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}vinyl]nicotinonitrile:

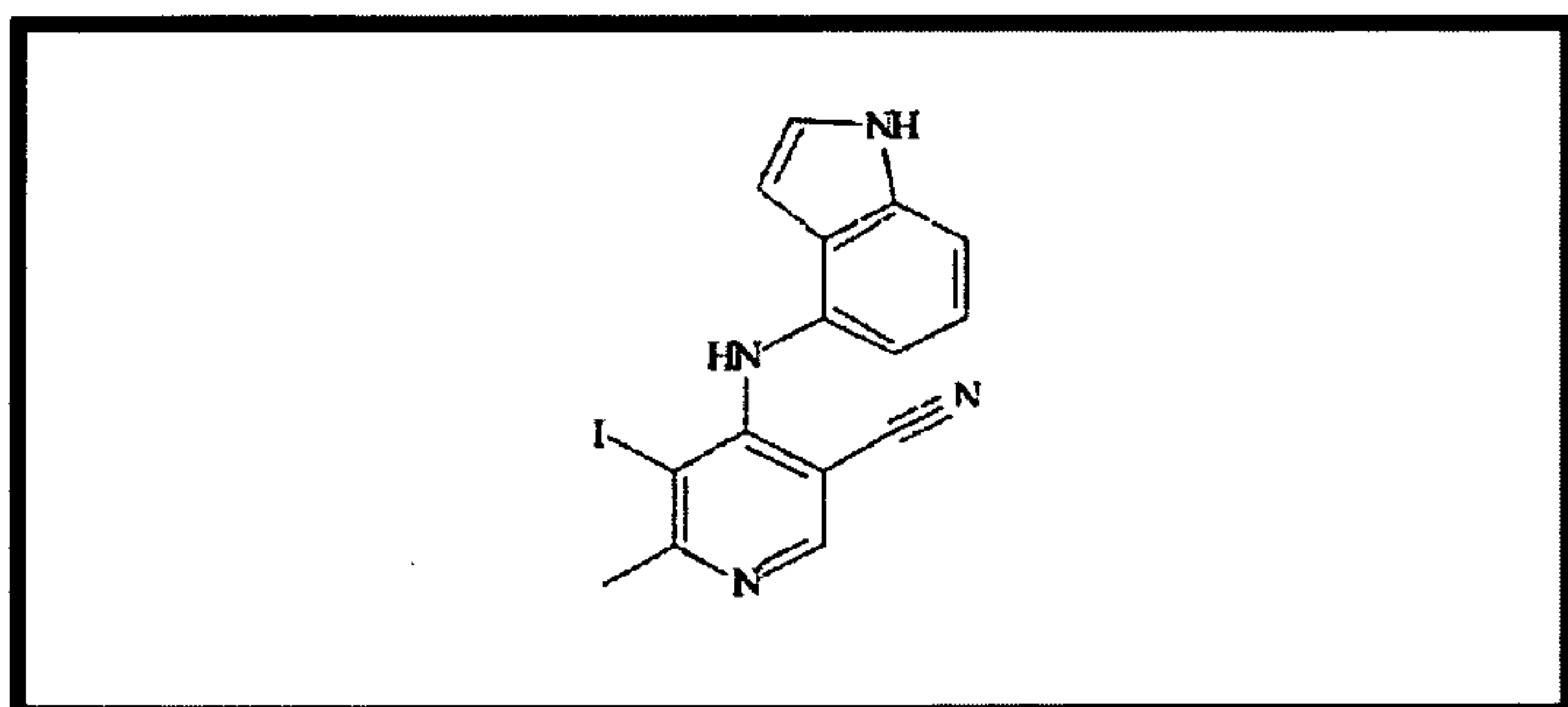
To a reaction mixture of 4-[(E)-2-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}vinyl]benzoic acid (70 mg, 0.18 mmol) and PyBOP (120 mg, 0.23 mmol) in 4 mL of CH₂Cl₂ was added diisopropylethylamine (63 μ L, 0.36 mmol) followed by 1-methylpiperazine (23 mg, 0.023 mmol). The resulting mixture was stirred at room temperature for 16 h and subsequently concentrated. The residue was purified by preparative HPLC providing 65 mg (77%) of 4-[(4-

methyl-1H-indol-5-yl)amino]-5-[(E)-2-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}vinyl]nicotinonitrile as a dark yellow solid; MS 477.4 (M+H); HPLC: 92% at 215 nm, rt = 5.4 min [a].



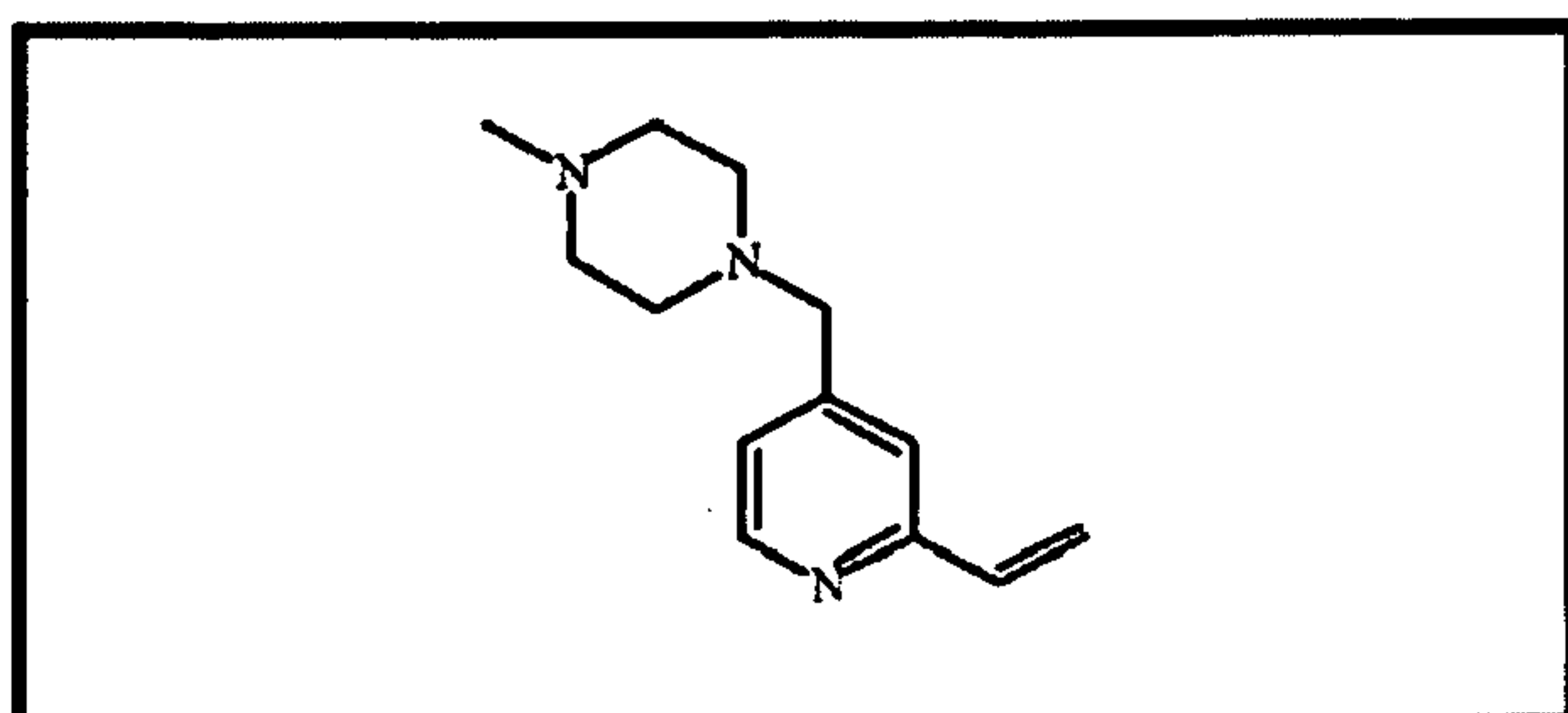
[00267] Preparation of 4-(1H-indol-4-ylamino)-5-iodonicotinonitrile:

4-(1H-indol-4-ylamino)-5-iodonicotinonitrile was prepared by the procedure described for 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile; MS: 361 [M+H].



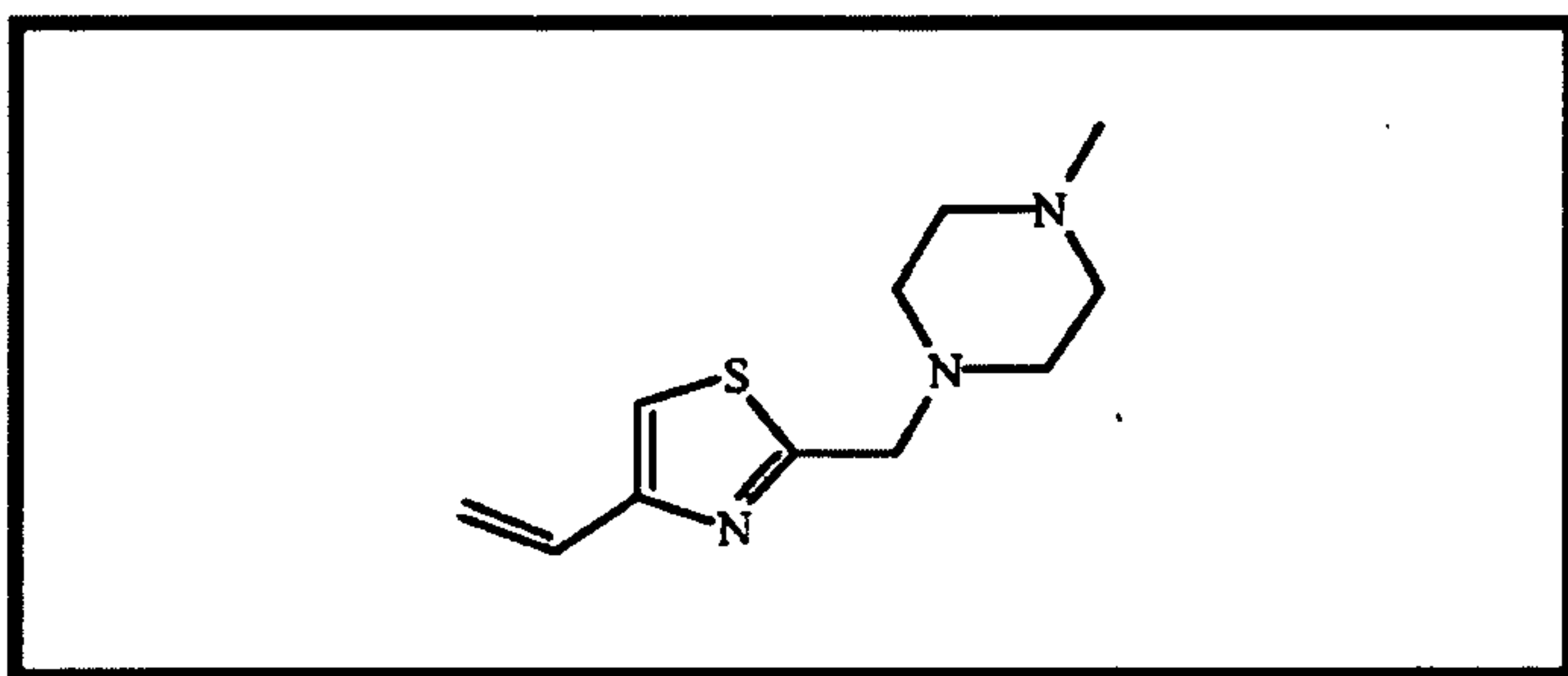
[00268] Preparation of 4-(1H-indol-4-ylamino)-5-iodo-6-methylnicotinonitrile:

4-(1H-indol-4-ylamino)-5-iodo-6-methylnicotinonitrile was prepared by the procedure described for 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile; MS: 375 [M+H].

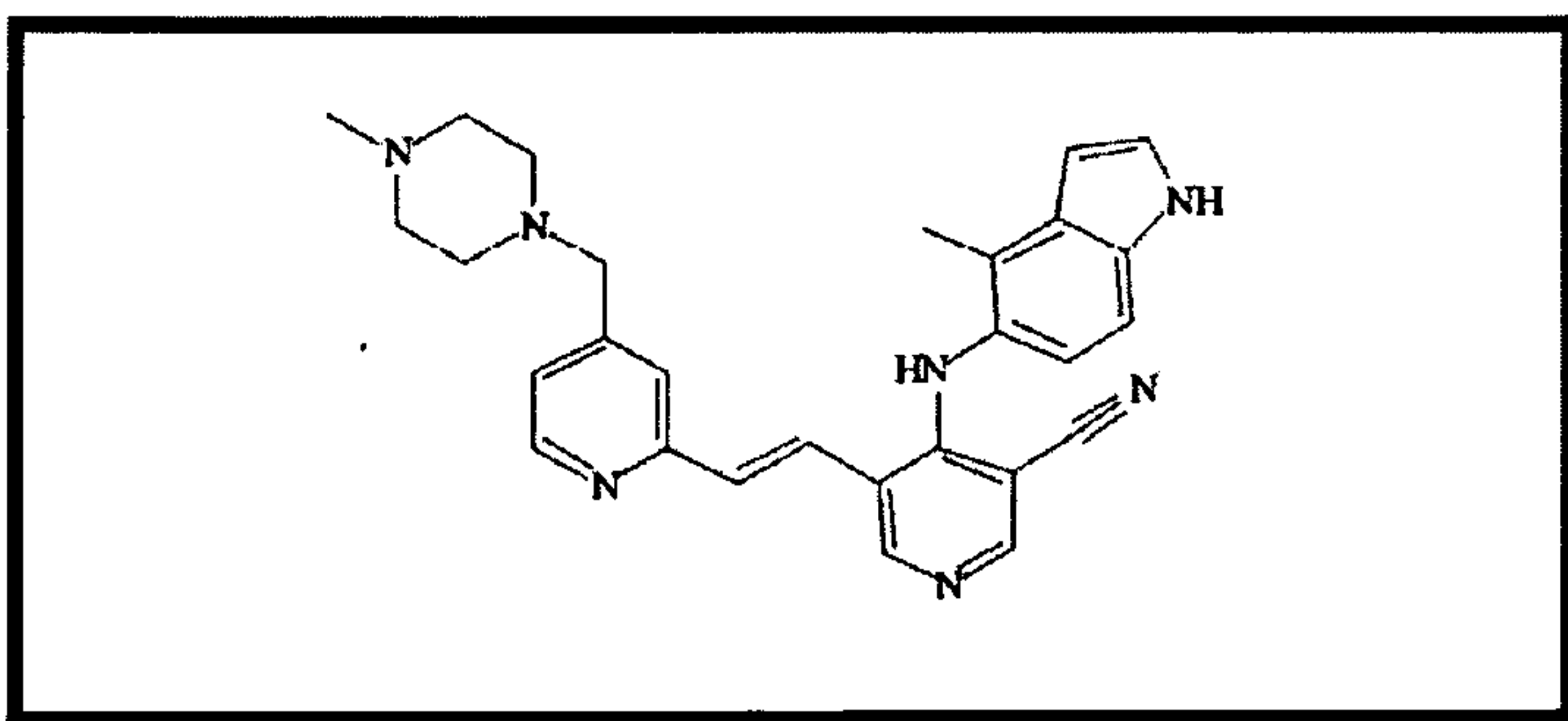


[00269] Preparation of 1-methyl-4-[(2-vinylpyridin-4-yl)methyl]piperazine:

A mixture of 1-[(2-bromo-4-pyridinyl)methyl]-4-methylpiperazine (1.0 g, 3.7 mmol), tributyl(vinyl)tin (1.78, 5.6 mmol), and Pd(PPh₃)₄ (218.3 mg, 0.19 mmol) in 17 mL of toluene was heated at reflux for 19 h. The mixture was cooled to room temperature and partitioned between dichloromethane and aqueous saturated sodium bicarbonate. The organic phase was dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography eluting with a gradient of 2% methanol in dichloromethane to 8% methanol in dichloromethane to provide 688 mg (86%) of 1-methyl-4-[(2-vinylpyridin-4-yl)methyl]piperazine as a yellow oil; MS 218.3 (M+H).

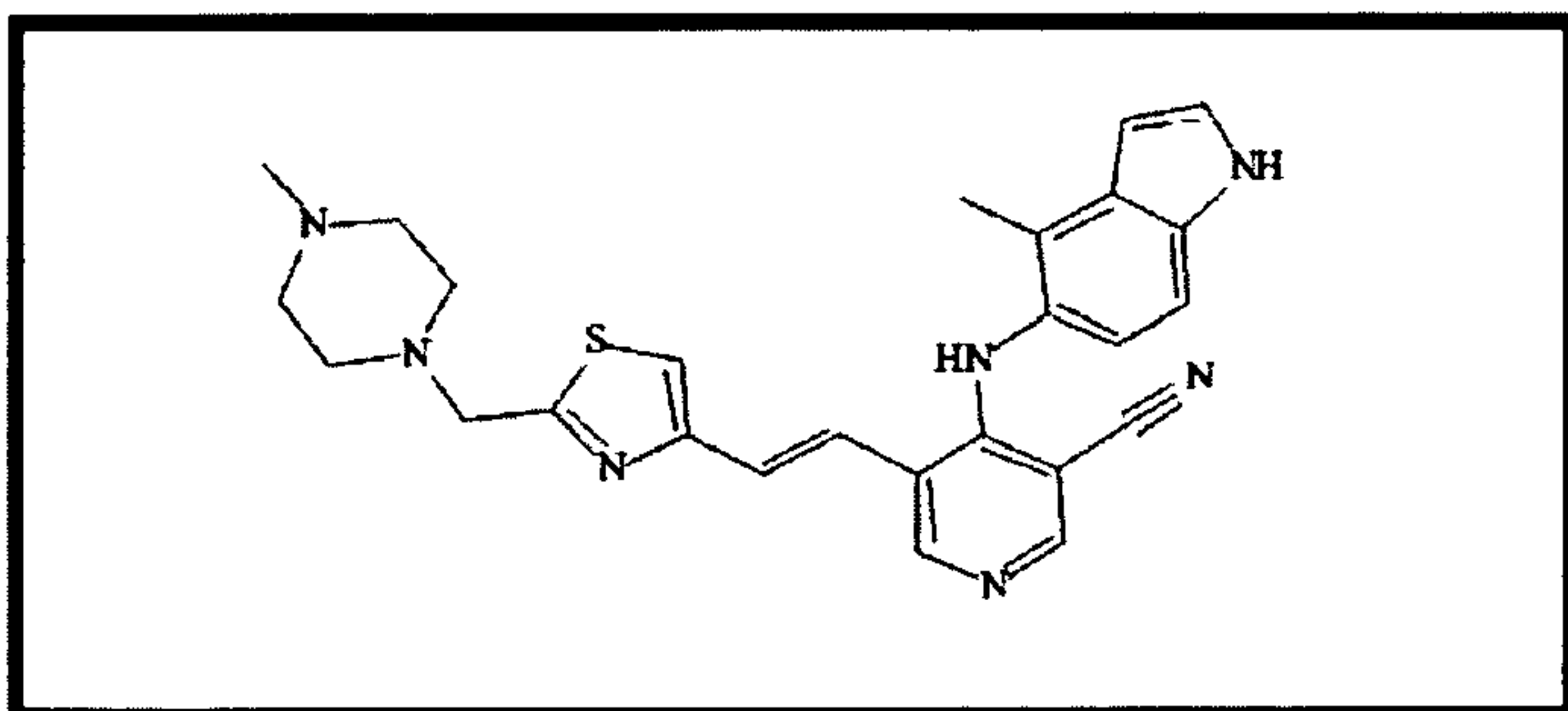
**[00270] Preparation of 1-methyl-4-[(4-vinyl-1,3-thiazol-2-yl)methyl]piperazine:**

Following the procedure to prepare 1-methyl-4-[(2-vinylpyridin-4-yl)methyl]piperazine, 1-methyl-4-[(4-vinyl-1,3-thiazol-2-yl)methyl] piperazine was prepared via the reaction of 1-[(4-bromo-1,3-thiazol-2-yl)methyl]-4-methylpiperazine with tributylvinyltin; MS 224.2 (M+H).



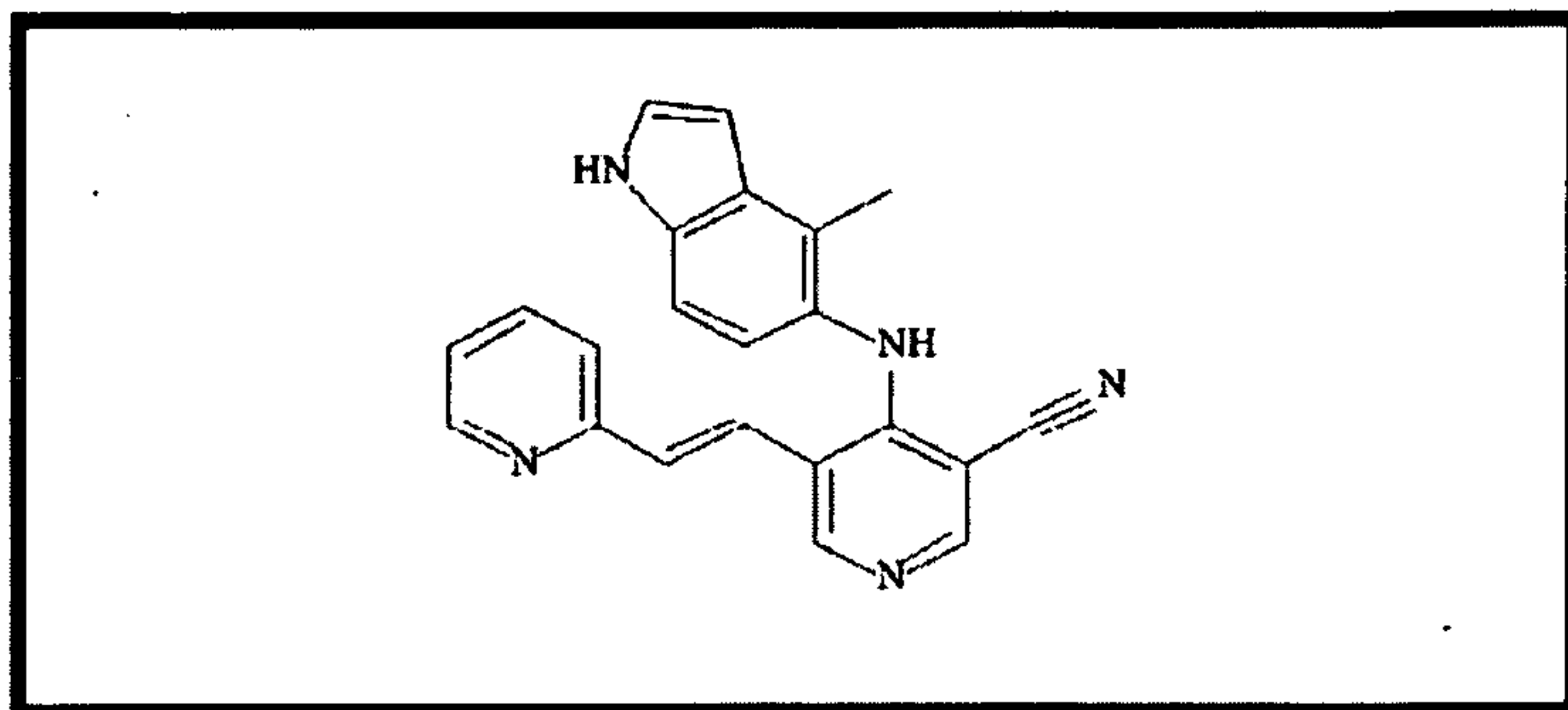
[00271] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{4-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}vinyl]nicotinonitrile:

A mixture of 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (150 mg, 0.40 mmol), 1-methyl-4-[(2-vinylpyridin-4-yl)methyl]piperazine (113.0 mg, 0.52 mmol), Pd(OAc)₂ (18 mg, 0.08 mmol) and tri(ortho-tolyl)phosphine (6.1 mg, 0.02 mmol) in 3.5 mL of DMF and 1.0 mL of TEA was heated at 95°C for 2 h. The mixture was cooled to room temperature, and partitioned between dichloromethane and aqueous saturated sodium bicarbonate. The organic phase was dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography, eluting with a gradient of 2% methanol in dichloromethane to 20% methanol in dichloromethane to provide 84.0 mg (45%) of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{4-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}vinyl]nicotinonitrile as a light tan solid; MS 464.3 (M+H); HPLC: 99.4% at 215 nm, *rt* = 4.6 min [a].



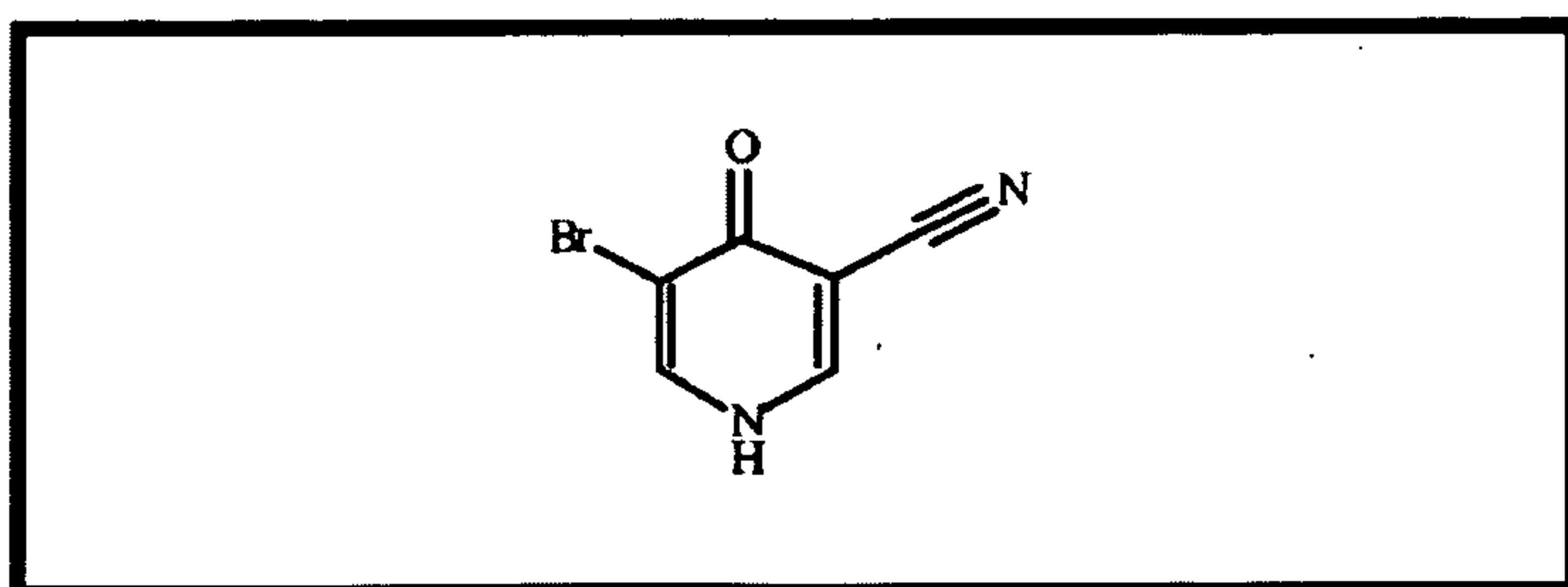
[00272] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{2-[(4-methylpiperazin-1-yl)methyl]-1,3-thiazol-4-yl}vinyl]nicotinonitrile:

Following the procedure to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{4-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}vinyl]nicotinonitrile, 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{2-[(4-methylpiperazin-1-yl)methyl]-1,3-thiazol-4-yl}vinyl]nicotinonitrile was prepared via the reaction of 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile with 1-methyl-4-[(4-vinyl-1,3-thiazol-2-yl)methyl]piperazine; MS 470.3 (M+H), HPLC: 98.5% at 215 nm, *rt* = 5.4 min [a].



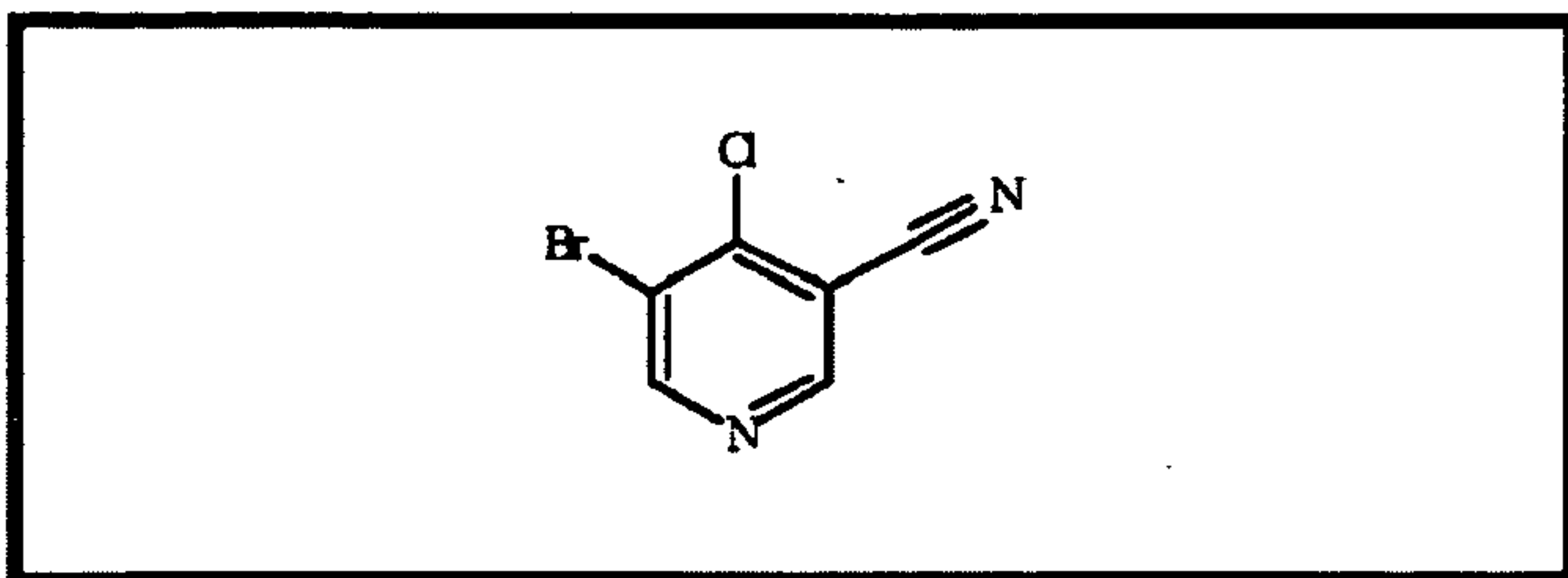
[00273] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-pyridin-2-ylvinyl]nicotinonitrile:

A mixture of 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (150 mg, 0.40 mmol), 2-vinylpyridine (54.6 mg, 0.52 mmol), Pd(OAc)₂ (18 mg, 0.08 mmol) and tri-*o*-tolylphosphine (6.1 mg, 0.02 mmol) in 2.5 mL of DMF and 0.50 mL of TEA was heated at 95°C for 3 h. The mixture was cooled to room temperature and concentrated *in vacuo*. The residue was purified by column chromatography, eluting with 20% to 50% ethyl acetate in hexane, ethyl acetate and 2% methanol in ethyl acetate to provide 74.1 mg (53%) of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-pyridin-2-ylvinyl]nicotinonitrile as a yellow solid; MS 352.2 (M+H), Analysis for C₂₂H₁₇N₅·0.7H₂O·0.14 CH₂Cl₂; Calcd: C, 70.74; H, 5.01; N, 18.63, Found: C, 70.38; H, 4.78; N, 18.61.

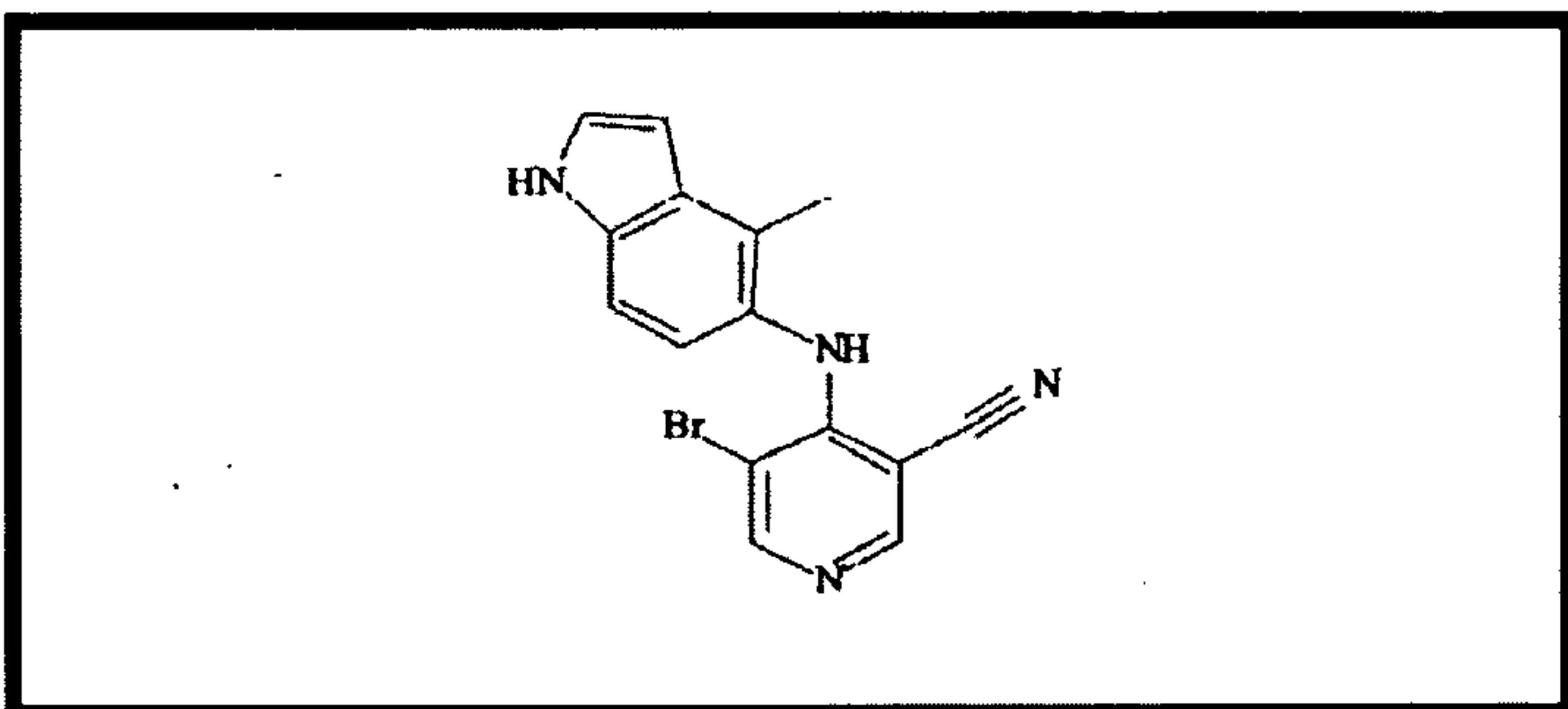


[00274] Preparation of 5-bromo-4-oxo-1,4-dihydropyridine-3-carbonitrile:

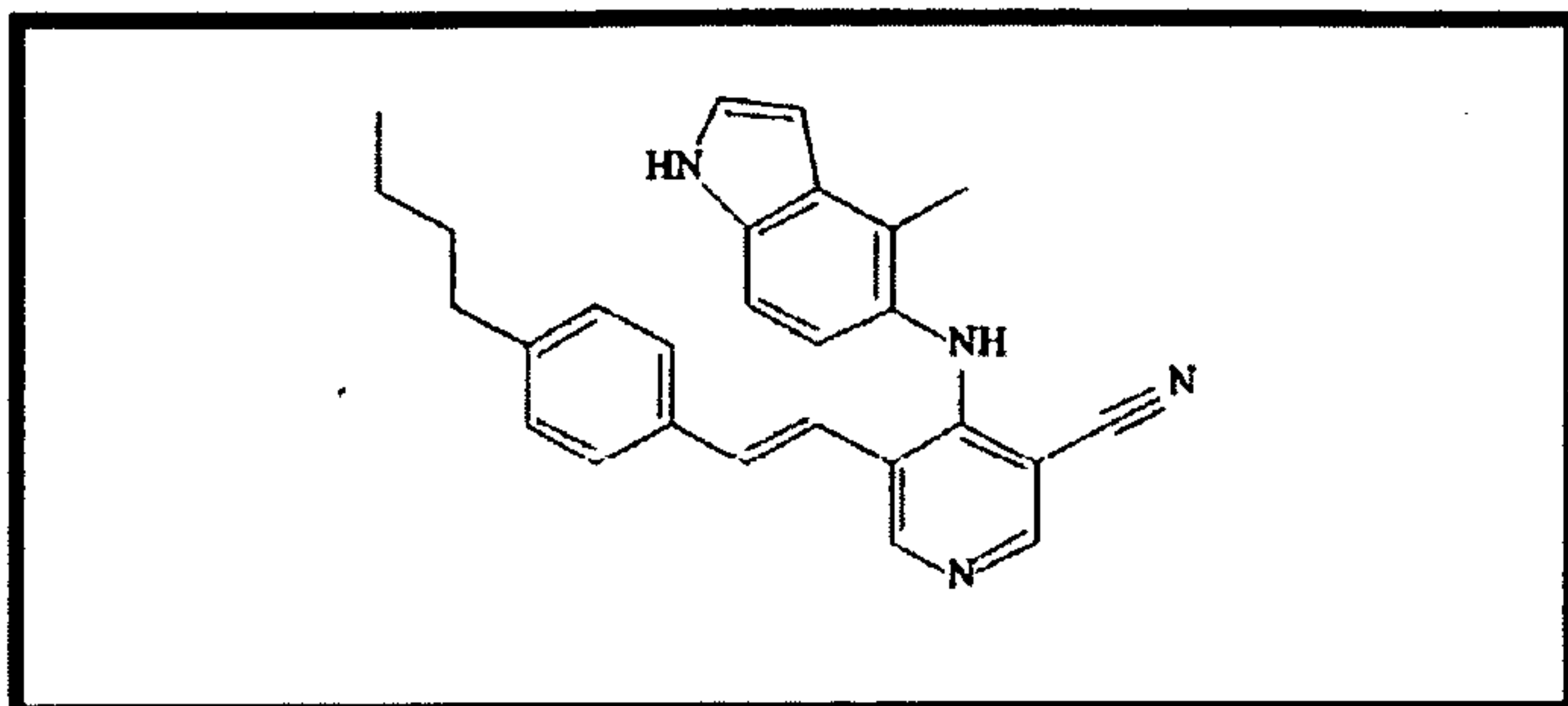
To a solution of 1,4-dihydro-4-oxonicotinonitrile (1.2 g, 9.99 mmol) in 30 mL of acetic acid was added dropwise a solution of bromine (1.92 g, 11.99 mmol) in 5.5 mL of acetic acid at 90°C over a period of 3 h. The resulting reaction mixture was further stirred at 90°C for 3 h. After cooling to room temperature, the mixture was concentrated *in vacuo*. The solid residue was triturated with ethanol to give 1.0 g (52%) of 5-bromo-4-oxo-1,4-dihydropyridine-3-carbonitrile as a light brown solid; MS 199.0, 201.0 (M+H).

**[00275] Preparation of 5-bromo-4-chloronicotinonitrile:**

A mixture of 5-bromo-4-oxo-1,4-dihydropyridine-3-carbonitrile (1.75 g, 8.79 mmol) in POCl₃ was heated at reflux for 3 h. After cooling to room temperature, the mixture was concentrated *in vacuo*. The residue was cooled in an ice bath and treated with aqueous saturated sodium bicarbonate. The aqueous suspension was extracted with dichloromethane. The combined extracts were washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography, eluting with a gradient of 10% dichloromethane/hexane to 60% dichloromethane/hexane to give 1.5 g (86%) of 5-bromo-4-chloronicotinonitrile as a white solid; MS 217.0, 219.0 (M+H).

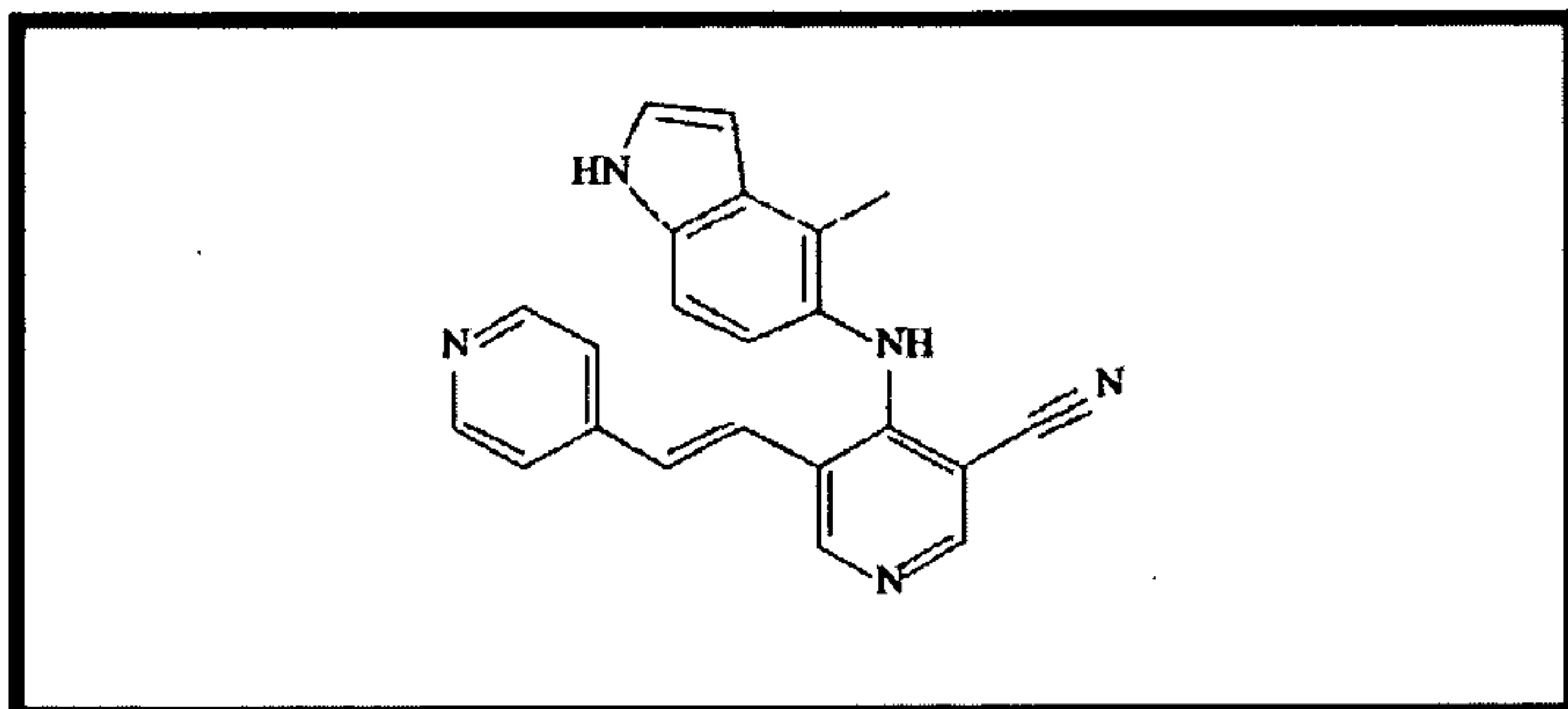
**[00276] Preparation of 5-bromo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:**

A mixture of 5-bromo-4-chloronicotinonitrile (1.40 g, 6.43 mmol), 5-amino-4-methylindole (0.94 g, 6.43 mmol) in 15 mL of ethanol was heated at reflux overnight, then cooled to room temperature. The precipitate was filtered and washed with ethanol twice and diethyl ether once, then air-dried. The resultant HCl salt was suspended in methanol, treated with conc. aqueous ammonium hydroxide and concentrated *in vacuo* to dryness. The solid residue was washed with water and diethyl ether to give 1.3 g (62%) of 5-bromo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile as a pale gray solid; MS 327.1, 329.1 (M+H).



[00277] Preparation of 5-[(E)-2-(4-butylphenyl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

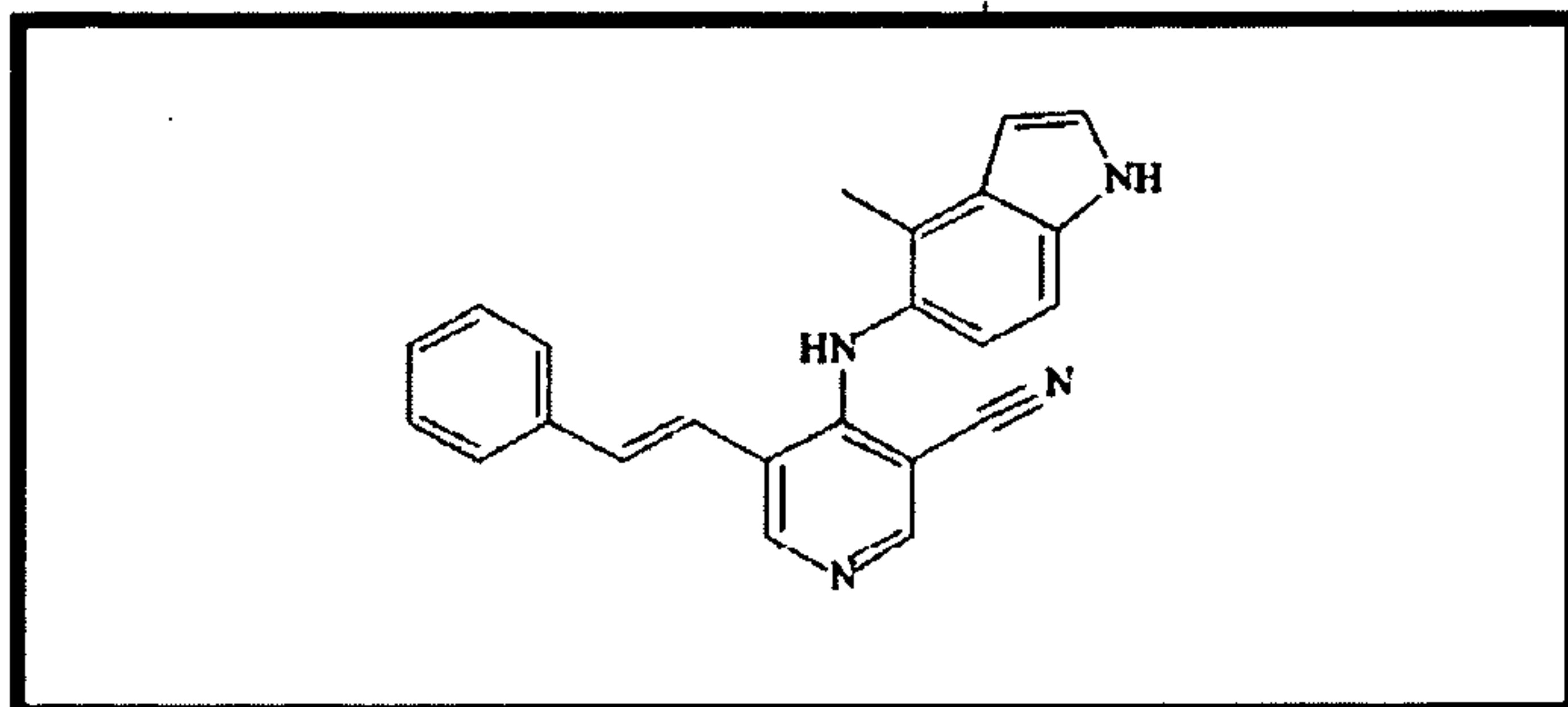
A mixture of 5-bromo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (130 mg, 0.40 mmol), 2-[2-(4-butylphenyl)vinyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (171,7 mg, 0.60 mmol) and $\text{Pd}(\text{PPh}_3)_4$ and 2.5 mL of aqueous saturated sodium bicarbonate in 5 mL of DME was heated at reflux for 4 h. The mixture was cooled to room temperature and partitioned between dichloromethane and water. The organic phase was dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography, eluting with a gradient of 10% ethyl acetate in hexane to 50% ethyl acetate in hexane to provide 95 mg (59%) of 5-[(E)-2-(4-butylphenyl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile as a pale yellow solid; MS 407.3 (M+H), HPLC: 96.2% at 215 nm rt = 12.5 min [a].



[00278] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-pyridin-4-ylvinyl]nicotinonitrile:

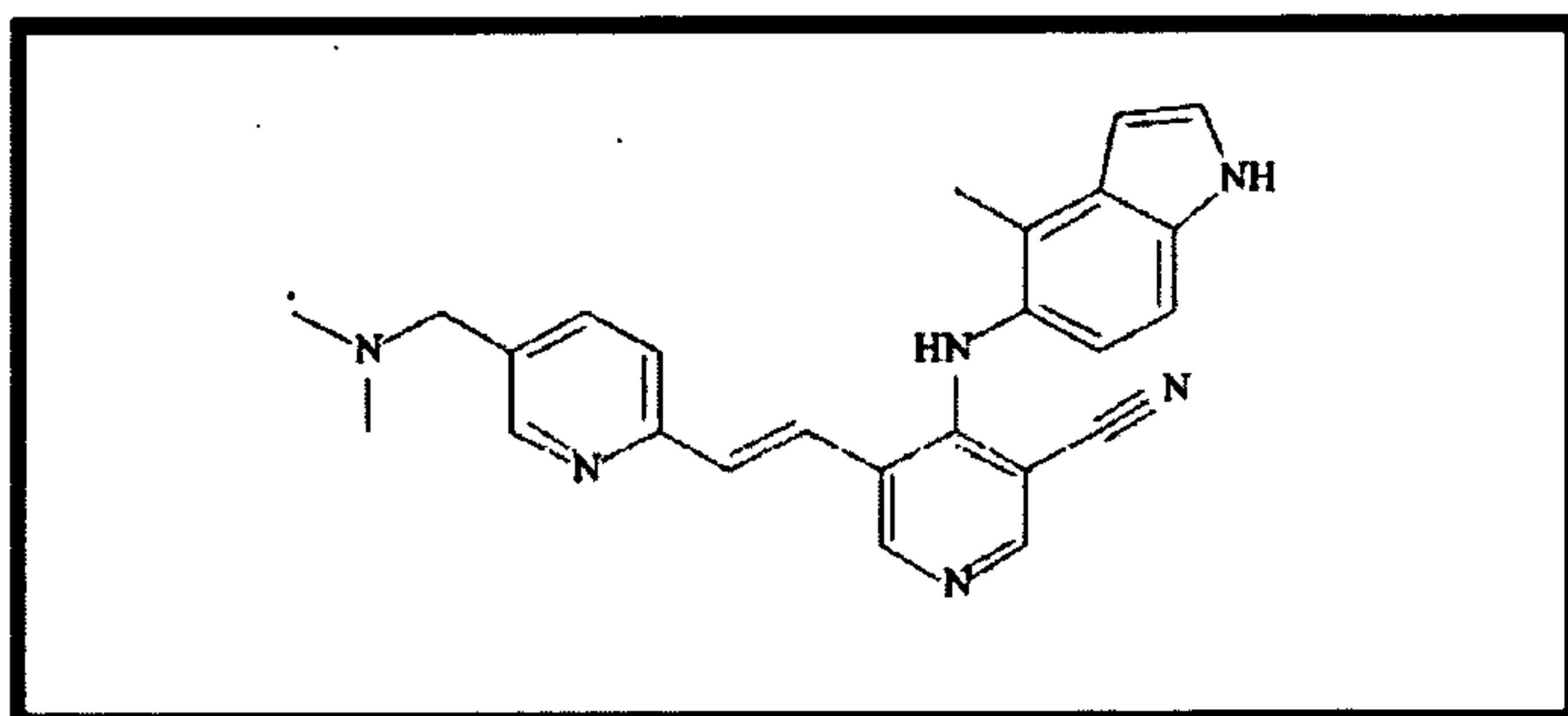
Following the procedure to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{4-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}vinyl]nicotinonitrile, 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-pyridin-4-ylvinyl]nicotinonitrile was prepared via the reaction of 5-iodo-4-[(4-methyl-

1H-indol-5-yl)amino]nicotinonitrile with 4-vinylpyridine; MS 352.3 (M+H), HPLC: 91.4% at 215 nm, rt = 4.9 min [a].



[00279] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-phenylvinyl]nicotinonitrile:

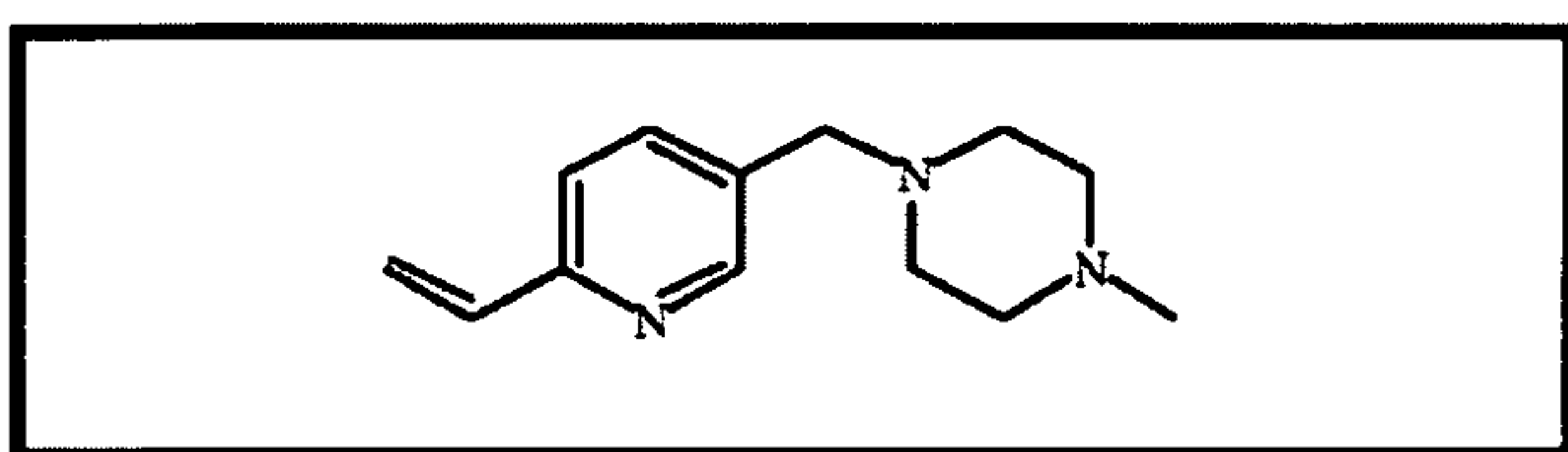
A mixture of 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (100 mg, 0.267 mmol), *trans*-2-phenylvinylboronic acid (44 mg, 0.294 mmol), tetrakis(triphenylphosphine)palladium(0) (15 mg, 0.013 mmol) in 4 mL of 1,2-dimethoxyethane and 3 mL of saturated aqueous sodium bicarbonate was heated at 95 °C overnight. The reaction was diluted with EtOAc, washed with water, dried over MgSO₄ and concentrated to give dark residue. The residue was purified by preparative TLC to give 13 mg (14%) of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-phenylvinyl]nicotinonitrile as a yellow solid, mp 203-205°C; MS 351.2 (M+H).



[00280] Preparation of 5-[(E)-2-{5-[(dimethylamino)methyl]pyridin-2-yl}vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

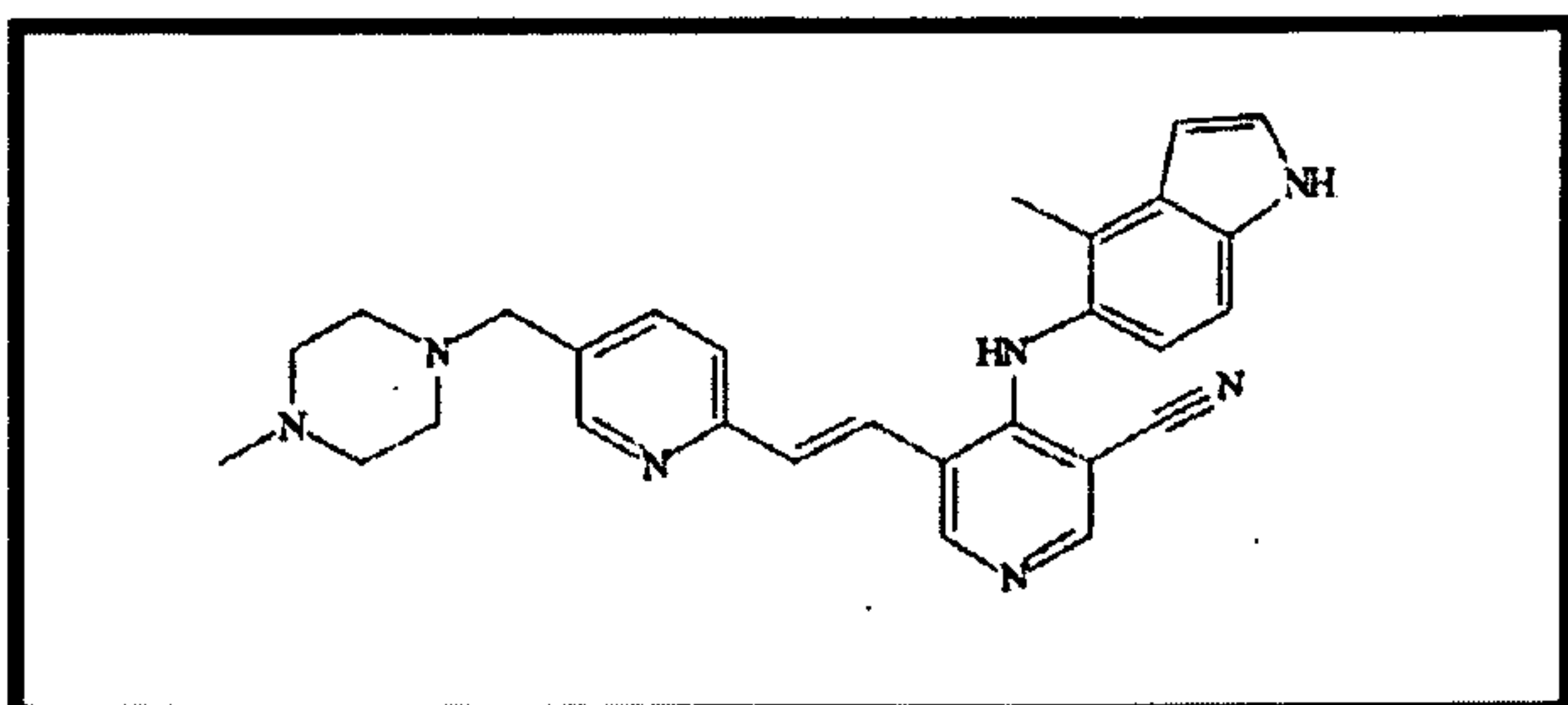
A mixture of 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (150 mg, 0.40 mmol), N,N-dimethyl-1-(6-vinylpyridin-3-yl)methanamine (78 mg, 0.48 mmol), palladium(II) acetate (18 mg,

0.08 mmol) and tri(ortho-tolyl)phosphine (6 mg, 0.02 mmol) in 2 mL of anhydrous *N,N*-dimethylformamide and 0.5 mL of triethylamine was heated at 100 °C for 2 h, cooled to room temperature, diluted with dichloromethane, washed with water, dried over MgSO₄ and concentrated to give dark residue. The crude product was purified by column chromatography, eluting with 5-10% gradient methanol in dichloromethane, to give 97 mg (59%) of 5-[(*E*)-2-{5-[(dimethylamino)methyl]pyridin-2-yl}vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile as a tan solid, mp 234-236°C; MS 409.3 (M+H).



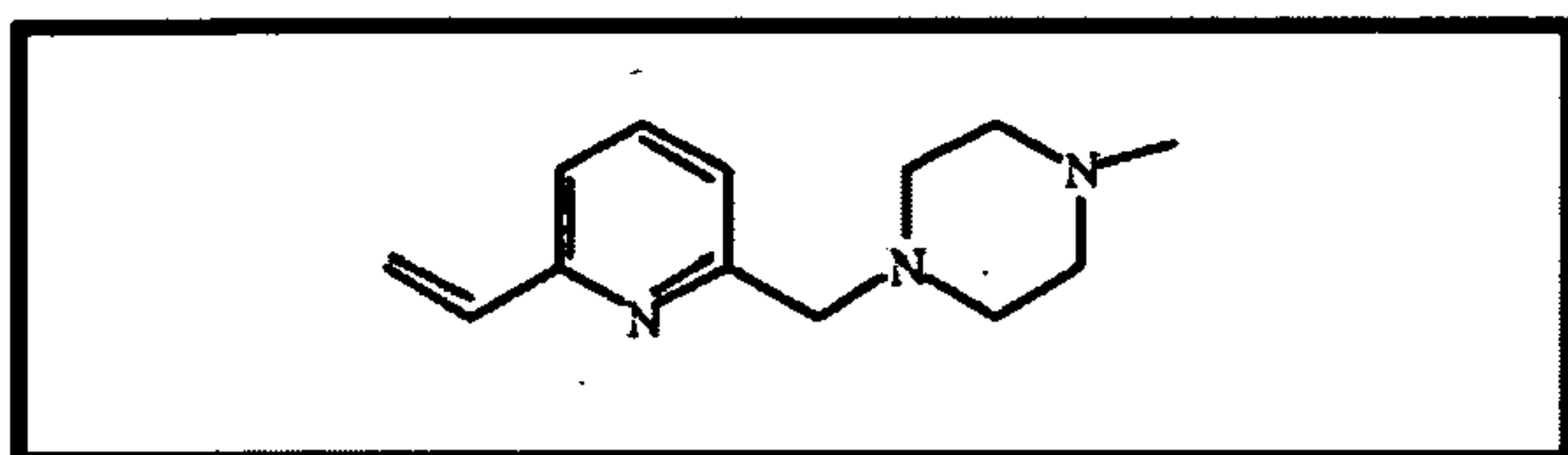
[00281] Preparation of 1-methyl-4-[(6-vinylpyridin-3-yl)methyl]piperazine:

1-[(6-bromo-3-pyridinyl)methyl]-4-methylpiperazine was prepared from 6-bromo-3-pyridine carboxaldehyde and 1-methylpiperazine via the procedure used to prepare 2-iodo-5[(4-methylpiperazin-1-yl)methyl]phenol. A mixture of 1-[(6-bromo-3-pyridinyl)methyl]-4-methylpiperazine (2.0 g, 7.40 mmol), tributylvinyltin (3.24 mL, 11.10 mmol), *trans*-dichlorobis(triphenylphosphine)palladium(II) (260 mg, 0.37 mmol) and copper iodide (71 mg, 0.37 mmol) in 40 mL of toluene was heated at reflux overnight. The reaction mixture was cooled, diluted with dichloromethane, washed with saturated aqueous sodium bicarbonate, filtered, dried over MgSO₄ and concentrated to give dark brown residue. The residue was purified by column chromatography (0 to 5% gradient methanol in dichloromethane) to give 1.03 g (64%) of 1-methyl-4-[(6-vinylpyridin-3-yl)methyl]piperazine as a light brown syrup; MS 218.3 (M+H).



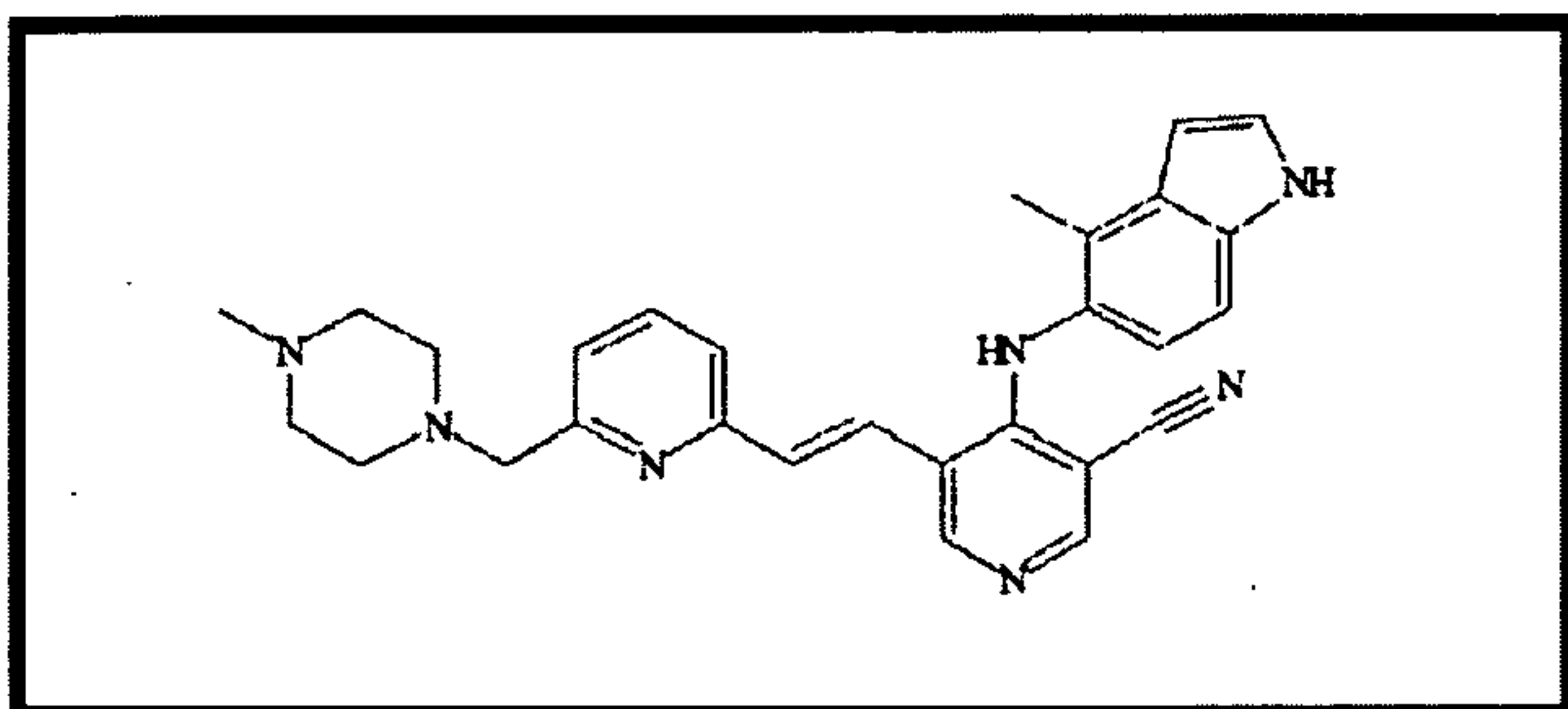
[00282] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}vinyl]nicotinonitrile:

The title compound was prepared from 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 1-methyl-4-[(6-vinylpyridin-3-yl)methyl]piperazine via the procedure used to prepare 5-[(E)-2-{5-[(dimethylamino)methyl]pyridin-2-yl}vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile, mp 193-196°C; MS 464.4 (M+H).



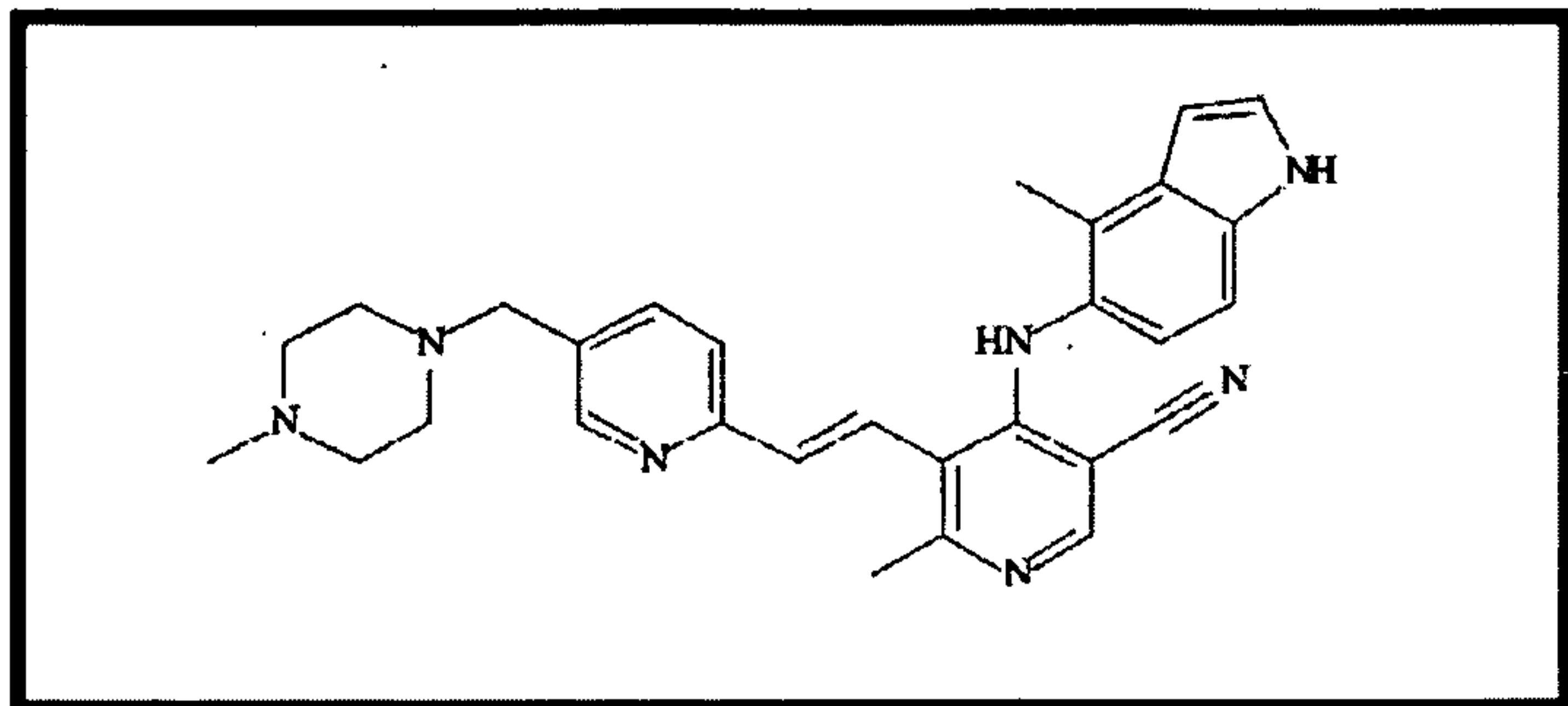
[00283] Preparation of 1-methyl-4-[(6-vinylpyridin-2-yl)methyl]piperazine:

The title compound was prepared analogously to 1-methyl-4-[(6-vinylpyridin-3-yl)methyl]piperazine beginning with 6-bromopicolinaldehyde; MS 218.3 (M+H).



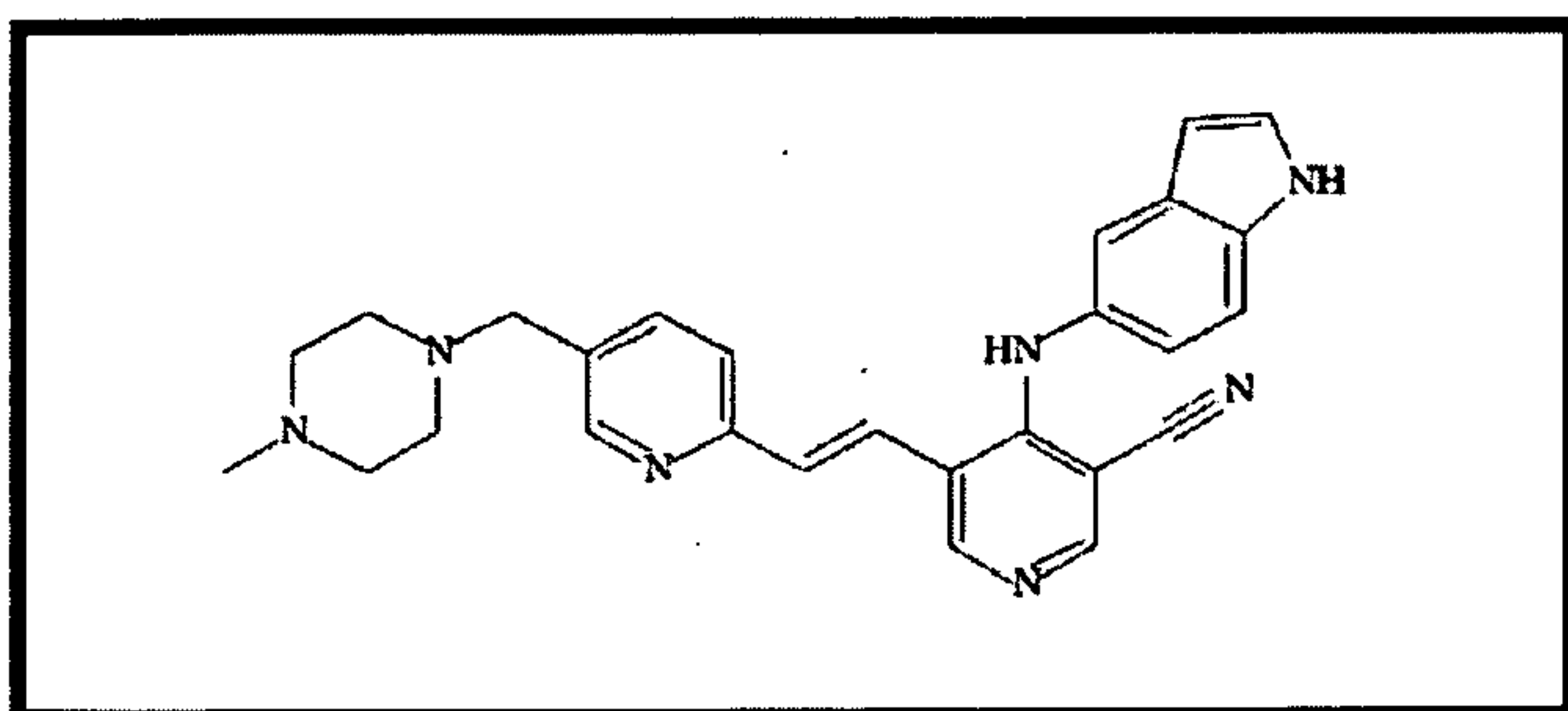
[00284] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{6-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}vinyl]nicotinonitrile:

The title compound was prepared from 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 1-methyl-4-[(6-vinylpyridin-2-yl)methyl]piperazine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{6-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}vinyl]nicotinonitrile; MS 464.3 (M+H).



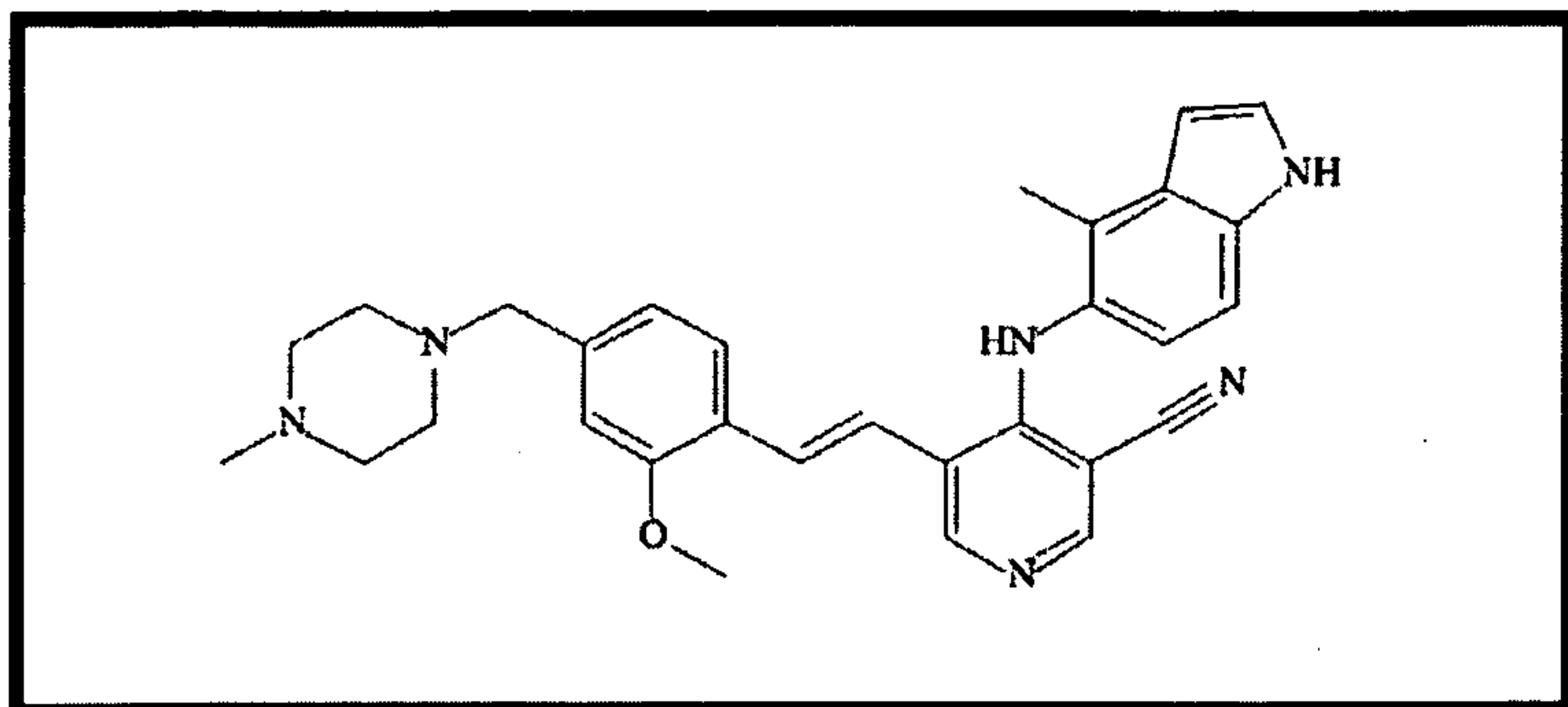
[00285] Preparation of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}vinyl]nicotinonitrile:

The title compound was prepared from 5-bromo-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 1-methyl-4-[(6-vinylpyridin-3-yl)methyl]piperazine via the procedure used to prepare 5-[(E)-2-{5-[(dimethylamino)methyl]pyridin-2-yl}vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile; MS 479.4 (M+H).



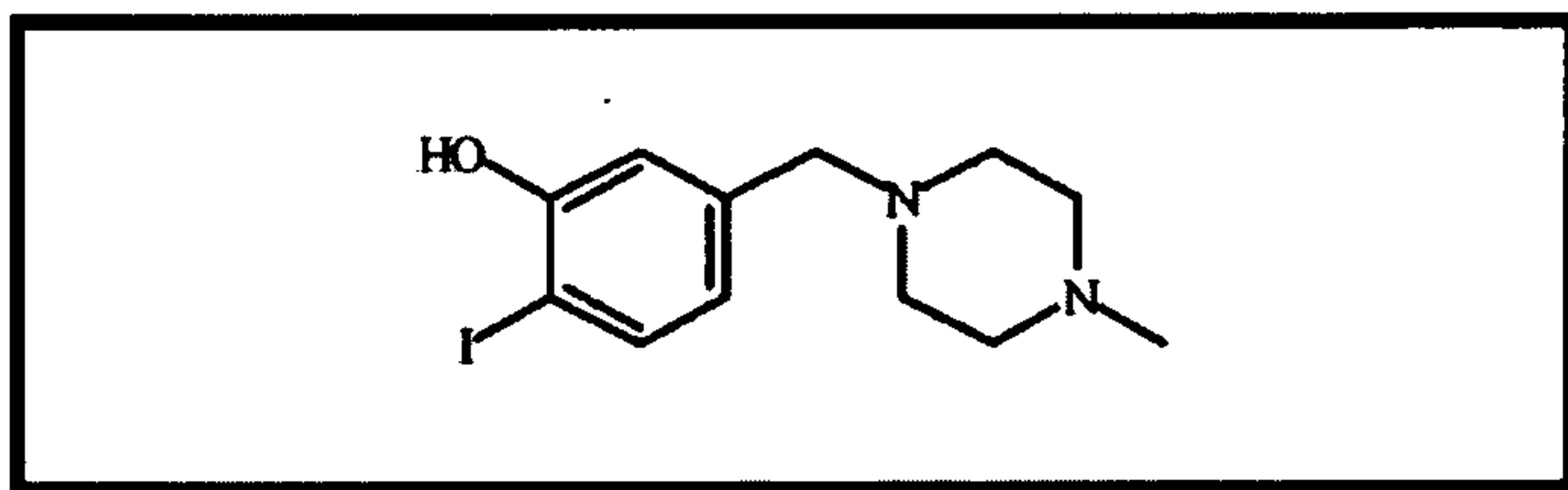
[00286] Preparation of 4-(1H-indol-5-ylamino)-5-[(E)-2-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}vinyl]nicotinonitrile:

The title compound was prepared from 4-(1H-indol-5-ylamino)-5-iodonicotinonitrile and 1-methyl-4-[(6-vinylpyridin-3-yl)methyl]piperazine via the procedure used to prepare 5-[(E)-2-{5-[(dimethylamino)methyl]pyridin-2-yl}vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile; MS 450.3 (M+H).



[00287] Preparation of 5-[(E)-2-{2-methoxy-4-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

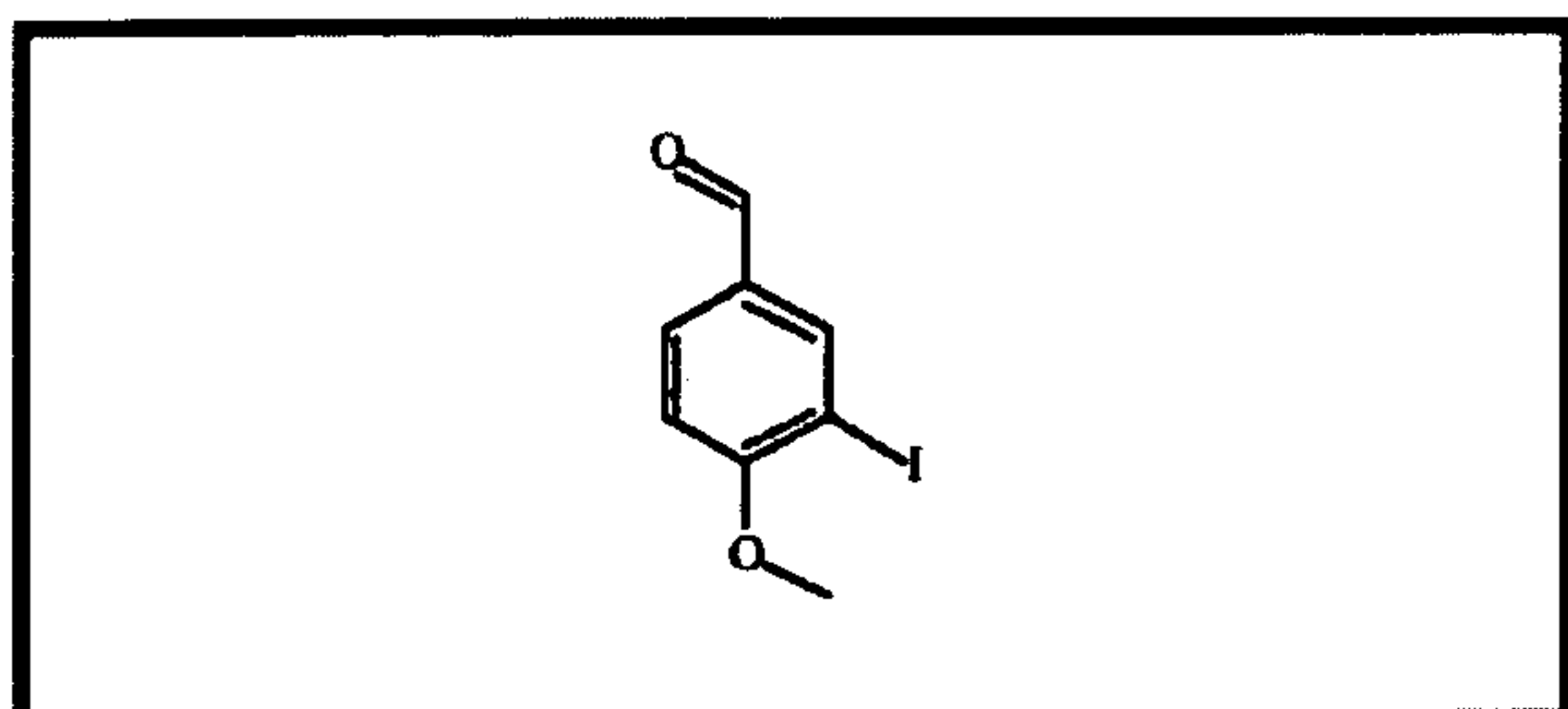
A mixture of 4-[(4-methyl-1H-indol-5-ylamino)]-5-vinylnicotinonitrile (200 mg, 0.73 mmol), 1-(4-iodo-3-methoxybenzyl)-4-methylpiperazine (210 mg, 0.61 mmol), palladium(II) acetate (27 mg, 0.12 mmol) and tri-*o*-toluenephosphine (9 mg, 0.03 mmol) and 0.5 mL of triethylamine in 2 mL of anhydrous *N,N*-dimethylformamide was heated at 120 °C for 4 h. The reaction was cooled to room temperature, diluted with dichloromethane, washed with saturated aqueous sodium bicarbonate, dried over MgSO₄ and concentrated to give dark residue. The crude product was purified by HPLC (ACN in H₂O/TFA) to give 86 mg (29%) of 5-[(E)-2-{2-methoxy-4-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile as a yellow solid; MS 493.3 (M+H); HPLC: 90.4% at 215 nm, rt = 7.2 min [a].



[00288] Preparation of 2-iodo-5-[(4-methylpiperazin-1-yl)methyl]phenol:

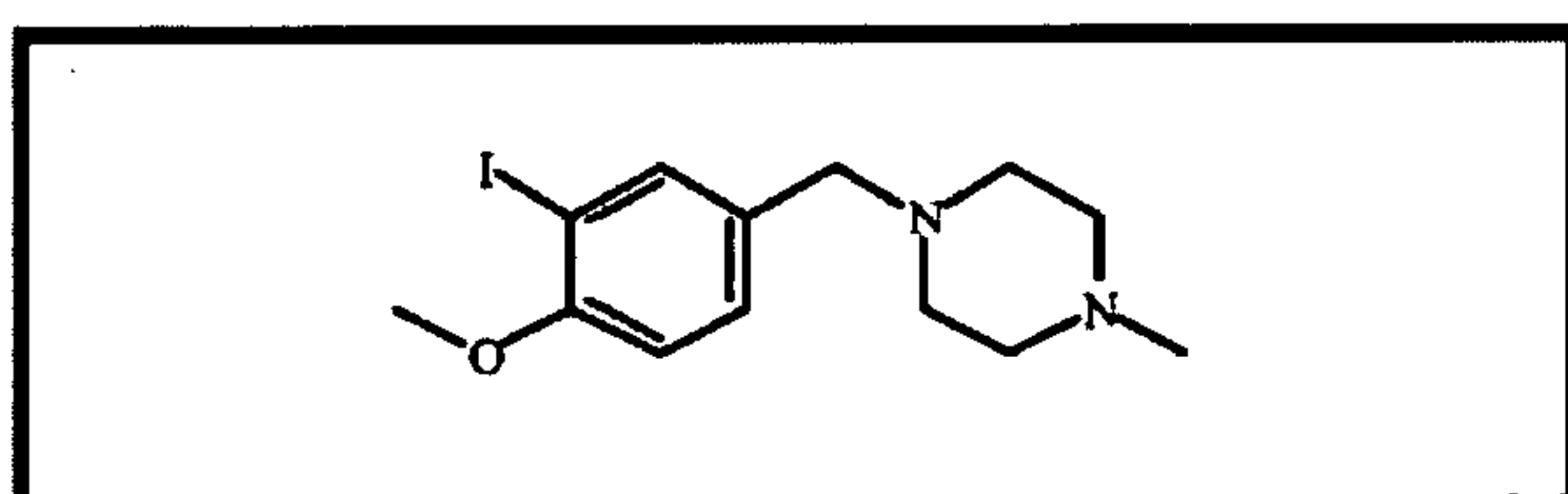
3-Hydroxy-4-iodobenzaldehyde (2.0 g, 8.06 mmol) and 1-methylpiperazine (4.0 g, 40.34 mmol) were dissolved in THF (100 mL). Upon cooling to 0 °C, sodium triacetoxyborohydride (8.6 g, 40.34 mmol) was added to the reaction solution along with catalytic amount of HOAc. The mixture was slowly warmed to room temperature and stirred overnight. The suspension was filtered, and the filtrate was diluted with dichloromethane, washed with saturated aqueous

sodium bicarbonate, dried over MgSO_4 and concentrated to give a light color syrup. The syrup was purified by column chromatography, eluting with 10-15% gradient methanol in dichloromethane, to give 2.36 g (88%) of 2-iodo-5-[(4-methylpiperazin-1-yl)methyl]phenol as a white solid; MS 333.2 (M+H).



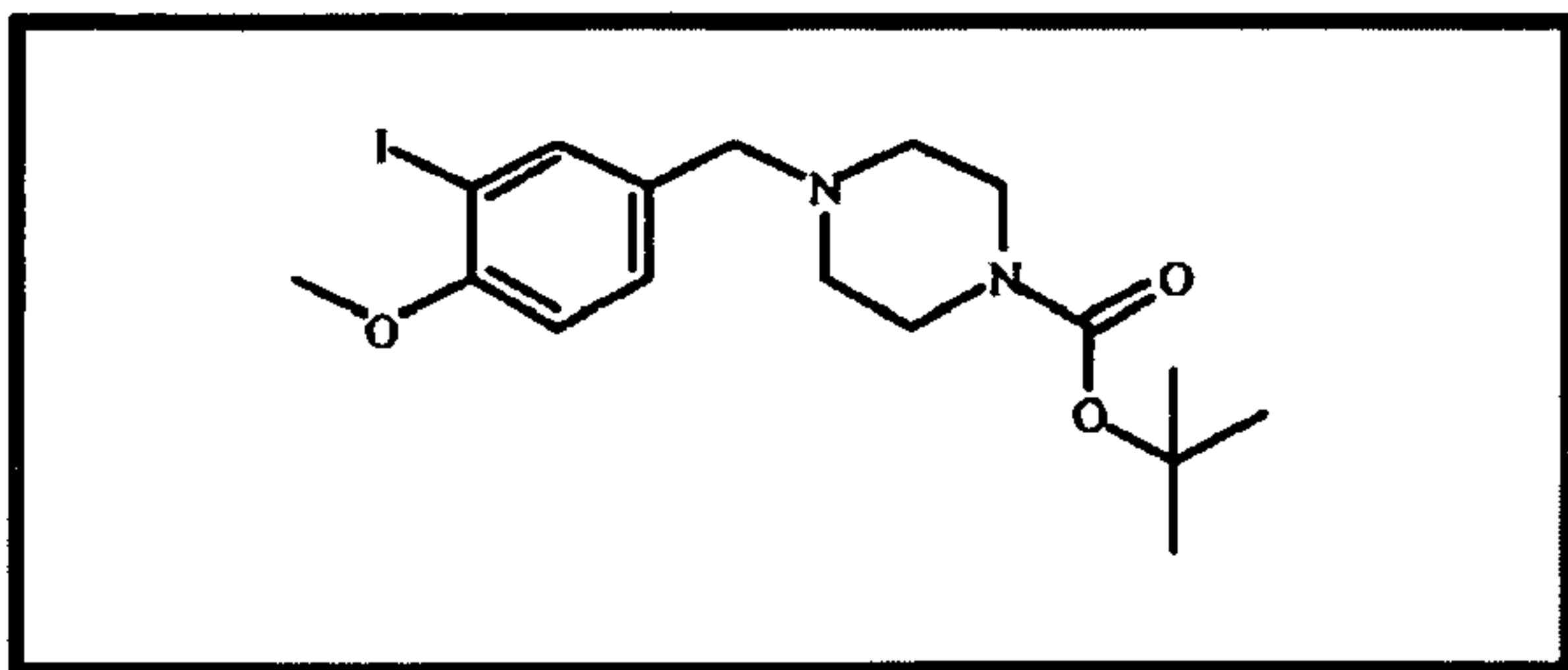
[00289] Preparation of 3-iodo-4-methoxybenzaldehyde:

A mixture of *p*-anisaldehyde (1.00 g, 7.34 mmol), iodine (932 mg, 3.67 mmol) and selectfluor (1.56 g, 4.40 mmol) in 75 mL of methanol was heated at 50 °C for 21 h. The reaction was cooled and diluted with dichloromethane, washed with saturated aqueous sodium bicarbonate, dried over MgSO_4 and concentrated to give a brown residue. The residue was purified by column chromatography, eluting with 20-40% gradient EtOAc in hexanes, to give 690 mg (36%) of 3-iodo-4-methoxybenzaldehyde as a yellow solid; MS 263.1 (M+H).

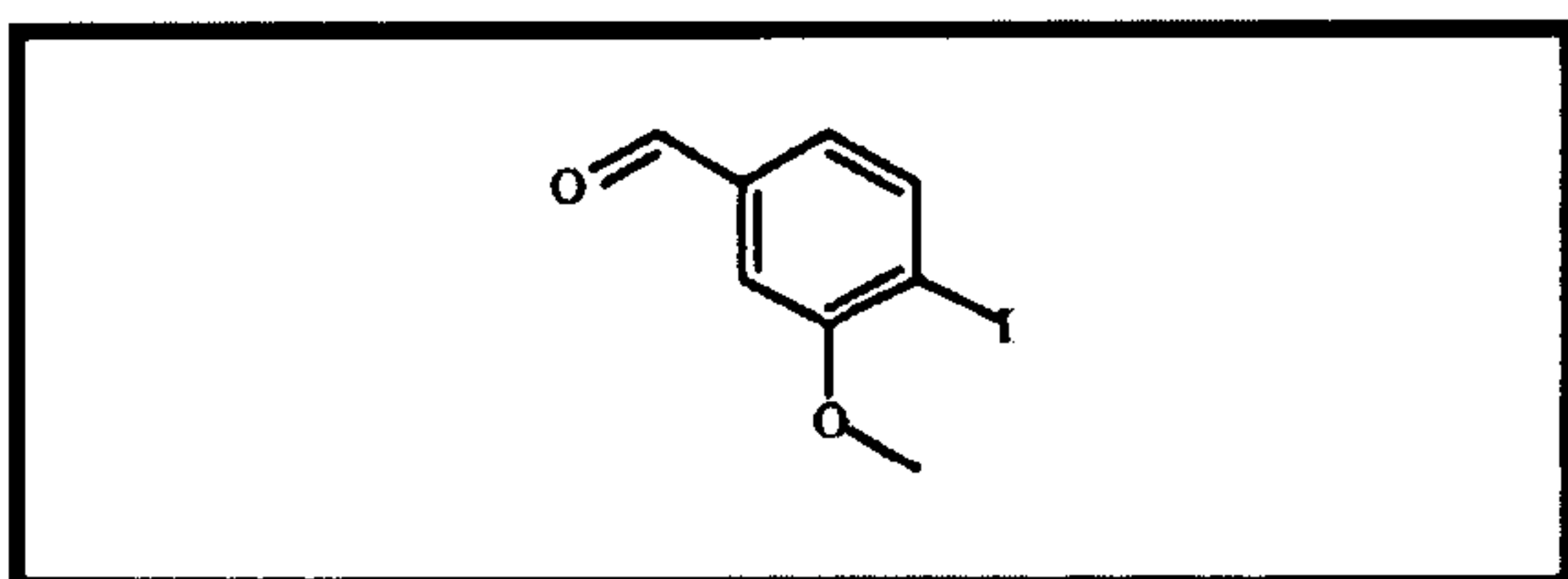


[00290] Preparation of 1-(3-iodo-4-methoxybenzyl)-4-methylpiperazine:

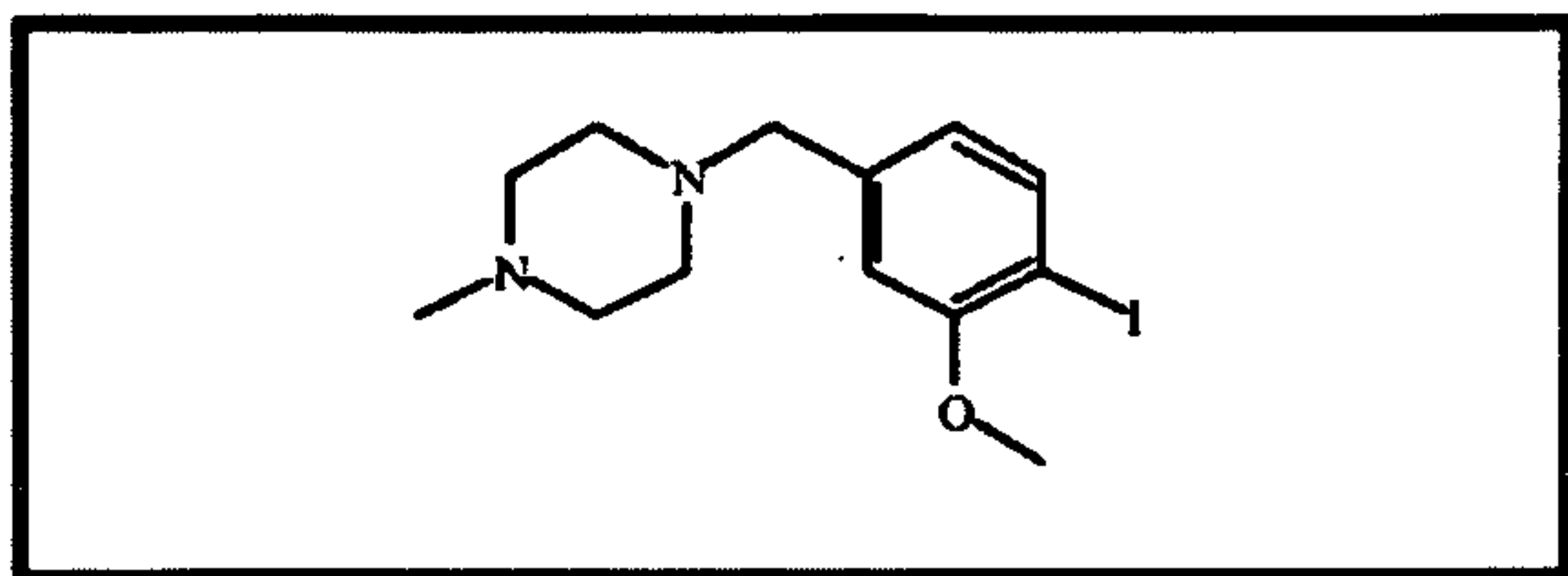
The title compound was prepared from 3-iodo-4-methoxybenzaldehyde and 1-methylpiperazine via the procedure used to prepare 2-iodo-5-[(4-methylpiperazin-1-yl)methyl]phenol; MS 347.2 (M+H).

**[00291] Preparation of tert-butyl 4-(3-iodo-4-methoxybenzyl)piperazine-1-carboxylate:**

3-iodo-4-methoxybenzaldehyde (300 mg, 1.14 mmol) and tert-butyl 1-piperazinecarboxylate (1.06 g, 5.70 mmol) was dissolved in THF (15 mL). Upon cooling to 0°C, sodium triacetoxyborohydride (1.21 g, 5.71 mmol) was added to the reaction solution along with a catalytic amount of HOAc. The mixture was slowly warmed to room temperature and was stirred overnight. The suspension was filtered and the filtrate was diluted with dichloromethane, washed with saturated aqueous sodium bicarbonate, dried over MgSO₄ and concentrated to give a light color syrup. The residue was purified by column chromatography, eluting with a 0-5% gradient methanol in dichloromethane to give 420 mg (85%) of tert-butyl 4-(3-iodo-4-methoxybenzyl)piperazine-1-carboxylate as a colorless gum; MS 433.3 (M+H).

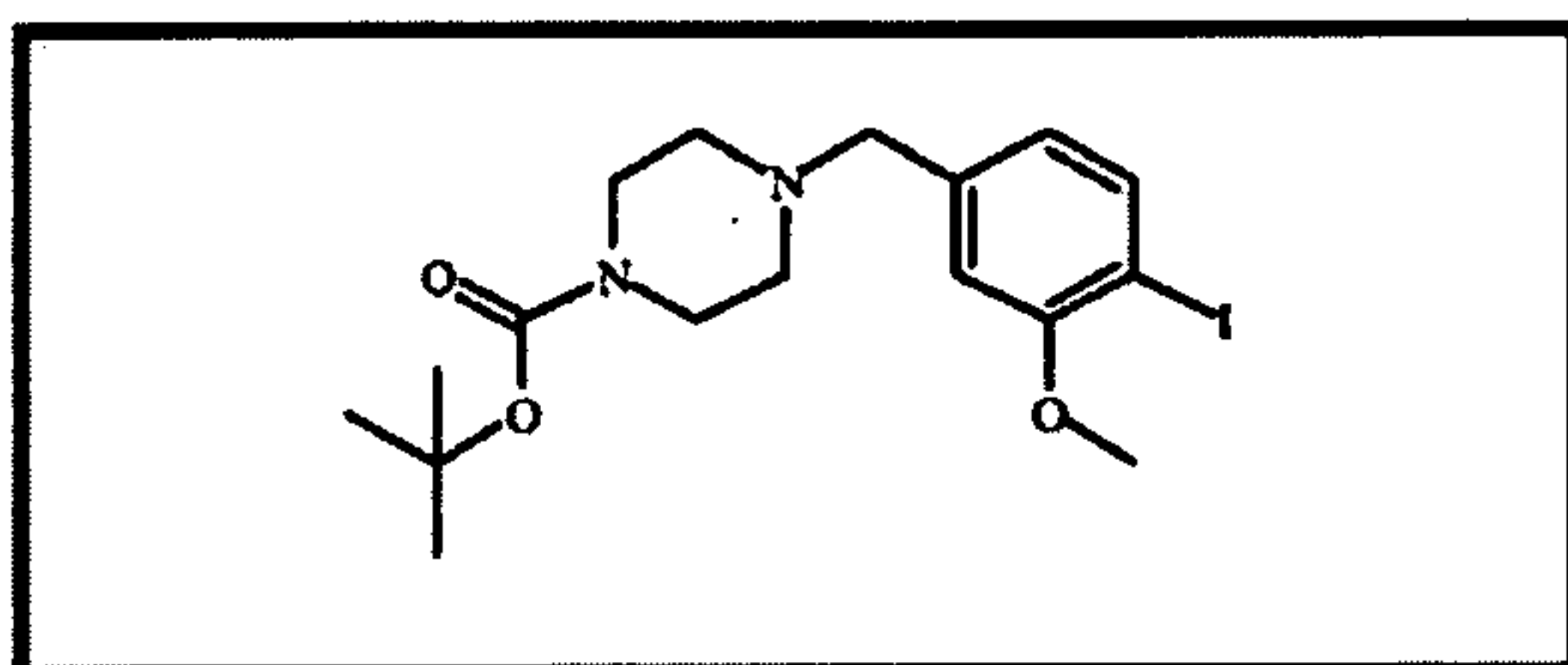
**[00292] Preparation of 4-iodo-3-methoxybenzaldehyde:**

A mixture of 3-hydroxy-4-iodobenzaldehyde (1.8 g, 7.26 mmol), iodomethane (3.2 g, 22.54 mmol) and potassium carbonate (1.51 g, 10.93 mmol) in 80 mL of acetone was heated at reflux for 2 h. The reaction was cooled and filtered. After the removal of the solvent from the filtrate, the residue was re-dissolved in EtOAc and washed with saturated aqueous sodium bicarbonate, dried over MgSO₄ and concentrated to give off-white solid. The solid was eluted through silica gel with 50% EtOAc in hexanes to give 1.85 g (97%) of 4-iodo-3-methoxybenzaldehyde as a white solid; MS 263.0 (M+H).



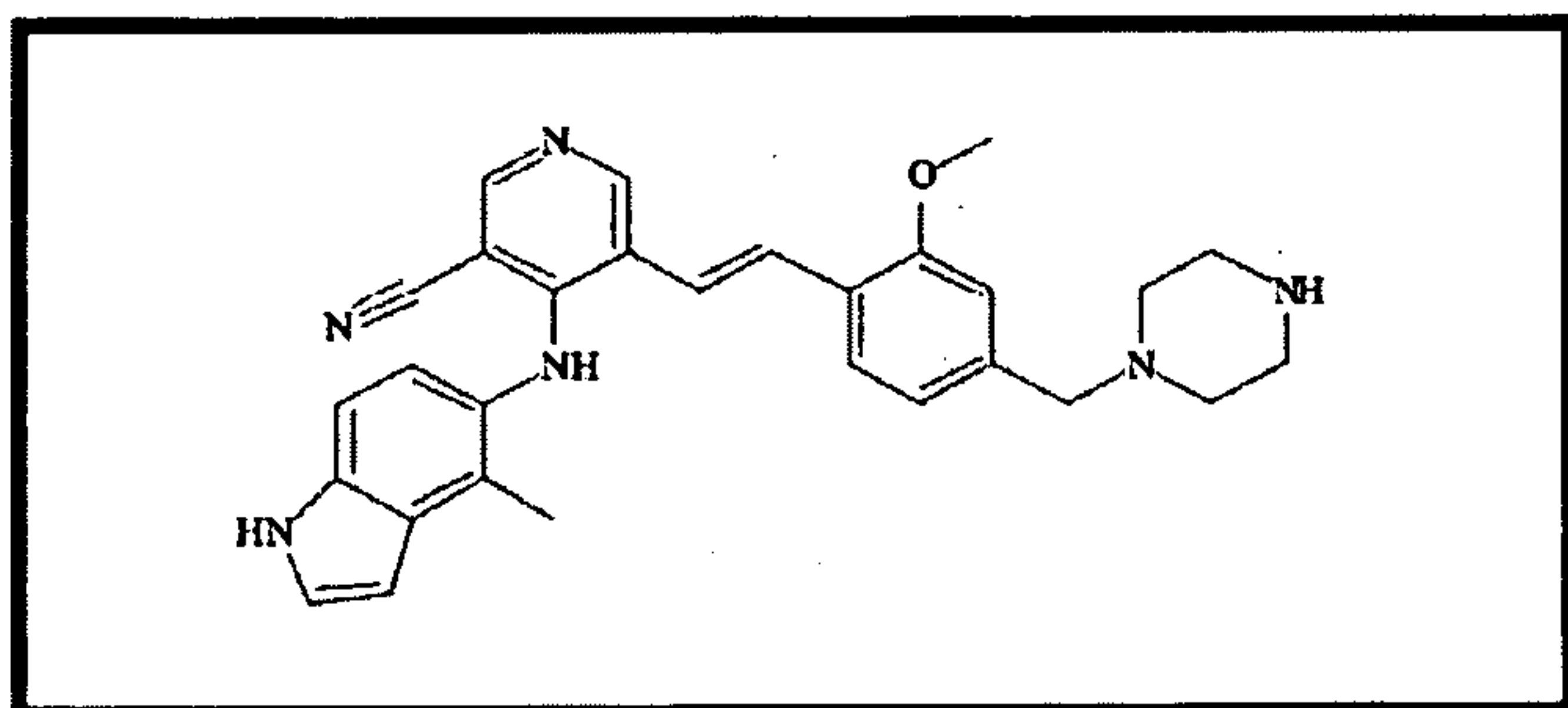
[00293] Preparation of 1-(4-iodo-3-methoxybenzyl)-4-methylpiperazine:

The title compound was prepared from 4-iodo-3-methoxybenzaldehyde and 1-methylpiperazine via the procedure used to prepare 2-iodo-5-[(4-methylpiperazin-1-yl)methyl]phenol; MS 347.1 (M+H).



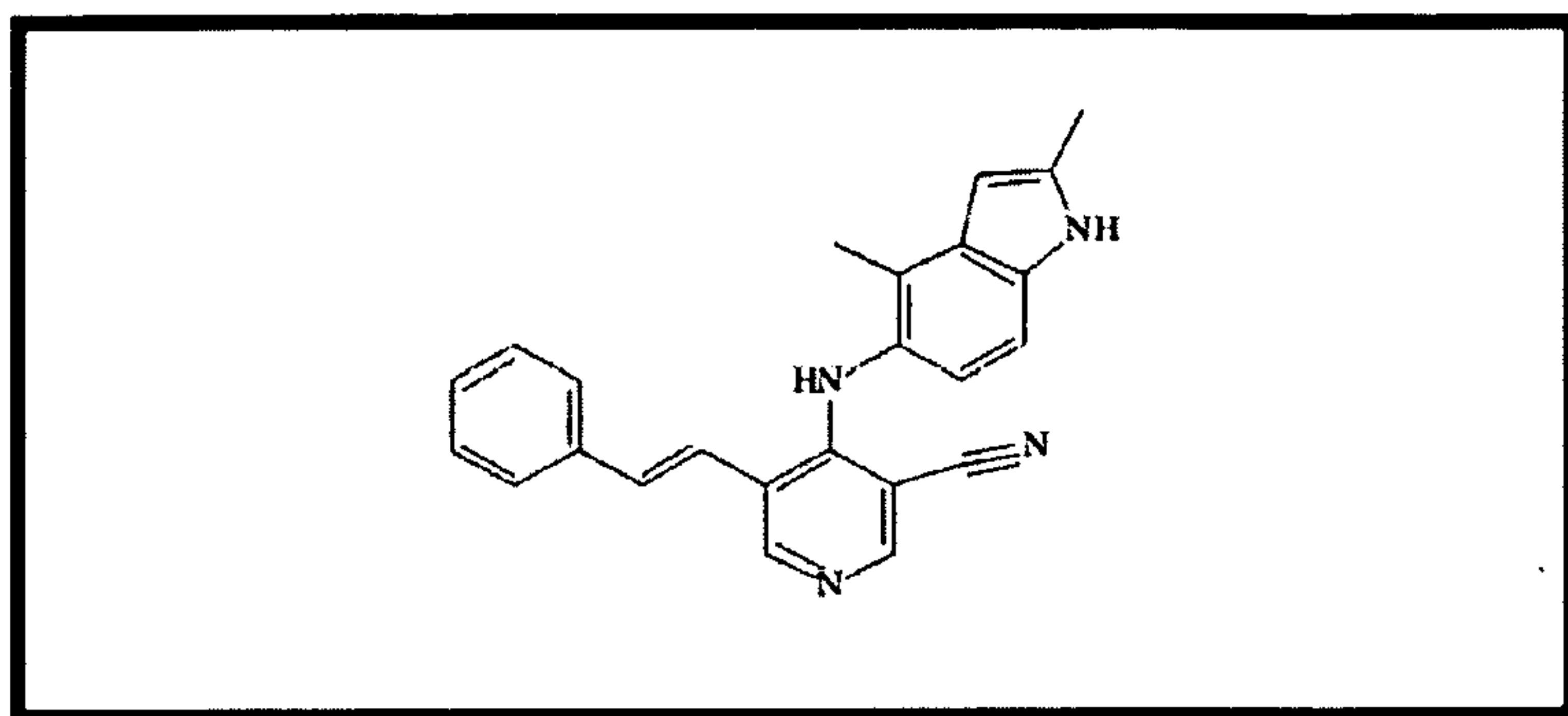
[00294] Preparation of tert-butyl 4-(4-iodo-3-methoxybenzyl)piperazine-1-carboxylate:

The title compound was prepared from 4-iodo-3-methoxybenzaldehyde and tert-butyl 1-piperazinecarboxylate via the procedure used to prepare tert-butyl 4-(3-iodo-4-methoxybenzyl)piperazine-1-carboxylate; MS 433.2 (M+H).



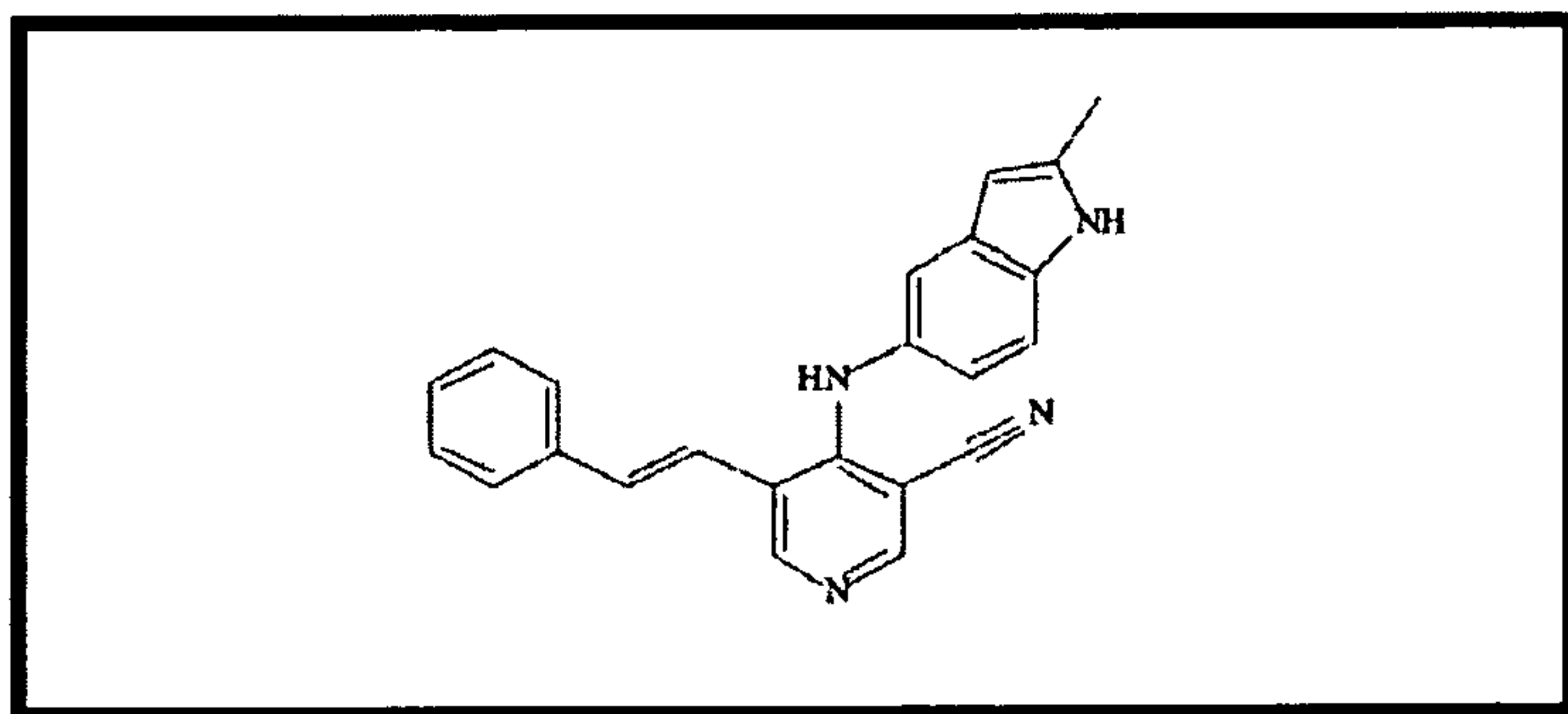
[00295] Preparation of 5-[(E)-2-[2-methoxy-4-(piperazin-1-ylmethyl)phenyl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

The title compound was prepared from 4-[(4-methyl-1H-indol-5-ylamino)]-5-vinylnicotinonitrile and tert-butyl 4-(4-iodo-3-methoxybenzyl)piperazine-1-carboxylate via the procedure used to prepare 5-[(E)-2-{2-methoxy-4-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile. The Boc group was removed with DCM/TFA; MS 479.5 (M+H), HPLC: rt = 2.50 min [d].



[00296] Preparation of 4-[(2,4-dimethyl-1H-indol-5-yl)amino]-5-[(E)-2-phenylvinyl]nicotinonitrile:

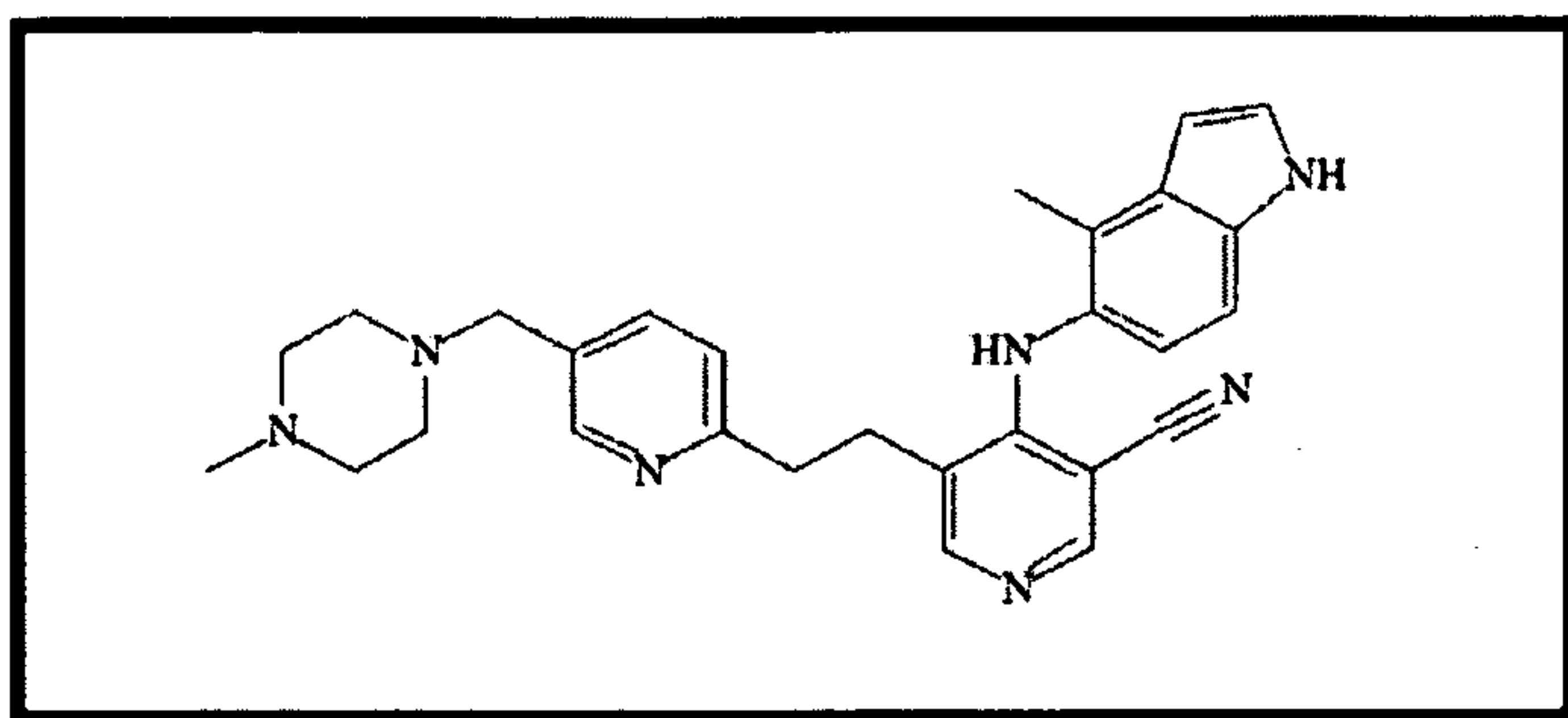
The title compound was prepared from 4-[(2,4-dimethyl-1H-indol-5-yl)amino]-5-iodonicotinonitrile and styrene via the procedure used to prepare 5-[(E)-2-(4-bromophenyl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile; MS 365.3 (M+H); HPLC rt = 10.2 min[a].



[00297] Preparation of 4-[(2-methyl-1H-indol-5-yl)amino]-5-[(E)-2-phenylvinyl]nicotinonitrile:

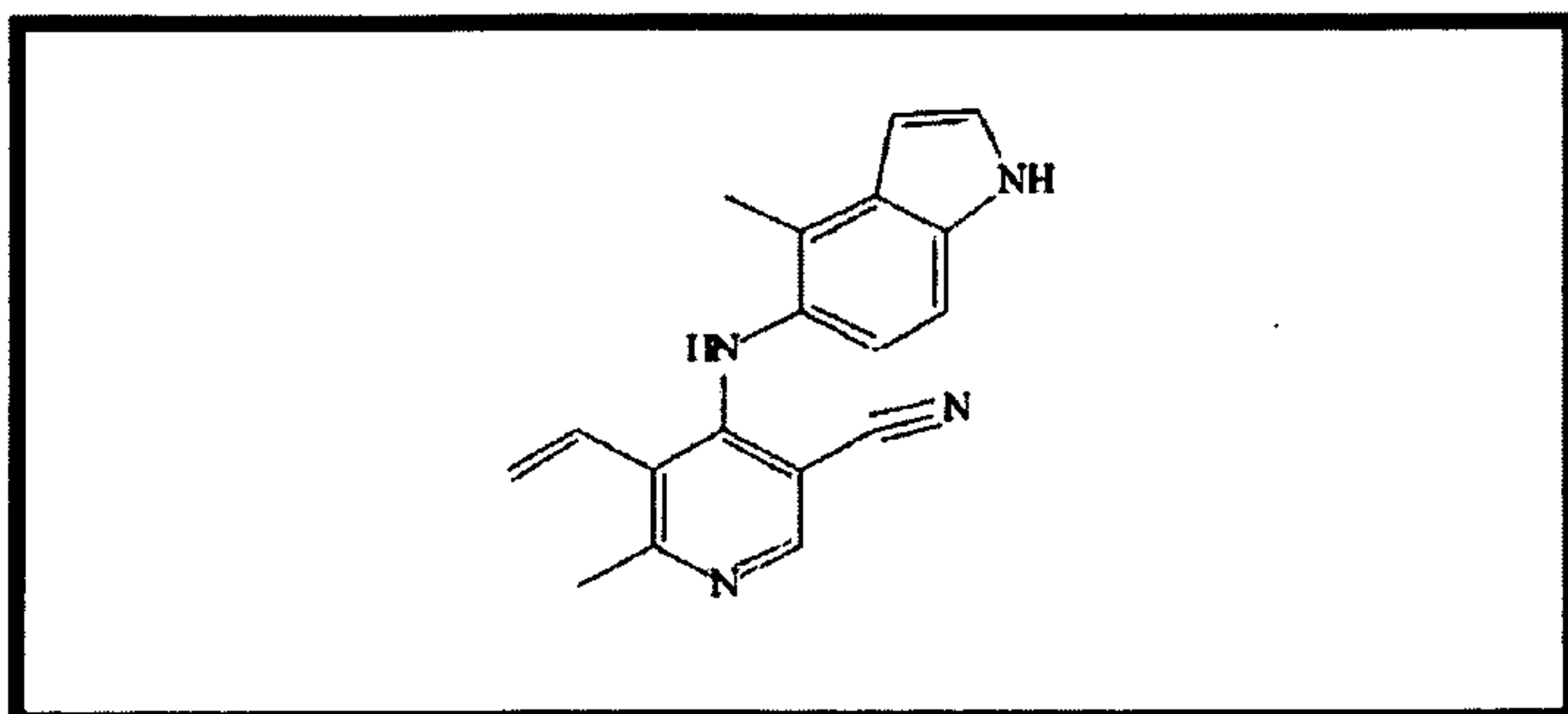
A mixture of 4-chloro-5-[(E)-2-phenylvinyl]nicotinonitrile (134 mg, 0.56 mmol) and 5-amino-2-methylindole (110 mg, 0.75 mmol) in 5 mL of ethanol was heated at reflux for 4.5 h. The resulting mixture was cooled slightly and filtered. The solid was washed with ethanol and ethyl

acetate then partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. The layers were separated and the organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was triturated with diethyl ether and the solid was collected by filtration washing with diethyl ether to give 52 mg (27%) of 4-[(2-methyl-1H-indol-5-yl)amino]-5-[(E)-2-phenylvinyl]nicotinonitrile as a light tan solid; MS 351.3 (M+H); HPLC: *rt* = 10.1 min[a].



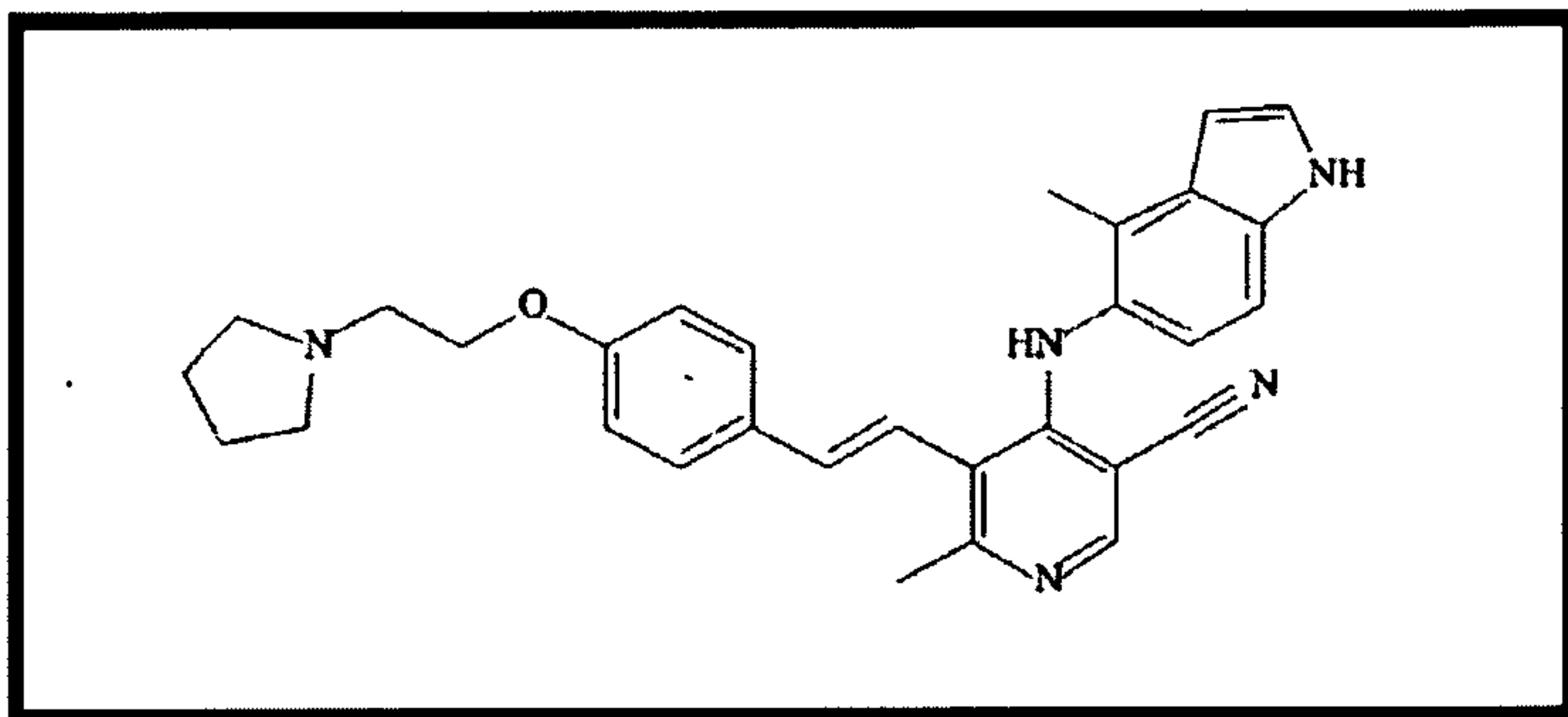
[00298] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-(2-{5-[(4-methyl piperazin-1-yl)methyl]pyridin-2-yl}ethyl)nicotinonitrile:

A mixture of 4-[(4-methyl-1H-indol-5-yl)amino]-5[(E)-2-{5-[(4-methylpiperazin-1-yl)methyl]pyridine-2-yl}vinyl]nicotinonitrile (100 mg, 0.216 mmol) and 20 mg of Pd/C (10% wt.) in 10 mL of methanol was shaken under hydrogen (50 psi) overnight. The reaction was filtered through celite. The filtrate was concentrated to dryness and the resultant solid was purified by HPLC, gradient ACN in H₂O/TFA, to give 30 mg (30%) of 4-[(4-methyl-1H-indol-5-yl)amino]-5-(2-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}ethyl)nicotinonitrile as an off-white solid; MS 466.3 (M+H); HPLC: 95.5% at 215 nm, *rt* = 4.2 min [a].

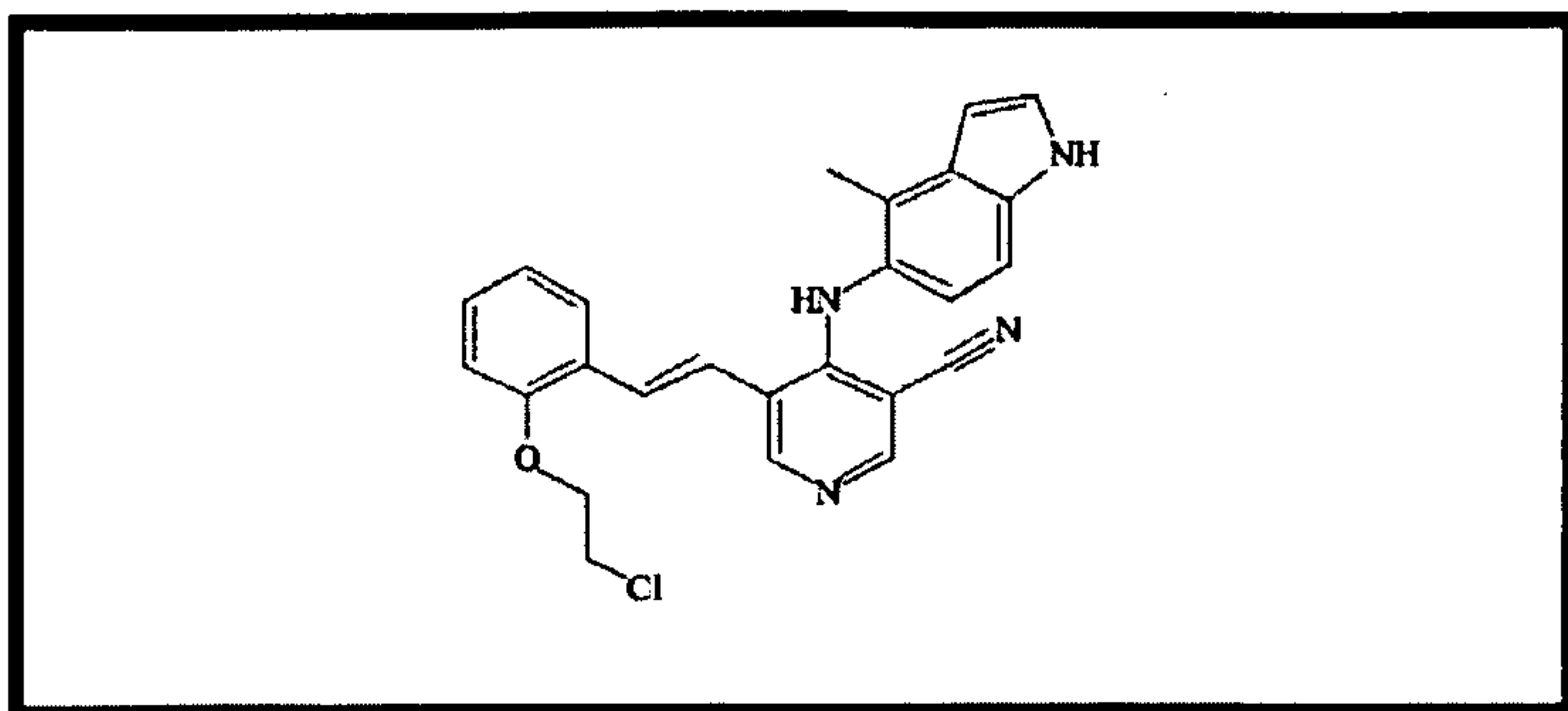


[00299] Preparation of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile:

A mixture of 5-iodo-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (250 mg, 0.64 mmol), tributyl(vinyl)stannane (307 mg, 0.97 mmol), copper iodide (6 mg, 0.032 mmol) and Pd(PPh₃)₂Cl₂ (18 mg, 0.026 mmol) in 7 mL of DMF was heated at 80°C for 5 h. The reaction was cooled to room temperature and the DMF was removed *in vacuo*. Sodium bicarbonate was added and the product was extracted into EtOAc. The organic layer was dried with magnesium sulfate and the solvent was removed to give 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile as a solid; MS 289.2 (M+H); HPLC: rt = 6.2 min [a].

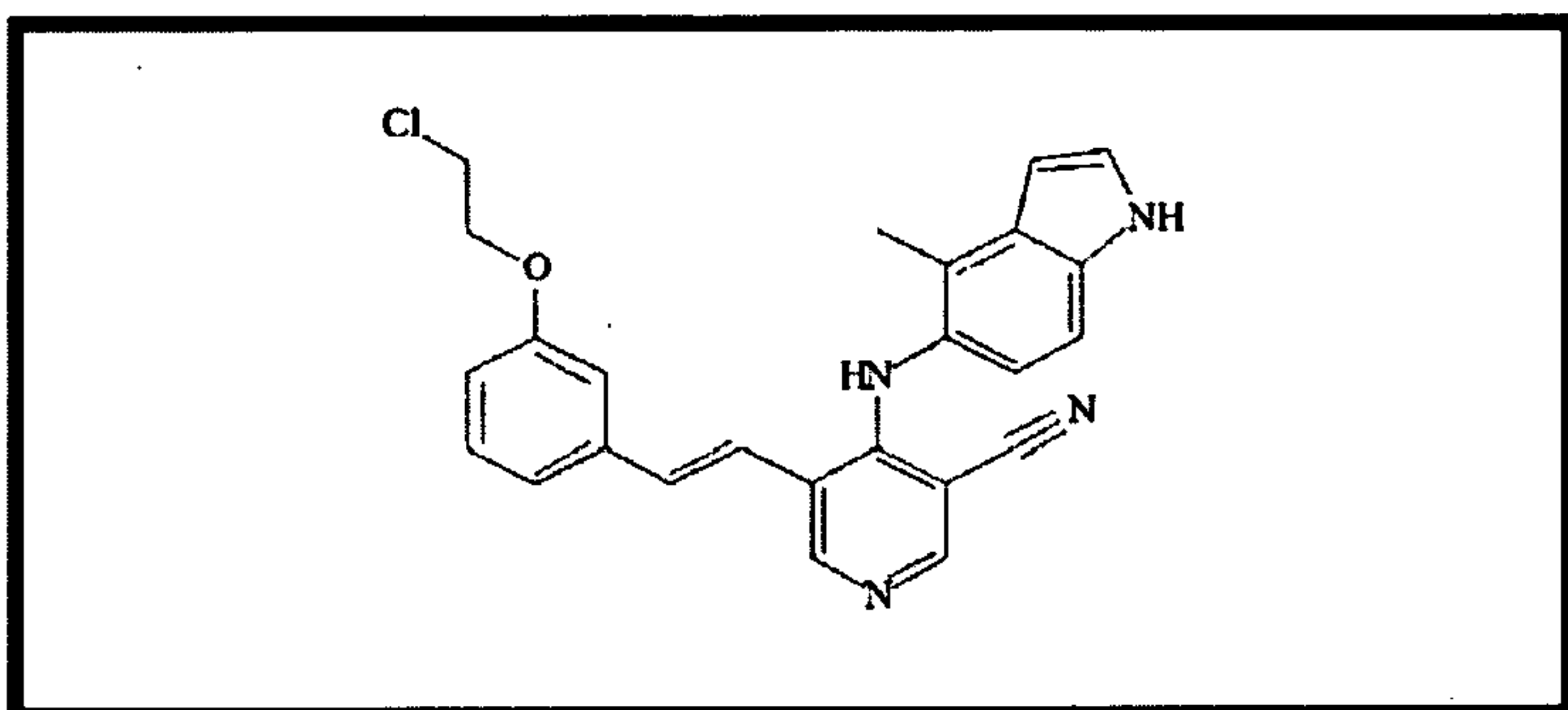
**[00300] Preparation of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(2-pyrrolidin-1-ylethoxy)phenyl]vinyl]nicotinonitrile:**

A mixture of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile (75 mg, 0.26 mmol), 1-(2-(4-bromophenoxy)ethyl)pyrrolidine (84 mg, 0.31 mmol), tri(ortho-tolyl)phosphine (11.9 mg, 0.039 mmol), palladium acetate (4.1 mg, 0.018 mmol) and triethylamine (79 mg, 0.78 mmol) in 3 mL of DMF was heated at 120°C for 2 h. An additional 0.039 mmol of tri(ortho-tolyl)phosphine and 0.018 mmol of palladium acetate were added and the reaction was flushed with N₂ and heated for an additional 1 h. The reaction was filtered and the filtrate was purified by HPLC to give 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(2-pyrrolidin-1-ylethoxy)phenyl]vinyl]nicotinonitrile as its TFA salt; MS 478.4 (M+H); HPLC: rt = 5.8 min [a].



[00301] Preparation of 5-((E)-2-[2-(2-chloroethoxy)phenyl]vinyl)-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

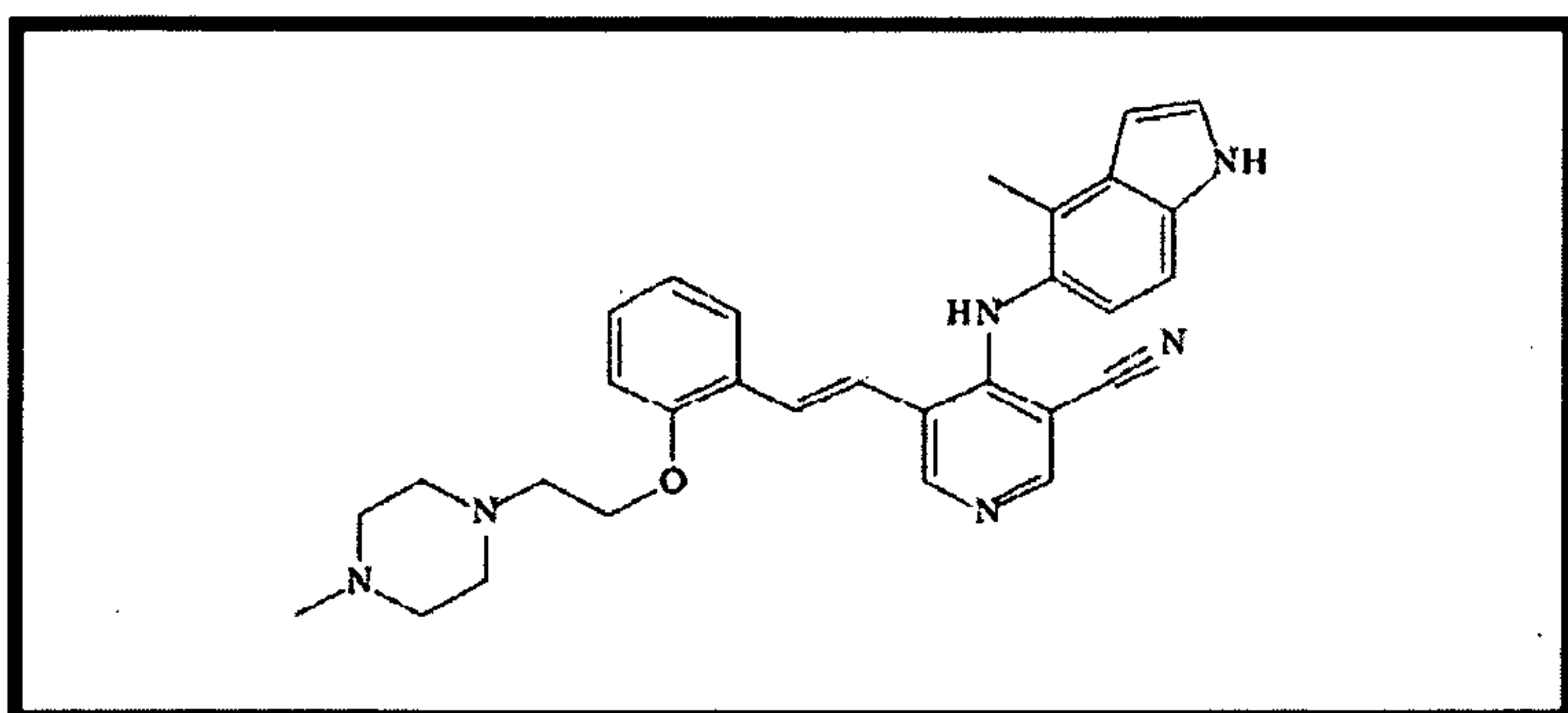
A mixture of 4-[(4-methyl-1H-indol-5-ylamino)]-5-vinylnicotinonitrile (373 mg, 1.36 mmol), 1-bromo-2-(2-chloroethoxy)benzene (387 mg, 1.63 mmol), tri(ortho-tolyl)phosphine (61 mg, 0.20 mmol), palladium acetate (22 mg, 0.10 mmol) and triethylamine (412 mg, 4.08 mmol) in 20 mL of DMF was heated at 120°C for 2 h. The reaction was diluted with EtOAc and washed with water. The crude material was purified by silica gel chromatography with a EtOAc/ hexane gradient. The product was further purified by HPLC to give 5-((E)-2-[2-(2-chloroethoxy)phenyl]vinyl)-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile as a solid; MS 429.2 (M+H); HPLC: rt = 15.2 min [a].



[00302] Preparation of 5-((E)-2-[3-(2-chloroethoxy)phenyl]vinyl)-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

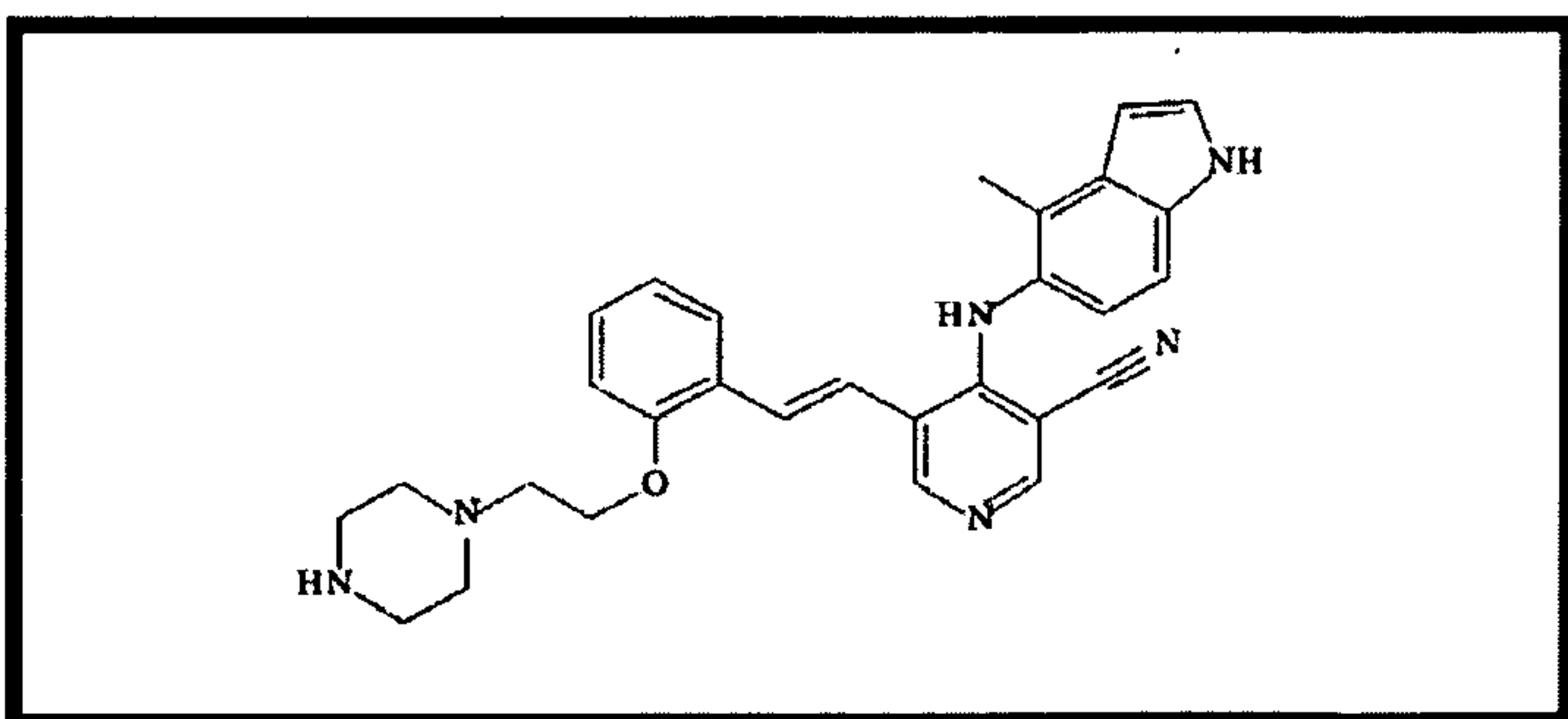
A mixture of 4-[(4-methyl-1H-indol-5-ylamino)]-5-vinylnicotinonitrile (450 mg, 1.64 mmol), 1-bromo-3-(2-chloroethoxy)benzene (466 mg, 1.97 mmol), tri(ortho-tolyl)phosphine (76 mg, 0.25 mmol), palladium acetate (29 mg, 0.13 mmol) and triethylamine (497 mg, 4.92 mmol) in 20 mL of DMF was heated at 120°C for 2 h. The reaction was diluted with EtOAc and washed with water. The organic extract was concentrated and the crude material was purified by silica gel

chromatography with an EtOAc / hexane gradient to give 5-((E)-2-[3-(2-chloroethoxy)phenyl]vinyl)-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile as a solid; MS 429.1 (M+H); HPLC: *rt* = 11.1 min [a].



[00303] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{2-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}vinyl]nicotinonitrile:

A mixture of 5-((E)-2-[2-(2-chloroethoxy)phenyl]vinyl)-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (75 mg, 0.18 mmol), 1-methyl piperazine (108 mg, 1.08 mmol) and sodium iodide (1.4 mg, 0.01 mmol) in 2 mL of DME was heated at 100°C overnight in a sealed vial. The reaction was concentrated and the crude material was purified by HPLC to give 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{2-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}vinyl]nicotinonitrile as a solid; MS 493.4 (M+H); HPLC: *rt* = 6.8 min [a].

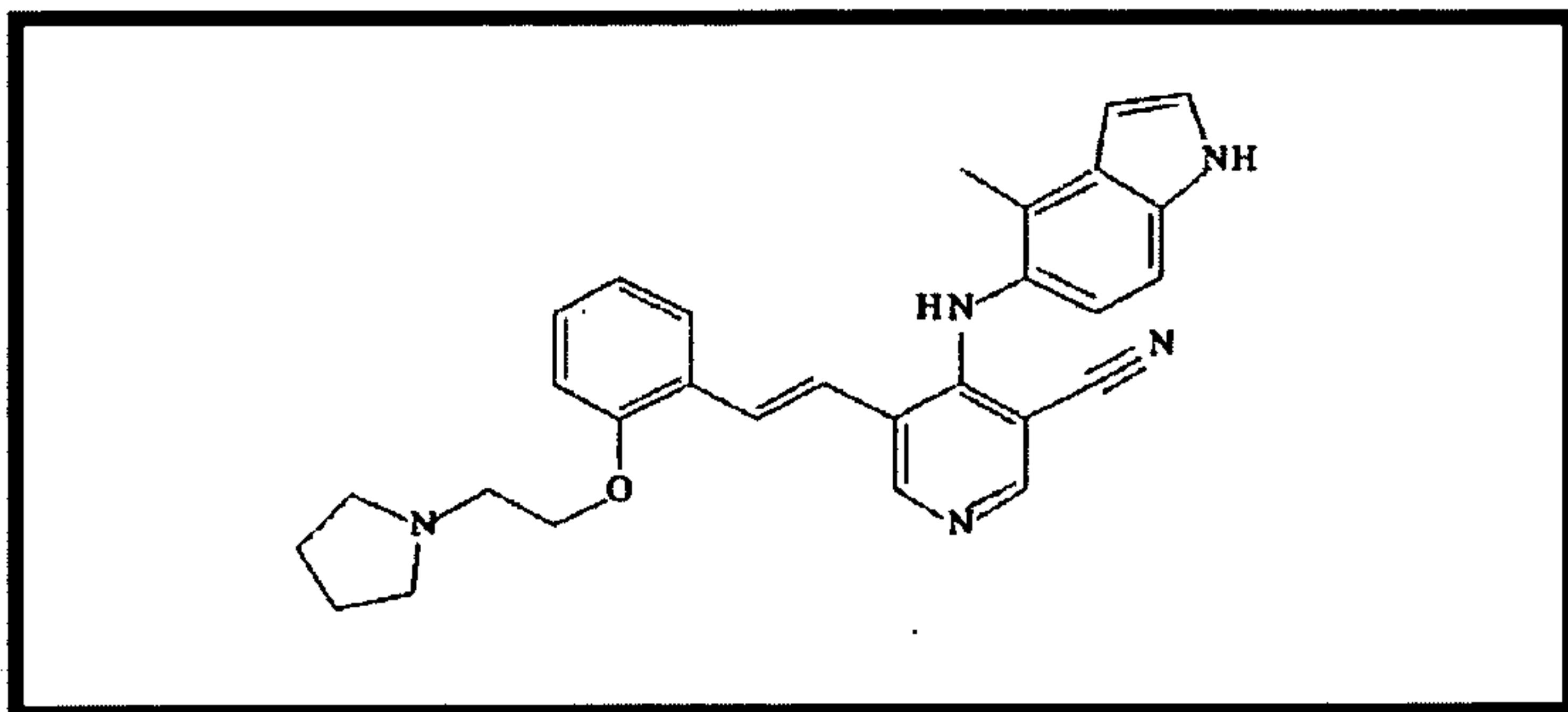


[00304] Preparation 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{2-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}vinyl]nicotinonitrile:

A mixture of 5-((E)-2-[2-(2-chloroethoxy)phenyl]vinyl)-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (90 mg, 0.21 mmol), tert-butyl piperazine-1-carboxylate (234 mg, 1.26 mmol) and sodium iodide (1.5 mg, 0.01 mmol) in 2 mL of DME was heated at 100°C overnight in a

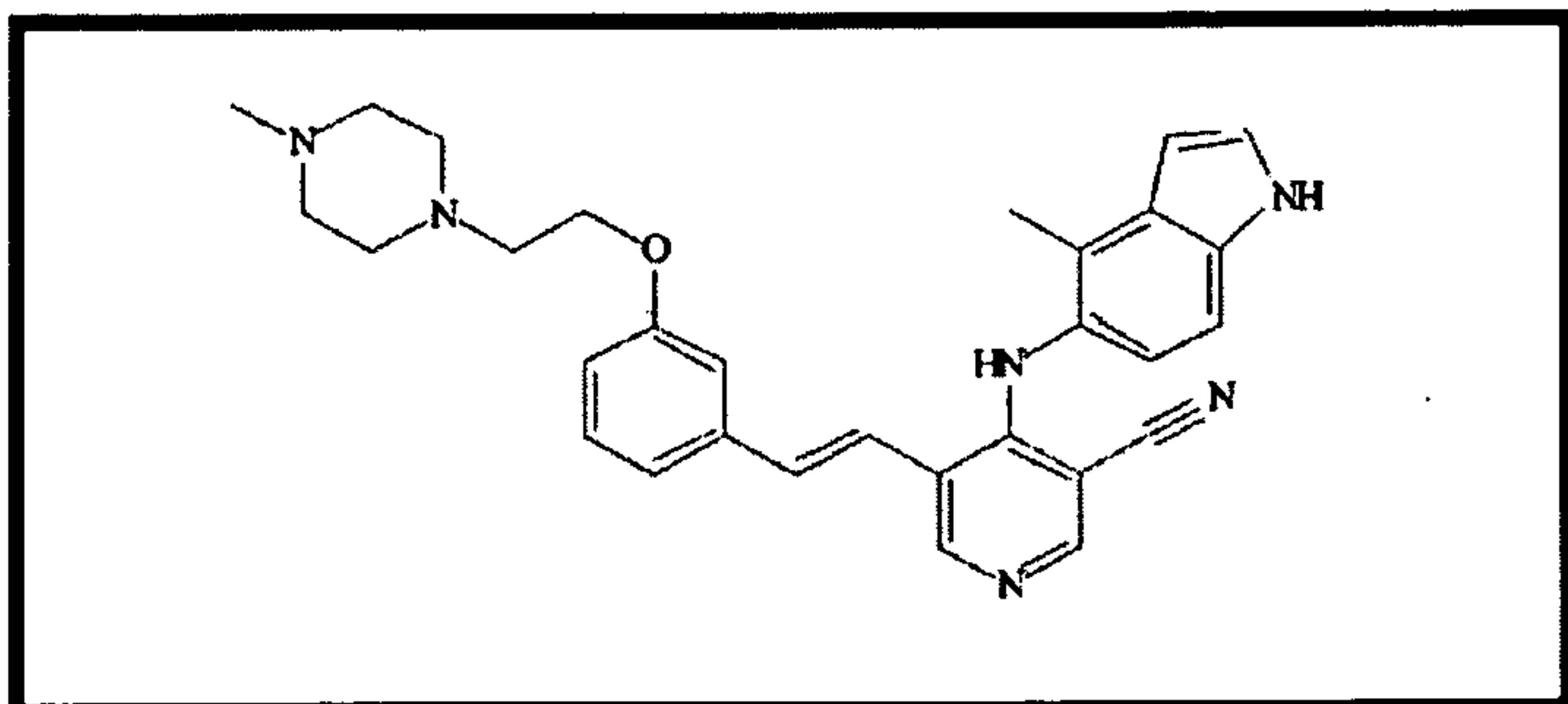
sealed vial to give (E)-tert-butyl 4-(2-(2-(2-(5-cyano-4-(4-methyl-1H-indol-5-ylamino)pyridin-3-yl)vinyl) phenoxy) ethyl)piperazine-1-carboxylate.

The crude intermediate, (E)-tert-butyl 4-(2-(2-(2-(5-cyano-4-(4-methyl-1H-indol-5-ylamino)pyridin-3-yl)vinyl)phenoxy)ethyl)piperazine-1-carboxylate, was treated with 2.2 mL of 10% trifluoroacetic acid/ DCM and stirred at room temperature for 1 h. The reaction was concentrated and the residue was purified by HPLC to give 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[2-(2-piperazin-1-ylethoxy)phenyl]vinyl]nicotinonitrile as its TFA salt; MS 479.4 (M+H); HPLC: rt = 6.3 min [a].



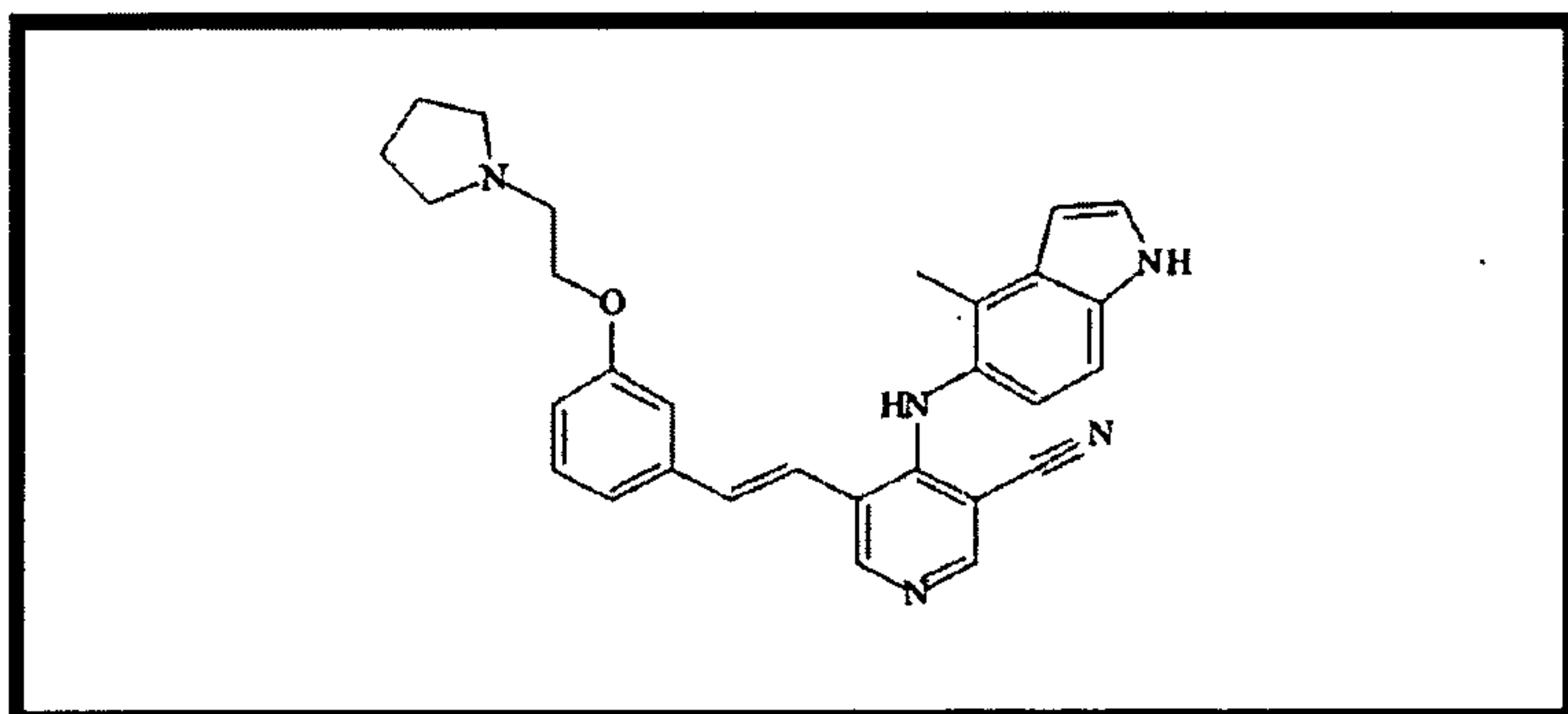
[00305] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[2-(2-pyrrolidin-1-ylethoxy)phenyl]vinyl]nicotinonitrile:

A mixture of 5-[(E)-2-[2-(2-chloroethoxy)phenyl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino] nicotinonitrile (75 mg, 0.18 mmol), pyrrolidine (77 mg, 1.08 mmol) and sodium iodide (1.4 mg, 0.01 mmol) in 2 mL of DME was heated at 100°C overnight in a sealed vial. The reaction was concentrated and the crude material was purified by HPLC to give 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[2-(2-pyrrolidin-1-ylethoxy)phenyl]vinyl]nicotinonitrile as its TFA salt; MS 464.3 (M+H); HPLC: rt = 7.0 min [a].



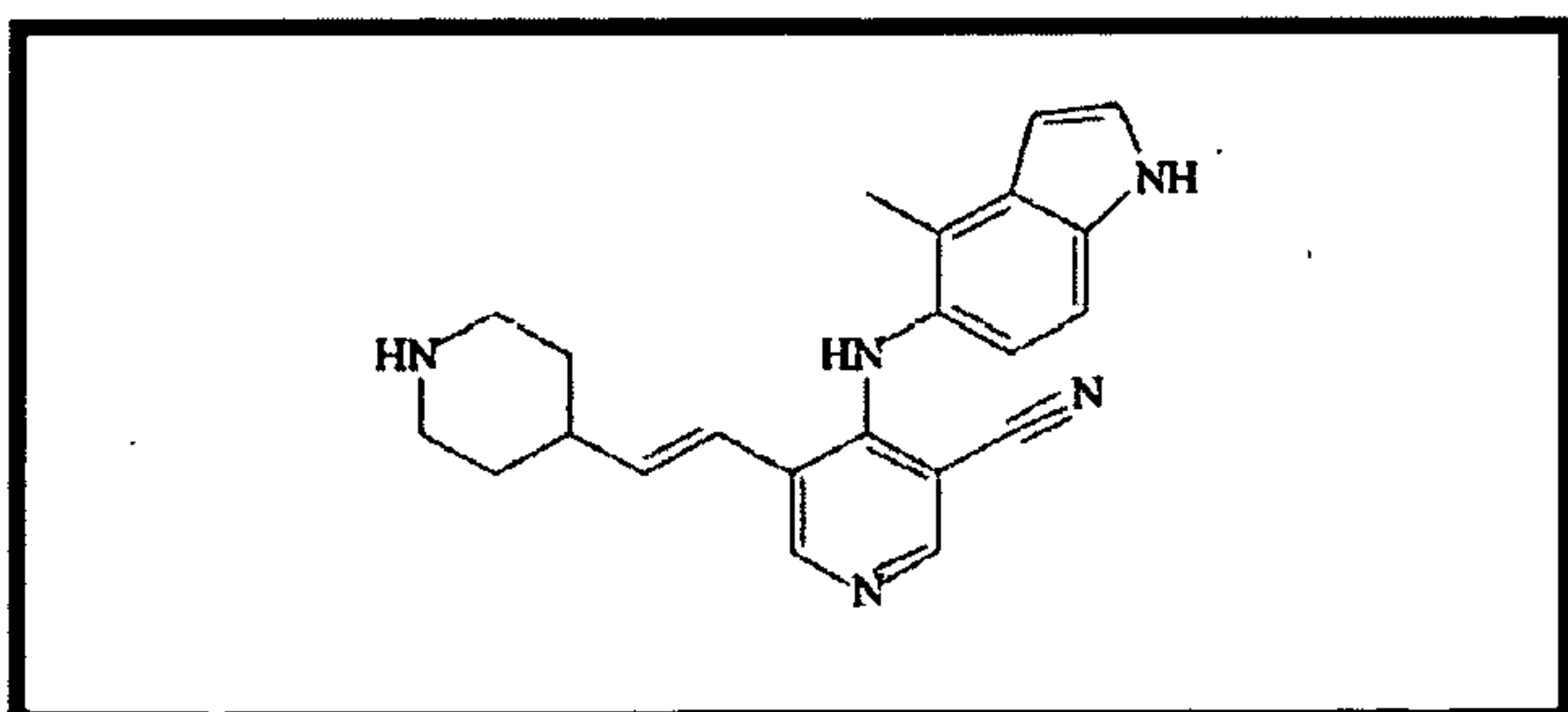
[00306] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{3-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}vinyl]nicotinonitrile:

A mixture of 5-[(E)-2-[3-(2-chloroethoxy)phenyl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino] nicotinonitrile (75 mg, 0.18 mmol), 1-methyl-piperazine (108 mg, 1.08 mmol) and sodium iodide (1.4 mg, 0.01 mmol) in 2 mL of DME was heated at 100°C overnight in a sealed vial. The reaction was concentrated and the crude material was purified by HPLC to give 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{3-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}vinyl] nicotinonitrile as its TFA salt; MS 493.3 (M+H); HPLC: rt = 6.2 min [a].



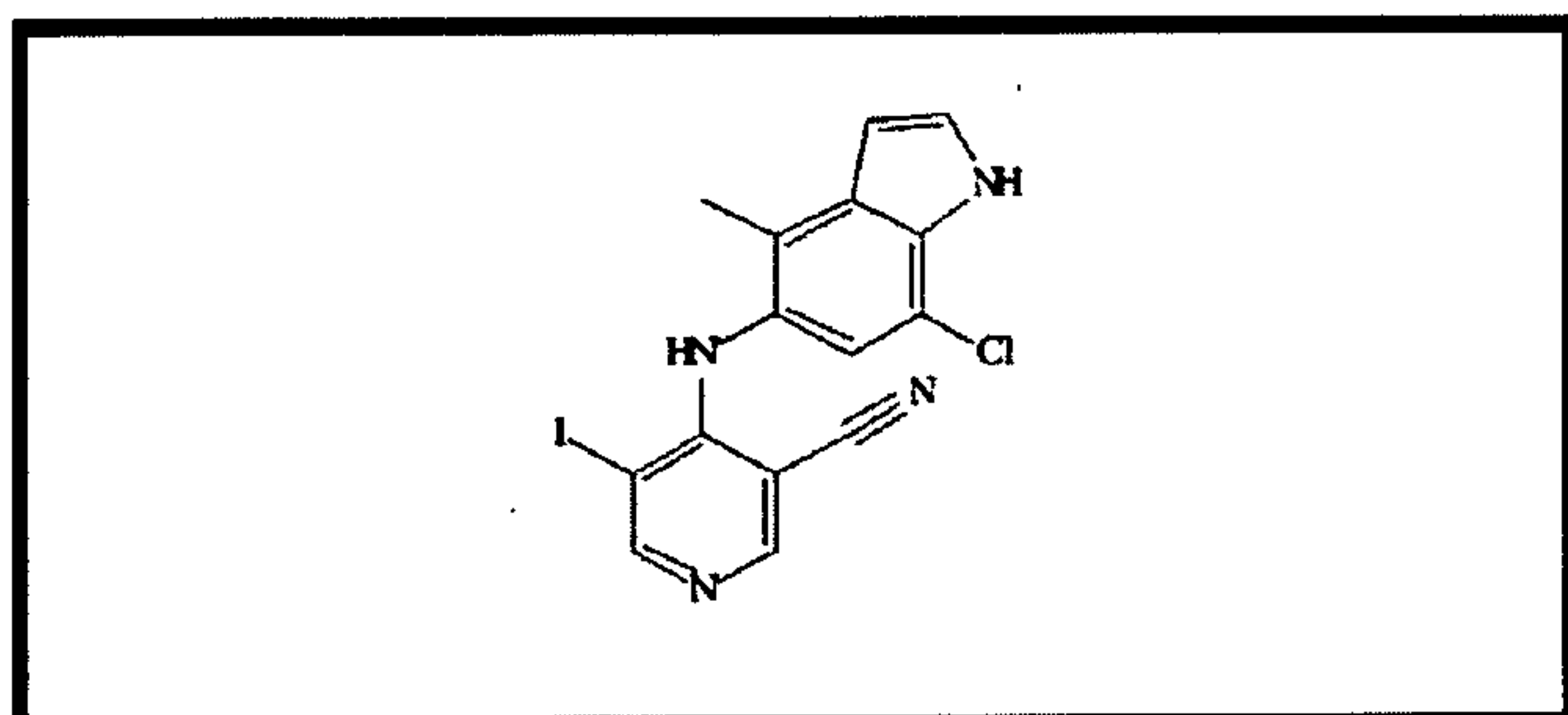
[00307] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[3-(2-pyrrolidin-1-ylethoxy)phenyl]vinyl]nicotinonitrile:

A mixture of 5-[(E)-2-[3-(2-chloroethoxy)phenyl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino] nicotinonitrile (75 mg, 0.18 mmol), pyrrolidine (77 mg, 1.08 mmol) and sodium iodide (1.4 mg, 0.01 mmol) in 2 mL of DME was heated at 100°C overnight in a sealed vial. The reaction was concentrated and the crude material was purified by HPLC to give 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[3-(2-pyrrolidin-1-ylethoxy)phenyl]vinyl]nicotinonitrile as its TFA salt; MS 464.3 (M+H); HPLC: rt = 6.6 min [a].

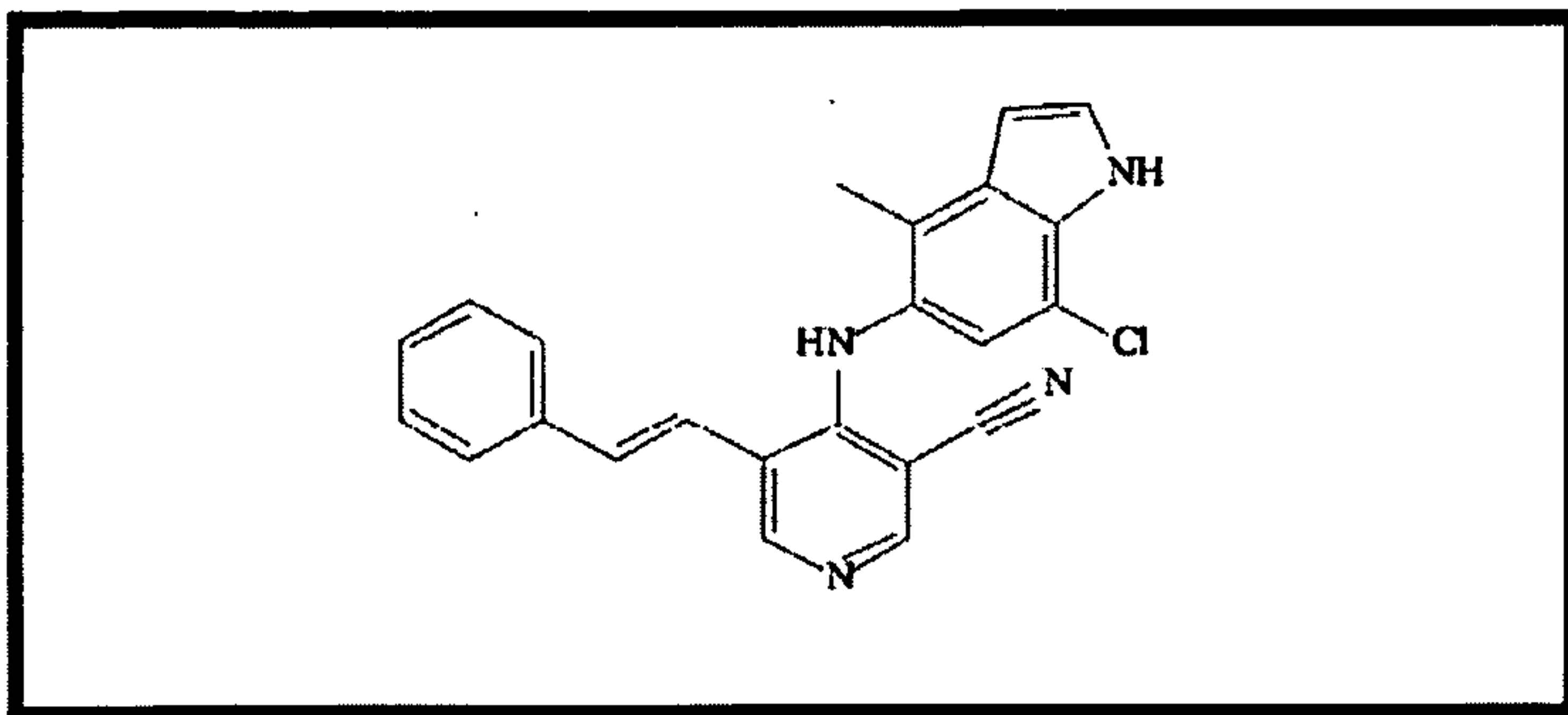


[00308] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-piperidin-4-ylvinyl]nicotinonitrile:

A mixture of 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (250 mg, 0.67 mmol), (E)-tert-butyl 4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)piperidine-1-carboxylate (452 mg, 1.34 mmol), cesium carbonate (437 mg, 1.34 mmol) and Pd(PPh₃)₄ (39.3 mg, 0.034 mmol) in 3 mL of DMSO was heated at 90°C for 16 h. The reaction mixture was cooled to room temperature and purified by HPLC. After purification both (E)-tert-butyl 4-(2-(5-cyano-4-(4-methyl-1H-indol-5-ylamino)pyridin-3-yl)vinyl)piperidine-1-carboxylate and 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-piperidin-4-ylvinyl]nicotinonitrile were observed due to the TFA buffer in the HPLC solvents. The mixture was diluted with DCM and treated with 0.70 mL of trifluoroacetic acid. Upon full conversion to 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-piperidin-4-ylvinyl]nicotinonitrile, the product was purified by HPLC to give 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-piperidin-4-ylvinyl]nicotinonitrile as a solid; HPLC: 96.2% at 215 nm, rt = 4.3 min [a]; MS = 358 (M+H).

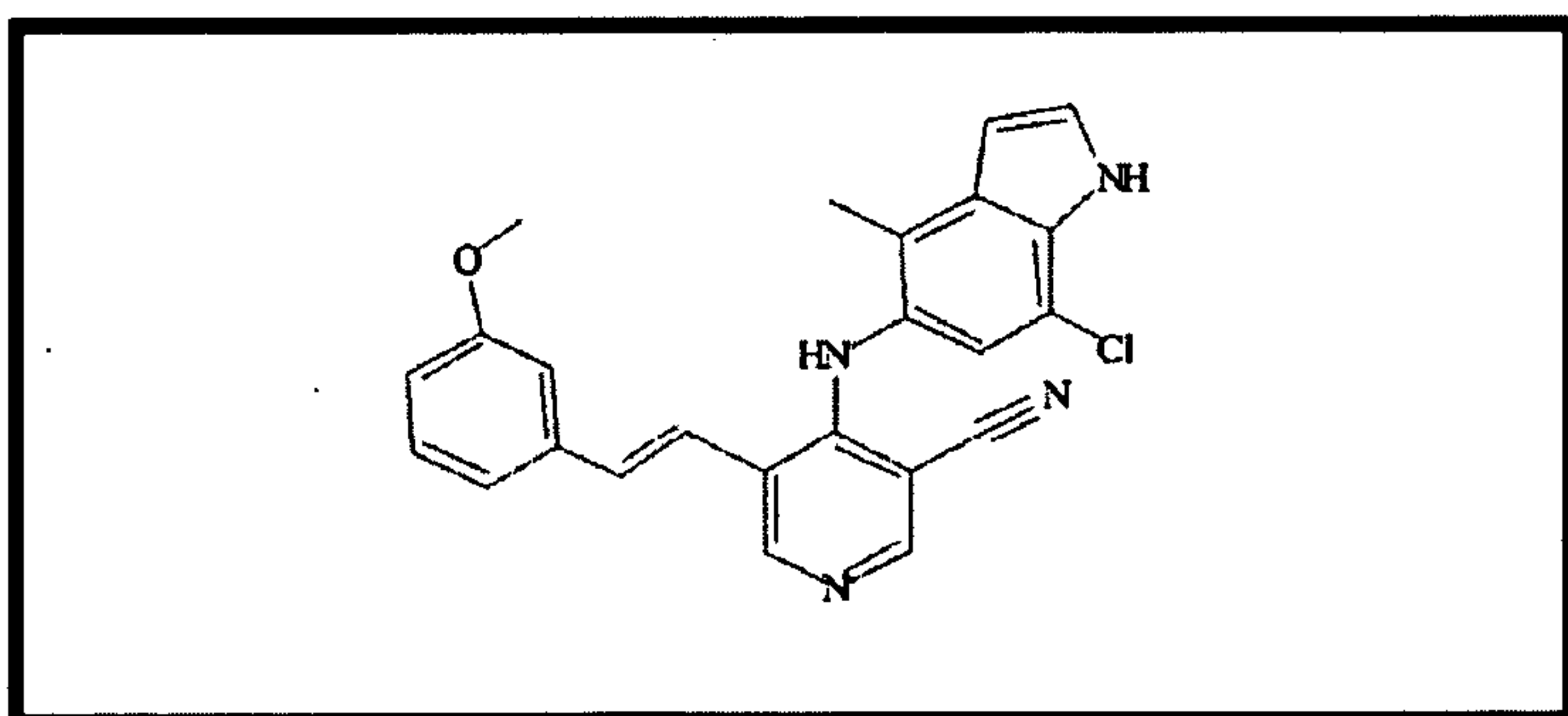
**[00309] Preparation of 4-[(7-chloro-4-methyl-1H-indol-5-yl)amino]-5-iodonicotinonitrile:**

A mixture of 4-chloro-5-iodonicotinonitrile (142 mg, 0.54 mmol) and 5-amino-7-chloro-4-methylindole (71 mg, 0.39 mmol) in 5 mL of ethanol was heated in a sealed tube at 95 °C for 72 h. The resulting mixture was cooled to room temperature. The reaction was diluted with ethyl acetate and washed with sodium bicarbonate solution. The organic phase was dried over magnesium sulfate. Flash column chromatography (ethyl acetate-hexanes 2 : 1) afforded 35 mg (15 %) of 4-[(7-chloro-4-methyl-1H-indol-5-yl)amino]-5-iodonicotinonitrile; MS 409.1 (M+H).



[00310] Preparation of 4-[(7-chloro-4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-phenylvinyl]nicotinonitrile:

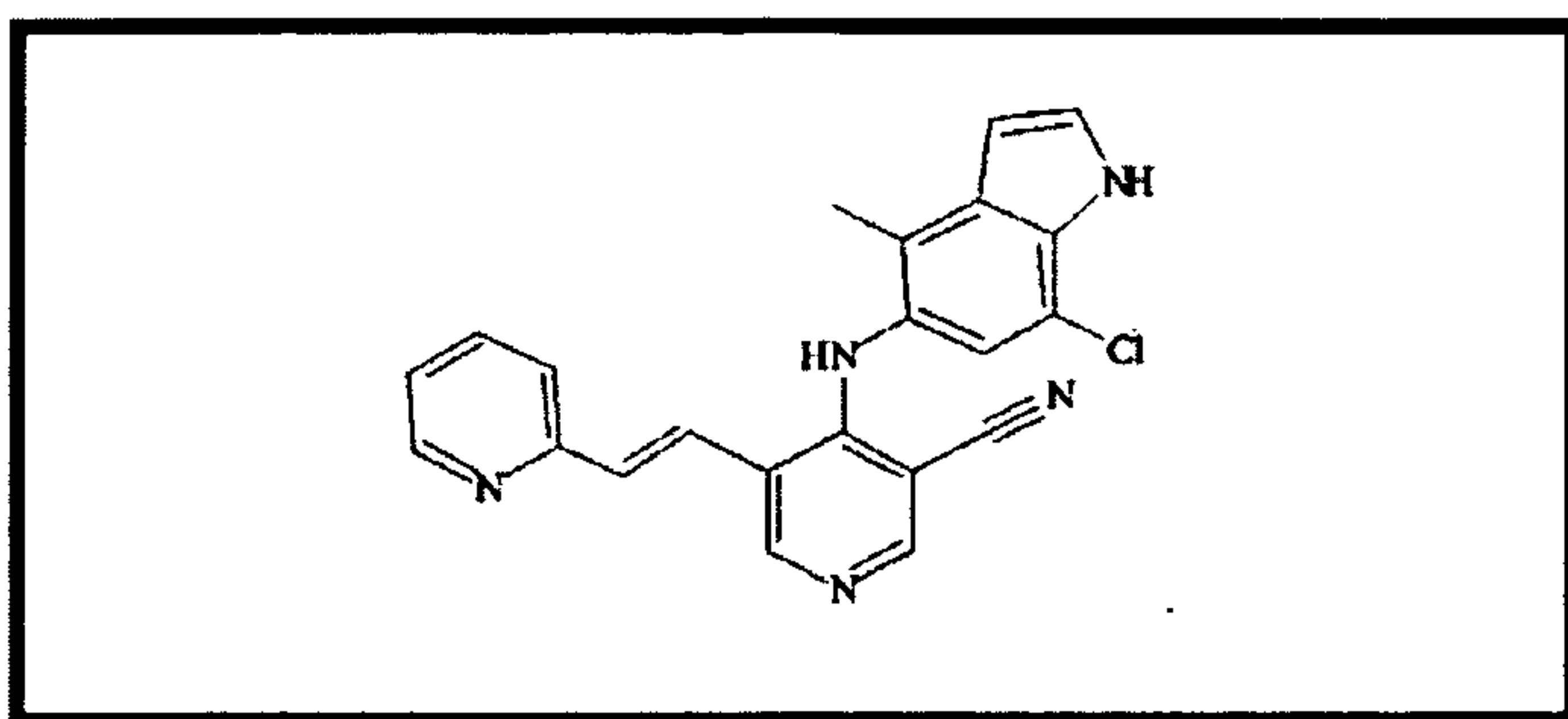
A mixture of 4-[(7-chloro-4-methyl-1H-indol-5-yl)amino]-5-iodonicotinonitrile (120mg, 0.29 mmol), trans-2-phenylvinylboronic acid (65 mg, 0.44 mmol), Pd(PPh₃)₂Cl₂ (103mg, 0.015mmol) and saturated aqueous NaHCO₃ (2.5 mL) in 3 mL DME was heated at 95°C for 4 h. The resulting mixture was cooled to room temperature, diluted with saturated aqueous sodium bicarbonate, and extracted into DCM. The organic layer was washed with brine and concentrated. The crude product was purified by column chromatography, eluting with hexanes and ethyl acetate(4:1), to give 51mg(54%) of 4-[(7-chloro-4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-phenylvinyl]nicotinonitrile as a yellow solid; MS 385.2(M+H); HPLC: 99.4% at 215 nm, rt = 10.9 min [a].



[00311] Preparation of 4-[(7-chloro-4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(3-methoxyphenyl)vinyl]nicotinonitrile:

A mixture of 4-[(7-chloro-4-methyl-1H-indol-5-yl)amino]-5-iodonicotinonitrile (120 mg, 0.29 mmol), trans-2-(3-methoxyphenyl)vinylboronic acid (115 mg, 0.44 mmol), Pd(PPh₃)₄ (170 mg,

0.015 mmol) and saturated aqueous NaHCO_3 (2 mL) in 3 mL DME was heated at 95°C for 4 h. The resulting mixture was cooled to room temperature, diluted with saturated aqueous sodium bicarbonate, and extracted into DCM. The organic layer was washed with brine and concentrated. The crude product was purified by column chromatography, eluting with hexanes and ethyl acetate (1:1), to give 41 mg (34%) of 4-[(7-chloro-4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(3-methoxyphenyl)vinyl]nicotinonitrile as a yellow solid; MS 415.5(M+H); HPLC: 91.4% at 215 nm, t_r = 10.8 min [a].



[00312] Preparation of 4-[(7-chloro-4-methyl-1*H*-indol-6-yl)amino]-5-[(*E*)-2-pyridine-2-yl vinyl])nicotinonitrile:

A mixture of 4-[(7-chloro-4-methyl-1*H*-indol-5-yl)amino]-5-iodonicotinonitrile (120 mg, 0.29 mmol), 2-vinylpyridine (61 mg, 0.58 mmol), tri(ortho-tolyl)phosphine (2.7 mg, 0.0087 mmol), $\text{Pd}(\text{OAc})_2$ (13.2 mg, 0.058 mmol) and Et_3N (2 mL) in 5 mL DMF was heated at 140°C for overnight. The resulting mixture was cooled to room temperature, diluted with saturated aqueous sodium bicarbonate, and extracted into DCM. The organic layer was washed by brine and concentrated. The crude product was purified by column chromatography, eluting with hexanes and ethyl acetate (1:1), to give 52 mg (45%) of 4-[(7-chloro-4-methyl-1*H*-indol-6-yl)amino]-5-[(*e*)-2-pyridine-2-ylvinyl])nicotinonitrile as a yellow solid; MS 386.5 (M+H); HPLC: 99.8% at 215 nm, t_r = 7.3 min [a].

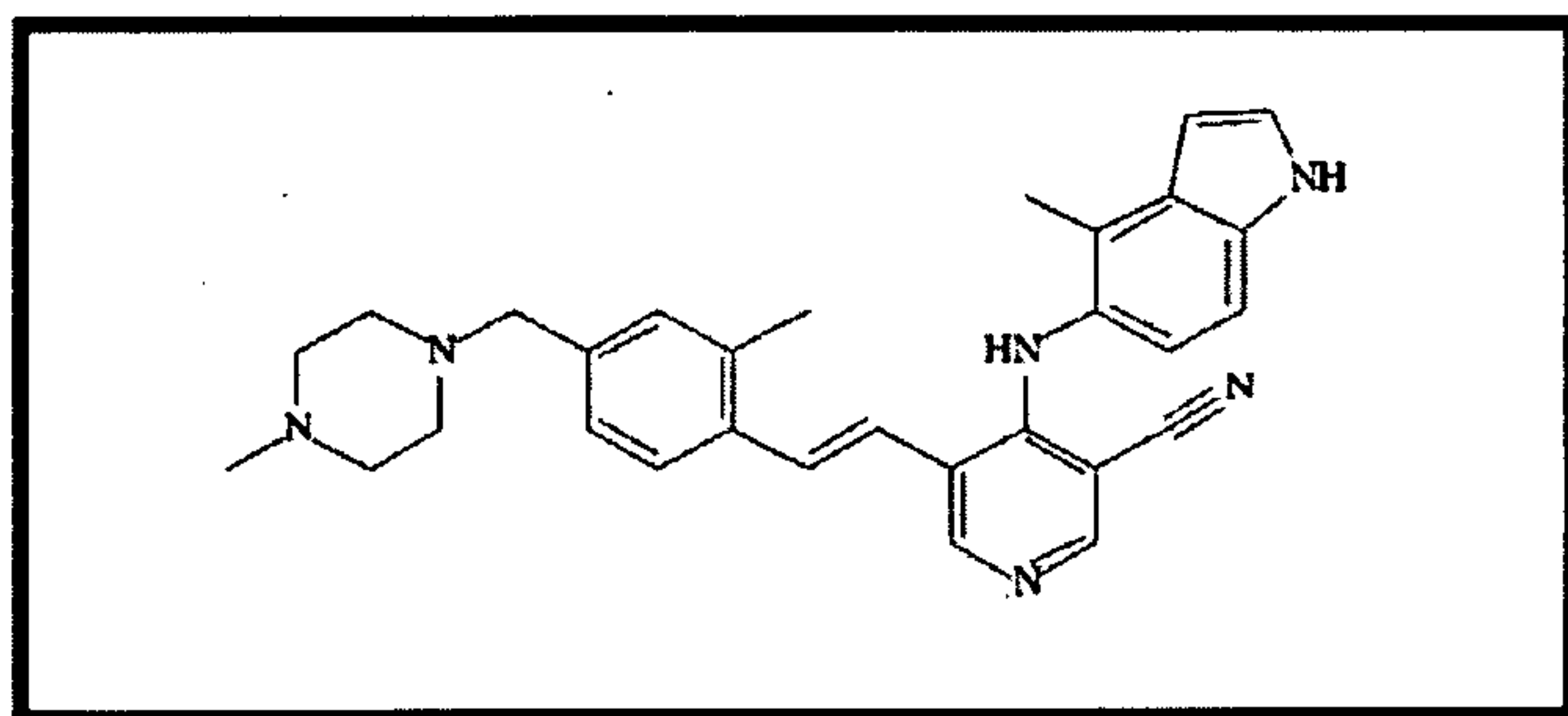
[00313] Preparation of 4-iodo-3-methylbenzaldehyde:

To a solution of 4-iodo-3-methylbenzonitrile (2.43 g, 10 mmol) in CH_2Cl_2 (70 mL) at -15 to -20°C under nitrogen was added DIBAL-H (12 mL, 12 mmol, 1M/heptane) such that the temperature was less than or equal to -15°C . After addition was complete, the reaction mixture was stirred an additional 10 min at -15 to -20°C . The reaction mixture was then quenched via dropwise

addition of aqueous 2N HCl such that the temperature was less than or equal to room temperature. The organic layer was separated and washed with water, dried over sodium sulfate and concentrated to give 2.13 g (87%) of 4-iodo-3-methylbenzaldehyde as yellow oil.

[00314] Preparation of 1-(4-iodo-3-methylbenzyl)-4-methylpiperazine:

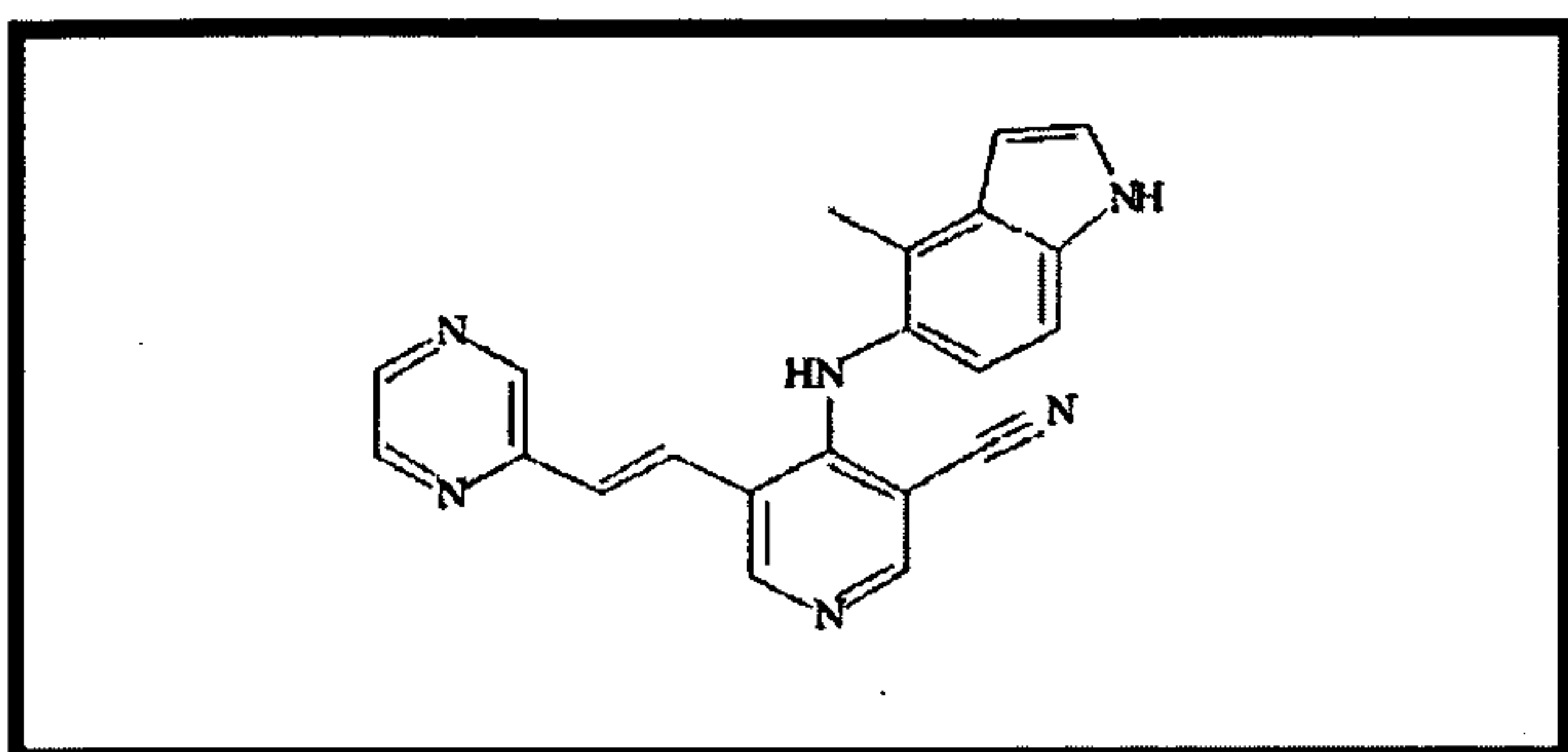
To a solution of 4-iodo-3-methylbenzaldehyde (1.47 g, 6 mmol) in a mixture of THF (60 mL) and EtOH (15 mL) at room temperature under nitrogen was added N-methylpiperazine (1.80 g, 18 mmol) followed by glacial acetic acid (1.80 g, 30 mmol). The reaction mixture was stirred at room temperature for 1 h. Sodium triacetoxyborohydride (6.36 g, 30 mmol) was added to the reaction mixture and the reaction was stirred at room temperature for 5 h. The reaction mixture was partitioned between EtOAc and aqueous 1N HCl. The aqueous layer was washed with EtOAc and treated with aqueous 1N NaOH whereupon solids precipitated. The solids were collected, dissolved in EtOAc, washed with water (thrice), then brine. The organic layer was dried over sodium sulfate, concentrated and the residue was purified by column chromatography eluting with a gradient of 50% EtOAc/hexane to 70% EtOAc/hexane to give 0.94 g (48%) of 1-(4-iodo-3-methylbenzyl)-4-methylpiperazine as a solid; MS 331.1 (M+H); HPLC: 98.4% at 215 nm, t_r = 11.4 min [a].



[00315] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{2-methyl-4-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]nicotinonitrile:

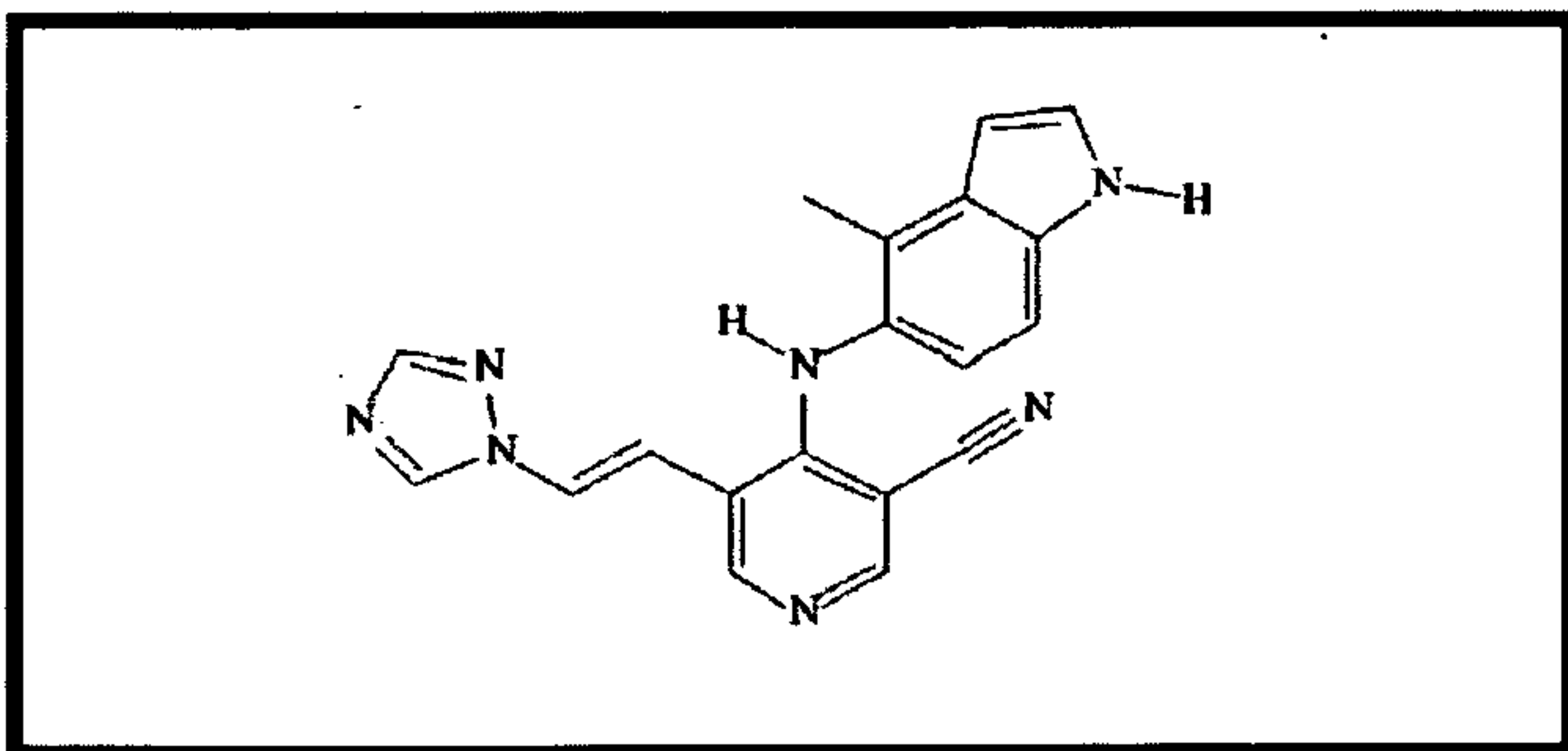
A mixture of 4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile (150 mg, 0.55 mmol), 1-(4-iodo-3-methylbenzyl)-4-methylpiperazine (165 mg, 0.5 mmol), 11 mg of tri(ortho-tolyl)phosphine and Pd(OAc)₂ (22mg) in 3 mL of DMF and 1 mL of Et₃N was heated at 120 °C for 3 h. After cooling to room temperature the reaction mixture was partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. The organic layer was dried over

magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography eluting with a gradient of ethyl acetate to 4% CH₃OH in ethyl acetate to give 201 mg (84%) of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{2-methyl-4-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]nicotinonitrile as a yellow solid; MS 477.3 (M+H); HPLC: 90.8% at 215 nm, rt = 6.1 min [a].



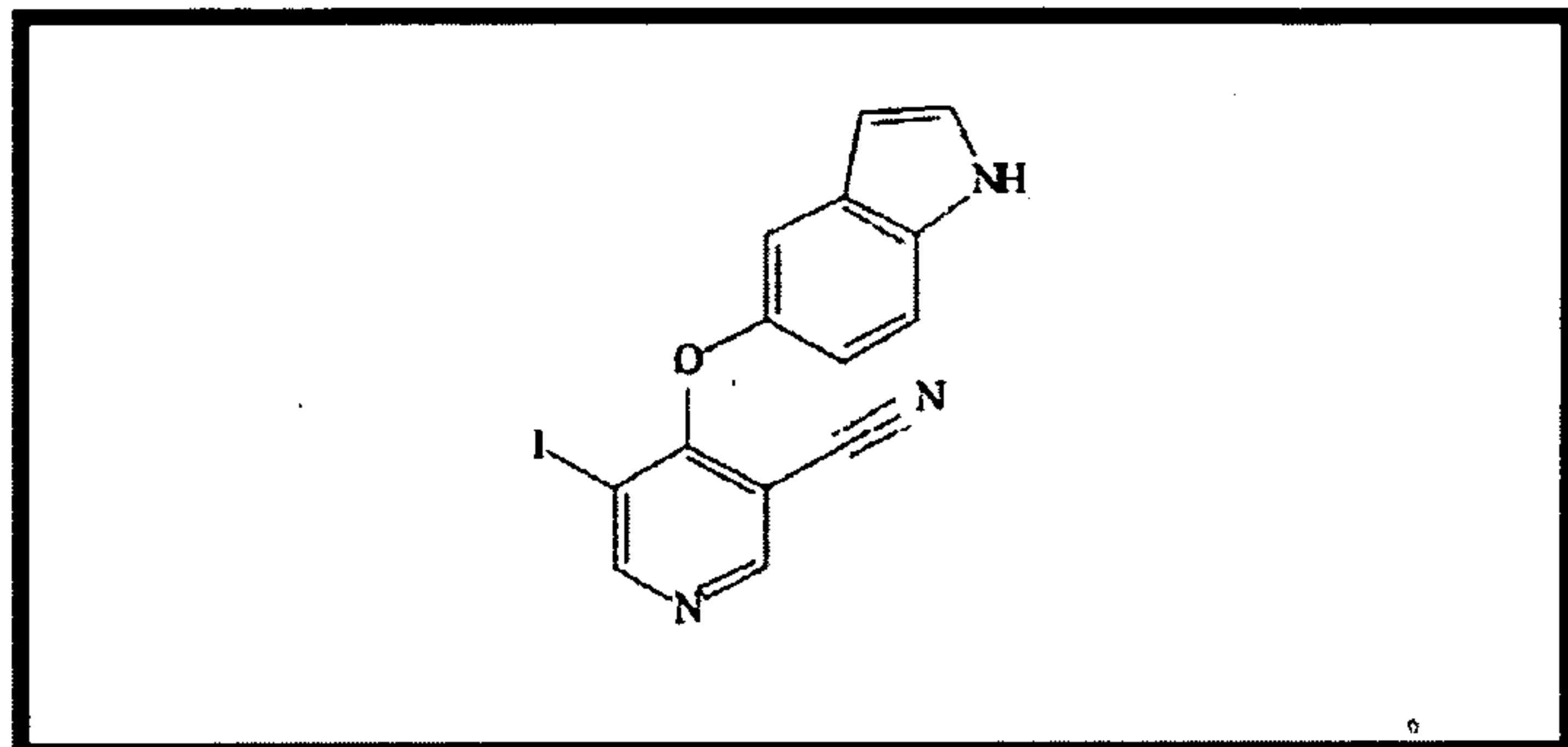
[00316] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)—2-pyrazin-2-yl vinyl] nicotinonitrile:

A mixture of 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (120 mg, 0.321 mmol), Pd(OAc)₂ (14.4 mg, 0.064 mmol), P(*o*-Tol)₃ (3.0 mg, 0.01 mmol) and 2-vinylpyrazine (70.2 μ L, 0.642 mmol) in DMF (5 mL) and Et₃N (2 mL) was stirred under nitrogen at 120 °C for 4 hours. The reaction was cooled to room temperature and concentrated *in vacuo*. The residue was suspended in EtOAc (5 mL) and filtered. The filter cake was washed with EtOAc (3 x 5 mL) and dried at 60 °C *in vacuo* to provide 52.2 mg (46%) of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)—2-pyrazin-2-ylvinyl]nicotinonitrile as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.33 (s, 3H), 6.51 (bs, 1H), 6.93 (d, J = 8.0 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.31-7.36 (m, 2H), 7.96 (d, J = 16.0 Hz, 1H), 8.32 (s, 1H), 8.51 (s, 1H), 8.63 (m, 2H), 8.93 (s, 1H), 9.01 (s, 1H), 11.14 (s, 1H); MS 353.2 (M+H).



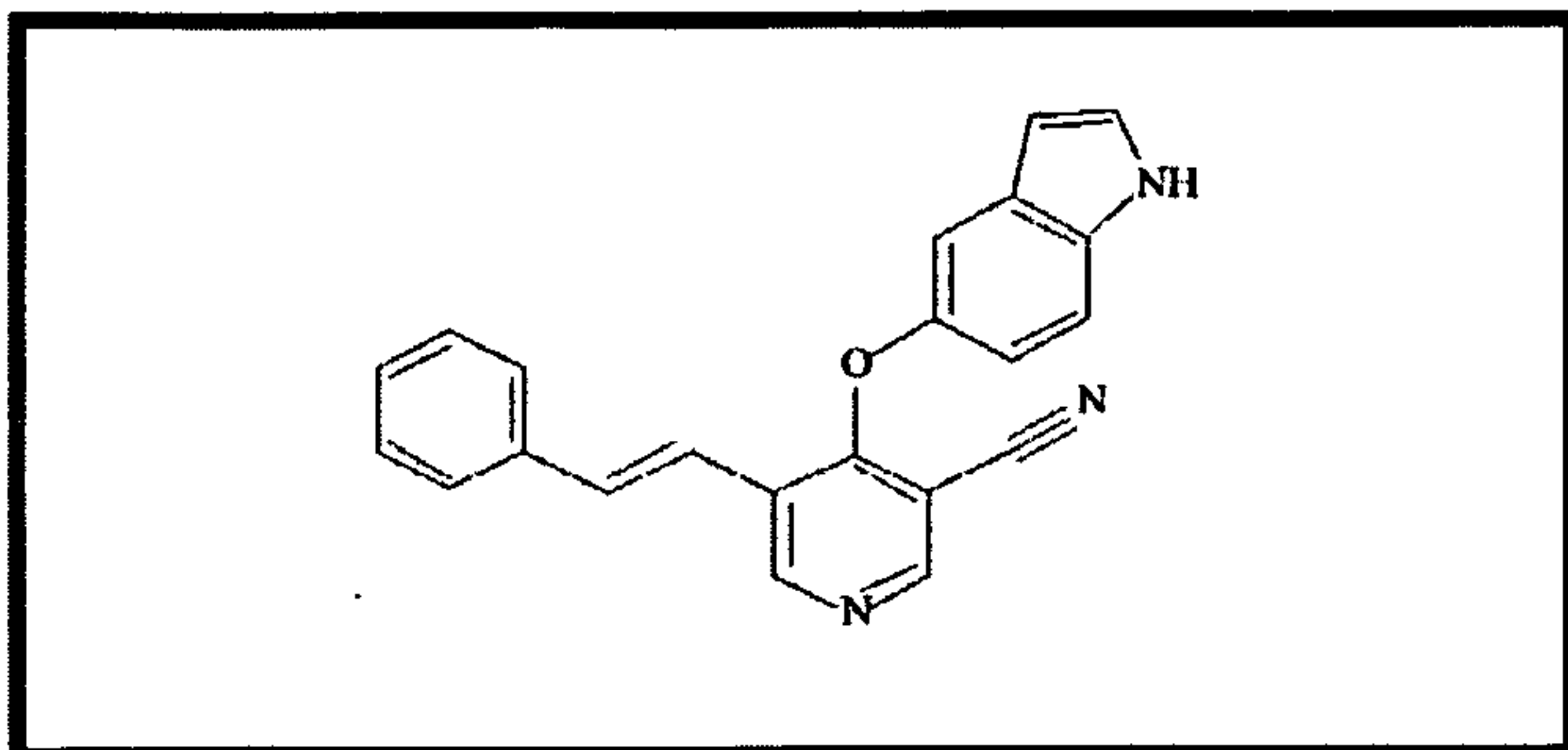
[00317] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)—2-(1H-1,2,4-triazol-1-yl)vinyl]nicotinonitrile:

The procedure for 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)—2-pyrazin-2-ylvinyl]nicotinonitrile was followed using 1-vinyl-1,2,4-triazole (110 mg, 0.642 mmol). The crude residue was purified by HPLC to provide 6.4 mg (6%) of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)—2-(1H-1,2,4-triazol-1-yl)vinyl]nicotinonitrile as a tan solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.33 (s, 3H), 6.51 (bs, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.35 (bs, 1H), 7.43 (d, *J* = 16 Hz, 1H), 7.92 (d, *J* = 16.0 Hz, 1H), 8.20 (s, 1H), 8.30 (s, 1H), 8.50 (s, 1H), 8.89 (m, 2H), 11.14 (s, 1H); MS 342.1 (M+H).



[00318] Preparation of 4-(1H-indol-5-yloxy)-5-iodonicotinonitrile:

A mixture of 4-chloro-5-iodonicotinonitrile (3.327 g, 12.58 mmol), 5-hydroxyindole (2.01g, 15.11 mmol) and 2.63 g of potassium carbonate in 50 mL of acetonitrile was heated at reflux for 3 h. The reaction mixture was cooled and poured into water. The solid was collected by filtration and dissolved in ethyl acetate, and washed with saturated aqueous sodium bicarbonate. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo. Trituration with ethyl acetate gave 960 mg (21%) of 4-(1H-indol-5-yloxy)-5-iodonicotinonitrile as a light tan solid. The filtrate was concentrated and the residue was recrystallized from ethyl acetate to give 510 mg (11%) of 4-(1H-indol-5-yloxy)-5-iodonicotinonitrile as an off-white solid, MS 362.0 (M+H)⁺; HPLC: 97.1% at 215 nm, *rt* = 14.1 min. Prodigy ODS3, 0.46 x 15 cm column: 1.0 mL/min, 20 min gradient of acetonitrile in water/TFA.

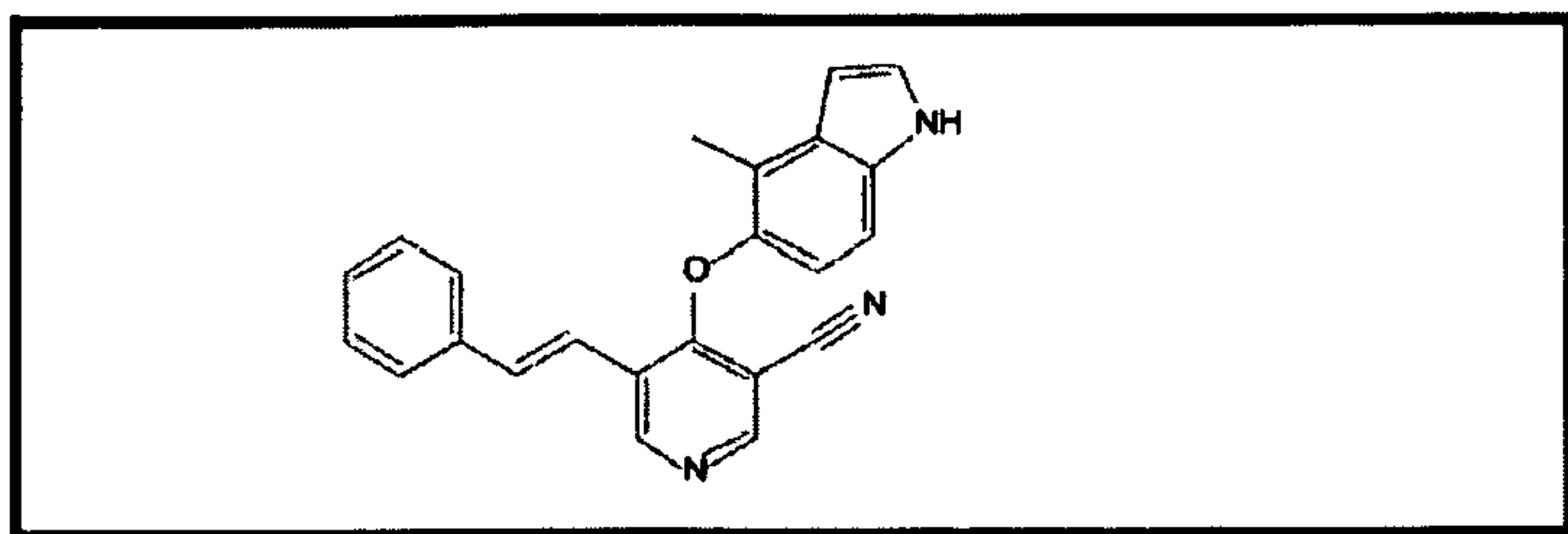


[00319] Preparation of 4-(1H-indol-5-yloxy)-5-[(E)-2-phenylvinyl]nicotinonitrile:

A mixture of 4-(1H-indol-5-yloxy)-5-iodonicotinonitrile (200 mg, 0.55 mmol), trans 2-phenylvinyl boronic acid (164 mg, 1.11 mmol) and 35 mg of $(\text{Ph}_3\text{P})_4\text{Pd}$ in 10 mL of dimethoxyethane and 5 mL of saturated aqueous sodium bicarbonate was heated at reflux for 1.5 h. The reaction mixture was cooled and partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo. Purification by flash column chromatography eluting with a gradient of 5:1 to 1:1 hexane:ethyl acetate gave 59 mg (32%) of 4-(1H-indol-5-yloxy)-5-[(E)-2-phenylvinyl]nicotinonitrile as a light tan solid, MS 338.2 (M+H)⁺; HPLC: 98.7% at 215 nm, rt = 16.5 min. Prodigy ODS3, 0.46 x 15 cm column: 1.0 mL/min, 20 min gradient of acetonitrile in water/TFA.

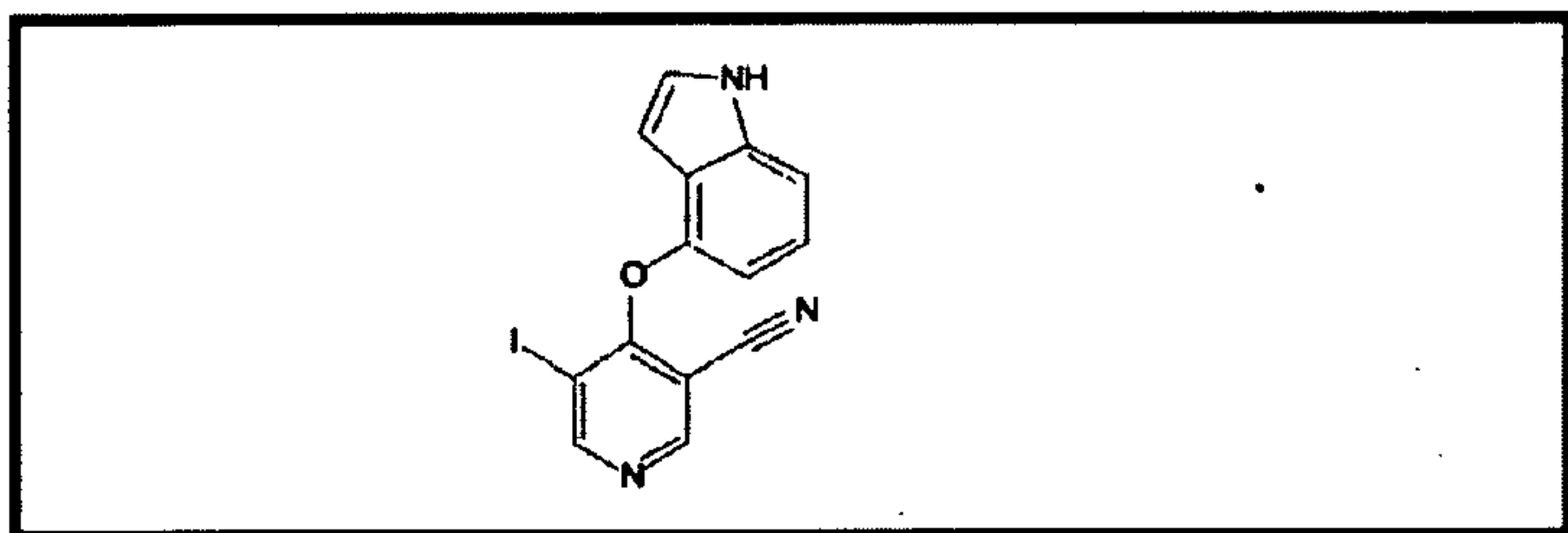
[00320] Preparation of 5-iodo-4-[(4-methyl-1H-indol-5-yl)oxy]nicotinonitrile:

4-Methyl-1H-indol-5-ol (0.664 g, 4.51 mmol), 4-chloro-5-iodonicotinonitrile (1.084 g, 4.1 mmol), and potassium carbonate (0.850 g, 6.15 mmol) were heated to 100° C in 20 mL acetonitrile for 2 h. The reaction was poured over water (75 mL) and the precipitate was filtered and washed with water to give 1.45 g of the title compound. HPLC: 98.5% at 215 nm, rt = 14.5 min [a]; MS: 376 [M+H].



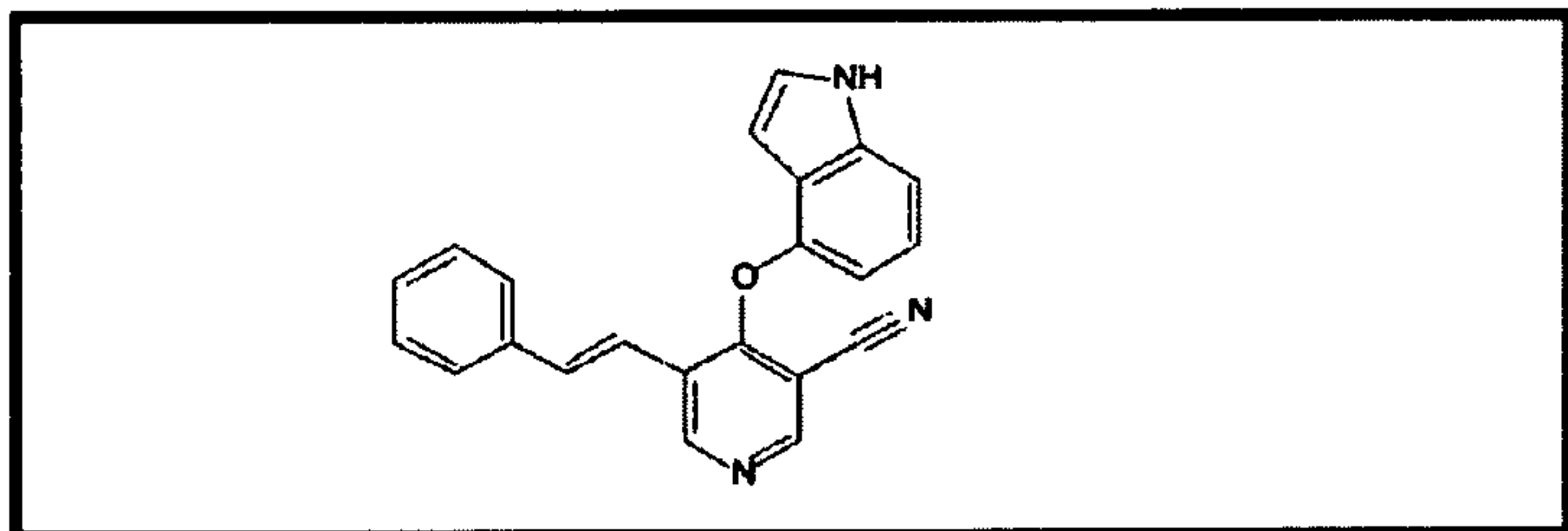
[00321] Preparation of 4-[(4-methyl-1H-indol-5-yl)oxy]-5-[(E)-2-phenylvinyl] nicotinonitrile:

5-Iodo-4-(4-methyl-1H-indol-5-yloxy)nicotinonitrile (100 mg, 0.267 mmol), (E)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane (73.6 mg, 0.320 mmol), and Pd(PPh₃)₂Cl₂ (22 mg, 0.03 mmol) were stirred in 3 mL DME and 0.5 mL of saturated aqueous NaHCO₃. The reaction was heated to 80° C overnight. The residue after concentration was dissolved in 2 mL DMSO. The mixture was filtered and the filtrate was purified by HPLC to give 40 mg of the title compound. MS: 352.1 (M+H); HPLC 99.6%, rt =17.1 min [a].



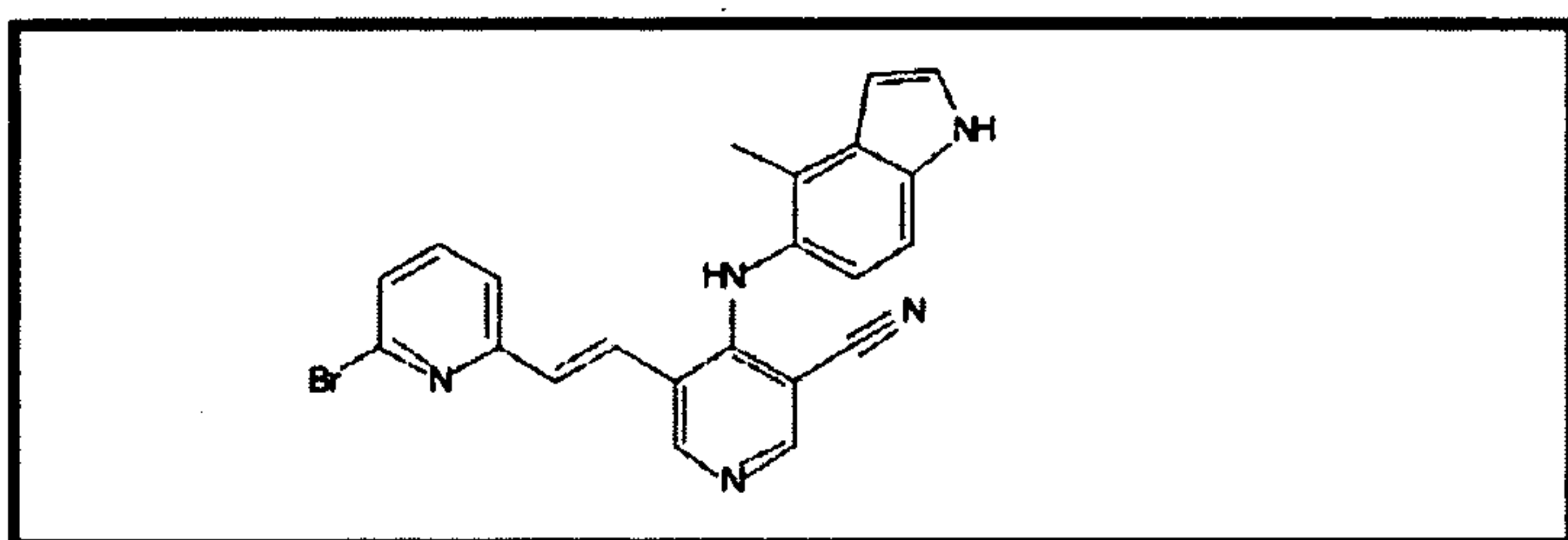
[00322] Preparation of 4-(1H-indol-4-yloxy)-5-iodonicotinonitrile:

4-Hydroxy indole (1.14 g, 8.6 mmol), 4-chloro-5-iodonicotinonitrile (2.06 g, 7.8 mmol), and potassium carbonate (1.6 g, 11.7 mmol) were heated to 100° C in 30 mL acetonitrile. After 1.5 h the reaction was cooled and quenched with 3 equivalents of acetic acid. The reaction was concentrated and re-dissolved in DCM/MeOH and subsequently evaporated onto silica gel. The desired product was purified by column chromatography (10% to 40% EtOAc in Hex) to give 1.85 g of material. This product was further purified by recrystallization from EtOH/water to give 850 mg of pure 4-(1H-indol-4-yloxy)-5-iodonicotinonitrile. HPLC: 95.9% at 215 nm, rt = 14.0 min [a]; MS: 362.1 [M+H].

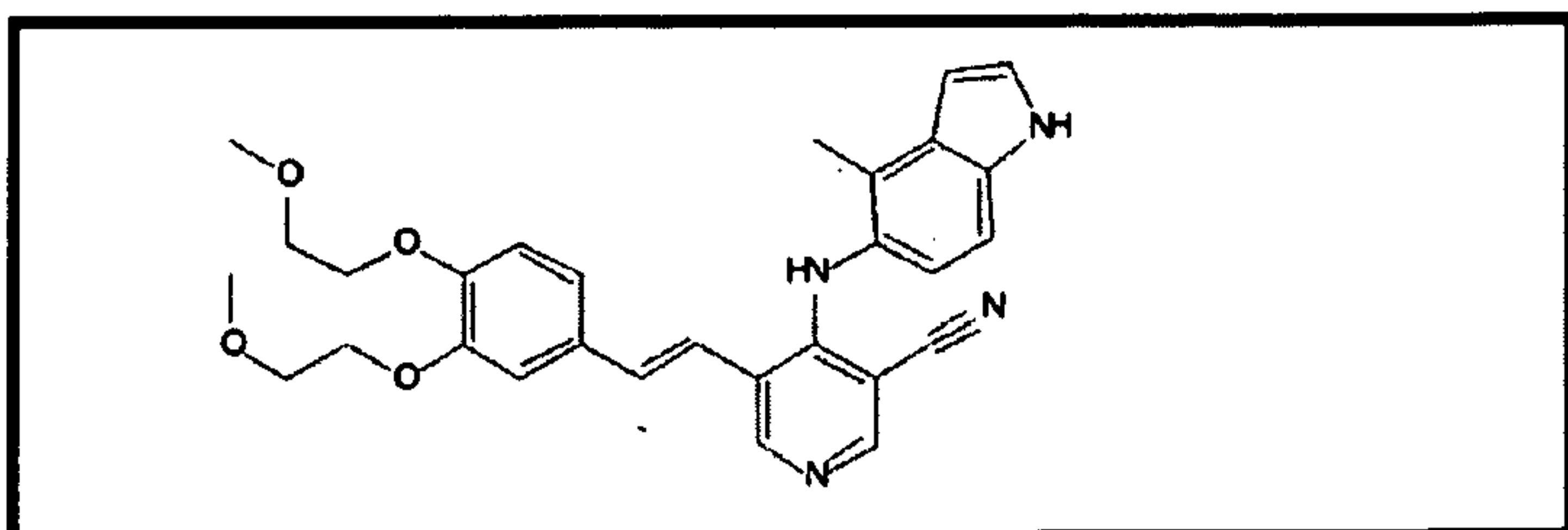


[00323] Preparation of 4-(1H-indol-4-yloxy)-5-[(E)-2-phenylvinyl]nicotinonitrile:

4-(1H-Indol-4-yloxy)-5-iodonicotinonitrile (0.41 mmol, 150 mg), (E)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane (142 mg, 0.62 mmol), Pd(PPh₃)₂Cl₂ (44 mg, 0.06 mmol), and sodium bicarbonate (0.3 mL of a saturated aqueous solution) were heated to 80° C for 4 h in 3 mL of DMSO. The reaction was filtered and the filtrate was purified by HPLC to give 60 mg of the title compound as a white solid. HPLC: rt =16.4 min [a]; HRMS: calculated 338.12879; found 338.1286.

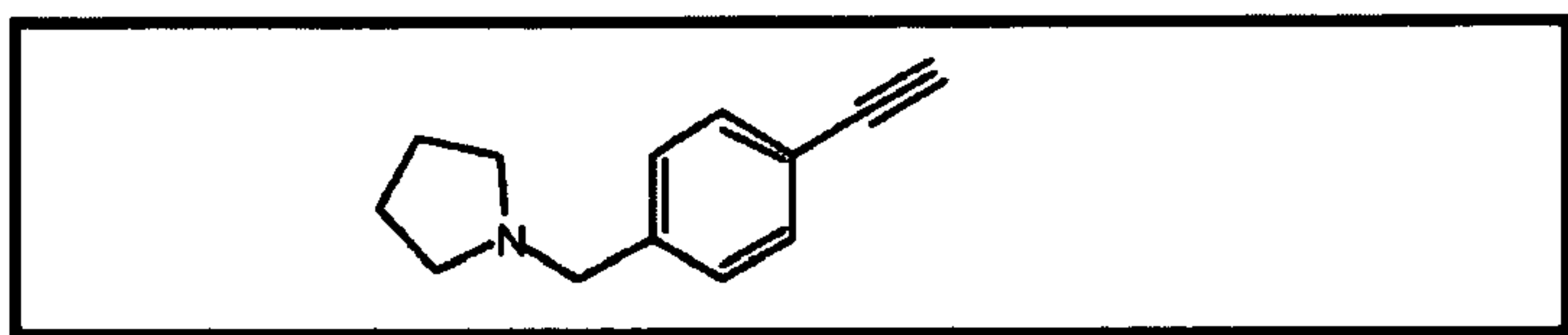
**[00324] Preparation of 5-[(E)-2-(6-bromopyridin-2-yl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile :**

4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile (60 mg, 0.22 mmol), 2,6-dibromopyridine (62 mg, 0.26 mmol), Pd(OAc)₂ (5 mg, 0.022 mmol), P(o-Tol)₃ (13 mg, 0.044 mmol), and triethyl amine (66 mg, 0.66 mmol) were heated to 90° C for 3 h in 2 mL DMF. The temperature was increased to 100 C and the reaction was heated overnight. LCMS indicated the reaction was complete. A significant amount of the double addition product (E)-5-(2-(6'-bromo-2,2'-bipyridin-6-yl)vinyl)-4-(4-methyl-1H-indol-5-ylamino)nicotinonitrile was observed (20-30%). The reaction was filtered and the product was isolated by preparative HPLC giving 18 mg of the desired (monoaddition) product. HPLC: 92.1%, rt = 9.7 min [a]; HRMS: calculated 430.06618, found 430.06591.



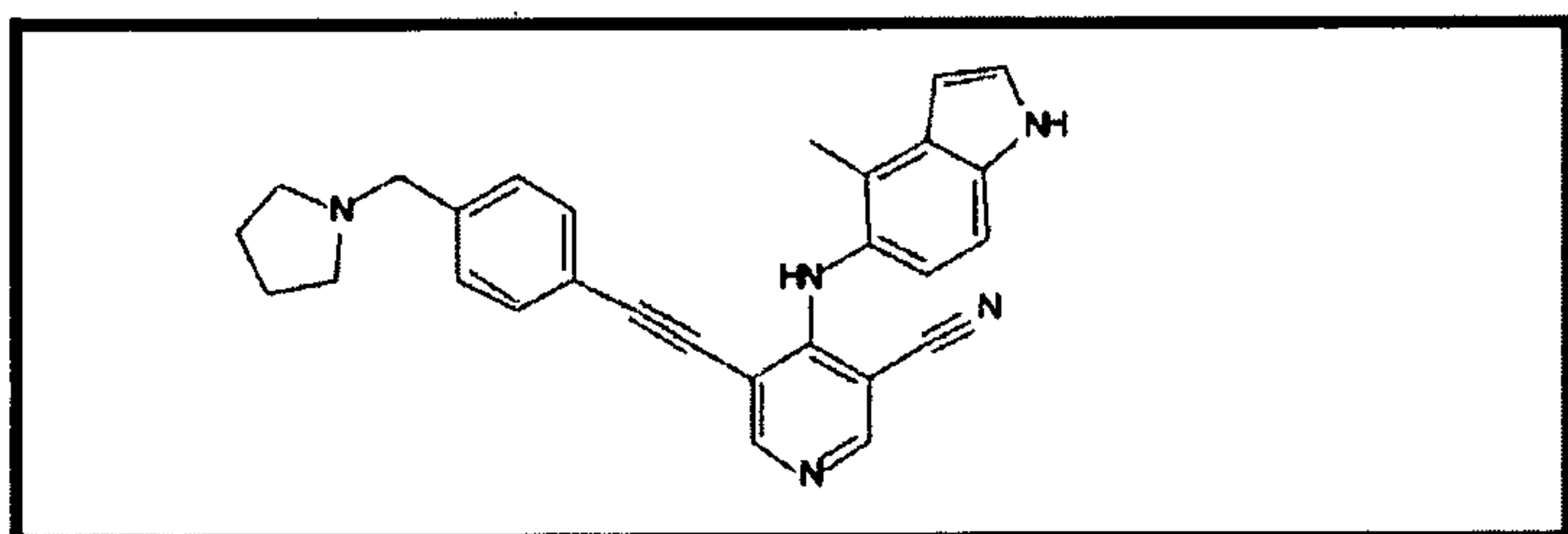
[00325] Preparation of 5-((E)-2-[3,4-bis(2-methoxyethoxy)phenyl]vinyl)-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile (75 mg, 0.27 mmol), 4-bromo-1,2-bis(2-methoxyethoxy)benzene (167 mg, 0.54 mmol), Pd(OAc)₂ (6 mg, 0.03 mmol), P(o-Tol)₃ (12 mg, 0.04 mmol), and triethylamine (83 mg, 0.83 mmol) were dissolved in 2 mL DMF and heated to 70 °C for 3 h. The temperature was increased to 100 °C and the reaction was heated overnight. The reaction was filtered and the filtrate was purified by HPLC to give 65 mg of the title compound. HPLC: 93.2%, rt = 9.2 min [a]; HRMS: calculated 499.23398, found 499.23254.



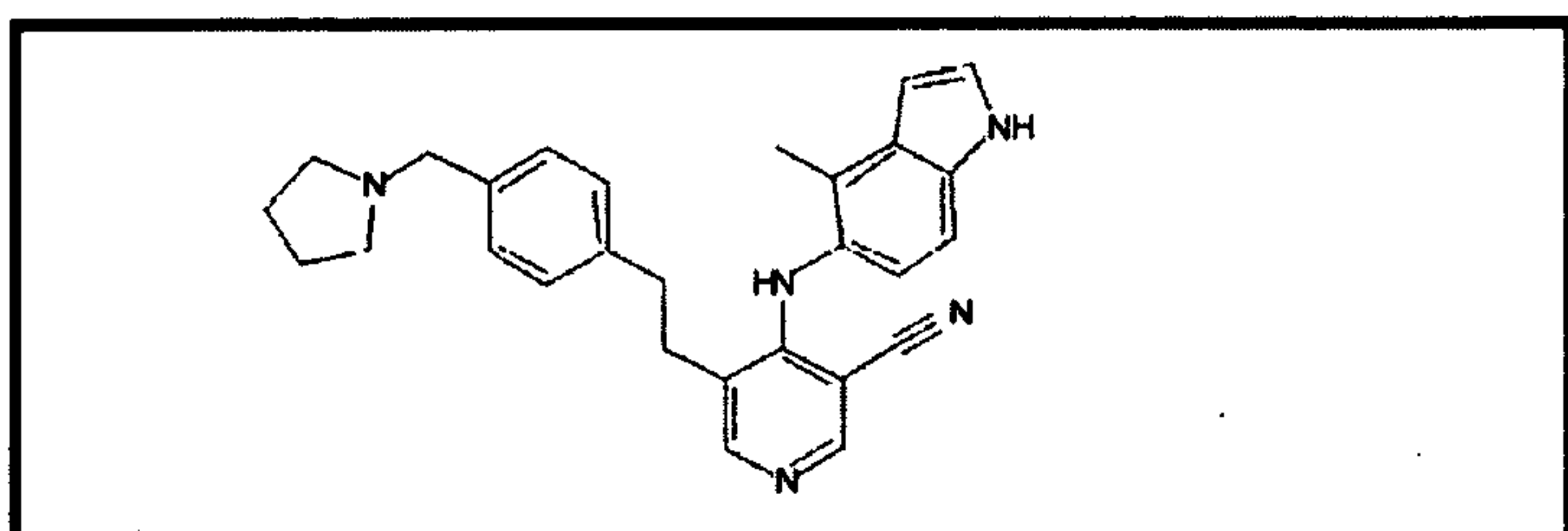
[00326] Preparation of 1-(4-ethynylbenzyl)pyrrolidine:

4-Ethynylbenzaldehyde (.5 g, 3.84 mmol) and pyrrolidine (0.328 g, 4.61 mmol) were stirred in 40 mL 1,2-dichloroethane. Sodium triacetoxyborohydride (1.629 g, 7.68 mmol) was added and the reaction was stirred over the weekend. The reaction was quenched with water (20 mL) and HOAc (2 eq) and stirred until bubbling ceased. The product was partitioned between dichloromethane and aqueous NaHCO₃. The product was extracted 2x into dichloromethane and dried over MgSO₄. The solution was concentrated to give 600 mg of a yellow oil. MS: 186.1 (M+H).



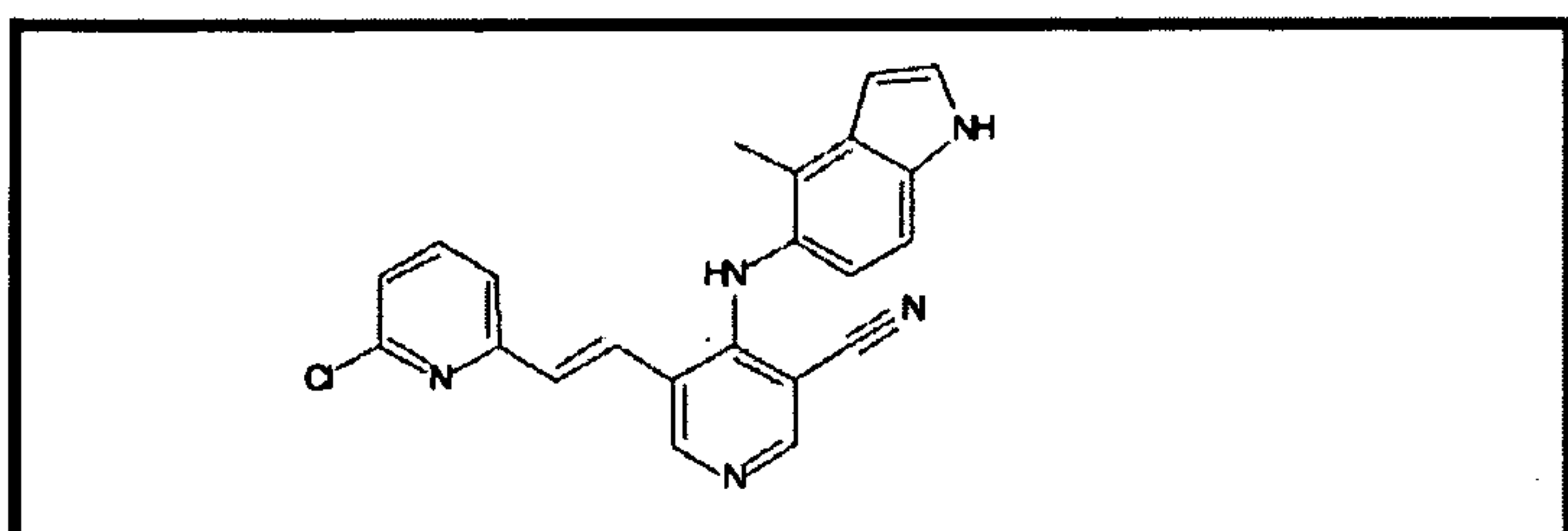
[00327] Preparation of 4-(4-methyl-1H-indol-5-ylamino)-5-((4-(pyrrolidin-1-ylmethyl)phenyl)ethynyl)nicotinonitrile:

5-Iodo-4-(4-methyl-1H-indol-5-ylamino)nicotinonitrile (250 mg, 0.67 mmol), 1-(4-ethynylbenzyl)pyrrolidine (136 mg, 0.375 mmol), Pd(PPh₃)₂Cl₂ (47 mg, 0.067 mmol), CuI (13 mg, 0.067 mmol), and triethylamine (270 mg, 2.67 mmol) were stirred at room temperature in 4 mL DMF. After 3 h the reaction was treated with a small amount of TFA (~50 μ L), filtered, and the filtrate was purified by HPLC. The residue (TFA salt) was treated with HCl/dioxane to make the HCl salt. Evaporation from ethanol gave a yellow solid, which was treated with 1 mL of EtOH and sonicated. The cloudy suspension was filtered and the filter cake was dried to give 22 mg of pure product. HPLC: 96.8%, *rt* = 7.2 min [a]; MS: 432.3 (M+H).



[00328] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(2-[4-(pyrrolidin-1-ylmethyl)phenyl]ethyl)nicotinonitrile:

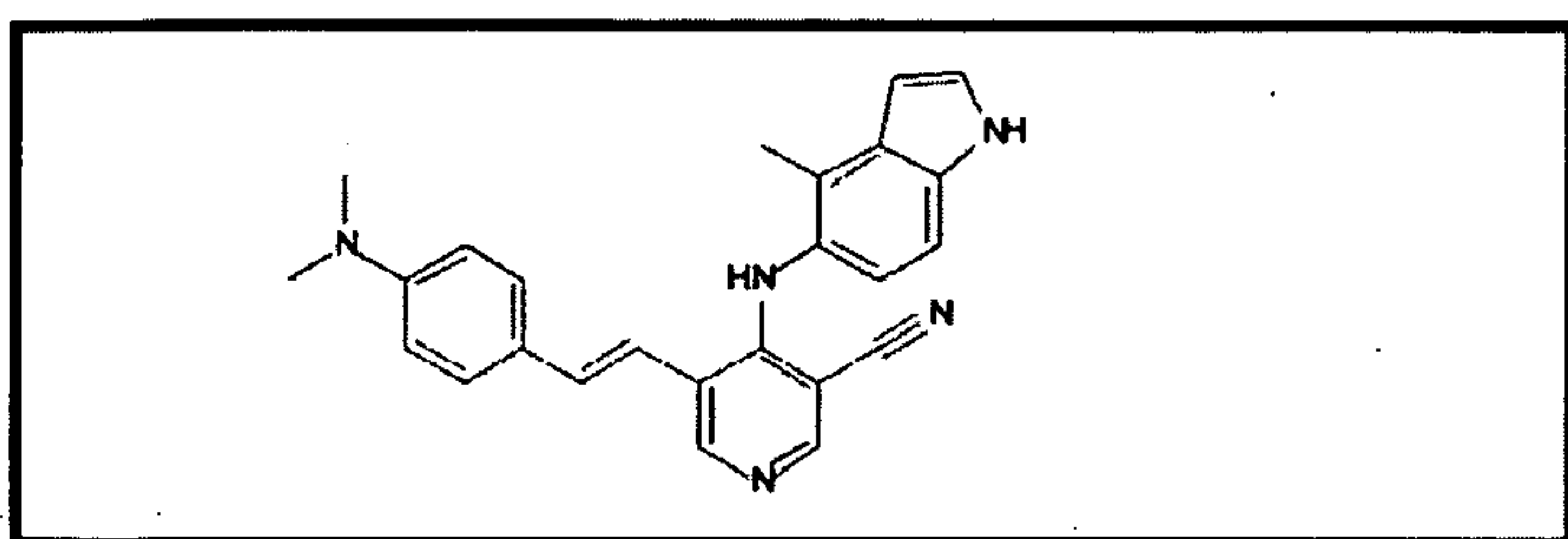
4-(4-Methyl-1H-indol-5-ylamino)-5-[(4-(pyrrolidin-1-ylmethyl)phenyl)ethynyl]nicotinonitrile (85 mg, 0.197 mmol) (hydrochloride salt) was dissolved in 10 mL ethanol and treated with 1 eq. of Et₃N. The reaction was treated with 25 mg of Pd/C and shaken under hydrogen (30 psi) for 2 h. The reaction was filtered, concentrated, and purified by HPLC to give 30 mg of the title compound as its free base. HPLC: 97.0%, *rt* = 5.3 min [a]; HRMS: calculated 436.24957, found 436.25152.



[00329] Preparation of 5-[(E)-2-(6-chloropyridin-2-yl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

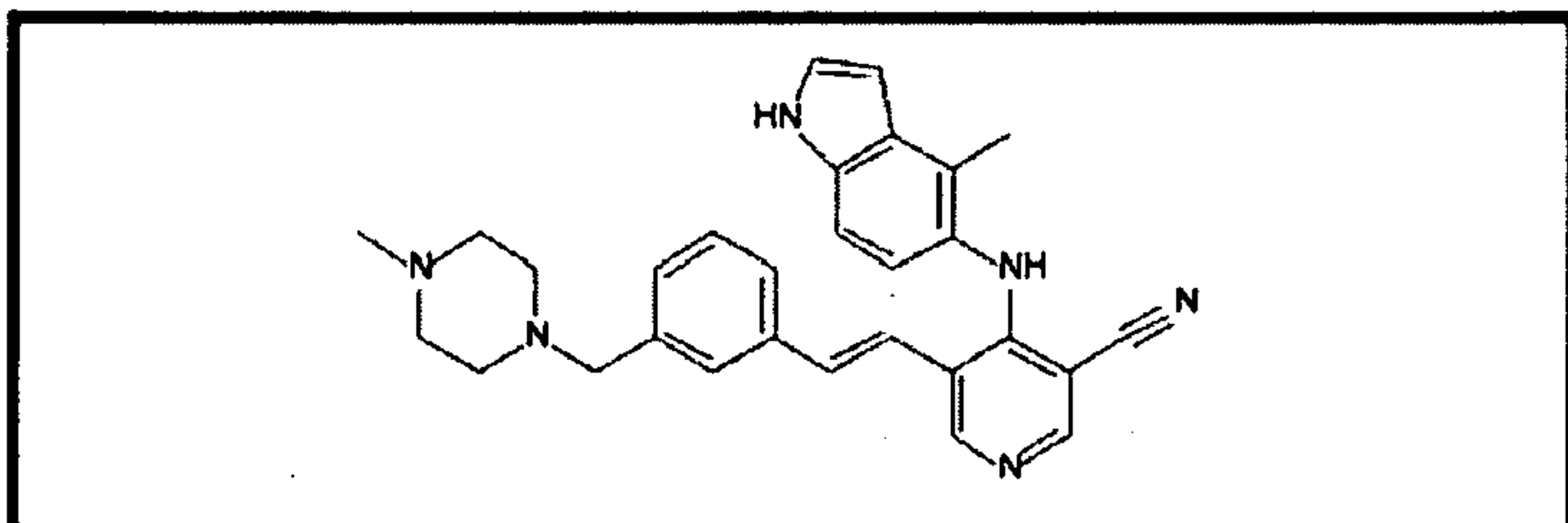
2-Bromo-6-chloropyridine (.66 mmol, 126 mg), 4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile (.55 mmol, 150 mg), Pd(OAc)₂ (0.055 mmol, 12 mg), triethylamine (1.6

mmol, 160 mg), and $P(o\text{-Tol})_3$ (0.11 mmol, 33 mg) were heated to 100° C in 5 mL DMF overnight. An additional 50 mg of 2-bromo-6-chloropyridine was added and the heating was continued for 2 h. The reaction was filtered and the filtrate was purified by reverse-phase chromatography (acetonitrile/water). The product fractions were concentrated the material was treated with 10 mL ethanol and heated gently for a few minutes. After cooling to room temperature and filtering, 65 mg of the title compound was obtained as a yellow solid. HPLC: 91.4%, rt = 9.2 min; HRMS: calculated 386.11670; found 386.11598.



[00330] Preparation of 5-[(E)-2-[4-(dimethylamino)phenyl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

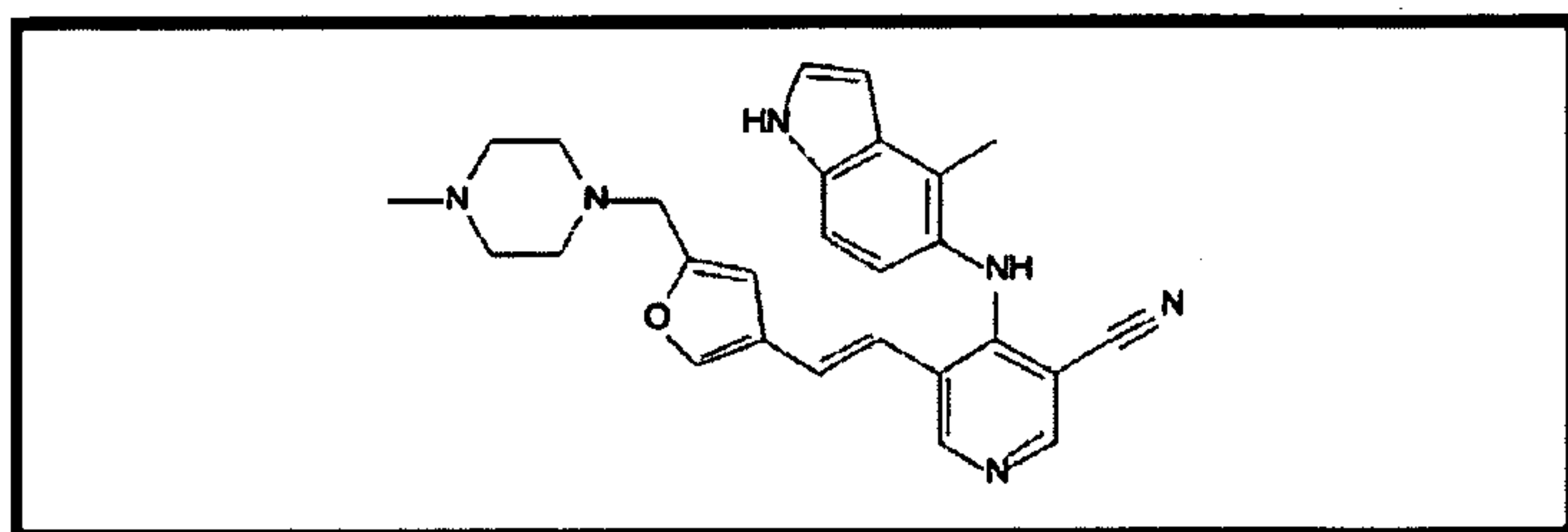
Following the procedure to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{4-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl} vinyl]nicotinonitrile, the title compound was prepared via the reaction of 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile with N,N-dimethyl-4-vinylaniline. MS 394.1 (M+H)⁺, HPLC purity 94.2% at 215 nm, rt = 8.6 min [a].



[00331] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{3-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]nicotinonitrile:

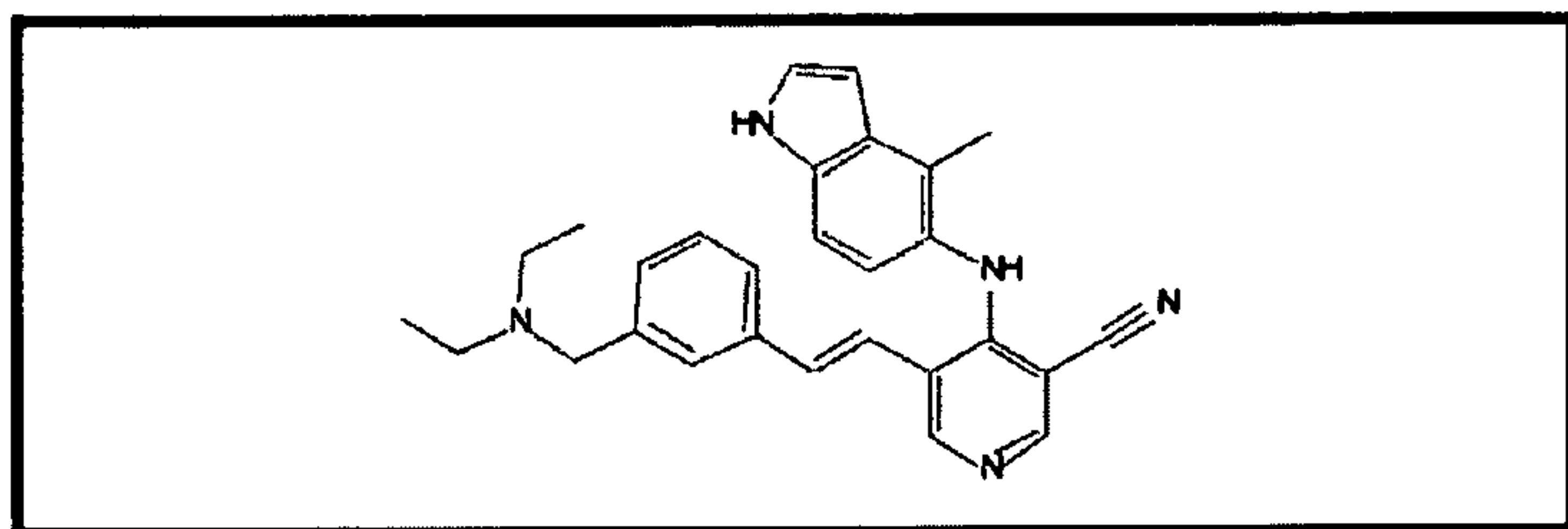
A mixture of 4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile (100 mg, 0.36 mmol), 1-(3-bromobenzyl)-4-methylpiperazine (116.3 mg, 0.43 mmol), $Pd(OAc)_2$ (16.2 mg, 0.072 mmol) and $P(o\text{-Tol})_3$ (7.7 mg, 0.025 mmol) in 3.0 mL of DMF and 0.75 mL of TEA was heated 120°C for 2.5 h. The mixture was cooled to room temperature, and was partitioned between dichloromethane and aqueous saturated sodium bicarbonate. The organic phase was dried

over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography, eluting with a gradient of 2% methanol in dichloromethane to 12% methanol in dichloromethane to provide 64.8 mg (39%) of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{3-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]nicotinonitrile as an off white solid, MS 463.3 (M+H)⁺, HPLC purity 95.5% at 215 nm, rt = 5.9 min [a].



[00332] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{5-[(4-methylpiperazin-1-yl)methyl]-3-furyl}vinyl]nicotinonitrile:

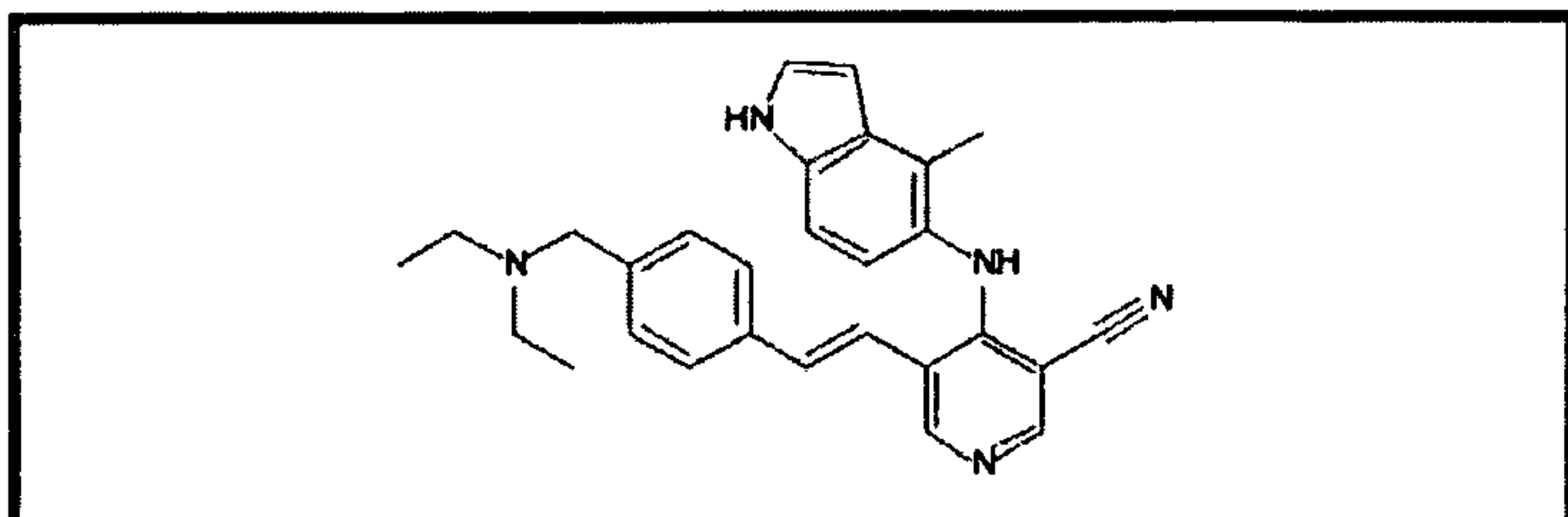
Following the procedure to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{3-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]nicotinonitrile, 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{5-[(4-methylpiperazin-1-yl)methyl]-3-furyl}vinyl]nicotinonitrile was prepared via the reaction of 4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile with 1-[(4-bromo-2-furyl)methyl]-4-methylpiperazine. MS 453.2 (M+H)⁺, HPLC purity 96.3% at 215 nm, rt=5.2 min [a].



[00333] Preparation of 5-[(E)-2-{3-[(diethylamino)methyl]phenyl}vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

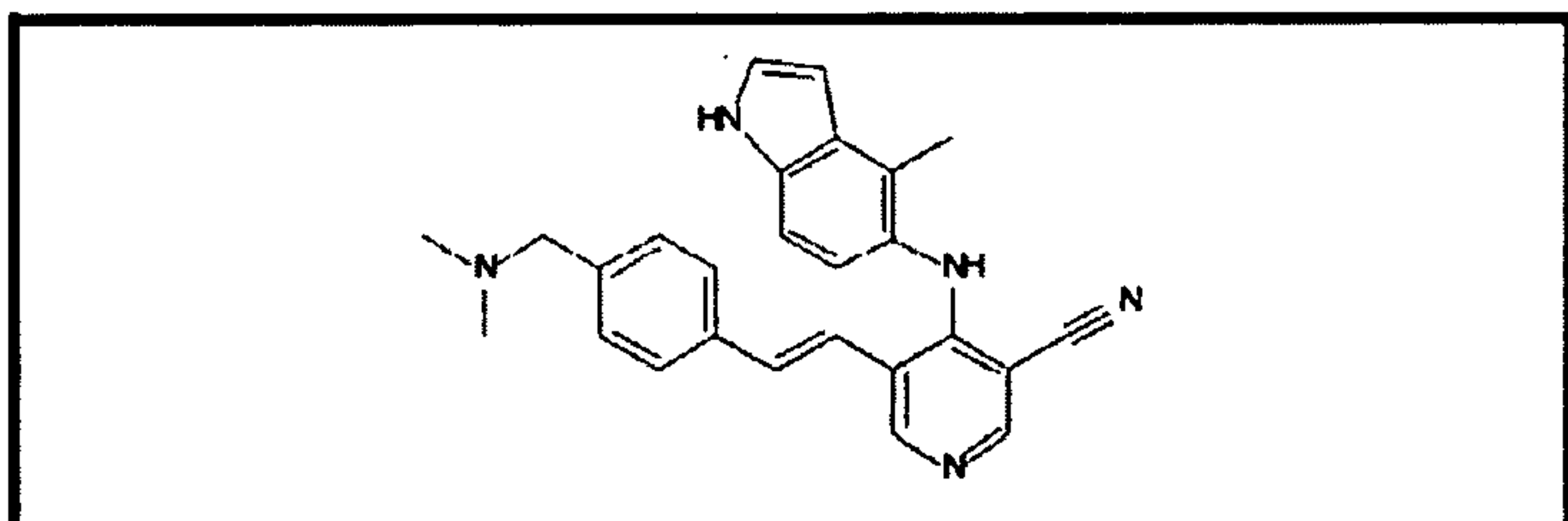
Following the procedure to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{3-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]nicotinonitrile, 5-[(E)-2-{3-[(diethylamino)methyl]phenyl}vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile was prepared via the reaction of

4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile with N-(3-bromobenzyl)-N,N-diethylamine. MS (ESI) m/z 436.1 (M+H)⁺, HPLC purity 91.1% at 215 nm, rt = 6.0 min [a].



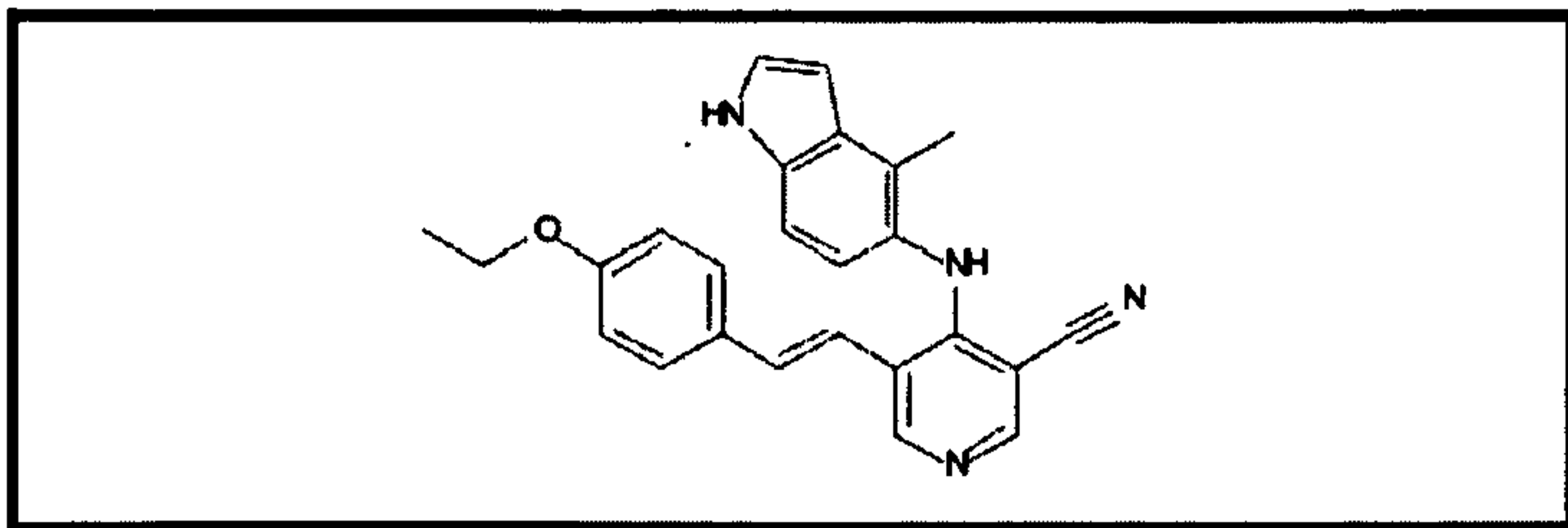
[00334] Preparation of 5-[(E)-2-{4-[(diethylamino)methyl]phenyl}vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

Following the procedure to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{3-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]nicotinonitrile, 4-[(4-methyl-1H-indol-5-yl) amino]-5-[(E)-2-{3-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]nicotinonitrile was prepared via the reaction of 4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile with N-(4-bromobenzyl)-N,N-diethylamine. MS (ESI) m/z 436.1 (M+H)⁺, HPLC purity 90.4% at 215 nm, rt = 5.9 min [a].



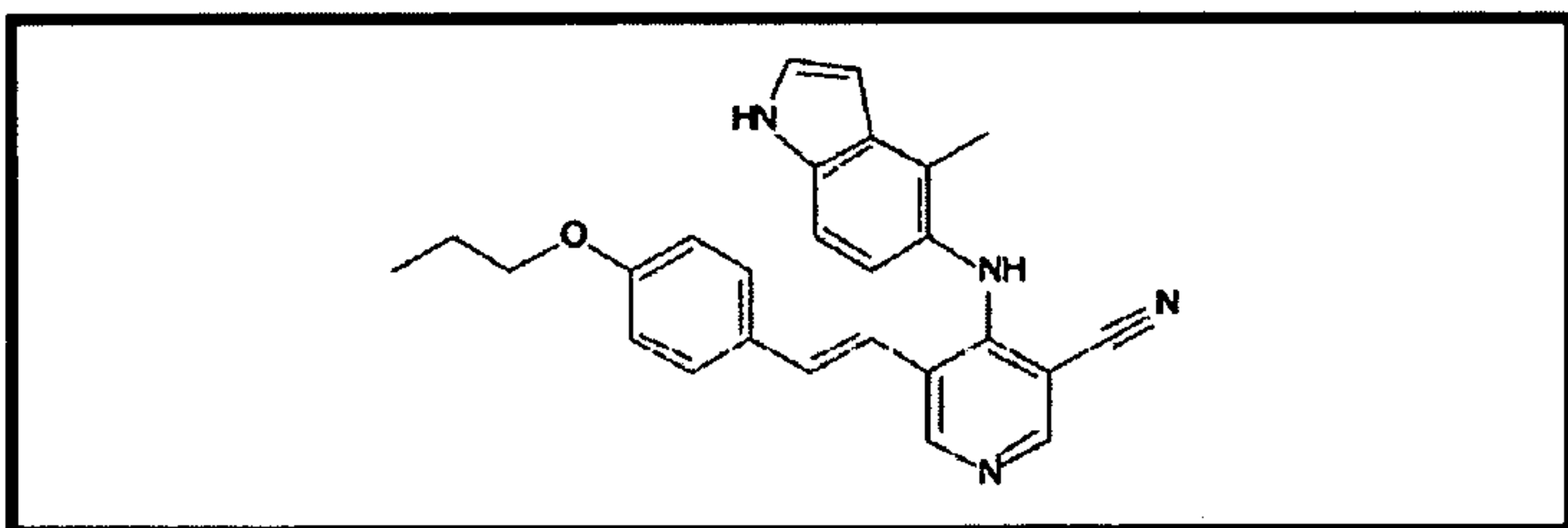
[00335] Preparation of 5-[(E)-2-{4-[(dimethylamino)methyl]phenyl}vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

Following the procedure to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{3-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]nicotinonitrile, 5-[(E)-2-{4-[(dimethylamino)methyl]phenyl}vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile was prepared via the reaction of 4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile with 1-(4-bromophenyl)-N,N-dimethylmethanamine. MS (ESI) m/z 408.2; (M+H)⁺, HPLC , rt = 5.4 min [a].



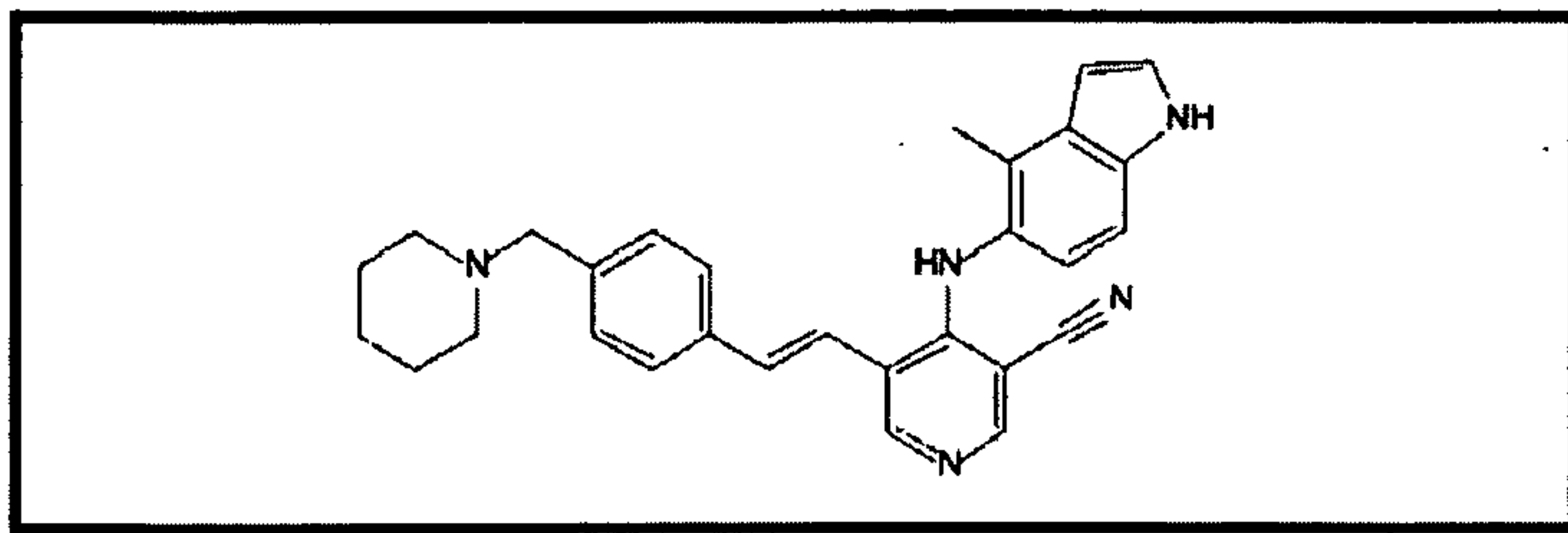
[00336] Preparation of 5-[(E)-2-(4-ethoxyphenyl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

Following the procedure to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{3-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]nicotinonitrile, 5-[(E)-2-(4-ethoxyphenyl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile was prepared via the reaction of 4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile with 4-iodophenetole. MS (ESI) m/z 395.2 ($M+H$)⁺, HPLC rt = 10.6 min [a].



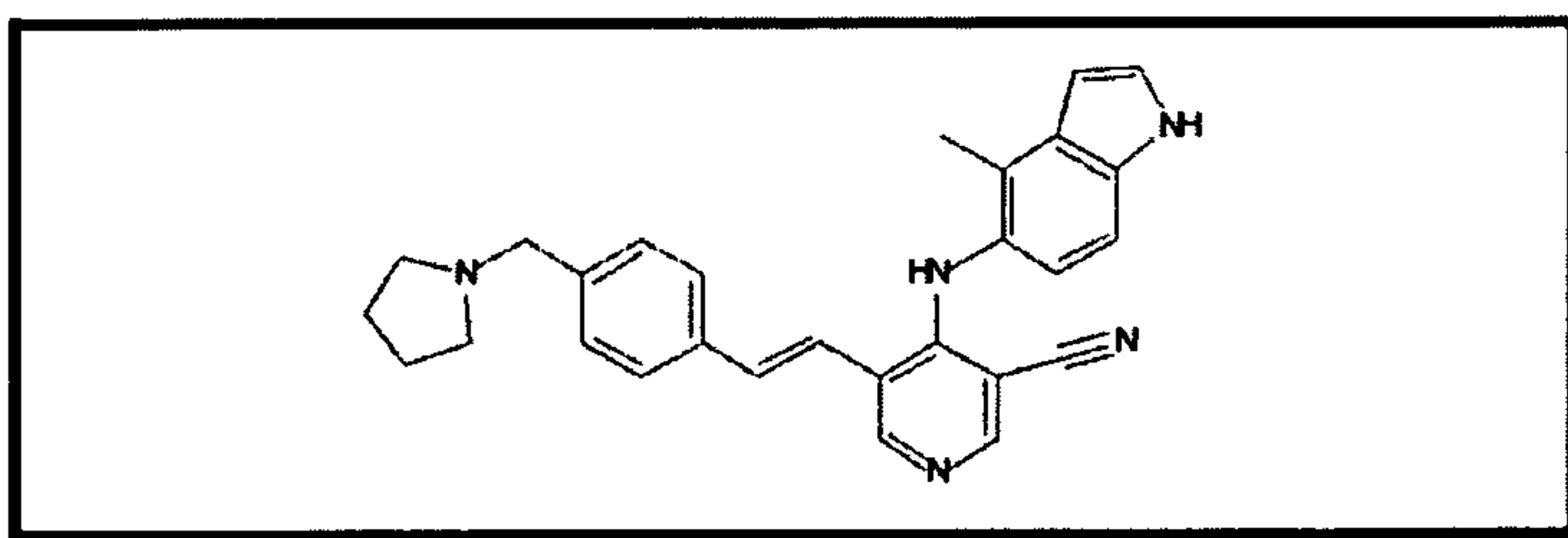
[00337] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4-propoxyphenyl)vinyl]nicotinonitrile:

Following the procedure to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{3-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]nicotinonitrile, 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4-propoxyphenyl)vinyl]nicotinonitrile was prepared via the reaction of 4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile with 4-*n*-propoxy-1-bromobenzene. MS (ESI) m/z 409.2 ($M+H$)⁺, HPLC purity 99.3% at 215 nm, rt = 11.6 min [a].



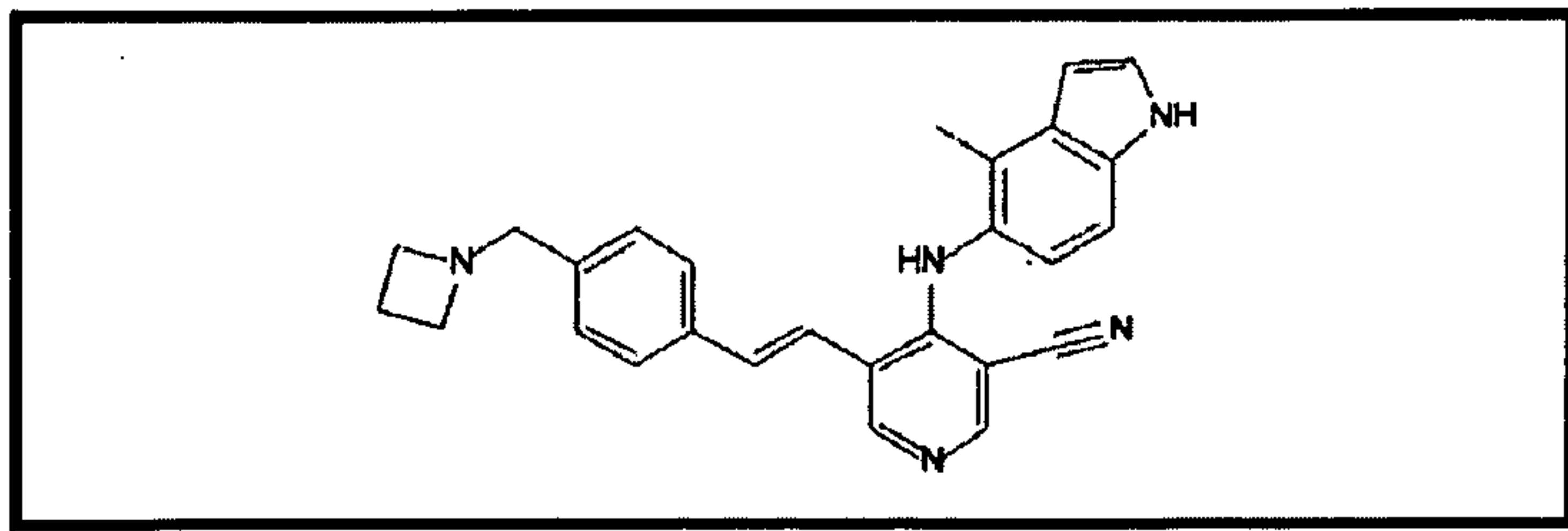
[00338] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(piperidin-1-ylmethyl)phenyl]vinyl]nicotinonitrile:

A reaction mixture of 5-[(E)-2-(4-formylphenyl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino] nicotinonitrile (70 mg, 0.185 mmol) and piperidine (79 mg, 0.926 mmol) in 3.0 mL of dichloromethane and 0.5 mL of 1-methyl-2-pyrrolidinone was stirred at room temperature for 30 minutes. To this was added $\text{NaBH}(\text{OAc})_3$ (196 mg, 0.926 mmol) over 10 min. The reaction mixture was stirred at room temperature for 20 h then concentrated. The residue was purified by HPLC (A: 0.1% NH_4OH in H_2O ; B: 0.1% NH_4OH in acetonitrile) providing 17 mg (20%) of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(piperidin-1-ylmethyl)phenyl]vinyl] nicotinonitrile as a pale yellow solid. MS 448.2 (M+H); HPLC 98% at 215 nm, rt = 6.0 min [a].



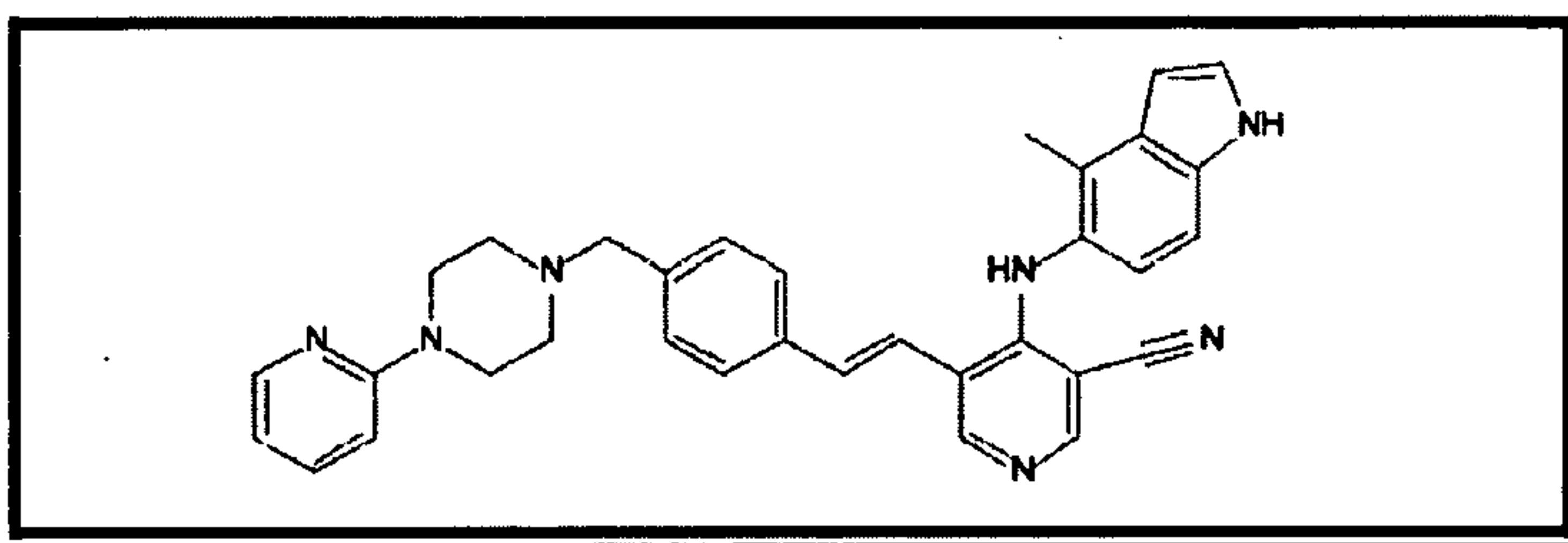
[00339] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(pyrrolidin-1-ylmethyl)phenyl]vinyl]nicotinonitrile:

The title compound was prepared from 5-[(E)-2-(4-formylphenyl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and pyrrolidine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(piperidin-1-ylmethyl)phenyl]vinyl]nicotinonitrile. MS 434.2 (M+H); HPLC 99.1 % at 215 nm, rt = 5.7 min [a].



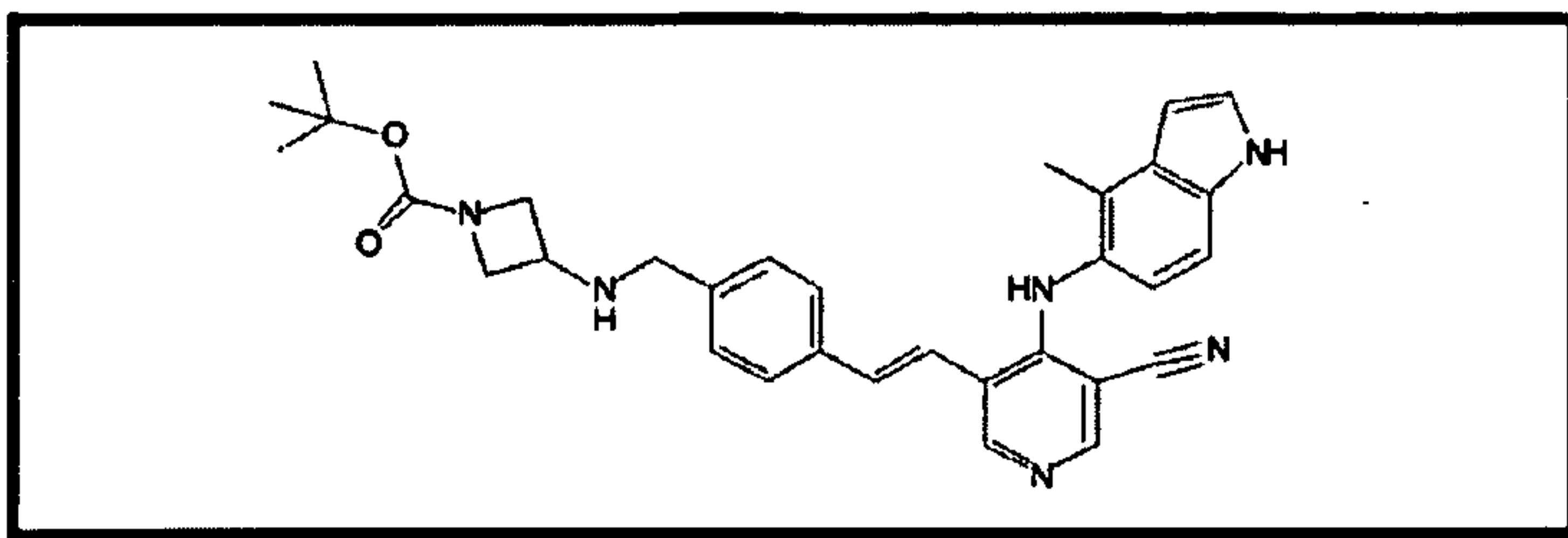
[00340] Preparation of 5-[(E)-2-[4-(azetidin-1-ylmethyl)phenyl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

The title compound was prepared from 5-[(E)-2-(4-formylphenyl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and azetidine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(piperidin-1-ylmethyl)phenyl]vinyl]nicotinonitrile. MS 420.2 (M+H); HPLC 98.3% at 215 nm, rt = 5.8 min [a].

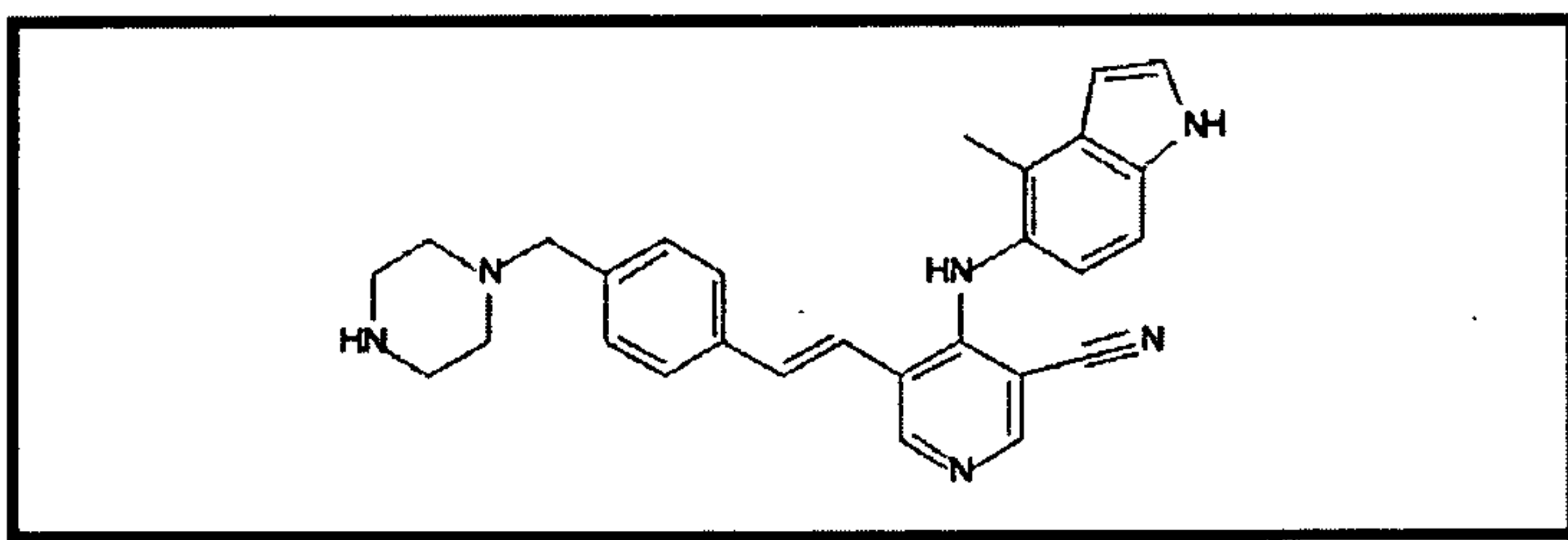


[00341] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{4-[(4-pyridin-2-yl)piperazin-1-yl)methyl]phenyl}vinyl]nicotinonitrile:

The title compound was prepared from 5-[(E)-2-(4-formylphenyl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 1-(2-pyridyl)piperazine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(piperidin-1-ylmethyl)phenyl]vinyl]nicotinonitrile. MS 526.3 (M+H); HPLC 96.8% at 215 nm, rt = 5.8 min [a].



[00342] Preparation of *tert*-butyl-3-({4-[(E)-2-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}vinyl]benzyl}amino)azetidine-1-carboxylate: The title compound was prepared from 5-[(E)-2-(4-formylphenyl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino] nicotinonitrile and *tert*-butyl 4-amino-1-azetidinecarboxylate via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-{(E)-2-[4-(piperidin-1-ylmethyl)phenyl]vinyl}nicotinonitrile. MS 535.3 (M+H); HPLC 97.5% at 215 nm, rt = 7.3 min [a].

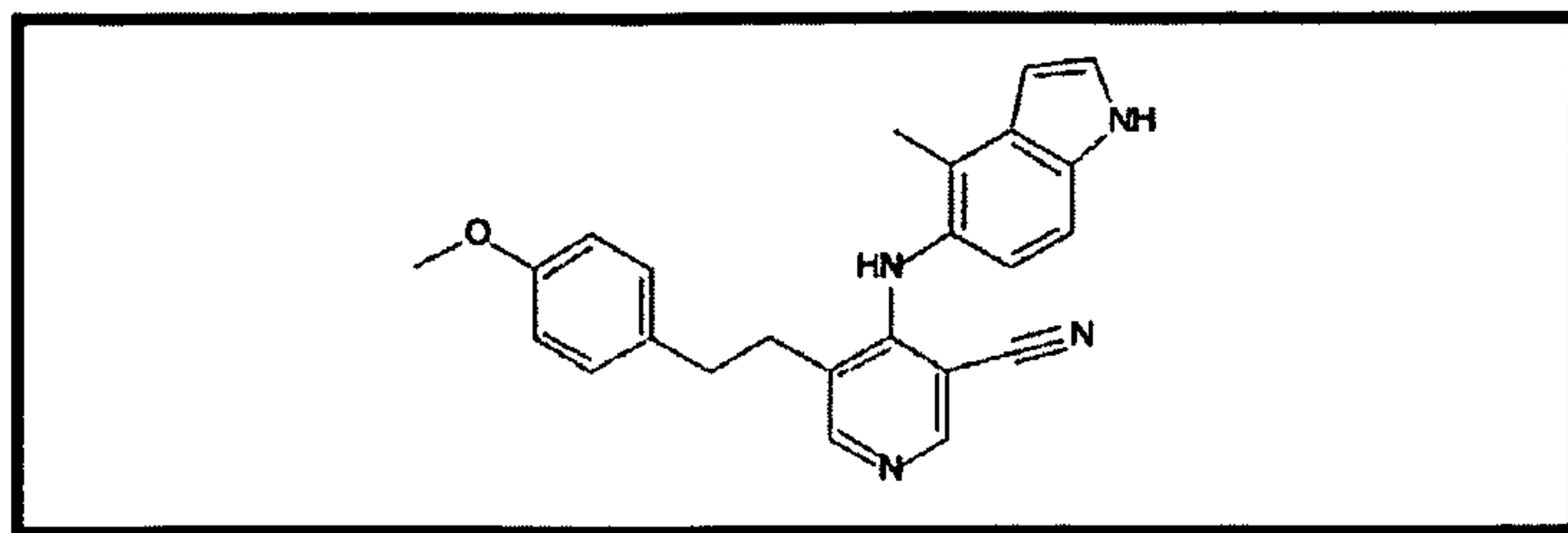


[00343] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-{(E)-2-[4-(piperazin-1-ylmethyl)phenyl]vinyl}nicotinonitrile:

tert-Butyl 4-{4-[(E)-2-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}vinyl]benzyl}piperazine-1-carboxylate was prepared from 5-[(E)-2-(4-formylphenyl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and *tert*-butyl 1-piperazinecarboxylate via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-{(E)-2-[4-(piperidin-1-ylmethyl)phenyl]vinyl}nicotinonitrile. MS 549.3.

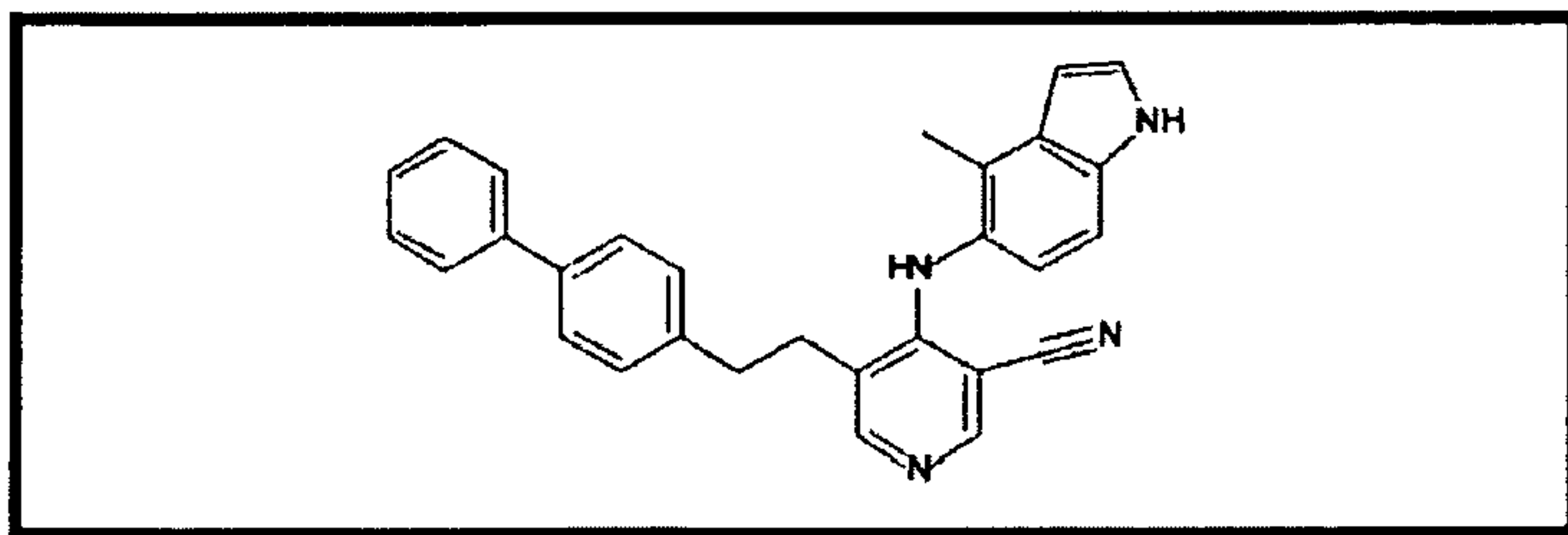
A solution of *tert*-butyl 4-{4-[(E)-2-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}vinyl]benzyl}piperazine-1-carboxylate (40 mg, 0.07 mmol) in 2.0 mL of dichloromethane was treated with trifluoroacetic acid (0.4 mL). The reaction mixture was stirred at room temperature for 3 h and subsequently concentrated. The residue was purified by preparative HPLC (A: 0.02%TFA in H₂O; B: acetonitrile) providing 34 mg (83%) of 4-[(4-methyl-1H-indol-5-yl)amino]-

5-[(E)-2-[4-(piperazin-1-ylmethyl) phenyl] vinyl]nicotinonitrile. MS (M+H) 449.3; HPLC 96.7% at 215 nm, rt = 5.2 min [a].



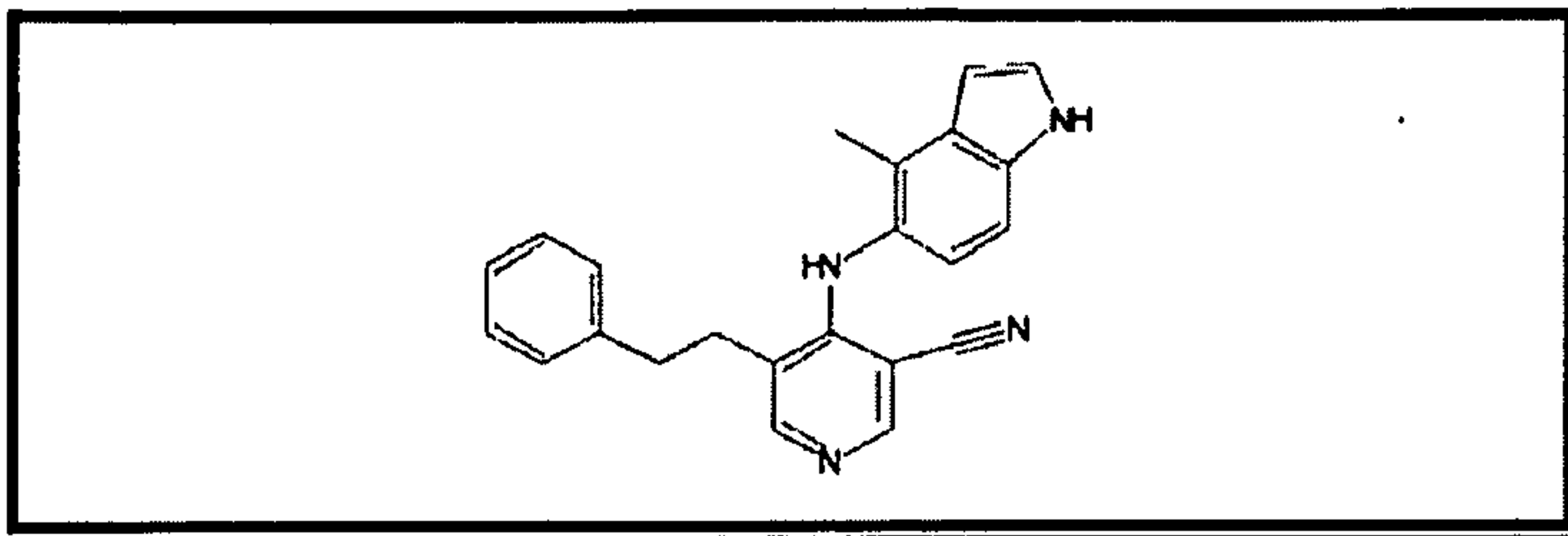
[00344] Preparation of 5-[2-(4-methoxyphenyl)ethyl]-4-[(4-methyl-1H-indol-5-yl)amino] nicotinonitrile:

A solution of 5-[(E)-2-(4-methoxyphenyl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (20 mg, 0.05 mmol) in CH₃OH (4 mL) was hydrogenated over 10% Pd/C (10 mg) at 50 psi of H₂ pressure at room temperature for 12 h then filtered through a pad of Celite under N₂. The filtrate was concentrated and the residue was dried in vacuo to give 20 mg (99%) of 5-[2-(4-methoxyphenyl)ethyl]-4-[(4-methyl-1H-indol-5-yl)amino] nicotinonitrile as a yellow solid. MS 383.2 (M+H); HPLC 84% at 215 nm, rt = 9.3 min [a].



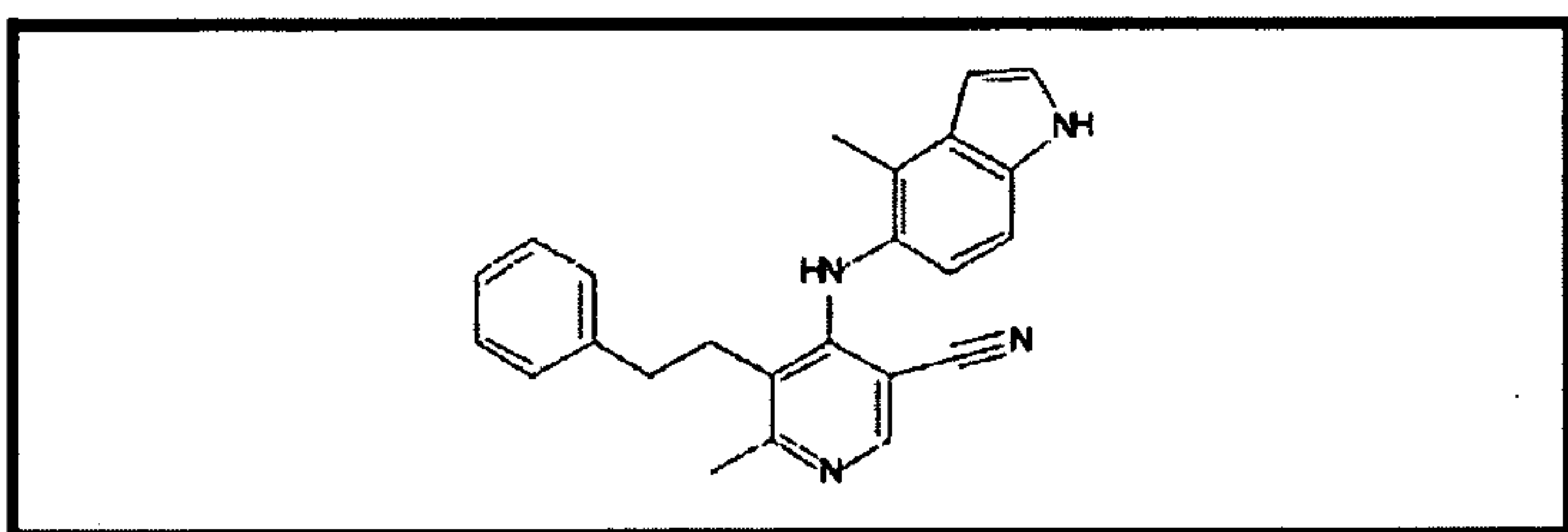
[00345] Preparation of 5-(2-biphenyl-4-ylethyl)-4-[(4-methyl-1H-indol-5-yl)amino] nicotinonitrile:

The title compound was prepared from 5-[(E)-2-biphenyl-4-ylvinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile via the procedure used to prepare 5-[2-(4-methoxyphenyl)ethyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile. MS 429.3 (M+H); HPLC 87.4 % at 215 nm, rt = 11.6 min [a].



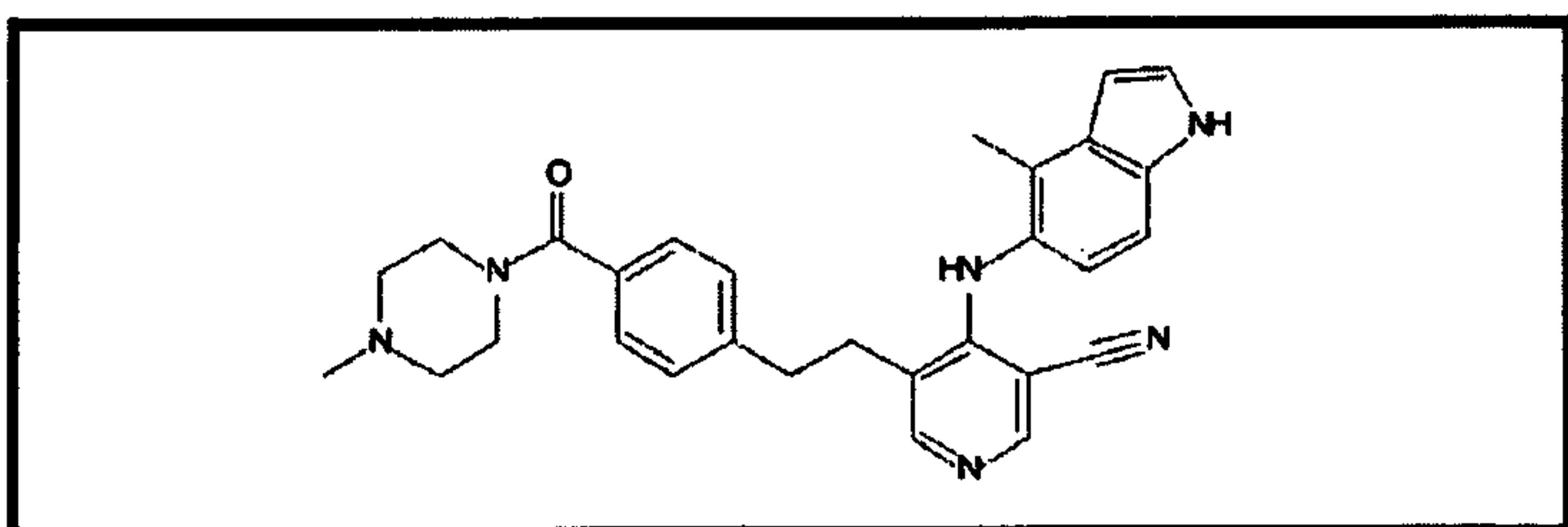
[00346] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-(2-phenylethyl)nicotinonitrile:

The title compound was prepared from 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-phenylvinyl]nicotinonitrile via the procedure used to prepare 5-[2-(4-methoxyphenyl)ethyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile. MS 353.2 (M+H); HPLC 96.6% at 215 nm, rt = 8.9 min [a].



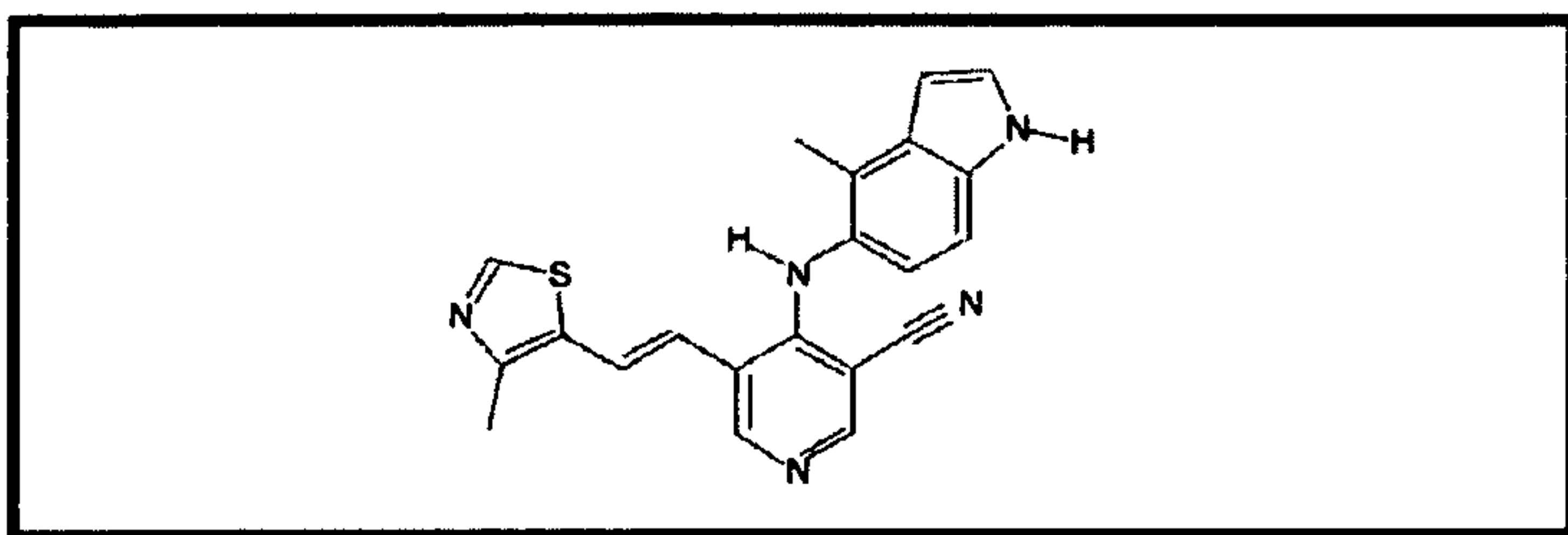
[00347] Preparation of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-(2-phenylethyl)nicotinonitrile:

The title compound was prepared from 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-phenylvinyl]nicotinonitrile via the procedure used to prepare 5-[2-(4-methoxyphenyl)ethyl]-4-[(4-methyl-1H-indol-5-yl)amino] nicotinonitrile. MS 367.2 (M+H); HPLC 97.7% at 215 nm, rt = 9.0 min [a].



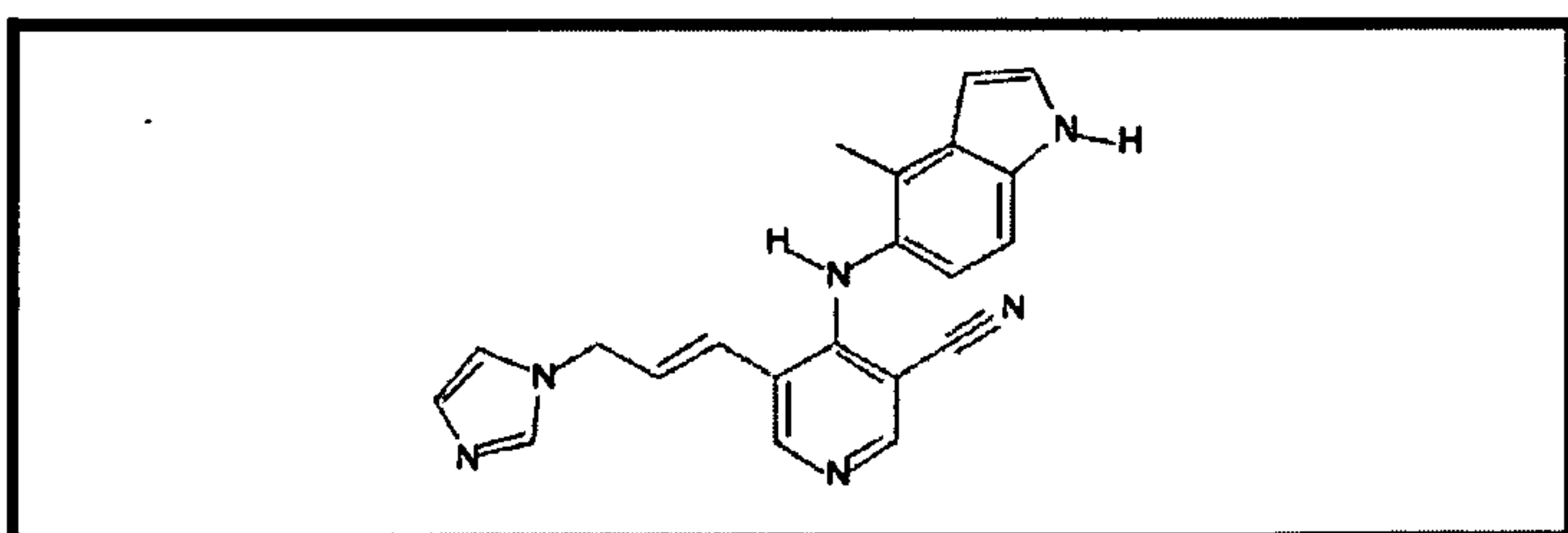
[00348] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-(2-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}ethyl)nicotinonitrile:

The title compound was prepared from 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}vinyl]nicotinonitrile via the procedure used to prepare 5-[2-(4-methoxyphenyl)ethyl]-4-[(4-methyl-1H-indol-5-yl)amino] nicotinonitrile. MS 479.2 (M+H); HPLC 95% at 215 nm, rt = 4.9 min [a].



[00349] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4-methyl-1,3-thiazol-5-yl)vinyl]nicotinonitrile:

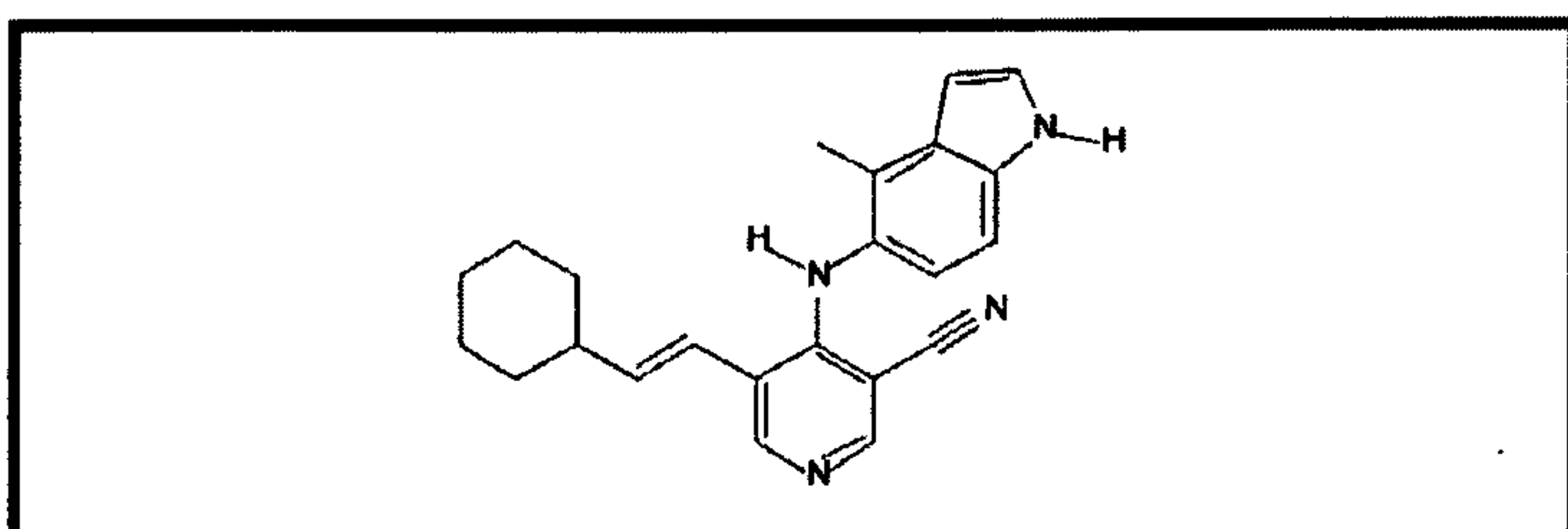
The procedure for 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-pyrazin-2-ylvinyl]nicotinonitrile was followed using 4-methyl-5-vinylthiazole (70.2 uL, 0.642 mmol). The crude residue was purified by HPLC to provide 3.3 mg (3%) of the title compound as a tan solid. MS 372.2 (M+H). HPLC rt = 7.5 min [a].



[00350] Preparation of 5-[(1E)-3-(1H-imidazol-1-yl)prop-1-en-1-yl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

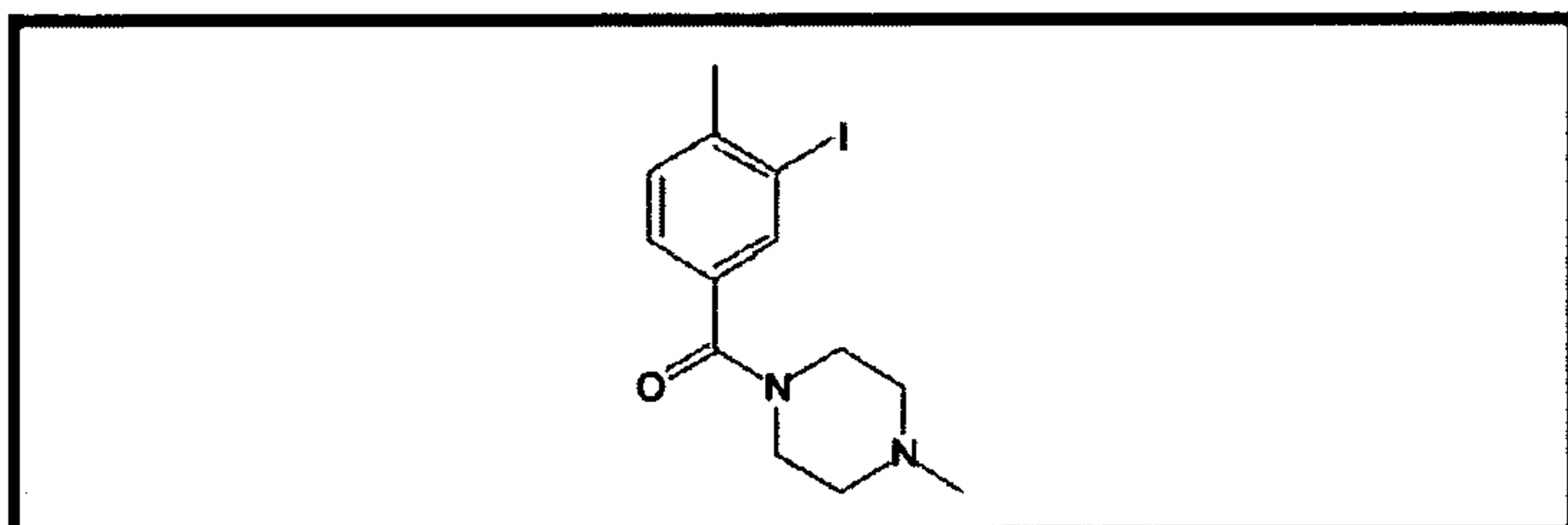
The procedure for 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-pyrazin-2-ylvinyl]nicotinonitrile was followed using 1-allylimidazole (69 uL, 0.642 mmol). The crude residue was purified by HPLC to provide 11.2 mg (10%) of the title compound as a tan solid. ¹H NMR (400 MHz,

DMSO- d_6) 2.30 (s, 3H), 4.72 (d, $J = 4$ Hz, 2H), 6.36 (m, 1H), 6.52 (bs, 1H), 6.85 (d, $J = 16$ Hz, 1H), 6.91 (m, 2H), 7.24 (m, 2H), 7.36 (bs, 1H), 7.71 (bs, 1H), 8.27 (s, 1H), 8.34 (s, 1H), 8.68 (s, 1H), 11.16 (s, 1H); MS 355.2 (M+H).



[00351] Preparation of 5-[(E)-2-cyclohexylvinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

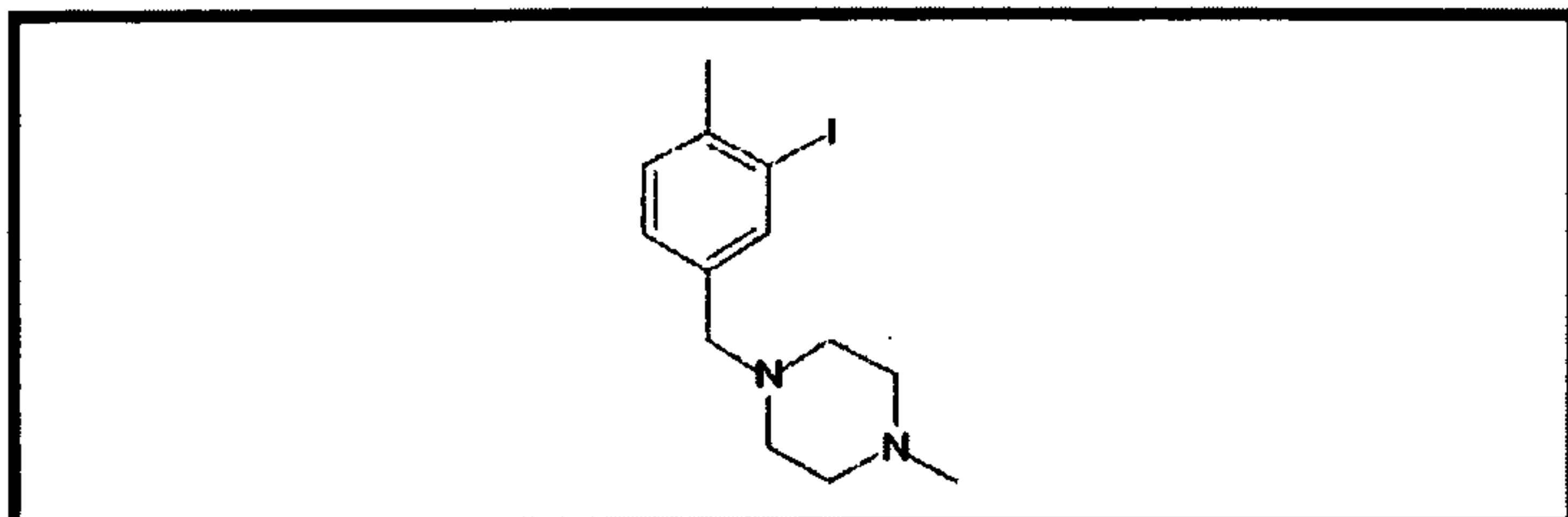
The procedure for 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-pyrazin-2-ylvinyl]nicotinonitrile was followed using vinylcyclohexane (88 μ L, 0.642 mmol). The crude residue was purified by HPLC to provide 3.0 mg (3%) of the title compound as a tan solid. MS 357.2 (M+H). HPLC t_r = 11.1 min [a].



[00352] Preparation of 1-(3-iodo-4-methylbenzoyl)-4-methylpiperazine:

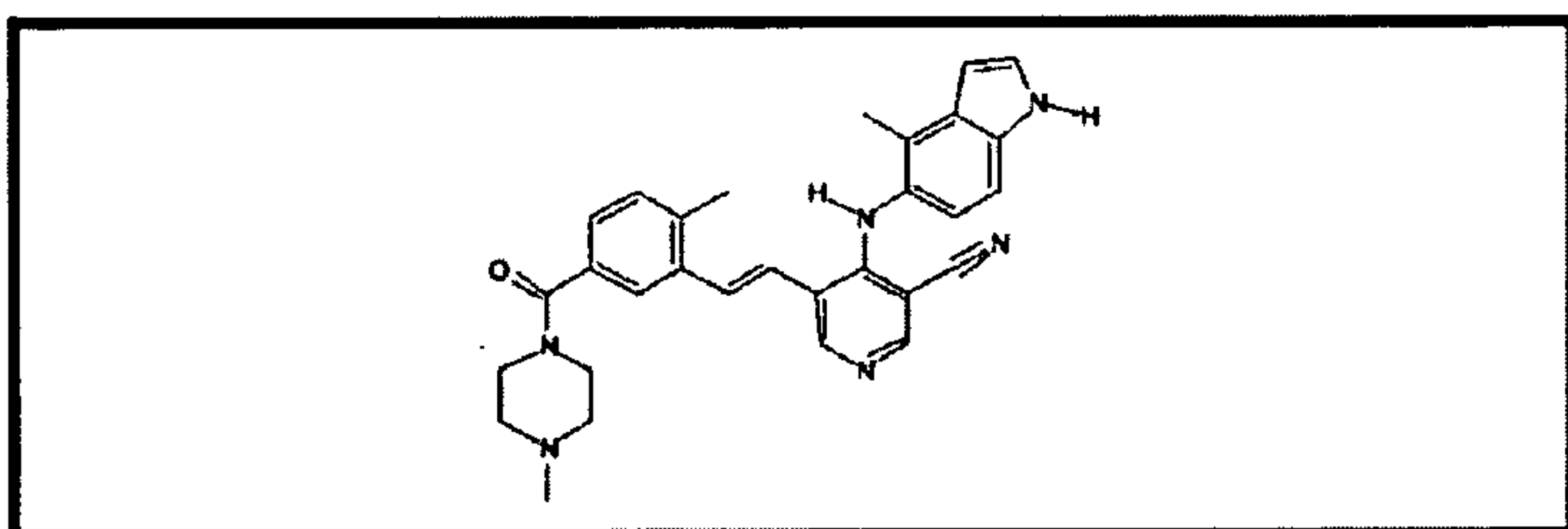
A mixture of 3-iodo-4-methylbenzoic acid (5.24 g, 20.0 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (4.22 g, 22 mmol) and DIEA (10.5 mL, 60 mmol) in dichloromethane (100 mL) was stirred for 10 minutes, after which N-methylpiperazine (2.44 mL, 22 mmol) was added. The reaction was stirred for 18 h before being washed with water (3 x 50 mL), 0.1 N aq. NaOH (2 x 50 mL) and brine (2 x 50 mL). The solution was dried with anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography using 100:10:1 DCM/MeOH/aq. NH_4OH to provide 3.54 g (52%) of the title

compound as a white solid. ^1H NMR (400 MHz, CDCl_3) 2.32-2.45 (m, 10H), 3.45 (m, 2 H), 3.76 (m, 2H), 7.26 (bs, 2H), 7.86 (s, 1H); MS 345.0 (M+H).



[00353] Preparation of 1-(3-iodo-4-methylbenzyl)-4-methylpiperazine:

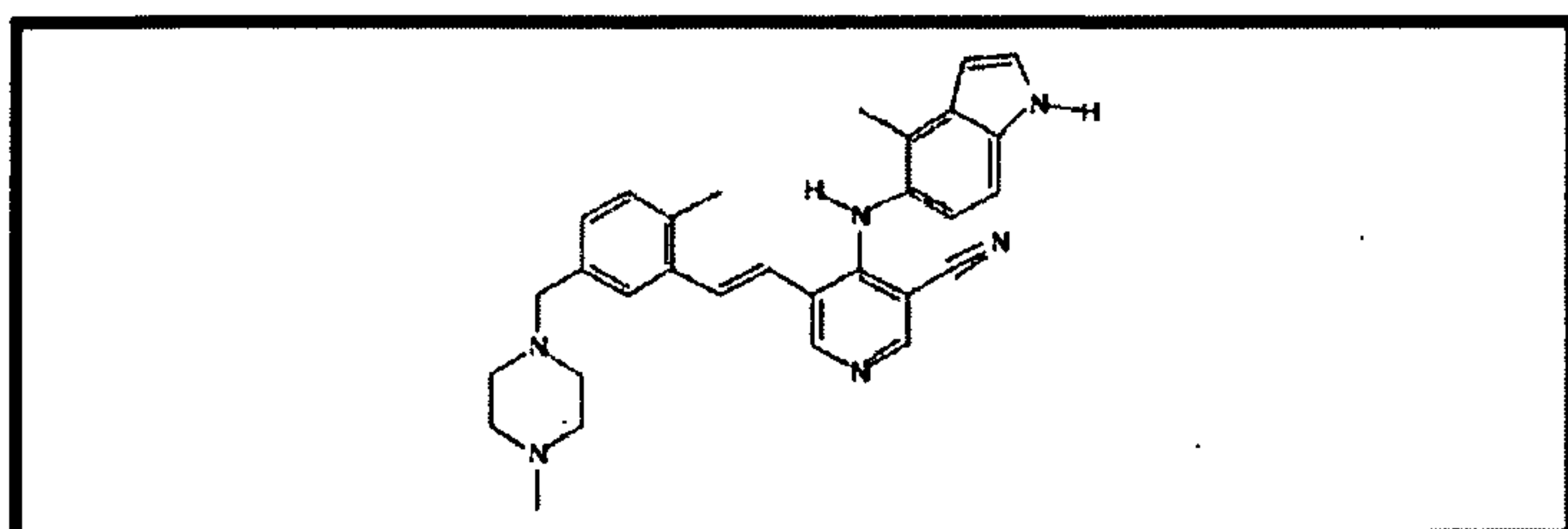
To a THF solution (5 mL) of 1-(3-iodo-4-methylbenzoyl)-4-methylpiperazine (300 mg, 0.87 mmol) at room temperature was added 1 M BH_3 -THF (2.6 mL, 2.6 mmol). The solution was heated to reflux for one hour. After cooling to room temperature, ethanol (2 mL) was added carefully. The solution was concentrated *in vacuo* and the residue purified by flash chromatography with 1:1 EtOAc/hexane to provide 172 mg (62%) of the title compound as a white solid. ^1H NMR (400 MHz, CDCl_3) 2.41 (s, 3H), 2.46-2.50 (m, 2 H), 2.63 (s, 3H), 2.74-2.83 (m, 4 H), 3.06-3.10 (m, 2 H), 3.49 (s, 2H), 7.25 (bs, 2H), 7.76 (s, 1H); MS 331.0 (M+H).



[00354] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{2-methyl-5-[(4-methylpiperazin-1-yl)carbonyl]phenyl}vinyl]nicotinonitrile:

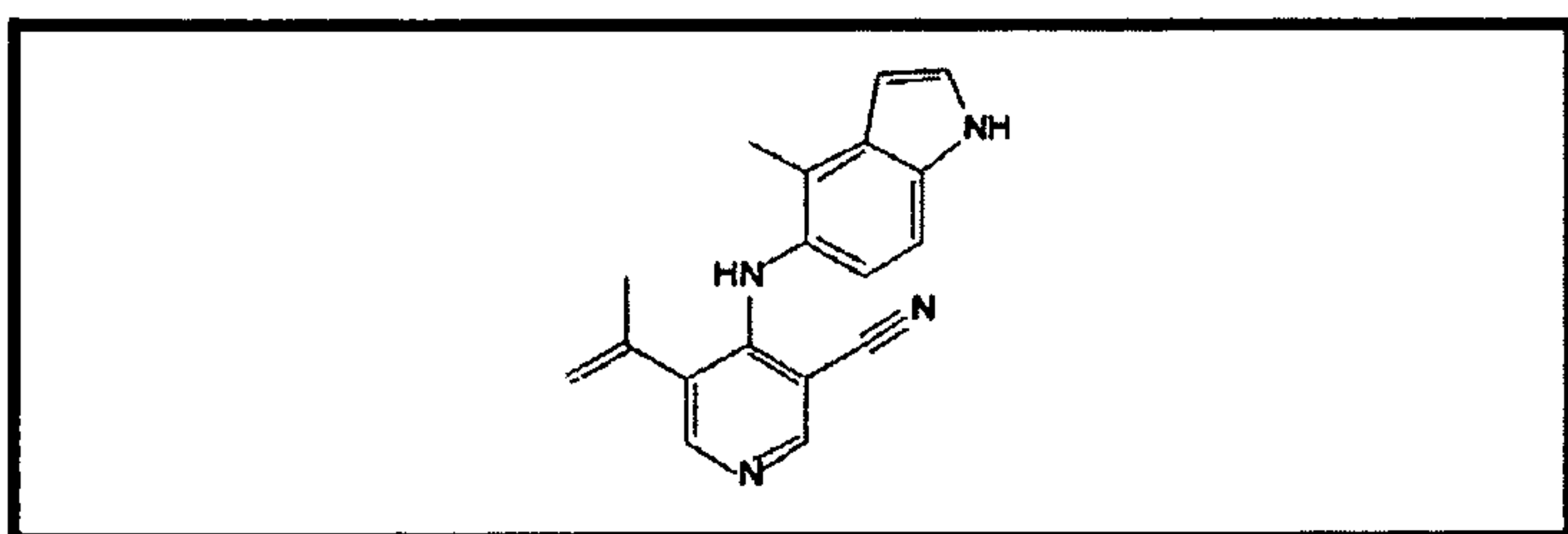
A mixture of 4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile (151 mg, 0.55 mmol), $\text{Pd}(\text{OAc})_2$ (22.5 mg, 0.1 mmol), $\text{P}(o\text{-Tol})_3$ (22.5 mg, 0.035 mmol), 1-(3-iodo-4-methylbenzoyl)-4-methylpiperazine (172 mg, 0.5 mmol), triethylamine (0.7 mL) and DMF (2.5 mL) was heated to 120° C for 3 hours. The cooled solution was diluted with EtOAc (100 mL), washed with water (3 x 20 mL), dried over anhydrous MgSO_4 , filtered and concentrated *in vacuo*. The residue was purified by flash chromatography using 100:10:1 dichloromethane/methanol/aq.

NH₄OH to provide 117 mg (48%) of the title compound as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) 2.18 (s, 3H), 2.33 (s, 3H), 2.47 (s, 3H), 3.34 (m, 8H), 6.54 (bs, 1H), 6.94 (d, *J* = 8 Hz, 1H), 7.20 (m, 3H), 7.40 (m, 3H), 7.86 (s, 1H), 8.28 (s, 1H), 8.64 (s, 1H), 8.92 (s, 1H), 11.20 (s, 1H); MS 491.4 (M+H).



[00355] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{2-methyl-5-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]nicotinonitrile:

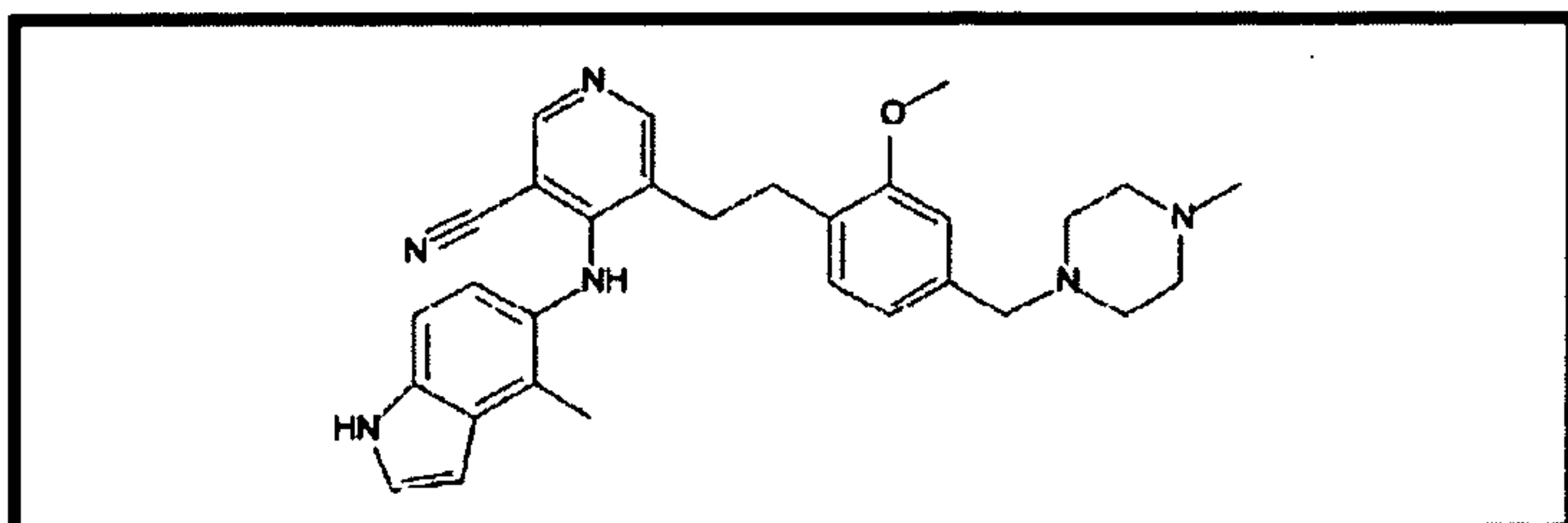
The procedure for 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{2-methyl-5-[(4-methylpiperazin-1-yl)carbonyl]phenyl}vinyl]nicotinonitrile was followed using 1-(3-iodo-4-methylbenzyl)-4-methylpiperazine (165 mg, 0.5 mmol). Flash chromatography provided 83.5 mg (35%) of the title compound as an amber glass. ¹H NMR (400 MHz, DMSO-*d*₆) 2.27 (s, 3H), 2.33 (s, 3H), 2.40 (s, 3H), 3.33 (m, 8H), 3.43 (bs, 2H), 6.53 (m, 1H), 6.95 (d, *J* = 8 Hz, 1H), 7.14 (m, 3H), 7.25 (d, *J* = 8 Hz, 1H), 7.31 (d, *J* = 4 Hz, 1H), 7.36 (m, 1H), 7.56 (s, 1H), 8.29 (s, 1H), 8.60 (s, 1H), 8.86 (s, 1H), 11.16 (s, 1H); MS 477.4 (M+H).



[00356] Preparation of 5-isopropenyl-4-[(4-methyl-1H-indol-5-yl)amino] nicotinonitrile:

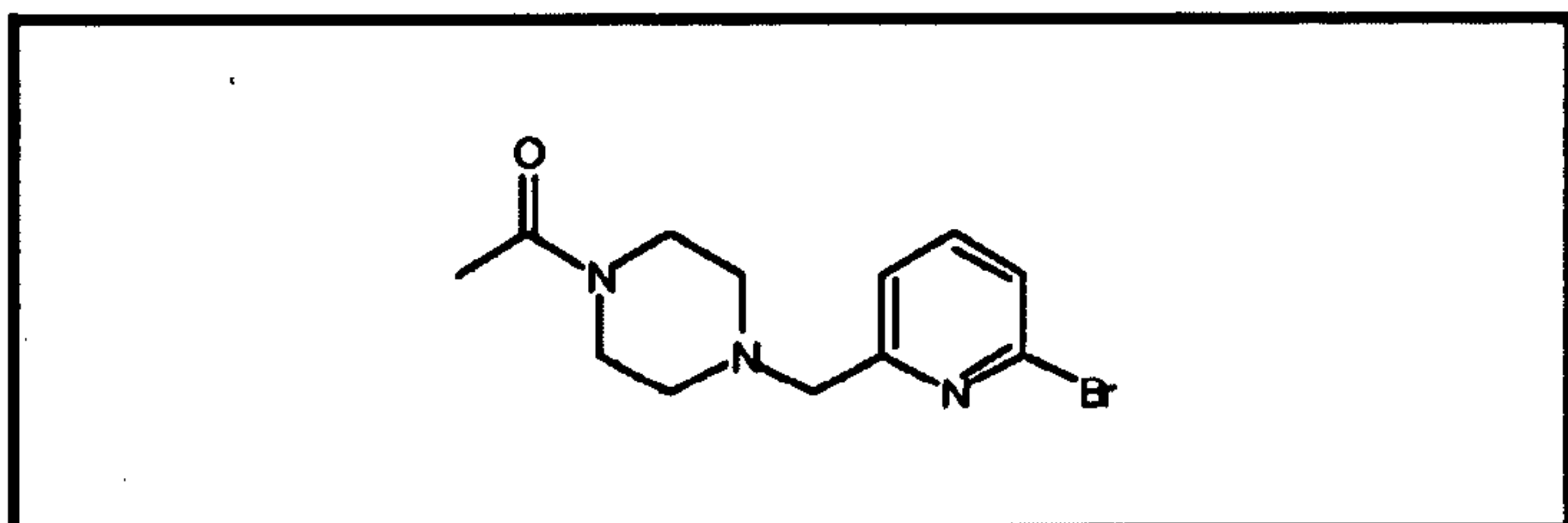
A mixture of 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (351 mg, 0.94 mmol), Pd(PPh₃)₄ (37 mg, 0.03 mmol) and 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (201 mg, 1.13 mmol) in 1,2-dimethoxyethane (5 mL) and saturated NaHCO₃ (5 mL) was heated to 80 °C for 20 h. The resulting mixture was cooled to room temperature. The reaction

was diluted with ethyl acetate (30 mL) and washed with sodium bicarbonate solution (30 mL) and brine (30 mL) sequentially. The organic phase was dried over magnesium sulfate and filtered through magneson. Flash column chromatography on silica gel (ethyl acetate-hexanes 1:1) afforded 231 mg (85 %) of the title compound; MS 289.2 (M+H). HPLC rt = 6.8 min [a].



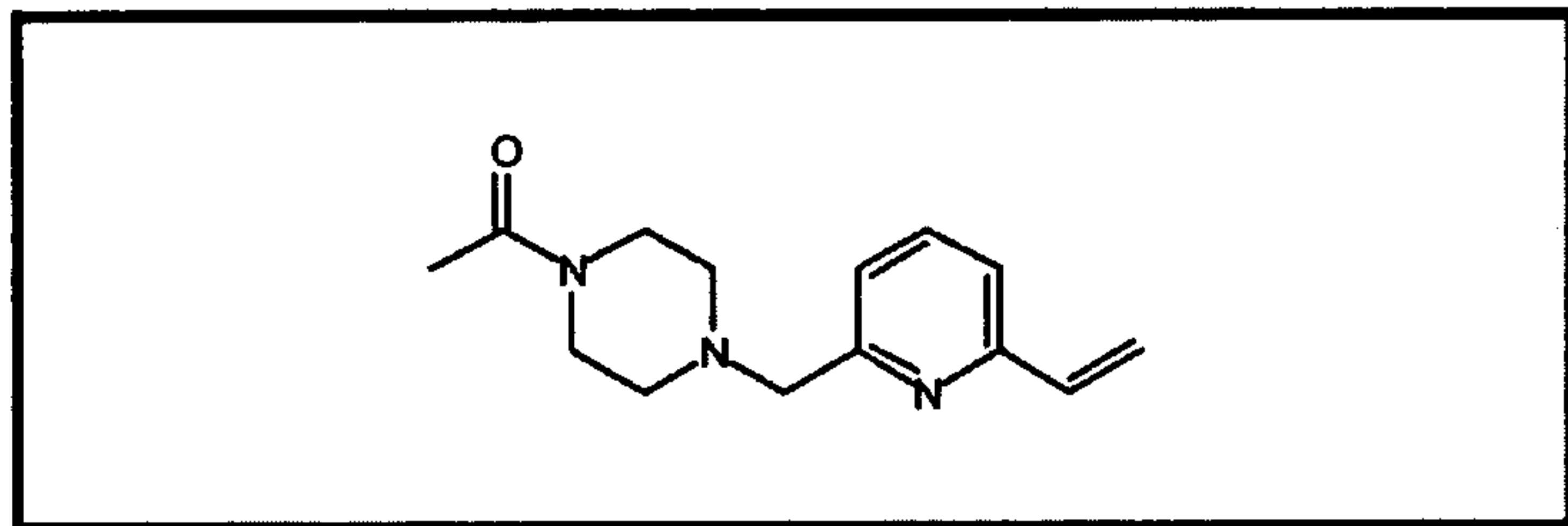
[00357] Preparation of 5-(2-(2-methoxy-4-((4-methylpiperazin-1-yl)methyl)phenyl)ethyl)-4-((4-methyl-1H-indol-5-yl)amino)nicotinonitrile:

4-((4-Methyl-1H-indol-5-yl)amino)-5-vinylnicotinonitrile (300 mg, 1.094 mmol) was dissolved in a mixture of DMF (3 ml) and triethylamine (0.75 ml) and subsequently treated with 1-(4-iodo-3-methoxybenzyl)-4-methylpiperazine (380 mg, 1.098 mmol), Pd(OAc)₂ (50 mg, 0.223 mmol) and P(o-Tol)₃ (17 mg, 0.056 mmol). The reaction mixture was stirred at 120 °C under nitrogen for 4 hr. Upon cooling to room temperature, the reaction was diluted with dichloromethane, washed with saturated aqueous sodium bicarbonate, dried over MgSO₄ and concentrated to give a dark residue. The residue was redissolved in methanol (20 ml) and treated with Pd/C (10% wt., 40 mg). The reaction was shaken under hydrogen gas (45 psi) for 18 hr. The resulting crude compound was purified by HPLC to give 12.5 mg (2.3%) of 5-(2-(2-methoxy-4-((4-methylpiperazin-1-yl)methyl)phenyl)ethyl)-4-((4-methyl-1H-indol-5-yl)amino)nicotinonitrile as a light tan solid. MS 495.2 (M+H); HPLC rt = 3.1 min [e].

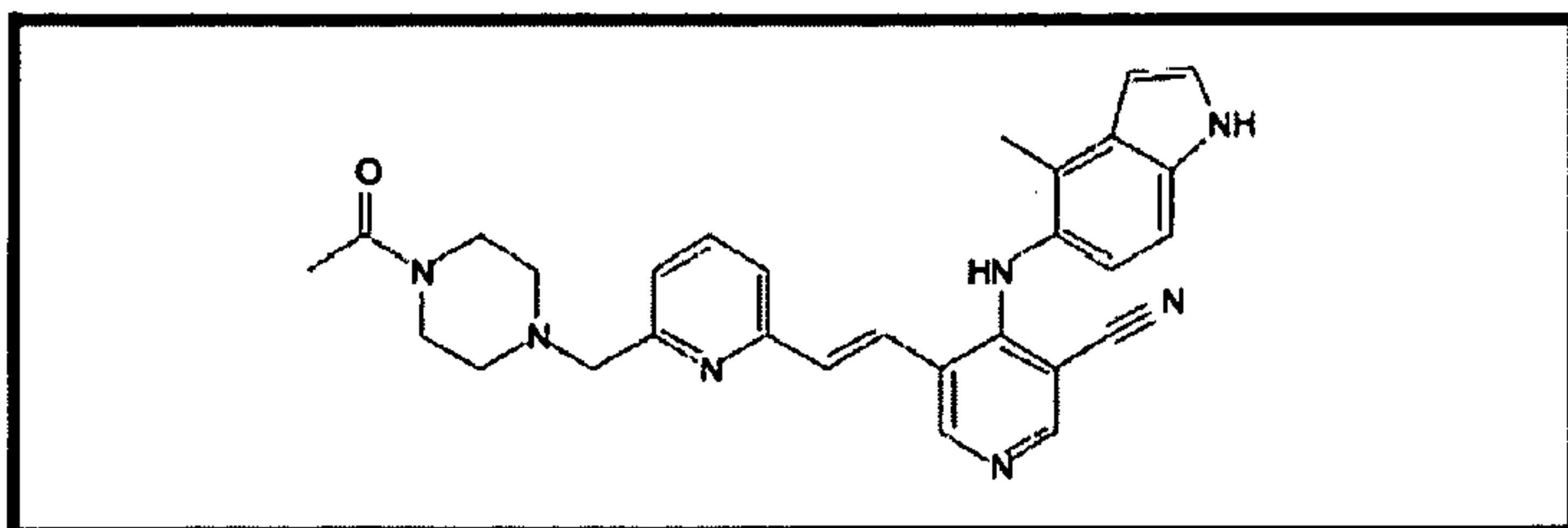


[00358] Preparation of 1-acetyl-4-[(6-bromopyridin-2-yl)methyl]piperazine:

6-Bromopyridine-2-carboxaldehyde (2.0 g, 10.75 mmol) and 1-acetylpiperazine (6.9 g, 53.75 mmol) were dissolved in THF (120 ml). Upon cooling to 0°C, sodium triacetoxyborohydride (11.39 g, 53.74 mmol) was added to the reaction solution with a catalytic amount of HOAc. The mixture was slowly warmed to room temperature and was stirred at room temperature overnight. The suspension was filtered, and the filtrate was diluted with dichloromethane, washed with saturated aqueous sodium bicarbonate, dried over MgSO₄ and concentrated to give a light color syrup. The syrup was purified by column chromatography, eluting with 10-15% gradient of methanol in dichloromethane, to give 2.36 g (88%) of 1-acetyl-4-[(6-bromopyridin-2-yl)methyl]piperazine as a light color syrup. MS 298.1 (M+H); HPLC rt = 3.6 min [a].

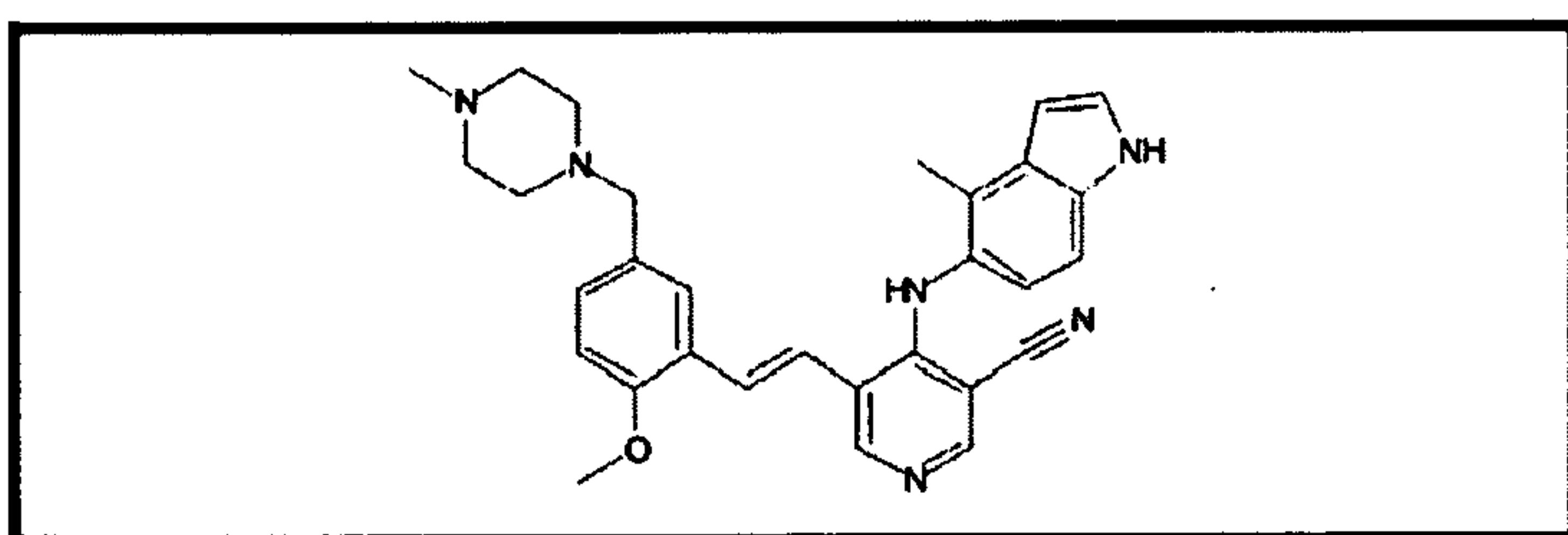
**[00359] Preparation of 1-acetyl-4-[(6-vinylpyridin-2-yl)methyl]piperazine:**

1-acetyl-4-[(6-bromopyridin-2-yl)methyl]piperazine (500 mg, 1.677 mmol) and tributylvinyltin (0.98 ml, 3.356 mmol) were dissolved in anhydrous toluene (10 ml). The solution was treated with Pd(PPh₃)₂Cl₂ (59 mg, 0.084 mmol) and CuI (16 mg, 0.084 mmol) and was heated to reflux overnight. Upon cooling, the reaction was filtered and the filtrate was partitioned between dichloromethane and saturated aqueous sodium bicarbonate then dried over MgSO₄ and concentrated to give a yellow syrup. The crude compound was purified by column chromatography, eluting with 5-15% gradient methanol in dichloromethane, to give 163 mg (40%) of 1-acetyl-4-[(6-vinylpyridin-2-yl)methyl]piperazine as a brown syrup. MS 246.2 (M+H); HPLC rt = 10.5 min [a].



[00360] Preparation of 5-[(E)-2-{6-[(4-acetylpiperazin-1-yl)methyl]pyridin-2-yl} vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

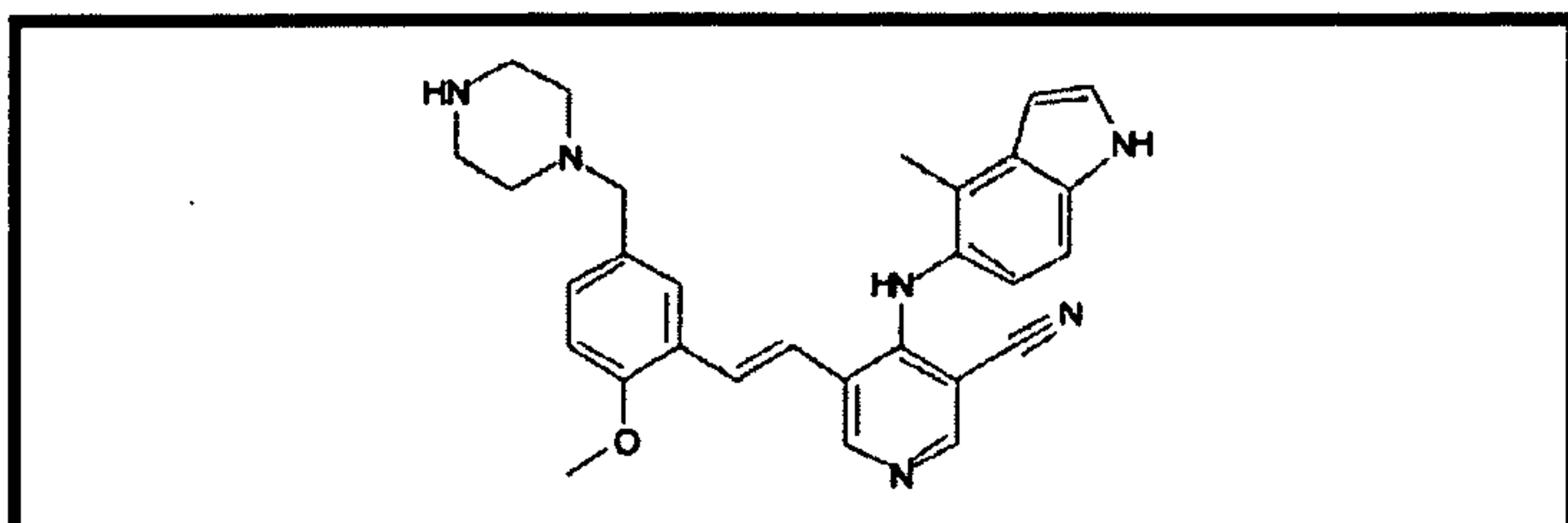
5-Iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (164 mg, 0.438 mmol) was dissolved in a mixture of DMF (2 ml) and triethylamine (0.5 ml) and treated with 1-acetyl-4-[(6-vinylpyridin-2-yl)methyl]piperazine (129 mg, 0.526 mmol), Pd(OAc)₂ (20 mg, 0.089 mmol) and P(o-Tol)₃ (7.0 mg, 0.023 mmol). The reaction mixture was stirred at 100 °C under nitrogen for 2 hr. The reaction was cooled to room temperature and diluted with dichloromethane, washed with saturated aqueous sodium bicarbonate, dried over MgSO₄ and concentrated to give a dark residue. The resulting crude compound was purified by column chromatography, eluting with 5-10% gradient methanol in dichloromethane, to give 100 mg (46%) of 5-[(E)-2-{6-[(4-acetylpiperazin-1-yl)methyl]pyridin-2-yl} vinyl]-4-[(4-methyl-1H-indol-5-yl)amino] nicotinonitrile as a yellow solid. MS 492.4 (M+H); HPLC rt = 5.1 min [a].



[00361] Preparation of 5-[(E)-2-{2-methoxy-5-[(4-methylpiperazin-1-yl)methyl]phenyl} vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

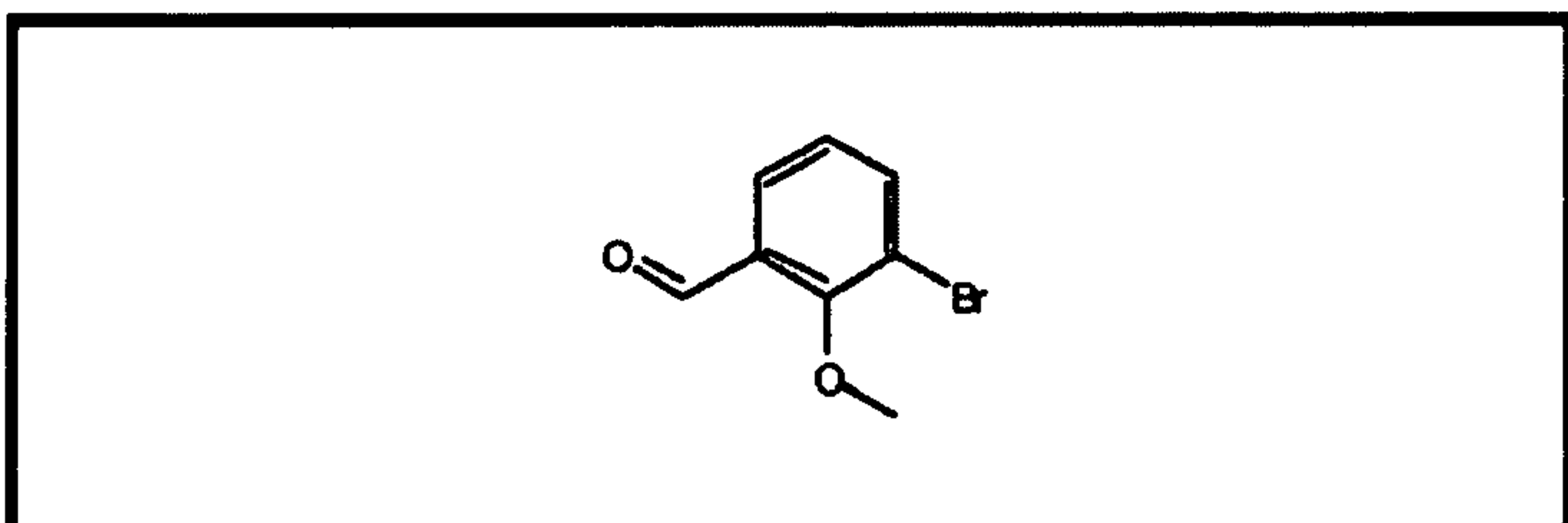
4-[(4-Methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile (100 mg, 0.36 mmol) was dissolved in a mixture of DMF (2 ml) and triethylamine (0.5 ml). 1-(3-Iodo-4-methoxybenzyl)-4-methylpiperazine (151 mg, 0.44 mmol), Pd(OAc)₂ (16 mg, 0.07 mmol) and P(o-Tol)₃ (6.0 mg, 0.02 mmol) were added and the reaction mixture was stirred at 120 °C under nitrogen for 8 hr. Upon cooling to room temperature, the reaction was diluted with dichloromethane, washed

with saturated aqueous sodium bicarbonate, dried over MgSO_4 and concentrated to give a dark residue. The resulting crude compound was purified by HPLC to give 78 mg (43%) of 5-[(E)-2-{2-methoxy-5-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile as a yellow solid. MS 493.4 (M+H); HPLC t_r = 5.7 min [a].



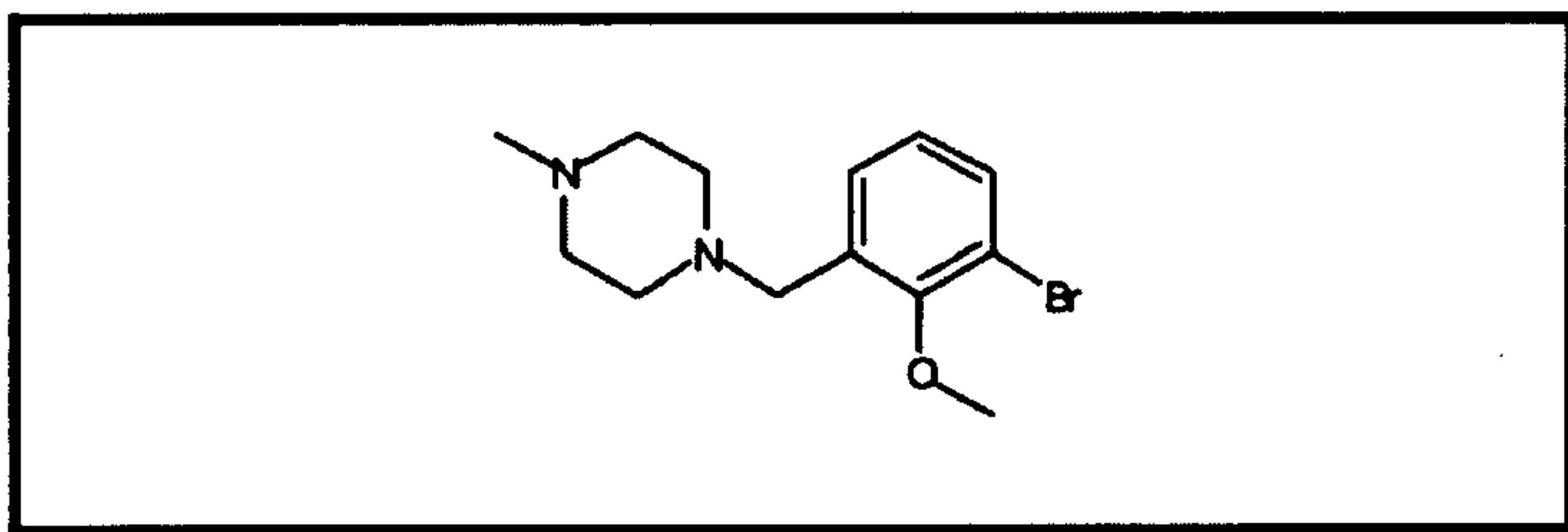
[00362] Preparation of 5-[(E)-2-[2-methoxy-5-(piperazin-1-ylmethyl) phenyl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

4-[(4-Methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile (200 mg, 0.73 mmol) was dissolved in a mixture of DMF (2 ml) and triethylamine (0.5 ml). *Tert*-Butyl 4-(3-iodo-4-methoxybenzyl)piperazine-1-carboxylate (380 mg, 0.88 mmol), $\text{Pd}(\text{OAc})_2$ (33 mg, 0.15 mmol) and $\text{P}(o\text{-Tol})_3$ (11mg, 0.04 mmol). The reaction mixture was stirred at 120°C under nitrogen for 8 hr then cooled to room temperature and diluted with dichloromethane. The solution was washed with saturated aqueous sodium bicarbonate, dried over MgSO_4 and concentrated to give a dark residue. The residue was redissolved in dichloromethane and trifluoroacetic acid (ratio 4:1) and stirred at room temperature for 2 hr. The reaction was quenched with saturated aqueous sodium bicarbonate, dried over MgSO_4 and concentrated to give a dark syrup. The resulting crude compound was purified by HPLC to give 12 mg (3.4%) of 5-[(E)-2-[2-methoxy-5-(piperazin-1-ylmethyl)phenyl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile as a yellow solid. MS 479.4 (M+H); HPLC t_r = 5.4 min [a].

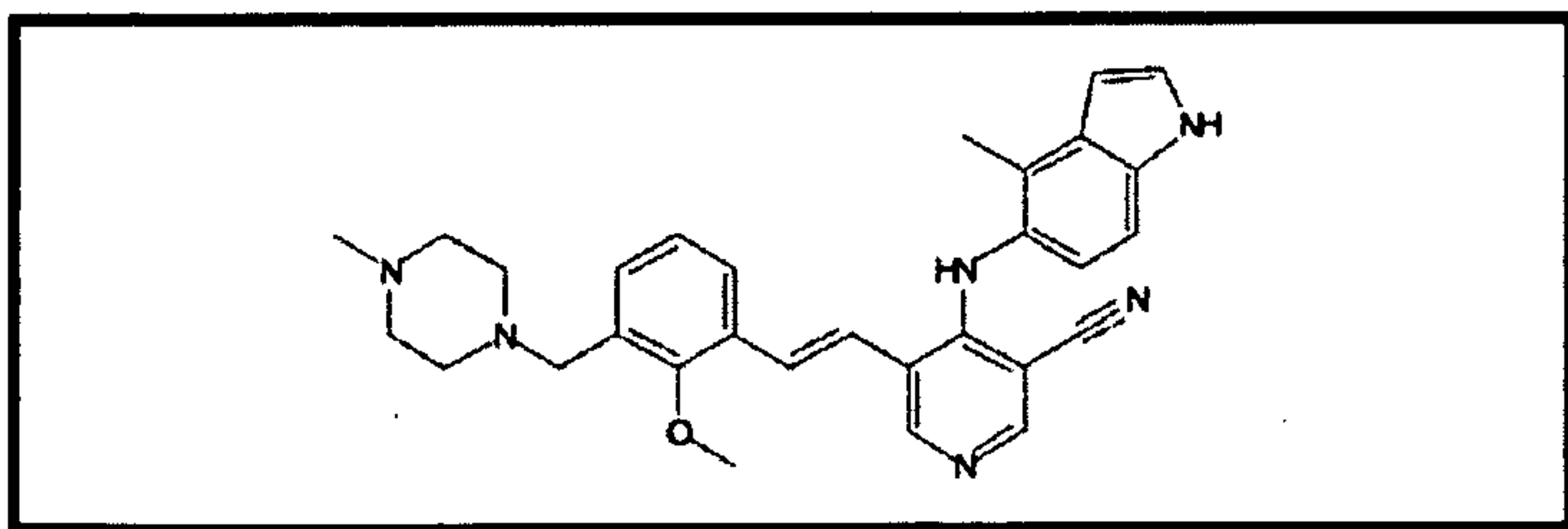


[00363] Preparation of 3-bromo-2-methoxybenzaldehyde:

3-Bromo-2-hydroxybenzaldehyde (5.0 g, 24.87 mmol) was dissolved in acetone (200 ml) and treated with iodomethane (5.3 g, 37.34 mmol) and potassium carbonate (5.2 g, 37.63 mmol). The mixture was heated to 60° C for 2 hr then cooled to room temperature and filtered. The filtrate was concentrated to dryness and re-dissolved in ethyl acetate. The solution was washed with saturated aqueous sodium bicarbonate and dried over MgSO₄. After concentration, the residue was passed through a layer of silica gel, which was eluted with 50% ethyl acetate in hexanes. The eluent was concentrated to give 2.0 g (93%) of 3-bromo-2-methoxybenzaldehyde as a colorless syrup. MS 215.0 (M+H); HPLC rt = 13.8 min [a].

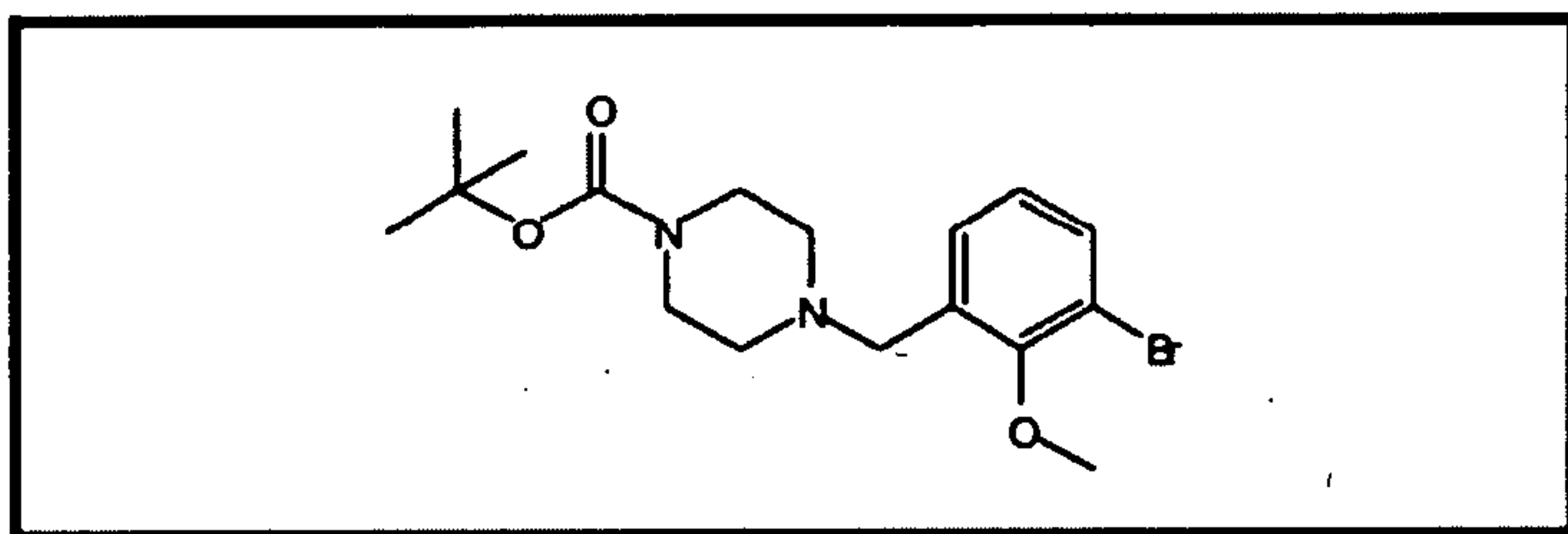
**[00364] Preparation of 1-(3-bromo-2-methoxybenzyl)-4-methylpiperazine:**

3-Bromo-2-methoxybenzaldehyde (1.00 g, 4.65 mmol) and 1-methylpiperazine (2.33 g, 23.26 mmol) were dissolved in THF (40 ml) and treated with sodium triacetoxyborohydride (4.93 g, 23.26 mmol) and acetic acid (a few drops). After stirring overnight at room temperature, the reaction was partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The organic extract was dried over MgSO₄, concentrated, and purified by column chromatography (5%-15% gradient methanol in dichloromethane) to give 500 mg (36%) of 1-(3-bromo-2-methoxybenzyl)-4-methylpiperazine as a colorless syrup. MS 299.0 (M+H); HPLC rt = 5.7 min [a].



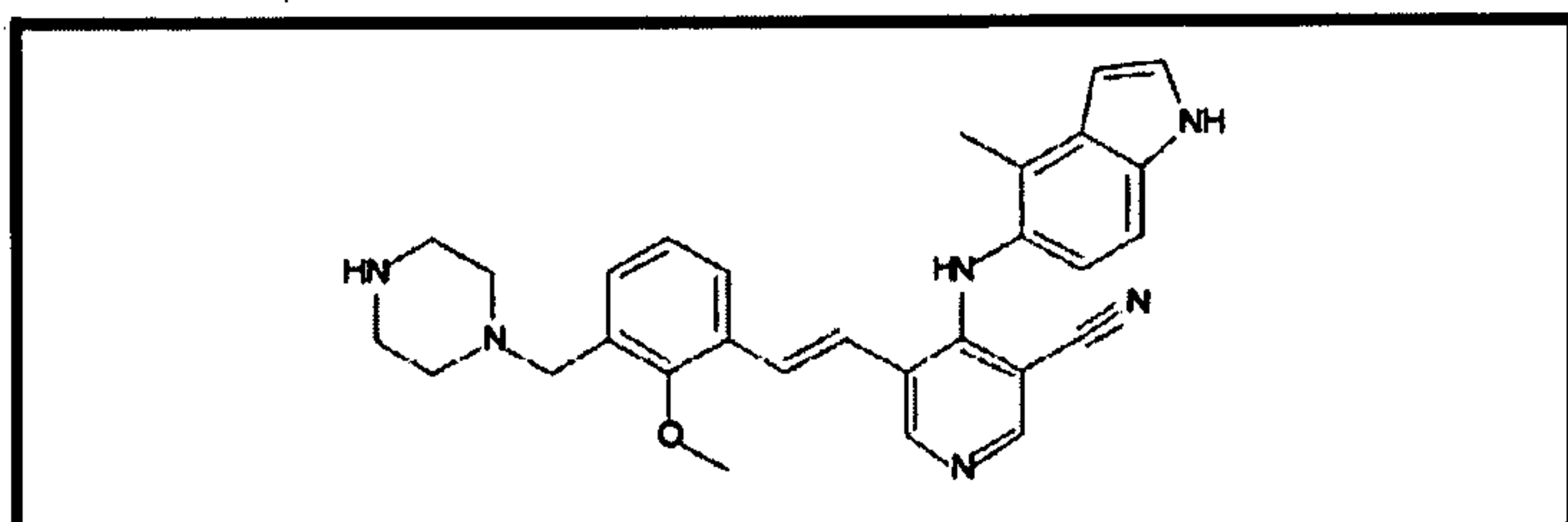
[00365] Preparation of 5-[(E)-2-{2-methoxy-3-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

4-[(4-Methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile (100 mg, 0.36 mmol) was dissolved in a mixture of DMF (2 ml) and triethylamine (0.5 ml). The solution was treated with 1-(3-bromo-2-methoxybenzyl)-4-methylpiperazine (132 mg, 0.44 mmol), Pd(OAc)₂ (16 mg, 0.07 mmol) and P(o-Tol)₃ (6.0 mg, 0.02 mmol) and heated to 120° C under nitrogen for 8 h. The reaction was cooled to room temperature and diluted with dichloromethane, washed with saturated aqueous sodium bicarbonate, dried over MgSO₄ and concentrated to give a dark residue. The resulting crude compound was purified by HPLC to give 58 mg (32%) of 5-[(E)-2-{2-methoxy-3-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile as a light yellow solid. MS 493.2 (M+H); HPLC rt = 5.7 min [a].



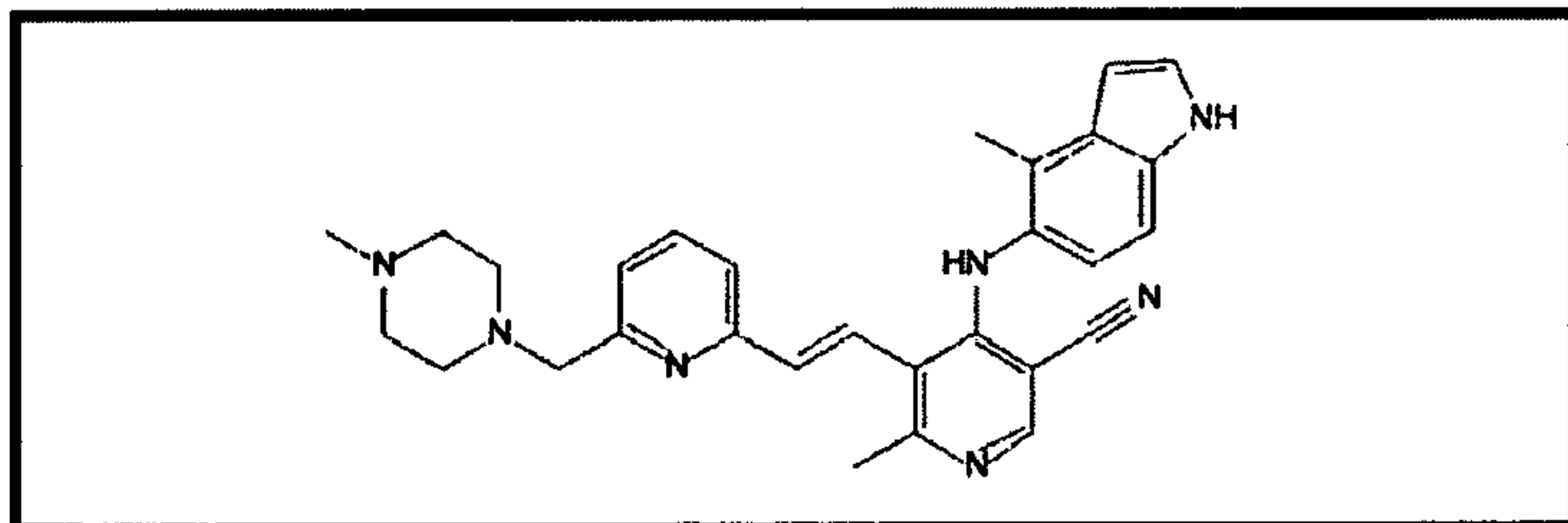
[00366] Preparation of tert-butyl 4-(3-iodo-2-methoxybenzyl)piperazine-1-carboxylate:

3-Bromo-2-methoxybenzaldehyde (1.50 g, 6.98 mmol) and 1-Boc-piperazine (6.50 g, 34.90 mmol) were dissolved in THF (60 ml) and treated with sodium triacetoxymethylborohydride (7.39 g, 34.87 mmol) and acetic acid (a few drops). The reaction was stirred at room temperature overnight then partitioned between dichloromethane and saturated aqueous sodium bicarbonate and dried over MgSO₄. The solution was concentrated to dryness and the residue was purified by column chromatography (0%-10% gradient methanol in dichloromethane) to give 1.8 g (67%) of tert-butyl 4-(3-iodo-2-methoxybenzyl)piperazine-1-carboxylate as a colorless syrup. MS 385.1 (M+H); HPLC rt = 8.7 min [a].



[00367] Preparation of 5-[(E)-2-[2-methoxy-3-(piperazin-1-ylmethyl)phenyl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

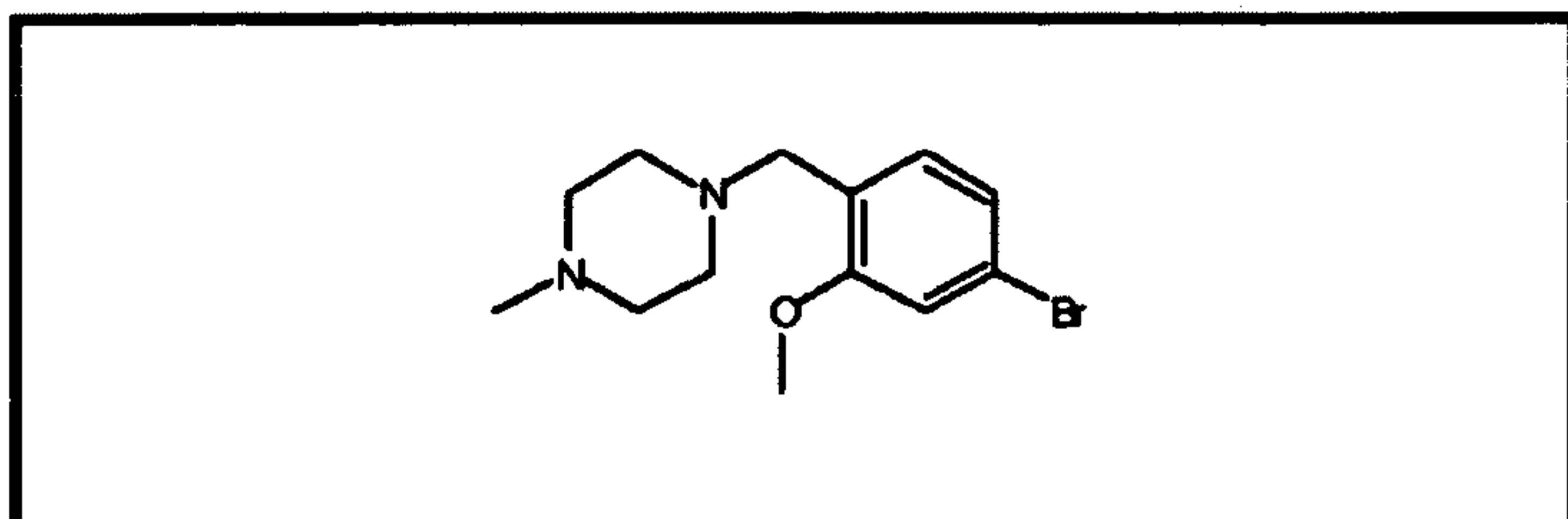
4-[(4-Methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile (200 mg, 0.73 mmol) was dissolved in a mixture of DMF (2 ml) and triethylamine (0.5 ml) and treated with *tert*-butyl 4-(3-iodo-2-methoxybenzyl)piperazine-1-carboxylate (339 mg, 0.88 mmol), Pd(OAc)₂ (33 mg, 0.15 mmol) and P(*o*-Tol)₃ (11 mg, 0.04 mmol). The reaction mixture was stirred at 120°C under nitrogen for 8 h then cooled and diluted with dichloromethane. The solution was washed with saturated aqueous sodium bicarbonate, dried over MgSO₄ and concentrated to give a dark residue. The residue was redissolved in dichloromethane and trifluoroacetic acid (ratio 4:1) and stirred at room temperature for 2 h. The reaction was quenched with saturated aqueous sodium bicarbonate, dried over MgSO₄ and concentrated to give a dark syrup. The resulting crude compound was purified by HPLC to give 39 mg (11%) of 5-[(E)-2-[2-methoxy-3-(piperazin-1-ylmethyl)phenyl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile as a light yellow solid. MS 479.2 (M+H); HPLC rt = 5.5 min [a].



[00368] Preparation of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl]vinyl]nicotinonitrile:

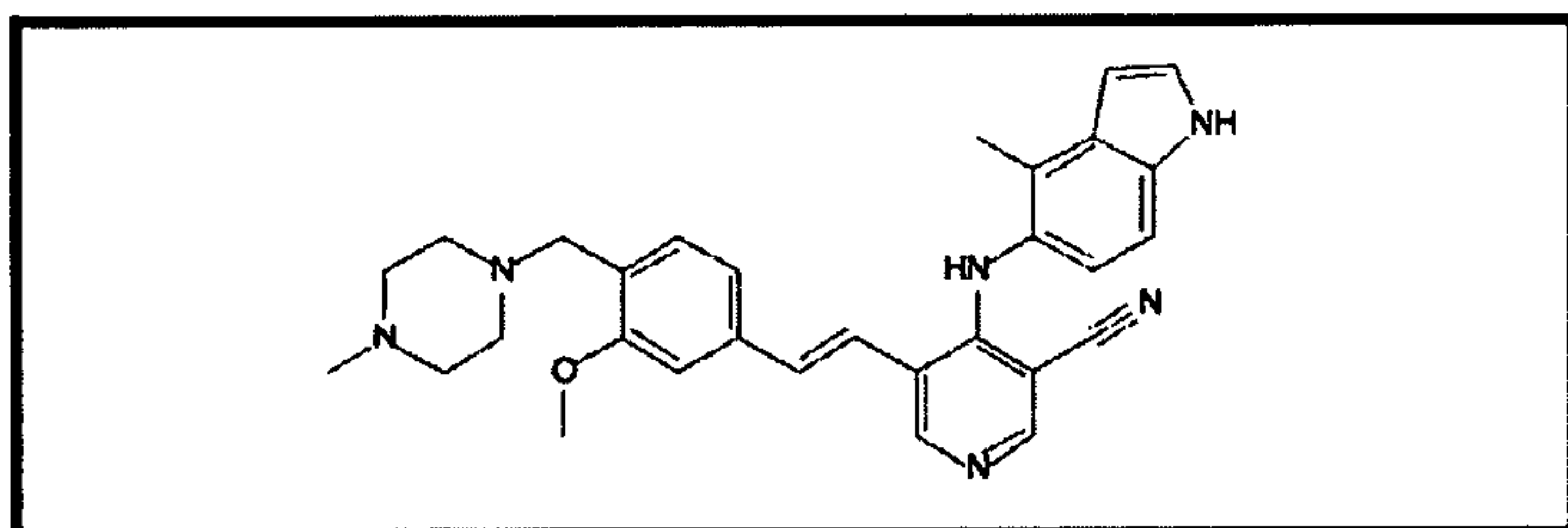
5-Bromo-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (200 mg, 0.586 mmol) was dissolved in a mixture of DMF (2 ml) and triethylamine (0.5 ml). The reaction was treated with 1-methyl-4-[(6-vinylpyridin-2-yl)methyl]piperazine (153 mg, 0.704 mmol), Pd(OAc)₂ (26 mg, 0.116 mmol) and P(*o*-Tol)₃ (9.0 mg, 0.030 mmol). The reaction mixture was stirred at 100° C under nitrogen for 8 h. Upon cooling to room temperature, the reaction was diluted with dichloromethane, washed with saturated aqueous sodium bicarbonate, dried over MgSO₄ and concentrated to give a dark residue. The resulting crude compound was purified by HPLC to give 89 mg (32%) of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl]vinyl]nicotinonitrile.

methylpiperazin-1-yl) methyl]pyridin-2-yl}vinyl]nicotinonitrile as a light purple solid. MS 478.3 (M+H); HPLC rt = 5.0 min [a].



[00369] Preparation of 1-(3-bromo-5-methoxybenzyl)-4-methylpiperazine:

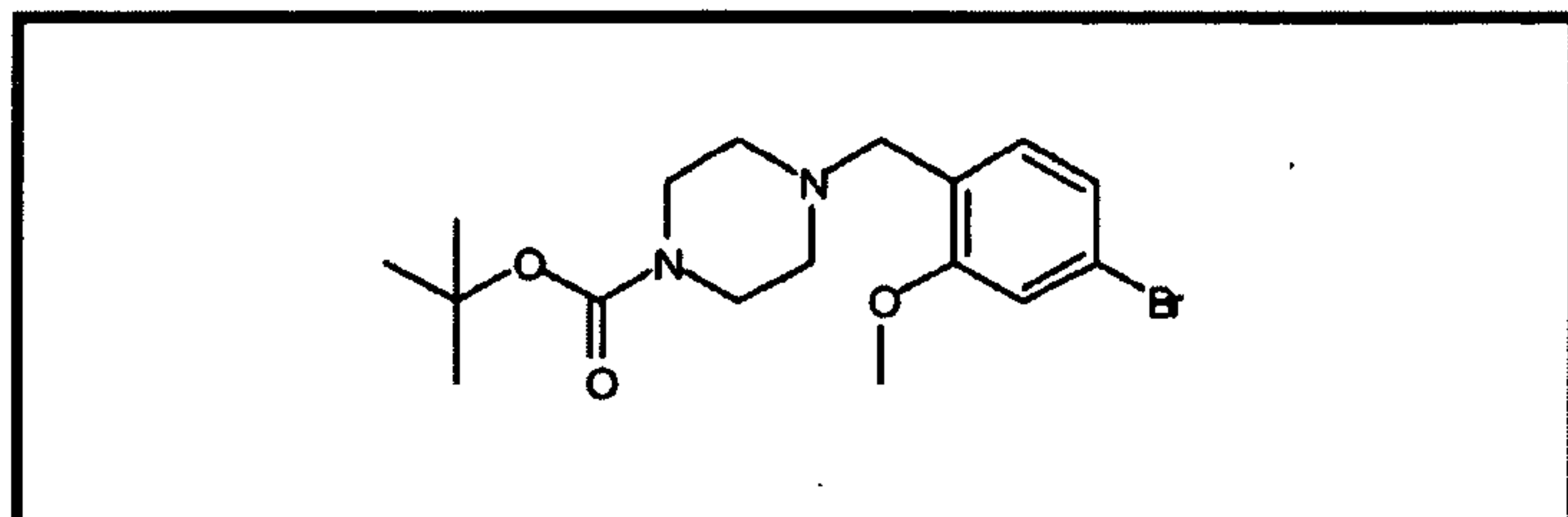
4-Bromo-2-hydroxybenzaldehyde (1.0 g, 4.65 mmol) and 1-methylpiperazine (2.33 g, 23.26 mmol) were dissolved in THF (40 ml) and treated with sodium triacetoxyborohydride (4.93 g, 23.26 mmol) and acetic acid (a few drops). The reaction was stirred at room temperature overnight then partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The solution was dried over MgSO_4 , concentrated, and purified by column chromatography (5% methanol in dichloromethane) to give 870 mg (63%) of 1-(3-bromo-5-methoxybenzyl)-4-methylpiperazine as a colorless syrup. MS 299.1 (M+H); HPLC rt = 5.1 min [a].



[00370] Preparation of 5-[(E)-2-{3-methoxy-4-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

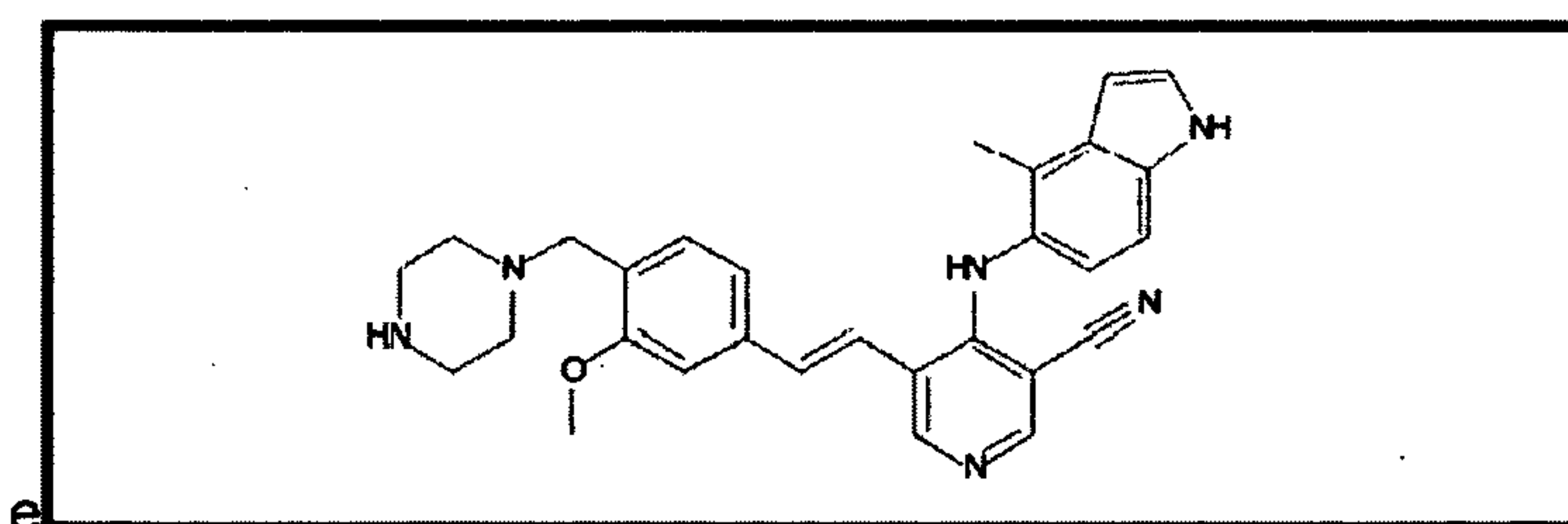
4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile (100 mg, 0.36 mmol) was dissolved in a mixture of DMF (2 ml) and triethylamine (0.5 ml) and treated with 1-(3-bromo-5-methoxybenzyl)-4-methylpiperazine (132 mg, 0.44 mmol), $\text{Pd}(\text{OAc})_2$ (16 mg, 0.07 mmol) and $\text{P}(\text{o-Tol})_3$ (6.0 mg, 0.02 mmol). The reaction mixture was stirred at 120°C under nitrogen for 8 h. The reaction was cooled to room temperature, diluted with dichloromethane, washed with saturated aqueous sodium bicarbonate, dried over MgSO_4 and concentrated to give a dark residue. The resulting crude compound was purified by HPLC to give 55 mg (31%) of 5-[(E)-2-

{3-methoxy-4-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile as a light yellow solid. MS 493.3 (M+H); HPLC rt = 5.3 min [a].



[00371] Preparation of tert-butyl 4-(3-bromo-5-methoxybenzyl)piperazine-1-carboxylate:

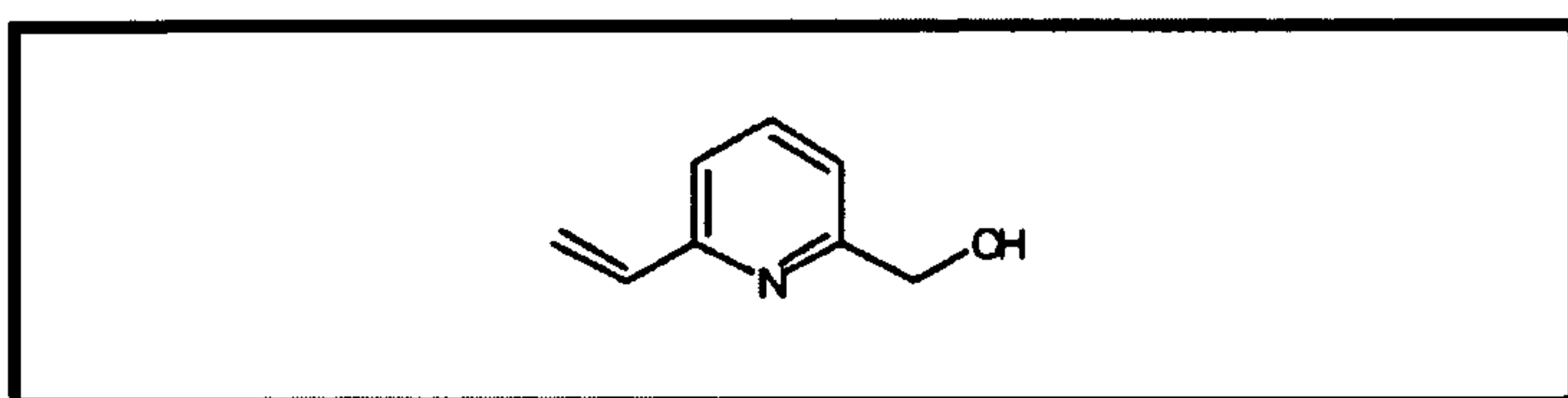
4-Bromo-2-hydroxybenzaldehyde (1.50 g, 6.98 mmol) and 1-Boc-piperazine (6.50 g, 34.90 mmol) were dissolved in THF (60 ml) and treated with sodium triacetoxyborohydride (7.39 g, 34.87 mmol) and acetic acid (a few drops). The reaction was stirred overnight at room temperature then partitioned between dichloromethane and saturated aqueous sodium bicarbonate. After drying over MgSO₄, the solution was concentrated and purified by column chromatography (0%-6% gradient methanol in dichloromethane) to give 2.4 g (89%) of tert-butyl 4-(3-bromo-5-methoxybenzyl)piperazine-1-carboxylate as a white solid. MS 385.1 (M+H); HPLC rt = 12.2 min [a].



[00372] Preparation of 5-[(E)-2-[3-methoxy-4-(piperazin-1-ylmethyl)phenyl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

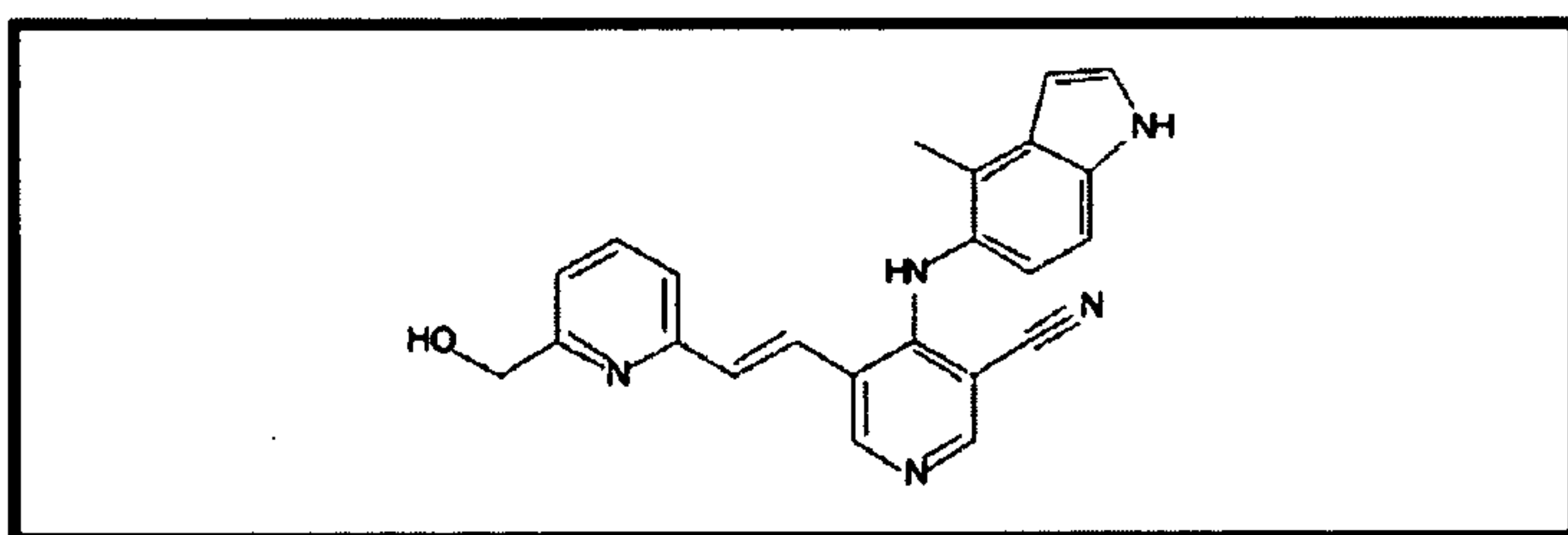
4-[(4-Methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile (200 mg, 0.73 mmol) was dissolved in a mixture of DMF (2 ml) and triethylamine (0.5 ml) and treated with *tert*-butyl 4-(3-bromo-5-methoxybenzyl)piperazine-1-carboxylate (562 mg, 1.46 mmol), Pd(OAc)₂ (33 mg, 0.15 mmol) and P(*o*-Tol)₃ (11mg, 0.04 mmol). The reaction mixture was stirred at 120° C under nitrogen

for 8 h. The reaction was cooled to room temperature and diluted with dichloromethane, washed with saturated aqueous sodium bicarbonate, dried over MgSO_4 and concentrated to give a dark residue. The residue was redissolved in dichloromethane and trifluoroacetic acid (ratio 4:1) and stirred at room temperature for 2 h. After quenching with saturated aqueous sodium bicarbonate, the organic layer was dried over MgSO_4 and concentrated to give a dark syrup. The resulting crude compound was purified by HPLC to give 32 mg (9.2%) of 5-[(E)-2-[3-methoxy-4-(piperazin-1-ylmethyl)phenyl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile as a light yellow solid. MS 479.3 (M+H); HPLC t_r = 5.0 min [a].



[00373] Preparation of (6-vinylpyridin-2-yl)methanol:

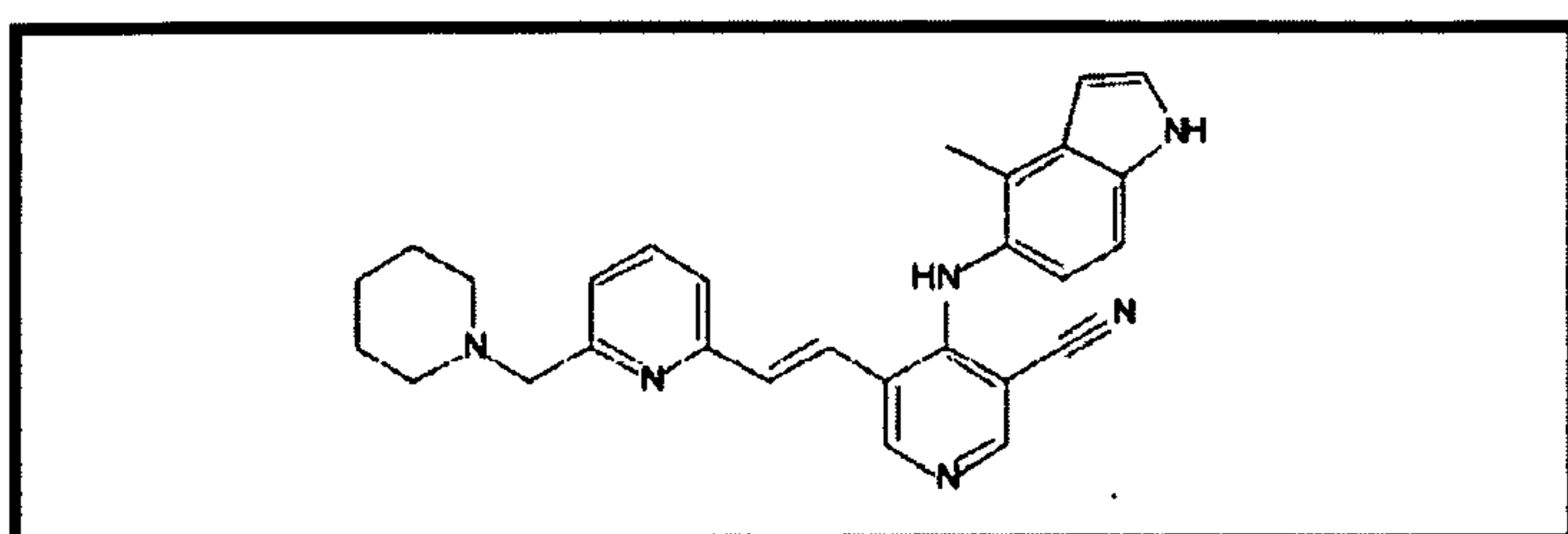
(6-Bromopyridine-2-yl)methanol (5.00 g, 26.59 mmol) and tributylvinyltin (15.5 ml, 53.09 mmol) were dissolved in anhydrous toluene (100 ml) and treated with $\text{Pd}(\text{PPh}_3)_4$ (1.54 g, 1.33 mmol). The reaction mixture was heated to reflux for 8 h then cooled to room temperature and filtered. The filtrate was partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The organic layer was dried over MgSO_4 and concentrated to give a yellow residue. The crude compound was purified by column chromatography (5-10% gradient methanol in dichloromethane) to give 2.06g (57%) of (6-vinylpyridin-2-yl)methanol as a yellow syrup. MS 136.1 (M+H).



[00374] Preparation of 5-[(E)-2-[6-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

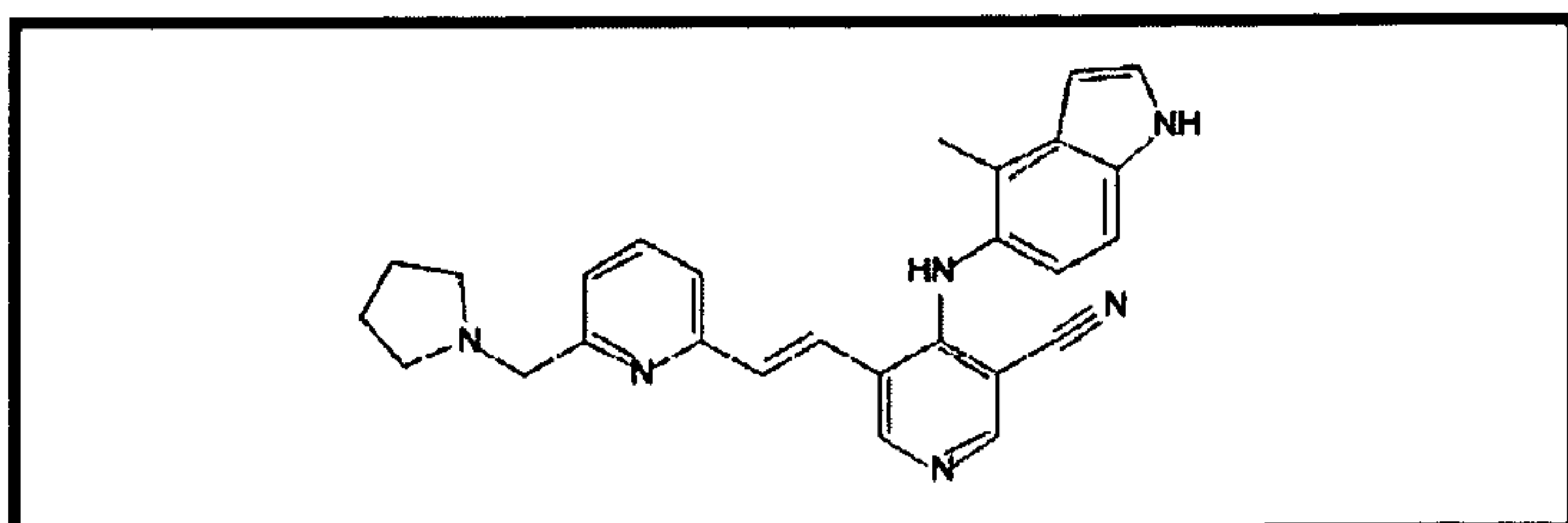
5-Iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (2.0 g, 5.34 mmol) was dissolved in a mixture of DMF (24 ml) and triethylamine (6 ml) and treated with (6-vinylpyridin-2-yl)methanol

(866 mg, 6.41 mmol), Pd(OAc)₂ (240 mg, 1.07 mmol) and P(*o*-Tol)₃ (82 mg, 0.27 mmol). The reaction mixture was stirred at 110° C under nitrogen for 5 h then cooled to room temperature and diluted with dichloromethane. The resulting solution was washed twice with saturated aqueous sodium bicarbonate. A precipitate formed during the 2nd wash and was collected by filtration and washed with dichloromethane and water giving 1.6 g (78%) of 5-[(E)-2-[6-(hydroxyl methyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile as a yellow solid. MS 382.1 (M+H); HPLC rt = 5.9 min [a].



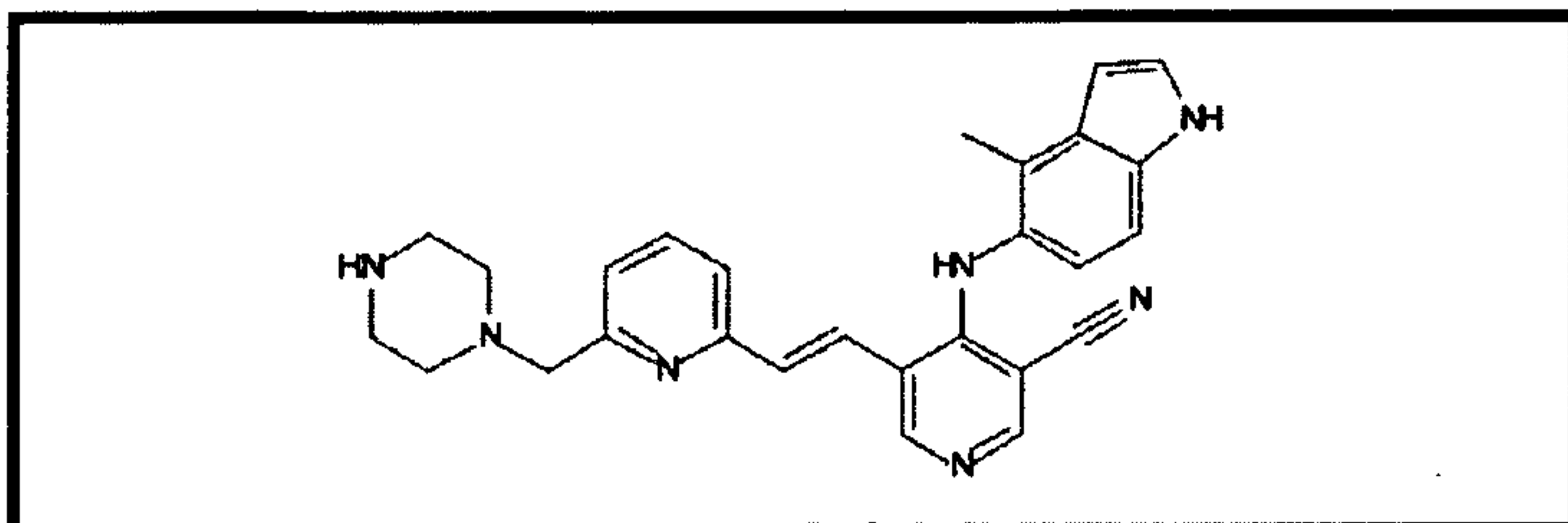
[00375] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-(piperidin-1-ylmethyl)pyridin-2-yl]vinyl]nicotinonitrile:

A solution of 5-[(E)-2-[6-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (100 mg, 0.262 mmol) in a mixture of THF (5 ml) and DMF (2.5 ml) was treated with triethylamine (183 µL, 1.313 mmol). The resulting solution was stirred under nitrogen at room temperature for 10 min then treated dropwise with methanesulfonyl chloride (61 µL, 0.788 mmol). The reaction was stirred overnight at room temperature then treated with piperidine (104 µL, 1.050 mmol). After allowing the reaction to continue stirring overnight, the solvent was removed and the residue was partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The organic layer was dried over MgSO₄ and concentrated to give a dark syrup. The resulting residue was purified by HPLC to give 29 mg (25%) of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-(piperidin-1-ylmethyl)pyridin-2-yl]vinyl]nicotinonitrile as a light yellow solid. MS 449.2 (M+H); HPLC rt = 5.8 min [a].



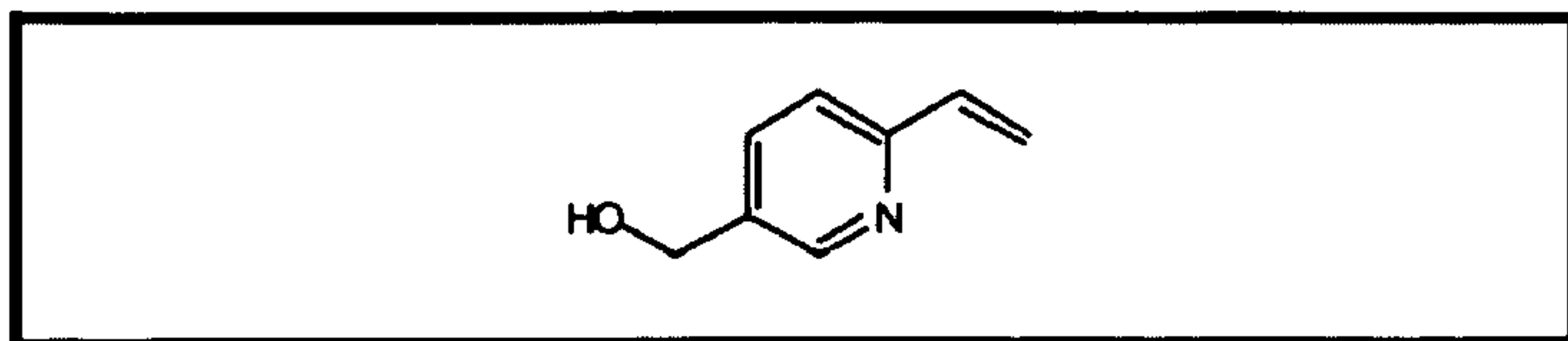
[00376] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-(pyrrolidin-1-ylmethyl)pyridin-2-yl]vinyl]nicotinonitrile:

The title compound was prepared from 5-[(E)-2-[6-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (200 mg, 0.524 mmol) and pyrrolidine by the procedure utilized for 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-(piperidin-1-ylmethyl)pyridin-2-yl]vinyl]nicotinonitrile. MS 435.2 (M+H); HPLC rt = 5.6 min [a].



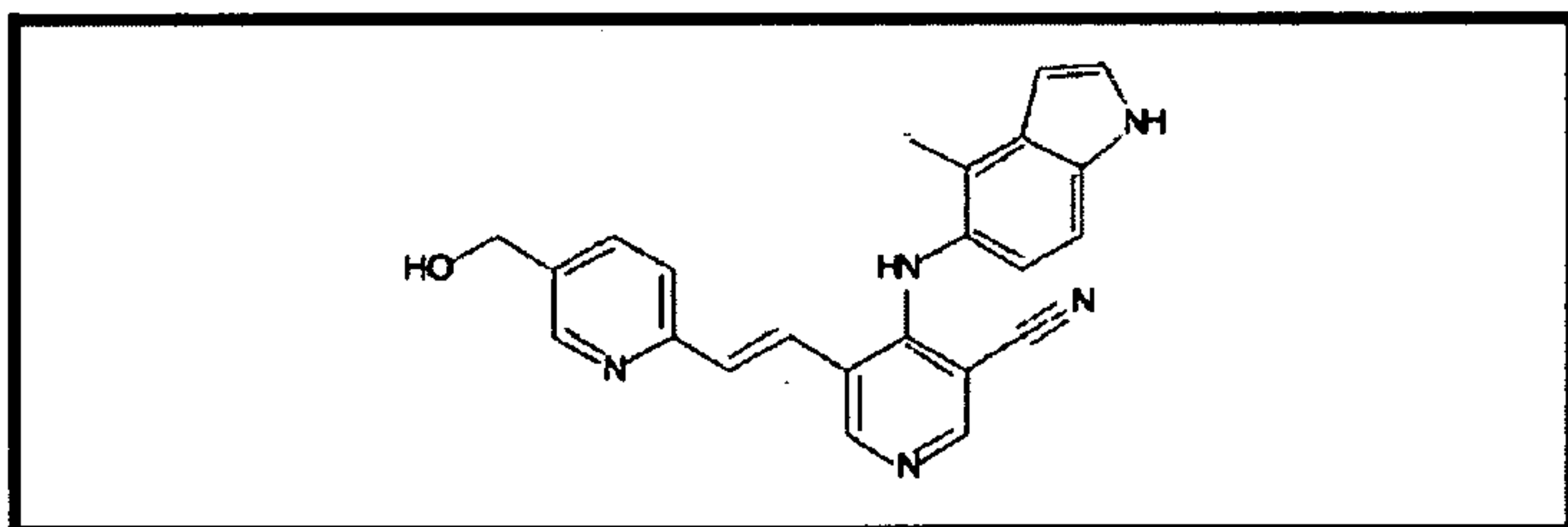
[00377] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-(piperazin-1-ylmethyl)pyridin-2-yl]vinyl]nicotinonitrile:

5-[(E)-2-[6-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (200 mg, 0.524 mmol) was dissolved in a solvent mixture of THF (10 ml) and DMF (5 ml) and treated with triethylamine (366 μ L, 2.626 mmol). The solution was stirred under nitrogen at room temperature for 10 min then treated dropwise with methanesulfonyl chloride (122 μ L, 1.577 mmol). The reaction was allowed to stir at room temperature for 2 h then treated with 1-Boc-piperazine (390 mg, 2.094 mmol). The reaction was allowed to stir for 8 h at room temperature. The solvent was removed and the residue was partitioned between CH_2Cl_2 and saturated aqueous sodium bicarbonate. The organic layer was dried over MgSO_4 and concentrated to give a dark syrup. The syrup was redissolved in dichloromethane and trifluoroacetic acid (ratio 4:1) and stirred at room temperature for 2 h. The reaction was quenched with saturated aqueous sodium bicarbonate, dried over MgSO_4 and concentrated to give a dark residue. The resulting crude material was purified by HPLC to give 48 mg (20%) of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-(piperazin-1-ylmethyl)pyridin-2-yl]vinyl]nicotinonitrile as a light yellow solid. MS 450.2 (M+H); HPLC rt = 5.0 min [a].



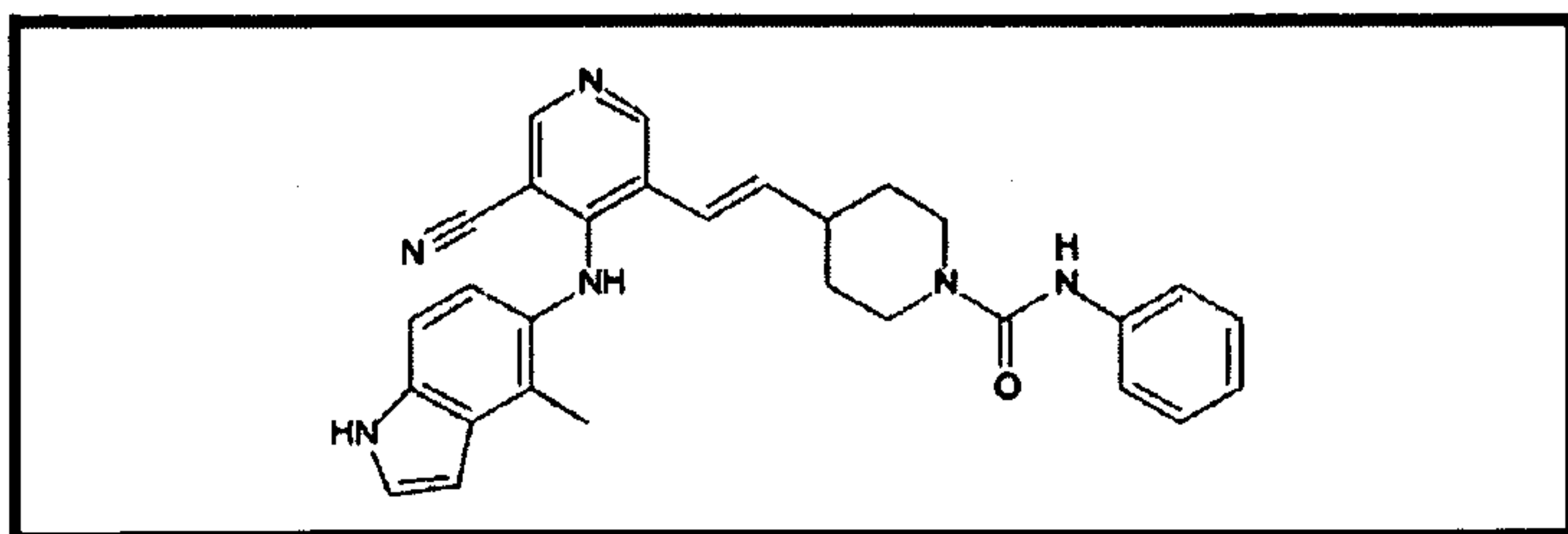
[00378] Preparation of (6-vinylpyridin-3-yl)methanol:

(6-Bromopyridine-3-yl)methanol (1.00 g, 5.313 mmol) and tributylvinyltin (3.10 ml, 10.617 mmol) were dissolved in anhydrous toluene (20 ml) and treated with $\text{Pd}(\text{PPh}_3)_4$ (308 mg, 0.266 mmol). The reaction mixture was heated to reflux for 3 h then cooled to room temperature and filtered. The filtrate was partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The organic layer was dried over MgSO_4 and concentrated to give a yellow residue. The crude compound was purified by column chromatography (3-8% gradient methanol in dichloromethane) to give 516 mg (31%) of (6-vinylpyridin-3-yl)methanol as a yellow syrup. MS 136.1 (M+H).



[00379] Preparation of 5-[(E)-2-[5-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (1.0 g, 2.67 mmol) was dissolved in a mixture of DMF (12 ml) and triethylamine (3 ml) and treated with (6-vinylpyridin-3-yl)methanol (433 mg, 3.20 mmol), $\text{Pd}(\text{OAc})_2$ (120 mg, 0.54 mmol) and $\text{P}(o\text{-Tol})_3$ (41 mg, 0.14 mmol). The reaction mixture was stirred at 110°C under nitrogen for 5 h. The reaction was cooled to room temperature and diluted with dichloromethane then washed twice with saturated aqueous sodium bicarbonate. A precipitate formed during the 2nd wash and was collected by filtration and washed with dichloromethane and water giving 610 mg (60%) of 5-[(E)-2-[5-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile as a yellow solid. MS 382.1 (M+H); HPLC t_r = 5.3 min [a].



[00380] Preparation of 4-[(E)-2-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}vinyl]-N-phenylpiperidine-1-carboxamide:

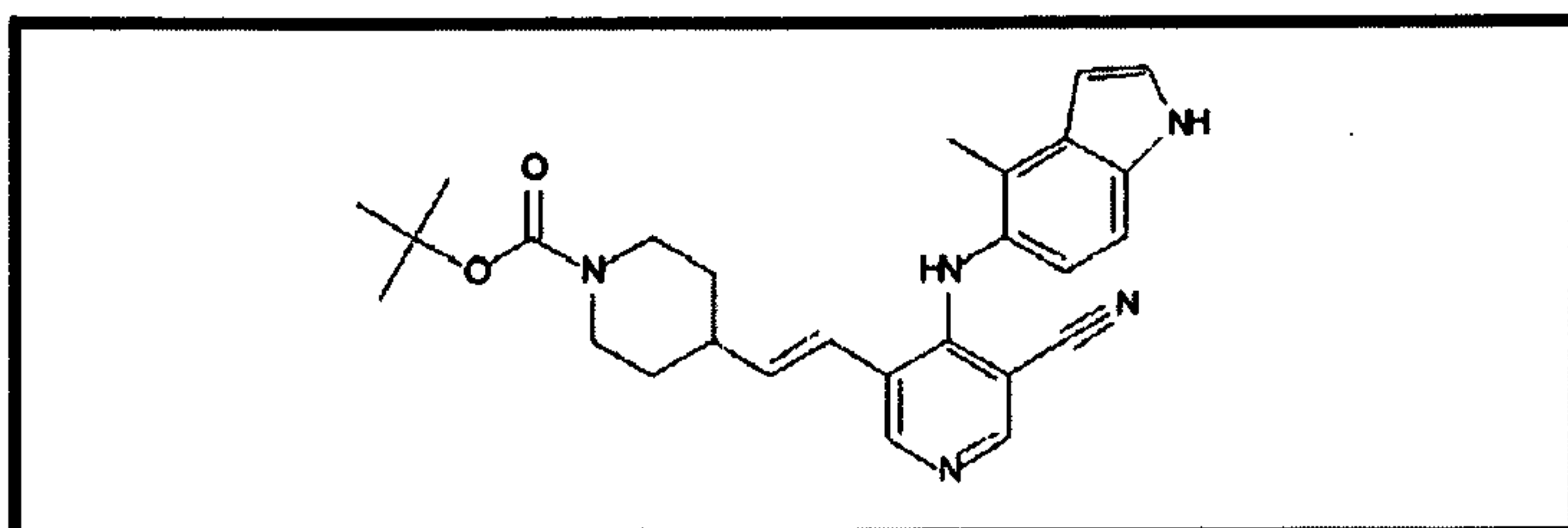
A mixture of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-piperidin-4-ylvinyl]nicotinonitrile as its TFA salt (61 mg, 0.13 mmol), phenyl isocyanate (20 mg, 0.17 mmol), and triethylamine (39 mg, 0.39 mmol) in 1 mL of DMF was stirred at room temperature for 45 min. The mixture was purified by HPLC to give 4-[(E)-2-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}vinyl]-N-phenylpiperidine-1-carboxamide. MS 477.2 (M+H); HPLC rt = 1.92 min [d].

[00381] Preparation of compounds in Table 10:

The compounds in Table 10 were prepared from 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-piperidin-4-ylvinyl]nicotinonitrile, the corresponding electrophile and triethylamine via the procedure used to prepare 4-[(E)-2-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}vinyl]-N-phenylpiperidine-1-carboxamide.

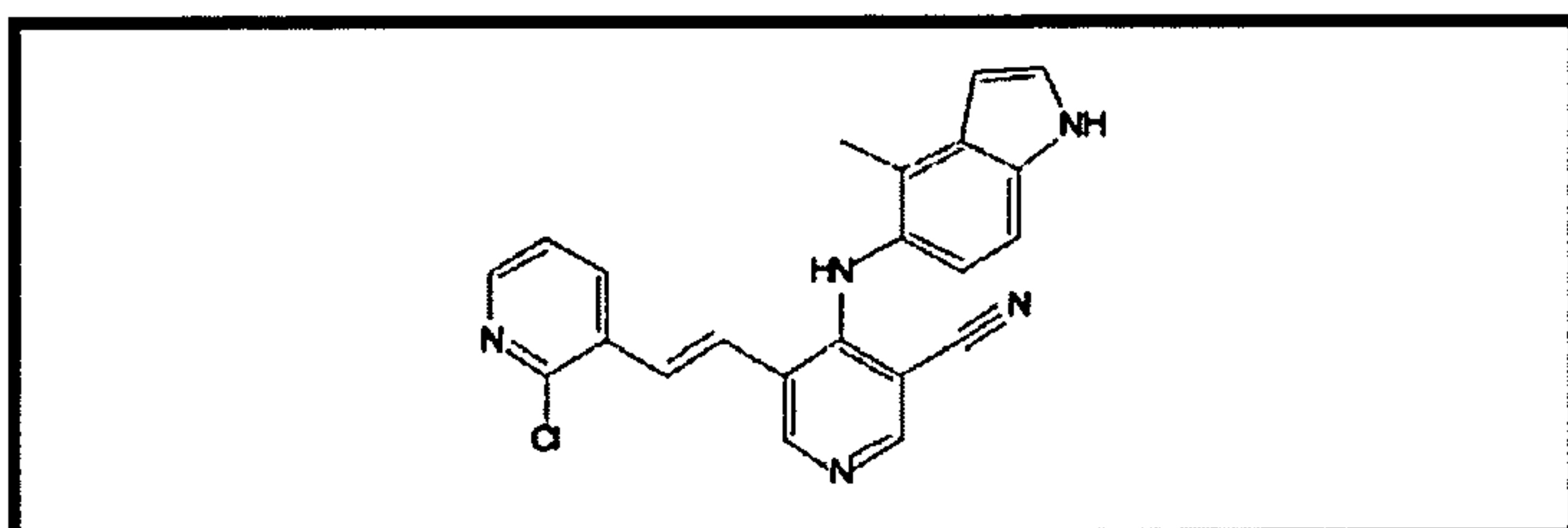
Table 10:

HPLC	MS	r.t.
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[1-(phenylsulfonyl)piperidin-4-yl]vinyl]nicotinonitrile	498.2	2.05 min. [d]
5-[(E)-2-(1-benzoylpiperidin-4-yl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	462.2	1.93 min. [d]
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[1-(3-phenylpropanoyl)piperidin-4-yl]vinyl]nicotinonitrile	490.3	2.04 min. [d]
4-[(E)-2-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}vinyl]-N-propylpiperidine-1-carboxamide	443.2	1.81 min. [d]
5-[(E)-2-[1-(isopropylsulfonyl)piperidin-4-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	464.2	1.89 min. [d]



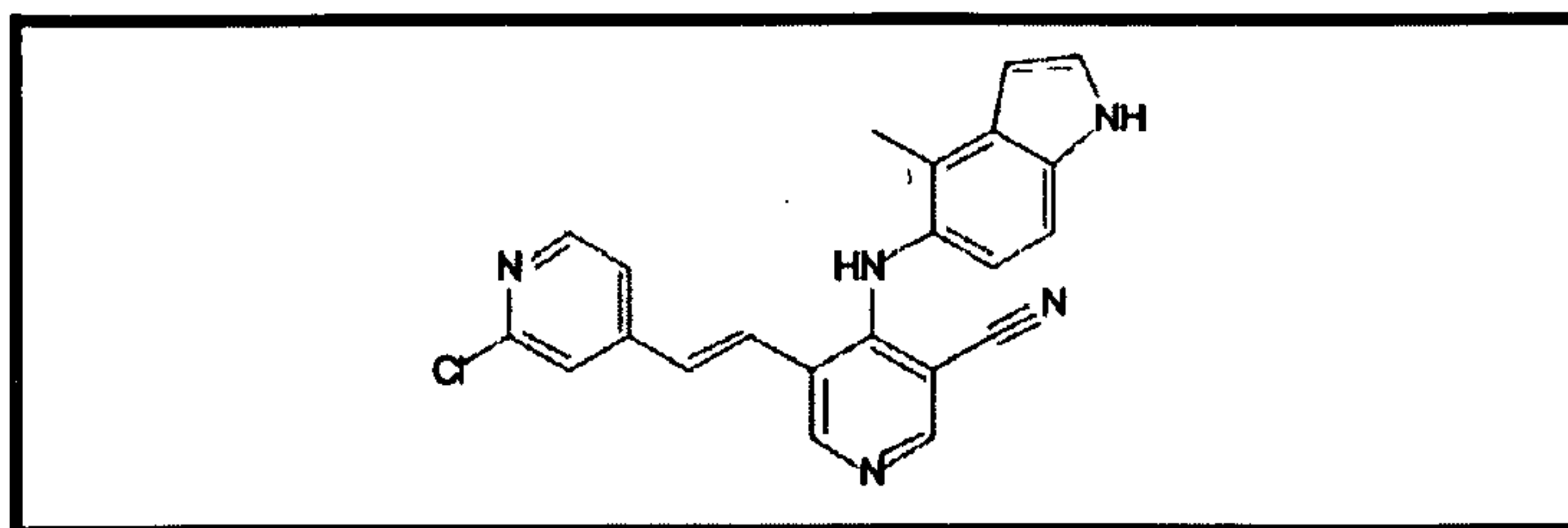
[00382] Preparation of tert-butyl 4-[(E)-2-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}vinyl]piperidine-1-carboxylate:

A mixture of 5-iodo-4-(4-methyl-1H-indol-5-ylamino)nicotinonitrile (843 mg, 2.26 mmol), (E)-tert-butyl 4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)piperidine-1-carboxylate (1.14 g, 3.38 mmol), cesium carbonate (1.47 g, 4.52 mmol) and Pd(PPh₃)₄ (130 mg, 0.11 mmol) in 9 mL of DMSO was heated to 90°C for 16 h. The reaction mixture was cooled to room temperature and filtered. The filtrate was purified by HPLC to give (E)-tert-butyl 4-(2-(5-cyano-4-(4-methyl-1H-indol-5-ylamino)pyridin-3-yl)vinyl) piperidine-1-carboxylate. MS 458.2 (M+H); HPLC rt = 10.6 min [a].



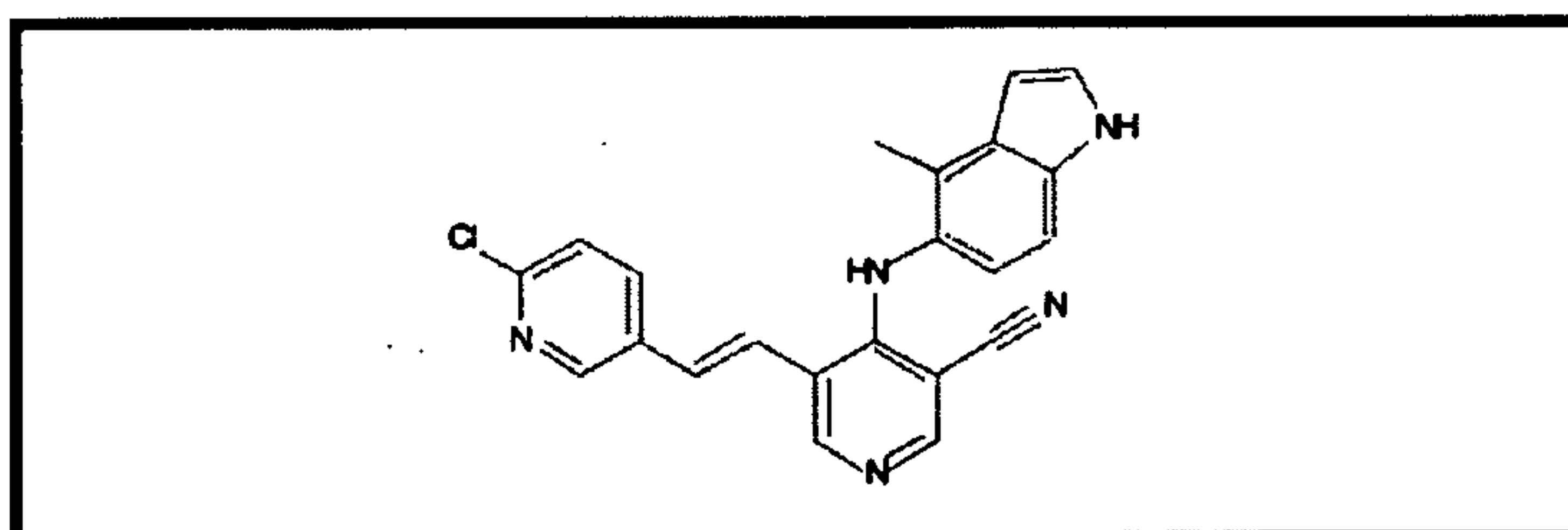
[00383] Preparation of 5-[(E)-2-(2-chloropyridin-3-yl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

A mixture of 5-iodo-4-(4-methyl-1H-indol-5-ylamino)nicotinonitrile (240 mg, 0.65 mmol), 2-chloro-3-vinylpyridine (75 mg, 0.54 mmol), P(o-Tol)₃ (25 mg, 0.08 mmol), Pd(OAc)₂ (9 mg, 0.04 mmol) and triethylamine (164 mg, 1.63 mmol) in 15 mL of DMF was heated to 120°C overnight. The reaction was cooled to room temperature and filtered. The filtrate was purified by HPLC to give 5-[(E)-2-(2-chloropyridin-3-yl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile as a solid. MS 386.1 (M+H); HPLC rt = 8.4 min [a].



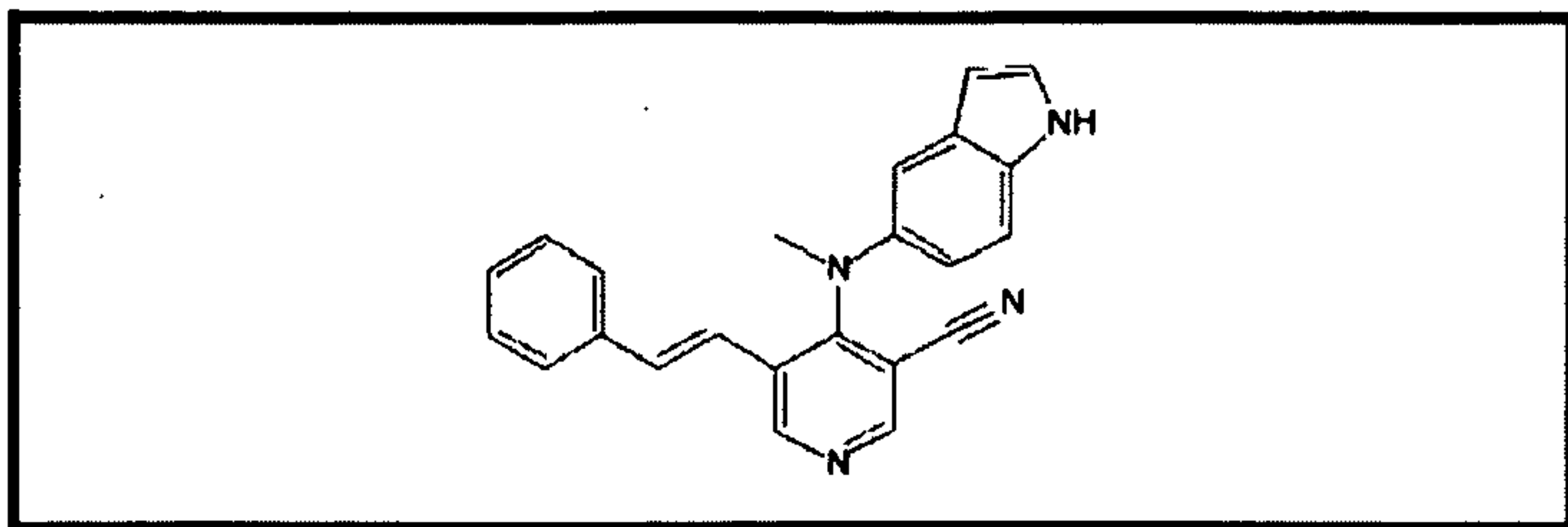
[00384] Preparation of 5-[(E)-2-(2-chloropyridin-4-yl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

A mixture of 4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile (100 mg, 0.36 mmol), 4-bromo-2-chloropyridine (90 mg, 0.47 mmol), $P(o\text{-Tol})_3$ (22 mg, 0.072 mmol), $\text{Pd}(\text{OAc})_2$ (16 mg, 0.072 mmol) and triethylamine (145 mg, 1.44 mmol) in 2 mL of DMF was heated to 120°C overnight. The reaction was cooled to room temperature and filtered. The filtrate was purified by HPLC to give 5-[(E)-2-(2-chloropyridin-4-yl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile as a solid. MS 386.1 (M+H); HPLC r_t = 8.8 min [a].



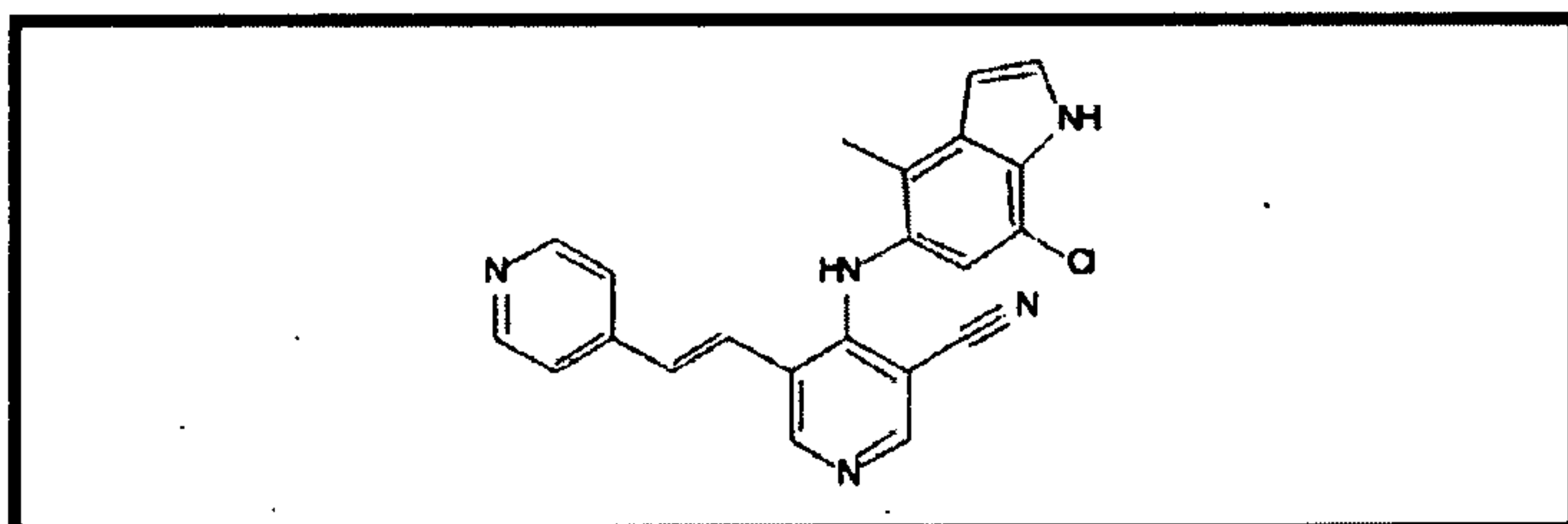
[00385] Preparation of 5-[(E)-2-(6-chloropyridin-3-yl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

A mixture of 4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile (200 mg, 0.73 mmol), 5-bromo-2-chloropyridine (155 mg, 0.80 mmol), $P(o\text{-Tol})_3$ (22 mg, 0.072 mmol), $\text{Pd}(\text{OAc})_2$ (16 mg, 0.072 mmol) and triethylamine (295 mg, 2.92 mmol) in 7 mL of DMF was heated to 120°C overnight. The reaction was cooled to room temperature and filtered. The filtrate was purified by HPLC to give 5-[(E)-2-(6-chloropyridin-3-yl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile as a solid. MS 386.1 (M+H); HPLC: r_t = 8.8 min [a].



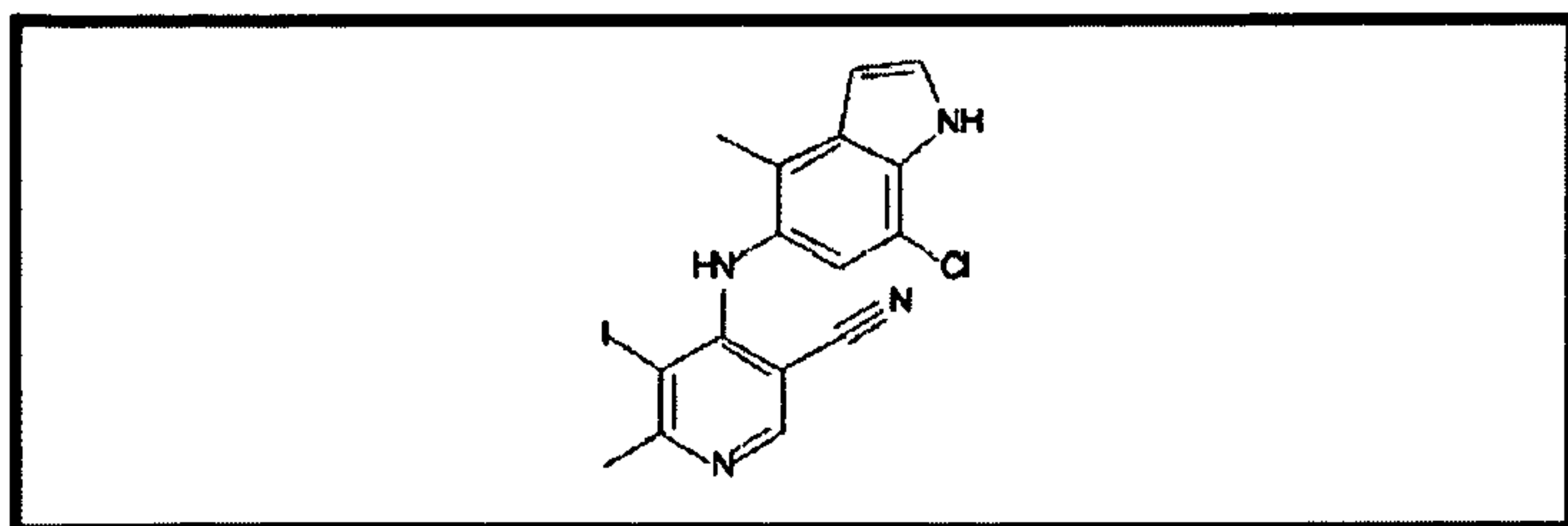
[00386] Preparation of 4-[1H-indol-5-yl(methyl)amino]-5-[(E)-2-phenylvinyl]nicotinonitrile:

A solution of 4-chloro-5-[(E)-2-phenylvinyl]nicotinonitrile (100 mg, 0.41 mmol) and *N*-methyl-1H-indol-5-amine (48 mg, 0.33 mmol) in ethanol (5 mL) was heated to 90° C for 72 h. The mixture was cooled to room temperature, diluted with saturated aqueous sodium bicarbonate and extracted with dichloromethane. The organic layer was washed with brine and concentrated *in vacuo*. The residue was purified by column chromatography with 4:1 hexane/ethyl acetate to provide 18 mg (13%) of the title compound as a yellow solid. MS 351.2 (M+H); HPLC *rt* = 12.5 min [a].



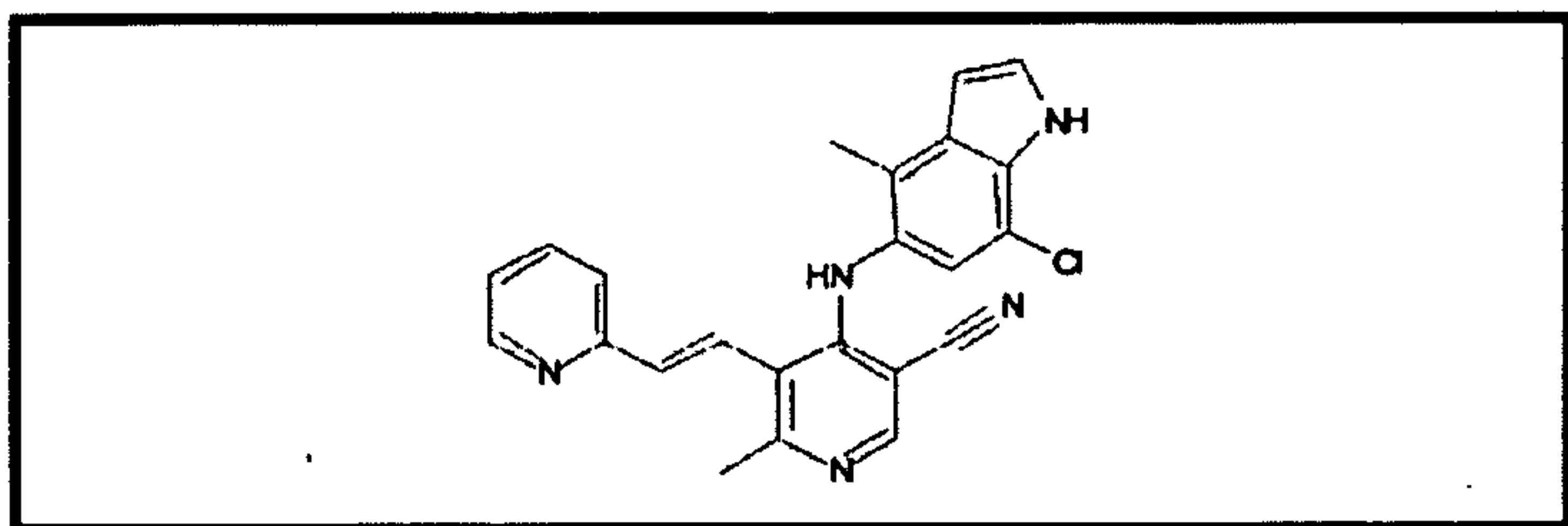
[00387] Preparation of 4-[(7-chloro-4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-pyridin-4-ylvinyl]nicotinonitrile:

A mixture of 4-[(7-chloro-4-methyl-1H-indol-5-yl)amino]-5-iodonicotinonitrile (120 mg, 0.29 mmol), 4-vinylpyridine (63 mg, 0.59 mmol), Pd(OAc)₂ (13 mg, 0.059 mMol), P(*o*-Tol)₃, and Et₃N (2 mL) in DMF (5 mL) was heated to 95°C overnight. The resulting mixture was cooled to room temperature, diluted with saturated aqueous sodium bicarbonate and extracted with dichloromethane. The combined organic extracts were washed with brine and concentrated *in vacuo*. The residue was purified by column chromatography (4:1 hexane/ethyl acetate) to provide 38 mg (31%) of the title compound as a yellow solid. MS 386.1 (M+H); HPLC *rt* = 5.4 min [a].



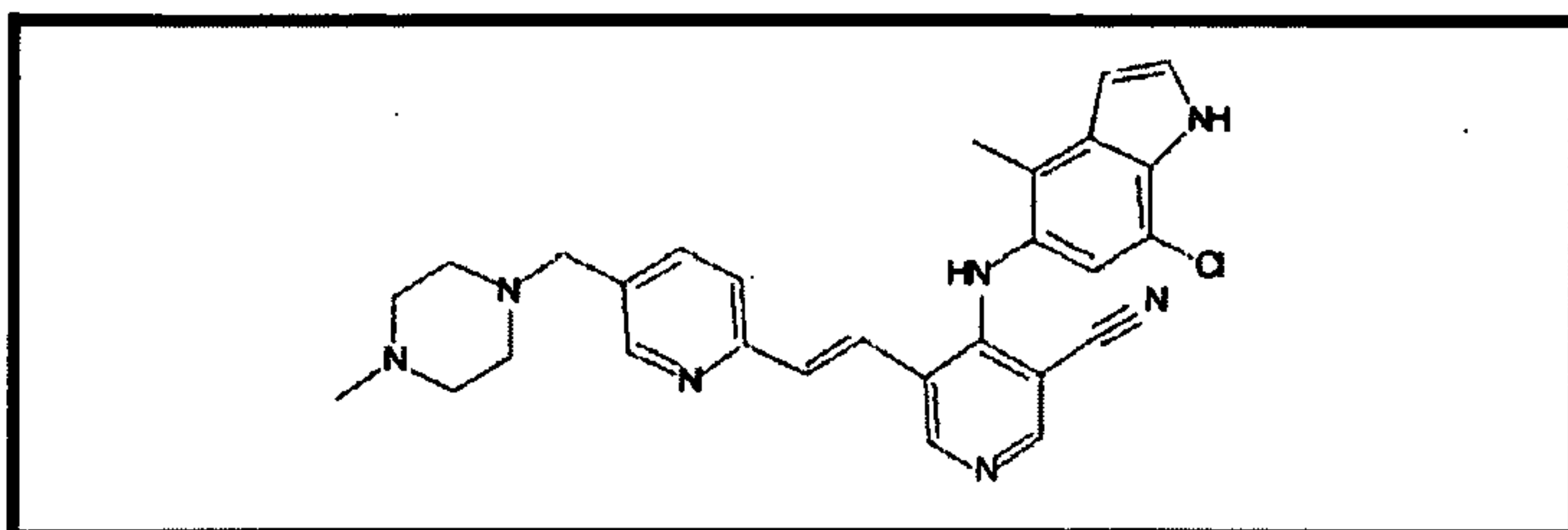
[00388] Preparation of 4-[(7-chloro-4-methyl-1H-indol-5-yl)amino]-5-iodo-6-methylnicotinonitrile:

A solution of 7-chloro-4-methyl-1H-indol-5-amine (537 mg, 3.0 mmol) and 4-chloro-5-iodo-6-methylnicotinonitrile (1.0 g, 6.0 mmol) in EtOH (10 mL) was heated to reflux for 72 h. The reaction mixture was cooled to room temperature and filtered. The filter cake was washed with EtOH and dried *in vacuo* to provide 610 mg (82%) of the title compound as yellow solid. MS 423.3 (M+H).



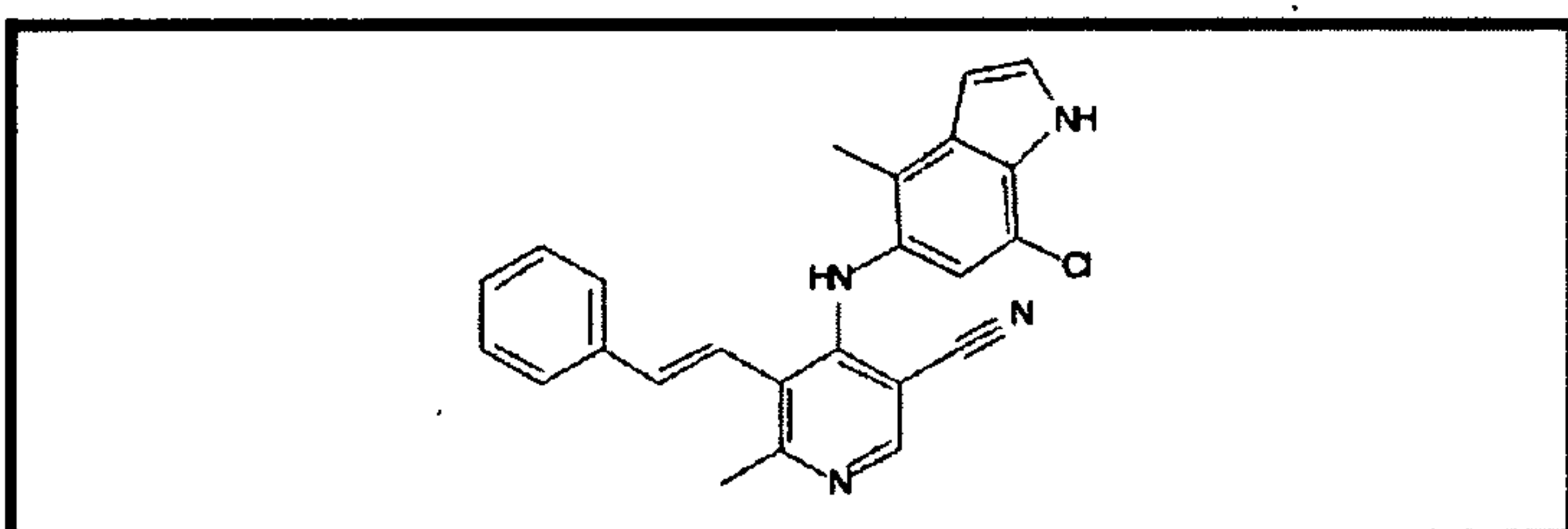
[00389] Preparation of 4-[(7-chloro-4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-pyridin-4-ylvinyl]nicotinonitrile:

A mixture of 4-[(7-chloro-4-methyl-1H-indol-5-yl)amino]-5-iodo-6-methylnicotinonitrile (130 mg, 0.28 mmol), 2-vinyl-pyridine (49 mg, 0.59 mmol), Pd(OAc)₂ (11 mg, 0.014 mmol), P(o-Tol)₃ (2.8 mg, 0.0084 mmol) and Et₃N (2 mL) in DMF (5 mL) was heated to 95° C overnight. The resulting mixture was cooled to room temperature, diluted with saturated aqueous sodium bicarbonate, extracted with dichloromethane. The organic layer was washed with brine and concentrated *in vacuo*. The crude product was purified by column chromatography (4:1 hexane/ethyl acetate) to provide 36 mg (30%) of the title compound as a yellow solid. MS 400.2 (M+H); HPLC 96.1% at 215 nm, rt = 6.8 min [a].



[00390] Preparation of 4-[(7-chloro-4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}vinyl]nicotinonitrile:

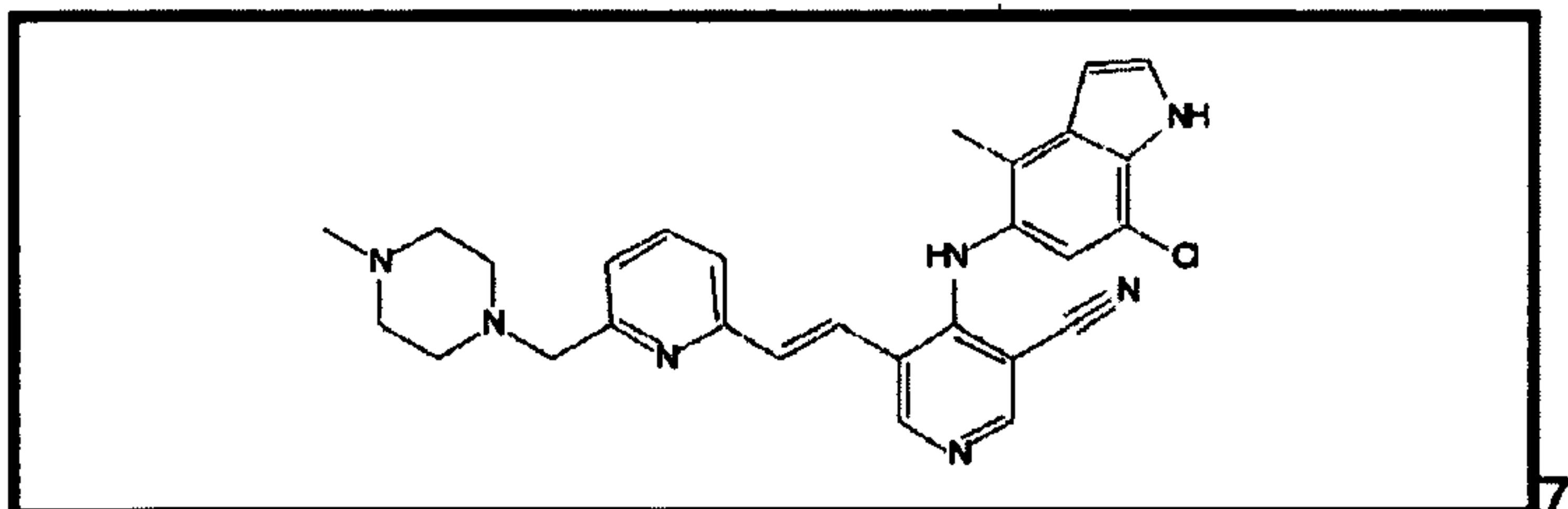
A mixture of 4-[(7-chloro-4-methyl-1H-indol-5-yl)-amino]-5-iodonicotinonitrile (120 mg, 0.29 mmol), 1-methyl-4[(6-vinylpyridin-3-yl)methyl]piperazine (128 mg, 0.59 mmol), Pd(OAc)₂ (13 mg, 0.059 mmol), P(*o*-Tol)₃, and Et₃N (2 mL) in DMF (5 mL) was heated to 95° C overnight. The resulting mixture was cooled to room temperature, diluted with saturated aqueous sodium bicarbonate, and extracted with dichloromethane. The organic layer was washed with brine and concentrated *in vacuo*. The crude product was purified by column chromatography with (4:1 hexane/ethyl acetate) to provide 60 mg (41%) of the title compound as a yellow solid. MS 499.1 (M+H); HPLC 93.6% at 215 nm, rt = 5.2 min [a].



[00391] Preparation of 4-[(7-chloro-4-methyl-1H-indol-5-yl)amino]-6-methyl-5-[(E)-2-phenylvinyl]nicotinonitrile:

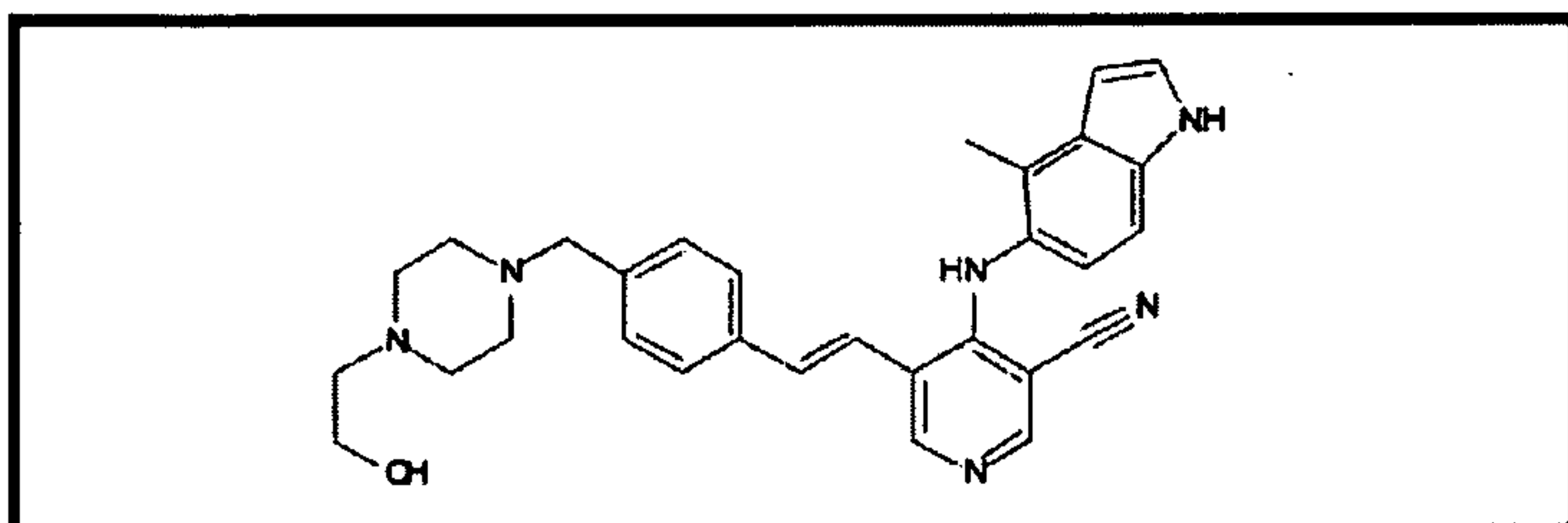
A mixture of 4-[(7-chloro-4-methyl-1H-indol-5-yl)amino]-5-iodo-6-methylnicotinonitrile (130 mg, 0.28 mmol), [(E)-2-phenylvinyl]boronic acid (68 mg, 0.59 mmol), Pd(PPh₃)₂Cl (11mg, 0.014mmol), NaHCO₃ (saturated aqueous, 3 ml) and DME (3ml) was heated at 95°C overnight. The resulting mixture was cooled to room temperature, diluted with saturated aqueous sodium bicarbonate, and extracted with DCM. The organic layer was washed with brine and concentrated. The crude product was purified by column chromatography (eluting with 4:1 hexanes/ethyl acetate) to give 36mg (30%) of 4-[(7-chloro-4-methyl-1H-indol-5-

yl)amino]-6-methyl-5-[(*E*)-2-phenylvinyl]nicotinonitrile as a yellow solid. MS 399.2(M+H); HPLC 96.2% at 215 nm, rt = 5.7 min [a].



[00392] Preparation of 4-[(7-chloro-4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{6-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}vinyl]nicotinonitrile:

A mixture of 4-[(7-chloro-4-methyl-1*H*-indol-5-yl)-amino]-5-iodonicotinonitrile (130 mg, 0.28 mmol), 1-methyl-4-(6-vinyl-pyridin-2-ylmethyl)-piperazine (128 mg, 0.59 mmol), Pd(OAc)₂ (11 mg, 0.014 mmol), P(*o*-Tol)₃ (2.8 mg, 0.0084 mmol) and Et₃N (2 mL) in DMF (5 mL) was heated to 95° C overnight. The resulting mixture was cooled to room temperature, diluted with saturated aqueous sodium bicarbonate and extracted with dichloromethane. The combined organic layers were washed with brine and concentrated *in vacuo*. The residue was purified by column chromatography (4:1 hexene/ethyl acetate) to provide 40 mg (27%) of the title compound as a yellow solid. MS 270.2 (M+H); rt = 10.5 min [a].



[00393] Preparation of 5-[(*E*)-2-(4-{4-(2-hydroxyethyl)piperazin-1-yl}methyl)phenyl]vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile:

A mixture of 5-[(*E*)-2-(4-formylphenyl)ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile (130 mg, 0.34 mmol), 2-piperazine-1-yl-ethanol (88 mg, 0.68 mmol), NaBH(AcO)₃ (358 mg, 1.7 mmol) in THF (5 mL) was stirred at room temperature overnight. The resulting mixture was diluted with saturated aqueous sodium bicarbonate and extracted with

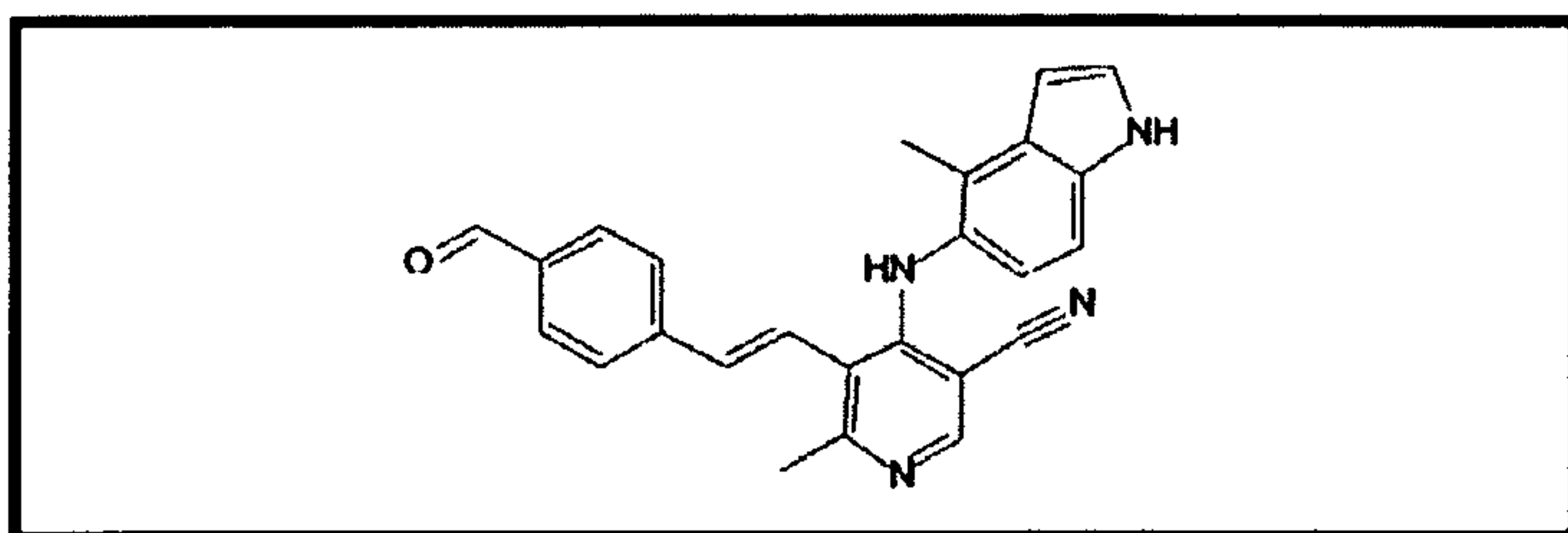
dichloromethane. The combined organic layers were washed with brine and concentrated *in vacuo*. The crude product was purified by HPLC to provide 71 mg (42%) of the title compound as a yellow solid; MS 493.2 (M+H).

[00394] Preparation of compounds in Table 11:

The compounds in Table 11 were prepared from 5-[(*E*)-2-(4-formylphenyl)ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile and the appropriate amine via the procedure described for 5-[(*E*)-2-(4-[[4-(2-hydroxyethyl)piperazin-1-yl]methyl]phenyl)vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile.

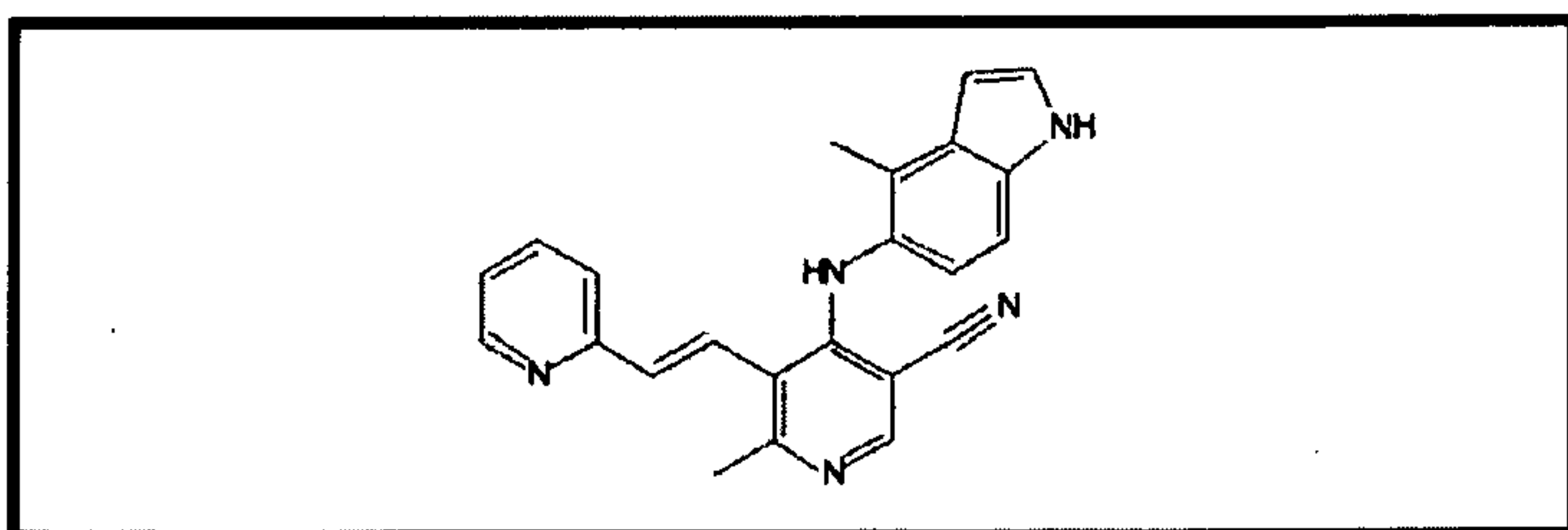
Compound name	MS	HPLC rt
5-[(<i>E</i>)-2-{4-[(4-hydroxypiperidin-1-yl)methyl]phenyl}vinyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	464.2 (M+H)	5.4 min [a]
5-[(<i>E</i>)-2-{4-[[3-(dimethylamino)propyl]amino]methyl}phenyl]vinyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	465.2 (M+H)	4.6 min [a]
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-{4-[(4-pyrrolidin-1-yl)piperidin-1-yl]methyl}phenyl]vinyl]nicotinonitrile	517.2 (M+H)	4.7 min [a]
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-{4-(thiomorpholin-4-ylmethyl)phenyl}vinyl]nicotinonitrile	466.1 (M+H)	6.1 min [a]
5-[(<i>E</i>)-2-{4-[(1,4'-bipiperidin-1'-yl)methyl]phenyl}ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	531.3 (M+H)	4.7 min [a]
5-[(<i>E</i>)-2-(4-[[3-ethoxypropyl]amino]methyl)phenyl]ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	466.3 (M+H)	6.4 min [a]
5-[(<i>E</i>)-2-{4-[(3-hydroxypyrrolidin-1-yl)methyl]phenyl}ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	450.2 (M+H)	5.5 min [a]
N-{4-[(<i>E</i>)-2-{5-cyano-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridin-3-yl}ethenyl]benzyl}-N-(2-piperidin-1-ylethyl)acetamide	267.2 (M+2H)	NA
5-[(<i>E</i>)-2-(4-[[4-(1-methylethyl)piperazin-1-yl]methyl]phenyl)ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	246.1 (M+2H)	5.6 min [a]
N-{4-[(<i>E</i>)-2-{5-cyano-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridin-3-yl}ethenyl]benzyl}-N-(2-pyrrolidin-1-ylethyl)acetamide	260.2 (M+2H)	NA
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-(4-[[2-pyridin-3-ylethyl]amino]methyl)phenyl]ethenyl]pyridine-3-carbonitrile	485.3 (M+H)	4.9 min [a]
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-(4-[[2-pyridin-2-ylethyl]amino]methyl)phenyl]ethenyl]pyridine-3-carbonitrile	485.3 (M+H)	5.9 min [a]
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-(4-[[3-morpholin-4-ylpropyl]amino]methyl)phenyl]ethenyl]pyridine-3-carbonitrile	507.1 (M+H)	4.9 min [a]

4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{4-[(4-morpholin-4-yl)piperidin-1-yl)methyl]phenyl}ethenyl]pyridine-3-carbonitrile	533.3 (M+H)	4.6 min [a]
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4-{[(2-morpholin-4-ylethyl)amino]methyl}phenyl)ethenyl]pyridine-3-carbonitrile	493.3 (M+H)	4.6 min [a]
5-[(E)-2-{4-[(4-cyclopentylpiperazin-1-yl)methyl]phenyl}ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	517.3 (M+H)	6.1 min [a]
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(morpholin-4-ylmethyl)phenyl]ethenyl]pyridine-3-carbonitrile	450.3 (M+H)	5.4 min [a]



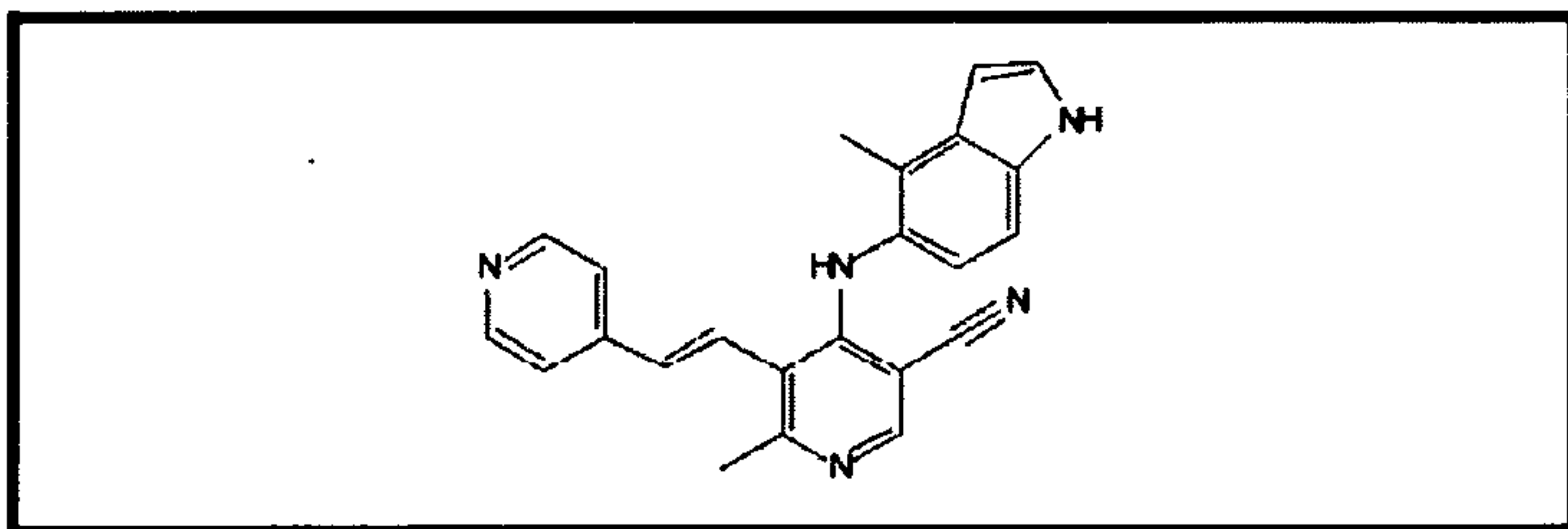
[00395] Preparation of 5-[(E)-2-(4-formylphenyl)ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

A mixture of 5-iodo-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (6.3 g, 16.2 mmol), 4-[(E)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl]benzaldehyde (3.5 g, 13.5 mmol), Pd(PPh₃)₄ (779 mg, 0.81 mmol), DME (150 mL) and saturated aqueous NaHCO₃ (100 mL) was stirred at 100° C overnight. The resulting mixture was cooled to room temperature, diluted with saturated aqueous sodium bicarbonate and extracted with dichloromethane. The combined organic layers were washed with brine and concentrated *in vacuo*. The residue was purified by chromatography (1:2 ethyl acetate/hexane) to provide 3.8 g (71%) of the title compound as a yellow solid. MS 393.20 (M+H).



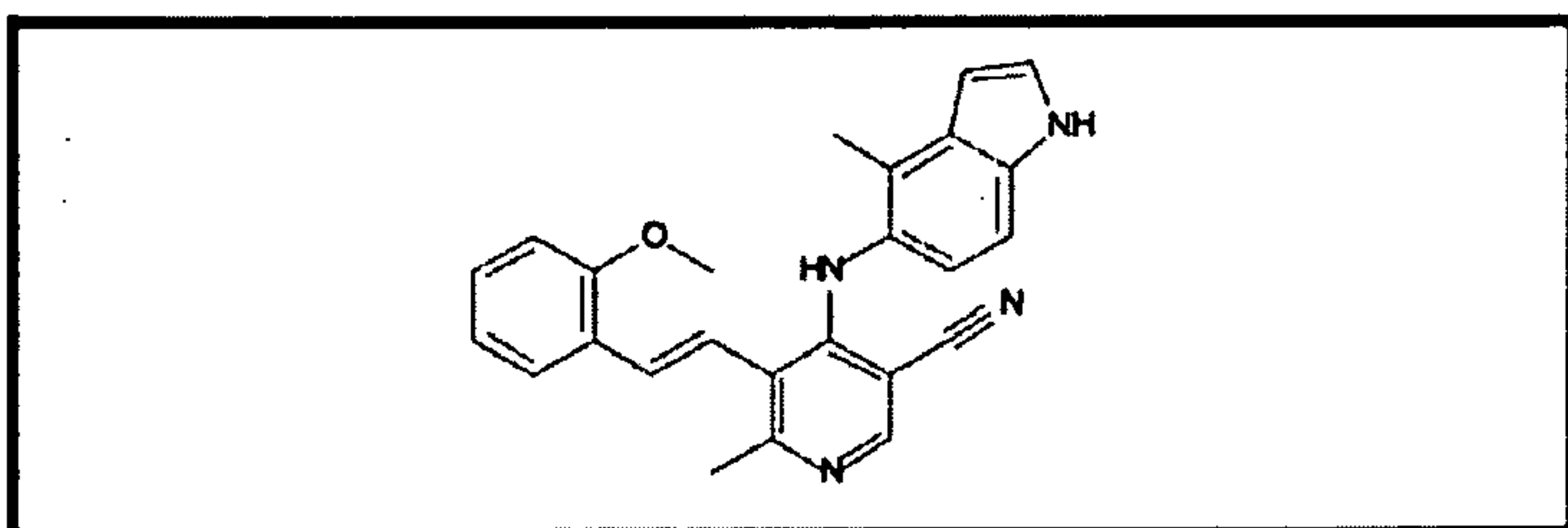
[00396] Preparation of 6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-pyridin-2-yl vinyl]nicotinonitrile:

A mixture of 5-iodo-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile (194 mg, 2.5 mmol), 2-vinylpyridine (63 mg, 0.6 mmol), P(*o*-Tol)₃ (15 mg), triethylamine (0.7 mL) and Pd(OAc)₂ (22 mg) in 2.5 mL of DMF was heated at 90 °C for 3 h. After cooling to room temperature, the reaction mixture was partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography eluting with a gradient of hexane/ethyl acetate to give 162 mg (89%) of the desired product as a light yellow solid. MS 366.2 (M+H); HPLC: 98.2% at 215 nm, 5.6 min [a].



[00397] Preparation of 6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-pyridin-4-yl vinyl]nicotinonitrile:

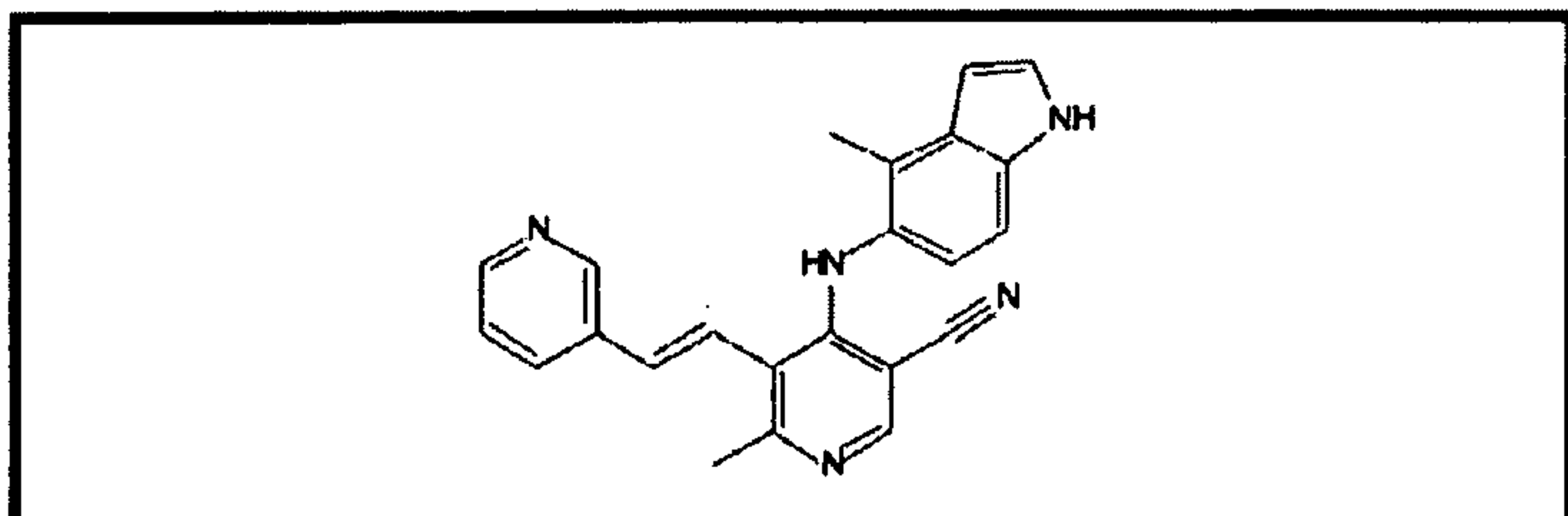
The title compound was prepared from 5-iodo-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile and 4-vinylpyridine via the procedure used to prepare 6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-pyridin-2-yl vinyl]nicotinonitrile to give 33 mg (18%) of the desired product as tan solid. MS 366.1 (M+H); HPLC: 4.0 min. [a].



[00398] Preparation of 5-[(*E*)-2-(2-methoxyphenyl)vinyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino] nicotinonitrile:

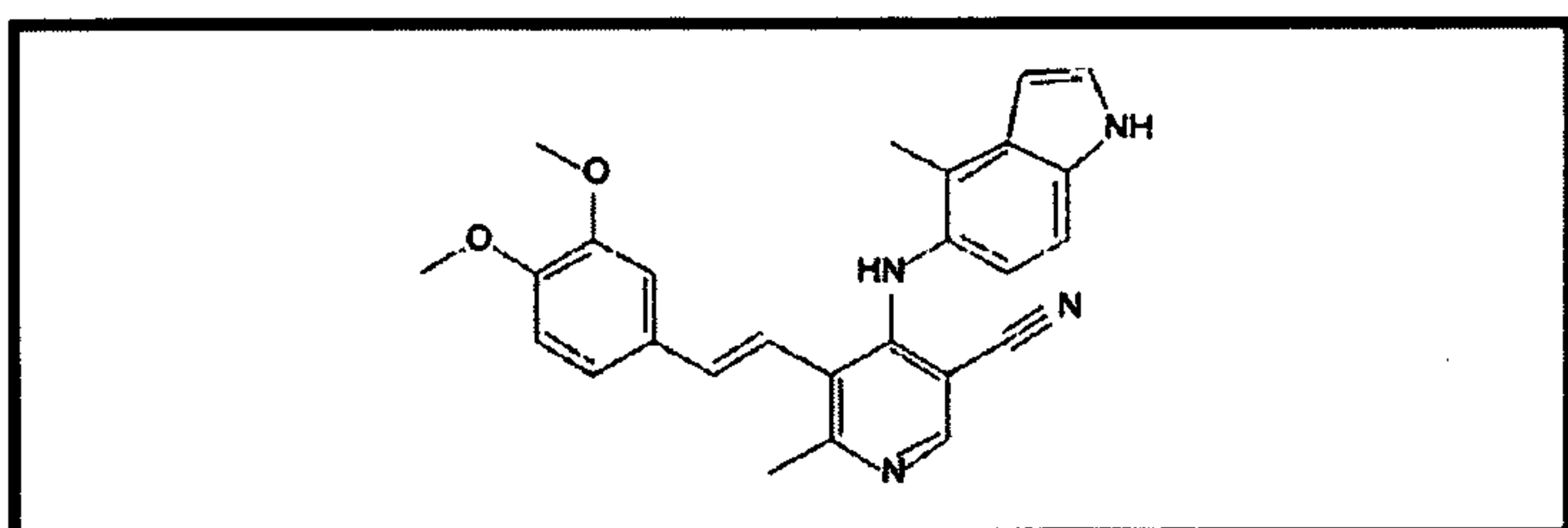
The title compound was prepared from 5-iodo-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile and 2-vinylanisole via the procedure used to prepare 6-methyl-4-[(4-

methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-pyridin-2-ylvinyl]nicotinonitrile to give 71 mg (36%) of the desired product as tan solid. MS 395.2 (M+H); HPLC: *rt* = 9.7 min [a].



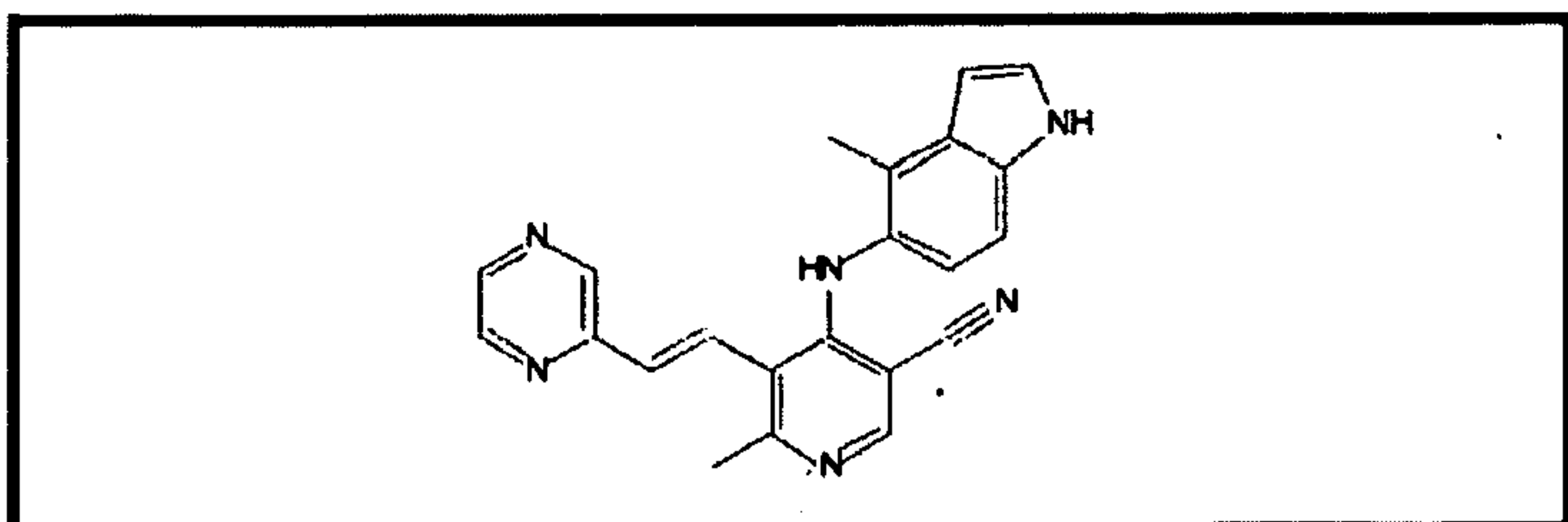
[00399] Preparation of 6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-pyridin-3-ylvinyl]nicotinonitrile:

The title compound was prepared from 5-iodo-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile and 3-vinylpyridine via the procedure used to prepare 6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-pyridin-2-ylvinyl]nicotinonitrile to give 31 mg (17%) of the desired product as tan solid. MS 366.2 (M+H); HPLC: 91.0% at 215 nm, 4.6 min [a].



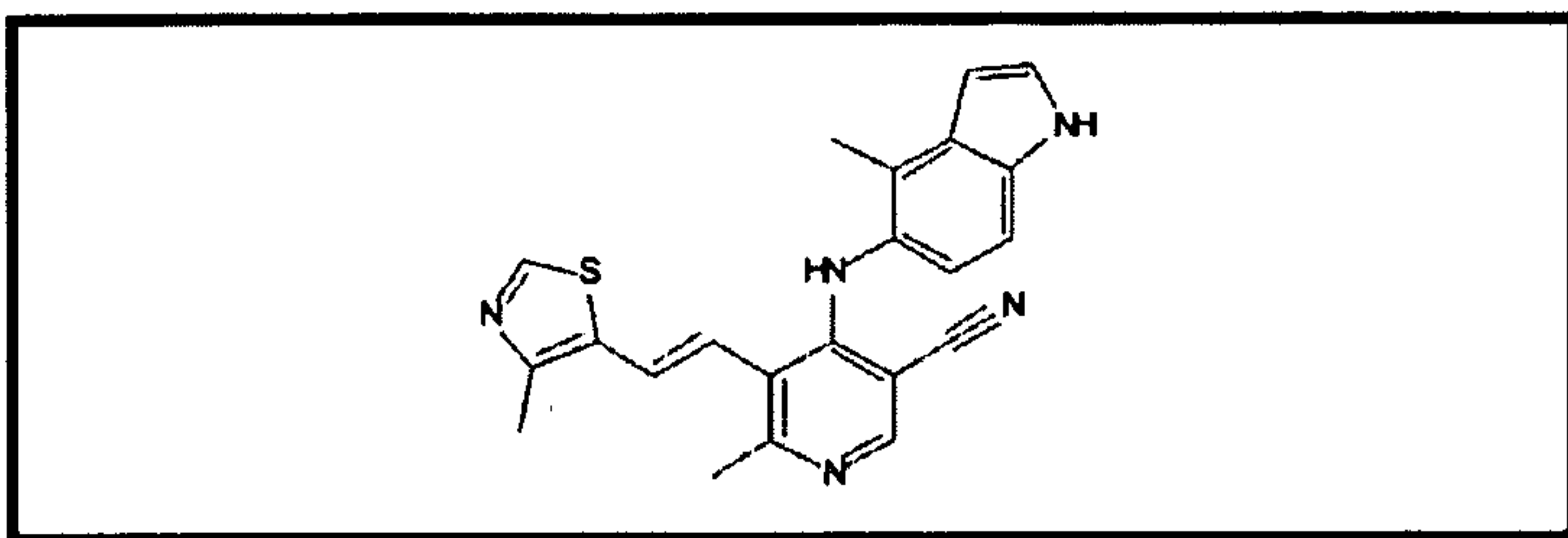
[00400] Preparation of 5-[(*E*)-2-(3,4-dimethoxyphenyl)vinyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino] nicotinonitrile:

The title compound was prepared from 5-iodo-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile and 3,4-dimethoxystyrene via the procedure used to prepare 6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-pyridin-2-ylvinyl]nicotinonitrile to give 82 mg (38%) of the desired product as tan solid. MS 425.3 (M+H); HPLC: 95.7% at 215 nm, *rt* = 9.1 min [a].



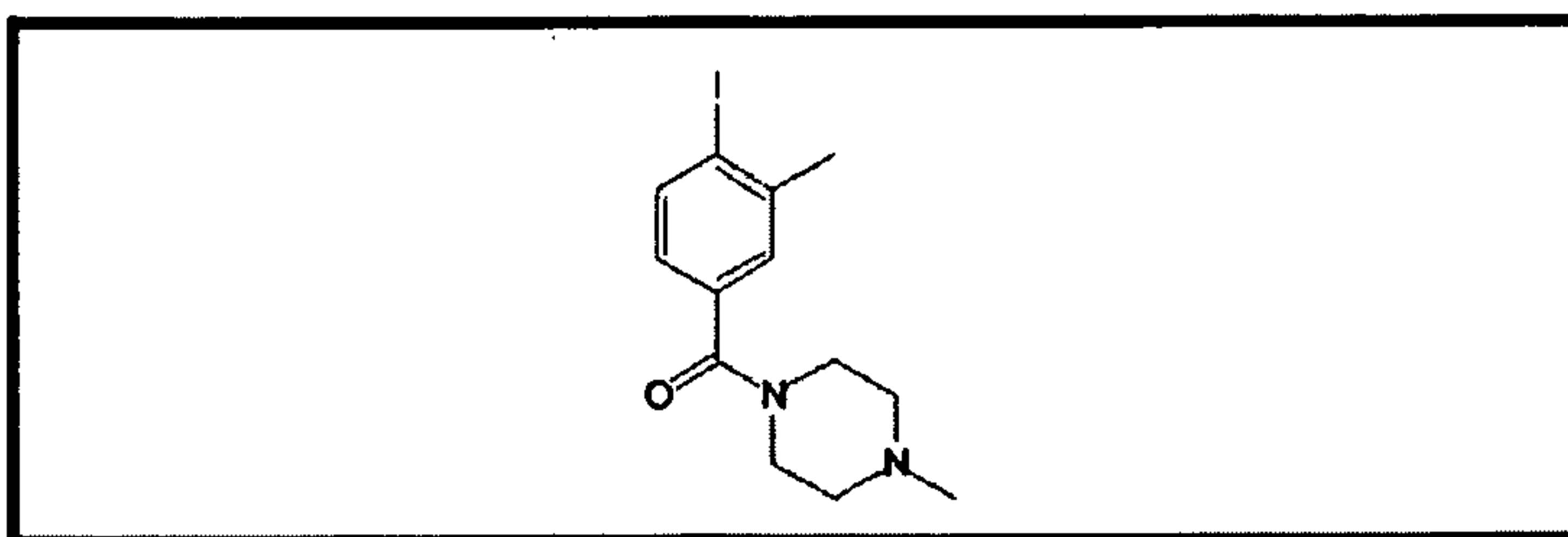
[00401] Preparation of 6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-pyrazin-2-yl vinyl]nicotinonitrile:

The title compound was prepared from 5-iodo-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile and 2-vinylpyrazine via the procedure used to prepare 6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-pyridin-2-ylvinyl]nicotinonitrile to give 164 mg (90%) of the desired product as yellow solid. MS 367.4 (M+H); HPLC: 97.4% at 215 nm, *rt* = 6.5 min [a].



[00402] Preparation of 6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(4-methyl-1,3-thiazol-5-yl)vinyl]nicotinonitrile:

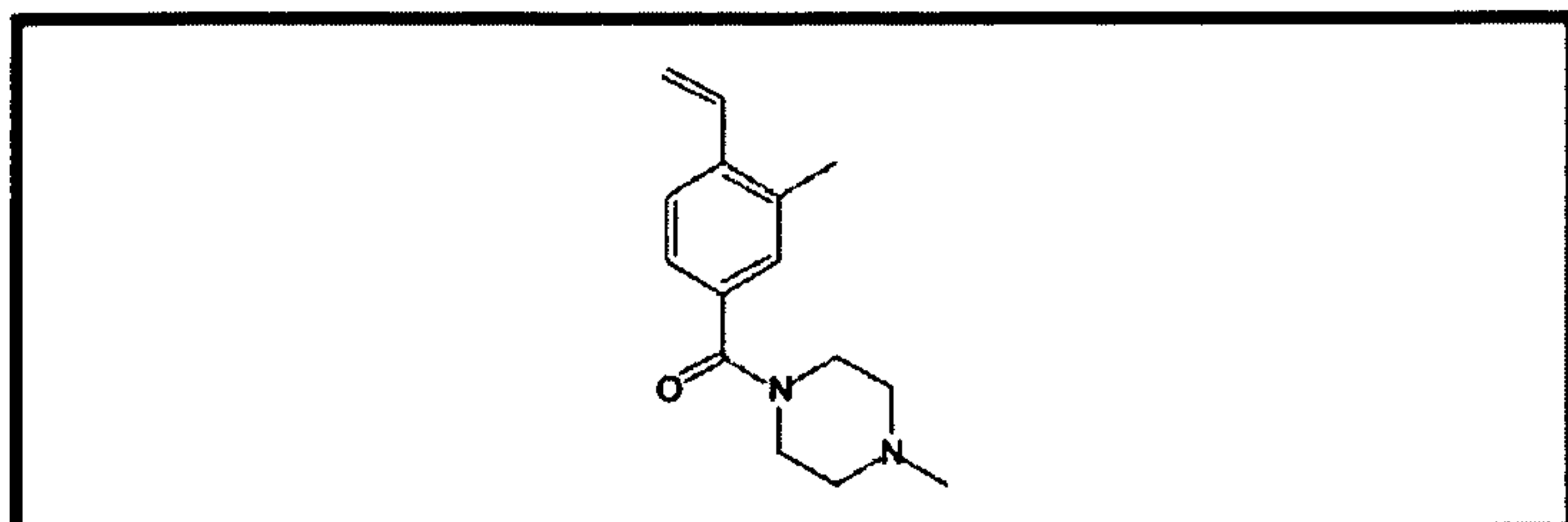
The title compound was prepared from 5-iodo-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile and 4-methyl-5-vinylthiazole via the procedure used to prepare 6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-pyridin-2-ylvinyl]nicotinonitrile to give 28 mg (15%) of the desired product as yellow solid. MS 386.2 (M+H); HPLC: *rt* = 5.6 min [a].



[00403] Preparation of 1-(4-iodo-3-methylbenzoyl)-4-methylpiperazine:

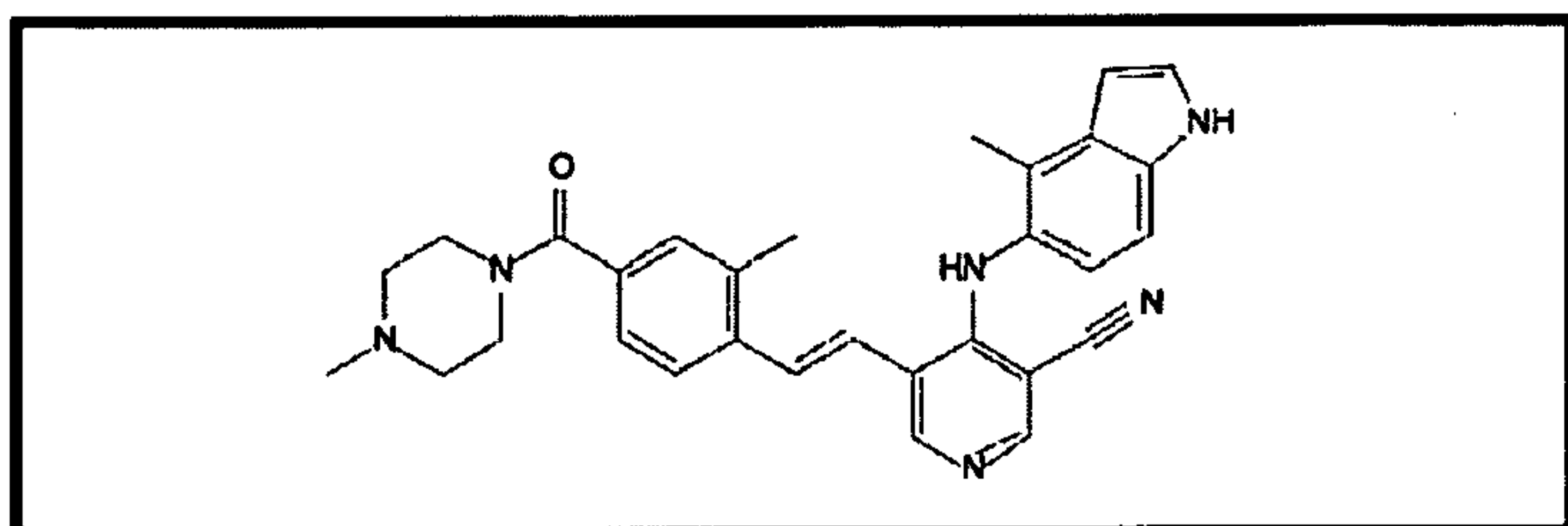
To a stirred solution of 4-iodo-3-methylbenzoic acid (1.57 g, 6 mmol) in DMF (18 mL) was added PyBOP (3.75 g, 7.2 mmol) at 0 °C followed by Hunig's base (1.94 g, 15 mmol) and *N*-methylpiperazine (1.21 g, 12 mmol). The solution was stirred at room temperature overnight. After removal of the volatile material, the reaction mixture was partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. The organic layer was dried over magnesium

sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography eluting with a gradient of hexane/ethyl acetate to give 2.01 g (98%) of the desired product as a light yellow oil. MS 345.0 (M+H); HPLC: 94.4% at 215 nm, *rt* = 6.8 min [a].



[00404] Preparation of 1-[(4-ethenyl-3-methylphenyl)carbonyl]-4-methyl piperazine:

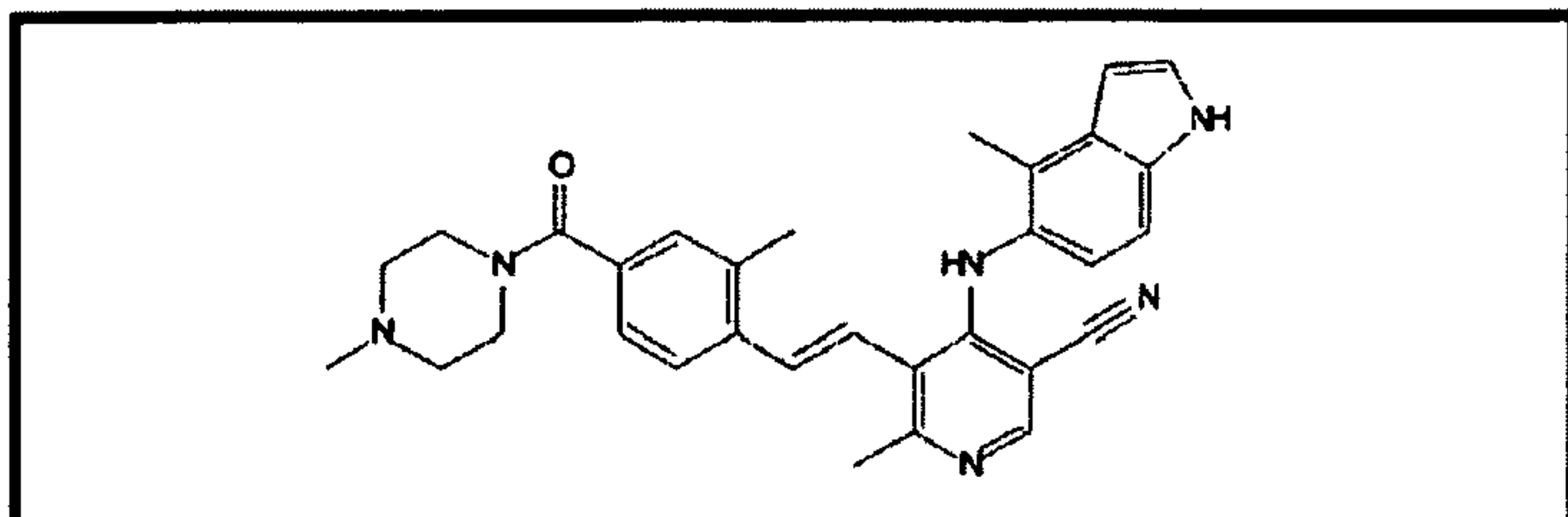
A mixture of 1-(4-iodo-3-methylbenzoyl)-4-methylpiperazine (840 mg, 2.4 mmol), tributylvinyltin (1.17 g, 3.7 mmol), and Pd(PPh₃)₄ (230 mg) in 10 mL of DMF was heated at 115 °C for 3 h. After cooling to room temperature, the reaction mixture was partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography eluting with a gradient of hexane/ethyl acetate to give 524 mg (88%) of the desired product as a light yellow oil. MS 245.2 (M+H); HPLC: 94.4% at 215 nm, *rt* = 6.0 min [a].



[00405] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{2-methyl-4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}vinyl]nicotinonitrile:

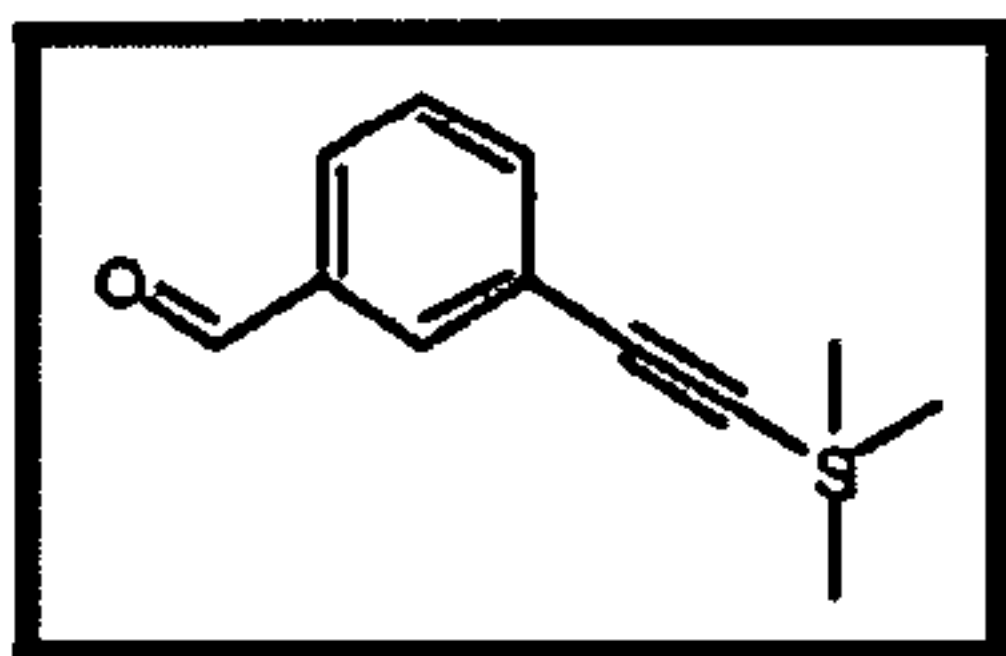
The title compound was prepared from 4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile and 1-(4-iodo-3-methylbenzoyl)-4-methylpiperazine via the procedure used to prepare 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-pyridin-2-ylvinyl]nicotinonitrile to give 123 mg

(50%) of the desired product as yellow solid. MS 491.2 (M+H); HPLC: 94.8% at 215 nm, rt = 5.4 min [a].



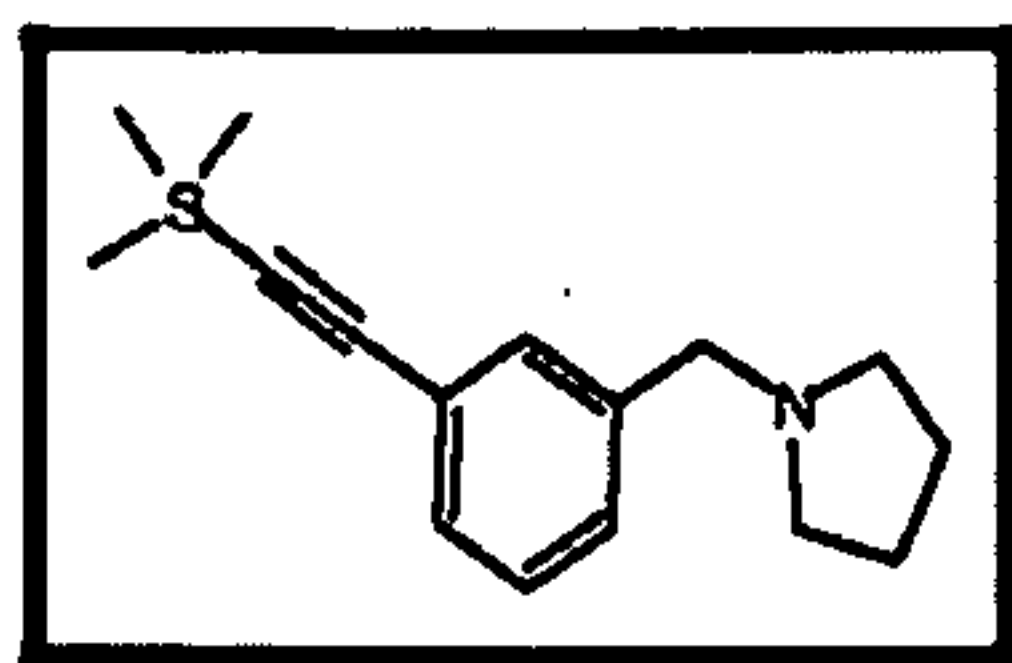
[00406] Preparation of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{2-methyl-4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}ethenyl]pyridine-3-carbonitrile:

The title compound was prepared from 5-iodo-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 1-[(4-ethenyl-3-methylphenyl)carbonyl]-4-methylpiperazine via the procedure used to prepare 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-pyridin-2-ylvinyl]nicotinonitrile to give 36 mg (15%) of the desired product as off-white solid. MS 505.4 (M+H); HPLC: 91.3% at 215 nm, rt = 5.4 min [a].



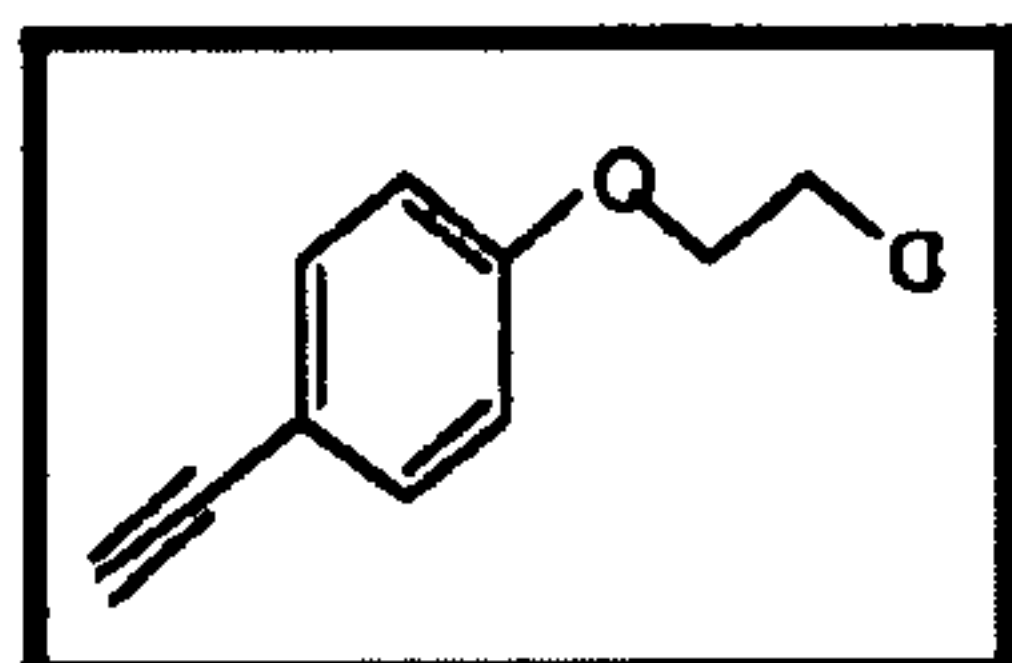
[00407] Preparation of 3-[(trimethylsilyl)ethynyl]benzaldehyde:

3-Bromobenzaldehyde (5 g, 27.0 mmol) was dissolved in 50 mL THF and treated with TMS-acetylene (29.7 mmol, 2.9 g) and Et₃N (81 mmol, 8.2 g). After stirring briefly, Pd(PPh₃)₄ (1.351 mmol, 1.6 g) was added and the reaction was stirred under N₂ at room temperature overnight. Subsequently, another 2 equivalents of TMS-acetylene (60 mmol, 6.0 g) was added followed by CuI (100 mg) and Et₃N (81 mmol, 8.2 g). The reaction was heated to 60° C overnight then evaporated onto silica gel and purified by chromatography (0 to 20% EtOAc in hexanes) to give 2.4 g of the title compound as a yellow oil. MS: 202 [M+].



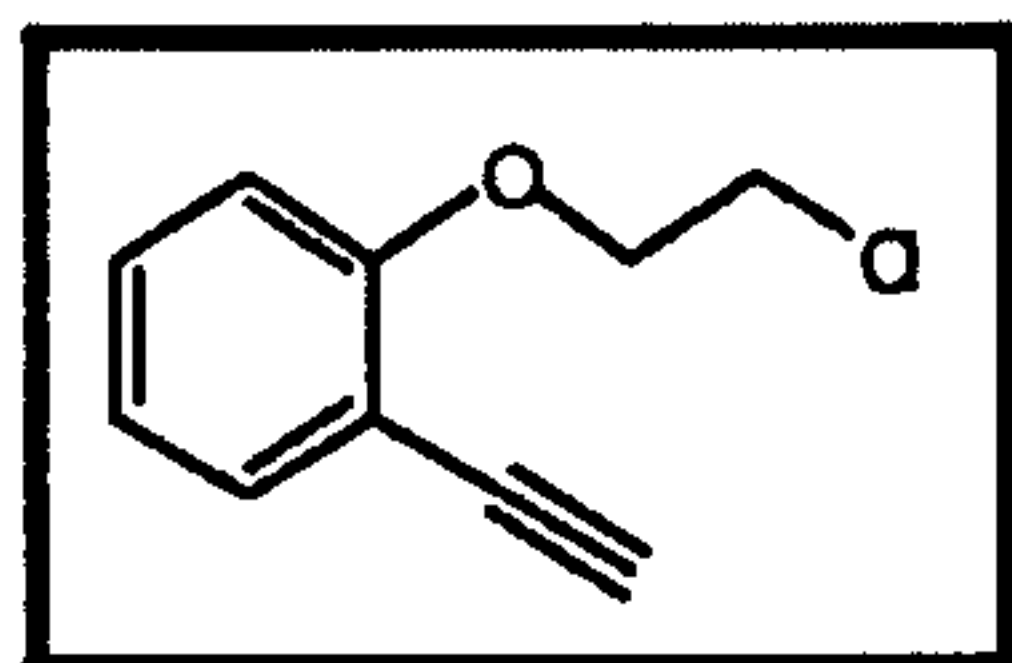
[00408] Preparation of 1-[3-[(trimethylsilyl)ethynyl]benzyl]pyrrolidine:

3-[(Trimethylsilyl)ethynyl]benzaldehyde (1.0 g, 4.9 mmol) was stirred in 30 mL DCM. Pyrrolidine (0.613 mL, 7.41 mmol) was added followed by 1 drop of HOAc. After stirring 5 minutes, NaBH(OAc)₃ (2.1 g, 9.9 mmol) was added and the reaction was stirred for 1h. Two equivalents of HOAc were added (~0.6 mL) and, after stirring for 1/2 h, the reaction was partitioned between DCM and dilute NaHCO₃. The aqueous layer was extracted 1x with DCM and the combined organic layers were dried over MgSO₄, filtered and concentrated to give 1.1 g of the title compound as an oil. MS: 258.2 [M+H].



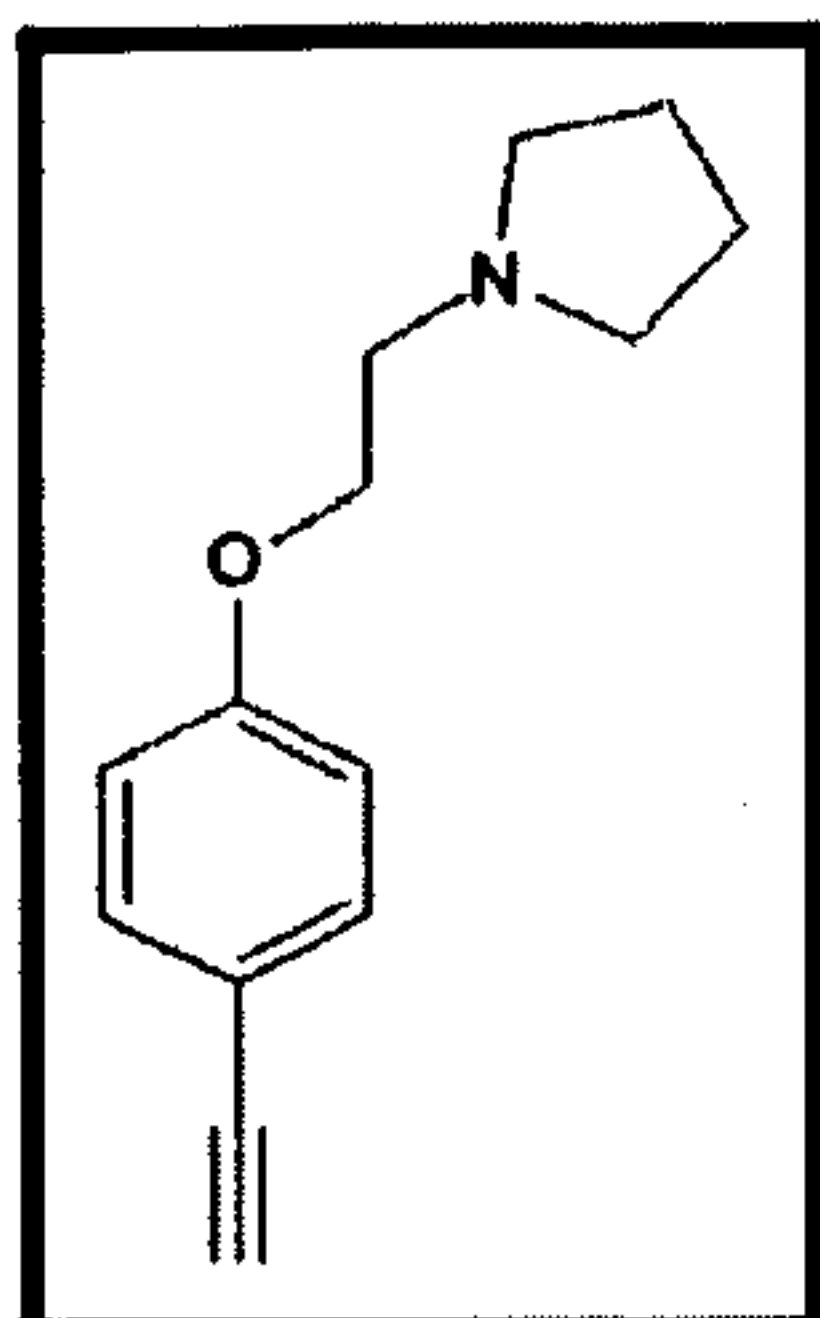
[00409] Preparation of 1-(2-chloroethoxy)-4-ethynylbenzene:

A mixture of 4-[(trimethylsilyl)ethynyl]phenol (700 mg, 3.68 mmol) (Mohamed Ahmed et al., Tetrahedron, 2004, 60, 9977), 2-chloroethyl 4-methylbenzenesulfonate (863 mg, 3.68 mmol), and cesium carbonate (1198 mg, 3.68 mmol) was stirred in 20 mL DMF at room temperature for 24 h. The reaction was poured over water and extracted with EtOAc. The organic phase was washed once with water then dried over MgSO₄, filtered, and concentrated. The product was purified by chromatography (5% to 25% EtOAc/Hex) to give 460 mg of the title compound. (Note that the TMS group fell off during the workup).

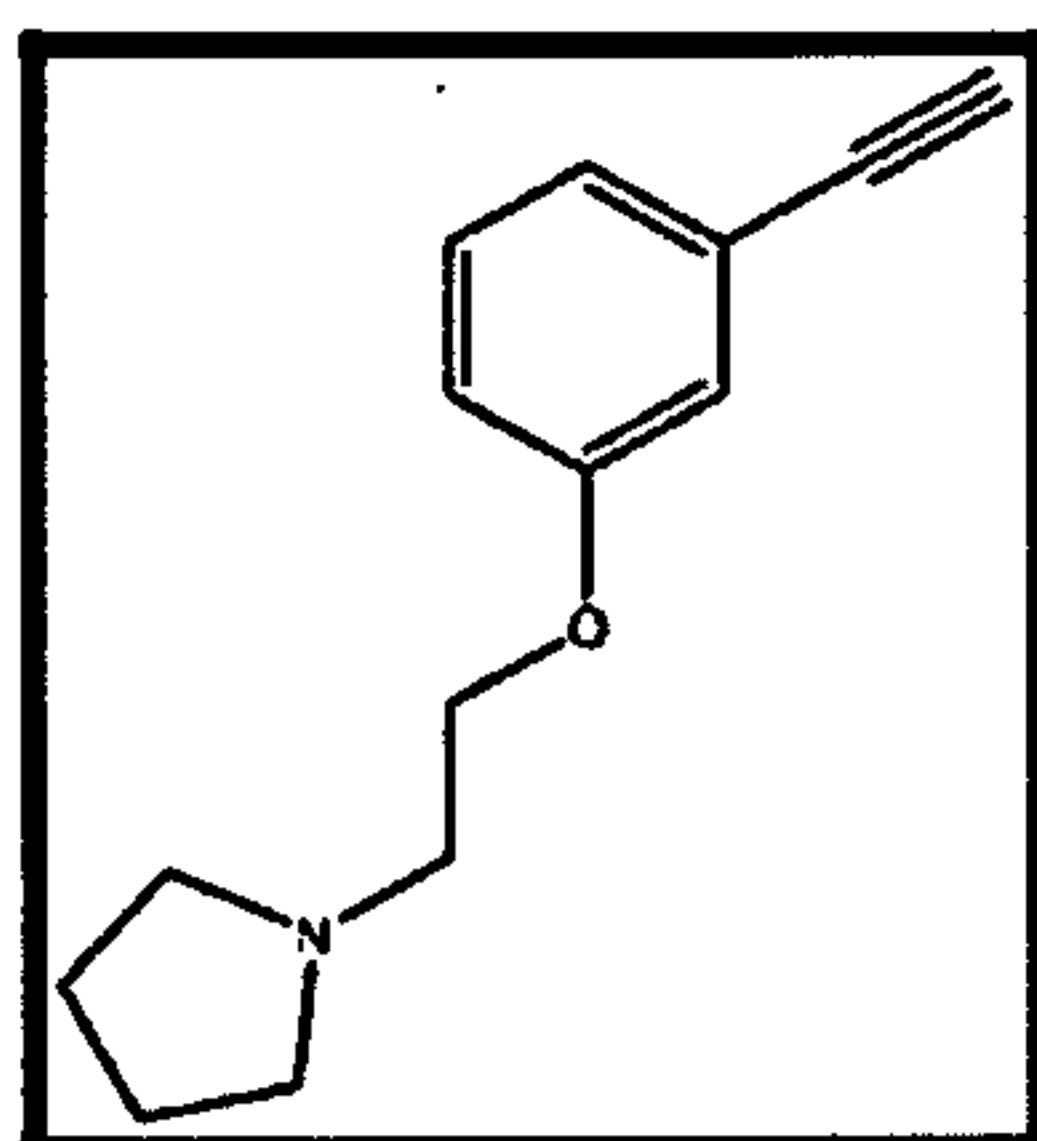


[00410] Preparation of 1-(2-chloroethoxy)-2-ethynylbenzene:

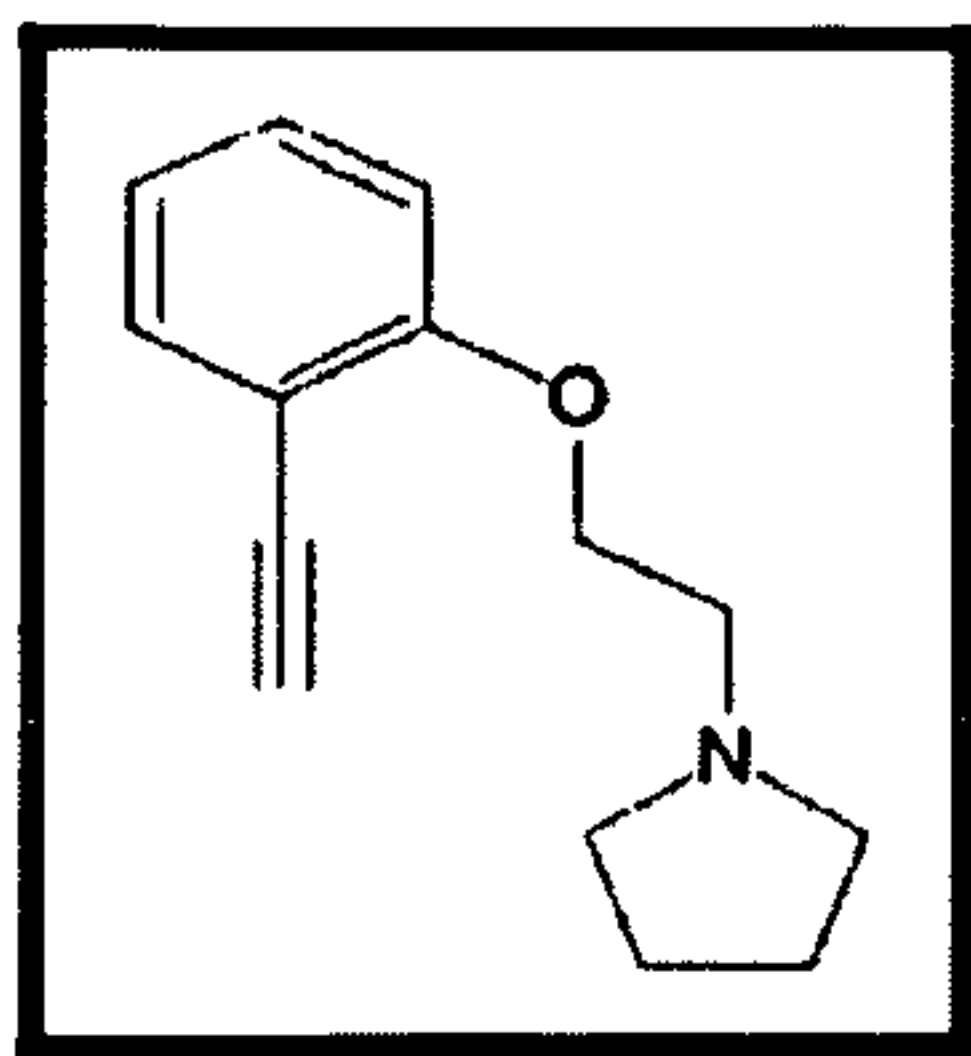
The title compound was prepared from 2-[(trimethylsilyl)ethynyl]phenol (Kabalka et. al., Tetrahedron, 2006, 62, 857) according to the procedure outlined for 1-(2-chloroethoxy)-4-ethynylbenzene.

**[00411] Preparation of 1-[2-(4-ethynylphenoxy)ethyl]pyrrolidine:**

A mixture of 1-(2-chloroethoxy)-4-ethynylbenzene (0.45 g, 2.491 mmol), sodium iodide (0.075 g, 0.498 mmol), and pyrrolidine (0.532 g, 7.47 mmol) was heated to 100° C in 5 mL DME in a sealed vial. After heating overnight the reaction was diluted with EtOAc then twice washed with water. The organic layer was dried over MgSO₄, filtered and concentrated to give 0.50 g of the title compound. MS: 216.1 [M+H].

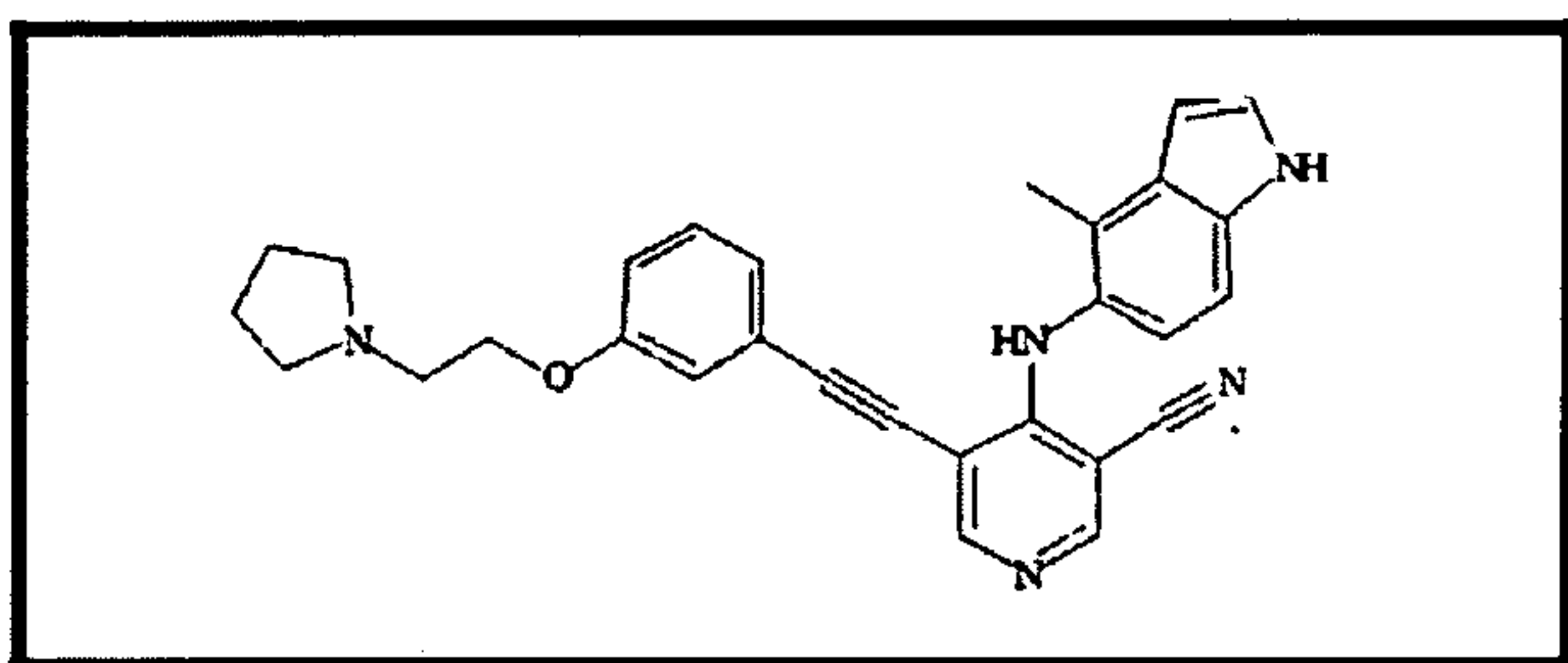
**[00412] Preparation of 1-[2-(3-ethynylphenoxy)ethyl]pyrrolidine:**

The title compound was prepared from 1-(2-chloroethoxy)-3-ethynylbenzene according to the procedure used for 1-[2-(4-ethynylphenoxy)ethyl]pyrrolidine. MS: 216.1 [M+H].



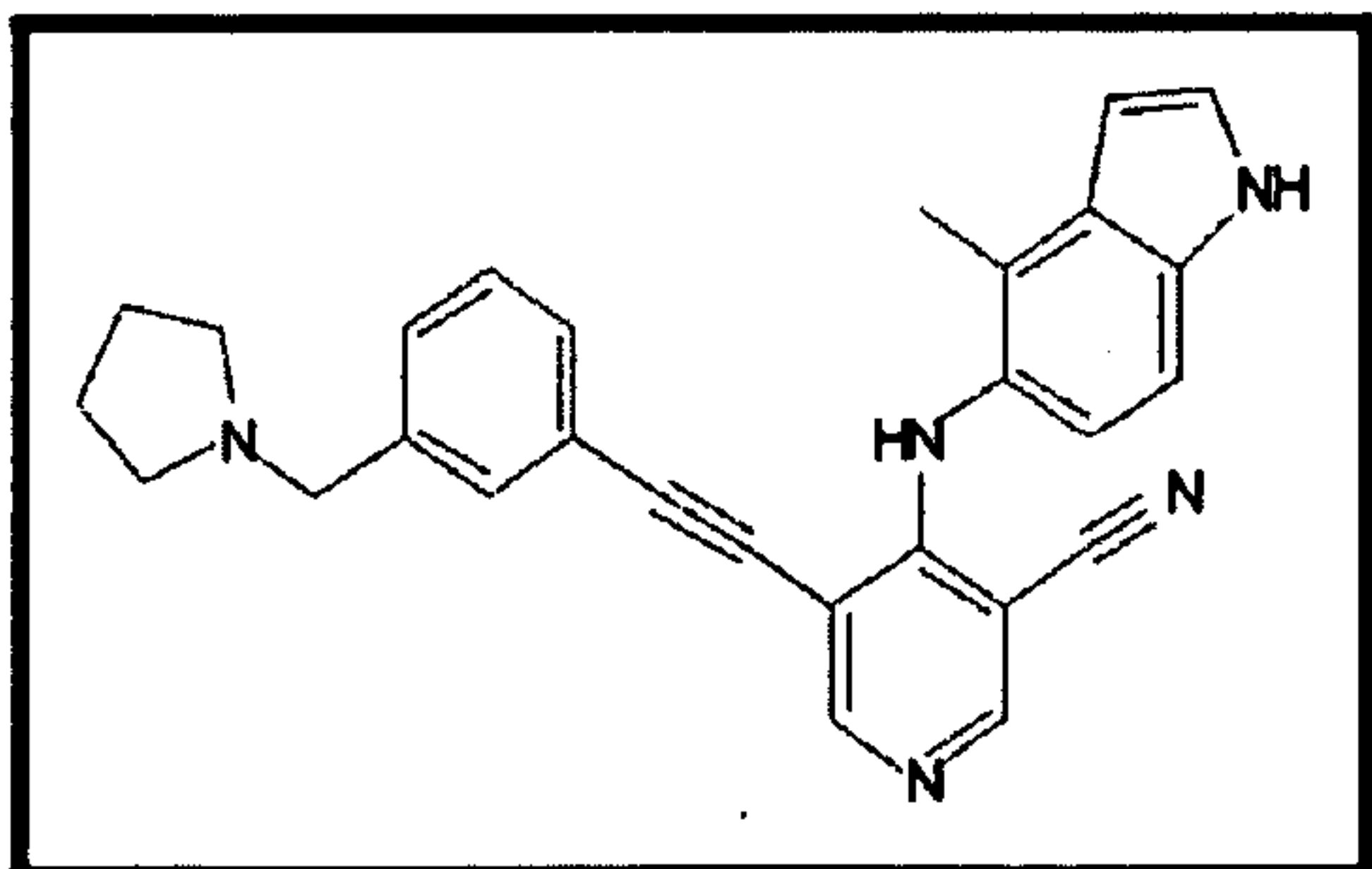
[00413] Preparation of 1-[2-(2-ethynylphenoxy)ethyl]pyrrolidine:

The title compound was prepared from 1-(2-chloroethoxy)-2-ethynylbenzene according to the procedure used for 1-[2-(4-ethynylphenoxy)ethyl]pyrrolidine. MS: 216.1 [M+H].



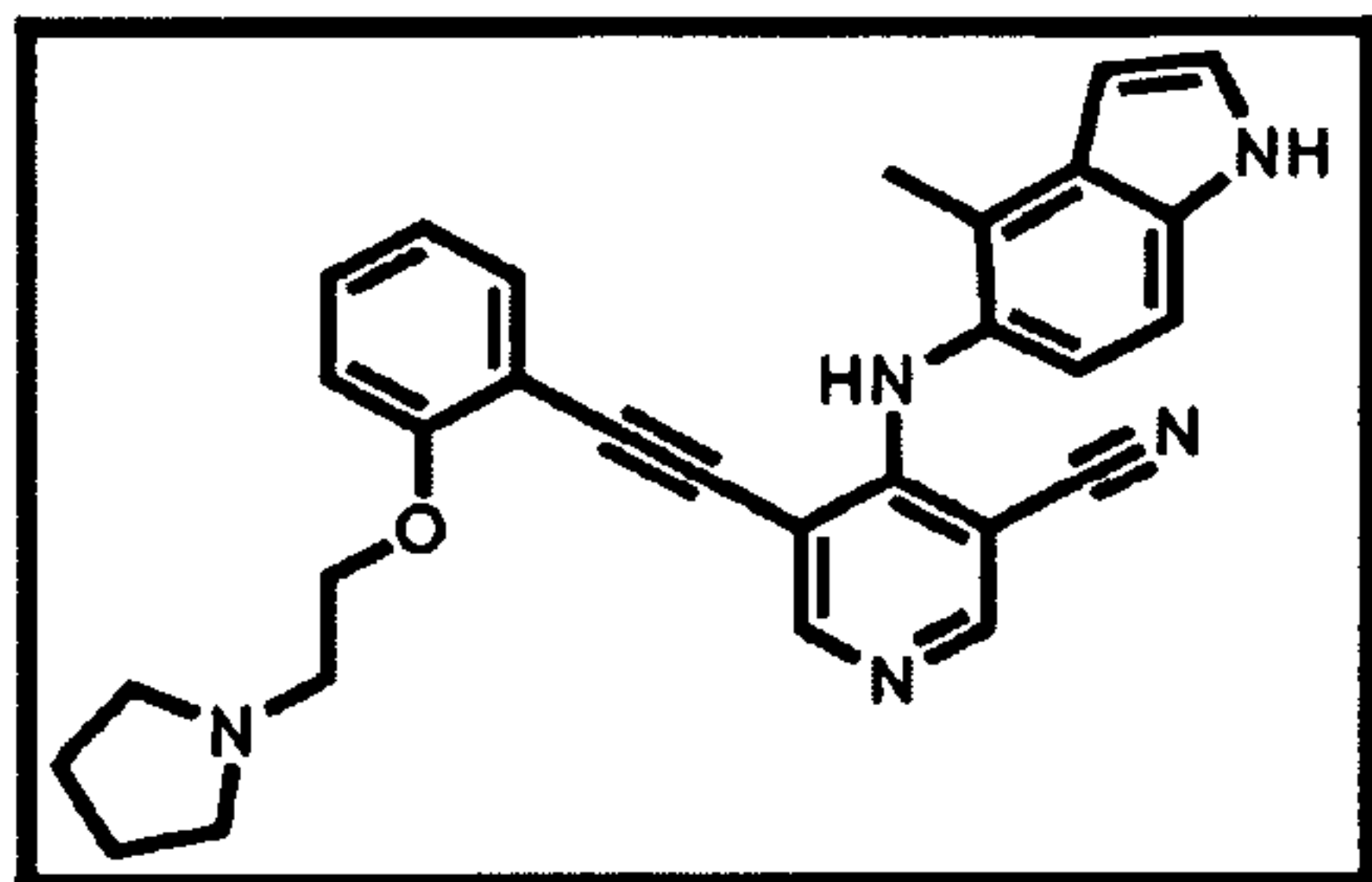
[00414] Preparation of 4-[(4-Methyl-1H-indol-5-yl)amino]-5-[[3-(2-pyrrolidin-1-ylethoxy)phenyl]ethynyl]nicotinonitrile:

A mixture of 5-Iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (94 mg, 0.25 mmol), 1-[2-(3-ethynylphenoxy)ethyl]pyrrolidine (59 mg, 0.28 mmol), Pd(PPh₃)₂Cl₂ (17 mg, 0.025 mmol), CuI (5 mg, 0.025 mmol), and Et₃N (101 mg, 1.0 mmol) was stirred in 2.5 mL DMF at room temperature for 3h. The reaction was filtered and the filtrate was purified by HPLC giving 72 mg of the title compound. MS (ESI) m/z 463.2; HPLC 97.6% at 215 nm, rt = 9.9 min [A].



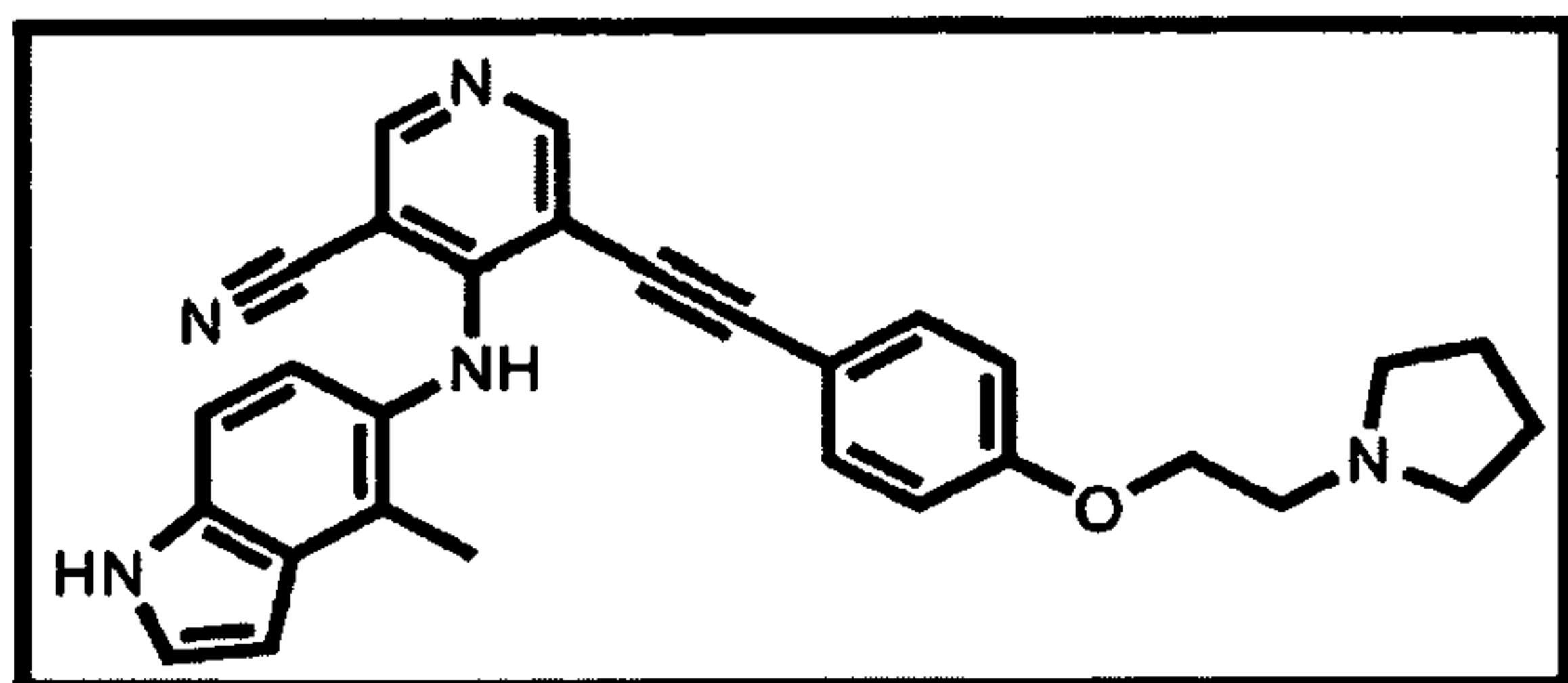
[00415] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[[3-(pyrrolidin-1-ylmethyl)phenyl] ethynyl]pyridine-3-carbonitrile:

A mixture of 1-{3-[(trimethylsilyl)ethynyl]benzyl}pyrrolidine (250 mg, 0.97 mmol), 5-iodo-4-(4-methyl-1H-indol-5-ylamino)nicotinonitrile (280 mg, 0.75 mmol), Pd(PPh₃)₂Cl₂ (52 mg, 0.075 mmol), Et₃N (151 mg, 1.5 mmol), and CuI (14 mg, 0.075 mmol) was stirred in 7 mL DMF at room temperature. TBAF (1M in THF, 0.97 mmol) was added and the reaction was stirred at room temperature for 1h. The reaction mixture was filtered and the filtrate was purified by HPLC to give 240 mg of the title compound. Trituration with EtOAc gave 70 mg of product. HPLC: 90.1% at 215 nm, rt = 7.3 min [a]; HRMS: calcd for C₂₈H₂₅N₅+H, 432.21827, found 432.2183.



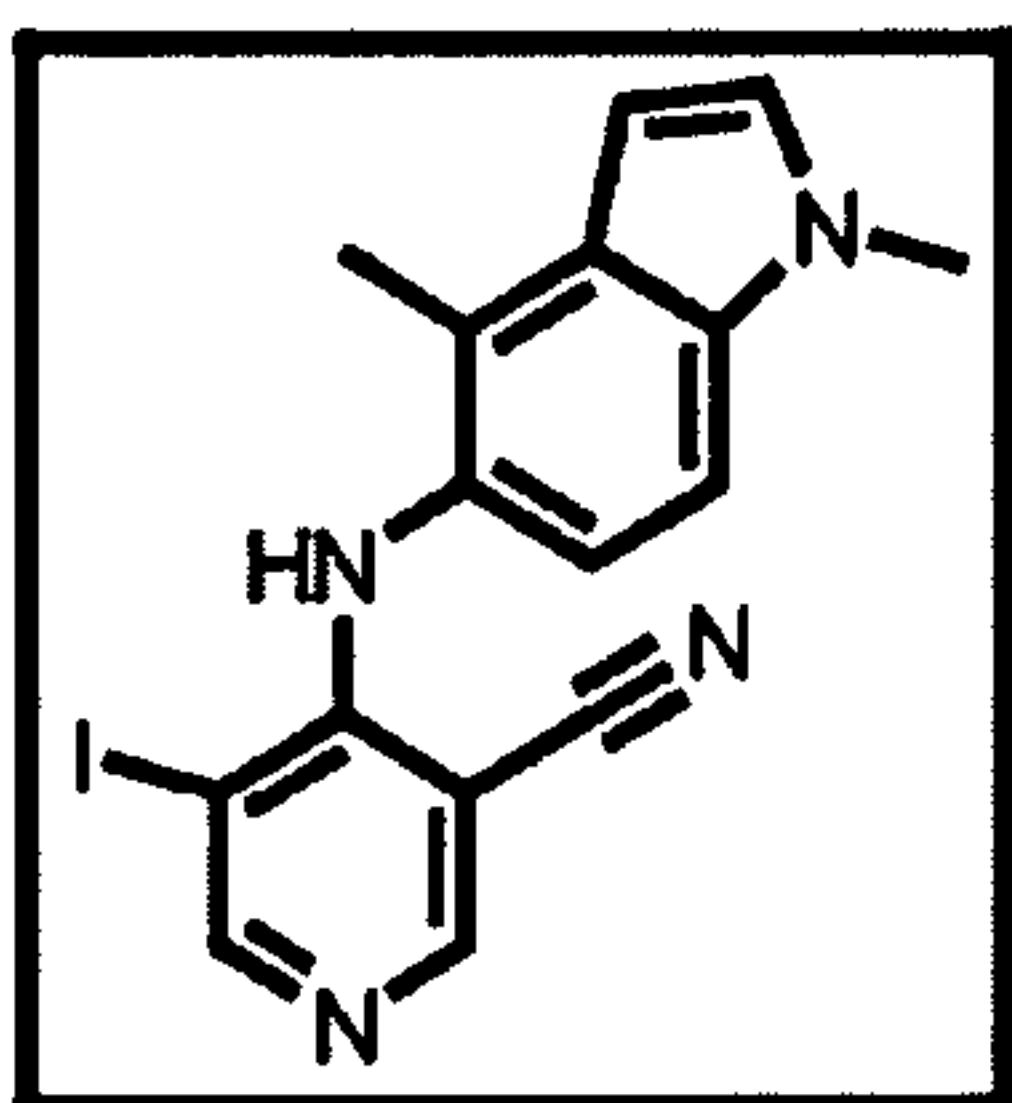
[00416] Preparation Of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[[2-(2-pyrrolidin-1-ylethoxy)phenyl]ethynyl]pyridine-3-carbonitrile:

A mixture of 1-[2-(2-ethynylphenoxy)ethyl]pyrrolidine (127 mg, 0.59 mmol), 5-iodo-4-(4-methyl-1H-indol-5-ylamino)nicotinonitrile (200 mg, 0.54 mmol), Pd(PPh₃)₂Cl₂ (37 mg, 0.053 mmol), CuI (10 mg, 0.053 mmol), and Et₃N (160 mg, 1.6 mmol) was stirred at room temperature in 5 mL DMF. After 3h the reaction was acidified with TFA (~50 μ L) and filtered. The filtrate was purified by preparative HPLC to give the TFA salt of the title compound. Treatment with HCl/dioxane and trituration with EtOH gave 140 mg (56%) of the title compound as its HCl salt. HRMS: 462.2286 (M+H); HPLC rt = 8.2 min [a].



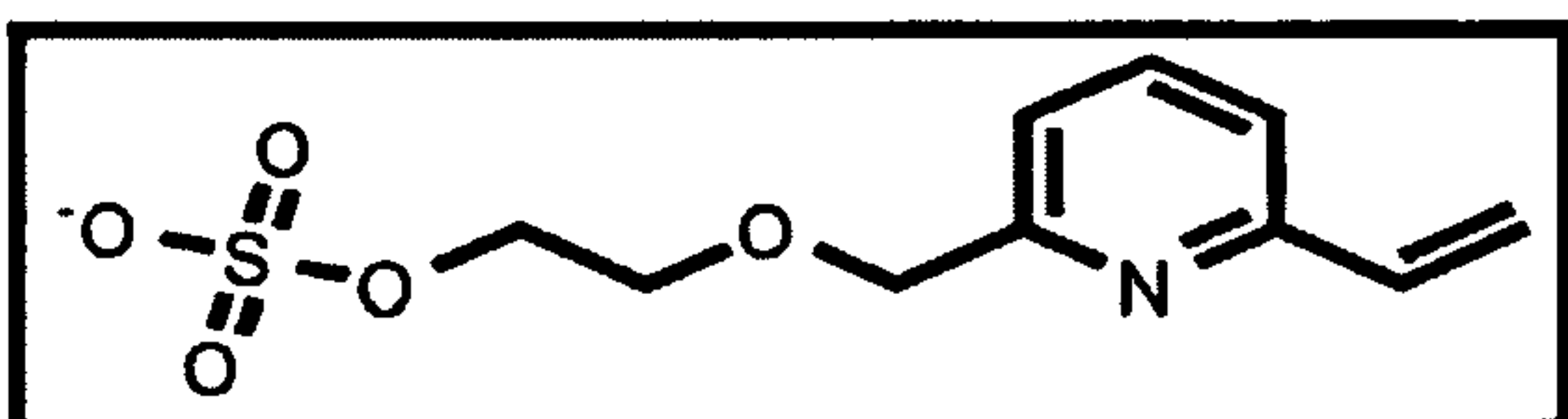
[00417] Preparation Of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[[4-(2-pyrrolidin-1-ylethoxy)phenyl]ethynyl]pyridine-3-carbonitrile:

The title compound was prepared from 5-iodo-4-(4-methyl-1H-indol-5-ylamino)nicotinonitrile and 1-[2-(4-ethynylphenoxy)ethyl]pyrrolidine according to the procedure utilized for 4-[(4-methyl-1H-indol-5-yl)amino]-5-[[2-(2-pyrrolidin-1-ylethoxy)phenyl]ethynyl]pyridine-3-carbonitrile. MS (ESI): 462.2 (M+H); HPLC *rt* = 1.77 min [d].



[00418] Preparation Of 4-[(1,4-dimethyl-1H-indol-5-yl)amino]-5-iodonicotinonitrile:

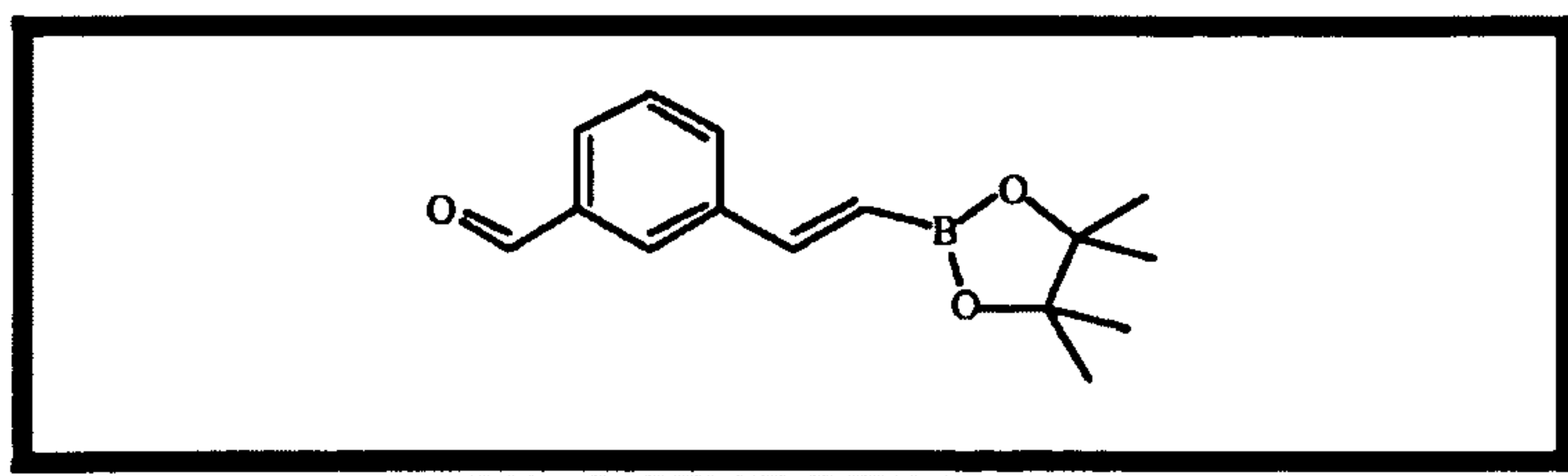
4-Chloro-5-iodonicotinonitrile (300 mg, 1.13 mmol) and 1,4-dimethyl-1H-indol-5-amine (218 mg, 1.36 mmol) were dissolved in ethanol (3 ml). The reaction mixture was heated at reflux overnight then cooled to room temperature and poured into saturated aqueous sodium bicarbonate. The precipitate formed was filtered and washed with water and methanol to give 401 mg (91%) of the title compound as a brown solid, MS 389.2 (M+H).



[00419] Preparation of 2-[(6-vinylpyridin-2-yl)methoxy]ethyl sulfate:

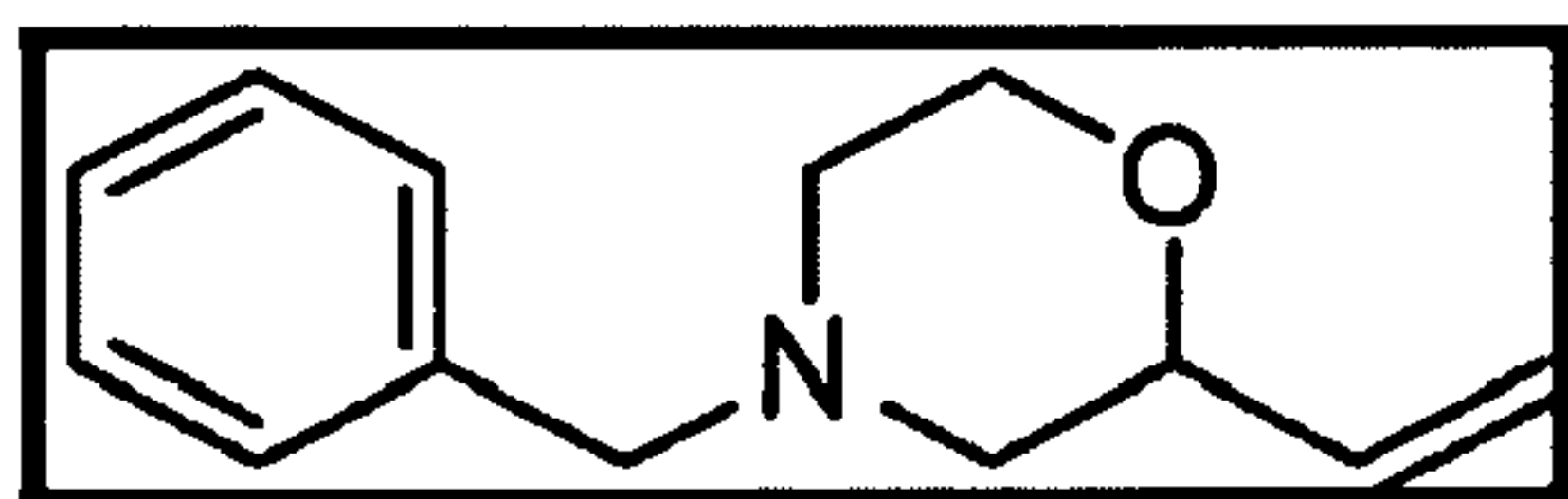
A solution of (6-vinylpyridin-2-yl)methanol (200 mg, 1.48 mmol) in anhydrous DMF (2.5 ml) was cooled to -45°C , followed by the addition of sodium hydride (95% wt., 45 mg, 1.78 mmol) in portions. The temperature was kept under -20°C during the addition. It was warmed to 0°C and stirred at this temperature for 1 hr. The solution was then cooled to -45°C , followed by the addition of 1,3,2-dioxathiolane-2,2-dioxide (226 mg, 1.78 mmol). The reaction mixture was slowly warmed to room temperature and stirred overnight. The solvent was removed, and the

residue was purified by HPLC to give 130 mg (34%) of the title compound as an off-white solid, MS 258.0 (M). HPLC: 92.7% at 215 nm, rt = 3.6 min [a].



[00420] Preparation of 3-[(E)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethenyl]benzaldehyde:

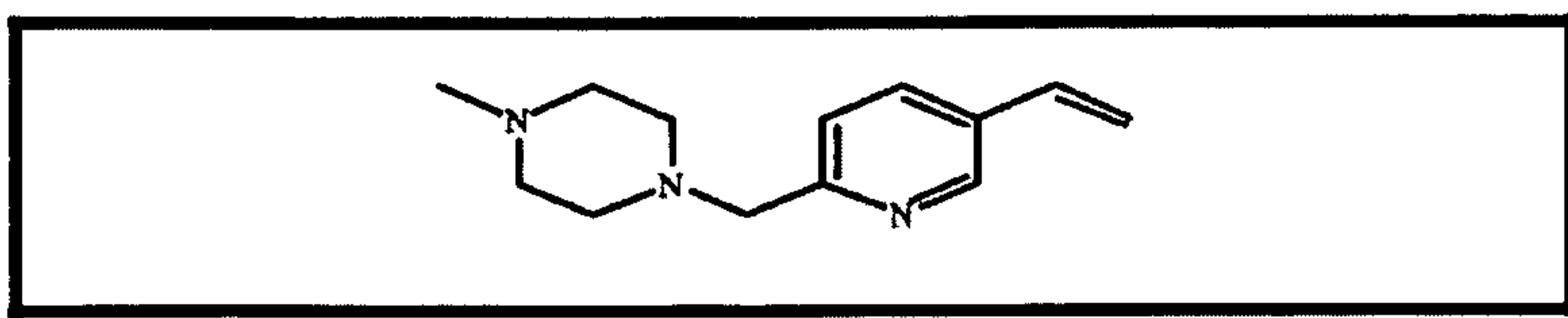
To a solution of 3-bromobenzaldehyde (5.0 g, 27 mmol), Pd(OAc)₂ (360 mg, 1.6 mmol) and 1,10-phenanthroline (320 mg, 1.61 mmol) in anhydrous CH₃CN (100 ml) at room temperature was added triethylamine (7.6 ml, 54.5 mmol) followed by the addition of vinylboronic acid pinacolester (5.6 ml, 33 mmol). The reaction mixture was heated to 65°C for 3 days, diluted with diethyl ether (700 ml), then washed successively with 10% HCl, H₂O and brine. Drying, filtration and evaporation gave a brown oil, which was purified by silica gel chromatography (CH₂CH₂), providing 1.65 g (24%) of the title compound as a dark-yellow oil. ¹H NMR (300 MHz, DMSO) 1.32 (s, 12H), 6.27 (d, 1H, J = 12 Hz), 7.43 (d, 1H, J = 12 Hz), 7.51 (t, 1H, J = 6.0 Hz), 7.73 (d, 1H, J = 6.0 Hz), 7.81 (d, 1H, J = 6.0 Hz), 7.97 (s, 1H), 10.03 (s, 1H); MS 259.2 (M+ H).



[00421] Preparation Of 4-Benzyl-2-Vinylmorpholine:

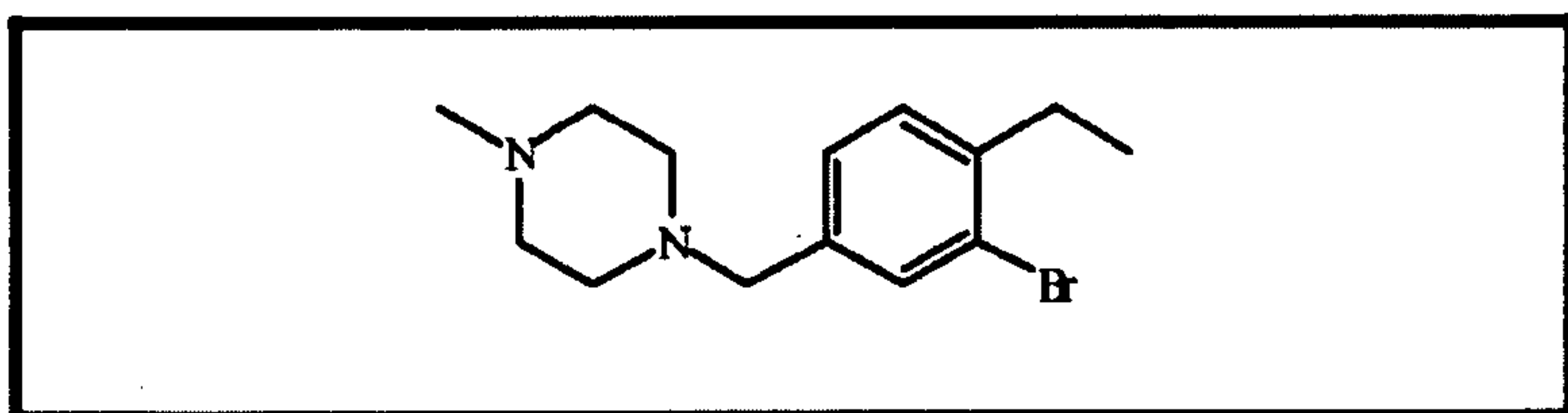
A solution of allylpalladium chloride dimer (126 mg, 0.34 mmol), BINAP (920 mg, 1.4 mmol) in dichloromethane (150 mL) was maintained at room temperature for 1 h. To the clear red solution was added 2-(benzylamino)ethanol (4.42 g, 28.1 mmol), (Z)-but-2-ene-1,4-diyl diacetate (5.47 g, 31.8 mmol) and potassium fluoride (3.80 g, 65 mmol) sequentially. The resulting yellow slurry was maintained at 40 °C for 24 h before filtration. The filtrate was concentrated and chromatographed. The fraction containing product was concentrated. The residue was dissolved in ethyl ether (20 mL) and added to a solution of camphorsulphonic acid

(3.5 g) in ethyl ether (500 mL). The precipitate was collected. The solid was basified with sodium bicarbonate solution. The organic portion was dried (magnesium sulfate) and concentrated to provide a solid (2.5 g); HPLC: 94.6%, t_r = 4.7 min [A].



[00422] Preparation of 1-methyl-4-[(5-vinylpyridin-2-yl)methyl]piperazine:

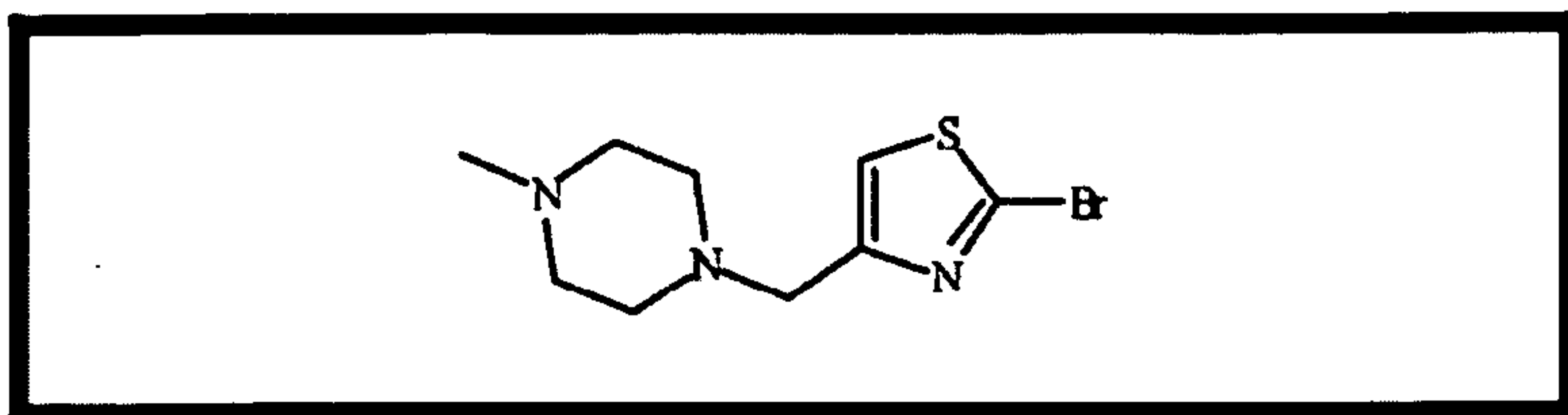
A mixture of 1-[(5-bromo-2-pyridinyl)methyl]-4-methylpiperazine (1.4 g, 5.07 mmol) (US2002026052 a1), vinyl tributyltin (2.31 g, 2.2 ml, 7.6 mmol) and $\text{Pd(PPh}_3)_4$ (293 mg, 0.25 mmol) in 23 ml of toluene was heated at reflux for 3 h, cooled to room temperature and partitioned between ethyl acetate and aqueous saturated sodium bicarbonate. The organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography, eluting with a gradient of 5% methanol in dichloromethane to 15% methanol in dichloromethane to 15% methanol in dichloromethane containing 1% of conc. aq. ammonium hydroxide to give 883.2 mg (80%) of 1-methyl-4-[(5-vinylpyridin-2-yl)methyl]piperazine as deep yellow oil, MS (ESI) m/z 218.1 (M+H)⁺.



[00423] Preparation of 1-(3-bromo-4-ethylbenzyl)-4-methylpiperazine:

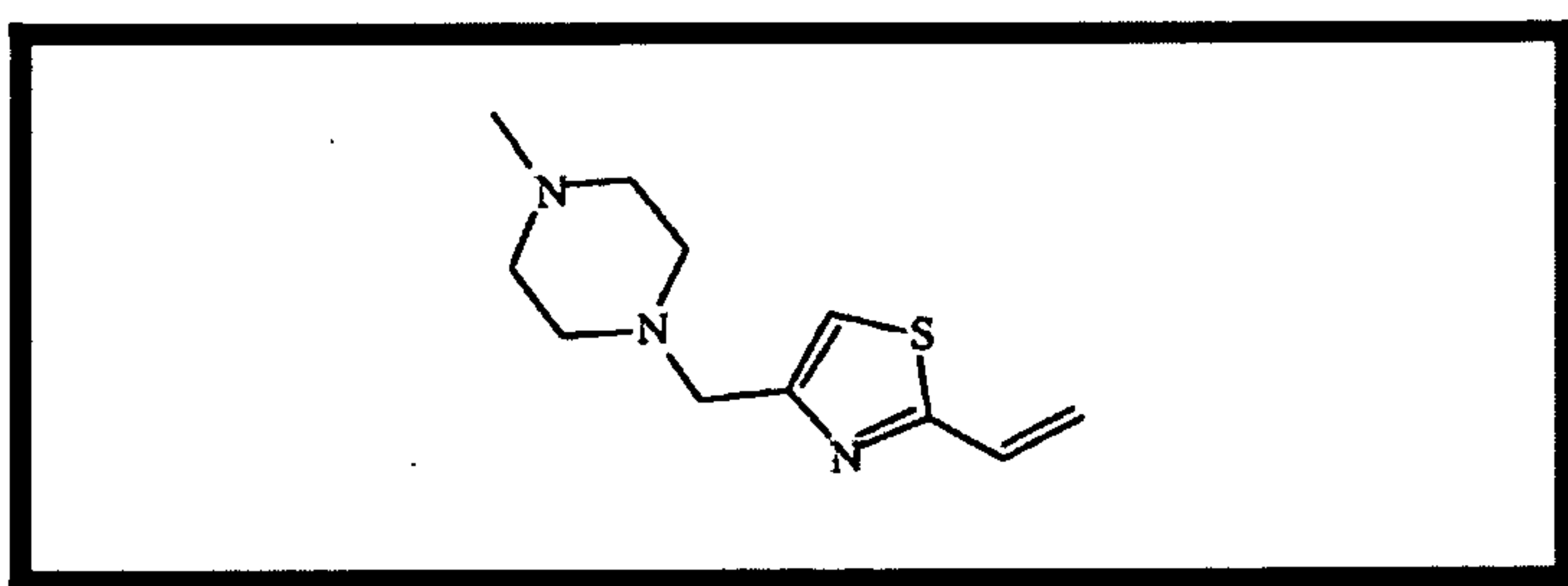
To a solution of 3-bromo-4-ethylbenzaldehyde (3.89 g, 18.3 mmol) (WO 2003099776 A1) and N-methyl-piperazine (9.2 g, 91.5 mmol) in 40 ml of dichloromethane at room temperature under nitrogen was added glacial acetic acid (2.2 g, 2.1 ml, 36.6 mmol). the reaction mixture was stirred at room temperature for 1 h. sodium triacetoxyborohydride (19.4 g, 91.5 mmol) was added to the reaction mixture in portions. The resulting mixture was stirred at room temperature overnight, then partitioned between dichloromethane and aqueous saturated sodium bicarbonate. The organic layer was washed with brine, dried over sodium sulfate,

filtered and concentrated *in vacuo*. the residue was purified by column chromatography, eluting with a gradient of 2% methanol in dichloromethane to 7% methanol in dichloromethane to give 4.2 g (77%) of 1-(3-bromo-4-ethylbenzyl)-4-methylpiperazine as a yellow oil, MS (ESI) 297.1, 299.1



[00424] Preparation of 1-[(2-bromo-1,3-thiazol-4-yl)methyl]-4-methylpiperazine:

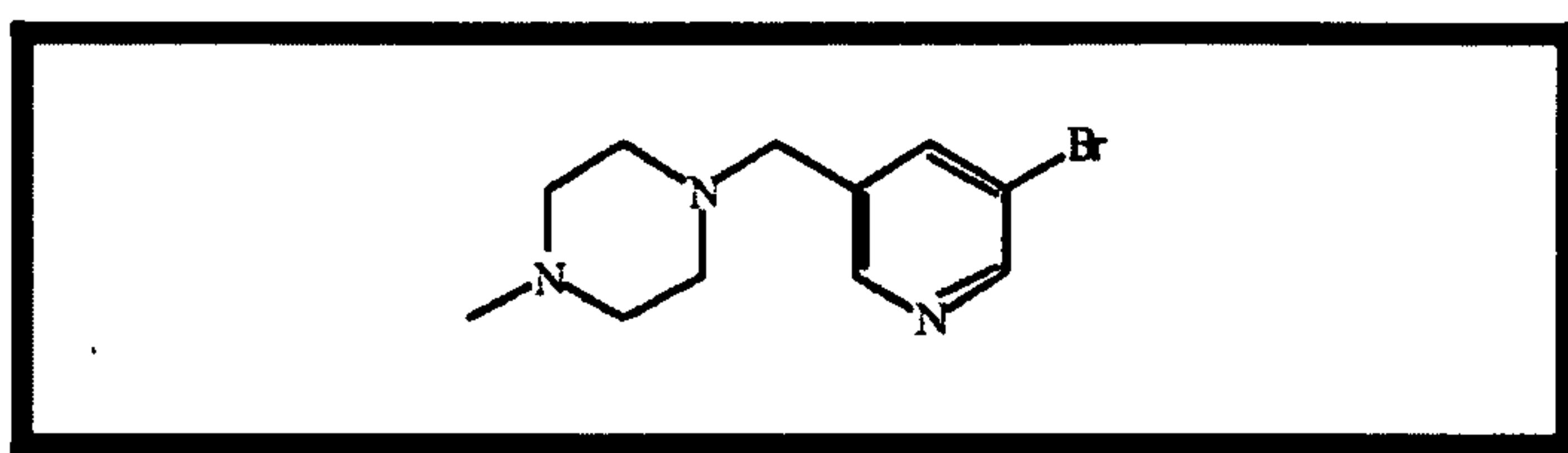
To a solution of 2-bromo-4-formylthiazole (1.0 g, 5.2 mmol), N-methyl-piperazine (2.6 g, 2.9 ml, 26 mmol) in 15 ml of dichloromethane at room temperature under nitrogen was added glacial acetic acid (629.4 mg, 0.6 ml, 10.4 mmol). The reaction mixture was stirred at room temperature for 1 h. Sodium triacetoxyborohydride (5.5 g, 26 mmol) was added to the reaction mixture in portions. The resulting mixture was stirred at room temperature overnight, then partitioned between dichloromethane and aqueous saturated sodium bicarbonate. The organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography, eluting with a gradient of 2% methanol in dichloromethane to 10% methanol in dichloromethane to give 940 mg (66%) of 1-[(2-bromo-1,3-thiazol-4-yl)methyl]-4-methylpiperazine as a white solid, MS (ESI) 276.2, 278.2



[00425] Preparation of 1-[(2-ethenyl-1,3-thiazol-4-yl)methyl]-4-methylpiperazine:

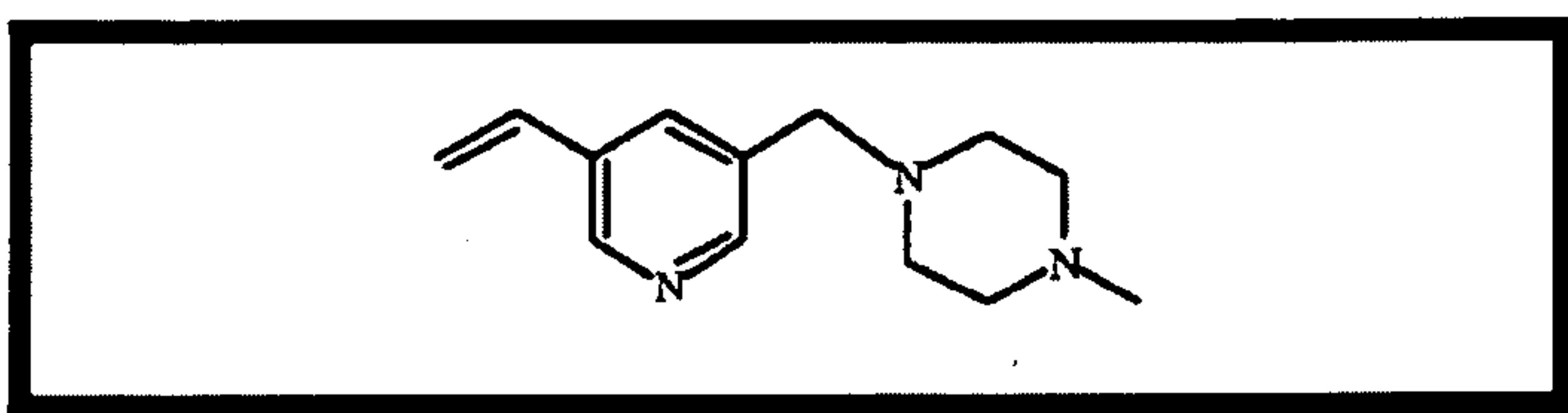
A mixture of 1-[(2-bromo-1,3-thiazol-4-yl)methyl]-4-methylpiperazine (749.5 mg, 2.71 mmol), vinyl tributyltin (1.30 g, 1.19 ml, 4.1 mmol) and Pd(Ph₃)₄ (156.6 mg, 0.14 mmol) in 14 ml of toluene was heated at reflux for 6 h, cooled to room temperature and partitioned between ethyl acetate and aqueous saturated sodium bicarbonate. The organic phase was washed with

brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography, eluting with a gradient of 5% methanol in dichloromethane to 10% methanol in dichloromethane to 10% methanol in dichloromethane containing 1% of conc. aq. ammonium hydroxide to give 354 mg (59%) of 1-[(2-ethenyl-1,3-thiazol-4-yl)methyl]-4-methylpiperazine as a deep yellow oil, MS (ESI) m/z 224.1 (M+H)+.



[00426] Preparation of 1-[(5-bromopyridin-3-yl)methyl]-4-methylpiperazine:

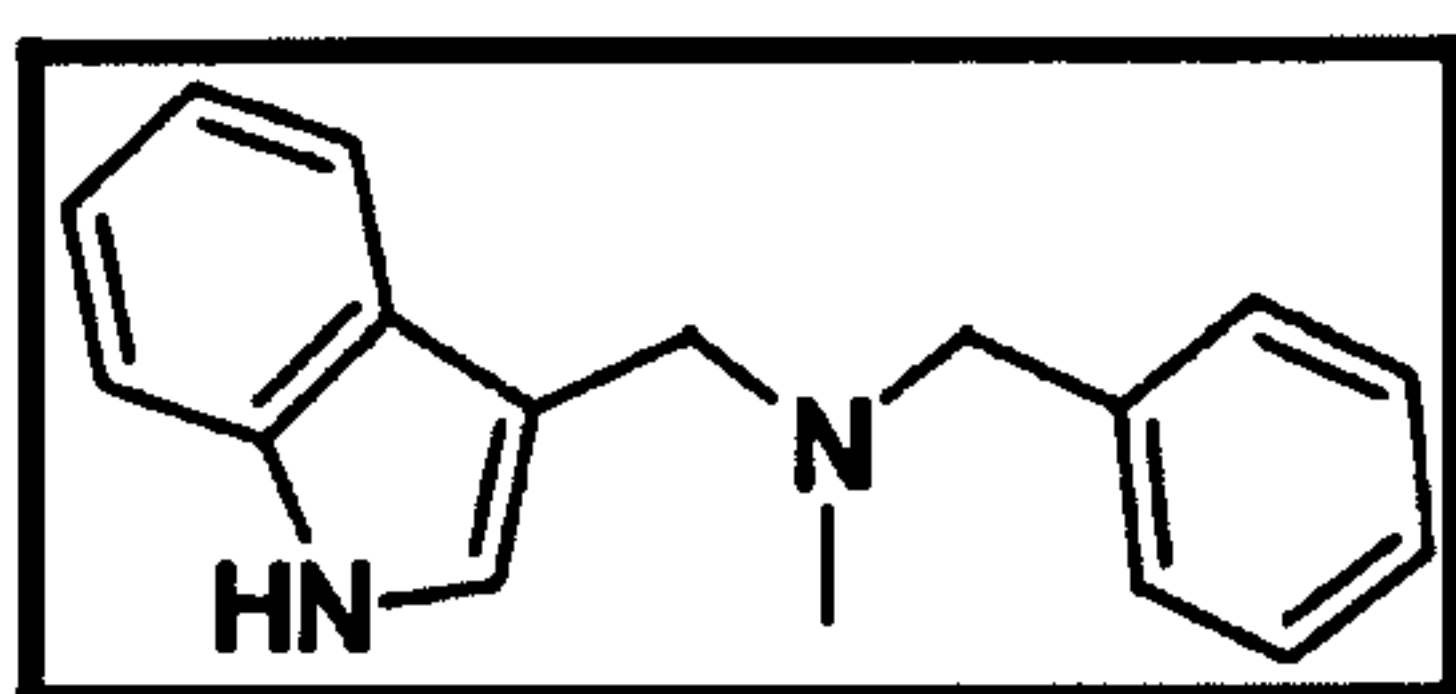
To a solution of 5-bromo-3-pyridine-carboxyaldehyde (1.5 g, 8.1 mmol), N-methyl-piperazine (4.03 g, 4.5 ml, 40.3 mmol) in 20 ml of dichloromethane at room temperature under nitrogen was added glacial acetic acid (966.8 mg, 0.92 ml, 16.1 mmol). The reaction mixture was stirred at room temperature for 1 h. Sodium triacetoxyborohydride (8.54 g, 40.3 mmol) was added to the reaction mixture in portions. The resulting mixture was stirred at room temperature overnight, then partitioned between dichloromethane and aqueous saturated sodium bicarbonate. The organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography, eluting with a gradient of 10% methanol in ethyl acetate to 20% methanol in ethyl acetate to 20% methanol in ethyl acetate containing 1% of conc. aq. ammonium hydroxide to give 2.1 g (95%) of 1-[(5-bromopyridin-3-yl)methyl]-4-methylpiperazine as a yellowish solid, MS (ESI) 270.1, 272.1.



[00427] Preparation of 1-methyl-4-[(5-vinylpyridin-3-yl)methyl]piperazine:

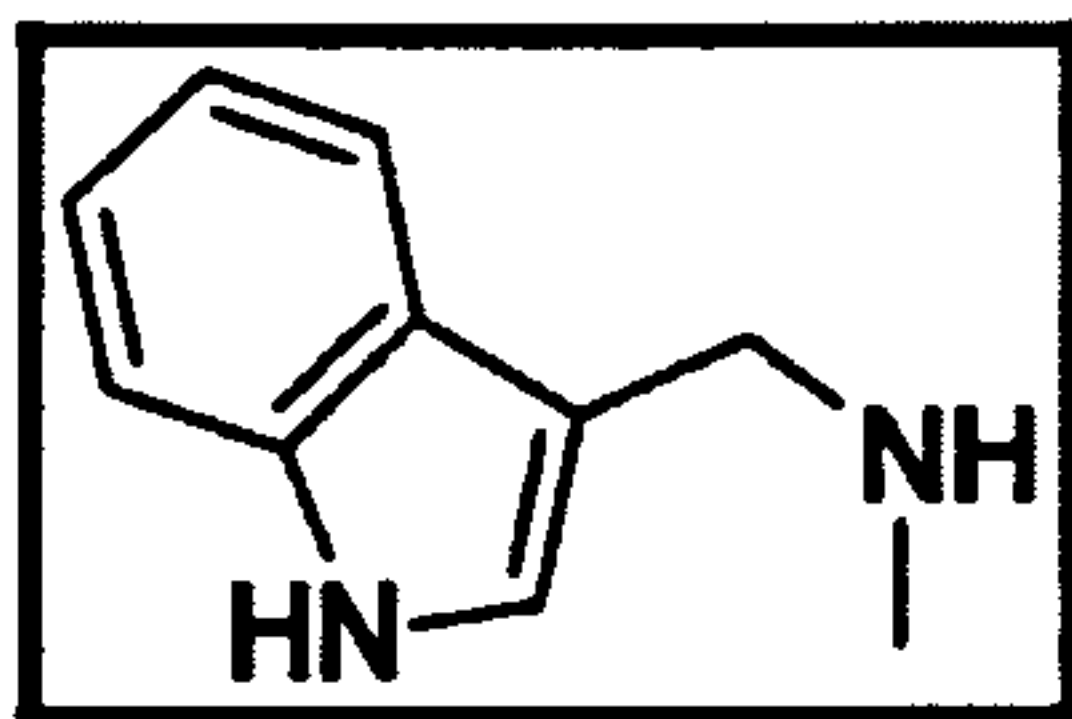
A mixture of 1-[(5-bromopyridin-3-yl)methyl]-4-methylpiperazine (1.32 g, 4.89 mmol), vinyl tributyltin (2.34 g, 2.16 mL, 7.3 mmol) and Pd(PPh₃)₄ (282.5 mg, 0.25 mmol) in 25 mL of

toluene was heated at reflux for 3 h, cooled to room temperature and partitioned between ethyl acetate and aqueous saturated sodium bicarbonate. The organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography, eluting with a gradient of 5% methanol in dichloromethane to 15% methanol in dichloromethane to 15% methanol in dichloromethane containing 1% of conc. aq. ammonium hydroxide to give 872 mg (82%) of 1-methyl-4-[(5-vinylpyridin-3-yl)methyl]piperazine as yellow oil, MS (ESI) m/z 218.1 (M+H)+.



[00428] Preparation of N-((1H-indol-3-yl)methyl)-N-methyl-1-phenylmethanamine:

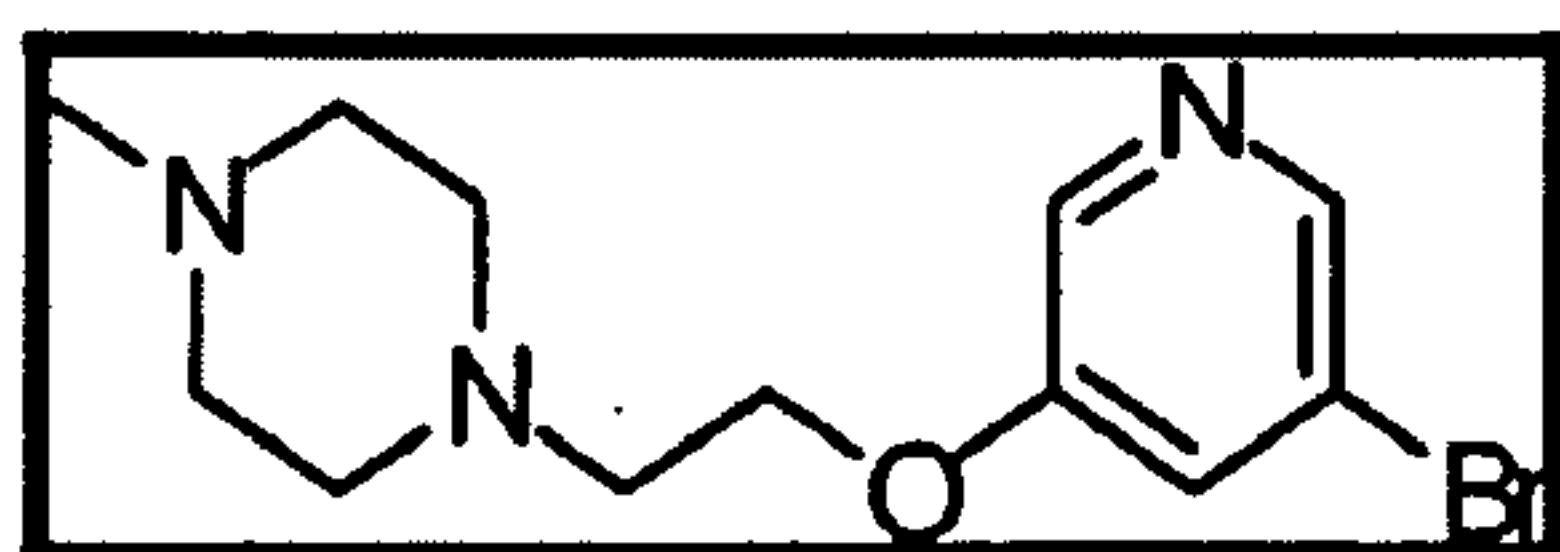
To a THF solution (10 mL) containing indole (586 mg, 5.0 mmol) and N-(methoxymethyl)-N-(trimethylsilylmethyl)benzylamine was added trifluoroacetic acid (1.0 mL). The reaction was stirred at room temperature overnight and was quenched with saturated aqueous NaHCO₃ (3 mL). The solvent was removed under vacuum and the residue partitioned between EtOAc (5 mL) and water (3 mL). The water was removed and the organic layer dried over anhydrous MgSO₄ and concentrated under vacuum to a residue. The title compound was isolated from the by-products N-((1H-indol-3-yl)methyl)-N-benzyl-1-(trimethylsilyl)methanamine and N-benzyl-1-(3-((benzyl((trimethylsilyl)methyl)amino)methyl)-1H-indol-1-yl)-N-methylmethanamine by preparative HPLC. MS 251.1 (M+H); HPLC t_r = 8.1 min [a].



[00429] Preparation of 1-(1H-indol-3-yl)-N-methylmethanamine dihydrochloride:

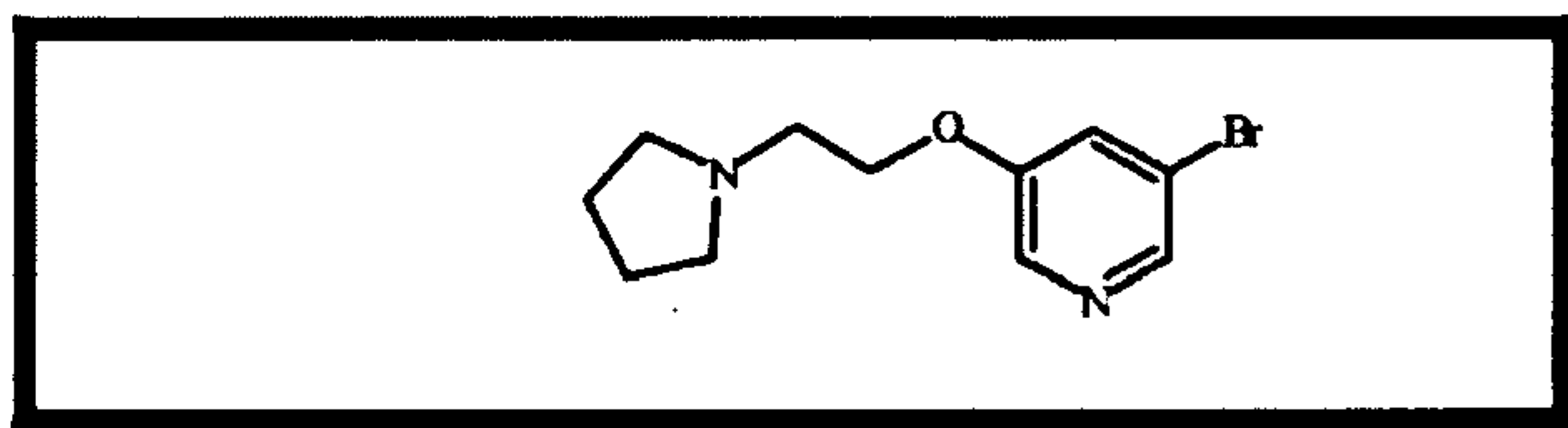
A methanol solution (10 mL) of N-((1H-indol-3-yl)methyl)-N-methyl-1-phenylmethanamine (100 mg, 0.4 mmol) was treated with 10% Pd/C and was stirred under hydrogen supplied by a rubber balloon. After stirring overnight, the mixture was filtered through magnesium silicate and the filtrate concentrated under vacuum. The residue was dissolved in 1:1 THF/Et₂O and

HCl gas bubbled into the solution. The resulting red solid was filtered and triturated with Et₂O. The solid was dried under vacuum at 60 °C overnight to provide the title compound (80 mg, 86%). MS 161.1 (M+H); HPLC rt = 4.0 min [a].



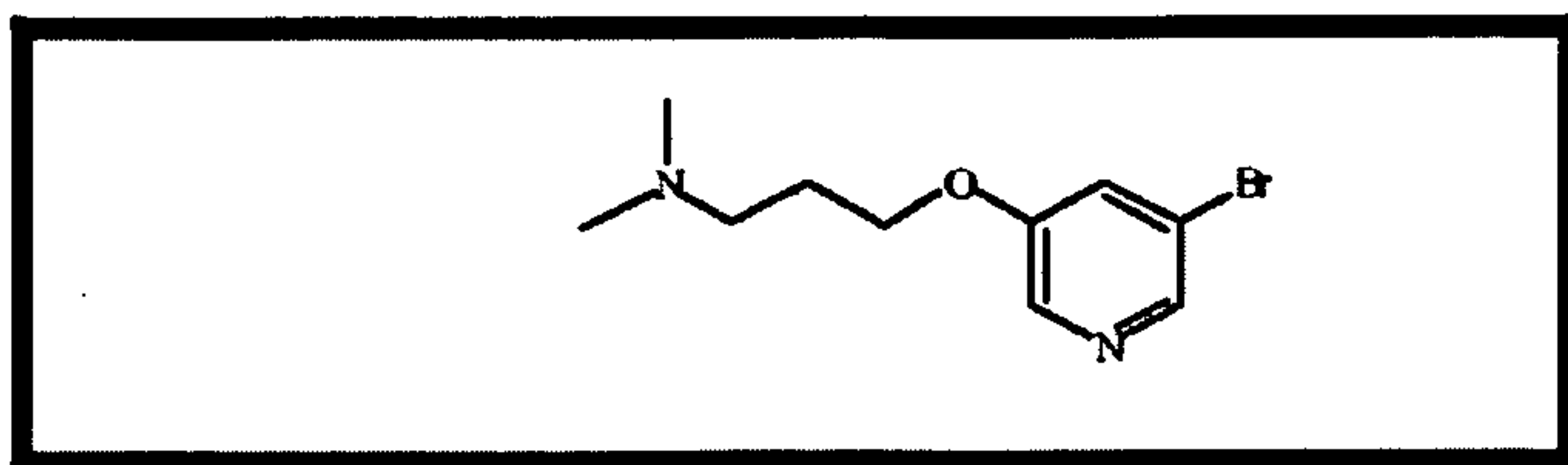
[00430] Preparation of 1-{2-[(5-bromopyridin-3-yl)oxy]ethyl}-4-methyl-piperazine:

To a THF (50 ml) solution of 5-bromo-pyridin-3-ol (500 mg, 2.87 mmol) cooled in a ice bath for 30 min was added 1,1'-(azodicarbonyl)-dipiperidine (1.1 ml, 4.31 mmol), tri-n-butylphosphine (1.06 ml, 4.31 mmol) and 2-(4-methyl-piperazine-1-yl)-ethanol with stirring. The ice bath was removed after 30 min. The reaction was stirred at room temperature overnight. The resulting mixture was added to saturated NaHCO₃ and ethyl acetate. The organic layer was washed with brine and concentrated *in vacuo*. The residue was purified by chromatography eluting with MeOH:DCM(1:10) to afford 450 mg (52%) of the title compound as a yellow solid. MS: (M+H) 300.19.



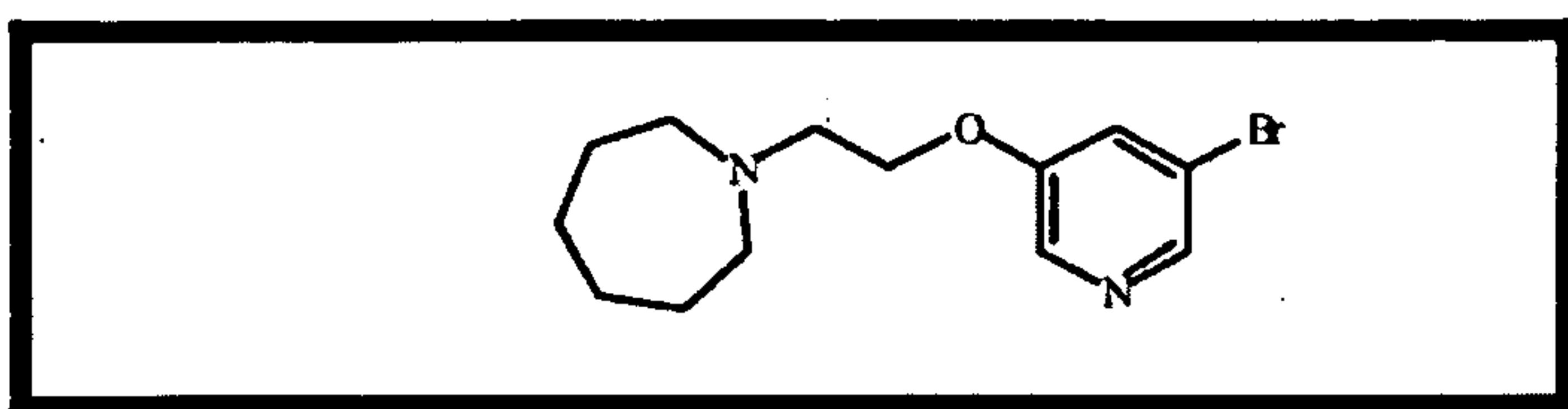
[00431] Preparation of 3-bromo-5-(2-pyrrolidin-1-yl-ethoxy)pyridine:

The title compound was prepared from 2-pyrrolidin-1-yl-ethanol and 5-bromo-pyridin-3-ol via the procedure used to prepare 1-{2-[(5-bromopyridin-3-yl)oxy]ethyl}-4-methyl-piperazine to afford 506 mg (65%) of the title compound as a yellow solid. MS: (M+H) 271.15.



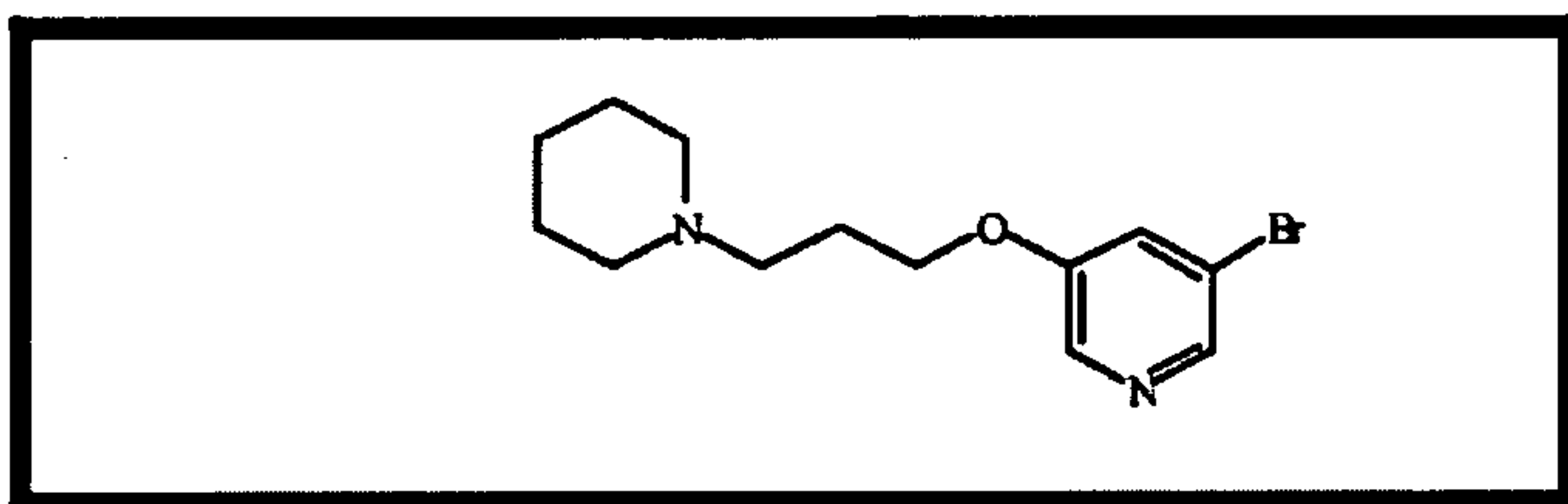
[00432] Preparation of 3-[(5-bromopyridin-3-yl)oxy]-N,N-dimethylpropan-1-amine:

The title compound was prepared from 3-dimethylamino-propan-1-ol and 5-bromo-pyridin-3-ol via the procedure used to prepare 1-{2-[(5-bromopyridin-3-yl)oxy]ethyl}-4-methyl-piperazine to afford 450 mg (61%) of the title compound as a yellow solid. MS: (M+H) 259.1.



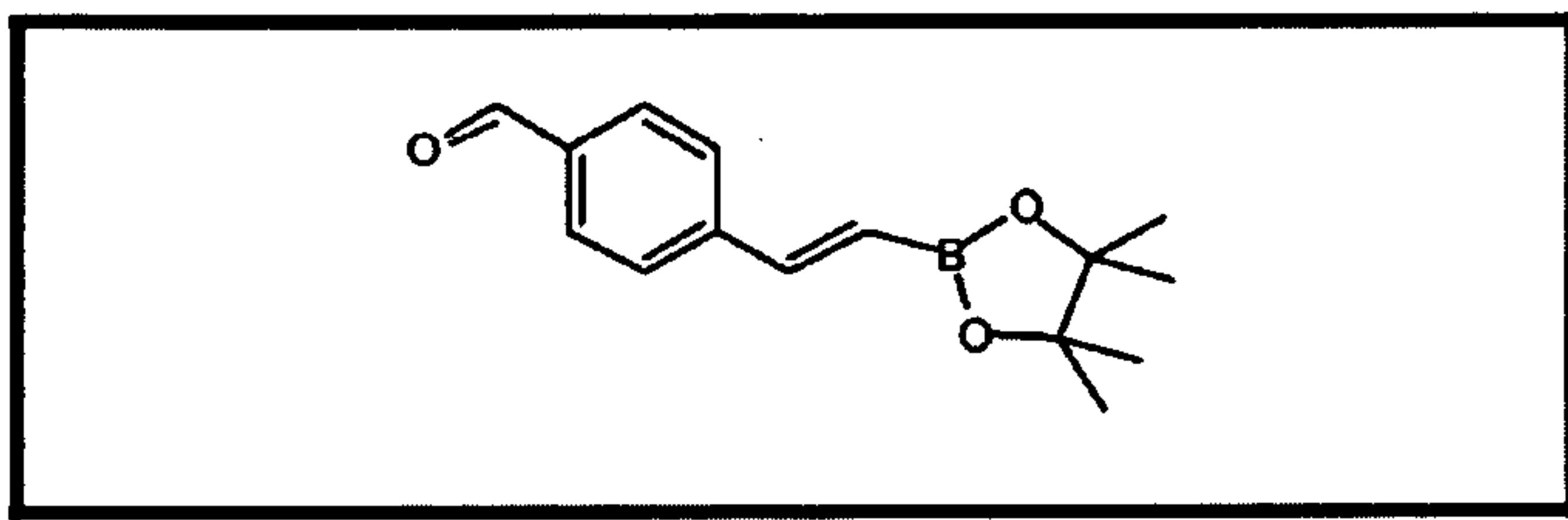
[00433] Preparation of 1-{2-[(5-bromopyridin-3-yl)oxy]ethyl}azepane:

The title compound was prepared from 2-azepan-1-yl-ethanol and 5-bromo-pyridin-3-ol via the procedure used to prepare 1-{2-[(5-bromopyridin-3-yl)oxy]ethyl}-4-methyl-piperazine to afford 510 mg (59%) of the title compound as a yellow solid. MS: (M+H) 299.1.



[00434] Preparation of 3-bromo-5-(3-piperidin-1-ylpropoxy)pyridine:

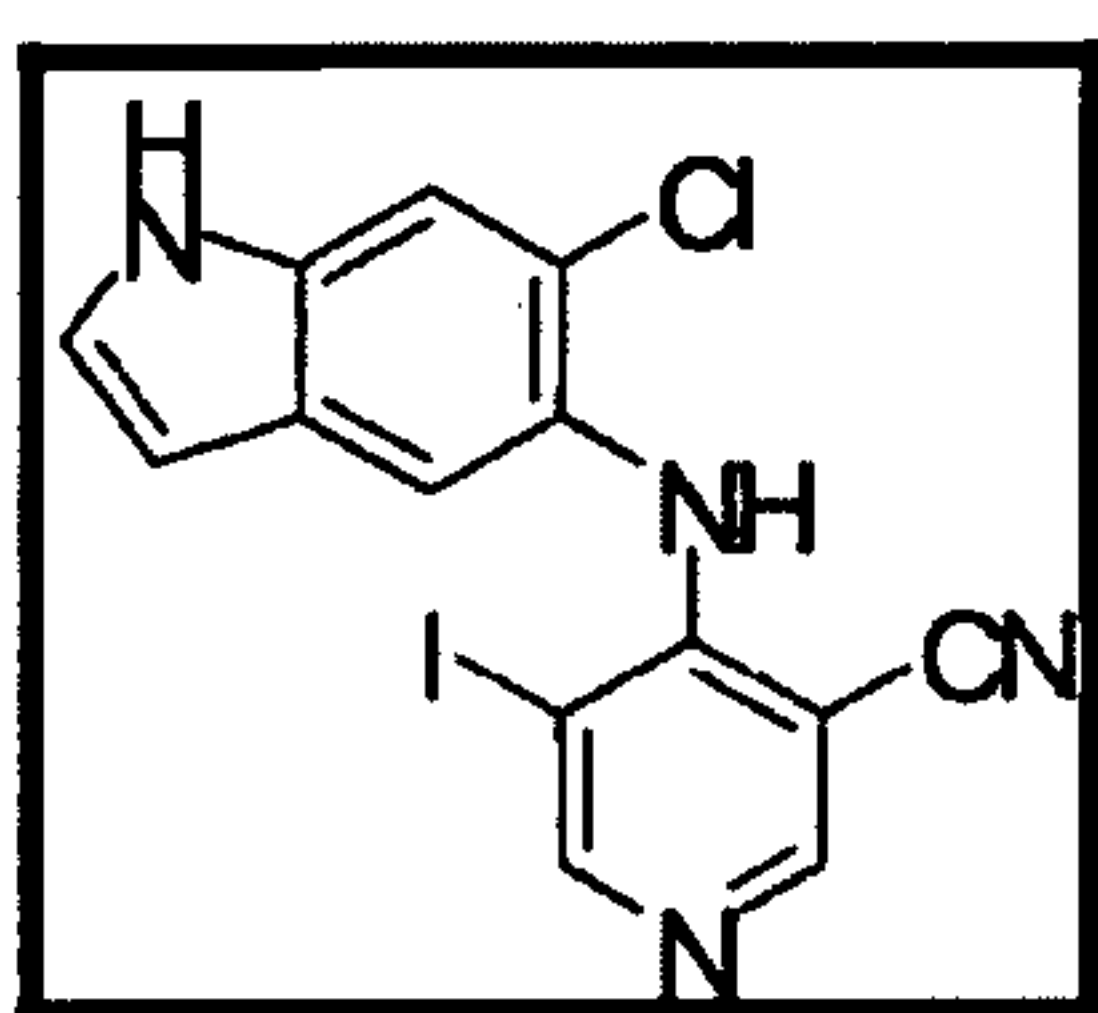
The title compound was prepared from 3-piperidin-1-yl-propan-1-ol and 5-bromo-pyridin-3-ol via the procedure used to prepare 1-{2-[(5-bromopyridin-3-yl)oxy]ethyl}-4-methyl-piperazine to afford 880 mg (64%) of the title compound as a yellow solid. MS: (M+H) 299.1.



[00435] Preparation of 4-[(E)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethenyl]benzaldehyde:

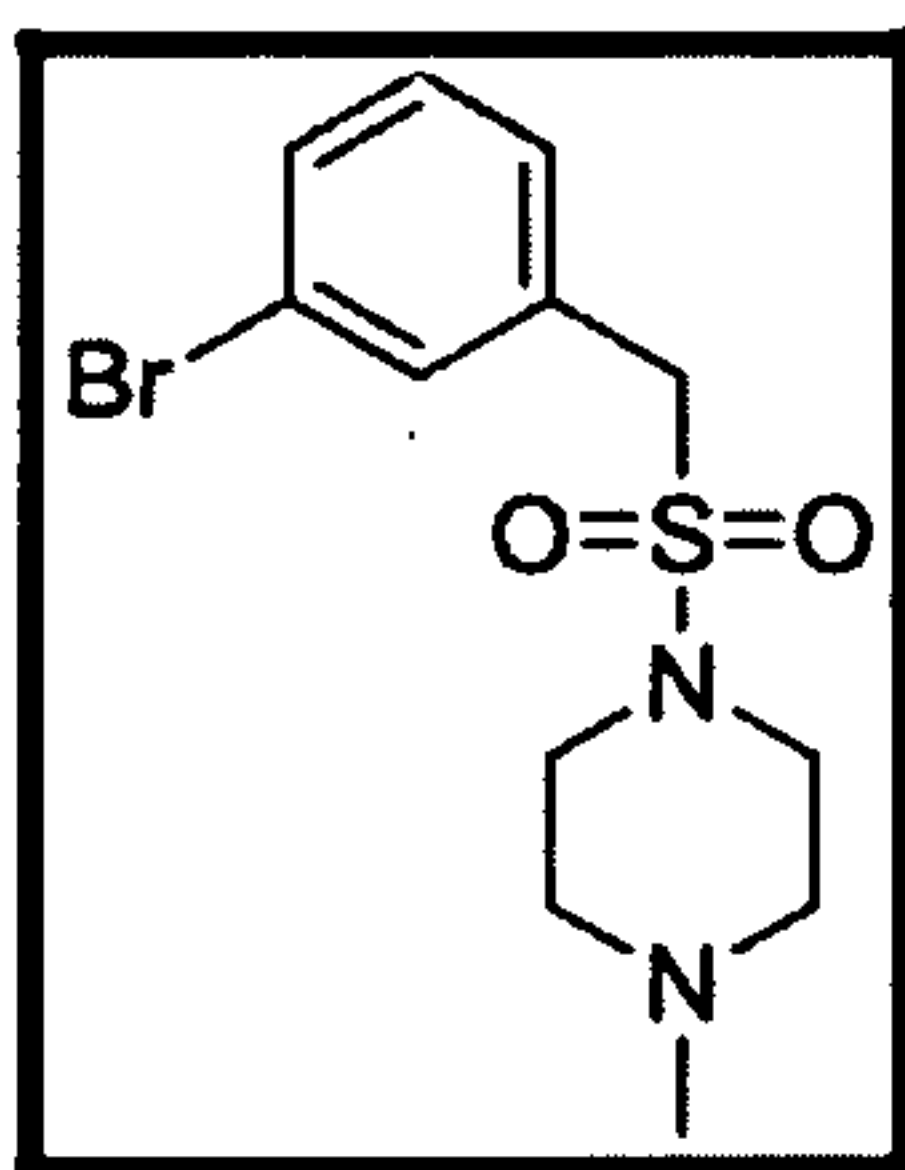
To a solution of 4-bromobenzaldehyde (10.0 g, 54 mmol), Pd(OAc)₂ (720 mg, 3.2 mmol) and 1,10-phenanthroline (624 mg, 3.1 mmol) in anhydrous CH₃CN (160 ml) at room temperature

was added triethylamine (15 ml, 107.5 mmol) followed by the addition of vinylboronic acid pinacolester (11 ml, 64.8 mmol). The reaction mixture was heated to 65°C for 3 days, diluted with diethyl ether (1400 ml), washed successively with 10% HCl, H₂O and brine. Drying, filtration and evaporation gave a brown oil, which was purified by silica gel chromatography (CH₂Cl₂), providing 7.0 g (50%) of the title compound as a yellow solid. ¹H NMR (300 MHz, DMSO) 1.24 (s, 12H), 6.35 (d, 1H, J = 12 Hz), 7.38 (d, 1H, J = 12 Hz), 7.82 (t, 2H), 7.89 (s, 1H), 7.91(s, 1H), 10.00 (s, 1H); MS 259.2 (M+H).



[00436] Preparation of 4-[(6-chloro-1H-indol-5-yl)amino]-5-iodopyridine-3-carbonitrile:

4-Chloro-5-iodonicotinonitrile (490 mg, 1.9 mmol) and 6-chloro-1H-indol-5-amine (320 mg, 1.9 mmol) was heated at reflux in 3 mL of EtOH for 16 h. The reaction was cooled to RT and the precipitate was collected by filtration. The filter cake was dried under reduced pressure to afford 164 mg of the title compound. HPLC rt = 11.3 min [a]; m/e 394.9 (M+H); HRMS: calculated 394.9555 found 394.9553 (M+H).



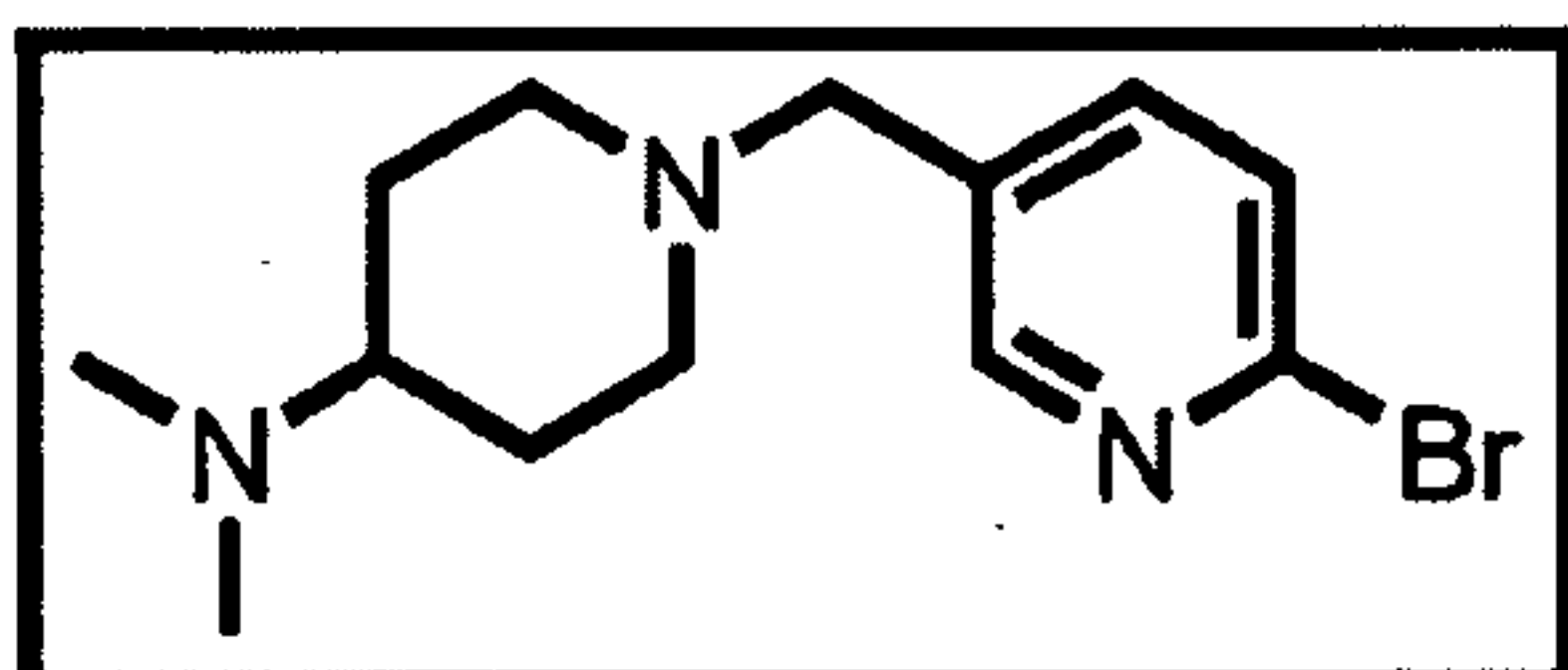
[00437] Preparation of 1-[(3-bromobenzyl)sulfonyl]-4-methylpiperazine:

A mixture of sodium 3-bromo-benzenemethanesulfonate (1.31 g, 4.8 mmol), POCl₃ (10 mL) and PCl₅ (2.0 g, 9.6 mmol) was heated to 85 °C for 2 h. The resulting reaction mixture was cooled to rt and poured onto ice. The mixture was partitioned between dichloromethane and water. The organic layer was dried (MgSO₄) and concentrated. A portion of the residue (0.27

g) was immediately dissolved in THF (10 mL) and the solution was treated with 1-methylpiperazine (100mg, 1 mmol). Upon completion, the reaction was quenched with sat sodium bicarbonate and dried (MgSO_4). Silica gel flash column chromatography with ethyl acetate and hexanes afforded desired product (195 mg, 20 %). HPLC t_r = 6.2 min [a]; MS m/e 333.0 (M+H).

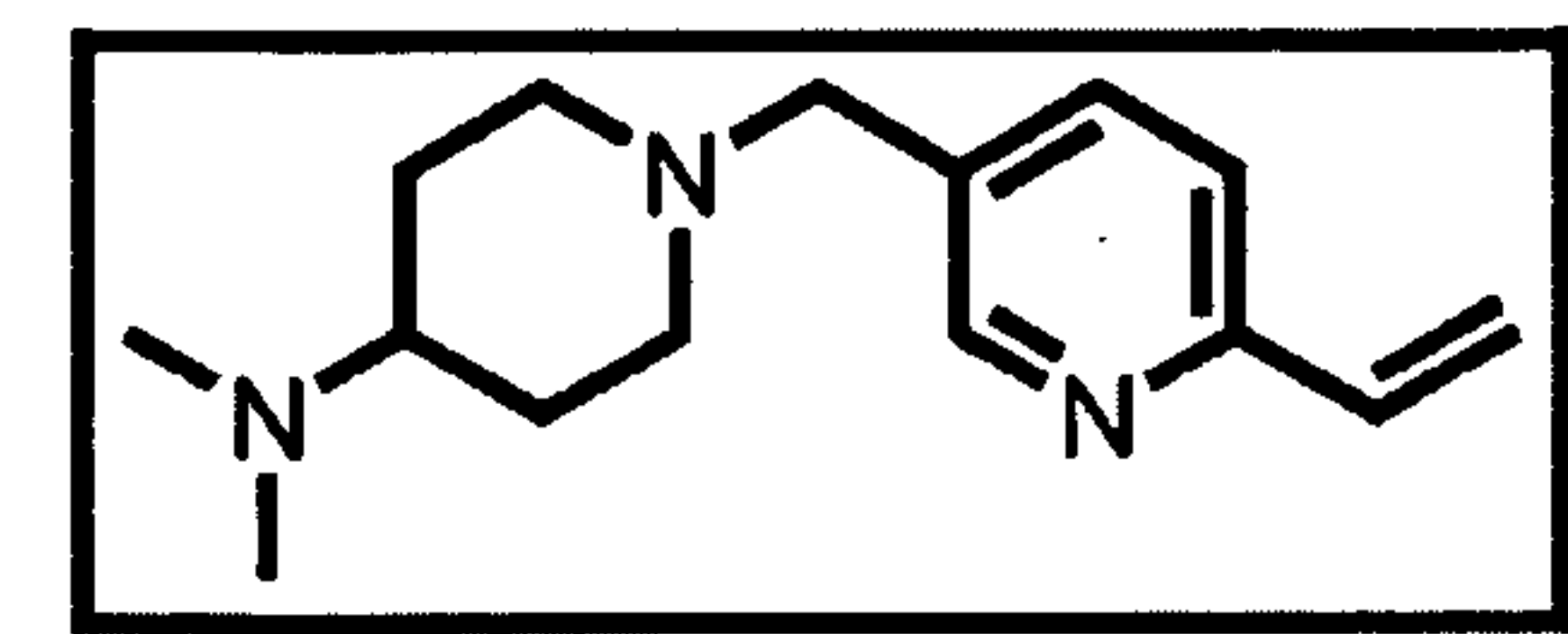
[00438] Preparation of 1-(3-bromobenzylsulfonyl)pyrrolidine:

The title compound was prepared via the route described for 1-[(3-bromobenzyl)sulfonyl]-4-methylpiperazine.



[00439] Preparation of 1-[(6-bromopyridin-3-yl)methyl]-N,N-dimethylpiperidin-4-amine:

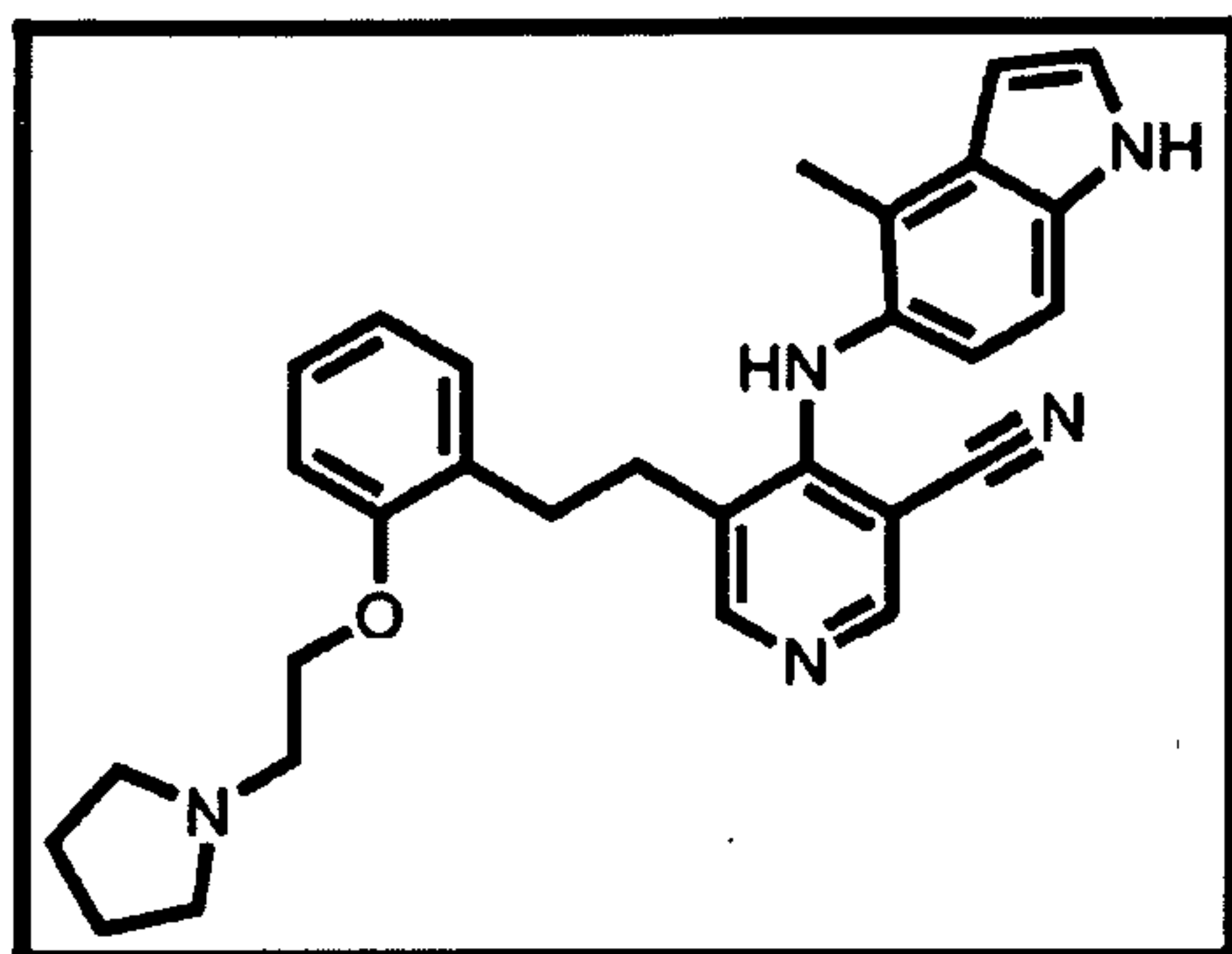
A mixture of 6-bromo-3-pyridinecarboxaldehyde (930 mg, 5.0 mmol) and 4-dimethylaminopiperidine (2.56 g, 20 mmol) in THF (40 mL) was stirred at room temperature for 1h. To this was added $\text{NaBH}(\text{OAc})_3$ (4.24 g, 20 mmol). The reaction mixture was stirred at room temperature for 20 h, diluted with ethyl acetate (100 mL), washed with saturated NaHCO_3 solution, H_2O , brine and dried (Na_2SO_4). Filtration and evaporation gave 780 mg (52%) of the title compound. MS 298.1 (M+H).



[00440] Preparation of N,N-dimethyl-1-[(6-vinylpyridin-3-yl)methyl]piperidin-4-amine:

A mixture of 1-[(6-bromopyridin-3-yl)methyl]-N,N-dimethylpiperidin-4-amine (596 mg, 2.0 mmol), tributyl(vinyl)tin (1.268 g, 4.0 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (116 mg, 0.1 mmol) in toluene (8 mL) was refluxed for 3.5 h, cooled to room temperature, diluted with ethyl acetate (50 mL), washed with saturated NaHCO_3 solution, H_2O , brine and dried (Na_2SO_4). Filtration and evaporation gave a brown oil, which was purified by silica gel chromatography (CH_2Cl_2 -

CH₃OH, 0% to 30% CH₃OH), providing 256 mg (52%) of the title compound as a sticky yellow oil. MS 246.2 (M+H).



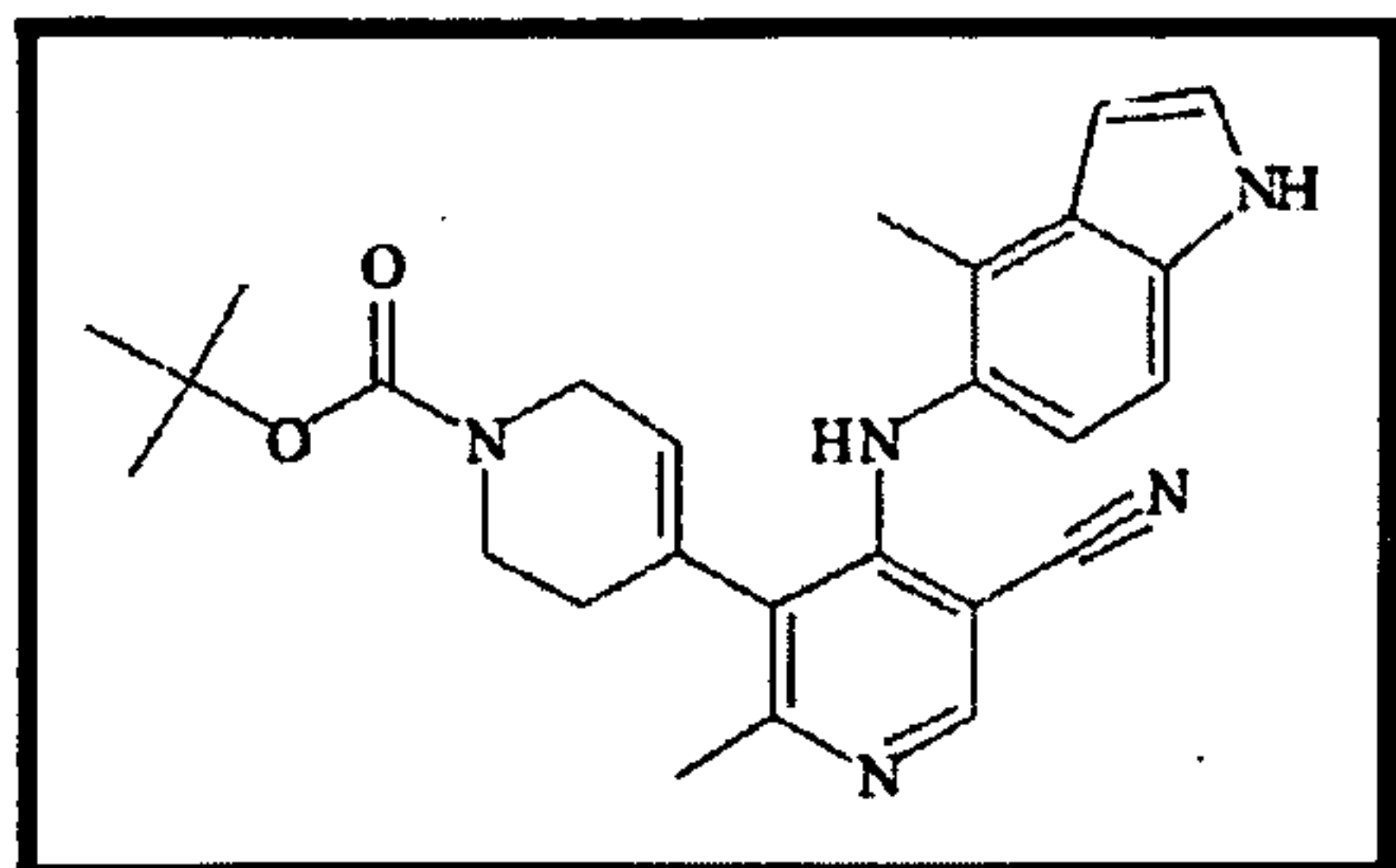
[00441] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-{2-[2-(2-pyrrolidin-1-ylethoxy)phenyl]ethynyl}pyridine-3-carbonitrile:

4-[(4-Methyl-1H-indol-5-yl)amino]-5-{[2-(2-pyrrolidin-1-ylethoxy)phenyl]ethynyl}pyridine-3-carbonitrile (100 mg, 0.22 mmol) and 10% Pd/C (15 mg) was treated with 10 mL of 1:1 EtOH/toluene (10 mL) and shaken under an atmosphere of 30 psi hydrogen for 3 days. The reaction mixture was filtered and the filtrate was concentrated and purified by HPLC to give 30 mg of the title compound. HPLC rt = 6.7 min [a]; HRMS: 466.2605 (M+H).

[00442] Table 12:

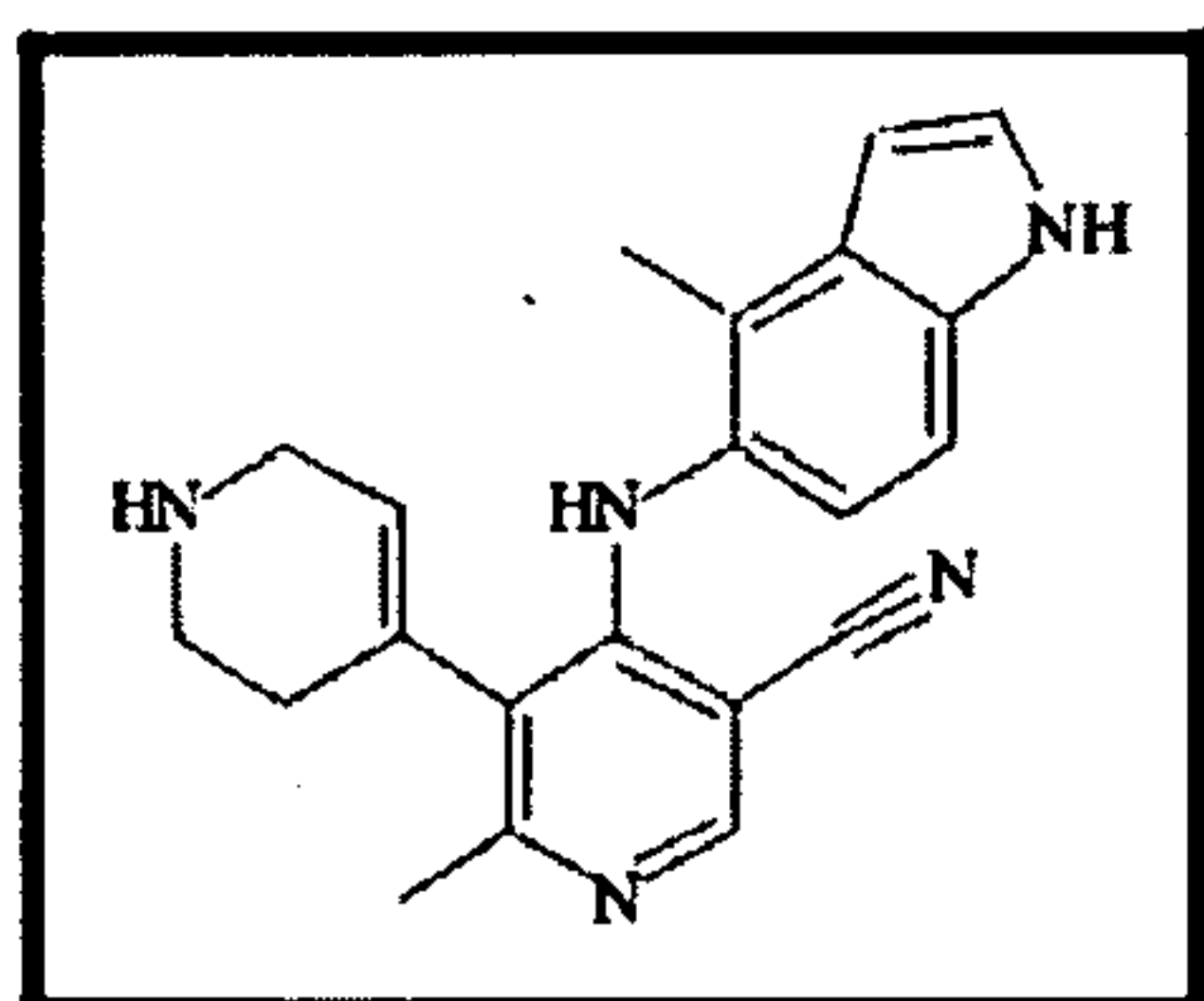
The following compounds were prepared from the indicated starting material following the procedure outlined for 4-[(4-methyl-1H-indol-5-yl)amino]-5-{2-[2-(2-pyrrolidin-1-ylethoxy)phenyl]ethynyl}pyridine-3-carbonitrile.

Compound Name	Starting material	MS (ESI)	HPLC rt
4-[(4-methyl-1H-indol-5-yl)amino]-5-{2-[3-(2-pyrrolidin-1-ylethoxy)phenyl]ethynyl}pyridine-3-carbonitrile	4-[(4-Methyl-1H-indol-5-yl)amino]-5-{[3-(2-pyrrolidin-1-ylethoxy)phenyl]ethynyl}nicotinonitrile	466.3 (M+H)	1.51 min (D)
4-[(4-methyl-1H-indol-5-yl)amino]-5-{2-[3-(pyrrolidin-1-ylmethyl)phenyl]ethynyl}pyridine-3-carbonitrile	4-[(4-methyl-1H-indol-5-yl)amino]-5-{[3-(pyrrolidin-1-ylmethyl)phenyl]ethynyl}pyridine-3-carbonitrile	436.3 (M+H)	5.5 min (A)
4-[(4-methyl-1H-indol-5-yl)amino]-5-{2-[4-(2-pyrrolidin-1-ylethoxy)phenyl]ethynyl}pyridine-3-carbonitrile	4-[(4-methyl-1H-indol-5-yl)amino]-5-{[4-(2-pyrrolidin-1-ylethoxy)phenyl]ethynyl}pyridine-3-carbonitrile	466.3 (M+H)	1.48 min (D)



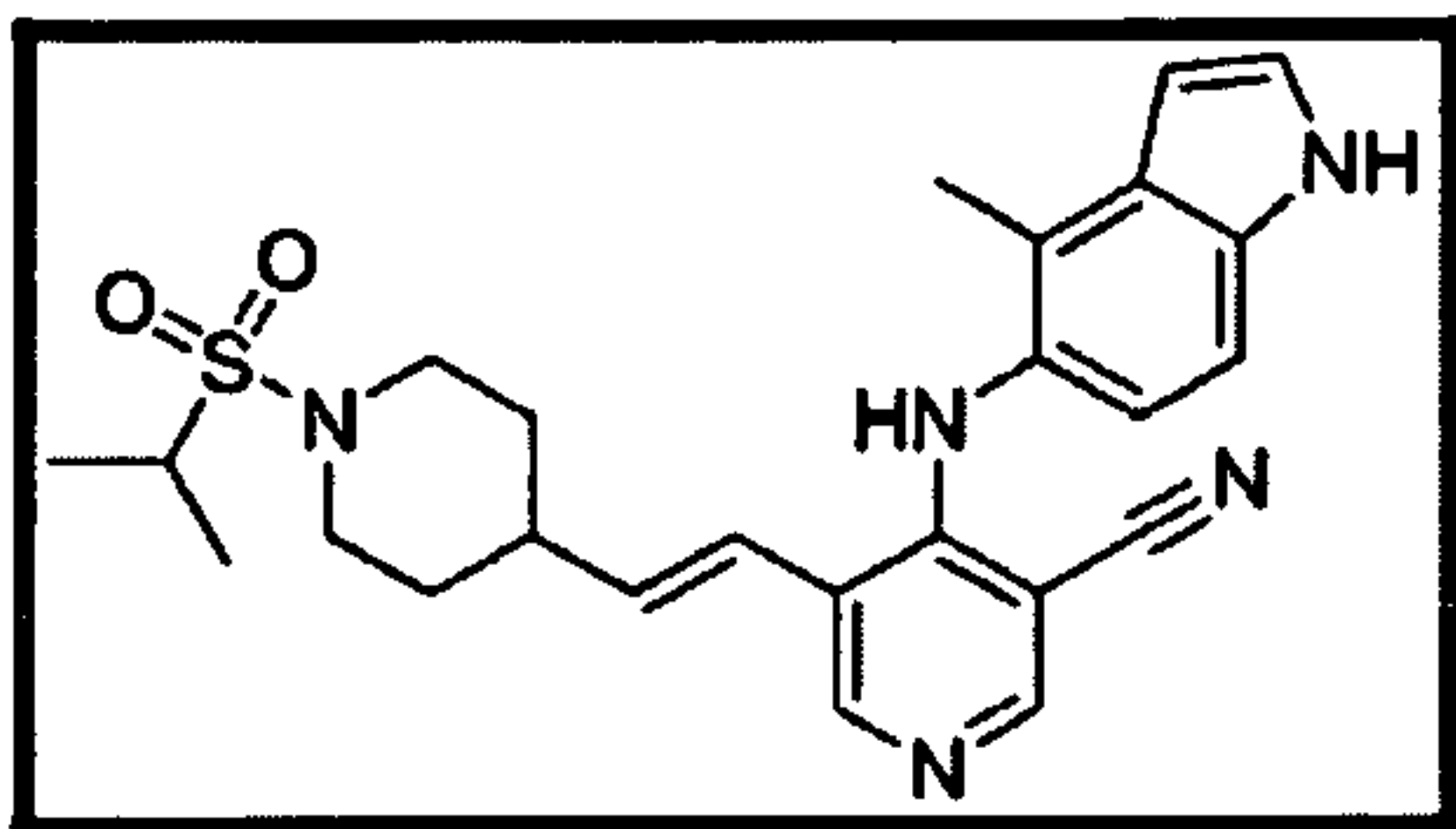
[00443] Preparation of tert-butyl 5-cyano-2-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-3',6'-dihydro-3,4'-bipyridine-1'(2'H)-carboxylate:

A mixture of 5-iodo-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (200 mg, 0.52 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)piperidine-1-carboxylate (191 mg, 0.62 mmol), Pd(PPh₃)₄ (72 mg, 0.62 mmol) and NaHCO₃ (aq. sat., 2 mL) in 5 mL of DME was heated to 100°C for 16 h. The reaction was diluted with ethyl acetate and washed with water. The solvents were removed and the residue was purified by chromatography using an ethyl acetate/ hexane gradient. Impurities were further removed by HPLC to give the title compound as a solid; MS 444.5 (M+H), HPLC rt = 9.8 min [a].



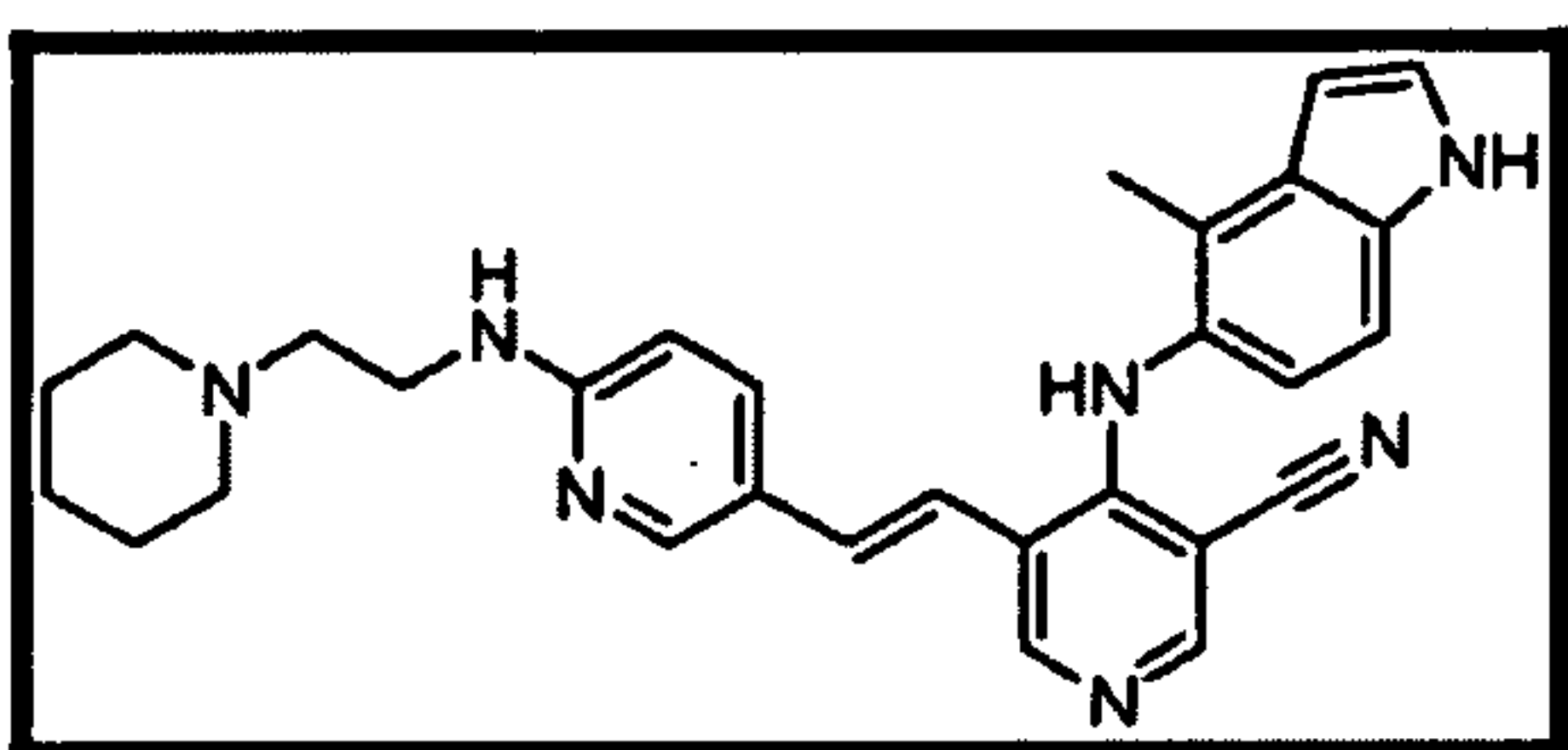
[00444] Preparation of 2-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile:

A solution of tert-butyl 5-cyano-2-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-3',6'-dihydro-3,4'-bipyridine-1'(2'H)-carboxylate (500 mg, 1.12 mmol) in 20% trifluoroacetic acid/ DCM (6 mL) was stirred at room temperature for 16 h. All solvents were removed in vacuo. Impurities were removed by HPLC purification to give the title compound as its TFA salt; MS 344.2 (M+H), HPLC rt = 3.8 min [b].



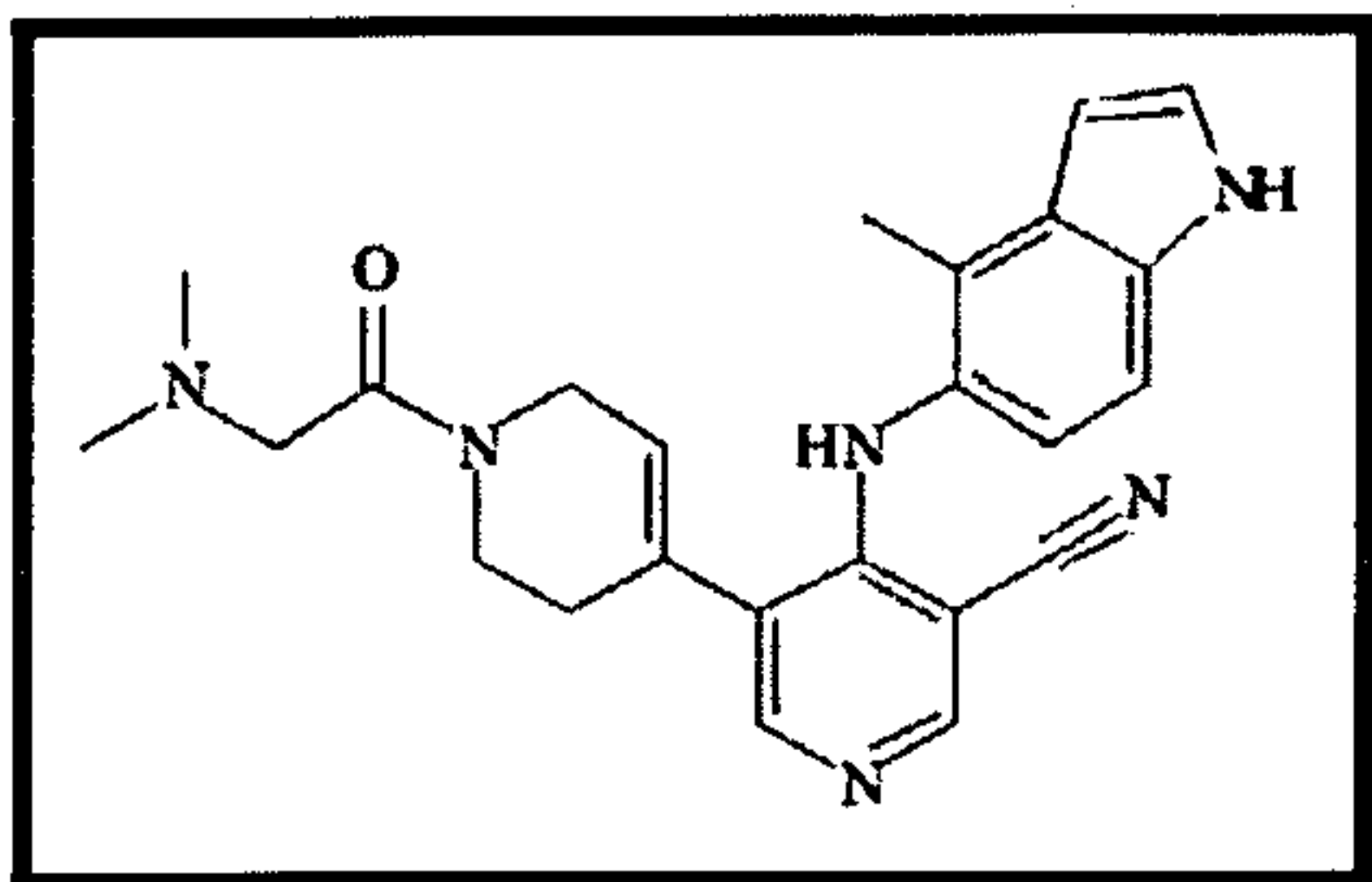
[00445] Preparation of 5-[(E)-2-[1-(isopropylsulfonyl)piperidin-4-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

A mixture of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-piperidin-4-ylvinyl]nicotinonitrile (61 mg, 0.13 mmol), propane-2-sulfonyl chloride (17 mg, 0.17 mmol), and triethylamine (39 mg; 0.39 mmol) was stirred at room temperature for 45 min. The reaction mixture was purified by HPLC to give 11.5 mg (19%) of the title compound as a solid; MS 464.2 (M+H), HPLC rt = 1.89 min [d].



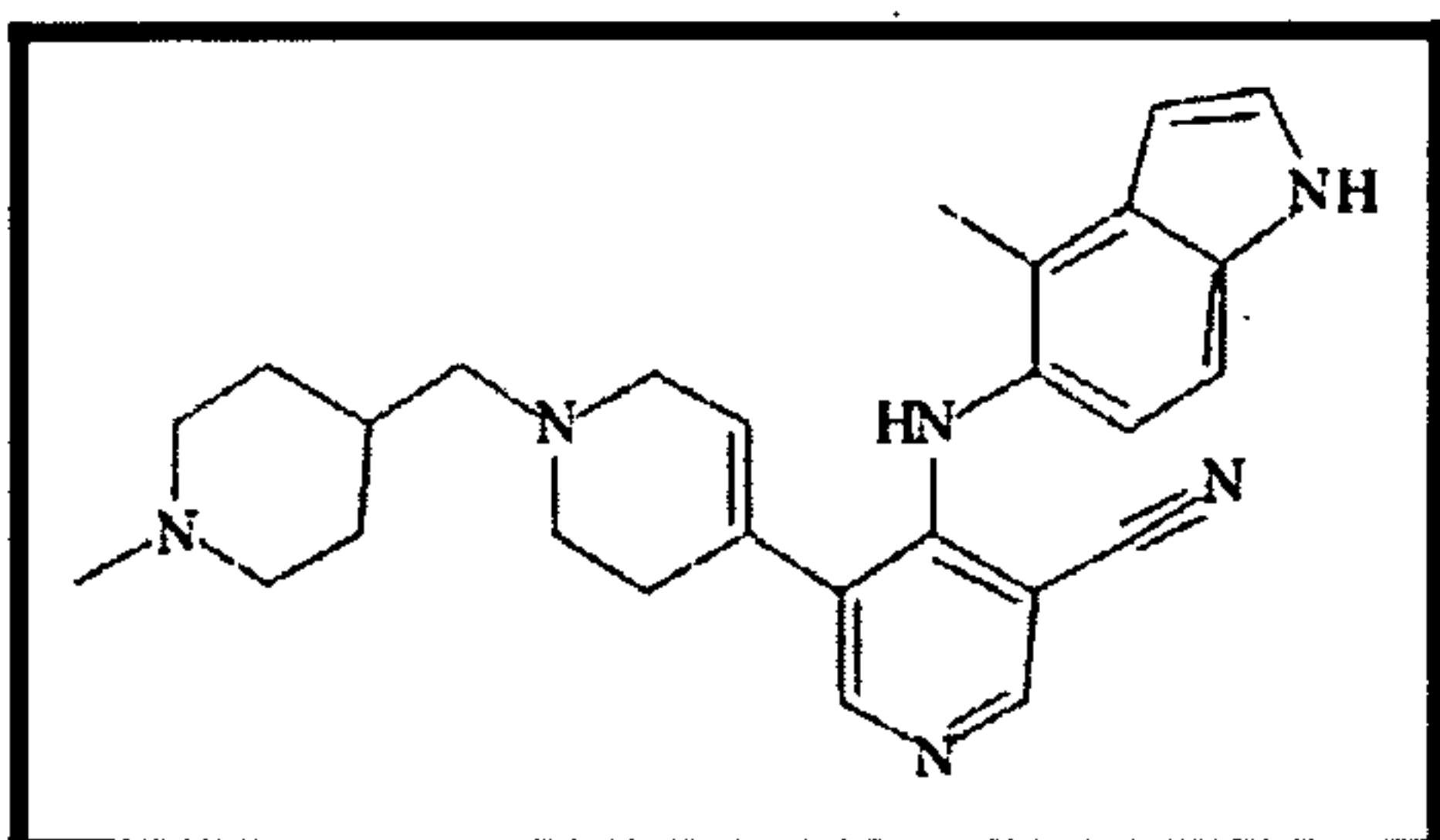
[00446] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{6-[(2-piperidin-1-yl)ethyl]amino}pyridin-3-yl]ethenyl]pyridine-3-carbonitrile:

A mixture of 5-[(E)-2-(6-chloropyridin-3-yl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (100 mg, 0.26 mmol), 2-(piperidin-1-yl)ethanamine (66 mg, 0.52 mmol), BINAP (16 mg, 0.026 mmol), Pd₂dba₃ (24 mg, 0.026 mmol), and potassium tertbutoxide (1M in THF, 1.04 mmol) was heated in THF at 65°C under N₂ and anhydrous conditions for 5 hr. The reaction was cooled to room temperature and the solvents were removed. The residue was redissolved in DMSO for purification by HPLC to give 17 mg (14% yield) of the title compound as a solid; MS 478.3 (M+H), HPLC rt = 1.48 min [d].



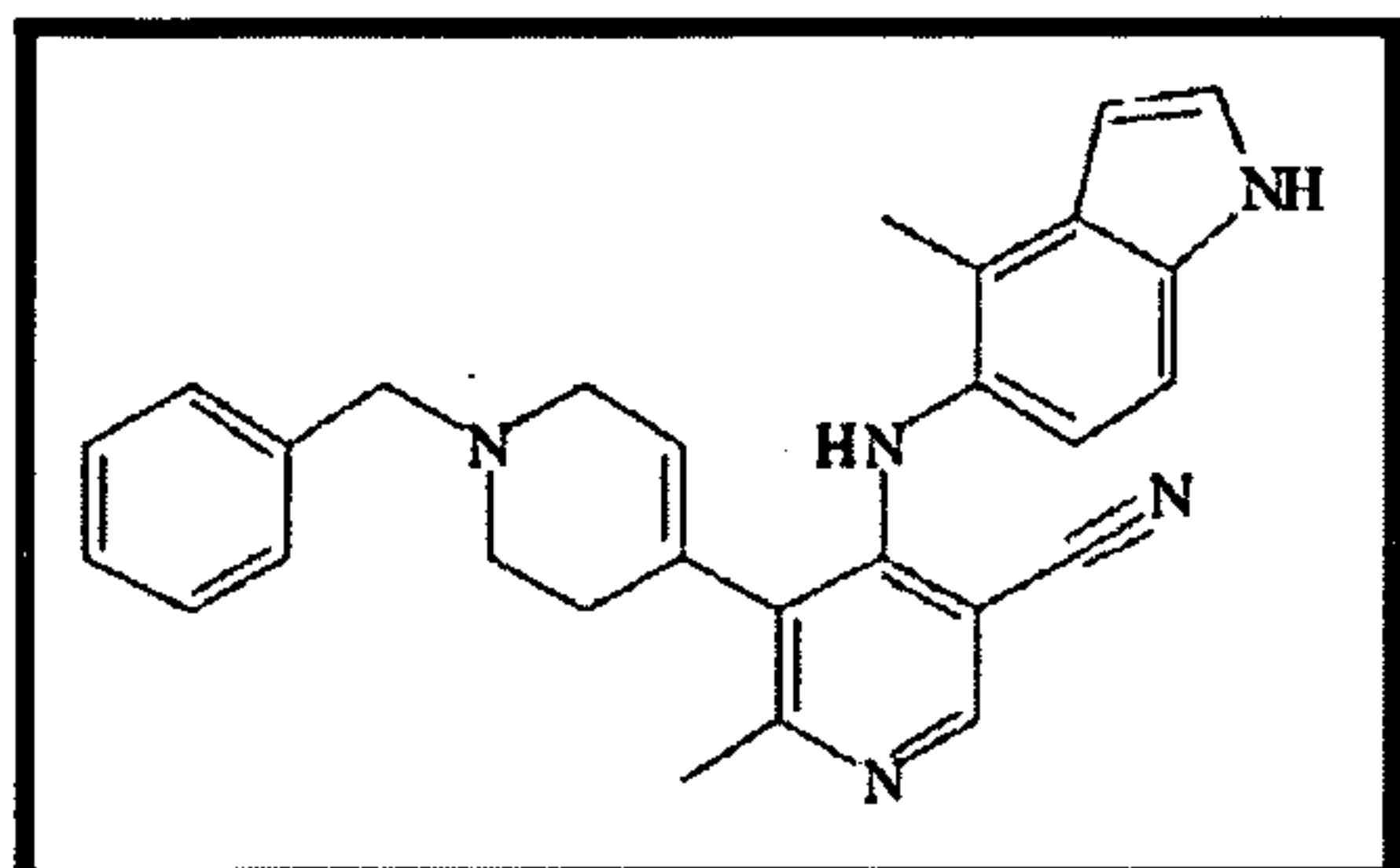
[00447] Preparation of 1'-(N,N-dimethylglycyl)-4-[(4-methyl-1H-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile:

The TFA salt of 4-[(4-methyl-1H-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile (80 mg, 0.18 mmol) was dissolved in 2:1 DCM/ methanol (3 mL) and treated with triethylamine (54 mg, 0.54 mmol). 2-(Dimethylamino)acetic acid (56 mg, 0.54 mmol) was added followed by 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (172 mg, 0.90 mmol). The reaction was stirred at room temperature for 36 h. The solvents were removed and the residue was redissolved in DMSO for purification by HPLC to give the title compound as a solid; MS 415.2 (M+H), HPLC rt = 4.6 min [a].



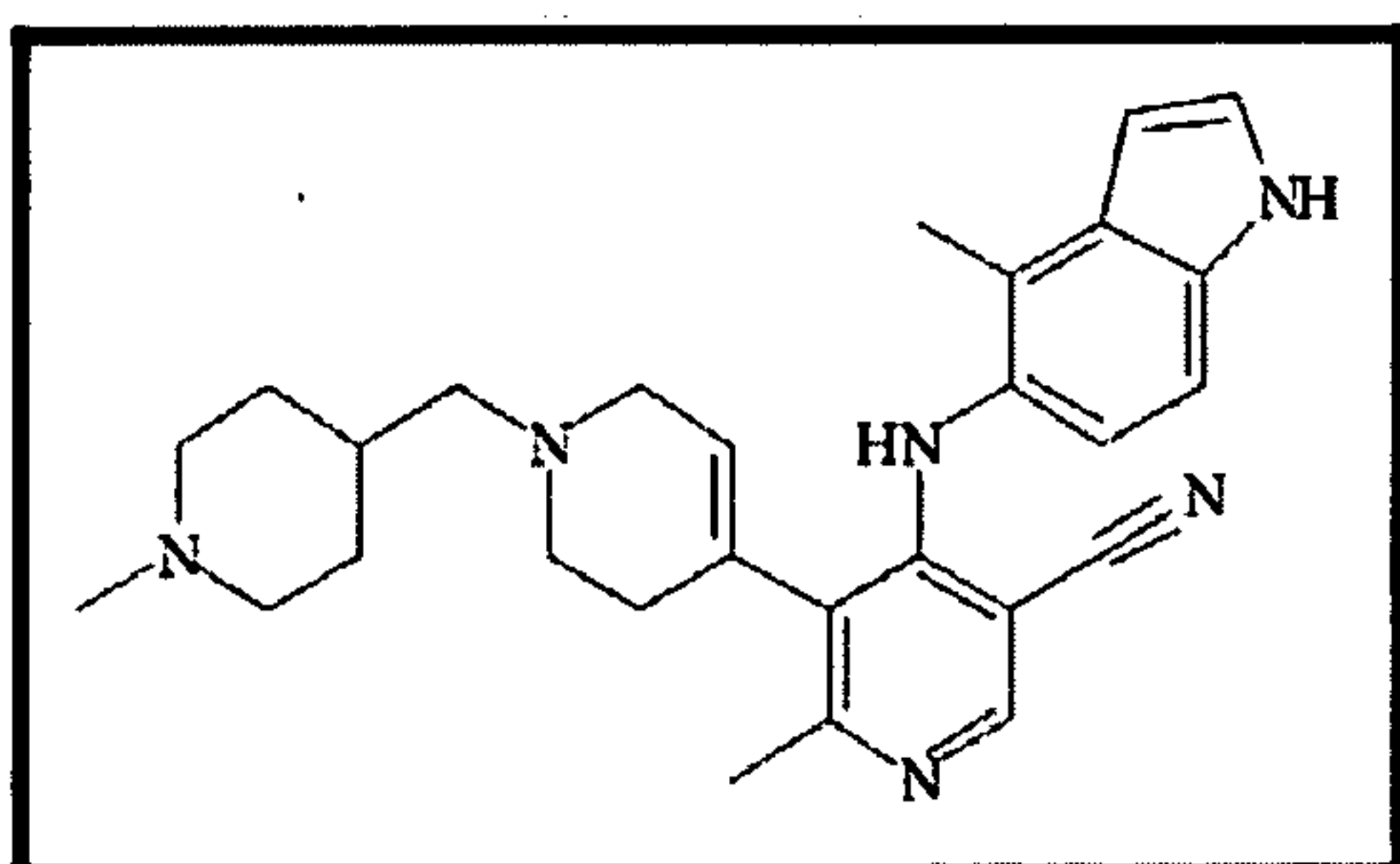
[00448] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-1'-[(1-methylpiperidin-4-yl)methyl]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile:

The TFA salt of 4-[(4-methyl-1H-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile (120 mg, 0.27 mmol) was combined with 1-methylpiperidine-4-carbaldehyde (41 mg, 0.33 mmol), sodium triacetoxyborohydride (171 mg, 0.81 mmol) and triethylamine (33 mg, 0.33 mmol) in 3 mL of DCE and stirred at room temperature for 16 h. The solvents were removed and the residue was redissolved in DMSO for purification by HPLC to give the title compound as its TFA salt; MS 441.2 (M+H), HPLC rt = 4.9 min [a].



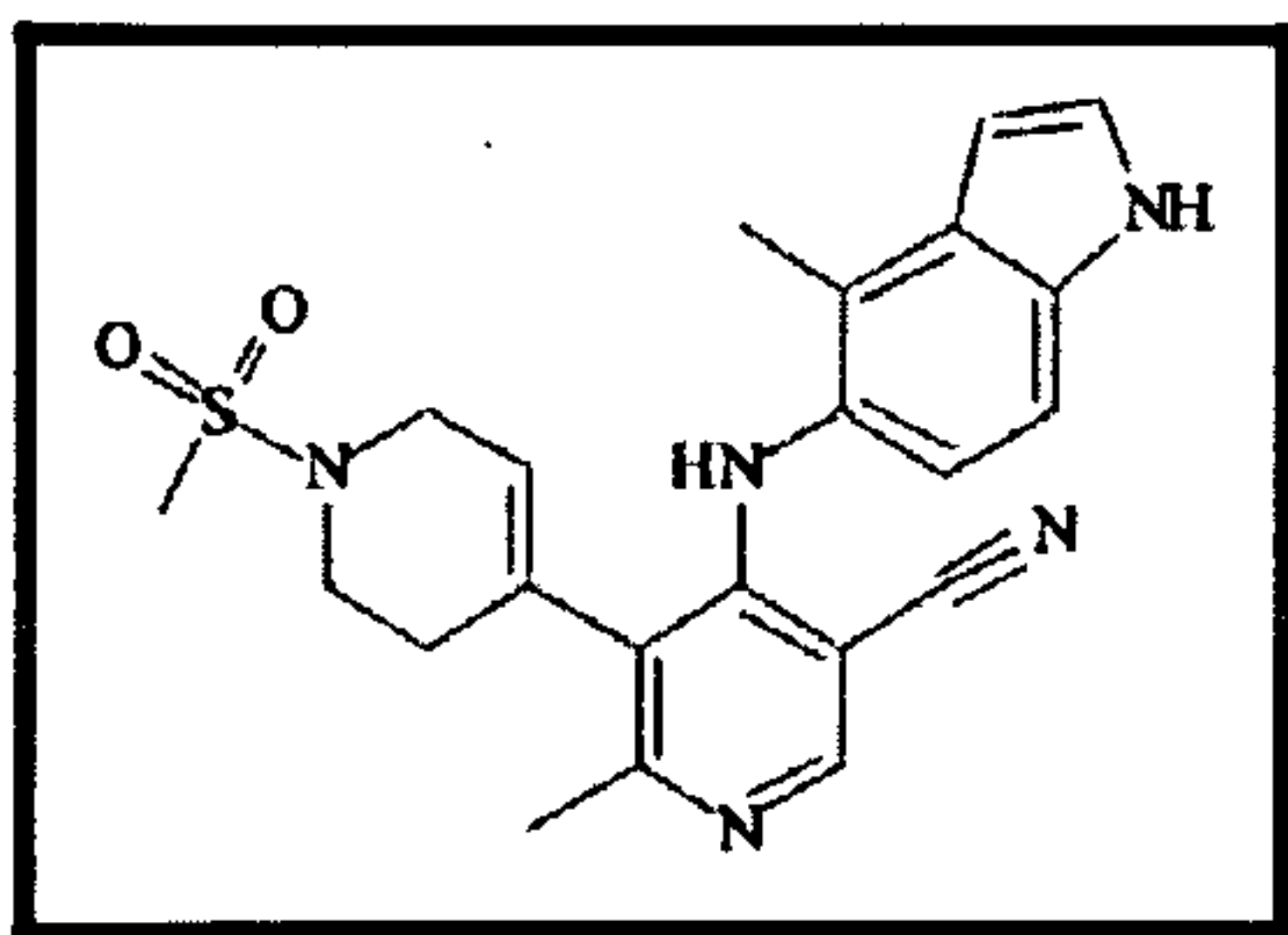
[00449] Preparation of 1'-benzyl-2-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile:

The TFA salt of 2-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile (100 mg, 0.22 mmol) was combined with benzaldehyde (28 mg, 0.26 mmol), sodium triacetoxyborohydride (140 mg, 0.66 mmol) and triethylamine (89 mg, 0.88 mmol) in 3 mL of DCE and stirred at room temperature for 2 h. The solvents were removed and the residue was redissolved in DMSO for purification by HPLC to give the title compound as its TFA salt; MS 434.2 (M+H), HPLC rt = 6.1 min [a].



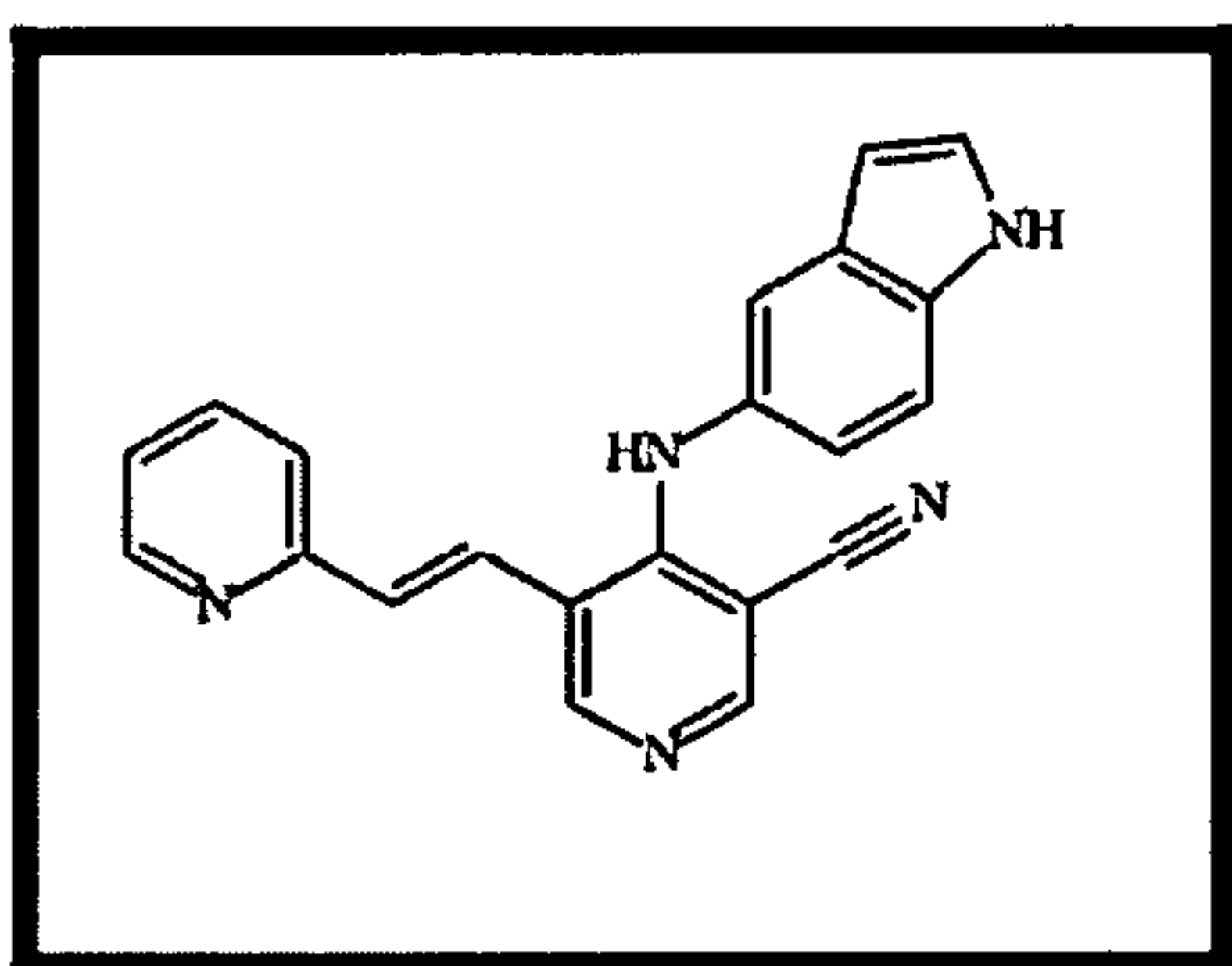
[00450] Preparation of 2-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-1'-[(1-methylpiperidin-4-yl)methyl]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile:

The TFA salt of 2-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile (100 mg, 0.22 mmol) was combined with 1-methylpiperidine-4-carbaldehyde (61 mg, 0.48 mmol), sodium triacetoxyborohydride (140 mg, 0.66 mmol) and triethylamine (89 mg, 0.88 mmol) in 3 mL of DCE and stirred at room temperature for 16 h. The solvents were removed and the residue was redissolved in DMSO for purification by HPLC to give the title compound as its TFA salt; MS 455.2 (M+H), HPLC rt = 4.7 min [a].



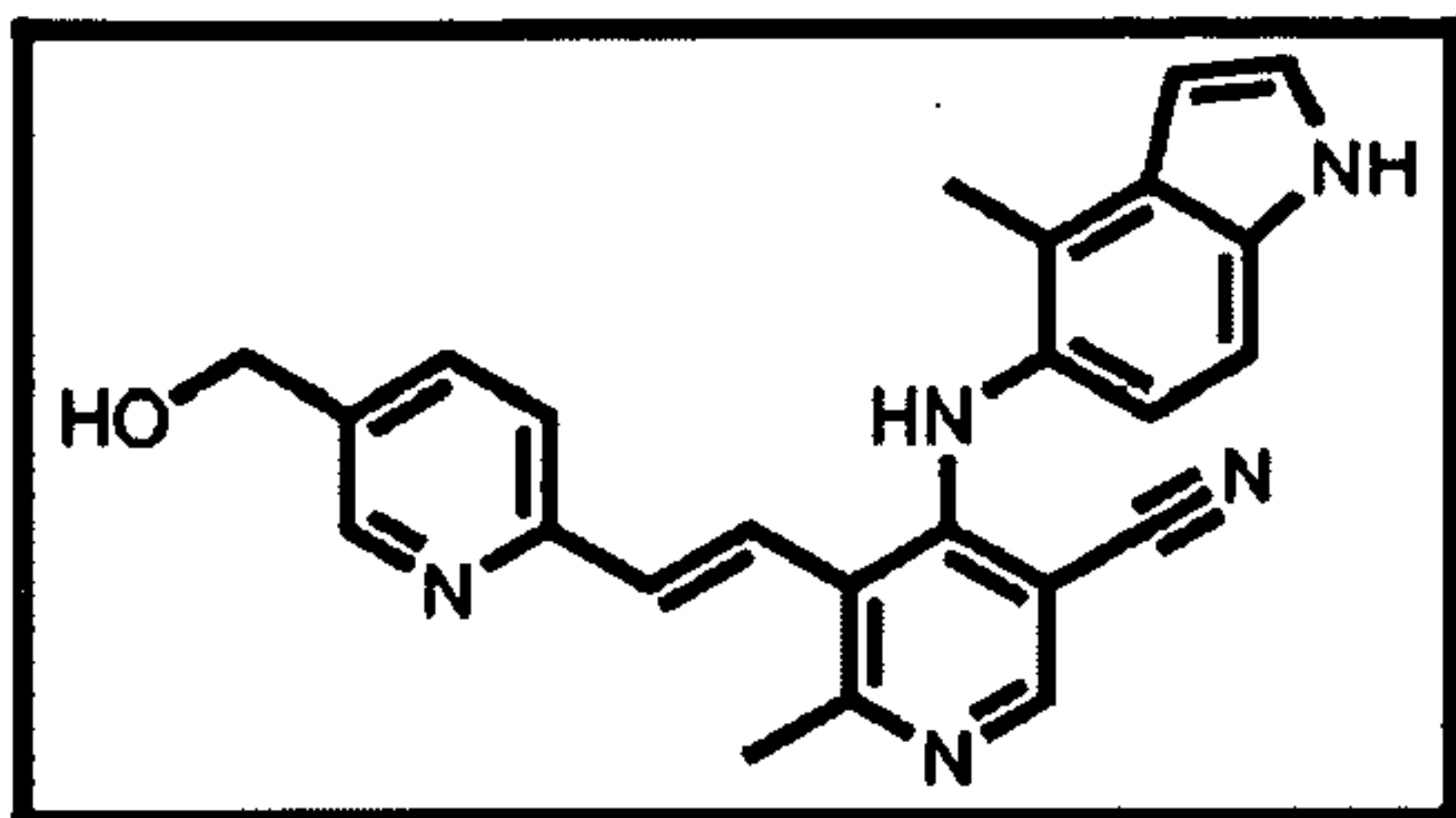
[00451] Preparation of 2-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-1'-(methanesulfonyl)-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile:

The TFA salt of 2-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile (100 mg, 0.22 mmol) was combined with methanesulfonyl chloride (30 mg, 0.26 mmol) and triethylamine (89 mg, 0.88 mmol) in 1 mL of DMF and stirred at room temperature for 2 h. The reaction was purified by HPLC to give the title compound as its TFA salt; MS 422.2 (M+H), HPLC *rt* = 7.6 min [a].



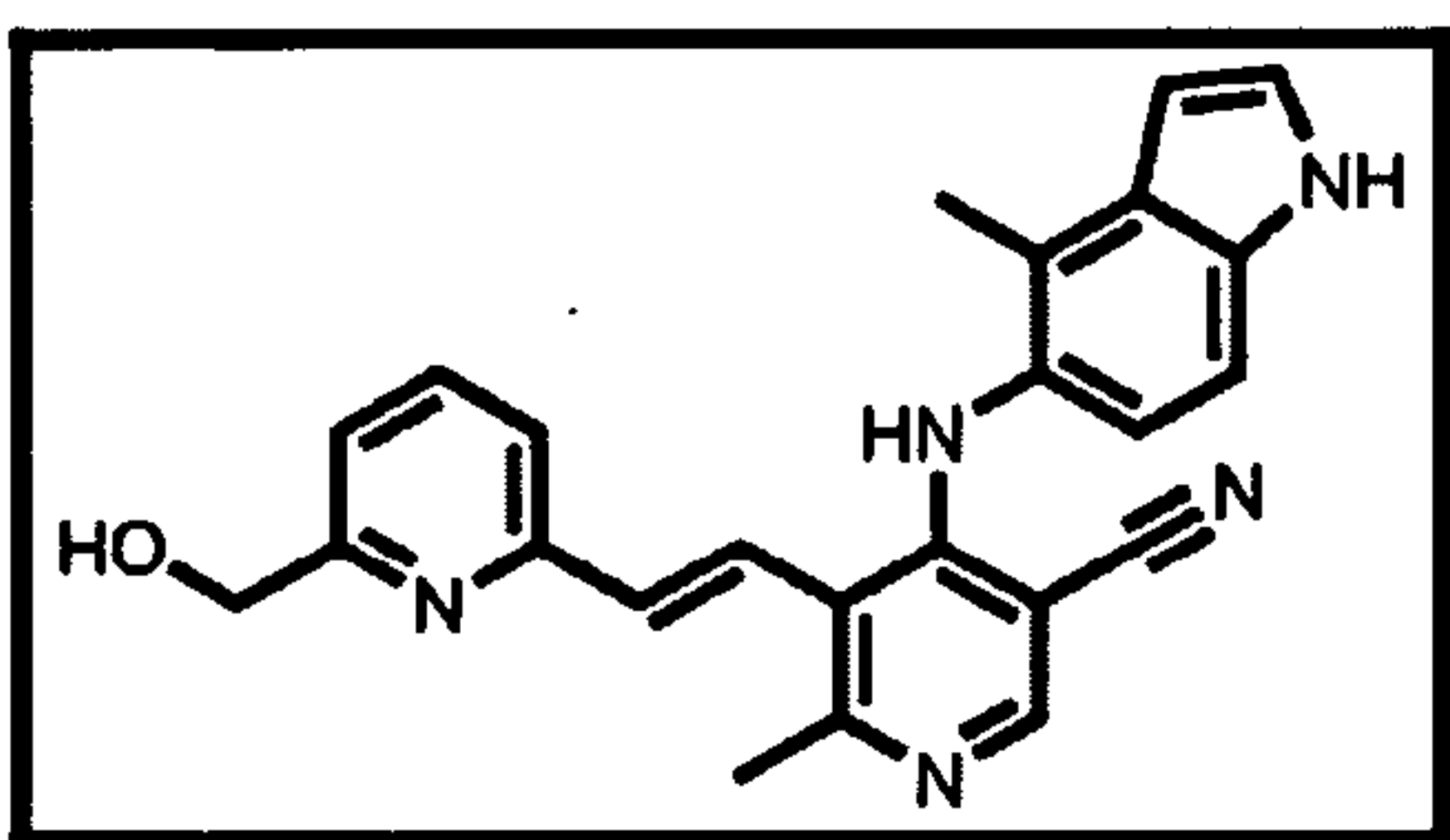
[00452] Preparation of 4-(1H-indol-5-ylamino)-5-[(E)-2-pyridin-2-ylethenyl]pyridine-3-carbonitrile :

A mixture of 4-(1H-indol-5-ylamino)-5-iodonicotinonitrile (200 mg, 0.55 mmol), 2-vinylpyridine (0.120 mL, 1.11 mmol), palladium(II)acetate (30 mg), tri(o-tolyl)phosphine (19 mg) and 0.500 mL of triethylamine in 5 mL of DMF was heated at 100°C for 30 min. After cooling to room temperature, the reaction mixture was partitioned between saturated aqueous sodium bicarbonate and dichloromethane. The organic layer was further extracted with ethyl acetate and the organic layers were combined, washed with brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography eluting with a gradient of 3:1 hexane : ethyl acetate to all ethyl acetate. Trituration with diethyl ether provided 19.8 mg (11%) of 4-(1H-indol-5-ylamino)-5-[(E)-2-pyridin-2-ylethenyl]pyridine-3-carbonitrile as a pale yellow solid: MS 338.1 (M+H), HPLC 98.0%, *rt* = 5.9 min [a].



[00453] Preparation of 5-((E)-2-((4-methyl-1H-indol-5-yl)amino)pyridin-3-carbonitrile)-6-methyl-4-((4-methyl-1H-indol-5-yl)amino)pyridine-3-carbonitrile:

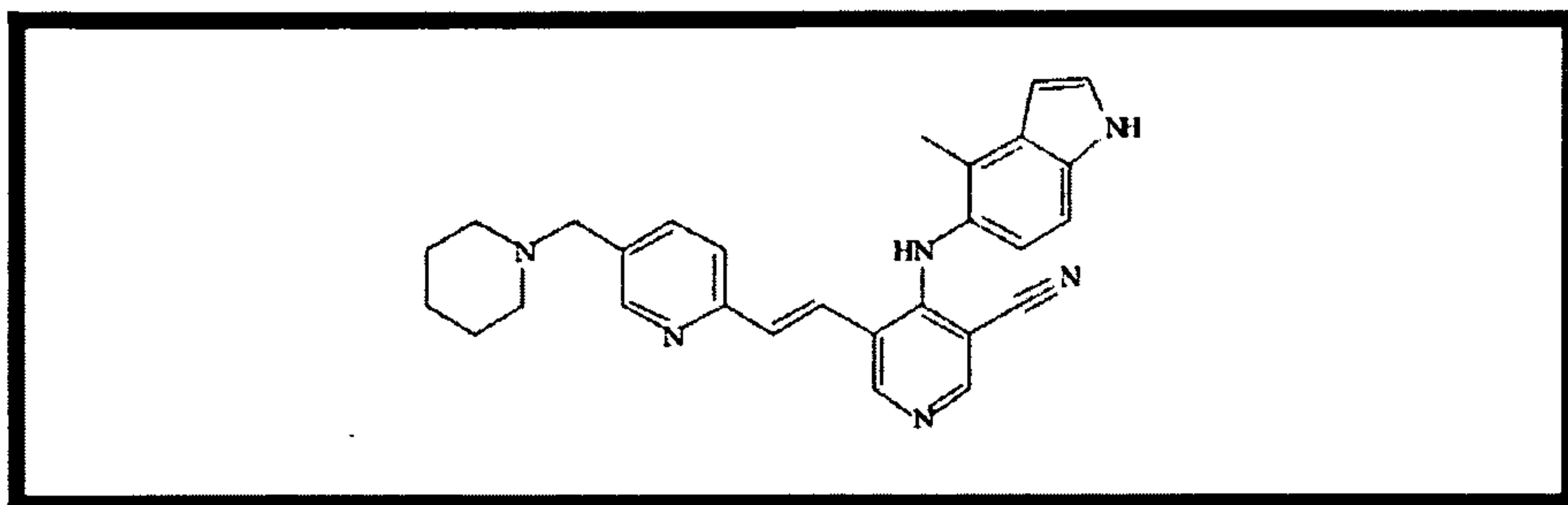
5-Iodo-6-methyl-4-((4-methyl-1H-indol-5-yl)amino)nicotinonitrile (3.0 g, 7.73 mmol) was dissolved in a mixture of DMF (40 ml) and triethylamine (10 ml) and subsequently treated with (6-vinylpyridin-3-yl)methanol (1.15 g, 8.51 mmol), Pd(OAc)₂ (347 mg, 1.55 mmol) and P(o-Tol)₃ (118 mg, 0.39 mmol). After stirring at 110 °C under nitrogen for 5 hr, the reaction was cooled and diluted with dichloromethane and washed one time with saturated aqueous sodium bicarbonate. A precipitate formed during a 2nd wash with saturated aqueous sodium bicarbonate. The precipitate was collected by filtration and washed with dichloromethane then water giving 2.08 g (68%) of the title compound as a tan solid, MS 396.3 (M+H); 93.9% at 215 nm, rt = 5.5 min [a].



[00454] Preparation of 5-((E)-2-((4-methyl-1H-indol-5-yl)amino)pyridin-3-carbonitrile)-6-methyl-4-((4-methyl-1H-indol-5-yl)amino)pyridine-3-carbonitrile:

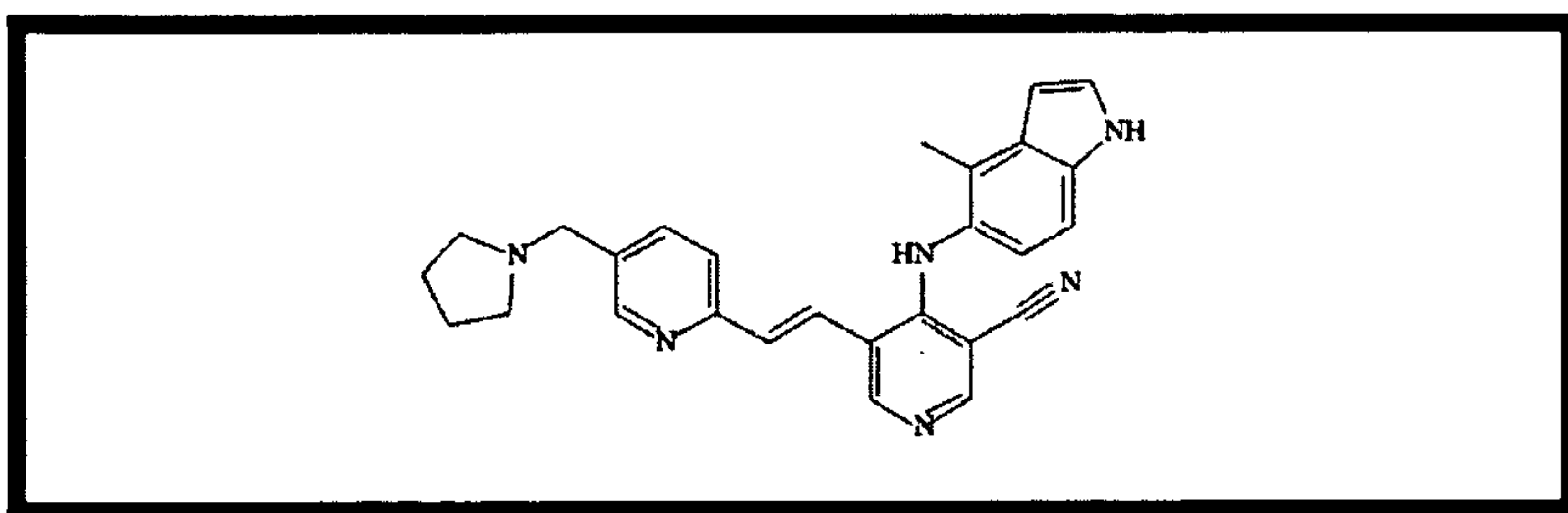
5-Iodo-6-methyl-4-((4-methyl-1H-indol-5-yl)amino)nicotinonitrile (3.0 g, 7.73 mmol) was dissolved in a mixture of DMF (40 ml) and triethylamine (10 ml), followed by the addition of (6-vinylpyridin-2-yl)methanol (1.05 g, 7.77 mmol), Pd(OAc)₂ (347 mg, 1.55 mmol) and P(o-Tol)₃ (118 mg, 0.39 mmol). The reaction mixture was stirred at 110 °C under nitrogen for 5 hr then cooled and diluted with dichloromethane. The organic layer was washed one time with saturated aqueous sodium bicarbonate. During a 2nd wash with saturated aqueous sodium bicarbonate, a precipitate formed and was collected by filtration. The solid was washed with

dichloromethane then water giving 2.31 g (76%) of the title compound as a tan solid, MS 396.3 (M+H); 94.7% at 215 nm, rt = 6.3 min [a].



[00455] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(piperidin-1-yl)ethyl]pyridin-2-yl]ethenyl]pyridine-3-carbonitrile:

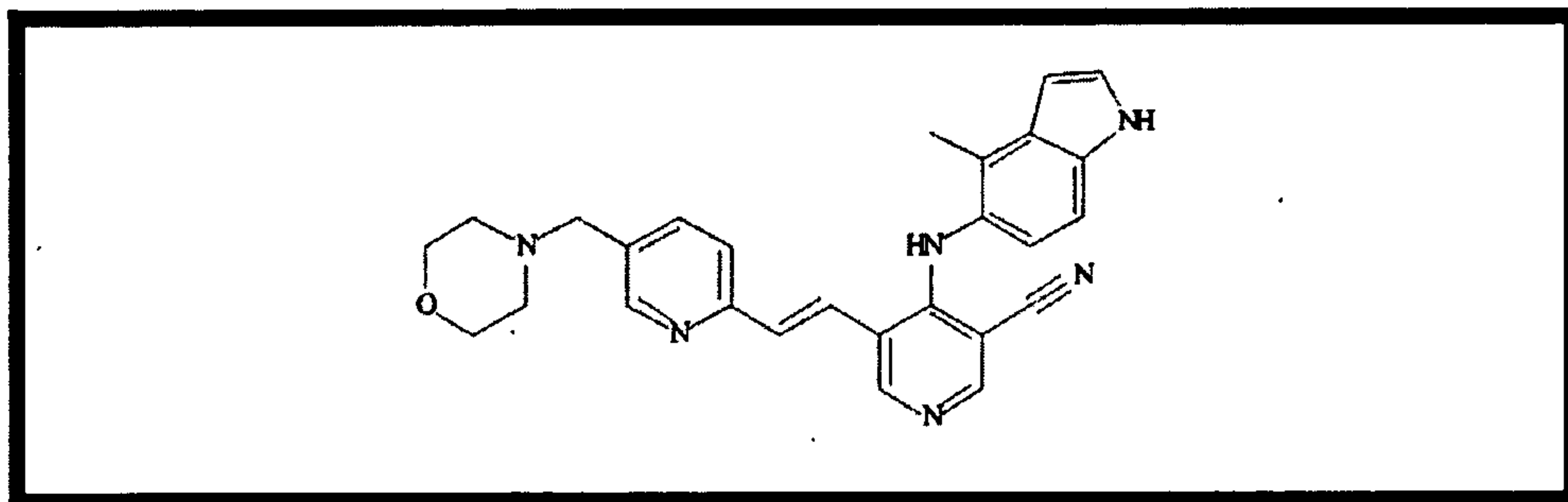
To the solution of 5-[(E)-2-[5-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (100 mg, 0.262 mmol) in solvent mixture THF (5 ml) and DMF (2.5 ml) was added triethylamine (183 μ L, 1.313 mmol). The solution was stirred under nitrogen at rt for 10 min. Methanesulfonyl chloride (61 μ L, 0.788 mmol) was added dropwise into the reaction mixture. After stirring under nitrogen at rt for 8 hours, piperidine (104 μ L, 1.050 mmol) was added and the reaction was stirred overnight. The solvent was removed and the residue was partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The organic layer was dried over MgSO_4 and concentrated to give dark syrup. The resulting crude compound was purified by HPLC to give 32 mg (27%) of the title compound as a yellow solid, MS 449.3 (M+H); 92.2% at 215 nm, 5.3 min [A].



[00456] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(pyrrolidin-1-yl)methyl]pyridin-2-yl]ethenyl]pyridine-3-carbonitrile:

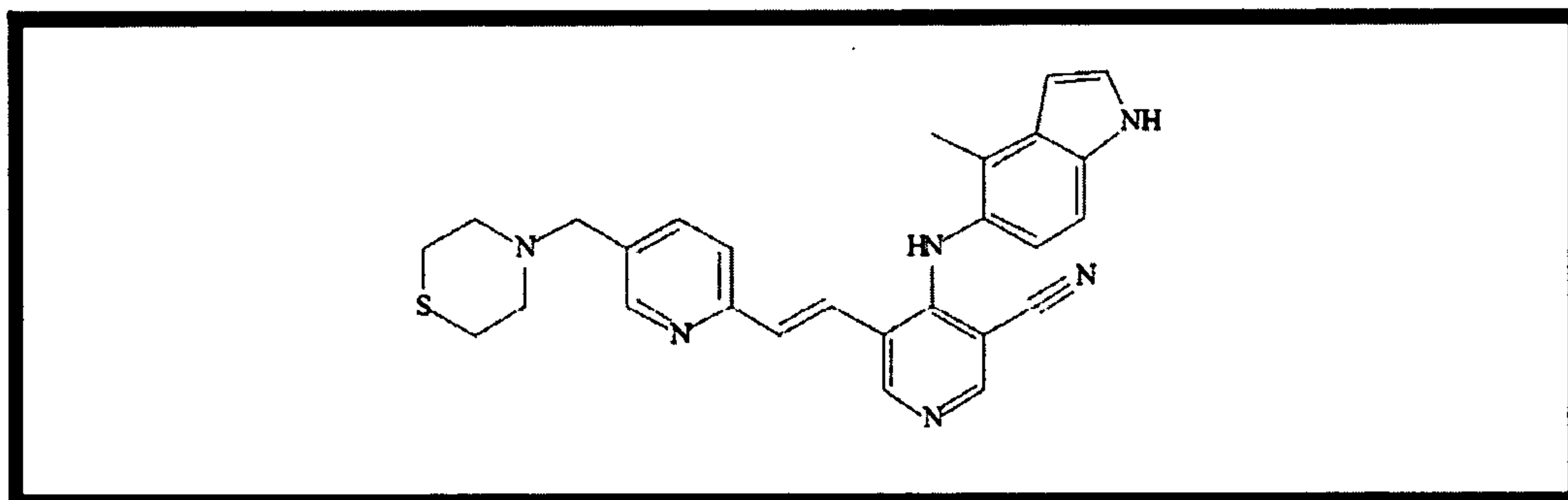
The title compound was prepared from 5-[(E)-2-[5-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and pyrrolidine via the procedure used to prepare 4-

[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(piperidin-1-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 435.3 (M+H); 90.3% at 215 nm, rt = 5.0 min [a].



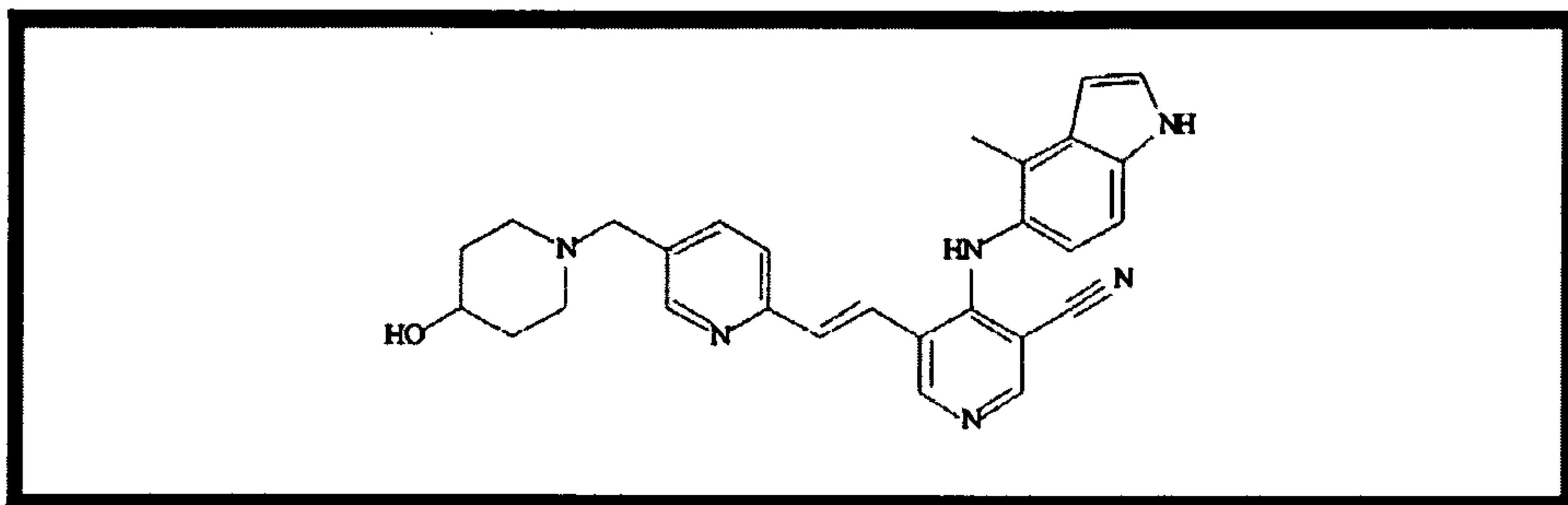
[00457] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(morpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[5-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and morpholine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(piperidin-1-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 451.3 (M+H); 91.8% at 215 nm, rt = 4.9 min [a].



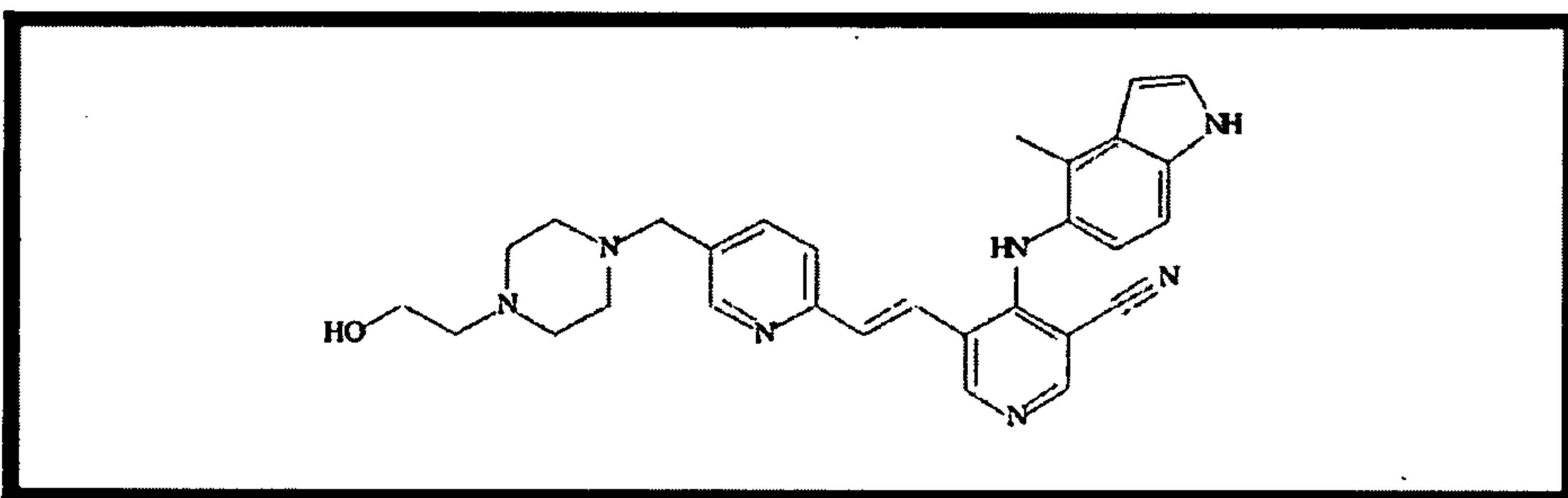
[00458] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(thiomorpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[5-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and thiomorpholine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(piperidin-1-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 467.2 (M+H); 95.2% at 215 nm, rt = 5.4 min [a].



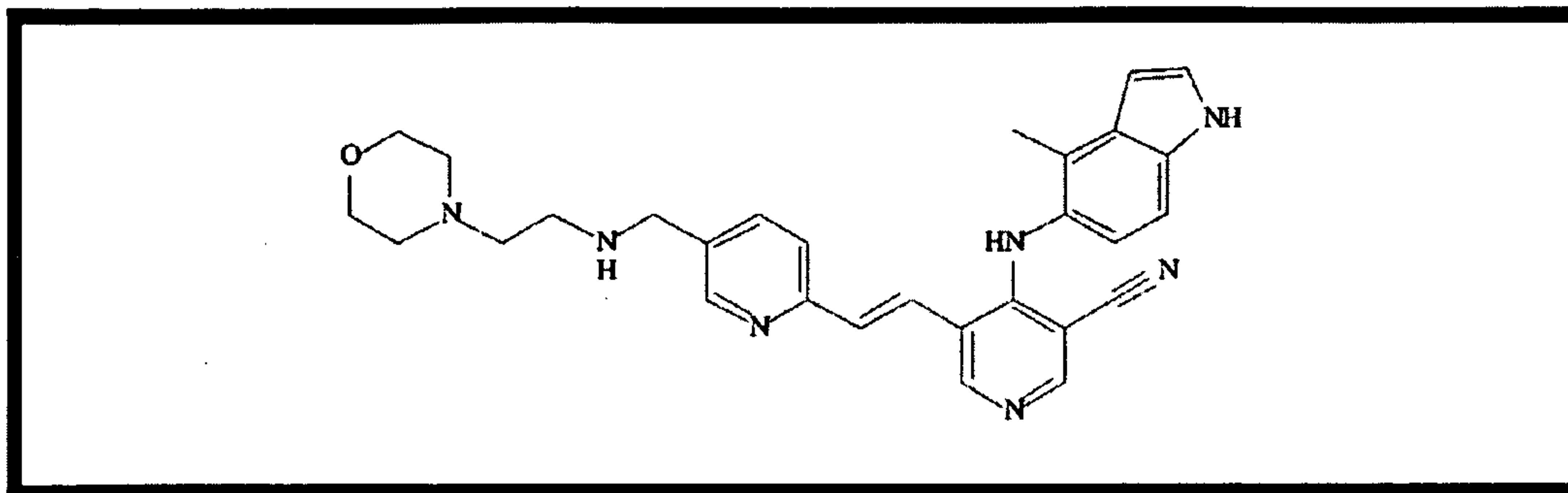
[00459] Preparation of 5-[(E)-2-{5-[(4-hydroxypiperidin-1-yl)methyl]pyridin-2-yl}ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[5-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 4-hydroxypiperidine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(piperidin-1-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 465.3 (M+H); HPLC *rt* = 4.7 min [a].



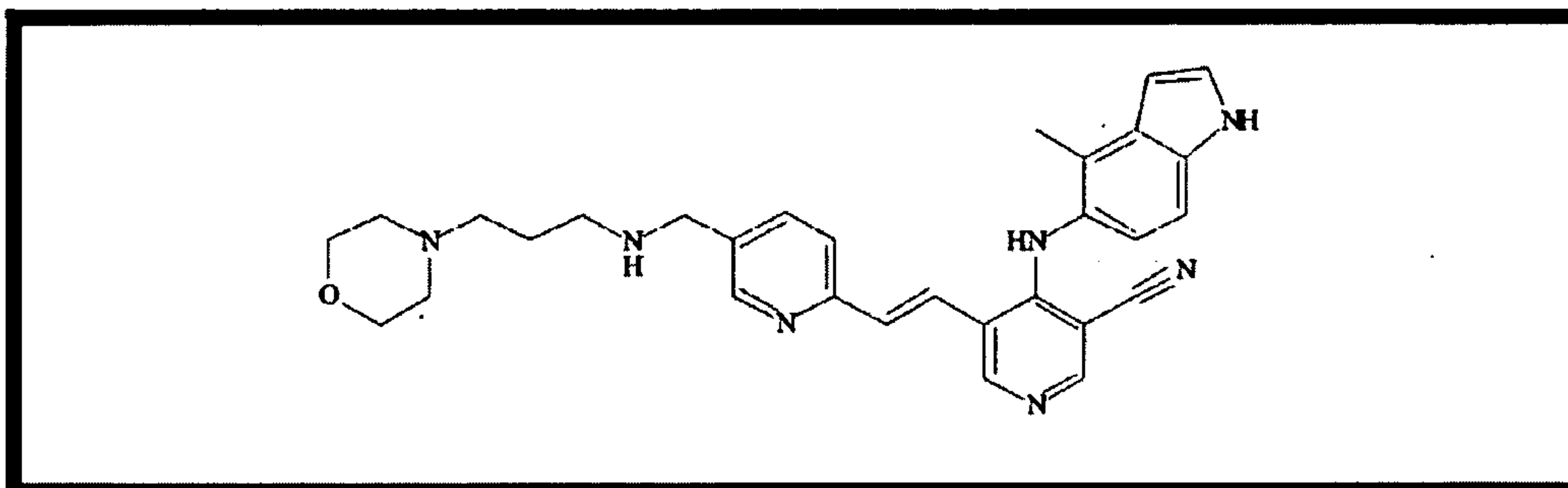
[00460] Preparation of 5-[(E)-2-{5-[(4-(2-hydroxyethyl)piperazin-1-yl)methyl]pyridin-2-yl}ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[5-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 4-(2-hydroxyethyl)piperazine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(piperidin-1-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 494.3 (M+H); 90.7% at 215 nm, *rt* = 4.7 min [a].



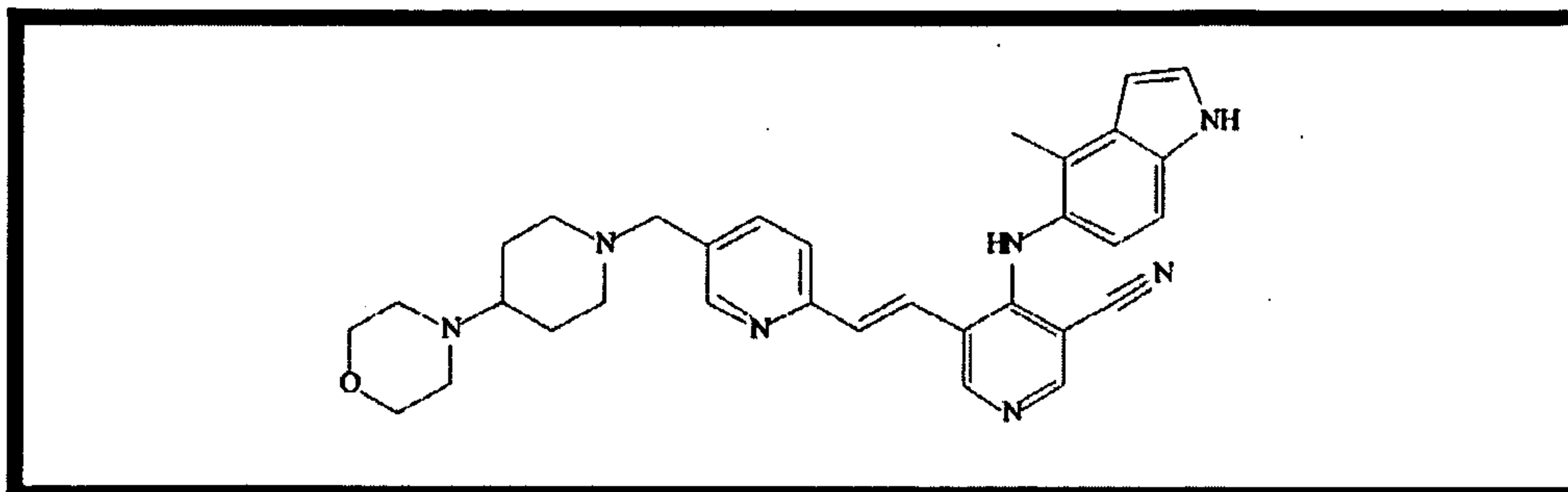
[00461] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(5-[(2-morpholin-4-ylethyl)amino]methyl)pyridin-2-yl)ethenyl]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[5-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 4-(2-aminoethyl)morpholine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(piperidin-1-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 494.3 (M+H); HPLC: 90.8% at 215 nm, *rt* = 4.4 min [a].



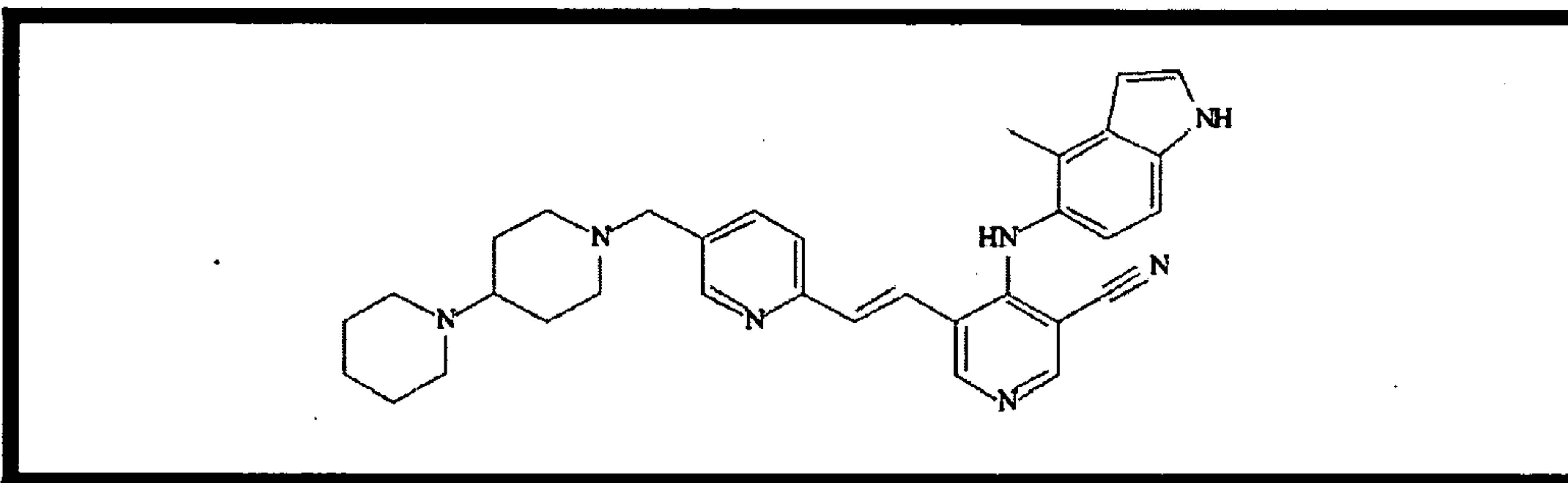
[00462] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(5-[(3-morpholin-4-ylpropyl)amino]methyl)pyridin-2-yl)ethenyl]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[5-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 4-(3-aminopropyl)morpholine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(piperidin-1-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 508.3 (M+H); HPLC: 98.2% at 215 nm, *rt* = 4.6 min [a].



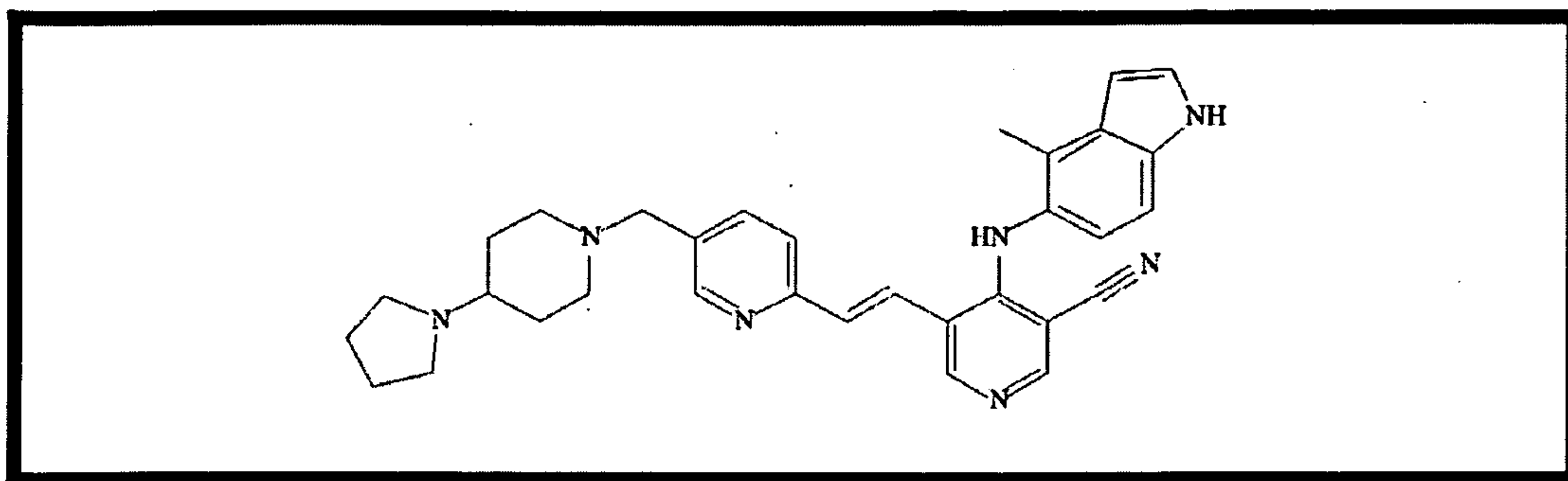
[00463] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{5-[(4-morpholin-4-yl)piperidin-1-yl)methyl]pyridin-2-yl}ethenyl]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[5-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 4-morpholinopiperidine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(piperidin-1-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 534.3 (M+H); HPLC: 98.1% at 215 nm, rt = 4.6 min [a].



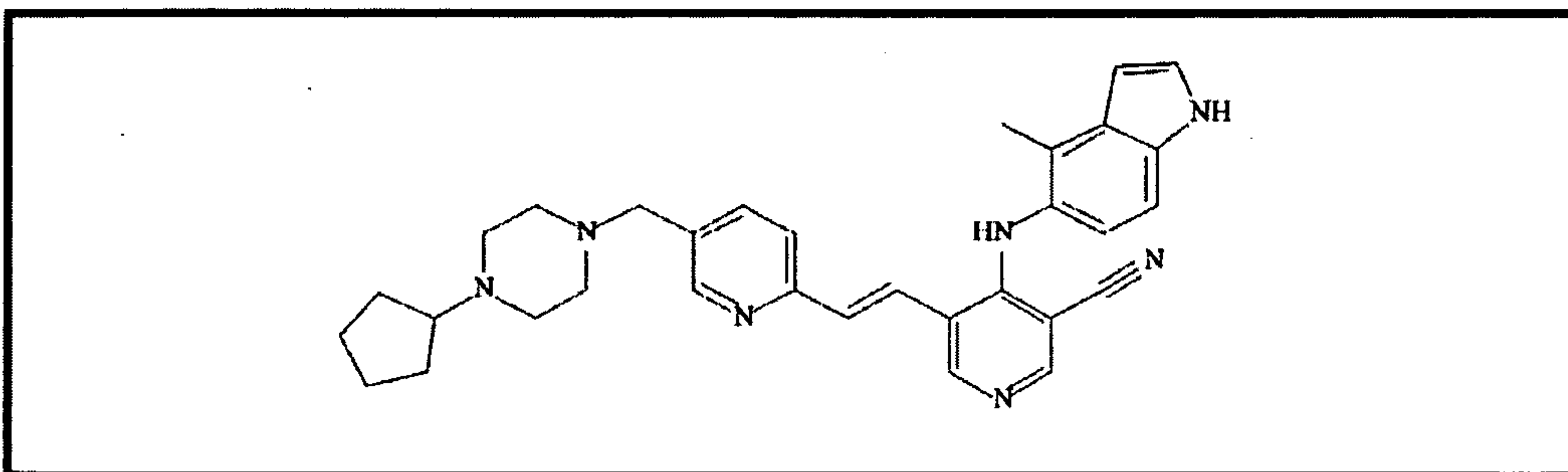
[00464] Preparation of 5-[(E)-2-[5-(1,4'-bipiperidin-1'-ylmethyl)pyridin-2-yl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[5-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 4-piperidinopiperidine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(piperidin-1-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 532.4 (M+H); HPLC: 97.7% at 215 nm, rt = 4.8 min [a].



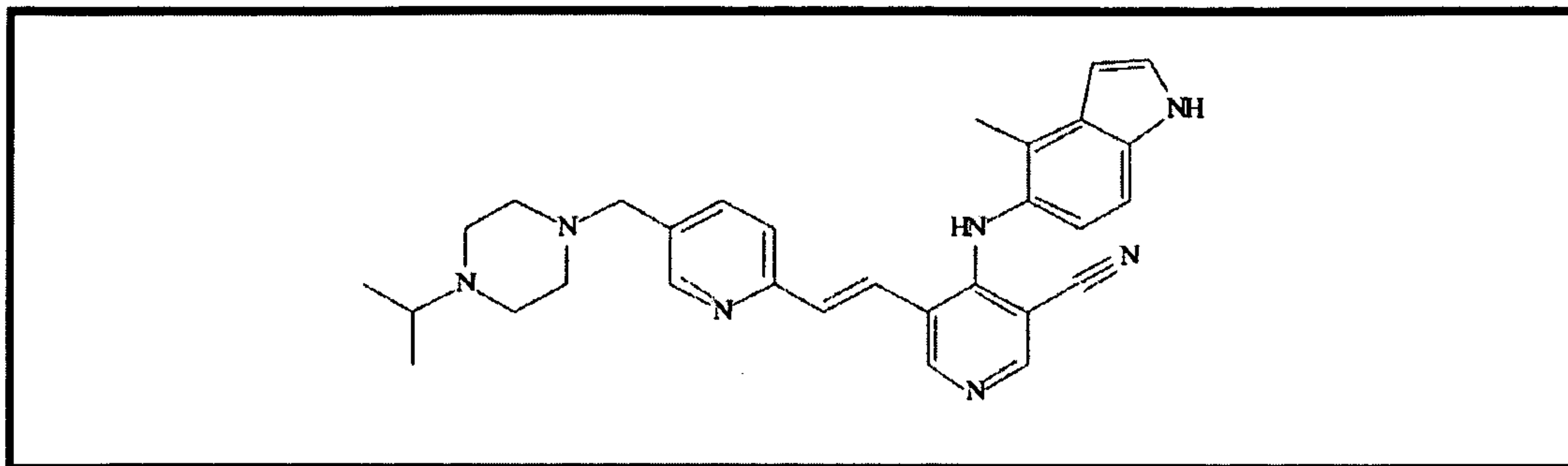
[00465] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{5-[(4-pyrrolidin-1-yl)piperidin-1-yl)methyl]pyridin-2-yl}ethenyl]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[5-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 4-pyrrolidinopiperidine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(piperidin-1-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 518.3 (M+H); HPLC: 97.4% at 215 nm, rt = 4.6 min [a].



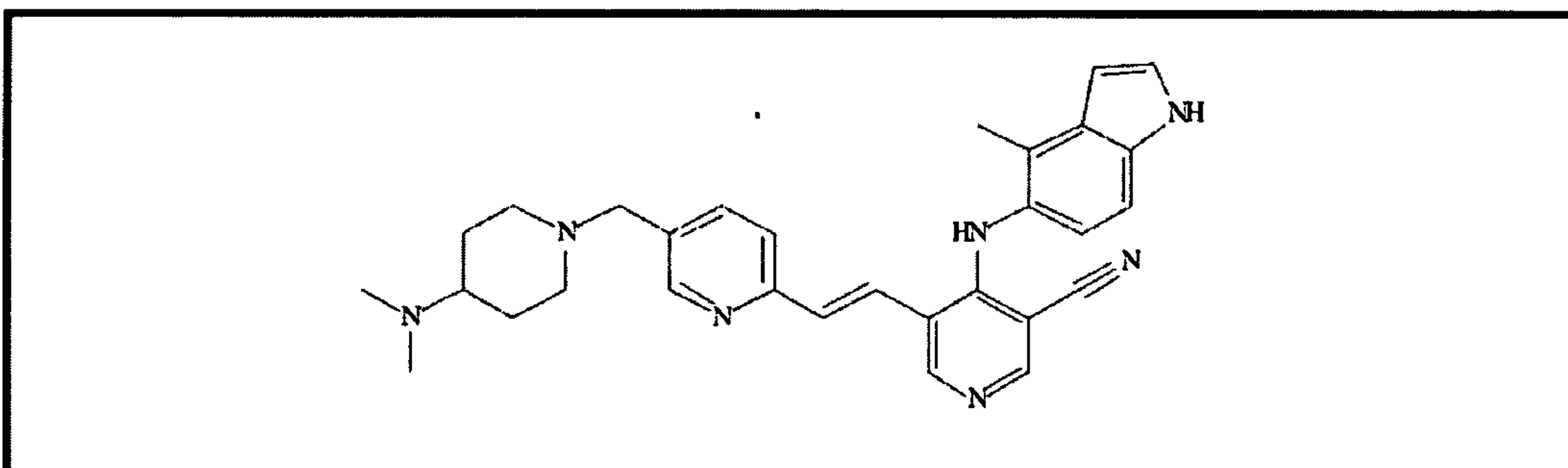
[00466] Preparation of 5-[(E)-2-{5-[(4-cyclopentylpiperazin-1-yl)methyl]pyridin-2-yl}ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[5-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 1-cyclopentylpiperazine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(piperidin-1-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 518.3 (M+H); HPLC: 97.1% at 215 nm, rt = 5.8 min [a].



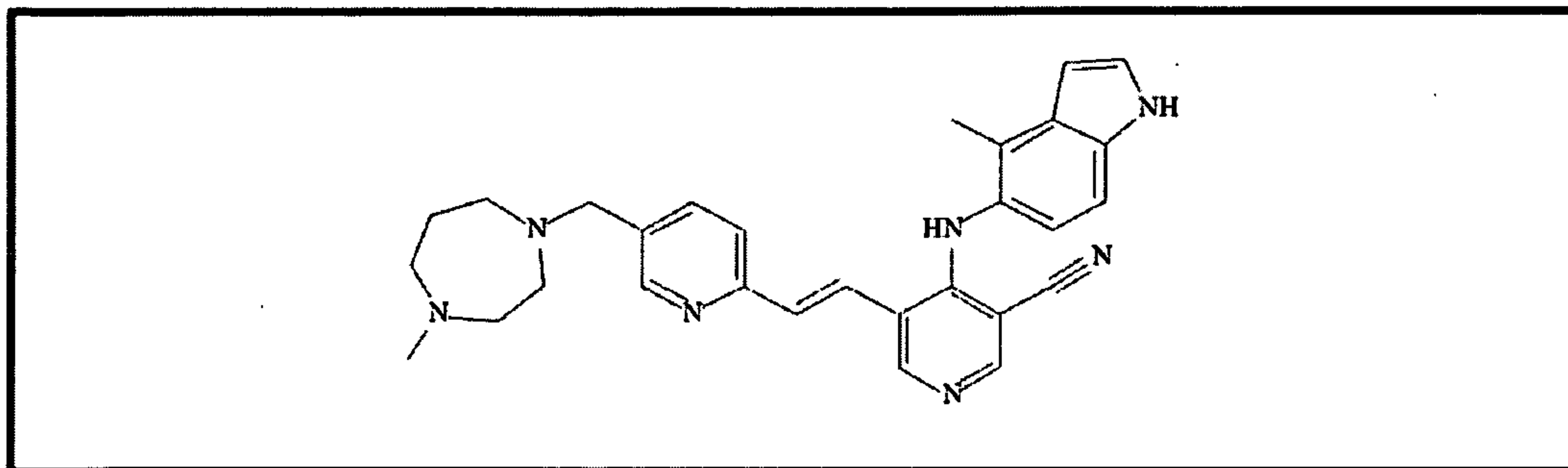
[00467] Preparation of 5-[(E)-2-(5-[[4-(1-methylethyl)piperazin-1-yl]methyl]pyridin-2-yl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[5-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 1-isopropylpiperazine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(piperidin-1-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 492.3 (M+H); HPLC: 96.6% at 215 nm, rt = 5.4 min [a].



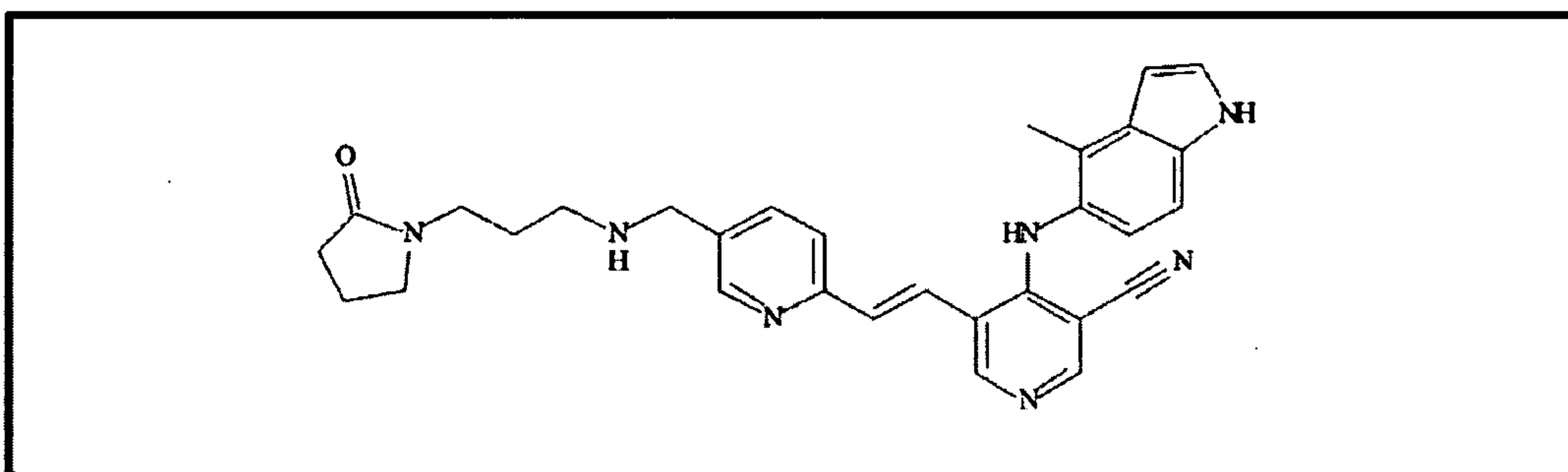
[00468] Preparation of 5-[(E)-2-(5-[[4-(dimethylamino)piperidin-1-yl]methyl]pyridin-2-yl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[5-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 4-dimethylaminopiperidine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(piperidin-1-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 492.3 (M+H); HPLC: 96.3% at 215 nm, rt = 4.5 min [a].



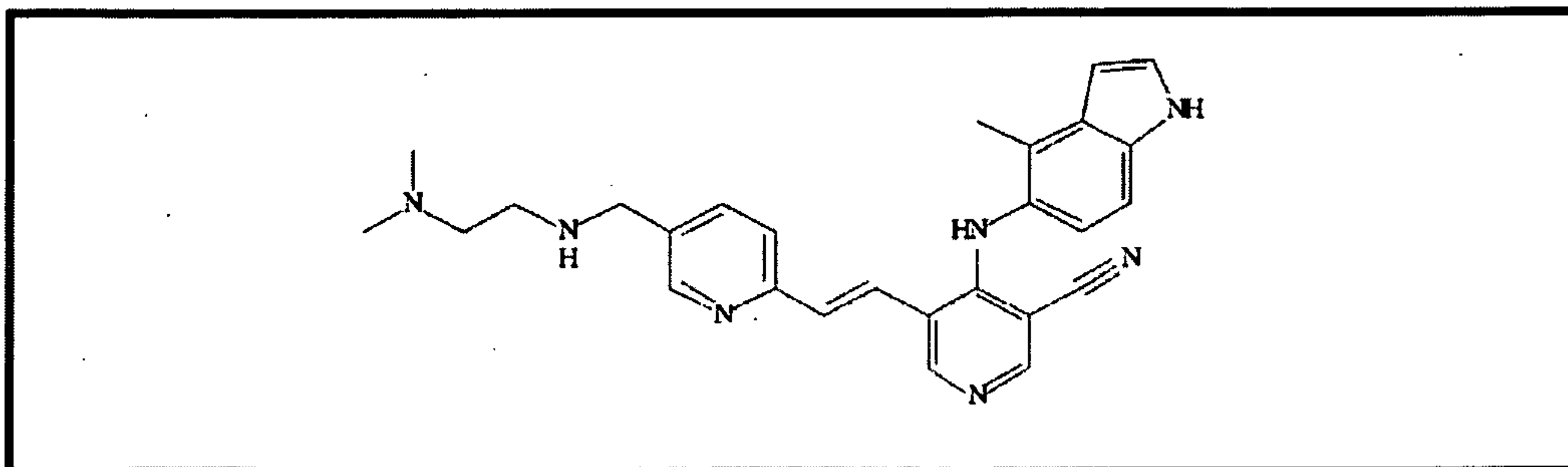
[00469] Preparation of 5-[(E)-2-{5-[(4-methyl-1,4-diazepan-1-yl)methyl]pyridin-2-yl}ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[5-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 1-methylhomopiperazine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(piperidin-1-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 478.3 (M+H); HPLC: 96.3% at 215 nm, rt = 4.5 min [a].



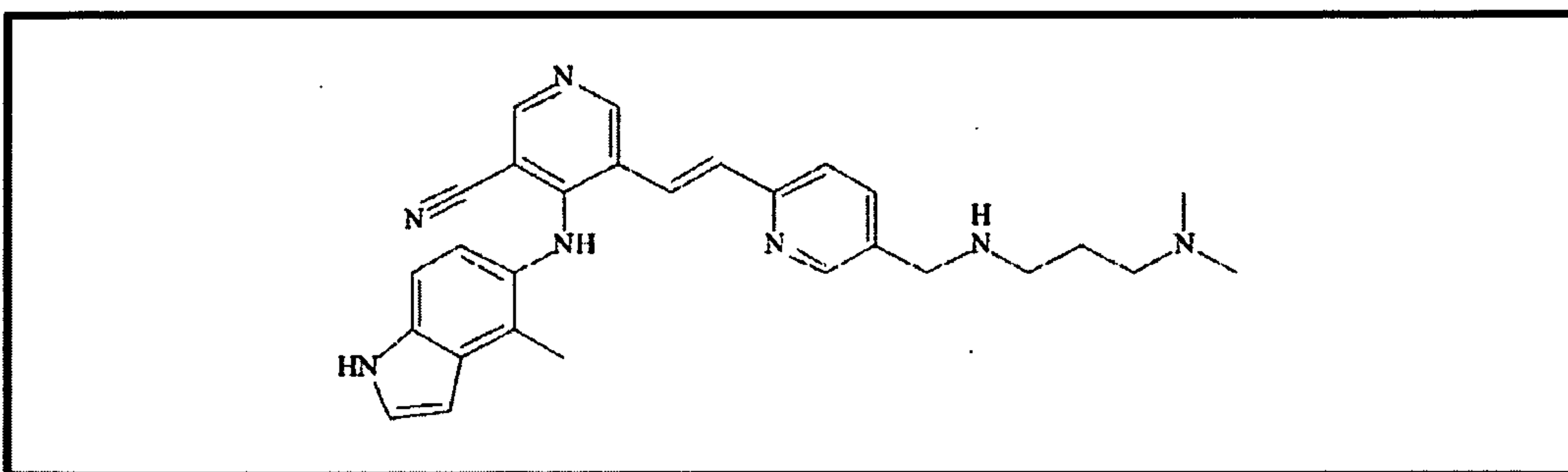
[00470] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-({[3-(2-oxo pyrrolidin-1-yl)propyl]amino}methyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[5-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 1-(3-aminopropyl)-2-pyrrolidinone via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(piperidin-1-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 506.3 (M+H); HPLC: 98.8% at 215 nm, rt = 5.6 min [a].



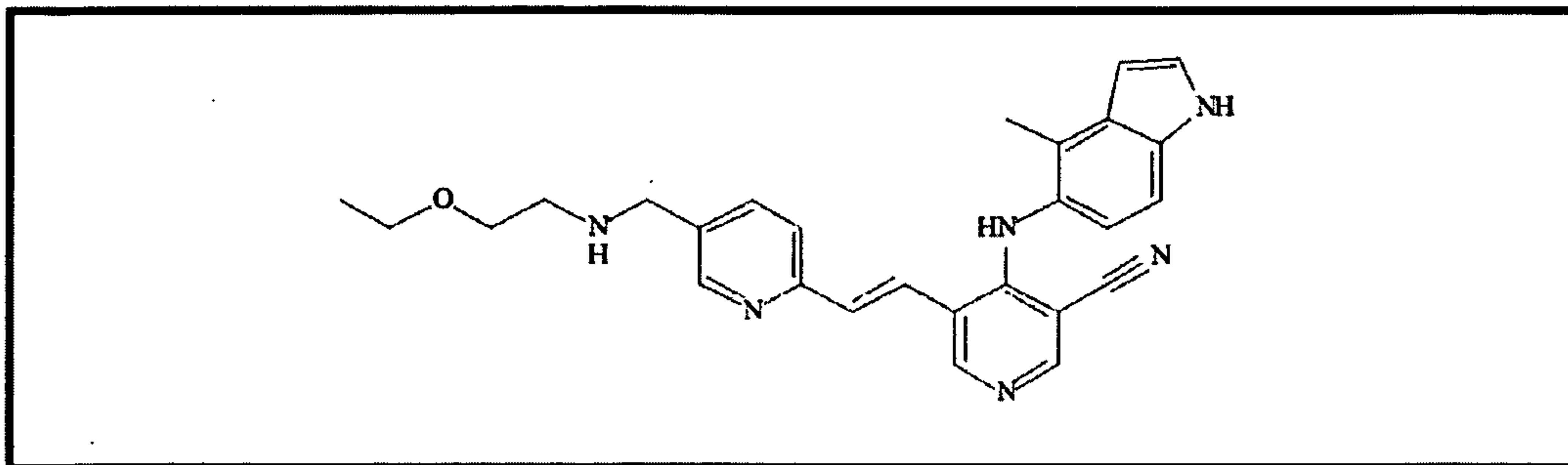
[00471] Preparation of 5-((E)-2-[5-((2-(dimethylamino)ethyl)amino)methyl)pyridin-2-yl]ethenyl)-4-((4-methyl-1H-indol-5-yl)amino)pyridine-3-carbonitrile:

The title compound was prepared from 5-((E)-2-[5-(hydroxymethyl)pyridin-2-yl]vinyl)-4-((4-methyl-1H-indol-5-yl)amino)nicotinonitrile and N,N-dimethylethylenediamine via the procedure used to prepare 4-((4-methyl-1H-indol-5-yl)amino)-5-((E)-2-[5-(piperidin-1-ylmethyl)pyridin-2-yl]ethenyl)pyridine-3-carbonitrile, MS 452.1 (M+H); HPLC: 90.9% at 215 nm, rt = 5.4 min [a].



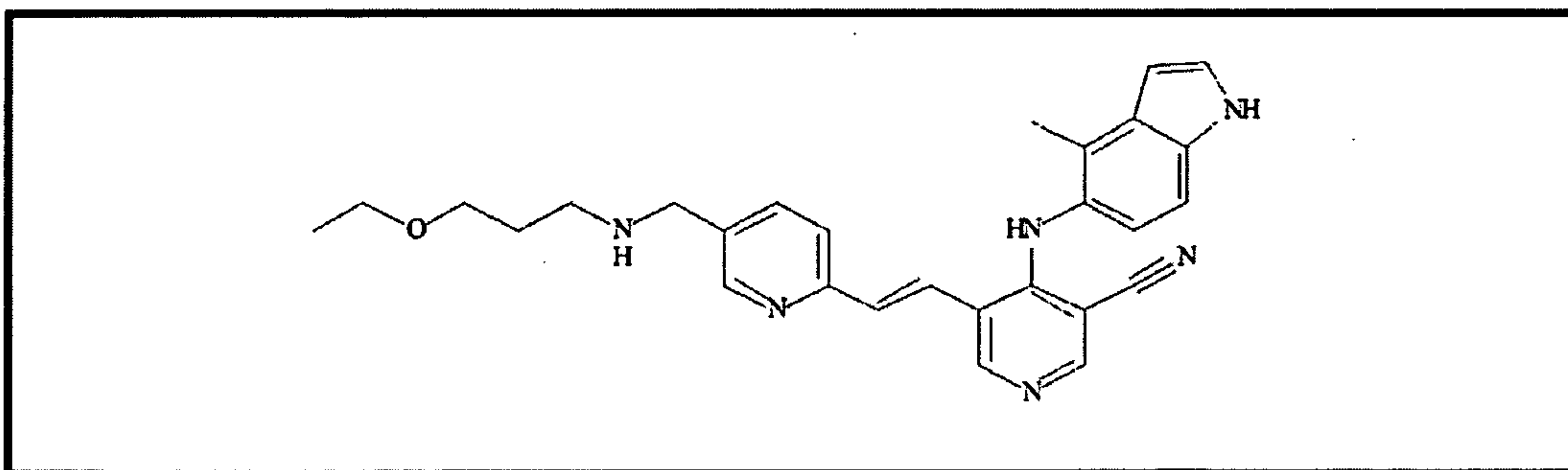
[00472] Preparation of 5-((E)-2-[5-((3-(dimethylamino)propyl)amino)methyl)pyridin-2-yl]ethenyl)-4-((4-methyl-1H-indol-5-yl)amino)pyridine-3-carbonitrile:

The title compound was prepared from 5-((E)-2-[5-(hydroxymethyl)pyridin-2-yl]vinyl)-4-((4-methyl-1H-indol-5-yl)amino)nicotinonitrile and 3-(dimethylamino)propylamine via the procedure used to prepare 4-((4-methyl-1H-indol-5-yl)amino)-5-((E)-2-[5-(piperidin-1-ylmethyl)pyridin-2-yl]ethenyl)pyridine-3-carbonitrile, MS 466.3 (M+H); HPLC: rt = 1.31 min [d].



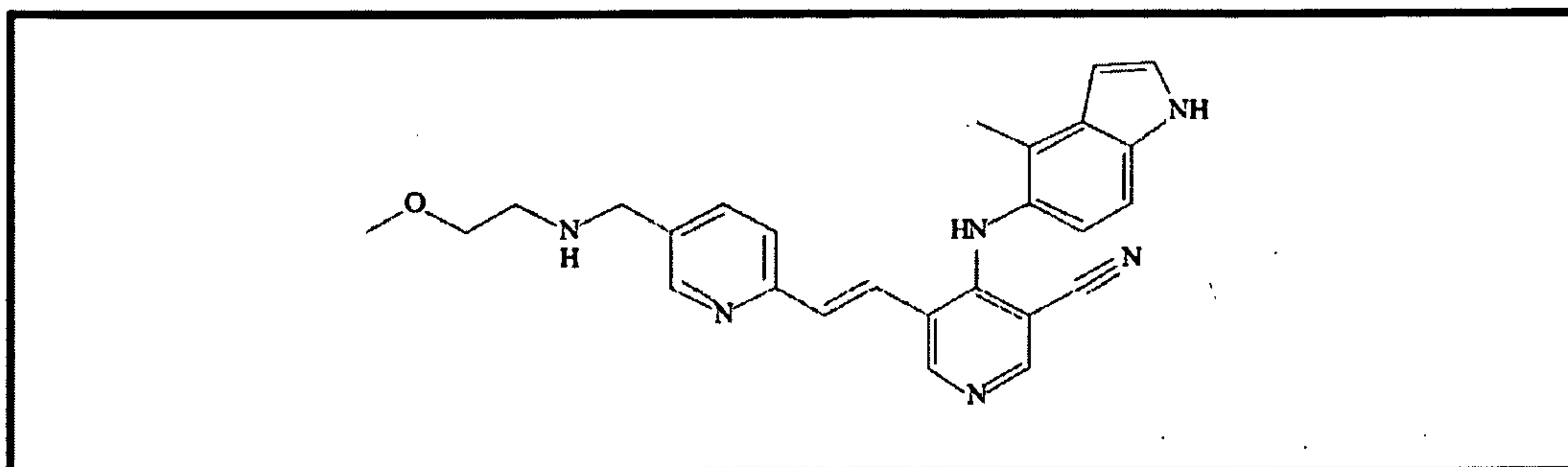
[00473] Preparation of 5-[(E)-2-(5-[(2-ethoxyethyl)amino]methyl)pyridin-2-yl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[5-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 2-ethoxyethylamine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(piperidin-1-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 453.1 (M+H); HPLC: rt = 6.5 min [a].



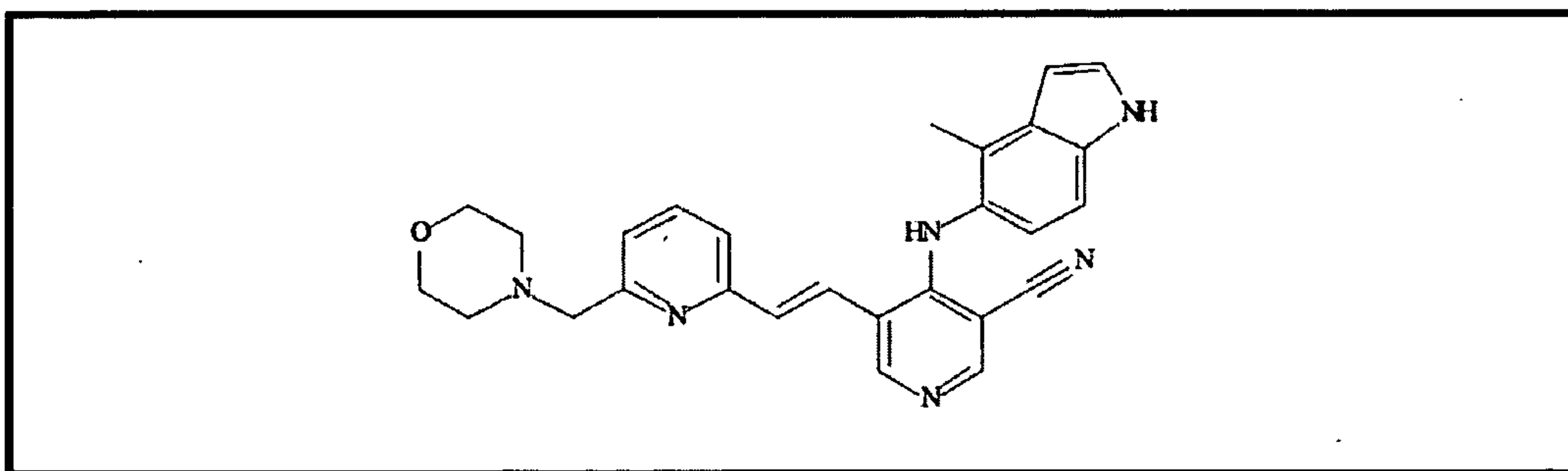
[00474] Preparation of 5-[(E)-2-(5-[(3-ethoxypropyl)amino]methyl)pyridin-2-yl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[5-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 3-ethoxypropylamine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(piperidin-1-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 467.1 (M+H); HPLC: 94.0% at 215 nm, rt = 6.7 min [a].



[00475] Preparation of 5-[(E)-2-(5-[(2-methoxyethyl)amino]methyl)pyridin-2-yl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

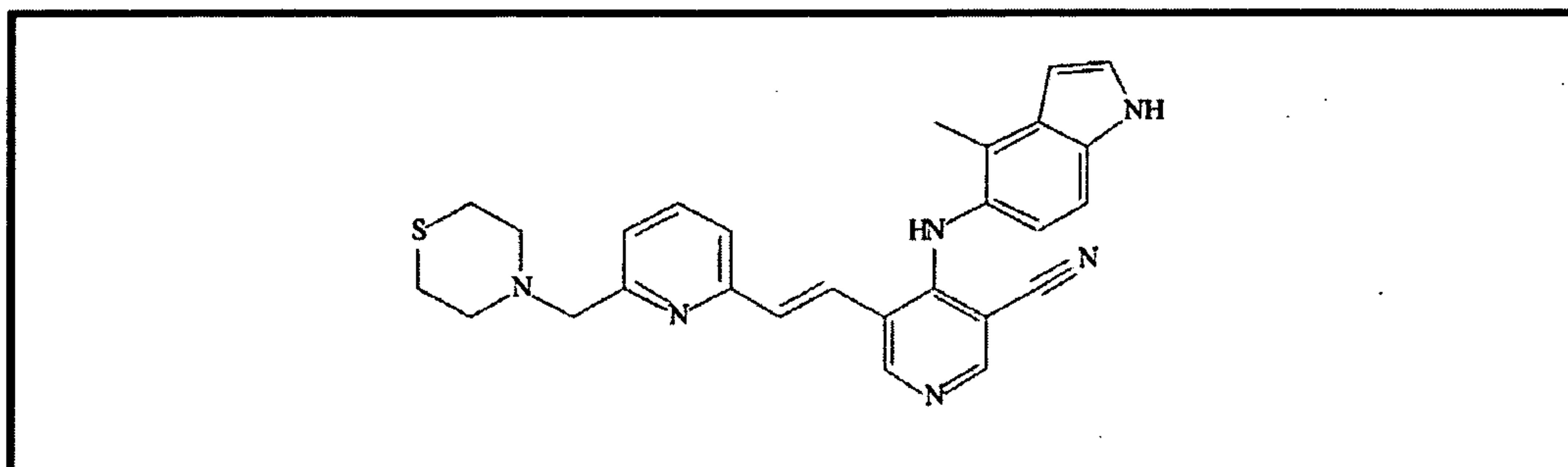
The title compound was prepared from 5-[(E)-2-[5-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 2-methoxyethylamine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(piperidin-1-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 439.1 (M+H); HPLC: 97.2% at 215 nm, rt = 6.1 min [a].



[00476] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-(morpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile:

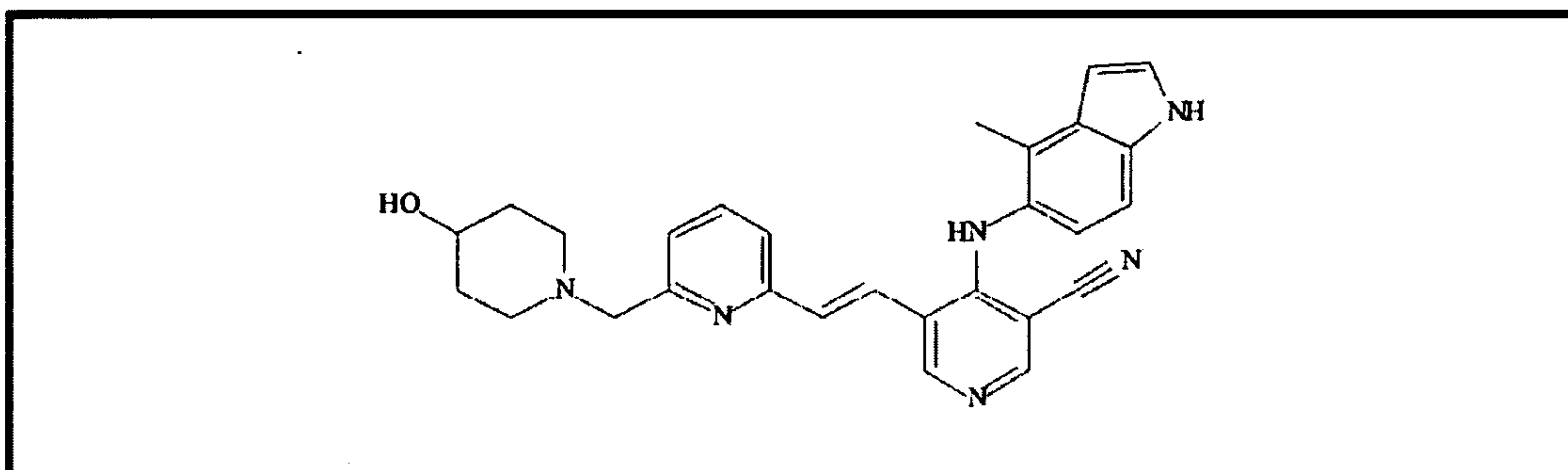
To a solution of 5-[(E)-2-[6-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (100 mg, 0.262 mmol) in a solvent mixture of THF (5 ml) and DMF (2.5 ml) was added triethylamine (183 μ L, 1.313 mmol). The solution was stirred under nitrogen at room temperature for 10 min. Methanesulfonyl chloride (61 μ L, 0.788 mmol) was added dropwise into the reaction mixture. The reaction was stirred under nitrogen at room temperature for 8 hours, followed by the addition of morpholine (100 μ L, 1.147 mmol). The reaction was stirred overnight. The solvent was evaporated and the residue was partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The organic solution was dried over MgSO_4 and concentrated to give a dark syrup. The resulting crude compound

was purified by HPLC to give 61 mg (52%) of the title compound as a yellow solid, MS 451.1 (M+H); HPLC: 96.7% at 215 nm, rt = 6.3 min [a].



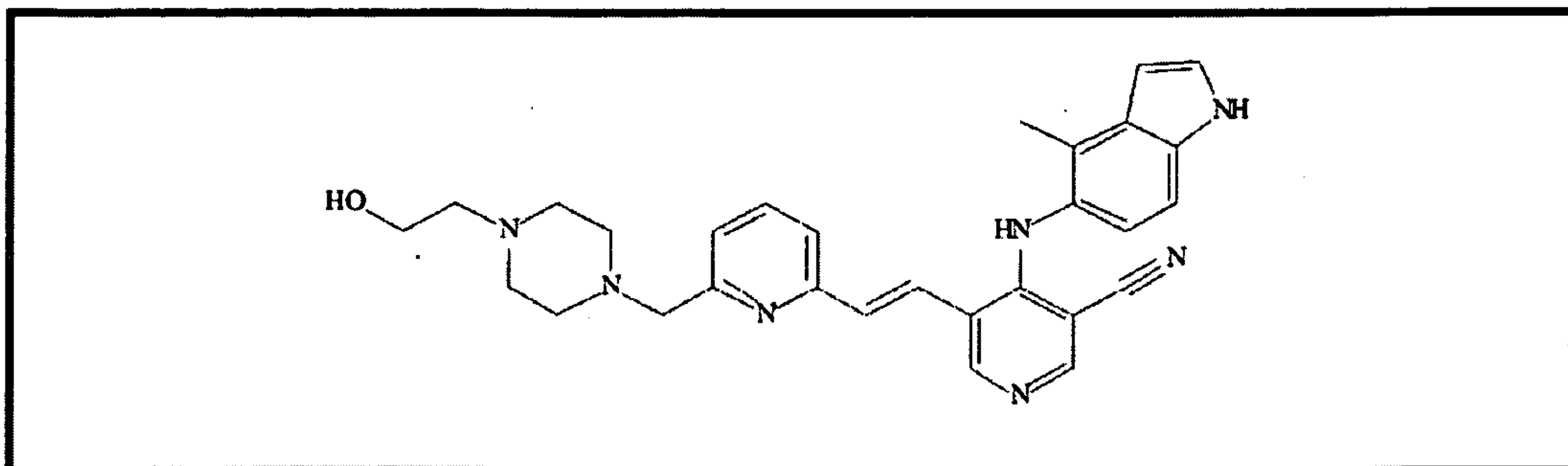
[00477] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-(thiomorpholin-4-yl)methyl]pyridin-2-yl]ethenyl]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[6-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and thiomorpholine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-(morpholin-4-yl)methyl]pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 467.1 (M+H); HPLC: 97.9% at 215 nm, rt = 6.8 min [a].



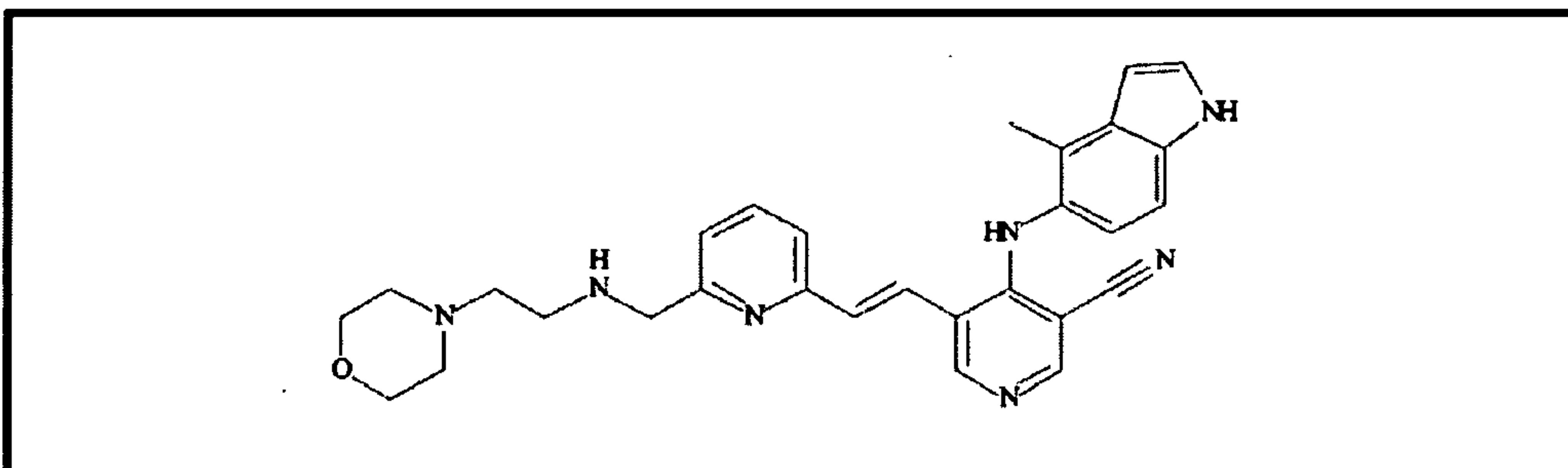
[00478] Preparation of 5-[(E)-2-[6-[(4-hydroxypiperidin-1-yl)methyl]pyridin-2-yl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[6-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 4-hydroxypiperidine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-(morpholin-4-yl)methyl]pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 465.1 (M+H); HPLC: 97.0% at 215 nm, rt = 6.2 min [a].



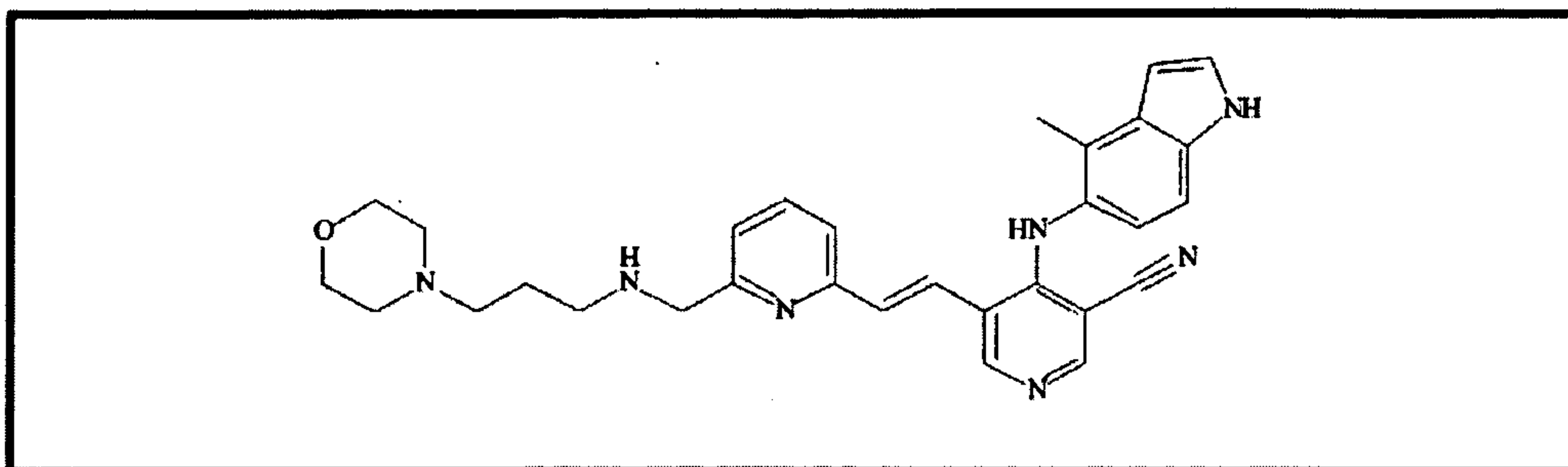
[00479] Preparation of 5-[(E)-2-(6-([4-(2-hydroxyethyl)piperazin-1-yl)methyl]pyridin-2-yl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[6-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 4-(2-hydroxyethyl)piperazine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-(morpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 494.1 (M+H); HPLC: 94.3% at 215 nm, rt = 5.8 min [a].



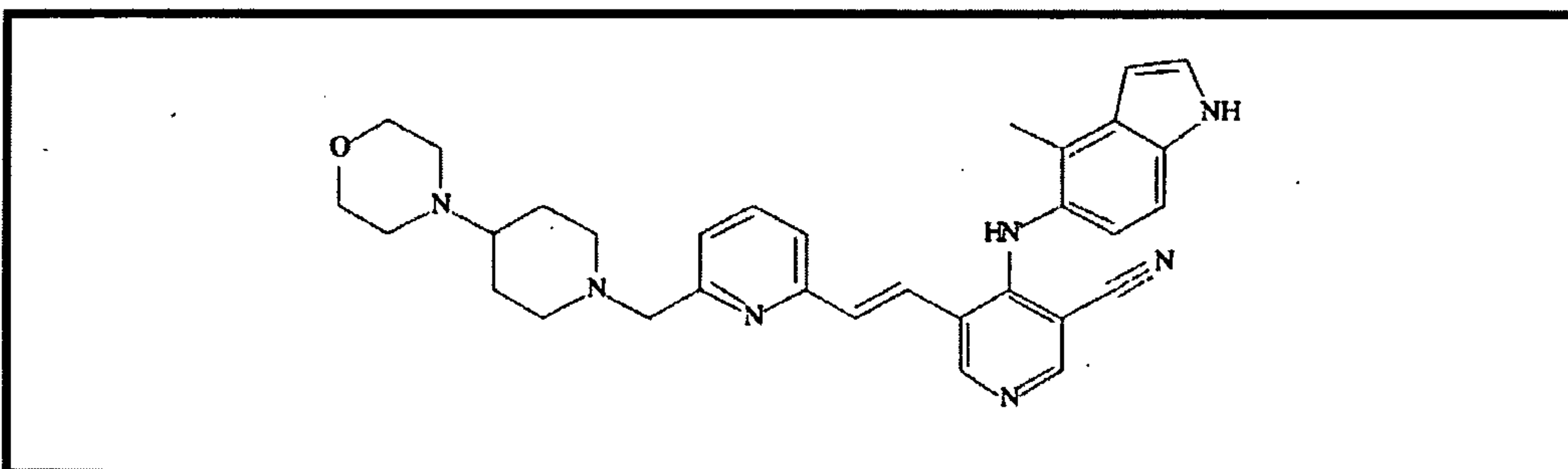
[00480] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(6-[(2-morpholin-4-ylethyl)amino]methyl]pyridin-2-yl)ethenyl]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[6-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 4-(2-aminoethyl)morpholine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-(morpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 494.1 (M+H); HPLC: 95.7% at 215 nm, rt = 6.1 min [a].



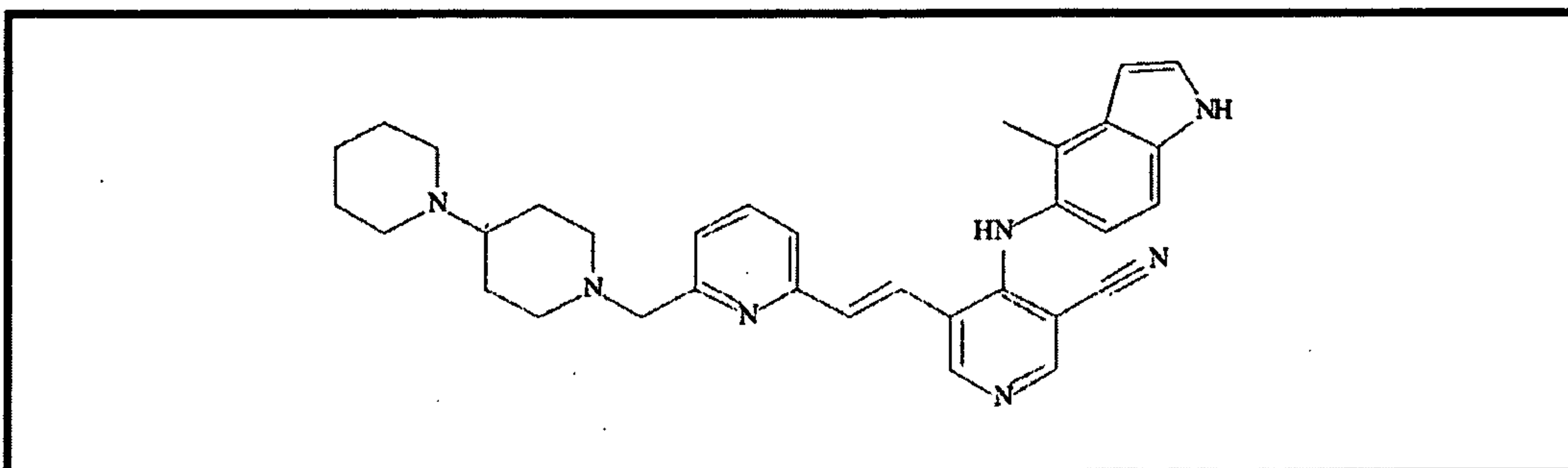
[00481] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(6-[(3-morpholin-4-yl)propyl]amino)methyl]pyridin-2-yl]ethenyl]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[6-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 4-(3-aminopropyl)morpholine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-(morpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 508.2 (M+H); HPLC: 97.1% at 215 nm, rt = 4.5 min [a].



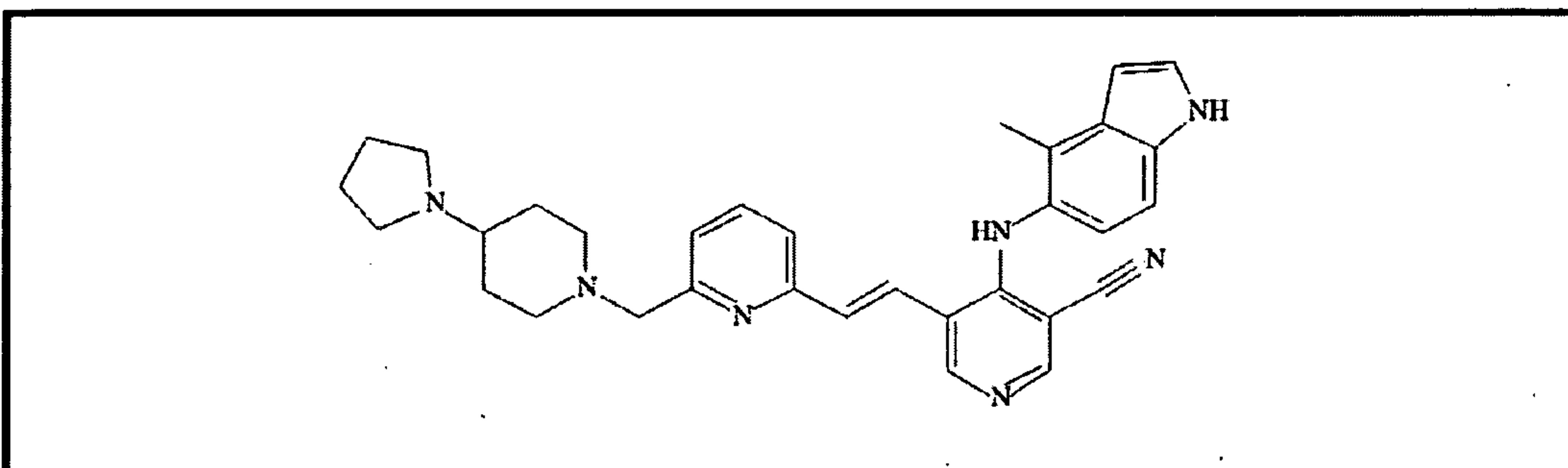
[00482] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(6-[(4-morpholin-4-yl)piperidin-1-yl]methyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[6-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 4-morpholinopiperidine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-(morpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 534.2 (M+H); HPLC: 96.1% at 215 nm, rt = 4.5 min [a].



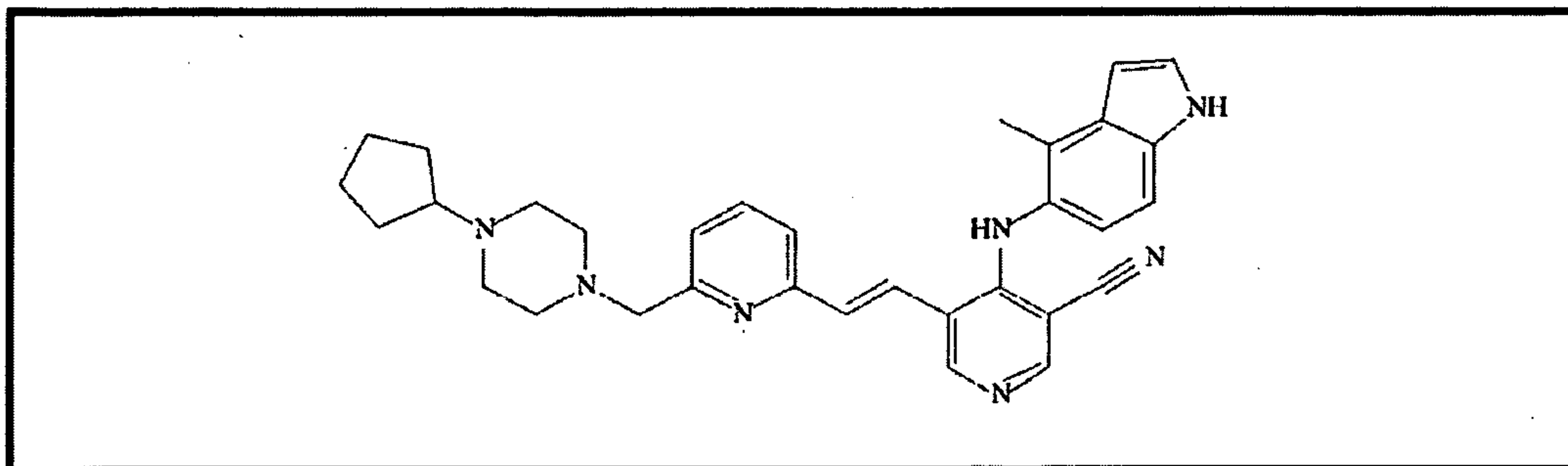
[00483] Preparation of 5-((E)-2-((6-(1,4'-bipiperidin-1'-yl)methyl)pyridin-2-yl)ethenyl)-4-((4-methyl-1H-indol-5-yl)amino)pyridine-3-carbonitrile:

The title compound was prepared from 5-((E)-2-((6-(hydroxymethyl)pyridin-2-yl)vinyl)-4-((4-methyl-1H-indol-5-yl)amino)nicotinonitrile and 4-piperidinopiperidine via the procedure used to prepare 4-((4-methyl-1H-indol-5-yl)amino)-5-((E)-2-((6-(morpholin-4-yl)methyl)pyridin-2-yl)ethenyl)pyridine-3-carbonitrile, MS 266.6 (M+2H); HPLC: 92.6% at 215 nm, rt = 4.6 min [a].



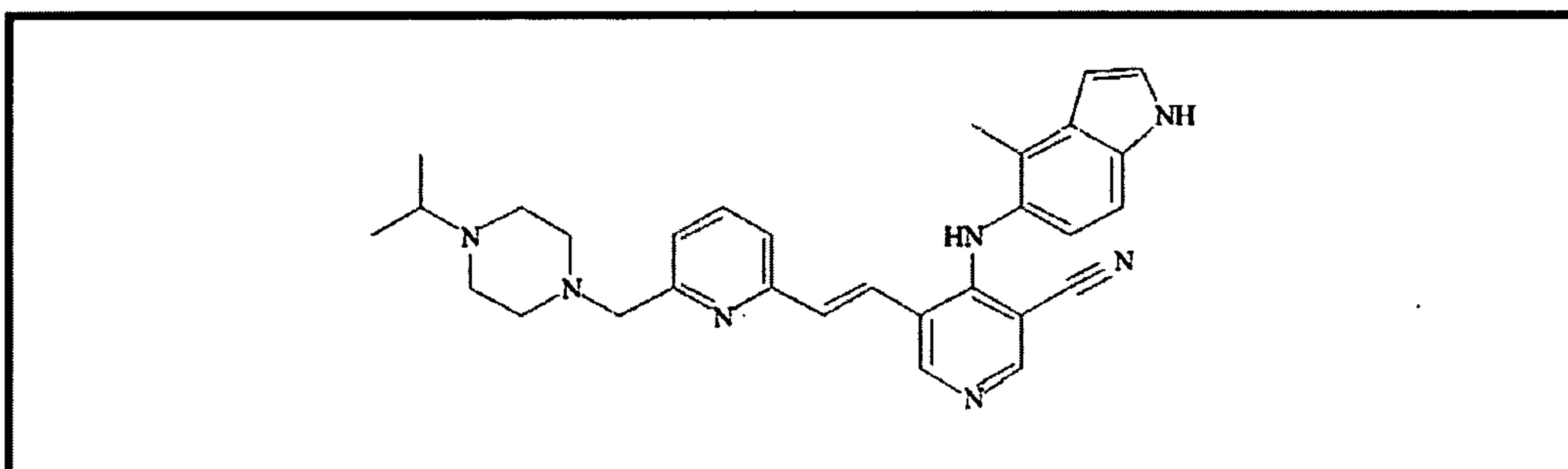
[00484] Preparation of 4-((4-methyl-1H-indol-5-yl)amino)-5-((E)-2-((6-((4-pyrrolidin-1-yl)piperidin-1-yl)methyl)pyridin-2-yl)ethenyl)pyridine-3-carbonitrile:

The title compound was prepared from 5-((E)-2-((6-(hydroxymethyl)pyridin-2-yl)vinyl)-4-((4-methyl-1H-indol-5-yl)amino)nicotinonitrile and 4-pyrrolidinopiperidine via the procedure used to prepare 4-((4-methyl-1H-indol-5-yl)amino)-5-((E)-2-((6-(morpholin-4-yl)methyl)pyridin-2-yl)ethenyl)pyridine-3-carbonitrile, MS 518.2 (M+H); HPLC: 91.8% at 215 nm, rt = 4.5 min [a].



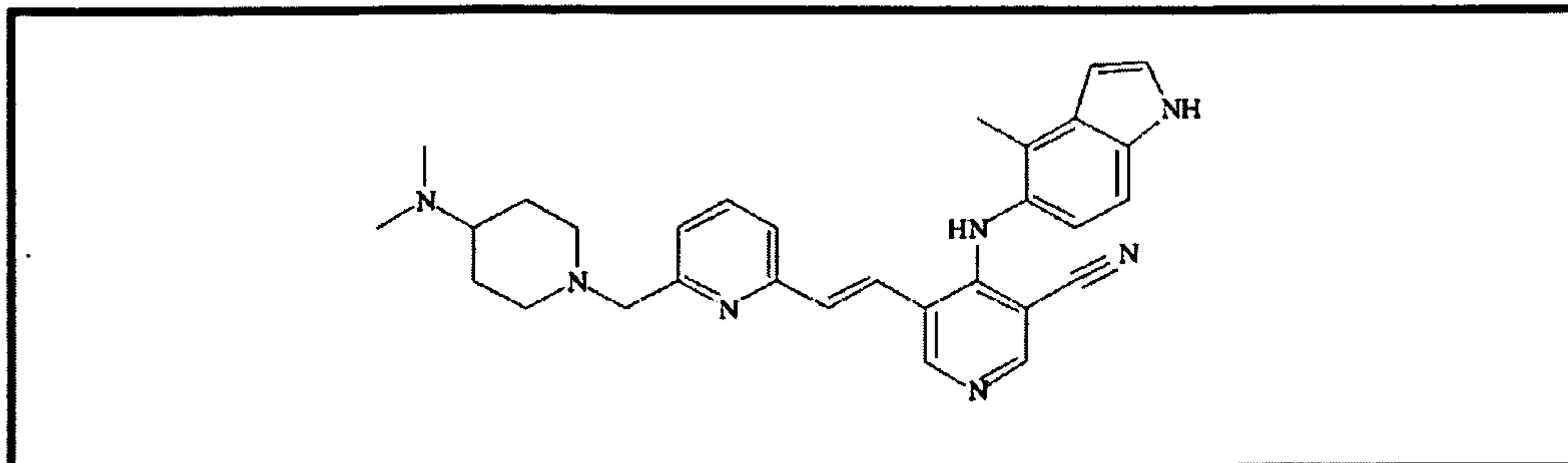
[00485] Preparation of 5-[(E)-2-{6-[(4-cyclopentylpiperazin-1-yl)methyl]pyridin-2-yl}ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[6-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 1-cyclopentylpiperazine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-(morpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 259.6 (M+2H); HPLC: 96.1% at 215 nm, rt = 6.3 min [a].



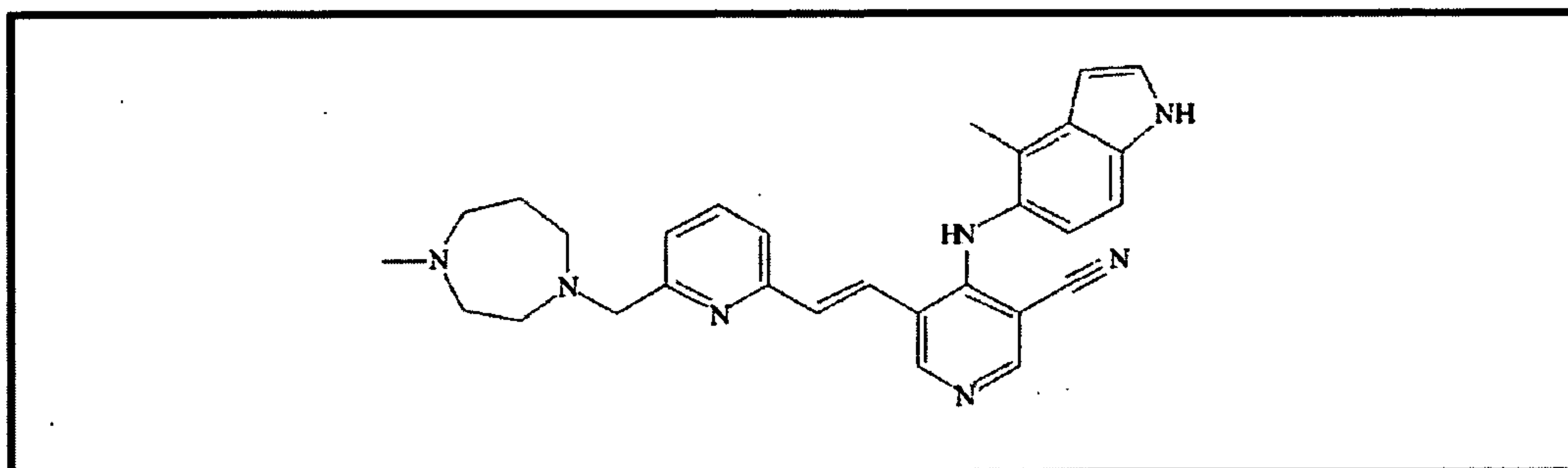
[00486] Preparation of 5-[(E)-2-{6-[(4-(1-methylethyl)piperazin-1-yl)methyl]pyridin-2-yl}ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[6-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 1-isopropylpiperazine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-(morpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 246.6 (M+2H); HPLC: rt = 4.3 min [a].



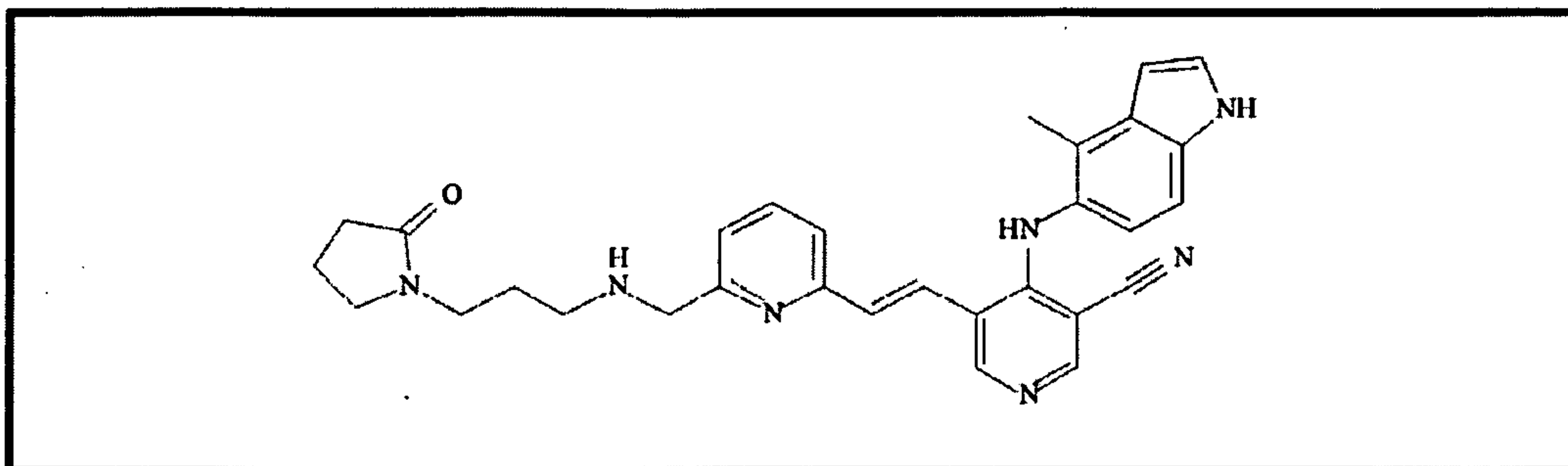
[00487] Preparation of 5-[(E)-2-(6-([4-(dimethylamino)piperidin-1-yl]methyl)pyridin-2-yl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[6-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 4-dimethylaminopiperidine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-(morpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 492.2 (M+H); HPLC: 92.6% at 215 nm, rt = 5.3 min [a].



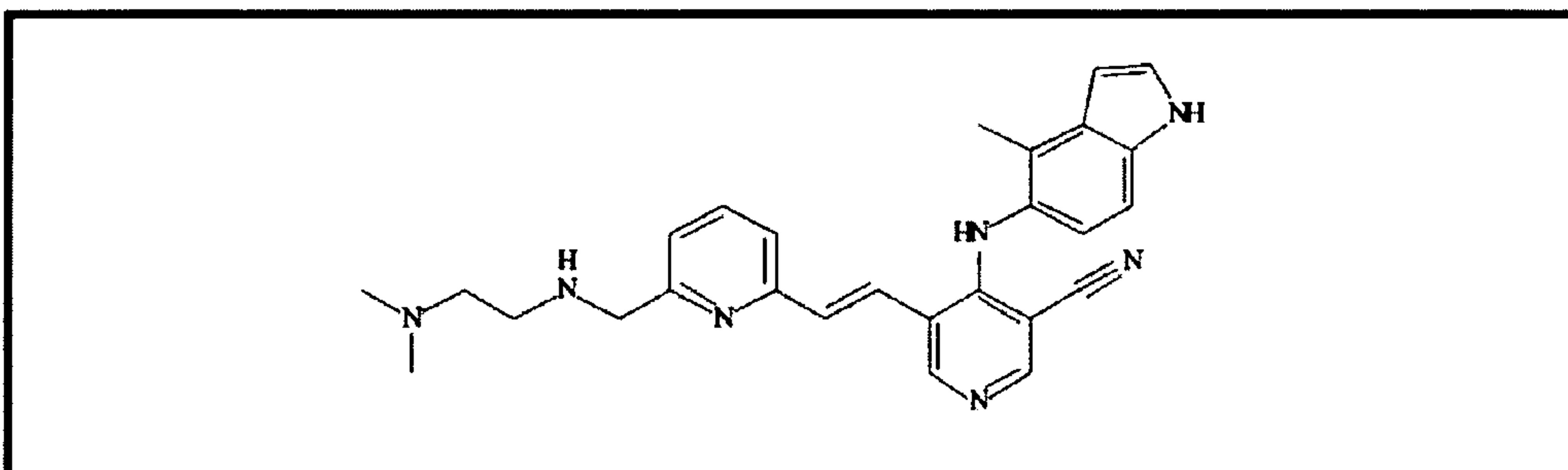
[00488] Preparation of 5-[(E)-2-(6-([1-methyl-1,4-diazepan-1-yl]methyl)pyridin-2-yl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[6-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 1-methylhomopiperazine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-(morpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 478.2 (M+H); HPLC: 92.2% at 215 nm, rt = 5.3 min [a].



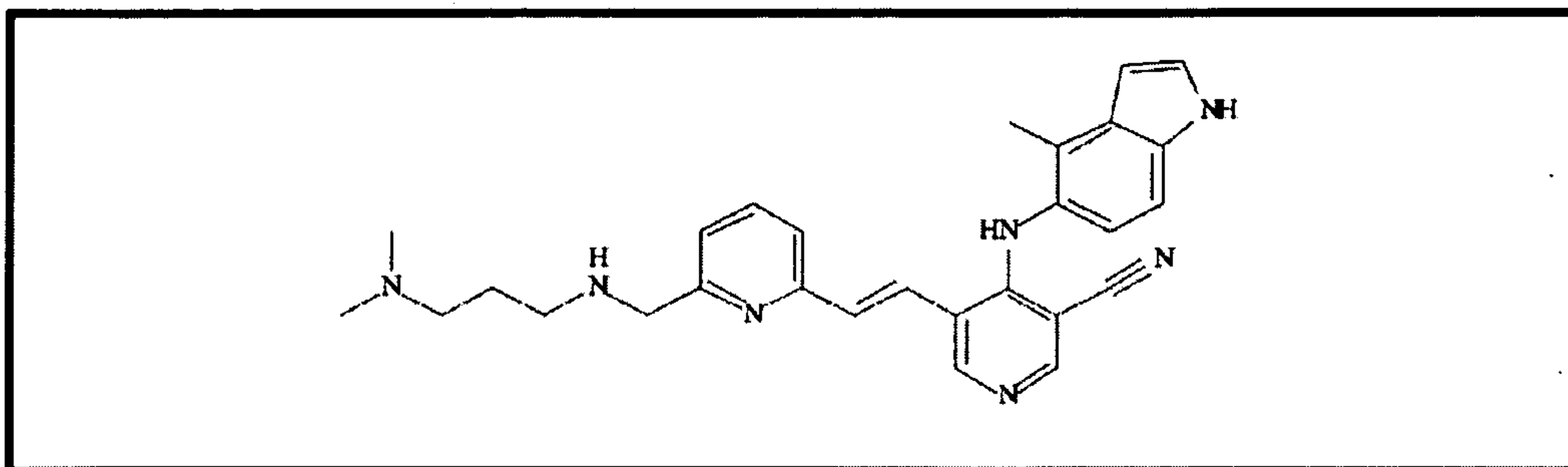
[00489] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-({[3-(2-oxo-pyrrolidin-1-yl)propyl]amino}methyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[6-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 1-(3-aminopropyl)-2-pyrrolidinone via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-(morpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 506.2 (M+H); HPLC: 99.5% at 215 nm, rt = 6.3 min [a].



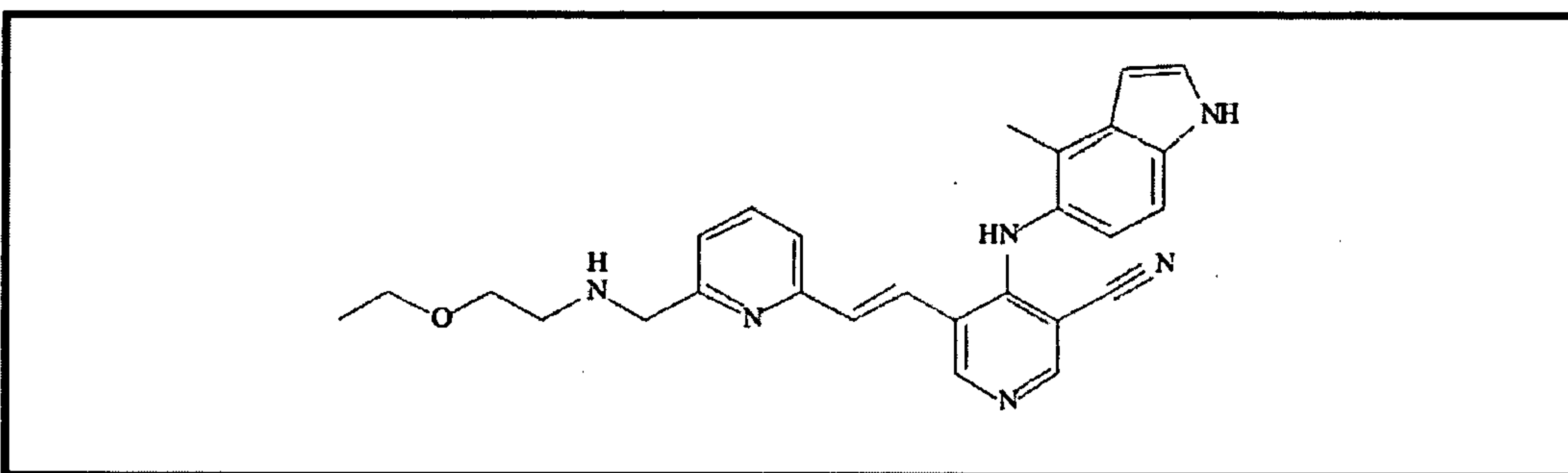
[00490] Preparation of 5-[(E)-2-[6-({[2-(dimethylamino)ethyl]amino}methyl)pyridin-2-yl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[6-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and N,N-dimethylethylenediamine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-(morpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 452.2 (M+H); HPLC: 90.5% at 215 nm, rt = 5.3 min [a].



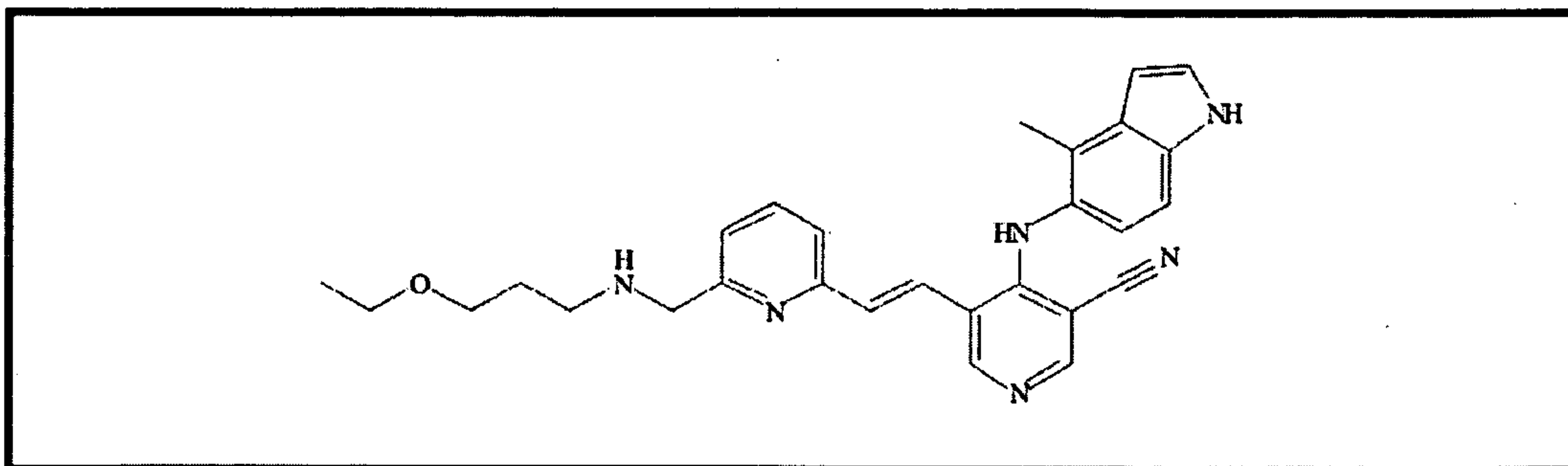
[00491] Preparation of 5-[(E)-2-[6-([3-(dimethylamino)propyl]amino)methyl]pyridin-2-yl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile

The title compound was prepared from 5-[(E)-2-[6-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 3-(dimethylamino)propylamine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-(morpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 466.2 (M+H); HPLC: 94.6% at 215 nm, rt = 5.3 min [a].



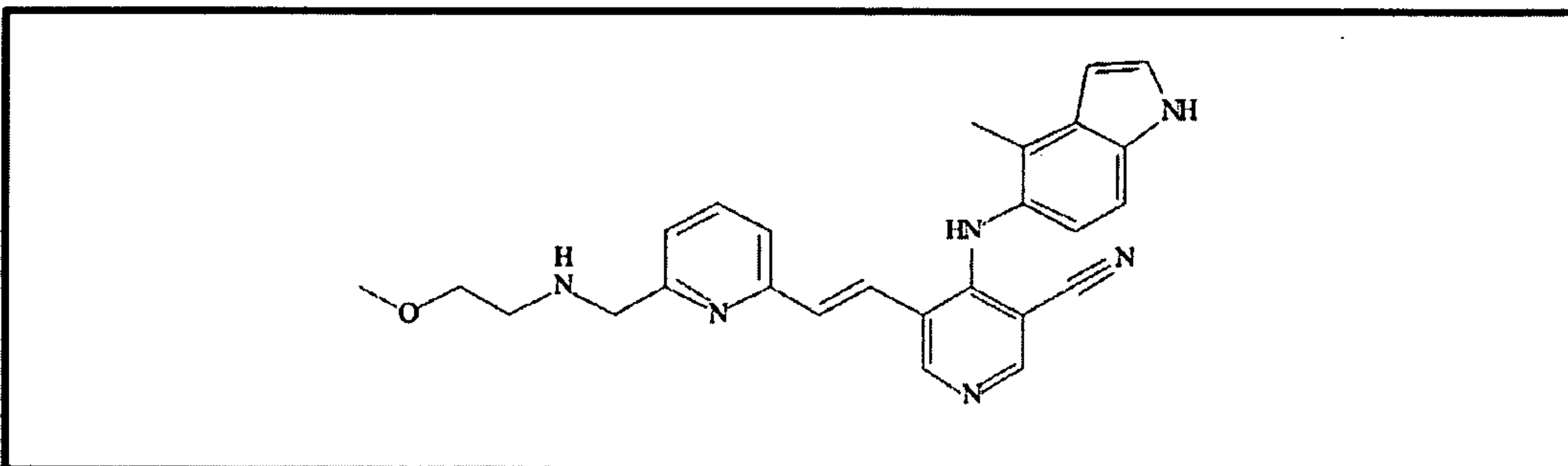
[00492] Preparation of 5-[(E)-2-[6-[(2-ethoxyethyl)amino]methyl]pyridin-2-yl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[6-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 2-ethoxyethylamine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-(morpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 453.2 (M+H); HPLC: 97.8% at 215 nm, rt = 6.5 min [a].



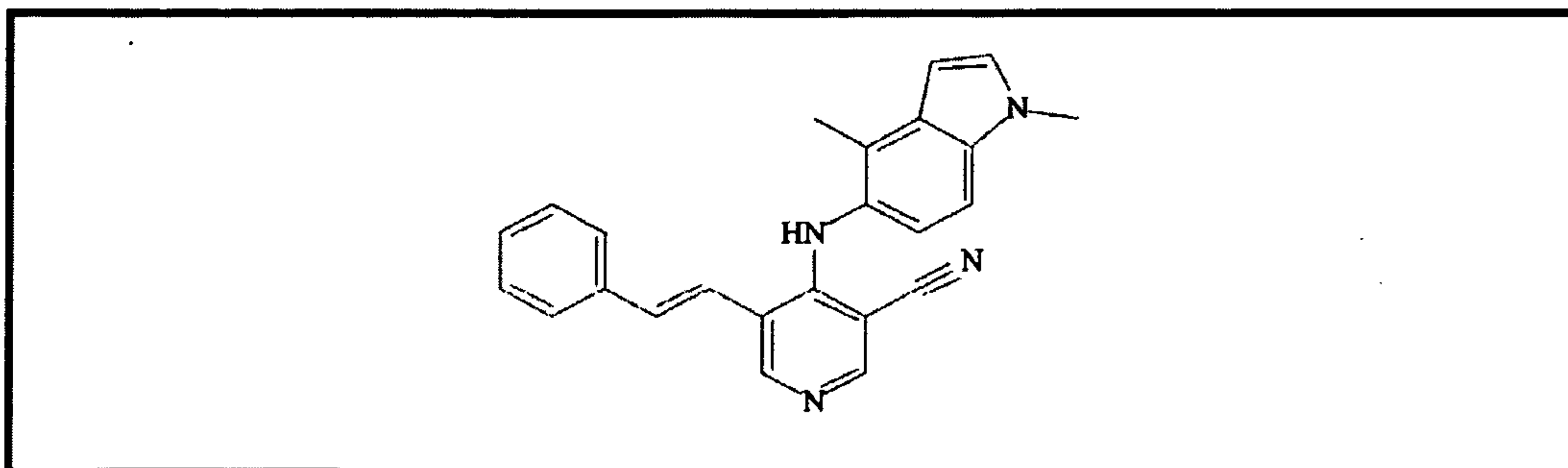
[00493] Preparation of 5-[(E)-2-(6-[(3-ethoxypropyl)amino]methyl)pyridin-2-yl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[6-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 3-ethoxypropylamine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-(morpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 467.2 (M+H).



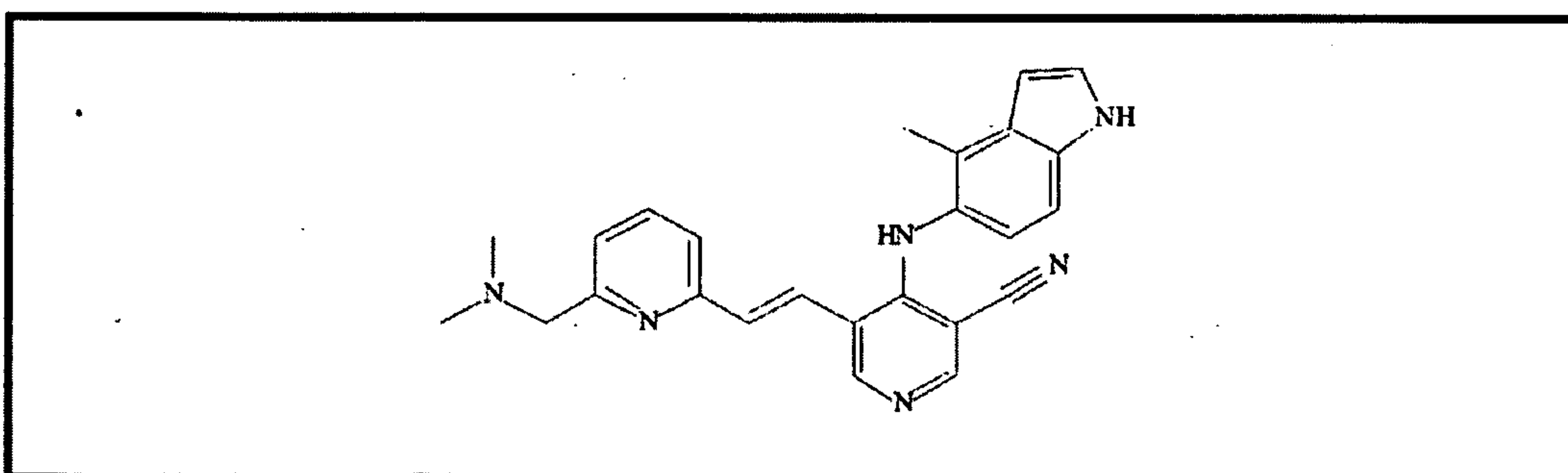
[00494] Preparation of 5-[(E)-2-(6-[(2-methoxyethyl)amino]methyl)pyridin-2-yl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[6-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 2-methoxyethylamine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-(morpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 439.2 (M+H); HPLC: 96.0% at 215 nm, rt = 6.2 min [a].



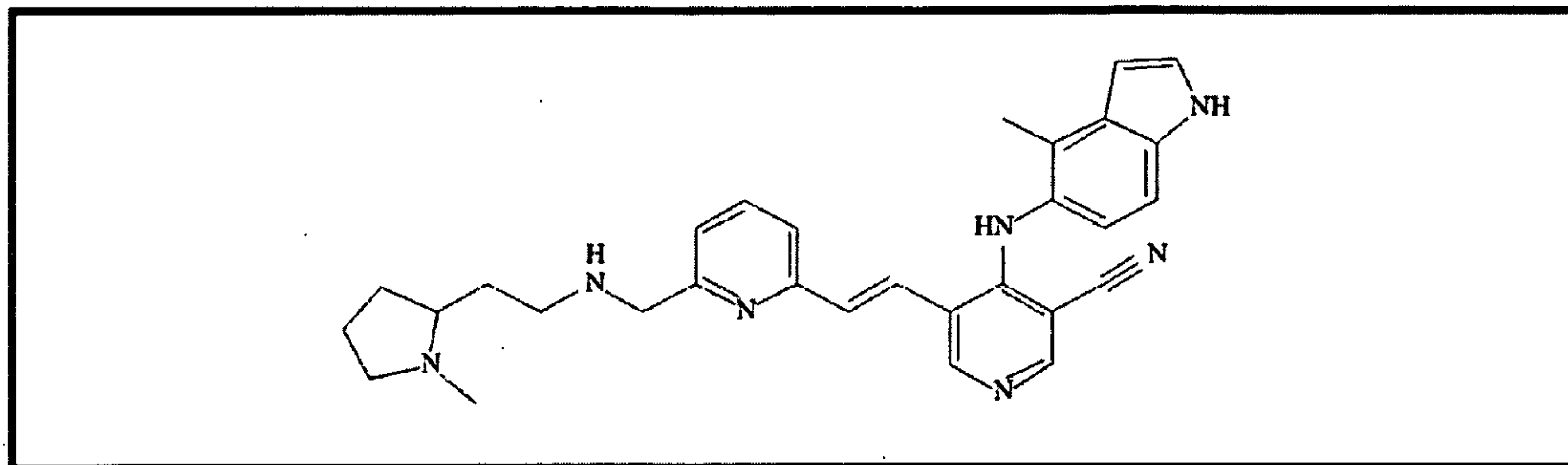
[00495] Preparation of 4-[(1,4-dimethyl-1H-indol-5-yl)amino]-5-[(E)-2-phenylethenyl]pyridine-3-carbonitrile:

4-[(1,4-Dimethyl-1H-indol-5-yl)amino]-5-iodonicotinonitrile (100 mg, 0.258 mmol) and 2-vinylphenylboronic acid (46 mg, 0.311 mmol) were dissolved in anhydrous DME (5 ml), followed by the addition of $\text{Pd}(\text{PPh}_3)_4$ (15 mg, 0.013 mmol) and saturated aqueous sodium bicarbonate (4 ml). The reaction mixture was heated at 100 °C overnight, then cooled to room temperature and diluted with dichloromethane, washed with saturated aqueous sodium bicarbonate, dried over MgSO_4 and concentrated to give a yellow residue. The crude compound was purified by HPLC to give 31 mg (33%) of 4-[(1,4-dimethyl-1H-indol-5-yl)amino]-5-iodonicotinonitrile as a yellow syrup, MS 365.1 (M+H); HPLC: 96.9% at 215 nm, t_r = 11.2 min [a].



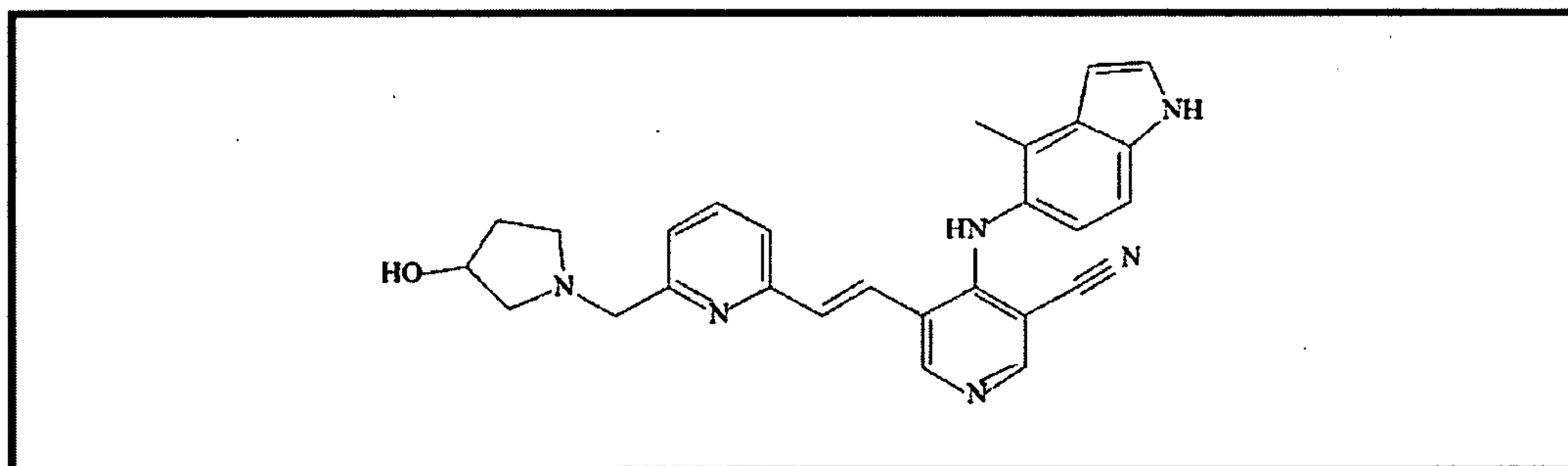
[00496] Preparation of 5-[(E)-2-{6-[(dimethylamino)methyl]pyridin-2-yl}ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[6-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and dimethylamine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-(morpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 409.3 (M+H); HPLC: t_r = 5.0 min [a].



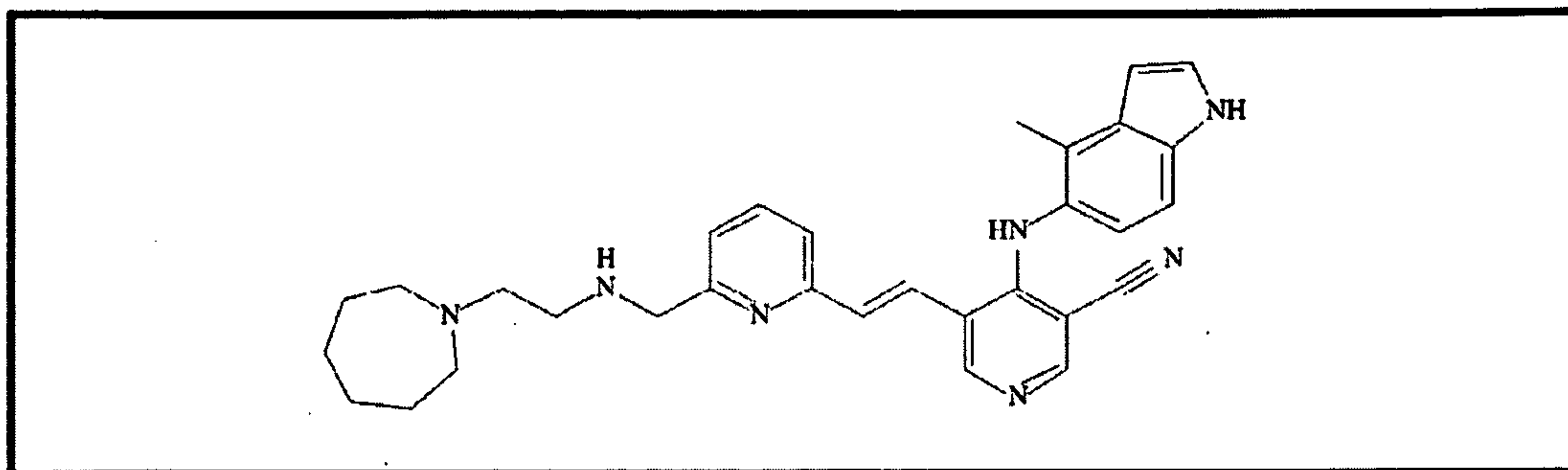
[00497] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-[(1-methylpyrrolidin-2-yl)ethyl]amino)methyl]pyridin-2-yl]ethenyl]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[6-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 2-(2-aminoethyl)-1-methylpyrrolidine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-(morpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 492.4 (M+H); HPLC: 94.2% at 215 nm, *rt* = 4.4 min [a].



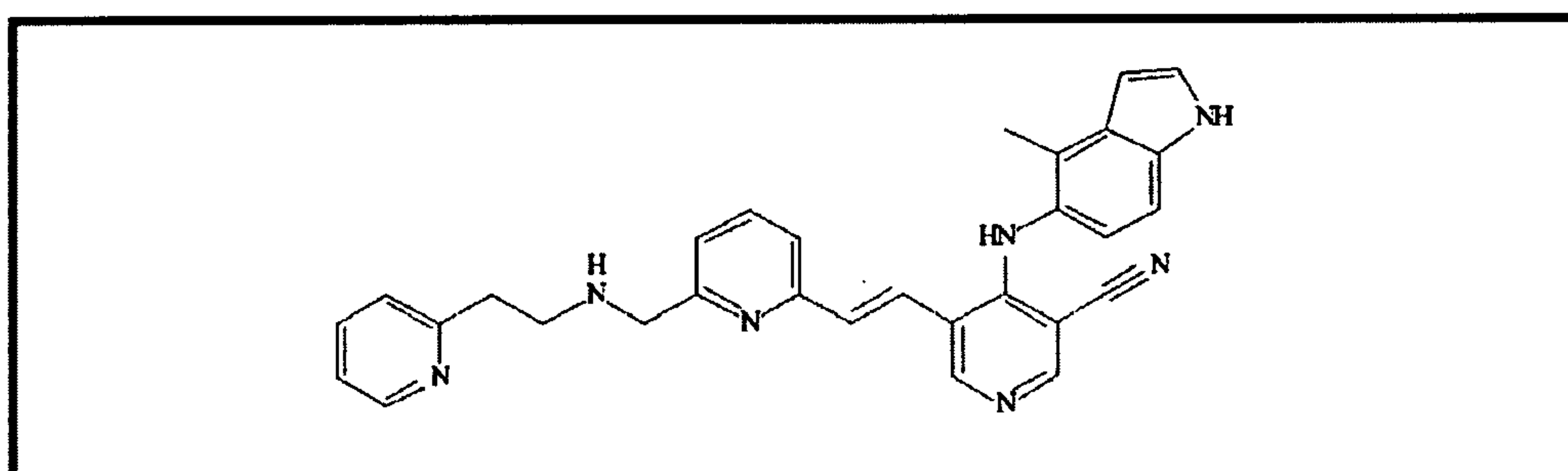
[00498] Preparation of 5-[(E)-2-[6-[(3-hydroxypyrrolidin-1-yl)methyl]pyridin-2-yl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[6-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 3-pyrrolidinol via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-(morpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 451.3 (M+H); HPLC: 96.3% at 215 nm, *rt* = 5.1 min [a].



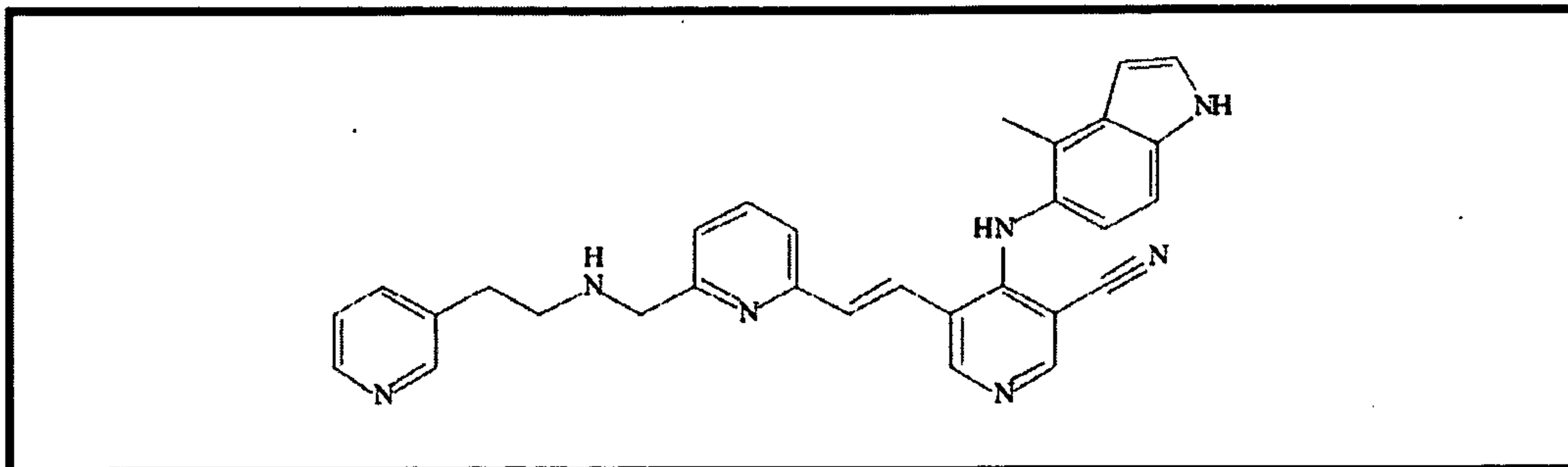
[00499] Preparation of 5-[(E)-2-(6-((2-azepan-1-ylethyl)amino)methyl)pyridin-2-yl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[6-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and N-2-aminoethyl homopiperidine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-(morpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 506.4 (M+H); HPLC: 92.6% at 215 nm, *rt* = 5.1 min [a].



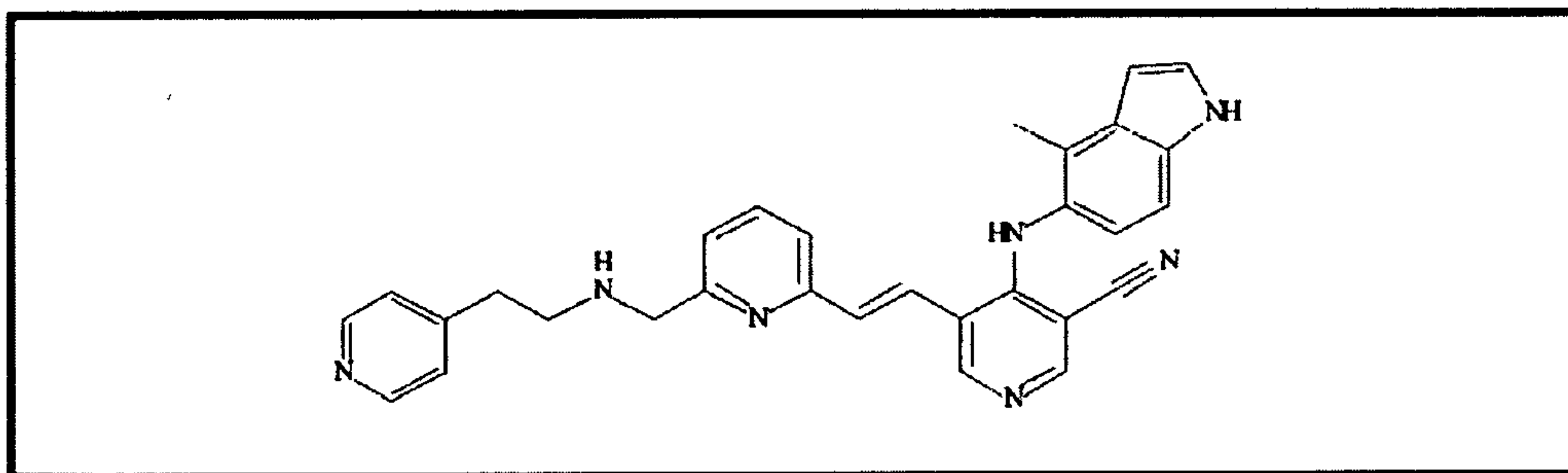
[00500] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(6-((2-pyridin-2-ylethyl)amino)methyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[6-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 2-(2-aminoethyl)pyridine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-(morpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 486.3 (M+H); HPLC: 93.5% at 215 nm, *rt* = 5.5 min [a].



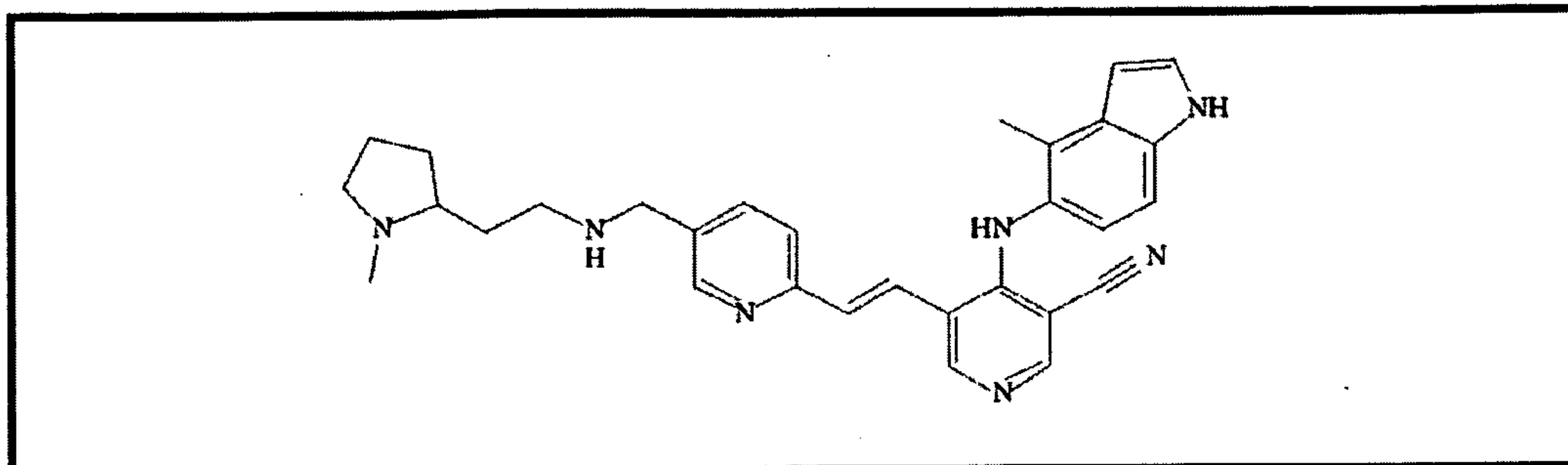
[00501] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(6-[(2-pyridin-3-ylethyl)amino]Methyl)pyridin-2-yl)ethenyl]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[6-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 3-(2-aminoethyl)pyridine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-(morpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 486.3 (M+H); HPLC: 95.6% at 215 nm, rt = 4.6 min [a].



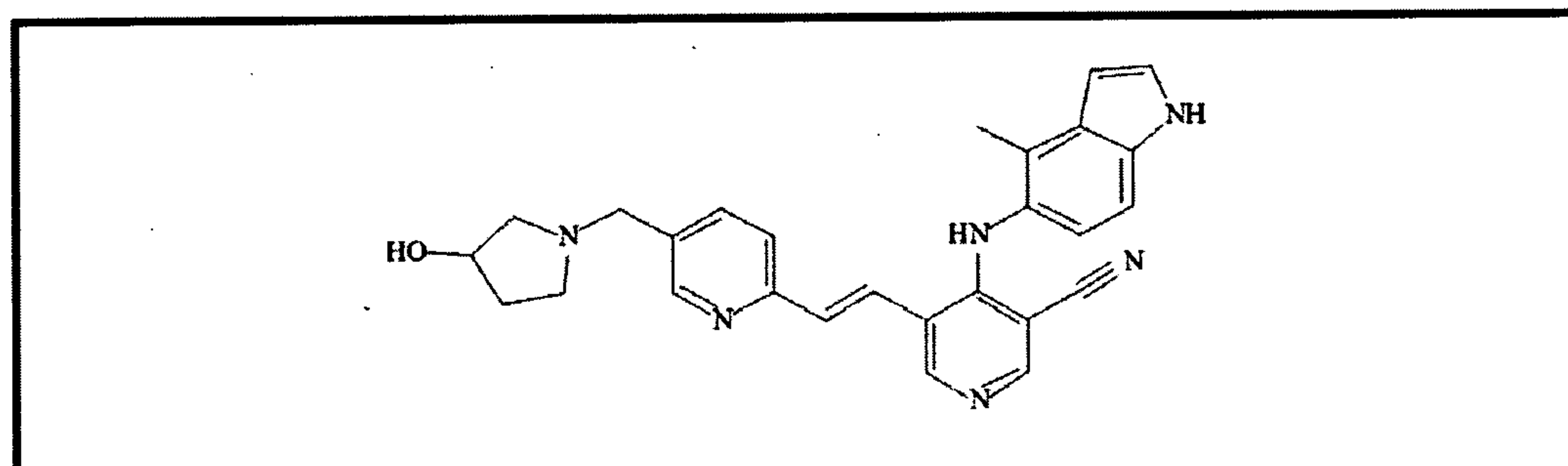
[00502] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(6-[(2-pyridin-4-ylethyl)amino]methyl)pyridin-2-yl)ethenyl]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[6-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 4-(2-aminoethyl)pyridine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-(morpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 486.3 (M+H); HPLC: 97.7% at 215 nm, rt = 4.3 min [a].



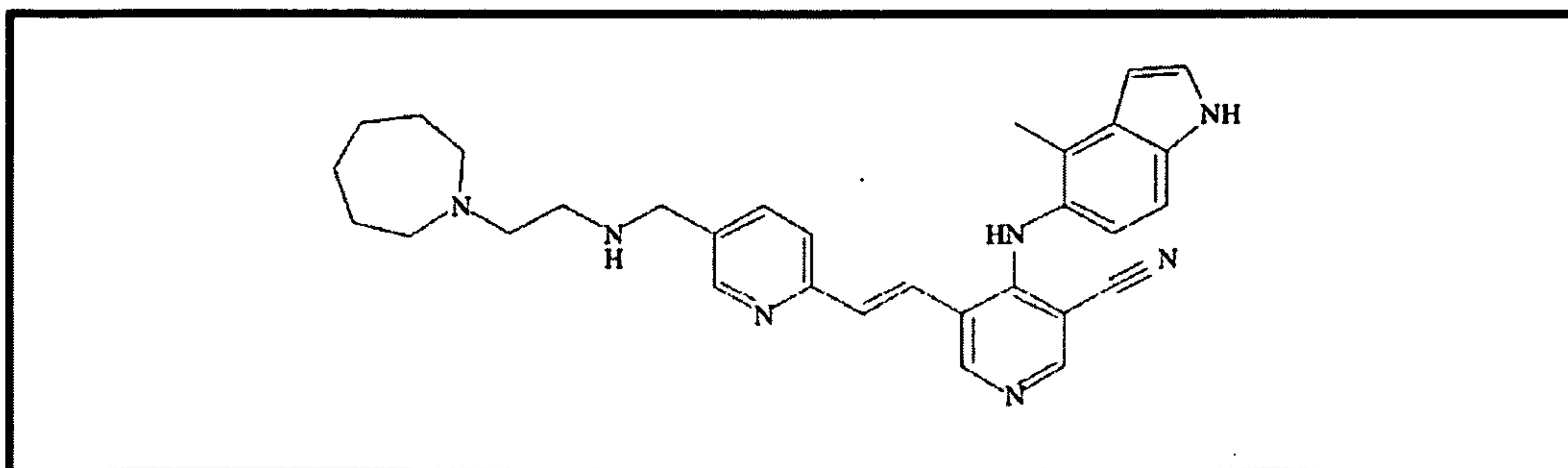
[00503] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-[(2-(1-methylpyrrolidin-2-yl)ethyl)amino]methyl]pyridin-2-yl]ethenyl]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[5-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 2-(2-aminoethyl)-1-methylpyrrolidine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(piperidin-1-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 492.4 (M+H); HPLC: 90.3% at 215 nm, $t_r = 4.1$ min [a].



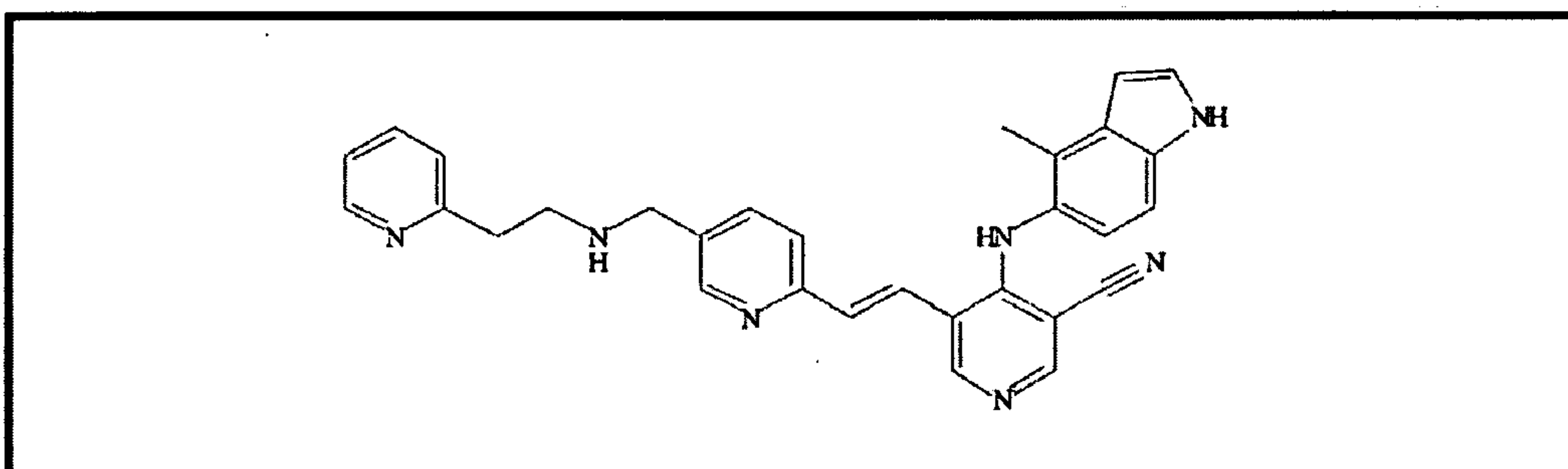
[00504] Preparation of 5-[(E)-2-[5-[(3-hydroxypyrrolidin-1-yl)methyl]pyridin-2-yl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[5-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 3-pyrrolidinol via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(piperidin-1-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 451.3 (M+H); HPLC: 94.5% at 215 nm, $t_r = 4.7$ min [a].



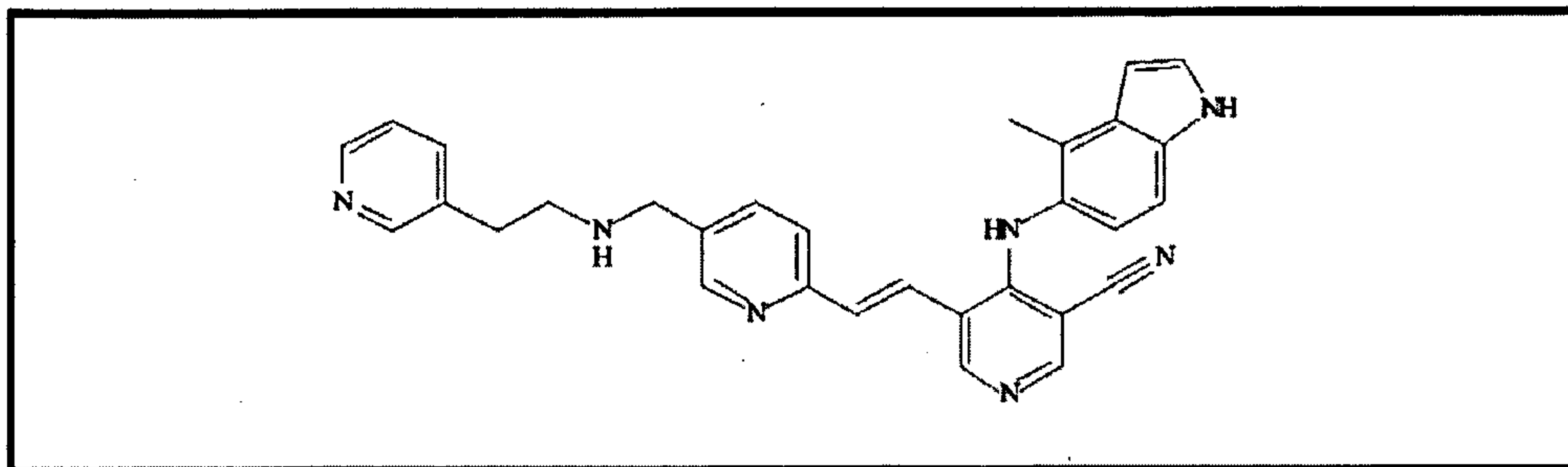
[00505] Preparation of 5-[(E)-2-(5-[(2-azepan-1-ylethyl)amino]methyl)pyridin-2-yl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[5-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and N-2-aminoethyl homopiperidine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(piperidin-1-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 506.4 (M+H); HPLC: 95.3% at 215 nm, t_r = 4.6 min [a].



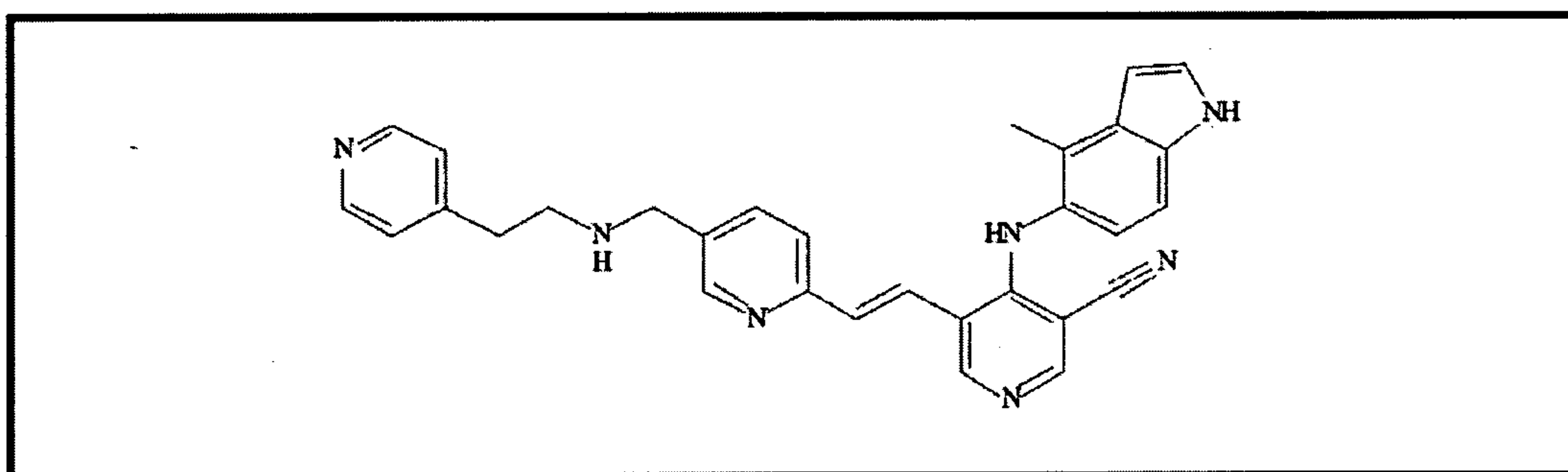
[00506] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(5-[(2-pyridin-2-ylethyl)amino]methyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[5-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 2-(2-aminoethyl)pyridine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(piperidin-1-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 486.3 (M+H); HPLC: 92% at 215 nm, t_r = 5.4 min [a].



[00507] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(5-[(2-pyridin-3-ylethyl)amino]methyl)pyridin-2-yl)ethenyl]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[5-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 3-(2-aminoethyl)pyridine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(piperidin-1-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 486.2 (M+H); HPLC: 97.2% at 254nm, rt = 1.39 min [d].



[00508] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(5-[(2-pyridin-4-ylethyl)amino]methyl)pyridin-2-yl)ethenyl]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-[5-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 4-(2-aminoethyl)pyridine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(piperidin-1-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile, MS 486.3 (M+H); HPLC: 99.6% at 215 nm, rt = 4.7 min [a].

TABLE 13:

The following compounds were synthesized from 5-[(E)-2-[6-(hydroxymethyl)pyridin-2-yl]ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile and the

corresponding amines via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-(morpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile: (HPLC method A)

Chemical Name	MS (M+H)	HPLC results
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-(piperidin-1-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile	463.4	96.8% at 215 nm, 6.3 min.
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-(pyrrolidin-1-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile	449.3	98.6% at 215 nm, 5.7 min.
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-(morpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile	465.3	98.8% at 215 nm, 5.4 min.
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-(thiomorpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile	481.3	99.1% at 215 nm, 5.8 min.
5-[(E)-2-[6-[(4-hydroxypiperidin-1-yl)methyl]pyridin-2-yl]ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	479.4	99.3% at 215 nm, 5.4 min.
5-[(E)-2-[6-[(4-(2-hydroxyethyl)piperazin-1-yl)methyl]pyridin-2-yl]ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	508.4	97.7% at 215 nm, 4.7 min.
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-[(2-morpholin-4-ylethyl)amino]methyl]pyridin-2-yl]ethenyl]pyridine-3-carbonitrile	508.4	97% at 215 nm, 4.4 min.
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-[(3-morpholin-4-ylpropyl)amino]methyl]pyridin-2-yl]ethenyl]pyridine-3-carbonitrile	522.4	98.5% at 215 nm, 3.9 min.
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-[(4-morpholin-4-ylpiperidin-1-yl)methyl]pyridin-2-yl]ethenyl]pyridine-3-carbonitrile	548.4	98.6% at 215 nm, 3.9 min.
5-[(E)-2-[6-(1,4'-bipiperidin-1'-ylmethyl)pyridin-2-yl]ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	546.4	98.6% at 215 nm, 4.0 min.
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-[(4-pyrrolidin-1-ylpiperidin-1-yl)methyl]pyridin-2-yl]ethenyl]pyridine-3-carbonitrile	532.4	98.6% at 215 nm, 3.9 min.
5-[(E)-2-[6-[(4-cyclopentylpiperazin-1-yl)methyl]pyridin-2-yl]ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	532.4	98.4% at 215 nm, 5.4 min.
6-methyl-5-[(E)-2-[6-[(4-(1-methylethyl)piperazin-1-yl)methyl]pyridin-2-yl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	506.4	95.2% at 215 nm, 3.8 min.
6-methyl-5-[(E)-2-[6-[(4-methyl-1,4-diazepan-1-yl)methyl]pyridin-2-yl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	492.4	93.3% at 215 nm, 4.1 min.
5-[(E)-2-[6-[(3-(dimethylamino)propyl)amino]methyl]pyridin-2-yl]ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	480.4	96.6% at 215 nm, 4.4 min.
5-[(E)-2-[6-[(2-ethoxyethyl)amino]methyl]pyridin-2-	467.3	97.3% at 215 nm, 5.7 min.

Chemical Name	MS (M+H)	HPLC results
yl)ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile		min.
5-[(E)-2-(6-[(3-ethoxypropyl)amino]methyl)pyridin-2-yl)ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	481.4	96.7% at 215 nm, 6.0 min.
5-[(E)-2-(6-[(dimethylamino)methyl]pyridin-2-yl)ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	423.3	98.9% at 215 nm, 5.2 min.
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(6-[(2-(1-methylpyrrolidin-2-yl)ethyl)amino]methyl)pyridin-2-yl]ethenyl}pyridine-3-carbonitrile	506.4	96.9% at 215 nm, 4.5 min.
5-[(E)-2-(6-[(3-hydroxypyrrolidin-1-yl)methyl]pyridin-2-yl)ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	465.4	93.6% at 215 nm, 5.5 min.
5-[(E)-2-(6-[(2-azepan-1-ylethyl)amino]methyl)pyridin-2-yl)ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	520.4	97.7% at 215 nm, 5.4 min.
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(6-[(2-pyridin-2-ylethyl)amino]methyl)pyridin-2-yl)ethenyl}pyridine-3-carbonitrile	500.4	98.3% at 215 nm, 5.6 min.
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(6-[(2-pyridin-3-ylethyl)amino]methyl)pyridin-2-yl)ethenyl}pyridine-3-carbonitrile	500.4	98% at 215 nm, 4.9 min.
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(6-[(2-pyridin-4-ylethyl)amino]methyl)pyridin-2-yl)ethenyl}pyridine-3-carbonitrile	500.4	95.3% at 215 nm, 4.8 min.

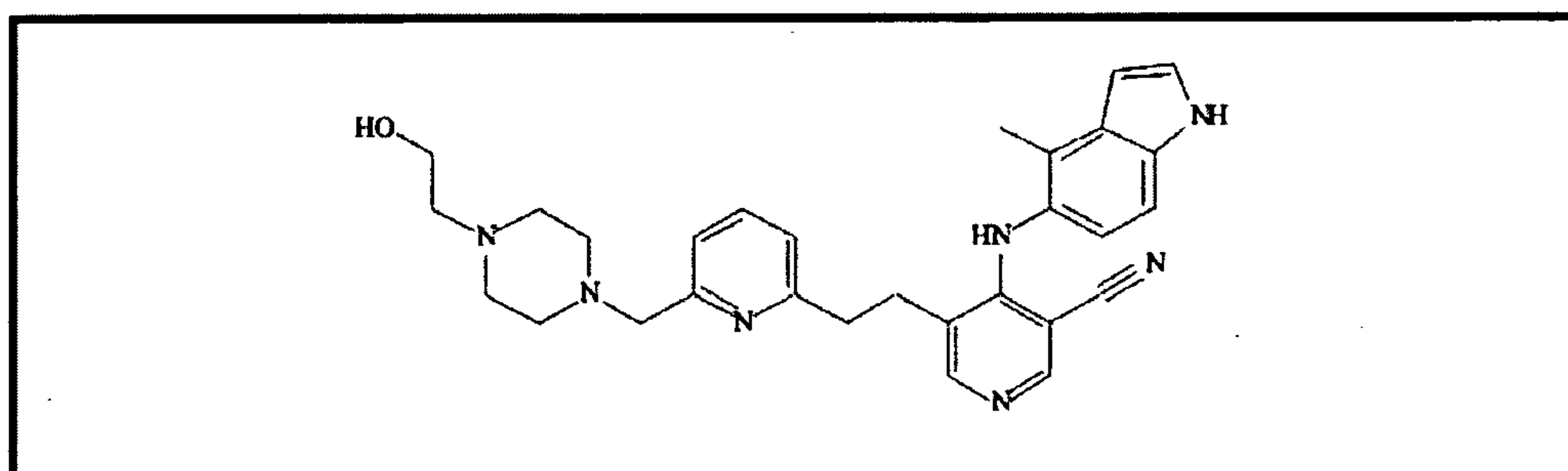
Table 14:

The following compounds were synthesized from 5-[(E)-2-[5-(hydroxymethyl)pyridin-2-yl]ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile and the corresponding amines via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(piperidin-1-ylmethyl)pyridin-2-yl]ethenyl}pyridine-3-carbonitrile: (HPLC method A)

Chemical Name	MS (M+H)	HPLC results
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(pyrrolidin-1-ylmethyl)pyridin-2-yl]ethenyl}pyridine-3-carbonitrile	449.3	98.0% at 215 nm, 4.6 min.
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(piperidin-1-ylmethyl)pyridin-2-yl]ethenyl}pyridine-3-carbonitrile	463.4	98.8% at 215 nm, 4.9 min.
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(morpholin-4-ylmethyl)pyridin-2-yl]ethenyl}pyridine-3-carbonitrile	465.3	99.3% at 215 nm, 4.4 min.
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(thiomorpholin-4-ylmethyl)pyridin-2-yl]ethenyl}pyridine-3-carbonitrile	481.3	96.6% at 215 nm, 5.0 min.

Chemical Name	MS (M+H)	HPLC results
yl]ethenyl}pyridine-3-carbonitrile		
5-[(E)-2-{5-[(4-hydroxypiperidin-1-yl)methyl]pyridin-2-yl}ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	479.3	97.0% at 215 nm, 4.4 min.
5-[(E)-2-(5-{[4-(2-hydroxyethyl)piperazin-1-yl]methyl}pyridin-2-yl)vinyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	508.4	97.4% at 215 nm, 4.4 min.
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(5-{[(2-morpholin-4-ylethyl)amino]methyl}pyridin-2-yl)ethenyl]pyridine-3-carbonitrile	508.3	97.8% at 215 nm, 4.3 min.
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(5-{[(3-morpholin-4-ylpropyl)amino]methyl}pyridin-2-yl)ethenyl]pyridine-3-carbonitrile	522.4	95.3% at 215 nm, 4.2 min.
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{5-[(4-morpholin-4-ylpiperidin-1-yl)methyl]pyridin-2-yl}ethenyl]pyridine-3-carbonitrile	548.4	97.4% at 215 nm, 4.2 min.
5-[(E)-2-{5-(1,4'-bipiperidin-1'-yl)methyl}pyridin-2-yl]ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	546.4	97.8% at 215 nm, 3.8 min.
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{5-[(4-pyrrolidin-1-yl)piperidin-1-yl)methyl]pyridin-2-yl}ethenyl]pyridine-3-carbonitrile	532.5	97.3% at 215 nm, 3.8 min.
5-[(E)-2-{5-[(4-cyclopentylpiperazin-1-yl)methyl]pyridin-2-yl}ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	532.4	96.3% at 215 nm, 5.2 min.
5-[(E)-2-{5-[(4-isopropylpiperazin-1-yl)methyl]pyridin-2-yl}vinyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	506.4	94.6% at 215 nm, 4.5 min.
6-methyl-5-[(E)-2-{5-[(4-methyl-1,4-diazepan-1-yl)methyl]pyridin-2-yl}vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	492.4	97.7% at 215 nm, 4.4 min.
5-[(E)-2-[5-{[(3-(dimethylamino)propyl)amino]methyl}pyridin-2-yl]vinyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	532.4	99.1% at 215 nm, 4.2 min.
5-[(E)-2-(5-{[(2-ethoxyethyl)amino]methyl}pyridin-2-yl)vinyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	467.4	92.2% at 215 nm, 5.8 min.
5-[(E)-2-(5-{[(3-ethoxypropyl)amino]methyl}pyridin-2-yl)vinyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	481.4	92.3% at 215 nm, 6.0 min.
5-[(E)-2-{5-[(dimethylamino)methyl]pyridin-2-yl}vinyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	423.4	96.5% at 215 nm, 5.1 min.
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-{[(2-(1-methylpyrrolidin-2-yl)ethyl]	506.5	92.2% at 215 nm, 4.4 min.

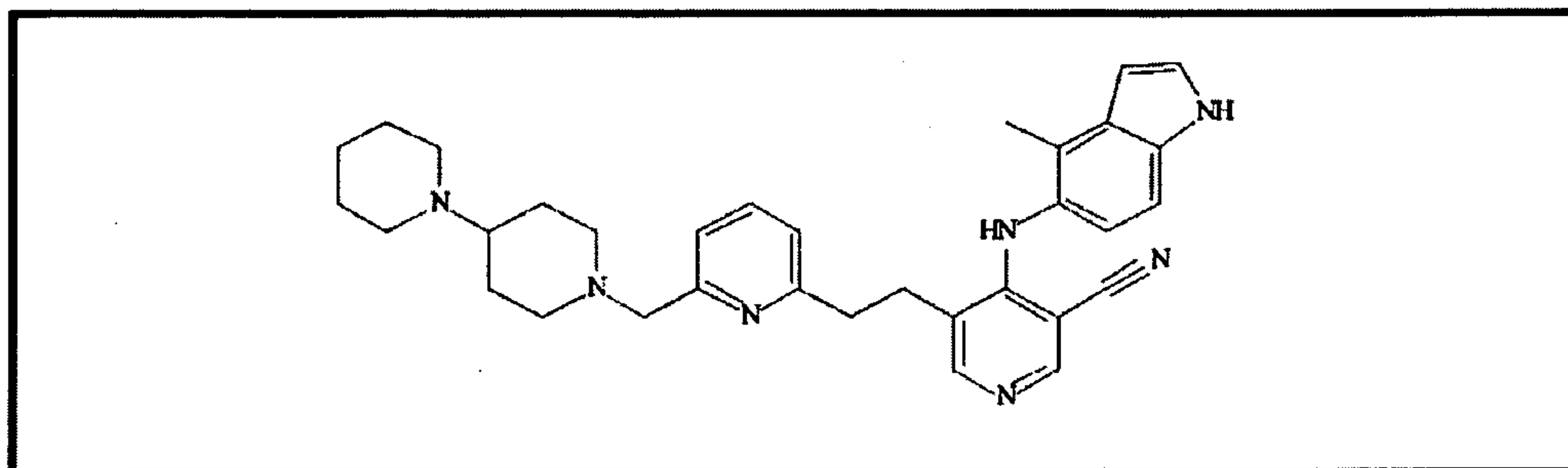
Chemical Name	MS (M+H)	HPLC results
amino}methyl}pyridin-2-yl}vinyl}nicotinonitrile		
5-[(E)-2-{5-[(3-hydroxypyrrolidin-1-yl)methyl]pyridin-2-yl}vinyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	465.4	95.5% at 215 nm, 5.1 min.
5-[(E)-2-(5-{[(2-azepan-1-ylethyl)amino]methyl}pyridin-2-yl}vinyl)-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	520.5	98.7% at 215 nm, 4.3 min.
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(5-{[(2-pyridin-2-ylethyl)amino]methyl}pyridin-2-yl}vinyl]nicotinonitrile	500.4	99.8% at 215 nm, 4.7 min.
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(5-{[(2-pyridin-3-ylethyl)amino]methyl}pyridin-2-yl}vinyl]nicotinonitrile	500.4	89.5% at 215 nm, 4.7 min.
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(5-{[(2-pyridin-4-ylethyl)amino]methyl}pyridin-2-yl}vinyl]nicotinonitrile	500.4	99.2% at 215 nm, 3.7 min.



[00509] Preparation of 5-[2-(6-[(4-(2-hydroxyethyl)piperazin-1-yl)methyl]pyridin-2-yl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

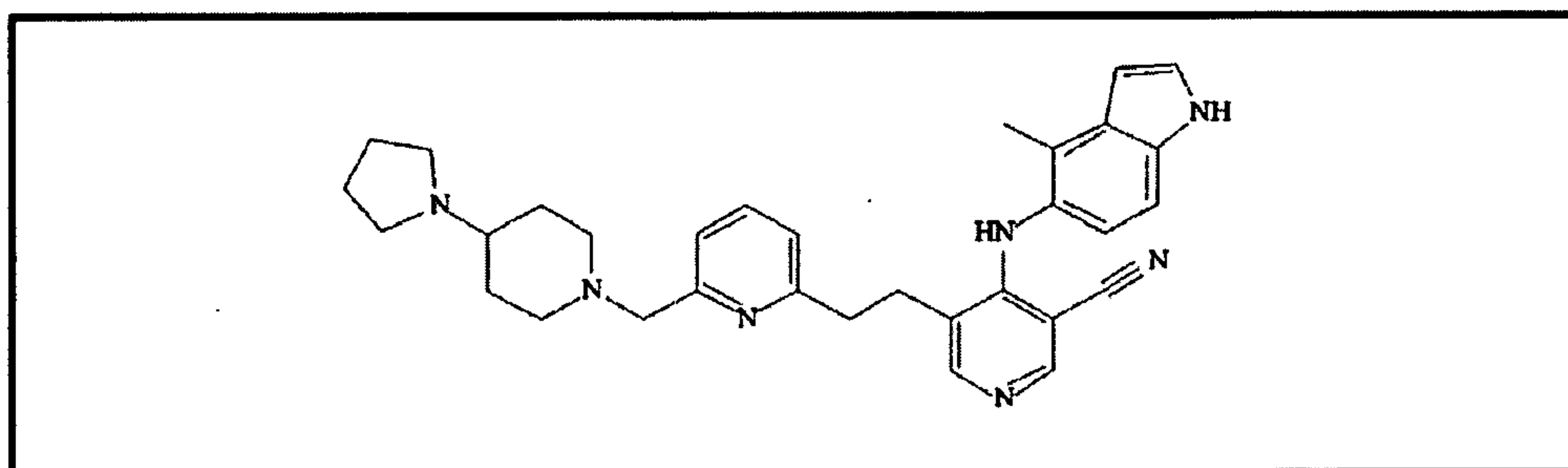
To a solution of 5-[(E)-2-[6-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (200 mg, 0.52 mmol) in a solvent mixture THF (5 ml) and DMF (2.5 ml) was added triethylamine (370 μ L, 2.65 mmol). The solution was stirred under nitrogen at room temperature for 10 min. Methanesulfonyl chloride (122 μ L, 1.58 mmol) was added dropwise into the reaction mixture. The reaction was stirred under nitrogen at room temperature for 8 hours, followed by the addition of 4-(2-hydroxyethyl)piperazine (200 μ L, 2.29 mmol). The reaction was stirred overnight. The solvent was evaporated and the residue was partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The organic solution was dried over MgSO_4 and concentrated to give dark syrup. The resulting crude compound was purified by HPLC to give 61 mg (52%) of alkene compound as a yellow solid. The alkene was then subjected to hydrogenation ($\text{H}_2(\text{g})$, 45 psi) with Pd/C (10% wt., 20 mg) in methanol (10 ml) overnight. The solution was filtered through celite and the filtrate was purified by HPLC

to give 20 mg (7.7%) of the title compound as an off-white solid, MS 496.2 (M+H); HPLC: 99.4% at 215 nm, rt = 4.5 min [a].



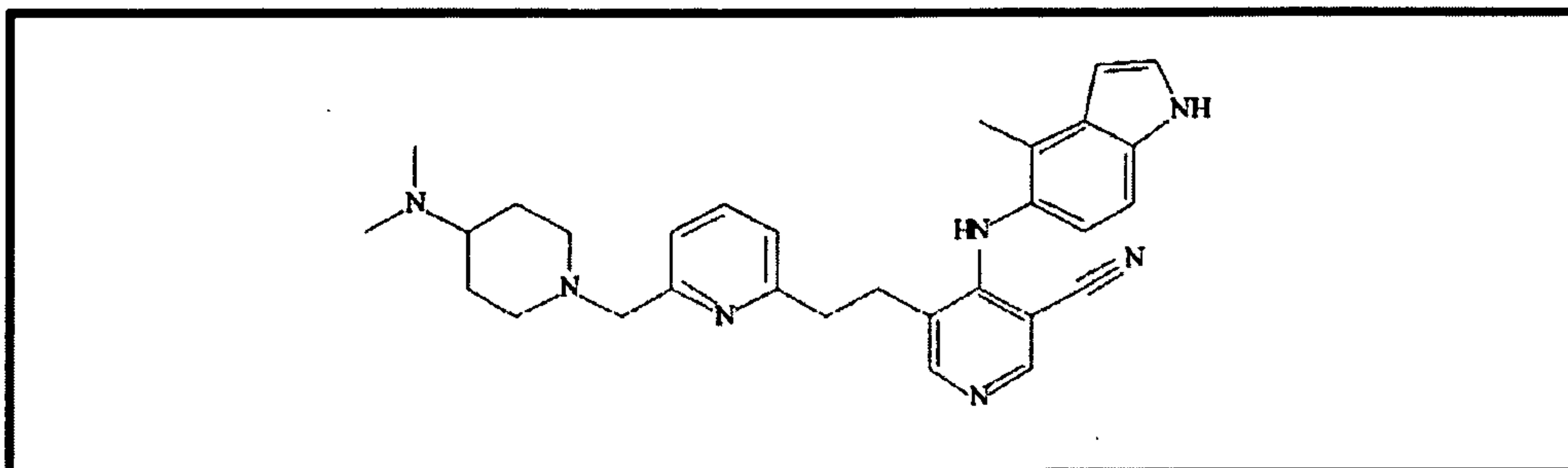
[00510] Preparation of 5-{2-[6-(1,4'-bipiperidin-1'-ylmethyl)pyridin-2-yl]ethyl}-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

The title compound was prepared from 5-[(E)-2-[6-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 4-piperidinopiperidine via the procedure used to prepare 5-[2-(6-{[4-(2-hydroxyethyl)piperazin-1-yl]methyl}pyridin-2-yl)ethyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile, MS 534.3 (M+H); HPLC: 99.5% at 215 nm, rt = 4.0 min [a].



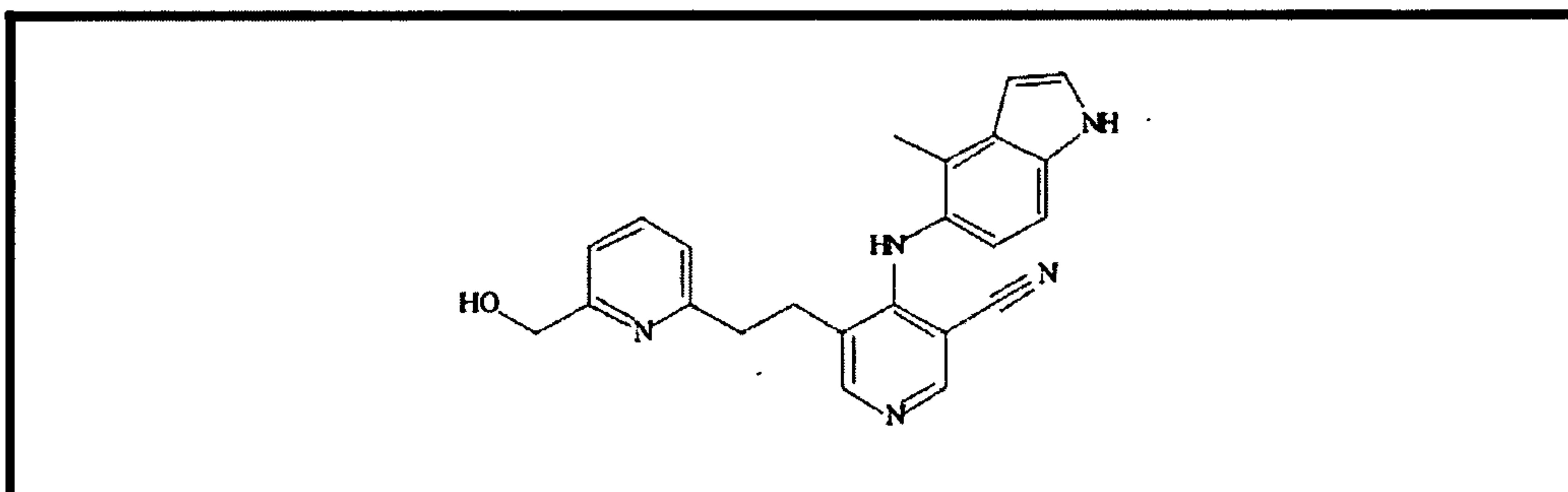
[00511] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-(2-{6-[(4-pyrrolidin-1-yl)piperidin-1-yl]methyl}pyridin-2-yl)ethyl)nicotinonitrile:

The title compound was prepared from 5-[(E)-2-[6-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 4-pyrrolidinopiperidine via the procedure used to prepare 5-[2-(6-{[4-(2-hydroxyethyl)piperazin-1-yl]methyl}pyridin-2-yl)ethyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile, MS 520.2 (M+H); HPLC: rt = 3.7 min [a].



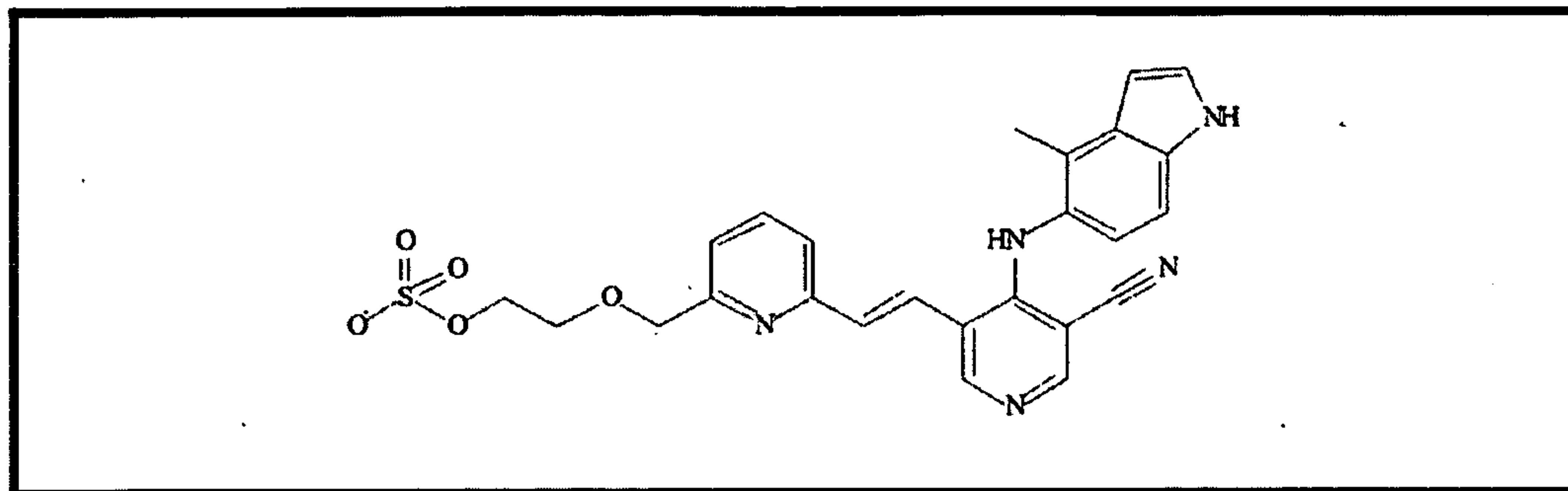
[00512] Preparation of 5-[2-(6-{[4-(dimethylamino)piperidin-1-yl]methyl}pyridin-2-yl)ethyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

The title compound was prepared from 5-[(E)-2-[6-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile and 4-dimethylaminopiperidine via the procedure used to prepare 5-[2-(6-{[4-(2-hydroxyethyl)piperazin-1-yl]methyl}pyridin-2-yl)ethyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile, MS 494.1 (M+H); HPLC: 99.4% at 215 nm, *rt* = 4.2 min [a].



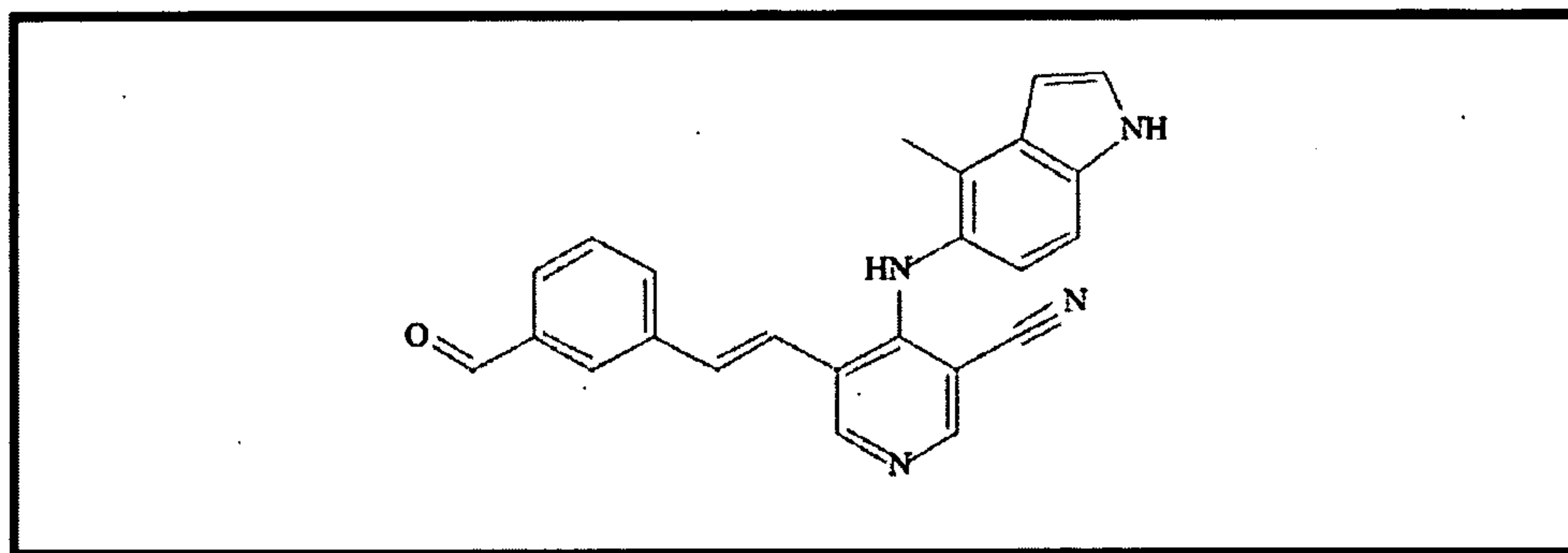
[00513] Preparation of 5-[2-[6-(hydroxymethyl)pyridin-2-yl]ethyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

To the solution of 5-[(E)-2-[6-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (800 mg, 2.10 mmol) in methanol (30 ml) was added Pd/C (10% wt., 30 mg). The reaction mixture was then subjected to hydrogenation (H₂ gas, 45 psi) overnight. The solution was filtered through celite and purified by HPLC to give 516 mg (64%) of the title compound as an off-white solid, MS 384.0 (M+H); HPLC: 94.5% at 215 nm, *rt* = 5.2 min [a].



[00514] Preparation of 2-((6-((E)-2-(5-cyano-4-((4-methyl-1H-indol-5-yl)amino)pyridin-3-yl)vinyl)pyridin-2-yl)methoxy)ethyl sulfate:

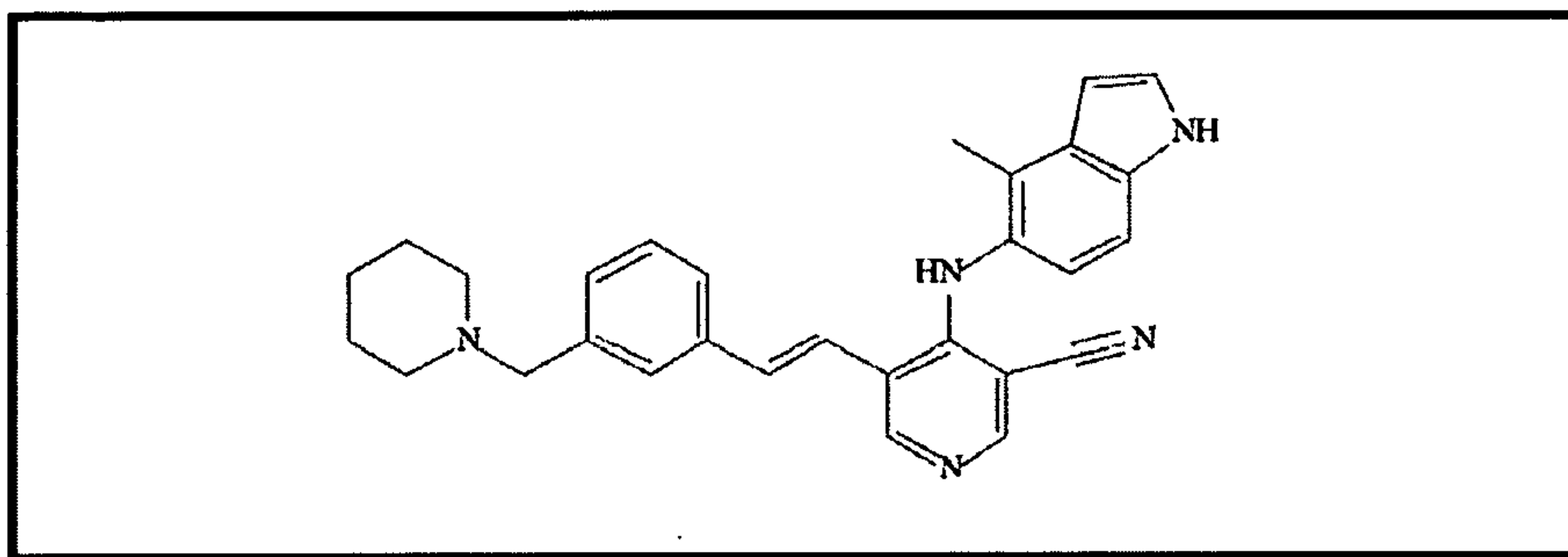
5-Iodo-4-((4-methyl-1H-indol-5-yl)amino)nicotinonitrile (90 mg, 0.24 mmol) was dissolved in a mixture of DMF (2 ml) and triethylamine (0.5 ml) and treated with 2-((6-vinylpyridin-2-yl)methoxy)ethyl sulfate (68 mg, 0.26 mmol), Pd(OAc)₂ (11 mg, 0.049 mmol) and P(o-Tol)₃ (4 mg, 0.013 mmol). The reaction mixture was stirred at 110 °C under nitrogen for 5 hr. Upon cooling, the reaction was diluted with dichloromethane and washed one time with saturated aqueous sodium bicarbonate. The solvent was removed, and the residue was purified by HPLC to give 20 mg (17%) of the title compound as a yellow solid, MS 504.2 (M); HPLC: 95.0% at 215 nm, rt = 6.7 min [a].



[00515] Preparation of 5-((E)-2-(3-formylphenyl)ethenyl)-4-((4-methyl-1H-indol-5-yl)amino)pyridine-3-carbonitrile:

To a reaction mixture of 3-((E)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethenyl)benzaldehyde (1.19 g, 4.61 mmol), 5-iodo-4-((4-methyl-1H-indol-5-yl)amino)nicotinonitrile (1.33 g, 3.55 mmol) and Pd(PPh₃)₄ (410 mg, 0.355 mmol) in 1,2-dimethoxyethane (16 mL) at room temperature was added saturated NaHCO₃ solution (8 mL).

The reaction mixture was heated to 100°C for 3.5 h, then stirred at room temperature overnight, quenched with H₂O and extracted with a mixture of THF-EtOAc (1:2) three times. The extracts were combined and washed with H₂O and brine. Drying, filtration and evaporation gave a brown solid, which was purified by silica gel chromatography (hexane-EtOAc, 10:1 to 2:1), providing the title compound in quantitative yield as a yellow solid. ¹HNMR(300 MHz, DMSO) 2.34 (s, 3H), 6.53 (s, 1H), 6.95 (d, J = 6.0 Hz, 1H), 7.31 (m, 3H), 7.60 (m, 2H), 7.82 (s, 1H), 7.95 (d, J = 6.0 Hz, 1H), 8.17 (s, 1H), 8.29 (s, 1H), 8.62 (s, 1H), 8.93 (s, 1H), 10.03 (s, 1H), 11.16 (s, 1H); MS 379.2 (M+H).



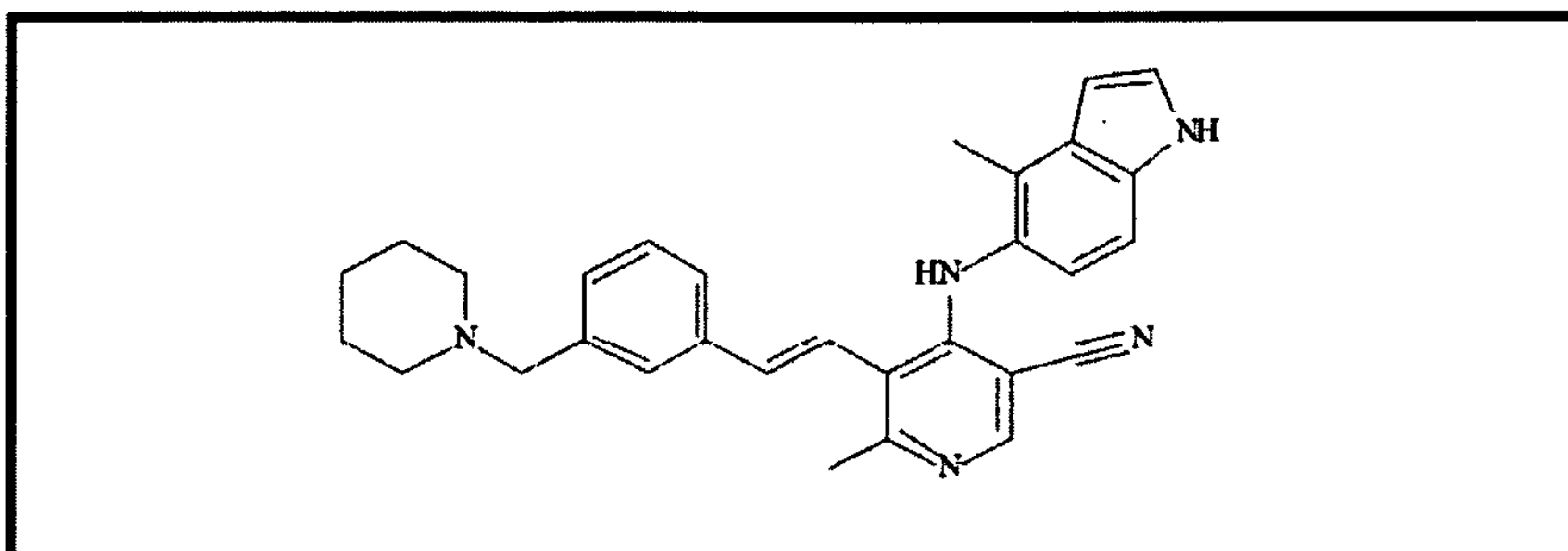
[00516] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[3-(piperidin-1-yl)methyl]phenyl]ethenyl]pyridine-3-carbonitrile:

A mixture of 5-[(E)-2-(3-formylphenyl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile (76 mg, 0.2 mmol) and piperidine (68 mg, 0.8 mmol) in THF (2.0 mL) was stirred at room temperature for 30 minutes. To this was added NaBH(OAc)₃ (170 mg, 0.8 mmol). The reaction mixture was stirred at room temperature for 20 h then concentrated. The residue was purified by HPLC providing 47 mg (53%) of the title compound as a pale yellow solid. MS 448.4 (M+H); HPLC: 99.1% at 215 nm, rt = 6.0 min [a].

[00517] Preparation of 5-[(E)-2-(3-formylphenyl)ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

The title compound was prepared from 3-[(E)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethenyl]benzaldehyde and 5-iodo-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile via the procedure used to prepare 5-[(E)-2-(3-formylphenyl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile. The crude was purified by silica gel chromatography (CH₂Cl₂-THF and CH₂Cl₂-CH₃OH, gradient), providing the title compound in quantitative yield as a yellow solid. ¹HNMR(300 MHz, DMSO) 2.31 (s, 3H), 2.51 (s, 3H), 6.49 (s, 1H), 6.90 (d, J = 9.0

Hz, 1H), 7.01 (d, J = 12.0 Hz, 1H), 7.30 (m, 2H), 7.57 (m, 2H), 7.82 (d, J = 6.0 Hz, 1H), 7.96 (d, J = 6.0 Hz, 1H), 8.16 (d, J = 12.0 Hz, 2H), 8.46 (s, 1H), 10.03 (s, 1H), 11.10 (s, 1H); MS 393.1 (M+H).



[00518] Preparation of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[3-(piperidin-1-ylmethyl)phenyl]ethenyl]pyridine-3-carbonitrile:

The title compound was prepared from 5-[(E)-2-(3-formylphenyl)ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile and piperidine via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[3-(piperidin-1-ylmethyl)phenyl]ethenyl]pyridine-3-carbonitrile. MS 462.3 (M+H); HPLC: 90.8% at 215 nm, rt = 5.9 min [a].

TABLE 15:

[00519] The compounds in table 15 were prepared from either 5-[(E)-2-(3-formylphenyl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile or 5-[(E)-2-(3-formylphenyl)ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile and the appropriate amine via the procedure described for 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[3-(piperidin-1-ylmethyl)phenyl]ethenyl]pyridine-3-carbonitrile and 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[3-(piperidin-1-ylmethyl)phenyl]ethenyl]pyridine-3-carbonitrile.

Compound name	MS (M+H)	HPLC rt [method]
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(3-[(2-morpholin-4-ylethyl)amino]methyl)phenyl]ethenyl]pyridine-3-carbonitrile	493.3	5.2 [a]
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[3-[(4-morpholin-4-ylpiperidin-1-yl)methyl]phenyl]ethenyl]pyridine-3-carbonitrile	533.0	4.7 [a]
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[3-[(4-pyrrolidin-1-ylpiperidin-1-yl)methyl]phenyl]ethenyl]pyridine-3-	517.1	4.7 [a]

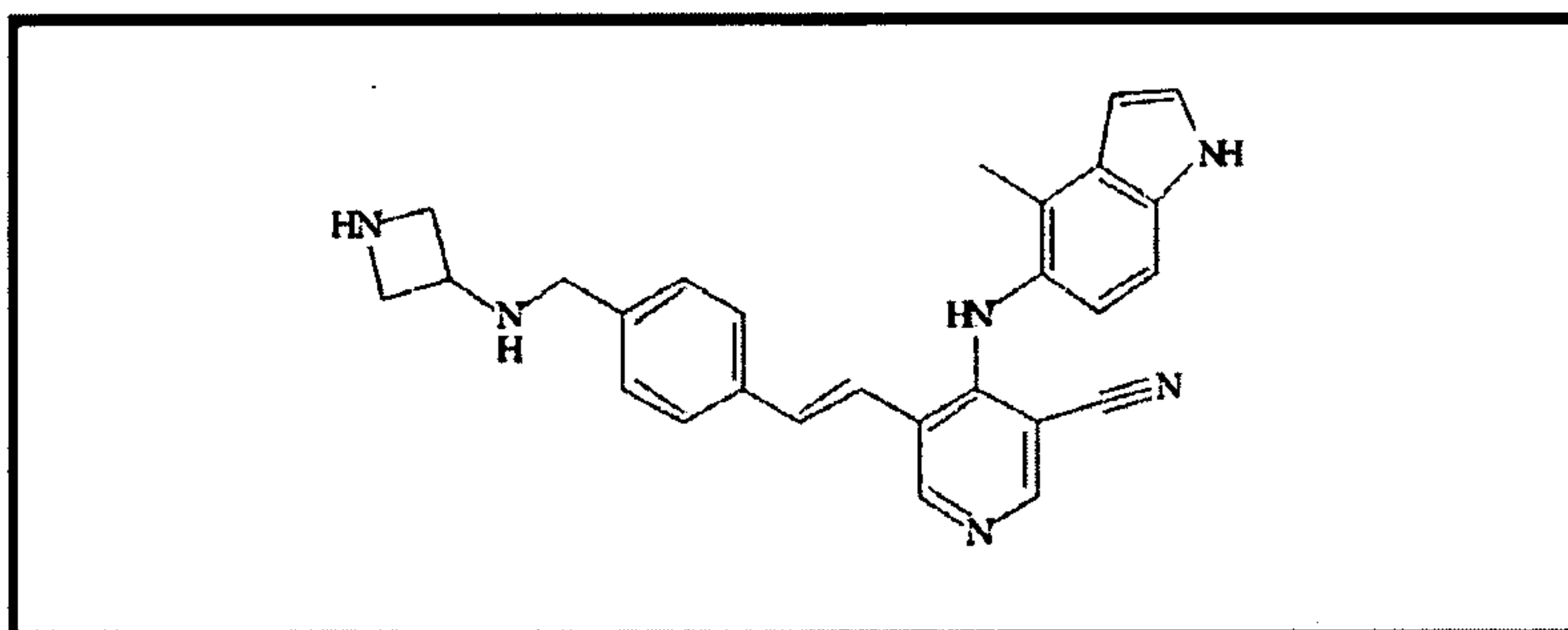
Compound name	MS (M+H)	HPLC rt [method]
carbonitrile		
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[3-[[2-(1-methylpyrrolidin-2-yl)ethyl]amino)methyl]phenyl]ethenyl]pyridine-3-carbonitrile	491.3	4.8 [a]
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[3-[[3-(2-oxopyrrolidin-1-yl)propyl]amino)methyl]phenyl]ethenyl]pyridine-3-carbonitrile	505.3	6.3 [a]
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[3-(morpholin-4-ylmethyl)phenyl]ethenyl]pyridine-3-carbonitrile	450.2	5.6 [a]
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[3-(pyrrolidin-1-ylmethyl)phenyl]ethenyl]pyridine-3-carbonitrile	434.3	5.8 [a]
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[3-(thiomorpholin-4-ylmethyl)phenyl]ethenyl]pyridine-3-carbonitrile	466.3	6.0 [a]
5-[(E)-2-(3-[[2-methoxyethyl]amino)methyl]phenyl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	438.2	6.3 [a]
5-[(E)-2-(3-[[4-(1-methylethyl)piperazin-1-yl]methyl]phenyl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	491.4	5.9 [a]
5-[(E)-2-(3-[[4-(2-hydroxyethyl)piperazin-1-yl]methyl]phenyl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	493.4	5.5 [a]
5-[(E)-2-(3-[[4-(2-hydroxyethyl)piperazin-1-yl]methyl]phenyl]ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	507.3	5.4 [a]
5-[(E)-2-(3-[[4-(dimethylamino)piperidin-1-yl]methyl]phenyl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	491.2	5.2 [a]
5-[(E)-2-(3-[[4-(dimethylamino)piperidin-1-yl]methyl]phenyl]ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	505.3	5.6 [a]
5-[(E)-2-(4-[[4-(dimethylamino)piperidin-1-yl]methyl]phenyl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	491.4	4.6 [a]
5-[(E)-2-(3-[[4-(cyclopentyl)piperazin-1-yl]methyl]phenyl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	259.2 (2M+H)	6.5 [a]
5-[(E)-2-(3-[[4-(4-hydroxypiperidin-1-yl)methyl]phenyl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	464.4	5.6 [a]
5-[(E)-2-(3-[[4-(4-hydroxypiperidin-1-yl)methyl]phenyl]ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	478.3	5.4 [a]
5-[(E)-2-(3-[[4-methyl-1,4-diazepan-1-yl]methyl]phenyl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	477.2	5.2 [a]
5-[(E)-2-(3-[[2-(dimethylamino)ethyl]amino)methyl]phenyl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	451.3	4.7 [a]

Compound name	MS (M+H)	HPLC rt [method]
5-[(E)-2-[3-([2-(dimethylamino)ethyl]amino)methyl]phenyl]ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	465.3	5.3 [a]
5-[(E)-2-[3-([3-(dimethylamino)propyl]amino)methyl]phenyl]ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	479.3	5.3 [a]
5-[(E)-2-[3-(1,4'-bipiperidin-1'-ylmethyl)phenyl]ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	545.3	4.7 [a]
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[3-[(3-morpholin-4-ylpropyl)amino]methyl]phenyl]vinyl]nicotinonitrile	521.2	5.2 [a]
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[3-[(4-methylpiperazin-1-yl)methyl]phenyl]ethenyl]pyridine-3-carbonitrile	477.3	5.5 [a]
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[3-[(4-morpholin-4-ylpiperidin-1-yl)methyl]phenyl]ethenyl]pyridine-3-carbonitrile	547.3	5.7 [a]
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[3-[(4-pyrrolidin-1-ylpiperidin-1-yl)methyl]phenyl]ethenyl]pyridine-3-carbonitrile	531.3	4.8 [a]
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[3-[(morpholin-4-ylmethyl)phenyl]ethenyl]pyridine-3-carbonitrile	464.2	5.4 [a]
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[3-[(pyrrolidin-1-ylmethyl)phenyl]ethenyl]pyridine-3-carbonitrile	448.3	5.8 [a]
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[3-[(thiomorpholin-4-ylmethyl)phenyl]ethenyl]pyridine-3-carbonitrile	480.3	5.9 [a]
6-methyl-5-[(E)-2-[3-[[4-(1-methylethyl)piperazin-1-yl]methyl]phenyl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	505.4	5.8 [a]
6-methyl-5-[(E)-2-[3-[(4-methyl-1,4-diazepan-1-yl)methyl]phenyl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	491.3	5.6 [a]
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[3-[(2-pyrrolidin-1-ylethyl)amino]methyl]phenyl]ethenyl]pyridine-3-carbonitrile	491.3	4.8 [a]
5-[(E)-2-[3-[(dimethylamino)methyl]phenyl]ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	422.3	5.5 [a]
5-[(E)-2-[3-[(3-hydroxypyrrolidin-1-yl)methyl]phenyl]ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	464.2	5.4 [a]
5-[(E)-2-[3-[(diethylamino)methyl]phenyl]ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	450.2	7.5 [a]

TABLE 16:

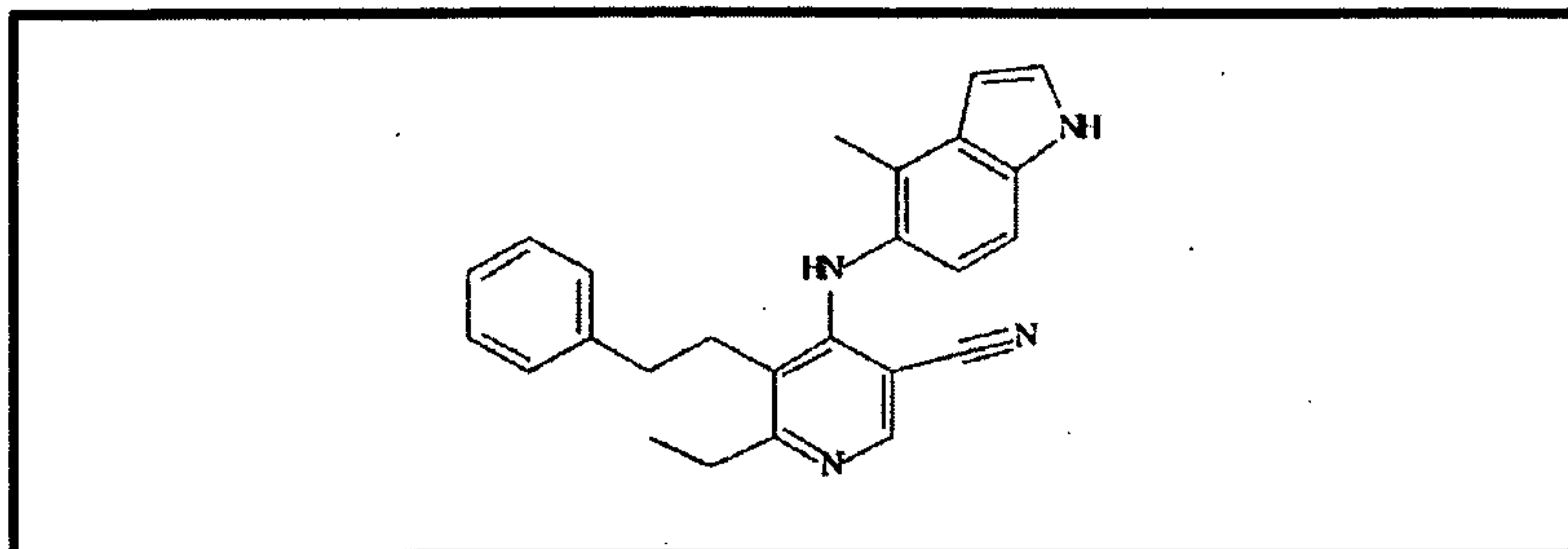
[00520] The compounds in the following table were prepared from 5-[(E)-2-(4-formylphenyl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile and the appropriate amine via the procedure described for 5-[(E)-2-(4-{[4-(2-hydroxyethyl)piperazin-1-yl]methyl}phenyl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile.

Compound name	MS (M+H)	HPLC rt [method]
5-[(E)-2-(4-{[(2-ethoxyethyl)amino]methyl}phenyl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	438.1	7.2 [a]
5-[(E)-2-(4-{[(2-ethoxyethyl)amino]methyl}phenyl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	452.1	6.7 [a]
4-[(4-methyl-1H-indol-5-yl)amino]-5-{(E)-2-[4-{[2-(1-methylpyrrolidin-2-yl)ethyl]amino}methyl]phenyl}ethenyl}pyridine-3-carbonitrile	491.1	5.3 [a]
5-[(E)-2-(4-{[(2-azepan-1-ylethyl)amino]methyl}phenyl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	505.2	6.8 [a]



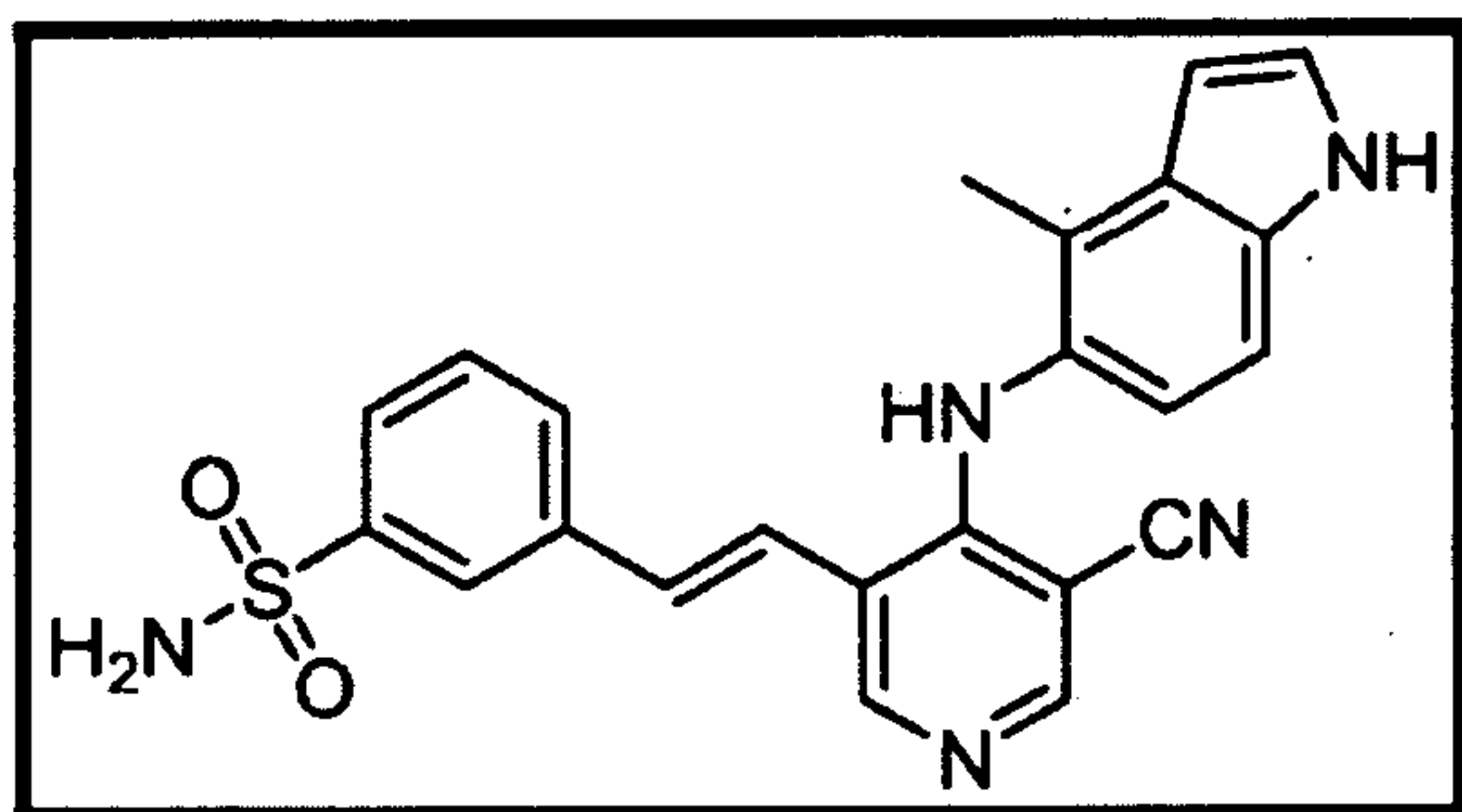
[00521] Preparation of 5-[(E)-2-(4-[(azetidin-3-ylamino)methyl]phenyl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

The title compound was prepared from tert-butyl 3-({4-[(E)-2-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}vinyl]benzyl}amino)azetidine-1-carboxylate via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-{(E)-2-[4-(piperazin-1-ylmethyl)phenyl]vinyl}nicotinonitrile. MS 435.2 (M+H); HPLC: 63.3% at 215 nm, rt = 4.5 min [a].



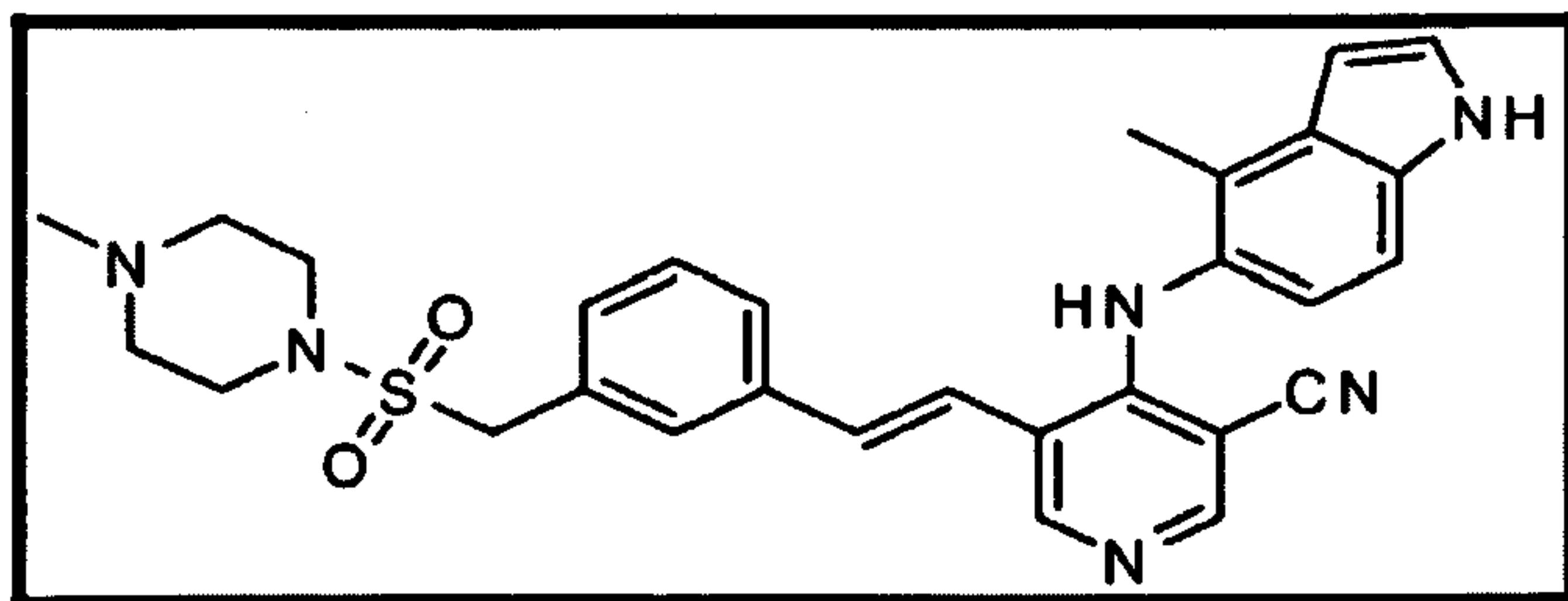
[00522] Preparation of 6-ethyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-(2-phenylethyl)pyridine-3-carbonitrile:

The title compound was prepared from 6-ethyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-phenylvinyl]nicotinonitrile via the procedure used to prepare 5-[2-(4-methoxyphenyl)ethyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile. MS 381.2 (M+H). HPLC: rt = 9.8 min [a].



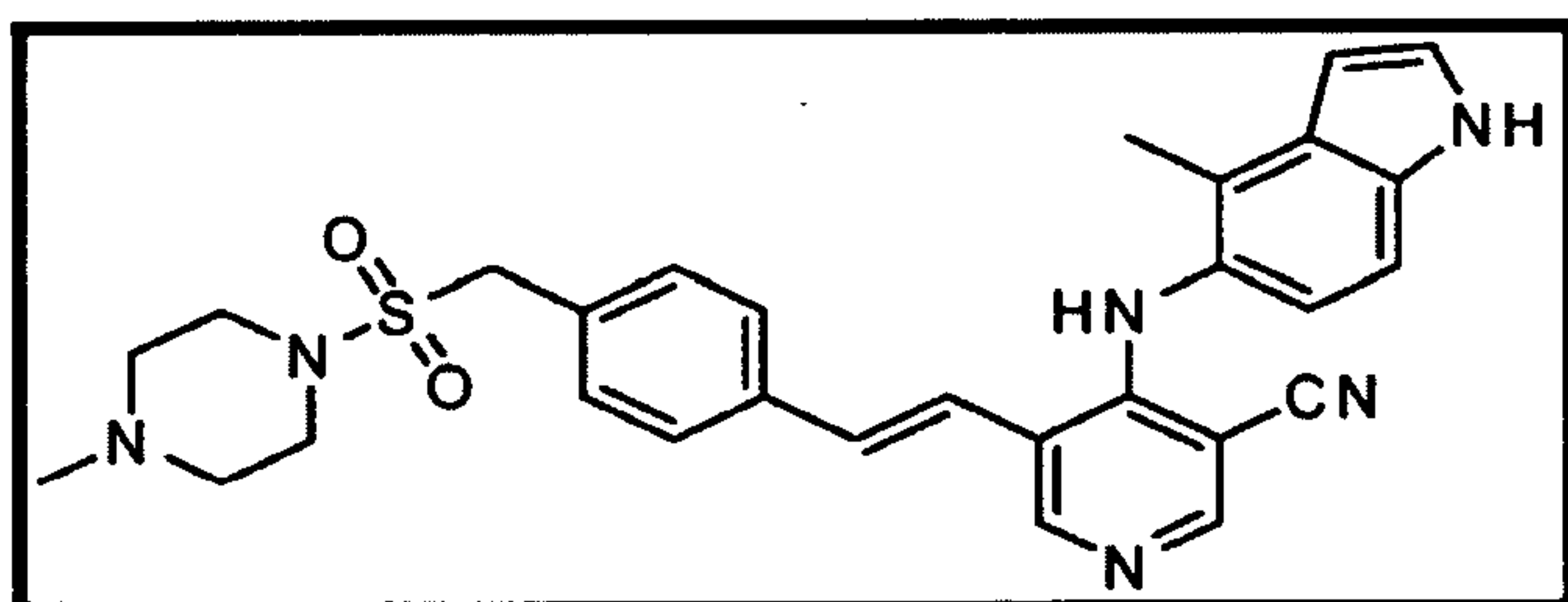
[00523] Preparation of 3-[(E)-2-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}vinyl]benzenesulfonamide:

4-[(4-Methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile (98 mg, 0.36 mmol), 3-bromobenzenesulfonamide (93 mg, 0.39 mmol), Pd(OAc)₂ (5.2 mg, 0.023 mmol), P(o-Tol)₃ (7.6 mg, 0.063 mmol), and triethylamine (726 mg, 7.2 mmol) were dissolved in 3 mL DMF and heated to 90° C for 16 h. The reaction was cooled to room temperature and partitioned between chloroform and saturated sodium bicarbonate. The organic portion was dried (magnesium sulfate) and concentrated. The residue was dissolved in DMSO and purified by HPLC to give 11 mg of the title compound. HPLC: rt = 7.4 min [a]; m/e 430.0 (M+H); HRMS: calculated 430.1332 found 430.1328 (M+H).



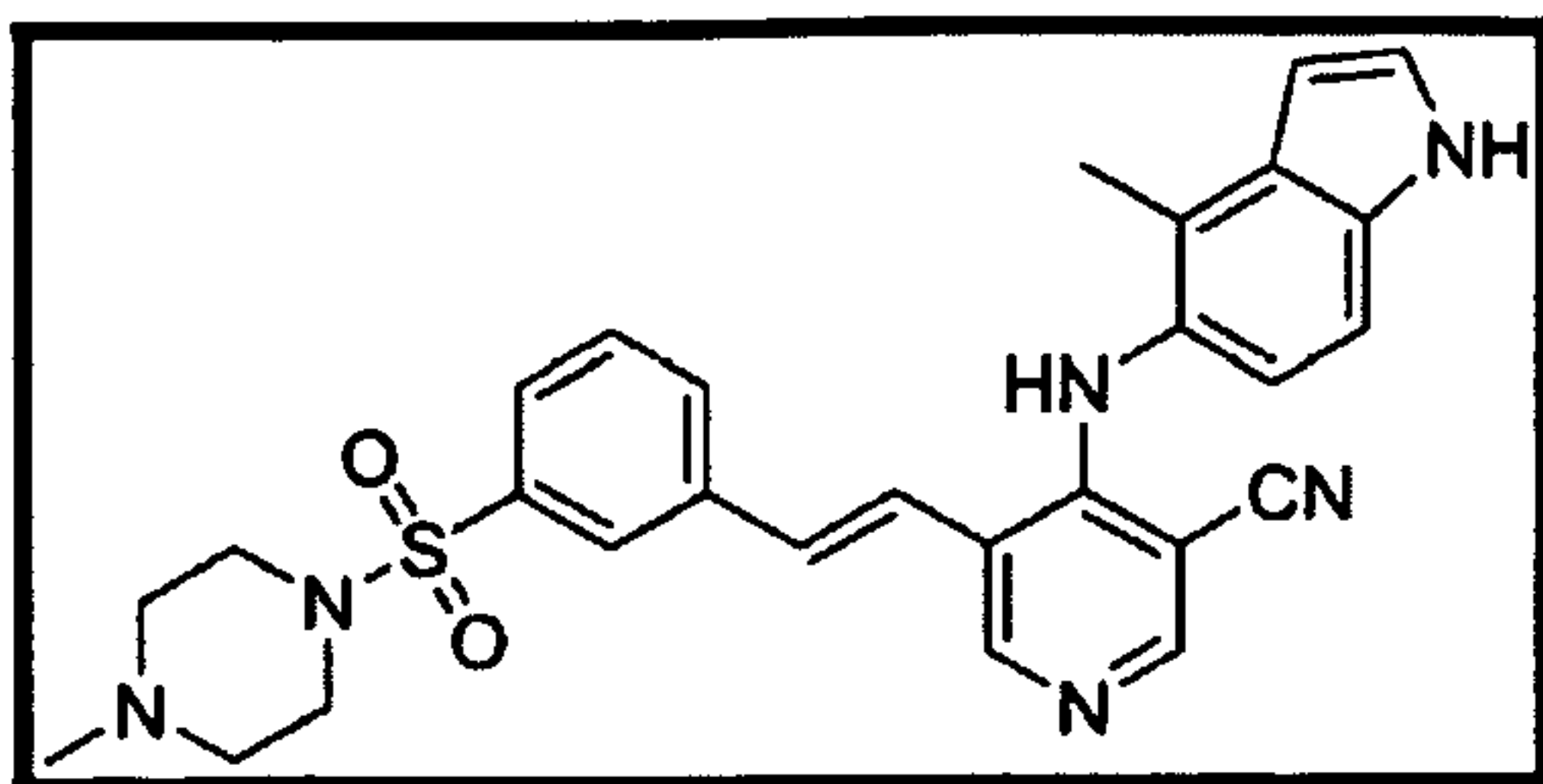
[00524] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(3-[(4-methylpiperazin-1-yl)sulfonyl]methyl)phenyl)ethenyl]pyridine-3-carbonitrile:

4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile (89 mg, 0.32 mmol), 1-[(3-bromobenzyl)sulfonyl]-4-methylpiperazine (125 mg, 0.38 mmol), Pd(OAc)₂ (8.0 mg, 0.036 mmol), P(o-Tol)₃ (32 mg, 0.11 mmol), and triethylamine (726 mg, 7.2 mmol) were dissolved in 3 mL DMF and heated to 90° C for 16 h. The reaction was cooled to room temperature and partitioned between chloroform and saturated sodium bicarbonate. The organic portion was dried (magnesium sulfate) and concentrated. The residue was dissolved in DMSO and purified by HPLC to give 101 mg of the title compound. HPLC: 94.2%, rt = 6.8 min [a]; m/e 527.3 (M+H); HRMS: calculated 527.2224 found 527.2221 (M+H).



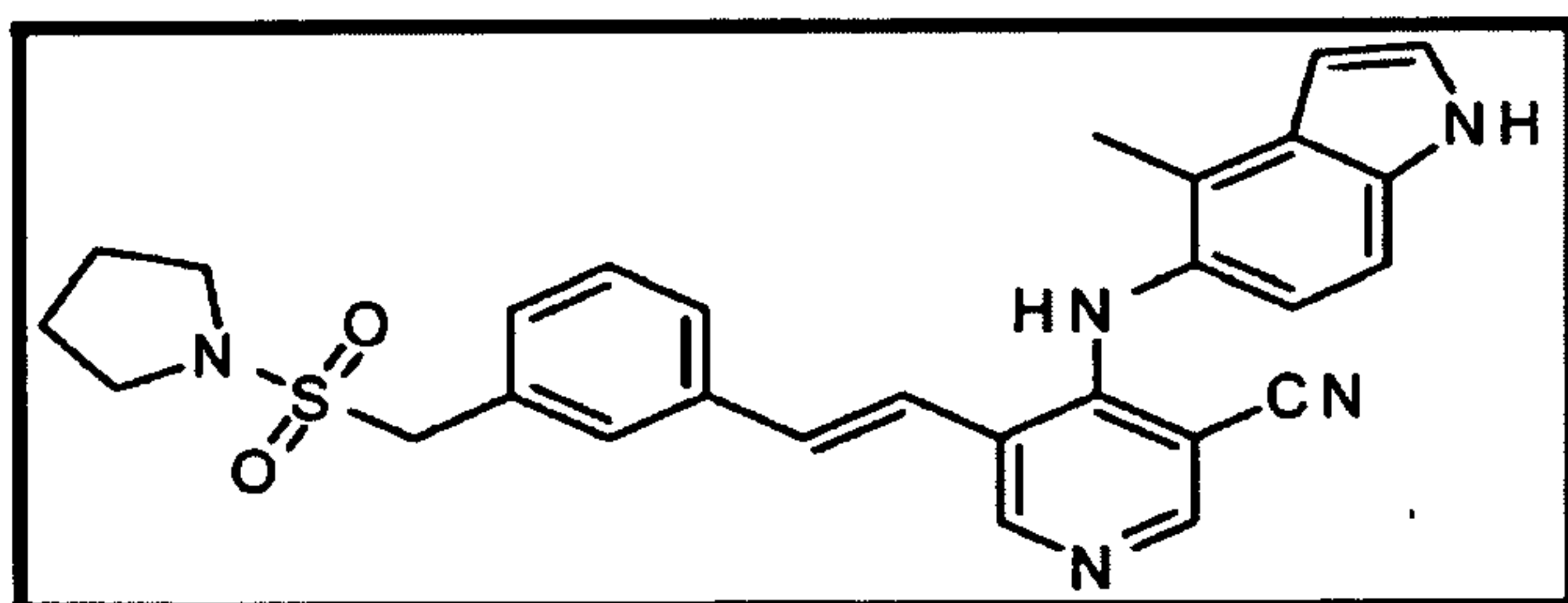
[00525] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4-[(4-methylpiperazin-1-yl)sulfonyl]methyl)phenyl)ethenyl]pyridine-3-carbonitrile:

4-[(4-Methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile (84 mg, 0.31 mmol), 1-(4-bromobenzylsulfonyl)-4-methylpiperazine (54 mg, 0.16 mmol), Pd(OAc)₂ (5.0 mg, 0.022 mmol), P(o-Tol)₃ (17 mg, 0.056 mmol), and triethylamine (726 mg, 7.2 mmol) were dissolved in 3 mL DMF and heated to 90° C for 16 h. The reaction was cooled to room temperature and partitioned between chloroform and saturated sodium bicarbonate. The organic portion was dried (magnesium sulfate) and concentrated. The residue was dissolved in DMSO and purified by HPLC to give 24 mg of the title compound. HPLC: rt = 6.7 min [a]; m/e 527.3 (M+H); HRMS: calculated 527.2224 found 523.2215 (M+H).



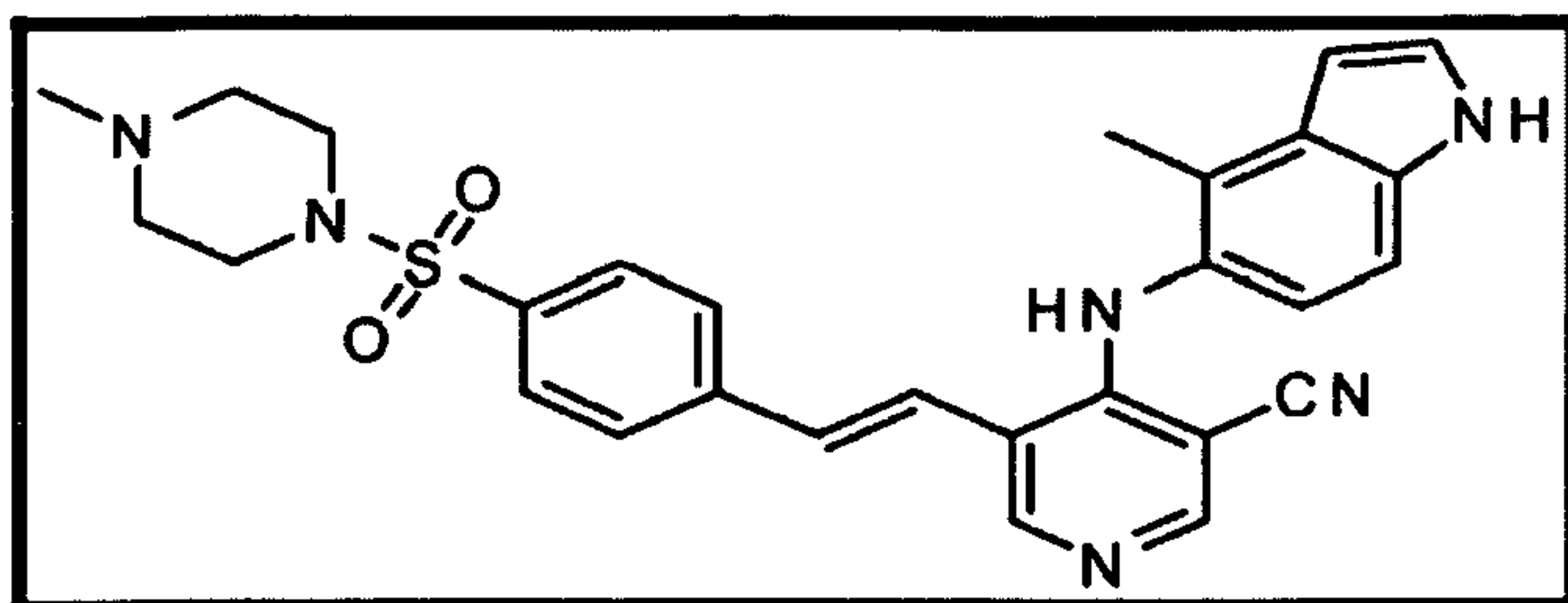
[00526] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{3-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}vinyl]nicotinonitrile:

4-[(4-Methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile (65 mg, 0.24 mmol), 1-(3-bromophenylsulfonyl)-4-methylpiperazine (76 mg, 0.24 mmol), Pd(OAc)₂ (5.0 mg, 0.022 mmol), P(o-Tol)₃ (11 mg, 0.036 mmol), and triethylamine (726 mg, 7.2 mmol) were dissolved in 2 mL DMF and heated to 90° C for 16 h. The reaction was cooled to room temperature and partitioned between chloroform and saturated sodium bicarbonate. The organic portion was dried (magnesium sulfate) and concentrated. The residue was dissolved in DMSO and purified by HPLC to give 101 mg of the title compound. HPLC: 98.9%, rt = 7.1 min [a]; m/e 513.2 (M+H); HRMS: calculated 513.2067 found 513.2065 (M+H).



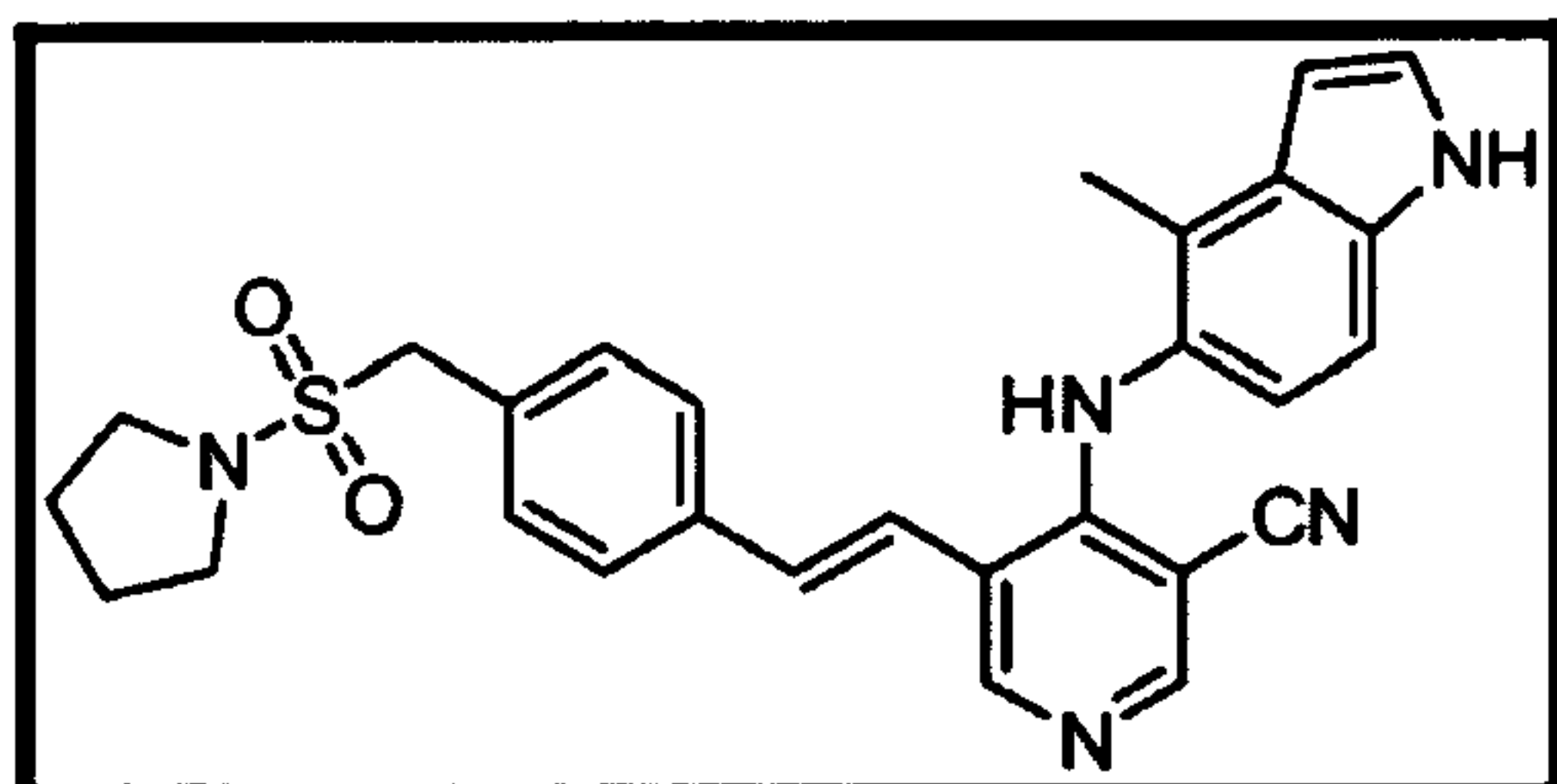
[00527] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{3-[(pyrrolidin-1-yl)sulfonyl]methyl}phenyl}ethenyl]pyridine-3-carbonitrile:

4-[(4-Methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile (66 mg, 0.24 mmol), 1-(3-bromobenzylsulfonyl)pyrrolidine (108 mg, 0.36 mmol), Pd(OAc)₂ (8.4 mg, 0.037 mmol), P(o-Tol)₃ (24 mg, 0.079 mmol), and triethylamine (726 mg, 7.2 mmol) were dissolved in 2 mL DMF and heated to 90° C for 16 h. The reaction was cooled to room temperature and partitioned between chloroform and saturated sodium bicarbonate. The organic portion was dried (magnesium sulfate) and concentrated. The residue was dissolved in DMSO and purified by HPLC to give 101 mg of the title compound. HPLC: 93.0%, rt = 10.1 min [a]; m/e 498.3 (M+H); HRMS: calculated 498.1958 found 498.1957 (M+H).



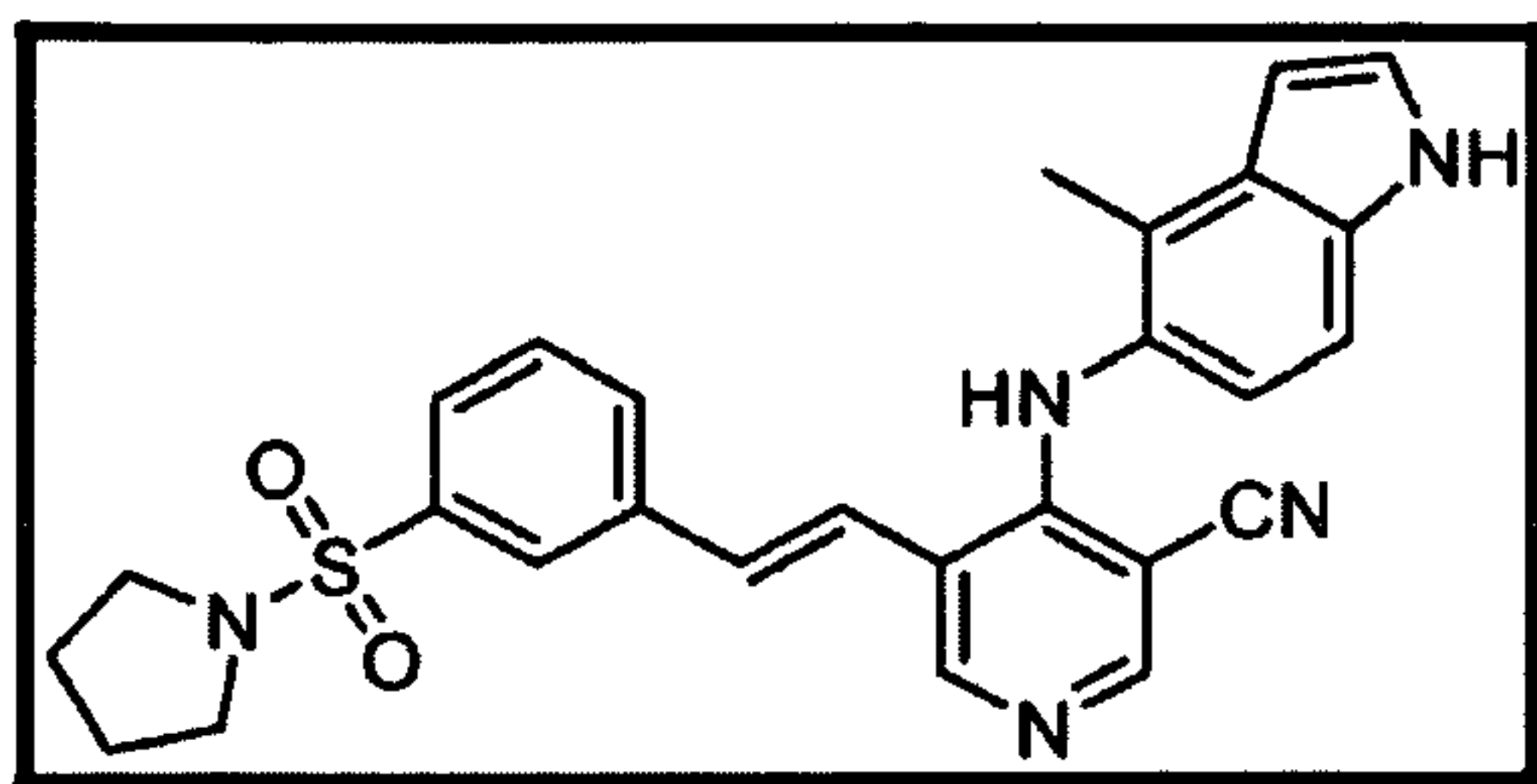
[00528] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}ethenyl]pyridine-3-carbonitrile:

4-[(4-Methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile (50 mg, 0.18 mmol), 1-(4-bromophenylsulfonyl)-4-methylpiperazine (58 mg, 0.18 mmol), Pd(OAc)₂ (3.5 mg, 0.016 mmol), P(o-Tol)₃ (11.2 mg, 0.037 mmol), and triethylamine (726 mg, 7.2 mmol) were dissolved in 5 mL DMF and heated to 90 °C for 16 h. The reaction was cooled to room temperature and partitioned between chloroform and saturated sodium bicarbonate. The organic portion was dried (magnesium sulfate) and concentrated. The residue was dissolved in DMSO and purified by HPLC to give 36 mg of the title compound. HPLC: 93.3%, rt = 6.4 min [a]; m/e 513.3 (M+H); HRMS: calculated 513.2067 found 513.2070 (M+H).



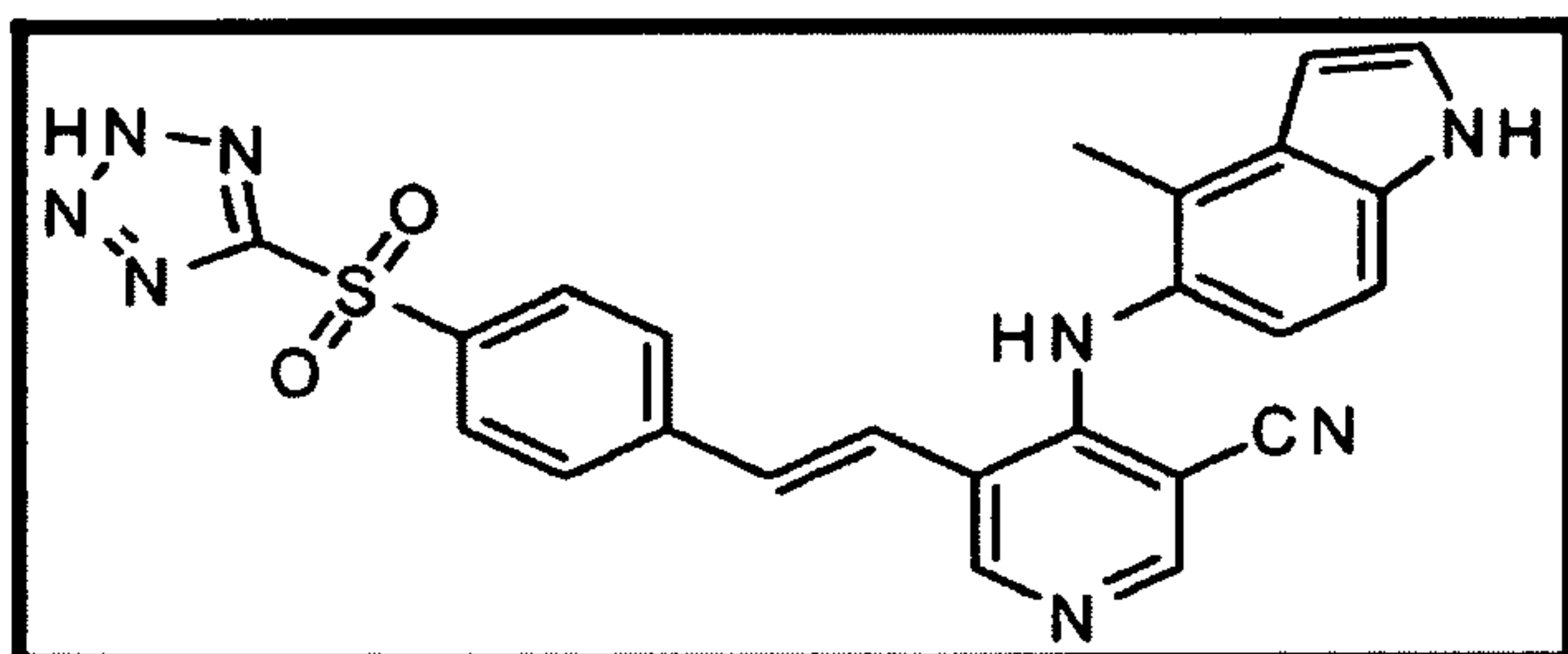
[00529] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{4-[(pyrrolidin-1-yl)sulfonyl]methyl}phenyl}vinyl]nicotinonitrile:

4-[(4-Methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile (96 mg, 0.35 mmol), 1-(4-bromobenzylsulfonyl)pyrrolidine (111 mg, 0.37 mmol), Pd(OAc)₂ (7.1 mg, 0.032 mmol), P(o-Tol)₃ (8.6 mg, 0.028 mmol), and triethylamine (726 mg, 7.2 mmol) were dissolved in 2 mL DMF and heated to 90° C for 16 h. The reaction was cooled to room temperature and partitioned between chloroform and saturated sodium bicarbonate. The organic portion was dried (magnesium sulfate) and concentrated. The residue was dissolved in DMSO and purified by HPLC to give 14 mg of the title compound. HPLC: 96.1%, rt = 9.6 min [a]; m/e 498.2 (M+H); HRMS: calculated 498.1958 found 498.1960 (M+H).



[00530] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[3-(pyrrolidin-1-yl)sulfonyl]phenyl]vinyl]nicotinonitrile:

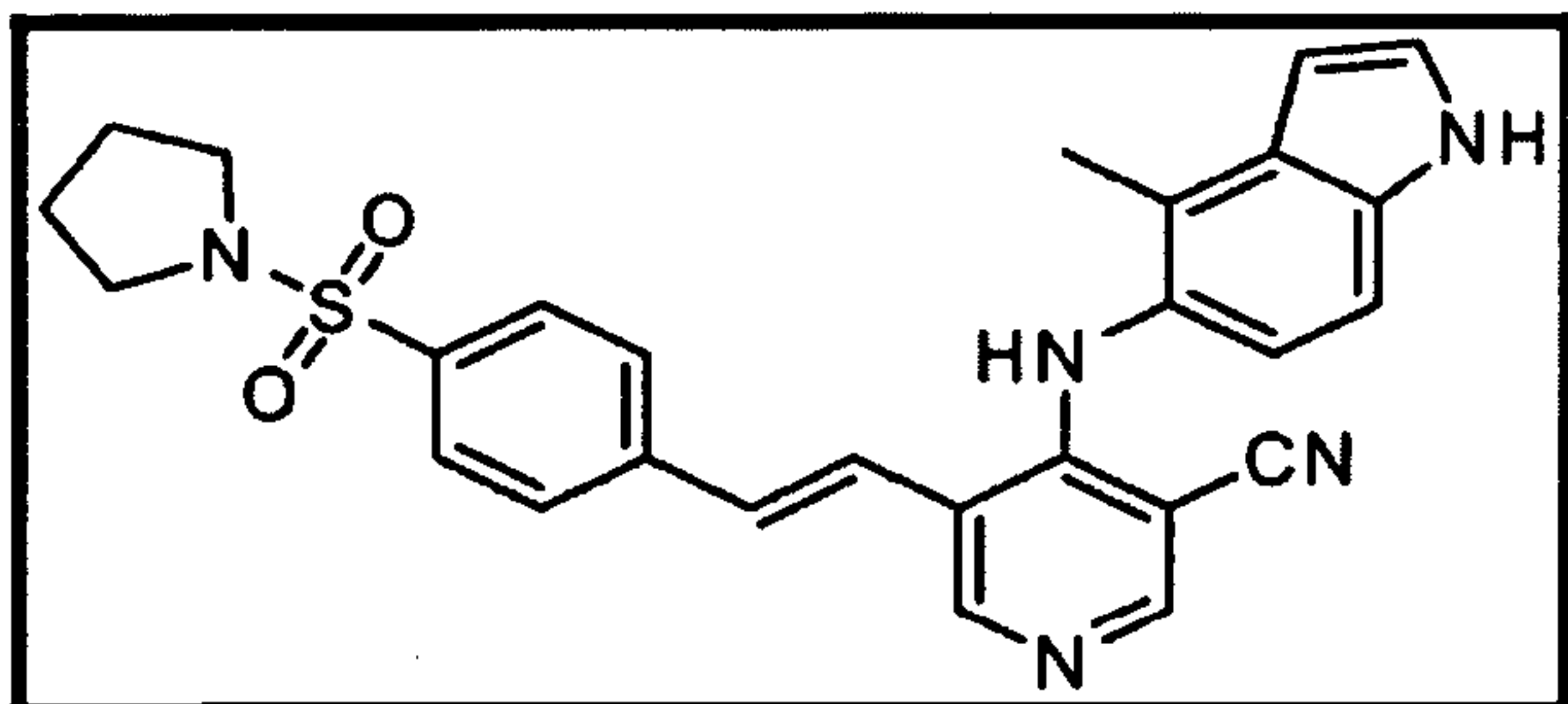
4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile (65 mg, 0.24 mmol), 1-(3-bromophenylsulfonyl)pyrrolidine (69 mg, 0.24 mmol), Pd(OAc)₂ (6 mg, 0.027 mmol), P(o-Tol)₃ (11 mg, 0.036 mmol), and triethylamine (726 mg, 7.2 mmol) were dissolved in 2 mL DMF and heated to 90° C for 16 h. The reaction was cooled to room temperature and partitioned between chloroform and saturated sodium bicarbonate. The organic portion was dried (magnesium sulfate) and concentrated. The residue was dissolved in DMSO and purified by HPLC to give 47 mg of the title compound. HPLC: 96.4%, rt = 10.6 min [a]; m/e 484.2 (M+H); HRMS: calculated 484.1804 found 484.1802 (M+H).



[00531] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(2H-tetrazol-5-yl)]phenyl]vinyl]nicotinonitrile:

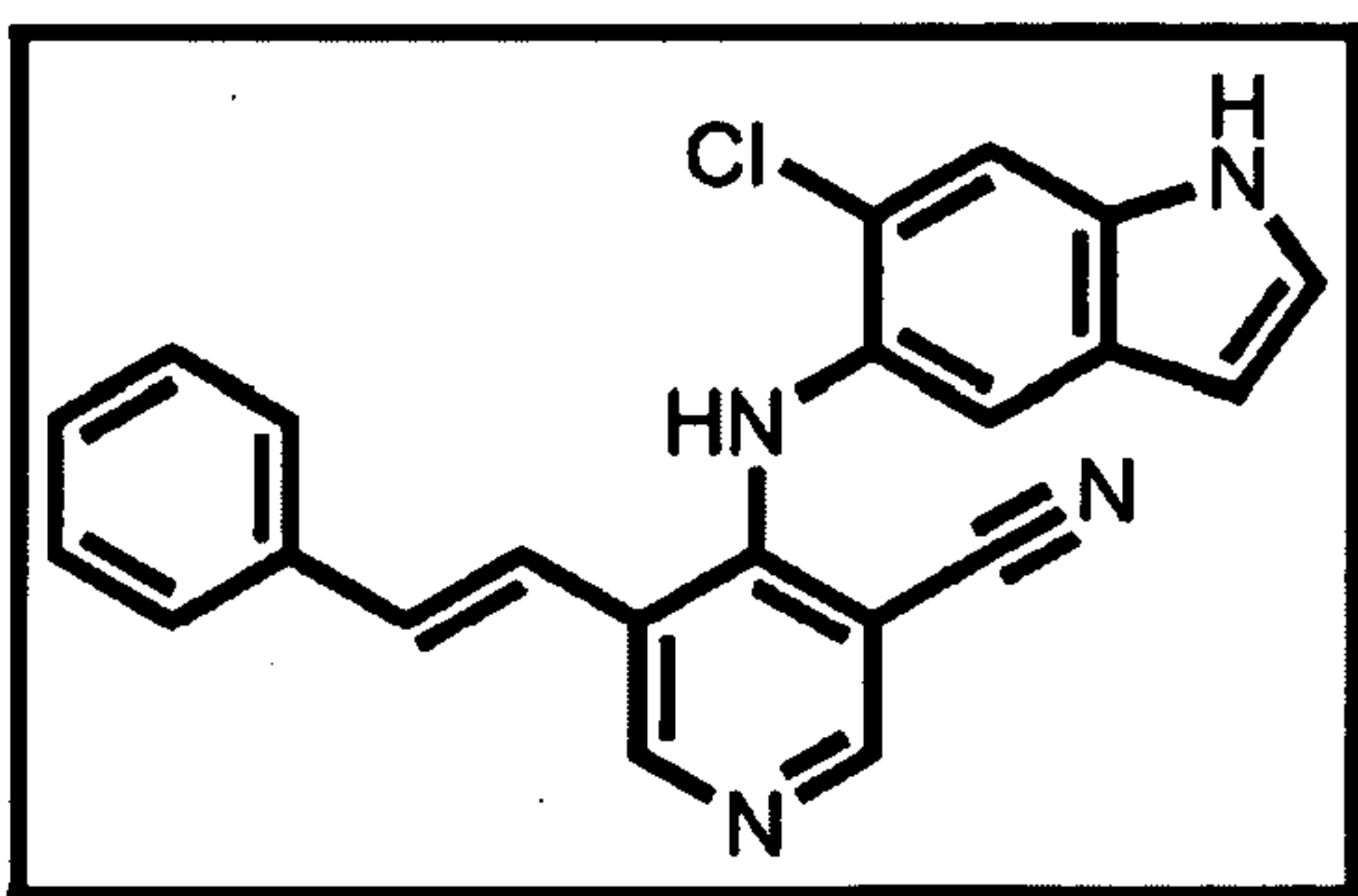
4-[(4-Methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile (61 mg, 0.22 mmol), 5-(4-bromophenyl)-2H-tetrazole (J. Med Chem. 1991, 1135) (50 mg, 0.22 mmol), Pd(OAc)₂ (11 mg, 0.05 mmol), P(o-Tol)₃ (15 mg, 0.05 mmol), and triethylamine (363 mg, 3.6 mmol) were dissolved in 2 mL DMF and heated to 90° C for 16 h. The reaction was cooled to room temperature and partitioned between chloroform and saturated sodium bicarbonate. The organic portion was dried (magnesium sulfate) and concentrated. The residue was dissolved in DMSO and

purified by HPLC to give 6 mg of the title compound. HPLC: $t_r = 8.0$ min [a]; m/e 419.2 (M+H); HRMS: calculated 419.1727 found 419.1731 (M+H).



[00532] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(pyrrolidin-1-ylsulfonyl)phenyl]ethenyl]pyridine-3-carbonitrile:

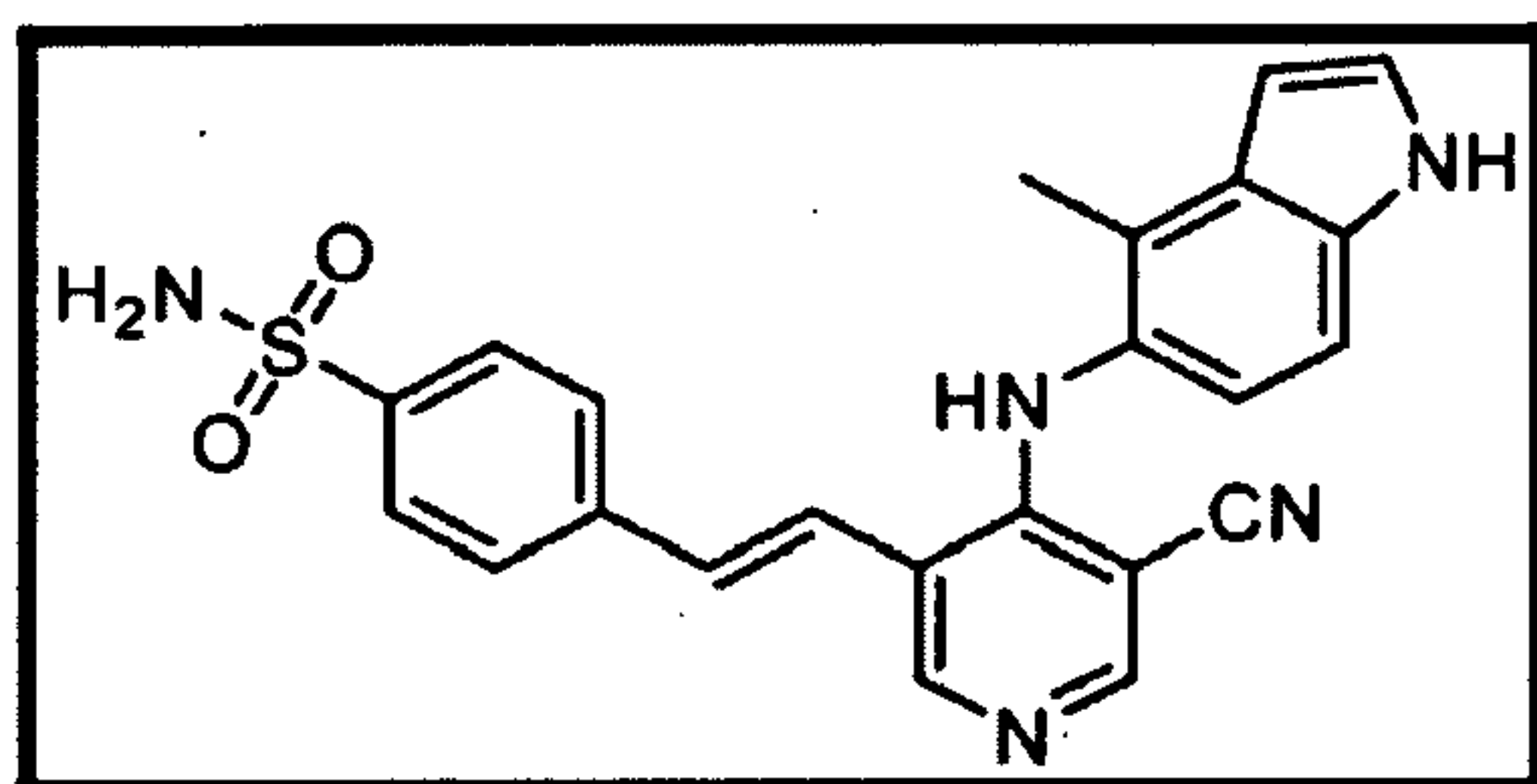
4-[(4-Methyl-1H-indol-5-yl)amino]-5-vinylpyridine-3-carbonitrile (50 mg, 0.18 mmol), 1-(4-bromophenylsulfonyl)-4-methylpiperazine (58 mg, 0.18 mmol), $\text{Pd}(\text{OAc})_2$ (3.5 mg, 0.016 mmol), $\text{P}(o\text{-Tol})_3$ (11.2 mg, 0.037 mmol), and triethylamine (726 mg, 7.2 mmol) were dissolved in 5 mL DMF and heated to 90°C for 16 h. The reaction was cooled to room temperature and partitioned between chloroform and saturated sodium bicarbonate. The organic portion was dried (magnesium sulfate) and concentrated. The residue was dissolved in DMSO and purified by HPLC to give 28 mg of the title compound. HPLC: 97.4%, $t_r = 9.9$ min [a]; m/e 484.2 (M+H); HRMS: calculated 484.1802 found 484.1801 (M+H).



[00533] Preparation of 4-[(6-chloro-1H-indol-5-yl)amino]-5-[(E)-2-phenylethenyl]pyridine-3-carbonitrile:

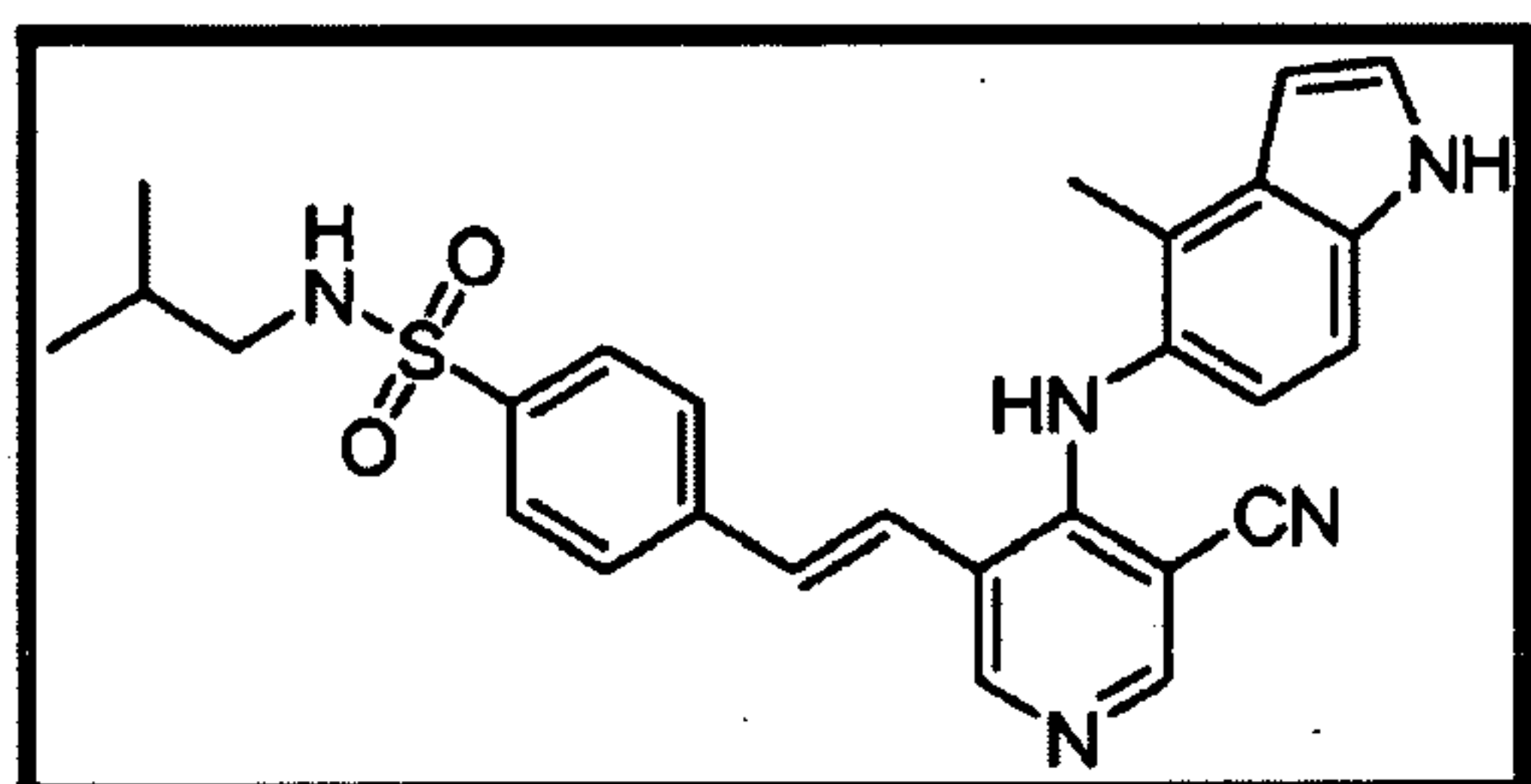
4-[(6-Chloro-1H-indol-5-yl)amino]-5-iodopyridine-3-carbonitrile (53 mg, 0.13 mmol), (E)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolanyl-2-yl)styrene (37 mg, 0.16 mmol), $\text{Pd}(\text{PPh}_3)_4$ (8.3 mg, 0.072 mmol), and saturated sodium bicarbonate (1 mL) was heated at reflux in 5 mL DME for

2 h. The reaction was cooled to room temperature and partitioned between ethyl acetate and saturated sodium bicarbonate. The organic portion was dried (magnesium sulfate) and concentrated. The residue was dissolved in DMSO and purified by HPLC to give 35 mg of the title compound. HPLC: 91.5%, *rt* = 10.3 min [a]; *m/e* 371.2 (M+H); HRMS: calculated 371.1058 found 371.1058 (M+H).



[00534] Preparation of 4-[(E)-2-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}vinyl]benzenesulfonamide:

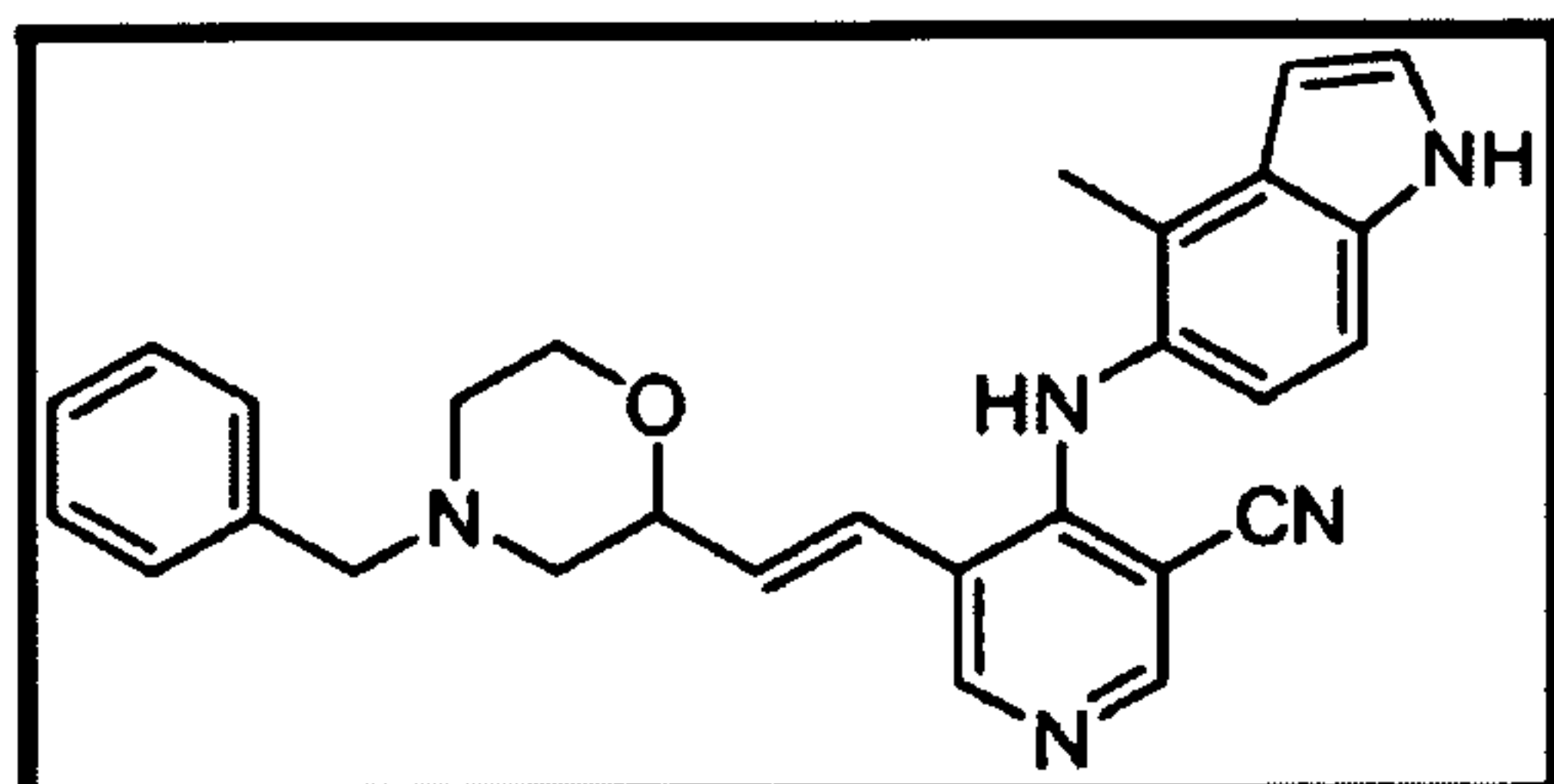
4-[(4-Methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile (70 mg, 0.26 mmol), 4-bromobenzenesulfonamide CL-4999 (70 mg, 0.30 mmol), Pd(OAc)₂ (7.2 mg, 0.032 mmol), P(*o*-Tol)₃ (11.2 mg, 0.037 mmol), and triethylamine (726 mg, 7.2 mmol) were dissolved in 2 mL DMF and heated to 90° C for 16 h. The reaction was cooled to room temperature and partitioned between chloroform and saturated sodium bicarbonate. The organic portion was dried (magnesium sulfate) and concentrated. The residue was dissolved in DMSO and purified by HPLC to give 22 mg of the title compound. HPLC: 97.7%, *rt* = 7.5 min [a]; *m/e* 430.1 (M+H); HRMS: calculated 430.1330 found 430.1332 (M+H).



[00535] Preparation of 4-[(E)-2-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}vinyl]-N-isobutylbenzenesulfonamide:

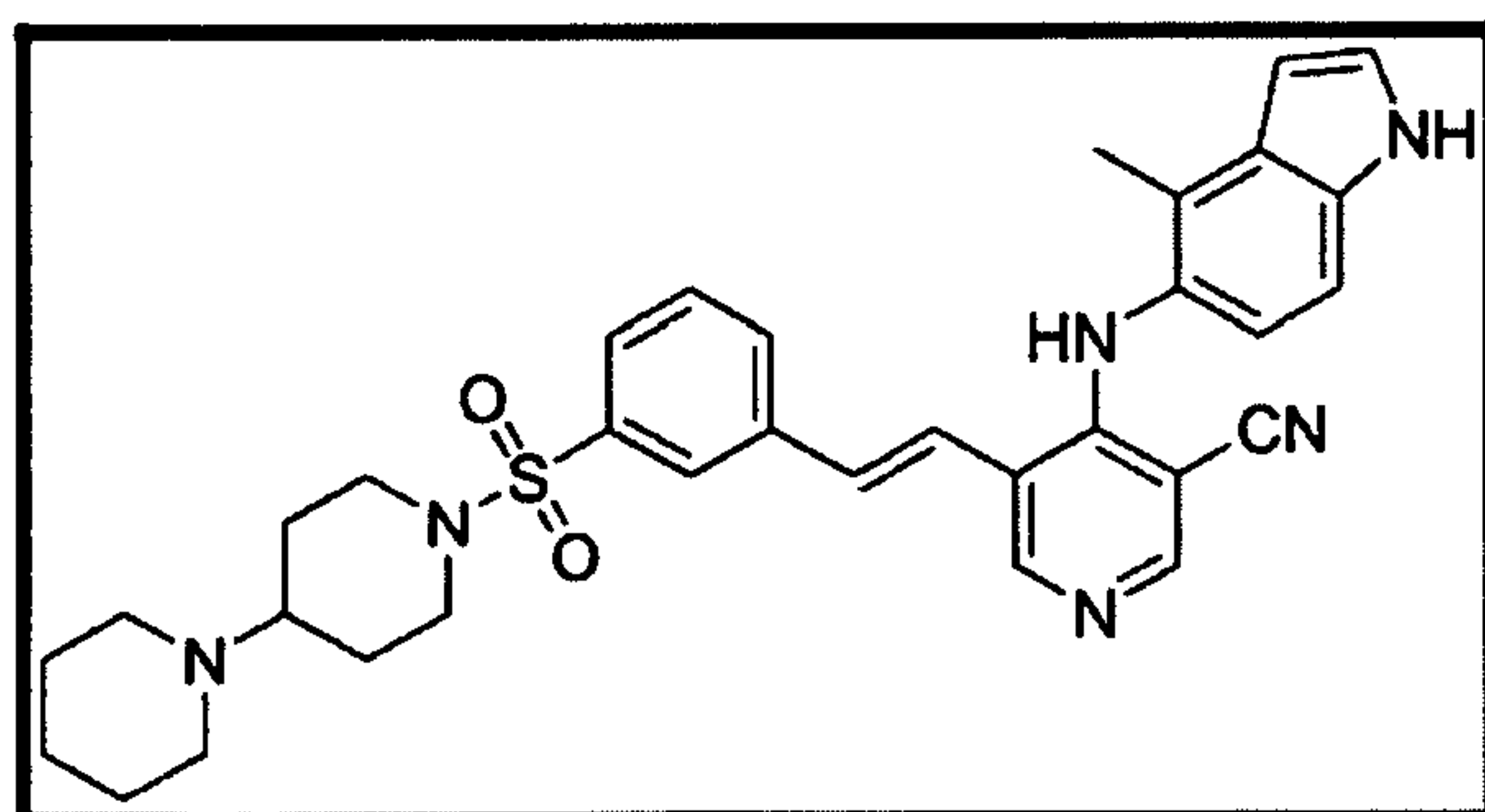
4-[(4-Methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile (90 mg, 0.33 mmol), 4-bromo-N-isobutylbenzenesulfonamide (93 mg, 0.32 mmol), Pd(OAc)₂ (7.2 mg, 0.032 mmol), P(*o*-Tol)₃

(9.7 mg, 0.037 mmol), and triethylamine (726 mg, 7.2 mmol) were dissolved in 2 mL DMF and heated to 90° C for 16 h. The reaction was cooled to room temperature and partitioned between chloroform and saturated sodium bicarbonate. The organic portion was dried (magnesium sulfate) and concentrated. The residue was dissolved in DMSO and purified by HPLC to give 5 mg of the title compound. HPLC: *rt* = 10.5 min [a]; *m/e* 486.2 (M+H); HRMS: calculated 486.1958 found 486.1959 (M+H).



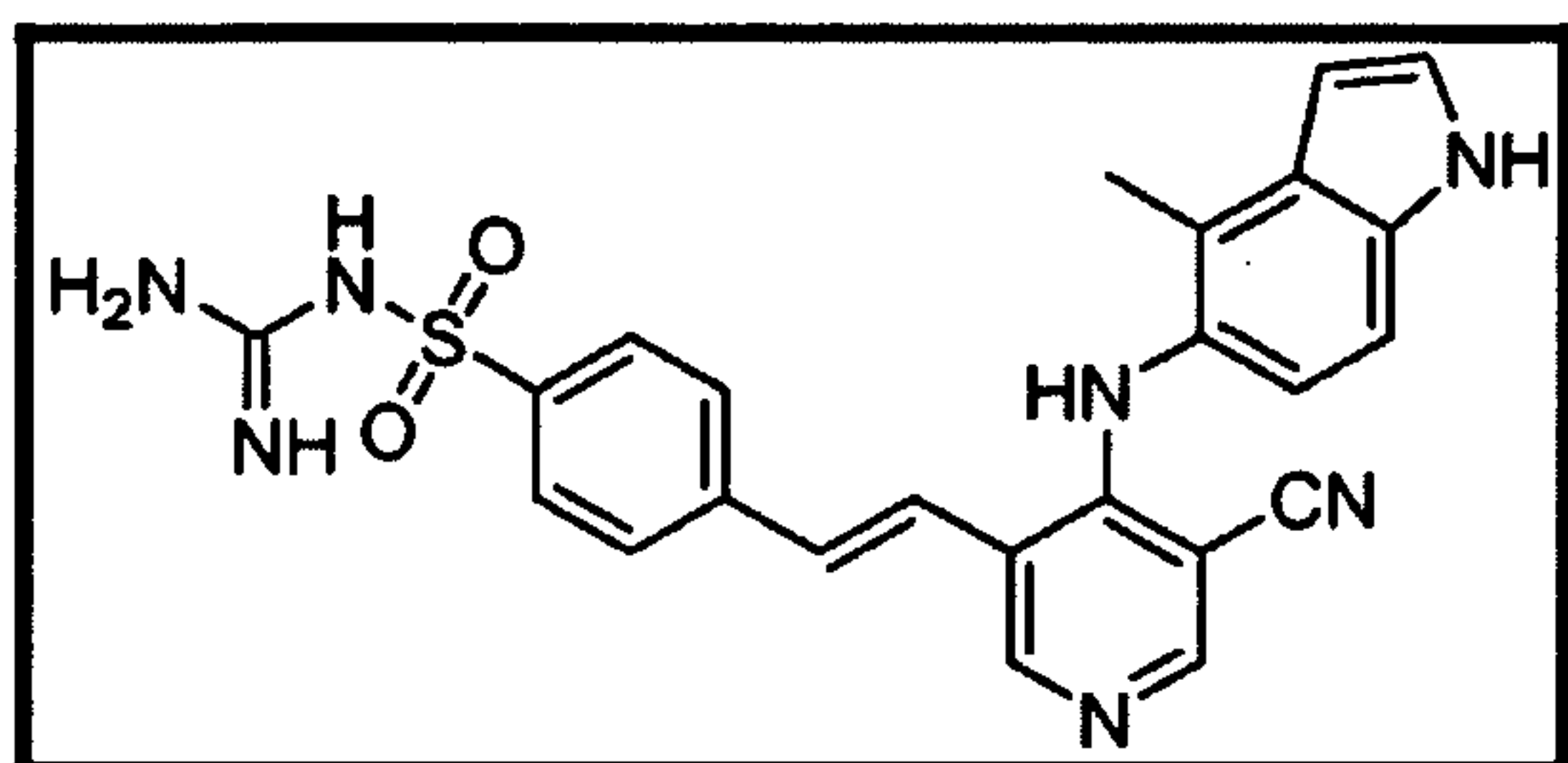
[00536] Preparation of 5-[(E)-2-(4-benzylmorpholin-2-yl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

4-[(4-methyl-1H-indol-5-yl)amino]-5-iodonicotinonitrile (2.1 g, 5.7 mmol), 4-benzyl-2-vinylmorpholine (1.2 mg, 5.7 mmol), Pd(OAc)₂ (65 mg, 0.28 mmol), P(*o*-Tol)₃ (96 mg, 0.31 mmol), and triethylamine (5.4 g, 54 mmol) were dissolved in 30 mL DMF and heated to 120° C for 2 h. The reaction was cooled to room temperature and partitioned between ethyl acetate and saturated sodium bicarbonate. The organic portion was dried (magnesium sulfate) and concentrated. A portion of the residue was dissolved in DMSO and purified by HPLC to give 11 mg of the title compound. HPLC: 92.0%, *rt* = 5.4 min [a]; *m/e* 450.3 (M+H); HRMS: calculated 450.2288 found 450.2289 (M+H).



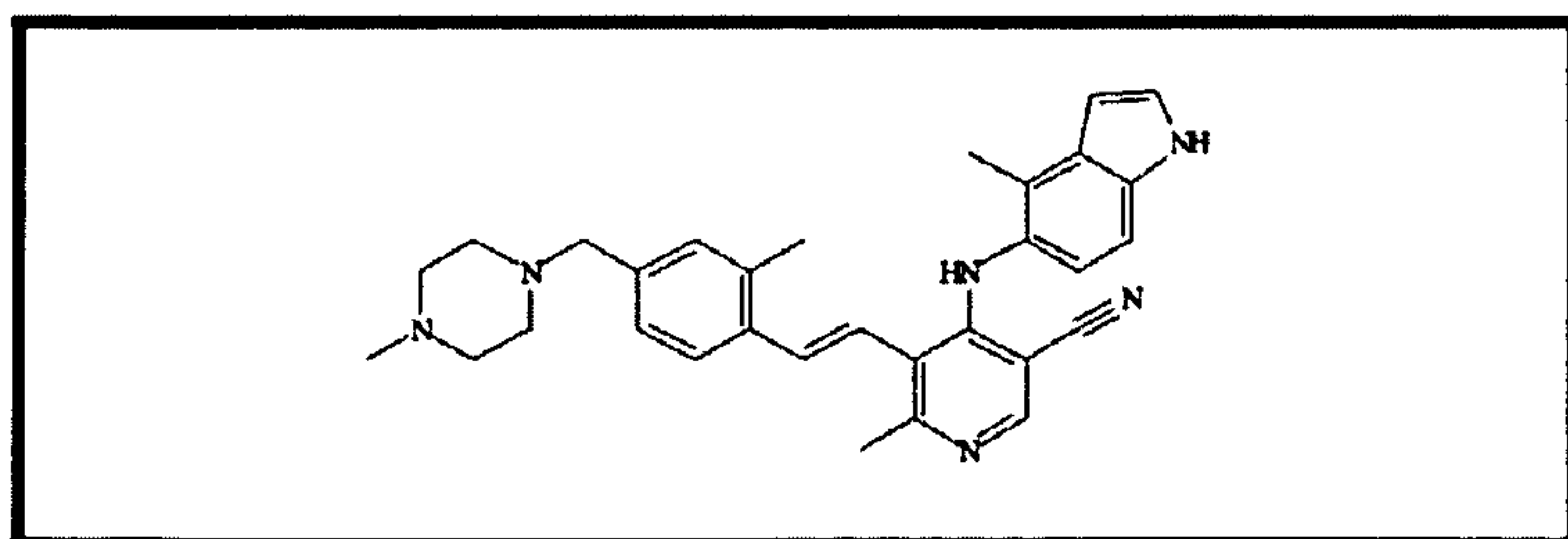
[00537] Preparation of 5-[(E)-2-[3-(1,4'-bipiperidin-1'-yl)sulfonyl]phenyl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile (107 mg, 0.39 mmol), 1'-(3-bromophenylsulfonyl)-1,4'-bipiperidine (151 mg, 0.39 mmol), Pd(OAc)₂ (7.0 mg, 0.031 mmol), P(o-Tol)₃ (14 mg, 0.046 mmol), and triethylamine (726 mg, 7.2 mmol) were dissolved in 2 mL DMF and heated to 90° C for 16 h. The reaction was cooled to room temperature and partitioned between chloroform and saturated sodium bicarbonate. The organic portion was dried (magnesium sulfate) and concentrated. The residue was dissolved in DMSO and purified by HPLC to give 13.1 mg of the title compound. HPLC: rt = 7.6 min [a]; m/e 581.5 (M+H); HRMS: calculated 581.2693 found 581.2693 (M+H).



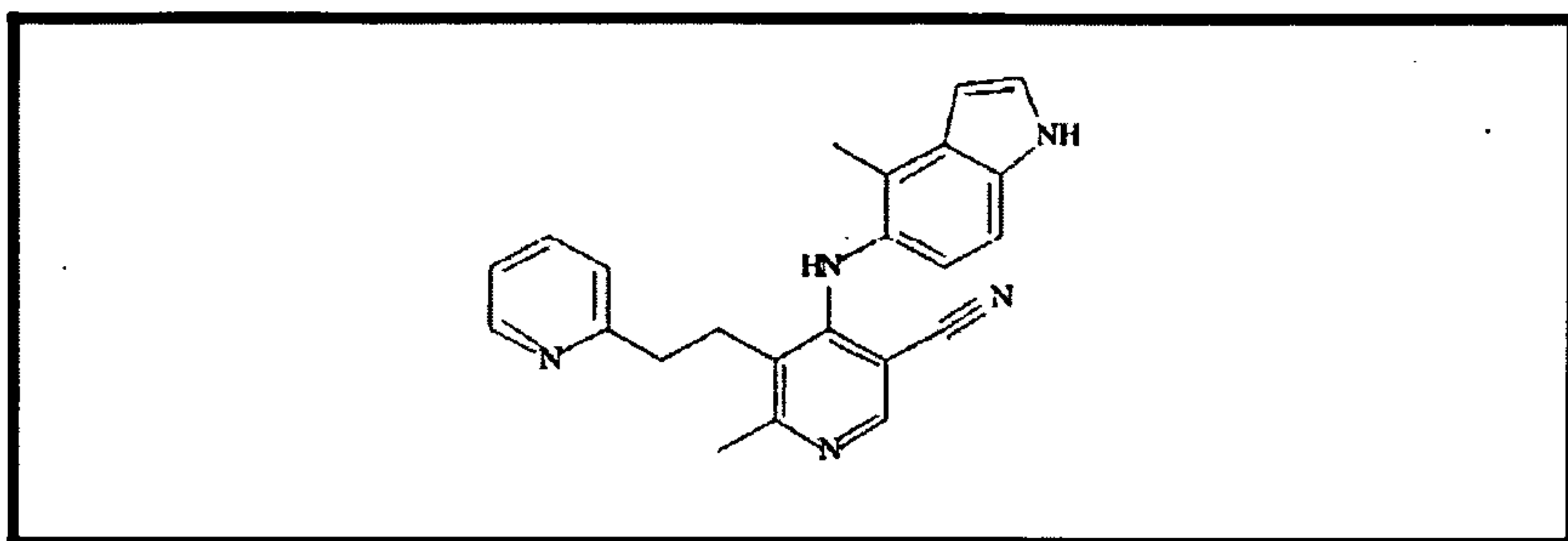
[00538] Preparation of N-carbamimidoyl-4-[(E)-2-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}vinyl]benzenesulfonamide:

4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile (90 mg, 0.33 mmol), 4-bromo-N-carbamimidoylbenzenesulfonamide (70 mg, 0.25 mmol), Pd(OAc)₂ (6.0 mg, 0.027 mmol), P(o-Tol)₃ (12 mg, 0.039 mmol), and triethylamine (726 mg, 7.2 mmol) were dissolved in 2 mL DMF and heated to 90° C for 16 h. The reaction was cooled to room temperature and partitioned between chloroform and saturated sodium bicarbonate. The organic portion was dried (magnesium sulfate) and concentrated. The residue was dissolved in DMSO and purified by HPLC to give 2.8 mg of the title compound. HPLC: 93.5%, rt = 7.3 min [a]; m/e 472.3 (M+H); HRMS: calculated 472.1550 found 472.1550 (M+H).m/e 204.1 (M+H)



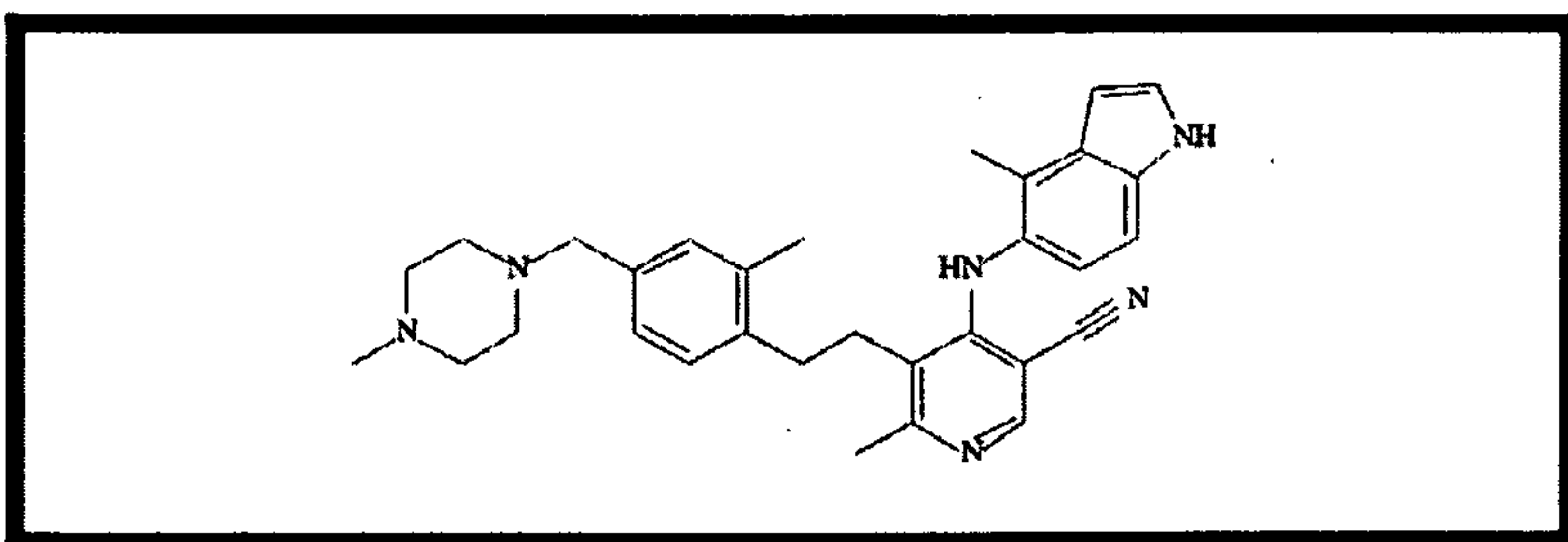
[00539] Preparation of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{2-methyl-4-[(4-methylpiperazin-1-yl)methyl]phenyl}ethenyl]pyridine-3-carbonitrile:

The title compound was prepared from 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile and 1-(4-iodo-3-methylbenzyl)-4-methylpiperazine via the procedure to prepare 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-pyridin-2-ylvinyl]nicotinonitrile to give 202 mg (83%) of the desired product as a tan solid, MS (ESI) m/z 491.3; HPLC: 98.0% at 215 nm, $rt = 5.5$ min [a].



[00540] Preparation of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-(2-pyridin-2-ylethyl)pyridine-3-carbonitrile:

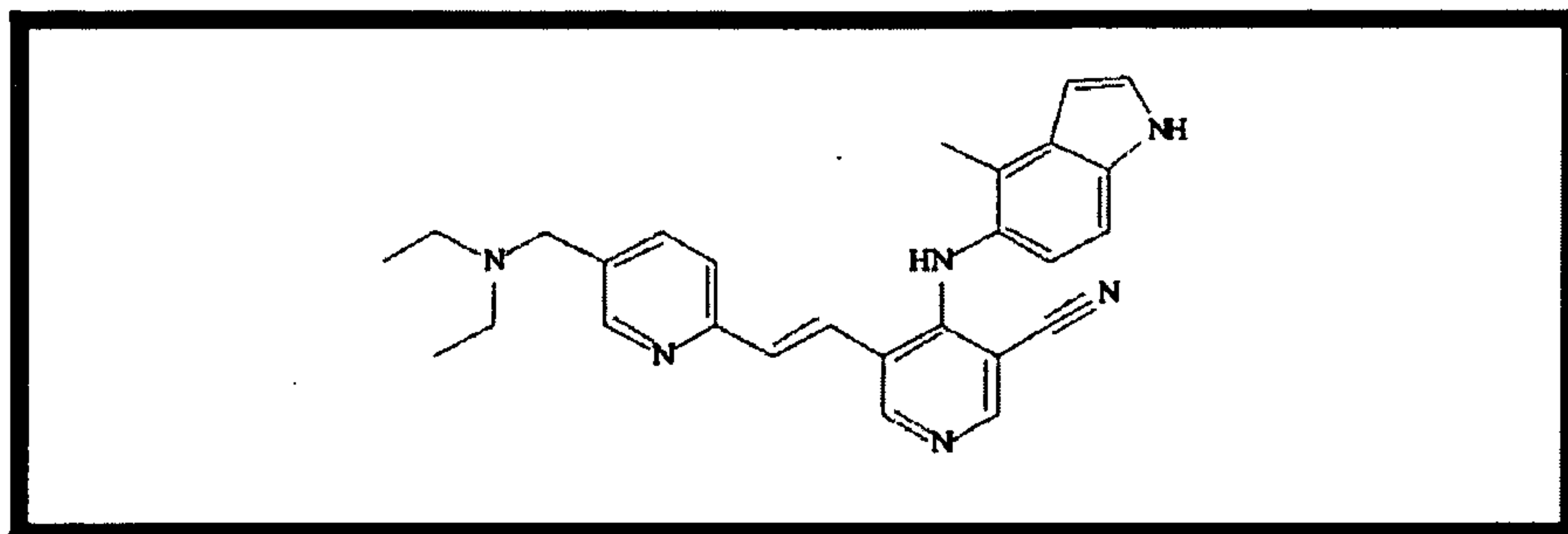
The title compound was prepared by the procedure described for the preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-(2-{6-[(4-pyrrolidin-1-yl)piperidin-1-yl)methyl]pyridin-2-yl}ethyl)nicotinonitrile and was isolated as a tan solid (80 mg, 79%). MS 368.2 (M+H); HPLC: 91.6% at 216 nm, $rt = 5.6$ min [a].



[00541] Preparation of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-(2-{2-methyl-4-[(4-methylpiperazin-1-yl)methyl]phenyl}ethyl)nicotinonitrile:

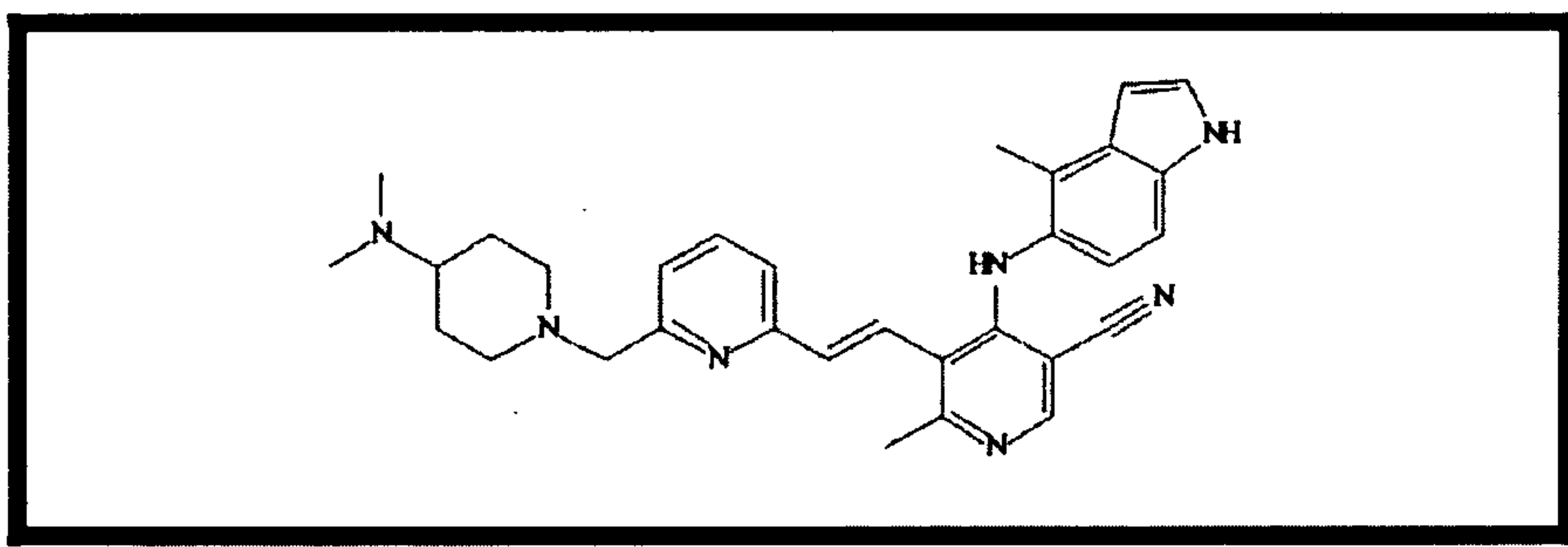
The title compound was prepared by the procedure described for the preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-(2-{6-[(4-pyrrolidin-1-yl)piperidin-1-yl)methyl]pyridin-2-yl}ethyl)nicotinonitrile

nicotinonitrile and was isolated as a tan solid (91 mg, 60%). MS 493.5 (M+H); HPLC: 91.4% at 216 nm, rt = 5.4 min [a].



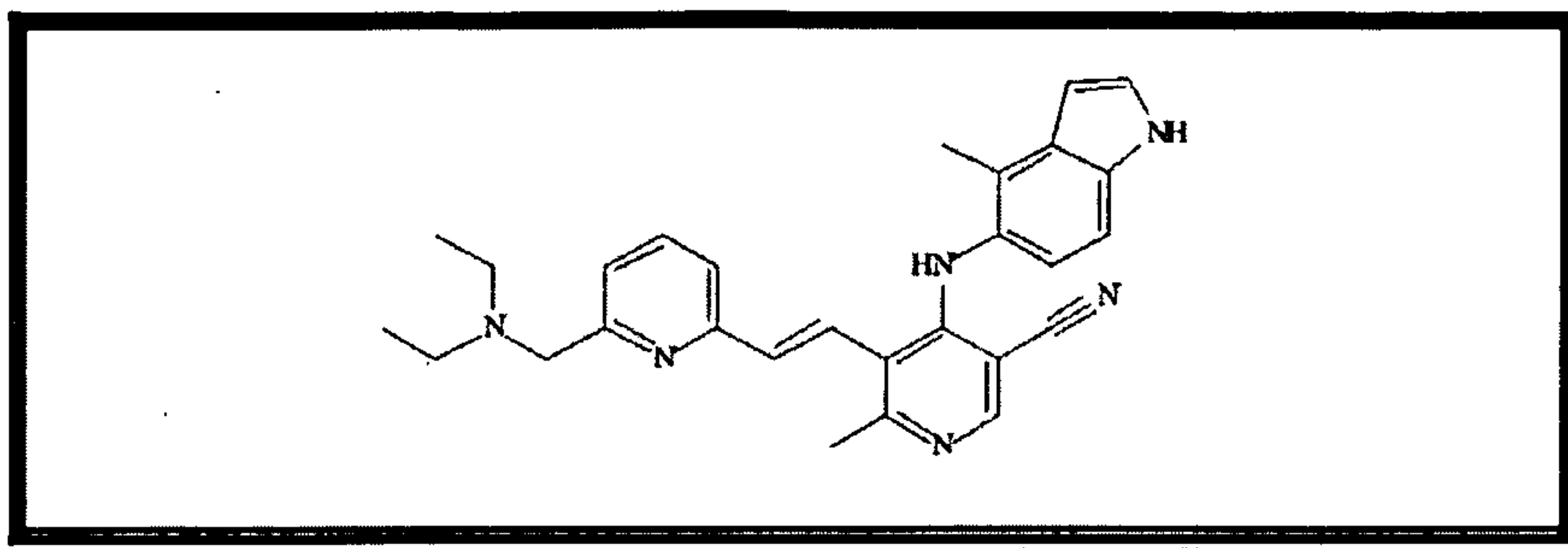
[00542] Preparation of 5-[(E)-2-{5-[(diethylamino)methyl]pyridin-2-yl}ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

The title compound was prepared by the procedure described for the preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(piperidin-1-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile and was isolated as a yellow solid (29 mg, 25%). MS 437.3 (M+H); HPLC: 96.6% at 216 nm, rt = 6.2 min [a].



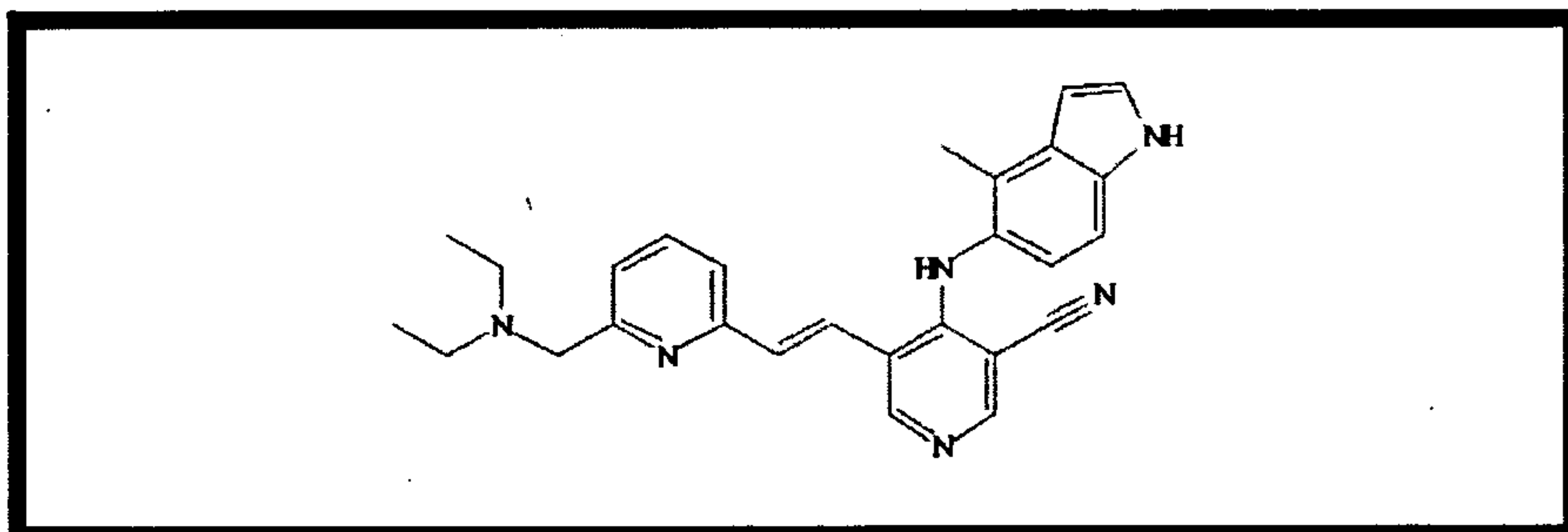
[00543] Preparation of 5-[(E)-2-{6-{[4-(dimethylamino)piperidin-1-yl]methyl}pyridin-2-yl}ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

The title compound was prepared by the procedure for the preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(piperidin-1-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile and was isolated as a yellow solid (16 mg, 14%). MS 506.4 (M+H); : 93.5% at 216 nm, rt = 4.8 min [a].



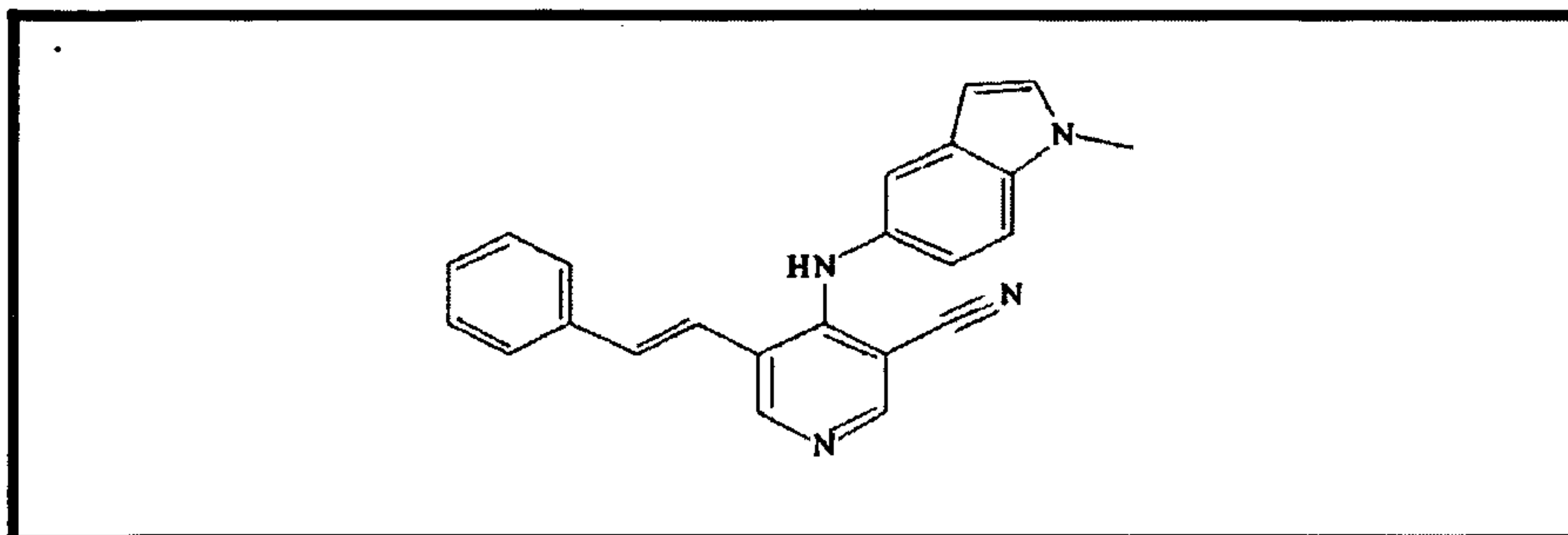
[00544] Preparation of 5-[(E)-2-{6-[(diethylamino)methyl]pyridin-2-yl}ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

The title compound was prepared by the procedure described for the preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(piperidin-1-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile and was isolated as a yellow solid (58 mg, 50%). MS 451.2 (M+H); HPLC: 99.2% at 216 nm, rt = 5.5 min [a].



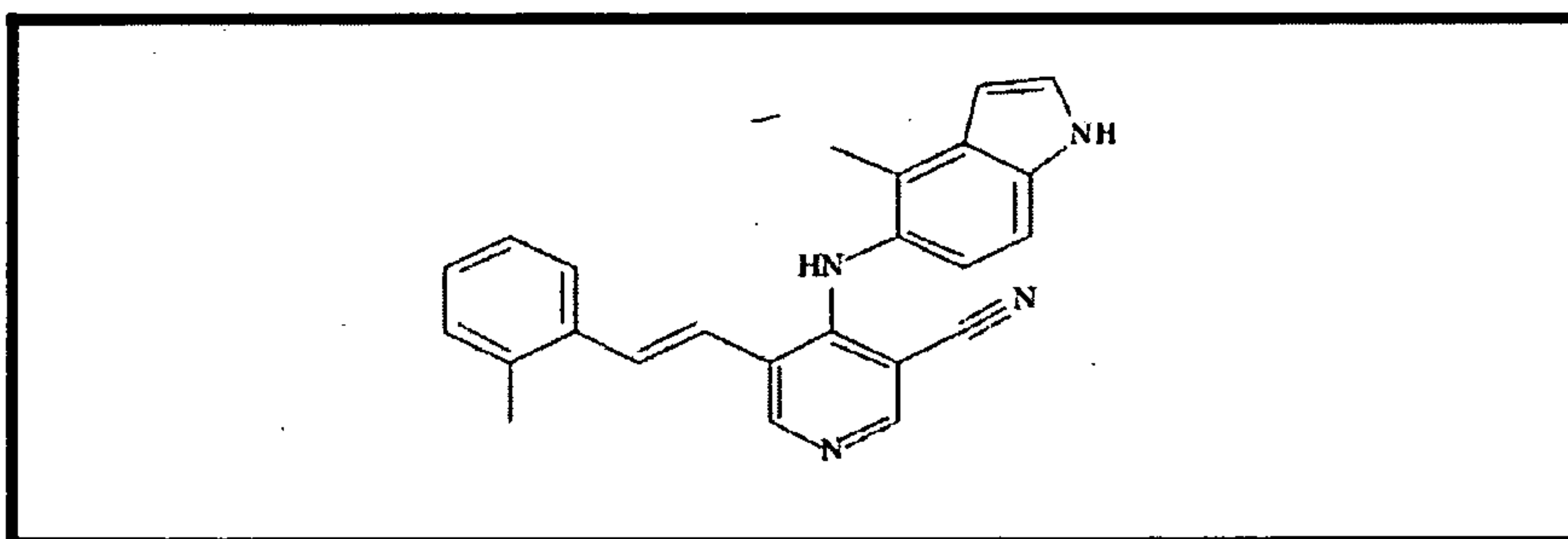
[00545] Preparation of 5-[(E)-2-{6-[(diethylamino)methyl]pyridin-2-yl}ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

The title compound was prepared by the procedure for the preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(piperidin-1-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile and was isolated as a yellow solid (78 mg, 69%). MS 437.2 (M+H); HPLC: 98.9% at 216 nm, rt = 5.8 min [a].



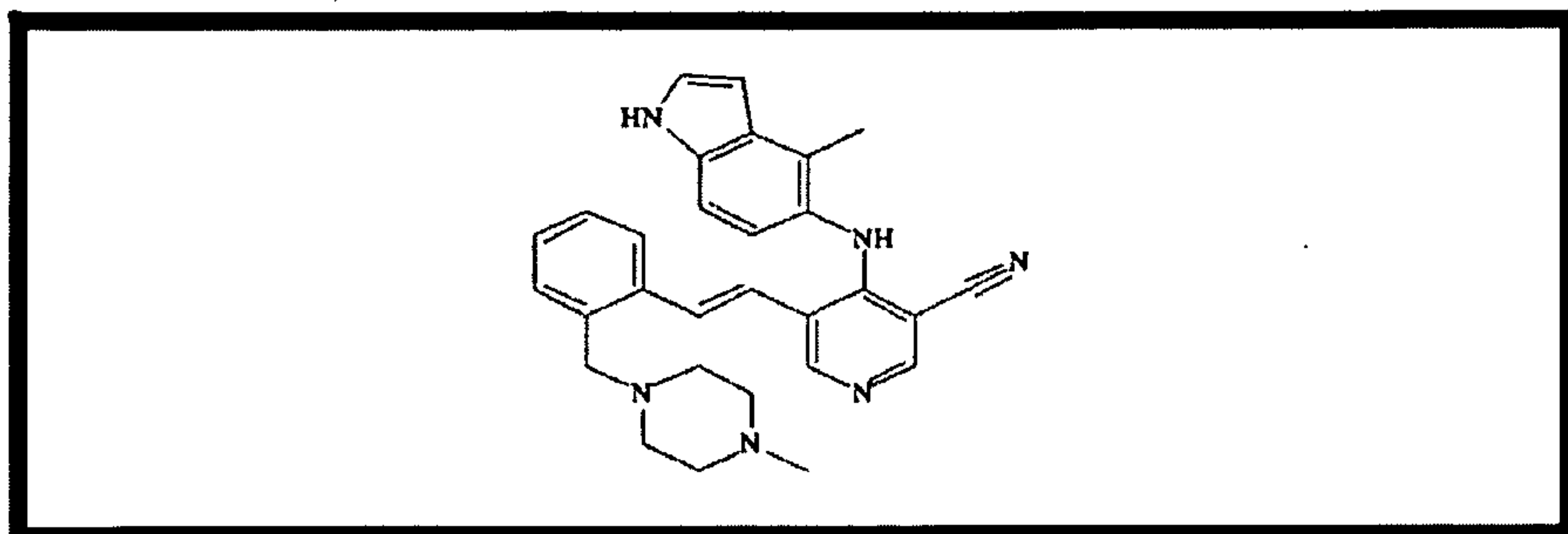
[00546] Preparation of 4-[(1-methyl-1H-indol-5-yl)amino]-5-[(E)-2-phenylethenyl]pyridine-3-carbonitrile:

A mixture of 4-chloro-5-[(E)-2-phenylvinyl]nicotinonitrile (120 mg, 0.5 mmol), 1-methyl-1H-indol-5-amine (Ian T. Forbes et al, *J. Med. Chem* 1993, 36, 1104) (73.1 mg, 0.5 mmol) in 3 mL of ethanol was heated at reflux for 17 h, then cooled to room temperature. The precipitate was filtered, washed with ethanol and diethyl ether. After drying in vacuo, 155.6 mg (81%) of 4-[(1-methyl-1H-indol-5-yl)amino]-5-[(E)-2-phenylethenyl]pyridine-3-carbonitrile was obtained as a yellow solid, MS (ESI) m/z 351.2 (M+H)⁺; HPLC: t_r = 10.3 min [a].



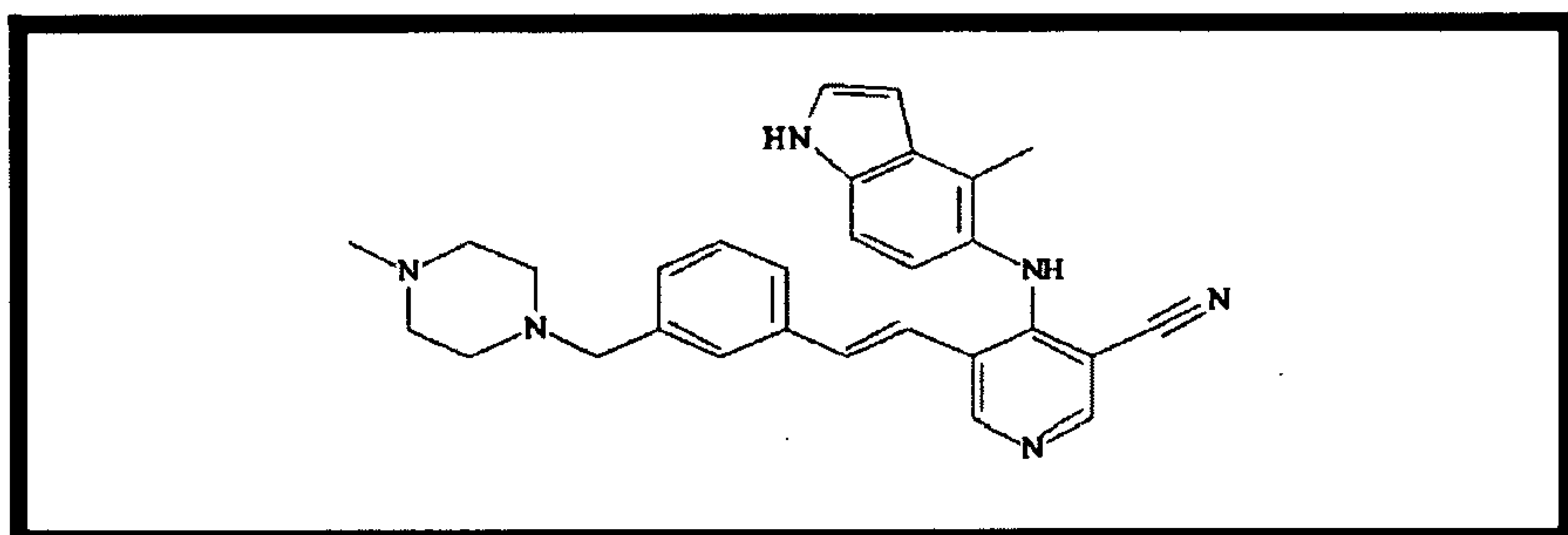
[00547] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(2-methylphenyl)ethenyl]pyridine-3-carbonitrile:

A mixture of 4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile (120 mg, 0.44 mmol), 2-iodotoluene (122.5 mg, 0.53 mmol), Pd(OAc)₂ (19.7 mg, 0.088 mmol) and tri-*o*-tolylphosphine (8.5 mg, 0.028 mmol) in 0.6 mL of triethylamine and 2.5 mL of DMF was heated at 120°C for 2 h, then cooled to room temperature and concentrated *in vacuo*. The residue was purified by column chromatography, eluting with a gradient of 5% ethyl acetate in dichloromethane to 15% ethyl acetate in dichloromethane to provide 83.0 mg (52%) of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(2-methylphenyl)ethenyl]pyridine-3-carbonitrile as a yellow solid, MS (ESI) m/z 365.2; HPLC: t_r = 14.8 min [b].



[00548] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{2-[(4-methylpiperazin-1-yl)methyl]phenyl}ethenyl]pyridine-3-carbonitrile:

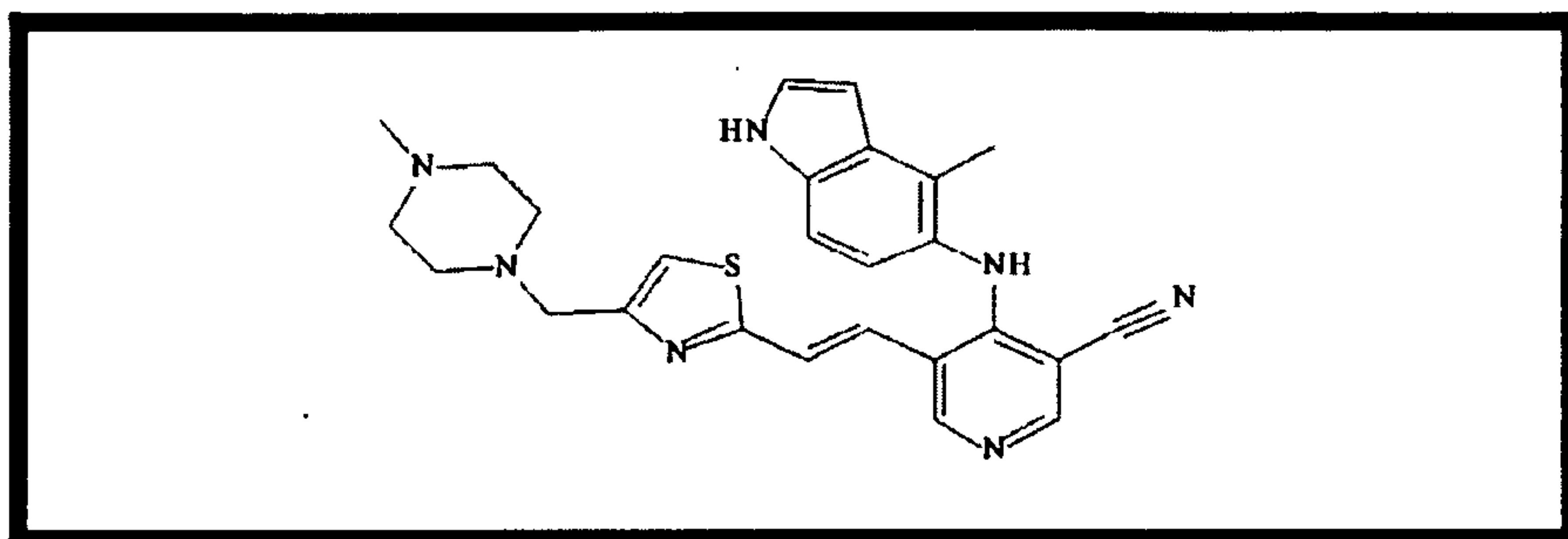
A mixture of 4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile (150 mg, 0.54 mmol), 1-(2-bromobenzyl)-4-methylpiperazine (218.0 mg, 0.81 mmol), Pd(OAc)₂ (49.4 mg, 0.22 mmol) and tri-*o*-tolylphosphine (32.8 mg, 0.108 mmol) in 0.6 mL of triethylamine and 2.5 mL of DMF was heated at 120°C for 4 h, then cooled to room temperature and concentrated *in vacuo*. The residue was purified by column chromatography, eluting with a gradient of 5% methanol in dichloromethane to 20% methanol in dichloromethane to provide 17.4 mg (7%) of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{2-[(4-methylpiperazin-1-yl)methyl]phenyl}ethenyl]pyridine-3-carbonitrile as a yellow solid, MS (ESI) *m/z* 463.2; HPLC: *rt* = 6.5 min [a].



[00549] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{3-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]nicotinonitrile:

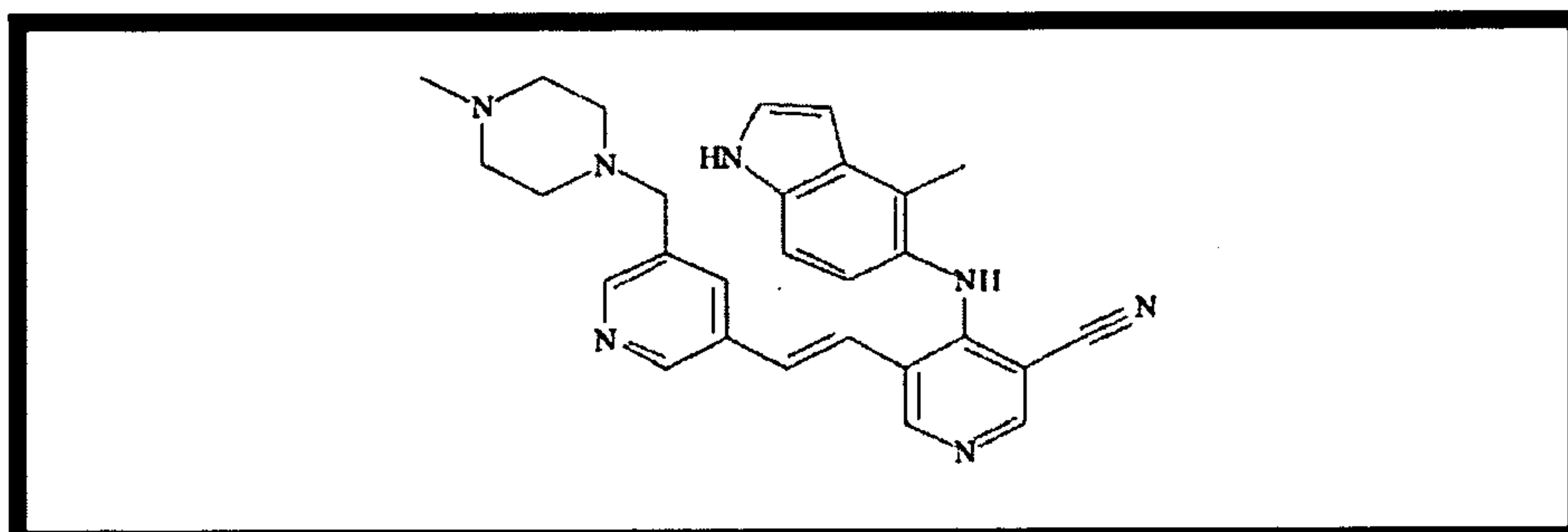
A mixture of 4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile (100 mg, 0.36 mmol), 1-(3-bromobenzyl)-4-methylpiperazine (116.3 mg, 0.43 mmol), Pd(OAc)₂ (16.2 mg, 0.072 mmol) and tri-*o*-tolylphosphine (7.7 mg, 0.025 mmol) in 0.75 mL of triethylamine and 3.0 mL of DMF was heated at 120°C for 2.5 h, then cooled to room temperature and partitioned between dichloromethane and aqueous saturated sodium bicarbonate. The organic phase was dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column

chromatography, eluting with a gradient of 2% methanol in dichloromethane to 12% methanol in dichloromethane to provide 64.8 mg (39%) of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{3-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]nicotinonitrile as an off white solid, MS (ESI) m/z 463.3; HPLC rt = 5.9 min [a].



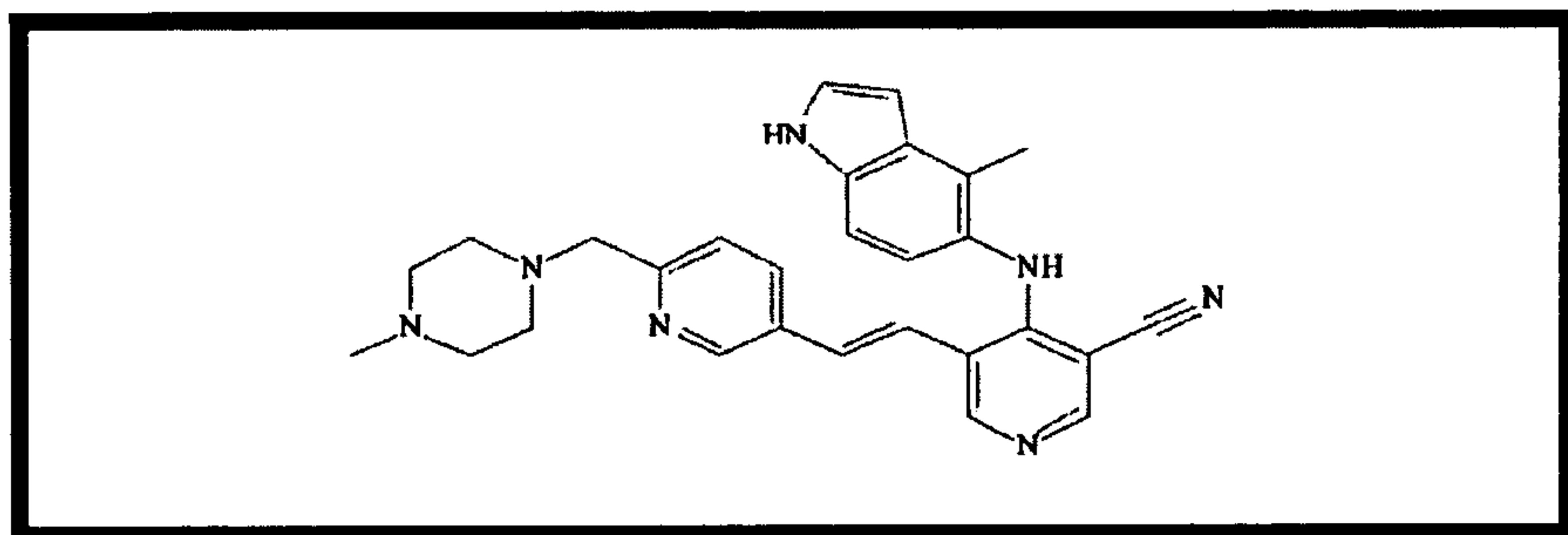
[00550] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{4-[(4-methylpiperazin-1-yl)methyl]-1,3-thiazol-2-yl}ethenyl]pyridine-3-carbonitrile:

A mixture of 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (297.0 mg, 0.79 mmol), 1-[(2-ethenyl-1,3-thiazol-4-yl)methyl]-4-methylpiperazine (120.0 mg, 0.53 mmol), $\text{Pd}(\text{OAc})_2$ (47.6 mg, 0.22 mmol) and tri-*o*-tolyl phosphine (22.6 mg, 0.074 mmol) in 1.0 mL of triethylamine and 3.5 mL of DMF was heated at 120°C for 3 h, then cooled to room temperature and partitioned between dichloromethane and aqueous saturated sodium bicarbonate. The organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography, eluting with a gradient of 5% methanol in dichloromethane to 20% methanol in dichloromethane to provide 103 mg (41%) of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{4-[(4-methylpiperazin-1-yl)methyl]-1,3-thiazol-2-yl}ethenyl]pyridine-3-carbonitrile as a yellow solid, MS (ESI) m/z 470.1; HPLC: rt = 5.1 min [a].



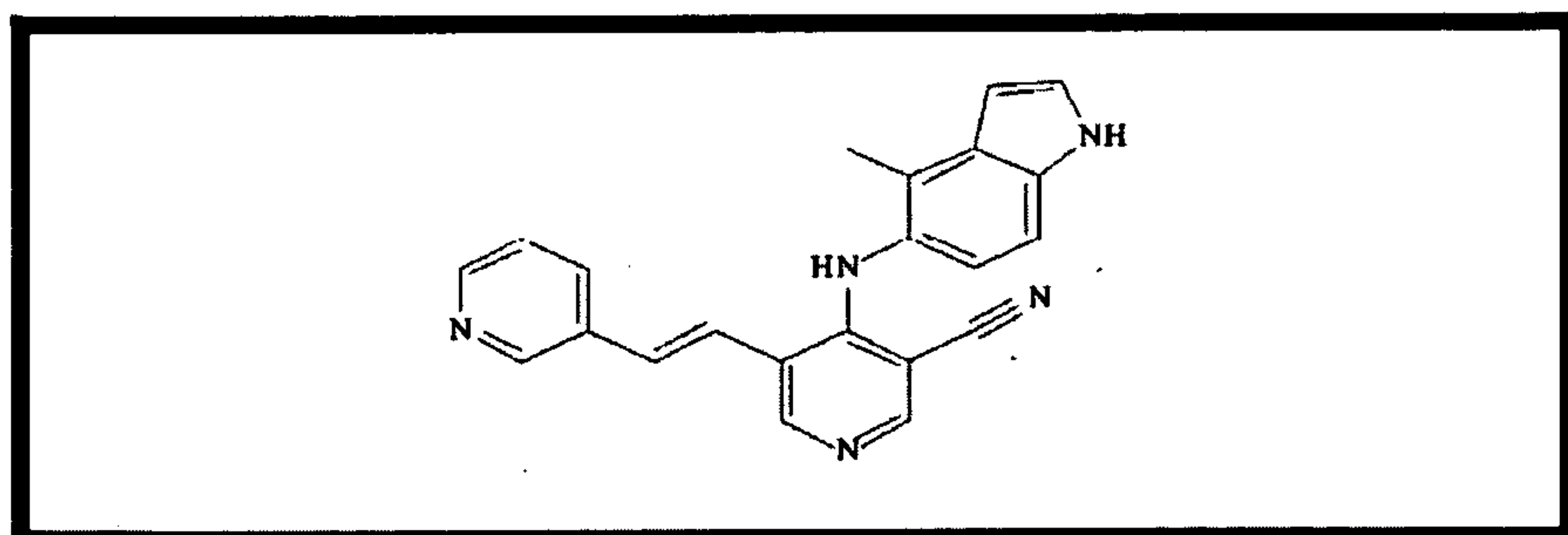
[00551] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-3-yl}ethenyl]pyridine-3-carbonitrile:

Following the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{4-[(4-methylpiperazin-1-yl)methyl]-1,3-thiazol-2-yl}ethenyl]pyridine-3-carbonitrile, 25.0 mg (10%) of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-3-yl}ethenyl]pyridine-3-carbonitrile was prepared as a yellow solid via the reaction of 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile with 1-methyl-4-[(5-vinylpyridin-3-yl)methyl]piperazine, MS (ESI) m/z 464.2; HPLC: t_r = 4.4 min [a].



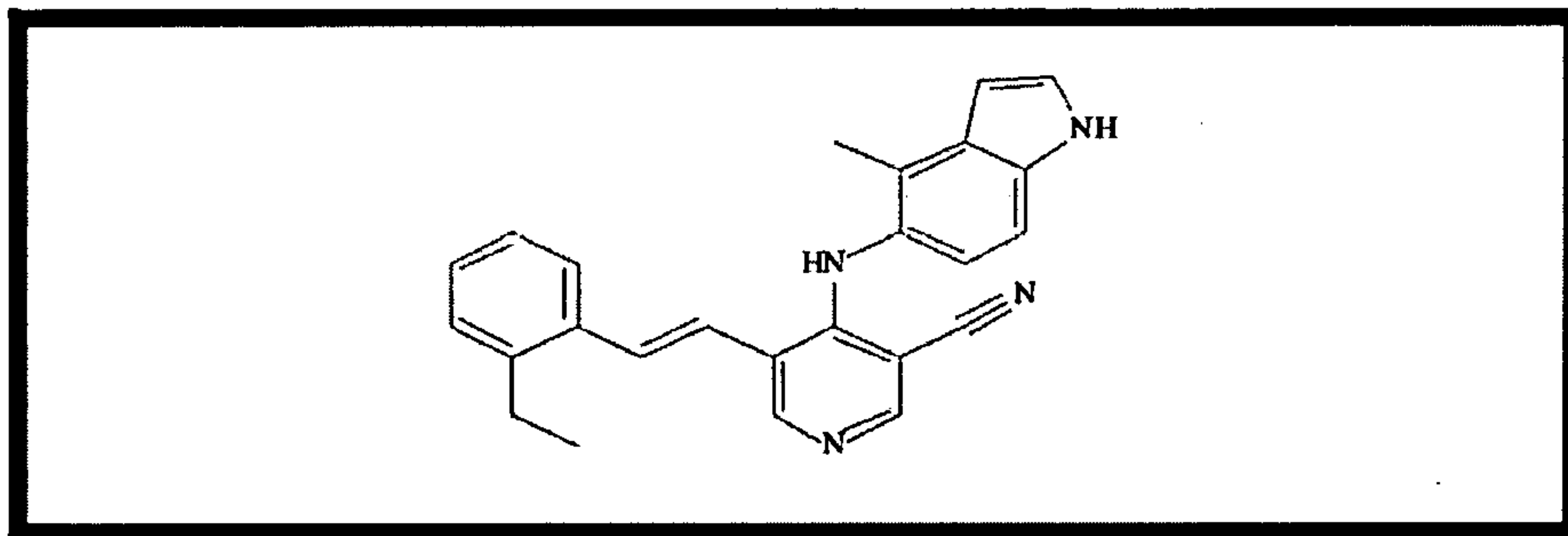
[00552] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{6-[(4-methylpiperazin-1-yl)methyl]pyridin-3-yl}ethenyl]pyridine-3-carbonitrile:

Following the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{4-[(4-methylpiperazin-1-yl)methyl]-1,3-thiazol-2-yl}ethenyl]pyridine-3-carbonitrile, 41.2 mg (16%) of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{6-[(4-methylpiperazin-1-yl)methyl]pyridin-3-yl}ethenyl]pyridine-3-carbonitrile was prepared as a yellow solid via the reaction of 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile with 1-methyl-4-[(5-vinylpyridin-2-yl)methyl]piperazine, MS (ESI) m/z 464.3; HPLC: t_r = 10.5 min [b].



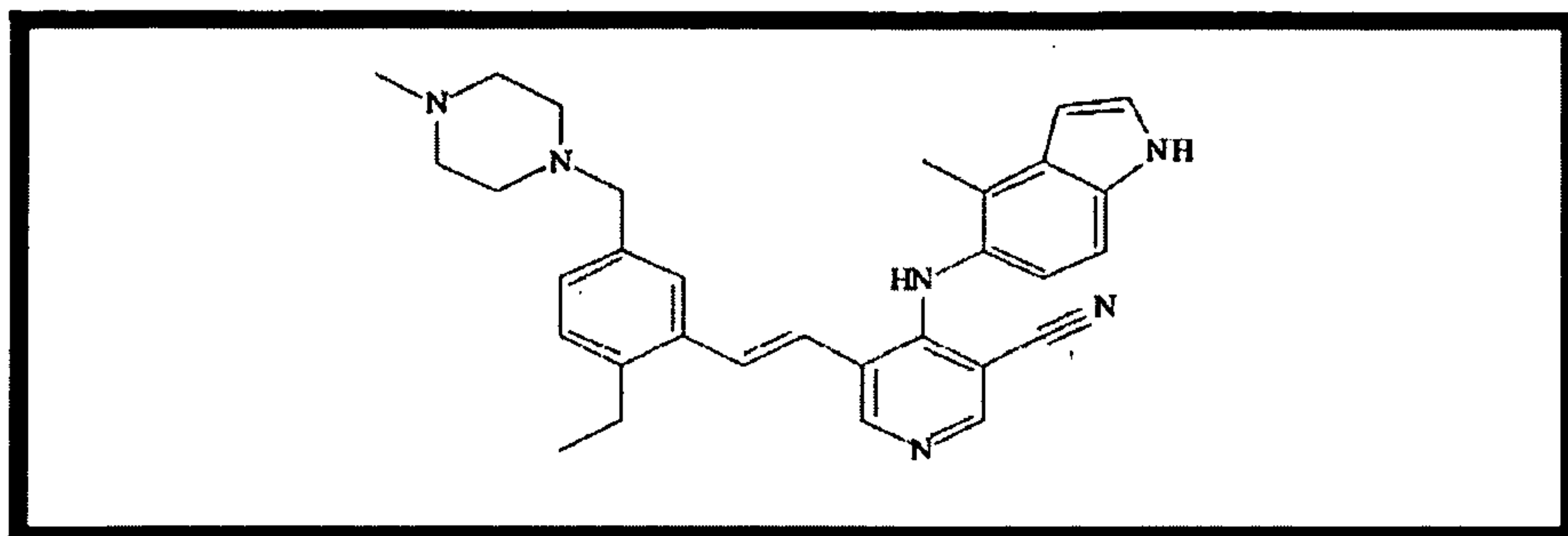
[00553] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-pyridin-3-ylethenyl]pyridine-3-carbonitrile:

A mixture of 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (150.0 mg, 0.40 mmol), 3-vinylpyridine (54.6 mg, 0.52 mmol), Pd(OAc)₂ (18 mg, 0.08 mmol) and tri-*o*-tolyl phosphine (8.5 mg, 0.028 mmol) in 0.70 mL of triethylamine and 2.5 mL of DMF was heated at 120°C for 3 h, then cooled to room temperature and partitioned between dichloromethane and aqueous saturated sodium bicarbonate. The organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography, eluting with a gradient of 2% methanol in ethyl acetate to 6% methanol in ethyl acetate to provide 14.3 mg (10%) of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-pyridin-3-ylethenyl]pyridine-3-carbonitrile as a deep yellow solid, MS (ESI) *m/z* 352.1; HPLC: *rt* = 5.6 min [a].



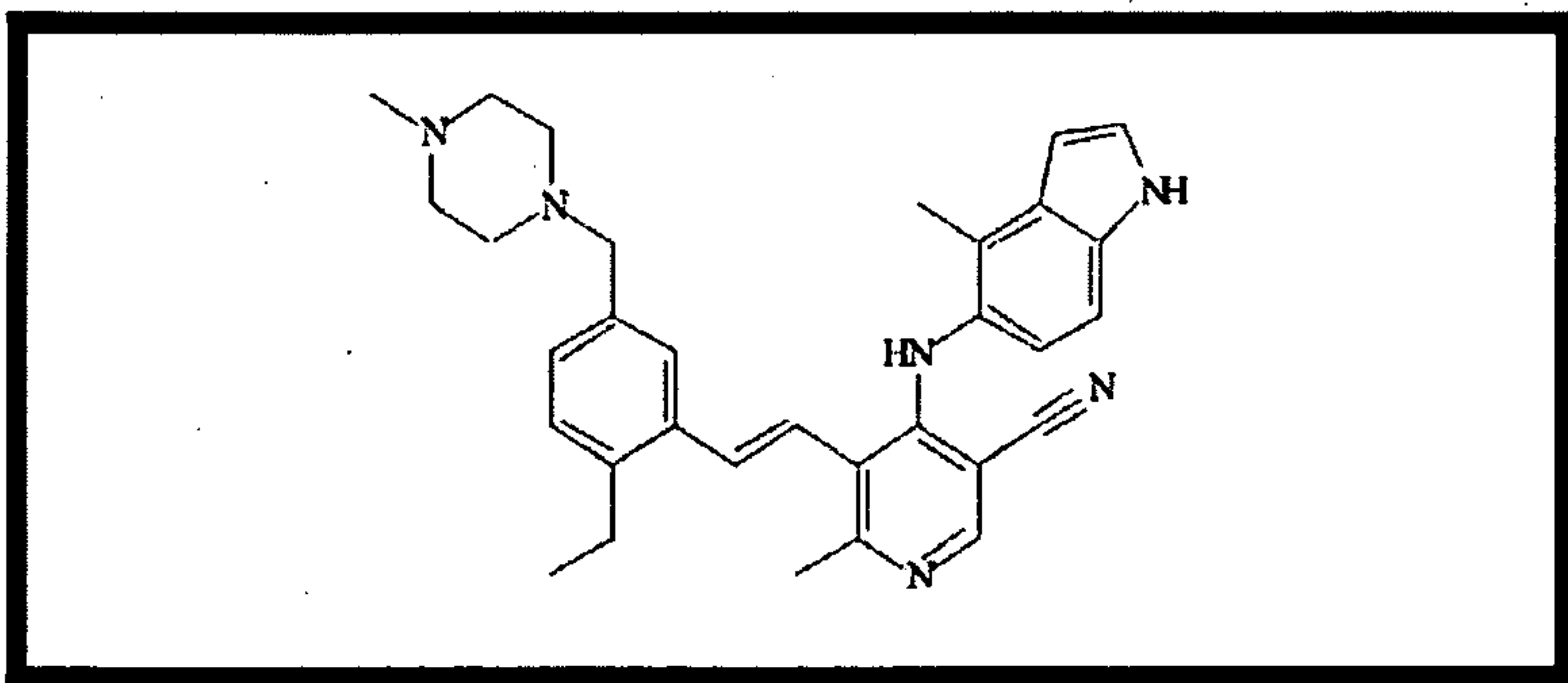
[00554] Preparation of 5-[(E)-2-(2-ethylphenyl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

Following the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(2-methylphenyl)ethenyl]pyridine-3-carbonitrile, 76.1 mg (46%) of 5-[(E)-2-(2-ethylphenyl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile was prepared as a yellow solid via the reaction of 4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile with 2-ethyl iodobenzene, MS (ESI) *m/z* 379.2; HPLC: *rt* = 11 min [a].



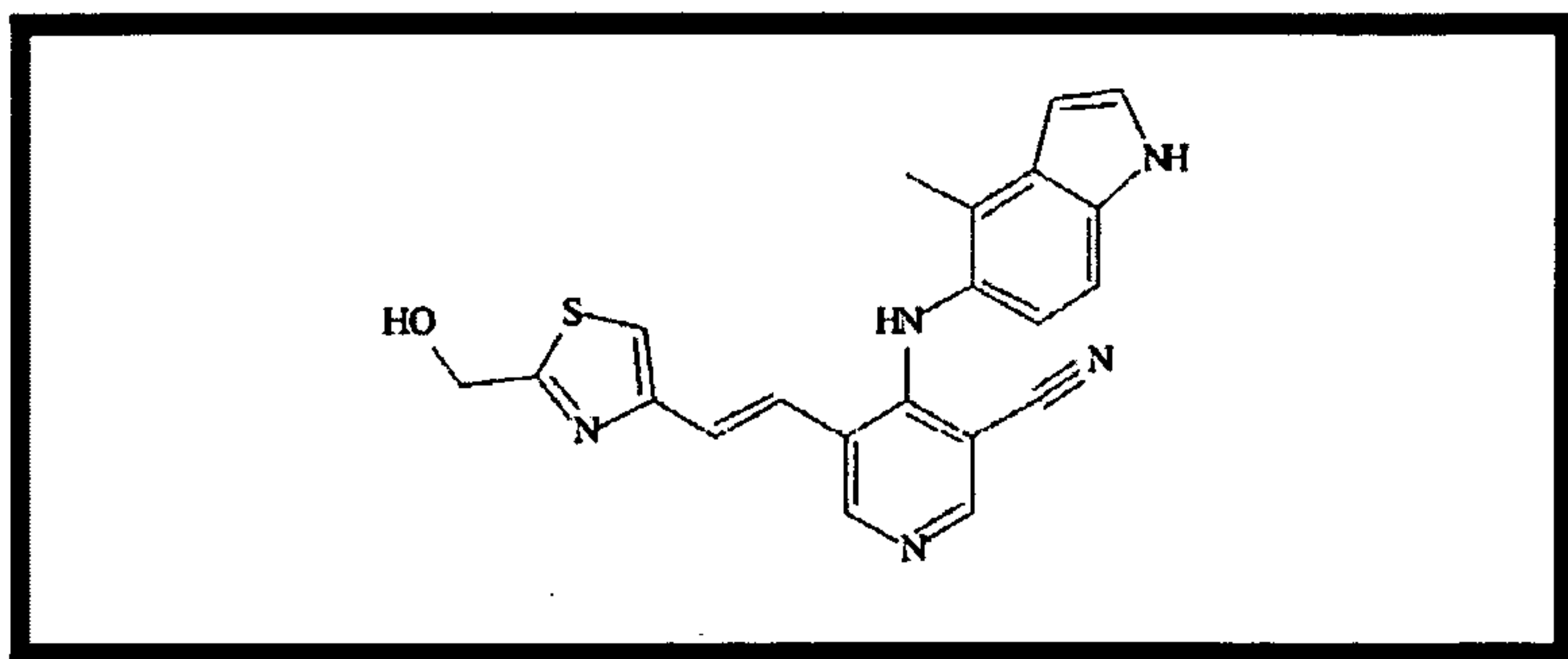
[00555] Preparation of 5-[(E)-2-{2-ethyl-5-[(4-methylpiperazin-1-yl)methyl]phenyl}ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

A mixture of 4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile (150.9 mg, 0.55 mmol), 1-(3-bromo-4-ethylbenzyl)-4-methylpiperazine (150 mg, 0.50 mmol), Pd(OAc)₂ (22.5 mg, 0.1 mmol) and tri-*o*-tolylphosphine (10.7 mg, 0.035 mmol) in 0.7 mL of triethylamine and 2.5 mL of DMF was heated at 120°C for 4 h. The resulting mixture was cooled to room temperature, partitioned between dichloromethane and aqueous saturated sodium bicarbonate. The organic phase was dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography, eluting with a gradient of 5% methanol in ethyl acetate to 20% methanol in ethyl acetate to 20% methanol in ethyl acetate containing 0.5% of conc. aq. ammonium hydroxide. Repurification by preparative TLC, developing with 15% methanol in dichloromethane provided 97.8 mg (39%) of 5-[(E)-2-{2-ethyl-5-[(4-methylpiperazin-1-yl)methyl]phenyl}ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile as a yellow solid, MS (ESI) *m/z* 491.1; HPLC: *rt* = 6.7 min [a].



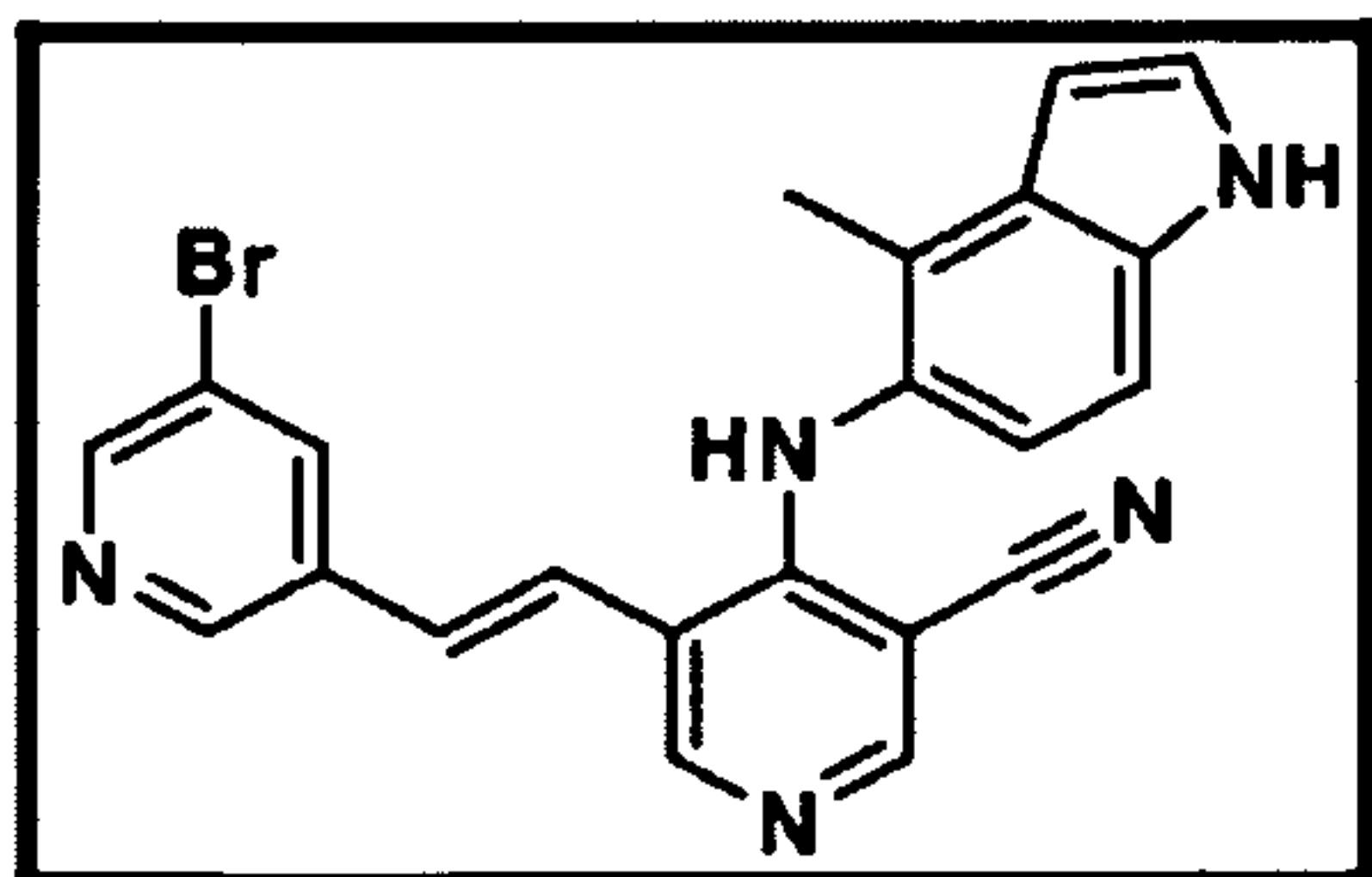
[00556] Preparation of 5-[(E)-2-{2-ethyl-5-[(4-methylpiperazin-1-yl)methyl]phenyl}ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

Following the procedure used to prepare 5-[(E)-2-{2-ethyl-5-[(4-methylpiperazin-1-yl)methyl]phenyl}ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile, 88.7 mg (35%) of 5-[(E)-2-{2-ethyl-5-[(4-methylpiperazin-1-yl)methyl]phenyl}ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile was prepared as an off-white solid via the reaction of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile with 1-(3-bromo-4-ethylbenzyl)-4-methylpiperazine, MS (ESI) m/z 505.1; HPLC: rt = 10.6 min [b].



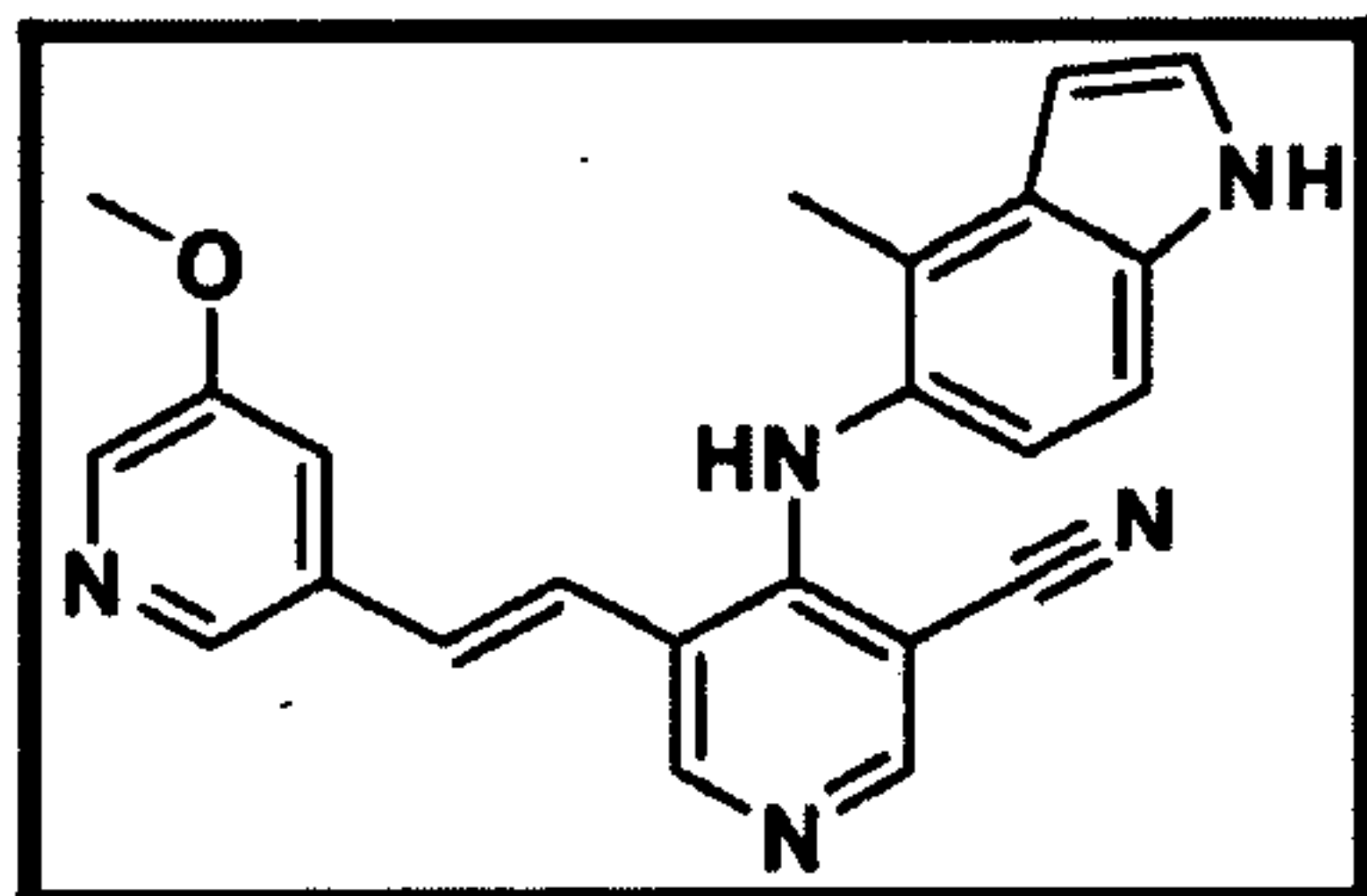
[00557] Preparation of 5-[(E)-2-[2-(hydroxymethyl)-1,3-thiazol-4-yl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

A mixture of 4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile (65 mmol), (4-bromo-1,3-thiazol-2-yl)methanol (Simeon, F. G. et al *J. Med. Chem.*, 2007, 50, 3256) (1.63 g, 8.40 mmol), $\text{Pd}(\text{OAc})_2$ (491.7 mg, 2.19 mmol) and tri-*o*-tolylphosphine (333.3 mg, 1.09 mmol) in 5 mL of triethylamine and 19 mL of DMF was heated at 120°C for 18 h. The resulting mixture was cooled to room temperature and partitioned between dichloromethane and aqueous saturated sodium bicarbonate. The organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography, eluting with a gradient of 50% ethyl acetate in hexane to 100% ethyl acetate to 1% methanol in ethyl acetate to provide 582.3 mg (41%) of 5-[(E)-2-[2-(hydroxymethyl)-1,3-thiazol-4-yl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile as a deep yellow solid, MS (ESI) m/z 388.1; HPLC: rt = 7.7 min [a].



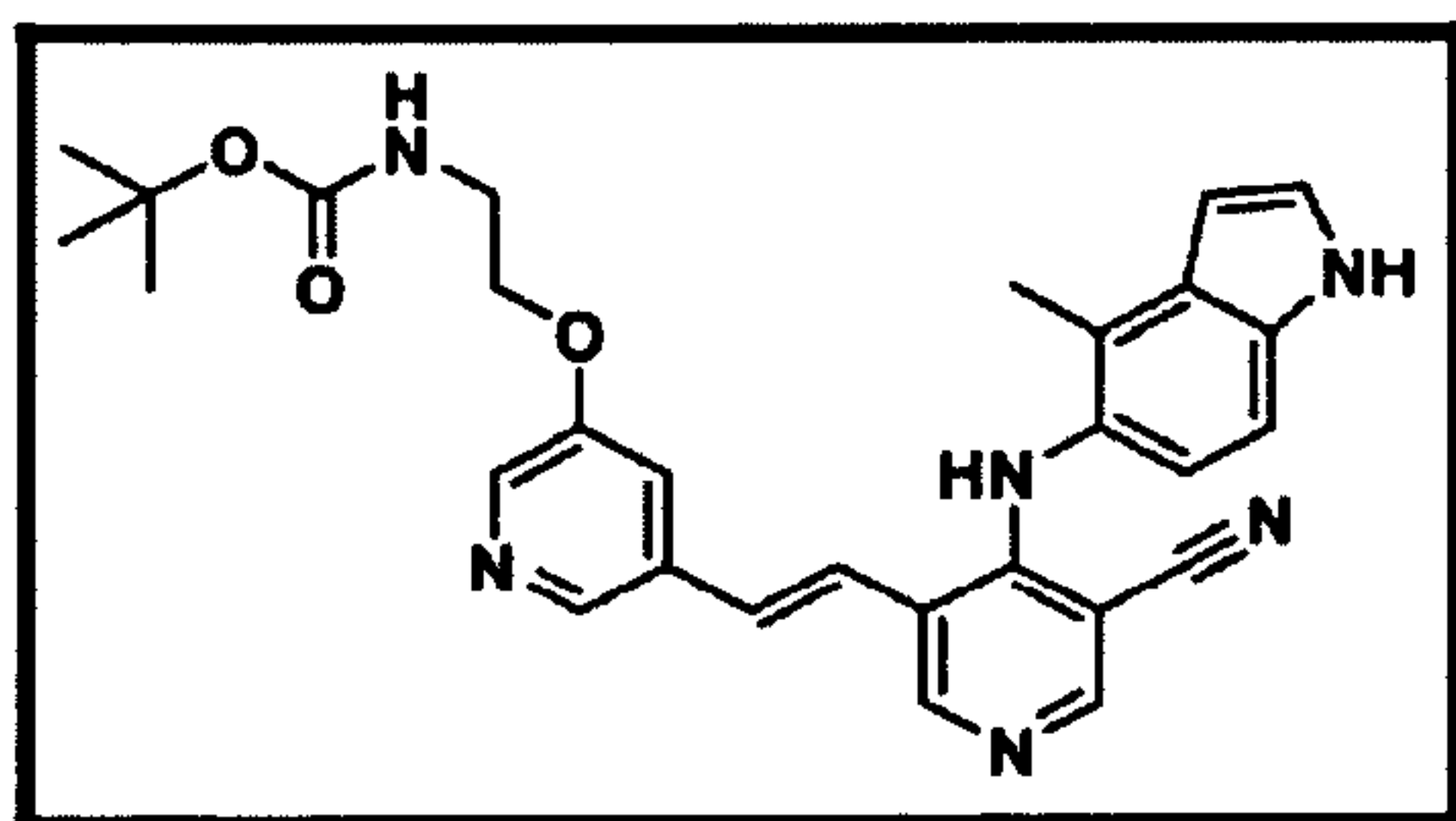
[00558] Preparation of 5-[(E)-2-(5-bromopyridin-3-yl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

To a DMF solution (11 mL) of 4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile (300 mg, 1.1 mmol) was added 3,5-dibromopyridine (379 mg, 1.6 mmol), Pd(OAc)₂ (25 mg, 0.11 mmol), P(o-Tol)₃ (34 mg, 0.11 mmol) and Et₃N (0.061 mL, 4.4 mmol). The solution was heated at 120 °C overnight. After cooling to room temperature, water (100 mL) was added to the rapidly stirred solution. The resulting precipitate was collected by vacuum filtration and purified by flash chromatography with 100:5:0.5 CH₂Cl₂/MeOH/saturated aqueous NH₄OH to provide the title compound (188 mg, 40%) as a white solid. MS 430.0 (M+H); HPLC: rt = 9.4 min [a].



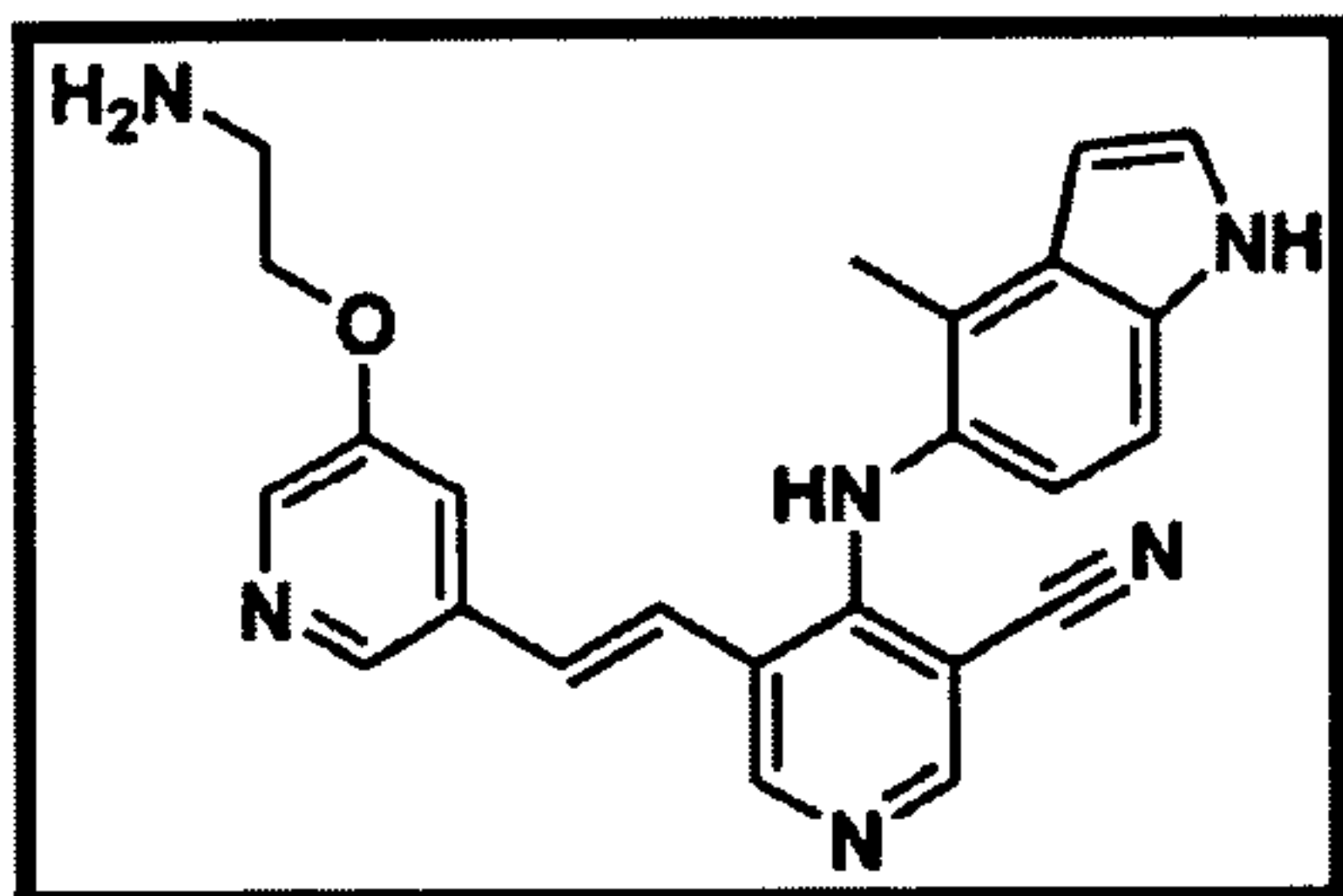
[00559] Preparation of 5-[(E)-2-(5-methoxypyridin-3-yl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

The procedure for the preparation of 5-[(E)-2-(5-bromopyridin-3-yl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile was followed using 3-bromo-5-methoxypyridine. The title compound was isolated as a yellow solid (170 mg, 41%). MS 382.1 (M+H); HPLC: 6.7 min [a].



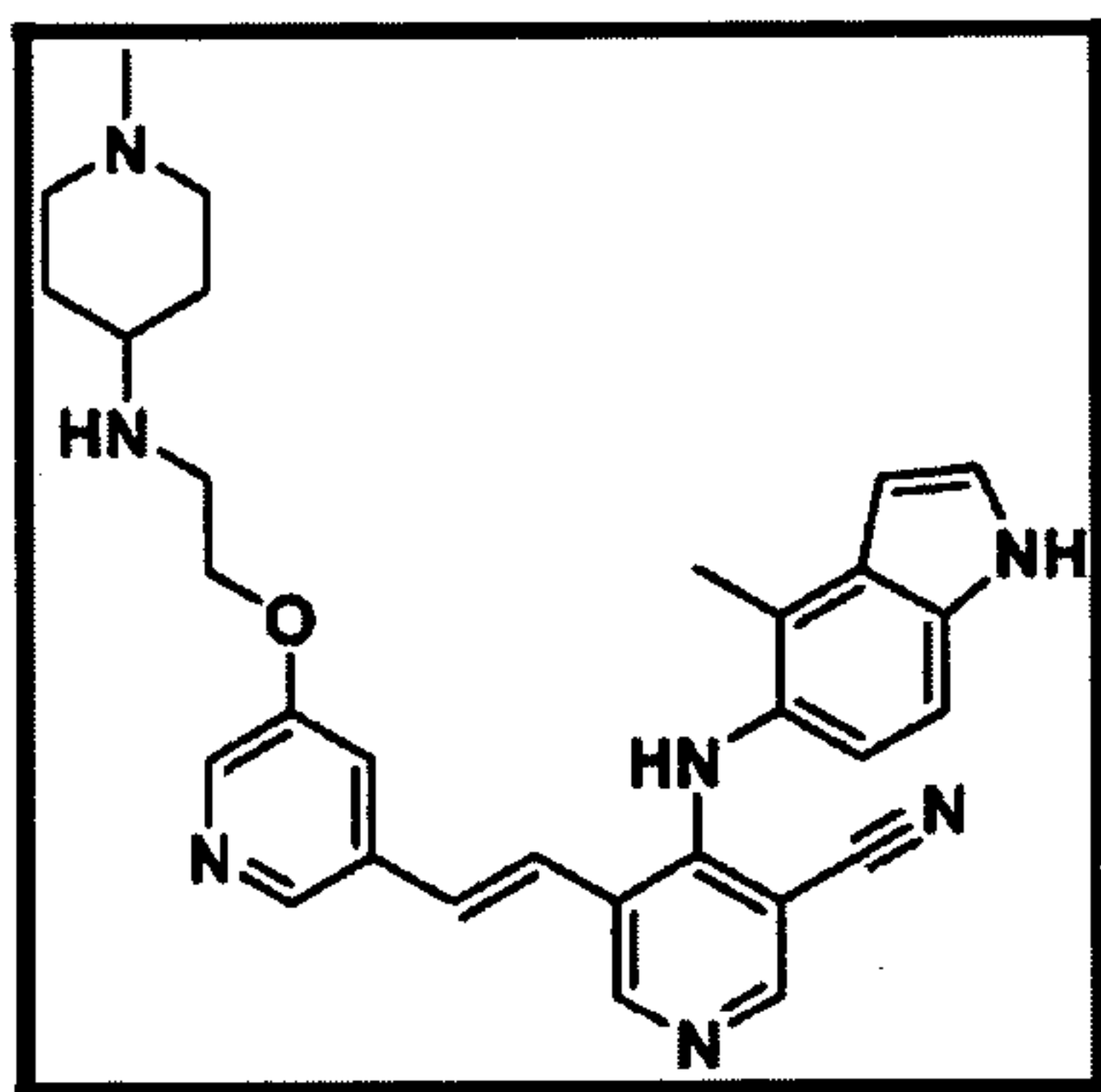
[00560] Preparation of tert-butyl [2-({5-[(E)-2-(5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl)ethenyl]pyridin-3-yl}oxy)ethyl]carbamate:

The procedure for the preparation of 5-[(E)-2-(5-bromopyridin-3-yl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile was followed using tert-butyl {2-[(5-bromopyridin-3-yl)oxy]ethyl}carbonate. The title compound was isolated as a yellow solid (450 mg, 81%). MS 511.2 (M+H); HPLC: rt = 8.9 min [a].



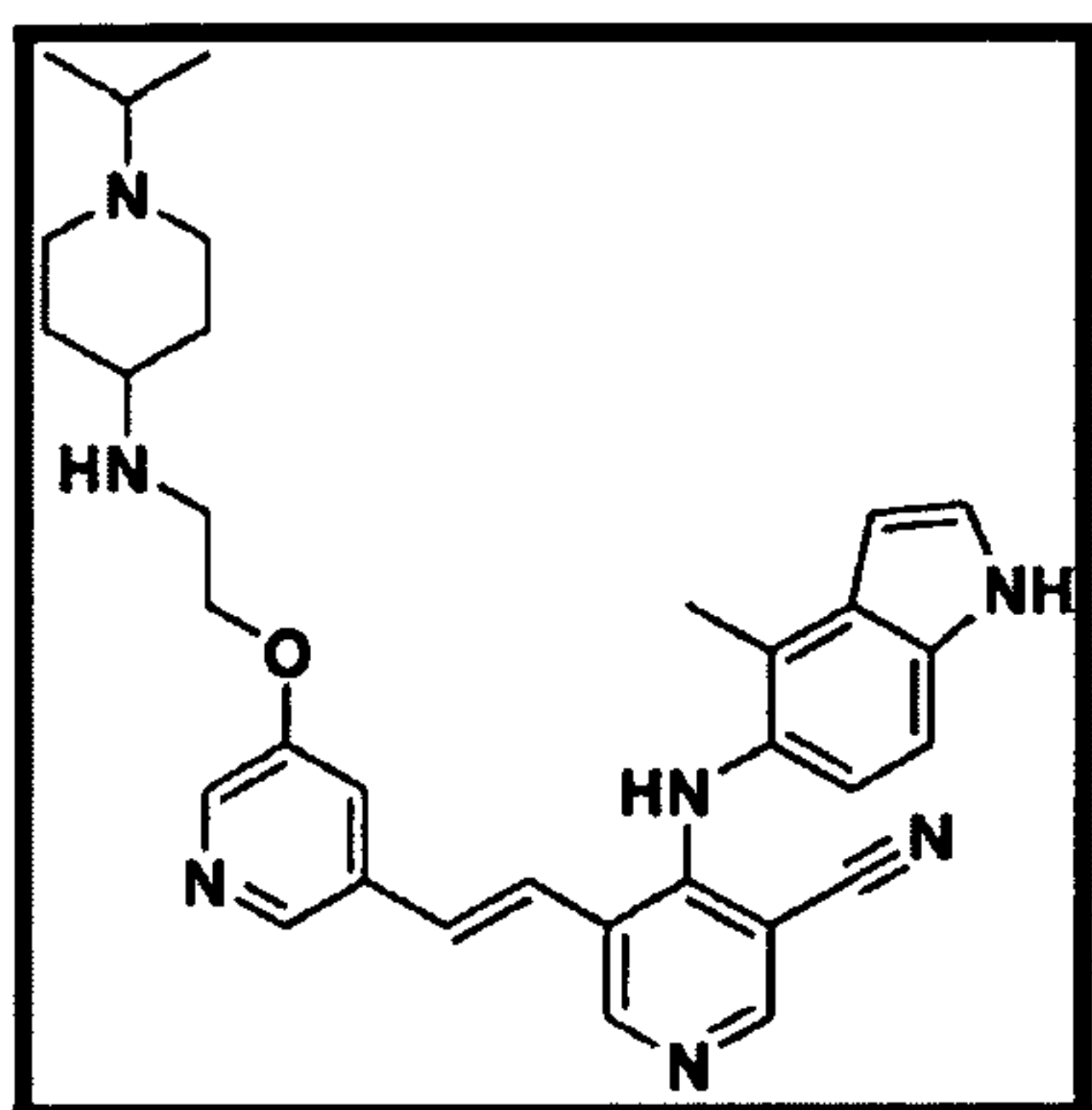
[00561] Preparation of 5-[(E)-2-[5-(2-aminoethoxy)pyridin-3-yl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

Tert-butyl [2-({5-[(E)-2-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}ethenyl]pyridin-3-yl}oxy)ethyl]carbamate (255 mg, 0.50 mmol) was added to a CH₂Cl₂ solution containing 10% TFA (10 mL). After 2 hours at room temperature, saturated aqueous NaHCO₃ (2 mL) was added and the solvent removed under vacuum. The residue was suspended in MeOH and filtered. The filtrate was condensed to a gum and triturated with Et₂O. The solid was dried under vacuum at 60 °C overnight to provide the title compound (200 mg, 98%) as a light red solid. MS 411.1 (M+H); HPLC: rt = 4.3 min [a].



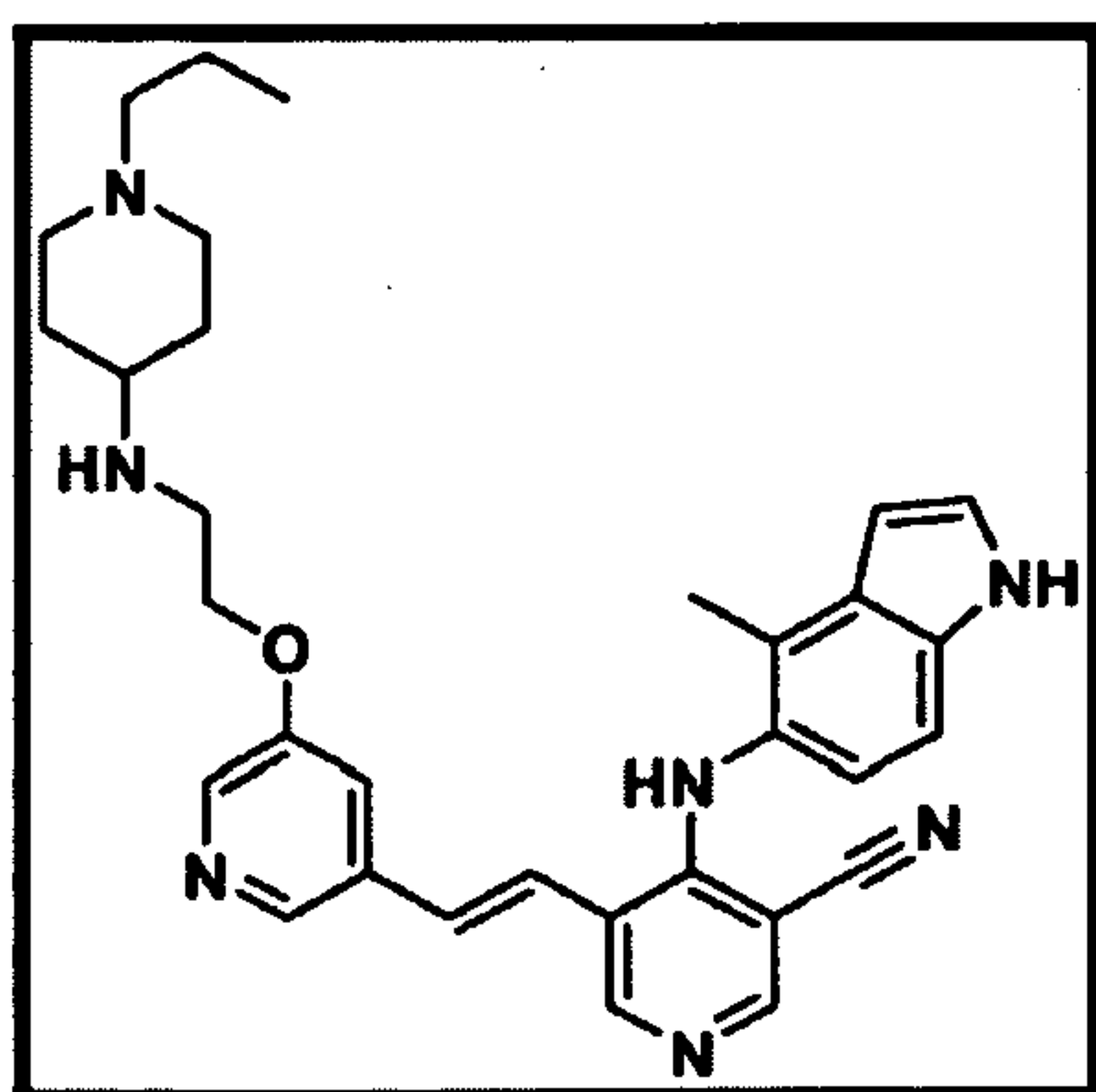
[00562] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(5-{2-[(1-methylpiperidin-4-yl)amino]ethoxy}pyridin-3-yl)ethenyl]pyridine-3-carbonitrile:

To a CH_2Cl_2 solution (5 mL) of 5-[(E)-2-[5-(2-aminoethoxy)pyridin-3-yl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile (200 mg, 0.49 mmol) was added $\text{NaBH}(\text{OAc})_3$ (156 mg, 0.74 mmol), AcOH (0.043 mL) and N-methyl-4-piperidone (0.070 mL, 0.58 mmol). The reaction was stirred at room temperature overnight. The solvent was removed under vacuum, and the residue partitioned between EtOAc (5 mL) and water (3 mL). The organic layer was dried over anhydrous MgSO_4 , filtered, and concentrated under vacuum. The residue was dissolved in DMSO and the title compound (3.0 mg, 2%) purified by preparative HPLC. MS 508.2 (M+H); HPLC: rt = 6.5 min [a].



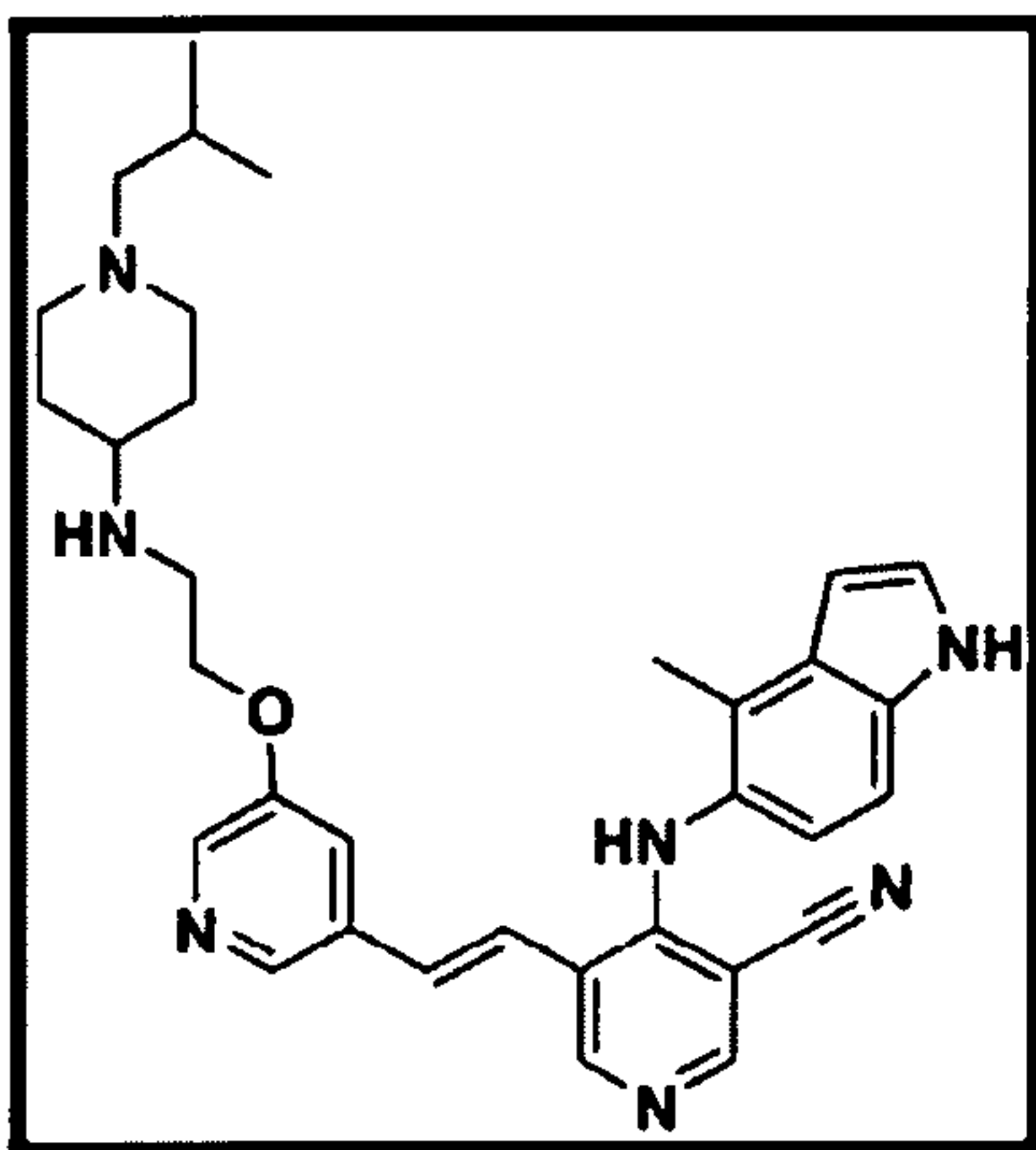
[00563] Preparation of 5-[(E)-2-[5-(2-{[1-(1-methylethyl)piperidin-4-yl]amino}ethoxy)pyridin-3-yl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

The procedure for the preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(5-{2-[(1-methylpiperidin-4-yl)amino]ethoxy}pyridin-3-yl)ethenyl]pyridine-3-carbonitrile was followed using N-iso-propyl-4-piperidone. The title compound (16 mg, 6%) was purified by preparative HPLC. MS 536.3 (M+H); HPLC: rt = 6.9 min [a].



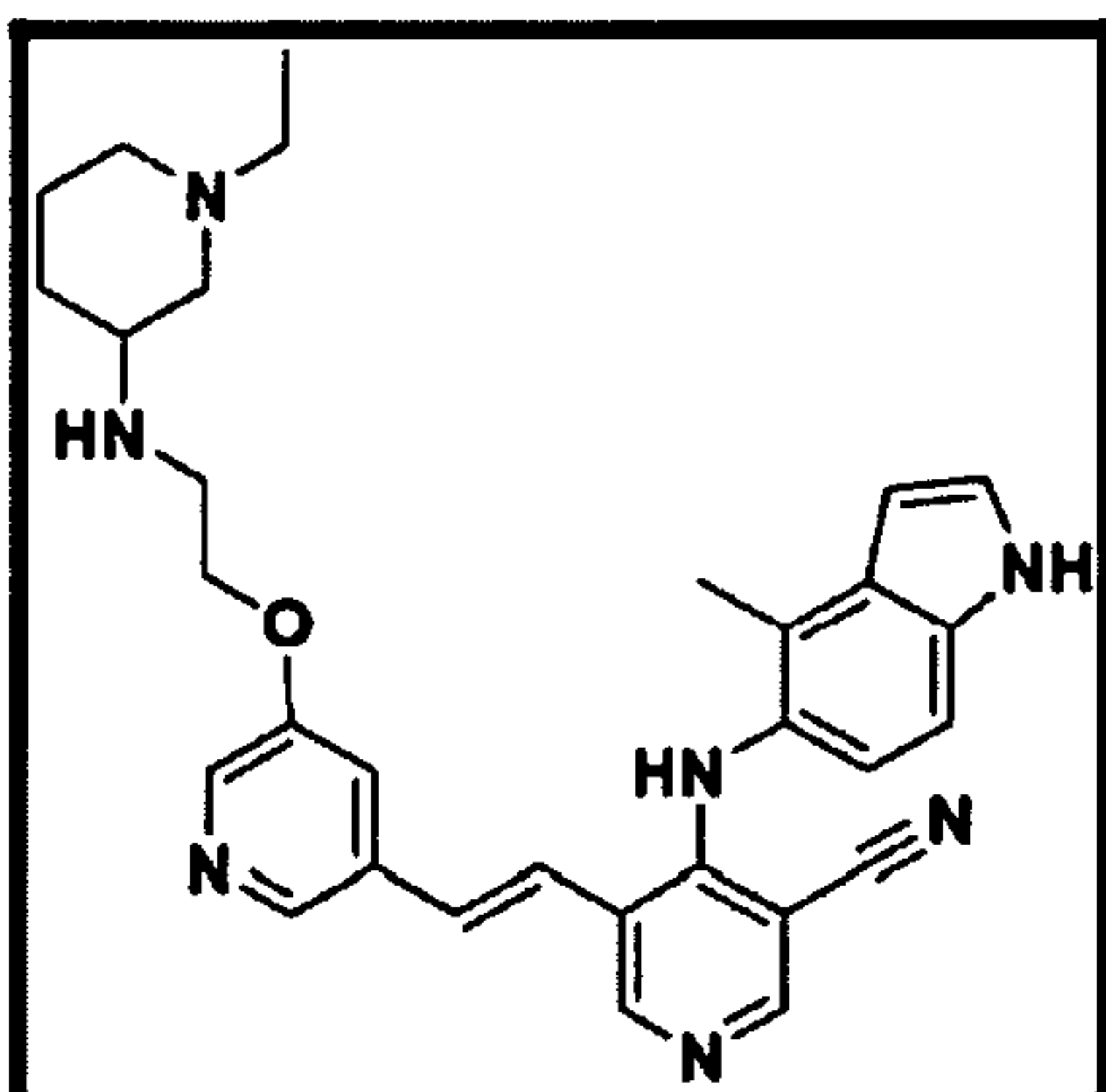
[00564] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(5-{2-[(1-propyl piperidin-4-yl)amino]ethoxy}pyridin-3-yl)ethenyl]pyridine-3-carbonitrile:

The procedure for the preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(5-{2-[(1-methylpiperidin-4-yl)amino]ethoxy}pyridin-3-yl)ethenyl]pyridine-3-carbonitrile was followed using N-propyl-4-piperidone. The title compound (19 mg, 7%) was purified by preparative HPLC. MS 536.3 (M+H); HPLC: rt = 6.9 min [a].



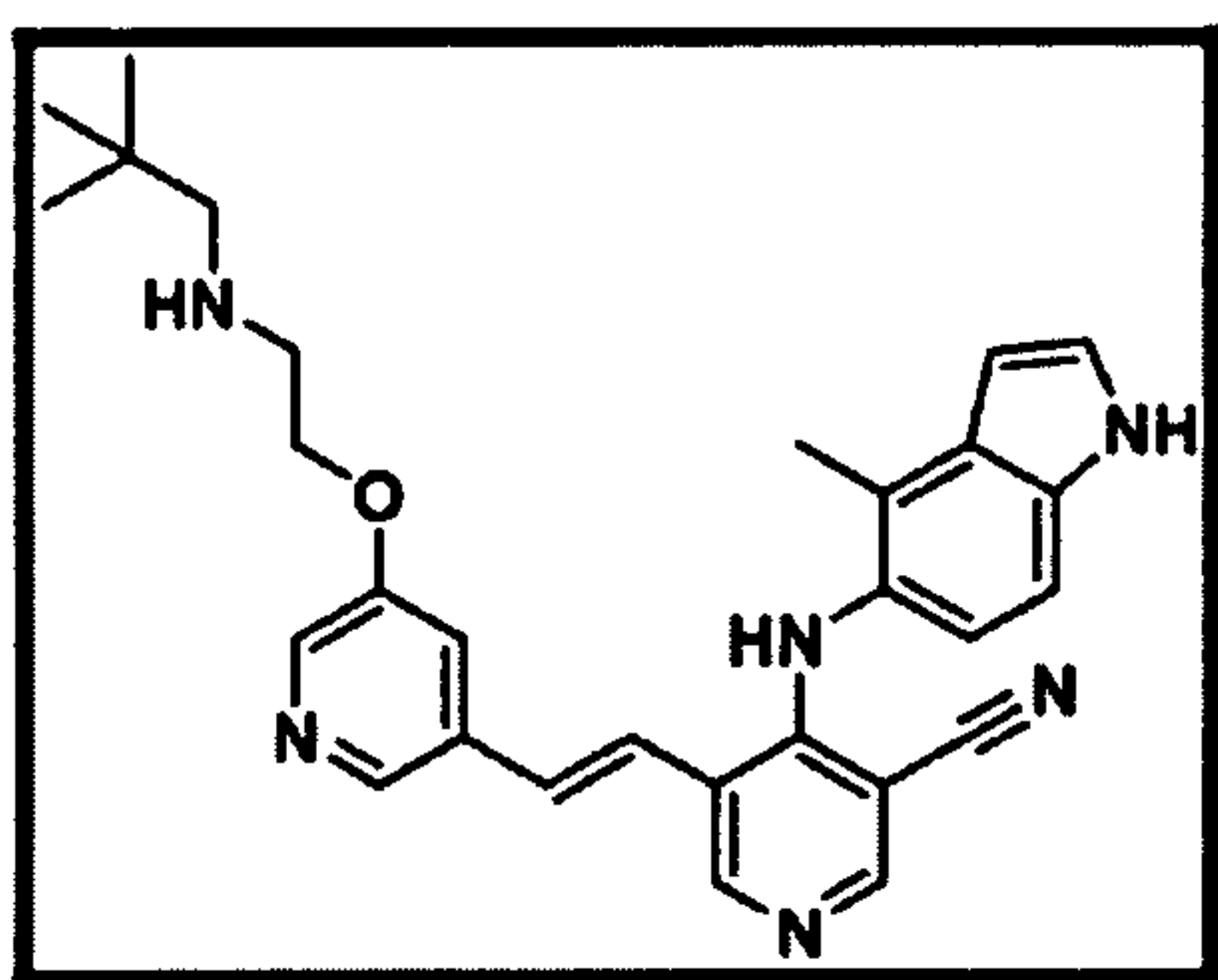
[00565] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(5-{2-[(1-(2-methyl propyl)piperidin-4-yl]amino}ethoxy)pyridin-3-yl)ethenyl]pyridine-3-carbonitrile:

The procedure for the preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(5-{2-[(1-(2-methyl propyl)piperidin-4-yl]amino}ethoxy)pyridin-3-yl)ethenyl]pyridine-3-carbonitrile was followed using N-iso-butyl-4-piperidone. The title compound (6 mg, 2%) was purified by preparative HPLC. MS 550.3 (M+H); HPLC: rt = 7.4 min [a].



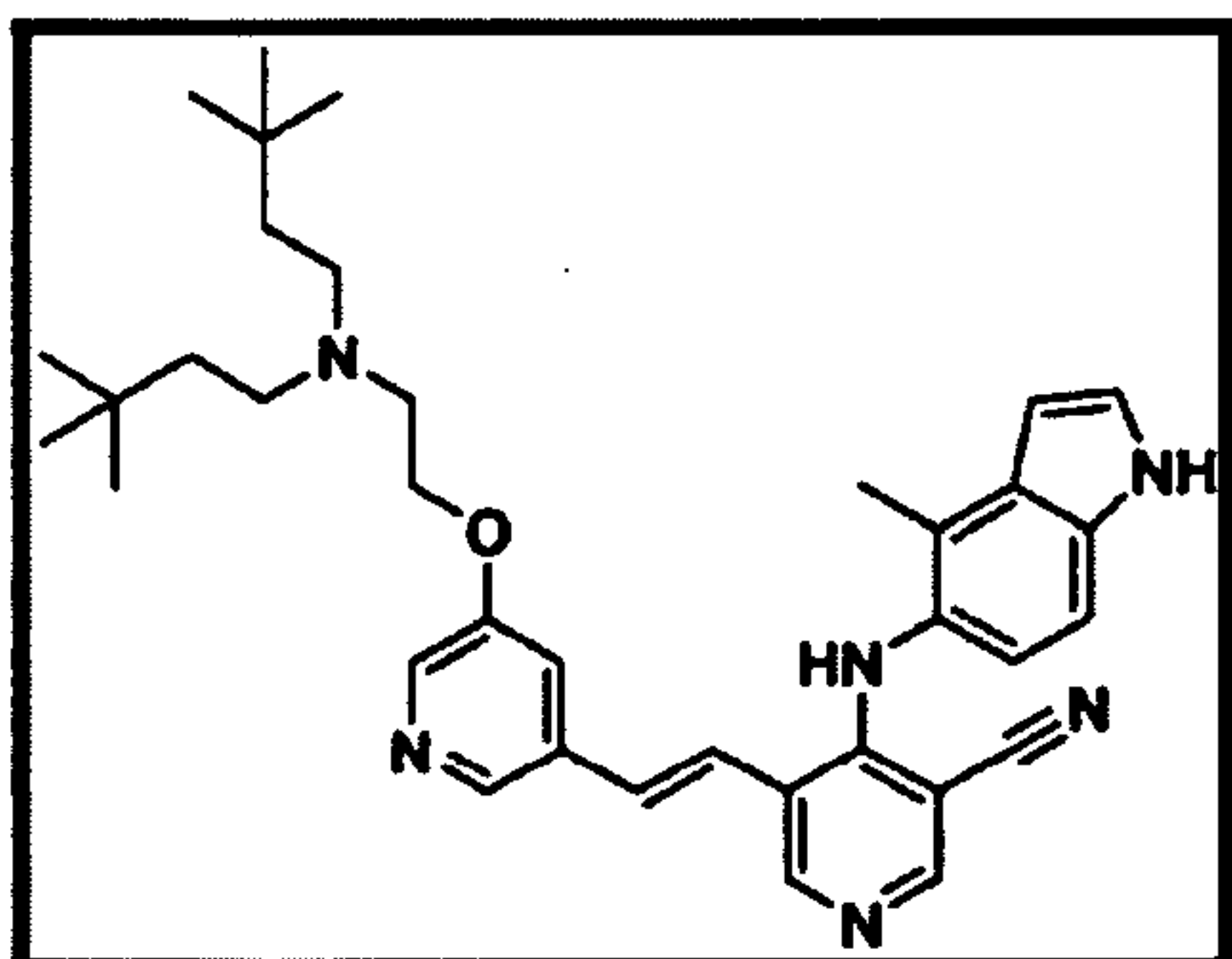
[00566] Preparation of 5-[(E)-2-(5-{2-[(1-ethylpiperidin-3-yl)amino]ethoxy}pyridin-3-yl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

The procedure for the preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(5-{2-[(1-methylpiperidin-4-yl)amino]ethoxy}pyridin-3-yl)ethenyl]pyridine-3-carbonitrile was followed using 1-ethyl-3-piperidone hydrochloride and N, N-di-iso-propylethylamine. The title compound (3 mg, 1%) was purified by preparative HPLC. MS 522.2 (M+H); HPLC: rt = 6.2 min [a].



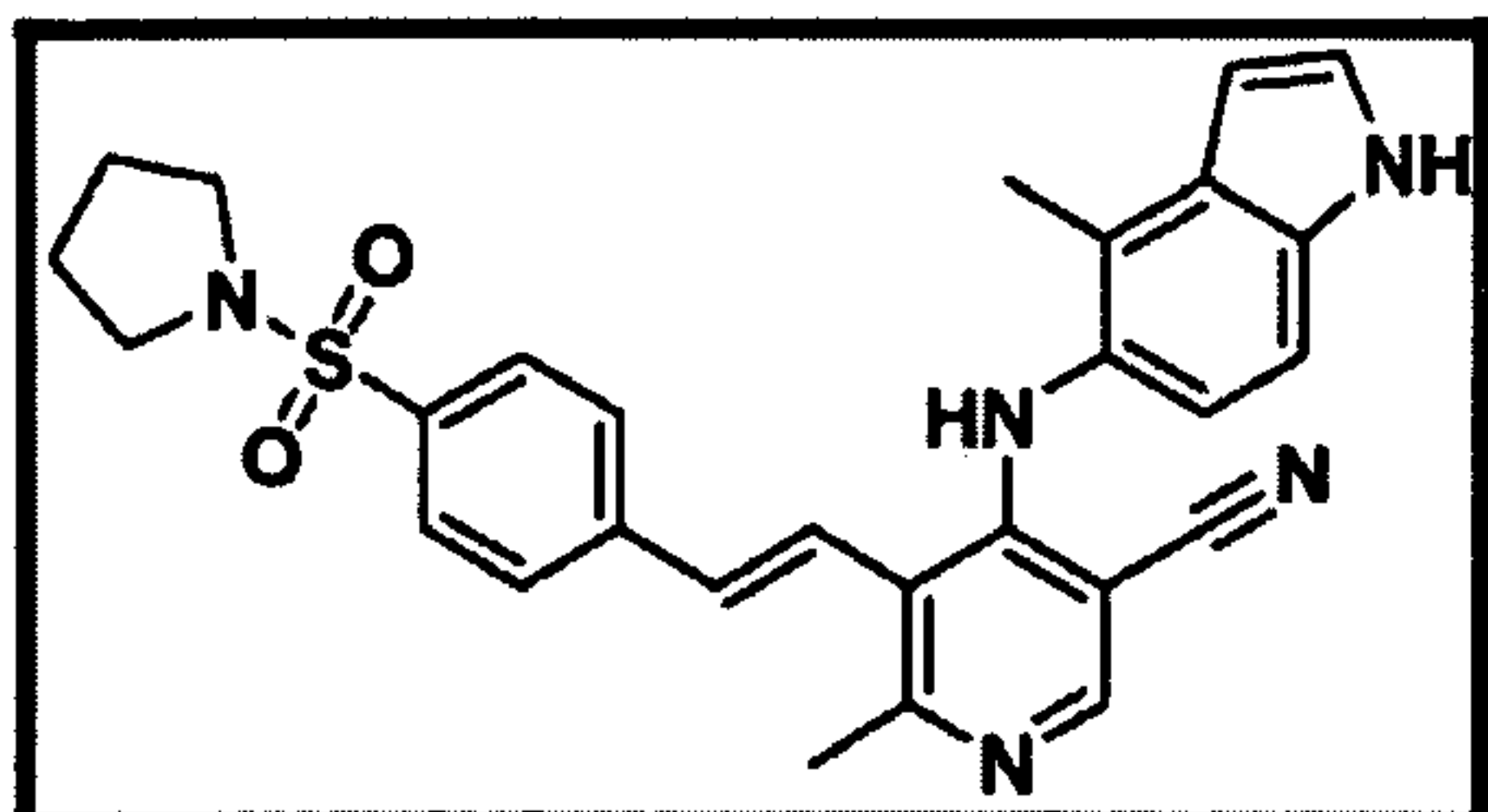
[00567] Preparation of 5-[(E)-2-(5-{2-[(2,2-dimethylpropyl)amino]ethoxy}pyridin-3-yl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

The procedure for the preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(5-{2-[(1-methylpiperidin-4-yl)amino]ethoxy}pyridin-3-yl)ethenyl]pyridine-3-carbonitrile was followed using trimethylacetaldehyde. The title compound (3 mg, 1%) was purified by preparative HPLC. MS 481.2 (M+H); HPLC: rt = 5.9 min [a].



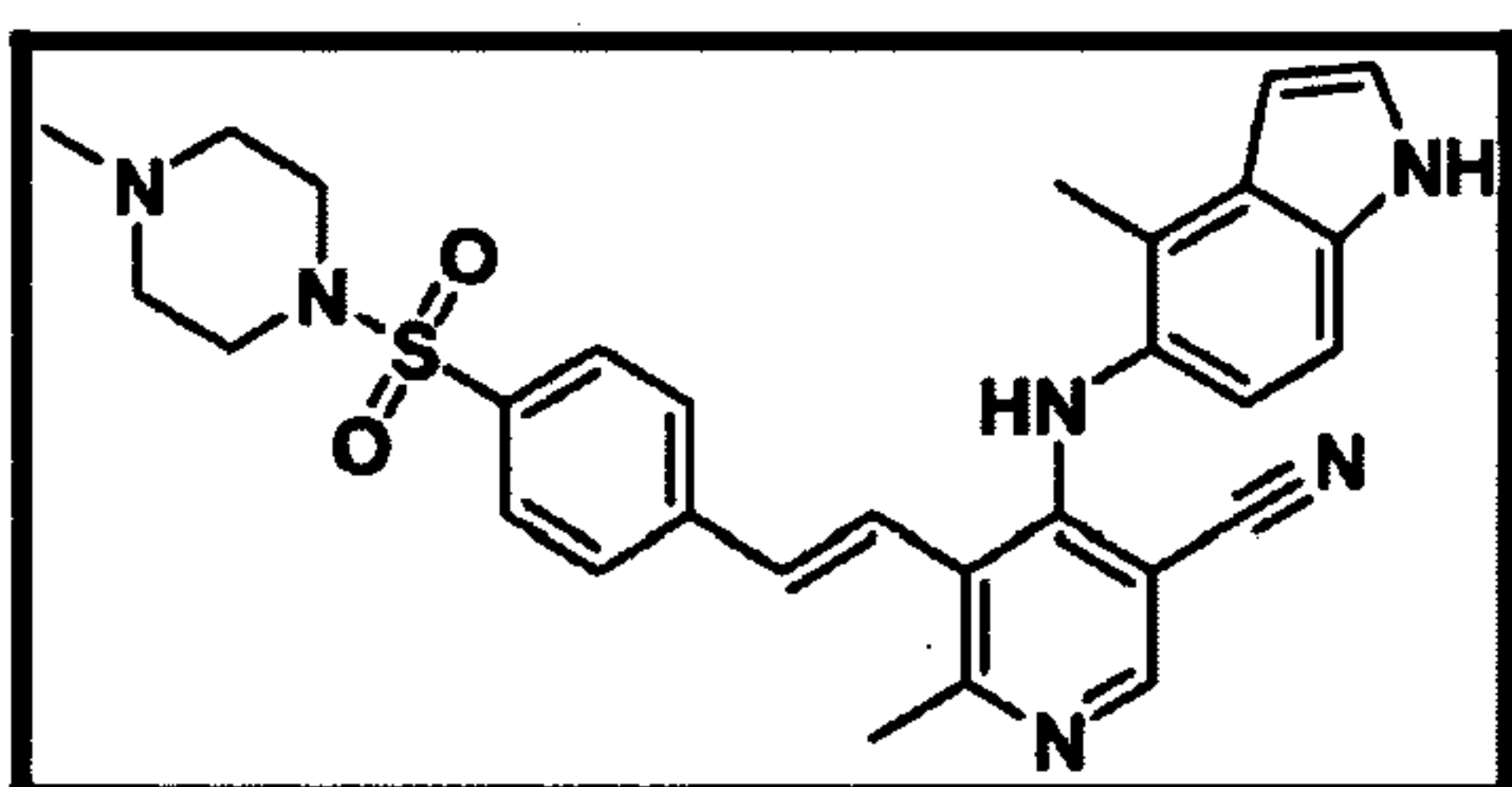
[00568] Preparation of 5-[(E)-2-(5-{2-[bis(3,3-dimethylbutyl)amino]ethoxy}pyridin-3-yl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile:

The procedure for the preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(5-{2-[(1-methylpiperidin-4-yl)amino]ethoxy}pyridin-3-yl)ethenyl]pyridine-3-carbonitrile was followed using 3,3-dimethylbutyraldehyde. The title compound (4 mg, 2%) was purified by preparative HPLC. MS 579.3 (M+H); HPLC: 8.9 min [a].



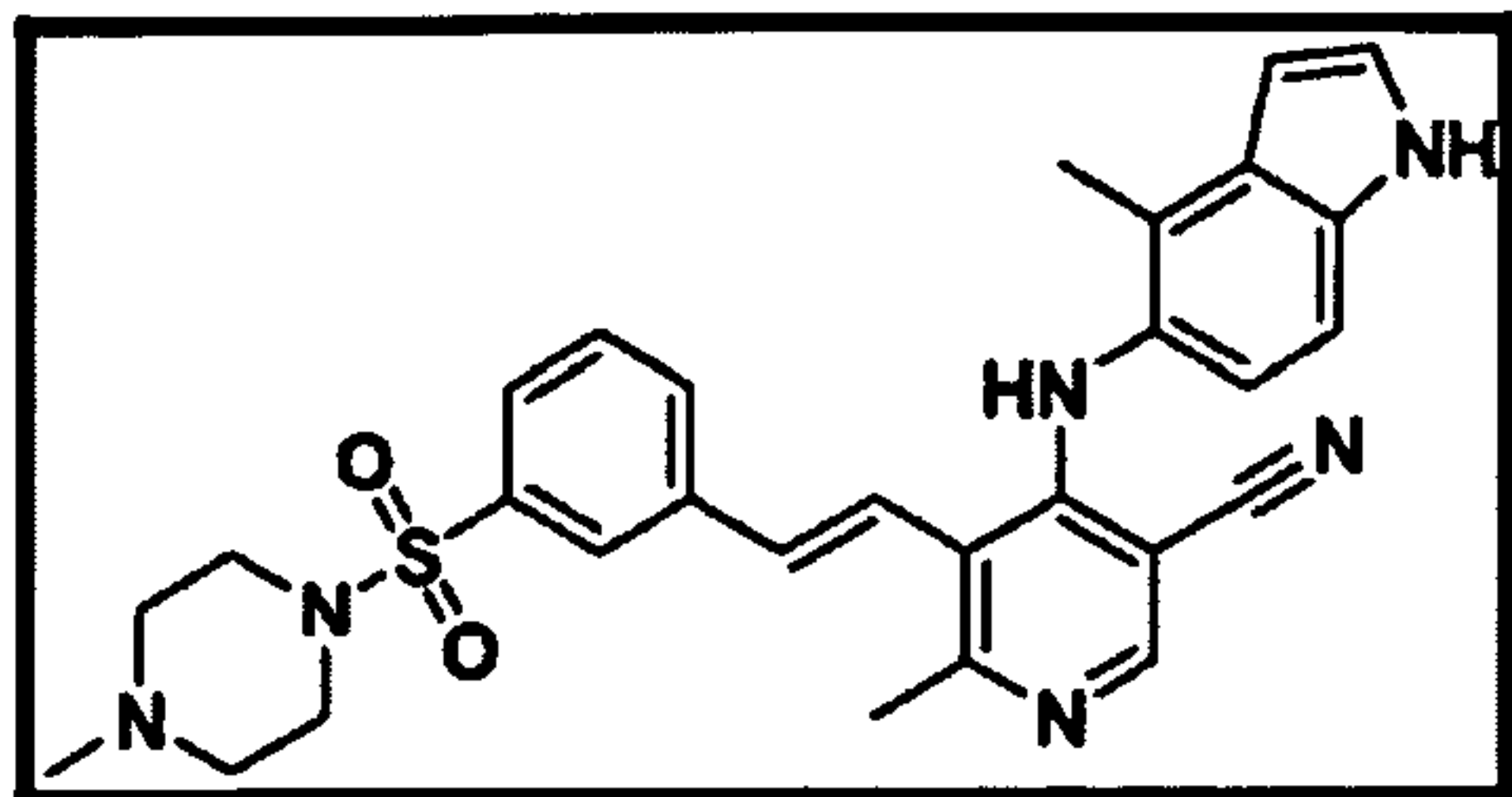
[00569] Preparation of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(pyrrolidin-1-ylsulfonyl)phenyl]ethenyl]pyridine-3-carbonitrile:

To a DMF solution (3 mL) was added 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile (58 mg, 0.20 mmol), Pd(OAc)₂ (5 mg, 0.02 mmol), P(o-Tol)₃ (6 mg, 0.02 mmol), Et₃N (0.11 mL, 0.8 mmol), and 1-[(4-bromophenyl)sulfonyl]pyrrolidine (87 mg, 0.3 mmol). The solution was heated at 100 °C overnight. The solution was cooled and filtered and the filtrate was purified by preparative HPLC to give the title compound (44 mg, 44 %). MS 498.1 (M+H); HPLC: rt = 9.3 min [a].



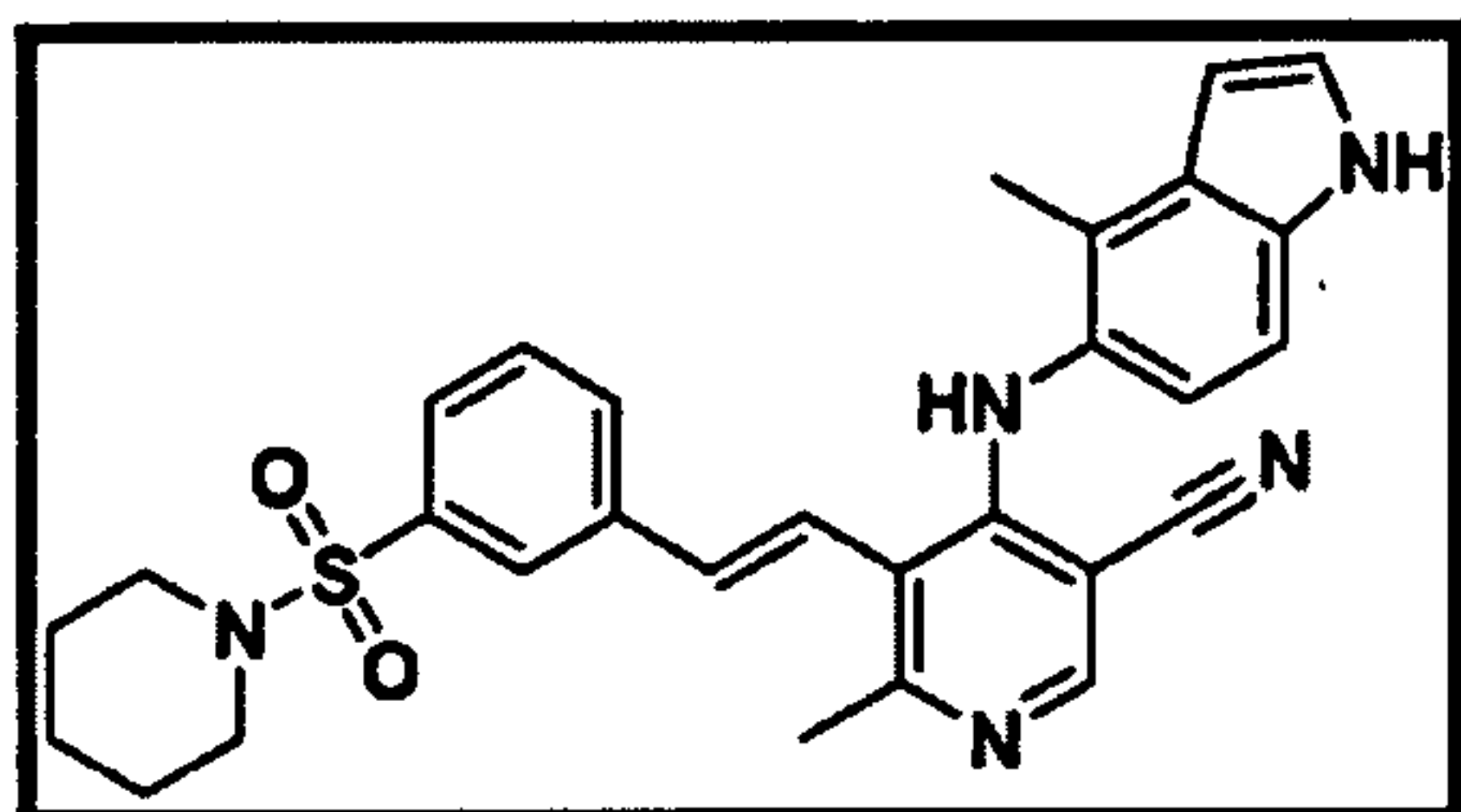
[00570] Preparation of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(4-methylpiperazin-1-yl)sulfonyl]phenyl]ethenyl]pyridine-3-carbonitrile:

The procedure for the preparation of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(pyrrolidin-1-ylsulfonyl)phenyl]ethenyl]pyridine-3-carbonitrile was followed using 1-[(4-bromo)sulfonyl]-4-methylpiperazine. The title compound (41 mg, 39%) was purified by preparative HPLC. MS 527.2 (M+H); HPLC: rt = 6.1 min [a].



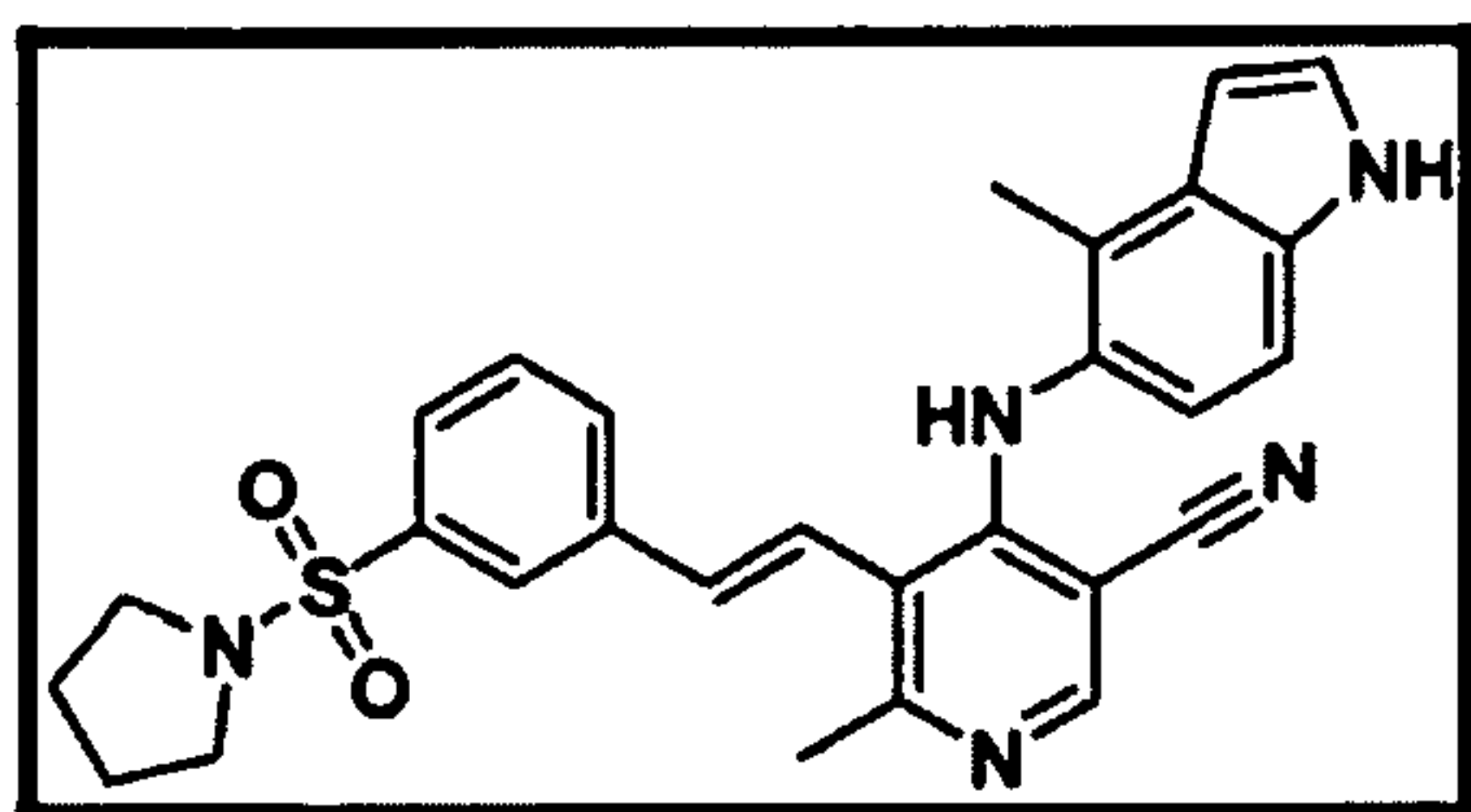
[00571] Preparation of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{3-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}ethenyl]pyridine-3-carbonitrile:

The procedure for the preparation of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(pyrrolidin-1-ylsulfonyl)phenyl]ethenyl]pyridine-3-carbonitrile was followed using 1-[(3-bromophenyl)sulfonyl]-4-methylpiperazine. The title compound (44 mg, 42%) was purified by preparative HPLC. MS 527.2 (M+H); HPLC: *rt* = 6.1 min [a].



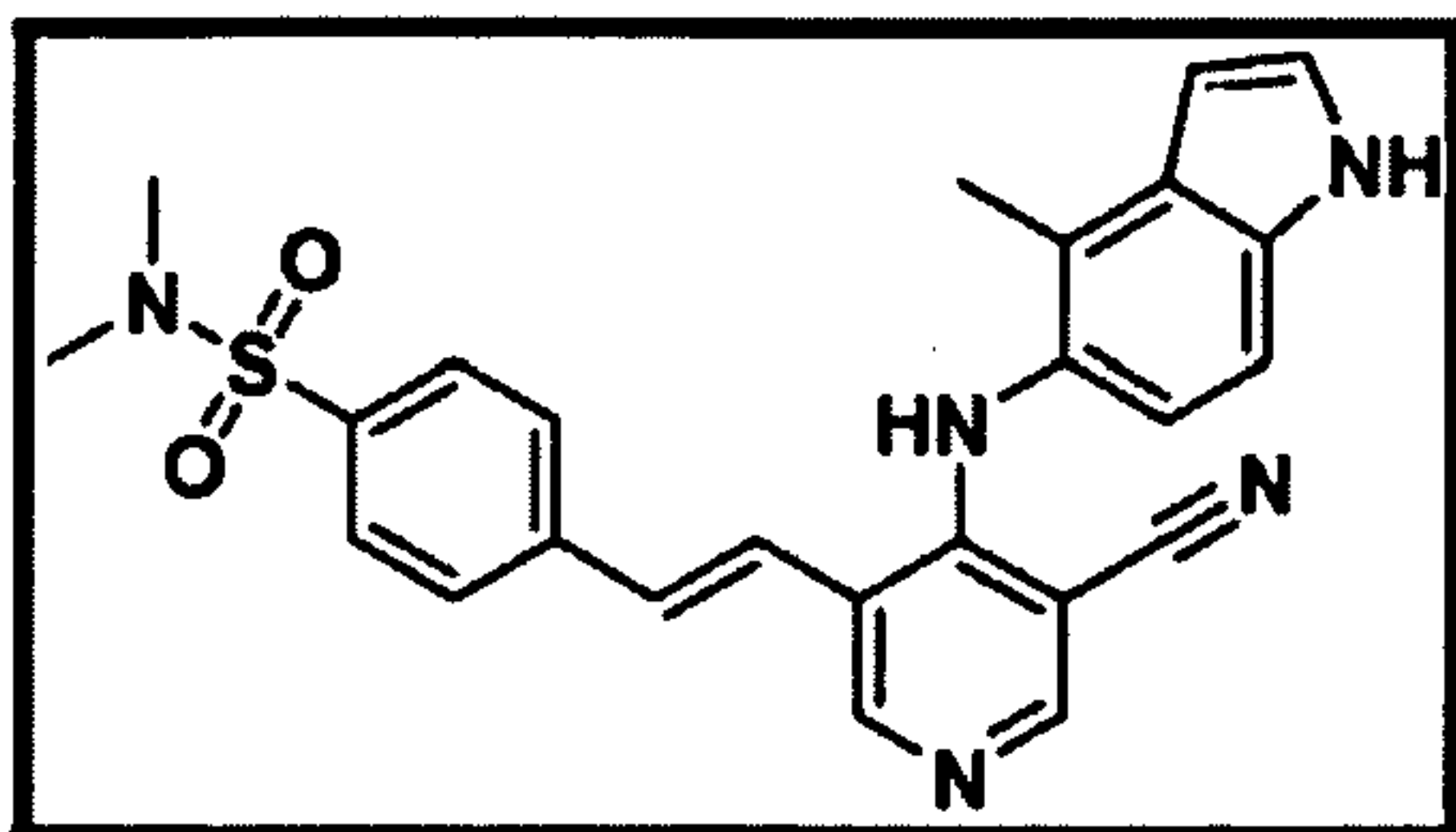
[00572] Preparation of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{3-(piperidin-1-ylsulfonyl)phenyl}ethenyl]pyridine-3-carbonitrile:

The procedure for the preparation of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(pyrrolidin-1-ylsulfonyl)phenyl]ethenyl]pyridine-3-carbonitrile was followed using 1-[(3-bromophenyl)sulfonyl]piperidine. The title compound (42 mg, 41%) was purified by preparative HPLC. MS 512.2 (M+H); HPLC: *rt* = 11.1 min [a].



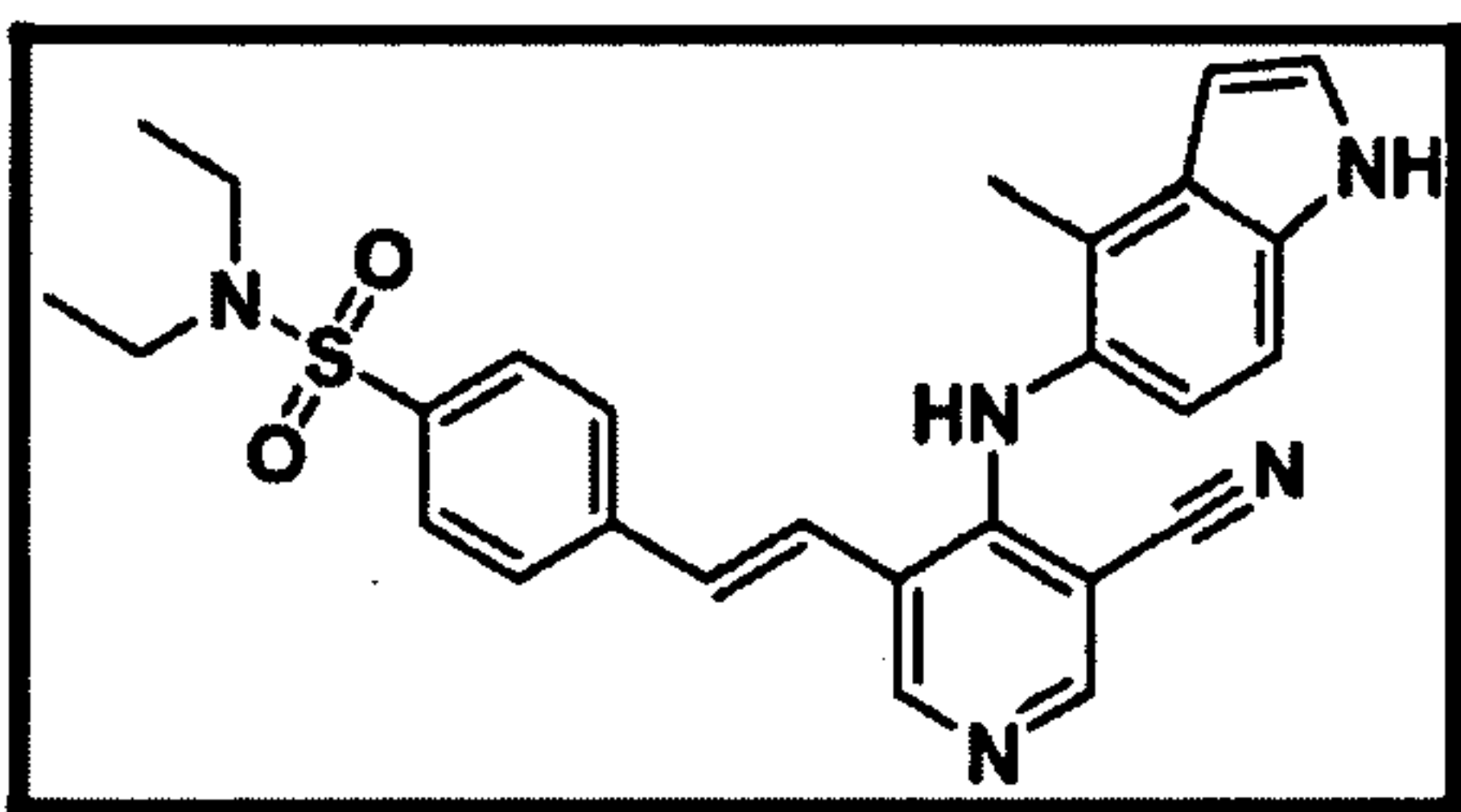
[00573] Preparation of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[3-(pyrrolidin-1-ylsulfonyl)phenyl]ethenyl]pyridine-3-carbonitrile:

The procedure for the preparation of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(pyrrolidin-1-ylsulfonyl)phenyl]ethenyl]pyridine-3-carbonitrile was followed using 1-[(3-bromophenyl)sulfonyl]pyrrolidine. The title compound (42 mg, 41%) was purified by preparative HPLC. MS 498.1 (M+H); HPLC: rt = 10.3 min [a].



[00574] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(N,N-dimethylbenzenesulfonyl)phenyl]ethenyl]pyridine-3-carbonitrile:

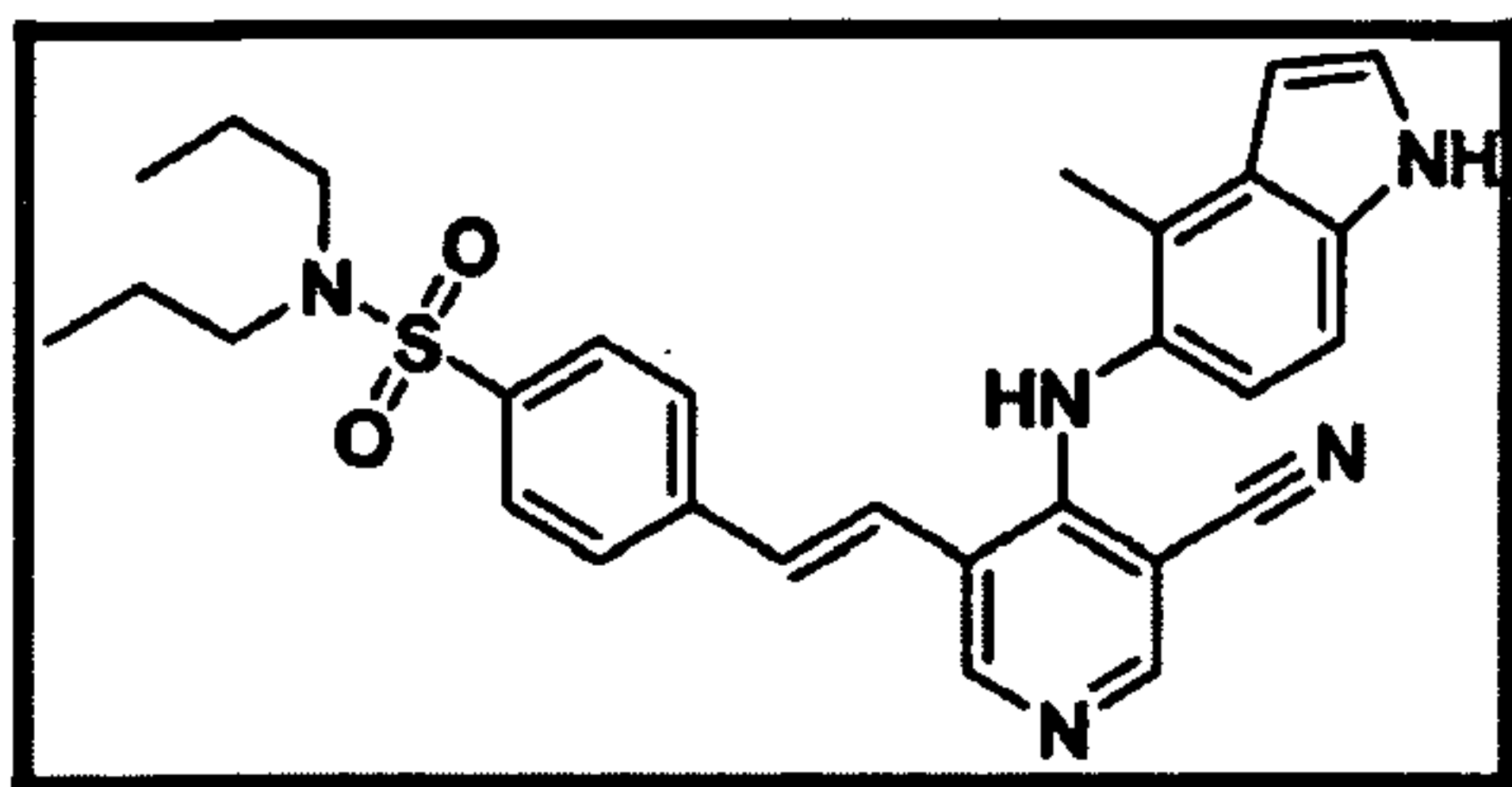
The procedure for the preparation of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(pyrrolidin-1-ylsulfonyl)phenyl]ethenyl]pyridine-3-carbonitrile was followed using 4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile and 4-bromo-N,N-dimethylbenzenesulfonamide. The title compound (19 mg, 21%) was purified by preparative HPLC. MS 458.0 (M+H); HPLC: rt = 9.4 min [a].



[00575] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(N,N-diethylbenzenesulfonyl)phenyl]ethenyl]pyridine-3-carbonitrile:

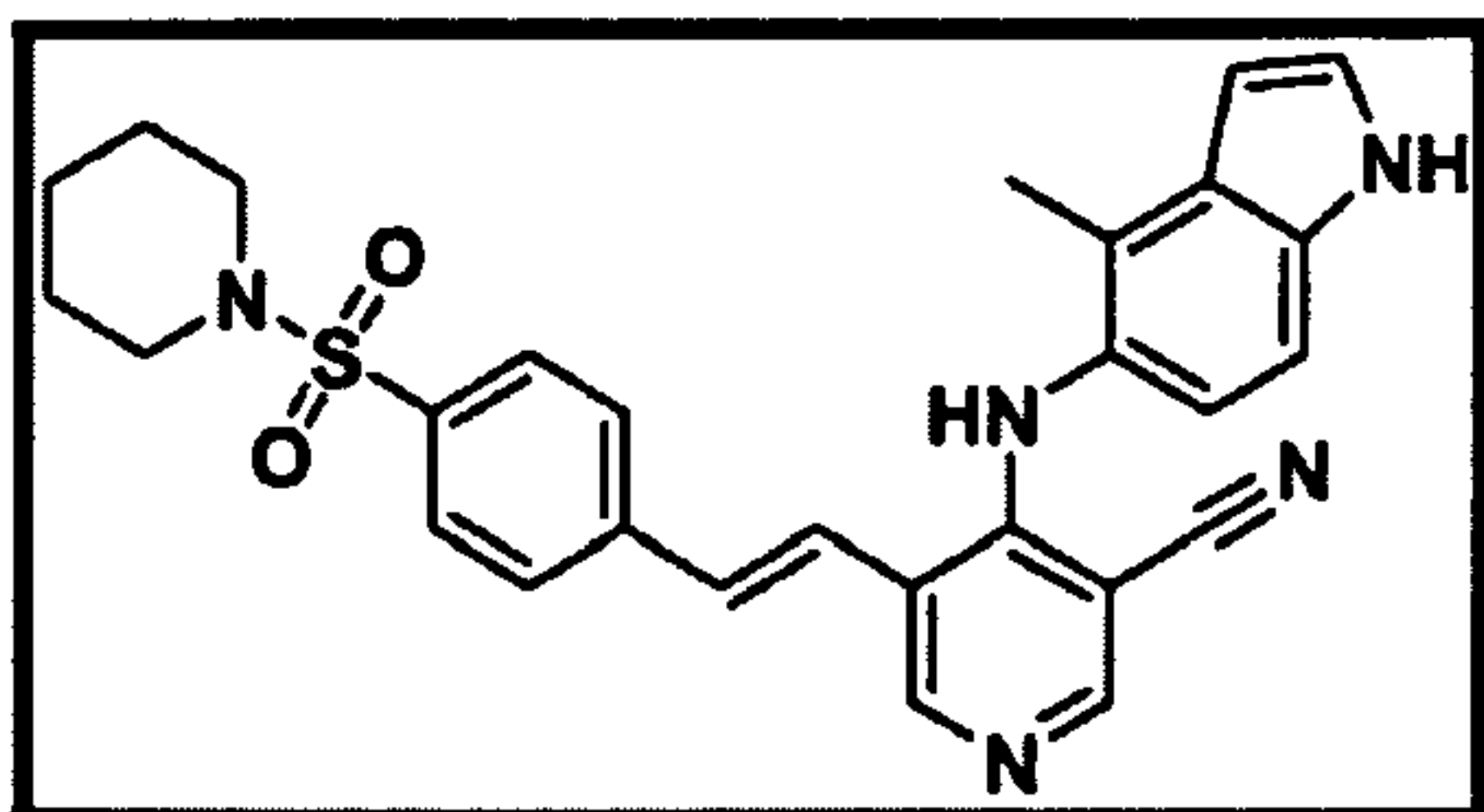
The procedure for the preparation of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(pyrrolidin-1-ylsulfonyl)phenyl]ethenyl]pyridine-3-carbonitrile was followed using 4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile and 4-bromo-N,N-diethylbenzenesulfonamide. The

title compound (19 mg, 20%) was purified by preparative HPLC. MS 486.1 (M+H); HPLC: rt = 10.7 min [a].



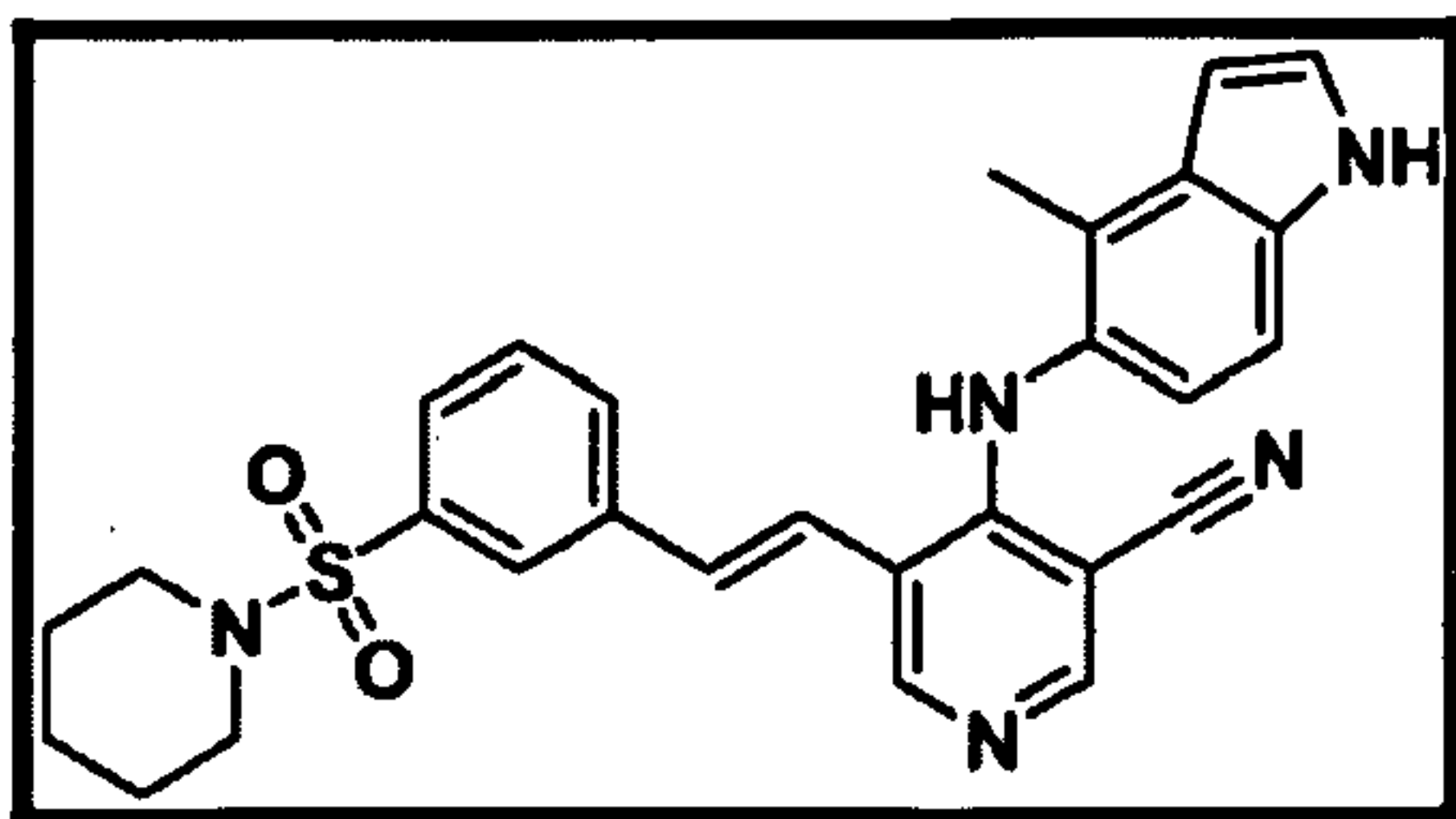
[00576] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(N,N-dipropylbenzenesulfonyl)phenyl]ethenyl]pyridine-3-carbonitrile:

The procedure for the preparation of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(pyrrolidin-1-ylsulfonyl)phenyl]ethenyl]pyridine-3-carbonitrile was followed using 4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile and 4-bromo-N,N-dipropylbenzenesulfonamide. The title compound (45 mg, 44%) was purified by preparative HPLC. MS 514.1 (M+H); HPLC: rt = 12.2 min [a].



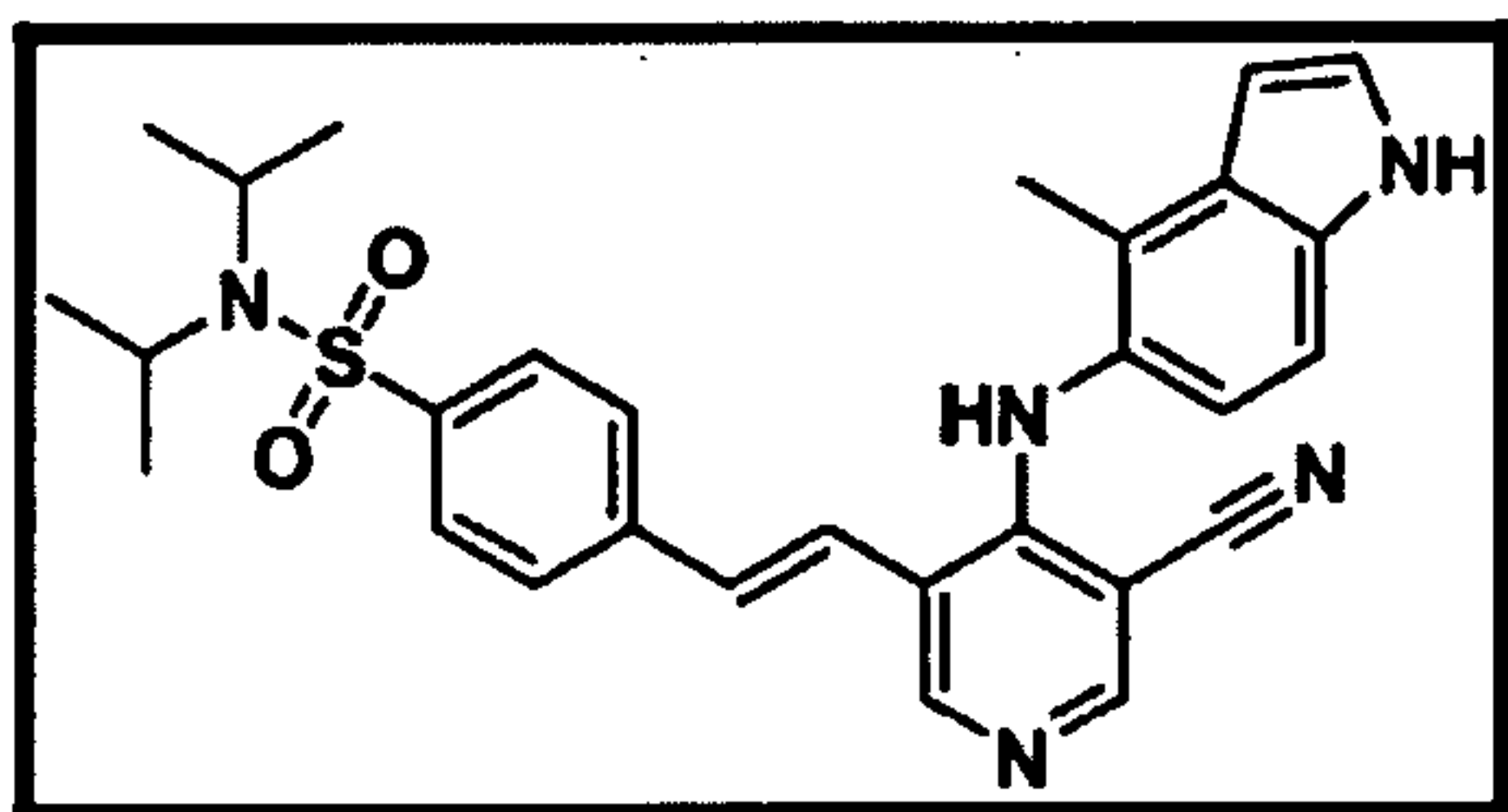
[00577] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(piperidin-1-ylsulfonyl)phenyl]ethenyl]pyridine-3-carbonitrile:

The procedure for the preparation of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(pyrrolidin-1-ylsulfonyl)phenyl]ethenyl]pyridine-3-carbonitrile was followed using 4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile and 1-[(4-bromophenyl)sulfonyl]piperidine. The title compound (43 mg, 44%) was purified by preparative HPLC. MS 498.0 (M+H); HPLC: rt = 11.3 min [a].



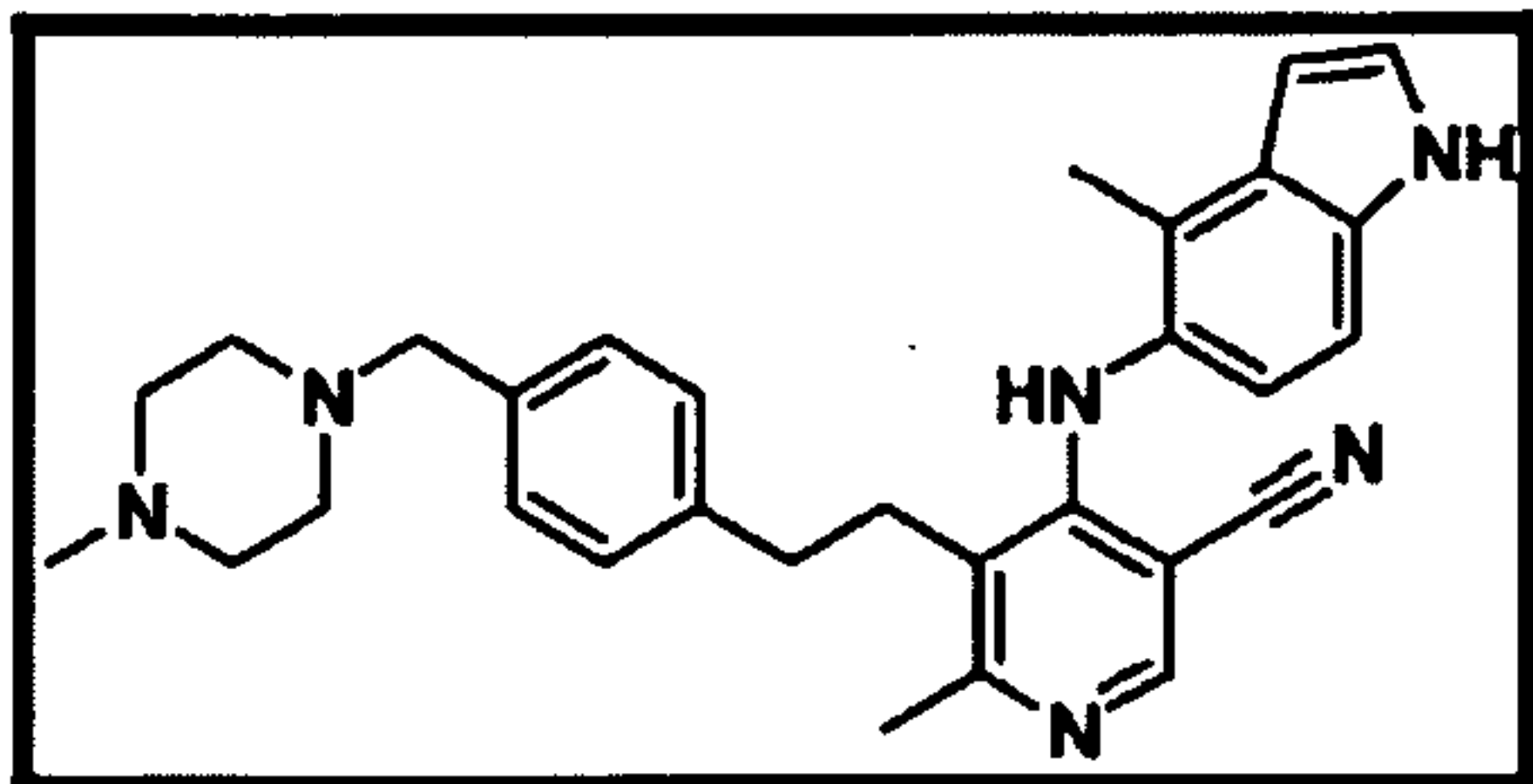
[00578] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[3-(piperidin-1-ylsulfonyl)phenyl]ethenyl]pyridine-3-carbonitrile:

The procedure for the preparation of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(pyrrolidin-1-ylsulfonyl)phenyl]ethenyl]pyridine-3-carbonitrile was followed using 4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile and 1-[(3-bromophenyl)sulfonyl]piperidine. The title compound (37 mg, 37%) was purified by preparative HPLC. MS 498.0 (M+H); HPLC: *rt* = 11.0 min [a].



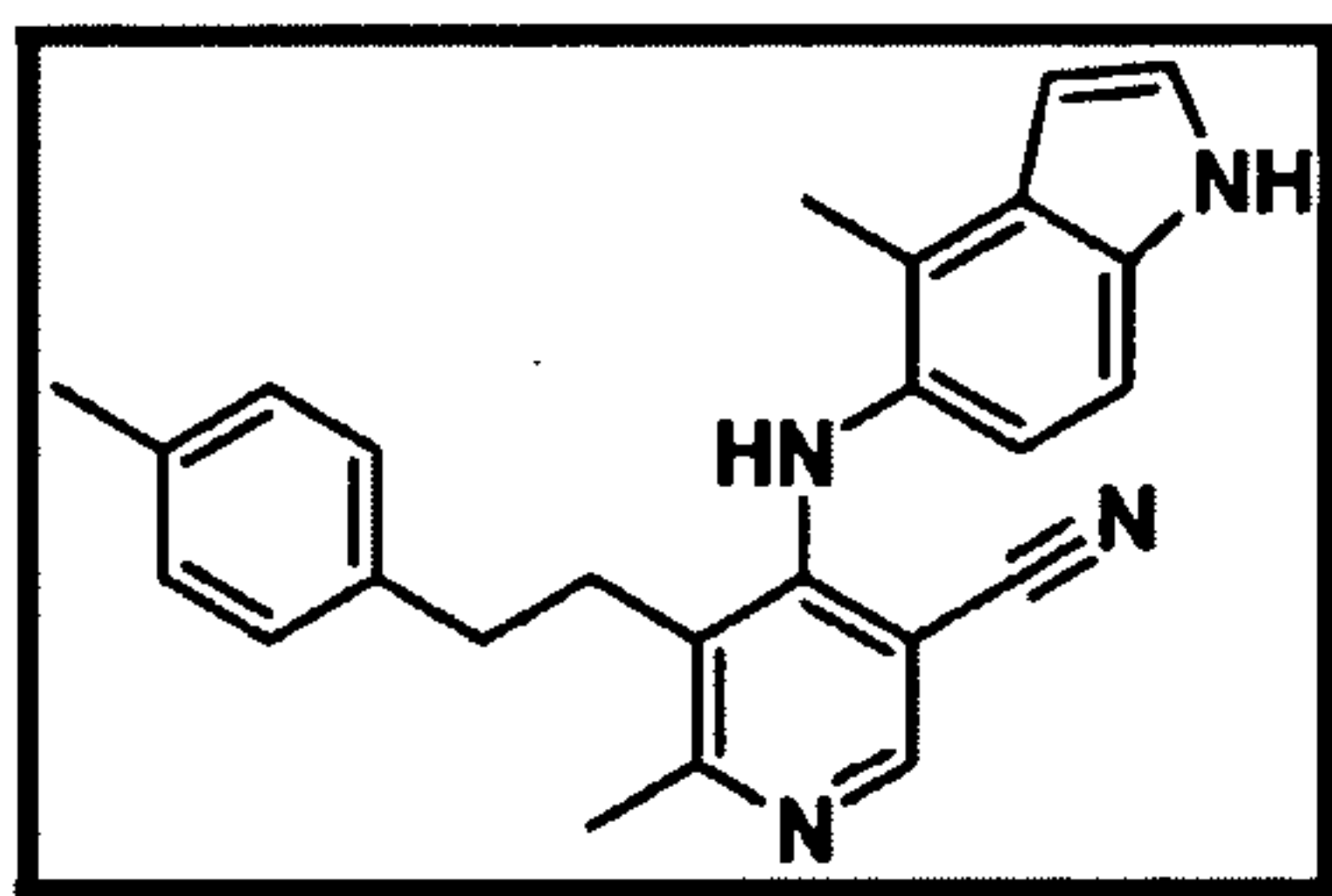
[00579] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(N,N-di-iso-propylbenzenesulfonyl)phenyl]ethenyl]pyridine-3-carbonitrile:

The procedure for the preparation of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(pyrrolidin-1-ylsulfonyl)phenyl]ethenyl]pyridine-3-carbonitrile was followed using 4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile and 4-bromo-N,N-di-iso-propylbenzenesulfonamide. The title compound (32 mg, 31%) was purified by preparative HPLC. MS 514.1 (M+H); HPLC: *rt* = 12.0 min [a].



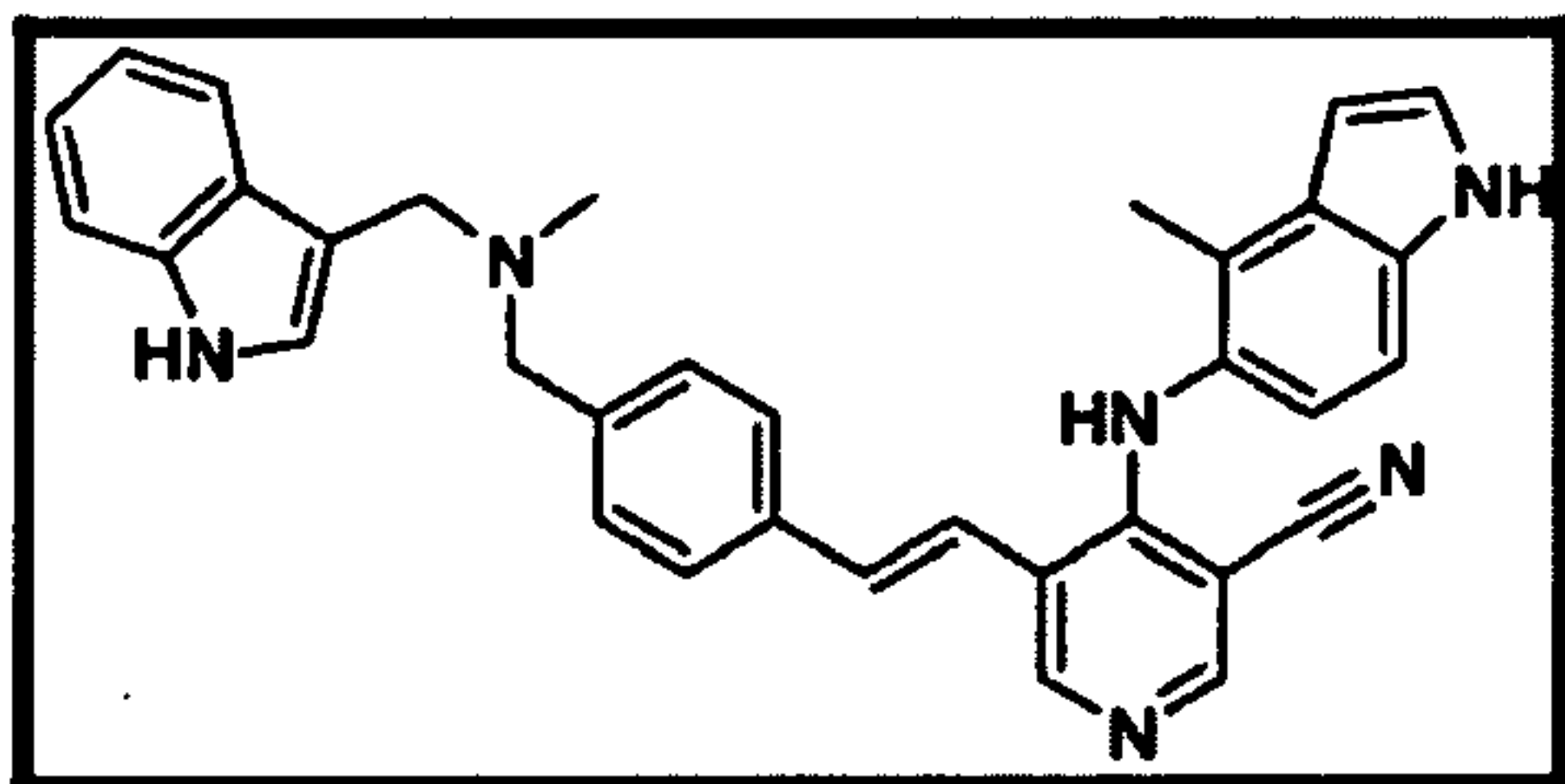
[00580] Preparation of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-(2-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}ethyl)pyridine-3-carbonitrile:

To pressure vessel containing a solution of EtOH (10 mL), THF (5 mL) and 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}ethenyl]pyridine-3-carbonitrile (150 mg, 0.31 mmol) was added 10% Pd on carbon (50 mg). The pressure vessel was charged with hydrogen (40 psi) and shaken overnight. The pressure was relieved and the solution filtered through magnesium silicate. The filtrate was concentrated under vacuum and the title compound (61 mg, 41%) was purified by preparative HPLC. MS 479.3 (M+H); HPLC:rt = 5.4 min [a].



[00581] Preparation of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[2-(4-methylphenyl)ethyl]pyridine-3-carbonitrile:

The procedure for the preparation of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-(2-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}ethyl)pyridine-3-carbonitrile was followed. The title compound (19 mg, 16%) was purified by preparative HPLC. MS 381.2 (M+H); HPLC: rt = 10.9 min [a].



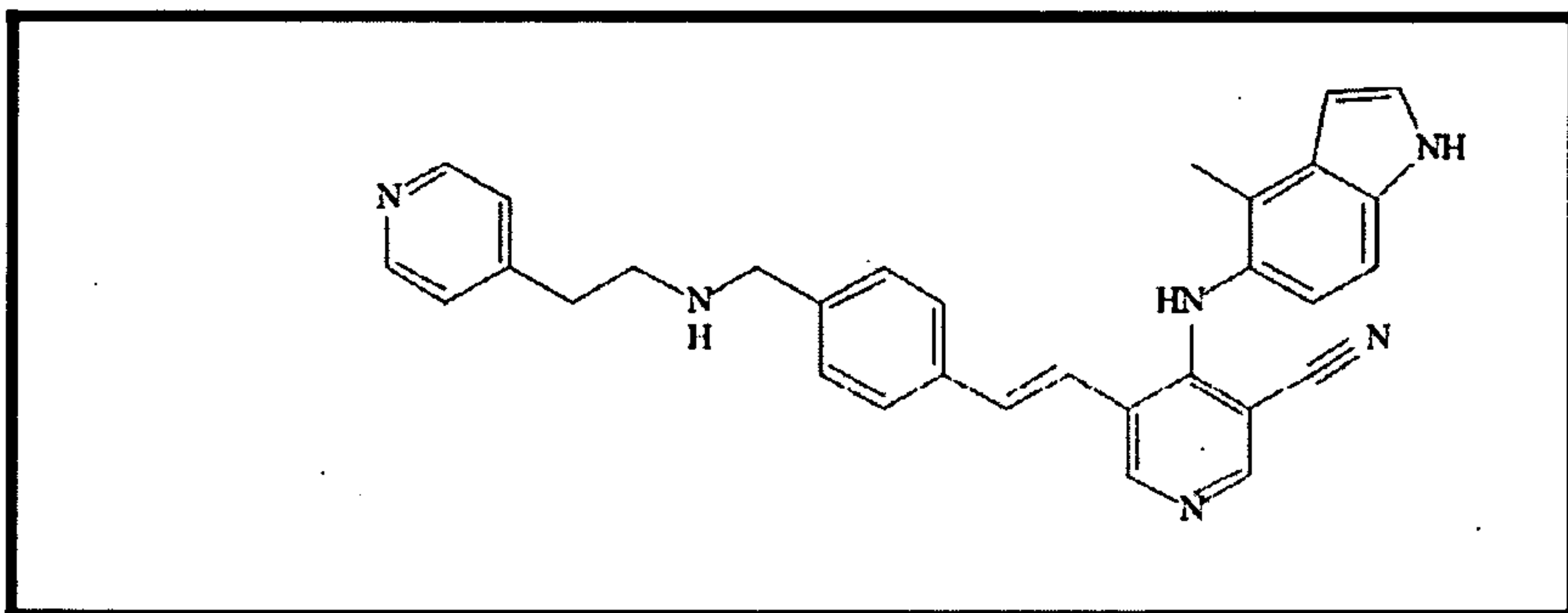
[00582] Preparation of 5-[(E)-2-(4-[(1H-indol-3-ylmethyl)(methyl)amino]methyl)phenyl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

To a 1:1 THF/MeOH solution (5 mL) of 5-[(E)-2-(4-formylphenyl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile (76 mg, 0.20 mmol) and 1-(1H-indol-3-yl)-N-

methylmethanamine dihydrochloride (70 mg, 0.3 mmol) was added N,N-diisopropylethylamine (0.11 mL, 0.6 mmol) and NaBH(OAc)₃ (212 mg, 1.0 mmol). The solution was stirred at room temperature overnight. The solvent was removed under vacuum and the residue was purified by preparative HPLC to provide the title compound (45 mg, 45%) MS 523.1 (M+H); HPLC: rt = 7.5 min [a].

[00583] Preparation of 5-[(E)-2-(4-formylphenyl)ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

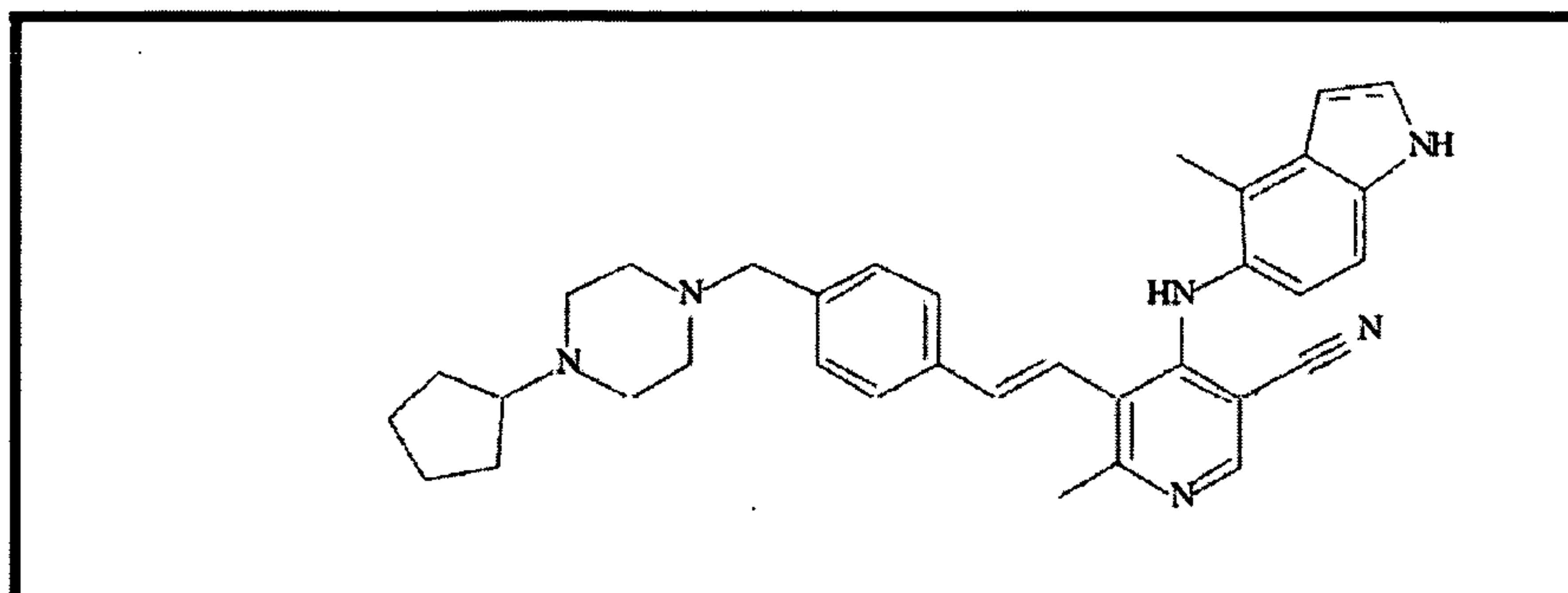
The title compound was prepared from 4-[(E)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethenyl]benzaldehyde and 5-iodo-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile via the procedure used to prepare 5-[(E)-2-(3-formylphenyl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile. The crude was purified by silica gel chromatography (CH₂Cl₂-THF and CH₂Cl₂-CH₃OH, gradient), providing 3.8 g (71%) of the title compound as a yellow solid. ¹HNMR(300 MHz, DMSO) 2.30 (s, 3H), 6.49 (s, 1H), 6.89 (d, 1H, J = 8.0 Hz), 7.25 (m, 2H), 7.57 (m, 3H), 7.85 (m, 3H), 8.18 (s, 1H), 8.47 (s, 1H), 10.00 (s, 1H), 11.10 (s, 1H); MS 393.1 (M+H).



[00584] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4-[(2-pyridin-4-yl ethyl) amino]methyl}phenyl)ethenyl]pyridine-3-carbonitrile:

A reaction mixture of 5-[(E)-2-(4-formylphenyl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile (130 mg, 0.34 mmol), 3-pyridin-4-yl-propylamine (83 mg, 0.68 mmol) in THF (2.0 mL) was stirred at room temperature for 30 minutes. To this was added NaBH(OAc)₃ (358 mg, 1.7 mmol). The reaction mixture was stirred at room temperature for 20 h, concentrated. The residue was purified by HPLC-MS (A: 0.1%NH₄OH in H₂O; B:

0.1%NH₄OH in acetonitrile), providing 35 mg (22%) of the title compound as a pale-yellow solid. MS 485.3 (M+H); HPLC: 97.01% at 215 nm, rt = 6.0 min [a].



[00585] Preparation of 5-[(E)-2-{4-[(4-cyclopentylpiperazin-1-yl)methyl]phenyl}ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

A reaction mixture of 5-[(E)-2-(4-formylphenyl)ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile (132 mg, 0.34 mmol), 4-pyrrolidin-1-yl-piperidine (104 mg, 0.68 mmol) in THF (2.0 mL) was stirred at room temperature for 30 minutes. To this was added NaBH(OAc)₃ (358 mg, 1.7 mmol). The reaction mixture was stirred at room temperature for 20 h, concentrated. The residue was purified by HPLC-MS (A: 0.1%NH₄OH in H₂O; B: 0.1%NH₄OH in acetonitrile), providing 35 mg (19%) of the title compound as a pale-yellow solid. MS 531.3 (M+H); HPLC: 94.2% at 215 nm, rt = 6.0 min [a].

Table 17:

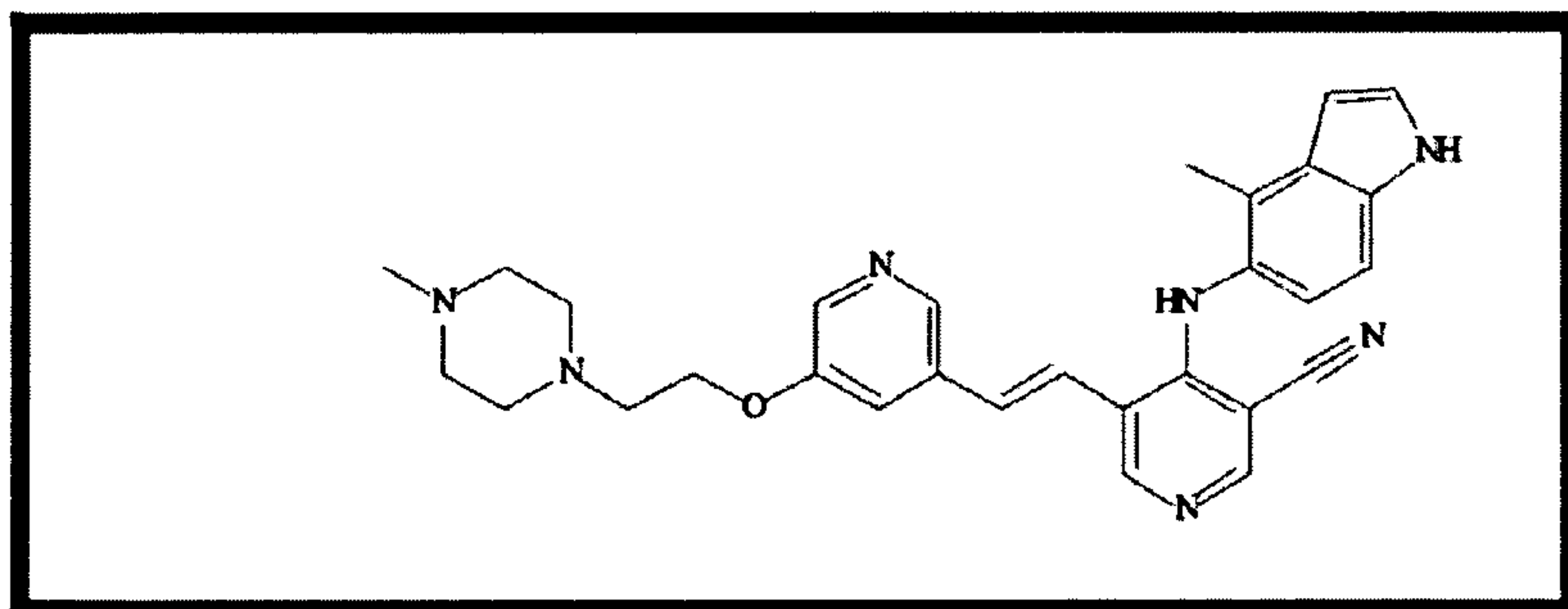
The compounds in table 17 were prepared from either 5-[(E)-2-(4-formylphenyl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile or 5-[(E)-2-(4-formylphenyl)ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile and the appropriate amine via the procedure described for and 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4-[(2-pyridin-4-ylethyl)amino]methyl)phenyl]ethenyl]pyridine-3-carbonitrile and 5-[(E)-2-{4-[(4-cyclopentylpiperazin-1-yl)methyl]phenyl}ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile.

Compound name	MS	HPLC rt
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4-[(2-piperidin-1-ylethyl)amino]methyl)phenyl]ethenyl]pyridine-3-carbonitrile	246.2 (M+H)	5.4 min [A]

4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4-[(2-pyrrolidin-1-ylethyl)amino]methyl)phenyl)ethenyl]pyridine-3-carbonitrile	477.4 (M+H)	5.2 min [A]
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-[(3-(4-methylpiperazin-1-yl)propyl)amino]methyl)phenyl]ethenyl]pyridine-3-carbonitrile	520.5 (M+H)	4.8 min [A]
5-[(E)-2-(3-[(4-(dimethylamino)piperidin-1-yl] methyl)phenyl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	491.2 (M+H)	5.2 min [A]
5-[(E)-2-(3-[(4-(dimethylamino)piperidin-1-yl]methyl)phenyl)ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	505.4 (M+H)	4.4 min [A]
5-[(E)-2-(4-[(3-ethoxypropyl)amino]methyl)phenyl)ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	480.4 (M+H)	6.2 min [A]
5-[(E)-2-(4-[(4-(2-hydroxyethyl)piperazin-1-yl]methyl)phenyl)ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	507.3 (M+H)	7.2 min [A]
5-[(E)-2-(4-[(3-hydroxypyrrolidin-1-yl)methyl] phenyl)ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	464.4 (M+H)	5.6 min [A]
5-[(E)-2-(4-[(4-hydroxypiperidin-1-yl)methyl]phenyl)ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	478.3 (M+H)	5.1 min [A]
5-[(E)-2-(4-[(4-methyl-1,4-diazepan-1-yl)methyl]phenyl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	477.3 (M+H)	4.6 min [A]
5-[(E)-2-(4-[(diethylamino)methyl]phenyl)ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	450.2 (M+H)	5.6 min [A]
5-[(E)-2-[3-(1,4'-bipiperidin-1'-yl)methyl]phenyl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	531.3 (M+H)	5.3 min [A]
5-[(E)-2-[4-[(1-ethylpyrrolidin-2-yl)methyl]amino]methyl]phenyl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	491.4 (M+H)	5.1 min [A]
5-[(E)-2-[4-[(1-ethylpyrrolidin-2-yl)methyl]amino]methyl]phenyl]ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	505.3 (M+H)	6.1 min [A]
5-[(E)-2-[4-[(2-(dimethylamino)ethyl)amino]methyl]phenyl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	226.1 (M+2H)	5.1 min [A]
5-[(E)-2-[4-[(2-(dimethylamino)ethyl)amino]methyl]phenyl]ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	465.3 (M+H)	4.8 min [A]
5-[(E)-2-[4-[(3-(dimethylamino)propyl)amino] methyl]phenyl]ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	479.4 (M+H)	4.9 min [A]
5-[(E)-2-[4-(1,4'-bipiperidin-1'-yl)methyl]phenyl]ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	545.3 (M+H)	4.0 min [A]
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4-[(2-morpholin-4-ylethyl)amino]methyl)phenyl)vinyl]	507.1 (M+H)	6.5 min [A]

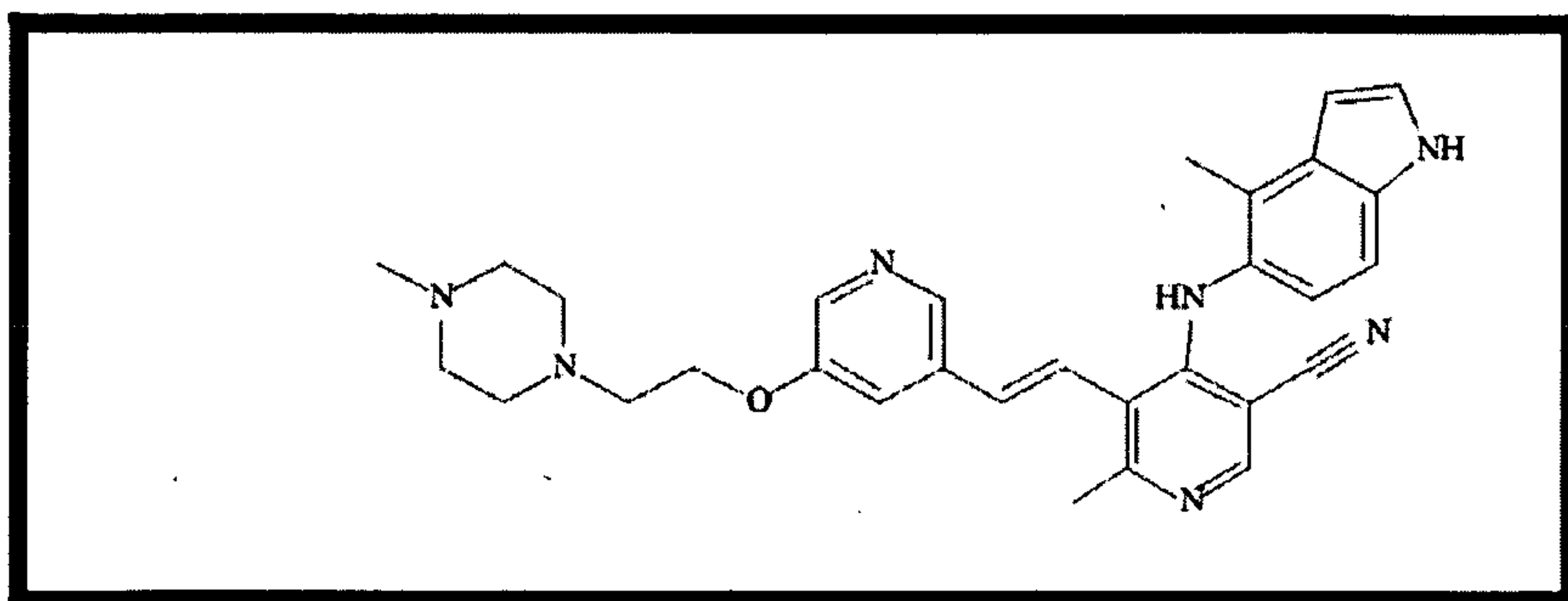
nicotinonitrile		
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4- [(2-piperidin-1-ylethyl)amino]methyl)phenyl)ethenyl] pyridine-3-carbonitrile	253.2 (M+2H)	5.1 min [A]
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4- [(2-pyridin-2-ylethyl)amino]methyl)phenyl)ethenyl] pyridine-3-carbonitrile	499.1 (M+H)	5.1 min [A]
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4- [(2-pyridin-3-ylethyl)amino]methyl)phenyl)ethenyl] pyridine-3-carbonitrile	499.1 (M+H)	4.7 min [A]
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4- [(2-pyridin-4-ylethyl)amino]methyl)phenyl)ethenyl] pyridine-3-carbonitrile	480.1 (M+H)	5.7 min [A]
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4- [(2-pyrrolidin-1-ylethyl)amino]methyl)phenyl)vinyl] nicotinonitrile	491.6 (M+H)	4.3 min [A]
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4- [(3-morpholin-4-ylpropyl)amino]methyl)phenyl) ethenyl]pyridine-3-carbonitrile	521.3 (M+H)	5.9 min [A]
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4- [(4-methylpiperazin-1-yl)methyl]phenyl)ethenyl] pyridine-3-carbonitrile	239.1 (M+2H)	5.1 min [A]
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4- [(4-pyrrolidin-1-ylpiperidin-1-yl)methyl]phenyl)ethenyl] pyridine-3-carbonitrile	531.4 (M+H)	4.2 min [A]
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4- [(3-(4-methylpiperazin-1-yl)propyl)amino]methyl) phenyl]ethenyl]pyridine-3-carbonitrile	520.5 (M+H)	4.6 min [A]
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4- (morpholin-4-ylmethyl)phenyl)ethenyl]pyridine-3- carbonitrile	232.6 (M+2H)	5.2 min [A]
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4- (piperidin-1-ylmethyl)phenyl)ethenyl]pyridine-3- carbonitrile	462.2 (M+H)	5.9 min [A]
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4- (pyrrolidin-1-ylmethyl)phenyl)ethenyl]pyridine-3- carbonitrile	448.2 (M+H)	6.0 min [A]
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4- (thiomorpholin-4-ylmethyl)phenyl)ethenyl]pyridine-3- carbonitrile	480.1 (M+H)	5.7 min [A]
6-methyl-5-[(E)-2-(4-[(4-(1-methylethyl)piperazin-1- yl)methyl]phenyl)ethenyl]-4-[(4-methyl-1H-indol-5-yl) amino]pyridine-3-carbonitrile	505.3 (M+H)	5.9 min [A]
6-methyl-5-[(E)-2-(4-[(4-methyl-1,4-diazepan-1-yl) methyl]phenyl)ethenyl]-4-[(4-methyl-1H-indol-5-yl) amino]pyridine-3-carbonitrile	491.3 (M+H)	4.3 min [A]
5-[(E)-2-(3-[(3-ethoxypropyl)amino]methyl)phenyl) ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3- carbonitrile	466.3 (M+H)	6.7 min [A]
5-[(E)-2-(3-[(2-ethoxyethyl)amino]methyl)phenyl) ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-	452.3 (M+H)	6.4 min [A]

carbonitrile		
5-[(E)-2-{3-[(dimethylamino)methyl]phenyl}ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	408.1 (M+2H)	6.2min [A]
5-[(E)-2-{3-[(2-azepan-1-ylethyl)amino]methyl}phenyl}ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	505.2 (M+H)	6.1min [A]
5-[(E)-2-{3-[(3-ethoxypropyl)amino]methyl}phenyl}ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	480.2 (M+H)	6.9min [A]
5-[(E)-2-{4-[(2-azepan-1-ylethyl)amino]methyl}phenyl}ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	519.4 (M+H)	5.4 [A]
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{4-[(2-(2-methylpyrrolidin-1-yl)ethyl)amino]methyl}phenyl}ethenyl]pyridine-3-carbonitrile	505.3 (M+H)	4.9min [A]
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{3-[(3-(4-methylpiperazin-1-yl)propyl)amino]methyl}phenyl}ethenyl]pyridine-3-carbonitrile	534.6 (M+H)	5.1min [A]
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{4-[(4-morpholin-4-yl)piperidin-1-yl]methyl}phenyl}ethenyl]pyridine-3-carbonitrile	534.6 (M+H)	6.0min [A]
(E)-4-(4-methyl-1H-indol-5-ylamino)-5-{3-[(2-(piperidin-1-yl)ethylamino)methyl]styryl}nicotinonitrile	491.3 (M+H)	5.1 min [A]



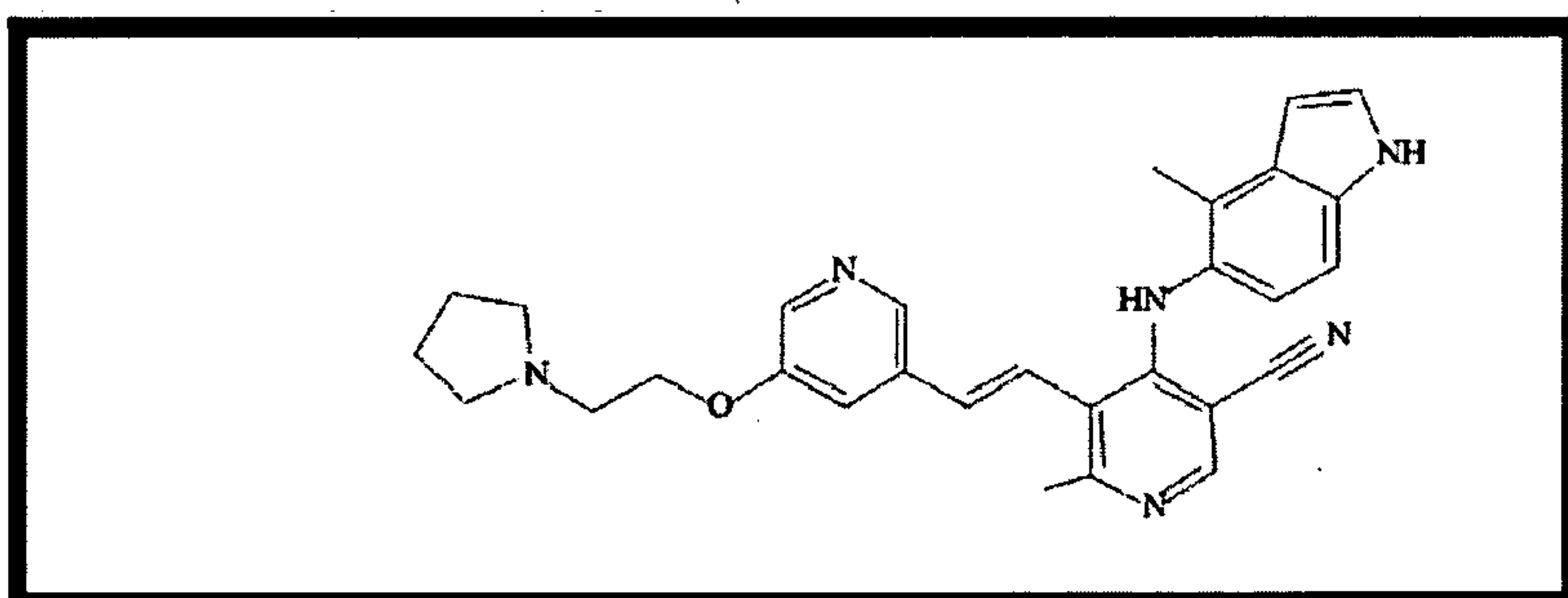
[00586] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{5-[2-(4-methylpiperazin-1-yl)ethoxy]pyridin-3-yl}ethenyl]pyridine-3-carbonitrile:

A DMF (5 ml) solution of 4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile (50 mg, 0.5 mmol), 1-{2-[(5-bromopyridin-3-yl)oxy]ethyl}-4-methyl-piperazine (173 mg, 0.6 mmol), Pd(OAc)₂ (23 mg, 0.01 mmol), P(o-tolyl)₃ and Et₃N (5 ml) was heated at 115°C overnight. The reaction mixture was cooled to room temperature, diluted with saturated NaHCO₃ and extracted with ethyl acetate. The organic layer was washed with brine and concentrated *in vacuo*. The residue was purified by preparative HPLC to afford 50 mg (21%) of the title compound as a yellow solid. MS: (M+H) 494.3, HPLC: *rt* = 4.9 min [a].



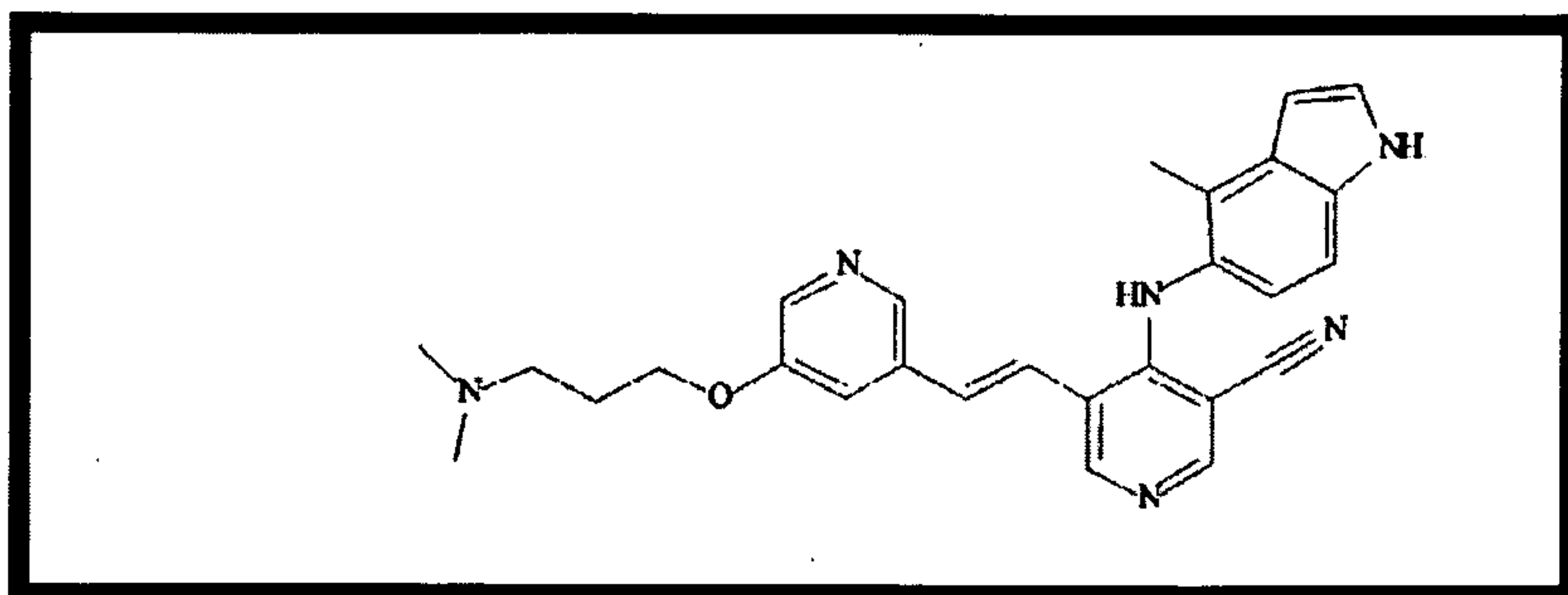
[00587] Preparation of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{5-[2-(4-methylpiperazin-1-yl)ethoxy]pyridin-3-yl}ethenyl]pyridine-3-carbonitrile:

The title compound was prepared from 1-{2-[(5-bromopyridin-3-yl)oxy]ethyl}-4-methylpiperazine and 6-methyl-4-(4-methyl-1H-indol-5-ylamino)-5-vinyl-nicotinonitrile via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{5-[2-(4-methylpiperazin-1-yl)ethoxy]pyridin-3-yl}ethenyl]pyridine-3-carbonitrile to afford 48 mg(18%) of the title compound as a yellow solid. MS: (M+H) 508.4. HPLC: 92.5% at 215 nm, rt = 4.1 min [a].



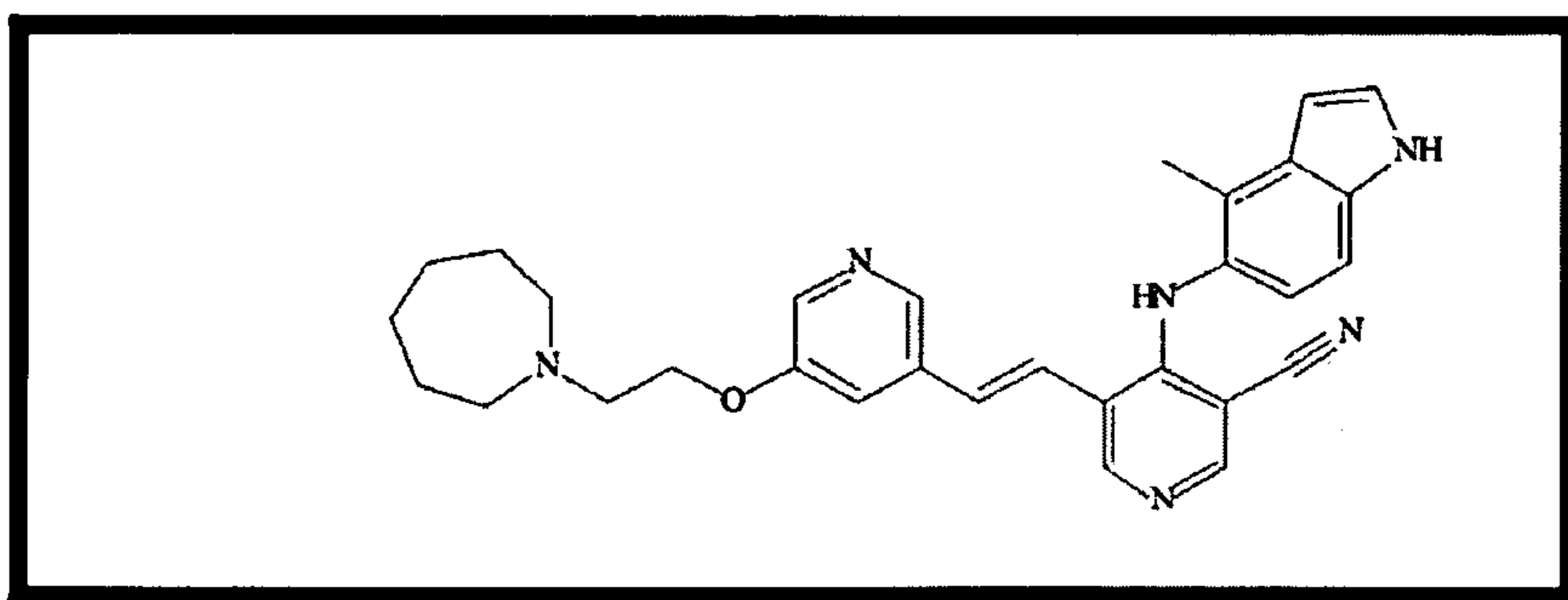
[00588] Preparation of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{5-[2-(2-pyrrolidin-1-ylethoxy)pyridin-3-yl}ethenyl]pyridine-3-carbonitrile:

The title compound was prepared from 3-bromo-5-(2-pyrrolidin-1-yl-ethoxy)pyridine and 6-methyl-4-(4-methyl-1H-indol-5-ylamino)-5-vinyl-nicotinonitrile via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{5-[2-(4-methylpiperazin-1-yl)ethoxy]pyridin-3-yl}ethenyl]pyridine-3-carbonitrile to afford 31 mg (12%) of the title compound as a yellow solid. MS: (M+H) 479.4. HPLC: rt = 4.9 min [a].



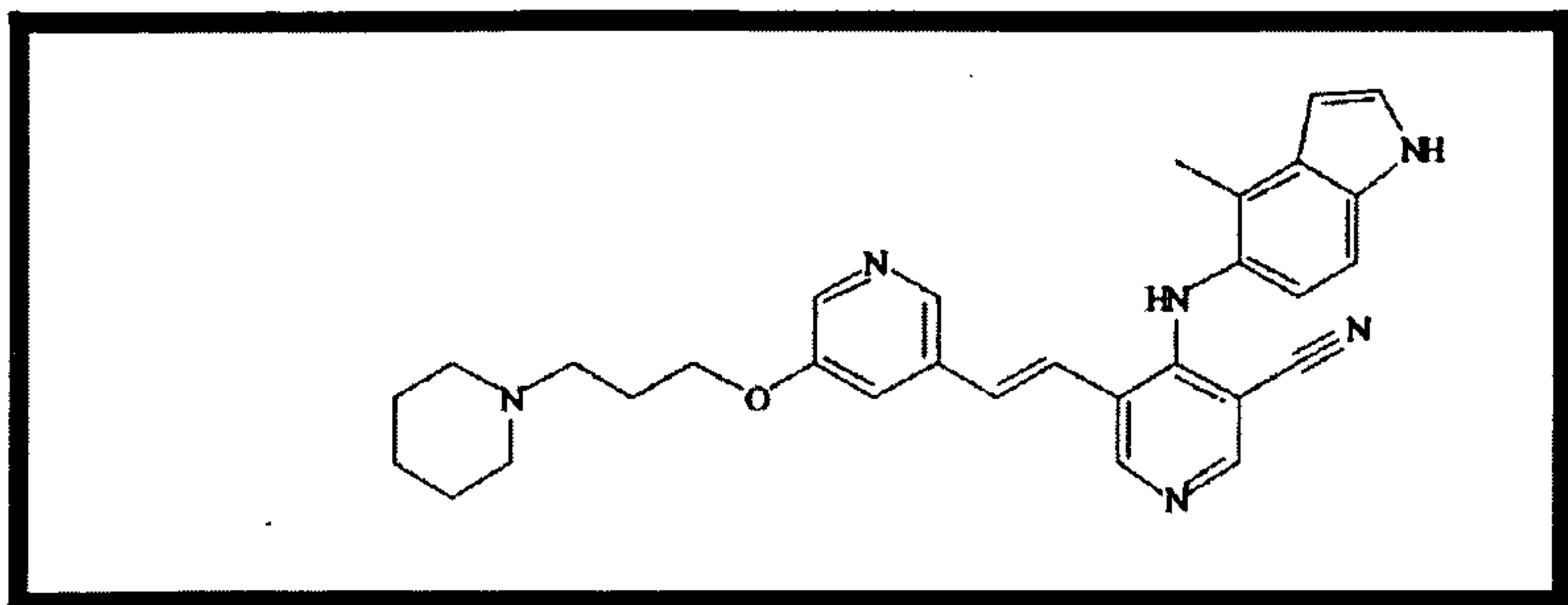
[00589] Preparation of 5-[(E)-2-{5-[3-(dimethylamino)propoxy]pyridin-3-yl}ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

The title compound was prepared from 3-[(5-bromopyridin-3-yl)oxy]-N,N-dimethylpropan-1-amine and 6-methyl-4-(4-methyl-1H-indol-5-ylamino)-5-vinyl-nicotinonitrile via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{5-[2-(4-methylpiperazin-1-yl)ethoxy]pyridin-3-yl}ethenyl]pyridine-3-carbonitrile to afford 31 mg (12%) of the title compound as a yellow solid. MS: (M+H) 453.3. HPLC: *rt* = 4.7 min [a].



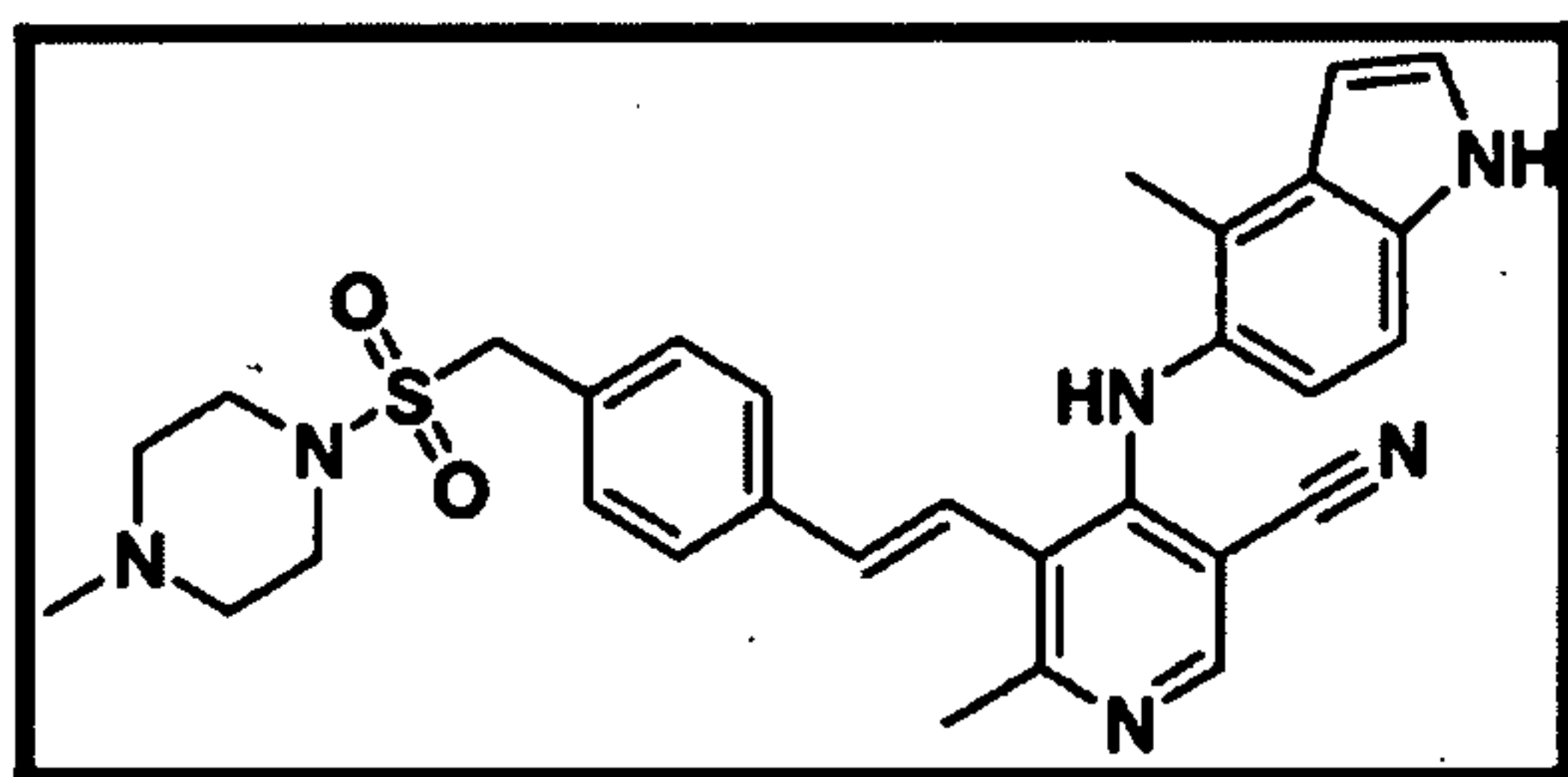
[00590] Preparation of 5-[(E)-2-{5-(2-azepan-1-ylethoxy)pyridin-3-yl}ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile:

The title compound was prepared from 1-{2-[(5-bromopyridin-3-yl)oxy]ethyl}azepane and 6-methyl-4-(4-methyl-1H-indol-5-ylamino)-5-vinyl-nicotinonitrile via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{5-[2-(4-methylpiperazin-1-yl)ethoxy]pyridin-3-yl}ethenyl]pyridine-3-carbonitrile to afford 31 mg (12%) of the title compound as a yellow solid. MS: (M+H) 493.4. HPLC: *rt* = 6.1 min [a].



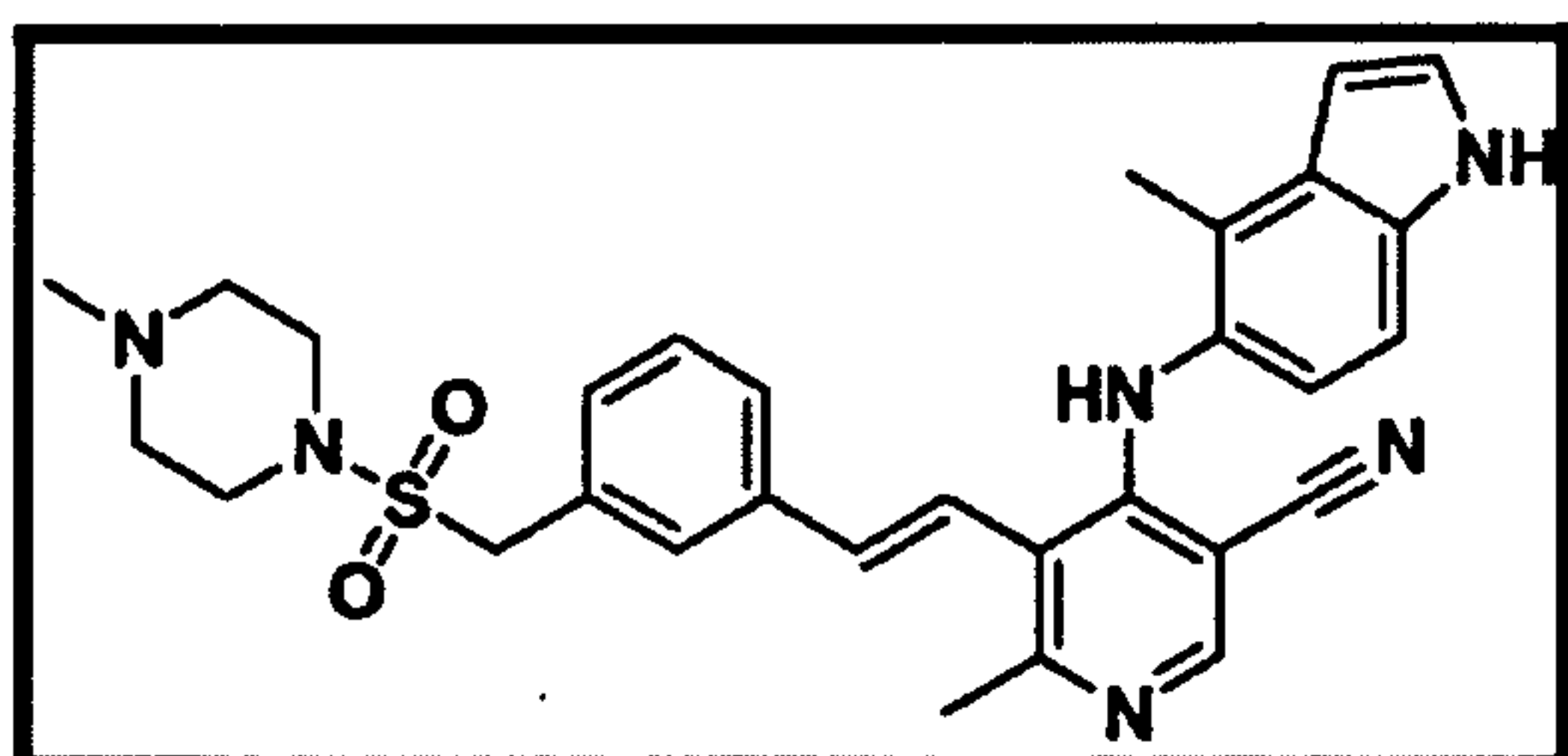
[00591] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(3-piperidin-1-ylpropoxy)pyridin-3-yl]ethenyl]pyridine-3-carbonitrile:

The title compound was prepared from 3-bromo-5-(3-piperidin-1-ylpropoxy)pyridine and 6-methyl-4-(4-methyl-1H-indol-5-ylamino)-5-vinyl-nicotinonitrile via the procedure used to prepare 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-[2-(4-methylpiperazin-1-yl)ethoxy]pyridin-3-yl]ethenyl]pyridine-3-carbonitrile to afford 45 mg(18%) of the title compound as a yellow solid. MS: (M+H) 493.4. HPLC: rt = 4.8 min [a].



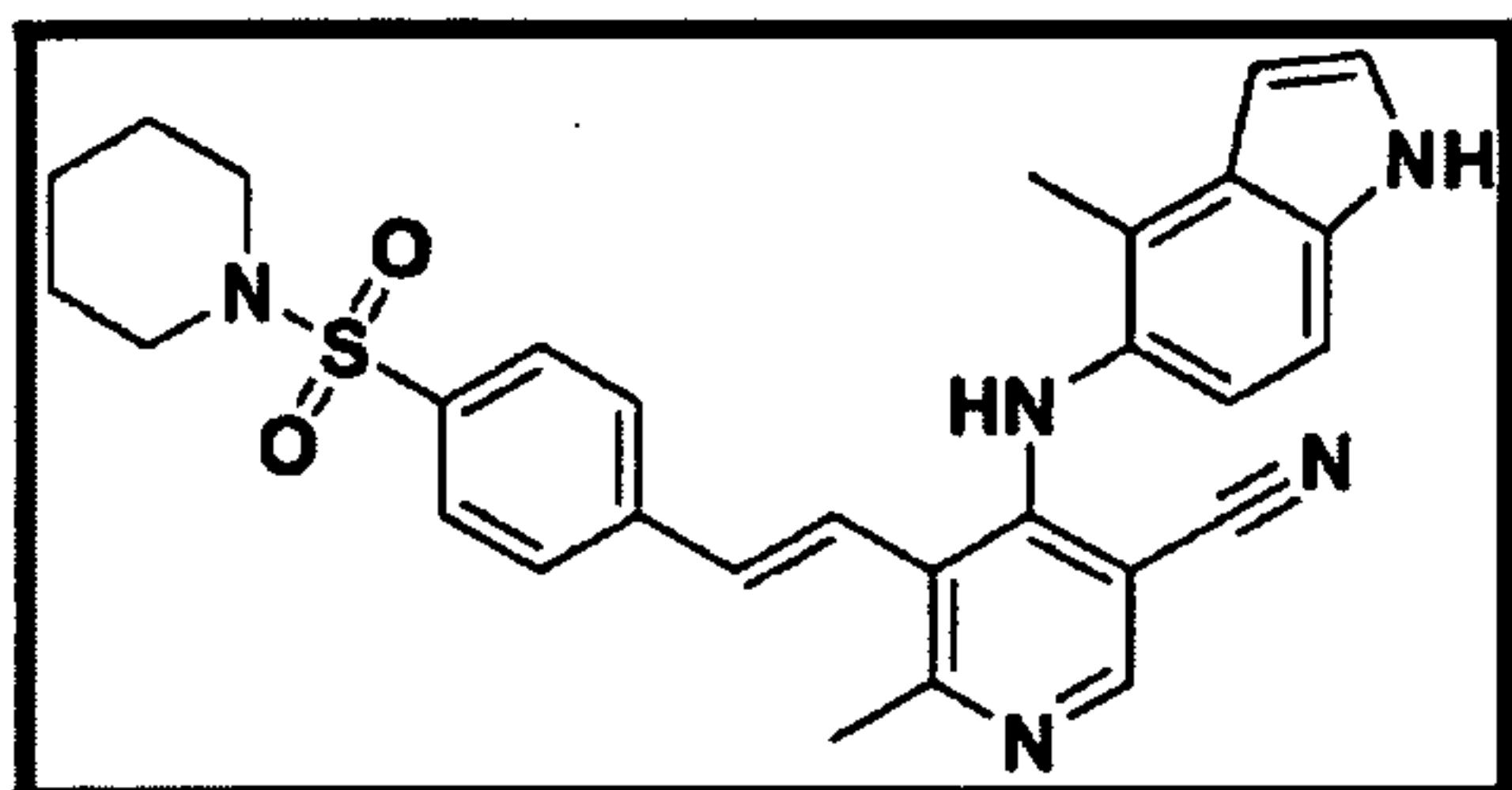
[00592] Preparation of 6-Methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-[(4-methylpiperazin-1-yl)sulfonyl]methyl]phenyl]ethenyl]pyridine-3-carbonitrile:

The procedure for the preparation of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(pyrrolidin-1-ylsulfonyl)phenyl]ethenyl]pyridine-3-carbonitrile was followed using 1-[(4-bromobenzyl)sulfonyl]-4-methylpiperazine. The title compound (19 mg, 23%) was purified by preparative HPLC. MS 541.6 (M+H); HPLC: rt = 6.2 min [a].



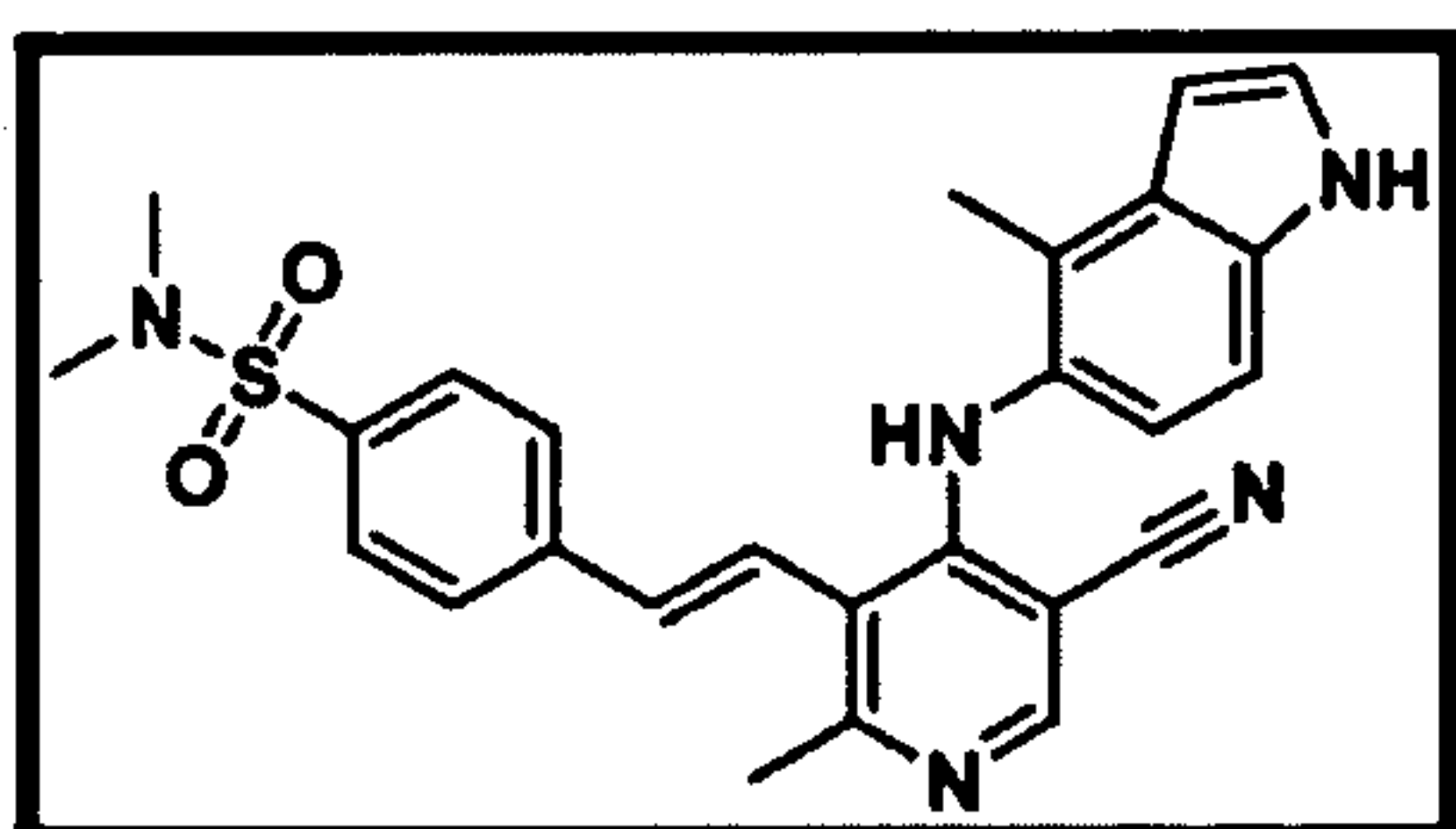
[00593] Preparation of 6-Methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{3-[(4-methylpiperazin-1-yl)sulfonyl]methyl}phenyl]ethenyl]pyridine-3-carbonitrile:

The procedure for the preparation of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(pyrrolidin-1-ylsulfonyl)phenyl]ethenyl]pyridine-3-carbonitrile was followed using 1-[(3-bromobenzyl)sulfonyl]-4-methylpiperazine. The title compound (25 mg, 31%) was purified by preparative HPLC. MS 541.6 (M+H); HPLC: *rt* = 6.4 min [a].



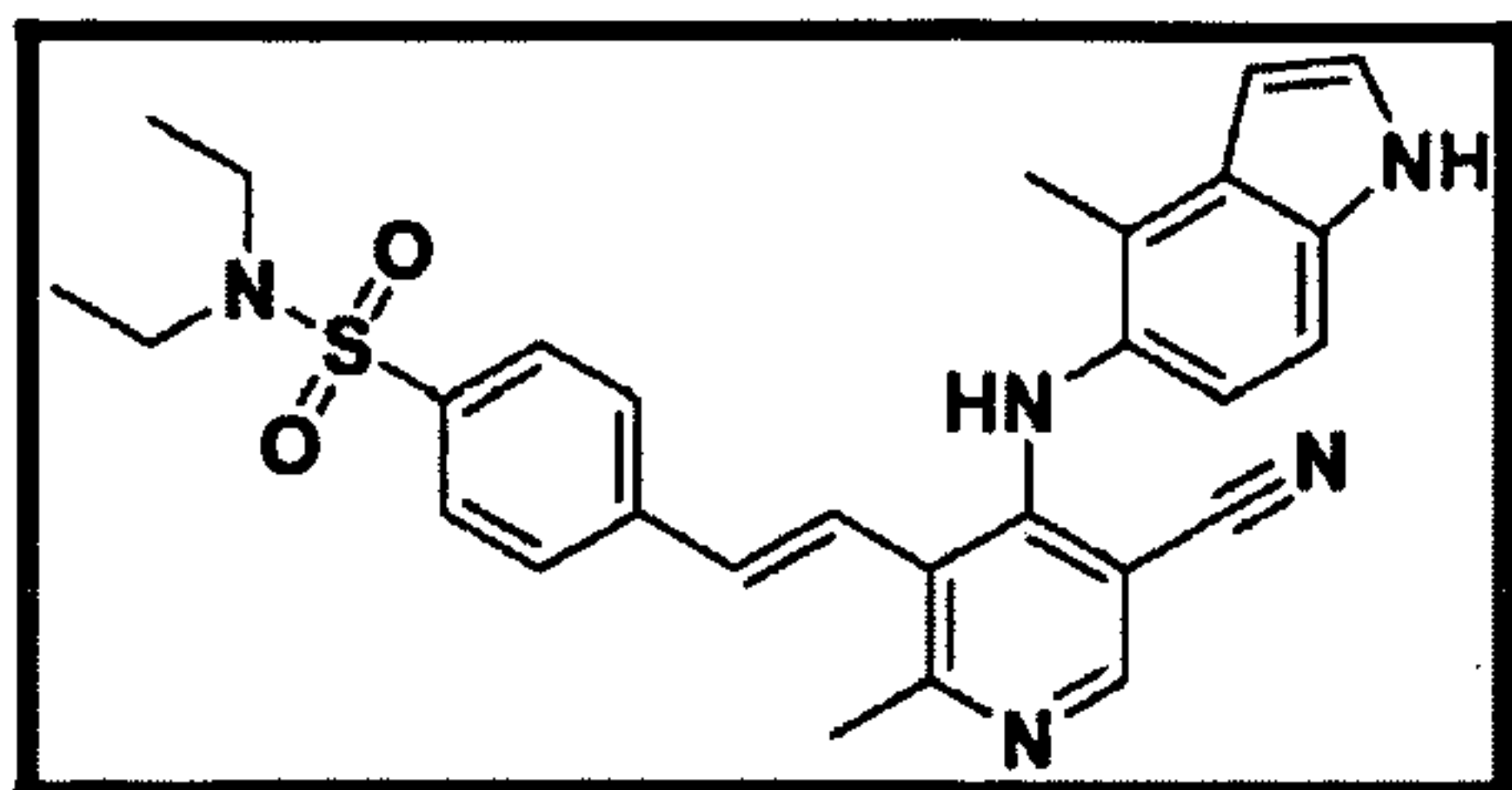
[00594] Preparation of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(piperidin-1-ylsulfonyl)phenyl]ethenyl]pyridine-3-carbonitrile:

The procedure for the preparation of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(pyrrolidin-1-ylsulfonyl)phenyl]ethenyl]pyridine-3-carbonitrile was followed using 1-[(4-bromophenyl)sulfonyl]piperidine. The title compound (24 mg, 31%) was purified by preparative HPLC eluting with CH₃CN (containing 0.01% NH₄OH)/water (containing 0.01% NH₄OH). MS 512.6 (M+H); HPLC: *rt* = 10.7 min [a].



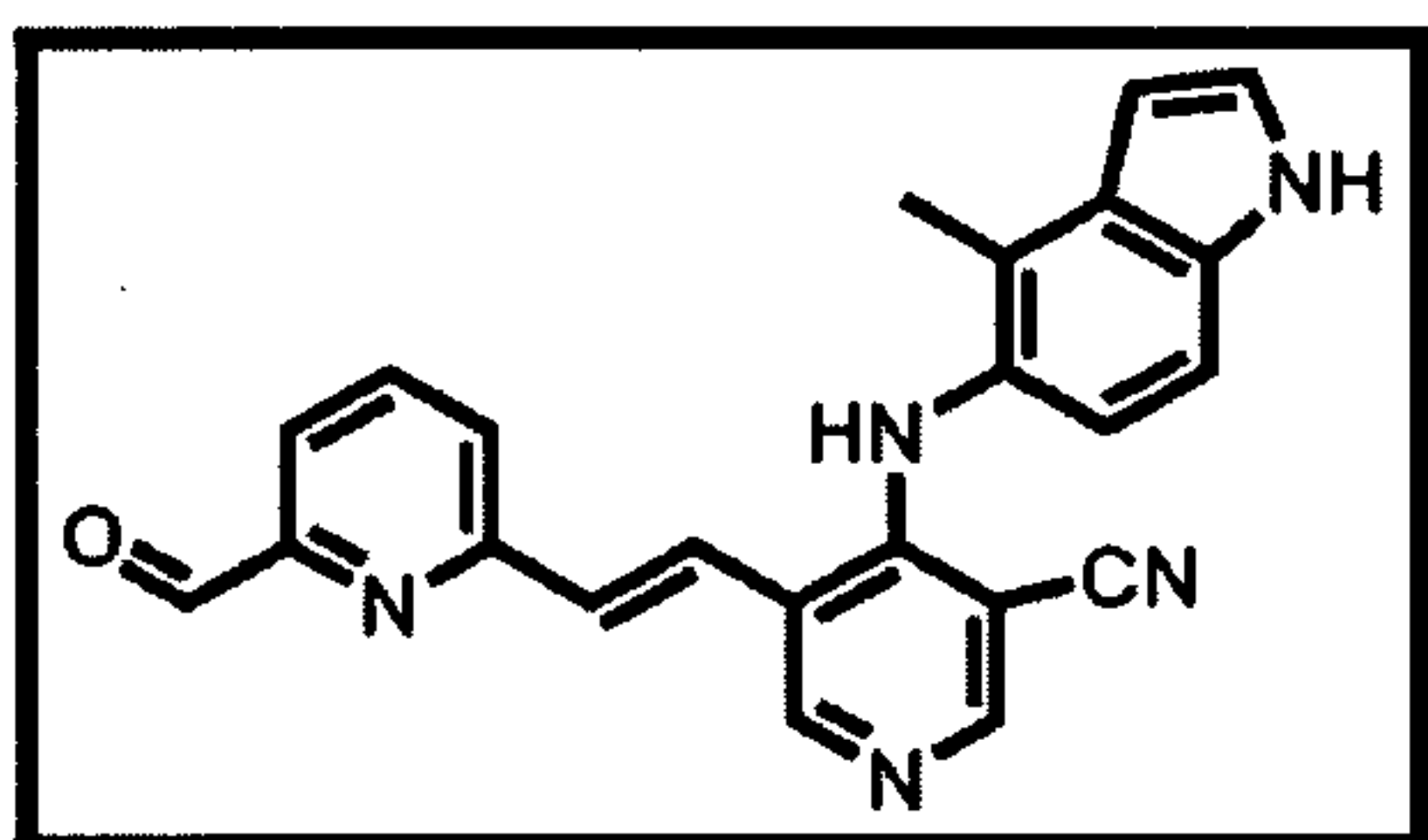
[00595] Preparation of 6-Methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(N,N-dimethylbenzenesulfonyl)phenyl]ethenyl]pyridine-3-carbonitrile:

The procedure for the preparation of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(pyrrolidin-1-ylsulfonyl)phenyl]ethenyl]pyridine-3-carbonitrile was followed using 4-bromo-N,N-dimethylbenzenesulfonamide. The title compound (20 mg, 28%) was purified by preparative HPLC. MS 472.5 (M+H); HPLC: *rt* = 9.2 min [a].



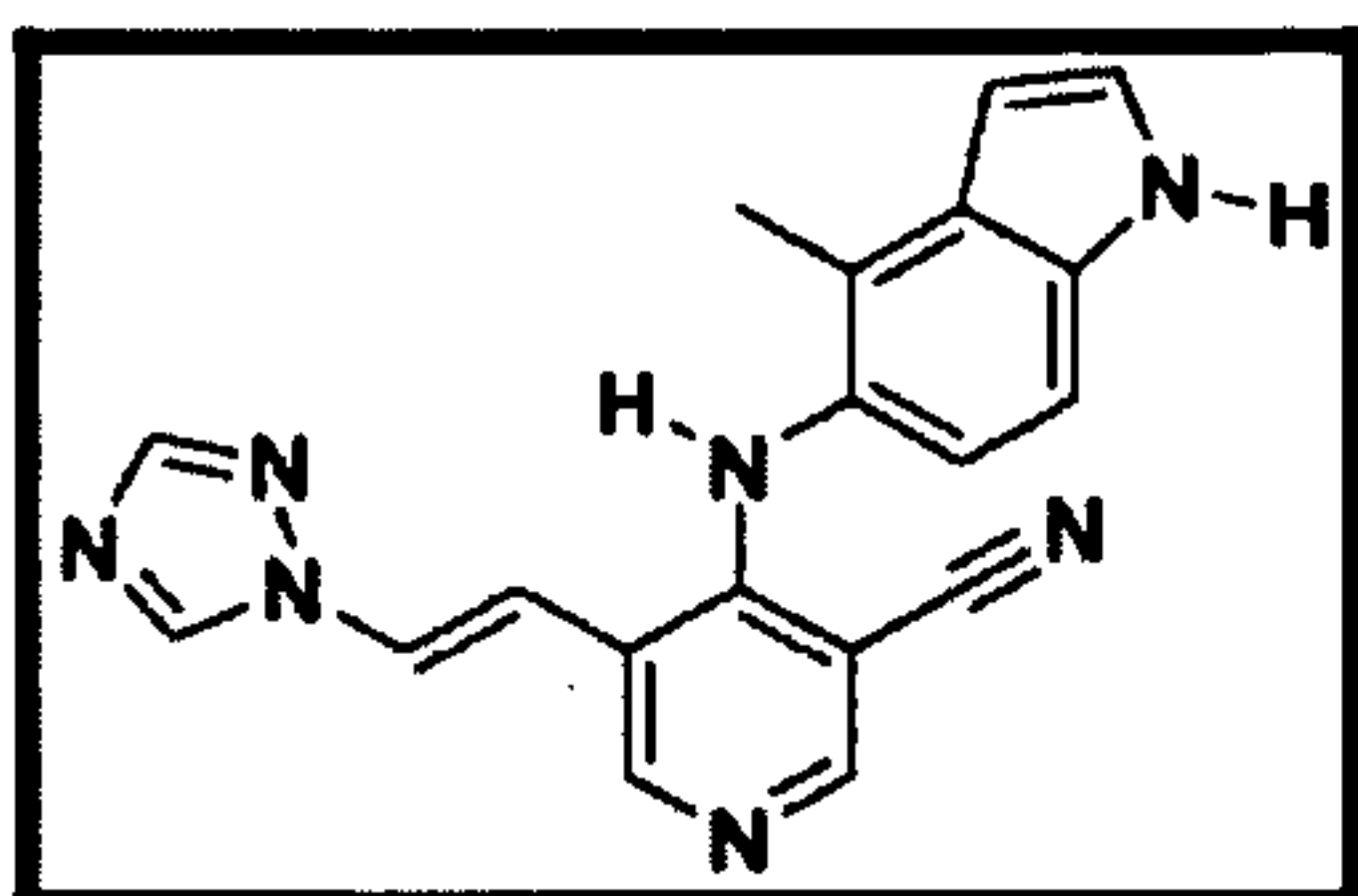
[00596] Preparation of 6-Methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(N,N-diethylbenzenesulfonyl)phenyl]ethenyl]pyridine-3-carbonitrile:

The procedure for the preparation of 6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(pyrrolidin-1-ylsulfonyl)phenyl]ethenyl]pyridine-3-carbonitrile was followed using 4-bromo-N,N-diethylbenzenesulfonamide. The title compound (41 mg, 55%) was purified by preparative HPLC. MS 500.6 (M+H); HPLC: *rt* = 10.5 min [a].



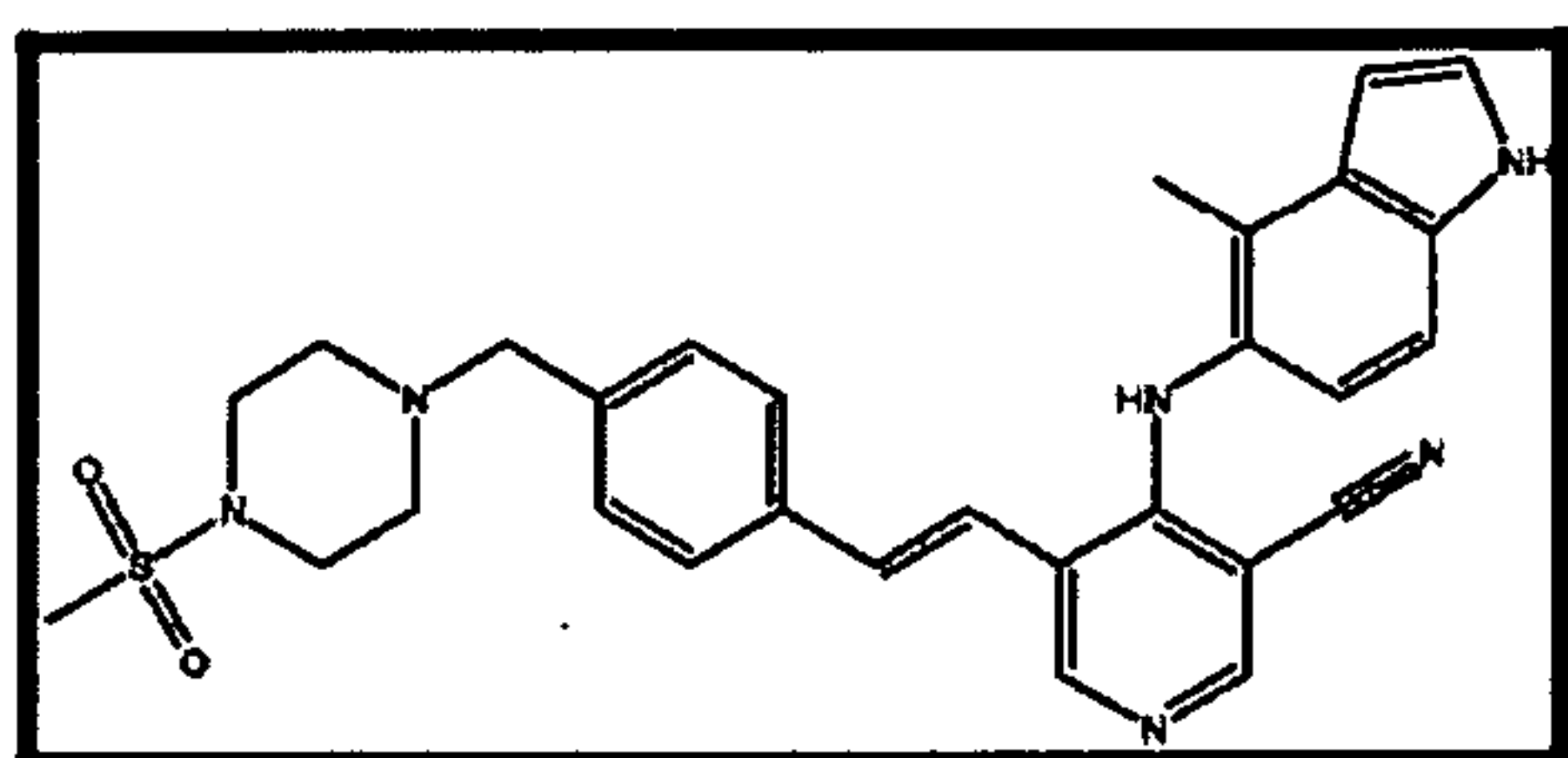
[00597] Preparation of (E)-5-[2-(6-formylpyridin-2-yl)vinyl]-4-(4-methyl-1H-indol-5-yl amino)nicotinonitrile:

A mixture of 5-[(E)-2-[6-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (38 mg, 0.1 mmol) and Dess-Martin periodinane (52 mg, 0.12 mmol) in CH₂Cl₂ (1.0 mL) was stirred overnight at room temperature, concentrated. The residue was purified by preparative HPLC providing 14 mg (37%) of the title compound as a yellow solid. ¹HNMR(300 MHz, DMSO) δ 2.33 (s, 3H), 6.50 (s, 1H), 6.94 (d, 1H, *J* = 6.9 Hz), 7.24 (d, 1H, *J* = 6.6 Hz), 7.35 (m, 2H), 7.80 (d, 1H, *J* = 6.0 Hz), 7.88 (d, 1H, *J* = 12 Hz), 8.02 (m, 2H), 8.33 (s, 1H); 8.65 (s, 1H), 8.97 (s, 1H); 9.96 (s, 1H), 11.14 (s, 1H); MS 380.1 (M+H).



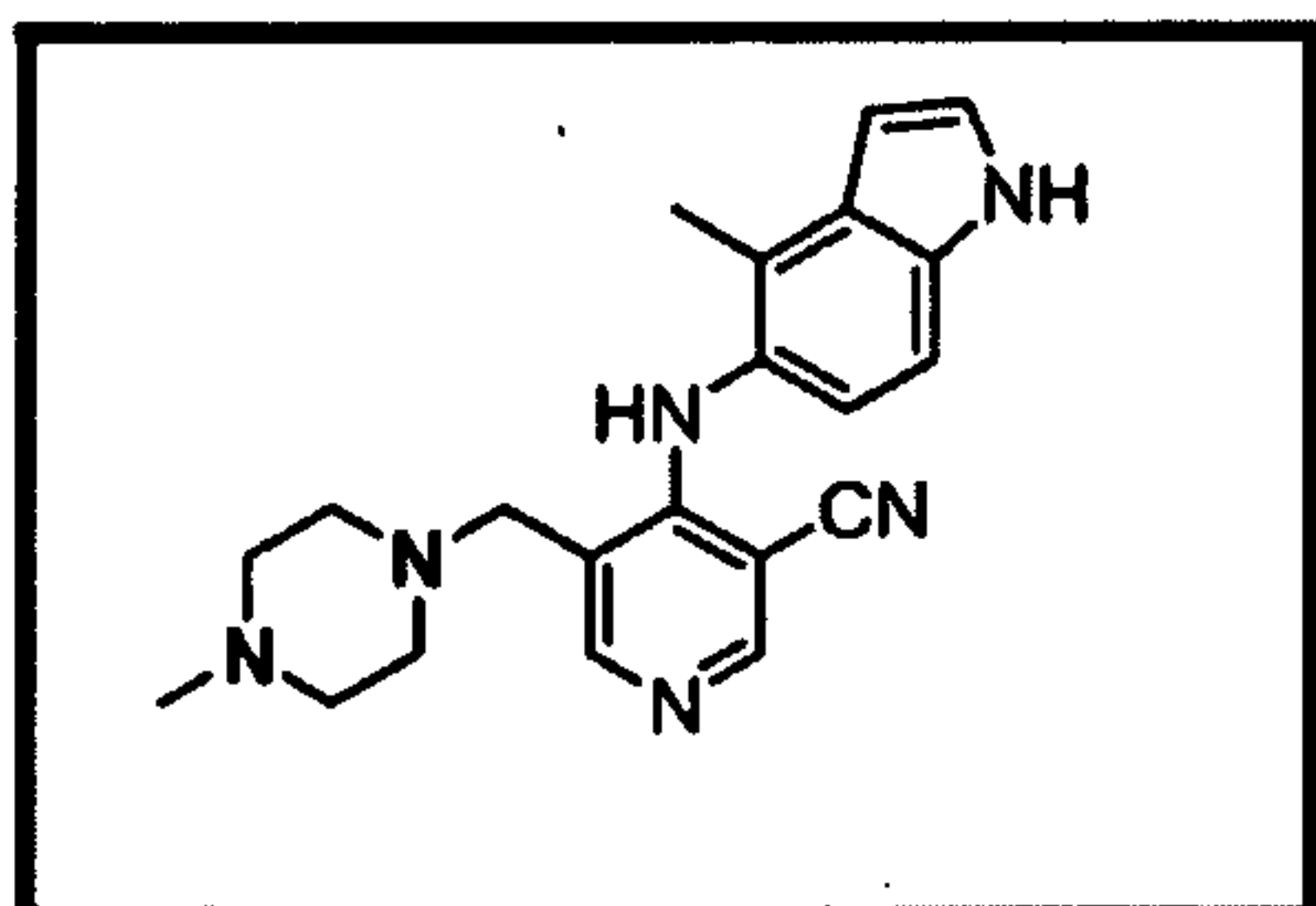
[00598] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(1H-1,2,4-triazol-1-yl)vinyl]nicotinonitrile:

The procedure for 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-pyrazin-2-ylvinyl]nicotinonitrile was followed using 1-vinyl-1,2,4-triazole. The crude residue was purified by HPLC to provide 6.4 mg (6%) of the title compound as a tan solid. MS 342.2 (M+H); HPLC: rt = 6.1 min [a].



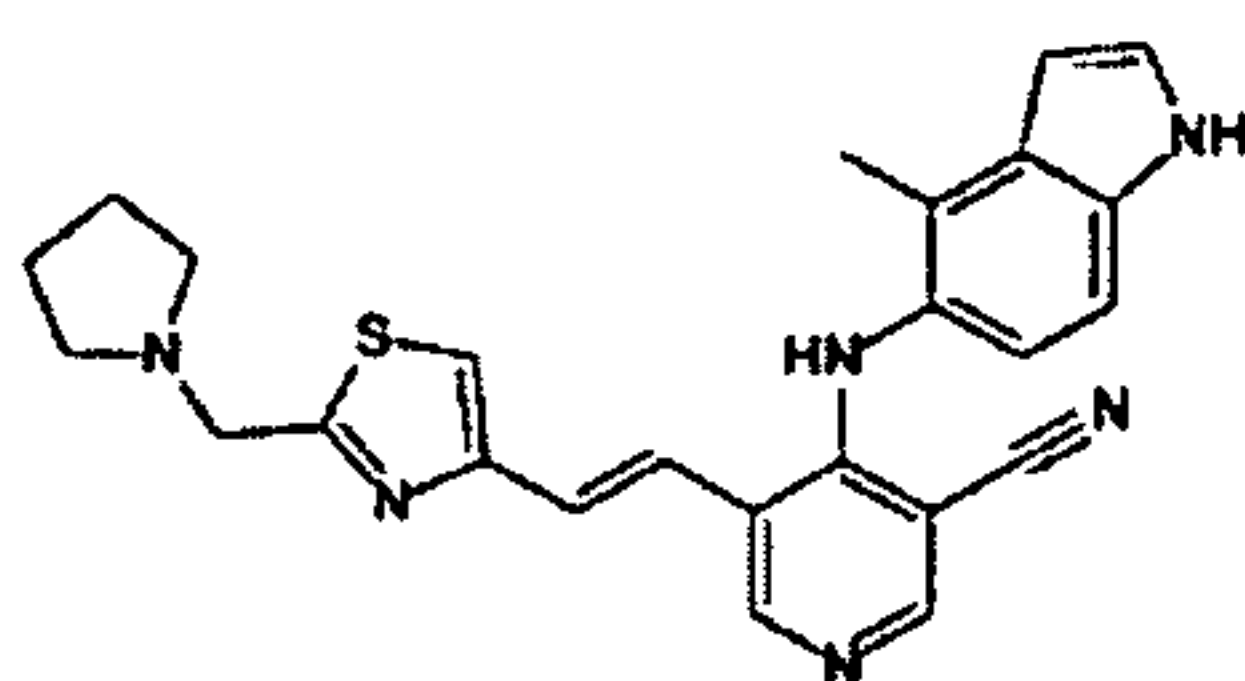
[00599] Preparation of 4-[(4-methyl-1h-indol-5-yl)amino]-5-[(e)-2-(4-{[4-(methylsulfonyl)piperazin-1-yl]methyl}phenyl)ethenyl]pyridine-3-carbonitrile:

To a 0°C mixture of 5-[(E)-2-(4-formylphenyl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile (100 mg, 0.26 mmol) and 1-methylsulfonylpiperazine (100 mg, 0.61 mmol) in 4 mL of dichloromethane and 1 mL of 1-methyl-2-pyrrolidinone was added sodium triacetoxyborohydride (320 mg, 1.51 mmol). After stirring at 0°C for 10 min, 2 drops of acetic acid were added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between aqueous sodium bicarbonate and ethyl acetate. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography eluting with a gradient of 1:1 hexane:ethyl acetate to ethyl acetate to 10% methanol in ethyl acetate. The fractions containing the desired product were combined, concentrated in vacuo and the residue triturated with diethyl ether to provide 64 mg (47%) of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4-{[4-(methylsulfonyl)piperazin-1-yl]methyl}phenyl)ethenyl]pyridine-3-carbonitrile as a pale yellow solid, MS 527.3 (M+H), HPLC: rt = 6.5 min [a].



[00600] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(4-methylpiperazin-1-yl)methyl]pyridine-3-carbonitrile:

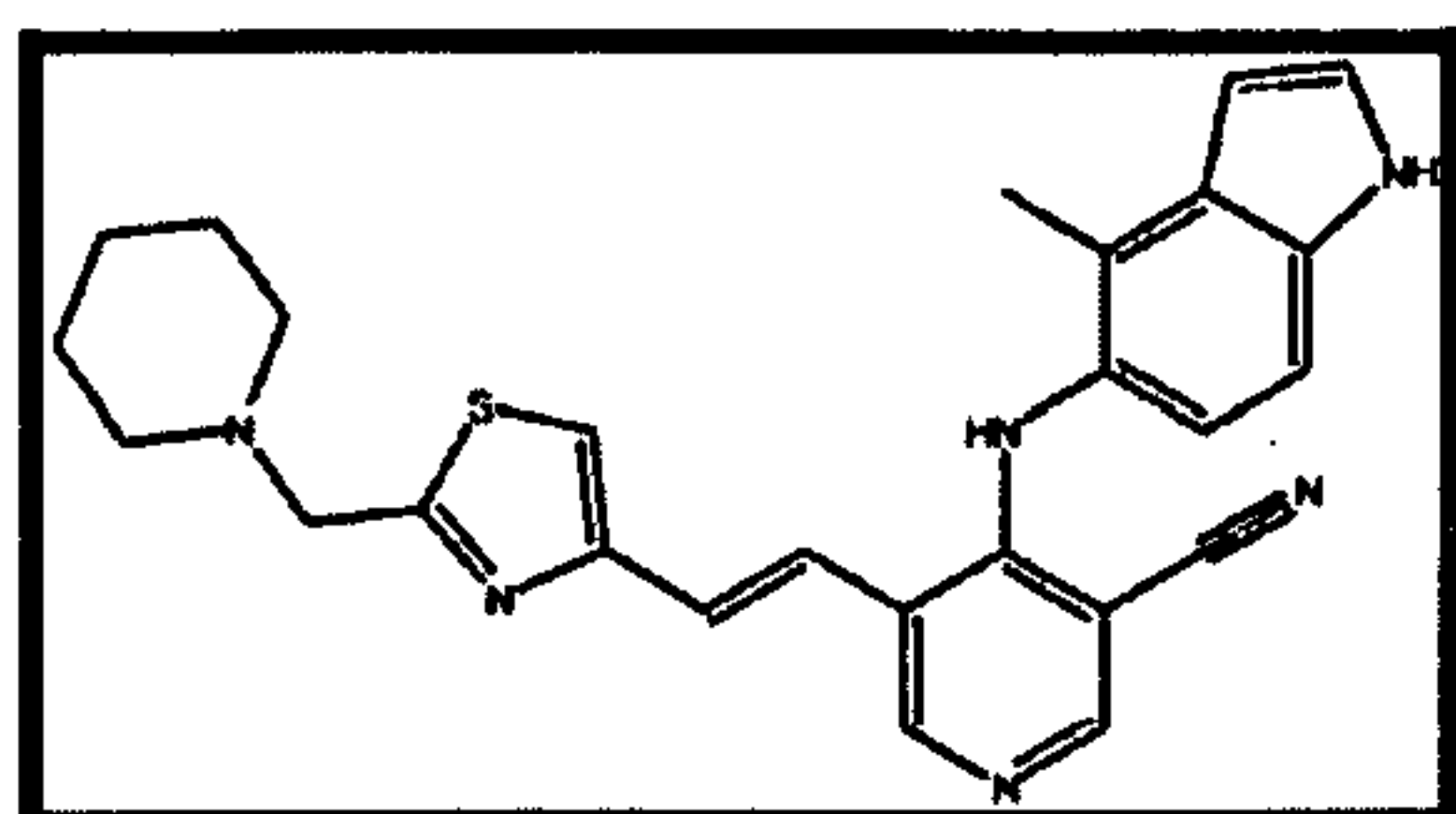
A mixture of 5-iodo-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile (374.2 mg, 1.0 mmol), potassium 1-methyl-4-trifluoroboratomethylpiperazine (242.1 mg, 1.1 mmol), Pd(OAc)₂ (11.2 mg, 0.05 mmol), XPhos (47.76 mg, 0.1 mmol) and cesium carbonate (1.14 g, 3.5 mmol) in 4.0 mL of THF/H₂O (10:1) was heated at 80°C for 24 h. Additional potassium 1-methyl-4-trifluoroboratomethylpiperazine (242.1 mg, 1.1 mmol), Pd(OAc)₂ (11.2 mg, 0.05 mmol) and XPhos (47.76 mg, 0.1 mmol) were added. The resulting mixture was heated at 80°C for an additional 18 h, then cooled to room temperature and partitioned between dichloromethane and water. The organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography, eluting with a gradient of 5% methanol in dichloromethane to 20% methanol in dichloromethane. Repurification by preparative HPLC (NH₃ condition) provided 15.2 mg (4%) of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(4-methylpiperazin-1-yl)methyl]pyridine-3-carbonitrile as a white solid, MS (ESI) m/z 361.3; HPLC: rt = 3.6 min [a].



[00601] Preparation of 4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[2-(pyrrolidin-1-yl)methyl]-1,3-thiazol-4-yl]ethenyl]pyridine-3-carbonitrile:

A solution of 5-[(E)-2-[2-(hydroxymethyl)-1,3-thiazol-4-yl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile (100 mg, 0.26 mmol) in 1.5 mL of DMF was cooled to -30°C, then triethylamine (52.6 mg, 72.2 µL, 0.52 mmol) followed by mesyl chloride (35.5 mg, 24 µL, 0.31 mmol) was added dropwise. The resulting mixture was warmed to 0°C slowly over 60 min. Water (7.5 mL) was added and extracted with dichloromethane. The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to give the mesylate intermediate. To the crude compound was added 1 mL of DMF, triethylamine (52.6 mg, 72.2 µL, 0.52 mmol) and pyrrolidine (37 mg, 43 µL, 0.52 mmol), the mixture was stirred at room temperature for 3 h then concentrated *in vacuo*. The residue was purified by preparative

HPLC (TFA condition) to provide 39 mg (34%) of 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[2-(pyrrolidin-1-ylmethyl)-1,3-thiazol-4-yl]ethenyl]pyridine-3-carbonitrile as a deep yellow solid, MS (ESI) *m/z* 441.2; HPLC: *rt* = 5.2 min [a].



[00602] Preparation of (E)-4-(4-methyl-1*H*-indol-5-ylamino)-5-{2-[2-(piperidin-1-ylmethyl)thiazol-4-yl]vinyl}nicotinonitrile:

The title compound was prepared according to the procedure described for 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[2-(pyrrolidin-1-ylmethyl)-1,3-thiazol-4-yl]ethenyl]pyridine-3-carbonitrile. MS (ESI) *m/z* 455.2; HPLC: *rt* = 5.3 min [a].

PKCθ IMAP ASSAY

[00603] The materials used include the following: human PKCθ full length enzyme (Panvera Cat# P2996); substrate peptide: 5FAM-RFARKGSLRQKNV-OH (Molecular Devices, RP7032); ATP (Sigma Cat # A2383); DTT (Pierce, 20291); 5x kinase reaction buffer (Molecular Devices, R7209); 5x binding buffer A (Molecular Devices, R7282), 5x binding buffer B (Molecular Devices, R7209); IMAP Beads (Molecular Devices, R7284); and 384-well plates (Corning Costar, 3710).

[00604] The reaction buffer was prepared by diluting the 5x stock reaction buffer and adding DTT to obtain a concentration of 3.0 mM. The binding buffer was prepared by diluting the 5x binding buffer A. A master mix solution was prepared using a 90% dilution of the reaction buffer containing 2x ATP (12 μM) and 2x peptide (200 nM). Compounds were diluted in DMSO to 20x of the maximum concentration for the IC₅₀ measurement. 27 μl of the master mix solution for each IC₅₀ curve was added to the first column in a 384-well plate and 3 μl of 20x compound in DMSO was added to each well. The final concentration of compound was 2x and 10% DMSO. DMSO was added to the rest of the master mix to increase the concentration to 10%. 10 μl of the master mix containing 10% DMSO was added to the rest of the wells on the plate except the 2nd column. 20 μl was transferred from the first column to

the 2nd column. The compounds were serially diluted in 2:1 ratio starting from the 2nd column. A 2x (2 nM) PKC θ solution was made in the reaction buffer. 10 μ l of the PKC θ solution was added to every well to achieve these final concentrations: PKC θ - 1 nM; ATP - 6 μ M; peptide - 100 nM; DMSO - 5%. Samples were incubated for 25 minutes at room temperature. The binding reagent was prepared by diluting the beads in 1x binding buffer to 800:1. 50 μ l of the binding reagent was added to every well and incubated for 20 minutes. FP was measured using Envision2100 (PerkinElmer Life Sciences). Wells with no ATP and wells with no enzyme were used as controls.

[00605] The results obtained are summarized in the table below.

Compound Name	PKC Theta Mean IC50 (nM)
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(1 <i>E</i>)-3-[(2-morpholin-4-ylethyl)amino]prop-1-en-1-yl]nicotinonitrile	396.8
<i>N</i> -{1-[(3 <i>E</i>)-4-{5-cyano-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl]piperidin-4-yl}propane-2-sulfonamide	22.2
5-[(1 <i>E</i>)-4-[4-(isopropylsulfonyl)piperazin-1-yl]but-1-en-1-yl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	10.6
<i>N</i> -{1-[(3 <i>E</i>)-4-{5-cyano-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl]piperidin-4-yl}ethane sulfonamide	21.8
<i>N</i> -{1-[(3 <i>E</i>)-4-{5-cyano-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl]piperidin-4-yl}benzene sulfonamide	22.7
5-[(1 <i>E</i>)-4-[(3 <i>R</i>)-3-aminopyrrolidin-1-yl]but-1-en-1-yl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	3.5
(3 <i>E</i>)-4-{5-cyano-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl (3 <i>R</i>)-3-aminopyrrolidine-1-carboxylate	3.2
5-[(1 <i>E</i>)-4-[(3 <i>S</i>)-3-aminopyrrolidin-1-yl]but-1-en-1-yl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	1.3
5-[(1 <i>E</i>)-4-(3-aminoazetidin-1-yl)but-1-en-1-yl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	8.9
5-[(1 <i>E</i>)-4-(1,4-diazepan-1-yl)but-1-en-1-yl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	3.6
5-[(1 <i>E</i>)-4-[4-(methylamino)piperidin-1-yl]but-1-en-1-yl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	9.3
5-[(1 <i>E</i>)-4-[(3 <i>R</i>)-3-aminopiperidin-1-yl]but-1-en-1-yl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	3.6
5-[(1 <i>E</i>)-4-[(3 <i>S</i>)-3-aminopiperidin-1-yl]but-1-en-1-yl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	6.8

5-((1E)-4-[4-(aminomethyl)piperidin-1-yl]but-1-en-1-yl)-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	5.7
5-((1E)-4-(2,5-diazabicyclo[2.2.1]hept-2-yl)but-1-en-1-yl)-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	3.8
4-[(4-methyl-1H-indol-5-yl)amino]-5-((1E)-4-(4-phenylpiperidin-1-yl)but-1-en-1-yl)nicotinonitrile	19.2
5-((1E)-4-[4-(dimethylamino)piperidin-1-yl]but-1-en-1-yl)-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	4.9
5-((1E)-4-(4-hydroxypiperidin-1-yl)but-1-en-1-yl)-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	6
4-[(4-methyl-1H-indol-5-yl)amino]-5-((1E)-4-(4-morpholin-4-ylpiperidin-1-yl)but-1-en-1-yl)nicotinonitrile	50.7
1'-glycyl-4-[(4-methyl-1H-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	10.6
1'-(2-methylalanyl)-4-[(4-methyl-1H-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	32.9
1'-b-alanyl-4-[(4-methyl-1H-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	23.5
4-[(4-methyl-1H-indol-5-yl)amino]-1'-D-valyl-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	34
4-[(4-methyl-1H-indol-5-yl)amino]-1'-L-valyl-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	23.2
4-[(4-methyl-1H-indol-5-yl)amino]-1'-D-prolyl-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	32.9
4-[(4-methyl-1H-indol-5-yl)amino]-1'-L-prolyl-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	23.7
4-[(4-methyl-1H-indol-5-yl)amino]-1'-(pyrrolidin-3-yl carbonyl)-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	22.4
5-((1E)-4-[(3R)-3-hydroxypiperidin-1-yl]but-1-en-1-yl)-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	71.3
5-((1E)-4-[(3S)-3-hydroxypiperidin-1-yl]but-1-en-1-yl)-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	116.5
5-[(E)-2-(4-formylphenyl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	58.2
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]nicotinonitrile	3.6
5-[(E)-2-(4-fluorophenyl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	23.9
4-[(2,4-dimethyl-1H-indol-5-yl)amino]-5-[(E)-2-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}vinyl]nicotinonitrile	24.1
5-benzyl-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	49.5
6-ethyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-phenylvinyl]nicotinonitrile	1,368.5
6-isopropyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-phenylvinyl]nicotinonitrile	19,414.6
5-[(E)-2-[2-methoxy-4-(piperazin-1-ylmethyl)phenyl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	0.5

6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[4-(2-pyrrolidin-1-ylethoxy)phenyl]vinyl]nicotinonitrile	56.5
5-(2-{2-methoxy-4-[(4-methylpiperazin-1-yl)methyl]phenyl}ethyl)-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	24.8
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-(2-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}ethyl) nicotinonitrile	20.1
4-[(4-methyl-1 <i>H</i> -indol-5-yl)oxy]-5-[(<i>E</i>)-2-phenylvinyl]nicotinonitrile	10,543
4-[(<i>E</i>)-2-{5-cyano-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridin-3-yl}vinyl]- <i>N</i> -phenylpiperidine-1-carboxamide	3.8
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[1-(phenylsulfonyl)piperidin-4-yl]vinyl]nicotinonitrile	25.8
5-[(<i>E</i>)-2-(1-benzoylpiperidin-4-yl)vinyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	2.4
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[1-(3-phenylpropanoyl)piperidin-4-yl]vinyl]nicotinonitrile	33.1
4-[(<i>E</i>)-2-{5-cyano-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridin-3-yl}vinyl]- <i>N</i> -propylpiperidine-1-carboxamide	5.7
5-[(<i>E</i>)-2-[1-(isopropylsulfonyl)piperidin-4-yl]vinyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	7.2
5-[(<i>E</i>)-2-[4-(dimethylamino)phenyl]vinyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	24.1
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-{6-[(2-piperidin-1-ylethyl)amino]pyridin-3-yl}ethenyl]pyridine-3-carbonitrile	16.8
5-[(<i>E</i>)-2-[5-[[3-(dimethylamino)propyl]amino]methyl]pyridin-2-yl]ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	4.7
5-[(<i>E</i>)-2-(6-[[3-ethoxypropyl]amino]methyl)pyridin-2-yl]ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	NA
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-(5-[[2-pyridin-3-ylethyl]amino]methyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile	6.3
5-[(<i>E</i>)-2-(3-{[4-(1-methylethyl)piperazin-1-yl]methyl}phenyl)ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	5.5
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-{3-(morpholin-4-ylmethyl)phenyl}ethenyl]pyridine-3-carbonitrile	1.2
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-(3-{[(2-morpholin-4-ylethyl)amino]methyl}phenyl)ethenyl]pyridine-3-carbonitrile	3.9
5-[(<i>E</i>)-2-(3-{[4-(dimethylamino)piperidin-1-yl]methyl}phenyl)ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	1.5

5-[(E)-2-{3-[(4-methyl-1,4-diazepan-1-yl)methyl]phenyl}ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	2.3
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{3-[(2-(1-methylpyrrolidin-2-yl)ethyl)amino]methyl}phenyl]ethenyl]pyridine-3-carbonitrile	0.6
5-[(E)-2-{3-[(2-(dimethylamino)ethyl)amino]methyl}phenyl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	2.7
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{3-[(3-(2-oxopyrrolidin-1-yl)propyl)amino]methyl}phenyl]ethenyl]pyridine-3-carbonitrile	6.7
5-[(E)-2-{3-[(2-methoxyethyl)amino]methyl}phenyl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	4.9
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{3-[(piperidin-1-yl)methyl]phenyl}ethenyl]pyridine-3-carbonitrile	24.2
5-[(E)-2-{3-[(1,4'-bipiperidin-1'-yl)methyl]phenyl}ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	6.8
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{3-[(4-pyrrolidin-1-yl)piperidin-1-yl]methyl}phenyl]ethenyl]pyridine-3-carbonitrile	36
5-[(E)-2-{3-[(4-(2-hydroxyethyl)piperazin-1-yl)methyl]phenyl}ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	8.4
5-[(E)-2-{3-[(4-(dimethylamino)piperidin-1-yl)methyl]phenyl}ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	4
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{3-[(4-morpholin-4-yl)piperidin-1-yl]methyl}phenyl]ethenyl]pyridine-3-carbonitrile	15.8
6-methyl-5-[(E)-2-{3-[(4-methyl-1,4-diazepan-1-yl)methyl]phenyl}ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	5.8
5-[(E)-2-{3-[(3-(dimethylamino)propyl)amino]methyl}phenyl]ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	2.4
5-[(E)-2-{3-[(2-(dimethylamino)ethyl)amino]methyl}phenyl]ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	4.4
6-methyl-5-[(E)-2-{5-[(4-methyl-1,4-diazepan-1-yl)methyl]pyridin-2-yl}vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	15

5-[(E)-2-[5-[[3-(dimethylamino)propyl]amino]methyl]pyridin-2-yl]vinyl]-6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	4.8
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(E)-2-[5-[[2-(1-methylpyrrolidin-2-yl)ethyl]amino]methyl]pyridin-2-yl]vinyl]nicotinonitrile	9.9
5-[(E)-2-(5-[[2-azepan-1-ylethyl]amino]methyl)pyridin-2-yl]vinyl]-6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	15
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(E)-2-(5-[[2-pyridin-2-ylethyl]amino]methyl)pyridin-2-yl]vinyl]nicotinonitrile	14.5
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(E)-2-(5-[[2-pyridin-4-ylethyl]amino]methyl)pyridin-2-yl]vinyl]nicotinonitrile	8.8
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-1'-[(1-methylpiperidin-4-yl)methyl]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	22.3
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(E)-2-(3-[[3-morpholin-4-ylpropyl]amino]methyl)phenyl]vinyl]nicotinonitrile	10.4
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(E)-2-(3-[[2-pyrrolidin-1-ylethyl]amino]methyl)phenyl]ethenyl]pyridine-3-carbonitrile	4.4
5-[(E)-2-[3-[(dimethylamino)methyl]phenyl]ethenyl]-6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	23
5-[(E)-2-[3-[(3-hydroxypyrrolidin-1-yl)methyl]phenyl]ethenyl]-6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	10.2
6-ethyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-(2-phenylethyl)pyridine-3-carbonitrile	NA
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(4-methylpiperazin-1-yl)methyl]pyridine-3-carbonitrile	NA
5-(3,4-dimethoxybenzyl)-4-(1 <i>H</i> -indol-5-ylamino)nicotinonitrile	671.1
5-(3,4-dimethoxybenzyl)-4-(1 <i>H</i> -indol-4-ylamino)nicotinonitrile	580.5
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(E)-2-phenylvinyl]nicotinonitrile	10.7
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(1 <i>E</i>)-3-pyrrolidin-1-ylprop-1-en-1-yl]nicotinonitrile	151.1
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(1 <i>E</i>)-3-(4-phenylpiperazin-1-yl)prop-1-en-1-yl]nicotinonitrile	113.5
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(1 <i>E</i>)-3-(4-methylpiperazin-1-yl)prop-1-en-1-yl]nicotinonitrile	31.1
<i>tert</i> -butyl 5-cyano-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-3',6'-dihydro-3,4'-bipyridine-1'(2' <i>H</i>)-carboxylate	42.5

4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(1 <i>E</i>)-3-morpholin-4-ylprop-1-en-1-yl]nicotinonitrile	50.6
5-[(1 <i>E</i>)-3-(3,4-dihydroisoquinolin-2(1 <i>H</i>)-yl)prop-1-en-1-yl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	35
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(1 <i>E</i>)-4-(4-methylpiperazin-1-yl)but-1-en-1-yl]nicotinonitrile	2.2
5-[(1 <i>E</i>)-3-aminoprop-1-en-1-yl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	8.5
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(1 <i>E</i>)-4-(4-phenylpiperazin-1-yl)but-1-en-1-yl]nicotinonitrile	67.7
5-[(1 <i>E</i>)-buta-1,3-dien-1-yl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	19.6
(3 <i>E</i>)-4-{5-cyano-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl indoline-1-carboxylate	5.2
(3 <i>E</i>)-4-{5-cyano-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl thiomorpholine-4-carboxylate 1,1-dioxide	30.7
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(1 <i>E</i>)-4-morpholin-4-ylbut-1-en-1-yl]nicotinonitrile	16.2
(3 <i>E</i>)-4-{5-cyano-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl morpholine-4-carboxylate	7.6
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(1 <i>E</i>)-4-pyrrolidin-1-ylbut-1-en-1-yl]nicotinonitrile	28.7
<i>tert</i> -butyl {1-[(2 <i>E</i>)-3-{5-cyano-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridin-3-yl}prop-2-en-1-yl]piperidin-4-yl} carbamate	244.3
<i>tert</i> -butyl 4-[(2 <i>E</i>)-3-{5-cyano-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridin-3-yl}prop-2-en-1-yl]piperazine-1-carboxylate	181.5
5-[(1 <i>E</i>)-3-(4-aminopiperidin-1-yl)prop-1-en-1-yl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	3.6
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(1 <i>E</i>)-3-piperazin-1-ylprop-1-en-1-yl]nicotinonitrile	12.4
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	143.2
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-1'-(methylsulfonyl)-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	9.3
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-1'-(phenylsulfonyl)-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	6.4
1'-acetyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	49.5
5-cyano- <i>N</i> -ethyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-3',6'-dihydro-3,4'-bipyridine-1'(2' <i>H</i>)-carboxamide	54.3
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-1'-[(1-methylpiperidin-4-yl)carbonyl]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	45.1
1'-benzyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	6.4

ethyl 5-cyano-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-3',6'-dihydro-3,4'-bipyridine-1'(2' <i>H</i>)-carboxylate	19.5
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(1 <i>E</i>)-4-piperidin-1-ylbut-1-en-1-yl]nicotinonitrile	35.2
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(1 <i>E</i>)-4-thiomorpholin-4-ylbut-1-en-1-yl]nicotinonitrile	13.6
5-[(1 <i>E</i>)-4-(1,3-dioxo-1,3-dihydro-2 <i>H</i> -isoindol-2-yl)but-1-en-1-yl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	6.3
1'-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	253.4
5-[(1 <i>E</i>)-4-(4-acetylpiperazin-1-yl)but-1-en-1-yl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	37.8
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(1 <i>E</i>)-4-[4-(methylsulfonyl)piperazin-1-yl]but-1-en-1-yl]nicotinonitrile	12
<i>tert</i> -butyl 4-[(3 <i>E</i>)-4-{5-cyano-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl]piperazine-1-carboxylate	34.7
<i>tert</i> -butyl {1-[(3 <i>E</i>)-4-{5-cyano-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl]piperidin-4-yl}carbamate	21.5
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(1 <i>E</i>)-5-(4-methylpiperazin-1-yl)pent-1-en-1-yl]nicotinonitrile	6.4
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(1 <i>E</i>)-5-morpholin-4-ylpent-1-en-1-yl]nicotinonitrile	34.2
(4 <i>E</i>)-5-{5-cyano-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridin-3-yl}pent-4-en-1-yl morpholine-4-carboxylate	21.3
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(1 <i>E</i>)-5-pyrrolidin-1-ylpent-1-en-1-yl]nicotinonitrile	14.9
5-[(1 <i>E</i>)-4-aminobut-1-en-1-yl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	5
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[3-(4-methylpiperazin-1-yl)propyl]nicotinonitrile	63.7
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[4-(4-methylpiperazin-1-yl)butyl]nicotinonitrile	26.9
5-[(1 <i>E</i>)-4-(4-aminopiperidin-1-yl)but-1-en-1-yl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	0.9
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(1 <i>E</i>)-4-piperazin-1-ylbut-1-en-1-yl]nicotinonitrile	4
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(1 <i>E</i>)-4-[(2-morpholin-4-ylethyl)amino]but-1-en-1-yl]nicotinonitrile	45.7
5-[(<i>E</i>)-2-{5-[(dimethylamino)methyl]pyridin-2-yl}vinyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	8
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}vinyl]nicotinonitrile	1.9
5-[(1 <i>E</i>)-4-[4-(ethylsulfonyl)piperazin-1-yl]but-1-en-1-yl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	12.1
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(1 <i>E</i>)-4-[4-(phenylsulfonyl)piperazin-1-yl]but-1-en-1-yl]nicotinonitrile	50.7

5-[(1 <i>E</i>)-4-[4-(2,2-dimethylpropanoyl)piperazin-1-yl]but-1-en-1-yl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	51.3
<i>N</i> -(1-[(3 <i>E</i>)-4-{5-cyano-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl]piperidin-4-yl)methanesulfonamide	16.4
<i>N</i> -(1-[(3 <i>E</i>)-4-{5-cyano-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl]piperidin-4-yl)acetamide	30.9
5-[(1 <i>E</i>)-4-(isopropylamino)but-1-en-1-yl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	104.8
5-[(1 <i>E</i>)-4-(cyclohexylamino)but-1-en-1-yl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	56.3
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(1 <i>E</i>)-4-(piperidin-4-ylamino)but-1-en-1-yl]nicotinonitrile	10.1
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-1'-(piperidin-4-ylcarbonyl)-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	12
<i>tert</i> -butyl 4-[(3 <i>E</i>)-4-{5-cyano-2-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl]piperazine-1-carboxylate	443.9
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(1 <i>E</i>)-5-piperidin-1-yl]pent-1-en-1-yl]nicotinonitrile	18.7
<i>tert</i> -butyl 4-[(4 <i>E</i>)-5-{5-cyano-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridin-3-yl}pent-4-en-1-yl]piperazine-1-carboxylate	203.4
<i>tert</i> -butyl {1-[(4 <i>E</i>)-5-{5-cyano-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridin-3-yl}pent-4-en-1-yl]piperidin-4-yl}carbamate	24.7
<i>tert</i> -butyl {1-[(3 <i>E</i>)-4-{5-cyano-2-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl]piperidin-4-yl}carbamate	170.6
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(1 <i>E</i>)-3-piperidin-1-yl]prop-1-en-1-yl]nicotinonitrile	189.1
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(1 <i>E</i>)-4-piperazin-1-yl]but-1-en-1-yl]nicotinonitrile	16.9
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-(4-piperazin-1-ylbutyl)nicotinonitrile	4.7
5-[4-(4-aminopiperidin-1-yl)butyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	5.2
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(1 <i>E</i>)-5-piperazin-1-yl]pent-1-en-1-yl]nicotinonitrile	2.8
5-[(1 <i>E</i>)-5-(4-aminopiperidin-1-yl)pent-1-en-1-yl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	5.2
5-[(1 <i>E</i>)-4-(4-aminopiperidin-1-yl)but-1-en-1-yl]-6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	45.5
5-[(1 <i>E</i>)-4-(dimethylamino)but-1-en-1-yl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	38.7
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(1 <i>E</i>)-4-[(1-methylpiperidin-4-yl)amino]but-1-en-1-yl]nicotinonitrile	13.1

5-((1E)-4-[(trans-4-hydroxycyclohexyl)amino]but-1-en-1-yl)-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	35.8
5-((1E)-5-(4-hydroxypiperidin-1-yl)pent-1-en-1-yl)-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	10.5
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-((1E)-4-[4-(methylsulfonyl)piperazin-1-yl]but-1-en-1-yl)nicotinonitrile	30
N-[1-[(3E)-4-{5-cyano-2-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl]piperidin-4-yl]methanesulfonamide	57.3
5-((1E)-4-(4-hydroxy-4-phenylpiperidin-1-yl)but-1-en-1-yl)-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	44.2
4-[(E)-2-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}vinyl]benzoic acid	63.4
5-((1E)-3-(4-hydroxypiperidin-1-yl)prop-1-en-1-yl)-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	143.2
tert-butyl 4-[(6-[(E)-2-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}vinyl]pyridin-3-yl)methyl]piperazine-1-carboxylate	72.3
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(piperazin-1-ylmethyl)pyridin-2-yl]vinyl]nicotinonitrile	5.2
tert-butyl 4-{4-[(E)-2-{5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl}vinyl]benzyl}piperazine-1-carboxylate	44
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}vinyl]nicotinonitrile	28.4
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4-methylphenyl)vinyl]nicotinonitrile	35.2
5-[(E)-2-(4-methoxyphenyl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	13.1
5-[(E)-2-biphenyl-4-ylvinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	57.2
4-[(2,4-dimethyl-1H-indol-5-yl)amino]-5-[(E)-2-phenylvinyl]nicotinonitrile	70.1
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{4-(trifluoromethyl)phenyl}vinyl]nicotinonitrile	115.2
5-[(E)-2-(4-chlorophenyl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	42.9
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(Z)-2-phenylvinyl]nicotinonitrile	79
5-((1E)-4-[(3R)-3-hydroxypyrrolidin-1-yl]but-1-en-1-yl)-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	13.7
5-((1E)-4-[(3S)-3-hydroxypyrrolidin-1-yl]but-1-en-1-yl)-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	23.9
5-((1E)-4-[4-(hydroxymethyl)piperidin-1-yl]but-1-en-1-yl)-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	39.4
5-((1E)-4-(4-methoxypiperidin-1-yl)but-1-en-1-yl)-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	41.6

4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-1'-(2-phenylethyl)-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	16.8
1'-(2-fluorobenzyl)-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	6.9
1'-(3-fluorobenzyl)-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	3.7
1'-(4-fluorobenzyl)-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	7.3
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(1 <i>E</i>)-4-[4-(pyrrolidin-1-ylcarbonyl)piperidin-1-yl]but-1-en-1-yl]nicotinonitrile	18.2
5-[(<i>E</i>)-2-(3-methoxyphenyl)vinyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	7
5-[(<i>E</i>)-2-(4-bromophenyl)vinyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	58.3
5-[(<i>E</i>)-2-(2-methoxyphenyl)vinyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	8.2
5-[(<i>E</i>)-2-(3,4-dimethoxyphenyl)vinyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	8.1
4-(1 <i>H</i> -indol-5-ylamino)-5-[(<i>E</i>)-2-phenylvinyl]nicotinonitrile	12.9
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-vinylnicotinonitrile	22.4
4-(1 <i>H</i> -indol-5-ylamino)-6-methyl-5-[(<i>E</i>)-2-phenylvinyl]nicotinonitrile	96.6
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-1'-(piperidin-4-ylmethyl)-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	6.1
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(1 <i>E</i>)-4-(3-oxo piperazin-1-yl)but-1-en-1-yl]nicotinonitrile	11
5-[(<i>E</i>)-2-(3-methoxyphenyl)vinyl]-6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	16.4
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-{4-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}vinyl]nicotinonitrile	13.6
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-{2-[(4-methylpiperazin-1-yl)methyl]-1,3-thiazol-4-yl}vinyl]nicotinonitrile	2.4
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-(2-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}ethyl)nicotinonitrile	12.3
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-{6-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}vinyl]nicotinonitrile	1.1
4-(1 <i>H</i> -indol-6-ylamino)-6-methyl-5-[(<i>E</i>)-2-phenylvinyl]nicotinonitrile	4,221.5
4-(1 <i>H</i> -indol-6-ylamino)-5-[(<i>E</i>)-2-phenylvinyl]nicotinonitrile	1,395
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[4-(2-pyrrolidin-1-ylethoxy)phenyl]vinyl]nicotinonitrile	9

5-[(E)-2-[4-(2-chloroethoxy)phenyl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	25
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(1E)-3-phenylprop-1-en-1-yl]nicotinonitrile	17.8
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}vinyl]nicotinonitrile	10.5
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-phenylvinyl]nicotinonitrile	9
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-pyridin-2-ylvinyl]nicotinonitrile	5
5-[(E)-2-(4-butylphenyl)vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	77.6
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-pyridin-4-ylvinyl]nicotinonitrile	6.6
6-methyl-4-[(2-methyl-1H-indol-5-yl)amino]-5-[(E)-2-phenylvinyl]nicotinonitrile	714.6
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-vinylnicotinonitrile	111.1
4-[(4,7-dimethyl-1H-indol-5-yl)amino]-5-[(E)-2-phenylvinyl]nicotinonitrile	33.6
4-[(7-chloro-4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-phenylvinyl]nicotinonitrile	77.5
4-[(7-chloro-4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(3-methoxyphenyl)vinyl]nicotinonitrile	26.3
4-[(7-chloro-4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-pyridin-2-ylvinyl]nicotinonitrile	28.6
4-[(2-methyl-1H-indol-5-yl)amino]-5-[(E)-2-phenylvinyl]nicotinonitrile	362.2
5-[(E)-2-(4-methoxyphenyl)vinyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	58.2
4-[(4-methyl-1H-indol-5-yl)amino]-5-(3-phenylpropyl)nicotinonitrile	31.8
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}vinyl]nicotinonitrile	3.6
4-(1H-indol-5-ylamino)-5-[(E)-2-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}vinyl]nicotinonitrile	16.5
4-(1H-indol-4-ylamino)-5-[(E)-2-phenylvinyl]nicotinonitrile	12.9
4-(1H-indol-4-ylamino)-6-methyl-5-[(E)-2-phenylvinyl]nicotinonitrile	25.3
5-[(E)-2-{2-methoxy-4-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	8.8
5-[(E)-2-[2-(2-chloroethoxy)phenyl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	5.1
5-[(E)-2-[3-(2-chloroethoxy)phenyl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	8.6

4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-{2-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}vinyl]nicotinonitrile	7.6
4-[1 <i>H</i> -indol-5-yl(methyl)amino]-5-[(<i>E</i>)-2-phenylvinyl]nicotinonitrile	438.2
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-{2-methyl-4-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]nicotinonitrile	5.3
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-{2-(2-piperazin-1-ylethoxy)phenyl}vinyl]nicotinonitrile	0.6
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-{2-(2-pyrrolidin-1-ylethoxy)phenyl}vinyl]nicotinonitrile	12.9
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-piperidin-4-ylvinyl]nicotinonitrile	6.1
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-{3-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}vinyl]nicotinonitrile	4.7
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-{3-(2-pyrrolidin-1-ylethoxy)phenyl}vinyl]nicotinonitrile	4.7
5-[2-(4-methoxyphenyl)ethyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	18.3
5-(2-biphenyl-4-ylethyl)-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	82.1
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-{3-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]nicotinonitrile	1.4
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-(2-phenylethyl)nicotinonitrile	34.2
4-[(7-chloro-4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-pyridin-4-ylvinyl]nicotinonitrile	71.6
4-[(7-chloro-4-methyl-1 <i>H</i> -indol-5-yl)amino]-6-methyl-5-[(<i>E</i>)-2-pyridin-2-ylvinyl]nicotinonitrile	74
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-pyridin-2-ylvinyl]nicotinonitrile	6.3
4-[(7-chloro-4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}vinyl]nicotinonitrile	16.3
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-(1 <i>H</i> -1,2,4-triazol-1-yl)vinyl]nicotinonitrile	11
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-(4-methyl-1,3-thiazol-5-yl)vinyl]nicotinonitrile	4.1
5-[(1 <i>E</i>)-3-(1 <i>H</i> -imidazol-1-yl)prop-1-en-1-yl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	19.5
5-[(<i>E</i>)-2-cyclohexylvinyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	26
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-pyridin-4-ylvinyl]nicotinonitrile	12.3
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-{5-[(4-methylpiperazin-1-yl)methyl]-3-furyl}vinyl]nicotinonitrile	2.9
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-{2-methyl-5-[(4-methylpiperazin-1-yl)carbonyl]phenyl}vinyl]nicotinonitrile	27.8

4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-{2-methyl-5-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]nicotinonitrile	16.1
4-[(7-chloro-4-methyl-1 <i>H</i> -indol-5-yl)amino]-6-methyl-5-[(<i>E</i>)-2-phenylvinyl]nicotinonitrile	282.6
4-[(7-chloro-4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-{6-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}vinyl]nicotinonitrile	4.8
5-[(<i>E</i>)-2-{6-[(4-acetylpiperazin-1-yl)methyl]pyridin-2-yl}vinyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	1.6
5-[(<i>E</i>)-2-{2-methoxy-5-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	4.9
5-[(<i>E</i>)-2-{2-methoxy-5-(piperazin-1-ylmethyl)phenyl}vinyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	1.2
5-[(<i>E</i>)-2-(2-methoxyphenyl)vinyl]-6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	8.2
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-pyridin-3-ylvinyl]nicotinonitrile	12.1
5-[(<i>E</i>)-2-(3,4-dimethoxyphenyl)vinyl]-6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	25.3
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-pyrazin-2-ylvinyl]nicotinonitrile	7.9
<i>tert</i> -butyl 4-[(<i>E</i>)-2-{5-cyano-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridin-3-yl}vinyl]piperidine-1-carboxylate	48.2
4-(1 <i>H</i> -indol-4-yloxy)-5-[(<i>E</i>)-2-phenylvinyl]nicotinonitrile	324.8
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-(4-methyl-1,3-thiazol-5-yl)vinyl]nicotinonitrile	3.2
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[4-(piperidin-1-ylmethyl)phenyl]vinyl]nicotinonitrile	4.1
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[4-(pyrrolidin-1-ylmethyl)phenyl]vinyl]nicotinonitrile	3.6
5-[(<i>E</i>)-2-(2-chloropyridin-3-yl)vinyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	4.2
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-{2-methyl-4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}vinyl]nicotinonitrile	23.4
5-[(<i>E</i>)-2-(4-{[4-(2-hydroxyethyl)piperazin-1-yl]methyl}phenyl)vinyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	4.7
5-[(<i>E</i>)-2-{4-[(4-hydroxypiperidin-1-yl)methyl]phenyl}vinyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	5.5
5-[(<i>E</i>)-2-[4-({[3-(dimethylamino)propyl]amino}methyl)phenyl]vinyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	1.2
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[4-(thiomorpholin-4-ylmethyl)phenyl]vinyl]nicotinonitrile	46.2

4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-{4-[(4-pyrrolidin-1-yl)piperidin-1-yl)methyl]phenyl}vinyl]nicotinonitrile	1.6
5-[(<i>E</i>)-2-{2-methoxy-3-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	5.8
5-[(<i>E</i>)-2-{2-methoxy-3-(piperazin-1-ylmethyl)phenyl}vinyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	7.3
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-{6-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}vinyl]nicotinonitrile	3
5-[(<i>E</i>)-2-{3-methoxy-4-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	2.3
5-[(<i>E</i>)-2-{3-methoxy-4-(piperazin-1-ylmethyl)phenyl}vinyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	2.2
5-isopropenyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	7.5
5-[(<i>E</i>)-2-{3-[(diethylamino)methyl]phenyl}vinyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	2.9
5-[(<i>E</i>)-2-{4-[(diethylamino)methyl]phenyl}vinyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	14.8
5-[(<i>E</i>)-2-(6-bromopyridin-2-yl)vinyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	0.7
5-[(<i>E</i>)-2-{3,4-bis(2-methoxyethoxy)phenyl}vinyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	31.8
5-[(<i>E</i>)-2-(4-formylphenyl)ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	58.2
5-[(<i>E</i>)-2-{4-(1,4'-bipiperidin-1'-ylmethyl)phenyl}ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	3.2
5-[(<i>E</i>)-2-(4-[(3-ethoxypropyl)amino]methyl)phenyl]ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	3.6
5-[(<i>E</i>)-2-(2-chloropyridin-4-yl)vinyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	7.2
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-{4-(piperazin-1-ylmethyl)phenyl}vinyl]nicotinonitrile	2.6
5-[(<i>E</i>)-2-{4-(azetidin-1-ylmethyl)phenyl}vinyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	3.3
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-(2-phenylethyl)nicotinonitrile	40.7
5-[(<i>E</i>)-2-{4-[(dimethylamino)methyl]phenyl}vinyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	10.5
5-[(<i>E</i>)-2-(4-ethoxyphenyl)vinyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	14.2
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-{4-[(4-pyridin-2-yl)piperazin-1-yl)methyl]phenyl}vinyl]nicotinonitrile	37.8

<i>tert</i> -butyl 3-({4-[(<i>E</i>)-2-{5-cyano-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridin-3-yl}vinyl]benzyl}amino)azetidine-1-carboxylate	61.1
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-(4-propoxyphenyl)vinyl]nicotinonitrile	66.4
5-[(<i>E</i>)-2-(6-chloropyridin-3-yl)vinyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	2.2
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-{2-[4-(pyrrolidin-1-ylmethyl)phenyl]ethyl}nicotinonitrile	13.4
5-[(<i>E</i>)-2-(6-chloropyridin-2-yl)vinyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	0.4
5-[(<i>E</i>)-2-[6-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	1.5
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[6-(piperidin-1-ylmethyl)pyridin-2-yl]vinyl]nicotinonitrile	4.3
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[6-(pyrrolidin-1-ylmethyl)pyridin-2-yl]vinyl]nicotinonitrile	1.6
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[6-(piperazin-1-ylmethyl)pyridin-2-yl]vinyl]nicotinonitrile	0.3
5-[(<i>E</i>)-2-[5-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	6.1
5-[(<i>E</i>)-2-{4-[(3-hydroxypyrrolidin-1-yl)methyl]phenyl}ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	6.3
<i>N</i> -{4-[(<i>E</i>)-2-{5-cyano-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridin-3-yl}ethenyl]benzyl}- <i>N</i> -(2-piperidin-1-ylethyl)acetamide	2.4
5-[(<i>E</i>)-2-(4-{[4-(1-methylethyl)piperazin-1-yl]methyl}phenyl)ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	3
<i>N</i> -{4-[(<i>E</i>)-2-{5-cyano-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridin-3-yl}ethenyl]benzyl}- <i>N</i> -(2-pyrrolidin-1-ylethyl)acetamide	2.2
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-(4-{[(2-pyridin-3-ylethyl)amino]methyl}phenyl)ethenyl]pyridine-3-carbonitrile	2.9
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-(4-{[(2-pyridin-2-ylethyl)amino]methyl}phenyl)ethenyl]pyridine-3-carbonitrile	10
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-(4-{[(3-morpholin-4-ylpropyl)amino]methyl}phenyl)ethenyl]pyridine-3-carbonitrile	0.9
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-(4-{[(4-morpholin-4-ylpiperidin-1-yl)methyl]phenyl}ethenyl]pyridine-3-carbonitrile	3.4
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-(4-{[(2-morpholin-4-ylethyl)amino]methyl}phenyl)ethenyl]pyridine-3-carbonitrile	22.1

5-[(E)-2-{4-[(4-cyclopentylpiperazin-1-yl)methyl]phenyl}ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	3.4
5-[(E)-2-(4-formylphenyl)ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	NA
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{4-(morpholin-4-ylmethyl)phenyl}ethenyl]pyridine-3-carbonitrile	39.7
5-[(E)-2-{4-[(azetidin-3-ylamino)methyl]phenyl}ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	1.5
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{2-methyl-4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}ethenyl]pyridine-3-carbonitrile	22.2
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}ethenyl]pyridine-3-carbonitrile	7.1
5-[(E)-2-{4-[(4-hydroxypiperidin-1-yl)methyl]phenyl}ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	11.7
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{4-(piperidin-1-ylmethyl)phenyl}ethenyl]pyridine-3-carbonitrile	17.4
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{4-(pyrrolidin-1-ylmethyl)phenyl}ethenyl]pyridine-3-carbonitrile	34.7
5-[(E)-2-{4-[(diethylamino)methyl]phenyl}ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	8.6
6-methyl-5-[(E)-2-{4-[(4-methyl-1,4-diazepan-1-yl)methyl]phenyl}ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	13.9
5-[(E)-2-(4-benzylmorpholin-2-yl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	57.3
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{2-[(4-methylpiperazin-1-yl)methyl]phenyl}ethenyl]pyridine-3-carbonitrile	9.9
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-3-yl}ethenyl]pyridine-3-carbonitrile	16.3
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{4-[(4-methylpiperazin-1-yl)methyl]-1,3-thiazol-2-yl}ethenyl]pyridine-3-carbonitrile	14.8
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{6-[(4-methylpiperazin-1-yl)methyl]pyridin-3-yl}ethenyl]pyridine-3-carbonitrile	6.6
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{5-(piperidin-1-ylmethyl)pyridin-2-yl}ethenyl]pyridine-3-carbonitrile	14.2
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{5-(pyrrolidin-1-ylmethyl)pyridin-2-yl}ethenyl]pyridine-3-carbonitrile	19.4

4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[5-(morpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile	56.4
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[5-(thiomorpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile	38.5
5-[(<i>E</i>)-2-[5-[(4-hydroxypiperidin-1-yl)methyl]pyridin-2-yl]ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	30.3
5-[(<i>E</i>)-2-[5-[(4-(2-hydroxyethyl)piperazin-1-yl)methyl]pyridin-2-yl]ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	6.2
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[5-[(2-morpholin-4-ylethyl)amino]methyl]pyridin-2-yl]ethenyl]pyridine-3-carbonitrile	15.3
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[4-(morpholin-4-ylmethyl)phenyl]ethenyl]pyridine-3-carbonitrile	43.4
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[4-[(2-pyridin-2-ylethyl)amino]methyl]phenyl]ethenyl]pyridine-3-carbonitrile	34.1
5-[(<i>E</i>)-2-[4-[(4-cyclopentylpiperazin-1-yl)methyl]phenyl]ethenyl]-6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	32
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[4-(thiomorpholin-4-ylmethyl)phenyl]ethenyl]pyridine-3-carbonitrile	187
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[4-[(2-pyridin-4-ylethyl)amino]methyl]phenyl]ethenyl]pyridine-3-carbonitrile	178.3
6-methyl-5-[(<i>E</i>)-2-[4-[(1-methylethyl)piperazin-1-yl]methyl]phenyl]ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	12.1
5-[(<i>E</i>)-2-[5-bromopyridin-3-yl]ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	0.8
<i>tert</i> -butyl [2-[(5-[(<i>E</i>)-2-[5-cyano-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridin-3-yl]ethenyl]pyridin-3-yl)oxy)ethyl]carbamate	21.3
5-[(<i>E</i>)-2-[5-methoxypyridin-3-yl]ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	5.5
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[2-methyl-4-[(4-methylpiperazin-1-yl)methyl]phenyl]ethenyl]pyridine-3-carbonitrile	9.4
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-(2-methylphenyl)ethenyl]pyridine-3-carbonitrile	15.5
5-[(<i>E</i>)-2-(2-ethylphenyl)ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	58
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[5-[(3-morpholin-4-ylpropyl)amino]methyl]pyridin-2-yl]ethenyl]pyridine-3-carbonitrile	5.1

4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-{5-[(4-morpholin-4-ylpiperidin-1-yl)methyl]pyridin-2-yl}ethenyl]pyridine-3-carbonitrile	5
5-[(<i>E</i>)-2-[5-(1,4'-bipiperidin-1'-ylmethyl)pyridin-2-yl]ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	2.7
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-{5-[(4-pyrrolidin-1-ylpiperidin-1-yl)methyl]pyridin-2-yl}ethenyl]pyridine-3-carbonitrile	2.3
5-[(<i>E</i>)-2-{5-[(4-cyclopentylpiperazin-1-yl)methyl]pyridin-2-yl}ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	2.4
5-[(<i>E</i>)-2-(5-{[4-(1-methylethyl)piperazin-1-yl]methyl}pyridin-2-yl)ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	7.4
5-[(<i>E</i>)-2-(5-{[4-(dimethylamino)piperidin-1-yl]methyl}pyridin-2-yl)ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	2.8
5-[(<i>E</i>)-2-{5-[(4-methyl-1,4-diazepan-1-yl)methyl]pyridin-2-yl}ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	3
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[5-({[3-(2-oxopyrrolidin-1-yl)propyl]amino}methyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile	4.4
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-(4-{[(3-morpholin-4-ylpropyl)amino]methyl}phenyl)ethenyl]pyridine-3-carbonitrile	32
5-[(<i>E</i>)-2-[4-(1,4'-bipiperidin-1'-ylmethyl)phenyl]ethenyl]-6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	6.9
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[4-[(4-morpholin-4-ylpiperidin-1-yl)methyl]phenyl]ethenyl]pyridine-3-carbonitrile	18
5-[(<i>E</i>)-2-[4-({[1-ethylpyrrolidin-2-yl]methyl}amino)methyl]phenyl]ethenyl]-6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	43.2
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-(2-pyridin-2-ylethyl)pyridine-3-carbonitrile	11.5
5-[(<i>E</i>)-2-[5-(2-aminoethoxy)pyridin-3-yl]ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	156.3
5-[(<i>E</i>)-2-{2-ethyl-5-[(4-methylpiperazin-1-yl)methyl]phenyl}ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	18
5-[(<i>E</i>)-2-{2-ethyl-5-[(4-methylpiperazin-1-yl)methyl]phenyl}ethenyl]-6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	14.5
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-pyridin-3-ylethenyl]pyridine-3-carbonitrile	7.6

5-[(E)-2-[5-[(2-(dimethylamino)ethyl)amino]methyl]pyridin-2-yl]ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	1.7
5-[(E)-2-(5-[(2-ethoxyethyl)amino]methyl)pyridin-2-yl]ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	3.2
5-[(E)-2-(5-[(3-ethoxypropyl)amino]methyl)pyridin-2-yl]ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	2.1
5-[(E)-2-(5-[(2-methoxyethyl)amino]methyl)pyridin-2-yl]ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	3.1
4-[(1,4-dimethyl-1 <i>H</i> -indol-5-yl)amino]-5-[(E)-2-phenylethenyl]pyridine-3-carbonitrile	192.4
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(E)-2-[6-(morpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile	1.5
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(E)-2-[6-(thiomorpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile	0.8
5-[(E)-2-[6-[(4-hydroxypiperidin-1-yl)methyl]pyridin-2-yl]ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	2
5-[(E)-2-[6-[(4-(2-hydroxyethyl)piperazin-1-yl)methyl]pyridin-2-yl]ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	0.7
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(E)-2-[6-[(2-morpholin-4-ylethyl)amino]methyl]pyridin-2-yl]ethenyl]pyridine-3-carbonitrile	1.3
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(E)-2-[6-[(3-morpholin-4-ylpropyl)amino]methyl]pyridin-2-yl]ethenyl]pyridine-3-carbonitrile	2.9
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(E)-2-[6-[(4-morpholin-4-ylpiperidin-1-yl)methyl]pyridin-2-yl]ethenyl]pyridine-3-carbonitrile	1.9
5-[(E)-2-[6-[(1,4'-bipiperidin-1'-yl)methyl]pyridin-2-yl]ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	0.4
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(E)-2-[6-[(4-pyrrolidin-1-ylpiperidin-1-yl)methyl]pyridin-2-yl]ethenyl]pyridine-3-carbonitrile	0.8
5-[(E)-2-[6-[(4-cyclopentylpiperazin-1-yl)methyl]pyridin-2-yl]ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	0.5
5-[(E)-2-[4-[(4-methyl-1,4-diazepan-1-yl)methyl]phenyl]ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	2.7
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(E)-2-[4-[(2-pyridin-4-ylethyl)amino]methyl]phenyl]ethenyl]pyridine-3-carbonitrile	1.7

5-[(E)-2-(6-([4-(1-methylethyl)piperazin-1-yl)methyl]pyridin-2-yl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	0.6
5-[(E)-2-(6-([4-(dimethylamino)piperidin-1-yl)methyl]pyridin-2-yl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	0.8
5-[(E)-2-(6-([4-methyl-1,4-diazepan-1-yl)methyl]pyridin-2-yl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	0.8
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[6-([3-(2-oxopyrrolidin-1-yl)propyl]amino)methyl]pyridin-2-yl)ethenyl]pyridine-3-carbonitrile	0.5
5-[(E)-2-[6-([2-(dimethylamino)ethyl]amino)methyl]pyridin-2-yl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	0.4
5-[(E)-2-[6-([3-(dimethylamino)propyl]amino)methyl]-2-yl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	2
5-[(E)-2-(6-([2-ethoxyethyl]amino)methyl)pyridin-2-yl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	1.9
5-[(E)-2-(6-([2-methoxyethyl]amino)methyl)pyridin-2-yl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	4.2
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-[2-(4-methylpiperazin-1-yl)ethoxy]pyridin-3-yl)ethenyl]pyridine-3-carbonitrile	6.7
5-[(E)-2-(4-[4-(2-hydroxyethyl)piperazin-1-yl)methyl]phenyl)ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	10
5-[(E)-2-(3-formylphenyl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	NA
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-[2-(4-methylpiperazin-1-yl)ethoxy]pyridin-3-yl)ethenyl]pyridine-3-carbonitrile	26.7
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-[(4-pyrrolidin-1-yl)piperidin-1-yl)methyl]phenyl)ethenyl]pyridine-3-carbonitrile	3.9
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(2-pyrrolidin-1-ylethoxy)pyridin-3-yl)ethenyl]pyridine-3-carbonitrile	17
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4-[[2-(piperidin-1-ylethyl)amino]methyl]phenyl)ethenyl]pyridine-3-carbonitrile	6
4-[(6-chloro-1H-indol-5-yl)amino]-5-[(E)-2-phenylethenyl]pyridine-3-carbonitrile	65
5-[(E)-2-[6-[(dimethylamino)methyl]pyridin-2-yl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	2.9

4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[6-[(2-(1-methylpyrrolidin-2-yl)ethyl)amino)methyl]pyridin-2-yl]ethenyl]pyridine-3-carbonitrile	0.7
5-[(<i>E</i>)-2-[6-[(3-hydroxypyrrolidin-1-yl)methyl]pyridin-2-yl]ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	2.3
5-[(<i>E</i>)-2-[6-[(2-azepan-1-ylethyl)amino)methyl]pyridin-2-yl]ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	0.3
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[6-[(2-pyridin-2-ylethyl)amino)methyl]pyridin-2-yl]ethenyl]pyridine-3-carbonitrile	1.8
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[6-[(2-pyridin-3-ylethyl)amino)methyl]pyridin-2-yl]ethenyl]pyridine-3-carbonitrile	1.7
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[6-[(2-pyridin-4-ylethyl)amino)methyl]pyridin-2-yl]ethenyl]pyridine-3-carbonitrile	2.1
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[5-[(2-(1-methylpyrrolidin-2-yl)ethyl)amino)methyl]pyridin-2-yl]ethenyl]pyridine-3-carbonitrile	3.1
5-[(<i>E</i>)-2-[5-[(3-hydroxypyrrolidin-1-yl)methyl]pyridin-2-yl]ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	11.6
5-[(<i>E</i>)-2-[5-[(2-azepan-1-ylethyl)amino)methyl]pyridin-2-yl]ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	2.7
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[5-[(2-pyridin-2-ylethyl)amino)methyl]pyridin-2-yl]ethenyl]pyridine-3-carbonitrile	10.4
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[5-[(2-pyridin-4-ylethyl)amino)methyl]pyridin-2-yl]ethenyl]pyridine-3-carbonitrile	5.6
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[4-(pyrrolidin-1-ylsulfonyl)phenyl]ethenyl]pyridine-3-carbonitrile	6
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl]ethenyl]pyridine-3-carbonitrile	22.6
5-[(<i>E</i>)-2-[4-[(2-(dimethylamino)ethyl)amino)methyl]phenyl]ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	3.7
5-[(<i>E</i>)-2-[5-[3-(dimethylamino)propoxy]pyridin-3-yl]ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	11.6
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[3-(piperidin-1-ylmethyl)phenyl]ethenyl]pyridine-3-carbonitrile	4.9
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[3-(pyrrolidin-1-ylmethyl)phenyl]ethenyl]pyridine-3-carbonitrile	2.9

5-[(E)-2-(3-[(4-(2-hydroxyethyl)piperazin-1-yl)methyl]phenyl)ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	1.5
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(E)-2-(3-[(4-pyrrolidin-1-yl)piperidin-1-yl)methyl]phenyl)ethenyl]pyridine-3-carbonitrile	1.0
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(E)-2-(3-[(4-morpholin-4-yl)piperidin-1-yl)methyl]phenyl)ethenyl]pyridine-3-carbonitrile	3.8
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(E)-2-(3-(thiomorpholin-4-ylmethyl)phenyl)ethenyl]pyridine-3-carbonitrile	18.6
5-[(E)-2-(3-[(4-cyclopentyl)piperazin-1-yl)methyl]phenyl)ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	0.8
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(E)-2-(4-[(2-pyrrolidin-1-ylethyl)amino]methyl)phenyl)ethenyl]pyridine-3-carbonitrile	2.2
5-[(E)-2-(3-formylphenyl)ethenyl]-6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	NA
5-[(E)-2-[5-(hydroxymethyl)pyridin-2-yl]ethenyl]-6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	17.8
5-[(E)-2-[6-(hydroxymethyl)pyridin-2-yl]ethenyl]-6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	5.9
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(E)-2-[6-(piperidin-1-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile	20.7
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(E)-2-[6-(pyrrolidin-1-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile	24.5
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(E)-2-[6-(morpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile	8.6
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(E)-2-[6-(thiomorpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile	6.6
5-[(E)-2-(6-[(4-hydroxypiperidin-1-yl)methyl]pyridin-2-yl)ethenyl]-6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	14.5
5-[(E)-2-(6-[(4-(2-hydroxyethyl)piperazin-1-yl)methyl]pyridin-2-yl)ethenyl]-6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	7.3
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(E)-2-(6-[(2-morpholin-4-ylethyl)amino]methyl)pyridin-2-yl)ethenyl]pyridine-3-carbonitrile	24.6

6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-(6- {[(3-morpholin-4-ylpropyl)amino]methyl}pyridin-2-yl) ethenyl]pyridine-3-carbonitrile	37.8
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-(6- [(4-morpholin-4-ylpiperidin-1-yl)methyl]pyridin-2-yl) ethenyl]pyridine-3-carbonitrile	13.5
5-[(<i>E</i>)-2-(6-(1,4'-bipiperidin-1'-ylmethyl)pyridin-2-yl) ethenyl]-6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl) amino]pyridine-3-carbonitrile	8.4
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-(6- [(4-pyrrolidin-1-ylpiperidin-1-yl)methyl]pyridin-2-yl) ethenyl]pyridine-3-carbonitrile	3.4
5-[(<i>E</i>)-2-(6-[(4-cyclopentylpiperazin-1-yl)methyl]pyridin- 2-yl)ethenyl]-6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl) amino]pyridine-3-carbonitrile	5.3
4-[(1-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-phenyl ethenyl]pyridine-3-carbonitrile	4,699.4
6-methyl-5-[(<i>E</i>)-2-(6-[(4-(1-methylethyl)piperazin-1-yl] methyl]pyridin-2-yl)ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5- yl)amino]pyridine-3-carbonitrile	6.2
6-methyl-5-[(<i>E</i>)-2-(6-[(4-methyl-1,4-diazepan-1-yl) methyl]pyridin-2-yl)ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5- yl)amino]pyridine-3-carbonitrile	5.6
5-[(<i>E</i>)-2-(6-[(3-(dimethylamino)propyl)amino]methyl) pyridin-2-yl)ethenyl]-6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5- yl)amino]pyridine-3-carbonitrile	4.2
5-[(<i>E</i>)-2-(6-[(2-ethoxyethyl)amino]methyl)pyridin-2-yl) ethenyl]-6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino] pyridine-3-carbonitrile	17.4
5-[(<i>E</i>)-2-(6-[(3-ethoxypropyl)amino]methyl)pyridin-2-yl) ethenyl]-6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino] pyridine-3-carbonitrile	5.5
5-[(<i>E</i>)-2-(6-[(dimethylamino)methyl]pyridin-2-yl)ethenyl]- 6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3- carbonitrile	19.4
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-(6- {[(2-(1-methylpyrrolidin-2-yl)ethyl)amino]methyl}pyridin- 2-yl)ethenyl]pyridine-3-carbonitrile	4.1
5-[(<i>E</i>)-2-(6-[(3-hydroxypyrrolidin-1-yl)methyl]pyridin-2- yl)ethenyl]-6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino] pyridine-3-carbonitrile	11.1
5-[(<i>E</i>)-2-(6-[(2-azepan-1-ylethyl)amino]methyl)pyridin- 2-yl)ethenyl]-6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino] pyridine-3-carbonitrile	1.8
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-(6- {[(2-pyridin-2-ylethyl)amino]methyl}pyridin-2-yl)ethenyl] pyridine-3-carbonitrile	15.2

6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-(6- {[(2-pyridin-3-ylethyl)amino]methyl}pyridin-2-yl)ethenyl] pyridine-3-carbonitrile	16
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-(6- {[(2-pyridin-4-ylethyl)amino]methyl}pyridin-2-yl)ethenyl] pyridine-3-carbonitrile	12.6
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[4-({[3-(4- methylpiperazin-1-yl)propyl]amino}methyl) phenyl]ethenyl]pyridine-3-carbonitrile	6.5
5-[(<i>E</i>)-2-[5-(2-azepan-1-ylethoxy)pyridin-3-yl]ethenyl]-4- [(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	11.5
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[4- ([3-(4-methylpiperazin-1-yl)propyl]amino)methyl) phenyl]ethenyl]pyridine-3-carbonitrile	12.3
5-[(<i>E</i>)-2-[4-({[2-(dimethylamino)ethyl]amino}methyl) phenyl]ethenyl]-6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl) amino]pyridine-3-carbonitrile	24.6
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-(4-({[2- piperidin-1-ylethyl]amino}methyl)phenyl)ethenyl] pyridine-3-carbonitrile	7.5
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[5-(3- piperidin-1-ylpropoxy)pyridin-3-yl]ethenyl]pyridine-3- carbonitrile	16.4
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-(5-{2-[(1- methylpiperidin-4-yl)amino]ethoxy}pyridin-3-yl) ethenyl]pyridine-3-carbonitrile	41.2
5-[(<i>E</i>)-2-[5-(2-{[1-(1-methylethyl)piperidin-4-yl]amino} ethoxy)pyridin-3-yl]ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5- yl)amino]pyridine-3-carbonitrile	10.7
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-(5-{2-[(1- propylpiperidin-4-yl)amino]ethoxy}pyridin-3-yl)ethenyl] pyridine-3-carbonitrile	15.1
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[5-(2-{[1-(2- methylpropyl)piperidin-4-yl]amino}ethoxy)pyridin-3-yl] ethenyl]pyridine-3-carbonitrile	25.9
5-[(<i>E</i>)-2-{3-[(4-hydroxypiperidin-1-yl)methyl]phenyl} ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3- carbonitrile	2.9
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-(3-({[4- methylpiperazin-1-yl)sulfonyl]methyl}phenyl)ethenyl] pyridine-3-carbonitrile	6.2
5-[(<i>E</i>)-2-[4-({[3-hydroxypyrrolidin-1-yl)methyl]phenyl} ethenyl]-6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino] pyridine-3-carbonitrile	18.7
5-[(<i>E</i>)-2-[4-({[3-(dimethylamino)propyl]amino}methyl) phenyl]ethenyl]-6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5- yl)amino]pyridine-3-carbonitrile	8.2
5-[(<i>E</i>)-2-[4-({[1-ethylpyrrolidin-2-yl)methyl]amino} methyl]phenyl]ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5- yl)amino]pyridine-3-carbonitrile	14.9

5-[(E)-2-(4-[(3-ethoxypropyl)amino]methyl)phenyl)ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	27.9
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{3-[(pyrrolidin-1-ylsulfonyl)methyl]phenyl}ethenyl]pyridine-3-carbonitrile	24.5
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4-[(4-methylpiperazin-1-yl)sulfonyl]methyl)phenyl)ethenyl]pyridine-3-carbonitrile	7.9
5-[(E)-2-(5-{2-[(1-ethylpiperidin-3-yl)amino]ethoxy}pyridin-3-yl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	18.2
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(piperidin-1-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile	11.4
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(pyrrolidin-1-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile	20.2
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(morpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile	42.3
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[5-(thiomorpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile	76.5
5-[(E)-2-{5-[(4-hydroxypiperidin-1-yl)methyl]pyridin-2-yl}ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	33.6
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(5-{[(2-morpholin-4-ylethyl)amino]methyl}pyridin-2-yl)ethenyl]pyridine-3-carbonitrile	21.1
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(5-{[(3-morpholin-4-ylpropyl)amino]methyl}pyridin-2-yl)ethenyl]pyridine-3-carbonitrile	15.8
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(5-{[(4-morpholin-4-ylpiperidin-1-yl)methyl]pyridin-2-yl}ethenyl]pyridine-3-carbonitrile	10.8
5-[(E)-2-[5-(1,4'-bipiperidin-1'-ylmethyl)pyridin-2-yl]ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	11.9
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(5-{[(4-pyrrolidin-1-ylpiperidin-1-yl)methyl]pyridin-2-yl}ethenyl]pyridine-3-carbonitrile	12.1
5-[(E)-2-{5-[(4-cyclopentylpiperazin-1-yl)methyl]pyridin-2-yl}ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	18.2
5-[(E)-2-[3-(1,4'-bipiperidin-1'-ylsulfonyl)phenyl]vinyl]-4-[(4-methyl-1H-indol-5-yl)amino]nicotinonitrile	1.3
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-(2-{2-methyl-4-[(4-methylpiperazin-1-	46.7

yl)methyl]phenyl)ethyl]nicotinonitrile	
1'-(<i>N,N</i> -dimethylglycyl)-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	53.5
4-[(<i>E</i>)-2-{5-cyano-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridin-3-yl}vinyl]- <i>N</i> -isobutylbenzenesulfonamide	120.7
5-[(<i>E</i>)-2-(5-{2-[(2,2-dimethylpropyl)amino]ethoxy}pyridin-3-yl)vinyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	46.1
5-[(<i>E</i>)-2-(5-{2-[bis(3,3-dimethylbutyl)amino]ethoxy}pyridin-3-yl)vinyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	344.6
5-[(<i>E</i>)-2-(5-{4-(2-hydroxyethyl)piperazin-1-yl}methyl)pyridin-2-yl}vinyl]-6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	11.9
5-[(<i>E</i>)-2-{5-[(4-isopropylpiperazin-1-yl)methyl]pyridin-2-yl}vinyl]-6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	8.2
5-[(<i>E</i>)-2-(5-{[(2-ethoxyethyl)amino]methyl}pyridin-2-yl)vinyl]-6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	25.8
5-[(<i>E</i>)-2-(5-{[(3-ethoxypropyl)amino]methyl}pyridin-2-yl)vinyl]-6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	23.9
5-[(<i>E</i>)-2-{5-[(dimethylamino)methyl]pyridin-2-yl}vinyl]-6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	21.3
5-[(<i>E</i>)-2-{5-[(3-hydroxypyrrolidin-1-yl)methyl]pyridin-2-yl}vinyl]-6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	40.6
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-(5-{[(2-pyridin-3-ylethyl)amino]methyl}pyridin-2-yl)vinyl]nicotinonitrile	21.9
5-[2-(6-{4-(2-hydroxyethyl)piperazin-1-yl}methyl)pyridin-2-yl]ethyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	27.8
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-(2-{6-[(4-pyrrolidin-1-yl)piperidin-1-yl]methyl}pyridin-2-yl)ethyl]nicotinonitrile	22
<i>tert</i> -butyl 5-cyano-2-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-3',6'-dihydro-3,4'-bipyridine-1'(2' <i>H</i>)-carboxylate	111.8
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-(4-{[(2-morpholin-4-ylethyl)amino]methyl}phenyl)vinyl]nicotinonitrile	13.1
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-(4-{[(2-pyrrolidin-1-ylethyl)amino]methyl}phenyl)vinyl]nicotinonitrile	3.7
<i>N</i> -carbamimidoyl-4-[(<i>E</i>)-2-{5-cyano-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridin-3-yl}vinyl]benzenesulfonamide	15.6
4-[(<i>E</i>)-2-{5-cyano-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridin-3-yl}vinyl]benzenesulfonamide	5.4

2-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	557.2
1'-benzyl-2-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	8.4
2-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-1'-[(1-methylpiperidin-4-yl)methyl]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	117.3
2-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-1'-(methylsulfonyl)-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile	19.8
5-{2-[6-(1,4'-bipiperidin-1'-ylmethyl)pyridin-2-yl]ethyl}-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	15.8
5-[2-(6-{[4-(dimethylamino)piperidin-1-yl]methyl}pyridin-2-yl)ethyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	5.8
5-{2-[6-(hydroxymethyl)pyridin-2-yl]ethyl}-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	NA
3-[(<i>E</i>)-2-{5-cyano-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridin-3-yl}vinyl]benzenesulfonamide	2.7
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-{4-[(pyrrolidin-1-ylsulfonyl)methyl]phenyl}vinyl]nicotinonitrile	7
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-{3-(pyrrolidin-1-ylsulfonyl)phenyl}vinyl]nicotinonitrile	6
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-{3-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}vinyl]nicotinonitrile	0.5
2-[(6-[(<i>E</i>)-2-{5-cyano-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridin-3-yl}vinyl]pyridin-2-yl)methoxy]ethyl sulfate	12.5
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-{4-(2 <i>H</i> -tetrazol-5-yl)phenyl}vinyl]nicotinonitrile	131.6
5-[(<i>E</i>)-2-{3-(1,4'-bipiperidin-1'-ylmethyl)phenyl}vinyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]nicotinonitrile	3.1
5-[(<i>E</i>)-2-(4-{[4-(dimethylamino)piperidin-1-yl]methyl}phenyl)ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	1.3
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-{3-(morpholin-4-ylmethyl)phenyl}ethenyl]pyridine-3-carbonitrile	27.6
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-{3-[(4-methylpiperazin-1-yl)methyl]phenyl}ethenyl]pyridine-3-carbonitrile	6.1
5-[(<i>E</i>)-2-{3-[(4-hydroxypiperidin-1-yl)methyl]phenyl}ethenyl]-6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	15.8
4-(1 <i>H</i> -indol-5-ylamino)-5-[(<i>E</i>)-2-pyridin-2-ylethenyl]pyridine-3-carbonitrile	23.9

6-methyl-5-[(<i>E</i>)-2-(3-[[4-(1-methylethyl)piperazin-1-yl]methyl]phenyl)ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	9
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[3-(pyrrolidin-1-ylmethyl)phenyl]ethenyl]pyridine-3-carbonitrile	14
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[3-(thiomorpholin-4-ylmethyl)phenyl]ethenyl]pyridine-3-carbonitrile	7.1
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[4-(pyrrolidin-1-ylsulfonyl)phenyl]ethenyl]pyridine-3-carbonitrile	20.5
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl]ethenyl]pyridine-3-carbonitrile	9.3
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[3-[(4-methylpiperazin-1-yl)sulfonyl]phenyl]ethenyl]pyridine-3-carbonitrile	0.4
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[3-(piperidin-1-ylsulfonyl)phenyl]ethenyl]pyridine-3-carbonitrile	4.8
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[3-(pyrrolidin-1-ylsulfonyl)phenyl]ethenyl]pyridine-3-carbonitrile	2.4
5-[(<i>E</i>)-2-[2-(hydroxymethyl)-1,3-thiazol-4-yl]ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	6.7
5-[(<i>E</i>)-2-(4-[(1 <i>H</i> -indol-3-ylmethyl)(methyl)amino]methyl)phenyl]ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	2.5
5-[(<i>E</i>)-2-[3-[(diethylamino)methyl]phenyl]ethenyl]-6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	19.9
5-[(<i>E</i>)-2-(4-[(2-methoxyethyl)amino]methyl)phenyl]ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	5.2
5-[(<i>E</i>)-2-(4-[(2-ethoxyethyl)amino]methyl)phenyl]ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	6.3
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[4-[[2-(1-methylpyrrolidin-2-yl)ethyl]amino]methyl]phenyl]ethenyl]pyridine-3-carbonitrile	0.9
5-[(<i>E</i>)-2-(4-[(2-azepan-1-ylethyl)amino]methyl)phenyl]ethenyl]-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	2.0
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-(2-[4-[(4-methylpiperazin-1-yl)methyl]phenyl]ethyl)pyridine-3-carbonitrile	11.1
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[2-(4-methylphenyl)ethyl]pyridine-3-carbonitrile	23.8

4-[(E)-2-(5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl)ethenyl]-N,N-dimethylbenzenesulfonamide	11.0
4-[(E)-2-(5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl)ethenyl]-N,N-diethylbenzenesulfonamide	8.7
4-[(E)-2-(5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl)ethenyl]-N,N-dipropylbenzenesulfonamide	354
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[4-(piperidin-1-ylsulfonyl)phenyl]ethenyl]pyridine-3-carbonitrile	11.5
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-[3-(piperidin-1-ylsulfonyl)phenyl]ethenyl]pyridine-3-carbonitrile	3.0
5-[(E)-2-(5-[(diethylamino)methyl]pyridin-2-yl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	15.8
5-[(E)-2-(6-[(4-(dimethylamino)piperidin-1-yl)methyl]pyridin-2-yl)ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	7.0
5-[(E)-2-(6-[(diethylamino)methyl]pyridin-2-yl)ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	66.3
5-[(E)-2-(6-[(diethylamino)methyl]pyridin-2-yl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	3.1
4-[(E)-2-(5-cyano-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl)ethenyl]-N,N-bis(1-methylethyl)benzenesulfonamide	405
5-[(E)-2-(3-[(2-azepan-1-ylethyl)amino]methyl)phenyl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	2.3
5-[(E)-2-(3-[(3-ethoxypropyl)amino]methyl)phenyl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	4.6
5-[(E)-2-(3-[(2-ethoxyethyl)amino]methyl)phenyl]ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	4.6
5-[(E)-2-(3-[(dimethylamino)methyl]phenyl)ethenyl]-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile	NA
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4-[(4-methylpiperazin-1-yl)sulfonyl]methyl)phenyl]ethenyl]pyridine-3-carbonitrile	NA
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(3-[(4-methylpiperazin-1-yl)sulfonyl]methyl)phenyl]ethenyl]pyridine-3-carbonitrile	NA
6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4-(piperidin-1-ylsulfonyl)phenyl)ethenyl]pyridine-3-carbonitrile	NA
4-[(E)-2-(5-cyano-2-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl)ethenyl]-N,N-dimethylbenzenesulfonamide	NA
4-[(E)-2-(5-cyano-2-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridin-3-yl)ethenyl]-N,N-diethylbenzenesulfonamide	NA

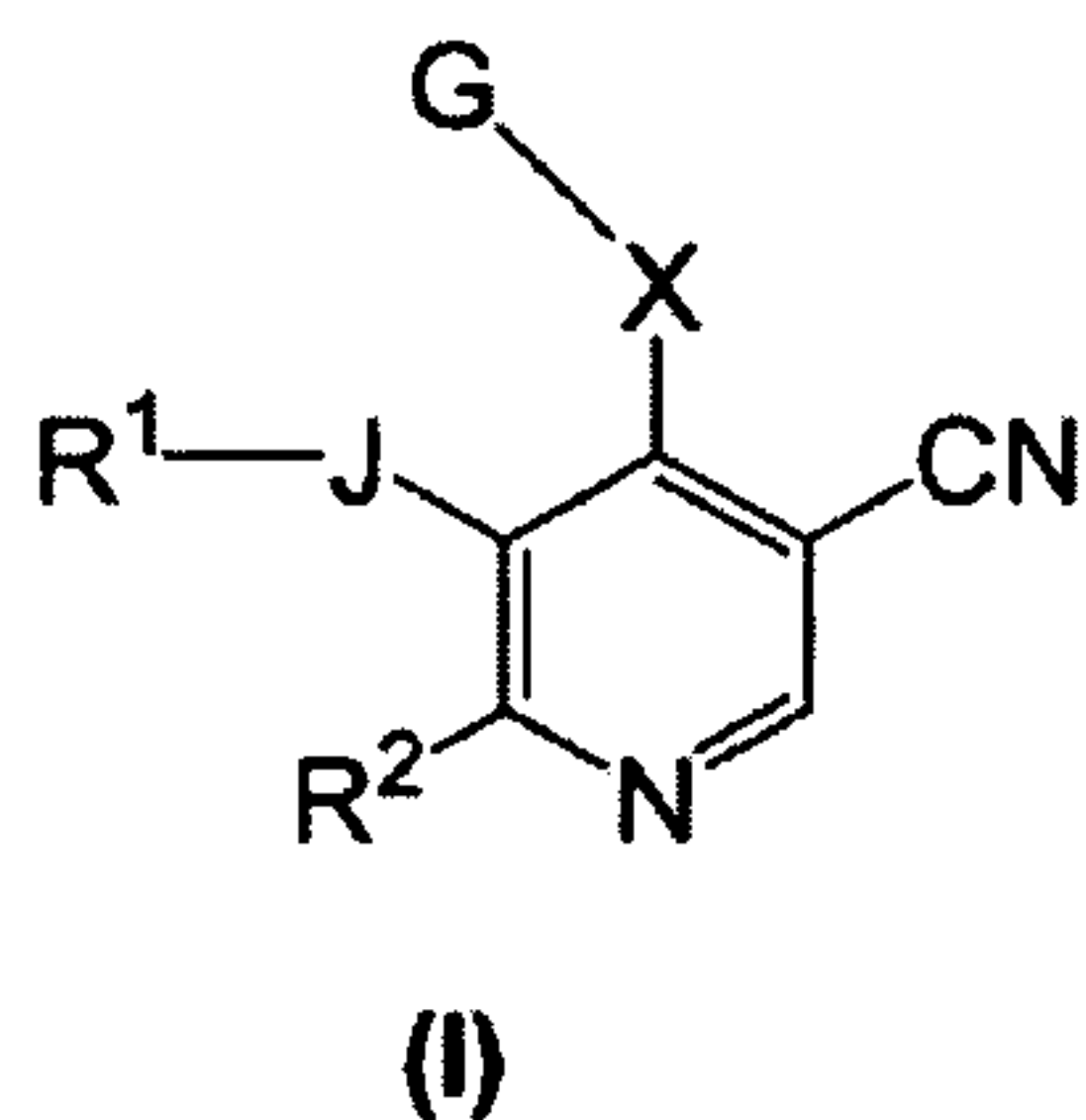
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-(4-{[4-(methylsulfonyl)piperazin-1-yl]methyl}phenyl)ethenyl]pyridine-3-carbonitrile	NA
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[3-({[3-(4-methylpiperazin-1-yl)propyl]amino}methyl)phenyl]ethenyl]pyridine-3-carbonitrile	NA
5-[(<i>E</i>)-2-(4-[(2-azepan-1-ylethyl)amino]methyl)phenyl)ethenyl]-6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	NA
5-[(<i>E</i>)-2-(3-[(3-ethoxypropyl)amino]methyl)phenyl)ethenyl]-6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]pyridine-3-carbonitrile	NA
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[4-({[2-(2-methylpyrrolidin-1-yl)ethyl]amino}methyl)phenyl]ethenyl]pyridine-3-carbonitrile	NA
4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-[2-(pyrrolidin-1-ylmethyl)-1,3-thiazol-4-yl]ethenyl]pyridine-3-carbonitrile	NA
6-methyl-4-[(4-methyl-1 <i>H</i> -indol-5-yl)amino]-5-[(<i>E</i>)-2-(4-[(2-pyridin-3-ylethyl)amino]methyl)phenyl)ethenyl]pyridine-3-carbonitrile	12.8

'NA' indicates data has not been measured

[00606] Many variations of the present invention not illustrated herein will occur to those skilled in the art. The present invention is not limited to the embodiments illustrated and described herein, but encompasses all the subject matter within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. A compound of formula (I):

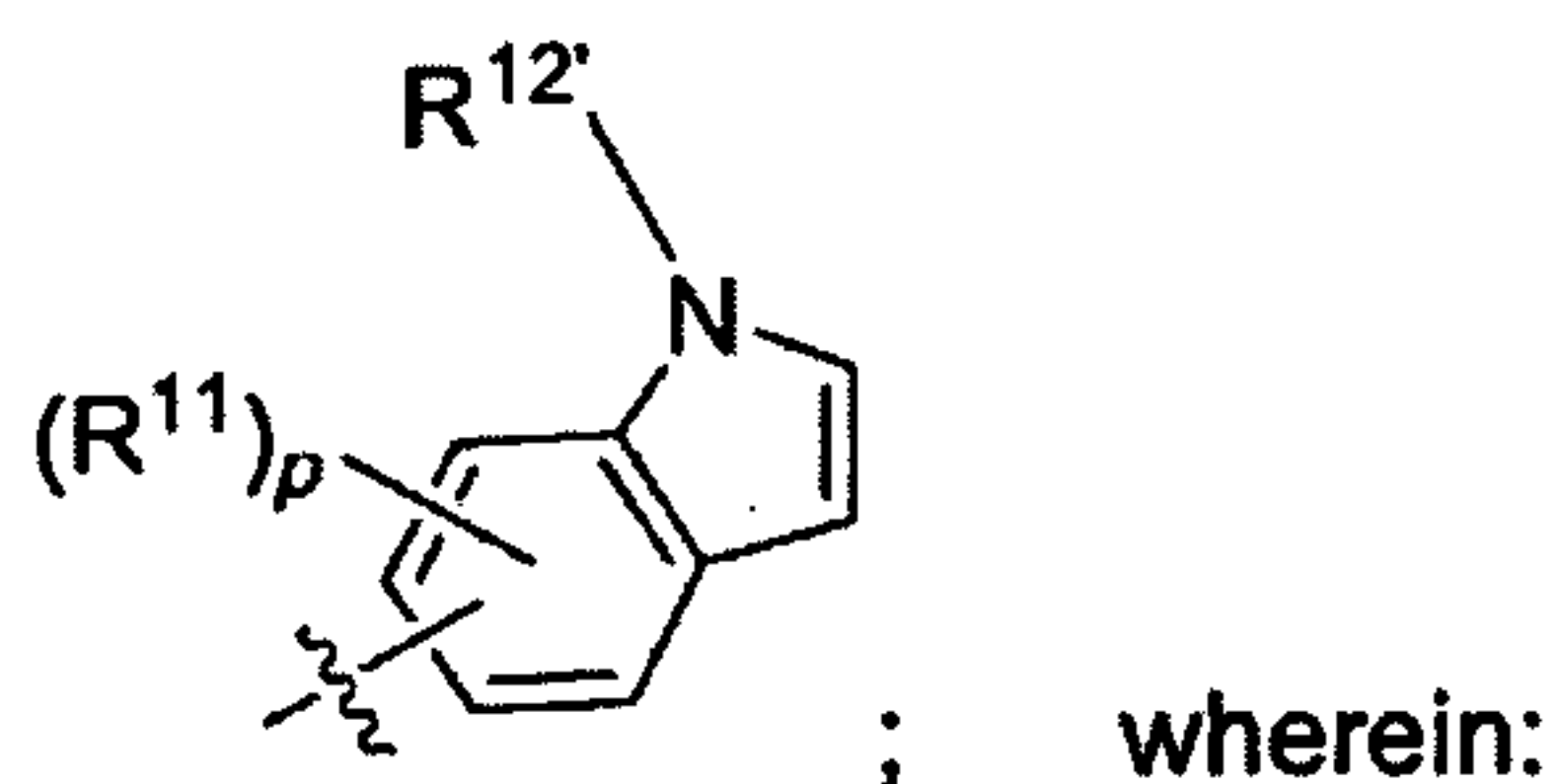


or a pharmaceutically acceptable salt thereof, wherein:

X is -O- or -N(R¹⁰)-; wherein

R¹⁰ is H or CH₃;

G is



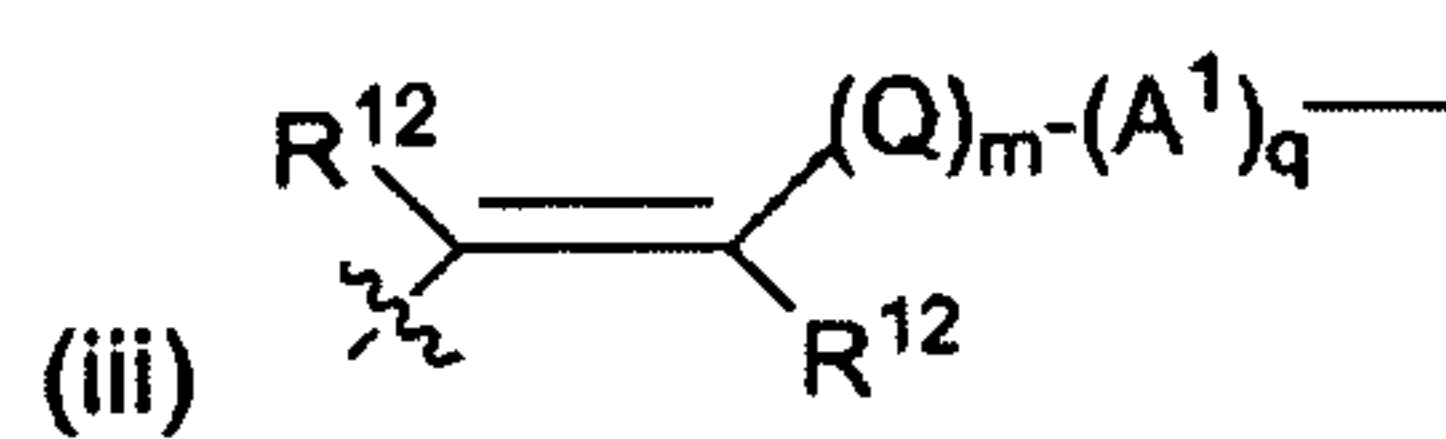
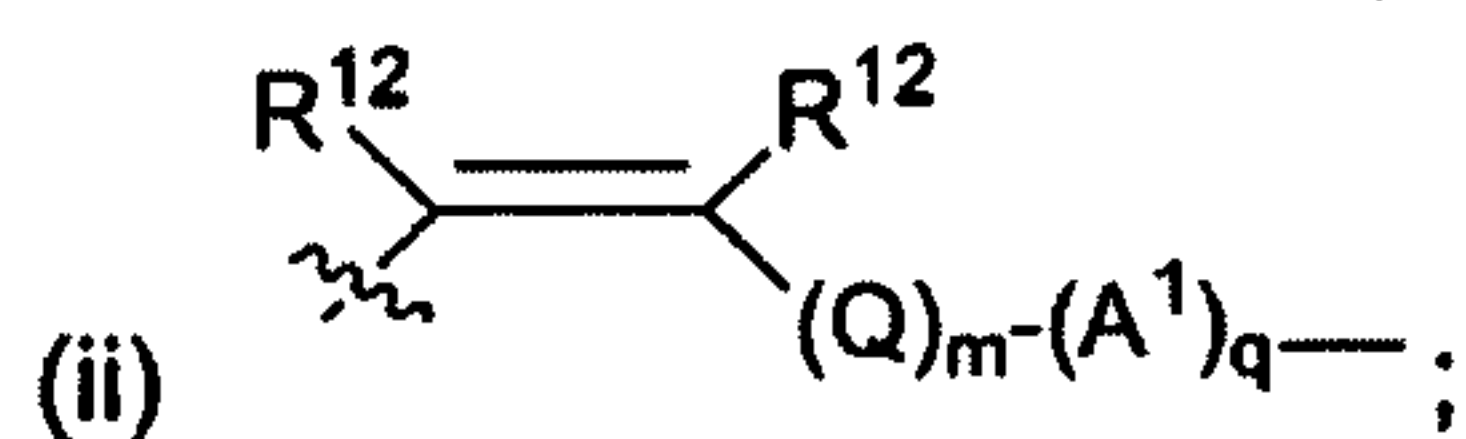
R¹¹ is, independently at each occurrence, selected from halo, -O-R^{12''}, C₁₋₄ alkyl, -CF₃ and -N(R^{12''})-R^{12''};

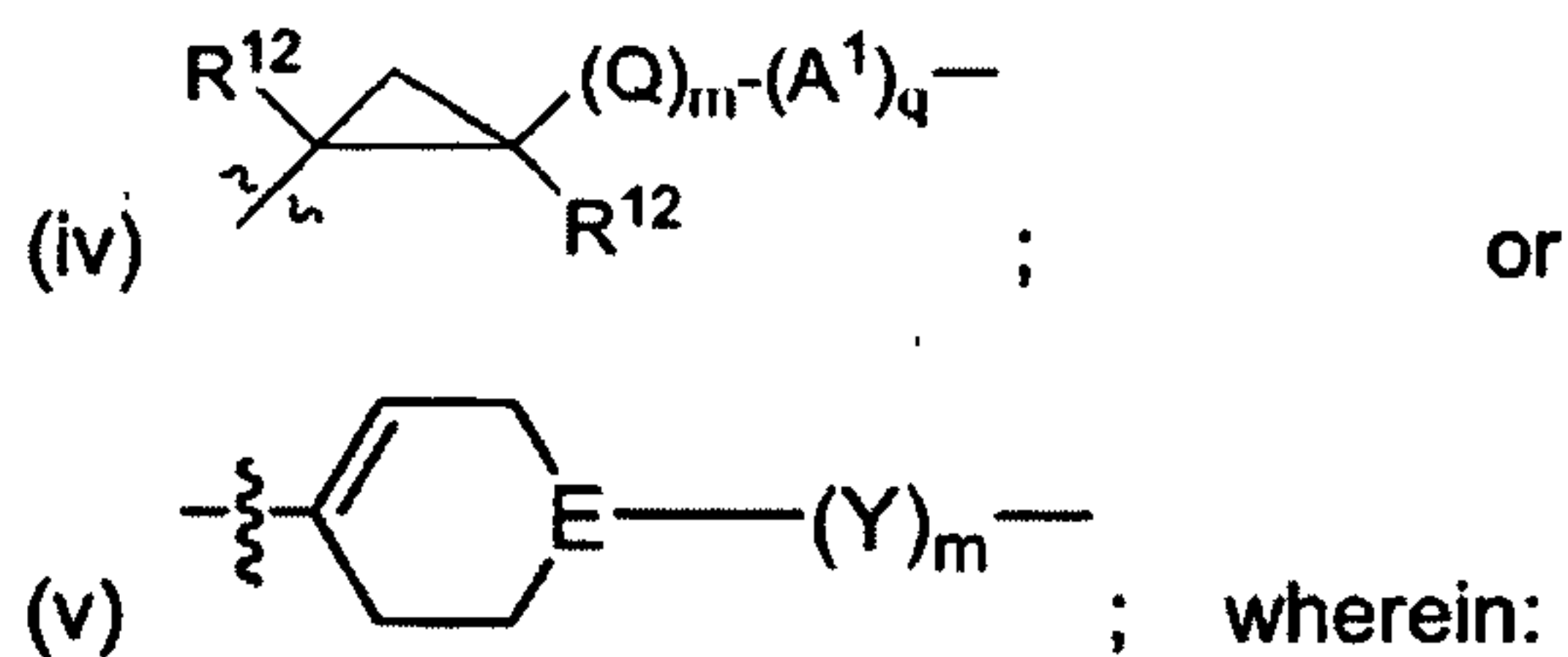
R^{12'} is, independently at each occurrence, H or CH₃;

R^{12''} is, independently at each occurrence, H or CH₃; and

p is 0, 1 or 2;

J is (i) -Q-(A¹)_q-;





Q is, independently at each occurrence, C₁₋₄ alkylene;

A¹ is (i) a C₆₋₁₀ aryl, (ii) a 5- to 10-membered hetero₁₋₃aryl, (iii) 3- to 10-membered hetero₁₋₃cyclyl or (iv) a 5- to 8-membered cycloalkyl, wherein each of (i)-(iv) is optionally substituted with 1 or 2 substituents independently selected from halo, -O-R¹³, C₁₋₄ alkyl, C₁₋₄ haloalkyl, formyl, -S-R¹³, -Q-O-R¹³, -Q-N(R¹³)-R¹³, -C(O)-O-R¹³, -C(O)-R¹³, -O-C(O)-R¹³, -C(O)-N(R¹³)-R¹³, -N(R¹³)-C(O)-R¹³, -S(O)₂-N(R¹³)-R¹³, -N(R¹³)-S(O)₂-R¹³, -O-Q-O-R¹³, -O-Q-N(R¹³)-R¹³, -N(R¹³)-Q-O-R¹³, -N(R¹³)-Q-N(R¹³)-R¹³, -O-C(O)-N(R¹³)-R¹³, -N(R¹³)-C(O)-O-R¹³, -S(O)₂-R¹³, -SO₂NH(NH)NH₂, -SO₂NH(NH)NR¹³R¹³ or wherein 2 substituents together on the same carbon atom form an oxo group;

R¹² is, independently at each occurrence, H or CH₃;

m and q are independently 0 or 1;

E is N or C(R¹²); wherein:

when E is N, Y is absent, -C(O)-, -C(O)-O-, -C(O)-N(R¹³)- or -S(O)₂-; and

when E is C(R¹²), Y is -O-, -C(O), -C(O)-O-, -O-C(O)-, -C(O)-N(R¹³)-, -O-C(O)-N(R¹³)-, -N(R¹³)-C(O)-, -N(R¹³)-C(O)-O-, -N(R¹³)-C(O)-N(R¹³)-, -S-, -S(O)-, -S(O)₂-, -S(O)₂-N(R¹³)- or -N(R¹³)-S(O)₂-;

R¹³ is, independently at each occurrence, selected from (i) an electron pair, (ii) H, (iii) C₁₋₆ alkyl, (iv) C₆₋₁₀ aryl, (v) 5- to 10-membered heteroaryl, (vi) 3- to 10-membered hetero₁₋₃cyclyl or (vii) two R¹³ together on the same carbon atom form a 4- to 8-membered ring containing 1-3 heteroatoms, wherein each of (iii)-(vi) is optionally substituted with 1-2 R¹⁴; and

R^{14} is, independently at each occurrence, (i) H, (ii) oxo when two R^{14} together on the same carbon atom are bound to an oxygen atom, (iii) C_{1-6} alkyl, (iv) C_{3-8} cycloalkyl, (v) C_{6-10} aryl, (vi) 5- to 10-membered heteroaryl, (vii) 3- to 10-membered hetero₁₋₃cyclyl, wherein each of (iii)-(vii) is optionally substituted with 1-2 C_{1-6} alkyl;

R^1 is C_{1-4} alkyl, C_{2-4} alkenyl or $-(L)_r(A^2-A^3)$, wherein:

L is $-(T)_r(Q)_u$, $-(Q)_u(T)_t$, or $-(T)_r(Q)_u(T)_t$, wherein:

T is, independently at each occurrence, -O-, -C(O)-, -C(O)-O-, -O-C(O)-, -C(O)-N(R^{13})-, -O-C(O)-N(R^{13})-, -N(R^{13})-, -N(R^{13})-C(O)-, -N[C(O) R^{13}]-, -N(R^{13})-C(O)-O-, -N(R^{13})-C(O)-N(R^{13})-, -S-, -S(O)-, -S(O)₂-, -S(O)₂-N(R^{13})- or -N(R^{13})-S(O)₂;

t is, independently at each occurrence, 0 or 1;

u is, independently at each occurrence, 0 or 1;

r is, independently at each occurrence, 0 or 1;

A^2 is (i) absent, (ii) C_{1-6} alkylene, (iii) a C_{6-10} arylene, (iv) 5- to 10-membered heteroarylene, (v) 3- to 10-membered hetero₁₋₃cyclylene or (vi) C_{3-8} cycloalkylene, wherein each of (ii)-(vi) is optionally substituted with 1 or 2 substituents independently selected from halo, -O- R^{13} , C_{1-4} alkyl, C_{1-4} haloalkyl, -S- R^{13} , -N(R^{13}) R^{13} , -Q-O- R^{13} , -Q-N(R^{13})- R^{13} , -C(O)-O- R^{13} , -O-C(O)- R^{13} , -C(O)-N(R^{13})- R^{13} , -N(R^{13})-C(O)- R^{13} , -S(O)₂-N(R^{13})- R^{13} , -N(R^{13})-S(O)₂- R^{13} , -O-Q-O- R^{13} , -O-Q-N(R^{13})- R^{13} , -N(R^{13})-Q-O- R^{13} , -N(R^{13})-Q-N(R^{13})- R^{13} , -O-C(O)-N(R^{13})- R^{13} , -N(R^{13})-C(O)-O- R^{13} , -S(O)₂- R^{13} , -OS(O)₂-OR¹³, -C(O)- R^{13} and oxo when 2 substituents together on the same carbon atom are bound to an oxygen atom; and

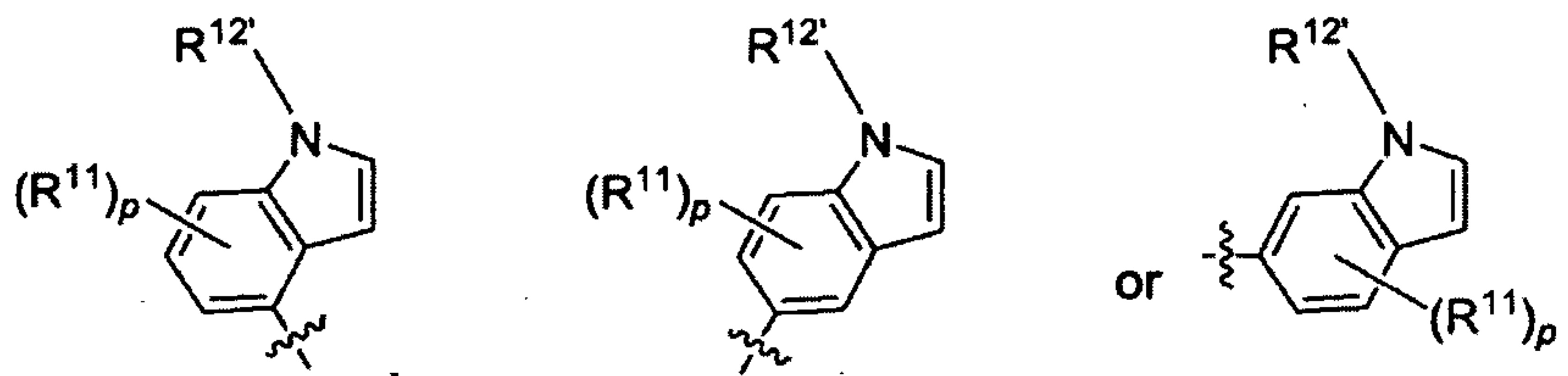
A^3 is (i) H, (ii) halo, (iii) -O- R^{14} , (iv) R^{13} , (v) -CHO, (vi) -S(O)-O- R^{13} , (vii) -N(R^{13}) R^{13} (viii) C_{6-10} aryl, (ix) 5- or 6-membered heteroaryl, (x) 3- to 10-membered hetero₁₋₃cyclyl or (xi) C_{3-8} cycloalkyl, wherein each of (viii)-(xi) is optionally substituted with 1 or 2 substituents independently selected from halo, -O- R^{13} , C_{1-4} alkyl, C_{1-4} haloalkyl, -S- R^{13} , -N(R^{13}) R^{13} , -Q-O- R^{13} , -Q-N(R^{13})- R^{13} ,

-C(O)-O-R¹³, -O-C(O)-R¹³, -C(O)-N(R¹³)-R¹³, -N(R¹³)-C(O)-R¹³,
 -S(O)₂-N(R¹³)-R¹³, -N(R¹³)-S(O)₂-R¹³, -O-Q-O-R¹³, -O-Q-N(R¹³)-R¹³,
 -N(R¹³)-Q-O-R¹³, -N(R¹³)-Q-N(R¹³)-R¹³, -O-C(O)-N(R¹³)-R¹³,
 -N(R¹³)-C(O)-O-R¹³, -S(O)₂-R¹³, -C(O)-R¹³ and oxo when 2 substituents
 together on the same carbon atom are bound to an oxygen atom;

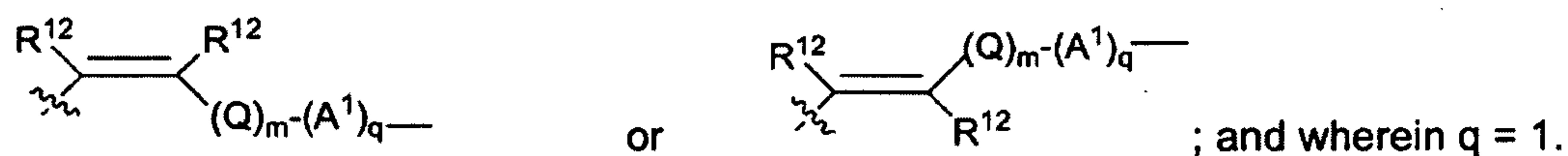
and

R² is H, C₁₋₄ alkyl or -CF₃.

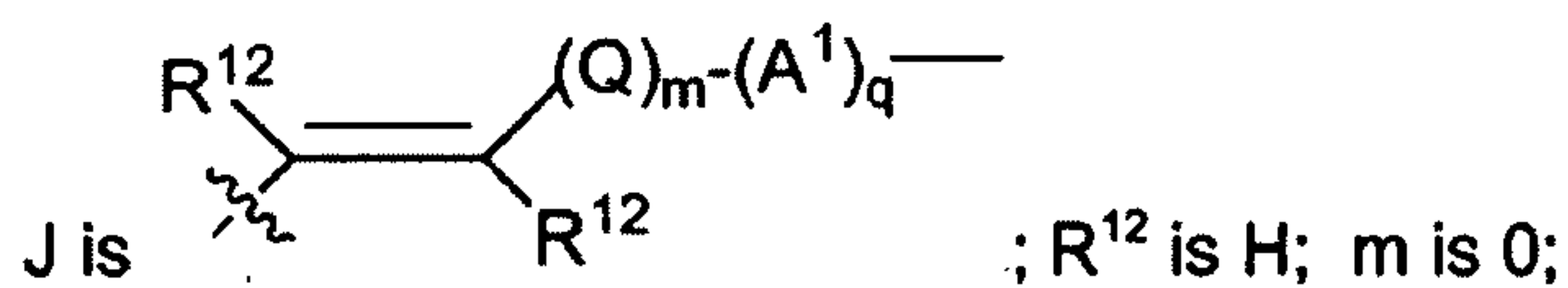
2. The compound of claim 1, wherein X is -N(R¹⁰)- and R¹⁰ is H.
3. The compound of claims 1 or 2, wherein R² is H or methyl.
4. The compound of claims 1 or 2, wherein G is



5. The compound of any of claims 1-4, wherein R^{12'} is H.
6. The compound of any of claims 1-5, wherein each R¹¹ is, independently at each occurrence, chloro or methyl.
7. The compound of any of claims 1-6, wherein G is indol-4-yl, indol-5-yl, 2-methylindol-5-yl, 4-methylindol-5-yl, 2,4-dimethylindol-5-yl, 4,7-dimethylindol-5-yl, 4-methyl-7-chloroindol-5-yl or indol-6-yl.
8. The compound of any of claims 1-7, wherein J is -Q-(A¹)_q-.
9. The compound of any of claims 1-7, wherein J is



10. The compound of any of claims 1-9, wherein R^{12} is H.
11. The compound of any of claims 1-10 wherein A^1 , where present, is optionally substituted C_{6-10} arylene or optionally substituted 5- to 10-membered hetero₁₋₃arylene.
12. The compound of claim 9, wherein:

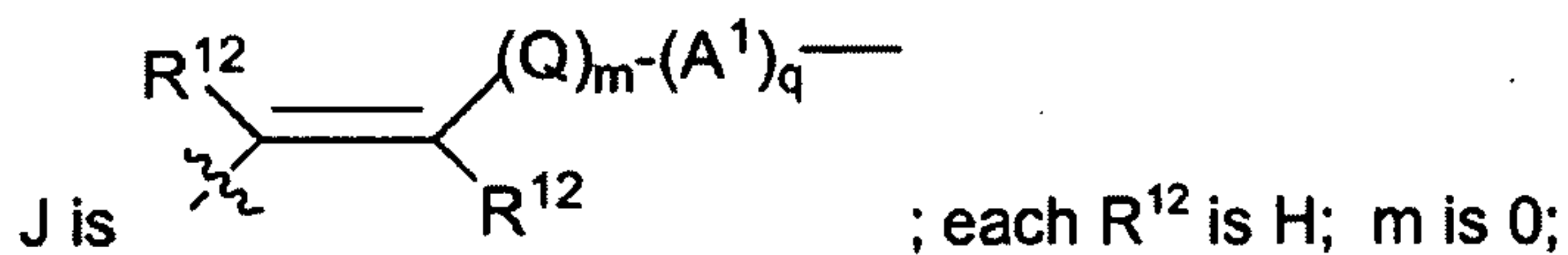


R^2 is H; X is $-(NR^{10})-$ and A^1 is optionally substituted C_{6-10} arylene or optionally substituted 5- to 10-membered hetero₁₋₃arylene.

13. The compound of any of claims 1-12, wherein Q, where present, is methylene, ethylene or trimethylene.



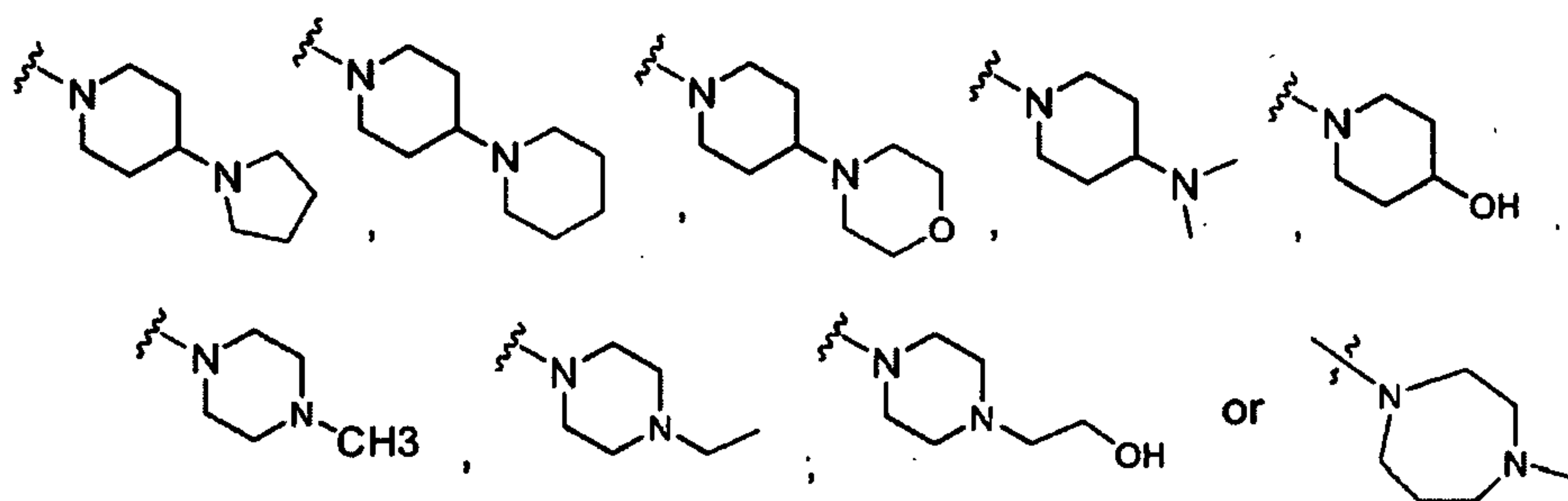
15. The compound of claim 12, wherein:



R^2 is H; X is $-(NR^{10})-$; A^1 is phenylene, pyridinyl, thiazolyl, or furanyl, each of which is optionally substituted; and R^1 is $-(L)_r \text{---} (A^2 \text{---} A^3)$, wherein L is $-(T)_t \text{---} (Q)_u \text{---}$ or $-(Q)_u \text{---} (T)_t \text{---}$.

16. The compound of claim 15, wherein t is 0, u is 1 and L is $-Q-$, wherein Q is methylene.

17. The compound of any of claims 1-16, wherein A^1 , where present, is phenylene, pyridinyl, thiazolyl or furanyl, each of which is optionally substituted.
18. The compound of claim 15, wherein A^1 is optionally substituted phenylene, T is $-O-$, u is 1 and A^3 is 3- to 7-membered hetero_{1,3}cycyl.
19. The compound of any of claims 1-18, wherein A^2 is absent.
20. The compound of any of claims 1-18, wherein A^2 , where present, is morpholinyl, piperidinyl, piperazinyl, pyrrolidinyl, azetidiny, thiomorpholinyl, thiomorpholinyl-1,1-dioxide, 1,3-dioxoisindolyl, oxopiperazinyl, 1,4-diazepanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,2,3,4-tetrahydroisoquinolinyl, indolinyl or cyclohexyl, wherein A^2 is optionally substituted.
21. The compound of any of claims 1-18, wherein A^2 may be present or absent and $-(A^2-A^3)$, where present, is:

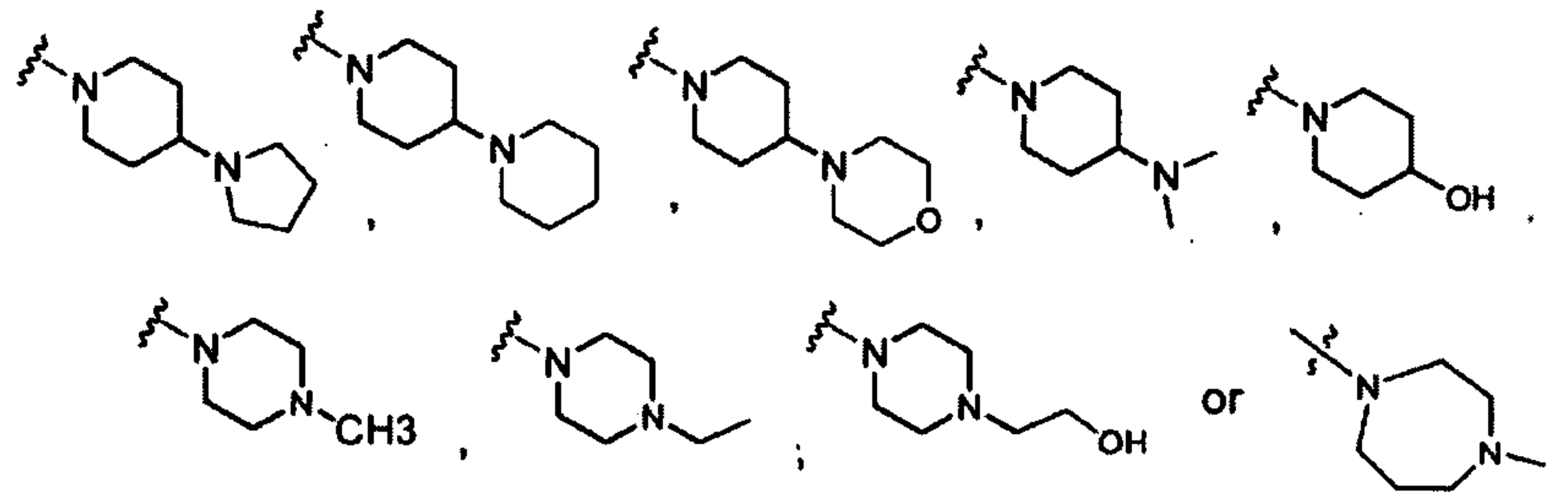


22. A compound of any of claims 1-21, wherein A^3 , when present, is $-NR^{13}R^{13}$, 5- to 10-membered heteroarylene or 3- to 10-membered hetero_{1,3}cyclylene, and wherein A^3 contains a nitrogen atom, joined via the nitrogen atom to A^2 , when present, or when A^2 is absent, joined via the nitrogen atom to an adjacent atom.
23. A compound according to claim 1 wherein J is J(ii) or J(iii) and $-(Q)_m-(A^1)_q-R_1$ is:
- (B1) $-A^3$, wherein m, q and r are 0 and A^2 is absent and A^3 is as defined in claim 1; or

- (B2) $-A^1-A^2-A^3$, wherein m is 0, q is 1, and r is 0 and wherein A^1 and A^3 are as defined in claim 1 and A^2 is C_{1-6} alkylene; or
- (B3) $-A^2-A^3$, wherein m , q and r are 0 and A^2 and A^3 are as defined in claim 1; or
- (B4) $-A^1-T-A^3$, wherein m is 0, q is 1, A^2 is absent, r is 1 and L is $-T-$ and A^1 , T and A^3 are as defined in claim 1; or
- (B5) $-A^1-T-A^2-A^3$, wherein m is 0, q and r are 1 and L is $-T-$ and A^1 , T , A^2 and A^3 are as defined in claim 1; or
- (B6) $-A^1-Q-T-A^2-A^3$, wherein m is 0, q and r are 1 and L is $-Q-T-$ and A^1 , T , A^2 and A^3 are as defined in claim 1; or
- (B7) $A^1-Q-A^2-A^3$, wherein m is 0, q and r are 1 and L is $-Q-$ and A^1 , Q , A^2 and A^3 are as defined in claim 1.

24. A compound according to claim 23 wherein J is $J(ii)$ or $J(iii)$ and:

- (C1) $(Q)_m-(A^1)_q-R_1$ is B1 and A^3 is optionally substituted C_6-C_{10} aryl, 5- or 6-membered heteroaryl, 3- to 10-membered hetero_{1,3}cyclyl or C_{3-8} cycloalkyl; or
- (C2) $-(Q)_m-(A^1)_q-R_1$ is B2 and A^1 is optionally substituted C_6-C_{10} aryl or optionally substituted 5- to 10- membered hetero_{1,3}aryl, and A^3 is $-N(R^{13})R^{13}$ or optionally substituted 3- to 10-membered hetero_{1,3}cyclyl wherein at least one heteroatom is a nitrogen atom and A^3 is joined via the nitrogen atom to A^2 .
- (C3) $-(Q)_m-(A^1)_q-R_1$ is B3 and $-(A^2-A^3)$ is:



or

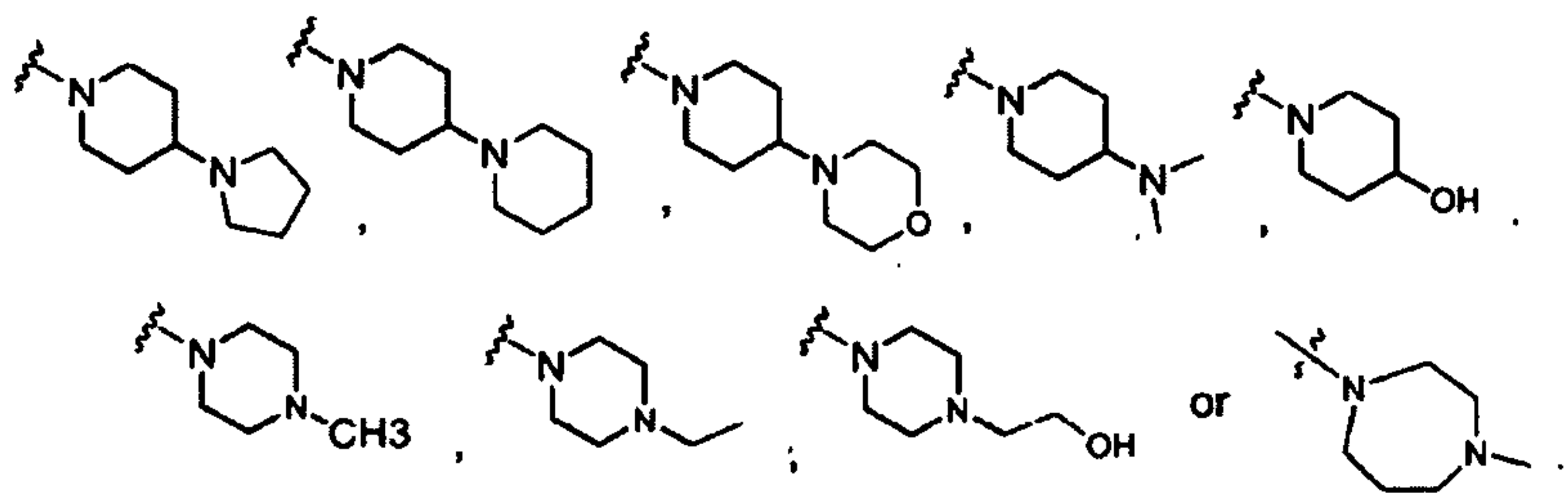
- (C4) $-(Q)_m-(A^1)_q-R_1$ is B4 and A^1 is optionally substituted C_{6-10} aryl or optionally substituted 5- to 10-membered hetero_{1,3}aryl and A^3 is optionally substituted

3- to 10-membered hetero_{1,3}cyclyl and T is -O-, -NH-, -C(O)-, or -C(O)-NH- or -S(O)₂-; or

(C5) -(Q)_m-(A¹)_q-R₁ is B5 and A² is alkylene and A¹ is optionally substituted C₆₋₁₀ aryl or optionally substituted 5- to 10-membered hetero_{1,3}aryl and A³ is optionally substituted 3- to 10-membered hetero_{1,3}cyclyl and T is -O-, -C(O)-, or -C(O)-NH- or -S(O)₂-; or

(C6) -(Q)_m-(A¹)_q-R₁ is B6 and A¹ is optionally substituted C₆₋₁₀ aryl or optionally substituted 5- to 10-membered hetero_{1,3}aryl and A² is alkylene or is absent, T is -O-, -NH-, -C(O)-, -C(O)-NH- or -S(O)₂- and A³ is -N(R¹³)R¹³ or optionally substituted 3- to 10-membered hetero_{1,3}cyclyl; or

(C7) -(Q)_m-(A¹)_q-R₁ is B7 and A¹ is optionally substituted C₆₋₁₀ aryl or optionally substituted 5- to 10-membered hetero_{1,3}aryl and wherein -(A²-A³) or -A³ when A² is absent is:



25. A compound, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from:

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(1*E*)-3-[(2-morpholin-4-ylethyl)amino]prop-1-en-1-yl]nicotinonitrile;

N-{1-[(3*E*)-4-{5-cyano-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl]piperidin-4-yl}propane-2-sulfonamide;

5-[(1*E*)-4-[4-(isopropylsulfonyl)piperazin-1-yl]but-1-en-1-yl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

N-{1-[(3*E*)-4-{5-cyano-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl]piperidin-4-yl}ethanesulfonamide;

N-{1-[(3*E*)-4-{5-cyano-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl]piperidin-4-yl}benzenesulfonamide;

- 5-[(1*E*)-4-[(3*R*)-3-aminopyrrolidin-1-yl]but-1-en-1-yl]-4-[(4-methyl-1*H*-indol-5-yl)amino] nicotinonitrile;
- (3*E*)-4-{5-cyano-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl (3*R*)-3-amino pyrrolidine-1-carboxylate;
- 5-[(1*E*)-4-[(3*S*)-3-aminopyrrolidin-1-yl]but-1-en-1-yl]-4-[(4-methyl-1*H*-indol-5-yl)amino] nicotinonitrile;
- 5-[(1*E*)-4-(3-aminoazetidin-1-yl)but-1-en-1-yl]-4-[(4-methyl-1*H*-indol-5-yl)amino] nicotinonitrile;
- 5-[(1*E*)-4-(1,4-diazepan-1-yl)but-1-en-1-yl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;
- 5-[(1*E*)-4-[4-(methylamino)piperidin-1-yl]but-1-en-1-yl]-4-[(4-methyl-1*H*-indol-5-yl)amino] nicotinonitrile;
- 5-[(1*E*)-4-[(3*R*)-3-aminopiperidin-1-yl]but-1-en-1-yl]-4-[(4-methyl-1*H*-indol-5-yl)amino] nicotinonitrile;
- 5-[(1*E*)-4-[(3*S*)-3-aminopiperidin-1-yl]but-1-en-1-yl]-4-[(4-methyl-1*H*-indol-5-yl)amino] nicotinonitrile;
- 5-[(1*E*)-4-[4-(aminomethyl)piperidin-1-yl]but-1-en-1-yl]-4-[(4-methyl-1*H*-indol-5-yl)amino] nicotinonitrile;
- 5-[(1*E*)-4-(2,5-diazabicyclo[2.2.1]hept-2-yl)but-1-en-1-yl]-4-[(4-methyl-1*H*-indol-5-yl)amino] nicotinonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(1*E*)-4-(4-phenylpiperidin-1-yl)but-1-en-1-yl] nicotinonitrile;
- 5-[(1*E*)-4-[4-(dimethylamino)piperidin-1-yl]but-1-en-1-yl]-4-[(4-methyl-1*H*-indol-5-yl)amino] nicotinonitrile;
- 5-[(1*E*)-4-(4-hydroxypiperidin-1-yl)but-1-en-1-yl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(1*E*)-4-(4-morpholin-4-ylpiperidin-1-yl)but-1-en-1-yl] nicotinonitrile;
- 1'-glycyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile;
- 1'-(2-methylalanyl)-4-[(4-methyl-1*H*-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile;
- 1'-β-alanyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-1'-D-valyl-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-1'-L-valyl-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile;

- 4-[(4-methyl-1*H*-indol-5-yl)amino]-1'-D-prolyl-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-1'-L-prolyl-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-1'-(pyrrolidin-3-ylcarbonyl)-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile;
- 5-[(1*E*)-4-[(3*R*)-3-hydroxypiperidin-1-yl]but-1-en-1-yl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;
- 5-[(1*E*)-4-[(3*S*)-3-hydroxypiperidin-1-yl]but-1-en-1-yl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;
- 5-[(*E*)-2-(4-formylphenyl)vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]nicotinonitrile;
- 5-[(*E*)-2-(4-fluorophenyl)vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;
- 4-[(2,4-dimethyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}vinyl]nicotinonitrile;
- 5-benzyl-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;
- 6-ethyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-phenylvinyl]nicotinonitrile;
- 6-isopropyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-phenylvinyl]nicotinonitrile;
- 5-[(*E*)-2-[2-methoxy-4-(piperazin-1-ylmethyl)phenyl]vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;
- 6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[4-(2-pyrrolidin-1-ylethoxy)phenyl]vinyl]nicotinonitrile;
- 5-(2-{2-methoxy-4-[(4-methylpiperazin-1-yl)methyl]phenyl}ethyl)-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-(2-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}ethyl)nicotinonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)oxy]-5-[(*E*)-2-phenylvinyl]nicotinonitrile;
- 4-[(*E*)-2-{5-cyano-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl}vinyl]-*N*-phenylpiperidine-1-carboxamide;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[1-(phenylsulfonyl)piperidin-4-yl]vinyl]nicotinonitrile;
- 5-[(*E*)-2-(1-benzoylpiperidin-4-yl)vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[1-(3-phenylpropanoyl)piperidin-4-yl]vinyl]nicotinonitrile;

4-[(*E*)-2-[5-cyano-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl]vinyl]-*N*-propylpiperidine-1-carboxamide;

5-[(*E*)-2-[1-(isopropylsulfonyl)piperidin-4-yl]vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

5-[(*E*)-2-[4-(dimethylamino)phenyl]vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[6-[(2-piperidin-1-ylethyl)amino]pyridin-3-yl]ethenyl]pyridine-3-carbonitrile;

5-[(*E*)-2-[5-[[3-(dimethylamino)propyl]amino]methyl]pyridin-2-yl]ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

5-[(*E*)-2-[6-[[3-ethoxypropyl]amino]methyl]pyridin-2-yl]ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[5-[[2-pyridin-3-ylethyl]amino]methyl]pyridin-2-yl]ethenyl]pyridine-3-carbonitrile;

5-[(*E*)-2-[3-(1,4'-bipiperidin-1'-ylmethyl)phenyl]ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

5-[(*E*)-2-[3-[[4-(1-methylethyl)piperazin-1-yl]methyl]phenyl]ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[3-(morpholin-4-ylmethyl)phenyl]ethenyl]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[3-[[2-morpholin-4-ylethyl]amino]methyl]phenyl]ethenyl]pyridine-3-carbonitrile;

5-[(*E*)-2-[3-[[4-(dimethylamino)piperidin-1-yl]methyl]phenyl]ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

5-[(*E*)-2-[3-[[4-methyl-1,4-diazepan-1-yl]methyl]phenyl]ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[3-[[2-(1-methylpyrrolidin-2-yl)ethyl]amino]methyl]phenyl]ethenyl]pyridine-3-carbonitrile;

5-[(*E*)-2-[3-[[2-(dimethylamino)ethyl]amino]methyl]phenyl]ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[3-[[3-(2-oxopyrrolidin-1-yl)propyl]amino]methyl]phenyl]ethenyl]pyridine-3-carbonitrile;

5-[(*E*)-2-(3-[(2-methoxyethyl)amino]methyl)phenyl]ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[3-(piperidin-1-ylmethyl)phenyl] ethenyl] pyridine-3-carbonitrile;

5-[(*E*)-2-[3-(1,4'-bipiperidin-1'-ylmethyl)phenyl]ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[3-[(4-pyrrolidin-1-yl)piperidin-1-yl)methyl] phenyl]ethenyl]pyridine-3-carbonitrile;

5-[(*E*)-2-(3-[[4-(2-hydroxyethyl)piperazin-1-yl]methyl]phenyl)ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

5-[(*E*)-2-(3-[[4-(dimethylamino)piperidin-1-yl]methyl]phenyl)ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[3-[(4-morpholin-4-yl)piperidin-1-yl)methyl] phenyl]ethenyl]pyridine-3-carbonitrile;

6-methyl-5-[(*E*)-2-[3-[(4-methyl-1,4-diazepan-1-yl)methyl]phenyl]ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

5-[(*E*)-2-[3-([3-(dimethylamino)propyl]amino)methyl]phenyl]ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

5-[(*E*)-2-[3-([2-(dimethylamino)ethyl]amino)methyl]phenyl]ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

6-methyl-5-[(*E*)-2-[5-[(4-methyl-1,4-diazepan-1-yl)methyl]pyridin-2-yl]vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

5-[(*E*)-2-[5-([3-(dimethylamino)propyl]amino)methyl]pyridin-2-yl]vinyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[5-([2-(1-methylpyrrolidin-2-yl) ethyl]amino) methyl]pyridin-2-yl]vinyl]nicotinonitrile;

5-[(*E*)-2-(5-[(2-azepan-1-ylethyl)amino]methyl)pyridin-2-yl]vinyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(5-([2-(2-pyridin-2-ylethyl)amino]methyl) pyridin-2-yl]vinyl]nicotinonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(5-([2-(2-pyridin-4-ylethyl)amino]methyl) pyridin-2-yl]vinyl]nicotinonitrile;

- 4-[(4-methyl-1*H*-indol-5-yl)amino]-1'-[(1-methylpiperidin-4-yl)methyl]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile;
- 6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(3-[(3-morpholin-4-ylpropyl)amino] methyl} phenyl)vinyl]nicotinonitrile;
- 6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(3-[(2-pyrrolidin-1-ylethyl)amino] methyl} phenyl)ethenyl]pyridine-3-carbonitrile;
- 5-[(*E*)-2-{3-[(dimethylamino)methyl]phenyl}ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino] pyridine-3-carbonitrile;
- 5-[(*E*)-2-{3-[(3-hydroxypyrrolidin-1-yl)methyl]phenyl}ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;
- 6-ethyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-(2-phenylethyl)pyridine-3-carbonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(4-methylpiperazin-1-yl)methyl]pyridine-3-carbonitrile;
- 5-(3,4-dimethoxybenzyl)-4-(1*H*-indol-5-ylamino)nicotinonitrile;
- 5-(3,4-dimethoxybenzyl)-4-(1*H*-indol-4-ylamino)nicotinonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-phenylvinyl]nicotinonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(1*E*)-3-pyrrolidin-1-ylprop-1-en-1-yl]nicotinonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(1*E*)-3-(4-phenylpiperazin-1-yl)prop-1-en-1-yl] nicotinonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(1*E*)-3-(4-methylpiperazin-1-yl)prop-1-en-1-yl] nicotinonitrile;
- tert*-butyl 5-cyano-4-[(4-methyl-1*H*-indol-5-yl)amino]-3',6'-dihydro-3,4'-bipyridine-1'(2'*H*)-carboxylate;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(1*E*)-3-morpholin-4-ylprop-1-en-1-yl]nicotinonitrile;
- 5-[(1*E*)-3-(3,4-dihydroisoquinolin-2(1*H*)-yl)prop-1-en-1-yl]-4-[(4-methyl-1*H*-indol-5-yl) amino] nicotinonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(1*E*)-4-(4-methylpiperazin-1-yl)but-1-en-1-yl] nicotinonitrile;
- 5-[(1*E*)-3-aminoprop-1-en-1-yl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(1*E*)-4-(4-phenylpiperazin-1-yl)but-1-en-1-yl] nicotinonitrile;
- 5-[(1*E*)-buta-1,3-dien-1-yl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

- (3*E*)-4-{5-cyano-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl indoline-1-carboxylate;
- (3*E*)-4-{5-cyano-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl thiomorpholine-4-carboxylate 1,1-dioxide;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(1*E*)-4-morpholin-4-ylbut-1-en-1-yl]nicotinonitrile;
- (3*E*)-4-{5-cyano-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl morpholine-4-carboxylate;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(1*E*)-4-pyrrolidin-1-ylbut-1-en-1-yl]nicotinonitrile;
- tert*-butyl {1-[(2*E*)-3-{5-cyano-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl}prop-2-en-1-yl]piperidin-4-yl}carbamate;
- tert*-butyl 4-[(2*E*)-3-{5-cyano-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl}prop-2-en-1-yl]piperazine-1-carboxylate;
- 5-[(1*E*)-3-(4-aminopiperidin-1-yl)prop-1-en-1-yl]-4-[(4-methyl-1*H*-indol-5-yl)amino] nicotinonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(1*E*)-3-piperazin-1-ylprop-1-en-1-yl]nicotinonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-1'-(methylsulfonyl)-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-1'-(phenylsulfonyl)-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile;
- 1'-acetyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile;
- 5-cyano-*N*-ethyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-3',6'-dihydro-3,4'-bipyridine-1'(2'*H*)-carboxamide;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-1'-[(1-methylpiperidin-4-yl)carbonyl]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile;
- 1'-benzyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile;
- ethyl 5-cyano-4-[(4-methyl-1*H*-indol-5-yl)amino]-3',6'-dihydro-3,4'-bipyridine-1'(2'*H*)-carboxylate;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(1*E*)-4-piperidin-1-ylbut-1-en-1-yl]nicotinonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(1*E*)-4-thiomorpholin-4-ylbut-1-en-1-yl]nicotinonitrile;
- 5-[(1*E*)-4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)but-1-en-1-yl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

1'-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile;

5-[(1*E*)-4-(4-acetylpiperazin-1-yl)but-1-en-1-yl]-4-[(4-methyl-1*H*-indol-5-yl)amino] nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(1*E*)-4-[4-(methylsulfonyl)piperazin-1-yl]but-1-en-1-yl] nicotinonitrile;

tert-butyl 4-[(3*E*)-4-{5-cyano-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl] piperazine-1-carboxylate;

tert-butyl {1-[(3*E*)-4-{5-cyano-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl] piperidin-4-yl}carbamate;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(1*E*)-5-(4-methylpiperazin-1-yl)pent-1-en-1-yl] nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(1*E*)-5-morpholin-4-ylpent-1-en-1-yl]nicotinonitrile;

(4*E*)-5-{5-cyano-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl}pent-4-en-1-yl morpholine-4-carboxylate;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(1*E*)-5-pyrrolidin-1-ylpent-1-en-1-yl]nicotinonitrile;

5-[(1*E*)-4-aminobut-1-en-1-yl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[3-(4-methylpiperazin-1-yl)propyl]nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[4-(4-methylpiperazin-1-yl)butyl]nicotinonitrile;

5-[(1*E*)-4-(4-aminopiperidin-1-yl)but-1-en-1-yl]-4-[(4-methyl-1*H*-indol-5-yl)amino] nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(1*E*)-4-piperazin-1-ylbut-1-en-1-yl]nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(1*E*)-4-[(2-morpholin-4-ylethyl)amino]but-1-en-1-yl] nicotinonitrile;

5-[(*E*)-2-{5-[(dimethylamino)methyl]pyridin-2-yl}vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino] nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}vinyl]nicotinonitrile;

5-[(1*E*)-4-[4-(ethylsulfonyl)piperazin-1-yl]but-1-en-1-yl]-4-[(4-methyl-1*H*-indol-5-yl)amino] nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(1*E*)-4-[4-(phenylsulfonyl)piperazin-1-yl]but-1-en-1-yl] nicotinonitrile;

5-[(1*E*)-4-[4-(2,2-dimethylpropanoyl)piperazin-1-yl]but-1-en-1-yl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

N-{1-[(3*E*)-4-{5-cyano-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl]piperidin-4-yl}methanesulfonamide;

N-{1-[(3*E*)-4-{5-cyano-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl]piperidin-4-yl}acetamide;

5-[(1*E*)-4-(isopropylamino)but-1-en-1-yl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

5-[(1*E*)-4-(cyclohexylamino)but-1-en-1-yl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(1*E*)-4-(piperidin-4-ylamino)but-1-en-1-yl] nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-1'-(piperidin-4-ylcarbonyl)-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile;

tert-butyl 4-[(3*E*)-4-{5-cyano-2-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl]piperazine-1-carboxylate;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(1*E*)-5-piperidin-1-ylpent-1-en-1-yl]nicotinonitrile;

tert-butyl 4-[(4*E*)-5-{5-cyano-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl}pent-4-en-1-yl]piperazine-1-carboxylate;

tert-butyl {1-[(4*E*)-5-{5-cyano-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl}pent-4-en-1-yl]piperidin-4-yl}carbamate;

tert-butyl {1-[(3*E*)-4-{5-cyano-2-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl]piperidin-4-yl}carbamate;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(1*E*)-3-piperidin-1-ylprop-1-en-1-yl]nicotinonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(1*E*)-4-piperazin-1-ylbut-1-en-1-yl]nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-(4-piperazin-1-ylbutyl)nicotinonitrile;

5-[4-(4-aminopiperidin-1-yl)butyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(1*E*)-5-piperazin-1-ylpent-1-en-1-yl]nicotinonitrile;

5-[(1*E*)-5-(4-aminopiperidin-1-yl)pent-1-en-1-yl]-4-[(4-methyl-1*H*-indol-5-yl)amino] nicotinonitrile;

5-[(1*E*)-4-(4-aminopiperidin-1-yl)but-1-en-1-yl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

5-[(1*E*)-4-(dimethylamino)but-1-en-1-yl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(1*E*)-4-[(1-methylpiperidin-4-yl)amino]but-1-en-1-yl]nicotinonitrile;
- 5-[(1*E*)-4-[(*trans*-4-hydroxycyclohexyl)amino]but-1-en-1-yl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;
- 5-[(1*E*)-5-(4-hydroxypiperidin-1-yl)pent-1-en-1-yl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;
- 6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(1*E*)-4-[4-(methylsulfonyl)piperazin-1-yl]but-1-en-1-yl]nicotinonitrile;
- N*-{1-[(3*E*)-4-{5-cyano-2-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl}but-3-en-1-yl]piperidin-4-yl}methanesulfonamide;
- 5-[(1*E*)-4-(4-hydroxy-4-phenylpiperidin-1-yl)but-1-en-1-yl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;
- 4-[(*E*)-2-{5-cyano-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl}vinyl]benzoic acid;
- 5-[(1*E*)-3-(4-hydroxypiperidin-1-yl)prop-1-en-1-yl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;
- tert*-butyl 4-[(6-[(*E*)-2-{5-cyano-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl}vinyl]pyridin-3-yl)methyl]piperazine-1-carboxylate;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[5-(piperazin-1-ylmethyl)pyridin-2-yl]vinyl]nicotinonitrile;
- tert*-butyl 4-{4-[(*E*)-2-{5-cyano-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl}vinyl]benzyl}piperazine-1-carboxylate;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}vinyl]nicotinonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(4-methylphenyl)vinyl]nicotinonitrile;
- 5-[(*E*)-2-(4-methoxyphenyl)vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;
- 5-[(*E*)-2-biphenyl-4-ylvinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;
- 4-[(2,4-dimethyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-phenylvinyl]nicotinonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[4-(trifluoromethyl)phenyl]vinyl]nicotinonitrile;
- 5-[(*E*)-2-(4-chlorophenyl)vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*Z*)-2-phenylvinyl]nicotinonitrile;

5-[(1*E*)-4-[(3*R*)-3-hydroxypyrrolidin-1-yl]but-1-en-1-yl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

5-[(1*E*)-4-[(3*S*)-3-hydroxypyrrolidin-1-yl]but-1-en-1-yl]-4-[(4-methyl-1*H*-indol-5-yl) amino]nicotinonitrile;

5-[(1*E*)-4-[4-(hydroxymethyl)piperidin-1-yl]but-1-en-1-yl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

5-[(1*E*)-4-(4-methoxypiperidin-1-yl)but-1-en-1-yl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-1'-(2-phenylethyl)-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile;

1'-(2-fluorobenzyl)-4-[(4-methyl-1*H*-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile;

1'-(3-fluorobenzyl)-4-[(4-methyl-1*H*-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile;

1'-(4-fluorobenzyl)-4-[(4-methyl-1*H*-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(1*E*)-4-[4-(pyrrolidin-1-ylcarbonyl)piperidin-1-yl]but-1-en-1-yl]nicotinonitrile;

5-[(*E*)-2-(3-methoxyphenyl)vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

5-[(*E*)-2-(4-bromophenyl)vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

5-[(*E*)-2-(2-methoxyphenyl)vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

5-[(*E*)-2-(3,4-dimethoxyphenyl)vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

4-(1*H*-indol-5-ylamino)-5-[(*E*)-2-phenylvinyl]nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-vinylnicotinonitrile;

4-(1*H*-indol-5-ylamino)-6-methyl-5-[(*E*)-2-phenylvinyl]nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-1'-(piperidin-4-ylmethyl)-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(1*E*)-4-(3-oxopiperazin-1-yl)but-1-en-1-yl] nicotinonitrile;

5-[(*E*)-2-(3-methoxyphenyl)vinyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{4-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl} vinyl]nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{2-[(4-methylpiperazin-1-yl)methyl]-1,3-thiazol-4-yl} vinyl]nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-(2-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl} ethyl)nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{6-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl} vinyl]nicotinonitrile;

4-(1*H*-indol-6-ylamino)-6-methyl-5-[(*E*)-2-phenylvinyl]nicotinonitrile;

4-(1*H*-indol-6-ylamino)-5-[(*E*)-2-phenylvinyl]nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[4-(2-pyrrolidin-1-ylethoxy)phenyl]vinyl] nicotinonitrile;

5-[(*E*)-2-[4-(2-chloroethoxy)phenyl]vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(1*E*)-3-phenylprop-1-en-1-yl]nicotinonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{5-[(4-methylpiperazin-1-yl)methyl] pyridin-2-yl}vinyl]nicotinonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-phenylvinyl]nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-pyridin-2-ylvinyl]nicotinonitrile;

5-[(*E*)-2-(4-butylphenyl)vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-pyridin-4-ylvinyl]nicotinonitrile;

6-methyl-4-[(2-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-phenylvinyl]nicotinonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-vinylnicotinonitrile;

4-[(4,7-dimethyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-phenylvinyl]nicotinonitrile;

4-[(7-chloro-4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-phenylvinyl]nicotinonitrile;

4-[(7-chloro-4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(3-methoxyphenyl)vinyl]nicotinonitrile;

4-[(7-chloro-4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-pyridin-2-ylvinyl]nicotinonitrile;

4-[(2-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-phenylvinyl]nicotinonitrile;

5-[(*E*)-2-(4-methoxyphenyl)vinyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-(3-phenylpropyl)nicotinonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}vinyl]nicotinonitrile;
- 4-(1*H*-indol-5-ylamino)-5-[(*E*)-2-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}vinyl]nicotinonitrile;
- 4-(1*H*-indol-4-ylamino)-5-[(*E*)-2-phenylvinyl]nicotinonitrile;
- 4-(1*H*-indol-4-ylamino)-6-methyl-5-[(*E*)-2-phenylvinyl]nicotinonitrile;
- 5-[(*E*)-2-{2-methoxy-4-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;
- 5-[(*E*)-2-[2-(2-chloroethoxy)phenyl]vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;
- 5-[(*E*)-2-[3-(2-chloroethoxy)phenyl]vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{2-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}vinyl]nicotinonitrile;
- 4-[1*H*-indol-5-yl(methyl)amino]-5-[(*E*)-2-phenylvinyl]nicotinonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{2-methyl-4-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]nicotinonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[2-(2-piperazin-1-ylethoxy)phenyl]vinyl] nicotinonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[2-(2-pyrrolidin-1-ylethoxy)phenyl]vinyl] nicotinonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-piperidin-4-ylvinyl]nicotinonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{3-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}vinyl]nicotinonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[3-(2-pyrrolidin-1-ylethoxy)phenyl]vinyl]nicotinonitrile;
- 5-[2-(4-methoxyphenyl)ethyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;
- 5-(2-biphenyl-4-ylethyl)-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{3-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]nicotinonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-(2-phenylethyl)nicotinonitrile;
- 4-[(7-chloro-4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-pyridin-4-ylvinyl]nicotinonitrile;

4-[(7-chloro-4-methyl-1*H*-indol-5-yl)amino]-6-methyl-5-[(*E*)-2-pyridin-2-ylvinyl] nicotinonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-pyridin-2-ylvinyl]nicotinonitrile;

4-[(7-chloro-4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{5-[(4-methylpiperazin-1-yl)methyl] pyridin-2-yl}vinyl]nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(1*H*-1,2,4-triazol-1-yl)vinyl]nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(4-methyl-1,3-thiazol-5-yl)vinyl]nicotinonitrile;

5-[(1*E*)-3-(1*H*-imidazol-1-yl)prop-1-en-1-yl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

5-[(*E*)-2-cyclohexylvinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-pyridin-4-ylvinyl]nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{5-[(4-methylpiperazin-1-yl)methyl]-3-furyl}vinyl] nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{2-methyl-5-[(4-methylpiperazin-1-yl)carbonyl] phenyl} vinyl]nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{2-methyl-5-[(4-methylpiperazin-1-yl)methyl] phenyl} vinyl]nicotinonitrile;

4-[(7-chloro-4-methyl-1*H*-indol-5-yl)amino]-6-methyl-5-[(*E*)-2-phenylvinyl]nicotinonitrile;

4-[(7-chloro-4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{6-[(4-methylpiperazin-1-yl)methyl] pyridin-2-yl}vinyl]nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl] nicotinonitrile;

5-[(*E*)-2-{6-[(4-acetylpiperazin-1-yl)methyl]pyridin-2-yl}vinyl]-4-[(4-methyl-1*H*-indol-5-yl) amino] nicotinonitrile;

5-[(*E*)-2-{2-methoxy-5-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]-4-[(4-methyl-1*H*-indol-5-yl) amino]nicotinonitrile;

5-[(*E*)-2-{2-methoxy-5-(piperazin-1-ylmethyl)phenyl}vinyl]-4-[(4-methyl-1*H*-indol-5-yl) amino]nicotinonitrile;

5-[(*E*)-2-(2-methoxyphenyl)vinyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-pyridin-3-ylvinyl]nicotinonitrile;

5-[(*E*)-2-(3,4-dimethoxyphenyl)vinyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino] nicotinonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-pyrazin-2-ylvinyl]nicotinonitrile;

tert-butyl 4-[(*E*)-2-{5-cyano-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl}vinyl]piperidine-1-carboxylate;

4-(1*H*-indol-4-yloxy)-5-[(*E*)-2-phenylvinyl]nicotinonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(4-methyl-1,3-thiazol-5-yl)vinyl]nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[4-(piperidin-1-ylmethyl)phenyl]vinyl] nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[4-(pyrrolidin-1-ylmethyl)phenyl]vinyl] nicotinonitrile;

5-[(*E*)-2-(2-chloropyridin-3-yl)vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{2-methyl-4-[(4-methylpiperazin-1-yl)carbonyl] phenyl} vinyl]nicotinonitrile;

5-[(*E*)-2-(4-{[4-(2-hydroxyethyl)piperazin-1-yl]methyl}phenyl)vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

5-[(*E*)-2-{4-[(4-hydroxypiperidin-1-yl)methyl]phenyl}vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino] nicotinonitrile;

5-[(*E*)-2-[4-({[3-(dimethylamino)propyl]amino}methyl)phenyl]vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[4-(thiomorpholin-4-ylmethyl)phenyl]vinyl] nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{4-[(4-pyrrolidin-1-yl)piperidin-1-yl]methyl} phenyl}vinyl]nicotinonitrile;

5-[(*E*)-2-{2-methoxy-3-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

5-[(*E*)-2-[2-methoxy-3-(piperazin-1-ylmethyl)phenyl]vinyl]-4-[(4-methyl-1*H*-indol-5-yl) amino]nicotinonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{6-[(4-methylpiperazin-1-yl)methyl] pyridin-2-yl}vinyl]nicotinonitrile;

5-[(*E*)-2-{3-methoxy-4-[(4-methylpiperazin-1-yl)methyl]phenyl}vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

5-[(*E*)-2-[3-methoxy-4-(piperazin-1-ylmethyl)phenyl]vinyl]-4-[(4-methyl-1*H*-indol-5-yl) amino]nicotinonitrile;

5-isopropenyl-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;
 5-[(*E*)-2-{3-[(diethylamino)methyl]phenyl}vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino] nicotinonitrile;
 5-[(*E*)-2-{4-[(diethylamino)methyl]phenyl}vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino] nicotinonitrile;
 5-[(*E*)-2-(6-bromopyridin-2-yl)vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;
 5-[(*E*)-2-[3,4-bis(2-methoxyethoxy)phenyl]vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino] nicotinonitrile;
 5-[(*E*)-2-(4-formylphenyl)ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;
 5-[(*E*)-2-[4-(1,4'-bipiperidin-1'-ylmethyl)phenyl]ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino] pyridine-3-carbonitrile;
 5-[(*E*)-2-(4-{[(3-ethoxypropyl)amino]methyl}phenyl)ethenyl]-4-[(4-methyl-1*H*-indol-5-yl) amino]pyridine-3-carbonitrile;
 5-[(*E*)-2-(2-chloropyridin-4-yl)vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;
 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-{(*E*)-2-[4-(piperazin-1-ylmethyl)phenyl]vinyl} nicotinonitrile;
 5-{(*E*)-2-[4-(azetidin-1-ylmethyl)phenyl]vinyl}-4-[(4-methyl-1*H*-indol-5-yl)amino] nicotinonitrile;
 6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-(2-phenylethyl)nicotinonitrile;
 5-[(*E*)-2-{4-[(dimethylamino)methyl]phenyl}vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino] nicotinonitrile;
 5-[(*E*)-2-(4-ethoxyphenyl)vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;
 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{4-[(4-pyridin-2-ylpiperazin-1-yl)methyl]phenyl} vinyl]nicotinonitrile;
tert-butyl 3-({4-[(*E*)-2-{5-cyano-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl}vinyl]benzyl amino)azetidine-1-carboxylate;
 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(4-propoxyphenyl)vinyl]nicotinonitrile;
 5-[(*E*)-2-(6-chloropyridin-3-yl)vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;
 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-{2-[4-(pyrrolidin-1-ylmethyl)phenyl]ethyl}nicotinonitrile;
 5-[(*E*)-2-(6-chloropyridin-2-yl)vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;
 5-{(*E*)-2-[6-(hydroxymethyl)pyridin-2-yl]vinyl}-4-[(4-methyl-1*H*-indol-5-yl)amino] nicotinonitrile;
 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-{(*E*)-2-[6-(piperidin-1-ylmethyl)pyridin-2-yl]vinyl} nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[6-(pyrrolidin-1-ylmethyl)pyridin-2-yl]vinyl] nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[6-(piperazin-1-ylmethyl)pyridin-2-yl]vinyl] nicotinonitrile;

5-[(*E*)-2-[5-(hydroxymethyl)pyridin-2-yl]vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino] nicotinonitrile;

5-[(*E*)-2-{4-[(3-hydroxypyrrolidin-1-yl)methyl]phenyl}ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino] pyridine-3-carbonitrile;

N-{4-[(*E*)-2-{5-cyano-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl}ethenyl]benzyl}-*N*-(2-piperidin-1-ylethyl)acetamide;

5-[(*E*)-2-(4-{4-(1-methylethyl)piperazin-1-yl}methyl)phenyl]ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

N-{4-[(*E*)-2-{5-cyano-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl}ethenyl]benzyl}-*N*-(2-pyrrolidin-1-ylethyl)acetamide;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(4-{[(2-pyridin-3-ylethyl)amino]methyl}phenyl)ethenyl]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(4-{[(2-pyridin-2-ylethyl)amino]methyl}phenyl)ethenyl]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(4-{[(3-morpholin-4-ylpropyl)amino]methyl}phenyl)ethenyl]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{4-[(4-morpholin-4-ylpiperidin-1-yl)methyl]phenyl}ethenyl]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(4-{[(2-morpholin-4-ylethyl)amino]methyl}phenyl)ethenyl]pyridine-3-carbonitrile;

5-[(*E*)-2-{4-[(4-cyclopentylpiperazin-1-yl)methyl]phenyl}ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

5-[(*E*)-2-(4-formylphenyl)ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[4-(morpholin-4-ylmethyl)phenyl]ethenyl] pyridine-3-carbonitrile;

5-[(*E*)-2-{4-[(azetidin-3-ylamino)methyl]phenyl}ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{2-methyl-4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}ethenyl]pyridine-3-carbonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{4-[(4-methylpiperazin-1-yl) methyl] phenyl}ethenyl]pyridine-3-carbonitrile;

5-[(*E*)-2-{4-[(4-hydroxypiperidin-1-yl)methyl]phenyl}ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl) amino]pyridine-3-carbonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[4-(piperidin-1-ylmethyl)phenyl] ethenyl]pyridine-3-carbonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[4-(pyrrolidin-1-ylmethyl)phenyl] ethenyl]pyridine-3-carbonitrile;

5-[(*E*)-2-{4-[(diethylamino)methyl]phenyl}ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino] pyridine-3-carbonitrile;

6-methyl-5-[(*E*)-2-{4-[(4-methyl-1,4-diazepan-1-yl)methyl]phenyl}ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

5-[(*E*)-2-(4-benzylmorpholin-2-yl)ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3- carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{2-[(4-methylpiperazin-1-yl)methyl]phenyl} ethenyl]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-3- yl}ethenyl]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{4-[(4-methylpiperazin-1-yl)methyl]-1,3-thiazol-2- yl}ethenyl]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{6-[(4-methylpiperazin-1-yl)methyl]pyridin-3- yl}ethenyl]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[5-(piperidin-1-ylmethyl)pyridin-2-yl]ethenyl} pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[5-(pyrrolidin-1-ylmethyl)pyridin-2-yl]ethenyl} pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[5-(morpholin-4-ylmethyl)pyridin-2-yl]ethenyl} pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[5-(thiomorpholin-4-ylmethyl)pyridin-2-yl] ethenyl]pyridine-3-carbonitrile;

5-[(*E*)-2-{5-[(4-hydroxypiperidin-1-yl)methyl]pyridin-2-yl}ethenyl]-4-[(4-methyl-1*H*-indol-5-yl) amino]pyridine-3-carbonitrile;

5-[(*E*)-2-(5-{[4-(2-hydroxyethyl)piperazin-1-yl]methyl}pyridin-2-yl)ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(5-{[(2-morpholin-4-ylethyl)amino]methyl} pyridin-2-yl)ethenyl]pyridine-3-carbonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-{(*E*)-2-[4-(morpholin-4-ylmethyl)phenyl]ethenyl}pyridine-3-carbonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(4-{[(2-pyridin-2-ylethyl)amino]methyl}phenyl)ethenyl]pyridine-3-carbonitrile;

5-[(*E*)-2-{4-[(4-cyclopentylpiperazin-1-yl)methyl]phenyl}ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-{(*E*)-2-[4-(thiomorpholin-4-ylmethyl)phenyl]ethenyl} pyridine-3-carbonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(4-{[(2-pyridin-4-ylethyl)amino]methyl}phenyl)ethenyl]pyridine-3-carbonitrile;

6-methyl-5-[(*E*)-2-(4-{[4-(1-methylethyl)piperazin-1-yl]methyl}phenyl)ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

5-[(*E*)-2-(5-bromopyridin-3-yl)ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

tert-butyl [2-({5-[(*E*)-2-{5-cyano-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl}ethenyl} pyridin-3-yl)oxy)ethyl]carbamate;

5-[(*E*)-2-(5-methoxypyridin-3-yl)ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{2-methyl-4-[(4-methylpiperazin-1-yl)methyl]phenyl}ethenyl]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(2-methylphenyl)ethenyl]pyridine-3-carbonitrile;

5-[(*E*)-2-(2-ethylphenyl)ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(5-{[(3-morpholin-4-ylpropyl)amino]methyl} pyridin-2-yl)ethenyl]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{5-[(4-morpholin-4-ylpiperidin-1-yl)methyl] pyridin-2-yl}ethenyl]pyridine-3-carbonitrile;

5-{(*E*)-2-[5-(1,4'-bipiperidin-1'-ylmethyl)pyridin-2-yl]ethenyl}-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{5-[(4-pyrrolidin-1-ylpiperidin-1-yl)methyl] pyridin-2-yl}ethenyl]pyridine-3-carbonitrile;

- 5-[(*E*)-2-{5-[(4-cyclopentylpiperazin-1-yl)methyl]pyridin-2-yl}ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;
- 5-[(*E*)-2-(5-{4-(1-methylethyl)piperazin-1-yl}methyl)pyridin-2-yl}ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;
- 5-[(*E*)-2-(5-{4-(dimethylamino)piperidin-1-yl}methyl)pyridin-2-yl}ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;
- 5-[(*E*)-2-{5-[(4-methyl-1,4-diazepan-1-yl)methyl]pyridin-2-yl}ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-{(*E*)-2-[5-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}methyl]pyridin-2-yl}ethenyl}pyridine-3-carbonitrile;
- 6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(4-{[(3-morpholin-4-ylpropyl)amino]methyl}phenyl)ethenyl]pyridine-3-carbonitrile;
- 5-{(*E*)-2-[4-(1,4'-bipiperidin-1'-ylmethyl)phenyl]ethenyl}-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;
- 6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(4-{[(4-morpholin-4-ylpiperidin-1-yl)methyl]phenyl}ethenyl]pyridine-3-carbonitrile;
- 5-{(*E*)-2-[4-{[(1-ethylpyrrolidin-2-yl)methyl]amino}methyl]phenyl}ethenyl}-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;
- 6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-(2-pyridin-2-ylethyl)pyridine-3-carbonitrile;
- 5-{(*E*)-2-[5-(2-aminoethoxy)pyridin-3-yl]ethenyl}-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;
- 5-[(*E*)-2-{2-ethyl-5-[(4-methylpiperazin-1-yl)methyl]phenyl}ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;
- 5-[(*E*)-2-{2-ethyl-5-[(4-methylpiperazin-1-yl)methyl]phenyl}ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-pyridin-3-ylethenyl]pyridine-3-carbonitrile;
- 5-{(*E*)-2-[5-{[2-(dimethylamino)ethyl]amino}methyl]pyridin-2-yl}ethenyl}-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;
- 5-[(*E*)-2-(5-{[(2-ethoxyethyl)amino]methyl}pyridin-2-yl)ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;
- 5-[(*E*)-2-(5-{[(3-ethoxypropyl)amino]methyl}pyridin-2-yl)ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

5-[(*E*)-2-(5-[[2-methoxyethyl]amino]methyl)pyridin-2-yl)ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

4-[(1,4-dimethyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-phenylethenyl]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[6-(morpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[6-(thiomorpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile;

5-[(*E*)-2-[6-[(4-hydroxypiperidin-1-yl)methyl]pyridin-2-yl]ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

5-[(*E*)-2-(6-[[4-(2-hydroxyethyl)piperazin-1-yl]methyl]pyridin-2-yl)ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(6-[[2-morpholin-4-ylethyl]amino]methyl)pyridin-2-yl)ethenyl]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(6-[[3-morpholin-4-ylpropyl]amino]methyl)pyridin-2-yl)ethenyl]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(6-[(4-morpholin-4-ylpiperidin-1-yl)methyl]pyridin-2-yl)ethenyl]pyridine-3-carbonitrile;

5-[(*E*)-2-[6-(1,4'-bipiperidin-1'-ylmethyl)pyridin-2-yl]ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(6-[(4-pyrrolidin-1-ylpiperidin-1-yl)methyl]pyridin-2-yl)ethenyl]pyridine-3-carbonitrile;

5-[(*E*)-2-(6-[(4-cyclopentylpiperazin-1-yl)methyl]pyridin-2-yl)ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

5-[(*E*)-2-(4-[(4-methyl-1,4-diazepan-1-yl)methyl]phenyl)ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(4-[[2-pyridin-4-ylethyl]amino]methyl)phenyl]ethenyl]pyridine-3-carbonitrile;

5-[(*E*)-2-(6-[[4-(1-methylethyl)piperazin-1-yl]methyl]pyridin-2-yl)ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

5-[(*E*)-2-(6-[[4-(dimethylamino)piperidin-1-yl]methyl]pyridin-2-yl)ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

5-[(*E*)-2-(6-[(4-methyl-1,4-diazepan-1-yl)methyl]pyridin-2-yl)ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[6-[[3-(2-oxopyrrolidin-1-yl)propyl]amino}methyl]pyridin-2-yl]ethenyl]pyridine-3-carbonitrile;

5-[(*E*)-2-[6-[[2-(dimethylamino)ethyl]amino}methyl]pyridin-2-yl]ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

5-[(*E*)-2-[6-[[3-(dimethylamino)propyl]amino}methyl]pyridin-2-yl]ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

5-[(*E*)-2-(6-[[2-ethoxyethyl]amino]methyl)pyridin-2-yl]ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

5-[(*E*)-2-(6-[[2-methoxyethyl]amino]methyl)pyridin-2-yl]ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{5-[2-(4-methylpiperazin-1-yl)ethoxy]pyridin-3-yl}ethenyl]pyridine-3-carbonitrile;

5-[(*E*)-2-(4-{[4-(2-hydroxyethyl)piperazin-1-yl]methyl}phenyl)ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

5-[(*E*)-2-(3-formylphenyl)ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{5-[2-(4-methylpiperazin-1-yl)ethoxy]pyridin-3-yl}ethenyl]pyridine-3-carbonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{4-[(4-pyrrolidin-1-yl)piperidin-1-yl]methyl}phenyl]ethenyl]pyridine-3-carbonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[5-(2-pyrrolidin-1-ylethoxy)pyridin-3-yl]ethenyl]pyridine-3-carbonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(4-[[2-piperidin-1-ylethyl]amino]methyl)phenyl]ethenyl]pyridine-3-carbonitrile;

4-[(6-chloro-1*H*-indol-5-yl)amino]-5-[(*E*)-2-phenylethenyl]pyridine-3-carbonitrile;

5-[(*E*)-2-{6-[(dimethylamino)methyl]pyridin-2-yl}ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[6-[[2-(1-methylpyrrolidin-2-yl)ethyl]amino}methyl]pyridin-2-yl]ethenyl]pyridine-3-carbonitrile;

5-[(*E*)-2-{6-[[3-hydroxypyrrolidin-1-yl]methyl]pyridin-2-yl}ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

5-[(*E*)-2-(6-[[2-azepan-1-ylethyl]amino]methyl)pyridin-2-yl]ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(6-[(2-pyridin-2-ylethyl)amino]methyl)pyridin-2-yl)ethenyl]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(6-[(2-pyridin-3-ylethyl)amino]methyl)pyridin-2-yl)ethenyl]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(6-[(2-pyridin-4-ylethyl)amino]methyl)pyridin-2-yl)ethenyl]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[5-({[2-(1-methylpyrrolidin-2-yl)ethyl]amino}methyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile;

5-[(*E*)-2-{5-[(3-hydroxypyrrolidin-1-yl)methyl]pyridin-2-yl}ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

5-[(*E*)-2-(5-[(2-azepan-1-ylethyl)amino]methyl)pyridin-2-yl)ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(5-[(2-pyridin-2-ylethyl)amino]methyl)pyridin-2-yl)ethenyl]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(5-[(2-pyridin-4-ylethyl)amino]methyl)pyridin-2-yl)ethenyl]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[4-(pyrrolidin-1-ylsulfonyl)phenyl]ethenyl]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl]ethenyl]pyridine-3-carbonitrile;

5-[(*E*)-2-[4-({[2-(dimethylamino)ethyl]amino}methyl)phenyl]ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

5-[(*E*)-2-{5-[3-(dimethylamino)propoxy]pyridin-3-yl}ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[3-(piperidin-1-ylmethyl)phenyl]ethenyl]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[3-(pyrrolidin-1-ylmethyl)phenyl]ethenyl]pyridine-3-carbonitrile;

5-[(*E*)-2-(3-{[4-(2-hydroxyethyl)piperazin-1-yl]methyl}phenyl)ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[3-[(4-pyrrolidin-1-yl)piperidin-1-yl]methyl]phenyl]ethenyl]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{3-[(4-morpholin-4-yl)piperidin-1-yl)methyl]phenyl}ethenyl]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{3-(thiomorpholin-4-ylmethyl)phenyl}ethenyl]pyridine-3-carbonitrile;

5-[(*E*)-2-{3-[(4-cyclopentylpiperazin-1-yl)methyl]phenyl}ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(4-{[(2-pyrrolidin-1-ylethyl)amino]methyl}phenyl)ethenyl]pyridine-3-carbonitrile;

5-[(*E*)-2-(3-formylphenyl)ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

5-[(*E*)-2-[5-(hydroxymethyl)pyridin-2-yl]ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

5-[(*E*)-2-[6-(hydroxymethyl)pyridin-2-yl]ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[6-(piperidin-1-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[6-(pyrrolidin-1-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[6-(morpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[6-(thiomorpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile;

5-[(*E*)-2-{6-[(4-hydroxypiperidin-1-yl)methyl]pyridin-2-yl}ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

5-[(*E*)-2-(6-{[4-(2-hydroxyethyl)piperazin-1-yl]methyl}pyridin-2-yl)ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(6-{[(2-morpholin-4-ylethyl)amino]methyl}pyridin-2-yl)ethenyl]pyridine-3-carbonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(6-{[(3-morpholin-4-ylpropyl)amino]methyl}pyridin-2-yl)ethenyl]pyridine-3-carbonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{6-[(4-morpholin-4-yl)piperidin-1-yl)methyl]pyridin-2-yl}ethenyl]pyridine-3-carbonitrile;

5-[(*E*)-2-[6-(1,4'-bipiperidin-1'-ylmethyl)pyridin-2-yl]ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[6-[(4-pyrrolidin-1-yl)piperidin-1-yl)methyl]pyridin-2-yl]ethenyl]pyridine-3-carbonitrile;

5-[(*E*)-2-[6-[(4-cyclopentylpiperazin-1-yl)methyl]pyridin-2-yl]ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

4-[(1-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-phenylethenyl]pyridine-3-carbonitrile;

6-methyl-5-[(*E*)-2-(6-{[4-(1-methylethyl)piperazin-1-yl)methyl]pyridin-2-yl}ethenyl)-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

6-methyl-5-[(*E*)-2-[6-[(4-methyl-1,4-diazepan-1-yl)methyl]pyridin-2-yl]ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

5-[(*E*)-2-[6-({[3-(dimethylamino)propyl]amino}methyl)pyridin-2-yl]ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

5-[(*E*)-2-(6-({[(2-ethoxyethyl)amino]methyl}pyridin-2-yl)ethenyl)-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

5-[(*E*)-2-(6-({[(3-ethoxypropyl)amino]methyl}pyridin-2-yl)ethenyl)-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

5-[(*E*)-2-[6-[(dimethylamino)methyl]pyridin-2-yl]ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[6-({[2-(1-methylpyrrolidin-2-yl)ethyl]amino}methyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile;

5-[(*E*)-2-[6-[(3-hydroxypyrrolidin-1-yl)methyl]pyridin-2-yl]ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

5-[(*E*)-2-(6-({[(2-azepan-1-ylethyl)amino]methyl}pyridin-2-yl)ethenyl)-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(6-({[(2-pyridin-2-ylethyl)amino]methyl}pyridin-2-yl)ethenyl]pyridine-3-carbonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(6-({[(2-pyridin-3-ylethyl)amino]methyl}pyridin-2-yl)ethenyl]pyridine-3-carbonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(6-({[(2-pyridin-4-ylethyl)amino]methyl}pyridin-2-yl)ethenyl]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[4-({[3-(4-methylpiperazin-1-yl)propyl]amino}methyl)phenyl]ethenyl]pyridine-3-carbonitrile;

5- $\{ (E) \}$ -2-[5-(2-azepan-1-ylethoxy)pyridin-3-yl]ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino] pyridine-3-carbonitrile

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5- $\{ (E) \}$ -2-[4- $\{ [3-(4\text{-methylpiperazin-1-yl})\text{propyl}] \}$ amino)methyl]phenyl]ethenyl]pyridine-3-carbonitrile;

5- $\{ (E) \}$ -2-[4- $\{ [2-(\text{dimethylamino})\text{ethyl}] \}$ amino)methyl]phenyl]ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5- $\{ (E) \}$ -2-[4- $\{ [2-(\text{piperidin-1-ylethyl})\text{amino}] \}$ methyl]phenyl]ethenyl]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5- $\{ (E) \}$ -2-[5-(3-piperidin-1-ylpropoxy)pyridin-3-yl]ethenyl]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5- $\{ (E) \}$ -2-[5- $\{ 2-[1-(\text{methylpiperidin-4-yl})\text{amino}] \}$ ethoxy] pyridin-3-yl]ethenyl]pyridine-3-carbonitrile;

5- $\{ (E) \}$ -2-[5-(2- $\{ [1-(1\text{-methylethyl})\text{piperidin-4-yl}] \}$ amino)ethoxy)pyridin-3-yl]ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5- $\{ (E) \}$ -2-[5- $\{ 2-[1-(\text{propylpiperidin-4-yl})\text{amino}] \}$ ethoxy] pyridin-3-yl]ethenyl]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5- $\{ (E) \}$ -2-[5-(2- $\{ [1-(2\text{-methylpropyl})\text{piperidin-4-yl}] \}$ amino)ethoxy)pyridin-3-yl]ethenyl]pyridine-3-carbonitrile;

5- $\{ (E) \}$ -2-[3- $\{ [4-(\text{hydroxypiperidin-1-yl})\text{methyl}] \}$ phenyl]ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5- $\{ (E) \}$ -2-[3- $\{ [4-(\text{methylpiperazin-1-yl})\text{sulfonyl}] \}$ methyl] phenyl]ethenyl]pyridine-3-carbonitrile;

5- $\{ (E) \}$ -2-[4- $\{ [3-(\text{hydroxypyrrolidin-1-yl})\text{methyl}] \}$ phenyl]ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

5- $\{ (E) \}$ -2-[4- $\{ [3-(\text{dimethylamino})\text{propyl}] \}$ amino)methyl]phenyl]ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

5- $\{ (E) \}$ -2-[4- $\{ [1-(\text{ethylpyrrolidin-2-yl})\text{methyl}] \}$ amino)methyl]phenyl]ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

5- $\{ (E) \}$ -2-[4- $\{ [3-(\text{ethoxypropyl})\text{amino}] \}$ methyl]phenyl]ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5- $\{ (E) \}$ -2-[3- $\{ [(\text{pyrrolidin-1-yl})\text{sulfonyl}] \}$ methyl] phenyl]ethenyl]pyridine-3-carbonitrile;

- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(4-[(4-methylpiperazin-1-yl)sulfonyl]methyl) phenyl]ethenyl]pyridine-3-carbonitrile;
- 5-[(*E*)-2-(5-{2-[(1-ethylpiperidin-3-yl)amino]ethoxy}pyridin-3-yl)ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;
- 6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[5-(piperidin-1-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile;
- 6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[5-(pyrrolidin-1-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile;
- 6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[5-(morpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile;
- 6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[5-(thiomorpholin-4-ylmethyl)pyridin-2-yl]ethenyl]pyridine-3-carbonitrile;
- 5-[(*E*)-2-{5-[(4-hydroxypiperidin-1-yl)methyl]pyridin-2-yl}ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;
- 6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(5-{[(2-morpholin-4-ylethyl)amino]methyl}pyridin-2-yl)ethenyl]pyridine-3-carbonitrile;
- 6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(5-{[(3-morpholin-4-ylpropyl)amino]methyl}pyridin-2-yl)ethenyl]pyridine-3-carbonitrile;
- 6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{5-[(4-morpholin-4-ylpiperidin-1-yl)methyl]pyridin-2-yl}ethenyl]pyridine-3-carbonitrile;
- 5-[(*E*)-2-[5-(1,4'-bipiperidin-1'-ylmethyl)pyridin-2-yl]ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;
- 6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{5-[(4-pyrrolidin-1-ylpiperidin-1-yl)methyl]pyridin-2-yl}ethenyl]pyridine-3-carbonitrile;
- 5-[(*E*)-2-{5-[(4-cyclopentylpiperazin-1-yl)methyl]pyridin-2-yl}ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;
- 5-[(*E*)-2-[3-(1,4'-bipiperidin-1'-ylsulfonyl)phenyl]vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;
- 6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-(2-{2-methyl-4-[(4-methylpiperazin-1-yl)methyl]phenyl}ethyl)nicotinonitrile;
- 1'-(*N,N*-dimethylglycyl)-4-[(4-methyl-1*H*-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile;

4-[(*E*)-2-{5-cyano-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl}vinyl]-*N*-isobutyl benzenesulfonamide;

5-[(*E*)-2-(5-{2-[(2,2-dimethylpropyl)amino]ethoxy}pyridin-3-yl)vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

5-[(*E*)-2-(5-{2-[bis(3,3-dimethylbutyl)amino]ethoxy}pyridin-3-yl)vinyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

5-[(*E*)-2-(5-{[4-(2-hydroxyethyl)piperazin-1-yl]methyl}pyridin-2-yl)vinyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

5-[(*E*)-2-(5-{[4-(2-hydroxyethyl)piperazin-1-yl]methyl}pyridin-2-yl)vinyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

5-[(*E*)-2-(5-{[(2-ethoxyethyl)amino]methyl}pyridin-2-yl)vinyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

5-[(*E*)-2-(5-{[(3-ethoxypropyl)amino]methyl}pyridin-2-yl)vinyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

5-[(*E*)-2-(5-{[(dimethylamino)methyl]pyridin-2-yl}vinyl)-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

5-[(*E*)-2-(5-{[(3-hydroxypyrrolidin-1-yl)methyl]pyridin-2-yl}vinyl)-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(5-{[(2-pyridin-3-ylethyl)amino]methyl}pyridin-2-yl)vinyl]nicotinonitrile;

5-[2-(6-{[4-(2-hydroxyethyl)piperazin-1-yl]methyl}pyridin-2-yl)ethyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-(2-{6-[(4-pyrrolidin-1-yl)piperidin-1-yl]methyl}pyridin-2-yl)ethyl]nicotinonitrile;

tert-butyl 5-cyano-2-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-3',6'-dihydro-3,4'-bipyridine-1'(2'*H*)-carboxylate;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(4-{[(2-morpholin-4-ylethyl)amino]methyl}phenyl)vinyl]nicotinonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(4-{[(2-pyrrolidin-1-ylethyl)amino]methyl}phenyl)vinyl]nicotinonitrile;

N-carbamimidoyl-4-[(*E*)-2-{5-cyano-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl}vinyl]benzenesulfonamide;

4-[(*E*)-2-{5-cyano-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl}vinyl]benzenesulfonamide;

2-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile;

1'-benzyl-2-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile;

2-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-1'-[(1-methylpiperidin-4-yl)methyl]-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile;

2-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-1'-(methylsulfonyl)-1',2',3',6'-tetrahydro-3,4'-bipyridine-5-carbonitrile;

5-{2-[6-(1,4'-bipiperidin-1'-ylmethyl)pyridin-2-yl]ethyl}-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

5-[2-(6-{[4-(dimethylamino)piperidin-1-yl]methyl}pyridin-2-yl)ethyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

5-{2-[6-(hydroxymethyl)pyridin-2-yl]ethyl}-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

3-[(*E*)-2-{5-cyano-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl}vinyl]benzenesulfonamide;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{4-[(pyrrolidin-1-ylsulfonyl)methyl]phenyl}vinyl]nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-{(*E*)-2-[3-(pyrrolidin-1-ylsulfonyl)phenyl] vinyl} nicotinonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{3-[(4-methylpiperazin-1-yl)sulfonyl]phenyl} vinyl]nicotinonitrile;

2-({6-[(*E*)-2-{5-cyano-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl}vinyl]pyridin-2-yl}methoxy)ethyl sulfate;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-{(*E*)-2-[4-(2*H*-tetrazol-5-yl)phenyl]vinyl}nicotinonitrile;

5-{(*E*)-2-[3-(1,4'-bipiperidin-1'-ylmethyl)phenyl]vinyl}-4-[(4-methyl-1*H*-indol-5-yl)amino]nicotinonitrile;

5-[(*E*)-2-(4-{[4-(dimethylamino)piperidin-1-yl]methyl}phenyl)ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-{(*E*)-2-[3-(morpholin-4-ylmethyl)phenyl] ethenyl}pyridine-3-carbonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-{3-[(4-methylpiperazin-1-yl)methyl] phenyl} ethenyl]pyridine-3-carbonitrile;

5-[(*E*)-2-{3-[(4-hydroxypiperidin-1-yl)methyl]phenyl}ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

- 4-(1*H*-indol-5-ylamino)-5-[(*E*)-2-pyridin-2-ylethenyl]pyridine-3-carbonitrile;
- 6-methyl-5-[(*E*)-2-(3-{[4-(1-methylethyl)piperazin-1-yl]methyl}phenyl)ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;
- 6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[3-(pyrrolidin-1-ylmethyl)phenyl] ethenyl] pyridine-3-carbonitrile;
- 6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[3-(thiomorpholin-4-ylmethyl)phenyl] ethenyl] pyridine-3-carbonitrile;
- 6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[4-(pyrrolidin-1-ylsulfonyl)phenyl] ethenyl]pyridine-3-carbonitrile;
- 6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[4-[(4-methylpiperazin-1-yl)sulfonyl] phenyl] ethenyl]pyridine-3-carbonitrile;
- 6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[3-[(4-methylpiperazin-1-yl)sulfonyl] phenyl] ethenyl]pyridine-3-carbonitrile;
- 6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[3-(piperidin-1-ylsulfonyl)phenyl] ethenyl] pyridine-3-carbonitrile;
- 6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[3-(pyrrolidin-1-ylsulfonyl)phenyl] ethenyl] pyridine-3-carbonitrile;
- 5-[(*E*)-2-[2-(hydroxymethyl)-1,3-thiazol-4-yl]ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino] pyridine-3-carbonitrile;
- 5-[(*E*)-2-(4-{[(1*H*-indol-3-ylmethyl)(methyl)amino]methyl}phenyl)ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;
- 5-[(*E*)-2-[3-[(diethylamino)methyl]phenyl]ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino] pyridine-3-carbonitrile;
- 5-[(*E*)-2-(4-{[(2-methoxyethyl)amino]methyl}phenyl)ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino] pyridine-3-carbonitrile;
- 5-[(*E*)-2-(4-{[(2-ethoxyethyl)amino]methyl}phenyl)ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino] pyridine-3-carbonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[4-{{[2-(1-methylpyrrolidin-2-yl)ethyl]amino} methyl} phenyl]ethenyl]pyridine-3-carbonitrile;
- 5-[(*E*)-2-(4-{[(2-azepan-1-ylethyl)amino]methyl}phenyl)ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino] pyridine-3-carbonitrile;
- 6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-(2-[4-[(4-methylpiperazin-1-yl)methyl] phenyl]ethyl) pyridine-3-carbonitrile;

- 6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[2-(4-methylphenyl)ethyl]pyridine-3-carbonitrile;
- 4-[(*E*)-2-{5-cyano-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl}ethenyl]-*N,N*-dimethyl benzenesulfonamide;
- 4-[(*E*)-2-{5-cyano-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl}ethenyl]-*N,N*-diethyl benzenesulfonamide;
- 4-[(*E*)-2-{5-cyano-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl}ethenyl]-*N,N*-dipropyl benzenesulfonamide;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-{(*E*)-2-[4-(piperidin-1-ylsulfonyl)phenyl] ethenyl}pyridine-3-carbonitrile;
- 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-{(*E*)-2-[3-(piperidin-1-ylsulfonyl)phenyl] ethenyl}pyridine-3-carbonitrile;
- 5-[(*E*)-2-{5-[(diethylamino)methyl]pyridin-2-yl}ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;
- 5-[(*E*)-2-(6-{[4-(dimethylamino)piperidin-1-yl]methyl}pyridin-2-yl)ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;
- 5-[(*E*)-2-(6-{[(diethylamino)methyl]pyridin-2-yl}ethenyl)-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;
- 5-[(*E*)-2-(6-{[(diethylamino)methyl]pyridin-2-yl}ethenyl)-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;
- 4-[(*E*)-2-{5-cyano-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl}ethenyl]-*N,N*-bis(1-methyl-ethyl)benzenesulfonamide;
- 5-[(*E*)-2-(3-{[(2-azepan-1-ylethyl)amino]methyl}phenyl)ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;
- 5-[(*E*)-2-(3-{[(3-ethoxypropyl)amino]methyl}phenyl)ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;
- 5-[(*E*)-2-(3-{[(2-ethoxyethyl)amino]methyl}phenyl)ethenyl]-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;
- 5-[(*E*)-2-(3-{[(dimethylamino)methyl]phenyl}ethenyl)-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;
- 6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(4-{[(4-methylpiperazin-1-yl) sulfonyl]methyl}phenyl)ethenyl]pyridine-3-carbonitrile;
- 6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(3-{[(4-methylpiperazin-1-yl)sulfonyl]methyl}phenyl)ethenyl]pyridine-3-carbonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[4-(piperidin-1-ylsulfonyl)phenyl] ethenyl] pyridine-3-carbonitrile;

4-[(*E*)-2-{5-cyano-2-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl}ethenyl]-*N,N*-dimethyl benzenesulfonamide;

4-[(*E*)-2-{5-cyano-2-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridin-3-yl}ethenyl]-*N,N*-diethyl benzenesulfonamide;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(4-{[4-(methylsulfonyl)piperazin-1-yl]methyl} phenyl) ethenyl]pyridine-3-carbonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[3-({[3-(4-methylpiperazin-1-yl)propyl] amino} methyl)phenyl]ethenyl]pyridine-3-carbonitrile;

5-[(*E*)-2-(4-{[(2-azepan-1-ylethyl)amino]methyl}phenyl)ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

5-[(*E*)-2-(3-({[3-ethoxypropyl]amino]methyl}phenyl)ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[4-({[2-(2-methylpyrrolidin-1-yl)ethyl] amino} methyl)phenyl]ethenyl]pyridine-3-carbonitrile;

4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[2-(pyrrolidin-1-ylmethyl)-1,3-thiazol-4-yl] ethenyl]pyridine-3-carbonitrile;

6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-(4-{[(2-pyridin-3-ylethyl)amino]methyl} phenyl)ethenyl]pyridine-3-carbonitrile;

6-ethyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[4-[(4-methylpiperazin-1-yl)methyl] phenyl]ethenyl]pyridine-3-carbonitrile;

6-ethyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[3-[(4-methylpiperazin-1-yl)methyl] phenyl] ethenyl]pyridine-3-carbonitrile;

6-ethyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[4-[(4-methylpiperazin-1-yl)methyl] phenyl] ethyl]pyridine-3-carbonitrile;

6-ethyl-4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-[3-[(4-methylpiperazin-1-yl)methyl] phenyl] ethyl]pyridine-3-carbonitrile;

5-[(*E*)-2-[4-[(dimethylamino)methyl]phenyl]ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino] pyridine-3-carbonitrile;

5-[(*E*)-2-(4-{[4-(dimethylamino)piperidin-1-yl]methyl}phenyl)ethenyl]-6-methyl-4-[(4-methyl-1*H*-indol-5-yl)amino]pyridine-3-carbonitrile;

5-[(E)-2-(5-{[4-(dimethylamino)piperidin-1-yl]methyl}pyridin-2-yl)ethenyl]-6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]pyridine-3-carbonitrile;

4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{5-[(4-methylpiperazin-1-yl)methyl]-3-thienyl}vinyl]nicotinonitrile;

4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{5-[(4-methylpiperazin-1-yl)methyl]-2-thienyl}vinyl]nicotinonitrile;

4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{5-[(4-methylpiperazin-1-yl)methyl]-2-furyl}vinyl]nicotinonitrile;

6-methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{2-[(4-methylpiperazin-1-yl)methyl]-1,3-thiazol-4-yl}vinyl]nicotinonitrile;

4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{2-[(1,4'-bipiperidin-1'-yl)methyl]-1,3-thiazol-4-yl}vinyl]nicotinonitrile;

4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{2-[(4-pyrrolidin-1-yl)piperidin-1-yl)methyl]-1,3-thiazol-4-yl}vinyl]nicotinonitrile;

4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{2-[(4-(dimethylamino)piperidin-1-yl)methyl]-1,3-thiazol-4-yl}vinyl]nicotinonitrile;

4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-{2-[(4-(dimethylamino)methyl]-1,3-thiazol-4-yl}vinyl]nicotinonitrile;

6-Methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4-{[pyrrolidin-1-ylsulfonyl]methyl}phenyl)ethenyl]pyridine-3-carbonitrile;

6-Methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(3-{[pyrrolidin-1-ylsulfonyl]methyl}phenyl)ethenyl]pyridine-3-carbonitrile;

4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4-{[piperidin-1-ylsulfonyl]methyl}phenyl)ethenyl]pyridine-3-carbonitrile;

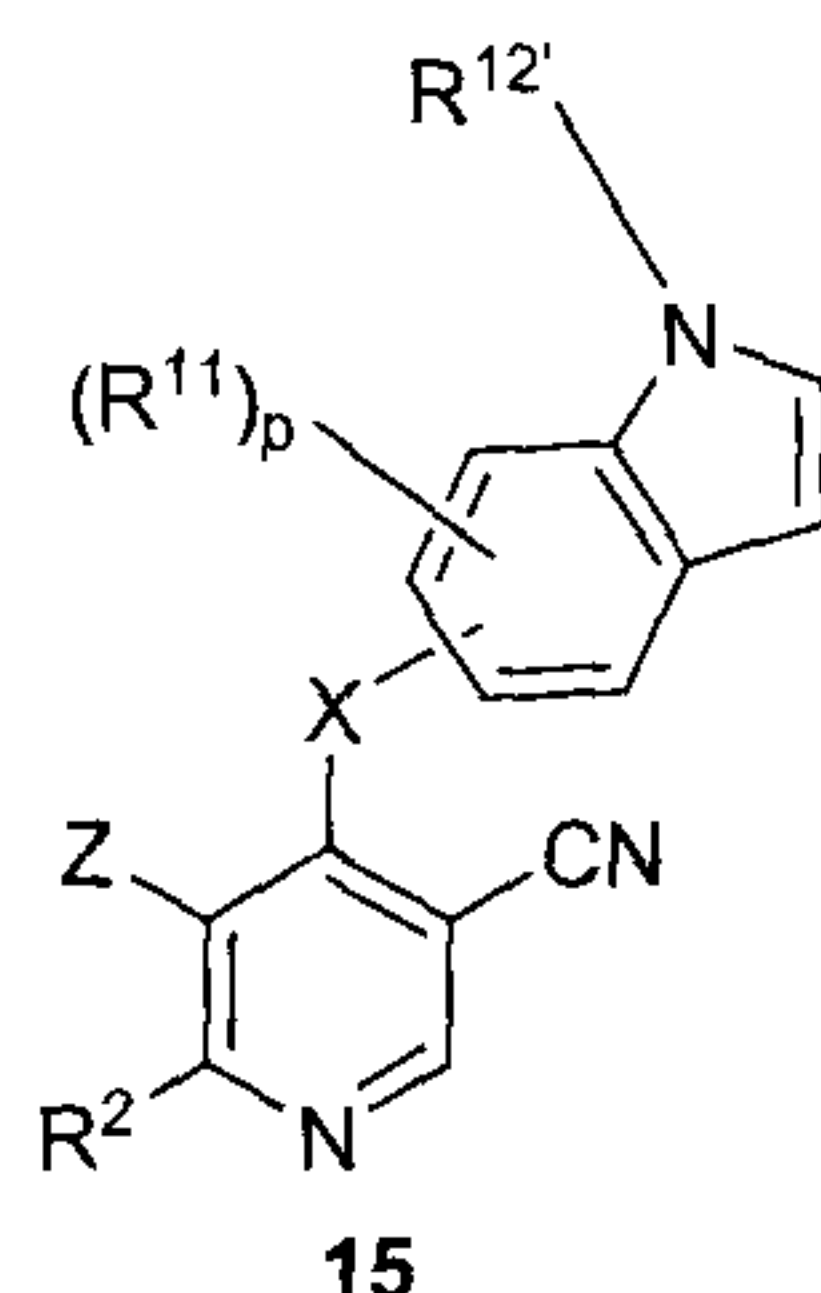
4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(3-{[piperidin-1-ylsulfonyl]methyl}phenyl)ethenyl]pyridine-3-carbonitrile;

6-Methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(4-{[piperidin-1-ylsulfonyl]methyl}phenyl)ethenyl]pyridine-3-carbonitrile; or

6-Methyl-4-[(4-methyl-1H-indol-5-yl)amino]-5-[(E)-2-(3-{[piperidin-1-ylsulfonyl]methyl}phenyl)ethenyl]pyridine-3-carbonitrile.

26. A compound of any of claims 1-25 or a pharmaceutically acceptable salt thereof for use in the reduction of an increased activity of protein kinase enzyme in a mammal.

27. A composition comprising a compound of any of claims 1-25, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.
28. A use of an effective amount of the compound of any of claims 1-25, or a pharmaceutically acceptable salt thereof in the reduction of an increased activity of an enzyme in a mammal, wherein the enzyme is a protein kinase.
29. A use of an effective amount of the compound of any of claims 1-25, or a pharmaceutically acceptable salt thereof in the treatment of inflammation, asthma, colitis, multiple sclerosis, psoriasis, rheumatoid arthritis, inflammatory bowel disease, joint inflammation, organ transplant and graft rejection, in a mammal.
30. A process for preparing a compound of formula I, wherein J is J(ii) or J(iii) as defined in claim 1, the process comprising reacting a compound of formula **15**

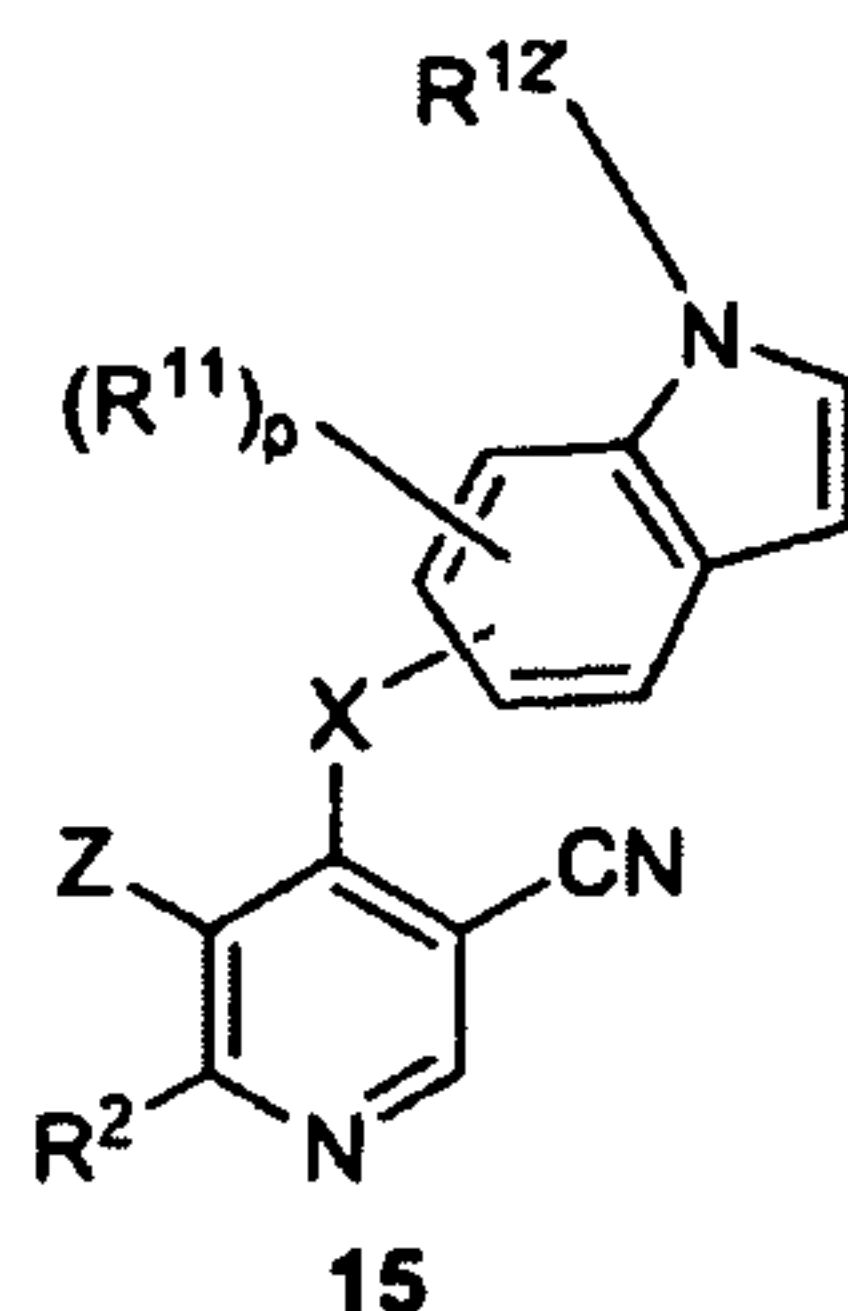


wherein R^2 , R^{11} , $R^{12'}$ and p are as defined in claim 1 and Z is I or Br;

in the presence of a Pd catalyst;

with a compound of formula R^1 -J-B(OR)₂, wherein J and R^1 are as defined in claim 1, and each R is, independently at each occurrence, H or C₁-C₆ alkyl; or two R groups together in -B(OR)₂, with R comprising C₁-C₆ alkylene, form a ring comprising boron, oxygen and carbon atoms.

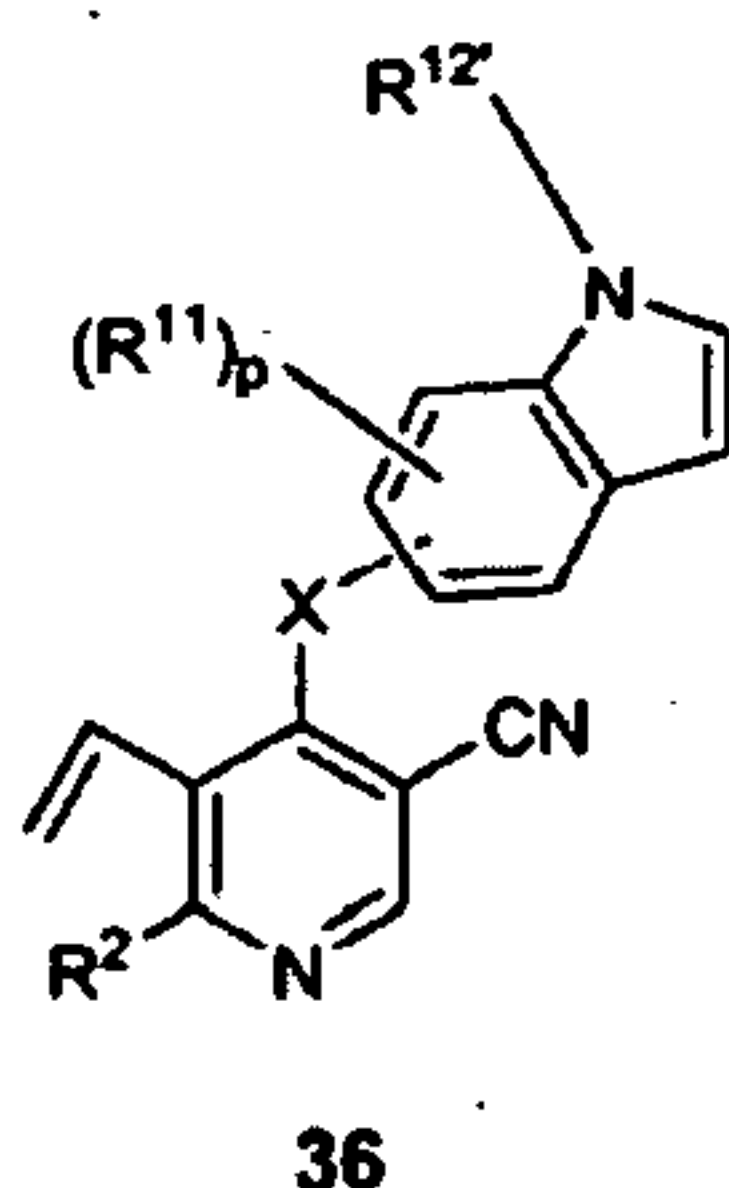
31. A process for preparing a compound of formula I, wherein J is J(iii) as defined in claim 1, the process comprising reacting a compound of formula 15



wherein R^2 , R^{11} , R^{12} and p are as defined in claim 1 and Z is I or Br;
in the presence of a Pd catalyst;

with a compound of formula $R^1-(A^1)_q(Q)_m$, wherein q is 1; m is 0 and R^1 is as defined in claim 1.

32. A process for preparing a compound of formula I, wherein J is J(iii) as defined in claim 1, comprising reacting a compound of formula 36

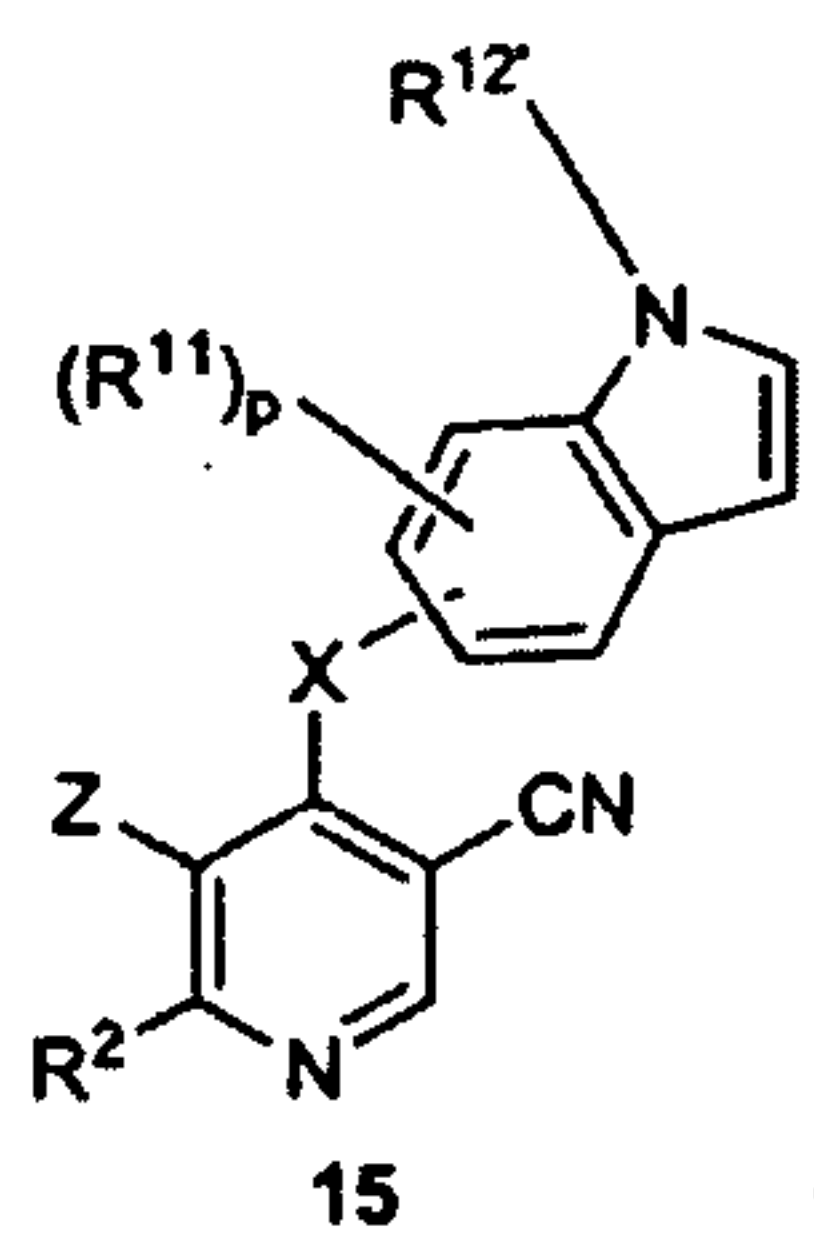


wherein R^2 , R^{11} , R^{12} and p are as defined in claim 1;

in the presence of a palladium catalyst;

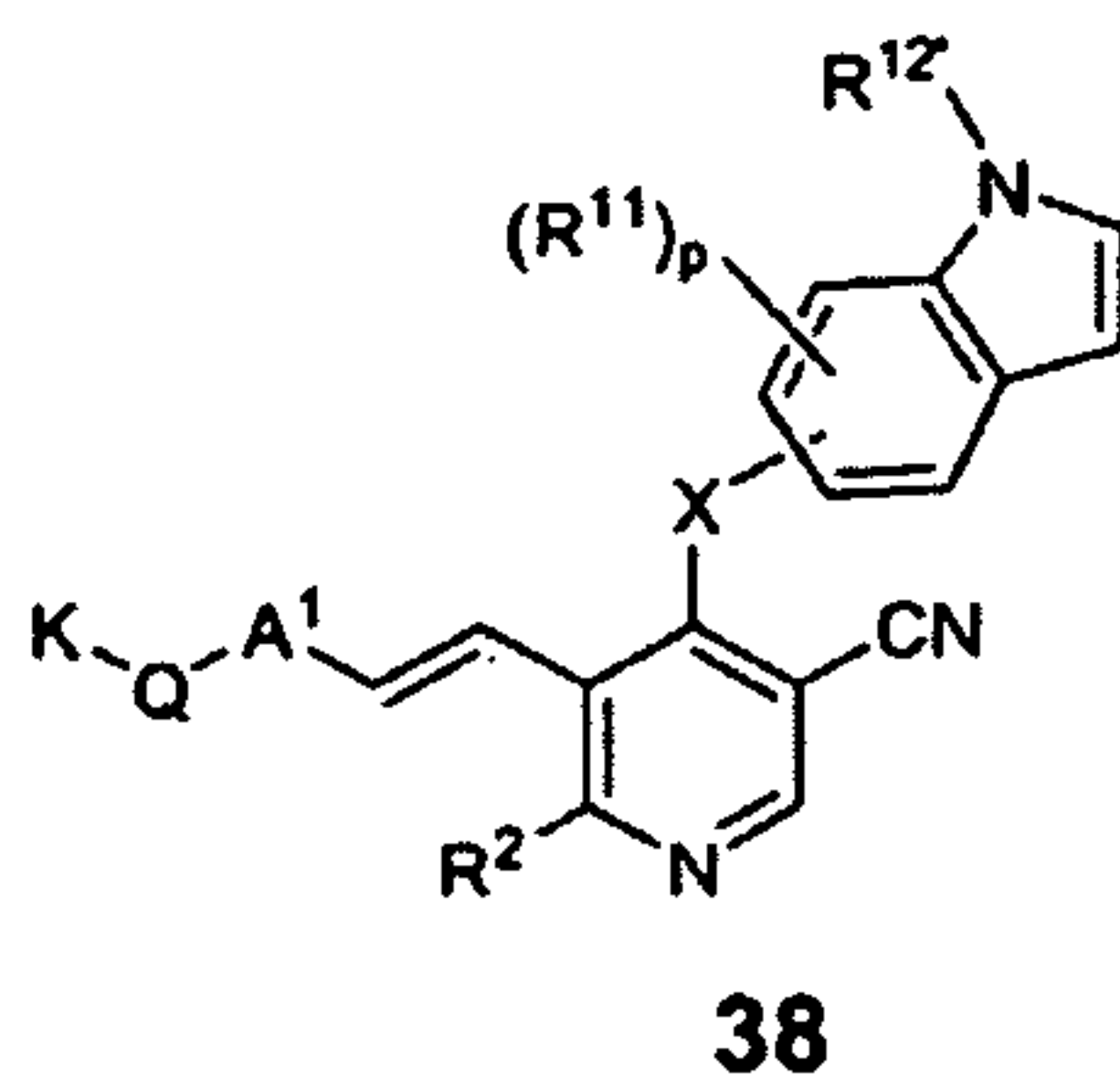
with a compound of formula R^1-A^1-Br or R^1-A^1-I , wherein R^1 and A^1 are as defined in claim 1.

33. The process of claim 32, wherein the compound of formula 36 is produced by a process comprising reacting a compound of formula 15



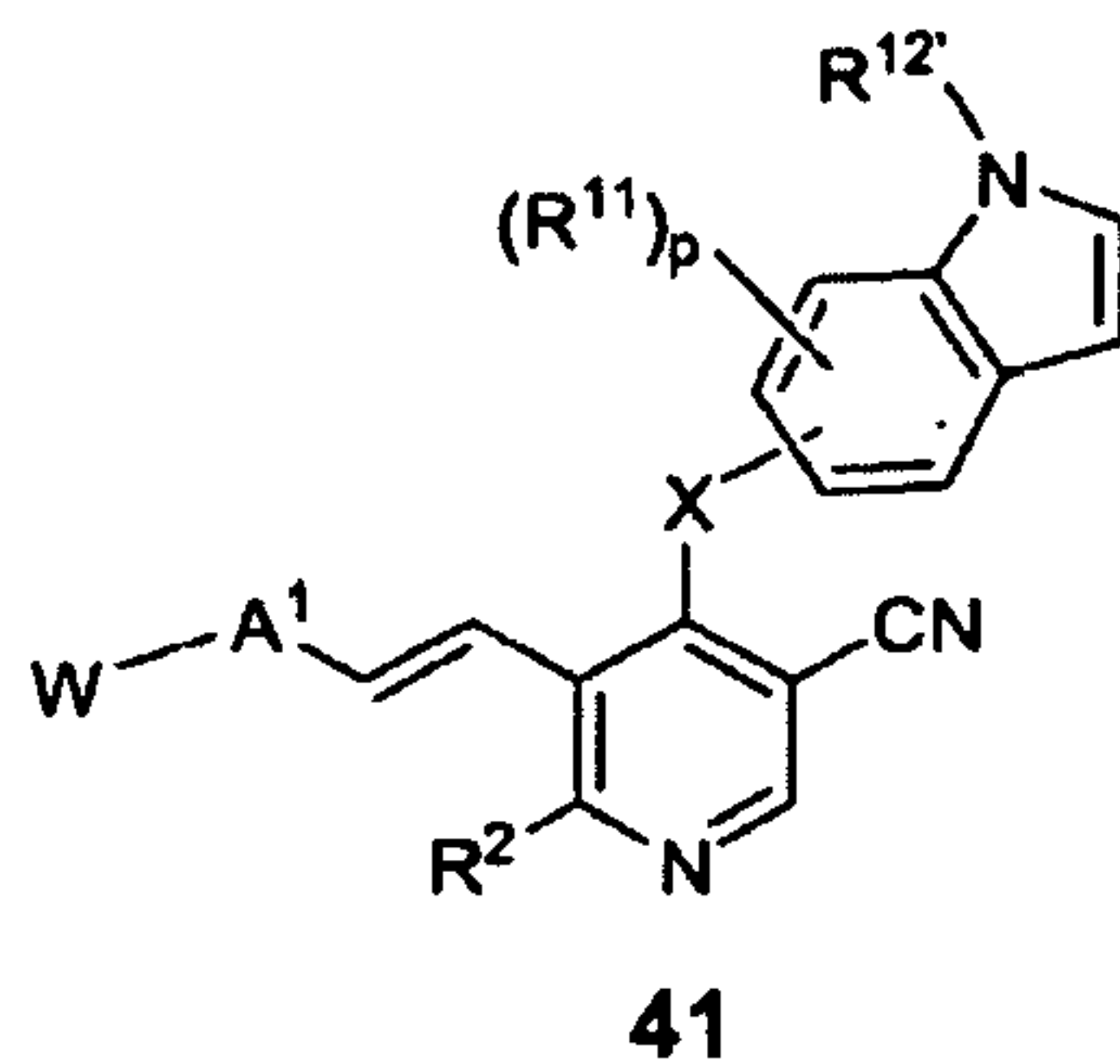
in the presence of a palladium catalyst,
with a vinyl reagent.

34. A process for preparing a compound of formula I wherein J is J(iii) as defined in claim 1, the process comprising first reacting a compound of formula 38



wherein K is OH; Q is methylene;
and A¹, R¹¹, R¹², p, X and R² are as defined in claim 1;
with an alcohol-activating agent to form an electrophile, followed by reacting the
electrophile with an amine R¹³R¹³NH, wherein R¹³ is as defined in claim 1, and
wherein the alcohol activating agent comprises a base and an alkyl or aryl sulfonyl
chloride.

35. A process for preparing a compound of formula I wherein J is J(iii) as defined in claim 1, the process comprising reacting a compound of formula 41



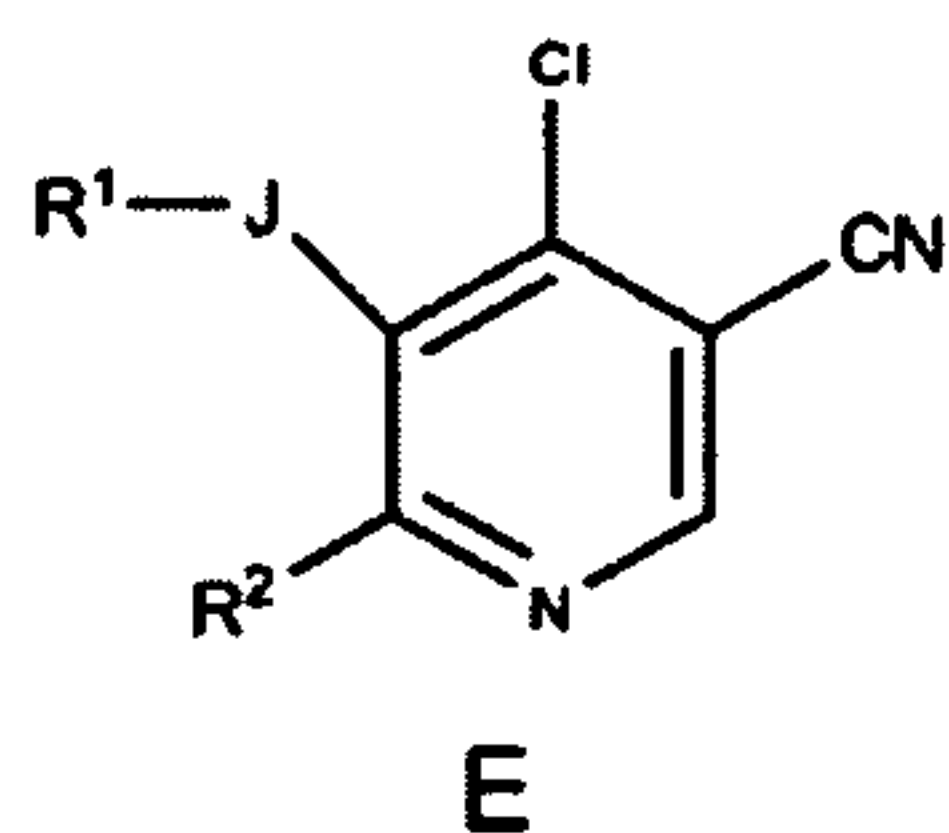
wherein W is CHO,

and A¹, R¹¹, R^{12'}, p, X and R² are as defined in claim 1;

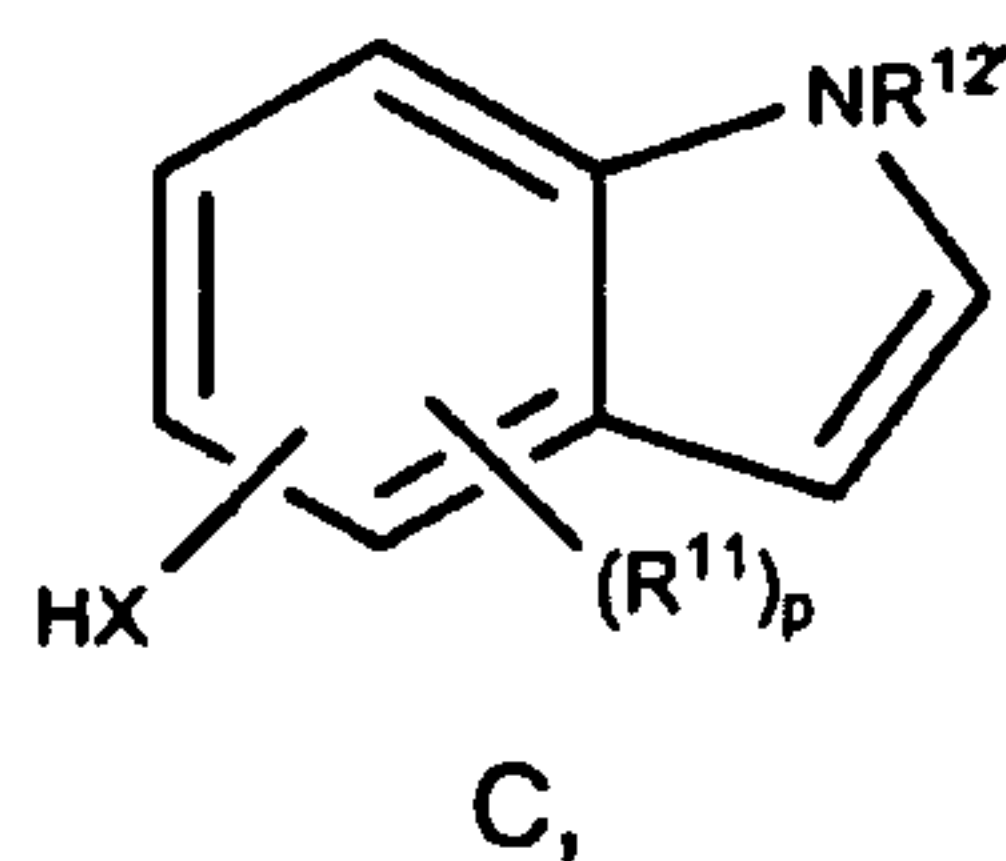
with an amine R¹³R¹³NH wherein R¹³ is as defined in claim 1;

in the presence of a reducing agent.

36. A process for making a compound according to any of claims 1-25 comprising reacting a compound of formula E



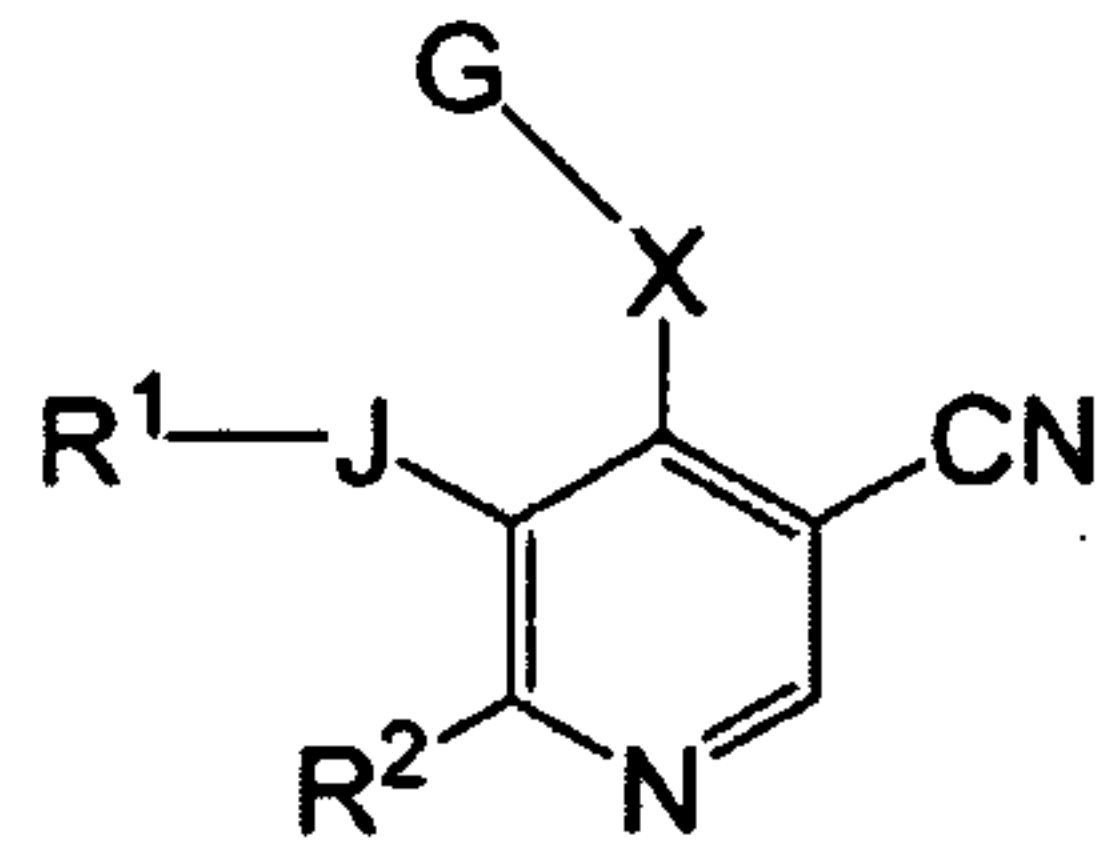
with a compound of formula C



wherein R¹, J, R², X, R¹¹, R^{12'} and p are as defined in claim 1.

37. A use of an effective amount of the compound of any of claims 1-25, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the reduction of an increased activity of an enzyme in a mammal, wherein the enzyme is a protein kinase.

38. A use of an effective amount of the compound of any of claims 1-25, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of inflammation, asthma, colitis, multiple sclerosis, psoriasis, rheumatoid arthritis, inflammatory bowel disease, joint inflammation, organ transplant and graft rejection, in a mammal.



(I)

