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(54) Titre : ALCOOLS D'ALCYNYLE UTILISES COMME INHIBITEURS DE KINASES
(54) Title: ALKYNYL ALCOHOLS AS KINASE INHIBITORS

(57) **Abrégé/Abstract:**

Selected compounds are effective for prophylaxis and treatment of inflammation and inflammatory disorders, such as NIK-mediated disorders. The invention encompasses novel compounds, analogs, prodrugs and pharmaceutically acceptable salts thereof, pharmaceutical compositions and methods for prophylaxis and treatment of diseases and other maladies or conditions involving, inflammation and the like.



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(54) **Title:** ALKYNYL ALCOHOLS AS KINASE INHIBITORS

(57) **Abstract:** Selected compounds are effective for prophylaxis and treatment of inflammation and inflammatory disorders, such as NIK-mediated disorders. The invention encompasses novel compounds, analogs, prodrugs and pharmaceutically acceptable salts thereof, pharmaceutical compositions and methods for prophylaxis and treatment of diseases and other maladies or conditions involving, inflammation and the like.



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DEMANDES OU BREVETS VOLUMINEUX

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CECI EST LE TOME __1__ DE __2__

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JUMBO APPLICATIONS / PATENTS

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

THIS IS VOLUME __1__ OF __2__

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

ALKYNYL ALCOHOLS AS KINASE INHIBITORS**FIELD OF THE INVENTION**

This invention is in the field of pharmaceutical agents and specifically relates to compounds, compositions, uses and methods for treating inflammation and inflammatory disorders.

BACKGROUND OF THE INVENTION

NIK is a member of the mitogen-activated protein kinase kinase kinase (MAP3K) family. It was originally identified as a serine/threonine protein kinase that interacts with TNF-receptor associated factor 2 (TRAF2) and stimulates the activation of the “classical” NF- κ B pathway (Malinin, N.L., *et al.*, (1997) *Nature* 385:540-4). NF- κ B is a group of conserved eukaryotic transcription factors that regulate the expression of genes critical for both innate and adaptive immune responses (Hayden, M.S., and Ghosh, S. (2008) *Cell* 132, 344-362). The most prevalent or “classical” form of NF- κ B is a heterodimer of p50 (also known as NF- κ B1) and p65 (RelA), which normally retains in the cytoplasm as an inactive complex with the inhibitory proteins termed I κ B. A wide variety of extracellular stimuli including the pro-inflammatory cytokine TNF can activate NF- κ B by rapidly inducing the degradation of I κ B (Chen, G., and D.V. Goeddel (2002) *Science* 296:1634-5). This allows NF- κ B to translocate into the nucleus, where it activates the transcription of downstream genes. The degradation of I κ B is dependent on the I κ B-kinase (IKK) complex that phosphorylates I κ B and tags it for proteasome-mediated degradation shortly after stimulation.

NIK has been suggested as an upstream kinase of IKK in the NF- κ B pathway, as it binds and stimulates the enzyme activity of the IKK complex (see Regnier, C.H., *et al.* (1997) *Cell* 90:373-83; Woronicz, J.D., *et al.* (1997) *Science* 278:866-9; and Ling, L., Z. Cao, and D.V. Goeddel. (1998) *Proc Natl Acad Sci USA* 95:3792-7). However, gene-targeting experiments have clearly demonstrated that both IKK and NF- κ B activation by various signals including TNF are normal in NIK-deficient cells (Yin, L., *et al.* (2001) *Science* 291:2162-5). To date, considerable evidence has accrued indicating that NIK is dispensable for the activation of the “classical” NF- κ B pathway. Instead, it is indispensable for the activation of a second major form of NF- κ B, consisting of a heterodimer of p52 (NF- κ B2) and RelB (see Hayden, M.S., and Ghosh, S. (2008) *Cell* 132, 344-362; Pomerantz, J.L., and D. Baltimore. (2002) *Mol Cell* 10:693-5; and Dixit, V., and T.W. Mak. (2002) *Cell* 111:615-9). In most types of cells, only a small amount of p52 is present relative to its precursor p100. Like I κ B, unprocessed p100 can function as a cytoplasmic inhibitor for NF- κ B (Hayden, M.S., and

Ghosh, S. (2008) *Cell* 132, 344-362). Overexpression of NIK promotes the processing of NF- κ B2 precursor p100 to its active form p52 (Xiao, G., *et al.* (2001) *Mol Cell* 7:401-9), which together with RelB binds DNA and activates the transcription of targeted genes. Moreover, p100 processing or NF- κ B2 activation is defective in the absence of functional NIK (see Pomerantz, J.L., and D. Baltimore. (2002) *Mol Cell* 10:693-5; and Dixit, V., and T.W. Mak. (2002) *Cell* 111:615-9).

NIK controls B cell maturation and secondary lymphoid organogenesis

NIK^{-/-} mice are grossly normal but show abnormal development of B cells and secondary lymphoid organs (Yin, L., *et al.* (2001) *Science* 291:2162-5). *NIK*^{-/-} mice lack all peripheral lymph nodes (LN) and fail to form Peyer's patches. The spleen and thymus also exhibit disrupted architecture. The number of mature B cells in *NIK*^{-/-} mice is reduced ~60% comparing to that in wild type (WT) mice. In contrast, the numbers of other types of immune cells, including T cells and macrophages, are essentially normal. *NIK*^{-/-} mice have undetectable levels of serum immunoglobulin A (IgA) and greatly reduced (>60 fold) levels of IgG_{2b}. *NIK*^{-/-} mice are severely compromised in their capacity to mount antibody responses to foreign antigen challenge. In spite of these defects, NF- κ B activation in response to TNF and many other stimuli are normal in the absence of NIK.

NIK^{-/-} mice share many deficits with alymphoplasia (*aly/aly*) mice (Miyawaki, S., *et al.* (1994) *Eur J Immunol* 24:429-34), a natural mutant strain that carries a single point mutation near the carboxyl-terminus of NIK (Shinkura, R., *et al.* (1999) *Nat Genet* 22:74-7; Fagarasan, S., *et al.* (2000) *J Exp Med* 191:1477-86; and Yamada, T., *et al.* (2000) *J Immunol* 165:804-12). *aly/aly* mice are characterized by the systemic absence of LN and Peyer's patches, and the disorganized spleen and thymus structures. In addition, they have a decreased level of IgM and extremely low levels of IgG and IgA. Mature B cell numbers are markedly reduced in *aly/aly* mice, which are deficient in both humoral and cell-mediated immune responses. However, the mutant mice are still sensitive to lipopolysaccharide (LPS)-induced endotoxic shock. Up-regulation of the NF- κ B-mediated genes in response to TNF and other pro-inflammatory cytokines is also intact in *aly/aly* mice.

NIK is required for BAFF-R signaling to B cell maturation

BAFF (also known as BLyS, TALL-1, THANK, and zTNF4) is a member of the TNF-family and primarily produced by macrophages, monocytes, and dendritic cells (Mackay, F., *et al.* (2003) *Annu Rev Immunol* 21:231-64; Locksley, R.M., *et al.* (2001) *Cell* 104:487-501;

Fagarasan, S., and T. Honjo. (2000) *Science* 290:89-92; and Waldschmidt, T.J., and R.J. Noelle. (2001) *Science* 293:2012-3). The binding of BAFF to its cognate receptor BAFF-R, which is almost exclusively expressed on B cells, stimulates B cell growth and function (Moore, P.A., *et al.* (1999) *Science* 285:260-3; Schneider, P., *et al.* (1999) *J Exp Med* 189:1747-56; Thompson, J.S., *et al.* (2001) *Science* 293:2108-11; and Yan, M., *et al.* (2002) *Curr Biol* 12:409-13). Evidence from extensive genetic and biochemical studies have made it clear that BAFF signals its activity through BAFF-R, which in turn initiates a NIK-dependent process, ultimately leading to the activation of the NF- κ B2 pathway.

The production of p52 appears to correlate with the process of B cell maturation as its levels progressively increase in the mature and terminally differentiated B cells (Liou, H.C., *et al.* (1994) *Mol Cell Biol* 14:5349-59). The treatment of B cells with BAFF readily induces the processing of p100 to p52 (Claudio, E., *et al.* (2002) *Nat Immunol* 3:958-65). In contrast, administration of BAFF-neutralizing soluble receptor proteins to mice inhibits p100 processing in vivo and lowers the basal p52 levels in B cells (Kayagaki, N., *et al.* (2002) *Immunity* 17:515-24). Moreover the enzyme activity of NIK is essential for BAFF-induced p100 processing to p52 (Xiao, G., *et al.* (2001) *Mol Cell* 7:401-9; and Senftleben, U., *et al.* (2001) *Science* 293:1495-9). Therefore, a NIK-specific small molecule inhibitor will provide a powerful tool for blocking BAFF/BAFF-R signaling activity.

NIK is required for LT β -R signaling to secondary lymphoid organogenesis

Lymphotoxin β receptor (LT β -R) signaling represents a second pathway that signals its activity by promoting NIK-dependent p100 processing (Pomerantz, J.L., and D. Baltimore. (2002) *Mol Cell* 10:693-5; Dixit, V., and T.W. Mak. (2002) *Cell* 111:615-9; and Locksley, R.M., *et al.* (2001) *Cell* 104:487-501). The binding of agonistic LT β -R antibody or its natural ligand, which is a heterotrimer of LT α and LT β (LT α / β 2), induces the processing of p100 to p52 (Dejardin, E., *et al.* (2002) *Immunity* 17:525-35; Muller, J.R., and U. Siebenlist. (2003). *J Biol Chem* 278:12006-12; Yilmaz, Z.B., *et al.* (2003) *Embo J* 22:121-30; and Fu, Y.X., and D.D. Chaplin. (1999) *Annu Rev Immunol* 17:399-433). LT β -R is expressed predominantly on the non-lymphoid cells such as stromal cells, while the expression of its ligand is restricted to the activated lymphocytes (Crowe, P.D., *et al.* (1994) *Science* 264:707-10; and Browning, J.L., *et al.* (1993) *Cell* 72:847-56). Administration of LT α in vivo or Tg mice overexpressing LT α leads to the ectopic formation of lymph node-like tissues (Rennert, P.D., *et al.* (1998) *Immunity* 9:71-9; and Luther, S.A., *et al.* (2000) *Immunity* 12:471-81). The blockade of LT β -R signaling by LT-neutralizing soluble receptor proteins results in the loss of secondary lymphoid organs

(Schrama, D., *et al.* (2001) *Immunity* 14:111-21). Mice with targeted disruption of genes encoding LT β -R or its ligand do not develop secondary lymphoid organs (Rennert, P.D., *et al.* (1996) *J Exp Med* 184:1999-2006; De Togni, P., *et al.* (1994) *Science* 264:703-7; and Futterer, A., *et al.* (1998) *Immunity* 9:59-70), a phenotype that is qualitatively similar to that of *NIK*^{-/-} mice. A stromal defect caused by impaired NIK-dependent LT β -R signaling may account for abnormal development of secondary lymphoid organs in *NIK*^{-/-} mice.

NIK is required for RANK signaling to osteoclastogenesis

NIK has also been known to play a critical role in the signaling pathways elicited by several other TNF-family cytokines, including CD27L, CD40L, TWEAK and RANKL (receptor activator of NF-kappaB ligand) (Ramakrishnan, P., *et al.* (2004) *Immunity* 21, 477-489). Mice lacking functional NIK have impaired RANKL-stimulated formation of osteoclasts (Novack, D.V., *et al.* (2003) *J Exp Med* 198, 771-781), which are multinucleated cells from bone marrow responsible for removing the mineralized matrix of bone tissues. In the absence of NIK, p100 expression is increased by RANKL, but its conversion to p52 is blocked, leading to cytosolic accumulation of p100. High levels of unprocessed p100 in osteoclast precursors from *NIK*^{-/-} mice or a nonprocessable form of the protein in wild-type cells impair RANKL-mediated osteoclastogenesis. NIK is also required for osteoclastogenesis in response to pathologic stimuli. Tumor-induced osteolysis in *NIK*^{-/-} mice is completely blocked while growth of tumor cells in the bone marrow is similar to WT controls (Vaira, S., *et al.* (2008) *Proc Natl Acad Sci USA* 105, 3897-3902).

Excess NIK-mediated NF- κ B2 signaling leads to autoimmunity

Overproduction of BAFF is known to associate with the pathogenesis of various autoimmune conditions in humans and animals (Kalled, S.L. (2002) *Curr Opin Investig Drugs* 3:1005-10). Transgenic mice overexpressing BAFF exhibit vastly increased numbers of B cells with severely enlarged secondary lymphoid organs and abnormally elevated levels of serum immunoglobulins. They also develop a systemic lupus erythematosus (SLE)-like autoimmune phenotype (Mackay, F., *et al.* (1999) *J Exp Med* 190:1697-710; Gross, J.A., *et al.* (2000) *Nature* 404:995-9; and Khare, S.D., *et al.* (2000) *Proc Natl Acad Sci USA* 97:3370-5). As BAFF Tg mice age, they develop a secondary pathology reminiscent of Sjögren's syndrome (SS), in which end organ damages are in the inflamed salivary and lacrimal glands (Groom, J., *et al.* (2002) *J Clin Invest* 109:59-68). In humans, BAFF levels correlate with the disease severity of autoimmune syndromes, including SLE, SS and rheumatoid arthritis (RA) (Groom,

J., *et al.* (2002) *J Clin Invest* 109:59-68; Zhang, J., *et al.* (2001) *J Immunol* 166:6-10; and Cheema, G.S., *et al.* (2001) *Arthritis Rheum* 44:1313-9).

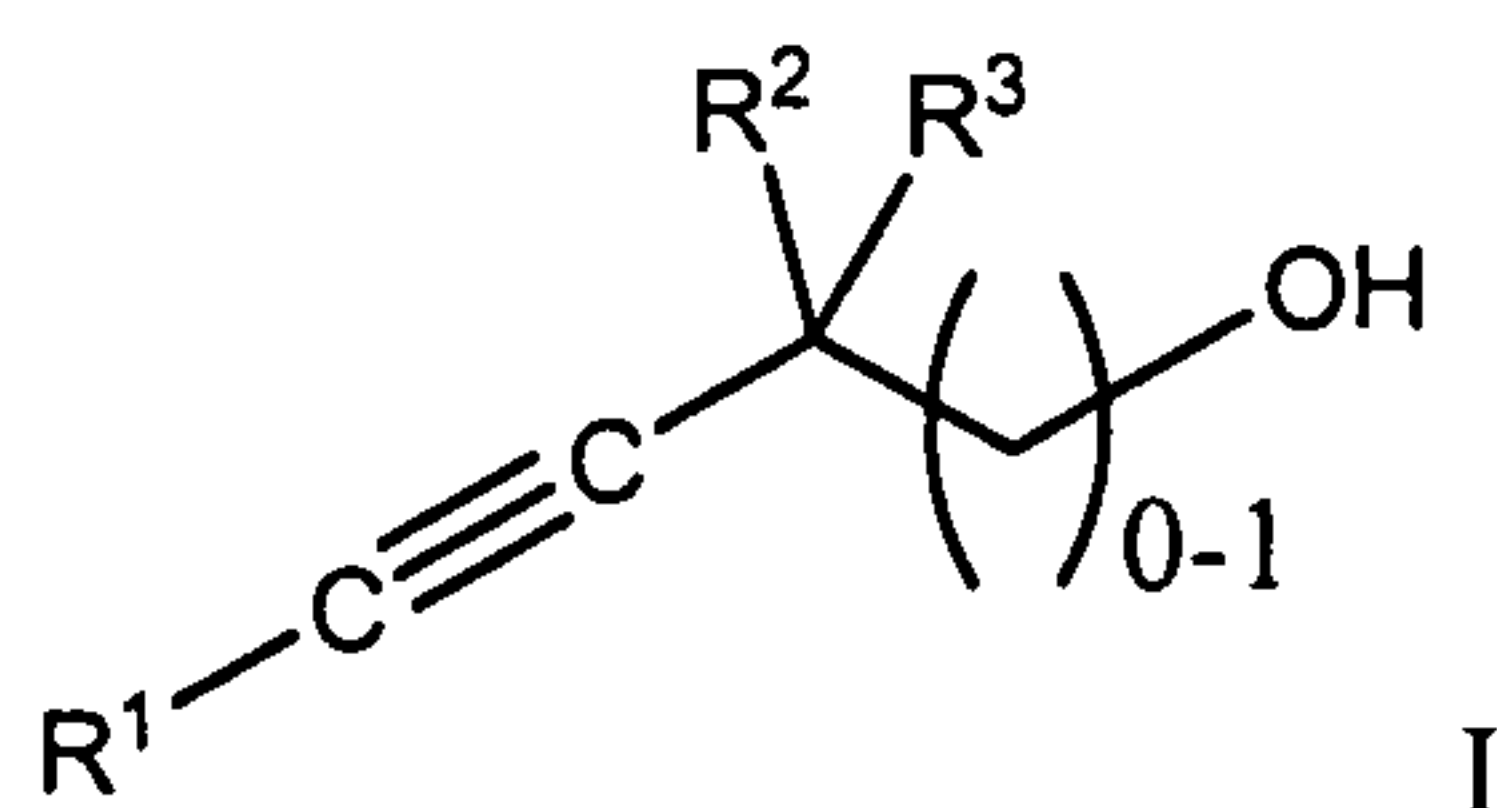
The formation of secondary lymphoid organ-like tissues is a prototypic feature of many chronic inflammatory and autoimmune conditions, including RA and inflammatory bowel diseases (IBD) (Fu, Y.X., and D.D. Chaplin. (1999) *Annu Rev Immunol* 17:399-433). Administration of soluble LT-neutralizing receptor proteins reverses the formation of lymphoid organ-like structures and prevents the development of colitis, arthritis, and insulin-dependent diabetes mellitus in mouse models (Shao, H., *et al.* (2003) *Eur J Immunol* 33:1736-43; Ettinger, R., *et al.* (2001) *J Exp Med* 193:1333-40; and Wu, Q., *et al.* (2001) *J Exp Med* 193:1327-32). *NIK^{-/-}* mice were completely resistant to antigen-induced arthritis (AIA) and to a genetic, spontaneous form of arthritis (Aya, K., *et al.* (2005) *J Clin Invest* 115, 1848-1854). These mice also showed significantly less osteoclastogenesis and bone erosion in the serum transfer arthritis model. NIK is important in both the immune and bone-destructive components of inflammatory arthritis, indicating that NIK-specific inhibitors have the potential for the treatment of these chronic inflammatory diseases.

Excess NIK-mediated NF- κ B2 activities lead to malignancy

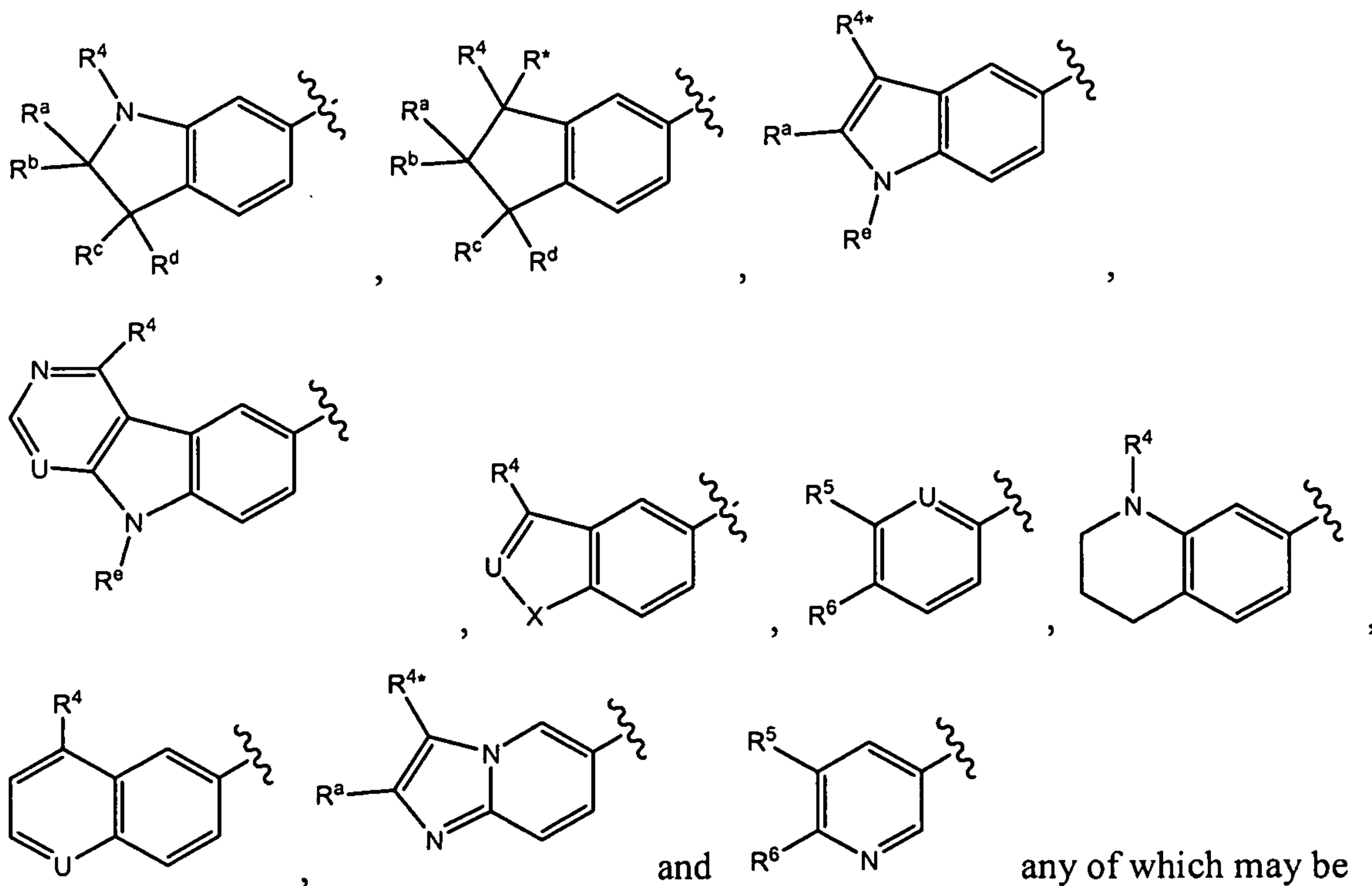
Intense B lymphocyte activities caused by excess NIK-mediated NF- κ B2 activities have been implicated in various types of cancer, in particular lymphoma, leukemia and multiple myeloma (Mackay, F., *et al.* (2003) *Annu Rev Immunol* 21:231-64; Saitoh, Y., *et al.* (2008) *Blood* 111, 5118-5129; Annunziata, C.M., *et al.* (2007) *Cancer Cell* 12, 115-130; and Keats, J.J., *et al.* (2007) *Cancer Cell* 12, 131-144). For example, the *BAFF* gene is located on a human chromosome locus frequently involved in chromosomal translocations in patients with Burkitt lymphoma-leukemia and elevated levels of BAFF are detected in sera from non-Hodgkin's lymphoma (NHL) patients. Overexpression of BAFF in mice causes the development of a submaxillary gland tumor that is composed essentially of hyperplastic B cells (Groom, J., *et al.* (2002) *J Clin Invest* 109:59-68). The *NF- κ B2* gene was cloned from a B cell lymphoma-associated chromosomal translocation (Neri, A., *et al.* (1991) *Cell* 67:1075-87). The translocation results in the production of a carboxyl-terminal truncated protein that is constitutively active and tumorigenic (Ciana, P., *et al.* (1997) *Oncogene* 14:1805-10; and Fracchiolla, N.S., *et al.* (1993) *Oncogene* 8:2839-45). NF- κ B2 rearrangements are present in ~2% of human lymphoid tumors. Overexpression of NIK also contributes to the tumorigenesis of adult T-cell leukemia and Hodgkin Reed-Sternberg cells (Saitoh, Y., *et al.* (2008) *Blood* 111, 5118-5129). NIK is also involved in the pathogenesis of multiple myeloma (MM)

DESCRIPTION OF THE INVENTION

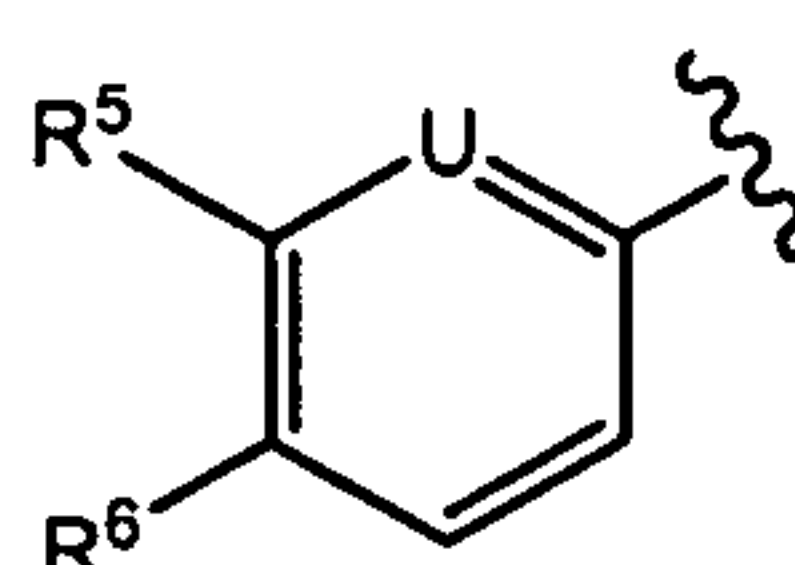
A compound of formula I

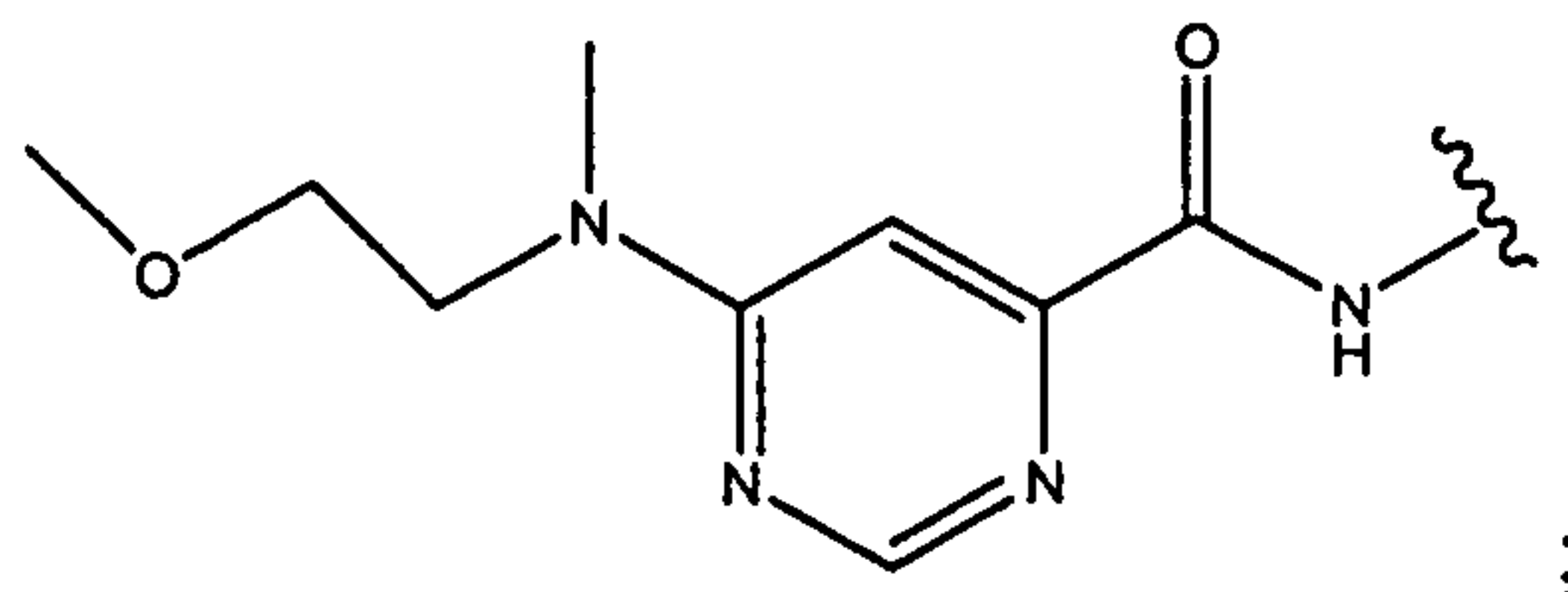


R^1 is selected from



optionally substituted with one or more R^x groups as allowed by valance;

provided that when R^1 is , where U is CH and R^6 is H, then R^5 is



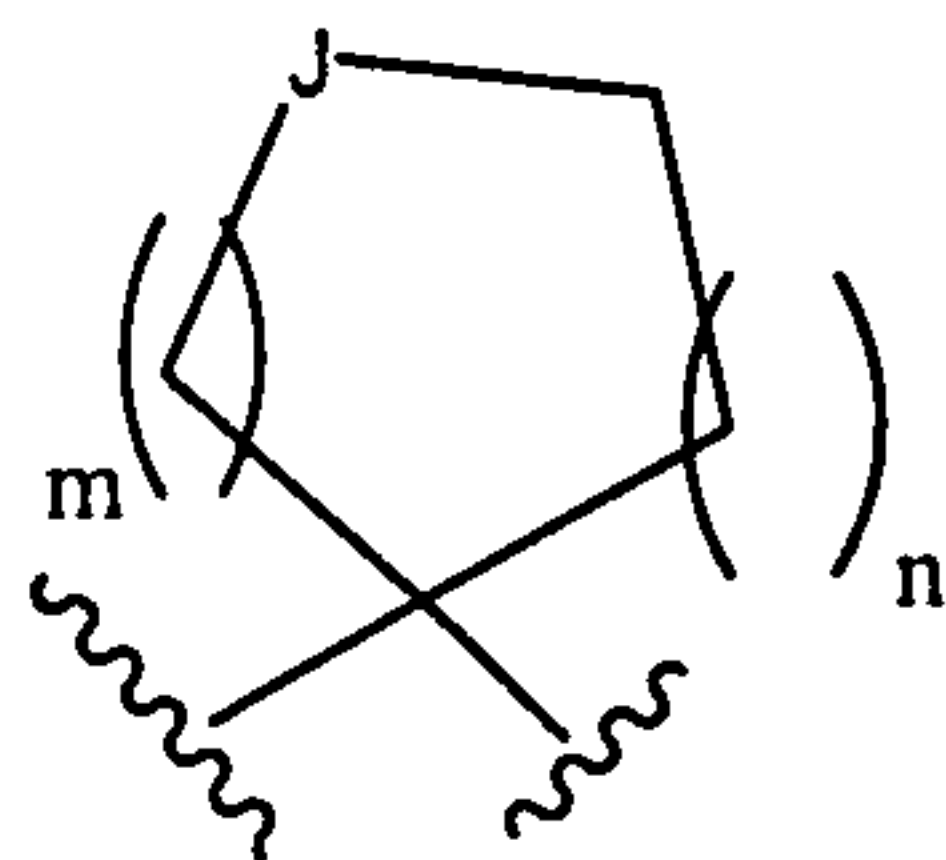
other than

R^2 is alkyl or haloalkyl;

R^3 is alkyl, cycloalkyl, haloalkyl, $-C(=O)R^7$, $-C(=O)OR^7$, $-C(=O)NR^8R^9$, aryl or heteroaryl

wherein either of said aryl or heteroaryl may be optionally substituted with one or more R^x as allowed by valance;

or R^2 and R^3 together with the carbon atom to which they are attached may combine to form

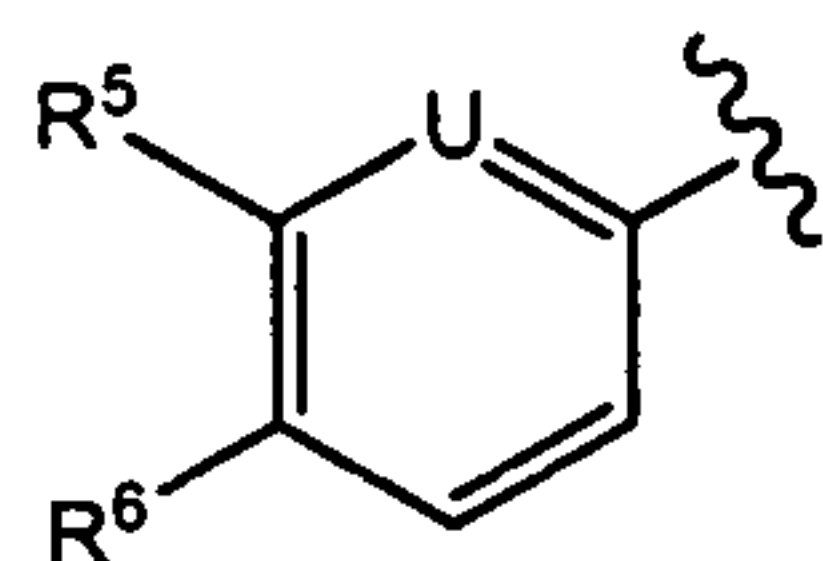


which may be optionally substituted with one or more R^x groups as allowed by valance;

R^4 and R^{4*} are independently

- i) pyridyl, pyrimidyl, pyrazinyl, triazinyl, purinyl, pyrrolopyrimidyl, triazolopyrimidyl, furopyrimidyl, thienopyrimidyl, oxazolopyrimidyl, or thiazolopyrimidyl, each of which is substituted with at least one R^{10} group, and any of which may be optionally substituted with one or more R^x groups as allowed by valance; or
- ii) oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, or $-C(=O)R^{7*}$ any of which may be optionally substituted with one or more R^x groups as allowed by valance;

provided R^4 is other than $-C(=O)R^{7*}$ when R^1 is



, where U is CH and R^6 is H, and R^5 is either

$-(CH_2)_k-N(R^8)(R^4)$ or $-(CH_2)_k-R^4$;

R^5 is $-(CH_2)_k-R^4$, $-(CH_2)_k-N(R^8)(R^4)$, $-(CH_2)_k-OR^4$, $-(CH_2)_k-C(=O)R^4$; $-(CH_2)_k-C(=O)OR^4$, $-(CH_2)_k-C(=O)N(R^8)(R^4)$ or $-(CH_2)_k-NR^8-C(=O)R^4$;

R^6 is H, halo, alkyl, $-(CH_2)_k-OR^{11}$, $-(CH_2)_k-N(R^{12})(R^{13})$, $-(CH_2)_k-C(=O)R^{11}$, $-(CH_2)_k-C(=O)OR^{11}$;

R^7 , R^{7*} and R^{7+} are each independently

- (i) H, or
- (ii) alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkylalkyl, heterocyclylalkyl, arylalkyl, heteroarylalkyl, alkoxyalkyl, hydroxyalkyl or NR^8R^9 -alkyl any of which may be optionally substituted with one or more R^x groups as allowed by valance;

R^8 , R^9 , R^{8+} and R^{9+} are each independently

- (i) H;
- (ii) alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkylalkyl, heterocyclylalkyl, arylalkyl, heteroarylalkyl, alkoxyalkyl, hydroxyalkyl or $(NR^{12}R^{13})$ -alkyl, any of which may be optionally substituted with one or more R^x groups as allowed by valance;
- (iii) or R^8 and R^9 together with the nitrogen atom to which they are attached may combine to form a heterocyclyl ring optionally substituted with one or more R^x groups as allowed by valance;
- (iv) or R^{8+} and R^{9+} together with the nitrogen atom to which they are attached may combine to form a heterocyclyl ring optionally substituted with one or more R^x groups as allowed by valance;

R^{10} is H, $-NR^{14}R^{15}$, or $-C(=O)NR^{14}R^{15}$;

R^{11} is

- (i) H, or
- (ii) alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkylalkyl, heterocyclylalkyl, arylalkyl or heteroarylalkyl any of which may be optionally substituted with one or more R^x groups as allowed by valance;

R^{12} and R^{13} are each independently

- (i) H;
- (ii) alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkylalkyl, heterocyclylalkyl, arylalkyl, heteroarylalkyl, alkoxyalkyl, hydroxyalkyl or (NR^8R^9) -alkyl, any of which may be optionally substituted with one or more R^x groups as allowed by valance;
- (iii) or R^{12} and R^{13} together with the nitrogen atom to which they are attached may combine to form a heterocyclyl ring optionally substituted with one or more R^x groups as allowed by valance;

R^{14} and R^{15} are each independently

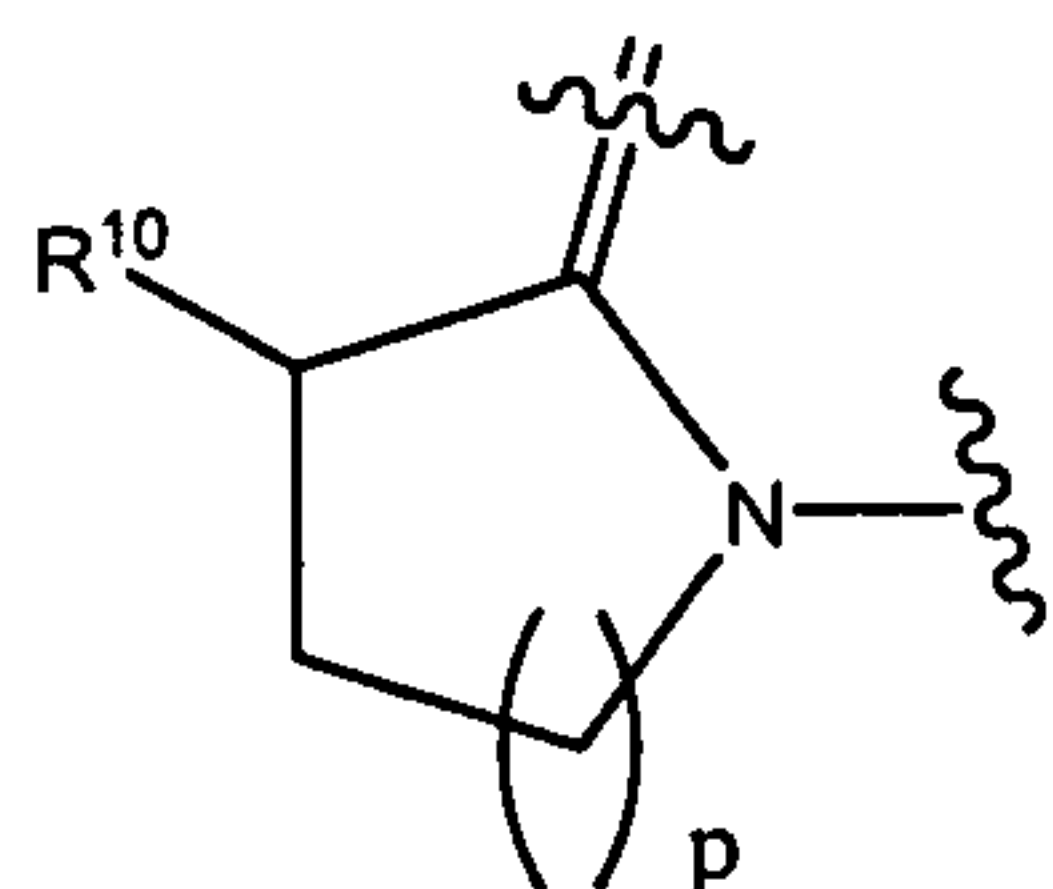
- (i) H;
- (ii) alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkylalkyl, heterocyclylalkyl, arylalkyl, heteroarylalkyl, alkoxyalkyl, hydroxyalkyl or $(NR^{12}R^{13})$ -alkyl, any of which may be optionally substituted with one or more R^x groups as allowed by valance;
- (iii) or R^{14} and R^{15} together with the nitrogen atom to which they are attached may combine to form a heterocyclyl ring optionally substituted with one or more R^x groups as allowed by valance;

R^a , R^b , R^c , R^d and R^* are each independently H or R^x

or R^a and R^b together with the carbon atom to which they are attached may combine to form a carbonyl group;

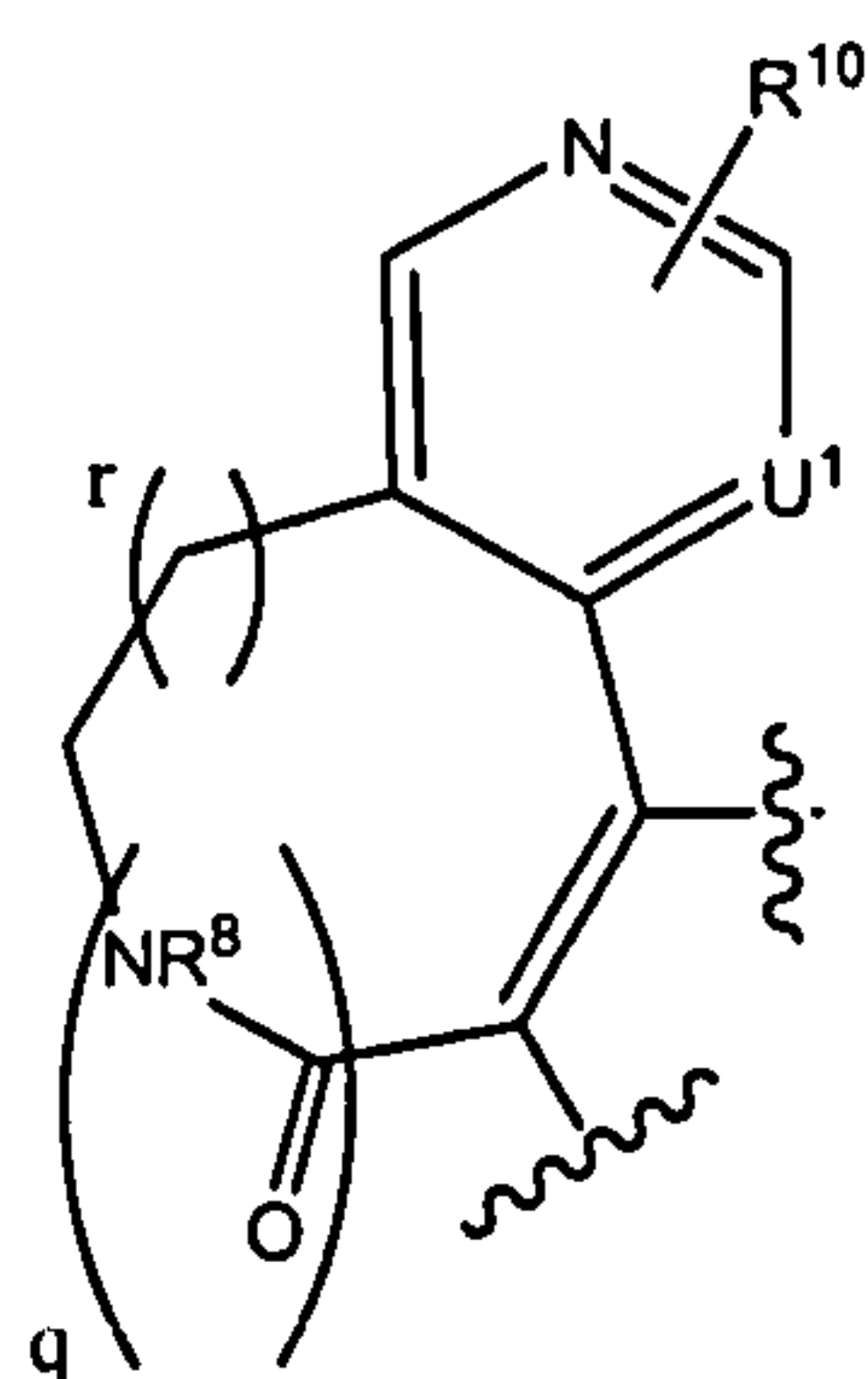
or R^b together with either R^c or R^* may combine to form a bond;

or R^a and R^c , together with the atoms to which they are respectively attached, may combine to form



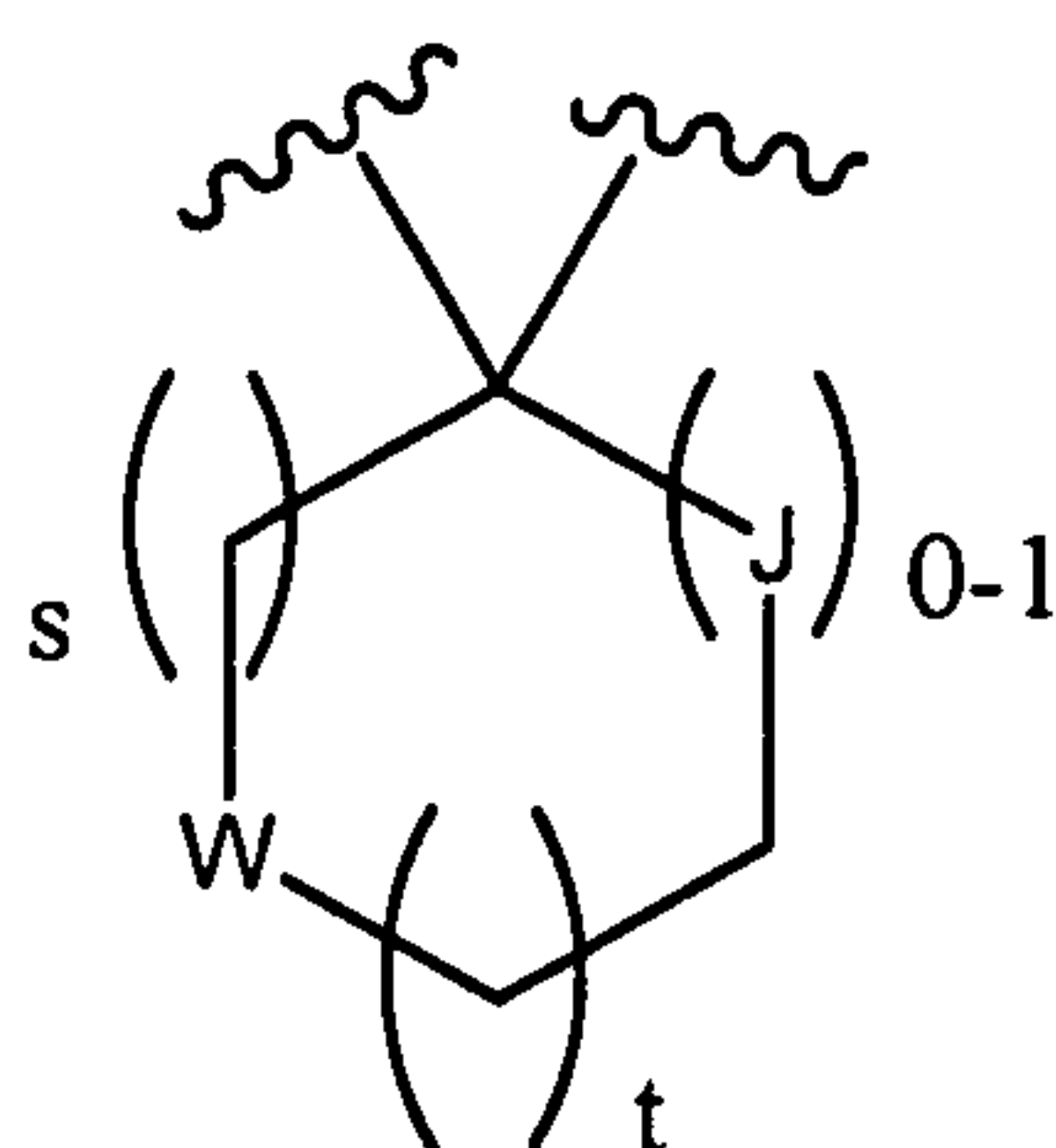
which may be optionally substituted with one or more R^x groups as allowed by valance;

or R^a and R^{4*} , together with the atoms to which they are respectively attached, may combine to form



which may be optionally substituted with one or more R^x groups as allowed by valance;

or R^c and R^d together with the carbon atom to which they are each attached may combine to form



which may be optionally substituted with one or more R^x groups as allowed by valance;

R^e is H, R^4 , or R^x ;

R^x is an optional substituent independently selected at each occurrence from halo, cyano, nitro, oxo, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, $-(alkylene)_q-OR^{7+}$, $-(alkylene)_q-S(O)_vR^{7+}$, $-(alkylene)_q-NR^{8+}R^{9+}$, $-(alkylene)_q-C(=O)R^{7+}$, $-(alkylene)_q-C(=S)R^{7+}$, $-(alkylene)_q-C(=O)OR^{7+}$, $-(alkylene)_q-OC(=O)R^{7+}$, $-(alkylene)_q-C(=S)OR^{7+}$, $-(alkylene)_q-C(=O)NR^{8+}R^{9+}$, $-(alkylene)_q-C(=S)NR^{8+}R^{9+}$, $-(alkylene)_q-N(R^{15})C(=O)NR^{8+}R^{9+}$, $-(alkylene)_q-N(R^{15})C(=S)NR^{8+}R^{9+}$, $-(alkylene)_q-N(R^{15})C(=O)R^{7+}$, $-(alkylene)_q-N(R^{15})C(=S)R^{7+}$, $-(alkylene)_q-OC(=O)NR^{8+}R^{9+}$, $-(alkylene)_q-OC(=S)NR^{8+}R^{9+}$, $-(alkylene)_q-SO_2NR^{8+}R^{9+}$, $-(alkylene)_q-N(R^{15})SO_2R^{7+}$, $-(alkylene)_q-N(R^{15})SO_2NR^{8+}R^{9+}$, $-(alkylene)_q-N(R^{15})C(=O)OR^{7+}$, $-(alkylene)_q-N(R^{15})C(=S)OR^{7+}$, or $-(alkylene)_q-N(R^{15})SO_2R^{7+}$;

wherein alkylene, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkyl groups may be further independently substituted with one or more $-(alkylene)_q-CN$, $-(alkylene)_q-OR^{7+}$, $-(alkylene)_q-S(O)_vR^{7+}$, $-(alkylene)_q-NR^{8+}R^{9+}$, $-(alkylene)_q-C(=O)R^{7+}$, $-(alkylene)_q-C(=S)R^{7+}$, $-(alkylene)_q-C(=O)OR^{7+}$, $-(alkylene)_q-OC(=O)R^{7+}$, $-(alkylene)_q-C(=S)OR^{7+}$, $-(alkylene)_q-C(=O)NR^{8+}R^{9+}$, $-(alkylene)_q-C(=S)NR^{8+}R^{9+}$, $-(alkylene)_q-N(R^{15})C(=O)NR^{8+}R^{9+}$, $-(alkylene)_q-N(R^{15})C(=S)NR^{8+}R^{9+}$, $-(alkylene)_q-N(R^{15})C(=O)R^{7+}$, $-(alkylene)_q-N(R^{15})C(=S)R^{7+}$, $-(alkylene)_q-OC(=O)NR^{8+}R^{9+}$, $-(alkylene)_q-OC(=S)NR^{8+}R^{9+}$, $-(alkylene)_q-SO_2NR^{8+}R^{9+}$, $-(alkylene)_q-N(R^{15})SO_2R^{7+}$, $-(alkylene)_q-N(R^{15})SO_2NR^{8+}R^{9+}$, $-(alkylene)_q-N(R^{15})C(=O)OR^{7+}$, $-(alkylene)_q-N(R^{15})C(=S)OR^{7+}$, or $-(alkylene)_q-N(R^{15})SO_2R^{7+}$;

J and W are independently $-CH_2-$, $-N(R^8)-$, $-O-$, or $-S(=O)_v-$,

X is $-O-$ or $-S(=O)_v-$

U and U^1 are independently CH or N

k at each occurrence is independently 0, 1, 2 or 3;

m is 1, 2 or 3

n is 0, 1 or 2

p is 1, 2 or 3

q at each occurrence is independently 0 or 1

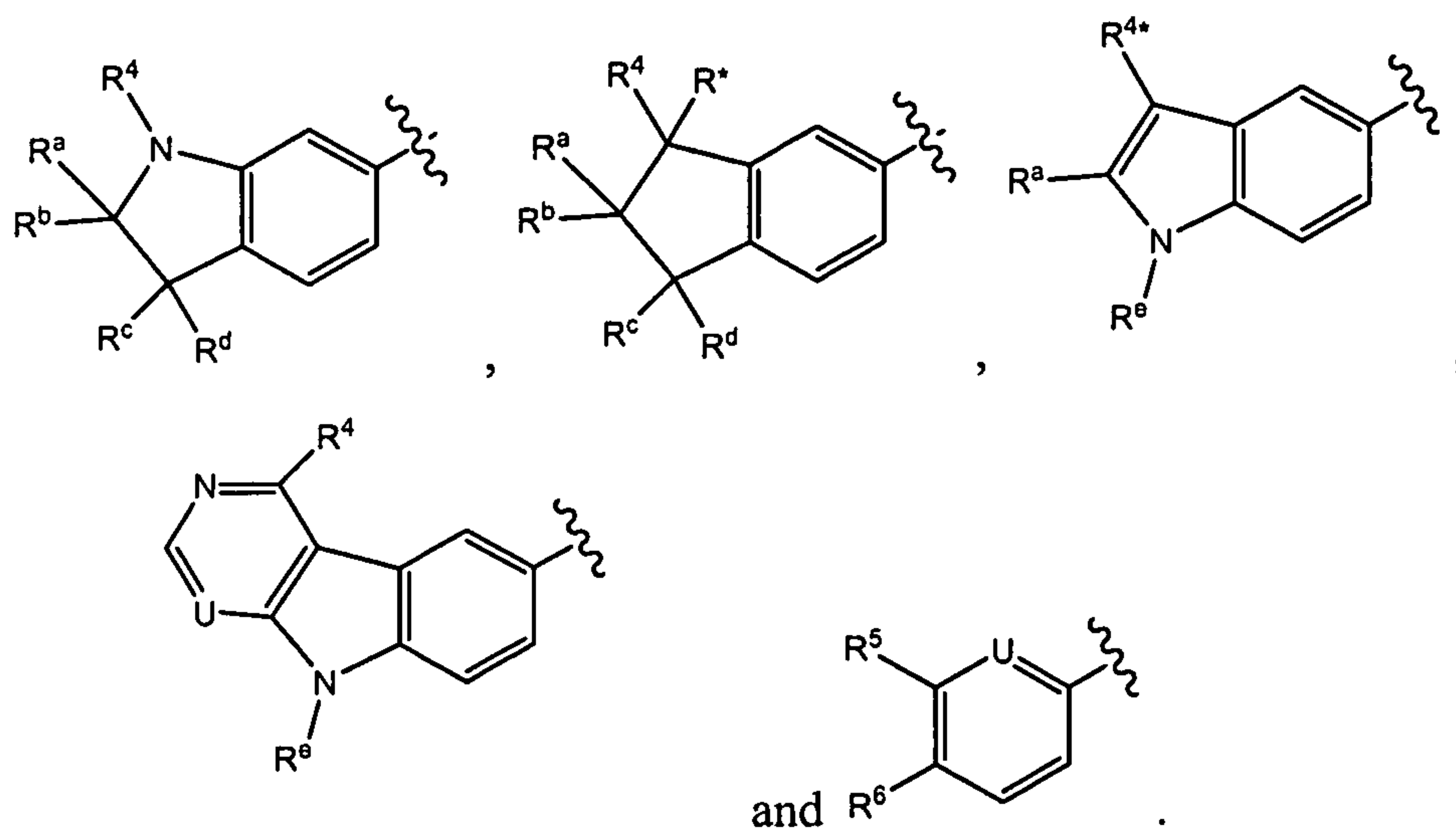
r is 0, 1, 2 or 3;

s is 1, 2 or 3

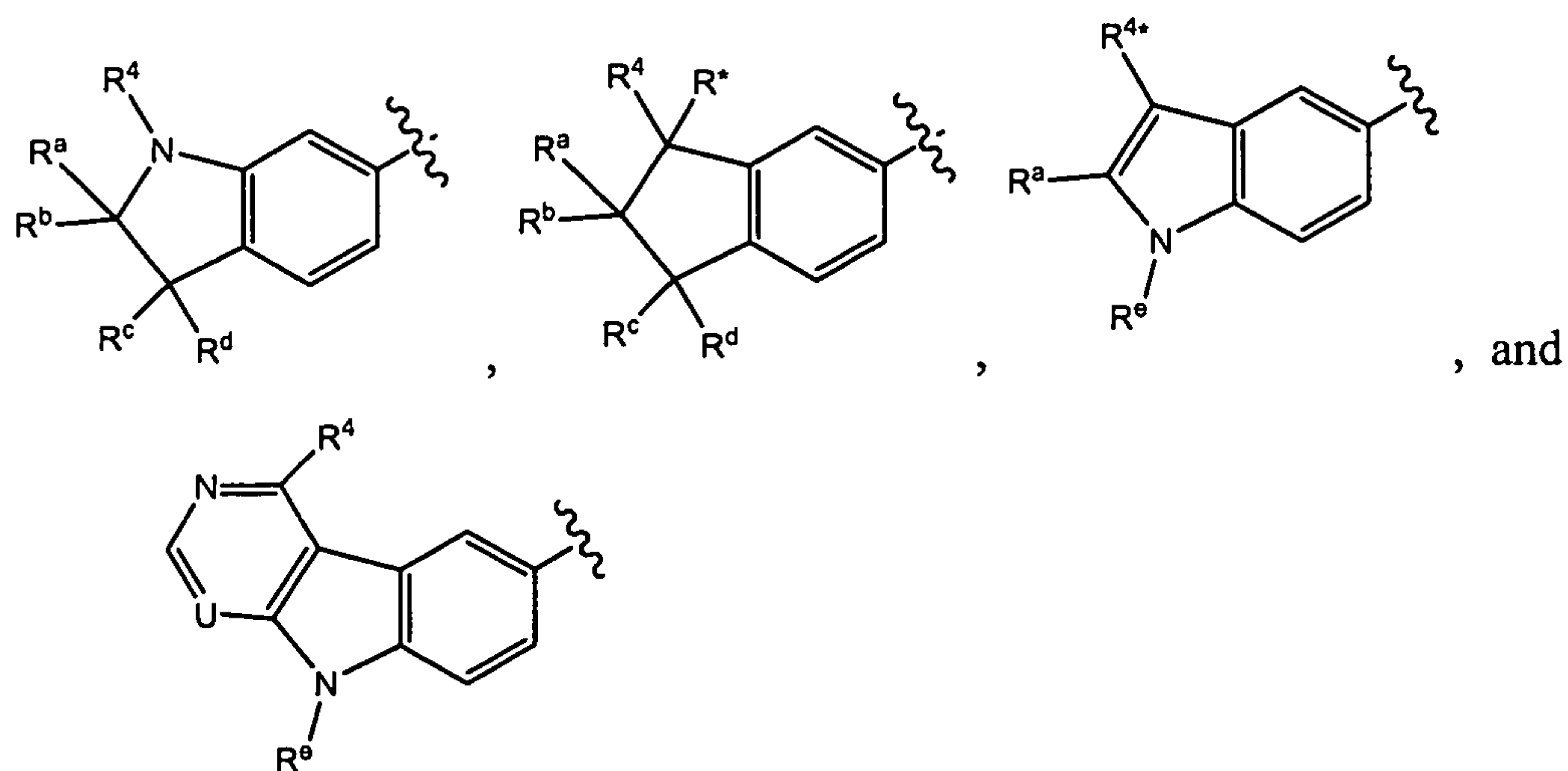
t is 0, 1 or 2

v at each occurrence is independently 0, 1 or 2

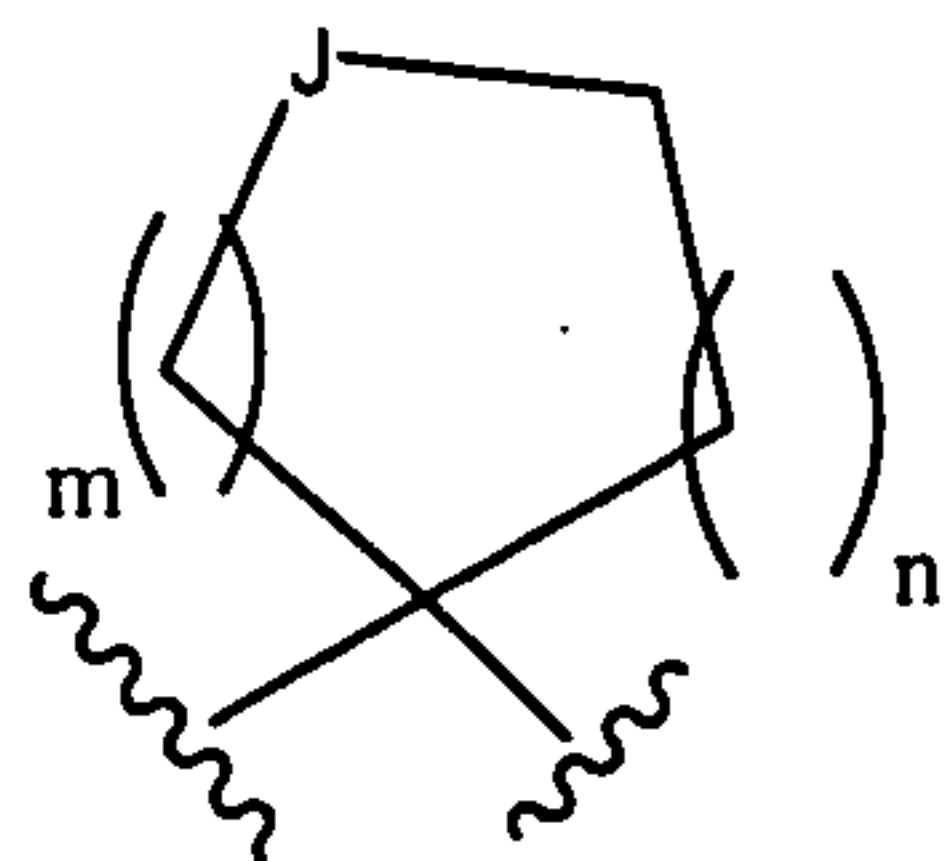
Preferred compounds of the current invention include compounds wherein R^1 is selected from



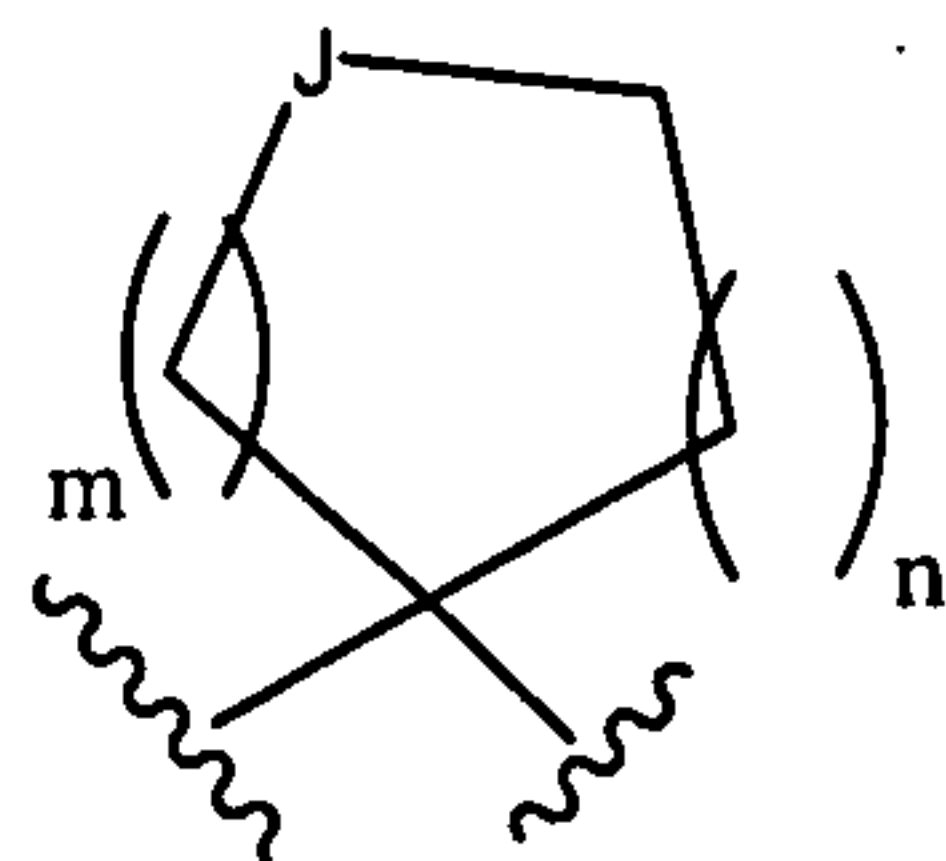
More preferred compounds of the current invention include compounds wherein R^1 is selected from



Preferred compounds of the present invention include compounds wherein R^2 is alkyl; and R^3 is pyrrolyl, furanyl, thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, phenyl, pyridyl, pyrimidyl, pyrazinyl, or oxadiazolyl any of which may be optionally substituted with one or more R^x as allowed by valance. or R^2 and R^3 together with the carbon atom to which they are attached may combine to form

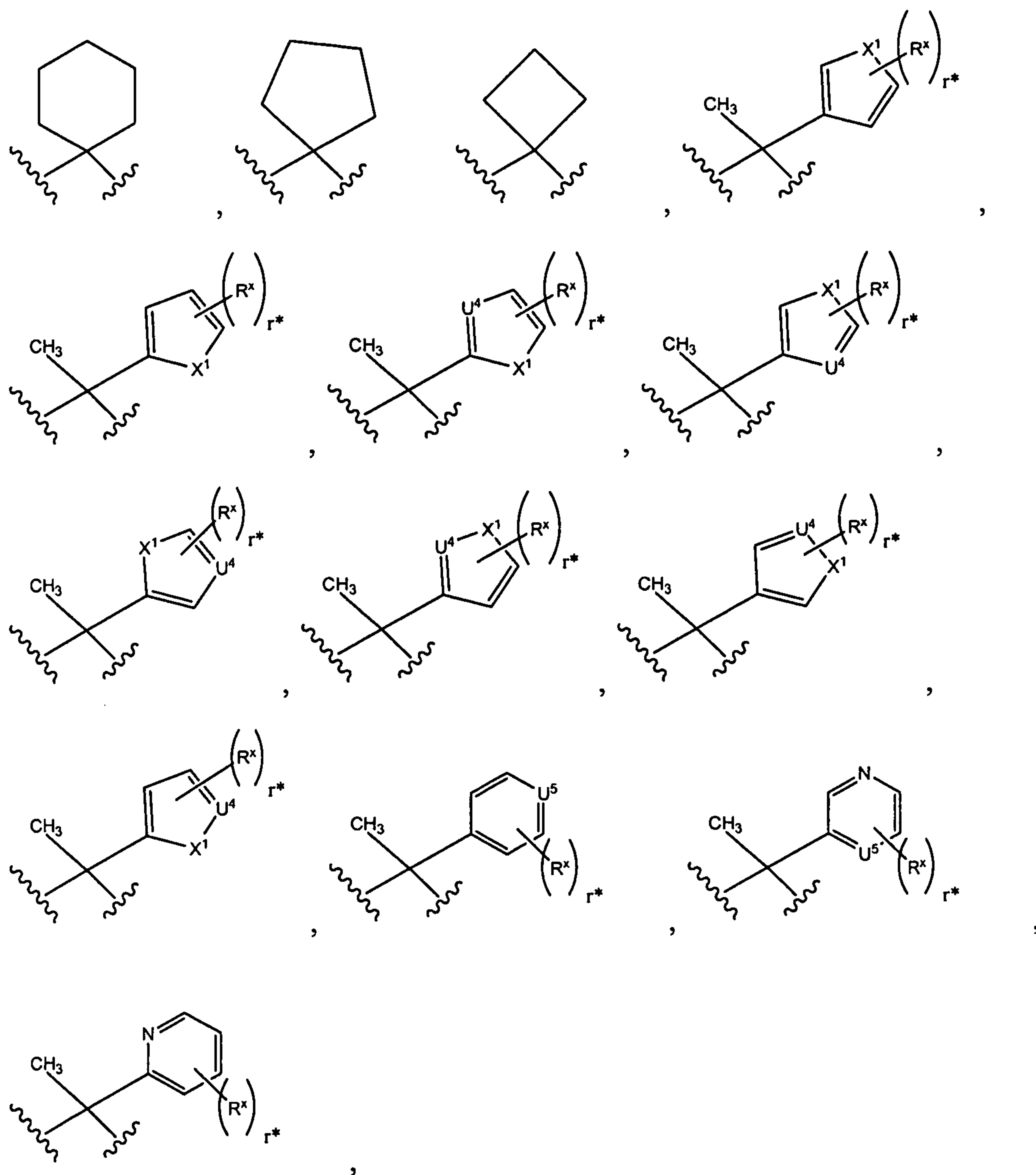


which may be optionally substituted with one or more R^x groups as allowed by valance; (especially preferred compounds include those where R^2 is alkyl; and R^3 is pyrrolyl, furanyl, thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, phenyl, pyridyl, pyrimidyl, pyrazinyl, or oxadiazolyl any of which may be optionally substituted with one or more R^x as allowed by valance; or R^2 and R^3 together with the carbon atom to which they are attached may combine to form



which may be optionally substituted with one or more R^x groups as allowed by valance).

Preferred compounds of the present invention include those wherein R^2 , R^3 and the carbon atom to which they are attached are selected from



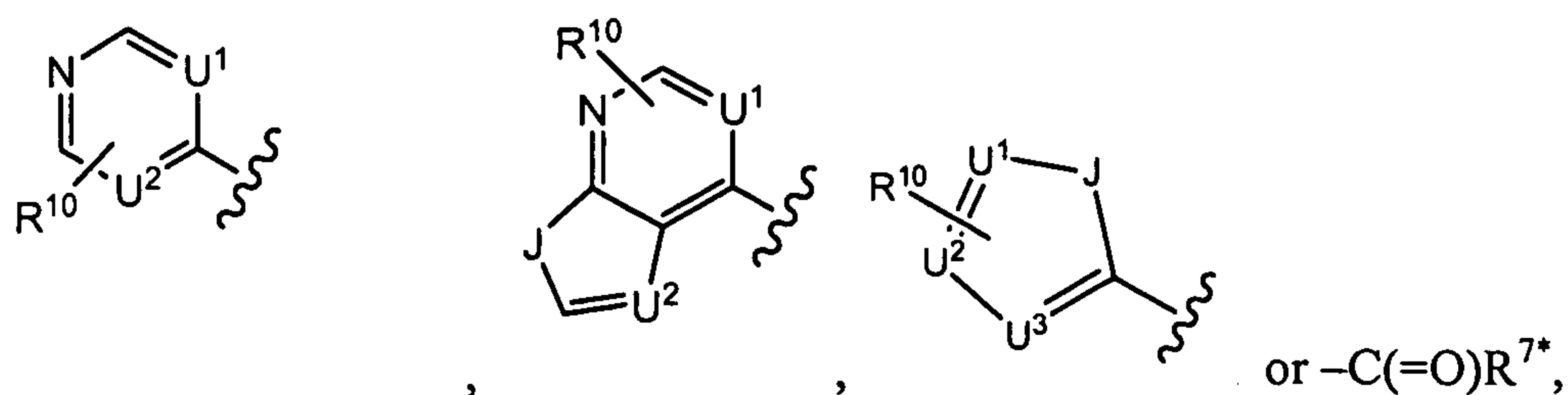
wherein

U^4 and U^5 are each independently N or CH

X^1 is NH, O or $S(O)_v$

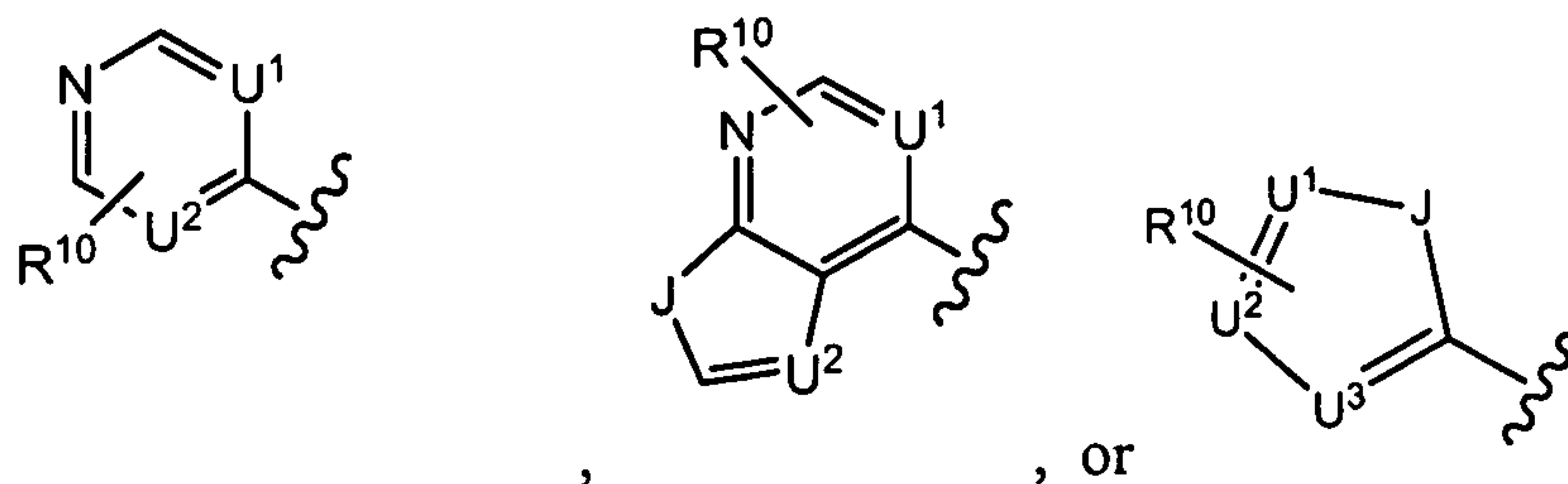
r^* is 0 or an integer up to three as allowed by valance.

Preferred compounds of the present invention further include compounds wherein R^4 is



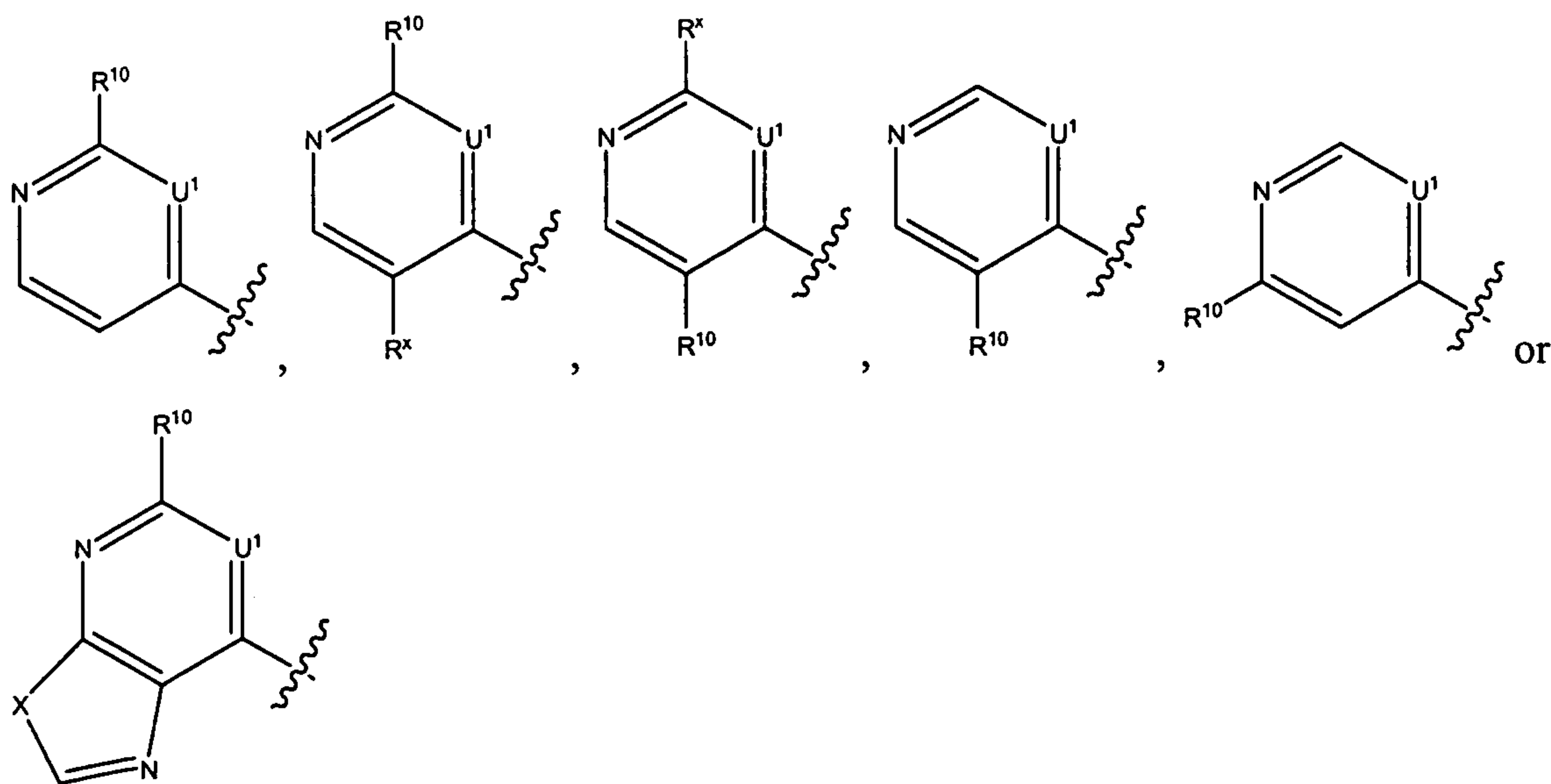
any of which may be optionally substituted, as allowed by valence, with up to three R^x groups independently selected from halo, cyano, alkyl, haloalkyl, alkenyl, alkynyl, aryl, $-(alkylene)_q-NR^{8+}R^{9+}$, $-(alkylene)_q-C(=O)NR^{8+}R^{9+}$, $-(alkylene)_q-OR^{7+}$, wherein R^{10} is H, $-NR^{14}R^{15}$, or $-C(=O)NR^{14}R^{15}$; and U^1 , U^2 and U^3 are independently CH or N.

Preferred compounds of the present invention further include compounds wherein R^4 is

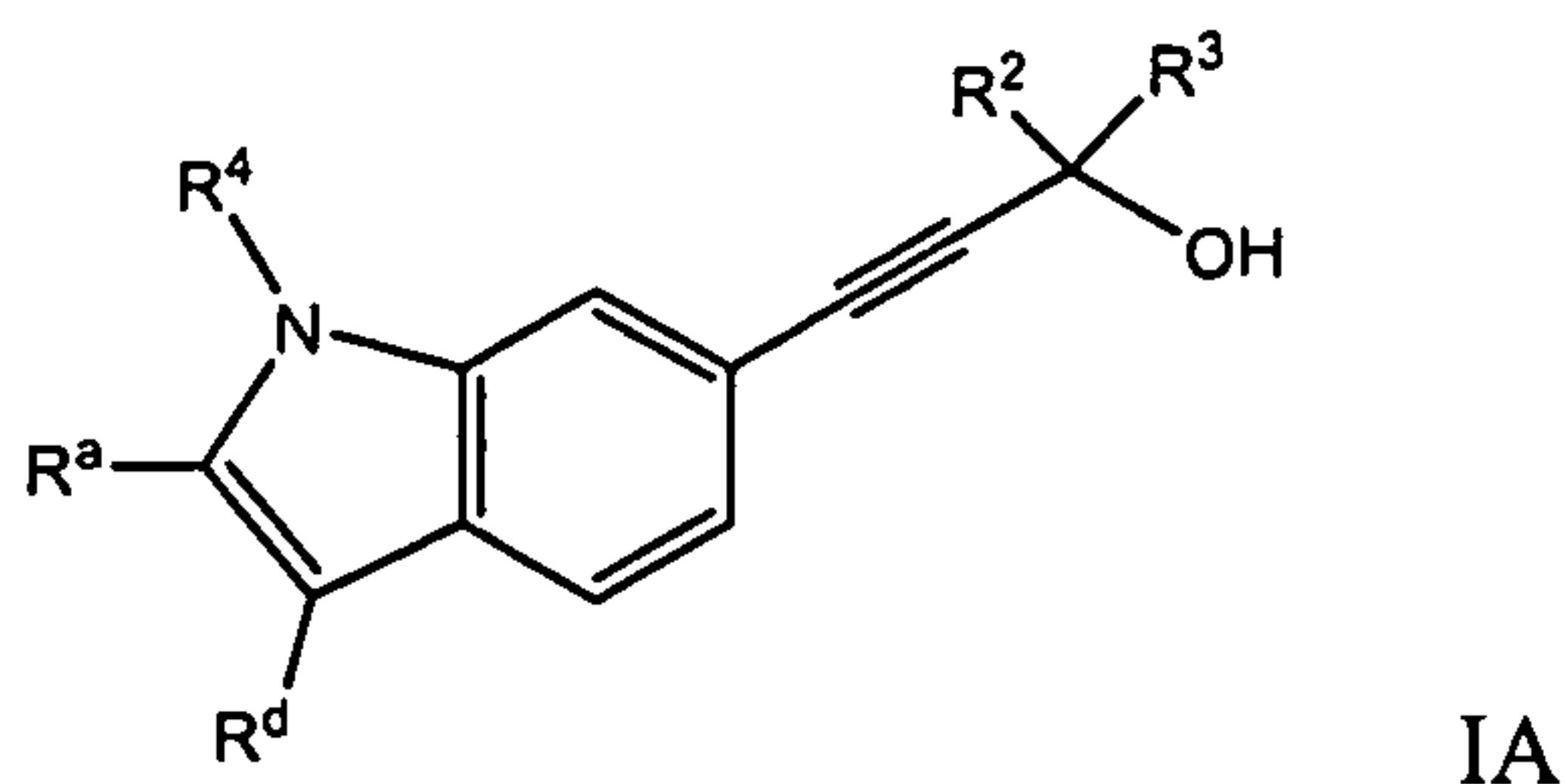


any of which may be optionally substituted, as allowed by valence, with up to three R^x groups independently selected from halo, cyano, alkyl, haloalkyl, alkenyl, alkynyl, aryl, $-(alkylene)_q-NR^{8+}R^{9+}$, $-(alkylene)_q-C(=O)NR^{8+}R^{9+}$, $-(alkylene)_q-OR^{7+}$, wherein R^{10} is H, $-NR^{14}R^{15}$, or $-C(=O)NR^{14}R^{15}$; and U^1 , U^2 and U^3 are independently CH or N.

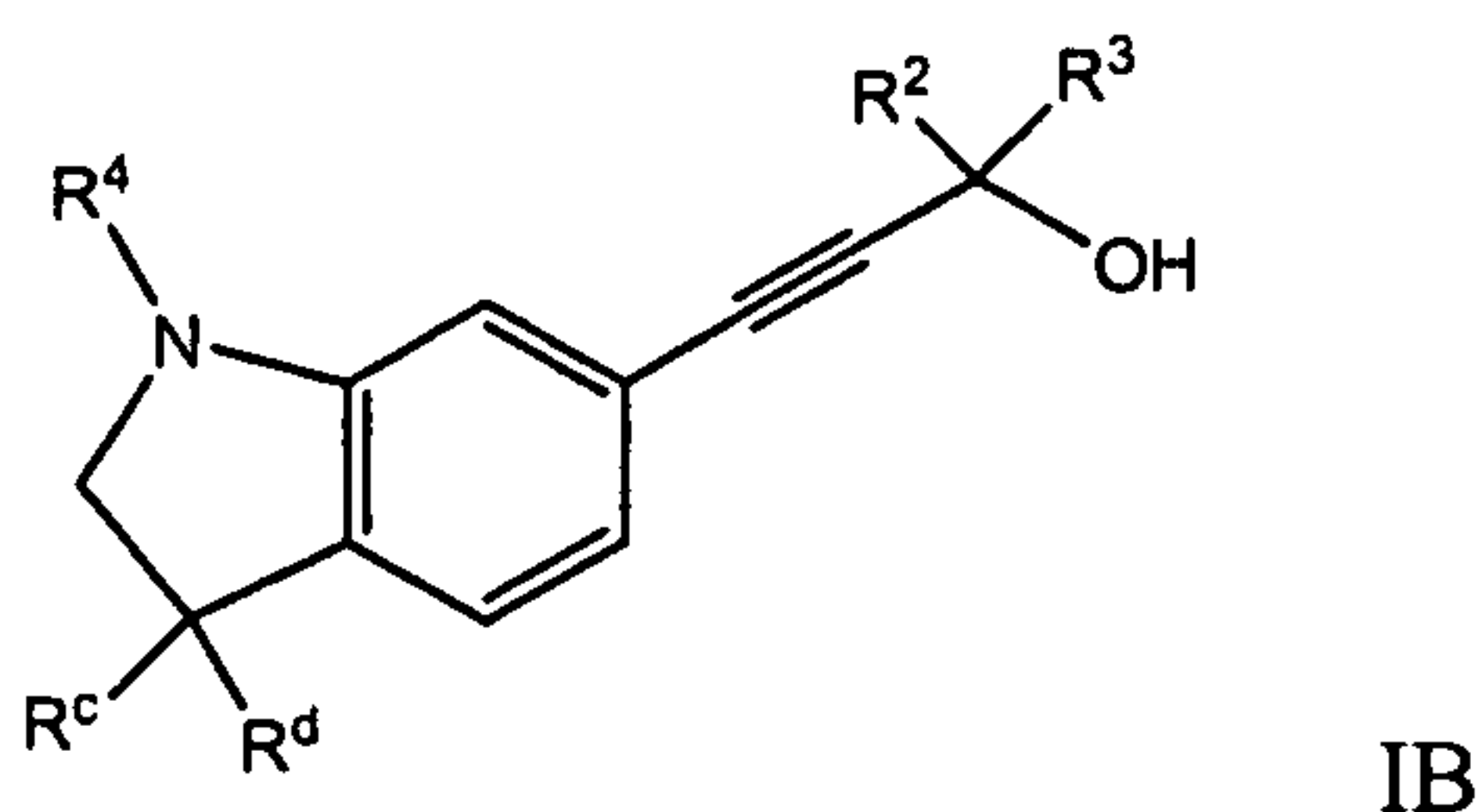
Preferred compounds of the present invention include compounds wherein R^4 is



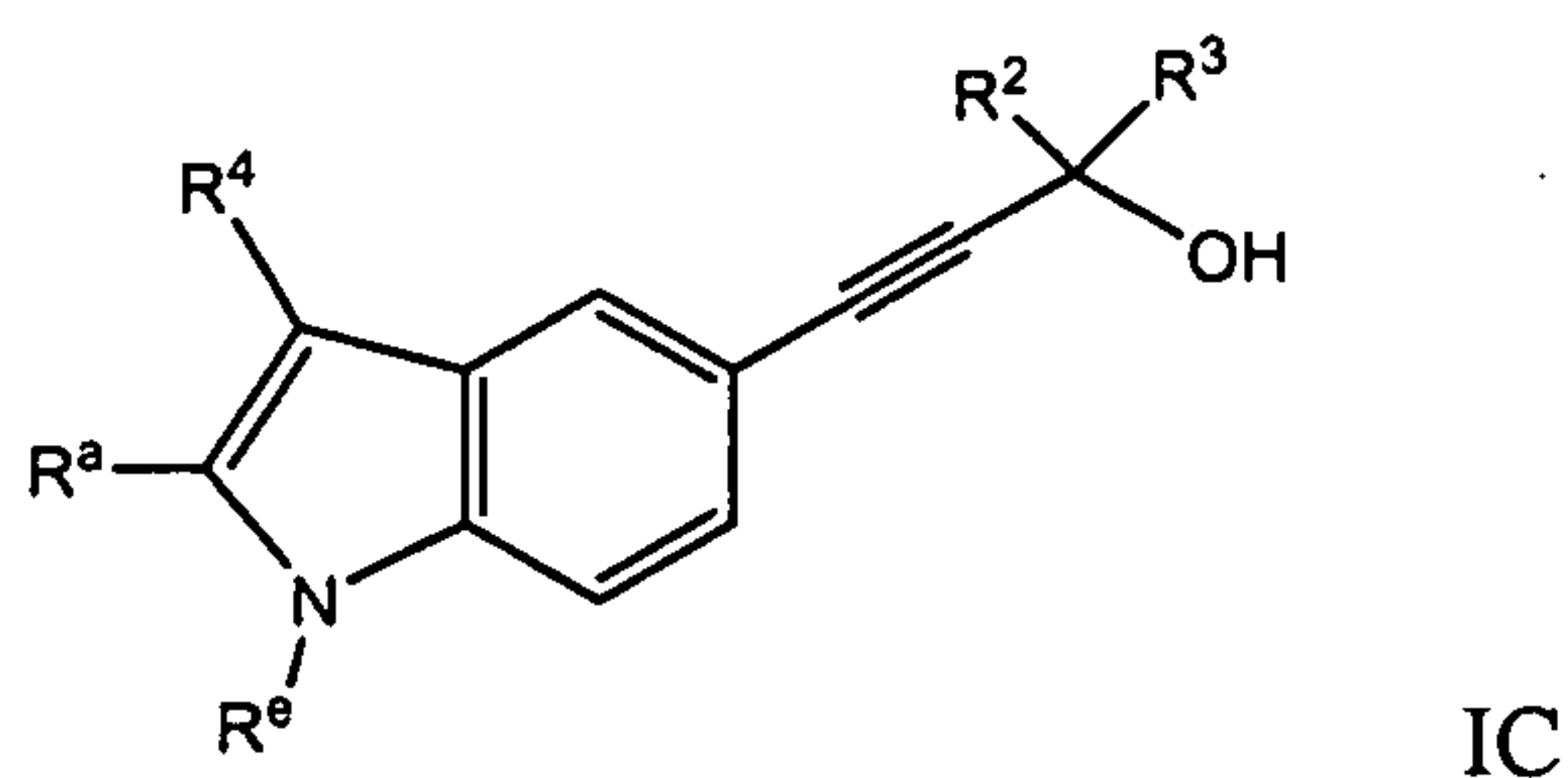
Preferred compounds of the present invention include compounds having the following formula IA



Preferred compounds of the present invention further include compounds having the following formula IB



Preferred compounds of the present invention further include compounds having the following formula IC



Preferred compounds of the present invention also include compounds having any and all combinations and sub-combinations of the preferred groups listed above.

Preferred compounds of the present invention include the compounds exemplified herein.

The present invention also relates to pharmaceutical compositions containing the above compounds, together with a pharmaceutically acceptable vehicle or carrier.

The present present invention also relates to a method of treating inflammation and/or inflammatory disorders in a subject using the above compounds.

The invention also relates to a method of treating NIK-mediated disorders in a subject using the above compounds.

INDICATIONS

Compounds of the present invention are useful in the treatment of inflammatory and autoimmune disorders, including RA and inflammatory bowel diseases (IBD), asthma, COPD, multiple sclerosis, colitis, arthritis, and insulin-dependent diabetes mellitus. Compounds of the present invention may also be useful in treating lymphoma, leukemia and multiple myeloma.

DEFINITIONS

The terms "agonist" and "agonistic" when used herein refer to or describe a molecule which is capable of, directly or indirectly, substantially inducing, promoting or enhancing HGF biological activity or HGF receptor activation.

The terms "treating," "treatment," and "therapy" as used herein refer to curative therapy, prophylactic therapy, and preventative therapy.

The term "mammal" as used herein refers to any mammal classified as a mammal, including humans, cows, horses, dogs and cats. In a preferred embodiment of the invention, the mammal is a human.

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

A "pharmaceutically-acceptable derivative" denotes any salt, ester of a compound of this invention, or any other compound which upon administration to a patient is capable of providing (directly or indirectly) a compound of this invention, or a metabolite or residue thereof, characterized by the ability to inhibit angiogenesis.

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

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

Where the term "alkyl" is used, either alone or within other terms such as "haloalkyl" and "alkylamino", it embraces linear or branched radicals having one to about twelve carbon

atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, isoamyl, hexyl and the like. Even more preferred are lower alkyl radicals having one or two carbon atoms. The term "alkylenyl" embraces bridging divalent alkyl radicals such as methylenyl and ethylenyl. The term "lower alkyl substituted with R²" does not include an acetal moiety.

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

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

Alkyl, alkylenyl, alkenyl, and alkynyl radicals may be optionally substituted with one or more functional groups such as halo, hydroxy, nitro, amino, cyano, haloalkyl, aryl, heteroaryl, heterocyclo and the like.

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

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

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

The term "alkoxy" embraces linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and *tert*-butoxy. Even more preferred are lower alkoxy radicals having one to three carbon atoms. Alkoxy radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy" radicals. Even more preferred are lower haloalkoxy radicals having one to three carbon atoms. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy.

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

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

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

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

The term heterocyclyl, (or heterocyclo) also embraces radicals where heterocyclic radicals are fused/condensed with aryl radicals: unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo [1,5-b]pyridazinyl]; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl]; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl]; and saturated, partially unsaturated and unsaturated condensed heterocyclic group containing 1 to 2 oxygen or sulfur atoms [e.g. benzofuryl, benzothienyl, 2,3-dihydro-benzo[1,4]dioxinyl and dihydrobenzofuryl].

The term "heteroaryl" denotes aryl ring systems that contain one or more heteroatoms selected from the group O, N and S, wherein the ring nitrogen and sulfur atom(s) are optionally oxidized, and nitrogen atom(s) are optionally quarternized. Examples include unsaturated 5 to 6 membered heteromonocyclyl group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl]; unsaturated 5- to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, 2-furyl, 3-furyl, etc.; unsaturated 5 to 6-membered heteromonocyclic group containing a sulfur atom, for example, 2-thienyl, 3-thienyl, etc.; unsaturated 5- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl]; unsaturated 5 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl].

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

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

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

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

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

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

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

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

The terms "heterocyclalkylenyl" and "heterocyclalkyl" embrace heterocyclic-substituted alkyl radicals. More preferred heterocyclalkyl radicals are "5- or 6-membered heteroarylalkyl" radicals having alkyl portions of one to six carbon atoms and a 5- or 6-membered heteroaryl radical. Even more preferred are lower heteroarylalkylenyl radicals having alkyl portions of one to three carbon atoms. Examples include such radicals as pyridylmethyl and thienylmethyl.

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

The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. Even more preferred are lower

alkylthio radicals having one to three carbon atoms. An example of "alkylthio" is methylthio, (CH₃S-).

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

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

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

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

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

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

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

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

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

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

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

The term "carboxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more carboxy radicals. More preferred carboxyalkyl radicals are "lower carboxyalkyl" radicals having one to six carbon atoms and one carboxy radical. Examples of such radicals include carboxymethyl, carboxypropyl, and the like. Even more preferred are lower carboxyalkyl radicals having one to three CH₂ groups.

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

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

The term "aralkylthio" embraces aralkyl radicals as described above, attached to a divalent sulfur atom. More preferred are phenyl-C₁-C₃-alkylthio radicals. An example of "aralkylthio" is benzylthio.

The term "aryloxy" embraces optionally substituted aryl radicals, as defined above, attached to an oxygen atom. Examples of such radicals include phenoxy.

The term "aralkoxy" embraces oxy-containing aralkyl radicals attached through an oxygen atom to other radicals. More preferred aralkoxy radicals are "lower aralkoxy" radicals

having optionally substituted phenyl radicals attached to lower alkoxy radical as described above.

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

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

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

The term "cycloalkylalkyl" embraces cycloalkyl-substituted alkyl radicals. Preferable cycloalkylalkyl radicals are "lower cycloalkylalkyl" radicals having cycloalkyl radicals attached to alkyl radicals having one to six carbon atoms. Even more preferred are "5-6-membered cycloalkylalkyl" attached to alkyl portions having one to three carbon atoms. Examples of such radicals include cyclohexylmethyl. The cycloalkyl in said radicals may be additionally substituted with halo, alkyl, alkoxy and hydroxy.

The term "cycloalkenyl" includes carbocyclic groups having one or more carbon-carbon double bonds including "cycloalkyldienyl" compounds. Preferred cycloalkenyl groups include C₃-C₆ rings. More preferred compounds include, for example, cyclopentenyl, cyclopentadienyl, cyclohexenyl and cycloheptadienyl.

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

The term(s) "Formulas I, II, III, IV, V, VI and VII" either alone or in combination includes any sub formulas.

The compounds of the invention are endowed with c-Met inhibitory activity.

The present invention also comprises the use of a compound of the invention, or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment either acutely or chronically of an angiogenesis mediated disease state, including those described previously. The compounds of the present invention are useful in the manufacture of an anti-cancer medicament. The compounds of the present invention are also useful in the manufacture of a medicament to attenuate or prevent disorders through inhibition of c-Met.

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

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

COMBINATIONS

While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more compounds of the invention or other agents. When administered as a combination, the therapeutic agents can be formulated as separate compositions that are administered at the same time or sequentially at different times, or the therapeutic agents can be given as a single composition.

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

Specifically, the administration of compounds of the present invention may be in conjunction with additional therapies known to those skilled in the art in the prevention or treatment of inflammatory disorders.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the accepted dosage ranges.

Also included in the family of compounds of the current are the pharmaceutically acceptable salts and solvates thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically acceptable. Suitable pharmaceutically acceptable acid addition salts of compounds of the current invention may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, arylaliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, adipic, butyric, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic,

mesylic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, ethanedisulfonic, benzenesulfonic, pantothenic, 2-hydroxyethanesulfonic, toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, camphoric, camphorsulfonic, digluconic, cyclopentanepropionic, dodecylsulfonic, glucoheptanoic, glycerophosphonic, heptanoic, hexanoic, 2-hydroxy-ethanesulfonic, nicotinic, 2-naphthalenesulfonic, oxalic, palmoic, pectinic, persulfuric, 2-phenylpropionic, picric, pivalic propionic, succinic, tartaric, thiocyanic, mesylic, undecanoic, stearic, algenic, β -hydroxybutyric, salicylic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of the current invention include metallic salts, such as salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc, or salts made from organic bases including primary, secondary and *tertiary* amines, substituted amines including cyclic amines, such as caffeine, arginine, diethylamine, N-ethyl piperidine, histidine, glucamine, isopropylamine, lysine, morpholine, N-ethyl morpholine, piperazine, piperidine, triethylamine, trimethylamine. All of these salts may be prepared by conventional means from the corresponding compound of the invention by reacting, for example, the appropriate acid or base with the compound of the current invention. When a basic group and an acid group are present in the same molecule, a compound of the current invention may also form internal salts.

GENERAL SYNTHETIC PROCEDURES

The following is a key of abbreviations which may appear in the specification:

HOAc	-	acetic acid
MeCN, CH ₃ CN	-	acetonitrile
NH ₃	-	ammonia
NH ₄ Cl	-	ammonium chloride
Ar	-	argon
HBTA	-	O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate
HATU	-	O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
PyBop	-	benzotriazol-1-yl-oxy-tripyrrolidino-phosphonium hexafluorophosphate
Pd ₂ (dba) ₃	-	bis(dibenzylideneacetone) palladium
BINAP	-	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
TEAC	-	bis(tetra-ethylammonium)carbonate
BBr ₃	-	boron tribromide

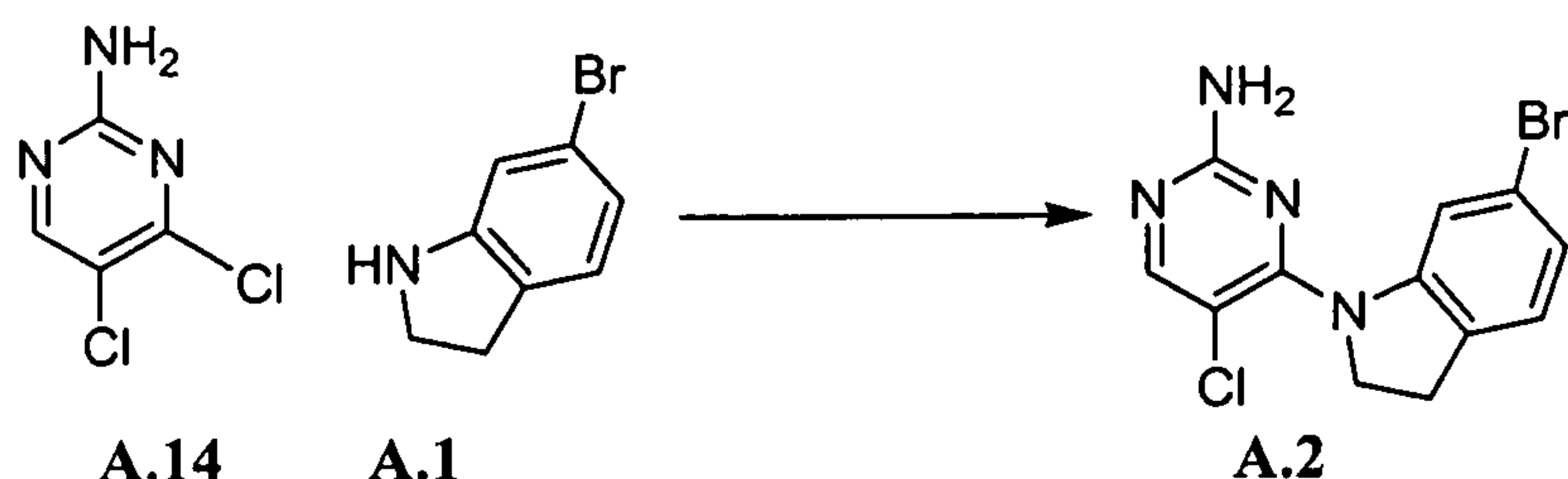
BSA	-	bovine serum albumin
Br ₂	-	bromine
BOC	-	butyloxycarbonyl
Cs ₂ CO ₃	-	cesium carbonate
CHCl ₃	-	chloroform
CDCl ₃	-	chloroform deuterated
Cu	-	copper
CuI	-	copper(I) iodide
Et ₂ O	-	diethyl ether
DBU	-	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL	-	diisobutylaluminum hydride
DIAD	-	diisopropyl azodicarboxylate
DIEA	-	diisopropylethylamine
DMF	-	dimethylformamide
DMAP	-	4-dimethylaminopyridine
DMSO	-	dimethylsulfoxide
EDC, EDCI	-	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
dppa	-	diphenylphosphoryl azide
EtOAc	-	ethyl acetate
FBS	-	fetal bovine serum
g	-	gram
h	-	hour
HBr	-	hydrobromic acid
HCl	-	hydrochloric acid
HOBt	-	1-hydroxybenzotriazole hydrate
H ₂	-	hydrogen
H ₂ O ₂	-	hydrogen peroxide
Fe	-	iron
LiHMDS	-	lithium bis(trimethylsilyl)-amide
LDA	-	Lithium diisopropylamide
MCPBA	-	<i>meta</i> -chloroperbenzoic acid
MgSO ₄	-	magnesium sulfate
MeOH, CH ₃ OH	-	methanol
MeI	-	methyl iodide

CH ₂ Cl ₂ , DCM	-	methylene chloride
NMP	-	N-methylpyrrolidinone
ML, ml	-	milliliter
N ₂	-	nitrogen
Pd/C	-	palladium on carbon
Pd(OAc) ₂	-	palladium acetate
Pd(OH) ₂	-	palladium hydroxide
Pd(PPh ₃) ₄	-	palladium tetrakis triphenylphosphine
Pd(dppf)Cl ₂	-	1,1-bis(diphenylphosphino)ferrocene palladium chloride
PBS	-	phosphate buffered saline
POCl ₃	-	phosphorous oxychloride
K ₂ CO ₃	-	potassium carbonate
KOH	-	potassium hydroxide
RT	-	room temperature
NaHCO ₃	-	sodium bicarbonate
NaBH ₄	-	sodium borohydride
NaBH ₃ CN	-	sodium cyanoborohydride
NaOtBu	-	sodium <i>tert</i> -butoxide
NaOH	-	sodium hydroxide
NaClO ₂	-	sodium chlorite
NaCl	-	sodium chloride
NaHPO ₄	-	sodium biphospate
NaH	-	sodium hydride
NaI	-	sodium iodide
Na ₂ SO ₄	-	sodium sulfate
TBTU	-	O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate
THF	-	tetrahydrofuran
Et ₃ N, TEA	-	triethylamine
TFA	-	trifluoroacetic acid
P(<i>t</i> -bu) ₃	-	tri(<i>tert</i> -butyl)phosphine
H ₂ O	-	water

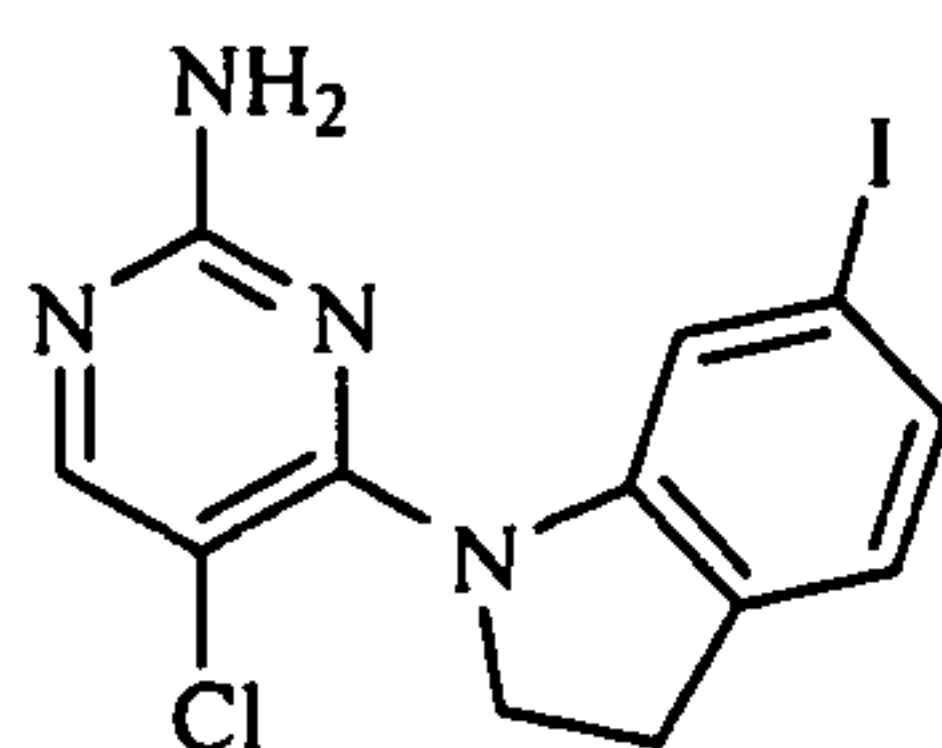
Compounds of the current invention may be synthesized according to the schemes illustrated in the following working examples, as well as through the schemes illustrated in the General Schemes Sections, and other methods known to those of skill in the art.

GENERAL SCHEMES—SECTION A

Building blocks and precursors.

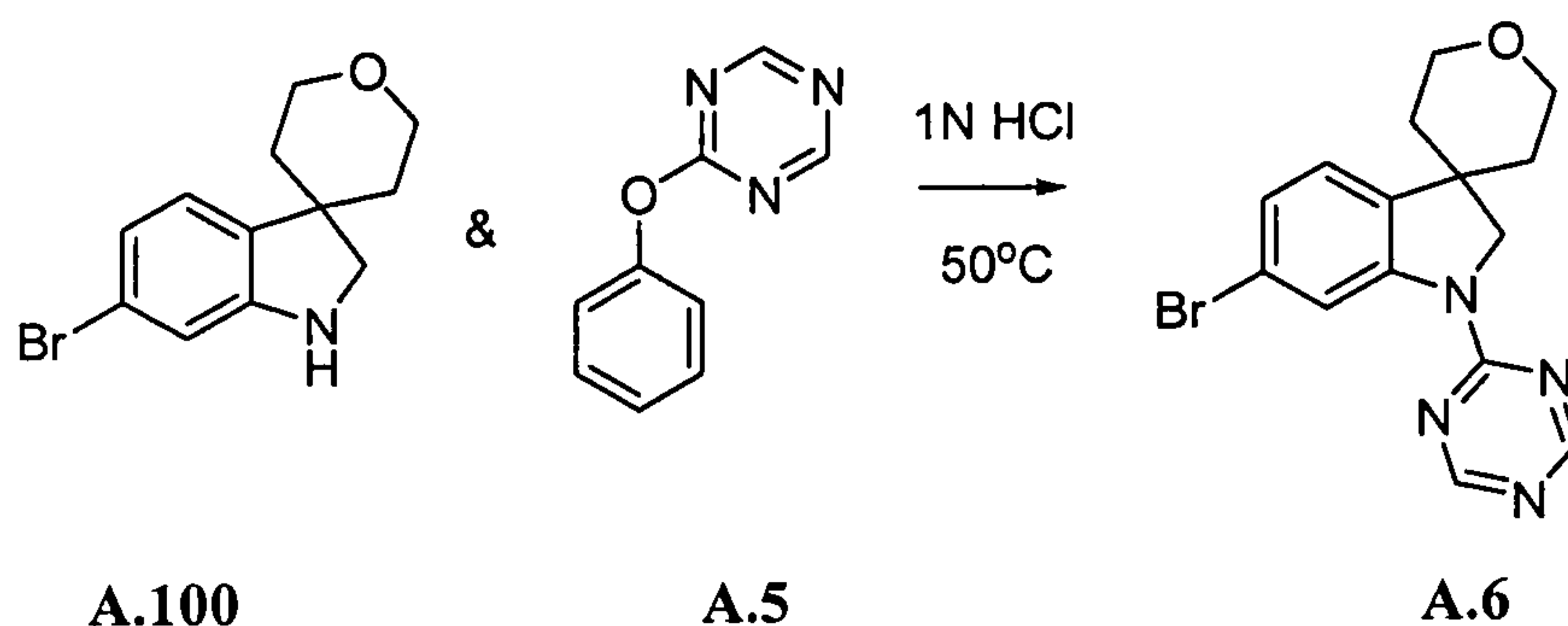


4-(6-bromoindolin-1-yl)-5-chloropyrimidin-2-amine (A.2). To a stirred solution of 4,5-dichloropyrimidin-2-amine(A.14) (1.8 g, 11 mmol) and 6-bromoindoline (A.1)(2.18 g, 1 eq) in dioxane (25 mL) was added HCl (1.25 M in EtOH, 11.4 mL) and the mixture was heated to 90 °C for 18 hrs. The reaction cooled to room temp and the solvent evaporated. The residue was suspended in 50 mL NH₄OH, and the precipitate was collected by filtration. Purification by flash chromatography on silica (10% 89:9:1 dichloromethane-methanol-NH₄OH in dichloromethane) yielded 1.86 g 4-(6-bromoindolin-1-yl)-5-chloropyrimidin-2-amine (A.2). ¹H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 8.07 (1 H, s), 7.69 (1 H, s), 7.09 (1 H, dd, *J*=8.0, 2.0 Hz), 7.07 (1 H, d, *J*=8.0 Hz), 5.08 (2 H, s), 4.35 (2 H, t, *J*=8.3 Hz), 3.11 (2 H, t, *J*=8.3 Hz) Mass Spectrum (ESI) *m/e* = 325.5 and 327.0 (*M*+1).

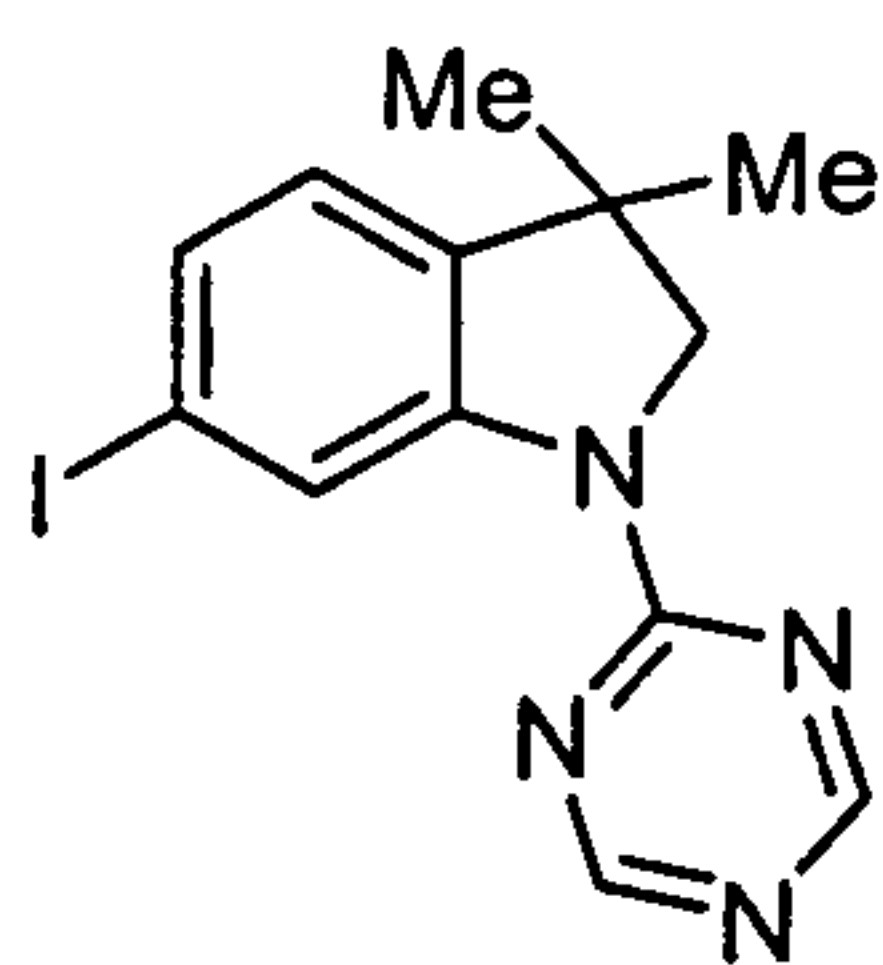


A.3

5-chloro-4-(6-iodoindolin-1-yl)pyrimidin-2-amine A.3 4-(6-bromoindolin-1-yl)-5-chloropyrimidin-2-amine **A.2** (1.25 g, 3.8 mmol), CuI (0.438 g, 2.3 mmol) and NaI (1.14 g, 7.6 mmol) were added to a Schlenk tube, evacuated and backfilled with argon. Under positive pressure of argon, the screw cap was replaced with a septum. N,N'-dimethylethylenediamine (0.41 mL, 3.8 mmol) in dioxane (5 mL) was added via syringe, and the screwcap was returned under positive pressure of argon. The reaction was sealed and heated to 110 °C with stirring for 20 hours. The mixture was cooled to room temperature, diluted with 15 mL 5% aq. NH₃, and poured into 100 mL water. The solution was extracted with dichloromethane and the combined extracts were dried over MgSO₄, filtered and evaporated. Purification by flash chromatography (30% ethyl acetate in hexane) gave 0.86 g 5-chloro-4-(6-iodoindolin-1-yl)pyrimidin-2-amine **A.3**. Mass Spectrum (ESI) m/e = 373.0 (M+1)



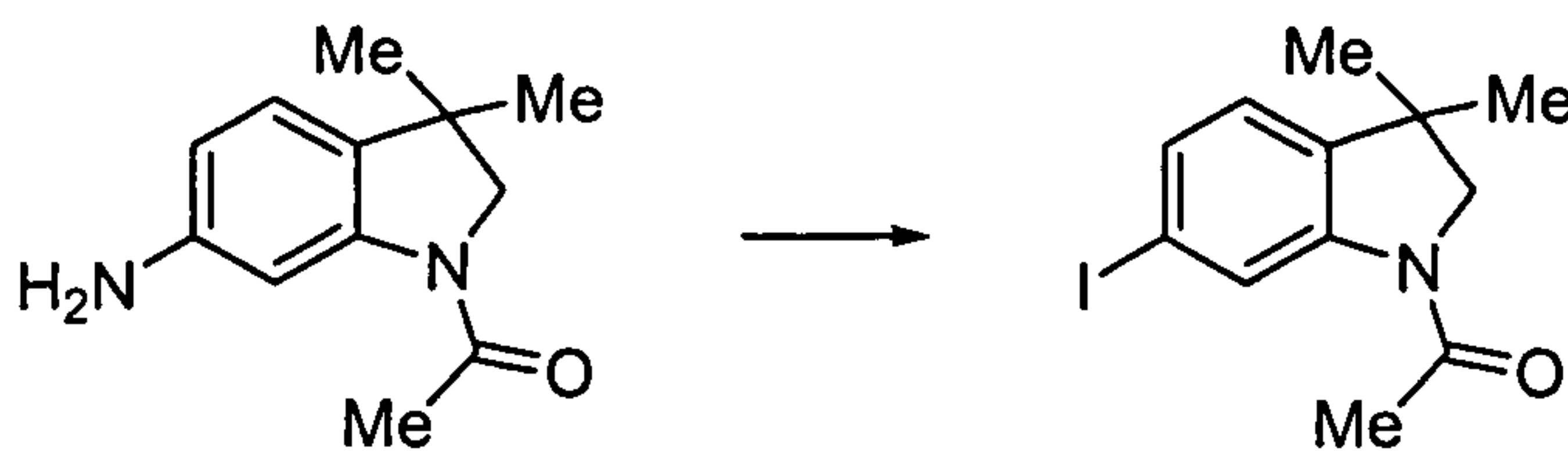
6-bromo-1-(1,3,5-triazin-2-yl)-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-pyran] A.6
 6-bromo-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-pyran] (177mg, 0.660 mmol) **A.100**, and 2-phenoxy-1,3,5-triazine **A.5** (171mg, 0.990 mmol) (R. Hirt, H. Nidecker, et al. (1950). *Helvetica Chimica Acta* 33(5): 1365-1369.), were added to a solution of isopropanol (5ml) and 1N HCl (1ml). The solution was heated to 50°C for 1hr before being cooled to room temperature. After diluting the solution with saturated NaHCO₃ it was extracted with ethyl acetate. The organics were dried over MgSO₄ before being concentrated under vacuum. The residue obtained was enriched by chromatography on silica eluting with 0.5% triethylamine/ 5%methanol/ dichloromethane. The fractions containing the product were combined and concentrated under vacuum. The residue obtained was diluted with ethyl acetate and washed with water. The organics were dried over MgSO₄ and then concentrated under vacuum. 6-bromo-1-(1,3,5-triazin-2-yl)-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-pyran] **A.6** (170mg) was obtained as a brownish solid.



A.7

6-iodo-3,3-dimethyl-1-(1,3,5-triazin-2-yl)-2,3-dihydro-1H-indole A.7 was synthesized from **A.10** by the procedure used to prepare **A.6**; the title compound was obtained as a brownish solid (117mg).

ESI-MS: $M + H^+$ 352.9 m/z.



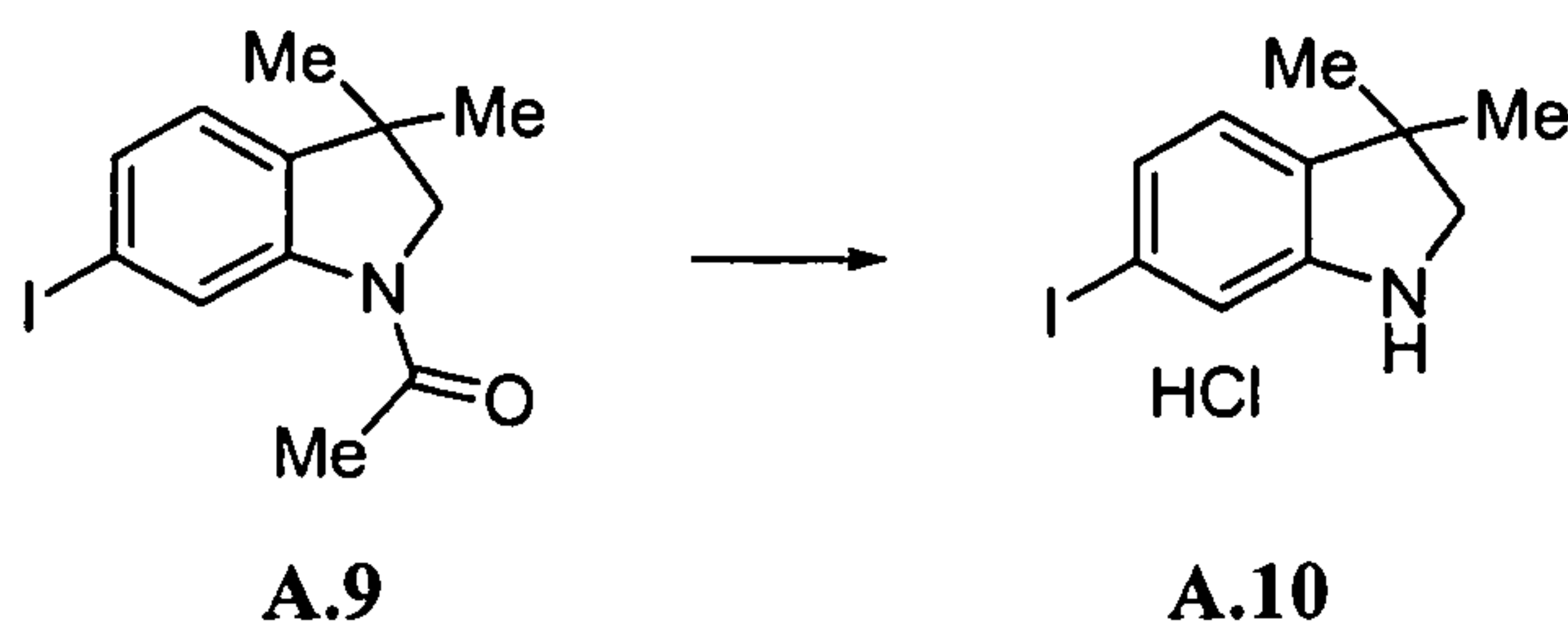
A.8

A.9

1-acetyl-6-iodo-3,3-dimethyl-2,3-dihydro-1H-indole A.9

In a 500ml three-necked round bottom flask equipped with an overhead stirrer, was combined 1-acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-amine **A.8** (6.98g, 34.22 mmol) [Chen, G., J. Adams, et al. WO 2002066470 p263] with 30ml of ice/water. The solution was cooled in an ice bath before concentrated HCl (6.8ml, 81.60 mmol) was added. A solution of NaNO₂ (2.48g, 35.93 mmol) dissolved in 30ml of water was added drop wise over a period of 10 minutes. After 30minutes a solution of KI (11.36g, 68.44 mmol) dissolved in 70ml of chloroform was added via an addition funnel over a period of 0.5hr. Then the brownish solution was stirred at room temperature until gas evolution ceased. Partitioned the solution in a separation funnel, and washed the organic layer with saturated NaHCO₃, followed by 5% Na₂S₂O₃. The organics were dried over MgSO₄ before being concentrated under vacuum to 1/10th the volume. Purified the residue obtained by chromatography on silica eluting with 20% hexane/dichloromethane. The fractions containing the product were combined and concentrated under vacuum to give 1-acetyl-6-iodo-3,3-dimethyl-2,3-dihydro-1H-indole **A.9** (6.95g, 65%) as a tan colored solid.

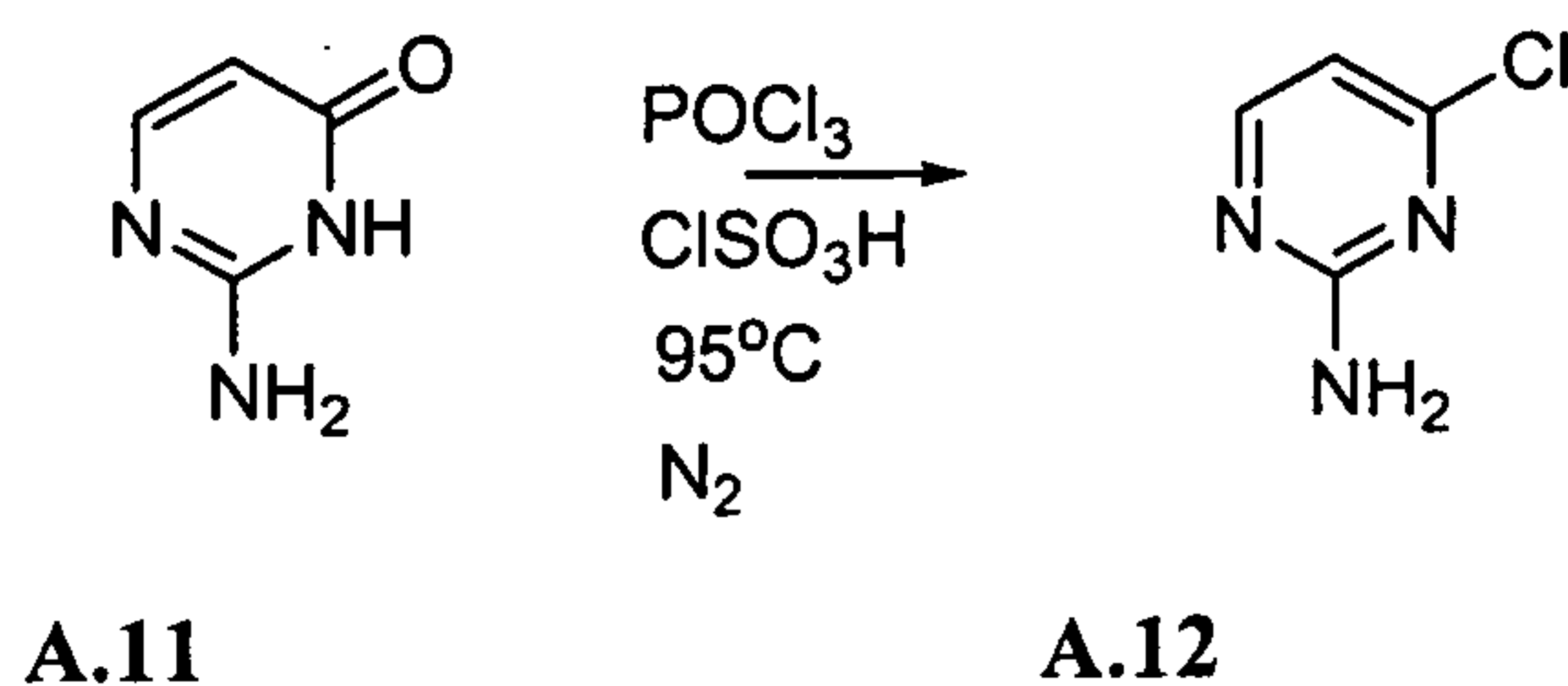
¹H NMR (500 MHz, (CD)₃SO) δ 8.39 (s, 1H), 7.37 (d, J = 7.8Hz, 1H), 7.08 (d, J = 7.8Hz, 1H), 3.85 (s, 2H), 2.16 (s, 3H), 1.29 (s, 6H); ESI MS: $M + H^+$ 316.0 m/z.



6-iodo-3,3-dimethyl-2,3-dihydro-1H-indole HCl A.10

1-acetyl-6-iodo-3,3-dimethyl-2,3-dihydro-1H-indole A.9 (6.95g, 22.08 mmol) was combined with methanol and concentrated HCl (25ml, 300 mmol). The solution was heated at a gentle reflux for 1hr before it was cooled to room temperature. After cooling the solution to 0°C a white solid was collected by filtration to afford 6-iodo-3,3-dimethyl-2,3-dihydro-1H-indole A.10 as the HCl salt (5.96g, 86%).

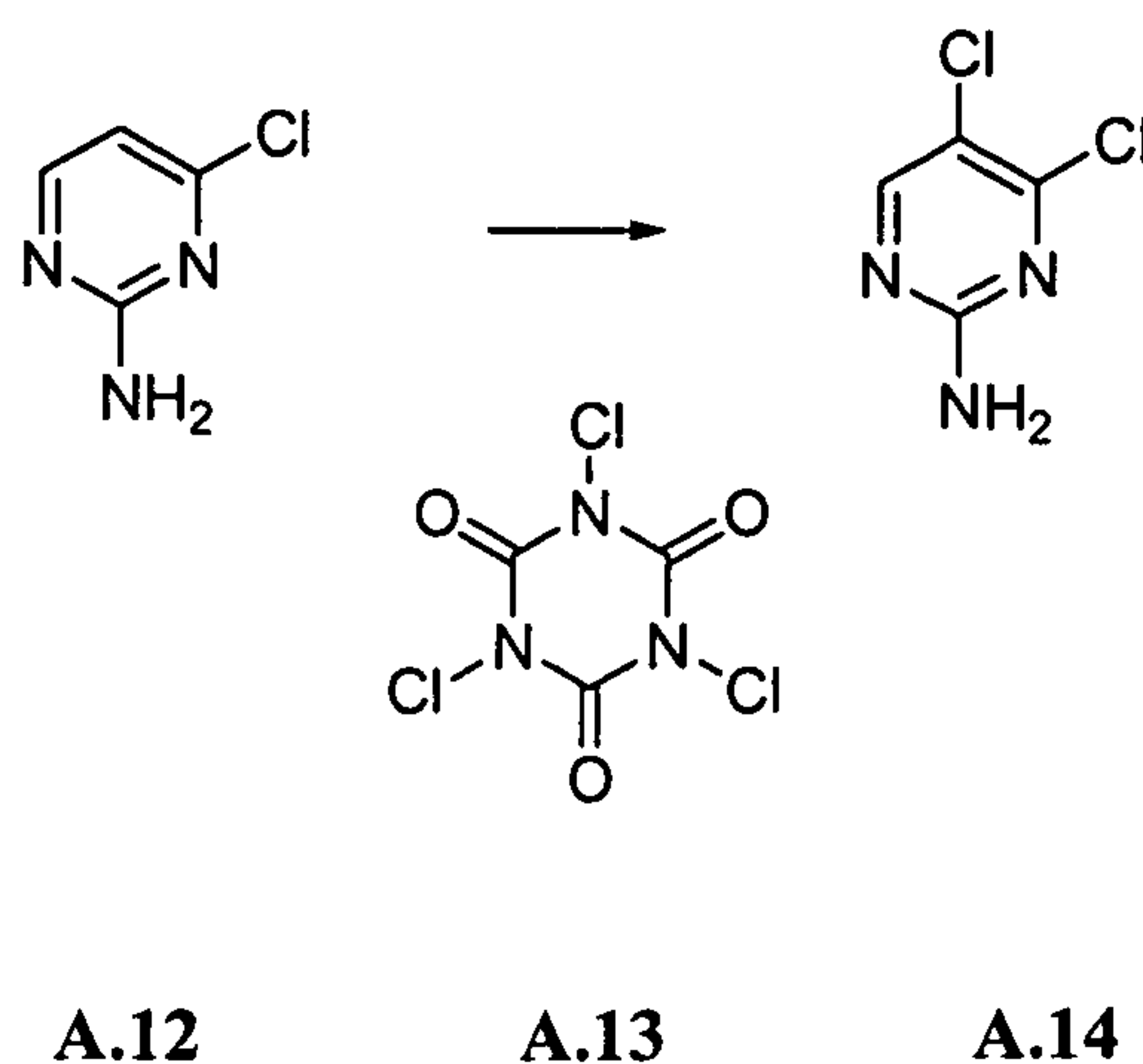
ESI MS: $M + H^+$ 274.0 m/z.



4-chloro-2-pyrimidinamine A.12

In a three neck 1L round bottom flask equipped with reflux condenser was added 2-amino-4(3H)-pyrimidinone A.11 (100g, 0.9 mol) (available from Toronto Research Chemicals) followed by POCl₃ (168 ml, 1.800mol) at room temperature and under an atmosphere of N₂. To this was cautiously added ClSO₃H (4.8ml, 72.01 mmol). The solution was heated to 95°C for 4 hrs, before it was cooled to room temperature. The solution was then cooled in an ice bath before it was poured into 700ml of ice water with vigorous stirring. Adjusted the pH to ~7 with NH₄OH (30% by weight) (temperature was held below 20°C). A tan colored solid was collected by filtration. The solid was dried under vacuum at 70°C overnight to afford 4-chloro-2-pyrimidinamine A.12 (108g, 92%) as an off white solid.

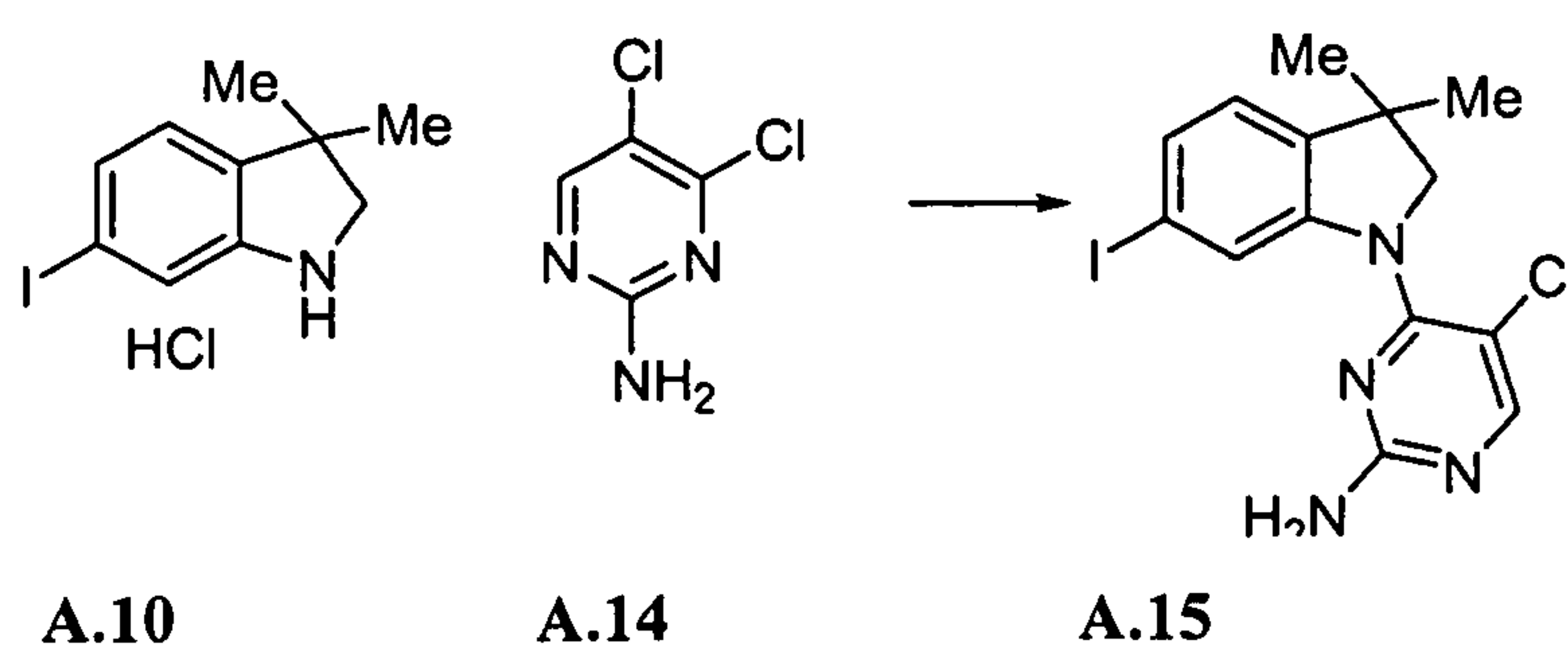
¹H NMR (400 MHz, (CD)₃SO) δ 8.17 (d, J = 5.2 Hz, 1H), 7.07 (br s, 2H), 6.64 (d, J = 5.2 Hz, 1H); ESI MS: $M + H^+$ 130.0 m/z.



4,5-dichloro-2-pyrimidinamine A.14

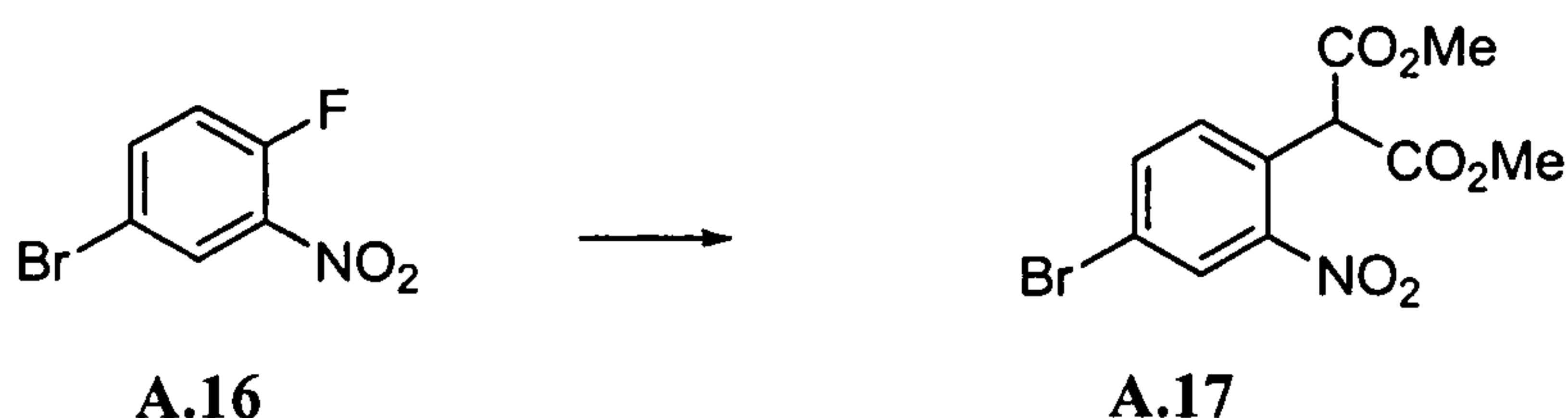
4-chloro-2-pyrimidinamine (50g, 450 mmol) A.12 was combined with trichloroisocyanuric acid A.13 (52g, 225 mmol) in 450ml of water, and 50 ml of acetic acid. The reaction was heated to 50°C with stirring for 20hrs. The solution was then cooled to room temperature before it was transferred into a 4L beaker. The pH of the solution was adjusted to ~6 with 10N NaOH (the temperature was held below 20°C by adding ice). The pH was then adjusted to ~7-8 with NaHCO₃. After stirring the solution for 4hrs a pink solid was filtered off and washed with water. The pink solid was added to 1L of water and stirred at room temperature for 1hr. The solid was collected by filtration, washed with water and dried under vacuum at 60°C to give 4,5-dichloro-2-pyrimidinamine A.14 (48g).

¹H NMR (500 MHz, (CD)₃SO) δ 8.37 (s, 1H), 7.33 (br s, 2H); ESI MS: M + H⁺ 164.9 m/z.



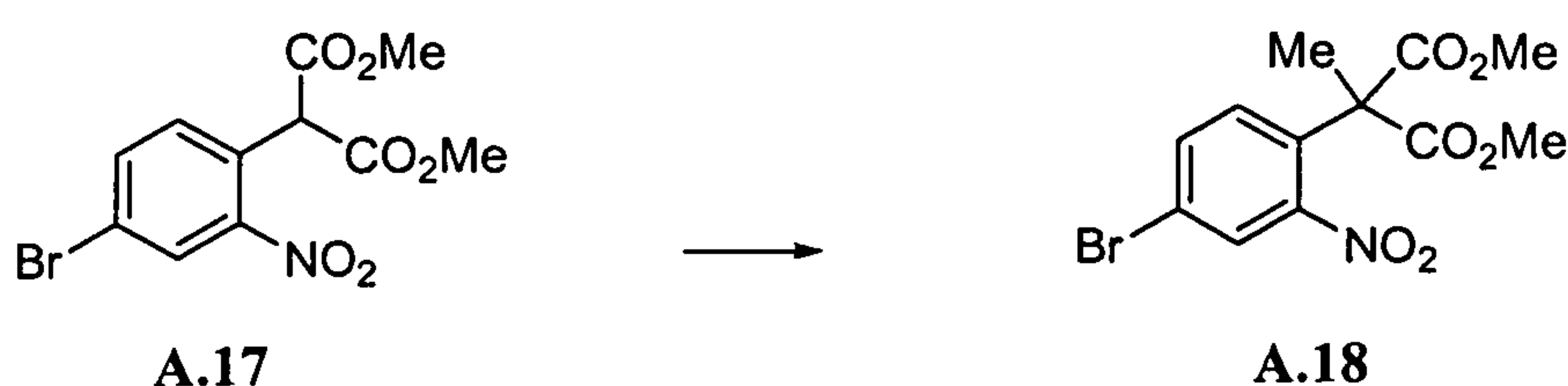
5-chloro-4-(6-iodo-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-2-pyrimidinamine A.15 This compound was prepared from A.10 and A.14 by the procedure used to prepare A.2

^1H NMR (500 MHz, (DMSO- d_6) δ 8.12 (s, 1H), 7.52 (d, $J = 1.5\text{Hz}$, 1H), 7.27 (dd, $J = 7.9\text{Hz}$, $J = 1.5\text{Hz}$, 1H), 7.03 (d, $J = 7.8\text{Hz}$, 1H), 6.69 (br s, 2H), 3.91 (s, 2H), 1.27 (s, 6H); ESI MS: $M + \text{H}^+$ 401.2 m/z.



Dimethyl 2-(4-bromo-2-nitrophenyl)malonate A.17 was prepared by the method of Quallich, G. J. and P. M. Morrissey (1993). *Synthesis* 51-53.

To a stirred ice-cooled solution of dimethyl malonate (44.12 g, 1.5 eq.) in dry DMF (200 mL) was added K_2CO_3 powder (90.5 g, 3 eq.) followed by 4-bromo-1-fluoro-2-nitrobenzene **A.16** (47.5 g, 218.2 mmol) through a syringe. The resulting mixture was stirred at ambient temperature for 24 h and then poured into ice and 2 N HCl aqueous solution. More aqueous 2 N HCl was added until the precipitation was complete. The precipitate was then collected by vacuum filtration, washed thoroughly with water and air-dried to give dimethyl 2-(4-bromo-2-nitrophenyl)malonate **A.17** in nearly quantitative yield. ^1H NMR (400 MHz, DMSO- d_6) δ 8.32 (d, $J = 2.0\text{Hz}$, 1H), 8.02 (dd, $J = 8.5, 2.0\text{Hz}$, 1H), 7.52 (d, $J = 8.5\text{Hz}$, 1H), 5.50 (s, 1H), 3.71 (s, 6H). LCMS-ESI (POS), M/Z , $M+1$: Found 331.9 and 334.0.

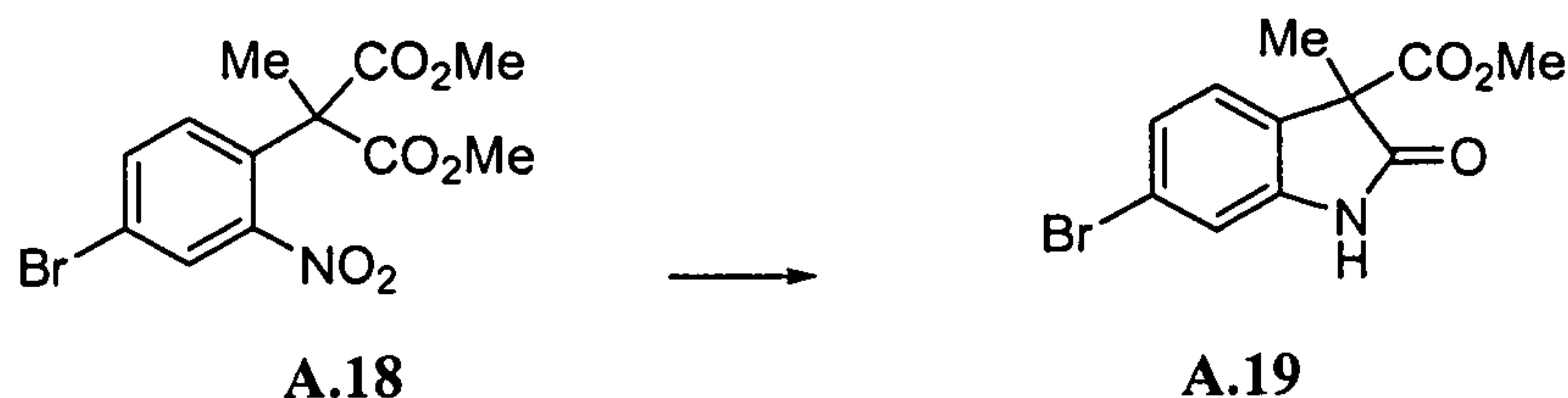


dimethyl (4-bromo-2-nitrophenyl)(methyl)propanedioate A.18

To a solution of dimethyl 2-(4-bromo-2-nitrophenyl)malonate **A.17** (70g, 210mmol) in 300ml of anhydrous DMF at 0°C was added K_2CO_3 (32g, 231.85mmol) under an atmosphere of nitrogen. The solution was stirred for 10minutes before adding MeI (13.41ml, 241.99mmol) over a period of 0.5hr. The solution was then allowed to slowly warm to room temperature. Stirred the solution at room temperature for 2 days before it was poured into ice cold saturated NH_4Cl (1.5L). A yellow solid was filtered off and washed with water. The yellowish solid was dissolved in ethyl acetate and transferred to a separation funnel. The organics were

washed with brine and dried over MgSO₄ before they were concentrated under vacuum to give dimethyl (4-bromo-2-nitrophenyl)(methyl)propanedioate **A.18** (71g, 97%) as a light brown solid.

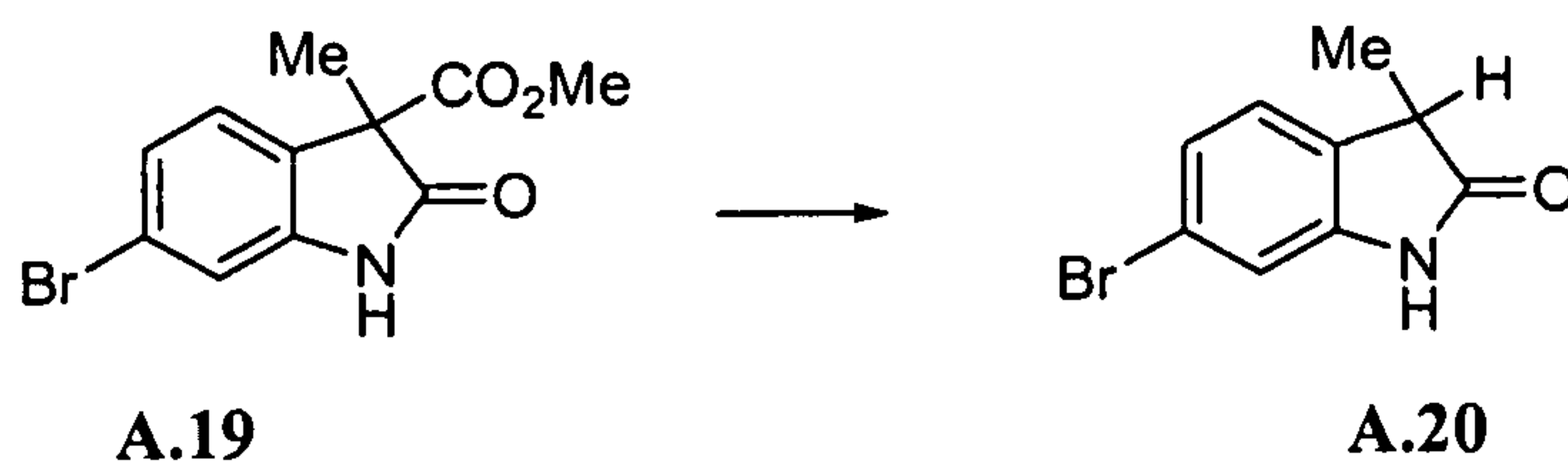
¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 8.27 (1 H, d, *J*=2.4 Hz), 7.96 (1 H, dd, *J*=8.6, 2.2 Hz), 7.42 (1 H, d, *J*=8.3 Hz), 3.66 (6 H, s), 1.88 (3 H, s); RPHPLC @ 8.593 min (95%).



methyl 6-bromo-3-methyl-2-oxo-2,3-dihydro-1H-indole-3-carboxylate A.19

To 450ml of glacial acetic acid was added dimethyl (4-bromo-2-nitrophenyl)(methyl)propanedioate **A.18** (71g, 205mmol) followed by Fe⁰ (34.35g, 615mmol). Heated the solution to 100°C in an oil bath for 1 hour before adding more Fe⁰ (11.45g, 205mmol). The solution was heated at 100°C for 3 hours before it was cooled to room temperature and concentrated under vacuum. The residue obtained was partially dissolved in ethyl acetate and a light brownish solid was filtered off and set aside. The filtrate was transferred to a separation funnel and washed with 1N HCl followed by brine. It was then dried over MgSO₄ and concentrated under vacuum. The solid obtained was triturated with ethyl acetate to give product (3g) as a white solid. The light brownish solid from the filtration was partially dissolved in 1N HCl and stirred at room temperature overnight. It was then transferred to a separation funnel and extracted with dichloromethane. A pale white solid was filtered from the organics and washed with water to give additional product (34g). The filtrate was dried over MgSO₄ and concentrated under vacuum to give a third crop of solid (11.8g). The combined solids were dried under vacuum to give methyl 6-bromo-3-methyl-2-oxo-2,3-dihydro-1H-indole-3-carboxylate **A.19** (48.4g, 83%) as a beige solid.

¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 10.83 (1H, s), 7.18 (2H, br s), 7.39 (1H, m), 3.58 (3H, s), 1.50 (3H, s); ESI-MS: M - 282.0 m/z.



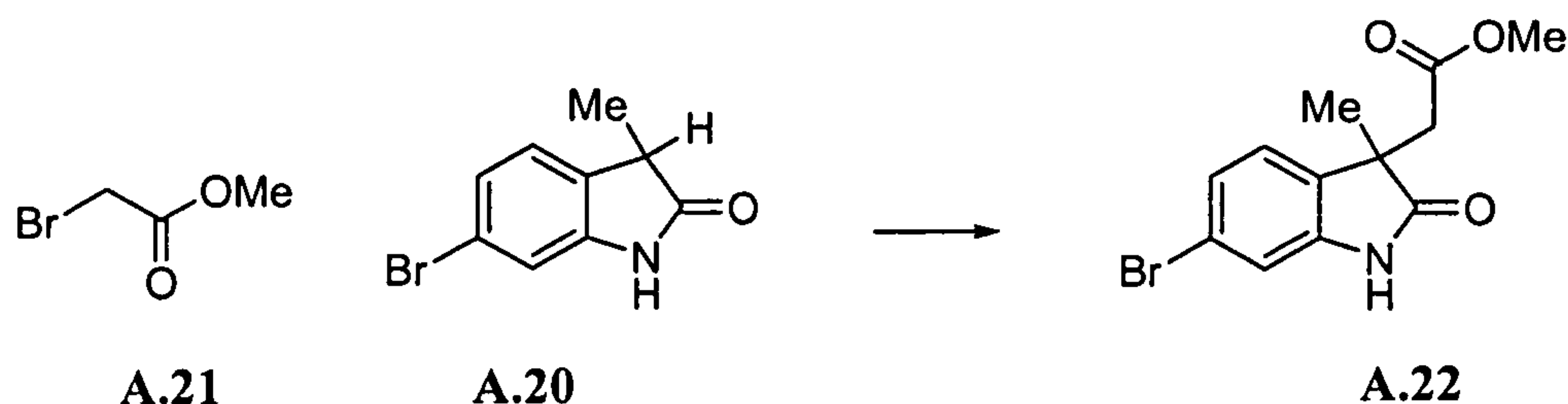
6-bromo-3-methyl-1,3-dihydro-2H-indol-2-one A.20

Methyl 6-bromo-3-methyl-2-oxo-2,3-dihydro-1H-indole-3-carboxylate **A.19** (32.04g, 112.8 mmol) was combined with TFA (100ml) and 30% aqueous H₂SO₄ (30ml). The solution was

heated to 80°C for 6 hours before being cooled to room temperature. After dilution with ice water, a precipitate was collected by filtration and dried under vacuum to give 6-bromo-3-methyl-1,3-dihydro-2H-indol-2-one **A.20** (29.9g) as a pink solid.

¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 10.44 (1 H, s), 7.21 (1 H, d, *J*=7.8 Hz), 7.12 (1 H, d, *J*=7.8 Hz), 6.95 (1 H, br. s.), 3.39 (1 H, q, *J*=7.5 Hz), 1.31 (3 H, d, *J*=7.8 Hz)

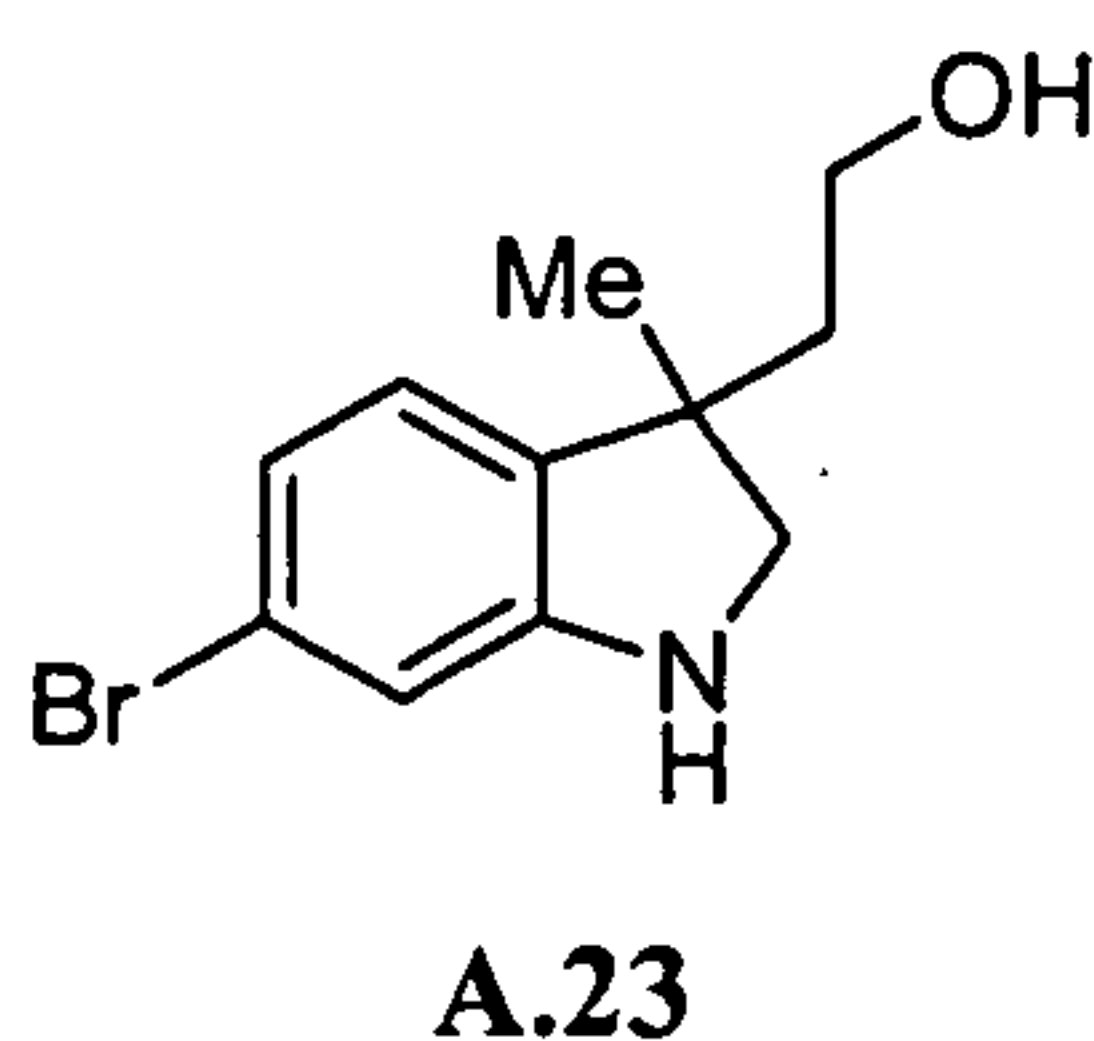
ESI-MS: *M* + *H*⁺ 226.0 *m/z*; RPHPLC @ 7.02min (97%).



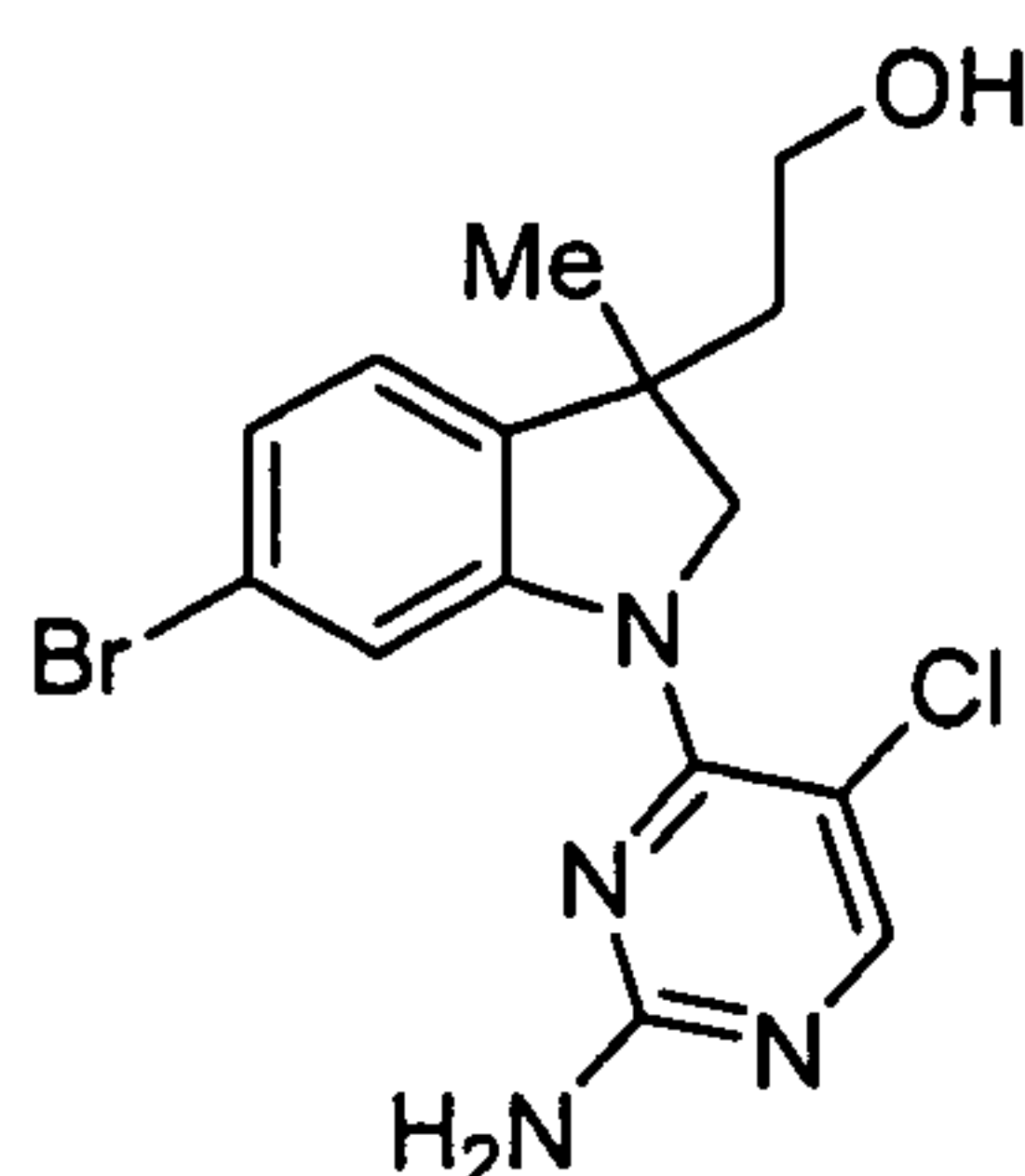
methyl (6-bromo-3-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl)acetate A.22

6-bromo-3-methyl-1,3-dihydro-2H-indol-2-one **A.20** (500mg, 2.21mmol) and Cs₂CO₃ (1.44g, 4.42mmol) were combined in 4ml of DMF. To this was then added methyl bromoacetate **A.21** (203μL, 2.21mmol) and the solution was stirred at room temperature for 2 hours. After diluting the solution with water and adjusting the pH to 2 with 1N HCl, the aqueous layer was and extracted with ethyl acetate. The organics were then concentrated under vacuum. The residue obtained was purified by CombiFlash chromatography eluting with a gradient of dichloromethane to 3% methanol/dichloromethane. The fractions containing the product were combined and concentrated under vacuum to give methyl (6-bromo-3-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl)acetate **A.22** (468mg) as an off white solid.

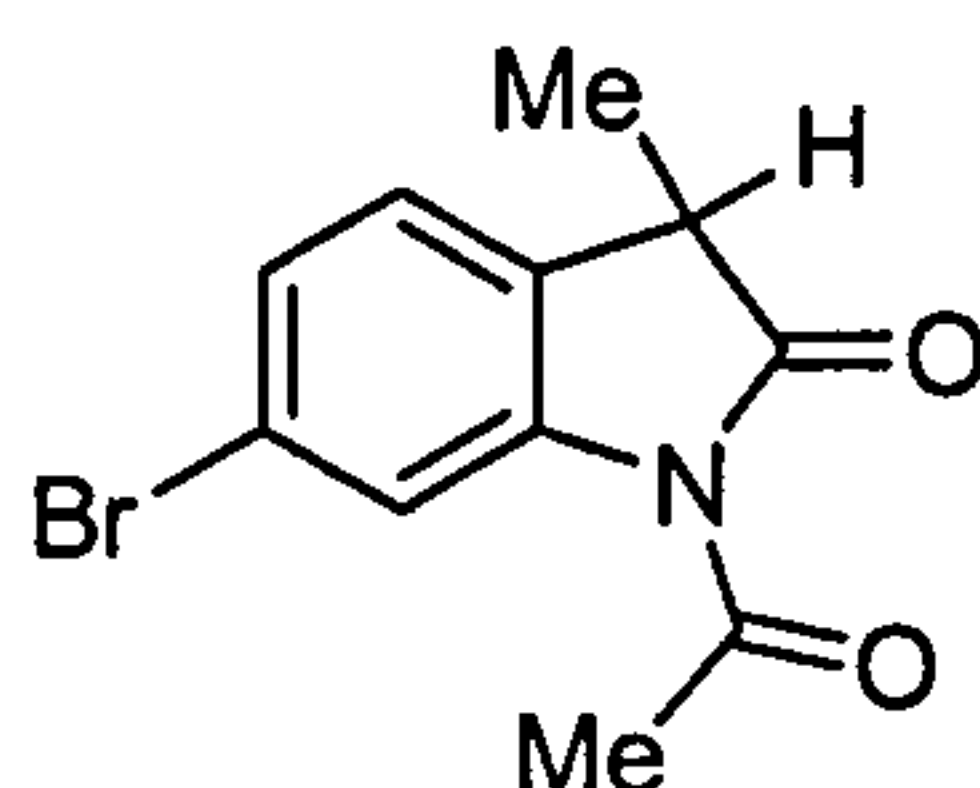
ESI-MS: *M* - 296.0 *m/z*.



2-(6-bromo-3-methyl-2,3-dihydro-1H-indol-3-yl)ethanol A.23 was synthesized by the procedure used to prepare **A.28**; the title compound was obtained as a light brown gum (crude). ESI-MS: *M* + 256.0 *m/z*.

**A.24**

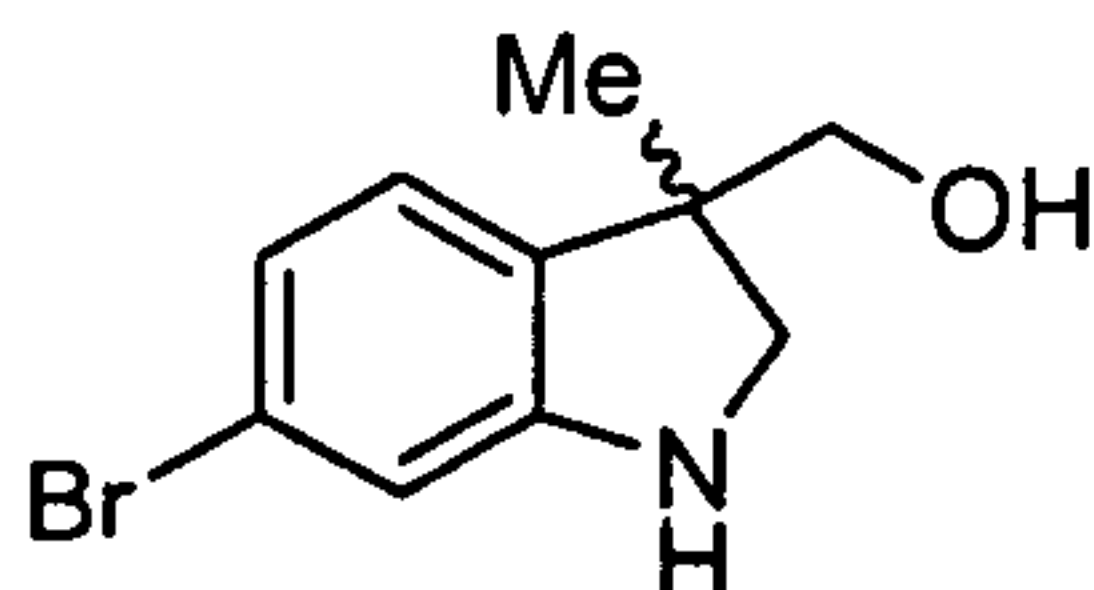
2-(6-bromo-3-methyl-1-(4-pyridinyl)-2,3-dihydro-1H-indol-3-yl)ethanol A.24 was synthesized by the procedure used to prepare A.2. The title compound was obtained as a brownish film (223mg).ESI-MS: M + 283.0 m/z.

**A.26**

1-acetyl-6-bromo-3-methyl-1,3-dihydro-2H-indol-2-one A.26

6-bromo-3-methyl-1,3-dihydro-2H-indol-2-one **A.20** (15g, 66.35mmol) was combined with 70ml of acetic anhydride. The solution was heated at 110°C for 2 days before it was concentrated under vacuum. The oil obtained was diluted with ethyl acetate and washed in succession with saturated NaHCO₃, water, and brine. The organics were dried over MgSO₄ before they were concentrated under vacuum. The residue obtained was heated in EtOH (80ml) to form a clear reddish solution. After cooling to -15°C and standing overnight, a light brown solid was collected by filtration as 1-acetyl-6-bromo-3-methyl-1,3-dihydro-2H-indol-2-one **A.26** (8.8g, 50%) .

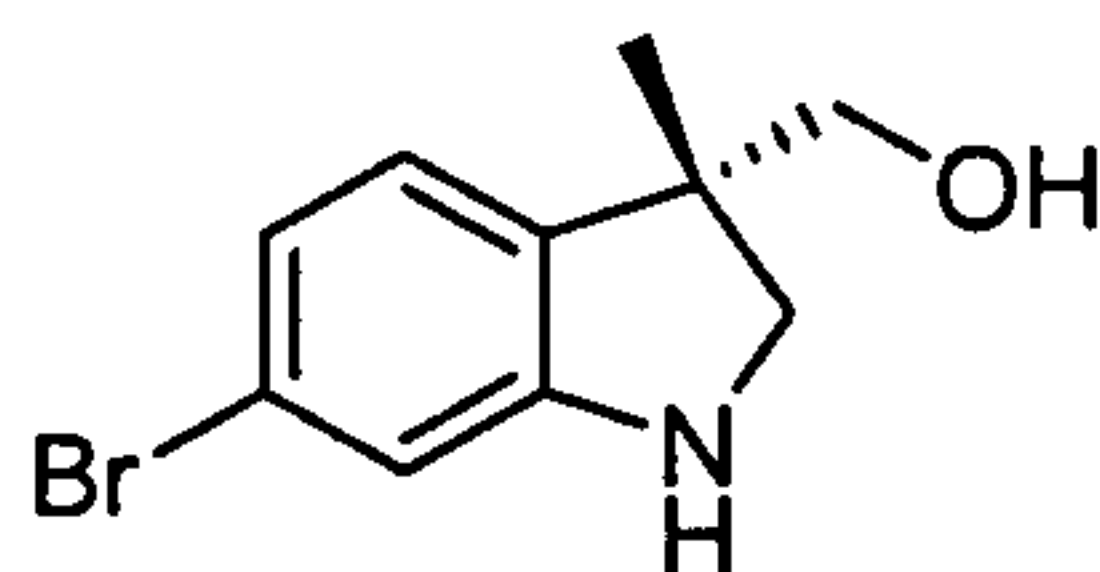
¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.25 (1 H, d, *J*=1.5 Hz), 7.43 (1 H, dd, *J*=7.8, 1.4 Hz), 7.38 (1 H, d, *J*=8.3 Hz), 3.78 (7 H, q, *J*=7.3 Hz), 2.56 (3 H, s), 1.42 (3 H, d, *J*=7.8 Hz).

**A.28**

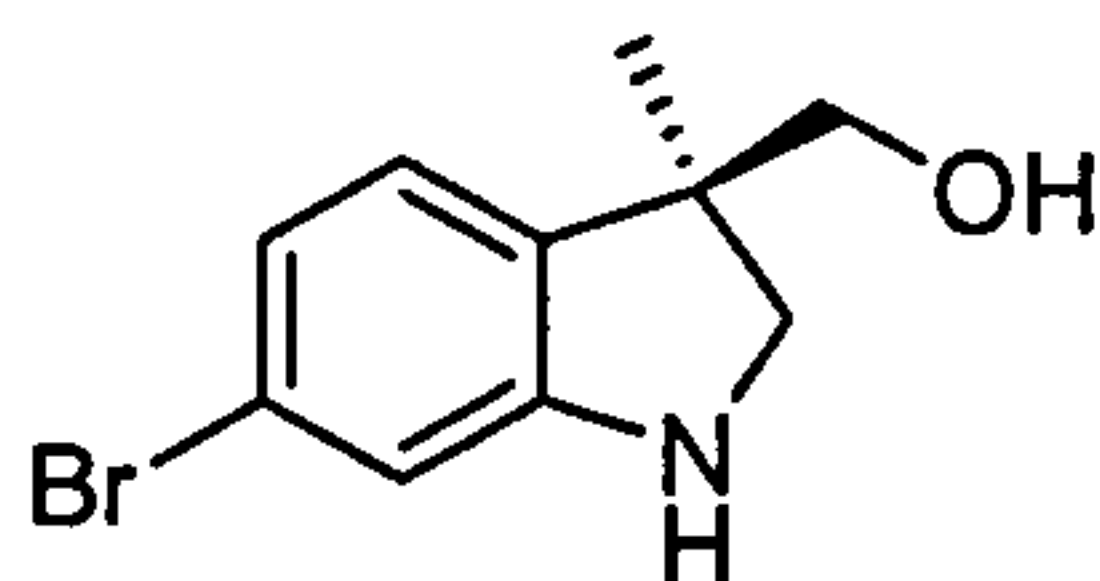
(6-bromo-3-methyl-2,3-dihydro-1H-indol-3-yl)methanol A.28

Under an atmosphere of N₂ a solution of methyl 6-bromo-3-methyl-2-oxo-2,3-dihydro-1H-indole-3-carboxylate **A.19** (5.0g, 17.5mmol) in anhydrous toluene (50ml), and was heated to 85°C. A solution of RedAl (3.4M in toluene)(15ml, 51mmol) was then cautiously added

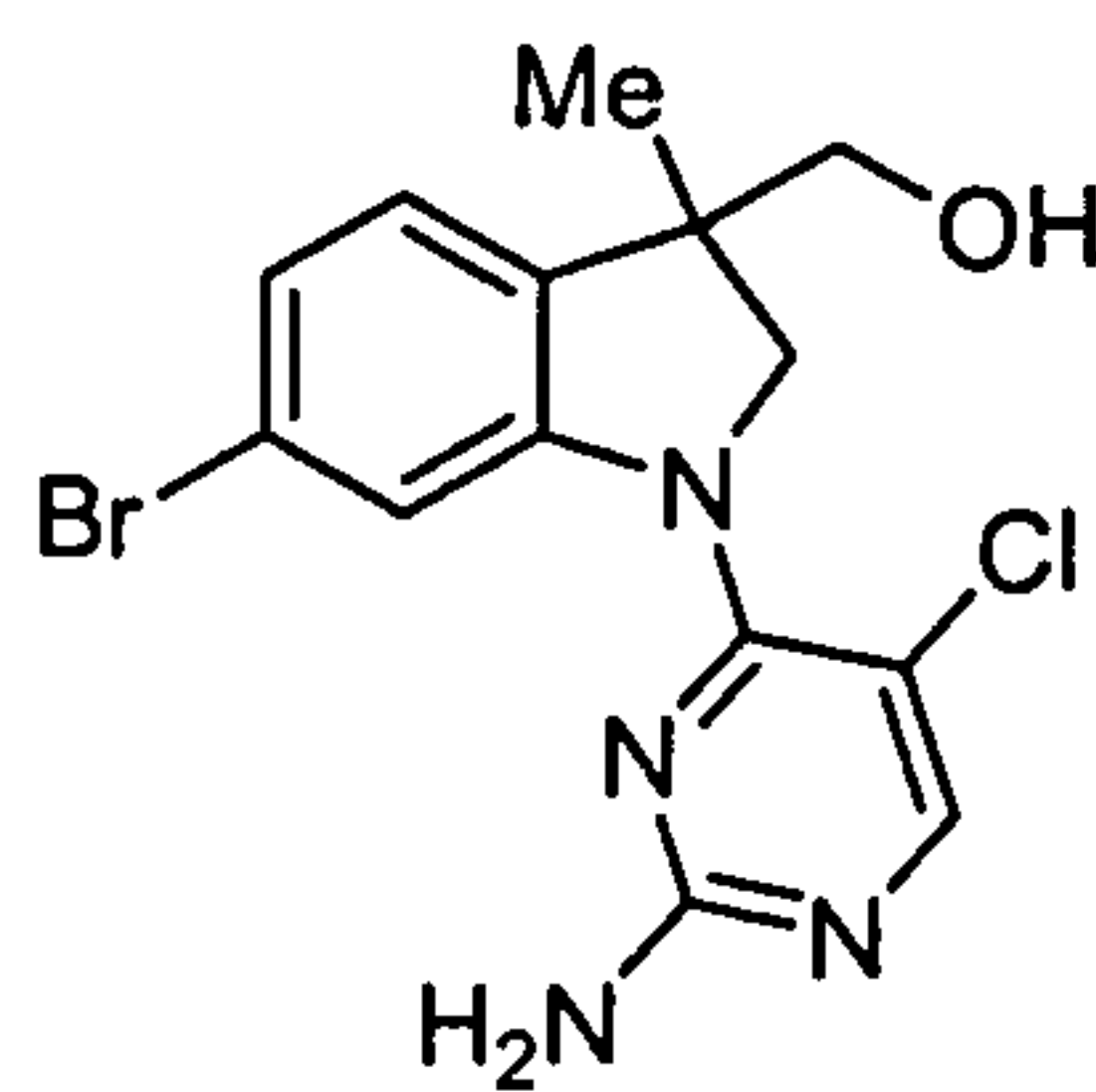
dropwise over a period of 25 minutes. Followed by the addition of more RedAl (3.4M in toluene) (10ml, 34mmol) over a period of 3min. At 45 minutes the solution was cooled to 0°C. The solution was quenched with the slow addition of 1N NaOH and then allowed to slowly warm to room temperature overnight. The next day the solution was filtered through a pad of celite and washed with ethyl acetate. The filtrate was washed with brine and then dried over MgSO₄. After concentrating the organics under vacuum the brown oil obtained was purified by flash chromatography eluting with 1.5% methanol/dichloromethane. The fractions containing the product were combined and concentrated under vacuum to give (6-bromo-3-methyl-2,3-dihydro-1H-indol-3-yl)methanol **A.28** (1.6g, 44%) as a clear light brown oil. ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 6.86 (1 H, d, *J*=7.8 Hz), 6.61 (1 H, dd, *J*=7.6, 1.7 Hz), 6.56 (1 H, d, *J*=2.0 Hz), 5.71 (1 H, s), 4.81 (1 H, t, *J*=5.6 Hz), 3.44 (1 H, d, *J*=7.8 Hz), 3.31 - 3.35 (1 H, m), 3.24 - 3.29 (1 H, m), 3.05 (1 H, dd, *J*=8.8, 2.0 Hz), 1.19 (3 H, s); ESI-MS: *M* + *H*⁺ 242.4 *m/z*.

**A.29**

((3S*)-6-bromo-3-methyl-2,3-dihydro-1H-indol-3-yl)methanol (A.29). This compound was resolved by chiral HPLC eluting as the second peak using an AD-H column with isocratic 15% isopropanol in hexane. [*a*]_D²³ = +29 (*c*=0.49 in methanol). Stereochemistry is arbitrarily assigned.

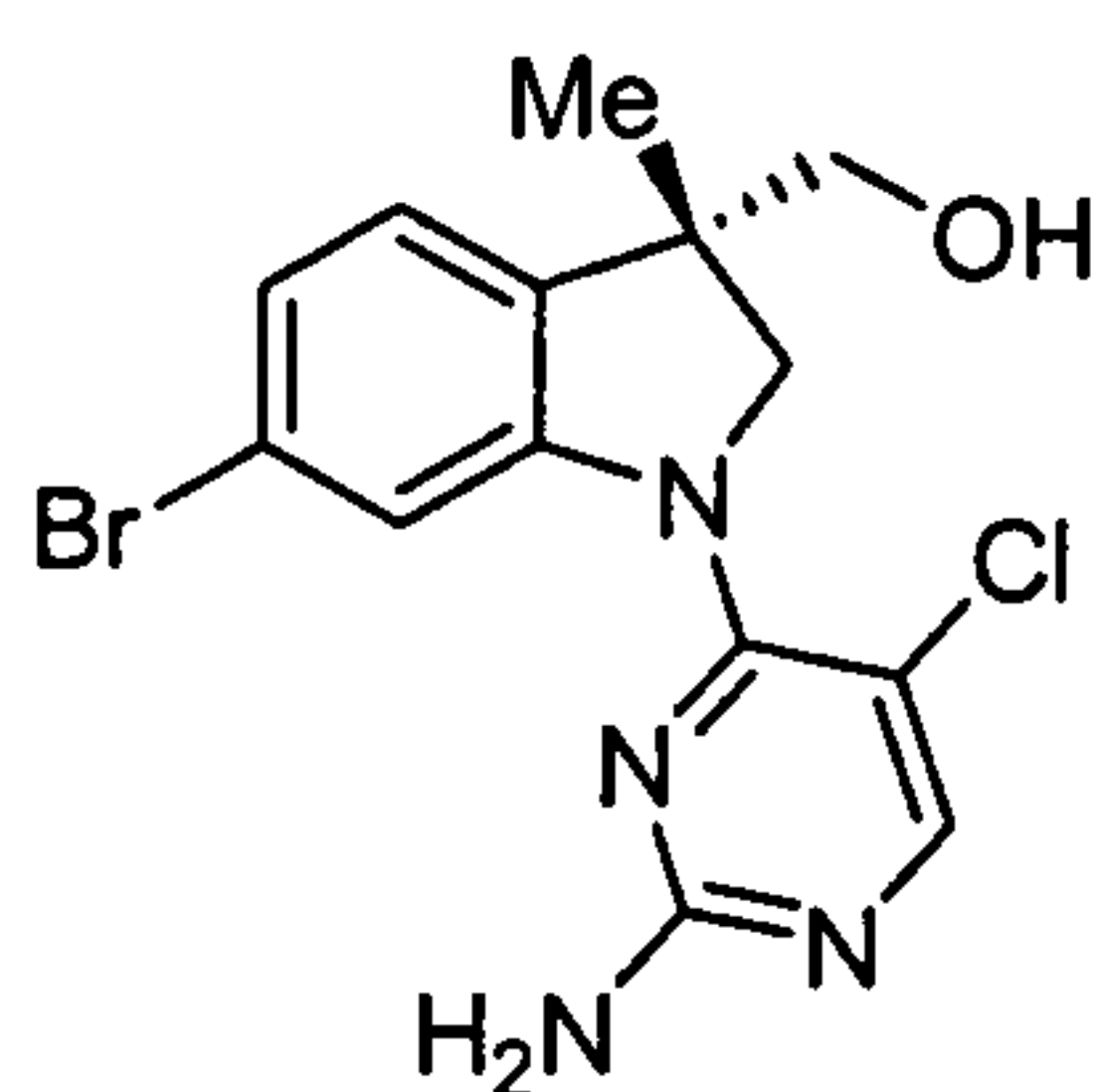
**A.30**

((3R*)-6-bromo-3-methyl-2,3-dihydro-1H-indol-3-yl)methanol (A.30). This compound was resolved by chiral HPLC eluting as the first peak using an AD-H column with isocratic 15% isopropanol in hexane. [*a*]_D²³ = -31.8 (*c*=0.49 in methanol). Stereochemistry is arbitrarily assigned.

**A.31**

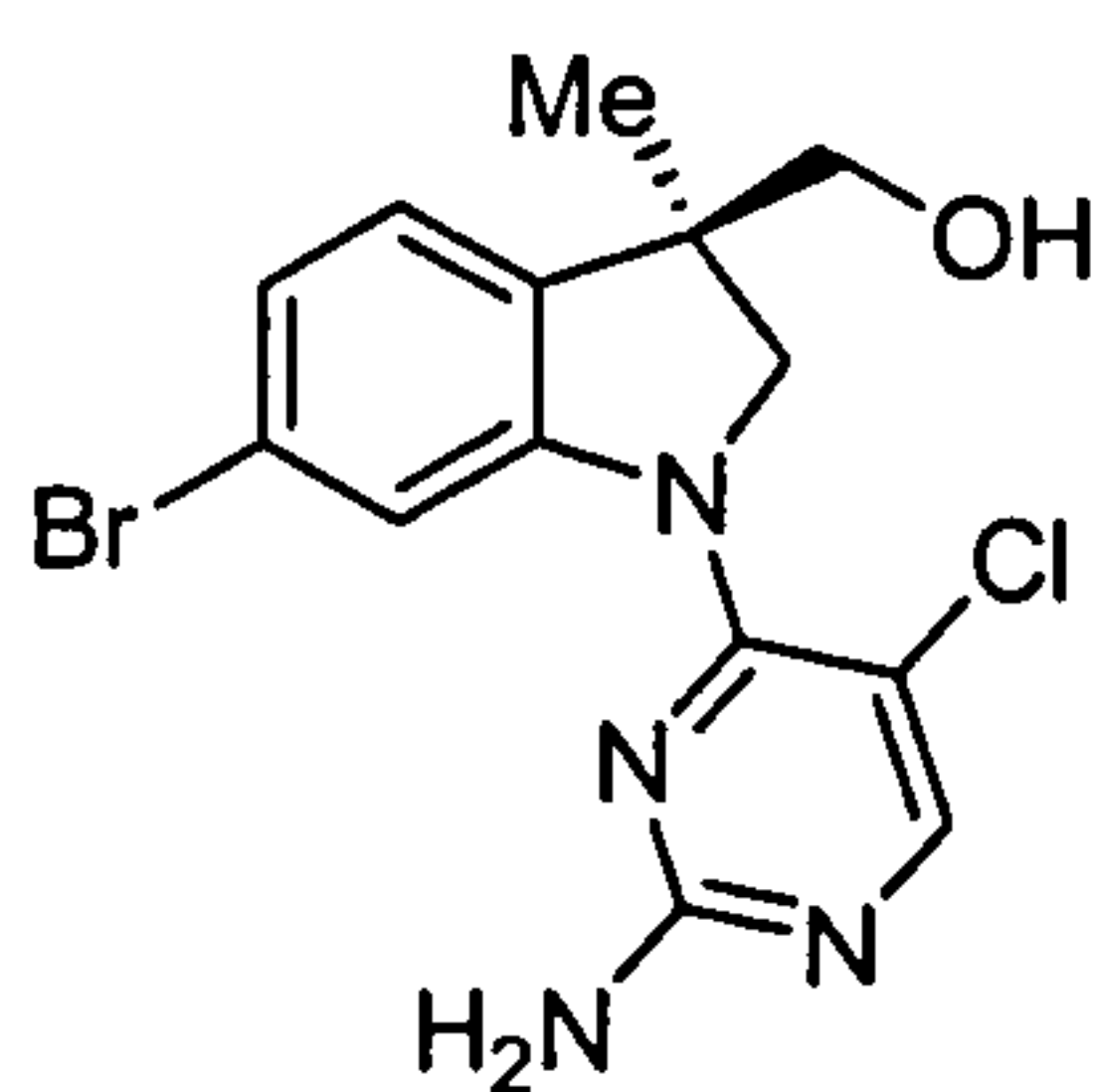
(1-(2-amino-5-chloro-4-pyrimidinyl)-6-bromo-3-methyl-2,3-dihydro-1H-indol-3-yl)methanol A.31 was synthesized from A.28 by the procedure used to prepare A.2; the title compound was obtained as an off white solid (193mg, 32%).

ESI-MS: $M + H^+$ 269.0 m/z.

**A.32**

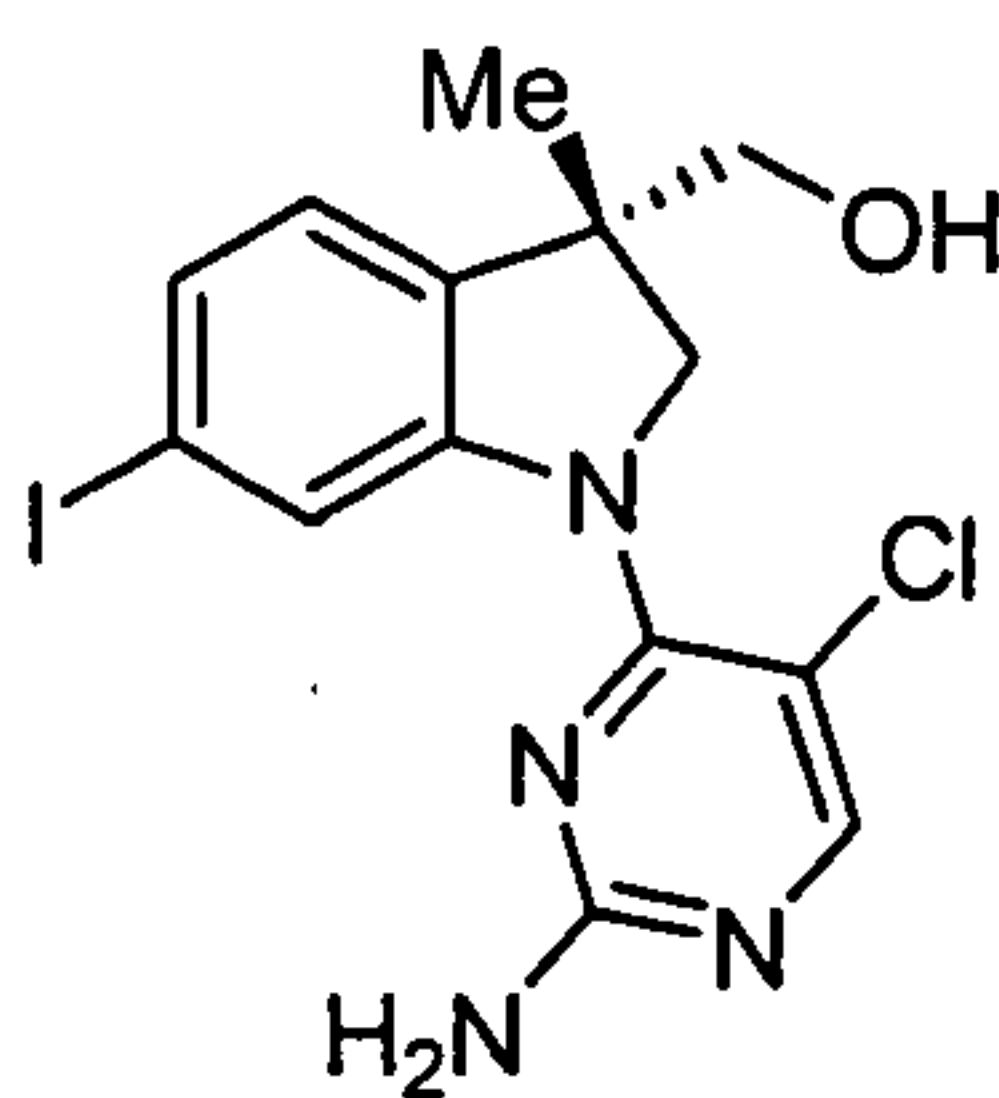
((3S*)-1-(2-amino-5-chloro-4-pyrimidinyl)-6-bromo-3-methyl-2,3-dihydro-1H-indol-3-yl)methanol A.32 was synthesized from A.29 by the procedure used to prepare A.2; the title compound was obtained as an orange solid (183mg). Stereochemistry is arbitrarily assigned.

ESI-MS: $M + H^+$ 269.0 m/z.

**A.33**

((3R*)-1-(2-amino-5-chloro-4-pyrimidinyl)-6-bromo-3-methyl-2,3-dihydro-1H-indol-3-yl)methanol A.33 was synthesized from A.30 by the procedure used to prepare A.2; the title compound was obtained as an orange solid (220 mg). Stereochemistry is arbitrarily assigned.

ESI-MS: $M + H^+$ 269.0 m/z.

**A.34**

((3S*)-1-(2-amino-5-chloro-4-pyrimidinyl)-6-iodo-3-methyl-2,3-dihydro-1H-indol-3-yl)methanol A.34

((3S*)-1-(2-amino-5-chloro-4-pyrimidinyl)-6-bromo-3-methyl-2,3-dihydro-1H-indol-3-yl)methanol **A.32** (90mg, 0.243mmol), CuI (3mg, 0.016mmol), NaI (72mg, 486mmol), and N,N'-dimethyl-1,2-ethanediamine (30μL, 0.281mmol) were combined in 6ml of n-BuOH under an atmosphere of nitrogen. The solution was heated to a reflux for 5 hours before adding more CuI (28mg, 0.147mmol), and NaI (172mg, 1.15mmol). 2 days later added more NaI (72mg, 486mmol) and continued to reflux overnight before it was cooled to room temperature. Diluted the solution with water and extracted with ethyl acetate. The organics were then washed with Brine and dried over MgSO₄ before being concentrated under vacuum. The residue obtained was purified by CombiFlash chromatography eluting with a gradient of 1%methanol/dichloromethane to 5%methanol/dichloromethane. The fractions containing the product were combined and concentrated under vacuum to give (1-(2-amino-5-chloro-4-pyrimidinyl)-6-iodo-3-methyl-2,3-dihydro-1H-indol-3-yl)methanol **A.34** (138mg) as a clear yellowish film.

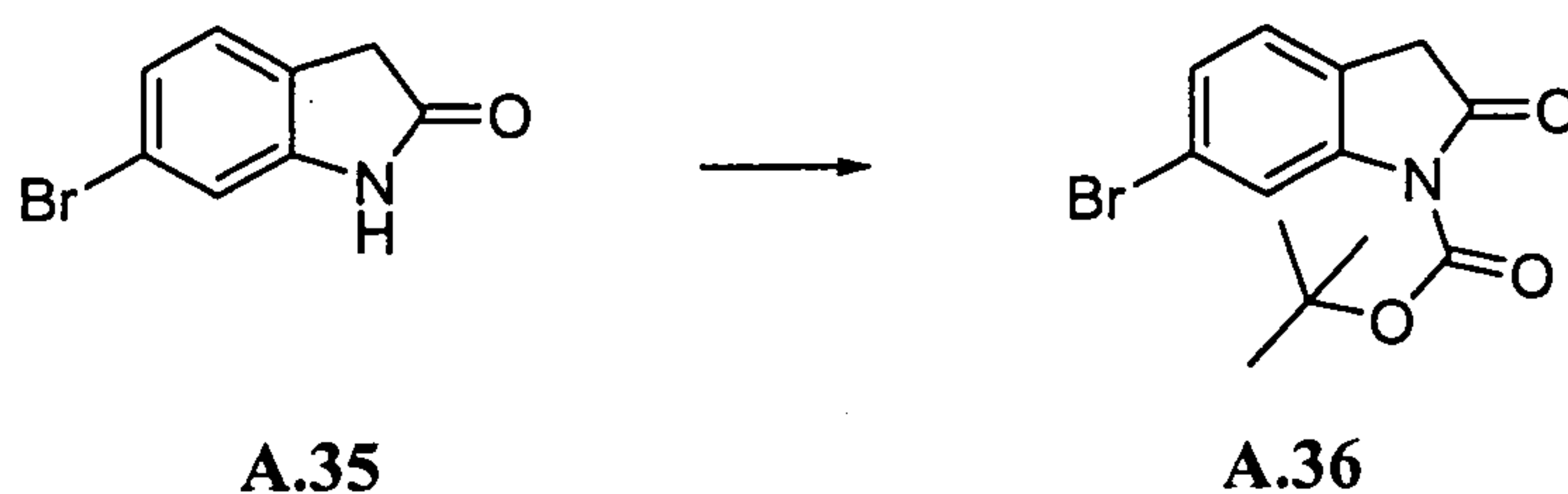
ESI-MS: M + H⁺ 417.0 m/z, Stereochemistry is arbitrarily assigned.

6-bromoindolin-2-one A.35

Ref. Quallich, G. J.; Morrissey, P. M. *Synthesis* 1993, 51-53.

To a stirred solution of methyl (4-bromo-2-nitrophenyl)acetate **A.97** (6.5 g, 23.7 mmol) in glacial acetic acid (80 mL) was added iron powder (6.6 g, 5 eq.) at room temperature. The resulting mixture was stirred in an oil bath preheated at 100 °C for 2 h at which time LC-MS showed completion. The mixture was filtered, while still warm, through a layer of celite and more glacial acetic acid was used to wash off the residual product. The filtrate was concentrated under high vacuum. The residue was mixed with ice and saturated NaHCO₃ aqueous solution and extracted with ethyl acetate (2 x). The combined organics were washed with saturated NaHCO₃ aqueous solution (1 x), brine (2 x) and dried over Na₂SO₄. The residue after concentration *in vacuo* was triturated with ethyl acetate/hexanes to give 6-bromoindolin-

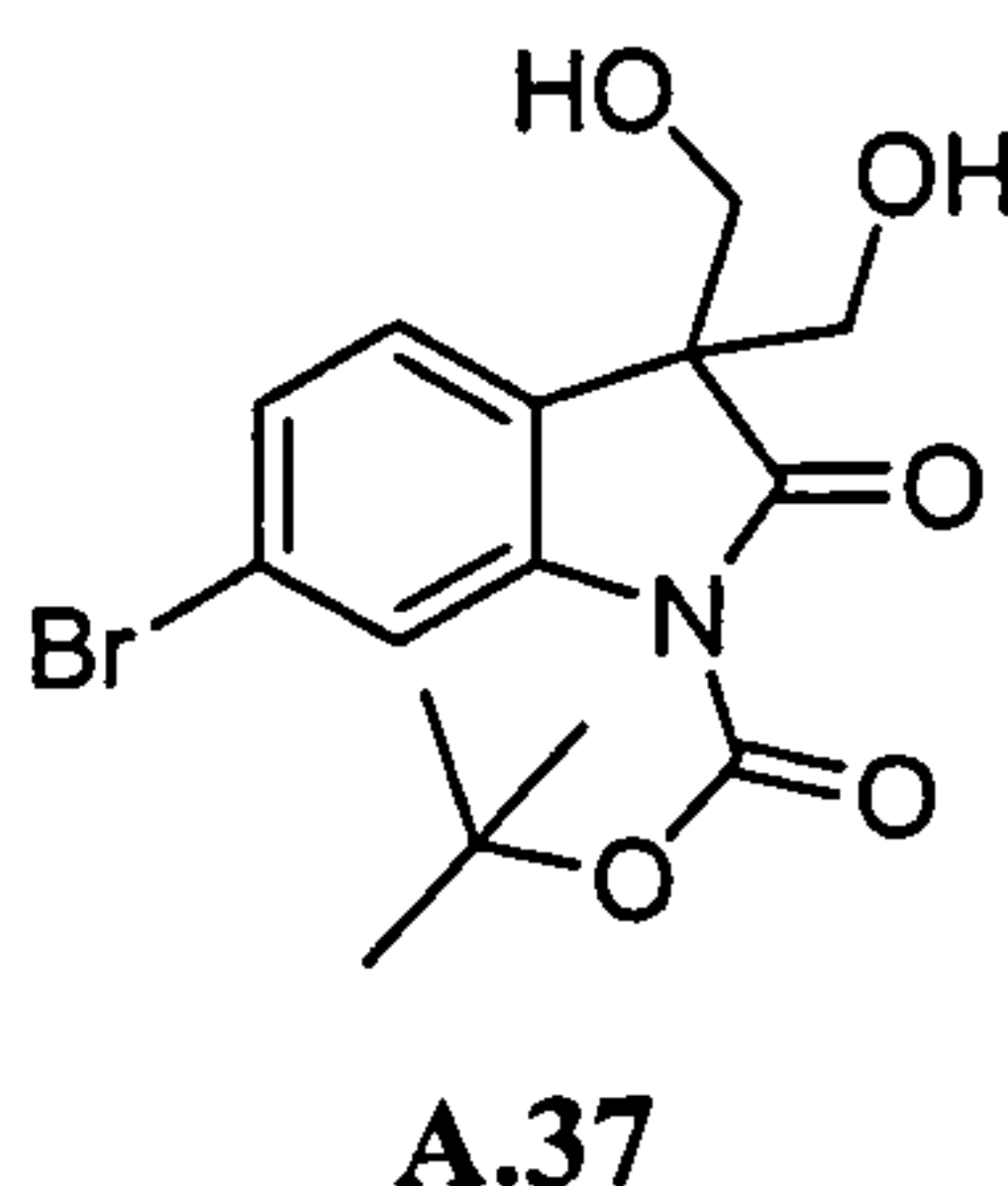
2-one **A.35** (4.8 g, 95 %) as an off-white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 10.48 (br s, 1H), 7.16 (d, $J = 6.4$ Hz, 1H), 7.11 (dd, $J = 6.4, 1.2$ Hz, 1H), 6.95 (d, $J = 1.2$ Hz, 1H), 3.45 (s, 2H). LCMS-ESI (POS), M/Z , $M+1$: Found 212.0 and 214.0.



tert*-butyl 6-bromo-2-oxo-2,3-dihydro-1H-indole-1-carboxylate **A.36*

(By analogy to Akai, S., T. Tsujino, et al. (2004). *J. Org. Chem.* 69(7): 2478-2486.)

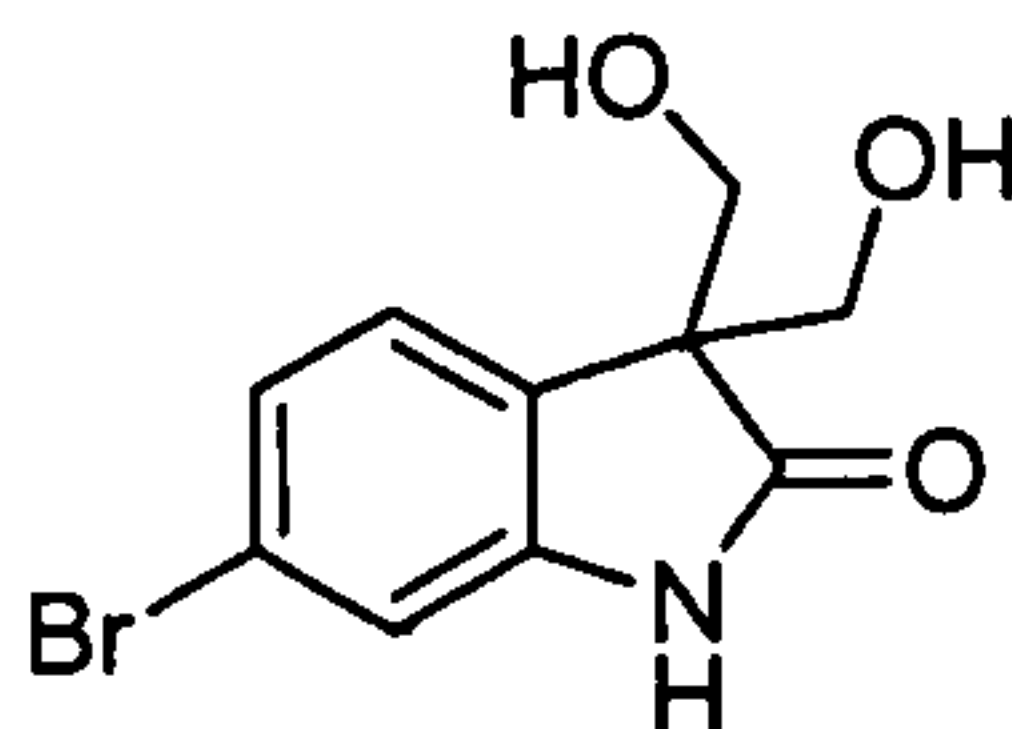
To a stirred mixture of 6-bromoindolin-2-one **A.35** (5.0 g, 23.6 mmol) and NaHCO_3 (10 eq., 21.0 g) in THF (130 mL) was added $(\text{Boc})_2\text{O}$ (2.5 eq., 14.0 g) at room temperature under N_2 . The resulting mixture was heated at reflux for 3 h. After cooling, the mixture was vacuum filtered through a layer of celite and the filter cake was thoroughly washed with THF. The filtrate was concentrated in vacuo and the residue was subjected to combi-flash column chromatography (ethyl acetate/hexanes) to give *tert*-butyl 6-bromo-2-oxo-2,3-dihydro-1H-indole-1-carboxylate **A.36** (6.0 g, 81% yield) as an off-white solid. ^1H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 8.04 (1 H, d, $J = 1.6$ Hz), 7.29 (1 H, dd, $J = 8.0, 1.8$ Hz), 7.11 (1 H, d, $J = 7.8$ Hz), 3.60 (2 H, s), 1.65 (9 H, s). LCMS-ESI (POS), M/Z , $M+\text{Na}^+$: Found 334.0 and 336.0.



tert*-butyl 6-bromo-3,3-bis(hydroxymethyl)-2-oxo-2,3-dihydro-1H-indole-1-carboxylate **A.37*

(By analogy to Akai Koichi Nakazawa, Masaki Hayashi, et al. (2001) *Tetrahedron: Asymmetry* 12(6): 897-901.) To a stirred mixture of *tert*-butyl 6-bromo-2-oxo-2,3-dihydro-1H-indole-1-carboxylate (1.8 g, 5.77 mmol) and K_2CO_3 (3.0 eq., 2.4 g) in THF (100 mL) was added paraformaldehyde (24.0 eq., 4.4 g) at room temperature. The resulting mixture was stirred at ambient temperature for 1 h. Upon workup, the mixture was poured into ice and saturated NaHCO_3 aqueous solution and extracted with ethyl acetate (2 X). The combined

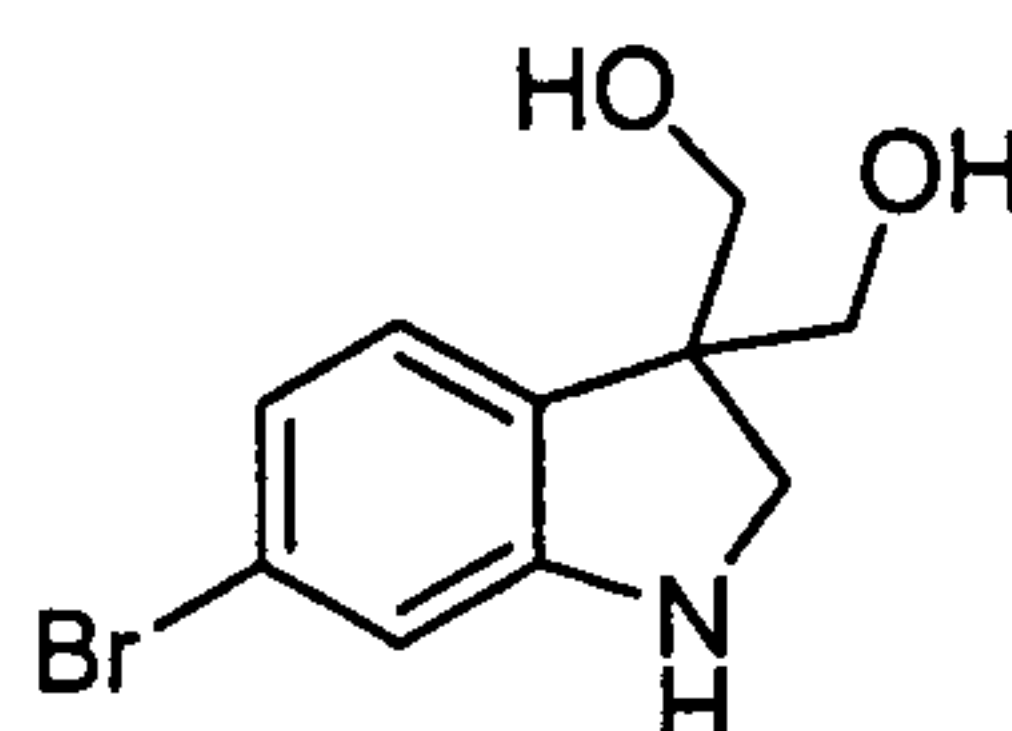
organics were washed with brine (1 X), dried over Na₂SO₄, and concentrated in vacuo. The residue was subjected to combi-flash column chromatography (methanol/dichloromethane) to give *tert*-butyl 6-bromo-3,3-bis(hydroxymethyl)-2-oxo-2,3-dihydro-1H-indole-1-carboxylate **A.37** (1.87 g, 87% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.89 (1 H, s), 7.41 (2 H, d, *J*=0.8 Hz), 4.96 (2 H, t, *J*=5.1 Hz), 3.62 - 3.76 (4 H, m), 1.57 (9 H, s). LCMS-ESI (POS), *M/Z*, *M*+Na⁺: Found 394.0 and 396.0.

**A.38**

6-bromo-3,3-bis(hydroxymethyl)-1,3-dihydro-2H-indol-2-one **A.38**

tert-butyl 6-bromo-3,3-bis(hydroxymethyl)-2-oxo-2,3-dihydro-1H-indole-1-carboxylate **A.37** (2.98g, 8.00mmol) was combined with 70ml of dichloromethane. To this was then added TFA (6ml) and the reaction was stirred at room temperature for 1 hour. Diluted the solution with dichloromethane and washed the organics with Brine. The aqueous washings were then extracted with ethyl acetate. The organics were combined and dried over Na₂SO₄ before they were concentrated under vacuum to give 6-bromo-3,3-bis(hydroxymethyl)-1,3-dihydro-2H-indol-2-one **A.38** (2.44g) as a white gum.

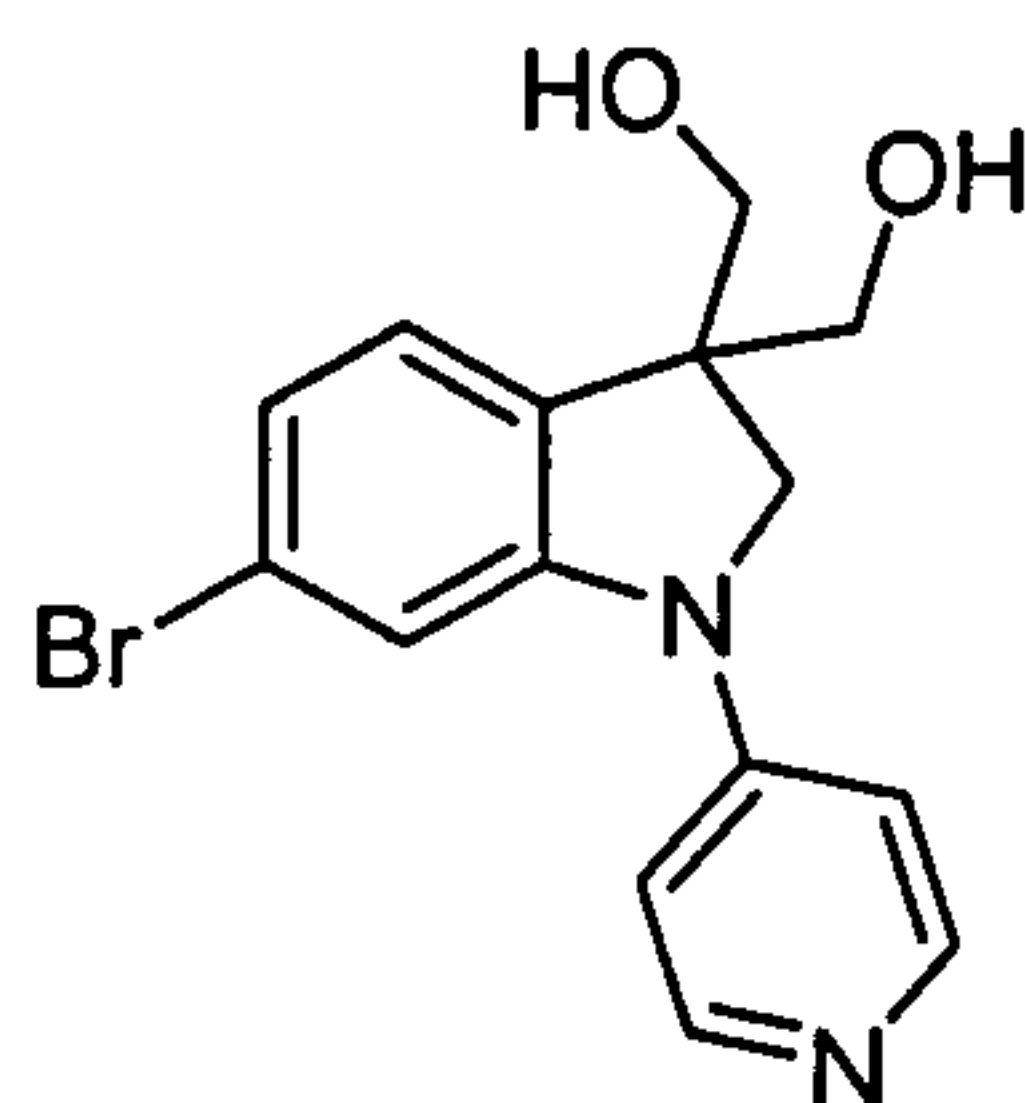
ESI-MS: *M* – 270.0 *m/z*.

**A.39**

(6-bromo-2,3-dihydro-1H-indole-3,3-diyl)dimethanol **A.39**

Under an atmosphere of nitrogen, 6-bromo-3,3-bis(hydroxymethyl)-1,3-dihydro-2H-indol-2-one **A.38** (2.30g, 8.45mmol) was dissolved in 5ml of anhydrous THF. The solution was cooled in an ice bath before adding BH₃ (10.1M in Me₂S, 4.2ml, 42.26mmol) over a period of 20min. The reaction was then stirred overnight at room temperature. The solution was diluted with 10ml of THF and quenched with the slow addition of ice followed by the slow addition of concentrated HCl (3ml). After warming the solution to room temperature it was stirred for 15 min and then concentrated under vacuum. The solution was diluted with methanol and

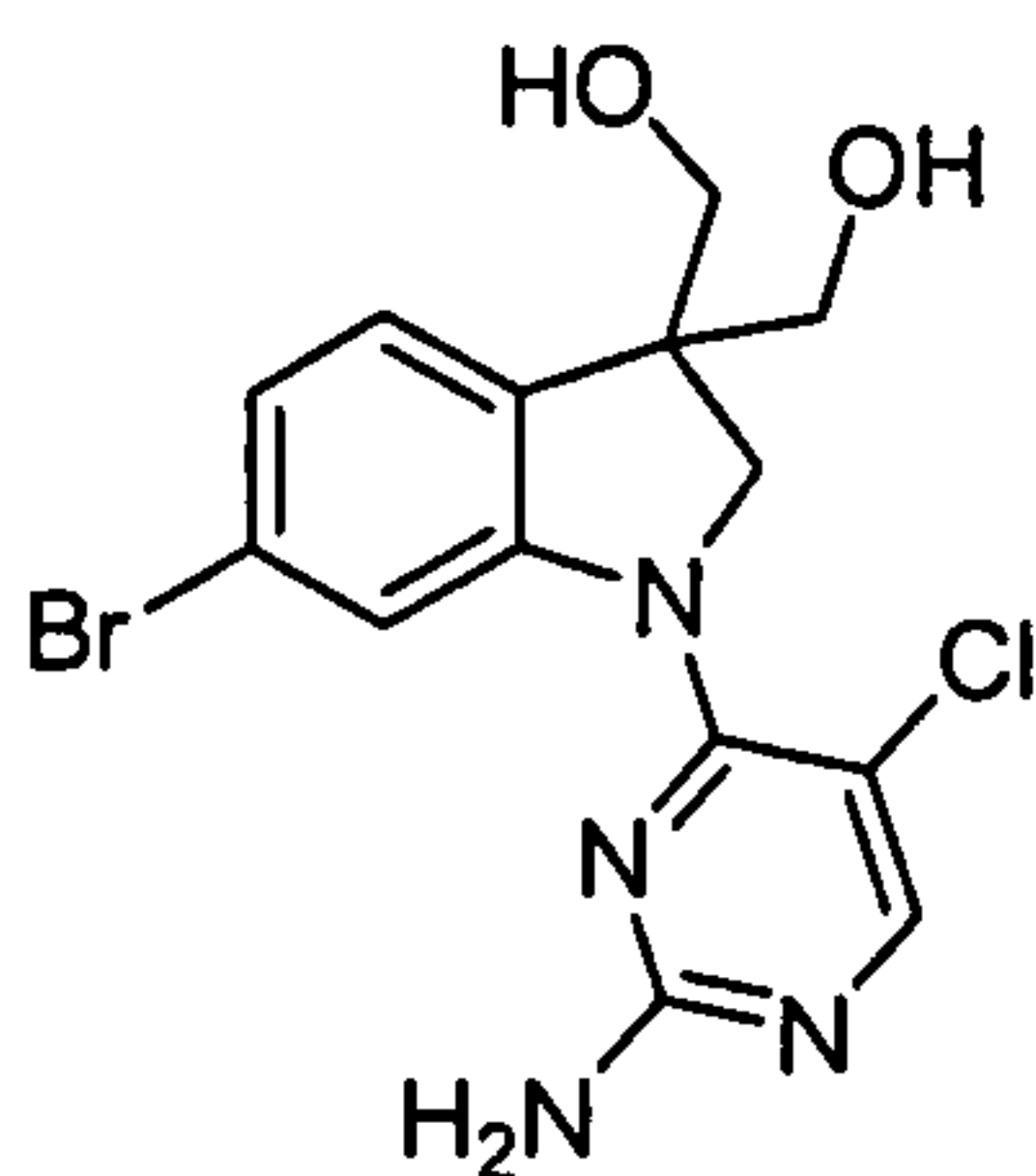
concentrated under vacuum, repeated four times to provide (6-bromo-2,3-dihydro-1H-indole-3,3-diyl)dimethanol **A.39** (1.9g,) as a white solid. ESI-MS: $M + H^+$ 258.0 m/z.



A.40

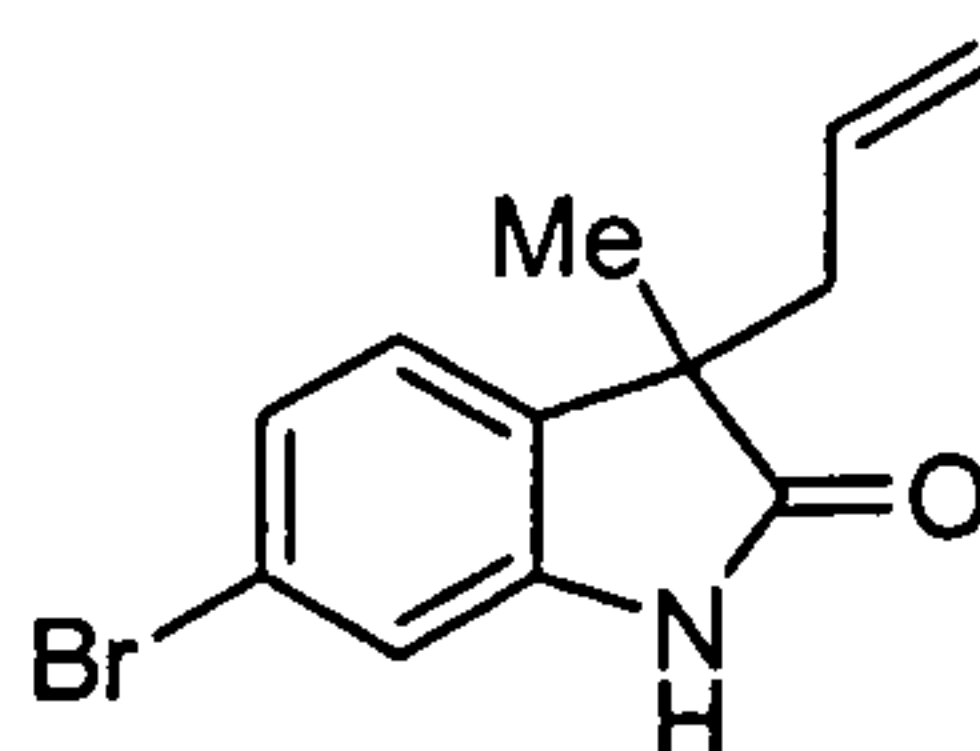
(6-bromo-1-(4-pyridinyl)-2,3-dihydro-1H-indole-3,3-diyl)dimethanol A.40

Under an atmosphere of nitrogen, 4-chloropyridine hydrochloride (**A.216**) (58mg, 0.387mmol) and (6-bromo-2,3-dihydro-1H-indole-3,3-diyl)dimethanol **A.39** (100mg, 0.387) were combined in 1.5ml of 1-pentanol and then heated to 140°C for 1.5hours. The solution was cooled to room temperature, diluted with saturated NaHCO_3 , and extracted with ethyl acetate. The organics were dried over Na_2SO_4 before being concentrated under vacuum. The residue obtained was purified by CombiFlash chromatography eluting with a gradient of 4%methanol/0.4%triethylamine/dichloromethane to 10%methanol/0.9%triethylamine/dichloromethane. The fractions containing the product were combined and concentrated under vacuum to give (6-bromo-1-(4-pyridinyl)-2,3-dihydro-1H-indole-3,3-diyl)dimethanol **A.40** (100mg) as a white solid. ESI-MS: $M + H^+$ 335.0 m/z.



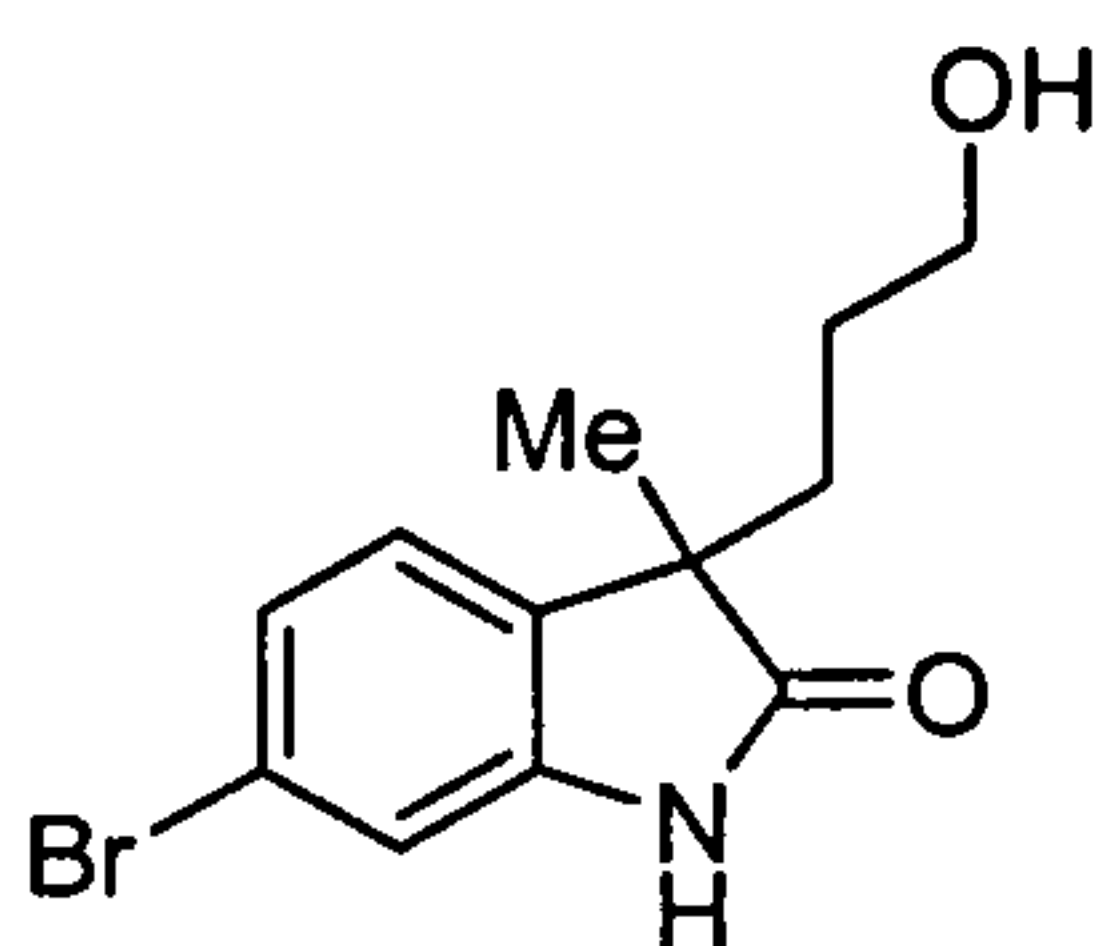
A.41

(1-(2-amino-5-chloro-4-pyrimidinyl)-6-bromo-2,3-dihydro-1H-indole-3,3-diyl)dimethanol A.41 was synthesized by the procedure used to prepare compound **A.2**. The title compound was obtained as a brownish film (1.8g). ESI-MS: $M + H^+$ 385.0 m/z.

**A.42**

6-bromo-3-methyl-3-(2-propen-1-yl)-1,3-dihydro-2H-indol-2-one A.42 was synthesized from **A.20** and allyl bromide by the procedure used to prepare **A.22**; the title compound was obtained as a light brown solid (300mg).

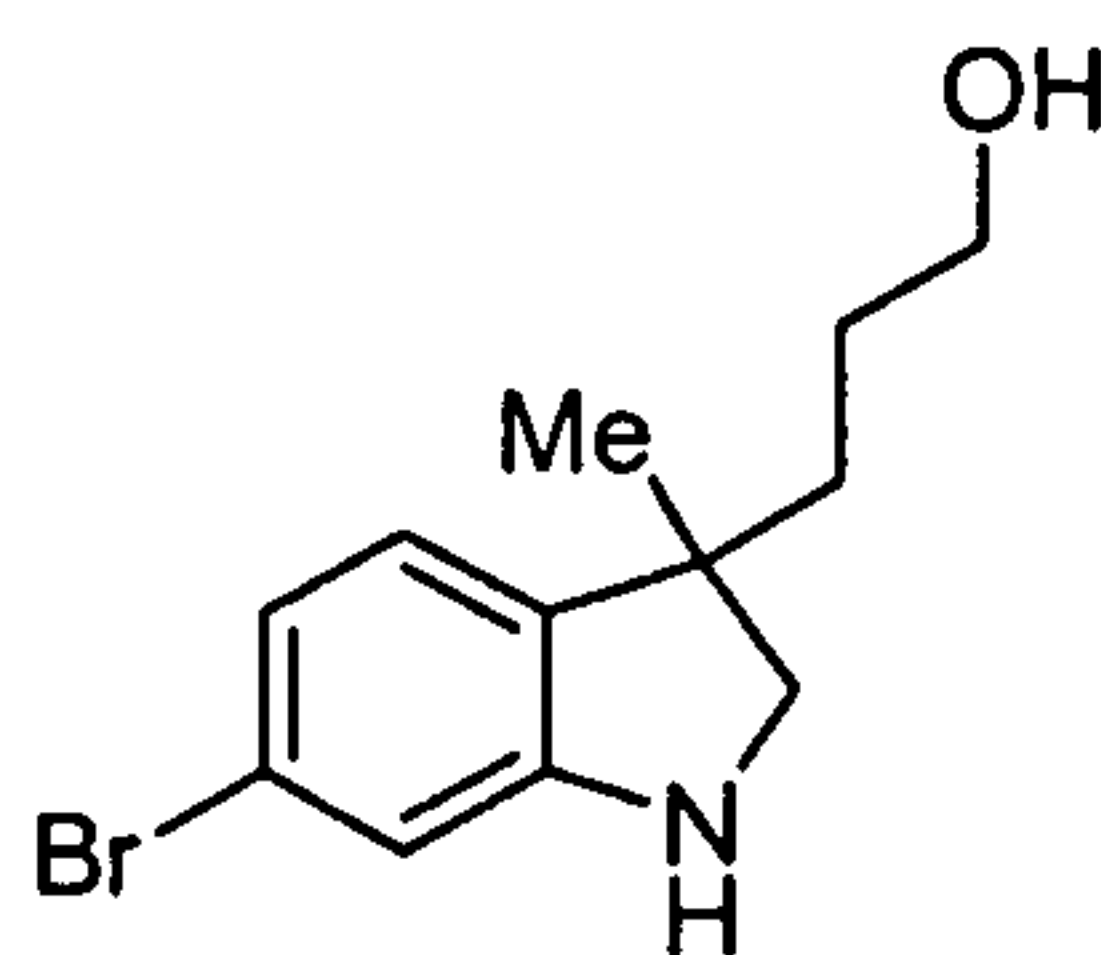
¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 10.47 (1 H, s), 7.22 (1 H, d, *J*=7.8 Hz), 7.14 (1 H, dd, *J*=7.8Hz, 1.4 Hz), 6.95 (1 H, d=1.9Hz), 5.29 - 5.43 (1 H, m), 4.84 - 4.99 (2 H, m), 2.45 - 2.53 (1 H, m), 2.33 - 2.42 (1 H, m, *J*=13.4, 7.6 Hz), 1.24 (3 H, s); ESI-MS: *M* – 264.0 *m/z*.

**A.43**

6-bromo-3-(3-hydroxypropyl)-3-methyl-1,3-dihydro-2H-indol-2-one A.43

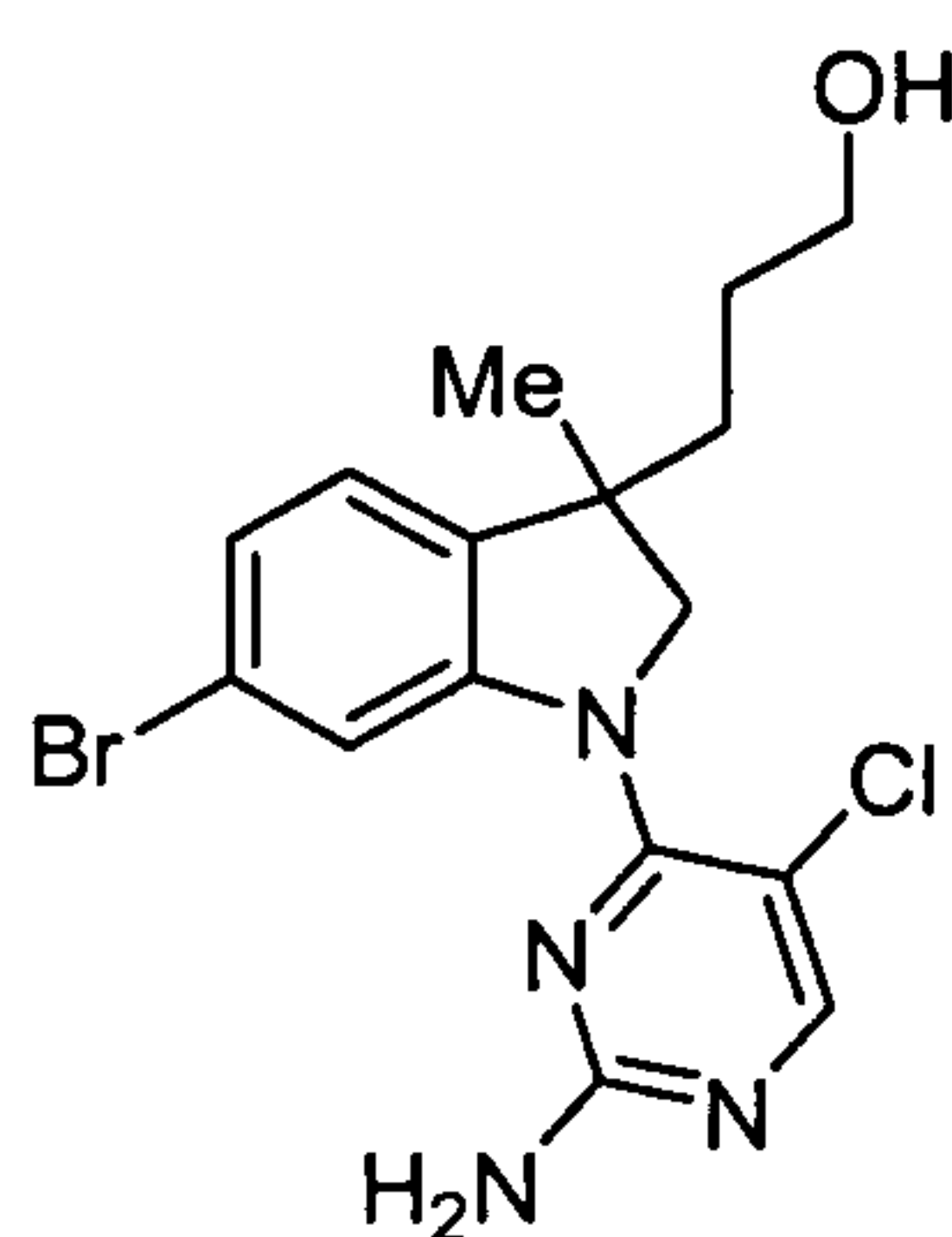
6-Bromo-3-methyl-3-(2-propen-1-yl)-1,3-dihydro-2H-indol-2-one **A.42** (300mg, 1.13mmol) was dissolved in 2ml of anhydrous THF under an atmosphere of nitrogen cooled in an ice bath. To this was added slowly 20ml of 9-BBN (0.5M in THF). The solution was allowed to warm to room temperature and stirred overnight. The next day the solution was cooled in an ice bath before slowly adding a solution of 2.25ml of 50% H₂O₂ and 25ml of 3N NaOH. After warming the solution to room temperature it was stirred for 3 hours. Diluted the solution with saturated NaHCO₃ and extracted with ethyl acetate. The combined organics were washed with Brine and dried over Na₂SO₄ before being concentrated under vacuum. The residue obtained was purified by CombiFlash chromatography eluting with a gradient of 2.5%methanol/dichloromethane to 5%methanol/dichloromethane. The fractions containing the product were combined and concentrated under vacuum to give 6-bromo-3-(3-hydroxypropyl)-3-methyl-1,3-dihydro-2H-indol-2-one **A.43** (271mg) as a light brown film.

ESI-MS: *M* + H⁺ 284.0 *m/z*.

**A.44**

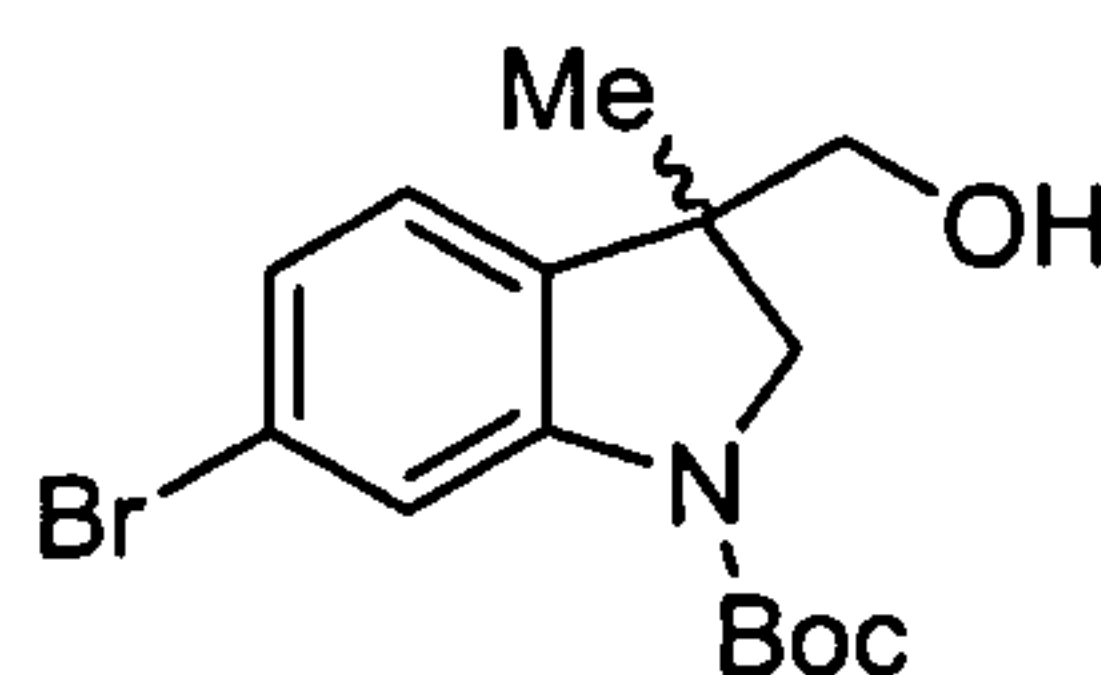
3-(6-bromo-3-methyl-2,3-dihydro-1H-indol-3-yl)-1-propanol A.44 was synthesized by the procedure used to prepare compound A.28; the title compound was obtained as a clear oil (62mg).

ESI-MS: $M + H^+$ 270.1 m/z.

**A.45**

3-(1-(2-amino-5-chloro-4-pyrimidinyl)-6-bromo-3-methyl-2,3-dihydro-1H-indol-3-yl)-1-propanol A.45 was synthesized by the procedure used to prepare compound A.2; the title compound was obtained as a tan colored solid (114mg).

ESI-MS: $M + H^+$ 397.1 m/z.

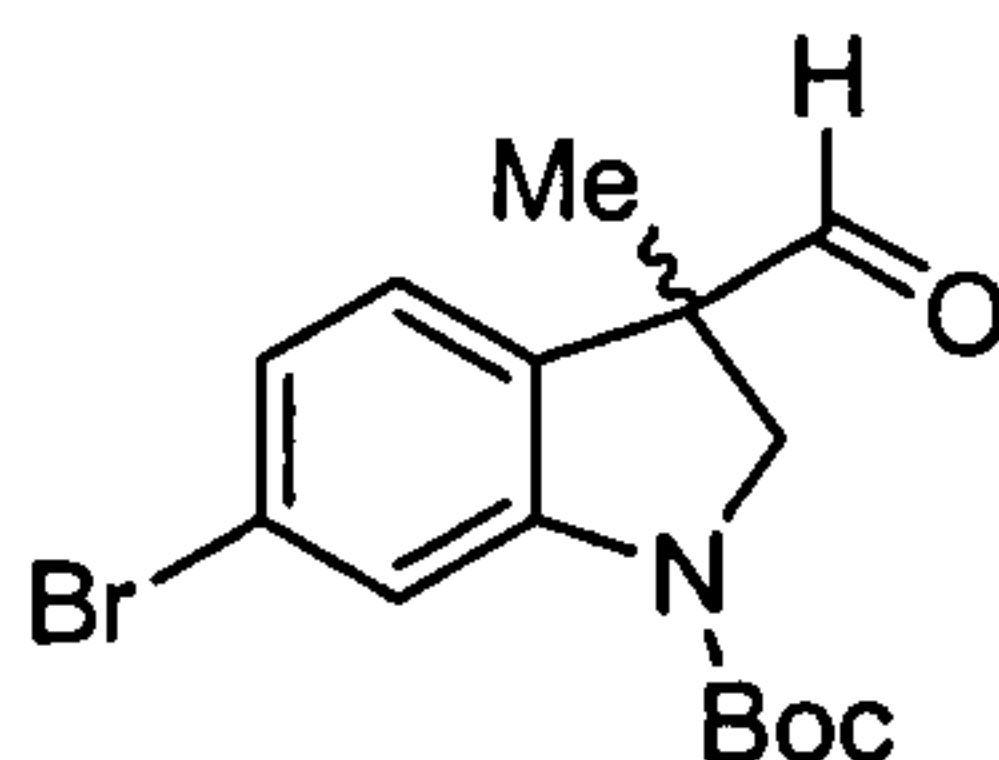
**A.46**

tert-butyl 6-bromo-3-(hydroxymethyl)-3-methyl-2,3-dihydro-1H-indole-1-carboxylate A.46

To a solution of (6-bromo-3-methyl-2,3-dihydro-1H-indol-3-yl)methanol A.28 (1.55g, 6.40mmol), and DIEA (1.23ml, 7.24mmol), in 30ml of dichloromethane was added Boc-anhydride (1.52g, 6.96mmol) at 0°C. The solution was then stirred overnight at room temperature before it was diluted with dichloromethane and washed with sat. NaHCO₃. The organics were dried over MgSO₄ before being concentrated under vacuum. Obtained *tert*-butyl

6-bromo-3-(hydroxymethyl)-3-methyl-2,3-dihydro-1H-indole-1-carboxylate **A.46** (2.04g) as a clear oil.

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.83 (br s, 1H), 7.141 (d, $J = 6.4$ Hz, 1H), 7.11 (dd, $J = 6.0$, 0.8 Hz, 1H), 4.98 (t, $J = 4.4$ Hz, 1H), 3.94 (d, $J = 8.8$, 1H), 3.50 (d, $J = 8.8$, 1H), 3.36 (dd, $J = 8.4$, 4.4 Hz, 1H), 3.33 (dd, $J = 8.8$, 4.4 Hz, 1H), 1.49 (s, 9 H), 1.22 (s, 3H); ESI-MS: $2\text{M} + \text{Na}^+$ 707.0 m/z.

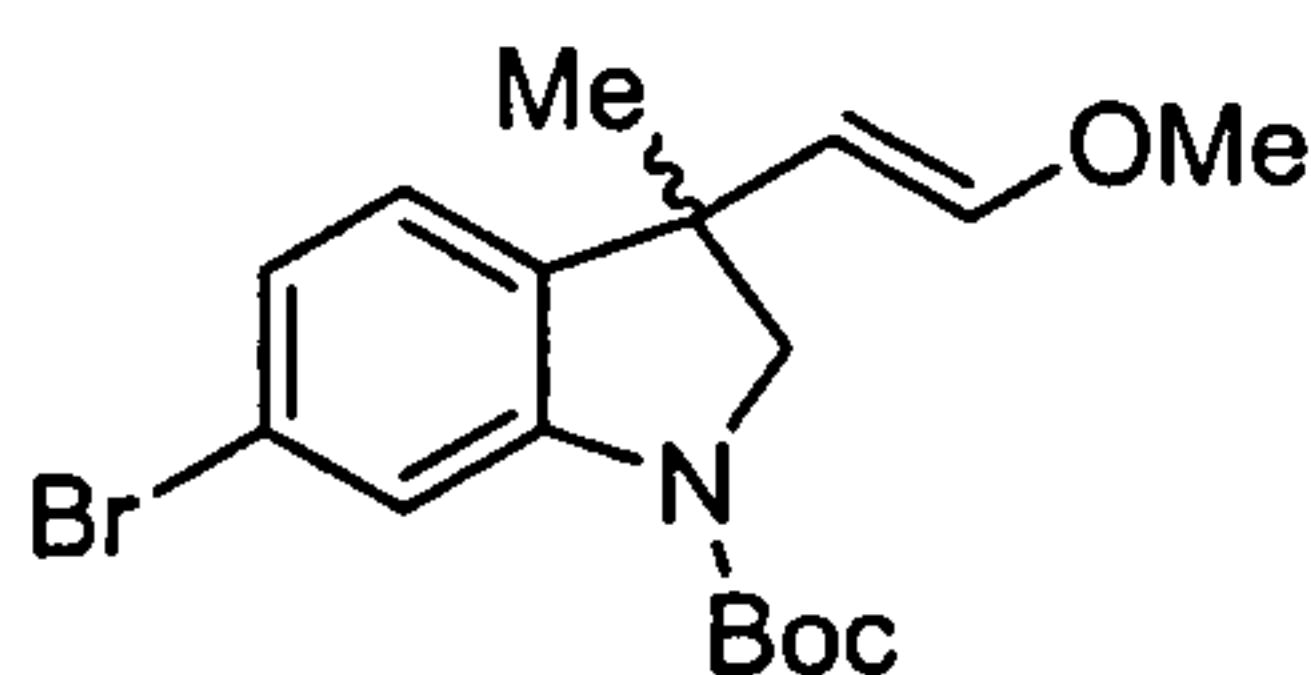


A.47

tert-butyl 6-bromo-3-formyl-3-methyl-2,3-dihydro-1H-indole-1-carboxylate A.47

tert-butyl 6-bromo-3-(hydroxymethyl)-3-methyl-2,3-dihydro-1H-indole-1-carboxylate **A.46** (5.23g, 15.28mmol) was dissolved in 25ml of dichloromethane and 25ml of acetonitrile. To this was added Dess-Martin Periodinane (16.9, 39.73mmol) and the solution was stirred at room temperature overnight. The next day the solution was concentrated under vacuum. The residue obtained was diluted with ether, filtered through a pad of celite, and washed with ether. The filtrate was partitioned with saturated NaHCO_3 and the aqueous layer was washed with ethyl acetate. The combined organics were dried over Na_2SO_4 before being concentrated under vacuum. The residue obtained was purified by CombiFlash chromatography eluting with 40% hexane/60% dichloromethane. The fractions containing the product were combined and concentrated under vacuum to give *tert*-butyl 6-bromo-3-formyl-3-methyl-2,3-dihydro-1H-indole-1-carboxylate **A.47** (2.50g, 48%) as a clear oil.

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 9.56 (1 H, s), 7.23 (1 H, d, $J=7.8$ Hz), 7.20 (1 H, dd, $J=7.8$, 1.9 Hz), 4.45 (1 H, d, $J=11.2$ Hz), 3.70 (1 H, d, $J=11.7$ Hz), 1.50 (9 H, br. s.), 1.45 (3 H, s).



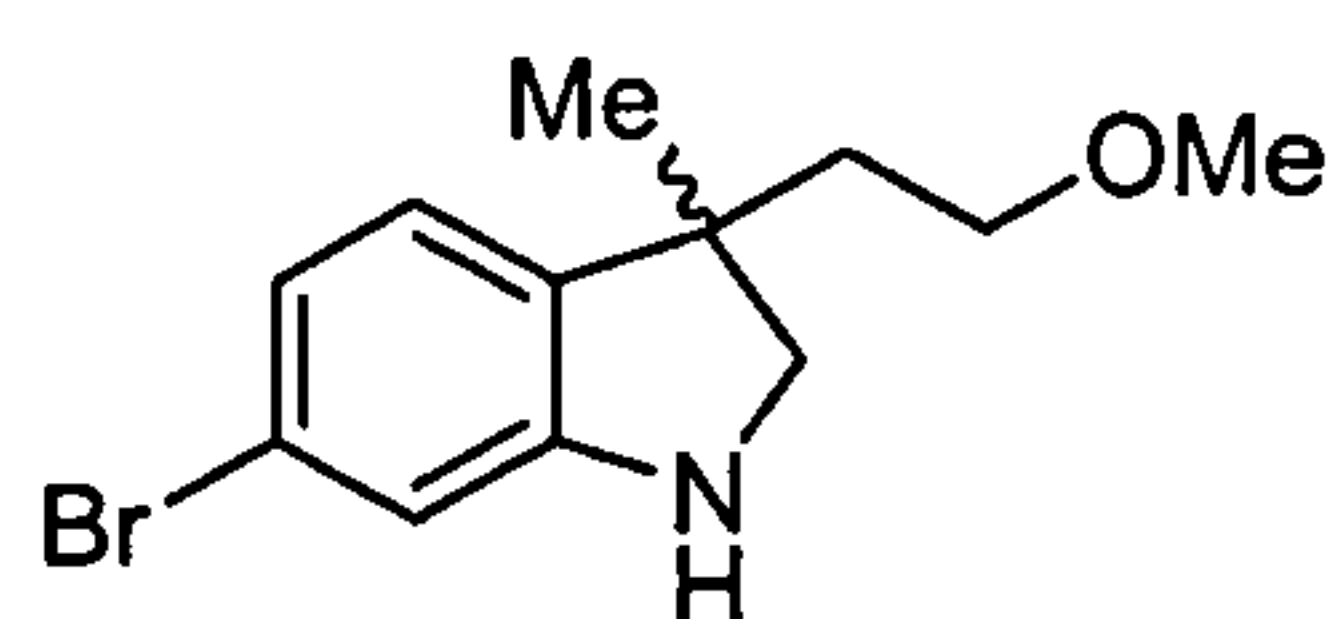
A.48

tert-butyl 6-bromo-3-((E)-2-methoxyethenyl)-3-methyl-2,3-dihydro-1H-indole-1-carboxylate A.48

To potassium *tert* butoxide (0.440g, 3.92 mmol) in 5ml of anhydrous THF under an atmosphere of N_2 was added (methoxymethyl)triphenylphosphine chloride (1.22g, 3.36mmol)

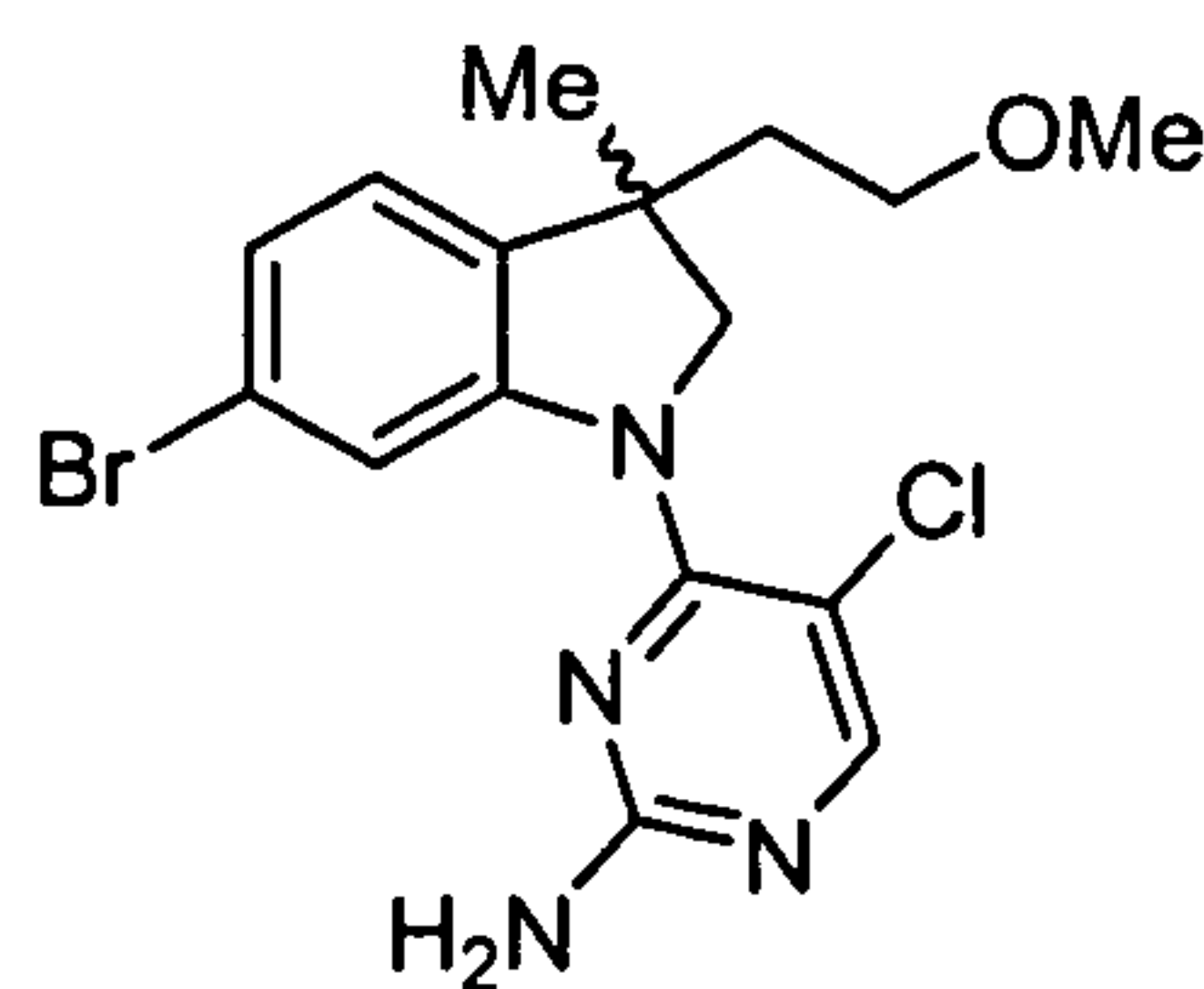
slowly. After 1.5 hours of stirring the solution was cooled in an ice bath before adding *tert*-butyl 6-bromo-3-formyl-3-methyl-2,3-dihydro-1H-indole-1-carboxylate **A.47** (0.970g, 2.05mmol) as a solution dissolved in 4ml of anhydrous THF. The solution was then warmed to room temperature and stirred for 2 hours before it was diluted with water and extracted with dichloromethane. The organics were dried over MgSO₄ before being concentrated under vacuum. The residue obtained was purified by CombiFlash chromatography eluting with a gradient of hexane to dichloromethane. The fractions containing the product were combined and concentrated under vacuum to give *tert*-butyl 6-bromo-3-((E)-2-methoxyethenyl)-3-methyl-2,3-dihydro-1H-indole-1-carboxylate (0.600g, 57%) as a light brown oil.

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.12 - 7.16 (2 H, m), 7.06 (1 H, d, *J*=7.8 Hz), 6.30 (1 H, d, *J*=12.7 Hz), 4.98 (1 H, d, *J*=13.2 Hz), 3.81 (1 H, d, *J*=10.8 Hz), 3.72 (1 H, d, *J*=10.8 Hz), 3.44 (3 H, s), 1.51 (9 H, s), 1.33 (3 H, s). See a 2:1 ratio of E:Z isomers.

**A.49**

6-bromo-3-(2-methoxyethyl)-3-methyl-2,3-dihydro-1H-indole **A.49**

tert-butyl 6-bromo-3-((E)-2-methoxyethenyl)-3-methyl-2,3-dihydro-1H-indole-1-carboxylate **A.48** (483mg, 1.31mmol) and NaBH(OAc)₃ (3.32g, 15.74 mmol) were combined in 10ml of dichloromethane. To this was added 1ml of TFA and the solution was stirred at room temperature over the weekend. The reaction was then quenched with 1N NaOH and extracted with ethyl acetate. The organic layer was dried over MgSO₄ and then concentrated under vacuum. The residue obtained was dissolved in 2ml of TFA and stirred at room temperature for 2 hours before it was concentrated under vacuum. The residue obtained was purified by CombiFlash chromatography eluting with dichloromethane to 2% methanol/dichloromethane. The fractions containing the product were combined and concentrated under vacuum to give 6-bromo-3-(2-methoxyethyl)-3-methyl-2,3-dihydro-1H-indole **A.49** (121mg) as a brownish film. ESI-MS: *M* + H⁺ 270.0 *m/z*.

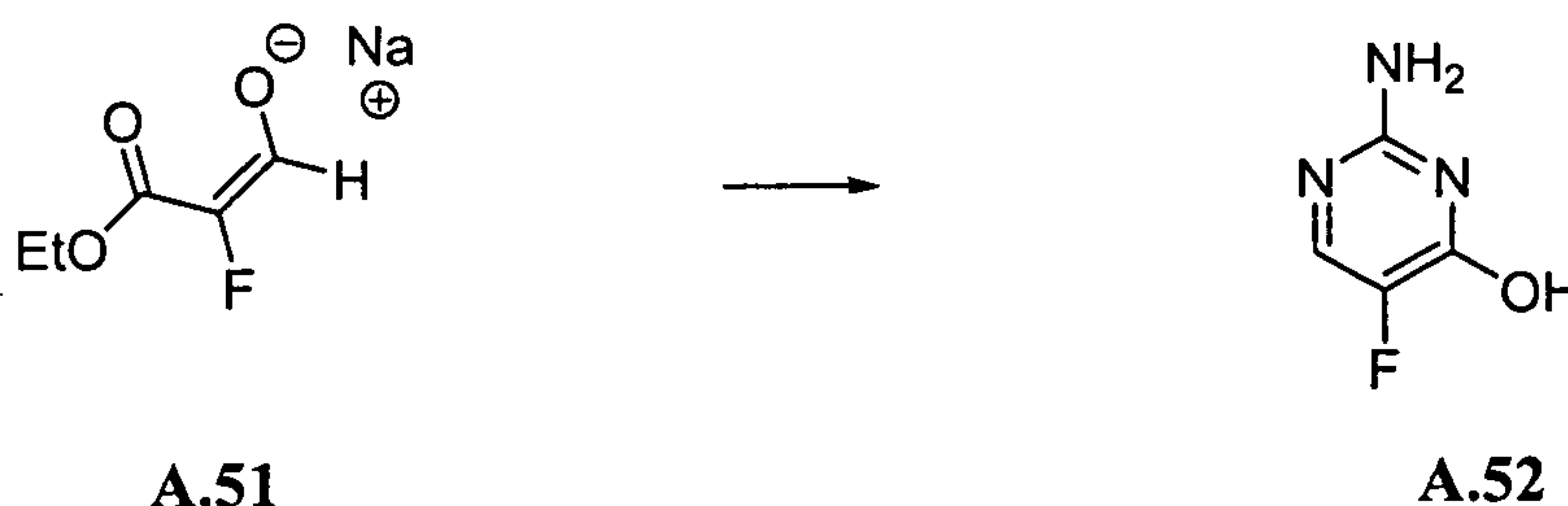
**A.50**

4-(6-bromo-3-(2-methoxyethyl)-3-methyl-2,3-dihydro-1H-indol-1-yl)-5-chloro-2-pyrimidinamine A.50 was synthesized from **A.49** and **A.14** by the procedure used to prepare **A.2**; the title compound was obtained as a yellowish film (20mg, 25%).

ESI-MS: $M + H^+$ 397.0 m/z.

sodium ethyl (2E)-2-fluoro-3-hydroxy-2-propenoate A.51

To 140ml of anhydrous ether was added in 1g portions NaH (60% in mineral oil) (6.76g, 169mmol) slowly at 0°C under an atmosphere of nitrogen. Absolute EtOH (0.8ml) was then added to the reaction, followed by the dropwise addition of a solution of ethylformate (13.65ml, 169mmol) and ethylfluoroacetate (16.3ml, 169mmol) in 100ml of ether over a period of 1.5hr. The addition funnel was rinsed with 20ml of ether and the solution was stirred for 19 hours at room temperature. After concentrating the solution under vacuum a pale yellow solid was obtained and carried on to the next step.

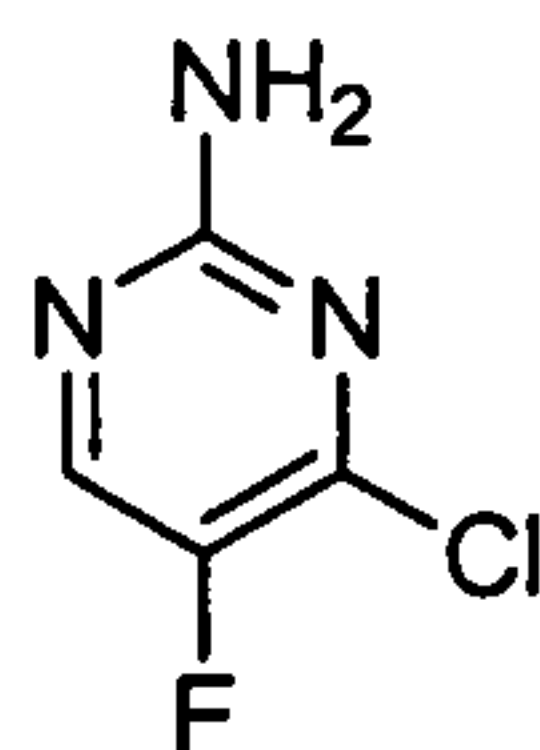


2-amino-5-fluoro-4-pyrimidinol A.52

[Biressi, e. a. (1963). *Gazz. Chim.Ital.* **93**: 1268]

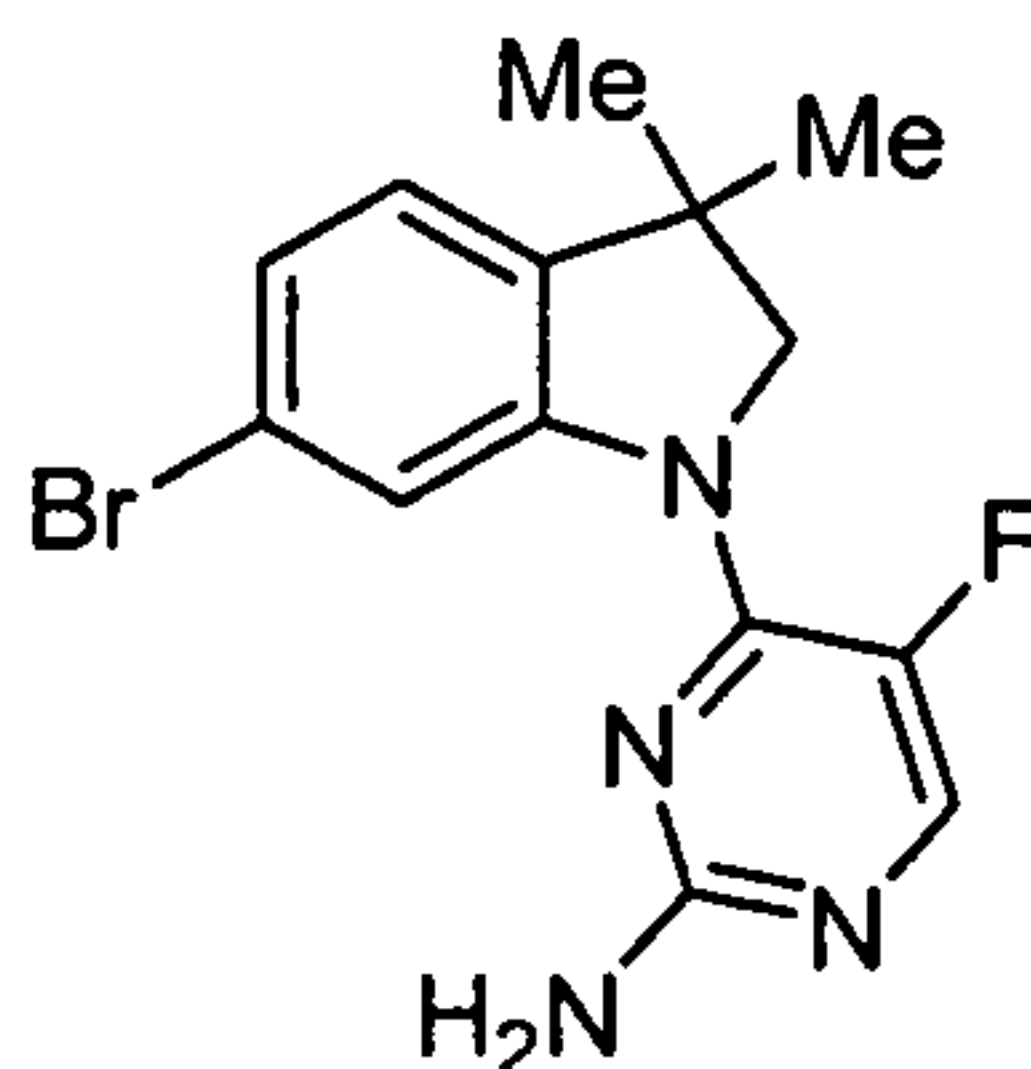
Guanidine HCl salt (49.5g, 518mmol) was neutralized by addition to a solution of NaOEt (2.68M in EtOH, 193ml) cooled in an ice bath. The solution was stirred for 30minutes before filtering off the sodium chloride generated through a Buchner funnel. The filtrate was then added to sodium ethyl (2E)-2-fluoro-3-hydroxy-2-propenoate **A.51** in 177ml of EtOH. The solution was heated to 90°C for 18hours and then it was concentrated under vacuum. To the residue obtained was added 200ml of water followed by concentrated HCl dropwise until a pH of 5 was reached. The solids were collected by filtration through a Buchner funnel and washed with 50ml of water to give 56.46g of a brownish solid. 46g of this material was purified by flash chromatography eluting with 5%water/acetonitrile. The fractions containing the product were combined and concentrated under vacuum to give 2-amino-5-fluoro-4-pyrimidinol **A.52** (12.53g) as a light brown solid.

¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 11.49 (1 H, br. s.), 7.62 (1 H, d, $J=3.9$ Hz), 6.54 (2 H, br. s.)

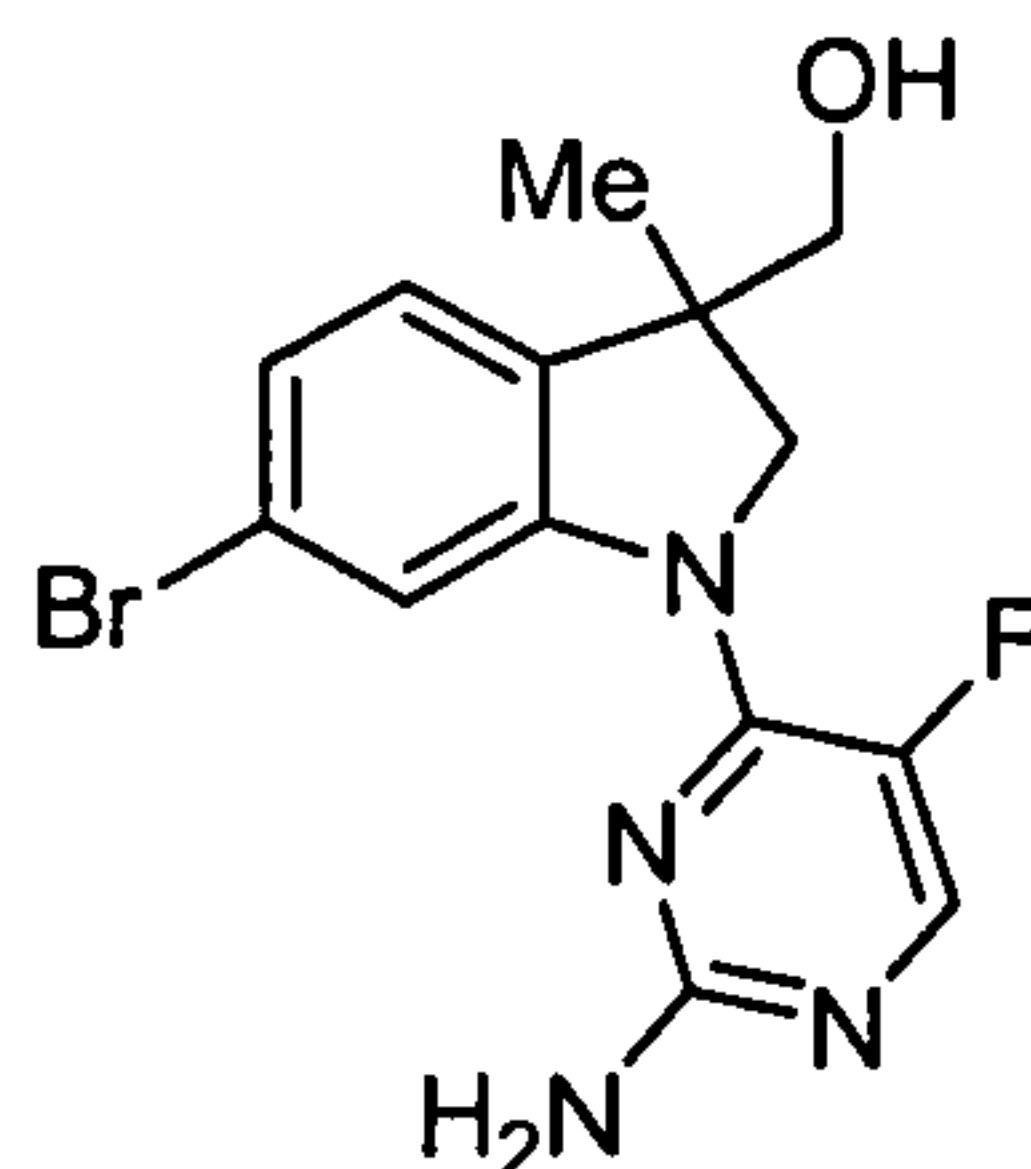
**A.53**

4-chloro-5-fluoro-2-pyrimidinamine A.53 was synthesized by the procedure used to prepare **A.12**; the title compound was obtained as a brown solid (8.66g).

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 8.38 (1 H, d, $J=1.5$ Hz), 7.06 (2 H, br. s.)

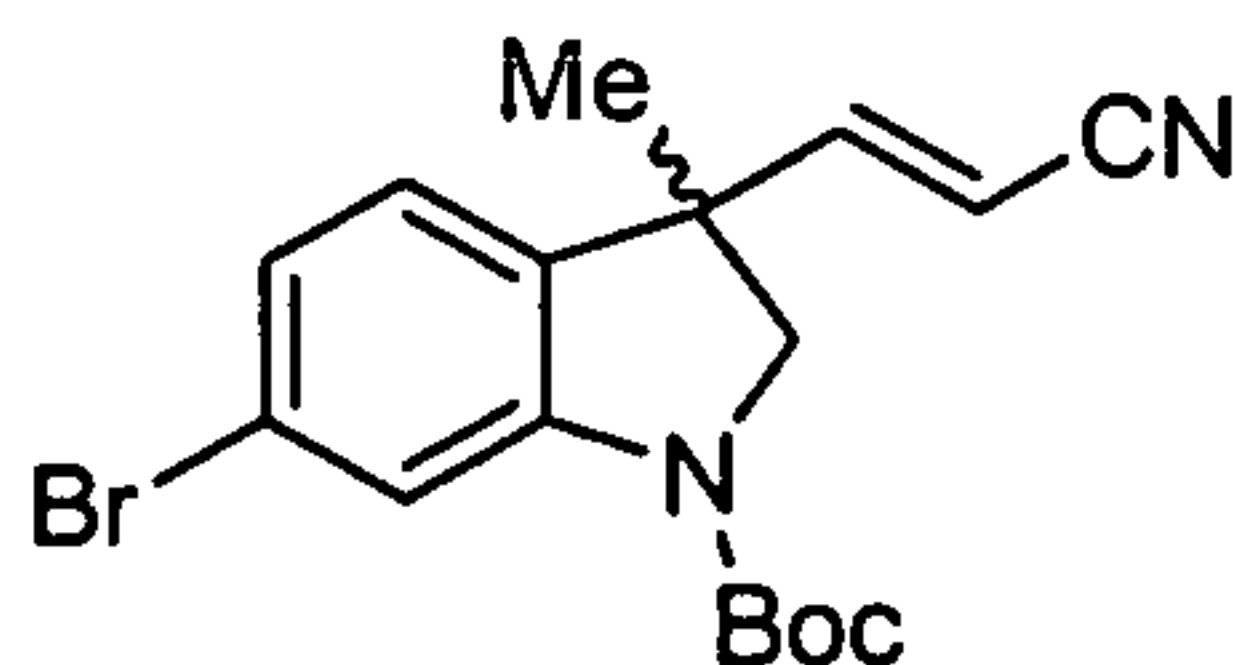
**A.55**

4-(6-bromo-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-5-fluoro-2-pyrimidinamine A.55 was synthesized from **A.53** and 6-bromo-3,3-dimethylindoline **A.54** [Atwal, K. S., F. N. Ferrara, et al. (1996) *J. Med. Chem* 39(1): 304-13] by the procedure used to prepare **A.2**; the title compound was obtained as a brown solid (500mg). ESI-MS: $\text{M} + \text{H}^+$ 337.0 m/z

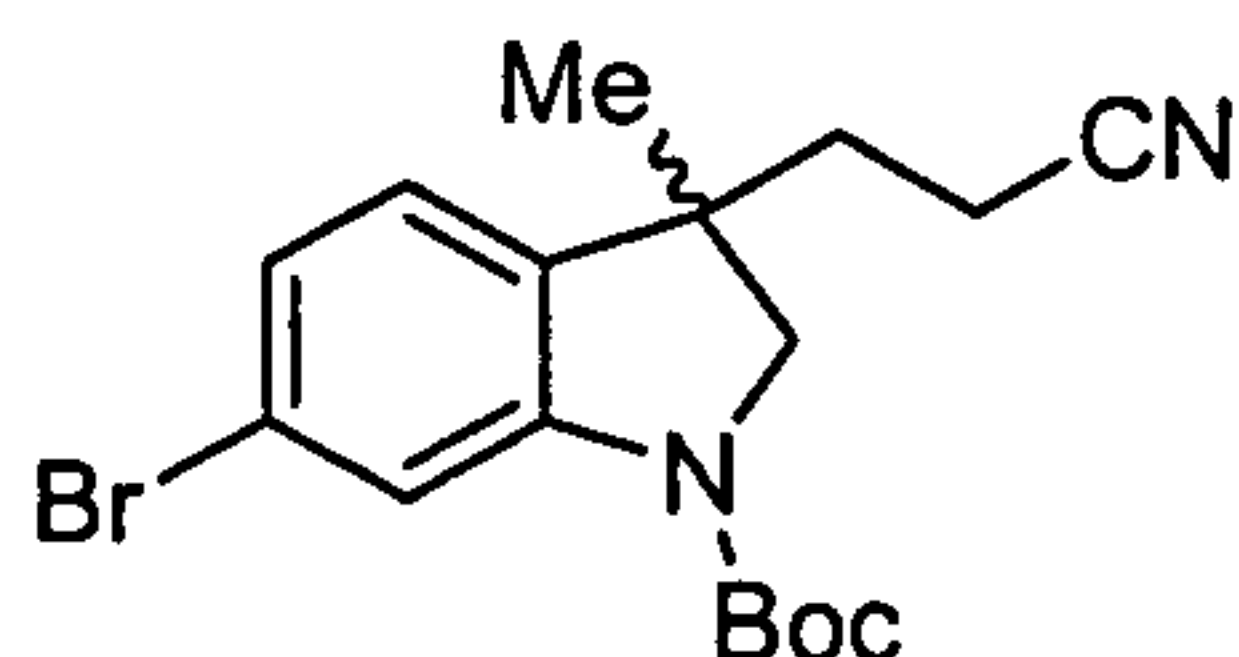
**A.56**

(1-(2-amino-5-fluoro-4-pyrimidinyl)-6-bromo-3-methyl-2,3-dihydro-1H-indol-3-yl)methanol A.56 was synthesized from **A.28** and **A.53** by the procedure used to prepare **A.2**; the title compound was obtained as a off white solid (129mg, 20%).

ESI-MS: $\text{M} + \text{H}^+$ 353.0 m/z

**A.57**

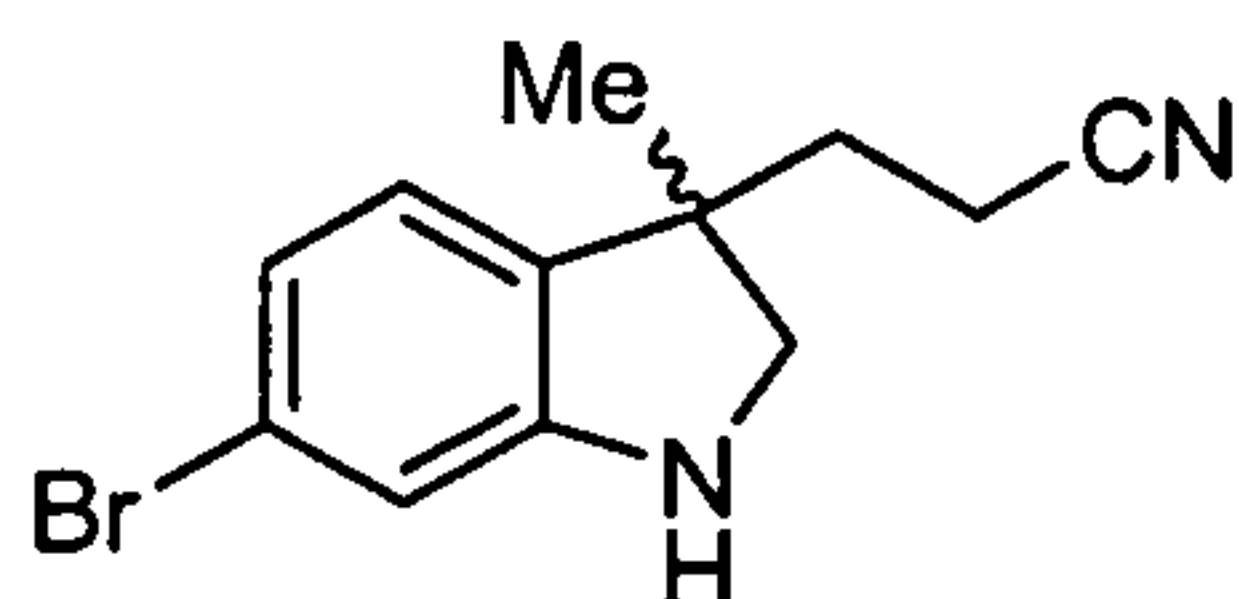
tert-butyl 6-bromo-3-((*E/Z*)-2-cyanoethenyl)-3-methyl-2,3-dihydro-1H-indole-1-carboxylate **A.57** was synthesized from **A.47** by the procedure used to prepare **A.48**. and carried on to the next reaction.



A.58

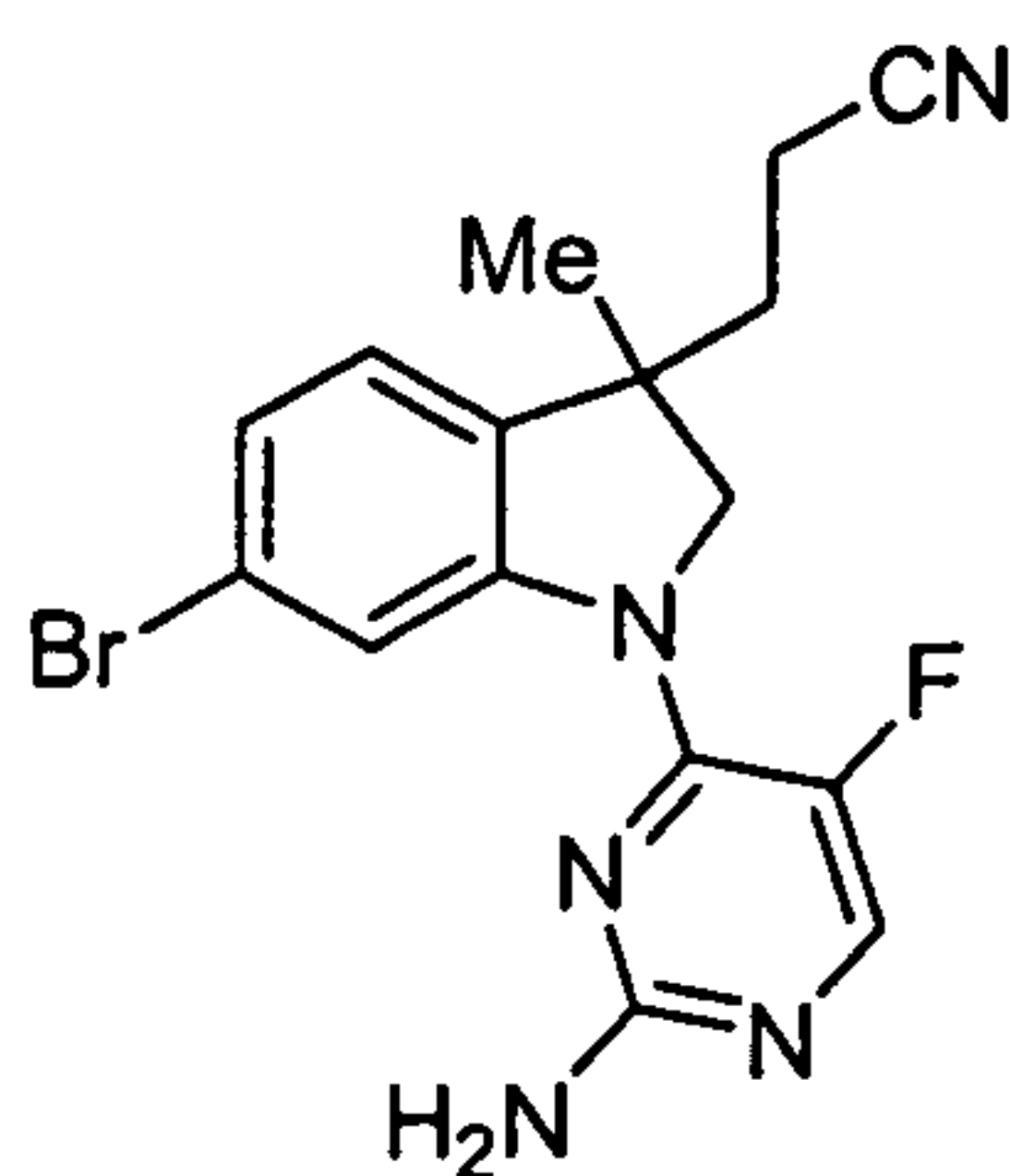
tert-butyl 6-bromo-3-(2-cyanoethyl)-3-methyl-2,3-dihydro-1H-indole-1-carboxylate **A.58**
tert-butyl 6-bromo-3-((*E/Z*)-2-cyanoethenyl)-3-methyl-2,3-dihydro-1H-indole-1-carboxylate **A.57** (290mg, 0.78mmol), was combined with NaBH₄ (50mg, 1.32mmol) in 10ml of dimethoxyethane and stirred at room temperature for 1 hour before being heated to 70°C for 2 hours. The solution was cooled to room temperature and then quenched with saturated NH₄Cl. methanol was added to the solution and it was then concentrated under vacuum. The methanol dilution and concentration sequence was repeated 3 times. The residue obtained was diluted with water and extracted with ether. The organics were dried over MgSO₄ before they were concentrated under vacuum. The residue obtained was purified by CombiFlash chromatography. The fractions containing the product were combined and concentrated under vacuum to give *tert*-butyl 6-bromo-3-(2-cyanoethyl)-3-methyl-2,3-dihydro-1H-indole-1-carboxylate **A.58** (228mg, 78%) as a clear oil.

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.84 (1 H, br. s.), 7.21 (1 H, d, *J*=), 7.15 (1 H, dd, *J*=7.8, 2.0Hz), 3.89 (1 H, d, *J*=11.7 Hz), 3.60 (1 H, d, *J*=11.2 Hz), 2.36 - 2.45 (1 H, m), 2.19 - 2.30 (1 H, m), 1.86 - 2.01 (2 H, m), 1.50 (9 H, s), 1.27 (3 H, s).



A.59

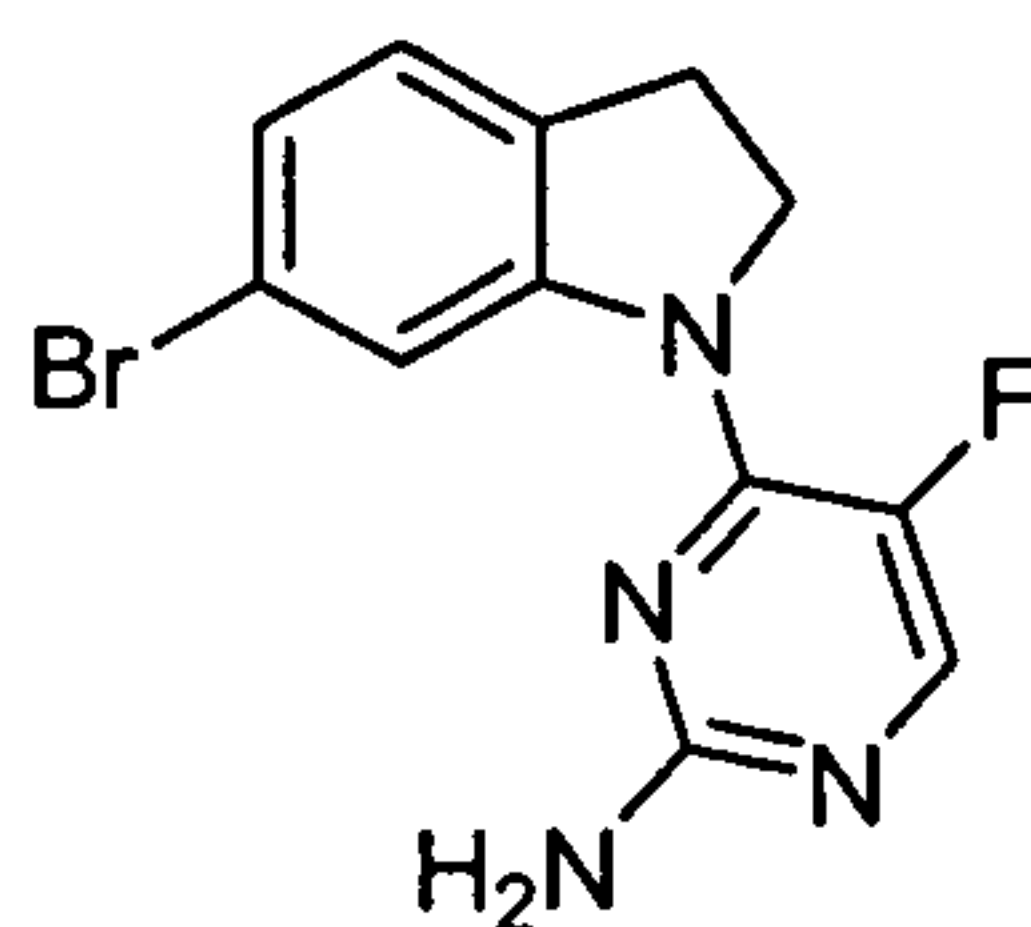
3-(6-bromo-3-methyl-2,3-dihydro-1H-indol-3-yl)propanenitrile **A.59** was synthesized by the procedure used to prepare **A.38** and carried on to the next step.

**A.60**

3-(1-(2-amino-5-fluoro-4-pyrimidinyl)-6-bromo-3-methyl-2,3-dihydro-1H-indol-3-yl)propanenitrile A.60 was synthesized by the procedure used to prepare A.2; the title compound was obtained as a brownish solid (137mg, 58%).

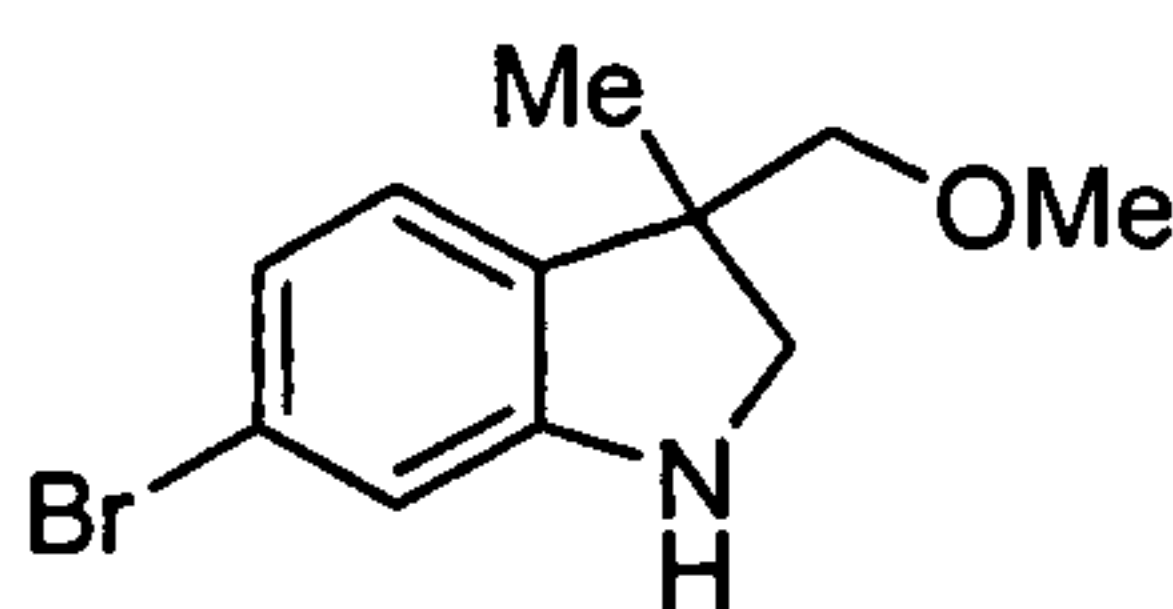
¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 8.41 (1 H, s), 8.22 (1 H, d, *J*=7.3 Hz), 7.51 (2 H, br. s.), 7.29 - 7.32 (2 H, m), 4.32 (1 H, dd, *J*=11.2, 5.4 Hz), 4.04 (1 H, dd, *J*=11.5, 4.6 Hz), 2.43 - 2.49 (1 H, m), 2.23 - 2.32 (1 H, m), 1.90 - 2.04 (2 H, m), 1.34 (3 H, s)

ESI-MS: *M* + *H*⁺ 376.0 *m/z*.

**A.61**

4-(6-bromo-2,3-dihydro-1H-indol-1-yl)-5-fluoro-2-pyrimidinamine A.61 was synthesized from A.1 and A.53 by the procedure used to prepare A.2; the title compound was obtained as a brown solid (273mg).

ESI-MS: *M* + *H*⁺ 309.0 *m/z*

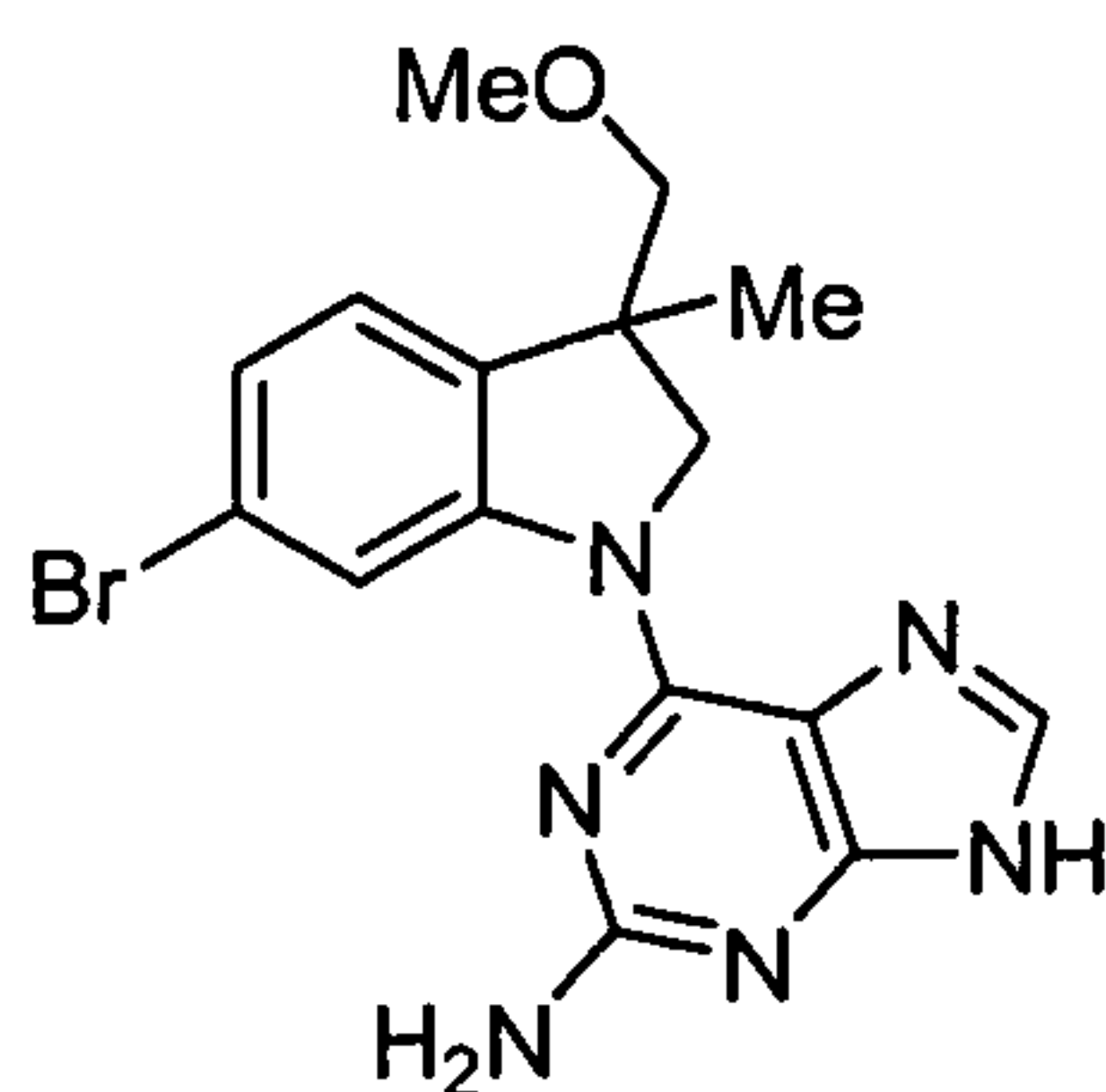
**A.69**

6-bromo-3-(methoxymethyl)-3-methyl-2,3-dihydro-1H-indole A.69

tert-butyl 6-bromo-3-(hydroxymethyl)-3-methyl-2,3-dihydro-1H-indole-1-carboxylate A.46 (450mg, 1.31mmol) was dissolved in 10ml of DMF under an atmosphere of nitrogen. To this was added NaH (60% in mineral oil) (78mg, 1.97mmol) and the solution was stirred at room temperature for 10minutes. MeI (0.085ml, 1.37mmol) was then added and the solution was

stirred for 3 hours. The solution was diluted with ice water extracted with ether. The organics were dried over MgSO_4 and then concentrated under vacuum. The residue obtained was purified by CombiFlash chromatography eluting with a gradient of dichloromethane to 1% methanol/dichloromethane. The fractions containing the product were combined and concentrated under vacuum. The residue obtained was dissolved in dichloromethane (3ml) and TFA (1.5ml) was added. The solution was stirred at room temperature overnight. The next day the solution was concentrated under vacuum to give 6-bromo-3-(methoxymethyl)-3-methyl-2,3-dihydro-1H-indole (170mg, 45%) **A.69**.

ESI-MS: $\text{M} + \text{H}^+$ 256.0 m/z

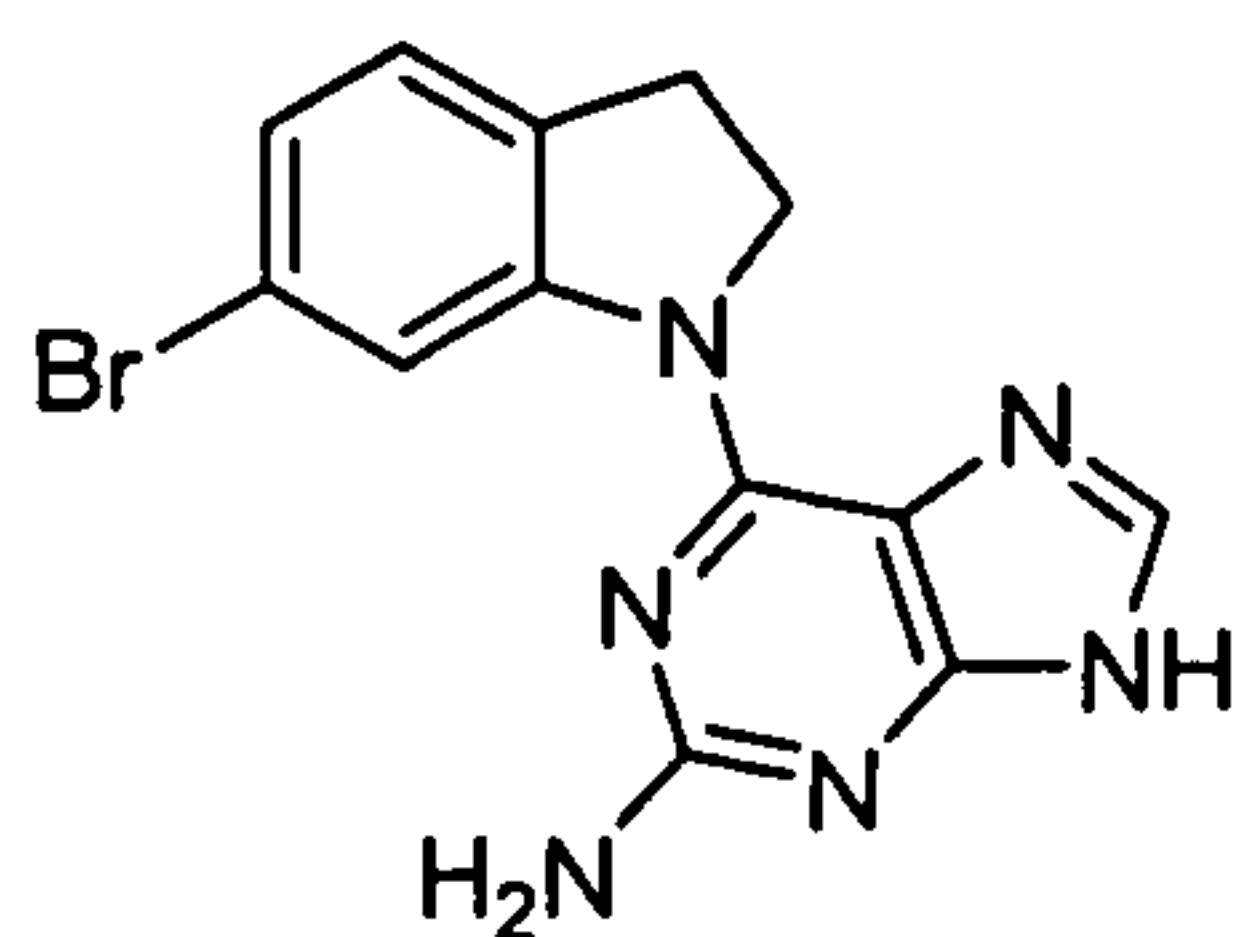


A.70

6-(6-bromo-3-(methoxymethyl)-3-methyl-2,3-dihydro-1H-indol-1-yl)-9H-purin-2-amine
A.70

6-bromo-3-(methoxymethyl)-3-methyl-2,3-dihydro-1H-indole **A.69** (170mg, 0.60mmol) was combined with 2-amino-6-chloropurine (200mg, 1.2mmol) in water (20ml). The pH was adjusted to 2 with 1N HCl and then the solution was heated to 70°C for 5 hours. The solution was cooled to room temperature and diluted with saturated NaHCO_3 and then extracted with ethyl acetate. The organics were dried over MgSO_4 and then concentrated under vacuum. The residue obtained was purified by CombiFlash chromatography eluting with 5% methanol/dichloromethane. The fractions containing the product were combined and concentrated under vacuum to give 6-(6-bromo-3-(methoxymethyl)-3-methyl-2,3-dihydro-1H-indol-1-yl)-9H-purin-2-amine (40mg, 17%) as a white solid.

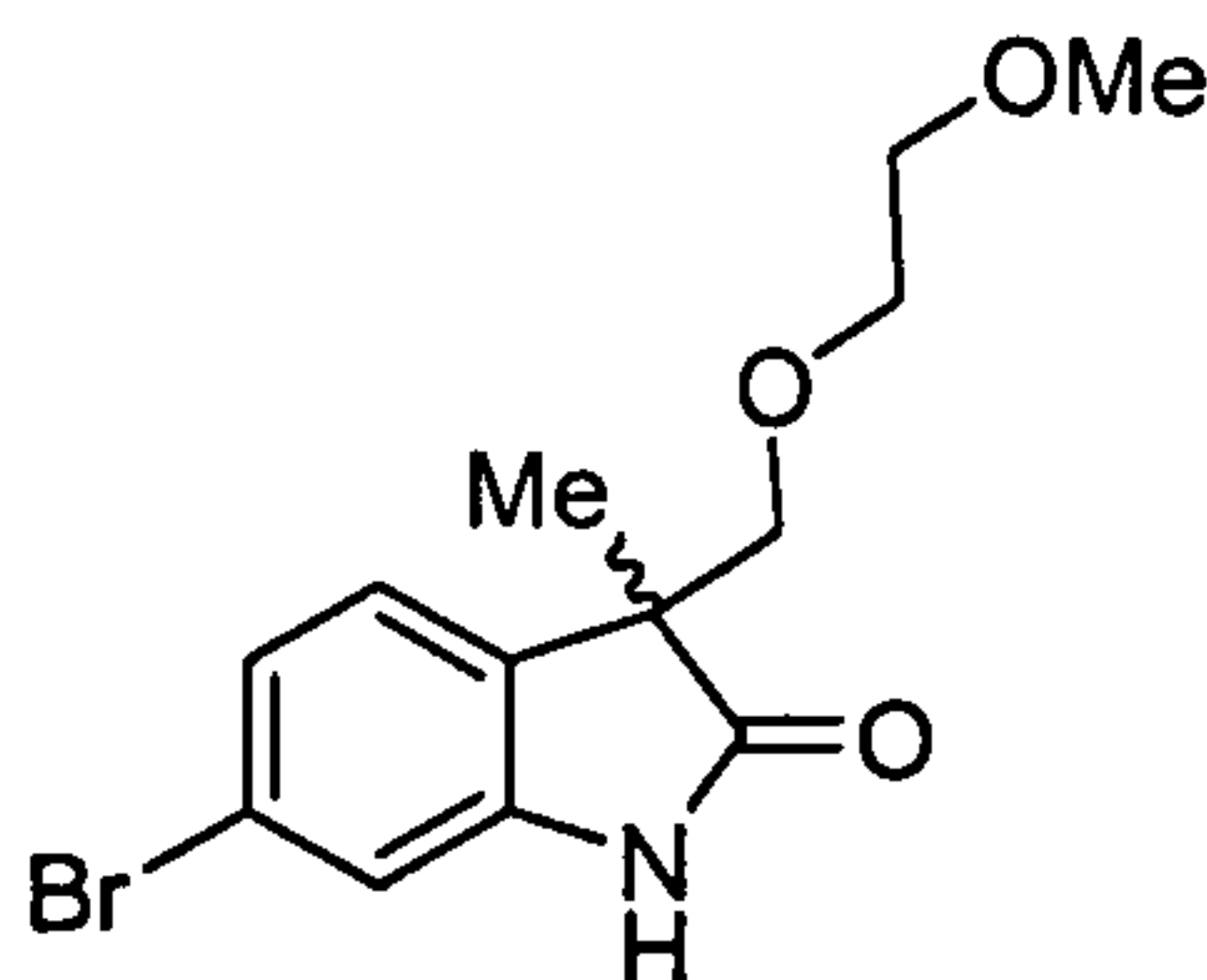
ESI-MS: $\text{M} + \text{H}^+$ 389.0 m/z



A.71

6-(6-bromo-2,3-dihydro-1H-indol-1-yl)-9H-purin-2-amine A.71 was synthesized from **A.1** by the procedure used to prepare **A.70**; the title compound was obtained as a white solid (538mg, 66%).

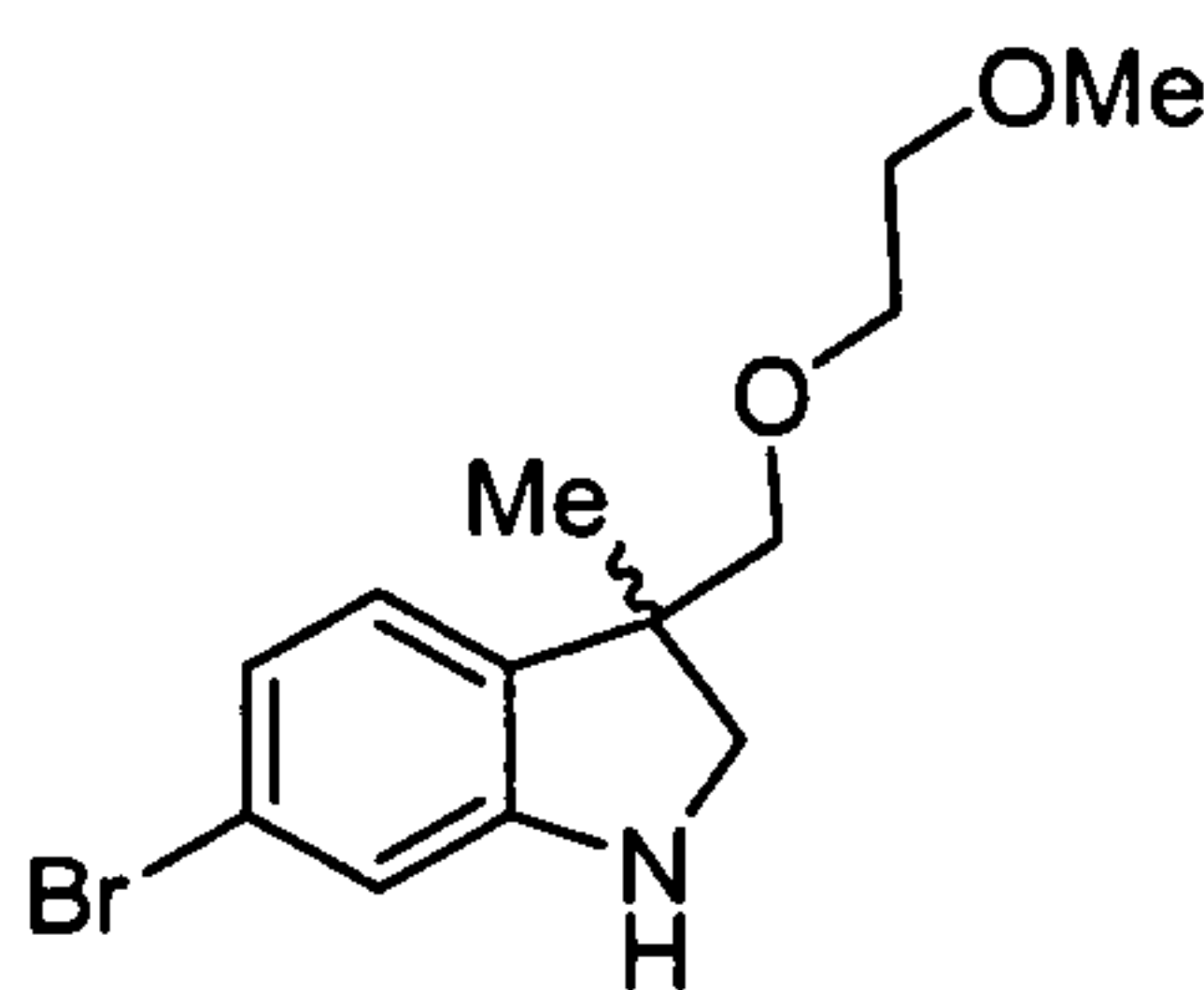
ESI-MS: $M + H^+$ 331.3 m/z.



A.74

6-bromo-3-((2-methoxyethoxy)methyl)-3-methyl-1,3-dihydro-2H-indol-2-one A.74

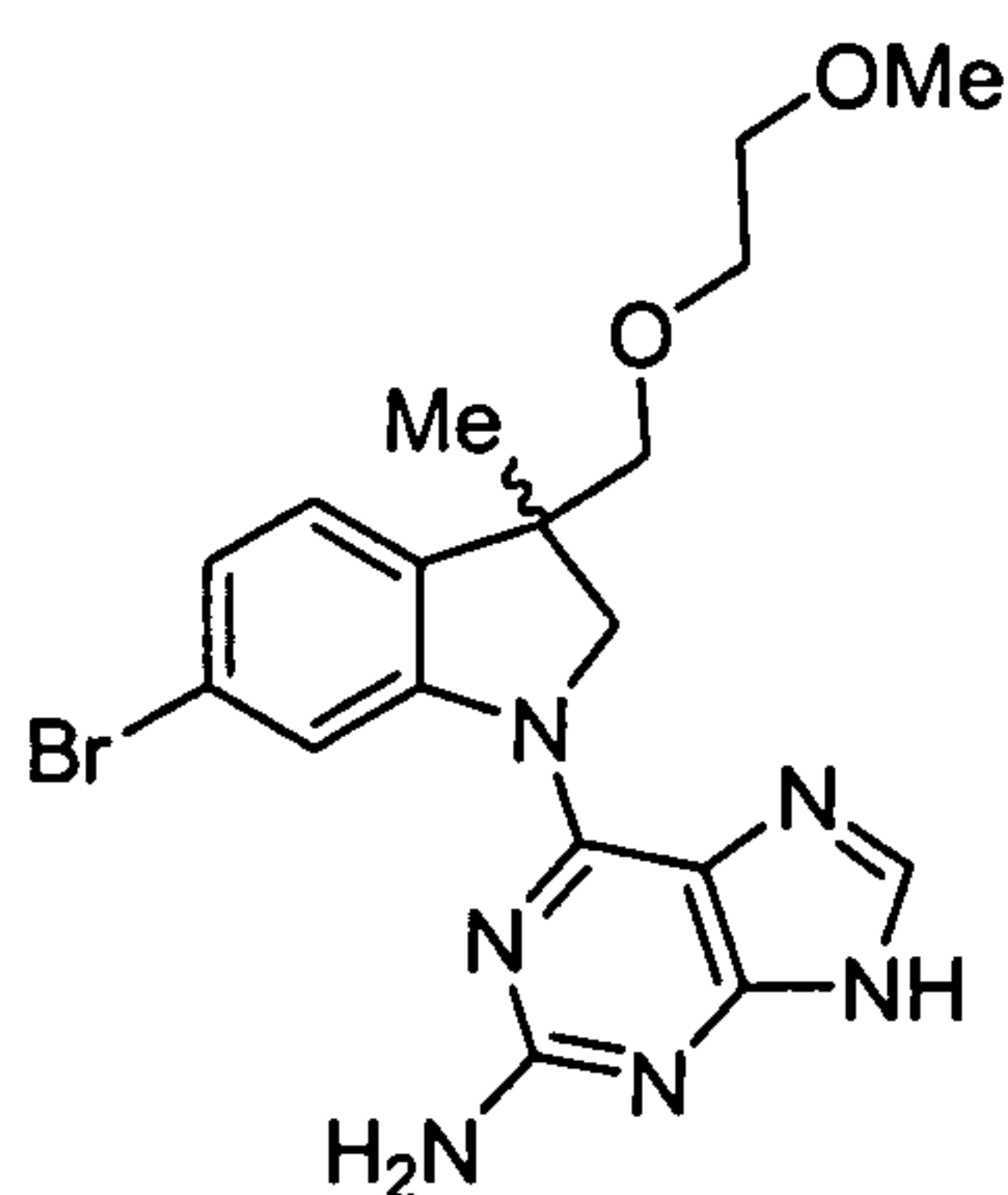
Under an atmosphere of nitrogen 1-acetyl-6-bromo-3-methyl-1,3-dihydro-2H-indol-2-one **A.26** (700mg, 2.61mmol) was dissolved in 4ml of anhydrous THF at 0°C. To this was cautiously added NaH (60% in mineral oil) (110mg, 2.74mmol) followed by MEMCl (0.596ml, 5.22mmol). The reaction was stirred at room temperature for 2hours. 10ml of EtOH was added followed by 10ml of 1N NaOH and the solution was stirred overnight. The next day the solution was diluted with saturated NH₄Cl and extracted with ethyl acetate. The organics were combined and washed with Brine before being dried over MgSO₄ and concentrated under vacuum. The residue obtained was purified by CombiFlash chromatography eluting with 20%ethyl acetate/dichloromethane. The fractions containing the product were combined and concentrated under vacuum to give 6-bromo-3-((2-methoxyethoxy)methyl)-3-methyl-1,3-dihydro-2H-indol-2-one (380mg) as a white solid.



A.75

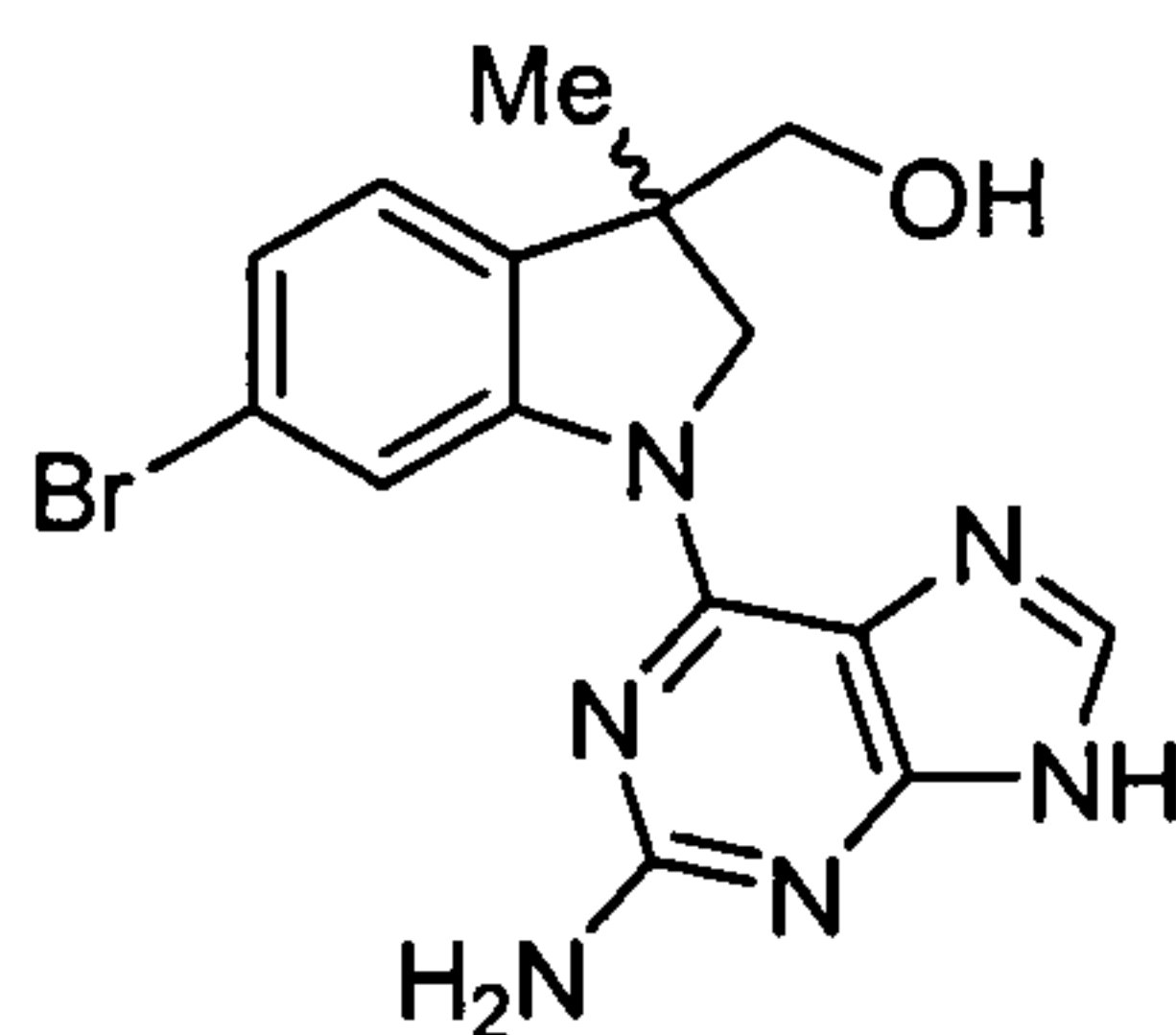
6-bromo-3-((2-methoxyethoxy)methyl)-3-methyl-2,3-dihydro-1H-indole A.75 was synthesized from **A.74** by the procedure used to prepare **A.28**; the title compound was obtained as a light brownish oil (322mg).

ESI-MS: $M + H^+$ 300.4 m/z.

**A.76**

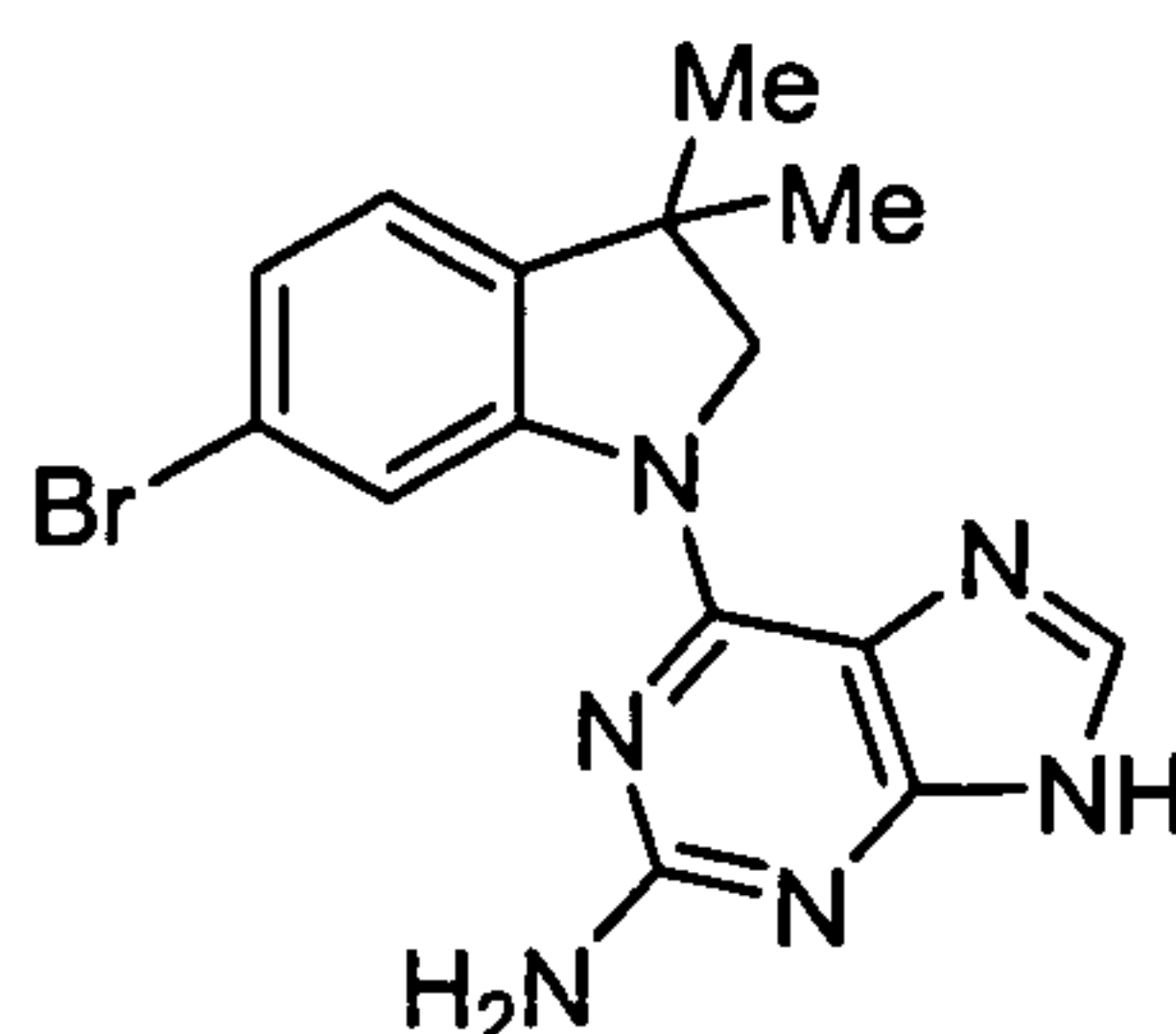
6-(6-bromo-3-((2-methoxyethoxy)methyl)-3-methyl-2,3-dihydro-1H-indol-1-yl)-9H-purin-2-amine A.76 was synthesized from A.75 by the procedure used to prepare A.70; the title compound was obtained as an off white solid (41mg, 17%).

ESI-MS: $M + H^+$ 433.3 m/z

**A.77**

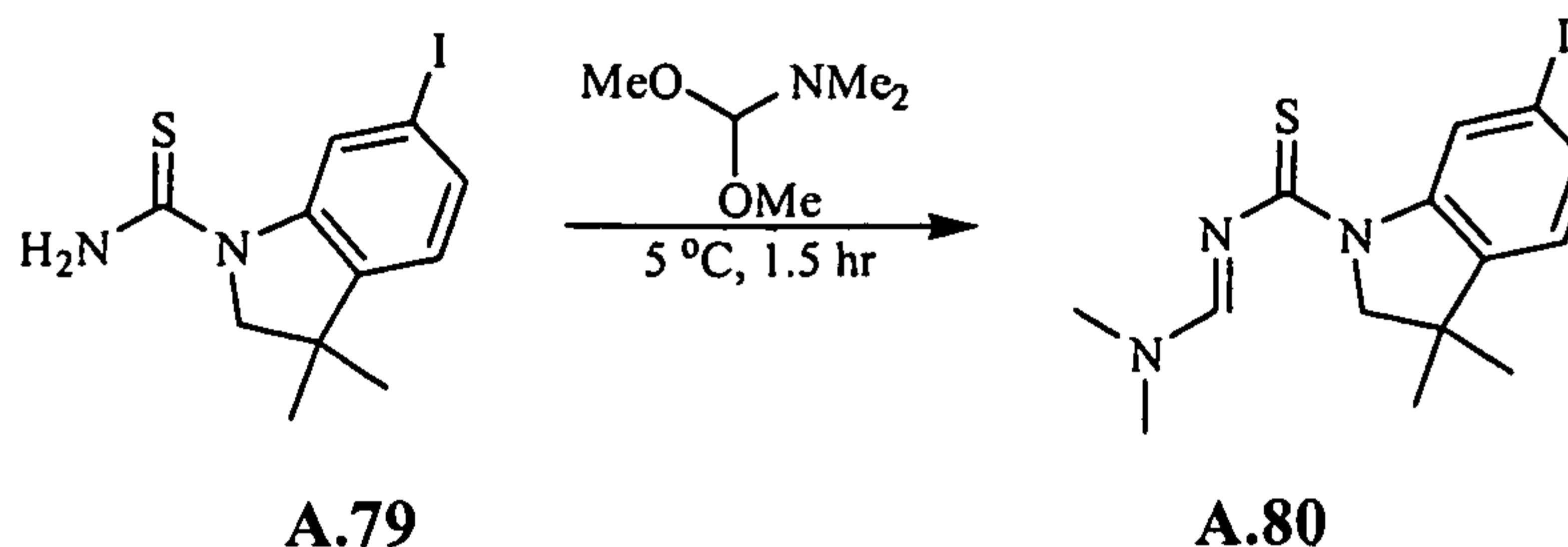
(1-(2-amino-9H-purin-6-yl)-6-bromo-3-methyl-2,3-dihydro-1H-indol-3-yl)methanol A.77 was synthesized from A.28 by the procedure used to prepare A.70; the title compound was obtained as an off white solid (40mg, 17%).

ESI-MS: $M + H^+$ 3757.1 m/z.

**A.78**

6-(6-bromo-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-9H-purin-2-amine A.78 was obtained as a white solid (170mg, 40%) from 6-bromo-3,3-dimethylindoline A.54 by the procedure used to prepare A.70.

ESI-MS: $M + H^+$ 359.0 m/z.

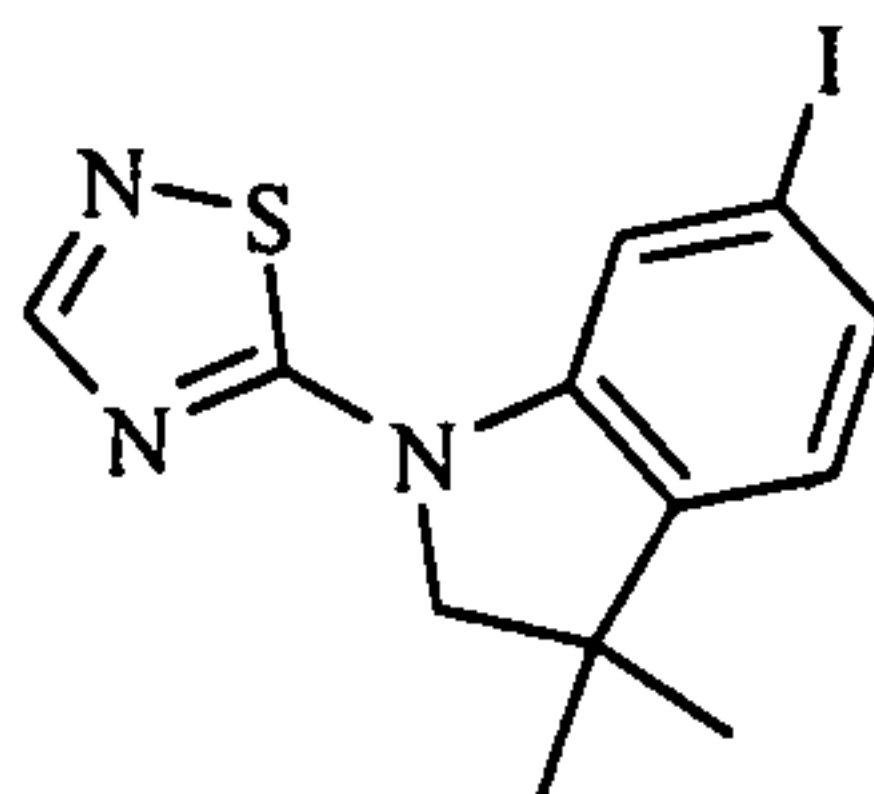


6-iodo-3,3-dimethylindoline-1-carbothioamide A.79

A.79 was prepared from **A.10** in analogy to the procedure of Zhang, M., R. Dally, et al. (2004). *Syn. Comm.* 34(21): 4023-4030.

N-((dimethylamino)methylene)-6-iodo-3,3-dimethylindoline-1-carbothioamide A.80

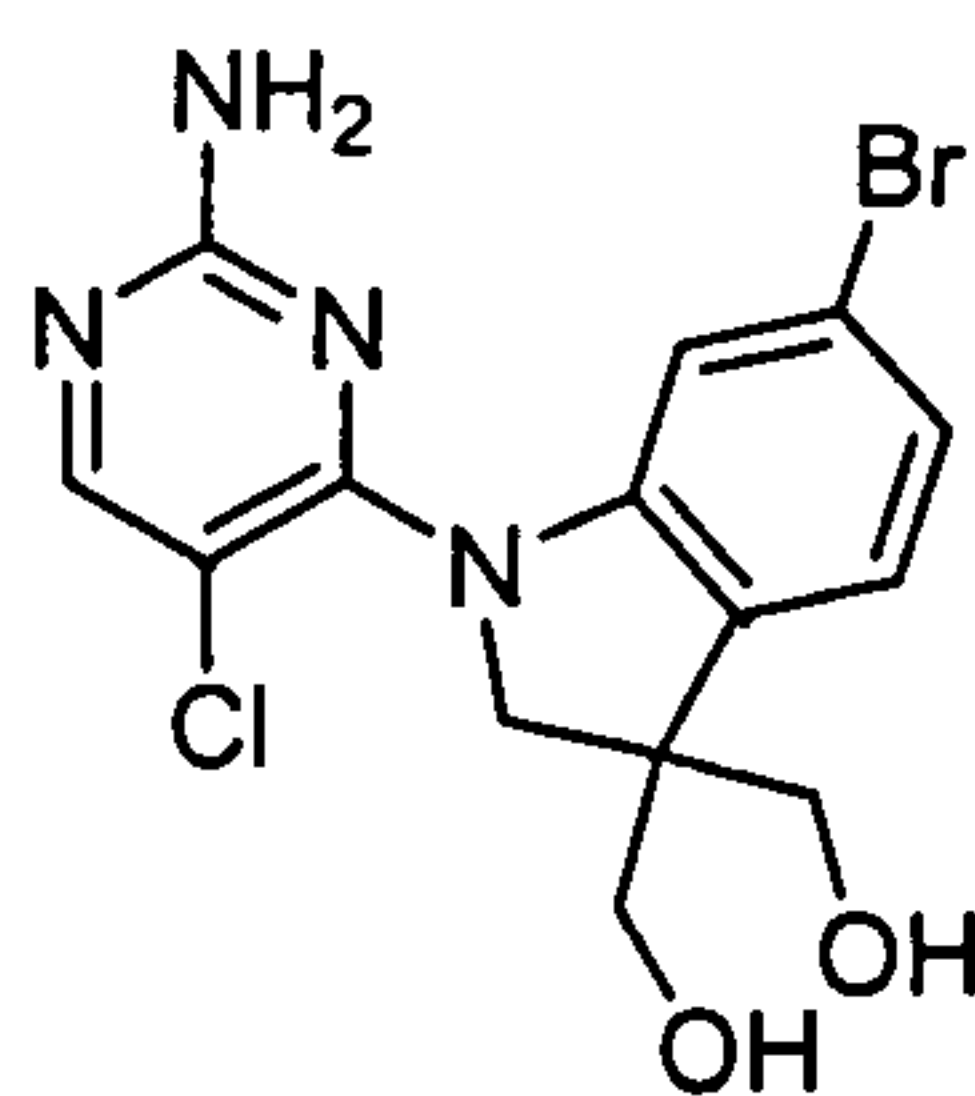
Dimethylformamide dimethoxyacetal (14.3 mL, 120 mmol) was cooled to 5 °C. 6-iodo-3,3-dimethylindoline-1-carbothioamide **A.79** (2.66 g, 8 mmol) was added slowly over 5 minutes, and the reaction stirred at 5 °C for 1.5 hours. Concentration under vacuum afforded **A.80** 3.1 g as an oil. ¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 8.80 (1 H, s), 8.76 (1 H, s), 7.37 (1 H, d, *J*=7.6 Hz), 7.11 (1 H, d, *J*=7.8 Hz), 4.16 (2 H, s), 3.27 (3 H, s), 3.16 (3 H, s), 1.28 (6 H, s)



A.81

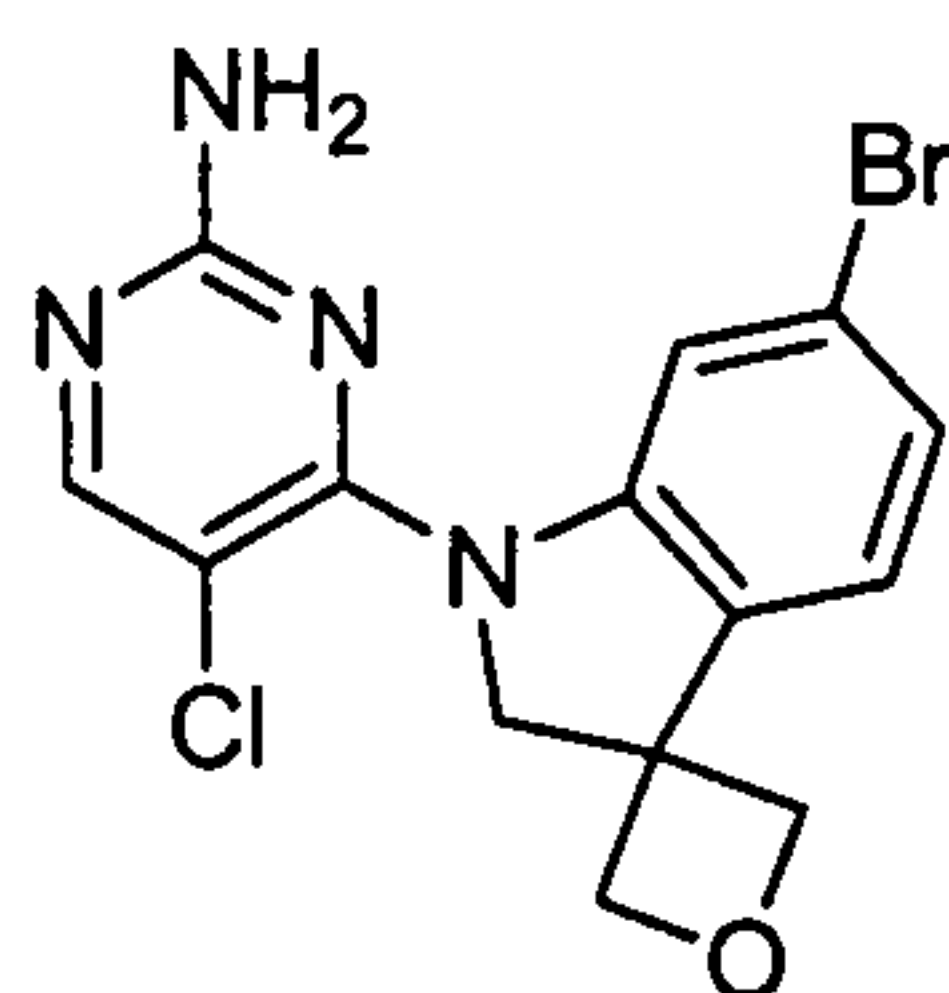
6-iodo-3,3-dimethyl-1-(1,2,4-thiadiazol-5-yl)indoline A.81

A solution of N-((dimethylamino)methylene)-6-iodo-3,3-dimethylindoline-1-carbothioamide **A.80** (3.1 g, 8 mmol), pyridine (1.31 mL, 16 mmol) and 20 mL EtOH was stirred at room temp. A solution of hydroxylaminesulfonic acid (0.905 g, 8 mmol) in 10 mL methanol was added all at once, and the mixture was heated to reflux 17 hours. The reaction was concentrated *in vacuo*, dissolved in dichloromethane and washed with water, 0.1 N NaOH and water again. Dried over MgSO₄, condensed, and the residue purified by flash chromatography (0-15-100% ethyl acetate in hexane) to give 1.5 g of 6-iodo-3,3-dimethyl-1-(1,2,4-thiadiazol-5-yl)indoline **A.81**. ¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 8.39 (1 H, s), 8.30 (1 H, s), 7.43 (1 H, d, *J*=7.8 Hz), 7.18 (1 H, d, *J*=7.8 Hz), 3.84 (2 H, s), 1.37 (6 H, s)



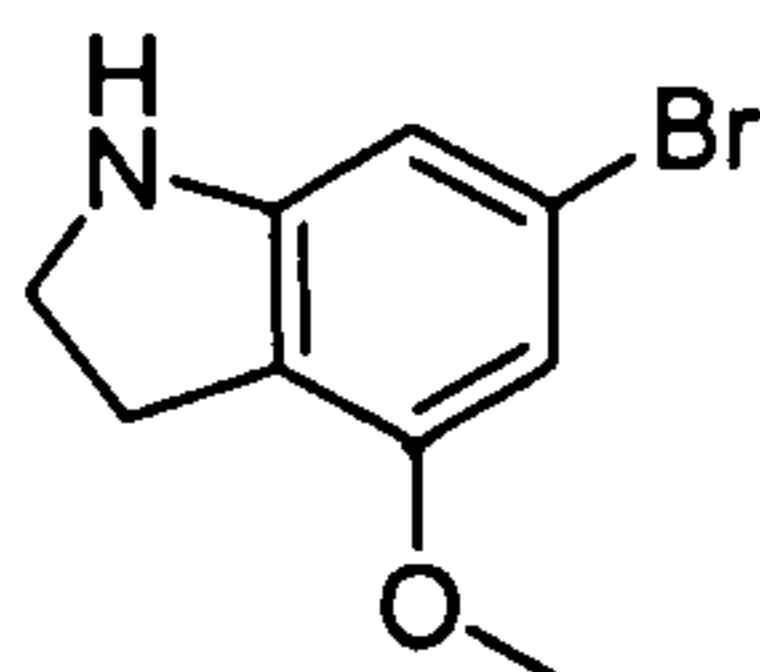
A.83

(1-(2-Amino-5-chloro-4-pyrimidinyl)-6-bromo-3-(hydroxymethyl)-2,3-dihydro-1H-indol-3-yl)methanol. A.83 was prepared from A.39 by the procedure used to prepare A.2. MS ESI (pos.) m/e: 385.0 (M+H).



A.84

4-(6-bromospiro[indoline-3,3'-oxetane]-1-yl)-5-chloropyrimidin-2-amine A.84. To a sealed tube containing (1-(2-amino-5-chloro-4-pyrimidinyl)-6-bromo-3-(hydroxymethyl)-2,3-dihydro-1H-indol-3-yl)methanol **A.83** (200.6 mg, 0.52 mmol) in pyridine (8.00 mL) was added potassium *tert*-butoxide (64.4 mg, 0.57 mmol) in portions. After 1 hour, *para*-toluene sulfonyl chloride (119.6 mg, 0.63 mmol) was added. Upon complete addition, additional potassium *tert*-butoxide (88.0 mg, 0.78 mmol) was added then the mixture was heated to 100 °C. After 3 hours, the reaction was carefully quenched with cold water then extracted three times with dichloromethane. After concentrating under reduced pressure, the residue (191 mg) was used as is for the preparation of examples **81** and **82**.

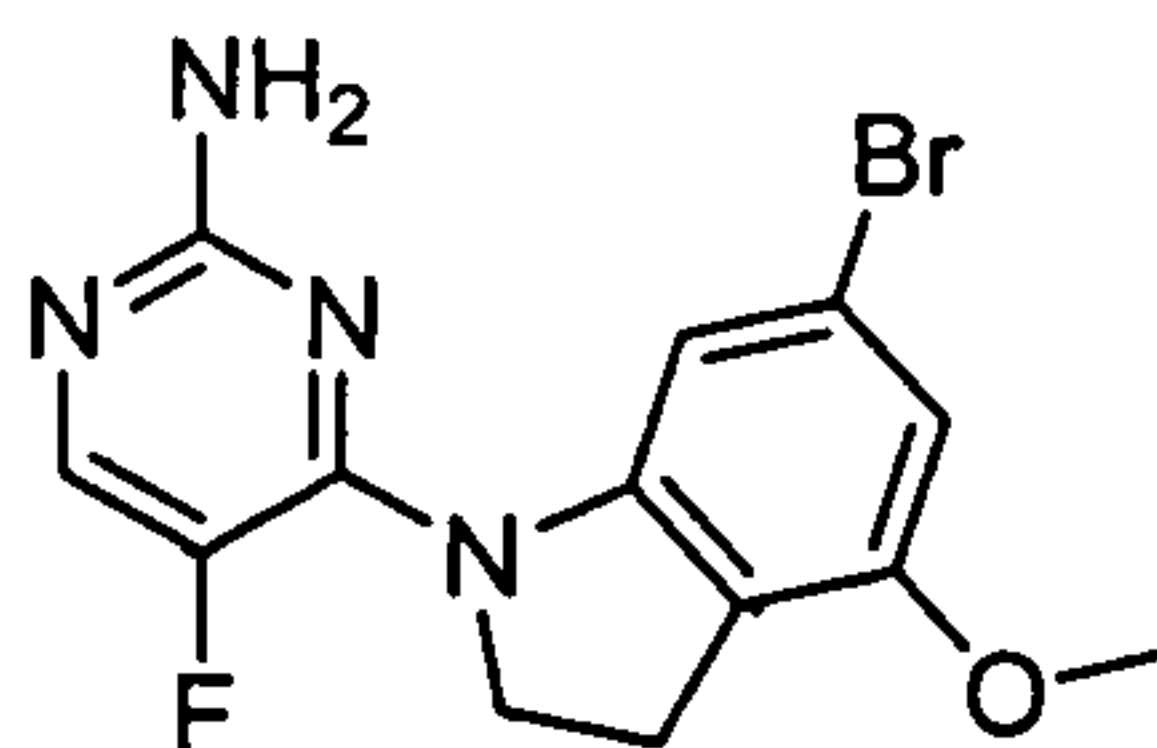


A.86

6-bromo-4-methoxyindoline A.86 To a stirred solution of 6-bromo-4-methoxy-1H-indole **A.85** (1.80 g, 7.98 mmol) in acetic acid (21 mL) at room temperature was added NaBH₃CN (1.5037 g, 23.93 mmol) and the mixture was stirred at room temperature for 1 hour. To the mixture was added water (100 mL) and the mixture was cooled to 0 °C. The mixture was

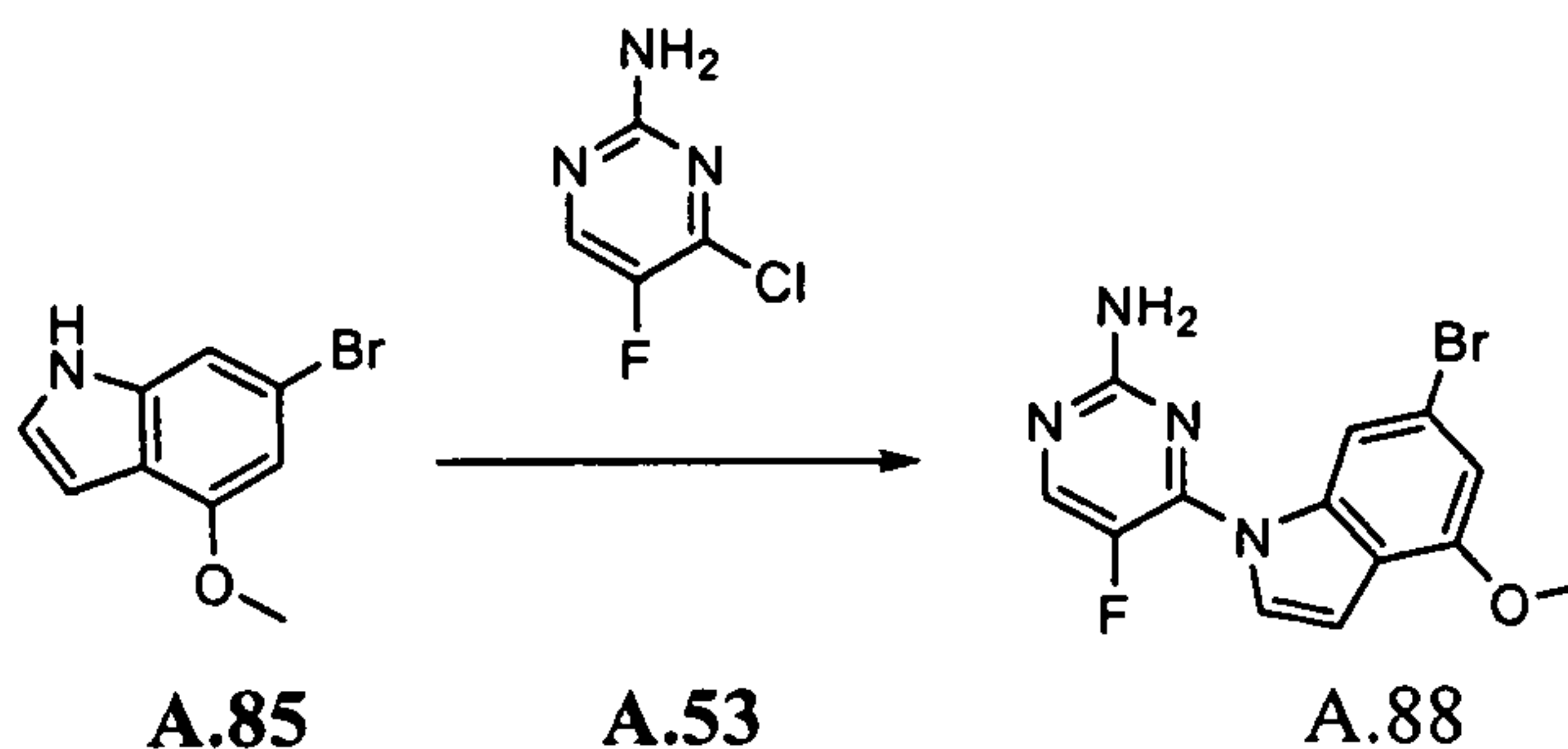
made basic with 10 N aqueous NaOH (35 mL) to pH 14. The mixture was extracted with ether (50 mL x 3). The combined organic layers were washed with water (50 mL x 2) and brine (50 mL x 2), dried over K₂CO₃, filtered, and concentrated under reduced pressure to give 6-bromo-4-methoxyindoline **A.86** (1.56 g, 85.7% yield) as a brown oil: ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 6.34 (1 H, d, *J*=1.4 Hz), 6.29 (1 H, d, *J*=1.4 Hz), 5.71 (1 H, s), 3.72 (3 H, s), 3.39 - 3.46 (2 H, m), 2.76 (2 H, t, *J*=8.7 Hz); Mass Spectrum (ESI) *m/e* = 228.1 [M+1 (⁷⁹Br)] and 230.1 [M+1 (⁸¹Br)].

4-(6-bromo-4-methoxyindolin-1-yl)-5-fluoropyrimidin-2-amine A.87



A.87

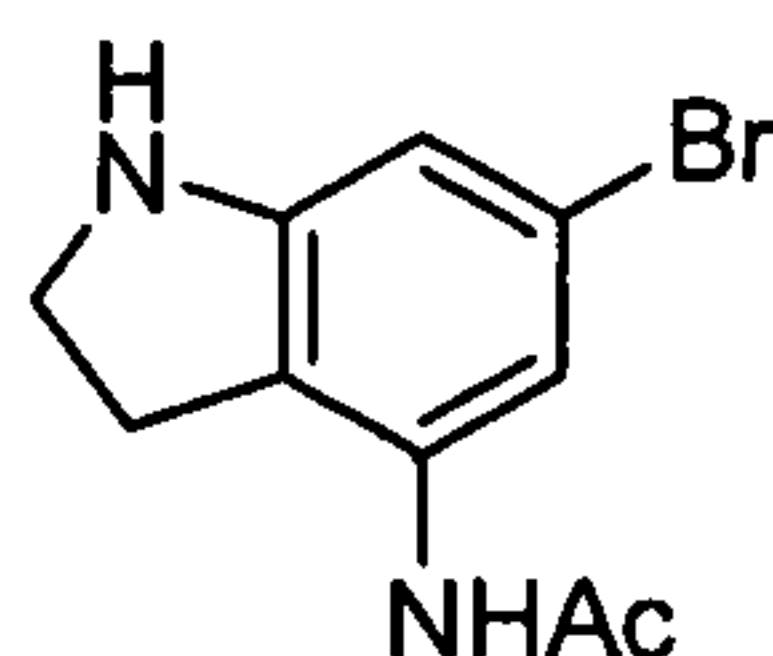
A mixture of 6-bromo-4-methoxyindoline (**A.86**), (0.8058 g, 5.46 mmol) and 4-chloro-5-fluoropyrimidin-2-amine (**A.53**), (1 g, 4.38 mmol) in 1,4-dioxane (10 mL) was stirred at 90 °C for 2 hours. The mixture was cooled to room temperature. The resulting precipitate was collected by suction filtration and washed with 1,4-dioxane to give a red solid. The product was purified by silica gel column chromatography using 10% of dichloromethane-methanol-NH₄OH (89:9:1) in dichloromethane as eluent to give 4-(6-bromo-4-methoxyindolin-1-yl)-5-fluoropyrimidin-2-amine (**A.87**) (0.882 g, 59.3% yield) as a yellow solid: ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.00 (1 H, d, *J*=6.0 Hz), 7.90 (1 H, s), 6.81 (1 H, d, *J*=1.4 Hz), 6.39 (2 H, s), 4.19 - 4.27 (2 H, m), 3.81 (3 H, s), 2.97 (2 H, t, *J*=8.7 Hz); Mass Spectrum (ESI) *m/e* = 339.0 [M+1 (⁷⁹Br)] and 341.0 [M+1 (⁸¹Br)].



4-(6-bromo-4-methoxy-1H-indol-1-yl)-5-fluoropyrimidin-2-amine A.88 was prepared from components **A.53** and **A.85** by the procedure described for compound **A.134**: ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.45 (1 H, d, *J*=4.1 Hz), 8.07 (1 H, s), 7.68 (1 H, t, *J*=3.2 Hz), 6.99 (2

H, s), 6.92 (1 H, d, $J=1.4$ Hz), 6.77 (1 H, d, $J=3.7$ Hz), 3.93 (3 H, s); Mass Spectrum (ESI) m/e = 337.0 [$M+1$ (^{79}Br)] and 339.0 [$M+1$ (^{81}Br)].

N-(6-bromoindolin-4-yl)acetamide

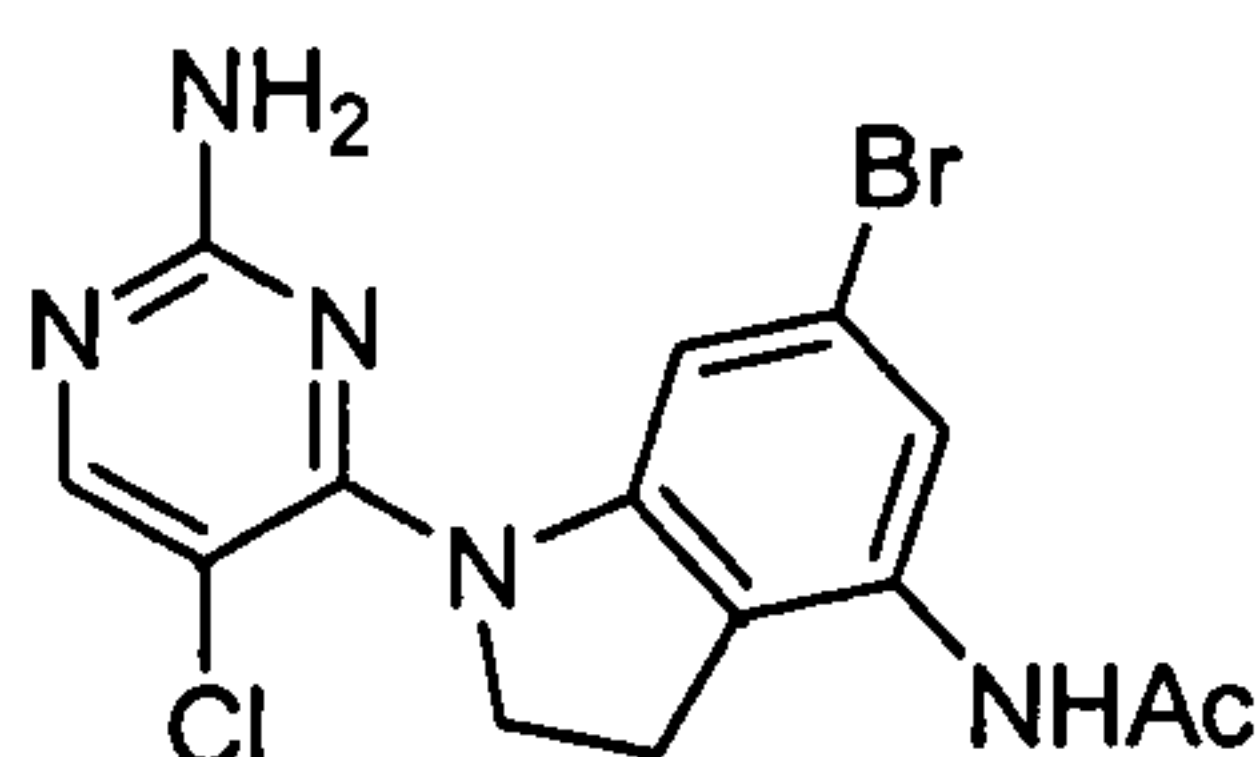


A.89

To a stirred solution of N-(6-bromo-1H-indol-4-yl)acetamide **A.138** (1.086 g, 4.29 mmol) in acetic acid (10 mL) at room temperature was added NaBH_3CN (0.8092 g, 12.88 mmol) and the mixture was stirred at room temperature for 19 hours. To the mixture was added water (50 mL) and the mixture was cooled to 0 °C. The mixture was made basic with 10 N aqueous NaOH (20 mL) to pH 14. The mixture was extracted with ether (50 mL x 2). The combined organic layers were washed with water (50 mL x 2) and brine (50 mL x 1), dried over K_2CO_3 , filtered, and concentrated under reduced pressure to give a brown solid. The brown solid was purified by silica gel column chromatography using 90% of ethyl acetate in hexane as eluent to give N-(6-bromoindolin-4-yl)acetamide **A.89** (0.6229 g, 56.9% yield) as a tan solid: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 9.25 (1 H, s), 7.09 (1 H, s), 6.37 (1 H, s), 5.75 (1 H, s), 3.42 (2 H, t, $J=9.1$ Hz), 2.82 (2 H, t, $J=8.2$ Hz), 2.03 (3 H, s)

Mass Spectrum (ESI) m/e = 255.0 [$M+1$ (^{79}Br)] and 257.0 [$M+1$ (^{81}Br)].

N-(1-(2-amino-5-chloropyrimidin-4-yl)-6-bromoindolin-4-yl)acetamide

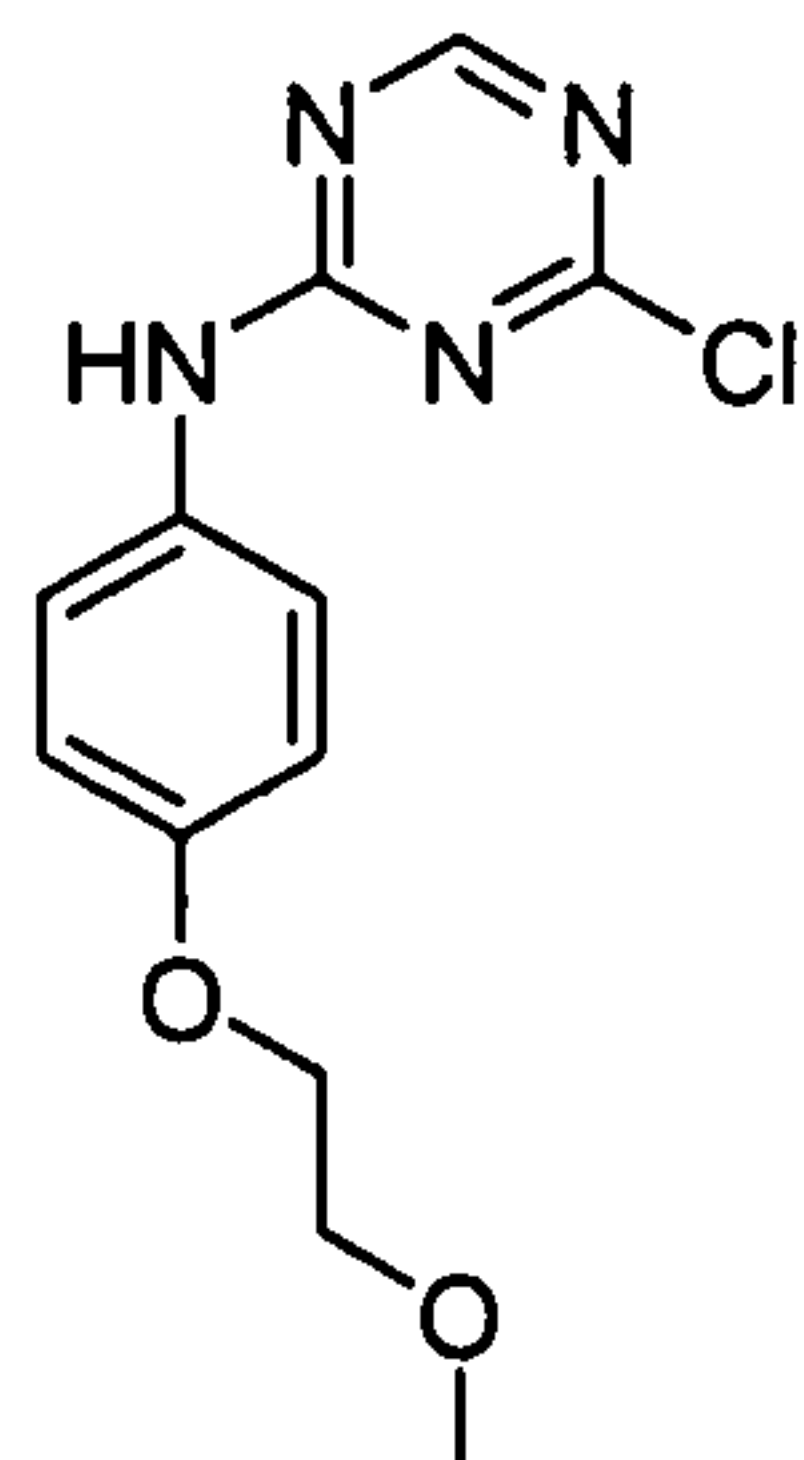


A.90

A mixture of N-(6-bromoindolin-4-yl)acetamide **A.89** (0.3109 g, 1.22 mmol), 4,5-dichloropyrimidin-2-amine **A.14** (0.1999 g, 1.22 mmol), and HCl (1.25 M sol. in EtOH, 0.3 mL, 0.375 mmol) in 1,4-dioxane (5 mL) was stirred at 90 °C for 27 hours. The mixture was concentrated under reduced pressure and purified by silica gel column chromatography using 0% to 100% of dichloromethane-methanol- NH_4OH (89:9:1) in dichloromethane as eluent to give N-(1-(2-amino-5-chloropyrimidin-4-yl)-6-bromoindolin-4-yl)acetamide **A.90** (0.3774 g, 80.9% yield) as an orange solid: ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 9.50 (1 H, s), 8.10 (1

H, s), 7.48 (1 H, s), 7.17 (1 H, s), 6.68 (2 H, s), 4.20 (2 H, t, $J=8.2$ Hz), 2.99 (2 H, t, $J=8.0$ Hz), 2.07 (3 H, s); Mass Spectrum (ESI) $m/e = 382.0$ [$M+1$ (^{79}Br)] and 384.0 [$M+1$ (^{81}Br)].

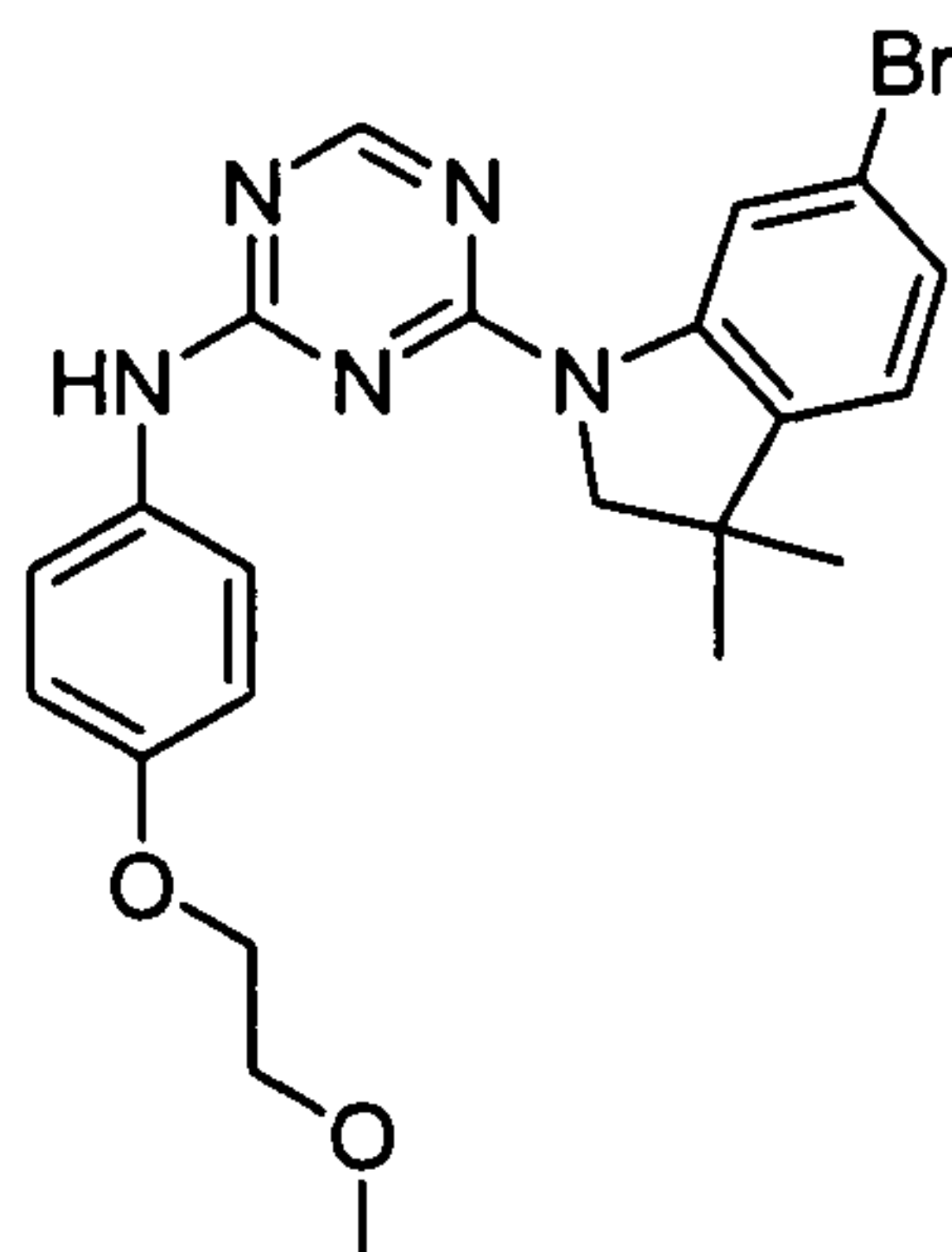
4-chloro-N-(4-(2-methoxyethoxy)phenyl)-1,3,5-triazin-2-amine



A.92

To a solution of 2,4-dichloro-1,3,5-triazine **A.91** (2 g, 13.34 mmol) in DMF (10 mL) at 0 °C were added DIEA (2.4 mL, 13.77 mmol) and 4-(2-methoxyethoxy)benzenamine (2.027 g, 12.12 mmol) and the mixture was stirred at 0 °C for 30 minutes and then room temperature for 1 hour. The mixture was diluted with ethyl acetate (100 mL) and washed with brine (50 mL x 1), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give a brown solid. The brown solid was purified by silica gel column chromatography using 30% of ethyl acetate in hexane as eluent to give 4-chloro-N-(4-(2-methoxyethoxy)phenyl)-1,3,5-triazin-2-amine **A.92** (2.887 g, 84.8% yield) as a white solid: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 10.58 (1 H, s), 8.56 (1 H, d, $J=5.9$ Hz), 7.51 (2 H, t, $J=9.5$ Hz), 6.96 (2 H, t, $J=7.9$ Hz), 4.04 - 4.11 (2 H, m), 3.65 (2 H, dd, $J=5.3, 3.8$ Hz), 3.31 (3 H, s); Mass Spectrum (ESI) $m/e = 281.0$ [$M+1$].

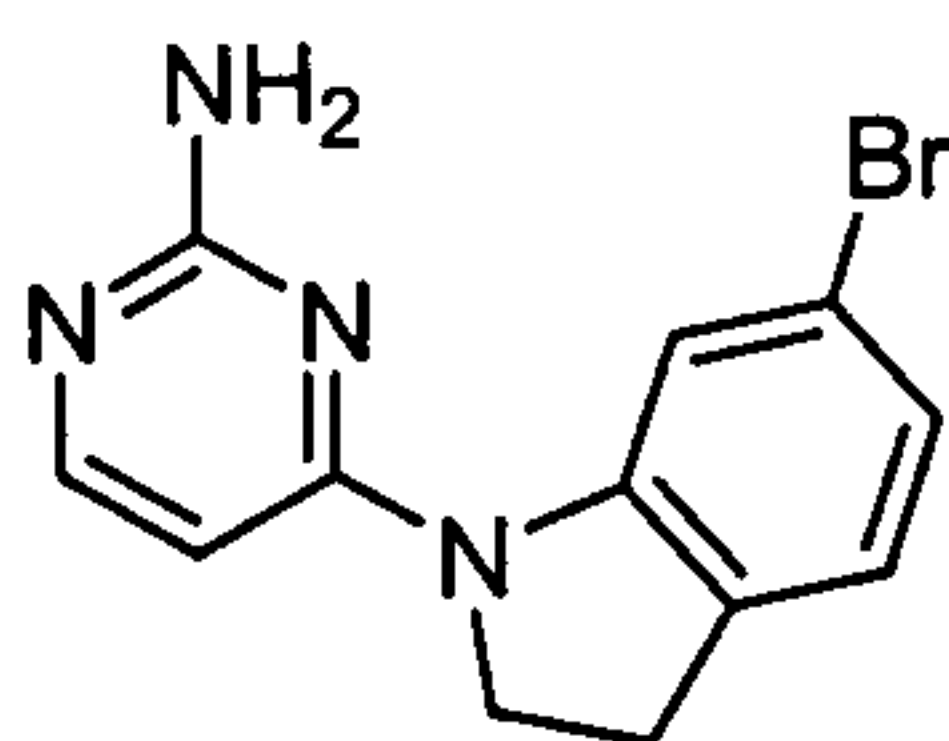
4-(6-bromo-3,3-dimethylindolin-1-yl)-N-(4-(2-methoxyethoxy)phenyl)-1,3,5-triazin-2-amine



A.93

A mixture of 4-chloro-N-(4-(2-methoxyethoxy)phenyl)-1,3,5-triazin-2-amine **A.92** (0.2483 g, 0.885 mmol), 6-bromo-3,3-dimethylindoline **A.54** (0.2 g, 0.885 mmol), and 1N aq. HCl (10 mL) was heated at reflux with stirring for 30 minutes. The mixture was cooled to 0 °C and neutralized with 2 N aq. NaOH to pH 8.0 with stirring. The aqueous layer was extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (50 mL x 1), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a brown solid. The product was purified by silica gel column chromatography using 30% to 50% gradient of ethyl acetate in hexane as eluent to give 4-(6-bromo-3,3-dimethylindolin-1-yl)-N-(4-(2-methoxyethoxy)phenyl)-1,3,5-triazin-2-amine **A.93** (0.1825 g, 43.9% yield) as a solid: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.74 (1 H, s), 8.09 - 8.58 (2 H, m), 7.49 (2 H, d, *J*=46.1 Hz), 7.08 - 7.26 (2 H, m), 6.95 (2 H, d, *J*=4.4 Hz), 4.05 - 4.11 (2 H, m), 3.95 (2 H, s), 3.62 - 3.68 (2 H, m), 3.30 (3 H, s), 1.31 (6 H, s); Mass Spectrum (ESI) *m/e* = 470.0 [M+1 (⁷⁹Br)] and 472.1 [M+1 (⁸¹Br)].

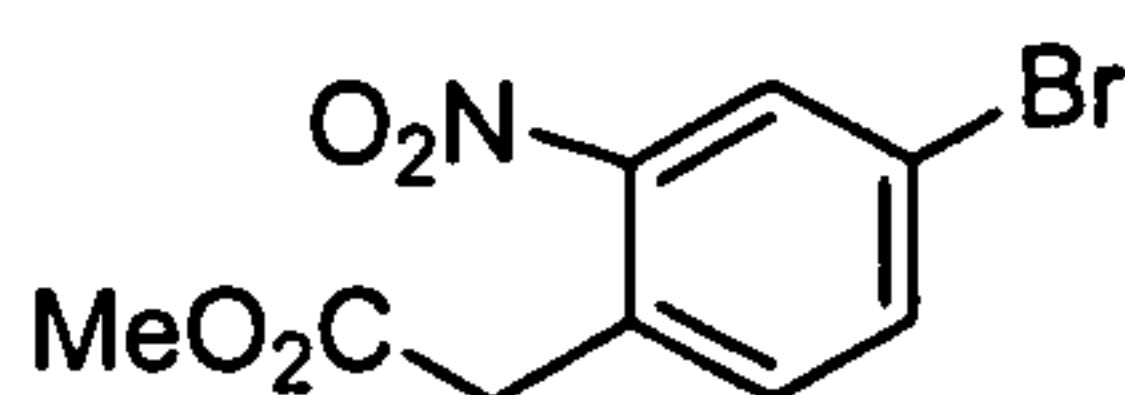
4-(6-bromoindolin-1-yl)pyrimidin-2-amine



A.95

A mixture of 6-bromoindoline **A.1** (3.96 g, 20 mmol) and 4-chloropyrimidin-2-amine **A.12** (3.3g, 20 mmol) in 1,4-dioxane (80 mL) was stirred at 90 °C for 21 hours. The mixture was cooled to room temperature. The resulting precipitate was collected by filtration and washed with ether (60 mL) to give 4-(6-bromoindolin-1-yl)pyrimidin-2-amine **A.95** (5.35 g, 92% yield) as a yellow solid: ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.72 (1 H, s), 8.06 (1 H, d, *J*=7.1 Hz), 7.36 (1 H, s), 7.26 (2 H, s), 7.16 (1 H, s), 6.42 (1 H, d, *J*=7.1 Hz), 4.18 (2 H, t, *J*=8.4 Hz), 3.19 (2 H, t, *J*=7.7 Hz); Mass Spectrum (ESI) *m/e* = 291.1 [M+1 (⁷⁹Br)] and 293.0 [M+1 (⁸¹Br)].

Methyl (4-bromo-2-nitrophenyl)acetate **A.97**

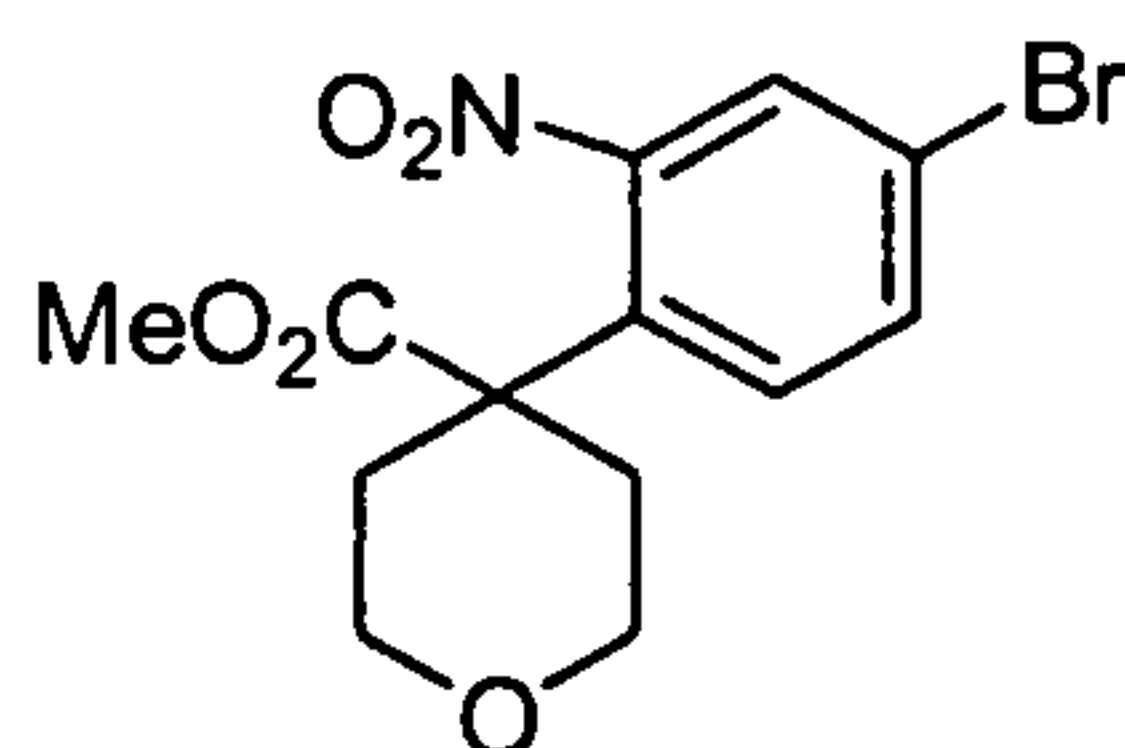


A.97

Ref. Quallich, G. J.; Morrissey, P. M. *Synthesis* **1993**, 51-53.

To a stirred solution of dimethyl 2-(4-bromo-2-nitrophenyl)malonate **A.17** (20 g, 60.2 mmol) in DMSO (200mL) was added lithium chloride (5.11 g, 2 eq.) followed by water (1.1 mL, 1 eq.) at room temperature. The resulting mixture was stirred at 100 °C for 2 days and at ambient temperature for 4 more days. The mixture was poured into water and extracted with ethyl acetate (2 x). The combined organics were washed with brine (2 x) and dried over Na₂SO₄. The residue after concentration *in vacuo* was subjected to Combi-Flash column chromatography (ethyl acetate/hexanes) to give methyl (4-bromo-2-nitrophenyl)acetate **A.97** (12 g, 73 %) as a light yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ 8.30 (d, *J* = 2.1 Hz, 1H), 7.98 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.56 (d, *J* = 8.2 Hz, 1H), 4.08 (s, 2H), 3.63 (s, 3H). LCMS-ESI (POS), *M/Z*, *M*+1: Found 274.0 and 276.0.

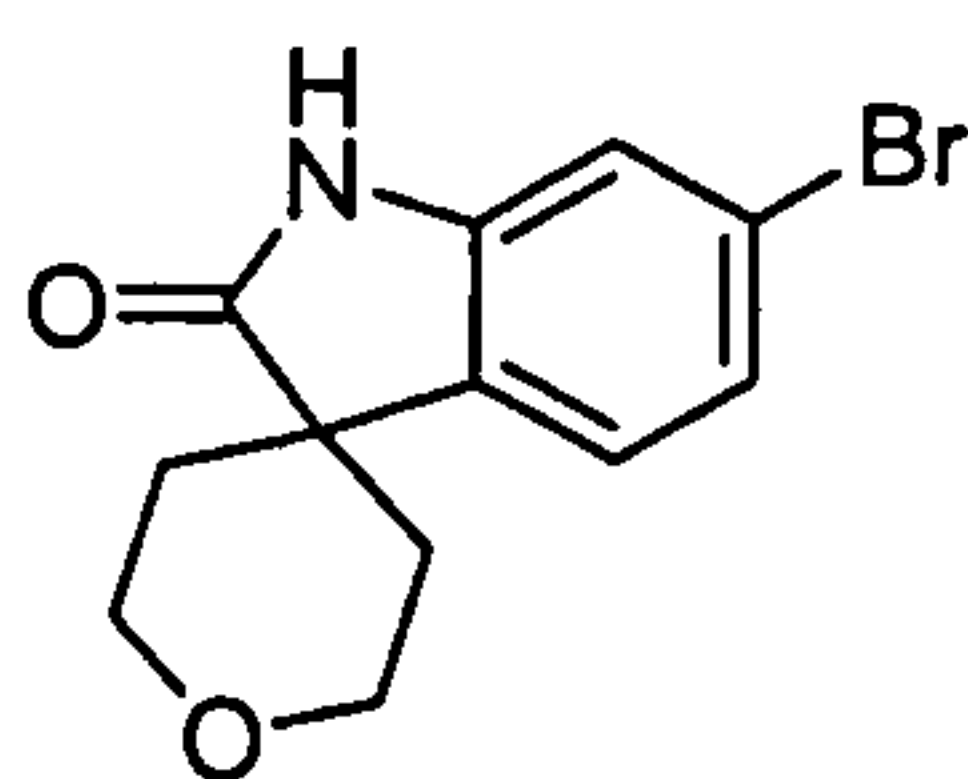
methyl 4-(4-bromo-2-nitrophenyl)-tetrahydro-2H-pyran-4-carboxylate



A.98

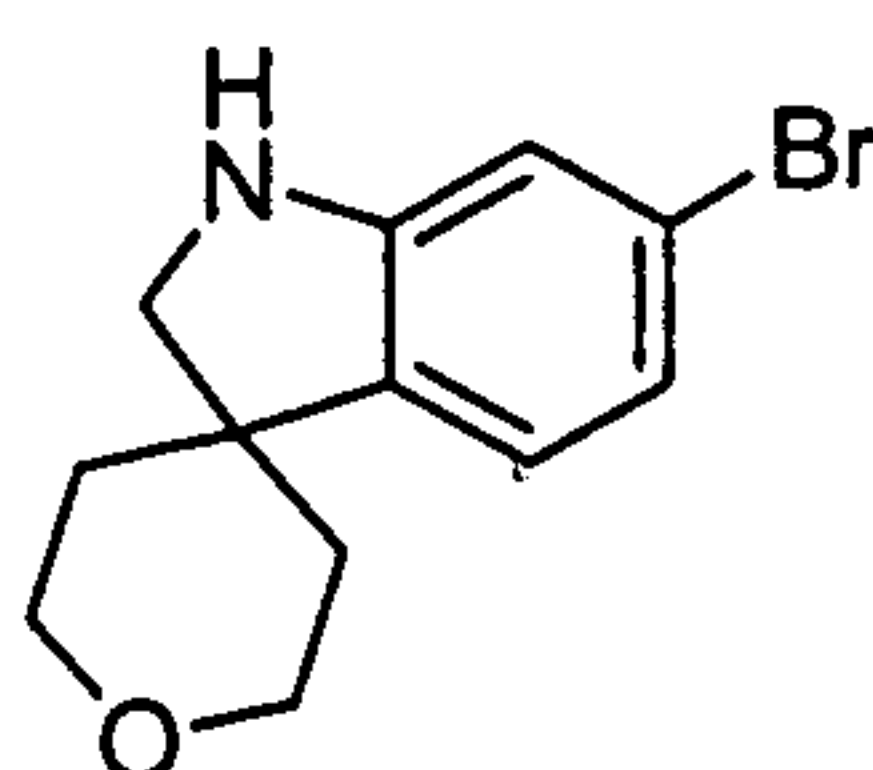
Sodium hydride (0.32 g, 8.03 mmol, 60% dispersion in oil) was added in portions at room temperature to a stirred solution of methyl 2-(4-bromo-2-nitrophenyl)acetate **A.97** (1 g, 3.65 mmol) in DMSO (15 mL). After the mixture was stirred at room temperature for 30 min, sodium iodide (0.055 g, 0.365 mmol) and bis(2-bromoethyl) ether (1.27 g, 5.47 mmol) were added. The resultant mixture was stirred at 40 °C. After 19 hours, the mixture was poured into brine with ice (~ 50 mL), extracted with ethyl acetate (50 mL, 3 times). The combined extracts were washed with brine (80 mL, 3 times), dried (Na₂SO₄), filtered, and concentrated under reduced pressure to give 1.69 g of a dark liquid. The product was purified by silica gel column chromatography using 0 to 50% gradient of ethyl acetate in *n*-hexane to give methyl 4-(4-bromo-2-nitrophenyl)-tetrahydro-2H-pyran-4-carboxylate **A.98** (0.45 g, 36%) as an orange syrup: ¹H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 7.89 (1 H, d, *J*=2.2 Hz), 7.75 (1 H, dd, *J*=8.6, 2.2 Hz), 7.50 (1 H, d, *J*=8.8 Hz), 3.87 - 3.94 (2 H, m), 3.66 - 3.77 (5 H, m), 2.33 (2 H, dd, *J*=14.1, 2.8 Hz), 1.99 - 2.05 (2 H, m); ESI-MS *m/z* 344.0 [(*M*+1) (⁷⁹Br)] and 346.0 [(*M*+1) (⁸¹Br)].

6-bromo-2',3',5',6'-tetrahydrospiro[indole-3,4'-pyran]-2(1H)-one

**A.99**

Methyl 4-(4-bromo-2-nitrophenyl)-tetrahydro-2H-pyran-4-carboxylate **A.98** (6.67 g, 19.4 mmol) was dissolved in acetic acid (97 mL), Fe powder (5.42 g, 96.97 mmol) was added and the resultant mixture was stirred at 100 °C for 2.5 hours. The hot mixture was filtered through a Celite pad and the pad was washed with acetic acid (250 mL). The filtrate was concentrated under reduced pressure to give a dark syrup. The product was purified by silica gel column chromatography using 0 to 100% gradient of ethyl acetate in *n*-hexane) to give 4.75 g of a reddish-pink solid. The solid was suspended in 50% of ethyl acetate in hexane (20 mL), filtered, and washed with 50% of ethyl acetate in hexane (40 mL) on the filter paper to give 6-bromo-2',3',5',6'-tetrahydrospiro[indole-3,4'-pyran]-2(1H)-one **A.99** (3.93 g, 72%) as an orange-pink solid: ¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 10.53 (1 H, s), 7.47 (1 H, d, *J*=7.8 Hz), 7.14 (1 H, dd, *J*=8.1, 1.0 Hz), 6.98 (1 H, d, *J*=1.0 Hz), 3.91 - 4.12 (2 H, m), 3.67 - 3.86 (2 H, m), 1.54 - 1.84 (4 H, m); ESI-MS *m/z* 282.0 [(*M*+1) (⁷⁹Br)] and 284.0 [(*M*+1) (⁸¹Br)].

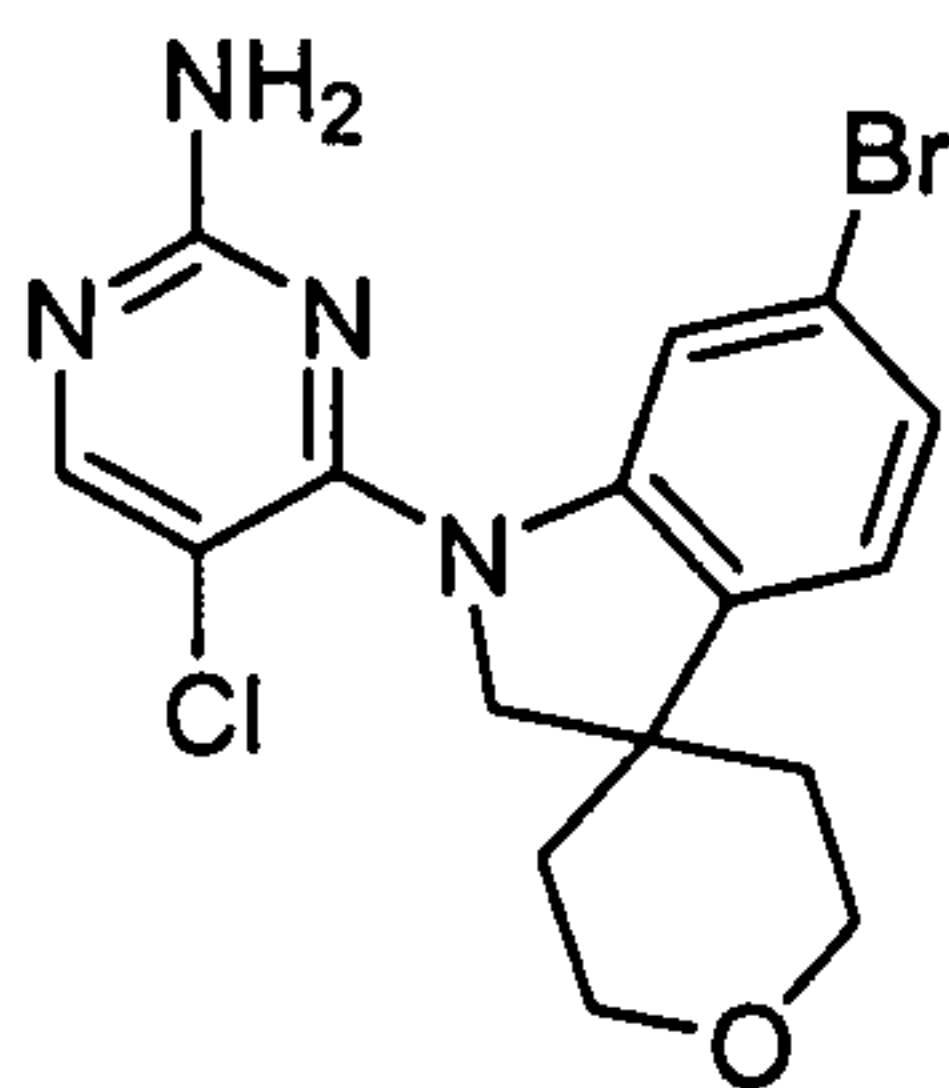
6-bromo-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-pyran] **A.100**

**A.100**

A heterogeneous mixture of 6-bromo-2',3',5',6'-tetrahydrospiro[indole-3,4'-pyran]-2(1H)-one **A.99** (3.5 g, 12.4 mmol) in toluene (25 mL) was stirred at 80 °C. To the heated mixture was added a solution of Red-Al (65% in toluene, 11.6 mL, 37.2 mmol) and the mixture was stirred at 80 °C. After 50 min, the mixture was cooled to 0 °C and quenched with 2 N of aqueous NaOH (31 mL, 62 mmol) with stirring. The mixture was extracted with ethyl acetate (100 mL, 2 times). The combined extracts were washed with brine (100 mL, 3 times), dried (Na₂SO₄), filtered, and concentrated under reduced pressure to give a green solid. The product was purified by silica gel column chromatography using 0 to 100% gradient of dichloromethane-methanol-NH₄OH (89:9:1) in dichloromethane) to give 6-bromo-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-pyran] **A.100** (2.13 g, 64%) as a yellow solid: ¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 6.91 - 6.99 (1 H, m), 6.66 (1 H, dd, *J*=7.8, 1.7 Hz), 6.59 (1

H, d, $J=1.7$ Hz), 5.85 (1 H, s), 3.70 - 3.87 (2 H, m), 3.36 - 3.51 (4 H, m), 1.65 - 1.84 (2 H, m), 1.39 - 1.57 (2 H, m); ESI-MS m/z 268.0 $[(M+1) (^{79}\text{Br})]$ and 270.0 $[(M+1) (^{81}\text{Br})]$.

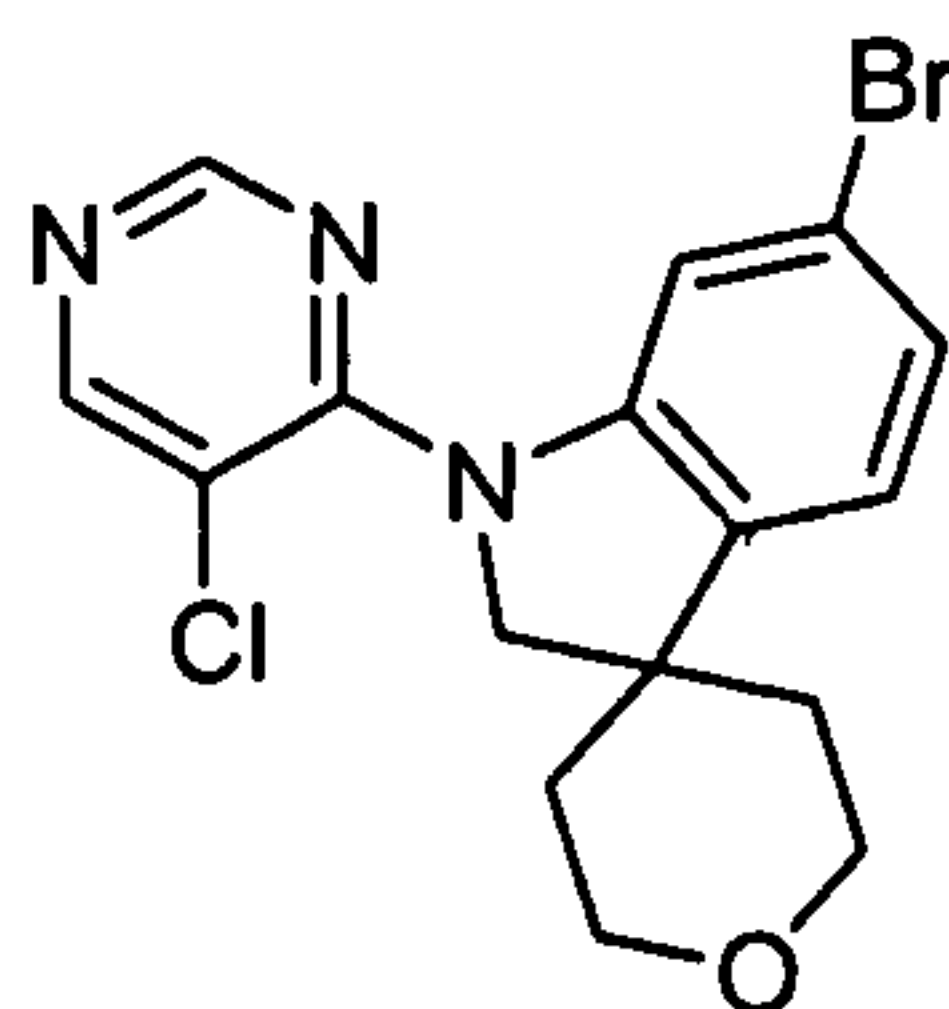
4-(6-bromo-2',3',5',6'-tetrahydrospiro[indole-3,4'-pyran]-1(2H)-yl)-5-chloro-2-pyrimidinamine



A.101

A mixture of 6-bromo-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-pyran]**A.100** (1 g, 3.73 mmol) and 4,5-dichloropyrimidin-2-amine **A.14** (1.223 g, 7.46 mmol) in 1 N aqueous HCl (60 mL) was stirred at 60 °C for 18.5 hours. The mixture was cooled to room temperature and poured into 2 N aqueous NaOH (180 mL) with ice. The mixture was extracted with ethyl acetate (100 mL x 2). The combined organic layers were washed with brine (100 mL x 2), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give a pink solid. The pink solid was purified by silica gel column chromatography using 0% to 100% gradient of ethyl acetate in hexane as eluent to give 4-(6-bromo-2',3',5',6'-tetrahydrospiro[indole-3,4'-pyran]-1(2H)-yl)-5-chloro-2-pyrimidinamine **A.101** (1.17 g, 79.4% yield) as a light yellow solid: ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 8.08 - 8.15 (1 H, m), 7.36 (1 H, s), 7.17 - 7.27 (1 H, m), 7.03 - 7.13 (1 H, m), 6.73 (2 H, s), 4.16 (2 H, s), 3.84 (2 H, dd, $J=11.6, 3.1$ Hz), 3.46 (2 H, t, $J=11.5$ Hz), 1.76 - 1.93 (2 H, m), 1.56 (2 H, d, $J=13.2$ Hz); Mass Spectrum (ESI) $m/e = 395.0$ $[M+1 (^{79}\text{Br})]$ and 397.0 $[M+1 (^{81}\text{Br})]$.

6-bromo-1-(5-chloropyrimidin-4-yl)-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-pyran]

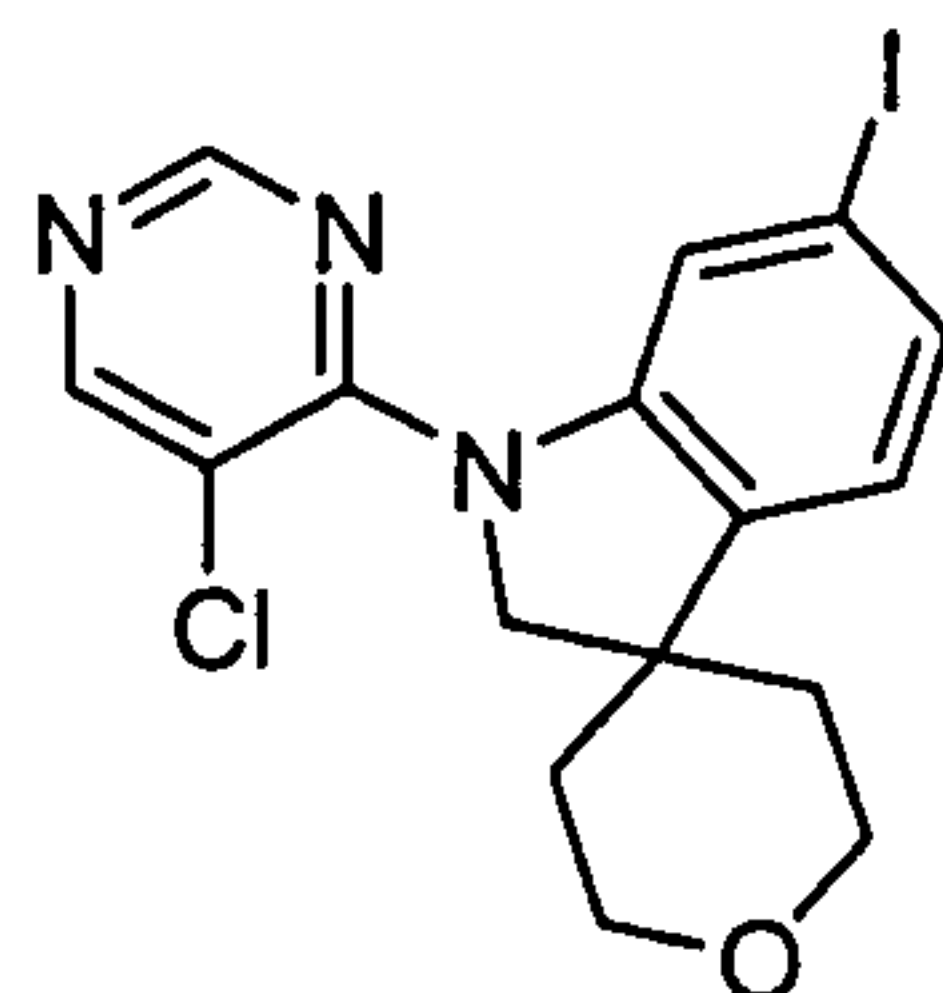


A.102

To a heterogeneous mixture of 4-(6-bromo-2',3',5',6'-tetrahydrospiro[indole-3,4'-pyran]-1(2H)-yl)-5-chloro-2-pyrimidinamine **A.101** (0.2 g, 0.505 mmol) in THF (1 mL) was added dropwise

isoamyl nitrite (0.34 mL, 2.53 mmol) with stirring and the mixture was heated at reflux for 1 hour. The mixture was poured into ice water (30 mL) and extracted with ethyl acetate (50 mL x 2). The combined organic layers were washed with brine (50 mL x 1), dried over MgSO_4 , filtered, and concentrated under reduced pressure to give a brown solid. The product was purified by silica gel column chromatography using 0% to 100% gradient of ethyl acetate in hexane as eluent to give 6-bromo-1-(5-chloropyrimidin-4-yl)-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-pyran] **A.102** (0.062 g, 32.2% yield) as a brown solid: ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 8.74 (1 H, s), 8.68 (1 H, s), 7.63 (1 H, d, $J=1.2$ Hz), 7.30 (1 H, d, $J=8.1$ Hz), 7.18 (1 H, dd, $J=7.9, 1.1$ Hz), 4.23 - 4.37 (2 H, m), 3.84 (2 H, dd, $J=11.9, 3.3$ Hz), 3.48 (2 H, t, $J=11.4$ Hz), 1.83 - 1.95 (2 H, m), 1.58 (2 H, d, $J=13.0$ Hz); Mass Spectrum (ESI) $m/e = 380.0$ [$\text{M}+1$ (^{79}Br)] and 382.0 [$\text{M}+1$ (^{81}Br)].

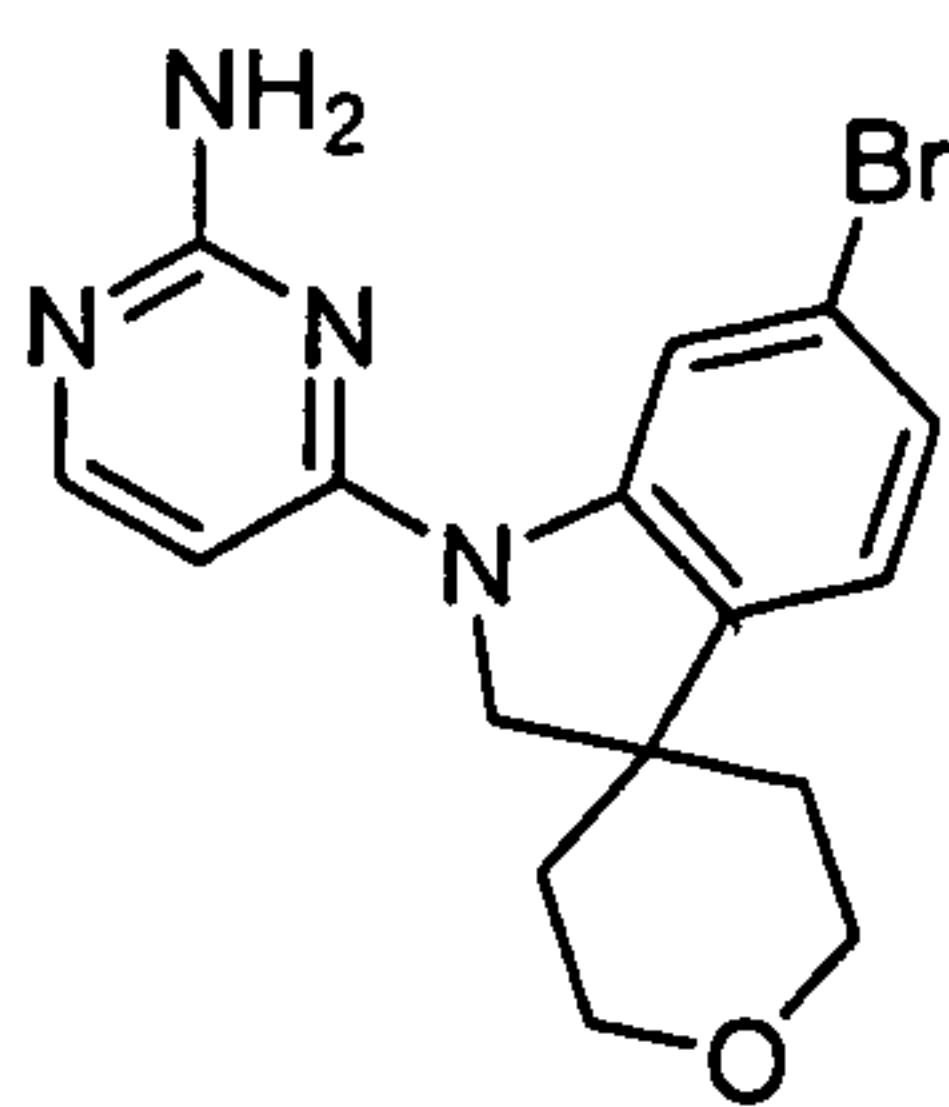
1-(5-chloropyrimidin-4-yl)-6-iodo-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-pyran]



A.103

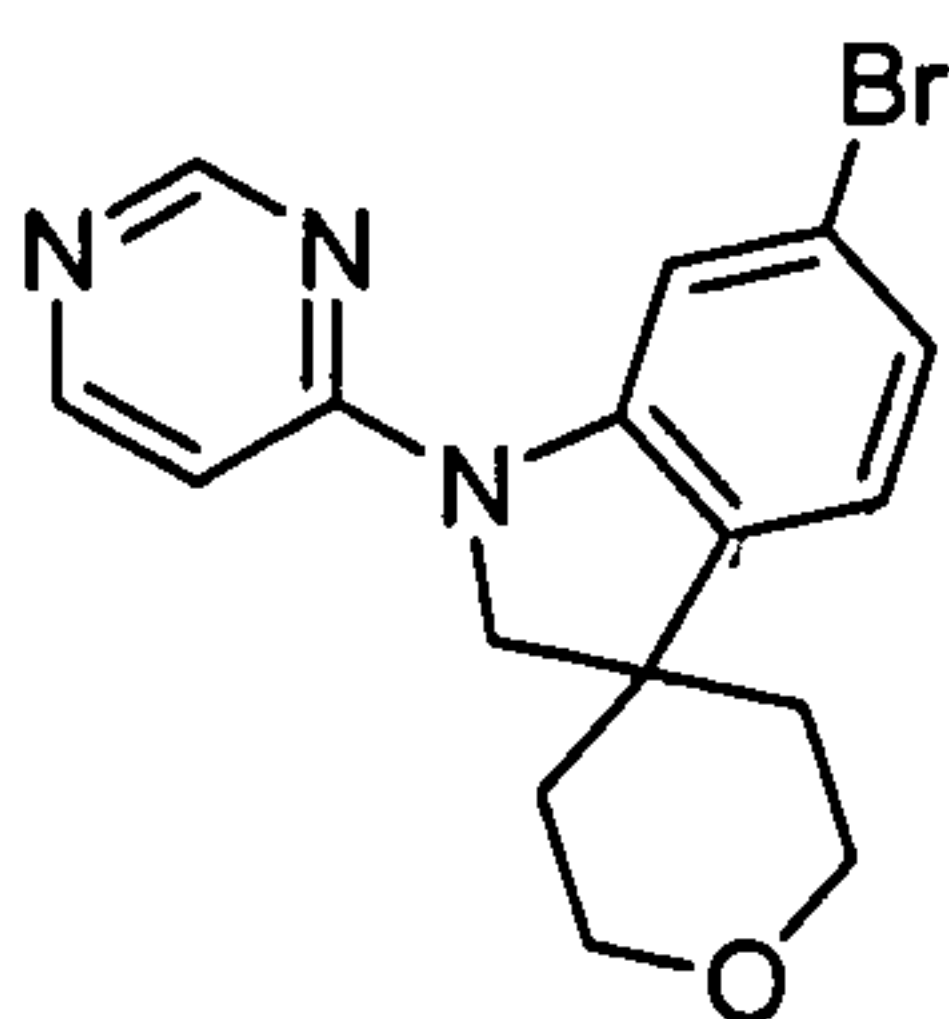
To a Schlenk tube were added 6-bromo-1-(5-chloropyrimidin-4-yl)-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-pyran] **A.102** (0.062 g, 0.16 mmol), CuI (0.0155 g, 0.081 mmol), NaI (0.049 g, 0.326 mmol), $\text{N1,N2-dimethylethane-1,2-diamine}$ (0.018 mL, 0.167 mmol), and 1,4-dioxane (0.33 mL) under argon and the mixture was stirred at 110 °C for 16 hours. The mixture was cooled to room temperature, diluted with 30% of aqueous ammonia (5 mL), poured into water (20 mL), and extracted with dichloromethane (15 mL x 3). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure to give a yellow solid. The yellow solid was purified by silica gel column chromatography using 0% to 100% gradient of ethyl acetate in hexane as eluent to give 1-(5-chloropyrimidin-4-yl)-6-iodo-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-pyran] **A.103** (0.0384 g, 55% yield) as a solid: ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 8.74 (1 H, s), 8.67 (1 H, s), 7.77 (1 H, s), 7.35 (1 H, d, $J=8.6$ Hz), 7.15 (1 H, d, $J=7.8$ Hz), 4.29 (2 H, s), 3.76 - 3.91 (2 H, m), 3.41 - 3.52 (2 H, m), 1.87 (2 H, d, $J=4.4$ Hz), 1.57 (2 H, d, $J=13.4$ Hz); Mass Spectrum (ESI) $m/e = 427.9$ [$\text{M}+1$].

4-(6-bromo-2',3',5',6'-tetrahydrospiro[indole-3,4'-pyran]-1(2H)-yl)pyrimidin-2-amine

**A.104**

A mixture of 6-bromo-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-pyran] **A.100** (0.5 g, 1.86 mmol) and 4-chloropyrimidin-2-amine **A.12** (0.4831 g, 3.73 mmol) in 1 N aqueous HCl (30 mL) was stirred at 60 °C for 17.5 hours. The mixture was cooled to room temperature and poured into 2 N aqueous NaOH (90 mL) with ice. The mixture was extracted with ethyl acetate (50 mL x 2). The combined organic layers were washed with brine (100 mL x 2), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a pink solid. The pink solid was purified by silica gel column chromatography using 0% to 100% gradient of dichloromethane-methanol-NH₄OH (89:9:1) in dichloromethane as eluent to give 4-(6-bromo-2',3',5',6'-tetrahydrospiro[indole-3,4'-pyran]-1(2*H*)-yl)pyrimidin-2-amine **A.104** (0.595 g, 88.3% yield) as a white solid: ¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 8.65 (1 H, d, *J*=1.5 Hz), 8.00 (1 H, d, *J*=5.9 Hz), 7.21 (1 H, d, *J*=8.1 Hz), 7.09 (1 H, dd, *J*=7.6, 1.5 Hz), 6.44 (2 H, s), 6.18 (1 H, d, *J*=5.9 Hz), 3.96 (2 H, s), 3.85 (2 H, dd, *J*=11.7, 3.7 Hz), 3.55 (2 H, t, *J*=11.7 Hz), 1.73 - 1.98 (2 H, m), 1.54 (2 H, d, *J*=13.0 Hz); Mass Spectrum (ESI) *m/e* = 361.0 [*M*+1 (⁷⁹Br)] and 363.1 [*M*+1 (⁸¹Br)].

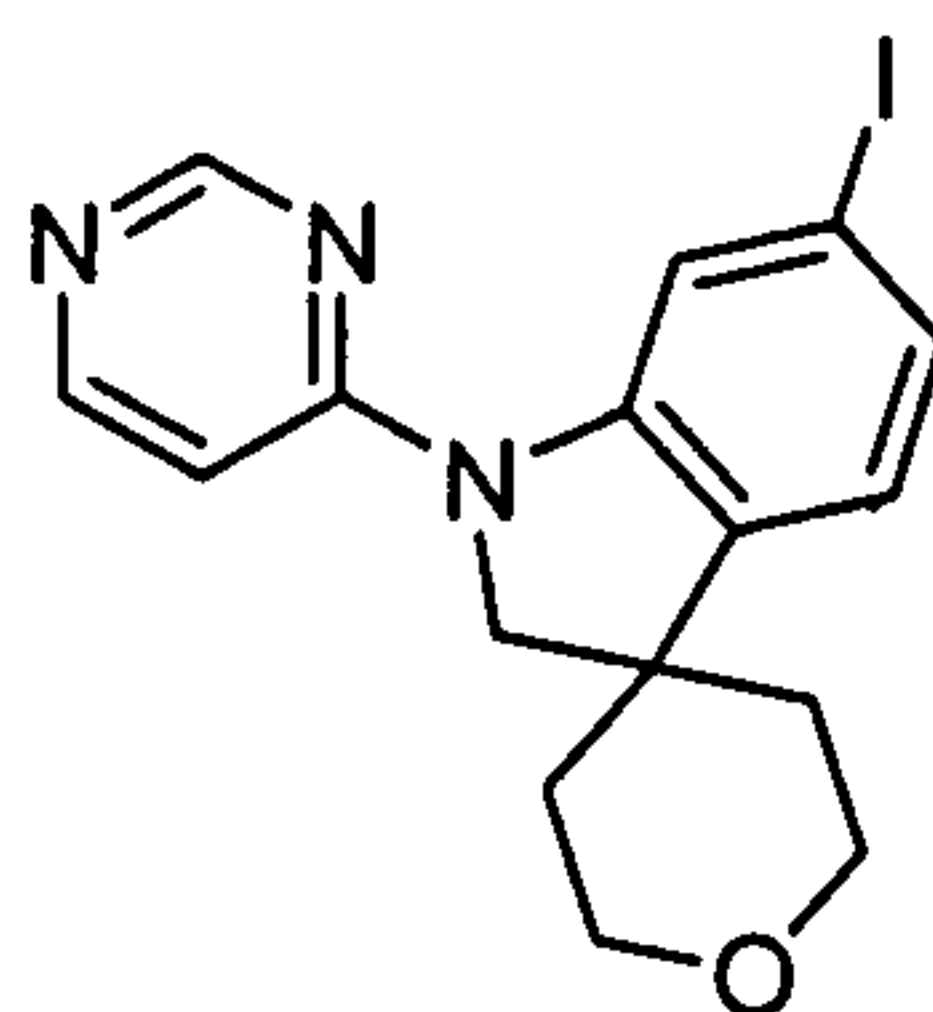
6-bromo-1-pyrimidin-4-yl-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-pyran]

**A.105**

To a heterogeneous mixture of 4-(6-bromo-2',3',5',6'-tetrahydrospiro[indole-3,4'-pyran]-1(2*H*)-yl)pyrimidin-2-amine **A.104** (0.3 g, 0.83 mmol) in THF (1.7 mL) was added dropwise isoamyl nitrite (0.56 mL, 4.15 mmol) with stirring and the mixture was heated at reflux for 45 hours. The mixture was poured into ice water (50 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (100 mL x 1), dried over MgSO₄, filtered, and concentrated under reduced pressure to give a brown solid. The product was

purified by silica gel column chromatography using 0% to 100% gradient of dichloromethane-methanol-NH₄OH (89:9:1) in dichloromethane as eluent to give 6-bromo-1-pyrimidin-4-yl-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-pyran] **A.105** (0.0631 g, 21.9% yield): ¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 8.82 (1 H, s), 8.67 (1 H, d, *J*=1.7 Hz), 8.49 (1 H, d, *J*=6.1 Hz), 7.29 (1 H, d, *J*=8.1 Hz), 7.18 (1 H, dd, *J*=7.9, 1.8 Hz), 7.03 (1 H, d, *J*=6.1 Hz), 4.07 (2 H, s), 3.87 (2 H, dd, *J*=11.7, 3.7 Hz), 3.57 (2 H, t, *J*=11.5 Hz), 1.79 - 2.01 (2 H, m), 1.58 (2 H, d, *J*=13.0 Hz); Mass Spectrum (ESI) *m/e* = 346.0 [*M*+1 (⁷⁹Br)] and 348.1 [*M*+1 (⁸¹Br)].

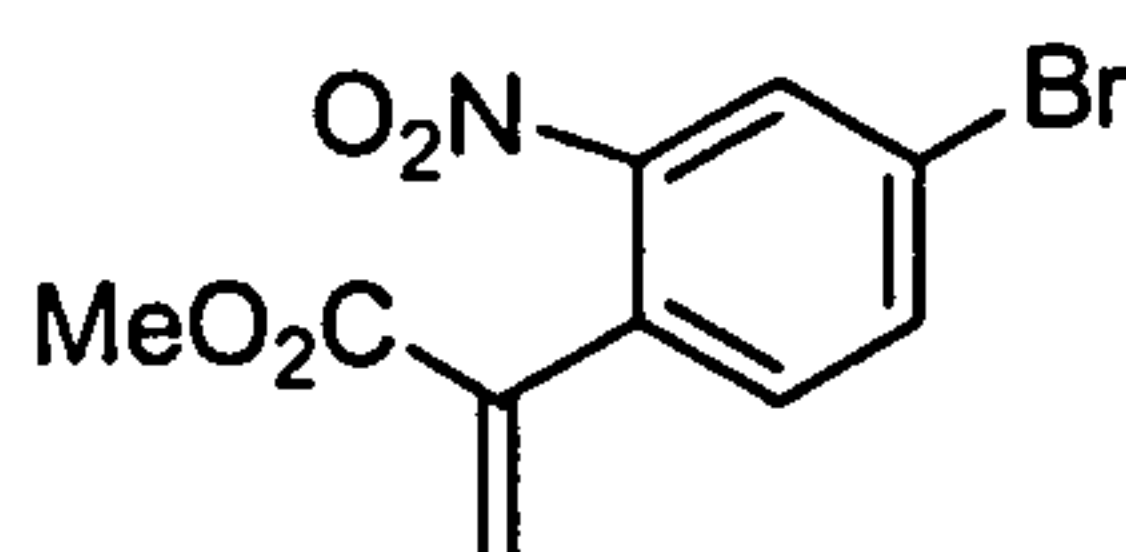
6-iodo-1-pyrimidin-4-yl-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-pyran]



A.106

To a Schlenk tube were added 6-bromo-1-pyrimidin-4-yl-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-pyran] **A.105** (0.0595 g, 0.172 mmol), CuI (0.0164 g, 0.086 mmol), NaI (0.0515 g, 0.344 mmol), N1,N2-dimethylethane-1,2-diamine (0.0185 mL, 0.172 mmol), and 1,4-dioxane (0.34 mL) under argon and the mixture was stirred at 110 °C for 21.5 hours. The mixture was cooled to room temperature, diluted with 30% of aqueous ammonia (5 mL), poured into water (20 mL), and extracted with dichloromethane (15 mL x 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure to give a yellow solid. The yellow solid was purified by silica gel column chromatography using 0% to 100% gradient of dichloromethane-methanol-NH₄OH (89:9:1) in dichloromethane as eluent to give 6-iodo-1-pyrimidin-4-yl-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-pyran] **A.106** (0.0464 g, 68.7% yield) as a solid: ¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 8.85 (1 H, d, *J*=1.5 Hz), 8.81 (1 H, s), 8.48 (1 H, d, *J*=5.9 Hz), 7.35 (1 H, dd, *J*=7.8, 1.5 Hz), 7.15 (1 H, d, *J*=7.8 Hz), 7.02 (1 H, d, *J*=5.6 Hz), 4.04 (2 H, s), 3.87 (2 H, dd, *J*=11.6, 4.0 Hz), 3.57 (2 H, t, *J*=11.4 Hz), 1.84 - 1.95 (2 H, m), 1.57 (2 H, d, *J*=13.2 Hz); Mass Spectrum (ESI) *m/e* = 394.0 [*M*+1].

methyl 2-(4-bromo-2-nitrophenyl)acrylate

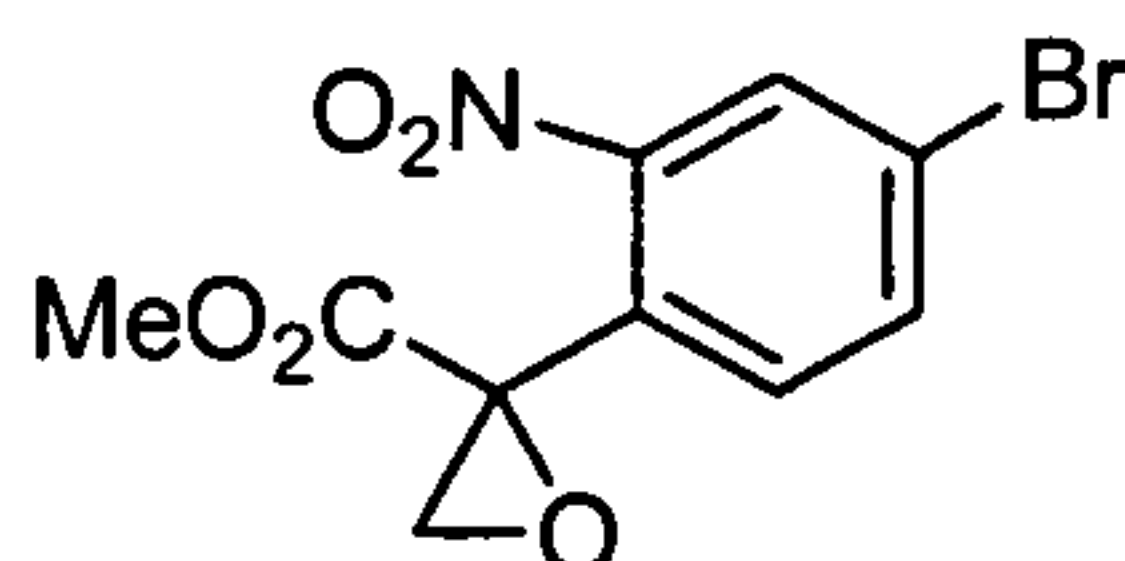


A.109

Methyl 2-(4-bromo-2-nitrophenyl)acrylate A.109

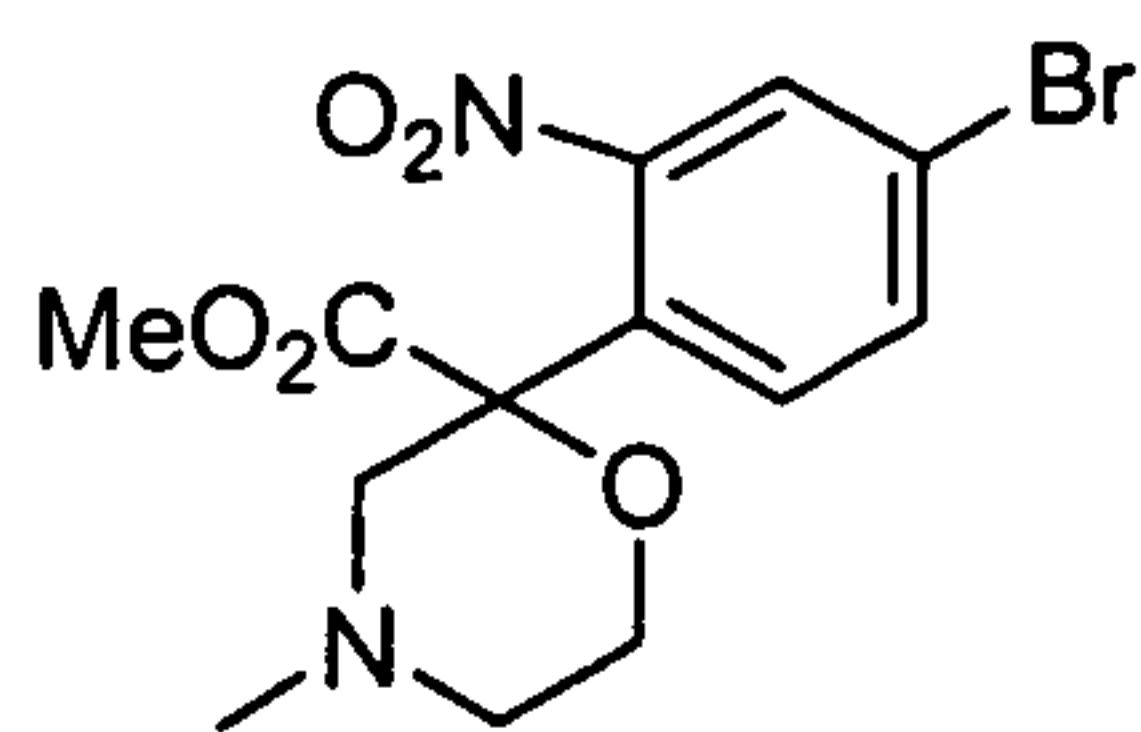
was prepared by the method of Selvakumar, N.; Azhagan, A. M.; Srinivas, D.; Krishna, G. *Tetrahedron Lett.* **2002**, *43*, 9175-9178.

To a stirred mixture of dimethyl 2-(4-bromo-2-nitrophenyl)malonate A.17 (8 g, 24.23 mmol) and formaldehyde (37 wt.% in water) (45 mL) was added a solution of K₂CO₃ (6.3 g, 1.9 eq.) in water (20 mL). The resulting mixture was stirred in an oil bath preheated at 60 °C for 6 h and then cooled to rt. The reaction mixture was poured into water, extracted with ethyl acetate (2 x). The combined organic extracts were washed with brine (2 x) and dried over Na₂SO₄. The residue after evaporation *in vacuo* was purified on a column of silica gel (ethyl acetate/hexanes) to afford methyl 2-(4-bromo-2-nitrophenyl)acrylate (8.5 g, 98% yield) as a colorless oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.31 (1 H, d, *J*=2.2 Hz), 8.03 (1 H, dd, *J*=8.2, 2.0 Hz), 7.51 (1 H, d, *J*=8.1 Hz), 6.49 (1 H, s), 6.14 (1 H, s), 3.65 (3 H, s). LCMS-ESI (POS), *M/Z*, *M*+Na⁺: Found 308.2 and 310.2.

methyl 2-(4-bromo-2-nitrophenyl)oxirane-2-carboxylate**A.110**

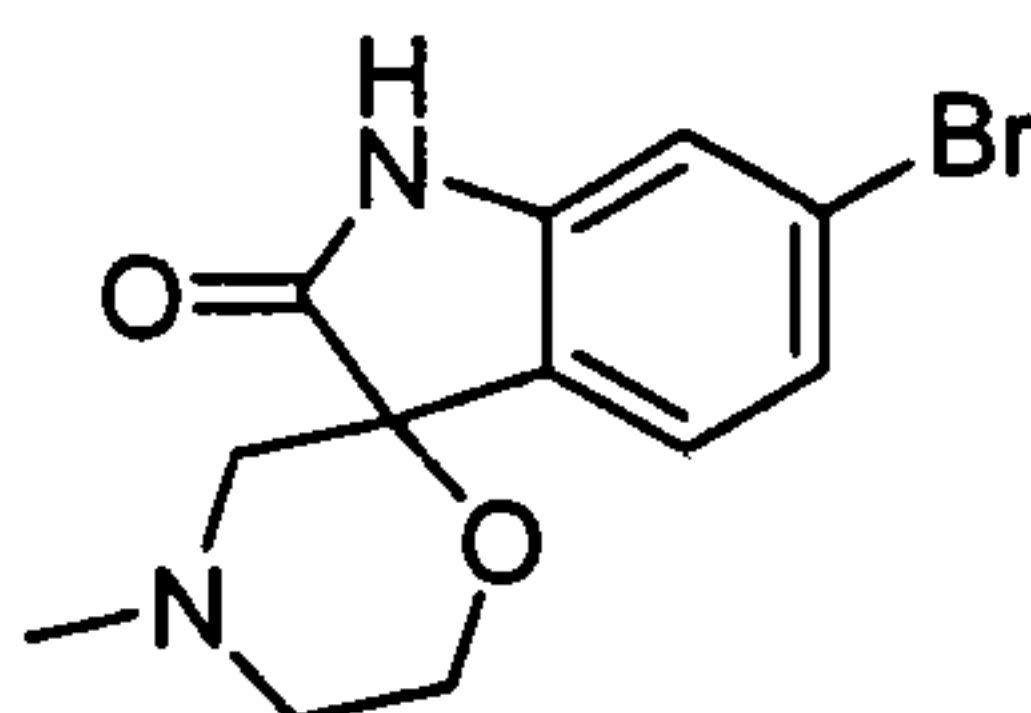
A solution of methyl 2-(4-bromo-2-nitrophenyl)acrylate A.109 (1.8603 g, 6.5 mmol) in chloroform (13 mL) was treated with 77% of *m*-CPBA (3.6434 g, 16.26 mmol) and heated at reflux for 48 hours. The mixture was cooled to room temperature, diluted with chloroform (150 mL), washed with 10% aqueous NaHSO₃ (100 mL), 10% aqueous NaHCO₃ (100 mL), and water (100 mL). The organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure to give a yellow oil. The yellow oil was purified by silica gel column chromatography using 0% to 70% gradient of ethyl acetate in hexane as eluent to give methyl 2-(4-bromo-2-nitrophenyl)oxirane-2-carboxylate A.110 (1.4664 g, 74.6% yield): ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.40 (1 H, d, *J*=2.0 Hz), 8.07 (1 H, dd, *J*=8.3, 2.0 Hz), 7.67 (1 H, d, *J*=8.3 Hz), 3.62 - 3.68 (3 H, m), 3.59 (1 H, d, *J*=5.6 Hz), 3.23 (1 H, d, *J*=5.9 Hz); Mass Spectrum (ESI) *m/e* = 301.9 [*M*+1 (⁷⁹Br)] and 304.0 [*M*+1 (⁸¹Br)].

methyl 2-(4-bromo-2-nitrophenyl)-4-methylmorpholine-2-carboxylate

**A.111**

A mixture of methyl 2-(4-bromo-2-nitrophenyl)oxirane-2-carboxylate **A.110** (1.4633 g, 4.84 mmol), THF (4.8 mL), and 2-(methylamino)ethanol (0.58 mL, 7.2 mmol) was stirred at 50 °C for 27 hours. The mixture was concentrated under reduced pressure to give methyl 2-(4-bromo-2-nitrophenyl)-2-hydroxy-3-((2-hydroxyethyl)(methyl)amino)propanoate as a dark red syrup: Mass Spectrum (ESI) $m/e = 377.0$ [$M+1$ (^{79}Br)] and 379.0 [$M+1$ (^{81}Br)]. The product was carried on to the next step. Methyl 2-(4-bromo-2-nitrophenyl)-2-hydroxy-3-((2-hydroxyethyl)(methyl)amino)propanoate (~ 4.84 mmol) was dissolved in 1,4-dioxane (7 mL), and powdery KOH (1.0863 g, 19.36 mmol) and tris(3,6-dioxahexyl)amine (0.019 g, 0.058 mmol) were added. To the mixture was added dropwise with stirring a solution of p-TsCl (1.2918 g, 6.78 mmol) in 1,4-dioxane (3 mL) over 3 minutes and the mixture was stirred at room temperature for 4 hours. The mixture was filtered. The filtrate was concentrated under reduced pressure and purified by silica gel column chromatography using 0% to 100% gradient of ethyl acetate in hexane as eluent to give methyl 2-(4-bromo-2-nitrophenyl)-4-methylmorpholine-2-carboxylate **A.111** (0.5133 g, 29.5% overall yield over two steps) as a yellow solid: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.04 (1 H, d, $J=2.0$ Hz), 7.87 (1 H, dd, $J=8.6, 2.0$ Hz), 7.64 (1 H, d, $J=8.6$ Hz), 3.68 - 3.74 (1 H, m), 3.67 (3 H, s), 3.16 - 3.27 (2 H, m), 2.54 - 2.65 (1 H, m), 2.30 - 2.38 (1 H, m), 2.16 - 2.26 (4 H, m); Mass Spectrum (ESI) $m/e = 359.0$ [$M+1$ (^{79}Br)] and 361.0 [$M+1$ (^{81}Br)].

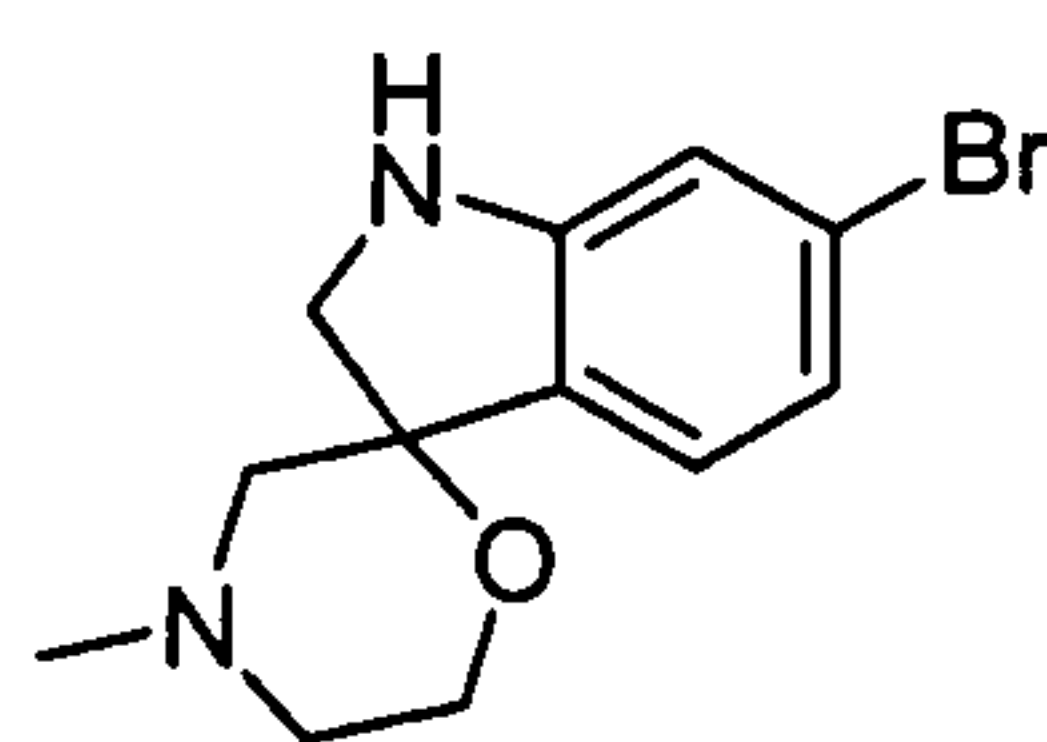
6-bromo-4'-methylspiro[indole-3,2'-[1,4]oxazinan]-2(1H)-one

**A.112**

A mixture of methyl 2-(4-bromo-2-nitrophenyl)-4-methylmorpholine-2-carboxylate **A.111** (0.5133 g, 1.43 mmol), acetic acid, and Fe (0.3991 g, 7.15 mmol) was stirred at 100 °C

for 2 hours. The hot mixture was filtered through a Celite pad and the pad was washed with acetic acid (100 mL). The filtrate was concentrated under reduced pressure and purified by silica gel column chromatography using 0% to 90% gradient of ethyl acetate in hexane as eluent to give 6-bromo-4'-methylspiro[indole-3,2'-[1,4]oxazinan]-2(1*H*)-one **A.112** (0.2645 g, 62.3% yield) as a white syrup: ¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 10.58 (1 H, s), 7.64 (1 H, d, *J*=7.8 Hz), 7.17 (1 H, dd, *J*=8.1, 1.7 Hz), 6.99 (1 H, d, *J*=1.5 Hz), 3.93 (2 H, dd, *J*=6.5, 3.1 Hz), 2.67 (1 H, d, *J*=11.7 Hz), 2.51 - 2.55 (1 H, m), 2.39 (1 H, d, *J*=11.5 Hz), 2.27 - 2.34 (1 H, m), 2.19 (3 H, s); Mass Spectrum (ESI) *m/e* = 297.0 [*M*+1 (⁷⁹Br)] and 298.9 [*M*+1 (⁸¹Br)].

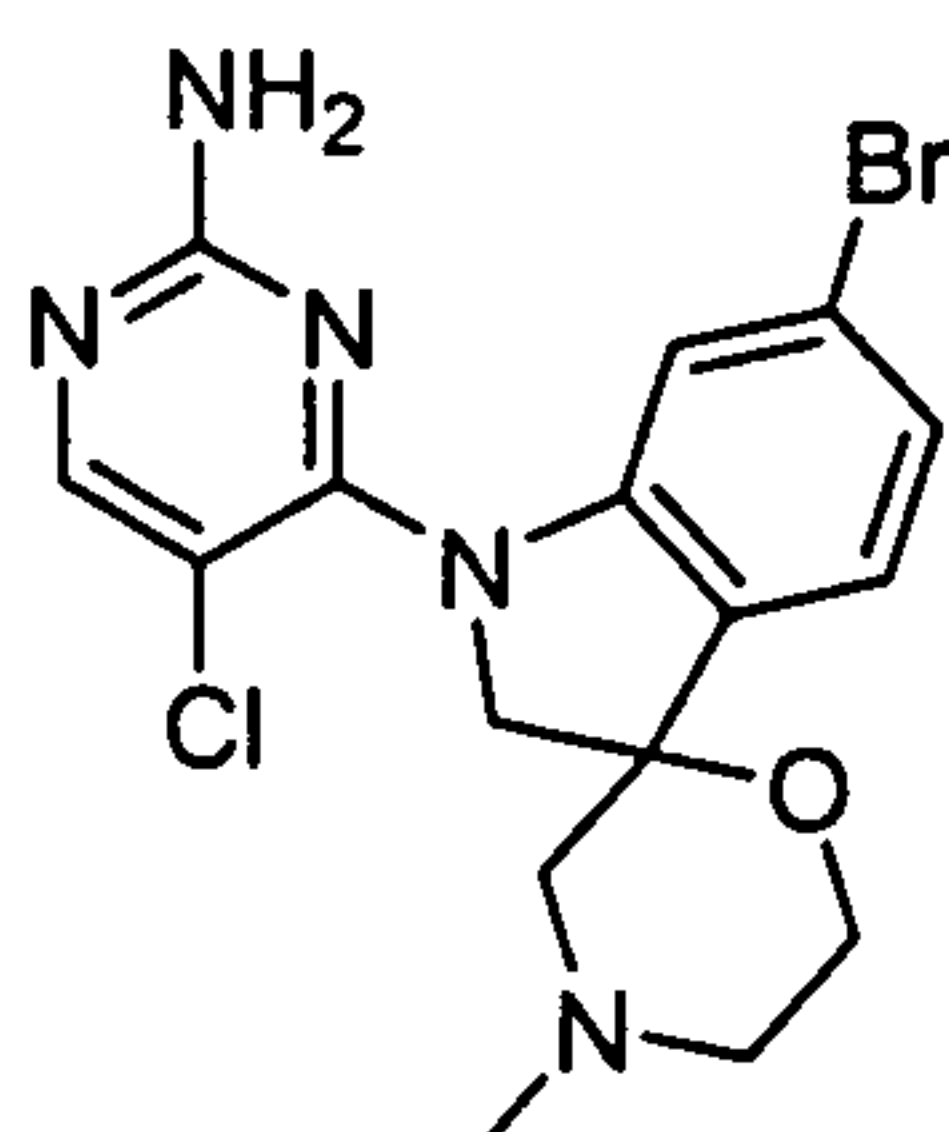
6-bromo-4'-methyl-1,2-dihydrospiro[indole-3,2'-[1,4]oxazinane]



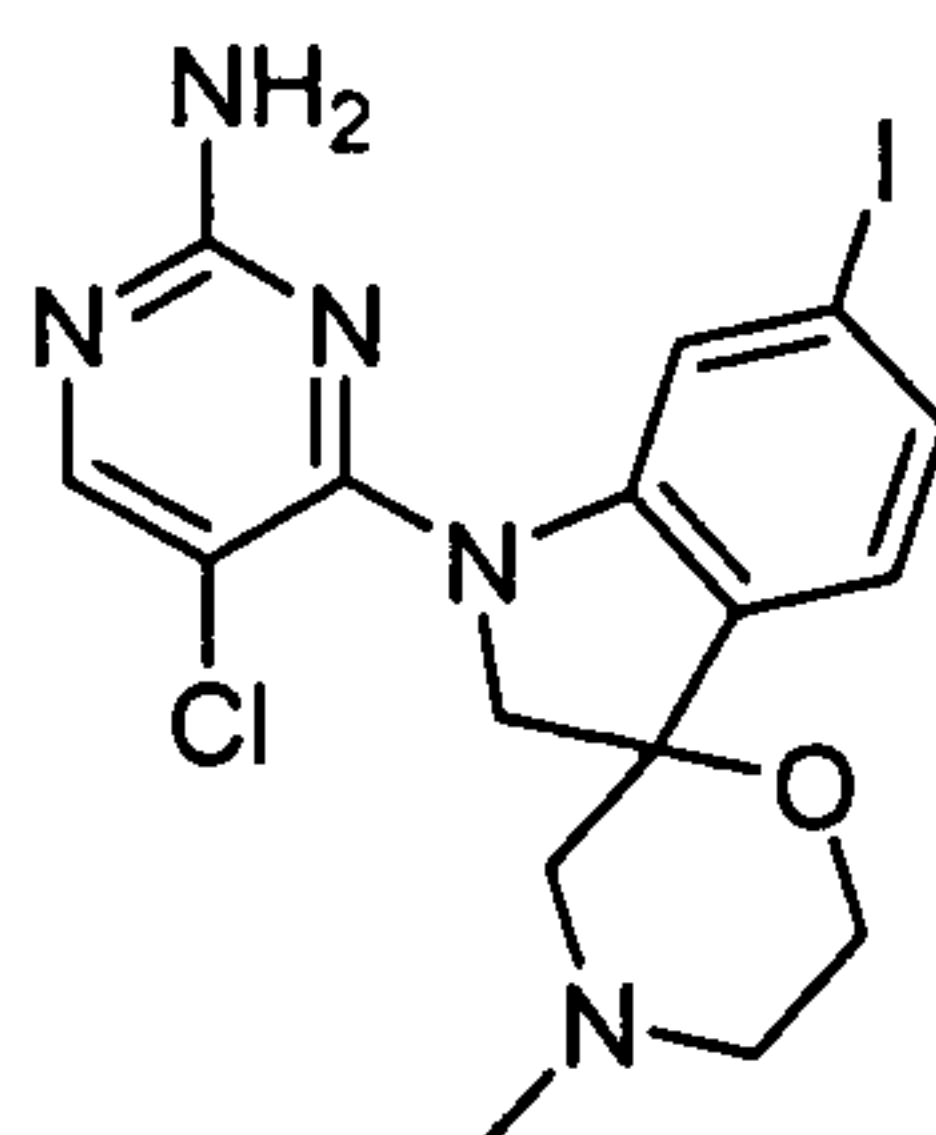
A.113

A heterogeneous mixture of 6-bromo-4'-methylspiro[indole-3,2'-[1,4]oxazinan]-2(1*H*)-one **A.112** (0.9598 g, 3.23 mmol) in toluene (6.5 mL) was stirred at 80 °C. A solution of Red-Al in toluene (3.2 M, 3 mL, 9.69 mmol) was added dropwise at 80 °C and the mixture was stirred at 80 °C for 40 minutes. The mixture was cooled to 0 °C, quenched with 2 N aqueous NaOH (8 mL, 16 mmol), and extracted with ethyl acetate (50 mL x 2). The combined organic layers were washed with brine (50 mL x 1), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a violet syrup. The product was purified by silica gel column chromatography using 0% to 100% gradient of dichloromethane-methanol-NH₄OH (89:9:1) in dichloromethane as eluent to give 6-bromo-4'-methyl-1,2-dihydrospiro[indole-3,2'-[1,4]oxazinane] **A.113** (0.4841 g, 52.9% yield) as a light yellow solid: ¹H NMR (400 MHz, *DMSO-d*₆) δ ppm 7.24 (1 H, d, *J*=8.2 Hz), 6.63 - 6.71 (2 H, m), 5.97 (1 H, s), 3.54 - 3.70 (2 H, m), 3.39 - 3.49 (2 H, m), 2.25 - 2.47 (4 H, m), 2.19 (3 H, s); Mass Spectrum (ESI) *m/e* = 283.0 [*M*+1 (⁷⁹Br)] and 285.0 [*M*+1 (⁸¹Br)].

4-(6-bromo-4'-methylspiro[indole-3,2'-[1,4]oxazinan]-1(2*H*)-yl)-5-chloropyrimidin-2-amine

**A.114**

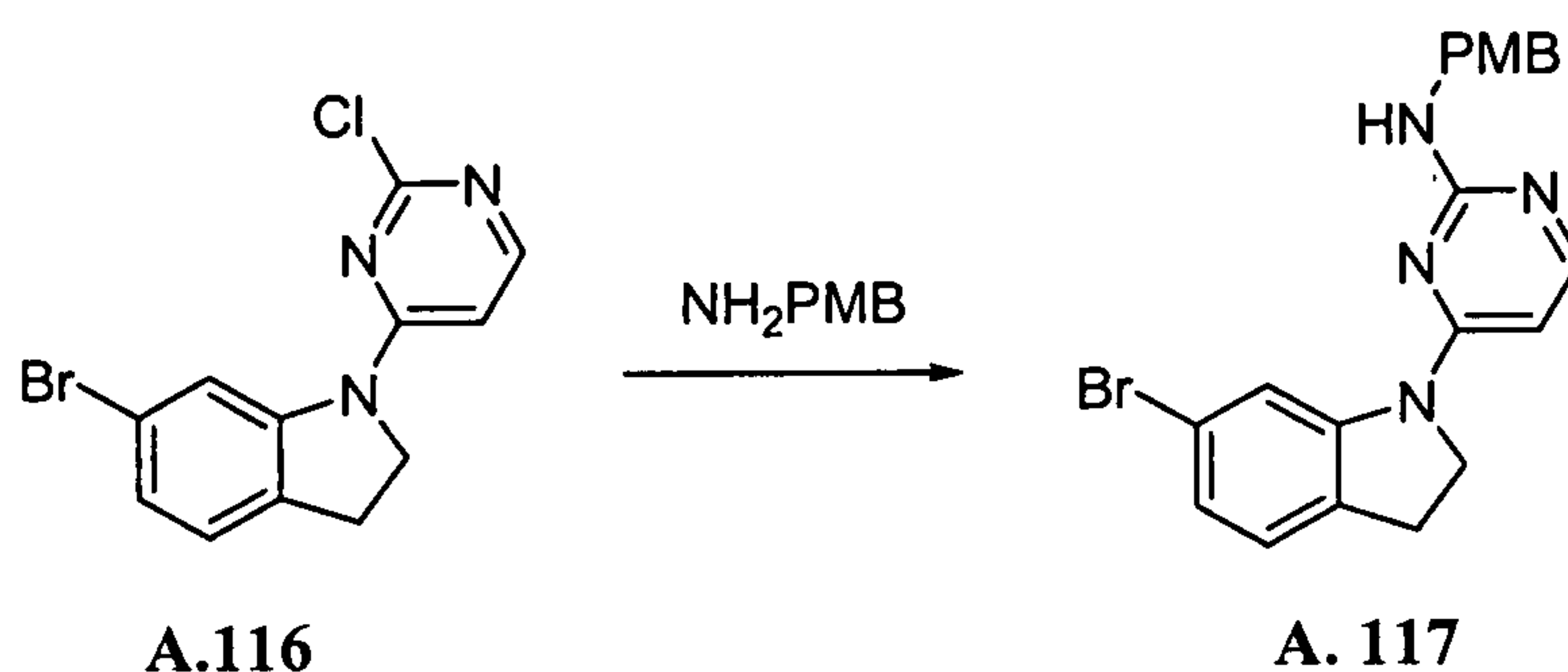
A mixture of 6-bromo-4'-methyl-1,2-dihydrospiro[indole-3,2'-[1,4]oxazinane] **A.113** (0.4149 g, 2.53 mmol) and 4,5-dichloropyrimidin-2-amine **A.14** (0.3582 g, 1.265 mmol) in 1 N aqueous HCl (20 mL) was stirred at 60 °C for 19 hours. The mixture was cooled to room temperature and poured into 2 N aqueous NaOH (60 mL) with ice. The mixture was extracted with ethyl acetate (50 mL x 2). The combined organic layers were washed with brine (50 mL x 2), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a yellow solid. The yellow solid was purified by silica gel column chromatography using 0% to 100% gradient of dichloromethane-methanol-NH₄OH (89:9:1) in dichloromethane as eluent to give 4-(6-bromo-4'-methylspiro[indole-3,2'-[1,4]oxazinan]-1(2*H*)-yl)-5-chloropyrimidin-2-amine **A.114** (0.1595 g, 30.7% yield) as an orange pink syrup: ¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 8.12 (1 H, s), 7.61 (1 H, d, *J*=1.7 Hz), 7.49 (1 H, d, *J*=7.8 Hz), 7.14 (1 H, dd, *J*=8.1, 1.7 Hz), 6.73 (2 H, s), 4.10 - 4.27 (2 H, m), 3.57 - 3.74 (2 H, m), 2.42 - 2.61 (3 H, m), 2.32 (1 H, s), 2.22 (3 H, s); Mass Spectrum (ESI) *m/e* = 410.0 [*M*+1 (⁷⁹Br)] and 412.0 [*M*+1 (⁸¹Br)].

**A. 115**

5-chloro-4-(6-iodo-4'-methylspiro[indole-3,2'-[1,4]oxazinan]-1(2*H*)-yl)pyrimidin-2-amine **A.115:**

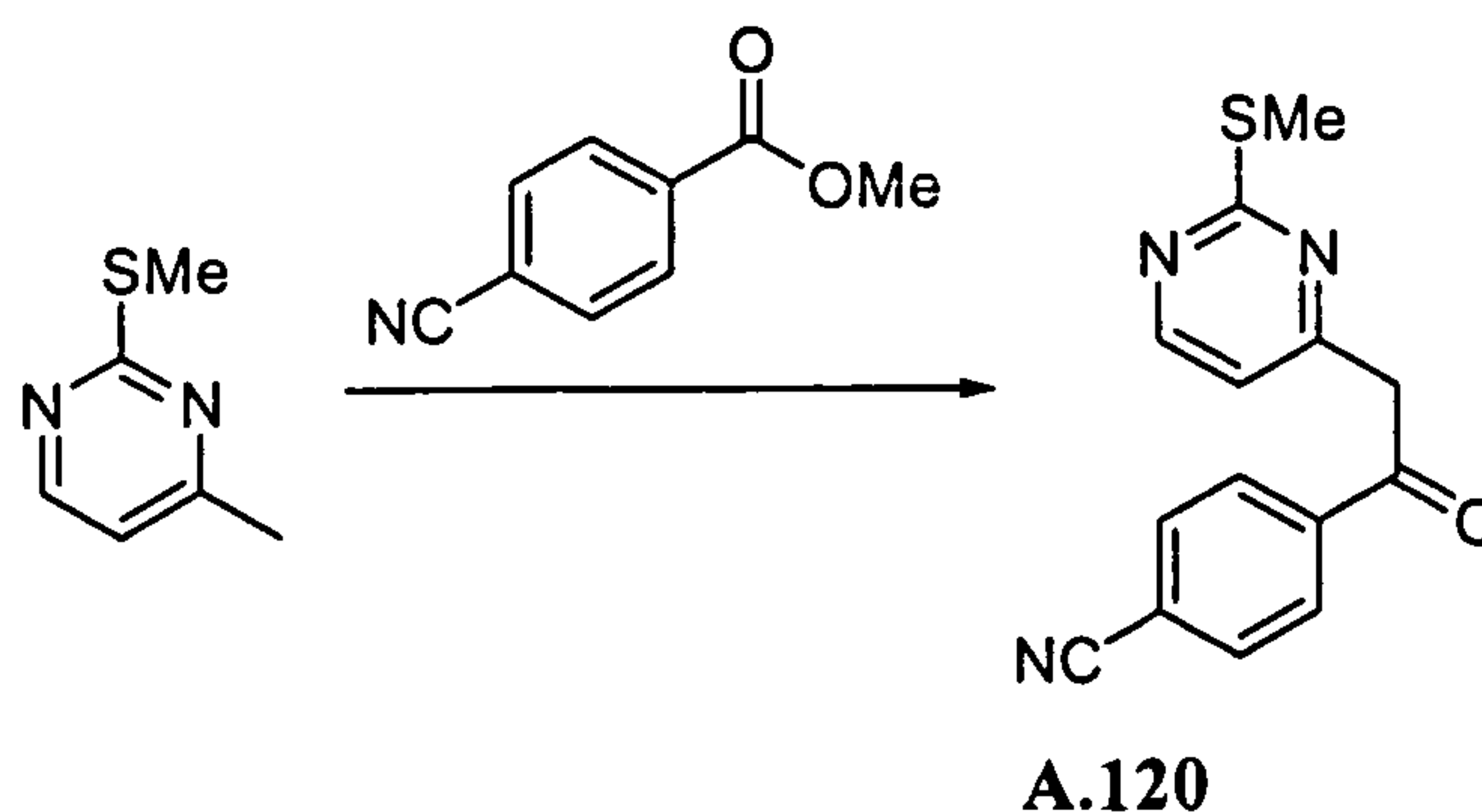
4-(6-bromo-4'-methylspiro[indole-3,2'-[1,4]oxazinan]-1(2*H*)-yl)-5-chloropyrimidin-2-amine **A.114** (0.1 g, 0.243 mmol), CuI (0.023 g, 0.122 mmol) and NaI (0.073 g, 0.487 mmol) were added to a Schlenk tube, evacuated and backfilled with argon. Under positive pressure of argon, the screw cap was replaced with a septum. *N,N'*-dimethylethylenediamine (0.026 mL,

0.243 mmol) in 1,4-dioxane (3 mL) was added via syringe, and the screwcap was returned under positive pressure of argon. The reaction was sealed and heated to 110 °C with stirring for 20 hours. The mixture was cooled to room temperature, diluted with 30% aqueous NH₃ (5 mL), and poured into water (20 mL). The solution was extracted with dichloromethane (15 mL x 3) and the combined extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The product was purified by silica gel column chromatography using 0% to 100% gradient of dichloromethane-methanol-NH₄OH (89:9:1) in dichloromethane as eluent to give 5-chloro-4-(6-iodo-4'-methylspiro[indole-3,2'-[1,4]oxazinan]-1(2*H*)-yl)pyrimidin-2-amine **A.115** (0.1023g on crude) as a brown syrup: Mass Spectrum (ESI) *m/e* = 458.0 [M+1].



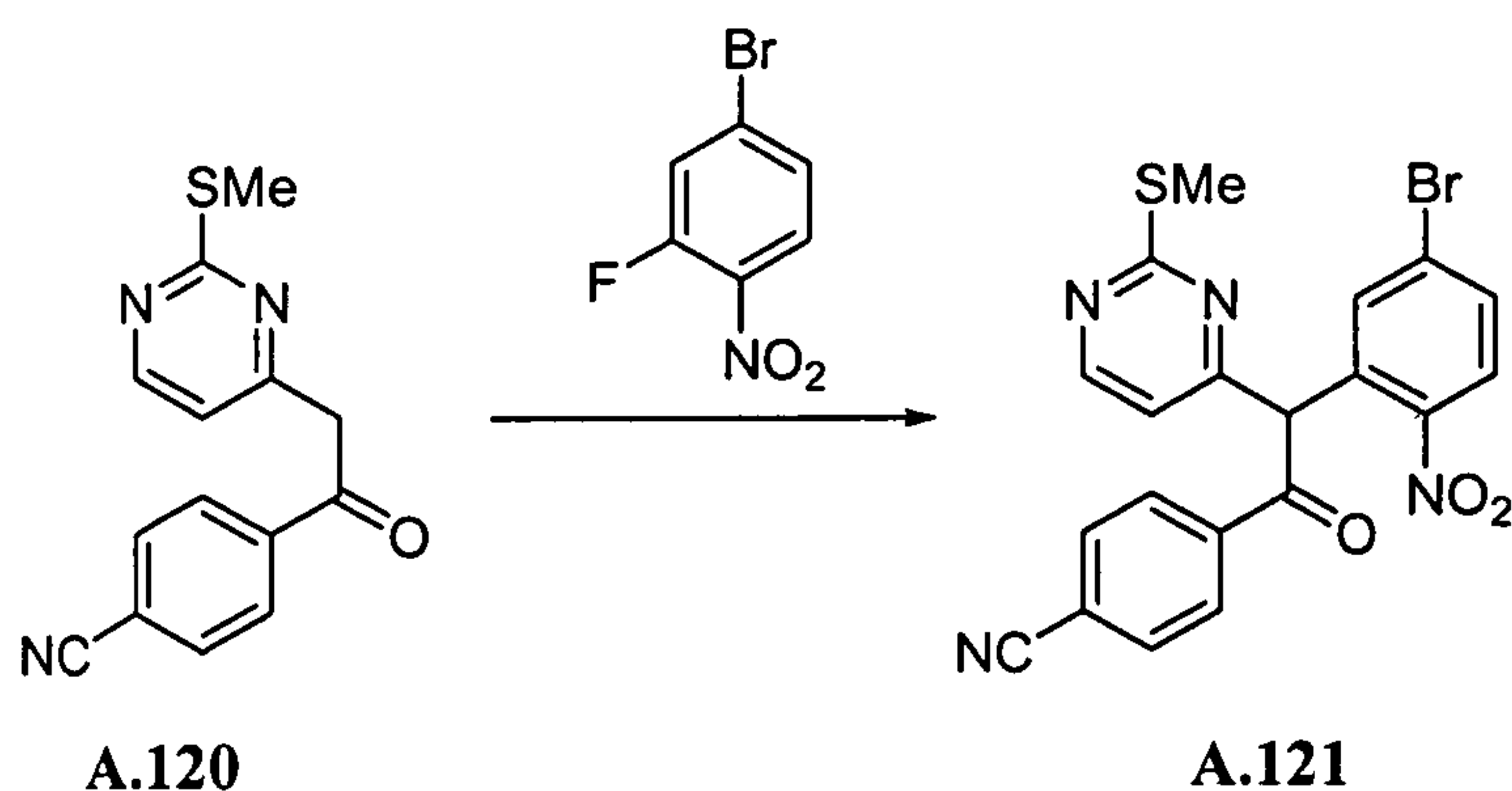
N-(4-methoxybenzyl)-4-(6-bromoindolin-1-yl)pyrimidin-2-amine (A.117): A mixture of 6-bromo-1-(2-chloropyrimidin-4-yl)indoline **A.116** (160 mg, 0.52 mmol) (prepared in analogy to compound **A.2**), PMBNH₂ (0.10 mL, 0.78 mmol) and K₂CO₃ (107.8 mg, 0.78 mmol) in THF (15 mL) was refluxed for 4 days. After cooled to room temperature, the mixture was diluted with ether, washed with water and brine, dried and concentrated. The residue was triturated in dichloromethane and the follow up filtration gave N-(4-methoxybenzyl)-4-(6-bromoindolin-1-yl)pyrimidin-2-amine **A.117** (148.2 mg, 69%): ¹H NMR (DMSO-*d*₆) δ 8.62(s, 1 H), 8.03(d, *J* = 6.0 Hz, 1 H), 7.52(dd, *J* = 6.0, 6.0 Hz, 1 H), 7.33-7.26(m, 2 H), 7.15 (d, *J* = 8.0 Hz, 1 H), 7.05 (d, *J* = 8.0 Hz, 1 H), 6.86 (d, *J* = 8.0 Hz, 2 H), 6.02(br, 1 H), 4.48 (d, *J* = 6.5 Hz, 2 H), 3.99 (t, *J* = 8.5 Hz, 2 H), 3.71(s, 3 H), 3.13 (t, *J* = 8.5 Hz, 2 H); *ms* 411.1 (M+H⁺).

4-(2-(2-(methylthio)pyrimidin-4-yl)acetyl)benzonitrile



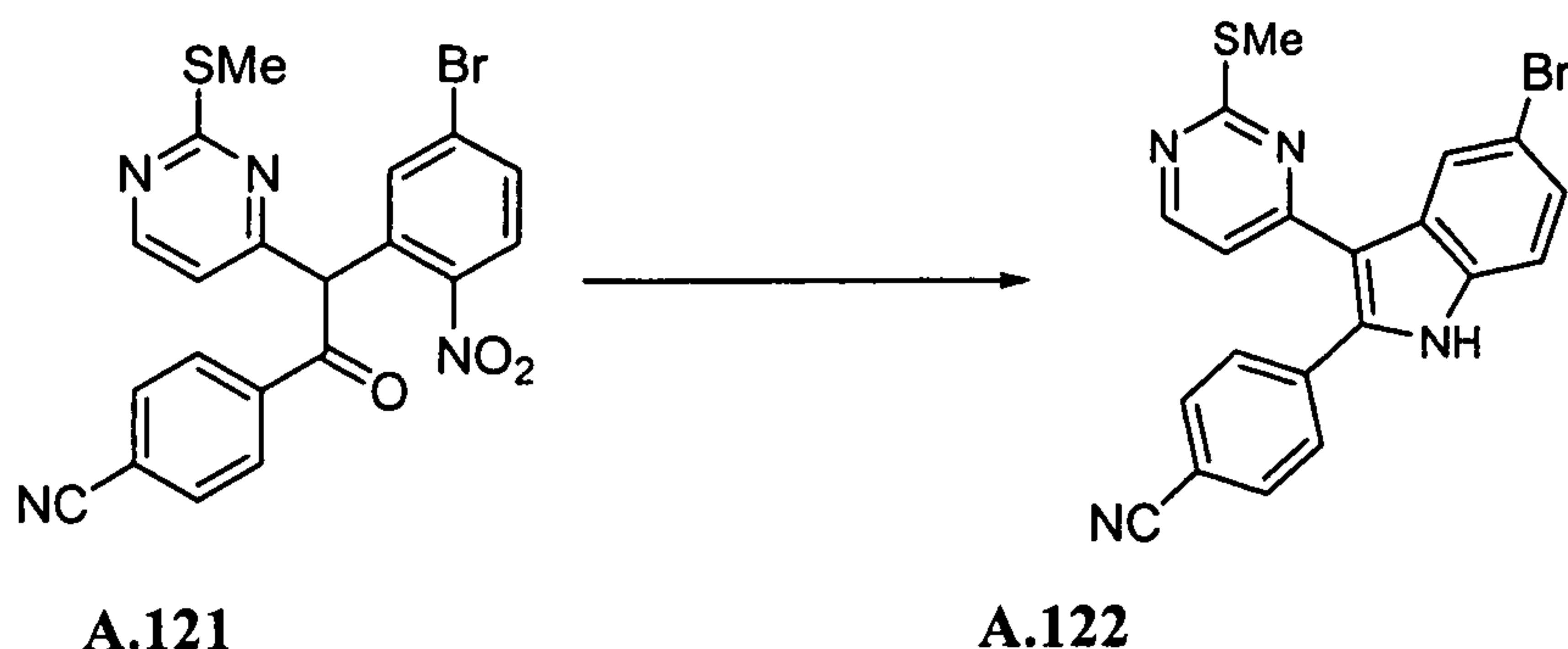
To a solution of sodium bis(trimethylsilyl) amide (2 M sol. in THF, 79 mL) was added a solution of 4-methyl-2-(methylthio)pyrimidine (10 g, 71.32 mmol) in THF (20 mL) at 0 °C, and the resulting solution was stirred at 0 °C for 40 minutes. A solution of methyl 4-cyanobenzoate (11.49 g, 71.32 mmol) in THF (30 mL) was then added dropwise over 10 minutes to the mixture, and the mixture was stirred while attaining ambient temperature over 2 hours. The reaction was quenched by addition of sat'd aq. NH₄Cl (100 mL) and extracted into ethyl acetate (250 mL x 2), and the combined organic layers were washed with brine (200 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a red solid. The red solid was suspended in hexane (150 mL), sonicated, filtered, and washed with hexane (200 mL) to give 4-(2-(2-(methylthio)pyrimidin-4-yl)acetyl)benzonitrile (**A.120**) (17.43 g, 90.8% yield) as an orange solid. The product was carried on without purification for the next step: Mass Spectrum (ESI) $m/e = 270.1$ (M+1).

4-(2-(5-bromo-2-nitrophenyl)-2-(2-(methylthio)pyrimidin-4-yl)acetyl)benzonitrile



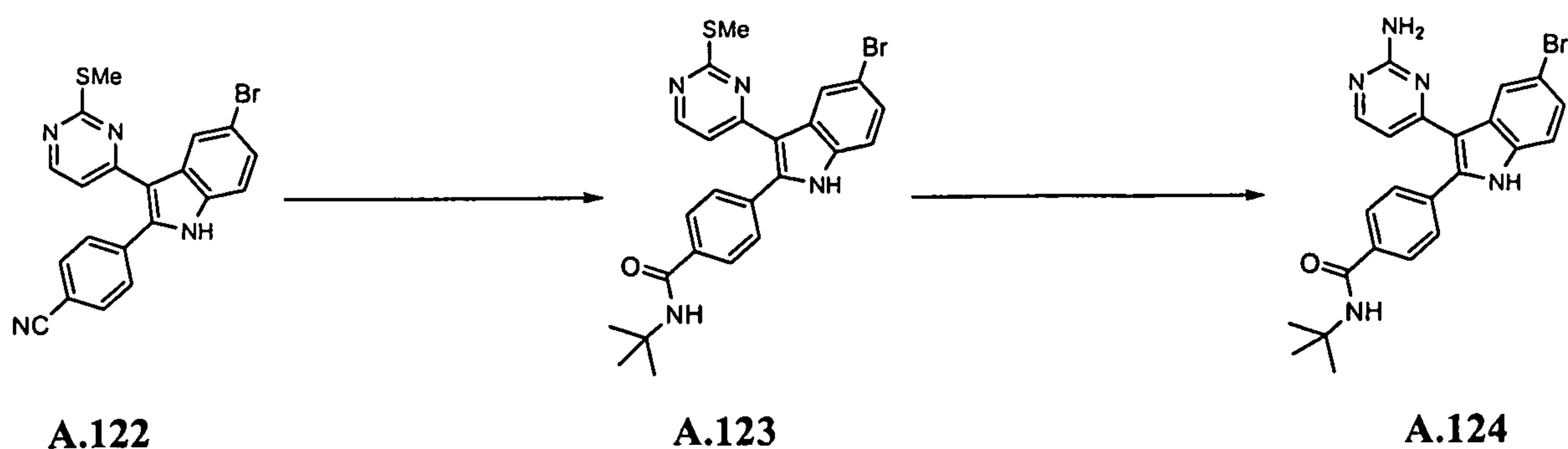
To a solution of 4-(2-(2-(methylthio)pyrimidin-4-yl)acetyl)benzonitrile **A.120** (1.80 g, 6.69 mmol) in DMSO (78 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 0.5348 g, 3.37 mmol) with stirring. After 5 minutes, to the mixture was added a solution of 4-bromo-2-fluoro-1-nitrobenzene (1.4709 g, 6.69 mmol) in DMSO (15 mL) with stirring, and the resulting mixture was stirred at room temperature for 18 hours. The mixture was poured into ice-water (200 mL) and extracted with ethyl acetate (300 mL x 2). The combined organic layers were washed with brine (300 mL x 2), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give 4-(2-(5-bromo-2-nitrophenyl)-2-(2-(methylthio)pyrimidin-4-yl)acetyl)benzonitrile **A.121** (2.836 g, 90.4% yield) as an orange solid. The product was carried on in the next step: Mass Spectrum (ESI) $m/e = 469.0$ [M+1 (⁷⁹Br)] and 471.0 [M+1 (⁸¹Br)].

4-(5-bromo-3-(2-(methylthio)pyrimidin-4-yl)-1H-indol-2-yl)benzonitrile



A mixture of 4-(2-(5-bromo-2-nitrophenyl)-2-(2-(methylthio)pyrimidin-4-yl)acetyl)benzonitrile **A.121** (2.836 g, 6.04 mmol), Fe (1.69 g, 30.2 mmol), and acetic acid (60 mL) was heated at 95 °C with stirring for 1 hour. The mixture was cooled to room temperature, filtered, washed the solid with acetic acid (100 mL), and dried to give 4.2992 g of brown solid. The brown solid was purified by silica gel column chromatography using 30% to 50% gradient of ethyl acetate in hexane and 95% of dichloromethane in methanol as eluent to give 4-(2-(2-(methylthio)pyrimidin-4-yl)acetyl)benzonitrile **A.122** (0.83 g, 32.6% yield over two steps): ¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 12.42 (1 H, s), 8.42 (1 H, d, *J*=5.5 Hz), 8.32 (1 H, d, *J*=1.8 Hz), 7.98 (2 H, d, *J*=8.7 Hz), 7.76 (2 H, d, *J*=8.2 Hz), 7.46 - 7.49 (1 H, m), 7.40 (1 H, dd, *J*=8.7, 1.8 Hz), 6.95 (1 H, d, *J*=5.5 Hz), 2.39 (3 H, s); Mass Spectrum (ESI) *m/e* = 421.0 [*M*+1 (⁷⁹Br)] and 423.0 [*M*+1 (⁸¹Br)].

4-(3-(2-aminopyrimidin-4-yl)-5-bromo-1H-indol-2-yl)-*N*-*tert*-butylbenzamide

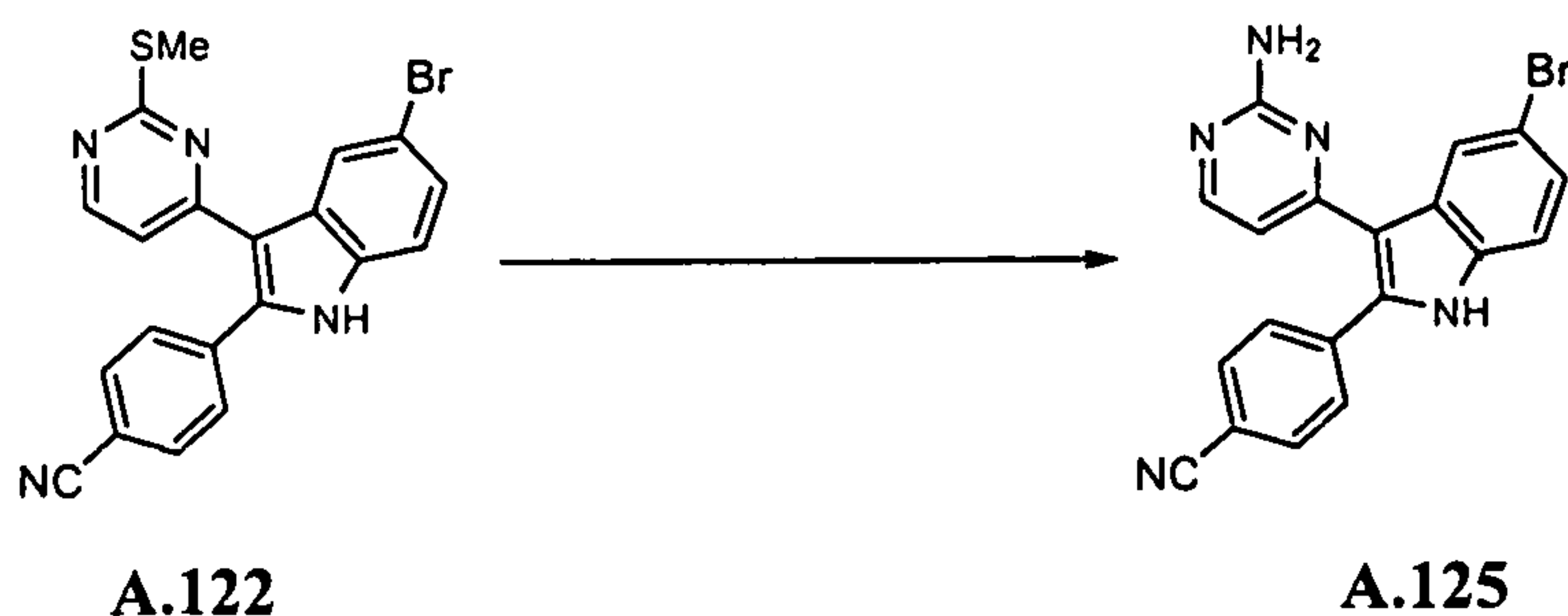


To a stirred solution of 4-(5-bromo-3-(2-(methylthio)pyrimidin-4-yl)-1H-indol-2-yl)benzonitrile **A.122** (0.527 g, 1.25 mmol) in *tert*-butyl acetate (2.7 mL, 20.0 mmol) was added conc. H₂SO₄ (0.062 mL, 1.12 mmol) at room temperature. The mixture was stirred at 42

°C for 25 minutes. The mixture was cooled to room temperature. To the mixture was added saturated aq. NaHCO₃ to neutralize. The mixture was extracted with ethyl acetate (50 mL x 2). The combined organic layers were washed with brine (50 mL x 1), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The product was purified by silica gel column chromatography using 50% of ethyl acetate in hexane as eluent to give 4-(5-bromo-3-(2-(methylthio)pyrimidin-4-yl)-1H-indol-2-yl)-N-*tert*-butylbenzamide **A.123** (0.477 g, 77% yield) as a yellow solid.

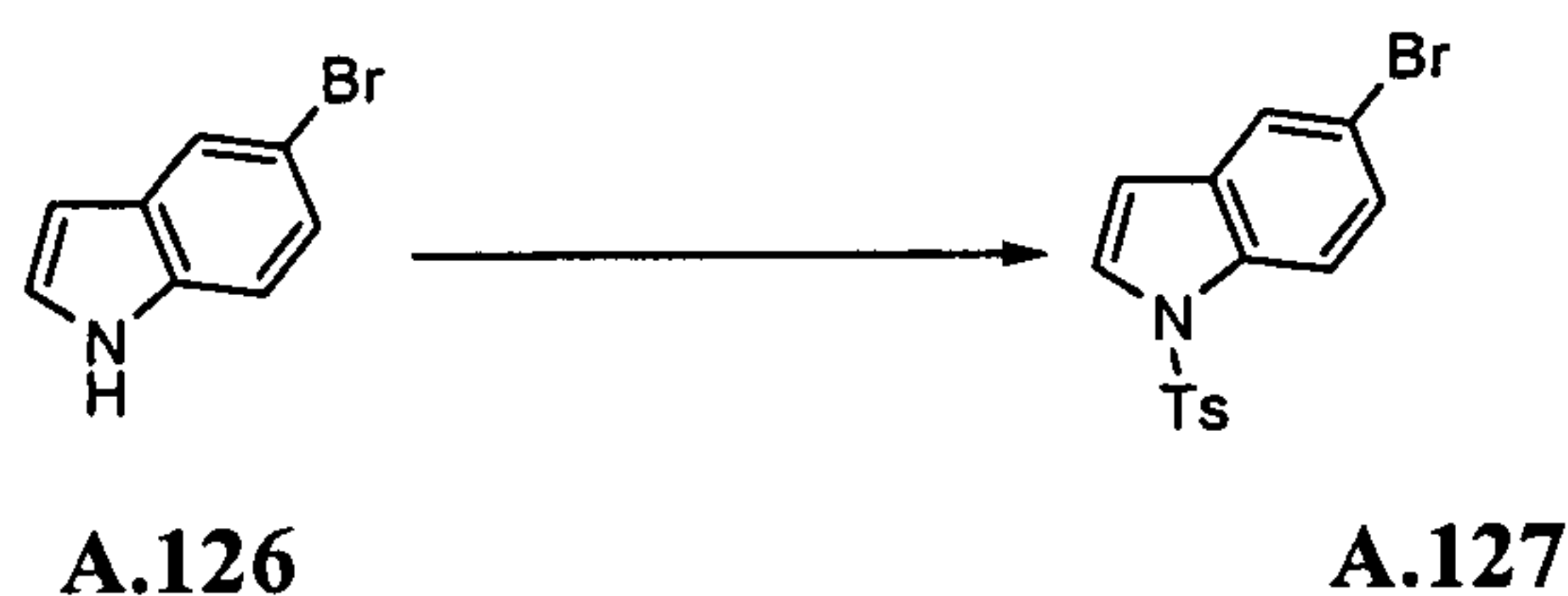
The yellow solid (0.477 g, 0.96 mmol) was dissolved in dichloromethane (20 mL) and treated with m-CPBA (0.7284 g, 2.4 mmol). The mixture was stirred at room temperature for 3 hr and concentrated under reduced pressure to give a yellow solid. The yellow solid was suspended in isopropanol (20 mL) and transferred to 150 mL of pressure vessel. To the mixture was added NH₄Cl (0.216 g, 4.04 mmol) and NH₄OH (28%, 20 mL), and the mixture was heated at 100 °C for 2 hours. The mixture was cooled to room temperature, diluted with ethyl acetate (200 mL), washed with sat'd aq. NaHCO₃ (100 mL x 3), brine (100 mL x 2), dried over MgSO₄, filtered, and concentrated under reduced pressure. The product was purified by silica gel column chromatography using 50% of ethyl acetate in hexane as eluent to give 4-(3-(2-aminopyrimidin-4-yl)-5-bromo-1H-indol-2-yl)-N-*tert*-butylbenzamide **A.124** (0.237 g, 53% yield) as a yellow solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.04 (1 H, s), 8.36 (1 H, d, *J*=1.9 Hz), 7.98 (1 H, d, *J*=5.2 Hz), 7.90 (2 H, d, *J*=8.4 Hz), 7.86 (1 H, s), 7.62 (2 H, d, *J*=8.4 Hz), 7.40 (1 H, d, *J*=8.5 Hz), 7.32 (1 H, dd, *J*=8.6, 1.9 Hz), 6.58 (2 H, s), 6.20 (1 H, d, *J*=5.2 Hz), 1.40 (9 H, s); Mass Spectrum (ESI) *m/e* = 464.0 [M+1 (⁷⁹Br)] and 466.1 [M+1 (⁸¹Br)].

4-(3-(2-aminopyrimidin-4-yl)-5-bromo-1H-indol-2-yl)benzonitrile



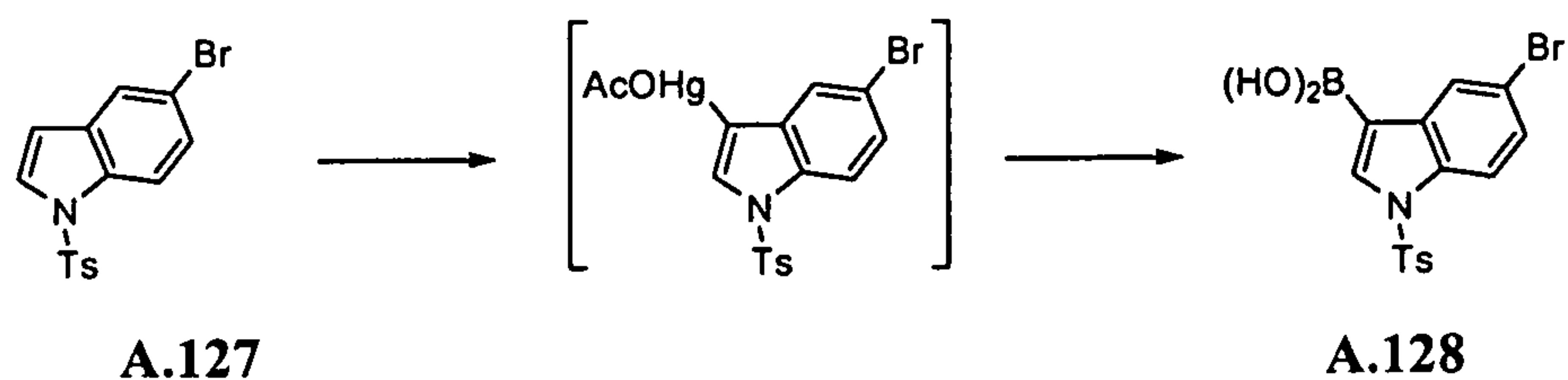
To a solution of 4-(5-bromo-3-(2-(methylthio)pyrimidin-4-yl)-1H-indol-2-yl)benzonitrile **A.122** (1.493 g, 3.54 mmol) in dichloromethane (70 mL) was added m-CPBA (77%, 1.9855 g, 8.86 mmol) and the mixture was stirred at room temperature for 17 hours. The mixture was concentrated under reduced pressure to give a yellow solid. The yellow solid was suspended in

isopropanol(70 mL) and transferred to 350 mL of pressure vessel. To the mixture was added NH_4Cl (0.7961 g, 14.88 mmol) and NH_4OH (28%, 70 mL) and the mixture was stirred at 100 °C for 6 hours. The mixture was diluted with ethyl acetate (200 mL) and washed with saturated aq. NaHCO_3 (100 mL x 3), brine (100 mL x 2), dried over MgSO_4 , filtered, and concentrated under reduced pressure. The product was purified by silica gel column chromatography using 30% of dichloromethane-methanol- NH_4OH (89:9:1) in dichloromethane as eluent to give 4-(3-(2-aminopyrimidin-4-yl)-5-bromo-1H-indol-2-yl)benzonitrile **A.125** (0.366 g, 26.4% overall yield over two steps) as a yellow solid: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 12.16 (1 H, s), 8.27 (1 H, d, $J=1.8$ Hz), 8.05 (1 H, d, $J=5.2$ Hz), 7.94 (2 H, d, $J=8.4$ Hz), 7.76 (2 H, d, $J=8.4$ Hz), 7.42 (1 H, d, $J=8.6$ Hz), 7.34 (1 H, dd, $J=8.6, 1.9$ Hz), 6.60 (2 H, s), 6.27 (1 H, d, $J=5.2$ Hz); Mass Spectrum (ESI) $m/e = 390.2$ [$\text{M}+1$ (^{79}Br)] and 392.3 [$\text{M}+1$ (^{81}Br)].

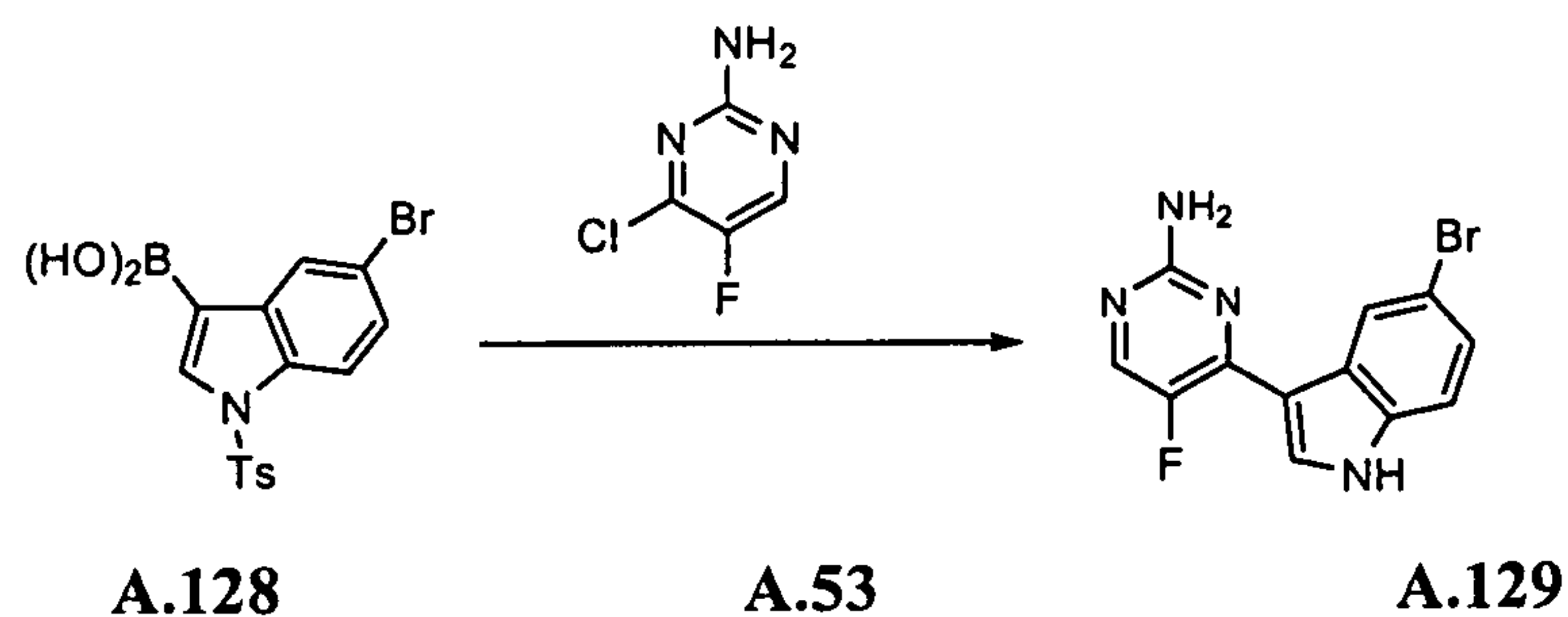


5-bromo-1-tosyl-1H-indole A.127 : To a suspension of sodium hydride (60% dispersion in mineral oil, 2.448 g, 61.2 mmol) in DMF (150 mL), a solution of 5-bromo-1H-indole **A.126** (10 g, 51 mmol) was added and the mixture was stirred at 0 °C for 1 hour. To the mixture was added a solution of *p*-TsCl (11.6695 g, 61.2 mmol) in DMF (50 mL) and the mixture was stirred at room temperature for 4.5 hours. The mixture was poured into water (500 mL) and the resulting precipitate was collected by suction filtration, washed with water (1 L), and dried to give 5-bromo-1-tosyl-1H-indole **A.127** (18. g, quantitative) as a white solid: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 7.78 - 7.93 (5 H, m), 7.44 - 7.52 (1 H, m), 7.39 (2 H, d, $J=8.1$ Hz), 6.81 (1 H, d, $J=3.7$ Hz), 2.32 (3 H, s); Mass Spectrum (ESI) $m/e = 350.0$ [$\text{M}+1$ (^{79}Br)] and 352.0 [$\text{M}+1$ (^{81}Br)].

5-bromo-1-tosyl-1H-indol-3-ylboronic acid

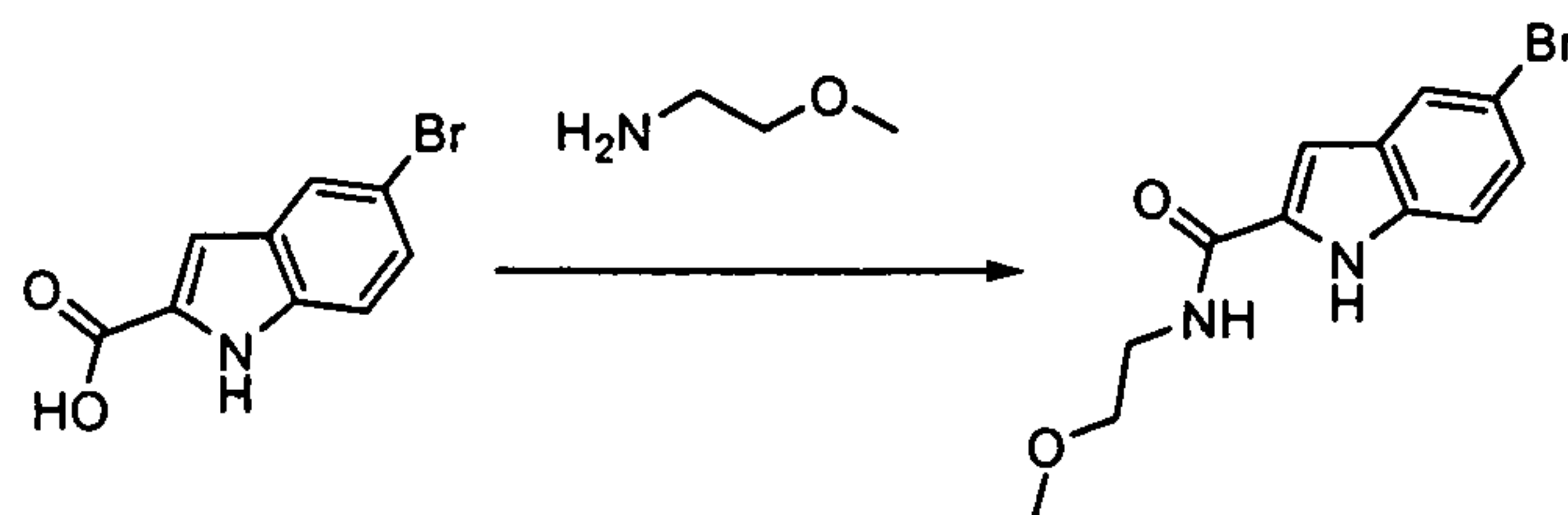


To a solution of 5-bromo-1-tosyl-1H-indole **A.127** (7.6 g, 21.7 mmol) in acetic acid (145 mL) was added $\text{Hg}(\text{OAc})_2$ (6.92 g, 21.7 mmol). After stirring at room temperature for 15 min, HClO_4 (5 drops) was added. The mixture was stirred at room temperature for 24 hours. The mixture was poured into water (200 mL) and the resulting precipitate was filtered, washed with water (1450 mL), and dried to give an off-white solid (12.33 g, 93.3% yield). The off white solid (5 g, 8.21 mmol) was dissolved in THF (164 mL) and to the solution at room temperature was added borane solution (1 M in THF, 41 mL, 41 mmol). After stirring at room temperature for 2 hours, to the mixture was slowly added water (49 mL). The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was extracted with ethyl acetate (150 mL x 2). The combined organic layers were washed with brine (60 mL x 1) and concentrated under reduced pressure to give a grey solid. The grey solid was suspended in hexane (100 mL), filtered, and washed with hexane (100 mL) to give 5-bromo-1-tosyl-1H-indol-3-ylboronic acid **A.128** (3.42 g, quantitative) as a grey solid. The product as a grey solid was carried on without purification for the next step.



4-(5-bromo-1H-indol-3-yl)-5-fluoropyrimidin-2-amine A.129: A mixture of 5-bromo-1-tosyl-1H-indol-3-ylboronic acid (**A.128**) (2.62 g, 6.65 mmol), 4-chloro-5-fluoropyrimidin-2-amine **A.53** (754 mg, 5.11 mmol), $\text{Pd}(\text{PPh}_3)_4$ (1.17 g, 1.02 mmol) and Na_2CO_3 (2M, 10 mL) in benzene (100 mL) and methanol (20 mL) was heated at 85 °C under N_2 for 24 hrs. After cooling to room temperature, the resultant mixture was diluted with ethyl acetate and filtered on a pad of Celite. The filtrates were concentrated, and the residue was charged with ethyl acetate (100 mL) and NaOH (2N, 10 mL). The mixture was heated at 90°C for 1 hr. After cooling to room temperature, the resultant mixture was diluted with ethyl acetate and washed with water and brine, dried and concentrated. Purification of the residue by flash chromatography over silica gel, using 5:4.5:0.25 ethyl acetate-hexane-methanol, gave 4-(5-bromo-1H-indol-3-yl)-5-fluoropyrimidin-2-amine (**A.129**) (900.0 mg, 57%): ^1H NMR

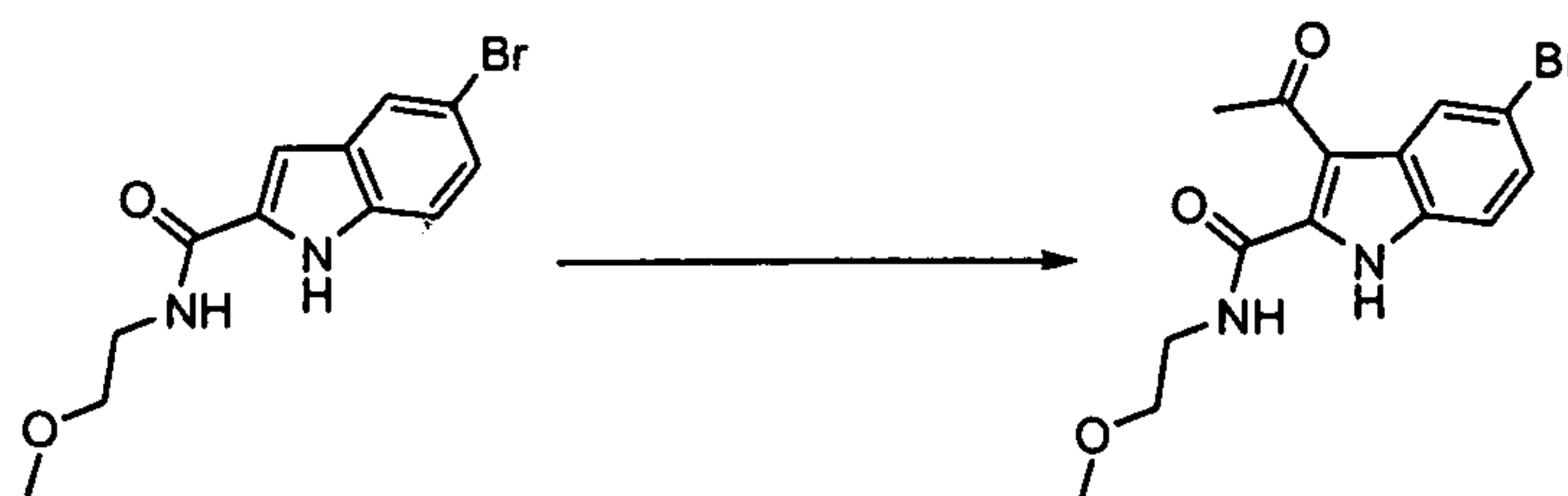
(DMSO- d_6) δ 12.04(s, 1 H), 8.87 (d, J = 2.0 Hz, 1 H), 8.21 (d, J = 4.0 Hz, 1 H), 8.15(s, 1 H), 7.47 (d, J = 8.5 Hz, 1 H), 7.29(dd, J = 8.5, 2.0 Hz, 1 H), 6.58(s, 2 H); ms 307.0 ($M+H^+$).



A.130

A.131

5-bromo-N-(2-methoxyethyl)-1H-indole-2-carboxamide A.131 : A mixture of 5-bromo-1H-indole-2-carboxylic acid A.130 (5 g, 20.82 mmol), 2-methoxyethylamine (2.2 mL, 24.99 mmol), EDC (4.7905 g, 24.99 mmol), DMAP (4.0706 g, 33.32 mmol), and dichloromethane (100 mL) was stirred at room temperature for 18 hours. The mixture was concentrated under reduced pressure to give a yellow solid. The solid was dissolved in ethyl acetate (200 mL), washed with 2N aq. HCl (100 mL x 1), water (100 mL x 1), saturated aq. NaHCO₃ (100 mL x 1), brine (100 mL x 1), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a yellow solid. The solid was suspended in ethyl acetate-methanol-dichloromethane (50 mL), sonicated, filtered, washed with dichloromethane. The filtrate was concentrated under reduced pressure and purified by silica gel column chromatography using 65% ethyl acetate in hexane as eluent to give 5-bromo-N-(2-methoxyethyl)-1H-indole-2-carboxamide A.131 (4.22 g, 68.2% yield) as a pale yellow solid: ¹H NMR (400 MHz, DMSO- d_6) δ ppm 11.76 (1 H, s), 8.60 (1 H, t, J =4.9 Hz), 7.83 (1 H, d, J =1.8 Hz), 7.35 - 7.41 (1 H, m), 7.25 - 7.31 (1 H, m), 7.11 (1 H, s), 3.40 - 3.51 (4 H, m), 3.28 (3 H, s); Mass Spectrum (ESI) m/e = 297.0 [$M+1$ (⁷⁹Br)] and 298.9 [$M+1$ (⁸¹Br)].



A.131

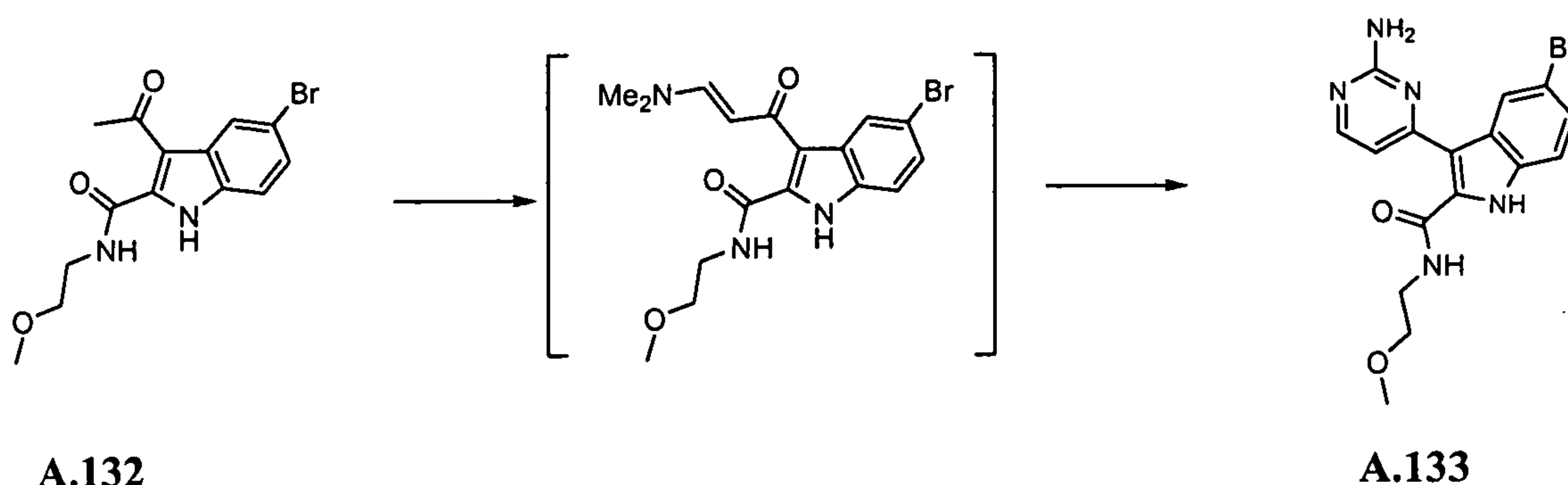
A.132

3-acetyl-5-bromo-N-(2-methoxyethyl)-1H-indole-2-carboxamide A.132:

To a cooled solution of AlCl₃ (5.6856 g, 42.64 mol) in dichloromethane (43 mL) was added dropwise acetic anhydride (4 mL, 42.64 mmol) at 0 °C with stirring. After stirring at 0 °C for

10 minutes, to the cooled mixture was added a suspension of 5-bromo-N-(2-methoxyethyl)-1H-indole-2-carboxamide **A.131** (4.22 g, 14.2 mmol) in dichloromethane (45 mL) at 0 °C and the mixture was allowed to warm to room temperature with stirring for 8 hours. The mixture was poured into ice water (250 mL) with stirring. The resulting precipitate was collected by suction filtration, washed with water (300 mL). The aq. layer was acidified with conc. HCl and extracted with ethyl acetate (350 mL x 2). The precipitate and the combined organic layers were combined, washed with brine (300 mL x 1), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give 3-acetyl-5-bromo-N-(2-methoxyethyl)-1H-indole-2-carboxamide **A.132** (4.30 g, 89.3% yield): ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.75 (1 H, s), 10.28 (1 H, s), 8.23 (1 H, d, *J*=1.8 Hz), 7.49 - 7.53 (1 H, m), 7.44 (1 H, dd, *J*=8.6, 2.0 Hz), 3.50 - 3.55 (4 H, m), 3.30 (3 H, s), 2.65 (3 H, s); Mass Spectrum (ESI) *m/e* = 339.2 [M+1 (⁷⁹Br)] and 341.2 [M+1 (⁸¹Br)].

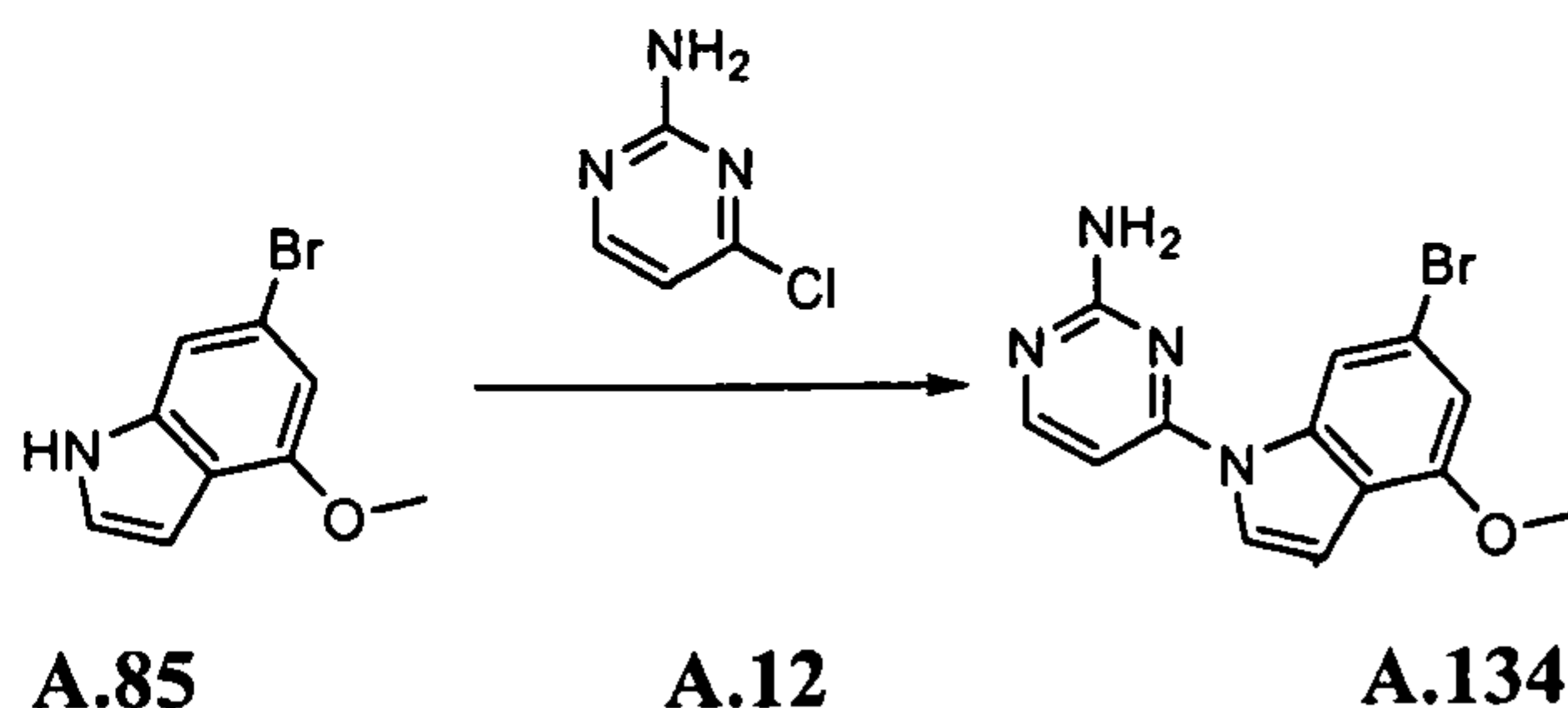
3-(2-aminopyrimidin-4-yl)-5-bromo-N-(2-methoxyethyl)-1H-indole-2-carboxamide



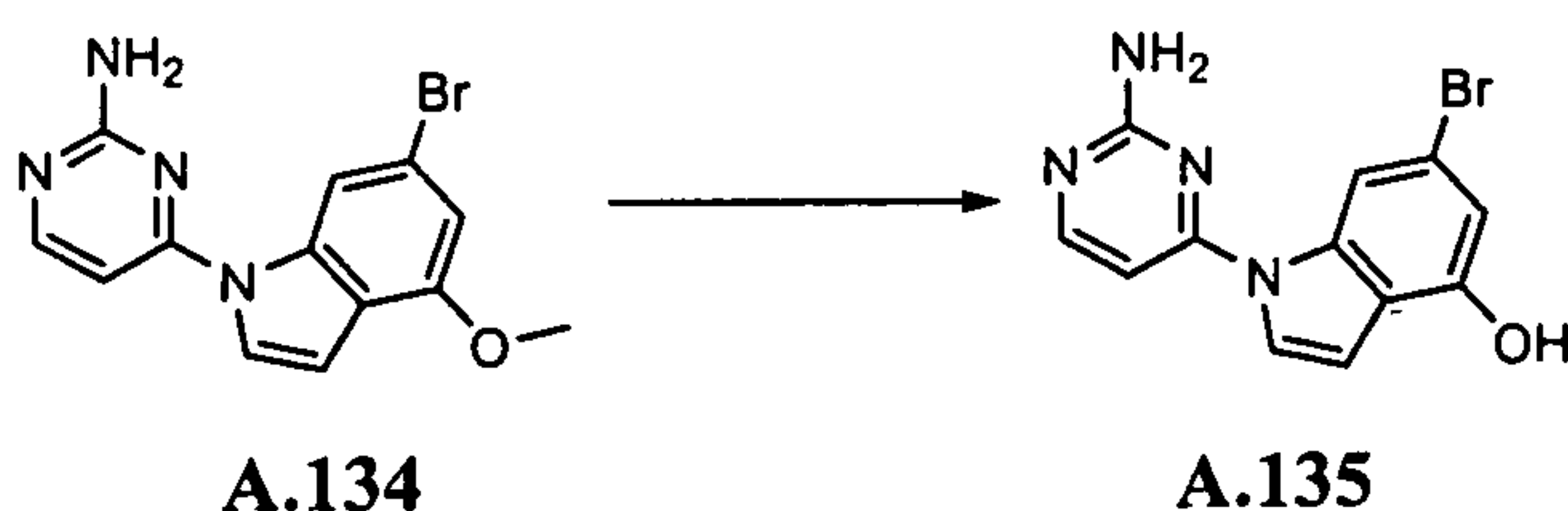
3-(2-aminopyrimidin-4-yl)-5-bromo-N-(2-methoxyethyl)-1H-indole-2-carboxamide **A.133**:

A mixture of 3-acetyl-5-bromo-N-(2-methoxyethyl)-1H-indole-2-carboxamide **A.132** (2 g, 5.9 mmol) in *t*-BuOCH(NMe₂)₂ (4.3 mL, 20.64 mmol) was stirred at 105 °C for 50 min. The mixture was cooled to room temperature. To the cooled mixture were added n-propanol (29 mL), guanidine·HCl (2.82 g, 29.48 mmol), and NaOMe/methanol (4.37 M sol., 4 mL, 17.69 mmol) and the mixture was stirred at 95 °C for 72 hours. The mixture was poured into ice water (100 mL) with stirring. The resulting precipitate was collected by suction filtration, washed with water (100 mL), and dried to give a tan solid. The product was purified by silica gel column chromatography using 95% of dichloromethane in methanol as eluent to give a tan solid. The tan solid was suspended in dichloromethane and filtered to give 3-(2-aminopyrimidin-4-yl)-5-bromo-N-(2-methoxyethyl)-1H-indole-2-carboxamide **A.133** (1.644 g, 71.4% yield) as a tan solid: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.32 (1 H, s), 11.14 (1 H, t, *J*=5.1 Hz), 8.39 (1 H, d, *J*=5.1 Hz), 8.04 (1 H, d, *J*=1.8 Hz), 7.48 - 7.54 (1 H, m), 7.41 (1 H,

dd, $J=8.8, 1.8$ Hz), 7.00 (1 H, d, $J=5.1$ Hz), 6.84 (2 H, s), 3.48 - 3.62 (4 H, m), 3.28 (3 H, s); Mass Spectrum (ESI) $m/e = 390.2$ [$M+1$ (^{79}Br)] and 392.3 [$M+1$ (^{81}Br)].

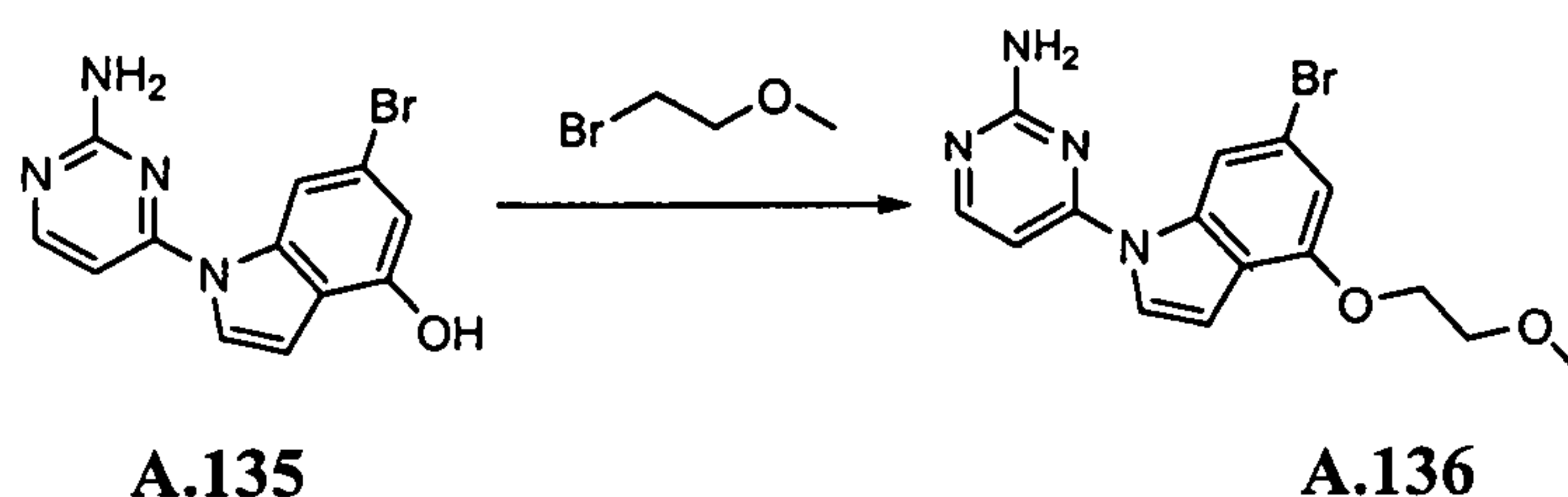


4-(6-bromo-4-methoxy-1H-indol-1-yl)pyrimidin-2-amine A.134: To a solution of 6-bromo-4-methoxy-1H-indole A.85 (2.117 g, 9.36 mmol) in DMF (46 mL) at room temperature was added Cs_2CO_3 (9.155 g, 28.1 mmol) followed by 4-chloropyrimidin-2-amine A.12 (1.456 g, 11.24 mmol) and the mixture was stirred at 80 °C for 21 hours. The mixture was poured into water (200 mL) and the aqueous layer was extracted with ethyl acetate (100 mL x 2). The combined organic layers were washed with brine (100 mL x 2), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give a brown solid. The product was purified by silica gel column chromatography using 65% ethyl acetate in hexane as eluent to give 4-(6-bromo-4-methoxy-1H-indol-1-yl)pyrimidin-2-amine A.134 (1.961 g, 65.6% yield) as an orange solid: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.55 (1 H, s), 8.27 (1 H, d, $J=5.9$ Hz), 7.95 (1 H, d, $J=4.0$ Hz), 6.89 - 7.04 (4 H, m), 6.75 (1 H, d, $J=3.7$ Hz), 3.92 (3 H, s); Mass Spectrum (ESI) $m/e = 319.0$ [$M+1$ (^{79}Br)] and 321.0 [$M+1$ (^{81}Br)].



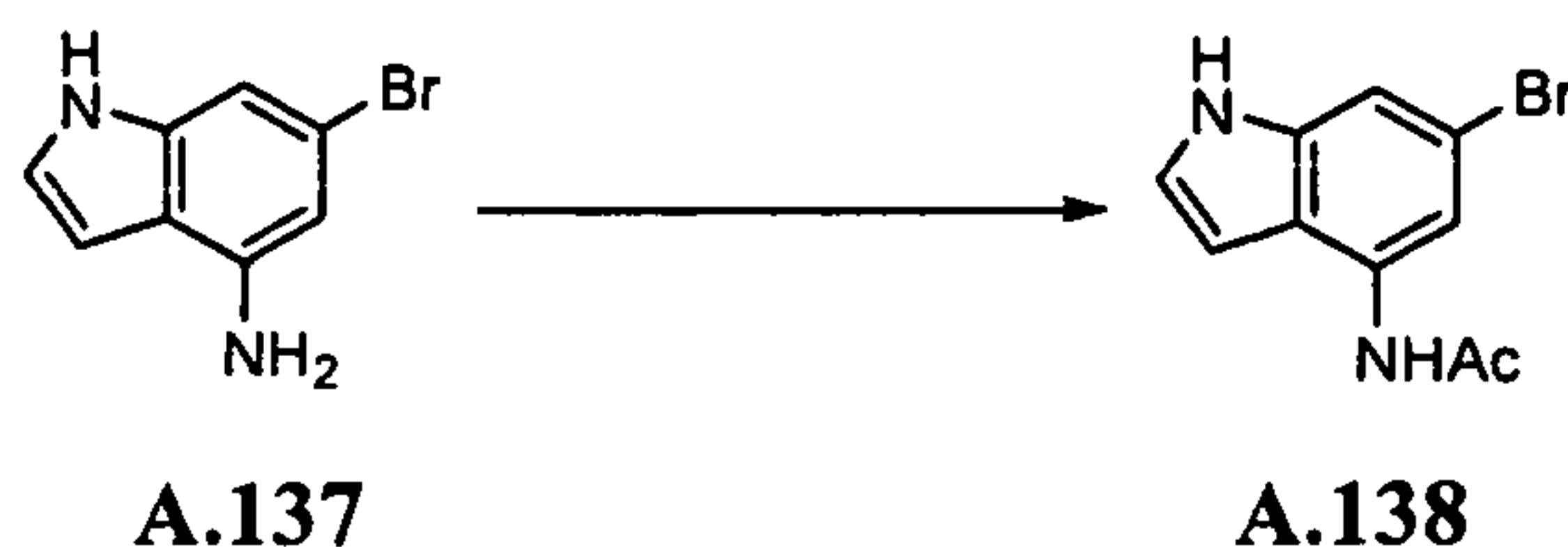
1-(2-aminopyrimidin-4-yl)-6-bromo-1H-indol-4-ol A.135 : To a solution of 4-(6-bromo-4-methoxy-1H-indol-1-yl)pyrimidin-2-amine A.134 (1.868 g, 5.85 mmol) in dichloromethane (50 mL) at 0 °C, was added BBr_3 (1 M sol. in dichloromethane, 29.26 mL, 29.26 mmol) dropwise. After stirring at 0 °C for 1.5 hours, the mixture was allowed to warm to room temperature. After stirring at room temperature for 48 hours, the mixture was quenched by adding water (100 mL). Then 1 N aqueous NaOH (200 mL) was added and the mixture was neutralized with 2 N aqueous HCl to pH 7.0. The the mixture was extracted with dichloromethane (100 mL x 3). The combined organic layers were washed with saturated

aqueous NaHCO₃ (100 mL x 1), brine (100 mL x 2), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a brown solid. The product was purified by silica gel column chromatography using 65% to 85% gradient of ethyl acetate in hexane as eluent to give 1-(2-aminopyrimidin-4-yl)-6-bromo-1H-indol-4-ol **A.135** (1.204 g, 67.4% yield) as a solid: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.16 (1 H, s), 8.37 - 8.40 (1 H, m), 8.26 (1 H, d, *J*=5.9 Hz), 7.89 (1 H, d, *J*=3.7 Hz), 6.92 (2 H, s), 6.90 (1 H, d, *J*=5.9 Hz), 6.78 (1 H, dd, *J*=3.7, 0.7 Hz), 6.74 (1 H, d, *J*=1.5 Hz); Mass Spectrum (ESI) *m/e* = 305.0 [M+1 (⁷⁹Br)] and 307.0 [M+1 (⁸¹Br)].



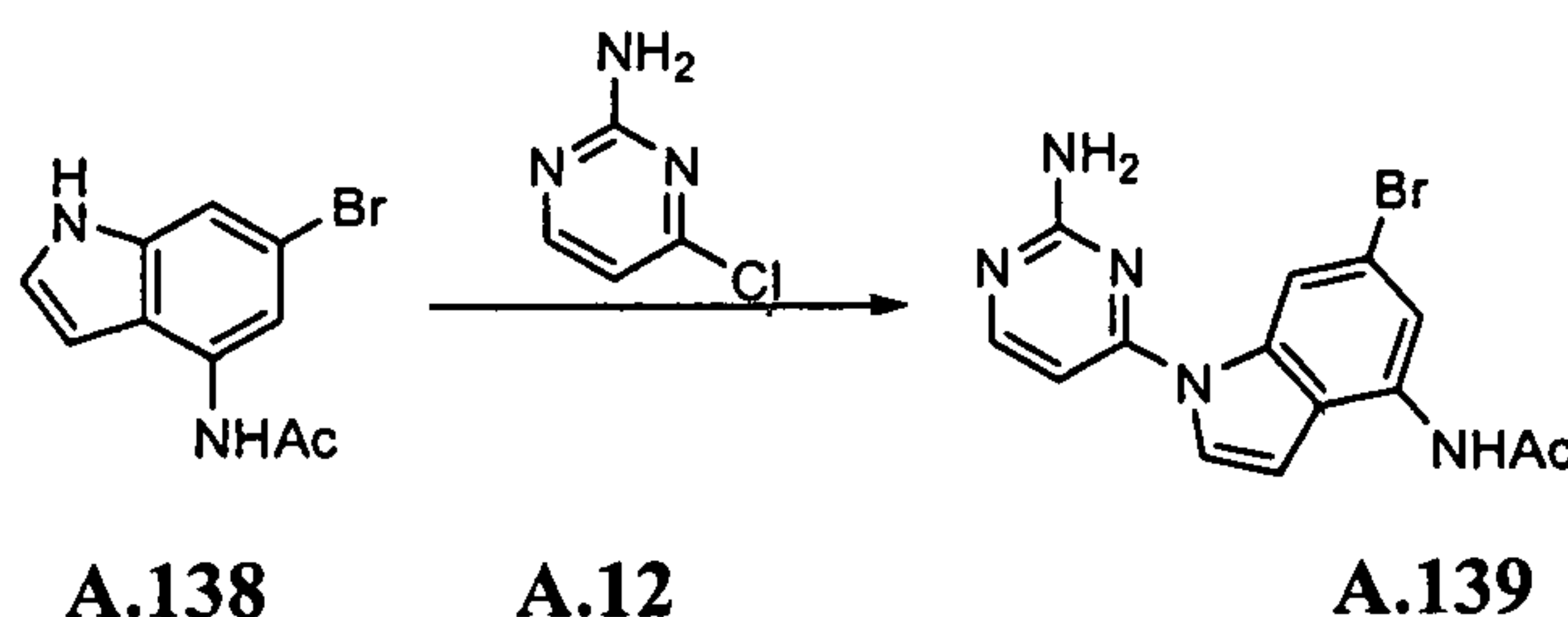
4-(6-bromo-4-(2-methoxyethoxy)-1H-indol-1-yl)pyrimidin-2-amine A.136:

A mixture of 1-(2-aminopyrimidin-4-yl)-6-bromo-1H-indol-4-ol **A.135** (0.5 g, 1.64 mmol), DMF (5 mL), Cs₂CO₃ (0.80 g, 2.46 mmol), and 1-bromo-2-methoxyethane (0.23 mL, 2.46 mmol) was stirred at room temperature for 4.5 hours. The mixture was poured into water (100 mL) with stirring. The aqueous mixture was extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (100 mL x 1), dried over MgSO₄, filtered, and concentrated under reduced pressure and The product was purified by silica gel column chromatography using 85% ethyl acetate in hexane as eluent to give 4-(6-bromo-4-(2-methoxyethoxy)-1H-indol-1-yl)pyrimidin-2-amine **A.136** (0.441 g, 74.1% yield) as a solid: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.55 (1 H, s), 8.27 (1 H, d, *J*=5.9 Hz), 7.95 (1 H, d, *J*=3.7 Hz), 6.96 (2 H, s), 6.93 (2 H, dd, *J*=3.7, 2.2 Hz), 6.73 (1 H, d, *J*=3.7 Hz), 4.23 - 4.29 (2 H, m), 3.71 - 3.77 (2 H, m), 3.35 (3 H, s); Mass Spectrum (ESI) *m/e* = 363.0 [M+1 (⁷⁹Br)] and 365.0 [M+1 (⁸¹Br)].

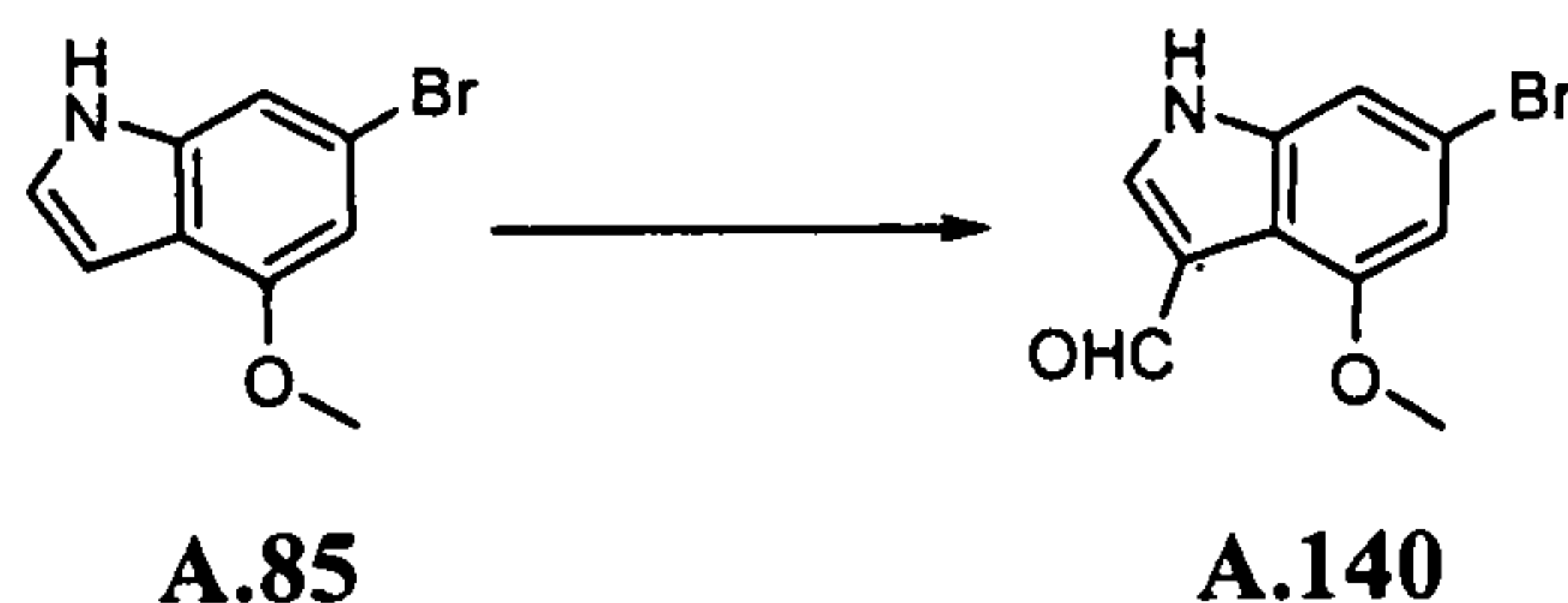


N-(6-bromo-1H-indol-4-yl)acetamide A.138: To a solution of 6-bromo-1H-indol-4-amine **A.137** (0.5 g, 2.37 mmol) in Benzene (20 mL) was added acetic anhydride (0.49 mL, 5.21 mmol) and the mixture was stirred at room temperature. After stirring at room temperature for

2 hours, the mixture was concentrated under reduced pressure to give a brown solid. The brown solid was purified by silica gel column chromatography using 50% ethyl acetate in hexane as eluent to give N-(6-bromo-1H-indol-4-yl)acetamide **A.138** (0.498 g, 83% yield) as a brown solid: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 11.23 (1 H, s), 9.70 (1 H, s), 7.91 (1 H, s), 7.27 - 7.33 (2 H, m), 6.79 (1 H, s), 2.16 (3 H, s); Mass Spectrum (ESI) $m/e = 253.0$ [$\text{M}+1$ (^{79}Br)] and 254.9 [$\text{M}+1$ (^{81}Br)].



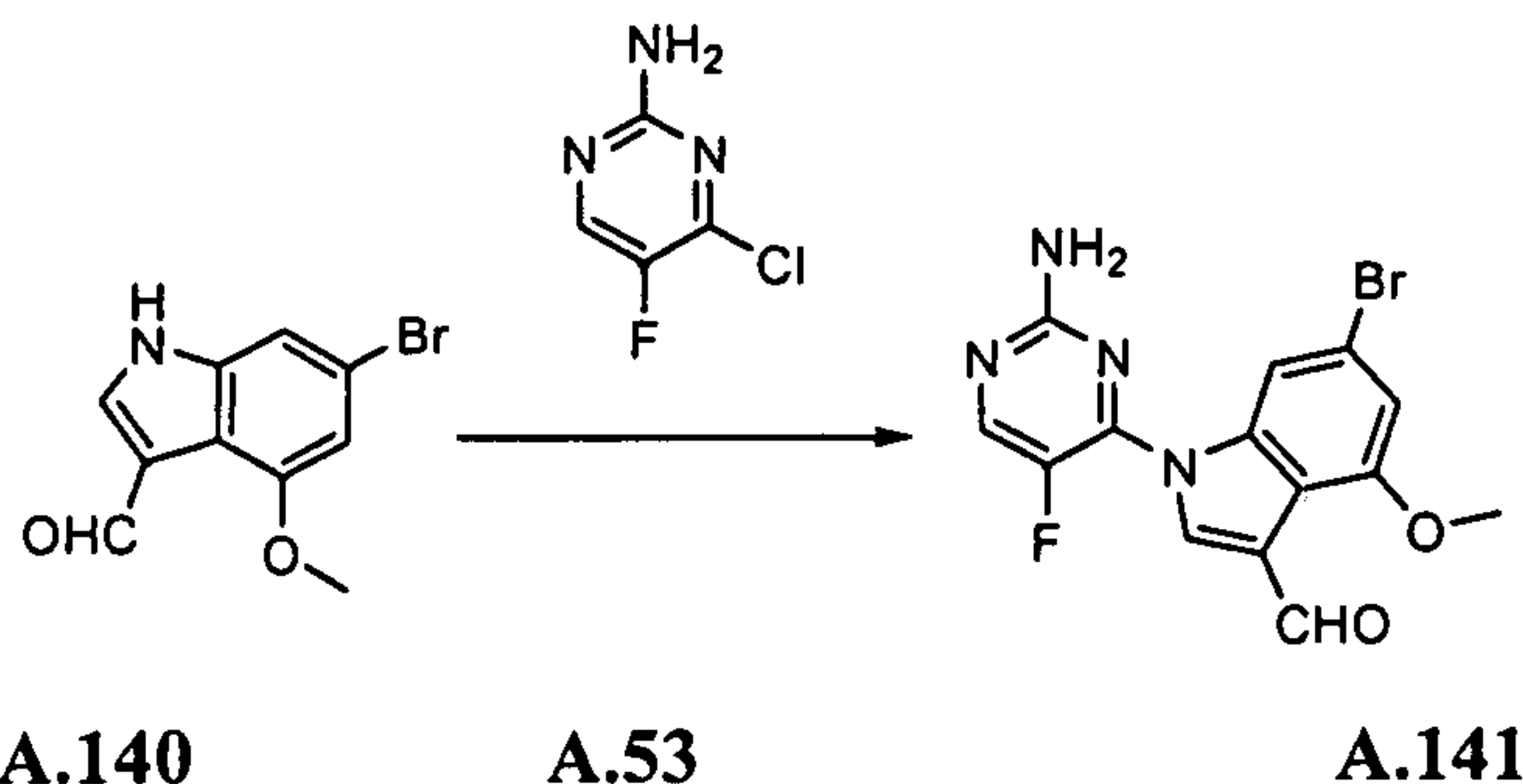
N-(1-(2-aminopyrimidin-4-yl)-6-bromo-1H-indol-4-yl)acetamide A.139: To a solution of N-(6-bromo-1H-indol-4-yl)acetamide **A.138** (0.498 g, 1.97 mmol) in DMF (10 mL) at room temperature was added Cs_2CO_3 (1.9233 g, 5.9 mmol) followed by 4-chloropyrimidin-2-amine **A.12** (0.306 g, 2.36 mmol) and the mixture was stirred at 80 °C for 23 hours. The mixture was poured into water (50 mL). The resulting precipitate was collected by suction filtration, washed with water (100 mL), dried, and purified by silica gel column chromatography using 30% to 100% gradient of dichloromethane-methanol- NH_4OH (89:9:1) in dichloromethane as eluent to give N-(1-(2-aminopyrimidin-4-yl)-6-bromo-1H-indol-4-yl)acetamide **A.139** (0.384 g, 56.3% yield) as a brown solid: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 9.83 (1 H, s), 8.68 (1 H, d, $J=1.1$ Hz), 8.28 (1 H, d, $J=5.5$ Hz), 8.07 (1 H, d, $J=1.1$ Hz), 8.03 (1 H, d, $J=4.0$ Hz), 7.12 (1 H, d, $J=3.7$ Hz), 6.98 (2 H, s), 6.92 (1 H, d, $J=5.5$ Hz), 2.17 (3 H, s); Mass Spectrum (ESI) $m/e = 345.9$ [$\text{M}+1$ (^{79}Br)] and 347.8 [$\text{M}+1$ (^{81}Br)].



6-bromo-4-methoxy-1H-indole-3-carbaldehyde **A.140**

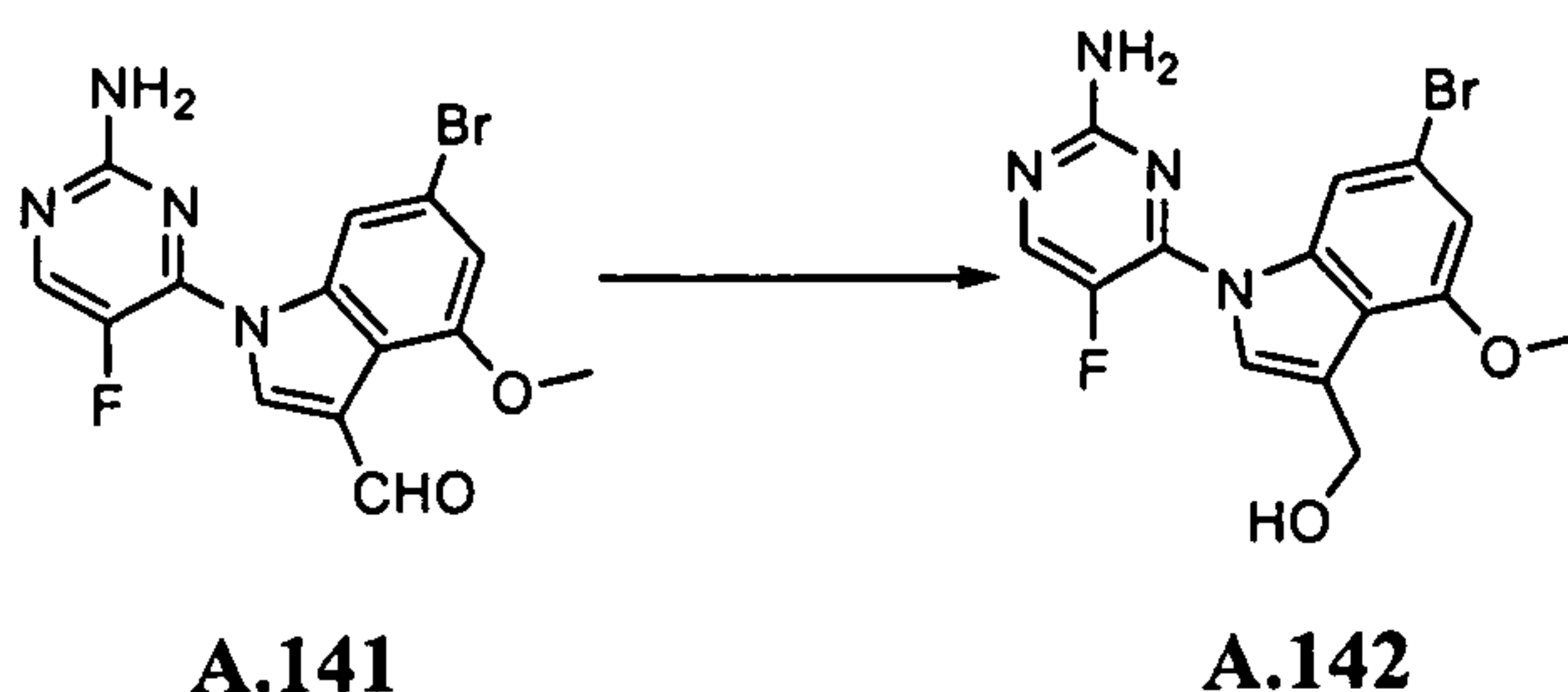
To a solution of 6-bromo-4-methoxy-1H-indole **A.85** (2.0 g, 8.85 mmol) in DMF (9 mL) was added (chloromethylene)dimethylammonium chloride (1.699 g, 13.27 mmol) and the mixture was stirred at room temperature for 24 hours. To the mixture was added water (50 mL) and 10 N aqueous NaOH (10 mL) and the mixture was heated at reflux for 1 hour. The mixture was

cooled to 0 °C. The resulting precipitate was collected by filtration to give 6-bromo-4-methoxy-1H-indole-3-carbaldehyde **A.140** (1.392 g, 61.9% yield) as a brown solid: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 12.26 (1 H, s), 10.26 (1 H, s), 8.05 (1 H, s), 7.30 (1 H, d, $J=1.5$ Hz), 6.89 (1 H, d, $J=1.1$ Hz), 3.95 (3 H, s); Mass Spectrum (ESI) $m/e = 253.9$ [$\text{M}+1$ (^{79}Br)] and 255.9 [$\text{M}+1$ (^{81}Br)].



1-(2-amino-5-fluoropyrimidin-4-yl)-6-bromo-4-methoxy-1H-indole-3-carbaldehyde

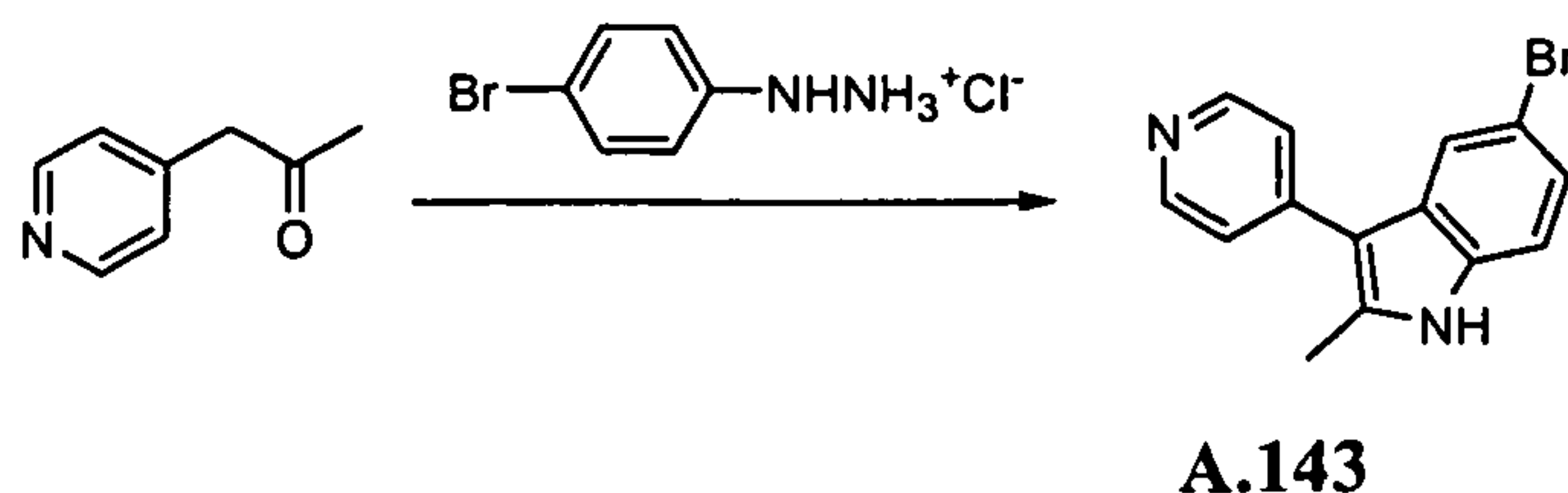
A.141: To a solution of 6-bromo-4-methoxy-1H-indole-3-carbaldehyde **A.140** (0.65 g, 2.56 mmol) in DMF (13 mL) at room temperature was added Cs_2CO_3 (2.50 g, 7.67 mmol) followed by 4-chloro-5-fluoropyrimidin-2-amine **A.53** (0.453 g, 3.07 mmol) and the mixture was stirred at 80 °C for 6 hours. The mixture was concentrated under reduced pressure and purified by silica gel column chromatography using 0% to 100% gradient of dichloromethane-methanol- NH_4OH (89:9:1) in dichloromethane as eluent to give 1-(2-amino-5-fluoropyrimidin-4-yl)-6-bromo-4-methoxy-1H-indole-3-carbaldehyde **A.141** (0.319 g, 34.2% yield) as a yellow solid: ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 10.39 (1 H, s), 8.56 (1 H, d, $J=3.7$ Hz), 8.32 (1 H, d, $J=2.7$ Hz), 7.95 (1 H, s), 7.13 (2 H, s), 7.12 (1 H, d, $J=1.4$ Hz), 4.01 (3 H, s); Mass Spectrum (ESI) $m/e = 365.0$ [$\text{M}+1$ (^{79}Br)] and 367.0 [$\text{M}+1$ (^{81}Br)].



(1-(2-amino-5-fluoropyrimidin-4-yl)-6-bromo-4-methoxy-1H-indol-3-yl)methanol A.142:

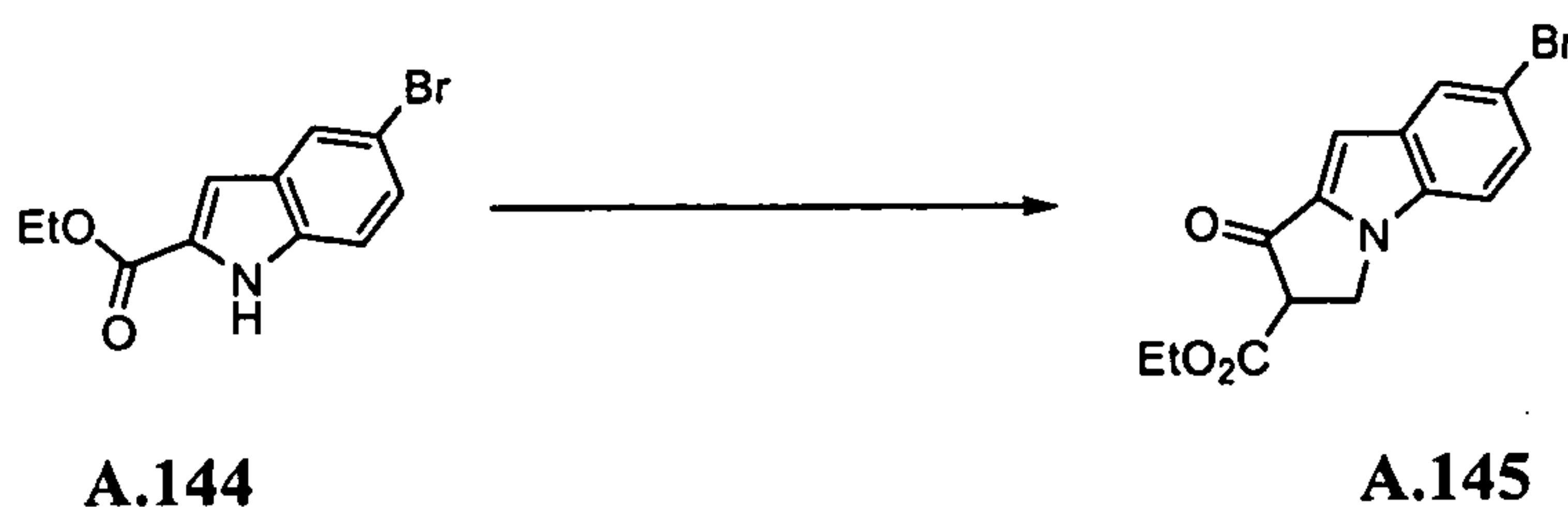
To a solution of 1-(2-amino-5-fluoropyrimidin-4-yl)-6-bromo-4-methoxy-1H-indole-3-carbaldehyde **A.141** (0.319 g, 0.874 mmol) in DMF-methanol (1:1, 10 mL) was added NaBH_4 (0.1432 g, 3.78 mmol) and the mixture was stirred at room temperature for 1 hour. To the mixture was added water (50 mL) with stirring. The resulting precipitate was collected by

filtration, washed with water (100 mL), and dried to give (1-(2-amino-5-fluoropyrimidin-4-yl)-6-bromo-4-methoxy-1H-indol-3-yl)methanol **A.142** (0.22 g, 68.4%) as a tan solid: ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 8.42 (1 H, d, $J=4.6$ Hz), 8.11 (1 H, s), 7.50 - 7.55 (1 H, m), 6.96 (2 H, s), 6.89 (1 H, d, $J=1.4$ Hz), 5.02 (1 H, t, $J=5.5$ Hz), 4.78 (2 H, dd, $J=5.5, 1.4$ Hz), 3.89 (3 H, s); Mass Spectrum (ESI) $m/e = 367.0$ [$\text{M}+1$ (^{79}Br)] and 369.0 [$\text{M}+1$ (^{81}Br)].



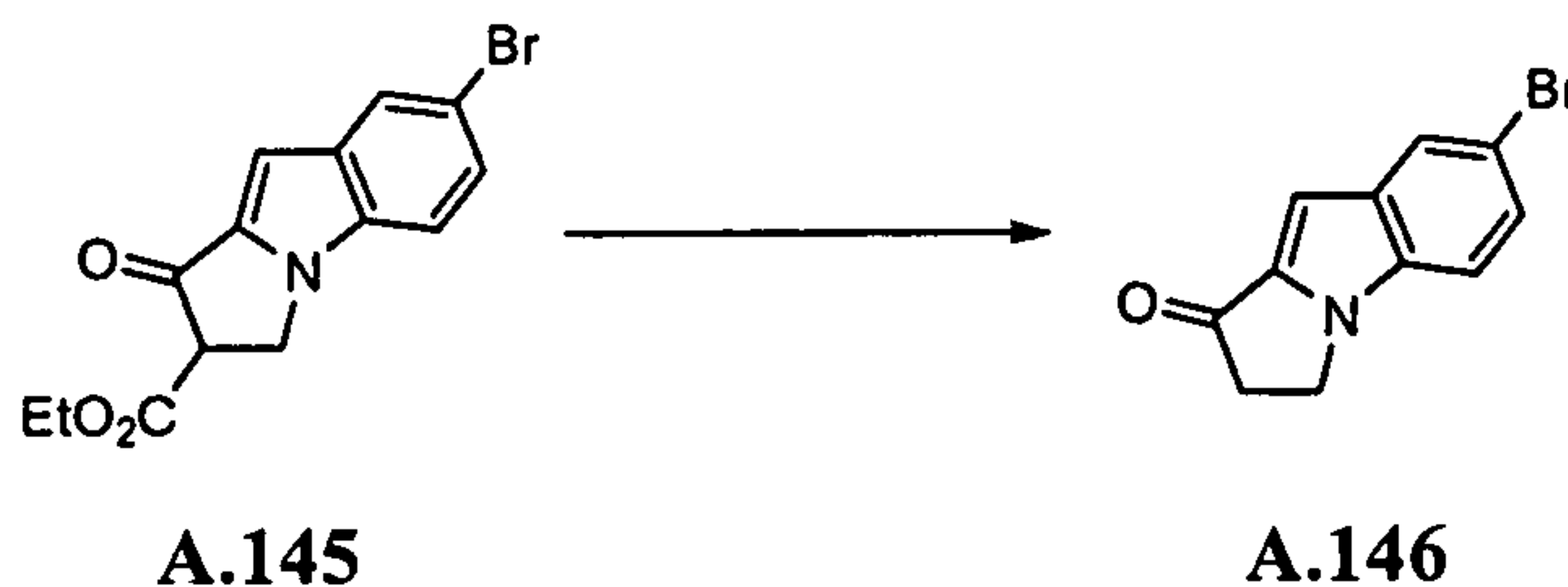
5-bromo-2-methyl-3-(pyridin-4-yl)-1H-indole **A.143**

4-pyridylacetone (2.69g, 0.02 mmol) and 4-bromophenylhydrazine hydrochloride (4.66g, 0.021 mmol) in 20 ml of n-propanol were heated. Conc. Sulfuric acid (2.92g) was added slowly to the mixture. The reaction was heated to reflux for 14 hr. After cooling, the solution was carefully quenched into sodium bicarbonate solution. Solids were collected by filtration and washed with water to give 5-bromo-2-methyl-3-(pyridin-4-yl)-1H-indole (5.65g, 99% yield on crude, ~78% pure by HPLC). A 1g portion was suspended in hot ethyl acetate (40ml). Filtration of the hot suspension afforded 0.3g of analytically pure 5-bromo-2-methyl-3-(pyridin-4-yl)-1H-indole **A.143**: Mp 248.1 °C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.66 (s, 1H); 8.602 (dd, $J=4.4, 1.6$ Hz, 1H); 7.737 (d, $J=2$ Hz, 1H); 7.491 (dd, $J=4.8, 1.6$ Hz, 1H); 7.350 (d, $J=8.4$ Hz, 1H); 7.228 (dd, $J=8.4, 2$ Hz, 1H); 2.529 (s, 3H) ppm; Mass Spectrum (ESI) $m/e = 287$ [$\text{M}+1$ (^{79}Br)] and 289 [$\text{M}+1$ (^{81}Br)]; CHN Found: 58.63%C; 3.99%H; 9.75%N; 27.70% Br Theory 58.56 %C; 3.86% H; 9.76% N; 27.83% Br.

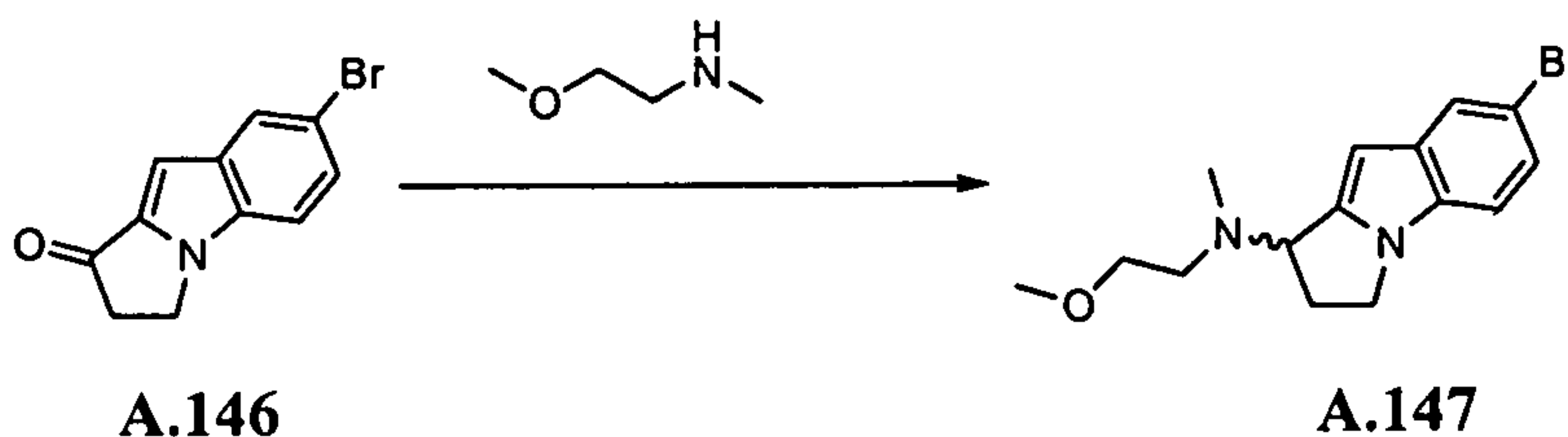


ethyl 7-bromo-1-oxo-2,3-dihydro-1H-pyrrolo[1,2-a]indole-2-carboxylate **A.145**: A mixture of ethyl 5-bromo-1H-indole-2-carboxylate **A.144** (9.94 g, 37.1 mmol), benzene (74 mL), and $t\text{-BuOK}$ (1 M sol. In $t\text{-BuOH}$, 37.1 mL, 37.1 mmol) was stirred at room temperature for 5 minutes. To the mixture was added ethyl acrylate (4.02 mL, 37.09 mmol) and the mixture was

heated under reflux for 24 hours. Water (100 mL) was added to the mixture with stirring. The mixture was acidified to pH 2.0 with 2 N aqueous HCl (20 mL) and diluted with ethyl acetate (100 mL). The organic layer was separated, washed with water (100 mL x 3), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give ethyl 7-bromo-1-oxo-2,3-dihydro-1H-pyrrolo[1,2-a]indole-2-carboxylate **A.145** (13.71 g on crude) as a yellow oil. The product was carried on to the next step: Mass Spectrum (ESI) $m/e = 322.0$ [$M+1$ (^{79}Br)] and 324.0 [$M+1$ (^{81}Br)].



7-bromo-2,3-dihydropyrrolo[1,2-a]indol-1-one A.146: A solution of 7-bromo-1-oxo-2,3-dihydro-1H-pyrrolo[1,2-a]indole-2-carboxylate **A.145** (37.09 mmol) in 95% of aqueous acetic acid (40 mL) was heated at reflux with stirring for 27 hours. Water (150 mL) was added to the mixture with stirring. The resulting precipitate was collected by filtration and washed with water (300 mL) and air-dried to give a brown solid. The brown solid was dissolved in ethyl acetate (500 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a brown solid. The brown solid was purified by silica gel column chromatography using 30% of ethyl acetate in hexane as eluent to give 7-bromo-2,3-dihydropyrrolo[1,2-a]indol-1-one **A.146** (4.27 g, 45% overall yield over two steps) as a yellow solid: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.98 (1 H, d, $J=1.8$ Hz), 7.62 (1 H, d, $J=8.8$ Hz), 7.46 (1 H, dd, $J=9.0, 2.0$ Hz), 6.91 (1 H, s), 4.46 (2 H, t, $J=6.2$ Hz), 3.17 - 3.22 (2 H, m); Mass Spectrum (ESI) $m/e = 250.0$ [$M+1$ (^{79}Br)] and 251.9 [$M+1$ (^{81}Br)].

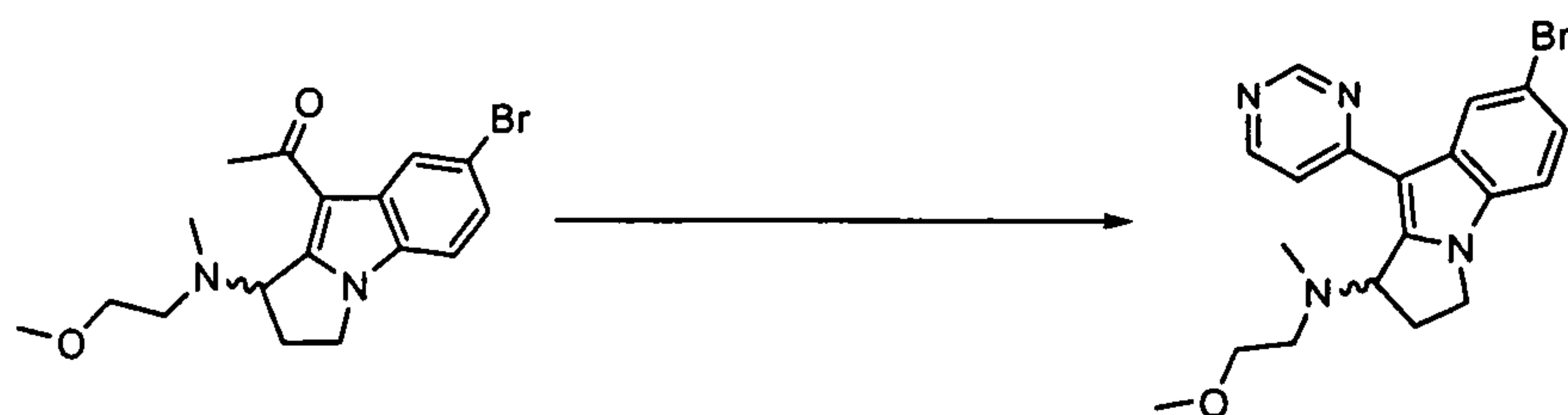


7-bromo-N-(2-methoxyethyl)-N-methyl-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-amine A.147: To a solution of 7-bromo-2,3-dihydropyrrolo[1,2-a]indol-1-one **A.146** (1.5 g, 5.998 mmol) in methanol-acetic acid (20:1, 30 mL), DMF (5 mL), and DCE (8 mL), was added 2-methoxy-N-methylethanamine (1.3 mL, 11.996 mmol) followed by NaBH₃CN (1.8845 g, 29.99 mmol) and then the mixture was stirred at 80 °C for 25 hours. The mixture was poured

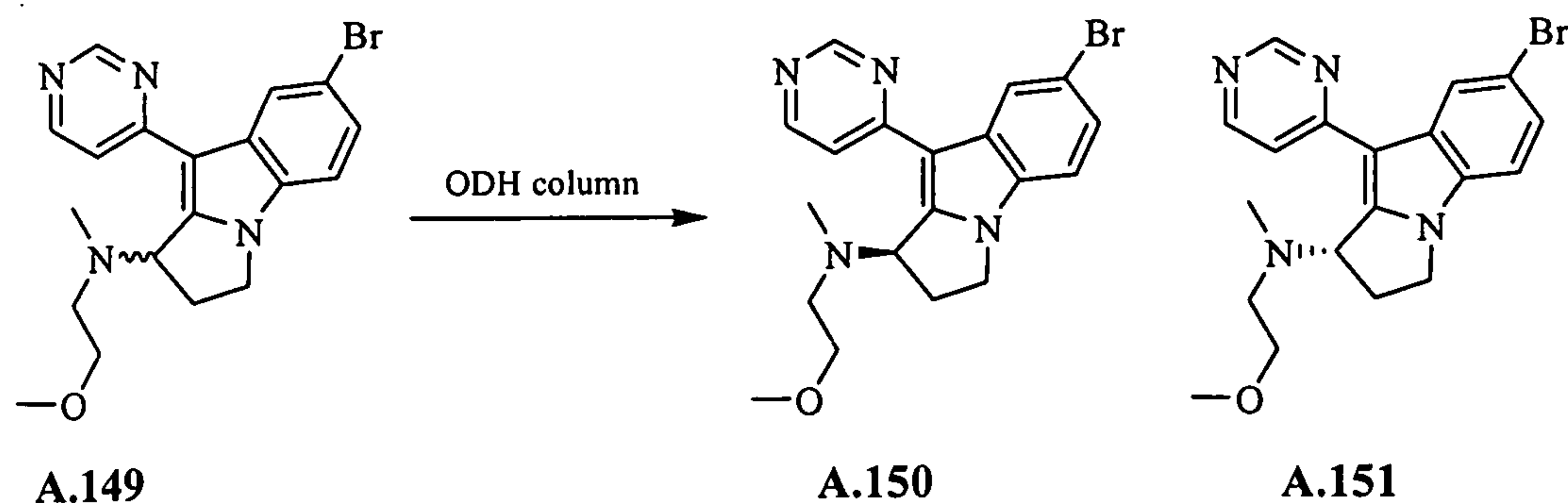
into saturated aqueous NaHCO_3 (250 mL) with stirring and basified to pH 10.0 with 2 N aqueous NaOH (40 mL). The mixture was extracted with dichloromethane (100 mL x 1). The combined organic layers were washed with water (100 mL x 2), brine (100 mL x 2), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give a yellow oil. The product was purified by silica gel column chromatography using 0% to 100% gradient of dichloromethane-methanol- NH_4OH (89:9:1) in dichloromethane as eluent to give 7-bromo-N-(2-methoxyethyl)-N-methyl-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-amine **A.147** (1.655 g, 85.4% yield) as a brown syrup: Mass Spectrum (ESI) $m/e = 323.0$ [$M+1$ (^{79}Br)] and 325.1 [$M+1$ (^{81}Br)].



1-(7-bromo-1-((2-methoxyethyl)(methyl)amino)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9-yl)ethanone A.148: To a cooled solution of AlCl_3 (1.95 g, 14.54 mmol) in dichloromethane (14 mL) was added dropwise acetic anhydride (1.37 mL, 14.54 mmol) at 0 °C with stirring. The mixture was stirred at 0 °C for 10 minutes. To the cooled mixture was added a solution of 7-bromo-N-(2-methoxyethyl)-N-methyl-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-amine **A.147** (1.567 g, 4.85 mmol) in dichloromethane (16 mL). The mixture was allowed to warm to room temperature and stirred at room temperature for 48 hours. The mixture was poured into ice water (100 mL) with stirring and extracted with dichloromethane (100 mL x 2). The combined organic layers were washed with saturated aqueous NaHCO_3 (100 mL x 1), brine (100 mL x 1), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The product was purified by silica gel column chromatography using 10% to 20% gradient of dichloromethane-methanol- NH_4OH (89:9:1) in dichloromethane as eluent to give 1-(7-bromo-1-((2-methoxyethyl)(methyl)amino)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9-yl)ethanone **A.148** (1.46 g, 82.4% yield) as a dark brown syrup: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.38 (1 H, d, $J=1.2$ Hz), 7.41 - 7.46 (1 H, m), 7.35 (1 H, dd, $J=8.6, 2.0$ Hz), 4.93 (1 H, dd, $J=8.4, 1.8$ Hz), 4.07 - 4.30 (2 H, m), 3.40 (2 H, t, $J=5.7$ Hz), 3.18 (3 H, s), 2.64 - 2.77 (2 H, m), 2.63 (3 H, s), 2.52 - 2.61 (1 H, m), 2.39 - 2.48 (1 H, m), 2.10 (3 H, s); Mass Spectrum (ESI) $m/e = 365.0$ [$M+1$ (^{79}Br)] and 367.1 [$M+1$ (^{81}Br)].

**A.148****A.149**

7-bromo-N-(2-methoxyethyl)-N-methyl-9-(pyrimidin-4-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-amine A.149: A mixture of 1-(7-bromo-1-((2-methoxyethyl)(methyl)amino)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9-yl)ethanone **A.148** (1 g, 2.74 mmol) in *t*-BuOCH(NMe₂)₂ (1.2 mL, 5.48 mmol) was stirred at 105 °C. After stirring at 105 °C for 2.5 hours, the mixture was cooled to room temperature. To the cooled mixture were added *n*-PrOH (26 mL), formamidine acetate (1.4251 g, 13.7 mmol), and NaOMe in methanol (4.37 M sol., 1.9 mL, 8.303 mmol) and the mixture was stirred at 95 °C for 48 hours. The mixture was poured into ice water (100 mL) with stirring. The aqueous mixture was extracted with dichloromethane (100 mL x 3). The combined organic layers were washed with brine (100 mL x 1), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The product was purified by silica gel column chromatography using 0% to 100% gradient of dichloromethane-methanol-NH₄OH (89:9:1) in dichloromethane as eluent to give 7-bromo-N-(2-methoxyethyl)-N-methyl-9-(pyrimidin-4-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-amine **A.149** (0.635 g, 57.8% yield) as a dark red syrup: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.13 (1 H, d, *J*=0.8 Hz), 8.88 (1 H, d, *J*=2.0 Hz), 8.59 (1 H, d, *J*=5.9 Hz), 8.28 (1 H, dd, *J*=5.7, 1.4 Hz), 7.41 - 7.47 (1 H, m), 7.32 - 7.38 (1 H, m), 4.93 (1 H, dd, *J*=8.4, 2.9 Hz), 4.13 - 4.28 (2 H, m), 3.45 (2 H, t, *J*=5.3 Hz), 3.25 (3 H, s), 2.68 - 2.80 (2 H, m), 2.52 - 2.65 (2 H, m), 2.11 (3 H, s); Mass Spectrum (ESI) *m/e* = 401.0 [M+1 (⁷⁹Br)] and 403.1 [M+1 (⁸¹Br)].

**A.149****A.150****A.151**

The racemic mixture **A.149** was separated on a Chiralcel OD-H column using 3% isocratic of isopropanol in hexane as eluent to give two separated isomers. The stereochemistry of the two

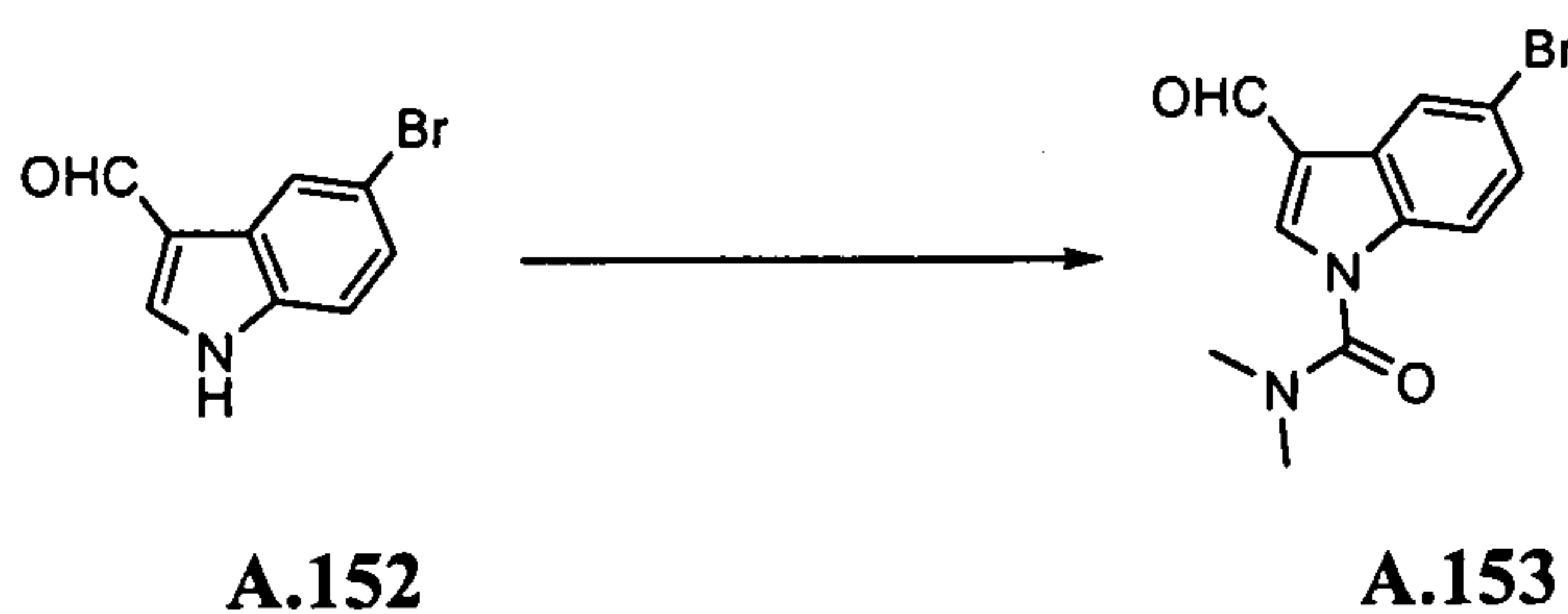
isomers was arbitrarily assigned the first peak **A.150** as R-isomer and the second peak **A.151** as S-isomer on OD-H column.

(1R*)-7-bromo-N-(2-methoxyethyl)-N-methyl-9-(pyrimidin-4-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-amine A.150

¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 9.13 (1 H, s), 8.88 (1 H, d, *J*=1.7 Hz), 8.60 (1 H, d, *J*=5.4 Hz), 8.29 (1 H, d, *J*=5.6 Hz), 7.45 (1 H, d, *J*=8.8 Hz), 7.36 (1 H, dd, *J*=8.6, 2.0 Hz), 4.93 (1 H, dd, *J*=8.3, 2.7 Hz), 4.13 - 4.28 (2 H, m), 3.46 (2 H, t, *J*=5.5 Hz), 3.25 (3 H, s), 2.70 - 2.80 (2 H, m), 2.52 - 2.66 (2 H, m), 2.11 (3 H, s)

(1S*)-7-bromo-N-(2-methoxyethyl)-N-methyl-9-(pyrimidin-4-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-amine A.151

¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 9.13 (1 H, s), 8.88 (1 H, d, *J*=1.7 Hz), 8.60 (1 H, d, *J*=5.4 Hz), 8.29 (1 H, d, *J*=5.6 Hz), 7.45 (1 H, d, *J*=8.8 Hz), 7.36 (1 H, dd, *J*=8.6, 2.0 Hz), 4.93 (1 H, dd, *J*=8.3, 2.7 Hz), 4.13 - 4.28 (2 H, m), 3.46 (2 H, t, *J*=5.5 Hz), 3.25 (3 H, s), 2.70 - 2.80 (2 H, m), 2.52 - 2.66 (2 H, m), 2.11 (3 H, s)



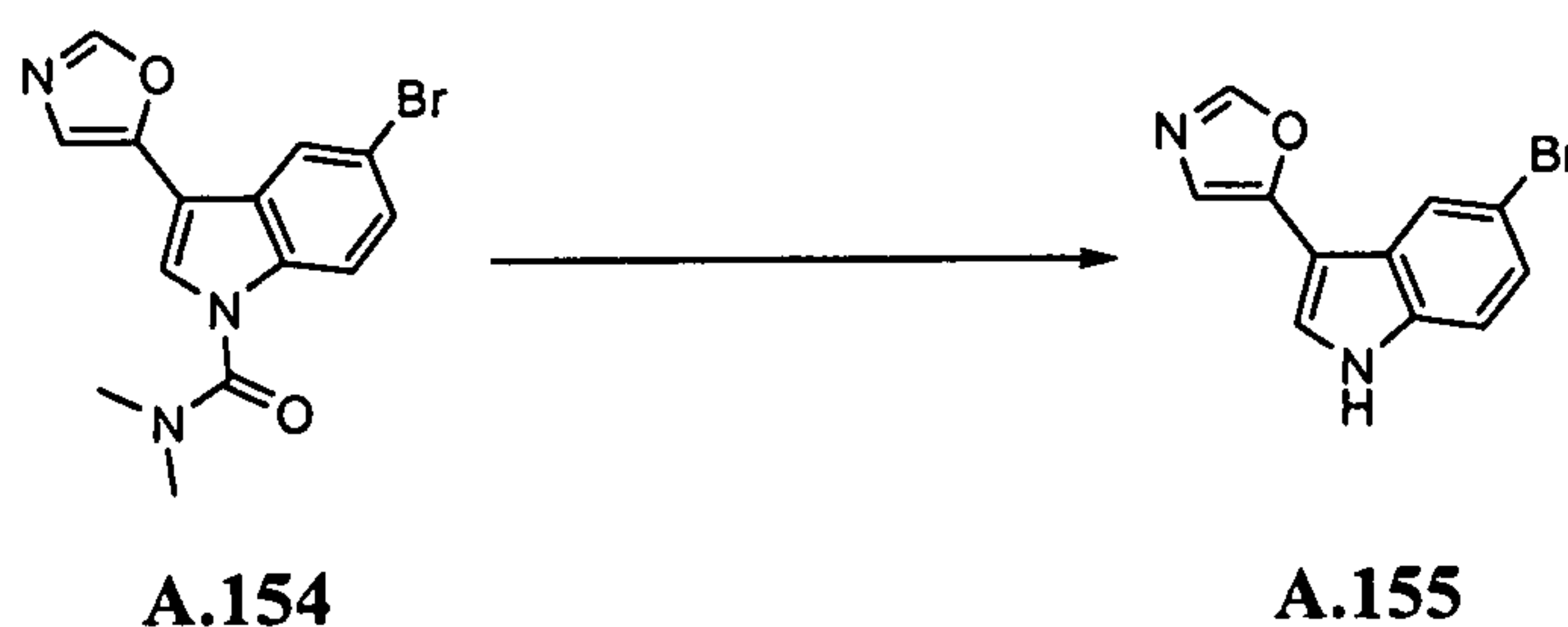
5-bromo-3-formyl-N,N-dimethyl-1H-indole-1-carboxamide A.153: To a 5-bromo-1H-indole-3-carbaldehyde **A.152** (2.69 g, 12.0 mmol) in DMF (34 mL) was added NaH (60% dispersion in mineral oil, 0.72 g, 18 mmol) at 0 °C and the mixture was allowed to warm to room temperature over 10 minutes. To the mixture was added dimethylcarbamic chloride (1.33 mL, 14.4 mmol) and the mixture was stirred at room temperature for 6 hours. To the mixture was added water (100 mL). The mixture was extracted with dichloromethane (100 mL x 2). The combined organic layers were washed with brine (100 mL x 1), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give an orange oil. The product was purified by silica gel column chromatography using 0% to 100% gradient of ethyl acetate in hexane as eluent to give 5-bromo-3-formyl-N,N-dimethyl-1H-indole-1-carboxamide **A.153** (3.50 g, 98.6% yield) as a yellow syrup: ¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 10.01 (1

H, s), 8.64 (1 H, s), 8.27 (1 H, s), 7.50 - 7.69 (2 H, m), 3.05 (6 H, s); Mass Spectrum (ESI) m/e = 295.0 [$M+1$ (^{79}Br)] and 297.0 [$M+1$ (^{81}Br)].



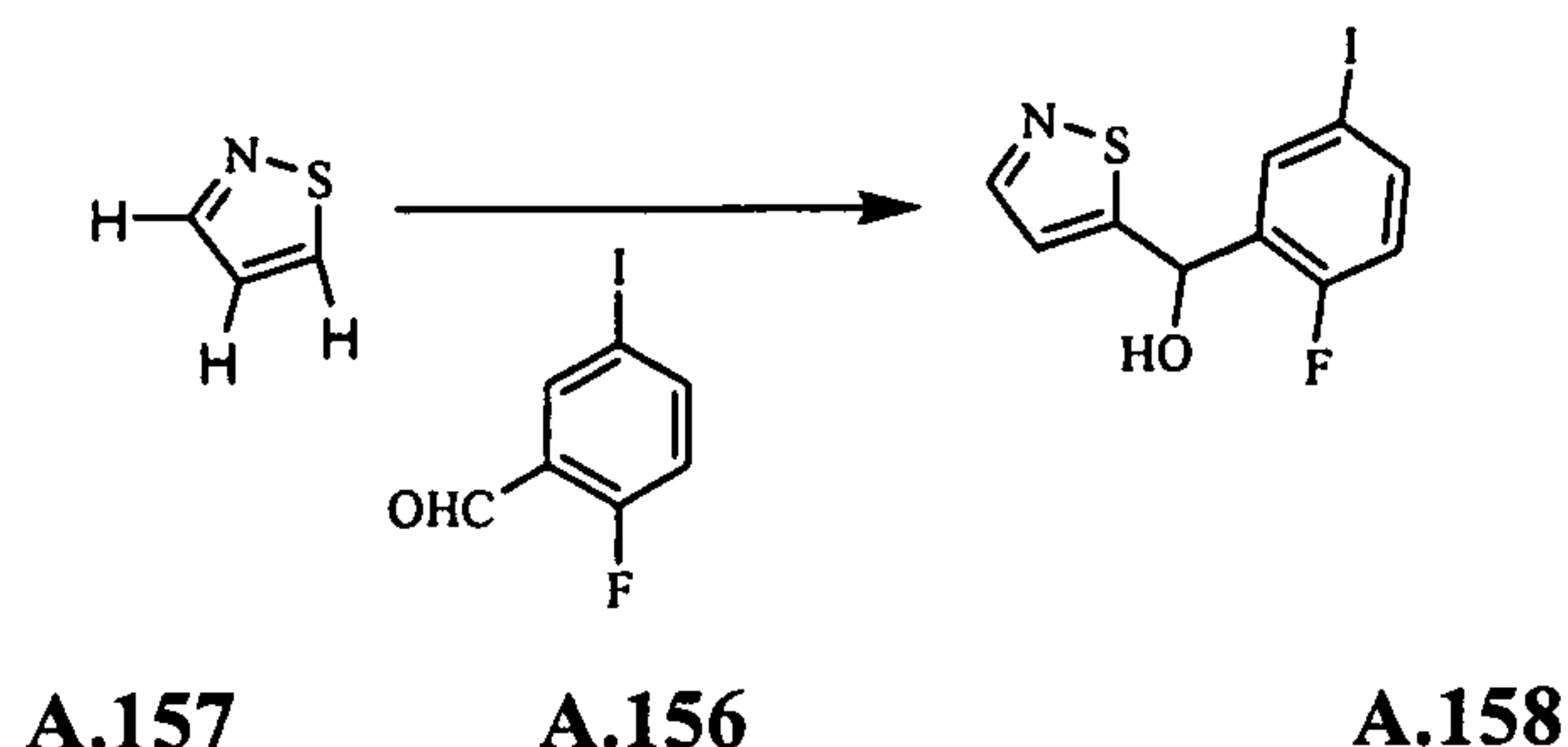
5-bromo-N,N-dimethyl-3-(oxazol-5-yl)-1H-indole-1-carboxamide A.154

To a solution of 5-bromo-3-formyl-N,N-dimethyl-1H-indole-1-carboxamide **A.153** (3.50 g, 11.84 mmol) in DME (150 mL) was added TosMIC (2.312 g, 11.84 mmol) followed by DBU (1.95 mL, 13.03 mmol) and the mixture was stirred at 80 °C for 2 hours. The mixture was cooled to room temperature and concentrated under reduced pressure to give a dark red syrup. The product was purified by silica gel column chromatography using % ethyl acetate in hexane as eluent to give 5-bromo-N,N-dimethyl-3-(oxazol-5-yl)-1H-indole-1-carboxamide **A.154** (2.755 g, 69.6% yield on crude) as a red syrup: ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 8.43 - 8.47 (1 H, m), 8.11 (2 H, s), 7.70 - 7.73 (1 H, m), 7.64 (1 H, d, $J=8.8$ Hz), 7.50 (1 H, dd, $J=8.8, 1.0$ Hz), 3.05 (6 H, s); Mass Spectrum (ESI) m/e = 334.0 [$M+1$ (^{79}Br)] and 336.0 [$M+1$ (^{81}Br)].

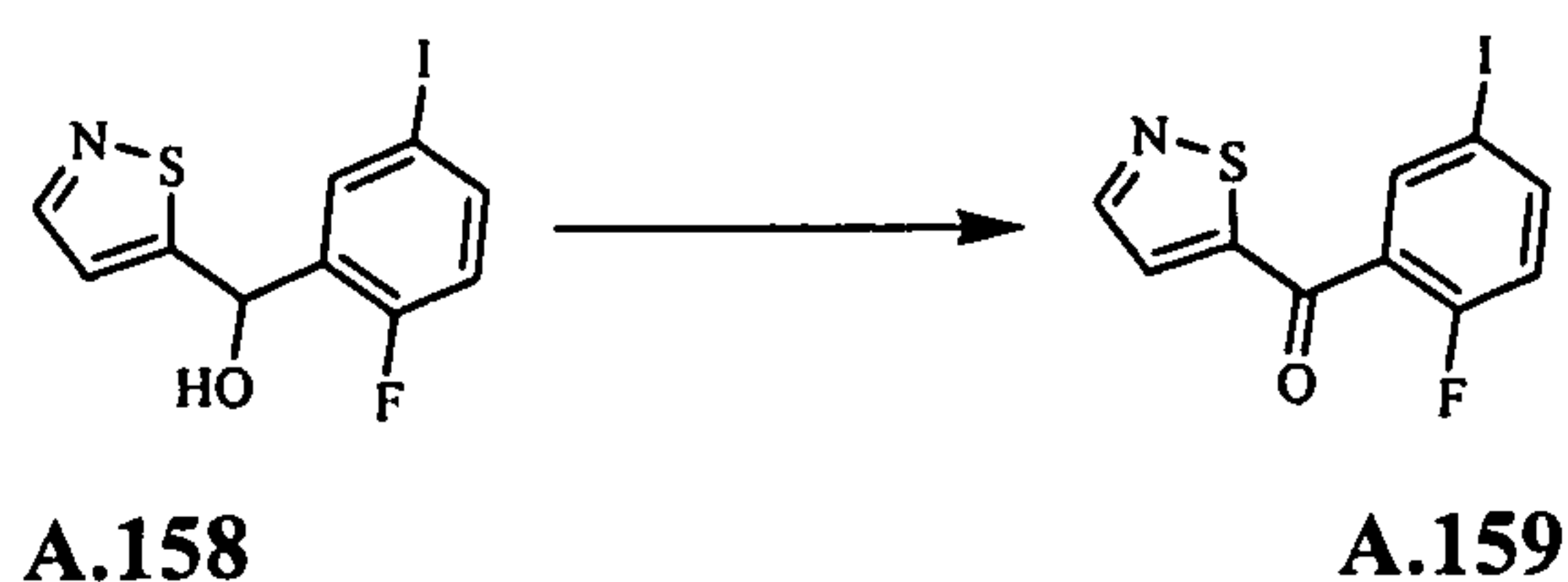


5-bromo-3-(oxazol-5-yl)-1H-indole A.155: To a solution of 5-bromo-N,N-dimethyl-3-(oxazol-5-yl)-1H-indole-1-carboxamide **A.154** (2.755 g, 8.24 mmol) in methanol (100 mL) at 0 °C was added 1N aqueous NaOH (22 mL) and the mixture was stirred at 0 °C for 2 hours. The mixture was partitioned between dichloromethane (100 mL) and saturated aqueous NH_4Cl (100 mL). The organic layer was separated, dried over MgSO_4 , filtered, and concentrated under reduced pressure. The product was purified by silica gel column chromatography using 0% to 100% gradient of ethyl acetate in hexane as eluent to give 5-bromo-3-(oxazol-5-yl)-1H-indole **A.155** (0.41 g, 18.9% yield) as a light yellow solid: ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 11.78 (1 H, s), 8.27 - 8.38 (1 H, m), 8.01 (1 H, d, $J=1.5$ Hz), 7.87 (1 H, s), 7.50 (1 H, s),

7.45 (1 H, d, $J=8.6$ Hz), 7.32 (1 H, dd, $J=8.6, 1.2$ Hz); Mass Spectrum (ESI) $m/e = 262.9$ [$M+1$ (^{79}Br)] and 265.0 [$M+1$ (^{81}Br)].

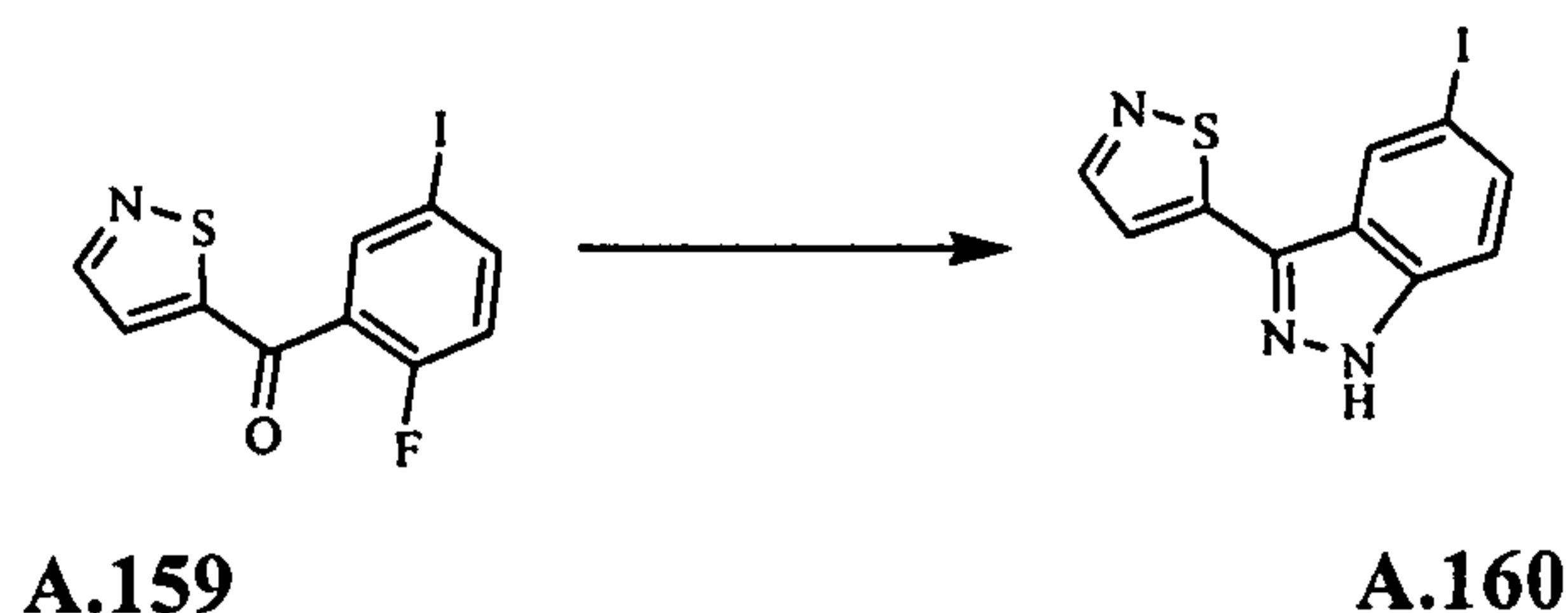


(2-fluoro-5-iodophenyl)(isothiazol-5-yl)methanol A.158: To a solution of isothiazole (A.157) (3.0 g, 35.3 mmol) in 50 mL THF at -78°C under argon was added n-butyllithium (1.6 M in hexane, 22.1 mL, 35.3 mmol) dropwise over 10 minutes. The mixture stirred at -78°C for 1.5 hours. A solution of 2-fluoro-5-iodobenzaldehyde (A.156) (7.35 g, 29.4 mmol) in 30 mL THF was added dropwise over 15 minutes, and the reaction stirred an additional 2 hours at -78°C . Water was added to quench the reaction, and the mixture warmed to 0°C . The solution was neutralized with 2 N HCl to pH 7, partitioned between water and dichloromethane, and the aqueous layer further extracted with dichloromethane. The combined organic extracts were washed with brine, dried over MgSO_4 and condensed. Purification by flash chromatography (0-15-100% ethyl acetate in hexane) gave 7.19 g (2-fluoro-5-iodophenyl)(isothiazol-5-yl)methanol A.158. ^1H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 8.30 (1 H, s), 7.76 (1 H, dd, $J=6.8, 2.2$ Hz), 7.56 (1 H, ddd, $J=8.6, 5.0, 2.3$ Hz), 6.97 (1 H, s), 6.79 (1 H, dd, $J=9.8, 8.8$ Hz), 6.37 (1 H, s)

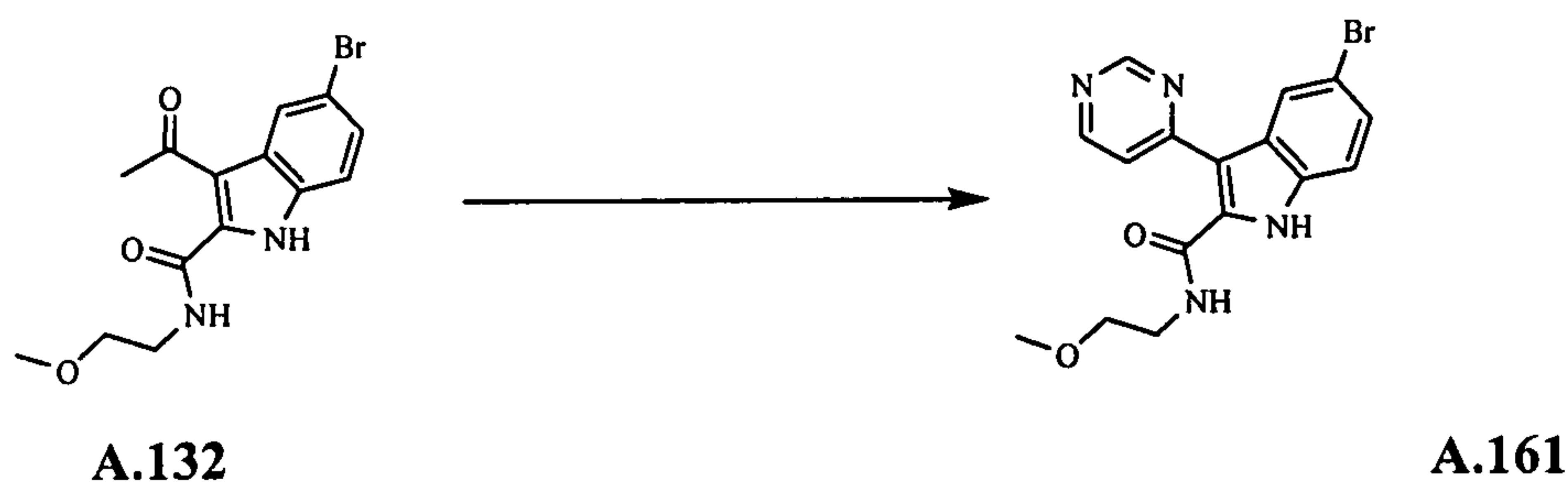


(2-fluoro-5-iodophenyl)(isothiazol-5-yl)methanone A.159: (2-fluoro-5-iodophenyl)(isothiazol-5-yl)methanol A.158 (7.19 g, 21.4 mmol) was stirred in 28 mL acetic acid at room temperature as CrO_3 (4.28 g, 42.9 mmol) was added portionwise. The resulting solution was heated to 100°C for 15 minutes. After cooling to room temperature, the mixture was partitioned between water and dichloromethane, and the aqueous layer was further extracted with dichloromethane. The combined organic extracts were washed with 2 M aq.

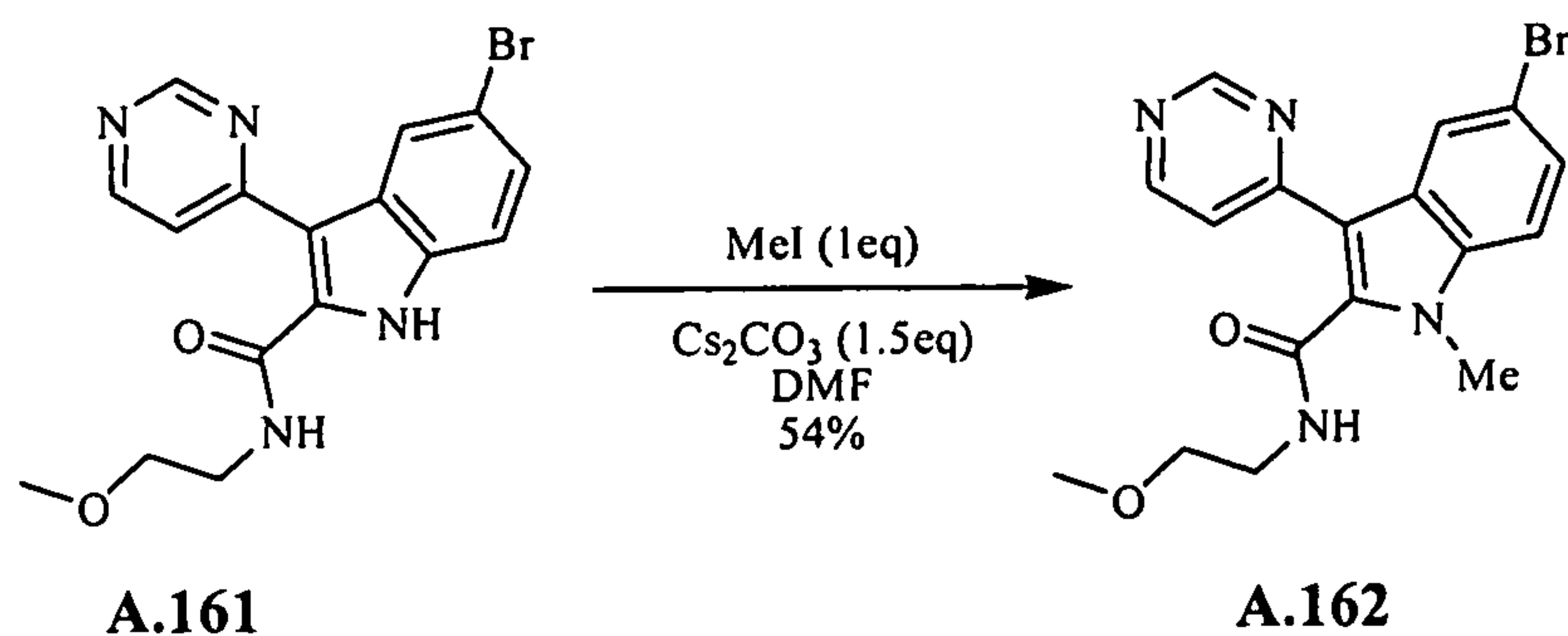
NaOH and water, dried over MgSO_4 and condensed to give 5.67 g (2-fluoro-5-iodophenyl)(isothiazol-5-yl)methanone **A.159**. ^1H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 8.60 (1 H, d, $J=1.2$ Hz), 7.94 (1 H, dd, $J=6.2, 2.1$ Hz), 7.84 - 7.92 (1 H, m), 7.57 (1 H, s), 7.01 (1 H, t, $J=9.0$ Hz)



5-iodo-3-(isothiazol-5-yl)-1H-indazole A.160: To a stirring solution of (2-fluoro-5-iodophenyl)(isothiazol-5-yl)methanone **A.159** (5.67 g, 17 mmol) in DMSO (17 mL) was added anhydrous hydrazine (2.14 mL, 68 mmol), and the resulting mixture was stirred at 80 °C. The heat was removed after 8 hours, water was added and the solution cooled to room temperature. The mixture was extracted into ethyl acetate, dried over MgSO_4 and condensed. Purification by flash chromatography (0-10-100% ethyl acetate in hexane) gave 0.714 g 5-iodo-3-(isothiazol-5-yl)-1H-indazole **A.160**. ^1H NMR (500 MHz, *DMSO-d*₆) δ ppm 13.76 (1 H, s), 8.66 (1 H, s), 8.52 (1 H, s), 8.13 (1 H, s), 7.72 (1 H, d, $J=8.8$ Hz), 7.51 (1 H, d, $J=8.8$ Hz)

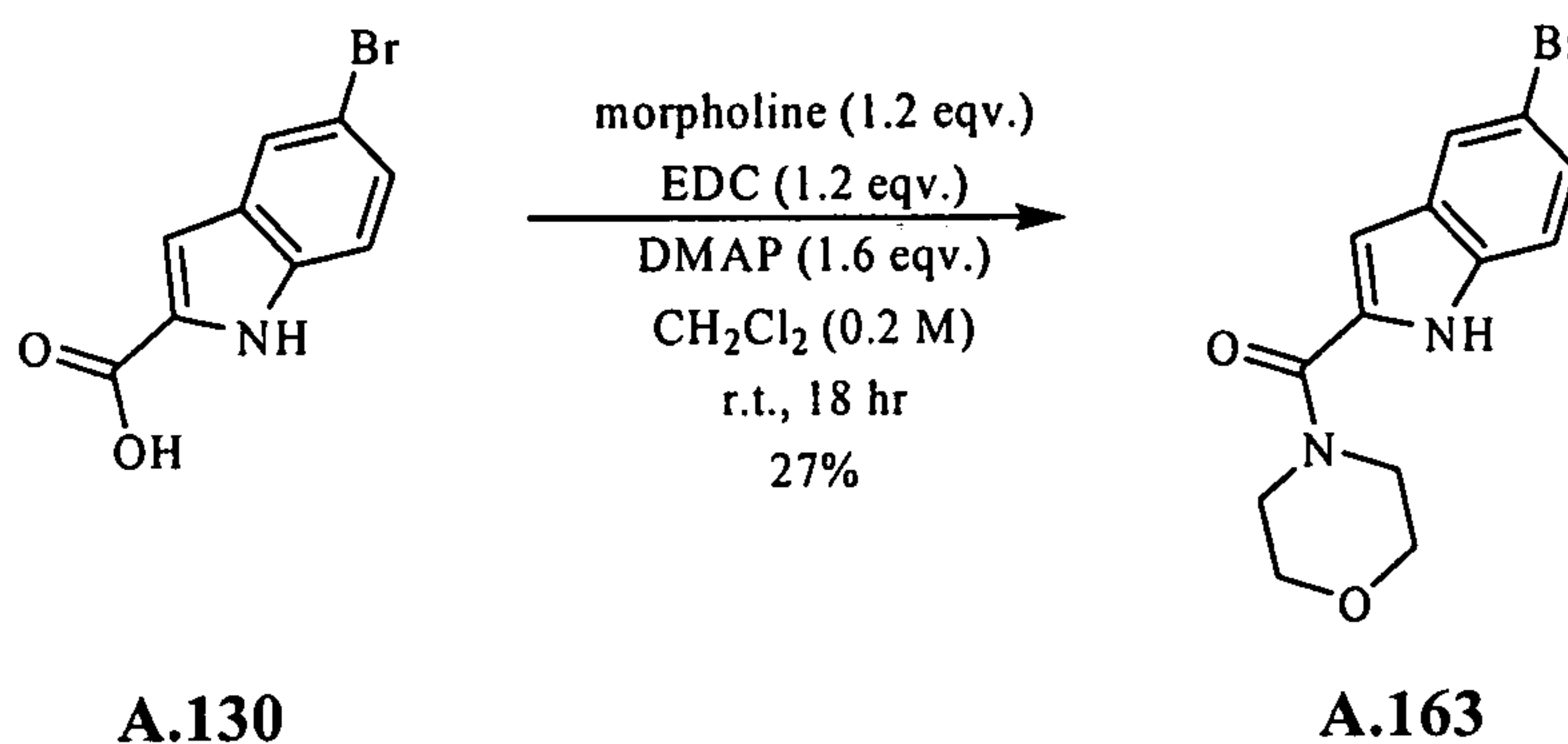


5-bromo-N-(2-methoxyethyl)-3-(pyrimidin-4-yl)-1H-indole-2-carboxamide A.161
This compound was prepared from compound **A.132** by the procedure used to prepare compound **A.149**.

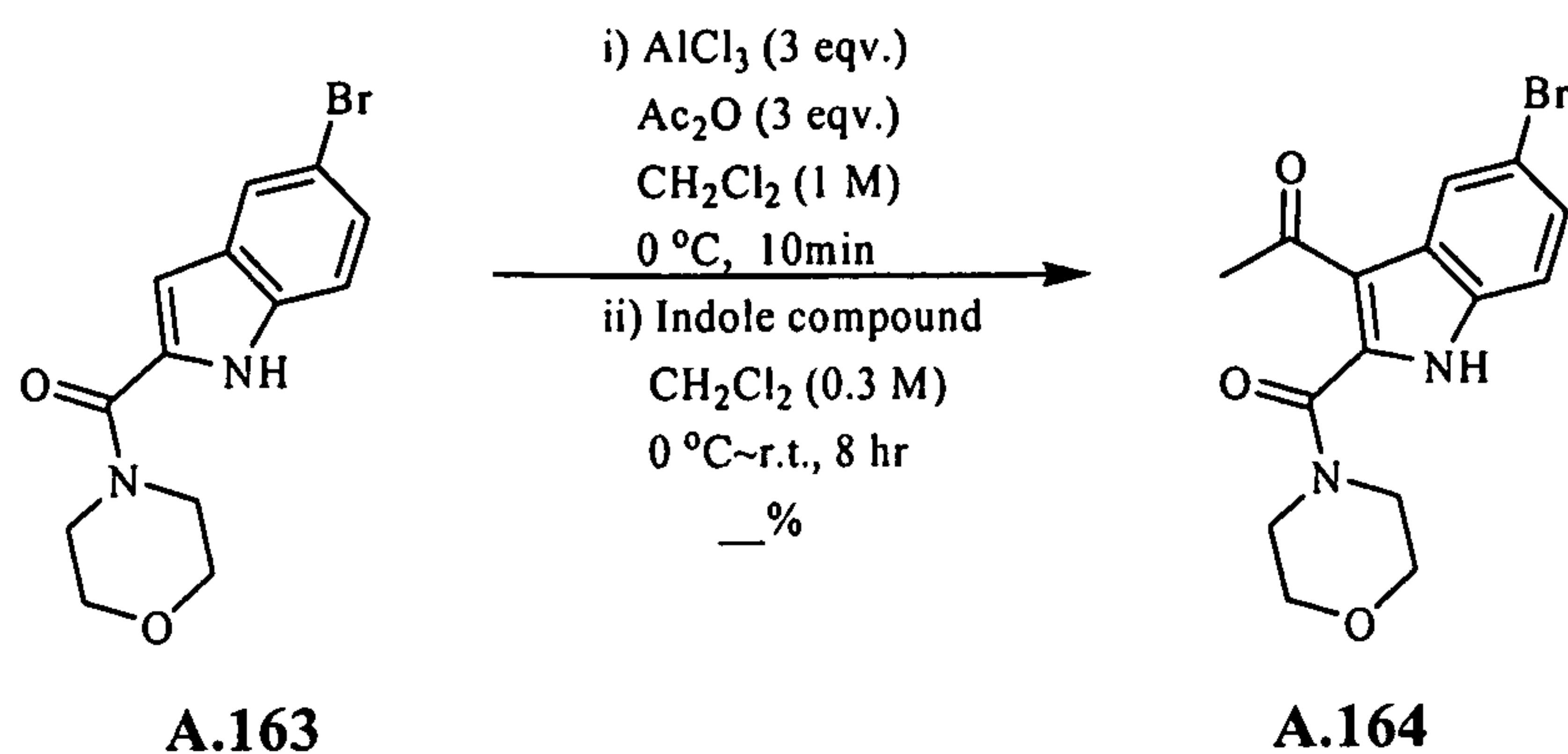


5-bromo-N-(2-methoxyethyl)-1-methyl-3-(pyrimidin-4-yl)-1H-indole-2-carboxamide (A.162)

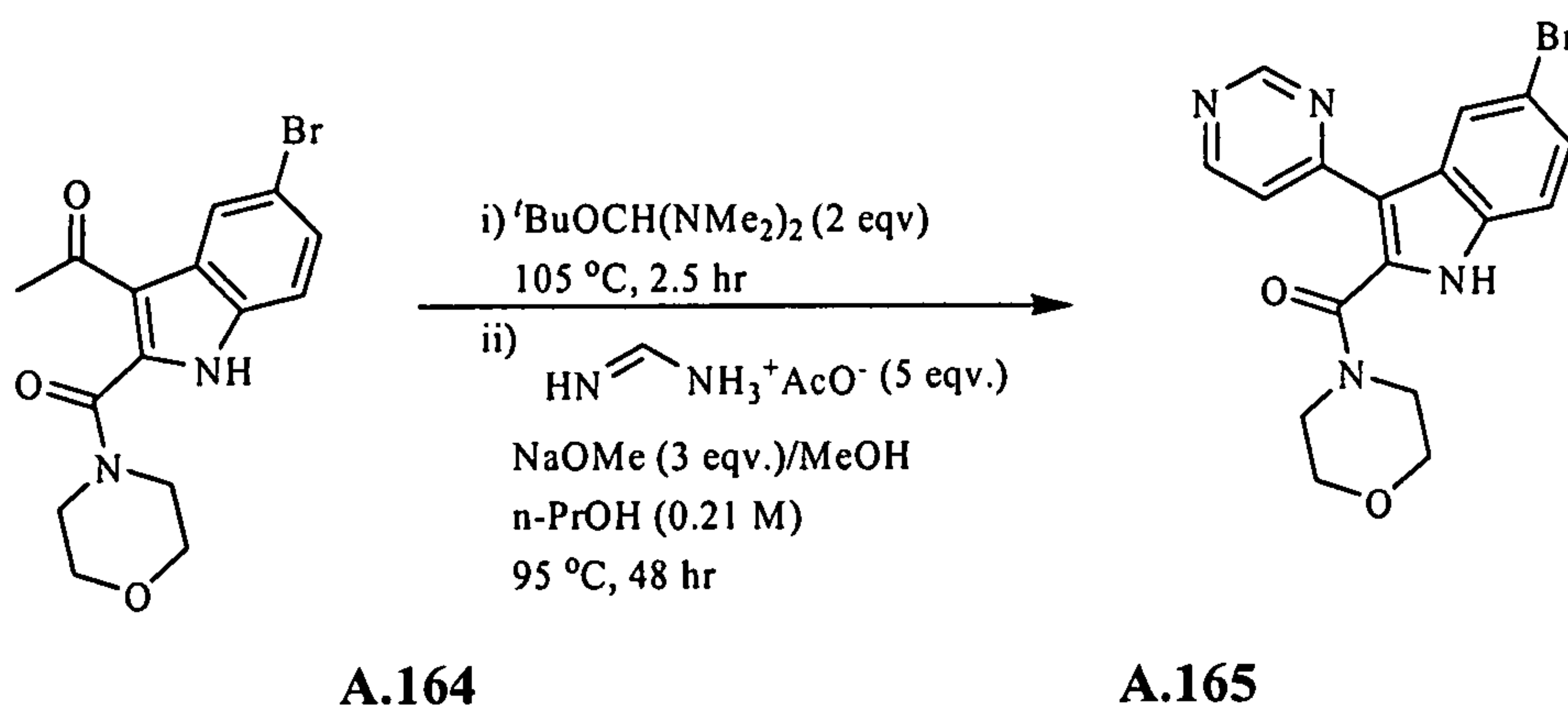
To a stirred solution of **A.161** (500 mg, 1.3 mmol) and Cs_2CO_3 (387 mg, 2.0 mmol) in 5 mL of DMF was added MeI (190 mg, 1.3 mmol) at room temperature and the mixture was stirred. After stirring overnight, the mixture was partitioned between DCM and water. The organic layer was washed with brine, dried over MgSO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by silical gel column chromatography using 0 to 100% gradient of DCM-MeOH- NH_4OH (89:9:1) in DCM to give 5-bromo-N-(2-methoxyethyl)-1-methyl-3-(pyrimidin-4-yl)-1H-indole-2-carboxamide **A.162** (273 mg, 54% yield): Mass Spectrum (ESI) $m/e = 389.0$ [$\text{M}+1$ (^{79}Br)] and 391.0 [$\text{M}+1$ (^{81}Br)].



(5-bromo-1H-indol-2-yl)(morpholino)methanone A.163: A mixture of **A.130** (3 g, 12.5 mmol), morpholine (1.31 mL, 15 mmol), DMAP (2.44 g, 20 mmol), and EDC (2.87 g, 15 mmol) was stirred in DCM (60 mL) at room temperature. After 18 hr, the mixture was concentrated under reduced pressure to give a yellow solid. The yellow solid was dissolved in EtOAc (200 mL). The mixture was washed with 2 N aq. HCl (100 mL), water (100 mL), sat. aq. NaHCO_3 , dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give a yellow solid (1.42 g). The yellow solid was triturated with acetone-EtOAc and the resulting solid was collected by filtration to give the desired product **A.163** (1.034 g, 27% yield) as a yellow solid: ^1H NMR (500 MHz, $\text{CHLOROFORM-}d$) δ ppm 9.32 (1 H, s), 7.80 (1 H, d, $J=1.7$ Hz), 7.40 (1 H, dd, $J=8.6, 1.7$ Hz), 7.33 (1 H, d, $J=8.6$), 6.72 (1 H, dd, $J=2.0, 0.7$ Hz), 3.96 (4 H, br. s.), 3.78 - 3.85 (4 H, m); Mass Spectrum (ESI) $m/e = 309.0$ [$\text{M}+1$ (^{79}Br)] and 311.0 [$\text{M}+1$ (^{81}Br)].

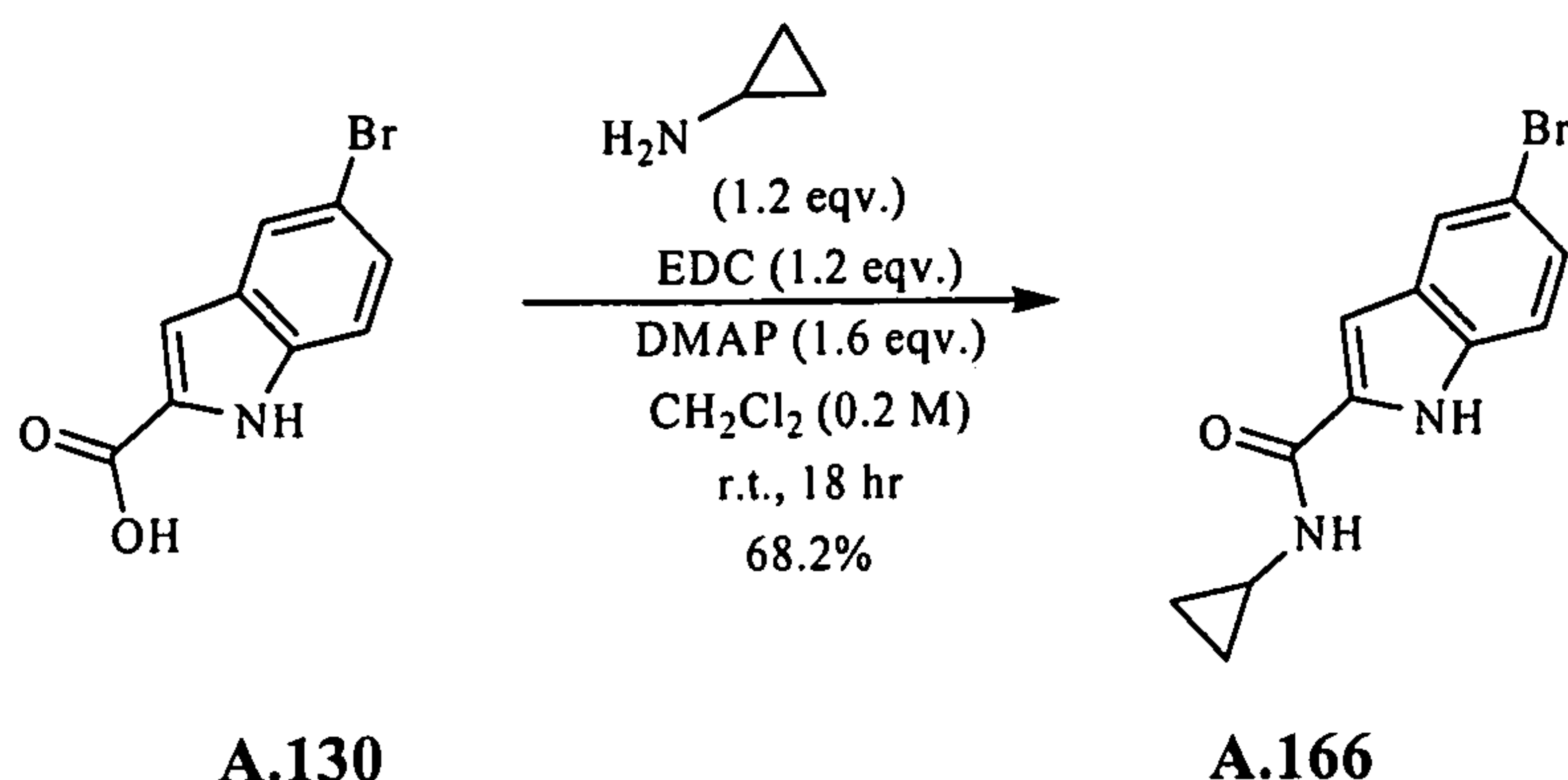


1-(5-bromo-2-(morpholine-4-carbonyl)-1H-indol-3-yl)ethanone A.164 was prepared from **A.163** by the procedure used to prepare compound **A.132**: ^1H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 10.08 (1 H, s), 8.12 (1 H, d, $J=1.7$ Hz), 7.36 (1 H, dd, $J=8.8$, 1.5 Hz), 7.21 (1 H, d, $J=8.8$ Hz), 3.67 (3 H, s), 2.55 - 2.71 (8 H, m); Mass Spectrum (ESI) m/e = 351.0 [$\text{M}+1$ (^{79}Br)] and 353.0 [$\text{M}+1$ (^{81}Br)].

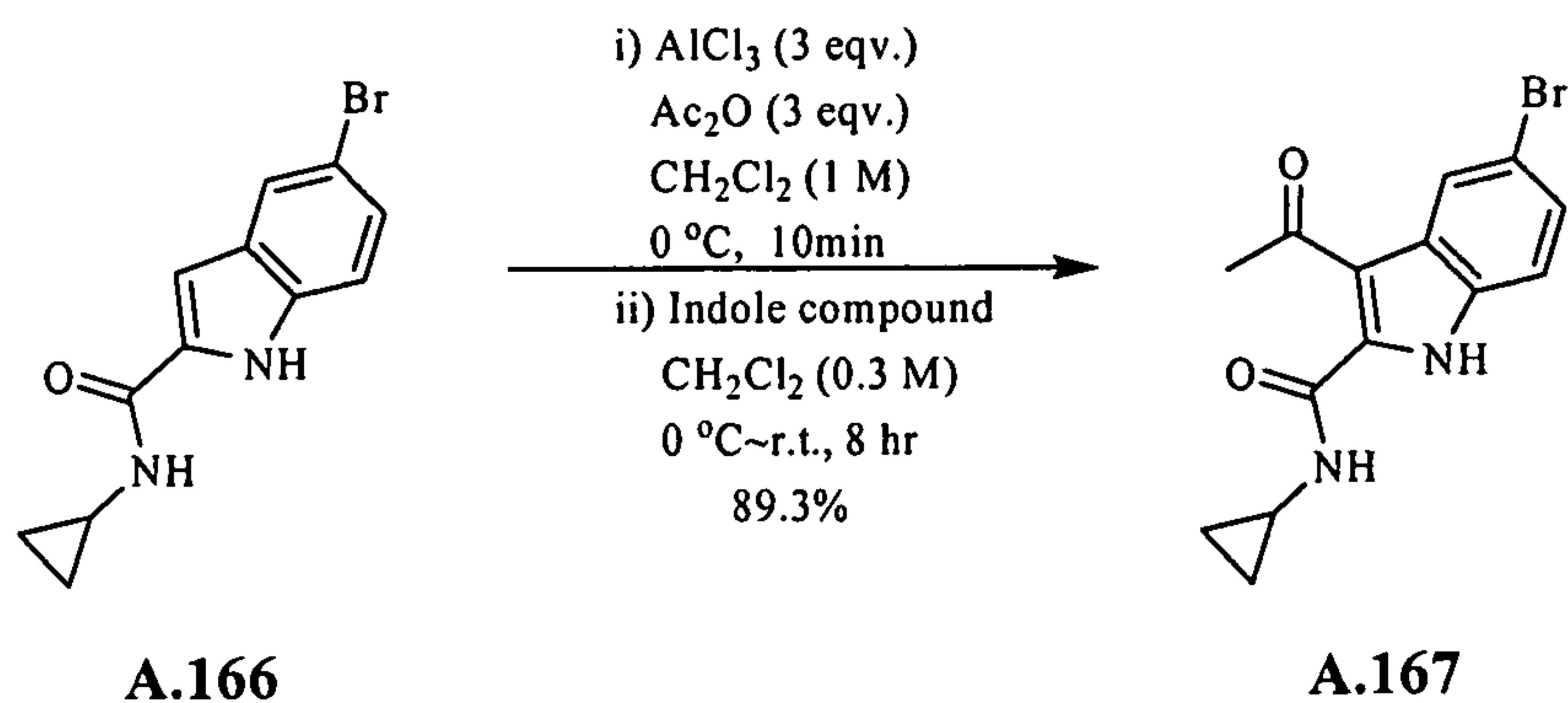


(5-bromo-3-(pyrimidin-4-yl)-1H-indol-2-yl)(morpholino)methanone A.165 was prepared from compound **A.164** by the procedure used to prepare compound **A.149**. ^1H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 9.95, (1H, s), 9.26 (1 H, s), 8.76 (1 H, d, $J=5.6$ Hz), 8.33 (1 H, s), 7.63 (1 H, dd, $J=5.4$, 1.2 Hz), 7.44 (1 H, dd, $J=8.6$, 1.7 Hz), 7.37 (1 H, d, $J=8.6$ Hz), 3.78 (m, 4H), 3.45 (m, 2H), 3.26 (m, 2H); Mass Spectrum (ESI) m/e = 387.0 [$\text{M}+1$ (^{79}Br)] and 389.0 [$\text{M}+1$ (^{81}Br)].

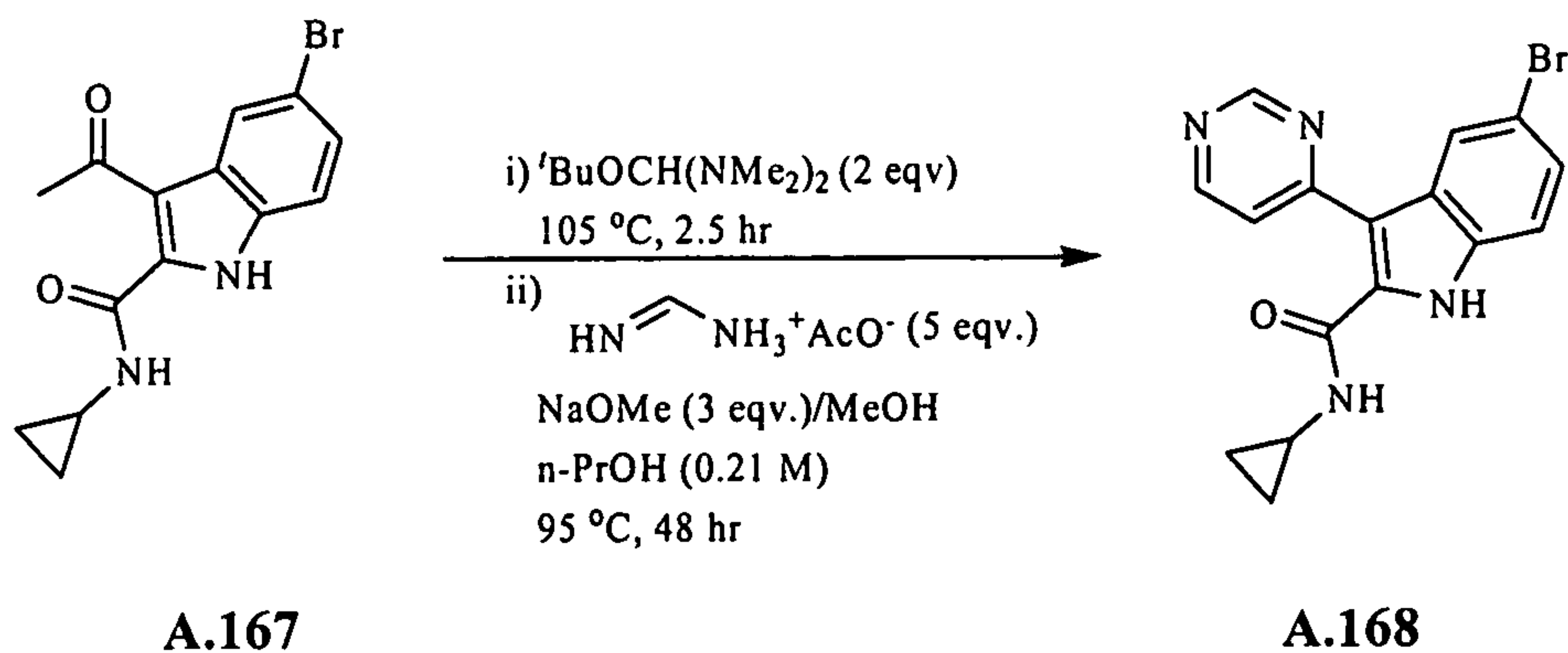
N-cyclopropyl-5-((R)-3-hydroxy-3-(4-methyl-5H-pyrrol-2-yl)but-1-ynyl)-3-(pyrimidin-4-yl)-1H-indole-2-carboxamide



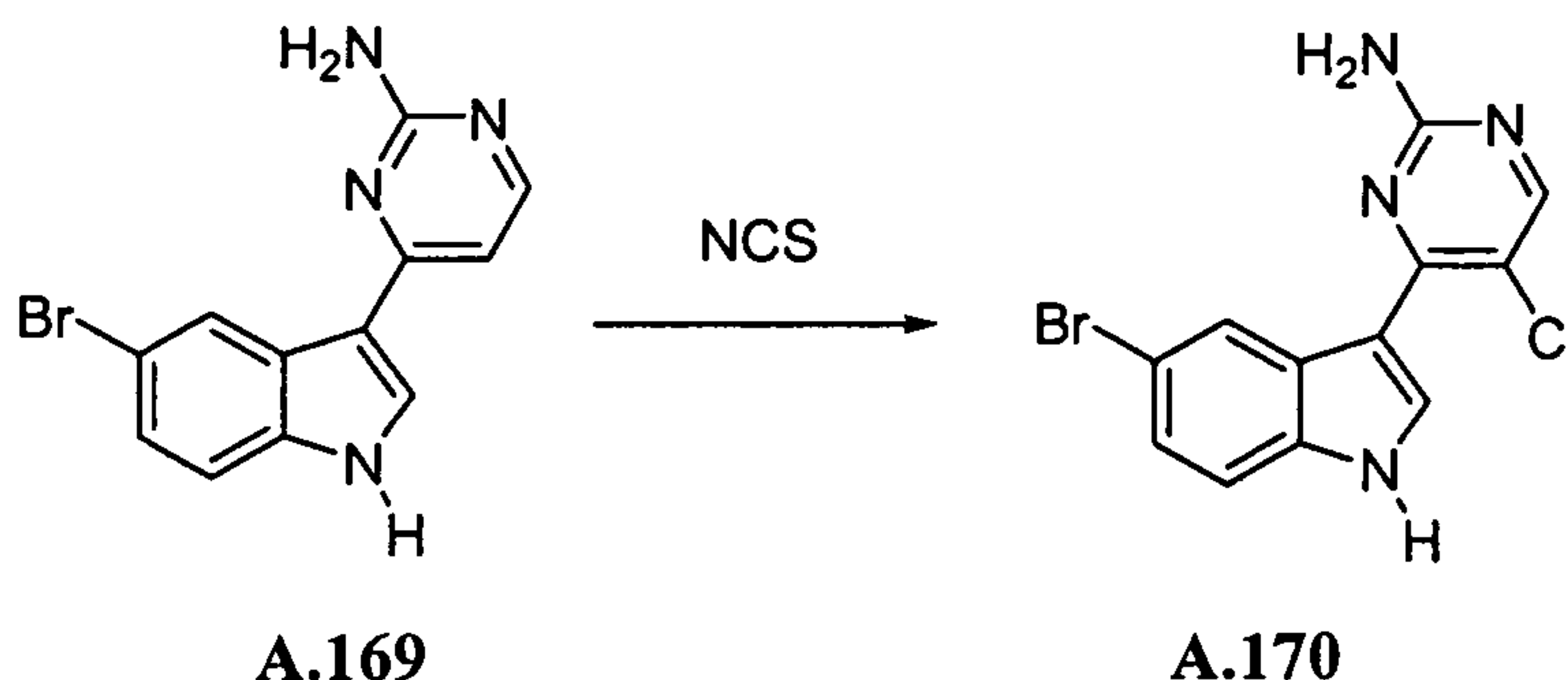
5-bromo-N-cyclopropyl-1H-indole-2-carboxamide A.166 was prepared from **A.130** by the procedure used to prepare compound **A.163**: ¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 11.77 (1 H, s), 8.54 (1 H, d, *J*=3.7 Hz), 7.81 (1 H, s), 7.38 (1 H, d, *J*=8.6 Hz), 7.27 (1 H, d, *J*=8.8 Hz), 7.07 (1 H, s), 2.86 (1 H, qd, *J*=7.4, 3.9 Hz), 0.73 (2 H, td, *J*=6.9, 5.0 Hz), 0.58 - 0.62 (2 H, m)



3-acetyl-5-bromo-N-cyclopropyl-1H-indole-2-carboxamide A.167 was prepared from compound **A.166** by the procedure used to prepare compound **A.164**: Mass Spectrum (ESI) *m/e* = 321.0 [*M*+1 (⁷⁹Br)] and 322.9 [*M*+1 (⁸¹Br)].

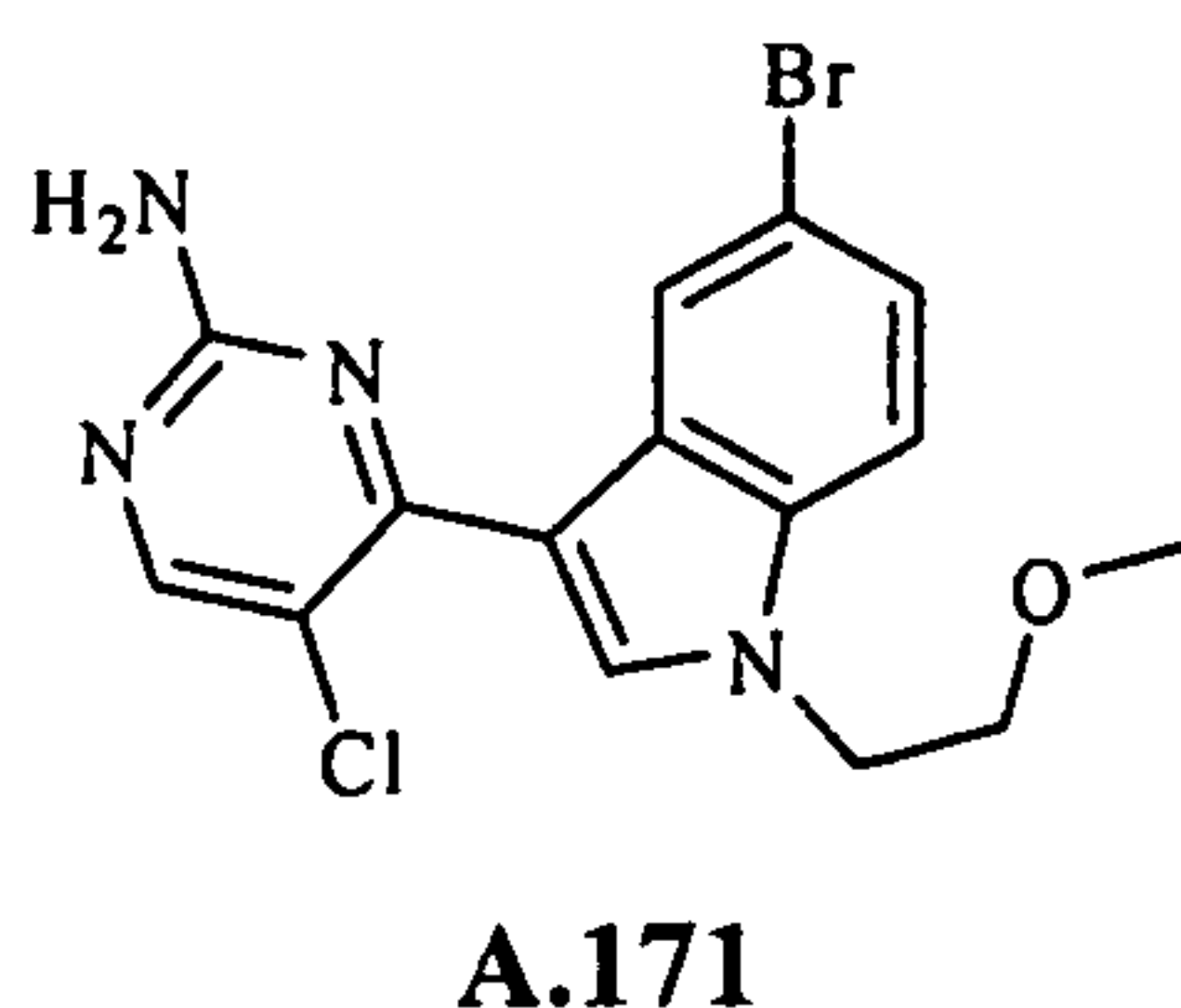


5-bromo-N-cyclopropyl-3-(pyrimidin-4-yl)-1H-indole-2-carboxamide A.168 was prepared from compound **A.167** by the procedure used to prepare compound **A.165**: Mass Spectrum (ESI) $m/e = 357.0$ [$M+1$ (^{79}Br)] and 359.0 [$M+1$ (^{81}Br)].

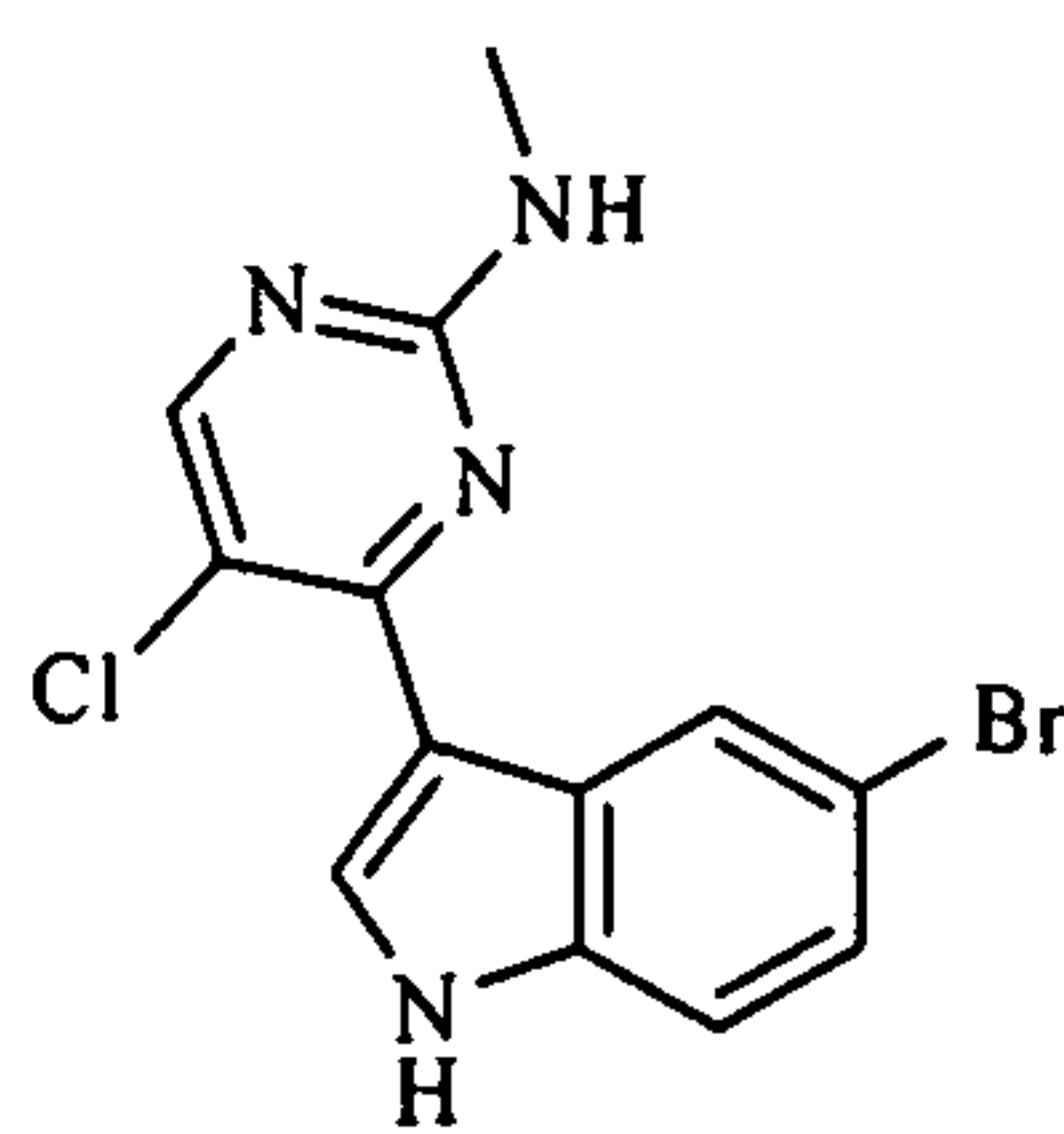


4-(5-bromo-1H-indol-3-yl)-5-chloropyrimidin-2-amine A.170: A mixture of N-chlorosuccinimide (500 mg, 3.74 mmol) and 4-(5-bromo-1H-indol-3-yl)pyrimidin-2-amine (**A.169**) (1.09 g, 3.74 mmol) [Fresneda, P. M., P. Molina, et al. (2000). *Tetrahedron Lett.* 41(24): 4777-4780] in CH_3CN (30 mL) was refluxed for 5 hrs. After cooling to room temperature, the mixture was triturated with ether. After filtration The product was purified by flash chromatography over silica gel, using 9.5:0.5 dichloromethane-methanol, to afford 4-(5-bromo-1H-indol-3-yl)-5-chloropyrimidin-2-amine (**A.170**)(810 mg, 67%): ^1H NMR (methanol- d_4) δ 8.78(s, 1 H), 8.47(s, 1 H), 8.21(s, 1 H), 7.41 (d, $J = 8.5$ Hz, 1 H), 7.35(d, $J = 8.5$ Hz, 1 H), 2.04(s, 2 H); ms 325.1 ($M+\text{H}^+$).

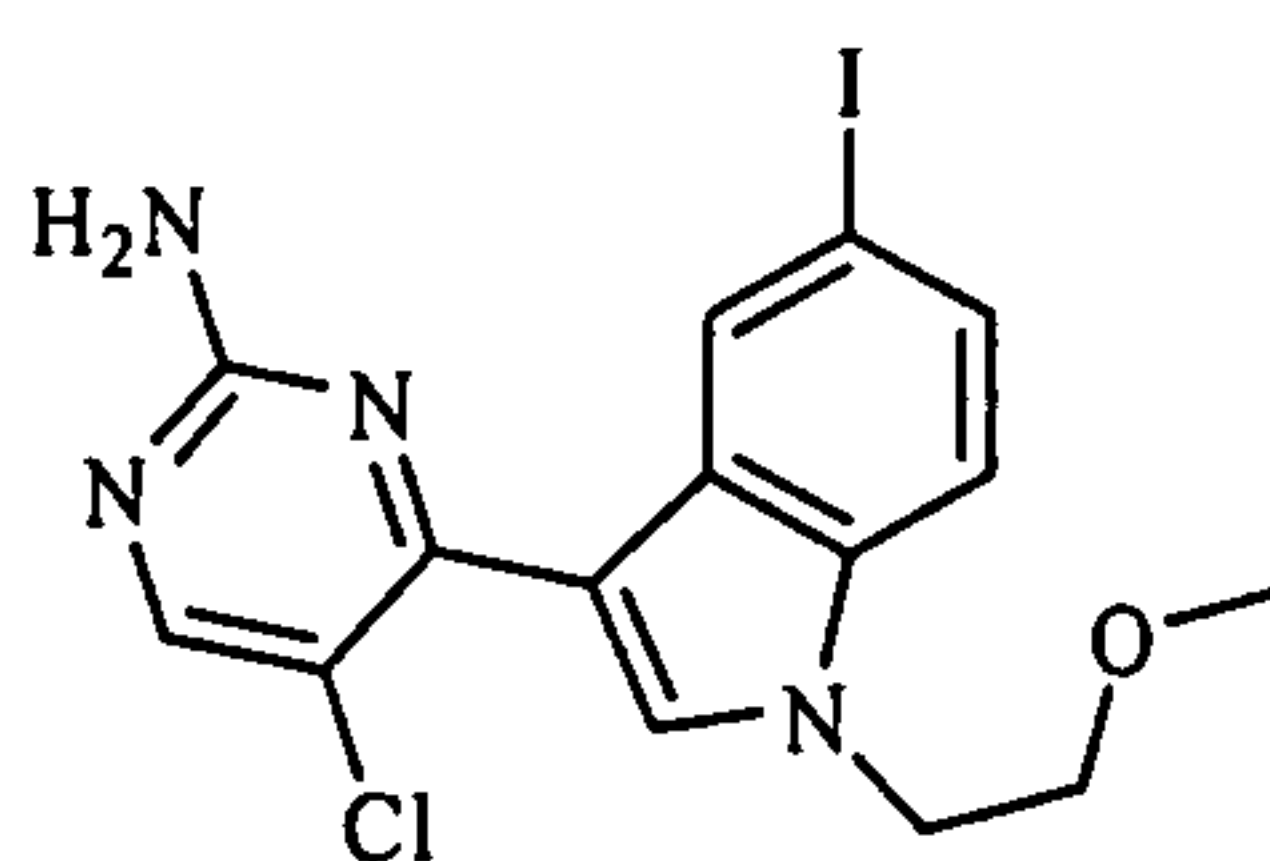
The following compounds **A.171**, **A.172**, and **A.173** were prepared using the same or analogous synthetic techniques and substituting with appropriate reagents as example **A.170**.



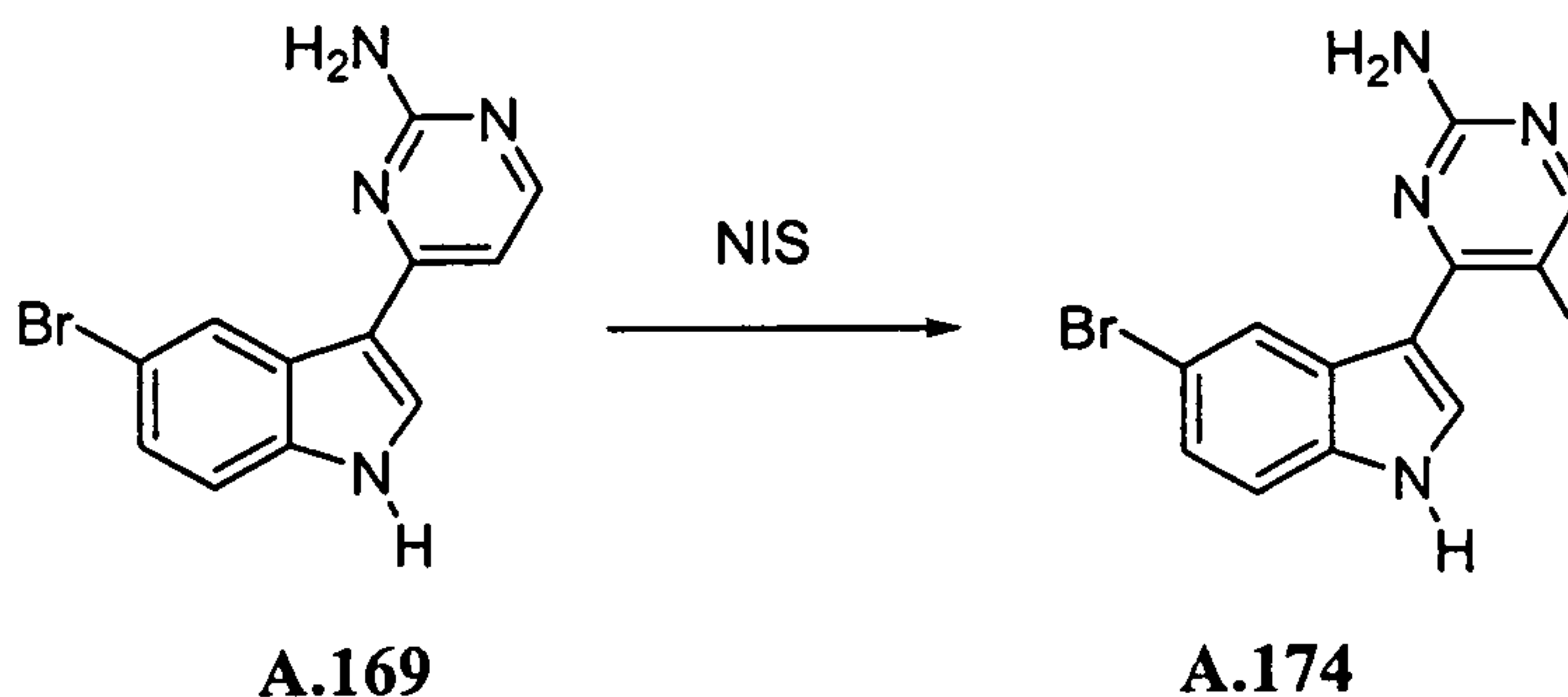
4-(5-bromo-1-(2-methoxyethyl)-1H-indol-3-yl)-5-chloropyrimidin-2-amine A.171 prepared from **A.180** : ms 381.0 ($M+\text{H}^+$).

**A.172**

4-(5-bromo-1H-indol-3-yl)-5-chloro-N-methylpyrimidin-2-amine A.172: prepared from A.177. ^1H NMR (DMSO- d_6) δ 11.35(s, 1 H), 8.29 (br, 1 H), 7.57-7.48(m, 1 H), 7.38-7.24(m, 2 H), 6.98-6.90(m, 1 H), 2.89 (br, 3 H); ms 337.0/339.0 ($\text{M}+\text{H}^+$).

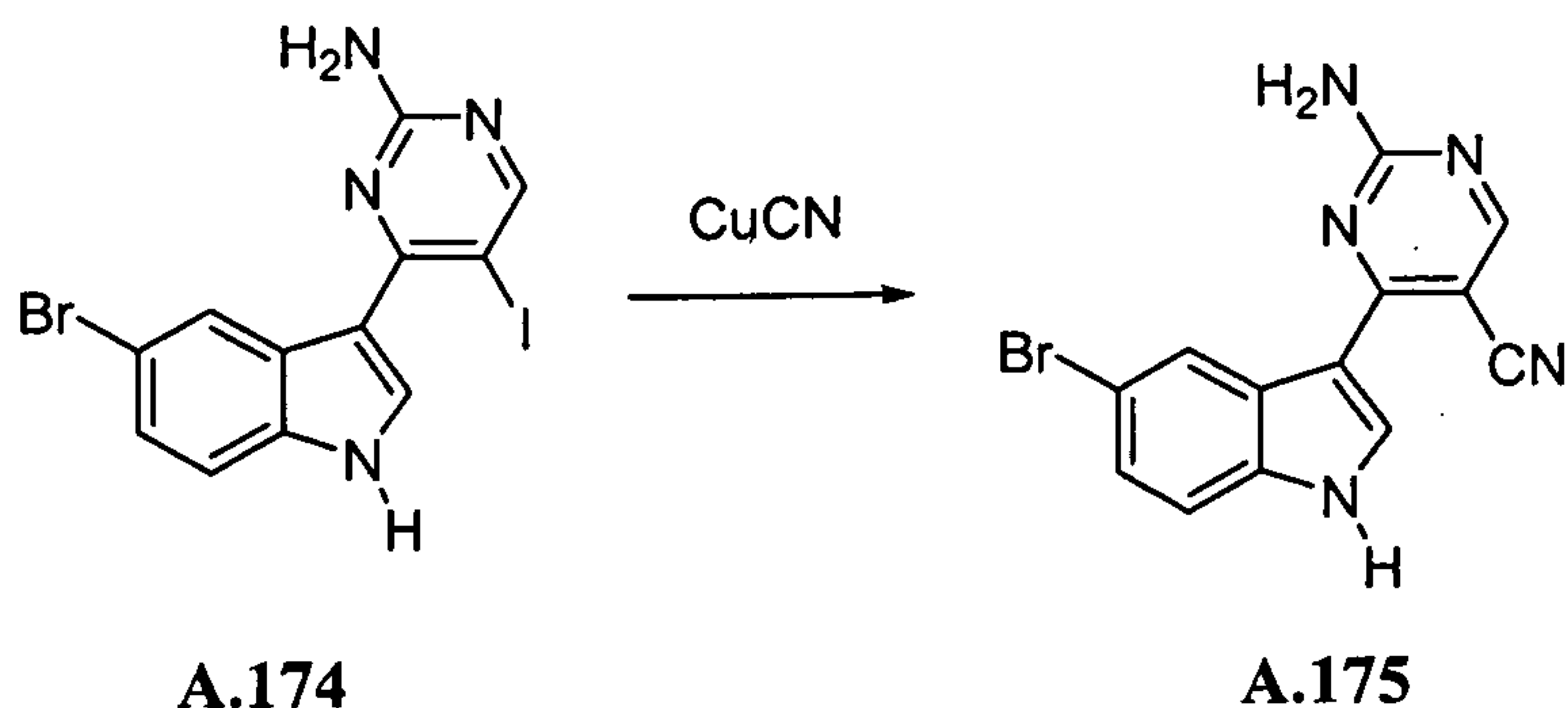
**A.173**

5-chloro-4-(5-iodo-1-(2-methoxyethyl)-1H-indol-3-yl)pyrimidin-2-amine A.173: prepared from A.181. ^1H NMR (DMSO- d_6) δ 8.91(s, 1 H), 8.44(s, 1 H), 8.20 (s, 1 H), 7.52-7.45(m, 2 H), 6.82(s, 2 H), 4.48-4.42(m, 2 H), 3.72-3.55(m, 2 H), 3.22(s, 3 H).

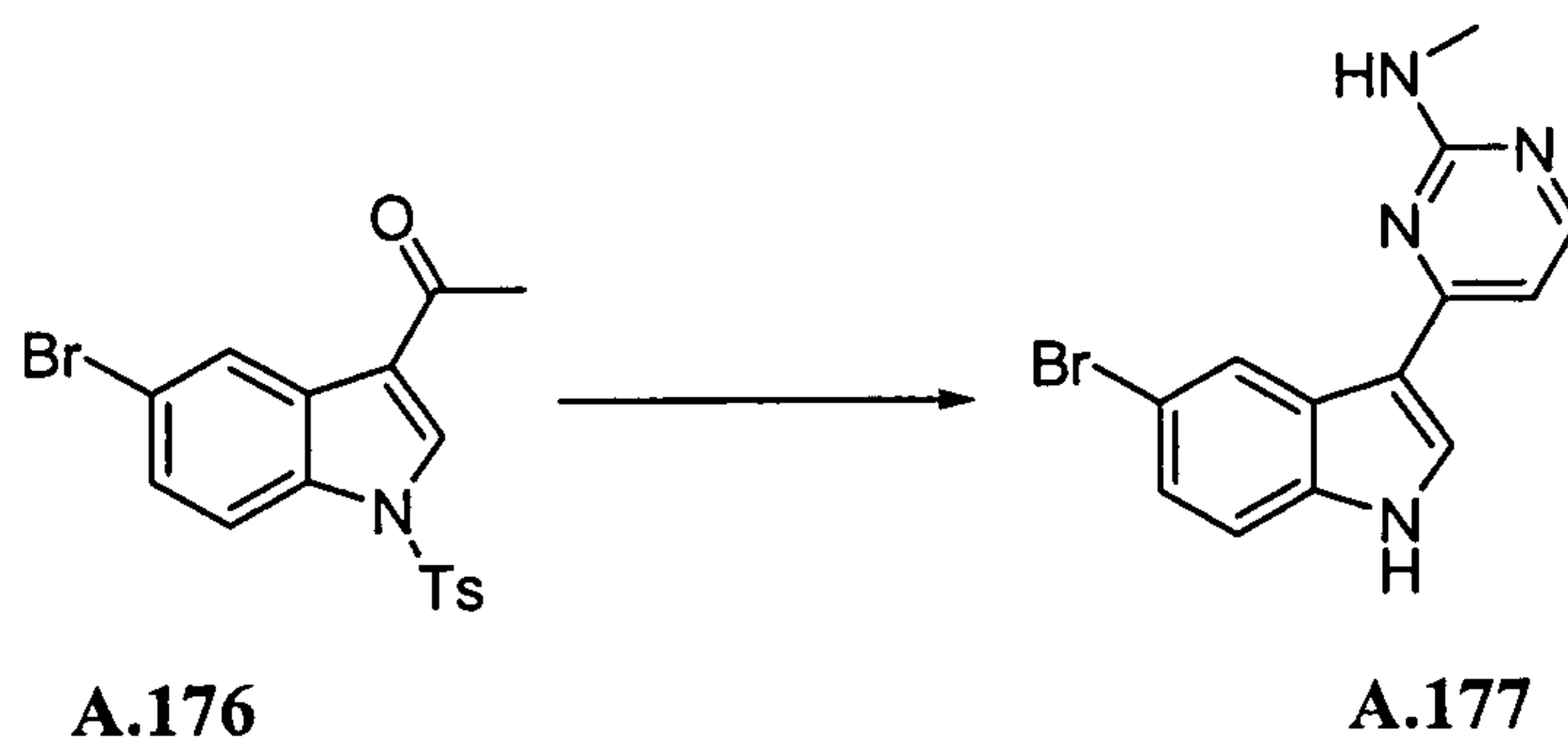
**A.169****A.174**

4-(5-bromo-1H-indol-3-yl)-5-iodopyrimidin-2-amine

A mixture of N-iodosuccinimide (1.17 g, 5.19 mmol) and 4-(5-bromo-1H-indol-3-yl)pyrimidin-2-amine (A.169) (500 mg, 1.73 mmol) in DMF (10 mL) was heated at 100 °C under N_2 for 1.5 hrs. After cooling to room temperature, the resultant mixture was poured onto ice. The precipitate was collected by filtration to afford 4-(5-bromo-1H-indol-3-yl)-5-iodopyrimidin-2-amine (A.174) (322.0 mg, 45%): ^1H NMR (DMSO- d_6) δ 11.86(s, 1 H), 8.56(s, 1 H), 8.44(s, 1 H), 8.37(s, 1 H), 7.43 (d, $J = 8.8$ Hz, 1 H), 7.29(d, $J = 8.8$ Hz, 1 H), 6.78(s, 2 H); ms 415.0 ($\text{M}+\text{H}^+$).

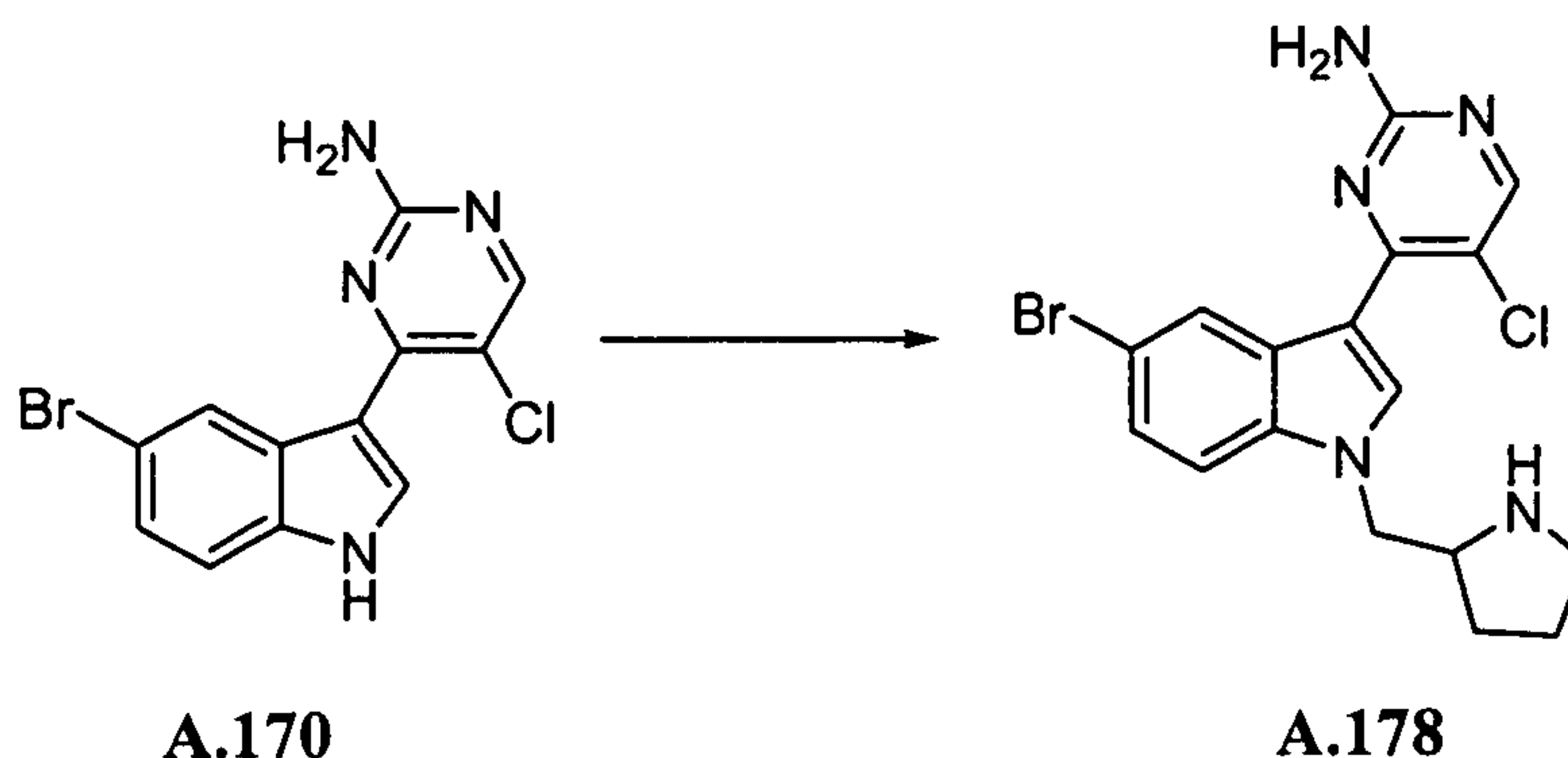


2-amino-4-(5-bromo-1H-indol-3-yl)pyrimidine-5-carbonitrile A.175: A mixture of 4-(5-bromo-1H-indol-3-yl)-5-iodopyrimidin-2-amine (**A.174**) (322.0 mg, 0.776 mmol) and CuCN (69.5 mg, 0.776 mmol) in DMF (10 mL) was heated at 100 °C under N₂ for 16 hrs. After cooling to room temperature, the resultant mixture was diluted with ether, washed with water and brine, dried and concentrated. Purification of the residue by flash chromatography over silica gel, using 5:4.5:0.5 ethyl acetate-hexane-methanol, gave 2-amino-4-(5-bromo-1H-indol-3-yl)pyrimidine-5-carbonitrile(**A.175**)(115.4 mg, 47%): ¹H NMR (DMSO- *d*₆) δ 12.12(s, 1 H), 8.78(s, 1 H), 8.60(s, 1 H), 8.51(s, 1 H), 7.84(br, 1 H), 7.59(br, 1 H), 7.50 (d, *J* = 8.0 Hz, 1 H), 7.38(d, *J* = 8.0 Hz, 1 H); ms 314.0 (M+H⁺).



4-(5-bromo-1H-indol-3-yl)-N-methylpyrimidin-2-amine A.177: A mixture of 1-(5-bromo-1-tosyl-1H-indol-3-yl)ethanone (**A.176**) [Fresneda, P. M., P. Molina, et al. (2000). *Tetrahedron Lett.* 41(24): 4777-4780] (5.0 g, 12.8 mmol) and *t*-BuOCH(NMe₂)₂ (5.3 mL, 25.6 mmol) was heated at 105 °C for 3 hrs. At room temperature, *n*-BuOH (15 mL), 1-methylguanidine (HCl salt, 2.1 g, 19.2 mmol) and MeONa (5.33 M in methanol, 7.2 mL) were added sequentially to the mixture. The resultant mixture was heated at 95 °C for 16 hrs. After cooling to room temperature, the resultant mixture was concentrated, and the residue was diluted with water and neutralized with HCl (1M) to pH 7. The mixture was concentrated and dissolved in methanol. After filtration to remove insoluble solid, the filtrates were collected and concentrated. Purification of the residue by flash chromatography over silica gel, using 9.5:0.5 dichloromethane-methanol, gave 4-(5-bromo-1H-indol-3-yl)-N-methylpyrimidin-2-amine

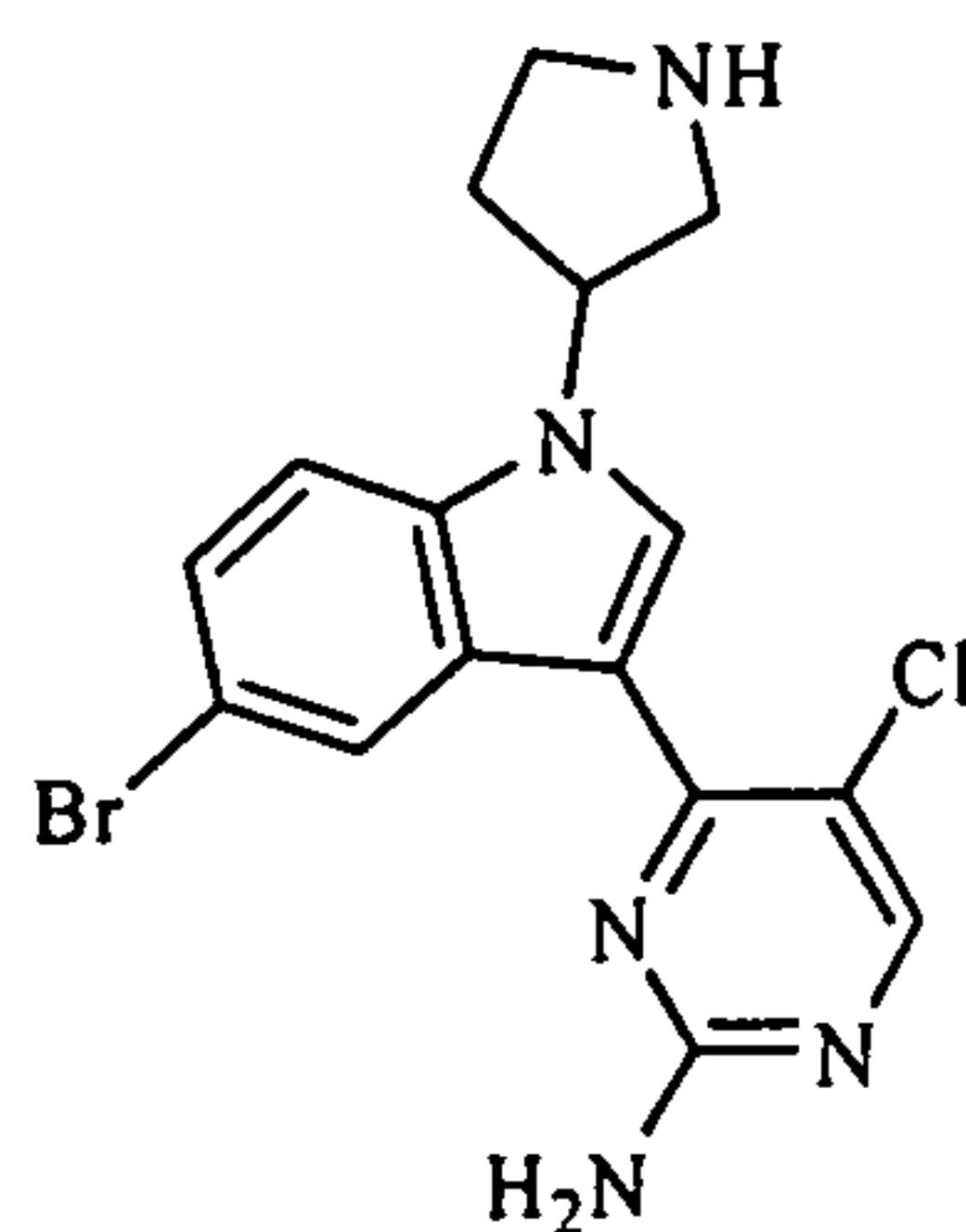
(A.177) (2.4 g, 62%): ^1H NMR (DMSO- d_6) δ 12.30(s, 1 H), 8.78 (s, 1 H), 8.60 (s, 1 H), 8.17 (d, $J = 6.0$ Hz, 1 H), 7.48(br, 1 H), 7.38 (d, $J = 8.5$ Hz, 1 H), 7.25(d, $J = 6.0$ Hz, 1 H), 7.12 (d, $J = 8.5$ Hz, 1 H), 3.01(br, 3 H); ms 303.1 ($\text{M}+\text{H}^+$).



4-(5-bromo-1-(pyrrolidin-2-ylmethyl)-1H-indol-3-yl)-5-chloropyrimidin-2-amine (A.178)

: Maleic acid (2.86g, 24.72 mmol) was added to pyrrolidin-2-ylmethanol(2.5g, 24.72 mmol) (A.170) in ethyl acetate (10 mL). The resultant mixture was stirred at room temperature for 2 hrs. After concentration, NaHCO_3 (10.38g, 123.6 mmol) in water (16 mL) was added to the residue. $(\text{BOC})_2\text{O}$ (6.47 g, 29.66 mmol) was then added. The mixture was stirred at room temperature for 16 hrs. After removing solid by filtration, the aqueous solution was extracted with ethyl acetate. The organics were dried and concentrated, gave crude N-BOC protected pyrrolidin-2-ylmethanol. To the crude N-BOC protected pyrrolidin-2-ylmethanol(2.5g, 12.43mmol) and triethylamine (4.16ml, 29.82 mmol) in ethyl acetate at 0°C , MsCl (1.16 mL, 14.91 mmol) was added and the mixture was stirred at 0°C for 2 hrs. The reaction was quenched with water and extracted with ethyl acetate. The organics were washed with 2N HCl , water, Sat. aq. NaHCO_3 , and brine, dried and concentrated. A portion of the residue(257.6 mg, 0.924mmol) was added to a mixture of Cs_2CO_3 (301.1 mg, 0.924 mmol) and 4-(5-bromo-1H-indol-3-yl)-5-chloropyrimidin-2-amine A.170 (100 mg, 0.308 mmol) in DMF (1 mL) and DMSO(1 mL). The mixture was heated at 110°C for 16 hrs. After cooling to room temperature, the mixture was diluted with ether, washed with water and brine, dried and concentrated. A portion of the residue (68.5mg, 0.135 mmol) was dissolved in dichloromethane (8 mL) and TFA (2mL) then was added. The mixture was stirred at room temperature for 1 hr, concentrated and diluted with methanol-dichloromethane (1:9). The solution was washed with Sat. aq. NaHCO_3 , and brine, dried and concentrated to afford 4-(5-bromo-1-(pyrrolidin-2-ylmethyl)-1H-indol-3-yl)-5-chloropyrimidin-2-amine (A.178) (32.0 mg, 58%): ^1H NMR (methanol- d_4) δ 8.78(s, 1 H), 8.43(s, 1 H), 8.15(s, 1 H), 7.42 (d, $J = 8.0$ Hz, 1

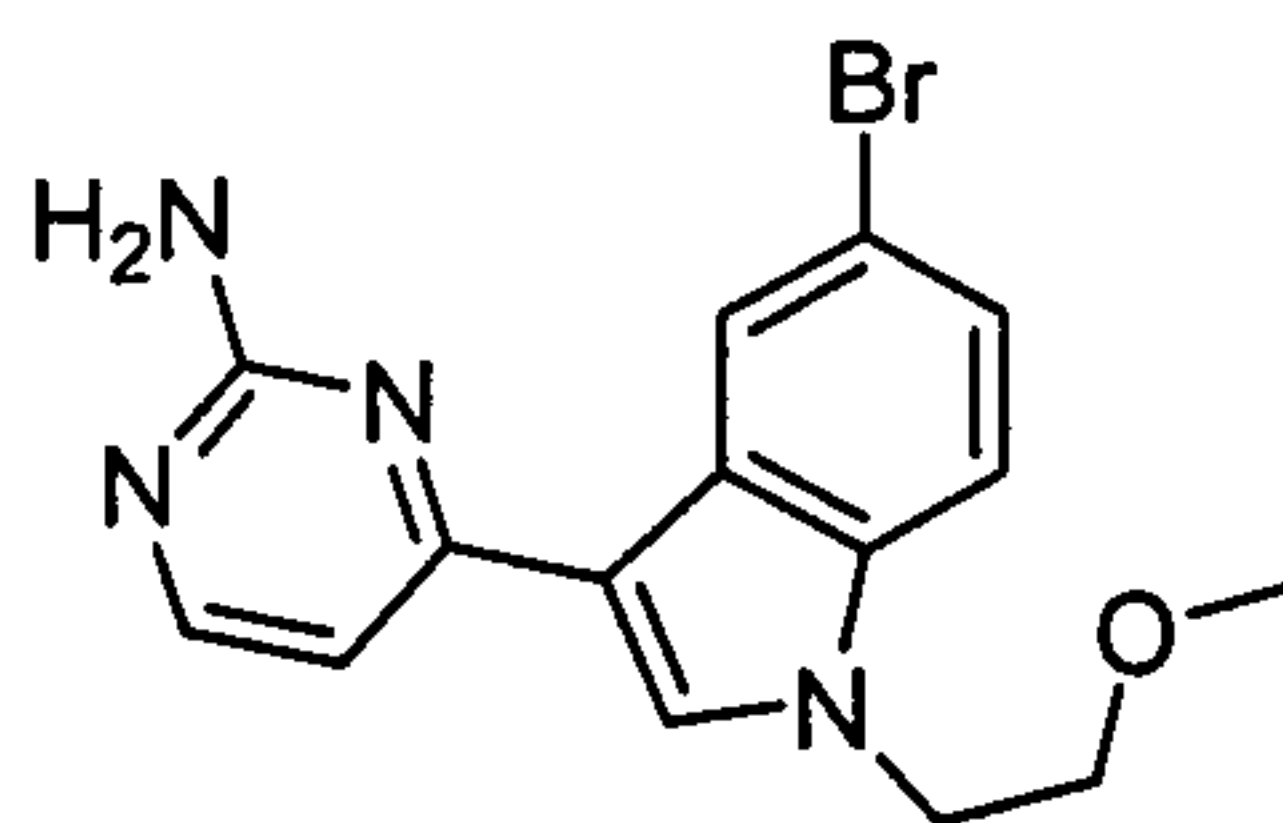
H), 7.38(d, $J = 8.0$ Hz, 1 H), 4.29-4.15(m, 2 H), 3.55-3.45(m, 1 H), 3.00-2.95(m, 1 H), 2.90-2.85(m, 1 H), 1.92-1.80(m, 2 H), 1.80-1.72(m, 1 H), 1.55-1.46(m, 1 H); ms 406.0 ($M+H^+$).



A.179

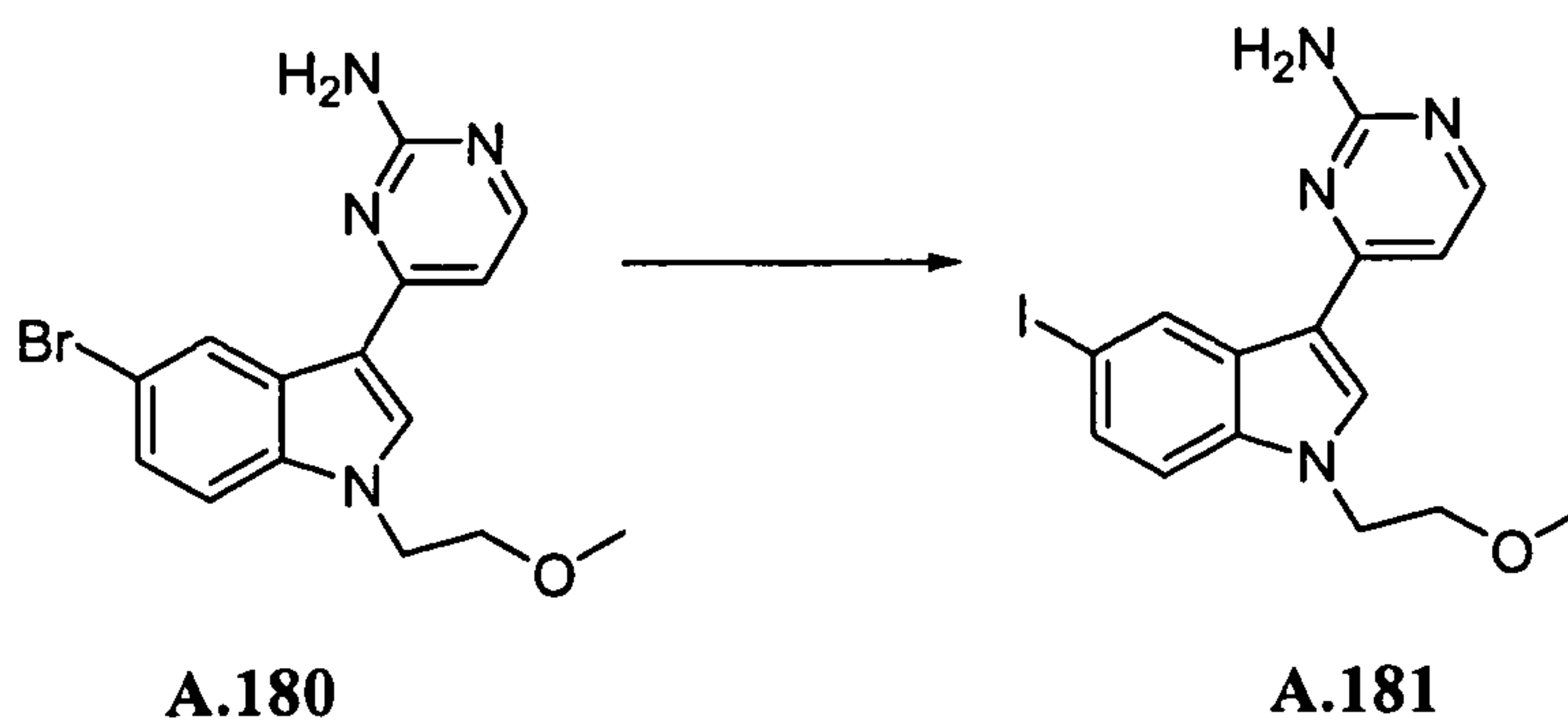
4-(5-bromo-1-(pyrrolidin-3-yl)-1H-indol-3-yl)-5-chloropyrimidin-2-amine A.179:

This compound was prepared by using the same or analogous synthetic techniques and substituting with appropriate reagents as for compound A.178. ^1H NMR (DMSO- d_6) δ 8.72(s, 1 H), 8.56(s, 1 H), 8.26(s, 1 H), 7.66(d, $J = 8.6$ Hz, 1 H), 7.44 (d, $J = 8.6$ Hz, 1 H), 6.87(br, 2 H), 5.39(br, 1 H), 3.72-3.63(m, 1 H), 3.40-3.15(m, 4 H), 2.55-2.45(m, 1 H), 2.35-2.25(m, 1 H).



A.180

4-(5-bromo-1-(2-methoxyethyl)-1H-indol-3-yl)pyrimidin-2-amine A.180: The title compound was prepared from compound A.169 by the method used for example 124. ^1H NMR (DMSO- d_6) δ 8.76(s, 1 H), 8.26(s, 1 H), 8.13 (d, $J = 5.0$ Hz, 1 H), 7.57(d, $J = 8.0$ Hz, 1 H), 7.35 (d, $J = 8.0$ Hz, 1 H), 6.96(d, $J = 5.0$ Hz, 1 H), 6.52(s, 2 H), 4.41 (t, $J = 5.0$ Hz, 2 H), 3.71 (t, $J = 5.0$ Hz, 2 H), 3.24(s, 3 H).



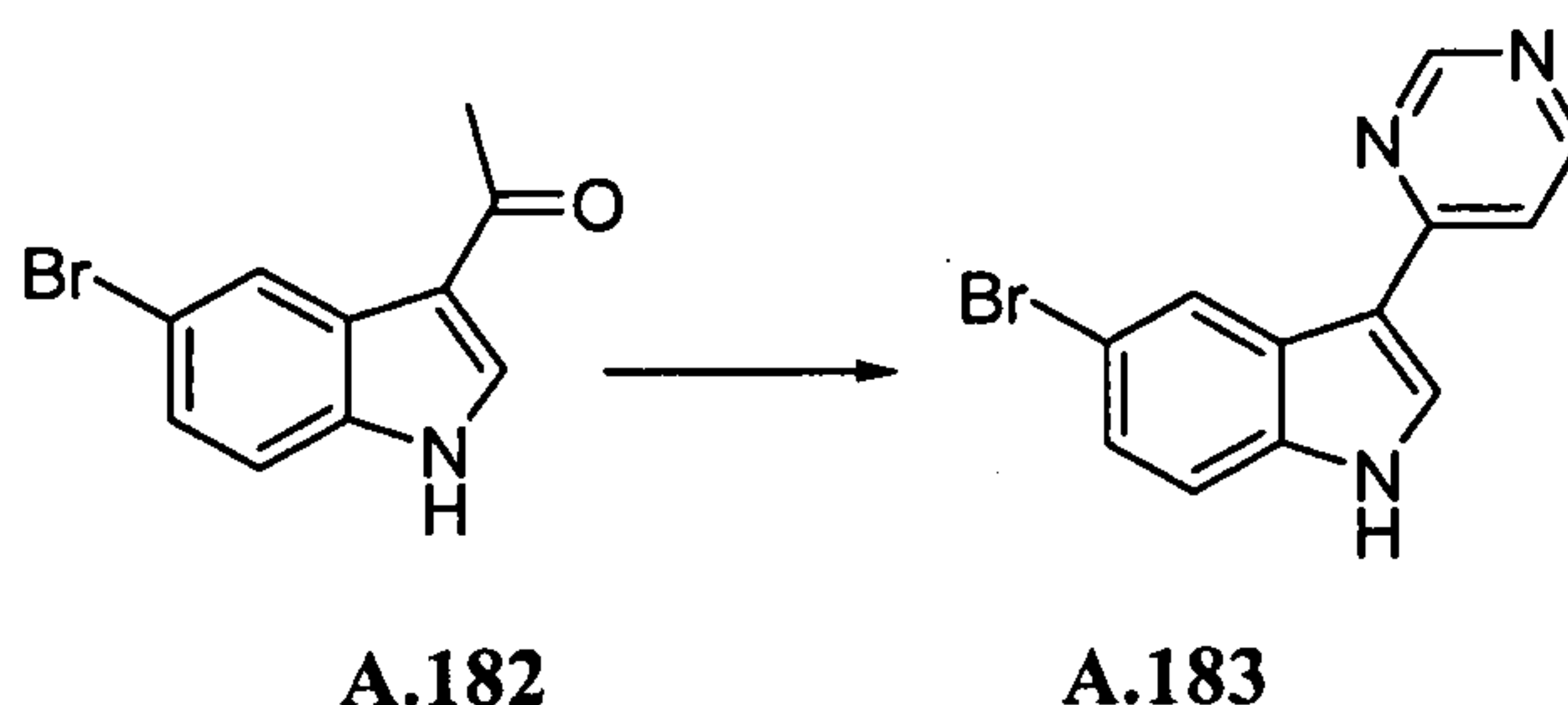
A.180

A.181

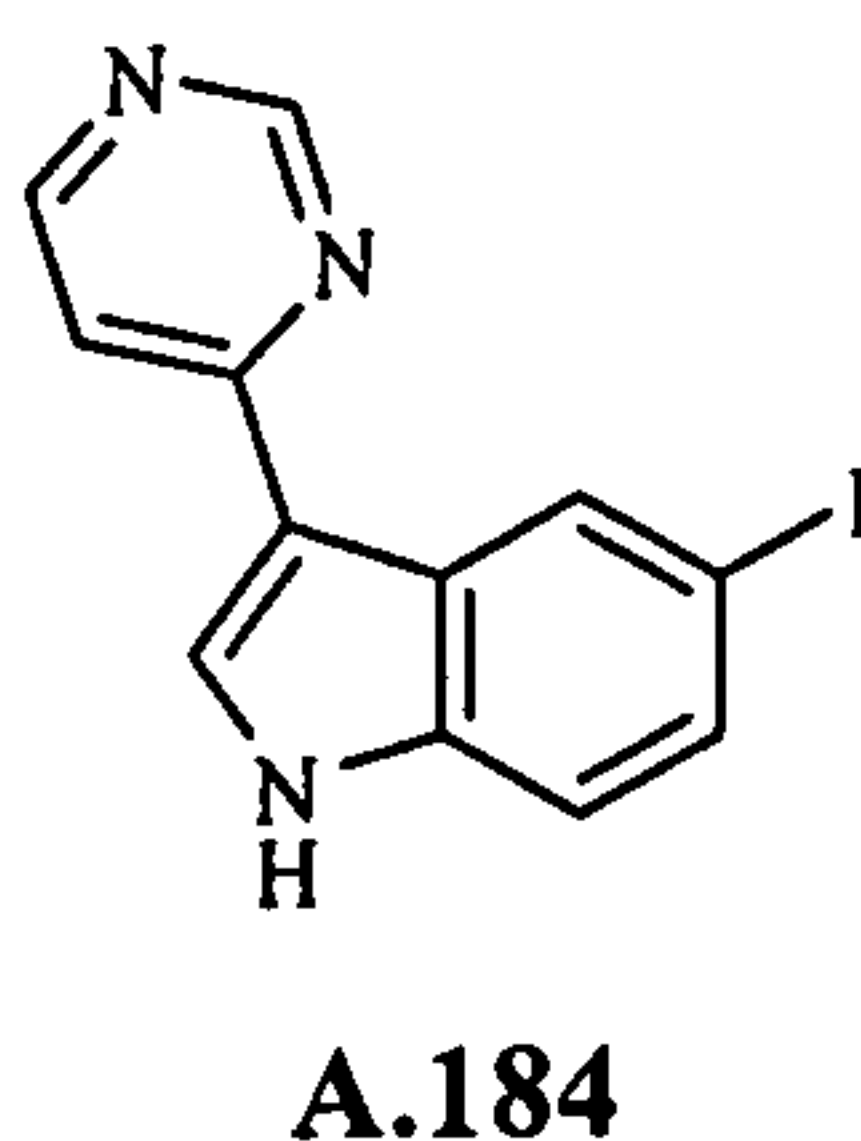
4-(5-iodo-1-(2-methoxyethyl)-1H-indol-3-yl)pyrimidin-2-amine A.181: To a mixture of 4-(5-bromo-1-(2-methoxyethyl)-1H-indol-3-yl)pyrimidin-2-amine (A.180) (445 mg, 1.28

mmol), NaI (383.7 mg, 2.56 mmol), and copper(I) iodide (42.0 mg, 0.22 mmol) in dioxane (20 mL) was added N¹,N²-dimethylethane-1,2-diamine (0.1 mL) under N₂ and heated at 110 °C under N₂ for 24 hrs. After cooled to room temperature, the resultant mixture was diluted with ether, washed with water and brine, dried and concentrated. Purification of the residue by flash chromatography over silica gel, using 4:5:1 ethyl acetate-hexane-methanol, gave 4-(5-iodo-1-(2-methoxyethyl)-1H-indol-3-yl)pyrimidin-2-amine (A.181) (358.9 mg, 70%): ¹H NMR (DMSO- *d*₆) δ 8.90(s, 1 H), 8.20(s, 1 H), 8.12 (d, *J* = 8.4 Hz, 1 H), 7.49(d, *J* = 8.4 Hz, 1 H), 7.44 (d, *J* = 8.4 Hz, 1 H), 6.93(d, *J* = 4.8 Hz, 1 H), 6.49(s, 2 H), 4.39 (t, *J* = 4.8 Hz, 2 H), 3.70 (t, *J* = 4.8 Hz, 2 H), 3.16(s, 3 H); ms 395.0 (M+H⁺).

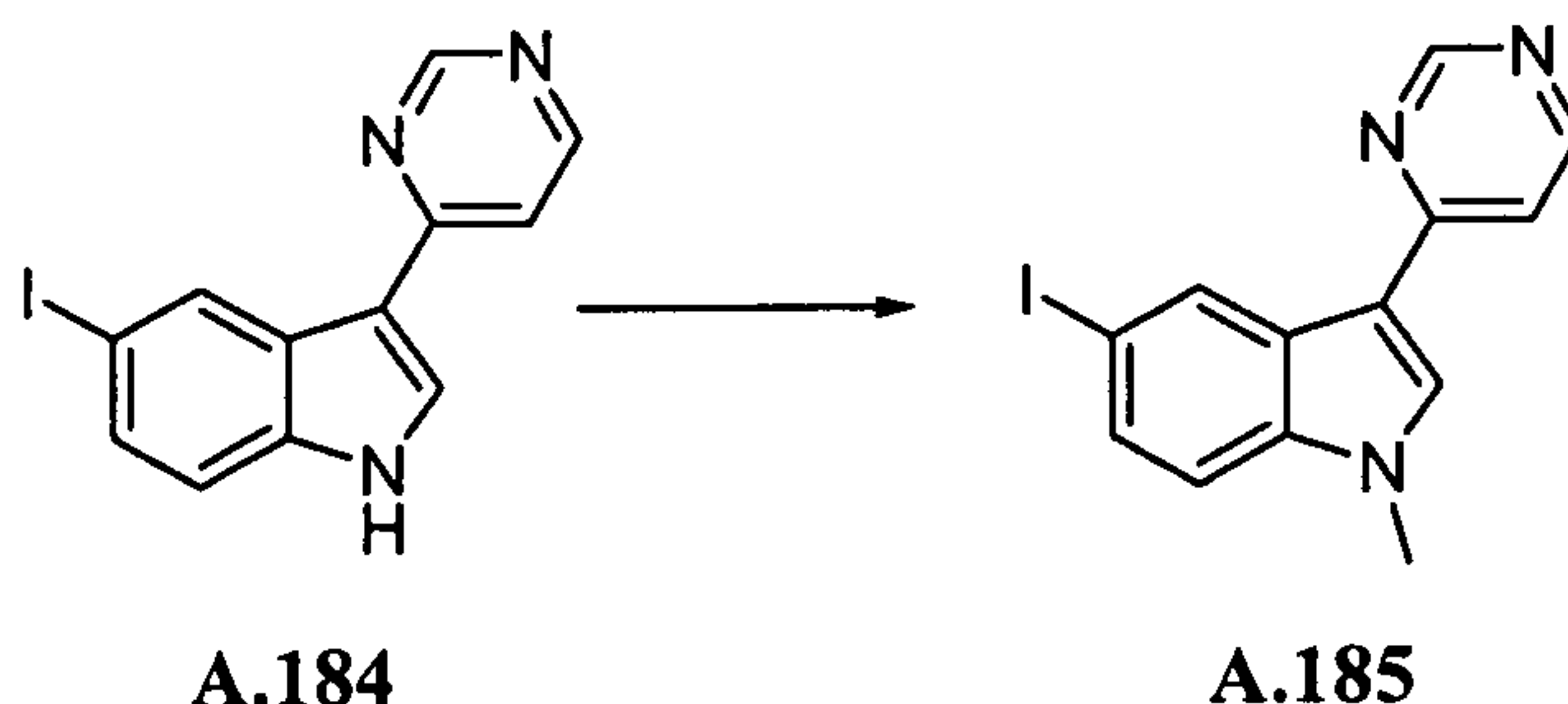
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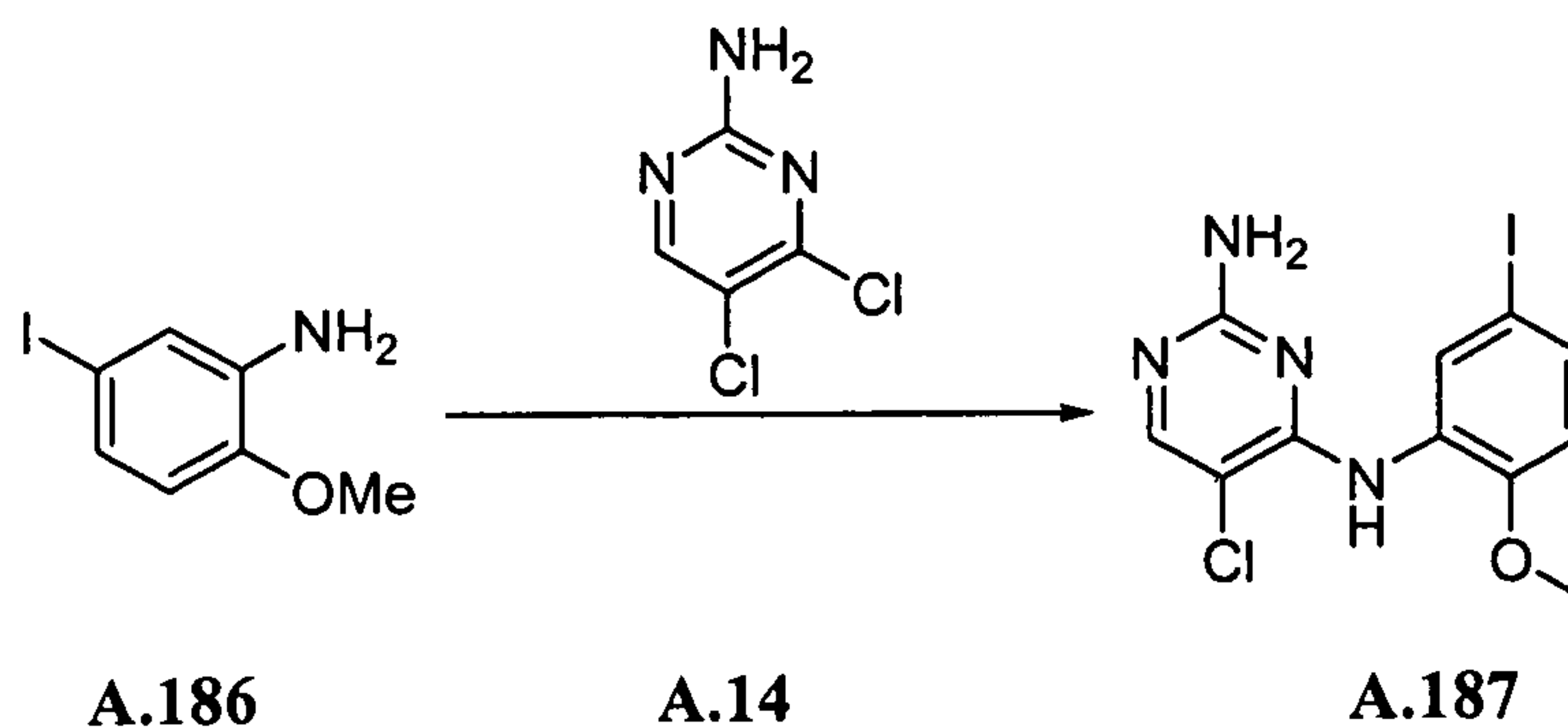
5-bromo-3-(pyrimidin-4-yl)-1H-indole A.183: To the mixture of 1-(5-bromo-1H-indol-3-yl)ethanone A.182 [Fresneda, P. M., P. Molina, et al. (2001). *Tetrahedron* **57**(12): 2355-2364.] (500 mg, 2.1 mmol) and N,N',N''-Methylidynetrisformamide (610 mg, 4.2 mmol) in NMP (5 ml) TsOH (199.7 mg, 1.05 mmol) was added. The mixture was heated at 185°C for 2 days. After cooled to room temperature, the resultant mixture was diluted with ethyl acetate, washed with water and brine, dried and concentrated. Purification of the residue by flash chromatography over silica gel, using 9.5:0.5 dichloromethane-methanol, gave 5-bromo-3-(pyrimidin-4-yl)-1H-indole (A.183) (118.6 mg, 74%): ¹H NMR (DMSO- *d*₆) δ 9.24(s, 1 H), 8.72(d, *J* = 1.8 Hz, 1 H), 8.63(d, *J* = 5.6 Hz, 1 H), 8.48(s, 1 H), 7.90(dd, *J* = 5.6, 1.8 Hz, 1 H), 7.46(d, *J* = 8.6 Hz, 1 H), 7.34(dd, *J* = 8.6, 1.5 Hz, 1 H); ms 274.0 (M+H⁺).



5-iodo-3-(pyrimidin-4-yl)-1H-indole A.184: This compound was prepared from A.183 by the procedure used for A.181: ^1H NMR (DMSO- d_6) δ 12.03(s, 1 H), 9.13(s, 1 H), 8.92(s, 1 H), 8.63 (d, $J = 5.6$ Hz, 1 H), 8.42(s, 1 H), 7.89 (d, $J = 5.6$ Hz, 1 H), 7.49(d, $J = 8.8$ Hz, 1 H), 7.24 (d, $J = 8.8$ Hz, 1 H); ms 322.0 ($\text{M}+\text{H}^+$).

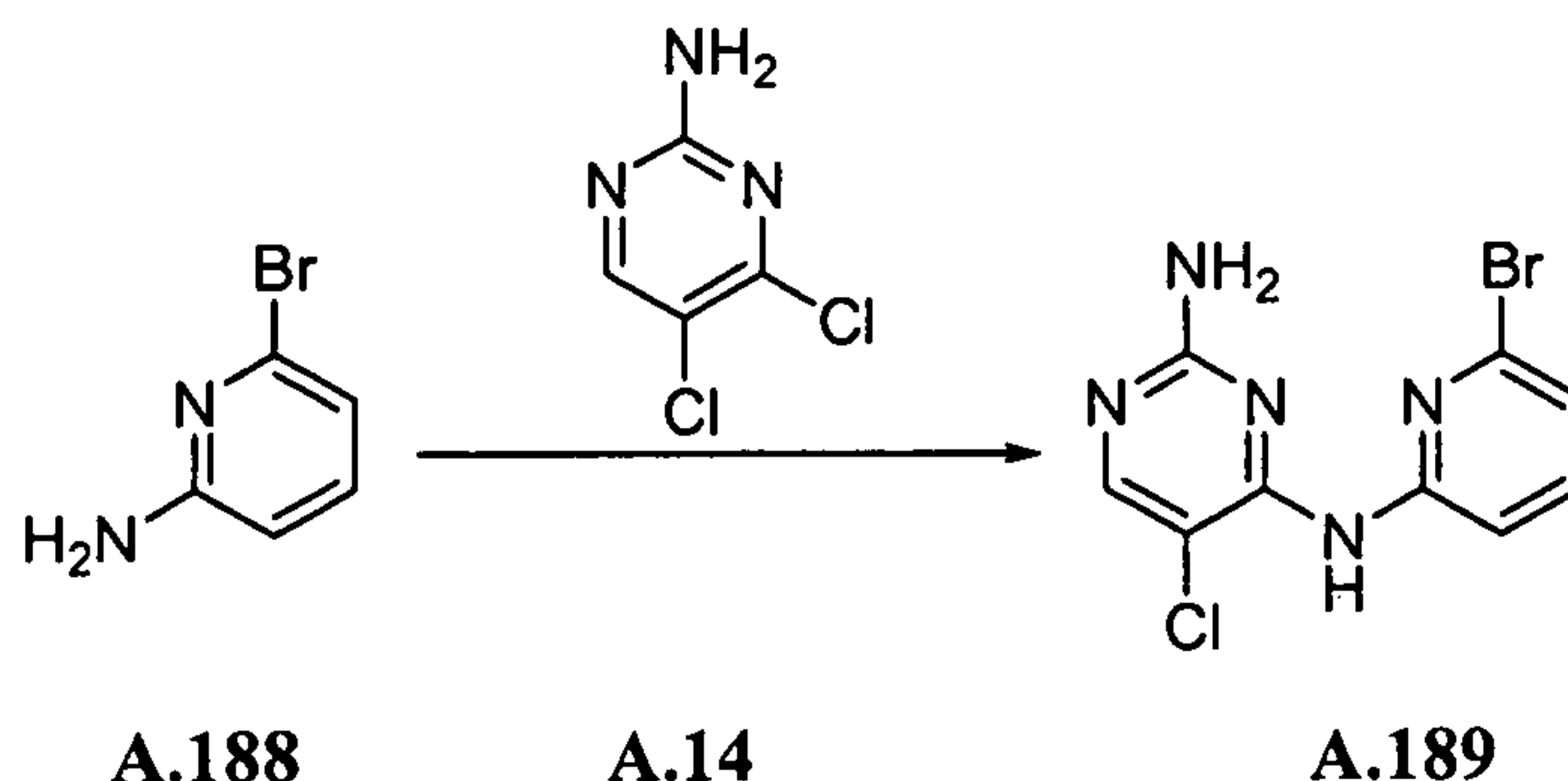


5-iodo-1-methyl-3-(pyrimidin-4-yl)-1H-indole A.185: A mixture of 5-iodo-3-(pyrimidin-4-yl)-1H-indole (A.184) (180 mg, 0.561 mmol), Dabco (6.3 mg, 0.0561 mmol), DMF (0.5 mL) and dimethyl carbonate (5 mL) was heated at 95°C for 16hrs. After cooling to room temperature, the resultant mixture was diluted with ethyl acetate, washed with water, aq. NH_4Cl and brine, dried and concentrated. Purification of the residue by flash chromatography over silica gel, using 9.5:0.5 dichloromethane-methanol, gave 5-iodo-1-methyl-3-(pyrimidin-4-yl)-1H-indole (A.185) (130 mg, 69%): ^1H NMR (DMSO- d_6) δ 9.13(s, 1 H), 8.92(d, $J = 1.8$ Hz, 1 H), 8.63(d, $J = 5.6$ Hz, 1 H), 8.45(s, 1 H), 7.81(d, $J = 5.6$ Hz, 1 H), 7.58(d, $J = 8.6$ Hz, 1 H), 7.44(d, $J = 8.6$ Hz, 1 H), 3.83(s, 1 H); ms 336.0 ($\text{M}+\text{H}^+$).

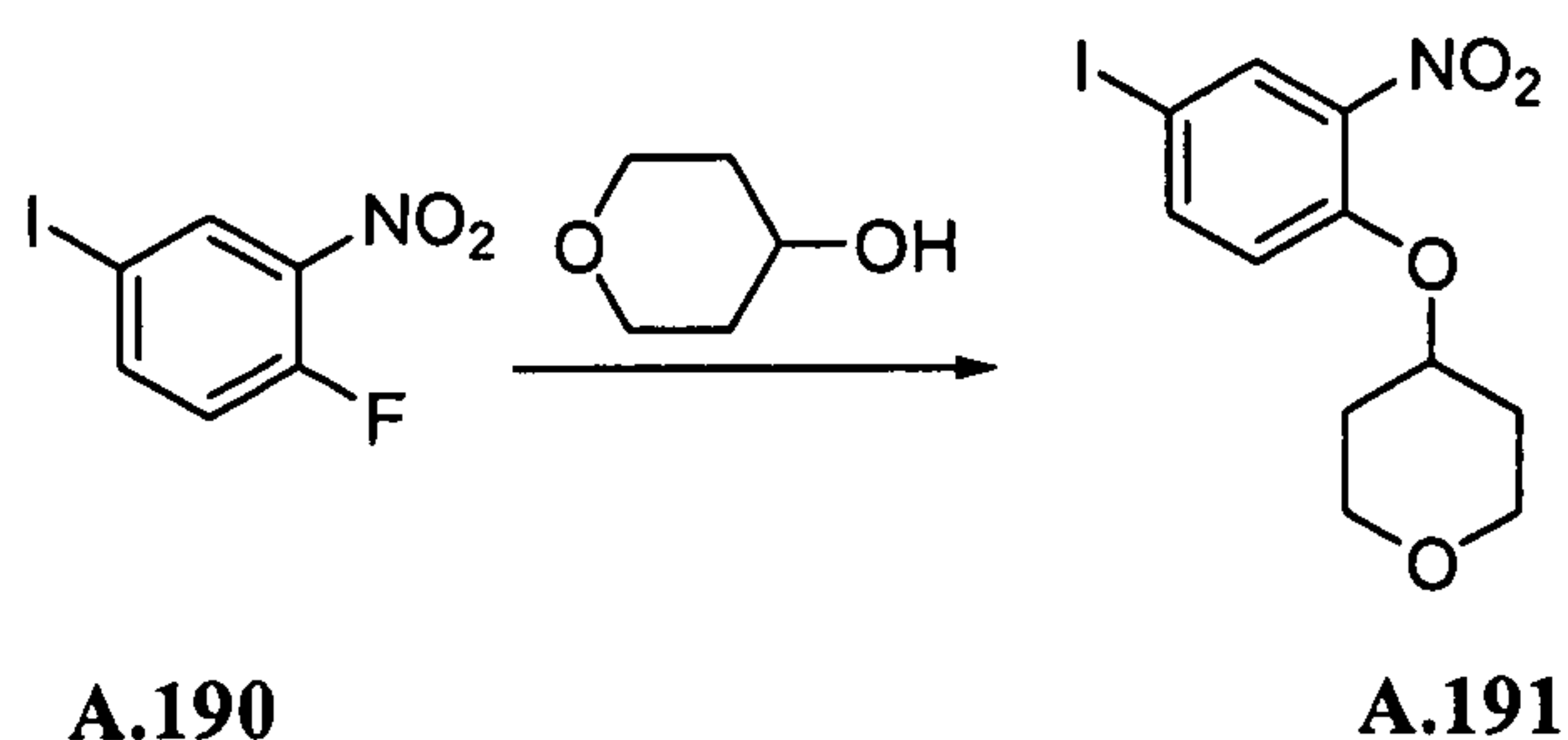


5-Chloro- N^4 -(5-iodo-2-methoxyphenyl)pyrimidine-2,4-diamine (A.187). To a flask containing 5-iodo-2-methoxybenzenamine (A.186) (472 mg, 1.9 mmol) in 1,4-dioxane (8.00 mL) was added 4,5-dichloropyrimidin-2-amine A.14 (622 mg, 3.8 mmol) and 1 N HCl (7.00 mL). The reaction was heated to 80 °C. After 3 hours, the mixture was cooled to room temperature then carefully neutralized with 1N NaOH. After extracting with ethyl acetate, the

solvent was removed under reduced pressure. Methanol was then added to the residue and heated to 50 °C. After 15 minutes, the solvent was removed to a volume of ~1.0 mL and cooled to room temperature. The solid was filtered and dried to yield **5-chloro-N⁴-(5-iodo-2-methoxyphenyl)pyrimidine-2,4-diamine (A.187)** (341 mg, 47.7%). ¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 8.53 (1 H, d, *J*=2.2 Hz), 7.97 (1 H, s), 7.85 (1 H, s), 7.40 (1 H, dd, *J*=8.6, 2.2 Hz), 6.90 (1 H, d, *J*=8.6 Hz), 6.58 (2 H, s), 3.86 (3 H, s). MS ESI (pos.) *m/e*: 376.9(M+H).

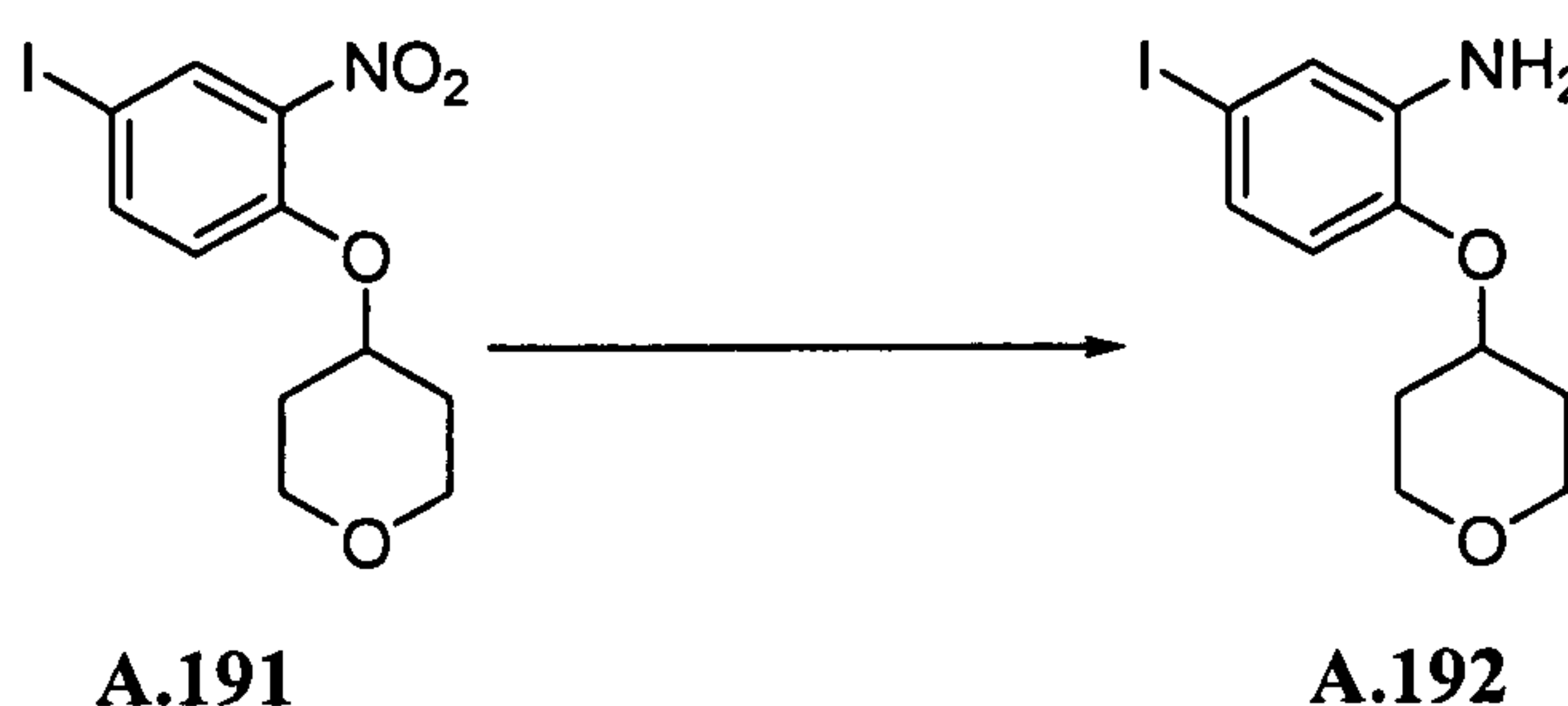


N⁴-(6-Bromopyridin-2-yl)-5-chloropyrimidine-2,4-diamine (A.189). To a dry flask containing 6-bromopyridin-2-amine **A.188** (1.25 g, 7.23 mmol) and dry DMF (20.0 mL) at 0 °C was added potassium *tert*-butoxide (973.9 mg, 8.68 mmol) in portions. After 1 hour, 4,5-dichloropyrimidin-2-amine **A.14** (1.18 g, 7.22 mmol) was added to the mixture then heated to 50 °C. Upon completion, the reaction was cooled to room temperature, then quenched with water. After extracting three times with ethyl acetate, the organic solvent was removed under reduced pressure. Methanol was added to the residue and heated to 45 °C. After 30 minutes, the solid was filtered hot then rinsed three times with methanol to yield **N⁴-(6-bromopyridin-2-yl)-5-chloropyrimidine-2,4-diamine (A.189)**. (1.012 g, 47%) ¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 8.56 (1 H, s), 8.39 (1 H, m), 8.06 (1 H, m), 7.72 (1 H, m), 7.30 (1 H, m), 6.74 (2 H, s).

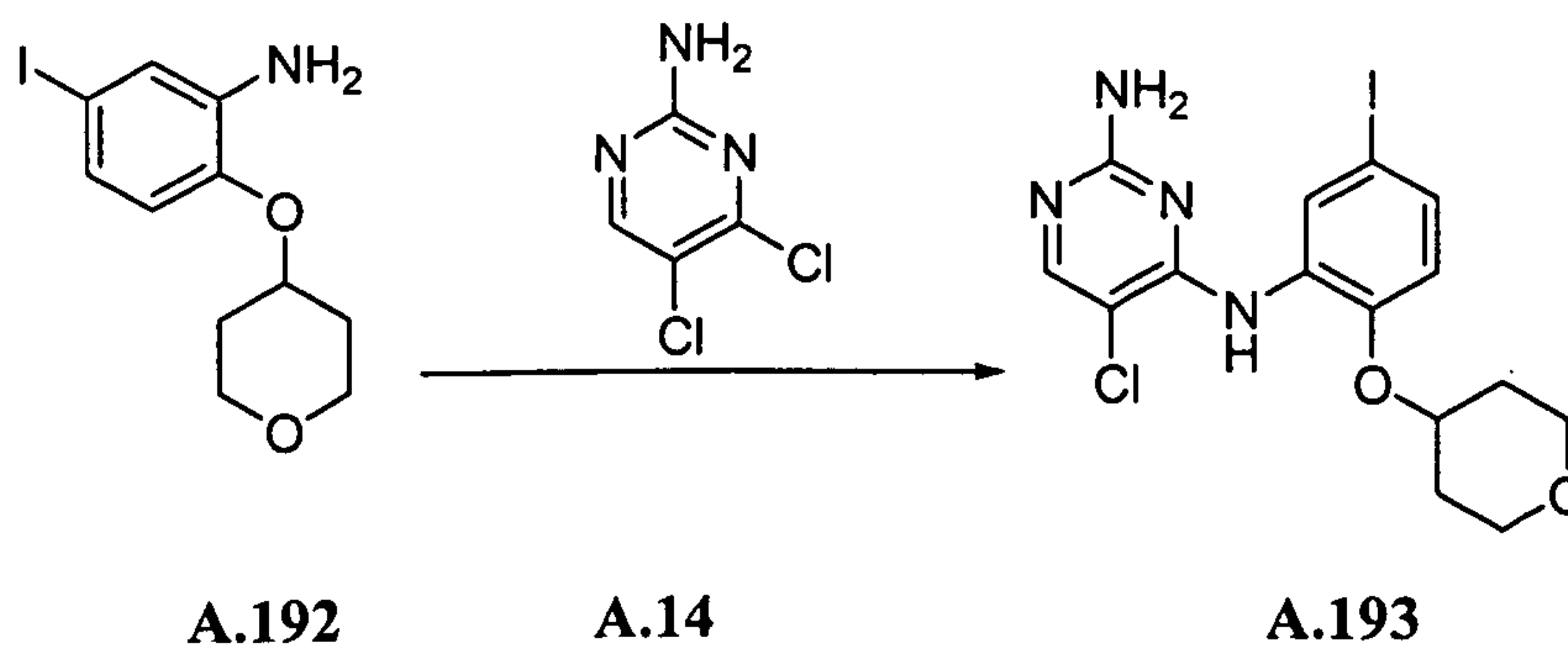


4-(4-Iodo-2-nitrophenoxy)-tetrahydro-2H-pyran (A.191). A dry flask containing tetrahydro-2H-pyran-4-ol (0.8 mL, 8.39 mmol) in dry DMF (13.00 mL) was cooled in an ice bath, then sodium hydride (60% wt. dispersion in oil) (336.2 mg, 8.41 mmol) was carefully

added in portions. After 15 minutes, 1-fluoro-4-iodo-2-nitrobenzene **A.190** [Prakash, G. K. S., T. Mathew, et al. (2004). *J. Amer. Chem. Soc.* **126**(48): 15770-15776.] was added, and the mixture was stirred at room temperature. After 21 hours, the reaction was carefully quenched with cold water then extracted three times with ethyl acetate. After removing the organic solvent under reduced pressure, the residue was purified by silica gel flash chromatography (0-50% ethyl acetate in hexanes) to afford **4-(4-iodo-2-nitrophenoxy)-tetrahydro-2H-pyran** (**A.191**) (2.02 g, 88%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 8.16 (1 H, d, $J=2.2$ Hz), 7.90 (1 H, dd, $J=8.8, 2.2$ Hz), 7.29 (1 H, t, $J=9.4$ Hz), 4.87 (1 H, m), 3.82 (2 H, m), 3.49 (2 H, ddd, $J=11.4, 7.9, 3.2$ Hz), 1.99 (2 H, m), 1.64 (2 H, m).

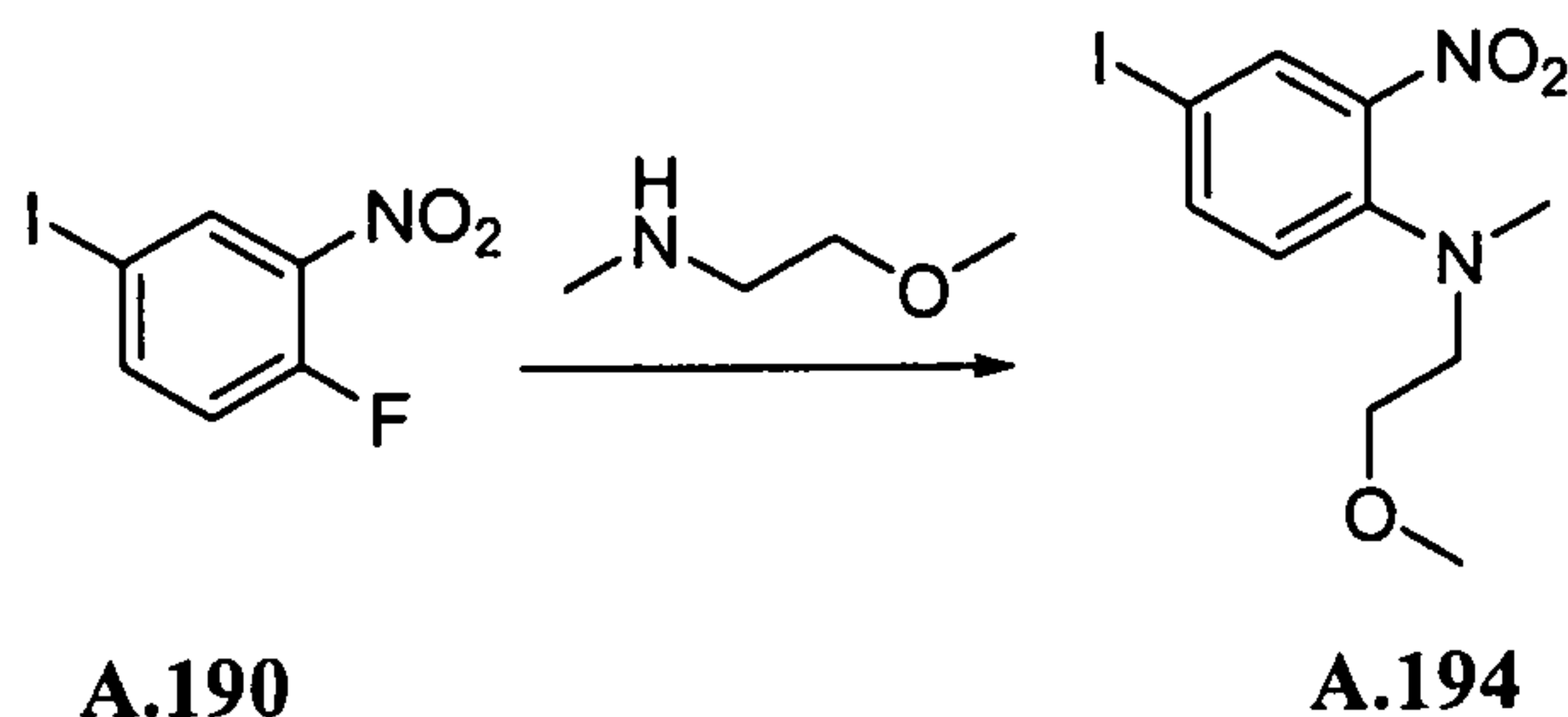


5-Iodo-2-(tetrahydro-2H-pyran-4-yloxy)benzenamine (A.192). To a flask containing 4-(4-iodo-2-nitrophenoxy)-tetrahydro-2H-pyran (**A.191**) (2.02 g, 5.78 mmol) and acetic acid (35.00 mL) was added iron powder (1.29 g, 23.1 mmol). The reaction was carefully heated to 100 °C. After 1.25 hours, the reaction was cooled to room temperature then filtered through celite. After rinsing the filter cake three times with ethyl acetate, the filtrate was washed once with brine then concentrated. The residue was purified by silica gel flash chromatography (0-100% ethyl acetate in hexanes) to afford **5-iodo-2-(tetrahydro-2H-pyran-4-yloxy)benzenamine** (**A.192**) (1.40 g, 76%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 6.96 (1 H, d, $J=2.0$ Hz), 6.77 (1 H, m), 6.65 (1 H, d, $J=8.3$ Hz), 4.93 (2 H, s), 4.46 (1 H, m), 3.87 (2 H, m), 3.46 (2 H, m), 1.91 (2 H, m), 1.63 (2 H, m). MS ESI (pos.) m/e : 320.0 ($\text{M}+\text{H}$).

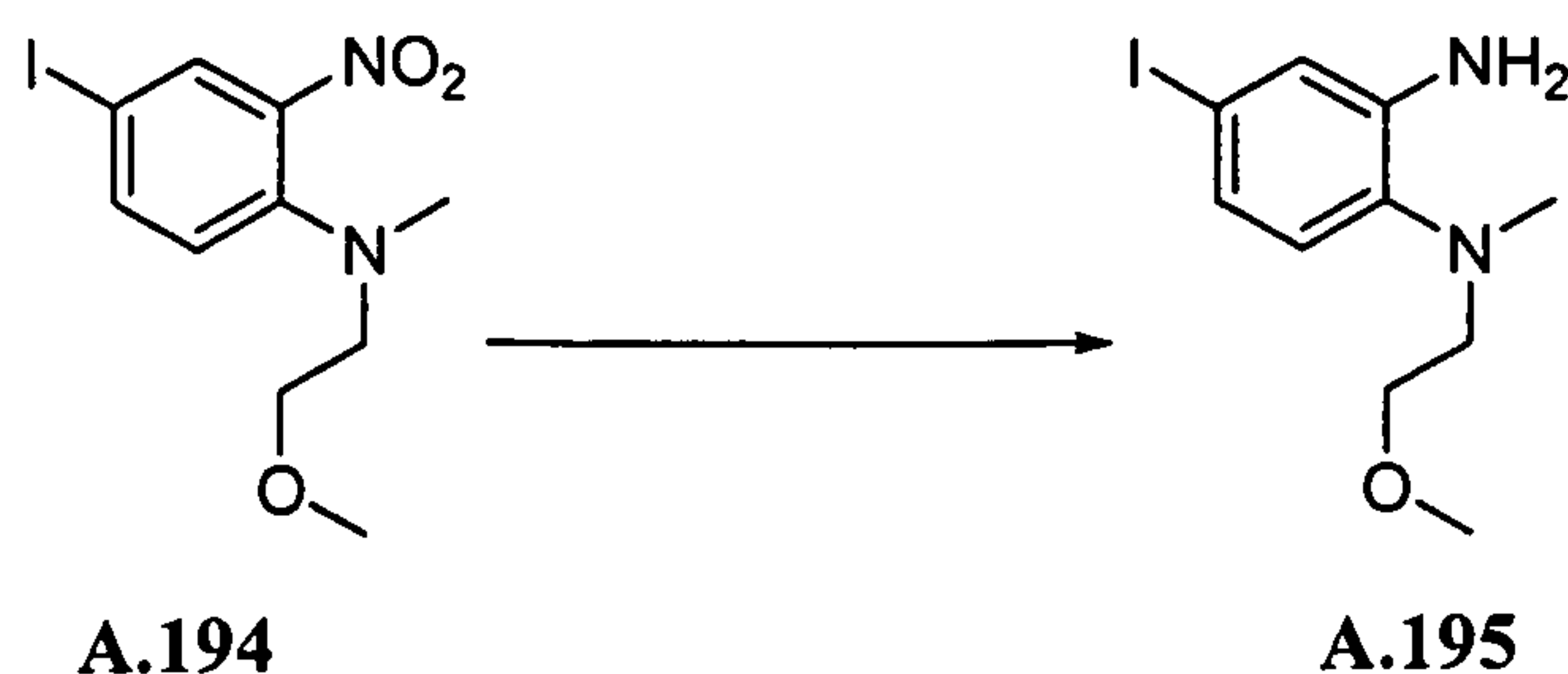


5-Chloro-N⁴-(5-iodo-2-(tetrahydro-2H-pyran-4-yloxy)phenyl)pyrimidine-2,4-diamine (A.193).

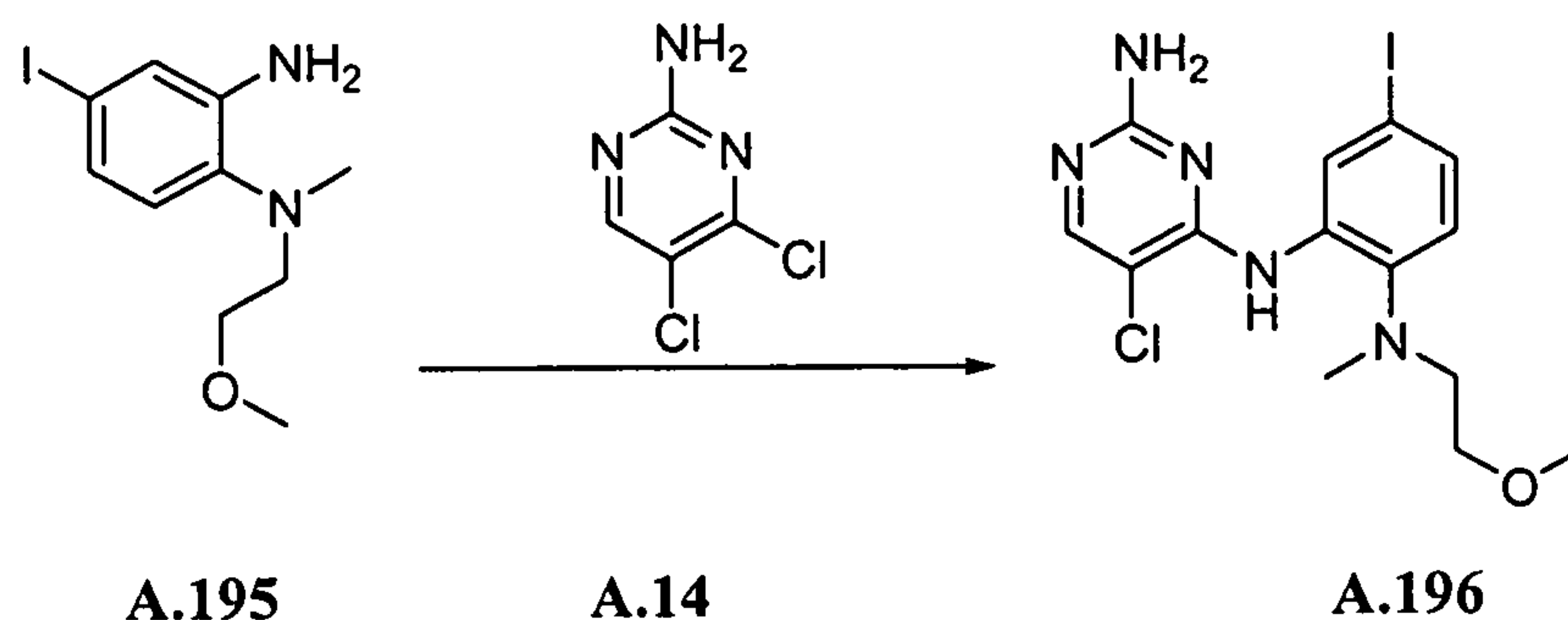
To a flask containing **5-iodo-2-(tetrahydro-2H-pyran-4-yloxy)benzenamine (A.192)** (1.40 g, 4.38 mmol) in 1,4-dioxane (11.00 mL) was added 4,5-dichloropyrimidin-2-amine **A.14** (1.44 g, 8.75 mmol) and 1 N HCl (9.00 mL). The reaction was heated to 80 °C. After 21 hours, the mixture was cooled to room temperature then carefully neutralized with 1N NaOH. After extracting with ethyl acetate, the solvent was removed under reduced pressure. Methanol was then added to the residue and heated to 50 °C. After 15 minutes, the solvent was removed to a volume of ~1.0 mL and cooled to room temperature. The solid was filtered and dried to yield **5-chloro-N⁴-(5-iodo-2-(tetrahydro-2H-pyran-4-yloxy)phenyl)pyrimidine-2,4-diamine (A.193)** (698 mg, 36 %). ¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 8.66 (1 H, d, *J*=2.0 Hz), 8.00 (2 H, m), 7.35 (1 H, dd, *J*=8.6, 2.0 Hz), 7.02 (1 H, m), 6.64 (2 H, s), 4.69 (1 H, dd, *J*=7.3, 3.7 Hz), 3.85 (2 H, m), 3.50 (2 H, ddd, *J*=11.2, 8.1, 2.9 Hz), 1.97 (2 H, d, *J*=12.5 Hz), 1.66 (2 H, m). MS ESI (pos.) *m/e*: 447.0 (M+H).



4-Iodo-N-(2-methoxyethyl)-N-methyl-2-nitrobenzenamine (A.194). A dry flask containing 2-methoxy-N-methylethanamine (1.2 mL, 11.2 mmol) in dry DMF (5.00 mL) was cooled in an ice bath, then sodium hydride (60% wt. dispersion in oil) (448.6 mg, 11.2 mmol) was carefully added in portions. After 15 minutes, 1-fluoro-4-iodo-2-nitrobenzene **A.190** (2.51 g, 9.4 mmol) was added, and the mixture was stirred at room temperature. After 19 hours, the reaction was carefully quenched with cold water then extracted three times with ethyl acetate. After removing the organic solvent under reduced pressure, the residue was purified by silica gel flash chromatography (0-30% ethyl acetate in hexanes) to afford **4-iodo-N-(2-methoxyethyl)-N-methyl-2-nitrobenzenamine (A.194)** (2.24 g, 71%). ¹H NMR (500 MHz, *MeOH*) δ ppm 7.95 (1 H, d, *J*=2.0 Hz), 7.69 (1 H, dd, *J*=8.8, 2.2 Hz), 7.06 (1 H, d, *J*=8.8 Hz), 3.57 (2 H, t, *J*=5.5 Hz), 3.37 (5 H, m), 2.86 (3 H, s). MS ESI (pos.) *m/e*: 337.0 (M+H).

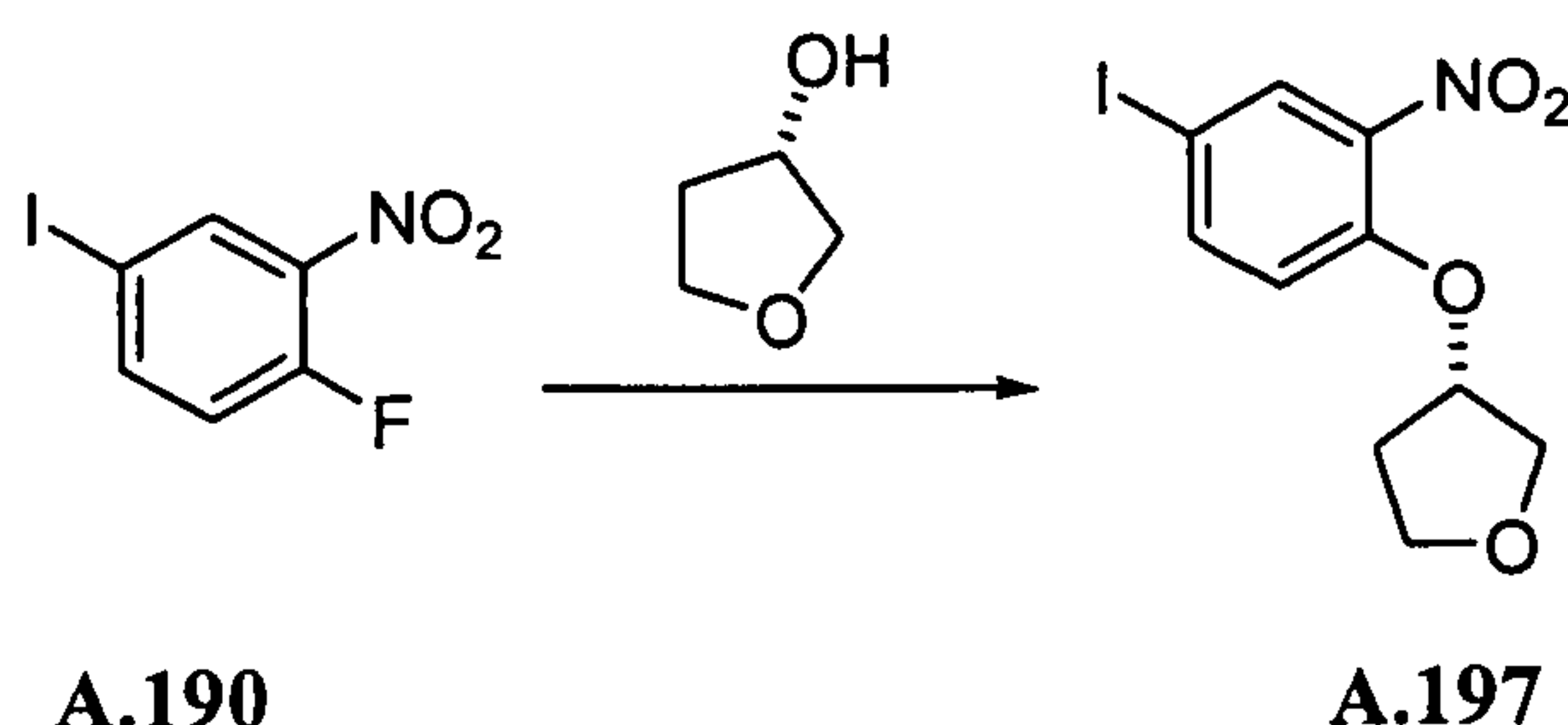


4-Iodo-*N*'-(2-methoxyethyl)-*N*'-methylbenzene-1,2-diamine (A.195). To a flask containing 4-iodo-*N*-(2-methoxyethyl)-*N*-methyl-2-nitrobenzenamine (A.194) (2.24 g, 6.65 mmol) and acetic acid (30.00 mL) was added iron powder (1.49 g, 26.7 mmol). The reaction was carefully heated to 100 °C. After 1 hour, the reaction was cooled to room temperature then filtered through celite. After rinsing the filter cake three times with ethyl acetate, the filtrate was washed once with brine then concentrated. The residue was purified by silica gel flash chromatography (0-100% ethyl acetate in hexanes) to afford 4-iodo-*N*'-(2-methoxyethyl)-*N*'-methylbenzene-1,2-diamine (A.195) (1.20 g, 59%). ¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 6.96 (1 H, d, *J*=2.0 Hz), 6.79 (1 H, dd, *J*=8.3, 2.0 Hz), 6.70 (1 H, d, *J*=8.1 Hz), 5.07 (2 H, s), 3.43 (2 H, t, *J*=5.5 Hz), 3.27 (3 H, s), 2.86 (2 H, t, *J*=5.5 Hz), 2.58 (3 H, s). MS ESI (pos.) *m/e*: 307.0 (*M*+*H*).

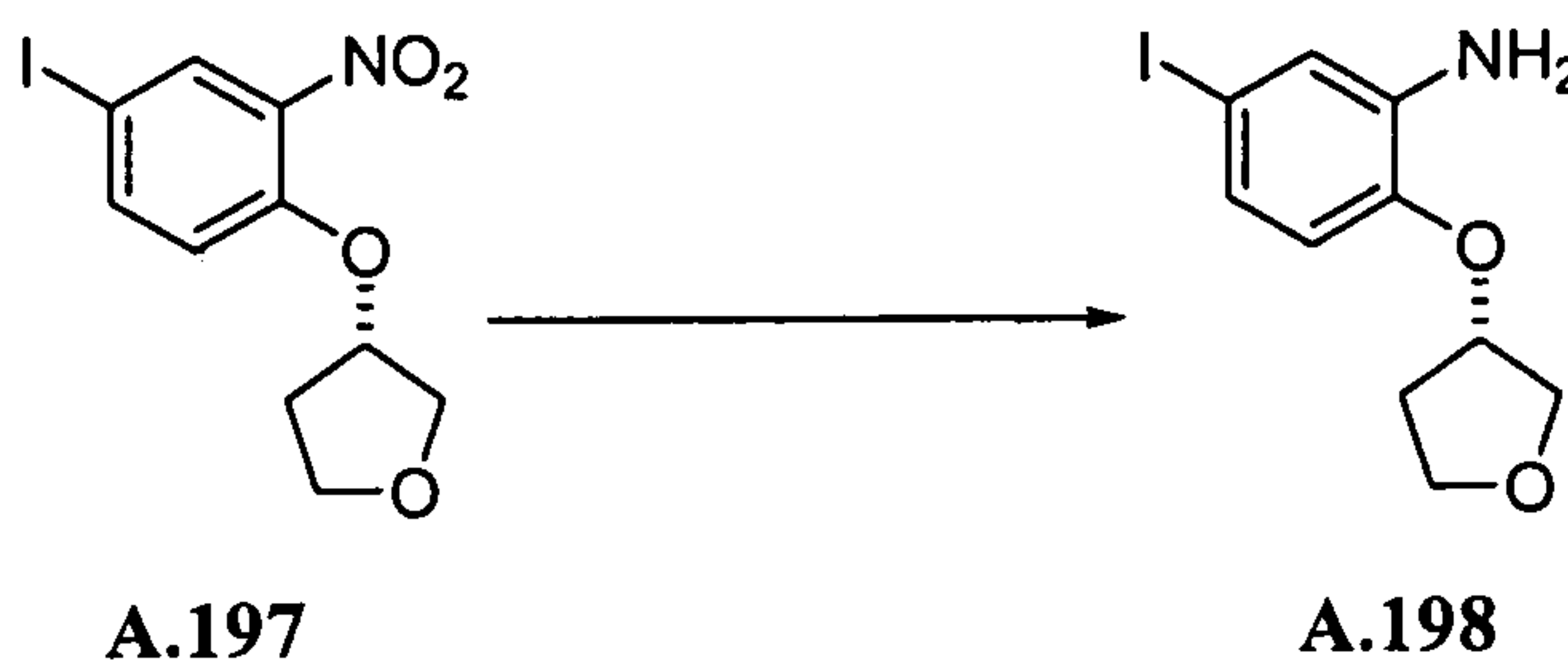


5-Chloro-*N*'-(5-iodo-2-((2-methoxyethyl)(methyl)amino)phenyl)pyrimidine-2,4-diamine (A.196). To a flask containing 4-iodo-*N*'-(2-methoxyethyl)-*N*'-methylbenzene-1,2-diamine (A.195) (1.20 g, 3.92 mmol) in 1,4-dioxane (11.00 mL) was added 4,5-dichloropyrimidin-2-amine A.14 (1.29 g, 7.84 mmol) and 1 N HCl (9.00 mL). The reaction was heated to 80 °C. After 19.5 hours, the mixture was cooled to room temperature then carefully neutralized with 1N NaOH. After extracting with ethyl acetate, the solvent was removed under reduced pressure. The residue was purified by silica gel flash chromatography (0-40% ethyl acetate in dichloromethane) to afford 5-chloro-*N*'-(5-iodo-2-((2-methoxyethyl)(methyl)amino)phenyl)-pyrimidine-2,4-diamine (A.196) (753 mg, 44%). ¹H

NMR (500 MHz, *DMSO-d*₆) δ ppm 8.77 (2 H, m), 7.99 (1 H, m), 7.37 (1 H, dd, *J*=8.2, 2.1 Hz), 7.11 (1 H, d, *J*=8.3 Hz), 6.63 (2 H, s), 3.36 (3 H, m), 3.17 (3 H, m), 2.98 (2 H, t, *J*=5.6 Hz), 2.63 (3 H, s). MS ESI (pos.) *m/e*: 434.0 (M+H).

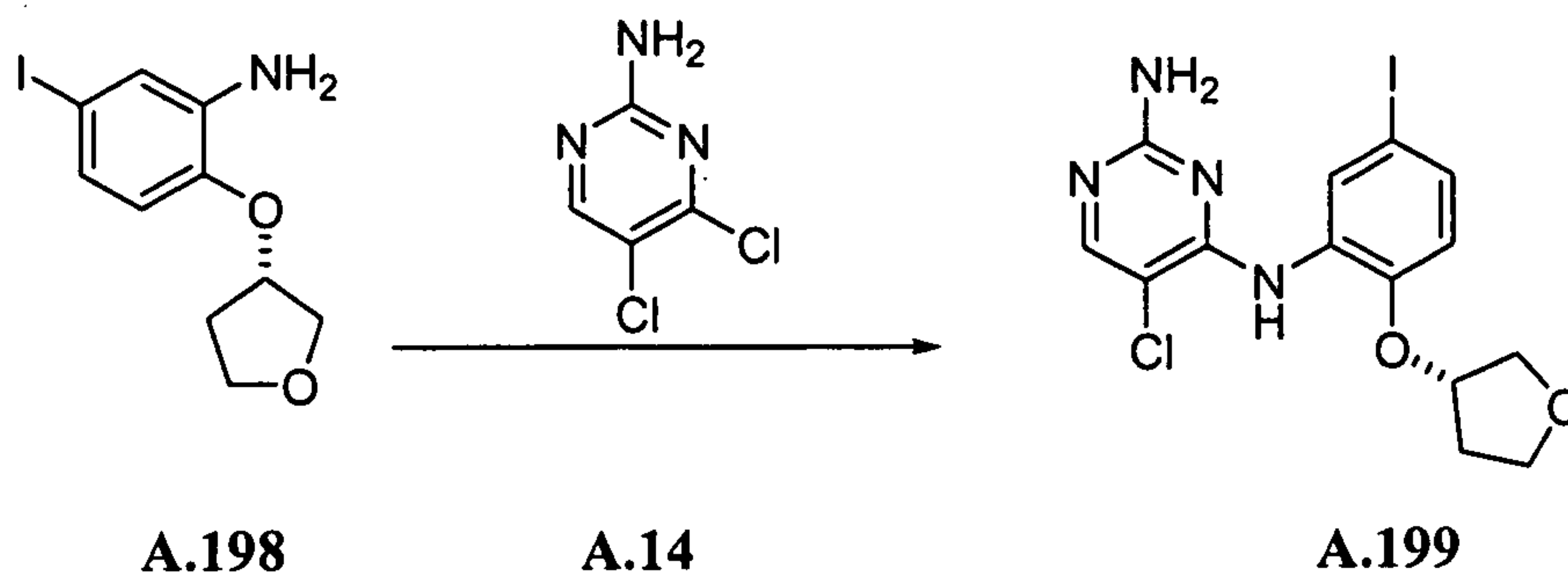


(S)-3-(4-Iodo-2-nitrophenoxy)-tetrahydrofuran (A.197). A dry flask containing 2(S)-tetrahydrofuran-3-ol (0.55 mL, 6.89 mmol) in dry DMF (10.00 mL) was cooled in an ice bath, then sodium hydride (60% wt. dispersion in oil) (275.5 mg, 6.89 mmol) was carefully added in portions. After 15 minutes, 1-fluoro-4-iodo-2-nitrobenzene **A.190** (1.47 g, 5.52 mmol) was added, and the mixture was stirred at room temperature. After 19.5 hours, the reaction was carefully quenched with cold water then extracted three times with ethyl acetate. After removing the organic solvent under reduced pressure, the residue was purified by silica gel flash chromatography (0-30% ethyl acetate in hexanes) to afford **(S)-3-(4-iodo-2-nitrophenoxy)-tetrahydrofuran (A.197)** (1.58 g, 85 %). ¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 8.18 (1 H, m), 7.95 (1 H, m), 7.20 (1 H, d, *J*=9.0 Hz), 5.23 (1 H, d, *J*=4.4 Hz), 3.91 (1 H, m), 3.81 (3 H, m), 2.26 (1 H, m), 1.99 (1 H, m).

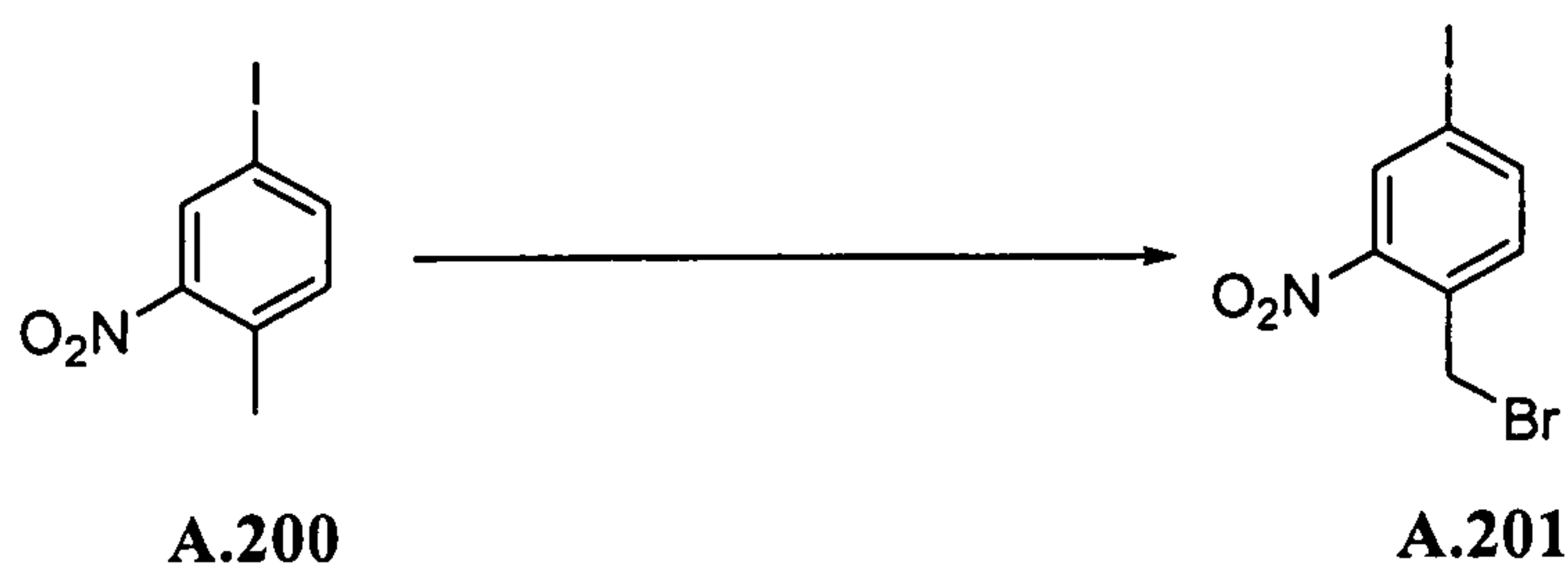


(S)-5-Iodo-2-(tetrahydrofuran-3-yloxy)benzenamine (A.198). To a flask containing **(S)-3-(4-iodo-2-nitrophenoxy)-tetrahydrofuran (A.197)** (1.58 g, 4.71 mmol) and acetic acid (35.00 mL) was added iron powder (1.05 g, 18.8 mmol). The reaction was carefully heated to 100 °C. After 1.75 hours, the reaction was cooled to room temperature then filtered through celite. After rinsing the filter cake three times with ethyl acetate, the filtrate was washed once with brine then concentrated. The residue was purified by silica gel flash chromatography (0-100% ethyl acetate in hexanes) to afford **(S)-5-iodo-2-(tetrahydrofuran-3-yloxy)benzenamine**

(A.198) (418.6 mg, 29%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 6.94 (1 H, d, $J=2.0$ Hz), 6.77 (1 H, dd, $J=8.3, 2.2$ Hz), 6.57 (1 H, m), 4.93 (1 H, s), 4.91 (2 H, ddd, $J=6.4, 4.3, 2.3$ Hz), 3.88 (2 H, m), 3.80 (2 H, m), 2.19 (1 H, m), 2.01 (1 H, m). MS ESI (pos.) m/e : 306.0 ($\text{M}+\text{H}$).

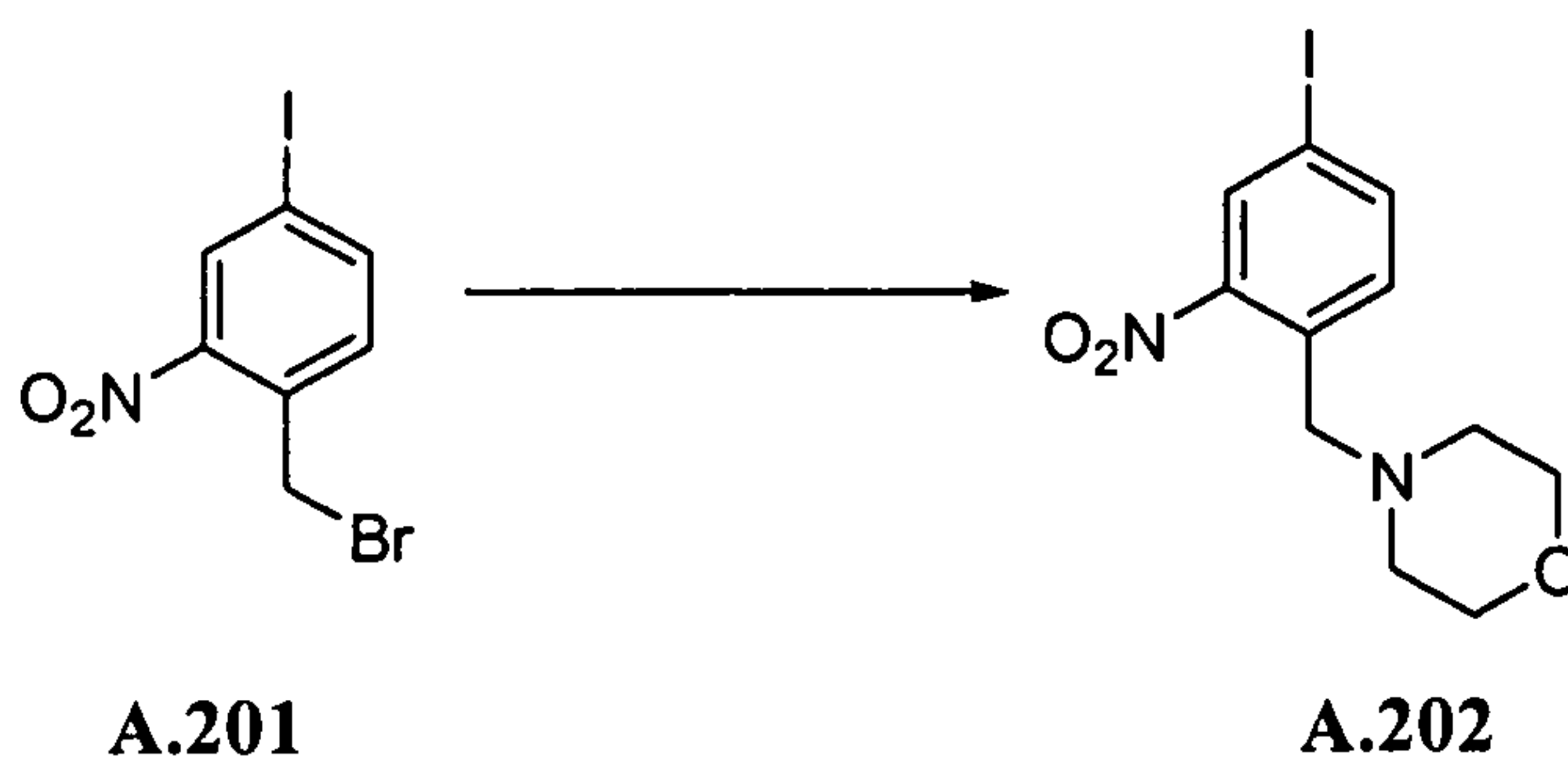


(S)-5-Chloro-*N'*-(5-iodo-2-(tetrahydrofuran-3-yloxy)phenyl)pyrimidine-2,4-diamine (A.199). To a flask containing (S)-5-iodo-2-(tetrahydrofuran-3-yloxy)benzenamine (A.198) (418.6 mg, 1.37 mmol) in 1,4-dioxane (5.00 mL) was added 4,5-dichloropyrimidin-2-amine A.14 (450.6 mg, 2.75 mmol) and 1 N HCl (5.00 mL). The reaction was heated to 80 °C. After 8 hours, the mixture was cooled to room temperature then carefully neutralized with 1N NaOH. After extracting with ethyl acetate, the solvent was removed under reduced pressure. Methanol was then added to the residue and heated to 50 °C. After 15 minutes, the solvent was removed to a volume of ~1.0 mL and cooled to room temperature. The solid was filtered and dried to yield (S)-5-chloro-*N'*-(5-iodo-2-(tetrahydrofuran-3-yloxy)phenyl)pyrimidine-2,4-diamine (A.199) (451.1 mg, 76%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 8.61 (1 H, d, $J=1.2$ Hz), 7.98 (1 H, s), 7.89 (1 H, s), 7.37 (1 H, dd, $J=8.6, 2.0$ Hz), 6.91 (1 H, d, $J=8.6$ Hz), 6.61 (2 H, s), 5.14 (1 H, m), 3.89 (1 H, dd, $J=10.5, 4.4$ Hz), 3.83 (1 H, q, $J=7.7$ Hz), 3.79 (2 H, m), 2.22 (1 H, td, $J=14.1, 8.3$ Hz), 2.03 (1 H, m). MS ESI (pos.) m/e : 432.9 ($\text{M}+\text{H}$).

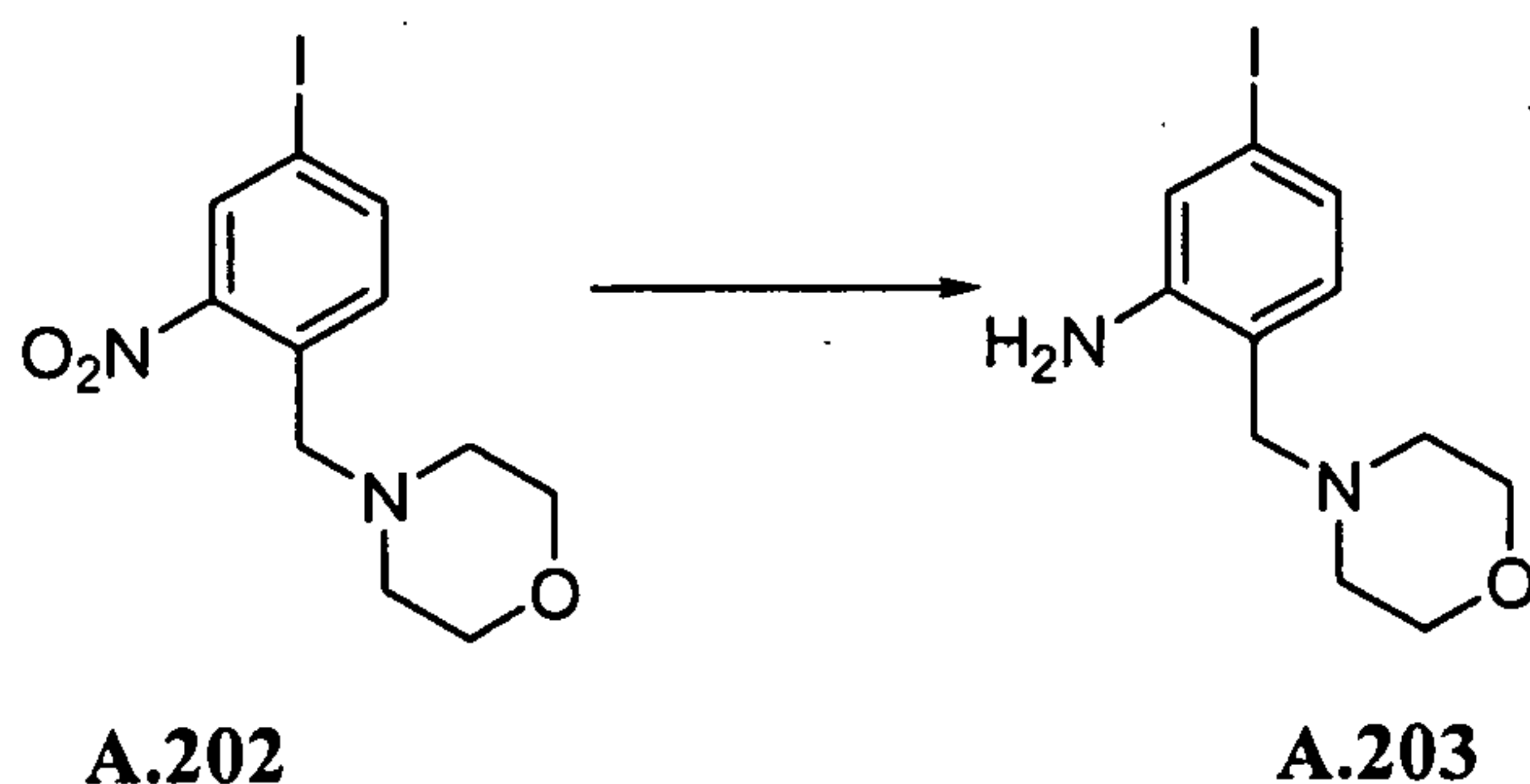


1-(Bromomethyl)-4-iodo-2-nitrobenzene (A.201). To a flask containing 4-iodo-1-methyl-2-nitrobenzene A.200 (2.52 g, 9.57 mmol) in dry CCl_4 (35.0 mL) was added *N*-bromosuccinimide (1.88 g, 10.5 mmol) and benzoyl peroxide (47.0 mg, 0.19 mmol). The mixture was heated to

reflux. After 20 hours, the reaction was cooled to room temperature then diluted with water. After extracting three times with dichloromethane, the organic solvent was removed under reduced pressure. The residue was purified by silica gel flash chromatography (6:1 hexane in dichloromethane) to afford **1-(bromomethyl)-4-iodo-2-nitrobenzene (A.201)** (1.37 g, 42%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 8.38 (1 H, m), 8.11 (1 H, dd, $J=8.1, 1.7$ Hz), 7.55 (1 H, m), 4.86 (2 H, s).

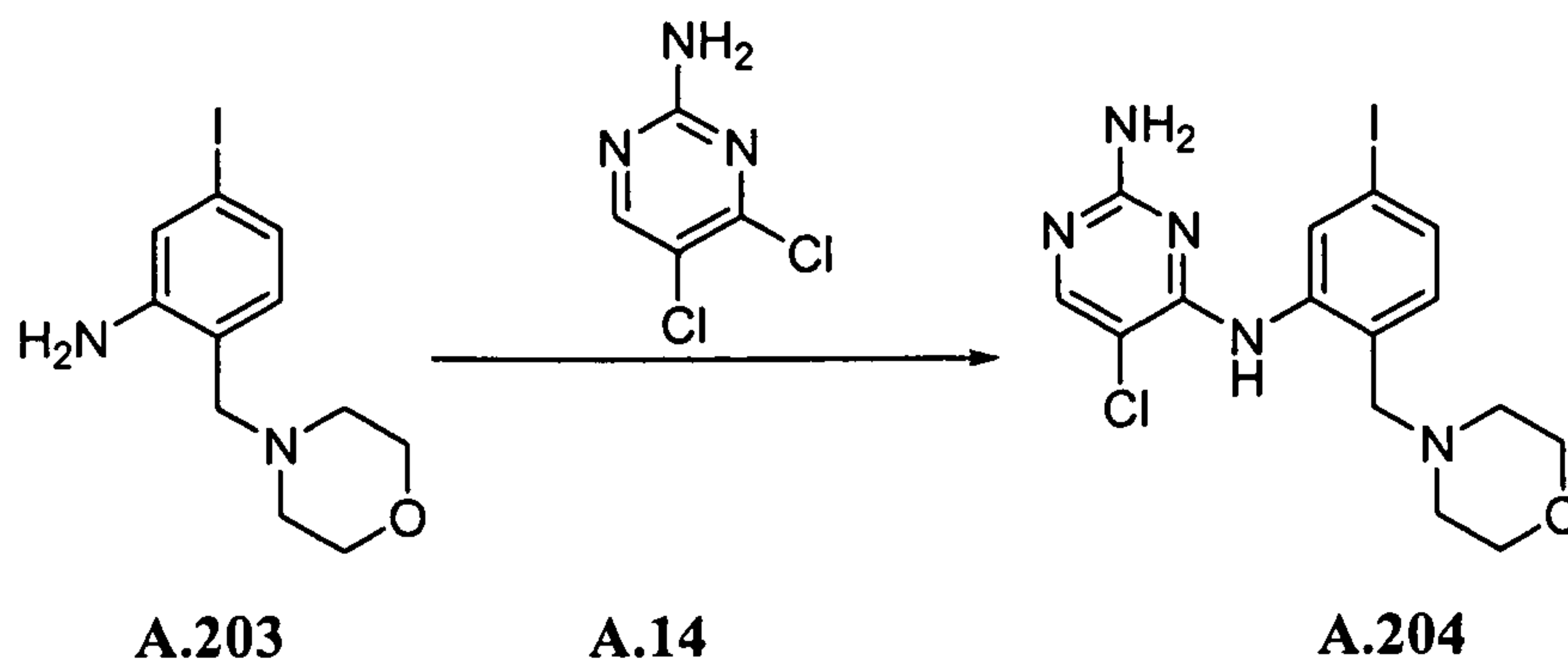


4-(4-Iodo-2-nitrobenzyl)morpholine (A.202). To a flask containing 1-(bromomethyl)-4-iodo-2-nitrobenzene (**A.201**) (1.30 g, 3.79 mmol) was added THF (20.0 mL) and morpholine (0.63 mL, 7.22 mmol). The mixture was stirred at room temperature for 37 hours then diluted with water. After extracting three times with dichloromethane, the organic solvent was removed under reduced pressure to yield **4-(4-iodo-2-nitrobenzyl)morpholine (A.202)**.

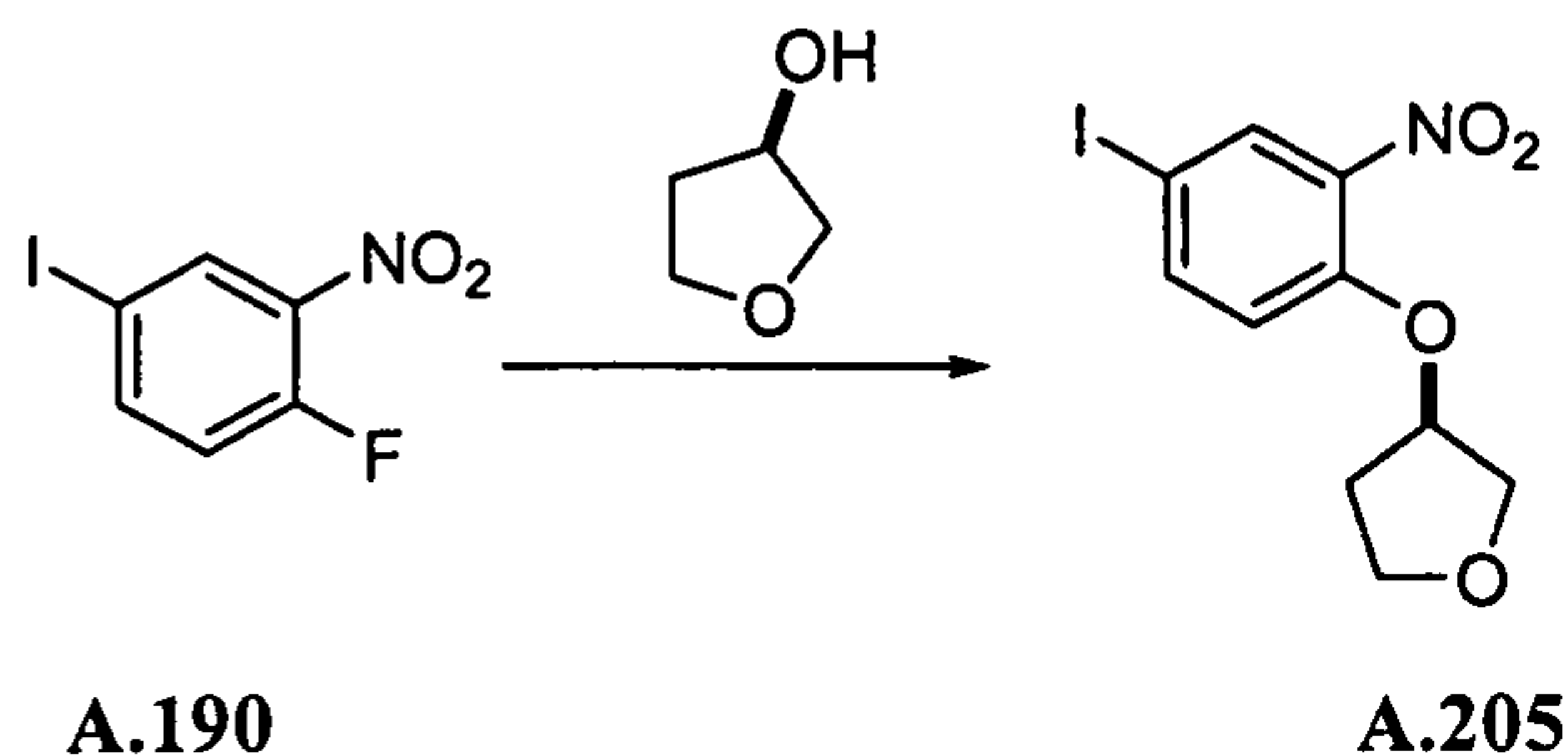


5-Iodo-2-(morpholinomethyl)benzenamine (A.203). To a flask containing 4-(4-iodo-2-nitrobenzyl)morpholine (**A.202**) (1.01 g, 2.90 mmol) and acetic acid (20.00 mL) was added iron powder (648.1 mg, 11.6 mmol). The reaction was carefully heated to 100°C . After 2 hours, the reaction was cooled to room temperature then filtered through celite. After rinsing the filter cake three times with ethyl acetate, the filtrate was washed once with brine then concentrated. The residue was purified by silica gel flash chromatography (0-100% ethyl acetate in hexanes) to afford **5-iodo-2-(morpholinomethyl)benzenamine (A.203)** (817.9 mg,

68 % for two steps.) ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 7.01 (1 H, m), 6.82 (1 H, m), 6.72 (1 H, d, $J=7.8$ Hz), 5.44 (2 H, s), 3.58 (4 H, m), 2.29 (4 H, m). MS ESI (pos.) m/e : 319.0 (M+H).

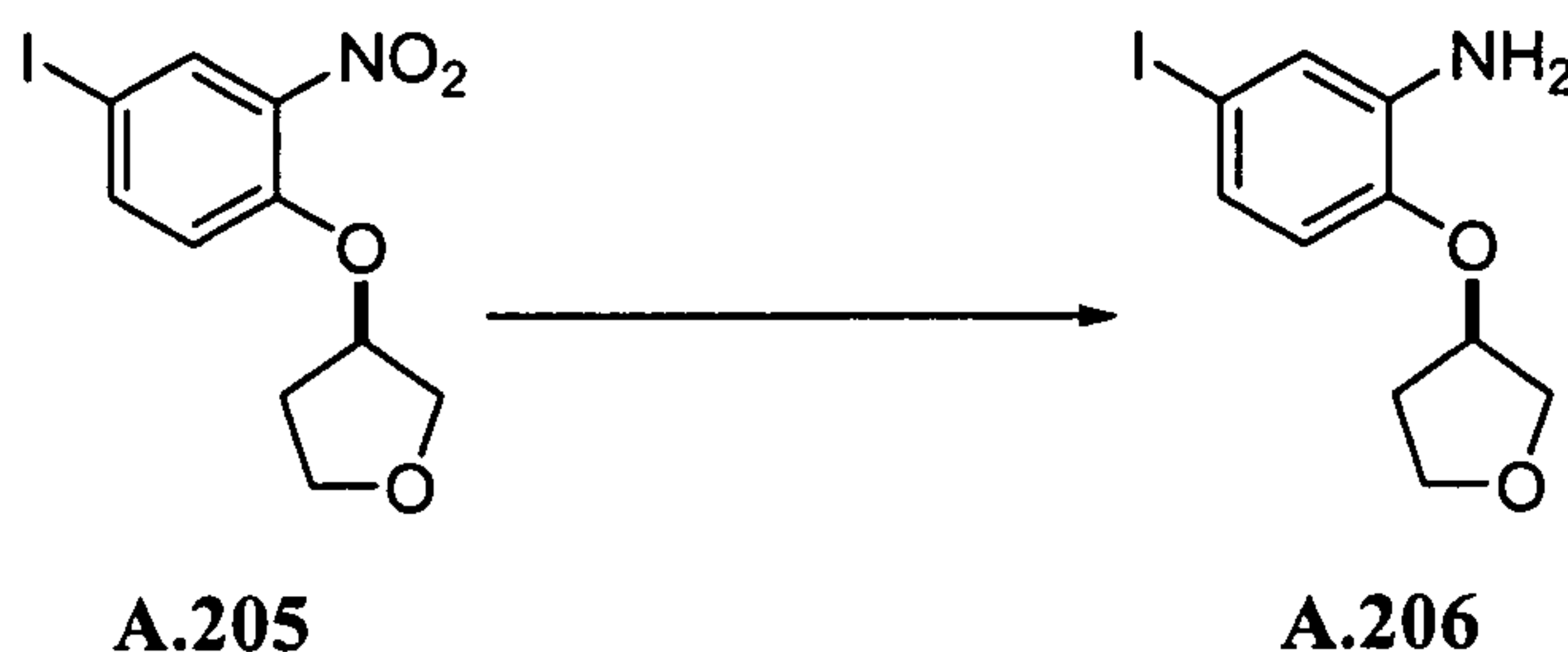


5-Chloro-*N'*-(5-iodo-2-(morpholinomethyl)phenyl)pyrimidine-2,4-diamine (A.204). To a flask containing 5-iodo-2-(morpholinomethyl)benzenamine (A.203) (817.9 mg, 2.57 mmol) in 1,4-dioxane (5.00 mL) was added 4,5-dichloropyrimidin-2-amine A.14 (842.9 mg, 5.14 mmol) and 1 N HCl (5.00 mL). The reaction was heated to 80 °C. After 8 hours, the mixture was cooled to room temperature then carefully neutralized with 1N NaOH. After extracting with dichloromethane, the solvent was removed under reduced pressure. Methanol was then added to the residue and heated to 50 °C. After 15 minutes, the solvent was removed to a volume of ~1.0 mL and cooled to room temperature. The solid was filtered and dried to yield **5-chloro-*N'*-(5-iodo-2-(morpholinomethyl)phenyl)-pyrimidine-2,4-diamine (A.204)** (502.1 mg, 44%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 9.93 (1 H, s), 8.60 (1 H, s), 7.98 (1 H, s), 7.36 (1 H, d, $J=7.8$ Hz), 7.01 (1 H, d, $J=7.8$ Hz), 6.53 (2 H, s), 3.60 (4 H, m), 3.53 (2 H, s), 2.38 (4 H, m). MS ESI (pos.) m/e : 445.9 (M+H).

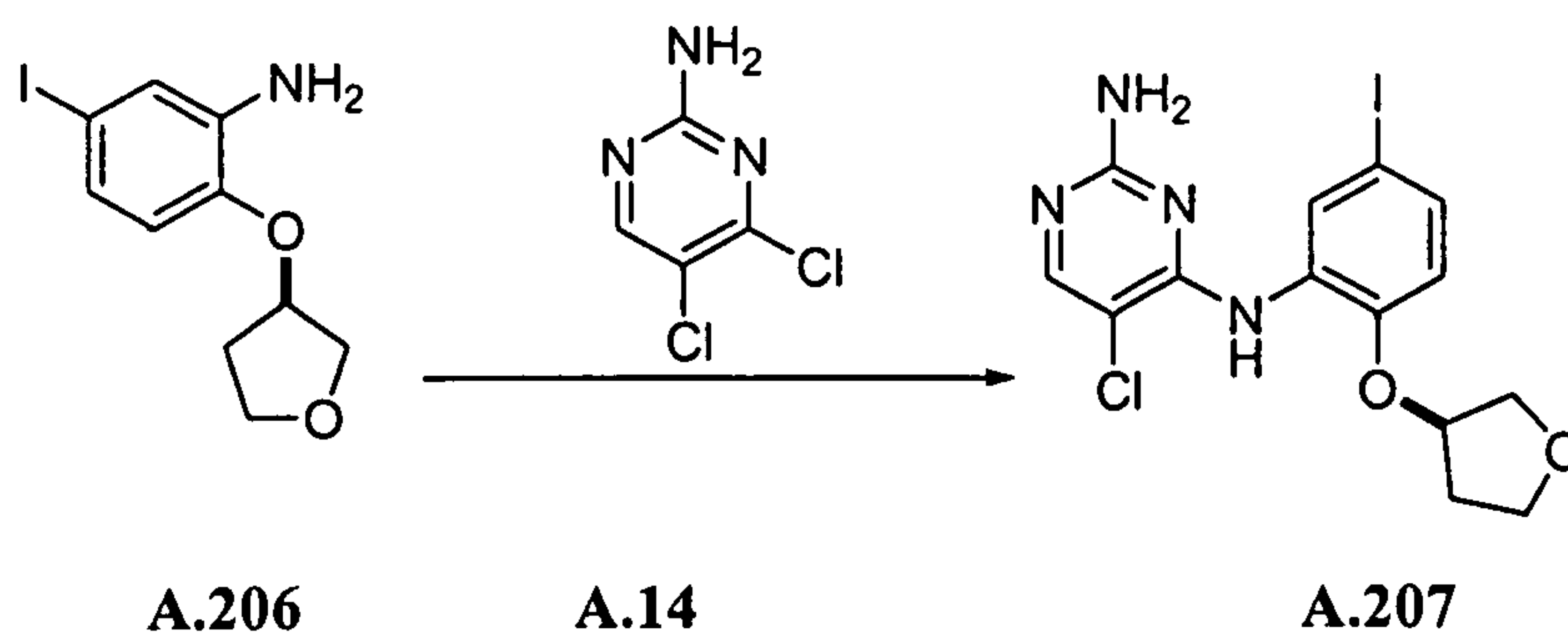


(*R*)-3-(4-Iodo-2-nitrophenoxy)-tetrahydrofuran (A.205). A dry flask containing 2(*R*)-tetrahydrofuran-3-ol (0.38 mL, 4.73 mmol) in dry DMF (10.00 mL) was cooled in an ice bath, then sodium hydride (60% wt. dispersion in oil) (189.6 mg, 4.74 mmol) was carefully added in portions. After 15 minutes, 1-fluoro-4-iodo-2-nitrobenzene A.190 (1.01 g, 3.78 mmol) was

added, and the mixture was stirred at room temperature. After 21 hours, the reaction was carefully quenched with cold water then extracted three times with ethyl acetate. After removing the organic solvent under reduced pressure, the residue was purified by silica gel flash chromatography (0-30% ethyl acetate in hexanes) to afford **(R)-3-(4-iodo-2-nitrophenoxy)-tetrahydrofuran (A.205)** (1.42 g, 89 %). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 8.18 (1 H, m), 7.94 (1 H, m), 7.18 (1 H, t, $J=9.4$ Hz), 5.24 (1 H, m), 3.91 (1 H, m), 3.81 (3 H, m), 2.27 (1 H, m), 1.99 (1 H, m).



(R)-5-Iodo-2-(tetrahydrofuran-3-yloxy)benzenamine (A.206). To a flask containing **(R)-3-(4-iodo-2-nitrophenoxy)-tetrahydrofuran (A.205)** (1.42 g, 4.22 mmol) and acetic acid (15.00 mL) was added iron powder (941.8 mg, 16.9 mmol). The reaction was carefully heated to 100 °C. After 1.5 hours, the reaction was cooled to room temperature then filtered through celite. After rinsing the filter cake three times with ethanol, the organic solvent was removed under reduced pressure to afford **(R)-5-iodo-2-(tetrahydrofuran-3-yloxy)benzenamine (A.206)** (501.9 mg, 39%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 6.94 (1 H, d, $J=2.2$ Hz), 6.76 (1 H, dd, $J=8.3, 2.2$ Hz), 6.55 (1 H, d, $J=8.3$ Hz), 4.93 (3 H, m), 3.88 (2 H, m), 3.80 (2 H, m), 2.19 (1 H, m), 2.01 (1 H, m). MS ESI (pos.) m/e : 306.0 ($\text{M}+\text{H}$).

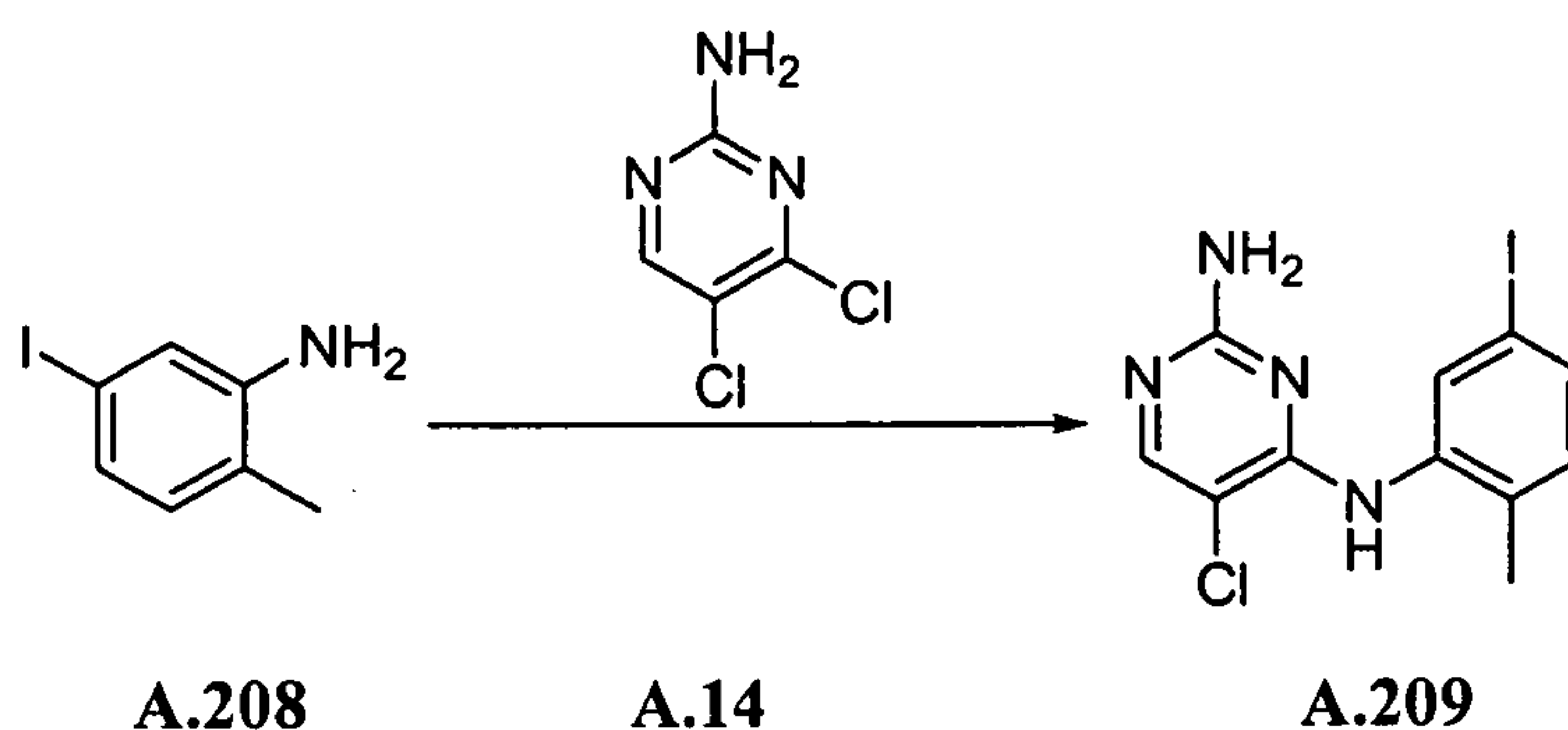


(R)-5-Chloro-*N'*-(5-iodo-2-(tetrahydrofuran-3-yloxy)phenyl)pyrimidine-2,4-diamine (A.207). To a flask containing **(R)-5-iodo-2-(tetrahydrofuran-3-yloxy)benzenamine (A.206)** (501.9 mg, 1.64 mmol) in 1,4-dioxane (5.00 mL) was added 4,5-dichloropyrimidin-2-amine

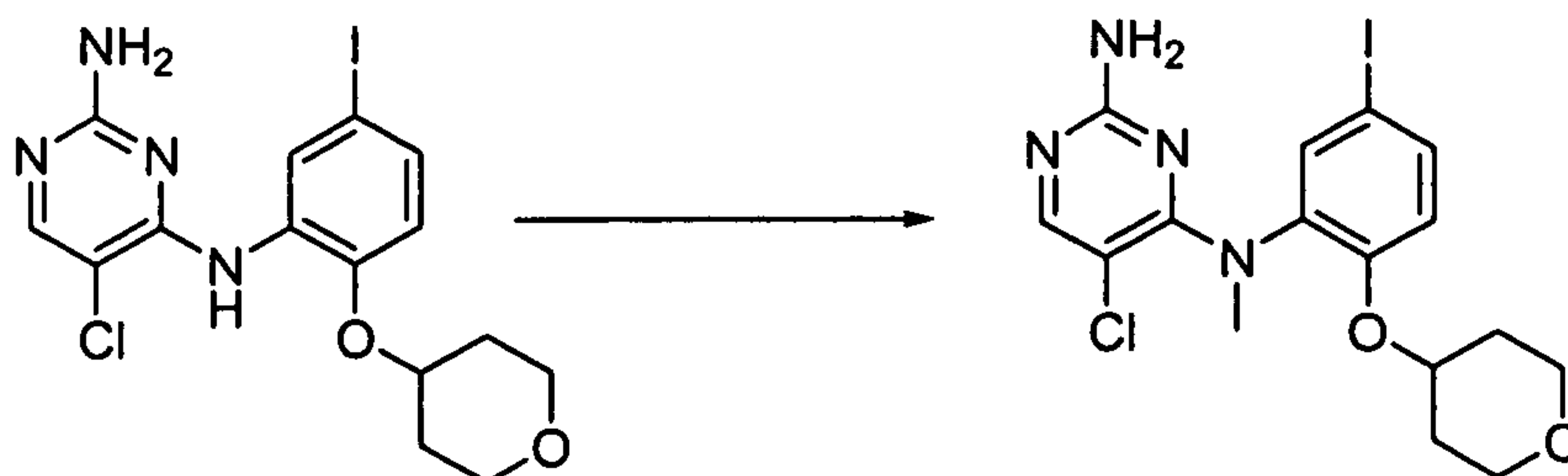
(A.14)(539.8 mg, 3.29 mmol) and 1 N HCl (5.00 mL). The reaction was heated to 80 °C.

After 19 hours, the mixture was cooled to room temperature then carefully neutralized with 1N NaOH. After extracting with ethyl acetate, the solvent was removed under reduced pressure.

Methanol was then added to the residue and heated to 50 °C. After 15 minutes, the solvent was removed to a volume of ~1.0 mL and cooled to room temperature. The solid was filtered and dried to yield (*R*)-5-chloro-*N*⁴-(5-iodo-2-(tetrahydrofuran-3-yloxy)phenyl)pyrimidine-2,4-diamine (A.207) (492.3 mg, 69 %). ¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 8.61 (1 H, s), 7.98 (1 H, s), 7.89 (1 H, s), 7.38 (1 H, d, *J*=2.0 Hz), 6.91 (1 H, d, *J*=8.6 Hz), 6.62 (2 H, s), 5.12 (1 H, s), 3.89 (1 H, s), 3.84 (3 H, m), (1 H, m), 2.01 (1 H, m). MS ESI (pos.) *m/e*: 433.0 (M+H).



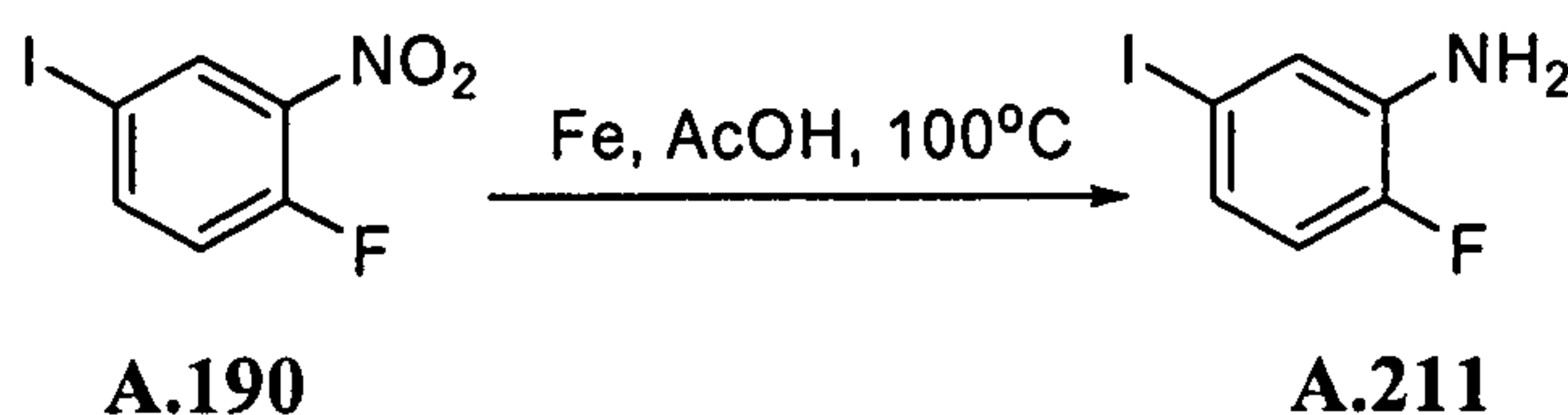
5-Chloro-*N*⁴-(5-iodo-2-methylphenyl)pyrimidine-2,4-diamine (A.209). To a flask containing 5-iodo-2-methylbenzenamine (A.208) (500.6 mg, 2.15 mmol) in 1,4-dioxane (5.00 mL) was added 4,5-dichloropyrimidin-2-amine (A.14) (704.7 mg, 4.30 mmol) and 1 N HCl (5.00 mL). The reaction was heated to 80 °C. After 8 hours, the mixture was cooled to room temperature then carefully neutralized with 1N NaOH. After extracting with ethyl acetate, the solvent was removed under reduced pressure. Isopropanol was then added to the residue and heated to 50 °C. After 15 minutes, the solvent was removed to a volume of ~1.0 mL and cooled to room temperature. The solid was filtered and dried to yield 5-chloro-*N*⁴-(5-iodo-2-methylphenyl)pyrimidine-2,4-diamine (A.209). (352.3 mg, 45%). ¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 8.34 (1 H, s), 7.87 (1 H, m), 7.63 (1 H, d, *J*=1.7 Hz), 7.48 (1 H, dd, *J*=7.9, 1.8 Hz), 7.06 (1 H, d, *J*=8.1 Hz), 6.26 (2 H, s), 2.10 (3 H, s). MS ESI (pos.) *m/e*: 360.9 (M+H).



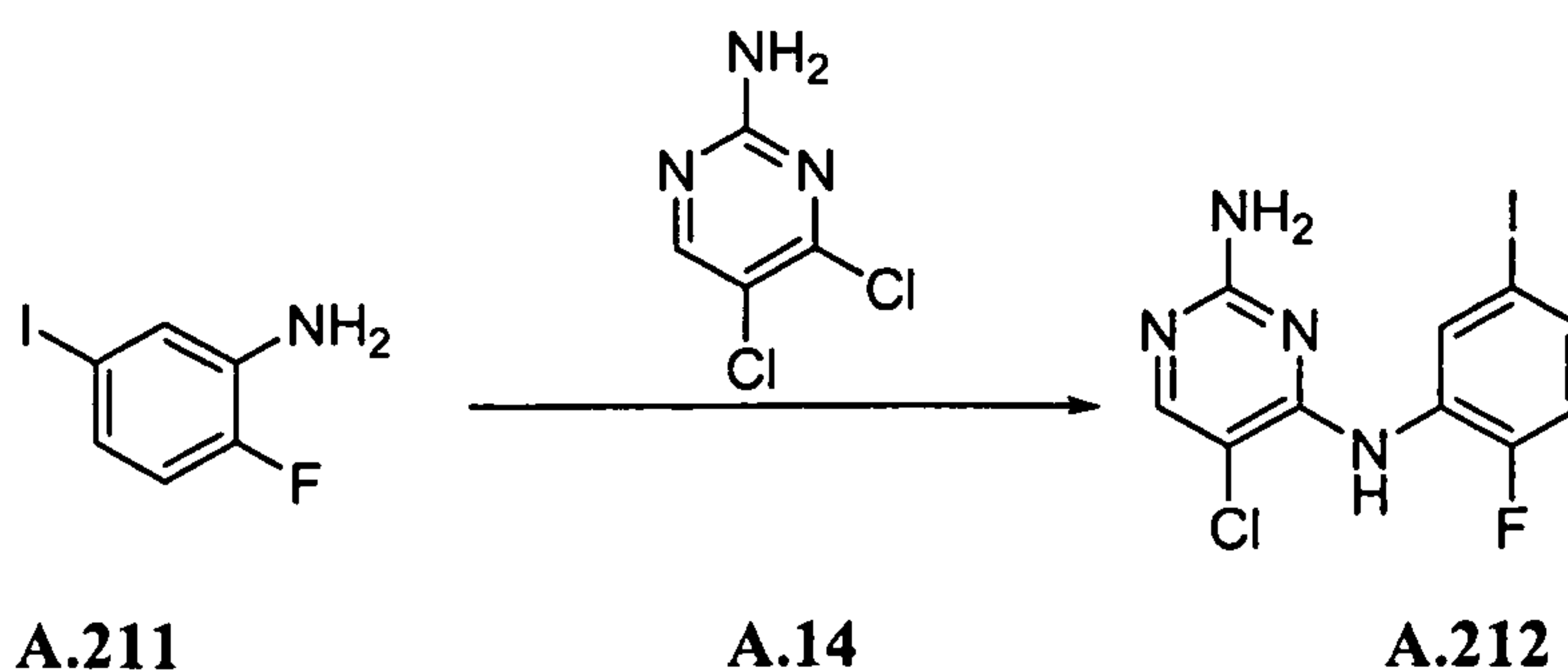
A.193

A.210

5-Chloro-*N*⁴-(5-iodo-2-(tetrahydro-2H-pyran-4-yloxy)phenyl)-*N*⁴-methylpyrimidine-2,4-diamine (A.210). A dry flask containing 5-chloro-*N*⁴-(5-iodo-2-(tetrahydro-2H-pyran-4-yloxy)phenyl)pyrimidine-2,4-diamine (A.193) (447.2 mg, 1.0 mmol) in dry DMF (8.00 mL) was cooled in an ice bath, then sodium hydride (60% wt. dispersion in oil) (40.9 mg, 1.02 mmol) was carefully added in portions. After 15 minutes, methyl iodide (0.056 mL, 0.90 mmol) was added, and the mixture was stirred at room temperature. After 1 hour, the reaction was carefully quenched with cold water then extracted three times with ethyl acetate. After concentration, the residue was purified by silica gel flash chromatography (50:1: 1 solution of dichloromethane: methanol: 2M ammonia in methanol) to afford **5-chloro-*N*⁴-(5-iodo-2-(tetrahydro-2H-pyran-4-yloxy)phenyl)-*N*⁴-methylpyrimidine-2,4-diamine (A.210)** (268.6 mg, 58.3%). MS ESI (pos.) *m/e*: 461.0 (M+H).

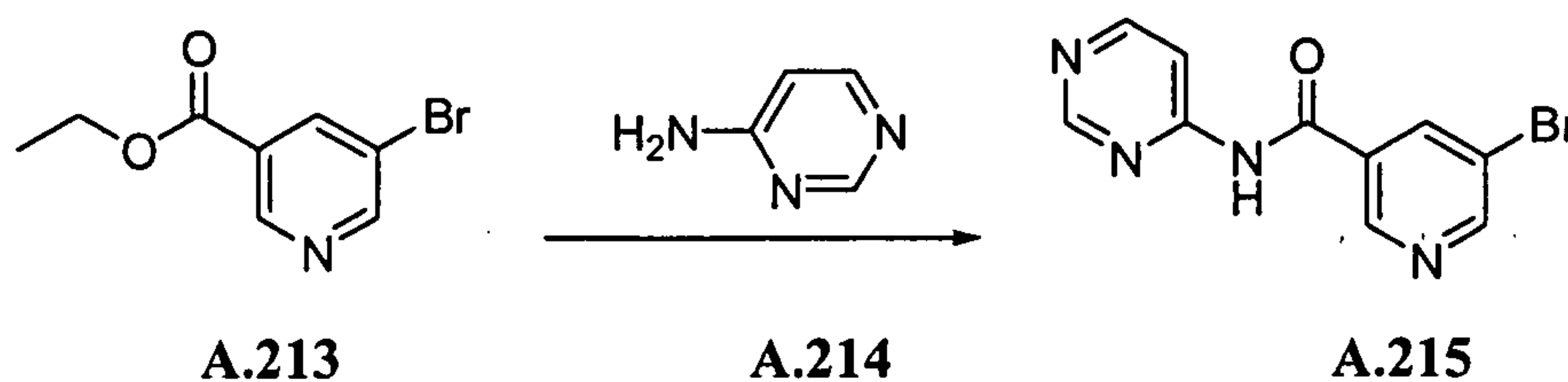


2-Fluoro-5-iodobenzanamine (A.211). To a flask containing 1-fluoro-4-iodo-2-nitrobenzene A.190 (717.1 mg, 2.69 mmol) and acetic acid (10.00 mL) was added iron powder (600.3 mg, 10.7 mmol). The reaction was carefully heated to 100 °C. After 1 hour, the reaction was cooled to room temperature then filtered through celite. After rinsing the filter cake three times with ethanol, the organic solvent was removed under reduced pressure to afford **2-fluoro-5-iodobenzanamine (A.211)** (609.7 mg, 96%). ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.10 (1 H, m), 6.80 (2 H, m), 5.35 (2 H, s). MS ESI (pos.) *m/e*: 237.9 (M+H).

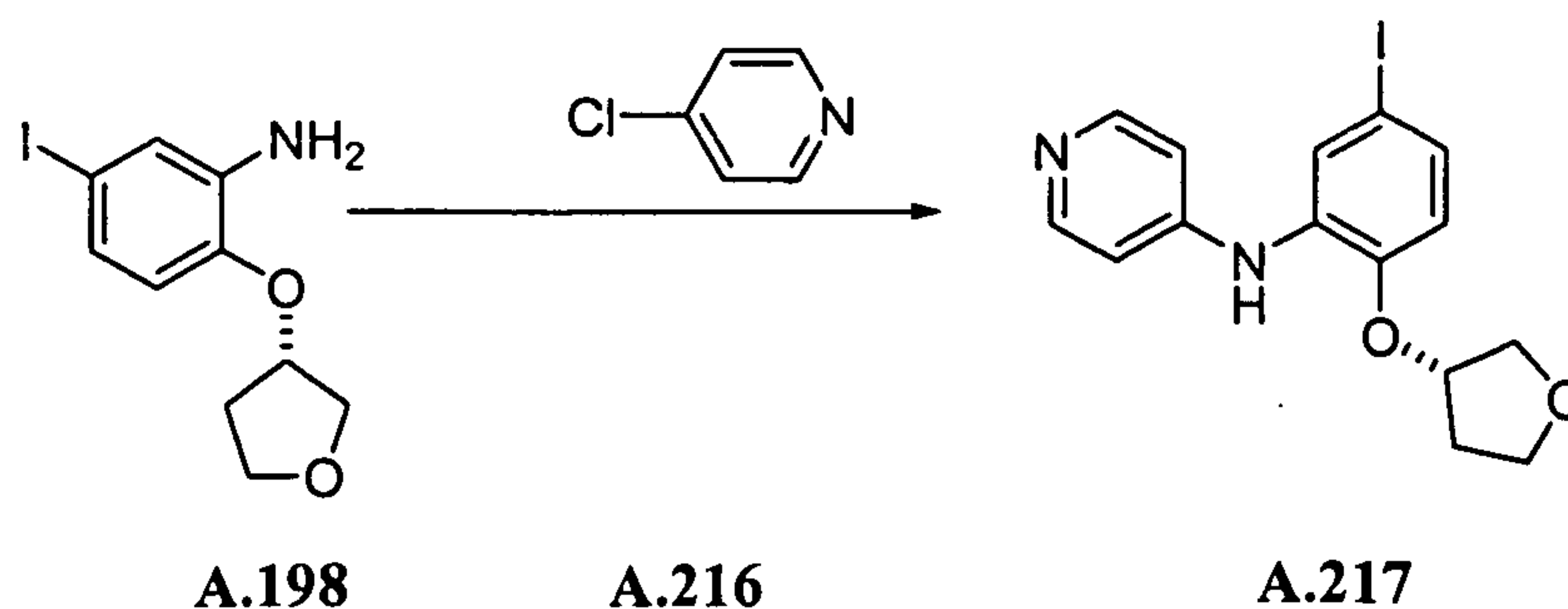


5-Chloro-*N*⁴-(2-fluoro-5-iodophenyl)pyrimidine-2,4-diamine (A.212). To a flask containing 2-fluoro-5-iodobenzanamine (A.211) (609.7 mg, 2.57 mmol) in 1,4-dioxane (5.00 mL) was added 4,5-dichloropyrimidin-2-amine (A.14) (844.0 mg, 5.15 mmol) and 1 N HCl

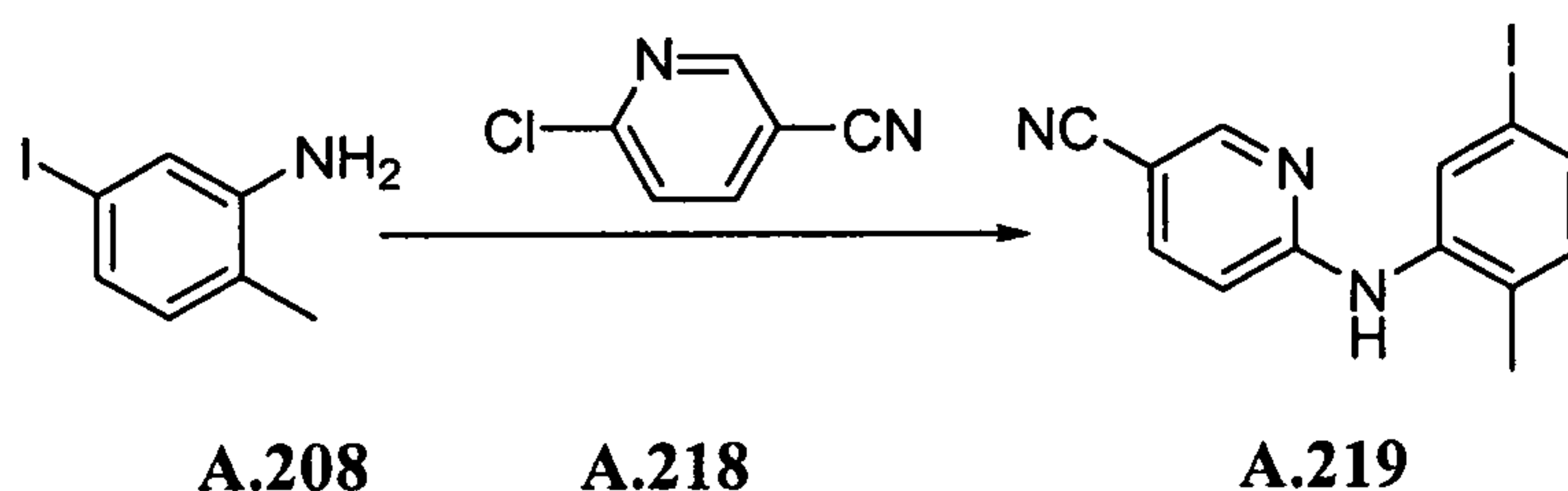
(5.00 mL). The reaction was heated to 80 °C. After 3 hours, the mixture was cooled to room temperature then carefully neutralized with 1N NaOH. After extracting with dichloromethane, the solvent was removed under reduced pressure. Ethyl acetate was then added to the residue and heated to 50 °C. After 15 minutes, the solvent was removed to a volume of ~1.0 mL and cooled to room temperature. The solid was filtered and dried to yield **5-chloro-*N*'-(2-fluoro-5-iodophenyl)pyrimidine-2,4-diamine (A.212)** (402.8 mg, 43 %). ¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 8.45 (1 H, s), 7.92 (1 H, m), 7.86 (1 H, dd, *J*=7.1, 2.2 Hz), 7.56 (1 H, ddd, *J*=8.5, 4.5, 2.2 Hz), 7.10 (1 H, dd, *J*=10.6, 8.7 Hz), 6.35 (2 H, s). MS ESI (pos.) *m/e*: 364.9 (*M*+*H*).



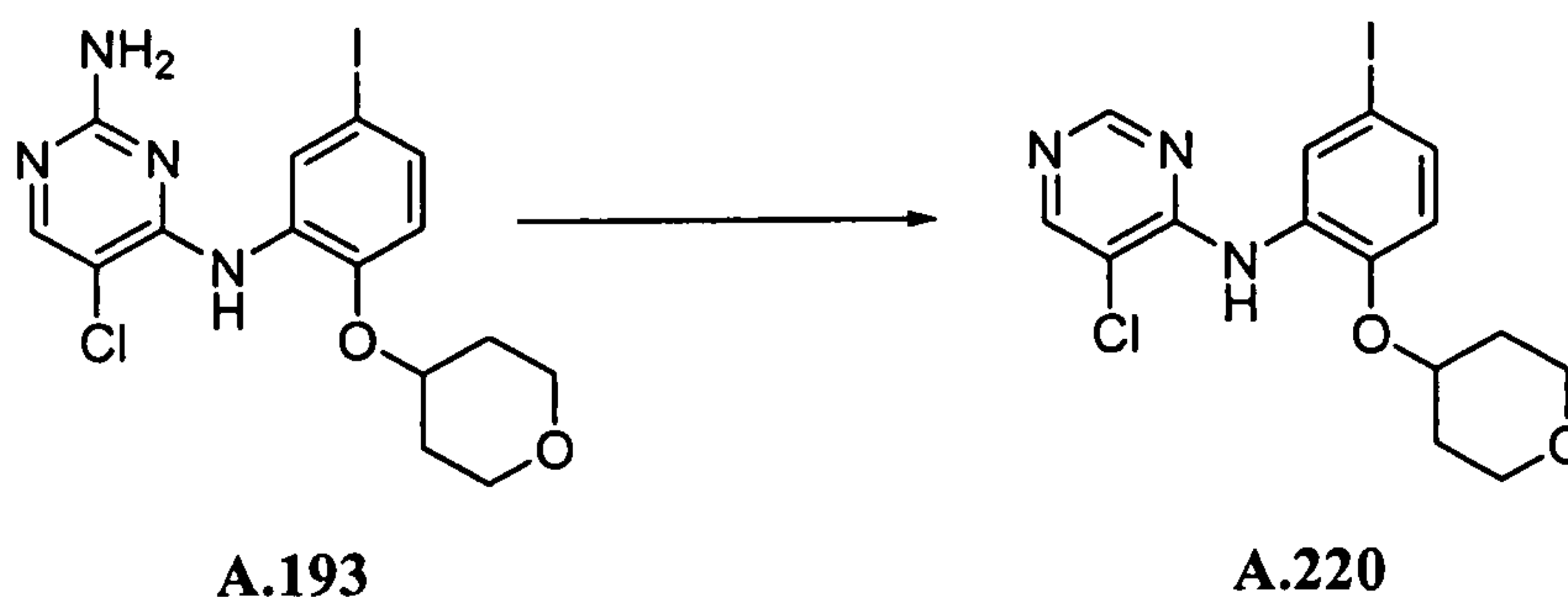
5-Bromo-*N*-(pyrimidin-4-yl)nicotinamide (A.215). A dry flask containing pyrimidin-4-amine **A.214** (208.9 mg, 2.2 mmol) in dry DMF (8.00 mL) was cooled in an ice bath, then potassium *tert*-butoxide (370.2 mg, 3.3 mmol) was carefully added in portions. After 15 minutes, ethyl 5-bromonicotinate **A.213** (759.7 mg, 3.3 mmol) was added, and the mixture was heated to 50 °C. After 1 hour, the reaction was carefully quenched with cold water then extracted three times with dichloromethane. After concentrating under reduced pressure, isopropanol was added to the residue and heated to 50 °C. After 15 minutes, the solvent was removed to a volume of ~1.0 mL and cooled to room temperature. The solid was filtered and dried to yield **5-bromo-*N*-(pyrimidin-4-yl)nicotinamide (A.215)** (200 mg, 33 %). ¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 11.57 (1 H, s), 9.08 (1 H, d, *J*=2.0 Hz), 8.98 (1 H, s), 8.93 (1 H, d, *J*=2.2 Hz), 8.76 (1 H, d, *J*=5.6 Hz), 8.60 (1 H, t, *J*=2.1 Hz), 8.19 (1 H, d, *J*=5.9 Hz). MS ESI (pos.) *m/e*: 279.0 (*M*+*H*).



(S)-N-(5-iodo-2-(tetrahydrofuran-3-yloxy)phenyl)pyridin-4-amine (A.217). To a flask containing (S)-5-iodo-2-(tetrahydrofuran-3-yloxy)benzenamine (A.198) (396.9 mg, 1.30 mmol) in pentanol (8.00 mL) was added 4-chloropyridine (A.216) (390.8 mg, 2.6 mmol). The reaction was heated to 140 °C. After 17 hours, the mixture was cooled to room temperature then carefully neutralized with 1N NaOH. After extracting with dichloromethane, the residue was purified by silica gel flash chromatography (30:1:1 solution of dichloromethane: methanol: 2M ammonia in methanol) to afford (S)-N-(5-iodo-2-(tetrahydrofuran-3-yloxy)phenyl)pyridin-4-amine (A.217) (298.6 mg, 60%). ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.15 (3 H, d, *J*=3.7 Hz), 7.51 (1 H, d, *J*=2.0 Hz), 7.39 (1 H, dd, *J*=8.6, 2.0 Hz), 6.88 (1 H, d, *J*=8.6 Hz), 6.73 (2 H, d, *J*=6.1 Hz), 4.99 (1 H, t, *J*=5.3 Hz), 3.86 (1 H, dd, *J*=10.0, 4.6 Hz), 3.74 (3 H, m), 2.19 (1 H, m), 1.94 (1 H, m). MS ESI (pos.) *m/e*: 382.9 (M+H).

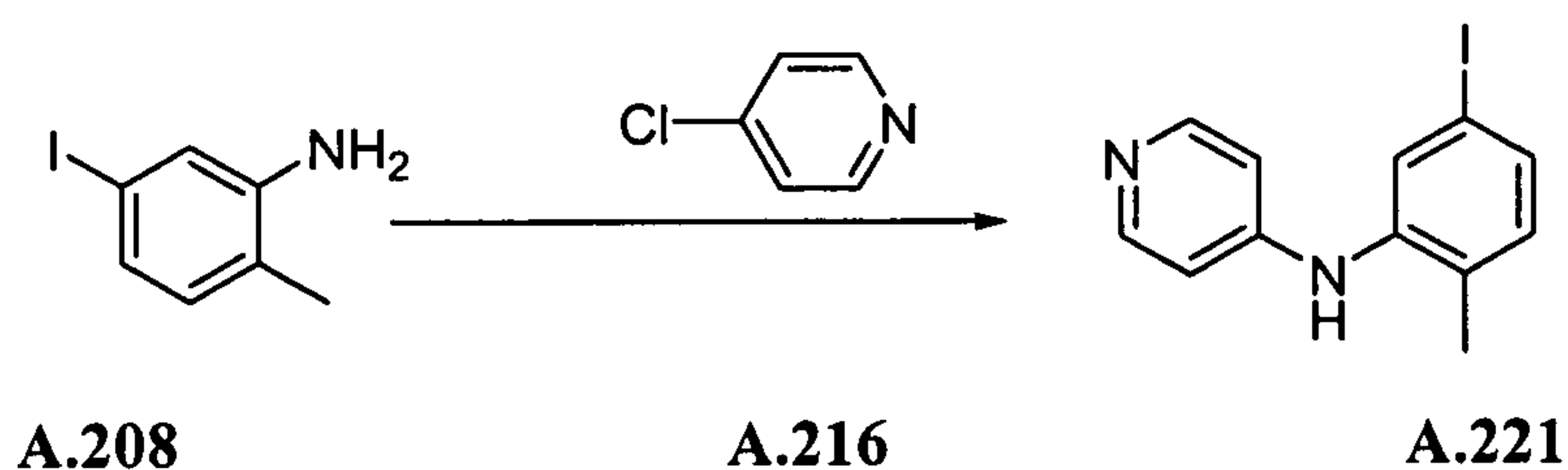


6-(5-Iodo-2-methylphenylamino)nicotinonitrile (A.219). To a flask containing 5-iodo-2-methylbenzenamine (A.208) (1.01 g, 4.32 mmol) in pentanol (16.00 mL) was added 6-chloronicotinonitrile (A.218) (1.20 g, 8.64 mmol) and 1 drop of concentrated hydrochloric acid. The reaction was heated to 140 °C. After 37 hours, the mixture was cooled to room temperature then carefully neutralized with 1N NaOH. After extracting with dichloromethane, the residue was purified by silica gel flash chromatography (3:1 hexanes: ethyl acetate) to afford 6-(5-iodo-2-methylphenylamino)nicotinonitrile (A.219) (907.8 mg, 63%). ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 9.13 (1 H, s), 8.49 (1 H, s), 7.82 - 7.90 (2 H, m), 7.45 (1 H, d, *J*=7.8 Hz), 7.07 (1 H, d, *J*=7.8 Hz), 6.81 (1 H, d, *J*=8.8 Hz), 2.16 (3 H, s). MS ESI (pos.) *m/e*: 336.0 (M+H).

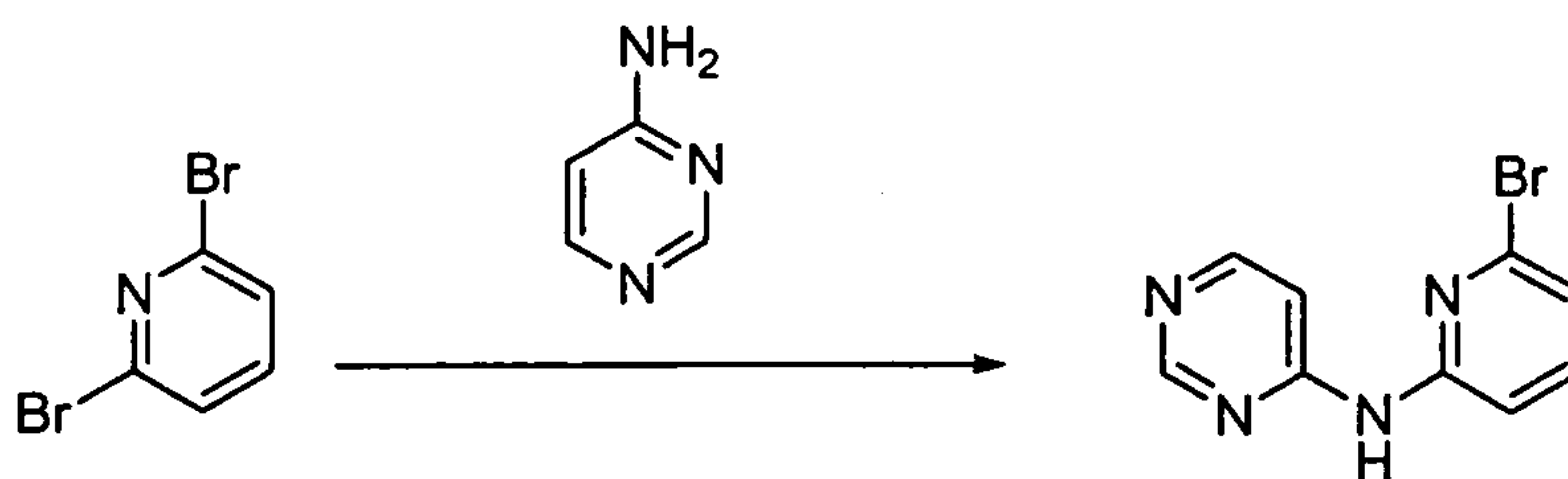


5-Chloro-*N*-(5-iodo-2-(tetrahydro-2H-pyran-4-yloxy)phenyl)pyrimidin-4-amine (A.220).

To a flask containing 5-chloro-*N*-(5-iodo-2-(tetrahydro-2H-pyran-4-yloxy)phenyl)pyrimidine-2,4-diamine (A.193) (500.2 mg, 1.12 mmol) in THF (5.00 mL) was added isoamyl nitrite (0.7 mL, 5.23 mmol) dropwise over 5 minutes. The reaction was heated to 70 °C. After 8 hours, the mixture was cooled to room temperature then carefully poured into ice water. After extracting with dichloromethane, the residue was concentrated then purified by silica gel flash chromatography (2:1 dichloromethane: ethyl acetate) to afford 5-chloro-*N*-(5-iodo-2-(tetrahydro-2H-pyran-4-yloxy)phenyl)pyrimidin-4-amine (A.220) (126.4 mg, 26%). ¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 8.60 (1 H, s), 8.54 (1 H, s), 8.44 (2 H, s), 7.45 (1 H, dd, *J*=8.6, 2.2 Hz), 7.04 (1 H, d, *J*=8.6 Hz), 4.68 (1 H, ddd, *J*=7.7, 3.8, 3.7 Hz), 3.79 (2 H, m), 3.48 (2 H, ddd, *J*=11.4, 8.1, 3.2 Hz), 1.99 (2 H, m), 1.62 (2 H, m). MS ESI (pos.) *m/e*: 432.1 (M+H).

**5-Chloro-*N*-(5-iodo-2-(tetrahydro-2H-pyran-4-yloxy)phenyl)pyrimidin-4-amine (A.221).**

To a flask containing 5-iodo-2-methylaniline (A.208) (502.8 mg, 2.16 mmol) in pentanol (10.00 mL) was added 4-chloropyridine (A.216) (647.5 mg, 4.32 mmol). The reaction was heated to 140 °C. After 4.5 days, the mixture was cooled to room temperature then filtered. The filtrate was concentrated then purified by silica gel flash chromatography (30:1:1 solution of dichloromethane: methanol: 2M ammonia in methanol) to afford *N*-(5-iodo-2-methylphenyl)pyridin-4-amine (A.221) (499 mg, 74%). ¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 8.36 (1 H, s), 8.18 (2 H, m), 7.53 (1 H, d, *J*=1.7 Hz), 7.44 (1 H, dd, *J*=7.8, 1.7 Hz), 7.09 (1 H, d, *J*=7.8 Hz), 6.64 (2 H, dd, *J*=4.8, 1.6 Hz), 2.13 (3 H, s).



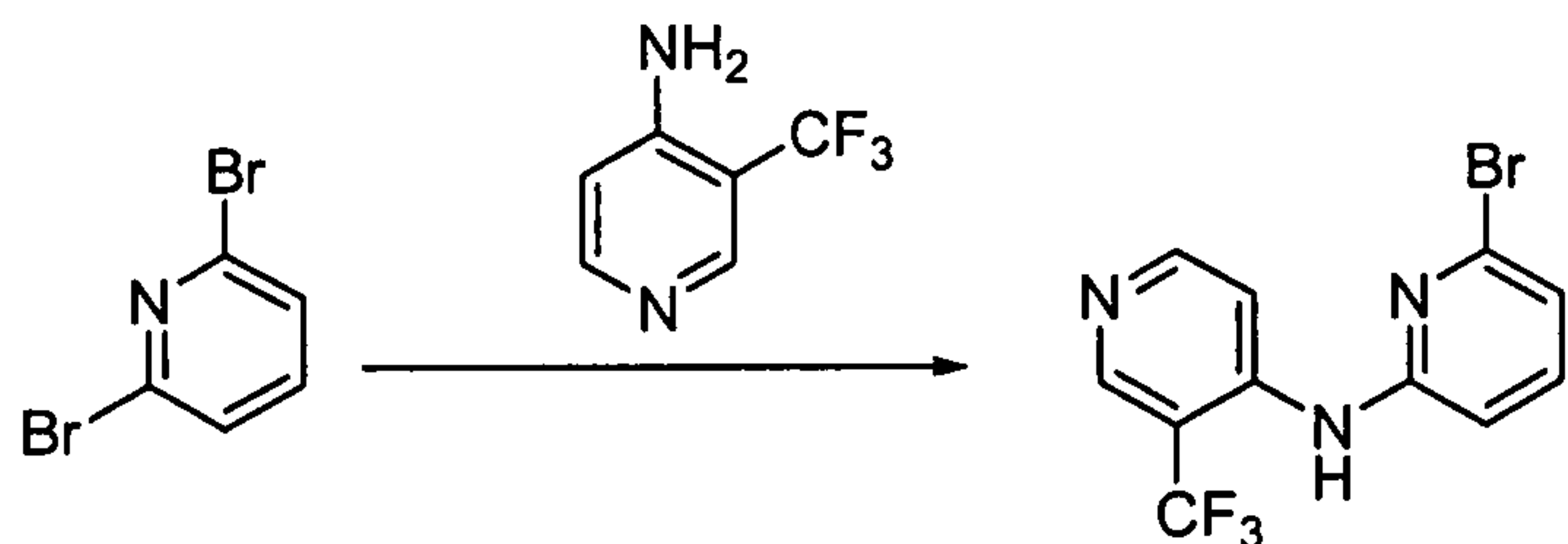
A.222

A.214

A.223

5-Chloro-N-(5-iodo-2-(tetrahydro-2H-pyran-4-yloxy)phenyl)pyrimidin-4-amine (A.223).

To a dry flask was added 2,6-dibromopyridine (A.222)(1.04 g, 4.41 mmol), pyrimidin-4-amine (A.214)(419.1 mg, 4.41 mmol), Pd₂(dba)₃ (80.9 mg, 0.083 mmol), Xantphos (153.3 mg, 0.27 mmol), cesium carbonate (2.01 g, 6.17 mmol), and dry dioxane (15.0 mL). After evacuating and backfilling with argon, the mixture was heated to 80 °C. After 18 hours, the reaction was cooled to room temperature then filtered through celite. After rinsing the celite three times with THF, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (100 % ethyl acetate) to afford *N*-(6-bromopyridin-2-yl)pyrimidin-4-amine (A.223) 510.7 mg, 46%). MS ESI (pos.) m/e: 251.0 (M+H).



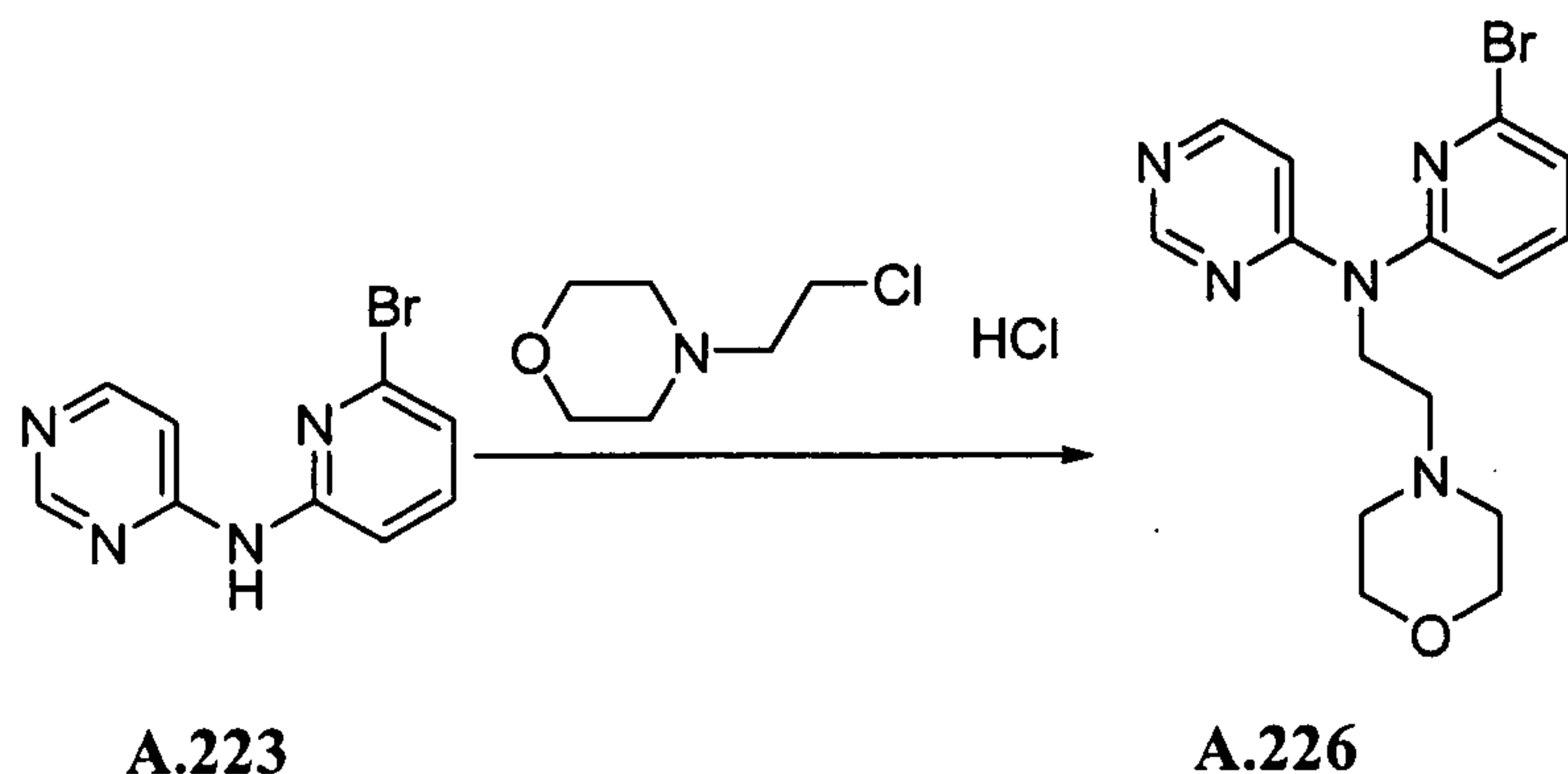
A.222

A.224

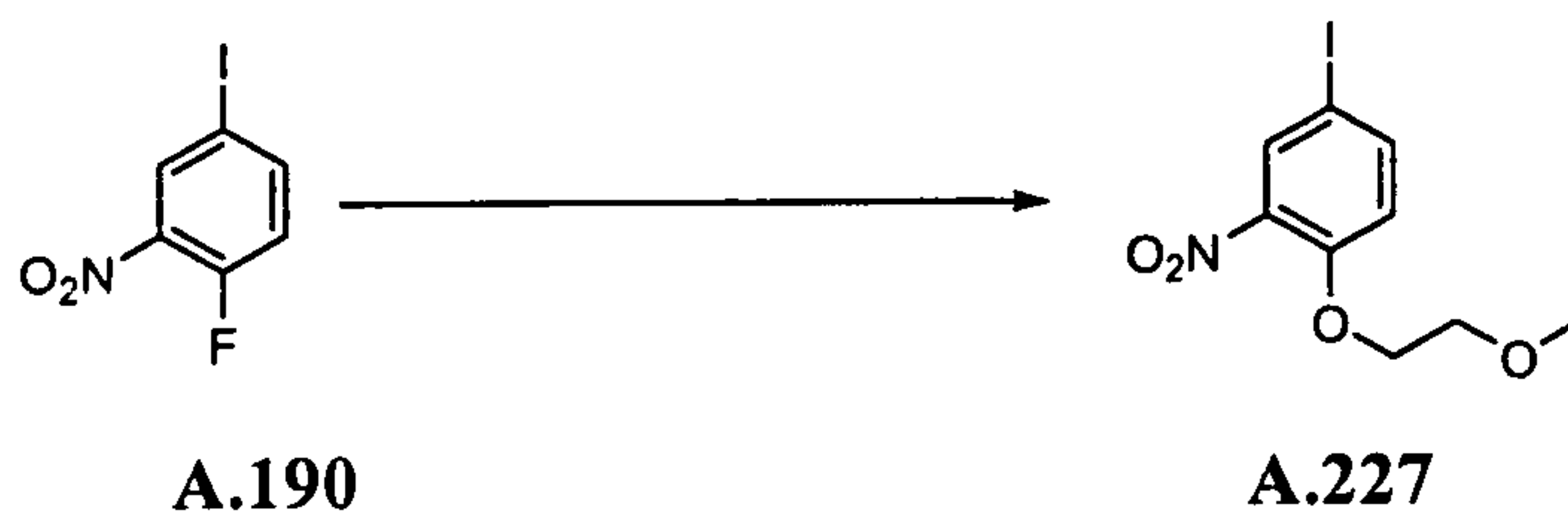
A.225

6-Bromo-N-(3-(trifluoromethyl)pyridin-4-yl)pyridin-2-amine (A.225). To a dry flask was added 2,6-dibromopyridine (A.222)(882.2 mg, 3.72 mmol), 3-(trifluoromethyl)pyridin-4-amine (A.224)(503.0 mg, 3.1 mmol), Pd₂(dba)₃ (57.7 mg, 0.063 mmol), Xantphos (108.4 mg, 0.19 mmol), cesium carbonate (1.41 g, 6.17 mmol), and dry dioxane (8 mL). After evacuating and backfilling with argon, the mixture was heated to 80 °C. After 19 hours, the reaction was cooled to room temperature then filtered through celite. After rinsing the celite three times with THF, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (80 % ethyl acetate in hexanes) to afford 6-bromo-N-(3-(trifluoromethyl)pyridin-4-yl)pyridin-2-amine (A.225) (708.9 mg, 72%). ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.88 (1 H, s), 8.74 (1 H, s), 8.61 (1 H, d, *J*=5.6 Hz), 7.96 (1 H, d,

$J=5.9$ Hz), 7.67 (1 H, t, $J=7.8$ Hz), 7.29 (1 H, d, $J=8.1$ Hz), 7.23 (1 H, d, $J=7.6$ Hz). MS ESI (pos.) m/e : 318.0 ($M+H$).



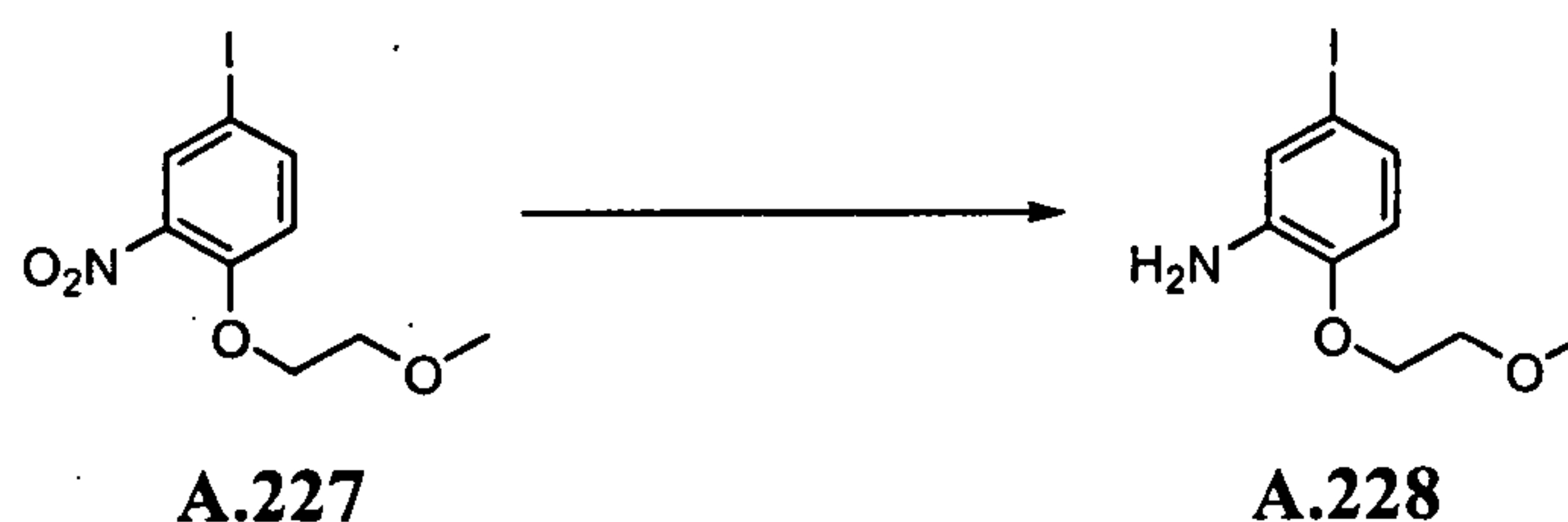
***N*-(6-bromopyridin-2-yl)-*N*-(2-morpholinoethyl)pyrimidin-4-amine (A.226).** A dry flask containing *N*-(6-bromopyridin-2-yl)pyrimidin-4-amine (A.223) (311.3 mL, 1.24 mmol) in dry DMF (4.00 mL) was cooled in an ice bath, then sodium hydride (60% wt. dispersion in oil) (61.1 mg, 1.53 mmol) was carefully added in portions. After 15 minutes, 4-(2-chloroethyl)morpholine hydrochloride in dichloromethane: pyridine (3:1) (277.4 mg, 1.49 mmol) was added dropwise, and the mixture was heated to 80 °C. After 21 hours, the reaction was carefully quenched with cold water then extracted three times with dichloromethane. After removing the organic solvent under reduced pressure, the residue was purified by silica gel flash chromatography (35:1:1 solution of dichloromethane: methanol: 2M ammonia in methanol) to afford *N*-(6-bromopyridin-2-yl)-*N*-(2-morpholinoethyl)pyrimidin-4-amine (A.226) (168.9 mg, 37%). ¹H NMR (500 MHz, *MeOH*) δ ppm 8.68 (1 H, s), 8.25 (1 H, d, $J=6.4$ Hz), 7.71 (1 H, t, $J=7.8$ Hz), 7.48 (2 H, m), 6.99 (1 H, dd, $J=6.2, 1.3$ Hz), 4.35 (2 H, t, $J=6.6$ Hz), 3.56 (4 H, m), 2.69 (2 H, t, $J=6.7$ Hz), 2.47 (4 H, m). MS ESI (pos.) m/e : 364.0 ($M+H$).



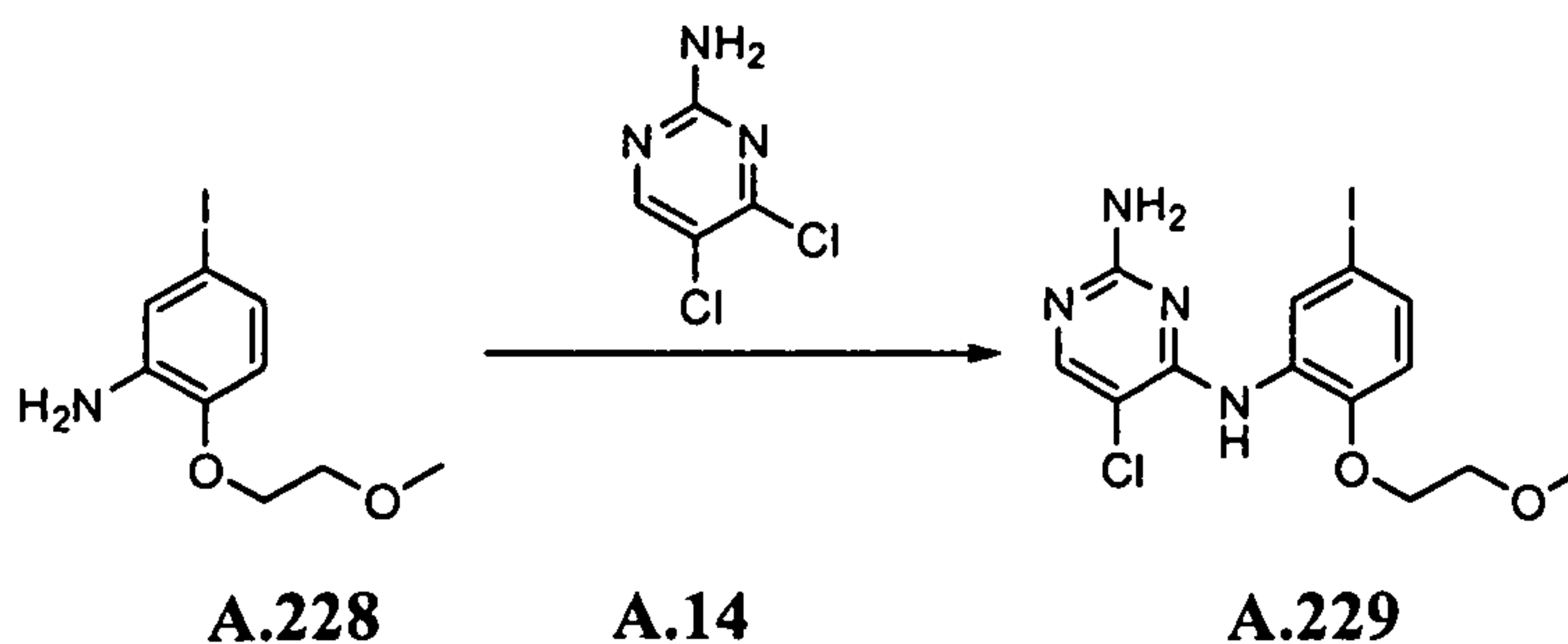
4-iodo-1-(2-methoxyethoxy)-2-nitrobenzene (A.227)

To a solution of 2-methoxyethanol (1.93 mL, 24.4 mmol) in DMF (24 mL) was added NaH (60% dispersion in mineral oil, 0.5865 g, 24.4 mmol) and the mixture was stirred at 0 °C for 1.5 hours. To the mixture was added a solution of 1-fluoro-4-iodo-2-nitrobenzene A.190 (5 g,

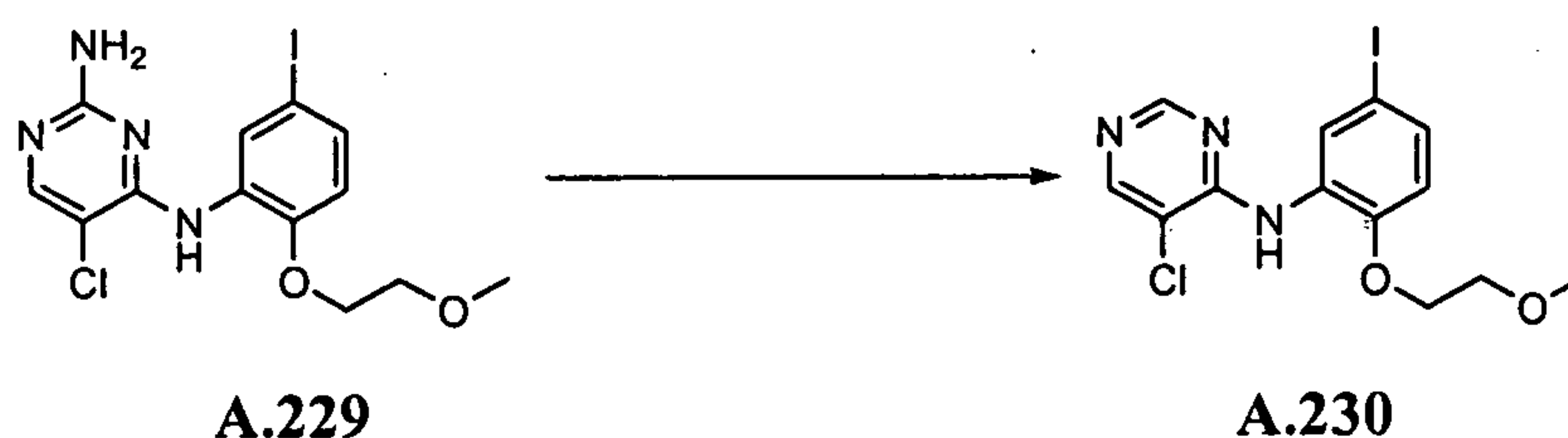
18.8 mmol) in DMF (6 mL) at 0 °C and the mixture was allowed to warm to room temperature with stirring. After stirring at room temperature for 21 hours, the mixture was poured into ice water (200 mL) and extracted with dichloromethane (100 mL x 3). The combined organic layers were washed with brine (150 mL x 1), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give an orange oil. The product was purified by silica gel column chromatography using 0% to 50% gradient of ethyl acetate in hexane as eluent to give 4-iodo-1-(2-methoxyethoxy)-2-nitrobenzene (**A.227**) (4.67 g, 77.2% yield) as an orange oil: ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.16 (1 H, d, *J*=2.2 Hz), 7.94 (1 H, dd, *J*=8.9, 2.3 Hz), 7.21 (1 H, d, *J*=8.8 Hz), 4.27 (2 H, dd, *J*=5.3, 3.8 Hz), 3.65 (2 H, dd, *J*=5.0, 3.8 Hz), 3.29 (3 H, s); Mass Spectrum (ESI) *m/e* = 324.0 [M+1].



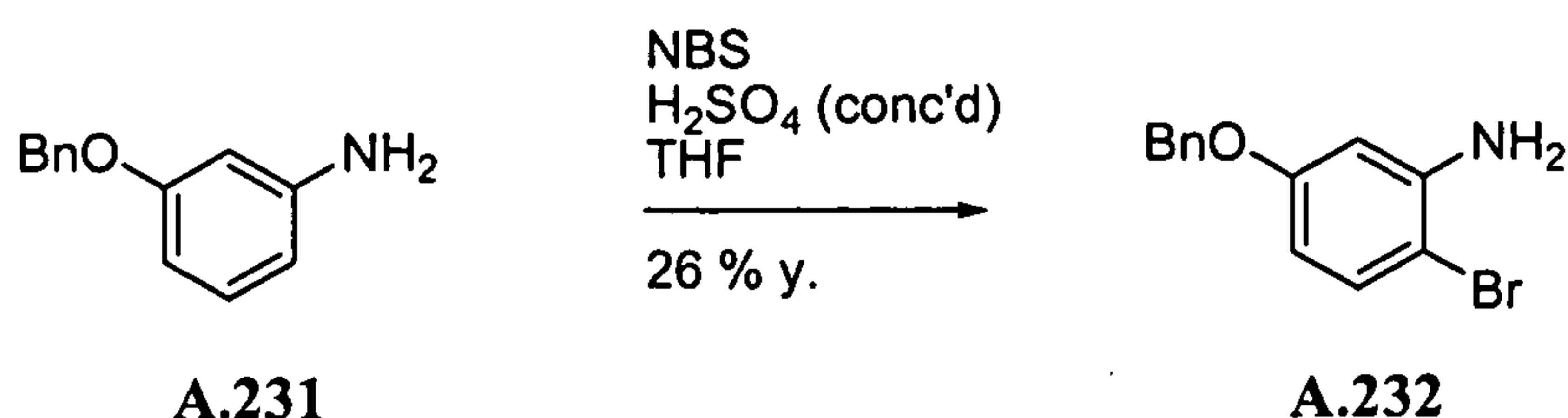
5-iodo-2-(2-methoxyethoxy)benzenamine (A.228): To a solution of 4-iodo-1-(2-methoxyethoxy)-2-nitrobenzene (**A.227**) (4.67 g, 14.45 mmol) in ethyl acetate (120 mL) was added SnCl₂·2H₂O (16.31 g, 72.27 mmol) and the mixture was heated at reflux for 5.5 hours. The mixture was cooled to room temperature. To the mixture was added 1 N aqueous HCl (140 mL, 140 mmol). The mixture was basified to pH 10.0 with 10 N aqueous NaOH and extracted with ethyl acetate (100 mL x 2). The combined organic layers were washed with brine (100 mL x 1), dried over MgSO₄, filtered, and concentrated under reduced pressure to give an orange oil. The product was purified by silica gel column chromatography using 10% to 100% gradient of ethyl acetate in hexane as eluent to give 5-iodo-2-(2-methoxyethoxy)benzenamine (**A.228**) (3.4984 g, 82.6% yield) as a yellow oil: ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 6.95 (1 H, d, *J*=2.2 Hz), 6.71 - 6.79 (1 H, m), 6.61 (1 H, d, *J*=8.3 Hz), 4.83 - 4.92 (2 H, m), 4.03 (2 H, dd, *J*=5.5, 3.8 Hz), 3.58 - 3.67 (2 H, m), 3.25 - 3.33 (3 H, m); Mass Spectrum (ESI) *m/e* = 294.0 [M+1].



5-chloro-N4-(5-iodo-2-(2-methoxyethoxy)phenyl)pyrimidine-2,4-diamine (A.229): A mixture of 5-iodo-2-(2-methoxyethoxy)benzenamine (A.228) (3 g, 10.24 mmol) and 4,5-dichloropyrimidin-2-amine (A.14) (1.679 g, 10.24 mmol) in 1,4-dioxane (25 mL) was stirred at 90 °C for 23 hours. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was suspended in NH₄OH (100 mL). The resulting precipitate was collected by suction filtration, washed with water (200 mL), and dried to give a tan solid. The tan solid was purified by silica gel column chromatography using 10% to 20% gradient of dichloromethane-methanol-NH₄OH (89:9:1) in dichloromethane as eluent to give a tan solid. The tan solid was washed with dichloromethane-methanol (1:1) and filtered to give 5-chloro-N4-(5-iodo-2-(2-methoxyethoxy)phenyl)pyrimidine-2,4-diamine (A.229) (2.31 g, 53.7% yield) as a light orange solid: ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.66 (1 H, d, *J*=2.0 Hz), 7.86 - 8.02 (2 H, m), 7.28 - 7.41 (1 H, m), 6.93 (1 H, d, *J*=8.6 Hz), 6.64 (2 H, s), 4.13 - 4.23 (2 H, m), 3.59 - 3.70 (2 H, m), 3.30 (3 H, s); Mass Spectrum (ESI) *m/e* = 421.0 [M+1].



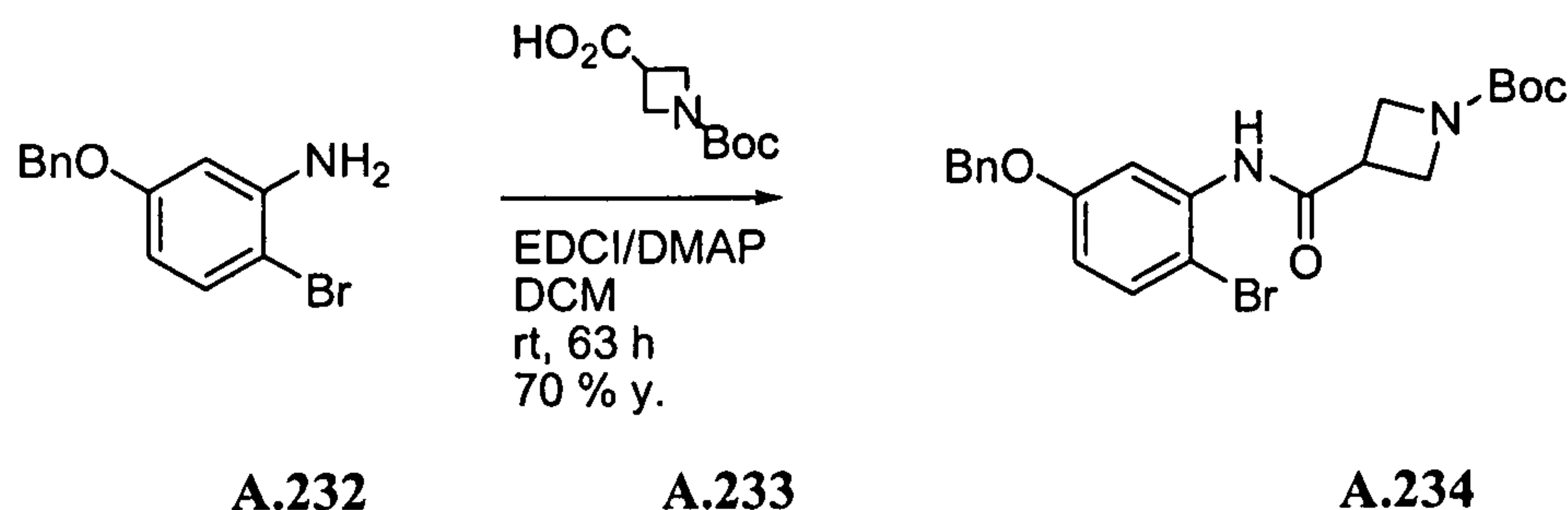
5-chloro-N-(5-iodo-2-(2-methoxyethoxy)phenyl)pyrimidin-4-amine (A.230): To a suspension of 5-chloro-N4-(5-iodo-2-(2-methoxyethoxy)phenyl)pyrimidine-2,4-diamine (A.229) (0.5 g, 1.19 mmol) in THF (1 mL) was added dropwise isoamyl nitrite (0.75 mL, 5.6 mmol) with stirring and the mixture was heated at reflux for 7 hours. The mixture was poured into ice water (50 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (100 mL x 1), dried over MgSO₄, filtered, and concentrated under reduced pressure to give an orange syrupy solid. The product was purified by silica gel column chromatography using 0% to 100% gradient of ethyl acetate in hexane as eluent to give 5-chloro-N-(5-iodo-2-(2-methoxyethoxy)phenyl)pyrimidin-4-amine (A.230) (0.148 g, 30.6% yield): ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.61 (1 H, s), 8.53 (1 H, s), 8.44 (1 H, d, *J*=2.2 Hz), 8.42 (1 H, s), 7.46 (1 H, dd, *J*=8.4, 1.8 Hz), 6.99 (1 H, d, *J*=8.6 Hz), 4.18 (2 H, dd, *J*=5.4, 3.7 Hz), 3.61 (2 H, dd, *J*=5.4, 3.7 Hz), 3.26 (3 H, s); Mass Spectrum (ESI) *m/e* = 406.0 [M+1].



5-(Benzyloxy)-2-bromoaniline A.232

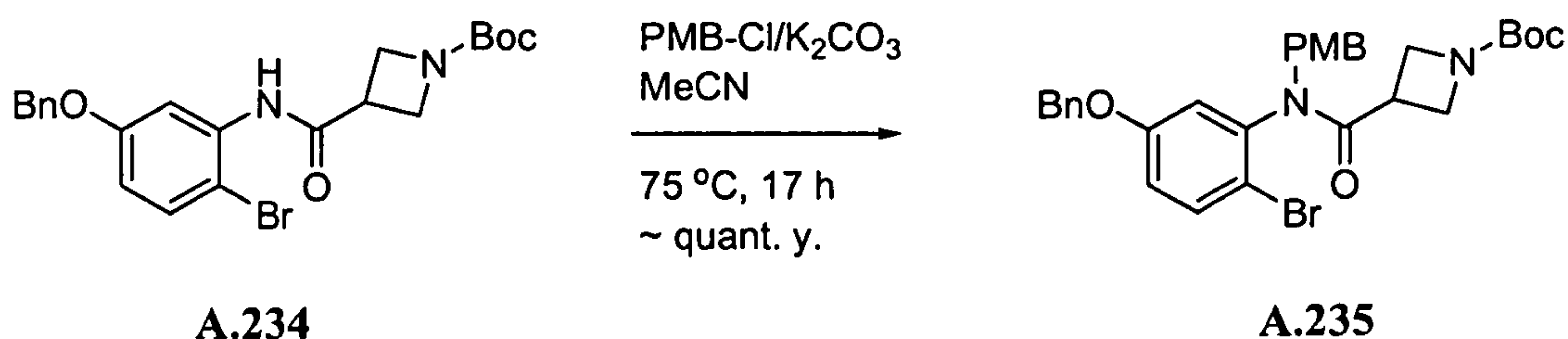
Ref. Boger, D. L., R. J. Wysocki, et al. (1990). *J. Amer. Chem. Soc.* **112**(13): 5230-5240.

A solution of 3-(benzyloxy)aniline A.231 (50 mmol, 10.0 g) in THF (100 mL) was stirred in an acetone-dry ice bath. To this solution was added a few drops of concentrated H₂SO₄. The mixture was stirred in the dry ice bath for 5 min before NBS (1.0 eq, 9.0 g) was added in one-gram portions over a period of 30 min. The resulting mixture was stirred in the acetone-dry ice bath for 1 h 15 min. Na₂CO₃ (1.5 g) was added and the dry ice bath was removed. The reaction mixture was allowed to warm up to room temperature, poured into ice and saturated Na₂CO₃ aqueous solution, and extracted with ethyl acetate (2 X). The combined organics were washed with brine (1 X), dried over Na₂SO₄, and concentrated in vacuo. The residue was subjected to combi-flash column chromatography (ethyl acetate/hexanes) to give 5-(benzyloxy)-2-bromoaniline A.232 (3.7 g, 26% yield) as a white solid. ¹H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 7.36 - 7.43 (4 H, m), 7.31 - 7.35 (1 H, m), 7.27 - 7.30 (1 H, m), 6.42 (1 H, d, *J*=2.7 Hz), 6.31 (1 H, dd, *J*=8.8, 2.7 Hz), 5.01 (2 H, s). LCMS-ESI (POS), *M/Z*, *M*+1: Found 278.0 and 280.0.

**3-((5-(Benzyloxy)-2-bromophenyl)carbamoyl)-1-azetidinecarboxylate**

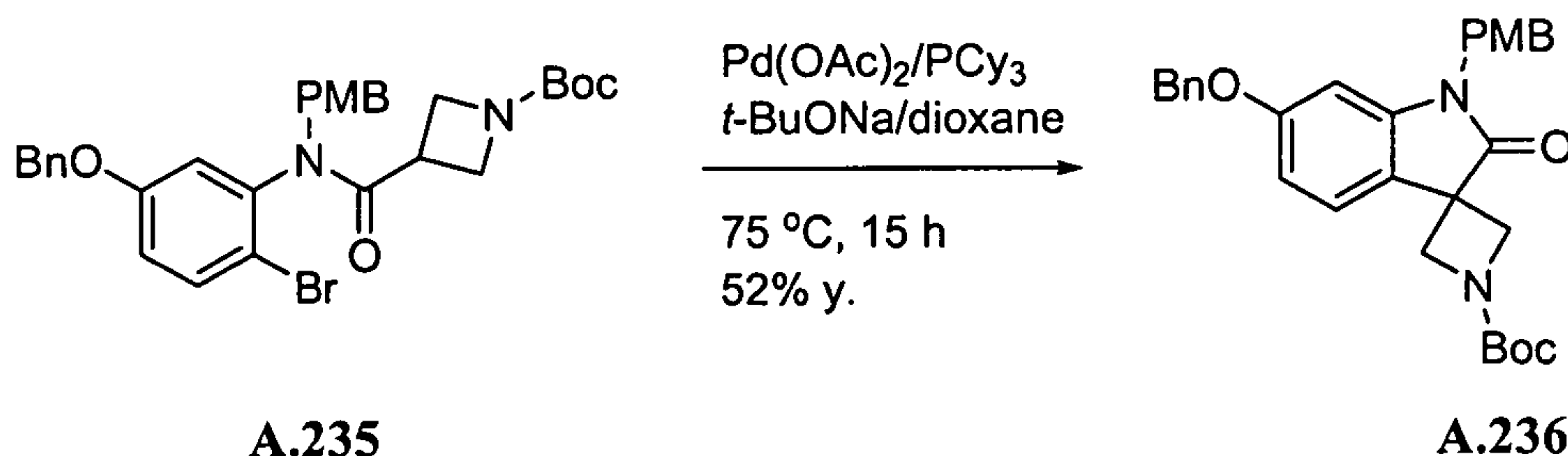
Ref. *Helv. Chim. Acta* 2000, 83, 1247-55.

To a stirred solution of 5-(benzyloxy)-2-bromoaniline A.232 (3.7 g, 13.1 mmol) and DMAP (1.3 eq, 2.1 g) in dichloromethane (90 mL) was added 1-(*tert*-butoxycarbonyl)-3-azetidinecarboxylic acid A.233 (1.0 eq, 2.7 g) in one portion followed by one-portion addition of EDCI (1.3 eq, 3.3 g) at room temperature. The resulting mixture was stirred at rt for 63 h. After the solvent was removed, water was added to the residue followed by extraction with ethyl acetate (2 X). The combined organics were washed with ice cold 2 N HCl aqueous solution (1 X), water (1 X), saturated Na₂CO₃ aqueous solution (1 X), brine (1 X), dried over Na₂SO₄, and concentrated in vacuo to give 3-((5-(benzyloxy)-2-bromophenyl)carbamoyl)-1-azetidinecarboxylate A.234. (4.2 g, 70% yield) as a sticky oil. LCMS-ESI (POS), *M/Z*, *M*+1: Found 361.0 and 363.0; 405.0 and 407.0; 483.0 and 485.0 (Na⁺).



***tert*-Butyl 3-((5-(benzyloxy)-2-bromophenyl)(4-methoxybenzyl)carbamoyl)-1-azetidinecarboxylate A.235**

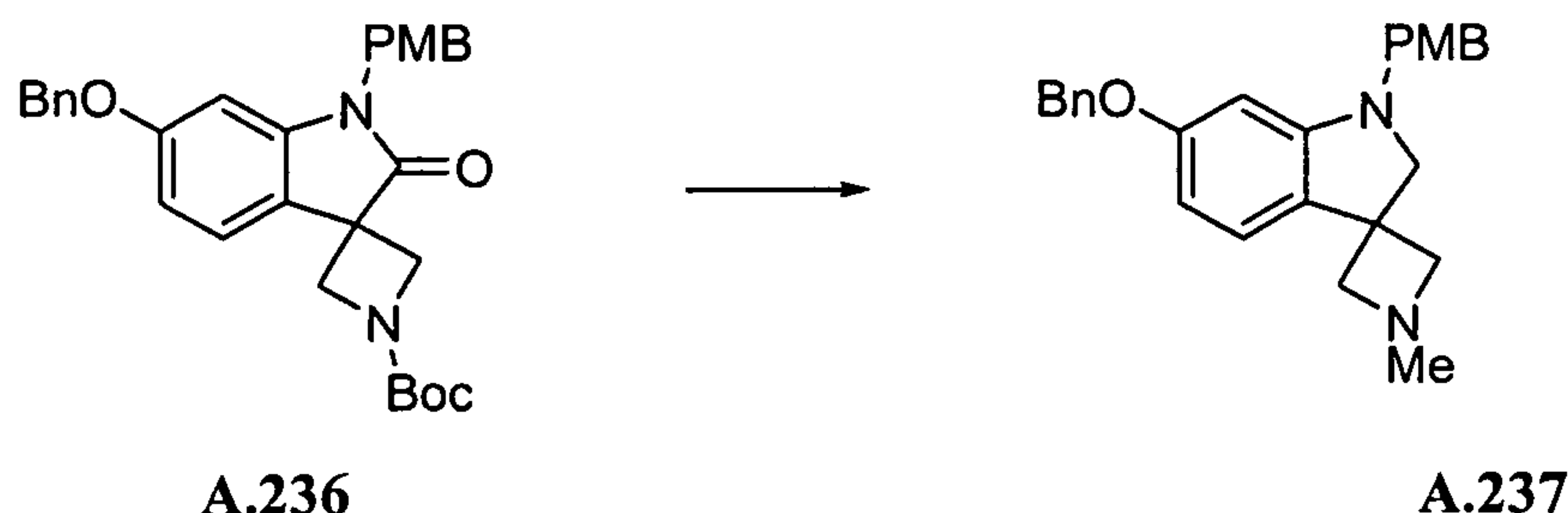
A mixture of 3-((5-(benzyloxy)-2-bromophenyl)carbamoyl)-1-azetidinecarboxylate **A.234** (4.2 g, 9.1 mmol), *p*-methoxybenzyl chloride (1.1 eq, 1.6 g), and K₂CO₃ (3.0 eq, 3.8 g) in acetonitrile (120 mL) was refluxed for 17 h. After cooled to room temperature, the mixture was vacuum filtered through a layer of celite and the filter cake was washed with more acetonitrile and ethyl acetate. The filtrate was concentrated in vacuo and the residue was subjected to combi-flash column chromatography (ethyl acetate/hexane) to give *tert*-butyl 3-((5-(benzyloxy)-2-bromophenyl) (4-methoxybenzyl)carbamoyl)-1-azetidinecarboxylate **A.235** (5.5 g, 100% yield) as a colorless sticky liquid. LCMS-ESI (POS), M/Z, M+1: Found 581.2 and 583.2; 525.0 and 527.0; 481.1 and 483.1.



***tert*-butyl 6'-(benzyloxy)-1'-(4-methoxybenzyl)-2'-oxospiro[azetidine-3,3'-indoline]-1-carboxylate (A.236)** was prepared according to the procedure reported in Lee, S. and J. F. Hartwig (2001). *J. Org. Chem.* **66**(10): 3402-3415.

To a 200 mL single-necked round bottom flask were placed *tert*-butyl 3-((5-(benzyloxy)-2-bromophenyl) (4-methoxybenzyl)carbamoyl)-1-azetidinecarboxylate **A.235** (5.5 g, 9.5 mmol), sodium *tert*-butoxide (1.5 eq, 1.4 g) and palladium (II) acetate (10 mol%, 0.21 g). The flask was subjected to 3 cycles of evacuation and back-filling with N₂. 1,4-dioxane was added followed by tricyclohexylphosphine (10 mol%, 0.27 g). The resulting mixture was stirred at 75 °C for 15 h. After cooling, the mixture was poured into ice and saturated NH₄Cl aqueous solution and extracted with ethyl acetate (2 X). The combined organics were washed with brine (1 X), dried over Na₂SO₄, and concentrated in vacuo. The residue was subjected to combi-flash column chromatography (ethyl acetate/hexanes) to give *tert*-butyl 6'-(benzyloxy)-1'-(4-

methoxybenzyl)-2'-oxo-1H-spiro[azetidine-3,3'-indoline]-1-carboxylate **A.236** (2.4 g, 52% yield) as a sticky liquid. ¹H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.31 - 7.44 (6 H, m), 7.19 (2 H, d, *J*=8.6 Hz), 6.83 (2 H, d, *J*=9.0 Hz), 6.67 (1 H, dd, *J*=8.2, 2.3 Hz), 6.43 (1 H, d, *J*=2.3 Hz), 5.02 (2 H, s), 4.78 (2 H, s), 4.39 (2 H, d, *J*=8.2 Hz), 4.05 (2 H, d, *J*=8.2 Hz), 3.78 (3 H, s), 1.50 (9 H, s). LCMS-ESI (POS), *M/Z*, *M*+1: Found 445.1; 523.2 (Na⁺).



6'-(Benzyloxy)-1'-(4-methoxybenzyl)-1-methyl-1',2'-dihydrospiro[azetidine-3,3'-indole] **A.237**

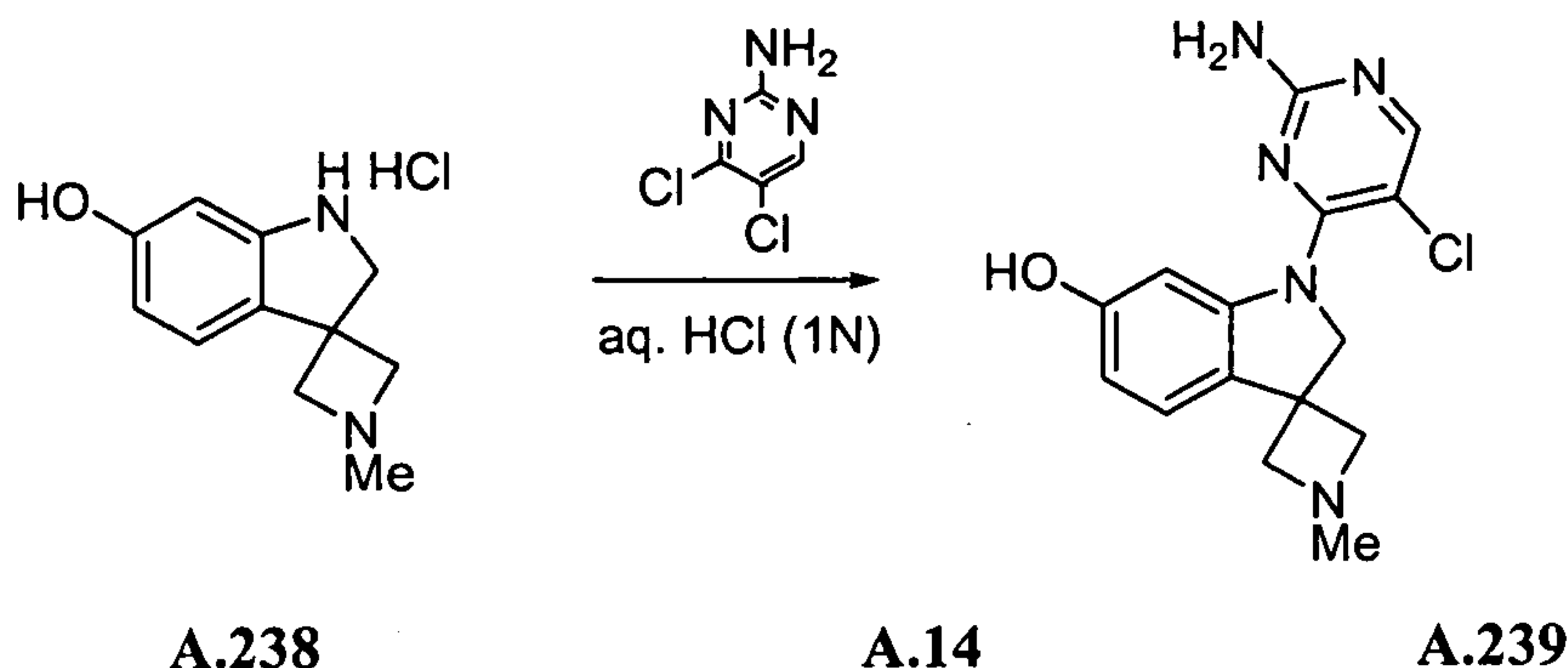
To a stirred solution of *tert*-butyl 6'-(benzyloxy)-1'-(4-methoxybenzyl)-2'-oxo-1H-spiro[azetidine-3,3'-indoline]-1-carboxylate **A.236** (2.4 g, 4.8 mmol) in dry toluene (80 mL), which was preheated at 80 °C in an oil bath, was dropwise added a solution of Red-AL in toluene (3 M) (9.5 mL, 6.0 eq.) under a nitrogen atmosphere. The resulting mixture was stirred at this temperature for 2 h. Upon workup, the mixture was cooled in an ice-salt bath before cautiously quenched with ice-cold aqueous 2 N NaOH. The mixture was further diluted with ice-cold aqueous 2 N NaOH and extracted with ethyl acetate (3 x). The combined organics were dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to give 6'-(benzyloxy)-1'-(4-methoxybenzyl)-1-methylspiro[azetidine-3,3'-indoline] (**A.237**) (1.9 g, 100% yield) as a sticky liquid. ¹H NMR (400 MHz, *DMSO-d*₆) δ ppm 7.29 - 7.45 (5 H, m), 7.19 - 7.24 (3 H, m), 6.83 - 6.89 (2 H, m), 6.35 (1 H, dd, *J*=8.0, 2.2 Hz), 6.19 (1 H, d, *J*=2.3 Hz), 5.02 (2 H, s), 4.18 (2 H, s), 3.81 (3 H, s), 3.55 (2 H, s), 3.40 - 3.45 (2 H, m), 3.26 - 3.32 (1 H, m). LCMS-ESI (POS), *M/Z*, *M*+1: Found 401.2.



1-methylspiro[azetidine-3,3'-indolin]-6'-ol hydrochloride (A.238**)**

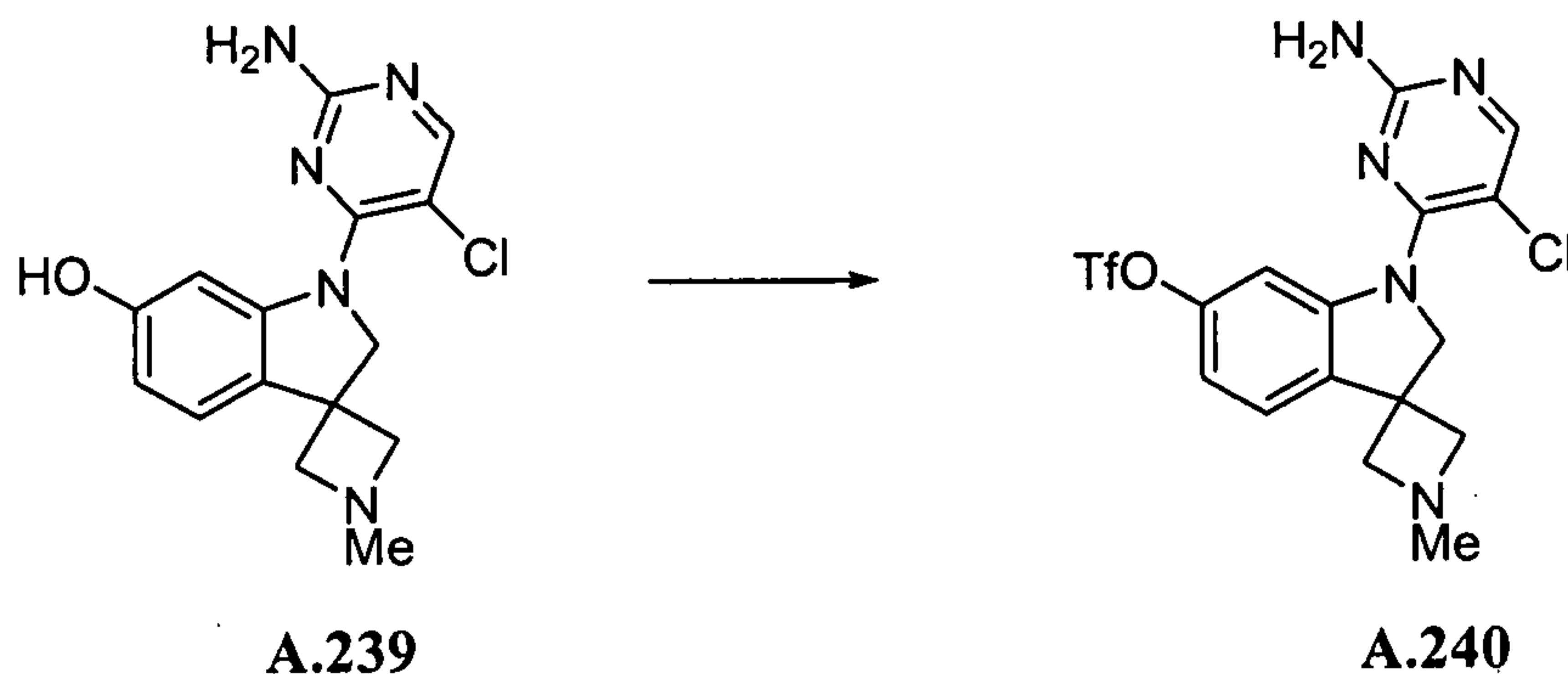
A mixture of 6'-(benzyloxy)-1'-(4-methoxybenzyl)-1-methylspiro[azetidine-3,3'-indoline] **A.237** (1.0 g, 2.5 mmol), Pd/C (10 wt% on activated C, wet) (not weighed), and 37% HCl aqueous solution (commercial) (3 mL) in EtOH (40 mL) was balloon hydrogenated for 15 h.

Upon workup, water was added and the mixture was vacuum filtered through a layer of celite. The filter cake was washed with EtOH/water (8:1, v/v). The filtrate was concentrated in vacuo to give 1-methylspiro[azetidine-3,3'-indolin]-6'-ol hydrochloride, **A.238** which was used directly in the next step. LCMS-ESI (POS), M/Z, M+1: Found 191.1.



1'-(2-amino-5-chloropyrimidin-4-yl)-1-methylspiro[azetidine-3,3'-indolin]-6'-ol A.239

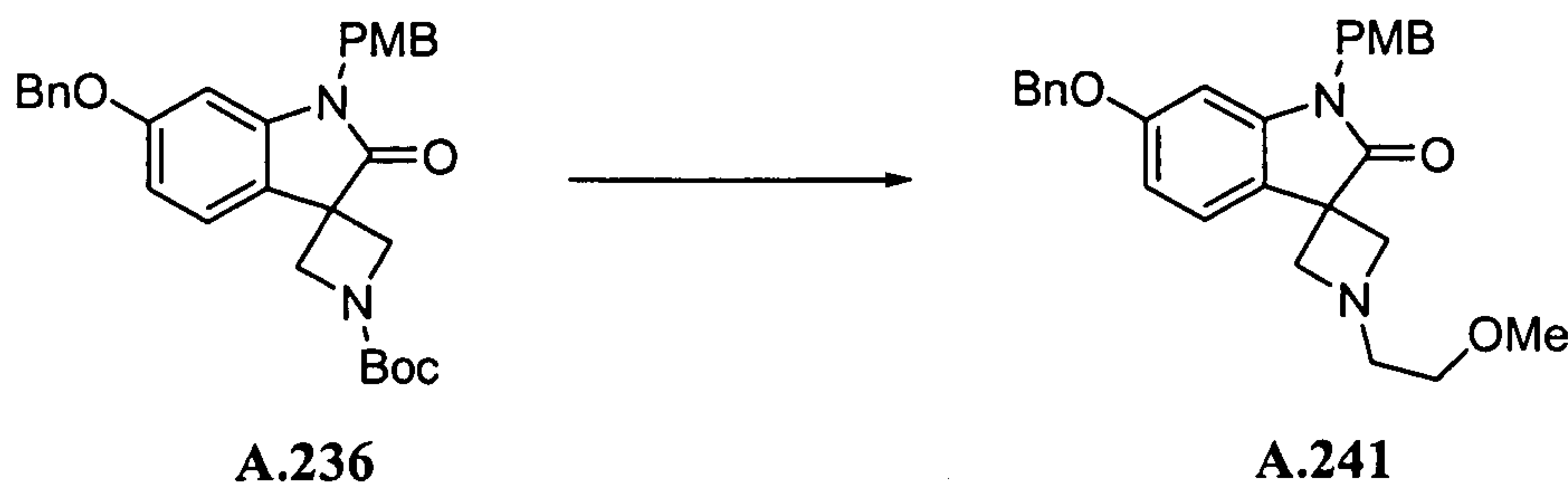
A mixture of 1-methylspiro[azetidine-3,3'-indolin]-6'-ol hydrochloride **A.238** (2.5 mmol) (assuming 100% yield in the previous step) and 4,5-dichloro-2-pyrimidinamine **A.14** (1.2 eq., 0.5 g) in 1N HCl aqueous solution was stirred at 60 °C for 21 h. Upon workup, the reaction mixture was cooled to room temperature and the precipitate was collected by vacuum filtration. The filter cake was washed with a small volume of ice cold 1N HCl aqueous solution and dried under high vacuum to give 1'-(2-amino-5-chloropyrimidin-4-yl)-1-methylspiro[azetidine-3,3'-indolin]-6'-ol HCl salt **A.239** (0.75 g, 85% over 2 steps) as an off-white solid. LCMS-ESI (POS), M/Z, M+1: Found 318.1.



1'-(2-amino-5-chloropyrimidin-4-yl)-1-methylspiro[azetidine-3,3'-indoline]-6'-yl trifluoromethanesulfonate A.240

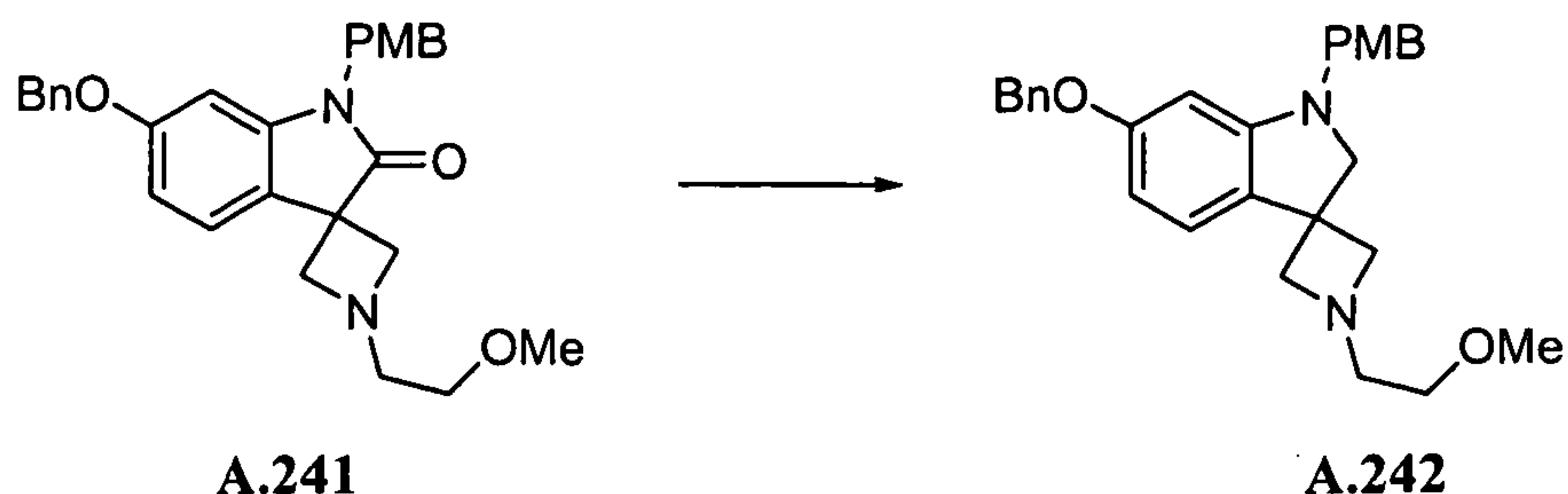
To a stirred mixture of 1'-(2-amino-5-chloropyrimidin-4-yl)-1-methylspiro[azetidine-3,3'-indolin]-6'-ol HCl salt **A.239** (0.65 g, 2.0 mmol) and triethylamine (4.0 eq., 1.1 mL) in dichloromethane (20 mL) was added 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (1.5 eq., 0.9 g) at room temperature. The resulting mixture was stirred for 24 h. Upon workup, the crude reaction mixture was subjected to combi-fash column chromatography (methanol/dichloromethane with triethylamine) to give

1'-(2-amino-5-chloropyrimidin-4-yl)-1-methylspiro[azetidine-3,3'-indoline]-6'-yl trifluoromethanesulfonate **A.240** (0.5 g, 60% yield) as an off-white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.13 (1 H, s), 7.71 (1 H, d, $J=8.2$ Hz), 7.52 (1 H, d, $J=2.3$ Hz), 7.06 (1 H, dd, $J=8.2, 2.3$ Hz), 6.67 (2 H, s), 4.49 (2 H, s), 3.36 - 3.41 (2 H, m), 3.31 - 3.34 (2 H, m), 2.29 (3 H, s). LCMS-ESI (POS), M/Z , $M+1$: Found 450.0.



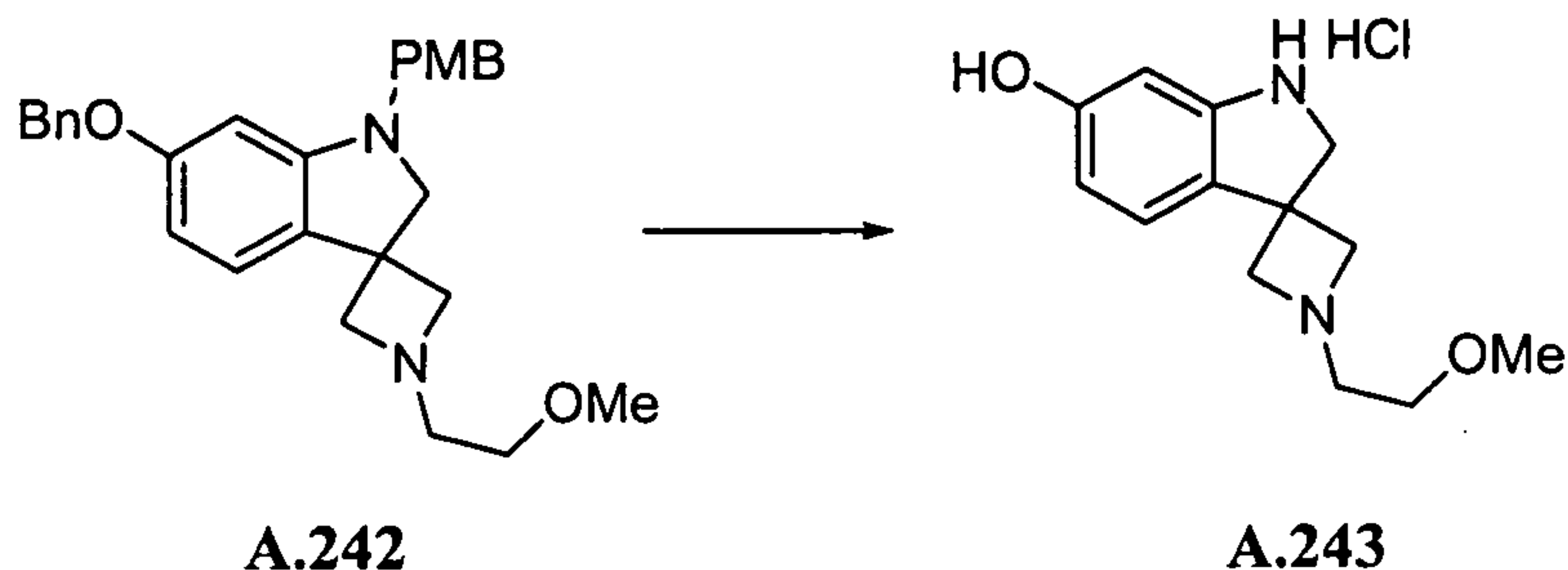
6'-(Benzyloxy)-1'-(4-methoxybenzyl)-1-(2-methoxyethyl)spiro[azetidine-3,3'-indolin]-2'-one **A.241**

To a stirred solution of *tert*-butyl 6'-(benzyloxy)-1'-(4-methoxybenzyl)-2'-oxo-1H-spiro[azetidine-3,3'-indoline]-1-carboxylate **A.236** (0.7 g, 1.40 mmol) in dichloromethane (10 mL) was added TFA (1.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The volatiles were removed in vacuo and the residue was dissolved in DMF (15 mL). To this solution were added Cs_2CO_3 (3.0 eq., 1.36 g) and 2-bromoethyl methyl ether (1.0 eq., 0.14 mL) sequentially at room temperature. The resulting mixture was stirred at room temperature for 3 days. Upon workup, the mixture was poured into ice and 2 N NaOH aqueous solution and extracted with ethyl acetate (2 X). The combined organics were washed with ice cold 2 N NaOH aqueous solution (1 X) and dried over Na_2SO_4 . The residue after concentration in vacuo was subjected to combi-flash column chromatography (methanol/dichloromethane with triethylamine) to give 6'-(benzyloxy)-1'-(4-methoxybenzyl)-1-(2-methoxyethyl)spiro[azetidine-3,3'-indolin]-2'-one **A.241** (0.23 g, 36% yield in 2 steps) as a sticky liquid. ^1H NMR (400 MHz, $\text{CHLOROFORM}-d$) δ ppm 7.65 (1 H, d, $J=7.8$ Hz), 7.29 - 7.44 (5 H, m), 7.19 (2 H, d, $J=8.6$ Hz), 6.82 (2 H, d, $J=8.6$ Hz), 6.67 (1 H, dd, $J=8.0, 2.2$ Hz), 6.41 (1 H, d, $J=2.3$ Hz), 5.01 (2 H, s), 4.77 (2 H, s), 3.77 (3 H, s), 3.65 - 3.72 (2 H, m), 3.61 (2 H, d, $J=7.0$ Hz), 3.49 (2 H, t, $J=5.5$ Hz), 3.38 (3 H, s), 2.85 (2 H, t, $J=5.7$ Hz). LCMS-ESI (POS), M/Z , $M+1$: Found 459.2.

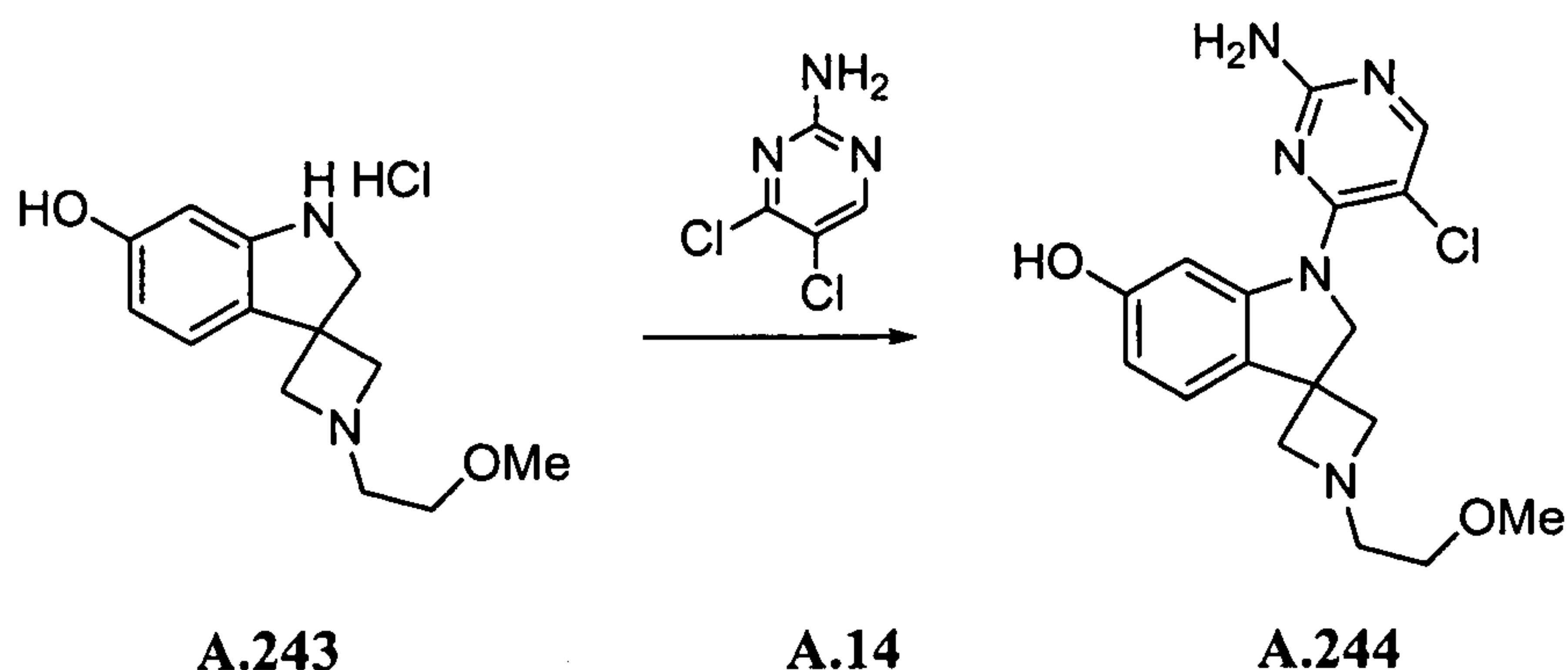


6'-(benzyloxy)-1'-(4-methoxybenzyl)-1-(2-methoxyethyl)spiro[azetidine-3,3'-indoline]

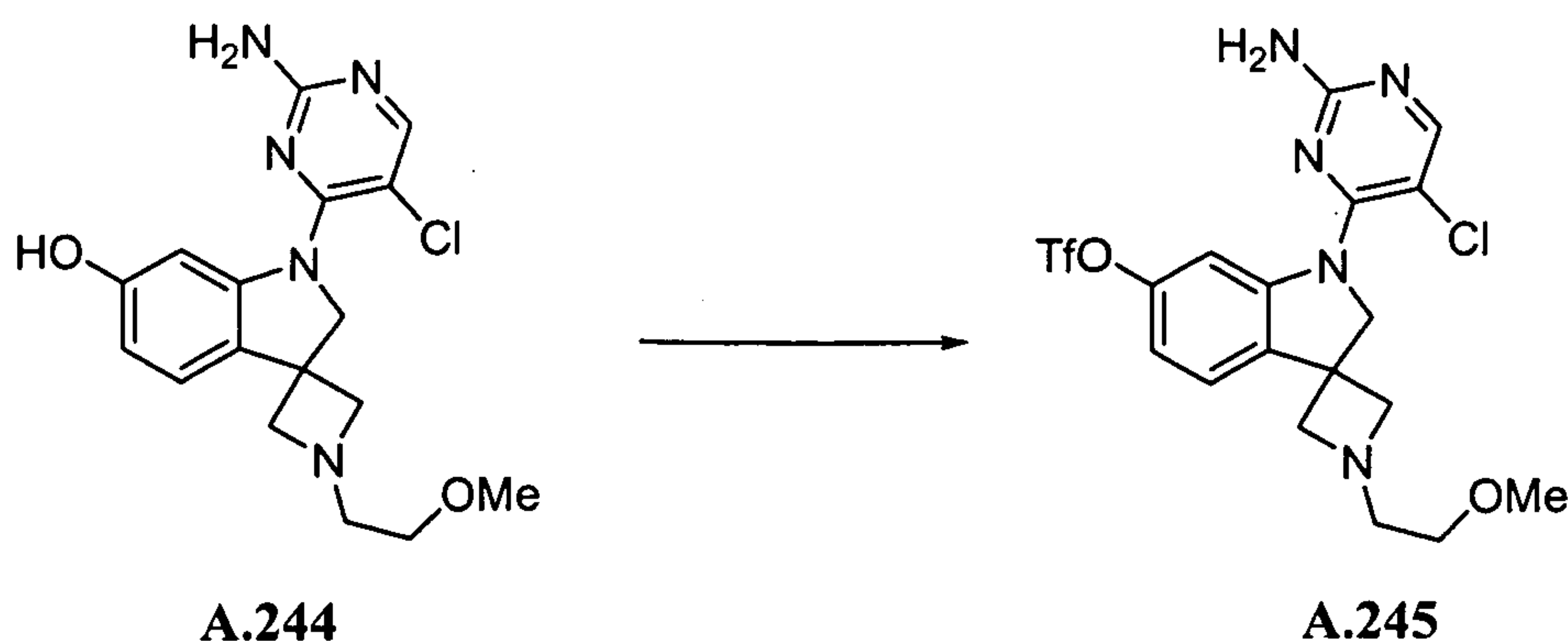
A.242 was prepared from 6'-(benzyloxy)-1'-(4-methoxybenzyl)-1-(2-methoxyethyl)spiro[azetidine-3,3'-indolin]-2'-one **A.241** using chemistry similar to that described for compound **A.237**. LCMS-ESI (POS), M/Z, M+1: Found 445.1.



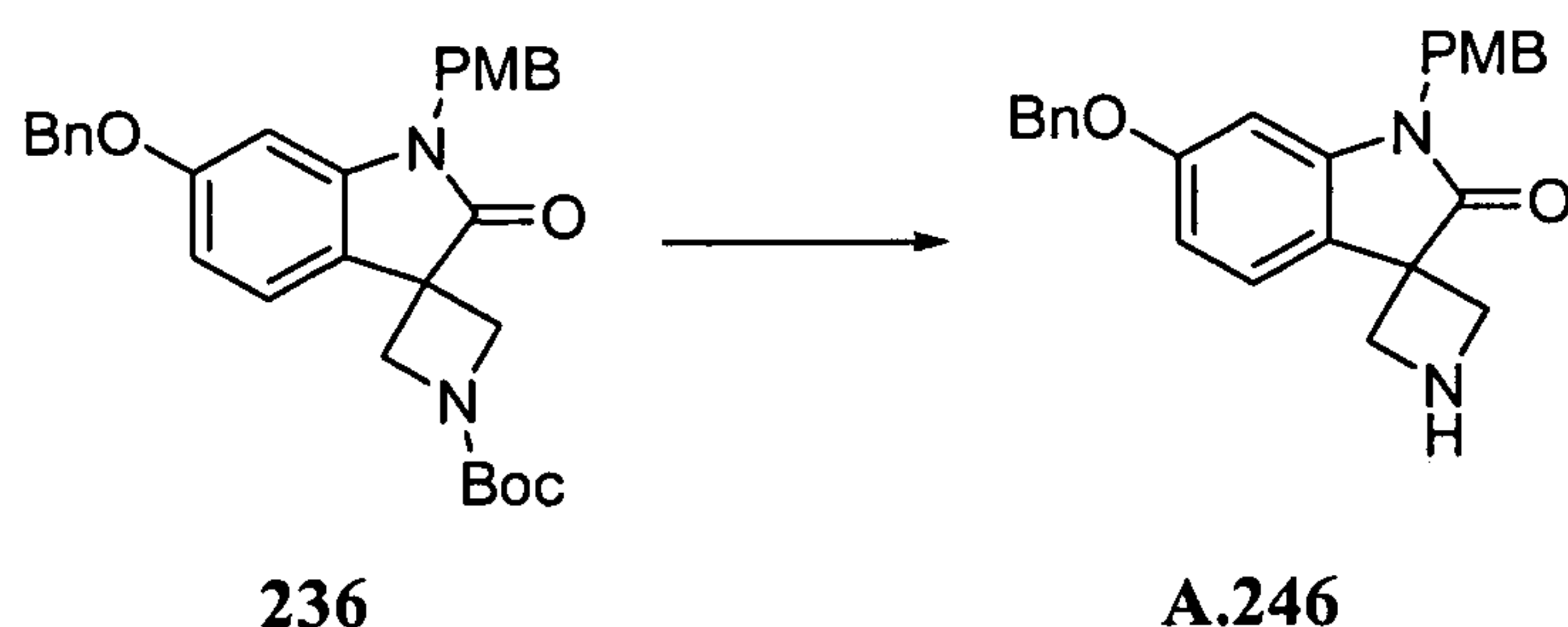
1-(2-methoxyethyl)spiro[azetidine-3,3'-indolin]-6'-ol hydrochloride A.243 was prepared from 6'-(benzyloxy)-1'-(4-methoxybenzyl)-1-(2-methoxyethyl)spiro[azetidine-3,3'-indoline] **A.242** using chemistry similar to that described for compound **A.238**. LCMS-ESI (POS), M/Z, M+1: Found 235.1.



1'-(2-amino-5-chloropyrimidin-4-yl)-1-(2-methoxyethyl)spiro[azetidine-3,3'-indolin]-6'-ol A.244 was prepared from 1-(2-methoxyethyl)spiro[azetidine-3,3'-indolin]-6'-ol hydrochloride **A.243** using chemistry similar to that described for compound **A.239**. LCMS-ESI (POS), M/Z, M+1: Found 362.0.

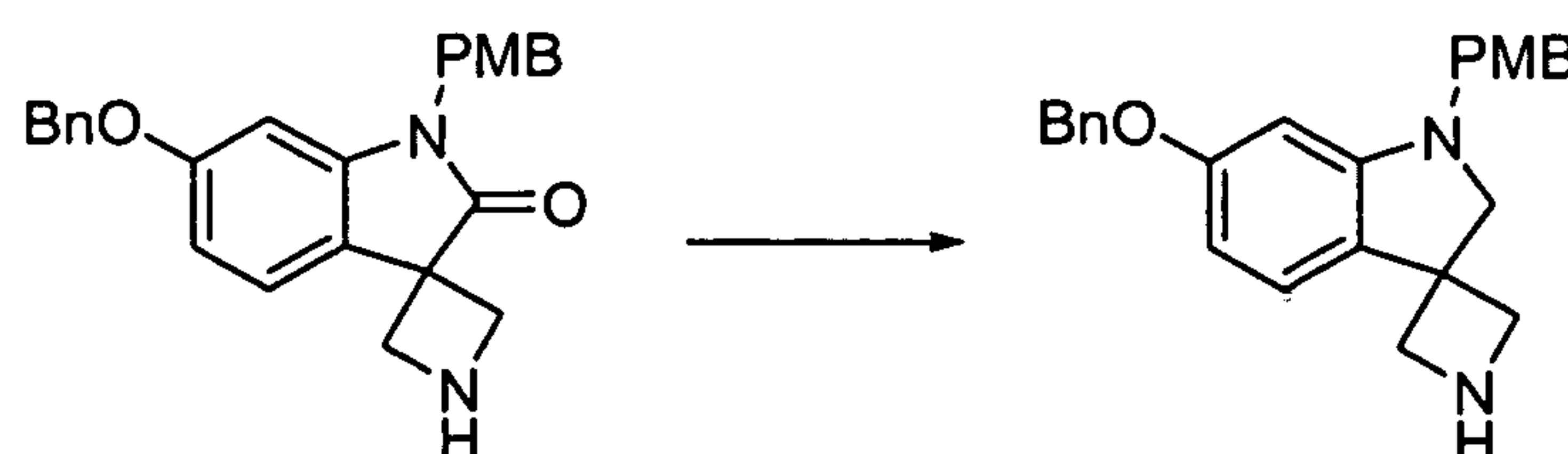


1'-(2-amino-5-chloropyrimidin-4-yl)-1-(2-methoxyethyl)spiro[azetidine-3,3'-indoline]-6'-yl trifluoromethanesulfonate A.245 was prepared from **1'-(2-amino-5-chloropyrimidin-4-yl)-1-(2-methoxyethyl)spiro[azetidine-3,3'-indolin]-6'-ol A.244** using chemistry similar to that described for compound **A.240**. ¹H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 8.09 (1 H, s), 7.59 (1 H, d, $J=2.3$ Hz), 7.54 (1 H, d, $J=8.2$ Hz), 6.89 (1 H, dd, $J=8.2, 2.3$ Hz), 5.11 (2 H, br. s.), 4.59 (2 H, s), 3.48 - 3.55 (2 H, m), 3.38 - 3.47 (4 H, m), 3.34 (3 H, s), 2.71 (2 H, t, $J=5.3$ Hz). LCMS-ESI (POS), M/Z , $M+1$: Found 494.0.



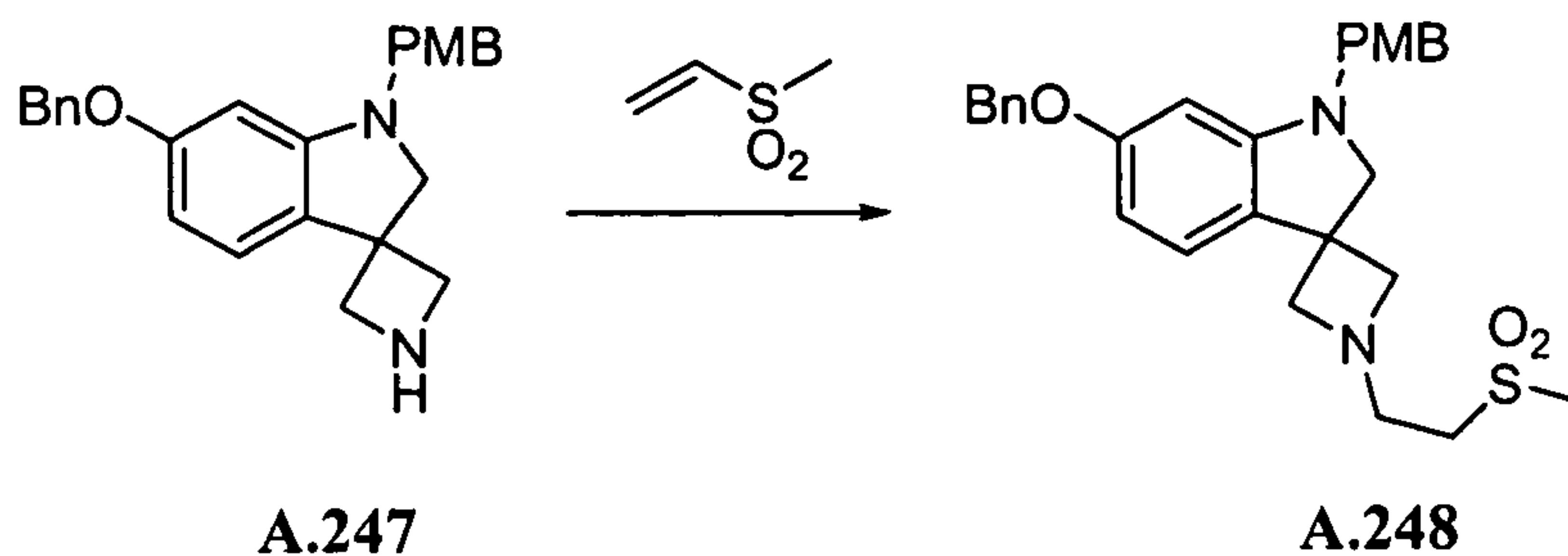
6'-(benzyloxy)-1'-(4-methoxybenzyl)spiro[azetidine-3,3'-indolin]-2'-one A.246

A stirred solution of *tert*-butyl 6'-(benzyloxy)-1'-(4-methoxybenzyl)-2'-oxo-1H-spiro[azetidine-3,3'-indoline]-1-carboxylate **A.236** (0.83 g, 0.16 mmol) in dichloromethane (10 mL) was treated with TFA (2.0 mL) at room temperature for 2 h. Upon workup, the crude mixture was poured into ice and 2 N NaOH aqueous solution and extracted with ethyl acetate (2 X). The combined organics were dried over Na₂SO₄ and concentrated in vacuo to give 6'-(Benzyloxy)-1'-(4-methoxybenzyl)spiro[azetidine-3,3'-indol]-2'-(1H)-one **A.246** which was directly taken onto the next step. LCMS-ESI (POS), M/Z , $M+1$: Found 401.0.



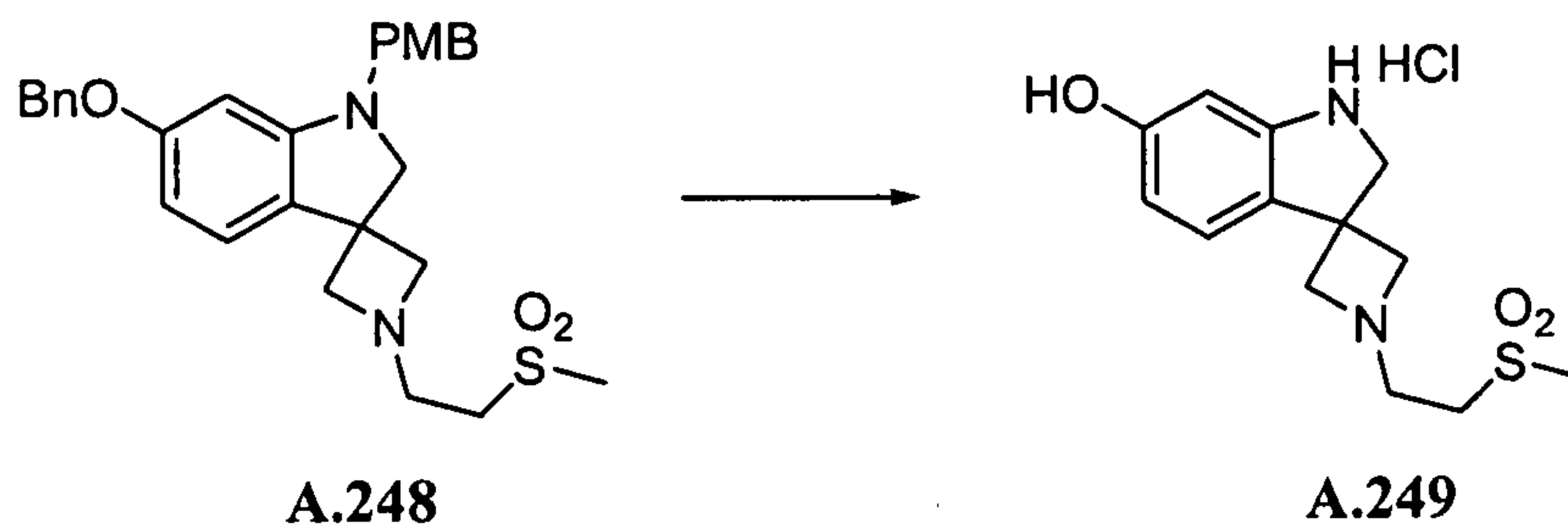
A.246**A.247**

6'-(benzyloxy)-1'-(4-methoxybenzyl)spiro[azetidine-3,3'-indoline] **A.247** was prepared from **6'-(benzyloxy)-1'-(4-methoxybenzyl)spiro[azetidine-3,3'-indolin]-2'-one** **A.246** using chemistry similar to that described for compound **A.237**. LCMS-ESI (POS), M/Z, M+1: Found 387.2.

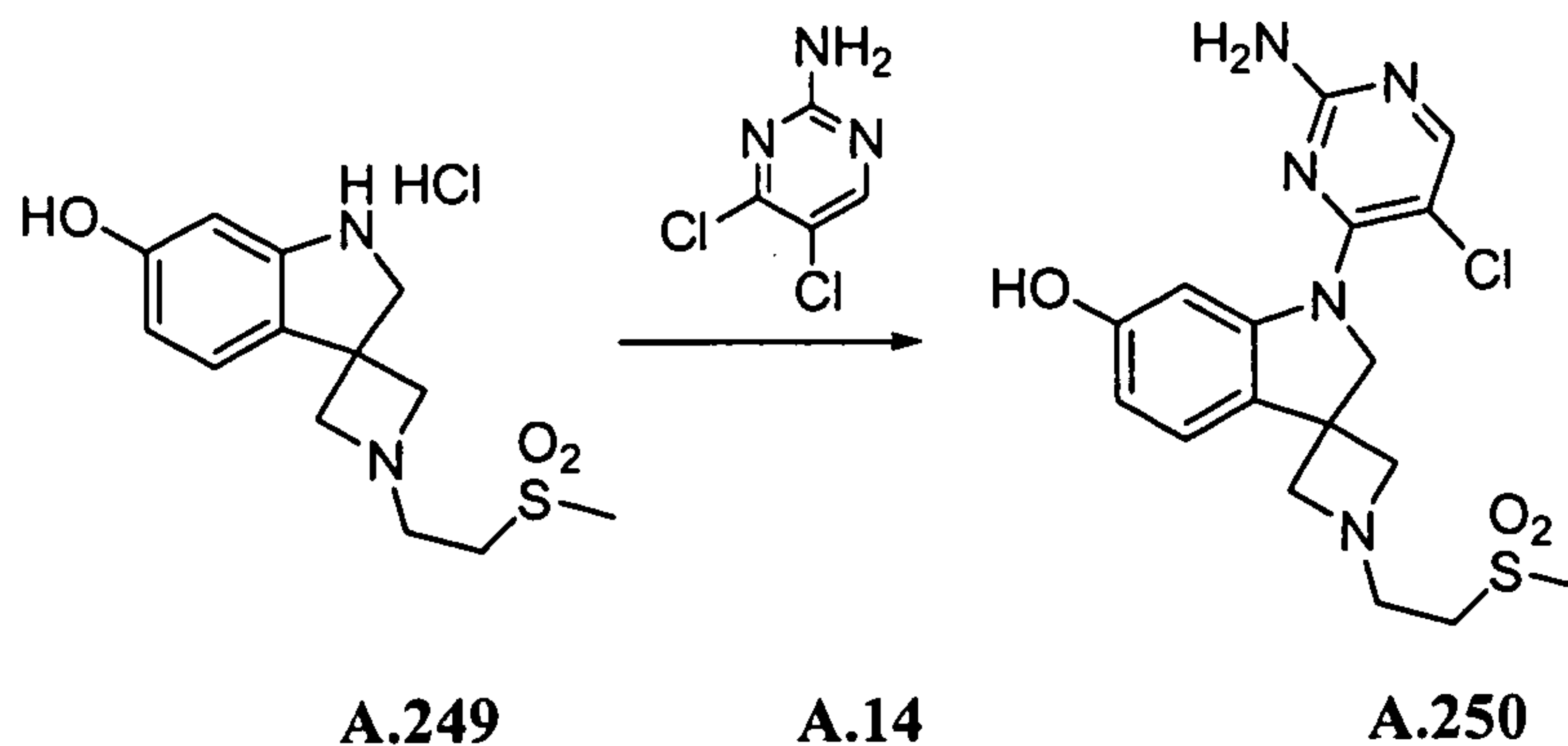


] 6'-(benzyloxy)-1'-(4-methoxybenzyl)-1-(2-(methylsulfonyl)ethyl)spiro[azetidine-3,3'-indoline] **A.248**

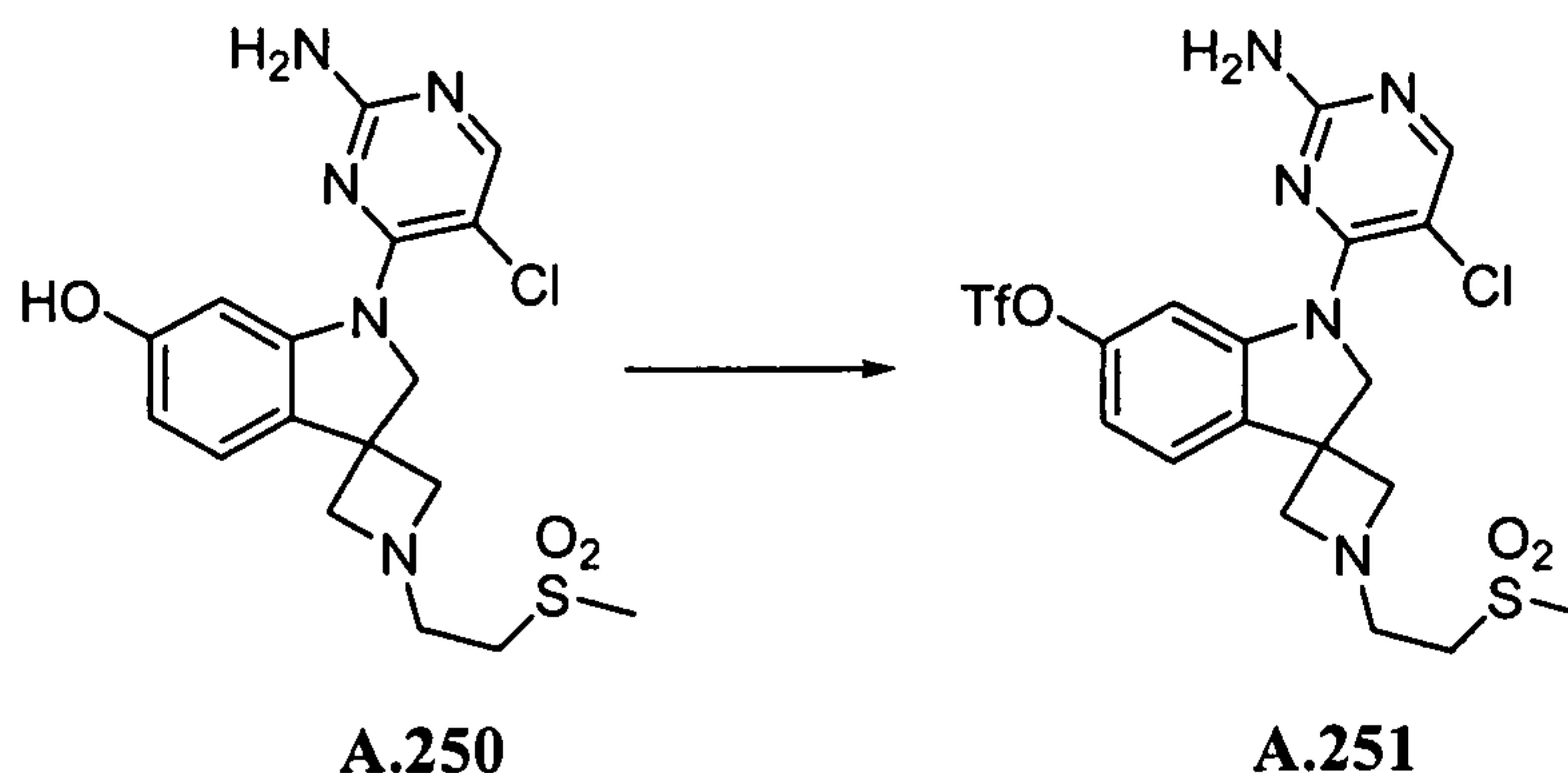
A mixture of **6'-(benzyloxy)-1'-(4-methoxybenzyl)spiro[azetidine-3,3'-indoline]** **A.247** and vinyl methyl sulfone (1.0 eq, 0.076 g) in a mixed solvents of methanol (20 mL) and ethyl acetate (5 mL) was stirred at reflux for 15 h. Upon workup, the volatiles were removed in vacuo to give **6'-(benzyloxy)-1'-(4-methoxybenzyl)-1-(2-(methylsulfonyl)ethyl)spiro[azetidine-3,3'-indoline]** **A.248** which was directly taken onto the next step. LCMS-ESI (POS), M/Z, M+1: Found 493.1.



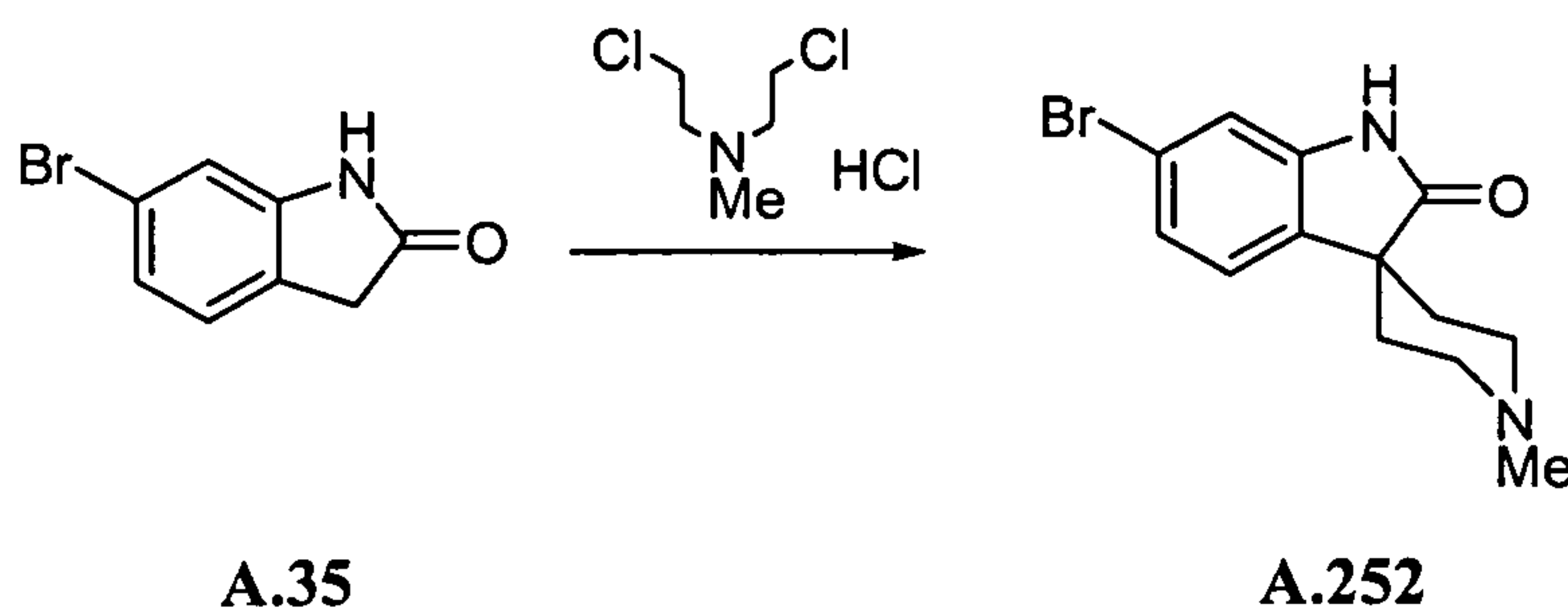
1-(2-(methylsulfonyl)ethyl)spiro[azetidine-3,3'-indolin]-6'-ol hydrochloride **A.249** was prepared from **6'-(benzyloxy)-1'-(4-methoxybenzyl)-1-(2-(methylsulfonyl)ethyl)spiro[azetidine-3,3'-indoline]** **A.248** using chemistry similar to that described for compound **A.238**. LCMS-ESI (POS), M/Z, M+1: Found 283.0.



1'-(2-amino-5-chloropyrimidin-4-yl)-1-(2-(methylsulfonyl)ethyl)spiro[azetidine-3,3'-indolin]-6'-ol A.250 was prepared from 1-(2-(methylsulfonyl)ethyl)spiro[azetidine-3,3'-indolin]-6'-ol hydrochloride A.249 and A.14 using chemistry similar to that described for compound A.239. LCMS-ESI (POS), M/Z, M+1: Found 410.0.



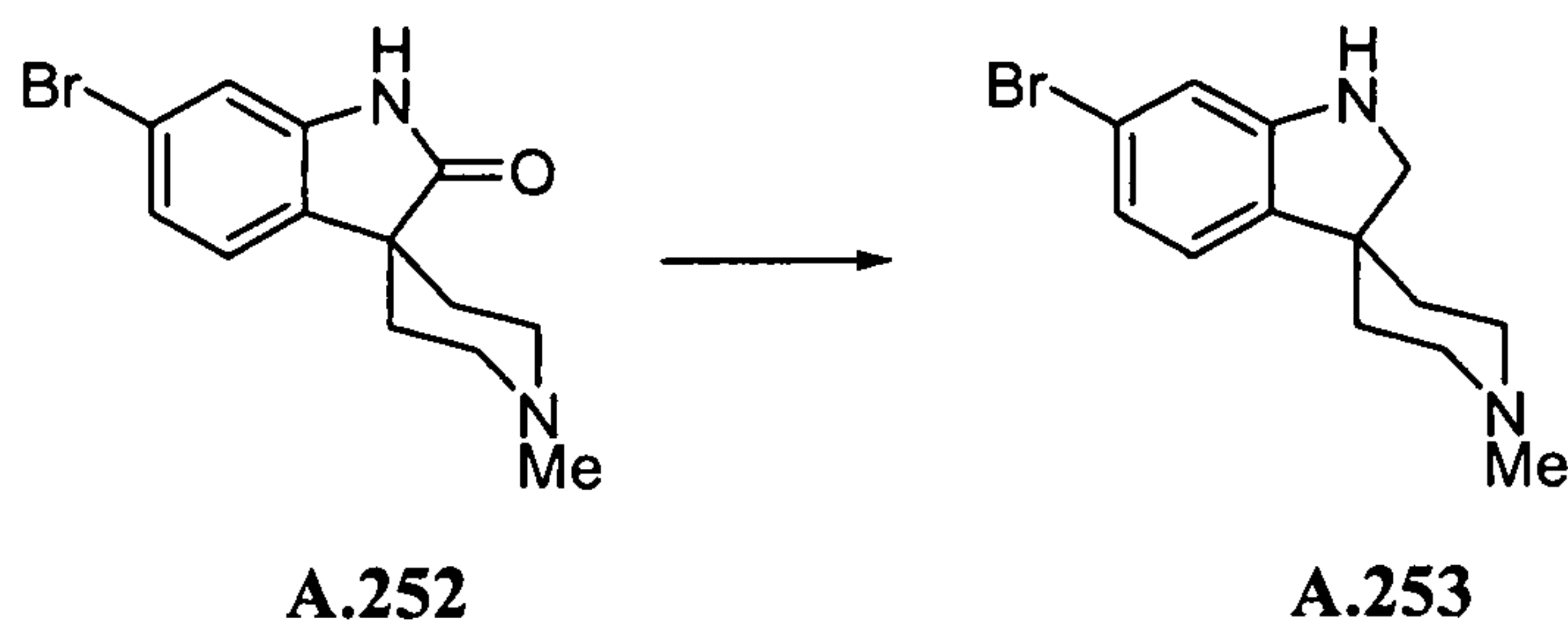
1'-(2-amino-5-chloropyrimidin-4-yl)-1-(2-(methylsulfonyl)ethyl)spiro[azetidine-3,3'-indoline]-6'-yl trifluoromethanesulfonate A.251 was prepared from 1'-(2-amino-5-chloropyrimidin-4-yl)-1-(2-(methylsulfonyl)ethyl)spiro[azetidine-3,3'-indolin]-6'-ol A.250 using chemistry similar to that described for compound A.240. LCMS-ESI (POS), M/Z, M+1: Found 542.0



6-Bromo-1'-methylspiro[indole-3,4'-piperidin]-2-one A.252 was prepared by the method of Goehring, R. R., *Org. Prep. Proced. Int.* 1995, 27(6), 691.

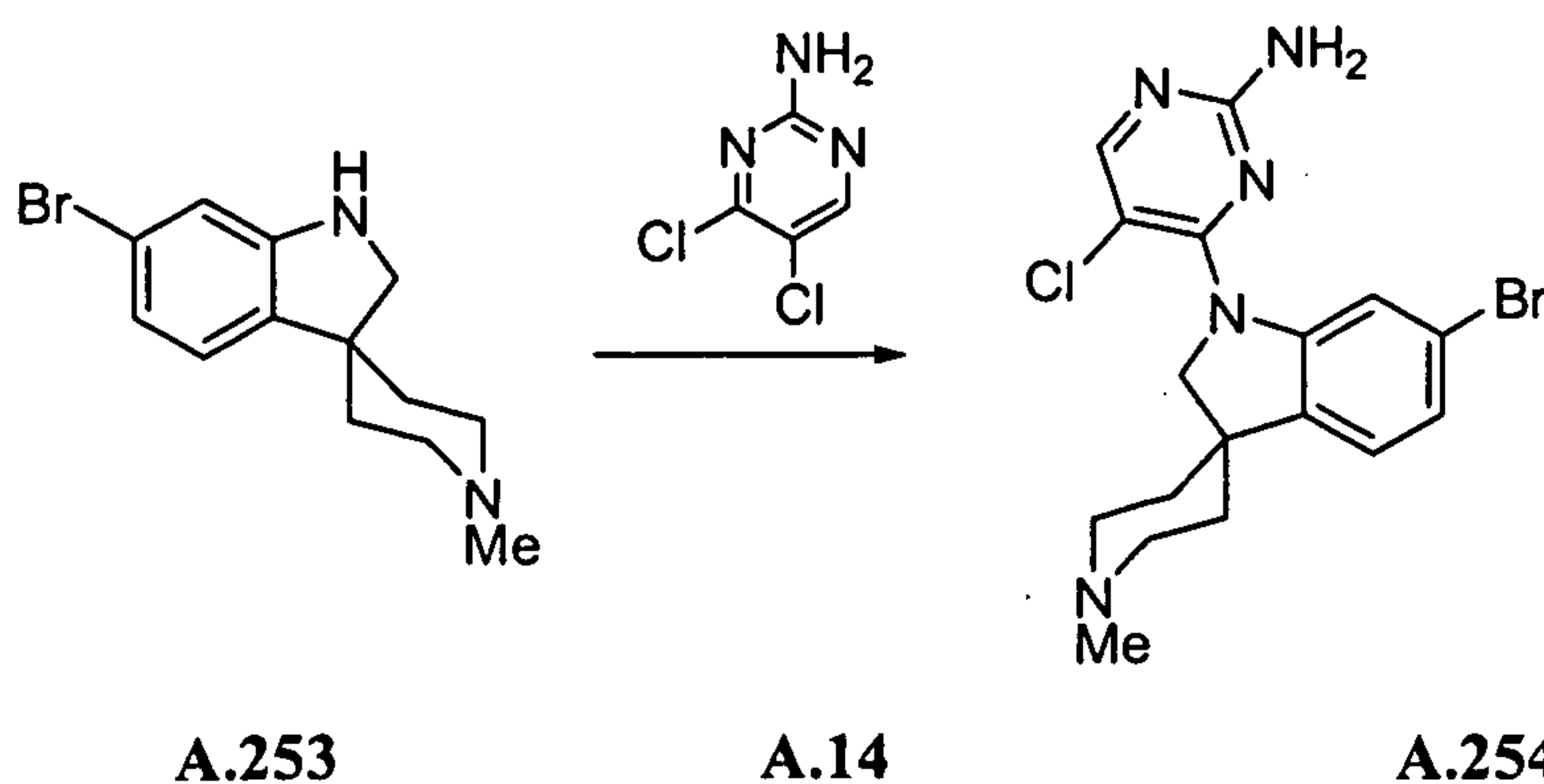
A stirred solution of 6-bromoindolin-2-one A.35 (4.4 g, 9.43 mmol) in dry THF (40 mL) was cooled to -78°C in an acetone-dry ice bath before a solution of NaHMDS in THF (2 M) (52 mL, 5 eq.) was dropwise introduced through a syringe under a nitrogen atmosphere over a period of 25 min. The resulting mixture was stirred at -78°C for 1 h 15 min before mechlorethamine hydrochloride was added in one portion as a solid. The resulting mixture was stirred at -78°C for 40 min and at ambient temperature for 3 days. The reaction mixture was cooled in an ice-water bath before quenched with water followed by ice and aqueous 2 N NaOH, and then extracted with ethyl acetate (3 x). The combined organics were dried over Na_2SO_4 . The residue after concentration *in vacuo* was subjected to Combi-Flash column

chromatography (methanol/triethylamine/dichloromethane) to give 6-bromo-1'-methylspiro[indole-3,4'-piperidin]-2-one **A.252** (4.0 g, 65 %) as an off-white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.54 (br s, 1H), 7.42 (d, $J = 7.8$ Hz, 1H), 7.15 (dd, $J = 7.8, 1.7$ Hz, 1H), 7.00 (d, $J = 1.7$ Hz, 1H), 2.95-2.75 (m, 4H), 1.90-1.65 (m, 4H). LCMS-ESI (POS), M/Z , $M+1$: Found 295.0 and 297.0.



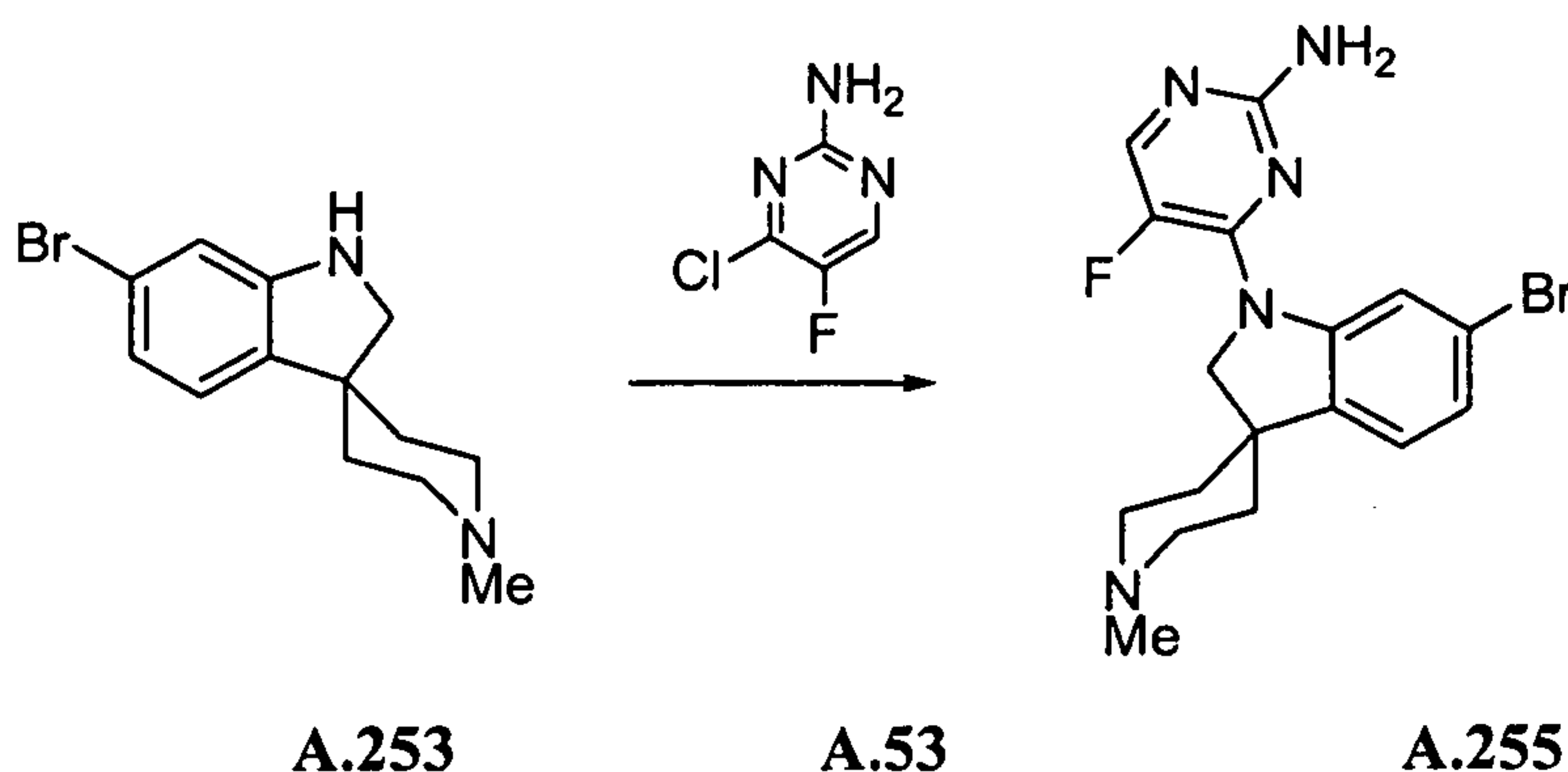
6-bromo-1'-methylspiro[indoline-3,4'-piperidine] A.253 was prepared by the method of Kucerovy, A.; Hathaway, J. S.; Mattner, P. G.; Repic, O. *Synth. Commun.* **1992**, 22, 729.

To a stirred solution of 6-bromo-1'-methylspiro[indole-3,4'-piperidin]-2-one **A.252** (1.5 g, 5.08 mmol) in dry toluene (80 mL), which was preheated at 80 °C in an oil bath, was dropwise added a solution of Red-AL in toluene (3 M) (5.1 mL, 3 eq.) under a nitrogen atmosphere. The resulting mixture was stirred at this temperature for 2 h. Upon workup the mixture was cooled in an ice-salt bath before quenched with ice-cold aqueous 2 N NaOH. The mixture was further diluted with ice-cold aqueous 2 N NaOH and extracted with ethyl acetate (3 x). The combined organics were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give pure 6-bromo-1'-methylspiro[indoline-3,4'-piperidine] **A.253** (> 90 % yield). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 6.91 (d, $J = 7.8$ Hz, 1H), 6.65 (dd, $J = 7.8, 1.7$ Hz, 1H), 6.58 (d, $J = 1.7$ Hz, 1H), 5.81 (br s, 1H), 3.38 (s, 2H), 2.69 (br d, $J = 11.6$ Hz, 2H), 2.19 (s, 3H), 1.97 (t, $J = 11.6$ Hz, 2H), 1.75 (td, $J = 12.7, 3.6$ Hz, 2H), 1.55 (d, $J = 12.7$ Hz, 2H). LCMS-ESI (POS), M/Z , $M+1$: Found 281.0 and 283.0.



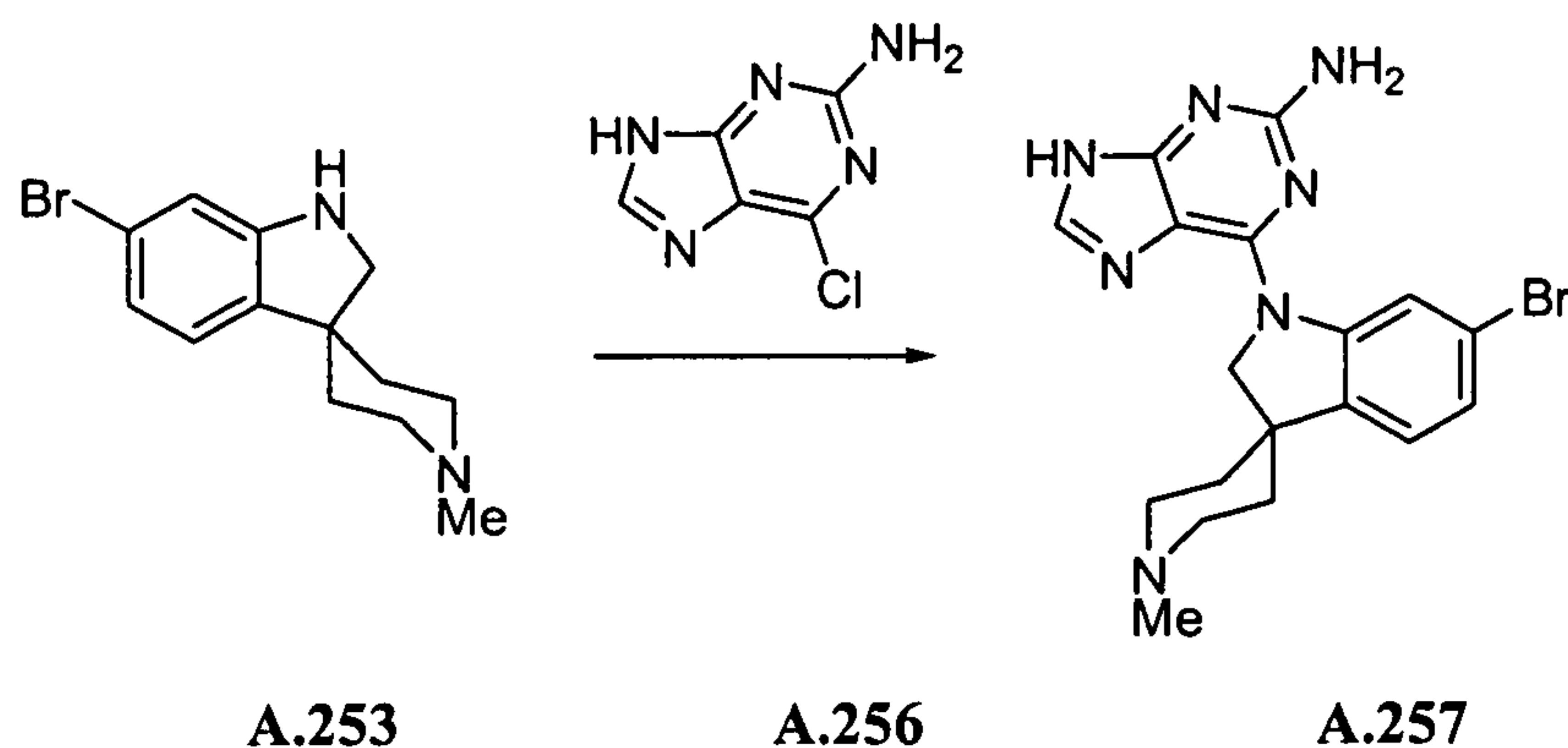
4-(6-bromo-1'-methylspiro[indoline-3,4'-piperidine]-1-yl)-5-chloropyrimidin-2-amine A.254 was prepared from 6-bromo-1'-methylspiro[indoline-3,4'-piperidine] **A.253** using chemistry similar to that described for compound **A.239**. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ

ppm 8.12 (1 H, s), 7.37 (1 H, s), 7.18 (1 H, d, $J=8.0$ Hz), 7.08 (1 H, d, $J=8.0$ Hz), 6.71 (2 H, s), 4.03 (2 H, s), 2.73 (2 H, d, $J=11.7$ Hz), 2.19 (3 H, s), 1.91 - 2.03 (2 H, m), 1.84 (2 H, td, $J=12.4, 3.3$ Hz), 1.59 (2 H, d, $J=12.8$ Hz). LCMS-ESI (POS), M/Z , $M+1$: Found 408.1 and 410.0.



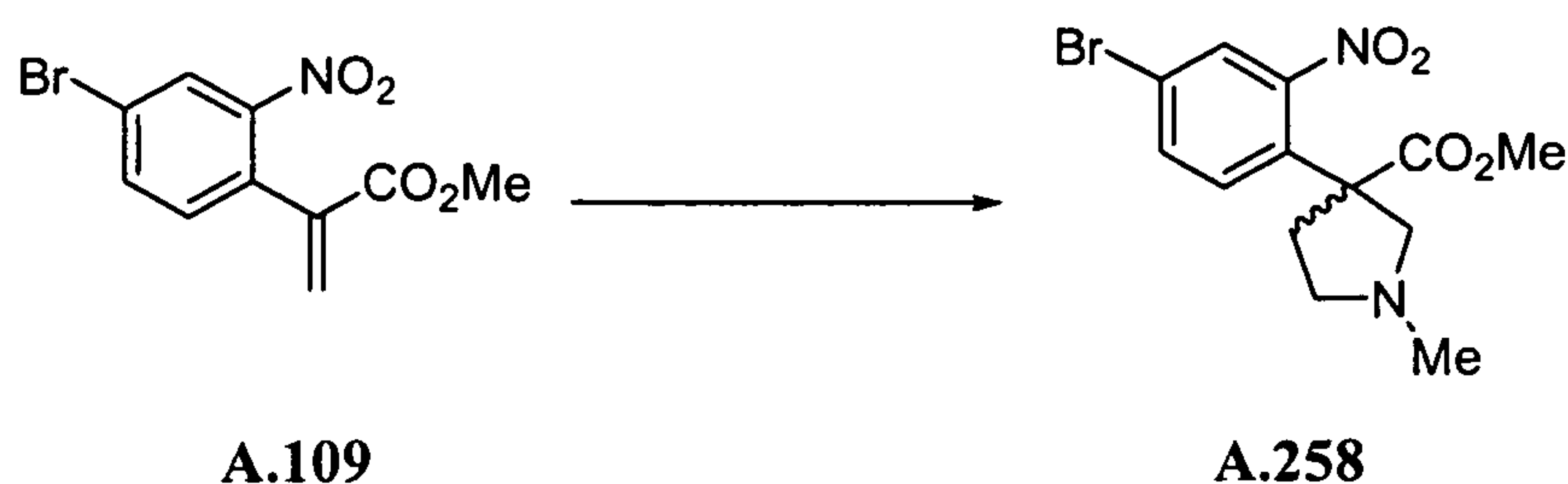
44-(6-bromo-1'-methylspiro[indoline-3,4'-piperidine]-1-yl)-5-fluoropyrimidin-2-amine

A.255 was prepared from 6-bromo-1'-methylspiro[indoline-3,4'-piperidine] **A.253** and 4-chloro-5-fluoro-2-pyrimidinamine **A.53** using chemistry similar to that described for compound **A.239**. (an off-white solid). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 8.14 (1 H, s), 8.03 (1 H, d, $J=5.9$ Hz), 7.17 - 7.23 (1 H, m), 7.09 - 7.15 (1 H, m), 6.43 (2 H, s), 4.06 (2 H, d, $J=4.2$ Hz), 2.74 (2 H, d, $J=11.5$ Hz), 2.20 (3 H, s), 1.95 (2 H, t, $J=11.5$ Hz), 1.79 - 1.90 (2 H, m), 1.61 (2 H, d, $J=13.0$ Hz). LCMS-ESI (POS), M/Z , $M+1$: Found 392.0 and 394.0.



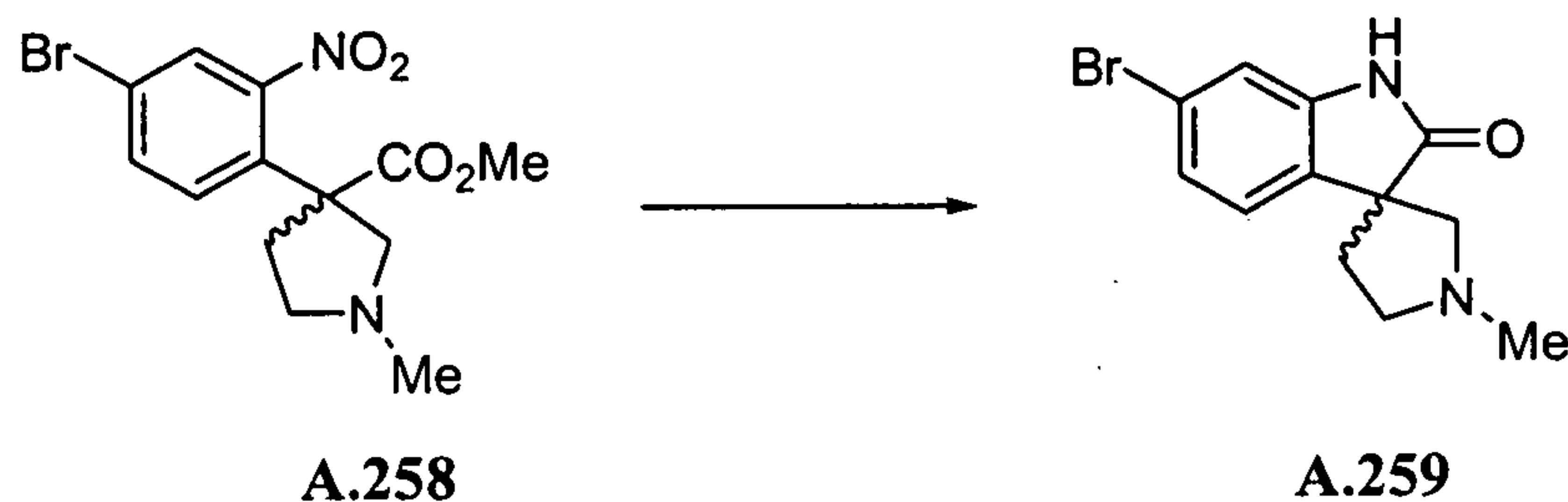
6-(6-bromo-1'-methylspiro[indoline-3,4'-piperidine]-1-yl)-9H-purin-2-amine **A.257** was

prepared from 6-bromo-1'-methylspiro[indoline-3,4'-piperidine] **A.253** and 6-chloro-9H-purin-2-amine **A.256** using chemistry similar to that described for compound **A.239**. (an off-white solid). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 8.77 (1 H, d, $J=1.7$ Hz), 7.87 (1 H, s), 7.16 - 7.22 (1 H, m), 7.09 - 7.14 (1 H, m), 6.14 (2 H, s), 4.60 (2 H, s), 2.78 (2 H, d, $J=11.5$ Hz), 2.23 (3 H, s), 1.95 - 2.05 (2 H, m), 1.87 (2 H, td, $J=12.8, 3.5$ Hz), 1.62 (2 H, d, $J=12.7$ Hz). LCMS-ESI (POS), M/Z , $M+1$: Found 414.1 and 416.1.



(rac)-Methyl 3-(4-bromo-2-nitrophenyl)-1-methylpyrrolidine-3-carboxylate was prepared by the method of Cravotto, G.; Giovenzana, G. B.; Pilati, T.; Sisti, M.; Palmisano, G. *J. Org. Chem.* **2001**, *66*, 8447-8453.

To a stirred solution of methyl 2-(4-bromo-2-nitrophenyl)acrylate **A.109** (5.5 g, 19.22 mmol) in toluene (180 mL) was added paraformaldehyde (7.34 g, 12 eq.) in one portion at rt. The 500 mL round-bottomed flask was fitted with a Dean-Stark reflux condenser filled with 3 Å molecular sieves and the resulting mixture was heated to reflux (~ 140 °C) under nitrogen. Sarcosine (5.24 g, 3 eq.) was added portionwise to the reaction mixture during a period of 1 h. Then the mixture was refluxed for a further 5.5 h. After cooling, the mixture was vacuum filtered and concentrated *in vacuo* and the residue was purified on a column of silica gel (methanol/dichloromethane) to give methyl 3-(4-bromo-2-nitrophenyl)-1-methylpyrrolidine-3-carboxylate **A.258** (4.7 g, 72% yield) as a light yellow solid. ¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 8.13 (1 H, br. s.), 7.94 (1 H, d, *J*=8.3 Hz), 7.79 (1 H, d, *J*=8.8 Hz), 3.54 (3 H, s), 3.24 (1 H, d, *J*=9.8 Hz), 2.87 (1 H, br. s.), 2.66 - 2.81 (2 H, m), 2.42 (1 H, q, *J*=8.0 Hz), 2.29 (3 H, s), 1.95 - 2.06 (1 H, m). LCMS-ESI (POS), *M/Z*, *M*+1: Found 343.3 and 345.3.

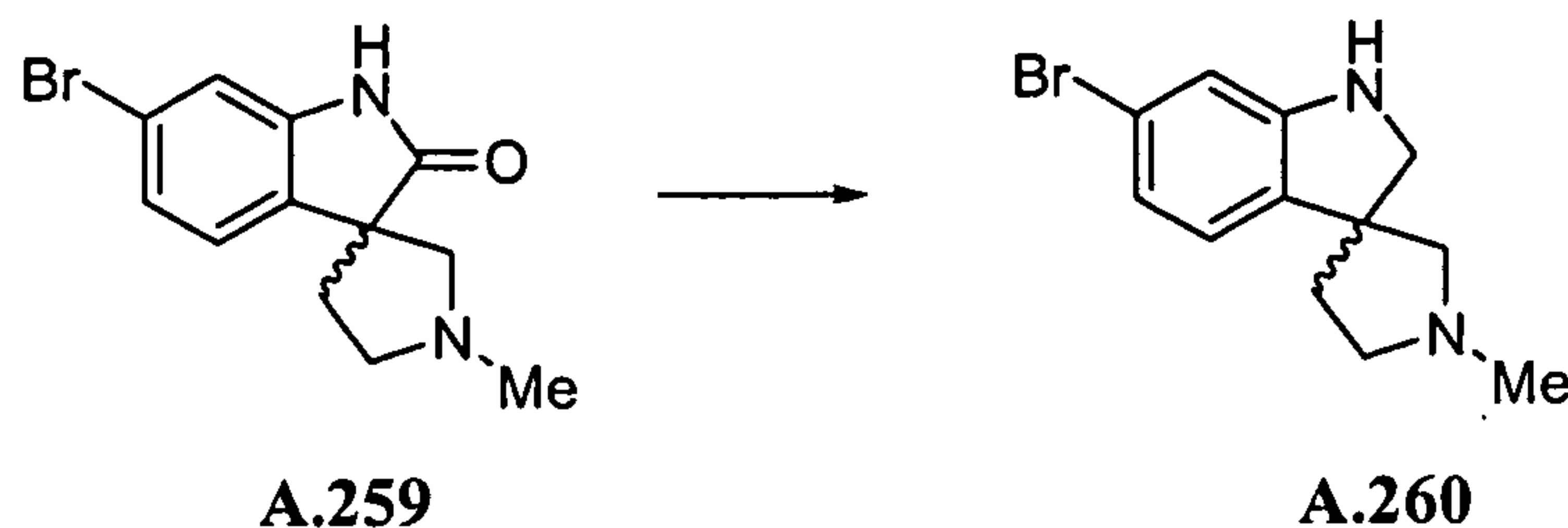


(rac)-6-bromo-1'-methylspiro[indoline-3,3'-pyrrolidin]-2-one **A.259**

Ref. Quallich, G. J.; Morrissey, P. M. *Synthesis* **1993**, 51-53.

To a stirred solution of methyl 3-(4-bromo-2-nitrophenyl)-1-methylpyrrolidine-3-carboxylate (4.7 g, 13.70 mmol) in glacial acetic acid (100 mL) was added iron powder (3.82 g, 5 eq.) and the resulting mixture was heated in an oil bath at 100 °C for 4 h. After cooling the mixture was vacuum filtered through a layer of celite. The filtrate was concentrated under high vacuum and the residue was purified on a column of silica gel (methanol/dichloromethane with triethylamine) to give 6-bromo-1'-methylspiro[indoline-3,3'-pyrrolidin]-2-one **A.259** in nearly quantitative yield as an off-white solid. ¹H NMR (400 MHz, *DMSO-d*₆) δ ppm 10.47 (1 H, br.

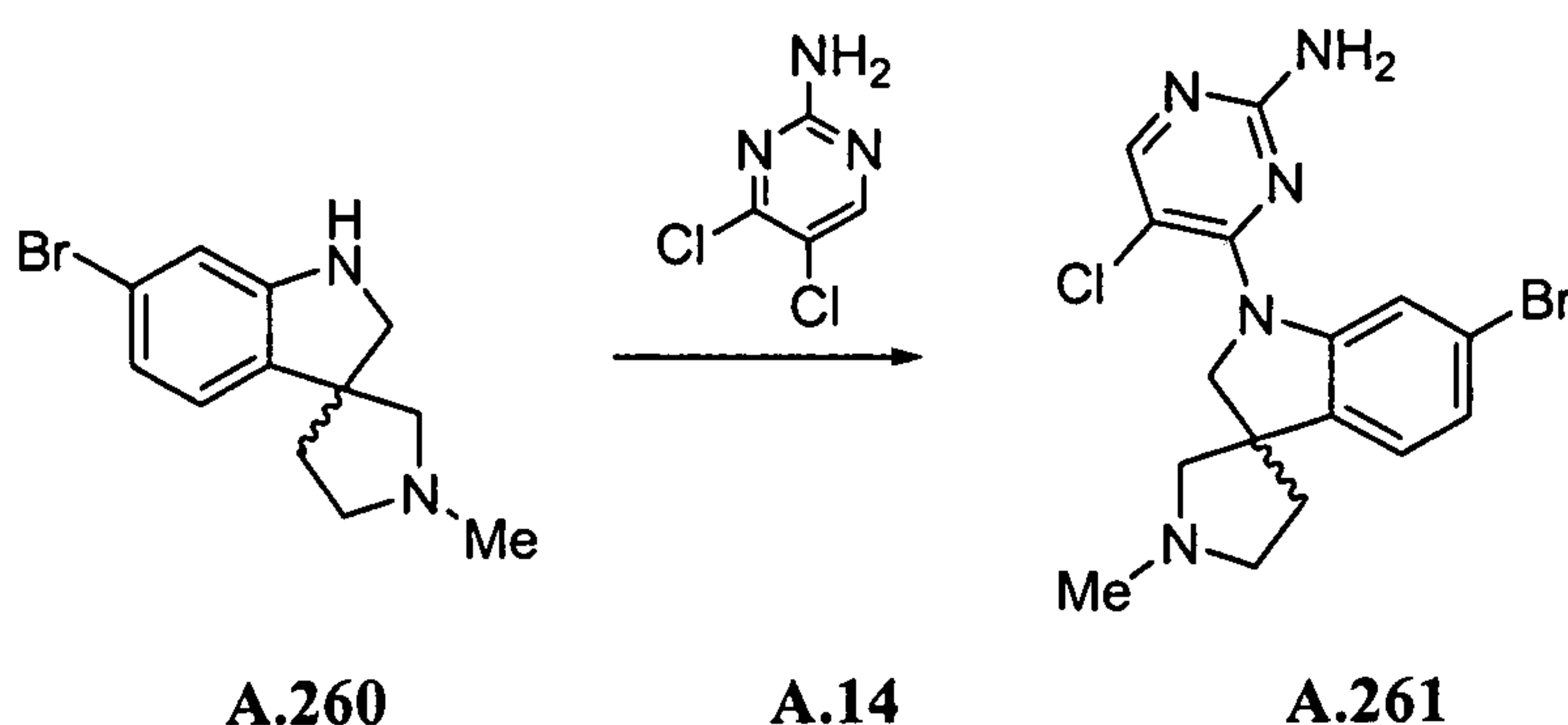
s.), 7.25 (1 H, d, $J=8.1$ Hz), 7.14 (1 H, d), 6.95 (1 H, d, $J=1.8$ Hz), 2.97 - 3.08 (1 H, m), 2.73 (1 H, d, $J=8.8$ Hz), 2.56 (1 H, d, $J=8.8$ Hz), 2.43 - 2.49 (1 H, m), 2.33 (3 H, s), 2.12 - 2.22 (1 H, m), 1.84 - 1.94 (1 H, m). LCMS-ESI (POS), M/Z , $M+1$: Found 281.4 and 283.3.



(rac)-6-bromo-1'-methylspiro[indoline-3,3'-pyrrolidine] A.260

Ref. KucEROVY, A.; Hathaway, J. S.; Mattner, P. G.; Repic, O. *Synth. Commun.* 1992, 22, 729.

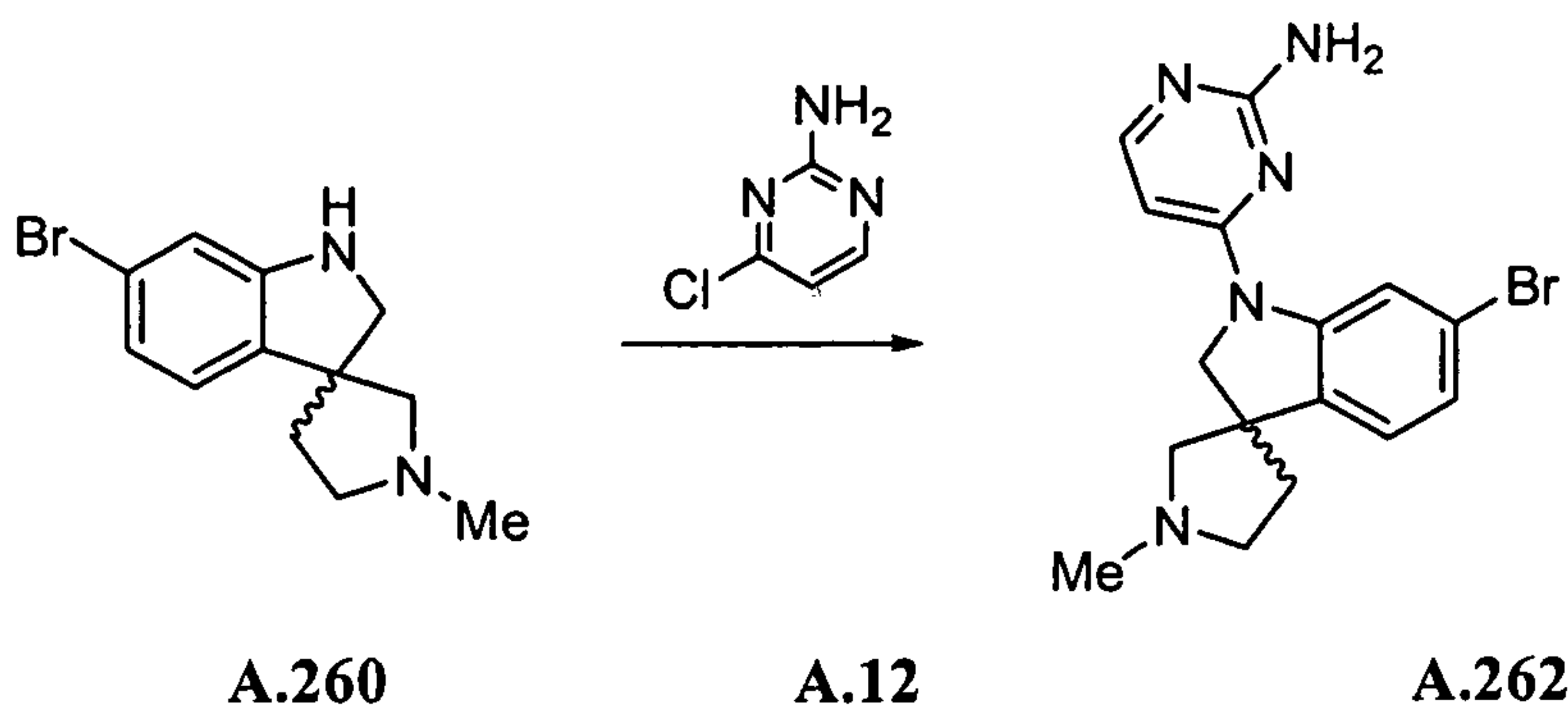
To a stirred solution of 6-bromo-1'-methylspiro[indoline-3,3'-pyrrolidin]-2-one **A.259** (3.5 g, 12.45 mmol) in dry toluene (40 mL) which was preheated at 85 °C in an oil bath was added dropwise a solution of Red-AL in toluene (3 M) (11 mL, 3 eq.) under nitrogen. The resulting mixture was heated at this temperature for 2 h and then cooled in an ice-salt bath followed by quenching with 2 N NaOH (aq.). After further dilution with 2 N NaOH (aq.), the mixture was extracted with ethyl acetate (3 x) and the combined extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give pure 6-bromo-1'-methylspiro[indoline-3,3'-pyrrolidine] **A.260** (> 90% yield) as an off-white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 6.97 (1 H, d, $J=7.4$ Hz), 6.67 (1 H, dd, $J=7.8, 1.6$ Hz), 6.59 (1 H, d, $J=2.0$ Hz), 5.75 (1 H, s), 3.39 - 3.43 (1 H, m), 3.31 - 3.34 (1 H, m), 2.61 - 2.69 (1 H, m), 2.59 (1 H, d, $J=9.0$ Hz), 2.51 - 2.56 (1 H, m), 2.37 (1 H, d, $J=9.0$ Hz), 2.26 (3 H, s), 1.83 - 2.01 (2 H, m). LCMS-ESI (POS), M/Z , $M+1$: Found 267.4 and 269.4.



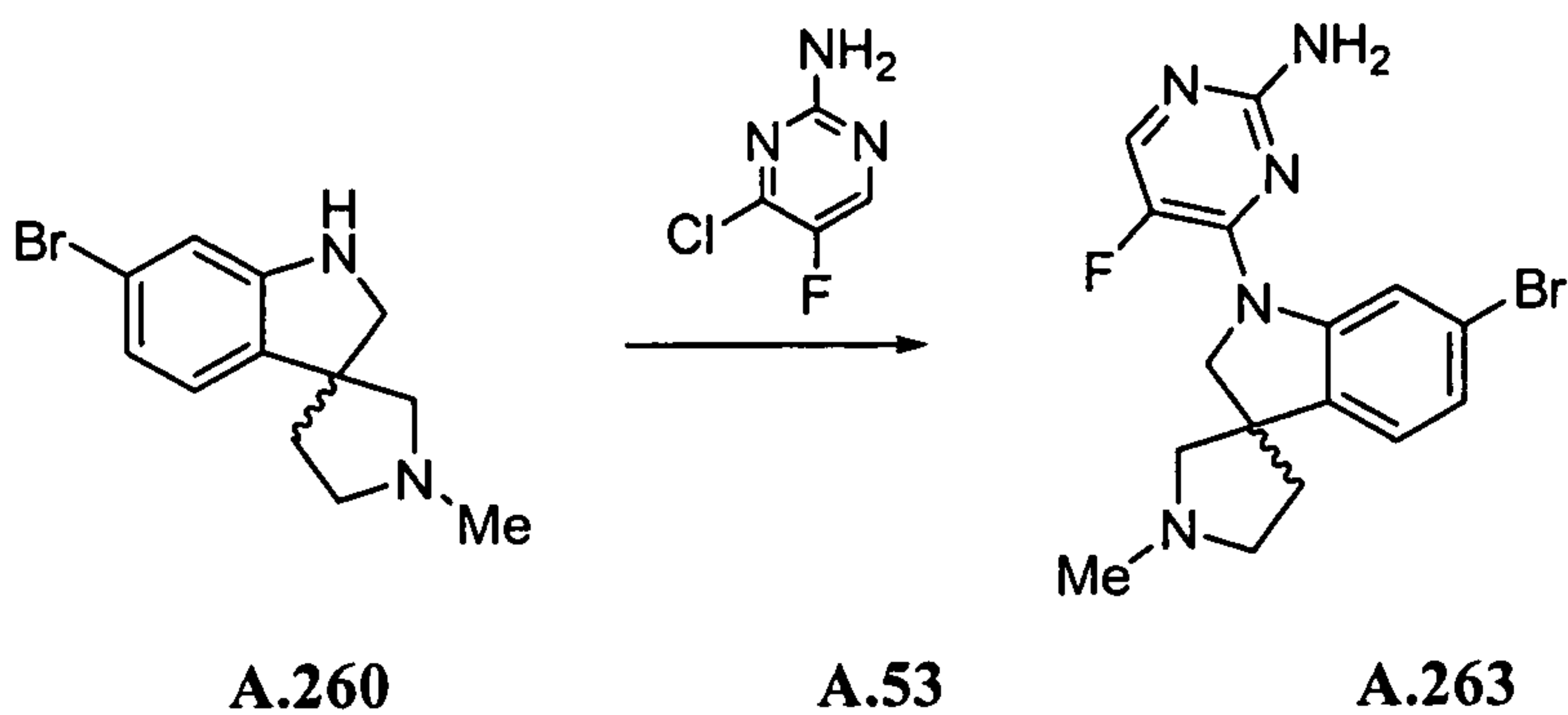
4-(6-bromo-1'-methylspiro[indoline-3,3'-pyrrolidine]-1-yl)-5-chloropyrimidin-2-amine A.261

A.261 was prepared from 6-bromo-1'-methylspiro[indoline-3,3'-pyrrolidine] **A.260** using chemistry similar to that described for compound **A.239**. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 8.10 (1 H, s), 7.45 (1 H, d, $J=2.0$ Hz), 7.23 (1 H, d, $J=8.3$ Hz), 7.11 (1 H, dd, $J=8.1, 1.7$ Hz), 6.69 (2 H, s), 4.16 (1 H, d), 4.08 (1 H, d), 2.70 - 2.77 (1 H, m), 2.67 (1 H, d, $J=9.3$ Hz),

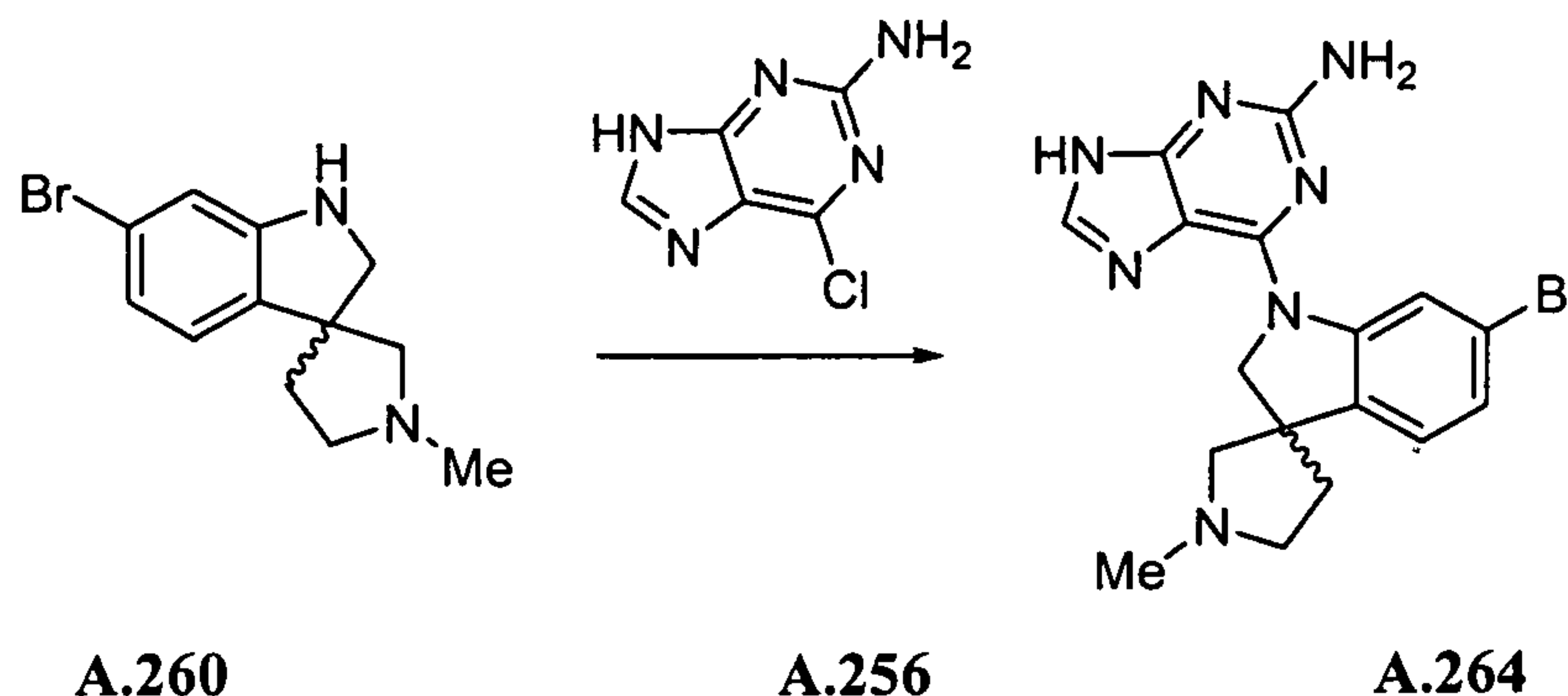
2.52 - 2.57 (1 H, m), 2.41 (1 H, d, $J=8.8$ Hz), 2.27 (3 H, s), 1.95 - 2.12 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 394.0 and 396.0.



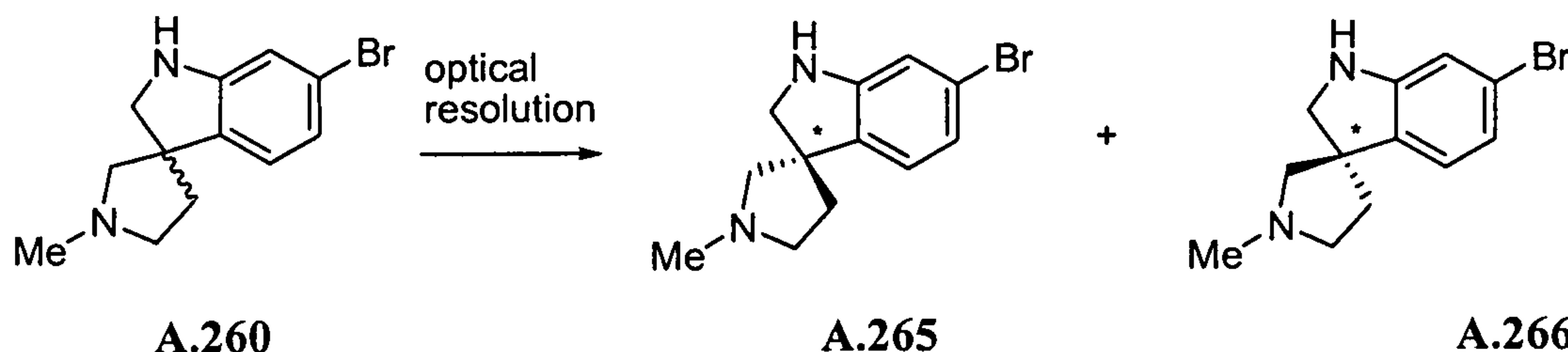
4-(6-bromo-1'-methylspiro[indoline-3,3'-pyrrolidine]-1-yl)pyrimidin-2-amine A.262 was prepared from 6-bromo-1'-methylspiro[indoline-3,4'-piperidine] **A.260** and 4-chloro-2-pyrimidinamine **A.12** using chemistry similar to that described for compound **A.239**. (an off-white solid). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 8.60 (1 H, d, $J=2.0$ Hz), 7.97 (1 H, d, $J=5.9$ Hz), 7.23 (1 H, d, $J=7.8$ Hz), 7.10 (1 H, dd, $J=7.8, 2.0$ Hz), 6.43 (2 H, br. s.), 6.04 (1 H, d, $J=5.9$ Hz), 3.93 - 3.99 (1 H, m), 3.85 - 3.91 (1 H, m), 2.76 (1 H, d, $J=5.9$ Hz), 2.68 (1 H, d, $J=8.8$ Hz), 2.55 - 2.63 (1 H, m), 2.48 (1 H, d), 2.29 (3 H, s), 2.03 - 2.13 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 360.0 and 362.0.



4-(6-bromo-1'-methylspiro[indoline-3,3'-pyrrolidine]-1-yl)-5-fluoropyrimidin-2-amine A.263 was prepared from 6-bromo-1'-methylspiro[indoline-3,4'-piperidine] **A.260** and 4-chloro-5-fluoro-2-pyrimidinamine **A.53** using chemistry similar to that described for compound **A.239**. (an off-white solid) ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.19 (1 H, d, $J=1.8$ Hz), 8.02 (1 H, d, $J=5.9$ Hz), 7.25 (1 H, d), 7.15 (1 H, dd, $J=8.1, 1.8$ Hz), 6.41 (2 H, s), 4.17 - 4.25 (1 H, m), 4.07 - 4.14 (1 H, m), 2.68 - 2.80 (2 H, m), 2.52 - 2.59 (1 H, m), 2.43 (1 H, d, $J=9.2$ Hz), 2.28 (3 H, s), 2.07 (2 H, t, $J=7.1$ Hz). LCMS-ESI (POS), M/Z, M+1: Found 378.0 and 380.0.

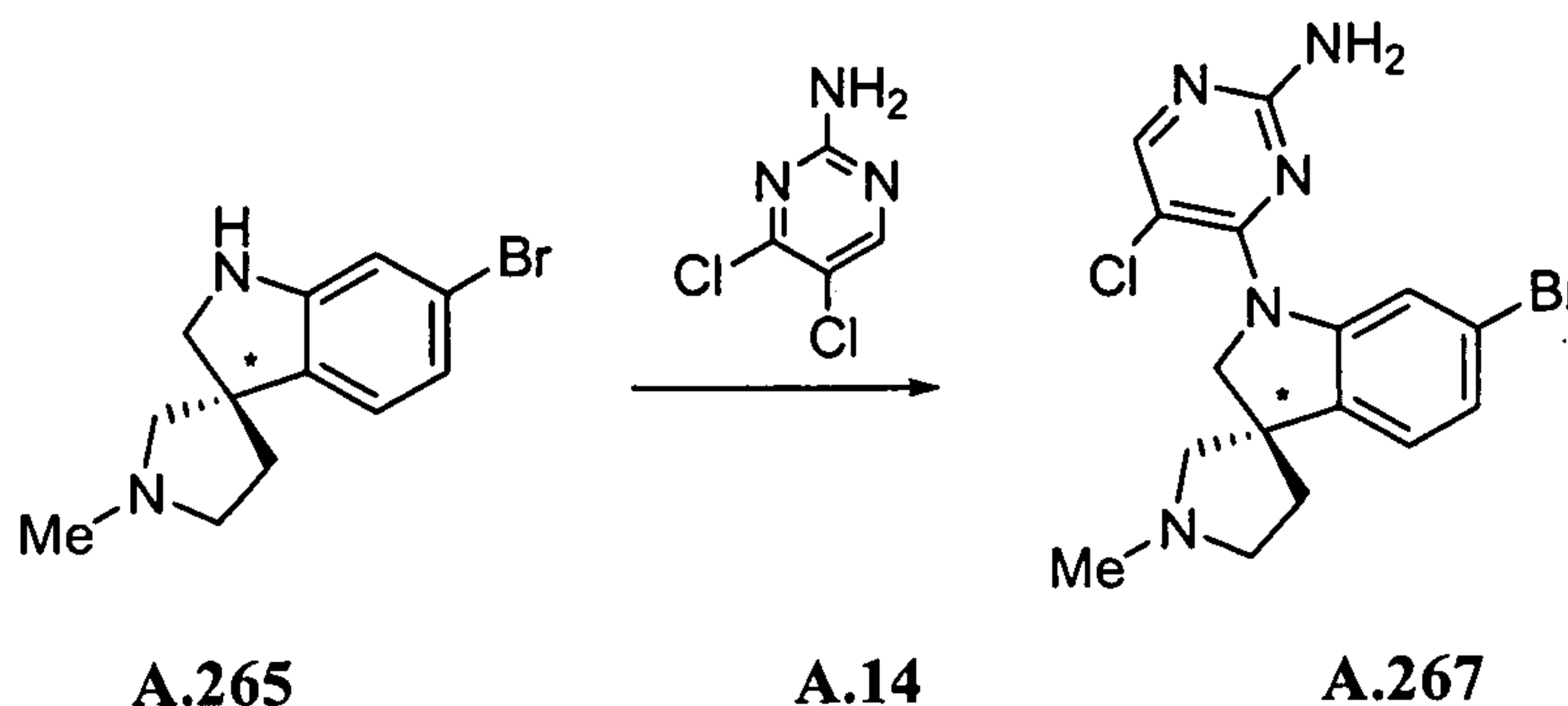


6-(6-bromo-1'-methylspiro[indoline-3,3'-pyrrolidine]-1-yl)-9H-purin-2-amine A.264 was prepared from 6-bromo-1'-methylspiro[indoline-3,4'-piperidine] **A.260** and 6-chloro-9H-purin-2-amine **A.256** using chemistry similar to that described for compound **A.239**. (an off-white solid) ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 12.37 (1 H, br. s.), 8.76 (1 H, d, $J=1.8$ Hz), 7.81 (1 H, s), 7.26 (1 H, d, $J=7.7$ Hz), 7.14 (1 H, dd, $J=8.1, 1.8$ Hz), 6.13 (2 H, s), 4.81 (1 H, d, $J=11.7$ Hz), 4.53 (1 H, d, $J=12.1$ Hz), 2.76 - 2.86 (1 H, m), 2.72 (1 H, d, $J=9.1$ Hz), 2.54 - 2.62 (1 H, m), 2.46 (2 H, d, $J=8.8$ Hz), 2.30 (3 H, s), 2.01 - 2.18 (2 H, m). LCMS-ESI (POS), M/Z , $M+1$: Found 400.1 and 402.1.

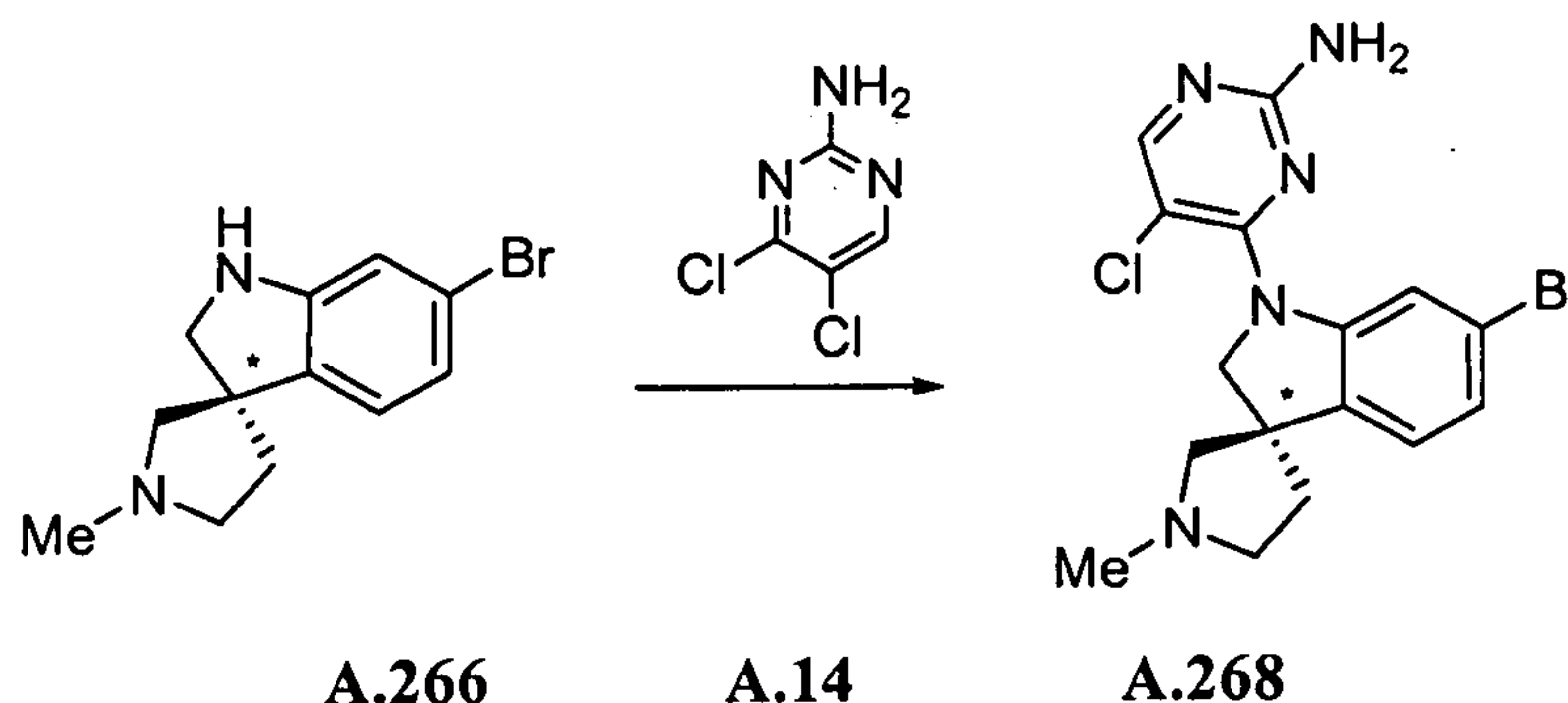


(3S*)-6-bromo-1'-methylspiro[indoline-3,3'-pyrrolidine] A.265 and **(3R*)-6-bromo-1'-methylspiro[indoline-3,3'-pyrrolidine] A.266** (stereochemistry arbitrarily assigned) were obtained from optical resolution of (rac)-6-bromo-1'-methylspiro[indoline-3,3'-pyrrolidine] **A.260** by the following method. Instrument: Agilent 1100 series. Column: OD-preparative (50 mm X 500 mm). Solvents: 1% isopropanol in hexanes. Gradient: isochratic. Amount of sample per injection: 250 mg in methanol (6 mL). Separation quality: baseline separation. The first peak eluting off of the OD column provided **(3S*)-6-bromo-1'-methylspiro[indoline-3,3'-pyrrolidine] A.265** in 94% ee. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 6.97 (1 H, d, $J=7.4$ Hz), 6.67 (1 H, dd, $J=7.8, 1.6$ Hz), 6.59 (1 H, d, $J=2.0$ Hz), 5.75 (1 H, s), 3.39 - 3.43 (1 H, m), 3.31 - 3.34 (1 H, m), 2.61 - 2.69 (1 H, m), 2.59 (1 H, d, $J=9.0$ Hz), 2.51 - 2.56 (1 H, m), 2.37 (1 H, d, $J=9.0$ Hz), 2.26 (3 H, s), 1.83 - 2.01 (2 H, m). LCMS-ESI (POS), M/Z , $M+1$: Found 267.4 and 269.4.

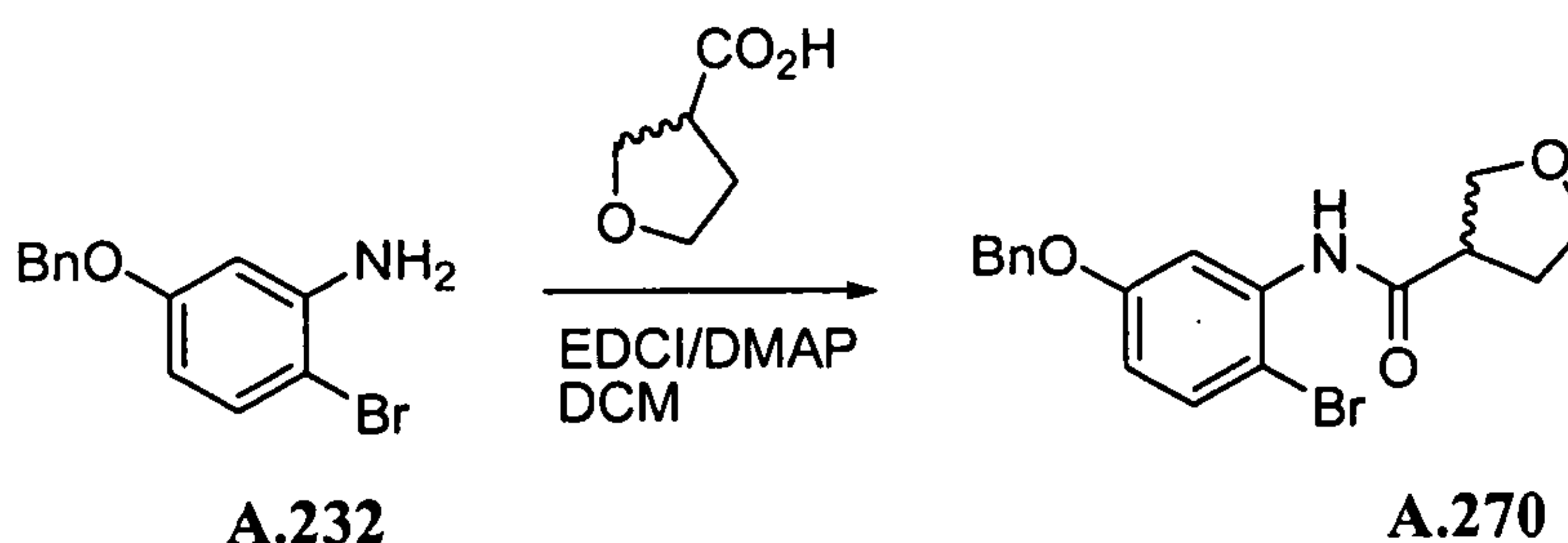
The second peak furnished (3R*)-6-bromo-1'-methylspiro[indoline-3,3'-pyrrolidine] **A.266** in 99% ee.



4-((3R*)-6-Bromo-1'-methylspiro[indole-3,3'-pyrrolidin]-1(2H)-yl)-5-chloro-2-pyrimidinamine A.267 was prepared from (3S*)-6-bromo-1'-methylspiro[indoline-3,3'-pyrrolidine] **A.265** using chemistry similar to that described for compound **A.239**. ¹H NMR (400 MHz, *DMSO-d*₆) δ ppm 8.10 (1 H, s), 7.45 (1 H, d, *J*=1.6 Hz), 7.23 (1 H, d, *J*=7.8 Hz), 7.10 (1 H, dd, *J*=7.8, 1.6 Hz), 6.68 (2 H, s), 4.16 (1 H, d), 4.08 (1 H, d), 2.69 - 2.78 (1 H, m), 2.67 (1 H, d, *J*=9.0 Hz), 2.52 - 2.58 (1 H, m), 2.42 (1 H, d, *J*=9.0 Hz), 2.27 (3 H, s), 1.97 - 2.12 (2 H, m). LCMS-ESI (POS), *M/Z*, *M*+1: Found 394.0 and 396.0.

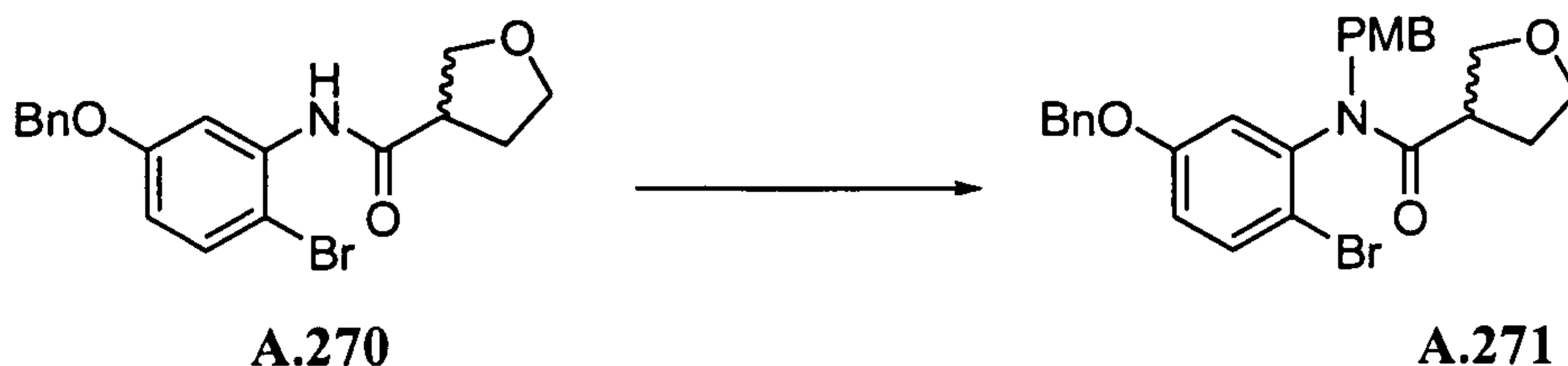


4-((3R*)-6-Bromo-1'-methylspiro[indole-3,3'-pyrrolidin]-1(2H)-yl)-5-chloro-2-pyrimidinamine A.268 was prepared from (3R*)-6-bromo-1'-methylspiro[indoline-3,3'-pyrrolidine] **A.266** using chemistry similar to that described for compound **A.239**.

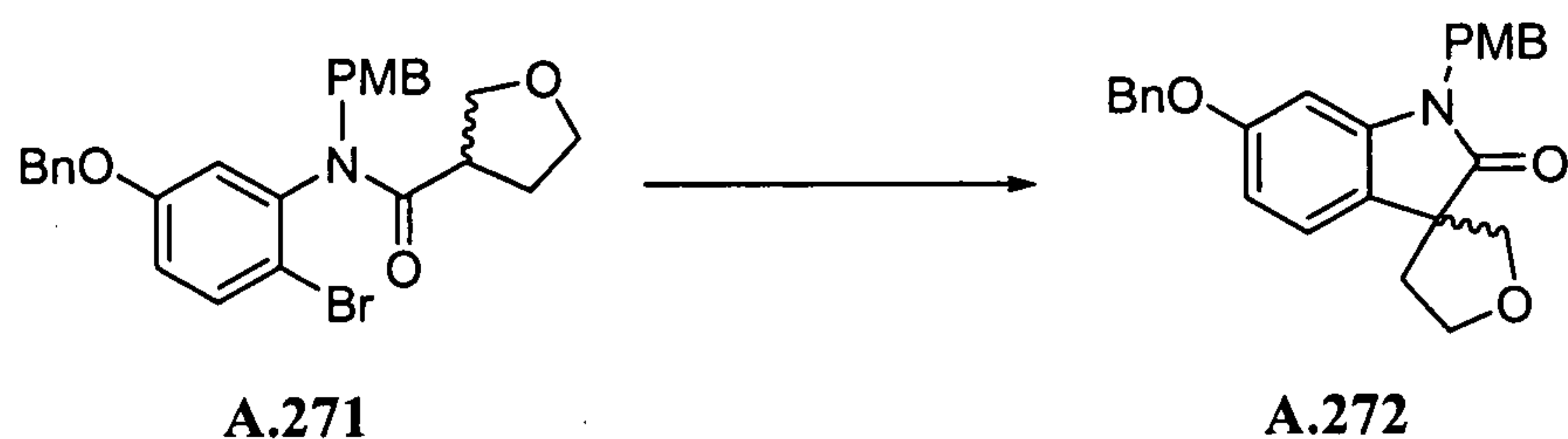


N-(5-(benzyloxy)-2-bromophenyl)tetrahydrofuran-3-carboxamide A.270 was prepared from 5-(benzyloxy)-2-bromoaniline **A.232** and tetrahydro-3-furancarboxylic acid using

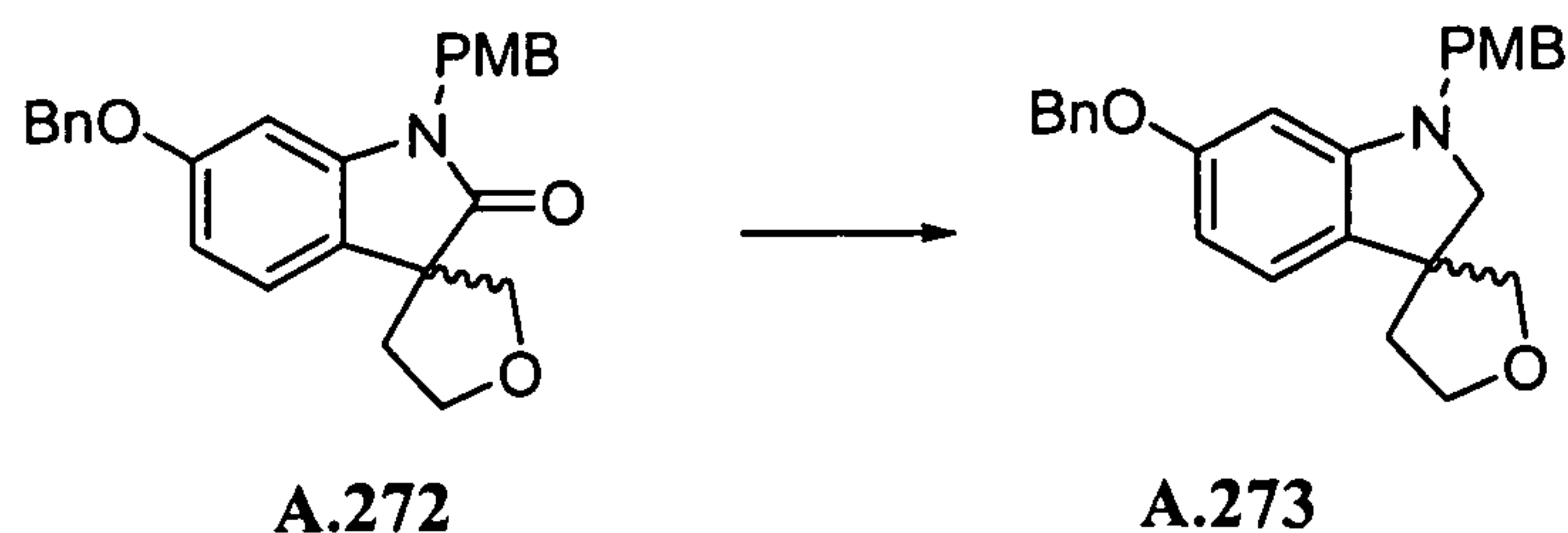
chemistry similar to that described for compound **A.234**. (a white solid) ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 9.46 (1 H, s), 7.53 (1 H, d, $J=8.6$ Hz), 7.28 - 7.47 (6 H, m), 6.84 (1 H, dd, $J=8.8, 2.9$ Hz), 5.09 (2 H, s), 3.92 (1 H, t, $J=8.0$ Hz), 3.77 (2 H, q, $J=6.8$ Hz), 3.70 (1 H, q, $J=7.0$ Hz), 3.22 - 3.28 (1 H, m), 2.09 (2 H, q, $J=6.8$ Hz). LCMS-ESI (POS), M/Z , $\text{M}+1$: Found 376.1 and 378.1.



N-(5-(benzyloxy)-2-bromophenyl)-N-(4-methoxybenzyl)tetrahydrofuran-3-carboxamide A.271 (a colorless viscous liquid), was prepared from N-(5-(benzyloxy)-2-bromophenyl)tetrahydrofuran-3-carboxamide **A.270** using chemistry similar to that described for compound **A.235**. ¹H NMR (400 MHz, *DMSO-d*₆) δ ppm 7.64 (1 H, d, *J*=9.0 Hz), 7.29 - 7.42 (6 H, m), 7.06 (2 H, dd, *J*=8.6, 2.7 Hz), 7.00 (1 H, dt, *J*=9.0, 3.5 Hz), 6.84 (2 H, dd, *J*=8.6, 2.7 Hz), 6.61 (1 H, t, *J*=3.1 Hz), 5.20 (1 H, dd, *J*=14.3, 3.3 Hz), 4.98 (2 H, s), 4.14 (1 H, d, *J*=14.1 Hz), 3.65 - 3.80 (6 H, m), 3.44 - 3.61 (2 H, m), 2.59 - 2.72 (1 H, m), 2.04 - 2.17 (1 H, m). LCMS-ESI (POS), *M/Z*, *M*+1: Found 496.1 and 498.1.

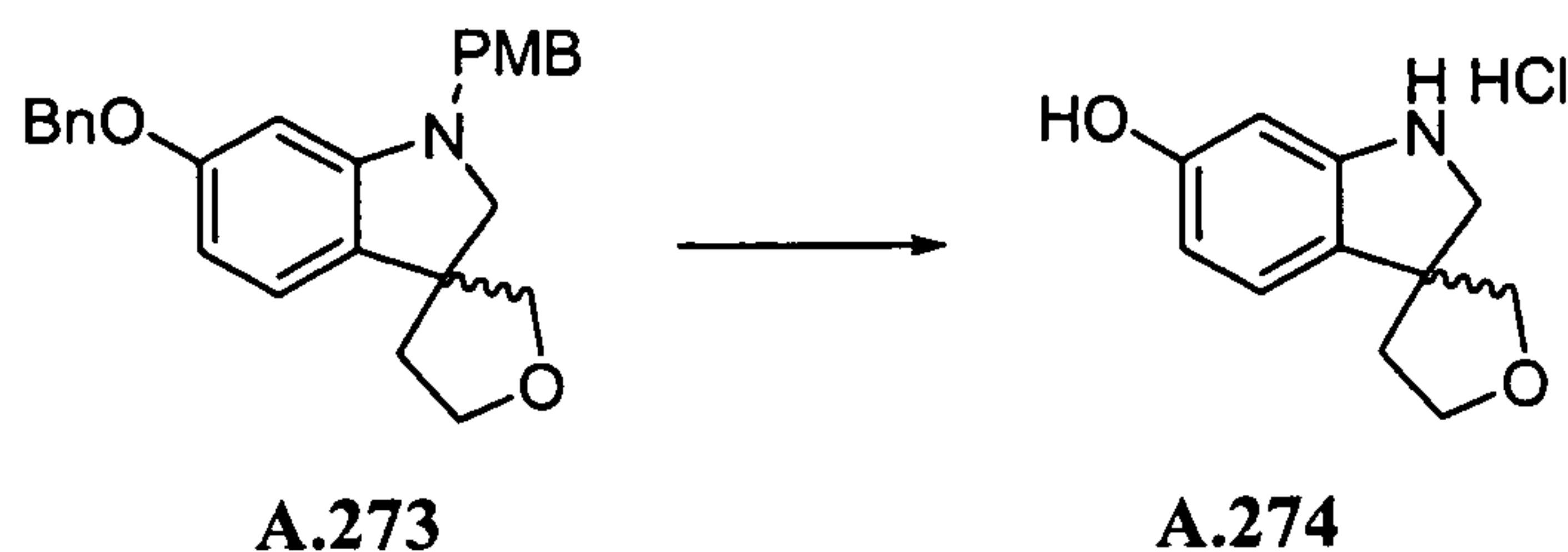


(rac)-6'6'-(benzyloxy)-1'-(4-methoxybenzyl)-4,5-dihydro-2H-spiro[furan-3,3'-indolin]-2'-one A.272 (a colorless viscous liquid) was prepared from N-(5-(benzyloxy)-2-bromophenyl)-N-(4-methoxybenzyl)tetrahydrofuran-3-carboxamide **A.271** using chemistry similar to that described for compound **A.236**. ¹H NMR (400 MHz, *DMSO-d*₆) δ ppm 7.29 - 7.46 (6 H, m), 7.18 - 7.26 (3 H, m), 6.87 (2 H, d, *J*=8.6 Hz), 6.62 - 6.68 (2 H, m), 5.06 (2 H, s), 4.81 (2 H, s), 4.05 - 4.15 (2 H, m), 3.85 - 3.90 (1 H, m), 3.77 (1 H, d, *J*=8.2 Hz), 3.71 (3 H, s), 2.32 (1 H, ddd, *J*=12.3, 7.4, 7.2 Hz), 2.08 (1 H, dt, *J*=12.6, 6.4 Hz). LCMS-ESI (POS), *M/Z*, *M*+1: Found 416.2.

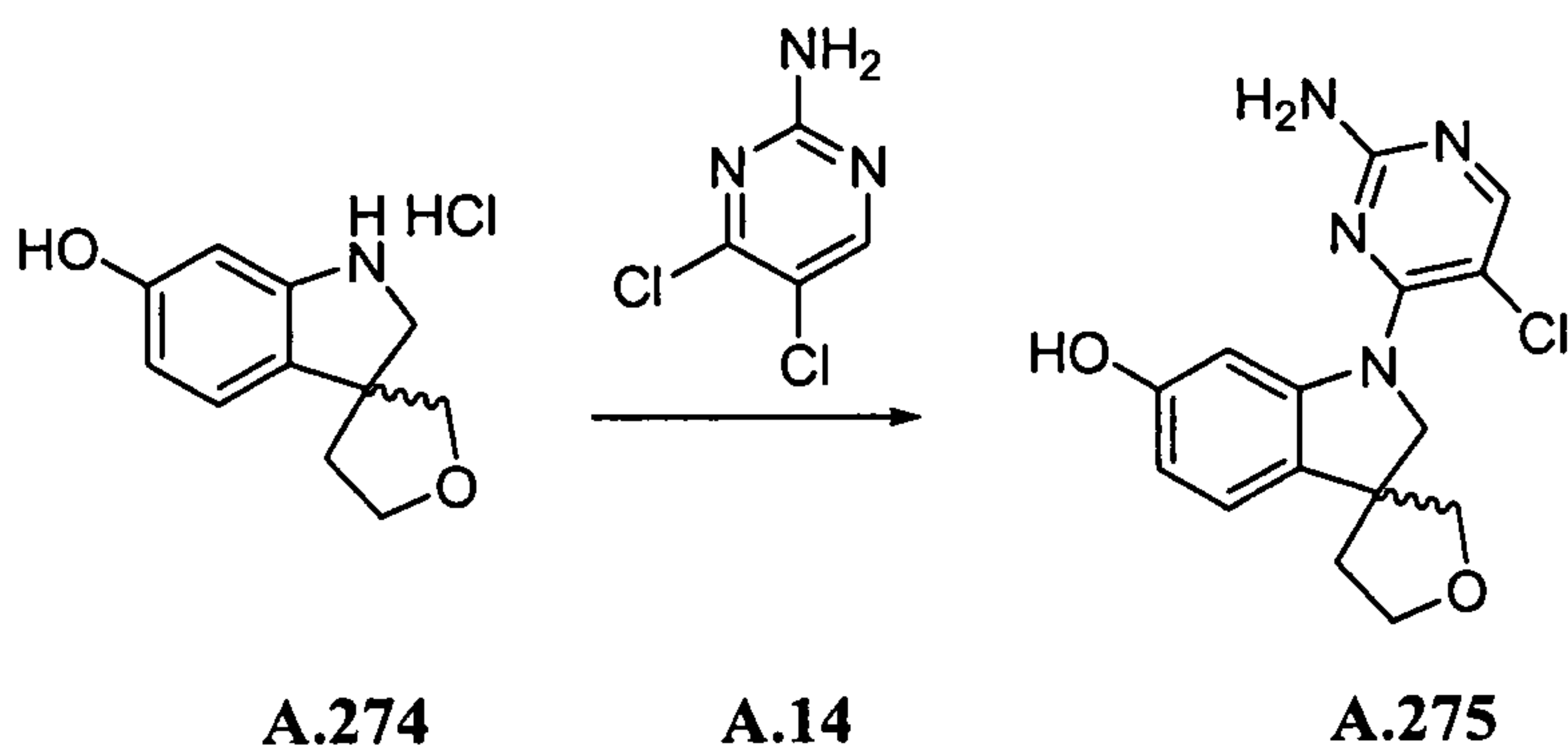


(rac)-6'-(benzyloxy)-1'-(4-methoxybenzyl)-4,5-dihydro-2H-spiro[furan-3,3'-indoline]

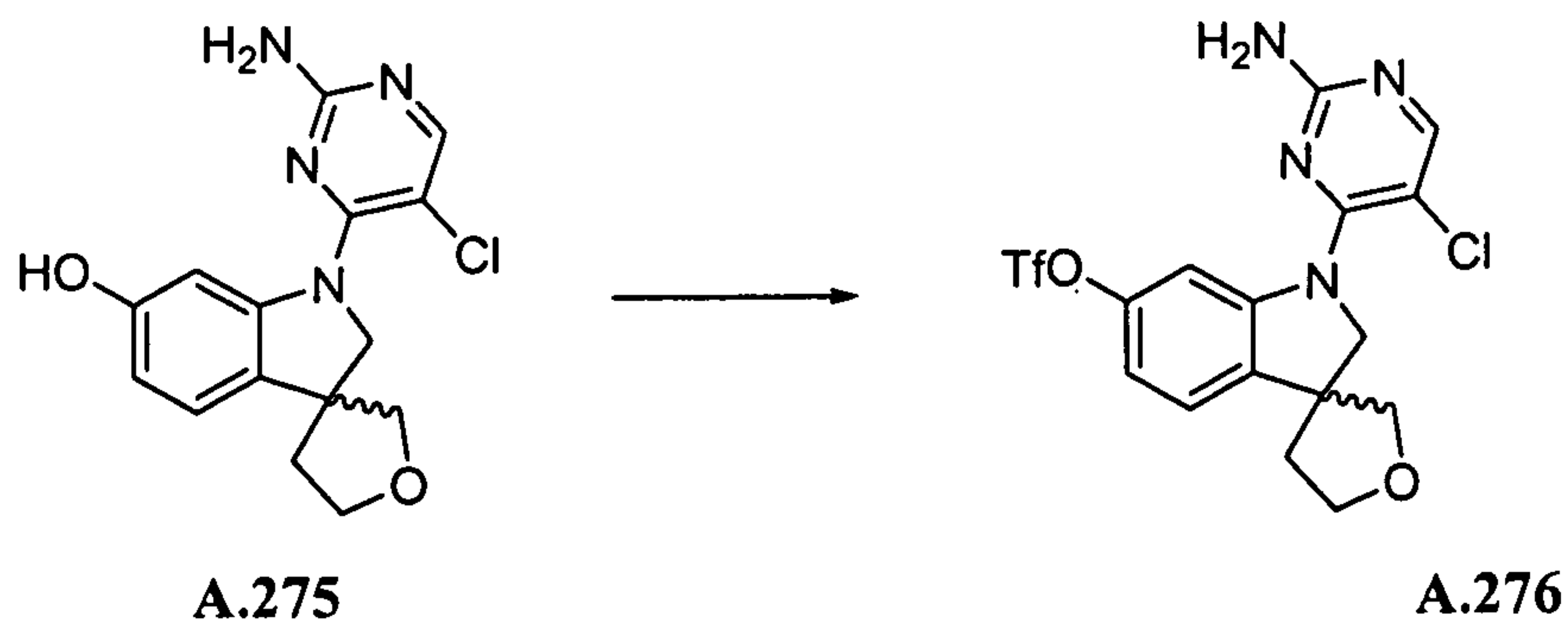
A.273 (a colorless viscous liquid) was prepared from 6'-(benzyloxy)-1'-(4-methoxybenzyl)-4,5-dihydro-2H-spiro[furan-3,3'-indolin]-2'-one **A.272** using chemistry similar to that described for compound **A.237**. LCMS-ESI (POS), M/Z, M+1: Found 402.2.



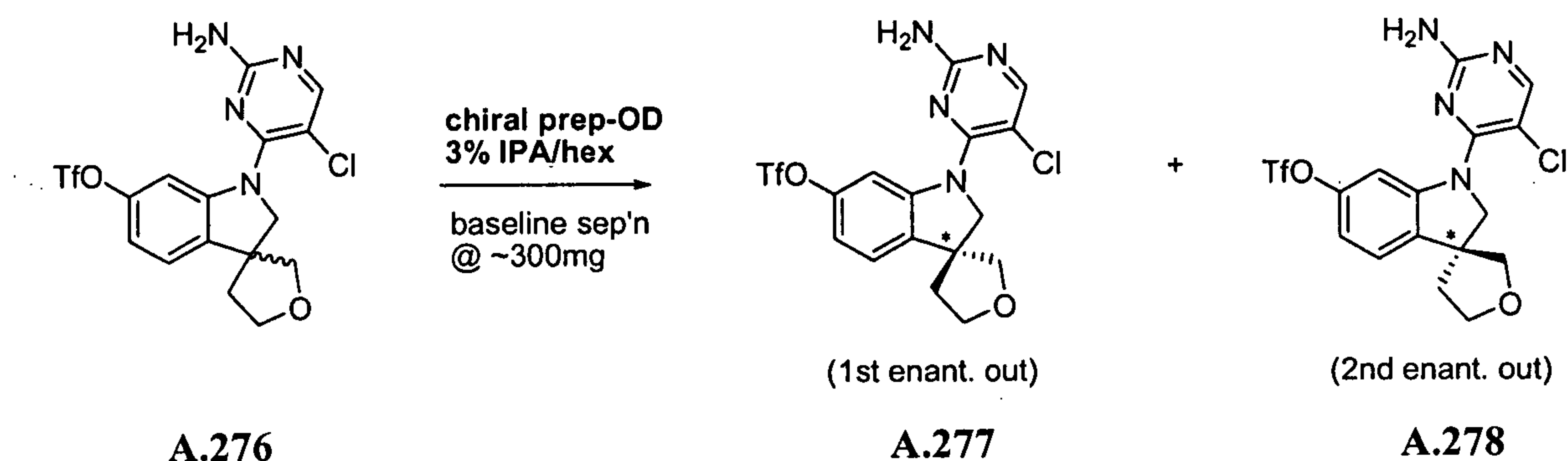
(rac)-1',2',4,5-Tetrahydrospiro[furan-3,3'-indol]-6'-ol hydrochloride A.274 (a colorless viscous liquid) was prepared from 6'-(benzyloxy)-1'-(4-methoxybenzyl)-4,5-dihydro-2H-spiro[furan-3,3'-indoline] **A.273** using chemistry similar to that described for compound **A.238**. LCMS-ESI (POS), M/Z, M+1: Found 192.1.



(rac)-1'-(2-Amino-5-chloro-4-pyrimidinyl)-1',2',4,5-tetrahydrospiro[furan-3,3'-indol]-6'-ol A.275 (an off-white solid) was prepared from 1',2',4,5-tetrahydrospiro[furan-3,3'-indol]-6'-ol hydrochloride **A.274** and 4,5-dichloro-2-pyrimidinamine **A.14** using chemistry similar to that described for compound **A.239**. ¹H NMR (400 MHz, *DMSO-d*₆) δ ppm 8.24 (1 H, s), 7.19 (1 H, br. s.), 7.12 (1 H, d, *J*=8.2 Hz), 6.52 (1 H, dd, *J*=7.8, 2.0 Hz), 4.18 - 4.38 (2 H, m), 3.91 - 4.02 (1 H, m), 3.87 (1 H, q, *J*=7.8 Hz), 3.78 (1 H, d, *J*=8.2 Hz), 3.54 (1 H, d, *J*=8.6 Hz), 2.05 - 2.23 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 319.1.



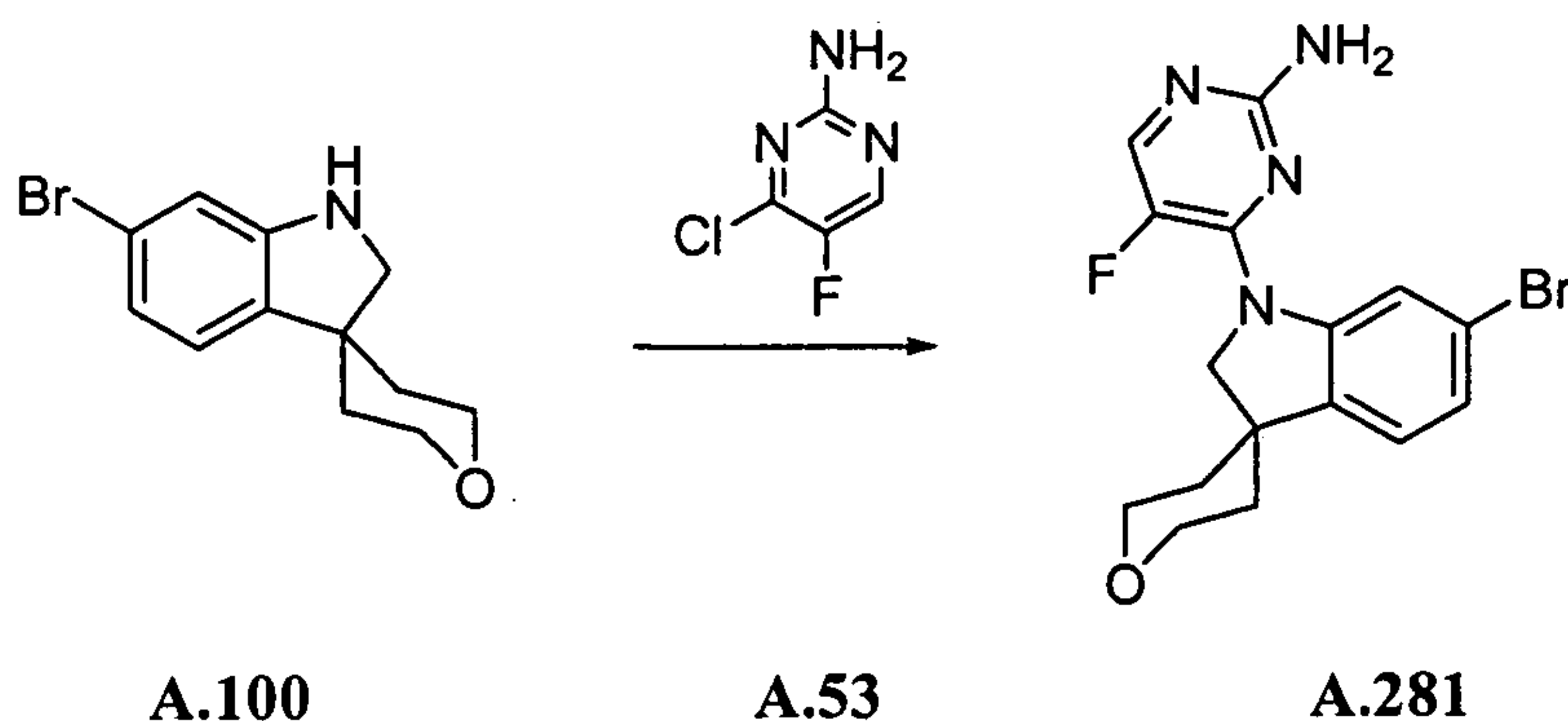
(rac)-1'-(2-amino-5-chloropyrimidin-4-yl)-4,5-dihydro-2H-spiro[furan-3,3'-indoline]-6'-yl trifluoromethanesulfonate **A.276** (a colorless solid) was prepared from 1'-(2-amino-5-chloro-4-pyrimidinyl)-1',2',4,5-tetrahydrospiro[furan-3,3'-indol]-6'-ol **A.275** using chemistry similar to that described for compound **A.240**. ¹H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 8.12 (1 H, s), 7.52 (1 H, d, $J=2.3$ Hz), 7.23 (1 H, d, $J=8.6$ Hz), 6.88 (1 H, dd, $J=8.2, 2.3$ Hz), 5.07 (2 H, br. s.), 4.38 (1 H, d), 4.27 (1 H, d), 4.07 - 4.15 (1 H, m), 3.99 - 4.07 (1 H, m), 3.88 (1 H, d), 3.79 (1 H, d), 2.26 - 2.36 (1 H, m), 2.14 - 2.22 (1 H, m). LCMS-ESI (POS), M/Z , $M+1$: Found 451.0.



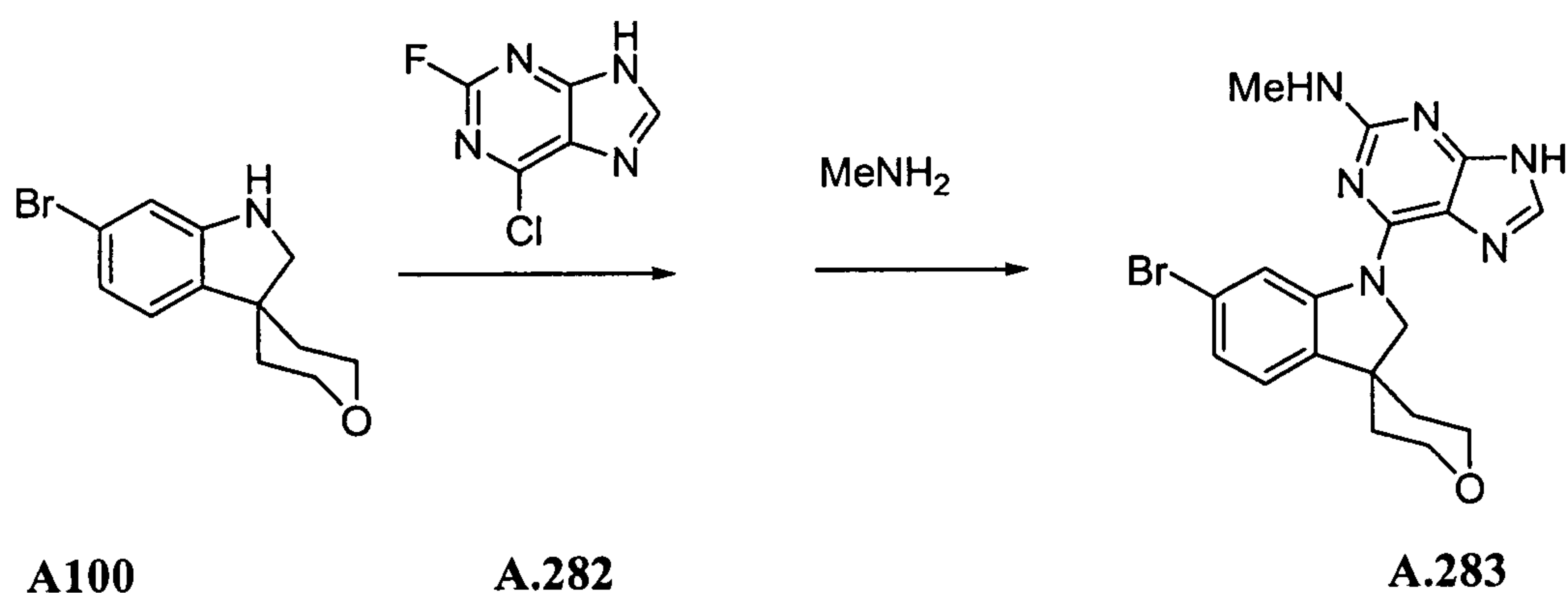
(3R*)-1'-(2-amino-5-chloropyrimidin-4-yl)-4,5-dihydro-2H-spiro[furan-3,3'-indoline]-6'-yl trifluoromethanesulfonate **A.277** and (3S*)-1'-(2-amino-5-chloropyrimidin-4-yl)-4,5-dihydro-2H-spiro[furan-3,3'-indoline]-6'-yl trifluoromethanesulfonate **A.278** were obtained from optical resolution of (rac)-1'-(2-amino-5-chloropyrimidin-4-yl)-4,5-dihydro-2H-spiro[furan-3,3'-indoline]-6'-yl trifluoromethanesulfonate by the following method. Instrument: Agilent 1100 series. Column: OD-preparative (50 mm X 500 mm). Solvents: 3% isopropanol in hexanes. Gradient: isochratic. Amount of sample per injection: 300 mg in methanol (6 mL). Separation quality: baseline separation. The first peak eluting off of the OD column provided (3R*)-1'-(2-amino-5-chloropyrimidin-4-yl)-4,5-dihydro-2H-spiro[furan-3,3'-indoline]-6'-yl trifluoromethanesulfonate **A.277** as an off-white solid.

The second peak furnished (3S*)-1'-(2-amino-5-chloropyrimidin-4-yl)-4,5-dihydro-2H-spiro[furan-3,3'-indoline]-6'-yl trifluoromethanesulfonate **A.278** as an off-white solid.

Stereochemistry arbitrarily assigned.

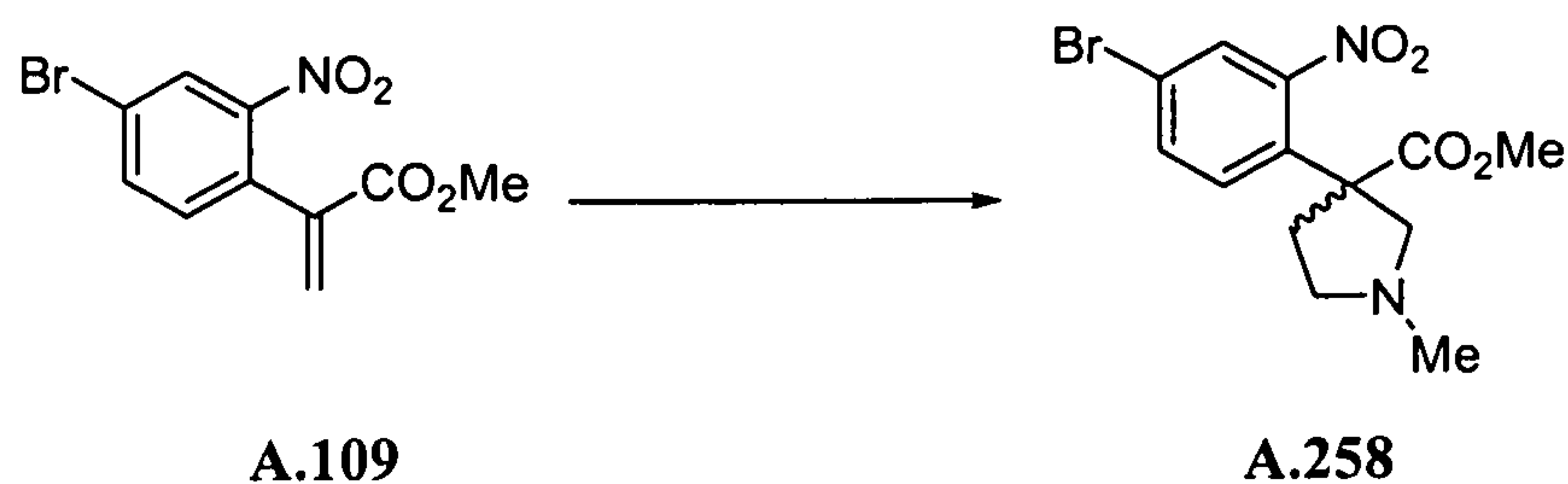


4-(6-Bromo-2',3',5',6'-tetrahydrospiro[indole-3,4'-pyran]-1(2H)-yl)-5-fluoro-2-pyrimidinamine A.281 (an off-white solid) was prepared from 6-bromo-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-pyran] (A.100) and 4-chloro-5-fluoro-2-pyrimidinamine A.53 using chemistry similar to that described for compound A.239. LCMS-ESI (POS), M/Z, M+1: Found 379.0 and 381.0.



6-(6-Bromo-2',3',5',6'-tetrahydrospiro[indole-3,4'-pyran]-1(2H)-yl)-N-methyl-9H-purin-2-amine A.283

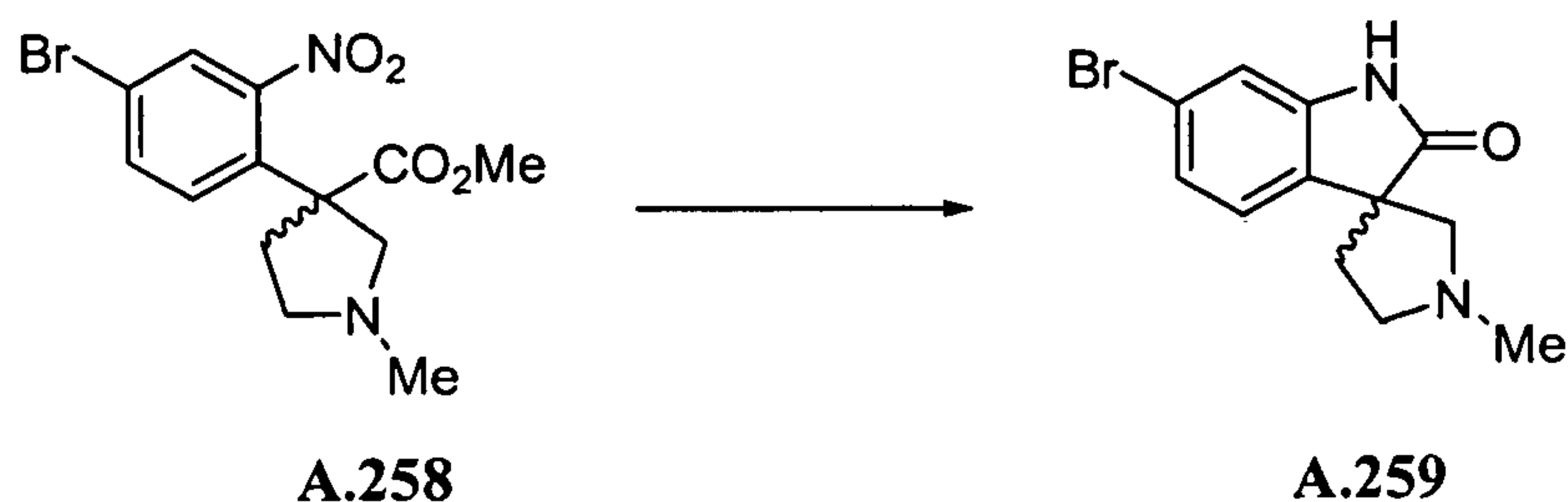
To a stirred solution of 6-bromo-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-pyran] (A.100) (0.24 g, 0.89 mmol) in t-butanol (12 mL) in a pressure vessel was added 6-chloro-2-fluoro-9H-purine A.282 (1.0 eq., 0.18 g) followed by Hunig's base (0.21 mL). The resulting mixture was stirred at 80 °C for 22 h. After cooling, methylamine (2 M solution in THF) was added to this mixture. The resulting mixture was stirred at 85 °C for 15 h. Upon workup, the volatiles were removed in vacuo and the residue was subjected to combi-flash column chromatography (methanol/dichloromethane) to give 6-(6-bromo-2',3',5',6'-tetrahydrospiro[indole-3,4'-pyran]-1(2H)-yl)-N-methyl-9H-purin-2-amine A.283. LCMS-ESI (POS), M/Z, M+1: Found 415.0 and 417.0.



(rac)-Methyl 3-(4-bromo-2-nitrophenyl)-1-methylpyrrolidine-3-carboxylate

was prepared by the method of Cravotto, G.; Giovenzana, G. B.; Pilati, T.; Sisti, M.; Palmisano, G. *J. Org. Chem.* **2001**, *66*, 8447-8453.

To a stirred solution of methyl 2-(4-bromo-2-nitrophenyl)acrylate **A.109** (5.5 g, 19.22 mmol) in toluene (180 mL) was added paraformaldehyde (7.34 g, 12 eq.) in one portion at rt. The 500 mL round-bottomed flask was fitted with a Dean-Stark reflux condenser filled with 3 Å molecular sieves and the resulting mixture was heated to reflux (~ 140 °C) under nitrogen. Sarcosine (5.24 g, 3 eq.) was added portionwise to the reaction mixture during a period of 1 h. Then the mixture was refluxed for a further 5.5 h. After cooling, the mixture was vacuum filtered and concentrated *in vacuo* and the residue was purified on a column of silica gel (methanol/dichloromethane) to give methyl 3-(4-bromo-2-nitrophenyl)-1-methylpyrrolidine-3-carboxylate **A.258** (4.7 g, 72% yield) as a light yellow solid. ¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 8.13 (1 H, br. s.), 7.94 (1 H, d, *J*=8.3 Hz), 7.79 (1 H, d, *J*=8.8 Hz), 3.54 (3 H, s), 3.24 (1 H, d, *J*=9.8 Hz), 2.87 (1 H, br. s.), 2.66 - 2.81 (2 H, m), 2.42 (1 H, q, *J*=8.0 Hz), 2.29 (3 H, s), 1.95 - 2.06 (1 H, m). LCMS-ESI (POS), *M/Z*, *M*+1: Found 343.3 and 345.3.

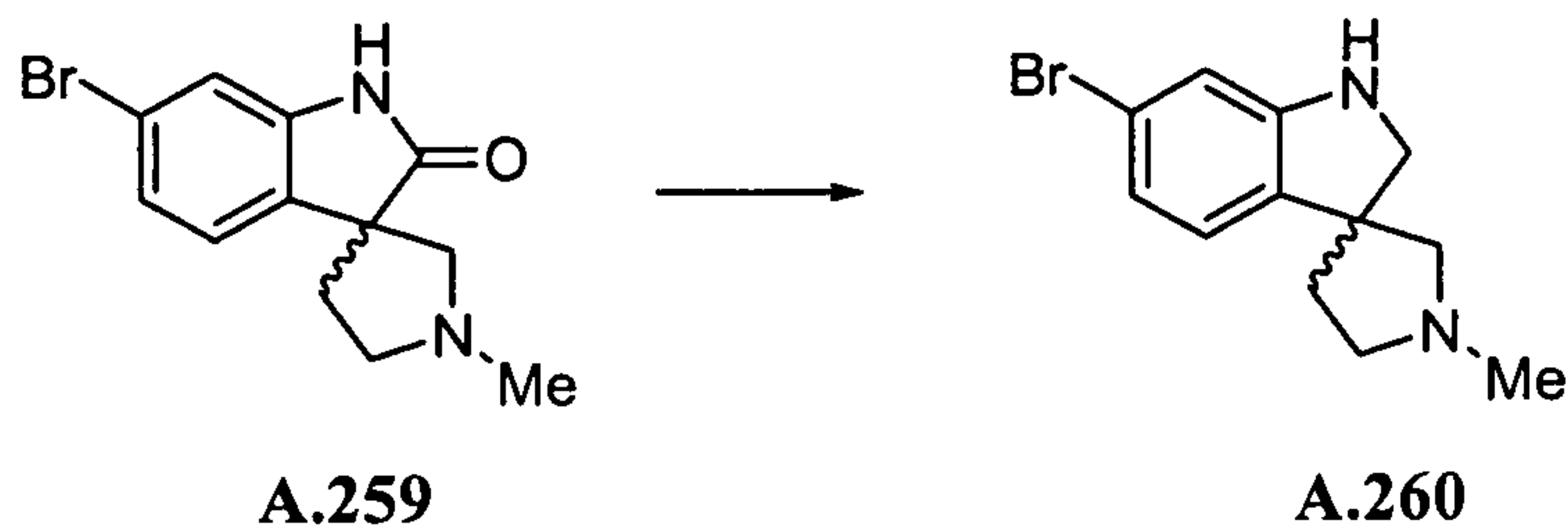


(rac)-6-bromo-1'-methylspiro[indoline-3,3'-pyrrolidin]-2-one

Ref. Quallich, G. J.; Morrissey, P. M. *Synthesis* **1993**, 51-53.

To a stirred solution of methyl 3-(4-bromo-2-nitrophenyl)-1-methylpyrrolidine-3-carboxylate (4.7 g, 13.70 mmol) in glacial acetic acid (100 mL) was added iron powder (3.82 g, 5 eq.) and the resulting mixture was heated in an oil bath at 100 °C for 4 h. After cooling the mixture was vacuum filtered through a layer of celite. The filtrate was concentrated under high vacuum and the residue was purified on a column of silica gel (methanol/dichloromethane with triethylamine) to give 6-bromo-1'-methylspiro[indoline-3,3'-pyrrolidin]-2-one in nearly quantitative yield as an off-white solid. ¹H NMR (400 MHz, *DMSO-d*₆) δ ppm 10.47 (1 H, br.

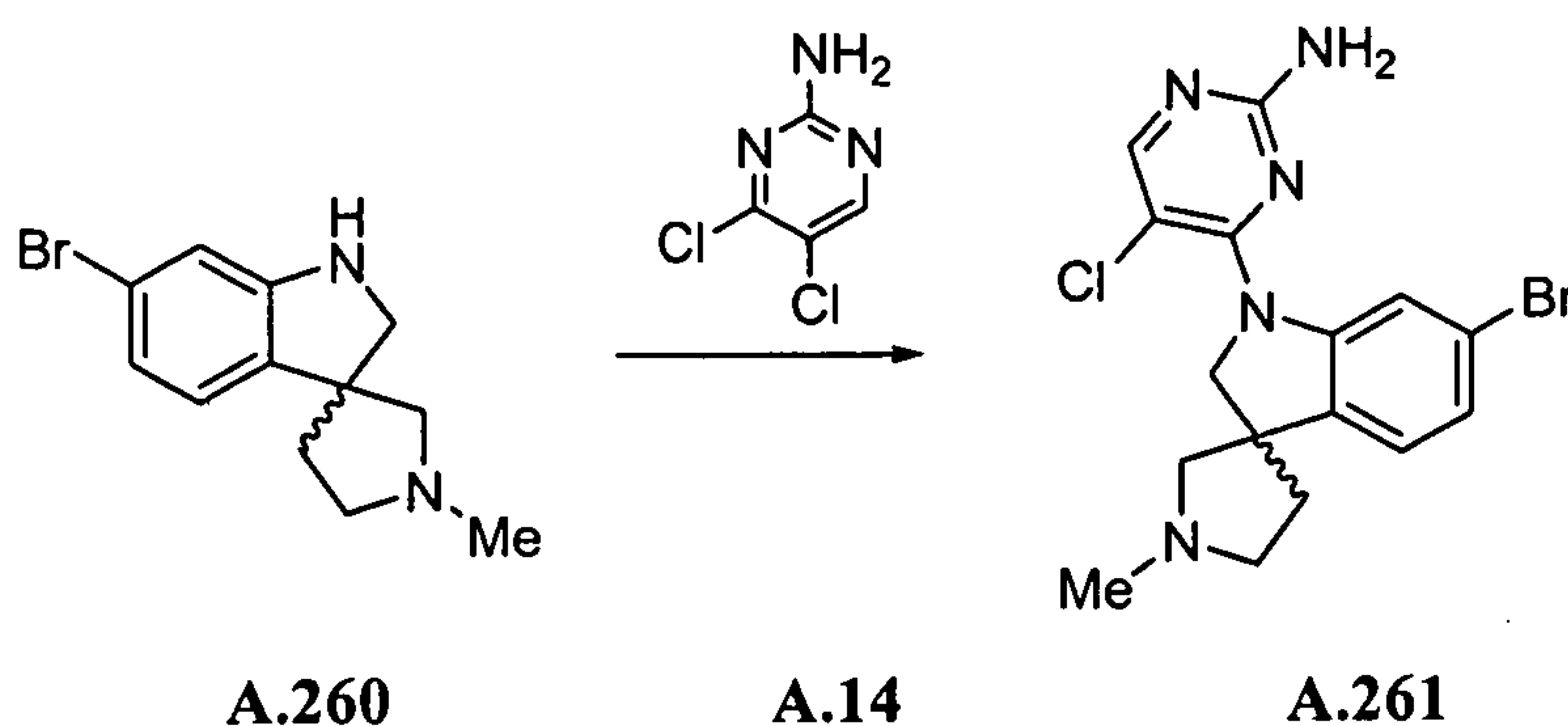
s.), 7.25 (1 H, d, $J=8.1$ Hz), 7.14 (1 H, d), 6.95 (1 H, d, $J=1.8$ Hz), 2.97 - 3.08 (1 H, m), 2.73 (1 H, d, $J=8.8$ Hz), 2.56 (1 H, d, $J=8.8$ Hz), 2.43 - 2.49 (1 H, m), 2.33 (3 H, s), 2.12 - 2.22 (1 H, m), 1.84 - 1.94 (1 H, m). LCMS-ESI (POS), M/Z , $M+1$: Found 281.4 and 283.3.



(rac)-6-bromo-1'-methylspiro[indoline-3,3'-pyrrolidine] A.260

Ref. Kucerovy, A.; Hathaway, J. S.; Mattner, P. G.; Repic, O. *Synth. Commun.* **1992**, 22, 729.

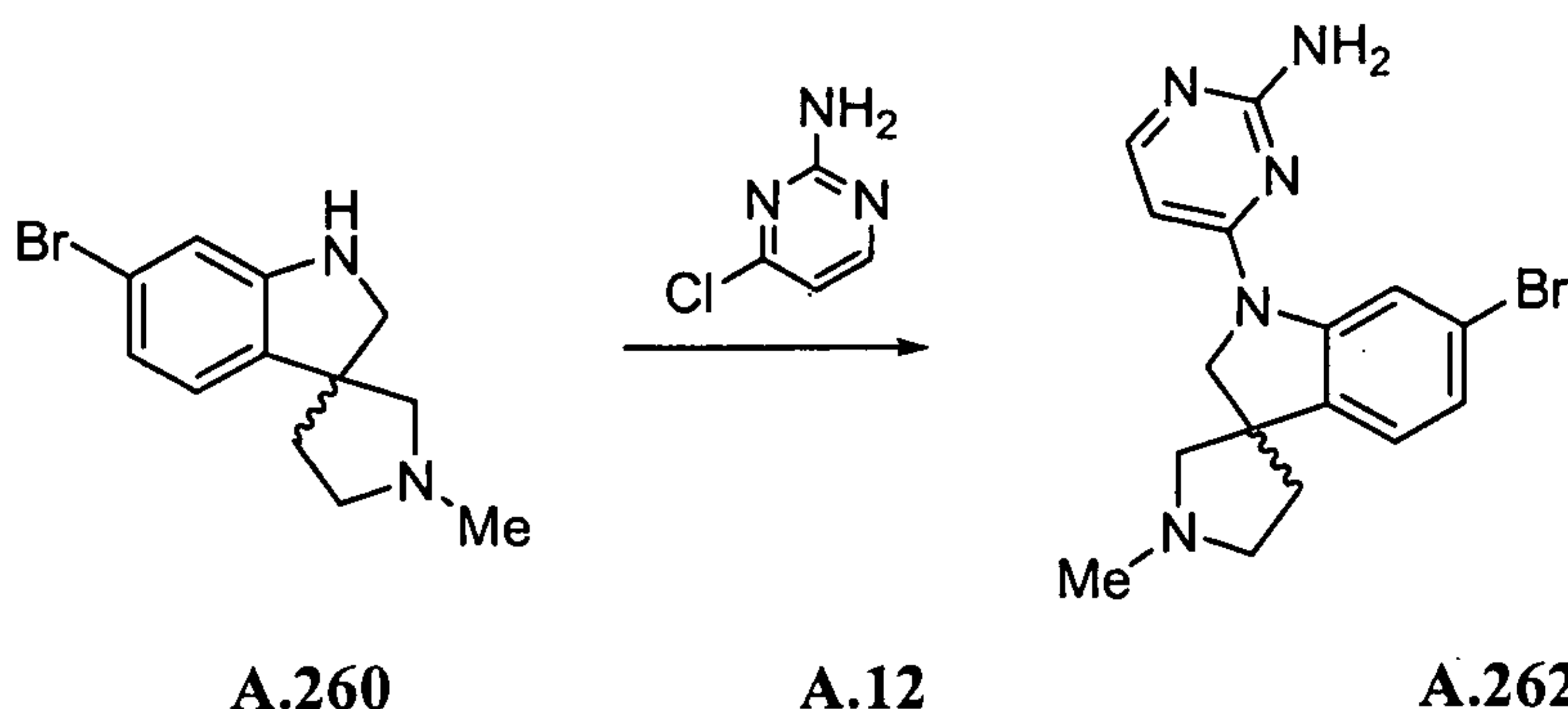
To a stirred solution of 6-bromo-1'-methylspiro[indoline-3,3'-pyrrolidin]-2-one A.259 (3.5 g, 12.45 mmol) in dry toluene (40 mL) which was preheated at 85 °C in an oil bath was added dropwise a solution of Red-AL in toluene (3 M) (11 mL, 3 eq.) under nitrogen. The resulting mixture was heated at this temperature for 2 h and then cooled in an ice-salt bath followed by quenching with 2 N NaOH (aq.). After further dilution with 2 N NaOH (aq.), the mixture was extracted with ethyl acetate (3 x) and the combined extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give pure 6-bromo-1'-methylspiro[indoline-3,3'-pyrrolidine] A.260 (> 90% yield) as an off-white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 6.97 (1 H, d, $J=7.4$ Hz), 6.67 (1 H, dd, $J=7.8, 1.6$ Hz), 6.59 (1 H, d, $J=2.0$ Hz), 5.75 (1 H, s), 3.39 - 3.43 (1 H, m), 3.31 - 3.34 (1 H, m), 2.61 - 2.69 (1 H, m), 2.59 (1 H, d, $J=9.0$ Hz), 2.51 - 2.56 (1 H, m), 2.37 (1 H, d, $J=9.0$ Hz), 2.26 (3 H, s), 1.83 - 2.01 (2 H, m). LCMS-ESI (POS), M/Z , $M+1$: Found 267.4 and 269.4.



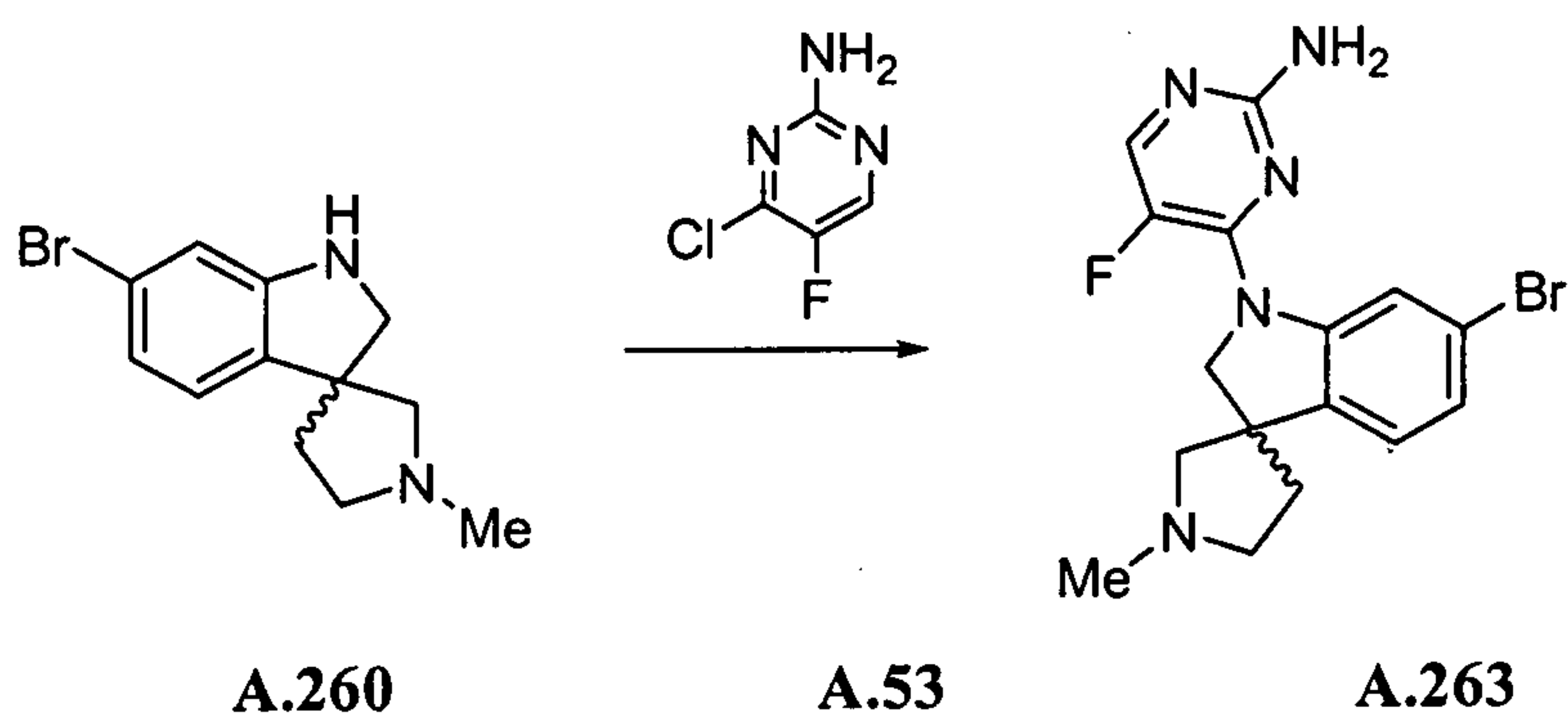
4-(6-bromo-1'-methylspiro[indoline-3,3'-pyrrolidine]-1-yl)-5-chloropyrimidin-2-amine A.261

A.261 was prepared from 6-bromo-1'-methylspiro[indoline-3,3'-pyrrolidine] A.260 using chemistry similar to that described for compound A.239. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 8.10 (1 H, s), 7.45 (1 H, d, $J=2.0$ Hz), 7.23 (1 H, d, $J=8.3$ Hz), 7.11 (1 H, dd, $J=8.1, 1.7$ Hz), 6.69 (2 H, s), 4.16 (1 H, d), 4.08 (1 H, d), 2.70 - 2.77 (1 H, m), 2.67 (1 H, d, $J=9.3$ Hz),

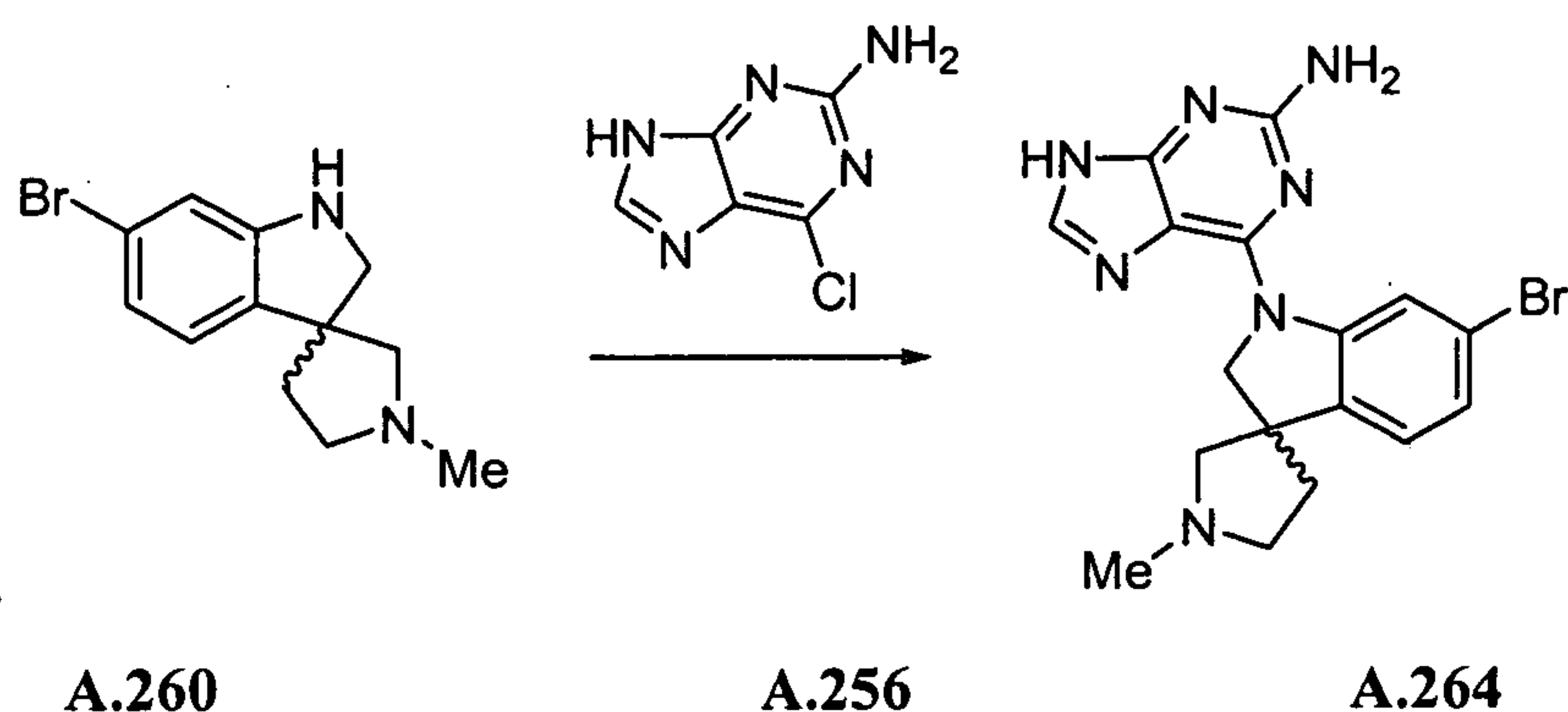
2.52 - 2.57 (1 H, m), 2.41 (1 H, d, $J=8.8$ Hz), 2.27 (3 H, s), 1.95 - 2.12 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 394.0 and 396.0.



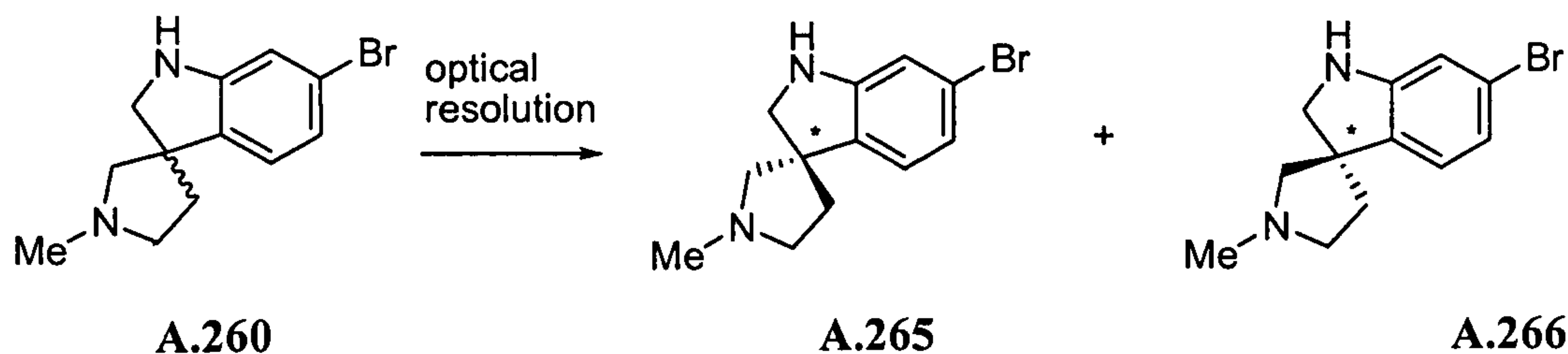
4-(6-bromo-1'-methylspiro[indoline-3,3'-pyrrolidine]-1-yl)pyrimidin-2-amine A.262 was prepared from 6-bromo-1'-methylspiro[indoline-3,4'-piperidine] **A.260** and 4-chloro-2-pyrimidinamine **A.12** using chemistry similar to that described for compound **A.239**. (an off-white solid). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 8.60 (1 H, d, $J=2.0$ Hz), 7.97 (1 H, d, $J=5.9$ Hz), 7.23 (1 H, d, $J=7.8$ Hz), 7.10 (1 H, dd, $J=7.8, 2.0$ Hz), 6.43 (2 H, br. s.), 6.04 (1 H, d, $J=5.9$ Hz), 3.93 - 3.99 (1 H, m), 3.85 - 3.91 (1 H, m), 2.76 (1 H, d, $J=5.9$ Hz), 2.68 (1 H, d, $J=8.8$ Hz), 2.55 - 2.63 (1 H, m), 2.48 (1 H, d), 2.29 (3 H, s), 2.03 - 2.13 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 360.0 and 362.0.



4-(6-bromo-1'-methylspiro[indoline-3,3'-pyrrolidine]-1-yl)-5-fluoropyrimidin-2-amine A.263 was prepared from 6-bromo-1'-methylspiro[indoline-3,4'-piperidine] **A.260** and 4-chloro-5-fluoro-2-pyrimidinamine **A.53** using chemistry similar to that described for compound **A.239**. (an off-white solid) ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.19 (1 H, d, $J=1.8$ Hz), 8.02 (1 H, d, $J=5.9$ Hz), 7.25 (1 H, d), 7.15 (1 H, dd, $J=8.1, 1.8$ Hz), 6.41 (2 H, s), 4.17 - 4.25 (1 H, m), 4.07 - 4.14 (1 H, m), 2.68 - 2.80 (2 H, m), 2.52 - 2.59 (1 H, m), 2.43 (1 H, d, $J=9.2$ Hz), 2.28 (3 H, s), 2.07 (2 H, t, $J=7.1$ Hz). LCMS-ESI (POS), M/Z, M+1: Found 378.0 and 380.0

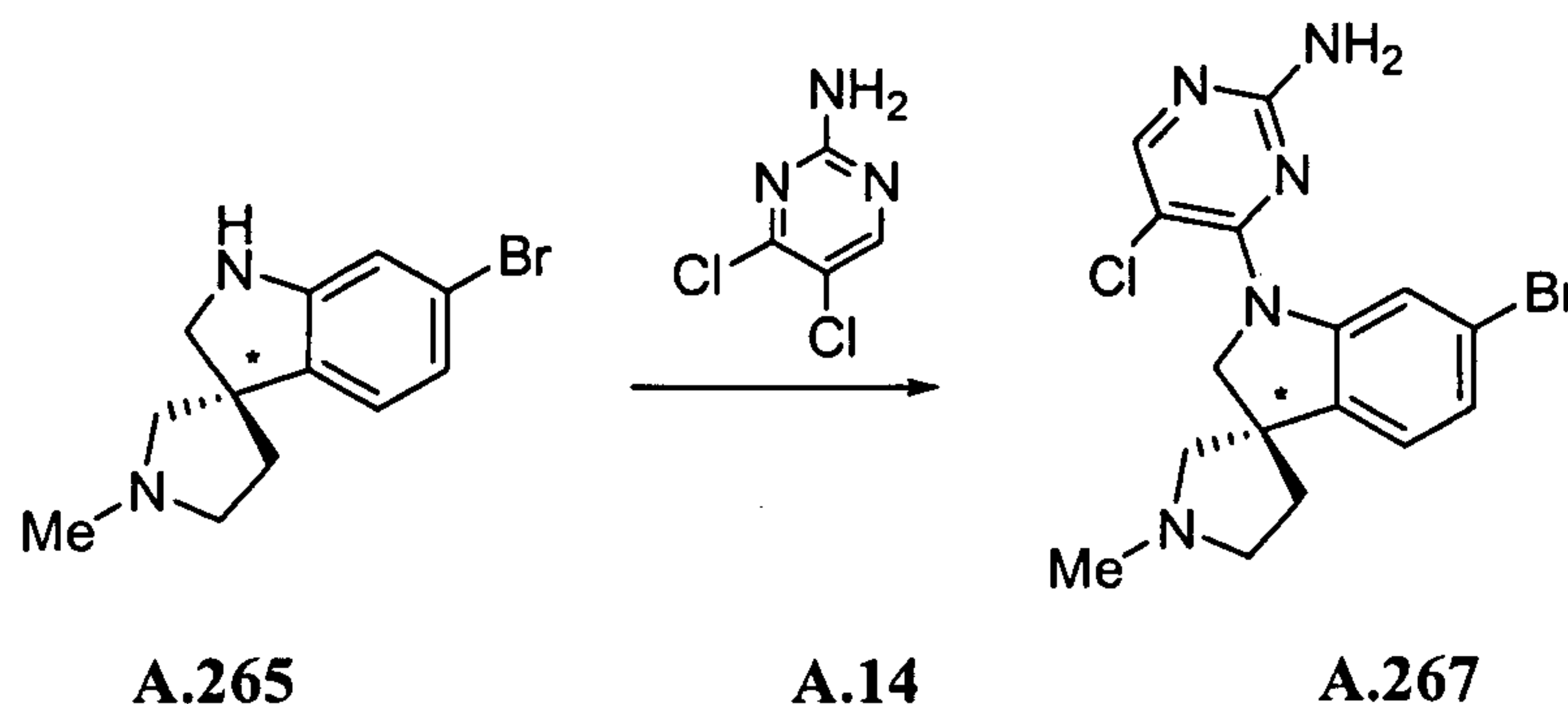


6-(6-bromo-1'-methylspiro[indoline-3,3'-pyrrolidine]-1-yl)-9H-purin-2-amine A.264 was prepared from 6-bromo-1'-methylspiro[indoline-3,4'-piperidine] **A.260** and 6-chloro-9H-purin-2-amine **A.256** using chemistry similar to that described for compound **A.239**. (an off-white solid) ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 12.37 (1 H, br. s.), 8.76 (1 H, d, $J=1.8$ Hz), 7.81 (1 H, s), 7.26 (1 H, d, $J=7.7$ Hz), 7.14 (1 H, dd, $J=8.1, 1.8$ Hz), 6.13 (2 H, s), 4.81 (1 H, d, $J=11.7$ Hz), 4.53 (1 H, d, $J=12.1$ Hz), 2.76 - 2.86 (1 H, m), 2.72 (1 H, d, $J=9.1$ Hz), 2.54 - 2.62 (1 H, m), 2.46 (2 H, d, $J=8.8$ Hz), 2.30 (3 H, s), 2.01 - 2.18 (2 H, m). LCMS-ESI (POS), M/Z , $M+1$: Found 400.1 and 402.1.

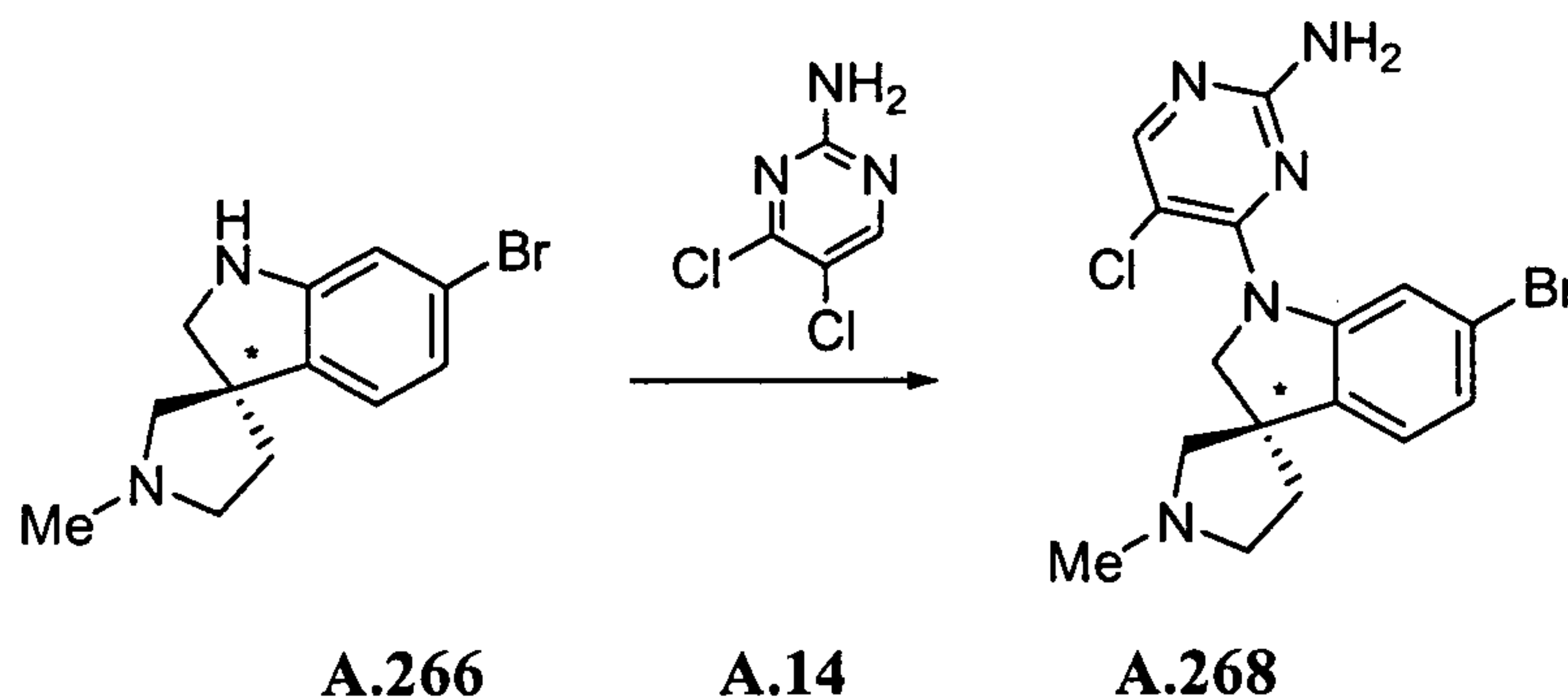


(3S*)-6-bromo-1'-methylspiro[indoline-3,3'-pyrrolidine] A.265 and **(3R*)-6-bromo-1'-methylspiro[indoline-3,3'-pyrrolidine] A.266** (stereochemistry arbitrarily assigned) were obtained from optical resolution of (rac)-6-bromo-1'-methylspiro[indoline-3,3'-pyrrolidine] **A.260** by the following method. Instrument: Agilent 1100 series. Column: OD-preparative (50 mm X 500 mm). Solvents: 1% isopropanol in hexanes. Gradient: isochratic. Amount of sample per injection: 250 mg in methanol (6 mL). Separation quality: baseline separation. The first peak eluting off of the OD column provided **(3S*)-6-bromo-1'-methylspiro[indoline-3,3'-pyrrolidine] A.265** in 94% ee. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 6.97 (1 H, d, $J=7.4$ Hz), 6.67 (1 H, dd, $J=7.8, 1.6$ Hz), 6.59 (1 H, d, $J=2.0$ Hz), 5.75 (1 H, s), 3.39 - 3.43 (1 H, m), 3.31 - 3.34 (1 H, m), 2.61 - 2.69 (1 H, m), 2.59 (1 H, d, $J=9.0$ Hz), 2.51 - 2.56 (1 H, m), 2.37 (1 H, d, $J=9.0$ Hz), 2.26 (3 H, s), 1.83 - 2.01 (2 H, m). LCMS-ESI (POS), M/Z , $M+1$: Found 267.4 and 269.4.

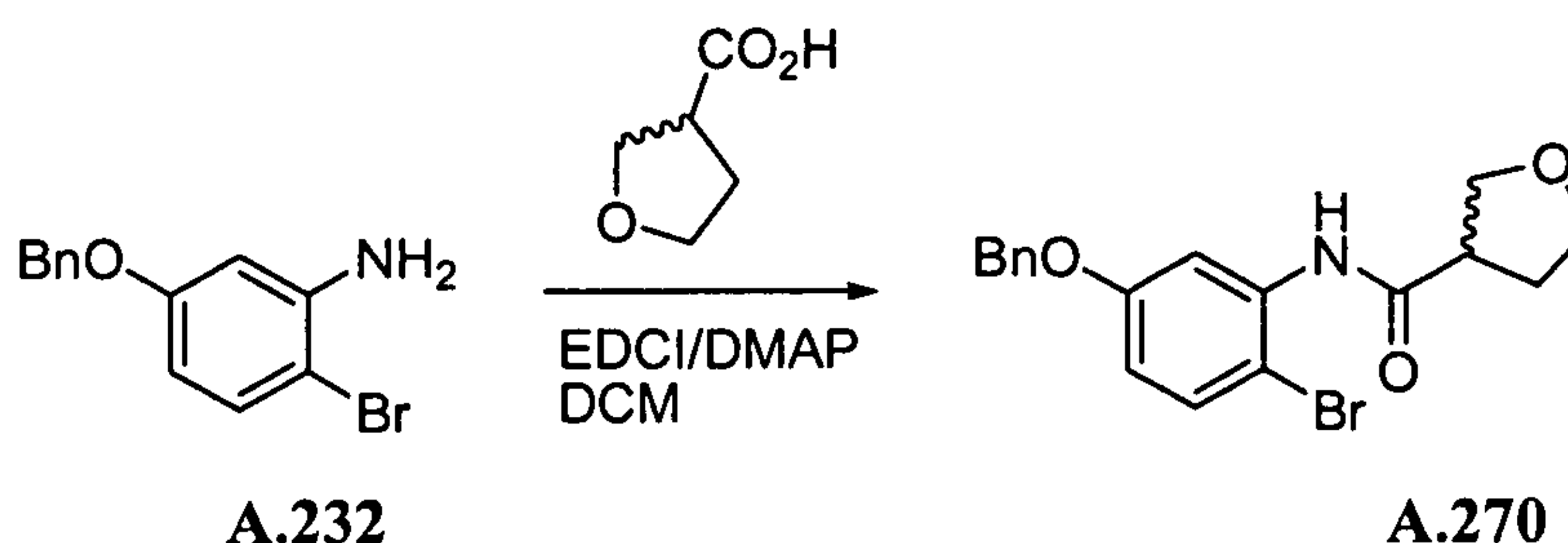
The second peak furnished (3R*)-6-bromo-1'-methylspiro[indoline-3,3'-pyrrolidine] **A.266** in 99% ee. (stereochemistry arbitrarily assigned.)



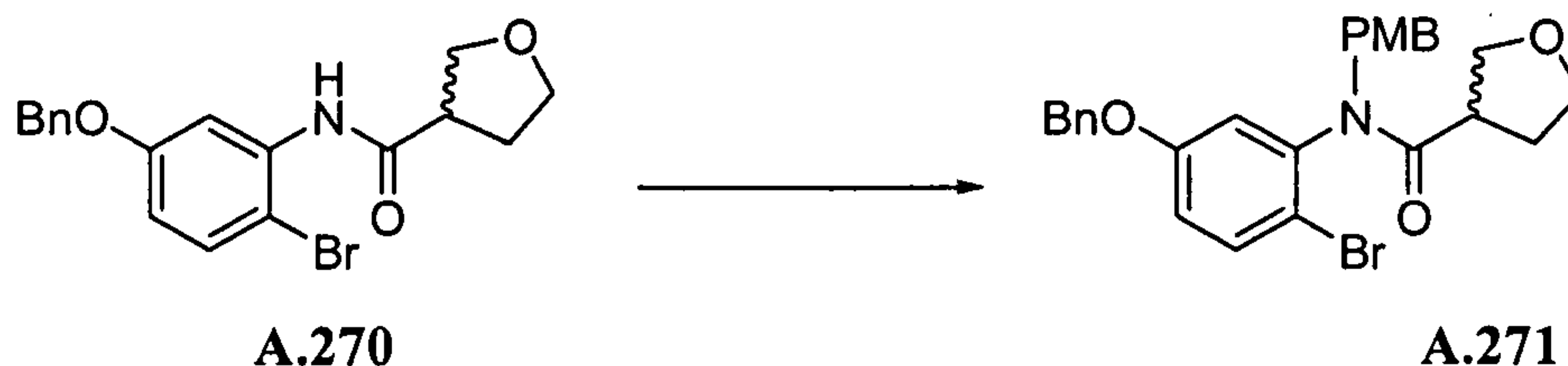
4-((3R*)-6-Bromo-1'-methylspiro[indole-3,3'-pyrrolidin]-1(2H)-yl)-5-chloro-2-pyrimidinamine A.267 was prepared from (3S*)-6-bromo-1'-methylspiro[indoline-3,3'-pyrrolidine] **A.265** using chemistry similar to that described for compound **A.239**. ¹H NMR (400 MHz, *DMSO-d*₆) δ ppm 8.10 (1 H, s), 7.45 (1 H, d, *J*=1.6 Hz), 7.23 (1 H, d, *J*=7.8 Hz), 7.10 (1 H, dd, *J*=7.8, 1.6 Hz), 6.68 (2 H, s), 4.16 (1 H, d), 4.08 (1 H, d), 2.69 - 2.78 (1 H, m), 2.67 (1 H, d, *J*=9.0 Hz), 2.52 - 2.58 (1 H, m), 2.42 (1 H, d, *J*=9.0 Hz), 2.27 (3 H, s), 1.97 - 2.12 (2 H, m). LCMS-ESI (POS), *M/Z*, *M*+1: Found 394.0 and 396.0.



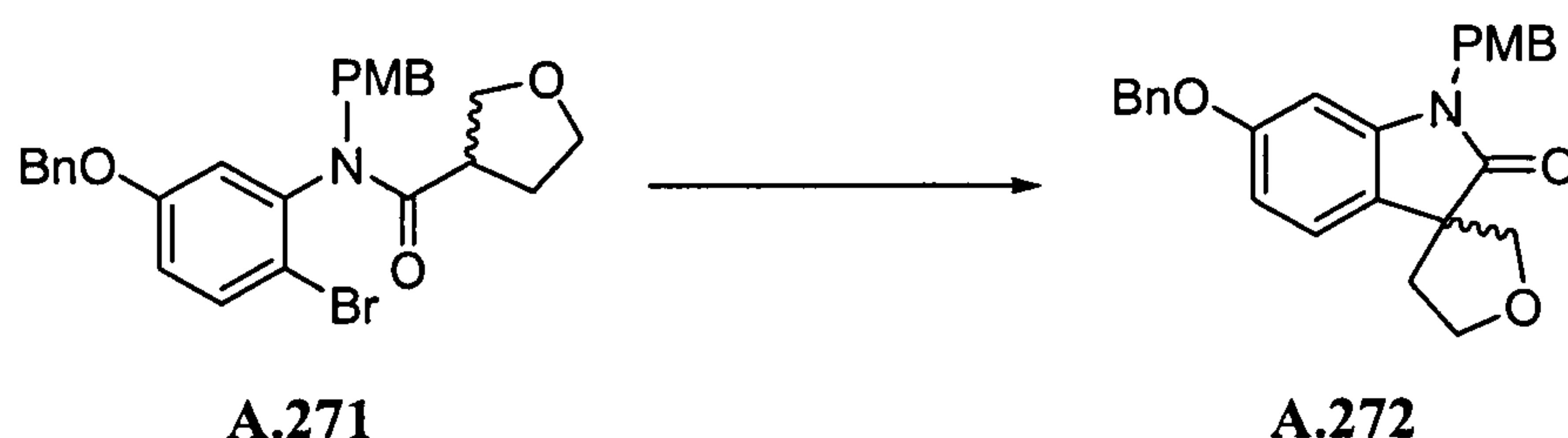
4-((3R*)-6-Bromo-1'-methylspiro[indole-3,3'-pyrrolidin]-1(2H)-yl)-5-chloro-2-pyrimidinamine A.268 was prepared from (3R*)-6-bromo-1'-methylspiro[indoline-3,3'-pyrrolidine] **A.266** using chemistry similar to that described for compound **A.239**.



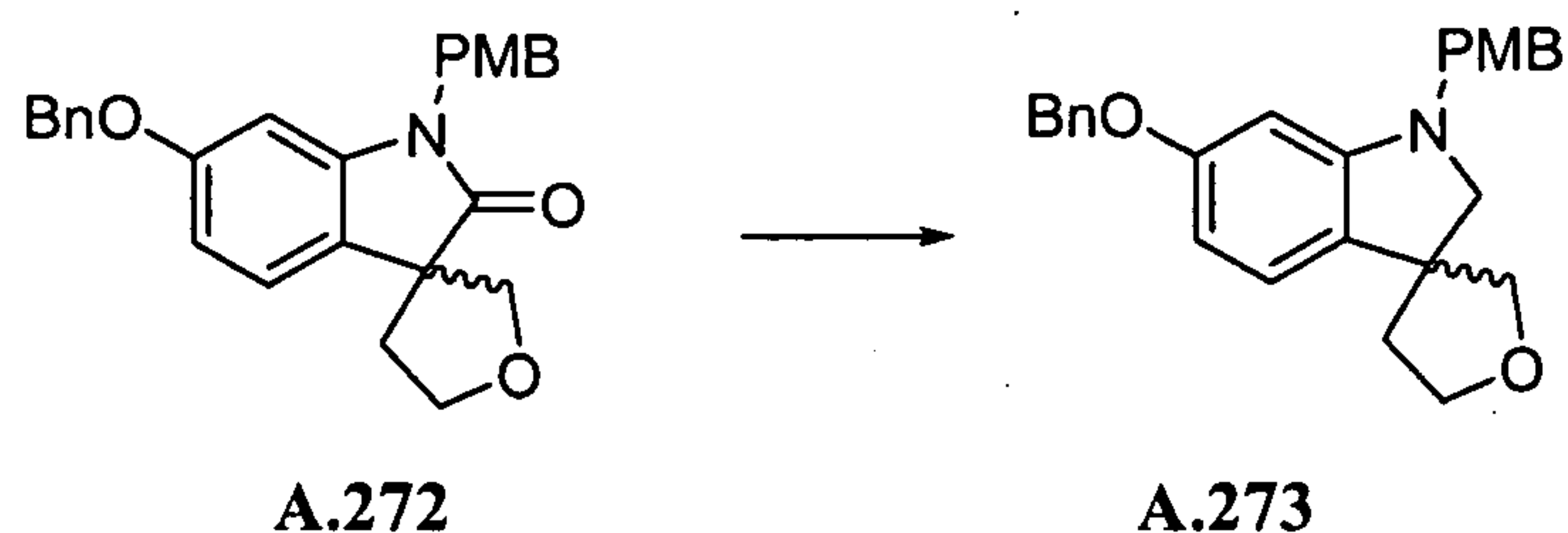
N-(5-(benzyloxy)-2-bromophenyl)tetrahydrofuran-3-carboxamide A.270 was prepared from 5-(benzyloxy)-2-bromoaniline **A.232** and tetrahydro-3-furancarboxylic acid using chemistry similar to that described for compound **A.234** (a white solid) ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 9.46 (1 H, s), 7.53 (1 H, d, $J=8.6$ Hz), 7.28 - 7.47 (6 H, m), 6.84 (1 H, dd, $J=8.8, 2.9$ Hz), 5.09 (2 H, s), 3.92 (1 H, t, $J=8.0$ Hz), 3.77 (2 H, q, $J=6.8$ Hz), 3.70 (1 H, q, $J=7.0$ Hz), 3.22 - 3.28 (1 H, m), 2.09 (2 H, q, $J=6.8$ Hz). LCMS-ESI (POS), M/Z , $M+1$: Found 376.1 and 378.1.



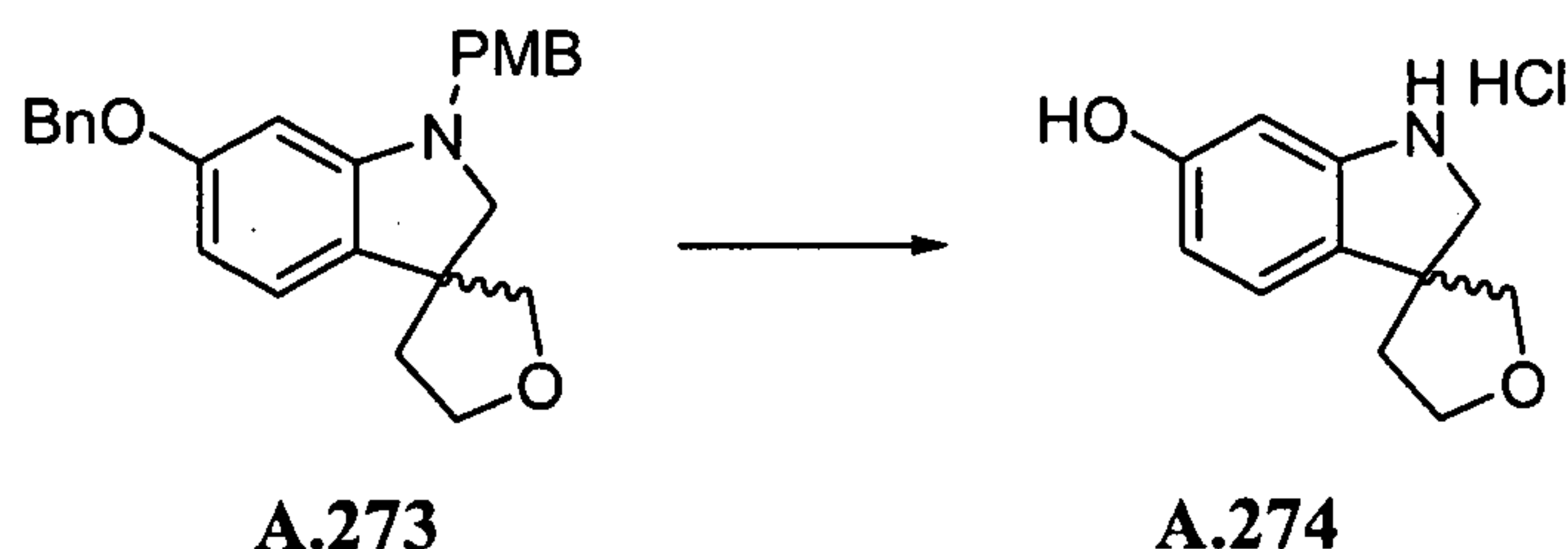
N-(5-(benzyloxy)-2-bromophenyl)-N-(4-methoxybenzyl)tetrahydrofuran-3-carboxamide A.271 (a colorless viscous liquid), was prepared from **N-(5-(benzyloxy)-2-bromophenyl)tetrahydrofuran-3-carboxamide A.270** using chemistry similar to that described for compound **A.235**. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 7.64 (1 H, d, $J=9.0$ Hz), 7.29 - 7.42 (6 H, m), 7.06 (2 H, dd, $J=8.6, 2.7$ Hz), 7.00 (1 H, dt, $J=9.0, 3.5$ Hz), 6.84 (2 H, dd, $J=8.6, 2.7$ Hz), 6.61 (1 H, t, $J=3.1$ Hz), 5.20 (1 H, dd, $J=14.3, 3.3$ Hz), 4.98 (2 H, s), 4.14 (1 H, d, $J=14.1$ Hz), 3.65 - 3.80 (6 H, m), 3.44 - 3.61 (2 H, m), 2.59 - 2.72 (1 H, m), 2.04 - 2.17 (1 H, m). LCMS-ESI (POS), M/Z , $M+1$: Found 496.1 and 498.1.



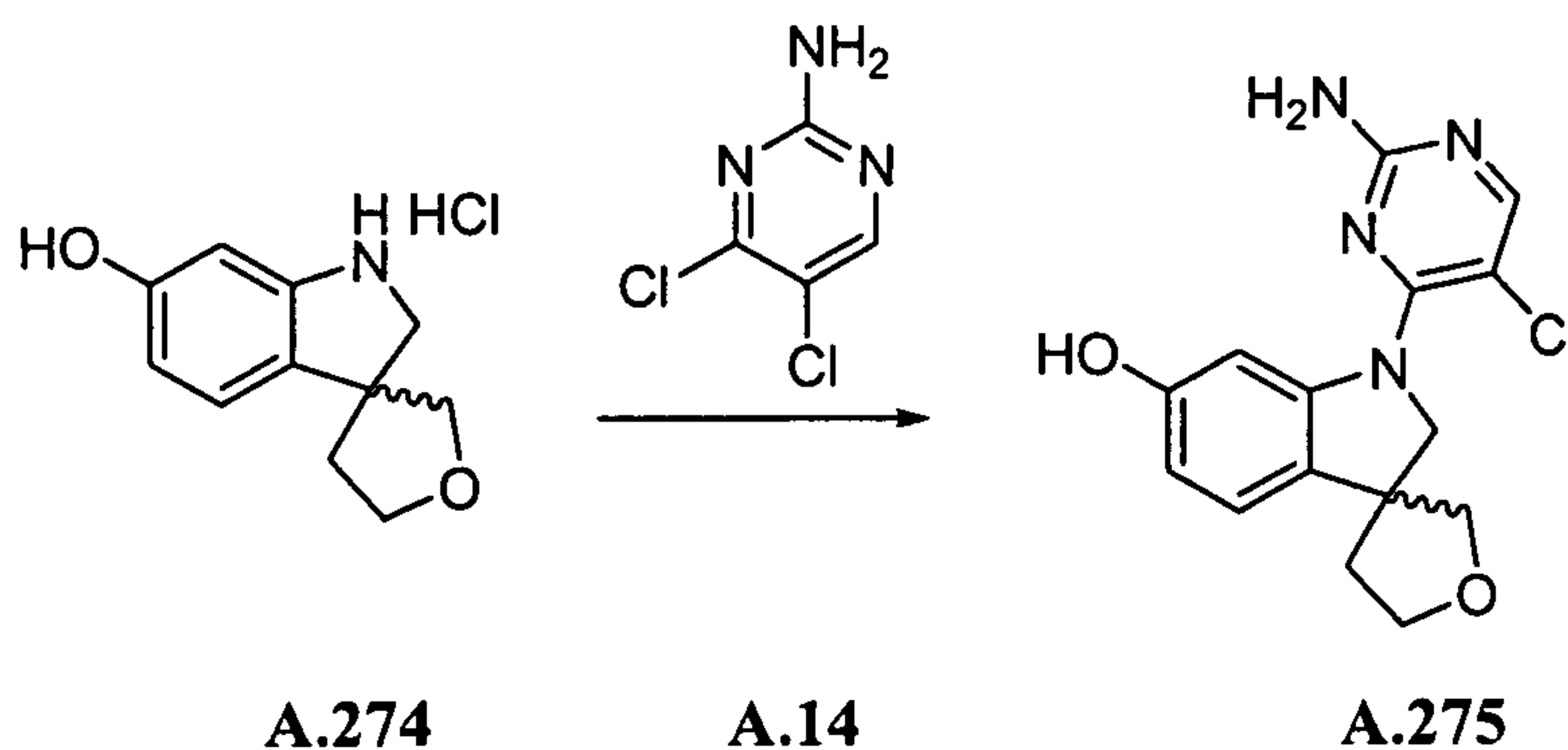
(rac)-6'6'-(benzyloxy)-1'-(4-methoxybenzyl)-4,5-dihydro-2H-spiro[furan-3,3'-indolin]-2'-one A.272 (a colorless viscous liquid) was prepared from **N-(5-(benzyloxy)-2-bromophenyl)-N-(4-methoxybenzyl)tetrahydrofuran-3-carboxamide A.271** using chemistry similar to that described for compound **A.236**. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 7.29 - 7.46 (6 H, m), 7.18 - 7.26 (3 H, m), 6.87 (2 H, d, $J=8.6$ Hz), 6.62 - 6.68 (2 H, m), 5.06 (2 H, s), 4.81 (2 H, s), 4.05 - 4.15 (2 H, m), 3.85 - 3.90 (1 H, m), 3.77 (1 H, d, $J=8.2$ Hz), 3.71 (3 H, s), 2.32 (1 H, ddd, $J=12.3, 7.4, 7.2$ Hz), 2.08 (1 H, dt, $J=12.6, 6.4$ Hz). LCMS-ESI (POS), M/Z , $M+1$: Found 416.2.



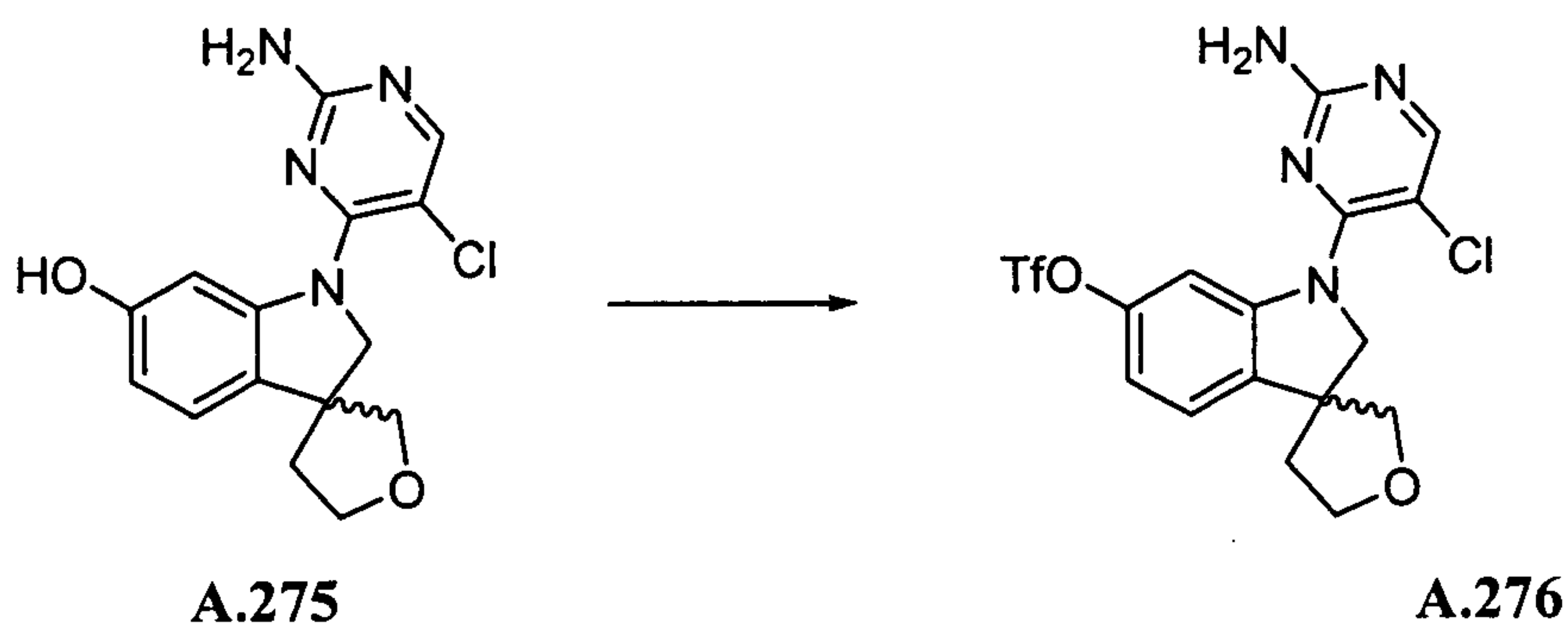
(rac)-6'-(benzyloxy)-1'-(4-methoxybenzyl)-4,5-dihydro-2H-spiro[furan-3,3'-indoline] A.273 (a colorless viscous liquid) was prepared from 6'-(benzyloxy)-1'-(4-methoxybenzyl)-4,5-dihydro-2H-spiro[furan-3,3'-indolin]-2'-one A.272 using chemistry similar to that described for compound A.237. LCMS-ESI (POS), M/Z, M+1: Found 402.2.



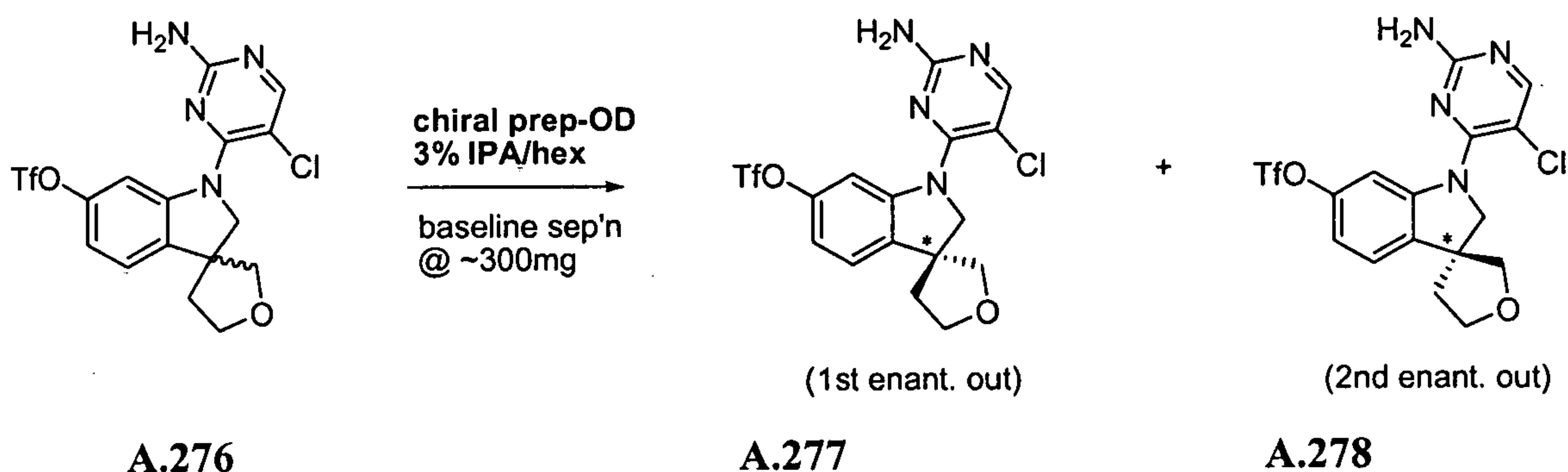
(rac)-1',2',4,5-Tetrahydrospiro[furan-3,3'-indol]-6'-ol hydrochloride A.274 (a colorless viscous liquid) was prepared from 6'-(benzyloxy)-1'-(4-methoxybenzyl)-4,5-dihydro-2H-spiro[furan-3,3'-indoline] A.273 using chemistry similar to that described for compound A.238. LCMS-ESI (POS), M/Z, M+1: Found 192.1.



(rac)-1'-(2-Amino-5-chloro-4-pyrimidinyl)-1',2',4,5-tetrahydrospiro[furan-3,3'-indol]-6'-ol A.275 (an off-white solid) was prepared from 1',2',4,5-tetrahydrospiro[furan-3,3'-indol]-6'-ol hydrochloride A.274 and 4,5-dichloro-2-pyrimidinamine A.14 using chemistry similar to that described for compound A.239. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.24 (1 H, s), 7.19 (1 H, br. s.), 7.12 (1 H, d, *J*=8.2 Hz), 6.52 (1 H, dd, *J*=7.8, 2.0 Hz), 4.18 - 4.38 (2 H, m), 3.91 - 4.02 (1 H, m), 3.87 (1 H, q, *J*=7.8 Hz), 3.78 (1 H, d, *J*=8.2 Hz), 3.54 (1 H, d, *J*=8.6 Hz), 2.05 - 2.23 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 319.1.



(rac)-1'-(2-amino-5-chloropyrimidin-4-yl)-4,5-dihydro-2H-spiro[furan-3,3'-indoline]-6'-yl trifluoromethanesulfonate **A.276** (a colorless solid) was prepared from 1'-(2-amino-5-chloro-4-pyrimidinyl)-1',2',4,5-tetrahydrospiro[furan-3,3'-indol]-6'-ol **A.275** using chemistry similar to that described for compound **A.240**. ¹H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 8.12 (1 H, s), 7.52 (1 H, d, *J*=2.3 Hz), 7.23 (1 H, d, *J*=8.6 Hz), 6.88 (1 H, dd, *J*=8.2, 2.3 Hz), 5.07 (2 H, br. s.), 4.38 (1 H, d), 4.27 (1 H, d), 4.07 - 4.15 (1 H, m), 3.99 - 4.07 (1 H, m), 3.88 (1 H, d), 3.79 (1 H, d), 2.26 - 2.36 (1 H, m), 2.14 - 2.22 (1 H, m). LCMS-ESI (POS), *M/Z*, *M*+1: Found 451.0.

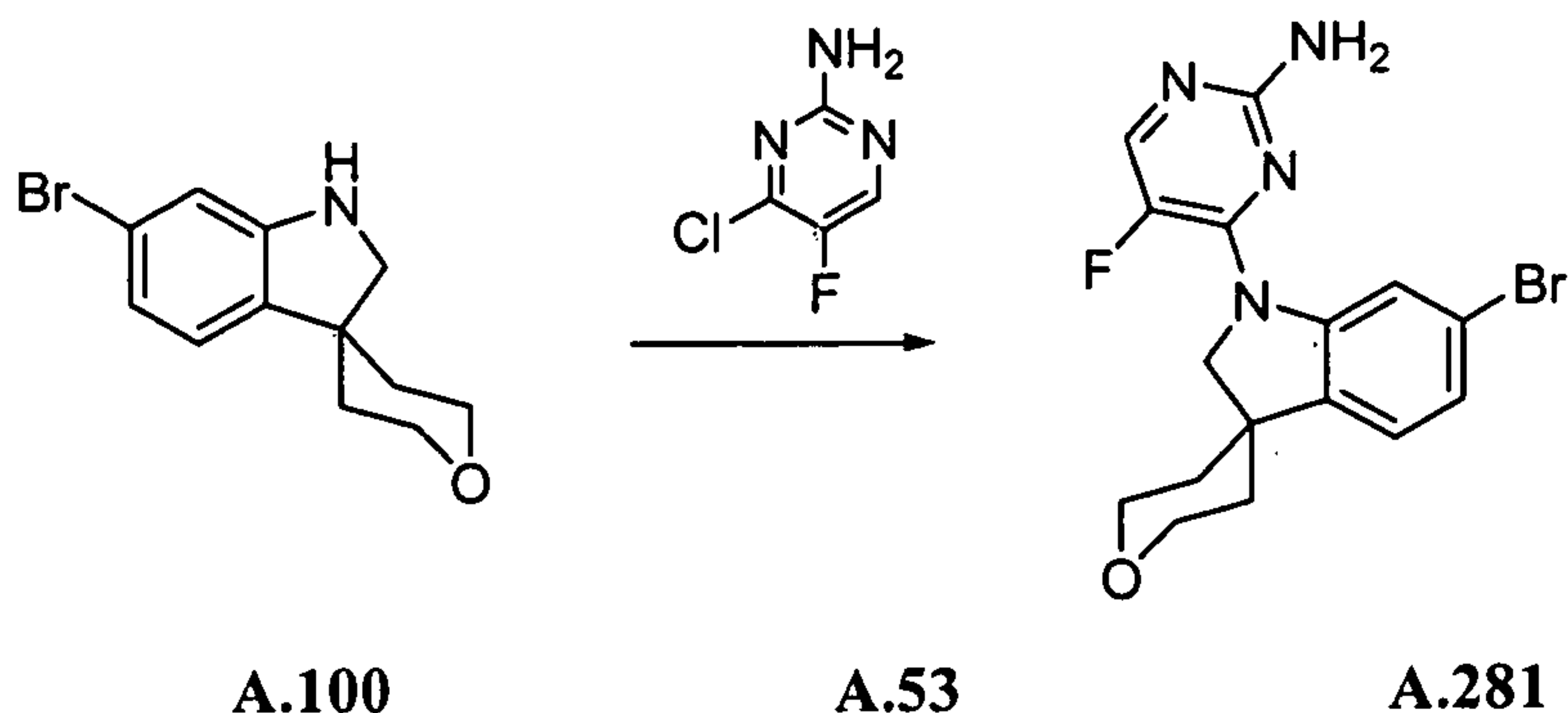


(3R^{*})-1'-(2-amino-5-chloropyrimidin-4-yl)-4,5-dihydro-2H-spiro[furan-3,3'-indoline]-6'-yl trifluoromethanesulfonate **A.277** and (3S^{*})-1'-(2-amino-5-chloropyrimidin-4-yl)-4,5-dihydro-2H-spiro[furan-3,3'-indoline]-6'-yl trifluoromethanesulfonate **A.278**

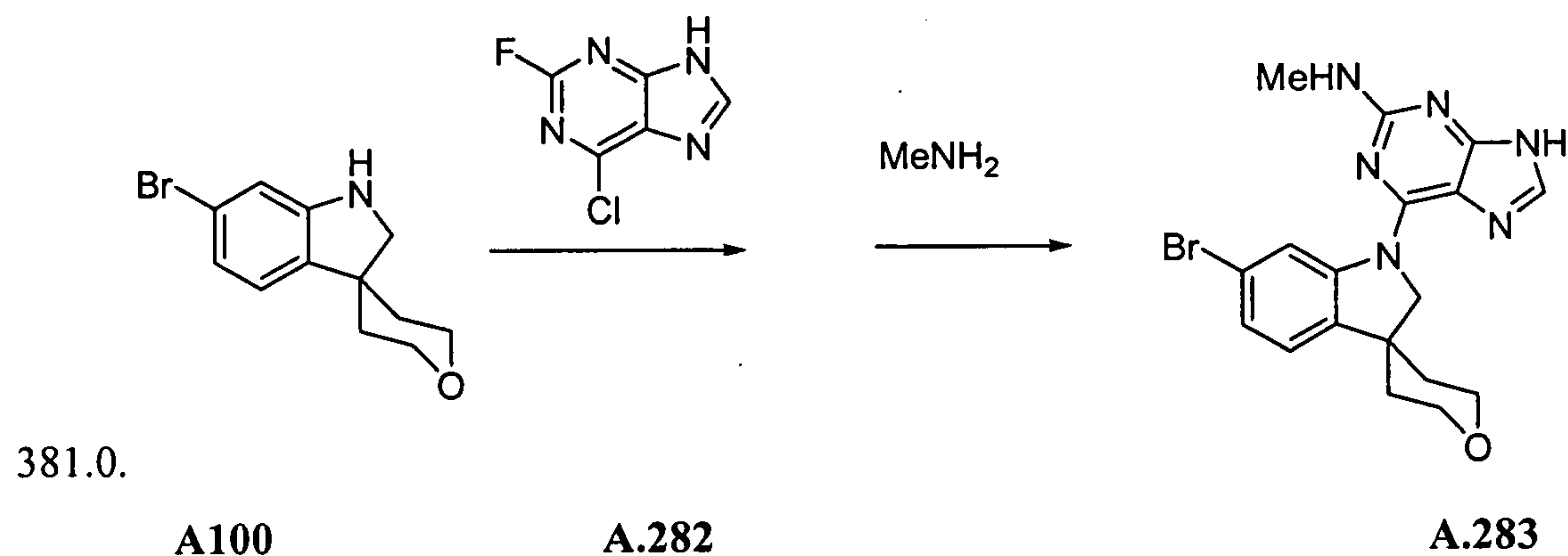
Optical resolution of (rac)-1'-(2-amino-5-chloropyrimidin-4-yl)-4,5-dihydro-2H-spiro[furan-3,3'-indoline]-6'-yl trifluoromethanesulfonate was accomplished by the following method. Instrument: Agilent 1100 series. Column: OD-preparative (50 mm X 500 mm). Solvents: 3% isopropanol in hexanes. Gradient: isochratic. Amount of sample per injection: 300 mg in methanol (6 mL). Separation quality: baseline separation. The first peak eluting off of the OD column provided (3R^{*})-1'-(2-amino-5-chloropyrimidin-4-yl)-4,5-dihydro-2H-spiro[furan-3,3'-indoline]-6'-yl trifluoromethanesulfonate **A.277** as an off-white solid.

The second peak furnished (3S^{*})-1'-(2-amino-5-chloropyrimidin-4-yl)-4,5-dihydro-2H-spiro[furan-3,3'-indoline]-6'-yl trifluoromethanesulfonate **A.278** as an off-white solid.

Stereochemistry arbitrarily assigned.

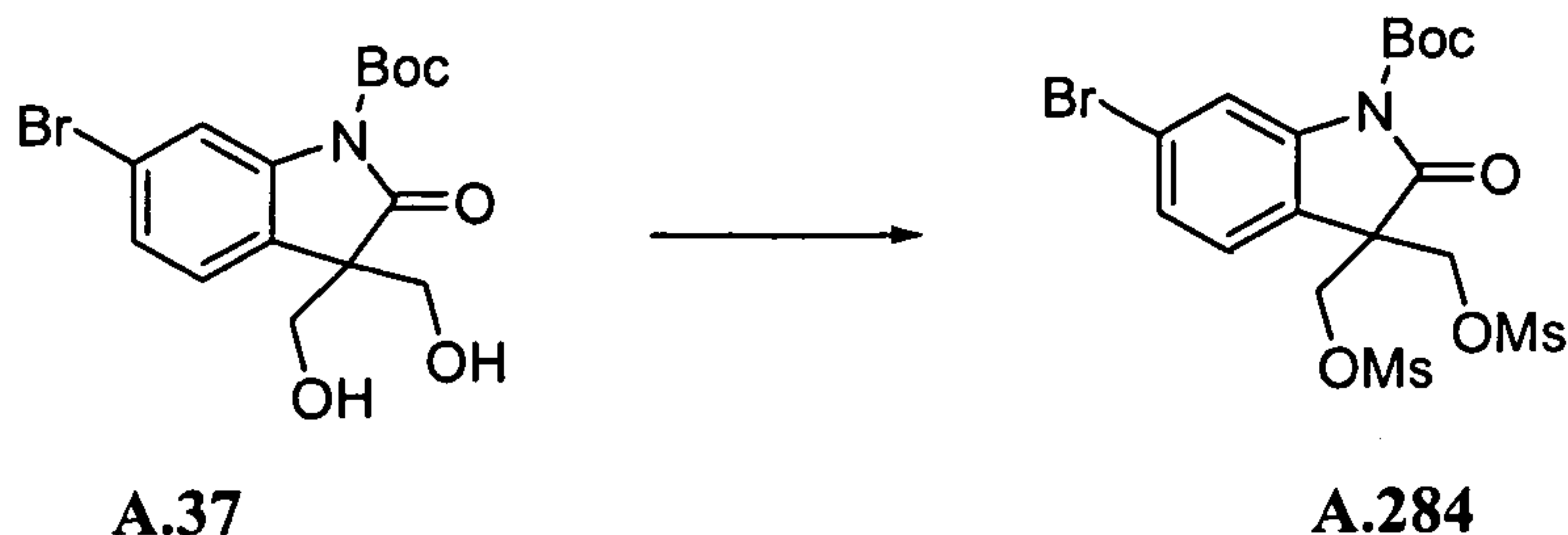


4-(6-Bromo-2',3',5',6'-tetrahydrospiro[indole-3,4'-pyran]-1(2H)-yl)-5-fluoro-2-pyrimidinamine A.281 (an off-white solid) was prepared from 6-bromo-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-pyran] (A.100) and 4-chloro-5-fluoro-2-pyrimidinamine A.53 using chemistry similar to that described for compound A.239. LCMS-ESI (POS), M/Z, M+1: Found 379.0 and



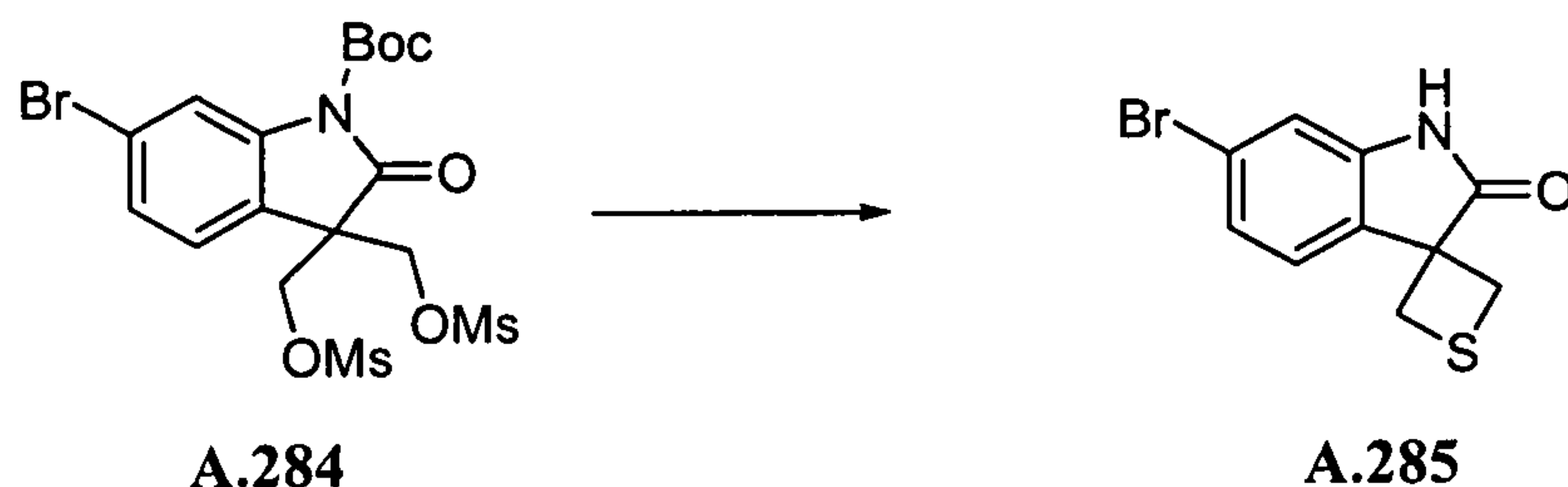
6-(6-Bromo-2',3',5',6'-tetrahydrospiro[indole-3,4'-pyran]-1(2H)-yl)-N-methyl-9H-purin-2-amine (A.283):

To a stirred solution of 6-bromo-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-pyran] (A.100) (0.24 g, 0.89 mmol) in t-butanol (12 mL) in a pressure vessel was added 6-chloro-2-fluoro-9H-purine A.282 (1.0 eq., 0.18 g) followed by Hunig's base (0.21 mL). The resulting mixture was stirred at 80 °C for 22 h. After cooling, methylamine (2 M solution in THF) was added to this mixture. The resulting mixture was stirred at 85 °C for 15 h. Upon workup, the volatiles were removed in vacuo and the residue was subjected to combi-flash column chromatography (methanol/dichloromethane) to give 6-(6-bromo-2',3',5',6'-tetrahydrospiro[indole-3,4'-pyran]-1(2H)-yl)-N-methyl-9H-purin-2-amine A.283. LCMS-ESI (POS), M/Z, M+1: Found 415.0 and 417.0.



***tert*-Butyl 6-bromo-3,3-bis(((methylsulfonyl)oxy)methyl)-2-oxo-2,3-dihydro-1H-indole-1-carboxylate (A.284):**

To a stirred ice cooled suspension of *tert*-butyl 6-bromo-3,3-bis(hydroxymethyl)-2-oxo-2,3-dihydro-1H-indole-1-carboxylate A.37 (4.68 g, 12.6 mmol) in dichloromethane (100 mL) was added triethylamine (9.0 mL) through a syringe followed by MsCl (2.0 eq., 2.91 g) also through a syringe. The resulting mixture was stirred at 0 °C for 2.5 h as TLC showed completion. Upon workup, the volatiles were removed in vacuo and the residue was dissolved in dichloromethane and subjected to combi-flash column chromatography (ethyl acetate/hexanes) to give *tert*-butyl 6-bromo-3,3-bis(((methylsulfonyl)oxy)methyl)-2-oxo-2,3-dihydro-1H-indole-1-carboxylate A.284 (5.2 g, 79% yield) as an off-white solid. ¹H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 8.14 (1 H, d, *J*=2.0 Hz), 7.42 (1 H, dd, *J*=8.0, 1.8 Hz), 7.31 (1 H, d), 4.56 (2 H, d, *J*=10.2 Hz), 4.45 (2 H, d, *J*=10.2 Hz), 2.96 (6 H, s), 1.66 (9 H, s).

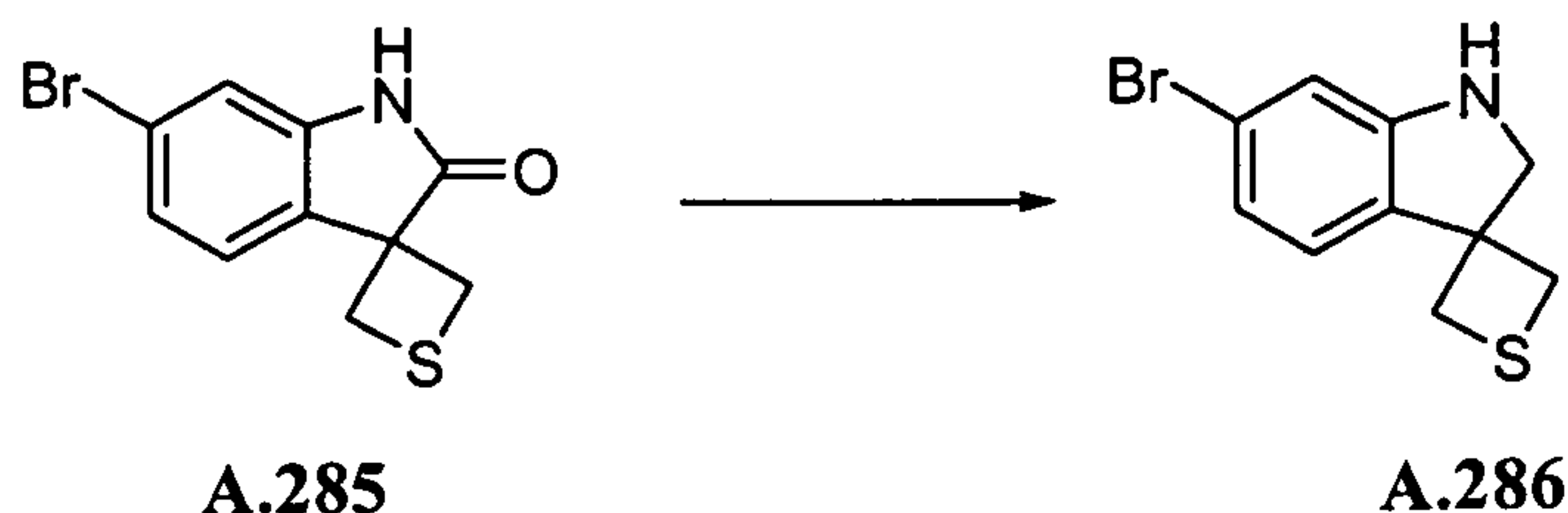


6-Bromospiro[indole-3,3'-thietan]-2(1H)-one A.285

Prepared by analogy to Roy, A., B. Achari, et al. (2006). *Tetrahedron Lett.* **47**(23): 3875-3879. To a 100 mL single necked round bottom flask were placed *tert*-butyl 6-bromo-3,3-bis(((methylsulfonyl)oxy)methyl)-2-oxo-2,3-dihydro-1H-indole-1-carboxylate (4.51 g, 8.54 mmol) A.284 and Na₂S (1.5 eq., 1.0 g) followed by DMF (40 mL) at room temperature under N₂. The resulting mixture was stirred in an oil bath preheated at 105 °C for 38 h. Upon workup, the mixture was poured into ice and saturated NH₄Cl aqueous solution and extracted with ethyl acetate (2 X). The combined organics were washed with brine (2 X), dried over Na₂SO₄, and concentrated in vacuo. The residue was subjected to combi-flash column chromatography (ethyl acetate/hexanes) to give 6-bromospiro[indole-3,3'-thietan]-2(1H)-one A.285 (0.58 g, 25% yield) as an off-white solid. ¹H NMR (400 MHz, *CHLOROFORM-d*₆) δ ppm 7.94 (1 H, d,

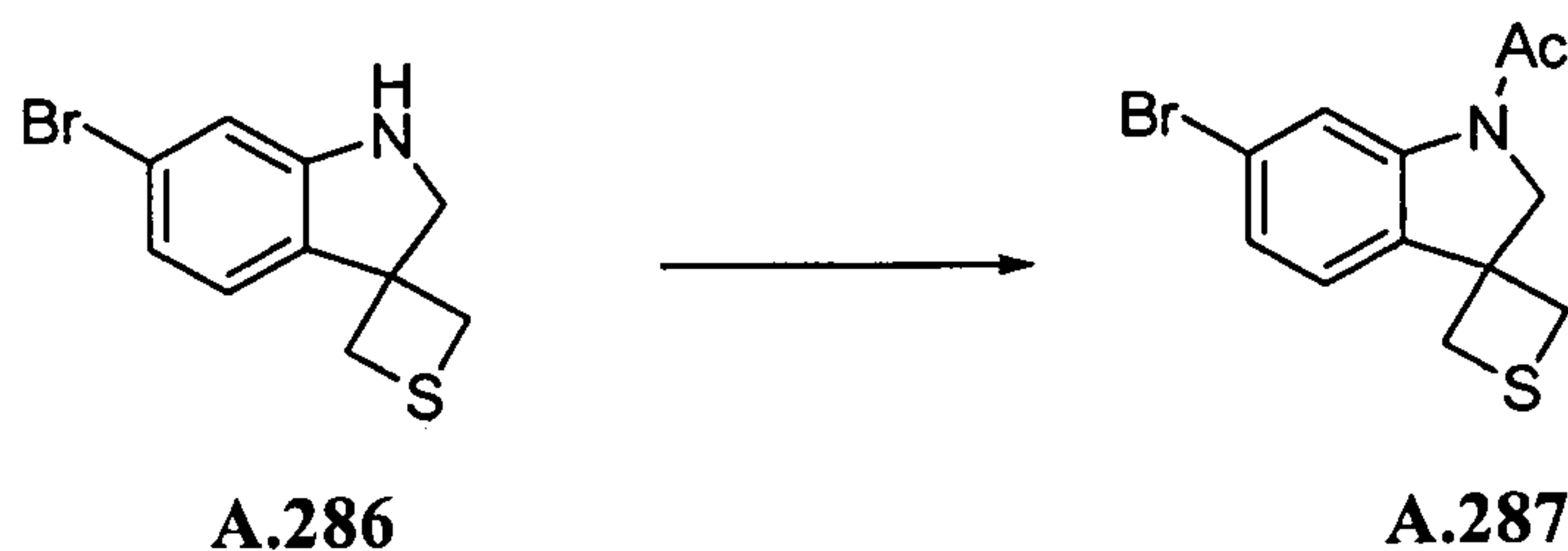
$J=7.8$ Hz), 7.86 (1 H, br. s.), 7.31 (1 H, dd, $J=8.0, 1.8$ Hz), 7.07 (1 H, d, $J=1.6$ Hz), 3.89 (2 H, d, $J=9.8$ Hz), 3.12 (2 H, d, $J=9.8$ Hz)

LCMS-ESI (NEG), M/Z, M-1: Found 268.0 AND 270.0.



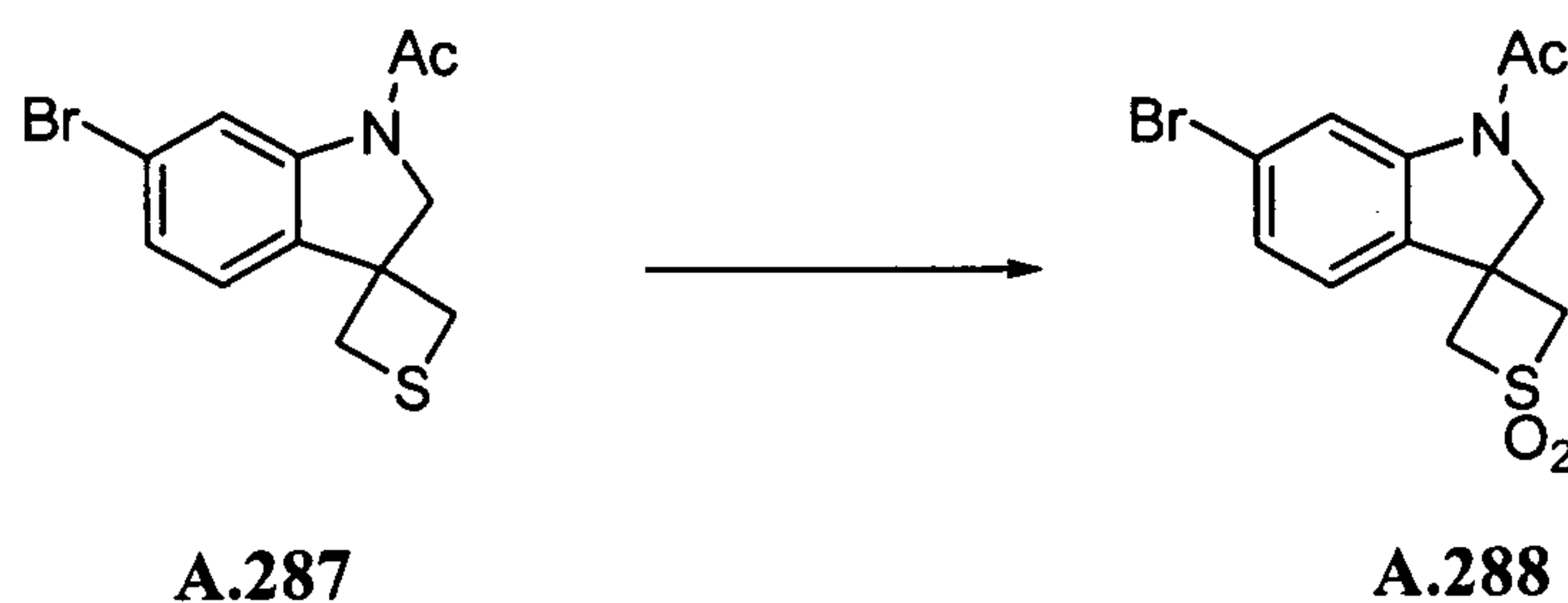
6-bromospiro[indoline-3,3'-thietane] A.286

To a stirred solution of 6-bromospiro[indole-3,3'-thietan]-2(1H)-one **A.285** (0.58 g, 2.15 mmol) in toluene (85 mL) preheated at 80 °C was added Red-AL in toluene (3 M) (5.0 eq., 3.5 mL) under a nitrogen atmosphere. The resulting mixture was stirred at this temperature for 40 min. Upon workup, the mixture was cooled in an ice-salt bath before quenched with ice-cold aqueous 2 N NaOH. The mixture was further diluted with ice-cold aqueous 2 N NaOH and extracted with ethyl acetate (2 x). The combined organics were dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to give 6-bromo-1,2-dihydrospiro[indole-3,3'-thietane] **A.286**, LCMS-ESI (POS), M/Z, M+1: Found 256.0 and 258.0.



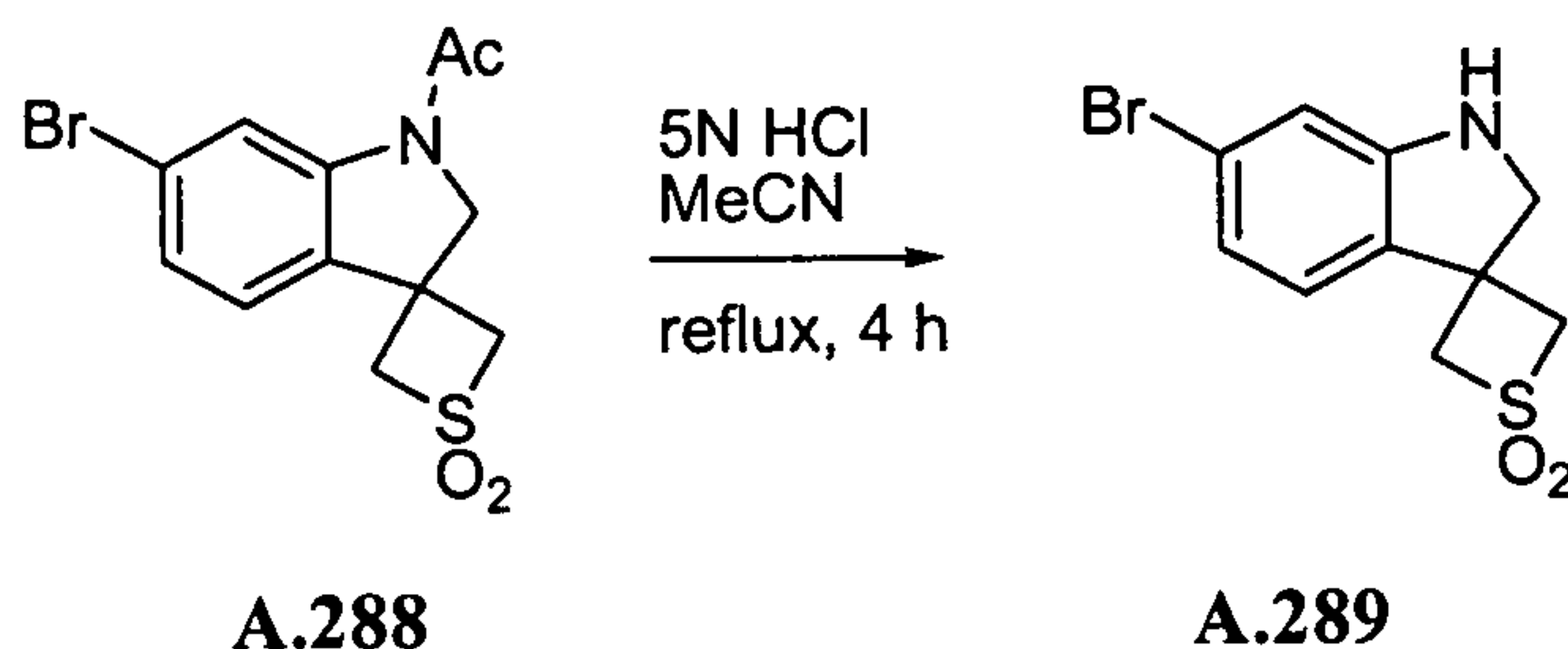
1-Acetyl-6-bromospiro[indoline-3,3'-thietane] A.287

To a stirred ice-cooled solution of crude 6-bromospiro[indoline-3,3'-thietane] **A.286** (2.1 mmol, 100% yield assumed from the previous step), triethylamine (2.0 eq., 0.43 g), and DMAP (catalytic amount) in dichloromethane (30 mL) was added AcCl (2.0 eq., 0.34 g) under N₂. The resulting mixture was stirred at 0 °C for 5 min and at ambient temperature for 3 h. Upon workup, the mixture was poured into ice and 2 N HCl aqueous solution and extracted with ethyl acetate (2 X). The combined organics were washed with brine (2 X), dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to give 1-acetyl-6-bromo-1,2-dihydrospiro[indole-3,3'-thietane] **A.287**. LCMS-ESI (POS), M/Z, M+1: Found 298.0 and 300.0.



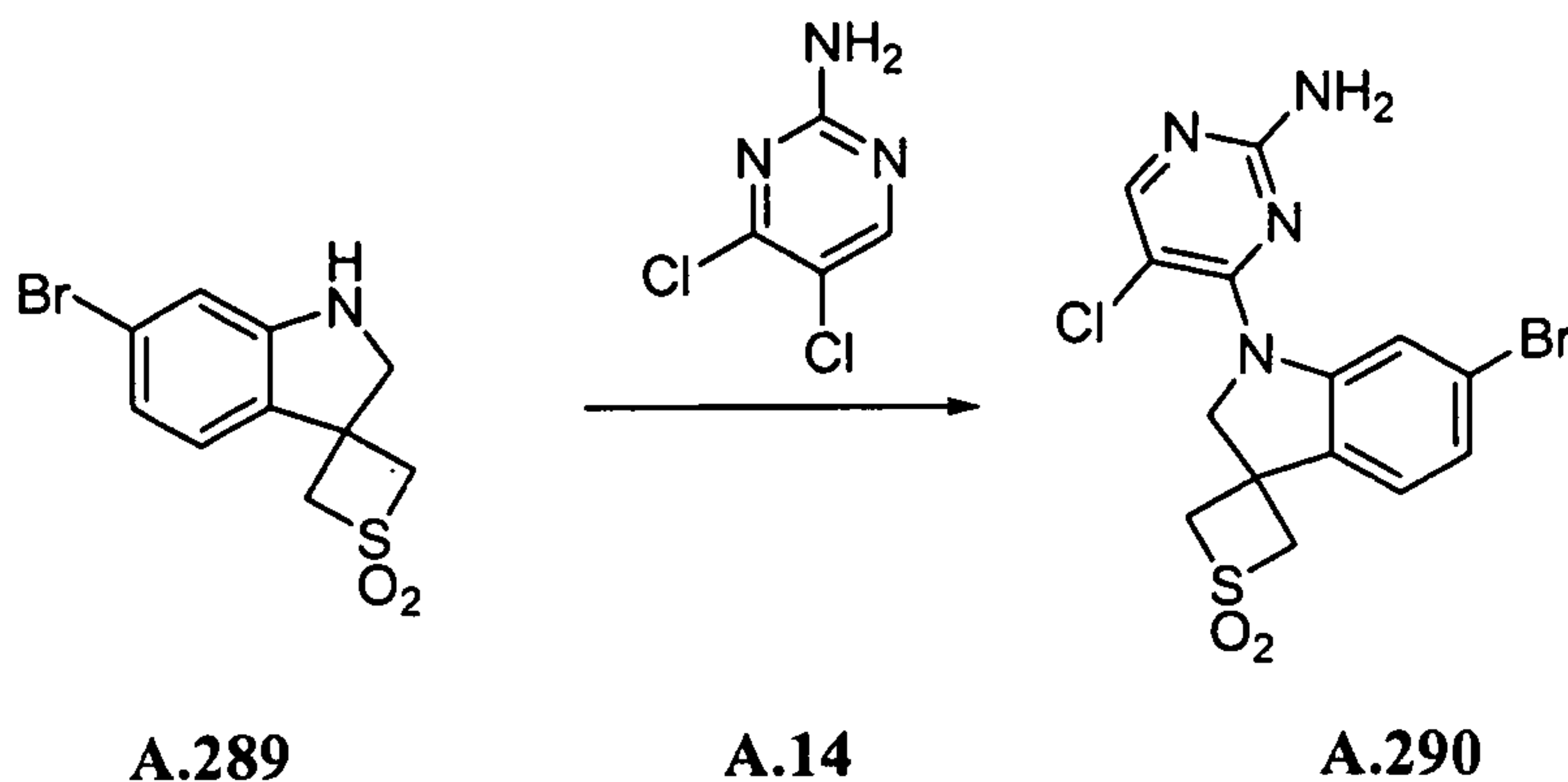
1-Acetyl-6-bromospiro[indoline-3,3'-thietane]1',1'-dioxide A.288

To a stirred ice-cooled suspension of 1-acetyl-6-bromospiro[indoline-3,3'-thietane] **A.287** (2.1 mmol, 100% yield assumed from the previous step) in a mixed solvent of methanol (40 mL), water (5 mL), and acetone (10 mL) was added a solution of oxone (2.0 eq., 2.6 g) in water (15 mL). The resulting mixture was stirred at ambient temperature for 20 h. Upon workup, the mixture was poured into ice and saturated NH_4Cl aqueous solution and extracted with ethyl acetate (2 X). The combined organics were washed with brine (1 X), dried over Na_2SO_4 , and concentrated in vacuo to give 1-acetyl-6-bromospiro[indoline-3,3'-thietane]1',1'-dioxide **A.288**. LCMS-ESI (POS), M/Z, M+1: Found 330.0 and 332.0.



6-bromospiro[indoline-3,3'-thietane]1',1'-dioxide A.289

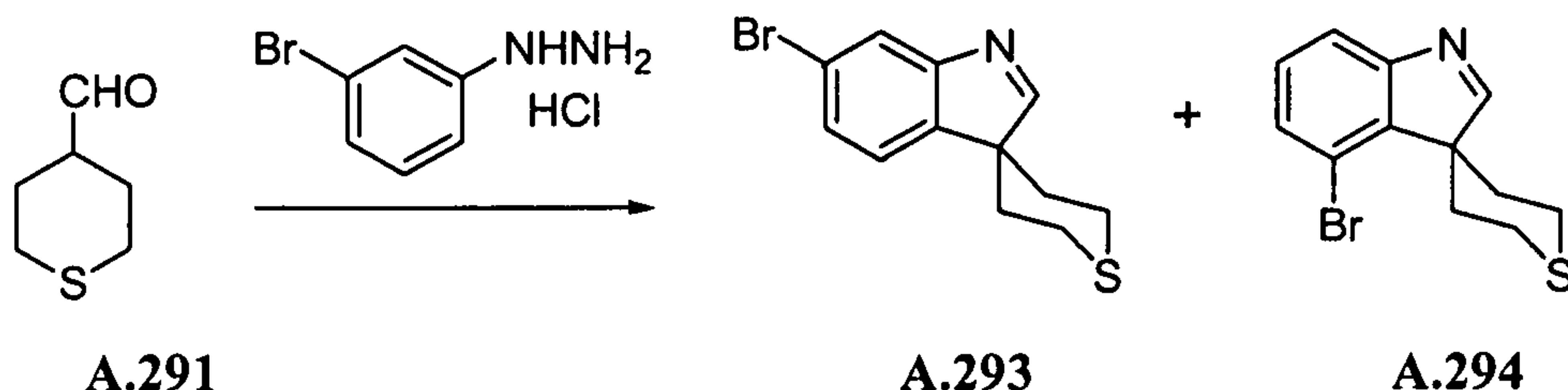
A mixture of 1-acetyl-6-bromospiro[indoline-3,3'-thietane]1',1'-dioxide **A.288** (2.1 mmol, assumed from the previous step) and 5 N HCl (8 mL) in methanol (20 mL) was refluxed for 3 h. The volatiles were removed in vacuo to give 6-bromospiro[indoline-3,3'-thietane]1',1'-dioxide **A.289**. LCMS-ESI (POS), M/Z, M+1: Found 288.0 and 290.0.



4-(6-Bromo-1',1'-dioxidospiro[indole-3,3'-thietan]-1(2H)-yl)-5-chloro-2-pyrimidinamine

A.290 (an off-white solid) was prepared from 6-bromospiro[indoline-3,3'-thietane]1',1'-dioxide **A.289** (2.1 mmol, assumed from the previous step) and 4,5-dichloro-2-pyrimidinamine

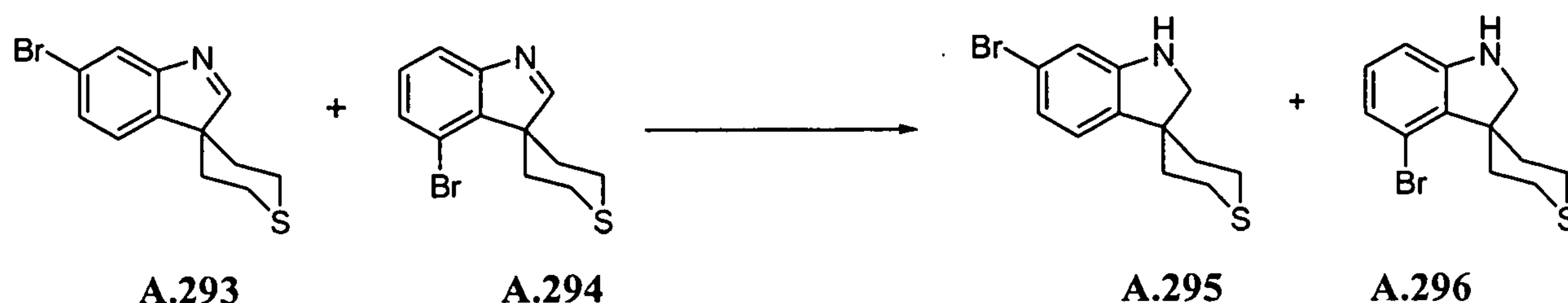
A.14 (2.0 eq., 0.65 g) using chemistry similar to that described for compound **A.239**. [45% yield over 5 steps from 6-bromospiro[indole-3,3'-thietan]-2(1H)-one **A.285**]. ¹H NMR (400 MHz, *DMSO-d*₆) δ ppm 8.15 (1 H, s), 7.59 (1 H, d, *J*=8.2 Hz), 7.44 (1 H, d, *J*=2.0 Hz), 7.21 (1 H, dd, *J*=8.0, 1.8 Hz), 6.76 (2 H, s), 4.62 (2 H, d), 4.43 - 4.57 (4 H, m). LCMS-ESI (POS), *M/Z*, *M*+1: Found 414.9 and 416.8.



6-Bromo-2',3',5',6'-tetrahydrospiro[indole-3,4'-thiopyran] (A.293) and 4-bromo-2',3',5',6'-tetrahydrospiro[indole-3,4'-thiopyran]

Ref. Maligres, P. E., I. Houpis, et al. (1997). *Tetrahedron* 53(32): 10983-10992.

To a stirred ice-cooled solution of tetrahydro-2H-thiopyran-4-carbaldehyde **A.291** (2.1 g, 16.1 mmol) in dichloromethane (30 mL) was added 3-bromophenylhydrazine hydrochloride (1.0 eq., 3.6 g) in one portion. The resulting mixture was stirred at 0 °C for 10 min before TFA (3.0 eq., 5.52 g) was dropwise added through a syringe. The resulting mixture was stirred at 0 °C for 10 min and then at ambient temperature for 4 h. Upon workup, the mixture was poured into ice and NH₃ water (28% commercial) and extracted with ethyl acetate (2 X). The combined organics were washed with brine (2 X), dried over anhydrous Na₂SO₄, and concentrated in vacuo. The residue was azeotroped with benzene (2 X) to give a mixture (4.9 g) of 6-bromo-2',3',5',6'-tetrahydrospiro[indole-3,4'-thiopyran] (**A.293**) and 4-bromo-2',3',5',6'-tetrahydrospiro[indole-3,4'-thiopyran] (**A.294**) in a ratio of (1 to 1.3). LCMS-ESI (POS), *M/Z*, *M*+1: Found 282.0 and 284.0.



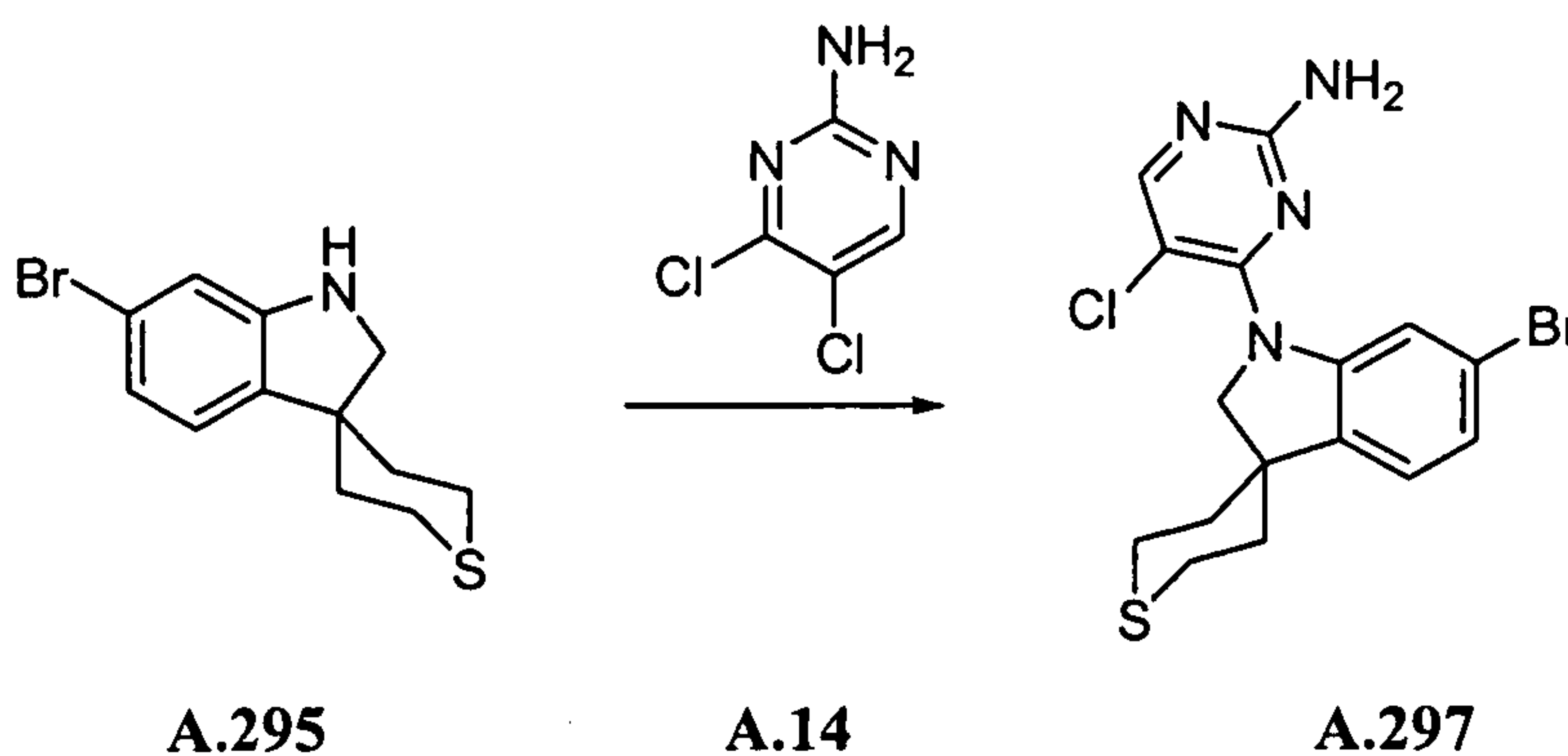
6-Bromo-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-thiopyran] (A.295) and 4-bromo-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-thiopyran] A.296

To a stirred solution of the mixture of 6-bromo-2',3',5',6'-tetrahydrospiro[indole-3,4'-thiopyran] (**A.293**) and 4-bromo-2',3',5',6'-tetrahydrospiro[indole-3,4'-thiopyran] (4.9 g) in toluene (80

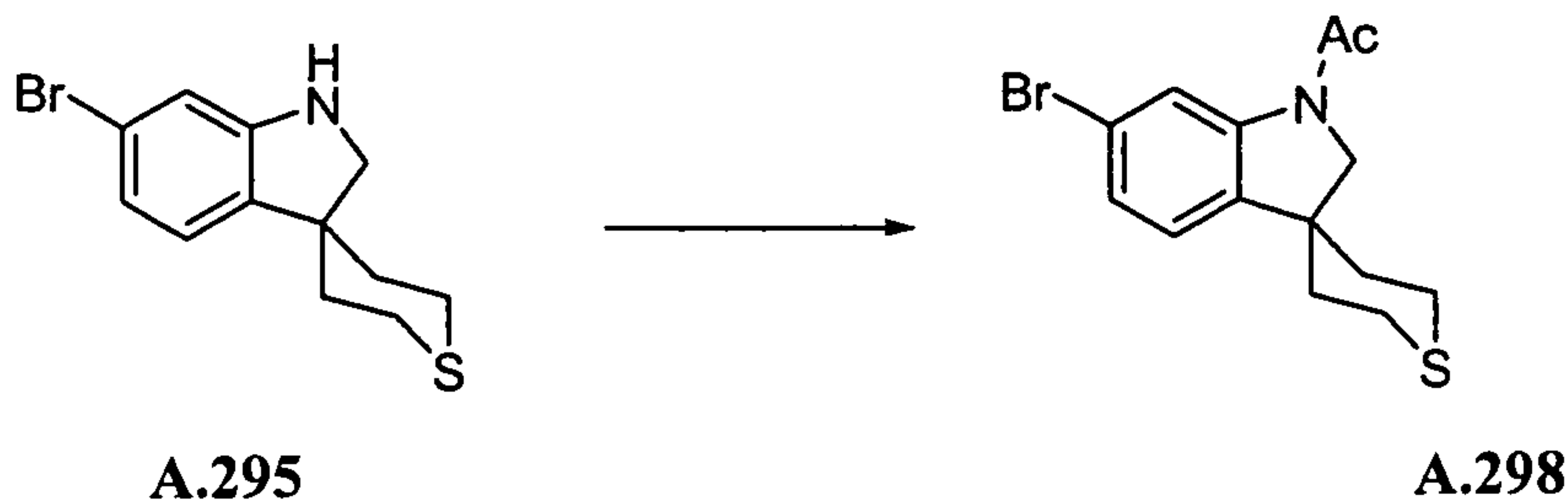
mL) preheated at 80 °C was dropwise added Red-AL (15 mL) under N₂. The resulting mixture was stirred at 80 °C for 1.5 h. Upon workup, the mixture was thoroughly cooled in an ice bath before carefully quenched with ice cold 2 N NaOH. The mixture was further diluted with ice-cold aqueous 2 N NaOH and extracted with ethyl acetate (3 x). The combined organics were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was subjected to combi-flash column chromatography (ethyl acetate/hexanes) to give 6-bromo-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-thiopyran] (A.295) (1.65 g, 36% yield in 2 steps) and 4-bromo-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-thiopyran] (A.296) (2.1 g, 46% yield in 2 steps) both as off-white solids.

6-bromo-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-thiopyran] A.295. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 6.89 - 6.94 (1 H, m), 6.81 - 6.87 (1 H, m), 6.75 (1 H, d, *J*=1.2 Hz), 3.78 (1 H, br. s.), 3.44 (2 H, s), 2.69 - 2.83 (2 H, m), 2.60 (2 H, d, *J*=14.1 Hz), 1.87 - 2.07 (4 H, m). LCMS-ESI (POS), *M/Z*, *M*+1: Found 284.0 and 286.0.

4-bromo-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-thiopyran] A.296. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 6.80 - 6.92 (2 H, m), 6.55 (1 H, d, *J*=7.4 Hz), 4.04 (0 H, br. s.), 3.51 (2 H, s), 2.75 - 2.90 (4 H, m), 2.53 - 2.63 (2 H, m), 1.88 - 1.99 (2 H, m). LCMS-ESI (POS), *M/Z*, *M*+1: Found 284.0 and 286.0.



4-(6-Bromo-2',3',5',6'-tetrahydrospiro[indole-3,4'-thiopyran]-1(2H)-yl)-5-chloro-2-pyrimidinamine A.297 (an off-white solid) was prepared from 6-bromo-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-thiopyran] A.295 and 4,5-dichloro-2-pyrimidinamine A.14 using chemistry similar to that described for compound A.239. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.08 (1 H, s), 7.63 (1 H, d, *J*=1.6 Hz), 7.12 - 7.20 (1 H, m), 7.06 (1 H, d, *J*=7.8 Hz), 5.24 (2 H, br. s.), 4.14 (2 H, s), 2.80 (2 H, ddd, *J*=14.6, 8.5, 6.3 Hz), 2.53 - 2.69 (2 H, m), 1.93 - 2.04 (4 H, m). LCMS-ESI (POS), *M/Z*, *M*+1: Found 411.0 and 412.9.

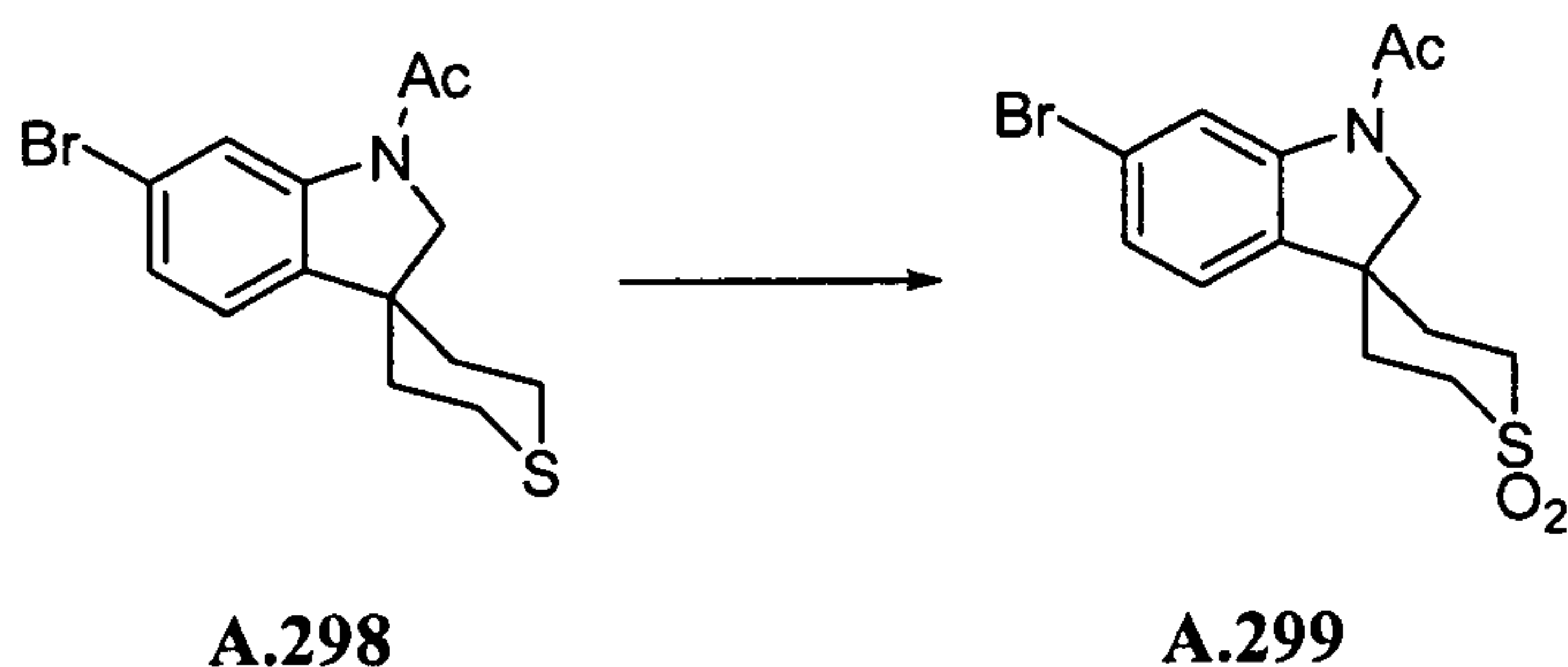


1-Acetyl-6-bromo-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-thiopyran] A.298

To a stirred ice-cooled solution of 6-bromo-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-thiopyran] A.295 (0.7 g, 2.46 mmol) and DMAP (catalytic amount) and triethylamine (1.5 eq., 0.37 g) in dichloromethane (25 mL) was added acetyl chloride through a syringe. The resulting mixture was stirred at 0 °C for 5 min and at ambient temperature for 1.5 h. Upon workup, the mixture was poured into ice and 2 N HCl aqueous solution and extracted with ethyl acetate (2 X). The combined organics were washed with brine (1 X), saturated NaHCO₃ aqueous solution (1 X), brine (1 X), and dried over anhydrous Na₂SO₄. The residue was subjected to combi-flash column chromatography (ethyl acetate/hexanes) to give 1-acetyl-6-bromo-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-thiopyran] A.298 (0.8 g, quantitative yield) as an off-white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.20 (1 H, s), 7.21 - 7.27 (1 H, m), 7.15 - 7.21 (1 H, m), 3.99 (2 H, s), 2.74 - 2.90 (2 H, m), 2.52 - 2.60 (2 H, m), 2.22 (3 H, s), 1.81 - 1.93 (4 H, m).

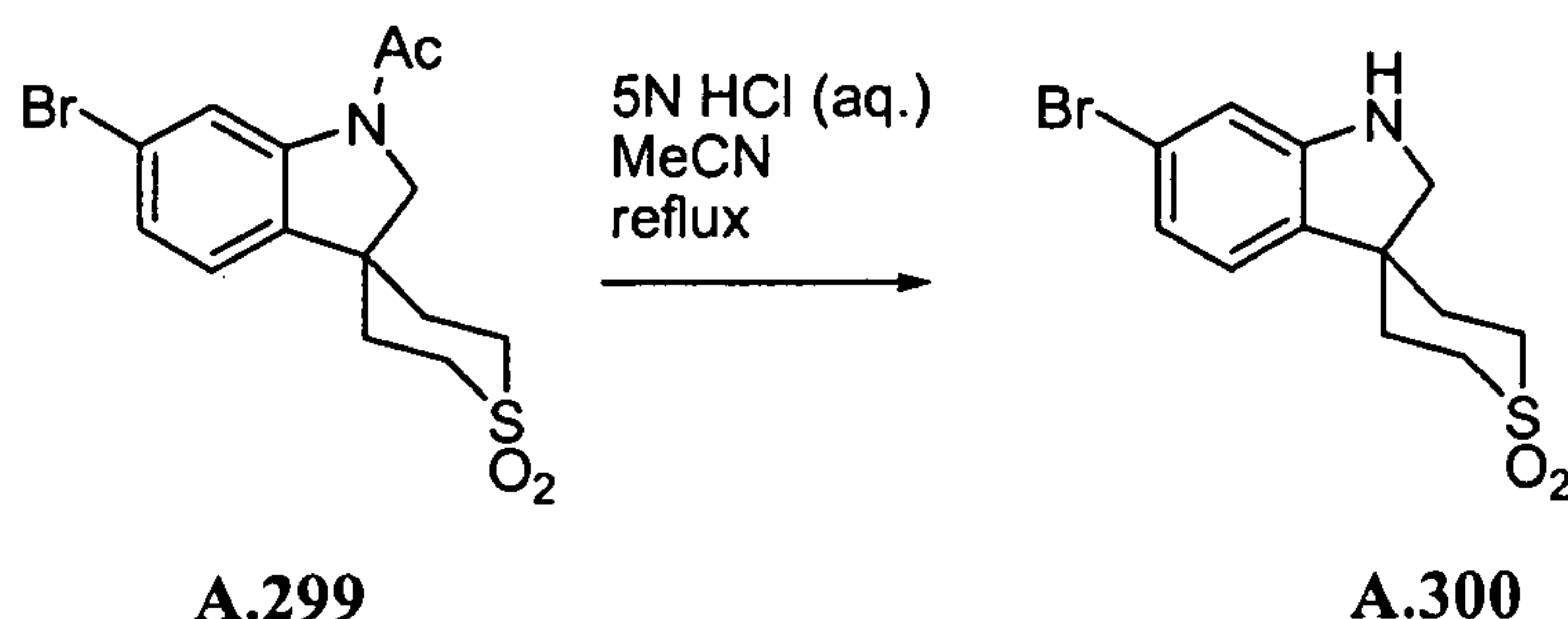
LCMS-ESI (POS), M/Z, M+1: Found 326.0 AND 328.0.



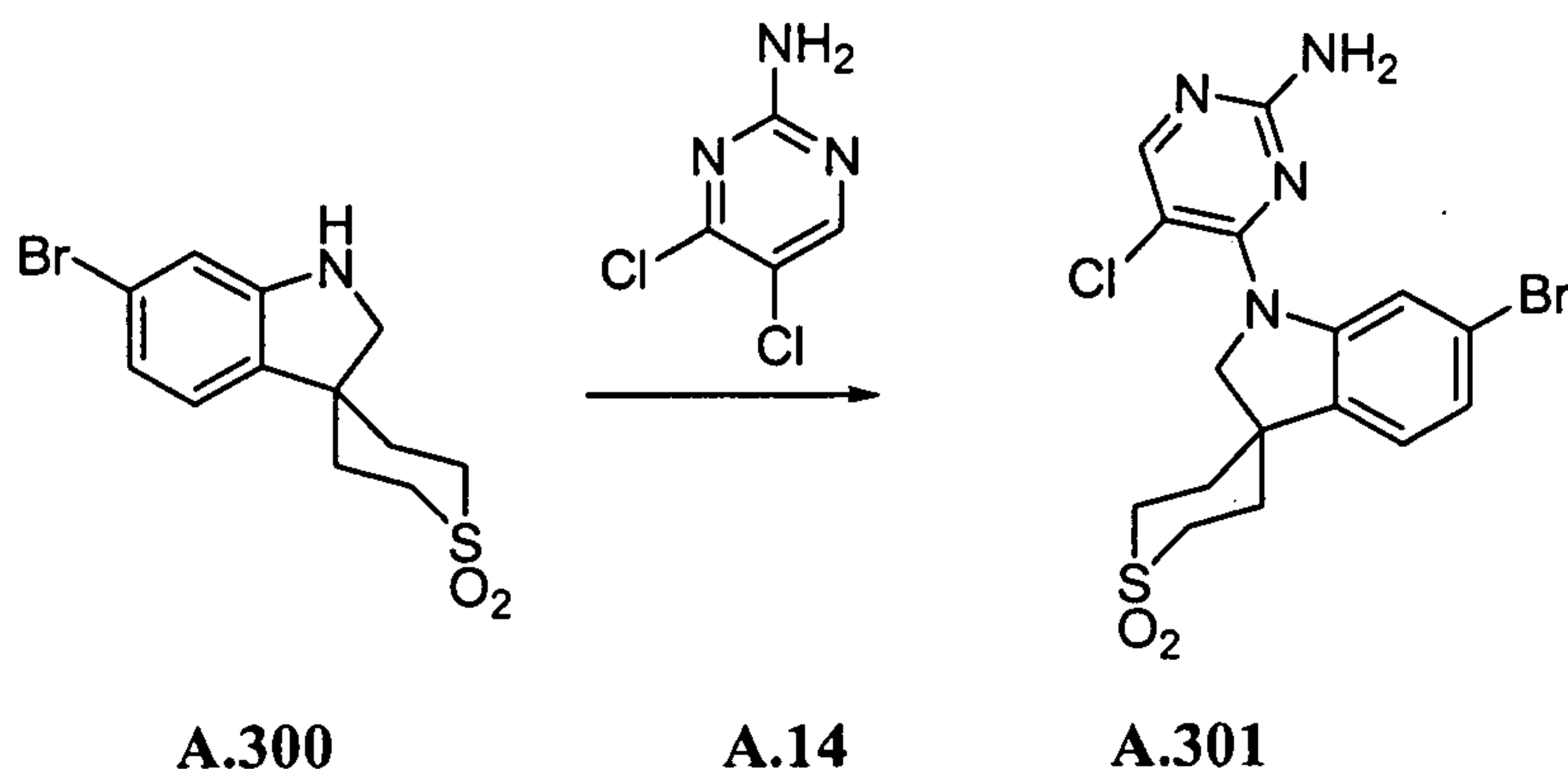
1-Acetyl-6-bromo-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-thiopyran] 1',1'-dioxide A.299

(a white solid) was prepared from 1-acetyl-6-bromo-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-thiopyran] A.298 using chemistry similar to that described for compound A.288.

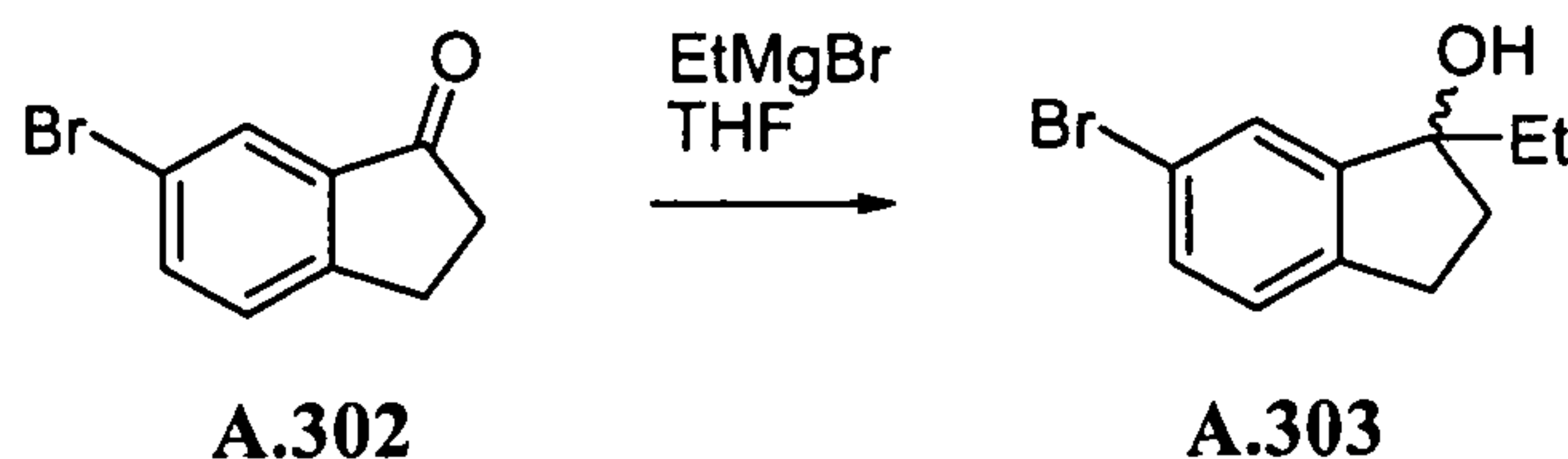
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.20 (1 H, s), 7.24 - 7.31 (1 H, m), 7.21 (1 H, dd, *J*=8.0, 1.8 Hz), 4.18 (2 H, s), 3.34 - 3.47 (2 H, m), 3.10 (2 H, d, *J*=12.9 Hz), 2.17 - 2.34 (5 H, m), 1.96 - 2.08 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 358.0 and 360.0.



6-Bromo-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-thiopyran] 1',1'-dioxide A.300 (an off-white solid) was prepared from 1-acetyl-6-bromo-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-thiopyran] 1',1'-dioxide **A.299** using chemistry similar to that described for compound **A.289**. LCMS-ESI (POS), M/Z, M+1: Found 316.0 and 318.0.



4-(6-Bromo-1',1'-dioxido-2',3',5',6'-tetrahydrospiro[indole-3,4'-thiopyran]-1(2H)-yl)-5-chloro-2-pyrimidinamine A.301 was prepared from 6-bromo-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-thiopyran] 1',1'-dioxide **A.300** and 4,5-dichloro-2-pyrimidinamine **A.14** using chemistry similar to that described for compound **A.239** in 92% as an off-white solid. ¹H NMR (400 MHz, *DMSO-d*₆) δ ppm 8.15 (1 H, s), 7.19 - 7.31 (2 H, m), 7.04 - 7.12 (1 H, m), 6.73 (2 H, s), 4.22 (2 H, s), 3.33 - 3.41 (2 H, m), 3.02 - 3.14 (2 H, m), 2.21 - 2.30 (2 H, m), 2.01 - 2.10 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 442.9 and 445.0.

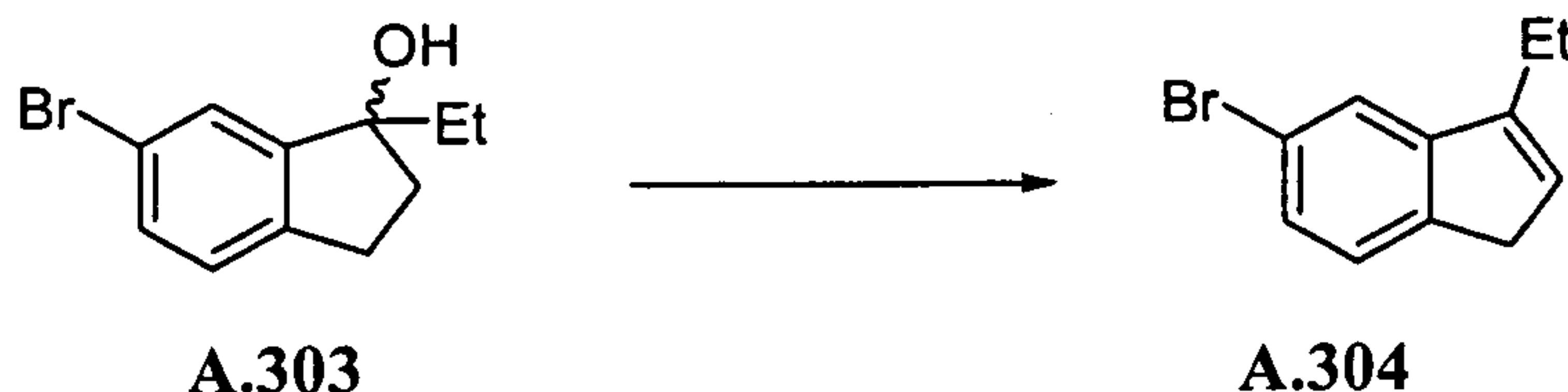


6-Bromo-1-ethyl-2,3-dihydro-1H-inden-1-ol

Ref. Shindo, M., Y. Sato, et al. (2001). *J. Org. Chem.* **66**(23): 7818-7824.

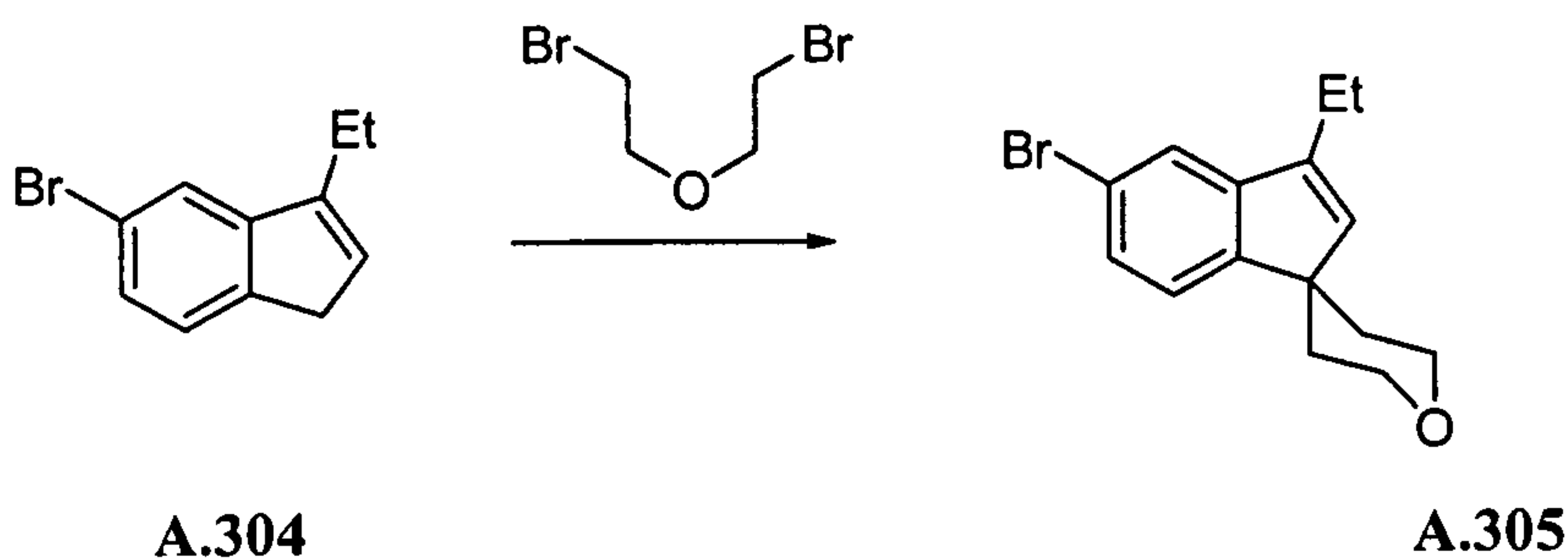
To a stirred solution of EtMgBr in THF (1.0 M, commercial) (2.0 eq., 50 mL) was dropwise added at room temperature a solution of 6-bromoindanone **A.302** (5.0 g, 23.69 mmol) in THF

(45 mL). The resulting mixture was stirred at ambient temperature overnight. Upon workup, the mixture was cooled in an ice water before carefully quenched with saturated NH_4Cl aqueous solution followed by extraction with ethyl acetate (2 X). The combined organics were washed with brine (2 X), dried over anhydrous Na_2SO_4 , and concentrated in vacuo to give 6-bromo-1-ethyl-2,3-dihydro-1H-inden-1-ol **A.303** as a colorless liquid. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 7.37 (1 H, d, $J=2.0$ Hz), 7.35 (1 H, dd, $J=8.1, 2.0$ Hz), 7.16 (1 H, d, $J=8.1$ Hz), 5.01 (1 H, s), 2.77 - 2.88 (1 H, m), 2.63 - 2.72 (1 H, m), 2.12 (1 H, ddd, $J=12.7, 8.3, 4.2$ Hz), 1.91 - 1.98 (1 H, m), 1.68 - 1.77 (1 H, m), 1.54 - 1.65 (1 H, m), 0.83 (3 H, t, $J=7.5$ Hz).



5-Bromo-3-ethyl-1H-indene **A.304**

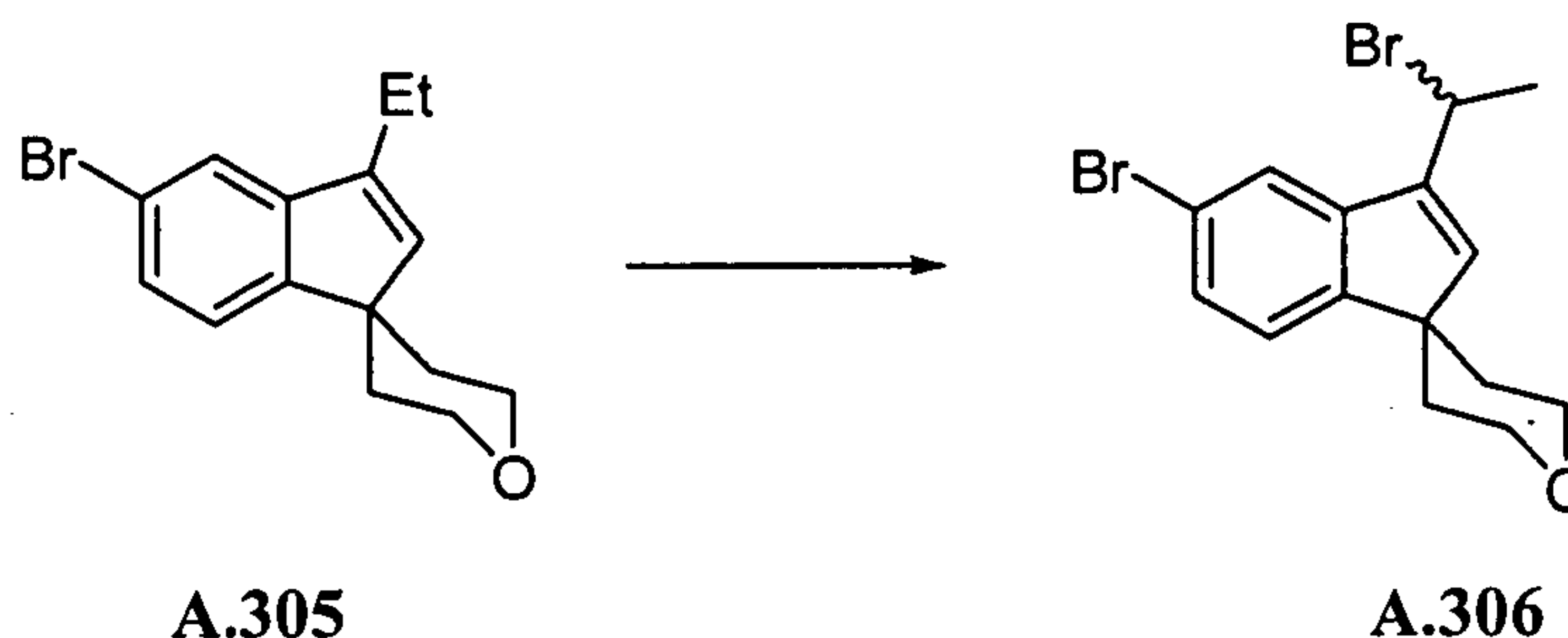
To a stirred solution of 6-bromo-1-ethyl-2,3-dihydro-1H-inden-1-ol (**A.303**) (23.69 mmol, assumed from the previous step) in dichloromethane (60 mL) was added TFA (0.5 mL) at room temperature. The resulting mixture was stirred at ambient temperature for 24 h. Upon workup, the mixture was concentrated in vacuo. The residue was subjected to combi-flash column chromatography (hexanes) to give 5-bromo-3-ethyl-1H-indene **A.304** (4.7 g, 90% in 2 steps) as a colorless liquid. ^1H NMR (400 MHz, $\text{CHLOROFORM}-d$) δ ppm 7.48 (1 H, s), 7.31 (2 H, s), 6.25 (1 H, s), 3.29 (2 H, d, $J=2.2$ Hz), 2.48 - 2.58 (2 H, m), 1.29 (3 H, t, $J=7.3$ Hz).



5-Bromo-3-ethyl-2',3',5',6'-tetrahydrospiro[indene-1,4'-pyran] **A.305**

To a stirred ice-cooled solution of 5-bromo-3-ethyl-1H-indene **A.304** (4.7 g, 21.07 mmol) in THF (20 mL) was dropwise added NaHMDS (2 M in THF) (2.0 eq., 21.1 mL) through a syringe under N_2 over a period of 10 min. The resulting mixture was stirred at 0°C for 50 min and then transferred through a cannula to a stirred ice-cooled solution of bis(2-bromoethyl)ether in THF (25 mL) under N_2 over a period of 35 min. The resulting mixture was stirred at 0°C for 35 min, then at ambient temperature for 2 days. Upon workup, the mixture was cooled thoroughly in an ice bath before quenched with saturated NH_4Cl aqueous solution

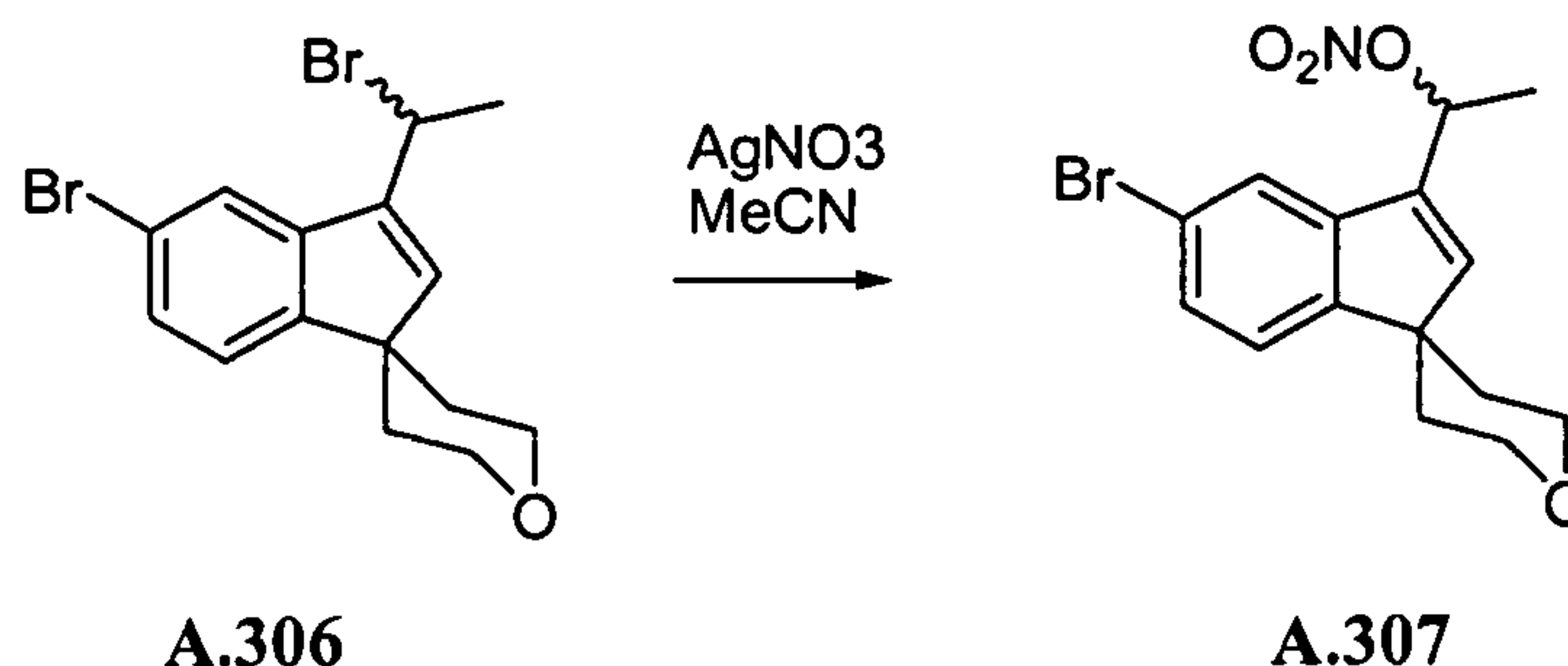
and extracted with ethyl acetate (2 X). The combined organics were washed with brine (2 X) and dried over anhydrous Na_2SO_4 . The residue after concentration in vacuo was subjected to combi-flash column chromatography (ethyl acetate/hexanes) to give 5-bromo-3-ethyl-2',3',5',6'-tetrahydrospiro[indene-1,4'-pyran] **A.305** (1.85 g, 30% yield) as a thick oil. ^1H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.41 (1 H, d, $J=1.5$ Hz), 7.35 (1 H, dd, $J=7.9, 1.6$ Hz), 7.23 (1 H, d, $J=7.7$ Hz), 6.64 (1 H, s), 4.07 (2 H, ddd, $J=11.7, 4.0, 2.6$ Hz), 3.77 (2 H, td, $J=11.9, 1.8$ Hz), 2.50 (2 H, qd, $J=7.4, 1.3$ Hz), 2.15 (2 H, td, $J=12.8, 4.4$ Hz), 1.22 - 1.31 (5 H, m). LCMS-ESI (POS), M/Z , $M+1$: Found 293.0 and 295.0.



5-Bromo-3-(1-bromoethyl)-2',3',5',6'-tetrahydrospiro[indene-1,4'-pyran] A.306

by analogy to Pettit, W. A. and J. W. Wilson (1977). *J. Amer. Chem. Soc.* **99**(19): 6372-6379.

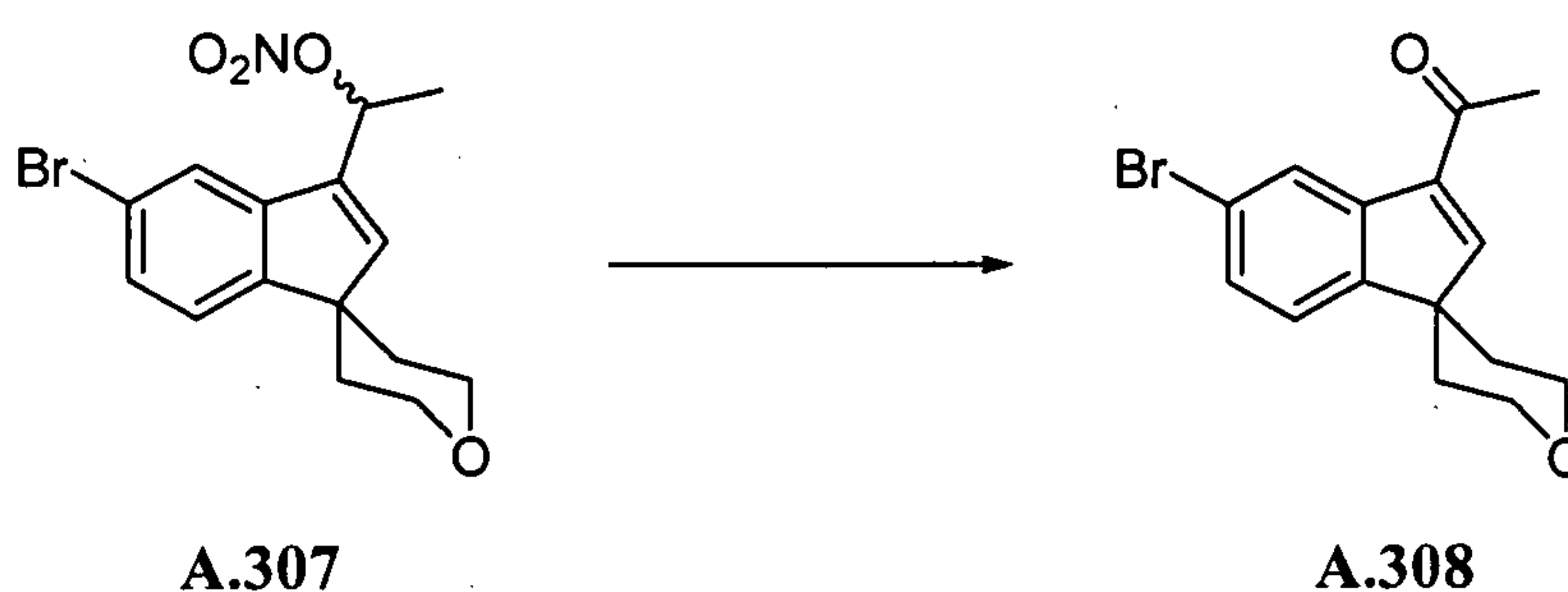
To a stirred solution of 5-bromo-3-ethyl-2',3',5',6'-tetrahydrospiro[indene-1,4'-pyran] **A.305** (1.2 g, 4.09 mmol) in CCl_4 (50 mL) was added NBS (1.02 eq., 0.75 g) followed by $(\text{BzO})_2$ (catalytic amount). The resulting mixture was heated at reflux for 6 h. The volume of the reaction mixture was reduced. After cooling, the mixture was subjected to combi-flash column chromatography (ethyl acetate/hexanes) to give 5-bromo-3-(1-bromoethyl)-2',3',5',6'-tetrahydrospiro[indene-1,4'-pyran] **A.306** (0.86 g, 56% yield) as a thick oil. ^1H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.65 (1 H, d, $J=1.8$ Hz), 7.41 (1 H, dd, $J=7.9, 1.6$ Hz), 7.25 (1 H, d, $J=8.1$ Hz), 6.96 (1 H, s), 5.09 - 5.15 (1 H, m), 4.03 - 4.12 (2 H, m), 3.76 (2 H, td, $J=11.9, 2.2$ Hz), 2.11 - 2.22 (2 H, m), 2.09 (3 H, d, $J=7.0$ Hz), 1.29 - 1.37 (2 H, m).



1-(5-Bromo-2',3',5',6'-tetrahydrospiro[indene-1,4'-pyran]-3-yl)ethyl nitrate A.307

Ref.: By analogy to Kinoshita, T., Takaishi, Y. et al. (1992) *J. Heterocycl. Chem.* **29**: 741-747

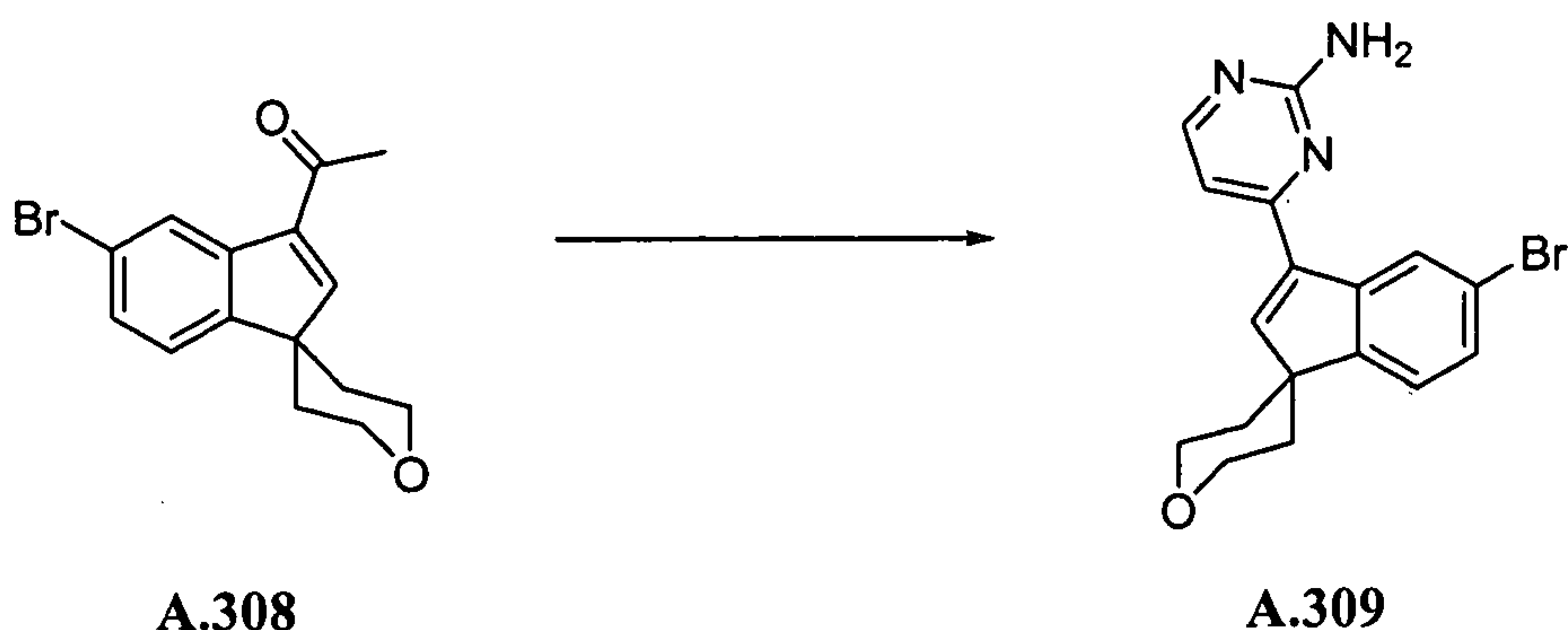
To a stirred solution of 5-bromo-3-(1-bromoethyl)-2',3',5',6'-tetrahydrospiro[indene-1,4'-pyran] **A.306** (0.95 g, 2.55 mmol) in acetonitrile (30 mL) at reflux was added a solution of silver nitrate (1.5 eq., 0.66 g) in acetonitrile (5 mL). The resulting mixture was heated at reflux for 2 h. After cooling, the mixture was filtered through a layer of celite and the filter cake was washed with ethyl acetate. The filtrate was concentrated in vacuo to give 1-(5-bromo-2',3',5',6'-tetrahydrospiro[indene-1,4'-pyran]-3-yl)ethyl nitrate **A.307** (1.0 g) as a thick film. ¹H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 7.50 (1 H, d, $J=1.7$ Hz), 7.42 (1 H, dd, $J=7.8, 1.7$ Hz), 7.25 - 7.28 (1 H, m), 6.98 (0 H, s), 6.02 (0 H, q, $J=6.4$ Hz), 4.04 - 4.12 (2 H, m), 3.68 - 3.81 (2 H, m), 2.14 - 2.23 (2 H, m), 1.71 (3 H, d, $J=6.6$ Hz), 1.23 - 1.32 (2 H, m). LCMS-ESI (POS), M/Z , $M+1$: Found 354.0 and 356.0.



1-(5-Bromo-2',3',5',6'-tetrahydrospiro[indene-1,4'-pyran]-3-yl)ethanone **A.308**

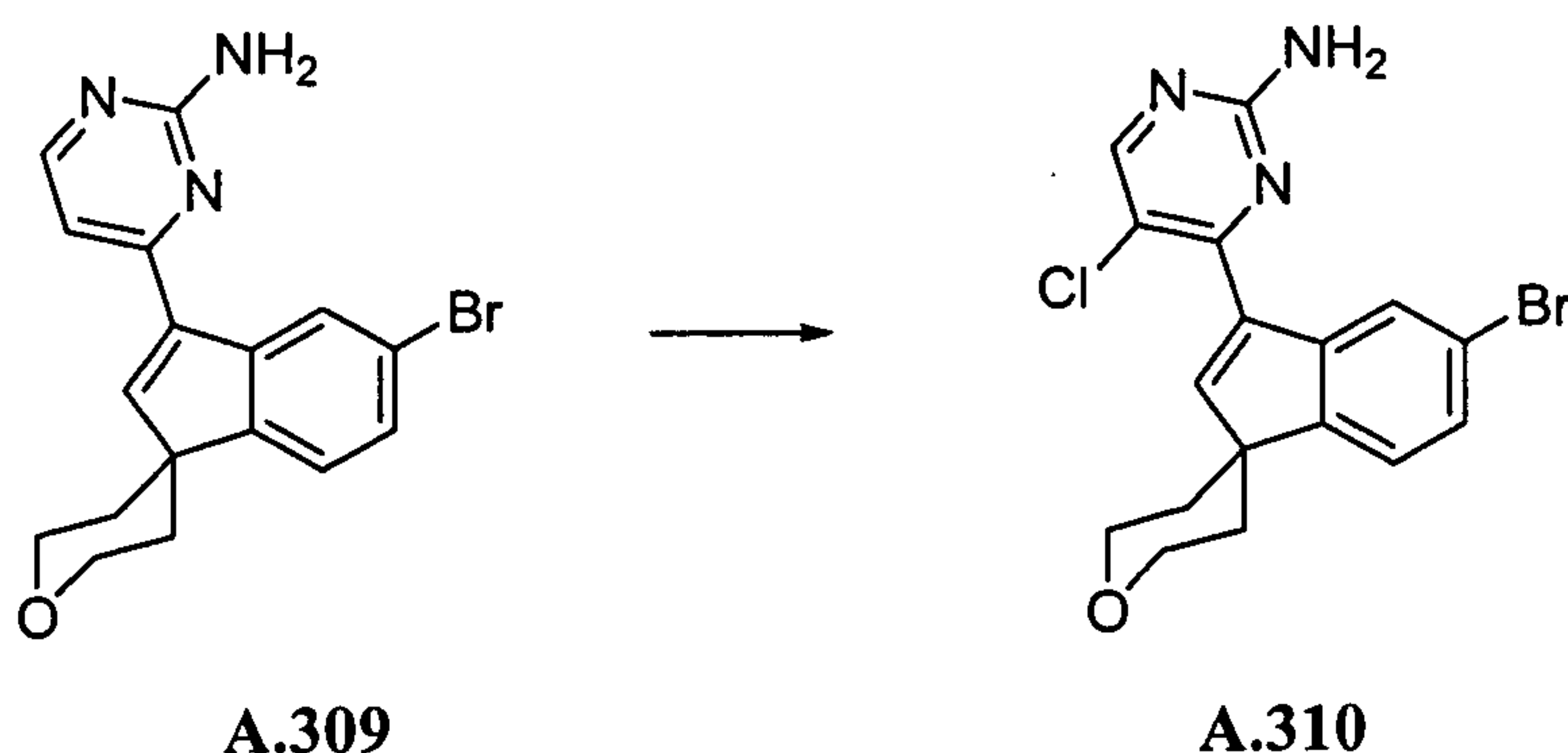
Ref. Using methods found in (1) Abdourazak, A. H., Z. Marcinow, et al. (1994). *Tetrahedron Lett.* **35**(23): 3857-3860; (2) Kornblum, N. and H. W. Frazier (1966). *J. Amer. Chem. Soc.* **88**(4): 865-866.

To a stirred solution of the crude 1-(5-bromo-2',3',5',6'-tetrahydrospiro[indene-1,4'-pyran]-3-yl)ethyl nitrate **A.307** (2.55 mmol, 100% yield assumed from the previous step) in DMSO (25 mL) was added at room temperature NaOAc (0.27 eq., 56 mg) followed by 2 drops of water through a pipette. The resulting mixture was stirred at 95 °C for 2 h at ambient temperature overnight. Upon workup, the mixture was poured into ice and brine and extracted with ethyl acetate (2 X). The combined organics were washed with brine (1 X), dried over anhydrous Na₂SO₄, and concentrated in vacuo. The residue was subjected to combi-flash column chromatography (ethyl acetate/hexanes) to give 1-(5-bromo-2',3',5',6'-tetrahydrospiro[indene-1,4'-pyran]-3-yl)ethanone **A.308** (0.3 g, 43% yield over 2 steps) as a light yellow solid. ¹H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 8.33 (1 H, d, $J=1.8$ Hz), 7.67 (1 H, s), 7.43 (1 H, dd, $J=8.1, 1.8$ Hz), 7.26 (1 H, m), 4.09 - 4.18 (2 H, m), 3.81 (2 H, td, $J=11.9, 2.2$ Hz), 2.54 (3 H, s), 2.22 (2 H, ddd, $J=13.8, 12.0, 4.6$ Hz). LCMS-ESI (POS), M/Z , $M+1$: Found 307.0 and 309.0.



4-(5-Bromo-2',3',5',6'-tetrahydrospiro[indene-1,4'-pyran]-3-yl)-2-pyrimidinamine A.309

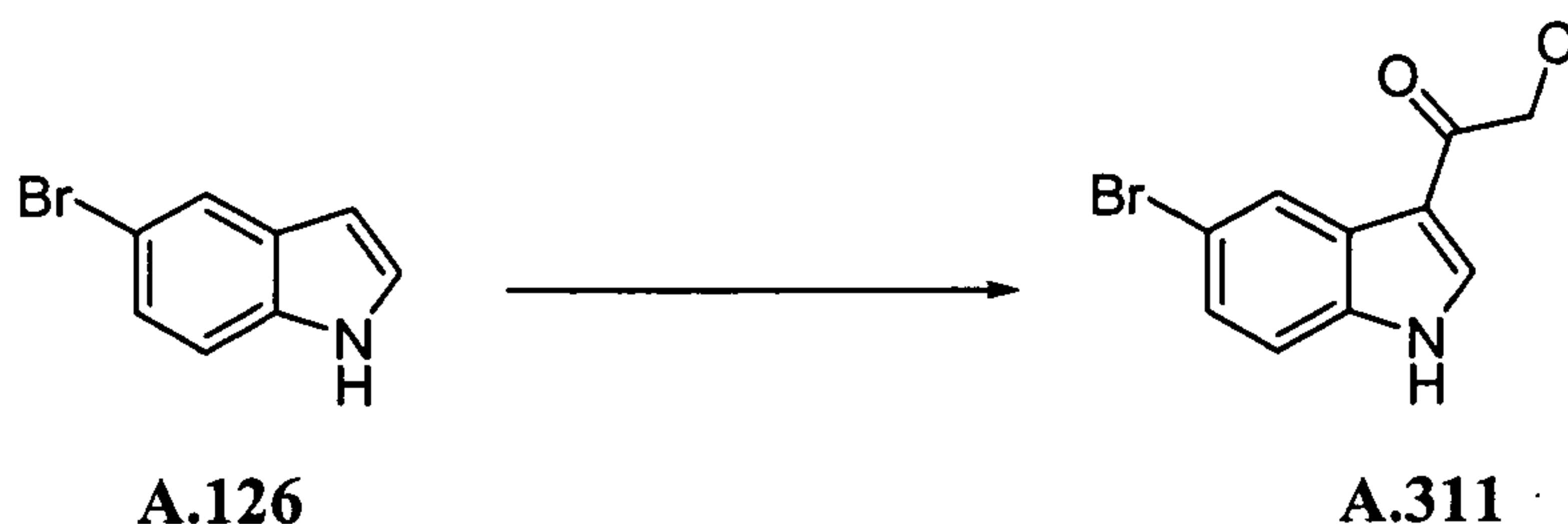
1-(5-Bromo-2',3',5',6'-tetrahydrospiro[indene-1,4'-pyran]-3-yl)ethanone **A.308** (85 mg, 0.28 mmol) was treated neat with $t\text{-BuOCH}(\text{NMe}_2)_2$ (2.3 eq., 0.11 g) at 105 °C under N_2 for 3 h. The mixture was cooled before $n\text{-PrOH}$ (8 mL), guanidine hydrochloride (5.0 eq., 0.13 g), and MeONa (5.53 M in methanol) (3.0 eq., 0.15 mL) were added sequentially. The resulting mixture was stirred at 95 °C for 3 h. Upon workup, the mixture was cooled and poured into ice and saturated NaHCO_3 aqueous solution and extracted with ethyl acetate (1 X). The organic layer was washed with brine (2 X), dried over anhydrous Na_2SO_4 , and concentrated in vacuo to give 4-(5-bromo-2',3',5',6'-tetrahydrospiro[indene-1,4'-pyran]-3-yl)-2-pyrimidinamine **A.309** (0.1 g, quant. yield) as a light yellow solid. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 8.38 (1 H, d, $J=5.1$ Hz), 8.27 (1 H, d, $J=2.0$ Hz), 7.53 (1 H, s), 7.45 (1 H, dd, $J=7.8, 2.0$ Hz), 7.23 - 7.33 (2 H, m), 6.99 (0 H, d, $J=5.1$ Hz), 5.17 (2 H, br. s.), 4.07 - 4.17 (2 H, m), 3.83 (2 H, td, $J=11.9, 1.8$ Hz), 2.24 (2 H, ddd, $J=13.4, 12.4, 4.5$ Hz), 1.39 (2 H, dd, $J=13.6, 1.3$ Hz). LCMS-ESI (POS), M/Z , $M+1$: Found 358.0 and 360.1.



4-(5-Bromo-2',3',5',6'-tetrahydrospiro[indene-1,4'-pyran]-3-yl)-5-chloro-2-pyrimidinamine A.310

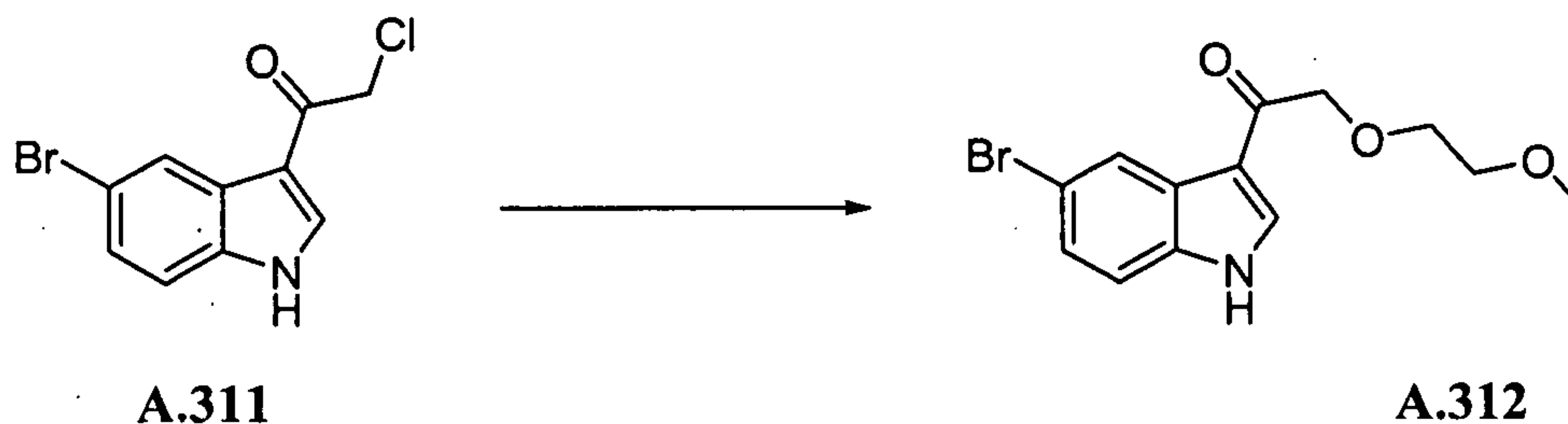
To a stirred solution of 4-(5-bromo-2',3',5',6'-tetrahydrospiro[indene-1,4'-pyran]-3-yl)-2-pyrimidinamine **A.309** (0.1 g, 0.277 mmol) in acetonitrile (18 mL) was added NCS (1.0 eq., 40 mg) in one portion. The resulting mixture was stirred at reflux for 5.5 h and then concentrated in vacuo. The residue was subjected to combi-flash column chromatography

(ethyl acetate/hexanes) to give 4-(5-bromo-2',3',5',6'-tetrahydrospiro[indene-1,4'-pyran]-3-yl)-5-chloro-2-pyrimidinamine **A.310** (65 mg, 60% yield) as an off-white solid. ^1H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 8.38 (1 H, s), 7.82 (1 H, d, $J=1.8$ Hz), 7.61 (1 H, s), 7.44 (1 H, dd, $J=7.9, 1.6$ Hz), 7.30 (1 H, d, $J=8.1$ Hz), 5.15 (2 H, br. s.), 4.07 - 4.18 (2 H, m), 3.82 (2 H, td, $J=12.1, 1.8$ Hz), 2.20 - 2.33 (2 H, m), 1.44 (2 H, dd, $J=13.5, 1.5$ Hz). LCMS-ESI (POS), M/Z , $M+1$: Found 392.0 and 394.0.



1-(5-Bromo-1H-indol-3-yl)-2-chloroethanone **A.311**

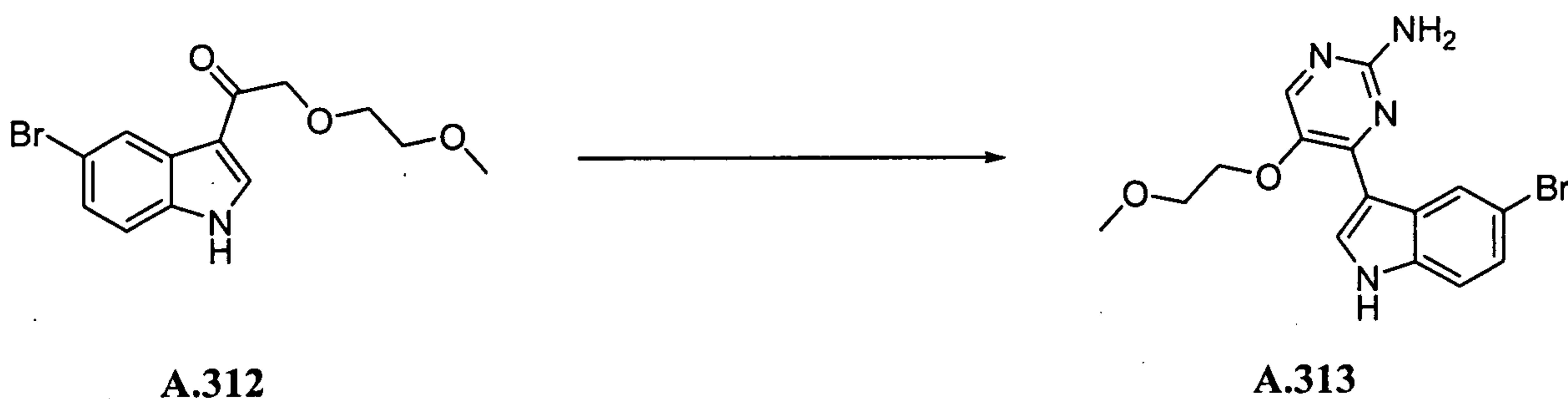
To stirred ice-cooled suspension of AlCl_3 (2.0 eq., 5.5 g) in dichloromethane (30 mL) was slowly added through a syringe chloroacetyl chloride (1.2 eq., 2.82 g) under a nitrogen atmosphere. This was followed by a solution of 5-bromoindole **A.126** (4.0 g, 20.4 mmol) in dichloromethane (35 mL). The resulting mixture was stirred at 0 °C for 10 min and at ambient temperature for 4 h. Upon workup, the mixture was poured into stirred ice and water and extracted with ethyl acetate (2 X). The combined organics were washed with brine (2 X), dried over Na_2SO_4 , and concentrated in vacuo. The residue was triturated with ethyl acetate/hexanes to give 1-(5-bromo-1H-indol-3-yl)-2-chloroethanone **A.311** (3.4 g, 61% yield) as an off-white solid. ^1H NMR (400 MHz, *DMSO-d*₆) δ ppm 12.33 (1 H, br. s.), 8.48 (1 H, d, $J=3.3$ Hz), 8.29 (1 H, d, $J=1.8$ Hz), 7.49 (1 H, d, $J=8.8$ Hz), 7.38 (1 H, dd, $J=8.6, 2.0$ Hz), 4.88 (2 H, s). LCMS-ESI (POS), M/Z , $M+1$: Found 271.9 and 273.9.



1-(5-Bromo-1H-indol-3-yl)-2-(2-methoxyethoxy)ethanone **A.312**

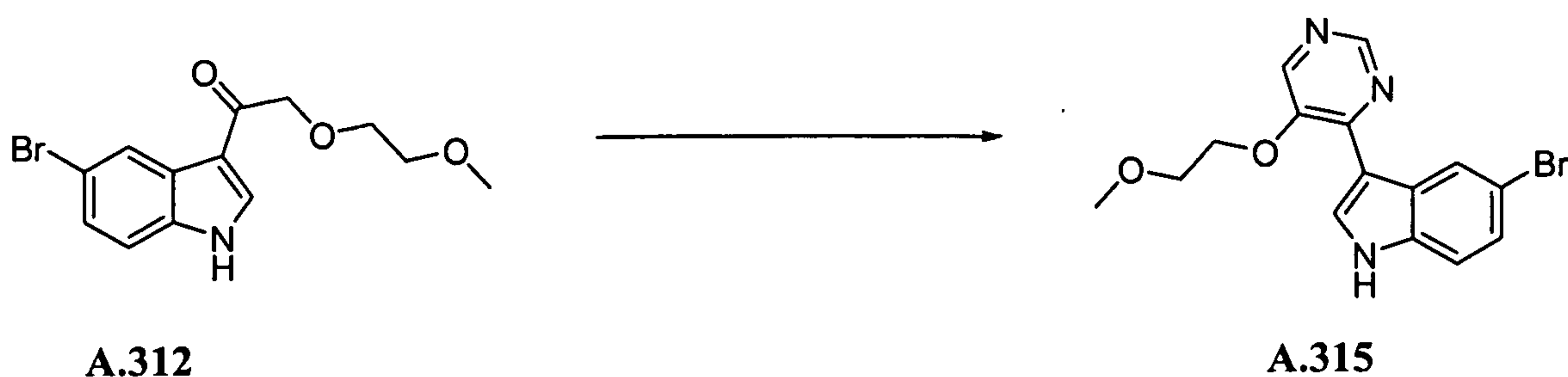
To a stirred ice-cooled suspension of NaH (commercial, 60% dispersion in mineral oil) (2.2 eq., 1.29 g) in DMF (25 mL) was added dropwise 2-methoxyethanol (2.0 eq., 2.24 g) through a syringe. The resulting mixture was stirred at 0 °C for 10 min before the ice bath was removed and a solution of 1-(5-bromo-1H-indol-3-yl)-2-chloroethanone **A.311** (4.0 g, 14.7 mmol) in

DMF (30 mL) was added through a syringe. The resulting mixture was stirred at ambient temperature for 2.5 h. Upon workup, the mixture was poured into ice and saturated NH_4Cl aqueous solution and extracted with ethyl acetate. The combined organics were washed with brine (2 X), dried over Na_2SO_4 , and concentrated in vacuo. The residue was triturated with ethyl acetate/hexanes to give 1-(5-bromo-1H-indol-3-yl)-2-(2-methoxyethoxy)ethanone **A.312** (4.2 g, 92% yield) as an off-white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 12.15 (1 H, br. s.), 8.42 (1 H, s), 8.31 (1 H, d, $J=1.8$ Hz), 7.47 (1 H, d, $J=8.4$ Hz), 7.36 (1 H, dd, $J=8.6, 2.0$ Hz), 4.56 (2 H, s), 3.63 - 3.71 (2 H, m), 3.52 (2 H, dd, $J=5.5, 3.7$ Hz), 3.27 (3 H, s). LCMS-ESI (POS), M/Z , $\text{M}+1$: Found 312.0 and 314.0.

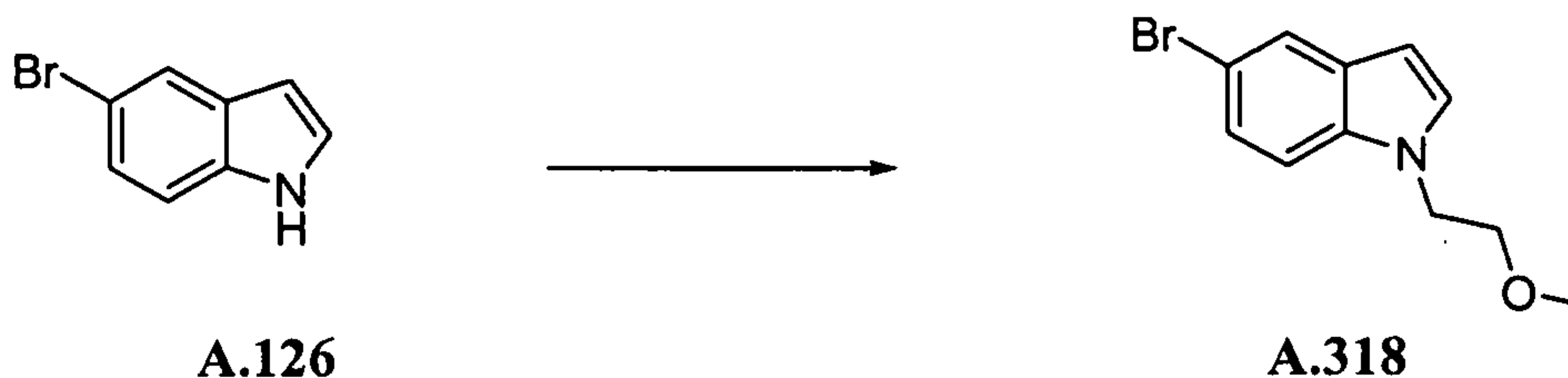


4-(5-Bromo-1H-indol-3-yl)-5-(2-methoxyethoxy)-2-pyrimidinamine **A.313**

1-(5-Bromo-1H-indol-3-yl)-2-(2-methoxyethoxy)ethanone **A.312** (4.0 g, 12.8 mmol) was treated neat with $t\text{-BuOCH}(\text{NMe}_2)_2$ (2.0 eq., 4.47 g) at 105°C under N_2 for 1.5 h. The mixture was cooled before $n\text{-PrOH}$ (35 mL), guanidine hydrochloride (5.0 eq., 6.2 g), and MeONa (5.53 M in methanol) (3.0 eq., 7.5 mL) were added sequentially. The resulting mixture was stirred at 95°C for 24 h. Upon workup, the mixture was cooled and poured into ice and saturated NaHCO_3 aqueous solution and extracted with ethyl acetate (3 X). The combined organics were washed with brine (2 X), dried over anhydrous Na_2SO_4 , and concentrated in vacuo to give 4-(5-bromo-1H-indol-3-yl)-5-(2-methoxyethoxy)-2-pyrimidinamine **A.313** (4.5 g, 97% yield) as a light yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 11.84 (1 H, s), 8.94 (1 H, d, $J=1.8$ Hz), 8.44 (1 H, s), 8.05 (1 H, s), 7.41 (1 H, d, $J=8.4$ Hz), 7.30 (1 H, dd, $J=8.6, 2.0$ Hz), 6.14 (2 H, s), 4.12 - 4.21 (2 H, m), 3.71 - 3.77 (2 H, m), 3.36 (3 H, s). LCMS-ESI (POS), M/Z , $\text{M}+1$: Found 363.0 and 364.9.

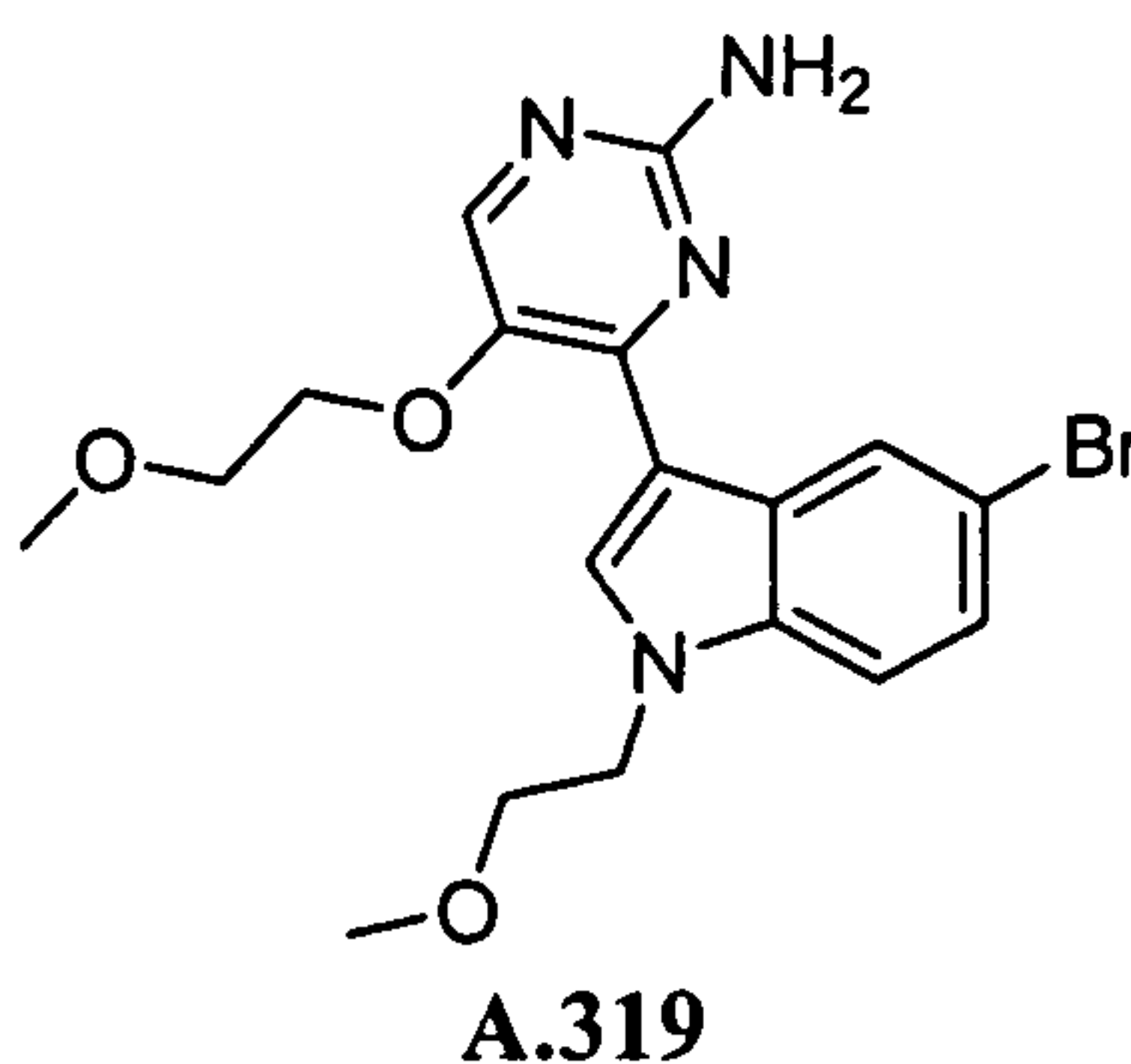


5-Bromo-3-(5-(2-methoxyethoxy)-4-pyrimidinyl)-1H-indole A.315 was prepared using chemistry similar to that described for compound A.313 except that imidoformamide hydrochloride was used in place of guanidine hydrochloride. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 12.01 (1 H, br. s.), 8.95 (1 H, d, $J=1.8$ Hz), 8.83 (1 H, s), 8.52 (1 H, s), 8.47 (1 H, s), 7.47 (1 H, d, $J=8.4$ Hz), 7.34 (1 H, dd, $J=8.6, 2.0$ Hz), 4.38 - 4.48 (2 H, m), 3.81 - 3.87 (2 H, m), 3.39 (3 H, s). LCMS-ESI (POS), M/Z , $M+1$: Found 348.0 and 350.0.



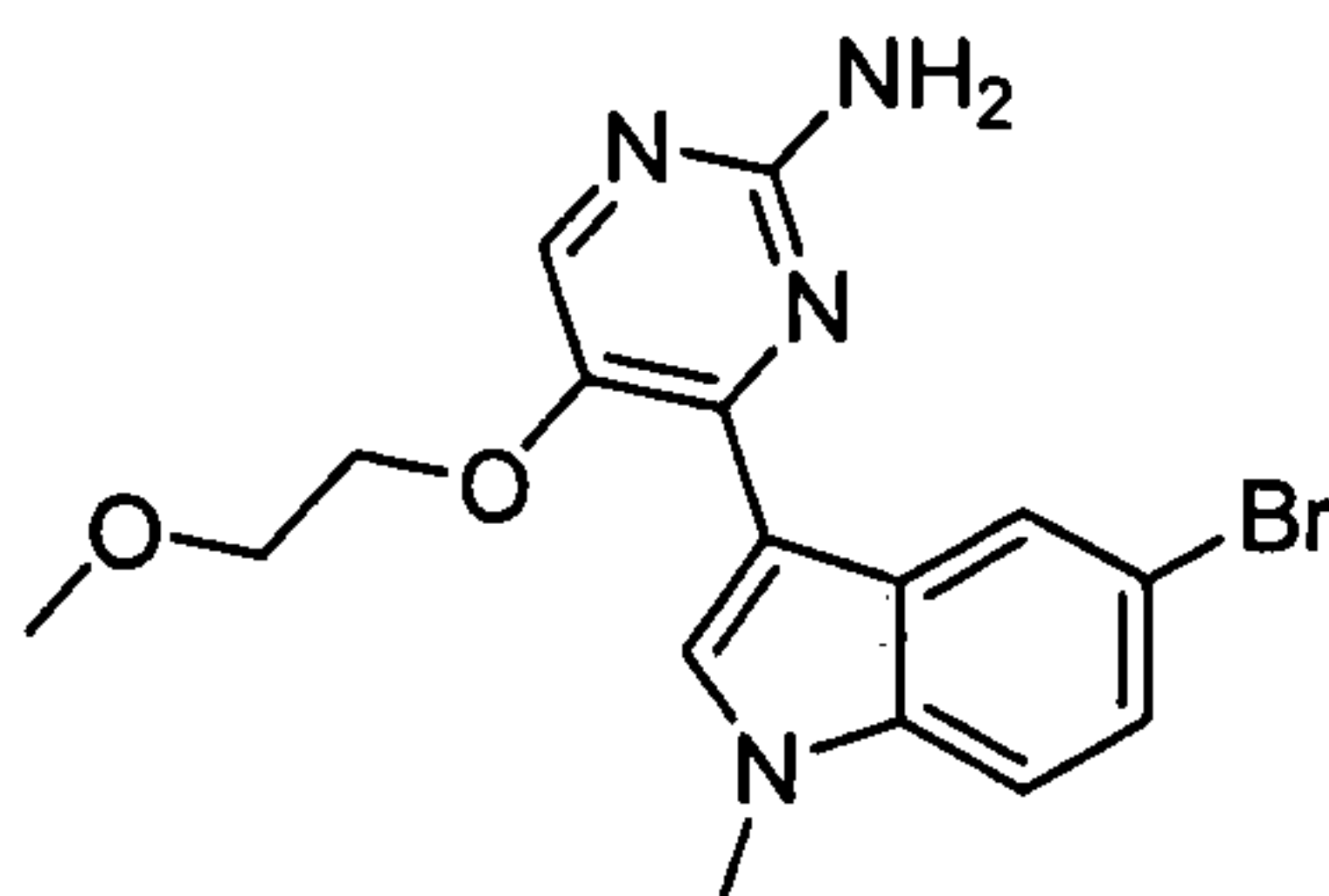
5-Bromo-1-(2-methoxyethyl)-1H-indole (A.318)

A stirred mixture of 5-bromoindole A.126 (3.0 g, 0.015 mol), 50% sodium hydroxide aqueous solution (30 mL), KI (catalytic amount), and tetrabutylammonium hydroxide (0.5 g, 10 mol %) in benzene (80 mL) was heated in an oil bath to reflux, at which time 1-bromo-2-methoxyethane (3.0 mL, 0.030 mol) was added through a syringe. The resulting mixture was heated at reflux for 1 h, at which time about 70 % conversion was observed and more 1-bromo-2-methoxyethane (1.0 mL) was added. The reaction continued for another hour at reflux and then stirred at 70 °C overnight. Upon workup, the mixture was poured into ice water and extracted with benzene (2 X). The combined organics were washed with brine (2 X), dried over anhydrous sodium sulfate, and concentrated in vacuo to give 5-bromo-1-(2-methoxyethyl)-1H-indole (A.318) in nearly quantitative yield as a nearly colorless oil. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.72 (d, $J = 1.5$ Hz, 1H), 7.48 (d, $J = 9.0$ Hz, 1H), 7.40 (d, $J = 3.0$ Hz, 1H), 7.23 (dd, $J = 9.0, 1.5$ Hz, 1H), 6.42 (d, $J = 3.0$ Hz, 1H), 4.33 (t, $J = 5.0$ Hz, 2H), 3.64 (t, $J = 5.0$ Hz, 2H), 3.20 (s, 3H). LCMS-ESI (POS), M/Z , $M+1$: Found 254.0 and 256.0.



4-(5-bromo-1-(2-methoxyethyl)-1H-indol-3-yl)-5-(2-methoxyethoxy)-2-pyrimidinamine A.319 was prepared in analogy to the procedure described for compound A.313 starting from

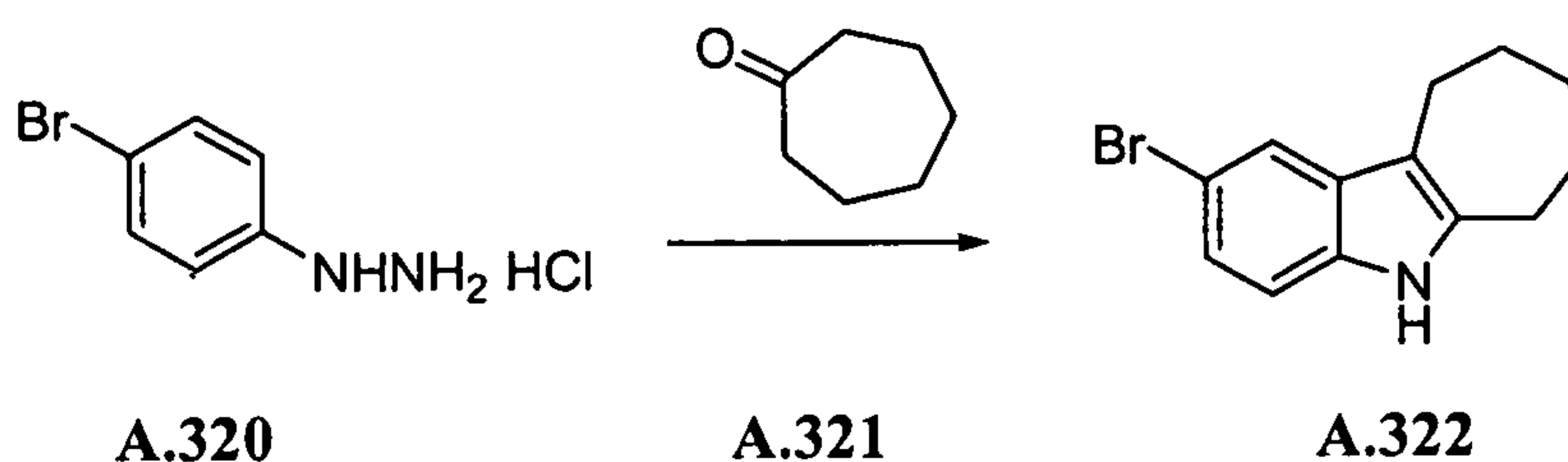
compound **A.318**. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.97 (d, $J = 2.0$ Hz, 1H), 8.47 (s, 1H), 8.08 (s, 1H), 7.58 (d, $J = 8.7$ Hz, 1H), 7.36 (dd, $J = 8.7, 2.0$ Hz, 1H), 6.19 (s, 2H), 4.42 (t, $J = 5.1$ Hz, 2H), 4.17 (t, $J = 4.4$ Hz, 2H), 3.76 (t, $J = 4.4$ Hz, 2H), 3.71 (t, $J = 5.1$ Hz, 2H), 3.39 (s, 3H), 3.25 (s, 3H). LCMS-ESI (POS), M/Z , $M+1$: Found 421.0 and 423.1.



4-(5-bromo-1-methyl-1H-indol-3-yl)-5-(2-methoxyethoxy)-2-pyrimidinamine A.317

A.317 was prepared in analogy to the procedure described for compound **A.313** starting from 5-bromo-1-methyl-1H-indole **A.316**.

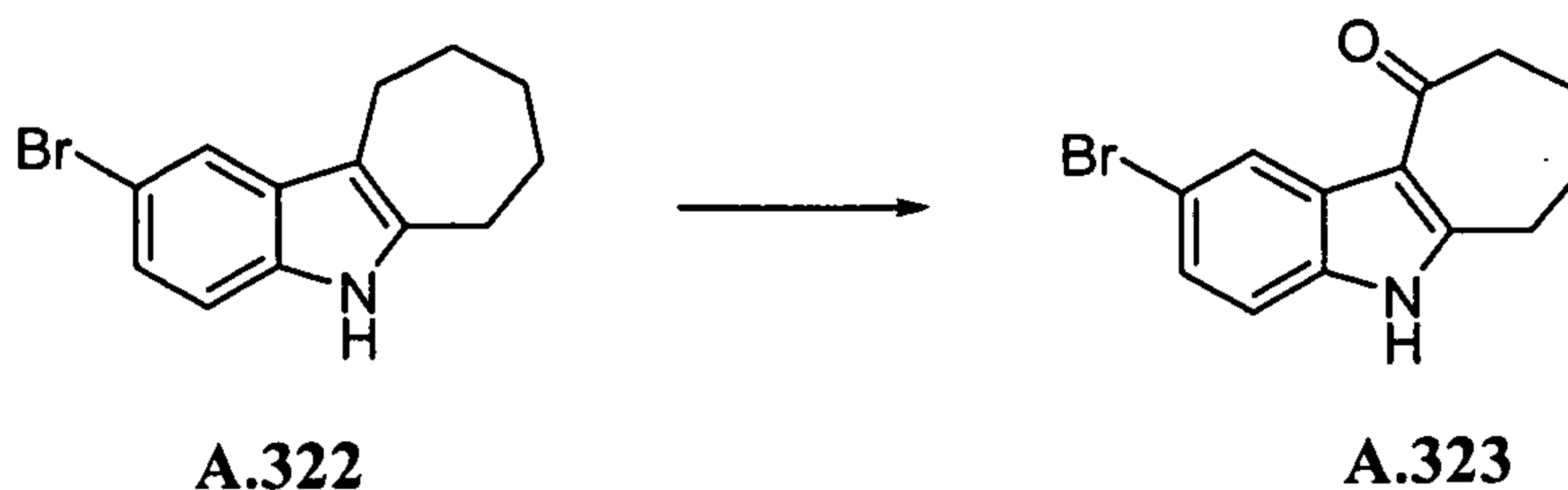
^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.97 (d, $J = 2.0$ Hz, 1H), 8.44 (s, 1H), 8.08 (s, 1H), 7.58 (d, $J = 8.7$ Hz, 1H), 7.36 (dd, $J = 8.7, 2.0$ Hz, 1H), 6.19 (s, 2H), 4.17 (t, $J = 4.5$ Hz, 2H), 3.88 (s, 3H), 3.76 (t, $J = 4.5$ Hz, 2H), 3.40 (s, 3H). LCMS-ESI (POS), M/Z , $M+1$: Found 377.0 and 379.0.



2-Bromo-5,6,7,8,9,10-hexahydrocyclohepta[b]indole A.322

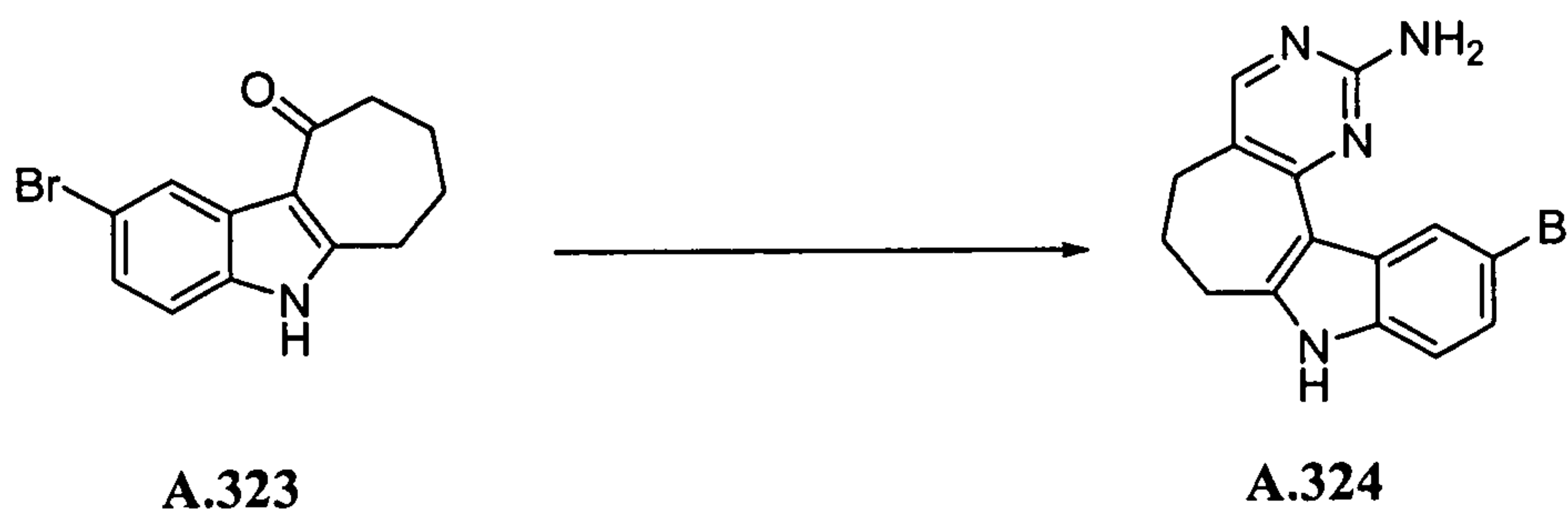
A suspension of (4-bromophenyl)hydrazine hydrochloride **A.320** (10 g, 44.7 mmol) in glacial acetic acid (150 mL) was added portion-wise into a stirred solution of cycloheptanone **A.321** (1.0 eq., 5.02 g) in glacial acetic acid (50 mL) preheated at 130 °C. The resulting mixture was heated to reflux (145 °C) for 2 h. Upon workup, the mixture was cooled and diluted with water while being stirred vigorously. The precipitate was collected by vacuum filtration and the filter cake was washed with water and air-dried to give 2-bromo-5,6,7,8,9,10-hexahydrocyclohepta[b]indole **A.322** (11.5 g, 98% yield) as an off-white solid. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 10.89 (1 H, br. s.), 7.52 (1 H, d, $J = 1.5$ Hz), 7.17 (1 H, d, $J = 8.3$ Hz),

7.04 (1 H, dd, $J=8.6, 1.7$ Hz), 2.75 - 2.86 (2 H, m), 2.66 - 2.73 (2 H, m), 1.77 - 1.88 (2 H, m), 1.59 - 1.72 (4 H, m). LCMS-ESI (POS), M/Z , $M+1$: Found 264.0 and 266.0.



2-Bromo-6,7,8,9-tetrahydrocyclohepta[b]indol-10(5H)-one A.323

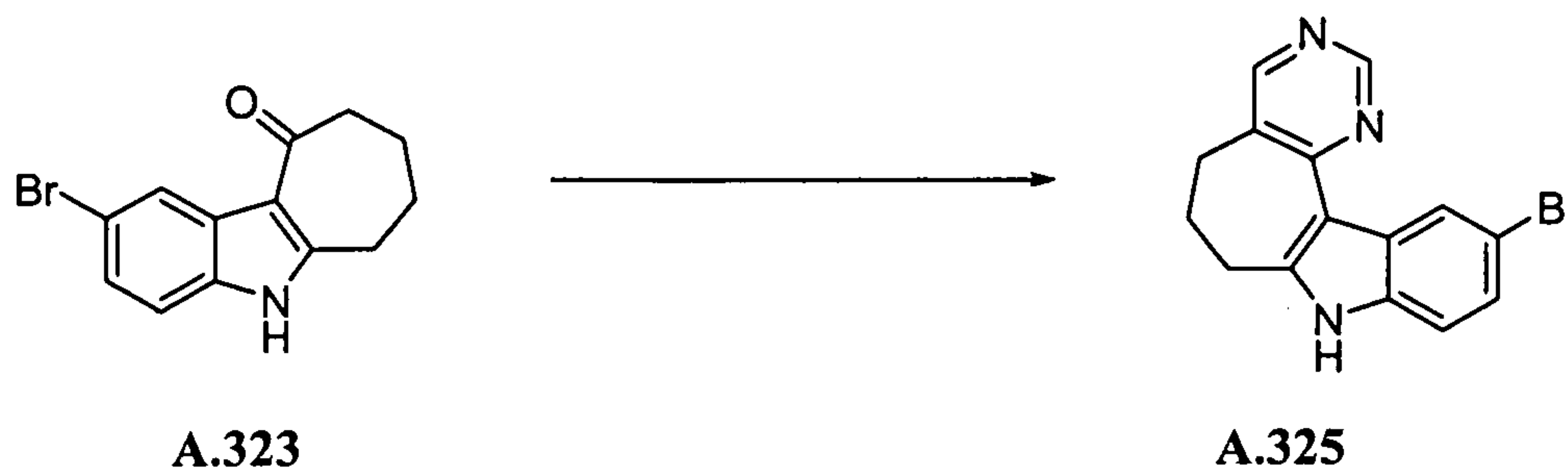
To a stirred ice-cooled solution of 2-bromo-5,6,7,8,9,10-hexahydrocyclohepta[b]indole A.322 (7.0 g, 26.5 mmol) in a mixed solvent consisting of THF and water (100 mL, v/v, 9:1) was added DDQ in two portions over a period of 15 min. The resulting mixture was stirred at 0 °C for 30 min and at ambient temperature for 2 h. Upon workup, water was added followed by saturated NaHCO_3 aqueous solution. The mixture was vigorously stirred and then allowed to settle. The precipitate was collected by vacuum filtration and the filter cake was washed with saturated NaHCO_3 aqueous solution followed by water. To the filtrate was added more water and the same operation was repeated as before to collect more precipitate. The filter cake was combined with that obtained from the first operation to give, after air-dried, 2-bromo-6,7,8,9-tetrahydrocyclohepta[b]indol-10(5H)-one A.323 (7.1 g, 96% yield) as an off-white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 11.93 (1 H, br. s.), 8.28 (1 H, d, $J=2.6$ Hz), 7.33 (1 H, d, $J=8.4$ Hz), 7.27 (1 H, dd, $J=8.4, 2.6$ Hz), 3.08 - 3.15 (2 H, m), 2.63 - 2.70 (2 H, m), 1.88 - 1.99 (2 H, m), 1.79 - 1.88 (2 H, m). LCMS-ESI (POS), M/Z , $M+1$: Found 278.0 and 280.0.



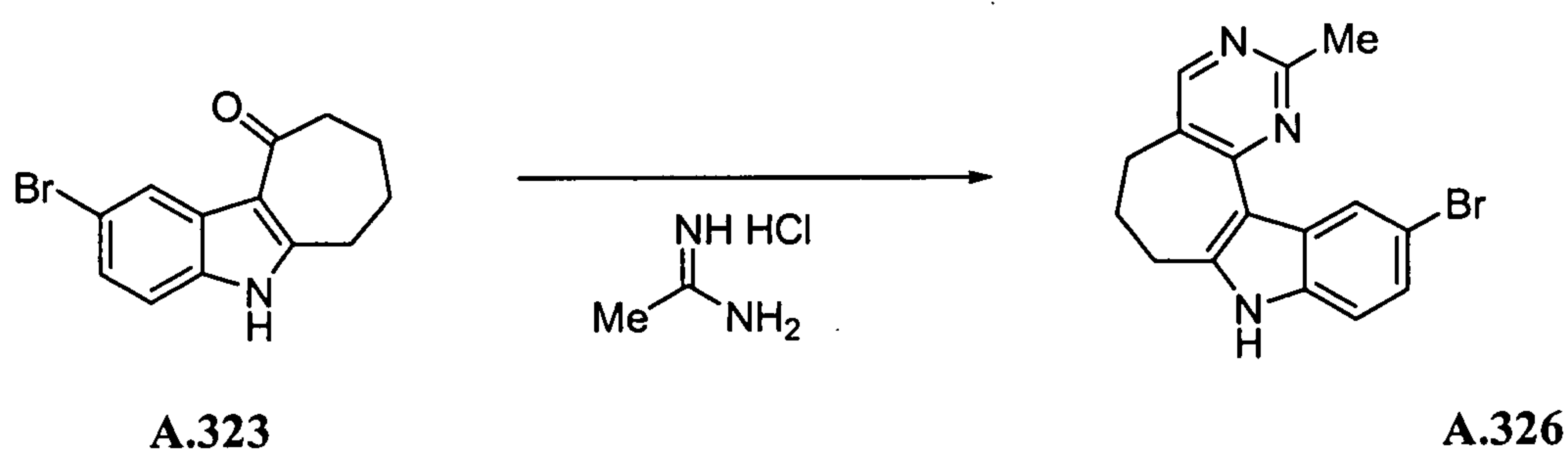
11-Bromo-5,6,7,8-tetrahydropyrimido[4',5':3,4]cyclohepta[1,2-b]indol-2-amine A.324

2-Bromo-6,7,8,9-tetrahydrocyclohepta[b]indol-10(5H)-one A.323 (4.9 g, 17.6 mmol) was treated neat with $t\text{-BuOCH}(\text{NMe}_2)_2$ (2.0 eq., 6.14 g) at 105 °C under N_2 for 14 h. The mixture was cooled before $n\text{-PrOH}$ (18 mL), guanidine hydrochloride (1.5 eq., 2.6 g), and MeONa (5.53 M in methanol) (1.5 eq., 5.5 mL) were added sequentially. The resulting mixture was stirred at 95 °C for 4 h and at ambient temperature for 24 h. Upon workup, the mixture was diluted with methanol and dichloromethane followed by silica gel. After concentration in

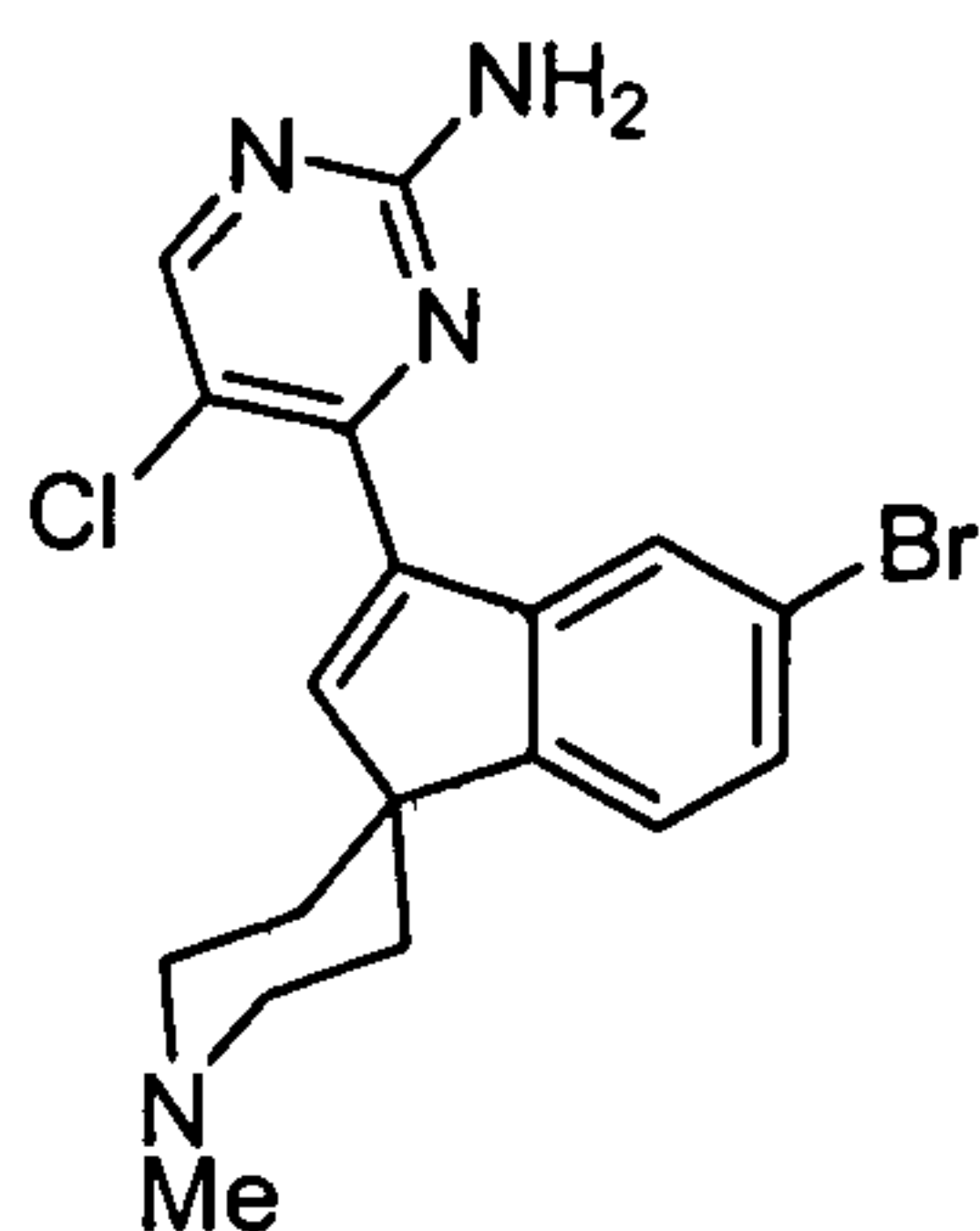
vacuo, the solid mixture was dry-loaded onto silica gel column (methanol/dichloromethane) to give 11-bromo-5,6,7,8-tetrahydropyrimido[4',5':3,4]cyclohepta[1,2-b]indol-2-amine **A.324** (4.2 g, 72% yield) as an off-white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 11.63 (1 H, s), 8.88 (1 H, d, $J=1.8$ Hz), 7.92 (1 H, s), 7.19 - 7.30 (2 H, m), 6.24 (2 H, s), 3.18 (2 H, t, $J=6.6$ Hz), 2.60 - 2.67 (2 H, m), 1.89 - 1.98 (2 H, m). LCMS-ESI (POS), M/Z , $M+1$: Found 329.0 and 331.0.



11-Bromo-5,6,7,8-tetrahydropyrimido[4',5':3,4]cyclohepta[1,2-b]indole A.325 was prepared using chemistry similar to that described for compound **A.324** except that imidoformamide hydrochloride was used in place of guanidine hydrochloride. LCMS-ESI (POS), M/Z , $M+1$: Found 313.9 and 316.0.

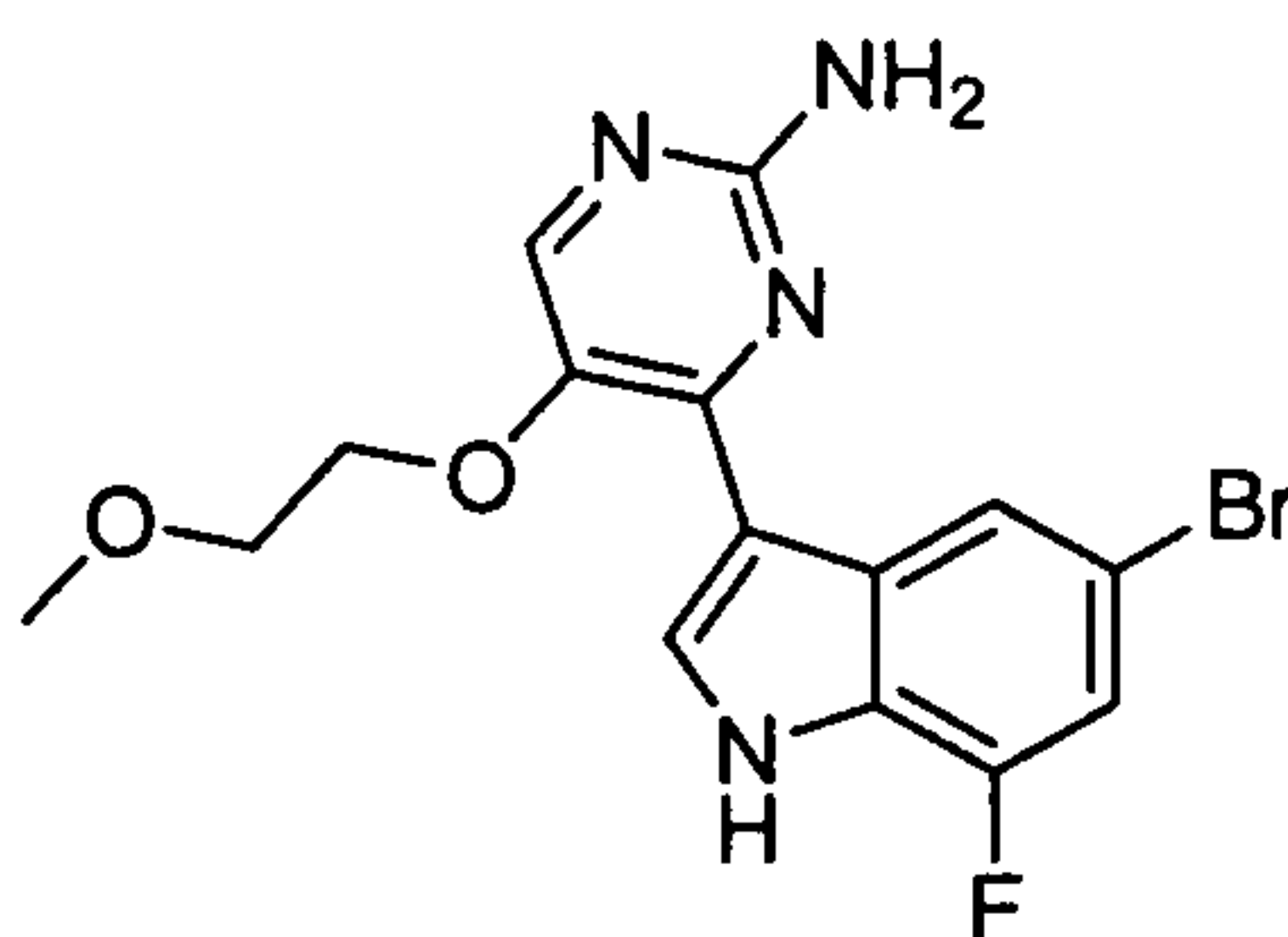


11-Bromo-2-methyl-5,6,7,8-tetrahydropyrimido[4',5':3,4]cyclohepta[1,2-b]indole A.326 was prepared using chemistry similar to that described for compound **A.324** using acetimidamide hydrochloride in place of guanidine hydrochloride. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 11.80 (1 H, s), 8.91 (1 H, d, $J=2.0$ Hz), 8.31 (1 H, s), 7.23 - 7.34 (2 H, m), 3.24 (2 H, t, $J=6.1$ Hz), 2.78 - 2.84 (2 H, m), 2.63 (3 H, s), 1.98 - 2.03 (2 H, m). LCMS-ESI (POS), M/Z , $M+1$: Found 328.0 and 330.1.



4-(5-bromo-1'-methylspiro[indene-1,4'-piperidin]-3-yl)-5-chloro-2-pyrimidinamine A.327

was prepared in the same manner as A.310 except that 2-chloro-N-(2-chloroethyl)-N-methylethanamine hydrochloride was used for the bisalkylation of A.304 and that 2 equivalents of brominating agent, i.e., NBS and NCS, were used in the allylic bromination step. LCMS-ESI (POS), M/Z, M+1: Found 405.1, 407.0 and 409.0.

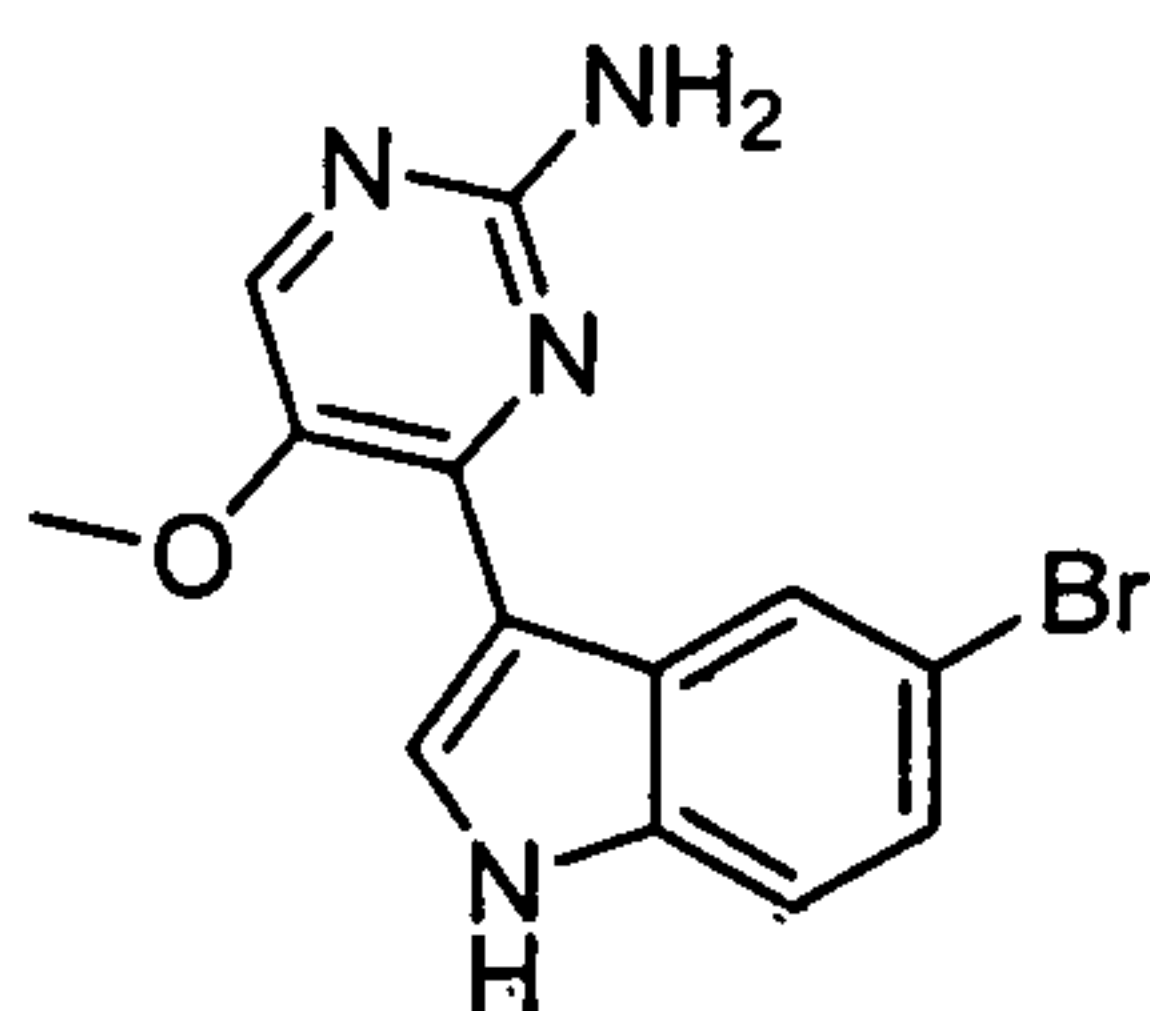


A.328

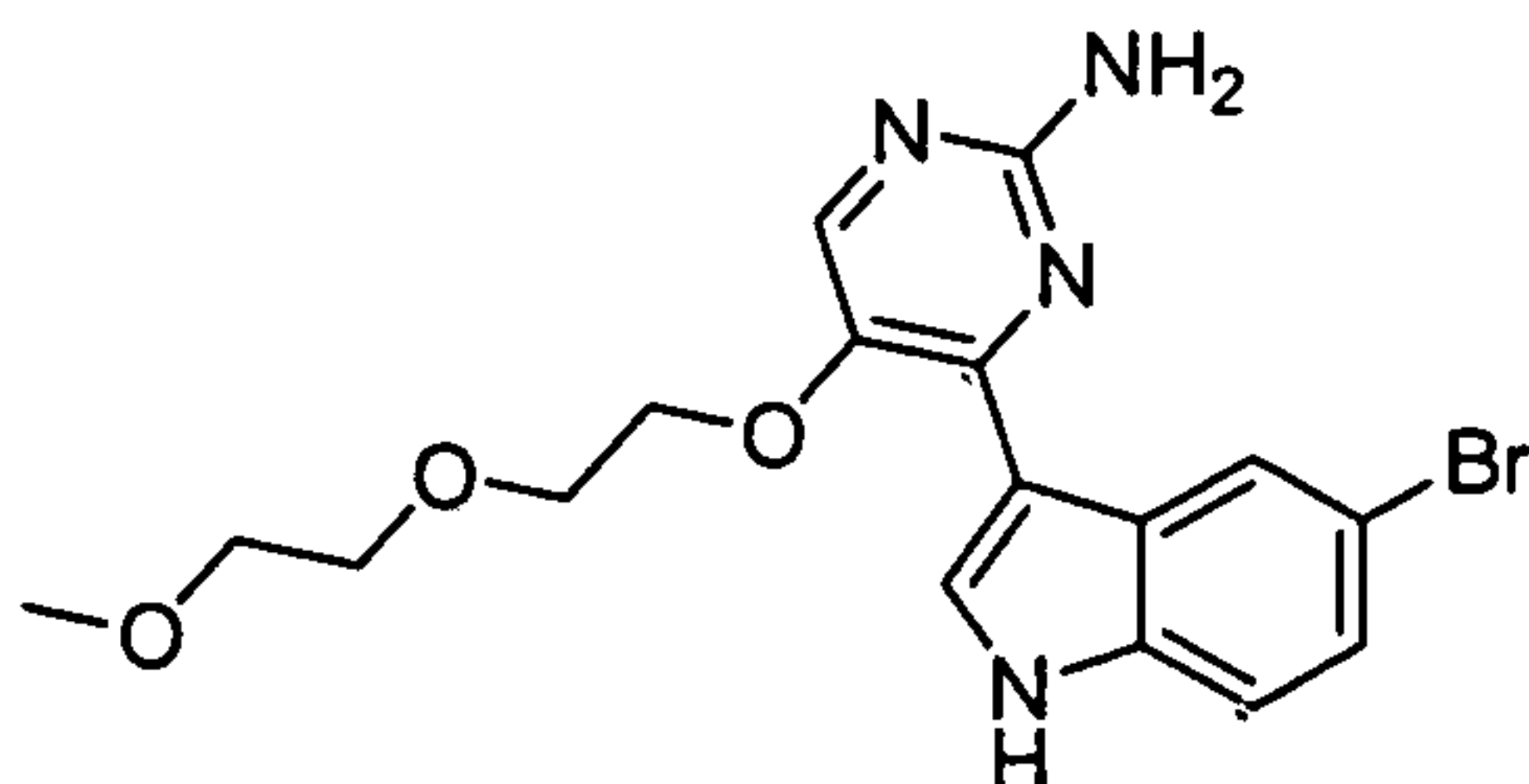
4-(5-bromo-7-fluoro-1H-indol-3-yl)-5-(2-methoxyethoxy)-2-pyrimidinamine A.328 was prepared starting with 5-bromo-7-fluoro-1H-indole using the procedures described for compound A.313.

^1H NMR (400 MHz, DMSO- d_6) δ 12.40 (s, 1H), 8.81 (d, $J = 1.6$ Hz, 1H), 8.49 (s, 1H), 8.11 (s, 1H), 7.30 (dd, $J = 10.4, 1.6$ Hz, 1H), 6.22 (s, 2H), 4.20 – 4.18 (m, 2H), 3.76 – 3.73 (m, 2H), 3.38 (s, 3H). LCMS-ESI (POS), M/Z, M+1: Found 381.0 and 383.0.

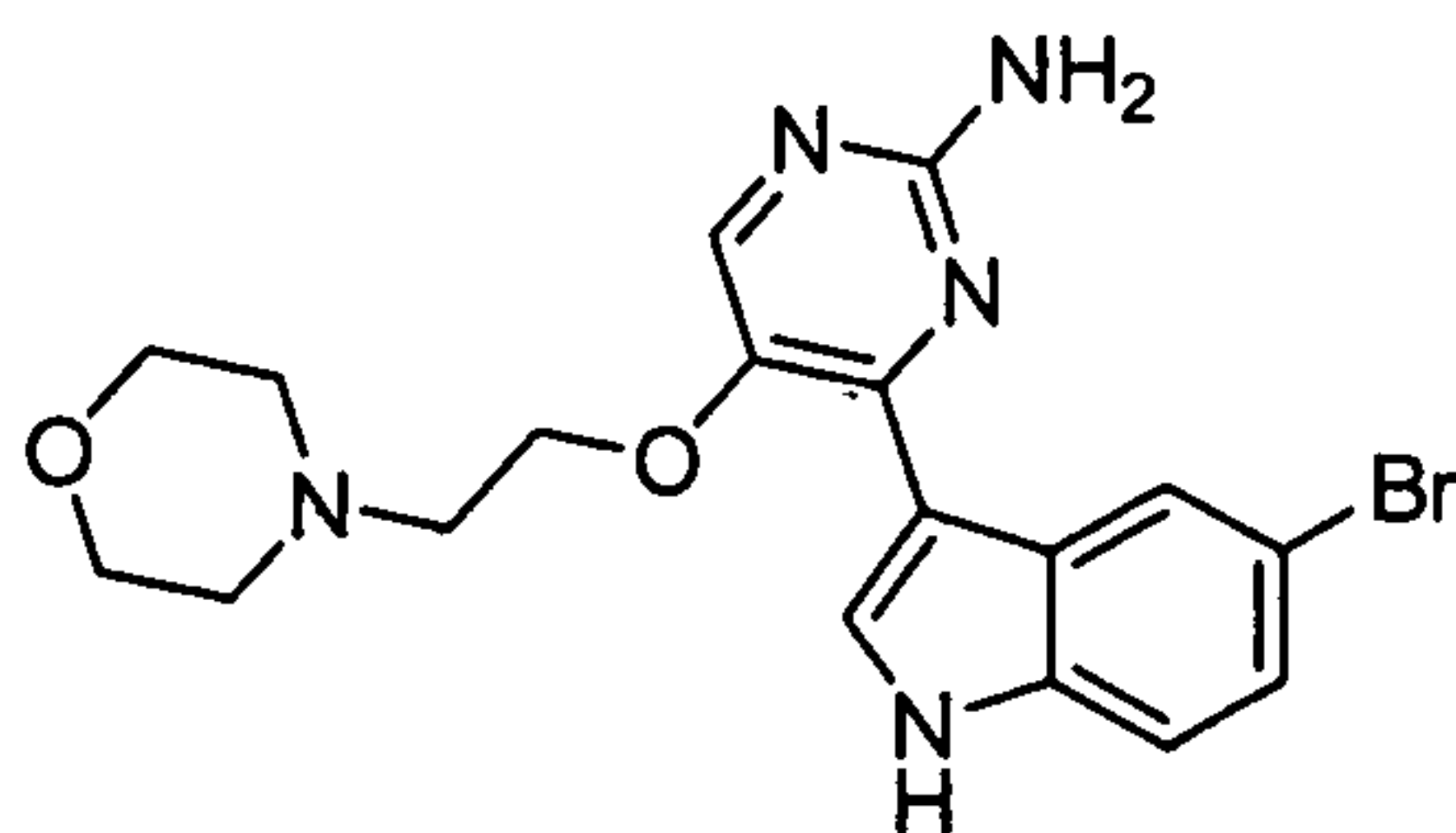
Compounds A.329-A.333 were prepared by the same procedures used to prepare compound A.313 beginning with compound A.311 and the appropriate alcohols as the point of diversification.

**A.329**

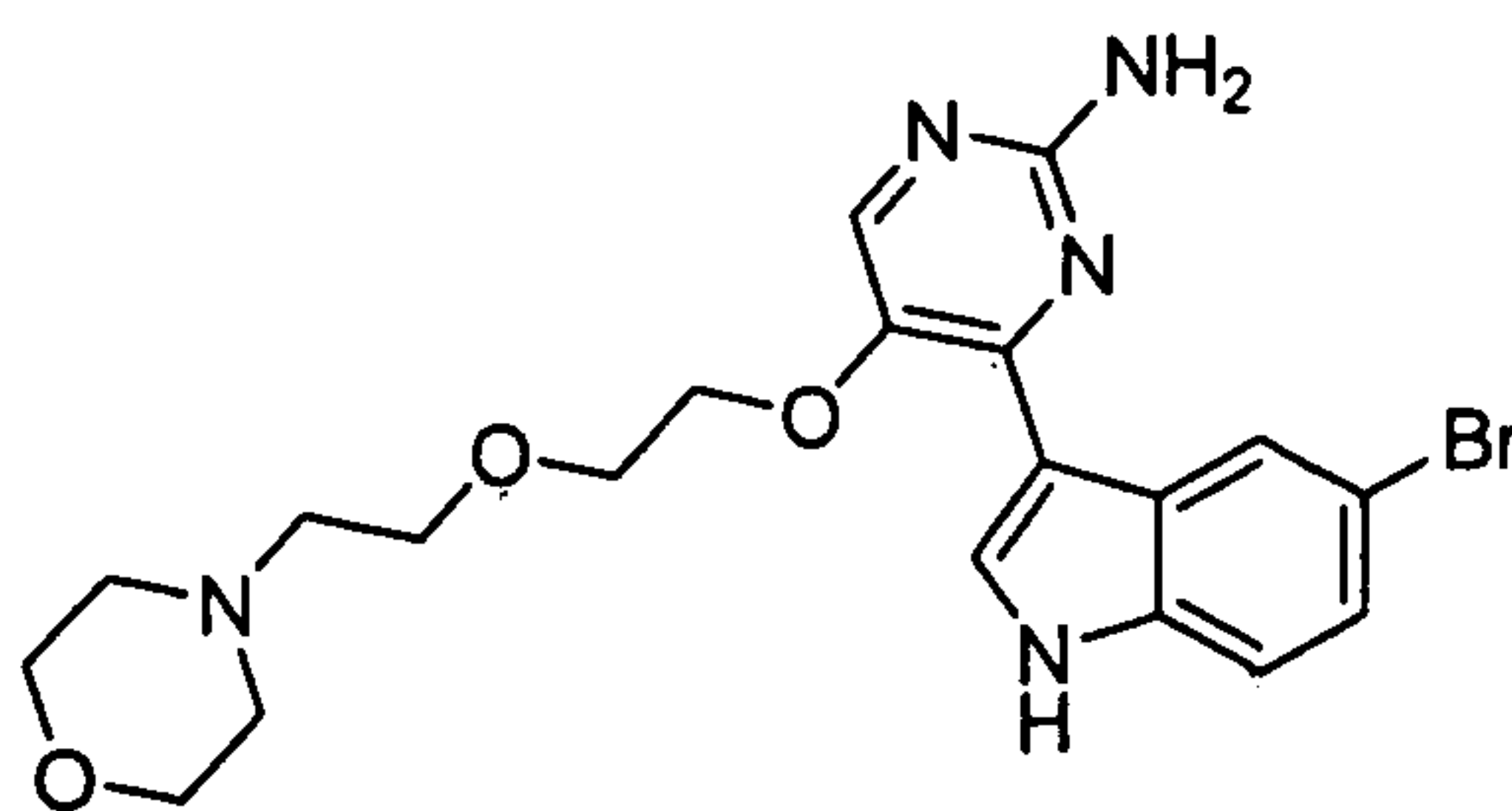
4-(5-bromo-1H-indol-3-yl)-5-methoxy-2-pyrimidinamine A.329 ^1H NMR (500 MHz, DMSO- d_6) δ 11.82 (s, 1H), 8.95 (d, $J = 2.0$ Hz, 1H), 8.32 (d, $J = 2.9$ Hz, 1H), 8.06 (s, 1H), 7.44 (d, $J = 8.6$ Hz, 1H), 7.30 (dd, $J = 8.6, 2.0$ Hz, 1H), 6.13 (s, 2H), 3.90 (s, 3H). LCMS-ESI (POS), M/Z, M+1: Found 319.0 and 321.0.

**A.330**

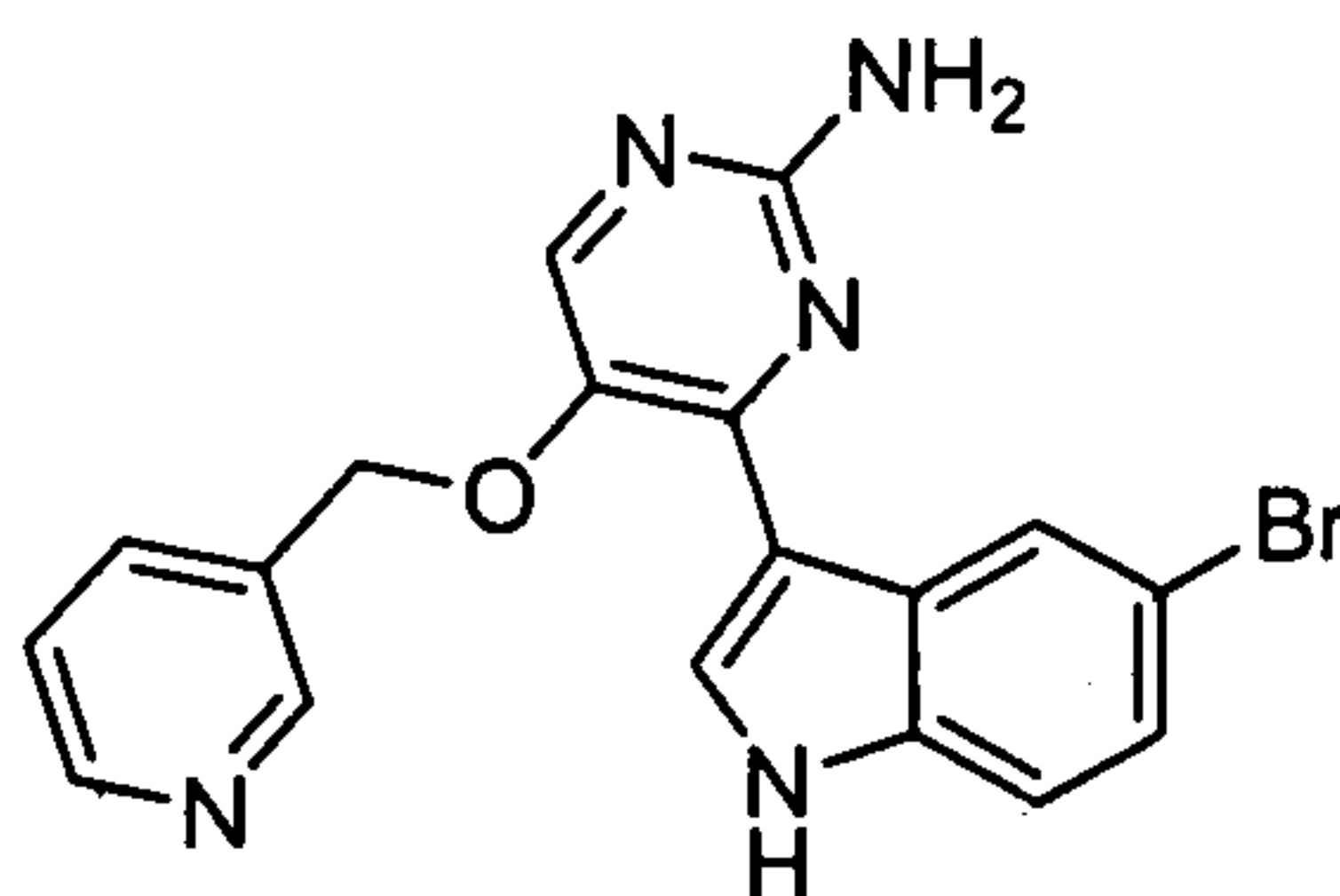
4-(5-bromo-1H-indol-3-yl)-5-(2-(2-methoxyethoxy)ethoxy)-2-pyrimidinamine A.330 ^1H NMR (500 MHz, DMSO- d_6) δ 11.80 (s, 1H), 8.95 (d, $J = 2.0$ Hz, 1H), 8.47 (s, 1H), 8.06 (s, 1H), 7.43 (d, $J = 8.5$ Hz, 1H), 7.30 (dd, $J = 8.5, 2.0$ Hz, 1H), 6.15 (s, 2H), 4.18 – 4.16 (m, 2H), 3.83 – 3.81 (m, 2H), 3.64 – 3.62 (m, 2H), 3.53 – 3.51 (m, 2H), 3.27 (s, 3H). LCMS-ESI (POS), M/Z, M+1: Found 407.0 and 409.0.

**A.331**

4-(5-bromo-1H-indol-3-yl)-5-(2-(4-morpholinyl)ethoxy)-2-pyrimidinamine A.331 ^1H NMR (400 MHz, DMSO- d_6) δ 11.89 (s, 1H), 8.97 (s, 1H), 8.73 (s, 1H), 8.09 (s, 1H), 7.44 (d, $J = 8.3$ Hz, 1H), 7.31 (d, $J = 8.3$ Hz, 1H), 6.14 (s, 2H), 4.16 (s, 2H), 3.65 (s, 4H), 2.76 (s, 2H), 2.52 (s, 4H). LCMS-ESI (POS), M/Z, M+1: Found 418.0 and 420.1.

**A.332****4-(5-bromo-1H-indol-3-yl)-5-(2-(2-(4-morpholinyl)ethoxy)ethoxy)-2-pyrimidinamine**

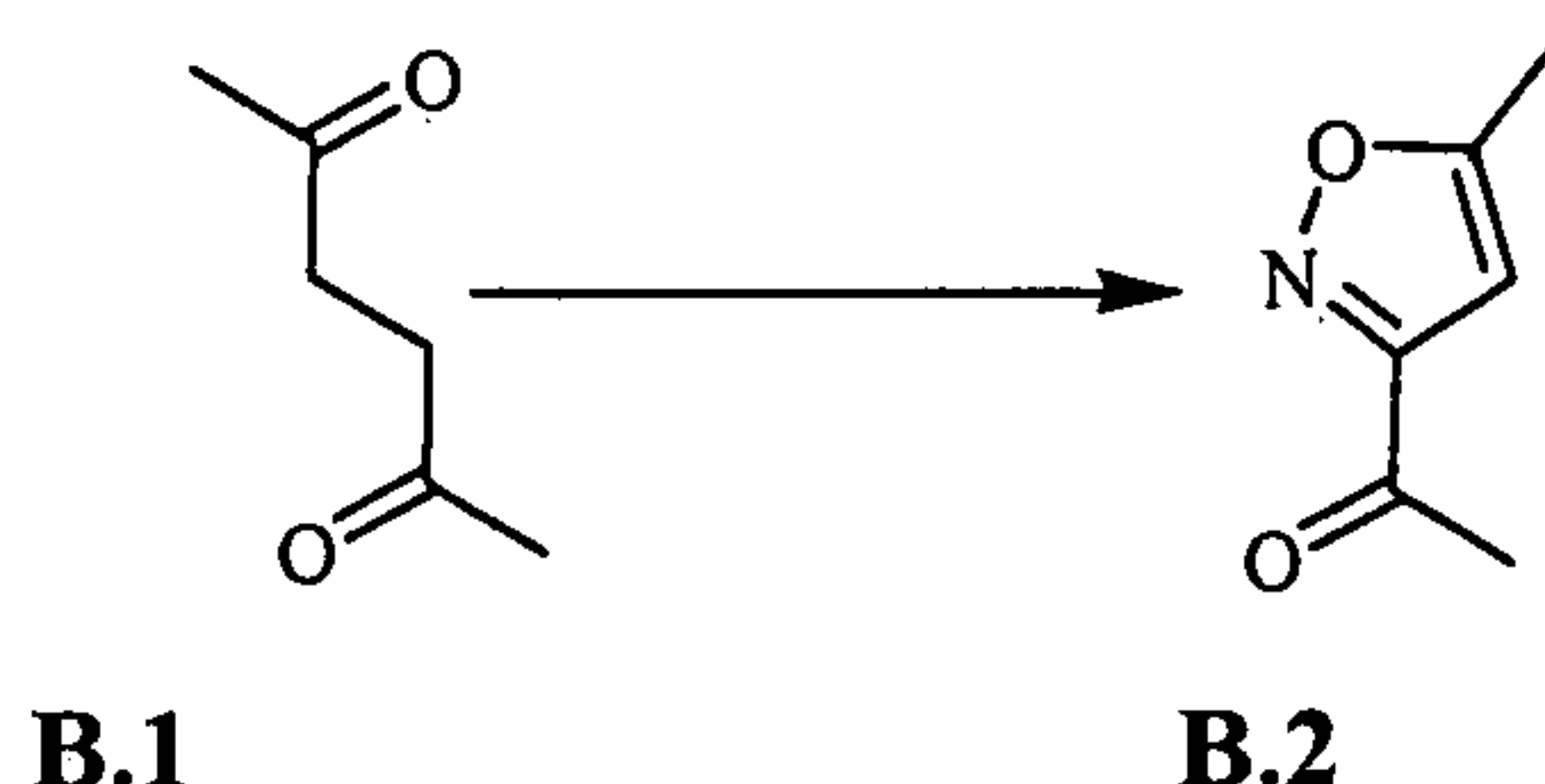
A.332 ^1H NMR (400 MHz, DMSO- d_6) δ 11.84 (s, 1H), 8.96 (d, J = 2.0 Hz, 1H), 8.45 (s, 1H), 8.08 (s, 1H), 7.44 (d, J = 8.6 Hz, 1H), 7.31 (dd, J = 8.6, 2.0 Hz, 1H), 6.15 (s, 2H), 4.18 (t, J = 4.4 Hz, 2H), 3.80 (t, J = 4.4 Hz, 2H), 3.61 (t, J = 5.9 Hz, 2H), 3.50 (t, J = 4.7 Hz, 4H), 2.39 (t, J = 4.7 Hz, 4H). LCMS-ESI (POS), M/Z , $M+1$: Found 462.0 and 464.0.

**A.333****4-(5-bromo-1H-indol-3-yl)-5-(3-pyridinylmethoxy)-2-pyrimidinamine A.333**

^1H NMR (400 MHz, DMSO- d_6) δ 11.84 (s, 1H), 8.95 (d, J = 1.9 Hz, 1H), 8.63 (d, J = 4.3 Hz, 1H), 8.46 (s, 1H), 8.11 (s, 1H), 7.87 (td, J = 7.7, 1.9 Hz, 1H), 7.58 (d, J = 7.7 Hz, 1H), 7.43 – 7.38 (m, 2H), 7.31 (dd, J = 8.6, 2.0 Hz, 1H), 6.19 (s, 2H), 5.27 (s, 2H). LCMS-ESI (POS), M/Z , $M+1$: Found 396.0 and 398.0.

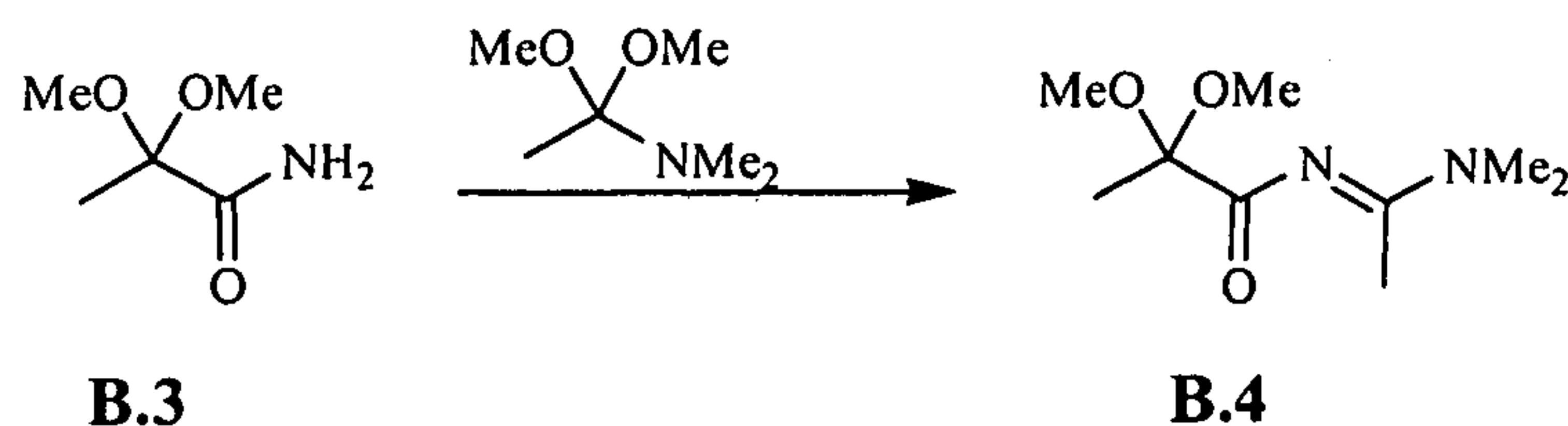
GENERAL SCHEMES—SECTION B

This section illustrates procedures for making ketone building blocks for alkynyl alcohols.

**1-(5-methylisoxazol-3-yl)ethanone B.2**

[Sauers, R. R.; Van Arnum, S. D., *J. Heterocycl. Chem.* **2003**, 40, (4), 655-658.]

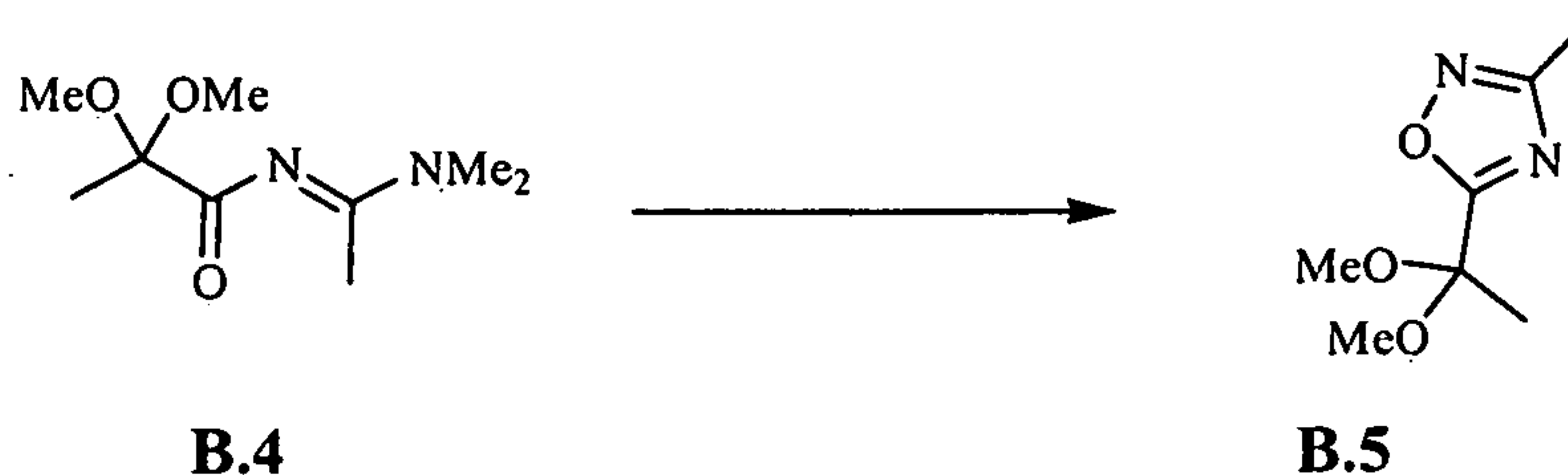
2,5-hexanedione **B.1** (10 g, 87.6 mmol) was heated to 40 °C, and conc. HCl (1 mL, 0.14 eq) was added. Ethylnitrite gas was generated by the dropwise addition of NaNO₂ (12.70 g, 184 mmol) in a solution of EtOH (5.6 mL) and water (50 mL) to a solution of H₂SO₄ (conc., 5.2 mL) in EtOH (5.6 mL) and water (50 mL). The ethylnitrite gas was bubbled through the acidic hexanedione solution for 2 hours while the temperature was maintained between 40-50 °C. The reaction was further stirred at 40 °C for 4 hours. After cooling to room temperature, 100 mL ether was added, and the organic layer was separated, washed with sat. NaHCO₃ and brine, dried over MgSO₄ and concentrated *in vacuo*. Purification by flash chromatography (10% ethyl acetate in hexane) gave 1-(5-methylisoxazol-3-yl)ethanone **B.2** (6.02 g). ¹H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 2.63 (3 H, s), 2.48 (3 H, s) Mass Spectrum (ESI) m/e = 126.1 (M+1)

**N-(1-(dimethylamino)ethylidene)-2,2-dimethoxypropanamide B.4**

[LaMattina, J. L.; Mularski, C. J., *J. Org. Chem.* **1984**, 49, (25), 4800-4805]

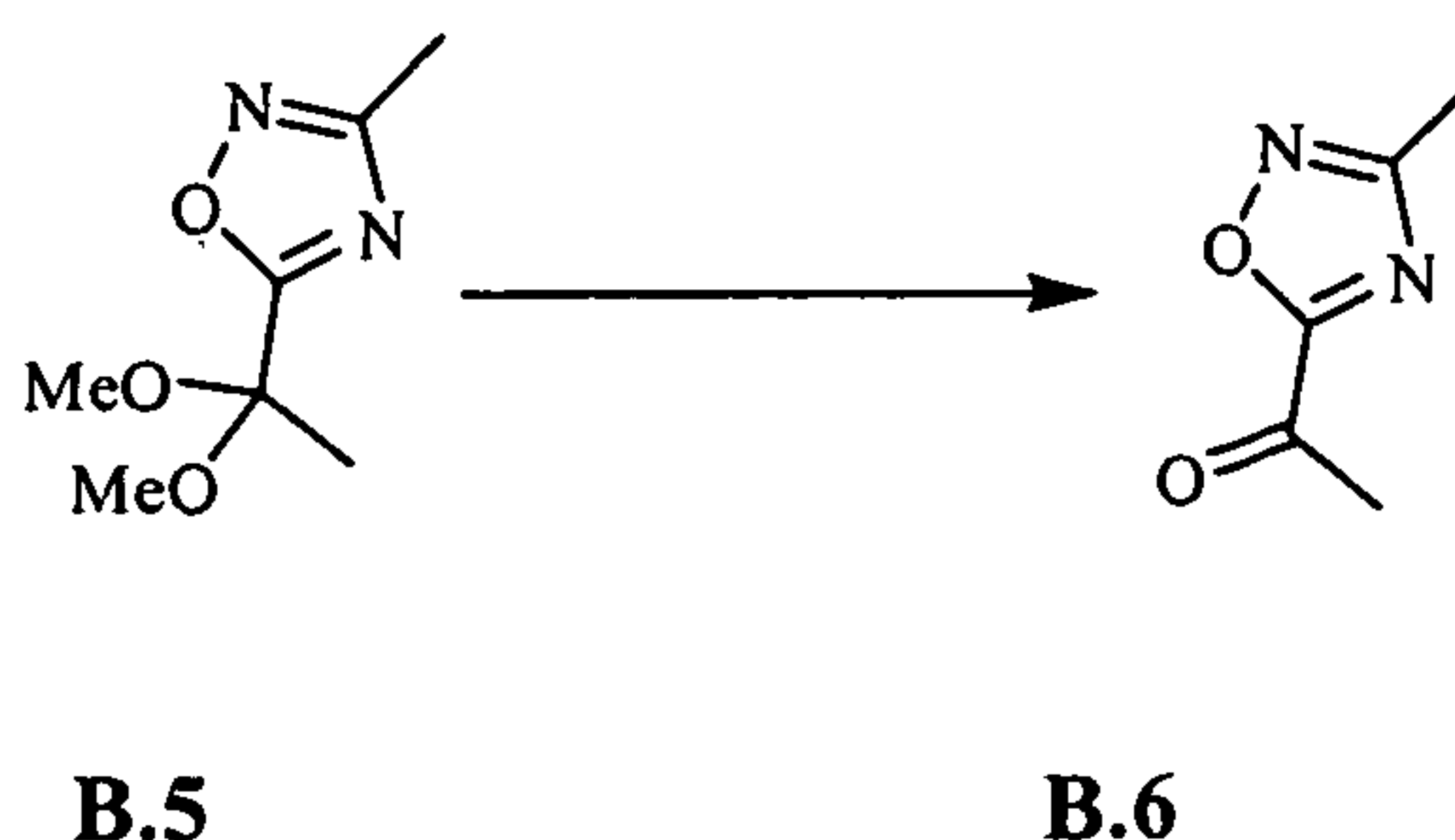
A mixture of 2,2-dimethoxypropionamide **B.3** (10 g, 75 mmol) and N,N-dimethylacetamide dimethylacetal (43.5 g, 326 mmol) was heated at reflux for 2 hours. The mixture was condensed *in vacuo* followed by distillation under reduced pressure to give N-(1-

(dimethylamino)ethylidene)-2,2-dimethoxypropanamide (12.30 g) as a yellow oil. ¹H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 3.31 (6 H, s), 3.10 (3 H, s), 3.09 (3 H, s), 2.27 (3 H, s), 1.48 (3 H, s) Mass Spectrum (ESI) m/e = 203.2 (M+1)



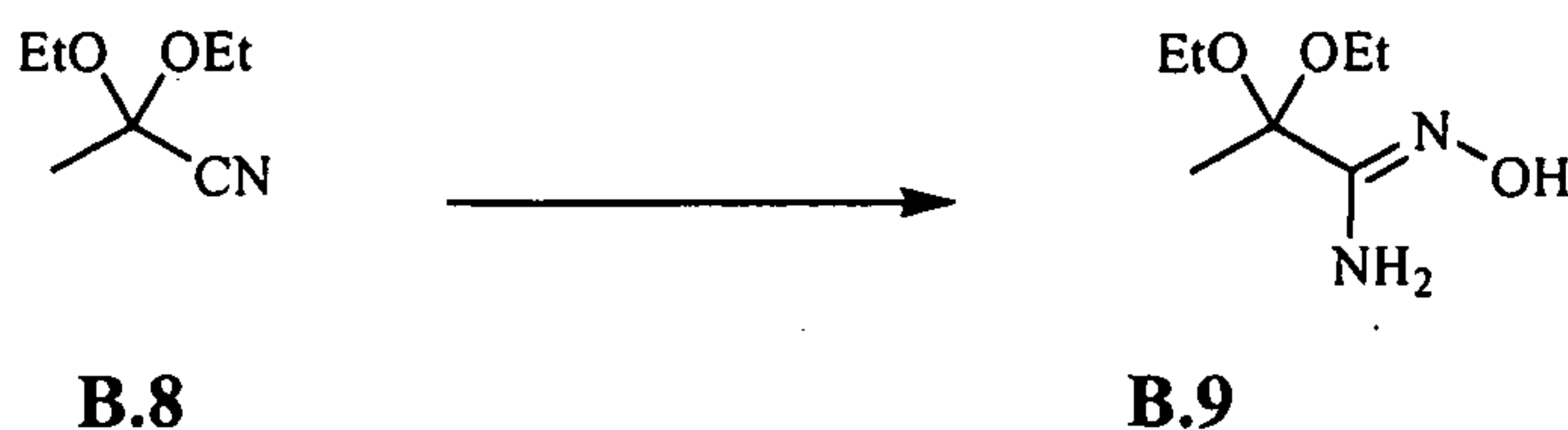
5-(1,1-dimethoxyethyl)-3-methyl-1,2,4-oxadiazole **B.5**

Hydroxylamine hydrochloride (3.8 g, 54 mmol) was dissolved in 120 mL 70 % aq. acetic acid, and NaOH (2.2 g, 54 mmol) was added. To the stirring solution was added a mixture of N-(1-(dimethylamino)ethylidene)-2,2-dimethoxypropanamide **B.4** in 60 mL dioxane. The reaction was heated to 100 °C for 30 minutes, cooled to room temperature and condensed *in vacuo*. Saturated aq. NaHCO₃ was added until the solution was slightly basic. The aqueous solution was then extracted with dichloromethane. The combined extracts were dried over MgSO₄ and evaporated to give a crude orange oil. The oil was distilled under reduced pressure to give 5-(1,1-dimethoxyethyl)-3-methyl-1,2,4-oxadiazole **B.5** (6.14 g) as a clear oil. ¹H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 3.28 (6 H, s), 2.39 (3 H, s), 1.70 (3 H, s)



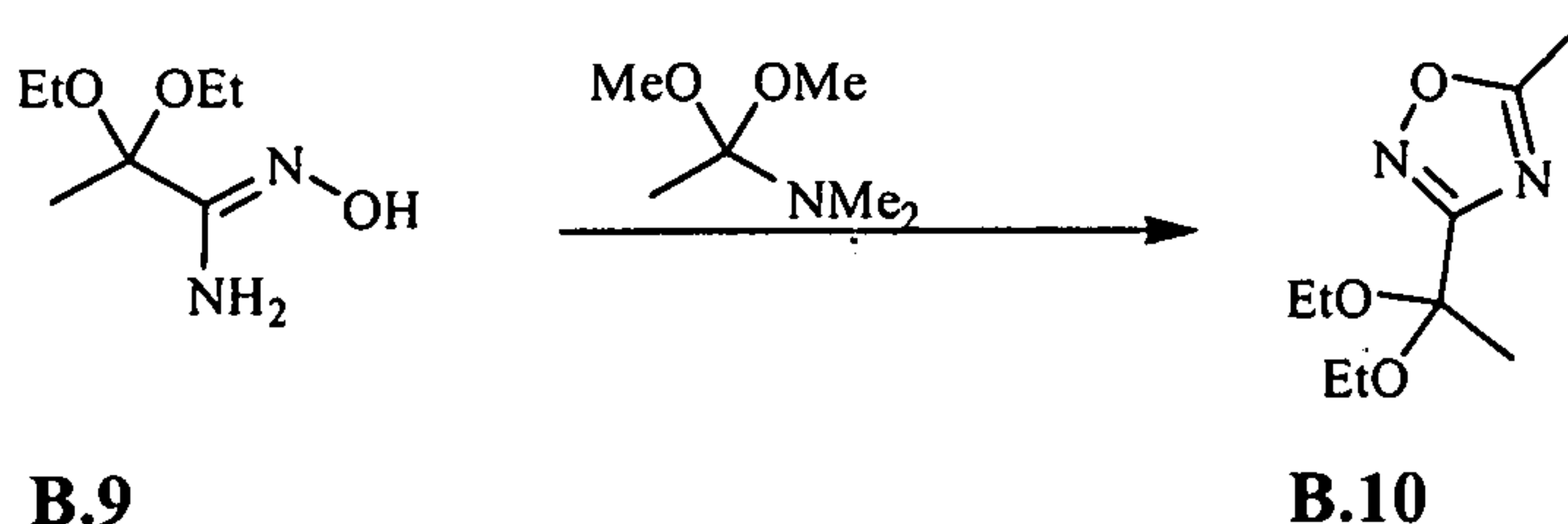
1-(3-methyl-1,2,4-oxadiazol-5-yl)ethanone **B.6** 5-(1,1-dimethoxyethyl)-3-methyl-1,2,4-oxadiazole **B.5** (6.1 g, 35.5 mmol) and pTsOH (7.42 g, 39 mmol) were stirred in 80 mL acetone at reflux for 2 hours. The mixture was cooled to room temperature, evaporated, and the residue was triturated with Na₂CO₃ (20% aq., 50 mL). The resulting solution was extracted with dichloromethane, and the combined extracts were dried over MgSO₄ and evaporated. The residue was distilled under reduced pressure to give 1-(3-methyl-1,2,4-oxadiazol-5-yl)ethanone

B.6 (1.91 g, 43%). ¹H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 2.76 (3 H, s), 2.53 (3 H, s)
Mass Spectrum (ESI) m/e = 127.2 (M+1)



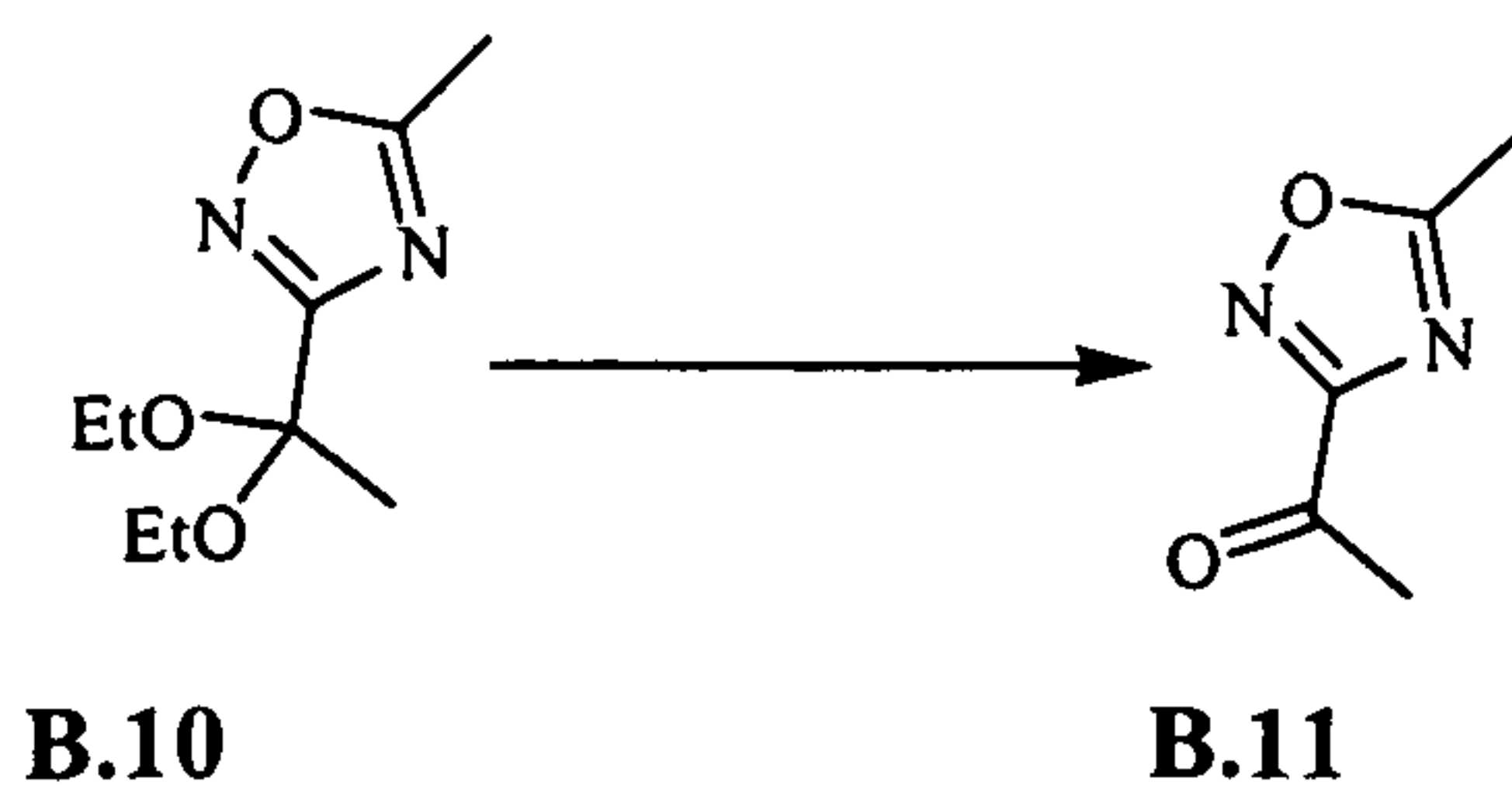
2,2-diethoxy-N'-hydroxypropanamidine **B.9**

To a stirring solution of $\text{NH}_2\text{OH}\cdot\text{HCl}$ (36.4 g, 524 mmol) and Na_2CO_3 (55.5 g, 524 mmol) in 150 mL water was added 2,2-diethoxypropanenitrile **B.8** (10 g, 70 mmol) in 200 mL methanol, and the mixture was stirred at reflux 17 hours. The reaction was cooled to room temperature, partitioned between water and dichloromethane, and the aqueous layer was further extracted with dichloromethane. The combined organic extracts were dried over MgSO_4 and evaporated to give 2,2-diethoxy-N'-hydroxypropanamidine **B.9** (3.59 g, 77%) as a white crystalline solid. ¹H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 4.87 (2 H, br. s.), 3.45 (4 H, q, $J=7.1$ Hz), 1.48 (3 H, s), 1.13 (6 H, t, $J=7.1$ Hz) Mass Spectrum (ESI) m/e = 177.2 (M+1)



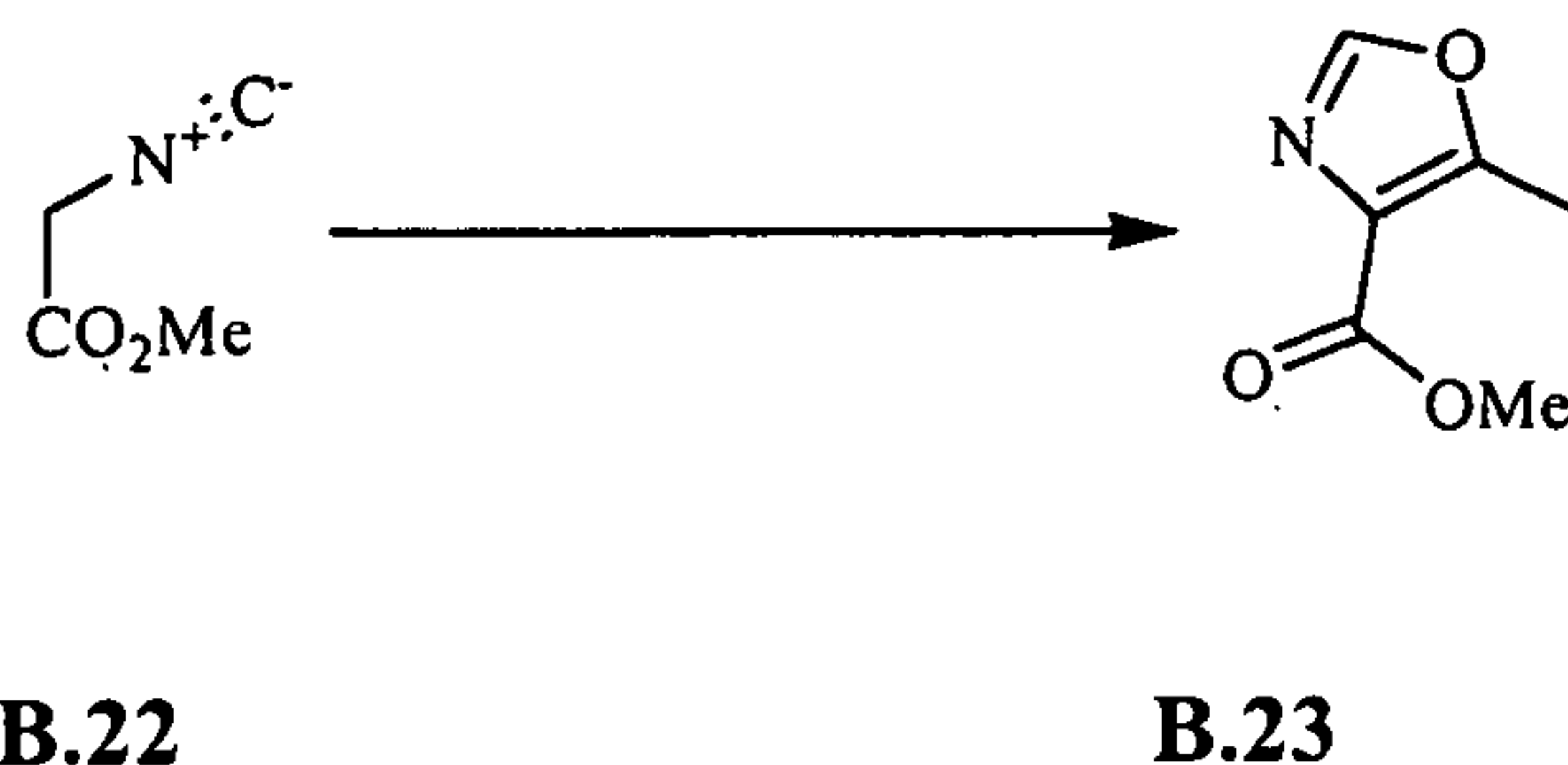
3-(1,1-diethoxyethyl)-5-methyl-1,2,4-oxadiazole **B.10**

A mixture of 2,2-diethoxy-N'-hydroxypropanamidine **B.9** (1.05 g, 6 mmol) and N,N-dimethylacetamide dimethylacetal (10 mL, 75 mmol) was heated at reflux for 4 hours. The mixture was condensed *in vacuo* followed by flash chromatography (30-100% gradient ethyl acetate in hexane) to give 3-(1,1-diethoxyethyl)-5-methyl-1,2,4-oxadiazole **B.10** (0.36 g, 66%). ¹H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 3.68 (2 H, dq, $J=9.1, 7.1, 7.0$ Hz), 3.52 (2 H, dq, $J=9.2, 7.2$ Hz), 2.63 (3 H, s), 1.75 (3 H, s), 1.27 (6 H, t, $J=7.0$ Hz) Mass Spectrum (ESI) m/e = 155.2 (M+OEt)



1-(5-methyl-1,2,4-oxadiazol-3-yl)ethanone B.11 This compound was prepared from **B.10** in 52% yield by the procedure used for compound **B.6**.

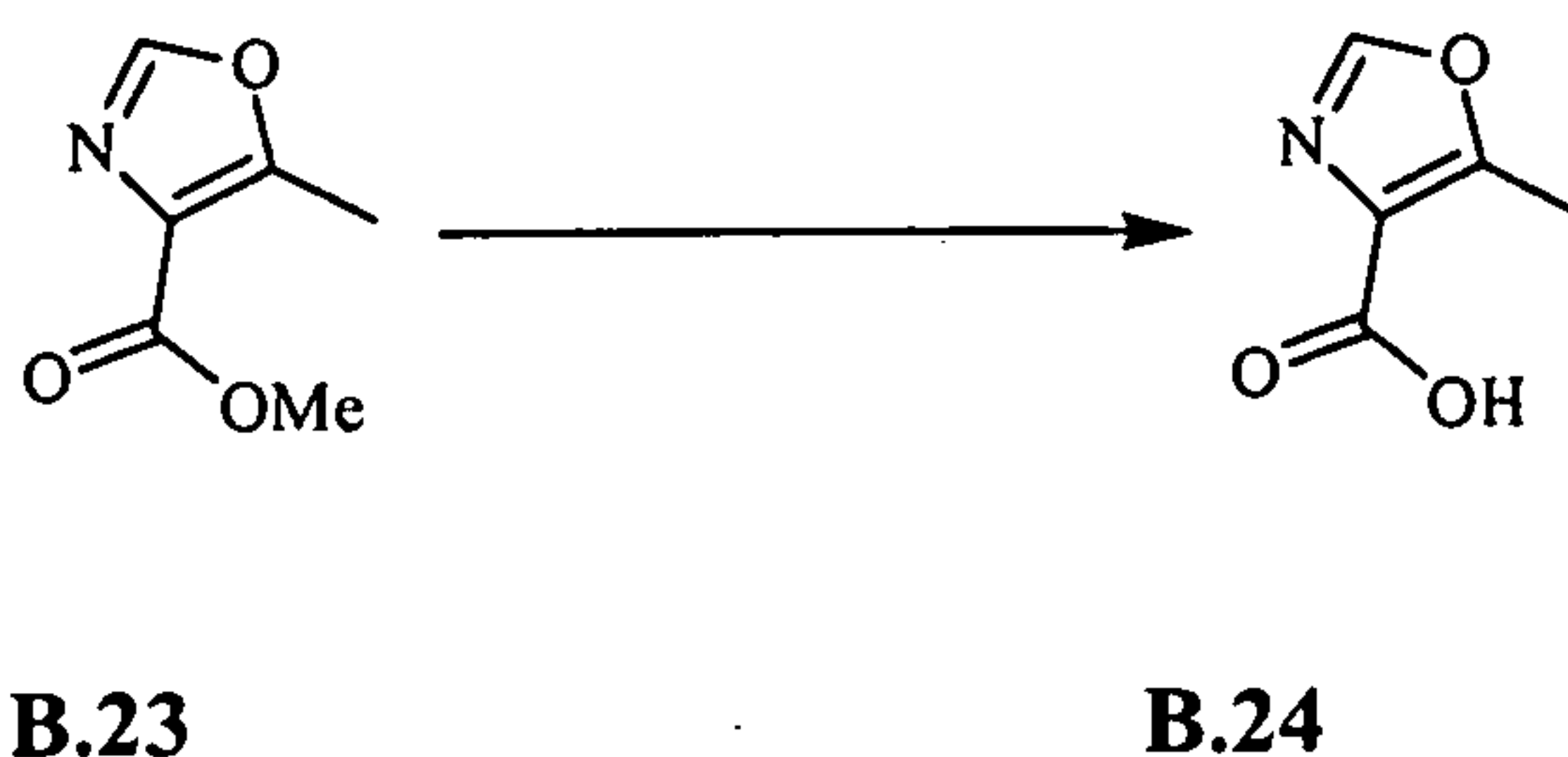
¹H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 2.70 (3 H, s), 2.69 (3 H, s) Mass Spectrum (ESI) $m/e = 127.2$ (M+1)



methyl 5-methyloxazole-4-carboxylate **B.23**

[Suzuki M.; Iwasaki T.; Miyoshi M.; Okumura K.; K., M.; *J. Org. Chem.* **1973**, 38, (20), 3571-3575.]

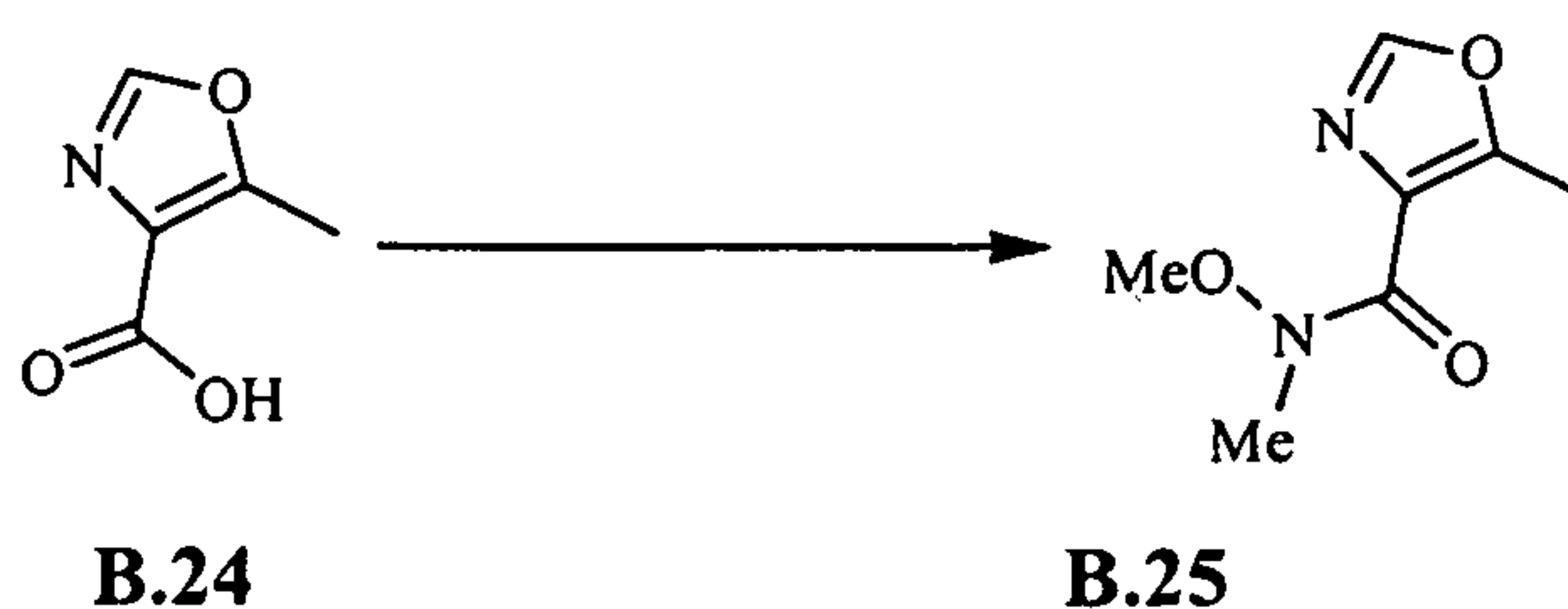
Methyl 2-isocyanoacetate **B.22** (5 g, 50.5 mmol) was stirred in THF (15 mL) at room temperature as DBU (7.55 mL, 50.5 mmol) was added, followed by 4.74 mL acetic anhydride. The reaction stirred at room temperature 17 hrs. After partitioning between ethyl acetate and water, the aqueous layer was further extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and condensed. The residue was purified by flash chromatography (50-100% gradient ethyl acetate in hexane) to give methyl 5-methyloxazole-4-carboxylate **B.23** (5.41 g, 76%) as a white solid. ¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 8.32 (1 H, s), 3.79 (3 H, s), 2.56 (3 H, s) Mass Spectrum (ESI) $m/e = (M+1)$



5-methyloxazole-4-carboxylic acid **B.24**

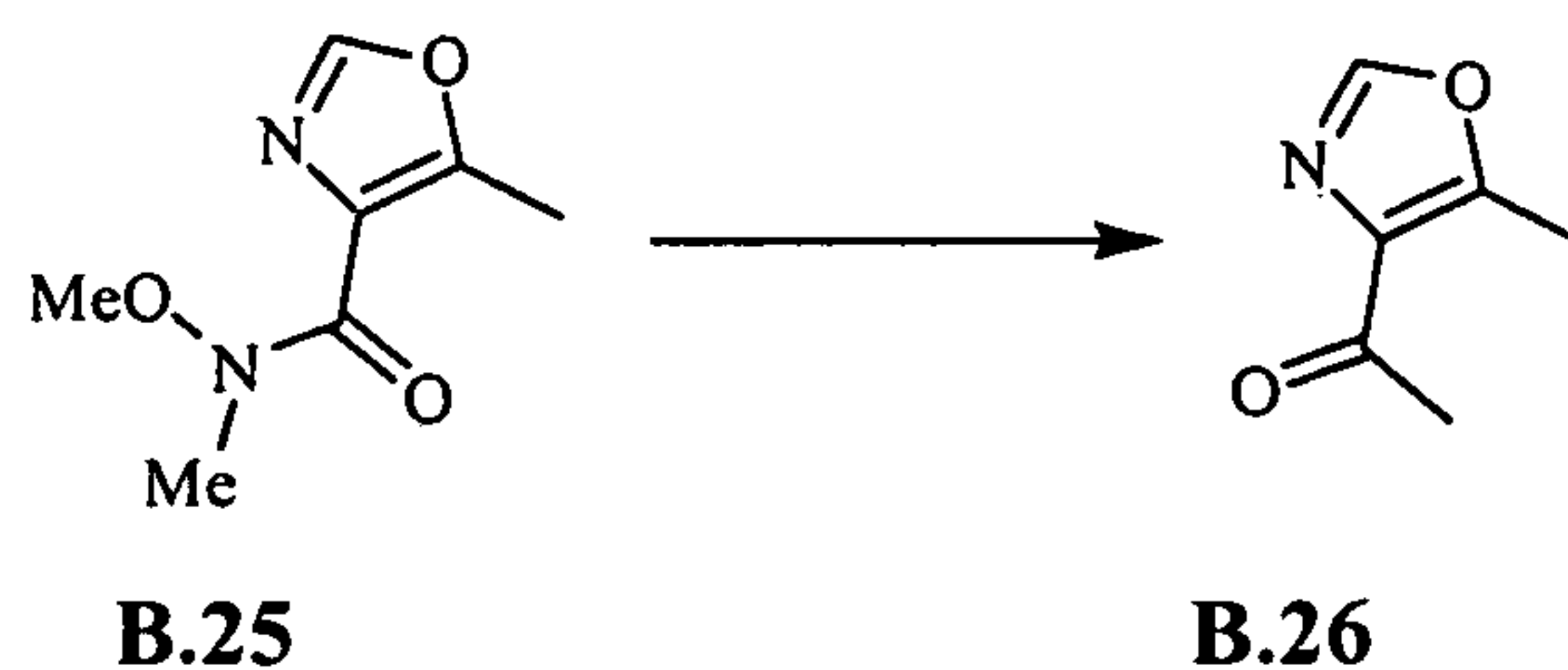
Methyl 5-methyloxazole-4-carboxylate **B.23** (1 g, 7.1 mmol) was dissolved in 4 mL THF and LiOH (0.205 g, 8.5 mmol) in 12 mL water was added. After 2 hours, the THF was evaporated,

and the aqueous layer was acidified with 6 N HCl and placed in the freezer to crystallize. The crystallized product was filtered and dried to give 5-methyloxazole-4-carboxylic acid. **B.24** (0.69 g, 77%) ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 12.92 (1 H, br. s.), 8.29 (1 H, s), 2.56 (3 H, s) Mass Spectrum (ESI) $m/e = (M+1)$



N-methoxy-N,5-dimethyloxazole-4-carboxamide **B.25**

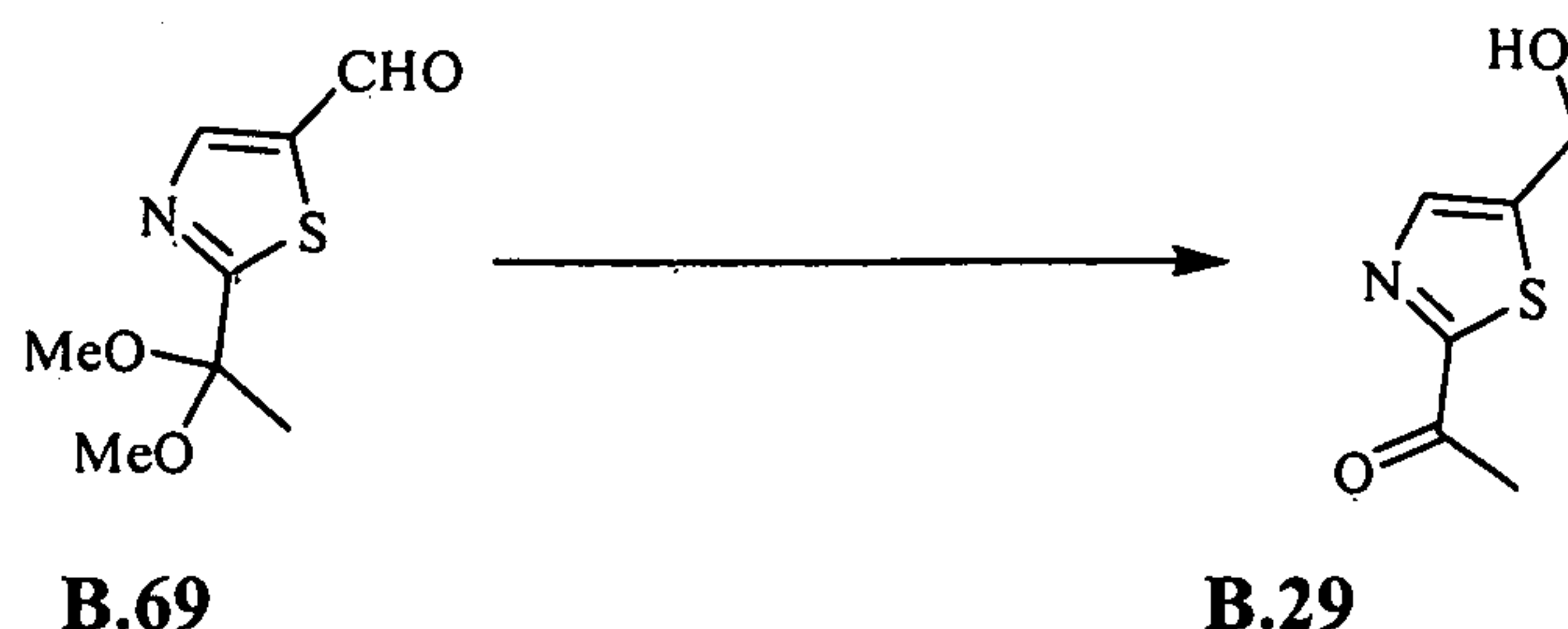
5-methyloxazole-4-carboxylic acid **B.24** (490 mg, 3.9 mmol) and CDI (940 mg, 5.8 mmol) were stirred in 3 mL DMF at room temperature for 4 hours. In a separate flask, triethylamine (2.36 g, 23.4 mmol) was added to a stirring solution of N-methoxymethanamine hydrochloride (1.90 g, 19.5 mmol) in DMF (16 mL) at 0 °C. To this solution was added the first mixture, and the reaction was allowed to warm to room temperature and stirred 17 hours. After being partitioned between water and ethyl acetate, the aqueous layer was further extracted with ethyl acetate, and the combined organic layers were dried over Mg SO_4 and condensed. The residue was purified by flash chromatography (1-100% gradient ethyl acetate in hexane) to give N-methoxy-N,5-dimethyloxazole-4-carboxamide **B.25** (425 mg, 64%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 8.31 (1 H, s), 3.73 (3 H, s), 3.29 (3 H, s), 2.46 (3 H, s) Mass Spectrum (ESI) $m/e = 170.9 (M+1)$



1-(5-methyloxazol-4-yl)ethanone **B.26**

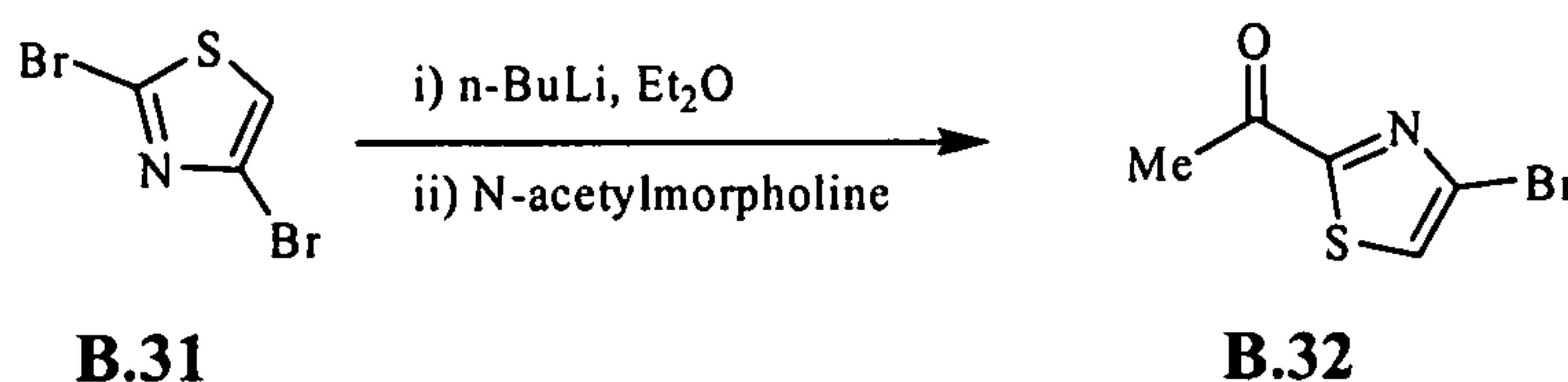
To a solution of N-methoxy-N,5-dimethyloxazole-4-carboxamide **B.25** (0.72 g, 4.2 mmol) in THF (30 mL) stirring at 0 °C was added methylmagnesium chloride (3.64 mL of 3 M solution in ether, 10.9 mmol). The reaction stirred at 0 °C 1h, was quenched with methanol and acidified with 1 N HCl. The solution was diluted with dichloromethane, washed with brine, dried over MgSO_4 and condensed. Flash chromatography (1-100% gradient ethyl acetate in hexane) provided 1-(5-methyloxazol-4-yl)ethanone **B.26** (106 mg, 20%). ^1H NMR (500

MHz, *DMSO-d*₆) δ ppm 8.31 (1 H, s), 3.73 (3 H, s), 3.29 (3 H, s), 2.46 (3 H, s) Mass Spectrum (ESI) $m/e = 126.2$ (M+1)



1-(5-(hydroxymethyl)thiazol-2-yl)ethanone **B.29**

2-(1,1-dimethoxyethyl)thiazole-5-carbaldehyde **B.69** (1.14 g, 5.7 mmol) in 10 mL methanol was stirred at 0 °C as NaBH₄ (0.215 g, 5.7 mmol) was added portionwise. The reaction mixture stirred for 5 minutes, was quenched with sat. aq. NH₄Cl and extracted into ethyl acetate. The combined extracts were dried over MgSO₄ and condensed to give 1.18 g yellow solid. The yellow solid (0.20 g, 1 mmol) was stirred in 8 mL water-acetone (1:1 ratio) as 0.4 mL conc. HCl was added. After 2 hours, sat. aq. NaHCO₃ was added neutralize to pH 7, and the aqueous solution was extracted with dichloromethane. The combined extracts were dried over MgSO₄ and evaporated to give 1-(5-(hydroxymethyl)thiazol-2-yl)ethanone **B.29** (154mg, 98%) as a colorless crystalline solid. ¹H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 7.87 (1 H, s), 4.96 (2 H, s), 2.71 (3 H, s)

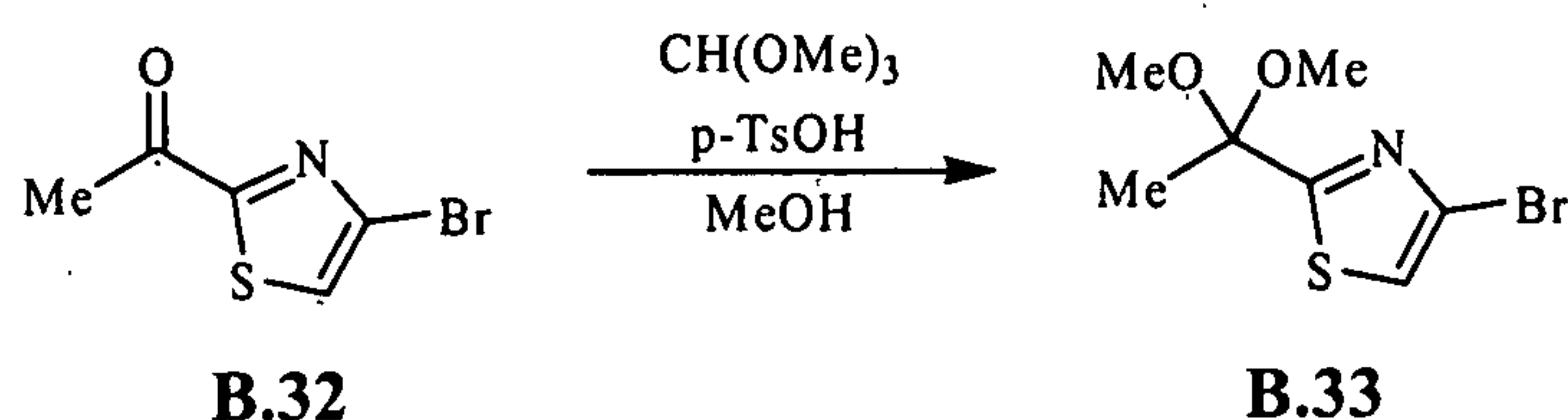


1-(4-bromothiazol-2-yl)ethanone **B.32**

[Ung, A. T.; Pyne, S. G., *Tetrahedron: Asym.* **1998**, 9, (8), 1395-1408]

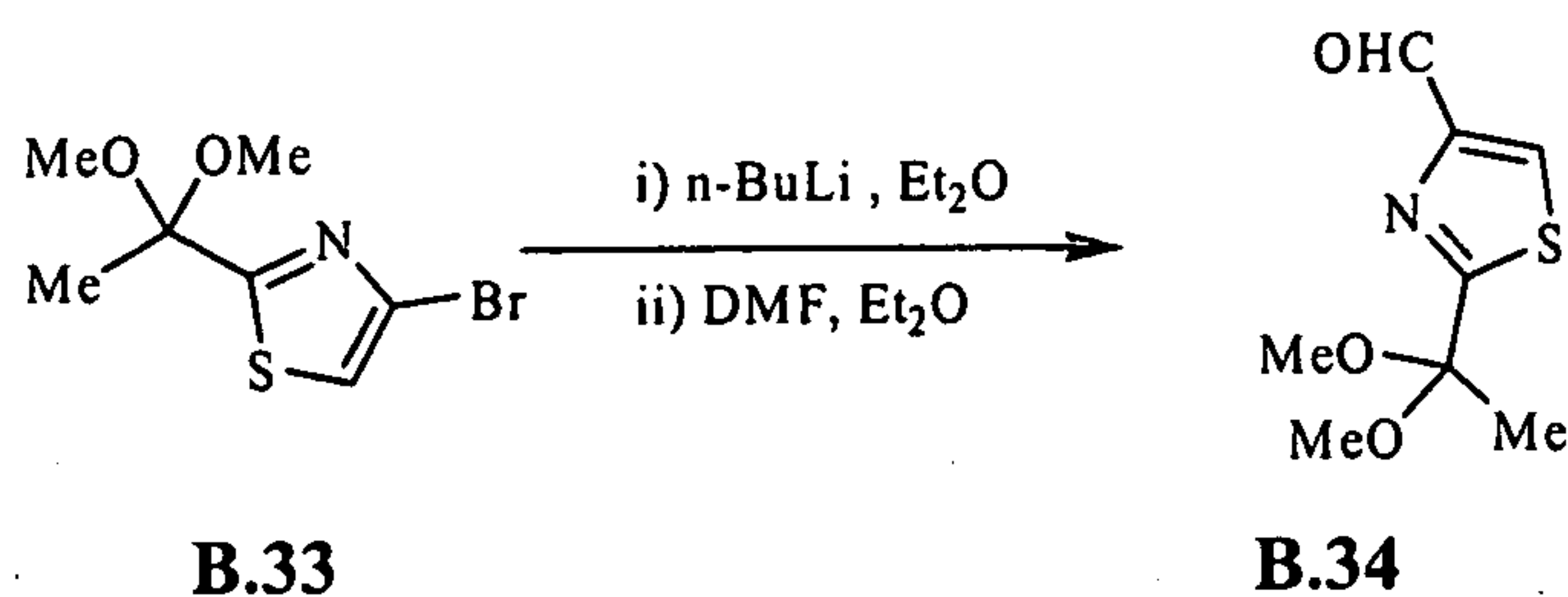
A solution of 2,4-dibromothiazole **B.31** (5.0128 g, 20.63 mmol) in ether (52 mL) was cooled to -78 °C. To the cooled solution was added n-BuLi (1.6 M sol. in hexane, 14.2 mL, 22.72 mmol) and the mixture was stirred at -78 °C for 30 minutes. To the cooled mixture was then added

dropwise N-acetylmorpholine (3.1 mL, 26.83 mmol). The mixture was stirred at -78 °C for 1.5 hours and then room temperature for 18 hours. The mixture was diluted with ether (200 mL), washed with saturated aqueous NaHCO₃ (100 mL x 1), dried over MgSO₄, filtered, and concentrated under reduced pressure. The product was purified by silica gel column chromatography using 0% to 50% gradient of ethyl acetate in hexane as eluent to give 1-(4-bromothiazol-2-yl)ethanone **B.32** (3.383 g, 79.5% yield): ¹H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 7.59 (1 H, s), 2.73 (3 H, s); Mass Spectrum (ESI) *m/e* = 205.9 [M+1 (⁷⁹Br)] and 207.9 [M+1 (⁸¹Br)].



4-bromo-2-(1,1-dimethoxyethyl)thiazole **B.33**

To a solution of 1-(4-bromothiazol-2-yl)ethanone **B.32** (3.383 g, 16.42 mmol) in dry methanol (55 mL) was added trimethyl orthoformate (9 mL, 82.27 mmol) and *p*-TsOH (2.8103 g, 14.77 mmol). The mixture was heated at reflux for 21.5 hours. The mixture was poured into saturated aqueous NaHCO₃ (100 mL). The aqueous layer was extracted with ethyl acetate (100 mL x 2). The combined organic layers were washed with 1 N aqueous NaOH (100 mL x 1), brine (100 mL x 1), dried over MgSO₄, filtered, and concentrated under reduced pressure to give a white solid. The product was purified by silica gel column chromatography using 10% ethyl acetate in hexane as eluent to give 4-bromo-2-(1,1-dimethoxyethyl)thiazole **B.33** (3.753 g, 90% yield) as a light yellow solid: ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.24 (1 H, s), 3.26 (6 H, s), 1.73 (3 H, s); Mass Spectrum (ESI) *m/e* = 219.9 [M+1 (⁷⁹Br)] and 221.9 [M+1 (⁸¹Br)].

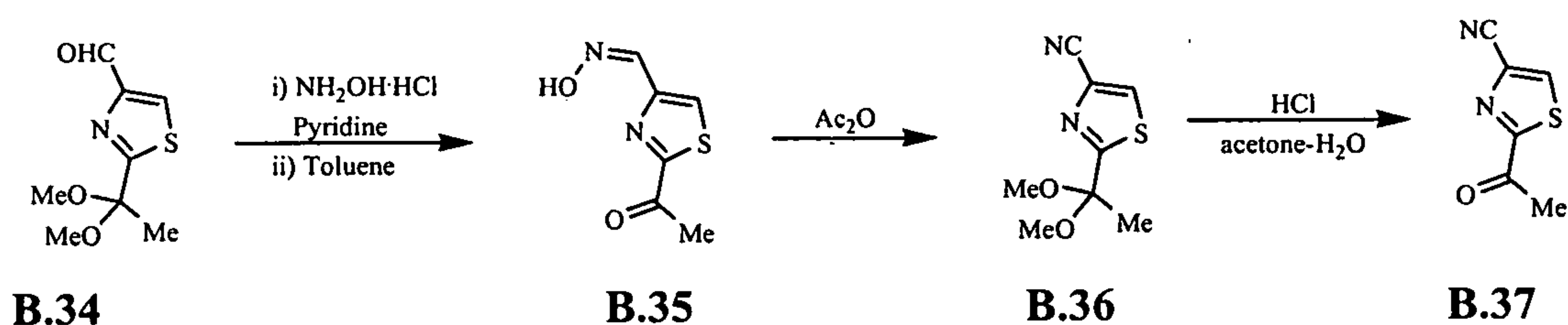


2-(1,1-dimethoxyethyl)thiazole-4-carbaldehyde

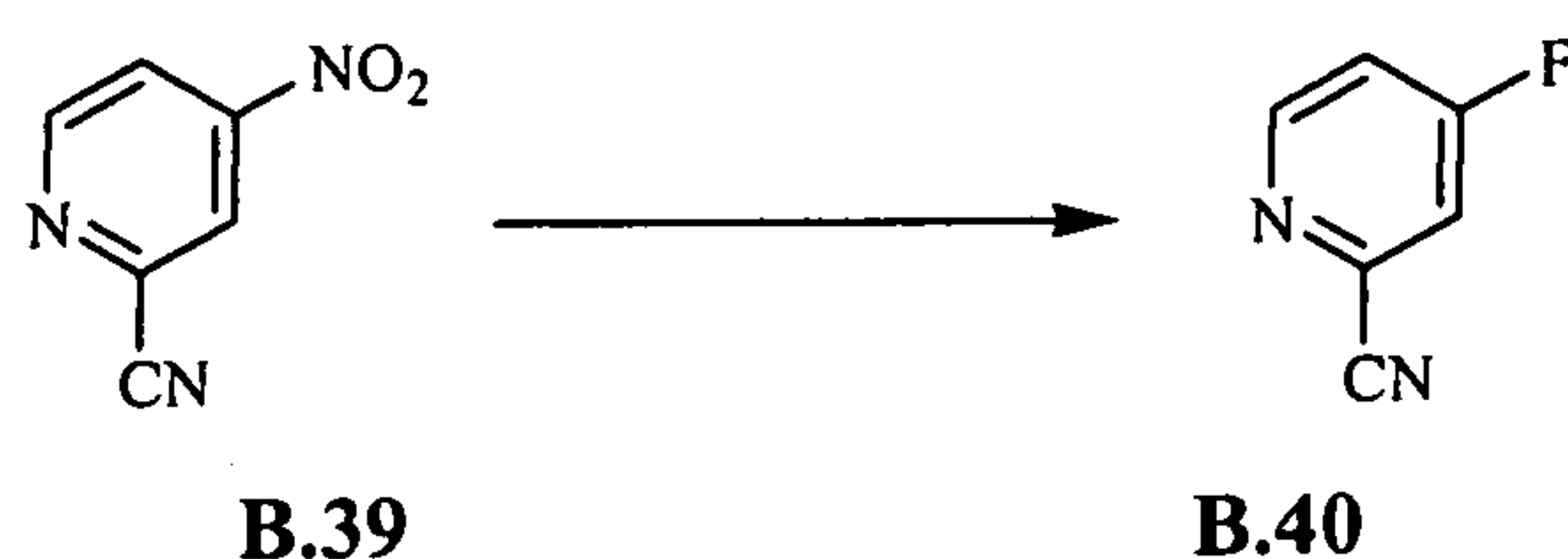
To a solution of 4-bromo-2-(1,1-dimethoxyethyl)thiazole **B.33** (3.753 g, 14.88 mmol) in ether (55 mL) at -78 °C was added dropwise *n*-BuLi (1.6 M sol in hexane, 10.2 mL, 16.37 mmol)

and the mixture was stirred at -78°C . After stirring at -78°C for 30 minutes, a solution of DMF (4.6 mL, 59.53 mmol) in ether (16 mL) was added to the mixture at -78°C and the mixture was stirred at -78°C for 20 minutes and allowed to warm to room temperature. After stirring at room temperature for 3.5 hours, water (50 mL) was added and the aqueous mixture was extracted with ethyl acetate (50 mL x 4). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure to give an orange oil. The product was purified by silica gel column chromatography using 0% to 100% gradient of ethyl acetate in hexane as eluent to give 2-(1,1-dimethoxyethyl)thiazole-4-carbaldehyde **B.34** (1.87 g, 62.4% yield) as a light yellow solid: ^1H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 10.10 (1 H, s), 8.19 (1 H, s), 3.29 (6 H, s), 1.78 (3 H, s); Mass Spectrum (ESI) $m/e = 202.1$ [M+1].

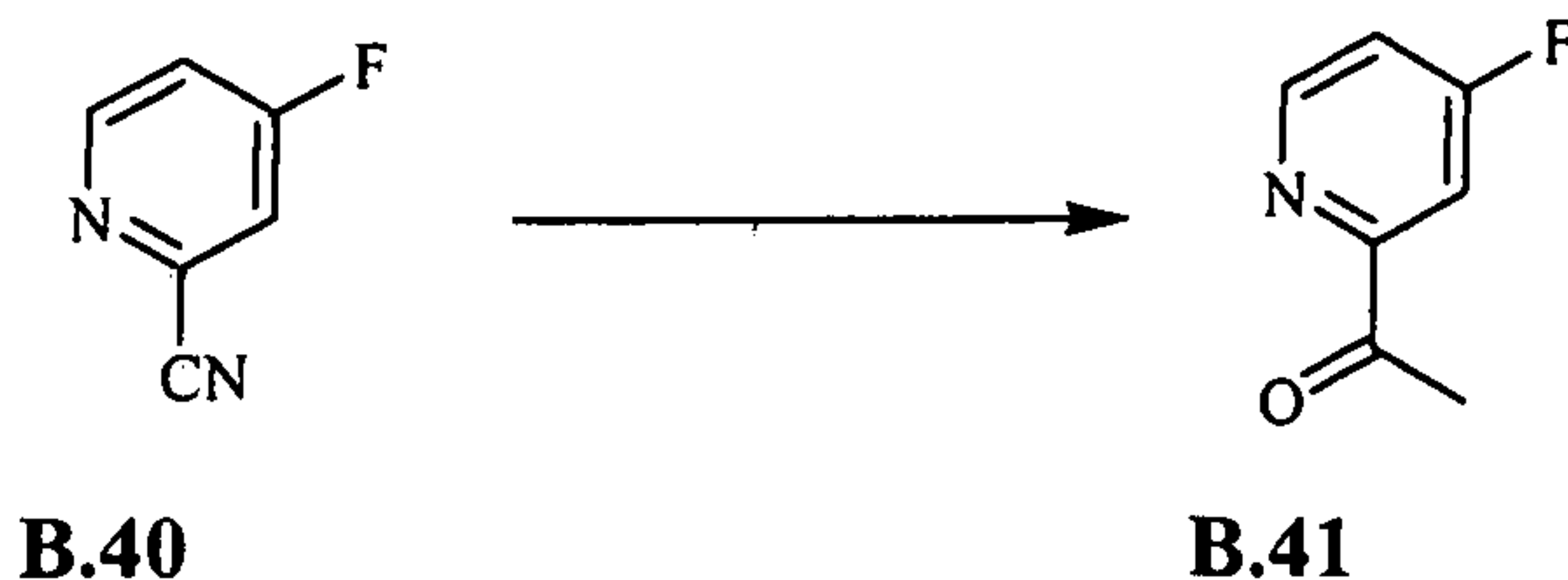
2-(1,1-Dimethoxyethyl)thiazole-4-carbaldehyde (**B.34**) was converted into 2-acetylthiazole-4-carbonitrile **B.37** in three steps by the method used for the preparation of 2-acetylthiazole-5-carbonitrile **B.71**.



4-fluoropicolinonitrile B.40 [Kuduk, S. D.; DiPardo, R. M.; Bock, M. G., *Org. Lett.* 2005, 7, (4), 577-580.]



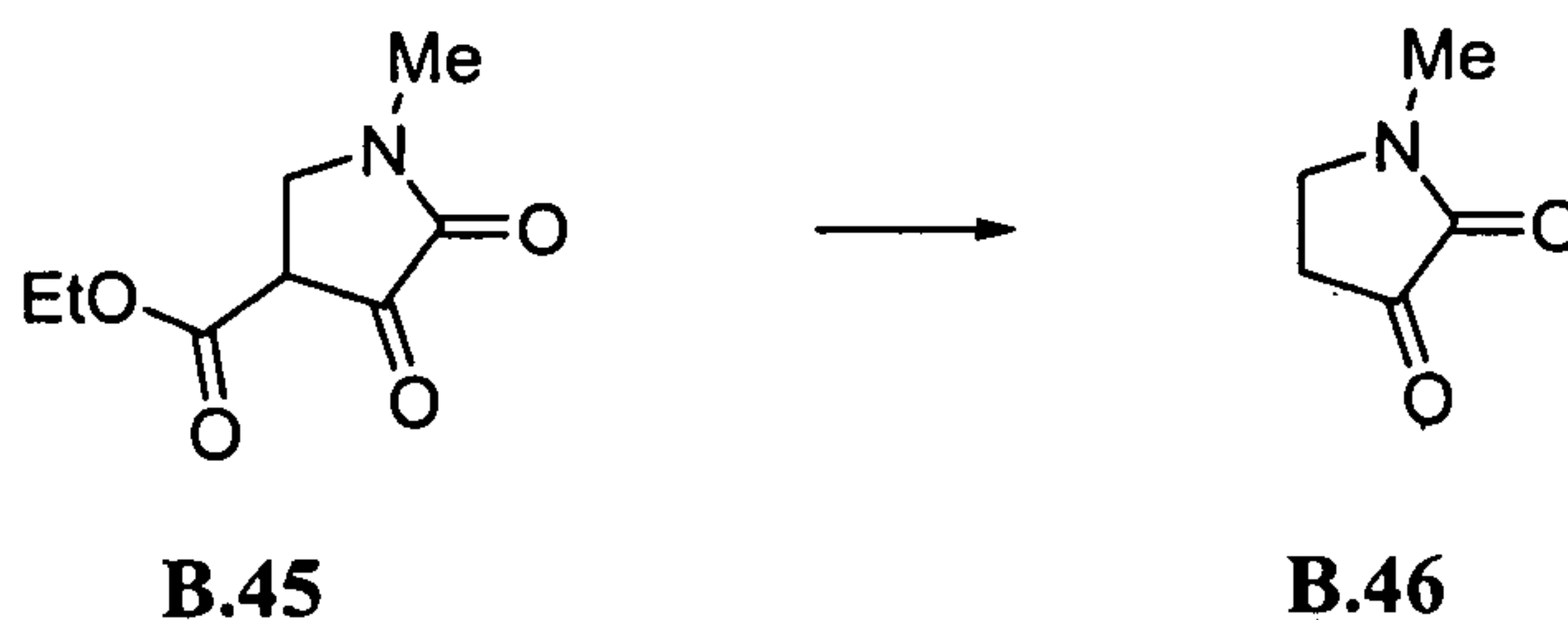
4-nitropicolonitrile **B.39** (5 g, 33.5 mmol) in 64 mL DMF was stirred at room temperature as 67 mL TBAF (1 M in THF, 67 mmol) was added. After 35 minutes, the reaction was poured into 500 mL 1:1 ethyl acetate-water. The organic layer was washed with water and brine, dried over Na_2SO_4 and condensed. The orange-brown residue was purified by flash chromatography (0-10-100% ethyl acetate in hexane) to give 4-fluoropicolinonitrile **B.40** (2.78 g, 68%). ^1H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 8.72 (1 H, dd, $J=7.9, 5.7$ Hz), 7.48 (1 H, dd, $J=8.1, 2.4$ Hz), 7.30 (1 H, ddd, $J=8.1, 5.6, 2.4$ Hz)



1-(4-fluoropyridin-2-yl)ethanone **B.41**

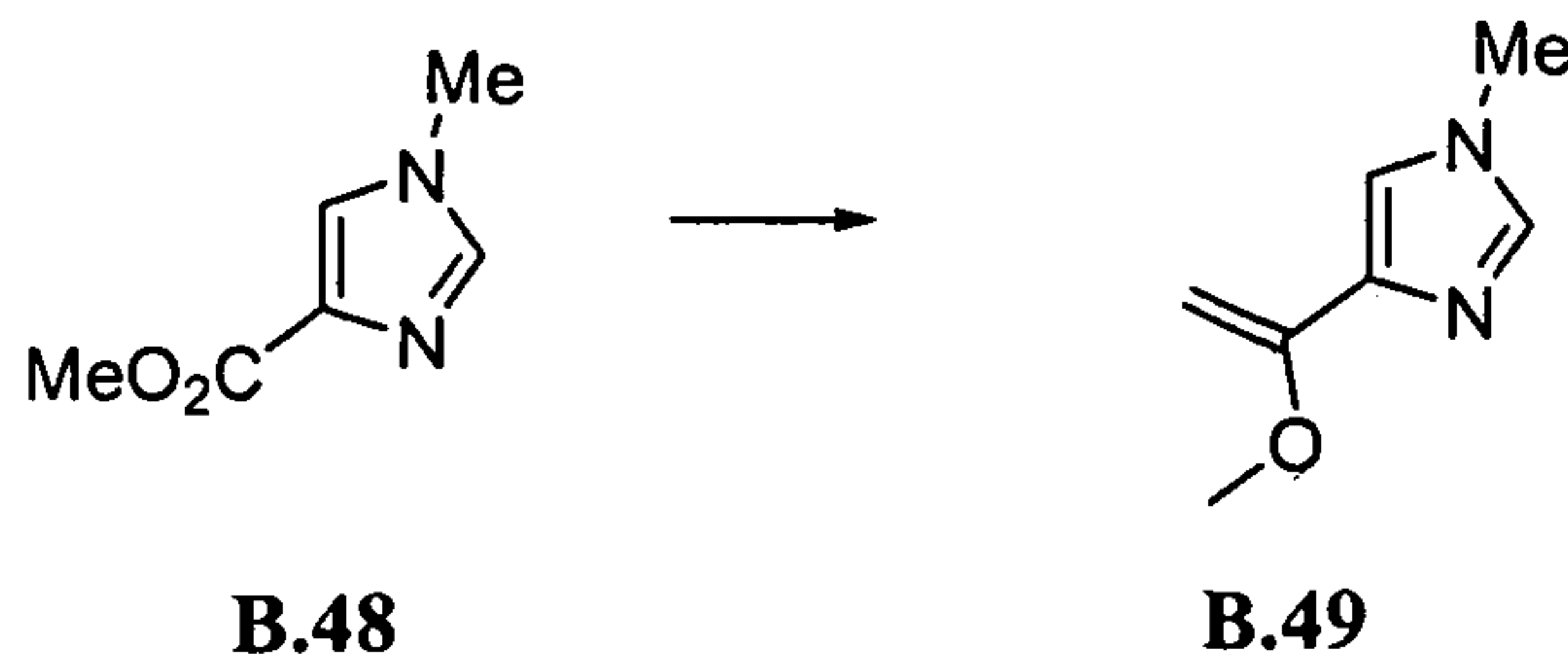
A solution of MeMgCl (3 M in THF, 22.5 mL, 67.5 mmol) was added to a stirring solution of 4-fluoropicolinonitrile **B.40** (2.75 g, 22.5 mmol) in 56 mL THF at 0 °C. The mixture stirred for 3 hours, gradually warming to room temperature. Sat. aq. NH₄Cl (5 mL) was added to quench the reaction, and the mixture was partitioned between ethyl acetate and water. The aqueous layer was further extracted with ethyl acetate, and the combined organic extracts were dried over Na₂SO₄ and condensed. Purification by flash chromatography (0-100% ethyl acetate in hexane) afforded 1-(4-fluoropyridin-2-yl)ethanone **B.41** (1.46g, 47%) as a yellow crystalline solid. ¹H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 8.67 (1 H, dd, *J*=8.1, 5.4 Hz), 7.77 (1 H, dd, *J*=9.3, 2.4 Hz), 7.21 (1 H, ddd, *J*=8.1, 5.5, 2.6 Hz), 2.74 (3 H, s)

1-methyl-2,3-pyrrolidinedione **B.46**



Ethyl 1-methyl-4,5-dioxo-3-pyrrolidinecarboxylate **B.45** (6.76g, 33.6mmol) [Southwick, P. L., E. P. Previc, et al. (1956). *J. Org. Chem.* **21**(10): 1087-1095.] was dissolved in 76ml of acetic acid and 11ml of 48% by weight HBr. The solution was heated to a gentle reflux for 1 hour. The reaction was then poured into 400ml of ice and stirred until the ice melted. The aqueous layer was extracted with chloroform. The pH of the aqueous layer was adjusted to ~7 with sat. NaHCO₃ and then extracted with dichloromethane. The organic layer was dried over MgSO₄ then concentrated under vacuum. The residue was triturated with ether and filtered to remove solids. The filtrates were concentrated under vacuum to give a reddish oil which was purified by CombiFlash chromatography eluting with acetonitrile/0.1% TFA. The fractions containing the product were concentrated under vacuum to give 1-methyl-2,3-pyrrolidinedione **B.46** (214mg).

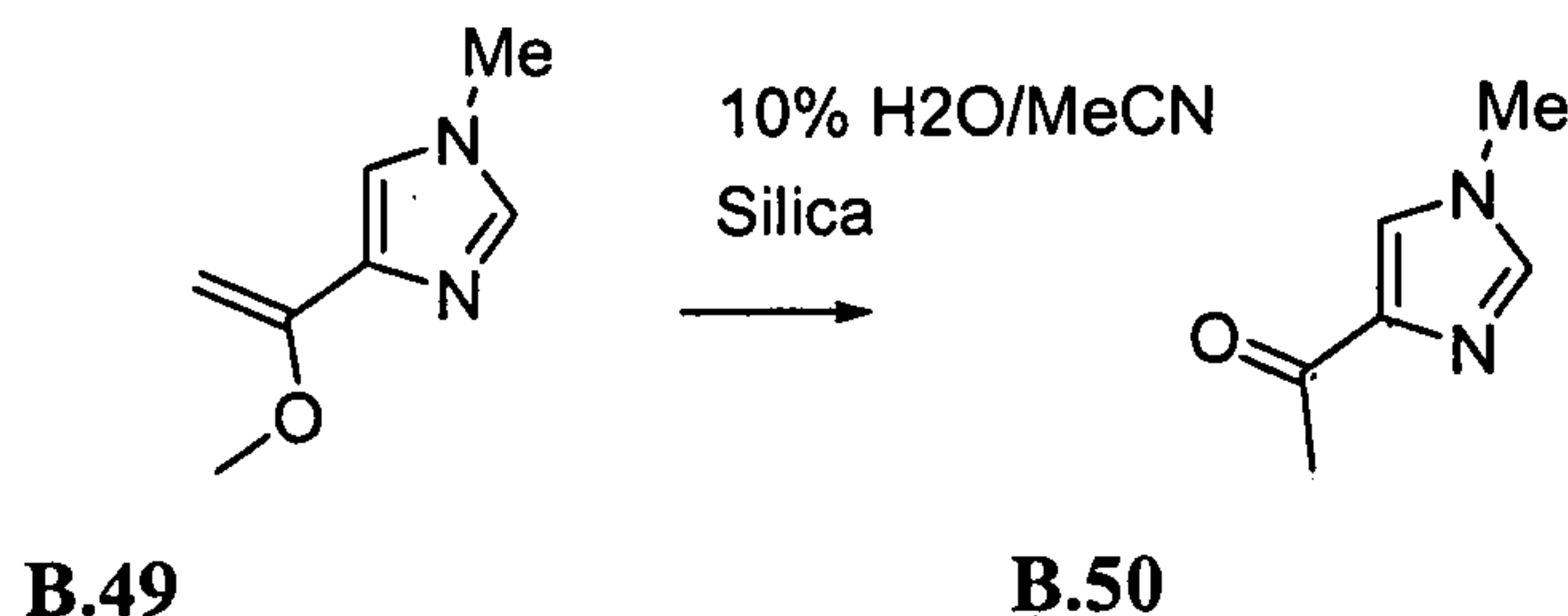
¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 3.56 (2 H, t, *J*=5.4 Hz), 2.97 (3 H, s), 2.62 (2 H, t, *J*=5.5 Hz)



4-(1-methoxyethenyl)-1-methyl-1H-imidazole **B.49**

Methyl 1-methyl-1H-imidazole-4-carboxylate **B.48** (250mg, 1.178mmol) was dissolved in 5ml of anhydrous pyridine and cooled to ~0°C under an atmosphere of nitrogen. Tebbe Reagent (0.5M in toluene) (3.57mL) was added slowly. The reaction was warmed to room temperature and stirred 2 hours. After cooling to 0°C, the reaction was quenched with 1ml of 40%NaOH and 2ml of water. The solution was diluted with 10ml of pyridine and stirred at r.t. for 1 hour. Solvents were removed under vacuum. The residue obtained was partially dissolved in methanol and filtered. The filtrate was then purified by CombiFlash chromatography eluting with a gradient of 2%methanol/dichloromethane to 10%methanol/dichloromethane. The fractions containing the product were combined and concentrated under vacuum to give 4-(1-methoxyethenyl)-1-methyl-1H-imidazole **B.49** as a brownish oil (249mg).

ESI-MS: $M + H^+$ 139.1 *m/z*

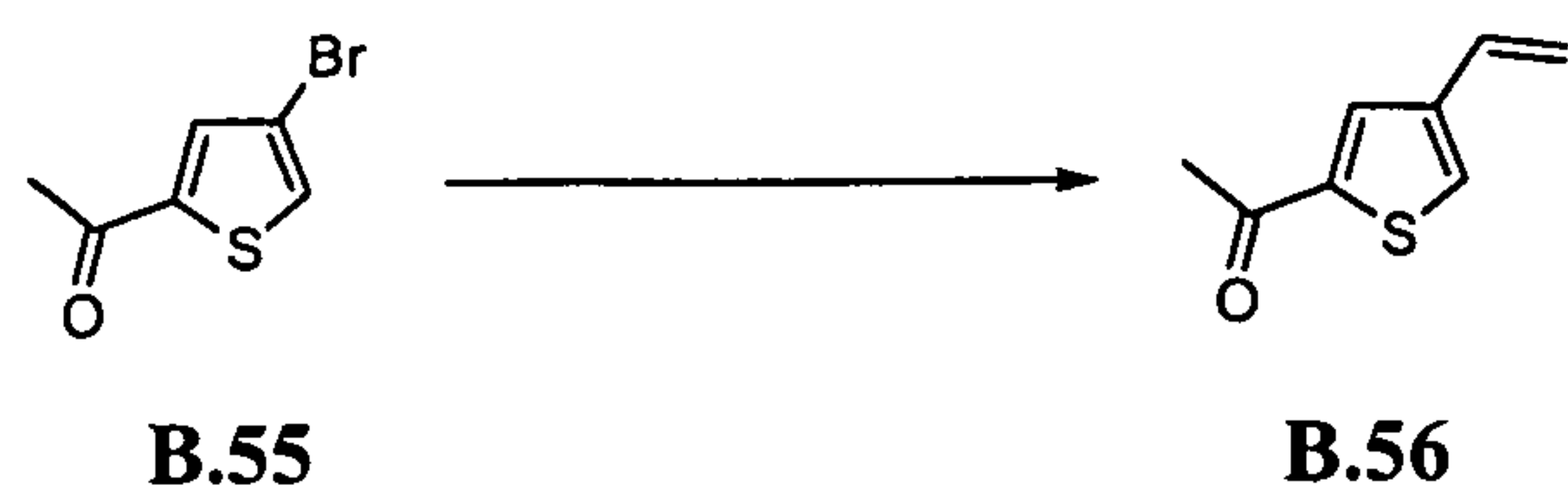


1-(1-methyl-1H-imidazol-4-yl)ethanone **B.50**

4-(1-methoxyethenyl)-1-methyl-1H-imidazole) **B.49** (249mg, 1.81mmol), was combined with 1.9 g of silica gel in 18ml of acetonitrile and 2ml of water. The solution was stirred at room temperature for 20 h and then diluted with 20ml of acetonitrile before filtering off the silica gel. The silica gel was washed with dichloromethane. The filtrate was concentrated under vacuum to give 1-(1-methyl-1H-imidazol-4-yl)ethanone **B.50** (70mg, 38%) as a white solid.

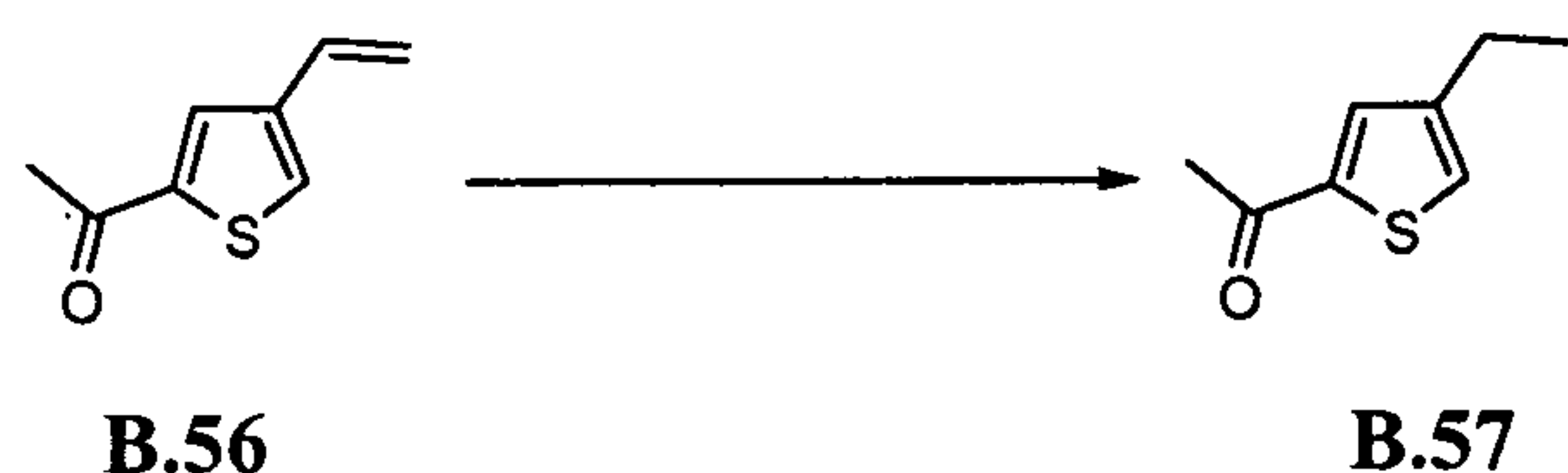
¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 7.85 (1 H, s), 7.70 (1 H, s), 3.70 (3 H, s), 2.37 (3 H, s)

1-(4-vinylthiophen-2-yl)ethanone **B.56**



A mixture of 1-(4-bromothiophen-2-yl)ethanone **B.55** (2 g, 9.75 mmol), 1,4-dioxane (32 mL), tributyl(vinyl)stannane (3.13 mL, 10.73 mmol), and Pd(PPh₃)₄ (0.5635 g, 0.49 mmol) was stirred at 100 °C for 14.5 hours. The mixture was concentrated under reduced pressure and purified by silica gel column chromatography using 0% to 40% gradient of ethyl acetate in hexane as eluent to give 1-(4-vinylthiophen-2-yl)ethanone **B.56** (1.22 g, 82.2% yield) as a yellow oil: ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.18 (1 H, s), 7.91 (1 H, s), 6.71 (1 H, dd, *J*=17.6, 10.8 Hz), 5.82 (1 H, d, *J*=17.6 Hz), 5.28 (1 H, d, *J*=11.0 Hz), 2.55 (3 H, s); Mass Spectrum (ESI) *m/e* = 153.1 [M+1].

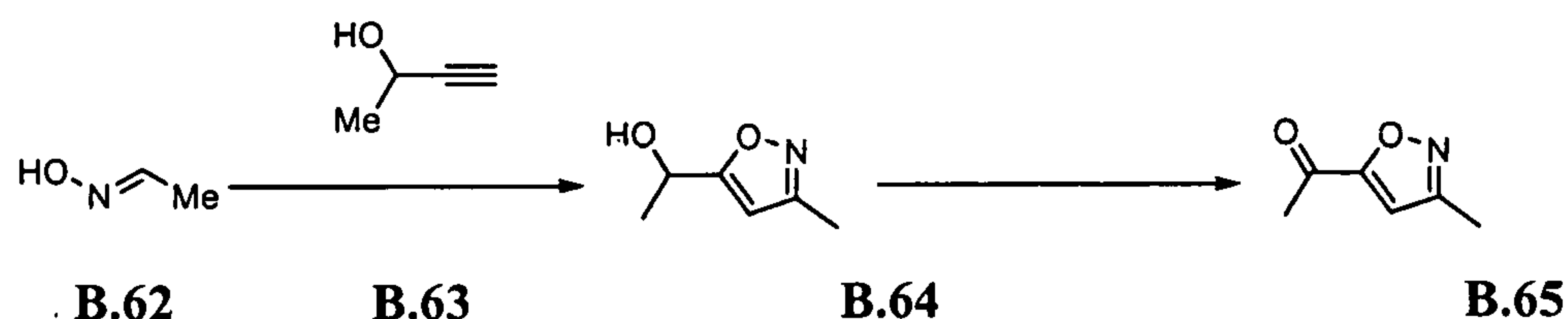
1-(4-ethylthiophen-2-yl)ethanone **B.57**



To a solution of 1-(4-vinylthiophen-2-yl)ethanone **B.56** (0.674 g, 4.43 mmol) in methanol (15 mL) was added 10% Pd/C (0.4714 g, 0.443 mmol) and the mixture was stirred under H₂ gas for 1 hour. The mixture was filtered through a Celite pad and the pad was washed with methanol. The filtrate was concentrated under reduced pressure to give 1-(4-ethylthiophen-2-yl)ethanone **B.57** (0.585 g, 85.7%) as a colorless oil: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.81 (1 H, s), 7.61 (1 H, s), 2.61 (2 H, q, *J*=7.4 Hz), 2.49 (3 H, s), 1.19 (3 H, t, *J*=7.6 Hz); Mass Spectrum (ESI) *m/e* = 155.1 [M+1].

1-(3-methylisoxazol-5-yl)ethanone **B.65**

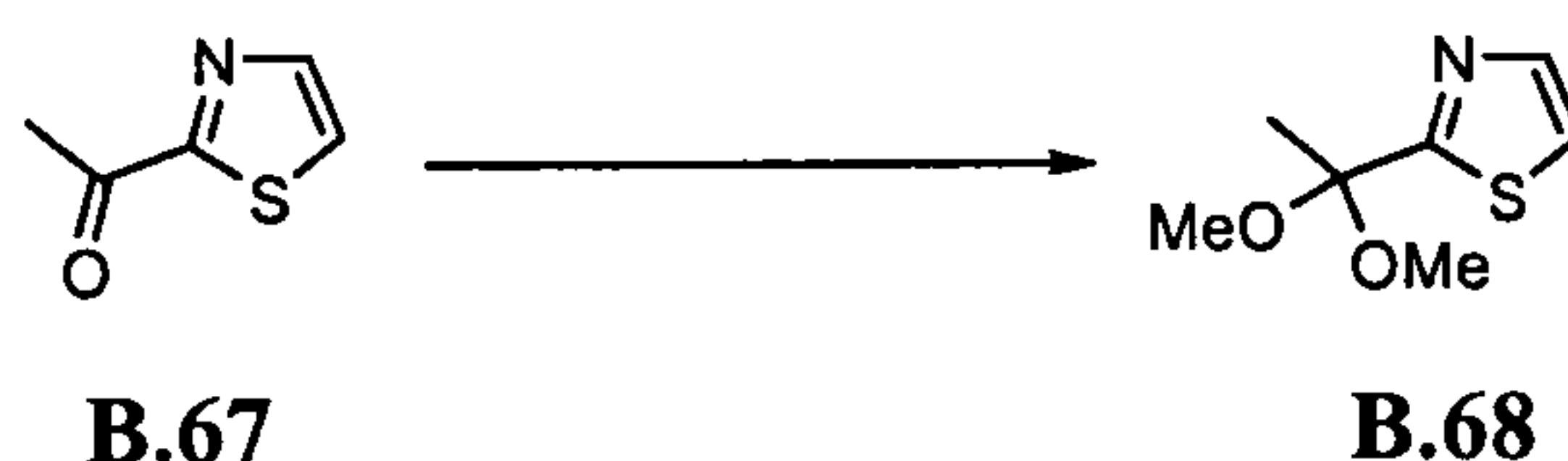
[Felman, S. W., I. Jirkovsky, et al. (1992). *J. Med. Chem.* 35(7): 1183-1190.]



To a solution of acetaldoxime **B.62** (10 g, 0.169 mmol), but-3-yn-2-ol **B.63** (11.84 g, 0.169 mmol), and triethylamine (2.4 mL, 0.0169 mmol) in dichloromethane (400 mL) at 0 °C was added sodium hypochlorite solution (6% aqueous, 440 mL) over 1 hour and the mixture was

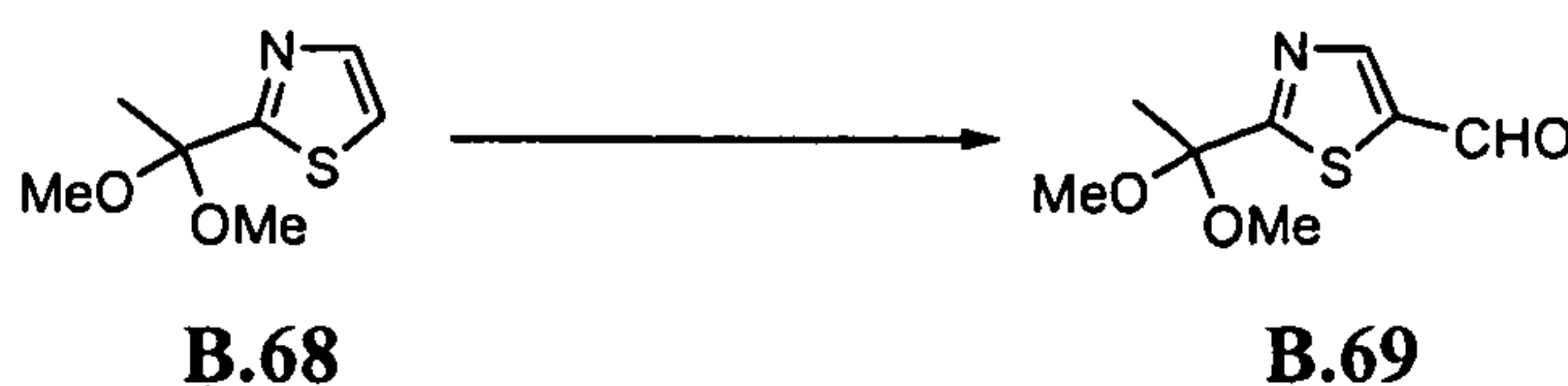
allowed to warm to room temperature, and stirred at room temperature for 19 h. The organic layer was separated. The aqueous layer was extracted with dichloromethane (100 mL x 2). The combined organic layers were washed with brine (200 mL x 1), dried over MgSO_4 , filtered, and concentrated under reduced pressure to give 1-(3-methylisoxazol-5-yl)ethanol **B.64** as a yellow oil. The product was used directly for the next step. To a solution of 1-(3-methylisoxazol-5-yl)ethanol **B.64** (9.54 g, 75.04 mmol) in acetone (417 mL) at 0 °C were added dropwise a solution of CrO_3 (19.06 g, 190.6 mmol) in water and 6 N H_2SO_4 (37.5 mL, 225.1 mmol) over 10 minutes. The mixture was allowed to warm to room temperature. After stirring at room temperature for 2.5 hours, saturated aqueous NaCl (100 mL) was added to the mixture. The aqueous mixture was extracted with dichloromethane (100 mL x 2). The combined organic layers were washed with brine (100 mL x 3), dried over MgSO_4 , filtered, and concentrated under reduced pressure to give a yellow solid. The yellow solid was purified by silica gel column chromatography using 0% to 50% gradient of ethyl acetate in hexane as eluent to give 1-(3-methylisoxazol-5-yl)ethanone **B.65** (2.57 g, 27.3% overall yield over two steps): ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 7.18 (1 H, s), 2.53 (3 H, s), 2.32 (3 H, s); Mass Spectrum (ESI) $m/e = 126.2$ [$\text{M}+1$].

2-(1,1-dimethoxyethyl)thiazole **B.68**



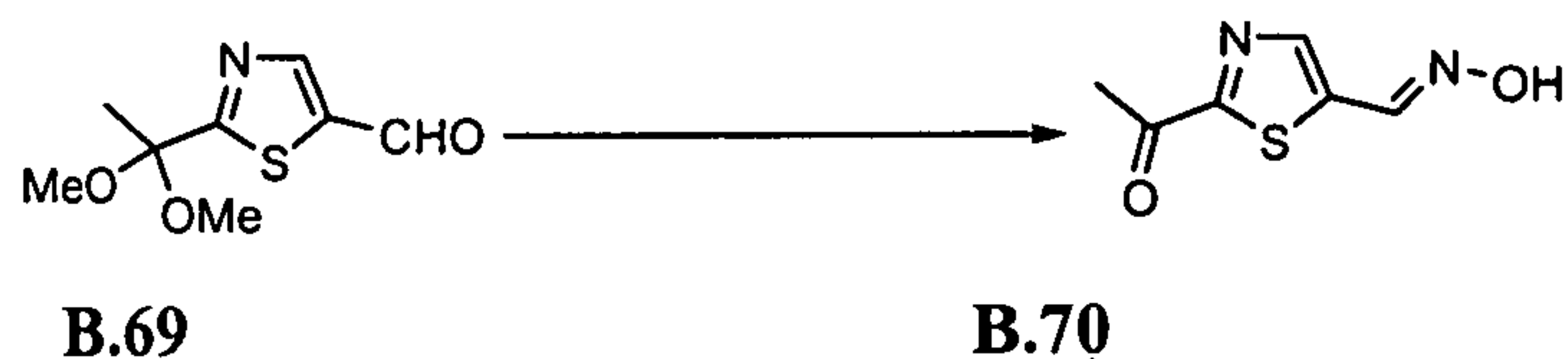
To a solution of 1-(thiazol-2-yl)ethanone **B.67** (10 g, 78.63 mmol) in dry methanol (260 mL) was added trimethyl orthoformate (86 mL, 786.35 mmol) and *p*-TsOH (13.462 g, 70.77 mmol). The mixture was heated at reflux for 23 hours. The mixture was poured into saturated aqueous NaHCO_3 (500 mL). The aqueous layer was extracted with ethyl acetate (200 mL x 4). The combined organic layers were washed with 1 N aqueous NaOH (300 mL), brine (300 mL x 1), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give a yellow oil. The product was purified by silica gel column chromatography using 25% ethyl acetate in hexane as eluent to give 2-(1,1-dimethoxyethyl)thiazole **B.68** (7.91 g, 58.1% yield) as a light yellow oil: ^1H NMR (400 MHz, $\text{CHLOROFORM}-d$) δ ppm 7.83 (1 H, d, $J=3.1$ Hz), 7.32 (1 H, d, $J=3.1$ Hz), 3.26 (6 H, s), 1.74 (3 H, s); Mass Spectrum (ESI) $m/e = 174.1$ [$\text{M}+1$].

2-(1,1-dimethoxyethyl)thiazole-5-carbaldehyde **B.69**

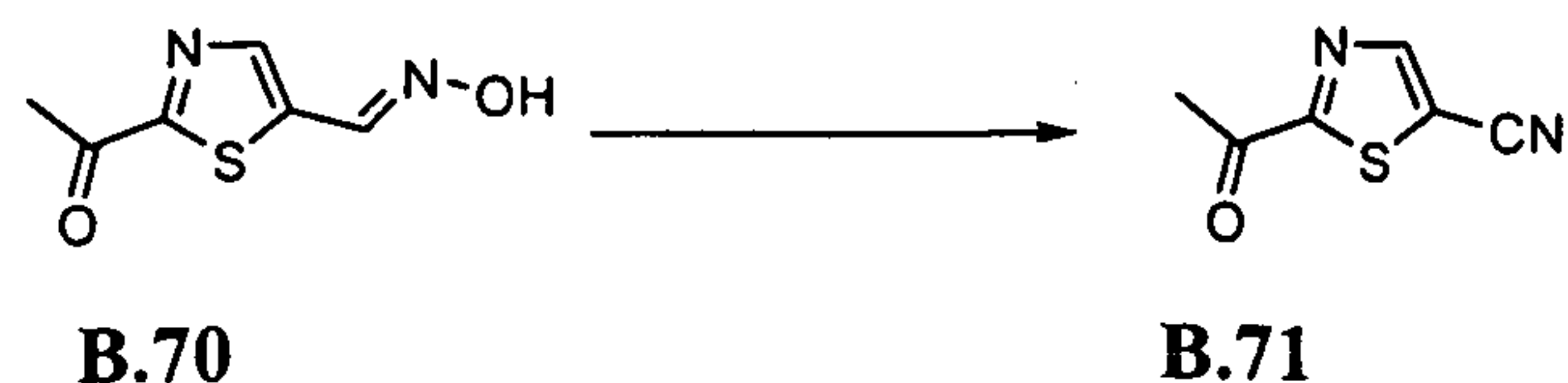


n-BuLi (1.6 M sol in hexane, 14.4 mL, 23.04 mmol) was added dropwise to a solution of 2-(1,1-dimethoxyethyl)thiazole **B.68** (4 g, 23.09 mmol) in THF (50 mL) at -78 °C. After stirring at -78 °C for 20 minutes, a solution of DMF (3.7 mL, 47.54 mmol) in THF (19 mL) was added and the mixture was stirred at -78 °C for 40 minutes. The reaction was allowed to warm to room temperature and stirred for 16 hours. Saturated aqueous NH₄Cl solution (50 mL) was added and the aqueous mixture was extracted with dichloromethane (100 mL x 4). The combined organic layers were washed with brine (100 mL x 1), dried over MgSO₄, filtered, and concentrated under reduced pressure to give a dark red oil. The product was purified by silica gel column chromatography using 0% to 70% gradient of ethyl acetate in hexane as eluent to give 2-(1,1-dimethoxyethyl)thiazole-5-carbaldehyde **B.69** (2.27 g, 48.9% yield) as a yellow solid: ¹H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 10.04 (1 H, s), 8.42 (1 H, s), 3.27 (6 H, s), 1.74 (3 H, s); Mass Spectrum (ESI) m/e = 202.0 [M+1].

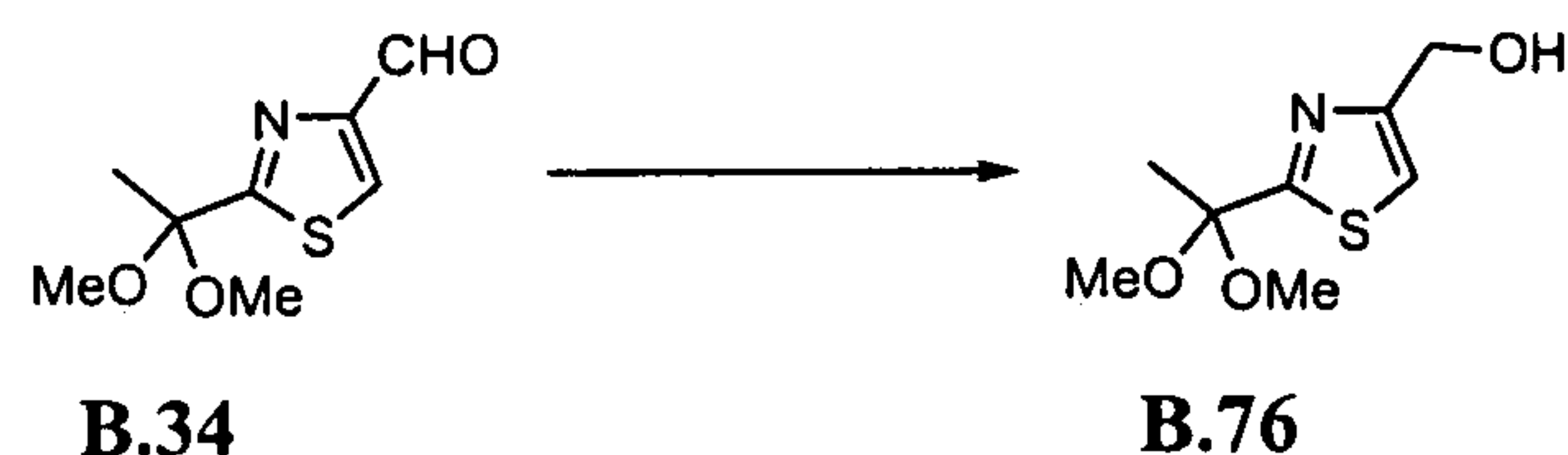
2-acetylthiazole-5-carbaldehyde oxime **B.70**



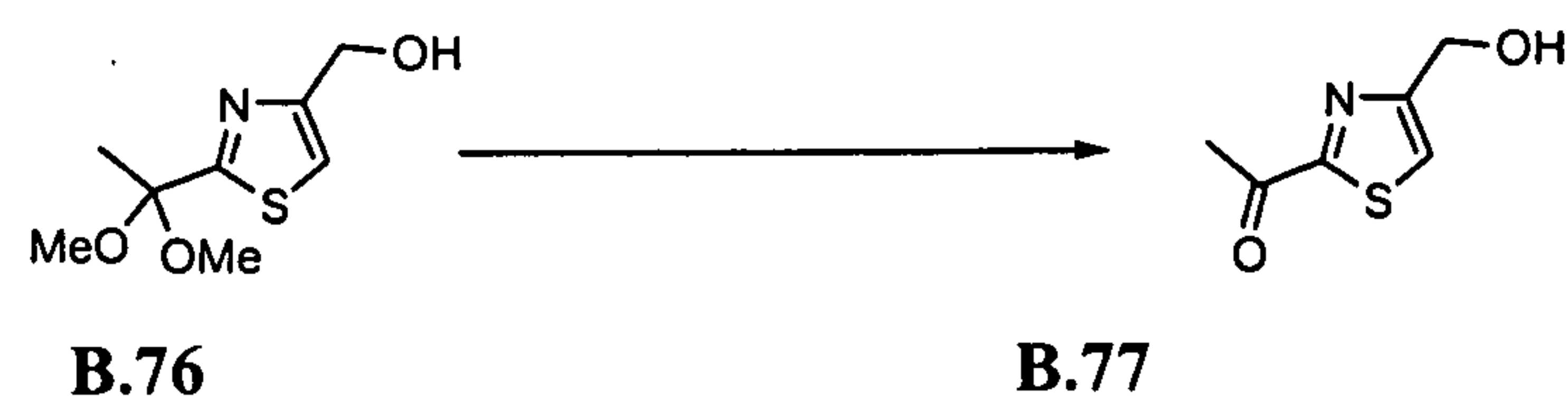
To a mixture of NH₂OH·HCl (0.38 g, 5.47 mmol) and pyridine (0.9 mL) was added 2-(1,1-dimethoxyethyl)thiazole-5-carbaldehyde **B.69** (1.1 g, 5.47 mmol) in installments over 1 minute. The mixture was stirred at room temperature for 20 minutes. Toluene (13 mL) was then added and the mixture was heated at reflux using a Dean-Stark water trap for 2 hours. The mixture was poured into ice water (100 mL) and extracted with ethyl acetate (100 mL x 2). The combined organic layers were washed with brine (100 mL x 1), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give 2-acetylthiazole-5-carbaldehyde oxime **B.70** (0.551 g, 59.2% yield) as an orange solid: ¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 12.77 (1 H, s), 8.44 (1 H, s), 8.14 (1 H, s), 2.65 (3 H, s); Mass Spectrum (ESI) m/e = 171.1 [M+1].

2-acetylthiazole-5-carbonitrile B.71

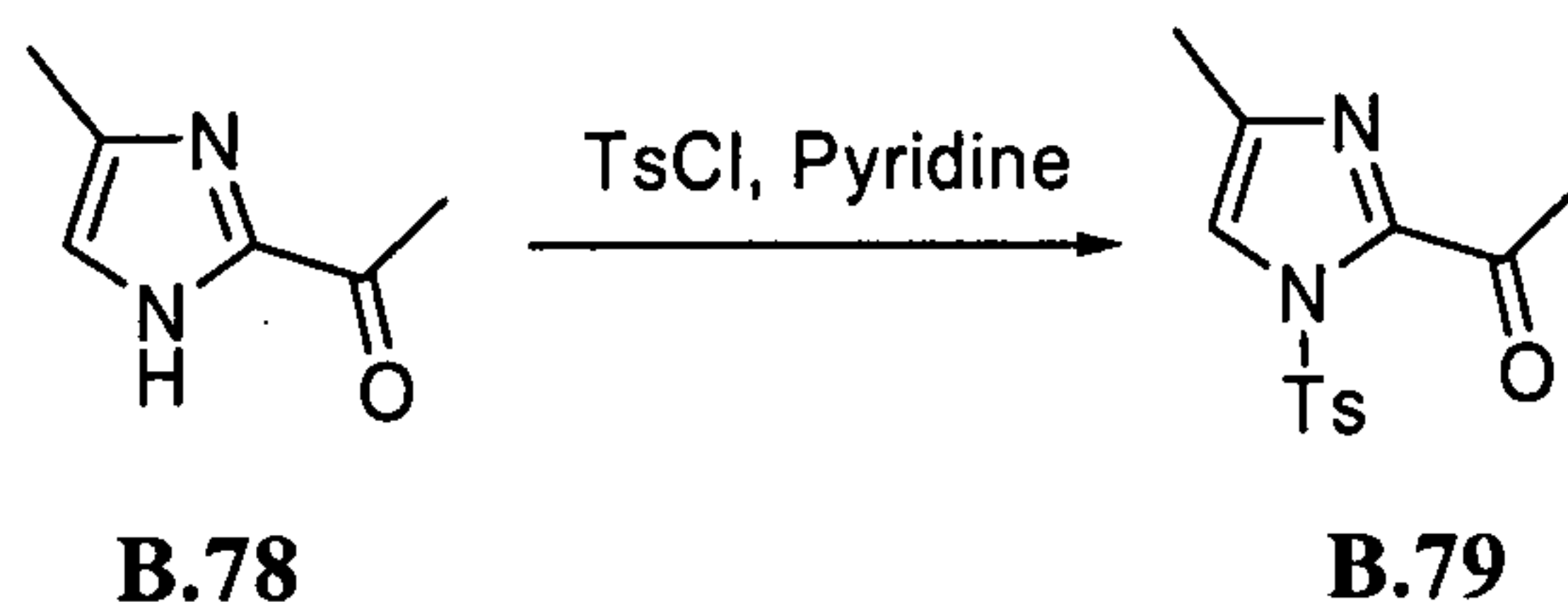
A suspension of 2-acetylthiazole-5-carbaldehyde oxime **B.70** (0.551 g, 3.24 mmol) in acetic anhydride (3 mL) was heated at reflux for 4 hours. The mixture was concentrated under reduced pressure and then treated with cold 2 N aqueous Na_2CO_3 (50 mL). The aqueous mixture was extracted with dichloromethane (50 mL x 3). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give a dark syrup. The product was purified by silica gel column chromatography using 0% to 50% gradient of ethyl acetate in hexane as eluent to give 2-acetylthiazole-5-carbonitrile **B.71** (0.268 g, 54.3% yield) as a light yellow solid: ^1H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 8.40 (1 H, s), 2.76 (3 H, s); Mass Spectrum (ESI) $m/e = 152.9$ [$\text{M}+1$].

(2-(1,1-dimethoxyethyl)thiazol-4-yl)methanol B.76

To a solution of 2-(1,1-dimethoxyethyl)thiazole-4-carbaldehyde **B.34** (0.369 g, 1.83 mmol) in methanol (3.5 mL) at 0 °C was added NaBH_4 (0.0694 g, 1.83 mmol) and the mixture was stirred for 1 hour. To the mixture was added saturated aqueous NH_4Cl (20 mL). The mixture was extracted with dichloromethane (50 mL x 3). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure to give (2-(1,1-dimethoxyethyl)thiazol-4-yl)methanol **B.76** (0.36 g, 96.6% yield) as a white solid: ^1H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.20 (1 H, s), 4.80 (2 H, s), 3.26 (6 H, s), 1.73 (3 H, s); Mass Spectrum (ESI) $m/e = 204.1$ [$\text{M}+1$].

1-(4-(hydroxymethyl)thiazol-2-yl)ethanone

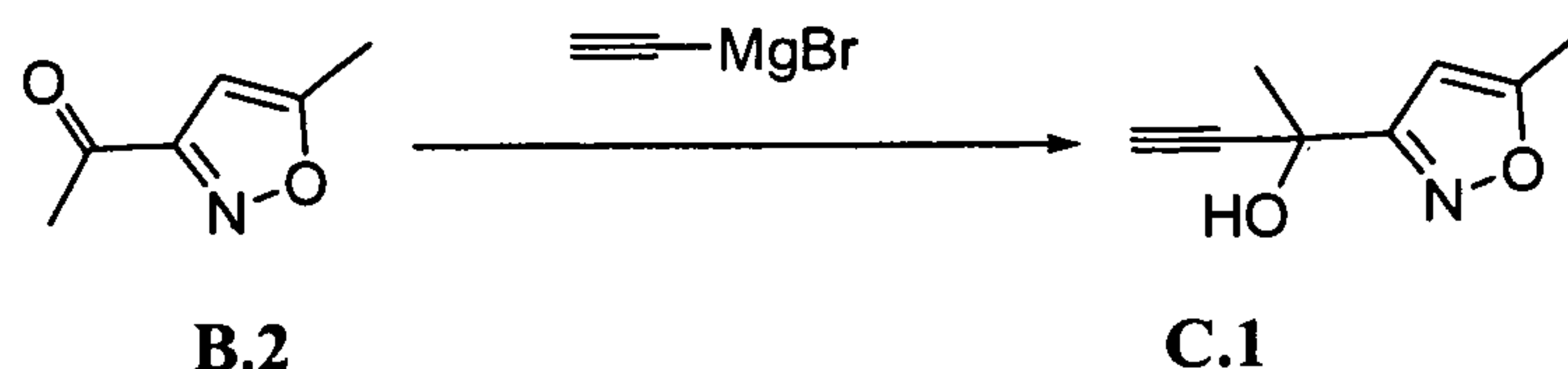
Conc. HCl (0.066 mL, 7.98 mmol) was added dropwise to a solution of (2-(1,1-dimethoxyethyl)thiazol-4-yl)methanol **B.76** (0.36 g, 1.77 mmol) in acetone-water (1:1, 13.6 mL) and the mixture was stirred at room temperature for 1 hour. The acetone was removed under reduced pressure. The mixture was diluted with dichloromethane (50 mL) and washed with saturated aqueous NaHCO₃ (25 mL x 2). The aqueous mixture was extracted with dichloromethane (50 mL x 1). The combined organic layers were washed with brine (50 mL x 1), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give colorless syrup. The product was purified by silica gel column chromatography using 0% to 100% gradient of ethyl acetate in hexane to give 1-(4-(hydroxymethyl)thiazol-2-yl)ethanone **B.77** (0.214 g, 77% yield): Mass Spectrum (ESI) $m/e = 158.1$ [M+1].



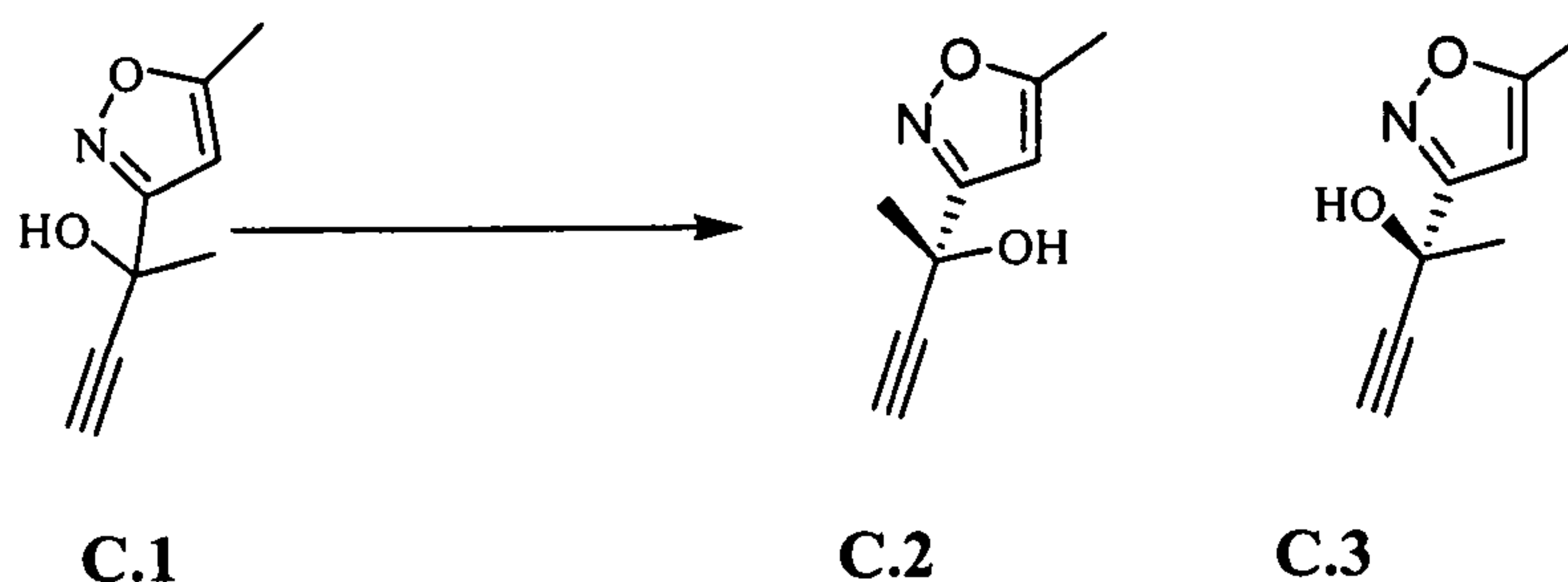
1-(4-Methyl-1-tosyl-1H-imidazol-2-yl)ethanone (B.79). *p*-Toluenesulfonyl chloride (1.275 g, 6.69 mmol) was added to a cold solution of 1-(4-methyl-1H-imidazol-2-yl)ethanone **B.78** (691.7 mg, 5.57 mmol) [Bell, A. S., S. F. Campbell, et al. (1989). *J. Med. Chem.* **32**(7): 1552-1558] in dry pyridine (10.00 mL) . The mixture was allowed to warm to room temperature then heated to 60 °C. Upon completion, the reaction was cooled, diluted with water and extracted three times with ethyl acetate. The ethyl acetate extracts were combined and washed once with brine, then dried over anhydrous sodium sulfate. After filtration and concentration, the residue was used without purification.

GENERAL SCHEMES—SECTION C

This section illustrates procedures for making alkynyl alcohol building blocks.



2-(5-methylisoxazol-3-yl)but-3-yn-2-ol C.1 To a stirring solution of ethynylmagnesium bromide (0.5 M in THF, 144 mL, 72 mmol) at 0 °C was added 1-(5-methylisoxazol-3-yl)ethanone (6.0 g, 48 mmol) **B.2** in THF (96 mL) slowly. The reaction was allowed to warm to room temperature and stirred for 3 hours. After being quenched with conc. aq. NH₄Cl (150 mL), the THF was removed *in vacuo* and the aqueous residue was extracted with ethyl acetate (100 mL x 2). The combined organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure to give a dark brown oil. The dark brown oil was purified by silica gel column chromatography using 10% of ethyl acetate in hexane as eluent to give 2-(5-methylisoxazol-3-yl)but-3-yn-2-ol **C.1** (4.16 g, 57% yield): ¹H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 3.15 (1 H, br. s.), 2.63 (1 H, s), 2.42 (3 H, s), 1.86 (3 H, s); Mass Spectrum (ESI) *m/e* = 152.1 [M+1].

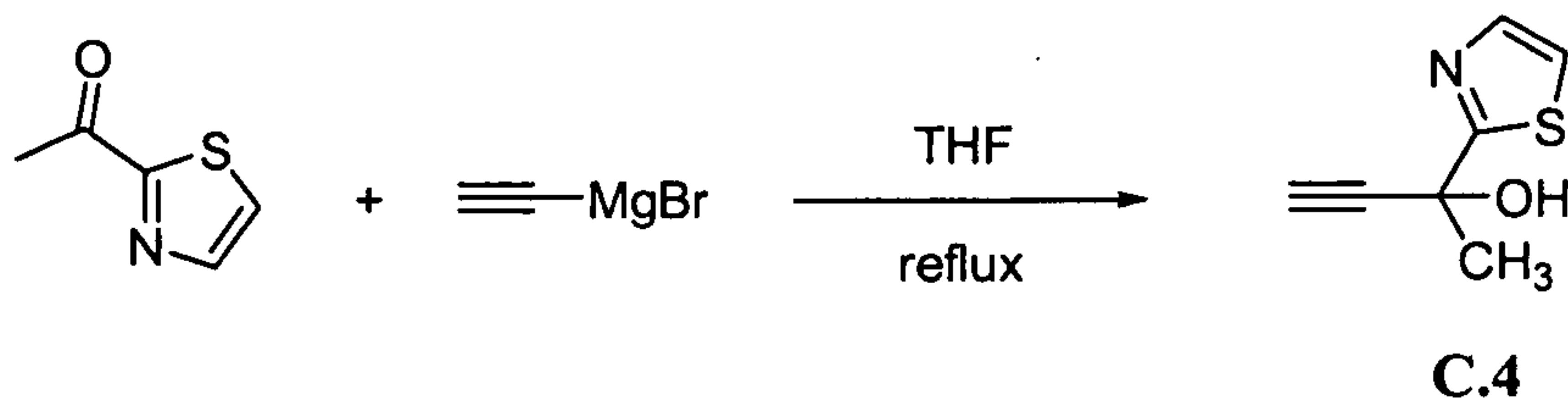


(R)-2-(5-methylisoxazol-3-yl)but-3-yn-2-ol C.2 and (S)-2-(5-methylisoxazol-3-yl)but-3-yn-2-ol C.3

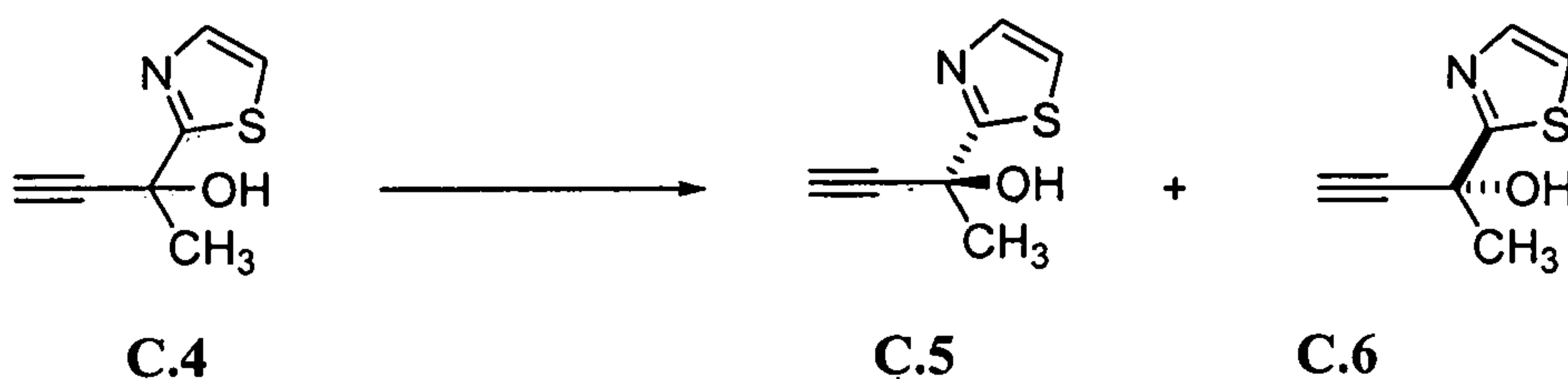
The racemic mixture **C.1** was separated on preparative chiral column (Chiralcel OD-H column) using isopropanol and hexane. The stereochemistry of each enantiomer was confirmed after conversion of **C.2** to **14** in Example 14 and **C.3** to **15** in Example 15. Based on the biochemical potency of **14** and **15**, compared to examples prepared from component **C.5** and **C.6**, the stereochemistry was confirmed as the first eluted enantiomer **C.2** as R-isomer and the second eluted enantiomer **C.3** as S-isomer.

(R)-2-(5-methylisoxazol-3-yl)but-3-yn-2-ol C.2: Mass Spectrum (ESI) $m/e = 152.1$ ($M+1$); $[\alpha]_D = -8.6$ ($c=0.14$ in methanol)

(S)-2-(5-methylisoxazol-3-yl)but-3-yn-2-ol C.3: Mass Spectrum (ESI) $m/e = 152.1$ ($M+1$); $[\alpha]_D = +11.6$ ($c=0.19$ in methanol)

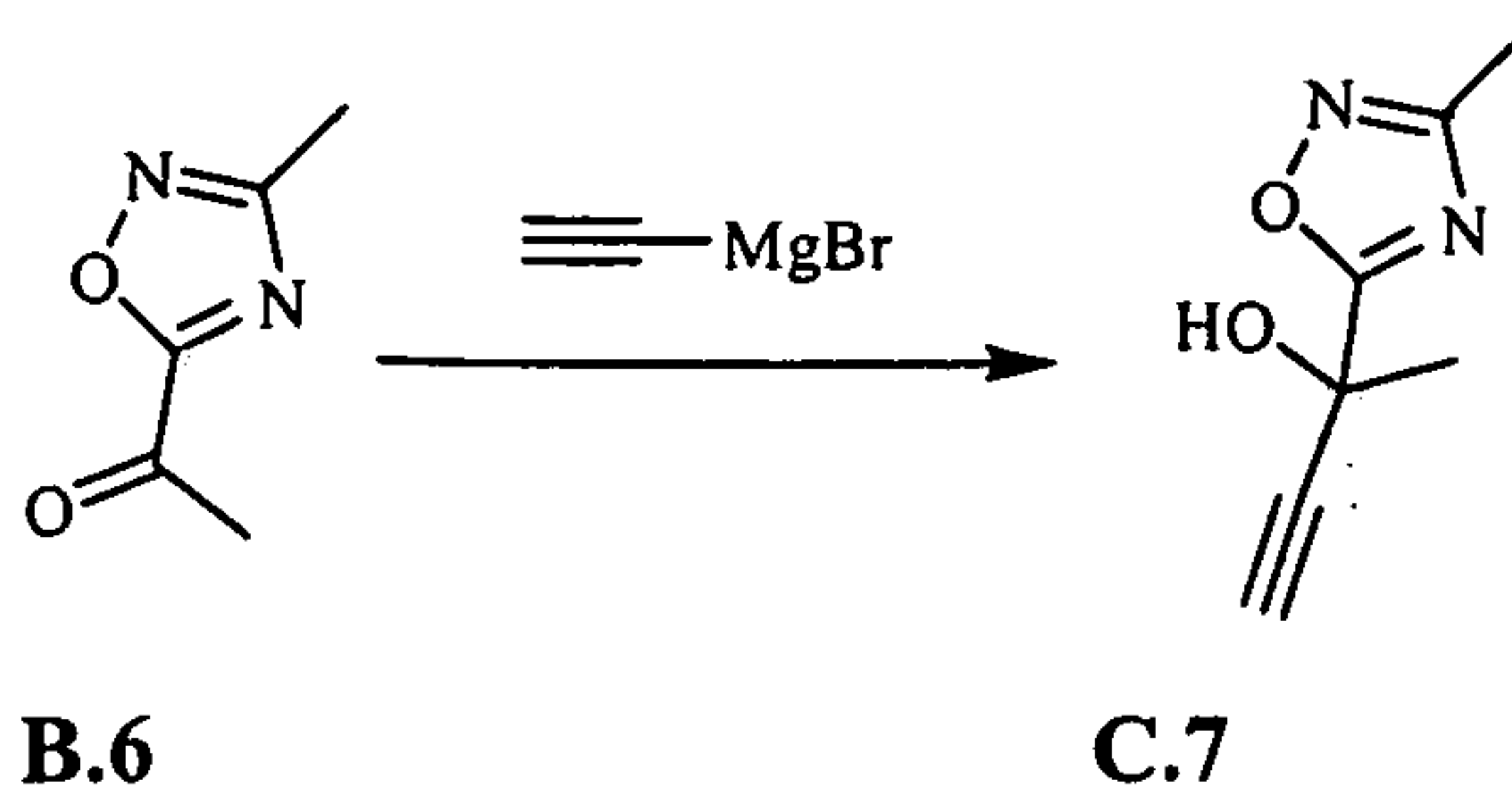


2-(Thiazol-2-yl)but-3-yn-2-ol C.4 : To a solution of 0.5 M ethynylmagnesium bromide (126 mL, 63 mmol) was added solution of 2-acetylthiazole (7.72 g, 60 mmol) in THF (60 mL) at room temperature then the mixture was refluxed for 30 min. The mixture was poured into iced 2N HCl (36 mL) and extracted with ethyl ether. The organic layers were washed with brine, dried, and concentrated. The residue was washed with dichloromethane/hexane co-solvent to give the titled compound **C.4** as white solid (8.45 g, 92%). ^1H NMR (400 MHz, CDCl_3) δ 8.02 (1H, d, $J = 3.0$ Hz), 7.69 (1H, d, $J = 3.0$ Hz), 2.76 (3H, s) ppm; LCMS-ESI (POS), M/Z , $M+1$: Found 154.1, Calculated 154.1.



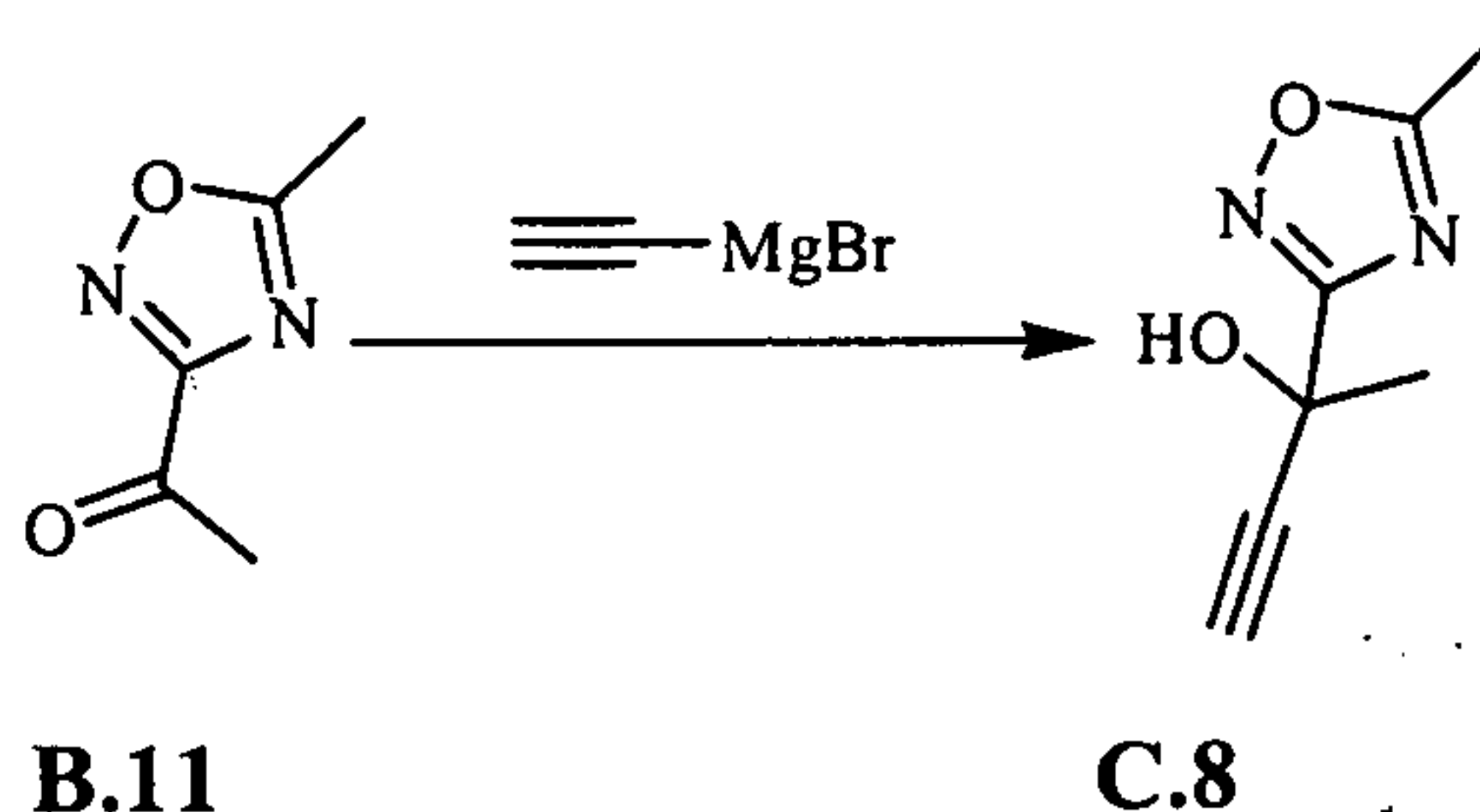
(R)-2-(Thiazol-2-yl)but-3-yn-2-ol: Racemic 2-(thiazol-2-yl)but-3yn-2-ol was resolved using chiral-HPLC (column: chiralcel-OD, 5 cm x 50 cm, 20 μ) eluting with 7% iso-propanol in hexane (flow rate: 100 mL/min). The first eluting compound is **(S)-2-(thiazol-2-yl)but-3-yn-2-ol C.5:** $[\alpha]_D = +37.6$ in methanol. Its absolute structure was determined by crystal-structure X-ray analysis.

The second eluting compound is **(R)-2-(thiazol-2-yl)but-3-yn-2-ol C.6 :** $[\alpha]_D = -30.4$; -34.3 in methanol; ^1H NMR (400 MHz, CDCl_3) δ 8.02 (1H, d, $J = 3.0$ Hz), 7.69 (1H, d, $J = 3.0$ Hz), 2.76 (3H, s) ppm; LCMS-ESI (POS), M/Z , $M+1$: Found 154.1, Calculated 154.1.



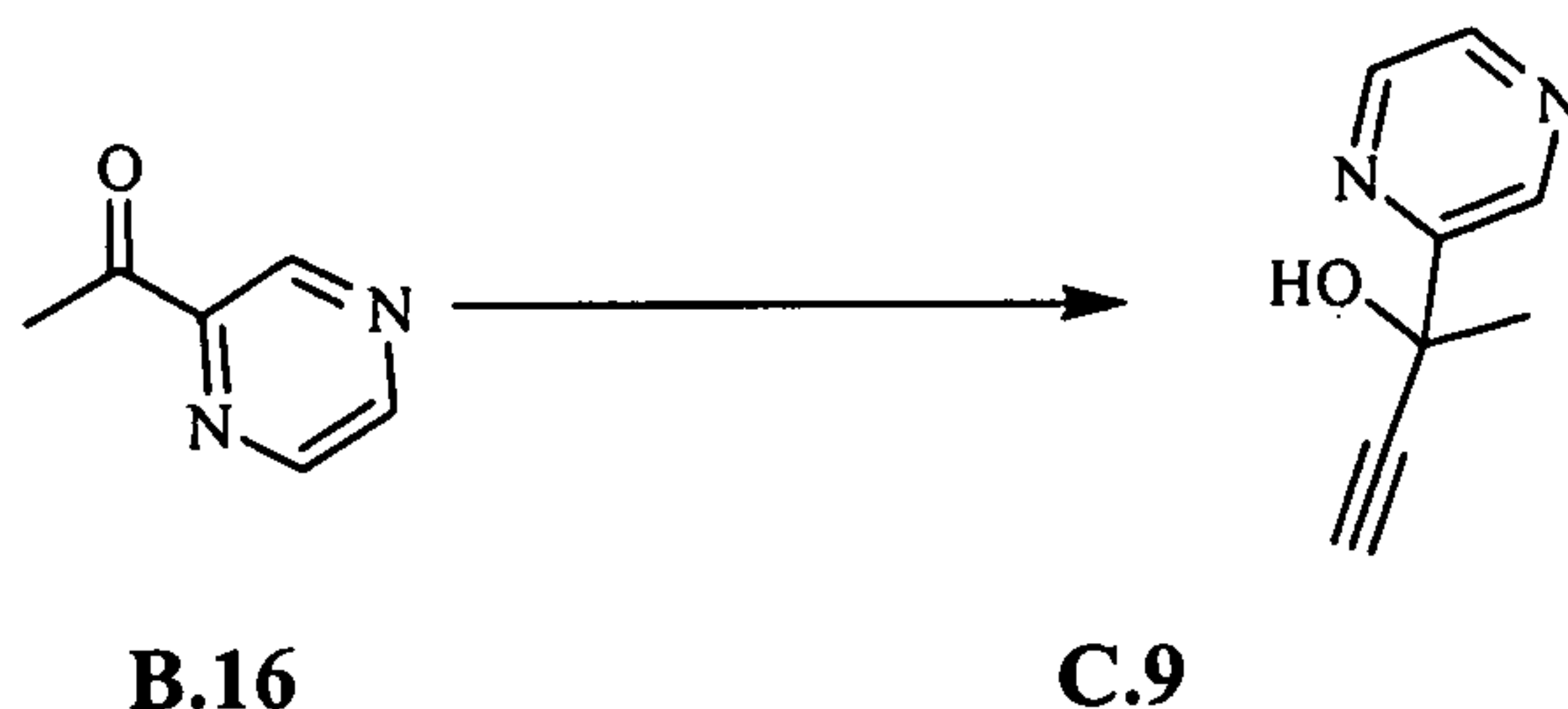
2-(3-methyl-1,2,4-oxadiazol-5-yl)but-3-yn-2-ol C.7 was prepared from **B.6** in 42% yield by the procedure used for compound **C.1**.

¹H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 3.87 (1 H, br. s.), 2.71 (1 H, s), 2.44 (3 H, s), 1.96 (3 H, s) Mass Spectrum (ESI) $m/e = 153.1$ (M+1)



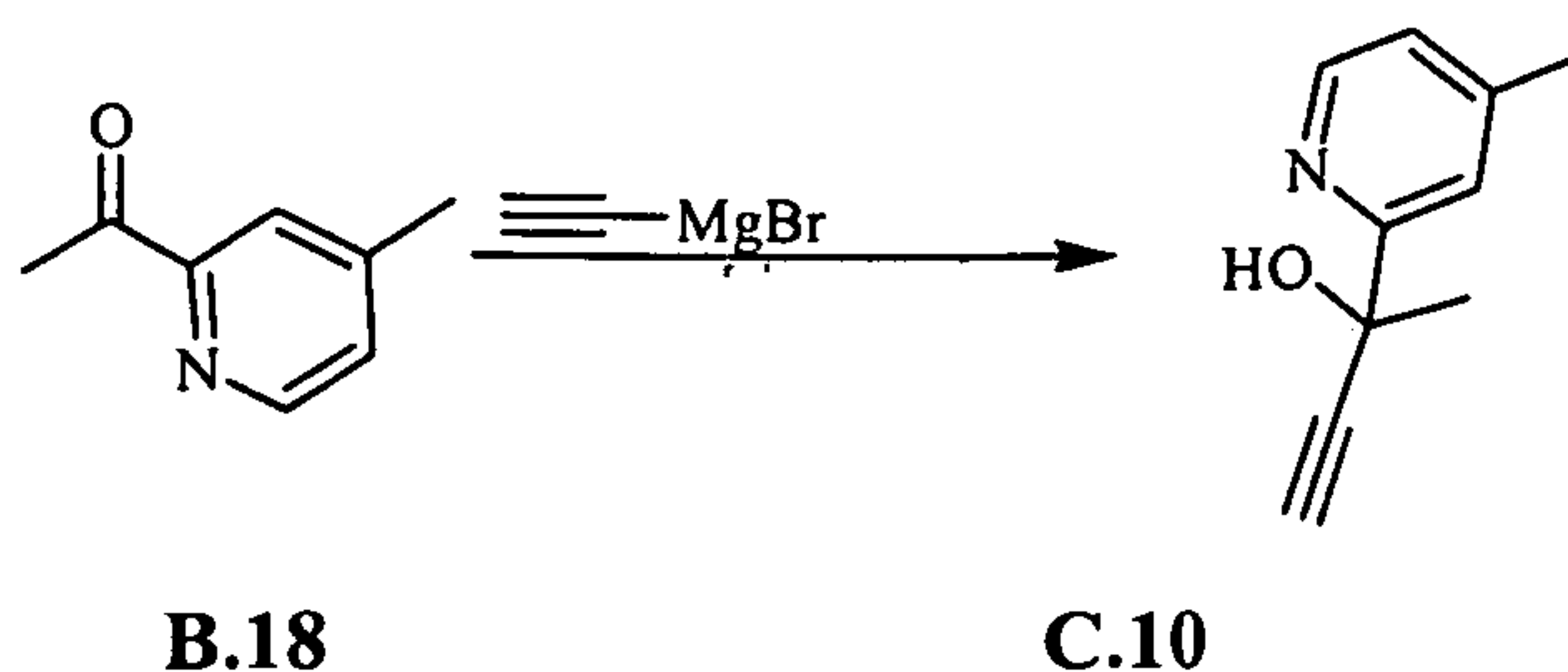
2-(5-methyl-1,2,4-oxadiazol-3-yl)but-3-yn-2-ol C.8 This compound was prepared from **B.11** in 72% yield by the procedure used for compound **C.1**.

¹H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 3.02 (1 H, br. s.), 2.68 (1 H, s), 2.64 (3 H, s), 1.94 (3 H, s) Mass Spectrum (ESI) $m/e = 153.1$ (M+1)

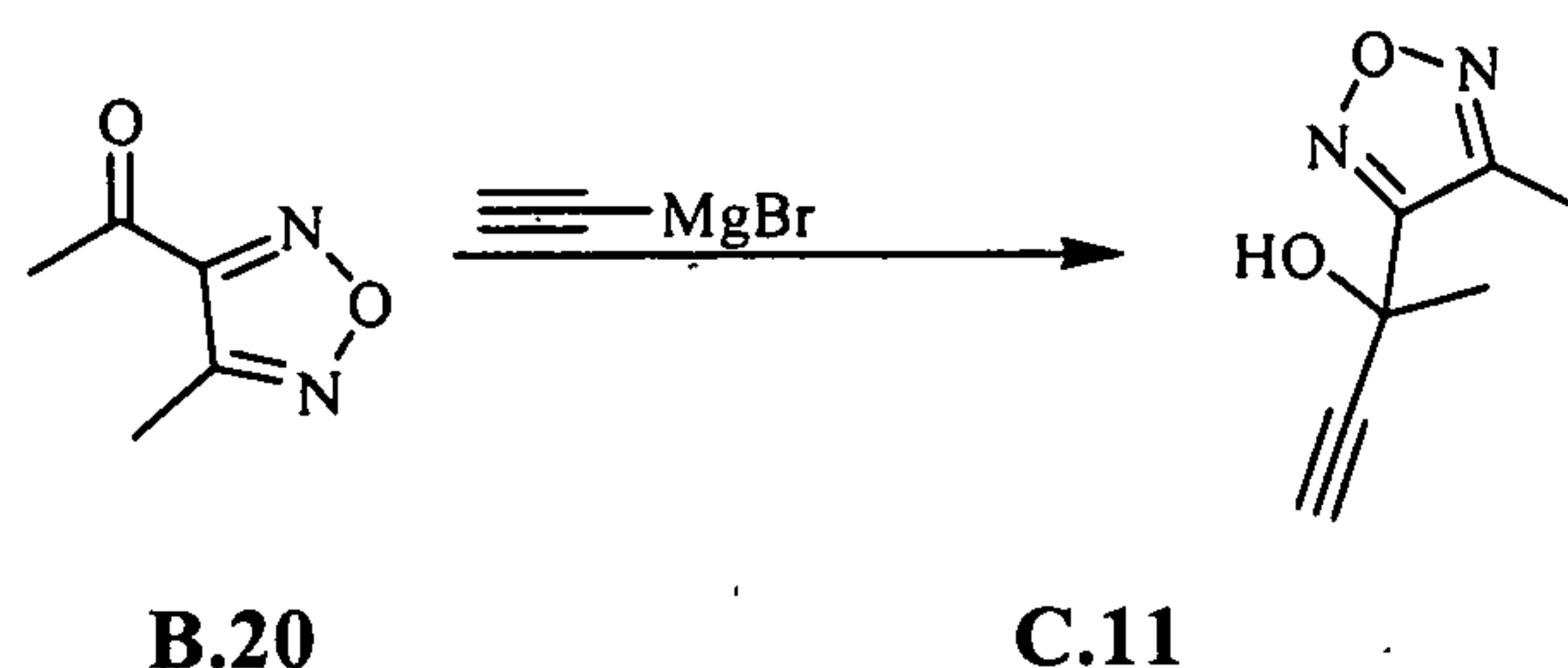


2-(pyrazin-2-yl)but-3-yn-2-ol C.9. This compound was prepared from 1-(pyrazin-2-yl)ethanone **B.16** in 81% yield by the procedure used for compound **C.1**.

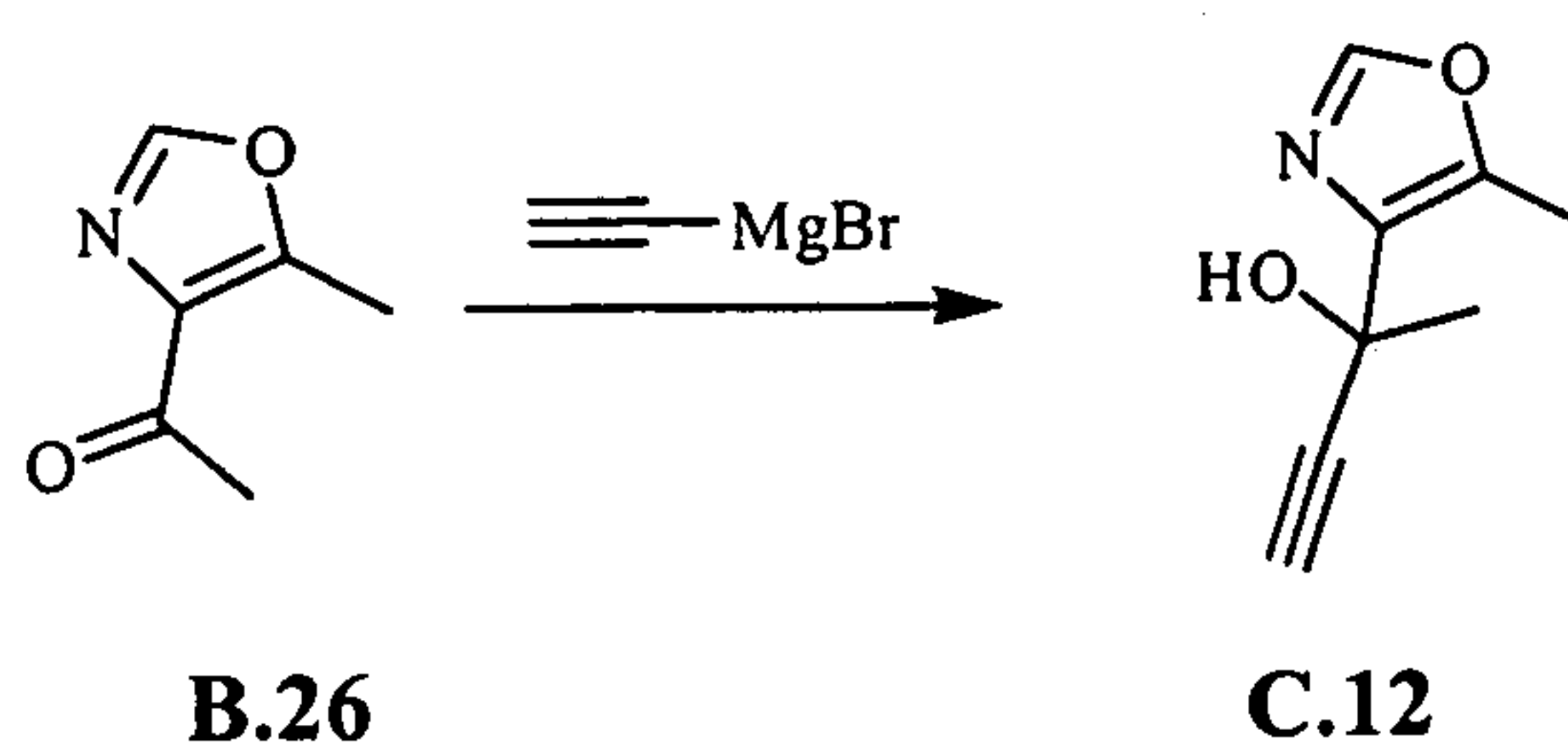
¹H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 8.98 (1 H, d, $J=1.2$ Hz), 8.55 (2 H, d, $J=18.6$ Hz), 4.24 (1 H, s), 2.65 (1 H, s), 1.86 (3 H, s) Mass Spectrum (ESI) $m/e = 149.1$ (M+1)



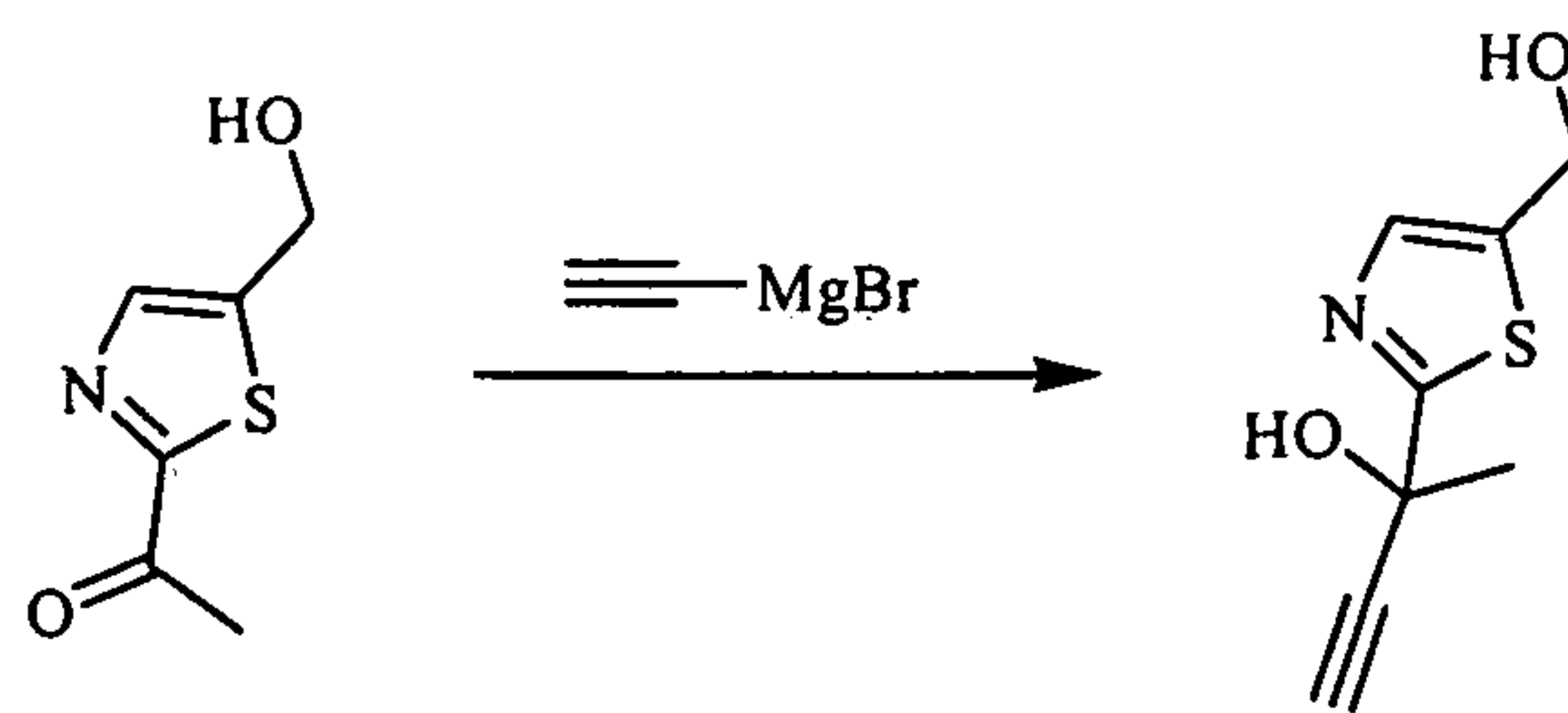
2-(4-methylpyridin-2-yl)but-3-yn-2-ol C.10. This compound was prepared from 1-(4-methylpyridin-2-yl)ethanone **B.18** in 35% yield by the procedure used for compound **C.1**. ¹H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 8.38 (1 H, d, $J=5.1$ Hz), 7.42 (1 H, s), 7.09 (1 H, d, $J=5.1$ Hz), 5.57 (1 H, s), 2.54 (1 H, s), 2.42 (3 H, s), 1.78 (3 H, s) Mass Spectrum (ESI) $m/e = 162.1$ (M+1)



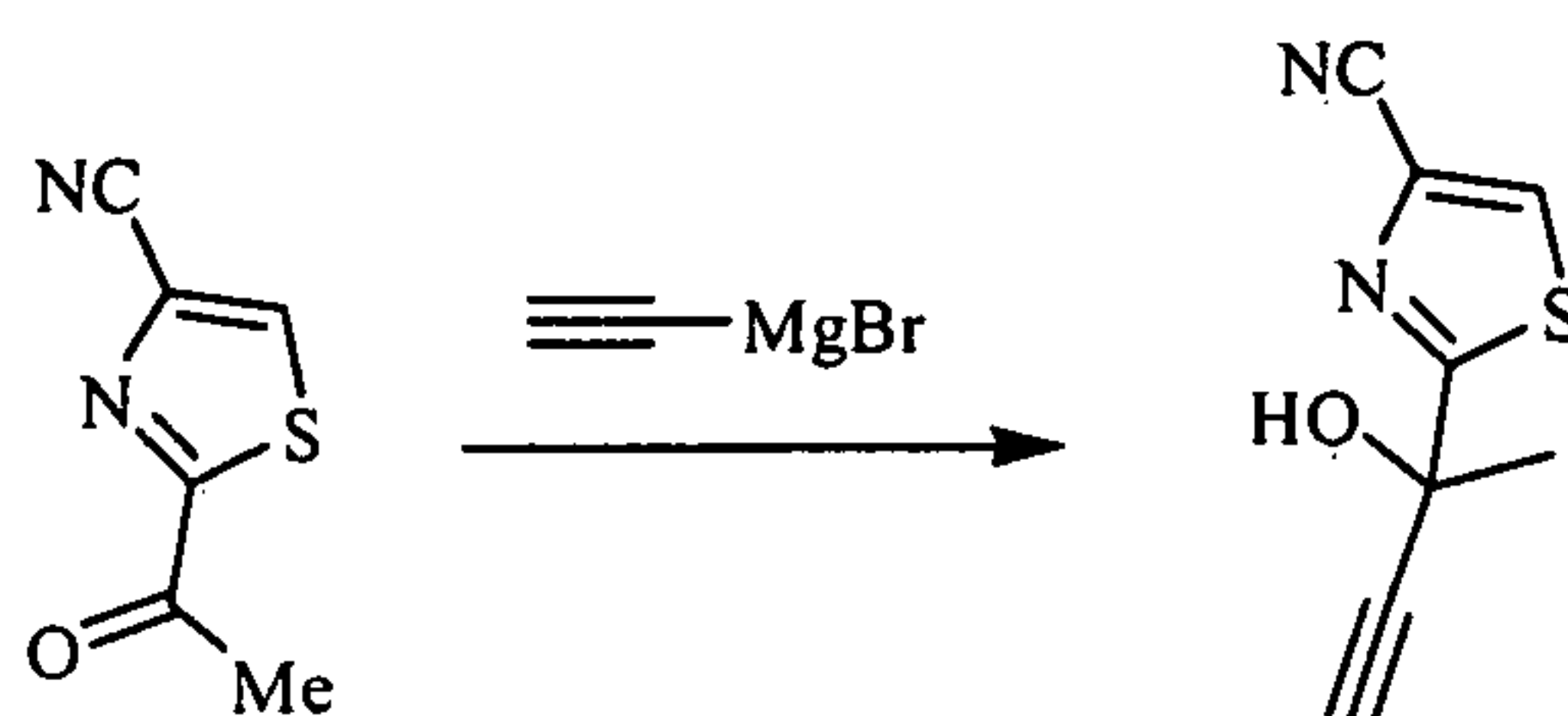
2-(4-methyl-1,2,5-oxadiazol-3-yl)but-3-yn-2-ol C.11. This compound was prepared from 1-(4-methyl-1,2,5-oxadiazol-3-yl)ethanone **B.20** in 94% yield by the procedure used for compound **C.1** ¹H NMR (400 MHz, *CHLOROFORM-d*₆) δ ppm 2.72 (1 H, s), 2.56 (3 H, s), 2.02 (3 H, s) Mass Spectrum (ESI) $m/e = 153.1$ (M+1)



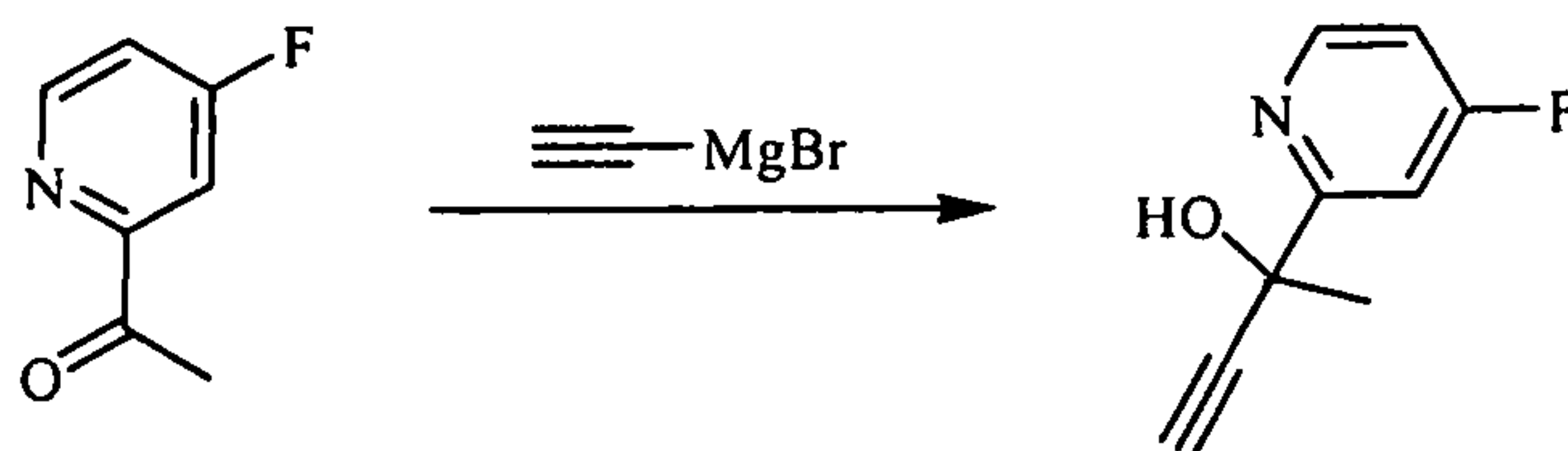
2-(5-methyloxazol-4-yl)but-3-yn-2-ol C.12 This compound was prepared from **B.26** in 45% yield by the procedure used for compound **C.1**. ¹H NMR Mass Spectrum (ESI) $m/e = 152.2$ (M+1)

**B.29****C.13****2-(5-(hydroxymethyl)thiazol-2-yl)but-3-yn-2-ol C.13**

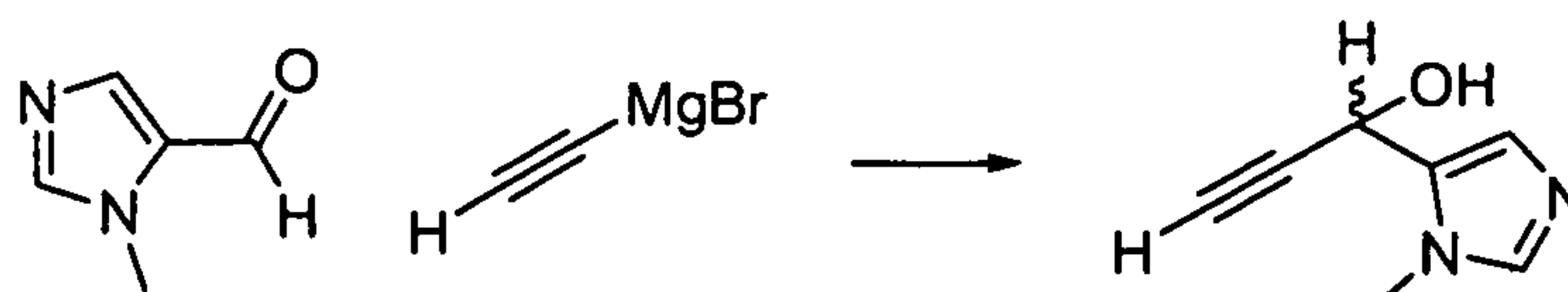
This compound was prepared from **B.29** in 44% yield by the procedure used for compound **C.1**.

**B.37****C.14****2-(2-hydroxybut-3-yn-2-yl)thiazole-4-carbonitrile C.14**

This compound was prepared from **B.37** in 10.5% yield by the procedure used for compound **C.1**. ¹H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 8.00 (1 H, s), 3.24 (1 H, s), 2.76 (1 H, s), 1.98 (3 H, s)

**B.41****C.15****2-(4-fluorophenyl)but-3-yn-2-ol C.15**

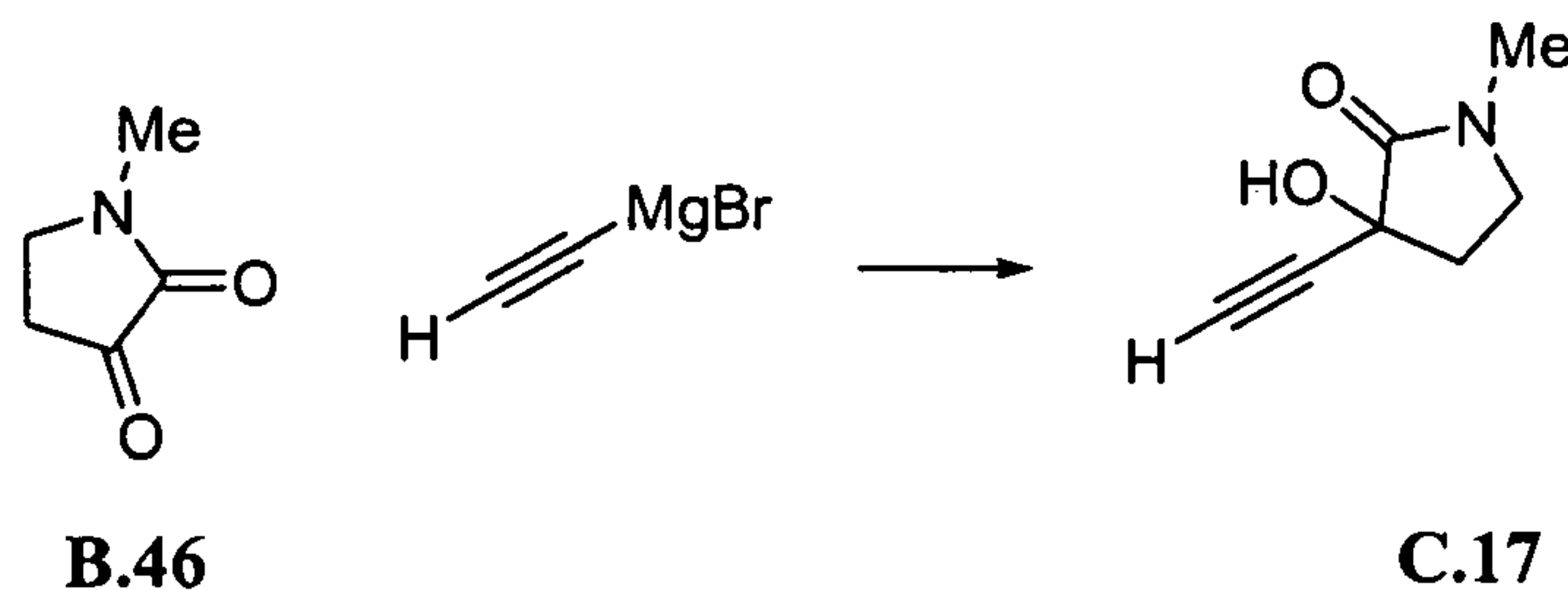
This compound was prepared from **B.41** in 61.5% yield by the procedure used for compound **C.1**. ¹H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 8.53 (1 H, dd, *J*=8.1, 5.6 Hz), 7.36 (1 H, dd, *J*=9.3, 2.4 Hz), 7.03 (1 H, ddd, *J*=7.9, 5.6, 2.1 Hz), 5.07 (1 H, s), 2.59 (1 H, s), 1.80 (3 H, s)

**B.43****C.16**

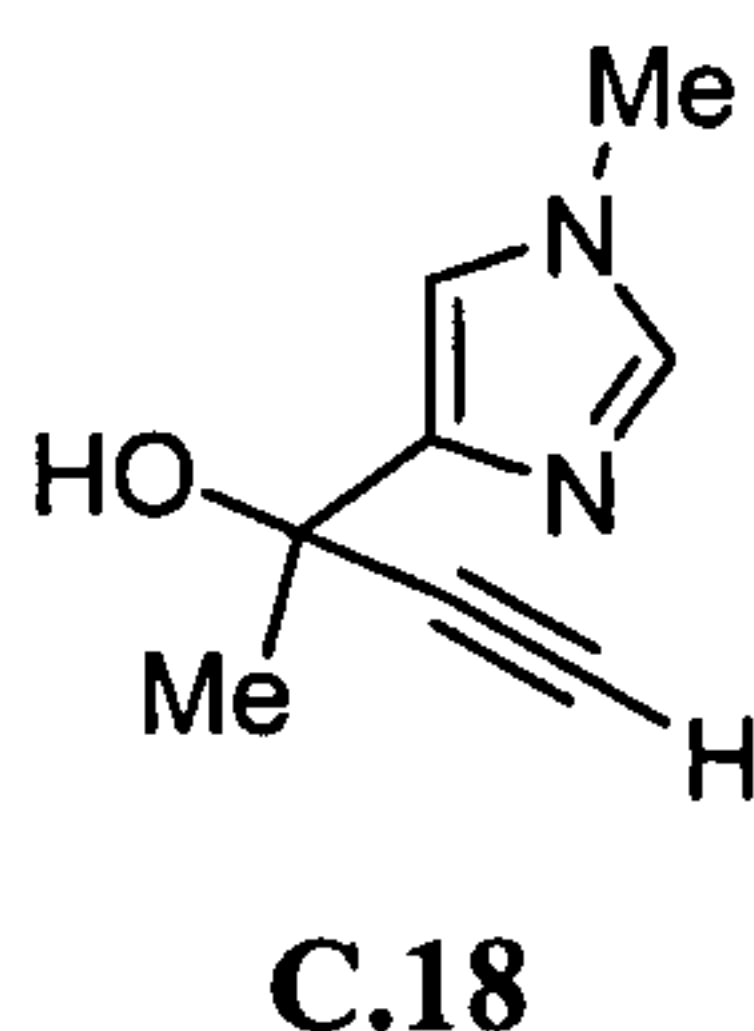
1-(1-methyl-1H-imidazol-5-yl)-2-propyn-1-ol C.16

This compound was prepared from **B.43** by the procedure used for compound **C.1**

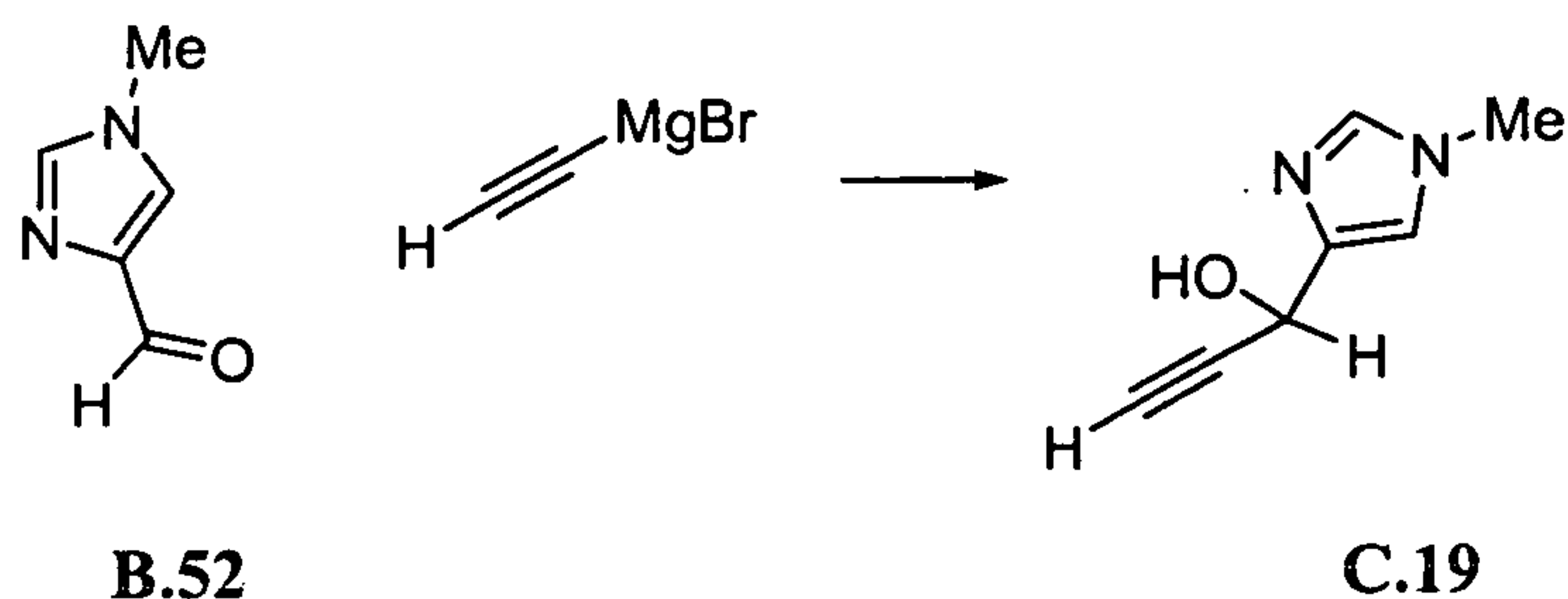
^1H NMR (500 MHz, DMSO- d_6) δ 7.56 (br s, 1H), 6.88 (br s, 1H), 6.05 (d, $J = 6.1$ Hz, 1H), 5.48 (dd, $J = 5.9$ Hz, $J = 2.2$ Hz, 1H), 3.66 (s, 3H), 3.53 (br d, $J = 2.2$ Hz, 1H); ESI MS: $M + H^+$ 137.1 m/z



3-ethynyl-3-hydroxy-1-methyl-2-pyrrolidinone C.17 was synthesized from **B.46** by the procedure used to prepare compound **C.1**; the title compound was obtained as a brownish oil (83mg). ESI-MS: $M + H^+$ 140.1 m/z

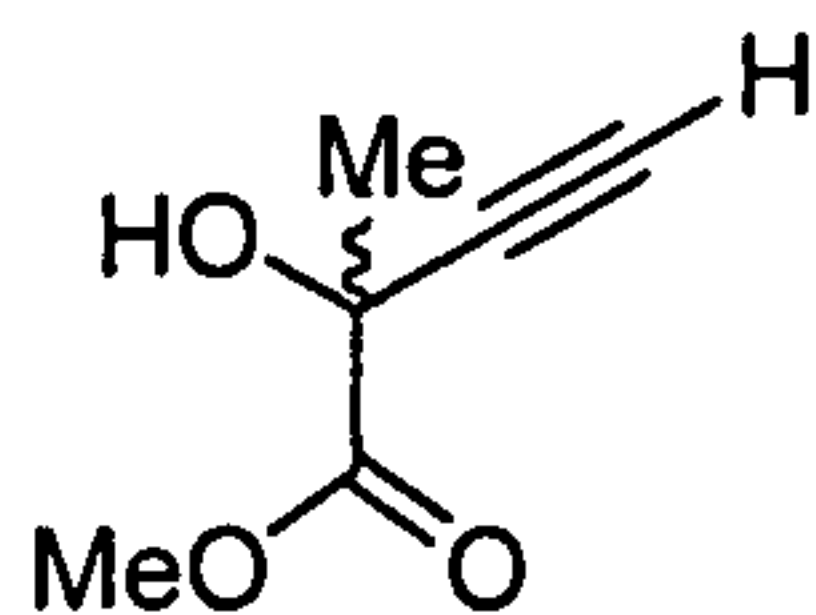


2-(1-methyl-1H-imidazol-4-yl)-3-butyn-2-ol C.18 was synthesized from **B.50** by the procedure used to prepare **C.1**; the title compound was obtained as a brownish oil (66mg). ESI-MS: $M + H^+$ 151.0 m/z

**1-(1-methyl-1H-imidazol-4-yl)prop-2-yn-1-ol C.19**

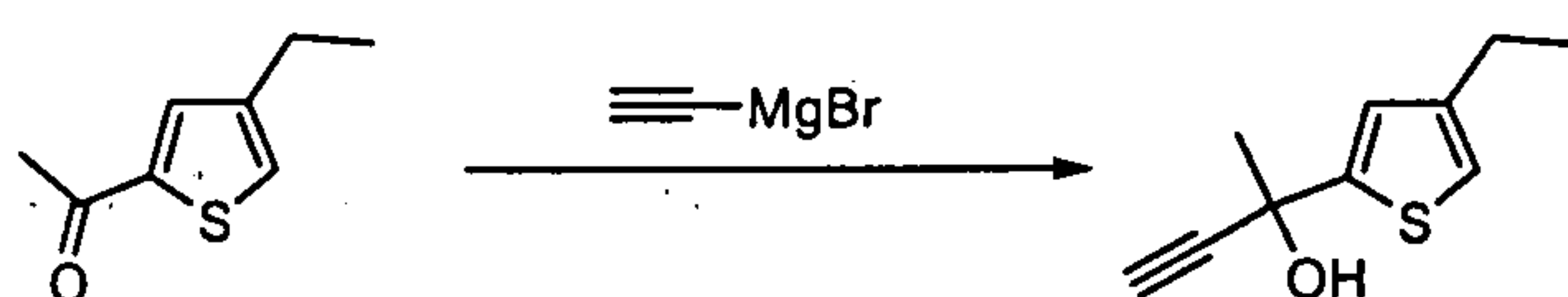
1-methyl-1H-imidazole-4-carbaldehyde **B.52** was used to prepare **C.19** by the procedure used to prepare **C.1**; the title compound was obtained as a yellow oil (654mg).

ESI-MS: $M + H^+$ 137.2 m/z

**C.20**

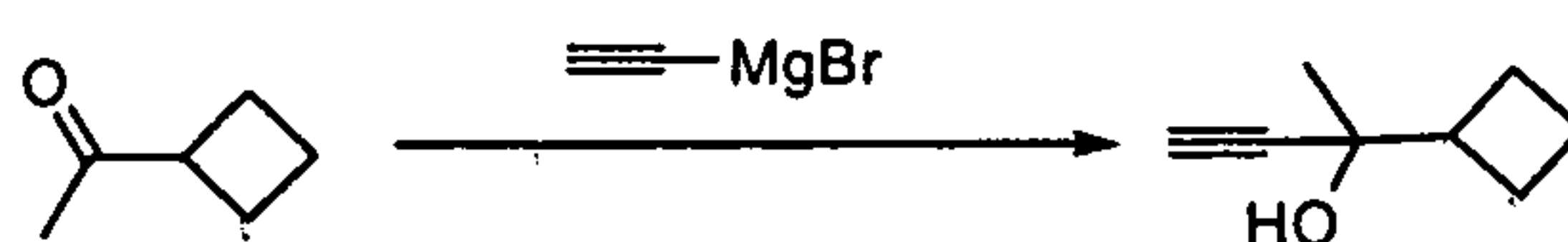
methyl 2-hydroxy-2-methyl-3-butynoate C.20 was synthesized as a yellowish oil (1.78g) from methyl pyruvate by the procedure used to prepare **C.1**. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 6.31 (1 H, s), 3.70 (3 H, s), 3.47 (1 H, s), 1.52 (3 H, s)

2-(4-ethylthiophen-2-yl)but-3-yn-2-ol

**B.57****C.21**

To a solution of 1-(4-ethylthiophen-2-yl)ethanone **B.57** (0.58 g, 3.76 mmol) in THF was added ethynylmagnesium bromide (0.5 M sol. in THF, 8.3 mL, 4.14 mmol) and the mixture was stirred at 60 °C for 30 minutes. The mixture was poured into cold 2 N aqueous HCl. The aqueous mixture was extracted with ether (50 mL x 2). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure to give a brown solid. The product was purified by silica gel column chromatography using 0% to 30% gradient of ethyl acetate in hexane as eluent to give 2-(4-ethylthiophen-2-yl)but-3-yn-2-ol **C.21** (0.43 g, 63.4% yield) as a yellow oil: ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 6.99 (1 H, d, $J=1.0$ Hz), 6.94 (1 H, d, $J=1.2$ Hz), 6.31 (1 H, s), 3.52 (1 H, s), 2.51 - 2.58 (2 H, m), 1.69 (3 H, s), 1.15 (3 H, t, $J=7.6$ Hz).

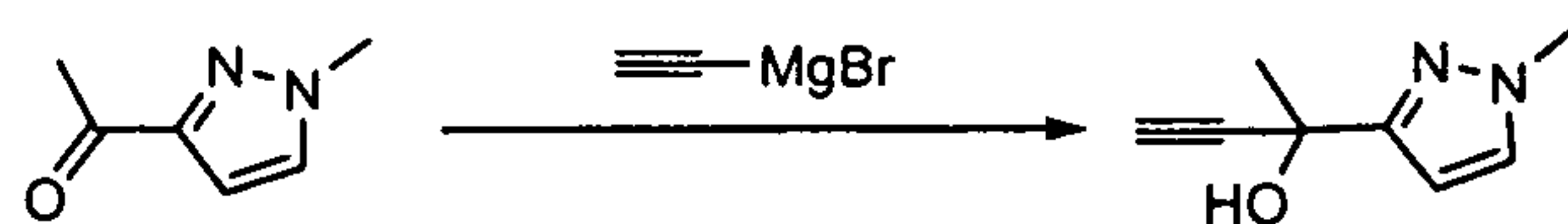
2-cyclobutylbut-3-yn-2-ol

**B.59****C.22**

To a stirring solution of ethynylmagnesium bromide (0.5 M in THF, 61.1 mL, 30.57 mmol) in THF (40.8 mL) at 0 °C was added dropwise 1-cyclobutylethanone **B.59** (2.2 mL, 20.38 mmol). The reaction was allowed to warm to room temperature and stirred for 2 hours. After being quenched with conc. aq. NH_4Cl (100 mL), the THF was removed *in vacuo* and the aqueous residue was extracted with ethyl acetate (100 mL x 2). The combined organic extracts

were dried over MgSO_4 , filtered, and concentrated under reduced pressure to give 2-cyclobutylbut-3-yn-2-ol **C.22** (1.57 g, 62% yield) as an orange oil: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 5.12 (1 H, s), 3.19 (1 H, s), 2.33 - 2.43 (1 H, m), 1.57 - 2.04 (6 H, m), 1.19 (3 H, s).

2-(1-methyl-1H-pyrazol-3-yl)but-3-yn-2-ol

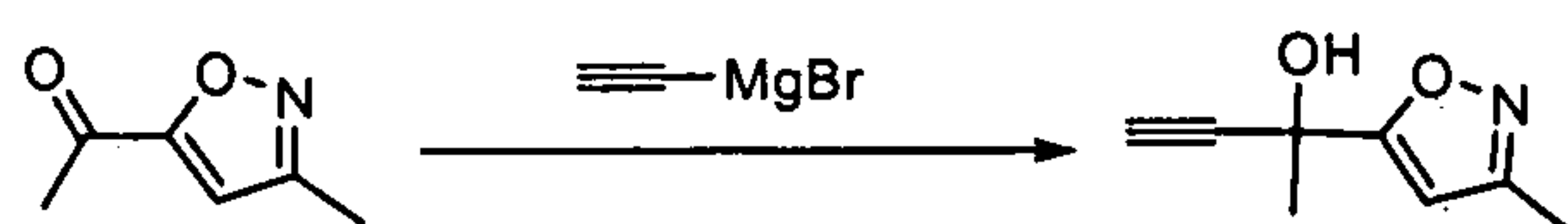


B.61

C.23

To a stirring solution of ethynylmagnesium bromide (0.5 M in THF, 121 mL, 60.4 mmol) at 0 °C was added 1-(1-methyl-1H-pyrazol-3-yl)ethanone **C.23** (5 g, 40.28 mmol) in THF (80 mL) slowly. The reaction was allowed to warm to room temperature and stirred for 4 hours. After being quenched with conc. aq. NH_4Cl (200 mL), the THF was removed *in vacuo* and the aqueous residue was extracted with ethyl acetate (200 mL x 2). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated under reduced pressure to give a yellow oil. The yellow oil was purified by silica gel column chromatography using 0% to 50% gradient of dichloromethane-methanol- NH_4OH (89:9:1) in dichloromethane as eluent to give 2-(1-methyl-1H-pyrazol-3-yl)but-3-yn-2-ol **C.23** (4.52 g, 74.7% yield): ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 7.55 (1 H, d, $J=2.0$ Hz), 6.22 (1 H, d, $J=2.3$ Hz), 5.78 (1 H, s), 3.78 (3 H, s), 3.28 (1 H, s), 1.65 (3 H, s); Mass Spectrum (ESI) $m/e = 151.1$ [$\text{M}+1$].

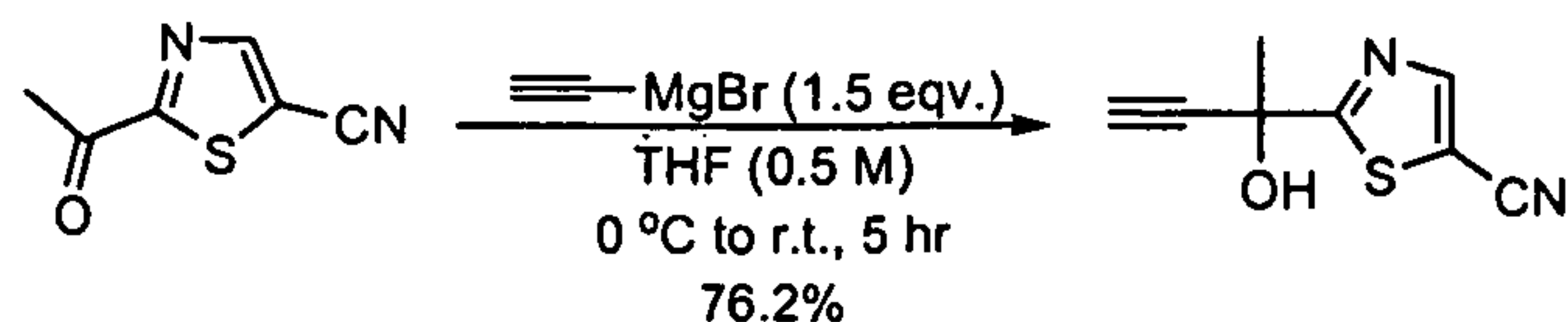
2-(3-methylisoxazol-5-yl)but-3-yn-2-ol **C.24**



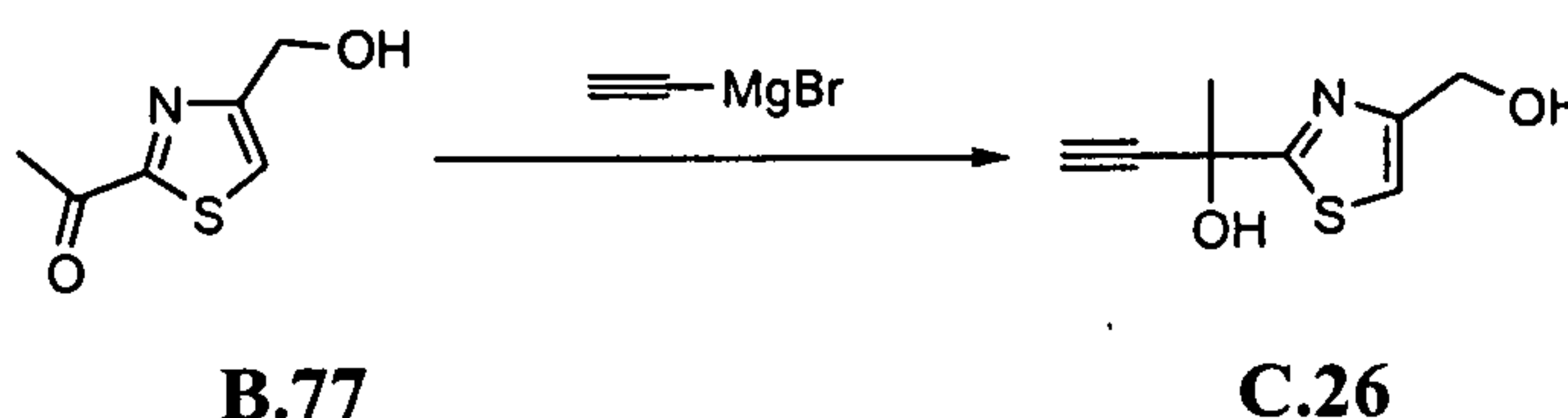
B.65

C.24

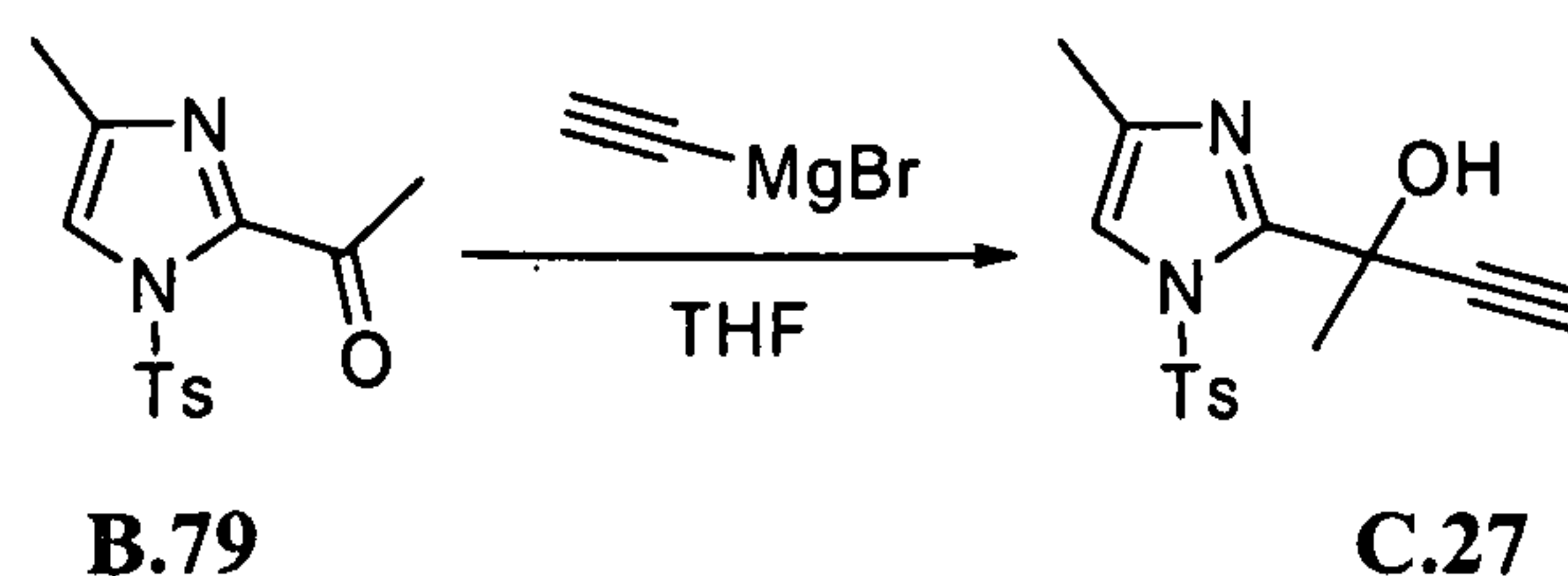
To a stirring solution of ethynylmagnesium bromide (0.5 M in THF, 62 mL, 30.76 mmol) at 0 °C was added 1-(3-methylisoxazol-5-yl)ethanone **B.65** (2.57 g, 20.5 mmol) in THF (41 mL) slowly. The reaction was allowed to warm to room temperature and stirred for 5 hours. After being quenched with conc. aq. NH_4Cl (100 mL), the THF was removed *in vacuo* and the aqueous residue was extracted with ethyl acetate (100 mL x 2). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated under reduced pressure to give 2-(3-methylisoxazol-5-yl)but-3-yn-2-ol **C.24** (3.2 g) as a brown oil: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 6.56 (1 H, s), 6.27 (1 H, s), 3.59 (1 H, s), 2.21 (3 H, s), 1.68 (3 H, s); Mass Spectrum (ESI) $m/e = 152.2$ [$\text{M}+1$].

2-(2-hydroxybut-3-yn-2-yl)thiazole-5-carbonitrile C.25**B.71****C.25**

2-acetylthiazole-5-carbonitrile **B.71** (0.262 g, 1.72 mmol) in THF (3.4 mL) was added slowly to a stirring solution of ethynylmagnesium bromide (0.5 M in THF, 5.2 mL, 2.58 mmol) at 0 °C. The reaction was allowed to warm to room temperature and stirred for 5 hours. After quenching with conc. aq. NH_4Cl (20 mL), the organic solvent was removed *in vacuo* and the aqueous residue was extracted with ethyl acetate (50 mL x 3). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated under reduced pressure to give a dark syrup. The dark syrup was purified by silica gel column chromatography using 0% to 50% gradient of ethyl acetate in hexane as eluent to give 2-(2-hydroxybut-3-yn-2-yl)thiazole-5-carbonitrile **C.25** (0.234 g, 76.2% yield) as a yellow syrup: ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 8.53 - 8.67 (1 H, m), 7.38 - 7.53 (1 H, m), 3.61 - 3.77 (1 H, m), 1.70 - 1.83 (3 H, m); Mass Spectrum (ESI) $m/e = 179.1$ [$\text{M}+1$].

2-(4-(hydroxymethyl)thiazol-2-yl)but-3-yn-2-ol C.26**B.77****C.26**

1-(4-(hydroxymethyl)thiazol-2-yl)ethanone **B.77** (0.214 g, 1.36 mmol) in THF (2.7 mL) was added slowly to a stirring solution of ethynylmagnesium bromide (0.5 M in THF, 6.8 mL, 3.4 mmol) at 0 °C. The reaction was allowed to warm to room temperature and stirred for 6 hours. After quenching with conc. aq. NH_4Cl (20 mL), the THF was removed *in vacuo* and the aqueous residue was extracted with ethyl acetate (50 mL x 2). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated under reduced pressure to give an orange oil. The orange oil was purified by silica gel column chromatography using 0% to 100% gradient of ethyl acetate in hexane as eluent to give 2-(4-(hydroxymethyl)thiazol-2-yl)but-3-yn-2-ol **C.26** (0.0794 g, 31.8% yield) as a white solid: Mass Spectrum (ESI) $m/e = 184.0$ [$\text{M}+1$].



2-(4-Methyl-1-((4-methylphenyl)sulfonyl)-1H-imidazol-2-yl)-3-butyn-2-ol (C.27). To a dry flask containing dry THF (10.00 mL) was added 0.5 M solution of ethynylmagnesium bromide in THF (14.5 mL, 7.25 mmol) then cooled to 0 °C. After 10 minutes, a pre-mixed solution of 1-(4-methyl-1-tosyl-1H-imidazol-2-yl)ethanone (777.7 mg, 2.79 mmol) in dry THF (5.00 mL) was added dropwise. Upon complete addition, the mixture was stirred at room temperature. After 4 hours, the reaction was quenched with saturated aq. ammonium chloride solution then extracted three times with ethyl acetate. After concentration, the residue was purified by silica gel flash chromatography (0-50% ethyl acetate in hexanes to afford **2-(4-methyl-1-((4-methylphenyl)sulfonyl)-1H-imidazol-2-yl)-3-butyn-2-ol (C.27)** (0.72 g, 85%). ¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 7.92 (2 H, d, *J*=8.6 Hz), 7.52 (1 H, d, *J*=1.2 Hz), 7.43 (2 H, d, *J*=8.3 Hz), 6.16 (1 H, s), 3.47 (1 H, s), 2.40 (3 H, s), 2.07 (3 H, s), 1.80 (3 H, s).

Additional alkynyl alcohols disclosure **C.28-C.69** were either commercially available or prepared as in the literature or in similar fashion from the corresponding ketones.

C.28. 1-ethynylcyclobutanol US5583227, 1996

C.29 2-(thiazol-4-yl)but-3-yn-2-ol (ketone precursor [38205-66-2])

C.30 2-(1-tosyl-1H-pyrazol-5-yl)but-3-yn-2-ol (derived from ketone [175277-40-4])

C.34 2-cyclopentylbut-3-yn-2-ol US4608388, 1986

C.35 2-methylbut-3-yn-2-ol [115-19-5]

C.36 1-ethynylcyclopentanol [17356-19-3]

C.37 1-ethynylcyclohexanol [978-27-3]

C.38 benzyl 2,2-dimethylbut-3-ynoate [204588-77-2]

C.40 4-ethynyltetrahydro-2H-pyran-4-ol US6130239, 2000

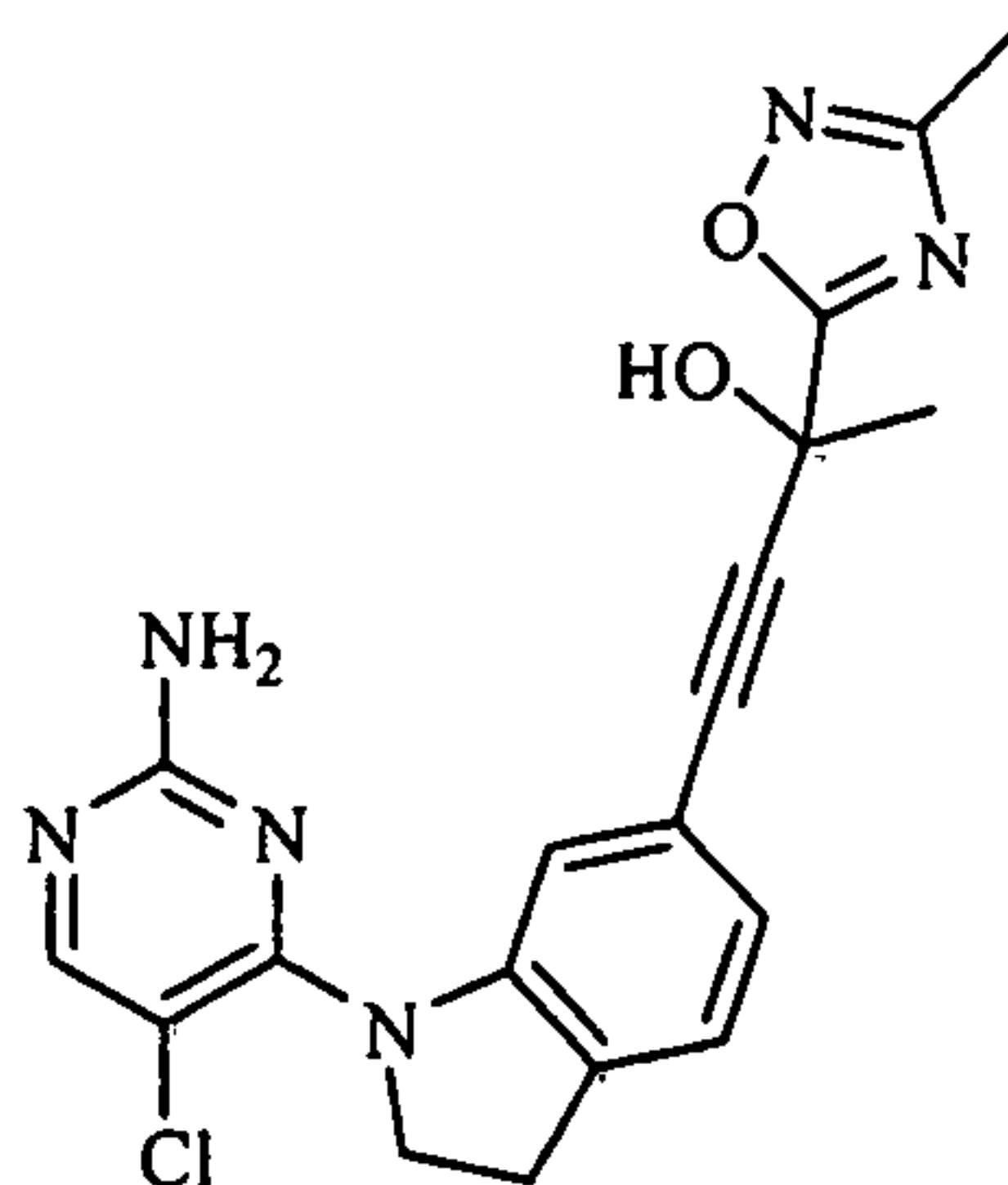
C.42 2-(thiophen-2-yl)but-3-yn-2-ol (Vaitiekunas, A. and F. F. Nord (1954). *J. Amer. Chem. Soc.* 76: 2733-2735)

C.43 3-ethynyltetrahydrothiophen-3-ol
(Karrer, P. and A. Kieso (1944). *Helv. Chim. Acta*, 27: 1285.)

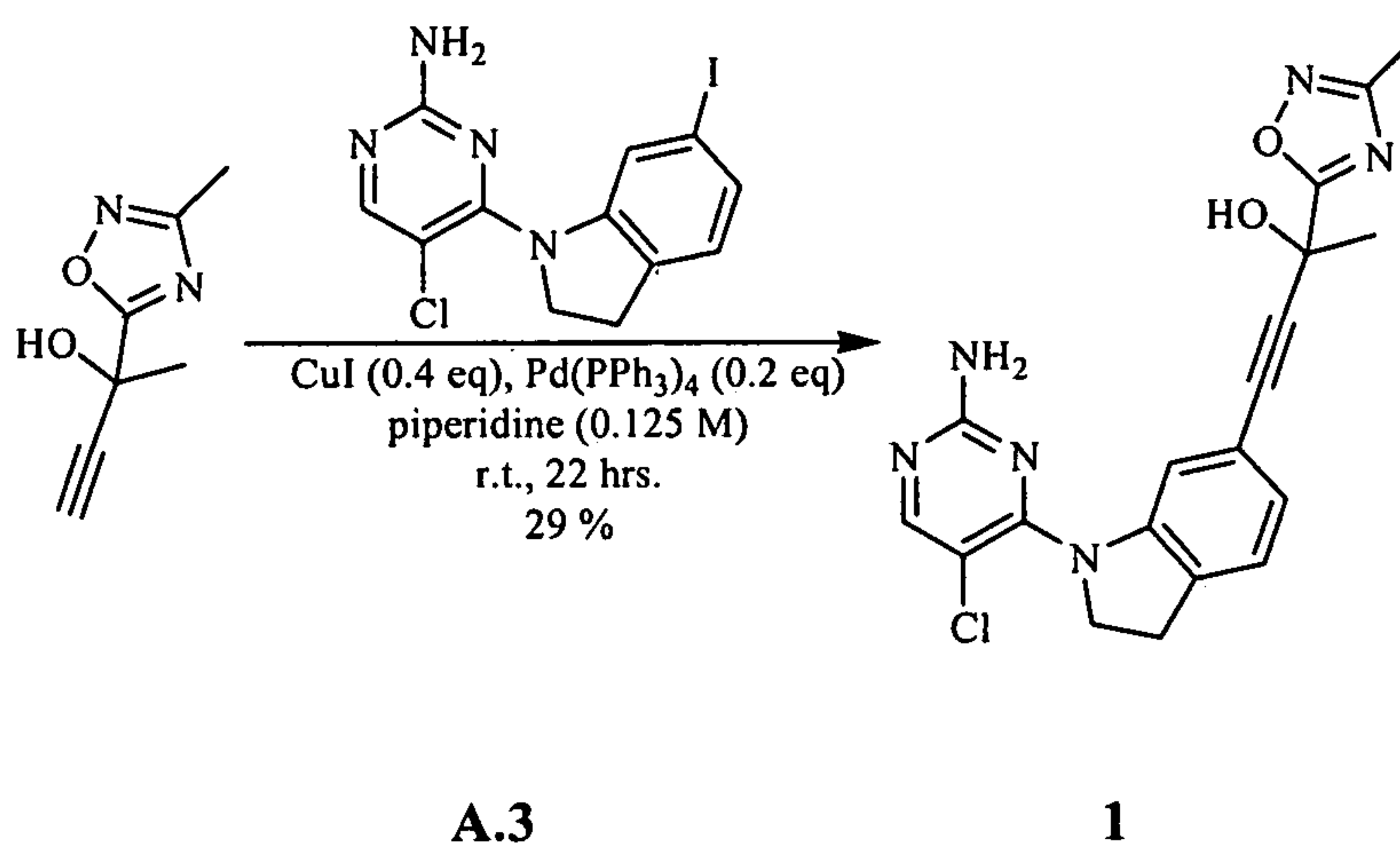
C.44 3-methylpent-1-yn-3-ol [77-75-8]

- C.45 3,4-dimethylpent-1-yn-3-ol [1482-15-1]
- C.46 3,4,4-trimethylpent-1-yn-3-ol [993-53-3]
- C.47 2-(pyridin-4-yl)but-3-yn-2-ol (ketone precursor [1122-54-9])
- C.48 2-(pyridin-3-yl)but-3-yn-2-ol (ketone precursor [350-03-8])
- C.49 2-(pyridin-2-yl)but-3-yn-2-ol (Wrobel, D. (1964). *Chemistry and Industry* 1758)
- C.50 2-phenylbut-3-yn-2-ol [127-66-2]
- C.51 1,1,1-trifluoro-2-phenylbut-3-yn-2-ol [99727-20-5]
- C.52 1,1,1-trifluoro-2-(3-fluorophenyl)but-3-yn-2-ol (ketone precursor [708-64-5])
- C.53 1,1,1-trifluoro-2-methylbut-3-yn-2-ol (Tarrant P., Warner D.A., et al. (1953). *J. Amer. Chem. Soc.* 75(17): 4360-4362.)
- C.54 2-(furan-2-yl)but-3-yn-2-ol (Semmelhack, M. F. and N. Jeong (1990). *Tetrahedron Lett.*, 31(5): 605-608.)
- C.55 2-(5-methylfuran-2-yl)but-3-yn-2-ol (ketone precursor [1193-79-9])
- C.56 2-(2,5-dimethylfuran-3-yl)but-3-yn-2-ol (ketone precursor [10599-70-9])
- C.57 2-(oxazol-2-yl)but-3-yn-2-ol (ketone precursor [77311-07-0])
- C.58 2-(5-methyloxazol-2-yl)but-3-yn-2-ol (ketone precursor Sauers, R. R. and S. D. Van Arnum (1987). *Tetrahedron Lett.* 28(47): 5797-5800)
- C.59 2-(thiophen-3-yl)but-3-yn-2-ol (ketone precursor [1468-83-3])
- C.60 2-(4-methylthiophen-2-yl)but-3-yn-2-ol (ketone precursor [13679-73-7])
- C.61 2-(3-methylthiophen-2-yl)but-3-yn-2-ol (ketone precursor [13679-72-6])
- C.62 2-(5-methylthiophen-2-yl)but-3-yn-2-ol (ketone precursor [13679-74-8])
- C.63 2-(5-chlorothiophen-2-yl)but-3-yn-2-ol (Vaitiekunas, A. and F. F. Nord (1954). *J. Amer. Chem. Soc.* 76: 2733-2735)
- C.64 2-(3-chlorothiophen-2-yl)but-3-yn-2-ol (ketone precursor [89581-82-8])
- C.65 2-(5-methylthiazol-2-yl)but-3-yn-2-ol
(ketone precursor: Koether, M. (1953). *Bull. Soc. Chim. Fr*: 702-705)
- C.66 2-(4-methylthiazol-2-yl)but-3-yn-2-ol (ketone precursor: Aldrich 656313)
- C.67 2-(4,5-dimethylthiazol-2-yl)but-3-yn-2-ol (ketone precursor: [7531-76-2])
- C.68 2-(2-methylthiazol-4-yl)but-3-yn-2-ol (ketone precursor [23002-78-0])
- C.69 2-(2,4-dimethylthiazol-5-yl)but-3-yn-2-ol (ketone precursor [38295-60-6])

Example 1



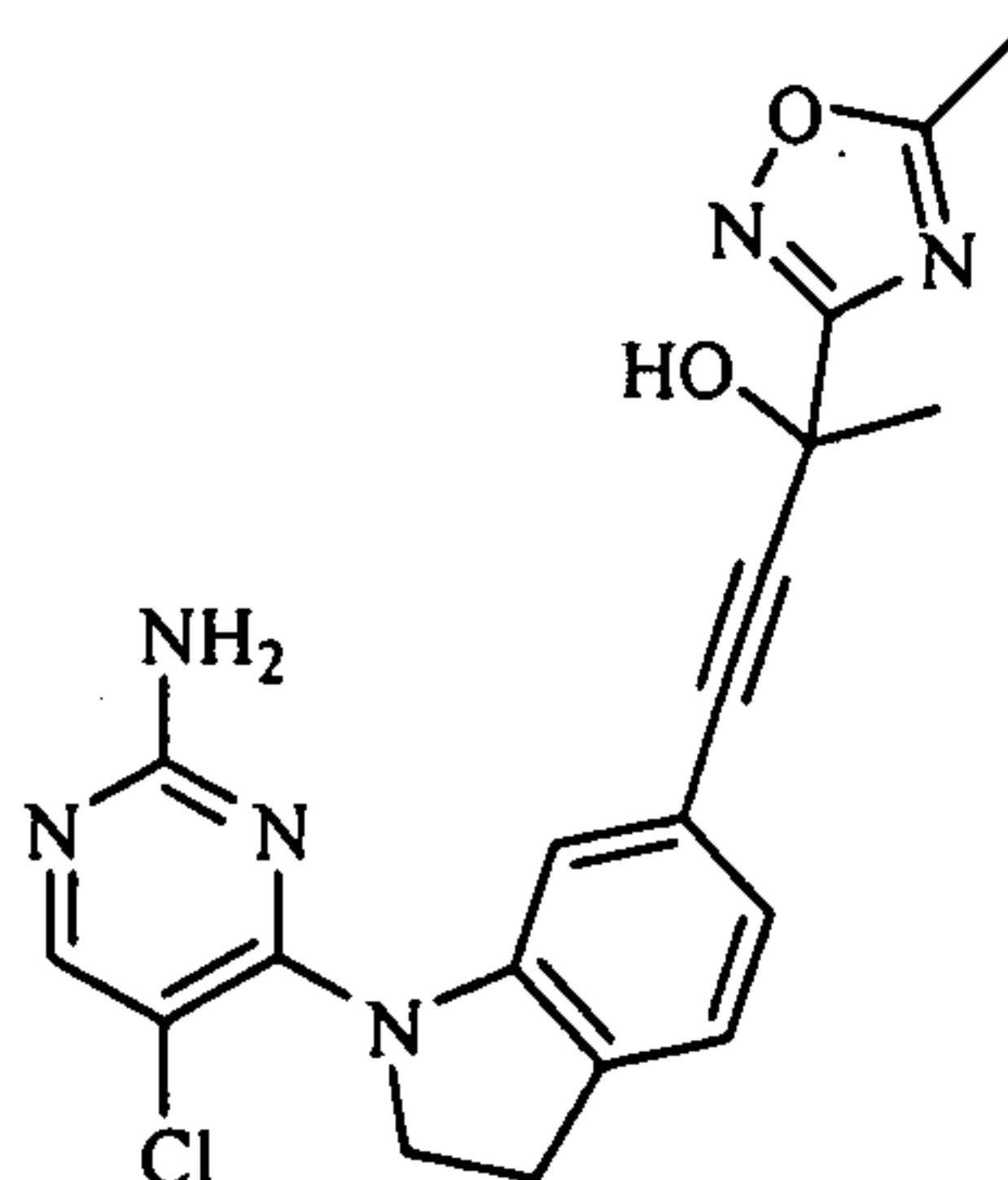
4-(1-(2-amino-5-chloropyrimidin-4-yl)indolin-6-yl)-2-(3-methyl-1,2,4-oxadiazol-5-yl)but-3-yn-2-ol



4-(1-(2-amino-5-chloropyrimidin-4-yl)indolin-6-yl)-2-(3-methyl-1,2,4-oxadiazol-5-yl)but-3-yn-2-ol (1): 5-chloro-4-(6-iodoindolin-1-yl)pyrimidin-2-amine (**A.3**) (100 mg, 0.27 mmol), CuI (21 mg, 0.11 mmol) and tetrakis(triphenylphosphine)palladium (64 mg, 0.055 mmol) was stirred under argon and 1.5 mL piperidine (previously degassed with argon) was added. To the stirring solution was added 2-(3-methyl-1,2,4-oxadiazol-5-yl)but-3-yn-2-ol (**C.7**) 61 mg, 0.4 mmol) in 1.5 mL piperidine, and the flask rinsed with 1 mL additional piperidine. The reaction stirred at room temperature for 22 hours. The mixture was condensed *in vacuo* and the residue purified by flash chromatography (10-100% gradient 89:9:1 dichloromethane-methanol-NH₄OH in dichloromethane) to give 31 mg 4-(1-(2-amino-5-chloropyrimidin-4-yl)indolin-6-yl)-2-(3-methyl-1,2,4-oxadiazol-5-yl)but-3-yn-2-ol (**1**). ¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 8.11 (1 H, s), 7.24 (1 H, d, *J*=7.3 Hz), 7.21 (1 H, s), 7.09 (1 H, s), 6.98 (1 H, d, *J*=7.6 Hz), 6.66 (2 H, s), 4.18 (2 H, t, *J*=8.2 Hz), 3.11 (2 H, t, *J*=7.8 Hz), 2.37 (3 H, s), 1.88 (3 H, s) Mass Spectrum (ESI) *m/e* = 397.0, 399.1 (*M*+1)

Examples 2-23 were prepared using same or analogous synthetic techniques and substituting with appropriate reagent as in **example 1**.

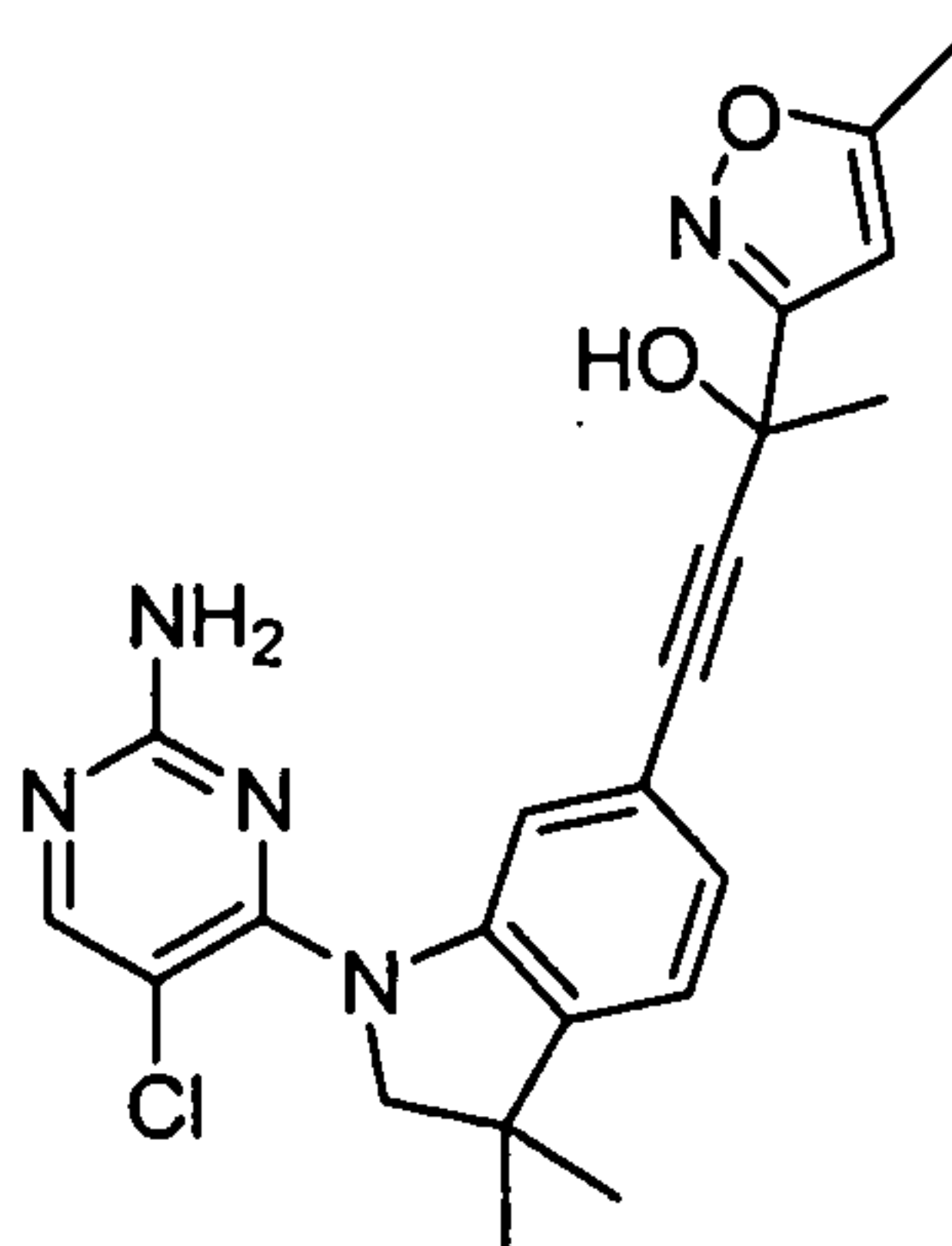
Example 2



2

4-(1-(2-amino-5-chloropyrimidin-4-yl)indolin-6-yl)-2-(5-methyl-1,2,4-oxadiazol-3-yl)but-3-yn-2-ol (2): (from components A.3 and C.8). ¹H NMR (400 MHz, *DMSO-d*₆) δ ppm 8.12 (1 H, s), 7.23 (1 H, d, *J*=7.8 Hz), 7.17 (1 H, s), 6.95 (1 H, d, *J*=7.4 Hz), 6.67 (2 H, s), 6.65 (1 H, s), 4.17 (2 H, t, *J*=8.0 Hz), 3.10 (2 H, t, *J*=7.8 Hz), 2.60 (3 H, s), 1.80 (3 H, s) Mass Spectrum (ESI) *m/e* = 397.1, 399.1 (*M*+1)

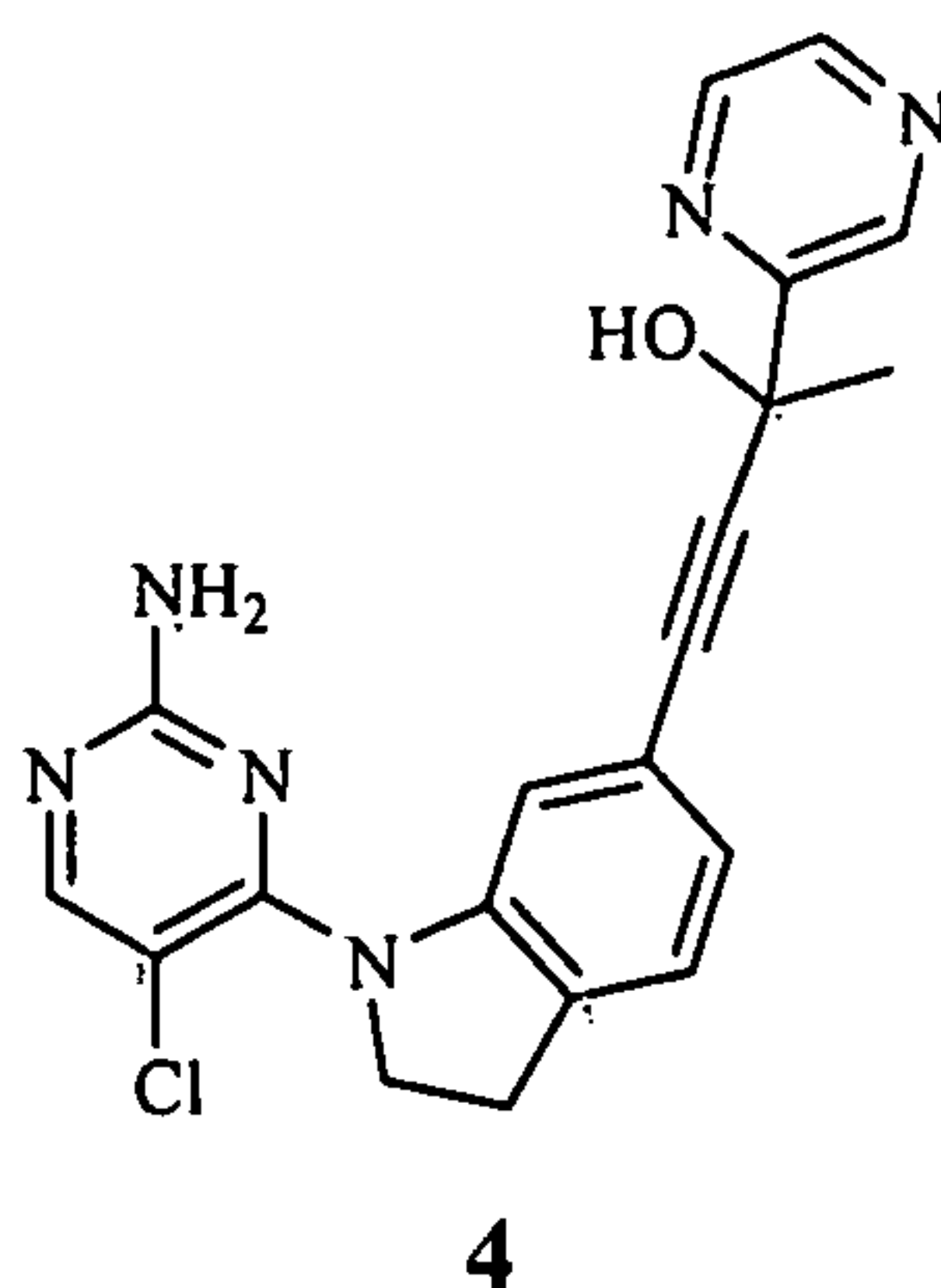
Example 3



3

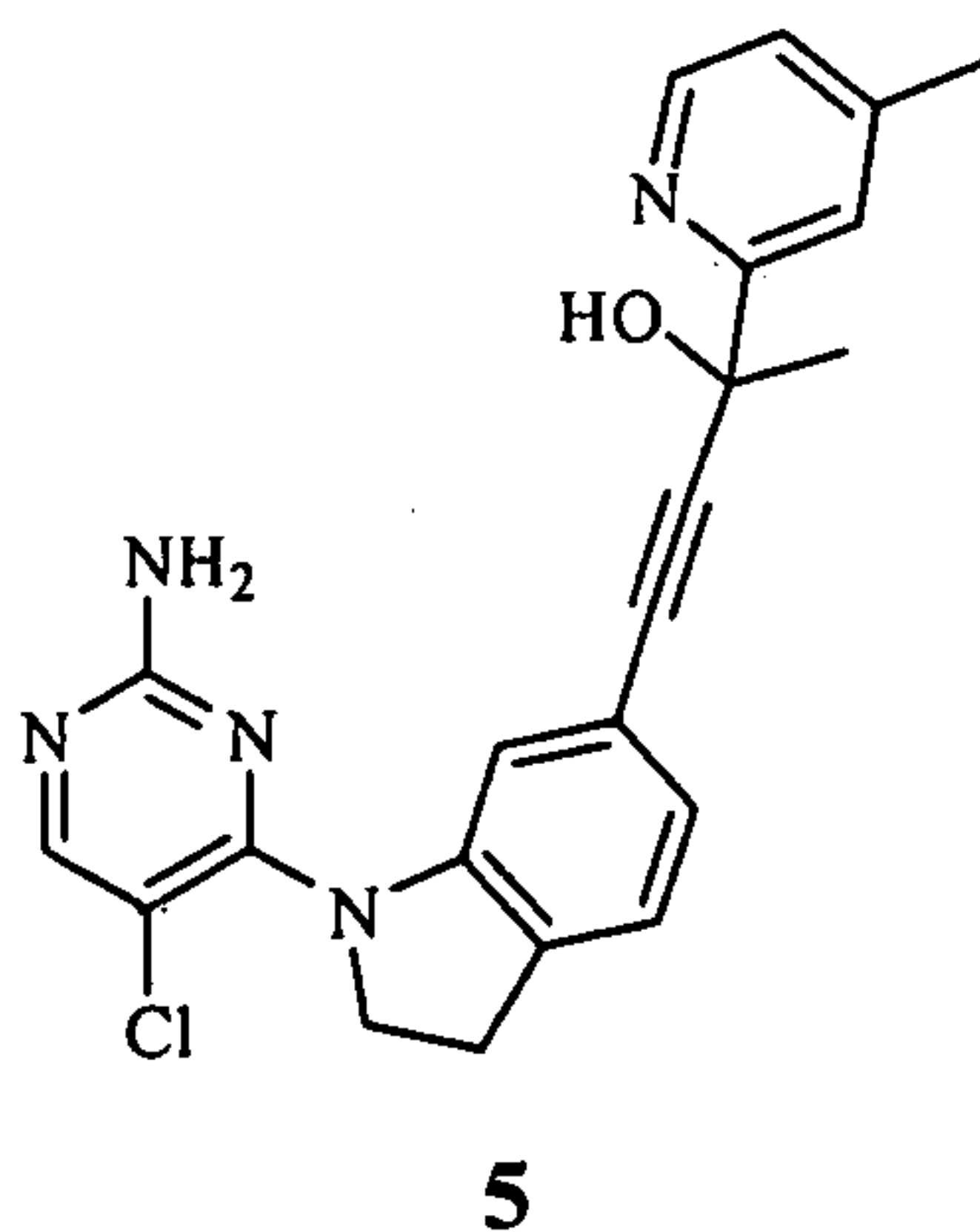
4-(1-(2-amino-5-chloropyrimidin-4-yl)-3,3-dimethylindolin-6-yl)-2-(5-methylisoxazol-3-yl)but-3-yn-2-ol (3): (from components A.15 and C.1) .

¹H NMR (400 MHz, *DMSO-d*₆) δ ppm 8.13 (1 H, s), 7.21 (1 H, d, *J*=7.4 Hz), 7.15 (1 H, s), 6.99 (1 H, d, *J*=7.8 Hz), 6.66 (2 H, s), 6.41 (1 H, s), 6.32 (1 H, s), 3.90 (2 H, s), 2.39 (3 H, s), 1.77 (3 H, s), 1.28 (6 H, s) Mass Spectrum (ESI) *m/e* = 424.1, 426.1 (*M*+1)

Example 4

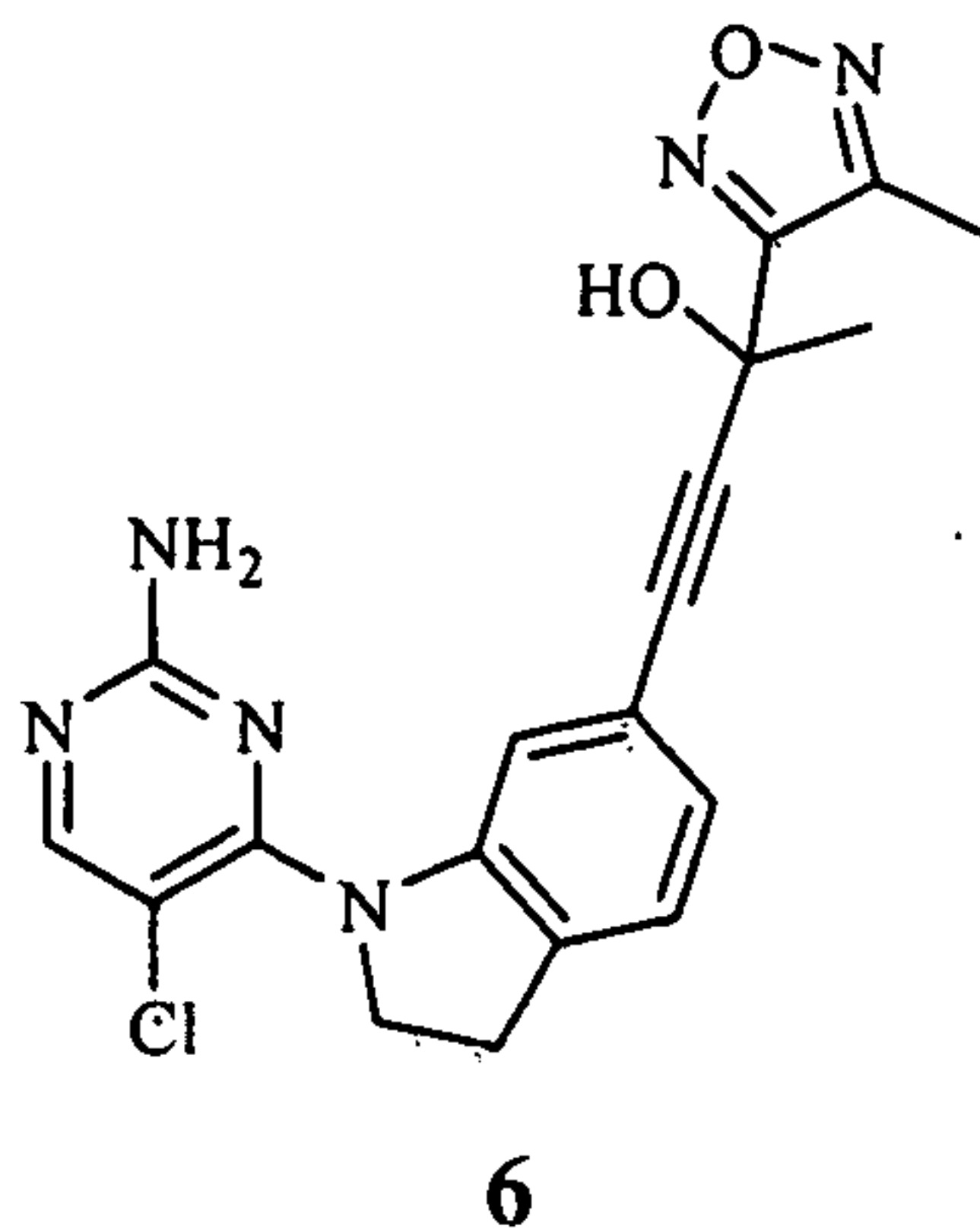
4-(1-(2-amino-5-chloropyrimidin-4-yl)indolin-6-yl)-2-(pyrazin-2-yl)but-3-yn-2-ol (4):
(from components A.3 and C.9).

Mass Spectrum (ESI) *m/e* = 393.1/395.1 (*M*+1)

Example 5

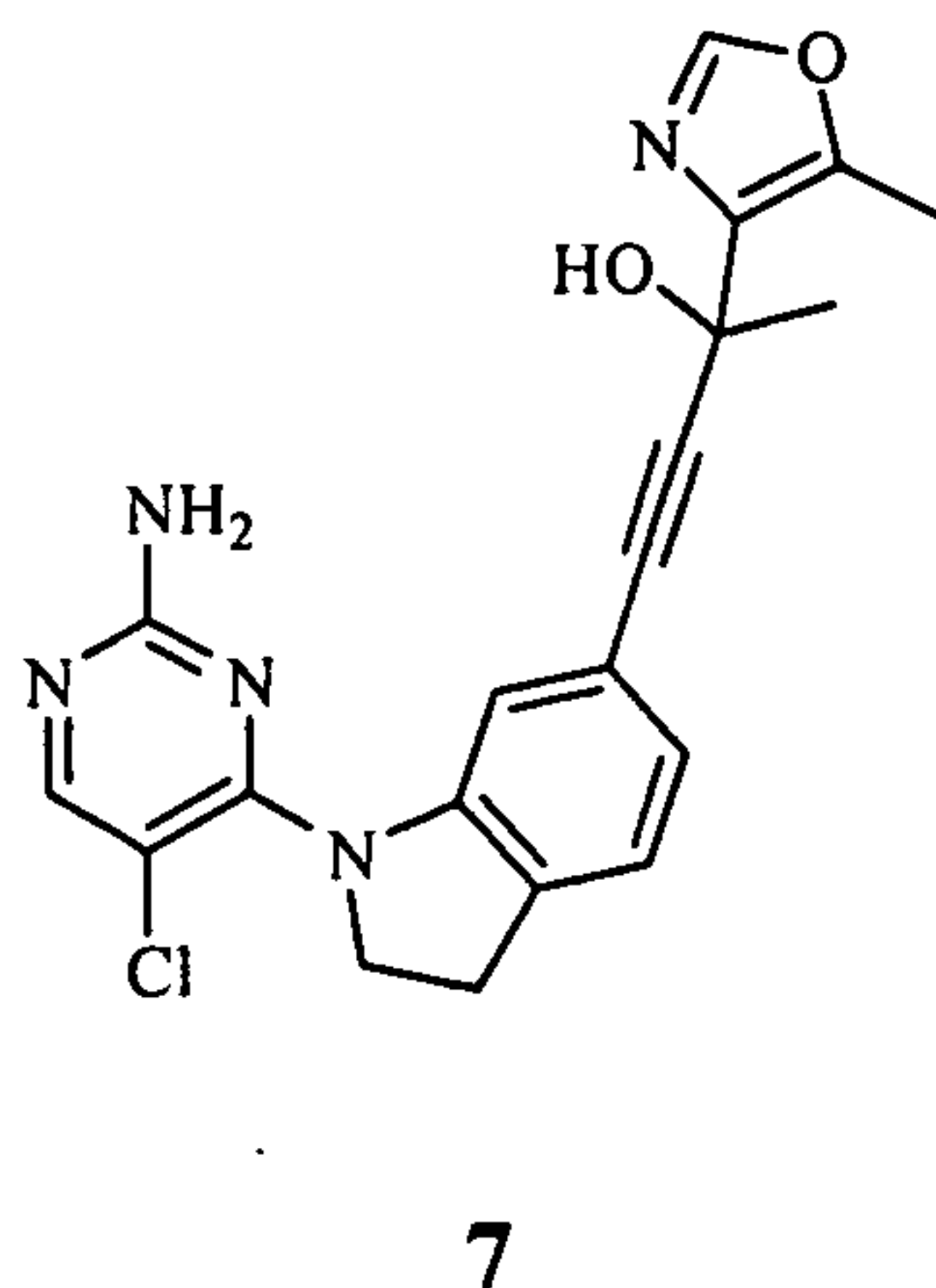
4-(1-(2-amino-5-chloropyrimidin-4-yl)indolin-6-yl)-2-(4-methylpyridin-2-yl)but-3-yn-2-ol (5): (from components A.3 and C.10).

¹H NMR (400 MHz, *DMSO-d*₆) δ ppm 8.38 (1 H, d, *J*=4.7 Hz), 8.10 (1 H, s), 7.57 (1 H, s), 7.20 (1 H, d, *J*=7.8 Hz), 7.13 (1 H, d, *J*=3.9 Hz), 7.10 (1 H, s), 6.90 (1 H, d, *J*=7.0 Hz), 6.66 (2 H, s), 6.22 (1 H, s), 4.15 (2 H, t, *J*=7.8 Hz), 3.08 (2 H, t, *J*=7.8 Hz), 2.35 (3 H, s), 1.76 (3 H, s) Mass Spectrum (ESI) *m/e* = (*M*+1)

Example 6

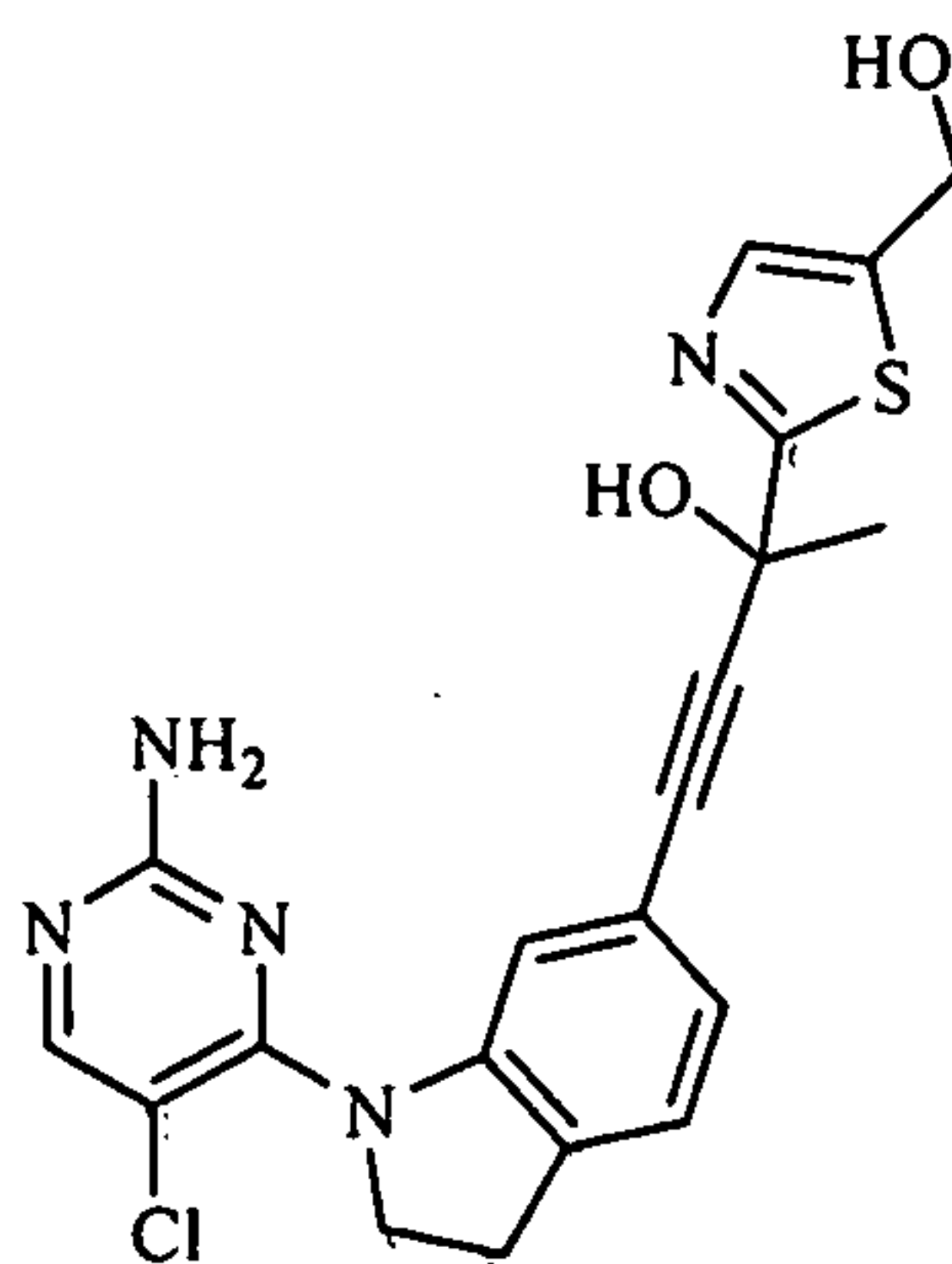
4-(1-(2-amino-5-chloropyrimidin-4-yl)indolin-6-yl)-2-(4-methyl-1,2,5-oxadiazol-3-yl)but-3-yn-2-ol (6): (from components A.3 and C.11).

¹H NMR (400 MHz, *DMSO-d*₆) δ ppm 8.11 (1 H, s), 7.24 (1 H, d, *J*=8.2 Hz), 7.21 (1 H, s), 6.98 (1 H, d, *J*=7.0 Hz), 6.80 (1 H, s), 6.67 (2 H, s), 4.17 (2 H, t, *J*=8.2 Hz), 3.10 (2 H, t, *J*=8.2 Hz), 2.53 (3 H, s), 1.92 (3 H, s) Mass Spectrum (ESI) *m/e* = 397.1, 399.1 (*M*+1)

Example 7

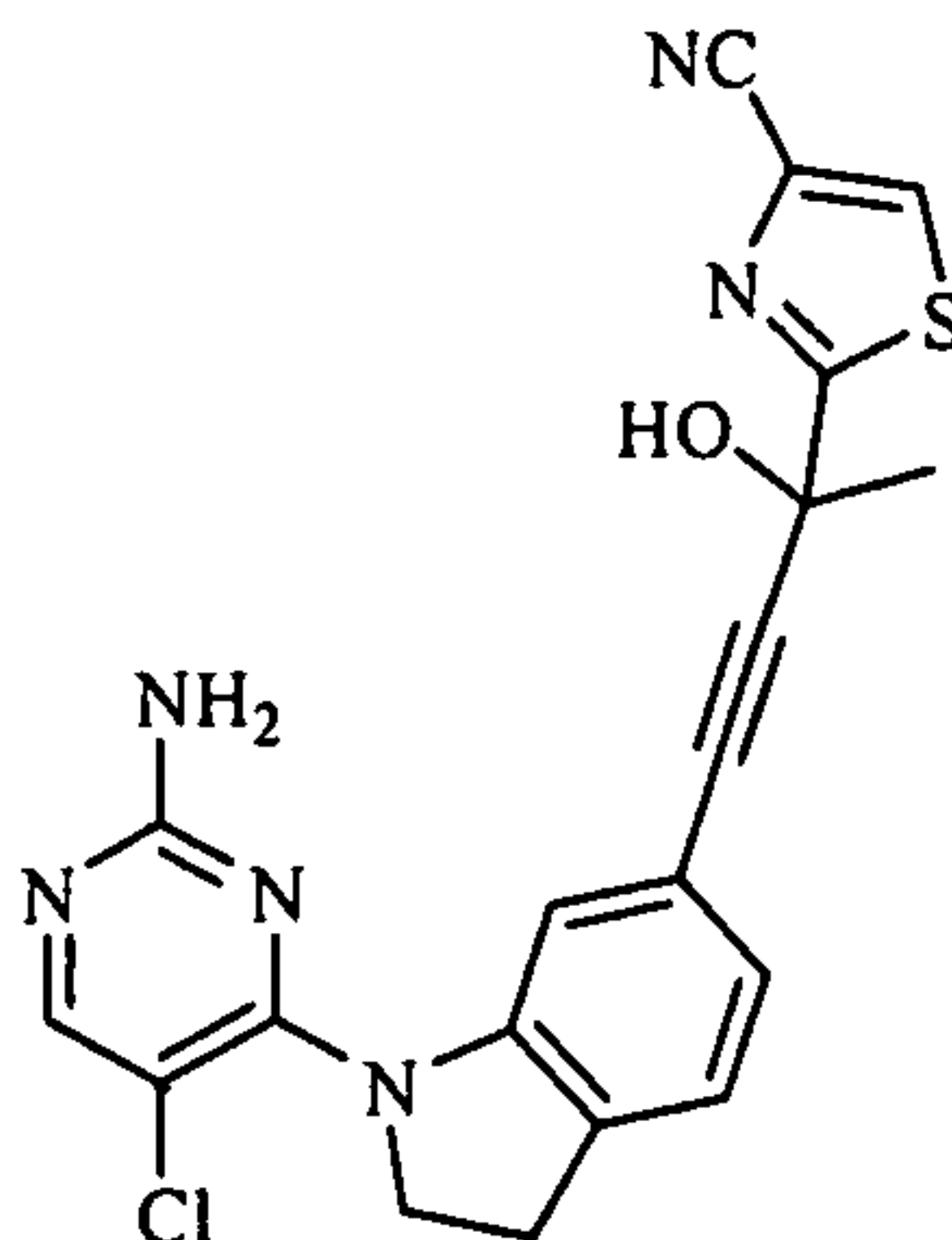
4-(1-(2-amino-5-chloropyrimidin-4-yl)indolin-6-yl)-2-(5-methyloxazol-4-yl)but-3-yn-2-ol (7): (from components A.3 and C.12).

¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 8.11 (1 H, s), 7.22 (1 H, d, *J*=7.3 Hz), 7.14 (1 H, s), 6.94 (1 H, d, *J*=7.6 Hz), 6.65 (2 H, s), 6.01 (1 H, s), 4.16 (2 H, t, *J*=8.2 Hz), 3.09 (2 H, t, *J*=7.5 Hz), 2.47 (3 H, s), 1.74 (3 H, s) Mass Spectrum (ESI) *m/e* = 428.0, 430.0 (*M*+1)

Example 8**8**

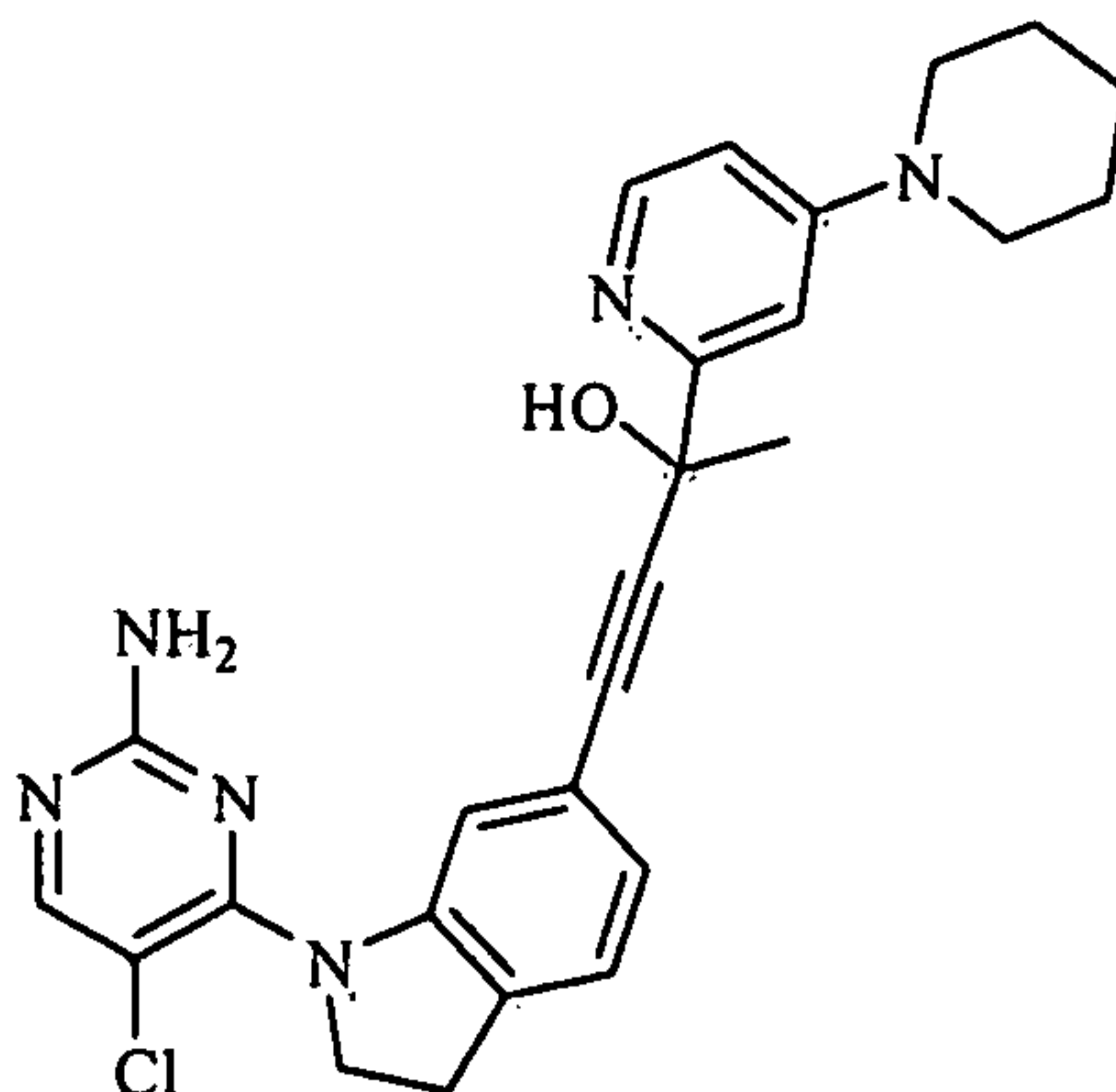
4-(1-(2-amino-5-chloropyrimidin-4-yl)indolin-6-yl)-2-(5-(hydroxymethyl)thiazol-2-yl)but-3-yn-2-ol (8): (from components A.3 and C.13).

¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 8.11 (1 H, s), 7.55 (1 H, s), 7.22 (1 H, d, *J*=6.4 Hz), 7.13 (1 H, s), 6.93 (1 H, d, *J*=6.8 Hz), 6.89 (1 H, s), 6.65 (2 H, s), 5.50 (1 H, s), 4.63 (2 H, s), 4.16 (2 H, s), 3.07 - 3.12 (2 H, m), 1.83 (3 H, s)

Example 9**9**

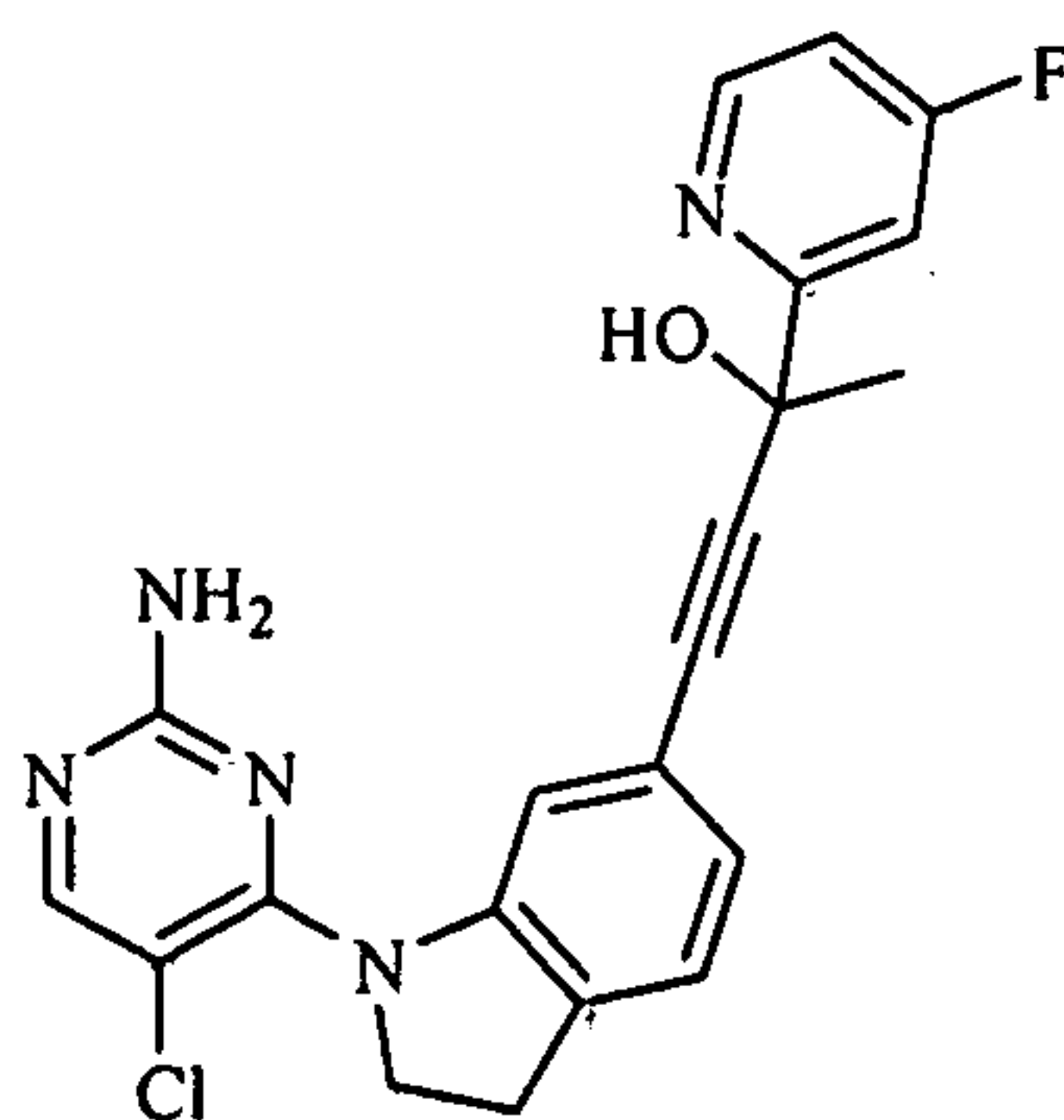
2-(4-(1-(2-amino-5-chloropyrimidin-4-yl)indolin-6-yl)-2-hydroxybut-3-yn-2-yl)thiazole-4-carbonitrile (9): (from components A.3 and C.14).

¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 8.82 (1 H, s), 7.36 (1 H, s), 7.17 - 7.25 (2 H, m), 6.97 (1 H, s), 6.67 (2 H, s), 4.18 (2 H, s), 3.11 (2 H, s), 1.86 (3 H, s)

Example 10**10**

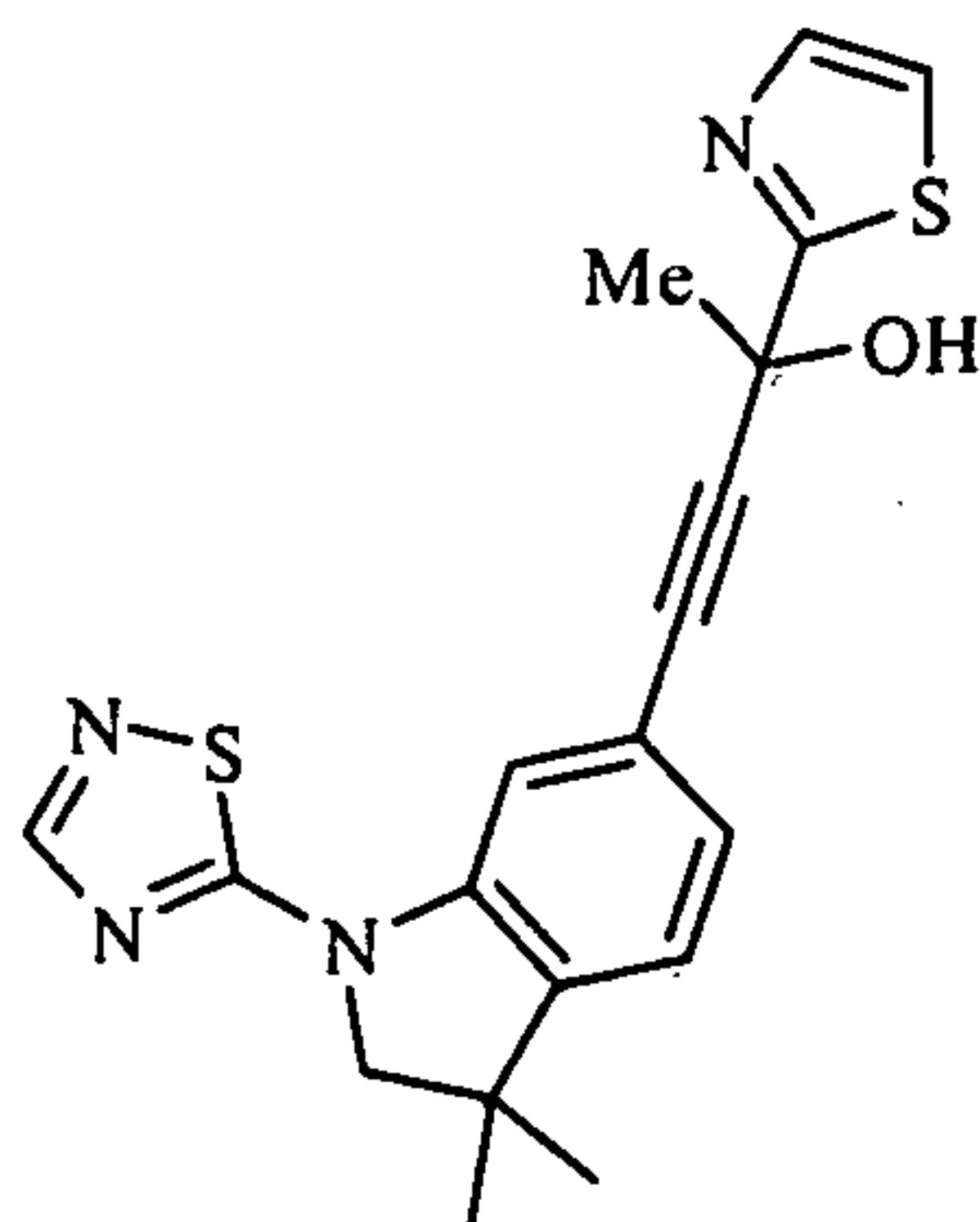
4-(1-(2-amino-5-chloropyrimidin-4-yl)indolin-6-yl)-2-(4-(piperidin-1-yl)pyridin-2-yl)but-3-yn-2-ol (10): (from components A.3 and C.15).

¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 8.14 (1 H, d, *J*=7.6 Hz), 8.12 (1 H, s), 7.57 (1 H, d, *J*=2.0 Hz), 7.39 - 7.47 (2 H, m), 7.10 (2 H, d, *J*=7.6 Hz), 6.65 (2 H, s), 6.44 (1 H, s), 6.22 (1 H, s), 4.22 - 4.33 (2 H, m), 3.67 - 3.88 (4 H, m), 3.20 (2 H, t, *J*=8.2 Hz), 1.59 - 1.75 (9 H, m)

Example 11**11**

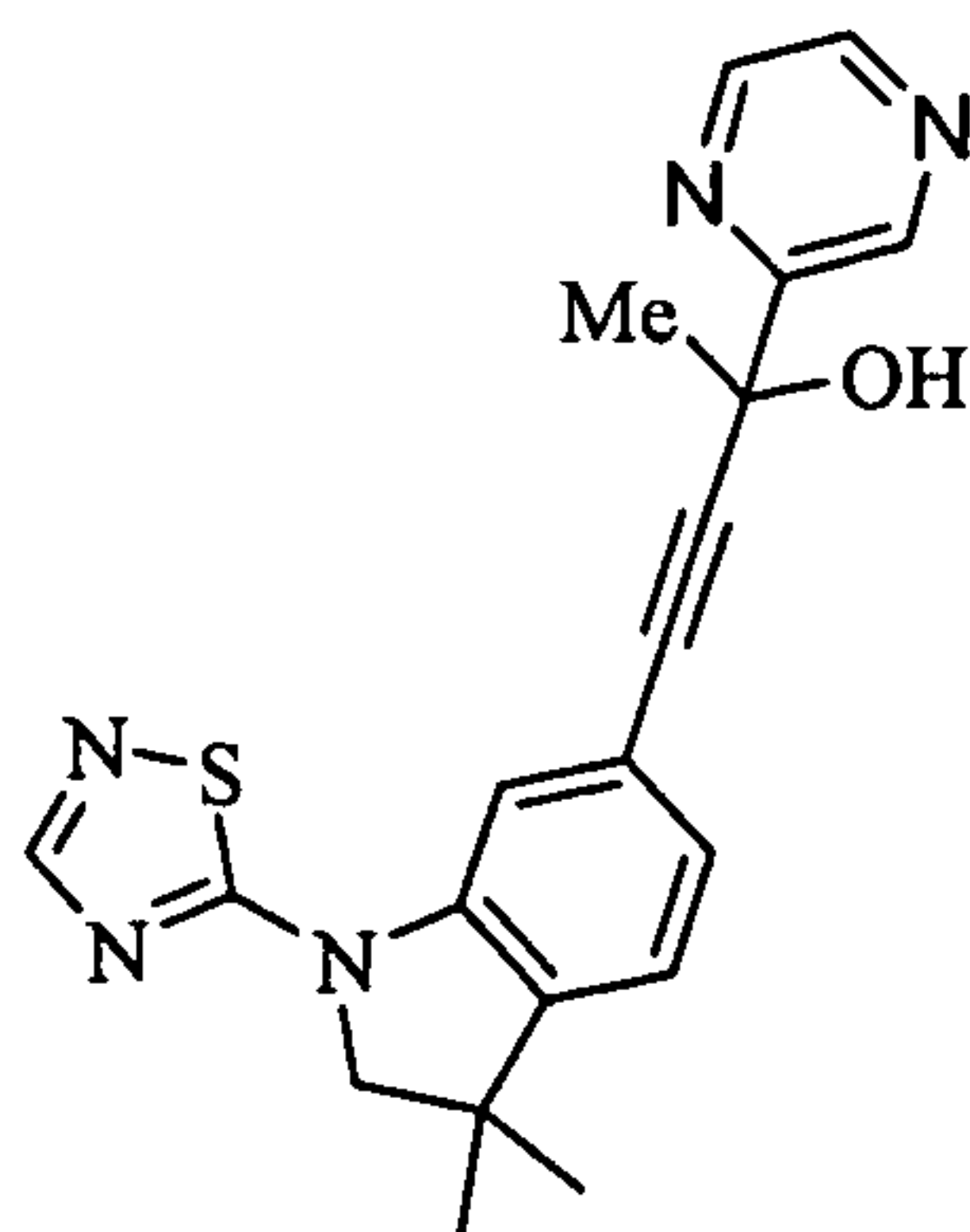
4-(1-(2-amino-5-chloropyrimidin-4-yl)indolin-6-yl)-2-(4-fluoropyridin-2-yl)but-3-yn-2-ol (11): (from components A.3 and C.15).

¹H NMR (400 MHz, *DMSO-d*₆) δ ppm 8.11 (1 H, s), 7.72 (1 H, d, *J*=7.4 Hz), 7.39 (1 H, d, *J*=7.8 Hz), 7.35 (1 H, s), 7.04 (1 H, d, *J*=7.0 Hz), 6.64 (2 H, s), 6.37 (1 H, d, *J*=2.3 Hz), 5.99 - 6.09 (2 H, m), 4.24 (2 H, t, *J*=7.8 Hz), 3.17 (2 H, t, *J*=8.0 Hz), 1.52 (3 H, s)

Example 12**12**

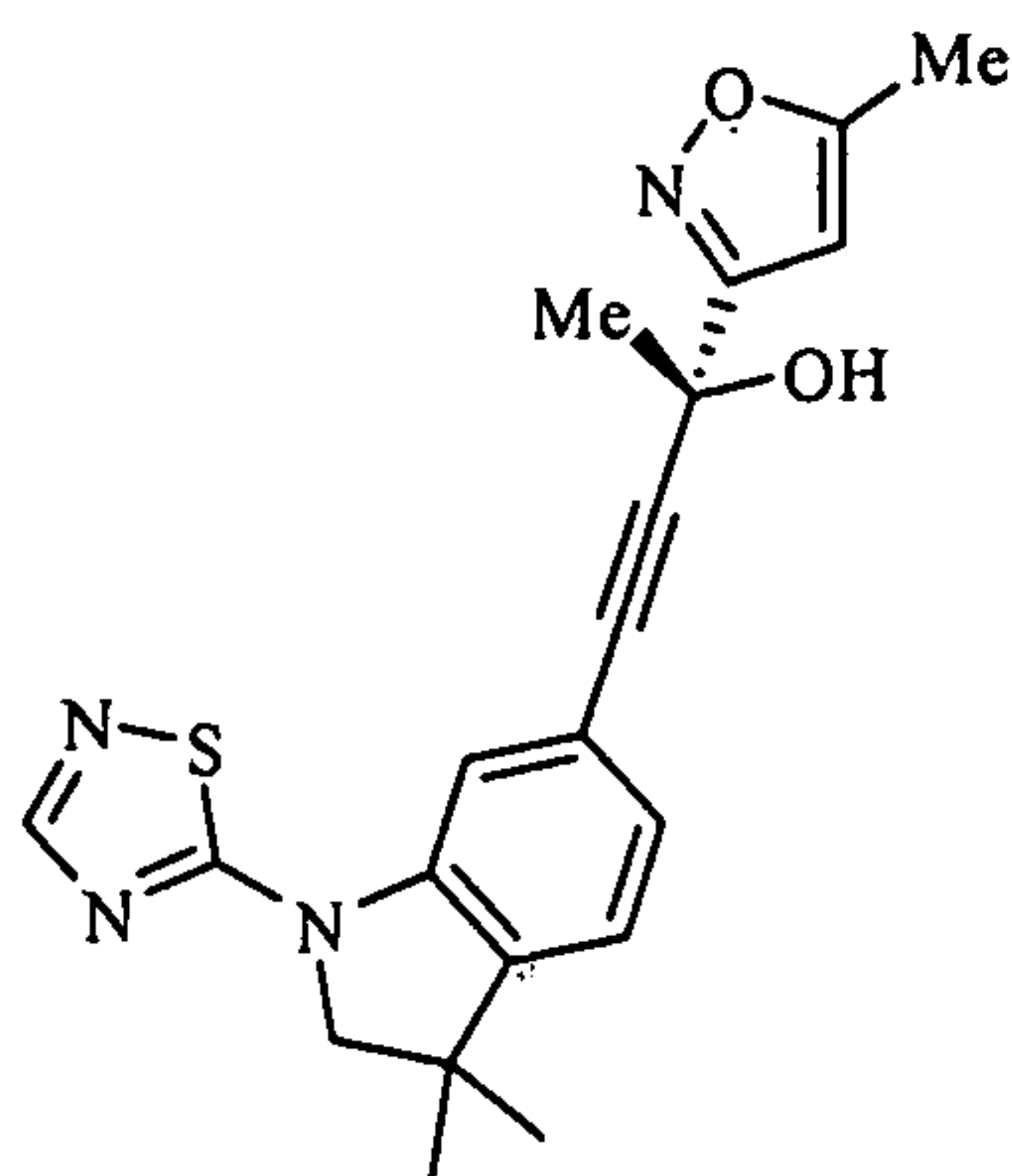
4-(3,3-dimethyl-1-(1,2,4-thiadiazol-5-yl)indolin-6-yl)-2-(thiazol-2-yl)but-3-yn-2-ol (12):
(from components A.81 and C.4 using).

¹H NMR (400 MHz, *DMSO-d*₆) δ ppm 8.38 (1 H, s), 7.97 (1 H, s), 7.78 (1 H, d, *J*=2.7 Hz), 7.69 (1 H, d, *J*=2.7 Hz), 7.36 (1 H, d, *J*=7.8 Hz), 7.15 (1 H, d, *J*=7.4 Hz), 7.06 (1 H, s), 3.87 (2 H, s), 1.88 (3 H, s), 1.38 (6 H, s)

Example 13**13**

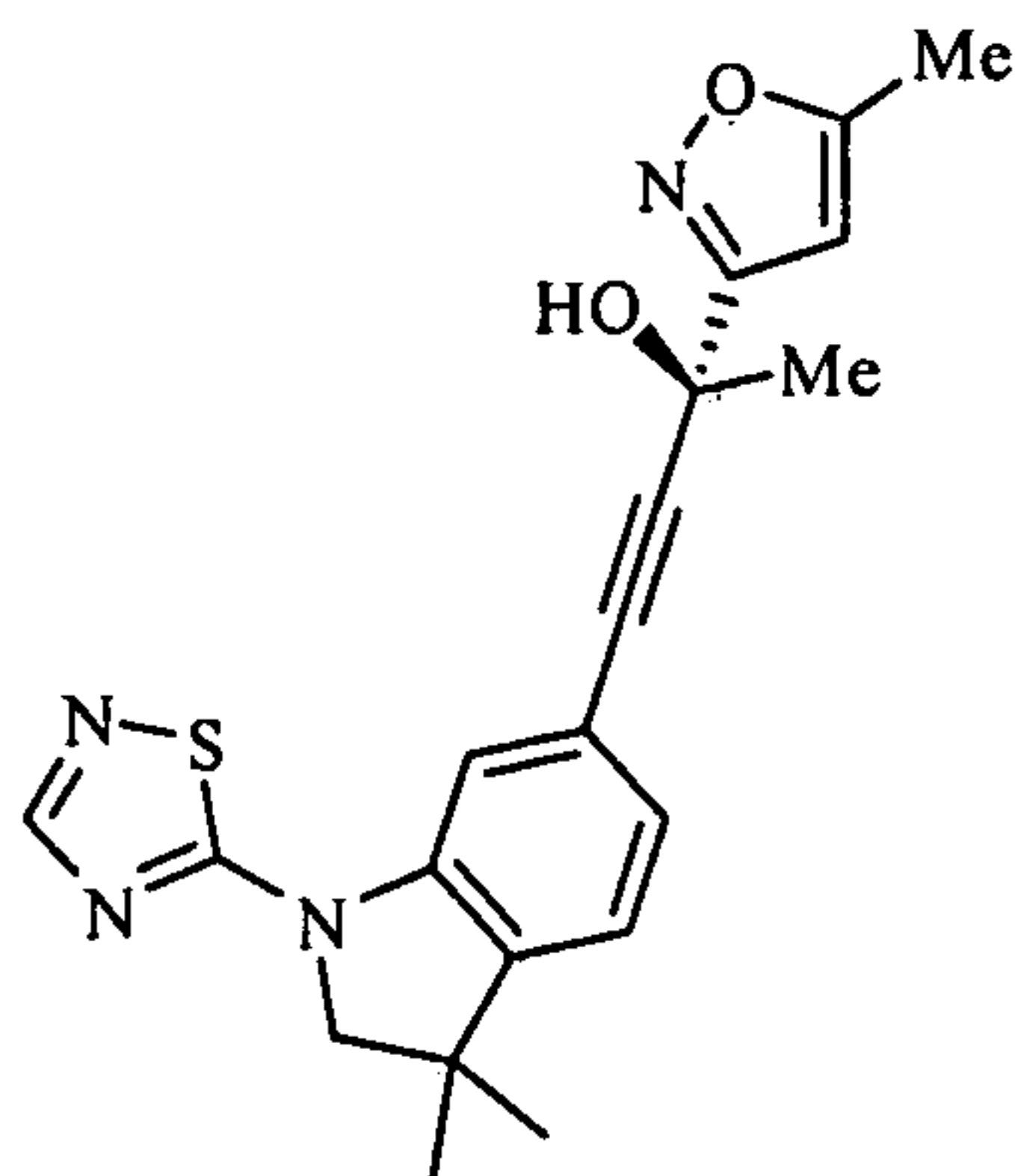
4-(3,3-dimethyl-1-(1,2,4-thiadiazol-5-yl)indolin-6-yl)-2-(pyrazin-2-yl)but-3-yn-2-ol (13):
(from components A.81 and C.14).

¹H NMR (400 MHz, *DMSO-d*₆) δ ppm 9.01 (1 H, s), 8.64 (2 H, dd, *J*=10.4, 1.8 Hz), 8.38 (1 H, s), 7.96 (1 H, s), 7.35 (1 H, d, *J*=7.4 Hz), 7.14 (1 H, d, *J*=7.8 Hz), 6.68 (1 H, s), 3.87 (2 H, s), 1.84 (3 H, s), 1.38 (6 H, s)

Example 14**14**

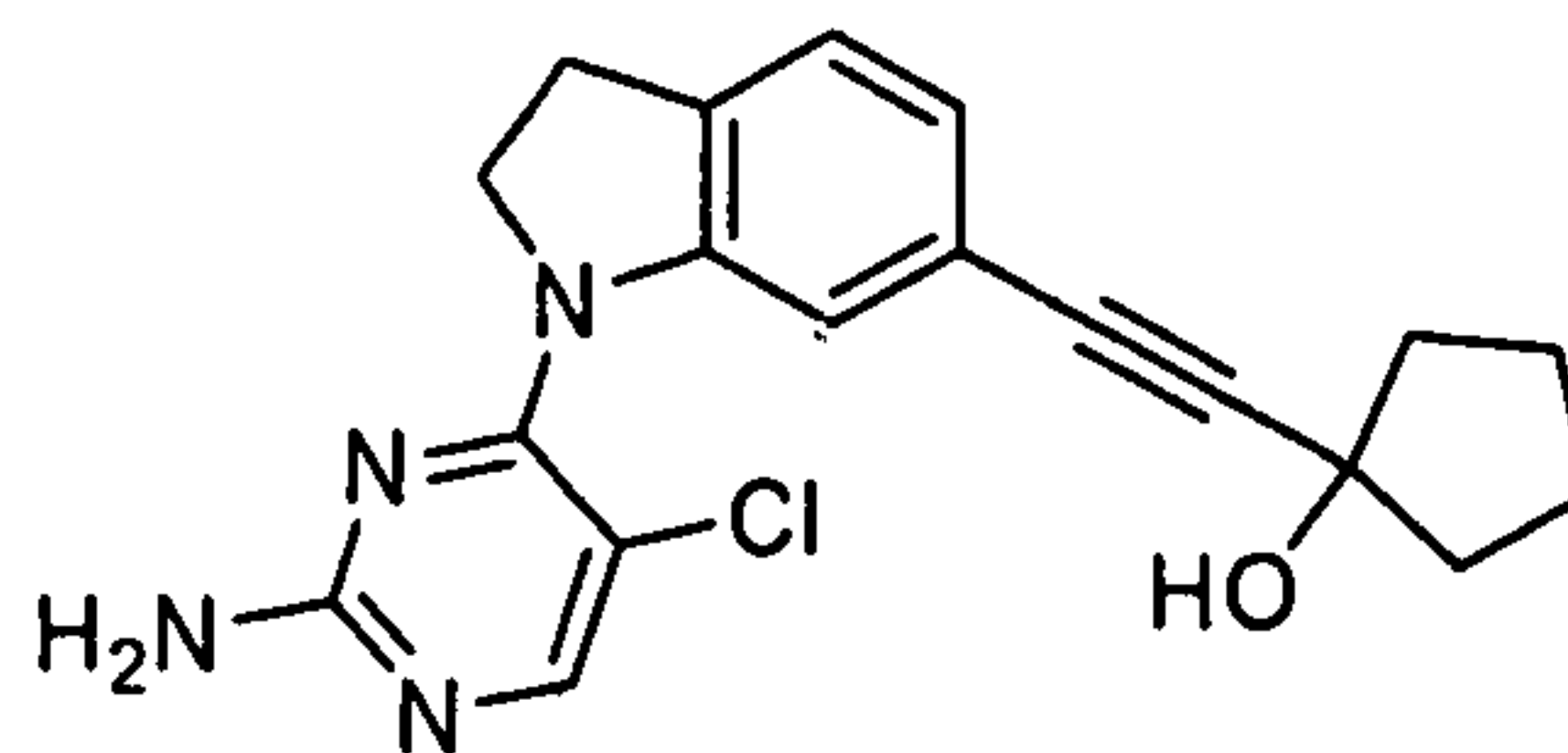
(R)-4-(3,3-dimethyl-1-(1,2,4-thiadiazol-5-yl)indolin-6-yl)-2-(5-methylisoxazol-3-yl)but-3-yn-2-ol (14): (from components A.81 and C.3).

¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 8.38 (1 H, s), 7.97 (1 H, s), 7.36 (1 H, d, *J*=7.3 Hz), 7.15 (1 H, d, *J*=7.3 Hz), 6.53 (1 H, s), 6.35 (1 H, s), 3.87 (2 H, s), 2.41 (3 H, s), 1.79 (3 H, s), 1.38 (6 H, s)

Example 15**15**

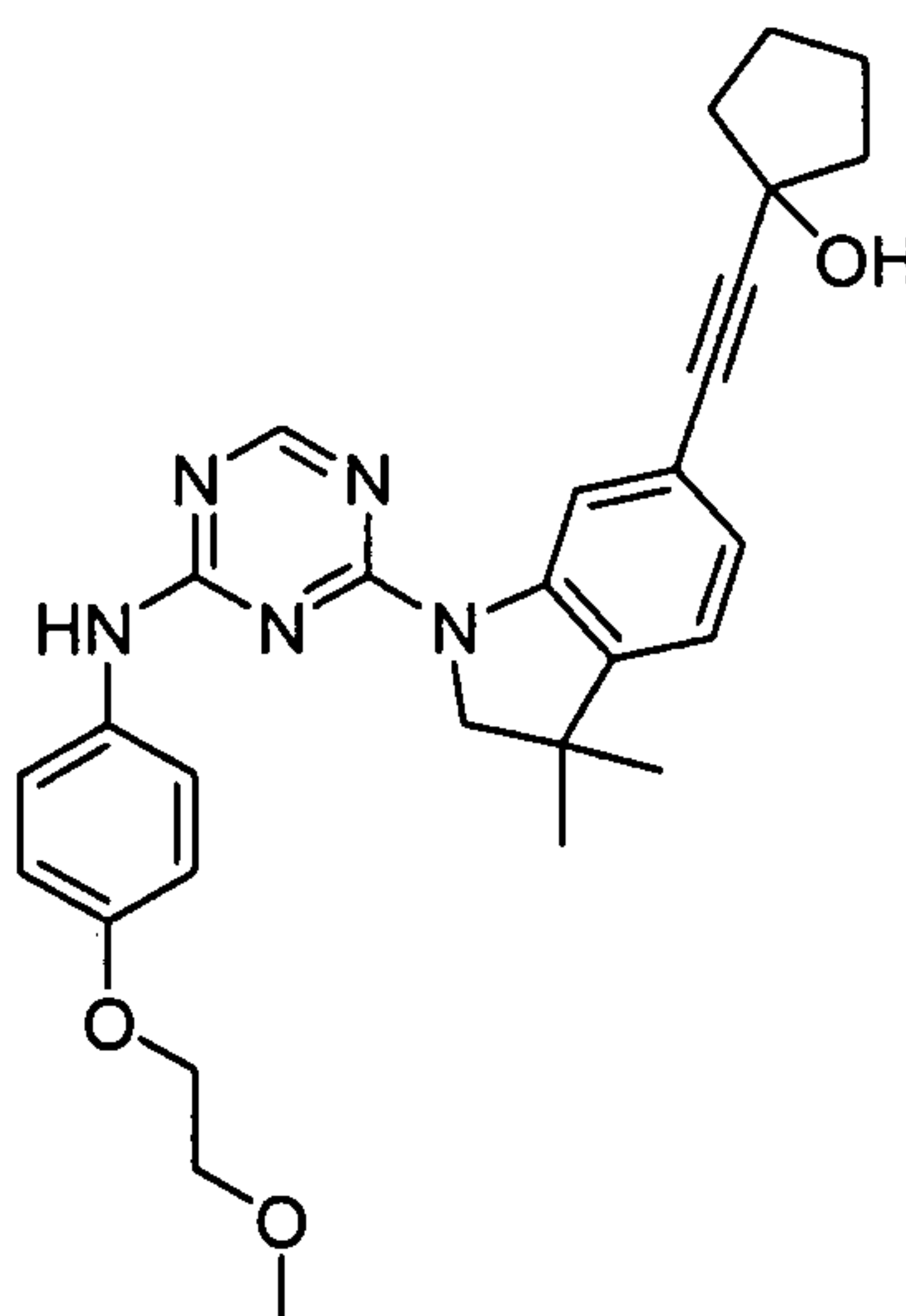
(S)-4-(3,3-dimethyl-1-(1,2,4-thiadiazol-5-yl)indolin-6-yl)-2-(5-methylisoxazol-3-yl)but-3-yn-2-ol (15): (from components A.81 and C.2).

¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 8.39 (1 H, s), 7.97 (1 H, s), 7.36 (1 H, d, *J*=7.6 Hz), 7.15 (1 H, d, *J*=7.3 Hz), 6.53 (1 H, s), 6.35 (1 H, s), 3.87 (2 H, s), 2.41 (3 H, s), 1.79 (3 H, s), 1.38 (6 H, s)

Example 16**16**

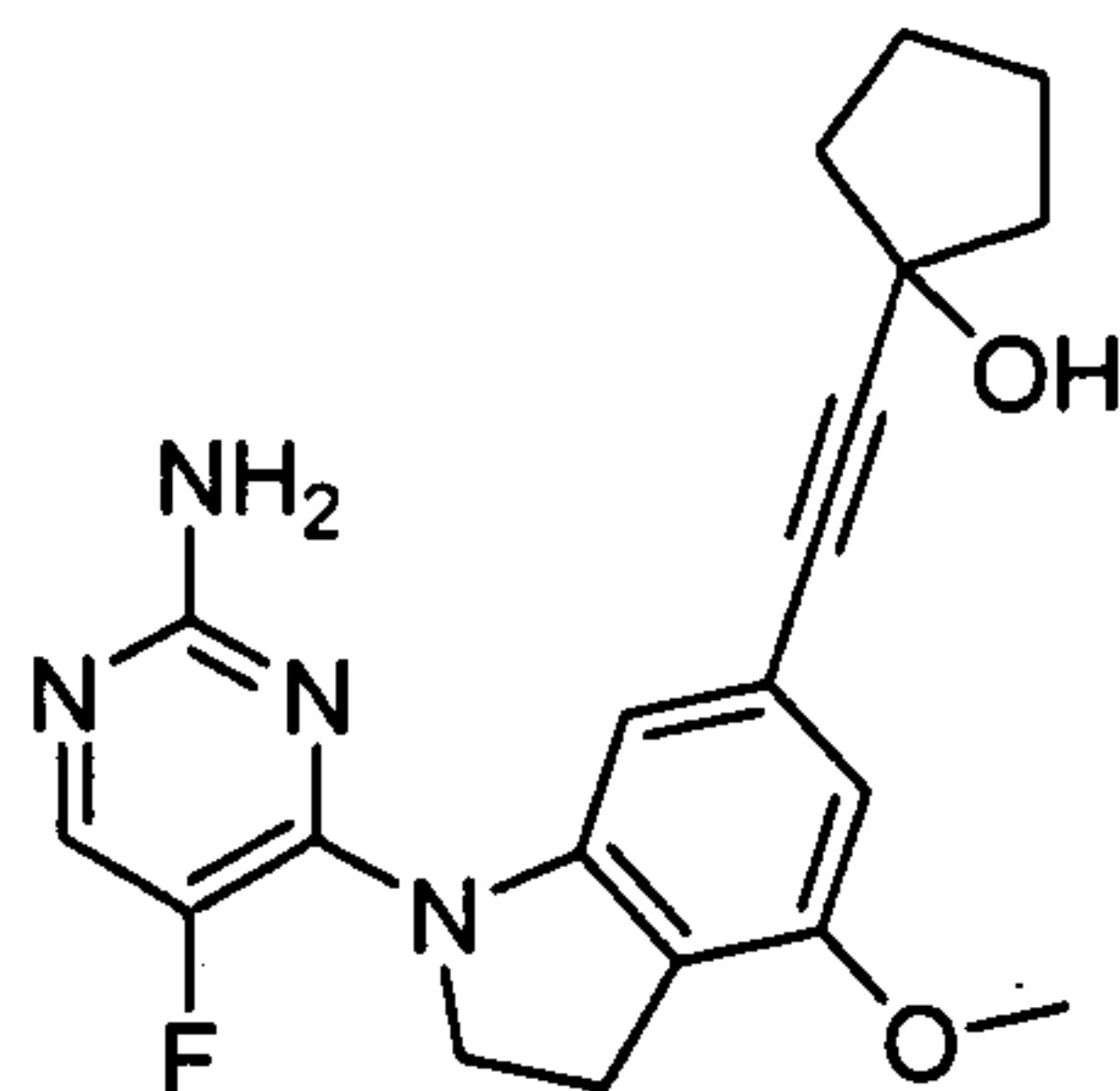
1-(2-(1-(2-amino-5-chloropyrimidin-4-yl)indolin-6-yl)ethynyl)cyclopentanol (16): (from components A.3 and C.36).

^1H NMR (methanol- d_4) δ 8.13(s, 1 H), 8.02(s, 1 H), 7.32 (d, J = 8.0 Hz, 1 H), δ 7.21(d, J = 8.0 Hz, 1 H), 4.61 (t, J = 8.0 Hz, 2 H), 3.25 (t, J = 8.0 Hz, 2 H), 2.10-1.96(m, 4 H), 1.90-1.70 (m, 4 H); ms 355.1 ($\text{M}+\text{H}^+$).

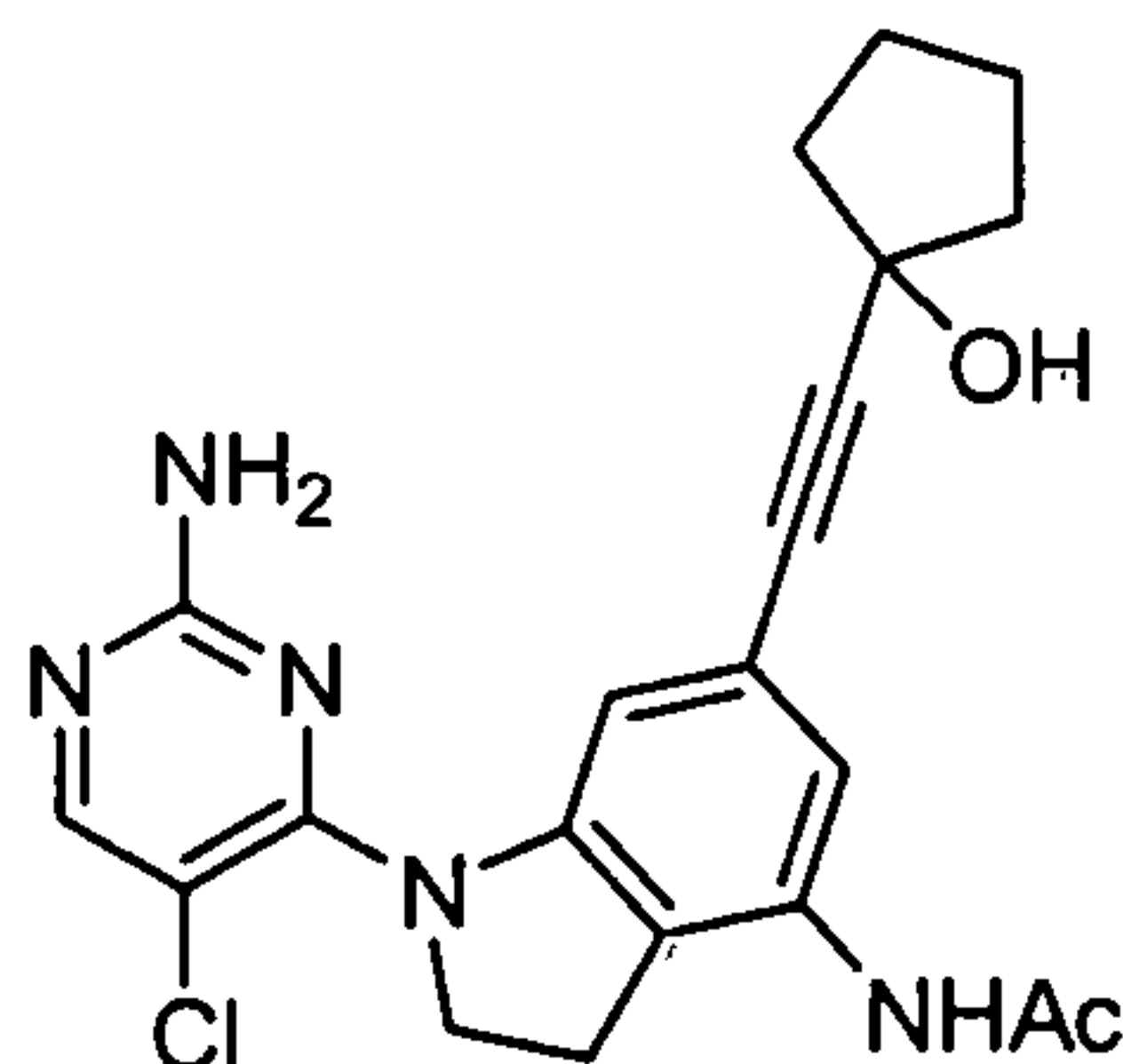
Example 17**17**

1-(2-(1-(4-(4-(2-methoxyethoxy)phenylamino)-1,3,5-triazin-2-yl)-3,3-dimethylindolin-6-yl)ethynyl)cyclopentanol (17): (from components A.93 and C.36).

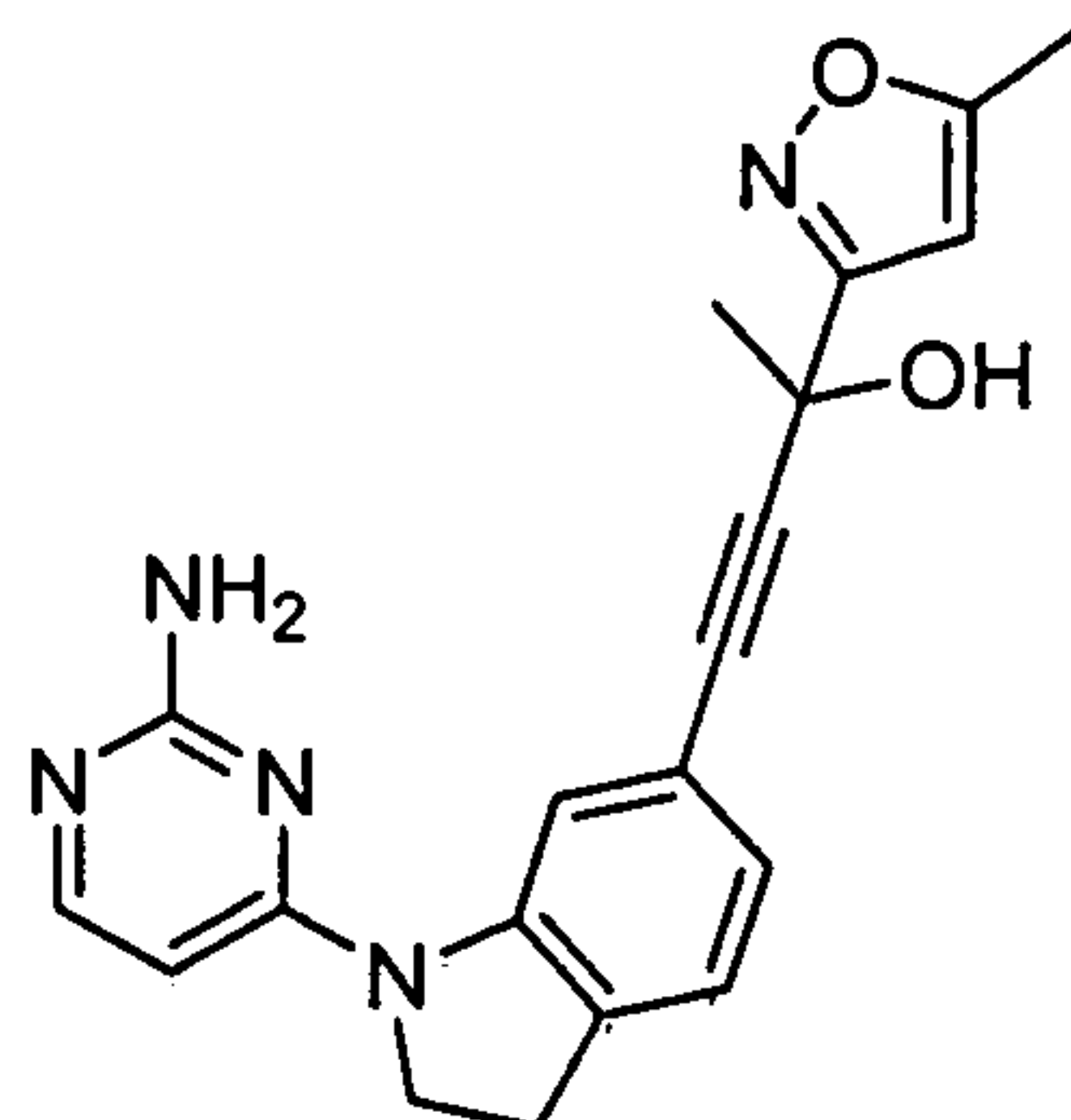
^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 9.76 (1 H, s), 8.39 (2 H, d, J =40.3 Hz), 7.60 (2 H, s), 7.26 (1 H, d, J =7.7 Hz), 7.05 (1 H, dd, J =7.5, 1.3 Hz), 6.94 (2 H, d, J =7.7 Hz), 5.28 (1 H, s), 4.07 (2 H, dd, J =5.5, 4.0 Hz), 3.96 (2 H, s), 3.65 (2 H, dd, J =5.3, 3.8 Hz), 3.30 (3 H, s), 1.81 - 1.97 (4 H, m), 1.62 - 1.80 (4 H, m), 1.33 (6 H, s); Mass Spectrum (ESI) m/e = 500.5 [$\text{M}+1$].

Example 18**18**

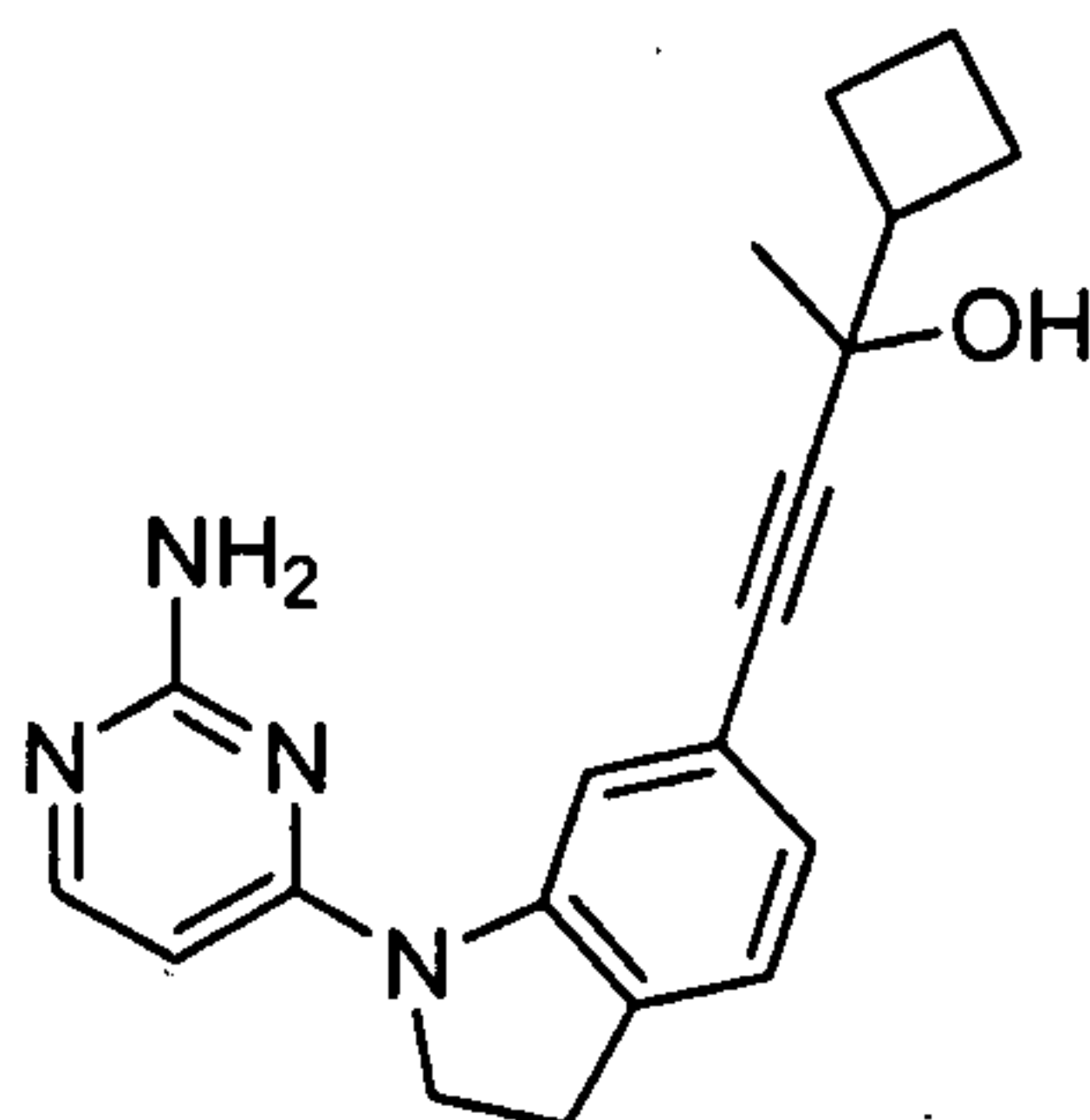
1-(2-(1-(2-amino-5-fluoropyrimidin-4-yl)-4-methoxyindolin-6-yl)ethynyl)cyclopentanol (18). (from components A.87 and C.36) ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 7.60 (1 H, s), 6.61 (1 H, s), 6.36 (2 H, s), 5.75 (1 H, s), 5.24 (1 H, s), 4.16 - 4.24 (2 H, m), 3.80 (3 H, s), 3.01 (2 H, t, $J=8.7$ Hz), 1.88 - 1.94 (4 H, m), 1.63 - 1.78 (4 H, m); Mass Spectrum (ESI) m/e = 369.1 [M+1].

Example 19**19**

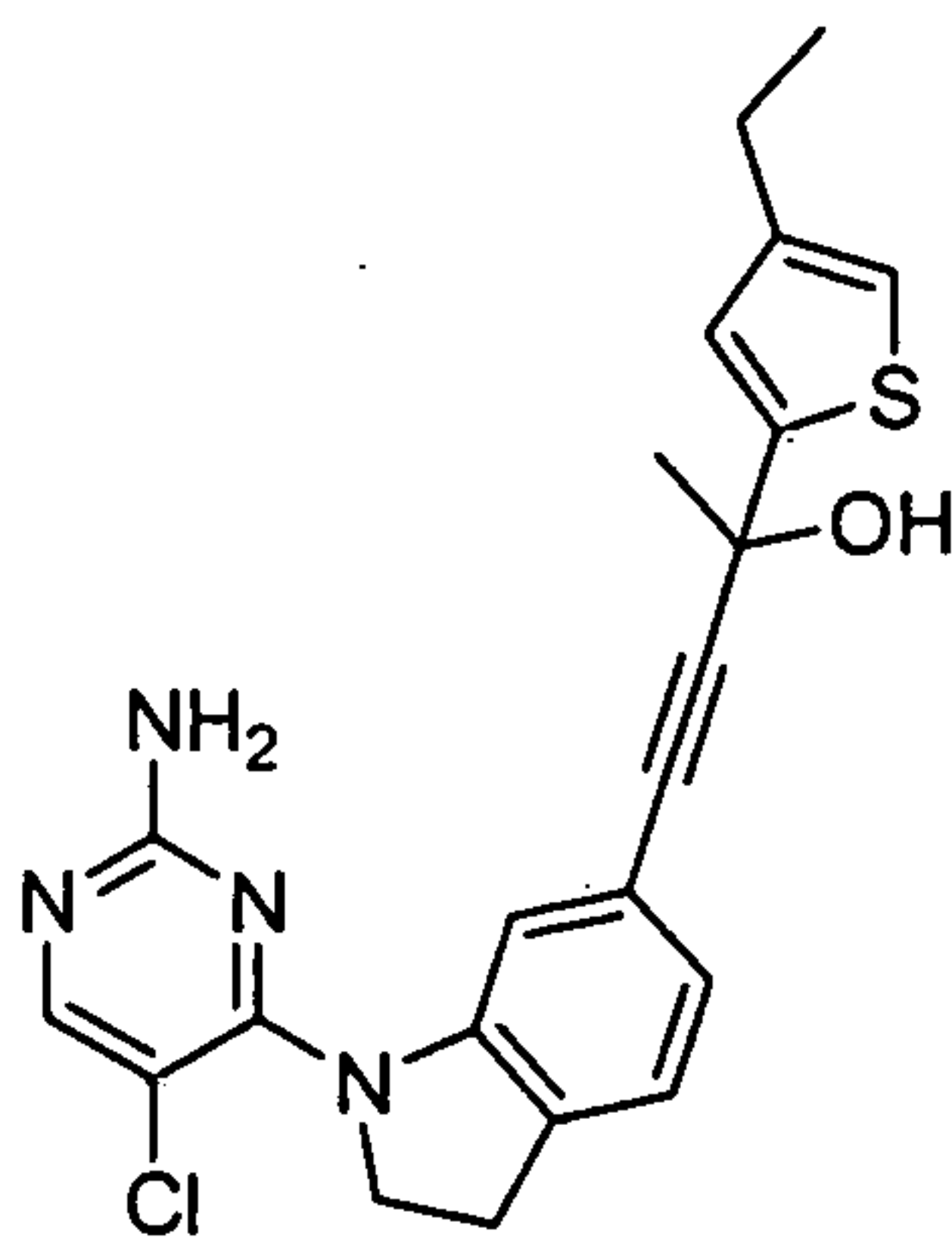
N-(1-(2-amino-5-chloropyrimidin-4-yl)-6-(2-(1-hydroxycyclopentyl)ethynyl)indolin-4-yl)acetamide (19). (from components A.90 and C.36) ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 9.43 (1 H, s), 8.11 (1 H, s), 7.31 (1 H, s), 6.88 (1 H, s), 6.66 (2 H, s), 5.27 (1 H, s), 4.15 (2 H, t, $J=8.2$ Hz), 3.02 (2 H, t, $J=8.2$ Hz), 2.07 (3 H, s), 1.80 - 1.93 (4 H, m), 1.61 - 1.76 (4 H, m); Mass Spectrum (ESI) m/e = 412.1 [M+1].

Example 20**20**

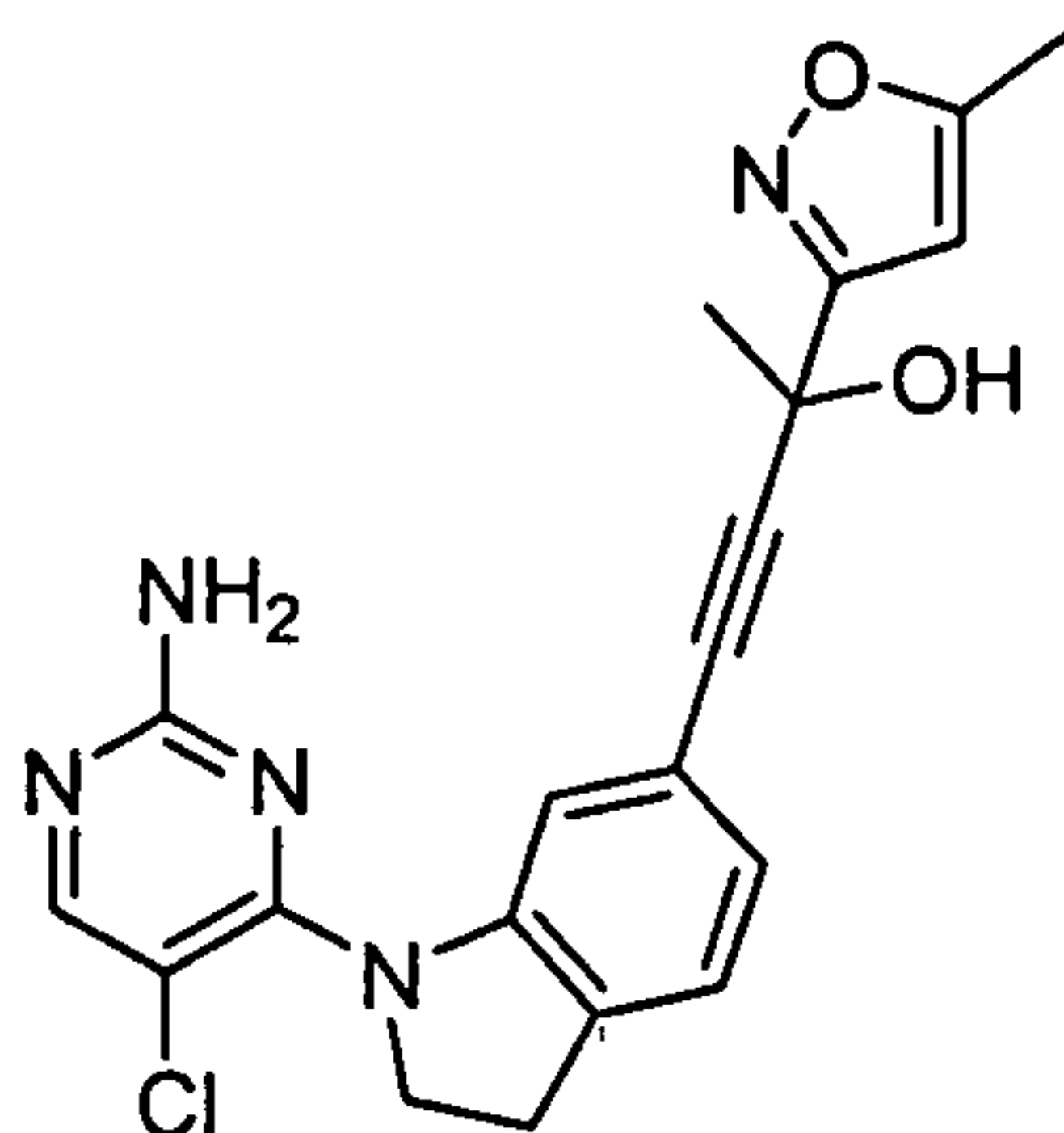
4-(1-(2-aminopyrimidin-4-yl)indolin-6-yl)-2-(5-methylisoxazol-3-yl)but-3-yn-2-ol (20). (from components A.95 and C.1) ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.43 (1 H, s), 7.99 (1 H, s), 7.19 (1 H, d, $J=7.8$ Hz), 6.96 (1 H, dd, $J=7.6, 1.4$ Hz), 6.28 - 6.42 (4 H, m), 6.04 (1 H, d, $J=5.5$ Hz), 3.97 (2 H, t, $J=8.6$ Hz), 3.17 (2 H, t, $J=8.6$ Hz), 2.40 (3 H, s), 1.81 (3 H, s); Mass Spectrum (ESI) $m/e = 362.4$ $[\text{M}+1]$.

Example 21**21**

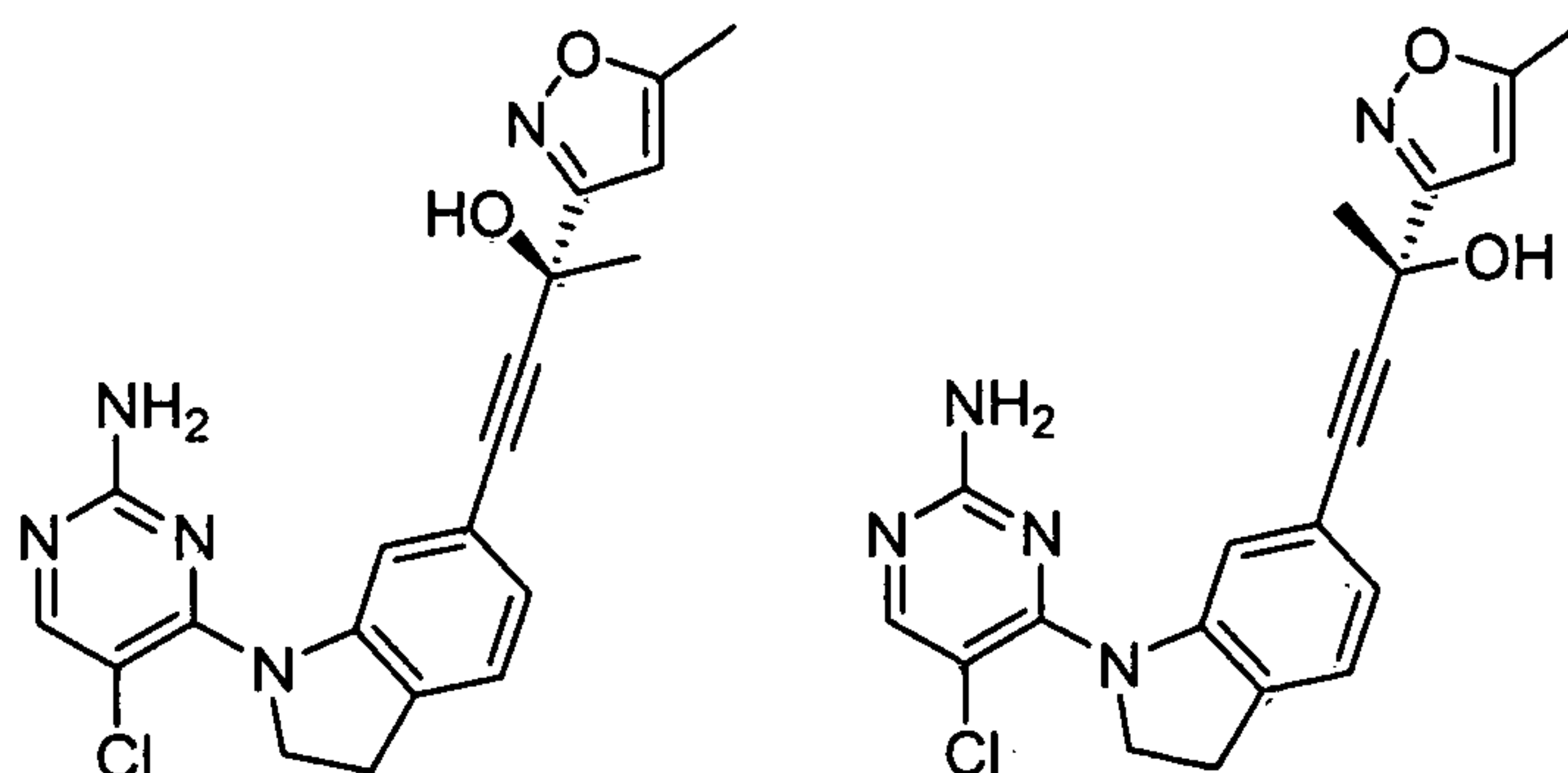
4-(1-(2-aminopyrimidin-4-yl)indolin-6-yl)-2-cyclobutylbut-3-yn-2-ol (21). (from components A.95 and C.22) ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.39 (1 H, s), 8.01 (1 H, s), 7.18 (1 H, d, $J=7.4$ Hz), 6.94 (1 H, dd, $J=7.4, 1.2$ Hz), 6.27 (2 H, s), 6.05 (1 H, s), 5.18 (1 H, s), 3.97 (2 H, t, $J=8.6$ Hz), 3.16 (2 H, t, $J=8.6$ Hz), 2.52 - 2.56 (1 H, m), 1.64 - 2.14 (6 H, m), 1.32 (3 H, s); Mass Spectrum (ESI) $m/e = 335.2$ $[\text{M}+1]$.

Example 22**22**

4-(1-(2-amino-5-chloropyrimidin-4-yl)indolin-6-yl)-2-(4-ethylthiophen-2-yl)but-3-yn-2-ol (22). (from components A.2 and C.26) ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 8.12 (1 H, s), 7.23 (1 H, d, $J=7.8$ Hz), 7.17 (1 H, s), 6.94 - 7.03 (3 H, m), 6.66 (2 H, s), 6.37 (1 H, s), 4.17 (2 H, t, $J=8.3$ Hz), 3.10 (2 H, t, $J=7.8$ Hz), 2.51 - 2.58 (2 H, m), 1.78 (3 H, s), 1.16 (3 H, t, $J=7.5$ Hz); Mass Spectrum (ESI) $m/e = 425.2$ [M+1].

Example 23**23**

4-(1-(2-amino-5-chloropyrimidin-4-yl)indolin-6-yl)-2-(5-methylisoxazol-3-yl)but-3-yn-2-ol (23). (from components A.2 and C.1) ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.11 (1 H, s), 7.22 (1 H, d, $J=7.4$ Hz), 7.17 (1 H, s), 6.95 (1 H, d, $J=7.4$ Hz), 6.65 (2 H, s), 6.42 (1 H, s), 6.33 (1 H, s), 4.17 (2 H, t, $J=8.2$ Hz), 3.10 (2 H, t, $J=8.2$ Hz), 2.39 (3 H, s), 1.77 (3 H, s); Mass Spectrum (ESI) $m/e = 396.1$ [M+1].

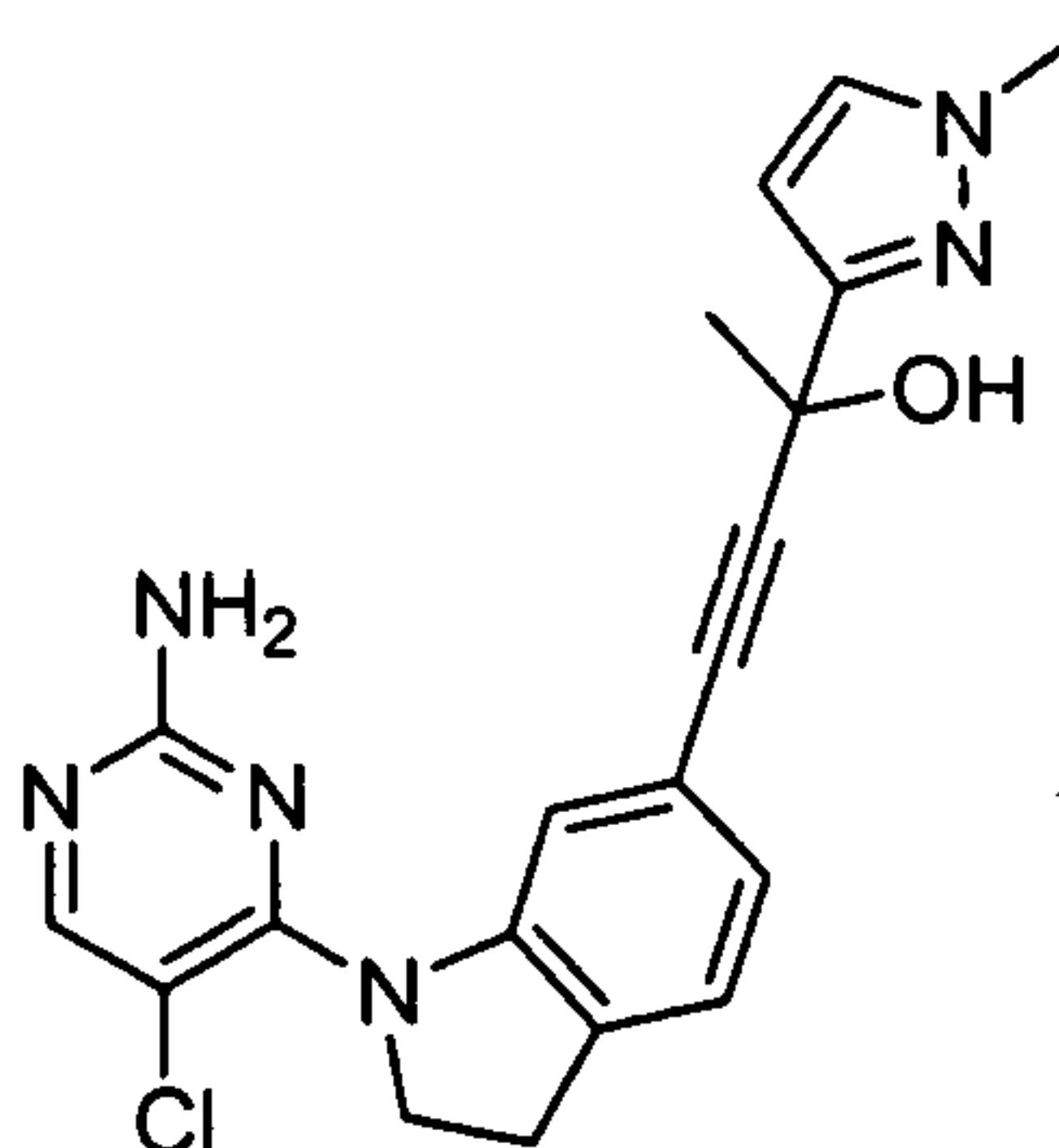
Example 24 and 25**24****25**

(S)-4-(1-(2-amino-5-chloropyrimidin-4-yl)indolin-6-yl)-2-(5-methylisoxazol-3-yl)but-3-yn-2-ol (**24**) and (R)-4-(1-(2-amino-5-chloropyrimidin-4-yl)indolin-6-yl)-2-(5-methylisoxazol-3-yl)but-3-yn-2-ol (**25**). The racemic mixture (**23**, 0.1 g) was separated on a preparative chiral column (AD-H Chiralpak, 250 x 20 mm) using 40% of isopropanol in hexane. The first eluted enantiomer (**24**) was assigned as (S)-4-(1-(2-amino-5-chloropyrimidin-4-yl)indolin-6-yl)-2-(5-methylisoxazol-3-yl)but-3-yn-2-ol (0.033 g) as a colorless syrup; the second eluted enantiomer (**25**) was assigned as (R)-4-(1-(2-amino-5-chloropyrimidin-4-yl)indolin-6-yl)-2-(5-methylisoxazol-3-yl)but-3-yn-2-ol (0.0325 g) as a white foam: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.11 (1 H, s), 7.22 (1 H, d, $J=7.4$ Hz), 7.16 (1 H, d, $J=0.8$ Hz), 6.95 (1 H, dd, $J=7.4$, 1.6 Hz), 6.65 (2 H, s), 6.41 (1 H, s), 6.33 (1 H, d, $J=0.8$ Hz), 4.17 (2 H, t, $J=8.2$ Hz), 3.10 (2 H, t, $J=8.4$ Hz), 2.39 (3 H, s), 1.77 (3 H, s); Mass Spectrum (ESI) $m/e = 396.1$ [$M+1$].

Stereochemical assignment based on biological activity and analogy to compounds of defined structure.

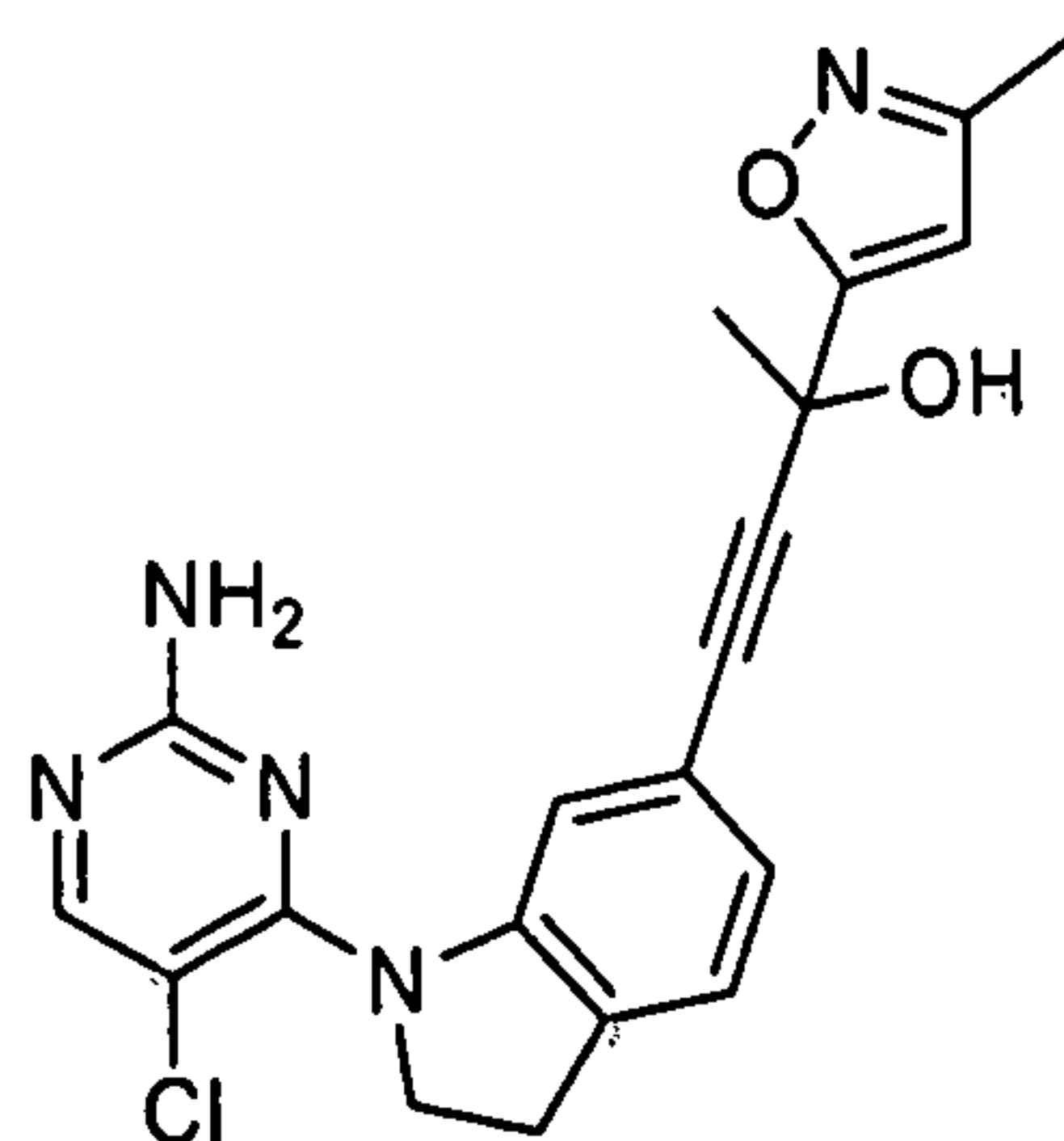
Example 26

Examples 26, 27 were prepared using same or analogous synthetic techniques and substituting with appropriate reagent as in **example 1**.

**26**

4-(1-(2-amino-5-chloropyrimidin-4-yl)indolin-6-yl)-2-(1-methyl-1H-pyrazol-3-yl)but-3-yn-2-ol (26). (from components A.2 and C.23) ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.12 (1 H, s), 7.57 (1 H, d, $J=2.0$ Hz), 7.20 (1 H, d, $J=7.4$ Hz), 7.12 (1 H, s), 6.92 (1 H, dd, $J=7.4, 1.2$ Hz), 6.64 (2 H, s), 6.29 (1 H, d, $J=2.0$ Hz), 5.87 (1 H, s), 4.16 (2 H, t, $J=8.2$ Hz), 3.80 (3 H, s), 3.09 (2 H, t, $J=8.2$ Hz), 1.75 (3 H, s); Mass Spectrum (ESI) $m/e = 395.2$ $[\text{M}+1]$.

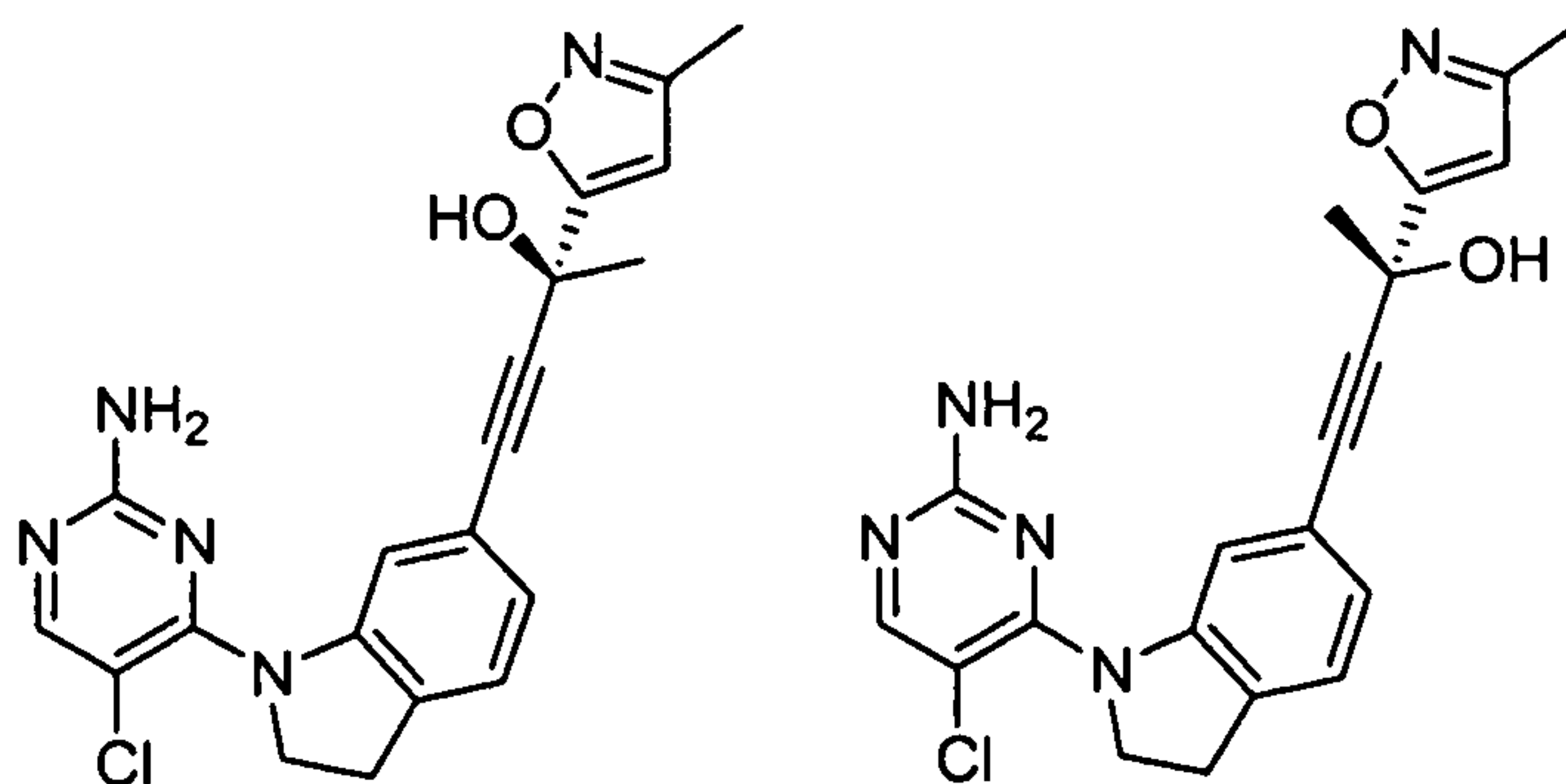
Example 27



27

4-(1-(2-amino-5-chloropyrimidin-4-yl)indolin-6-yl)-2-(3-methylisoxazol-5-yl)but-3-yn-2-ol (27). (from components A.2 and C.24) ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.11 (1 H, s), 7.18 - 7.26 (2 H, m), 6.98 (1 H, dd, $J=7.6, 1.4$ Hz), 6.65 (2 H, s), 6.63 (1 H, s), 6.35 (1 H, s), 4.17 (2 H, t, $J=8.2$ Hz), 3.11 (2 H, t, $J=8.2$ Hz), 2.22 (3 H, s), 1.77 (3 H, s); Mass Spectrum (ESI) $m/e = 396.1$ $[\text{M}+1]$.

Example 28 and 29



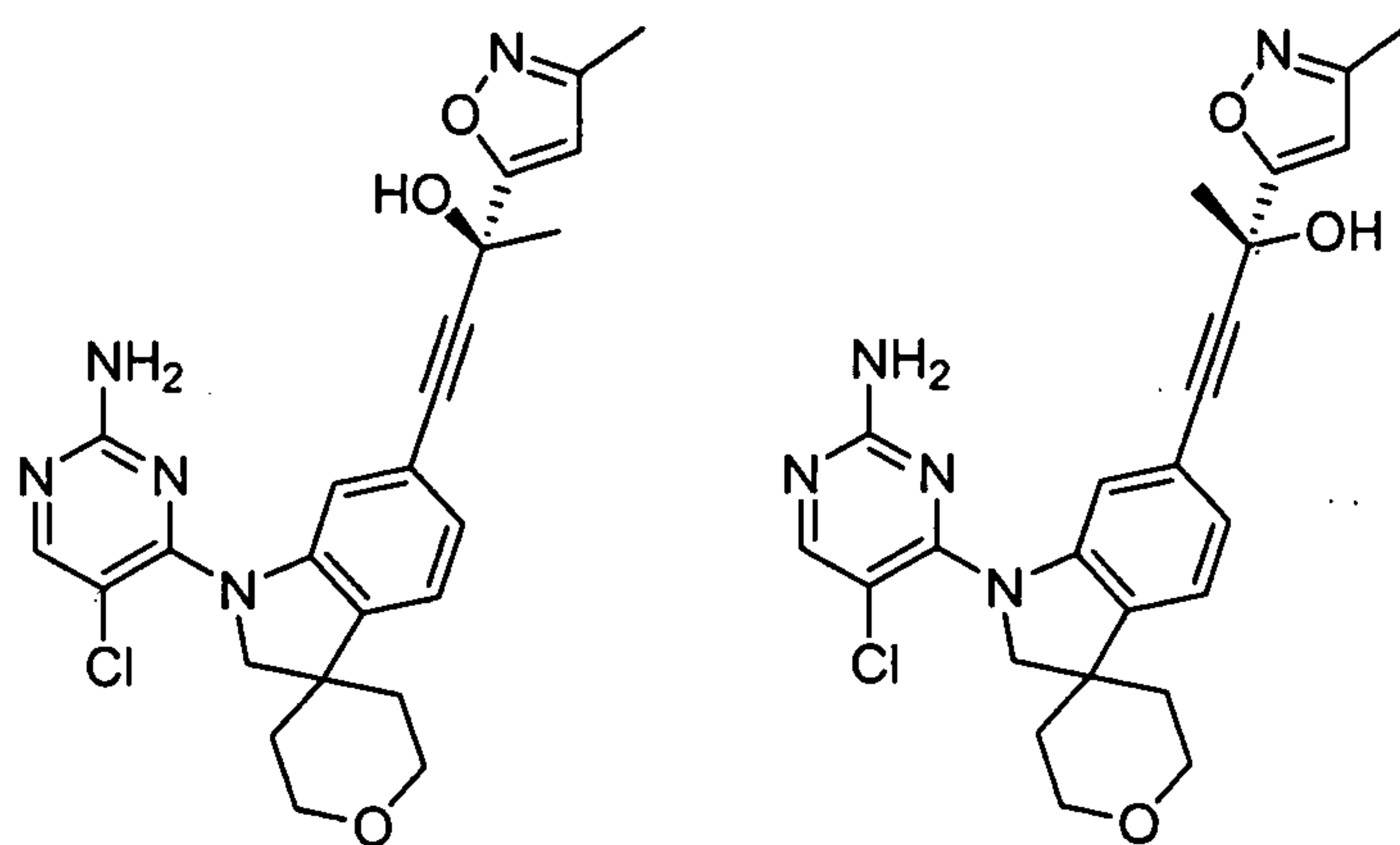
28

29

(S)-4-(1-(2-amino-5-chloropyrimidin-4-yl)indolin-6-yl)-2-(3-methylisoxazol-5-yl)but-3-yn-2-ol (28) and (R)-4-(1-(2-amino-5-chloropyrimidin-4-yl)indolin-6-yl)-2-(3-methylisoxazol-5-yl)but-3-yn-2-ol (29). The racemic mixture (27) (0.0978 g) was separated on a preparative chiral column (AD-H Chiralpak, 250 x 20 mm) using 40% of isopropanol in hexane. The first

eluted enantiomer (**28**) was assigned as (S)-4-(1-(2-amino-5-chloropyrimidin-4-yl)indolin-6-yl)-2-(3-methylisoxazol-5-yl)but-3-yn-2-ol (0.033 g) as a colorless syrup; the second eluted enantiomer (**29**) was assigned as (R)-4-(1-(2-amino-5-chloropyrimidin-4-yl)indolin-6-yl)-2-(3-methylisoxazol-5-yl)but-3-yn-2-ol (0.0325 g) as a white foam: ^1H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 8.11 (1 H, s), 7.17 - 7.26 (2 H, m), 6.98 (1 H, dd, $J=7.6, 1.4$ Hz), 6.65 (2 H, s), 6.63 (1 H, s), 6.35 (1 H, s), 4.17 (2 H, t, $J=8.4$ Hz), 3.11 (2 H, t, $J=8.2$ Hz), 2.22 (3 H, s), 1.77 (3 H, s); Mass Spectrum (ESI) $m/e = 396.1$ [M+1].

Example 30 and 31



30

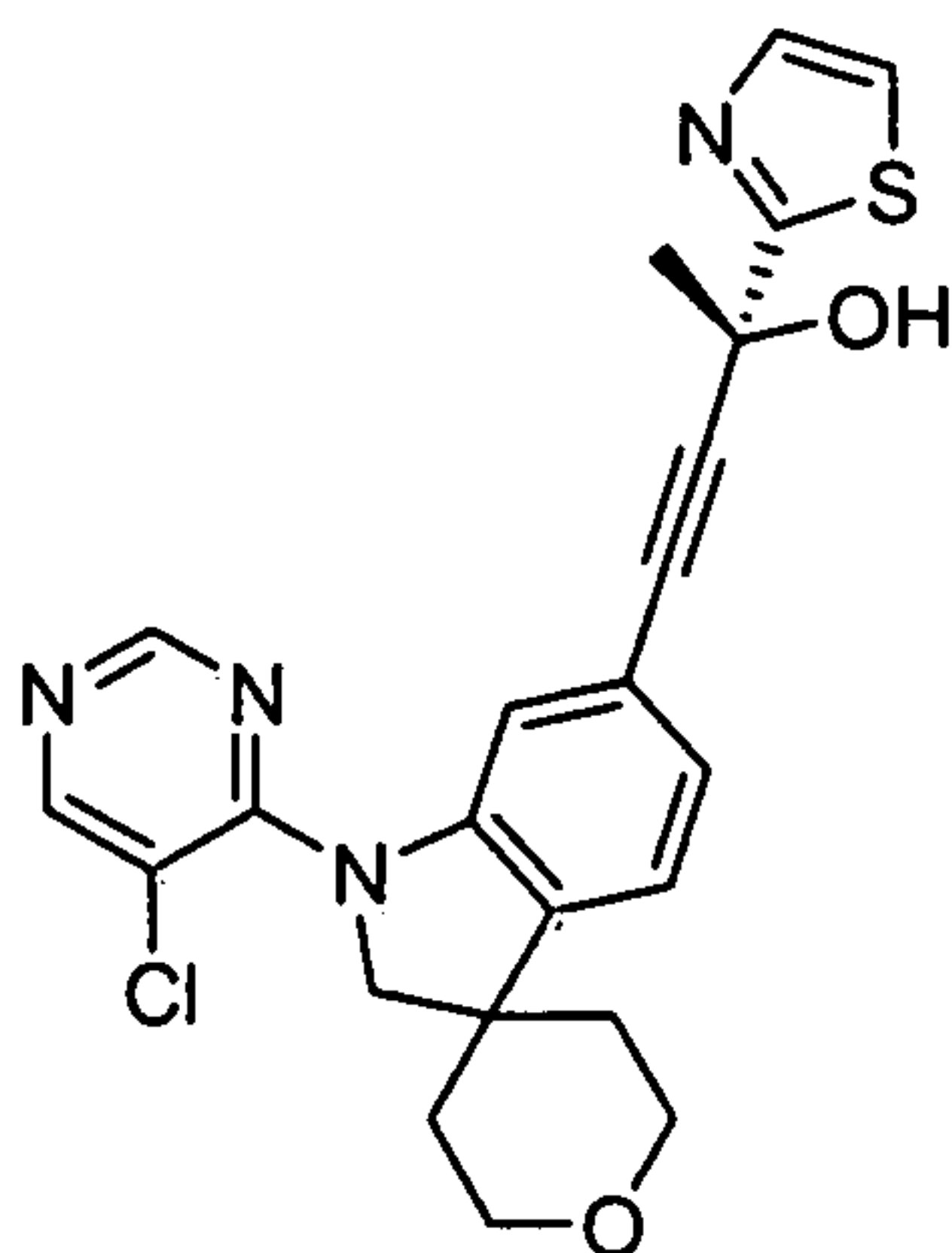
31

(2S)-4-(1-(2-amino-5-chloro-4-pyrimidinyl)-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-pyran]-6-yl)-2-(3-methyl-5-isoxazolyl)-3-butyn-2-ol (**30**) and (2R)-4-(1-(2-amino-5-chloro-4-pyrimidinyl)-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-pyran]-6-yl)-2-(3-methyl-5-isoxazolyl)-3-butyn-2-ol (**31**). The racemic mixture, prepared from components A.101 and C.24 by the procedure of example 1, was separated on a preparative chiral column (OD-H Chiralpak, 250 x 20 mm) using 20% of isopropanol in hexane. The first eluted enantiomer (**30**) was assigned as (2S)-4-(1-(2-amino-5-chloro-4-pyrimidinyl)-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-pyran]-6-yl)-2-(3-methyl-5-isoxazolyl)-3-butyn-2-ol (0.0337 g, 11.4% yield) as a brown solid; the second eluted enantiomer (**31**) was assigned as (2R)-4-(1-(2-amino-5-chloro-4-pyrimidinyl)-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-pyran]-6-yl)-2-(3-methyl-5-isoxazolyl)-3-butyn-2-ol (0.0254 g, 8.6% yield) as a brown solid: ^1H NMR (400 MHz, *DMSO-d*₆) δ ppm 8.14 (1 H, s), 7.29 (1 H, d, $J=7.8$ Hz), 7.13 (1 H, s), 7.02 (1 H, dd, $J=7.6, 1.4$ Hz), 6.70 (2 H, s), 6.63 (1 H, s), 6.35 (1 H, s), 4.14 (2 H, s), 3.84 (2 H, dd, $J=11.9$,

2.5 Hz), 3.47 (2 H, t, $J=11.3$ Hz), 2.22 (3 H, s), 1.83 - 1.95 (2 H, m), 1.77 (3 H, s), 1.56 (2 H, d, $J=13.3$ Hz); Mass Spectrum (ESI) $m/e = 466.1$ [M+1].

Example 32

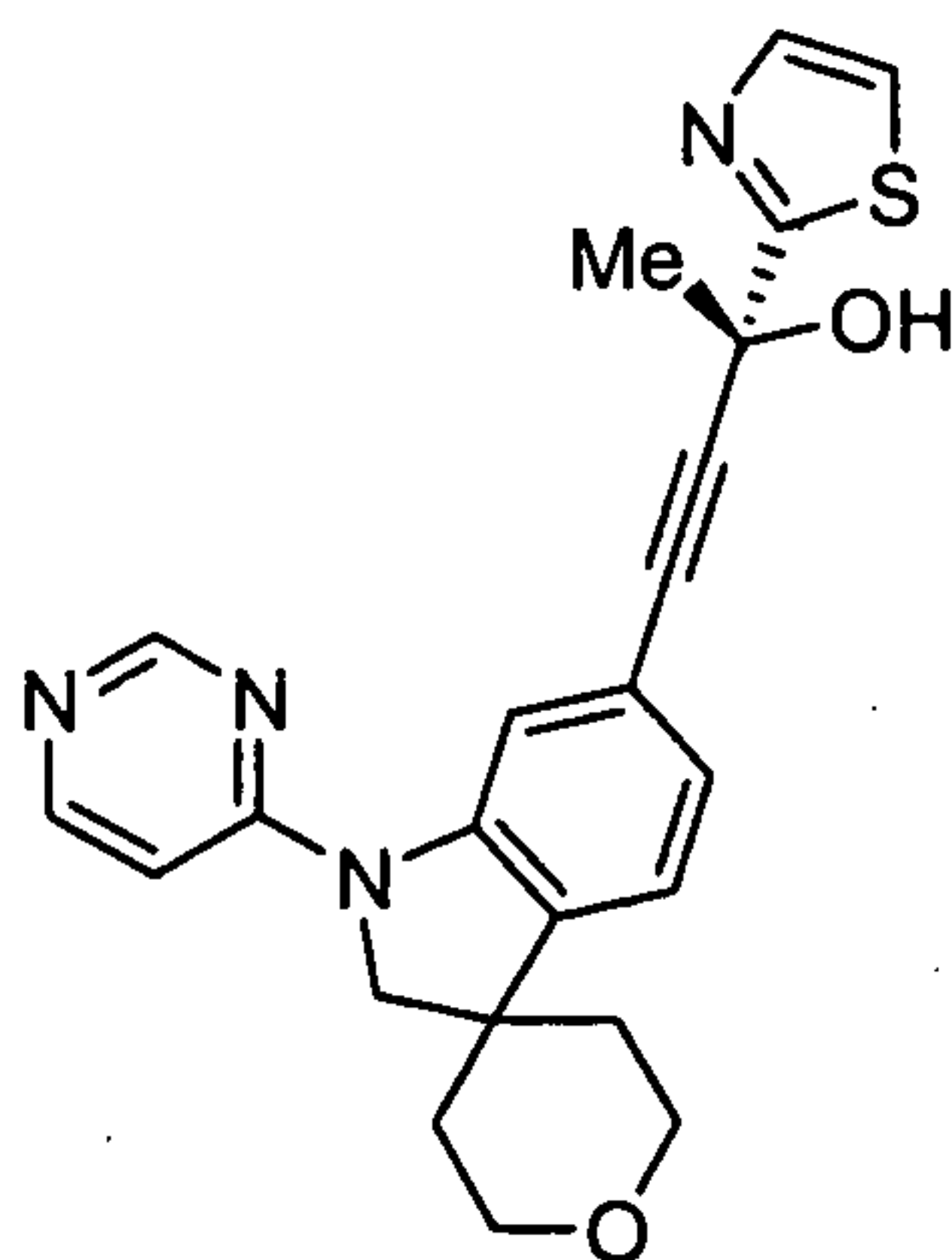
Examples 32-39 were prepared using same or analogous synthetic techniques and substituting with appropriate reagent as in **example 1**.



32

(2R)-4-[1-(5-chloropyrimidin-4-yl)-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-pyran]-6-yl]-2-(1,3-thiazol-2-yl)but-3-yn-2-ol (32). (from components A.103 and C.6) ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 8.70 (2 H, d), 7.76 (1 H, s), 7.67 (1 H, d, $J=2.0$ Hz), 7.45 (1 H, s), 7.34 (1 H, d, $J=7.6$ Hz), 7.07 (1 H, d, $J=7.8$ Hz), 7.01 (1 H, s), 4.31 (2 H, s), 3.84 (2 H, dd, $J=11.9$, 3.3 Hz), 3.47 (2 H, t, $J=11.5$ Hz), 1.77 - 1.94 (5 H, m), 1.56 (2 H, d, $J=13.0$ Hz); Mass Spectrum (ESI) $m/e = 453.1$ [M+1].

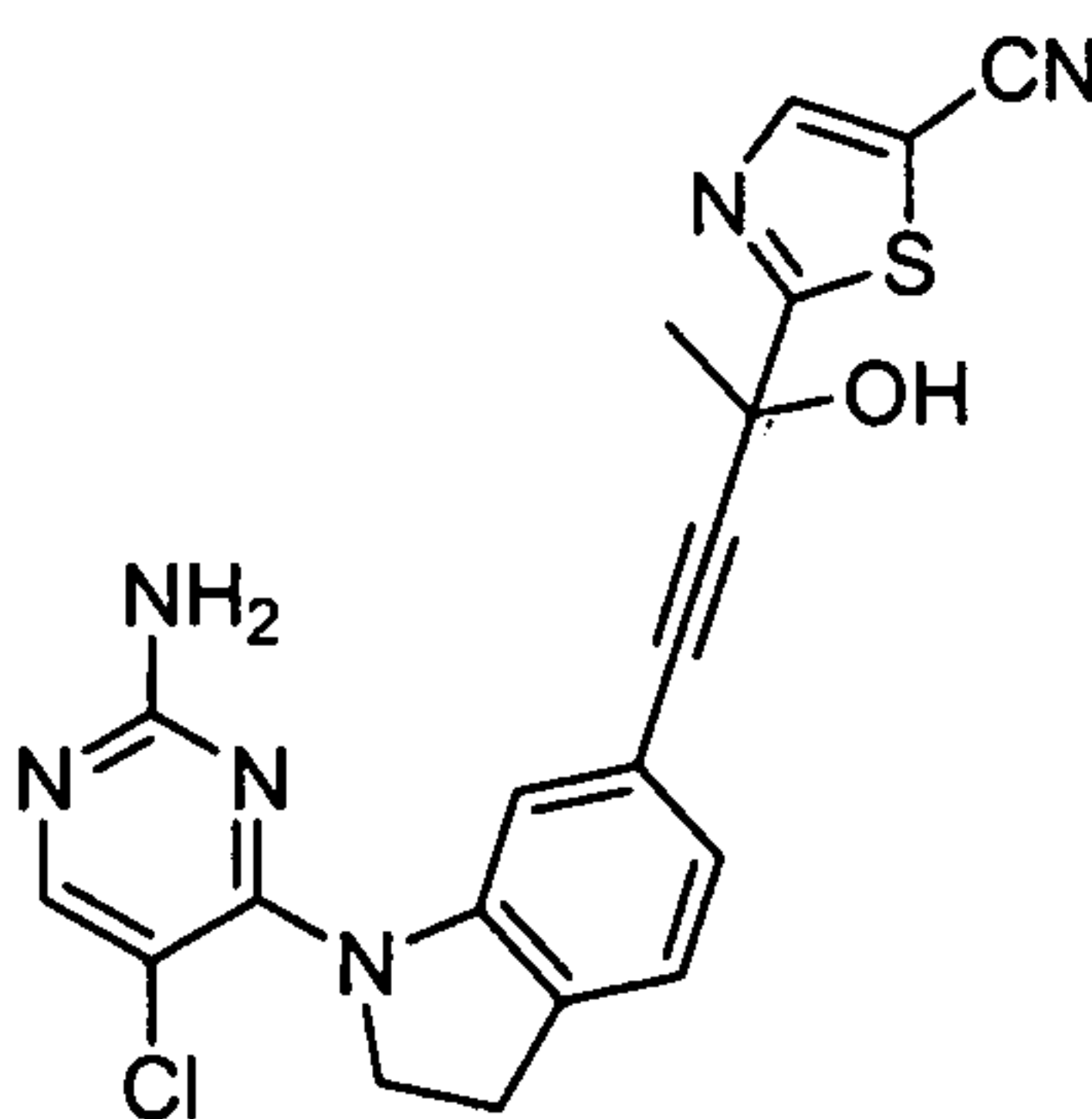
Example 33



33

(2*R*)-4-(1-pyrimidin-4-yl-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-pyran]-6-yl)-2-(1,3-thiazol-2-yl)but-3-yn-2-ol (33). (from components A.106 and C.6) ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 8.50 (1 H, s), 7.78 (1 H, s), 7.69 (1 H, s), 7.33 (1 H, d, $J=7.1$ Hz), 7.07 (1 H, d, $J=3.9$ Hz), 7.04 (1 H, s), 4.04 (2 H, s), 3.87 (2 H, d, $J=9.5$ Hz), 3.57 (2 H, t, $J=12.0$ Hz), 1.82 - 1.99 (5 H, m), 1.57 (2 H, d, $J=13.0$ Hz); Mass Spectrum (ESI) $m/e = 418.51$ $[\text{M}+1]$.

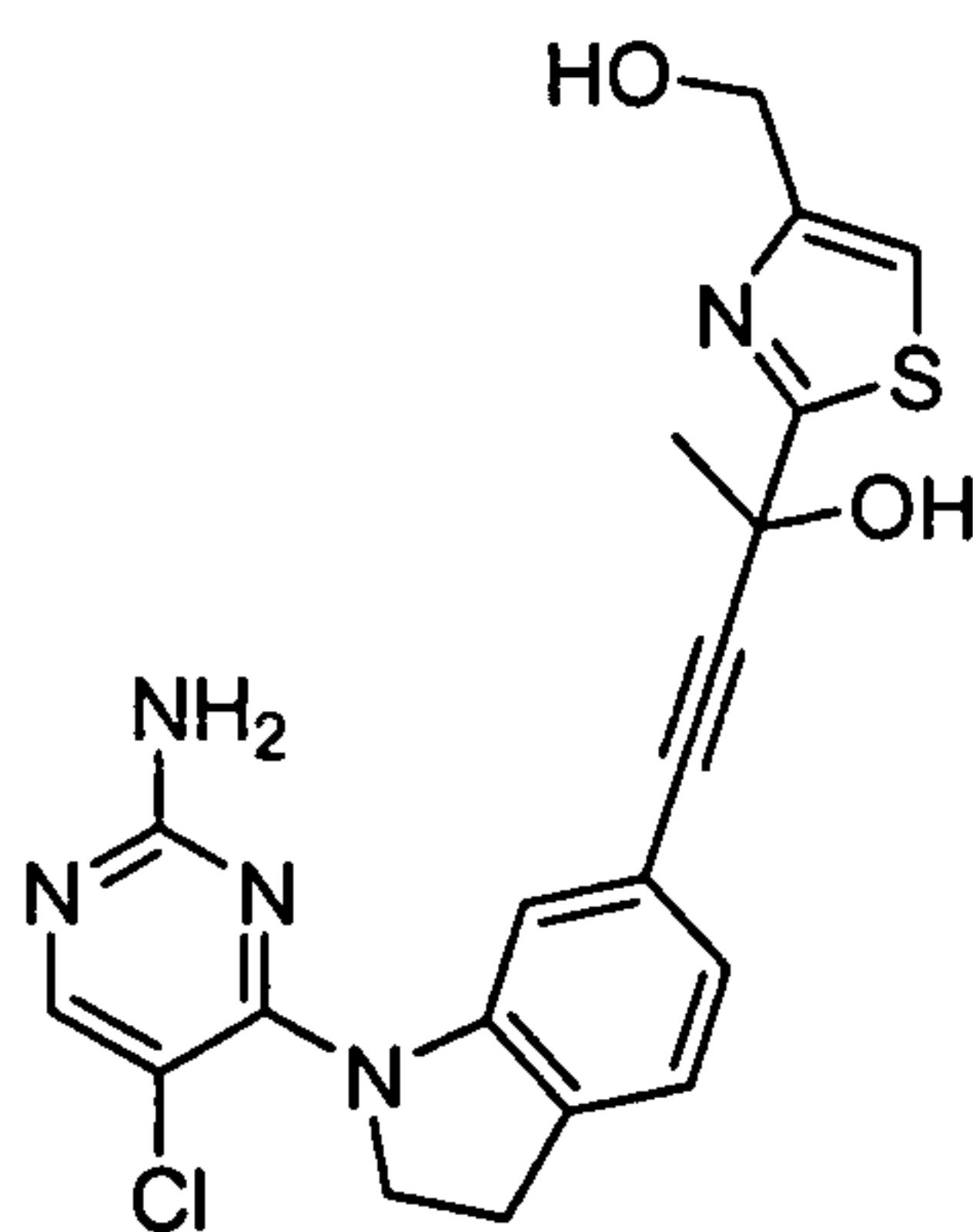
Example 34



34

2-(4-(1-(2-amino-5-chloropyrimidin-4-yl)indolin-6-yl)-2-hydroxybut-3-yn-2-yl)thiazole-5-carbonitrile (34). (from components A.2 and C.14) ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.62 (1 H, s), 8.12 (1 H, s), 7.52 (1 H, s), 7.23 (1 H, d, $J=7.8$ Hz), 7.17 (1 H, s), 6.95 (1 H, d, $J=7.8$ Hz), 6.68 (2 H, s), 4.16 (2 H, t, $J=8.2$ Hz), 3.10 (2 H, t, $J=8.0$ Hz), 1.87 (3 H, s); Mass Spectrum (ESI) $m/e = 423.1$ $[\text{M}+1]$.

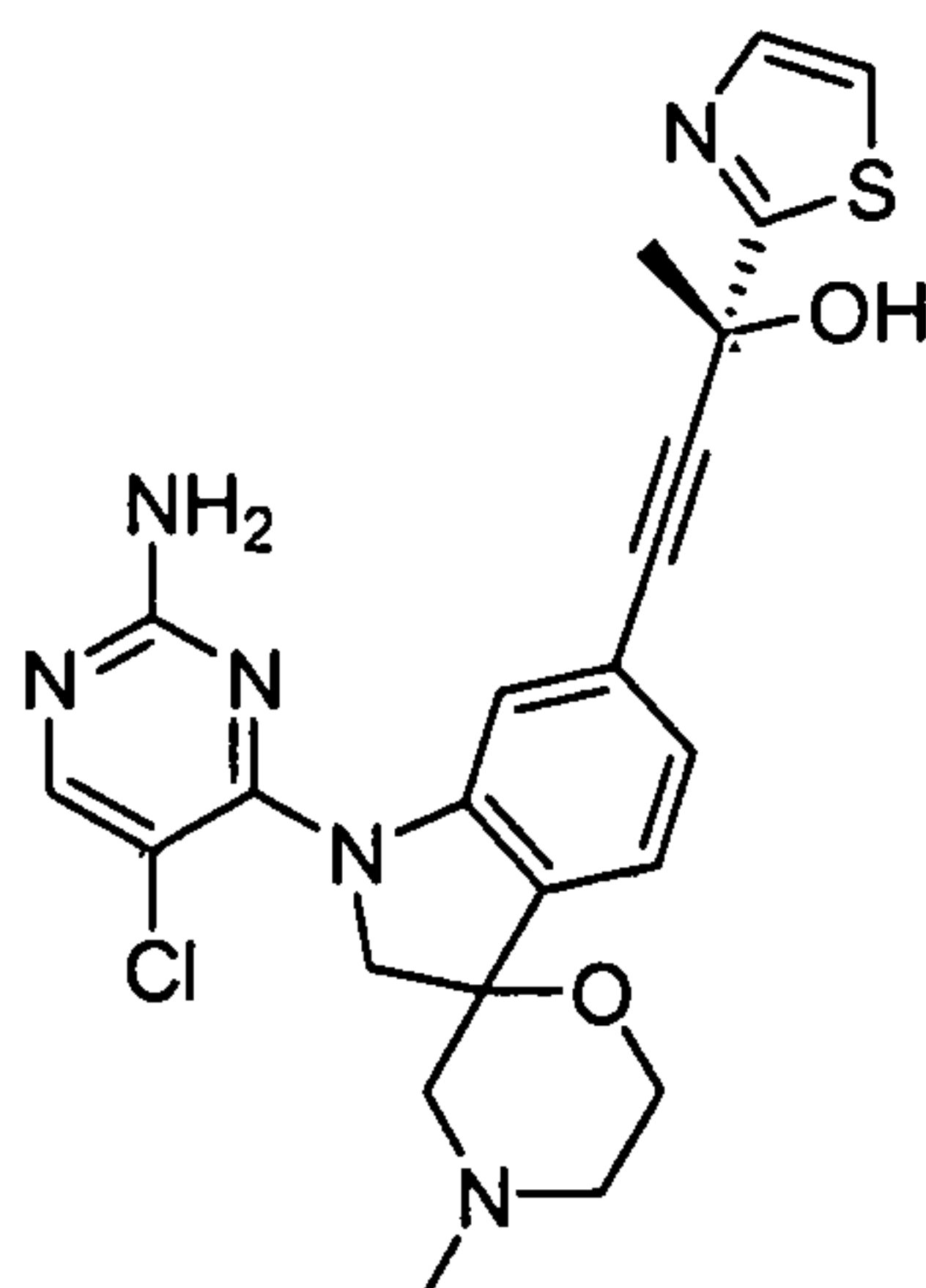
Example 35



35

4-(1-(2-amino-5-chloropyrimidin-4-yl)indolin-6-yl)-2-(4-(hydroxymethyl)thiazol-2-yl)but-3-yn-2-ol (35). (from components A.2 and C.26) ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 8.11 (1 H, s), 7.35 (1 H, d, $J=1.0$ Hz), 7.22 (1 H, d, $J=7.8$ Hz), 7.15 (1 H, s), 6.87 - 6.97 (2 H, m), 6.66 (2 H, s), 5.29 (1 H, t, $J=5.7$ Hz), 4.53 (2 H, d, $J=5.9$ Hz), 4.16 (2 H, t, $J=7.9$ Hz), 3.10 (2 H, t, $J=8.1$ Hz), 1.84 (3 H, s); Mass Spectrum (ESI) $m/e = 428.0$ $[\text{M}+1]$.

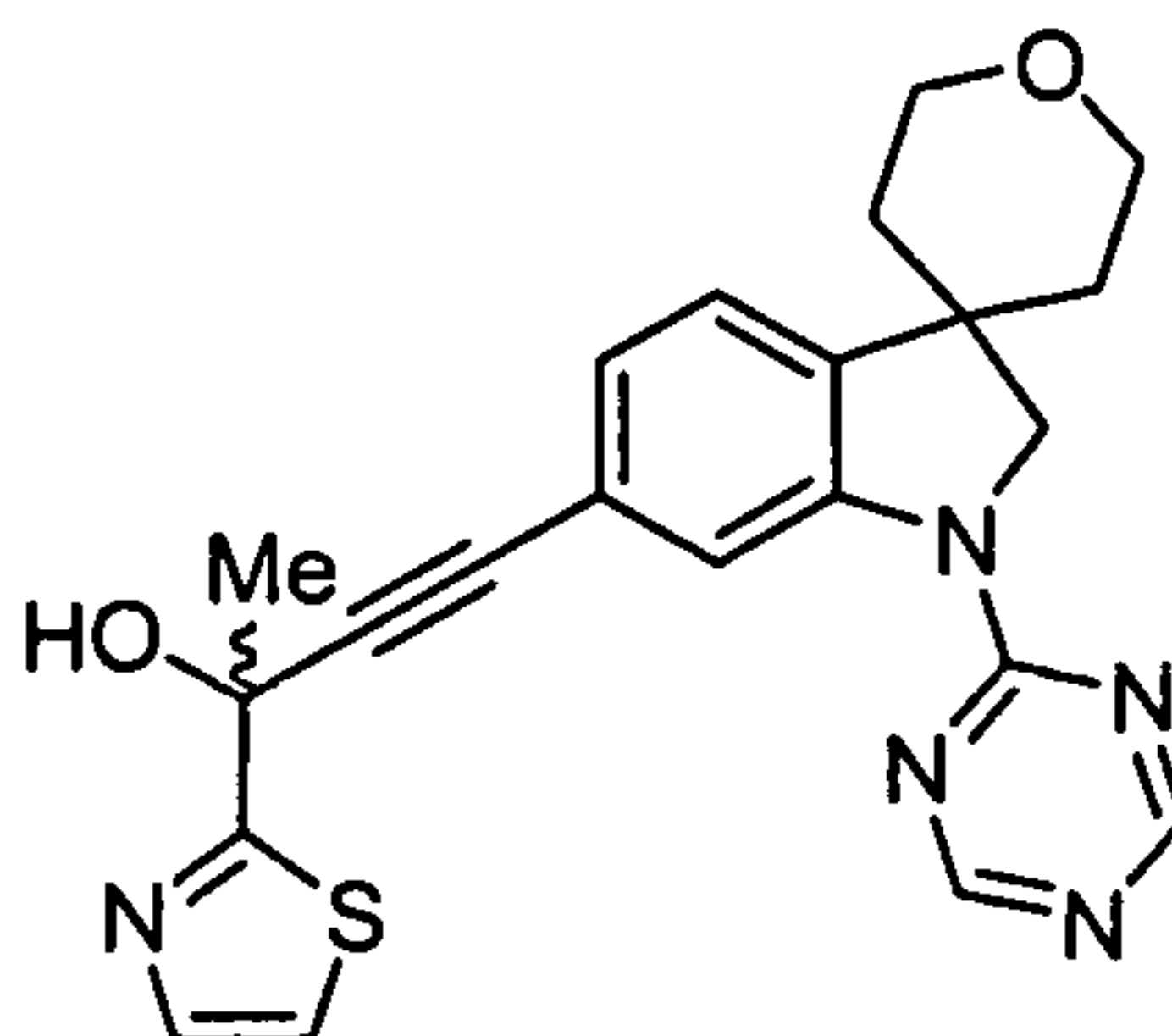
Example 36



36

(2R)-4-[1-(2-amino-5-chloropyrimidin-4-yl)-4'-methyl-1,2-dihydrospiro[indole-3,2'-[1,4]oxazinan]-6-yl]-2-(1,3-thiazol-2-yl)but-3-yn-2-ol (36). (from components A.114 and C.6) ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 8.14 (1 H, s), 7.76 (1 H, d, $J=3.2$ Hz), 7.67 (1 H, d, $J=3.2$ Hz), 7.54 (1 H, d, $J=6.8$ Hz), 7.32 (1 H, s), 6.96 - 7.04 (2 H, m), 6.70 (2 H, s), 4.08 - 4.24 (2 H, m), 3.57 - 3.75 (2 H, m), 2.43 - 2.61 (3 H, m), 2.32 (1 H, s), 2.22 (3 H, s), 1.86 (3 H, s); Mass Spectrum (ESI) $m/e = 483.1$ $[\text{M}+1]$.

Example 37

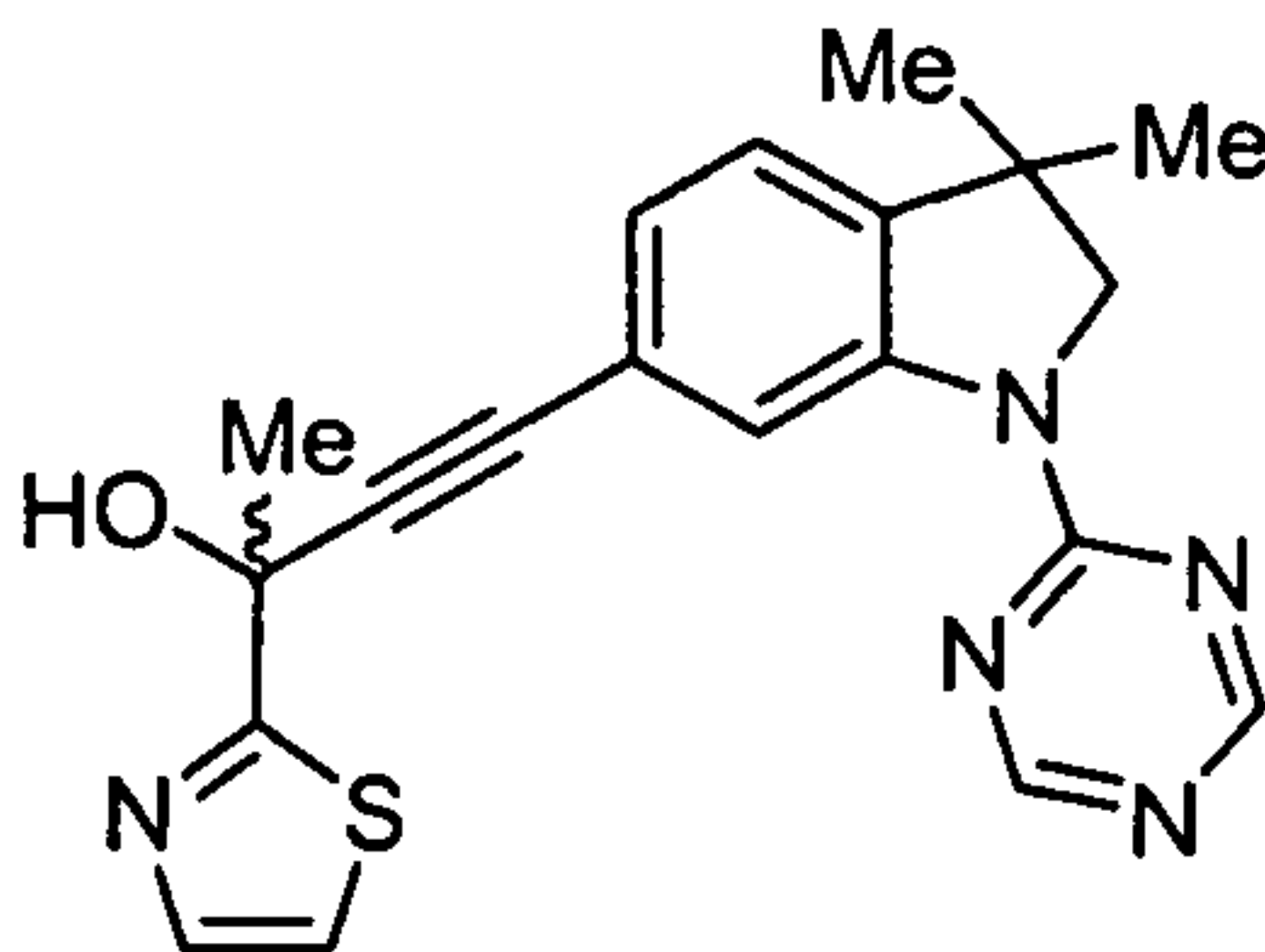


37

2-(1,3-thiazol-2-yl)-4-(1-(1,3,5-triazin-2-yl)-1,2,2',3',5',6'-hexahydrospiro[indole-3,4'-pyran]-6-yl)-3-butyn-2-ol (37) (from components A.6 and C.4)

¹H NMR (500 MHz, (CD₃)₂CO) δ 8.70 (s, 2H), 8.37 (br m, 1H), 7.65 (br m, 1H), 7.46 (br m, 1H), 7.26 (br m, 1H), 7.08 (br m, 1H), 5.84 (s, 1H), 4.15 (s, 2H), 3.82 (br m, 2H), 3.51 (br m, 2H), 1.98 (br m, 2H) 1.89 (s, 3H), 1.52 (br m, 2H); ESI-MS: M + H⁺ 420.1 m/z; RPHPLC elutes @ 6.783min (94%).

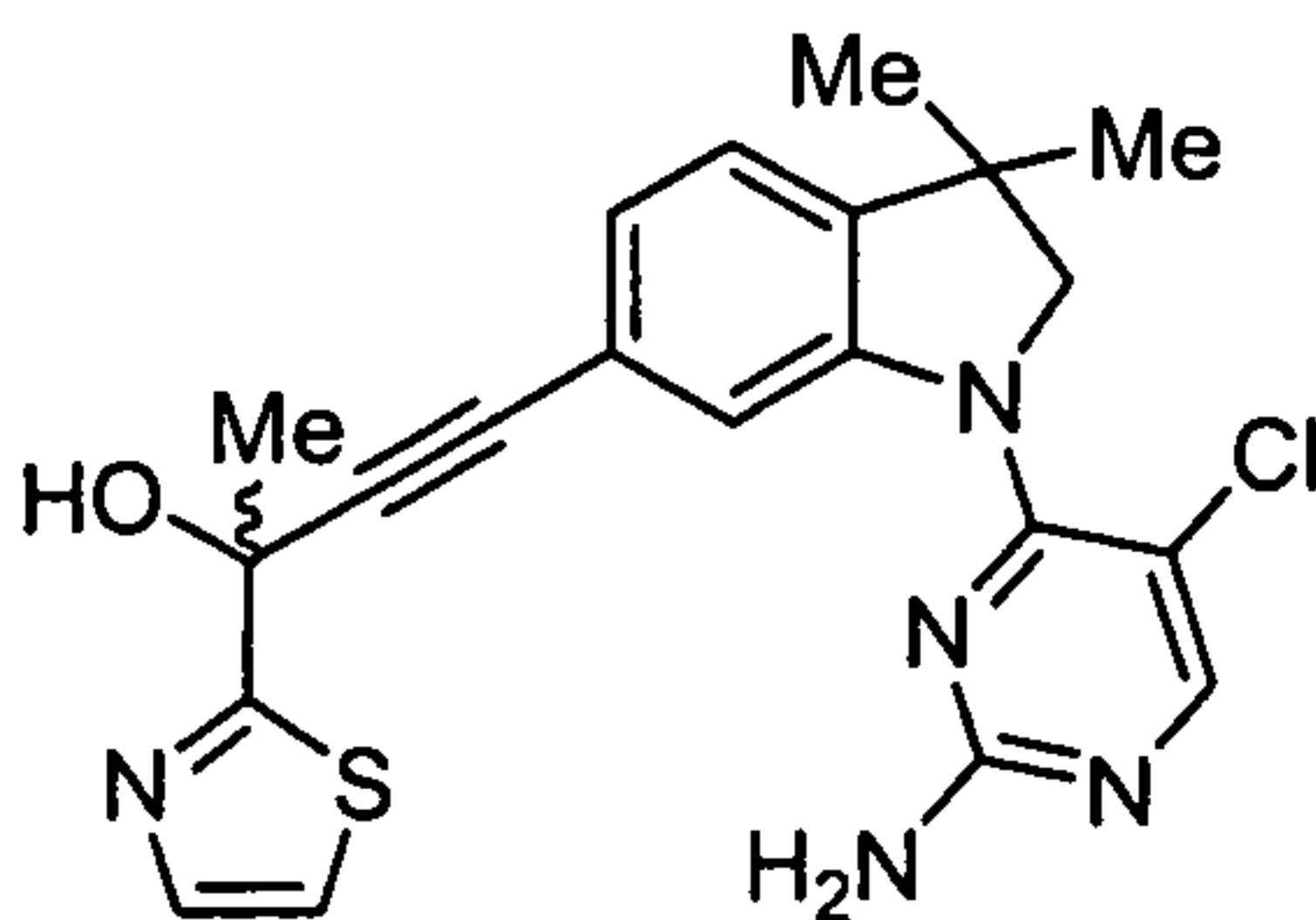
Example 38



38

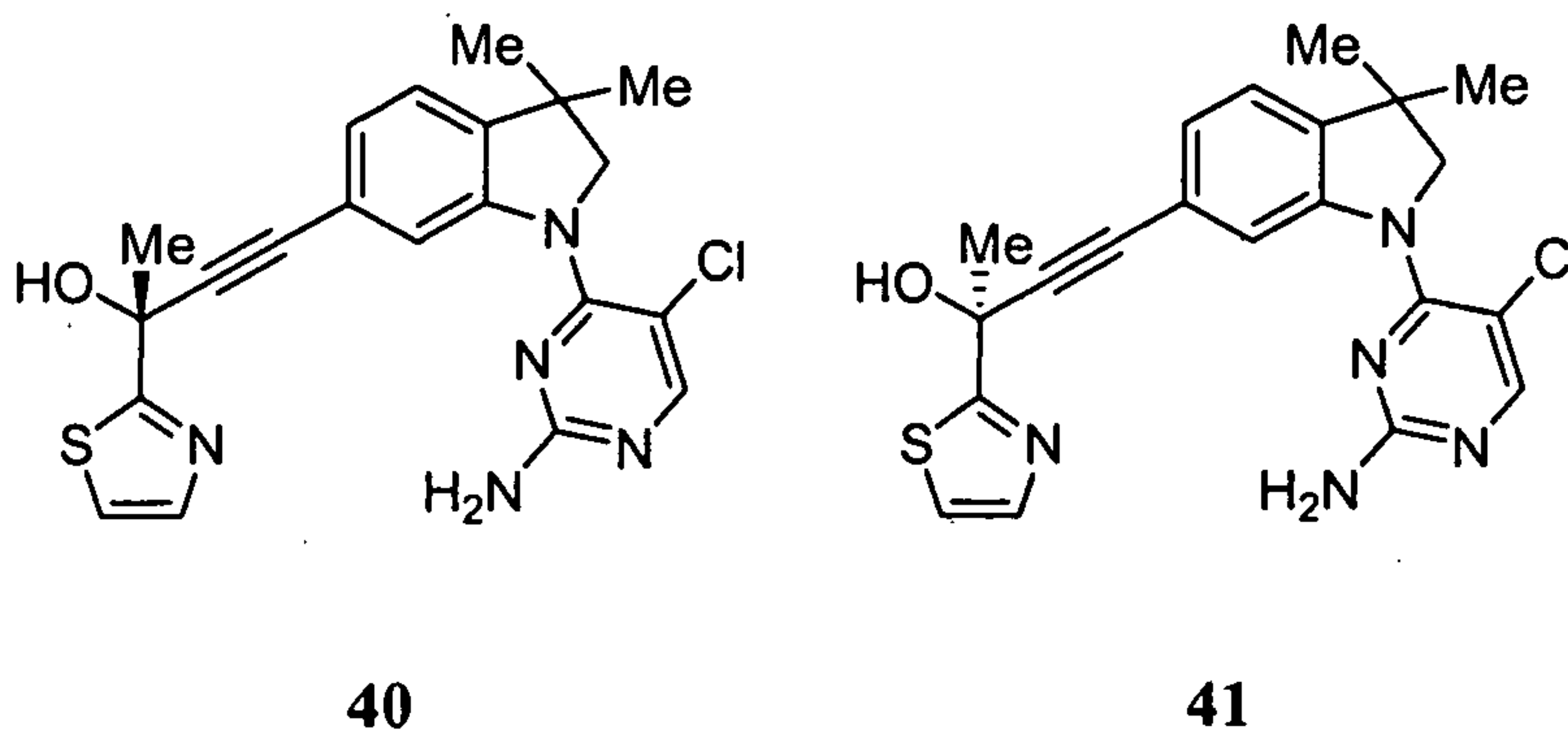
4-(3,3-dimethyl-1-(1,3,5-triazin-2-yl)-2,3-dihydro-1H-indol-6-yl)-2-(1,3-thiazol-2-yl)-3-butyn-2-ol (38): (from components A.7 and C.4). ¹H NMR (400 MHz, DMSO-d₆) δ 8.89 (br s, 2H), 8.34 (d, J = 1 Hz, 1H), 7.77 (d, J = 3.4 Hz, 1H), 7.69 (d, J = 3.25 Hz, 1H), 7.34 (d, J = 7.7 Hz, 1H), 7.15 (dd, J = 7.7 Hz, J = 1.3 Hz, 1H), 7.06 (s, 1H), 3.99 (s, 2H), 1.88 (s, 3H), 1.34 (s, 6H); ESI-MS: M + H⁺ 378.1 m/z; RPHPLC elutes @ 7.894 min (95%).

Example 39



39

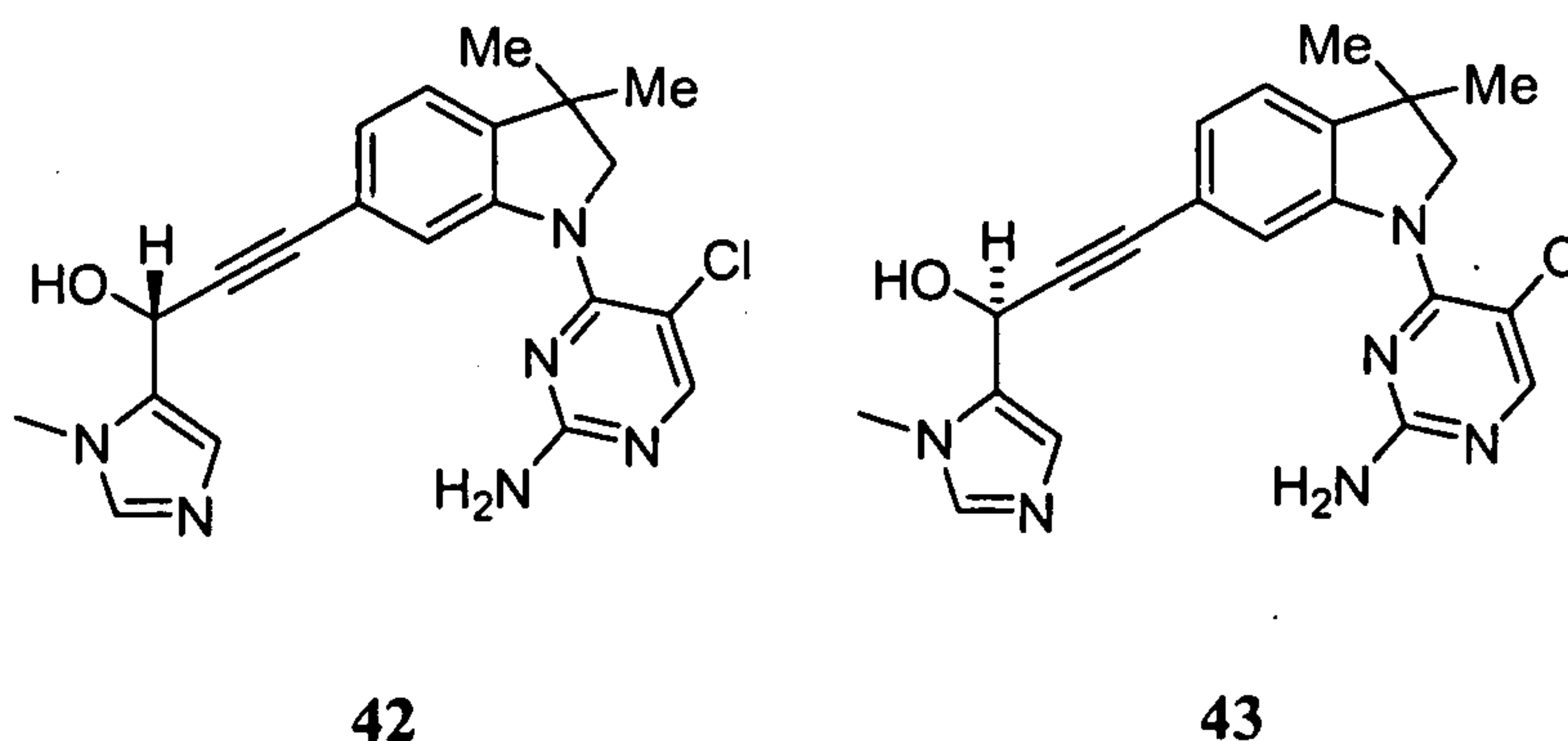
4-(1-(2-amino-5-chloro-4-pyrimidinyl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-(1,3-thiazol-2-yl)-3-butyn-2-ol (39) from components A.15 and C.4. ¹H NMR (400 MHz, DMSO-d₆) δ 8.12 (s, 1 H), 7.76 (d, J = 3.2 Hz, 1H), 7.67 (d, J = 3.2 Hz, 1H), 7.21 (d, J = 7.6 Hz, 1H), 7.12 (d, J = 1 Hz, 1H), 6.98 (dd, J = 8 Hz, J = 1.3 Hz, 1H), 6.93 (s, 1H), 6.65 (br s, 2H), 3.89 (s, 2H), 1.85 (s, 3H), 1.28 (s, 6H); ESI-MS: M + H⁺ 426.1 m/z; RPHPLC @ 6.602 min (95%).

Example 40 and 41

(2R)-4-(1-(2-amino-5-chloro-4-pyrimidinyl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-(1,3-thiazol-2-yl)-3-butyn-2-ol (40) The racemic mixture (39) was separated on a preparative chiral column AD-H eluting with 18%iPrOH/hexane then with 30%iPrOH/hexane. The first peak to elute gave (2R)-4-(1-(2-amino-5-chloro-4-pyrimidinyl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-(1,3-thiazol-2-yl)-3-butyn-2-ol (**40**) (76mg, 22%) as a tan colored solid.

¹H NMR (500 MHz, DMSO-d₆) δ 8.12 (s, 1 H), 7.76 (d, J = 3.2 Hz, 1H), 7.67 (d, J = 3.2 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 7.13 (d, J = 1 Hz, 1H), 6.99 (dd, J = 7.6 Hz, J = 1.1 Hz, 1H), 6.96 (s, 1H), 6.68 (br s, 2H), 3.9 (s, 2H), 1.86 (s, 3H), 1.29 (s, 6H); ESI-MS: M + H⁺ 426.1 m/z; RPHPLC @ 6.609 min (97%); [α]₂₀^D = -45.2°

(2S)-4-(1-(2-amino-5-chloro-4-pyrimidinyl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-(1,3-thiazol-2-yl)-3-butyn-2-ol (41) The second peak to elute gave (2S)-4-(1-(2-amino-5-chloro-4-pyrimidinyl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-(1,3-thiazol-2-yl)-3-butyn-2-ol (**41**) as a tan colored solid (76mg, 24%). Stereochemistry assigned by biological activity and analogy to compounds of defined structure.

Example 42 and 43

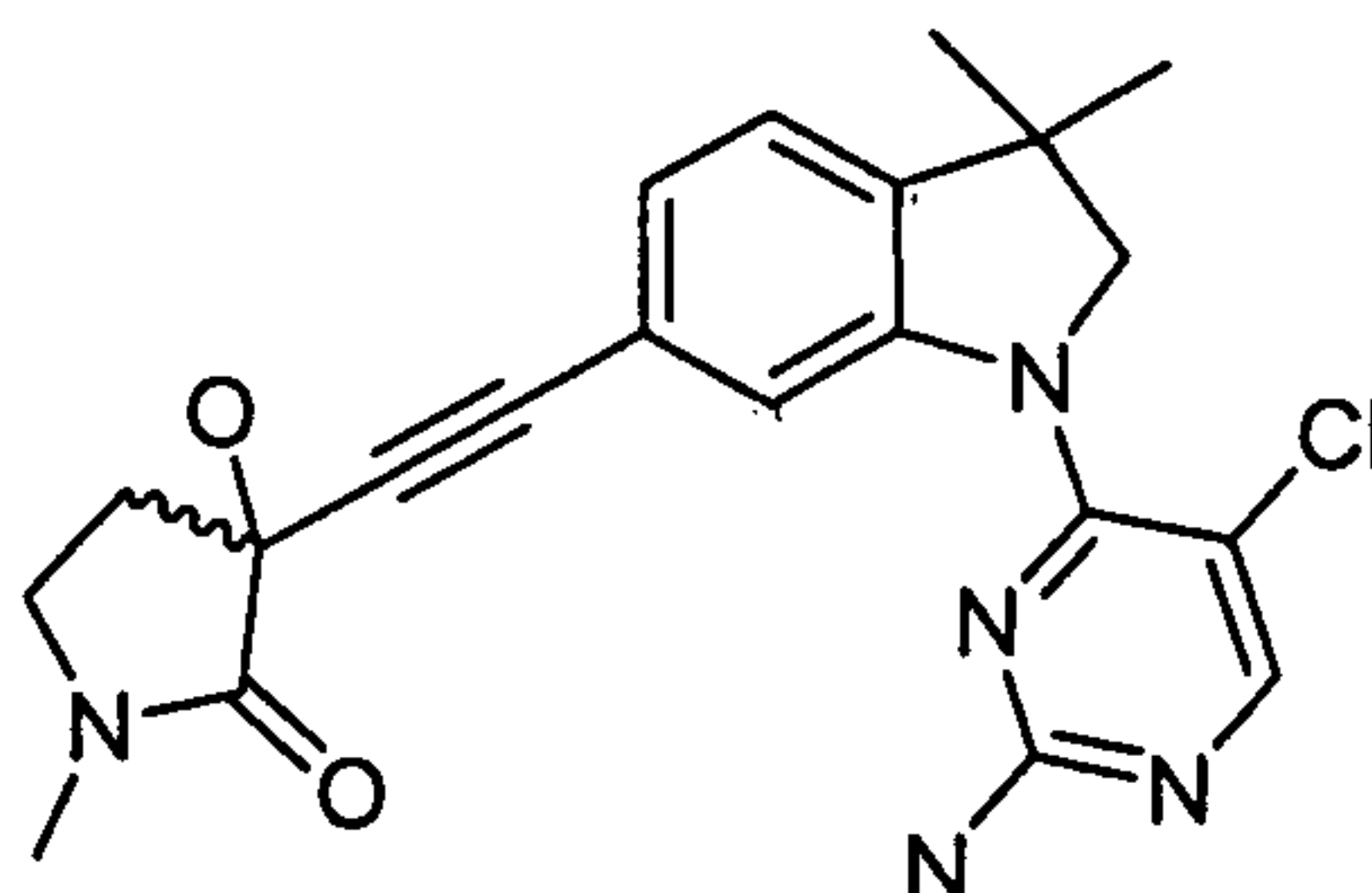
(1R*)-3-(1-(2-amino-5-chloro-4-pyrimidinyl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-1-(1-methyl-1H-imidazol-5-yl)-2-propyn-1-ol (42) The racemic mixture prepared from components A.15 and C.16 by the procedure of example 1, was separated on a preparative chiral column AD-H eluting with 25%iPrOH/hexane afforded (1R*)-3-(1-(2-amino-5-chloro-4-pyrimidinyl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-1-(1-methyl-1H-imidazol-5-yl)-2-propyn-1-ol (42) as an off white solid (11mg, 22%). Stereochemistry arbitrarily assigned as R for the second peak to elute from the chiral column.

¹H NMR (500 MHz, (CDCl₃) δ 7.94 (s, 1H), 7.48 (br s, 1H), 7.19 (br s, 1H), 7.02 (br s, 1H), 7.01 (br s, 2H), 5.62 (s, 1H), 4.98 (s, 2H), 4.34 (s, 2H), 3.71 (s, 3H), 1.25 (s, 6H); ESI MS: M + H⁺ 409.1 m/z; RPHPLC @ 5.218 min (95%); Analytical chiral column AD-H (isocratic 25% iPrOH/ hexane) elutes @ 13.318 min.

(1S*)-3-(1-(2-amino-5-chloro-4-pyrimidinyl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-1-(1-methyl-1H-imidazol-5-yl)-2-propyn-1-ol (43): The first peak to elute from the chiral column afforded (1S*)-3-(1-(2-amino-5-chloro-4-pyrimidinyl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-1-(1-methyl-1H-imidazol-5-yl)-2-propyn-1-ol (43) as an off white solid (18mg, 36%).

Example 44

Examples 44-48 were prepared using same or analogous synthetic techniques and substituting with appropriate reagent as in **example 1**.



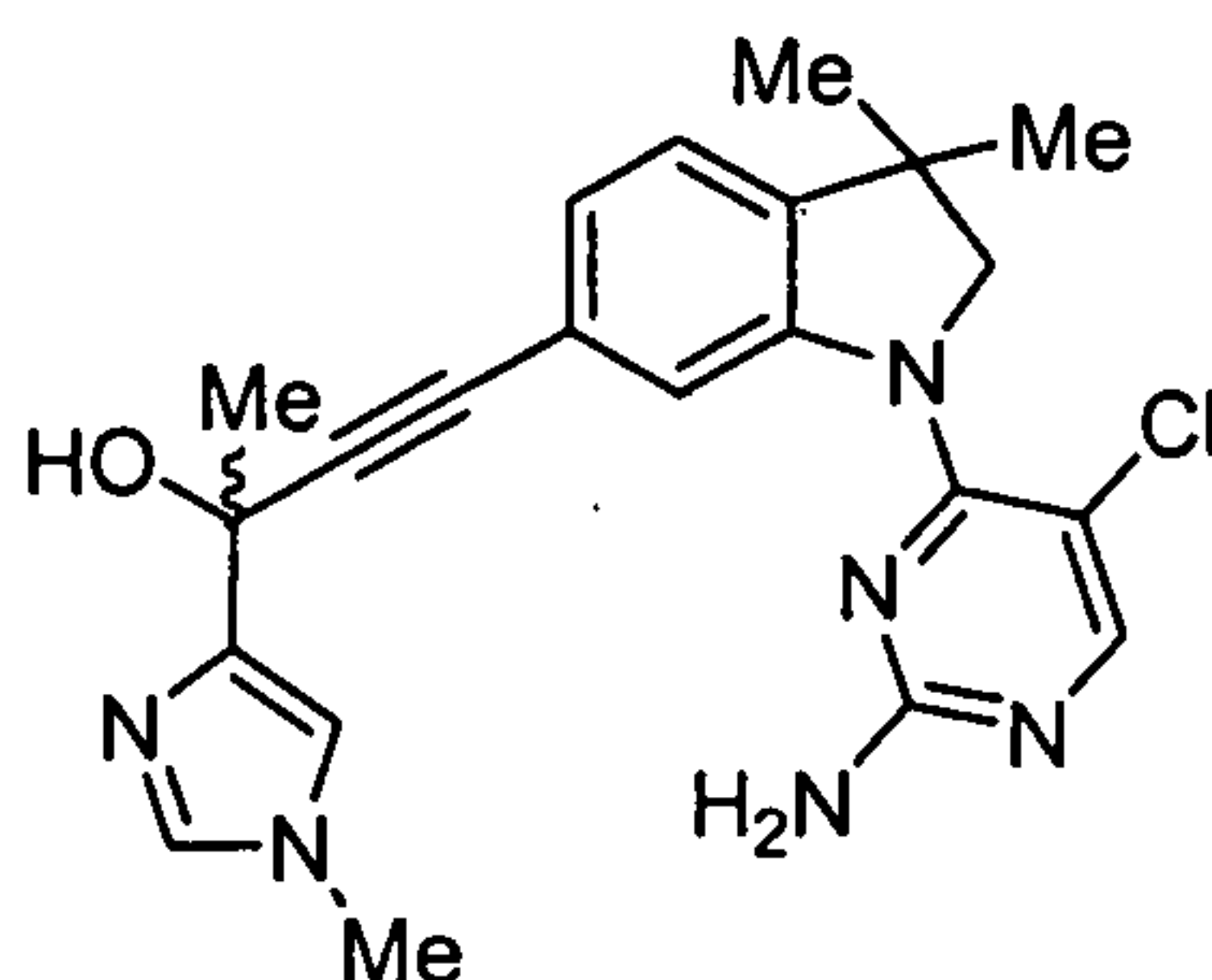
44

(3S)-3-((1-(2-amino-5-chloro-4-pyrimidinyl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)ethynyl)-3-hydroxy-1-methyl-2-pyrrolidinone (44). The title compound prepared from components A.15 and C.17 was obtained as a light brown film (116mg, 47%).

¹H NMR (500 MHz, DMSO-d₆) δ 8.05 (s, 1H), 7.15 (d, J = 7.6 Hz, 1H), 7.09 (br s, 1H), 6.92 (br d, J = 8.3 Hz, 1H), 6.61 (br s, 2H), 6.33 (s, 1H), 3.84 (s, 2H), 3.26 (m, 2H), 2.71 (s, 3H),

2.33 (m, 1H) , 2.08 (m, 1H), 1.21 (s, 6H); ESI-MS: $M + H^+$ 412.1 m/z; RPHPLC elutes @ 5.960 min (97%).

Example 45

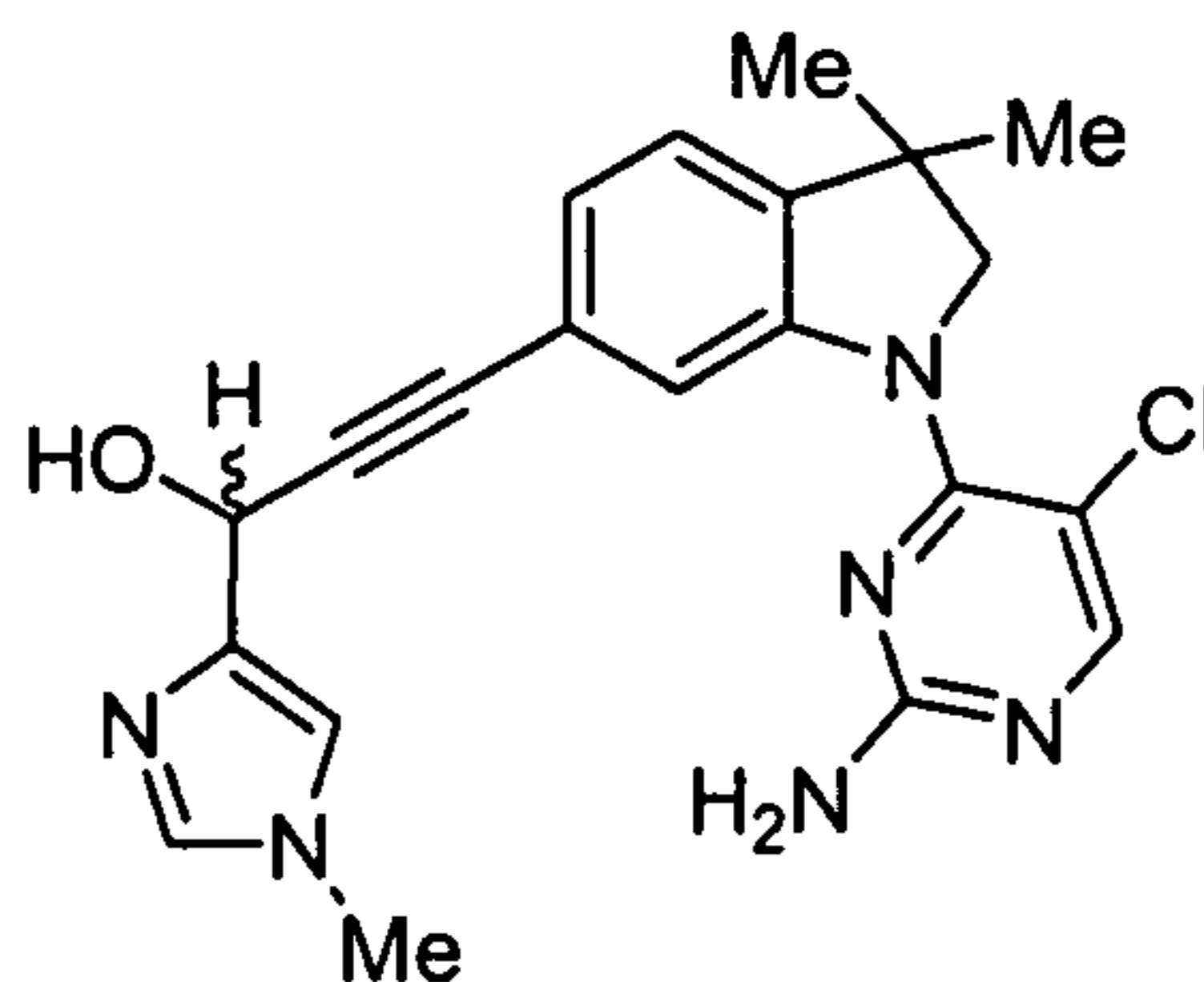


45

4-(1-(2-amino-5-chloro-4-pyrimidinyl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-(1-methyl-1H-imidazol-4-yl)-3-butyn-2-ol (45). The title compound prepared from components **A.15** and **C.18** was obtained as a yellow solid (5mg, 3%).

^1H NMR (500 MHz, CDCl_3) δ 7.98 (s, 1H), 7.49 (br s, 1H), 7.19 (br s, 2H), 7.02 (br d, $J = 7$ Hz, 1H), 6.99 (br d, $J = 7$ Hz, 1H), 6.91 (br s, 1H), 4.93 (br s, 1H), 3.94 (s, 2H), 3.60 (s, 3H), 1.85 (s, 3H); 1.18 (s, 6H); ESI-MS: $M + H^+$ 425.8 m/z; RPHPLC @ 6.633 min (97%).

Example 46



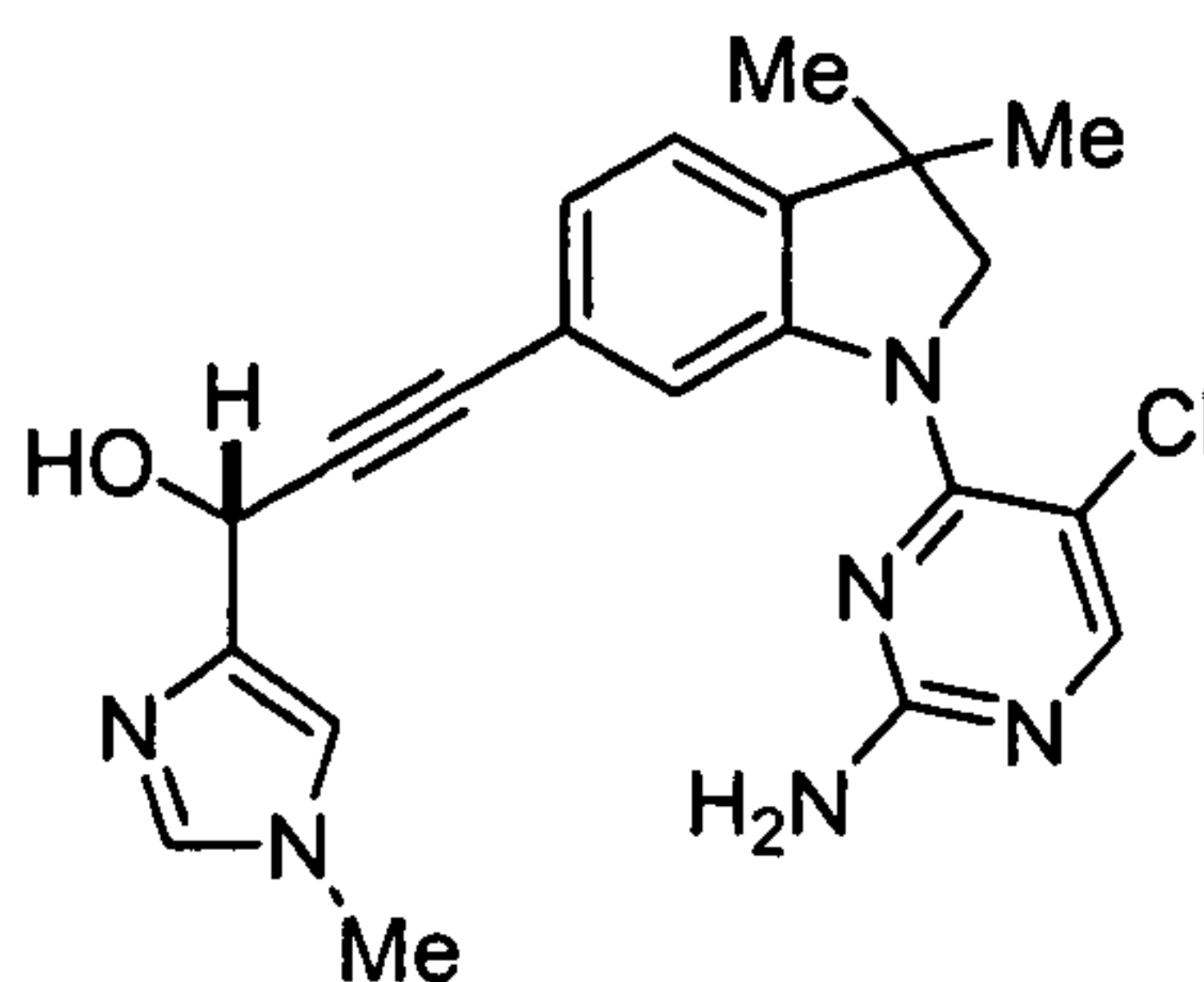
46

3-(1-(2-amino-5-chloro-4-pyrimidinyl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-1-(1-methyl-1H-imidazol-4-yl)-2-propyn-1-ol (46) The title compound prepared from components **A.15** and **C.19** was obtained as a yellow solid (162mg, 86%).

^1H NMR (500 MHz, DMSO-d_6) δ 8.12 (s, 1 H), 7.51 (br s, 1H), 7.22 (d, $J = 7.5$ Hz, 1H), 7.19 (d, $J = 1.2$ Hz, 1H), 7.13 (s, 1H), 7.02 (dd, $J = 7.6$ Hz, $J = 1.2$ Hz, 1H), 6.68 (br s, 2H), 5.76 (d,

$J = 6.1$ Hz, 1H), 5.41(d, $J = 6.2$ Hz, 1H), 3.91 (s, 2H), 3.63 (s, 3H), 1.29 (s, 6H); ESI-MS: $M + H^+$ 409.1 m/z; RPHPLC @ 5.245min (~85%).

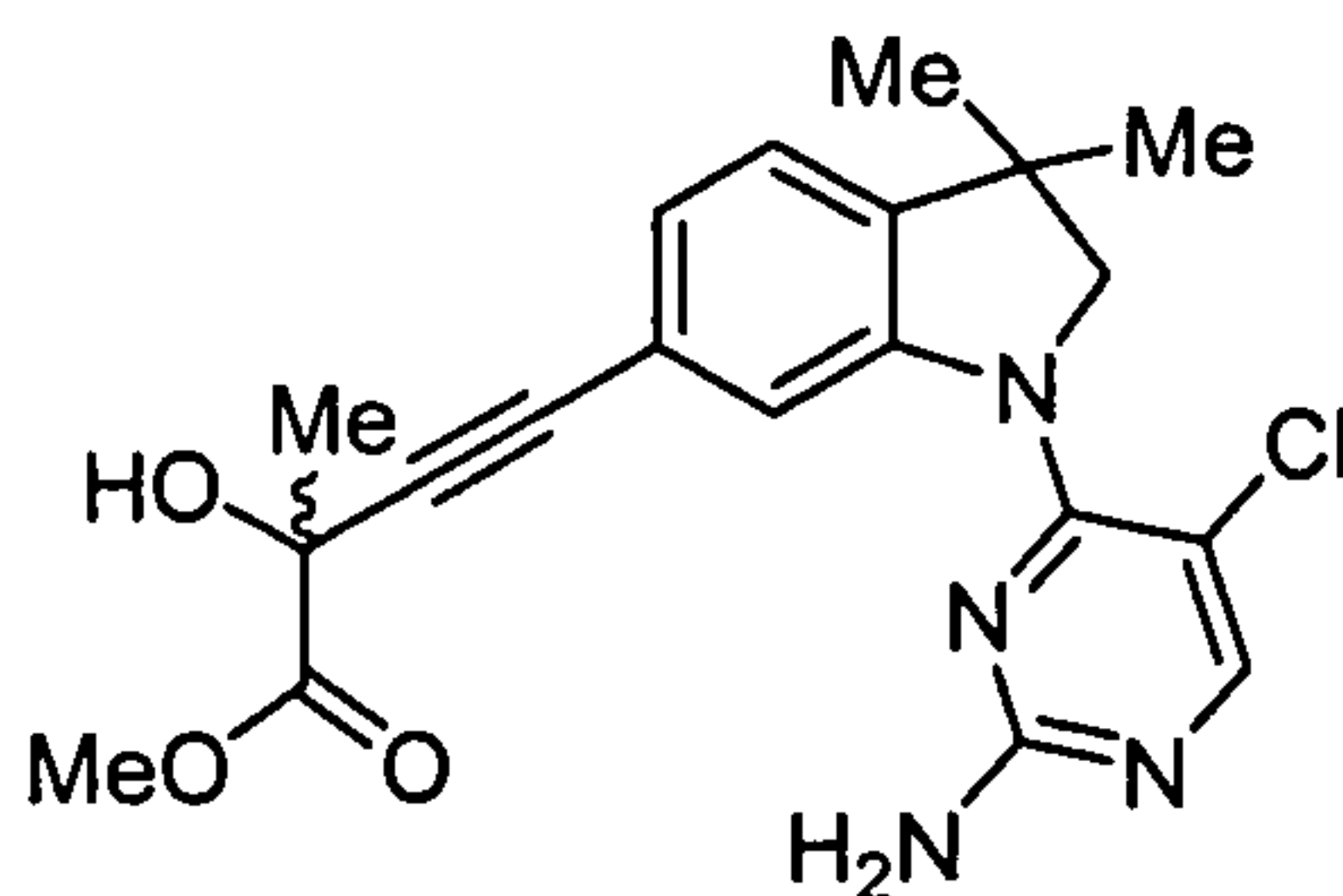
Example 47



47

(1R*)-3-(1-(2-amino-5-chloro-4-pyrimidinyl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-1-(1-methyl-1H-imidazol-4-yl)-2-propyn-1-ol (47) Separation of the enantiomers of example 46 on a preparative chiral column AD-H eluting with 30%iPrOH/hexane afforded (1R*)-3-(1-(2-amino-5-chloro-4-pyrimidinyl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-1-(1-methyl-1H-imidazol-4-yl)-2-propyn-1-ol (47) as a light yellow solid (40mg, 21%). Stereochemistry assigned as R for the second peak to elute from the chiral column based on biological activity.

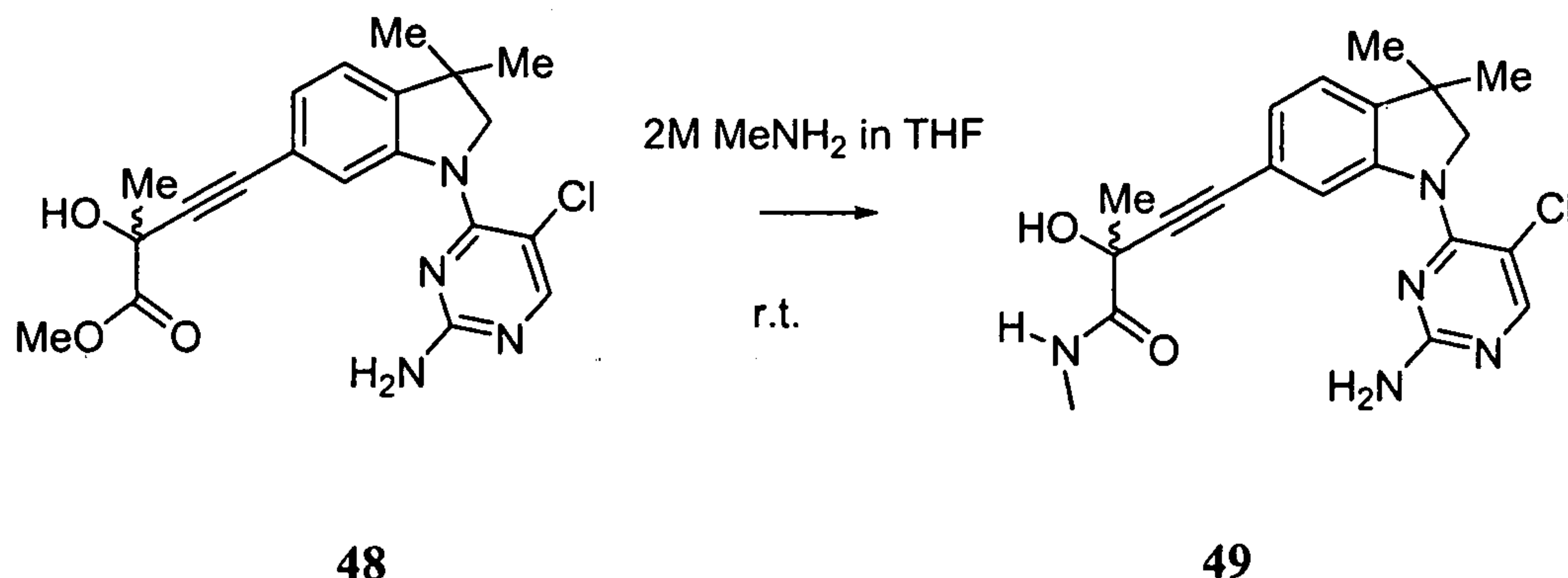
Example 48



48

methyl 4-(1-(2-amino-5-chloro-4-pyrimidinyl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-hydroxy-2-methyl-3-butynoate (48) (prepared from components A.15 and C.20). 1H NMR (400 MHz, DMSO- d_6) δ 8.12 (s, 1 H), 7.22 (d, $J = 7.6$ Hz, 1H), 7.15 (d, $J = 1$ Hz, 1H), 6.99 (dd, $J = 7.6$ Hz, $J = 1.2$ Hz, 1H), 6.66 (s, 2H), 6.39 (s, 1H), 3.73 (s, 3H), 3.30 (s, 2H), 1.62 (s, 3H), 1.28 (s, 6H); ESI-MS: $M + H^+$ 401.0 m/z; RPHPLC @ 6.530min (97%).

Example 49

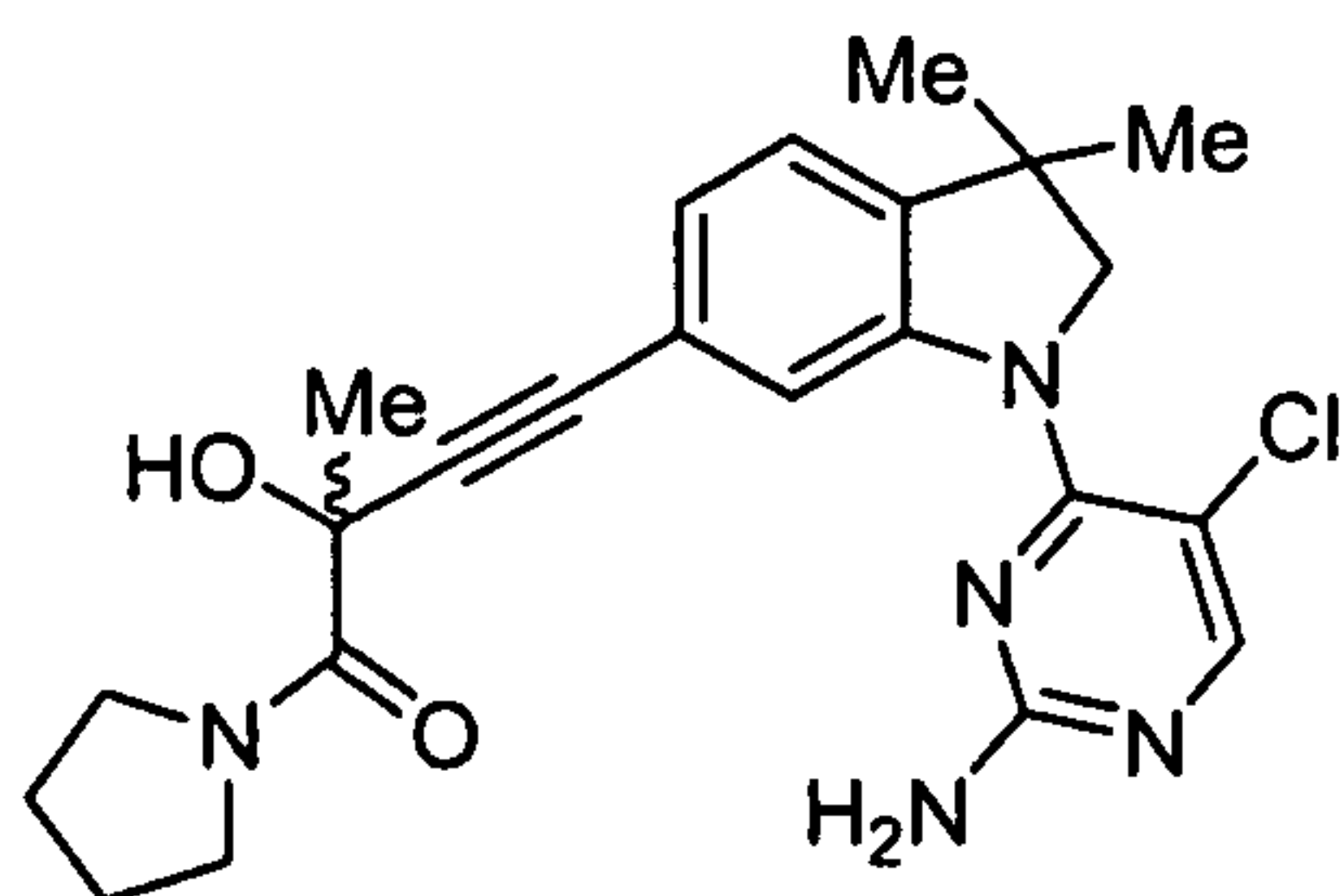


4-(1-(2-amino-5-chloro-4-pyrimidinyl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-hydroxy-N,2-dimethyl-3-butyamide (49)

methyl 4-(1-(2-amino-5-chloro-4-pyrimidinyl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-hydroxy-2-methyl-3-butynoate **48** (22mg, 0.056mmol) was dissolved in 2ml of 2M Methylamine in THF. The reaction was stirred at 40°C for 4 h and then concentrated under vacuum. The residue was purified by CombiFlash chromatography eluting with a gradient of 40%ethyl acetate/dichloromethane to 100% ethyl acetate. The fractions containing pure product were combined and concentrated under vacuum to give 4-(1-(2-amino-5-chloro-4-pyrimidinyl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-hydroxy-N,2-dimethyl-3-butyamide (16mg, 71%) (**49**) as a white solid.

¹H NMR (500 MHz,DMSO-d₆) δ 8.13 (s, 1 H), 7.89 (br m, 1H), 7.22 (d, J = 7.6 Hz, 1H), 7.12 (s, 1H), 6.98 (dd, J = 7.8 Hz, J = 1.2 Hz, 1H), 6.68 (s, 2H), 6.41 (s, 1H), 3.90 (s, 2H), 2.65(d, J = 4.6 Hz, 3H), 1.57 (s, 3H), 1.29 (s, 6H); ESI-MS: M + H⁺ 400.1 m/z; RPHPLC @ 5.820 min (97%).

Example 50



50

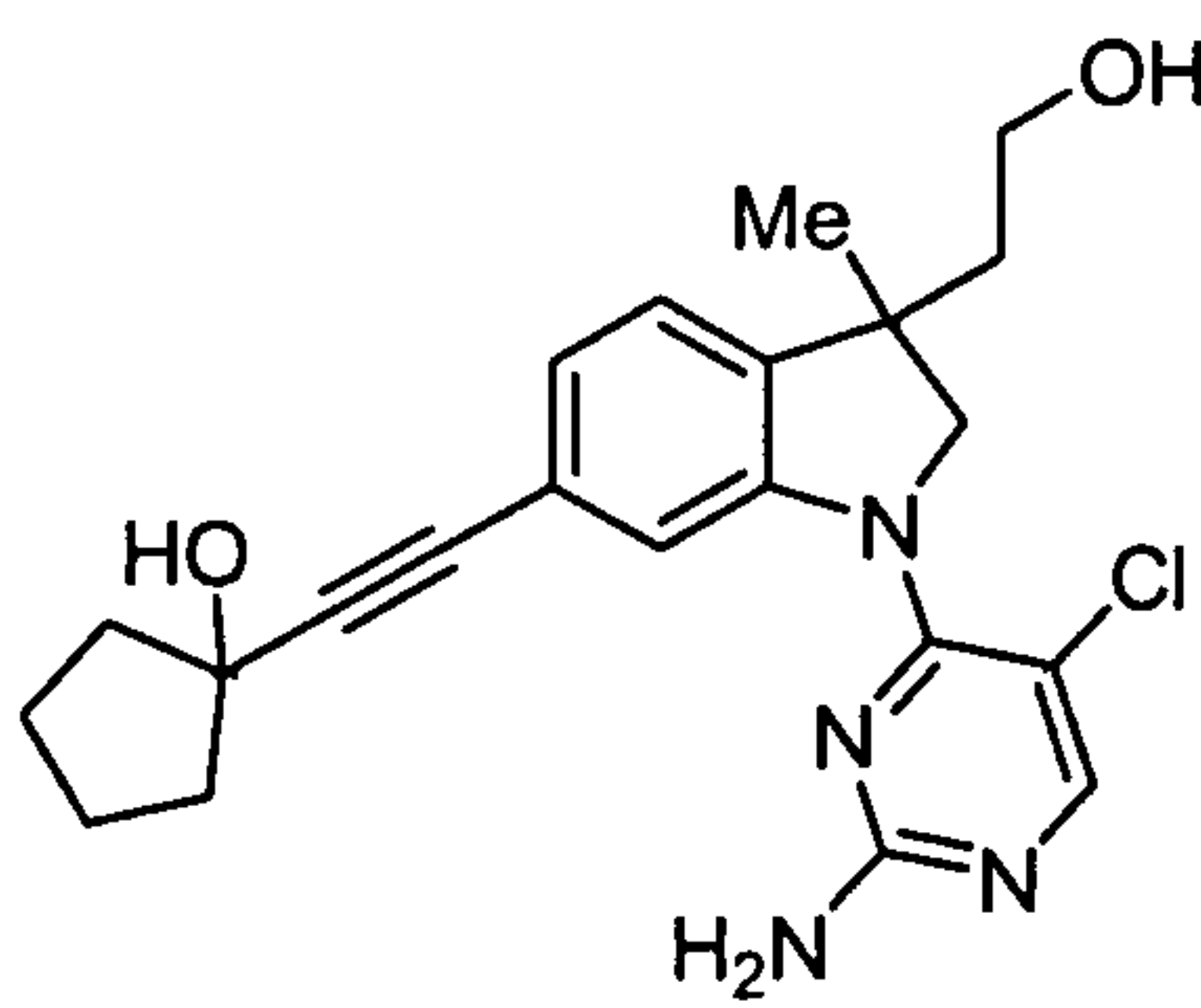
4-(1-(2-amino-5-chloro-4-pyrimidinyl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-methyl-1-oxo-1-(1-pyrrolidinyl)-3-butyne-2-ol (50) was isolated as a side product from the synthesis

of methyl 4-(1-(2-amino-5-chloro-4-pyrimidinyl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-hydroxy-2-methyl-3-butynoate (**48**); the title compound was obtained as a brownish solid (38mg, 10%).

¹H NMR (400 MHz, DMSO-d₆) δ 8.11 (s, 1 H), 7.21 (d, J = 7.6 Hz, 1H), 7.15 (s, 1H), 6.99 (dd, J = 7.6 Hz, J = 1.2 Hz, 1H), 6.66 (s, 2H), 5.98 (s, 1H), 3.88 (s, 2H), 3.84 (m, 2H), 3.36 (m, 2H), 1.84 (m, 2H), 1.80 (m, 2H), 1.60 (s, 3H), 1.28 (s, 6H); ESI-MS: M + H⁺ 440.2 m/z; RPHPLC @ 6.726min (97%).

Example 51

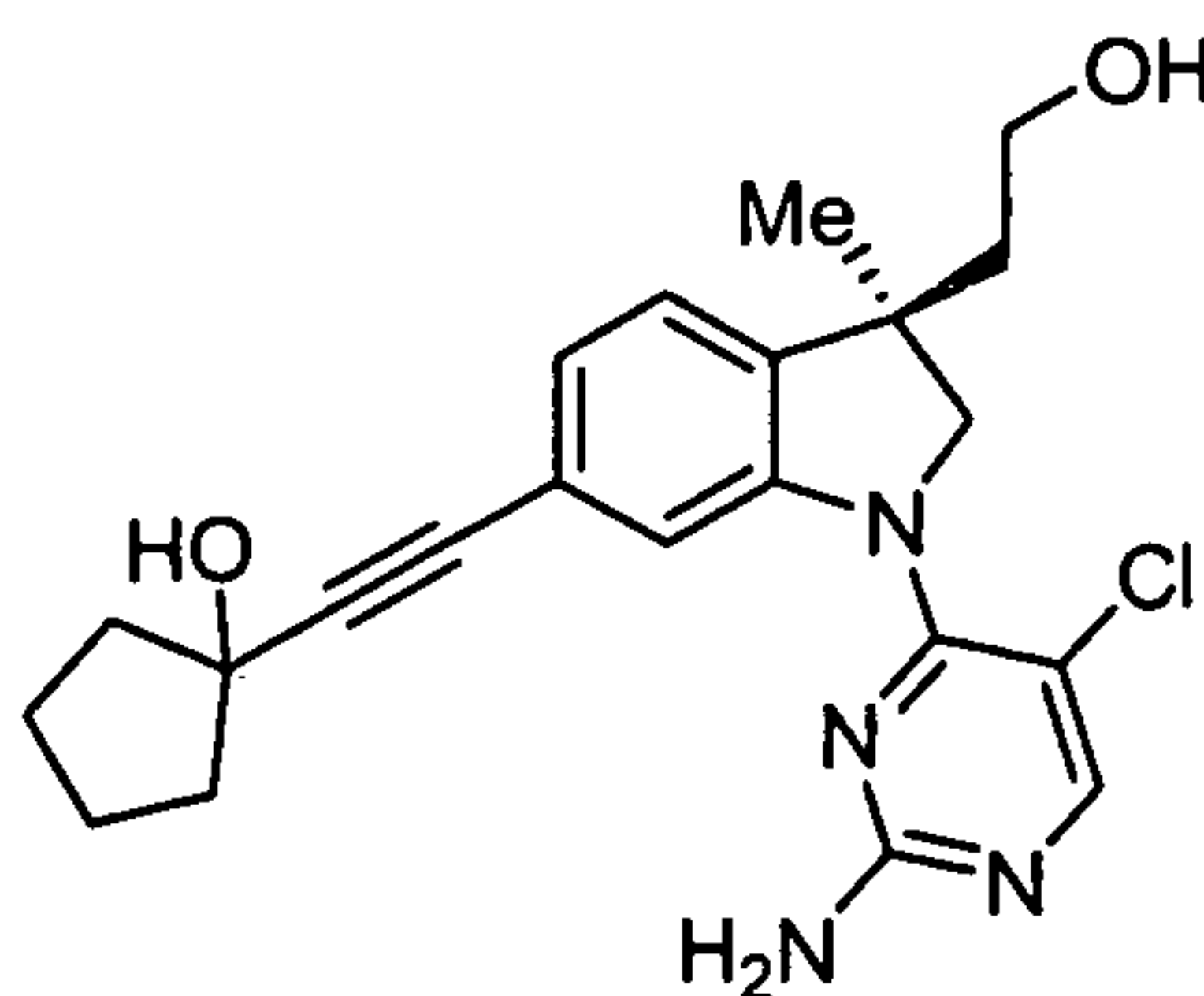
Examples 51-56 were prepared using same or analogous synthetic techniques and substituting with appropriate reagent as in **example 1**.



51

1-((1-(2-amino-5-chloro-4-pyrimidinyl)-3-(2-hydroxyethyl)-3-methyl-2,3-dihydro-1H-indol-6-yl)ethynyl)cyclopentanol (51) (prepared from components **A.24** and **C.36**) ¹H NMR (500 MHz, DMSO-d₆) δ 8.11 (s, 1 H), 7.16 (d, J = 7.8 Hz, 1H), 7.10 (d, J = 1.5 Hz, 1H), 6.95 (dd, J = 7.8 Hz, J = 1.4 Hz, 1H), 6.66 (br s, 2H), 5.25 (s, 1H), 4.41 (t, J = 4.9 Hz, 1H), 4.10 (d, J = 10.7 Hz, 1 H), 3.84 (d, J = 10.7 Hz, 1H), 3.33-3.47 (m, 2H), 1.64-1.91 (m, 8H), 1.27 (s, 3H); ESI-MS: M + H⁺ 413.2 m/z; RPHPLC @ 6.110 min (95%).

Example 52

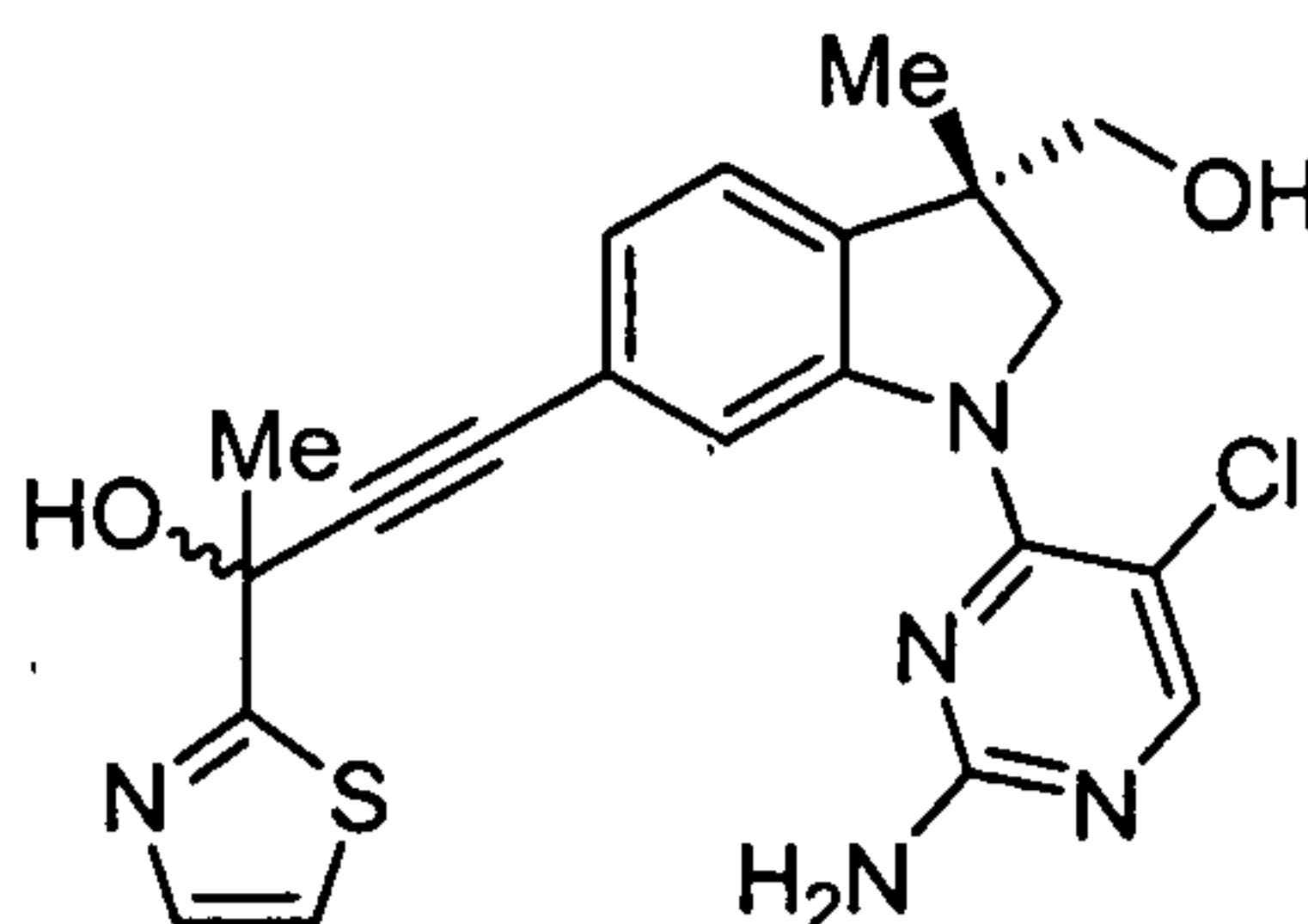


52

1-(((3R*)-1-(2-amino-5-chloro-4-pyrimidinyl)-3-(2-hydroxyethyl)-3-methyl-2,3-dihydro-1H-indol-6-yl)ethynyl)cyclopentanol (52) The enantiomers of example 51 were separated on a preparative chiral column AD-H eluting with 15% iPrOH/hexane. the pure fractions were combined and concentrated under vacuum to give the title compound as a clear film (7mg, 23%). The stereochemistry for the first peak to elute from the chiral column was arbitrarily assigned as R*.

¹H NMR (400 MHz, CD₃Cl₃) δ 8.01 (s, 1 H), 7.55 (s, 1H), 7.08 (br m, 2H), 5.46 (br s, 2H), 4.28 (d, J = 10.5 Hz, 1H), 4.04 (d, J = 11.5 Hz, 1H), 3.61 (t, J = 6.5 Hz, 2H), 1.96-2.07 (br m, 2H), 1.7-1.9 (br m, 8H), 1.95 (s, 3H); ESI-MS: M + H⁺ 413.2 m/z; RPHPLC @ 6.178 min (95%); [α]_{D20} = -35°

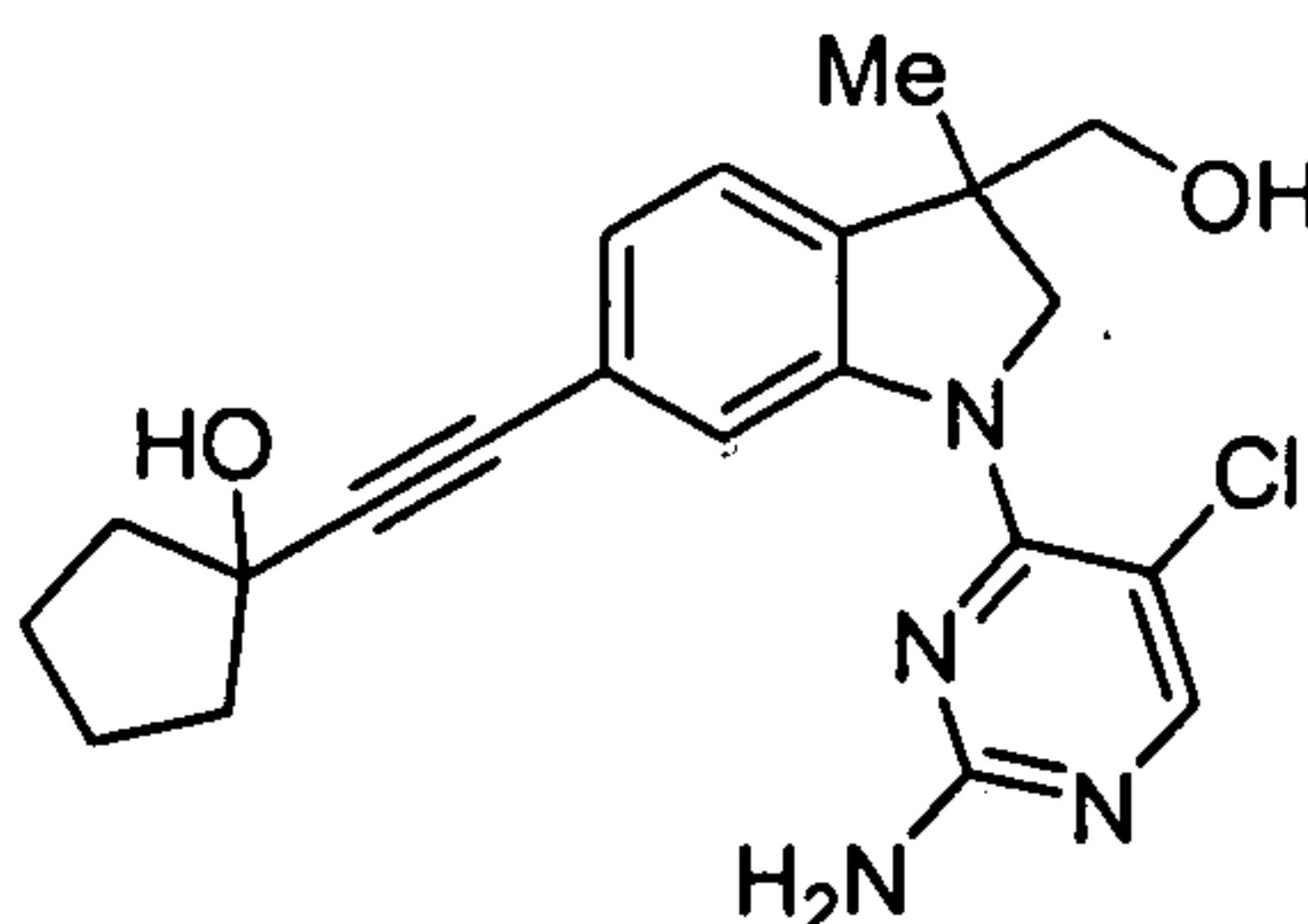
Example 53



53

4-((3S*)-1-(2-amino-5-chloro-4-pyrimidinyl)-3-(hydroxymethyl)-3-methyl-2,3-dihydro-1H-indol-6-yl)-2-(1,3-thiazol-2-yl)-3-butyn-2-ol (53) (prepared from components A.32 and C.4) ¹H NMR (400 MHz, DMSO-d₆) δ 8.16 (br s, 1 H), 7.76 (br s, 1H), 7.67 (br s, 1H), 7.19 (m, 2H), 6.96 (m, 2H), 6.64 (br s, 2H), 5.01 (t, J = 5.3 Hz, 1H), 4.14 (d, J = 10.3 Hz, 1 H), 3.80 (d, J = 10.3 Hz, 1H), 3.38 (m, 2H), 1.86 (s, 3H), 1.28 (s, 3H); ESI-MS: M + H⁺ 442.1 m/z; RPHPLC @ 5.577 min (95%). Stereochemistry is arbitrarily assigned.

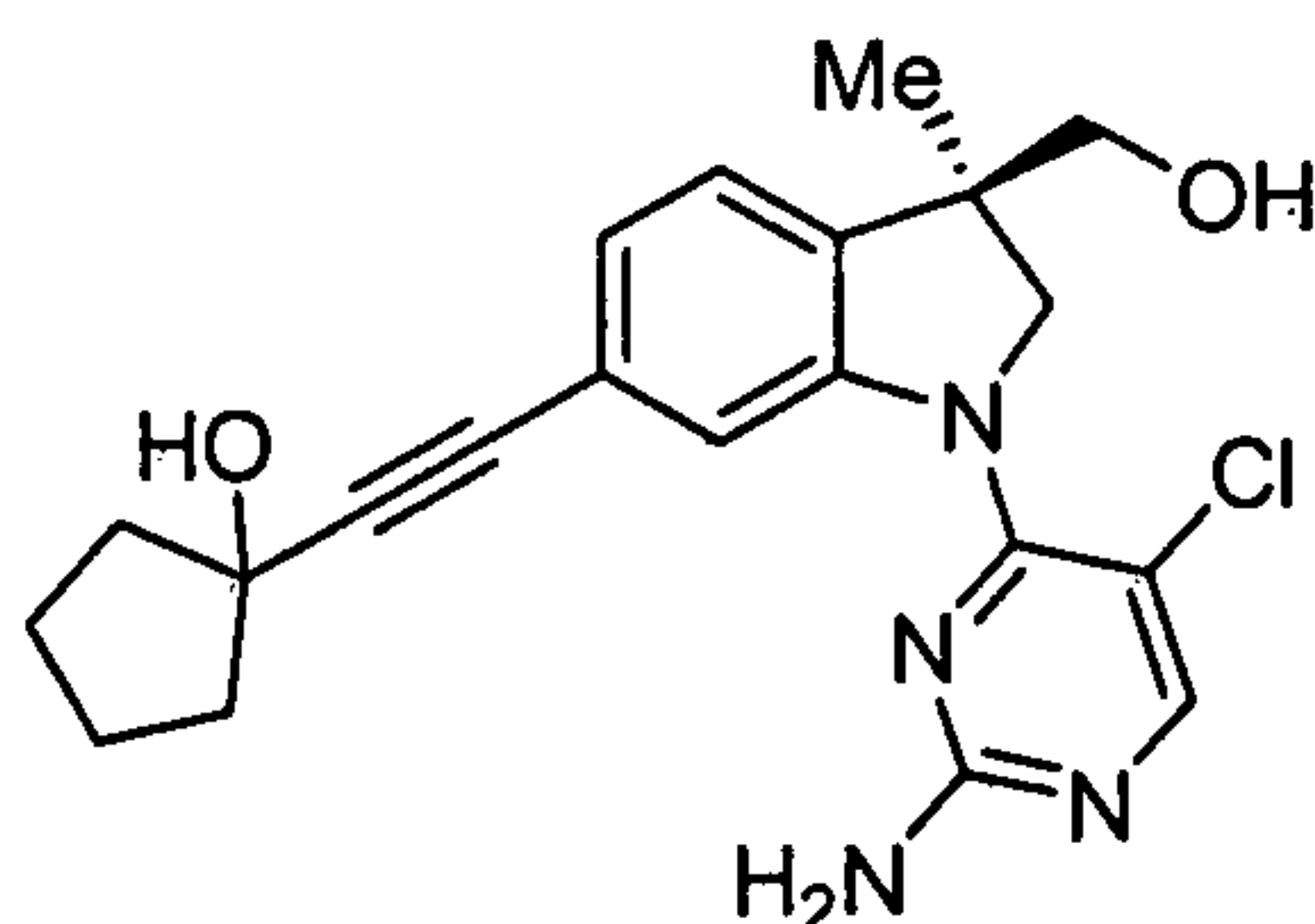
Example 54



54

1-(((1-(2-amino-5-chloro-4-pyrimidinyl)-3-(hydroxymethyl)-3-methyl-2,3-dihydro-1H-indol-6-yl)ethynyl)cyclopentanol (54) (prepared from components A.30 and C.36) ^1H NMR (500 MHz, $(\text{CD})_3\text{SO}$) δ 8.10 (s, 1 H), 7.17 (s, 1H), 7.16 (d, $J = 8.3$ Hz, 1H), 6.94 (dd, $J = 7.4$ Hz, $J = 1.5$ Hz, 1H), 6.64 (br s, 2H), 5.24 (s, 1H), 5.00 (t, $J = 5.4$ Hz, 1H), 4.14 (d, $J = 10.3$ Hz, 1 H), 3.80 (d, $J = 10.3$ Hz, 1H), 3.33 (m, 2H), 1.64-1.74 (m, 4H), 1.80-1.90 (m, 4H), 1.27 (s, 3 H); ESI-MS: $M + \text{H}^+$ 399.1 m/z; RPHPLC @ 6.050 min (97%)..

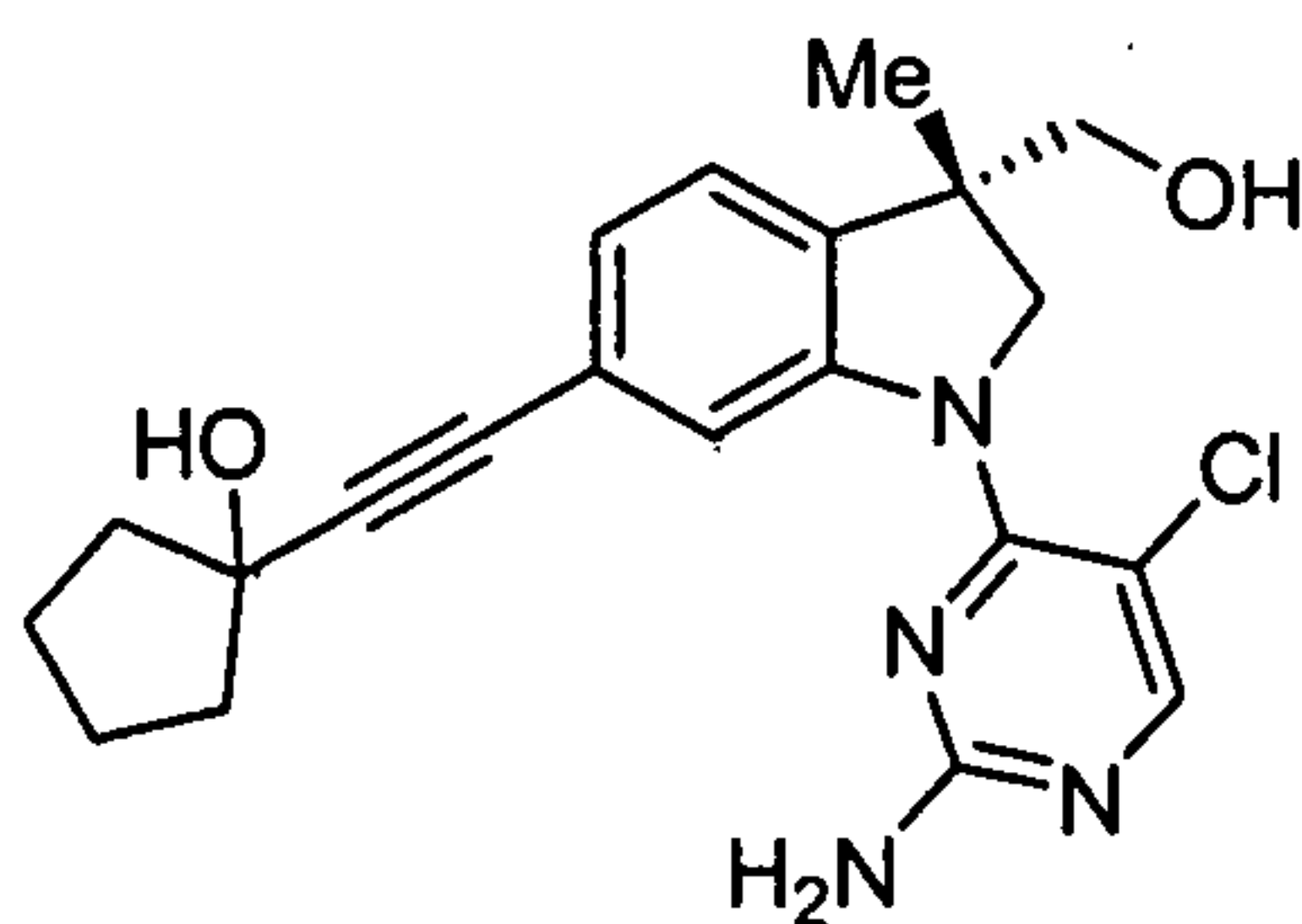
Example 55



55

1-(((3R*)-1-(2-amino-5-chloro-4-pyrimidinyl)-3-(hydroxymethyl)-3-methyl-2,3-dihydro-1H-indol-6-yl)ethynyl)cyclopentanol (55) (prepared from components A.33 and C.36) . ^1H NMR (500 MHz, DMSO- d_6) δ 8.09 (s, 1 H), 7.17 (s, 1H), 7.16 (d, $J = 8.3$ Hz, 1H), 6.94 (dd, $J = 7.9$ Hz, $J = 1.5$ Hz, 1H), 6.64 (br s, 2H), 5.25 (s, 1H), 5.01 (t, $J = 5.4$ Hz, 1H), 4.13 (d, $J = 10.3$ Hz, 1 H), 3.80 (d, $J = 10.3$ Hz, 1H), 3.33 (m, 2H), 1.85-1.91 (m, 4H), 1.64-1.75 (m, 4H), 1.27 (s, 3H); ESI-MS: $M + \text{H}^+$ 399.1 m/z; RPHPLC @ 6.104 min (95%); $[\alpha]_{\text{D}20} = -40.9$. Stereochemistry is arbitrarily assigned.

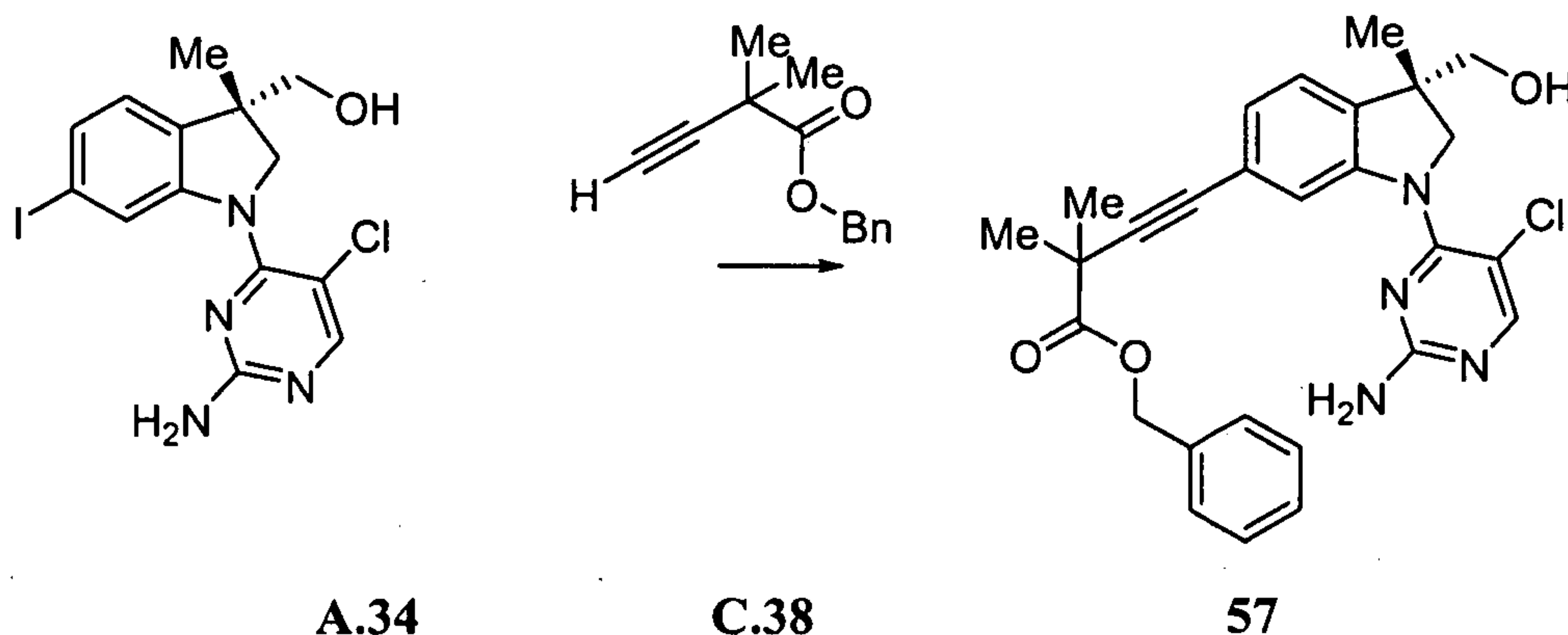
Example 56



56

1-(((3S*)-1-(2-amino-5-chloro-4-pyrimidinyl)-3-(hydroxymethyl)-3-methyl-2,3-dihydro-1H-indol-6-yl)ethynyl)cyclopentanol (56) (prepared from components A.32 and C.36) . ^1H NMR (500 MHz, DMSO- d_6) δ 8.09 (s, 1 H), 7.17 (s, 1H), 7.16 (d, $J = 8.3$ Hz, 1H), 6.94 (dd, $J = 7.8$ Hz, $J = 1.5$ Hz, 1H), 6.64 (br s, 2H), 5.25 (s, 1H), 5.01 (t, $J = 5.3$ Hz, 1H), 4.14 (d, $J =$

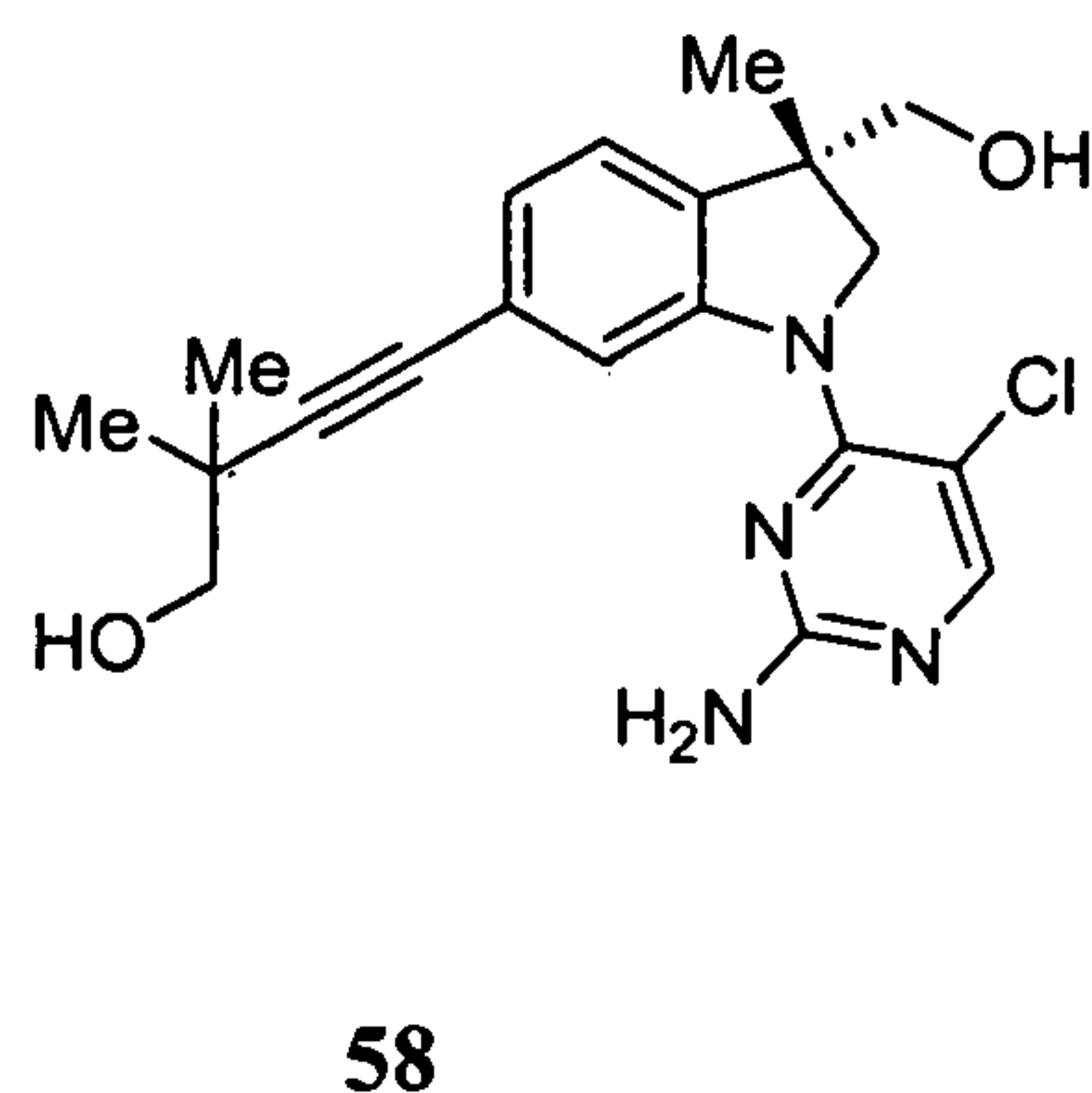
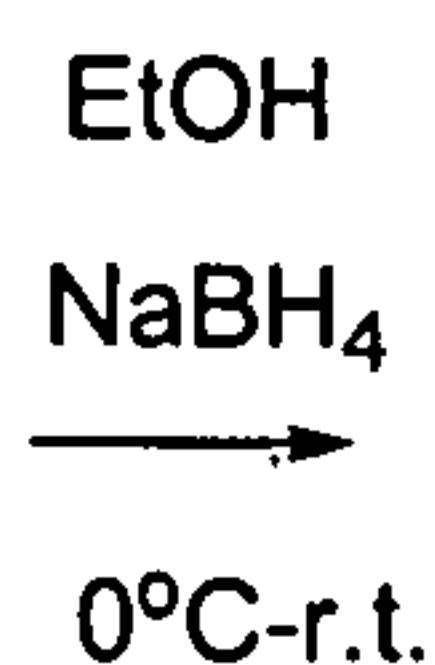
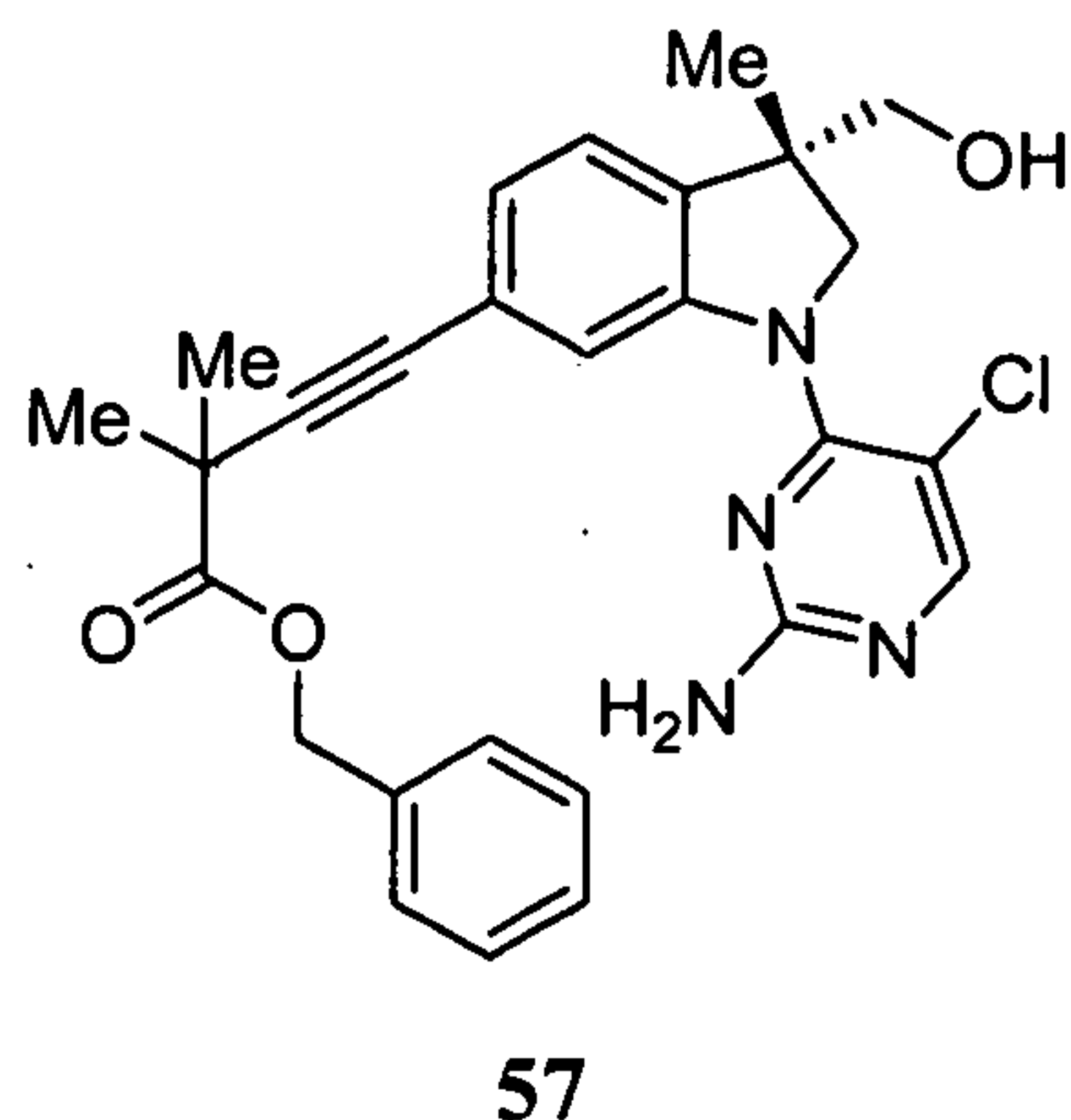
10.8 Hz, 1 H), 3.80 (d, $J = 10.3$ Hz, 1H), 3.33 (m, 2H), 1.82-1.91 (m, 4H), 1.64-1.75 (m, 4H), 1.27 (s, 3H); ESI-MS: $M + H^+$ 399.1 m/z; RPHPLC @ 6.104 min (95%); $[\alpha]_{D20} = +48.2$. Stereochemistry is arbitrarily assigned.

Example 57

benzyl 4-((3S*)-1-(2-amino-5-chloro-4-pyrimidinyl)-3-(hydroxymethyl)-3-methyl-2,3-dihydro-1H-indol-6-yl)-2,2-dimethyl-3-butynoate (57)

benzyl 2,2-dimethyl-3-butynoate **C.38** (available from Beta Pharma Inc.) (267mg, 1.32mmol), and (1-(2-amino-5-chloro-4-pyrimidinyl)-6-iodo-3-methyl-2,3-dihydro-1H-indol-3-yl)methanol **A.34** (138mg, 0.33mmol) were combined in 3ml of DMF and 1.5ml of triethylamine. Argon was bubbled through the solution for ~1min before adding $PdCl_2(PPh_3)_2$ (50mg, 0.067mmol). The reaction was heated overnight at 30°C. More benzyl 2,2-dimethyl-3-butynoate (267mg, 1.32mmol) and $PdCl_2(PPh_3)_2$ (50mg, 0.067mmol) were added. The solution was heated at 40°C for 1 day before it was diluted with water and extracted with ethyl acetate. The organics were washed with Brine and dried over Na_2SO_4 before being concentrated under vacuum. The residue obtained was purified by CombiFlash chromatography eluting with a gradient of 1% methanol/dichloromethane to 2% methanol/dichloromethane. The fractions containing the product were combined and concentrated under vacuum to give benzyl 4-((3S*)-1-(2-amino-5-chloro-4-pyrimidinyl)-3-(hydroxymethyl)-3-methyl-2,3-dihydro-1H-indol-6-yl)-2,2-dimethyl-3-butynoate (**57**) (105mg) as a white solid.

ESI-MS: $M + H^+$ 491.2 m/z, Stereochemistry is arbitrarily assigned.

Example 58

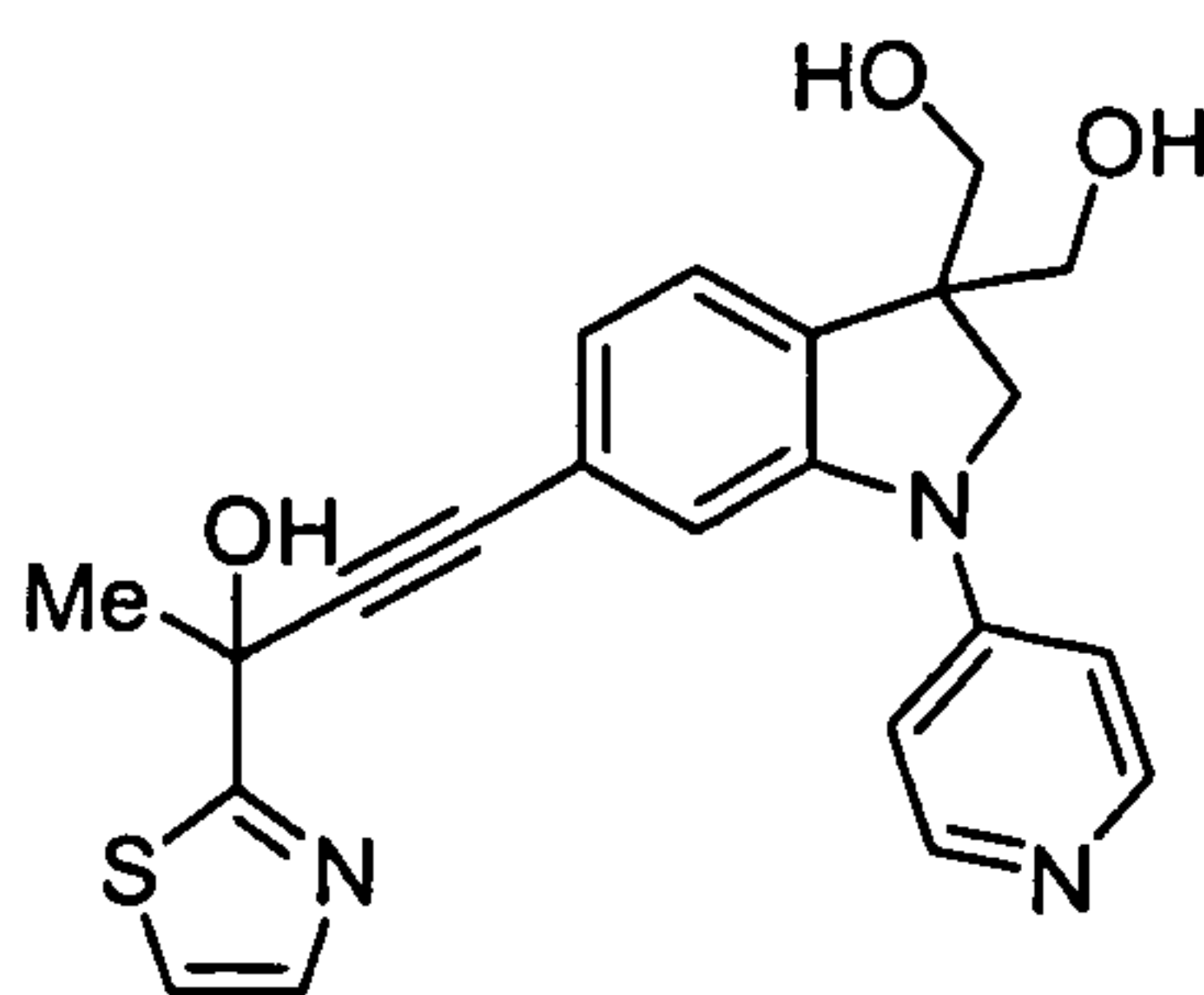
4-((3S*)-1-(2-amino-5-chloro-4-pyrimidinyl)-3-(hydroxymethyl)-3-methyl-2,3-dihydro-1H-indol-6-yl)-2,2-dimethyl-3-butyn-1-ol (58)

benzyl 4-((3S*)-1-(2-amino-5-chloro-4-pyrimidinyl)-3-(hydroxymethyl)-3-methyl-2,3-dihydro-1H-indol-6-yl)-2,2-dimethyl-3-butynoate (**57**) (100mg, 0.204) in absolute EtOH (5ml) was cooled in an ice bath before adding NaBH₄ (77mg, 2.03mmol). The solution was then allowed to warm to room temperature. After stirring the reaction at room temperature for 3 days it was cooled in an ice bath and quenched with saturated NH₄Cl. Diluted the solution with water and extracted with ethyl acetate. The organics were then washed with Brine, dried over Na₂SO₄ and concentrated under vacuum. The residue obtained was purified by CombiFlash chromatography eluting with a gradient of 2.5% methanol/dichloromethane to 5% methanol/dichloromethane. The fractions containing the product were combined and concentrated under vacuum to give 4-((3S*)-1-(2-amino-5-chloro-4-pyrimidinyl)-3-(hydroxymethyl)-3-methyl-2,3-dihydro-1H-indol-6-yl)-2,2-dimethyl-3-butyn-1-ol (**58**) (25mg, 31%).

¹H NMR (400 MHz, DMSO-d₆) δ 8.09 (s, 1 H), 7.16 (s, 1H), 7.13 (d, J = 7.7 Hz, 1H), 6.91 (br d, J = 7.6 Hz, 1H), 6.63 (br s, 2H), 4.99 (t, J = 4.9 Hz, 1H), 4.91 (t, J = 5.8 Hz, 1H), 4.14 (d, J = 10.3 Hz, 1 H), 3.79 (d, J = 10.3 Hz, 2H), 3.33 (m, 4H), 1.27 (s, 3H), 1.18 (s, 6H); ESI-MS: M + H⁺ 387.2 m/z; RPHPLC @ 5.885 min (95%). Stereochemistry is arbitrarily assigned.

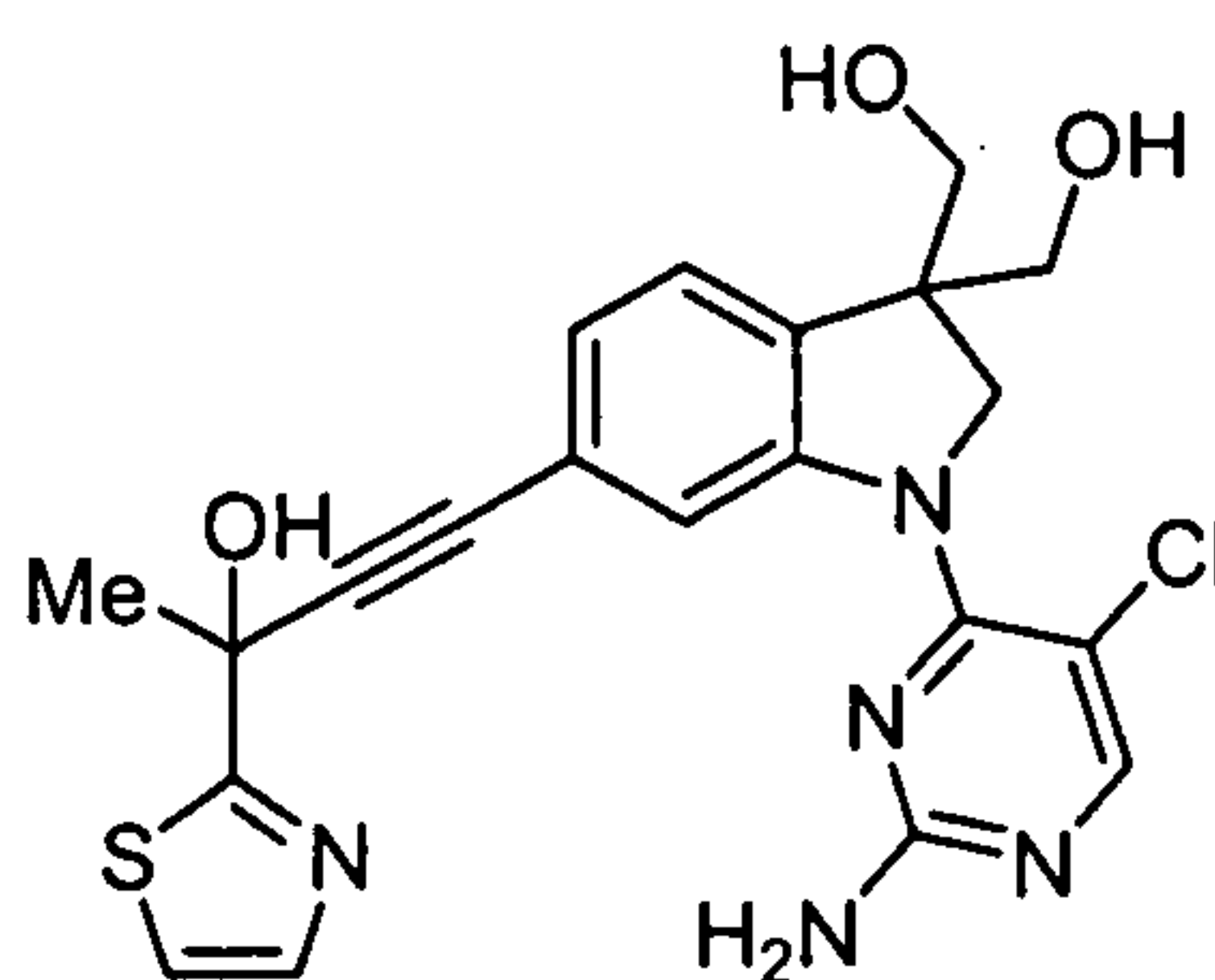
Example 59

Examples 59-80 were prepared using same or analogous synthetic techniques and substituting with appropriate reagent as in **example 1**.



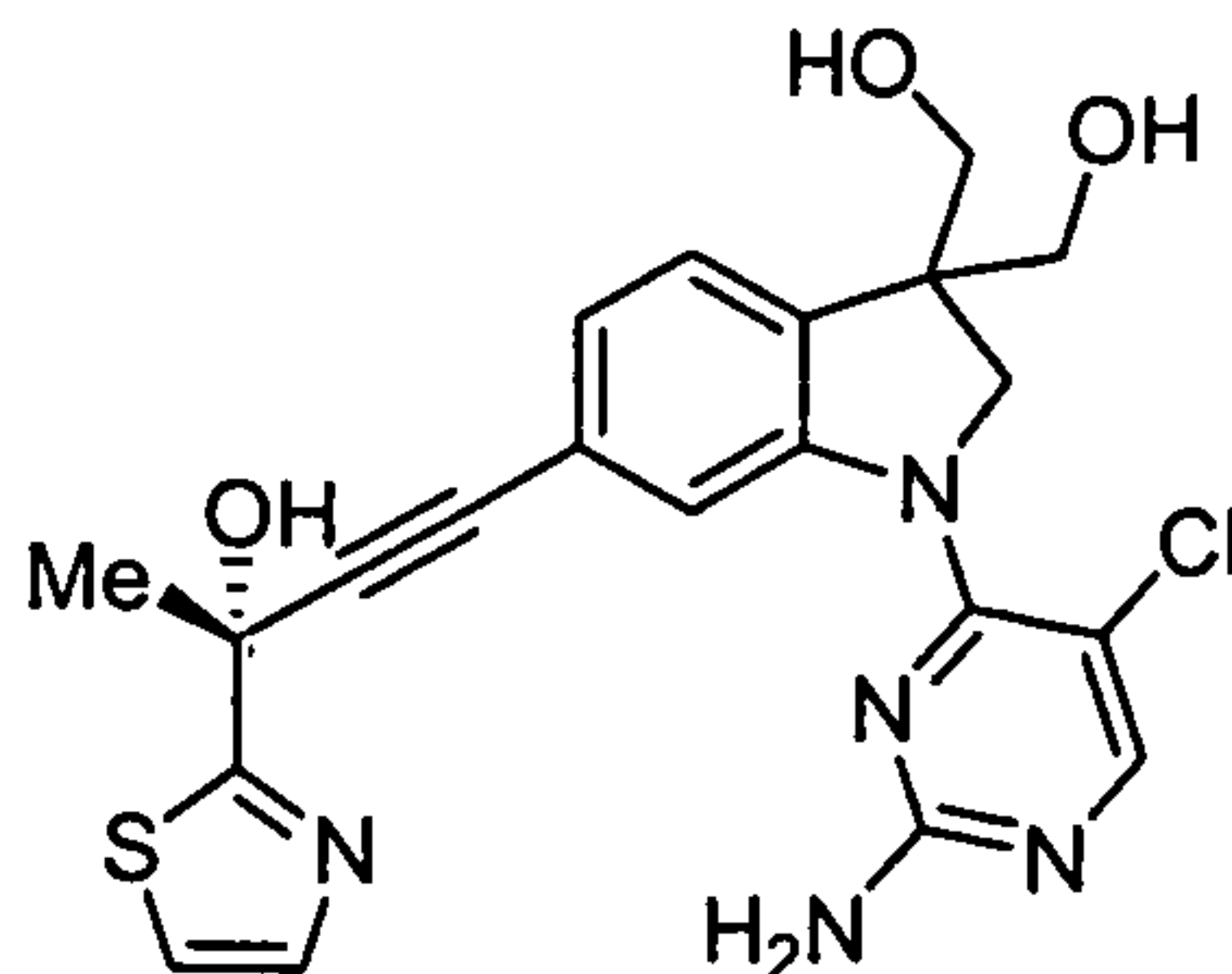
59

4-(3,3-bis(hydroxymethyl)-1-(4-pyridinyl)-2,3-dihydro-1H-indol-6-yl)-2-(1,3-thiazol-2-yl)-3-butyn-2-ol (59) (prepared from components A.38 and C.4). ^1H NMR (500 MHz, DMSO- d_6) δ 8.39 (br m, 2 H), 7.78 (d, $J = 3.18$ Hz, 1H), 7.68 (d, $J = 3.48$ Hz, 1H), 7.28 (d, $J = 7.8$ Hz, 1H), 7.26 (d, $J = 1$ Hz, 1H), 7.16 (br m, 2H), 7.00 (s, 1H), 6.95 (dd, $J = 7.6$ Hz, $J = 1.25$ Hz, 1H), 4.93 (s, 2H), 3.88 (s, 2H), 3.58 (m, 4H), 1.88 (s, 3H); ESI-MS: $M + H^+$ 408.1 m/z; RPHPLC @ 4.559 min (93%).

Example 60

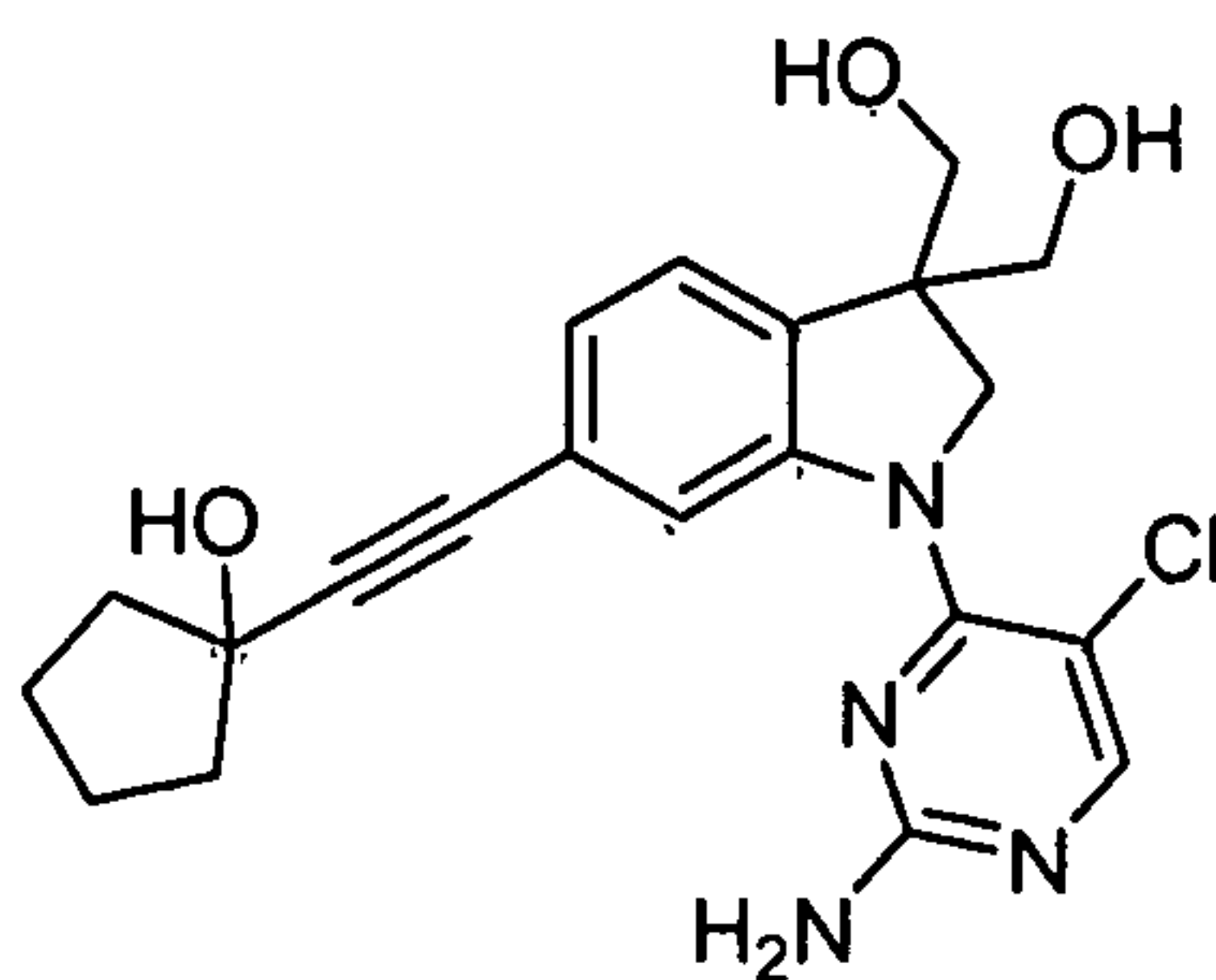
60

4-(1-(2-amino-5-chloro-4-pyrimidinyl)-3,3-bis(hydroxymethyl)-2,3-dihydro-1H-indol-6-yl)-2-(1,3-thiazol-2-yl)-3-butyn-2-ol (60) (prepared from components A.39 and C.4). ^1H NMR (400 MHz, DMSO- d_6) δ 8.10 (s, 1 H), 7.75 (d, $J = 3.2$ Hz, 1H), 7.66 (d, $J = 3.2$ Hz, 1H), 7.24 (d, $J = 1$ Hz, 1H), 7.22 (d, $J = 7.7$ Hz, 1H), 6.94 (dd, $J = 7.6$ Hz, $J = 1.3$, 1H), 6.93 (s, 1H), 6.61 (br s, 2H), 4.88 (t, $J = 5.2$, 2H), 4.05 (s, 2H), 3.50-3.58 (m, 4H), 1.86 (s, 3H); ESI-MS: $M + H^+$ 458.0 m/z; RPHPLC @ 4.785 min (95%).

Example 61**61**

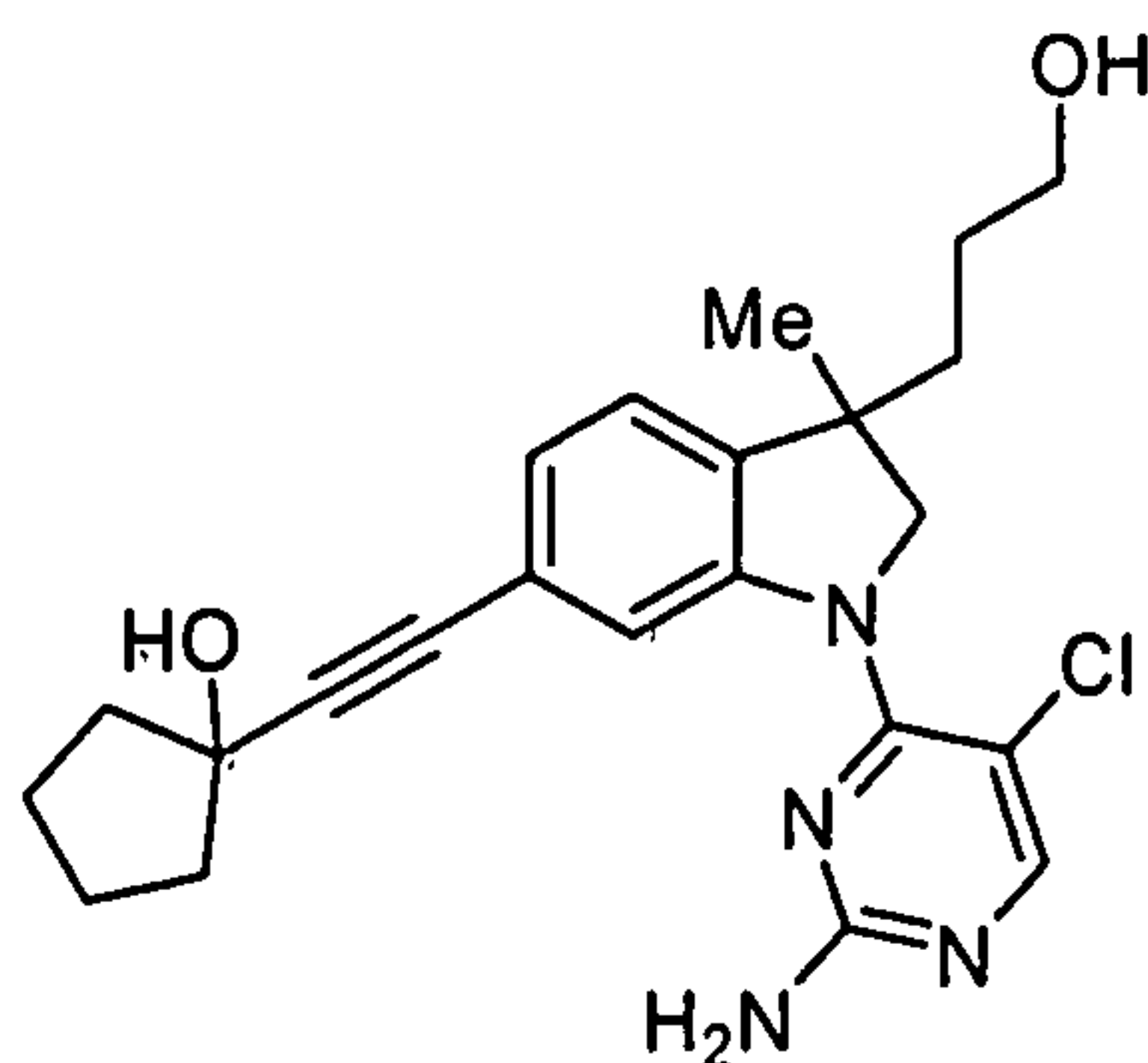
(2R)-4-(1-(2-amino-5-chloro-4-pyrimidinyl)-3,3-bis(hydroxymethyl)-2,3-dihydro-1H-indol-6-yl)-2-(1,3-thiazol-2-yl)-3-butyn-2-ol (61) Separated the racemic mixture of example 60 on a preparative chiral column AD-H eluting with 17% iPrOH/hexane, the title compound was obtained as a clear film (9mg, 2%). Stereochemistry for the second peak to elute assigned as R based on biological activity.

¹H NMR (500 MHz, methanol- *d*₄) δ 8.04 (br s, 1 H), 7.78 (d, *J* = 3.4 Hz, 1H), 7.65 (br m, 1H), 7.56 (d, *J* = 3.4 Hz, 1H), 7.27 (d, *J* = 7.8 Hz, 1H), 7.10 (dd, *J* = 7.6 Hz, *J* = 1.2, 1H), 4.26 (s, 2H), 3.75 (m, 4H), 3.37 (s, 1H), 1.95 (s, 3H); ESI-MS: *M* + *H*⁺ 458.0 *m/z*; RPHPLC @ 4.822 min (95%).

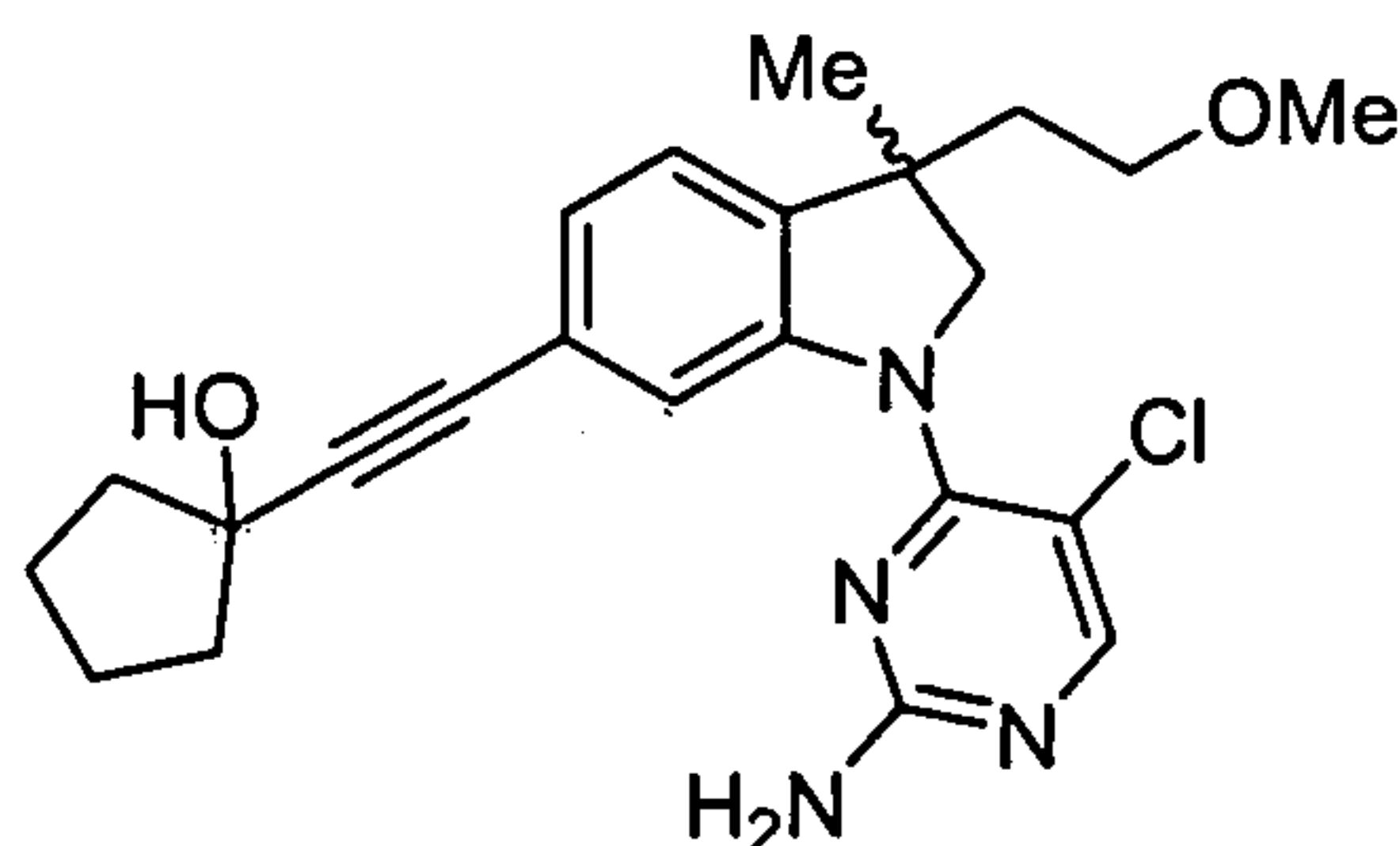
Example 62**62**

1-((1-(2-amino-5-chloro-4-pyrimidinyl)-3,3-bis(hydroxymethyl)-2,3-dihydro-1H-indol-6-yl)ethynyl)cyclopentanol (62). The title compound prepared from components A.39 and C.36 was obtained as a brownish solid (100mg, 77%).

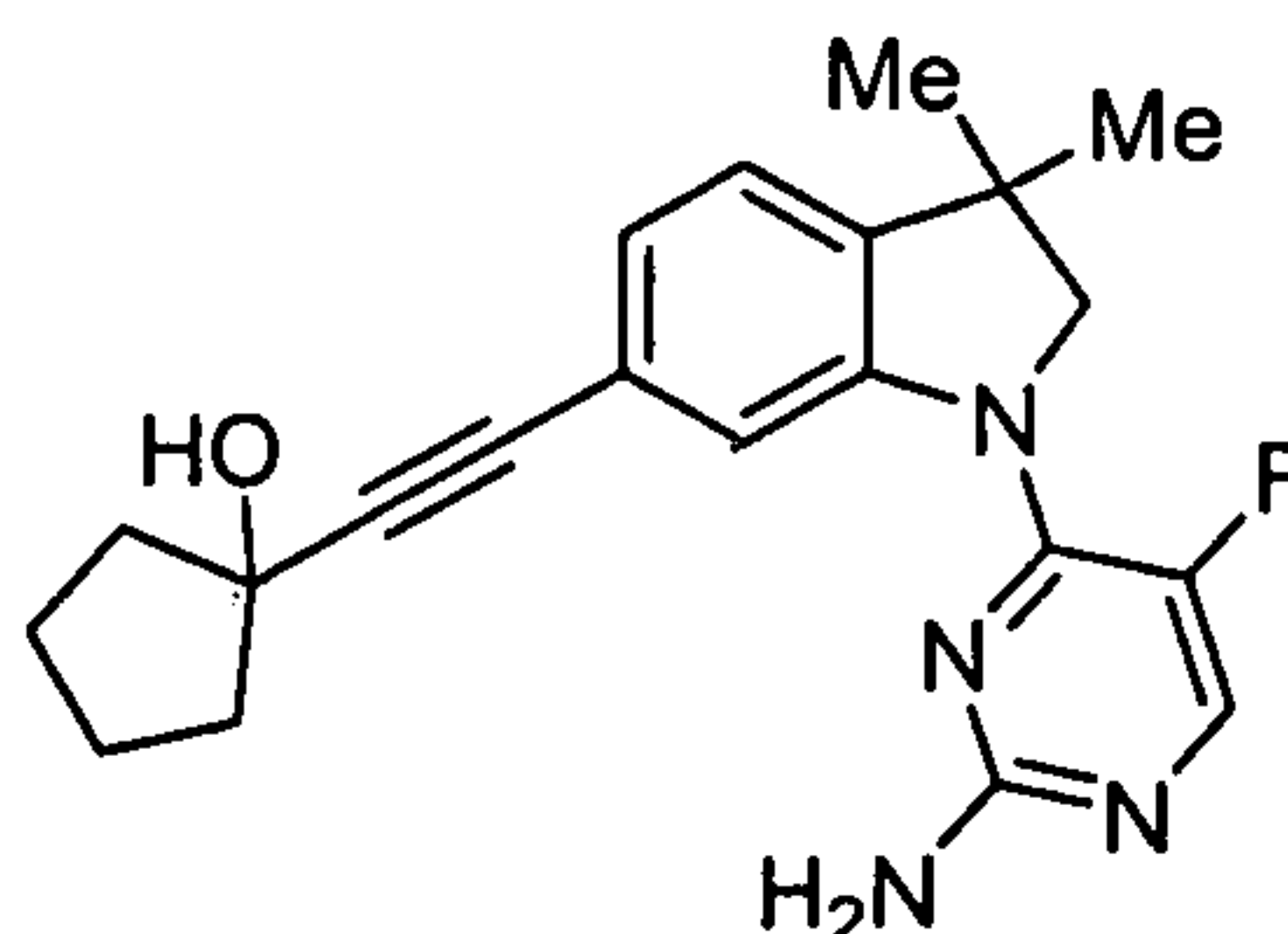
¹H NMR (400 MHz, DMSO-*d*₆) δ 8.12 (br s, 1 H), 7.23 (d, *J* = 1 Hz, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 6.92 (dd, *J* = 7.6 Hz, *J* = 1.3 Hz, 1H), 6.61 (br s, 2H), 5.24 (s, 1H), 4.87 (t, *J* = 5.2 Hz, 2H), 4.05 (s, 1 H), 3.50-3.58 (m, 4H), 1.82-1.92 (m, 4H), 1.64-1.74 (m, 4H); ESI-MS: *M* + *H*⁺ 415.1 *m/z*; RPHPLC @ 5.138 min (95%).

Example 63**63**

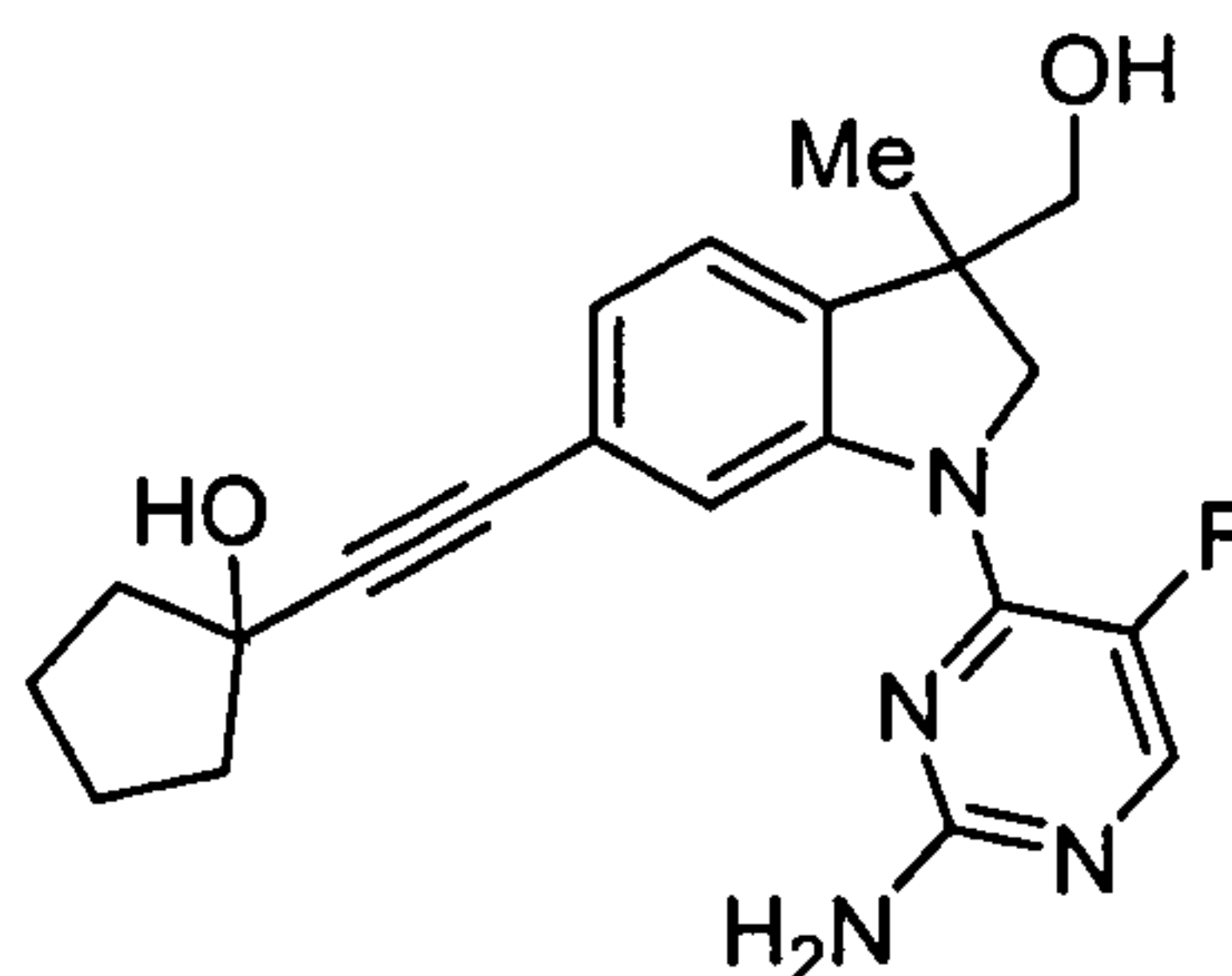
1-((1-(2-amino-5-chloro-4-pyrimidinyl)-3-(3-hydroxypropyl)-3-methyl-2,3-dihydro-1H-indol-6-yl)ethynyl)cyclopentanol (63) (prepared from components A.43 and C.36). ^1H NMR (500 MHz, DMSO- d_6) δ 8.11 (s, 1 H), 7.15 (m, 2H), 6.96 (d, $J = 7.7$ Hz, 1H), 6.67 (s, 1H), 5.28 (s, 1H), 4.36 (t, $J = 5.1$ Hz, 1H), 3.96 (d, $J = 10.2$ Hz, 1H), 3.88 (d, $J = 10.3$ Hz, 1 H), 3.32 (m, 2H), 1.85-1.92 (m, 4H), 1.65-1.77 (m, 4H), 1.64-1.52 (m, 2H), 1.42-1.35 (m, 1H), 1.29 (s, 3H) 1.26-1.20 (m, 1H); ESI-MS: $M + H^+$ 427.3 m/z ; RPHPLC @ 6.254 min (95%).

Example 64**64**

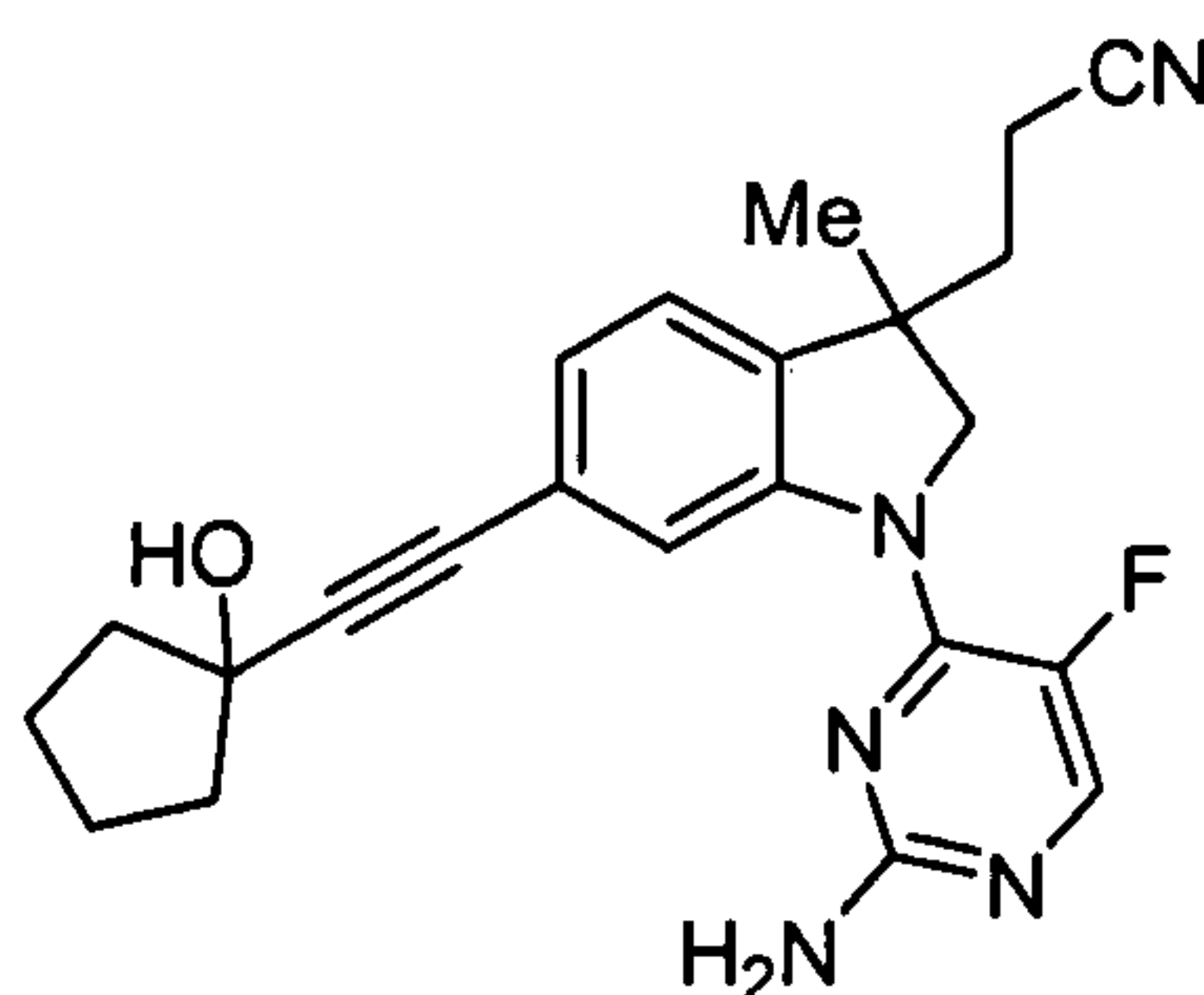
1-((1-(2-amino-5-chloro-4-pyrimidinyl)-3-(2-methoxyethyl)-3-methyl-2,3-dihydro-1H-indol-6-yl)ethynyl)cyclopentanol (64) prepared from components A.48 and C.36). ^1H NMR (500 MHz, CDCl_3) δ 8.04 (br s, 1 H), 7.56 (s, 1H), 7.11 (d, $J = 7.8$ Hz, 1H), 7.06 (d, $J = 7.9$ Hz, 1H), 5.31 (br s, 2H), 4.30 (d, $J = 10.8$ Hz, 1H), 3.99 (d, $J = 10.2$ Hz, 1H), 3.26-3.35 (m, 2 H), 1.85-2.11 (m, 8H), 1.76-1.82 (m, 2H), 1.36 (s, 3H); ESI-MS: $M + H^+$ 427.1 m/z ; RPHPLC @ 7.083 min (94%).

Example 65**65**

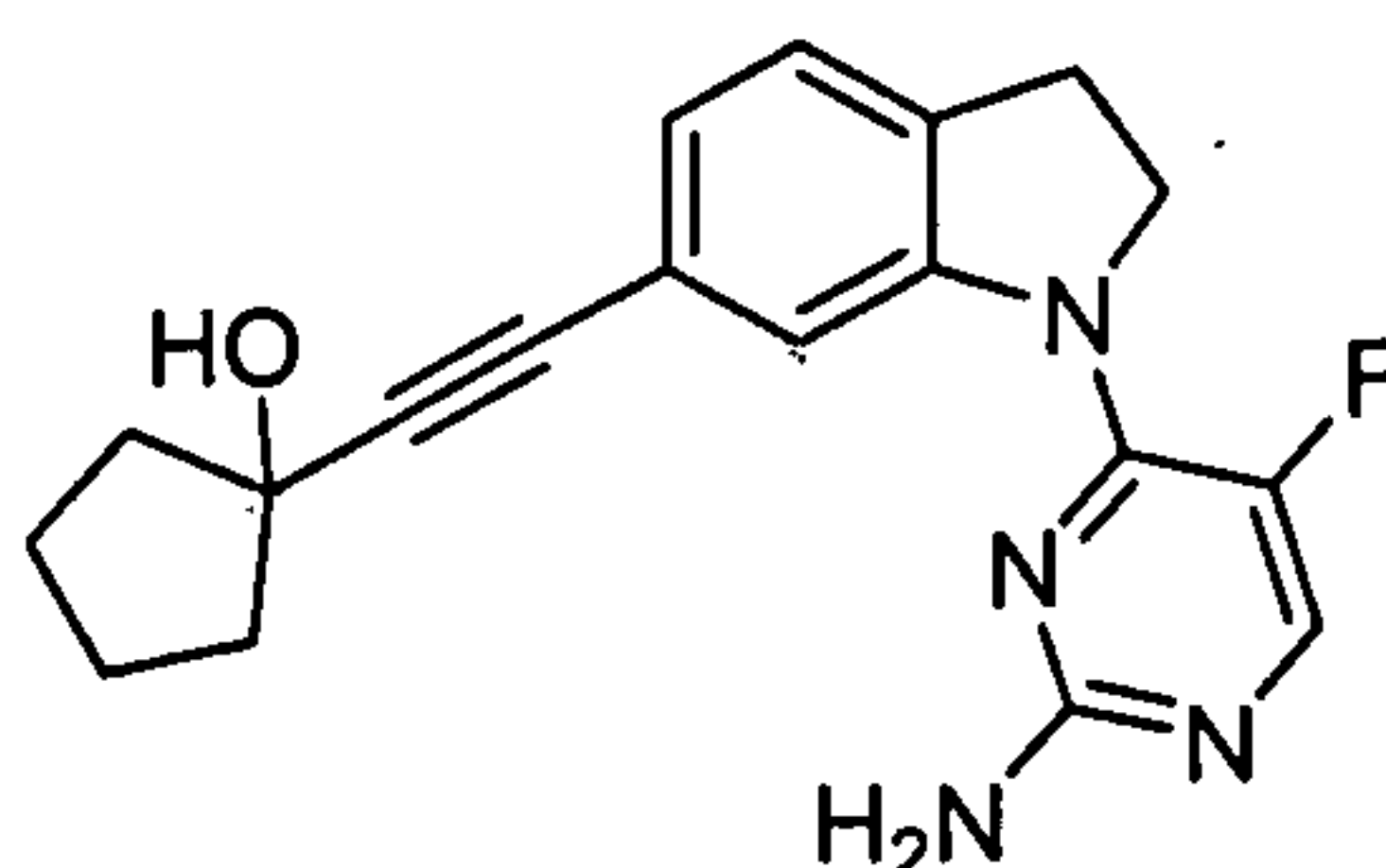
1-((1-(2-amino-5-fluoro-4-pyrimidinyl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)ethynyl)cyclopentanol (65) prepared from components **A.54** and **C.36**. ^1H NMR (500 MHz, $(\text{CD})_3\text{SO}$) δ 8.02 (d, $J = 5.4$ Hz, 1H), 7.83 (br s, 1H), 7.21 (d, $J = 7.9$ Hz, 1H), 7.00 (dd, $J = 7.8$ Hz, $J = 1.5$ Hz, 1H), 6.35 (br s, 2H), 5.24 (s, 1H), 3.94 (d, $J = 3.9$ Hz, 2H), 1.87-1.92 (m, 4H), 1.65-1.77 (m, 4H), 1.29 (s, 6H); ESI-MS: $\text{M} + \text{H}^+$ 367.5 m/z; RPHPLC @ 6.955 min (95%).

Example 66**66**

1-((1-(2-amino-5-fluoro-4-pyrimidinyl)-3-(hydroxymethyl)-3-methyl-2,3-dihydro-1H-indol-6-yl)ethynyl)cyclopentanol (66) prepared from components **A.56** and **C.36**. ^1H NMR (500 MHz, $(\text{CD})_3\text{SO}$) δ 8.01 (d, $J = 5.9$ Hz, 1H), 7.88 (s, 1H), 7.18 (d, $J = 7.8$ Hz, 1H), 6.98 (dd, $J = 7.3$ Hz, $J = 1.0$ Hz, 1H), 6.33 (br s, 2H), 5.24 (s, 1H), 5.02 (t, $J = 5.4$ Hz, 1H), 4.23 (dd, $J = 11.3$ Hz, $J = 5.4$ Hz, 1H), 3.79 (d, $J = 10.3$ Hz, $J = 3.9$ Hz, 1H), 3.36 (d, $J = 6.9$ Hz, 2H), 1.88-1.92 (m, 4H), 1.65-1.76 (m, 4H), 1.28 (s, 3H); ESI-MS: $\text{M} + \text{H}^+$ 383.2 m/z; RPHPLC @ 5.853 min (97%).

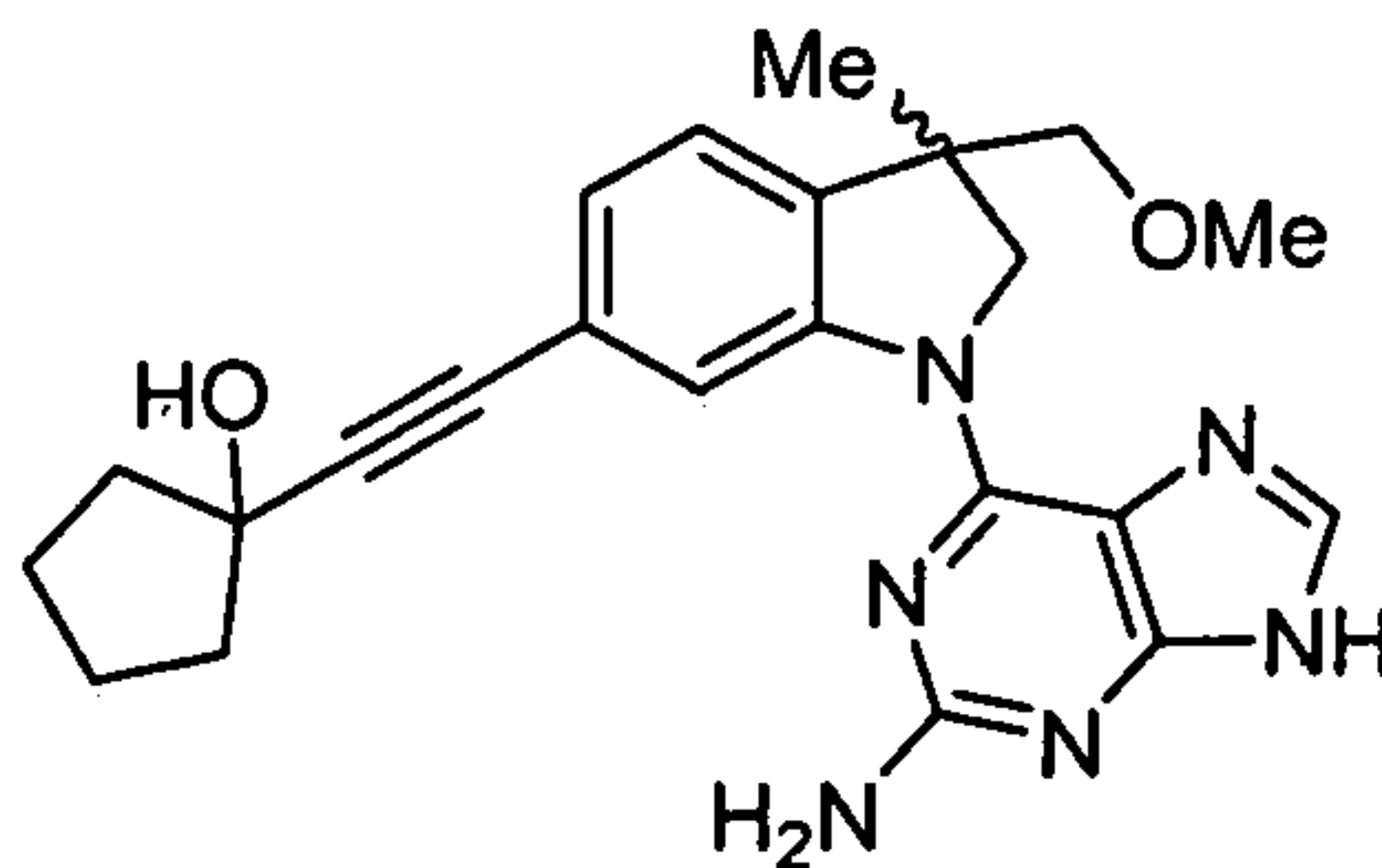
Example 67**67**

3-(1-(2-amino-5-fluoro-4-pyrimidinyl)-6-((1-hydroxycyclopentyl)ethynyl)-3-methyl-2,3-dihydro-1H-indol-3-yl)propanenitrile (67) (prepared from components A.60 and C.36). ^1H NMR (500 MHz, $(\text{CD})_3\text{SO}$) δ 8.04 (br s, 1H) 7.84 (s, 1H), 7.23 (d, $J = 7.8$ Hz, 1H), 7.01 (dd, $J = 7.8$ Hz, $J = 1.5$ Hz, 1H), 6.36 (br s, 2H), 5.25 (s, 1H), 4.14 (dd, $J = 10.8$ Hz, $J = 4.4$ Hz, 1H), 3.89 (dd, $J = 11.2$ Hz, $J = 3.9$ Hz, 1H), 2.41-2.48 (m, 1H), 2.23-2.30 (m, 1H), 1.91-1.99 (m, 4H), 1.90 (m, 2H), 1.65-1.76 (m, 4H); ESI-MS: $M + \text{H}^+$ 406.1 m/z ; RPHPLC @ 6.502 min (97%).

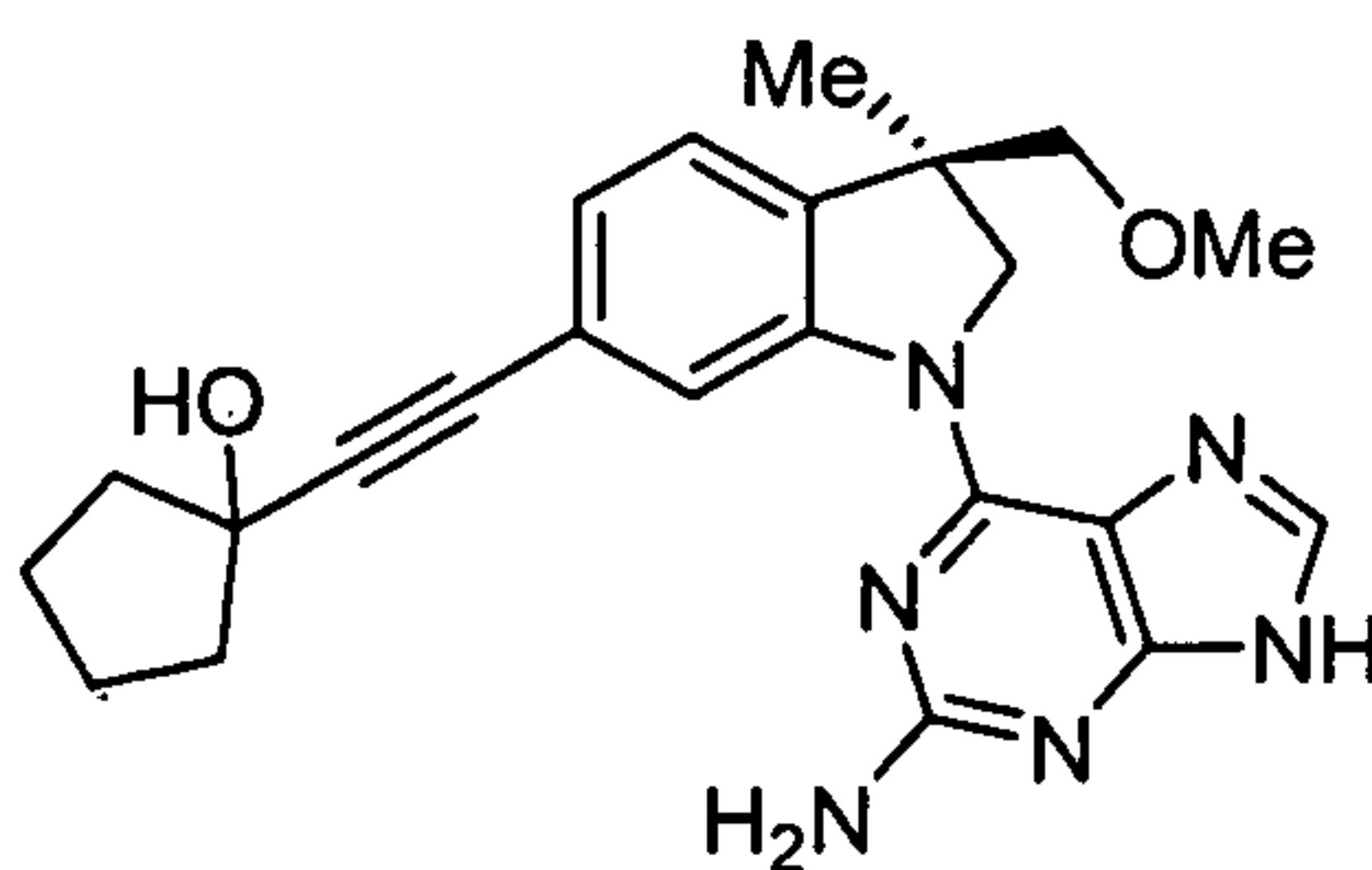
Example 68**68**

1-((1-(2-amino-5-fluoro-4-pyrimidinyl)-2,3-dihydro-1H-indol-6-yl)ethynyl)cyclopentanol (68). The title compound prepared from components A.61 and C.36, was obtained as a light brownish solid (8mg, 3%).

^1H NMR (500 MHz, $(\text{CD})_3\text{SO}$) δ 8.01 (s, 1H), 7.89 (br s, 1H), 7.20 (d, $J = 7.9$ Hz, 1H), 6.95 (dd, $J = 7.8$ Hz, $J = 1.5$ Hz, 1H), 6.34 (br s, 2H), 5.24 (s, 1H), 4.18-4.23 (m, 2H), 3.14 (t, $J = 8.3$ Hz, 2H), 1.88-1.92 (m, 4H), 1.65-1.76 (m, 4H); ESI-MS: $M + \text{H}^+$ 339.4 m/z ; RPHPLC @ 6.268 min (95%).

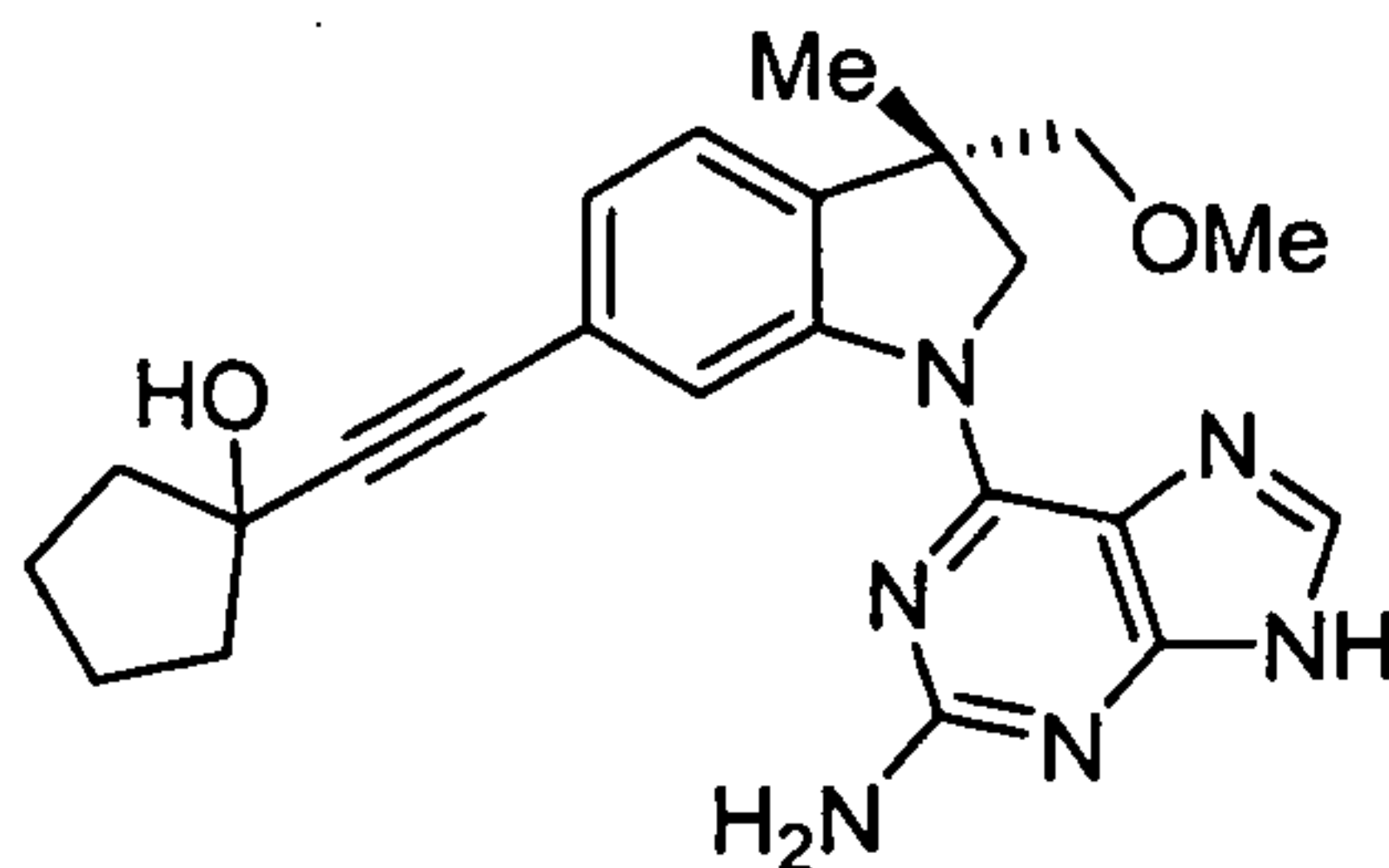
Example 69**69**

1-((1-(2-amino-9H-purin-6-yl)-3-(methoxymethyl)-3-methyl-2,3-dihydro-1H-indol-6-yl)ethynyl)cyclopentanol (69) (prepared from components A.70 and C.36). ^1H NMR (500 MHz, $(\text{CD})_3\text{SO}$) δ 12.36 (br s, 1H), 8.56 (br s, 1H), 7.80 (s, 1H), 7.21 (d, $J = 7.8$ Hz, 1H), 6.98 (br d, $J = 7.4$ Hz, 1H), 6.03 (br s, 2H), 5.24 (s, 1H), 4.75 (d, $J = 11.7$ Hz, 1H), 4.30 (d, $J = 11.7$ Hz, 1H), 3.38 (m; 2H), 3.24 (s, 3H), 1.90-1.95 (m, 4H), 1.66-1.77 (m, 4H), 1.33 (s, 3H); ESI-MS: $\text{M} + \text{H}^+$ 419.2 m/z ; RPHPLC @ 6.418 min (95%).

Example 70**70**

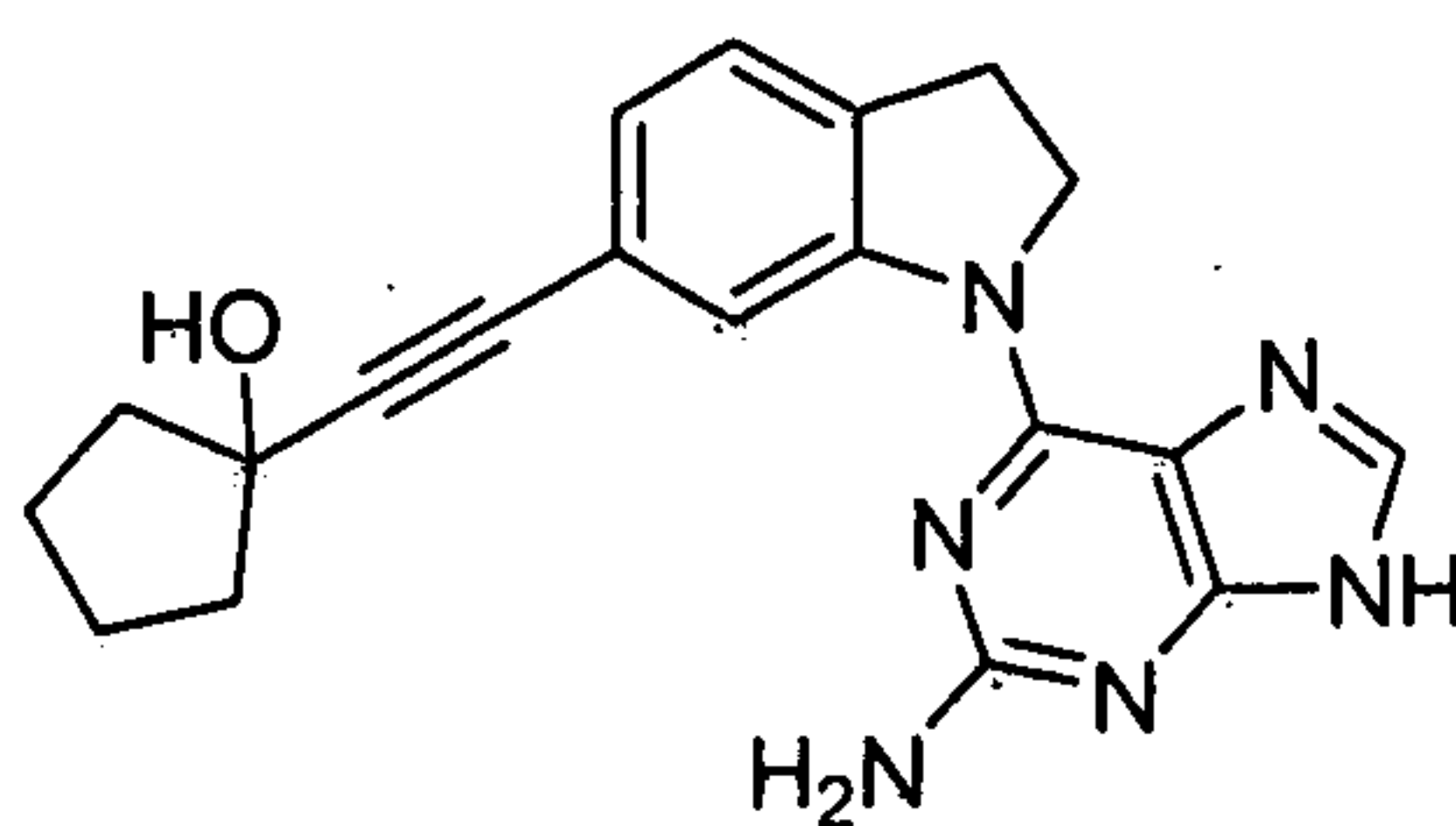
1-(((3R*)-1-(2-amino-9H-purin-6-yl)-3-(methoxymethyl)-3-methyl-2,3-dihydro-1H-indol-6-yl)ethynyl)cyclopentanol (70) The racemic mixture was separated on a preparative chiral column AD-H eluting with 30% iPrOH/hexane; the title compound was obtained as an off white solid (13mg, 7%). Arbitrarily assigned stereochemistry as R* for the second peak to elute from the chiral column.

^1H NMR (500 MHz, $(\text{CD})_3\text{SO}$) δ 12.37 (br s, 1H), 8.56(d, $J = 1.4$ Hz, 1H), 7.80 (s, 1H), 7.22 (d, $J = 7.4$ Hz, 1H), 6.99 (dd, $J = 7.8$ Hz, $J = 1.5$ Hz, 1H), 6.03 (br s, 2H), 5.25 (s, 1H), 4.76 (d, $J = 11.8$ Hz, 1H), 4.31 (d, $J = 11.8$ Hz, 1H), 3.39 (m, 2H), 3.25 (s, 3H), 1.91-1.94 (m, 4H), 1.67-1.79 (m, 4H), 1.34 (s, 3H); ESI-MS: $\text{M} + \text{H}^+$ 419.2 m/z ; RPHPLC @ 6.412 min (95%). $[\alpha]_{\text{D}20} = -55^\circ$.

Example 71**71**

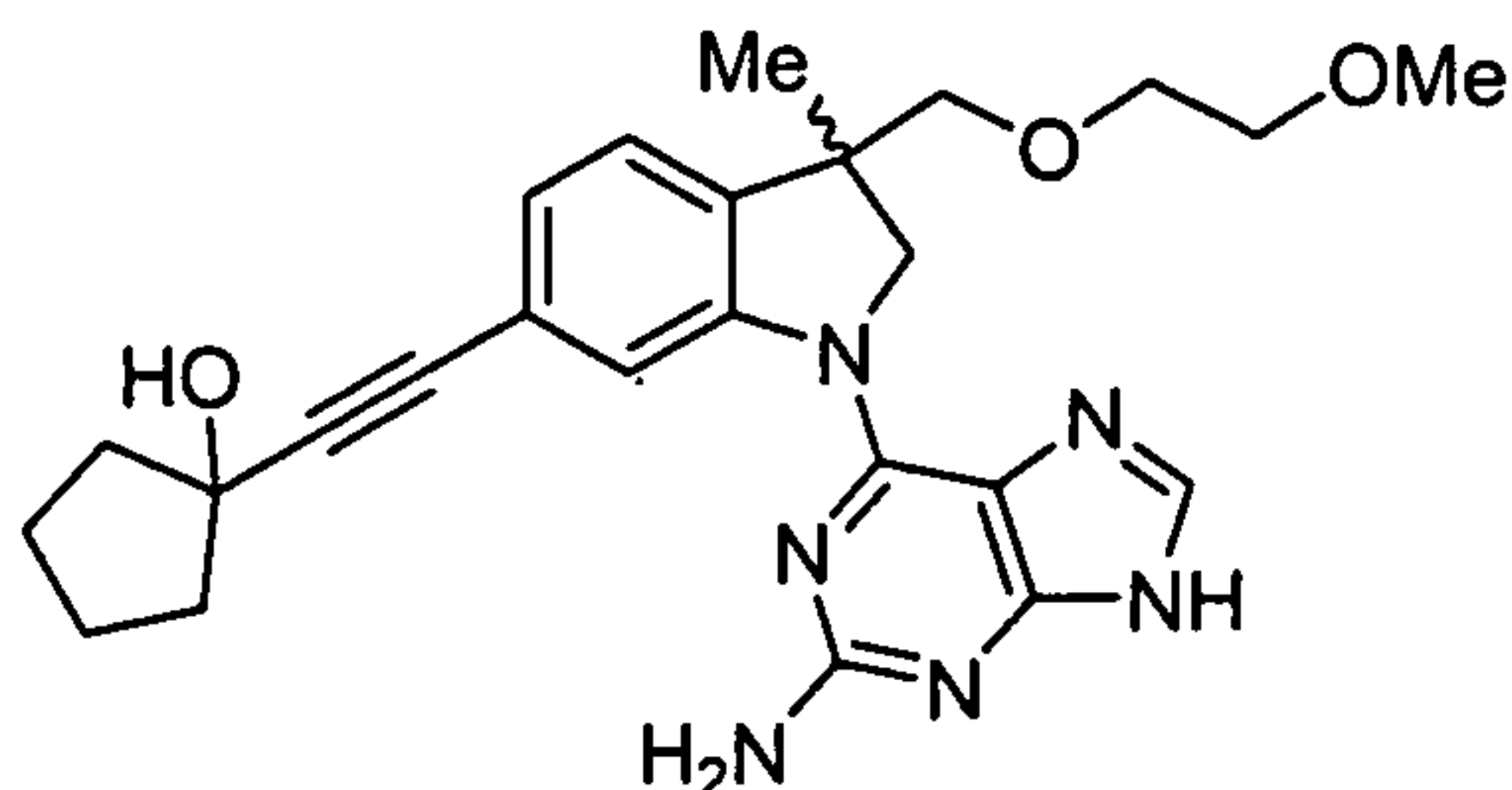
1-(((3S*)-1-(2-amino-9H-purin-6-yl)-3-(methoxymethyl)-3-methyl-2,3-dihydro-1H-indol-6-yl)ethynyl)cyclopentanol (71) ; The title compound (arbitrarily assigned stereochemistry as S*) was the first peak to elute from the chiral column and was obtained as an off white solid (25mg, 15%). .

¹H NMR (500 MHz, (CD)₃SO) δ 12.36 (br s, 1H), 8.56 (d, J = 1.0 Hz, 1H), 7.80 (s, 1H), 7.22 (d, J = 7.9 Hz, 1H), 6.99 (dd, J = 7.8 Hz, J = 1.5 Hz, 1H), 6.04 (br s, 2H), 5.25 (s, 1H), 4.76 (d, J = 11.7 Hz, 1 H), 4.31 (d, J = 11.8 Hz, 1H), 3.39 (m, 2H), 3.25 (s, 3H), 1.91-1.95 (m, 4H), 1.67-1.78 (m, 4H), 1.34 (s, 3H); ESI-MS: M + H⁺ 419.2 m/z; RPHPLC @ 6.425 min (95%).
[α]_{D20} = +55°.

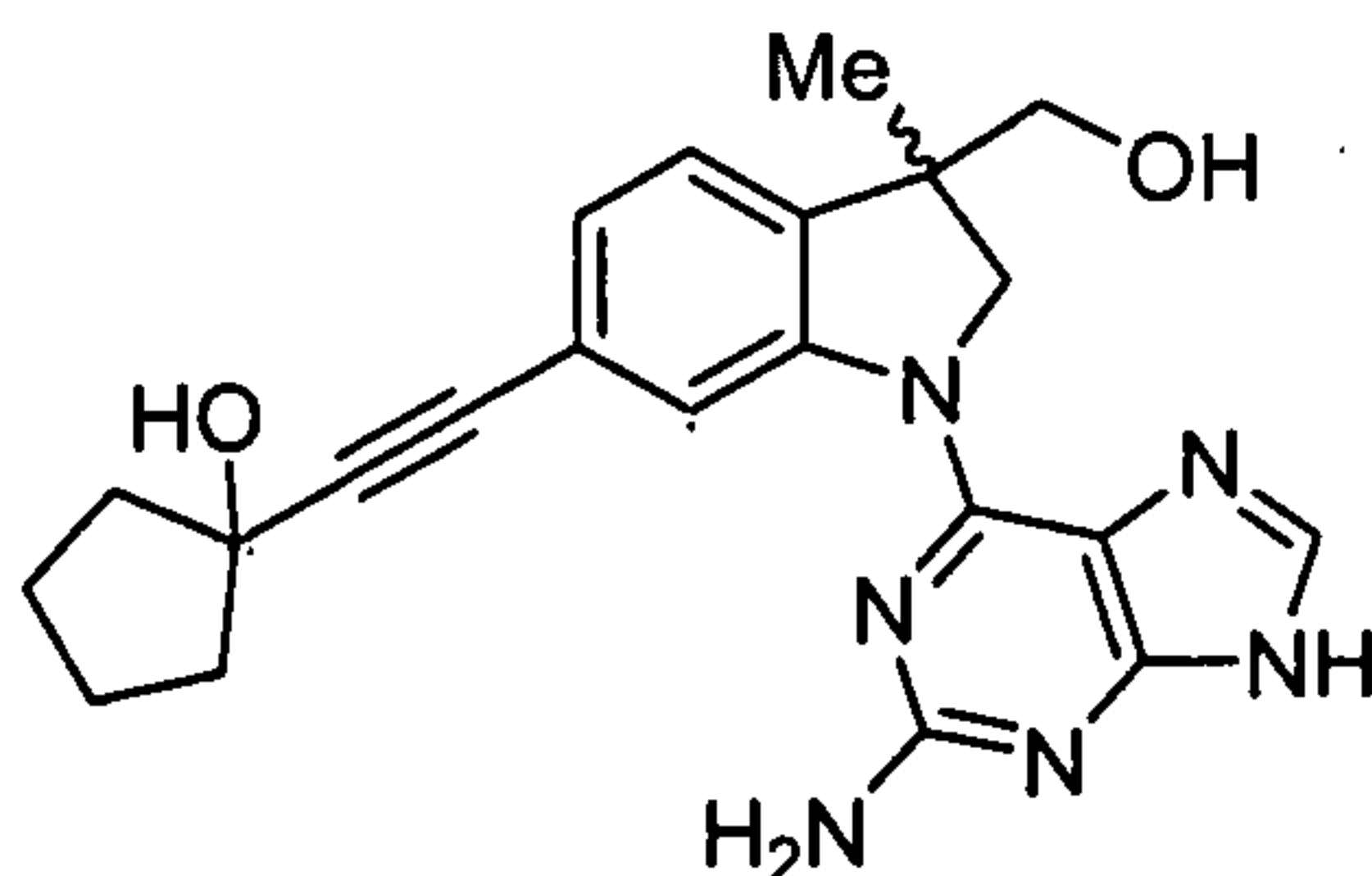
Example 72**72**

1-((1-(2-amino-9H-purin-6-yl)-2,3-dihydro-1H-indol-6-yl)ethynyl)cyclopentanol (72)

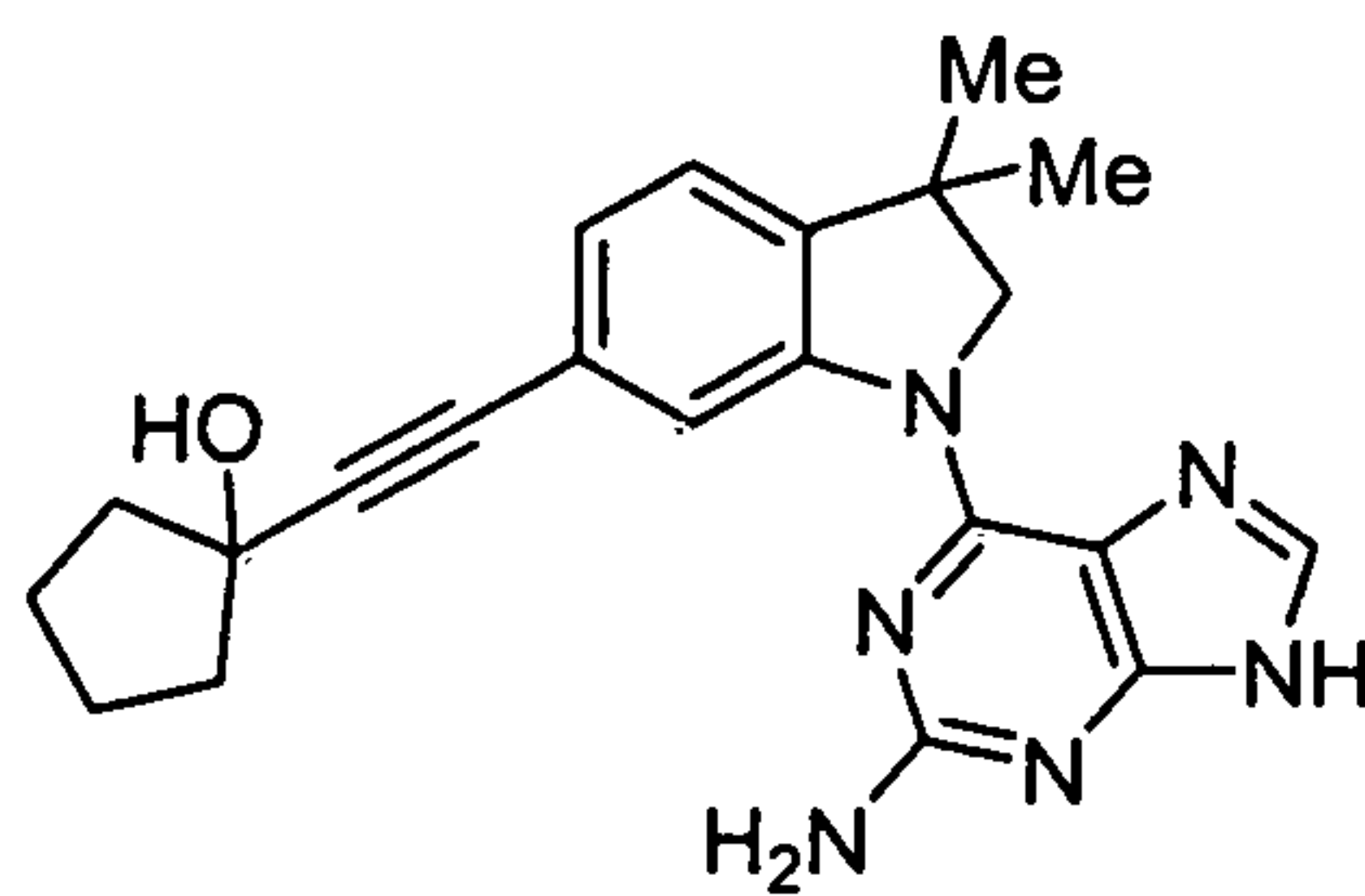
(prepared from components A.72 and C.36). ¹H NMR (500 MHz, (CD)₃SO) δ 12.35 (s, 1H), 8.57 (d, J = 1Hz, 1H), 7.81 (s, 1H), 7.20 (d, J = 7.4 Hz, 1H), 6.95 (dd, J = 7.9 Hz, J = 1.4, 1H), 6.02 (br s, 2H), 5.24 (s, 1H), 4.71 (t, J = 8.3 Hz, 2H), 3.20 (t, J = 8.3 Hz, 2H), 1.90-1.95 (m, 4H), 1.66-1.77 (m, 4H); ESI-MS: M + H⁺ 361.1 m/z; RPHPLC @ 6.044 min (95%).

Example 73**73**

1-((1-(2-amino-9H-purin-6-yl)-3-((2-methoxyethoxy)methyl)-3-methyl-2,3-dihydro-1H-indol-6-yl)ethynyl)cyclopentanol (73) (prepared from components A.76 and C.36). ^1H NMR (500 MHz, $(\text{CD})_3\text{SO}$) δ 12.37 (br s, 1H), 8.55 (br s, 1H), 7.80 (br s, 1H), 7.22 (d, $J = 7.3$ Hz, 1H), 6.98 (br d, $J = 7.9$ Hz, 1H), 6.04 (br s, 2H), 5.24 (br s, 1H), 4.74 (d, $J = 11.8$ Hz, 1H), 4.31 (d, $J = 11.7$ Hz, 1H), 3.50 (t, $J = 5.4$ Hz, 2H), 3.47 (s, 2H), 3.40 (t, 4.4 Hz, 2H), 3.18 (s, 3H), 1.90-1.95 (m, 4H), 1.65-1.77 (m, 4H), 1.34 (s, 3H); ESI-MS: $M + \text{H}^+$ 463.5 m/z ; RPHPLC @ 6.005 min (95%).

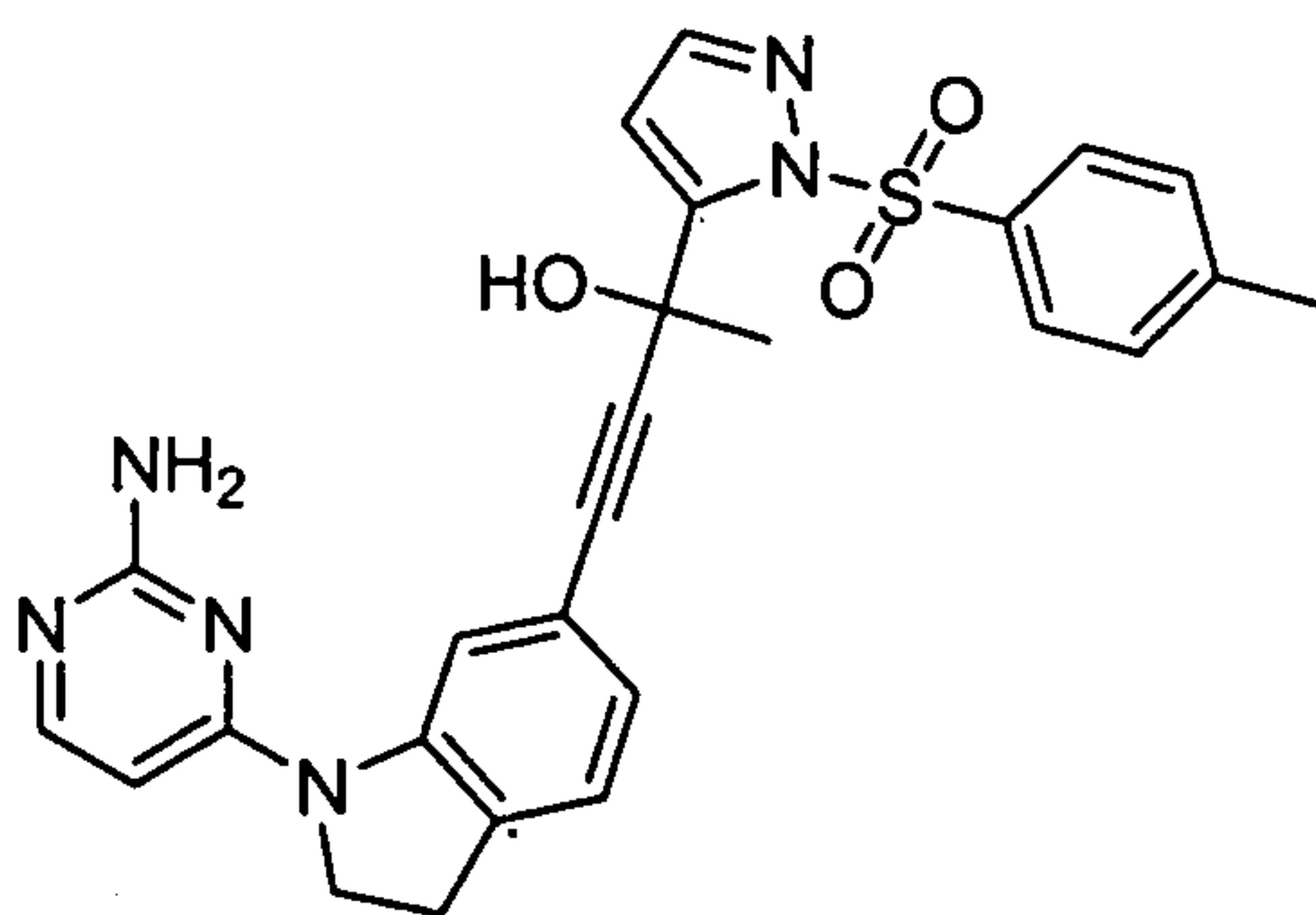
Example 74**74**

1-((1-(2-amino-9H-purin-6-yl)-3-(hydroxymethyl)-3-methyl-2,3-dihydro-1H-indol-6-yl)ethynyl)cyclopentanol (74) (prepared from components A.77 and C.36). ^1H NMR (500 MHz, $(\text{CD})_3\text{SO}$) δ 12.35 (br s, 1H), 8.54 (d, $J = 1$ Hz, 1H), 7.80 (s, 1H), 7.18 (d, $J = 7.9$ Hz, 1H), 6.98 (dd, $J = 7.9$ Hz, $J = 1.5$ Hz, 1H), 6.02 (br s, 2H), 5.24 (br s, 1H), 5.02 (t, $J = 5.4$ Hz, 1H), 4.80 (d, $J = 11.7$ Hz, 1H), 4.24 (d, $J = 11.8$ Hz, 1H), 1.90-1.94 (m, 4H), 1.65-1.77 (m, 4H), 1.31 (s, 3H); ESI-MS: $M + \text{H}^+$ 405.4 m/z ; RPHPLC @ 5.623 min (95%).

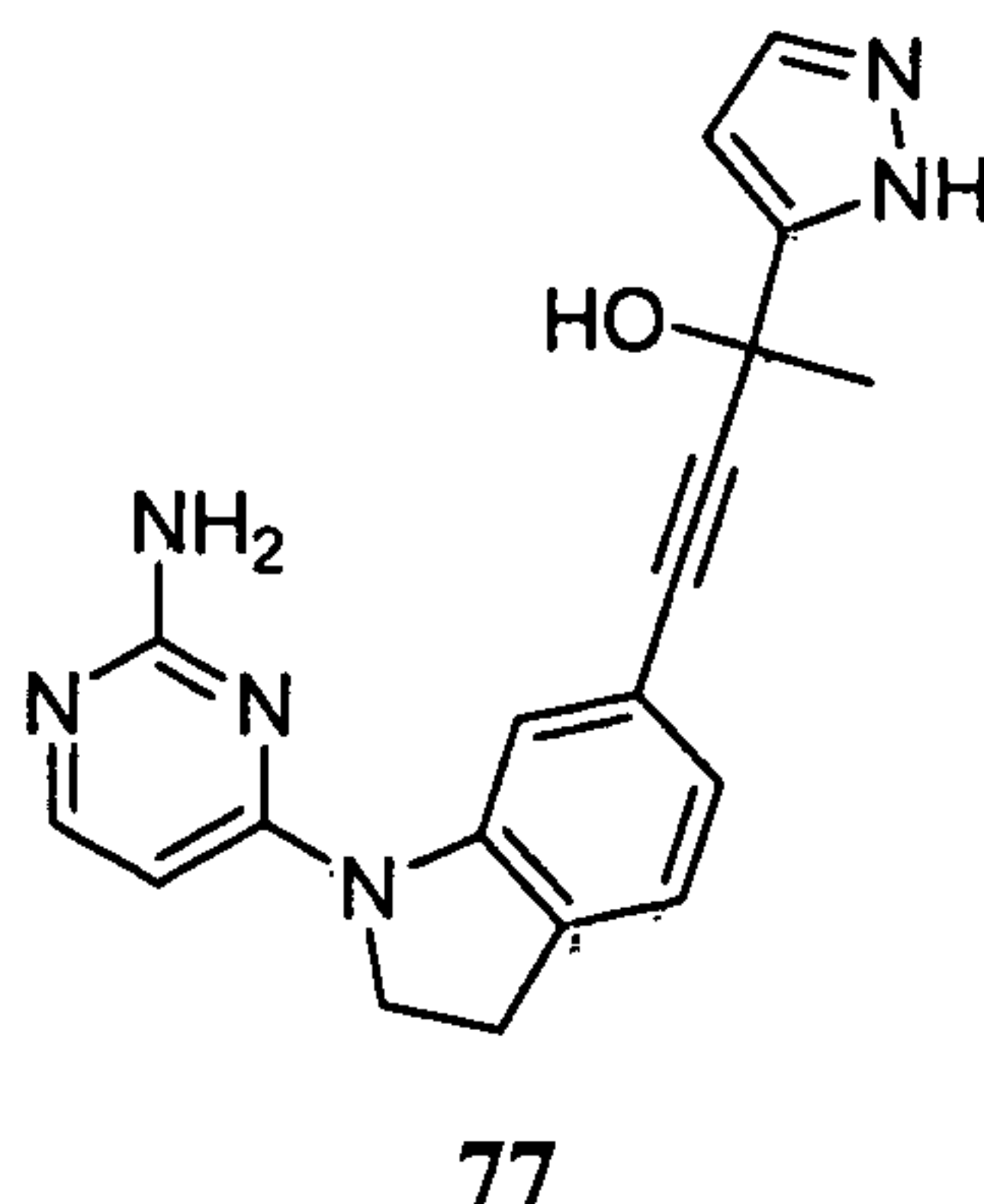
Example 75**75**

1-((1-(2-amino-9H-purin-6-yl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)ethynyl)cyclopentanol (75). The title compound prepared from components A.78 and C.36 was obtained as a white solid (70mg, 44%).

¹H NMR (400 MHz, (CD)₃SO) δ 12.34 (s, 1H), 8.53 (d, J = 1.3 Hz, 1H), 7.80 (s, 1H), 7.21 (d, J = 7.6 Hz, 1H), 7.00 (dd, J = 7.6 Hz, J = 1.4 Hz, 1H), 6.03 (br s, 2H), 5.23 (s, 1H), 4.48 (s, 2 H), 1.88-1.93 (m, 4H), 1.66-1.77 (m, 4H), 1.33 (s, 6H); ESI-MS: M + H⁺ 389.5 m/z; RPHPLC @ 6.495 min (95%).

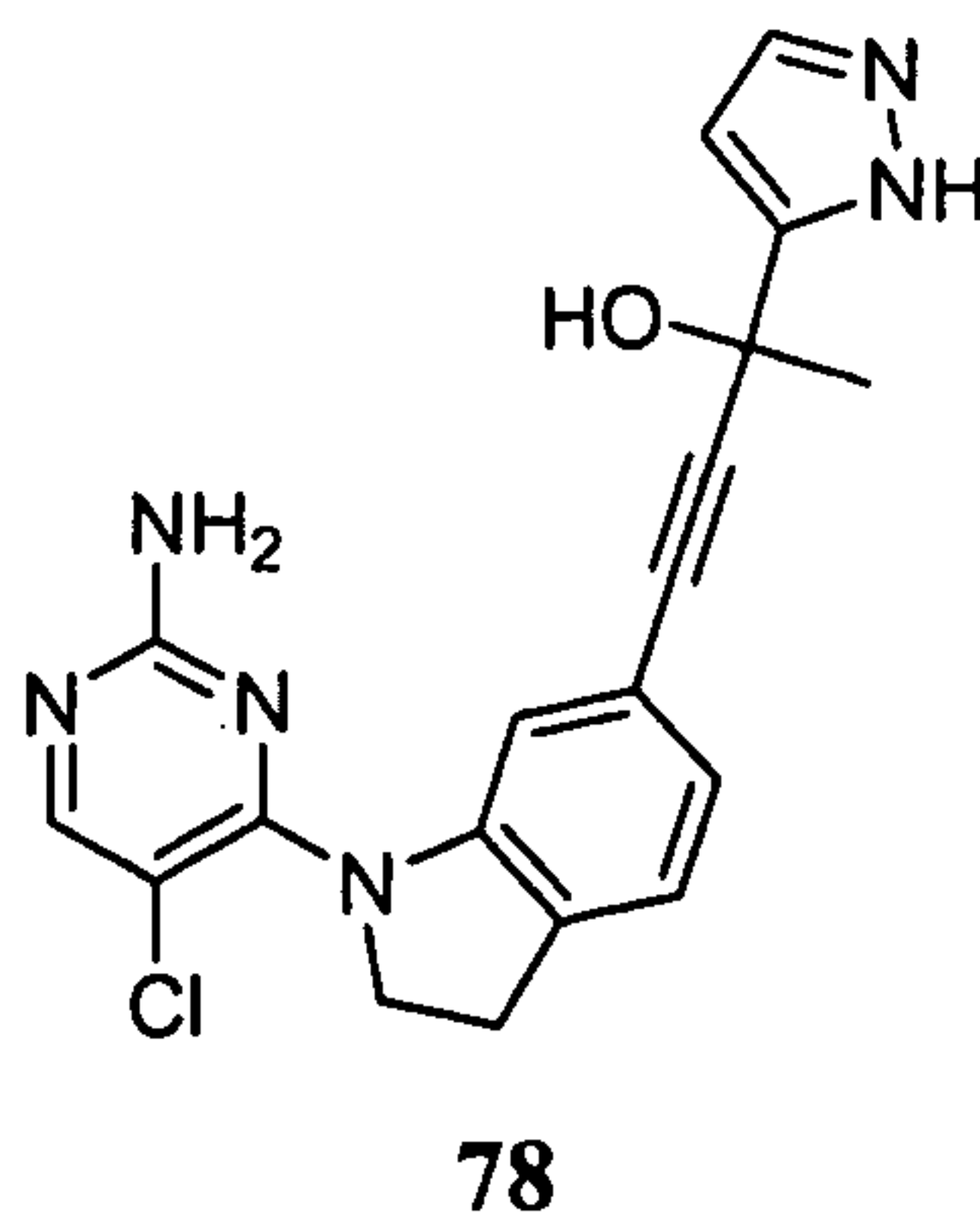
Example 76**76**

4-(1-(2-Amino-4-pyrimidinyl)-2,3-dihydro-1H-indol-6-yl)-2-(1-((4-methylphenyl)sulfonyl)-1H-pyrazol-5-yl)-3-butyn-2-ol (76) was prepared from components A.95 and C.30. ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.40 (2 H, s), 7.99 (1 H, s), 7.88 (2 H, d, J=7.8 Hz), 7.46 (2 H, d, J=7.6 Hz), 7.19 (1 H, s), 6.89 (1 H, d, J=7.6 Hz), 6.73 (1 H, s), 6.33 (2 H, s), 6.29 (1 H, s), 6.04 (1 H, s), 3.93 - 4.01 (2 H, m), 3.16 (2 H, s), 2.36 (3 H, s), 1.75 (3 H, s). MS ESI (pos.) m/e: 501.2 (M+H).

Example 77

4-(1-(2-Amino-4-pyrimidinyl)-2,3-dihydro-1H-indol-6-yl)-2-(1H-pyrazol-5-yl)-3-butyn-2-ol (77). To a flask containing 4-(1-(2-amino-4-pyrimidinyl)-2,3-dihydro-1H-indol-6-yl)-2-(1-((4-methylphenyl)sulfonyl)-1H-pyrazol-5-yl)-3-butyn-2-ol (76) (21.7 mg, 0.043 mmol) in methanol (3.00 mL) was added 5 M NaOH (1.00 mL). This mixture was stirred at room temperature for 45 minutes then diluted with water. After extracting three times with ethyl acetate, the organic solvent was removed under reduced pressure. The residue was purified by silica gel flash chromatography (0-100% methanol in dichloromethane) afford a mixture of tautomers of **4-(1-(2-amino-4-pyrimidinyl)-2,3-dihydro-1H-indol-6-yl)-2-(1H-pyrazol-5-yl)-3-butyn-2-ol** and **4-(1-(2-amino-4-pyrimidinyl)-2,3-dihydro-1H-indol-6-yl)-2-(1H-pyrazol-3-yl)-3-butyn-2-ol** (10.2 mg, 68%). ¹H NMR (400 MHz, *DMSO-d*₆) δ ppm 12.55 (1 H, m), 8.39 (1 H, m), 7.98 (1 H, m), 7.63 (1 H, m), 7.18 (1 H, d, *J*=7.4 Hz), 6.94 (1 H, m), 6.29 (2 H, m), 6.04 (1 H, d, *J*=5.9 Hz), 3.97 (2 H, t, *J*=8.6 Hz), 3.16 (3 H, t, *J*=8.4 Hz), 1.81 (3 H, s). MS ESI (pos.) *m/e*: 347.2 (M+H).

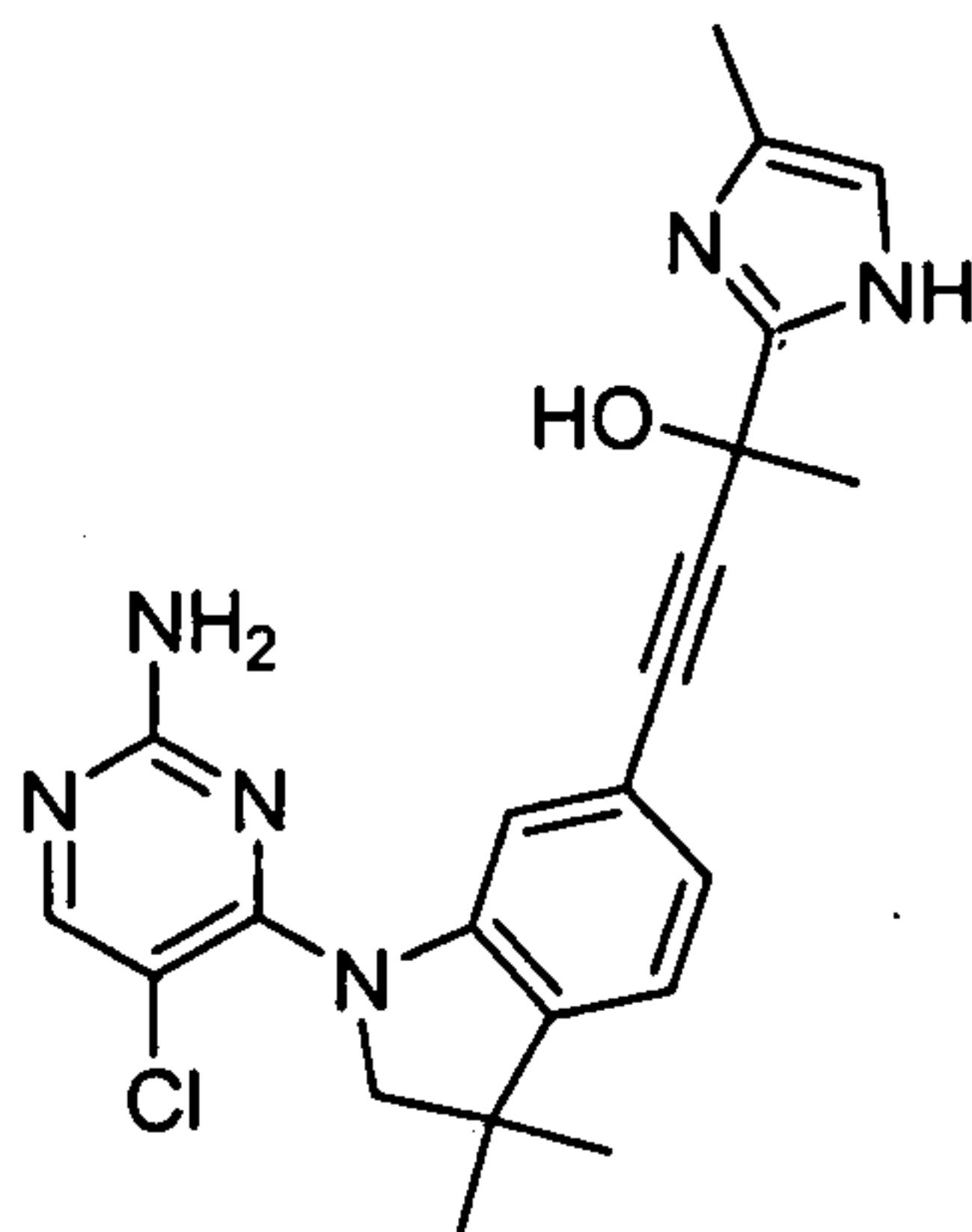
Examples **78-80** were prepared using same or analogous synthetic techniques and substituting with appropriate reagent as in **example 77**.

Example 78

4-(1-(2-Amino-5-chloro-4-pyrimidinyl)-2,3-dihydro-1H-indol-6-yl)-2-(1H-pyrazol-5-yl)-3-butyn-2-ol (78). (prepared from components A.2 and C.30).

¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 12.58 (1H, m), 8.11 (1 H, m), 7.21 (1 H, d, *J*=7.6 Hz), 7.15 (1 H, m), 6.94 (1 H, d, *J*=6.8 Hz), 6.65 (2 H, s), 6.31 (1 H, s), 4.16 (2 H, t, *J*=8.2 Hz), 3.09 (2 H, t, *J*=8.2 Hz), 1.77 (3 H, s). MS ESI (pos.) *m/e*: 381.1 (M+H).

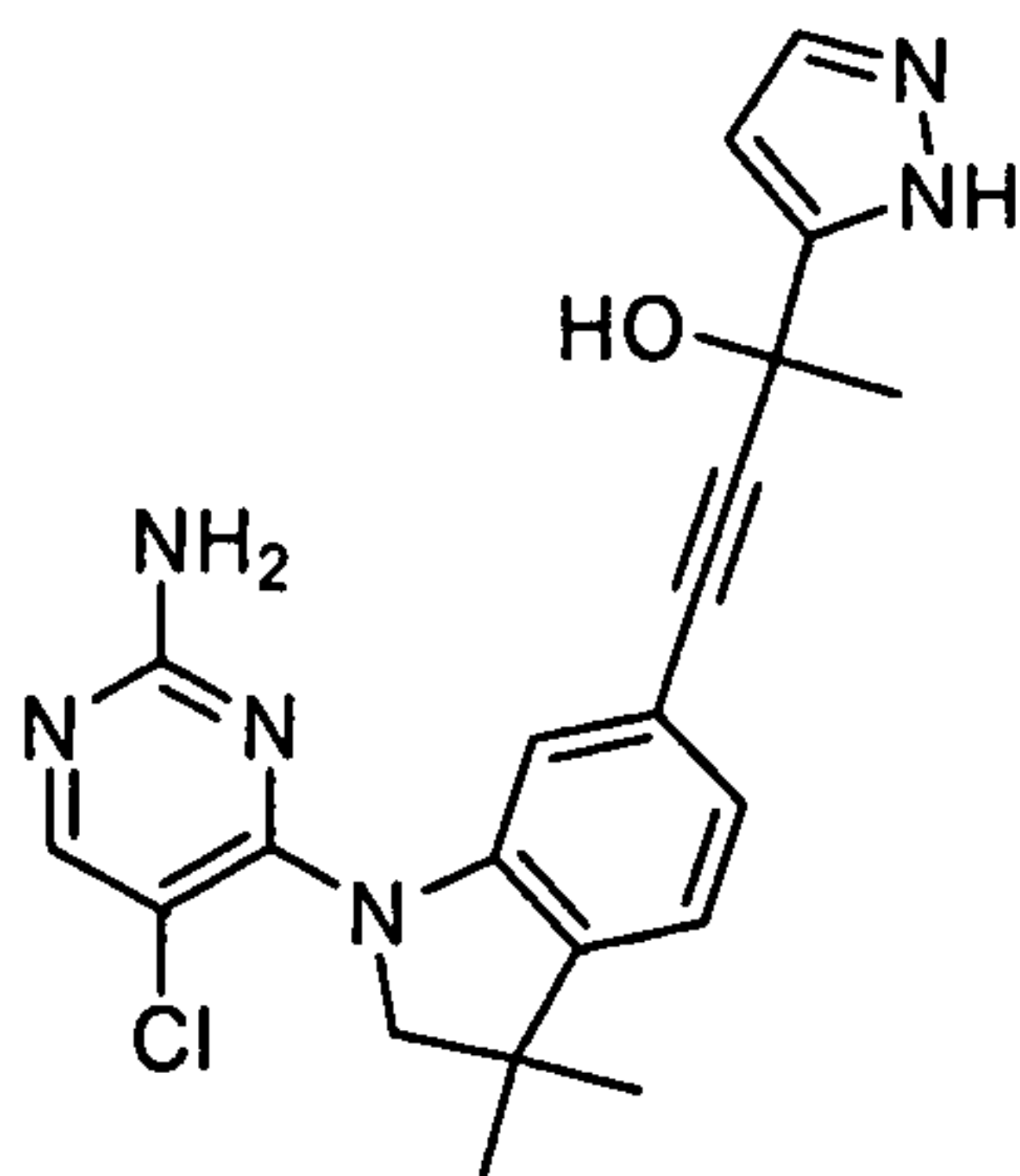
Example 79



79

4-(1-(2-Amino-5-chloro-4-pyrimidinyl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-(4-methyl-1H-imidazol-2-yl)-3-butyn-2-ol (79) (prepared from components A.15 and C.27). MS ESI (pos.) *m/e*: 423.1 (M+H).

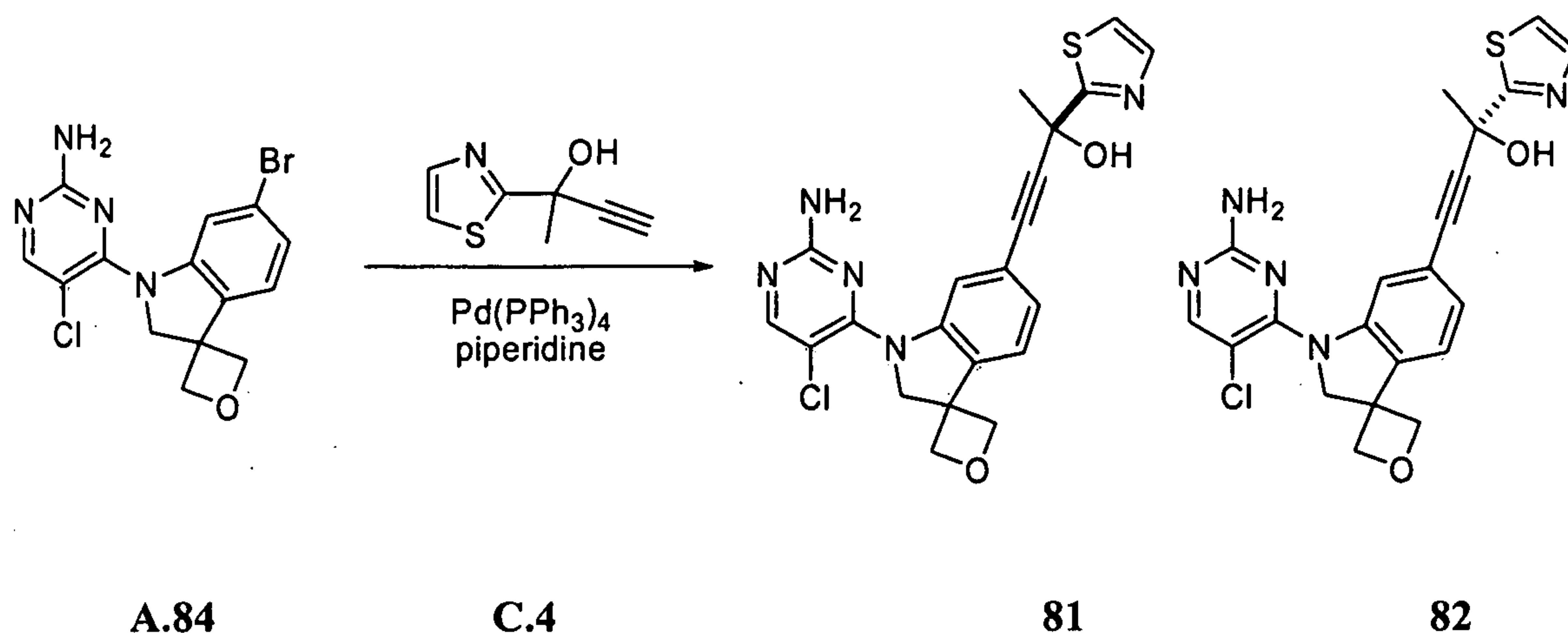
Example 80



80

4-(1-(2-amino-5-chloropyrimidin-4-yl)-3,3-dimethylindolin-6-yl)-2-(1H-pyrazol-5-yl)but-3-yn-2-ol and 4-(1-(2-amino-5-chloropyrimidin-4-yl)-3,3-dimethylindolin-6-yl)-2-(1H-pyrazol-3-yl)but-3-yn-2-ol (80) (prepared from components A.15 and C.30). MS ESI (pos.) *m/e*: 409.1 (M+H).

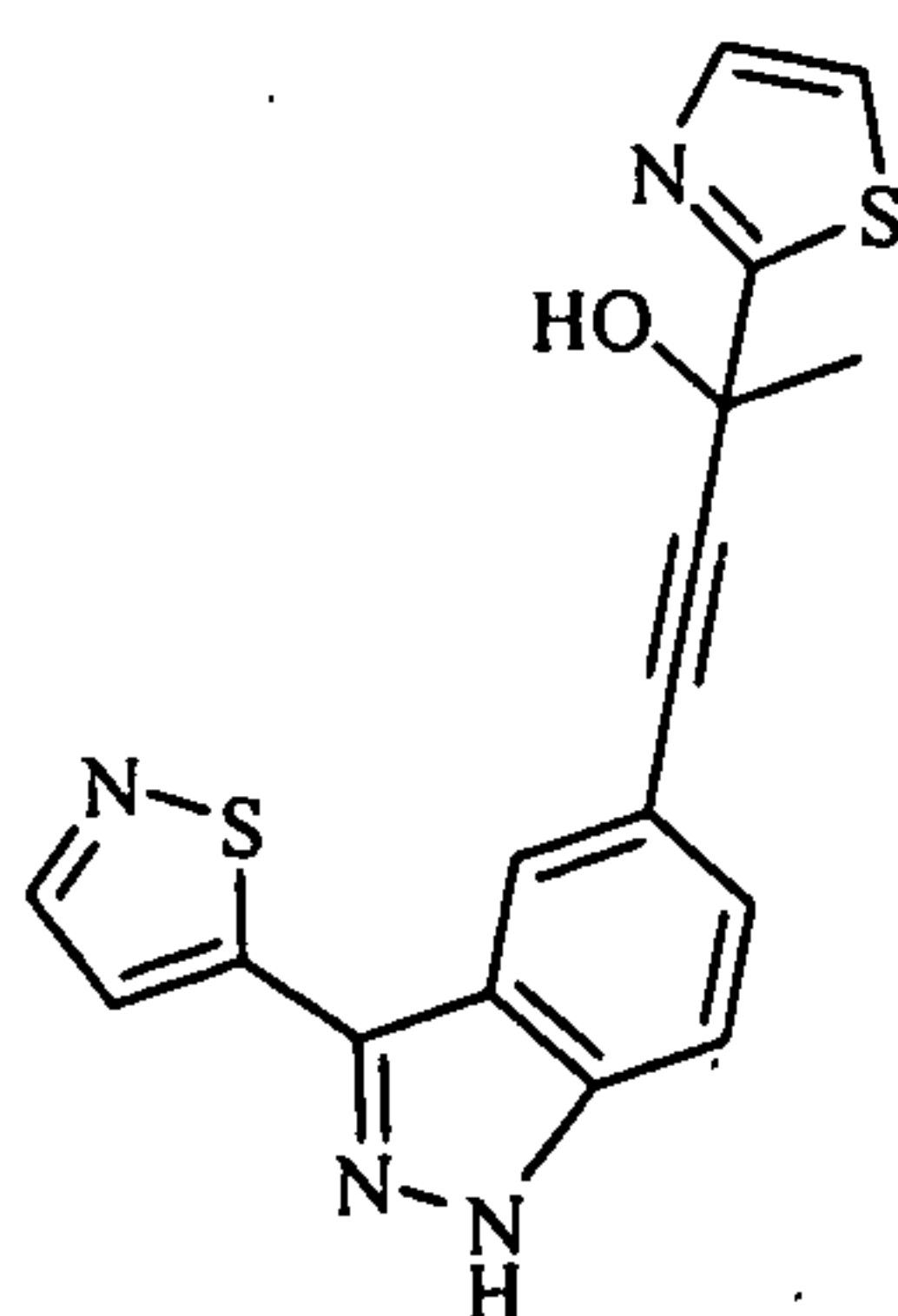
Example 81 and 82



To a flask containing bromo oxetane **A.84** (191.2 mg, 0.52 mmol), 2-(thiazol-2-yl)but-3-yn-2-ol **C.4** (319.0 mg, 2.08 mmol), and $\text{Pd(PPh}_3)_4$ (90.0 mg, 0.078 mmol) was added piperidine (5.0 mL). After heating at 80 °C for 20 hours, the organic solvent was removed under reduced pressure. The residue was purified by silica gel flash chromatography (45:1: 1 solution of dichloromethane: methanol: 2M ammonia in methanol) to afford mixture of enantiomers. The enantiomers were separated with Chiral HPLC using an AD-H column with isocratic 17% isopropanol in hexanes. The first eluted enantiomer (**81**) was a brown solid; the second eluted enantiomer (**82**) also a brown solid was assigned as (R)-4-(1-(2-amino-5-chloropyrimidin-4-yl)spiro[indoline-3,3'-oxetane]-6-yl)-2-(thiazol-2-yl)but-3-yn-2-ol based on biological activity: ^1H NMR (500 MHz, methanol- d_4) δ ppm 8.04 (1 H, s), 7.76 (1 H, d, $J=3.2$ Hz), 7.67 (1 H, d, $J=7.8$ Hz), 7.63 (1 H, d, $J=1.2$ Hz), 7.55 (1 H, d, $J=3.4$ Hz), 7.21 (1 H, dd, $J=7.7, 1.3$ Hz), 4.89 (4 H, m), 4.61 (2 H, s), 1.93 (3 H, m). MS ESI (pos.) m/e : 440.0 (M+H).

Examples 83-118 were prepared using the same or analogous synthetic techniques and substituting with appropriate reagents as in **example 1**.

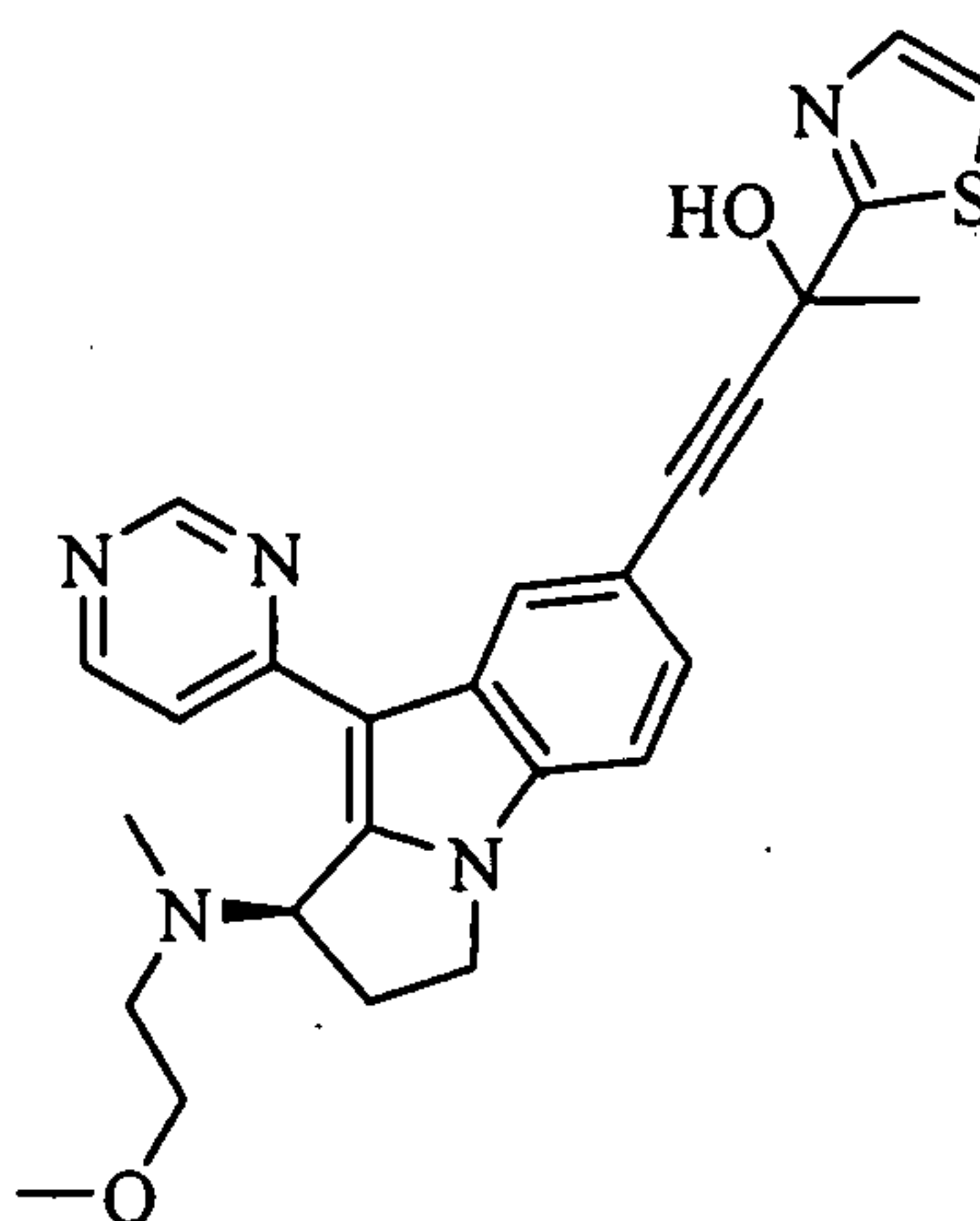
Example 83



83

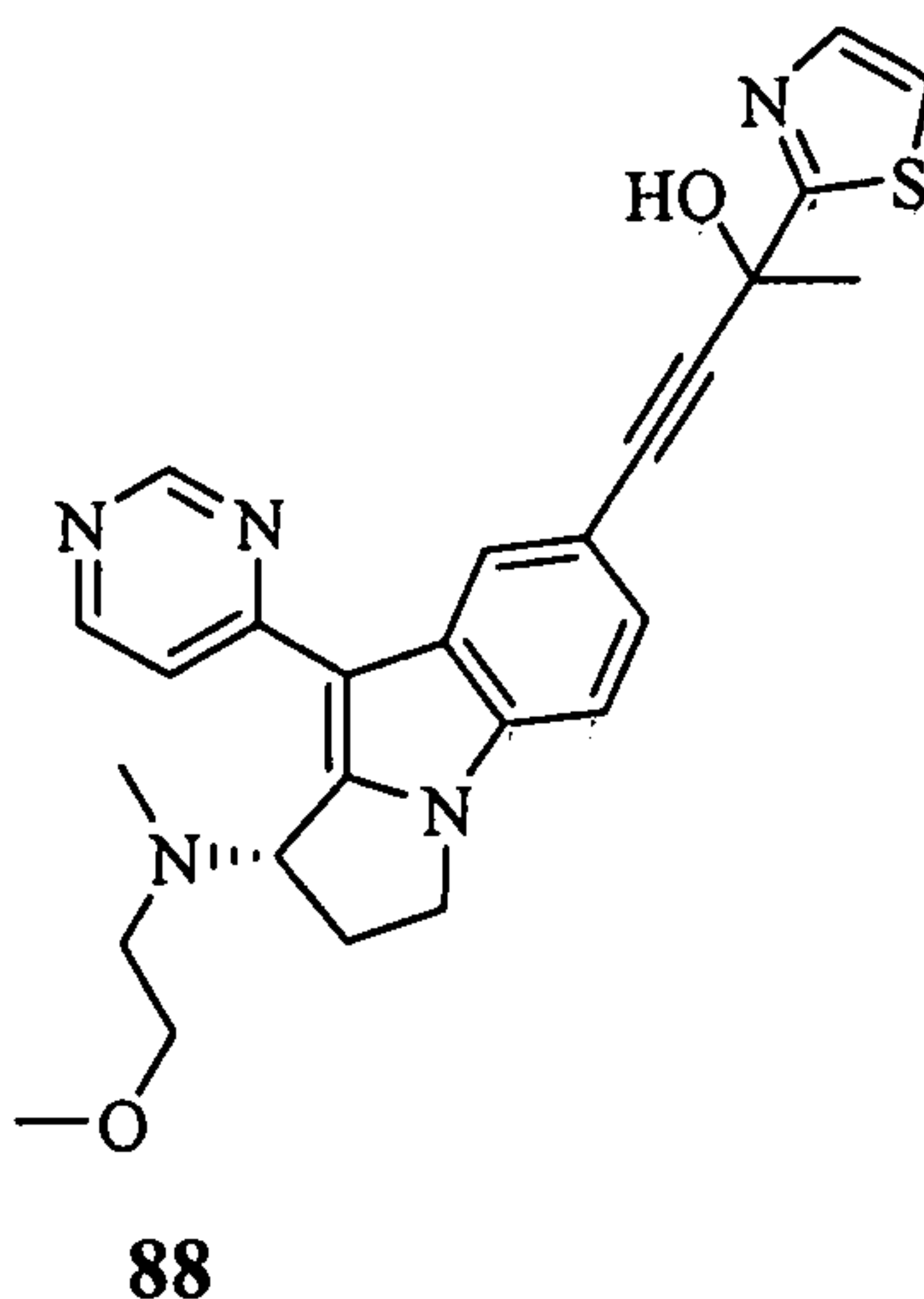
4-(3-(isothiazol-5-yl)-1H-indazol-5-yl)-2-(thiazol-2-yl)but-3-yn-2-ol (83) (prepared from components A.160 and C.4). ¹H NMR (400 MHz, *DMSO-d*₆) δ ppm 13.80 (1 H, s), 8.66 (1 H, d, *J*=1.6 Hz), 8.20 (1 H, s), 8.14 (1 H, d, *J*=1.2 Hz), 7.78 (1 H, d, *J*=3.1 Hz), 7.69 (1 H, d, *J*=3.1 Hz), 7.66 (1 H, d, *J*=8.6 Hz), 7.47 (1 H, d, *J*=8.6 Hz), 7.03 (1 H, s), 1.92 (3 H, s)

Example 87

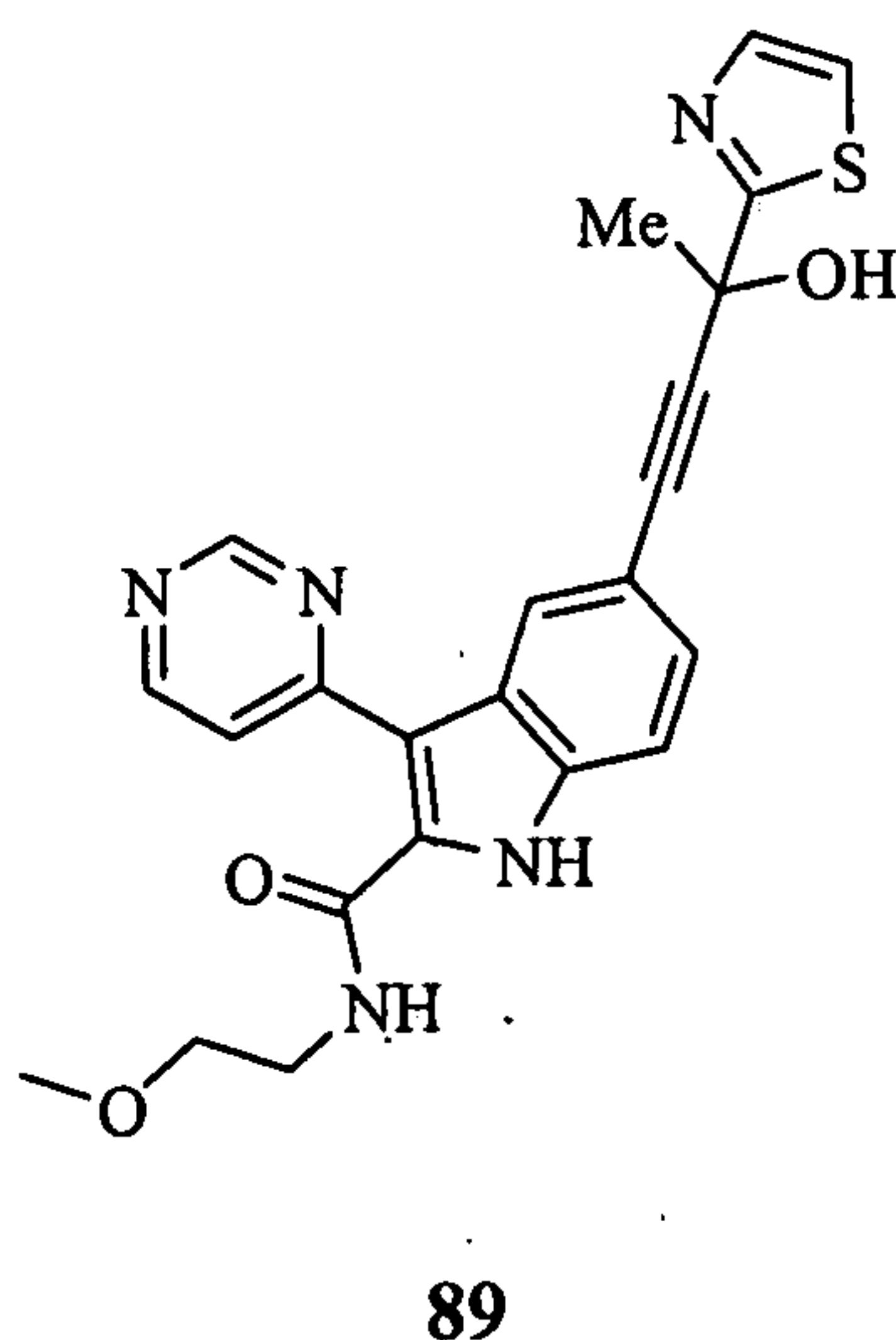


87

4-((R*)-1-((2-methoxyethyl)(methyl)amino)-9-(pyrimidin-4-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-7-yl)-2-(thiazol-2-yl)but-3-yn-2-ol (87). (Prepared from components A.150 and C.4) ¹H NMR (500 MHz, *DMSO-d*₆) δ ppm 9.14 (1 H, s), 8.79 (1 H, s), 8.59 (1 H, d, *J*=5.4 Hz), 8.29 (1 H, d, *J*=5.4 Hz), 7.78 (1 H, d, *J*=3.2 Hz), 7.69 (1 H, d, *J*=3.2 Hz), 7.46 (1 H, d, *J*=8.3 Hz), 7.25 (1 H, d, *J*=8.3 Hz), 7.01 (1 H, s), 4.91 (1 H, d, *J*=6.1 Hz), 4.21 (2 H, t, *J*=8.1 Hz), 3.45 (2 H, t, *J*=5.0 Hz), 3.25 (3 H, s), 2.74 (2 H, dd, *J*=12.6, 6.0 Hz), 2.53 - 2.63 (2 H, m), 2.11 (3 H, s), 1.90 (3 H, s)

Example 88

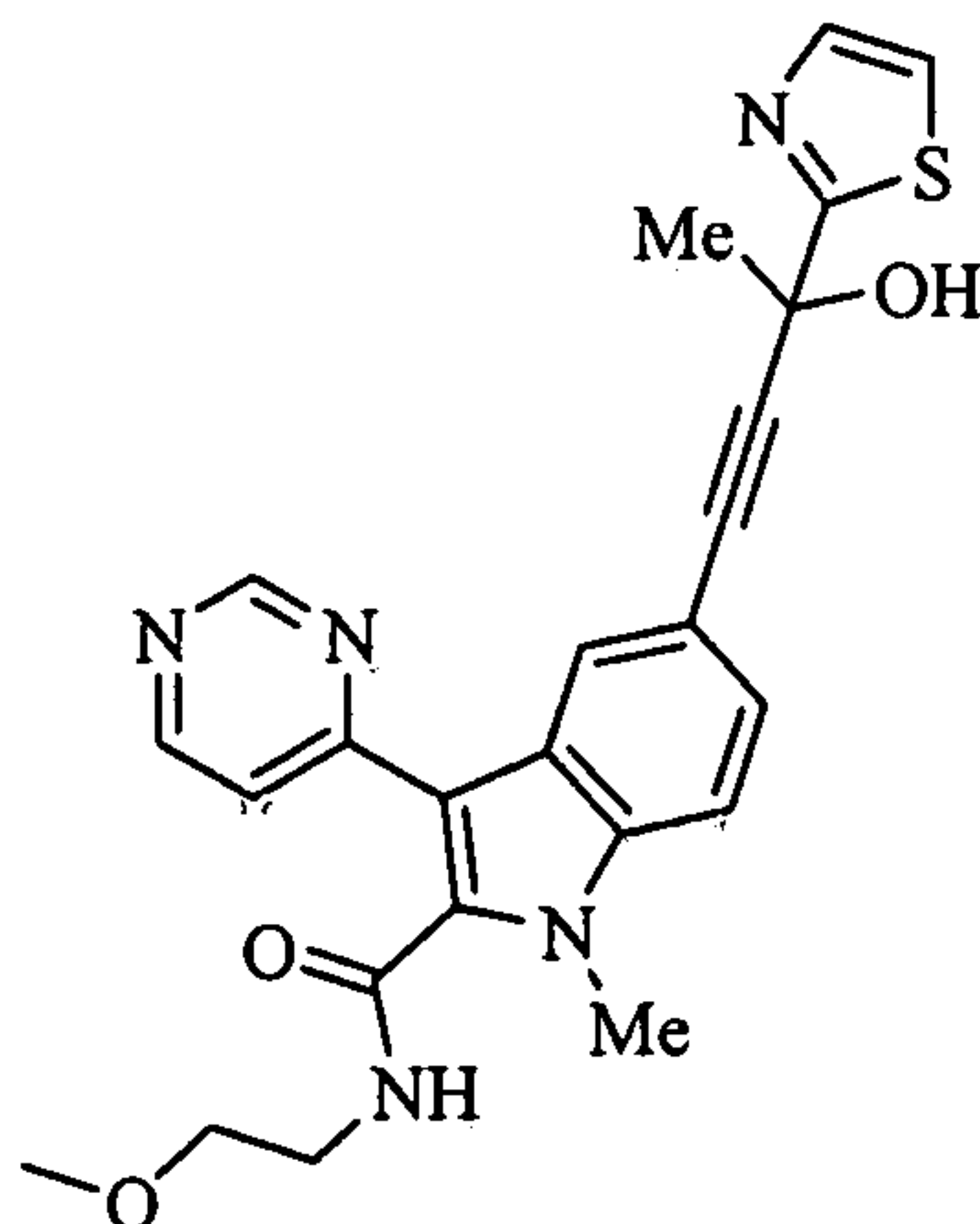
4-((S*)-1-((2-methoxyethyl)(methyl)amino)-9-(pyrimidin-4-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-7-yl)-2-(thiazol-2-yl)but-3-yn-2-ol (88). Prepared from components **A.151** and **C.4**. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 8.92 (1 H, s), 8.57 (1 H, s), 8.37 (1 H, d, $J=5.4$ Hz), 8.07 (1 H, d, $J=5.1$ Hz), 7.56 (1 H, d, $J=2.7$ Hz), 7.46 (1 H, d, $J=2.9$ Hz), 7.23 (1 H, d, $J=8.1$ Hz), 7.03 (1 H, d, $J=8.3$ Hz), 6.78 (1 H, s), 4.69 (1 H, d, $J=6.6$ Hz), 3.99 (2 H, t, $J=7.8$ Hz), 3.23 (2 H, s), 3.02 (3 H, s), 2.48 - 2.55 (2 H, m, $J=12.0, 5.9$ Hz), 2.31 - 2.41 (2 H, m), 1.89 (3 H, s), 1.68 (3 H, s)

Example 89

5-(3-hydroxy-3-(thiazol-2-yl)but-1-ynyl)-N-(2-methoxyethyl)-3-(pyrimidin-4-yl)-1H-indole-2-carboxamide (89). (prepared from components **A.161** and **C.4**). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 10.36 (1 H, s), 9.24 (1 H, s), 8.85 (1 H, d, $J=5.5$ Hz), 8.13 (1 H, s), 7.88 (1

H, d, $J=5.5$ Hz), 7.77 (1 H, d, $J=3.1$ Hz), 7.68 (1 H, d, $J=3.1$ Hz), 7.55 (1 H, d, $J=8.2$ Hz), 7.33 (1 H, d, $J=8.6$ Hz), 7.00 (1 H, s), 3.51 (4 H, s), 1.89 (3 H, s)

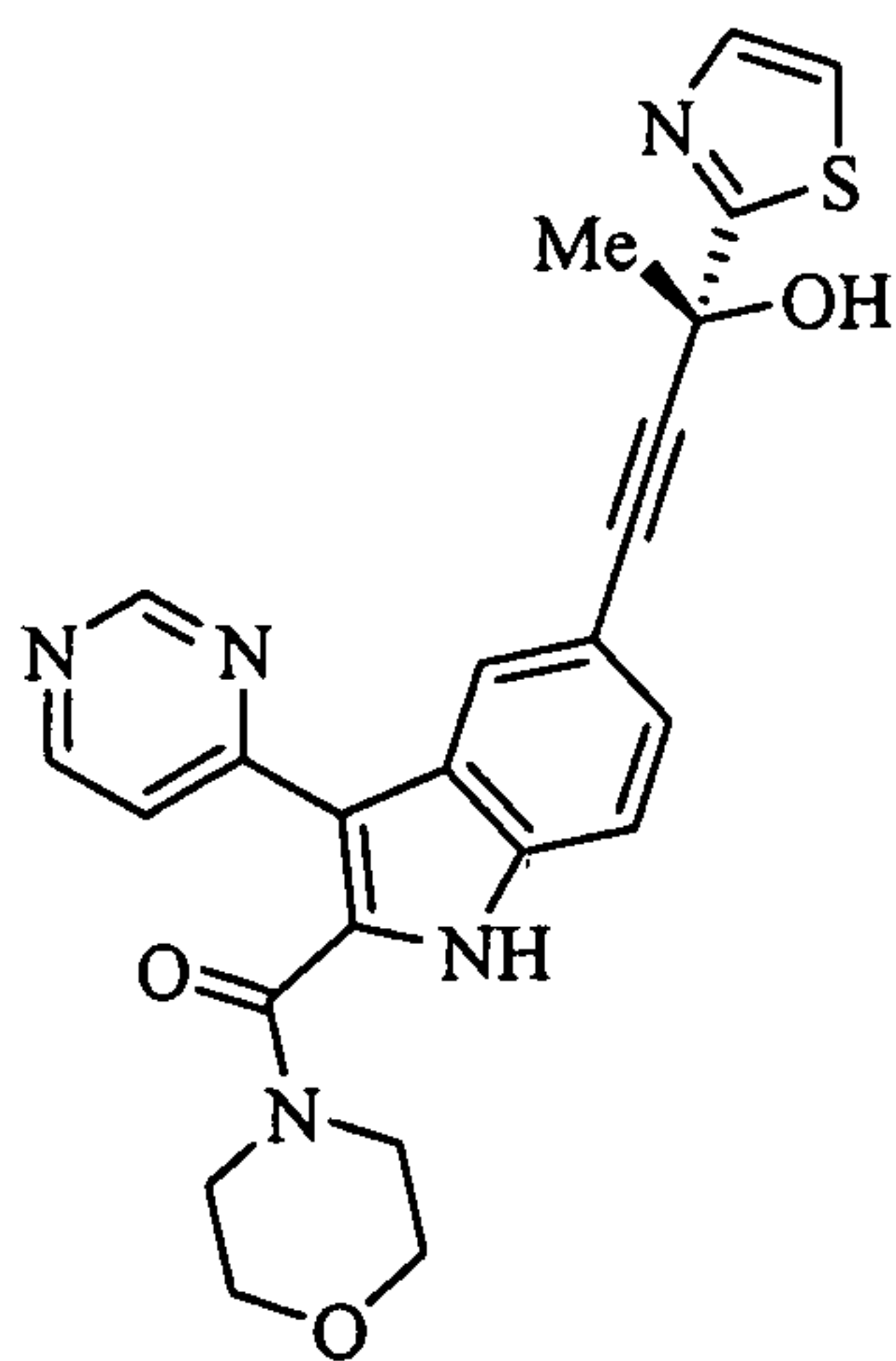
Example 90



90

5-(3-hydroxy-3-(thiazol-2-yl)but-1-ynyl)-N-(2-methoxyethyl)-1-methyl-3-(pyrimidin-4-yl)-1H-indole-2-carboxamide (90) (prepared from components A.162 and C.4). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 9.23 (1 H, s), 9.15 (1 H, s), 8.71 (1 H, d, $J=5.4$ Hz), 8.55 (1 H, s), 7.79 (1 H, d, $J=3.2$ Hz), 7.70 (1 H, d, $J=3.2$ Hz), 7.65 (1 H, d, $J=8.6$ Hz), 7.61 (1 H, dd, $J=5.5, 1.1$ Hz), 7.38 (1 H, dd, $J=8.6, 1.5$ Hz), 7.02 (1 H, s), 3.80 (3 H, s), 3.51 (4 H, s), 3.29 (3 H, s), 1.91 (3 H, s)

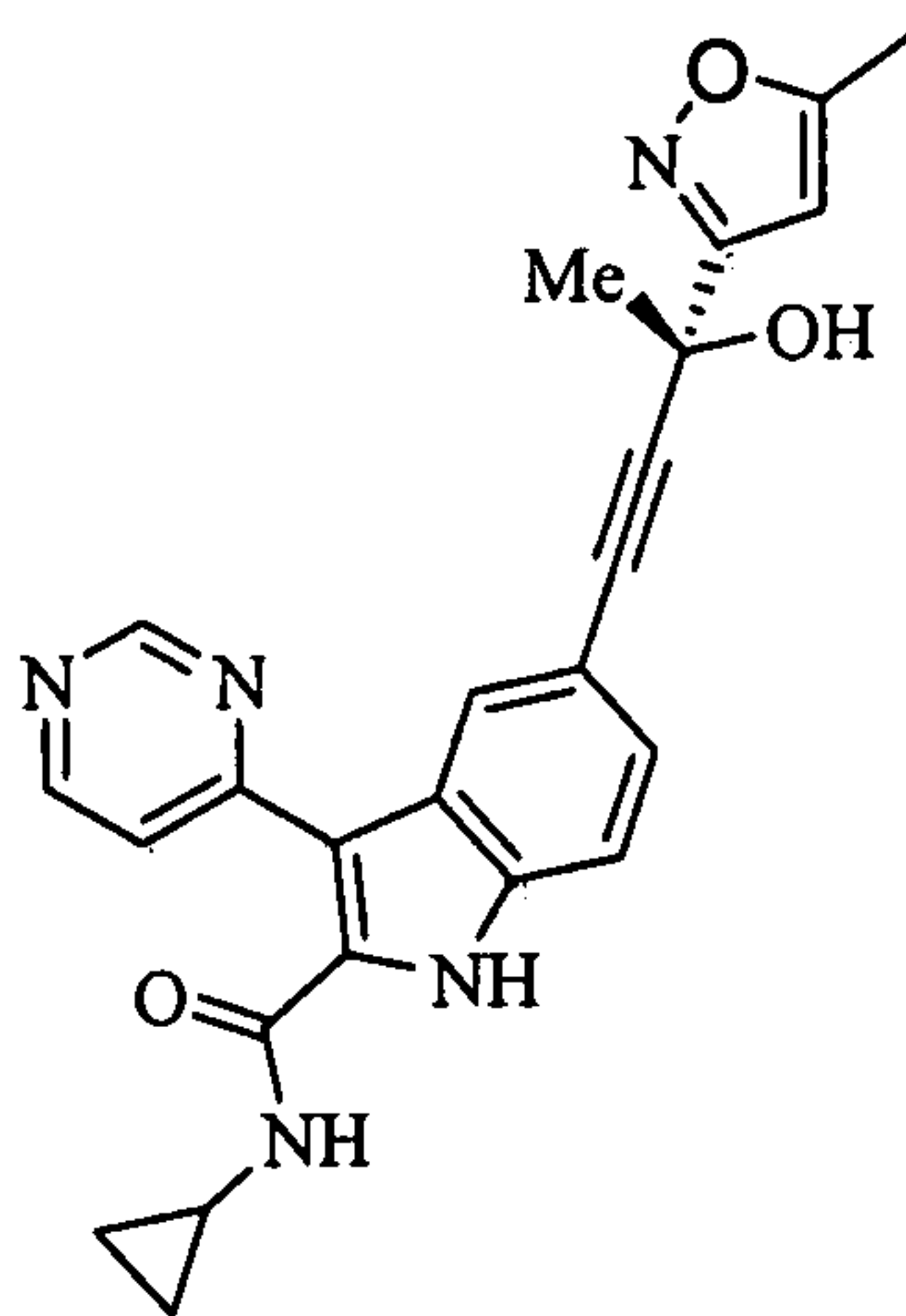
Example 91



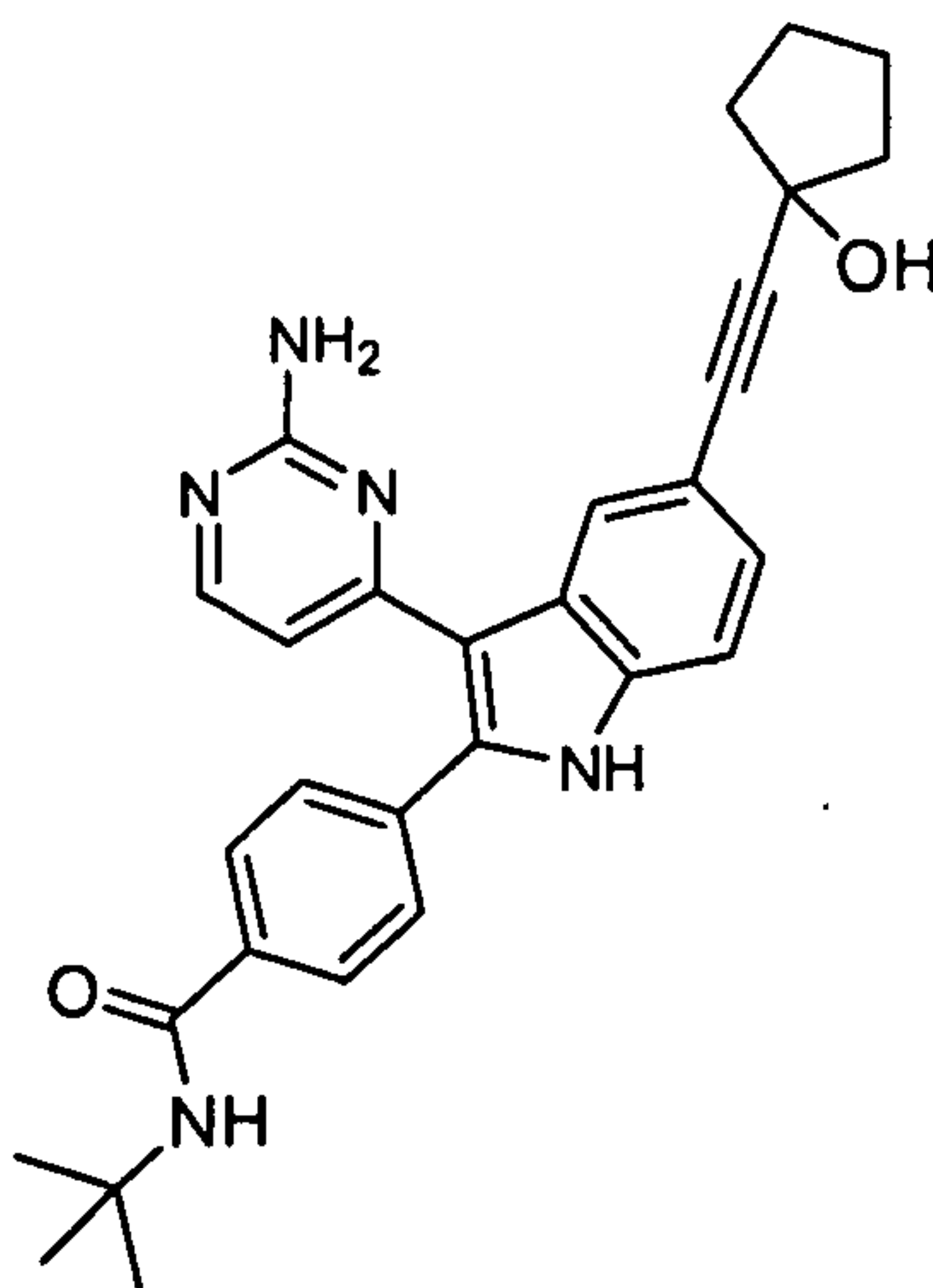
91

(5-((R)-3-hydroxy-3-(thiazol-2-yl)but-1-ynyl)-3-(pyrimidin-4-yl)-1H-indol-2-yl)(morpholino)methanone (91) (prepared from components A.165 and C.6). ^1H NMR (500

MHz, *DMSO-d*₆) δ ppm 12.53 (1 H, s), 9.22 (1 H, s), 8.41 (1 H, s), 7.78 (1 H, s), 7.68 (1 H, s), 7.63 (1 H, s), 7.49 (1 H, d, *J*=6.4 Hz), 7.31 (1 H, d, *J*=6.6 Hz), 7.00 (1 H, s), 3.67 - 3.76 (4 H, m), 3.38 - 3.42 (2 H, m), 3.12 - 3.21 (2 H, m), 1.90 (3 H, s)

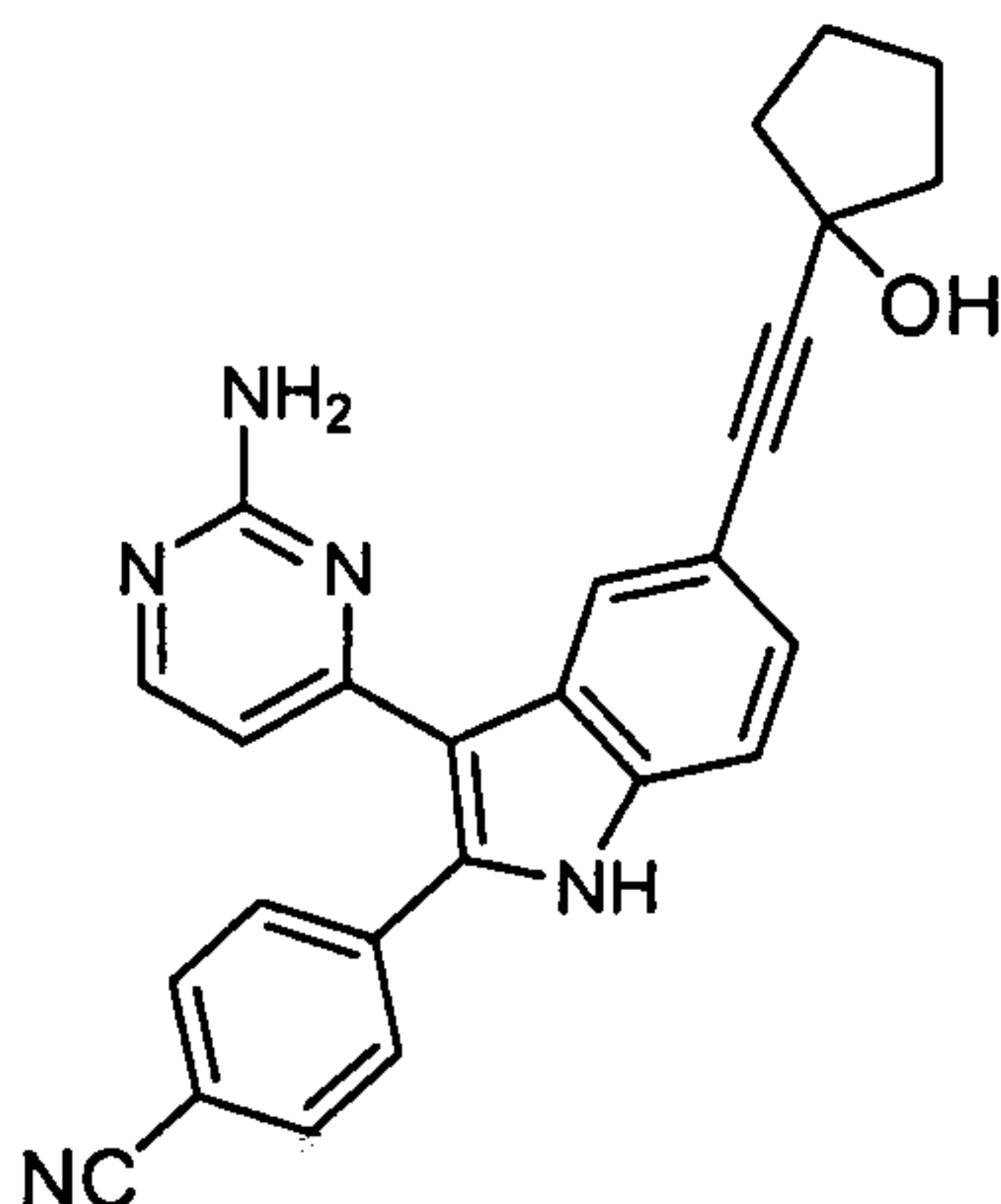
Example 92**92**

N-cyclopropyl-5-((R)-3-hydroxy-3-(4-methyl-5H-pyrrol-2-yl)but-1-ynyl)-3-(pyrimidin-4-yl)-1H-indole-2-carboxamide (92) (prepared from components A.168 and C.2). ¹H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 11.49 (1 H, s), 10.42 (1 H, s), 9.11 (1 H, s), 7.86 (1 H, s), 7.77 (1 H, d, *J*=5.1 Hz), 7.43 (1 H, d, *J*=8.6 Hz), 7.33 (1 H, d, *J*=8.6 Hz), 7.20 (3 H, s), 6.12 (1 H, s), 2.91 - 3.05 (1 H, m), 2.38 (3 H, s), 1.91 (3 H, s), 0.82 - 0.88 (2 H, m), 0.57 - 0.63 (2 H, m)

Example 93**93**

4-(3-(2-aminopyrimidin-4-yl)-5-(2-(1-hydroxycyclopentyl)ethynyl)-1H-indol-2-yl)-N-tert-butylbenzamide (93) (prepared from components A.124 and C.36). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 12.00 (1 H, s), 8.15 (1 H, s), 8.02 (1 H, d, $J=5.0$ Hz), 7.89 (2 H, d, $J=8.2$ Hz), 7.85 (1 H, s), 7.62 (2 H, d, $J=8.2$ Hz), 7.42 (1 H, d, $J=8.2$ Hz), 7.21 (1 H, dd, $J=8.2, 1.4$ Hz), 6.58 (2 H, s), 6.25 (1 H, d, $J=5.0$ Hz), 5.23 (1 H, s), 1.85 - 1.96 (4 H, m), 1.63 - 1.78 (4 H, m), 1.40 (9 H, s); Mass Spectrum (ESI) $m/e = 494.2$ [M+1].

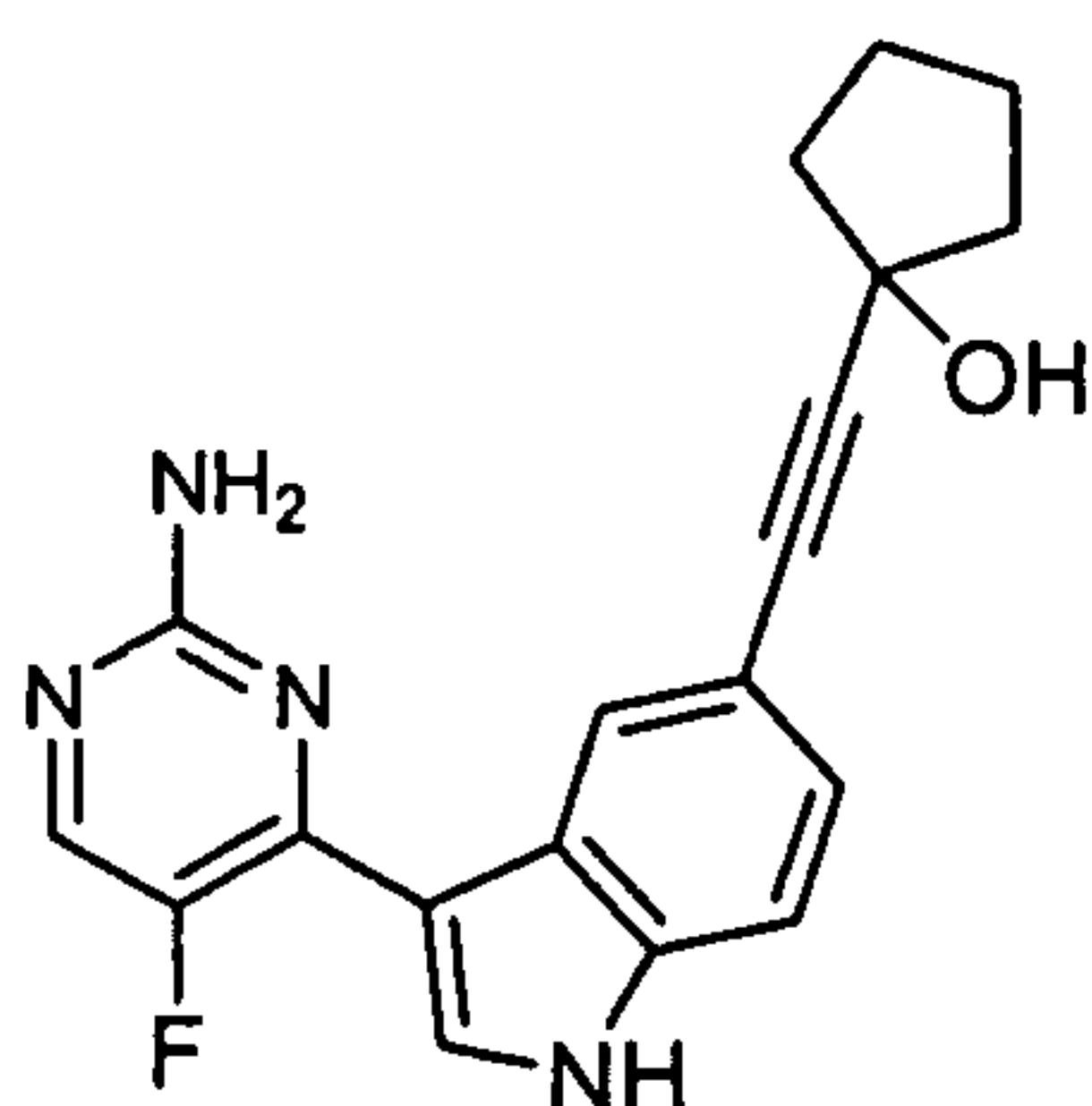
Example 94



94

4-(3-(2-aminopyrimidin-4-yl)-5-(2-(1-hydroxycyclopentyl)ethynyl)-1H-indol-2-yl)benzonitrile (94) (prepared from components A.125 and C.36). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 12.12 (1 H, s), 8.09 (1 H, d, $J=5.0$ Hz), 8.05 (1 H, s), 7.93 (2 H, d, $J=8.2$ Hz), 7.76 (2 H, d, $J=8.2$ Hz), 7.44 (1 H, d, $J=8.2$ Hz), 7.23 (1 H, dd, $J=8.5, 1.1$ Hz), 6.59 (2 H, s), 6.33 (1 H, d, $J=5.5$ Hz), 5.24 (1 H, s), 1.84 - 1.97 (4 H, m), 1.62 - 1.80 (4 H, m); Mass Spectrum (ESI) $m/e = 420.1$ [M+1].

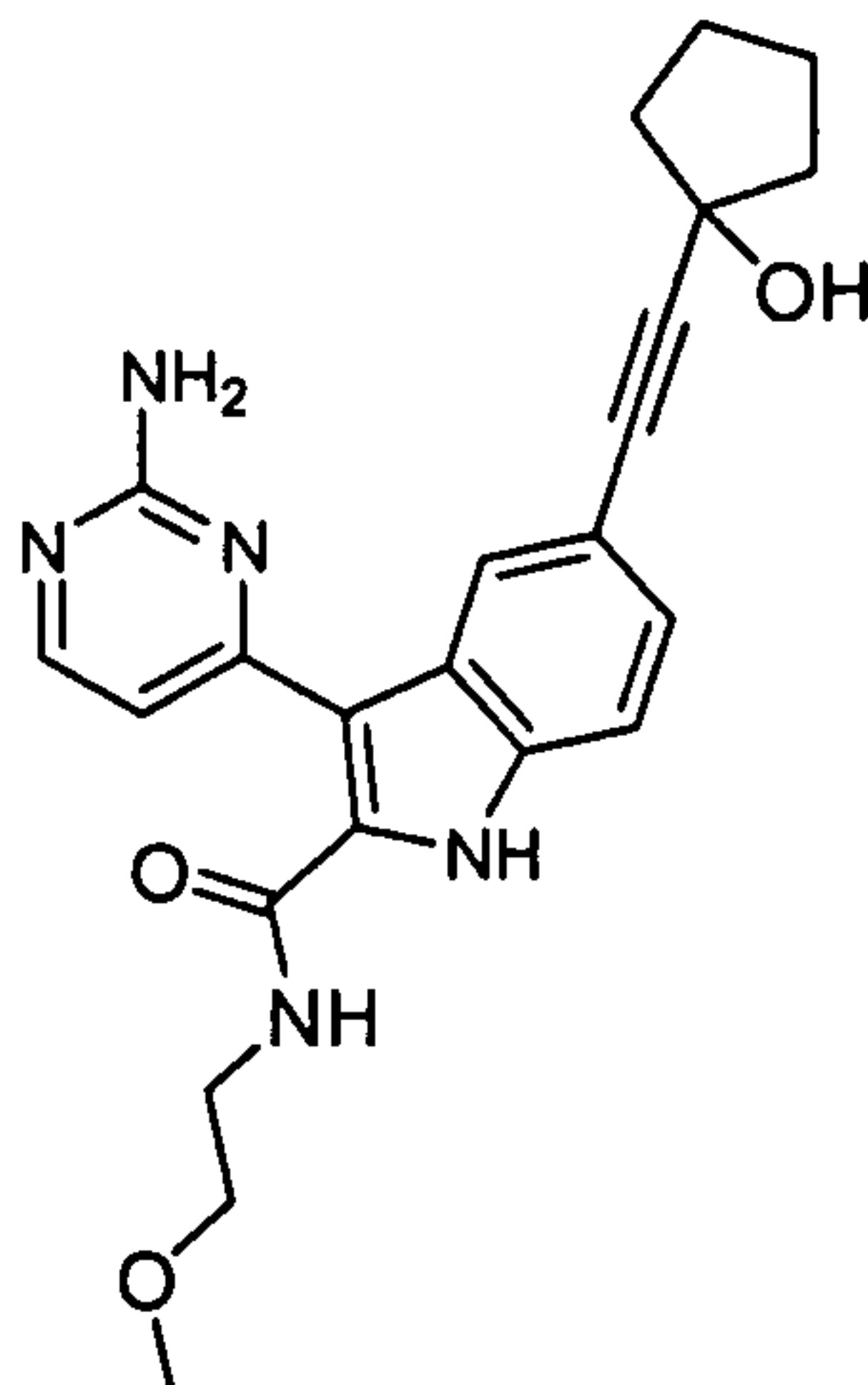
Example 95



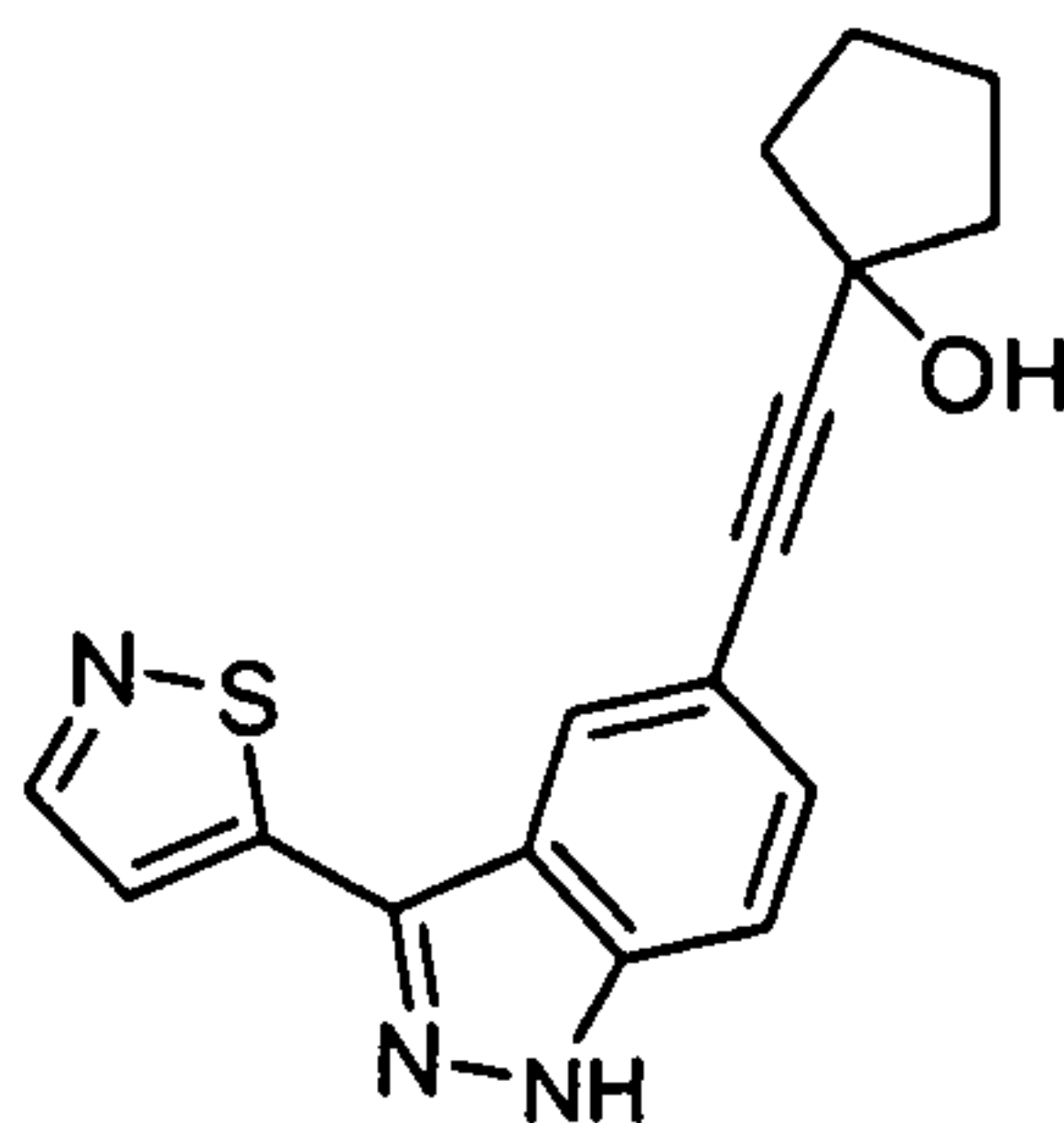
95

1-(2-(3-(2-amino-5-fluoropyrimidin-4-yl)-1H-indol-5-yl)ethynyl)cyclopentanol (95).

(prepared from components A.129 and C.36). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 11.96 (1 H, s), 8.67 (1H, s), 8.18 (1 H, d, $J=4.0$ Hz), 8.10 (1 H, d, $J=2.6$ Hz), 7.45 (1 H, d, $J=8.3$ Hz), 7.22 (1 H, dd, $J=8.4$, 1.5 Hz), 6.50 (2 H, s), 5.21 (1H, s), 1.93 (4H, m), 1.72 (4H, m); Mass Spectrum (ESI) $m/e = 337.1$ $[\text{M}+1]$.

Example 96**96**

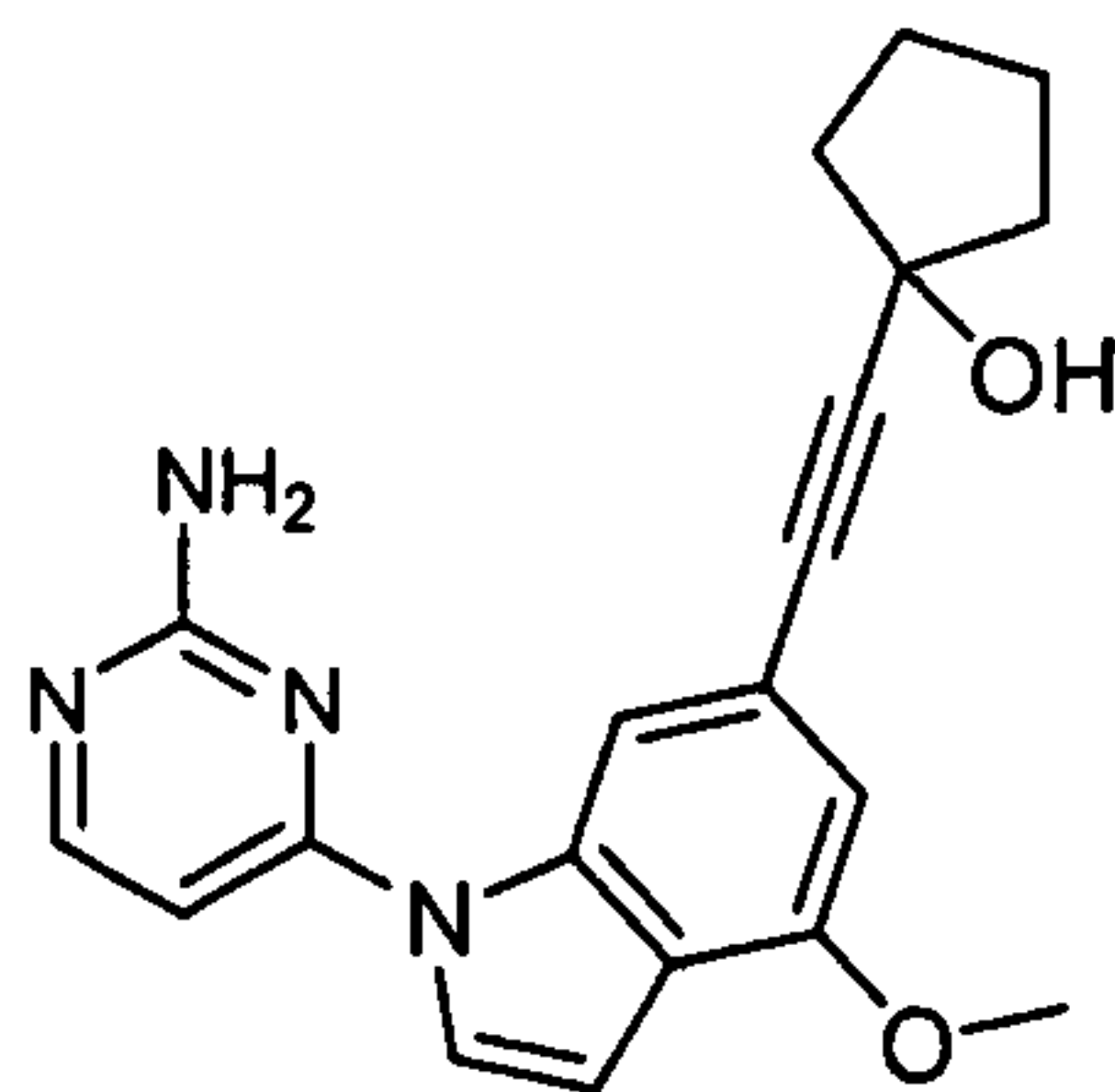
3-(2-aminopyrimidin-4-yl)-5-(2-(1-hydroxycyclopentyl)ethynyl)-N-(2-methoxyethyl)-1H-indole-2-carboxamide (96) (prepared from components A.133 and C.36). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 12.29 (1 H, s), 11.21 (1 H, t, $J=5.1$ Hz), 8.41 (1 H, d, $J=5.1$ Hz), 7.88 (1 H, s), 7.53 (1 H, d, $J=8.4$ Hz), 7.29 (1 H, dd, $J=8.4$, 1.5 Hz), 7.00 (1 H, d, $J=5.1$ Hz), 6.84 (2 H, s), 5.25 (1 H, s), 3.50 - 3.62 (4 H, m), 3.28 (3 H, s), 1.83 - 1.96 (4 H, m), 1.62 - 1.80 (4 H, m); Mass Spectrum (ESI) $m/e = 420.1$ $[\text{M}+1]$.

Example 97**97**

1-(2-(3-(isothiazol-5-yl)-1H-indazol-5-yl)ethynyl)cyclopentanol (97) (prepared from components A.160 and C.36).

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 13.76 (1 H, s), 8.66 (1 H, d, $J=1.8$ Hz), 8.16 (1 H, s), 8.13 (1 H, d, $J=1.8$ Hz), 7.64 (1 H, d, $J=8.4$ Hz), 7.45 (1 H, dd, $J=8.6, 1.3$ Hz), 5.31 (1 H, s), 1.88 - 1.97 (4 H, m), 1.63 - 1.82 (4 H, m); Mass Spectrum (ESI) $m/e = 310.3$ [M+1].

Example 98

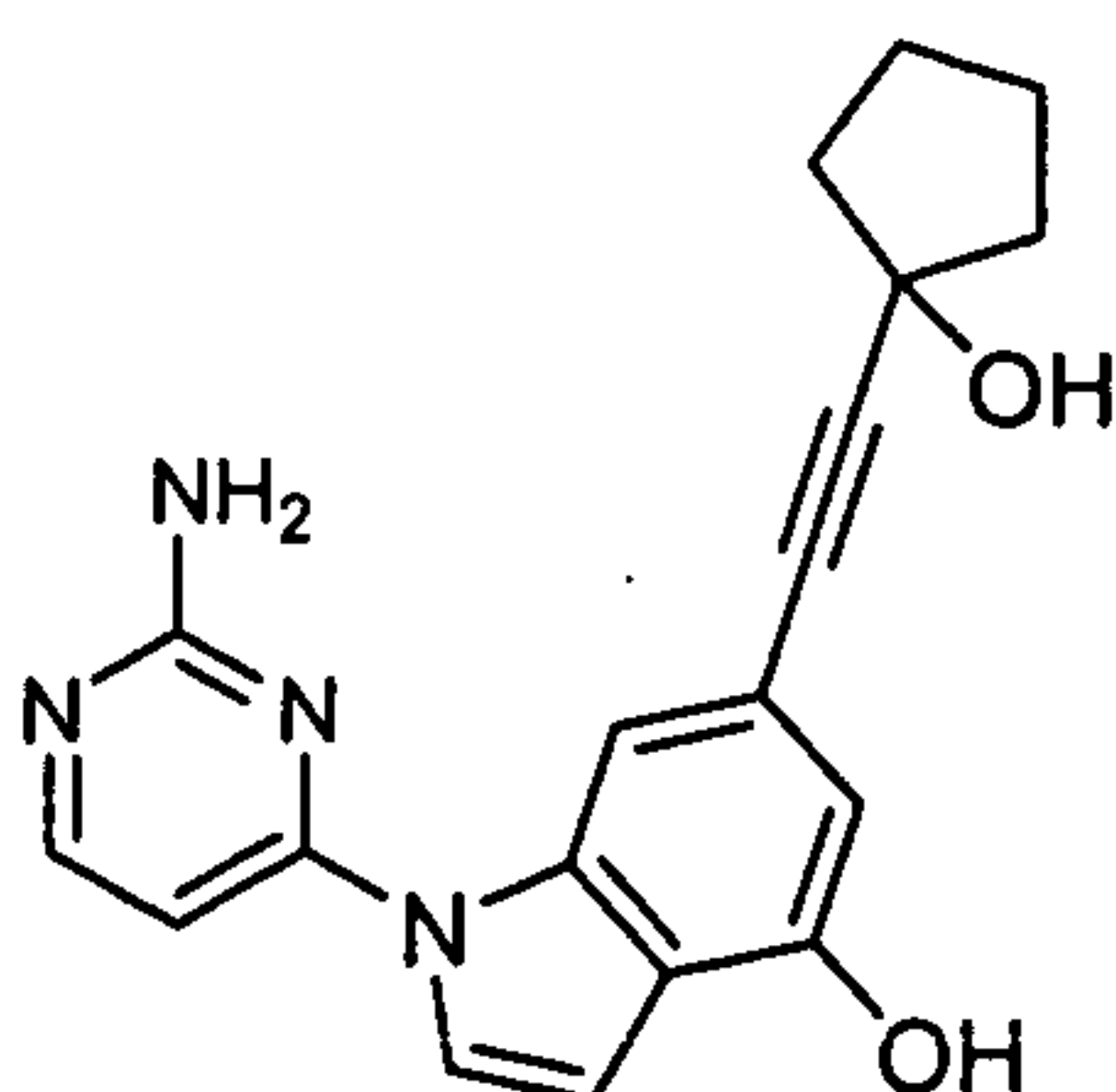


98

1-(2-(1-(2-aminopyrimidin-4-yl)-4-methoxy-1H-indol-6-yl)ethynyl)cyclopentanol (98)

(prepared from components A.134 and C.36). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.25 - 8.31 (2 H, m), 7.97 (1 H, d, $J=3.7$ Hz), 6.89 - 6.97 (3 H, m), 6.75 (1 H, d, $J=3.7$ Hz), 6.70 (1 H, s), 5.25 (1 H, s), 3.91 (3 H, s), 1.95 (4 H, t, $J=5.9$ Hz), 1.65 - 1.85 (4 H, m); Mass Spectrum (ESI) $m/e = 349.1$ [M+1].

Example 99

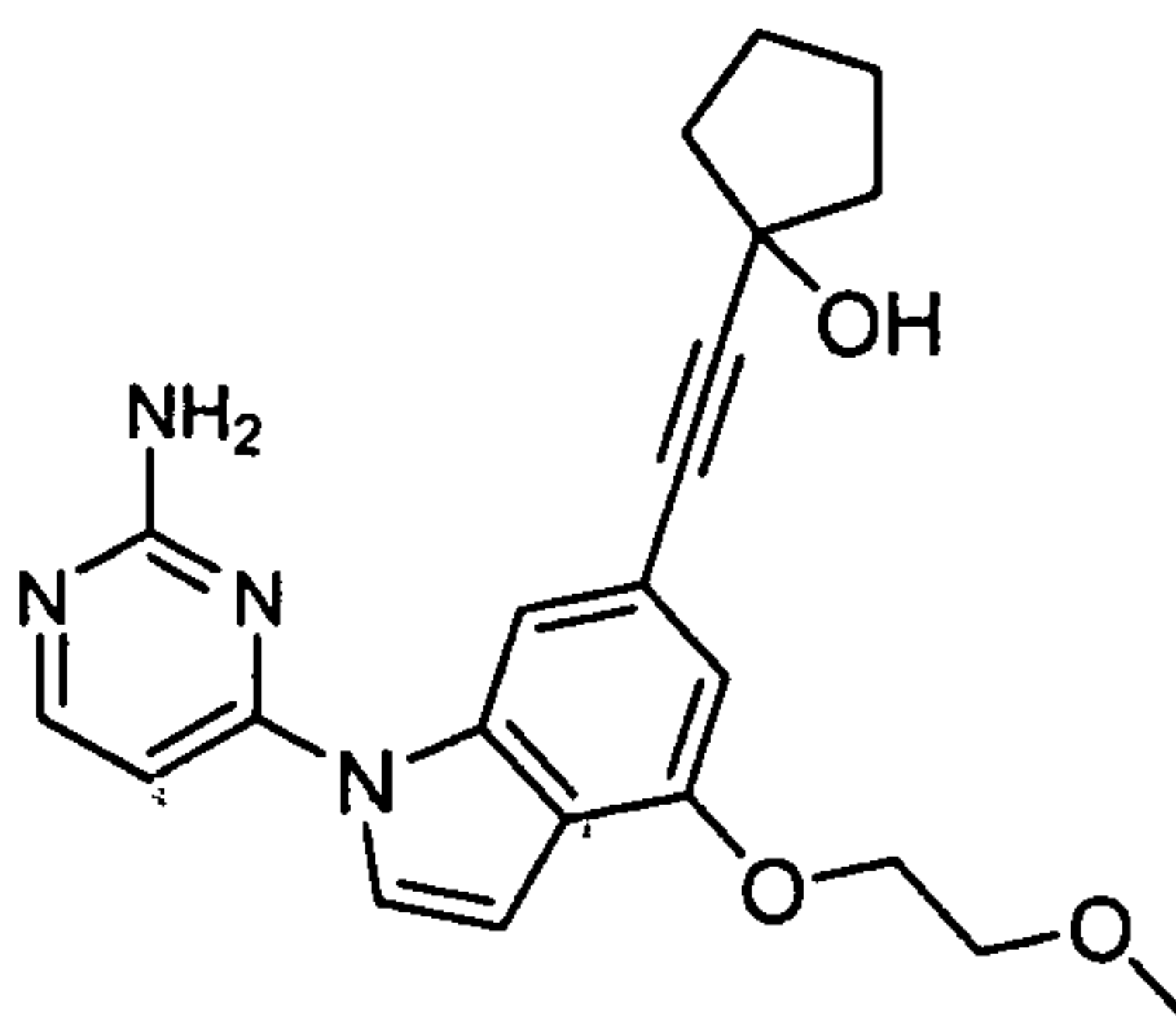


99

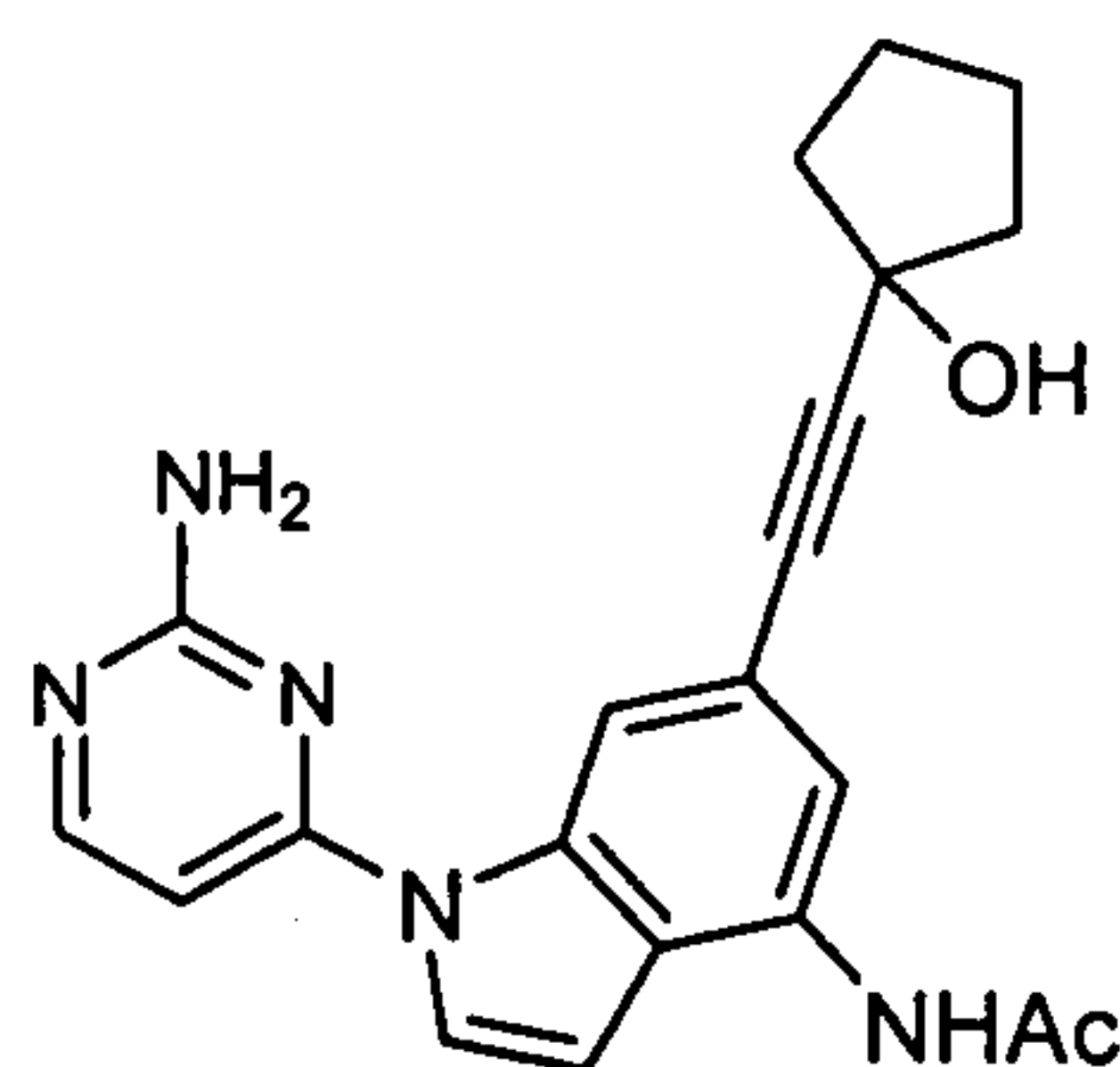
1-(2-(1-(2-aminopyrimidin-4-yl)-6-(2-(1-hydroxycyclopentyl)ethynyl)-1H-indol-4-yl)cyclopentanol (99)

(prepared from components A.135 and C.36). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 9.87 (1 H, s), 8.28 (1 H, s), 8.11 (1 H, s), 7.91 (1 H, d, $J=3.7$ Hz), 6.89 (3 H, d, $J=5.5$ Hz), 6.78 (1 H, d,

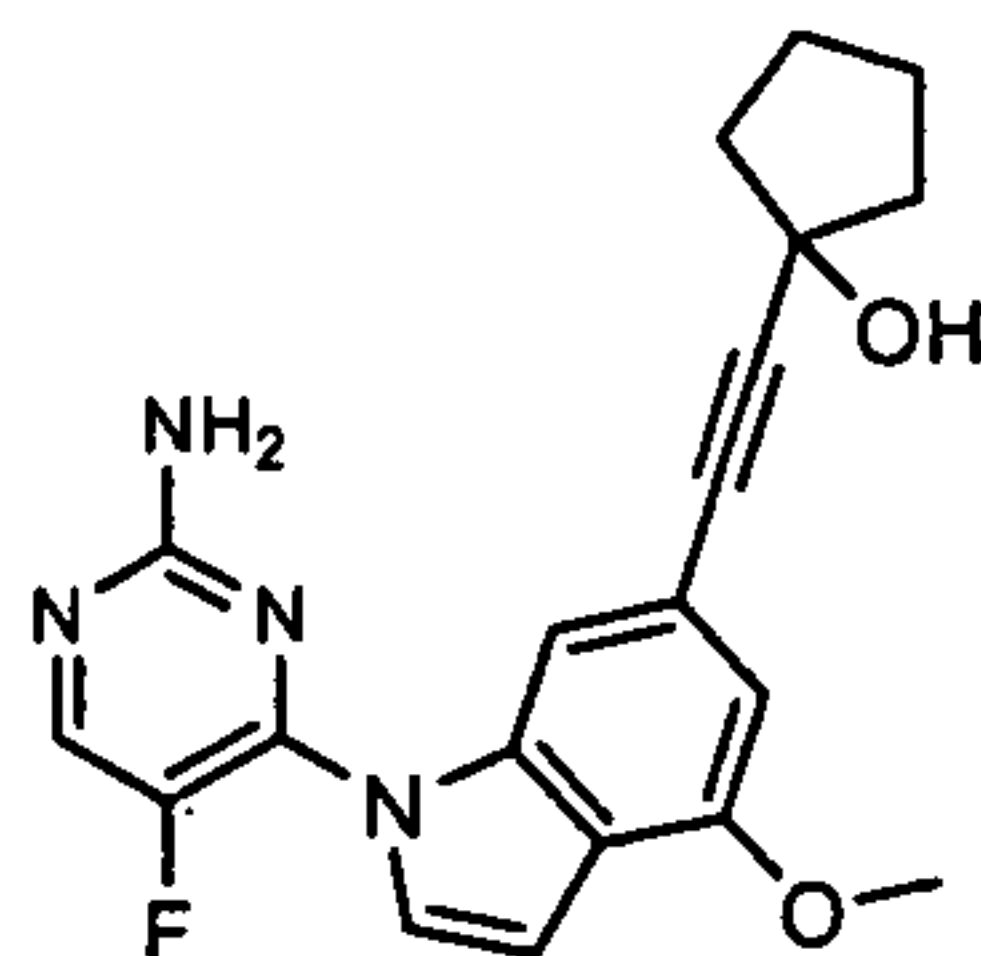
$J=3.7$ Hz), 6.58 (1 H, d, $J=1.1$ Hz), 5.24 (1 H, s), 1.88 - 1.96 (4 H, m), 1.64 - 1.80 (4 H, m); Mass Spectrum (ESI) $m/e = 335.1$ [M+1].

Example 100**100**

1-(2-(1-(2-aminopyrimidin-4-yl)-4-(2-methoxyethoxy)-1H-indol-6-yl)ethynyl)cyclopentanol (100) (prepared from components A.136 and C.36). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.24 - 8.31 (2 H, m), 7.97 (1 H, d, $J=4.0$ Hz), 6.89 - 6.96 (3 H, m), 6.72 - 6.75 (1 H, m), 6.71 (1 H, d, $J=0.7$ Hz), 5.25 (1 H, s), 4.25 (2 H, dd, $J=5.5, 3.7$ Hz), 3.70 - 3.77 (2 H, m), 3.36 (3 H, s), 1.89 - 1.97 (4 H, m), 1.63 - 1.81 (4 H, m); Mass Spectrum (ESI) $m/e = 393.1$ [M+1].

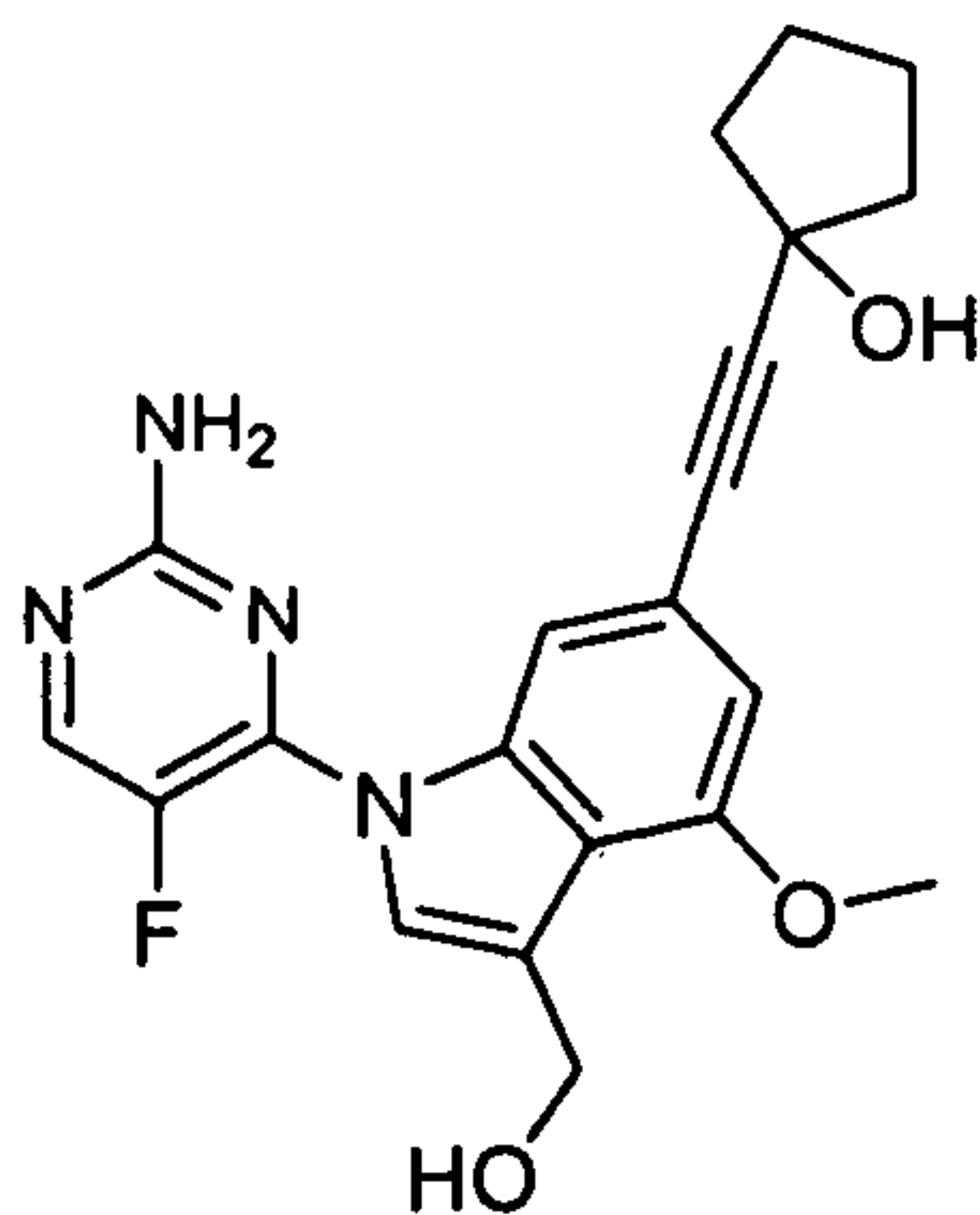
Example 101**101**

N-(1-(2-aminopyrimidin-4-yl)-6-(2-(1-hydroxycyclopentyl)ethynyl)-1H-indol-4-yl)acetamide (101) (prepared from components A.139 and C.36). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 9.74 (1 H, s), 8.40 (1 H, s), 8.29 (1 H, d, $J=5.5$ Hz), 8.05 (1 H, d, $J=3.7$ Hz), 7.88 (1 H, s), 7.09 (1 H, d, $J=3.7$ Hz), 6.95 (2 H, s), 6.91 (1 H, d, $J=5.5$ Hz), 5.28 (1 H, s), 2.17 (3 H, s), 1.89 - 1.97 (4 H, m), 1.65 - 1.79 (4 H, m); Mass Spectrum (ESI) $m/e = 376.1$ [M+1].

Example 102**102**

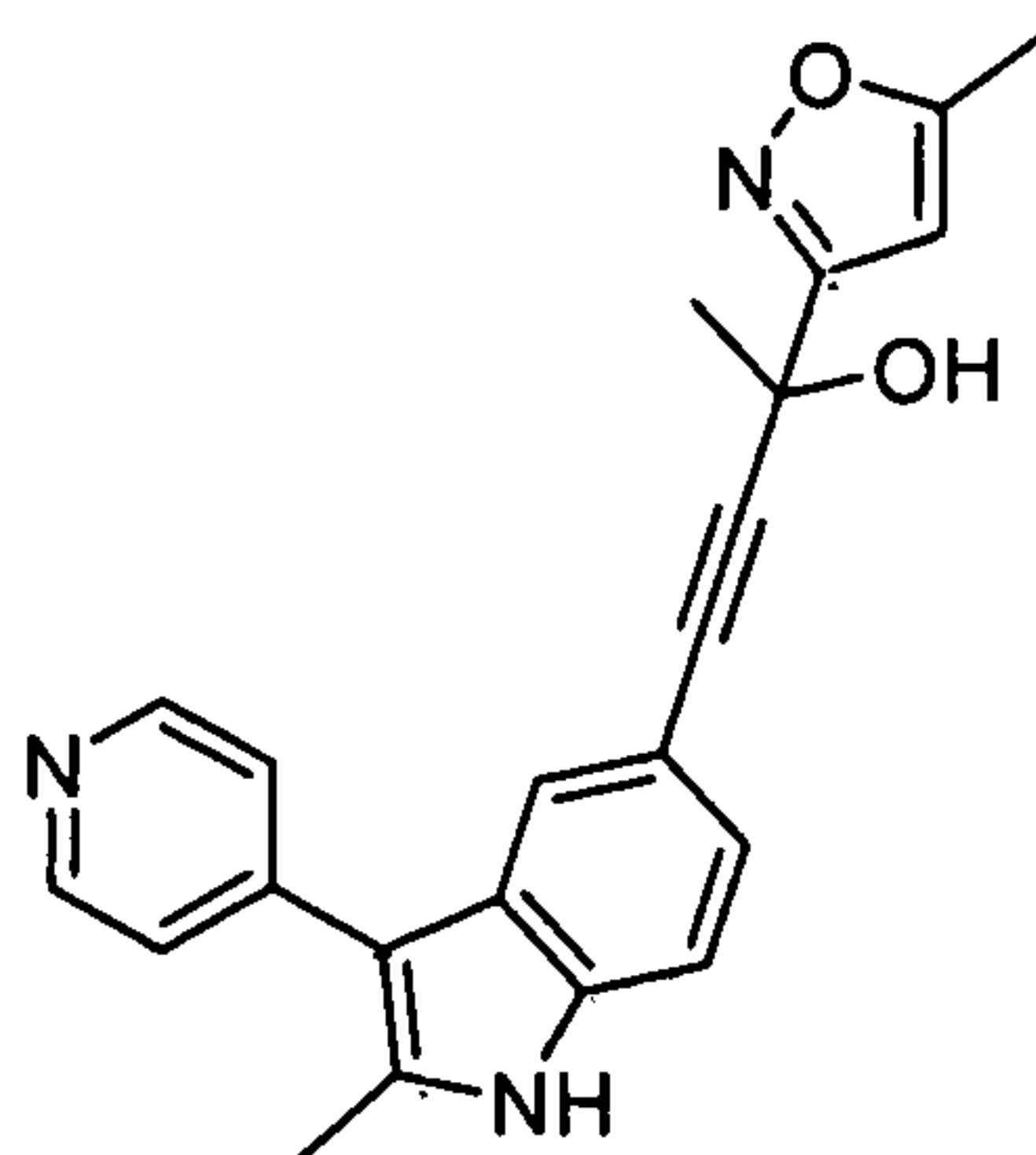
1-((1-(2-amino-5-fluoropyrimidin-4-yl)-4-methoxy-1H-indol-6-yl)ethynyl)cyclopentanol

(102) (prepared from components **A.88** and **C.36**). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.46 (1 H, d, $J=4.0$ Hz), 7.79 (1 H, d, $J=1.1$ Hz), 7.70 (1 H, t, $J=3.3$ Hz), 6.97 (2 H, s), 6.77 (1 H, dd, $J=3.5, 0.9$ Hz), 6.71 (1 H, d, $J=1.1$ Hz), 5.26 (1 H, s), 3.92 (3 H, s), 1.87 - 1.98 (4 H, m), 1.63 - 1.82 (4 H, m); Mass Spectrum (ESI) $m/e = 367.1$ $[\text{M}+1]$.

Example 103**103**

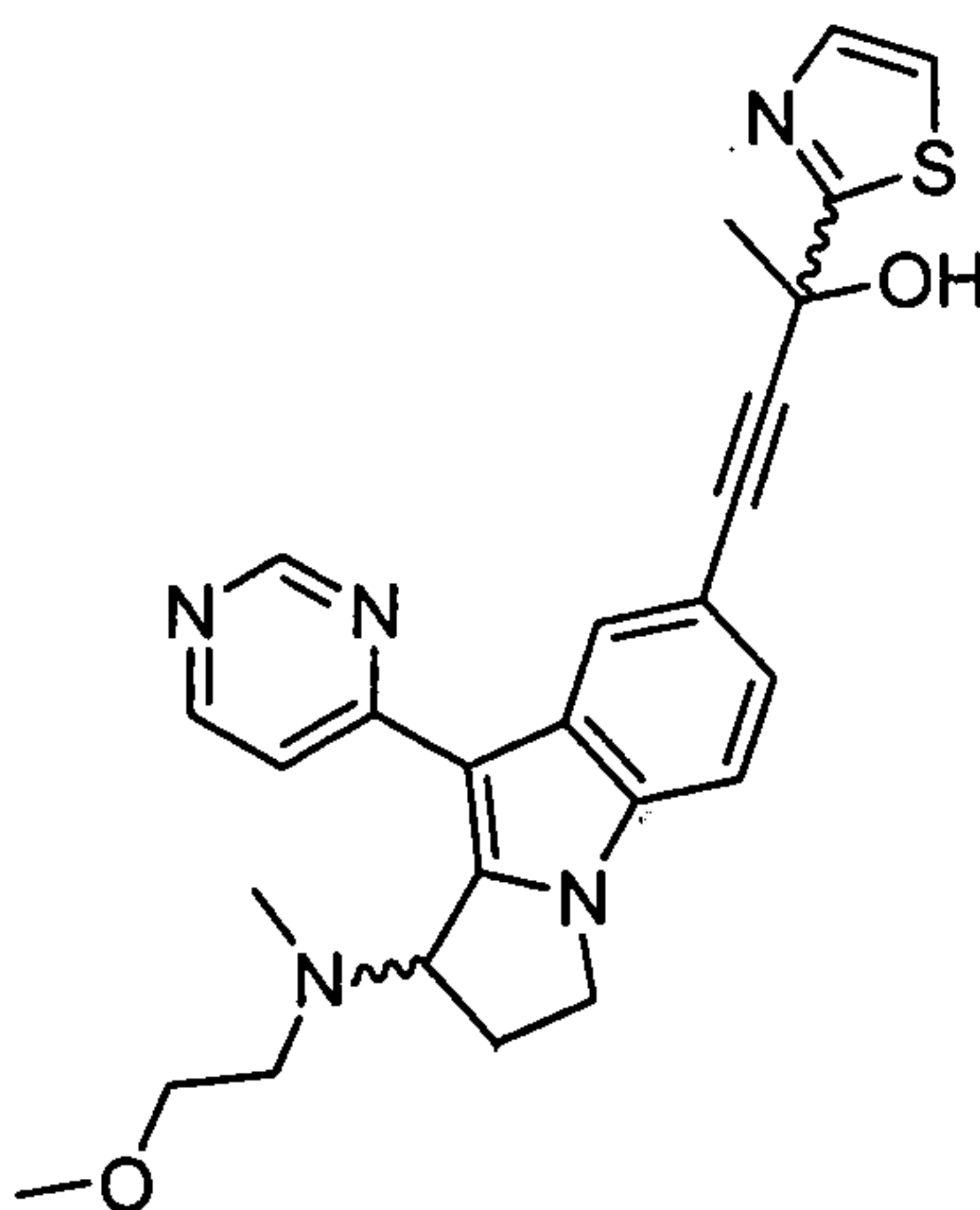
1-(2-(1-(2-amino-5-fluoropyrimidin-4-yl)-3-(hydroxymethyl)-4-methoxy-1H-indol-6-yl)ethynyl)cyclopentanol **(103)** (prepared from components **A.142** and **C.36**).

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 8.43 (1 H, d, $J=3.2$ Hz), 7.82 (1 H, s), 7.54 (1 H, s), 6.93 (2 H, s), 6.67 (1 H, s), 5.26 (1 H, s), 5.00 (1 H, t, $J=5.3$ Hz), 4.78 (2 H, d, $J=5.0$ Hz), 3.88 (3 H, s), 1.92 (4 H, s), 1.63 - 1.81 (4 H, m); Mass Spectrum (ESI) $m/e = 397.1$ $[\text{M}+1]$.

Example 104**104**

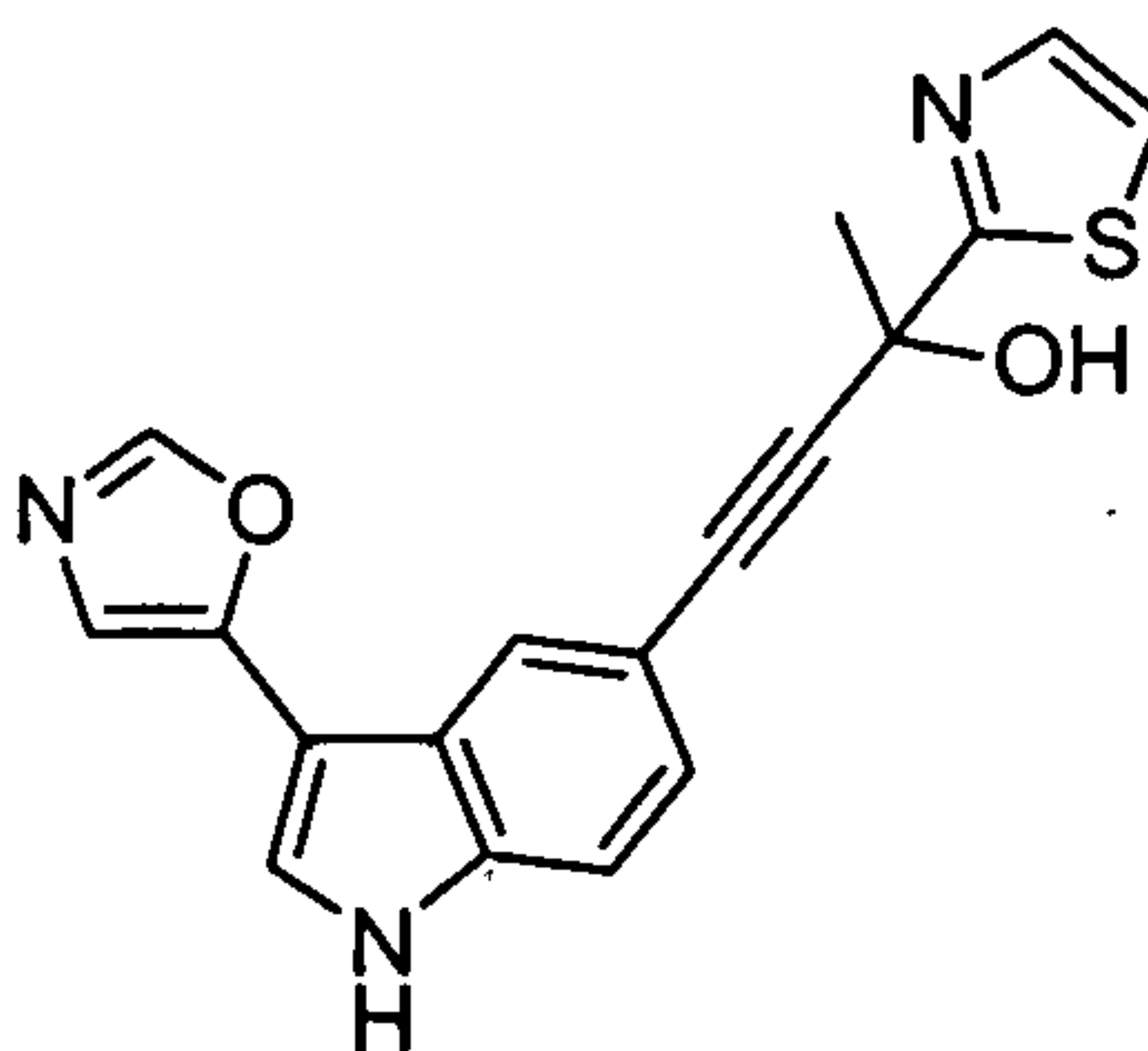
4-(2-methyl-3-(pyridin-4-yl)-1H-indol-5-yl)-2-(5-methylisoxazol-3-yl)but-3-yn-2-ol (104)

(prepared from components A.143 and C.1). ^1H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 11.65 (1 H, s), 8.61 (2 H, d, $J=5.5$ Hz), 7.65 (1 H, s), 7.48 (2 H, d, $J=5.9$ Hz), 7.37 (1 H, d, $J=8.6$ Hz), 7.15 (1 H, dd, $J=8.4, 1.0$ Hz), 6.35 (2 H, d, $J=14.5$ Hz), 2.52 (3 H, s), 2.40 (3 H, s), 1.78 (3 H, s); Mass Spectrum (ESI) $m/e = 358.1$ [M+1].

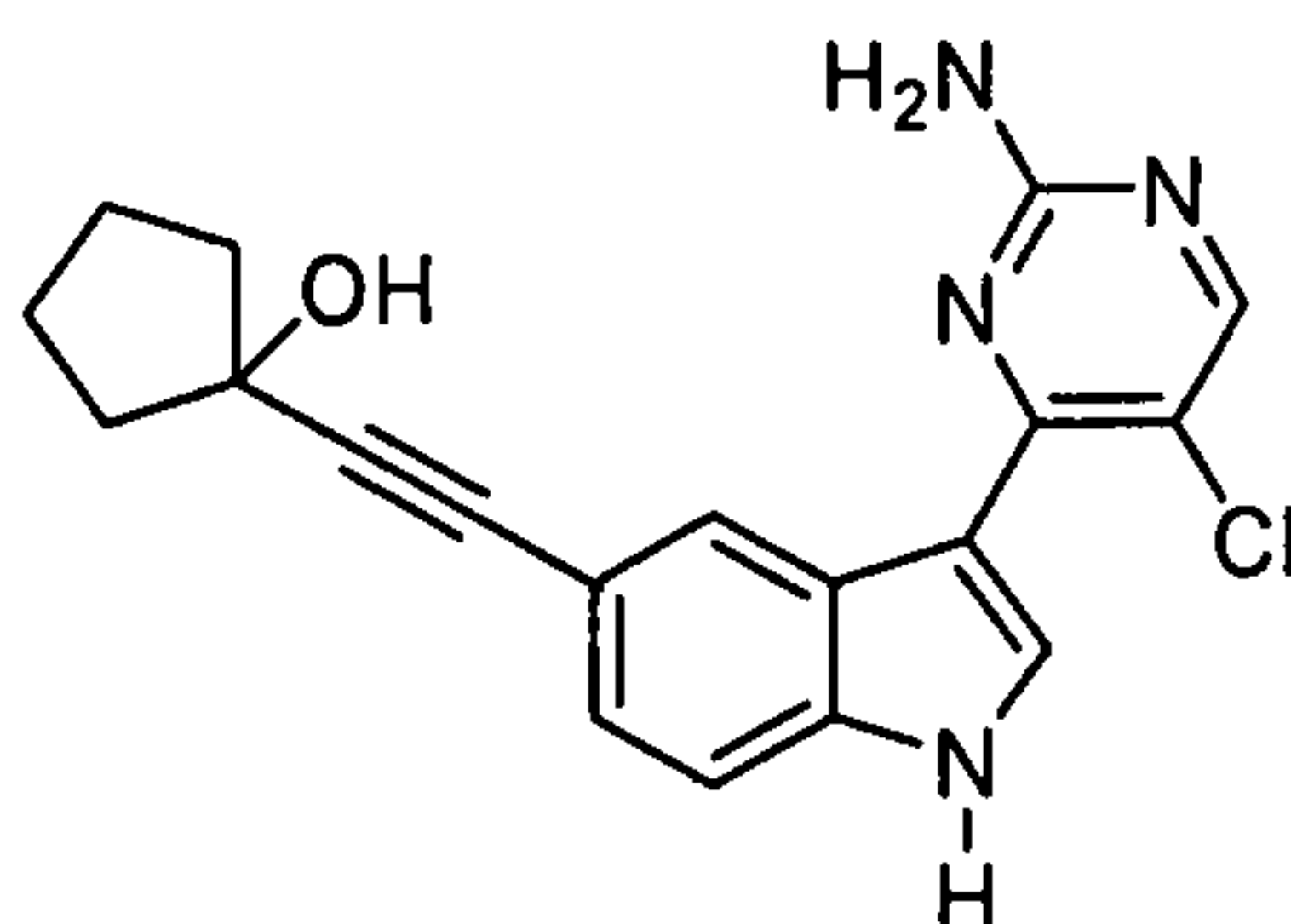
Example 105**105**

4-(1-((2-methoxyethyl)(methyl)amino)-9-(pyrimidin-4-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-7-yl)-2-(thiazol-2-yl)but-3-yn-2-ol (105) (prepared from components A.149 and C.4).

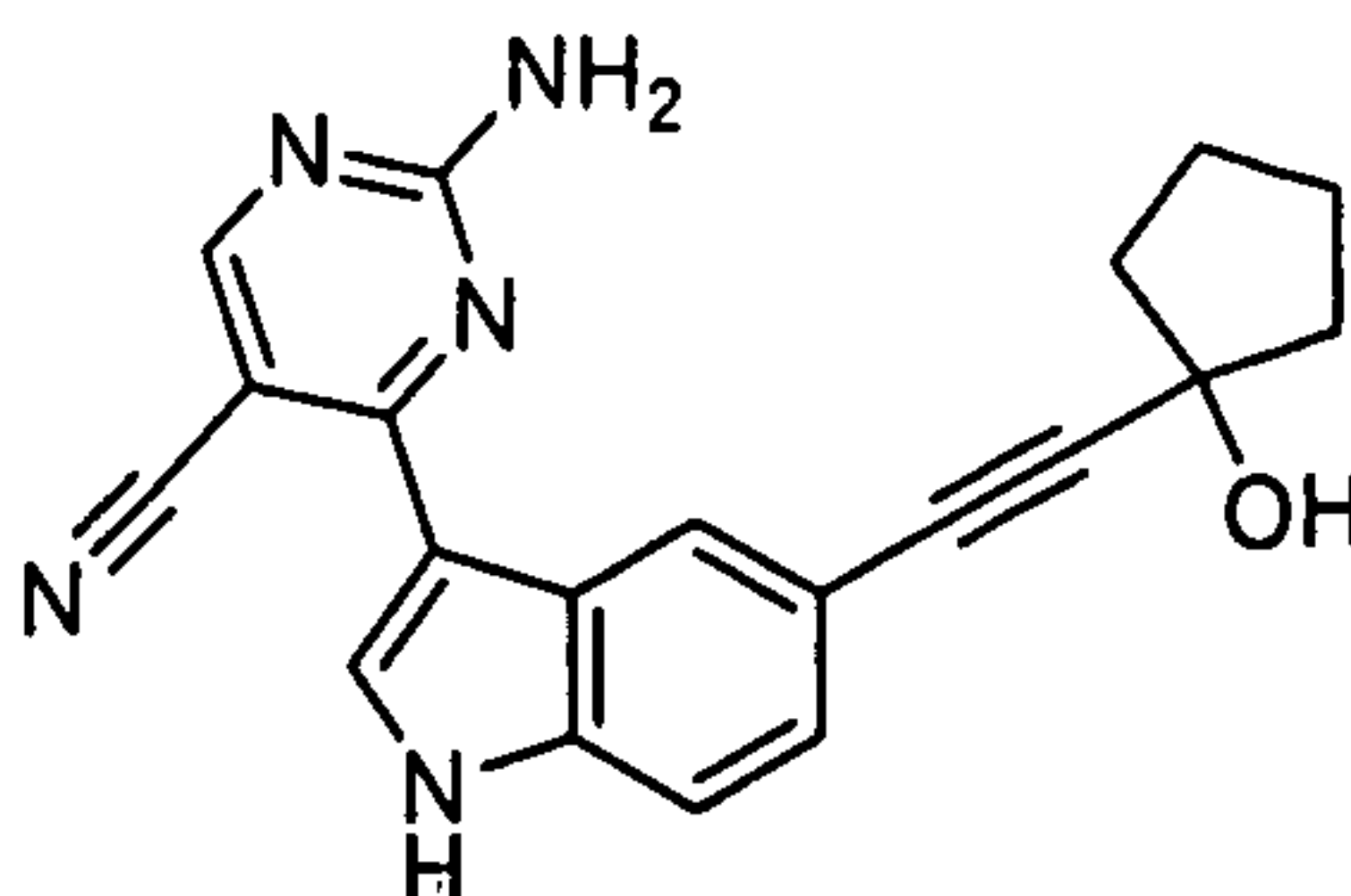
^1H NMR (400 MHz, *DMSO-d*₆) δ ppm 9.14 (1 H, s), 8.79 (1 H, d, $J=0.8$ Hz), 8.59 (1 H, d, $J=5.5$ Hz), 8.30 (1 H, dd, $J=5.5, 1.2$ Hz), 7.78 (1 H, d, $J=3.1$ Hz), 7.68 (1 H, d, $J=3.1$ Hz), 7.46 (1 H, d, $J=8.6$ Hz), 7.25 (1 H, dd, $J=8.4, 1.0$ Hz), 6.99 (1 H, s), 4.92 (1 H, dd, $J=8.2, 2.7$ Hz), 4.16 - 4.29 (2 H, m), 3.46 (2 H, t, $J=5.5$ Hz), 3.25 (3 H, s), 2.69 - 2.81 (2 H, m), 2.52 - 2.66 (2 H, m), 2.12 (3 H, s), 1.90 (3 H, s); Mass Spectrum (ESI) $m/e = 474.2$ [M+1].

Example 106**106**

4-(3-(oxazol-5-yl)-1H-indol-5-yl)-2-(thiazol-2-yl)but-3-yn-2-ol (106) (prepared from components **A.155** and **C.4**). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 11.79 (1 H, s), 8.36 (1 H, s), 7.91 (1 H, s), 7.88 (1 H, d, $J=2.7$ Hz), 7.78 (1 H, d, $J=2.7$ Hz), 7.68 (1 H, d, $J=3.1$ Hz), 7.42 - 7.51 (2 H, m), 7.23 (1 H, d, $J=8.2$ Hz), 6.96 (1 H, s), 1.90 (3 H, s); Mass Spectrum (ESI) m/e = 336.1 $[\text{M}+1]$.

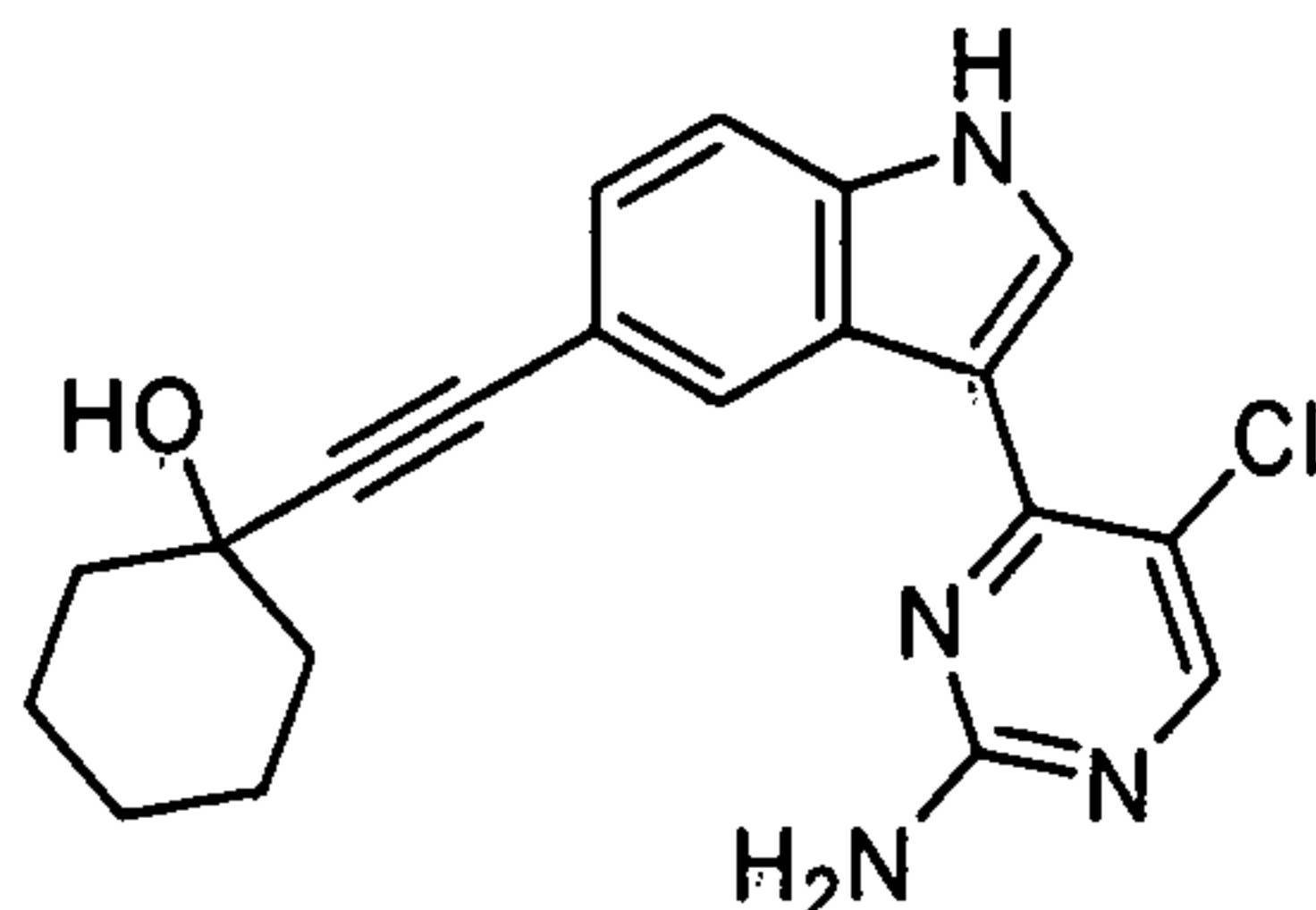
Example 107**107**

1-(2-(3-(2-amino-5-chloropyrimidin-4-yl)-1H-indol-5-yl)ethynyl)cyclopentanol (107) (prepared from components **A.170** and **C.36**). ^1H NMR (methanol- d_4) δ 8.67(s, 1 H), 8.45(s, 1 H), 8.21(s, 1 H), 7.43 (d, $J = 8.5$ Hz, 1 H), δ 7.29(d, $J = 8.5$ Hz, 1 H), 2.12-2.03(m, 4 H), 1.94-1.81(m, 4 H); ms 353.4 ($\text{M}+\text{H}^+$).

Example 108**108**

2-amino-4-(5-(2-(1-hydroxycyclopentyl)ethynyl)-1H-indol-3-yl)pyrimidine-5-carbonitrile (108) (prepared from components A.175 and C.36). ^1H NMR (methanol- d_4) δ 8.75(s, 1 H), 8.55(s, 1 H), 8.52(s, 1 H), 7.45 (d, $J = 8.5$ Hz, 1 H), δ 7.32(d, $J = 8.5$ Hz, 1 H), 2.15-2.03(m, 4 H), 1.95-1.78 (m, 4 H); ms 344.2 ($\text{M}+\text{H}^+$).

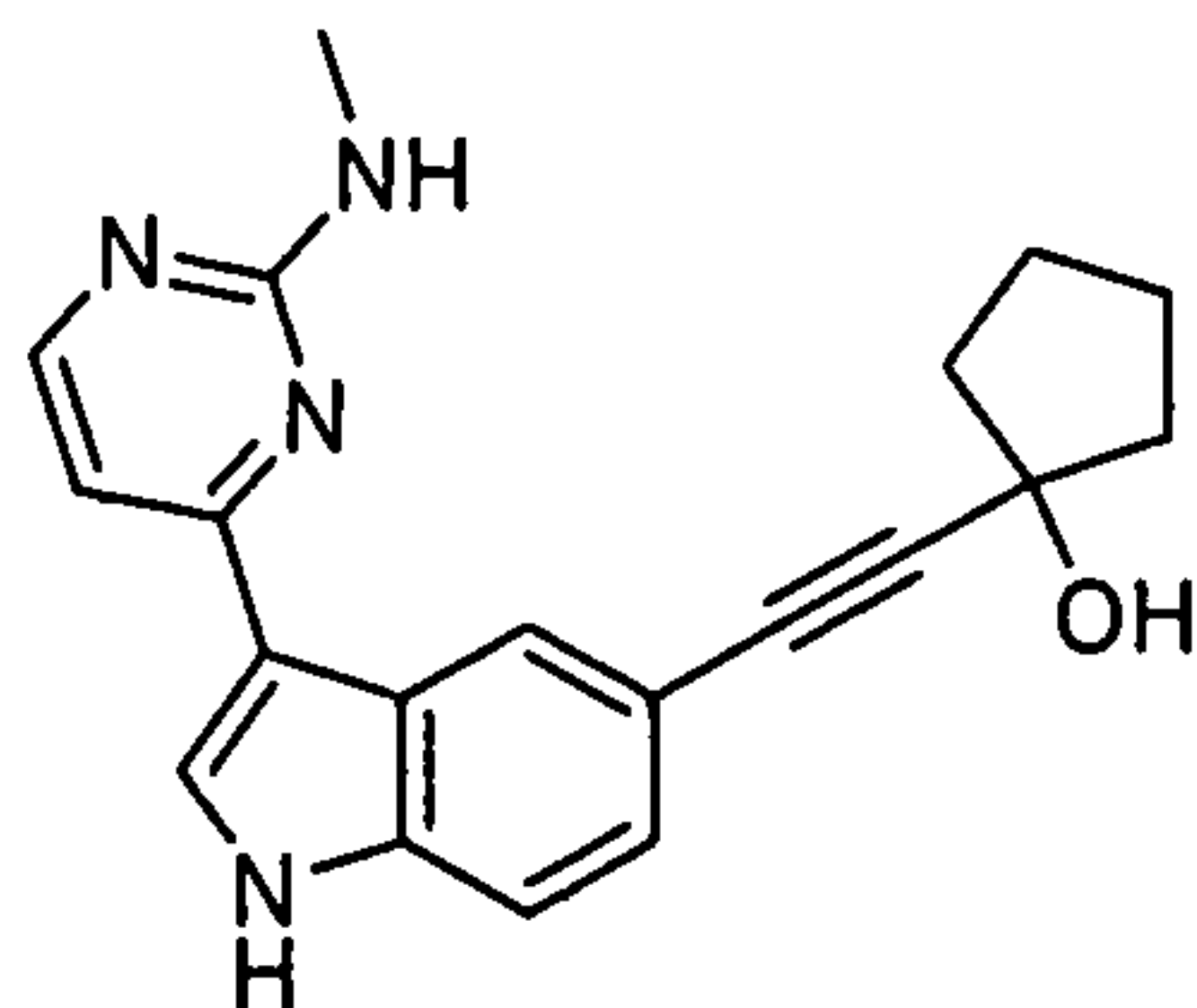
Example 109



109

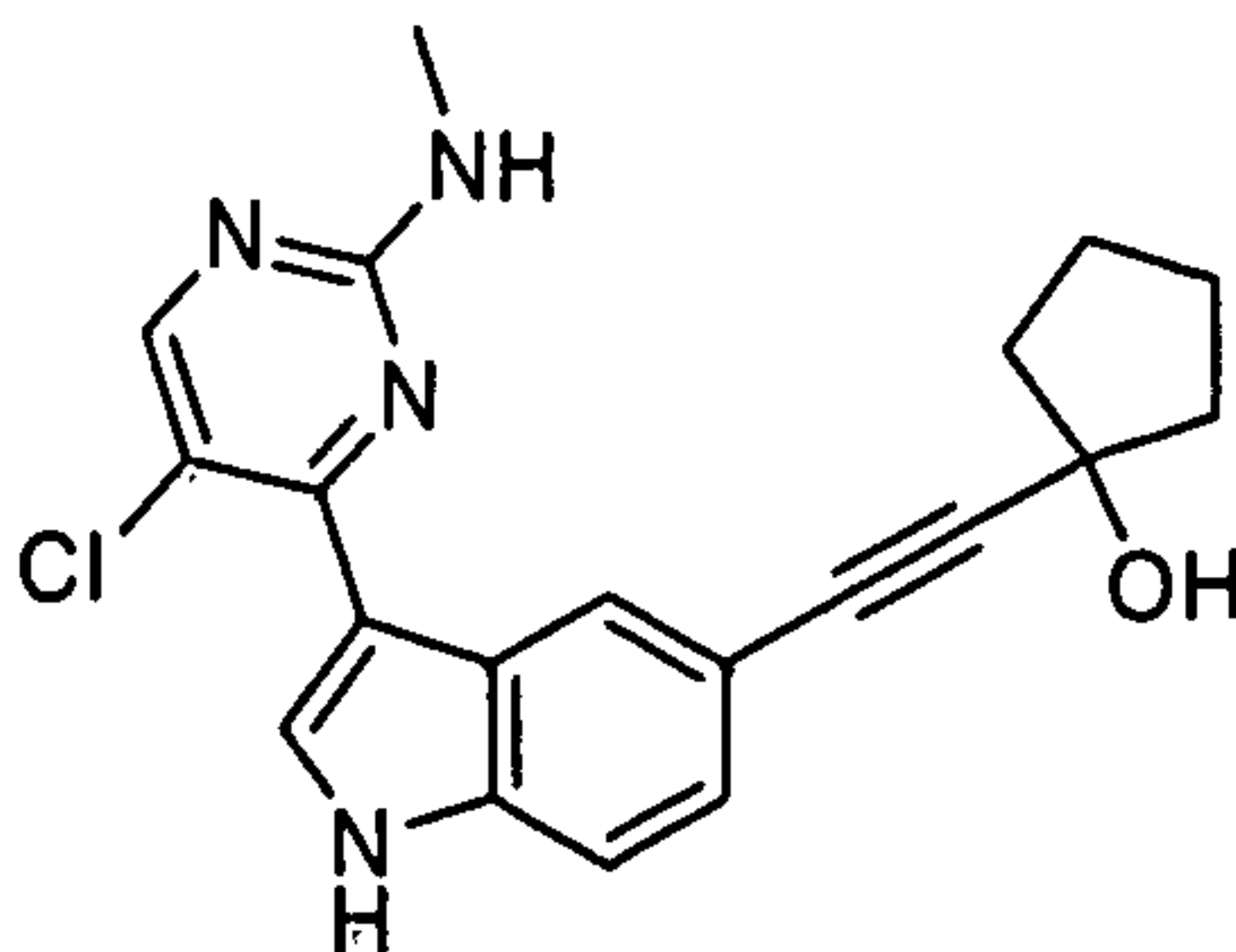
1-(2-(3-(2-amino-5-chloropyrimidin-4-yl)-1H-indol-5-yl)ethynyl)cyclohexanol (109) (prepared from components A.170 and C.9). ^1H NMR (DMSO- d_6) δ 8.50(s, 1 H), 8.39(s, 1 H), 8.27(s, 1 H), 7.45 (d, $J = 8.2$ Hz, 1 H), δ 7.21(d, $J = 8.2$ Hz, 1 H), 6.79(s, 2 H), 5.29(s, 1 H), 1.92-1.80(m, 2 H), 1.70-1.45(m, 7 H), 1.35-1.20(m, 1 H); ms 367.1 ($\text{M}+\text{H}^+$).

Example 111

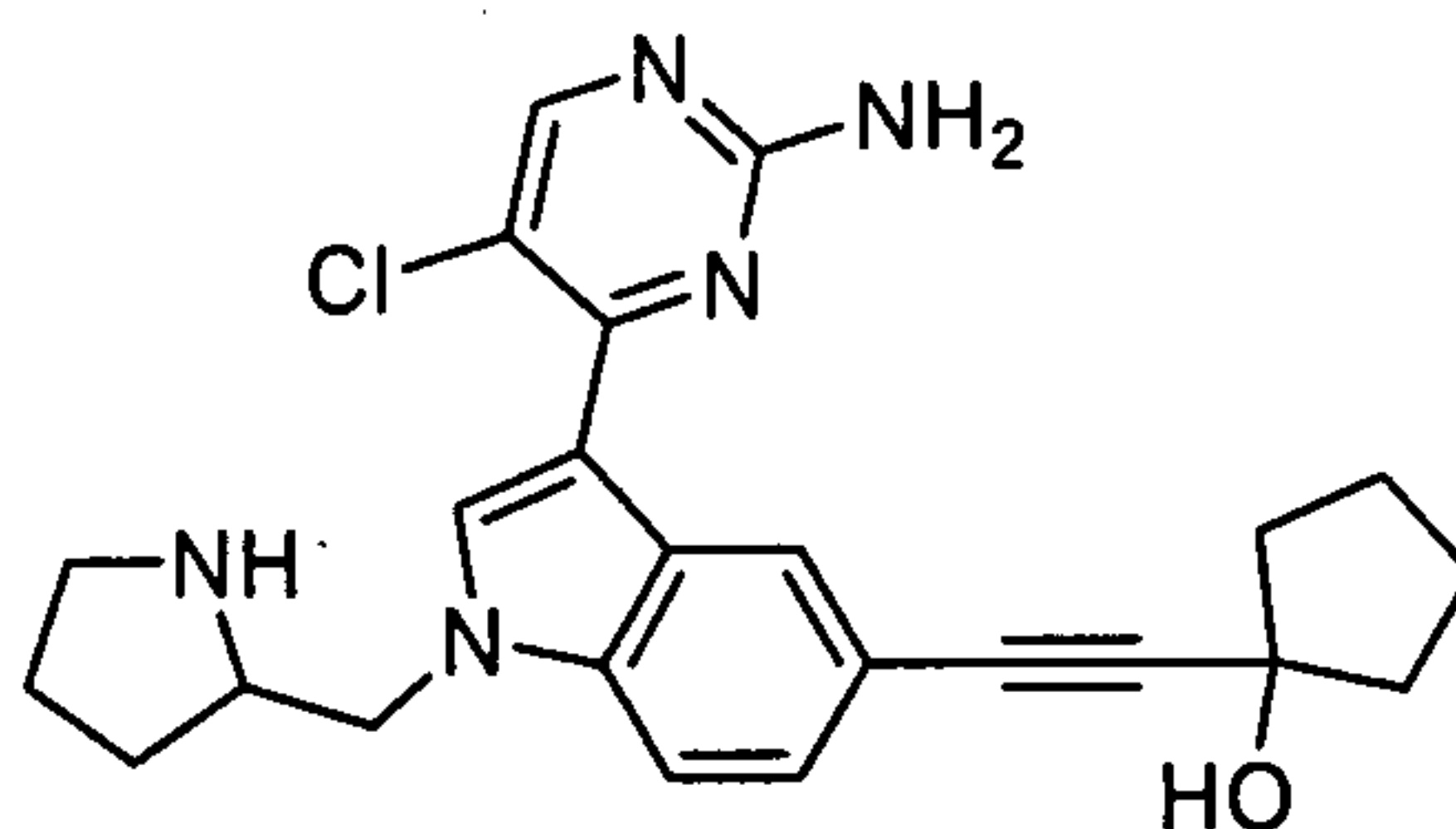


111

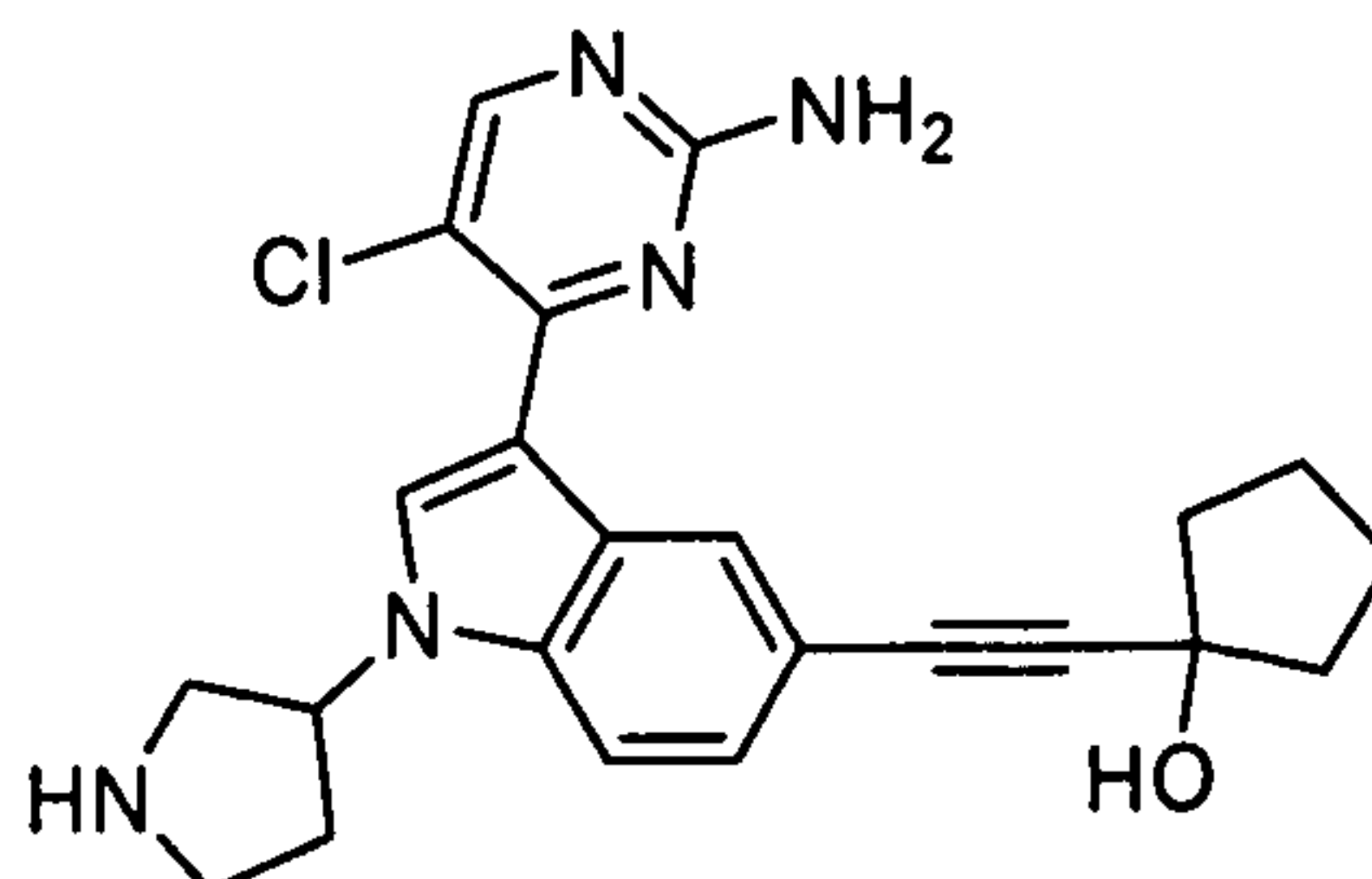
1-(2-(3-(2-(methylamino)pyrimidin-4-yl)-1H-indol-5-yl)ethynyl)cyclopentanol (111) (prepared from components A.177 and C.36). ^1H NMR (DMSO- d_6) δ 11.84(s, 1 H), 8.63(s, 1 H), 8.28(s, 1 H), 8.16(d, $J = 5.0$ Hz, 1 H), 7.43 (d, $J = 8.5$ Hz, 1 H), δ 7.20(d, $J = 8.5$ Hz, 1 H), 7.01(d, $J = 5.0$ Hz, 1 H), 6.93(br, 1 H), 5.27(s, 1 H), 2.92(br, 1 H), 2.91(s, 3 H), 1.93-1.85(m, 4 H), 1.80-1.65(m, 4 H); ms 333.1 ($\text{M}+\text{H}^+$).

Example 112**112**

1-(2-(3-(5-chloro-2-(methylamino)pyrimidin-4-yl)-1H-indol-5-yl)ethynyl)cyclopentanol (112) (prepared from components A.172 and C.36). ^1H NMR (DMSO- d_6) δ 11.99(s, 1 H), 8.65(br, 1 H), 8.50(s, 1 H), 8.30(s, 1 H), 7.48 (d, $J = 8.5$ Hz, 1 H), 7.30(br, 1 H), 7.23(d, $J = 8.5$ Hz, 1 H), 2.94(br, 4 H), 1.93-1.85(m, 4 H), 1.80-1.65(m, 4 H); ms 367.1 ($\text{M}+\text{H}^+$).

Example 113**113**

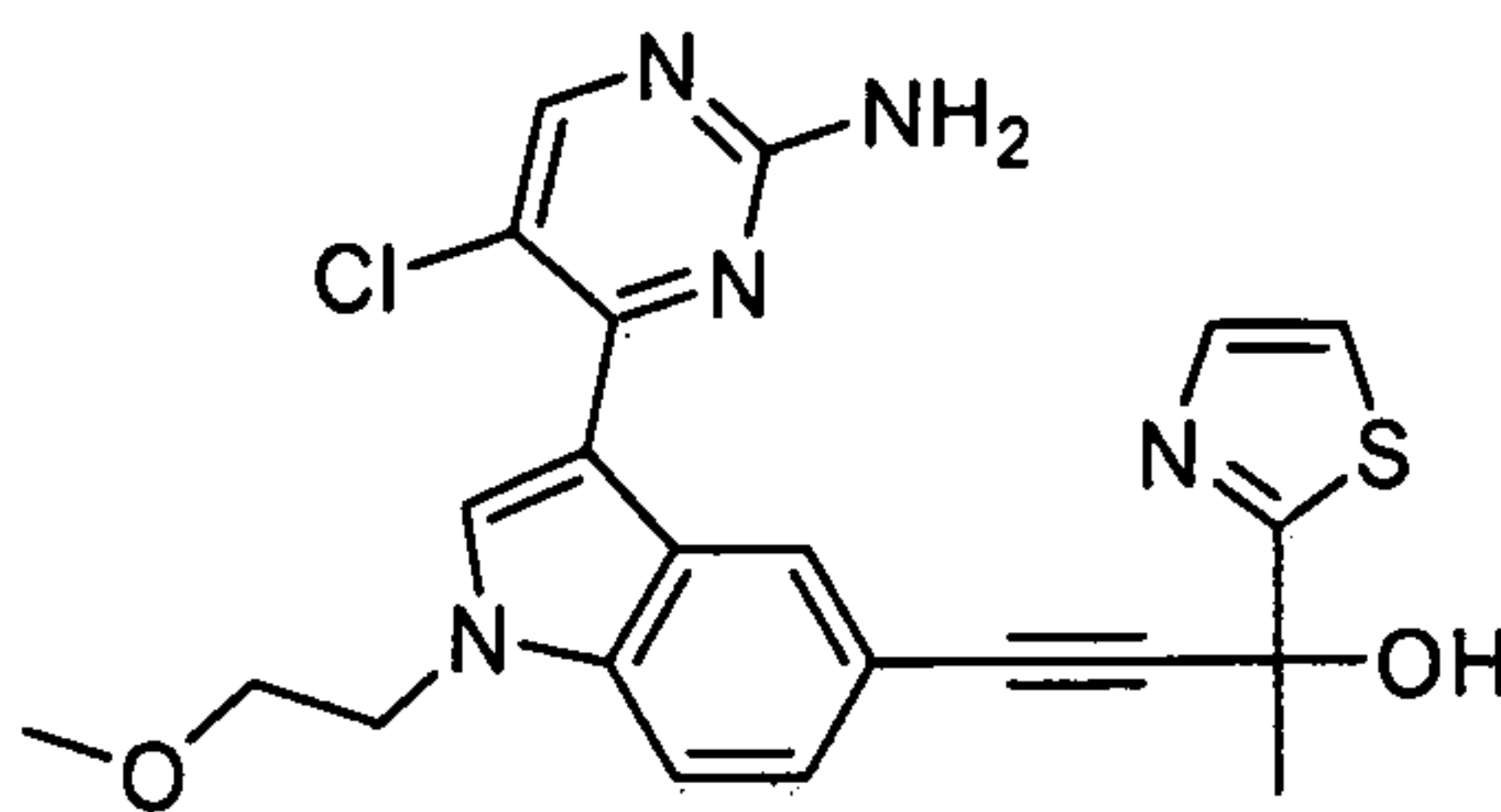
1-(2-(3-(2-amino-5-chloropyrimidin-4-yl)-1-(pyrrolidin-2-ylmethyl)-1H-indol-5-yl)ethynyl)cyclopentanol (113) (prepared from components A.178 and C.36). ^1H NMR (DMSO- d_6) δ 8.66(s, 1 H), 8.47(s, 1 H), 8.18(s, 1 H), 7.50(d, $J = 8.4$ Hz, 1 H), 7.32 (d, $J = 8.4$ Hz, 1 H), 4.34-4.24(m, 2 H), 3.60-3.52(m, 1 H), 3.10-2.95(m, 1 H), 2.90-2.85(m, 1 H), 2.15-1.98(m, 4 H), 1.98-1.70(m, 7 H), 1.55-1.50(m, 1 H); ms 436.1 ($\text{M}+\text{H}^+$).

Example 114**114**

1-(2-(3-(2-amino-5-chloropyrimidin-4-yl)-1-(pyrrolidin-3-yl)-1H-indol-5-yl)ethynyl)cyclopentanol (114) (prepared from components A.179 and C.36). ^1H NMR

(DMSO- d_6) δ 8.63(s, 1 H), 8.47(s, 1 H), 8.21(s, 1 H), 7.55(d, $J = 8.6$ Hz, 1 H), 7.34 (d, $J = 8.6$ Hz, 1 H), 5.25(br, 1 H), 3.57-3.52(m, 1 H), 3.31-3.26(m, 1 H), 3.21-3.15(m, 2 H), 2.55-2.45(m, 1 H), 2.28-2.20(m, 1 H), 2.10-2.00(m, 5 H), 1.92-1.78(m, 4 H); ms 422.2 ($M+H^+$).

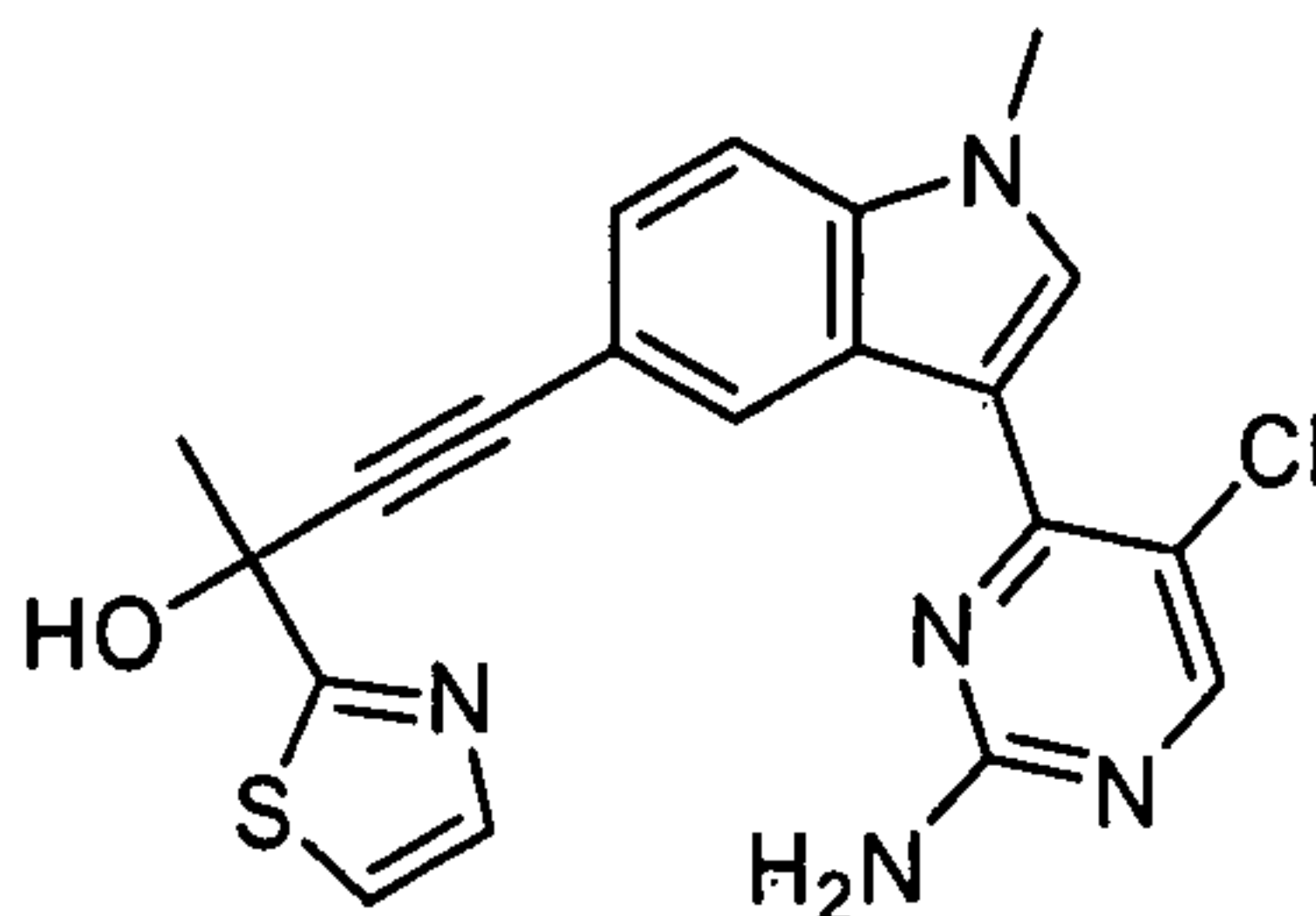
Example 115



115

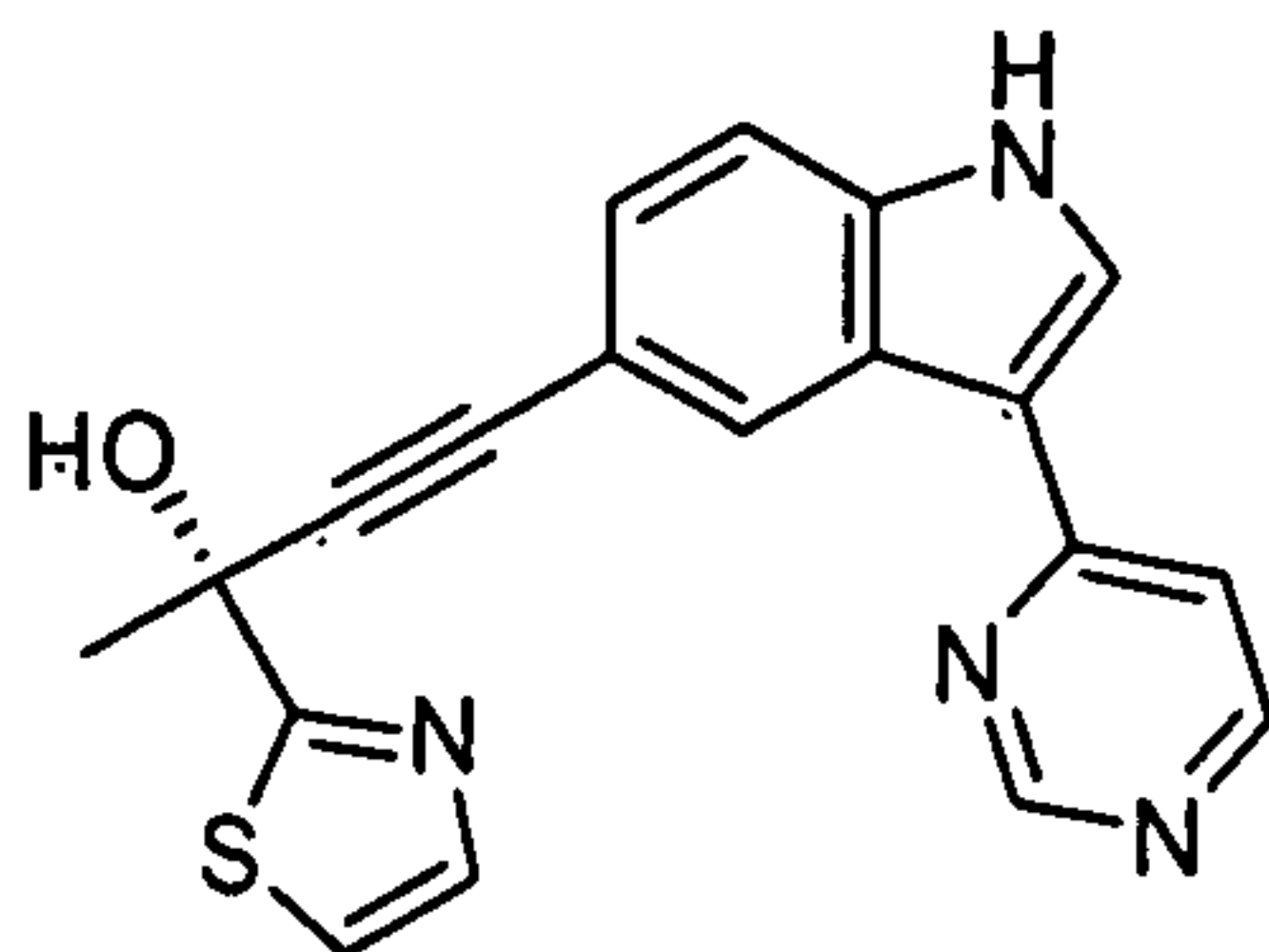
4-(3-(2-amino-5-chloropyrimidin-4-yl)-1-(2-methoxyethyl)-1H-indol-5-yl)-2-(thiazol-2-yl)but-3-yn-2-ol (115) (prepared from components A.171 and C.4). ^1H NMR (DMSO- d_6) δ 8.58(s, 1 H), 8.50(s, 1 H), 8.27(s, 1 H), 7.78(d, $J = 3.1$ Hz, 1 H), 7.69(d, $J = 3.1$ Hz, 1 H), 7.63(d, $J = 8.8$ Hz, 1 H), 7.29(d, $J = 8.8$ Hz, 1 H), 7.05-6.75(br, 2 H), 4.48 (t, $J = 5.3$ Hz, 2 H), 3.70 (t, $J = 5.3$ Hz, 2 H), 3.24(s, 3 H), 1.93(s, 3 H); ms 454.1 ($M+H^+$).

Example 116

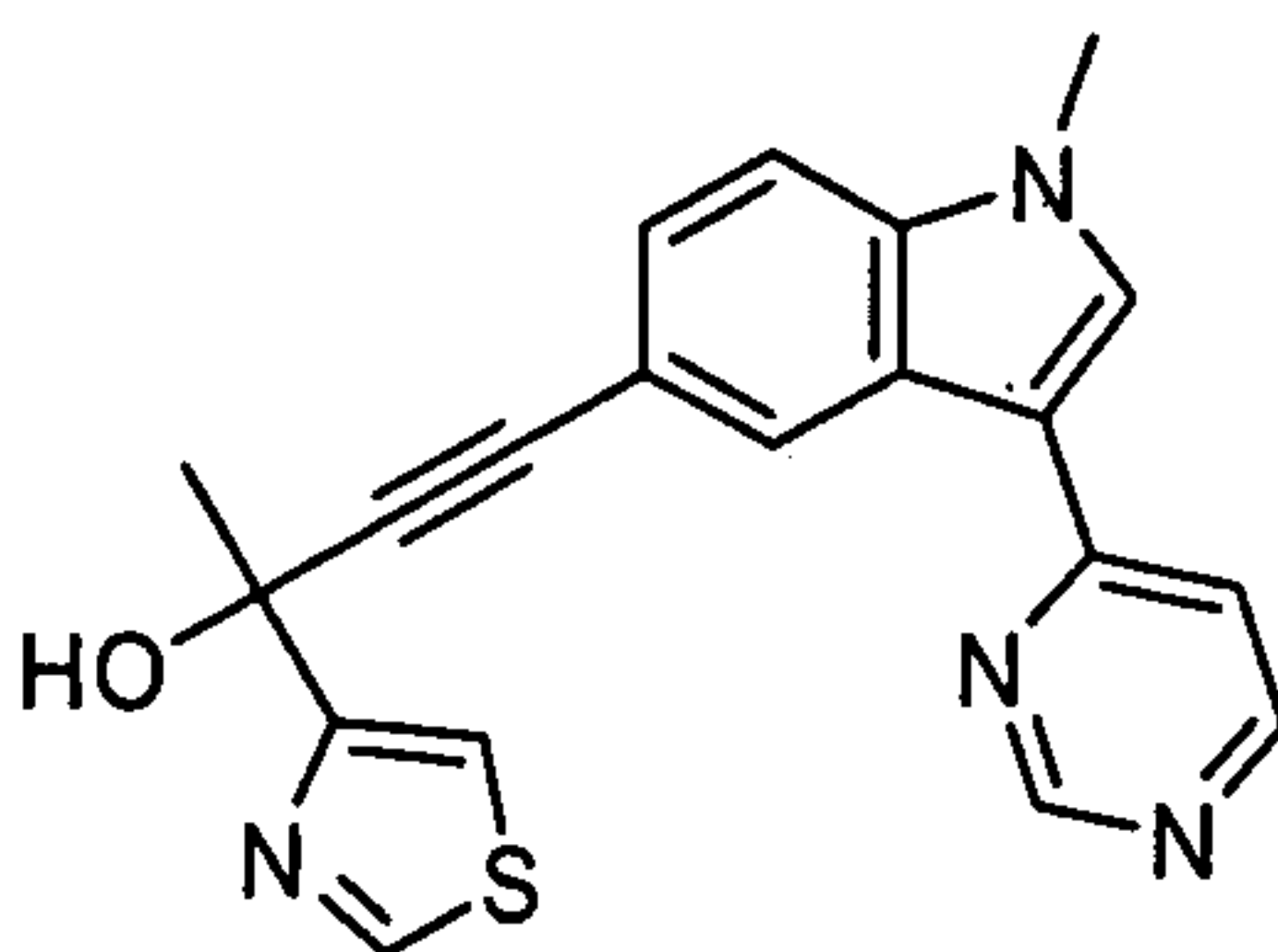


116

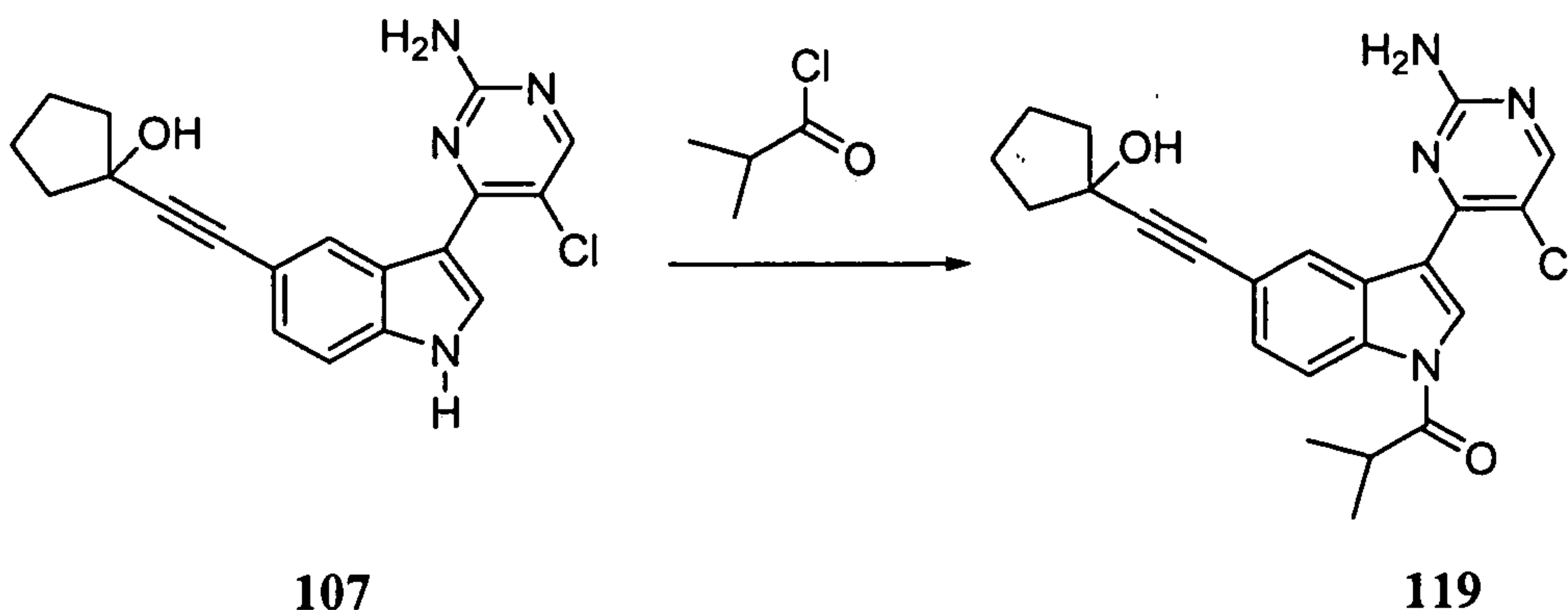
4-(3-(2-amino-5-chloropyrimidin-4-yl)-1-methyl-1H-indol-5-yl)-2-(thiazol-2-yl)but-3-yn-2-ol (116) (prepared from components A.xxx and C.4). ^1H NMR (methanol- d_4) δ 8.80(s, 1 H), 8.40(s, 1 H), 8.16 (s, 1 H), 7.79(d, $J = 3.3$ Hz, 1 H), 7.58(d, $J = 3.3$ Hz, 1 H), 7.42(d, $J = 8.5$ Hz, 1 H), 7.37(d, $J = 8.5$ Hz, 1 H), 5.51(s, 1 H), 3.90(s, 3 H), 2.01(s, 3 H); ms 410.0 ($M+H^+$).

Example 117**117**

(2R)-4-(3-(pyrimidin-4-yl)-1H-indol-5-yl)-2-(thiazol-2-yl)but-3-yn-2-ol (117) (prepared from components A.184 and C.6). ^1H NMR (DMSO- d_6) δ 12.06(s, 1 H), 9.14(s, 1 H), 8.64(s, 1 H), 8.62 (s, 1 H), 8.47(d, J = 2.4 Hz, 1 H), 7.90(d, J = 5.6 Hz, 1 H), 7.78(d, J = 2.4 Hz, 1 H), 7.68(d, J = 3.6 Hz, 1 H), 7.48(d, J = 8.4 Hz, 1 H), 7.24(d, J = 8.4 Hz, 1 H), 6.92(s, 1 H), 1.90(s, 3 H); ms 347.1 ($\text{M}+\text{H}^+$).

Example 118**118**

4-(1-methyl-3-(pyrimidin-4-yl)-1H-indol-5-yl)-2-(thiazol-4-yl)but-3-yn-2-ol (118) (prepared from components A.89 and C.29). ^1H NMR (DMSO- d_6) δ 9.13(s, 1 H), 9.05(s, 1 H), 8.64 (s, 1 H), 8.62 (s, 1 H), 8.44 (s, 1 H), 7.83(d, J = 4.2 Hz, 1 H), 7.66 (s, 1 H), 7.56(d, J = 8.8 Hz, 1 H), 7.32 (d, J = 8.8 Hz, 1 H), 6.29 (s, 1 H), 3.90 (s, 3 H), 1.85(s, 3 H); MS 361.1 ($\text{M}+\text{H}^+$).

Example 119

DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS
COMPREND PLUS D'UN TOME.**

CECI EST LE TOME __1__ DE __2__

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

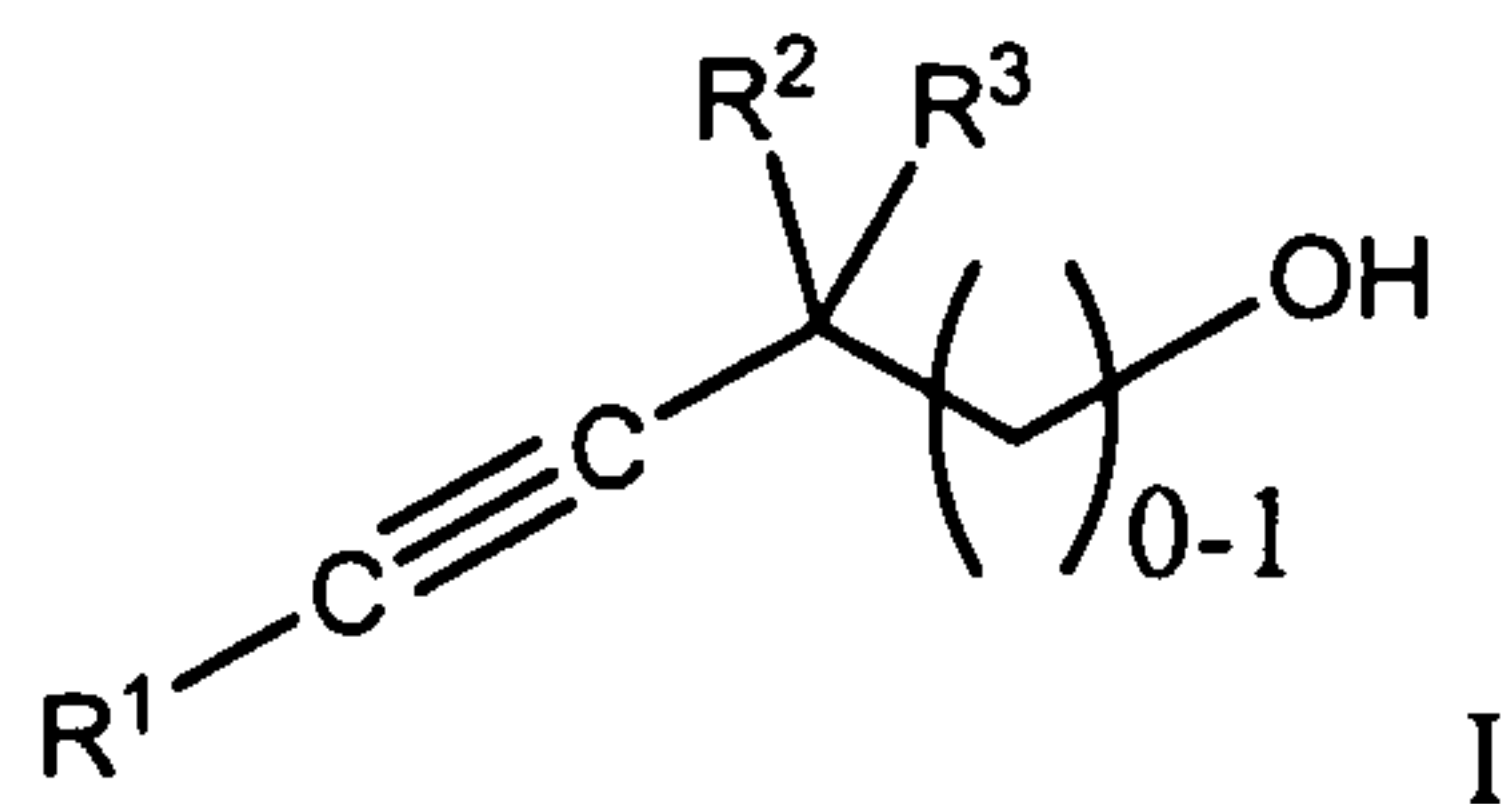
JUMBO APPLICATIONS / PATENTS

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

THIS IS VOLUME __1__ OF __2__

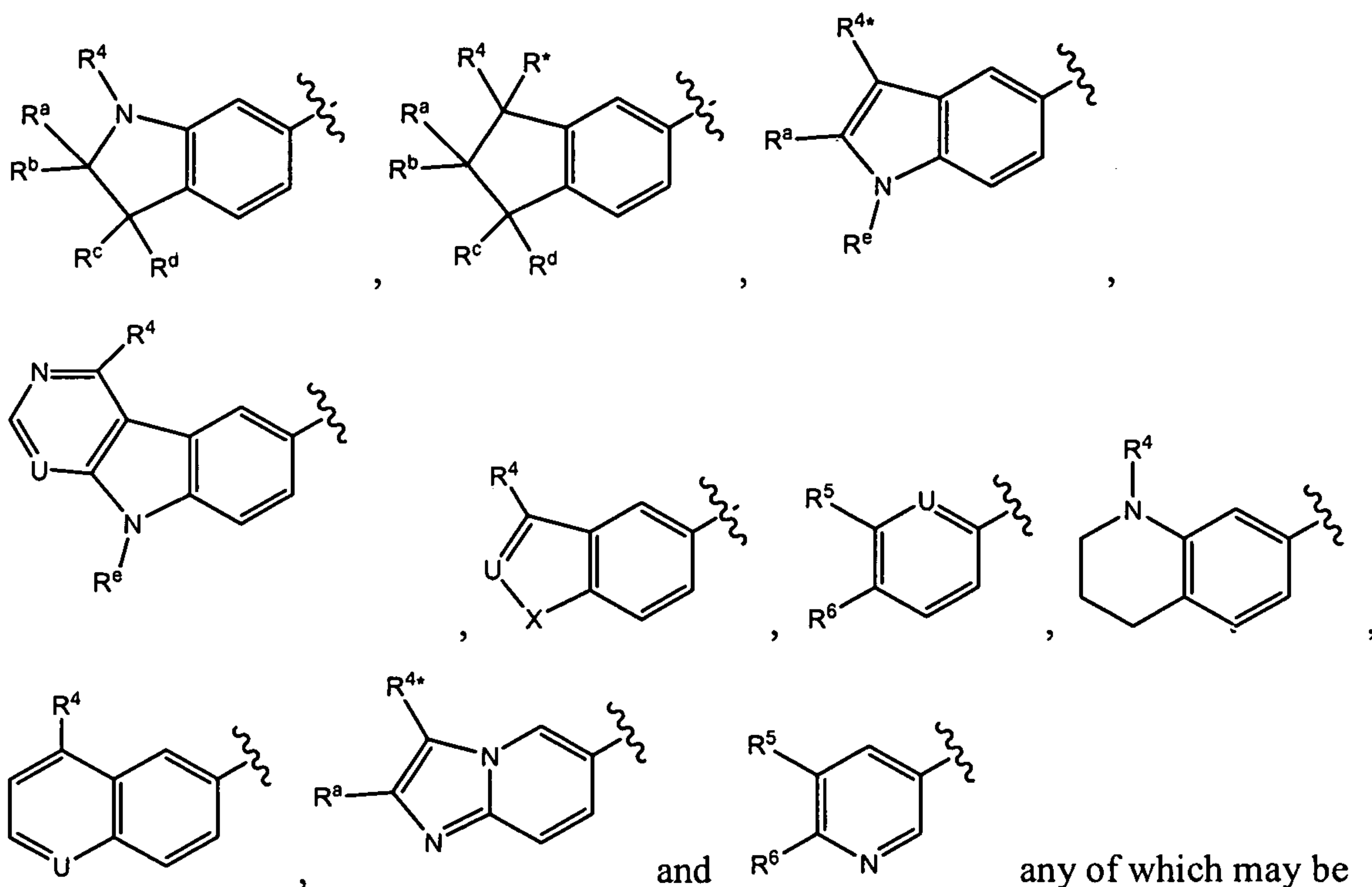
NOTE: For additional volumes please contact the Canadian Patent Office.

1. A compound of formula I

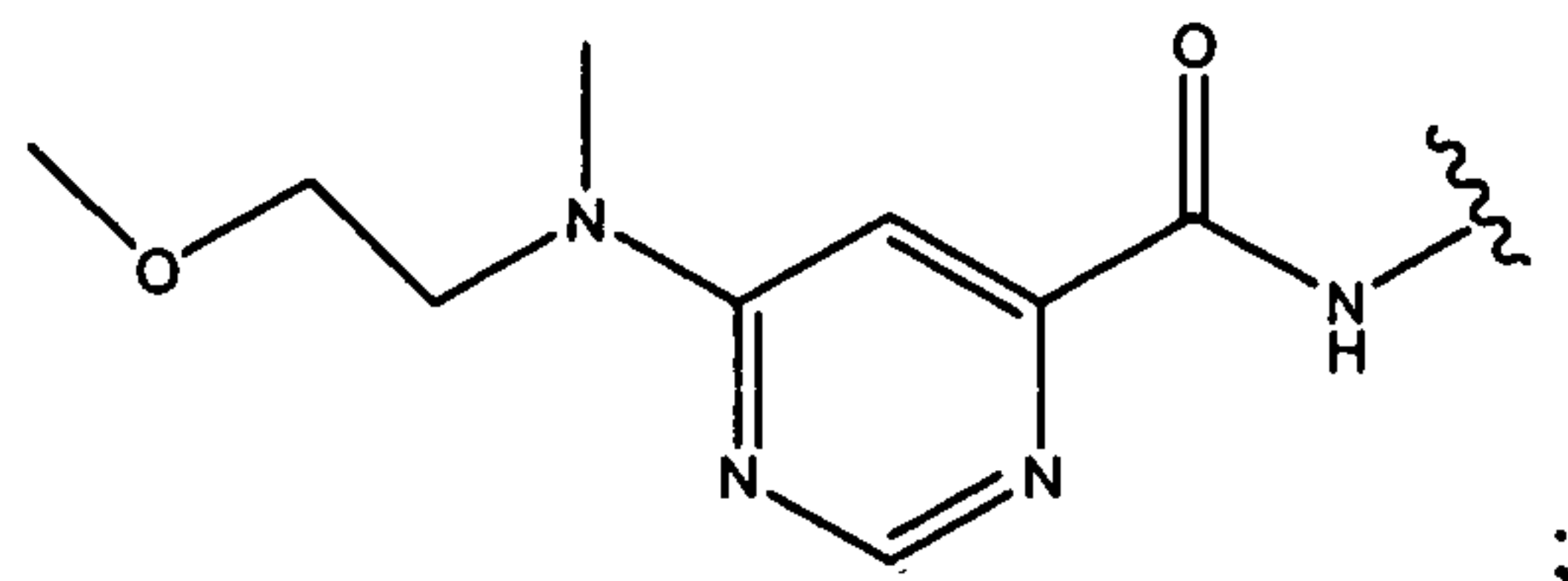
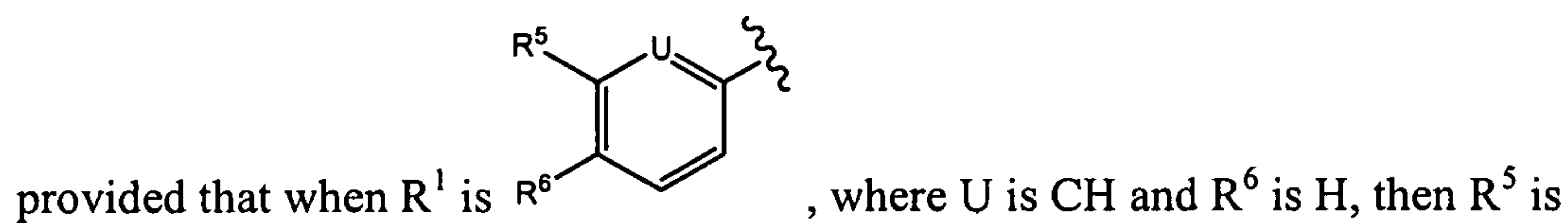


enantiomers, diastereomers and salts thereof wherein

R^1 is selected from



optionally substituted with one or more R^x groups as allowed by valance;



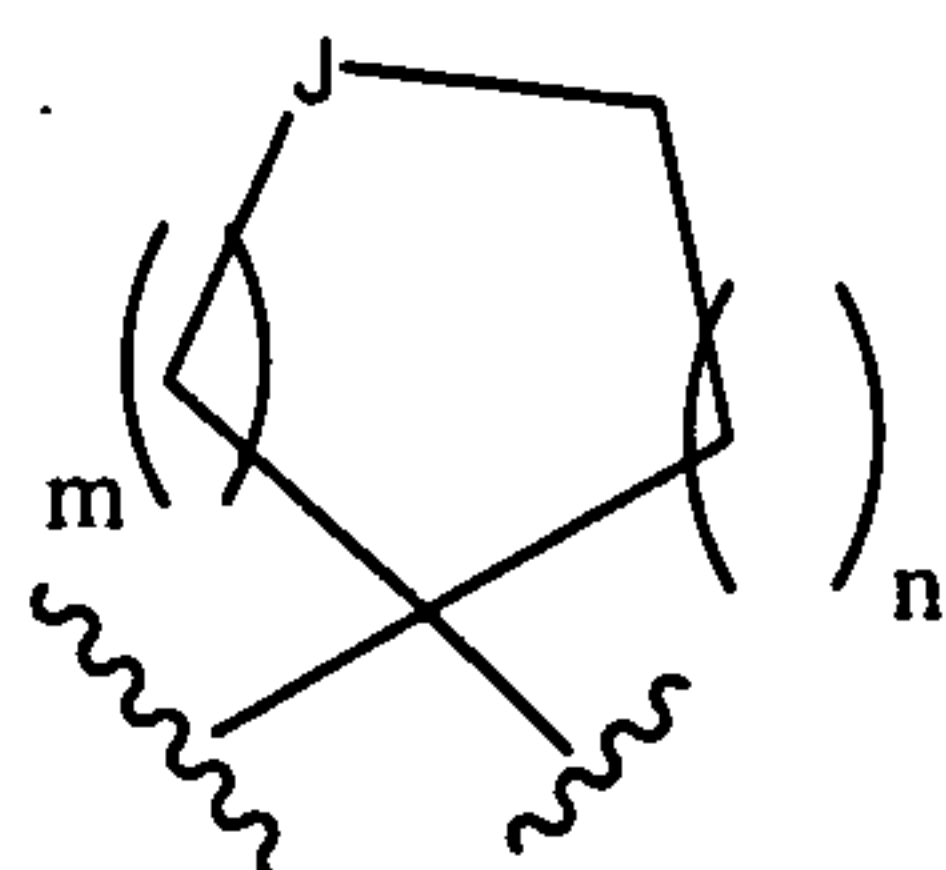
other than

R^2 is alkyl or haloalkyl;

R^3 is alkyl, cycloalkyl, haloalkyl, $-C(=O)R^7$, $-C(=O)OR^7$, $-C(=O)NR^8R^9$, aryl or heteroaryl

wherein either of said aryl or heteroaryl may be optionally substituted with one or more R^x as allowed by valance;

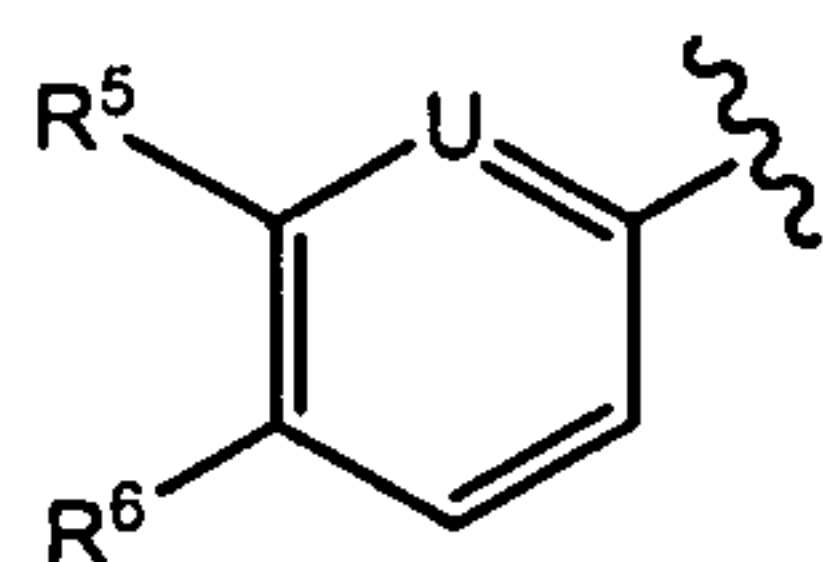
or R^2 and R^3 together with the carbon atom to which they are attached may combine to form



which may be optionally substituted with one or more R^x groups as allowed by valance; R^4 and R^{4*} are independently

- i) pyridyl, pyrimidyl, pyrazinyl, triazinyl, purinyl, pyrrolopyrimidyl, triazolopyrimidyl, furopyrimidyl, thienopyrimidyl, oxazolopyrimidyl, or thiazolopyrimidyl, each of which is substituted with at least one R^{10} group, and any of which may be optionally substituted with one or more R^x groups as allowed by valance; or
- ii) oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, or $-C(=O)R^{7*}$ any of which may be optionally substituted with one or more R^x groups as allowed by valance;

provided R^4 is other than $-C(=O)R^{7*}$ when R^1 is



, where U is CH and R^6 is H , and R^5 is either

$-(CH_2)_k-N(R^8)(R^4)$ or $-(CH_2)_k-R^4$;

R^5 is $-(CH_2)_k-R^4$, $-(CH_2)_k-N(R^8)(R^4)$, $-(CH_2)_k-OR^4$, $-(CH_2)_k-C(=O)R^4$; $-(CH_2)_k-C(=O)OR^4$, $-(CH_2)_k-C(=O)N(R^8)(R^4)$ or $-(CH_2)_k-NR^8-C(=O)R^4$;

R^6 is H , halo, alkyl, $-(CH_2)_k-OR^{11}$, $-(CH_2)_k-N(R^{12})(R^{13})$, $-(CH_2)_k-C(=O)R^{11}$, $-(CH_2)_k-C(=O)OR^{11}$;

R^7 , R^{7*} and R^{7+} are each independently

(i) H , or

(ii) alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkylalkyl, heterocyclalkyl, arylalkyl, heteroarylalkyl, alkoxyalkyl, hydroxyalkyl or NR^8R^9 -alkyl any of which may be optionally substituted with one or more R^x groups as allowed by valance;

R^8 , R^9 , R^{8+} and R^{9+} are each independently

(i) H ;

(ii) alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkylalkyl, heterocyclalkyl, arylalkyl, heteroarylalkyl, alkoxyalkyl, hydroxyalkyl or

(NR¹²R¹³)-alkyl, any of which may be optionally substituted with one or more R^x groups as allowed by valance;

(iii) or R⁸ and R⁹ together with the nitrogen atom to which they are attached may combine to form a heterocyclyl ring optionally substituted with one or more R^x groups as allowed by valance;

(iv) or R⁸⁺ and R⁹⁺ together with the nitrogen atom to which they are attached may combine to form a heterocyclyl ring optionally substituted with one or more R^x groups as allowed by valance;

R¹⁰ is H, -NR¹⁴R¹⁵, or -C(=O)NR¹⁴R¹⁵;

R¹¹ is

(i) H, or

(ii) alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkylalkyl, heterocyclylalkyl, arylalkyl or heteroarylalkyl any of which may be optionally substituted with one or more R^x groups as allowed by valance;

R¹² and R¹³ are each independently

(i) H;

(ii) alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkylalkyl, heterocyclylalkyl, arylalkyl, heteroarylalkyl, alkoxyalkyl, hydroxyalkyl or (NR⁸R⁹)-alkyl, any of which may be optionally substituted with one or more R^x groups as allowed by valance;

(iii) or R¹² and R¹³ together with the nitrogen atom to which they are attached may combine to form a heterocyclyl ring optionally substituted with one or more R^x groups as allowed by valance;

R¹⁴ and R¹⁵ are each independently

(i) H;

(ii) alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkylalkyl, heterocyclylalkyl, arylalkyl, heteroarylalkyl, alkoxyalkyl, hydroxyalkyl or (NR¹²R¹³)-alkyl, any of which may be optionally substituted with one or more R^x groups as allowed by valance;

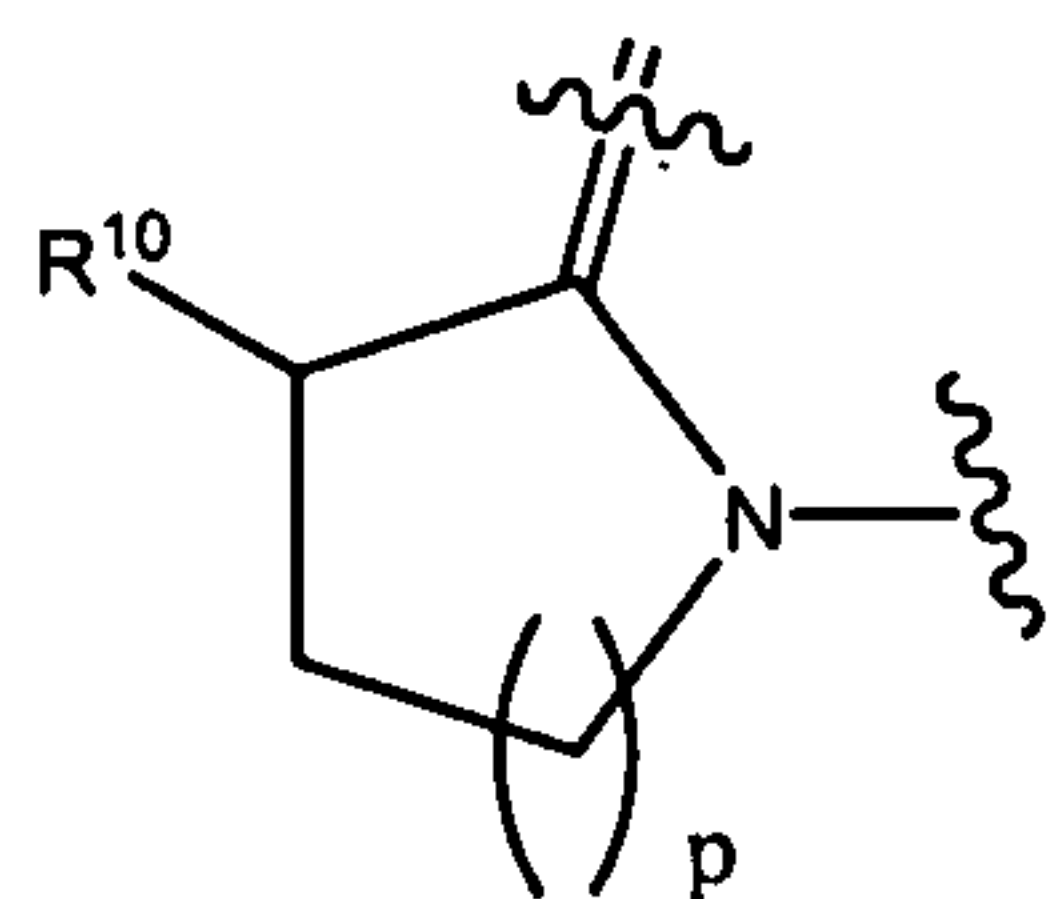
(iii) or R¹⁴ and R¹⁵ together with the nitrogen atom to which they are attached may combine to form a heterocyclyl ring optionally substituted with one or more R^x groups as allowed by valance;

R^a, R^b, R^c, R^d and R^{*} are each independently H or R^x

or R^a and R^b together with the carbon atom to which they are attached may combine to form a carbonyl group;

or R^b together with either R^c or R^* may combine to form a bond;

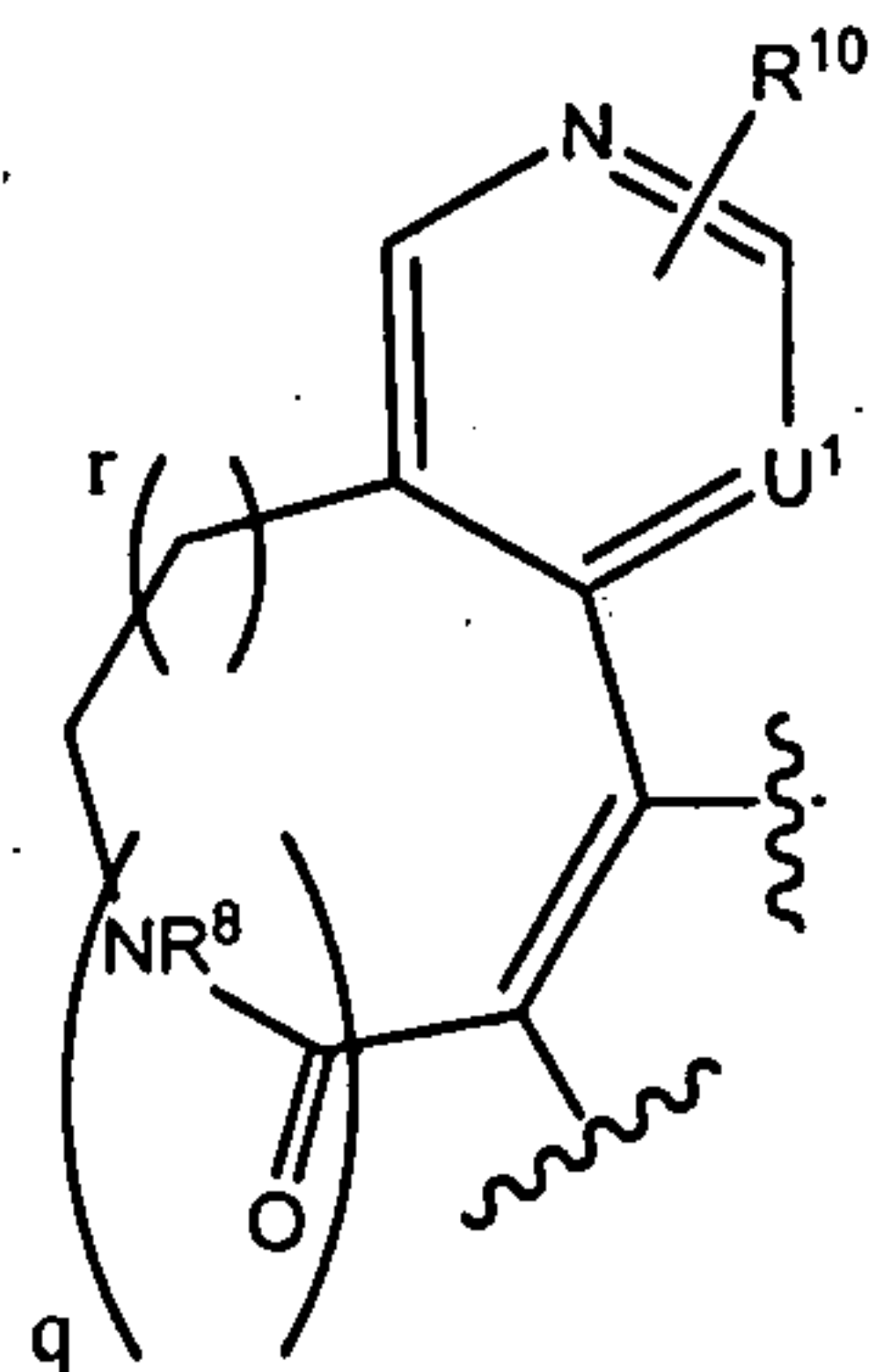
or R^a and R^e , together with the atoms to which they are respectively attached, may combine to form



which may be optionally substituted with one or more R^x

groups as allowed by valance;

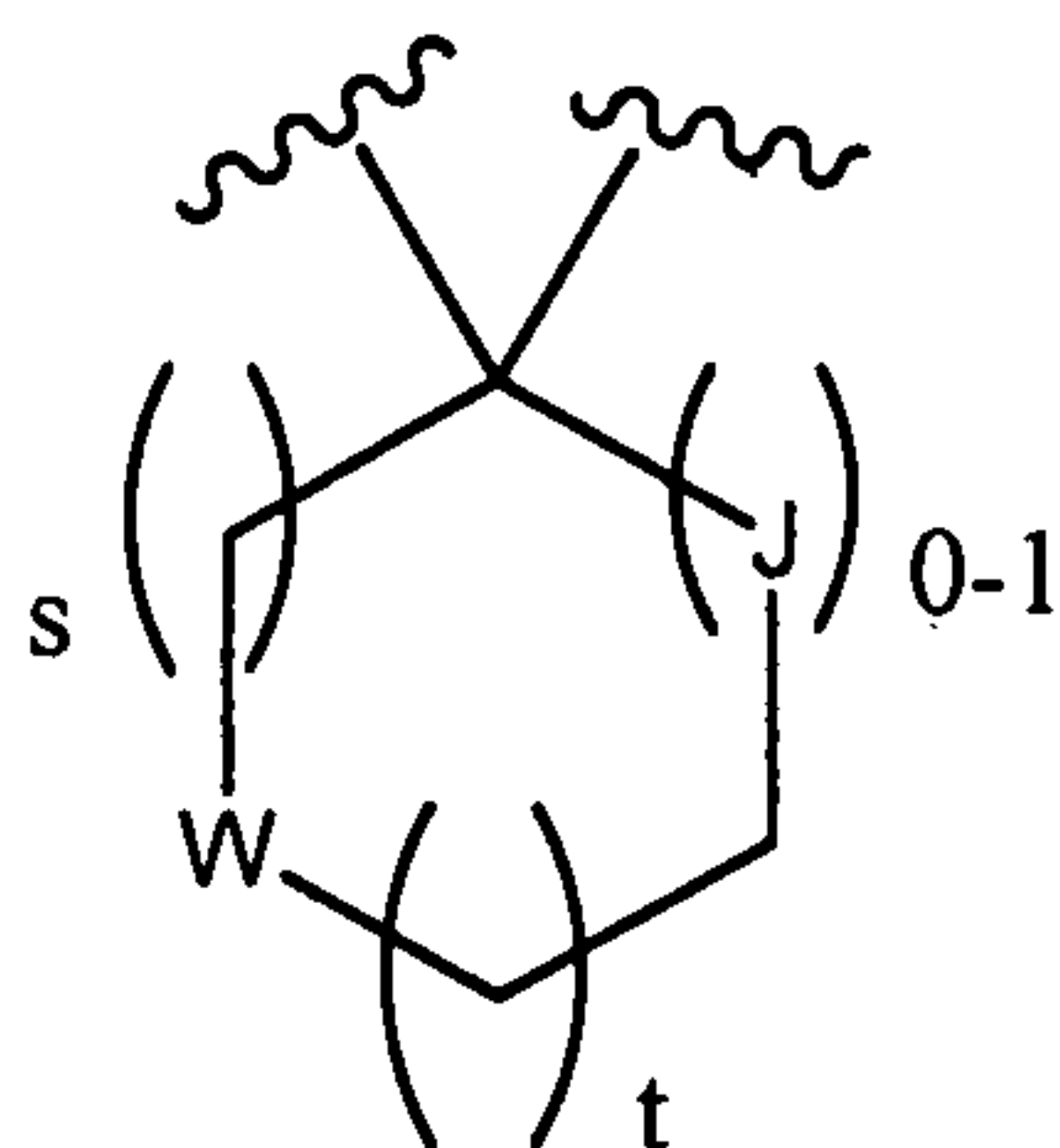
or R^a and R^{4*} , together with the atoms to which they are respectively attached, may combine to form



which may be optionally substituted with one or more R^x

groups as allowed by valance;

or R^c and R^d together with the carbon atom to which they are each attached may combine to form



which may be optionally substituted with one or more R^x groups as allowed by valance;

R^e is H, R^4 , or R^x ;

R^x is an optional substituent independently selected at each occurrence from halo, cyano, nitro, oxo, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl,

arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, $-(\text{alkylene})_q-\text{OR}^{7+}$,
 $-(\text{alkylene})_q-\text{S(O)}_v\text{R}^{7+}$, $-(\text{alkylene})_q-\text{NR}^{8+}\text{R}^{9+}$, $-(\text{alkylene})_q-\text{C(=O)}\text{R}^{7+}$, $-(\text{alkylene})_q-\text{C(=S)}\text{R}^{7+}$,
 $-(\text{alkylene})_q-\text{C(=O)}\text{OR}^{7+}$, $-(\text{alkylene})_q-\text{OC(=O)}\text{R}^{7+}$, $-(\text{alkylene})_q-\text{C(=S)}\text{OR}^{7+}$,
 $-(\text{alkylene})_q-\text{C(=O)}\text{NR}^{8+}\text{R}^{9+}$, $-(\text{alkylene})_q-\text{C(=S)}\text{NR}^{8+}\text{R}^{9+}$, $-(\text{alkylene})_q-\text{N(R}^{15})\text{C(=O)}\text{NR}^{8+}\text{R}^{9+}$,
 $-(\text{alkylene})_q-\text{N(R}^{15})\text{C(=S)}\text{NR}^{8+}\text{R}^{9+}$, $-(\text{alkylene})_q-\text{N(R}^{15})\text{C(=O)}\text{R}^{7+}$,
 $-(\text{alkylene})_q-\text{N(R}^{15})\text{C(=S)}\text{R}^{7+}$, $-(\text{alkylene})_q-\text{OC(=O)}\text{NR}^{8+}\text{R}^{9+}$, $-(\text{alkylene})_q-\text{OC(=S)}\text{NR}^{8+}\text{R}^{9+}$,
 $-(\text{alkylene})_q-\text{SO}_2\text{NR}^{8+}\text{R}^{9+}$, $-(\text{alkylene})_q-\text{N(R}^{15})\text{SO}_2\text{R}^{7+}$, $-(\text{alkylene})_q-\text{N(R}^{15})\text{SO}_2\text{NR}^{8+}\text{R}^{9+}$,
 $-(\text{alkylene})_q-\text{N(R}^{15})\text{C(=O)}\text{OR}^{7+}$, $-(\text{alkylene})_q-\text{N(R}^{15})\text{C(=S)}\text{OR}^{7+}$, or $-(\text{alkylene})_q-\text{N(R}^{15})\text{SO}_2\text{R}^{7+}$;

wherein alkylene, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkyl groups may be further independently substituted with one or more $-(\text{alkylene})_q-\text{CN}$,
 $-(\text{alkylene})_q-\text{OR}^{7+}$, $-(\text{alkylene})_q-\text{S(O)}_n\text{R}^{7+}$, $-(\text{alkylene})_q-\text{NR}^{8+}\text{R}^{9+}$, $-(\text{alkylene})_q-\text{C(=O)}\text{R}^{7+}$,
 $-(\text{alkylene})_q-\text{C(=S)}\text{R}^{7+}$, $-(\text{alkylene})_q-\text{C(=O)}\text{OR}^{7+}$, $-(\text{alkylene})_q-\text{OC(=O)}\text{R}^{7+}$,
 $-(\text{alkylene})_q-\text{C(=S)}\text{OR}^{7+}$, $-(\text{alkylene})_q-\text{C(=O)}\text{NR}^{8+}\text{R}^{9+}$, $-(\text{alkylene})_q-\text{C(=S)}\text{NR}^{8+}\text{R}^{9+}$,
 $-(\text{alkylene})_q-\text{N(R}^{15})\text{C(=O)}\text{NR}^{8+}\text{R}^{9+}$, $-(\text{alkylene})_q-\text{N(R}^{15})\text{C(=S)}\text{NR}^{8+}\text{R}^{9+}$,
 $-(\text{alkylene})_q-\text{N(R}^{15})\text{C(=O)}\text{R}^{7+}$, $-(\text{alkylene})_q-\text{N(R}^{15})\text{C(=S)}\text{R}^{7+}$, $-(\text{alkylene})_q-\text{OC(=O)}\text{NR}^{8+}\text{R}^{9+}$,
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 $-(\text{alkylene})_q-\text{N(R}^{15})\text{SO}_2\text{NR}^{8+}\text{R}^{9+}$, $-(\text{alkylene})_q-\text{N(R}^{15})\text{C(=O)}\text{OR}^{7+}$,
 $-(\text{alkylene})_q-\text{N(R}^{15})\text{C(=S)}\text{OR}^{7+}$, or $-(\text{alkylene})_q-\text{N(R}^{15})\text{SO}_2\text{R}^{7+}$;

J and W are independently $-\text{CH}_2-$, $-\text{N(R}^8)-$, $-\text{O}-$, or $-\text{S(=O)}_v-$,

X is $-\text{O}-$ or $-\text{S(=O)}_v-$

U and U^1 are independently CH or N

k at each occurrence is independently 0, 1, 2 or 3;

m is 1, 2 or 3

n is 0, 1 or 2

p is 1, 2 or 3

q at each occurrence is independently 0 or 1

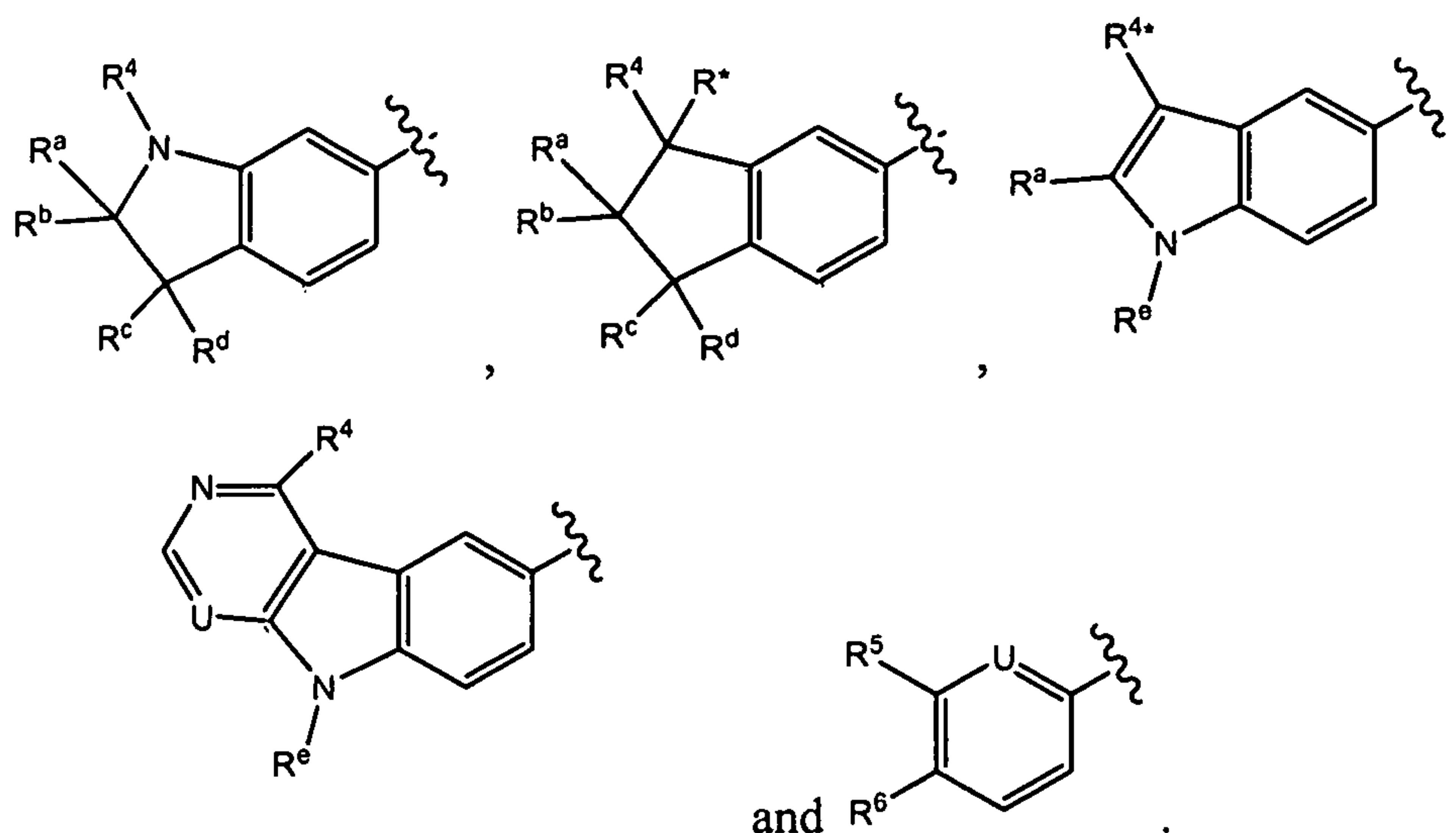
r is 0, 1, 2 or 3;

s is 1, 2 or 3

t is 0, 1 or 2

v at each occurrence is independently 0, 1 or 2

2. A compound of claim 1 wherein R^1 is selected from

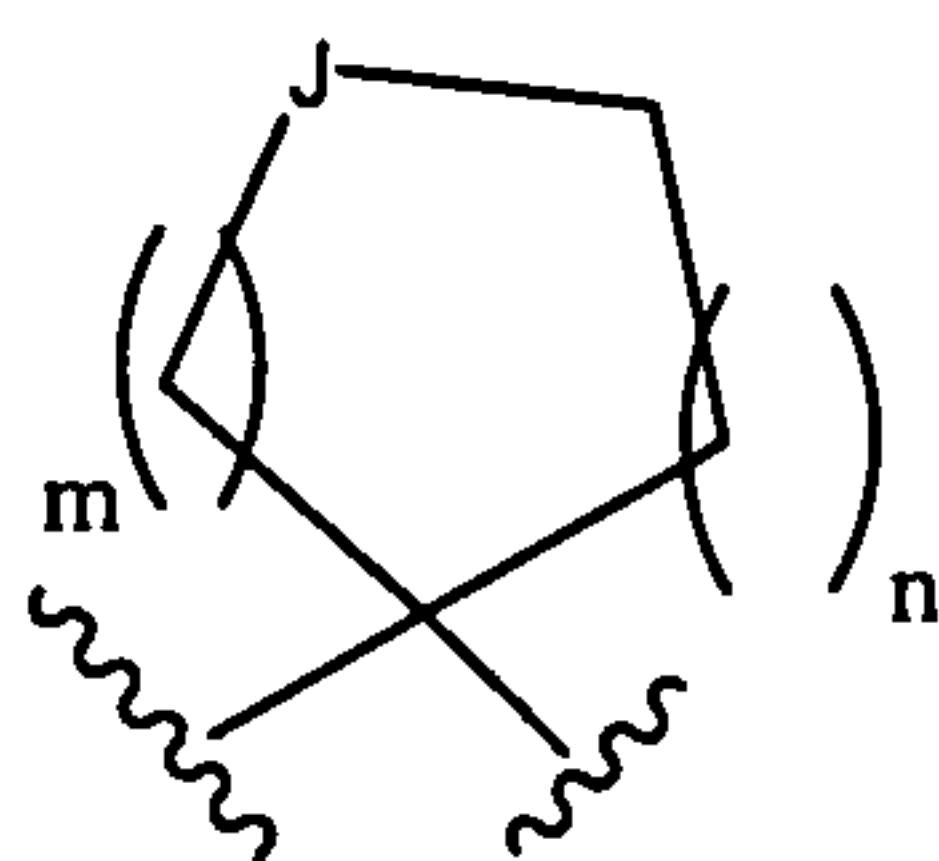


3. A compound of claim 1 wherein

R^2 is alkyl; and

R^3 is pyrrolyl, furanyl, thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, phenyl, pyridyl, pyrimidyl, pyrazinyl, or oxadiazolyl any of which may be optionally substituted with one or more R^x as allowed by valance.

or R^2 and R^3 together with the carbon atom to which they are attached may combine to form



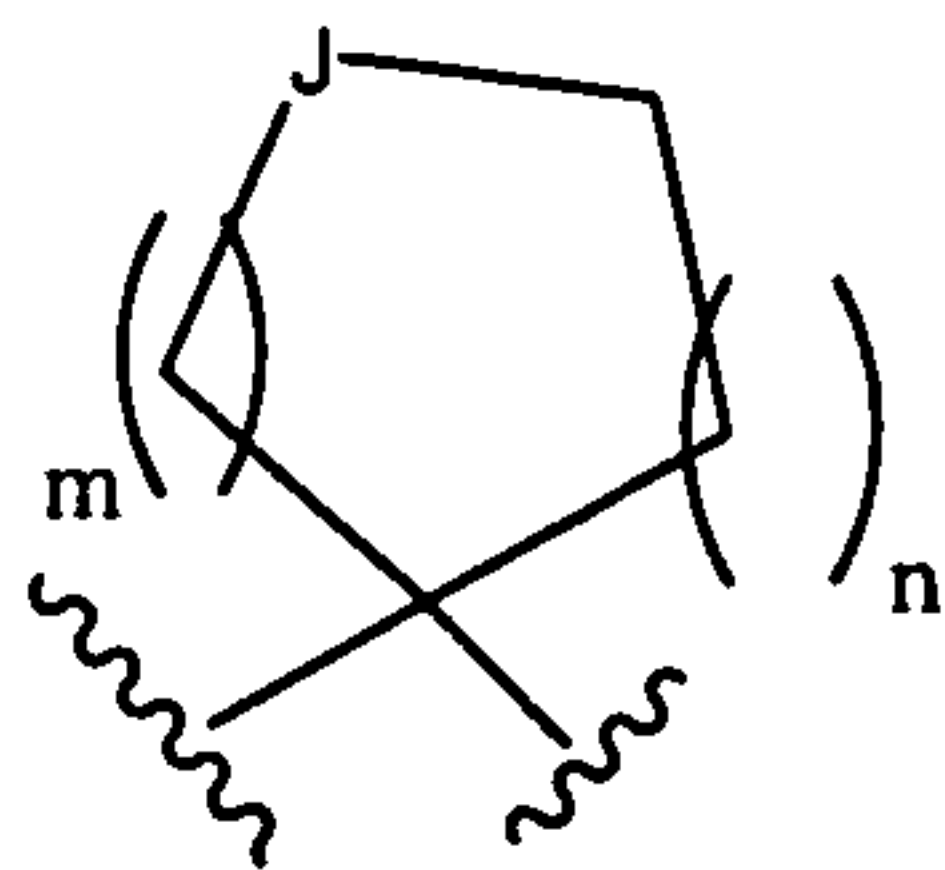
which may be optionally substituted with one or more R^x groups as allowed by valance;

4. A compound of claim 2 wherein

R^2 is alkyl; and

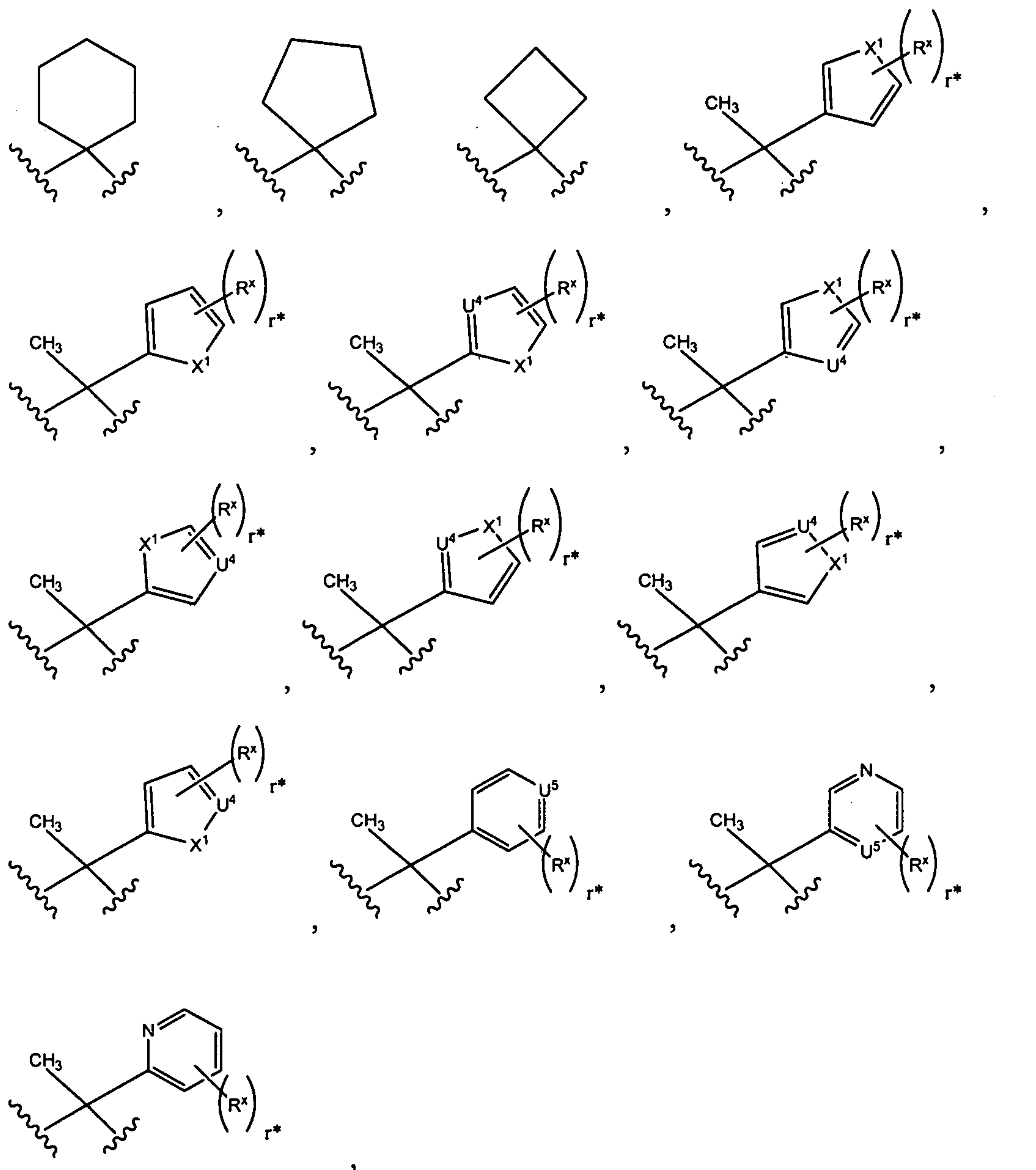
R^3 is pyrrolyl, furanyl, thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, phenyl, pyridyl, pyrimidyl, pyrazinyl, or oxadiazolyl any of which may be optionally substituted with one or more R^x as allowed by valance;

or R^2 and R^3 together with the carbon atom to which they are attached may combine to form



which may be optionally substituted with one or more R^x groups as allowed by valance;

5. A compound of claim 3 wherein R^2 , R^3 and the carbon atom to which they are attached are selected from

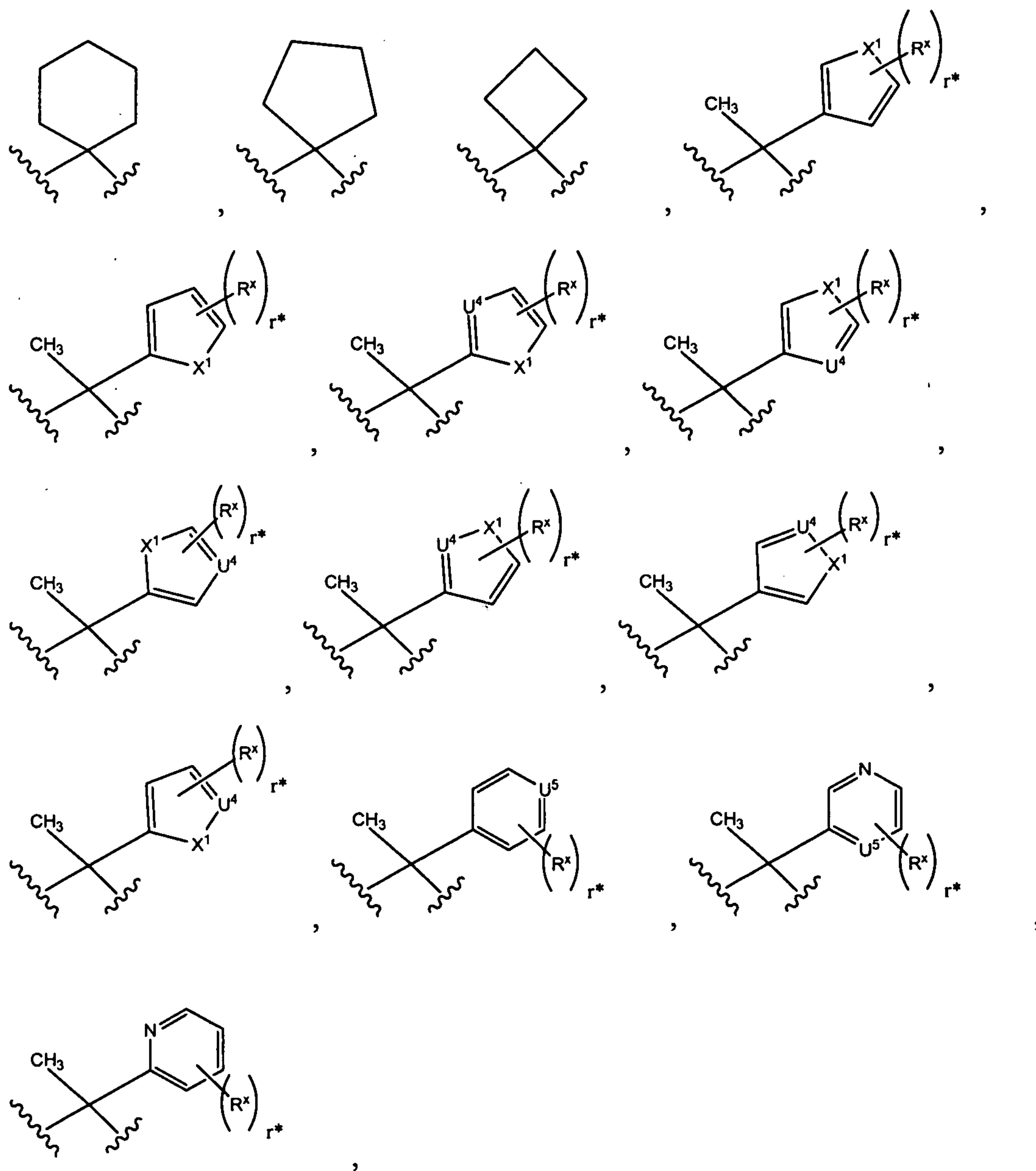


wherein

U^4 and U^5 are each independently N or CH

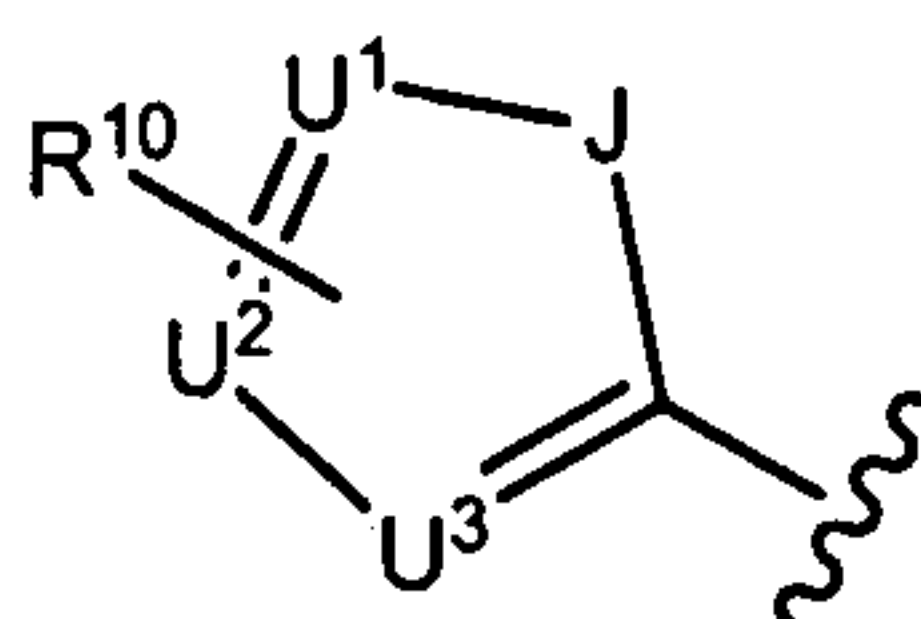
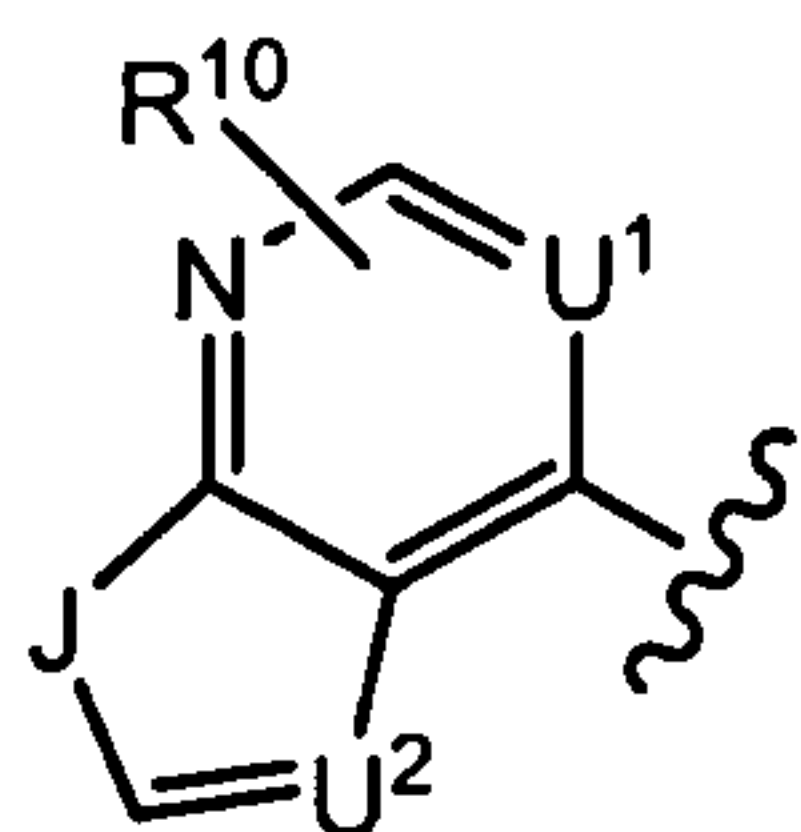
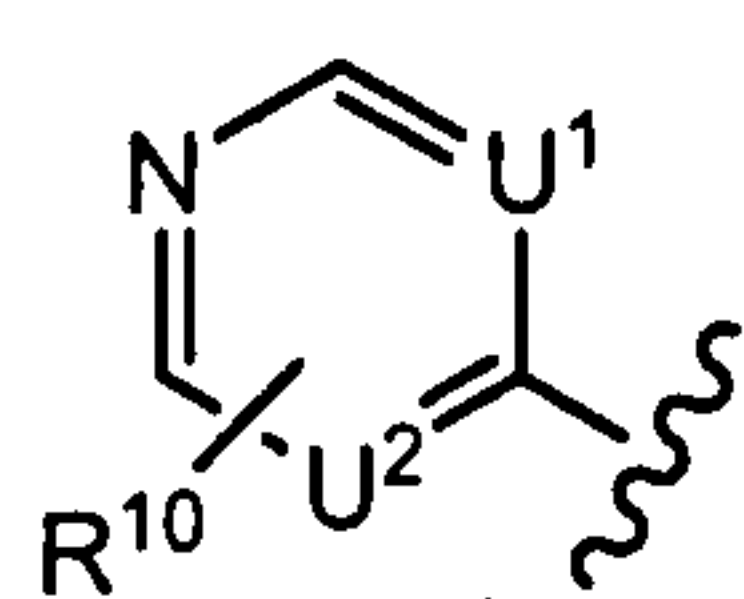
X^1 is NH, O or $S(O)_v$

6. A compound of claim 4 wherein R², R³ and the carbon atom to which they are attached are selected from



r^* is 0 or an integer up to three as allowed by valance.

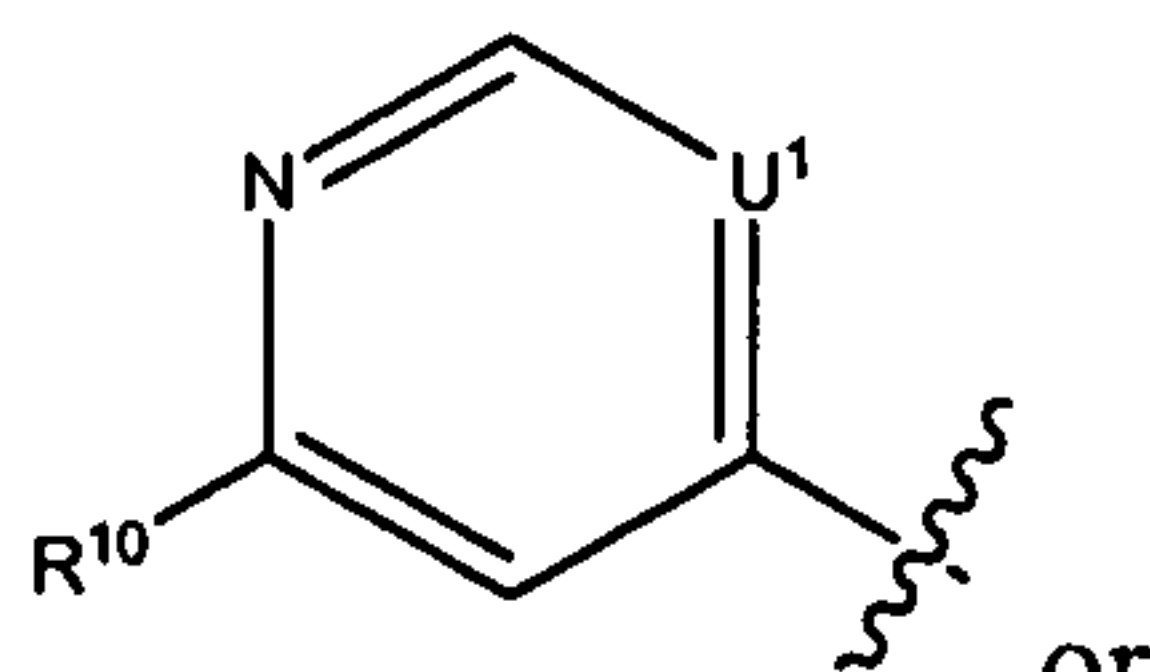
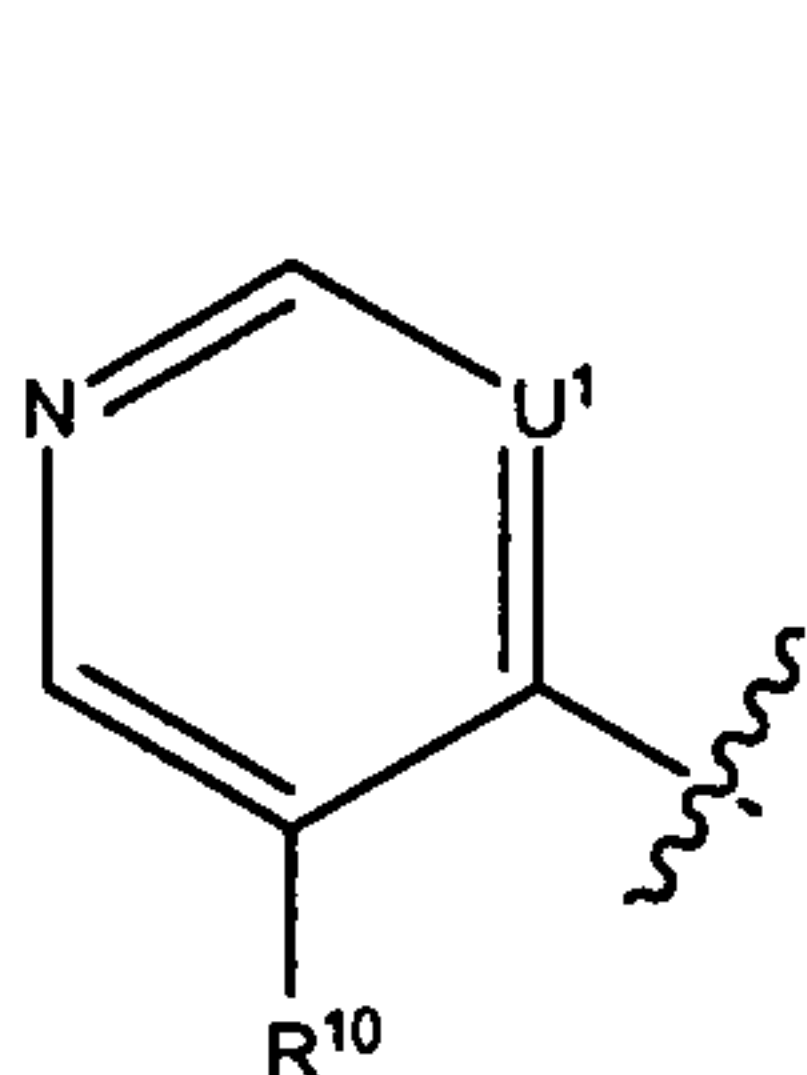
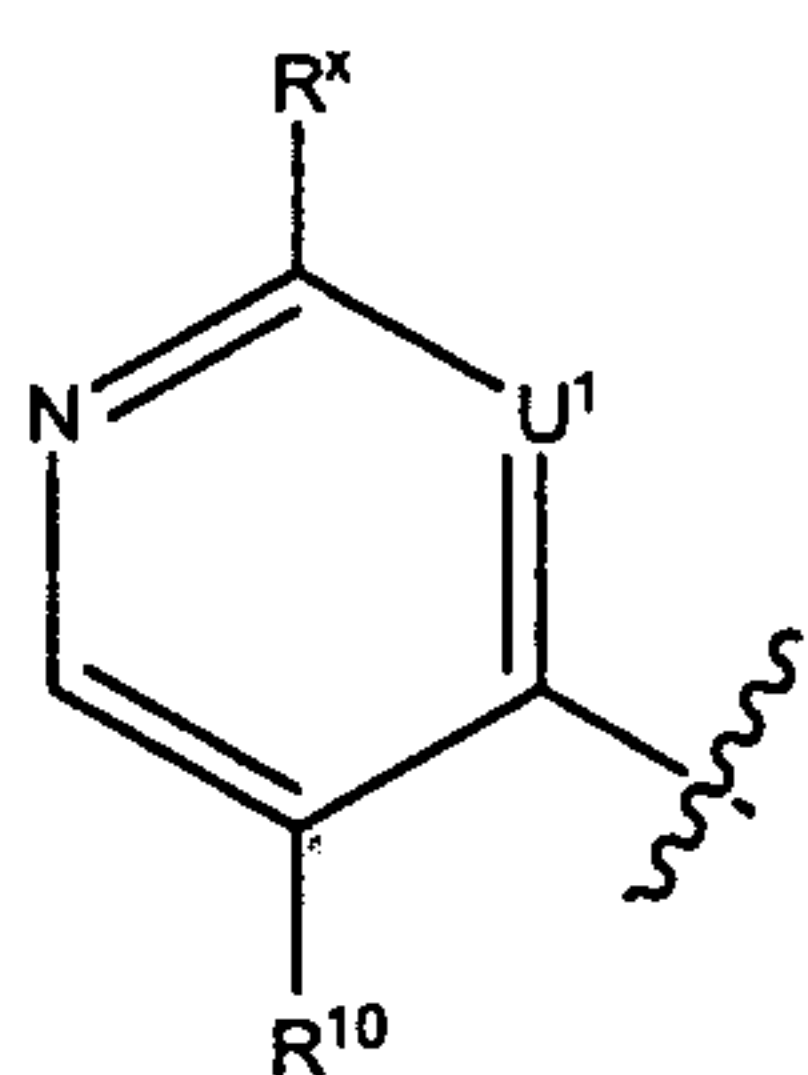
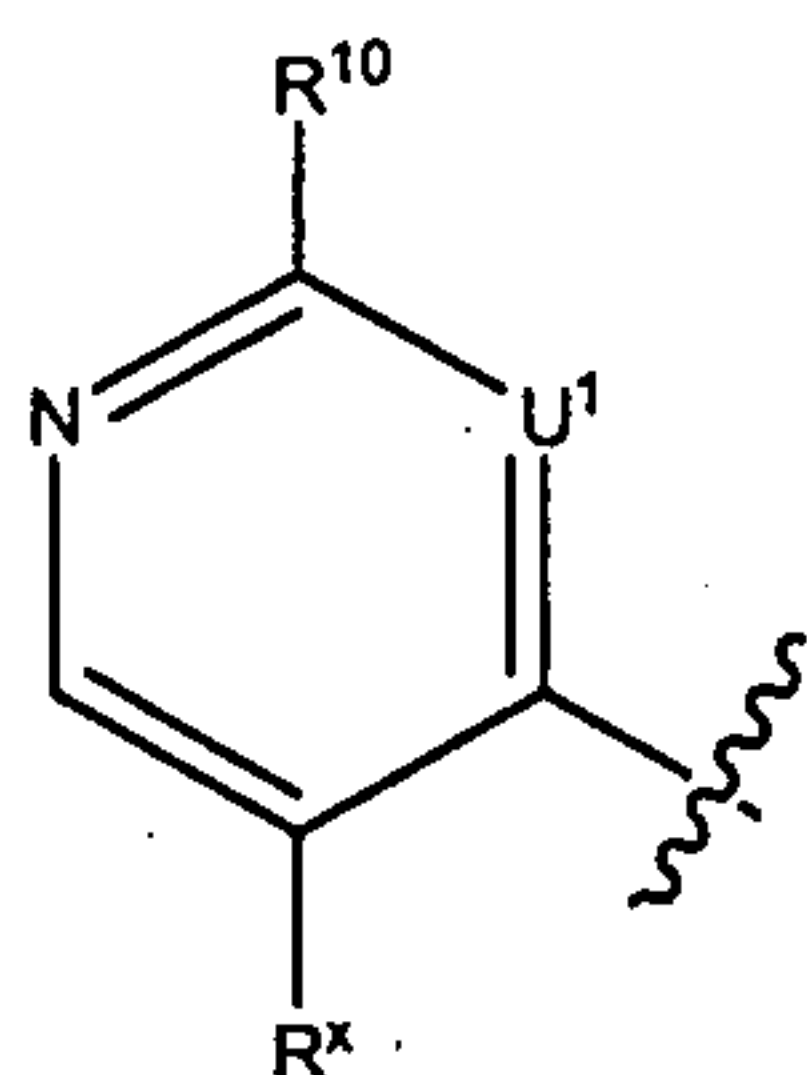
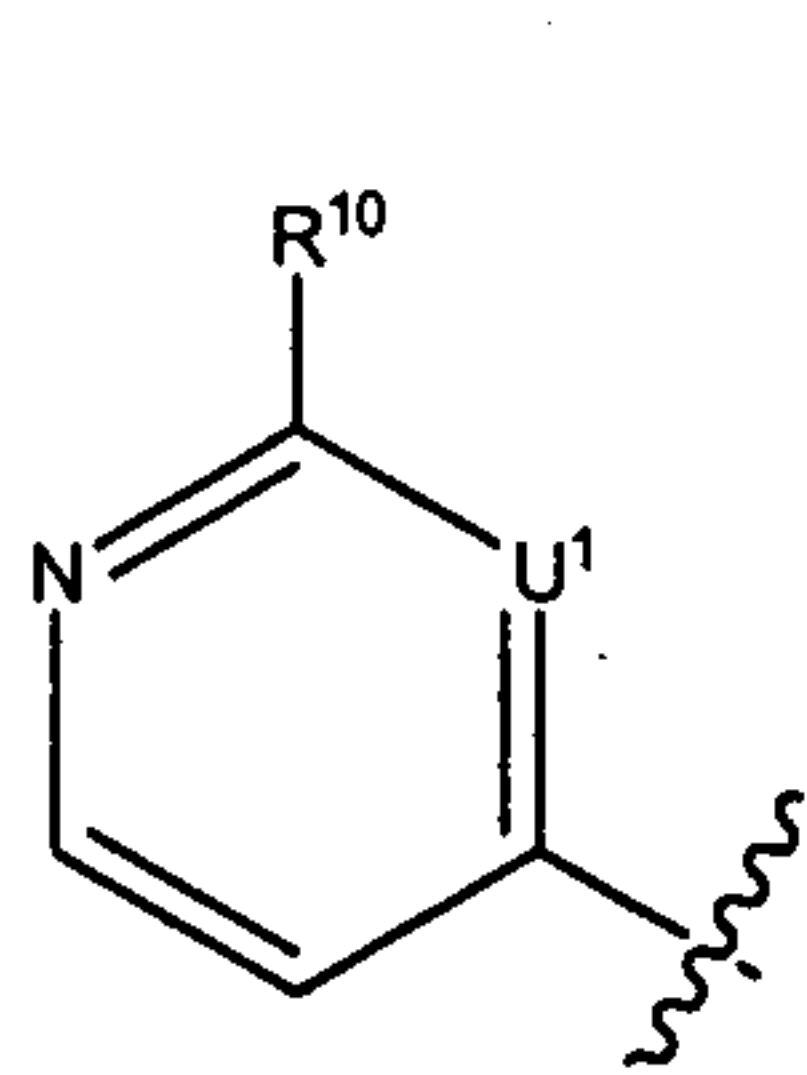
- 382 -



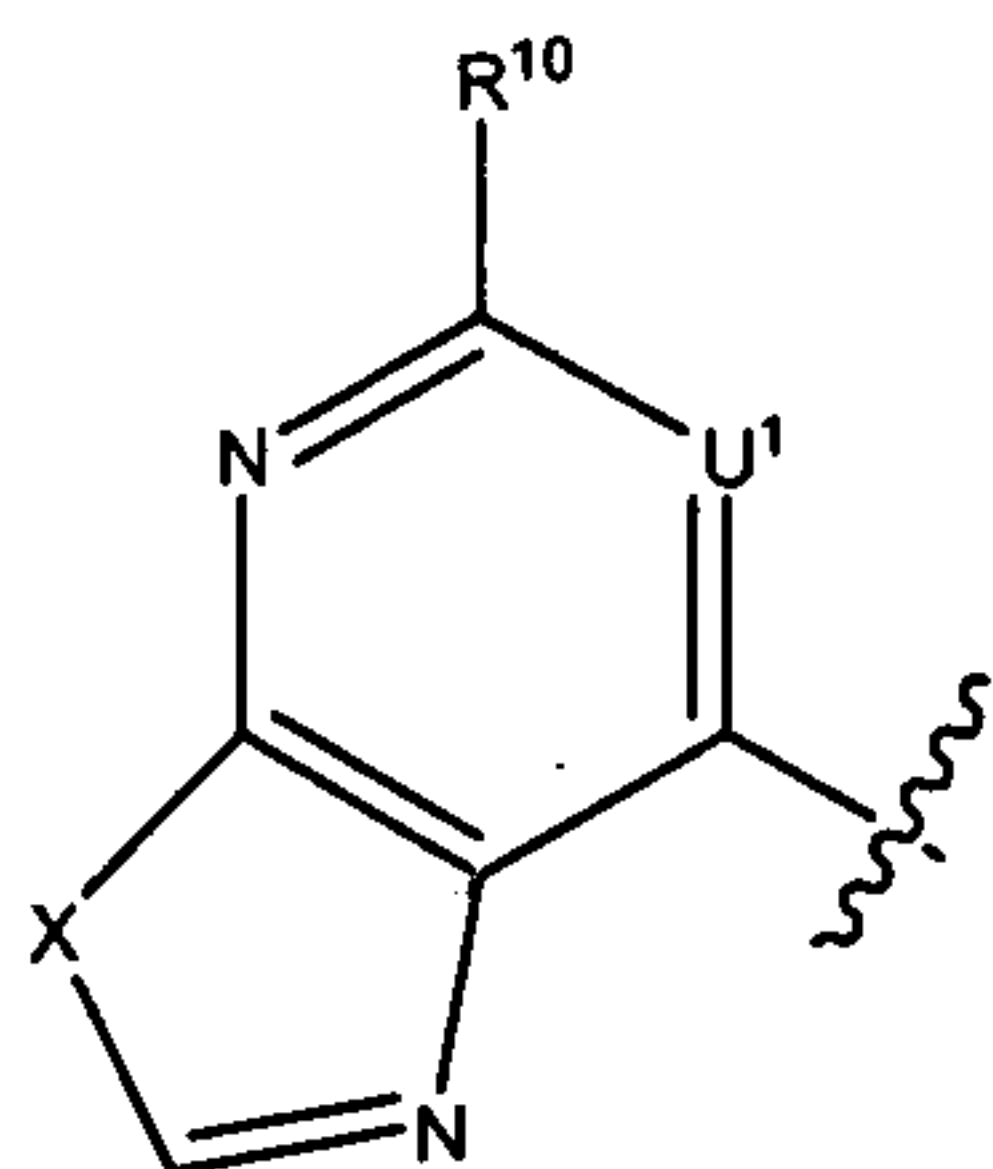
or $-C(=O)R^{7*}$,

any of which may be optionally substituted, as allowed by valance, with up to three R^x groups independently selected from halo, cyano, alkyl, haloalkyl, alkenyl, alkynyl, aryl, $-(alkylene)_q-NR^{8+}R^{9+}$, $-(alkylene)_q-C(=O)NR^{8+}R^{9+}$, $-(alkylene)_q-OR^{7+}$, wherein R^{10} is H, $-NR^{14}R^{15}$, or $-C(=O)NR^{14}R^{15}$; and U^1 , U^2 and U^3 are independently CH or N.

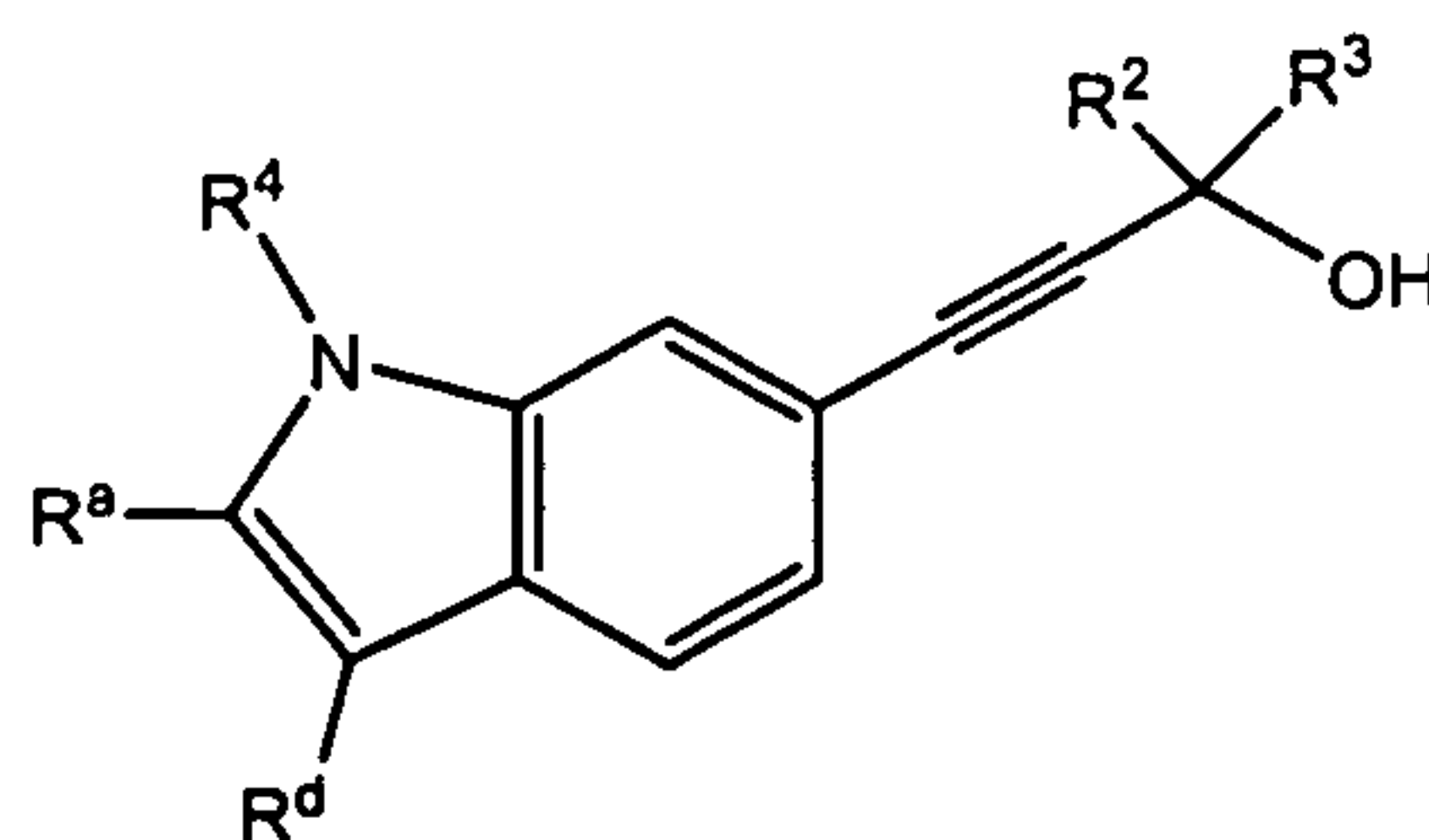
8. A compound of claim 7 wherein R^4 is



or

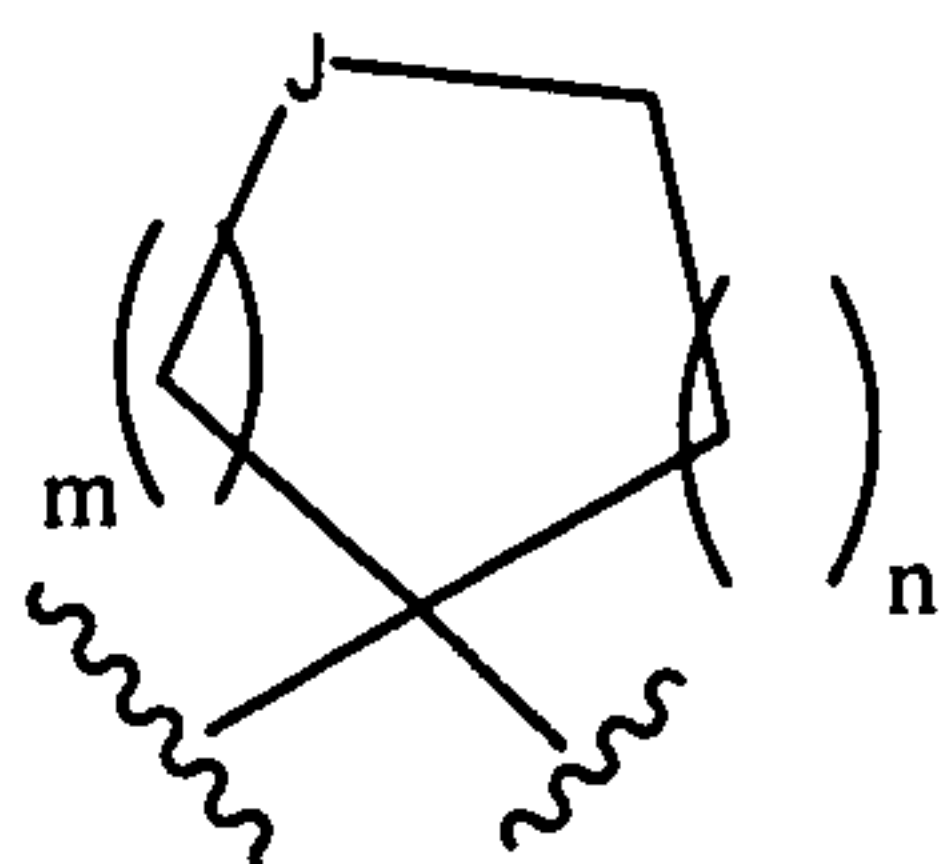


9. A compound of claim 1 having the following formula IA

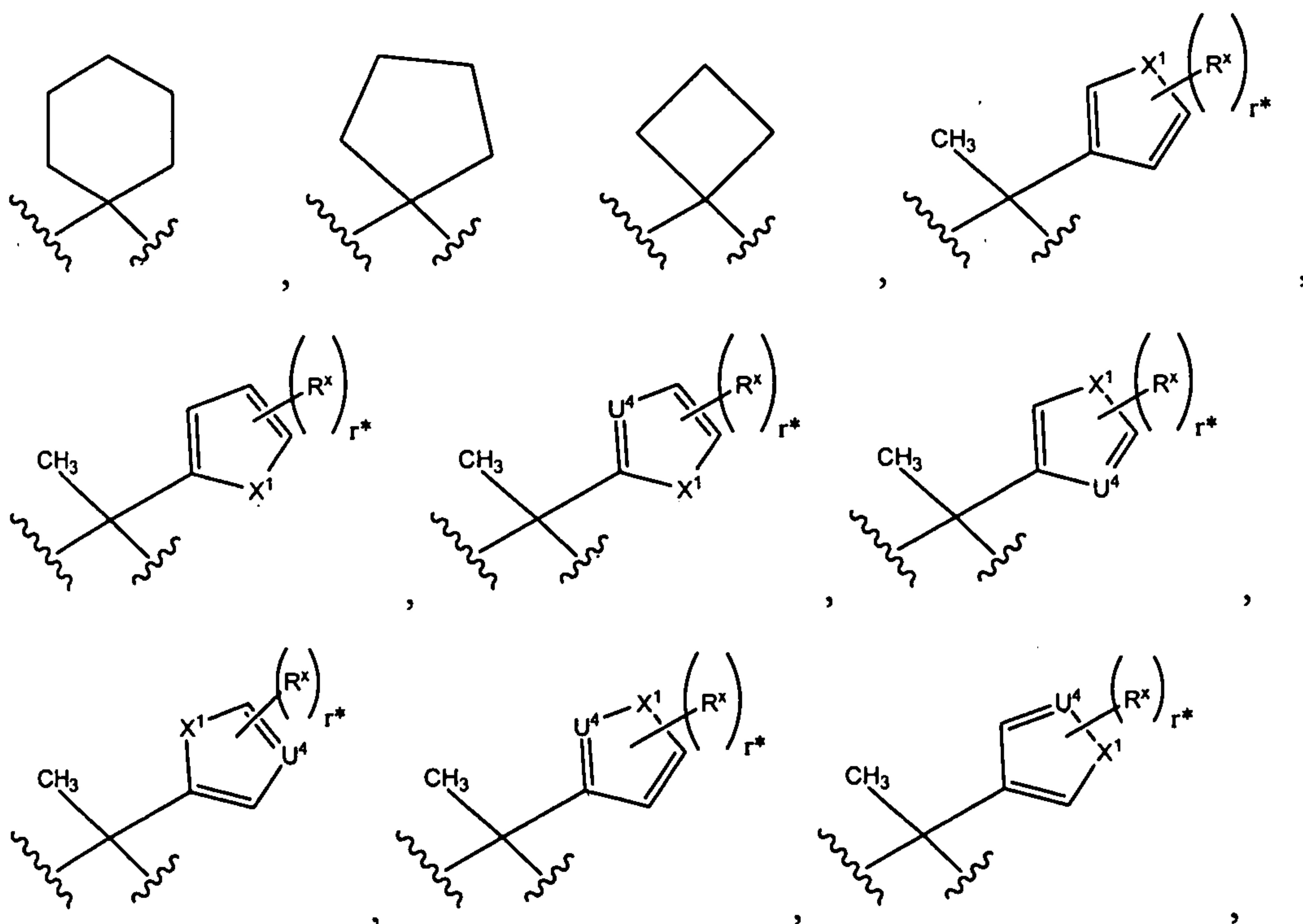


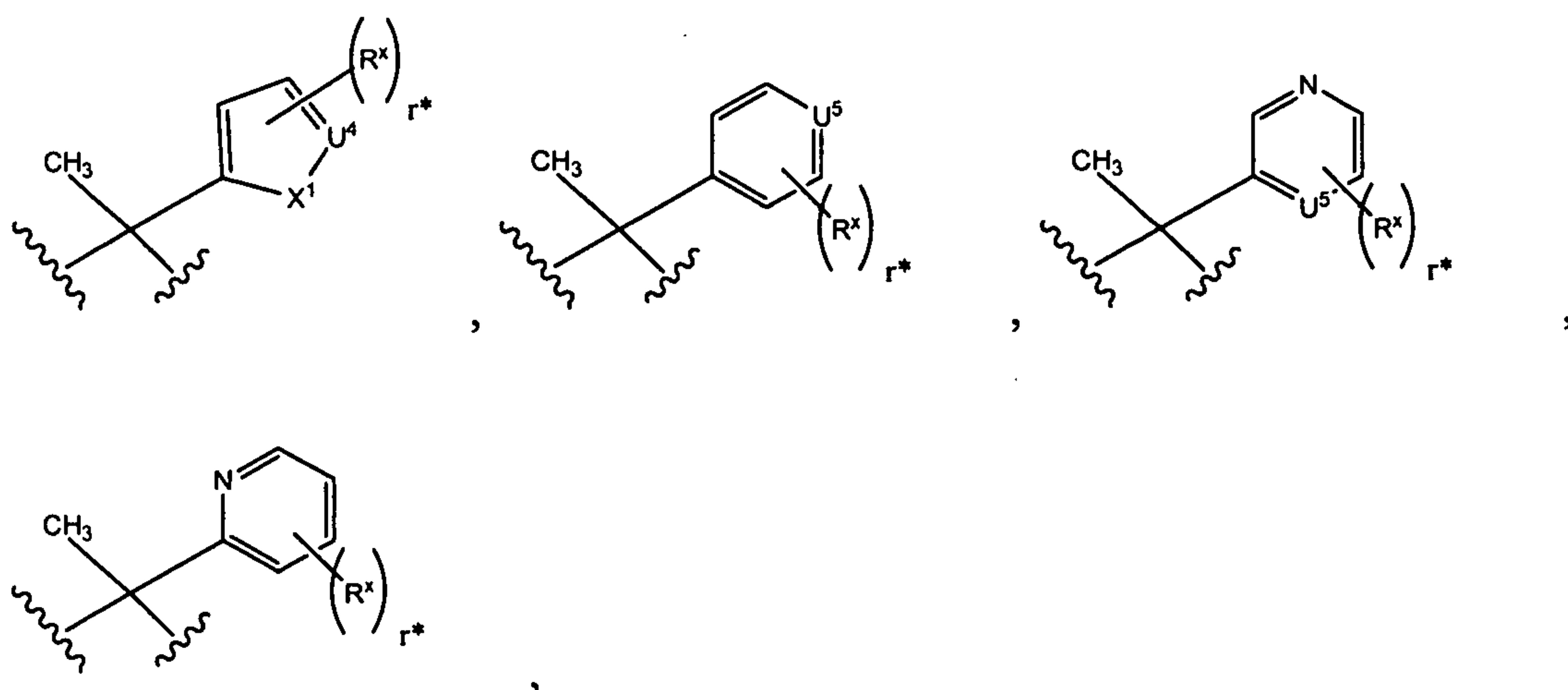
IA

R^3 is pyrrolyl, furanyl, thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, phenyl, pyridyl, pyrimidyl, pyrazinyl, or oxadiazolyl any of which may be optionally substituted with one or more R^x as allowed by valance;
or R^2 and R^3 together with the carbon atom to which they are attached may combine to form



11. A compound of claim 10 wherein R², R³ and the carbon atom to which they are attached are selected from





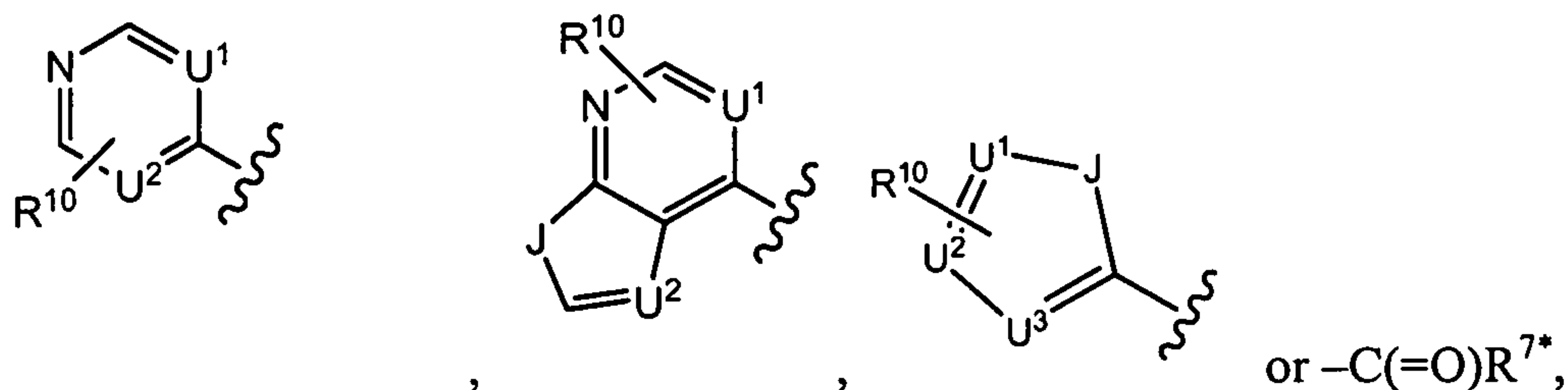
wherein

U^4 and U^5 are each independently N or CH

X^1 is NH, O or $S(O)_v$

r^* is 0 or an integer up to three as allowed by valance.

12. A compound according to any of claims 9, 10 or 11 wherein R^4 is



or $-C(=O)R^{7*}$,

any of which may be optionally substituted, as allowed by valance, with up to three R^x

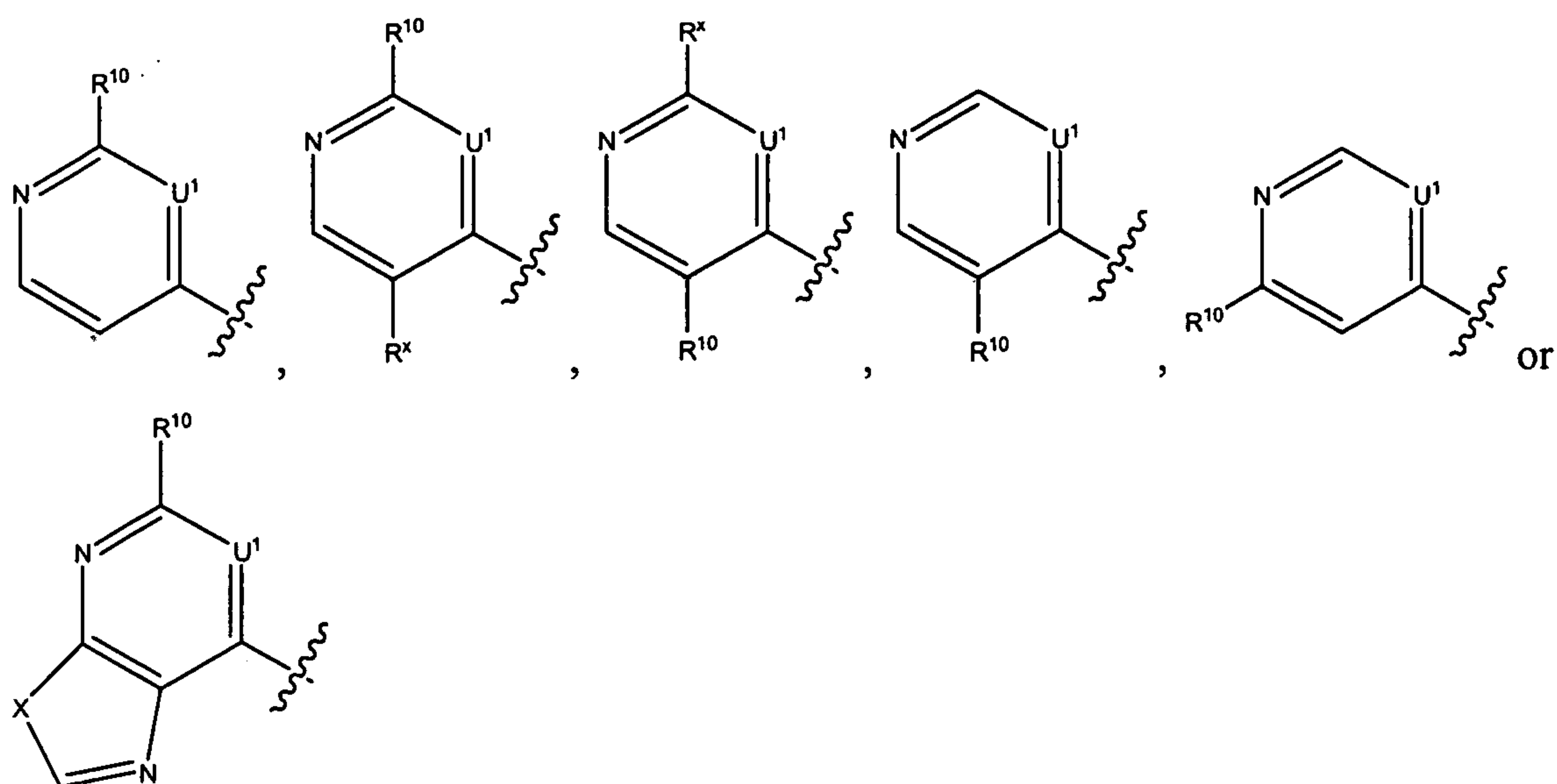
groups independently selected from halo, cyano, alkyl, haloalkyl, alkenyl, alkynyl,

aryl, $-(alkylene)_q-NR^{8+}R^{9+}$, $-(alkylene)_q-C(=O)NR^{8+}R^{9+}$, $-(alkylene)_q-OR^{7+}$,

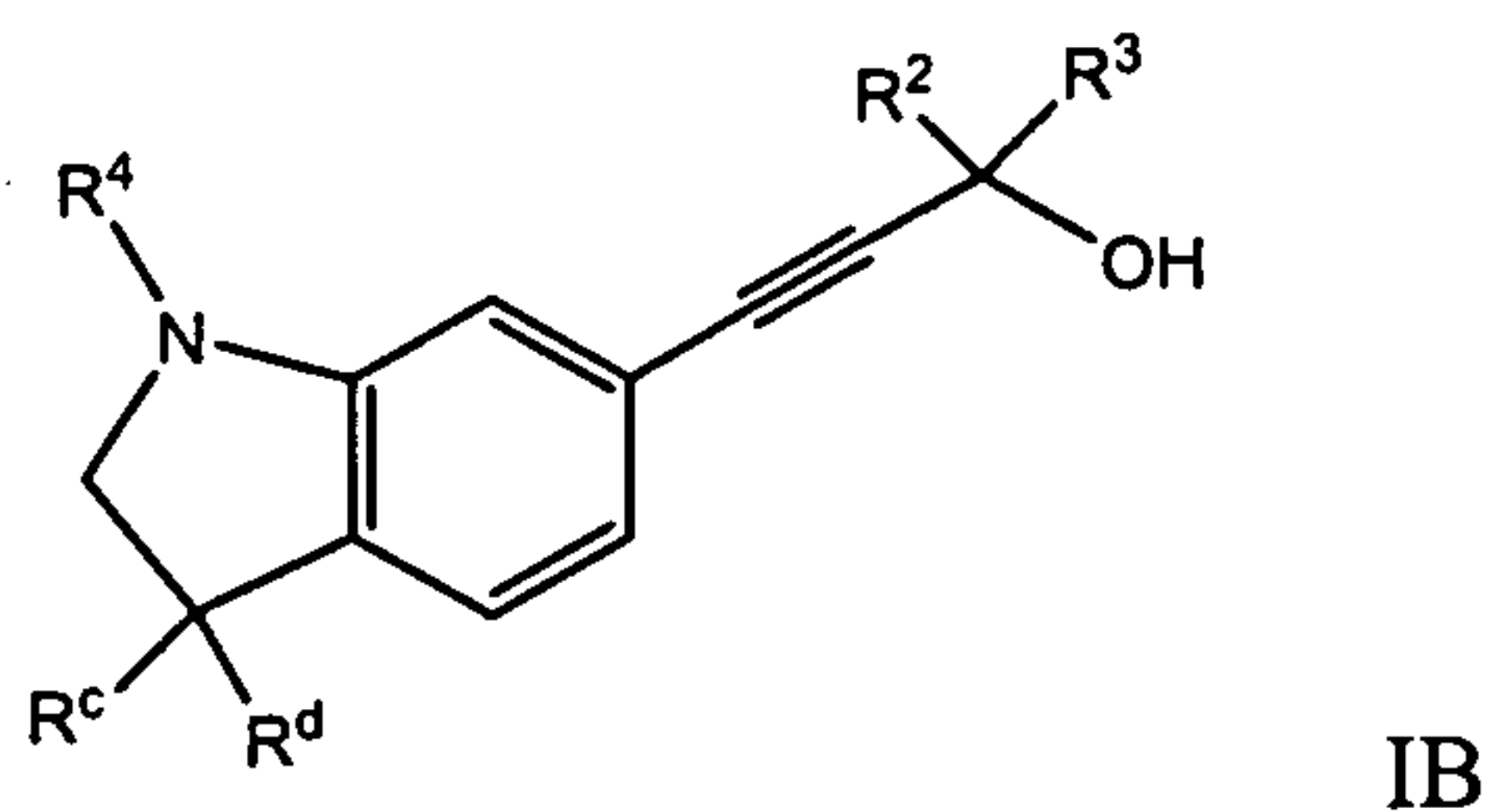
wherein R^{10} is H, $-NR^{14}R^{15}$, or $-C(=O)NR^{14}R^{15}$; and

U^1 , U^2 and U^3 are independently CH or N.

13. A compound of claim 12 wherein R^4 is



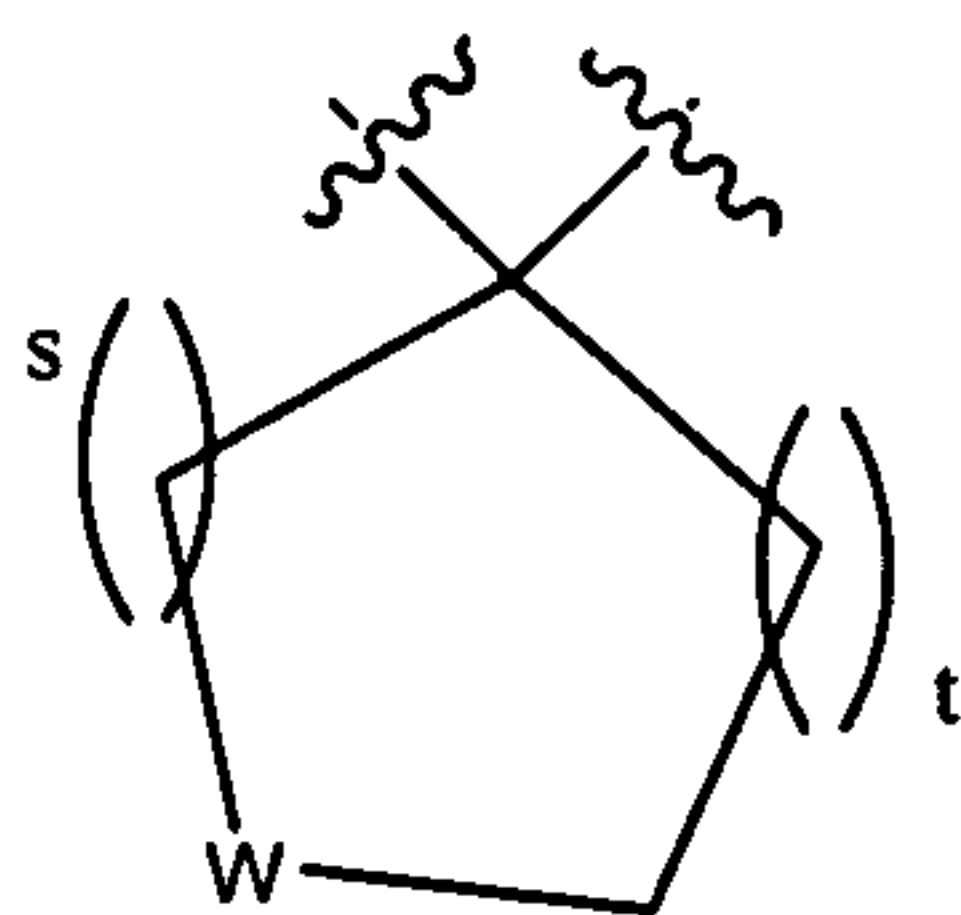
14. A compound of claim 1 having the following formula IB



wherein

R^c and R^d are independently hydrogen, alkyl, (hydroxy)alkyl, (alkoxy)alkyl and ((alkoxy)alkoxy)alkyl;

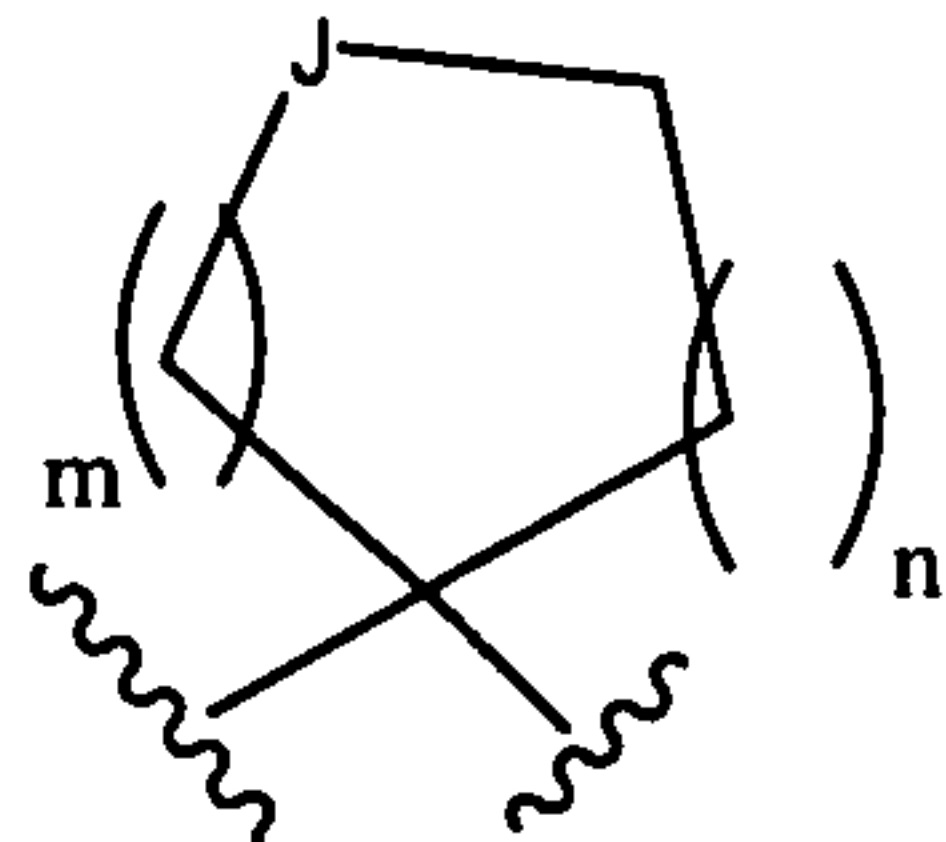
or R^c and R^d together with the carbon atom to which they are each attached may combine to form



which may be optionally substituted with one or more R^x groups as allowed by valance;

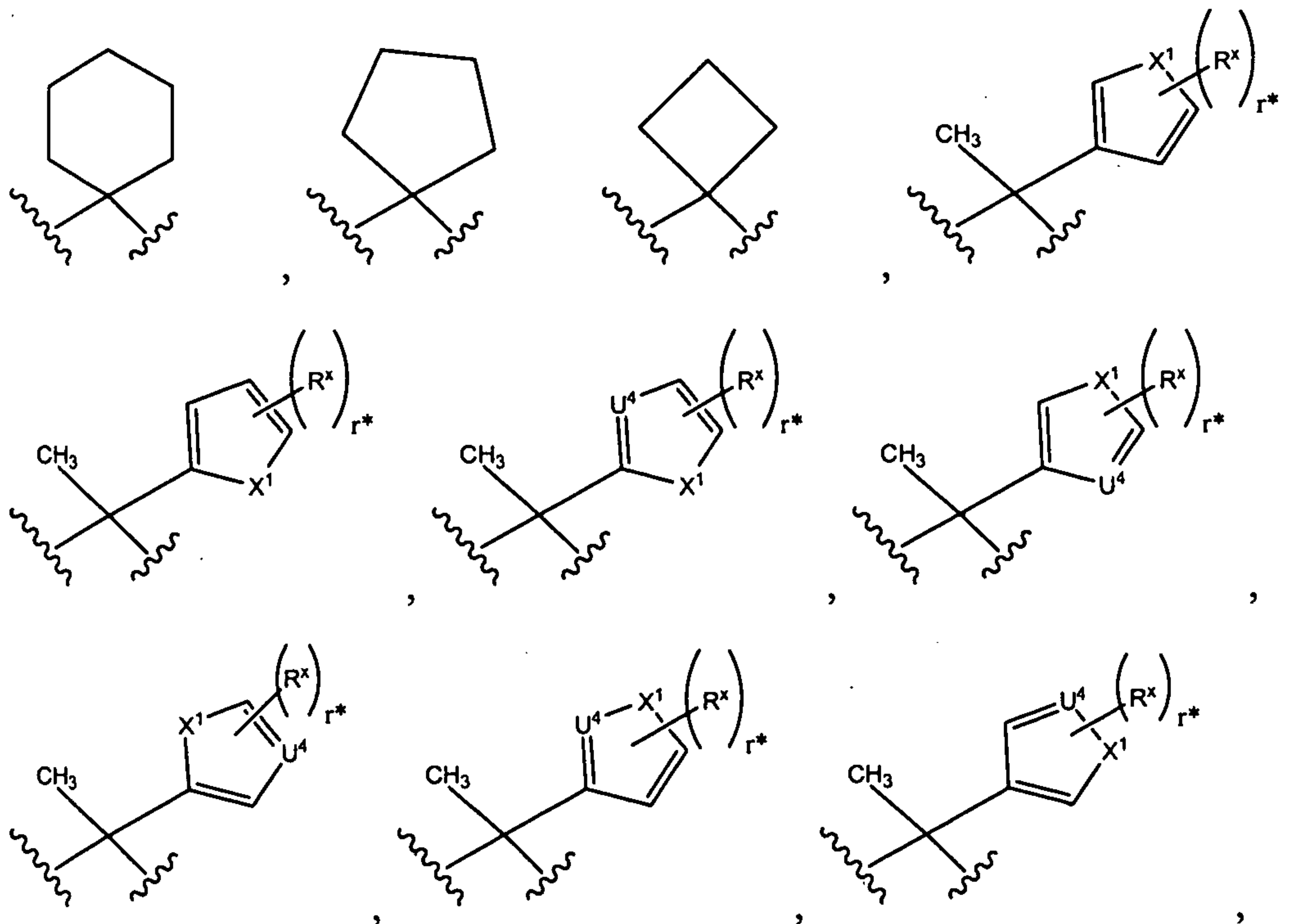
15. A compound of claim 14 wherein R² is alkyl; and

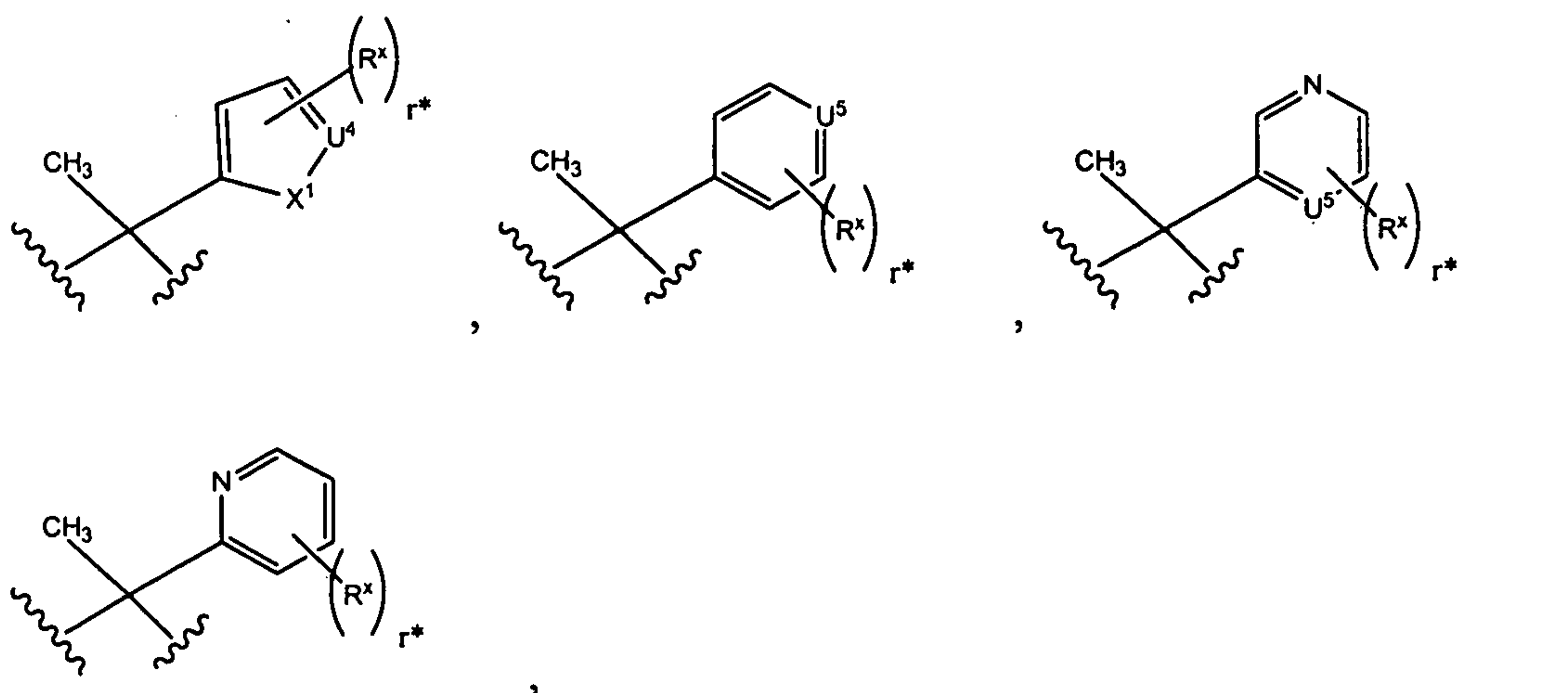
R^3 is pyrrolyl, furanyl, thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, phenyl, pyridyl, pyrimidyl, pyrazinyl, or oxadiazolyl any of which may be optionally substituted with one or more R^x as allowed by valance;
or R^2 and R^3 together with the carbon atom to which they are attached may combine to form



which may be optionally substituted with one or more R^x groups as allowed by valance;

16. A compound of claim 15 wherein R^2 , R^3 and the carbon atom to which they are attached are selected from





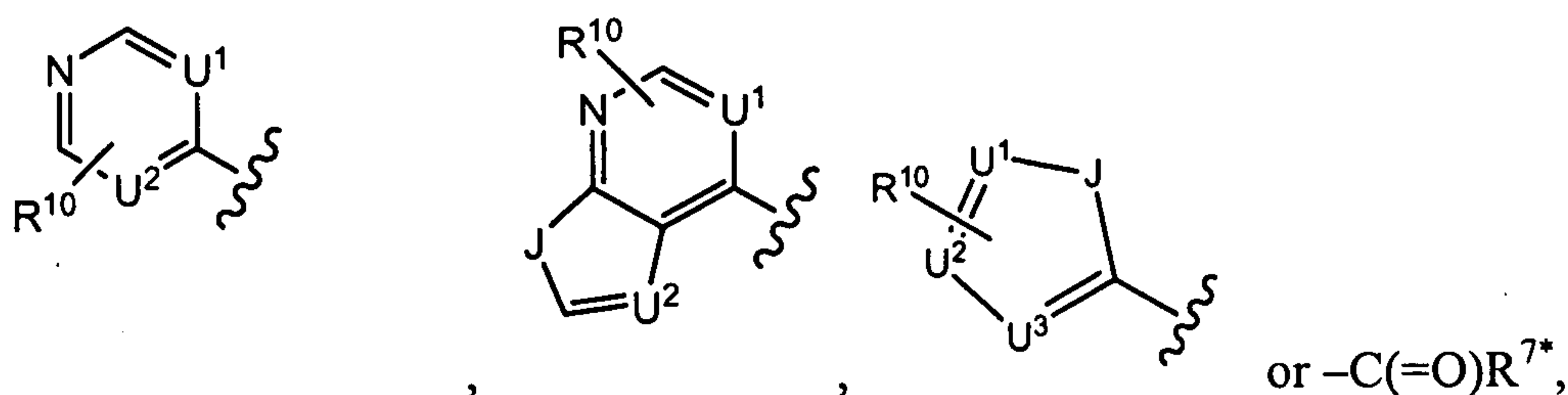
wherein

U^4 and U^5 are each independently N or CH

X^1 is NH, O or $S(O)_v$

r^* is 0 or an integer up to three as allowed by valance.

17. A compound according to any of claims 14, 15 or 16 wherein R^4 is

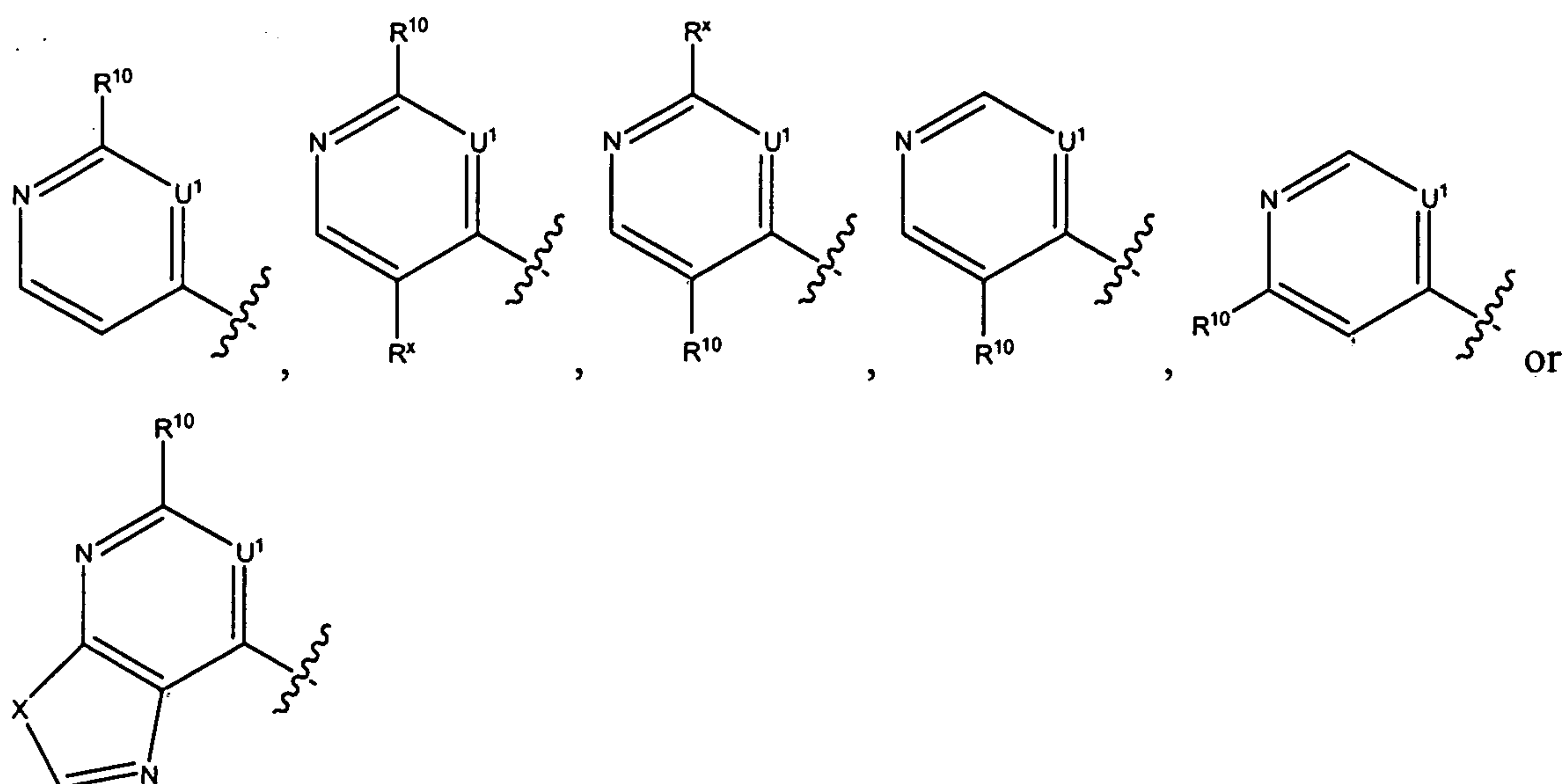


any of which may be optionally substituted, as allowed by valance, with up to three R^x groups independently selected from halo, cyano, alkyl, haloalkyl, alkenyl, alkynyl, aryl, $-(alkylene)_q-NR^{8+}R^{9+}$, $-(alkylene)_q-C(=O)NR^{8+}R^{9+}$, $-(alkylene)_q-OR^{7+}$,

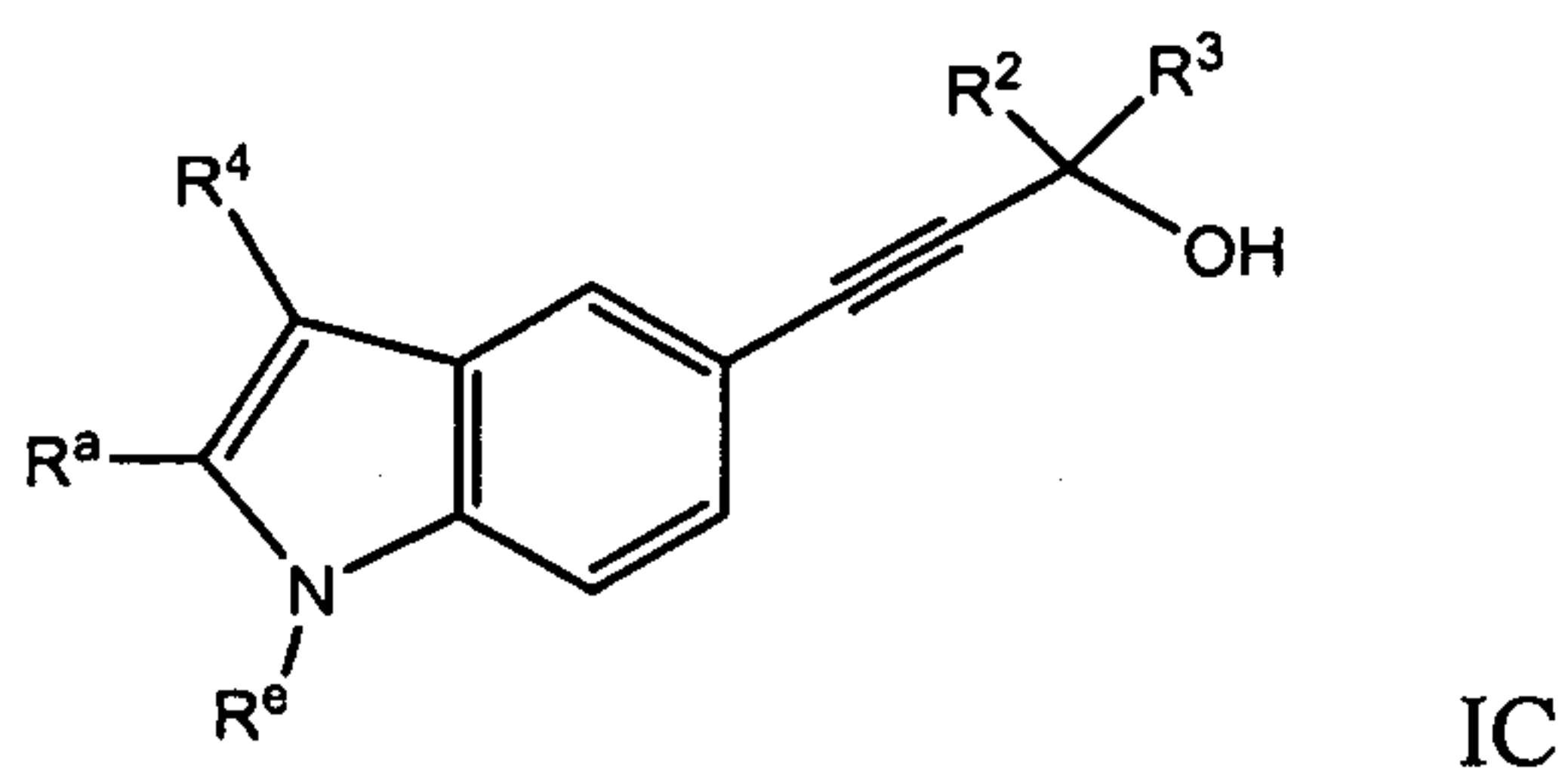
wherein R^{10} is H, $-NR^{14}R^{15}$, or $-C(=O)NR^{14}R^{15}$; and

U^1 , U^2 and U^3 are independently CH or N.

18. A compound of claim 17 wherein R^4 is



19. A compound of claim 1 having the following formula IC

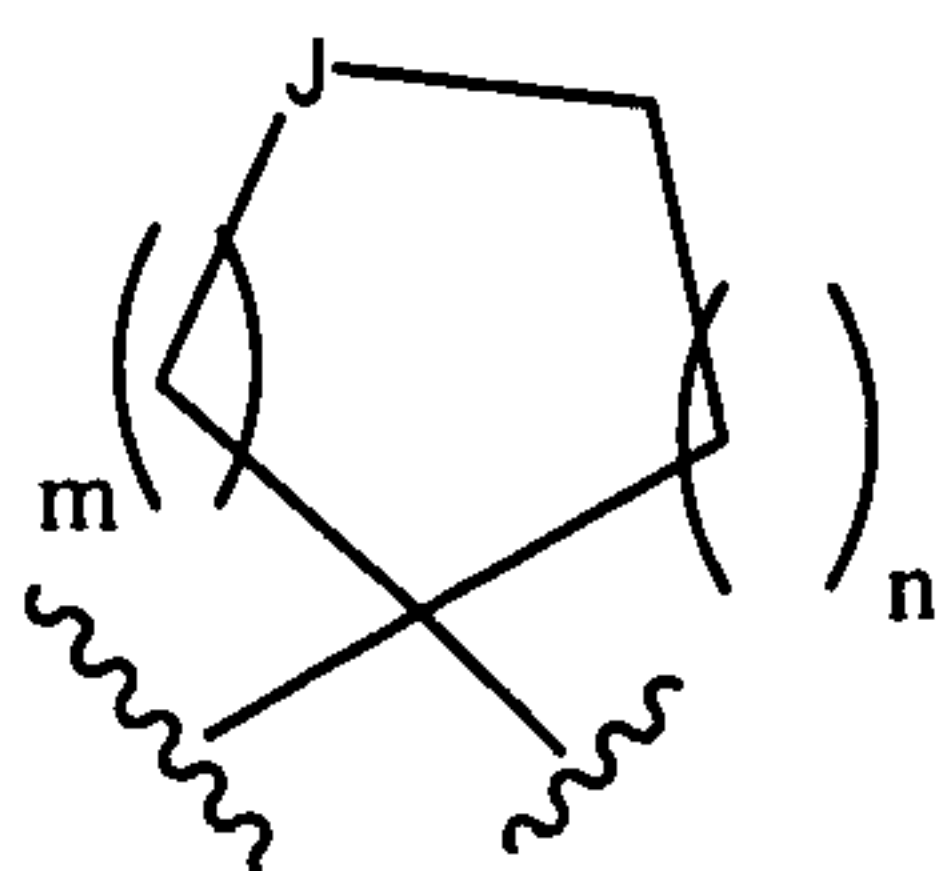


20. A compound of claim 19 wherein

R^2 is alkyl; and

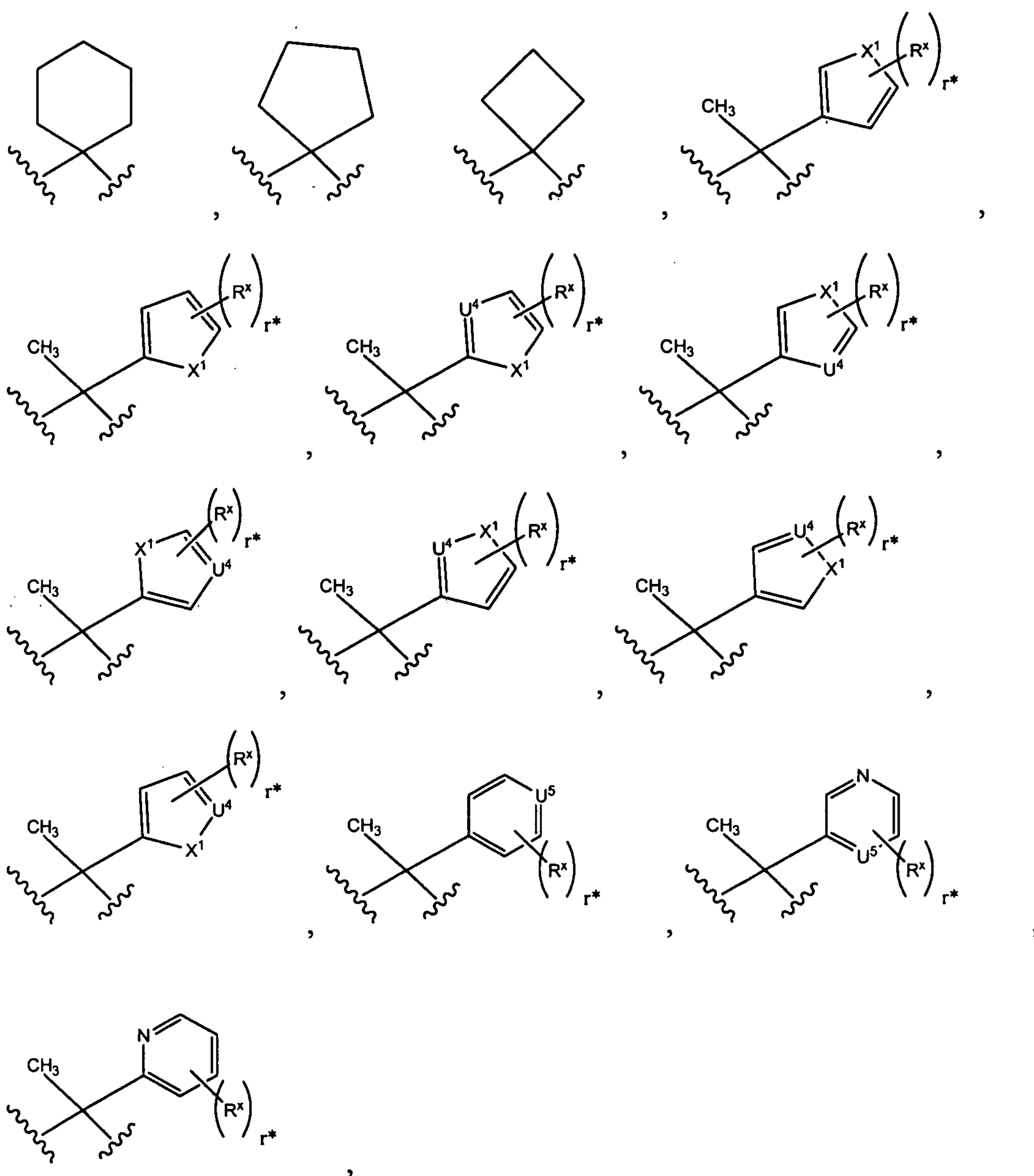
R^3 is pyrrolyl, furanyl, thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, phenyl, pyridyl, pyrimidyl, pyrazinyl, or oxadiazolyl any of which may be optionally substituted with one or more R^x as allowed by valance;

or R^2 and R^3 together with the carbon atom to which they are attached may combine to form



which may be optionally substituted with one or more R^x groups as allowed by valance;

21. A compound of claim 20 wherein R^2 , R^3 and the carbon atom to which they are attached are selected from



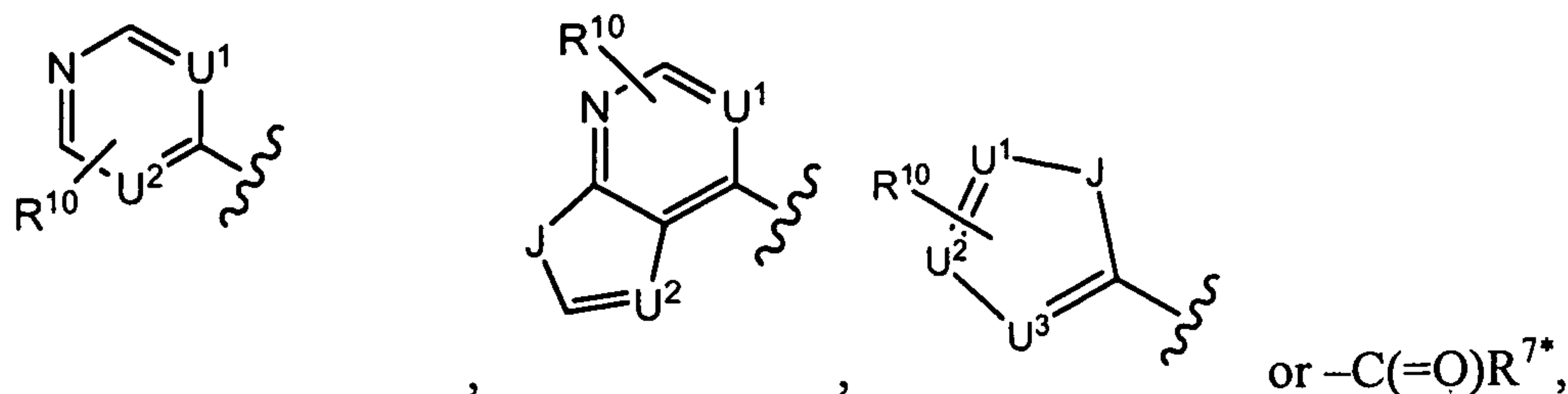
wherein

U⁴ and U⁵ are each independently N or CH

X¹ is NH, O or S(O)_v

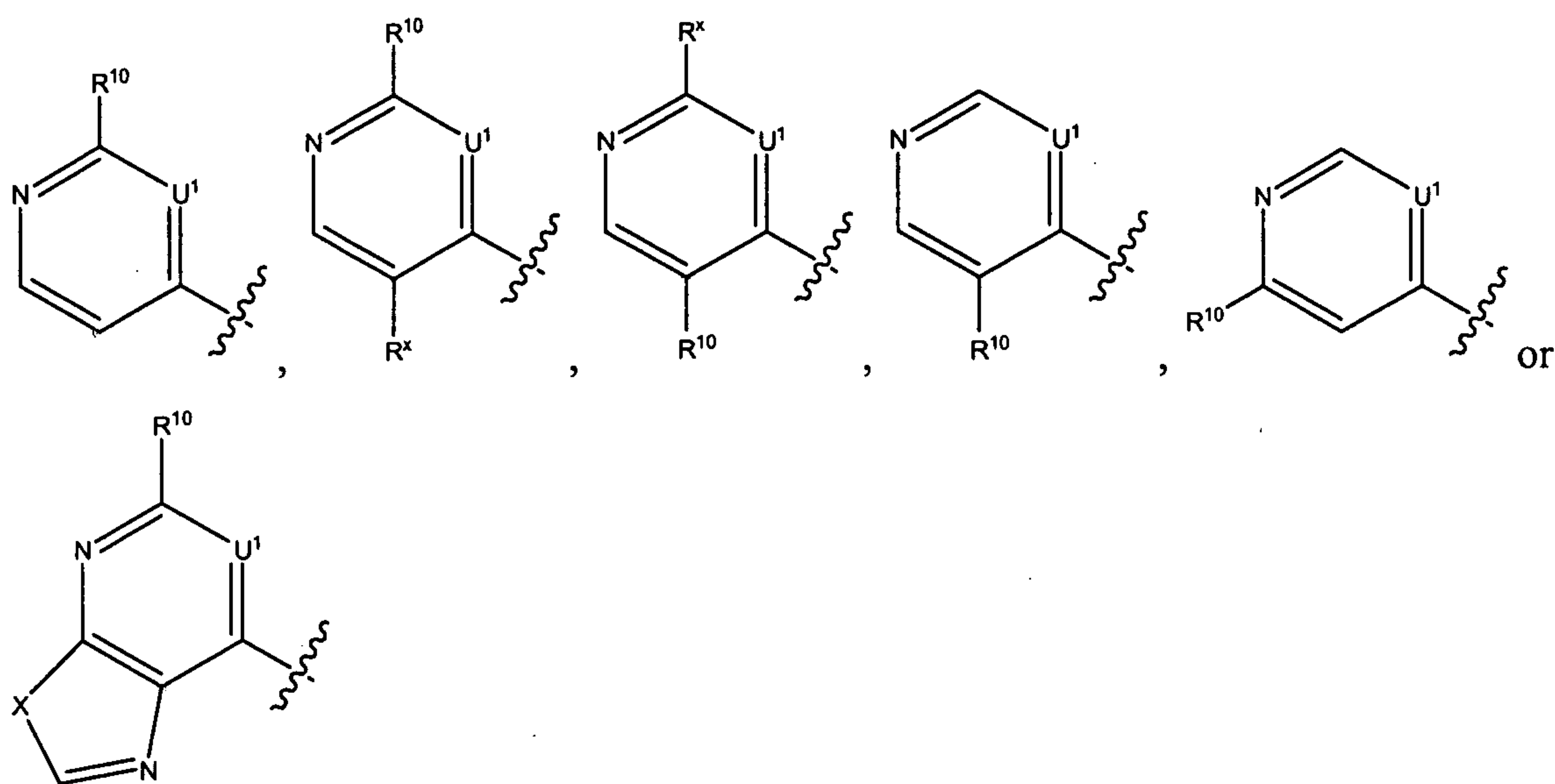
r* is 0 or an integer up to three as allowed by valance.

22. A compound according to any of claims 19, 20 or 21 wherein R⁴ is



any of which may be optionally substituted, as allowed by valance, with up to three R^x groups independently selected from halo, cyano, alkyl, haloalkyl, alkenyl, alkynyl, aryl, $-(alkylene)_q-NR^{8+}R^{9+}$, $-(alkylene)_q-C(=O)NR^{8+}R^{9+}$, $-(alkylene)_q-OR^{7+}$, wherein R^{10} is H, $-NR^{14}R^{15}$, or $-C(=O)NR^{14}R^{15}$; and U^1 , U^2 and U^3 are independently CH or N.

23. A compound of claim 22 wherein R^4 is



24. A pharmaceutical composition comprising a compound according to claim 1 together with a pharmaceutically acceptable vehicle, adjuvant or diluent.

25. A method of treating an inflammatory condition comprising administering to a patient in need of such treatment a pharmaceutically effective amount of a compound according to claim 1.

26. A method of claim 25 wherein the inflammatory condition is selected from asthma, COPD, rhinitis, multiple sclerosis, IBD, arthritis, rheumatoid arthritis, dermatitis, endometriosis and transplant rejection.

5 27. A method of treating lymphoma, leukemia or multiple myeloma comprising administering to a patient in need of such treatment a pharmaceutically effective amount of a compound according to claim 1.

10 28. A use of a pharmaceutically effective amount of a compound according to claim 1, for treating an inflammatory condition in a patient in need of such treatment.

15 29. A use of a pharmaceutically effective amount of a compound according to claim 1, for the preparation of a medicament for treating an inflammatory condition in a patient in need of such treatment.

 30. A use of a pharmaceutically effective amount of a compound according to claim 1, for treating lymphoma, leukemia or multiple myeloma in a patient in need of such treatment.

20 31. A use of a pharmaceutically effective amount of a compound according to claim 1, for the preparation of a medicament for treating lymphoma, leukemia or multiple myeloma in a patient in need of such treatment.