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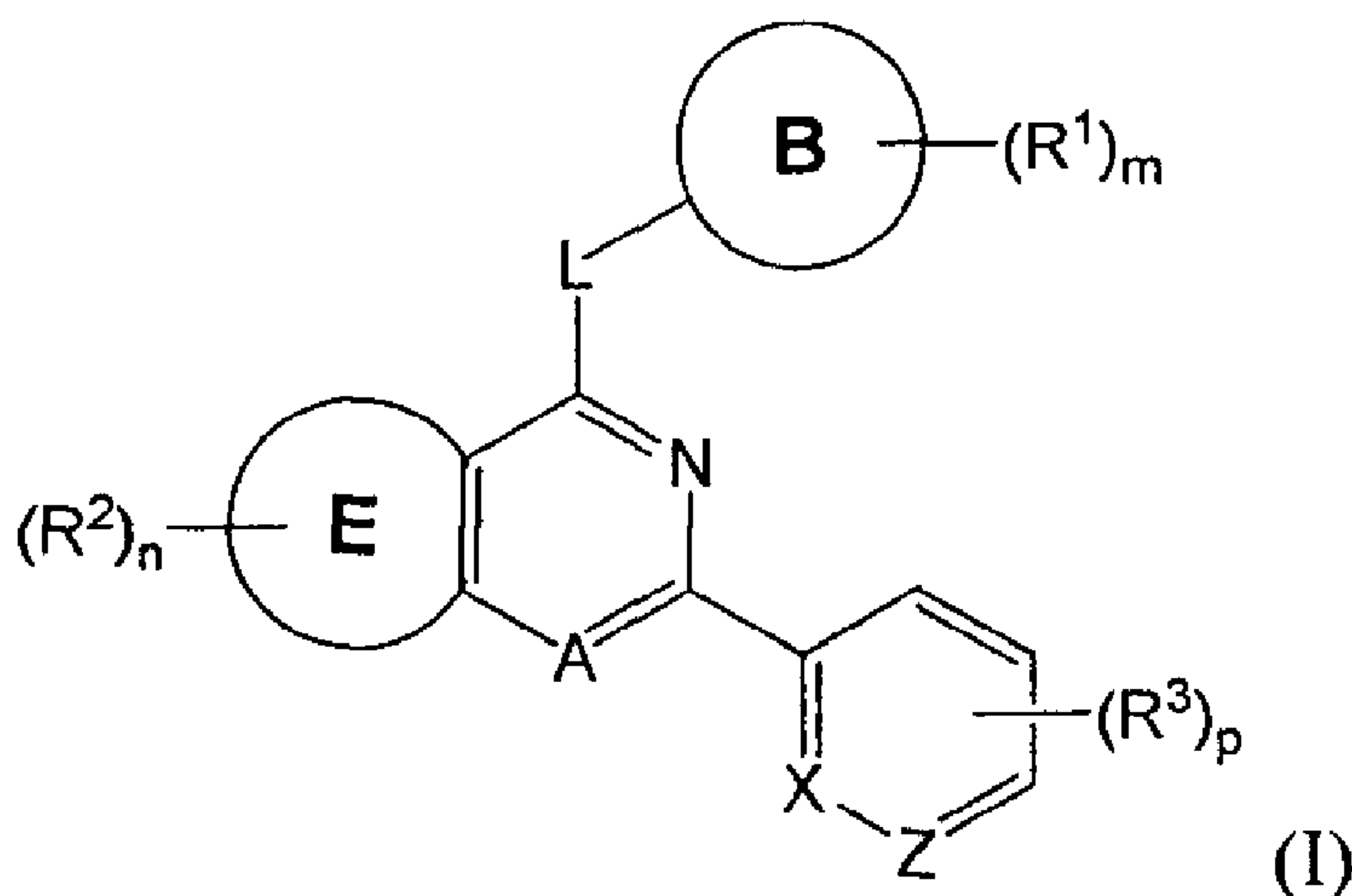
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(54) Titre : COMPOSES THERAPEUTIQUES ET PROCEDES D'UTILISATION ASSOCIES
(54) Title: THERAPEUTIC COMPOUNDS AND RELATED METHODS OF USE



(57) Abrégé/Abstract:

Provided herein are compounds that modulate striatal-enriched tyrosine phosphatase (STEP) and may be useful for treating disorders associated with STEP. Exemplary compounds are compounds of formula (I) and salts thereof. Exemplary disorders include schizophrenia and cognitive deficit.

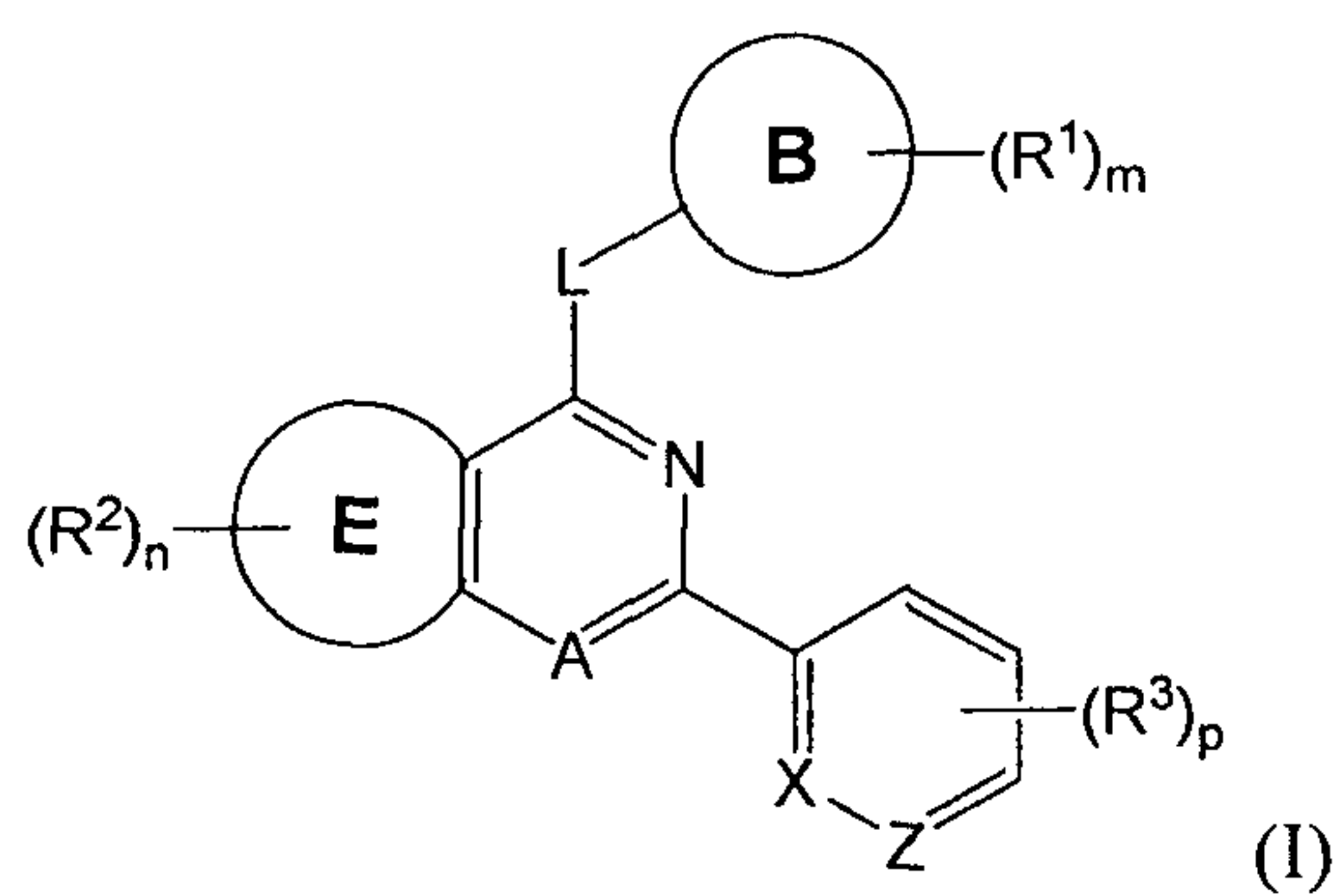
(see formula I)



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Abstract

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DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS
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CECI EST LE TOME __1__ DE __3__

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 __3__

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THERAPEUTIC COMPOUNDS AND RELATED METHODS OF USE

BACKGROUND OF INVENTION

Tyrosine phosphorylation of synaptic receptors and signaling molecules regulates synaptic activity. A number of protein tyrosine phosphatases specifically expressed within the brain have been identified, including STEP (for STriatal-Enriched tyrosine Phosphatase, also known as PTPN5). Recent evidence suggests that STEP plays an important role in synaptic plasticity, for review see (Braithwaite SP, et al., (2006), Trends Neurosci, 29 (8): 452; Baum ML, et al., (2010), Commun Integr Biol, 3 (5): 419). STEP is specifically expressed within neurons of the central nervous system. As its name indicates, the highest expression level is within the striatum. However, more recent work has found that it is expressed at lower levels in multiple brain regions including the neocortex, amygdala, hippocampus, and embryonic spinal cord.

Four groups of proteins that STEP regulates have been identified: the mitogen-activated protein kinases (MAPKs), the tyrosine kinase Fyn, the N-methyl-D-aspartate (NMDA) receptor complex (specifically the NR2B subunit) and AMPA receptors (specifically, GluR2, (Zhang Y, et al., (2008), J Neurosci, 28 (42): 10561)). Three additional new substrates for STEP have also been recently discovered: proline-rich tyrosine kinase 2 (Pyk2; Xu J, et al., (2010), Abstracts of the Society for Neuroscience Meetings), the fragile X mental retardation protein (FMRP) (Goebel-Goody SM, et al., (2010), Abstracts of the Society for Neuroscience Meetings) and the cell-death mediator Bak (Fox JL, et al., (2010), EMBO J, 29 (22): 3853). Tyrosine

phosphorylation of one member of the MAPK family, the extracellular signal regulated kinase (ERK), is necessary for the expression and maintenance of synaptic plasticity in many brain regions, and disruption of the ERK pathway leads to a disruption of learning and memory. One of the functions of these src and Pyk2 kinases is to phosphorylate NMDA receptors, thereby modulating their channel conductance properties and facilitating their movement toward the surface of neuronal plasma membranes. Pyk2 and Fyn tyrosine kinases are activated by phosphorylation on tyrosine residues. NR2B phosphorylation on Tyrosine 1452 inhibits the receptor endocytosis. STEP acts as direct or indirect brake of NMDAR mediated signaling by either respectively dephosphorylating NR2B or its associated kinases, Pyk2 and Fyn. Activation of AMPA, NMDA receptors and MAPKs are required for the induction of several forms of long-term potentiation (LTP) and long-term depression (LTD). Hippocampal LTP is increased in transgenic mice model of Alzheimer lacking STEP (Zhang Y, et al., (2010), Proc Natl Acad Sci U S A, 107 (44): 19014). NR2B and AMPA receptor surface expression is increased in STEP KO mice. AMPA receptor endocytosis in group I metabotropic glutamate receptor I (mGluR) mediated LTD is mediated by a tyrosine phosphatase. AMPA receptor endocytosis induced by activation of group I mGluR is blocked in STEP KO mice suggesting that STEP might also control mGluR mediated LTD.

Compounds that inhibit STEP activity should mimic the effects observed with the STEP KO and may be useful for treating conditions mediated by abnormal NMDA-receptor (NMDA-Rs) and/or MAP kinase pathway signaling. Both may mediate cognition, learning and memory, neurogenesis, and may also affect neuronal plasticity, pain perception, mood and anxiety, and neuroendocrine regulation.

Modulation of NMDA-Rs:

STEP decreases the tyrosine phosphorylation level of NMDA-Rs. Less phosphorylated NMDA-Rs have lower conductance states and thus will allow less current and fewer ions to pass. The NMDA-Rs will therefore be functionally less active (Alvestad RM, et al., (2003), J Biol Chem, 278 (13): 11020), which can lead to schizophrenic symptoms. Hypofunction of NMDA-Rs has been linked to

schizophrenia. For example, phencyclidine, ketamine, and other noncompetitive antagonists at NMDA-type glutamate receptors can exacerbate symptoms in patients (Lahti AC, et al., (1995), *Neuropsychopharmacology*, 13 (1): 9) and may produce a range of psychotic symptoms in volunteers that are similar to those of schizophrenic patients. NMDA-R hypofunction is also linked to psychosis and drug addiction (Javitt DC and Zukin SR, (1991), *Am J Psychiatry*, 148 (10): 1301). Chronic treatment of atypical antipsychotic clozapine and risperidone in mice result in significant increase of phosphorylation of ERK, NR2B and Pyk2 on tyrosine residues recognized by STEP (Carty NC, et al., (2010), Abstracts of the Society for Neuroscience Meetings). Treatment of these anti-psychotics also enhances cAMP and STEP phosphorylation. Since PKA mediated phosphorylation of STEP is known to inactivate STEP, these results suggest that STEP inhibition mediates the beneficial effect of antipsychotic drugs. Recent studies have linked abnormal NMDA-R activity and expression of STEP to the cognitive decline observed in Alzheimer's disease or transgenic mice expressing mutant APP (Tg2576 mice) (Snyder EM, et al., (2005), *Nat Neurosci*, 8 (8): 1051; Hynd MR, et al., (2004), *J Neurochem*, 90 (4): 913; Kurup P, et al., (2010), *Channels (Austin)*, 4 (5)). More specifically, STEP KO mice are less susceptible to PCP-induced hyperlocomotion and PCP-induced cognitive deficits in the object recognition tasks (Carty NC, et al., (2010), Abstracts of the Society for Neuroscience Meetings). Compared to the Tg2576 mice expressing STEP, Tg2576 lacking STEP gene showed rescue in their deficits in hippocampal LTP and in different behavioral cognitive tasks. Altogether, these results suggest that STEP inhibitors might represent a novel class of drugs that can treat both positive symptoms and cognitive deficit associated with schizophrenia.

Medications that modulate glutamatergic neurotransmission via NMDA-Rs may be also effective in treatment for mood and anxiety disorders. Administration of NMDA-R antagonists has anxiolytic effects in rodent models of anxiety (Falls WA, et al., (1992), *J Neurosci*, 12 (3): 854; Miserendino MJ, et al., (1990), *Nature*, 345 (6277): 716). NMDA-Rs antagonist like ketamine has been shown to be effective in drug-resistant unipolar depression (Machado-Vieira R, et al., (2009), *Pharmacol Ther*, 123 (2): 143).

Abnormal balance between the activity of NMDA receptors at synaptic (prosurvival linked to ERK activation) and extrasynaptic (proapoptotic linked to p38 activation) sites has been proposed in cellular and mouse model of Huntington Disease (HD) (Milnerwood AJ, et al., Neuron, 65 (2): 178). YAC128 mouse model (containing high number of glutamine repeat on huntingtin) of HD showed an increased activity of extrasynaptic NMDA receptors (NR2B subunit) and require p38 and caspase-6 cleavage activation. In YAC128 mice, NR2B synaptic expression is associated with high STEP expression and activity and a reduction in NR2B expression and phosphorylation (Gladding CM, et al., (2010), Abstracts of the Society for Neuroscience Meetings). Extrasynaptic NMDA receptors couple preferentially to excitotoxicity via calpain-mediated cleavage of STEP and activation of p38 (Xu J, et al., (2009), J Neurosci, 29 (29): 9330). Inhibiting STEP activity might therefore shift the balance toward the NMDA receptor/ERK synaptic prosurvival signaling pathway.

Modulation of ERK pathway:

STEP inhibition may translate into activation of ERK1/2 kinases, for example, in the central nervous system (CNS). Activation of the ERK pathway in the CNS can mediate neurotrophic pathways involved in cellular resilience. ERK signaling directly affects Bak phosphorylation through inhibition of STEP to promote cell survival (Fox JL, et al., (2010), EMBO J, 29 (22): 3853). BDNF and other neurotrophins can block apoptosis and increase cell survival of different type of CNS neurons *in vitro* and *in vivo* via stimulation of the ERK pathway. Mood stabilizers effective in bipolar disorder like valproate and lithium may be potent activators of ERK activity. This effect on ERK activation is believed to be responsible for the neurotrophic effects of mood stabilizers observed *in vitro* or in brains of treated patients with bipolar disorder, for review see (Engel SR, et al., (2009), Mol Psychiatry, 14 (4): 448; Chen G and Manji HK, (2006), Curr Opin Psychiatry, 19 (3): 313; Machado-Vieira R, et al., (2009), Bipolar Disord, 11 Suppl 2 92). *In vivo* disruption of STEP activity was shown to activate MAPK pathway, leading to significant rescue from neuronal cell death after pilocarpine-induced status epilepticus (Choi YS, et al., (2007), J Neurosci, 27 (11): 2999). Increasing cellular resilience could therefore limit or reduce neuronal

loss in several neurologic disorders. Recent work has suggested a positive role for STEP inhibition in fragile X syndrome (FXS). This disorder results from the mutation of *fmr1* gene coding for the fragile X mental retardation protein (FMRP). STEP binds to FMRP and its expression is dysregulated in FXS. FMR KO mice model displayed audiogenic seizures. FMR KO mice lacking STEP gene show a significant reduction of these seizures (Goebel-Goody SM, et al., (2010), Abstracts of the Society for Neuroscience Meetings), suggesting that STEP modulators might be therapeutic approach for FXS.

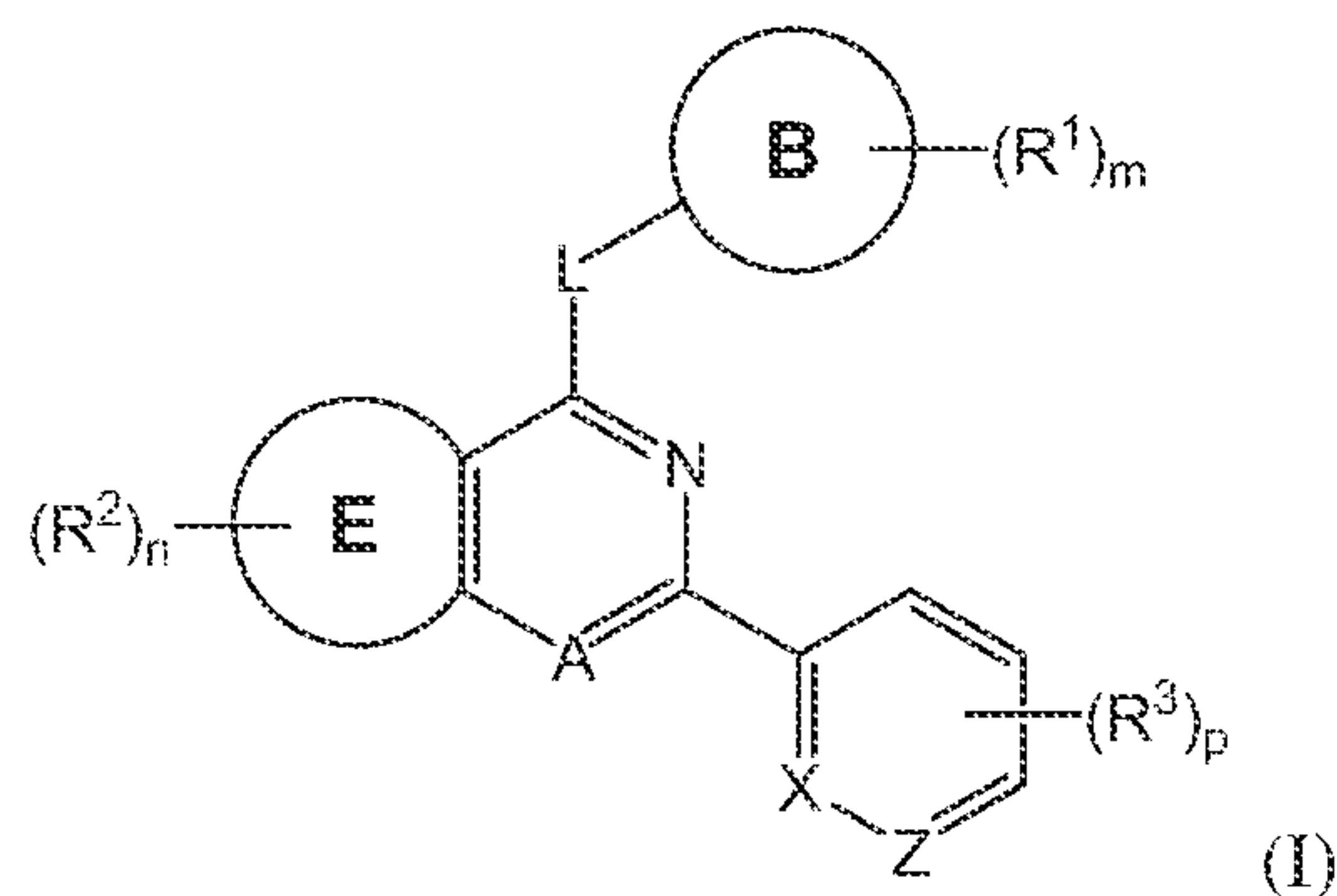
Various substituted heterocyclic compounds are disclosed in the art. For example, WO 02/062767 discloses quinazoline derivatives; WO 03/000188 discloses quinazolines and uses thereof; WO 2005/042501 discloses norepinephrine reuptake inhibitors for the treatment of central nervous system disorders; WO2006/058201 discloses heterocyclic and bicyclic compounds, compositions and methods; WO 2007/104560 discloses substituted 4-amino-quinazoline derivatives as regulators of metabotropic glutamate receptors and their use for producing drugs; WO 2007/133773 discloses CDKI pathway inhibitors; WO 2008/009078 discloses 4,6-DL- and 2,4,6-trisubstituted quinazoline derivatives useful for treating viral infections; WO 2009/000085 discloses quinoline and quinazoline derivatives useful as modulators of gated ion channels; US 2009/0143399 discloses protein kinase inhibitors; and Japan Publication Number 2007-084494A discloses substituted bicyclic compounds.

SUMMARY OF INVENTION

Described herein are compounds, pharmaceutical compositions containing the compounds, and methods of using the compounds to treat a disorder, e.g., schizophrenia or cognitive deficit, in a subject. The compounds disclosed herein include quinoline- and quinazoline-containing compounds that modulate (e.g., inhibit) the activity of STEP.

The present invention provides therapeutic compounds, pharmaceutical composition comprising said compounds, use of said compounds and method for treating or preventing a disorder as described in items 1 to 42 below.

Item 1. A compound of formula (I):



or a salt thereof,

wherein:

A is CR⁴ or N;

B is aryl, cyclyl or a 5- or 6-membered heteroaryl;

m is 0, 1, 2, 3, 4 or 5;

E is aryl or a 5-membered heteroaryl;

n is 0, 1, 2, 3 or 4;

when E is aryl, n is 0, 1, 2, 3 or 4; and when E is a 5-membered heteroaryl, n is 0, 1, 2 or 3;

L is NR⁵, S, O or a direct bond;

one of X and Z is N and the other is CH;

p is 0, 1, 2, 3 or 4;

each R¹, R² and R³ is independently C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silyloxyalkynyl, silylalkoxy, silylalkoxyalkyl, -CN, oxo, -NO₂, -C(O)OR^a, -C(Y)NR^bR^{b'}, -NR^cC(Y)R^{c'}, -NR^bR^{b'}, -OC(O)NR^bR^{b'}, -NR^cC(O)OR^{c'}, -SO₂NR^bR^{b'}, -NR^cSO₂R^{c'}, -NR^cC(Y)NR^bR^{b'}, -OR^d, -SR^{d'}, -C(Y)R^e or -S(O)_qR^f, each of which is optionally substituted with 1-3 R⁶; wherein two R¹, together with the atoms to which they are attached, may form an optionally substituted cyclyl, heterocyclyl, aryl or heteroaryl ring;

R^4 is hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, $-CN$, $-NO_2$, $-C(O)OR^a$, $-C(Y)NR^bR^{b'}$, $-NR^cC(Y)R^{c'}$, $-NR^bR^{b'}$, $-OC(O)NR^bR^{b'}$, $-NR^cC(O)OR^{c'}$, $-SO_2NR^bR^{b'}$, $-NR^cSO_2R^{c'}$, $-NR^cC(Y)NR^bR^{b'}$, $-OR^d$, $-SR^{d'}$, $-C(Y)R^e$ or $-S(O)_qR^f$, each of which is optionally substituted with 1-3 R^6 ;

R^5 is hydrogen; or when m is not 0, R^5 and one R^1 may be taken together with the atoms to which they are attached to form an optionally substituted heteroaryl or heterocyclyl ring;

each R^6 is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, oxo, thioxo, $-CN$, $-NO_2$, $-C(O)OR^a$, $-C(Y)NR^bR^{b'}$, $-NR^cC(Y)R^{c'}$, $-NR^bR^{b'}$, $-OC(O)NR^bR^{b'}$, $-NR^cC(O)OR^{c'}$, $-SO_2NR^bR^{b'}$, $-NR^cSO_2R^{c'}$, $-NR^cC(Y)NR^bR^{b'}$, $-OR^d$, $-SR^{d'}$, $-C(Y)R^e$ or $-S(O)_qR^f$, each of which is optionally substituted with 1-3 R^7 ;

each R^7 is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, oxo, thioxo, $-CN$, $-NO_2$, $-C(O)OR^a$, $-C(Y)NR^bR^{b'}$, $-NR^cC(Y)R^{c'}$, $-NR^bR^{b'}$, $-OC(O)NR^bR^{b'}$, $-NR^cC(O)OR^{c'}$, $-SO_2NR^bR^{b'}$, $-NR^cSO_2R^{c'}$, $-NR^cC(Y)NR^bR^{b'}$, $-OR^d$, $-SR^{d'}$, $-C(Y)R^e$ or $-S(O)_qR^f$, each of which is optionally substituted with 1-3 R^9 ;

each R^9 is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, oxo, thioxo, $-CN$, $-NO_2$, $-C(O)OR^a$, $-C(Y)NR^bR^{b'}$, $-NR^cC(Y)R^{c'}$, $-NR^bR^{b'}$, $-OC(O)NR^bR^{b'}$, $-NR^cC(O)OR^{c'}$, $-SO_2NR^bR^{b'}$, $-NR^cSO_2R^{c'}$, $-NR^cC(Y)NR^bR^{b'}$, $-OR^d$, $-SR^{d'}$, $-C(Y)R^e$ or $-S(O)_qR^f$, each of which is optionally substituted with 1-3 R^9 ;

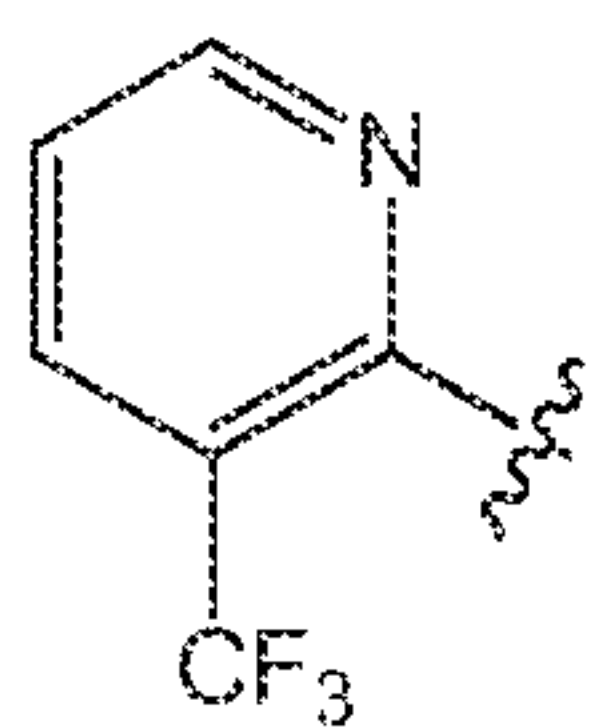
$\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{O})\text{OR}^c$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^c$, $-\text{NR}^c\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^d$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$;

Y is O or S;

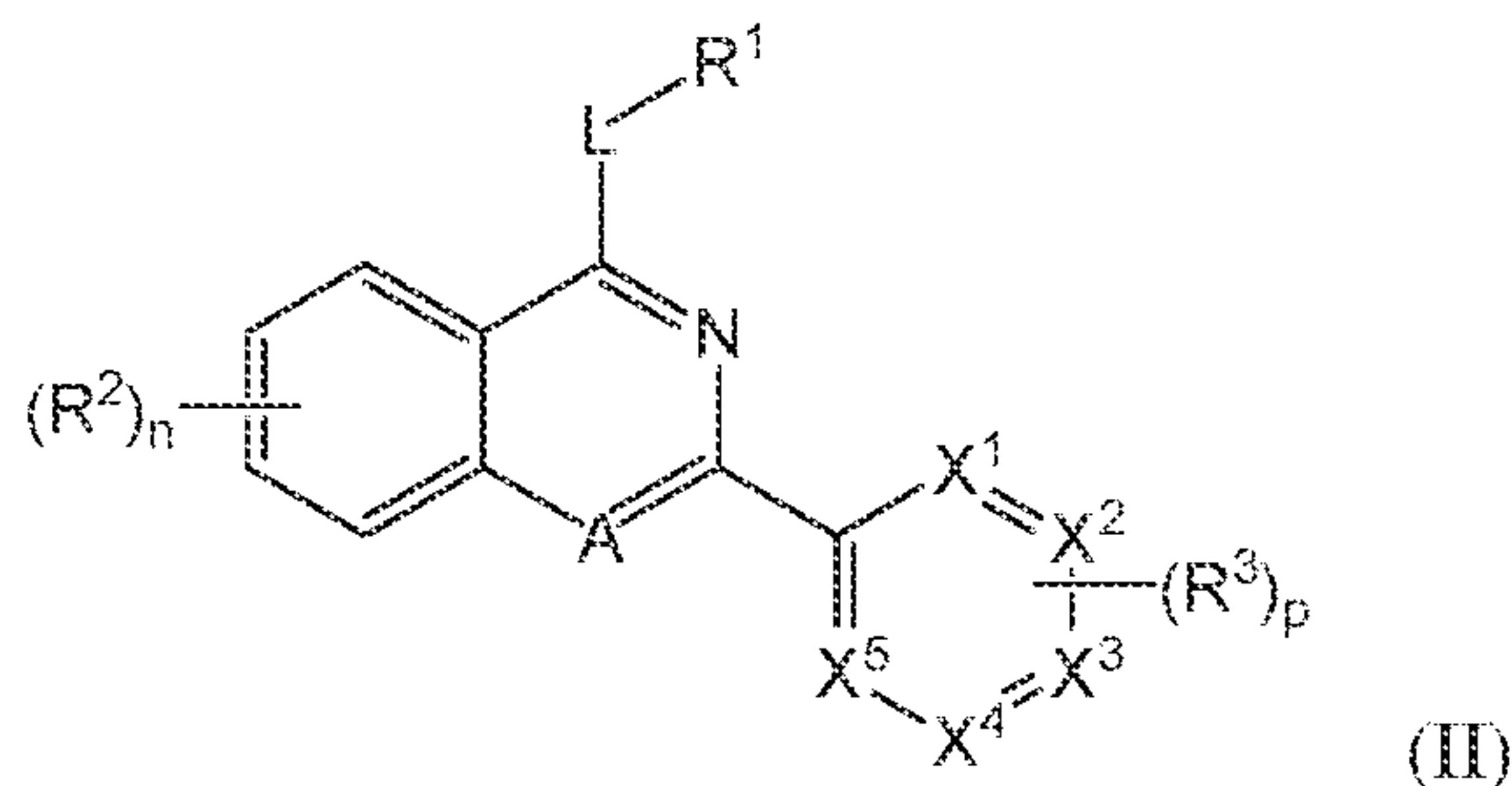
q is 1 or 2 and

each R^a , R^b , $\text{R}^{b'}$, R^c , $\text{R}^{c'}$, R^d , $\text{R}^{d'}$, R^e and R^f is independently hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, acyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy or silylalkoxyalkyl;

wherein when B is phenyl, two R^1 are not taken together to form a pyrazole ring;
and



when B is phenyl, R^2 is not
a compound of formula (II):



or a salt thereof,

wherein:

L is CR^4R^5 , O, $\text{C}(\text{O})$, $\text{NR}^6\text{C}(\text{O})$ or NR^7 ;

A is N;

each X^1 , X^2 , X^3 , X^4 and X^5 is independently CH or N, provided that at least two of X^1 , X^2 , X^3 , X^4 and X^5 are N;

n is 0, 1, 2, 3 or 4;

p is 0, 1, 2 or 3;

R^1 is C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl or heterocyclylalkyl, each of which is optionally substituted with 1-5 R^9 ; wherein R^1 or R^9 is optionally taken together with one of R^4 , R^5 , R^6 or R^7 , and the atoms to which they are attached, to form a cyclyl, heterocyclyl, aryl or heteroaryl ring that is optionally substituted with 1-3 R^{10} ;

each R^2 and R^3 is independently hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, $-CN$, $-NO_2$, $-C(O)OR^a$, $-C(Y)NR^bR^{b'}$, $-NR^cC(Y)R^{c'}$, $-NR^bR^{b'}$, $-OC(O)NR^bR^{b'}$, $-NR^cC(O)OR^{c'}$, $-SO_2NR^bR^{b'}$, $-NR^cSO_2R^{c'}$, $-NR^cC(Y)NR^bR^{b'}$, $-OR^d$, $-SR^{d'}$, $-C(Y)R^e$ or $-S(O)_qR^f$; each of which is optionally substituted with 1-3 R^{11} ;

each R^4 , R^5 , R^6 and R^7 is independently hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, $-CN$, $-NO_2$, $-C(O)OR^a$, $-C(Y)NR^bR^{b'}$, $-NR^cC(Y)R^{c'}$, $-NR^bR^{b'}$, $-OC(O)NR^bR^{b'}$, $-NR^cC(O)OR^{c'}$, $-SO_2NR^bR^{b'}$, $-NR^cSO_2R^{c'}$, $-NR^cC(Y)NR^bR^{b'}$, $-OR^d$, $-SR^{d'}$, $-C(Y)R^e$ or $-S(O)_qR^f$;

each R^9 , R^{10} and R^{11} is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, oxo, thioxo, $-CN$, $-NO_2$, $-C(O)OR^a$, $-C(Y)NR^bR^{b'}$, $-NR^cC(Y)R^{c'}$, $-NR^bR^{b'}$, $-OC(O)NR^bR^{b'}$, $-NR^cC(O)OR^{c'}$, $-SO_2NR^bR^{b'}$, $-NR^cSO_2R^{c'}$, $-NR^cC(Y)NR^bR^{b'}$, $-OR^d$, $-SR^{d'}$, $-C(Y)R^e$ or $-S(O)_qR^f$, each of which is optionally substituted with 1-3 R^{12} ;

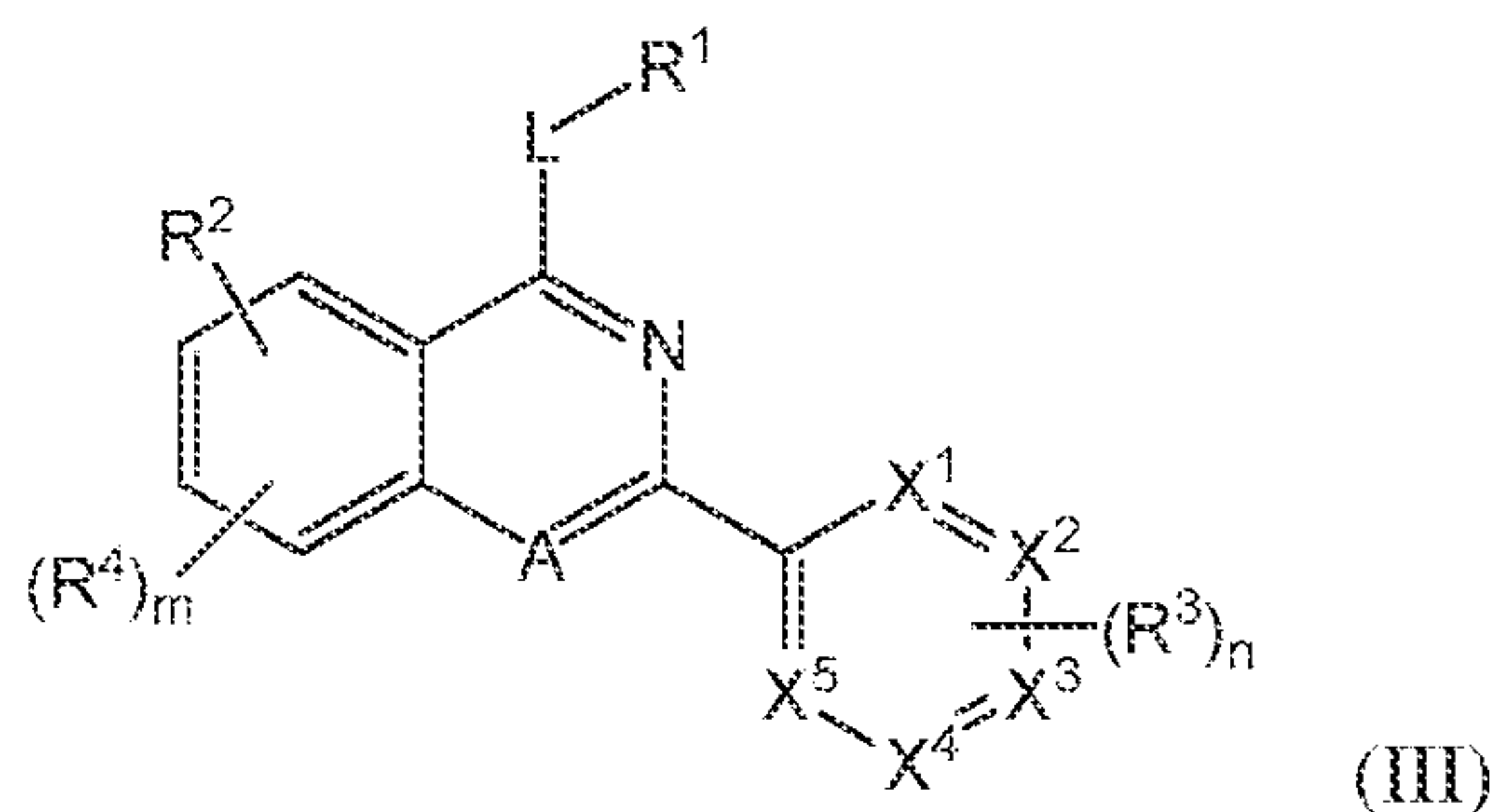
wherein, two R^9 , two R^{10} or two R^{11} is optionally taken together with the atoms to which they are attached to form an optionally substituted cyclyl, heterocyclyl, aryl or heteroaryl ring;

R^{12} is $-OR^d$;

Y is O or S;

q is 1 or 2 and

each R^a , R^b , $R^{b'}$, R^c , $R^{c'}$, R^d , $R^{d'}$, R^e , $R^{e'}$ and R^f is independently hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, acyl, cyclyl, heterocyclyl, aryl, heteroaryl, cyclylalkyl, heterocyclylalkyl, arylalkyl or heteroarylalkyl and a compound of formula (III):



or a salt thereof,

wherein:

A is CH or N;

L is O, a direct bond or NR^6 ;

one of X^1 , X^2 , X^3 , X^4 and X^5 is N and the others are CH;

m is 1, 2 or 3;

n is 1, 2, 3 or 4;

R^1 is hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, alkoxyalkyl, hydroxyalkyl, heteroaryl, heteroarylalkyl, arylalkyl, $-C(Y)R^e$, cyclyl, cyclylalkyl or heterocyclyl, each of which is optionally substituted with 1-3 R^7 ;

R^2 is aryl or heteroaryl, each of which is optionally substituted with 1-5 R^9 ;

each R^3 or R^4 is independently hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, $-CN$, $-NO_2$, $-C(O)OR^a$, $-C(Y)NR^bR^{b'}$, $-NR^cC(Y)R^{c'}$, $-NR^bR^{b'}$, $-OC(O)NR^bR^{b'}$, $-NR^cC(O)OR^{c'}$, $-SO_2NR^bR^{b'}$, $-NR^cSO_2R^{c'}$, $-NR^cC(Y)NR^bR^{b'}$, $-OR^d$, $-SR^{d'}$, $-C(Y)R^e$ or $-S(O)_qR^f$, each of which is optionally substituted with 1-3 R^{10} ;

R^6 is hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, cyclyl or heterocyclyl, each of which is optionally substituted with 1-3 R^{11} ;

each R^7 , R^9 and R^{10} is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, oxo, thioxo, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^{c'}$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{O})\text{OR}^{c'}$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^{c'}$, $-\text{NR}^c\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^d$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$, each of which is optionally substituted with 1-3 R^{12} ; wherein two R^7 , two R^9 or two R^{10} are optionally be taken together with the atoms to which they are attached to form an optionally substituted cyclyl, heterocyclyl, aryl or heteroaryl ring;

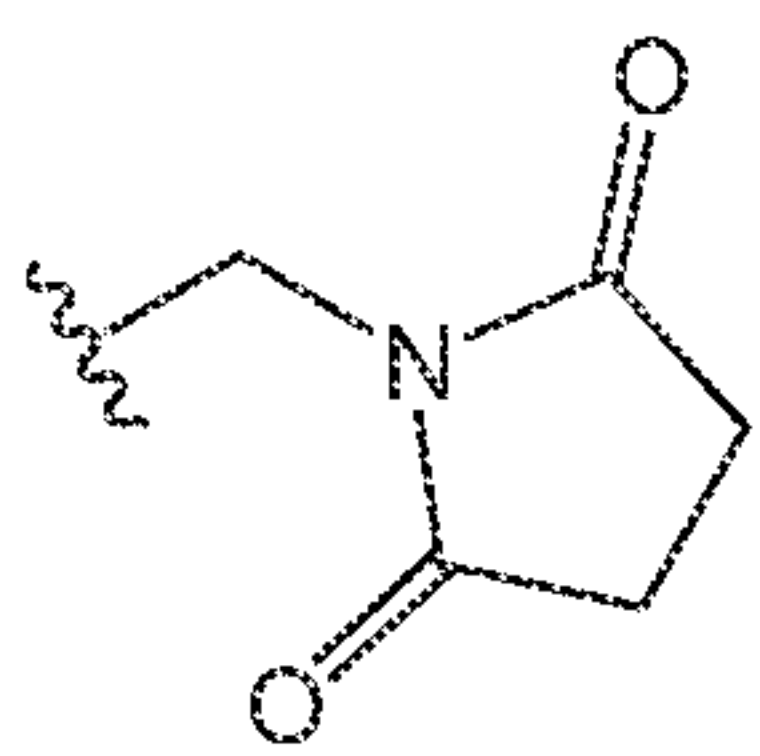
each R^{11} and R^{12} is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, oxo, thioxo, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^{c'}$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{O})\text{OR}^{c'}$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^{c'}$, $-\text{NR}^c\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^d$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$, each of which is optionally substituted with 1-3 R^{13} ;

R^{13} is independently C_1 - C_8 alkyl, haloalkyl, halo, heterocyclyl, cyclyl, oxo or $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$;

Y is independently O or S;

q is 1 or 2 ;and

each R^a , R^b , $R^{b'}$, R^c , $R^{c'}$, R^d , $R^{d'}$, R^e and R^f is independently hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, acyl, haloalkyl alkoxyalkyl, alkylaminoalkyl, dialkylaminoalkyl, cyclyl, heterocyclyl, aryl, heteroaryl, cyclylalkyl, heterocyclylalkyl, arylalkyl or heteroarylalkyl;



with proviso R^9 is not

Item 2. The compound according to item 1 represented by general formula(I) or a salt thereof,

wherein:

A is CR^4 or N;

B is aryl, cyclyl or a 5- or 6-membered heteroaryl;

m is 0, 1, 2, 3, 4 or 5;

n is 0, 1, 2, 3 or 4;

E is aryl or a 5-membered heteroaryl;

when E is aryl, n is 0, 1, 2, 3 or 4; and when E is a 5-membered heteroaryl, n is 0, 1, 2 or 3;

L is NR^5 , S, O or a direct bond;

one of X and Z is N and the other is CH;

p is 0, 1, 2, 3 or 4;

each R^1 , R^2 and R^3 is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silyloxyalkynyl, silylalkoxy, silylalkoxyalkyl, $-CN$, oxo, $-NO_2$, $-C(O)OR^a$, $-C(Y)NR^bR^{b'}$, $-NR^cC(Y)R^c$, $-NR^bR^{b'}$, $-OC(O)NR^bR^{b'}$, $-NR^cC(O)OR^c$, $-SO_2NR^bR^{b'}$, $-NR^cSO_2R^c$, $-NR^cC(Y)NR^bR^{b'}$, $-OR^d$, $-SR^d$, $-C(Y)R^e$ or $-S(O)_qR^f$, each of which is optionally substituted with 1-3 R^6 ; wherein two R^1 , together with the atoms to which they are attached, may form an optionally substituted cyclyl, heterocyclyl, aryl or heteroaryl ring;

R^4 is hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl,

alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^{c'}$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{O})\text{OR}^{c'}$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^{c'}$, $-\text{NR}^c\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^{d'}$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$, each of which is optionally substituted with 1-3 R^6 ;

R^5 is hydrogen; or when m is not 0, R^5 and one R^1 may be taken together with the atoms to which they are attached to form an optionally substituted heteroaryl or heterocyclyl ring;

each R^6 is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, oxo, thioxo, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^{c'}$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{O})\text{OR}^{c'}$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^{c'}$, $-\text{NR}^c\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^{d'}$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$, each of which is optionally substituted with 1-3 R^7 ;

each R^7 is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, oxo, thioxo, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^{c'}$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{O})\text{OR}^{c'}$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^{c'}$, $-\text{NR}^c\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^{d'}$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$, each of which is optionally substituted with 1-3 R^9 ;

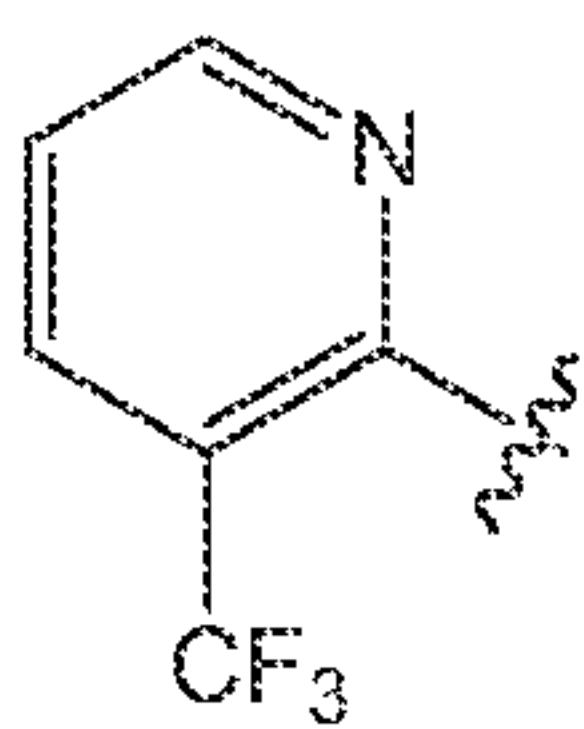
each R^9 is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, oxo, thioxo, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^{c'}$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{O})\text{OR}^{c'}$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^{c'}$, $-\text{NR}^c\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^{d'}$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$;

Y is O or S;

q is 1 or 2; and

each R^a , R^b , $R^{b'}$, R^c , $R^{c'}$, R^d , $R^{d'}$, R^e and R^f is independently hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, acyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy or silylalkoxyalkyl;

wherein when B is phenyl, two R^1 are not taken together to form a pyrazole ring; and



when B is phenyl, R^2 is not

Item 3. The compound according to item 2 represented by general formula (I) or a salt thereof,

wherein:

A is CH or N;

B is aryl, cyclyl or a 5- or 6-membered heteroaryl;

m is 0, 1, 2, 3 or 4;

E is aryl or a 5-membered heteroaryl;

n is 0, 1 or 2;

when E is aryl, n is 0, 1 or 2 and when E is a 5-membered heteroaryl, n is 0 or 1;

p is 0, 1 or 2;

each R^1 , R^2 and R^3 is independently C_1 - C_8 alkyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silyloxyalkynyl, $-\text{CN}$, oxo, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^c$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^{d'}$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$, each of which is optionally substituted with 1-3 R^6 ; wherein two R^1 , together with the atoms to which they are attached, may form an optionally substituted cyclyl, heterocyclyl, aryl or heteroaryl ring;

each R^6 is independently C_1 - C_8 alkyl, heterocyclyl, heterocyclalkyl, hydroxyalkyl, halo, haloalkyl, haloalkoxy, alkoxyalkyl, oxo, $-CN$, $-NO_2$, $-C(O)OR^a$, $-C(Y)NR^bR^{b'}$, $-NR^cC(Y)R^{c'}$, $-NR^bR^{b'}$, $-OR^d$ or $-C(Y)R^e$, each of which is optionally substituted with 1-3 R^7 ;

each R^7 is oxo; and

each R^a , R^b , $R^{b'}$, R^c , $R^{c'}$, R^d , $R^{d'}$, R^e and R^f is independently hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, acyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclalkyl, heterocyclalkyl, haloalkyl, dialkylaminoalkyl, hydroxyalkyl or alkoxyalkyl.

Item 4. The compound according to item 3 represented by general formula (I) or a salt thereof,

wherein:

B or two R1 and B are taken together to form a group is phenyl, dihydroindenyl, dihydrobenzoxazinyl, dihydrobenzodioxinyl, chromenyl, tetrahydroquinoxalinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, dihydroquinolinyl, quinolyl, isoquinolinyl, tetrahydroquinazolinyl, indolyl, dihydrobenzothiazolyl, dihydrobenzimidazolyl, dihydrobenzoxazolyl, isoindolyl, dihydroisobenzofuranyl, benzofuryl, benzothienyl, benzodioxolyl, indolyl, indazolyl, benzoimidazolyl, benzotriazolyl, benzisoxazolyl, benzoxazolyl, benzothiazolyl, benzoxadiazolyl, dihydrocyclopentathiophenyl, tetrahydrobenzothiophenyl, thienyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, thiadiazolyl, pyrrolyl or pyridyl;

E is phenyl, thienyl or pyrrolyl ;

when E is phenyl , n is 1 or 2; and when E is thienyl, n is 0 or 1;

each R^1 , R^2 and R^3 is independently C_1 - C_8 alkyl , C_2 - C_8 alkynyl, phenyl, thienyl, pyrrolyl, oxadiazolyl, pyridyl, benzodioxolyl, furyl, pyrimidinyl, oxazolyl, isoxazolyl, pyrazolyl, C_3 - C_8 cycloalkyl, piperidyl, pyrrolidinyl, morpholinyl, dioxolanyl, phenylalkyl, thiomorpholinylalkyl, pyrrolidinylalkyl, morpholinylalkyl, piperidylalkyl, piperazinylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxyalkyl, silyloxyalkynyl, $-CN$, $-NO_2$, oxo, $-C(O)OR^a$, $-C(Y)NR^bR^{b'}$, $-NR^cC(Y)R^{c'}$, $-NR^bR^{b'}$, $-OC(O)NR^bR^{b'}$, --

$\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^{d'}$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$, each of which is optionally substituted with 1-3 R^6 ;

each R^6 is independently C_1 - C_8 alkyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, morpholinylalkyl, dialkylaminoalkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, oxo, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^{c'}$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^b\text{R}^{b'}$, alkoxyalkyl, $-\text{OR}^d$ or $-\text{C}(\text{Y})\text{R}^e$; and

each R^a , R^b , $\text{R}^{b'}$, R^c , $\text{R}^{c'}$, R^d , $\text{R}^{d'}$, R^e and R^f is independently hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, C_3 - C_8 cycloalkyl, phenyl, pyridyl, dihydroindenyl, morpholinyl, tetrahydropyranyl, piperidyl, pyrrolidinyl, piperazinyl, thiomorpholinyl, phenylalkyl, thienylalkyl, furylalkyl, pyridylalkyl, tetrahydropyranylalkyl, dihydroindenylalkyl, tetrahydrofurylalkyl, hydroxyalkyl, thiazolylalkyl, pyrazolylalkyl, morpholinylalkyl, pyrrolidinylalkyl, dialkylaminoalkyl, piperidylalkyl, benzodioxolylalkyl, dihydrobenzodioxinylalkyl, benzothienylalkyl, C_3 - C_8 cycloalkylalkyl, oxazolidinylalkyl, haloalkyl or alkoxyalkyl.

Item 5. The compound according to item 3 represented by general formula (I) or a salt thereof,

wherein:

B or two R^1 and B are taken together to form a group is phenyl, dihydroindenyl, dihydrobenzoxazinyl, dihydrobenzodioxinyl, chromenyl, tetrahydroquinoxalyl, tetrahydroisoquinolyl, tetrahydroquinolyl, dihydroquinolyl, quinolyl, isoquinolyl, tetrahydroquinazolinyl, indolyl, dihydrobenzothiazolyl, dihydrobenzimidazolyl, dihydrobenzoxazolyl, isoindolyl, dihydroisobenzofuranyl, benzofuryl, benzothienyl, benzodioxolyl, indolyl, indazolyl, benzoimidazolyl, benzotriazolyl, benzisoxazolyl, benzoxazolyl, benzothiazolyl, benzoxadiazolyl, dihydrocyclopentathiophenyl, tetrahydrobenzothienyl, thienyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, thiadiazolyl, pyrrolyl or pyridyl;

E is phenyl, thienyl or pyrrolyl ;

when E is phenyl, n is 0, 1 or 2; and when E is thienyl, n is 0 or 1;

each R^1 , R^2 and R^3 is independently C_1 - C_8 alkyl, C_2 - C_8 alkynyl, phenyl, thienyl, pyrrolyl, oxazolyl, oxadiazolyl, pyridyl, benzodioxolyl, furyl, pyrimidinyl, isoxazolyl,

pyrazolyl, C₃-C₈ cycloalkyl, piperidyl, pyrrolidinyl, morpholinyl, dioxolanyl, phenylalkyl, thiomorpholinylalkyl, pyrrolidinylalkyl, morpholinylalkyl, piperidylalkyl, piperazinylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxyalkyl, silyloxyalkynyl, -CN, -NO₂, oxo, -C(O)OR^a, -C(Y)NR^bR^{b'}, -NR^bR^{b'}, -NR^cC(Y)R^{c'}, -OC(O)NR^bR^{b'}, -SO₂NR^bR^{b'}, -OR^d, -SR^{d'}, -C(Y)R^e or -S(O)_qR^f, each of which is optionally substituted with 1-3 R⁶;

each R⁶ is independently C₁-C₈ alkyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, morpholinylalkyl, dialkylaminoalkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, oxo, -CN, -NO₂, -C(O)OR^a, -NR^cC(Y)R^{c'}, -C(Y)NR^bR^{b'}, -NR^bR^{b'}, alkoxyalkyl, -OR^d or -C(Y)R^e, each of which is optionally substituted with 1-3 R⁷;

R⁷ is oxo; and

each R^a, R^b, R^{b'}, R^c, R^{c'}, R^d, R^{d'}, R^e and R^f is independently hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₃-C₈ cycloalkyl, phenyl, pyridyl, dihydroindenyl, morpholinyl, tetrahydropyranyl, piperidyl, pyrrolidinyl, piperazinyl, thiomorpholinyl, phenylalkyl, thienylalkyl, furylalkyl, pyridylalkyl, tetrahydropyranylalkyl, dihydroindenylalkyl, tetrahydrofurylalkyl, hydroxyalkyl, thiazolylalkyl, pyrazolylalkyl, morpholinylalkyl, pyrrolidinylalkyl, dialkylaminoalkyl, piperidylalkyl, benzodioxolylalkyl, dihydrobenzodioxinylalkyl, benzothienylalkyl, C₃-C₈ cycloalkylalkyl, oxazolidinylalkyl, haloalkyl, or alkoxyalkyl.

Item 6. The compound according to item 5 represented by general formula (I) or a salt thereof,

wherein:

R¹ is C₁-C₈ alkyl, phenyl, thienyl, pyrrolyl, oxazolyl, C₃-C₈ cycloalkyl, dioxolanyl, phenylalkyl, halo, haloalkyl, haloalkoxy, alkoxyalkyl, -CN, oxo, -NO₂, -C(O)OR^a, -C(Y)NR^bR^{b'}, -NR^cC(Y)R^{c'}, -SO₂NR^bR^{b'}, -OR^d, -SR^{d'}, -C(Y)R^e or -S(O)_qR^f, each of which is optionally substituted with 1-3 R⁶;

R² is C₁-C₈ alkyl, C₂-C₈ alkynyl, phenyl, thienyl, pyridyl, benzodioxolyl, furyl, pyrimidinyl, isoxazolyl, pyrazolyl, C₃-C₈ cycloalkyl, pyrrolidinyl, morpholinyl, thiomorpholinylalkyl, pyrrolidinylalkyl, morpholinylalkyl, piperidylalkyl,

piperazinylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxyalkyl, silyloxyalkynyl, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$ or $-\text{C}(\text{Y})\text{R}^e$, each of which is optionally substituted with 1-3 R^6 ;

R^3 is C_1 - C_8 alkyl, halo, haloalkyl, $-\text{NR}^b\text{R}^{b'}$ or $-\text{OR}^d$, each of which is optionally substituted with 1-3 R^6 .

Item 7. The compound according to item 4 or 6 represented by general formula (I) or a salt thereof,

wherein:

R^1 is C_1 - C_8 alkyl, phenyl, thienyl, pyrrolyl, oxazolyl, C_3 - C_8 cycloalkyl, dioxolanyl, phenylalkyl, halo, haloalkyl, haloalkoxy, alkoxyalkyl, $-\text{CN}$, oxo, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^{c'}$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^{d'}$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$;

R^2 is C_1 - C_8 alkyl, C_2 - C_8 alkynyl, phenyl, thienyl, pyridyl, benzodioxolyl, furyl, pyrimidinyl, isoxazolyl, pyrazolyl, C_3 - C_8 cycloalkyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinylalkyl, pyrrolidinylalkyl, morpholinylalkyl, piperiridinylalkyl, piperazinylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxyalkyl, silyloxyalkynyl, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$;

R^3 is C_1 - C_8 alkyl, halo, haloalkyl, $-\text{NR}^b\text{R}^{b'}$ or $-\text{OR}^d$.

Item 8. The compound according to item 7 represented by general formula (I) or a salt thereof,

wherein:

B or two R^1 and B are taken together to form a group is phenyl, dihydroindenyl, dihydrobenzoxazinyl, dihydrobenzodioxinyl, chromenyl, tetrahydroisoquinolyl, tetrahydroquinolyl, dihydroquinolyl, quinolyl, tetrahydroquinazolinyl, indolinyl, dihydrobenzothiazolyl, dihydrobenzimidazolyl, dihydrobenzoxazolyl, isoindolinyl, benzofuryl, benzothienyl, benzodioxolyl, indolyl, indazolyl, benzoimidazolyl, benzotriazolyl, benzisoxazolyl, benzoxazolyl, benzothiazolyl, benzoxadiazolyl,

tetrahydrobenzothienyl, thienyl, thiazolyl, imidazolyl, pyrazolyl, thiadiazolyl or pyridyl;

m is 1, 2, 3 or 4;

R¹ is C₁-C₈ alkyl, halo, haloalkyl, haloalkoxy, alkoxyalkyl, -CN, oxo, -NO₂, -C(O)OR^a, -C(Y)NR^bR^{b'}, -NR^cC(Y)R^{c'}, -SO₂NR^bR^{b'}, -OR^d, or -S(O)_qR^f;

R² is C₁-C₈ alkyl, C₃-C₈ cycloalkyl, thiomorpholinylalkyl, pyrrolidinylalkyl, morpholinylalkyl, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxyalkyl, -CN, -NO₂, -C(O)OR^a, -C(Y)NR^bR^{b'}, -NR^bR^{b'}, -OR^d, -C(Y)R^e or -S(O)_qR^f;

each R^a, R^b, R^{b'}, R^c, R^{c'}, R^d, R^{d'}, R^e and R^f is independently hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₃-C₈ cycloalkyl, phenyl, dihydroindenyl, morpholinyl, tetrahydropyranyl, piperidyl, pyrrolidinyl, thiomorpholinyl, phenylalkyl, thienylalkyl, pyridylalkyl, tetrahydropyranylalkyl, dihydroindenylalkyl, tetrahydrofurylalkyl, hydroxyalkyl, morpholinylalkyl, pyrrolidinylalkyl, dialkylaminoalkyl, piperidylalkyl, benzodioxolylalkyl, dihydrobenzodioxinylalkyl, C₃-C₈ cycloalkylalkyl, haloalkyl or alkoxyalkyl.

Item 9. The compound according to item 1 represented by general formula (II) or a salt thereof,

wherein:

L is CR⁴R⁵, O, C(O), NR⁶C(O) or NR⁷;

A is N;

each X¹, X², X³, X⁴ and X⁵ is independently CH or N, provided that at least two of X¹, X², X³, X⁴ and X⁵ are N;

n is 0, 1, 2, 3 or 4;

p is 0, 1, 2 or 3;

R¹ is C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl or heterocyclylalkyl, each of which is optionally substituted with 1-5 R⁹; wherein R¹ or R⁹ is optionally taken together with one of R⁴, R⁵, R⁶ or R⁷, and the atoms to which they are attached to

form a cyclyl, heterocyclyl, aryl or heteroaryl ring that is optionally substituted with 1-3 R¹⁰;

each R² and R³ is independently hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, -CN, -NO₂, -C(O)OR^a, -C(Y)NR^bR^{b'}, -NR^cC(Y)R^{c'}, -NR^bR^{b'}, -OC(O)NR^bR^{b'}, -NR^cC(O)OR^{c'}, -SO₂NR^bR^{b'}, -NR^cSO₂R^{c'}, -NR^cC(Y)NR^bR^{b'}, -OR^d, -SR^{d'}, -C(Y)R^e or -S(O)_qR^f, each of which is optionally substituted with 1-3 R¹¹;

each R⁴, R⁵, R⁶ and R⁷ is independently hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, -CN, -NO₂, -C(O)OR^a, -C(Y)NR^bR^{b'}, -NR^cC(Y)R^{c'}, -NR^bR^{b'}, -OC(O)NR^bR^{b'}, -NR^cC(O)OR^{c'}, -SO₂NR^bR^{b'}, -NR^cSO₂R^{c'}, -NR^cC(Y)NR^bR^{b'}, -OR^d, -SR^{d'}, -C(Y)R^e or -S(O)_qR^f;

each R⁹, R¹⁰ and R¹¹ is independently C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, oxo, thioxo, -CN, -NO₂, -C(O)OR^a, -C(Y)NR^bR^{b'}, -NR^cC(Y)R^{c'}, -NR^bR^{b'}, -OC(O)NR^bR^{b'}, -NR^cC(O)OR^{c'}, -SO₂NR^bR^{b'}, -NR^cSO₂R^{c'}, -NR^cC(Y)NR^bR^{b'}, -OR^d, -SR^{d'}, -C(Y)R^e or -S(O)_qR^f, each of which is optionally substituted with 1-3 R¹²; wherein two R⁸, two R⁹, two R¹⁰ or two R¹¹ is optionally taken together with the atoms to which they are attached to form an optionally substituted cyclyl, heterocyclyl, aryl or heteroaryl ring;

R¹² is -OR^d;

Y is O or S;

q is 1 or 2; and

each R^a, R^b, R^{b'}, R^c, R^{c'}, R^d, R^{d'}, R^e, R^{e'} and R^f is independently hydrogen,

C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, acyl, cyclyl, heterocyclyl, aryl, heteroaryl, cyclylalkyl, heterocyclalkyl, arylalkyl, or heteroarylalkyl.

Item 10. The compound according to item 9 represented by general formula (II) or a salt thereof,

L is NR⁷;

n is 0, 1 or 2;

p is 0;

R¹ is C₁-C₈ alkyl, aryl or heteroaryl;

each R² and R³ is independently hydrogen, C₁-C₈ alkyl, aryl, halo, heterocyclalkyl, -NR^cC(Y)R^c, -NR^bR^{b'} or -OR^d, each of which is optionally substituted with 1-3 R¹¹;

R⁷ is hydrogen; and

each R⁹, R¹⁰ and R¹¹ is independently C₁-C₈ alkyl, heterocyclyl, halo, haloalkyl, haloalkoxy, -CN, -C(O)OR^a, -C(Y)NR^bR^{b'}, -OR^d or -C(Y)R^e;

Y is O;

each R^a, R^b, R^{b'}, R^c, R^{c'}, R^d, R^{d'}, R^e, R^{e'} and R^f is independently hydrogen, C₁-C₈ alkyl, cyclyl, heterocyclyl, aryl, or heteroaryl.

Item 11 .The compound according to item 10 represented by general formula (II) or a salt thereof,

wherein:

R¹ is C₁-C₈ alkyl, phenyl or benzodioxolyl;

each R² and R³ is independently hydrogen, C₁-C₈ alkyl, phenyl, halo, morpholinylalkyl, -NR^cC(Y)R^c, -NR^bR^{b'} or -OR^d;

R⁹ is independently C₁-C₈ alkyl, morpholinyl, tetrahydropyranyl, halo, haloalkyl, haloalkoxy, -CN, -C(O)OR^a, -C(Y)NR^bR^{b'}, -OR^d or -C(Y)R^e; and

each R^a, R^b, R^{b'}, R^c, R^{c'}, R^d, R^{d'}, R^e, R^{e'} and R^f is independently hydrogen, C₁-C₈ alkyl, C₃-C₈ cycloalkyl, tetrahydropyranyl, phenyl, or pyridyl.

Item 12. The compound according to item 10 represented by general formula (II) or a salt thereof,

wherein:

R^1 is C_1 - C_8 alkyl, phenyl or benzodioxolyl;

each R^2 and R^3 is independently hydrogen, C_1 - C_8 alkyl, phenyl, halo, morpholinylalkyl, $-NR^cC(Y)R^c$, $-NR^bR^{b'}$ or $-OR^d$, each of which is optionally substituted with 1-3 R^{11} ;

each R^9 , R^{10} and R^{11} is independently C_1 - C_8 alkyl, morpholinyl, tetrahydropyranyl, halo, haloalkyl, haloalkoxy, $-CN$, $-C(O)OR^a$, $-C(Y)NR^bR^{b'}$, $-OR^d$ or $-C(Y)R^e$; and

each R^a , R^b , $R^{b'}$, R^c , $R^{c'}$, R^d , $R^{d'}$, R^e , $R^{e'}$ and R^f is independently hydrogen, C_1 - C_8 alkyl, C_3 - C_8 cycloalkyl, tetrahydropyranyl, phenyl, or pyridyl.

Item 13. The compound according to item 12 represented by general formula (II) or a salt thereof, wherein:

R^2 is C_1 - C_8 alkyl, phenyl, halo, morpholinylalkyl, $-NR^cC(Y)R^c$, $-NR^bR^{b'}$ or $-OR^d$, each of which is optionally substituted with 1-3 R^{11} ;

R^3 is hydrogen;

R^9 is halo, haloalkoxy, $-CN$, $-C(O)OR^a$ or $-C(Y)NR^bR^{b'}$; and

R^{11} is C_1 - C_8 alkyl, morpholinyl, tetrahydropyranyl, halo, $-CN$, $-OR^d$ or $-C(Y)R^e$;

Item 14. The compound according to item 11 or 13 represented by general formula (II) or a salt thereof, wherein:

R^2 is C_1 - C_8 alkyl, phenyl, halo, morpholinylalkyl, $-NR^cC(Y)R^c$, $-NR^bR^{b'}$ or $-OR^d$;

R^3 is hydrogen; and

R^9 is halo, haloalkoxy, $-CN$, $-C(O)OR^a$ or $-C(Y)NR^bR^{b'}$.

Item 15. The compound according to item 1 represented by general formula (III) or a salt thereof,

wherein:

A is CH or N;

L is O, a direct bond or NH;

one of X^1 , X^2 , X^3 , X^4 and X^5 is N and the others are CH;

m is 1, 2 or 3;

n is 1, 2, 3 or 4;

R^1 is hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, alkoxyalkyl, hydroxyalkyl, heteroaryl, heteroarylalkyl, arylalkyl, $-C(Y)R^e$, cyclyl, cyclylalkyl or heterocyclyl, each of which is optionally substituted with 1-3 R^7 ;

R^2 is aryl or heteroaryl, each of which is optionally substituted with 1-5 R^9 ;

each R^3 or R^4 is independently hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, $-CN$, $-NO_2$, $-C(O)OR^a$, $-C(Y)NR^bR^{b'}$, $-NR^cC(Y)R^c$, $-NR^bR^{b'}$, $-OC(O)NR^bR^{b'}$, $-NR^cC(O)OR^c$, $-SO_2NR^bR^{b'}$, $-NR^cSO_2R^c$, $-NR^cC(Y)NR^bR^{b'}$, $-OR^d$, $-SR^d$, $-C(Y)R^e$ or $-S(O)_qR^f$, each of which is optionally substituted with 1-3 R^{10} ;

each R^7 , R^9 and R^{10} is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, oxo, thioxo, $-CN$, $-NO_2$, $-C(O)OR^a$, $-C(Y)NR^bR^{b'}$, $-NR^cC(Y)R^c$, $-NR^bR^{b'}$, $-OC(O)NR^bR^{b'}$, $-NR^cC(O)OR^c$, $-SO_2NR^bR^{b'}$, $-NR^cSO_2R^c$, $-NR^cC(Y)NR^bR^{b'}$, $-OR^d$, $-SR^d$, $-C(Y)R^e$ or $-S(O)_qR^f$, each of which is optionally substituted with 1-3 R^{12} ; wherein two R^7 or two R^9 are optionally be taken together with the atoms to which they are attached to form an optionally substituted cyclyl, heterocyclyl, aryl or heteroaryl ring;

R^{12} is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, oxo, thioxo, $-CN$, $-NO_2$, $-C(O)OR^a$, $-C(Y)NR^bR^{b'}$, $-NR^cC(Y)R^c$, $-NR^bR^{b'}$, $-OC(O)NR^bR^{b'}$, $-NR^cC(O)OR^c$, $-SO_2NR^bR^{b'}$, $-NR^cSO_2R^c$, $-NR^cC(Y)NR^bR^{b'}$, $-OR^d$, $-SR^d$, $-C(Y)R^e$ or $-S(O)_qR^f$, each of which is optionally substituted with 1-3 R^{13} ;

R^{13} is independently C_1 - C_8 alkyl, haloalkyl, halo, heterocyclyl, cyclyl, oxo or $-C(Y)NR^bR^{b'}$;

Y is O or S;

q is 1 or 2; and

each R^a , R^b , $R^{b'}$, R^c , $R^{c'}$, R^d , $R^{d'}$, R^e and R^f is independently hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, acyl, cyclyl, heterocyclyl, aryl, haloalkyl, alkoxyalkyl, alkylaminoalkyl, dialkylaminoalkyl, heteroaryl, cyclylalkyl, heterocyclalkyl, arylalkyl or heteroarylalkyl..

Item 16. The compound according to item 15 represented by general formula (III) or a salt thereof,

wherein:

m is 1;

n is 1;

R^1 is hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, heteroaryl, heterocyclyl, arylalkyl, cyclylalkyl, heteroarylalkyl, alkoxyalkyl, hydroxyalkyl or $-C(O)R^e$, each of which is optionally substituted with 1-3 R^7 ;

R^2 is aryl, heteroaryl or benzofuryl, each of which is optionally substituted with 1-5 R^9 ;

each R^3 or R^4 is independently hydrogen, C_1 - C_8 alkyl, halo, haloalkyl or $-OR^d$;

R^6 is hydrogen or C_1 - C_8 alkyl;

each R^7 and R^9 is independently C_1 - C_8 alkyl, aryl, heteroaryl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, alkoxyalkyl, oxo, $-CN$, $-NO_2$, $-C(O)OR^a$, $-C(O)NR^bR^{b'}$, $-NR^bR^{b'}$, $-OR^d$, $-C(O)R^e$ or $-S(O)_qR^f$, each of which is optionally substituted with 1-3 R^{12} ;

R^{12} is independently C_1 - C_8 alkyl, oxo, halo, haloalkyl, $-CN$, $-C(O)NR^bR^{b'}$ or $-C(O)R^e$ each of which is optionally substituted with 1-3 R^{13} ;

R^{13} is independently C_1 - C_8 alkyl, halo or heterocyclyl; and

each R^a , R^b , $R^{b'}$, R^c , $R^{c'}$, R^d , $R^{d'}$, R^e and R^f is independently hydrogen, C_1 - C_8 alkyl, cyclyl, heterocyclyl, arylalkyl, alkoxyalkyl, heterocyclalkyl, heteroarylalkyl, alkylaminoalkyl, dialkylaminoalkyl or phenyl.

Item 17. The compound according to Item 16 represented by general formula (III) or a salt thereof,

wherein:

R^1 is hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, alkoxyalkyl, hydroxyalkyl, imidazolyl, pyridylalkyl, phenylalkyl, oxazolylalkyl, thienylalkyl, thiazolidinyl isoindolyl, $-C(O)R^c$, dihydroindenyl, C_3 - C_8 cycloalkyl, C_3 - C_8 cycloalkylalkyl, piperidyl, morpholinyl, pyrrolidinyl, azetidyl or piperazinyl, each of which is optionally substituted with 1-3 R^7 ;

R^2 is phenyl, naphthyl, benzofuryl, indazolyl, benzothienyl, pyridyl, pyrimidinyl, dihydrobenzodioxinyl, benzodioxolyl, benzoimidazolyl, isoxazolyl, pyrazolyl, indolinyl or benzoisoxazolyl, each of which is optionally substituted with 1-5 R^9 ;

each R^3 or R^4 is independently hydrogen, C_1 - C_8 alkyl, halo, haloalkyl or $-OR^d$;

R^6 is hydrogen or C_1 - C_8 alkyl;

each R^7 and R^9 is independently C_1 - C_8 alkyl, phenyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, alkoxyalkyl, oxo, $-CN$, $-NO_2$, $-C(O)OR^a$, $-C(O)NR^bR^{b'}$, $-NR^bR^{b'}$, $-OR^d$, $-C(O)R^c$ or $-S(O)_qR^f$; and

each R^a , R^b , $R^{b'}$, R^c , $R^{c'}$, R^d , $R^{d'}$, R^e and R^f is independently hydrogen, C_1 - C_8 alkyl, C_3 - C_8 cycloalkyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, tetrahydropyranyl, phenylalkyl, alkoxyalkyl, morpholinylalkyl, oxazolidinylalkyl, imidazolylalkyl, tetrahydropyranylalkyl, pyridylalkyl, pyrazolylalkyl, tetrazolylalkyl, thiazolylalkyl, pyrrolylalkyl, benzoxazolylalkyl, indazolylalkyl, dihydrobenzoxazinylalkyl, tetrahydrofurylalkyl, tetrahydrofuryl, alkylaminoalkyl, dialkylaminoalkyl or phenyl.

Item 18. The compound according to item 16 represented by general formula (III) or a salt thereof,

wherein:

R^1 is hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, alkoxyalkyl, hydroxyalkyl, imidazolyl, furylalkyl, pyridylalkyl, phenylalkyl, oxazolylalkyl, thienylalkyl, thiazolidinyl, isoindolyl, $-C(O)R^c$, dihydroindenyl, C_3 - C_8 cycloalkyl,

C₃-C₈ cycloalkylalkyl, piperidyl, morpholinyl, pyrrolidinyl, azetidinyll or piperazinyl, each of which is optionally substituted with 1-3 R⁷;

R² is phenyl, naphthyl, benzofuryl, indazolyl, benzothienyl, pyridyl, pyrimidinyl, dihydrobenzodioxinyl, benzodioxolyl, benzoimidazolyl, isoxazolyl, pyrazolyl, indolinyl or benzisoxazolyl, each of which is optionally substituted with 1-5 R⁹;

each R³ or R⁴ is independently hydrogen, C₁-C₈ alkyl, halo, haloalkyl or -OR^d;

R⁶ is hydrogen or C₁-C₈ alkyl;

each R⁷ and R⁹ is independently C₁-C₈ alkyl, phenyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, alkoxyalkyl, oxo, -CN, -NO₂, -C(O)OR^a, -C(O)NR^bR^{b'}, -NR^bR^{b'}, -OR^d, -C(O)R^e or -S(O)_qR^f, each of which is optionally substituted with 1-3 R¹²;

R¹² is independently C₁-C₈ alkyl, oxo, halo, haloalkyl, -CN, -C(O)NR^bR^{b'} or -C(O)R^e, each of which is optionally substituted with 1-3 R¹³;

R¹³ is independently C₁-C₈ alkyl, halo or pyrrolidinyl; and

each R^a, R^b, R^{b'}, R^c, R^{c'}, R^d, R^{d'}, R^e and R^f is independently hydrogen, C₁-C₈ alkyl, C₃-C₈ cycloalkyl, pyrrolidinyl, piperidyl, morpholinyl, piperazinyl, tetrahydropyranyl, phenylalkyl, alkoxyalkyl, morpholinylalkyl, oxazolidinylalkyl, imidazolylalkyl, tetrahydropyranylalkyl, pyridylalkyl, pyrazolylalkyl, tetrazolylalkyl, thiazolylalkyl, pyrrolylalkyl, benzoxazolylalkyl, indazolylalkyl, dihydrobenzoxazinylalkyl, tetrahydrofurylalkyl, tetrahydrofuryl, alkylaminoalkyl, dialkylaminoalkyl or phenyl.

Item 19. The compound according to item 18 represented by general formula (III) or a salt thereof,

wherein:

A is N;

R³ is hydrogen, C₁-C₈ alkyl, halo, haloalkyl, or -OR^d;

R⁴ is hydrogen, C₁-C₈ alkyl, halo, or -OR^d;

R⁷ is C₁-C₈ alkyl, phenyl, halo, haloalkyl, oxo, -C(O)OR^a, -C(O)NR^bR^{b'} or -OR^d each of which is optionally substituted with 1-3 R¹²;

R⁹ is C₁-C₈ alkyl, phenyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, alkoxyalkyl, -CN, -NO₂, -C(O)NR^bR^{b'}, -C(O)OR^a, -NR^bR^{b'}, -OR^d, -C(O)R^e or -S(O)_qR^f, each of which is optionally substituted with 1-3 R¹²; and

each R^a , R^b , $R^{b'}$, R^c , $R^{c'}$, R^d , $R^{d'}$, R^e and R^f is independently hydrogen, C_1 - C_8 alkyl, C_3 - C_8 cycloalkyl, pyrrolidinyl, piperidyl, morpholinyl, piperazinyl, tetrahydropyranyl, phenylalkyl, alkoxyalkyl, morpholinylalkyl, oxazolidinylalkyl, imidazolylalkyl, tetrahydropyranylalkyl, pyridylalkyl, pyrazolylalkyl, tetrazolylalkyl, thiazolylalkyl, pyrrolylalkyl, benzoxazolylalkyl, indazolylalkyl, tetrahydrofurylalkyl, dihydrobenzoxazinylalkyl, tetrahydrofuryl, alkylaminoalkyl, dialkylaminoalkyl or phenyl.

Item 20. The compound according to item 17 or 19 represented by general formula (III) or a salt thereof,

wherein:

A is N;

R^3 is hydrogen, C_1 - C_8 alkyl, halo, haloalkyl, or $-OR^d$;

R^4 is hydrogen, C_1 - C_8 alkyl, halo, or $-OR^d$;

R^7 is C_1 - C_8 alkyl, phenyl, halo, haloalkyl, oxo, $-C(O)OR^a$, $-C(O)NR^bR^{b'}$ or $-OR^d$;

R^9 is C_1 - C_8 alkyl, phenyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, alkoxyalkyl, $-CN$, $-NO_2$, $-C(O)NR^bR^{b'}$, $-C(O)OR^a$, $-NR^bR^{b'}$, $-OR^d$, $-C(O)R^e$ or $-S(O)_qR^f$; and

each R^a , R^b , $R^{b'}$, R^c , $R^{c'}$, R^d , $R^{d'}$, R^e and R^f is independently hydrogen, C_1 - C_8 alkyl, C_3 - C_8 cycloalkyl, pyrrolidinyl, piperidyl, morpholinyl, piperazinyl, tetrahydropyranyl, phenylalkyl, alkoxyalkyl, morpholinylalkyl, oxazolidinylalkyl, imidazolylalkyl, tetrahydropyranylalkyl, pyridylalkyl, pyrazolylalkyl, tetrazolylalkyl, thiazolylalkyl, pyrrolylalkyl, benzoxazolylalkyl, indazolylalkyl, tetrahydrofurylalkyl, tetrahydrofuryl, dihydrobenzoxazinylalkyl, alkylaminoalkyl, dialkylaminoalkyl or phenyl.

Item 21. The compound according to item 20 represented by general formula (III) or a salt thereof,

wherein:

R^1 is hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, alkoxyalkyl, hydroxyalkyl, imidazolyl, furylalkyl, pyridylalkyl, phenylalkyl, oxazolylalkyl, thienylalkyl, isoindolyl, $-C(O)R^e$, dihydroindenyl, C_3 - C_8 cycloalkyl,

C₃-C₈ cycloalkylalkyl, piperidyl, morpholinyl, pyrrolidinyl, azetidinyll or piperazinyl, each of which is optionally substituted with 1-3 R⁷;

R² is phenyl, which is optionally substituted with 1-5 R⁹; and

each R^a, R^b, R^{b'}, R^c, R^{c'}, R^d, R^{d'}, R^e and R^f is independently hydrogen, C₁-C₈ alkyl, pyrrolidinyl, morpholinyl, tetrahydropyranyl, alkoxyalkyl, morpholinylalkyl, tetrahydropyranylalkyl, pyridylalkyl, thiazolylalkyl, pyrrolylalkyl, tetrahydrofuryl, alkylaminoalkyl or phenyl.

Item 22. A pharmaceutical composition comprising the compound according to any one of items 1 to 21 or a salt thereof as an active ingredient and a pharmaceutically acceptable carrier.

Item 23. The pharmaceutical composition according to item 22 for preventing or treating central nervous system diseases.

Item 24. The pharmaceutical composition according to item 23 for treating or preventing central nervous system disorders selected from the group consisting of schizophrenia; refractory, intractable or chronic schizophrenia; emotional disturbance; psychotic disorder; mood disorder; bipolar I type disorder; bipolar II type disorder; depression; endogenous depression; major depression; melancholy and refractory depression; dysthymic disorder; cyclothymic disorder; panic attack; panic disorder; agoraphobia; social phobia; obsessive-compulsive disorder; post-traumatic stress disorder; generalized anxiety disorder; acute stress disorder; hysteria; somatization disorder; conversion disorder; pain disorder; hypochondriasis; factitious disorder; dissociative disorder; sexual dysfunction; sexual desire disorder; sexual arousal disorder; erectile dysfunction; anorexia nervosa; bulimia nervosa; sleep disorder; adjustment disorder; alcohol abuse; alcohol intoxication; drug addiction; stimulant intoxication; narcotism; anhedonia; iatrogenic anhedonia; anhedonia of a psychic or mental cause; anhedonia associated with depression; anhedonia associated with schizophrenia; delirium; cognitive impairment; cognitive impairment associated with Alzheimer's disease,

Parkinson's disease and other neurodegenerative diseases; cognitive impairment caused by Alzheimer's disease; Parkinson's disease and associated neurodegenerative diseases; cognitive impairment of schizophrenia; cognitive impairment caused by refractory, intractable or chronic schizophrenia; vomiting; motion sickness; obesity; migraine; pain (ache) ; mental retardation; autism disorder (autism); Tourette's disorder; tic disorder; attention-deficit/hyperactivity disorder; conduct disorder; and Down's syndrome.

Item 25. A process for producing a pharmaceutical composition comprising mixing a compound of the formula (I), (II), or (III) or a salt thereof according to any one of items 1 to 21 with a pharmaceutically acceptable carrier.

Item 26. Use of a compound of the formula (I), (II) or (III) or a salt thereof according to any one of items 1 to 21 as a drug.

Item 27. Use of the compound according to any one of items 1 to 21 represented by general formula(I), (II) or (III) or a salt thereof as a STEP inhibitor .

Item 28. A method of treating a disorder that would benefit by the modulation of STEP (e.g., by activation of inhibition of STEP) in a subject, the method comprising administering to a compound of formula (I), (II) or (III) or a salt thereof according to any one of items 1 to 21.

Item 29. The method of item 28, wherein the disorder is schizophrenia.

Item 30. The method of item 28, wherein the disorder is cognitive deficit.

Item 31. The method of item 28, wherein the compound of formula (I), (II), or (III) is administered in combination with an additional therapeutic agent.

Item 32. The method of item 28, wherein the additional therapeutic agent is an atypical antipsychotic.

Item 33. The method of item 28, wherein the additional therapeutic agent is selected from the group consisting of aripiprazole, clozapine, ziprasidone, risperidone, quetiapine, olanzapine, amisulpride, asenapine, iloperidone, melperone, paliperidone, perospirone, sertindole and sulpiride.

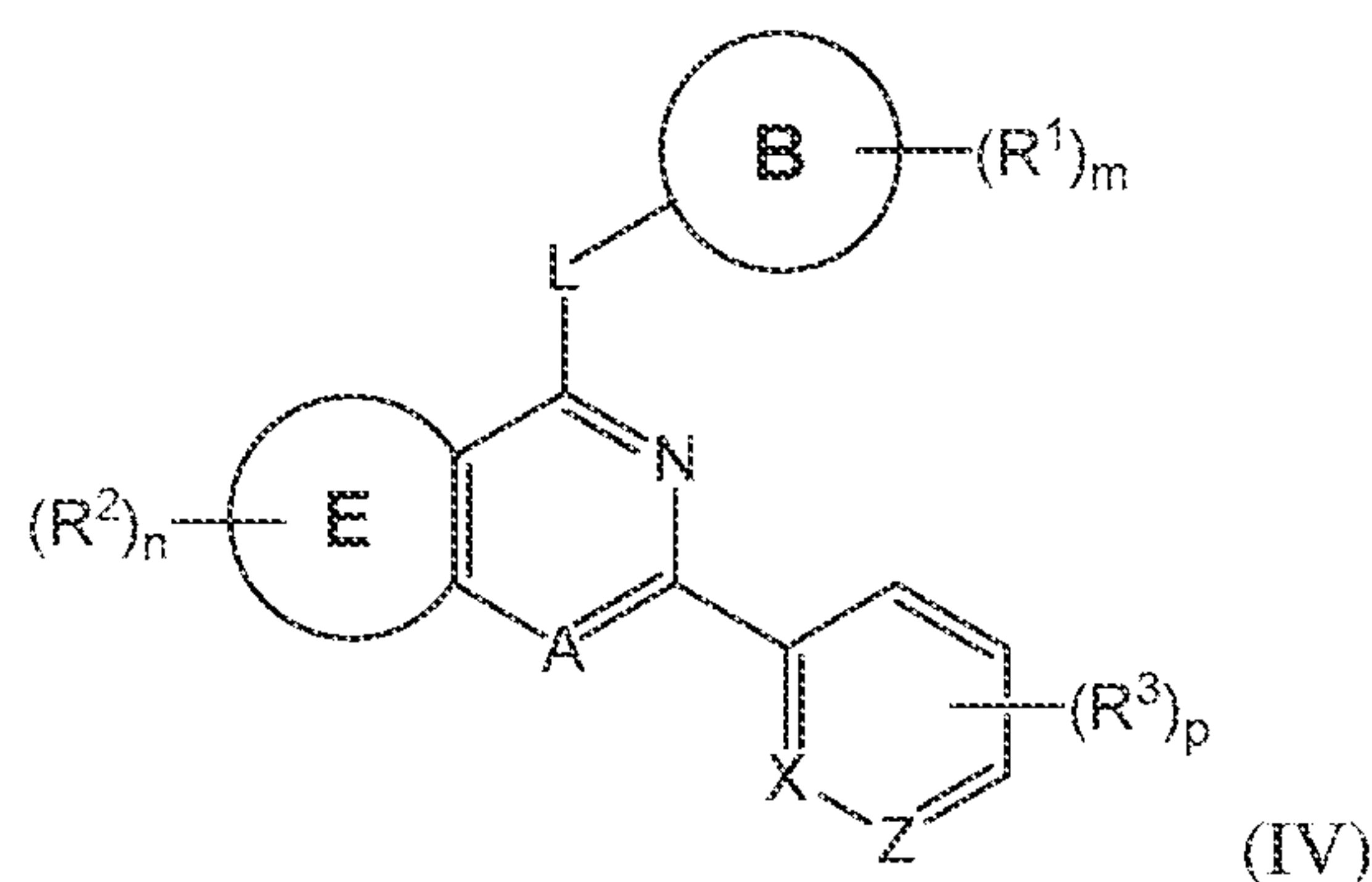
Item 34. The method of item 28, wherein the additional therapeutic agent is a typical antipsychotic.

Item 35. The method of item 28, wherein the additional therapeutic agent is selected from the group consisting of haloperidol, molindone, loxapine, thioridazine, molindone, thiothixene, pimozide, fluphenazine, trifluoperazine, mesoridazine, chlorprothixene, chlorpromazine, perphenazine, triflupromazine and zuclopenthixol.

Item 36. A kit comprising a composition comprising a compound of formula (I), (II), or (III) or a salt thereof according to any one of items 1 to 21 and an acceptable carrier.

Item 37. A kit comprising a pharmaceutical composition comprising a compound of formula (I), (II), or (III) or a salt thereof according to any one of items 1 to 21 and a pharmaceutically acceptable carrier.

Item 38. A compound of formula (IV):



wherein:

A is CH, CR⁴ or N;

B is aryl or a 5- or 6-membered heteroaryl;

m is 0, 1, 2, 3, 4 or 5;

E is aryl or a 5-membered heteroaryl;

when E is aryl, n is 1, 2, 3 or 4; and when E is a 5-membered heteroaryl, n is 0, 1, 2 or 3;

L is NR⁵ or O;

one of X and Z is N and the other is CH;

p is 0, 1, 2, 3 or 4;

each R¹, R² and R³ is independently C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, -CN, -NO₂, -C(O)OR^a, -C(Y)NR^bR^{b'}, -NR^cC(Y)R^{c'}, -NR^bR^{b'}, -OC(O)NR^bR^{b'}, -NR^cC(O)OR^{c'}, -SO₂NR^bR^{b'}, -NR^cSO₂R^{c'}, -NR^cC(Y)NR^bR^{b'}, -OR^d, -SR^{d'}, -C(Y)R^e or -S(O)_qR^f, each of which may be optionally substituted with 1-3 R⁶; wherein two R¹, together with the atoms to which they are attached, may form an optionally substituted cyclyl, heterocyclyl, aryl or heteroaryl ring;

R⁴ is hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, -CN, -NO₂, -C(O)OR^a, -C(Y)NR^bR^{b'}, -NR^cC(Y)R^{c'}, -NR^bR^{b'}, -OC(O)NR^bR^{b'}, -NR^cC(O)OR^{c'}, -

$\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^{c'}$, $-\text{NR}^c\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^{d'}$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$, each of which may be optionally substituted with 1-3 R^6 ;

R^5 is hydrogen; or when m is not 0, R^5 and 1 R^1 may be taken together with the atoms to which they are attached to form an optionally substituted heteroaryl or heterocyclyl ring;

each R^6 is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, oxo, thiono, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^{c'}$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{O})\text{OR}^{c'}$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^{c'}$, $-\text{NR}^c\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^{d'}$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$, each of which may be optionally substituted with 1-3 R^7 ;

each R^7 is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, oxo, thiono, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^{c'}$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{O})\text{OR}^{c'}$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^{c'}$, $-\text{NR}^c\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^{d'}$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$;

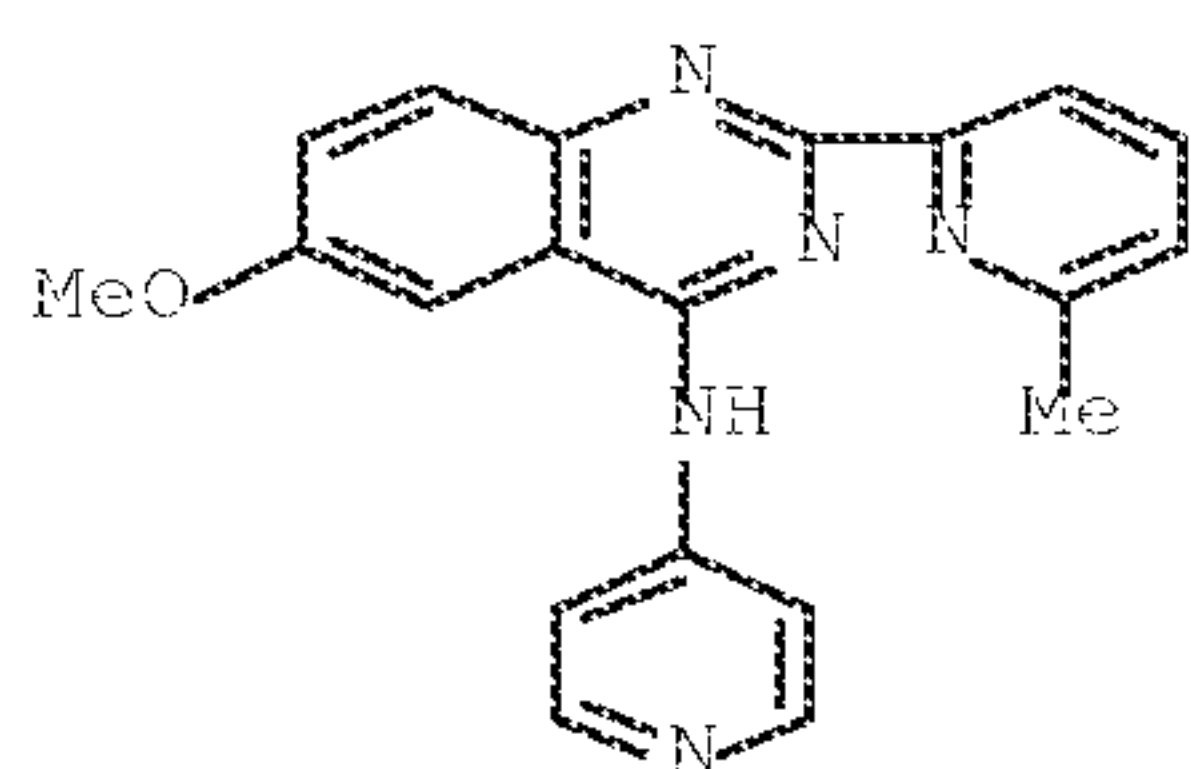
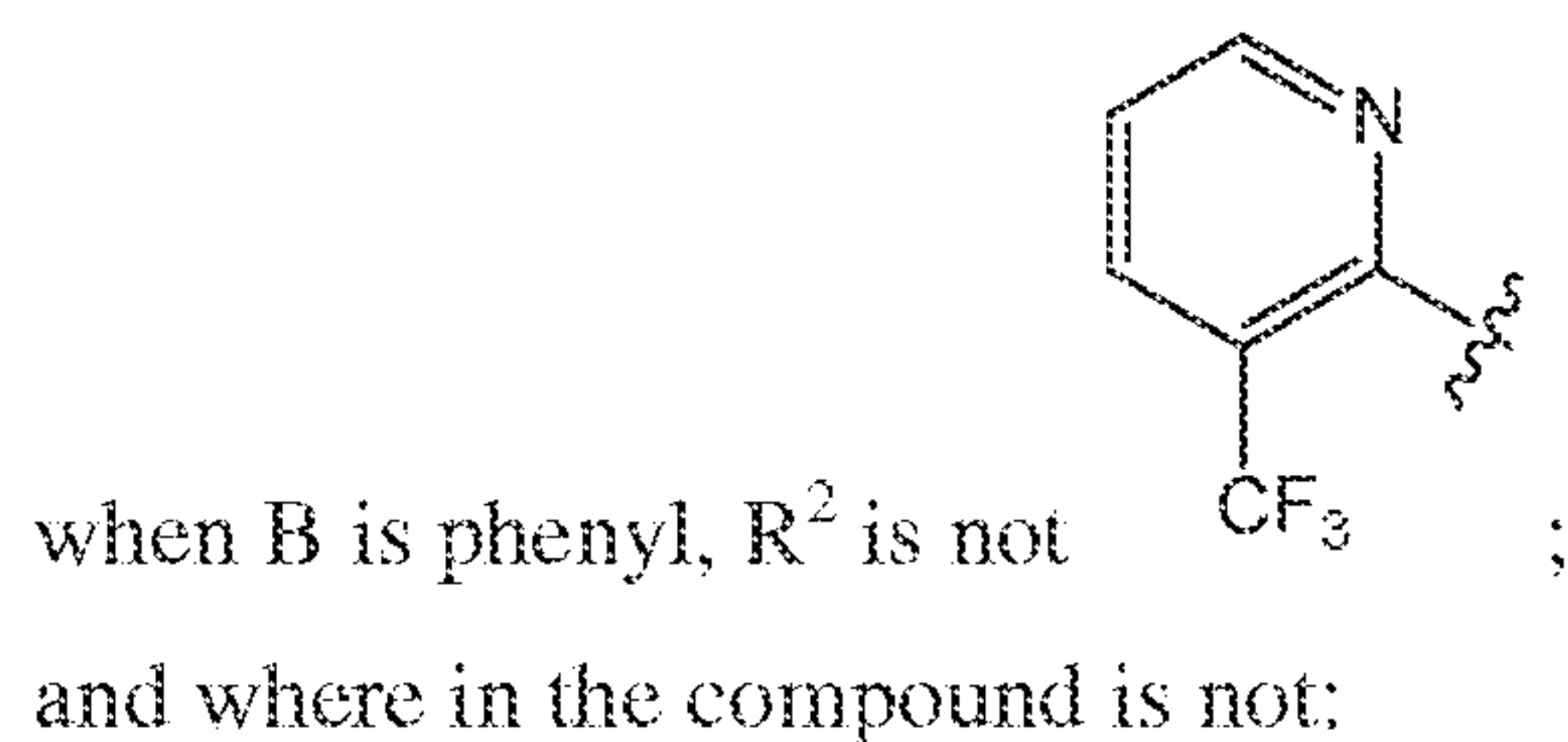
each Y is independently O or S;

q is 1 or 2; and

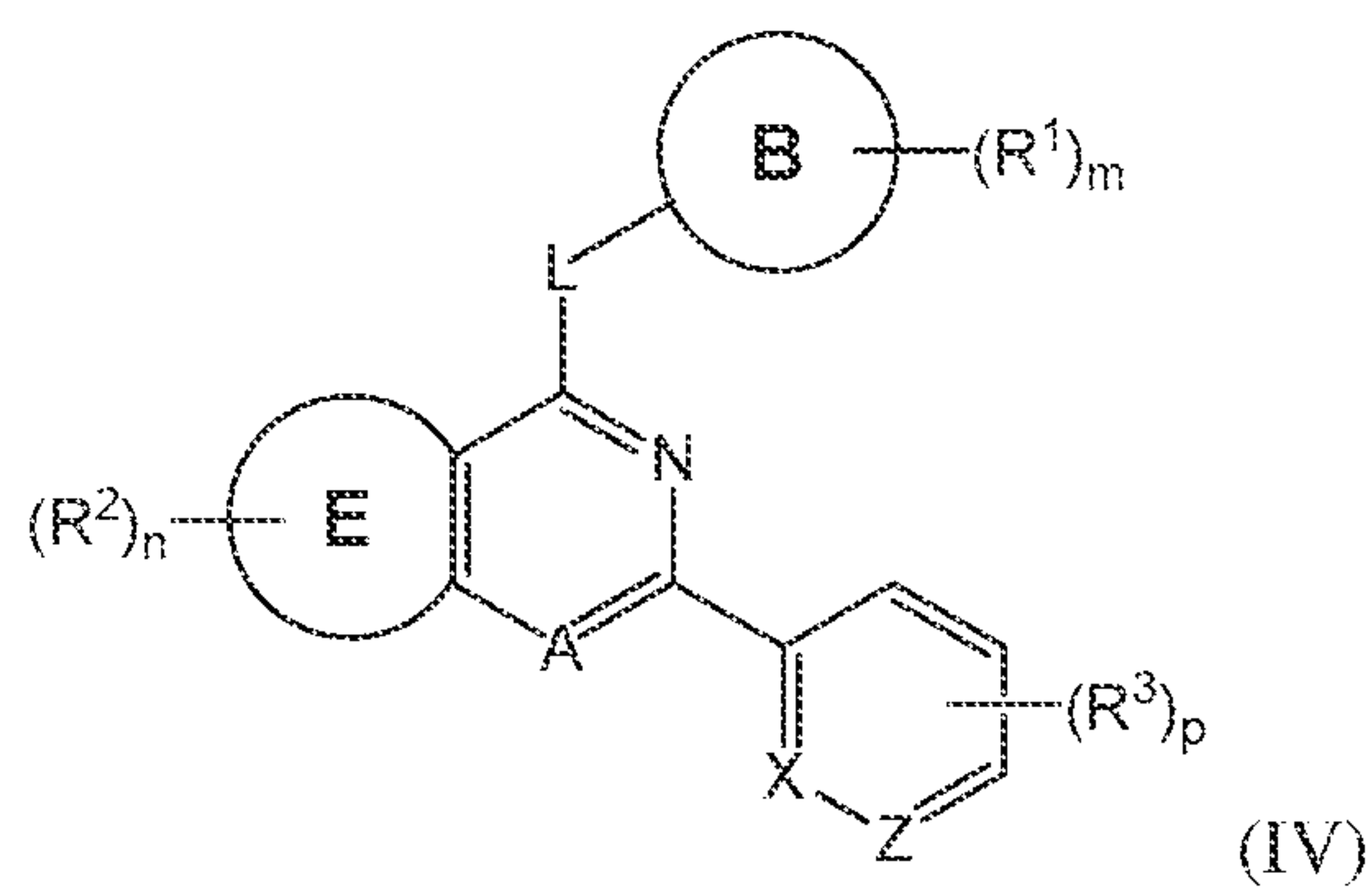
each R^a , R^b , $\text{R}^{b'}$, R^c , $\text{R}^{c'}$, R^d , $\text{R}^{d'}$, R^e , $\text{R}^{e'}$ and R^f is independently selected from hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, acyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy and silylalkoxyalkyl, each of which may be optionally substituted with 1-3 R^6 , wherein R^b and $\text{R}^{b'}$, together with the atoms to which they are attached, may form an optionally substituted cyclyl or heterocyclyl ring;

or a pharmaceutically acceptable derivative or prodrug thereof,

wherein when B is phenyl, two R^1 are not taken together to form a pyrazole ring;



Item 39. A compound of formula (IV) :



wherein:

A is CH, CR⁴ or N;

B is aryl or a 5-membered heteroaryl;

E is aryl or a 5-membered heteroaryl;

L is NR⁵ or O;

one of X and Z is N and the other is CH;

m is 0, 1, 2, 3, 4 or 5;

n is 1, 2, 3 or 4;

p is 0, 1, 2, 3 or 4;

each R^1 and R^3 is independently C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl,

heterocyclalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^c$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{O})\text{OR}^c$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^c$, $-\text{NR}^c\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^d$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$, each of which may be optionally substituted with 1-3 R^6 ; wherein two R^1 , together with the atoms to which they are attached, may form an optionally substituted cyclalkyl, heterocyclalkyl, or aryl ring;

each R^2 is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, cyclalkyl, heterocyclalkyl, aralkyl, heteroaralkyl, cyclalkyl, heterocyclalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^c$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{O})\text{OR}^c$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^c$, $-\text{NR}^c\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^d$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$, each of which may be optionally substituted with 1-3 R^6 ; wherein two R^1 , together with the carbons to which they are attached, may form an optionally substituted cyclalkyl, heterocyclalkyl, aryl or heteroaryl ring;

R^4 is hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclalkyl, heterocyclalkyl, aralkyl, heteroaralkyl, cyclalkyl, heterocyclalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^c$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{O})\text{OR}^c$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^c$, $-\text{NR}^c\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^d$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$, each of which may be optionally substituted with 1-3 R^6 ;

R^5 is hydrogen; or when m is not 0, R^5 and 1 R^1 may be taken together with the atoms to which they are attached to form an optionally substituted heteroaryl or heterocyclalkyl ring;

each R^6 is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclalkyl, heterocyclalkyl, aralkyl, heteroaralkyl, cyclalkyl, heterocyclalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, oxo, thiono, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^c$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{O})\text{OR}^c$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^c$, $-\text{NR}^c\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^d$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$, each of which may be optionally substituted with 1-3 R^6 ;

$\text{OC(O)NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C(O)OR}^{c'}$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^{c'}$, $-\text{NR}^c\text{C(Y)NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^{d'}$, $-\text{C(Y)R}^e$ or $-\text{S(O)}_q\text{R}^f$, each of which may be optionally substituted with 1-3 R^7 ;

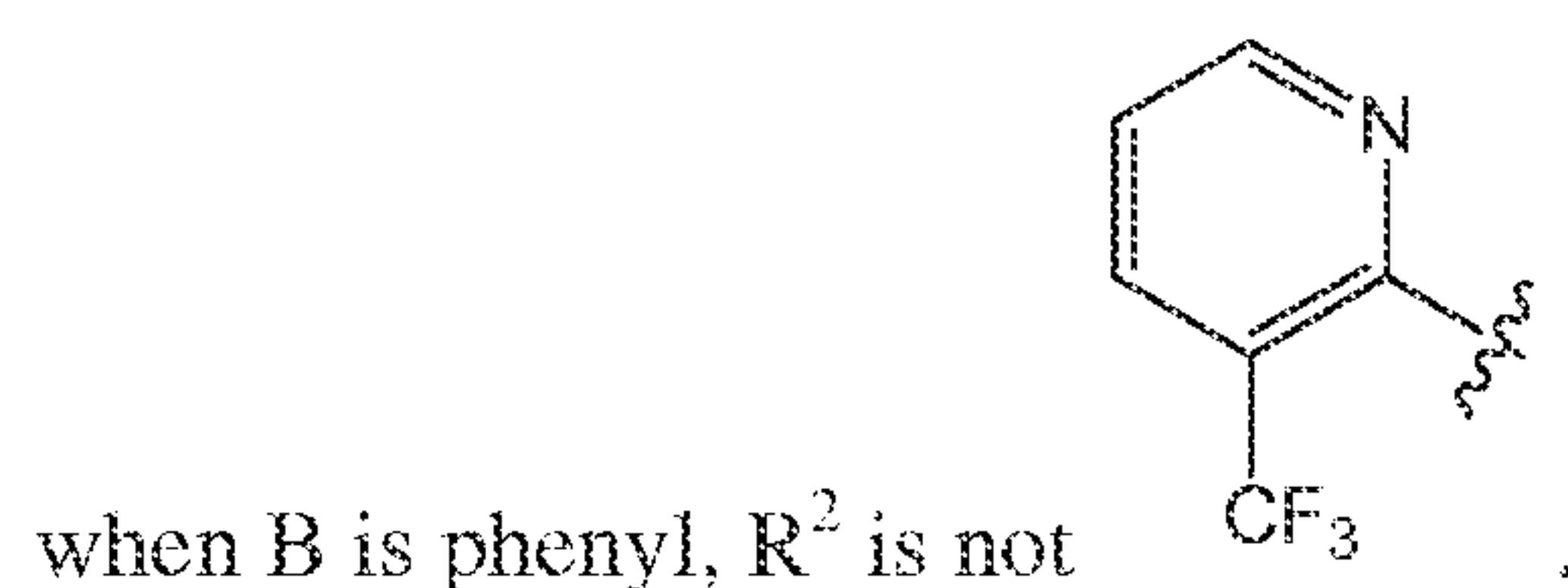
each R^7 is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, oxo, thiono, $-\text{CN}$, $-\text{NO}_2$, $-\text{C(O)OR}^a$, $-\text{C(Y)NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C(Y)R}^{c'}$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC(O)NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C(O)OR}^{c'}$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^{c'}$, $-\text{NR}^c\text{C(Y)NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^{d'}$, $-\text{C(Y)R}^e$ or $-\text{S(O)}_q\text{R}^f$;

Y is O or S;

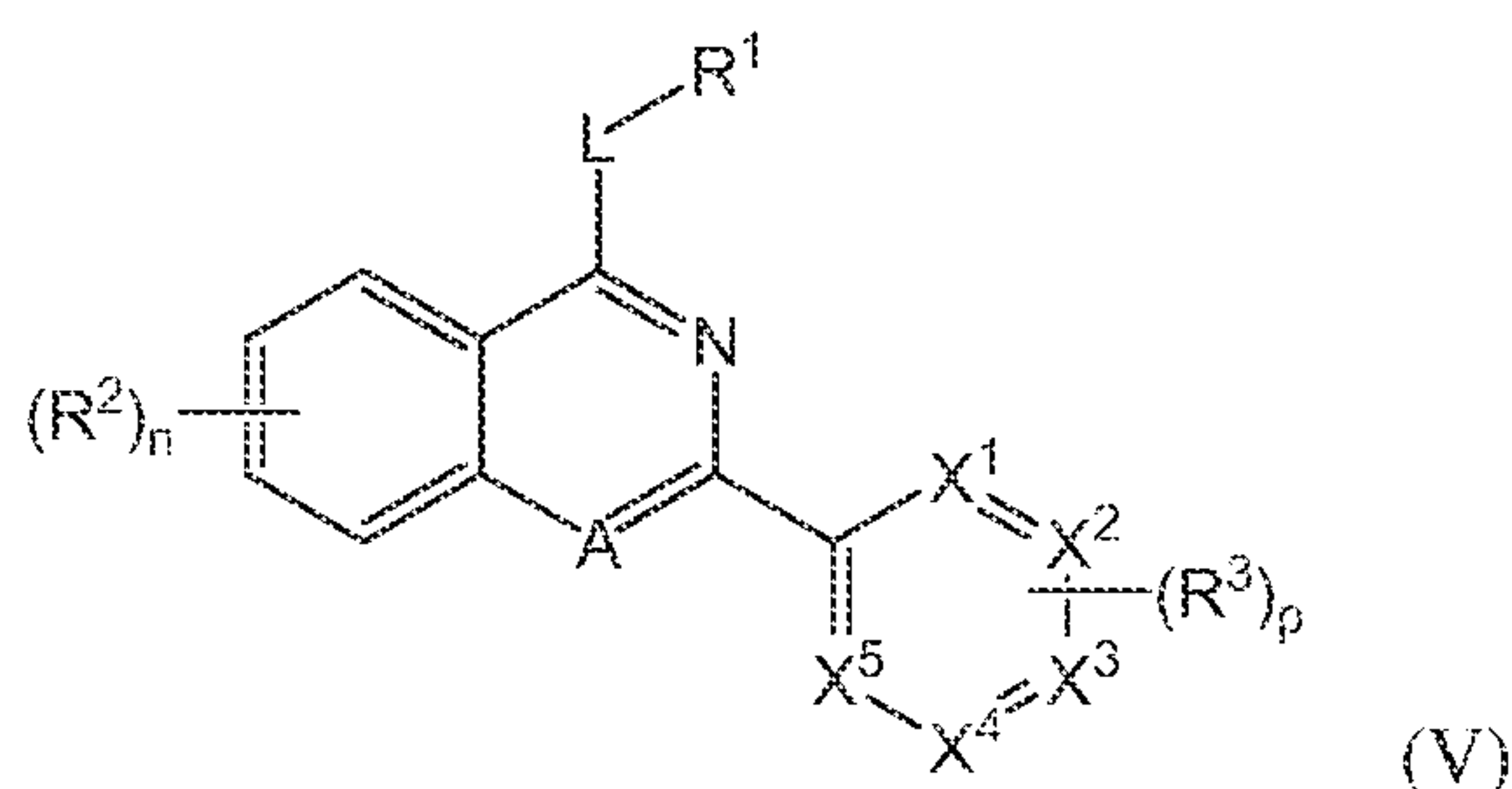
q is 1 or 2; and

each R^a , R^b , $\text{R}^{b'}$, R^c , $\text{R}^{c'}$, R^d , $\text{R}^{d'}$, R^e , $\text{R}^{e'}$ and R^f is independently selected from hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, acyl, cyclyl, heterocyclyl, aryl, heteroaryl, cyclylalkyl, heterocyclylalkyl, aralkyl and heteroaralkyl, each of which may be optionally further substituted with 1-3 R^6 , wherein R^b and $\text{R}^{b'}$, together with the atoms to which they are attached, may form an optionally substituted cyclyl or heterocyclyl ring;.

wherein when B is phenyl, two R^1 are not taken together to form a pyrazole ring; and



Item 40. A compound of formula (V) :



wherein:

L is CR^4R^5 , O, $\text{C}(\text{O})$, $\text{NR}^6\text{C}(\text{O})$, or NR^7 ;

A is CR^8 , CH or N;

each X^1 , X^2 , X^3 , X^4 and X^5 is independently CH or N, provided that at least two of X^1 , X^2 , X^3 , X^4 and X^5 are N;

n is 0, 1, 2, 3 or 4;

p is 0, 1, 2 or 3;

R^1 is C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl or heterocyclylalkyl, each of which may be optionally substituted with 1-5 R^9 ; wherein R^1 or R^9 may optionally be taken together with one of R^4 , R^5 , R^6 or R^7 , and the atoms to which they are attached, to form a cyclyl, heterocyclyl, aryl or heteroaryl ring that is optionally substituted with 1-3 R^{10} ;

each R^2 and R^3 is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^c$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{O})\text{OR}^c$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^c$, $-\text{NR}^c\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^d$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$; each of which is optionally substituted with 1-3 R^{11} ;

each R^4 , R^5 , R^6 and R^7 is independently H, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^c$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{O})\text{OR}^c$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^c$, $-\text{NR}^c\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^d$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$;

each R^8 , R^9 , R^{10} and R^{11} is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy,

silylalkoxyalkyl, oxo, thiono, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^{c'}$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{O})\text{OR}^{c'}$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^{c'}$, $-\text{NR}^c\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^{d'}$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$, each of which may be optionally further substituted; wherein two R^8 , two R^9 , two R^{10} or two R^{11} may optionally be taken together with the atoms to which they are attached to form an optionally substituted cyclyl, heterocyclyl, aryl or heteroaryl ring;

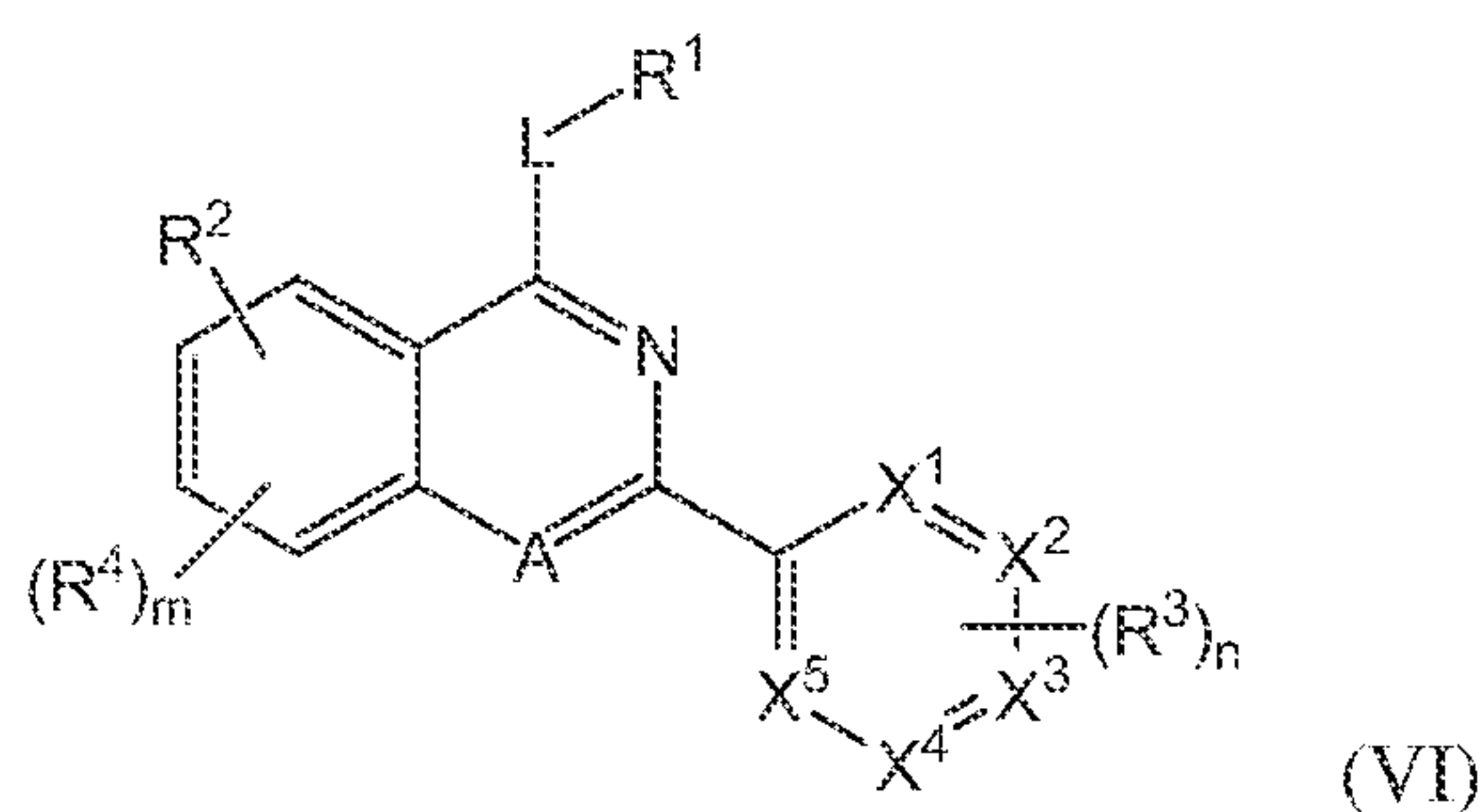
each Y is independently O or S;

q is 1 or 2; and

each R^a , R^b , $\text{R}^{b'}$, R^c , $\text{R}^{c'}$, R^d , $\text{R}^{d'}$, R^e , $\text{R}^{e'}$ and R^f is independently selected from hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, acyl, cyclyl, heterocyclyl, aryl, heteroaryl, cyclylalkyl, heterocyclylalkyl, aralkyl and heteroaralkyl, each of which may be optionally substituted with 1-3 R^8 ,

or a pharmaceutically acceptable derivative or prodrug thereof.

Item 41. A compound of formula (VI):



wherein:

A is CR^5 , CH or N;

L is O or NR^6 ;

1, 2 or 3 of X^1 , X^2 , X^3 , X^4 and X^5 are N and the others are CH;

m is 0, 1, 2 or 3;

n is 0, 1, 2, 3 or 4;

R^1 is hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, cyclyl or heterocyclyl, each of which is optionally substituted with 1-3 R^7 ; or when L is NR^6 ,

R^1 or R^7 may be taken together with R^6 and the atoms to which they are attached to form a heterocyclyl or heteroaryl ring that is optionally substituted with 1-3 R^8 ;

R^2 is aryl or heteroaryl, each of which is optionally substituted with 1-5 R^9 ;

each R^3 , R^4 and R^5 is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^{c'}$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{O})\text{OR}^{c'}$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^{c'}$, $-\text{NR}^c\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^{d'}$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$, each of which is optionally substituted with 1-3 R^{10} ;

R^6 is hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, cyclyl or heterocyclyl, each of which is optionally substituted with 1-3 R^{11} ;

each R^7 , R^8 , R^9 and R^{10} is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, oxo, thiono, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^{c'}$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{O})\text{OR}^{c'}$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^{c'}$, $-\text{NR}^c\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^{d'}$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$, each of which is optionally substituted with 1-3 R^{12} ; wherein two R^7 , two R^8 , two R^9 or two R^{10} may optionally be taken together with the atoms to which they are attached to form an optionally substituted cyclyl, heterocyclyl, aryl or heteroaryl ring;

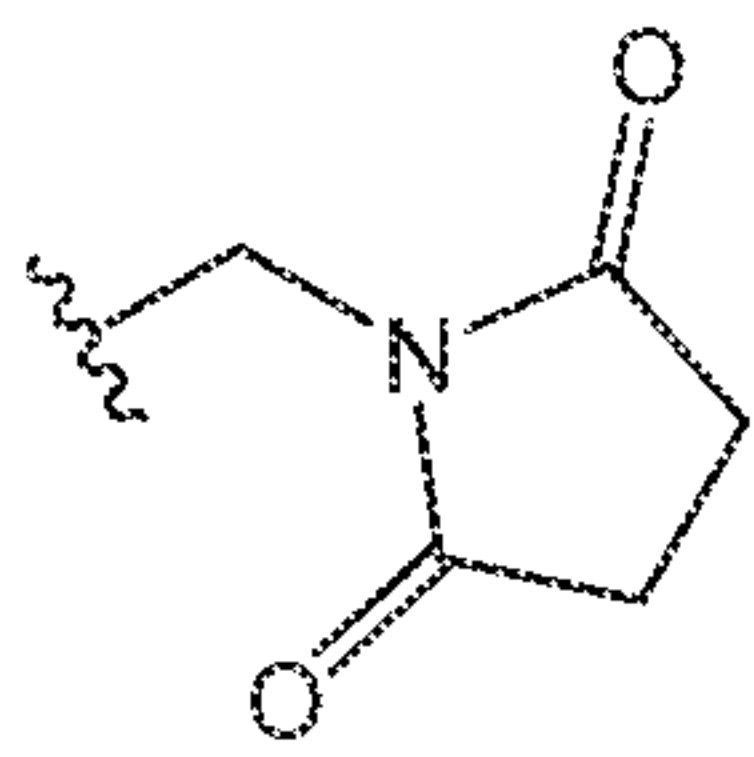
each R^{11} and R^{12} is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, oxo, thiono, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^{c'}$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{O})\text{OR}^{c'}$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^{c'}$, $-\text{NR}^c\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^{d'}$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$;

each Y is independently O or S;

q is 1 or 2; and

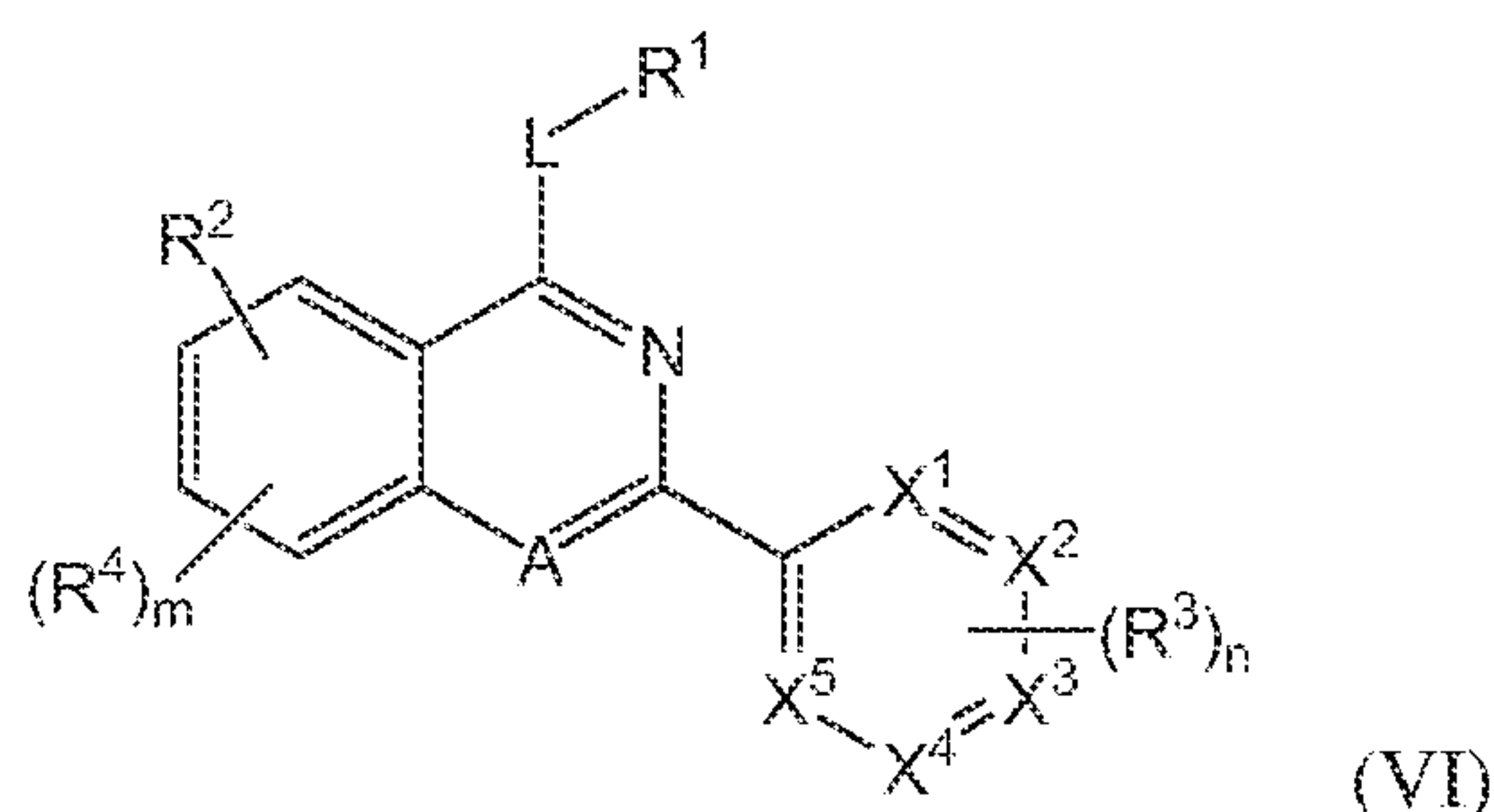
each R^a , R^b , $R^{b'}$, R^c , $R^{c'}$, R^d , $R^{d'}$, R^e , $R^{e'}$ and R^f is independently selected from hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, acyl, cyclyl, heterocyclyl, aryl, heteroaryl, cyclylalkyl, heterocyclalkyl, aralkyl and heteroaralkyl, each of which may be optionally substituted with 1-3 R^7 ;

or a pharmaceutically acceptable derivative or prodrug thereof,



wherein when R^1 is cyclopropyl, R^9 is not:

Item 42. A compound of formula (VI):



wherein:

A is CR^5 , CH or N;

L is O or NR^6 ;

1, 2 or 3 of X^1 , X^2 , X^3 , X^4 and X^5 are N and the others are CH;

m is 0, 1, 2 or 3;

n is 0, 1, 2, 3 or 4;

R^1 is hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, cyclyl or heterocyclyl, each of which is optionally substituted with 1-3 R^7 ; or when L is NR^6 , R^1 or R^7 may be taken together with R^6 and the atoms to which they are attached to form a heterocyclyl or heteroaryl ring that is optionally substituted with 1-3 R^8 ;

R^2 is aryl or heteroaryl, each of which is optionally substituted with 1-5 R^9 ;

each R^3 , R^4 and R^5 is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl,

heterocyclalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^{c'}$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{O})\text{OR}^{c'}$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^{c'}$, $-\text{NR}^c\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^{d'}$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$, each of which is optionally substituted with 1-3 R^{10} ;

R^6 is hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, cyclyl or heterocyclyl, each of which is optionally substituted with 1-3 R^{11} ;

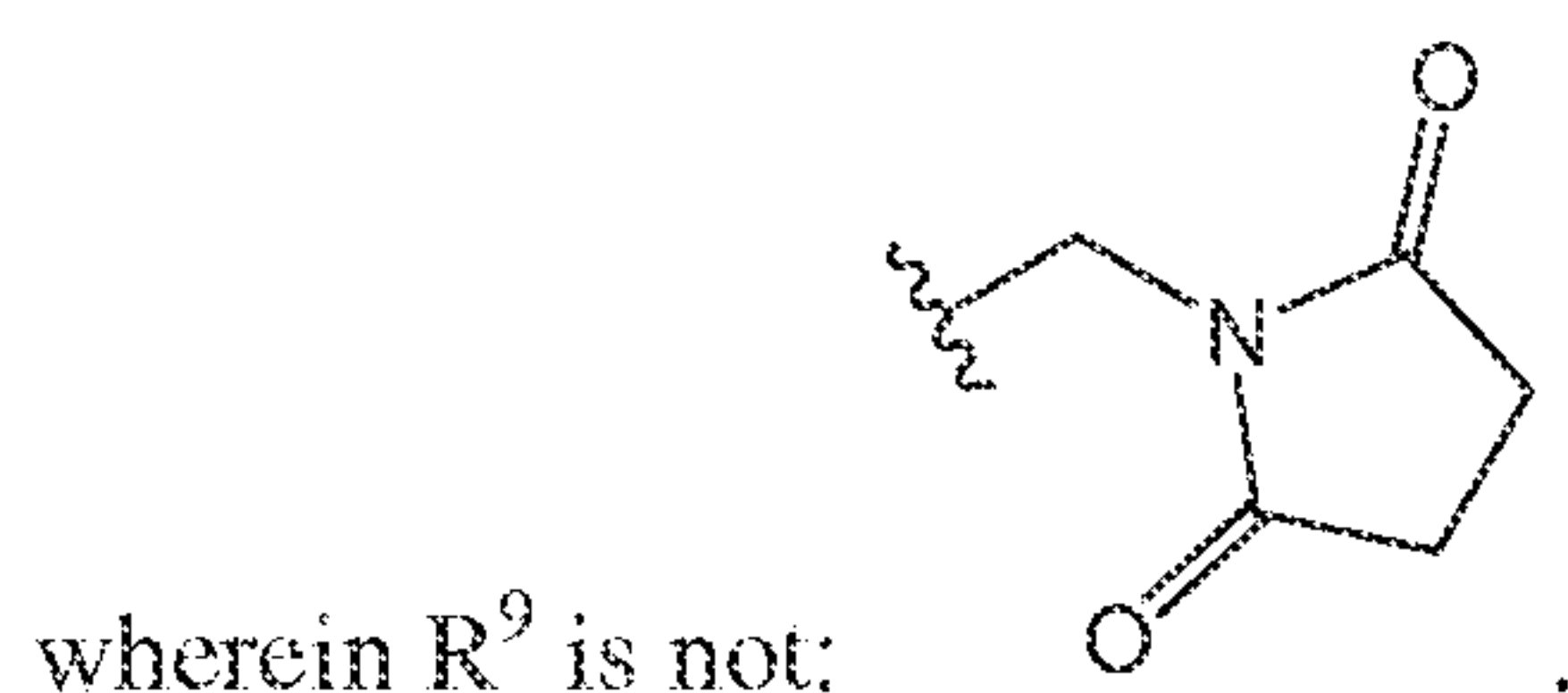
each R^7 , R^8 , R^9 and R^{10} is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclalkyl, heterocyclalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, oxo, thiono, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^{c'}$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{O})\text{OR}^{c'}$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^{c'}$, $-\text{NR}^c\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^{d'}$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$, each of which is optionally substituted with 1-3 R^{12} ; wherein two R^7 , two R^8 , two R^9 or two R^{10} may optionally be taken together with the atoms to which they are attached to form an optionally substituted cyclyl, heterocyclyl, aryl or heteroaryl ring;

each R^{11} and R^{12} is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclalkyl, heterocyclalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, oxo, thiono, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^{c'}$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{O})\text{OR}^{c'}$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^{c'}$, $-\text{NR}^c\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^{d'}$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$;

each Y is independently O or S;

q is 1 or 2; and

each R^a , R^b , $\text{R}^{b'}$, R^c , $\text{R}^{c'}$, R^d , $\text{R}^{d'}$, R^e , $\text{R}^{e'}$ and R^f is independently selected from hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, acyl, cyclyl, heterocyclyl, aryl, heteroaryl, cyclalkyl, heterocyclalkyl, aralkyl and heteroaralkyl, each of which may be optionally substituted with 1-3 R^7 ;



Compounds of Formula (I)

The following aspects and embodiments relate to compounds of formula (I).

Item 2. The compound according to item 1 represented by general formula (I) or a salt thereof,

wherein:

A is CR^4 or N;

B is aryl, cyclyl or a 5- or 6-membered heteroaryl;

m is 0, 1, 2, 3, 4 or 5;

n is 0, 1, 2, 3 or 4;

E is aryl or a 5-membered heteroaryl;

when E is aryl, n is 0, 1, 2, 3 or 4; and when E is a 5-membered heteroaryl, n is 0, 1, 2 or 3;

L is NR^5 , S, O or a direct bond;

one of X and Z is N and the other is CH;

p is 0, 1, 2, 3 or 4;

each R^1 , R^2 and R^3 is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silyloxyalkynyl, silylalkoxy, silylalkoxyalkyl, $-CN$, oxo, $-NO_2$, $-C(O)OR^a$, $-C(Y)NR^bR^{b'}$, $-NR^cC(Y)R^{c'}$, $-NR^bR^{b'}$, $-OC(O)NR^bR^{b'}$, $-NR^cC(O)OR^{c'}$, $-SO_2NR^bR^{b'}$, $-NR^cSO_2R^{c'}$, $-NR^cC(Y)NR^bR^{b'}$, $-OR^d$, $-SR^{d'}$, $-C(Y)R^e$ or $-S(O)_qR^f$, each of which is optionally substituted with 1-3 R^6 ; wherein two R^1 , together with the atoms to which they are attached, may form an optionally substituted cyclyl, heterocyclyl, aryl or heteroaryl ring;

R^4 is hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, $-CN$, $-NO_2$, $-C(O)OR^a$, $-C(Y)NR^bR^{b'}$, $-NR^cC(Y)R^{c'}$, $-NR^bR^{b'}$, $-OC(O)NR^bR^{b'}$, $-NR^cC(O)OR^{c'}$, $-SO_2NR^bR^{b'}$, $-NR^cSO_2R^{c'}$, $-NR^cC(Y)NR^bR^{b'}$, $-OR^d$, $-SR^d$, $-C(Y)R^e$ or $-S(O)_qR^f$, each of which is optionally substituted with 1-3 R^6 ;

R^5 is hydrogen; or when m is not 0, R^5 and one R^1 may be taken together with the atoms to which they are attached to form an optionally substituted heteroaryl or heterocyclyl ring;

each R^6 is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, oxo, thioxo, $-CN$, $-NO_2$, $-C(O)OR^a$, $-C(Y)NR^bR^{b'}$, $-NR^cC(Y)R^{c'}$, $-NR^bR^{b'}$, $-OC(O)NR^bR^{b'}$, $-NR^cC(O)OR^{c'}$, $-SO_2NR^bR^{b'}$, $-NR^cSO_2R^{c'}$, $-NR^cC(Y)NR^bR^{b'}$, $-OR^d$, $-SR^d$, $-C(Y)R^e$ or $-S(O)_qR^f$, each of which is optionally substituted with 1-3 R^7 ;

each R^7 is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, oxo, thioxo, $-CN$, $-NO_2$, $-C(O)OR^a$, $-C(Y)NR^bR^{b'}$, $-NR^cC(Y)R^{c'}$, $-NR^bR^{b'}$, $-OC(O)NR^bR^{b'}$, $-NR^cC(O)OR^{c'}$, $-SO_2NR^bR^{b'}$, $-NR^cSO_2R^{c'}$, $-NR^cC(Y)NR^bR^{b'}$, $-OR^d$, $-SR^d$, $-C(Y)R^e$ or $-S(O)_qR^f$, each of which is optionally substituted with 1-3 R^9 ;

each R^9 is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, oxo, thioxo, $-CN$, $-NO_2$, $-C(O)OR^a$, $-C(Y)NR^bR^{b'}$, $-NR^cC(Y)R^{c'}$, $-$

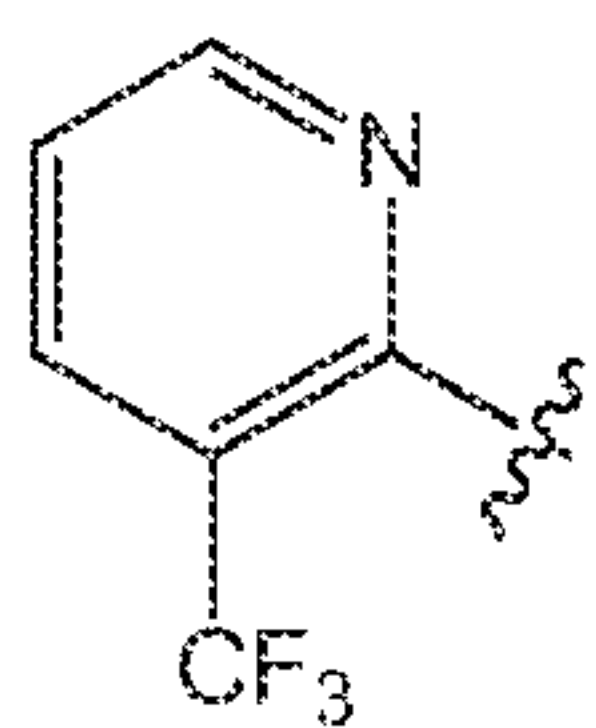
$\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{O})\text{OR}^c$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^c$, $-\text{NR}^c\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^d$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$;

Y is O or S;

q is 1 or 2; and

each R^a , R^b , $\text{R}^{b'}$, R^c , $\text{R}^{c'}$, R^d , $\text{R}^{d'}$, R^e and R^f is independently hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, acyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy or silylalkoxyalkyl;

wherein when B is phenyl, two R^1 are not taken together to form a pyrazole ring;
and



Item 3. The compound according to item 2 represented by general formula (I) or a salt thereof,

wherein:

A is CH or N;

B is aryl, cyclyl or a 5- or 6-membered heteroaryl;

m is 0, 1, 2, 3 or 4;

E is aryl or a 5-membered heteroaryl;

n is 0, 1 or 2;

when E is aryl, n is 0, 1 or 2 and when E is a 5-membered heteroaryl, n is 0 or 1;

p is 0, 1 or 2;

each R^1 , R^2 and R^3 is independently C_1 - C_8 alkyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silyloxyalkynyl, $-\text{CN}$, oxo, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^c$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^d$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$, each

of which is optionally substituted with 1-3 R^6 ; wherein two R^1 , together with the atoms to which they are attached, may form an optionally substituted cyclyl, heterocyclyl, aryl or heteroaryl ring;

each R^6 is independently C_1 - C_8 alkyl, heterocyclyl, heterocyclylalkyl, hydroxyalkyl, halo, haloalkyl, haloalkoxy, alkoxyalkyl, oxo, $-CN$, $-NO_2$, $-C(O)OR^a$, $-C(Y)NR^bR^{b'}$, $-NR^cC(Y)R^c$, $-NR^bR^{b'}$, $-OR^d$ or $-C(Y)R^e$, each of which is optionally substituted with 1-3 R^7 ;

each R^7 is oxo; and

each R^a , R^b , $R^{b'}$, R^c , $R^{c'}$, R^d , $R^{d'}$, R^e and R^f is independently hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, acyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl, heterocyclylalkyl, haloalkyl, dialkylaminoalkyl, hydroxyalkyl or alkoxyalkyl.

Item 4. The compound according to item 3 represented by general formula (I) or a salt thereof,

wherein:

B or two R^1 and B are taken together to form a group is phenyl, dihydroindenyl, dihydrobenzoxazinyl, dihydrobenzodioxinyl, chromenyl, tetrahydroquinoxaliny, tetrahydroisoquinolinyl, tetrahydroquinolinyl, dihydroquinolinyl, quinolyl, isoquinolinyl, tetrahydroquinazolinyl, indolinyl, dihydrobenzothiazolyl, dihydrobenzimidazolyl, dihydrobenzoxazolyl, isoindolinyl, dihydroisobenzofuranyl, benzofuryl, benzothienyl, benzodioxolyl, indolyl, indazolyl, benzoimidazolyl, benzotriazolyl, benzisoxazolyl, benzoxazolyl, benzothiazolyl, benzoxadiazolyl, dihydrocyclopentathiophenyl, tetrahydrobenzothiophenyl, thienyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, thiadiazolyl, pyrrolyl or pyridyl;

E is phenyl, thienyl or pyrrolyl;

when E is phenyl, n is 1 or 2; and when E is thienyl, n is 0 or 1;

each R^1 , R^2 and R^3 is independently C_1 - C_8 alkyl, C_2 - C_8 alkynyl, phenyl, thienyl, pyrrolyl, oxadiazolyl, pyridyl, benzodioxolyl, furyl, pyrimidinyl, oxazolyl, isoxazolyl, pyrazolyl, C_3 - C_8 cycloalkyl, piperidyl, pyrrolidinyl, morpholinyl, dioxolanyl, phenylalkyl, thiomorpholinylalkyl, pyrrolidinylalkyl, morpholinylalkyl, piperidylalkyl,

piperazinylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxyalkyl, silyloxyalkynyl, $-\text{CN}$, $-\text{NO}_2$, oxo, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^{c'}$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^{d'}$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$, each of which is optionally substituted with 1-3 R^6 ;

each R^6 is independently C_1 - C_8 alkyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, morpholinylalkyl, dialkylaminoalkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, oxo, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^{c'}$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^b\text{R}^{b'}$, alkoxyalkyl, $-\text{OR}^d$ or $-\text{C}(\text{Y})\text{R}^e$; and

each R^a , R^b , $\text{R}^{b'}$, R^c , $\text{R}^{c'}$, R^d , $\text{R}^{d'}$, R^e and R^f is independently hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, C_3 - C_8 cycloalkyl, phenyl, pyridyl, dihydroindenyl, morpholinyl, tetrahydropyranyl, piperidyl, pyrrolidinyl, piperazinyl, thiomorpholinyl, phenylalkyl, thienylalkyl, furylalkyl, pyridylalkyl, tetrahydropyranylalkyl, dihydroindenylalkyl, tetrahydrofurylalkyl, hydroxyalkyl, thiazolylalkyl, pyrazolylalkyl, morpholinylalkyl, pyrrolidinylalkyl, dialkylaminoalkyl, piperidylalkyl, benzodioxolylalkyl, dihydrobenzodioxinylalkyl, benzothienylalkyl, C_3 - C_8 cycloalkylalkyl, oxazolidinylalkyl, haloalkyl, or alkoxyalkyl.

Item 5. The compound according to item 3 represented by general formula (I) or a salt thereof,

wherein:

B or two R1 and B are taken together to form a group is phenyl, dihydroindenyl, dihydrobenzoxazinyl, dihydrobenzodioxinyl, chromenyl, tetrahydroquinoxalyl, tetrahydroisoquinolyl, tetrahydroquinolyl, dihydroquinolyl, quinolyl, isoquinolyl, tetrahydroquinazolinyl, indolinyl, dihydrobenzothiazolyl, dihydrobenzimidazolyl, dihydrobenzoxazolyl, isoindolinyl, dihydroisobenzofuranyl, benzofuryl, benzothienyl, benzodioxolyl, indolyl, indazolyl, benzoimidazolyl, benzotriazolyl, benzisoxazolyl, benzoxazolyl, benzothiazolyl, benzoxadiazolyl, dihydrocyclopentathiophenyl, tetrahydrobenzothienyl, thienyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, thiadiazolyl, pyrrolyl or pyridyl;

E is phenyl, thienyl or pyrrolyl,;

when E is phenyl, n is 0, 1 or 2; and when E is thienyl, n is 0 or 1;

each R^1 , R^2 and R^3 is independently C_1 - C_8 alkyl, C_2 - C_8 alkynyl, phenyl, thienyl, pyrrolyl, oxazolyl, oxadiazolyl, pyridyl, benzodioxolyl, furyl, pyrimidinyl, isoxazolyl, pyrazolyl, C_3 - C_8 cycloalkyl, piperidyl, pyrrolidinyl, morpholinyl, dioxolanyl, phenylalkyl, thiomorpholinylalkyl, pyrrolidinylalkyl, morpholinylalkyl, piperidylalkyl, piperazinylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxyalkyl, silyloxyalkynyl, $-CN$, $-NO_2$, oxo, $-C(O)OR^a$, $-C(Y)NR^bR^{b'}$, $-NR^bR^{b'}$, $-NR^cC(Y)R^{c'}$, $-OC(O)NR^bR^{b'}$, $-SO_2NR^bR^{b'}$, $-OR^d$, $-SR^{d'}$, $-C(Y)R^e$ or $-S(O)_qR^f$, each of which is optionally substituted with 1-3 R^6 ;

each R^6 is independently C_1 - C_8 alkyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, morpholinylalkyl, dialkylaminoalkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, oxo, $-CN$, $-NO_2$, $-C(O)OR^a$, $-NR^cC(Y)R^{c'}$, $-C(Y)NR^bR^{b'}$, $-NR^bR^{b'}$, alkoxyalkyl, $-OR^d$ or $-C(Y)R^e$, each of which is optionally substituted with 1-3 R^7 ;

R^7 is oxo; and

each R^a , R^b , $R^{b'}$, R^c , $R^{c'}$, R^d , $R^{d'}$, R^e and R^f is independently hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, C_3 - C_8 cycloalkyl, phenyl, pyridyl, dihydroindenyl, morpholinyl, tetrahydropyranyl, piperidyl, pyrrolidinyl, piperazinyl, thiomorpholinyl, phenylalkyl, thienylalkyl, furylalkyl, pyridylalkyl, tetrahydropyranylalkyl, dihydroindenylalkyl, tetrahydrofurylalkyl, hydroxyalkyl, thiazolylalkyl, pyrazolylalkyl, morpholinylalkyl, pyrrolidinylalkyl, dialkylaminoalkyl, piperidylalkyl, benzodioxolylalkyl, dihydrobenzodioxinylalkyl, benzothienylalkyl, C_3 - C_8 cycloalkylalkyl, oxazolidinylalkyl, haloalkyl, or alkoxyalkyl.

Item 6. The compound according to item 5 represented by general formula (I) or a salt thereof,

wherein:

R^1 is C_1 - C_8 alkyl, phenyl, thienyl, pyrrolyl, oxazolyl, C_3 - C_8 cycloalkyl, dioxolanyl, phenylalkyl, halo, haloalkyl, haloalkoxy, alkoxyalkyl, $-CN$, oxo, $-NO_2$, $-C(O)OR^a$, $-C(Y)NR^bR^{b'}$, $-NR^cC(Y)R^{c'}$, $-SO_2NR^bR^{b'}$, $-OR^d$, $-SR^{d'}$, $-C(Y)R^e$ or $-S(O)_qR^f$, each of which is optionally substituted with 1-3 R^6 ;

R^2 is C_1 - C_8 alkyl, C_2 - C_8 alkynyl, phenyl, thienyl, pyridyl, benzodioxolyl, furyl, pyrimidinyl, isoxazolyl, pyrazolyl, C_3 - C_8 cycloalkyl, pyrrolidinyl, morpholinyl, thiomorpholinylalkyl, pyrrolidinylalkyl, morpholinylalkyl, piperidinylalkyl, piperazinylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxyalkyl, silyloxyalkynyl, $-CN$, $-NO_2$, $-C(O)OR^a$, $-C(Y)NR^bR^{b'}$, $-NR^bR^{b'}$, $-OC(O)NR^bR^{b'}$, $-OR^d$ or $-C(Y)R^e$, each of which is optionally substituted with 1-3 R^6 ;

R^3 is C_1 - C_8 alkyl, halo, haloalkyl, $-NR^bR^{b'}$ or $-OR^d$, each of which is optionally substituted with 1-3 R^6 .

Item 7. The compound according to item 4 or 6 represented by general formula (I) or a salt thereof,

wherein:

R^1 is C_1 - C_8 alkyl, phenyl, thienyl, pyrrolyl, oxazolyl, C_3 - C_8 cycloalkyl, dioxolanyl, phenylalkyl, halo, haloalkyl, haloalkoxy, alkoxyalkyl, $-CN$, oxo, $-NO_2$, $-C(O)OR^a$, $-C(Y)NR^bR^{b'}$, $-NR^cC(Y)R^{c'}$, $-SO_2NR^bR^{b'}$, $-OR^d$, $-SR^d$, $-C(Y)R^e$ or $-S(O)_qR^f$;

R^2 is C_1 - C_8 alkyl, C_2 - C_8 alkynyl, phenyl, thienyl, pyridyl, benzodioxolyl, furyl, pyrimidinyl, isoxazolyl, pyrazolyl, C_3 - C_8 cycloalkyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinylalkyl, pyrrolidinylalkyl, morpholinylalkyl, piperidinylalkyl, piperazinylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxyalkyl, silyloxyalkynyl, $-CN$, $-NO_2$, $-C(O)OR^a$, $-C(Y)NR^bR^{b'}$, $-NR^bR^{b'}$, $-OC(O)NR^bR^{b'}$, $-OR^d$, $-C(Y)R^e$ or $-S(O)_qR^f$;

R^3 is C_1 - C_8 alkyl, halo, haloalkyl, $-NR^bR^{b'}$ or $-OR^d$.

Item 8. The compound according to item 7 represented by general formula (I) or a salt thereof,

wherein:

B or two R^1 and B are taken together to form a group is phenyl, dihydroindenyl, dihydrobenzoxazinyl, dihydrobenzodioxinyl, chromenyl, tetrahydroisoquinolyl, tetrahydroquinolyl, dihydroquinolyl, quinolyl, tetrahydroquinazolinyl, indolinyl,

dihydrobenzothiazolyl, dihydrobenzimidazolyl, dihydrobenzoxazolyl, isoindolinyl, benzofuryl, benzothienyl, benzodioxolyl, indolyl, indazolyl, benzoimidazolyl, benzotriazolyl, benzisoxazolyl, benzoxazolyl, benzothiazolyl, benzoxadiazolyl, tetrahydrobenzothienyl, thienyl, thiazolyl, imidazolyl, pyrazolyl, thiadiazolyl or pyridyl;

m is 1, 2, 3 or 4;

R^1 is C_1 - C_8 alkyl, halo, haloalkyl, haloalkoxy, alkoxyalkyl, $-CN$, oxo, $-NO_2$, $-C(O)OR^a$, $-C(Y)NR^bR^{b'}$, $-NR^cC(Y)R^{c'}$, $-SO_2NR^bR^{b'}$, $-OR^d$, or $-S(O)_qR^f$;

R^2 is C_1 - C_8 alkyl, C_3 - C_8 cycloalkyl, thiomorpholinylalkyl, pyrrolidinylalkyl, morpholinylalkyl, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxyalkyl, $-CN$, $-NO_2$, $-C(O)OR^a$, $-C(Y)NR^bR^{b'}$, $-NR^bR^{b'}$, $-OR^d$, $-C(Y)R^e$ or $-S(O)_qR^f$;

each R^a , R^b , $R^{b'}$, R^c , $R^{c'}$, R^d , $R^{d'}$, R^e and R^f is independently hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, C_3 - C_8 cycloalkyl, phenyl, dihydroindenyl, morpholinyl, tetrahydropyranyl, piperidyl, pyrrolidinyl, thiomorpholinyl, phenylalkyl, thienylalkyl, pyridylalkyl, tetrahydropyranylalkyl, dihydroindenylalkyl, tetrahydrofurylalkyl, hydroxyalkyl, morpholinylalkyl, pyrrolidinylalkyl, dialkylaminoalkyl, piperidylalkyl, benzodioxolylalkyl, dihydrobenzodioxinylalkyl, C_3 - C_8 cycloalkylalkyl, haloalkyl or alkoxyalkyl.

In some embodiments, A is N. In some embodiments, A is CH. In some embodiments, A is CR^4 .

In some embodiments, B is aryl (e.g., phenyl).

In some embodiments, m is 0.

In some embodiments, m is 1. In some embodiments, m is 2. In some embodiments, m is 3.

In some embodiments, R^1 is in the ortho position. In some embodiments, R^1 is in the meta position. In some embodiments, R^1 is in the para position.

In some embodiments, R^1 is C_1 - C_8 alkyl (e.g., methyl or tert-butyl). In some embodiments, R^1 is heteroaryl (e.g., oxazolyl, oxadiazolyl or quinazolinyl).

In some embodiments, R^1 is heteroaryl substituted with 1-3 R^6 (e.g., 1 R^6).

In some embodiments, R^1 is oxadiazolyl substituted with 1 R^6 . In some embodiments, R^6 is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, R^1 is heteroaryl substituted with 2 R^6 . In some embodiments, R^1 is quinazolinyl substituted with 2 R^6 . In some embodiments, one R^6 is halo (e.g., bromo) and the other is heteroaryl (e.g., pyridyl).

In some embodiments, m is 1 and R^1 is halo (e.g., fluoro, chloro or bromo). In some embodiments, m is 2 and each R^1 is halo (e.g., fluoro, chloro or bromo). In some embodiments, m is 3 and each R^1 is halo (e.g., fluoro, chloro or bromo). In some embodiments, R^1 is haloalkyl (e.g., trifluoromethyl). In some embodiments, R^1 is haloalkoxy (e.g., difluoromethoxy or trifluoromethoxy).

In some embodiments, R^1 is haloalkoxy substituted with 1 R^6 . In some embodiments, R^1 is $-O-CF_2-R^6$. In some embodiments, R^6 is $-C(Y)NR^bR^{b'}$. In some embodiments, Y is O, R^b is hydrogen and $R^{b'}$ is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, R^1 is $-O-CF_2-CH_2-R^6$. In some embodiments, R^6 is $-OR^d$. In some embodiments, R^d is hydrogen. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, R^6 is $-NR^bR^{b'}$. In some embodiments, R^b and $R^{b'}$ are each independently C_1 - C_8 alkyl (e.g., R^b and $R^{b'}$ are both methyl). In some embodiments, R^6 is heterocyclyl (e.g., morpholino).

In some embodiments, R^1 is aminoalkyl. In some embodiments, R^1 is $-CH_2NH_2$. In some embodiments, R^1 is alkylaminoalkyl. In some embodiments, R^1 is $-CH_2NHCH_2CH_2CH_3$. In some embodiments, R^1 is dialkylaminoalkyl. In some embodiments, R^1 is $-CH_2N(CH(CH_3)_2)_2$.

In some embodiments, R^1 is hydroxyalkyl. In some embodiments, R^1 is $-CH_2OH$.

In some embodiments, R^1 is $-CN$.

In some embodiments, R^1 is $-NO_2$.

In some embodiments, R^1 is $-C(O)OR^a$. In some embodiments, R^a is hydrogen. In some embodiments, R^a is C_1 - C_8 alkyl (e.g., methyl or ethyl).

In some embodiments, R^1 is $-NR^cC(Y)R^{c'}$. In some embodiments, one of R^c and $R^{c'}$ is hydrogen and the other is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, R^1 is $-OR^d$. In some embodiments, R^d is hydrogen. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl or ethyl).

In some embodiments, R^1 is $-SO_2NR^bR^{b'}$. In some embodiments, R^b and $R^{b'}$ are both hydrogen.

In some embodiments, R^1 is $-C(Y)R^e$. In some embodiments, Y is O. In some embodiments, R^e is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, R^e is heterocyclyl (e.g., pyrrolidinyl, piperidinyl or morpholino).

In some embodiments, R^1 is $-C(Y)NR^bR^{b'}$. In some embodiments, Y is S. In some embodiments, Y is O. In some embodiments, R^b and $R^{b'}$ are both hydrogen. In some embodiments, R^b is hydrogen. In some embodiments, R^b is hydrogen and $R^{b'}$ is aralkyl. In some embodiments, R^b is hydrogen and $R^{b'}$ is optionally substituted benzyl. In some embodiments, $R^{b'}$ is C_1 - C_8 alkyl, e.g., methyl, ethyl, C_3 alkyl (e.g., n-propyl or isopropyl), C_4 alkyl (e.g., n-butyl, sec-butyl or tert-butyl), C_5 alkyl (e.g., n-pentyl, isopentyl or pentan-3-yl), C_6 alkyl (e.g., n-hexyl or 3,3-dimethylbutan-2-yl), or C_7 alkyl (e.g., n-heptyl or 2-heptyl).

In some embodiments, $R^{b'}$ is bicyclyl (e.g., indanyl). In some embodiments, $R^{b'}$ is heterocyclyl, e.g., a 6-membered heterocyclyl. In some embodiments, $R^{b'}$ is a 6-membered oxygen-containing heterocyclyl (e.g., tetrahydropyranyl). In some embodiments, $R^{b'}$ is a 6-membered nitrogen-containing heterocyclyl (e.g., piperidinyl).

In some embodiments, $R^{b'}$ is aralkyl. In some embodiments, the alkyl is a C_1 - C_8 alkyl (e.g., C_1 , C_2 , C_3 or C_4 alkyl). In some embodiments, the alkyl is a straight-chain alkyl. In some embodiments, the alkyl is a branched alkyl. In some embodiments, the aryl is phenyl. In some embodiments, $R^{b'}$ is benzyl. In some embodiments, $R^{b'}$ is phenylethyl.

In some embodiments, $R^{b'}$ is heteroaralkyl. In some embodiments, the alkyl is a C_1 - C_8 alkyl (e.g., C_1 , C_2 or C_3 alkyl). In some embodiments, the alkyl is a straight-chain alkyl. In some embodiments, the alkyl is a branched alkyl. In some embodiments, the heteroaryl is pyridyl. In some embodiments, the heteroaryl is furanyl. In some embodiments, the heteroaryl is thiazolyl. In some embodiments, the heteroaryl is thienyl.

In some embodiments, $R^{b'}$ is cyclylalkyl. In some embodiments, the alkyl is a C_1 - C_8 alkyl (e.g., C_1 alkyl). In some embodiments, the cyclyl group is cyclopropyl. In some embodiments, the cyclyl group is cyclopentyl. In some embodiments, the cyclyl group is a bicyclic group. In some embodiments, the bicyclic group is indanyl. In some embodiments, $R^{b'}$ is heterocyclylalkyl. In some embodiments, the alkyl is a C_1 - C_8 alkyl (e.g., C_1 alkyl). In some embodiments, the heterocyclyl group is tetrahydropyranyl.

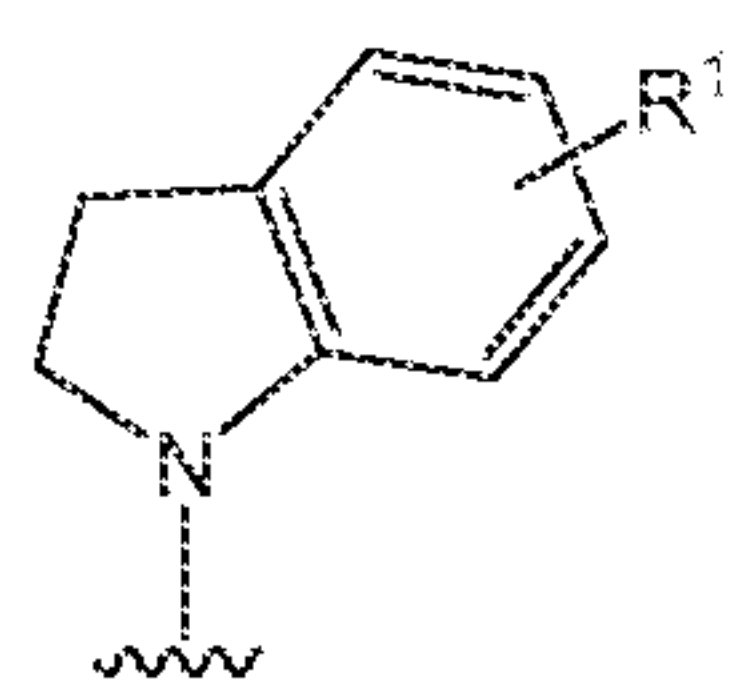
In some embodiments, $R^{b'}$ is haloalkyl (e.g., fluoroethyl, difluoroethyl, trifluoroethyl or trifluoropropyl).

In some embodiments, $R^{b'}$ is alkoxyalkyl. In some embodiments, the alkyl is a C_1 - C_8 alkyl (e.g., C_1 , C_2 , C_3 or C_4 alkyl). In some embodiments, the alkyl is a straight-chain alkyl. In some embodiments, the alkyl is a branched alkyl. In some embodiments, the alkoxy is methoxy.

In some embodiments, R^b and $R^{b'}$ are each independently C_1 - C_8 alkyl (e.g., R^b and $R^{b'}$ are both methyl, both ethyl, or both isopropyl).

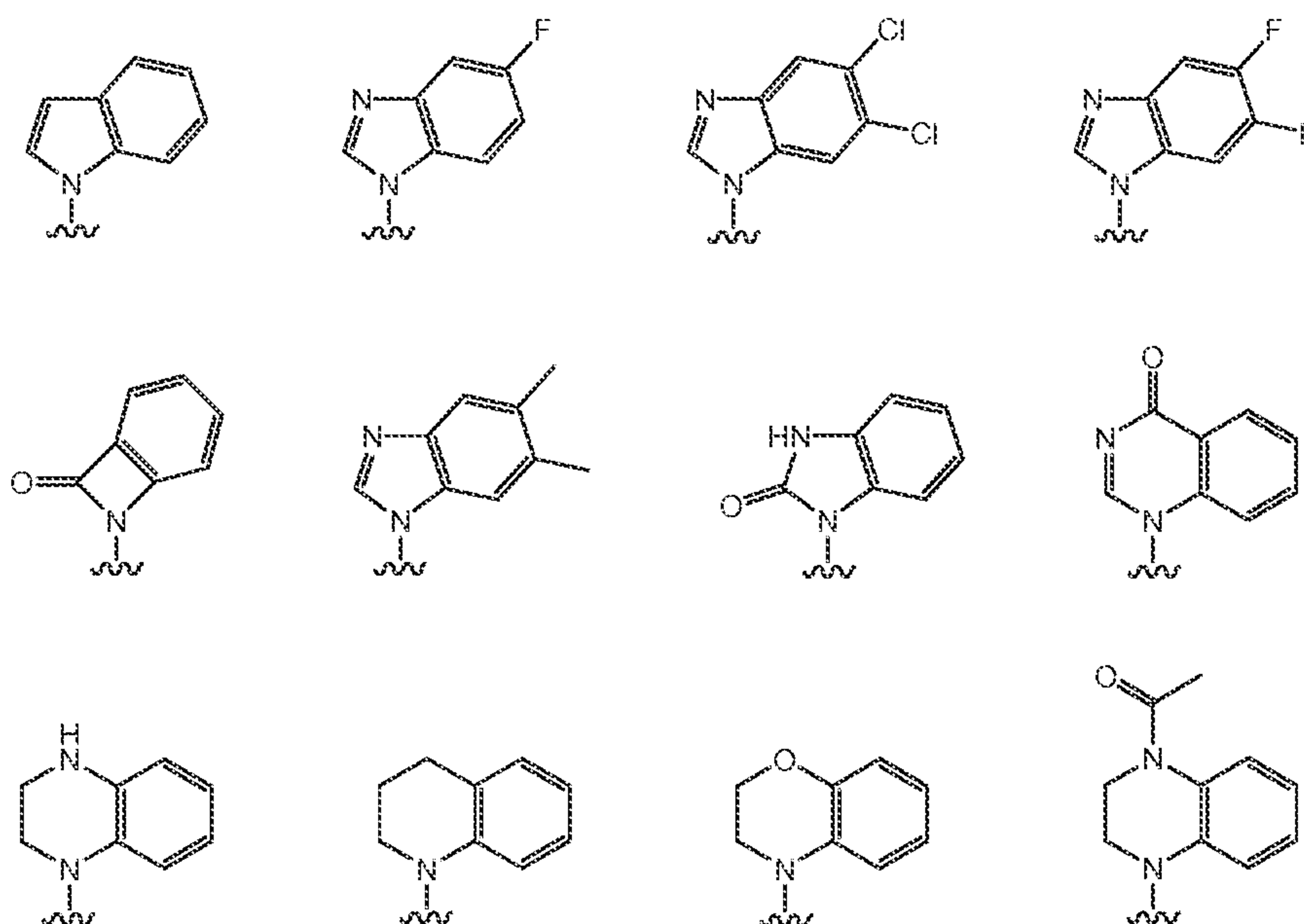
In some embodiments, two R^1 and B are taken together to form a bicyclic heteroaryl or heterocyclic ring.

In some embodiments, two R^1 and B are taken together to form



In some embodiments, R^1 is halo. In some embodiments, R^1 is at the 6, 7, or 8 position.

In some embodiments, two R^1 and B are taken together to form a group selected from:



In some embodiments, R^2 is aryl.

In some embodiments, each R^1 is independently C_1 - C_8 alkyl (e.g., each R^1 is methyl). In some embodiments, each R^1 is independently halo (e.g., each R^1 is fluoro or each R^1 is chloro). In some embodiments, one R^1 is fluoro and the other is chloro. In some embodiments, one R^1 is chloro and the other is bromo.

In some embodiments, each R^1 is independently $-OR^d$. In some embodiments, each R^d is independently C_1 - C_8 alkyl (e.g., each R^d is methyl).

In some embodiments, one R^1 is halo (e.g., chloro) and the other is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, one R^1 is halo (e.g., fluoro) and the other is heterocyclalkyl (e.g., $-\text{CH}_2$ -heterocycl). In some embodiments, the heterocycl is morpholino. In some embodiments, the heterocycl is pyrrolidinyl. In some embodiments, the heterocycl is piperazinyl. In some embodiments, the piperazinyl is substituted with 1 R^6 . In some embodiments, R^6 is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, one R^1 is halo (e.g., fluoro or chloro) and the other is haloalkyl (e.g., trifluoromethyl).

In some embodiments, one R^1 is halo (e.g., chloro) and the other is haloalkoxy (e.g., difluoromethoxy or trifluoromethoxy).

In some embodiments, one R^1 is halo (e.g., chloro) and the other is $-\text{C}(\text{O})\text{OR}^a$. In some embodiments, R^a is hydrogen.

In some embodiments, one R^1 is halo (e.g., fluoro or chloro) and the other is $-C(Y)NR^bR^{b'}$. In some embodiments, Y is O. In some embodiments, R^b and $R^{b'}$ are both hydrogen. In some embodiments, one of R^b and $R^{b'}$ is hydrogen and the other is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, one R^1 is halo (e.g., chloro) and the other is $-NR^cC(Y)R^c$. In some embodiments, Y is O. In some embodiments, R^c is hydrogen and $R^{c'}$ is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, one R^1 is halo (e.g., fluoro or chloro) and the other is $-OR^d$. In some embodiments, R^d is hydrogen. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, one R^1 is halo (e.g., fluoro or chloro) and the other is $-CN$.

In some embodiments, one R^1 is halo (e.g., chloro) and the other is $-NO_2$.

In some embodiments, one R^1 is $-C(O)OR^a$ and the other is $-NO_2$. In some embodiments, R^a is hydrogen.

In some embodiments, one R^1 is $-C(O)OR^a$ and the other is $-OR^d$. In some embodiments, each R^a and R^d is hydrogen.

In some embodiments, one R^1 is $-C(Y)NR^bR^{b'}$ and the other is haloalkyl (e.g., trifluoromethyl). In some embodiments, R^b and $R^{b'}$ are both hydrogen.

In some embodiments, one R^1 is $-C(Y)NR^bR^{b'}$ and the other is haloalkoxy (e.g., trifluoromethoxy). In some embodiments, R^b and $R^{b'}$ are both hydrogen.

In some embodiments, one R^1 is $-C(Y)NR^bR^{b'}$ and the other is $-S(O)_qR^f$. In some embodiments, R^b and $R^{b'}$ are both hydrogen. In some embodiments, R^f is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, one R^1 is $-C(Y)NR^bR^{b'}$ and the other is $-CN$. In some embodiments, R^b and $R^{b'}$ are both hydrogen.

In some embodiments, one R^1 is $-OR^d$ and the other is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, one R^1 is $-OR^d$ and the other is haloalkyl (e.g., trifluoromethyl). In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl).

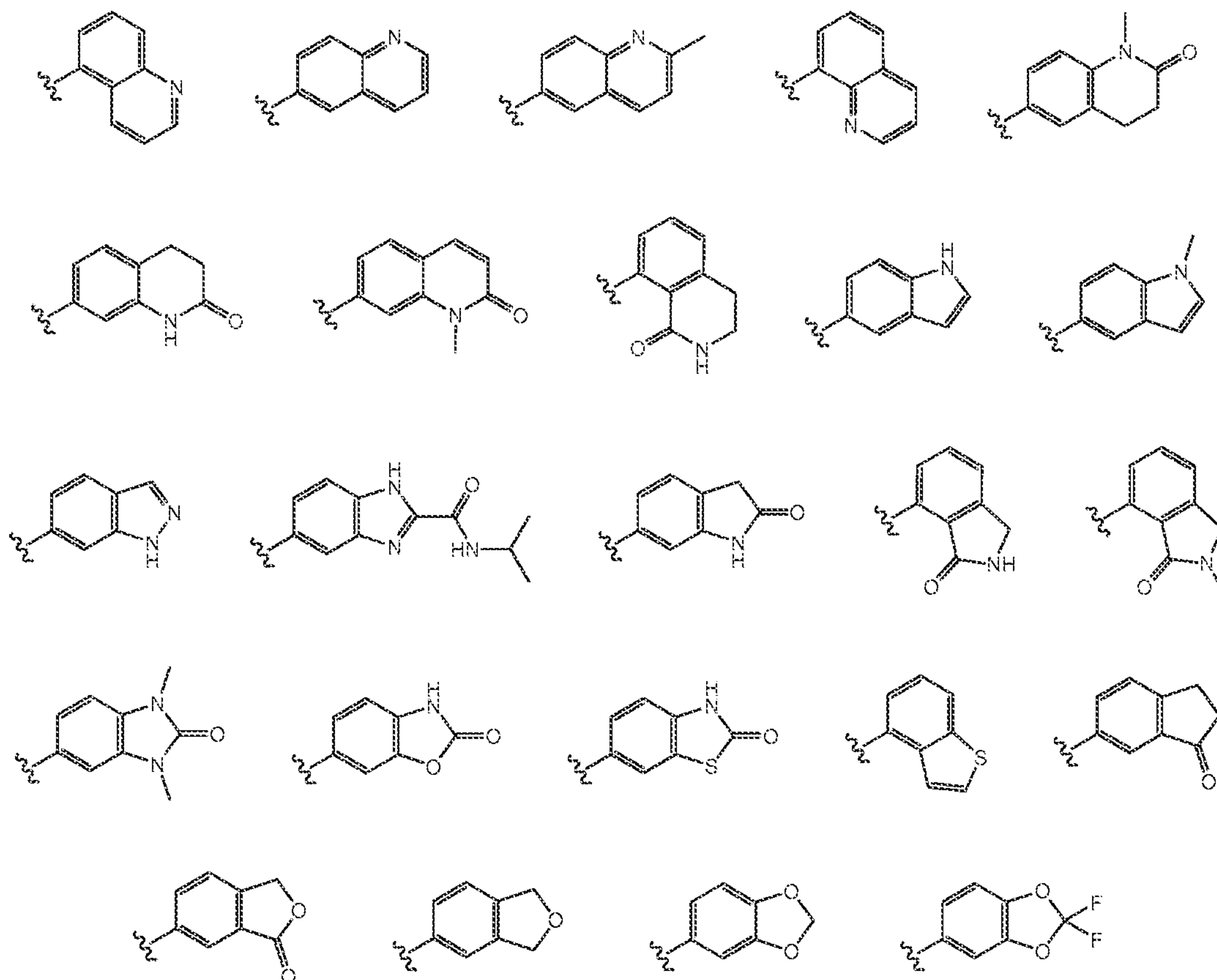
In some embodiments, one R^1 is $-OR^d$ and the other is $-C(O)OR^a$. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, R^a is hydrogen. In some embodiments, R^a is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, one R^1 is $-OR^d$ and the other is $-NR^cC(O)R^{c'}$. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, R^c is hydrogen and $R^{c'}$ is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, one R^1 is haloalkyl (e.g., trifluoromethyl) and the other is $-CN$.

In some embodiments, two R^1 , together with the atoms to which they are attached, are taken together to form a cyclyl ring (e.g., a substituted cyclyl ring). In some embodiments, two R^1 , together with the atoms to which they are attached, are taken together to form a heterocyclyl ring (e.g., a substituted heterocyclyl ring). In some embodiments, two R^1 , together with the atoms to which they are attached, are taken together to form a heteroaryl ring (e.g., a substituted heteroaryl ring).

In some embodiments, two R^1 and ring B are taken together to form a group selected from:



In some embodiments, R^2 is aryl.

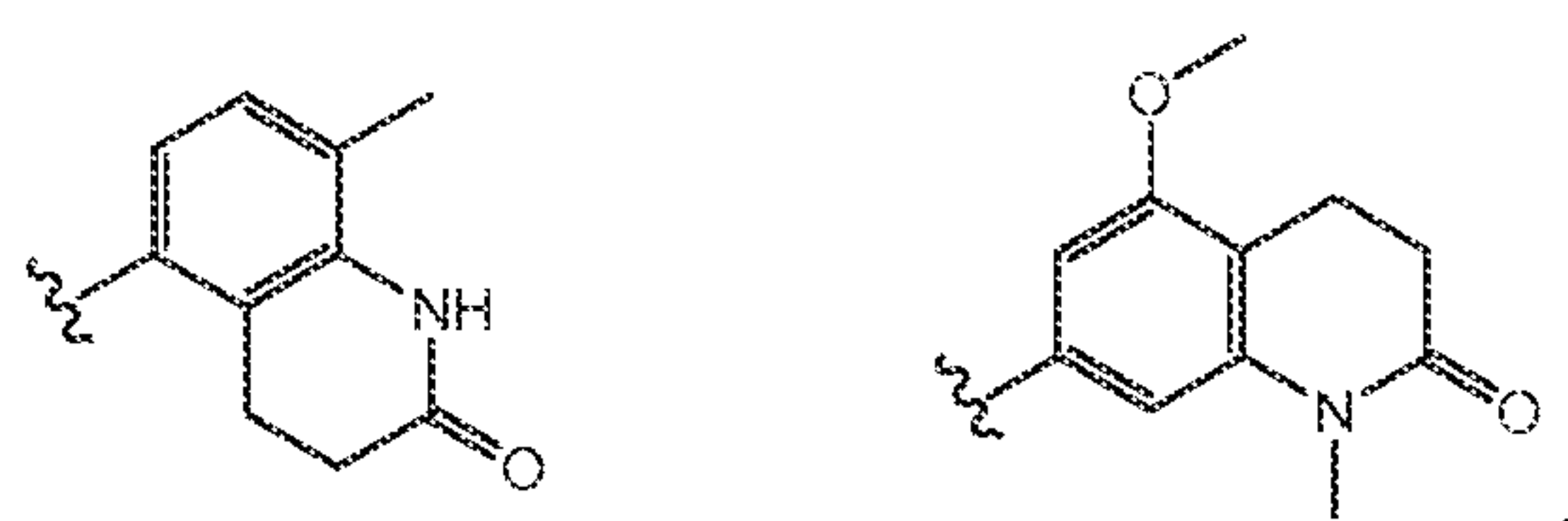
In some embodiments, each R^1 is independently halo (e.g., all three R^1 are fluoro or all three R^1 are chloro).

In some embodiments, two R^1 are independently halo (e.g., both are chloro) and the other is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, two R^1 are independently halo (e.g., both are chloro) and the other is heteroaryl (e.g., pyrrolyl). In some embodiments, two R^1 are independently halo (e.g., both are fluoro) and the other is $-C(Y)NR^bR^{b'}$ (e.g., $-C(O)NH_2$). In some embodiments, two R^1 are independently C_1 - C_8 alkyl (e.g., both are methyl) and the other is halo (e.g., chloro or bromo).

In some embodiments, one R^1 is C_1 - C_8 alkyl (e.g., methyl), and two R^1 , together with the atoms to which they are attached, are taken together to form a heterocyclyl ring.

In some embodiments, one R^1 is $-OR^d$, and two R^1 , together with the atoms to which they are attached, are taken together to form a heterocyclyl ring. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, three R^1 and ring B are taken together to form a group selected from:

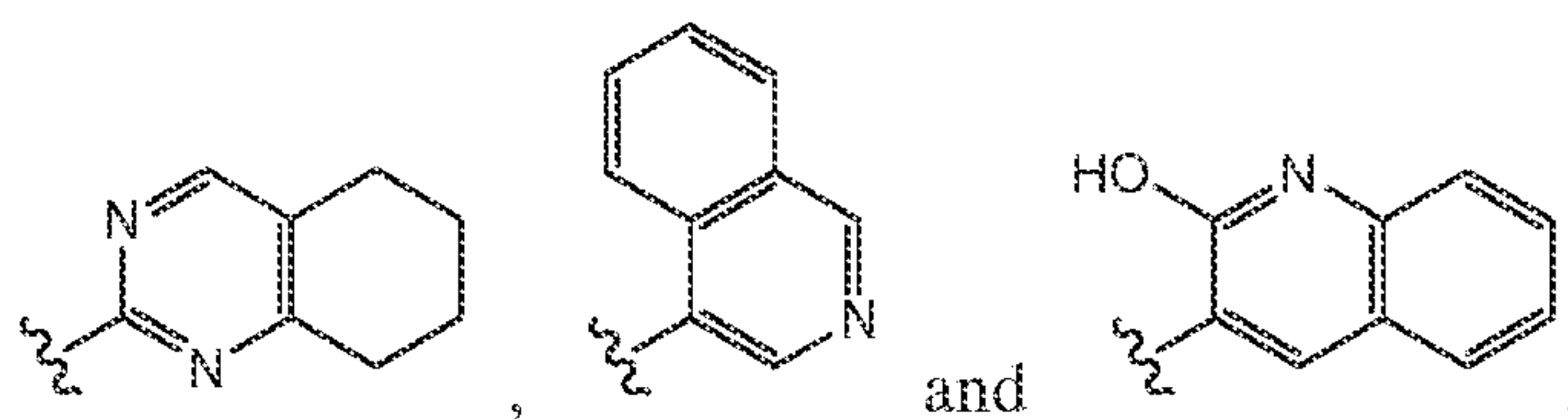


In some embodiments, B is a 6-membered heteroaryl.

In some embodiments, B is pyridyl. In some embodiments, B is 3-pyridyl. In some embodiments, m is 2. In some embodiments, two R^1 , together with the atoms to which they are attached, are taken together to form an aryl ring (e.g., a phenyl ring). In some embodiments, m is 3. In some embodiments, one R^1 is $-OR^d$, and two R^1 , together with the atoms to which they are attached, are taken together to form an aryl ring (e.g., a phenyl ring). In some embodiments, R^d is hydrogen.

In some embodiments, B is pyrazolyl. In some embodiments, m is 2. In some embodiments, two R^1 , together with the atoms to which they are attached, are taken together to form a cyclyl ring (e.g., a cyclohexyl ring).

In some embodiments, B is selected from:



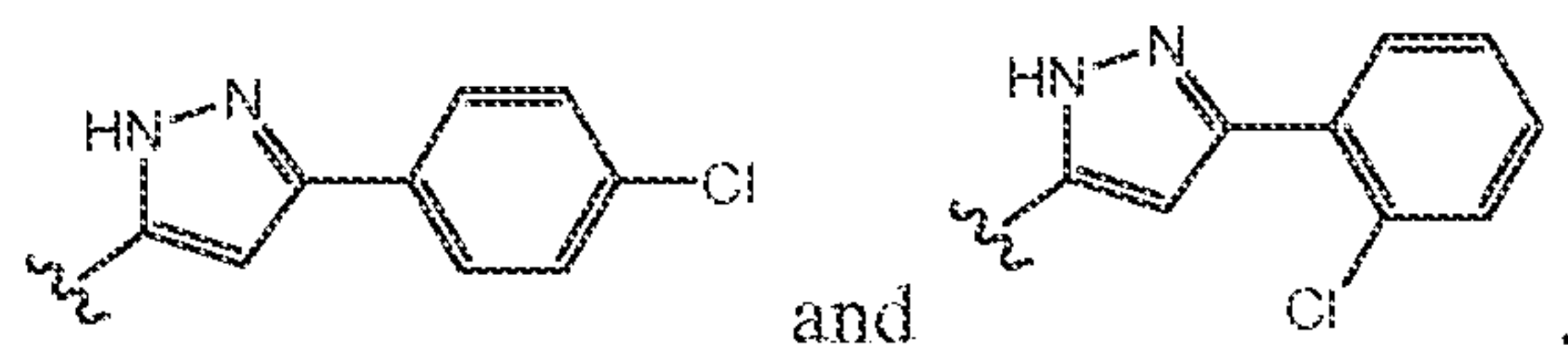
In some embodiments, B is a 5-membered heteroaryl (e.g., pyrazolyl).

In some embodiments, m is 1.

In some embodiments, R^1 is aryl (e.g., phenyl).

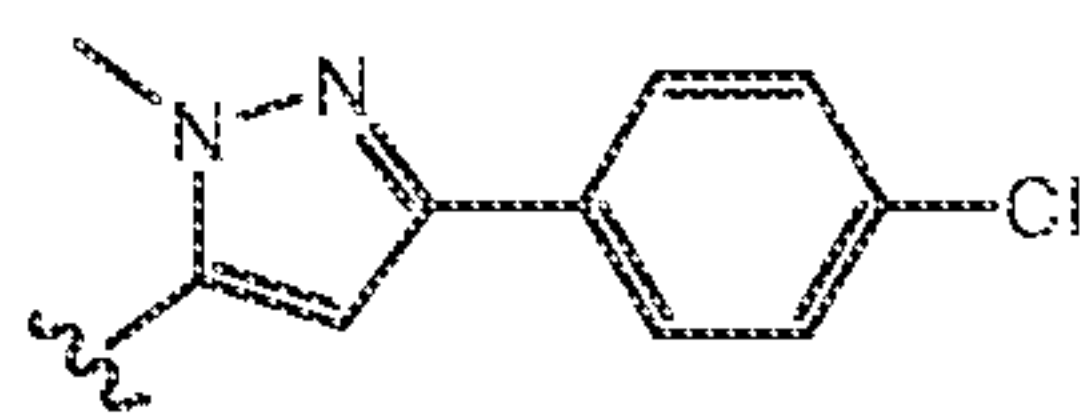
In some embodiments, R^1 is phenyl substituted with 1 R^6 .

In some embodiments, R^6 is halo (e.g., chloro). In some embodiments, R^1 is selected from:

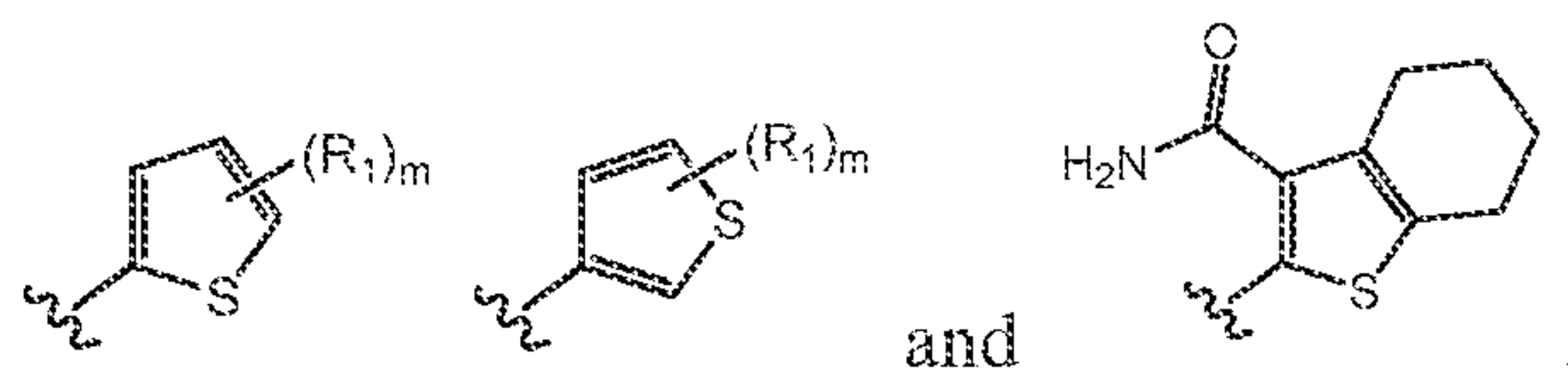


In some embodiments, m is 2.

In some embodiments, one R^1 is C_1 - C_8 alkyl (e.g., methyl) and the other is aryl (e.g., phenyl). In some embodiments, the aryl is phenyl substituted with 1 R^6 . In some embodiments, R^6 is halo (e.g., chloro). In some embodiments, R^1 is:



In some embodiments, B is thienyl. In some embodiments, B is selected from:



In some embodiments, m is 1. In some embodiments, m is 2. In some embodiments m is 2 and two R^1 , together with the atoms to which they are attached, form an optionally substituted cyclyl, heterocyclyl, aryl or heteroaryl ring

In some embodiments, R^1 is $-C(O)OR^a$. In some embodiments, R^a is C_1 - C_8 alkyl (e.g., ethyl).

In some embodiments, R^1 is $-C(Y)NR^bR^{b'}$. In some embodiments, Y is O. In some embodiments, R^b and $R^{b'}$ are both hydrogen.

In some embodiments, m is 2.

In some embodiments, one R^1 is C_1 - C_8 alkyl (e.g., methyl) and the other is $-C(Y)NR^bR^{b'}$. In some embodiments, Y is O. In some embodiments, R^b and $R^{b'}$ are both hydrogen.

In some embodiments, B is thiazolyl.

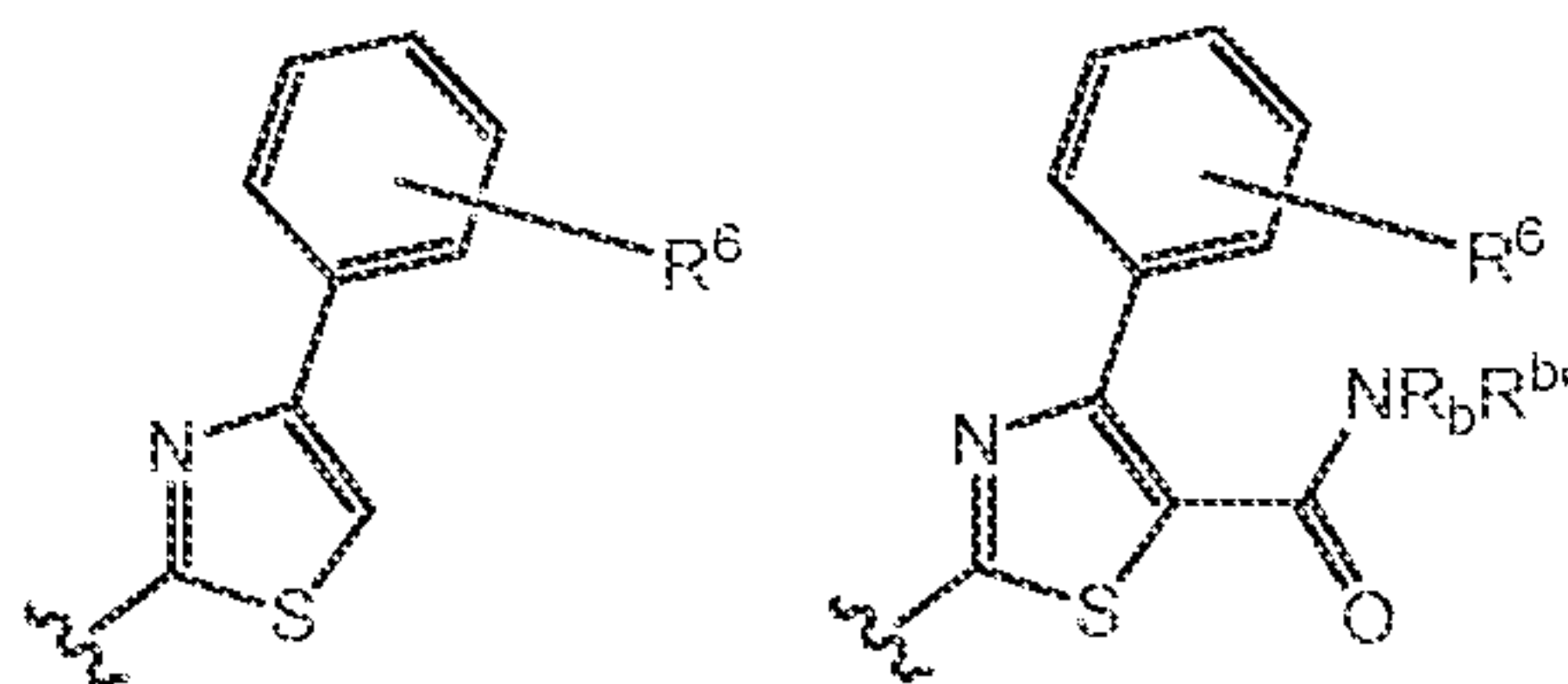
In some embodiments, m is 1.

In some embodiments, R^1 is aryl (e.g., phenyl).

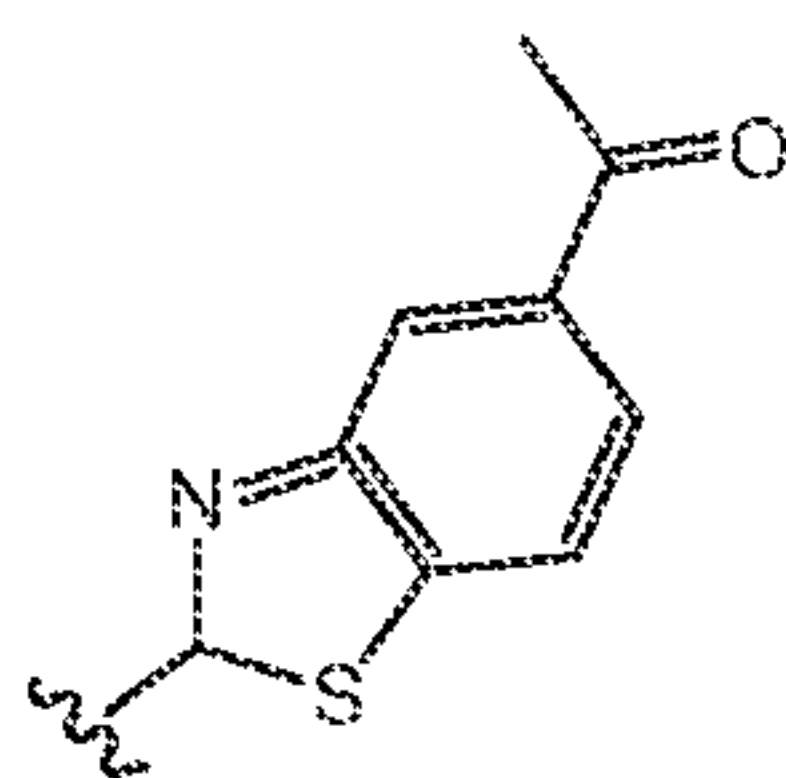
In some embodiments, m is 2.

In some embodiments, two R^1 , together with the atoms to which they are attached, form an aryl ring. In some embodiments, the aryl ring is substituted with $-C(Y)R^e$. In some embodiments, Y is O. In some embodiments, R^e is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, B is:



In some embodiments, B is:



In some embodiments, E is aryl (e.g., phenyl).

In some embodiments, n is 1.

In some embodiments, R^2 is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, R^2 is C_1 - C_8 alkyl substituted with 1-3 R^6 . In some embodiments, R^2 is C_1 alkyl substituted with 1 R^6 .

In some embodiments, R^6 is $-NR^bR^{b'}$. In some embodiments, R^b and $R^{b'}$ are each independently C_1 - C_8 alkyl (e.g., R^b and $R^{b'}$ are both methyl, or R^b and $R^{b'}$ are both ethyl). In some embodiments, one of R^b and $R^{b'}$ is hydrogen and the other is haloalkyl (e.g., trifluoroethyl).

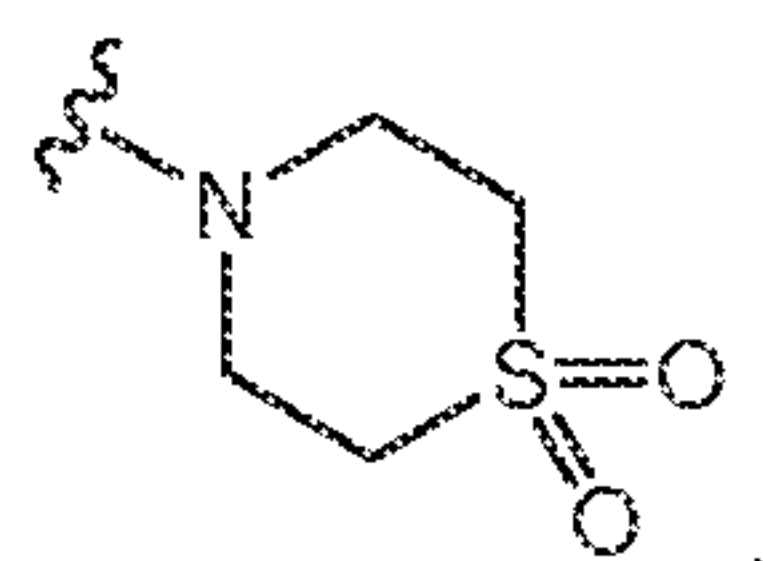
In some embodiments, R^6 is $-OR^d$. In some embodiments, R^d is cyclyl (e.g., cyclopentyl). In some embodiments, R^d is heterocyclylalkyl (e.g., $-CH_2$ -tetrahydropyranyl).

In some embodiments, R^2 is C_2 alkyl substituted with 1 R^6 .

In some embodiments, R^6 is $-C(Y)NR^bR^{b'}$. In some embodiments, Y is O. In some embodiments, R^b and $R^{b'}$ are both hydrogen. In some embodiments, R^b and $R^{b'}$ are each independently C_1 - C_8 alkyl (e.g., R^b and $R^{b'}$ are both methyl). In some

embodiments, one of R^b and $R^{b'}$ is hydrogen and the other is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, R^6 is $-C(Y)R^e$. In some embodiments, Y is O. In some embodiments, R^e is heterocyclyl (e.g., morpholino or thiomorpholino). In some embodiments, R^e is thiomorpholino substituted with 2 R^7 . In some embodiments, each R^7 is oxo. In some embodiments, R^e is:



In some embodiments, R^2 is C_3 alkyl substituted with 1 R^6 .

In some embodiments, R^6 is $-C(Y)NR^bR^{b'}$. In some embodiments, Y is O. In some embodiments, R^b and $R^{b'}$ are both hydrogen. In some embodiments, R^b and $R^{b'}$ are each independently C_1 - C_8 alkyl (e.g., R^b and $R^{b'}$ are both methyl). In some embodiments, one of R^b and $R^{b'}$ is hydrogen and the other is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, R^6 is $-NR^cC(Y)R^{c'}$. In some embodiments, Y is O. In some embodiments, R^c and $R^{c'}$ are each independently C_1 - C_8 alkyl (e.g., R^c and $R^{c'}$ are both methyl).

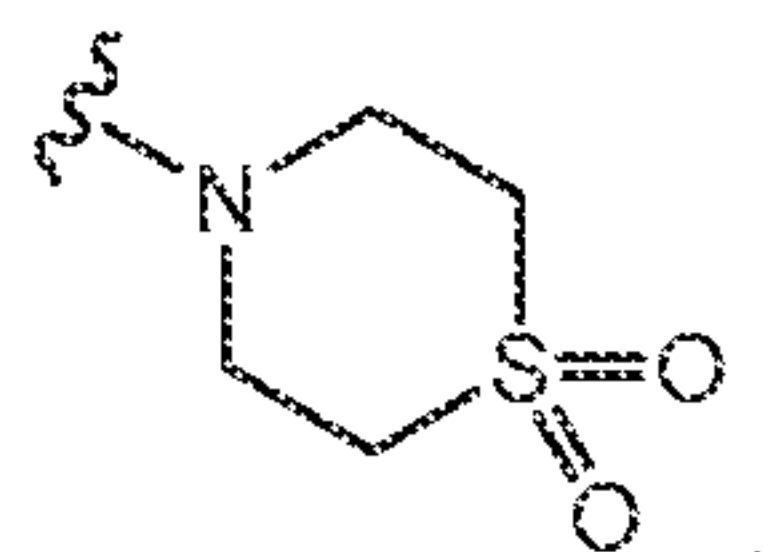
In some embodiments, R^6 is $-OR^d$. In some embodiments, R^d is hydrogen. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, R^6 is silyloxy (e.g., tert-butyldimethylsilyloxy).

In some embodiments, R^6 is $-C(Y)R^e$. In some embodiments, Y is O. In some embodiments, R^e is heterocyclyl (e.g., morpholino).

In some embodiments, R^2 is C_2 - C_8 alkynyl. In some embodiments, R^2 is C_2 - C_8 alkynyl substituted with 1 R^6 (e.g., C_3 alkynyl substituted with 1 R^6). In some embodiments, R^2 is $-C\equiv C-CH_2-R^6$. In some embodiments, R^6 is $-NR^bR^{b'}$. In some embodiments, R^b and $R^{b'}$ are each independently C_1 - C_8 alkyl (e.g., R^b and $R^{b'}$ are both methyl). In some embodiments, R^6 is $-OR^d$. In some embodiments, R^d is hydrogen. In some embodiments, R^6 is silyloxy (e.g., tert-butyldimethylsilyloxy). In some embodiments, R^6 is heterocyclyl (e.g., morpholino or thiomorpholino). In some

embodiments, R^6 is thiomorpholino substituted with 2 R^7 . In some embodiments, each R^7 is oxo. In some embodiments, R^6 is:



In some embodiments, R^2 is aryl (e.g., phenyl). In some embodiments, R^2 is unsubstituted phenyl.

In some embodiments, R^2 is phenyl substituted with 1 R^6 .

In some embodiments, R^6 is heterocyclalkyl (e.g., $-\text{CH}_2$ -morpholino). In some embodiments, R^6 is haloalkyl (e.g., trifluoromethyl). In some embodiments, R^6 is $-\text{CN}$. In some embodiments, R^6 is $-\text{OR}^d$. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, R^6 is $-\text{C}(\text{Y})\text{R}^e$. In some embodiments, Y is O. In some embodiments, R^e is heterocyclalkyl (e.g., morpholino).

In some embodiments, R^2 is phenyl substituted with 2 R^6 .

In some embodiments, each R^6 is independently $-\text{OR}^d$. In some embodiments, each R^d is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, one R^6 is halo (e.g., fluoro) and the other is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, one R^6 is $-\text{C}(\text{O})\text{OR}^a$ and the other is $-\text{OR}^d$. In some embodiments, R^a and R^d are each independently C_1 - C_8 alkyl (e.g., R^a and R^d are both methyl).

In some embodiments, R^2 is heteroaryl.

In some embodiments, R^2 is isoxazolyl. In some embodiments, R^2 is isoxazolyl substituted with 2 R^6 . In some embodiments, each R^6 is independently C_1 - C_8 alkyl (e.g., R^6 is methyl).

In some embodiments, R^2 is pyrazolyl. In some embodiments, R^2 is pyrazolyl substituted with 1 R^6 . In some embodiments, R^6 is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, R^2 is pyridyl. In some embodiments, R^2 is unsubstituted pyridyl. In some embodiments, R^2 is pyridyl substituted with 1 R^6 . In some embodiments, R^6 is halo (e.g., fluoro). In some embodiments, R^6 is $-\text{NR}^b\text{R}^{b'}$. In some embodiments, R^b and $R^{b'}$ are each hydrogen. In some embodiments, R^6 is $-\text{OR}^d$. In some embodiments, R^d is hydrogen. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, R^6 is heterocyclalkyl (e.g., morpholino or

piperazinyl). In some embodiments, R^6 is piperazinyl substituted with 1 R^7 . In some embodiments, R^7 is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, R^2 is pyrimidinyl.

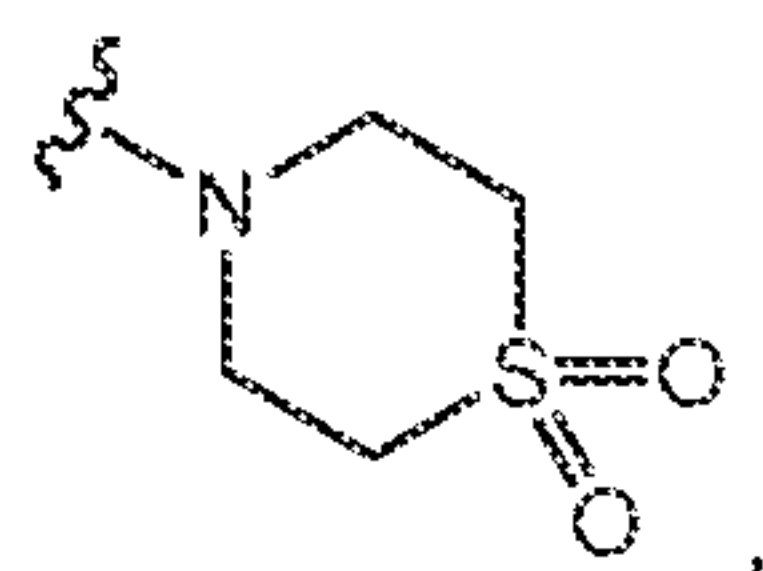
In some embodiments, R^2 is pyridazinyl.

In some embodiments, R^2 is cyclyl (e.g., cyclopropyl).

In some embodiments, R^2 is heterocyclyl (e.g., morpholino or pyrrolidinyl).

In some embodiments, R^2 is aralkyl (e.g., benzyl).

In some embodiments, R^2 is heterocyclylalkyl. In some embodiments, the alkyl is C_1 alkyl. In some embodiments, the alkyl is C_2 alkyl. In some embodiments, the alkyl is C_3 alkyl. In some embodiments, the heterocyclyl is piperidinyl. In some embodiments, the heterocyclyl is piperazinyl. In some embodiments, the heterocyclyl is piperazinyl substituted with 1 R^6 . In some embodiments, R^6 is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, the heterocyclyl is pyrrolidinyl. In some embodiments, the heterocyclyl is morpholino. In some embodiments, the heterocyclyl is thiomorpholino. In some embodiments, the heterocyclyl is thiomorpholino substituted with 2 R^6 . In some embodiments, each R^6 is oxo. In some embodiments, the heterocyclyl is:



In some embodiments, R^2 is halo (e.g., fluoro, chloro, bromo or iodo).

In some embodiments, R^2 is haloalkyl (e.g., trifluoromethyl).

In some embodiments, R^2 is haloalkoxy (e.g., trifluoromethoxy).

In some embodiments, R^2 is $-CN$.

In some embodiments, R^2 is $-NO_2$.

In some embodiments, R^2 is $-C(O)OR^a$. In some embodiments, R^a is hydrogen. In some embodiments, R^a is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, R^2 is $-C(Y)NR^bR^{b'}$. In some embodiments, Y is O . In some embodiments, R^b and $R^{b'}$ are each hydrogen. In some embodiments, R^b and $R^{b'}$ are each independently C_1 - C_8 alkyl (e.g., R^b and $R^{b'}$ are both methyl). In some embodiments, one of R^b and $R^{b'}$ is hydrogen and the other is C_1 - C_8 alkyl (e.g., methyl).

or ethyl). In some embodiments, one of R^b and $R^{b'}$ is hydrogen and the other is heterocyclalkyl (e.g., $-\text{CH}_2\text{-CH}_2\text{-morpholino}$). In some embodiments, one of R^b and $R^{b'}$ is hydrogen and the other is haloalkyl (e.g., trifluoroethyl).

In some embodiments, R^2 is $-\text{NR}^b\text{R}^{b'}$. In some embodiments, R^b and $R^{b'}$ are both hydrogen. In some embodiments, R^b and $R^{b'}$ are each independently $\text{C}_1\text{-C}_8$ alkyl (e.g., R^b and $R^{b'}$ are both methyl). In some embodiments, one of R^b and $R^{b'}$ is hydrogen and the other is $\text{C}_1\text{-C}_8$ alkyl (e.g., methyl). In some embodiments, one of R^b and $R^{b'}$ is hydrogen and the other is heterocycl (e.g., tetrahydropyranyl). In some embodiments, one of R^b and $R^{b'}$ is hydrogen and the other is heterocyclalkyl. In some embodiments, the alkyl is C_1 alkyl. In some embodiments, the alkyl is C_2 alkyl. In some embodiments, the alkyl is C_3 alkyl. In some embodiments, the heterocycl is morpholino. In some embodiments, the heterocycl is pyrrolidinyl. In some embodiments, the heterocycl is tetrahydrofuranyl. In some embodiments, the heterocycl is tetrahydropyranyl. In some embodiments, one of R^b and $R^{b'}$ is hydrogen and the other is hydroxyalkyl. In some embodiments, the alkyl is C_2 alkyl. In some embodiments, one of R^b and $R^{b'}$ is hydrogen and the other is alkoxyalkyl. In some embodiments, the alkyl is C_2 alkyl. In some embodiments, the alkyl is C_3 alkyl. In some embodiments, the alkoxy is methoxy. In some embodiments, one of R^b and $R^{b'}$ is hydrogen and the other is $-\text{C}(\text{Y})\text{R}^e$. In some embodiments, Y is O. In some embodiments, R^e is $\text{C}_1\text{-C}_8$ alkyl (e.g., methyl). In some embodiments, R^e is heterocycl. In some embodiments, R^e is tetrahydropyranyl.

In some embodiments, R^2 is $-\text{OR}^d$.

In some embodiments, R^d is hydrogen. In some embodiments, R^d is $\text{C}_1\text{-C}_8$ alkyl (e.g., methyl).

In some embodiments, R^d is ethyl. In some embodiments, R^d is C_3 alkyl (e.g., isopropyl or n-propyl). In some embodiments, R^d is optionally substituted heteroaralkyl. In some embodiments, R^d is optionally substituted pyridinylalkyl.

In some embodiments, R^d is n-propyl. In some embodiments, R^d is cyclyl (e.g., cyclopentyl).

In some embodiments, R^d is heteroaralkyl (e.g., $-\text{CH}_2\text{-pyridyl}$).

In some embodiments, R^d is heterocyclalkyl. In some embodiments, the alkyl is C_1 alkyl. In some embodiments, the alkyl is C_2 alkyl. In some embodiments, the alkyl is C_3 alkyl. In some embodiments, the alkyl is C_4 alkyl. In some embodiments, the heterocycl is morpholino. In some embodiments, the heterocycl is piperidyl. In some embodiments, the heterocycl is tetrahydrofuranyl. In some embodiments, R^d is cyclalkyl (e.g., $-\text{CH}_2\text{-cyclobutyl}$).

In some embodiments, R^d is alkoxyalkyl. In some embodiments, the alkyl is C_2 alkyl. In some embodiments, the alkyl is C_3 alkyl. In some embodiments, the alkoxy is methoxy.

In some embodiments, R^d is dialkylaminoalkyl. In some embodiments, the alkyl is C_2 alkyl. In some embodiments, the alkyl is C_3 alkyl. In some embodiments, the dialkylamino is dimethylamino.

In some embodiments, R^2 is $-\text{C}(\text{Y})\text{R}^e$. In some embodiments, Y is O. In some embodiments, R^e is heterocycl. In some embodiments, R^e is piperidyl. In some embodiments, R^e is pyrrolidinyl. In some embodiments, R^e is piperazinyl. In some embodiments, R^e is morpholino. In some embodiments, R^e is thiomorpholino.

In some embodiments, n is 2.

In some embodiments, each R^2 is independently halo (e.g., each R^2 is chloro).

In some embodiments, each R^2 is independently $-\text{OR}^d$.

In some embodiments, each R^d is $C_1\text{-}C_8$ alkyl.

In some embodiments, each R^2 is methoxy. In some embodiments, one R^2 is methoxy and the other is ethoxy. In some embodiments, one R^2 is methoxy and the other is propoxy. In some embodiments, one R^2 is methoxy and the other is isopropoxy.

In some embodiments, one R^2 is methoxy and the other is ethoxy substituted with 1 R^6 . In some embodiments, R^6 is $-\text{NR}^b\text{R}^{b'}$. In some embodiments, R^b and $R^{b'}$ are each independently $C_1\text{-}C_8$ alkyl (e.g., R^b and $R^{b'}$ are both methyl). In some embodiments, R^6 is $-\text{OR}^d$. In some embodiments, R^d is $C_1\text{-}C_8$ alkyl (e.g., methyl).

In some embodiments, one R^2 is methoxy and the other is propoxy substituted with 1 R^6 . In some embodiments, R^6 is $-\text{OR}^d$. In some embodiments, R^d is $C_1\text{-}C_8$ alkyl (e.g., methyl).

In some embodiments, one R^2 is $-OR^d$ and the other is C_1-C_8 alkyl (e.g., methyl). In some embodiments, R^d is C_1-C_8 alkyl (e.g., methyl or ethyl).

In some embodiments, one R^2 is $-OR^d$ and the other is halo (e.g., chloro). In some embodiments, R^d is C_1-C_8 alkyl (e.g., methyl).

In some embodiments, one R^2 is $-OR^d$ and the other is $-CN$. In some embodiments, R^d is C_1-C_8 alkyl (e.g., methyl).

In some embodiments, one R^2 is $-OR^d$ and the other is $-C(O)OR^a$. In some embodiments, R^d and R^a are both hydrogen.

In some embodiments, one R^2 is $-OR^d$ and the other is C_1-C_8 alkyl (e.g., methyl). In some embodiments, R^d is C_1-C_8 alkyl (e.g., methyl).

In some embodiments, one R^2 is $-OR^d$ and the other is $-C(Y)R^e$. In some embodiments, R^d is C_1-C_8 alkyl (e.g., methyl). In some embodiments, Y is O . In some embodiments, R^e is heterocyclyl (e.g., morpholino).

In some embodiments, one R^2 is halo (e.g., chloro or bromo) and the other is C_1-C_8 alkyl (e.g., methyl).

In some embodiments, one R^2 is C_1-C_8 alkyl (e.g., methyl) and the other is $-CN$.

In some embodiments, one R^2 is C_1-C_8 alkyl (e.g., methyl) and the other is heteroaryl (e.g., pyridyl). In some embodiments, the pyridyl is substituted with 1 R^6 . In some embodiments, R^6 is $-OR^d$. In some embodiments, R^d is C_1-C_8 alkyl (e.g., methyl).

In some embodiments, one R^2 is C_1-C_8 alkyl (e.g., methyl) and the other is heterocyclylalkyl (e.g., $-CH_2$ -morpholino).

In some embodiments, p is 0.

In some embodiments, p is 1.

In some embodiments, R^3 is C_1-C_8 alkyl (e.g., methyl). In some embodiments, R^3 is halo (e.g., chloro). In some embodiments, R^3 is haloalkyl (e.g., trifluoromethyl). In some embodiments, R^3 is oxo.

In some embodiments, R^3 is $-OR^d$. In some embodiments, R^d is hydrogen. In some embodiments, R^d is C_1-C_8 alkyl (e.g., methyl).

In some embodiments, R^3 is $-NR^bR^{b'}$. In some embodiments, R^b and $R^{b'}$ are both hydrogen. In some embodiments, one of R^b and $R^{b'}$ is hydrogen and the other is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, R^3 is heterocyclyl (e.g., piperazinyl). In some embodiments, R^3 is piperazinyl substituted with 1 R^6 . In some embodiments, R^6 is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, E is a 5-membered heteroaryl ring.

In some embodiments, E is a thiophene ring.

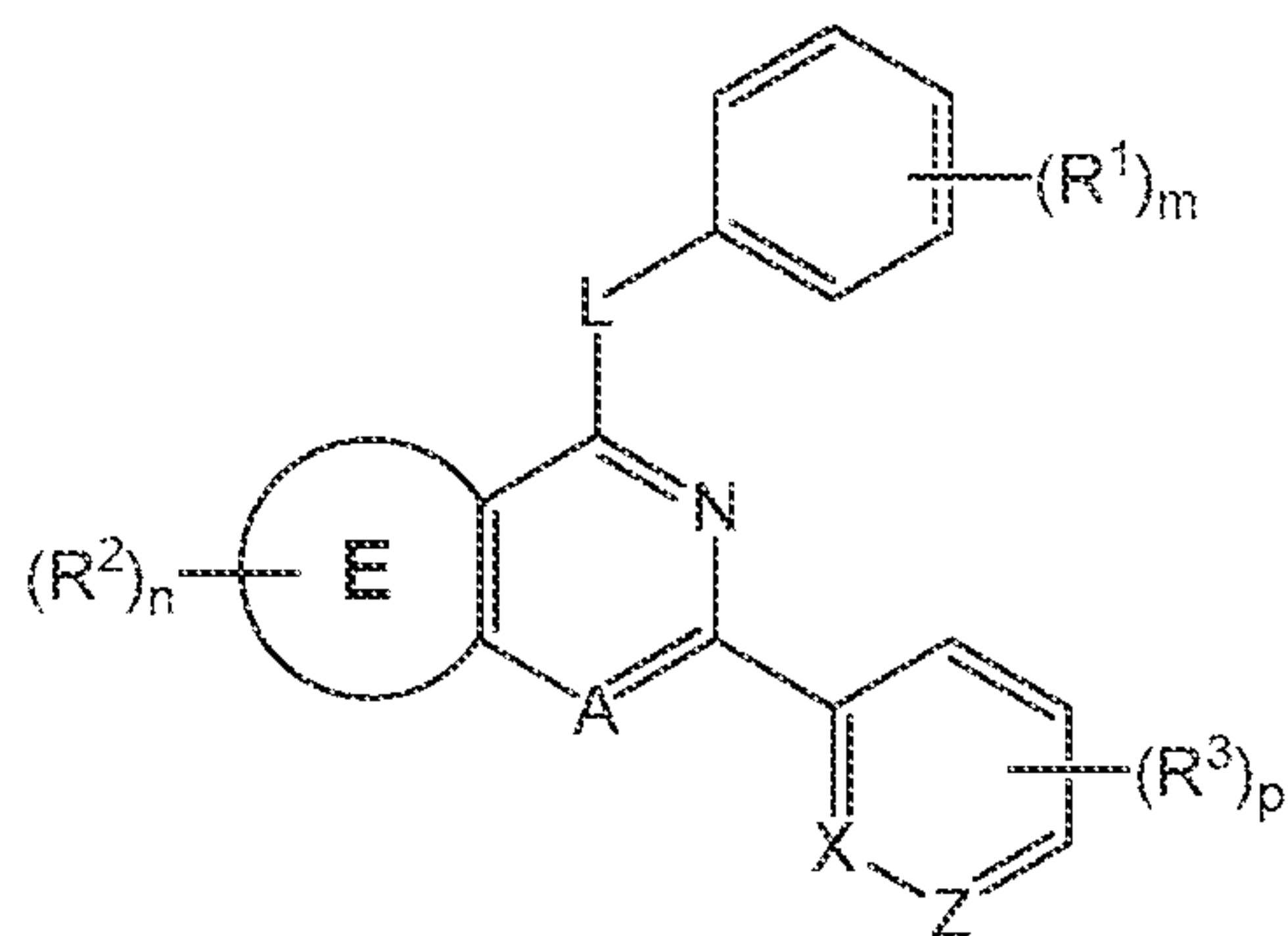
In some embodiments, E is a pyrrole ring.

In some embodiments, n is 1. In some embodiments, R^2 is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, E is an N-methylpyrrole ring.

In some embodiments, L is NR^5 . In some embodiments, R^5 is hydrogen.

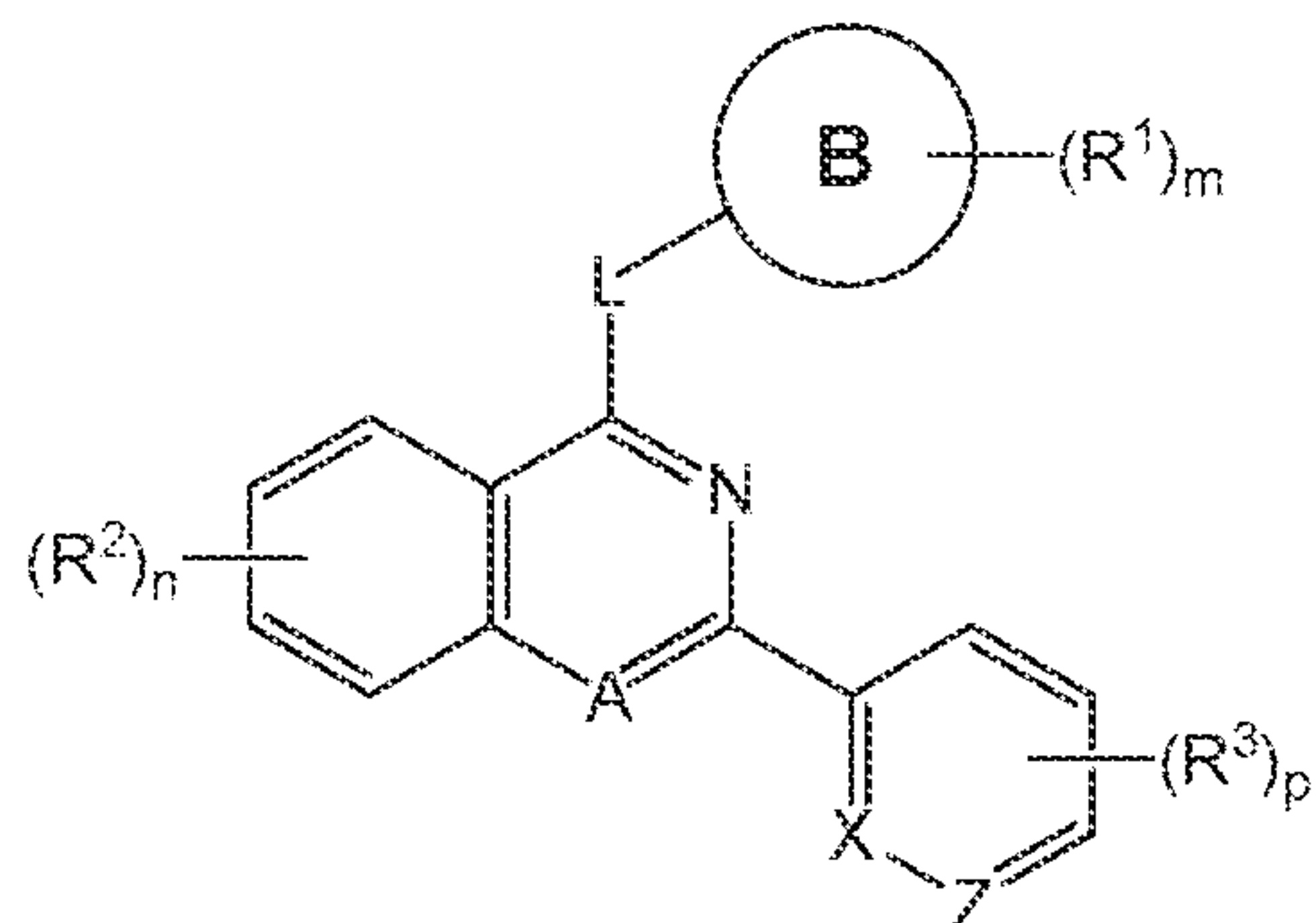
In some embodiments, L is O.

In some embodiments, the compound is:

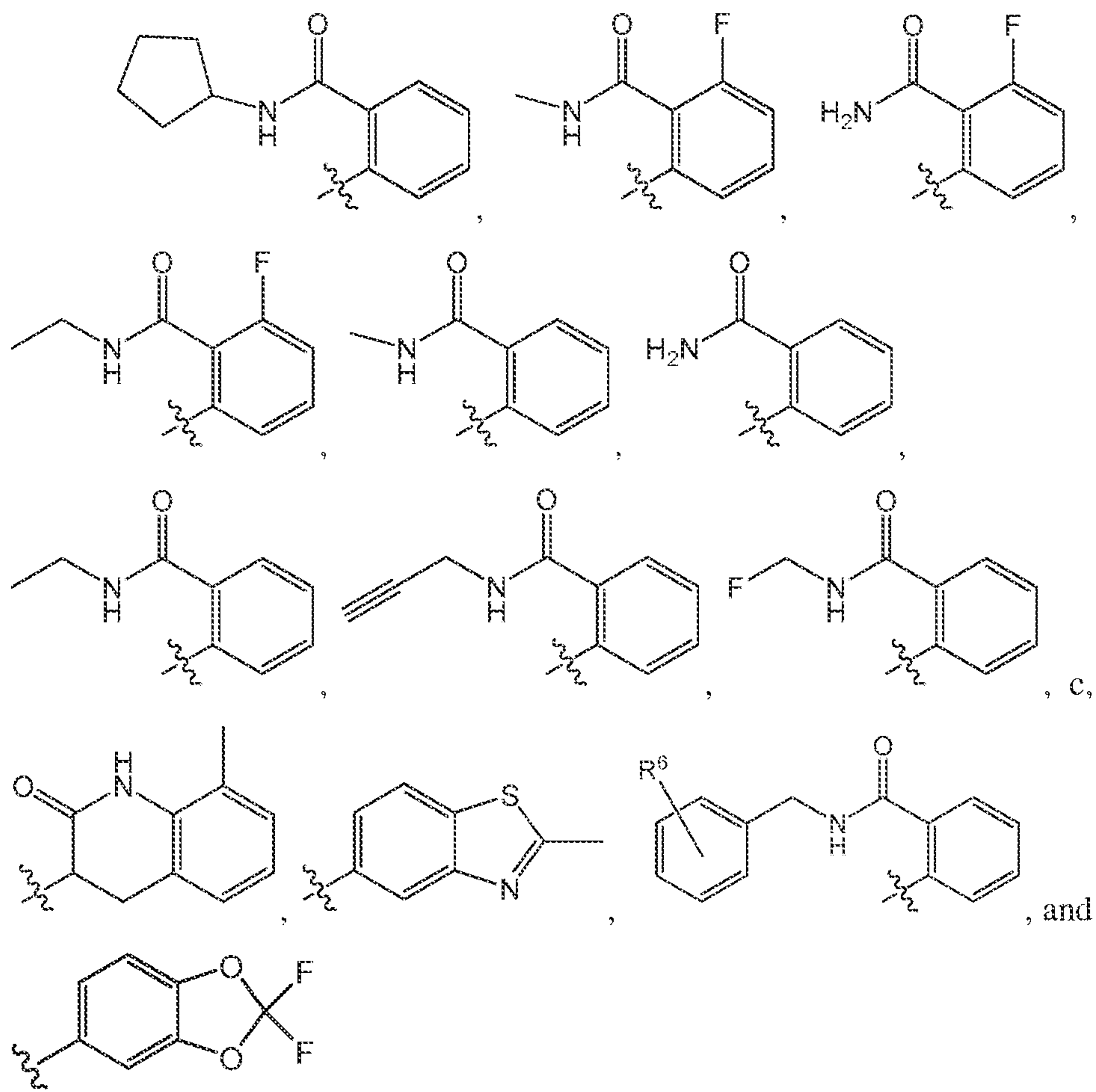
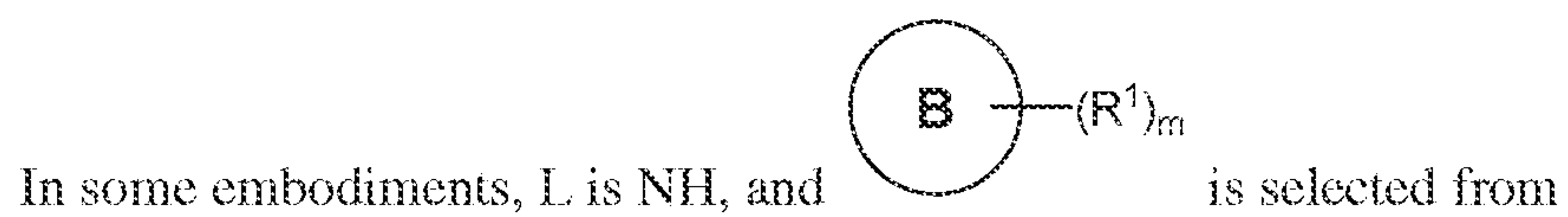
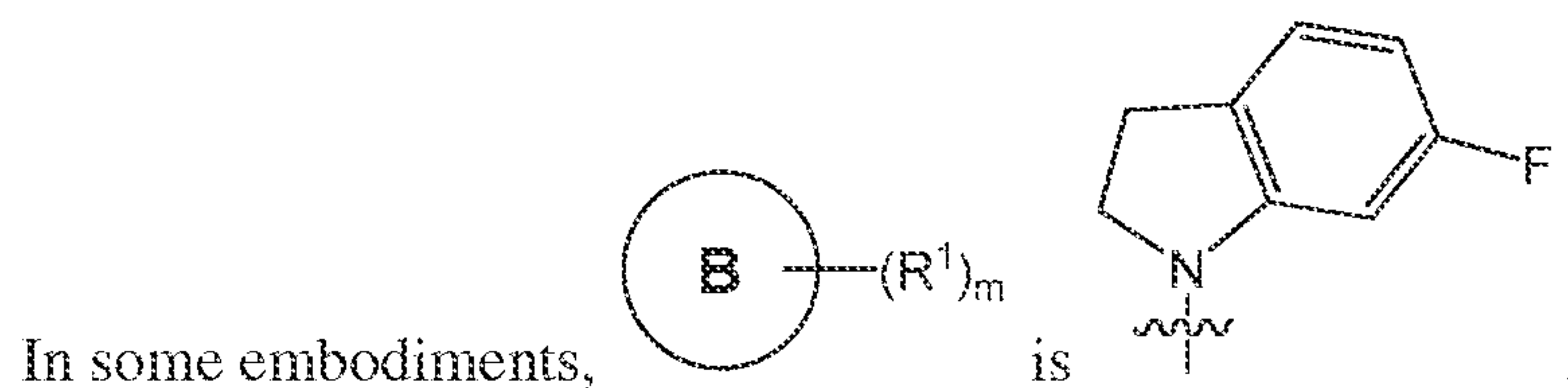
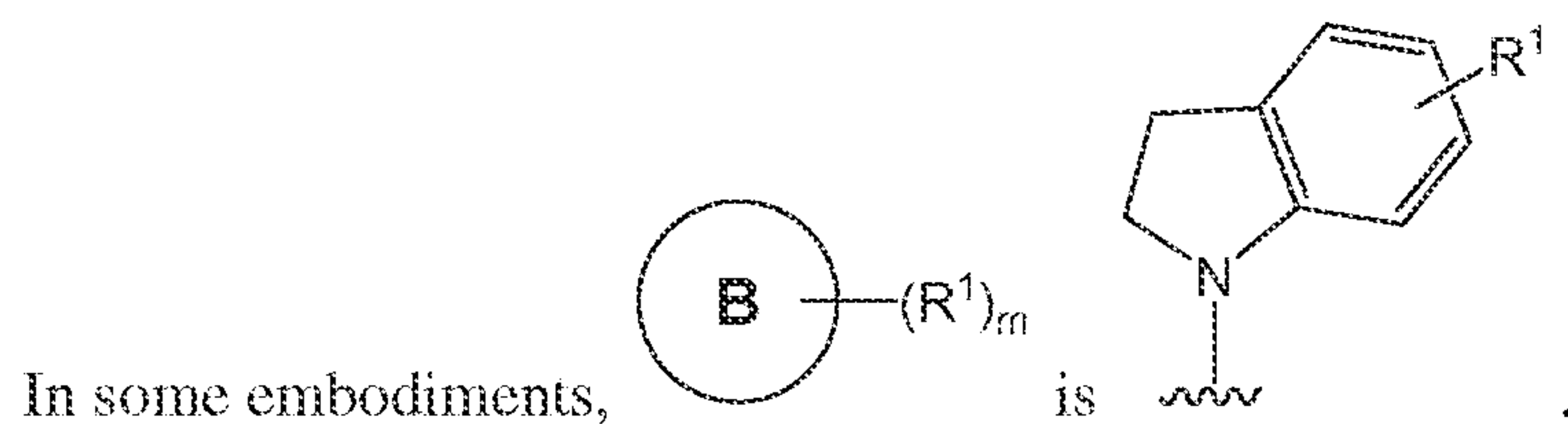


In some embodiments, R^2 is C_1 - C_4 alkoxy. In some embodiments, R^2 is halo. In some embodiments, R^1 is $-C(Y)NR^bR^{b'}$.

In some embodiments, the compound is:

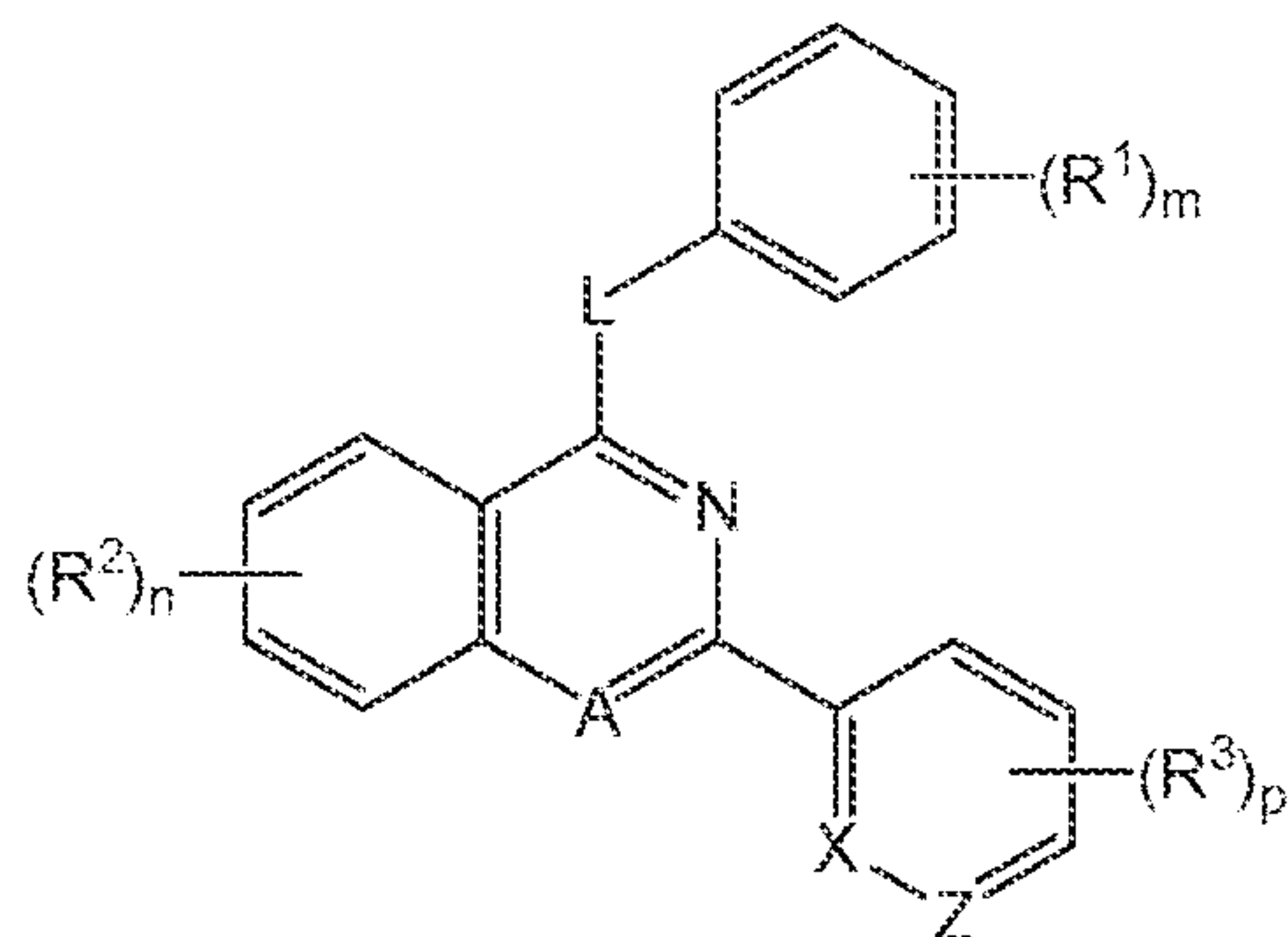


In some embodiments, R^2 is C_1 - C_4 alkoxy. In some embodiments, R^2 is halo.
 In some embodiments, R^1 is $-C(Y)NR^bR^{b'}$.



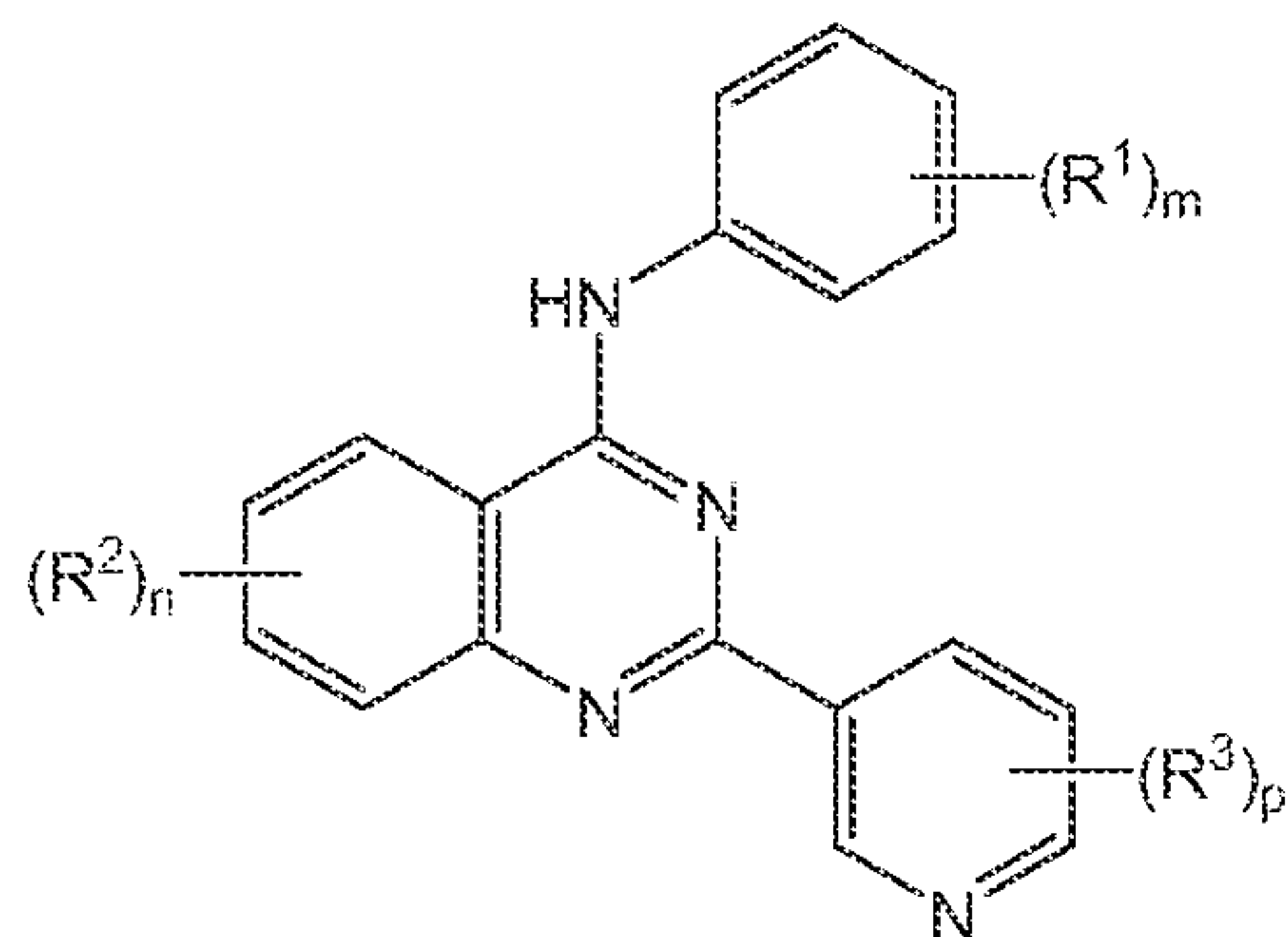
In some embodiments R^6 is halo.

In some embodiments, the compound is:



In some embodiments, R^1 is $-C(Y)NR^bR^{b'}$. In some embodiments, R^1 is halo. In some embodiments, R^2 is C_1 - C_4 alkoxy. In some embodiments, R^2 is halo. In some embodiments, m is 2 and two R^1 are 3,4-dichloro; 3,4-difluoro, 3,5- dichloro; 3,5-difluoro; 3-chloro,4-fluoro; or 3-chloro,5-fluoro. In some embodiments, R^2 is $-C(O)NR^bR^{b'}$ and R^3 is H. In some embodiments, R^b and $R^{b'}$ are H. In some embodiments, R^b and $R^{b'}$ are independently C_1 - C_4 alkyl or halo-substituted C_1 - C_4 alkyl. In some embodiments, R^b is methyl and $R^{b'}$ is trifluoroethyl. In some embodiments, R^1 is C_1 - C_4 alkoxy or halo-substituted C_1 - C_4 alkoxy. In some embodiments, n and p are zero.

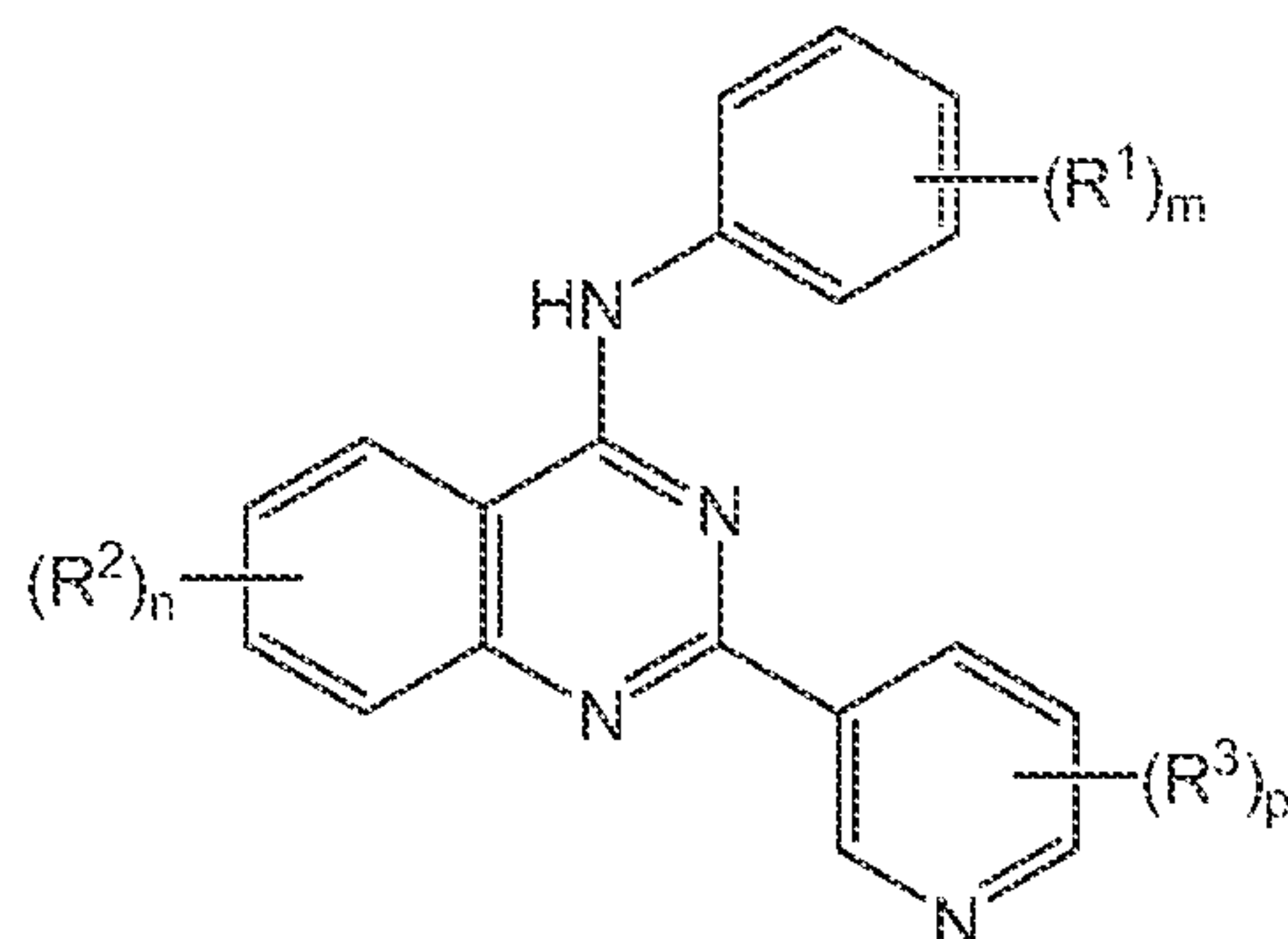
In some embodiments, the compound is:



In some embodiments, R^1 is $-C(Y)NR^bR^{b'}$. In some embodiments, R^1 is halo. In some embodiments, R^2 is C_1 - C_4 alkoxy. In some embodiments, R^2 is halo. In some embodiments, m is 2 and two R^1 are 3,4-dichloro; 3,4-difluoro, 3,5- dichloro; 3,5-difluoro; 3-chloro,4-fluoro; or 3-chloro,5-fluoro. In some embodiments, R^2 is $-C(O)NR^bR^{b'}$ and R^3 is H. In some embodiments, R^b and $R^{b'}$ are H. In some

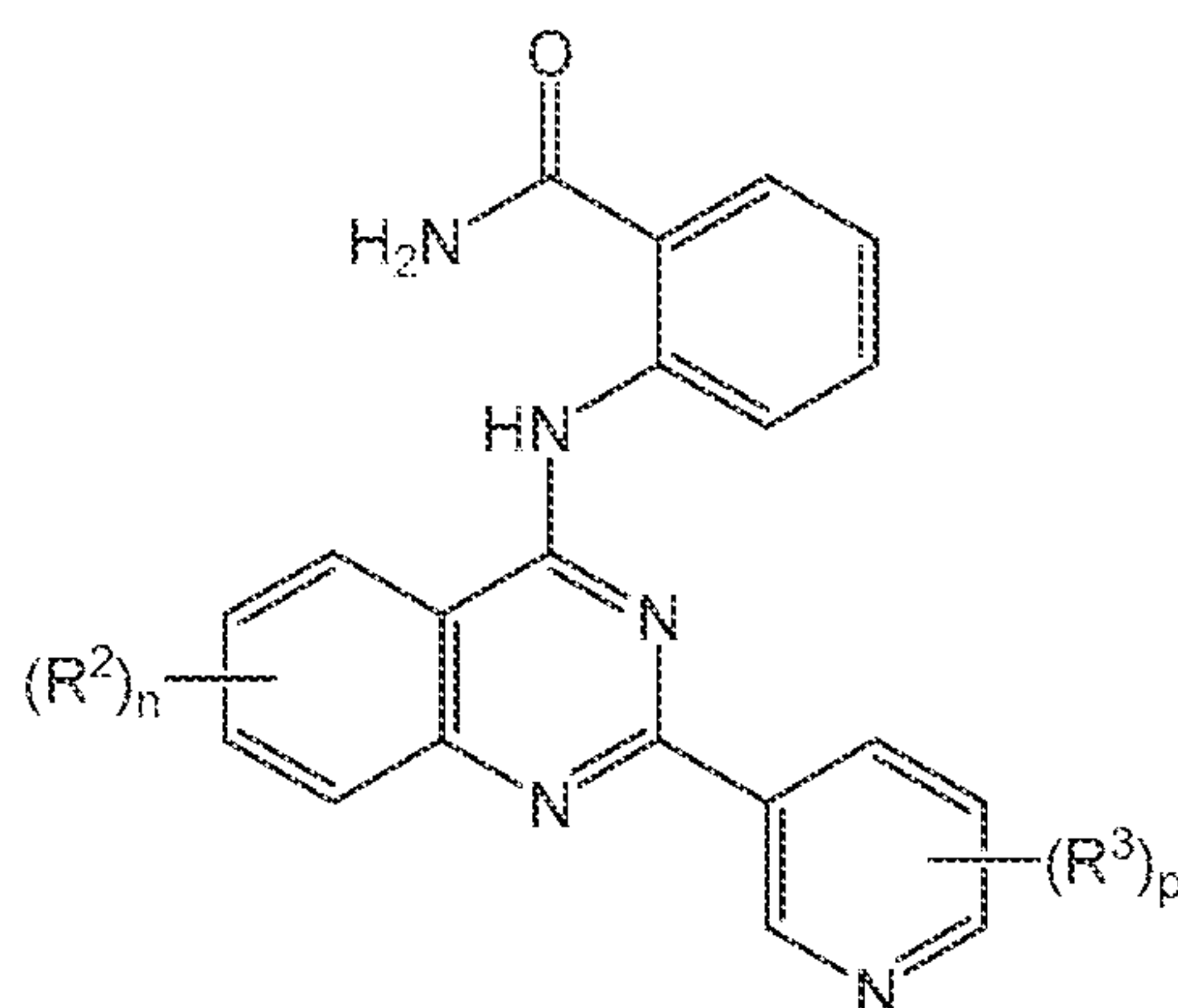
embodiments, R^b and $R^{b'}$ are independently C_1 - C_4 alkyl or halo-substituted C_1 - C_4 alkyl. In some embodiments, R^b is methyl and $R^{b'}$ is trifluoroethyl. In some embodiments, R^1 is C_1 - C_4 alkoxy or halo-substituted C_1 - C_4 alkoxy. In some embodiments, n and p are zero.

In some embodiments, the compound is:



In some embodiments, R^1 is $-C(Y)NR^bR^{b'}$. In some embodiments, R^1 is halo. In some embodiments, R^2 is C_1 - C_4 alkoxy. In some embodiments, R^2 is halo. In some embodiments, m is 2 and two R^1 are 3,4-dichloro; 3,4-difluoro, 3,5-dichloro; 3,5-difluoro; 3-chloro,4-fluoro; or 3-chloro,5-fluoro. In some embodiments, R^2 is $-C(O)NR^bR^{b'}$ and R^3 is H. In some embodiments, R^b and $R^{b'}$ are H. In some embodiments, R^b and $R^{b'}$ are independently C_1 - C_4 alkyl or halo-substituted C_1 - C_4 alkyl. In some embodiments, R^b is methyl and $R^{b'}$ is trifluoroethyl. In some embodiments, R^1 is C_1 - C_4 alkoxy or halo-substituted C_1 - C_4 alkoxy. In some embodiments, n and p are zero.

In some embodiments, the compound is:



In some embodiments, R^1 is $-C(Y)NR^bR^{b'}$. In some embodiments, R^1 is halo. In some embodiments, R^2 is C_1 - C_4 alkoxy. In some embodiments, R^2 is halo. In some embodiments, m is 2 and two R^1 are 3,4-dichloro; 3,4-difluoro, 3,5- dichloro; 3,5-difluoro; 3-chloro,4-fluoro; or 3-chloro,5-fluoro. In some embodiments, R^2 is $-C(O)NR^bR^{b'}$ and R^3 is H. In some embodiments, R^b and $R^{b'}$ are H. In some embodiments, R^b and $R^{b'}$ are independently C_1 - C_4 alkyl or halo-substituted C_1 - C_4 alkyl. In some embodiments, R^b is methyl and $R^{b'}$ is trifluoroethyl. In some embodiments, R^1 is C_1 - C_4 alkoxy or halo-substituted C_1 - C_4 alkoxy. In some embodiments, n and p are zero.

Compounds of Formula (II)

The following aspects and embodiments relate to compounds of formula (II).
Item 9. The compound according to item 1 represented by general formula (II) or a salt thereof,

wherein:

L is CR^4R^5 , O, $C(O)$, $NR^6C(O)$ or NR^7 ;

A is N;

each X^1 , X^2 , X^3 , X^4 and X^5 is independently CH or N, provided that at least two of X^1 , X^2 , X^3 , X^4 and X^5 are N;

n is 0, 1, 2, 3 or 4;

p is 0, 1, 2 or 3;

R^1 is C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl or heterocyclylalkyl, each of which is optionally substituted with 1-5 R^9 ; wherein R^1 or R^9 is optionally taken together with one of R^4 , R^5 , R^6 or R^7 , and the atoms to which they are attached to form a cyclyl, heterocyclyl, aryl or heteroaryl ring that is optionally substituted with 1-3 R^{10} ;

each R^2 and R^3 is independently hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy,

silylalkoxyalkyl, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^{c'}$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{O})\text{OR}^{c'}$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^{c'}$, $-\text{NR}^c\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^{d'}$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$, each of which is optionally substituted with 1-3 R^{11} ;

each R^4 , R^5 , R^6 and R^7 is independently hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^{c'}$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{O})\text{OR}^{c'}$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^{c'}$, $-\text{NR}^c\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^{d'}$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$;

each R^9 , R^{10} and R^{11} is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, oxo, thioxo, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^{c'}$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{O})\text{OR}^{c'}$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^{c'}$, $-\text{NR}^c\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^{d'}$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$, each of which is optionally substituted with 1-3 R^{12} ; wherein two R^8 , two R^9 , two R^{10} or two R^{11} is optionally taken together with the atoms to which they are attached to form an optionally substituted cyclyl, heterocyclyl, aryl or heteroaryl ring;

R^{12} is $-\text{OR}^d$;

Y is O or S;

q is 1 or 2; and

each R^a , R^b , $\text{R}^{b'}$, R^c , $\text{R}^{c'}$, R^d , $\text{R}^{d'}$, R^e , $\text{R}^{e'}$ and R^f is independently hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, acyl, cyclyl, heterocyclyl, aryl, heteroaryl, cyclylalkyl, heterocyclylalkyl, arylalkyl, or heteroarylalkyl.

Item 10. The compound according to item 9 represented by general formula (II) or a salt thereof,

L is NR^7 ;

n is 0, 1 or 2;

p is 0;

R¹ is C₁-C₈ alkyl, aryl or heteroaryl;

each R² and R³ is independently hydrogen, C₁-C₈ alkyl, aryl, halo, heterocyclalkyl, -NR^cC(Y)R^c, -NR^bR^{b'} or -OR^d, each of which is optionally substituted with 1-3 R¹¹;

R⁷ is hydrogen; and

each R⁹, R¹⁰ and R¹¹ is independently C₁-C₈ alkyl, heterocyclalkyl, halo, haloalkyl, haloalkoxy, -CN, -C(O)OR^a, -C(Y)NR^bR^{b'}, -OR^d or -C(Y)R^e;

Y is O;

each R^a, R^b, R^{b'}, R^c, R^{c'}, R^d, R^{d'}, R^e, R^{e'} and R^f is independently hydrogen, C₁-C₈ alkyl, cyclyl, heterocyclalkyl, aryl or heteroaryl.

Item 11 .The compound according to item 10 represented by general formula (II) or a salt thereof,

wherein:

R¹ is C₁-C₈ alkyl, phenyl or benzodioxolyl;

each R² and R³ is independently hydrogen, C₁-C₈ alkyl, phenyl, halo, morpholinyalkyl, -NR^cC(Y)R^c, -NR^bR^{b'} or -OR^d;

R⁹ is independently C₁-C₈ alkyl, morpholinyalkyl, tetrahydropyranyl, halo, haloalkyl, haloalkoxy, -CN, -C(O)OR^a, -C(Y)NR^bR^{b'}, -OR^d or -C(Y)R^e; and

each R^a, R^b, R^{b'}, R^c, R^{c'}, R^d, R^{d'}, R^e, R^{e'} and R^f is independently hydrogen, C₁-C₈ alkyl, C₃-C₈ cycloalkyl, tetrahydropyranyl, phenyl or pyridyl.

Item 12. The compound according to item 10 represented by general formula (II) or a salt thereof,

wherein:

R¹ is C₁-C₈ alkyl, phenyl or benzodioxolyl;

each R² and R³ is independently hydrogen, C₁-C₈ alkyl, phenyl, halo, morpholinyalkyl, -NR^cC(Y)R^c, -NR^bR^{b'} or -OR^d, each of which is optionally substituted with 1-3 R¹¹;

each R^9 , R^{10} and R^{11} is independently C_1 - C_8 alkyl, morpholinyl, tetrahydropyranyl, halo, haloalkyl, haloalkoxy, $-\text{CN}$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$ or $-\text{C}(\text{Y})\text{R}^e$; and
 each R^a , R^b , $R^{b'}$, R^c , $R^{c'}$, R^d , $R^{d'}$, R^e , $R^{e'}$ and R^f is independently hydrogen, C_1 - C_8 alkyl, C_3 - C_8 cycloalkyl, tetrahydropyranyl, phenyl, or pyridyl.

Item 13. The compound according to item 12 represented by general formula (II) or a salt thereof, wherein:

R^2 is C_1 - C_8 alkyl, phenyl, halo, morpholinylalkyl, $-\text{NR}^c\text{C}(\text{Y})\text{R}^c$, $-\text{NR}^b\text{R}^{b'}$ or $-\text{OR}^d$, each of which is optionally substituted with 1-3 R^{11} ;

R^3 is hydrogen;

R^9 is halo, haloalkoxy, $-\text{CN}$, $-\text{C}(\text{O})\text{OR}^a$ or $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$; and

R^{11} is C_1 - C_8 alkyl, morpholinyl, tetrahydropyranyl, halo, $-\text{CN}$, $-\text{OR}^d$ or $-\text{C}(\text{Y})\text{R}^e$;

Item 14. The compound according to item 11 or 13 represented by general formula (II) or a salt thereof, wherein:

R^2 is C_1 - C_8 alkyl, phenyl, halo, morpholinylalkyl, $-\text{NR}^c\text{C}(\text{Y})\text{R}^c$, $-\text{NR}^b\text{R}^{b'}$ or $-\text{OR}^d$;

R^3 is hydrogen; and

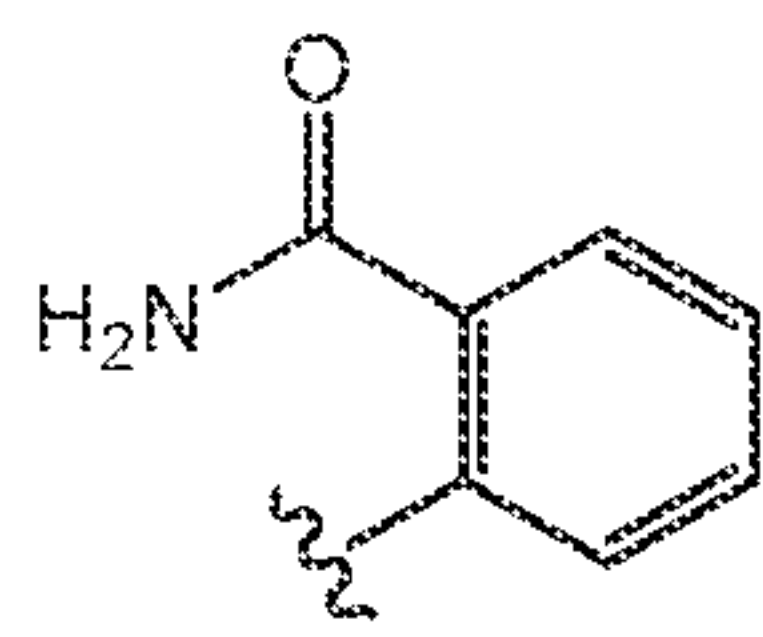
R^9 is halo, haloalkoxy, $-\text{CN}$, $-\text{C}(\text{O})\text{OR}^a$ or $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$.

In some embodiments, A is CH. In some embodiments, A is N.

In some embodiments, L is NR^7 . In some embodiments, R^7 is H.

In some embodiments, R^1 is aryl (e.g., phenyl).

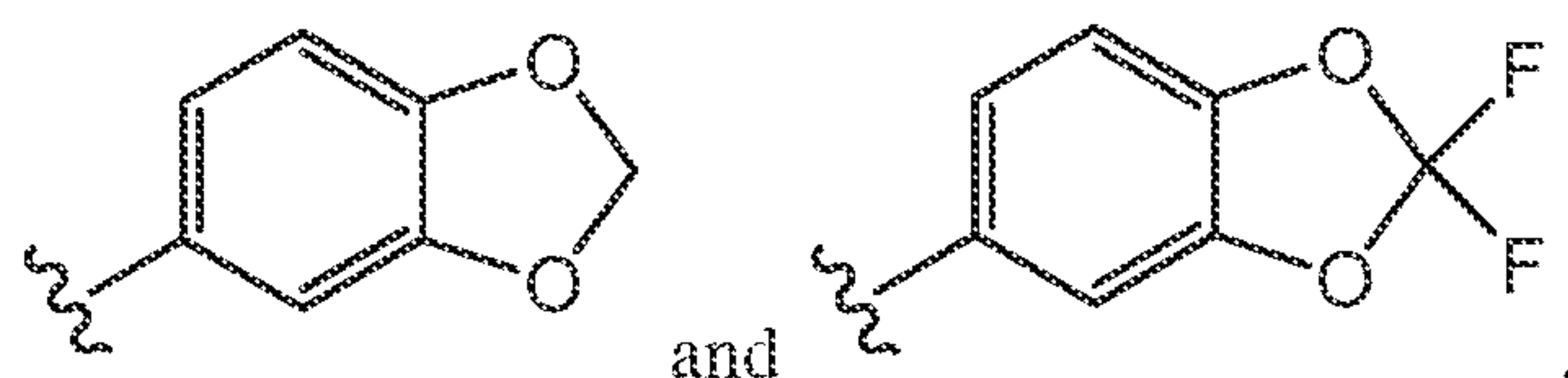
In some embodiments, R^1 is phenyl substituted with 1 R^9 . In some embodiments, R^1 is phenyl substituted with 1 R^9 in the ortho position. In some embodiments, R^1 is phenyl substituted with 1 R^9 in the meta position. In some embodiments, R^9 is haloalkoxy (e.g., difluoromethoxy or trifluoromethoxy). In some embodiments, R^9 is $-\text{CN}$. In some embodiments, R^9 is $-\text{C}(\text{O})\text{OR}^a$. In some embodiments, R^a is hydrogen. In some embodiments, R^9 is $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$. In some embodiments, Y is O. In some embodiments, R^b and $R^{b'}$ are both hydrogen. In some embodiments, R^1 is:



In some embodiments, one of R^b and $R^{b'}$ is hydrogen and the other is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, R^1 is phenyl substituted with 2 R^9 . In some embodiments, each R^9 is independently halo (e.g., each R^9 is fluoro or each R^9 is chloro). In some embodiments, one R^9 is fluoro and the other is chloro. In some embodiments, one R^9 is halo (e.g., chloro) and the other is haloalkoxy (e.g., difluoromethoxy or trifluoromethoxy).

In some embodiments, 2 R^9 are taken together with the atoms to which they are attached to form a heterocyclyl ring, e.g., a 5-membered heterocyclyl ring (e.g., a dioxole ring). In some embodiments, the dioxole ring is unsubstituted. In some embodiments, the dioxole ring is substituted. In some embodiments, the dioxole ring is substituted with two fluoro substituents. In some embodiments, R^1 is selected from:



In some embodiments, R^1 is aralkyl (e.g., benzyl). In some embodiments, R^1 is aralkyl substituted with 2 R^9 (e.g., benzyl substituted with 2 R^9). In some embodiments, 2 R^9 substituents are on the phenyl ring. In some embodiments, each R^9 is independently halo (e.g., each R^9 is chloro).

In some embodiments, R^1 is alkyl (e.g., methyl).

In some embodiments, n is 0.

In some embodiments, n is 1.

In some embodiments, R^2 is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, R^2 is C_1 - C_8 alkyl substituted with 1 R^{11} (e.g., methyl substituted with 1 R^{11}). In some embodiments, R^{11} is heterocyclyl (e.g., morpholino).

In some embodiments, R^2 is aryl (e.g., phenyl). In some embodiments, R^2 is phenyl substituted with 1 R^{11} . In some embodiments, R^{11} is $-\text{CN}$. In some embodiments, R^{11} is $-\text{OR}^d$. In some embodiments, R^d is $\text{C}_1\text{-C}_8$ alkyl (e.g., methyl). In some embodiments, R^{11} is halo.

In some embodiments, R^2 is halo (e.g., fluoro, chloro, bromo or iodo).

In some embodiments, R^2 is $-\text{NR}^c\text{C}(\text{Y})\text{R}^{c'}$. In some embodiments, R^c is hydrogen. In some embodiments, Y is O. In some embodiments, $R^{c'}$ is alkyl (e.g., methyl). In some embodiments, $R^{c'}$ is aryl (e.g., phenyl). In some embodiments, $R^{c'}$ is phenyl substituted with 1 R^8 . In some embodiments, R^8 is $-\text{OR}^d$. In some embodiments, R^d is $\text{C}_1\text{-C}_8$ alkyl (e.g., methyl).

In some embodiments, $R^{c'}$ is heteroaryl. In some embodiments, $R^{c'}$ is furanyl. In some embodiments, $R^{c'}$ is pyridyl. In some embodiments, $R^{c'}$ is pyridyl substituted with 1 R^8 . In some embodiments, R^8 is $-\text{OR}^d$. In some embodiments, R^d is $\text{C}_1\text{-C}_8$ alkyl (e.g., methyl).

In some embodiments, $R^{c'}$ is cyclyl (e.g., cyclohexyl). In some embodiments, $R^{c'}$ is cyclohexyl substituted with 1 R^8 . In some embodiments, R^8 is $-\text{OR}^d$. In some embodiments, R^d is $\text{C}_1\text{-C}_8$ alkyl (e.g., methyl).

In some embodiments, $R^{c'}$ is heterocyclyl (e.g., tetrahydropyranyl).

In some embodiments, R^2 is $-\text{NR}^b\text{R}^{b'}$. In some embodiments, R^b and $R^{b'}$ are both hydrogen. In some embodiments, R^b and $R^{b'}$ are each independently $\text{C}_1\text{-C}_8$ alkyl (e.g., R^b and $R^{b'}$ are both methyl).

In some embodiments, R^2 is $-\text{OR}^d$. In some embodiments, R^d is $\text{C}_1\text{-C}_8$ alkyl (e.g., methyl or ethyl). In some embodiments, R^d is ethyl substituted with 1 R^8 . In some embodiments, R^8 is $-\text{OR}^d$. In some embodiments, R^d is $\text{C}_1\text{-C}_8$ alkyl (e.g., methyl). In some embodiments, R^2 is $-\text{OCH}_2\text{CH}_2\text{OCH}_3$. In some embodiments, R^2 is $-\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CH}_3$. In some embodiments, R^2 is $-\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$.

In some embodiments, n is 2.

In some embodiments, one R^2 is $\text{C}_1\text{-C}_8$ alkyl (e.g., methyl) and the other is halo (e.g., chloro).

In some embodiments, one R^2 is $-OR^d$ and the other is halo (e.g., chloro). In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl).

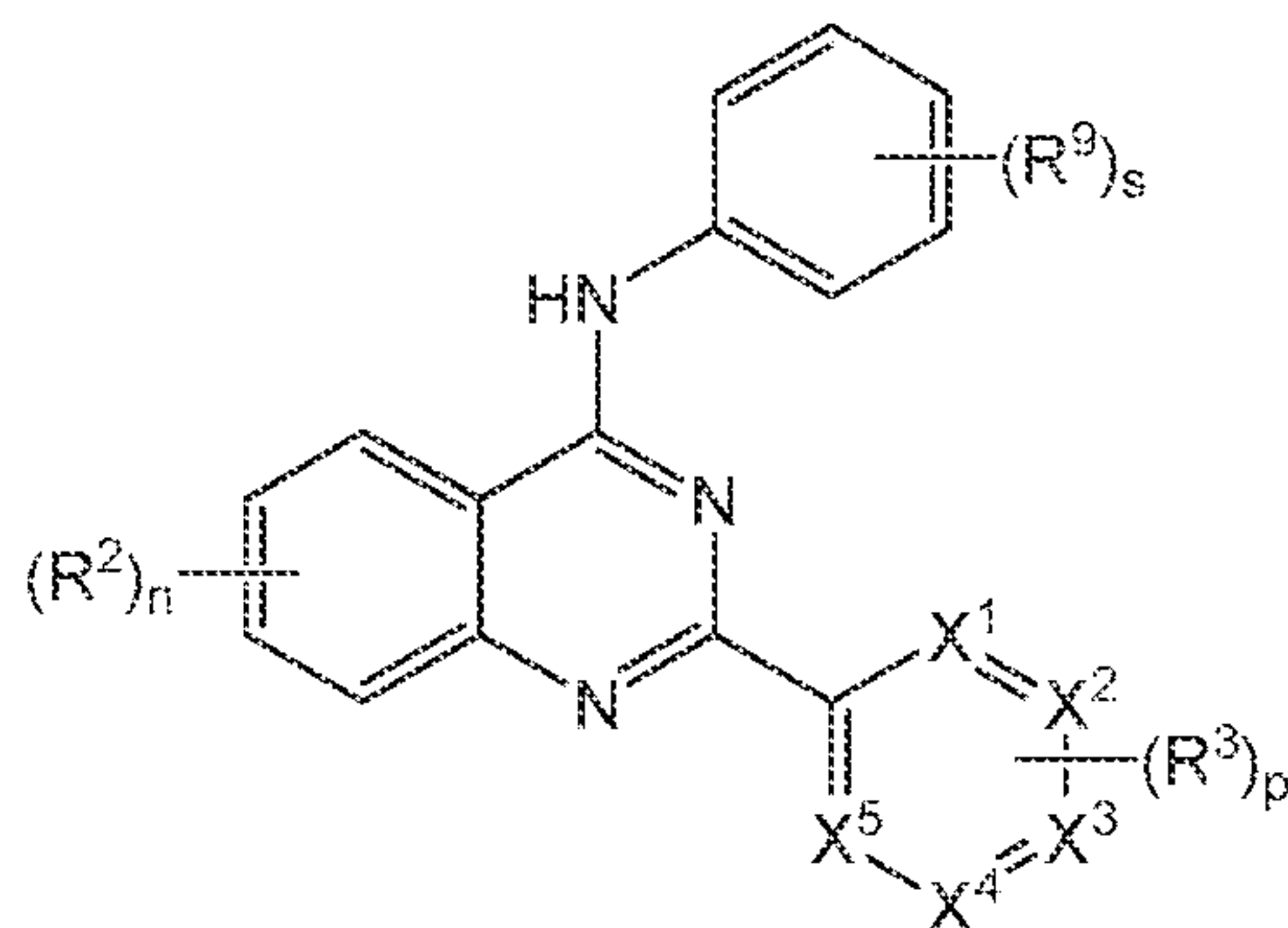
In some embodiments, X^1 and X^4 are N and X^2 , X^3 and X^5 are CH.

In some embodiments, X^1 and X^3 are N and X^2 , X^4 and X^5 are CH.

In some embodiments, X^2 and X^3 are N and X^1 , X^4 and X^5 are CH.

In some embodiments, X^2 and X^4 are N and X^1 , X^3 and X^5 are CH.

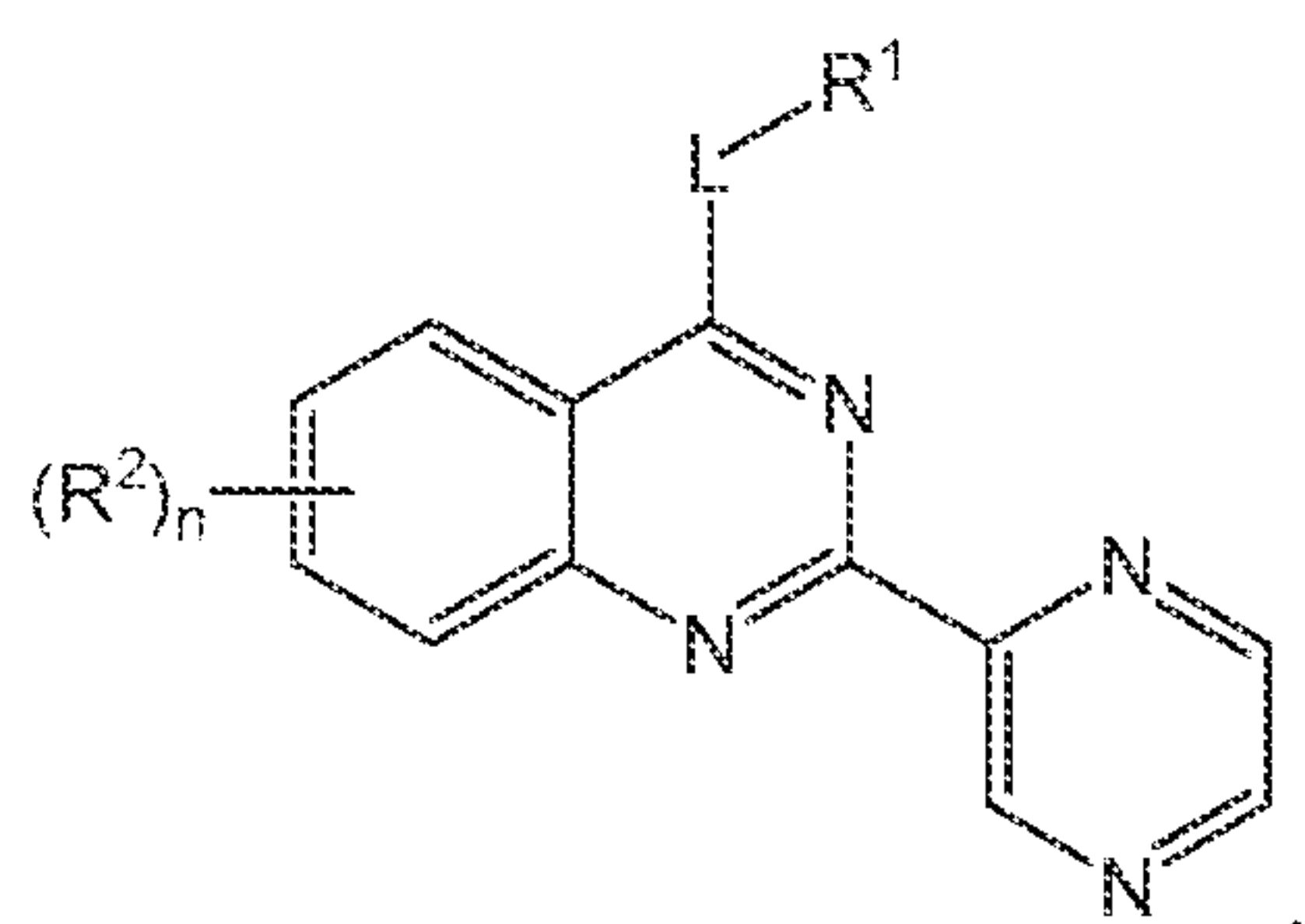
In some embodiments, the compound is:



wherein s is 0, 1, 2, 3 or 4.

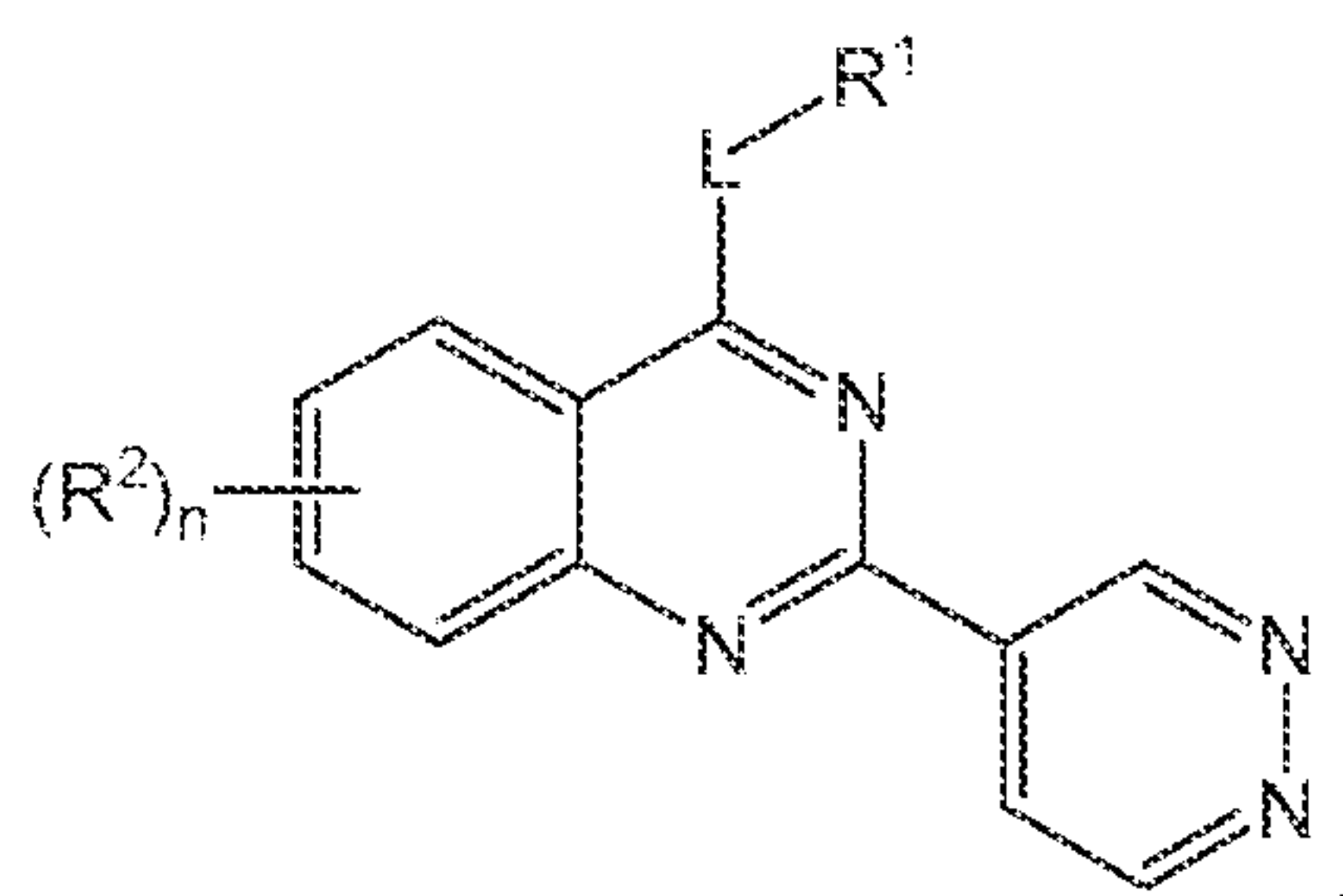
In some embodiments, R^9 is $-C(O)NH_2$, C_1 - C_4 alkoxy, or substituted C_1 - C_4 alkoxy. In some embodiments, R^9 is halo.

In some embodiments, the compound is:



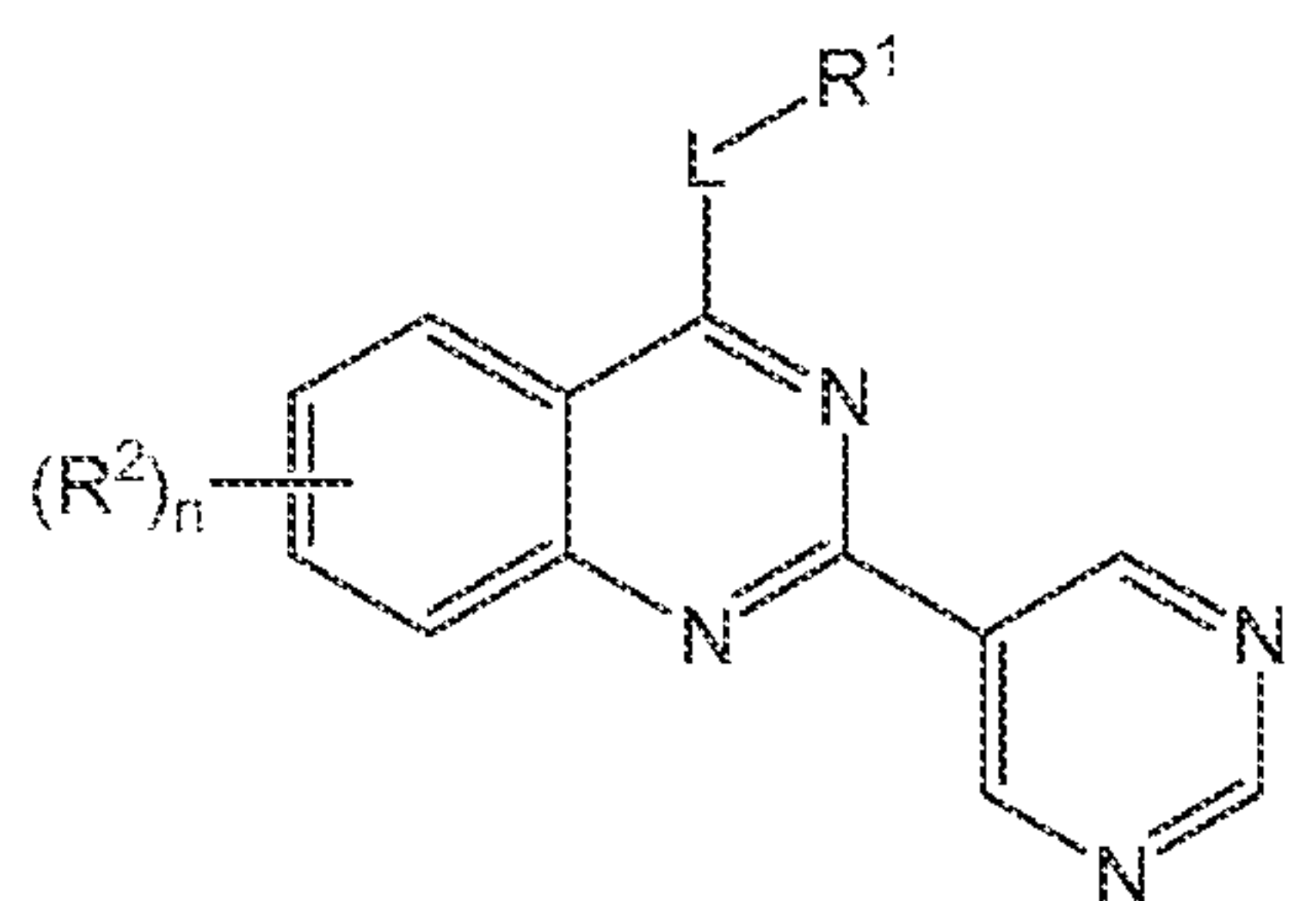
In some embodiments, R_1 is selected from methyl, cyclohexyl, t -butyl, and pyridinyl. In some embodiments, R_1 is heteroaralkyl (e.g., $-CH_2$ -pyridyl). In some embodiments, LR^1 is $NH(CH_3)$.

In some embodiments, the compound is:



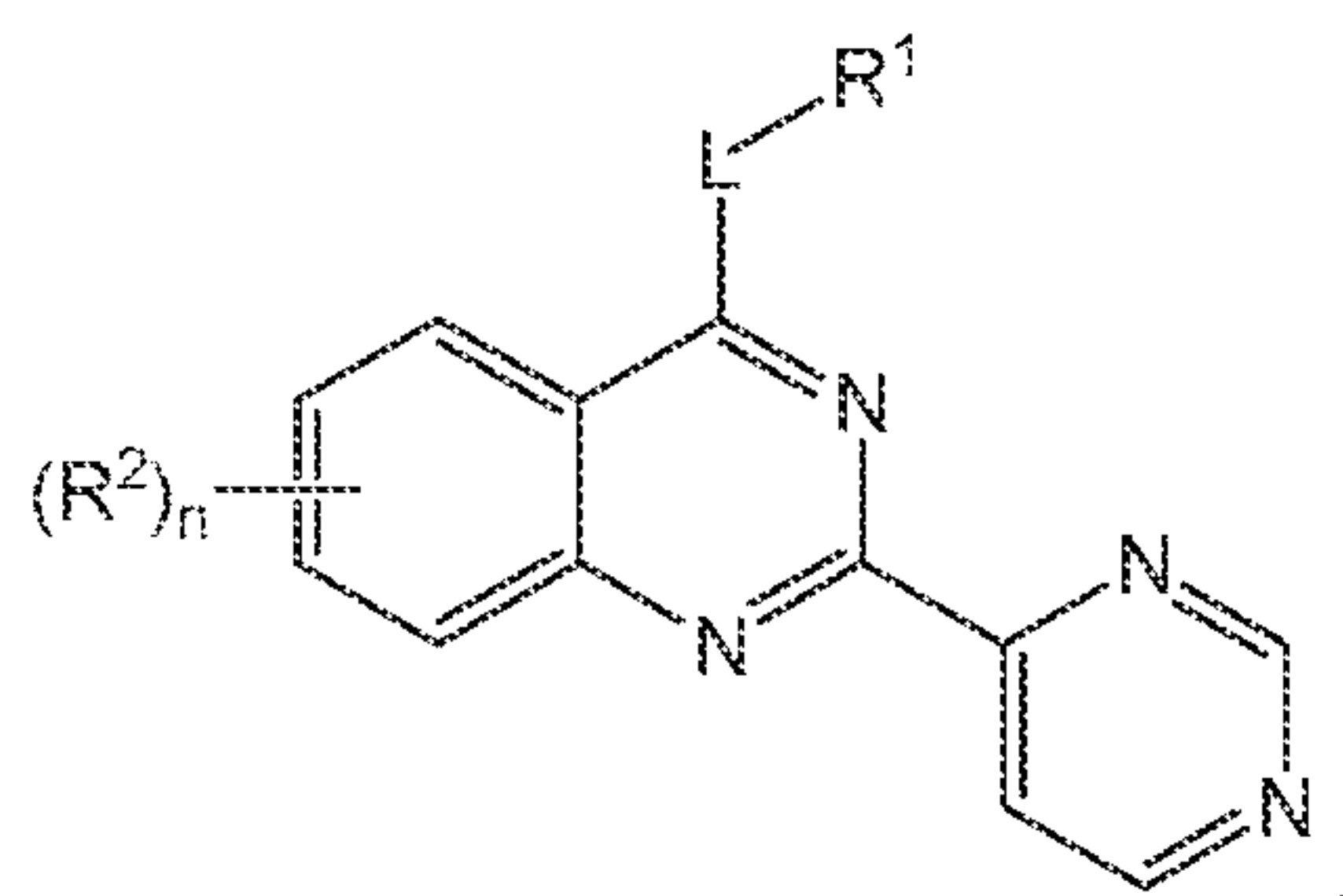
In some embodiments, R_1 is selected from methyl, cyclohexyl, t-butyl, and pyridinyl. In some embodiments, R_1 is heteroaralkyl (e.g., $-\text{CH}_2\text{-pyridyl}$). In some embodiments, LR^1 is $\text{NH}(\text{CH}_3)$.

In some embodiments, the compound is:



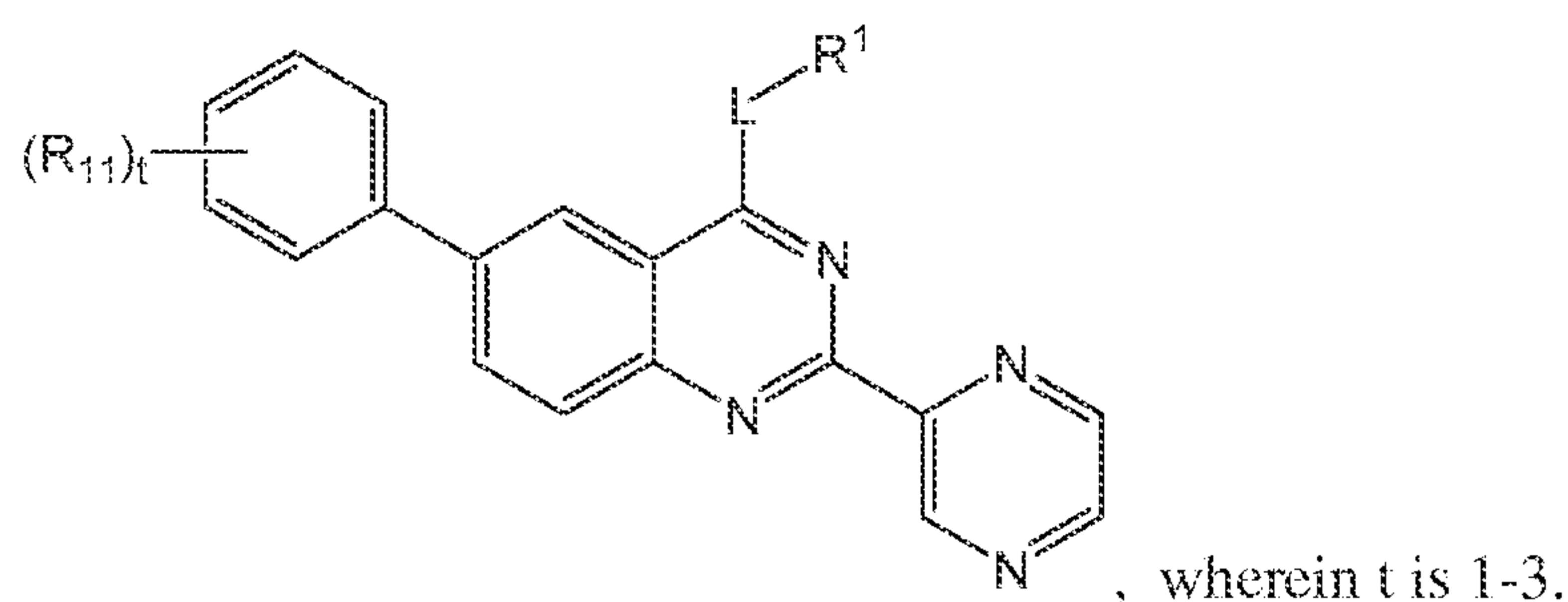
In some embodiments, R_1 is selected from methyl, cyclohexyl, t-butyl, and pyridinyl. In some embodiments, R_1 is heteroaralkyl (e.g., $-\text{CH}_2\text{-pyridyl}$). In some embodiments, LR^1 is $\text{NH}(\text{CH}_3)$.

In some embodiments, the compound is:



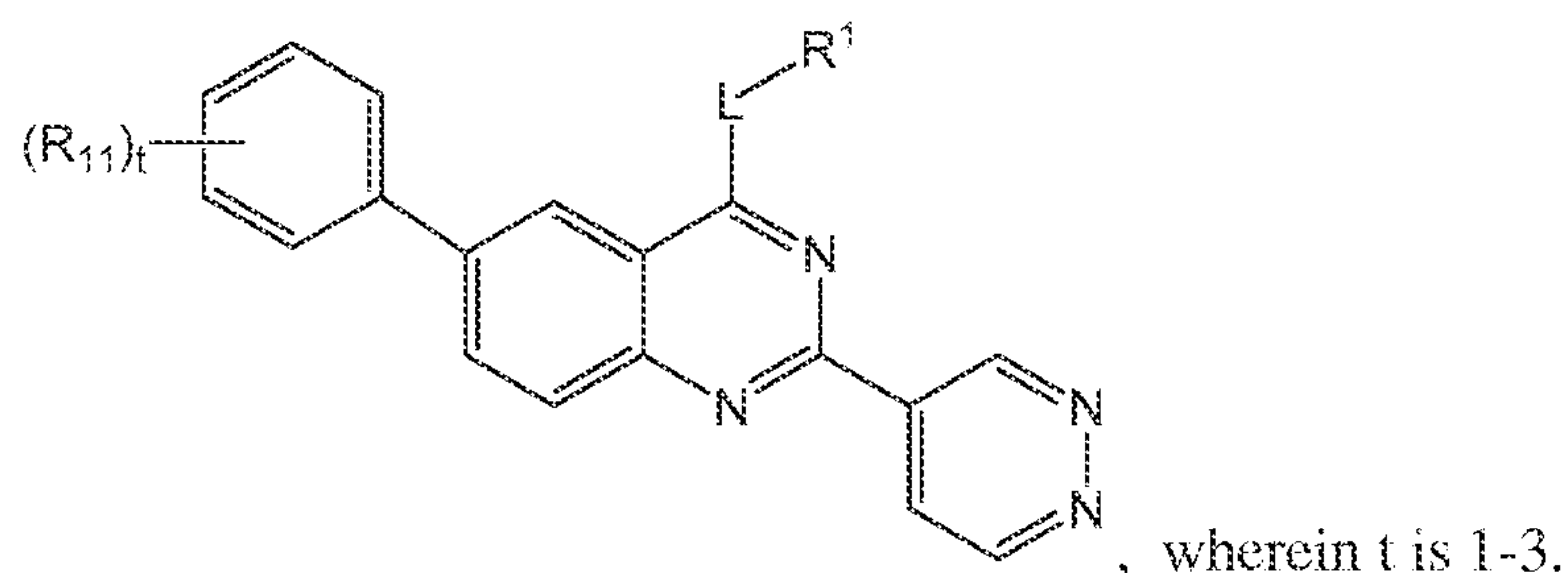
In some embodiments, R_1 is selected from methyl, cyclohexyl, t-butyl, and pyridinyl. In some embodiments, R_1 is heteroaralkyl (e.g., $-\text{CH}_2\text{-pyridyl}$). In some embodiments, LR^1 is $\text{NH}(\text{CH}_3)$.

In some embodiments, the compound is:



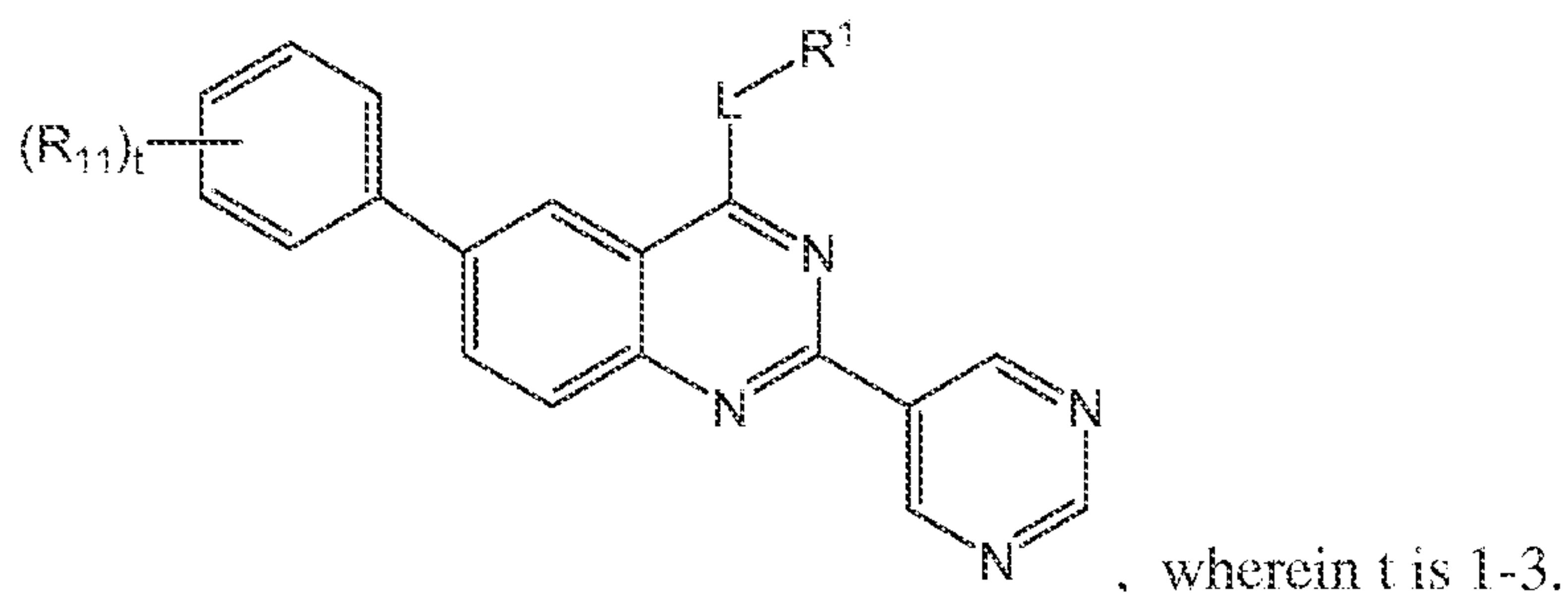
In some embodiments, R_1 is selected from methyl, cyclohexyl, t-butyl, and pyridinyl. In some embodiments, R_1 is heteroaralkyl (e.g., $-\text{CH}_2\text{-pyridyl}$). In some embodiments, LR^1 is $\text{NH}(\text{CH}_3)$. In some embodiments, R^{11} is independently halo, nitrile, $\text{C}_1\text{-C}_4$ alkoxy, $-\text{C}(\text{O})\text{NH}_2$, hydroxy, or $\text{C}_1\text{-C}_4$ hydroxyalkyl. In some embodiments, R^{11} is fluoro. In some embodiments, R^{11} is methoxy, ethoxy, or methoxyethoxy ether. In some embodiments, R^{11} is $-\text{OCH}_2\text{CH}_2\text{OCH}_3$. In some embodiments, R^{11} is $-\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CH}_3$. In some embodiments, R^{11} is $-\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$.

In some embodiments, the compound is:



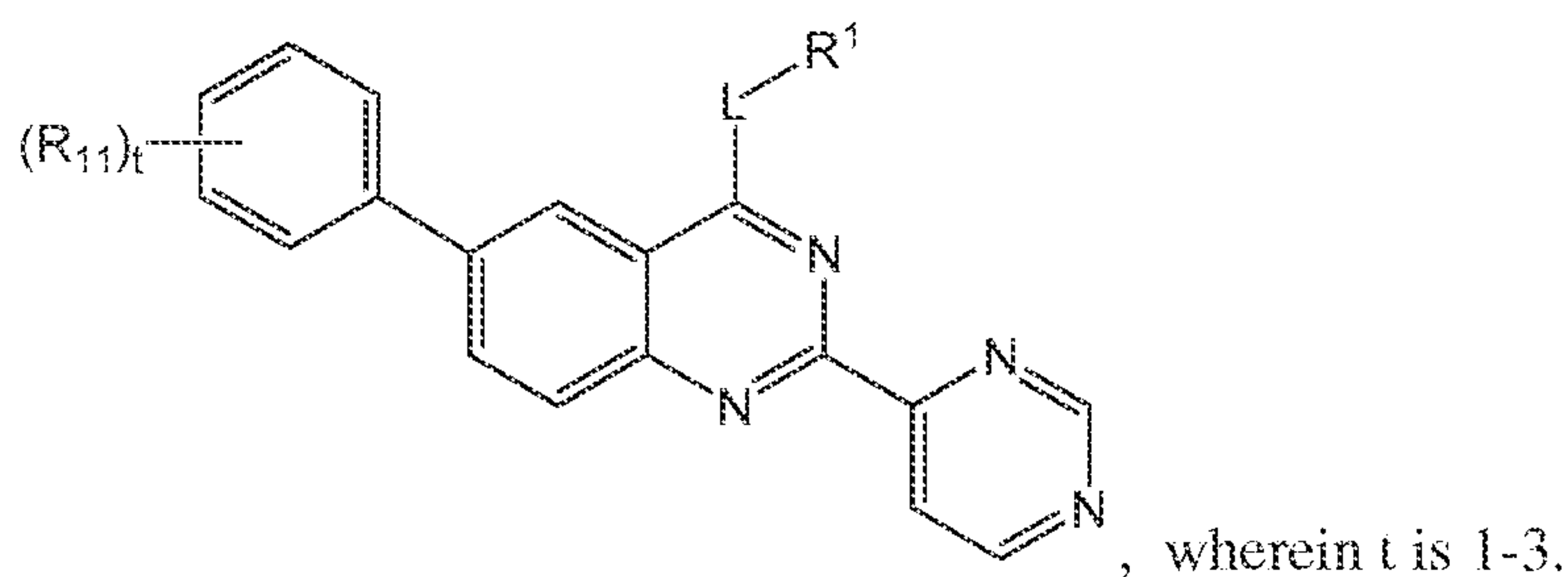
In some embodiments, R_1 is selected from methyl, cyclohexyl, t-butyl, and pyridinyl. In some embodiments, LR^1 is $\text{NH}(\text{CH}_3)$. In some embodiments, R^{11} is independently halo, nitrile, $\text{C}_1\text{-C}_4$ alkoxy, $-\text{C}(\text{O})\text{NH}_2$, hydroxy, or $\text{C}_1\text{-C}_4$ hydroxyalkyl. In some embodiments, R^{11} is fluoro. In some embodiments, R^{11} is methoxy, ethoxy, or methoxyethoxy ether. In some embodiments, R^{11} is $-\text{OCH}_2\text{CH}_2\text{OCH}_3$. In some embodiments, R^{11} is $-\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CH}_3$. In some embodiments, R^{11} is $-\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$.

In some embodiments, the compound is:



In some embodiments, R_1 is selected from methyl, cyclohexyl, t-butyl, and pyridinyl. In some embodiments, LR^1 is $NH(CH_3)$. In some embodiments, R^{11} is independently halo, nitrile, C_1 - C_4 alkoxy, $-C(O)NH_2$, hydroxy, or C_1 - C_4 hydroxyalkyl. In some embodiments, R^{11} is fluoro. In some embodiments, R^{11} is methoxy, ethoxy, or methoxyethoxy ether. In some embodiments, R^{11} is $-OCH_2CH_2OCH_3$. In some embodiments, R^{11} is $-OCH_2CH_2OCH_2CH_2CH_3$. In some embodiments, R^{11} is $-OCH_2CH_2OCH_2CH_2OCH_3$.

In some embodiments, the compound is:



In some embodiments, R_1 is selected from methyl, cyclohexyl, t-butyl, and pyridinyl. In some embodiments, LR^1 is $NH(CH_3)$. In some embodiments, R^{11} is independently halo, nitrile, C_1 - C_4 alkoxy, $-C(O)NH_2$, hydroxy, or C_1 - C_4 hydroxyalkyl. In some embodiments, R^{11} is fluoro. In some embodiments, R^{11} is methoxy, ethoxy, or methoxyethoxy ether. In some embodiments, R^{11} is $-OCH_2CH_2OCH_3$. In some embodiments, R^{11} is $-OCH_2CH_2OCH_2CH_2CH_3$. In some embodiments, R^{11} is $-OCH_2CH_2OCH_2CH_2OCH_3$.

Compounds of Formula (III)

The following aspects and embodiments relate to compounds of formula (III).

Item 15. The compound according to item 1 represented by general formula (III) or a salt thereof,

wherein:

A is CH or N;

L is O, a direct bond or NH;

one of X^1 , X^2 , X^3 , X^4 and X^5 is N and the others are CH;

m is 1, 2 or 3;

n is 1, 2, 3 or 4;

R^1 is hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, alkoxyalkyl, hydroxyalkyl, heteroaryl, heteroarylalkyl, arylalkyl, $-C(Y)R^e$, cyclyl, cyclylalkyl or heterocyclyl, each of which is optionally substituted with 1-3 R^7 ;

R^2 is aryl or heteroaryl, each of which is optionally substituted with 1-5 R^9 ;

each R^3 or R^4 is independently hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, $-CN$, $-NO_2$, $-C(O)OR^a$, $-C(Y)NR^bR^{b'}$, $-NR^cC(Y)R^{c'}$, $-NR^bR^{b'}$, $-OC(O)NR^bR^{b'}$, $-NR^cC(O)OR^{c'}$, $-SO_2NR^bR^{b'}$, $-NR^cSO_2R^{c'}$, $-NR^cC(Y)NR^bR^{b'}$, $-OR^d$, $-SR^d$, $-C(Y)R^e$ or $-S(O)_qR^f$, each of which is optionally substituted with 1-3 R^{10} ;

each R^7 , R^9 and R^{10} is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, oxo, thioxo, $-CN$, $-NO_2$, $-C(O)OR^a$, $-C(Y)NR^bR^{b'}$, $-NR^cC(Y)R^{c'}$, $-NR^bR^{b'}$, $-OC(O)NR^bR^{b'}$, $-NR^cC(O)OR^{c'}$, $-SO_2NR^bR^{b'}$, $-NR^cSO_2R^{c'}$, $-NR^cC(Y)NR^bR^{b'}$, $-OR^d$, $-SR^d$, $-C(Y)R^e$ or $-S(O)_qR^f$, each of which is optionally substituted with 1-3 R^{12} ; wherein two R^7 or two R^9 are optionally be taken together with the atoms to which they are attached to form an optionally substituted cyclyl, heterocyclyl, aryl or heteroaryl ring;

R^{12} is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl, heterocyclylalkyl, halo,

haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, oxo, thioxo, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^c$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{O})\text{OR}^c$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^c$, $-\text{NR}^c\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^d$, $-\text{C}(\text{Y})\text{R}^c$ or $-\text{S}(\text{O})_q\text{R}^f$, each of which is optionally substituted with 1-3 R^{13} ;

R^{13} is independently C_1 - C_8 alkyl, haloalkyl, halo, heterocyclyl, cyclyl, oxo or $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$;

Y is O or S;

q is 1 or 2; and

each R^a , R^b , $\text{R}^{b'}$, R^c , R^c , R^d , $\text{R}^{d'}$, R^e and R^f is independently hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, acyl, cyclyl, heterocyclyl, aryl, haloalkyl, alkoxyalkyl, alkylaminoalkyl, dialkylaminoalkyl, heteroaryl, cyclylalkyl, heterocyclylalkyl, arylalkyl or heteroarylalkyl..

Item 16. The compound according to item 15 represented by general formula (III) or a salt thereof,

wherein:

m is 1;

n is 1;

R^1 is hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, heteroaryl, heterocyclyl, arylalkyl, cyclylalkyl, heteroarylalkyl, alkoxyalkyl, hydroxyalkyl or $-\text{C}(\text{O})\text{R}^e$, each of which is optionally substituted with 1-3 R^7 ;

R^2 is aryl, heteroaryl or benzofuryl, each of which is optionally substituted with 1-5 R^9 ;

each R^3 or R^4 is independently hydrogen, C_1 - C_8 alkyl, halo, haloalkyl or $-\text{OR}^d$;

R^6 is hydrogen or C_1 - C_8 alkyl;

each R^7 and R^9 is independently C_1 - C_8 alkyl, aryl, heteroaryl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, alkoxyalkyl, oxo, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{C}(\text{O})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$, each of which is optionally substituted with 1-3 R^{12} ;

R^{12} is independently C_1 - C_8 alkyl, oxo, halo, haloalkyl, $-\text{CN}$, $-\text{C}(\text{O})\text{NR}^b\text{R}^{b'}$ or $-\text{C}(\text{O})\text{R}^e$ each of which is optionally substituted with 1-3 R^{13} ;

R^{13} is independently C_1 - C_8 alkyl, halo or heterocyclyl; and

each R^a , R^b , $R^{b'}$, R^c , $R^{c'}$, R^d , $R^{d'}$, R^e and R^f is independently hydrogen, C_1 - C_8 alkyl, cyclyl, heterocyclyl, arylalkyl, alkoxyalkyl, heterocyclalkyl, heteroarylalkyl, alkylaminoalkyl, dialkylaminoalkyl or phenyl.

Item 17. The compound according to Item 16 represented by general formula (III) or a salt thereof,

wherein:

R^1 is hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, alkoxyalkyl, hydroxyalkyl, imidazolyl, pyridylalkyl, phenylalkyl, oxazolylalkyl, thienylalkyl, thiazolidinyl isoindolyl, $-\text{C}(\text{O})\text{R}^e$, dihydroindenyl, C_3 - C_8 cycloalkyl, C_3 - C_8 cycloalkylalkyl, piperidyl, morpholinyl, pyrrolidinyl, azetidyl or piperazinyl, each of which is optionally substituted with 1-3 R^7 ;

R^2 is phenyl, naphthyl, benzofuryl, indazolyl, benzothienyl, pyridyl, pyrimidinyl, dihydrobenzodioxinyl, benzodioxolyl, benzoimidazolyl, isoxazolyl, pyrazolyl, indolinyl or benzoisoxazolyl, each of which is optionally substituted with 1-5 R^9 ;

each R^3 or R^4 is independently hydrogen, C_1 - C_8 alkyl, halo, haloalkyl or $-\text{OR}^d$;

R^6 is hydrogen or C_1 - C_8 alkyl;

each R^7 and R^9 is independently C_1 - C_8 alkyl, phenyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, alkoxyalkyl, oxo, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{C}(\text{O})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$; and

each R^a , R^b , $R^{b'}$, R^c , $R^{c'}$, R^d , $R^{d'}$, R^e and R^f is independently hydrogen, C_1 - C_8 alkyl, C_3 - C_8 cycloalkyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, tetrahydropyranyl, phenylalkyl, alkoxyalkyl, morpholinylalkyl, oxazolidinylalkyl, imidazolylalkyl, tetrahydropyranylalkyl, pyridylalkyl, pyrazolylalkyl, tetrazolylalkyl, thiazolylalkyl, pyrrolylalkyl, benzoxazolylalkyl, indazolylalkyl, dihydrobenzoxazinylalkyl, tetrahydrofurylalkyl, tetrahydrofuryl, alkylaminoalkyl, dialkylaminoalkyl or phenyl.

Item 18. The compound according to item 16 represented by general formula (III) or a salt thereof,

wherein:

R^1 is hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, alkoxyalkyl, hydroxyalkyl, imidazolyl, furylalkyl, pyridylalkyl, phenylalkyl, oxazolylalkyl, thienylalkyl, thiazolidinyl, isoindolyl, $-C(O)R^e$, dihydroindenyl, C_3 - C_8 cycloalkyl, C_3 - C_8 cycloalkylalkyl, piperidyl, morpholinyl, pyrrolidinyl, azetidyl or piperazinyl, each of which is optionally substituted with 1-3 R^7 ;

R^2 is phenyl, naphthyl, benzofuryl, indazolyl, benzothienyl, pyridyl, pyrimidinyl, dihydrobenzodioxinyl, benzodioxolyl, benzoimidazolyl, isoxazolyl, pyrazolyl, indolinyl or benzisoxazolyl, each of which is optionally substituted with 1-5 R^9 ;

each R^3 or R^4 is independently hydrogen, C_1 - C_8 alkyl, halo, haloalkyl or $-OR^d$;

R^6 is hydrogen or C_1 - C_8 alkyl;

each R^7 and R^9 is independently C_1 - C_8 alkyl, phenyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, alkoxyalkyl, oxo, $-CN$, $-NO_2$, $-C(O)OR^a$, $-C(O)NR^bR^{b'}$, $-NR^bR^{b'}$, $-OR^d$, $-C(O)R^e$ or $-S(O)_qR^f$, each of which is optionally substituted with 1-3 R^{12} ;

R^{12} is independently C_1 - C_8 alkyl, oxo, halo, haloalkyl, $-CN$, $-C(O)NR^bR^{b'}$ or $-C(O)R^e$, each of which is optionally substituted with 1-3 R^{13} ;

R^{13} is independently C_1 - C_8 alkyl, halo or pyrrolidinyl; and

each R^a , R^b , $R^{b'}$, R^c , $R^{c'}$, R^d , $R^{d'}$, R^e and R^f is independently hydrogen, C_1 - C_8 alkyl, C_3 - C_8 cycloalkyl, pyrrolidinyl, piperidyl, morpholinyl, piperazinyl, tetrahydropyranyl, phenylalkyl, alkoxyalkyl, morpholinylalkyl, oxazolidinylalkyl, imidazolylalkyl, tetrahydropyranylalkyl, pyridylalkyl, pyrazolylalkyl, tetrazolylalkyl, thiazolylalkyl, pyrrolylalkyl, benzoxazolylalkyl, indazolylalkyl, dihydrobenzoxazinylalkyl, tetrahydrofurylalkyl, tetrahydrofuryl, alkylaminoalkyl, dialkylaminoalkyl or phenyl.

Item 19. The compound according to item 18 represented by general formula (III) or a salt thereof,

wherein:

A is N;

R^3 is hydrogen, C_1 - C_8 alkyl, halo, haloalkyl, or $-OR^d$;

R^4 is hydrogen, C_1 - C_8 alkyl, halo, or $-OR^d$;

R^7 is C_1 - C_8 alkyl, phenyl, halo, haloalkyl, oxo, $-C(O)OR^a$, $-C(O)NR^bR^{b'}$ or $-OR^d$ each of which is optionally substituted with 1-3 R^{12} ;

R^9 is C_1 - C_8 alkyl, phenyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, alkoxyalkyl, $-CN$, $-NO_2$, $-C(O)NR^bR^{b'}$, $-C(O)OR^a$, $-NR^bR^{b'}$, $-OR^d$, $-C(O)R^e$ or $-S(O)_qR^f$, each of which is optionally substituted with 1-3 R^{12} ; and

each R^a , R^b , $R^{b'}$, R^c , $R^{c'}$, R^d , $R^{d'}$, R^e and R^f is independently hydrogen, C_1 - C_8 alkyl, C_3 - C_8 cycloalkyl, pyrrolidinyl, piperidyl, morpholinyl, piperazinyl, tetrahydropyranyl, phenylalkyl, alkoxyalkyl, morpholinylalkyl, oxazolidinylalkyl, imidazolylalkyl, tetrahydropyranylalkyl, pyridylalkyl, pyrazolylalkyl, tetrazolylalkyl, thiazolylalkyl, pyrrolylalkyl, benzoxazolylalkyl, indazolylalkyl, tetrahydrofurylalkyl, dihydrobenzoxazinylalkyl, tetrahydrofuryl, alkylaminoalkyl, dialkylaminoalkyl or phenyl;.

Item 20. The compound according to item 17 or 19 represented by general formula

(III) or a salt thereof,

wherein:

A is N;

R^3 is hydrogen, C_1 - C_8 alkyl, halo, haloalkyl, or $-OR^d$;

R^4 is hydrogen, C_1 - C_8 alkyl, halo, or $-OR^d$;

R^7 is C_1 - C_8 alkyl, phenyl, halo, haloalkyl, oxo, $-C(O)OR^a$, $-C(O)NR^bR^{b'}$ or $-OR^d$;

R^9 is C_1 - C_8 alkyl, phenyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, alkoxyalkyl, $-CN$, $-NO_2$, $-C(O)NR^bR^{b'}$, $-C(O)OR^a$, $-NR^bR^{b'}$, $-OR^d$, $-C(O)R^e$ or $-S(O)_qR^f$; and

each R^a , R^b , $R^{b'}$, R^c , $R^{c'}$, R^d , $R^{d'}$, R^e and R^f is independently hydrogen, C_1 - C_8 alkyl, C_3 - C_8 cycloalkyl, pyrrolidinyl, piperidyl, morpholinyl, piperazinyl, tetrahydropyranyl, phenylalkyl, alkoxyalkyl, morpholinylalkyl, oxazolidinylalkyl, imidazolylalkyl, tetrahydropyranylalkyl, pyridylalkyl, pyrazolylalkyl, tetrazolylalkyl, thiazolylalkyl, pyrrolylalkyl, benzoxazolylalkyl, indazolylalkyl, tetrahydrofurylalkyl, tetrahydrofuryl, dihydrobenzoxazinylalkyl, alkylaminoalkyl, dialkylaminoalkyl or phenyl.

Item 21. The compound according to item 20 represented by general formula (III) or a salt thereof,

wherein:

R^1 is hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, alkoxyalkyl, hydroxyalkyl, imidazolyl, furylalkyl, pyridylalkyl, phenylalkyl, oxazolylalkyl, thienylalkyl, isoindolyl, $-C(O)R^c$, dihydroindenyl, C_3 - C_8 cycloalkyl, C_3 - C_8 cycloalkylalkyl, piperidyl, morpholinyl, pyrrolidinyl, azetidyl or piperazinyl, each of which is optionally substituted with 1-3 R^7 ;

R^2 is phenyl, which is optionally substituted with 1-5 R^9 ; and

each R^a , R^b , $R^{b'}$, R^c , $R^{c'}$, R^d , $R^{d'}$, R^e and R^f is independently hydrogen, C_1 - C_8 alkyl, pyrrolidinyl, morpholinyl, tetrahydropyranyl, alkoxyalkyl, morpholinylalkyl, tetrahydropyranylalkyl, pyridylalkyl, thiazolylalkyl, pyrrolylalkyl, tetrahydrofuryl, alkylaminoalkyl or phenyl.

In some embodiments, R^1 is C_1 - C_8 alkyl, which is optionally substituted with 1-3 R^7 ; or when L is NR^6 , R^1 and R^6 may be taken together with the atoms to which they are attached to form a heterocyclyl or heteroaryl ring that is optionally substituted with 1-3 R^8 .

In some embodiments, A is CH. In some embodiments, A is N.

In some embodiments, L is NR^6 . In some embodiments, R^6 is hydrogen.

In some embodiments, R^1 is C_1 - C_8 alkyl, e.g., methyl, ethyl, C_3 alkyl (e.g., n-propyl or isopropyl), C_4 alkyl (e.g., n-butyl, isobutyl or tert-butyl), or C_5 alkyl (e.g., pentan-3-yl).

In some embodiments, R^1 is C_1 - C_8 alkyl substituted with 1-3 R^7 (e.g., C_1 - C_8 alkyl substituted with 1 R^7). In some embodiments, R^1 is methyl substituted with 1 R^7 . In some embodiments, R^7 is cyclyl (e.g., cyclopropyl). In some embodiments, R^7 is aryl (e.g., phenyl).

In some embodiments, R^1 is ethyl substituted with 1 R^7 . In some embodiments, R^7 is aryl (e.g., phenyl). In some embodiments, R^7 is $-OR^d$. In some embodiments, R^d is aryl (e.g., phenyl).

In some embodiments, R^1 is n-propyl substituted with 1 R^7 . In some embodiments, R^7 is $-OR^d$. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., C_3 alkyl, e.g., n-propyl).

In some embodiments, R^1 is C_1 - C_8 alkyl substituted with 3 R^7 . In some embodiments, R^1 is ethyl substituted with 3 R^7 . In some embodiments, each R^7 is independently halo (e.g., each R^7 is fluoro). In some embodiments, R^1 is 2,2,2-trifluoroethyl.

In some embodiments, R^1 is C_2 - C_8 alkenyl, e.g., C_3 alkenyl (e.g., $-\text{CH}_2\text{CH}=\text{CH}_2$).

In some embodiments, R^1 is C_2 - C_8 alkynyl, e.g., C_3 alkynyl (e.g., $-\text{CH}_2\text{C}\equiv\text{CH}$).

In some embodiments, R^1 is cyclyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl). In some embodiments, the cyclyl group is a bicyclic group (e.g., indanyl).

In some embodiments, R^1 is heterocyclyl (e.g., piperidyl). In some embodiments, R^1 is piperidyl substituted with 1 R^7 . In some embodiments, R^7 is $-\text{C}(\text{Y})\text{R}^e$. In some embodiments, Y is O. In some embodiments, R^e is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, R^7 is $-\text{OR}^d$.

In some embodiments, R^6 is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, R^1 and R^6 are taken together with the atoms to which they are attached to form a heterocyclyl ring (e.g. a pyrrolidine ring).

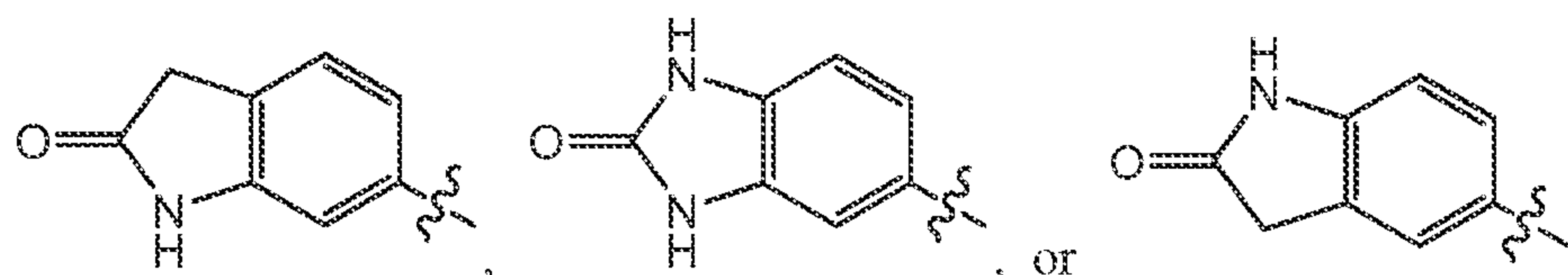
In some embodiments, R^1 and R^6 are taken together with the atoms to which they are attached to form a heteroaryl ring (e.g., an imidazole ring).

In some embodiments, L is O.

In some embodiments, R^1 is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, R^2 is aryl (e.g., phenyl). In some embodiments, R^2 is unsubstituted phenyl. In some embodiments, R^2 is phenyl substituted with 1-3 R^9 . In some embodiments, R^2 is phenyl substituted with 1 R^9 .

In some embodiments, R^2 is:



In some embodiments, R^9 is halo (e.g., fluoro or chloro). In some embodiments, R^9 is $-\text{CN}$. In some embodiments, R^9 is $-\text{NO}_2$. In some embodiments, R^9 is haloalkoxy (e.g., trifluoroethoxy). In some embodiments, R^9 is $-\text{NR}^b\text{R}^{b'}$. In some embodiments, R^b and $R^{b'}$ are each independently C_1 - C_8 alkyl (e.g., R^b and $R^{b'}$ are both methyl).

In some embodiments, R^9 is $-\text{OR}^d$. In some embodiments, R^9 is $-\text{OCH}_2\text{CH}_2\text{OCH}_3$. In some embodiments, R^9 is $-\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CH}_3$. In some embodiments, R^9 is $-\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$. In some embodiments, R^d is hydrogen. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, R^d is ethyl.

In some embodiments, R^9 is hydroxyalkyl (e.g., $-\text{CH}_2\text{OH}$). In some embodiments, R^9 is alkoxyalkyl (e.g., $-\text{CH}_2\text{-O-CH}_3$). In some embodiments, R^9 is $-\text{C}(\text{O})\text{R}^e$. In some embodiments, R^e is heterocyclyl (e.g., morpholino). In some embodiments, R^9 is $-\text{S}(\text{O})_q\text{R}^f$. In some embodiments, q is 1. In some embodiments, R^f is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, R^2 is phenyl substituted with 2 R^9 . In some embodiments, each R^9 is independently halo (e.g., each R^9 is fluoro). In some embodiments, each R^9 is independently $-\text{OR}^d$. In some embodiments, each R^d is independently C_1 - C_8 alkyl (e.g., each R^d is methyl).

In some embodiments, R^2 is heteroaryl. In some embodiments, R^2 is a 6-membered heteroaryl. In some embodiments, R^2 is a 6-membered nitrogen-containing heteroaryl, e.g., pyridyl. In some embodiments, R^2 is unsubstituted pyridyl.

In some embodiments, R^2 is pyridyl substituted with 1 R^9 . In some embodiments, R^9 is $-\text{OR}^d$. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, R^2 is a 5-membered heteroaryl. In some embodiments, R^2 is a 5-membered nitrogen-containing heteroaryl (e.g., pyrrolyl or oxazolyl).

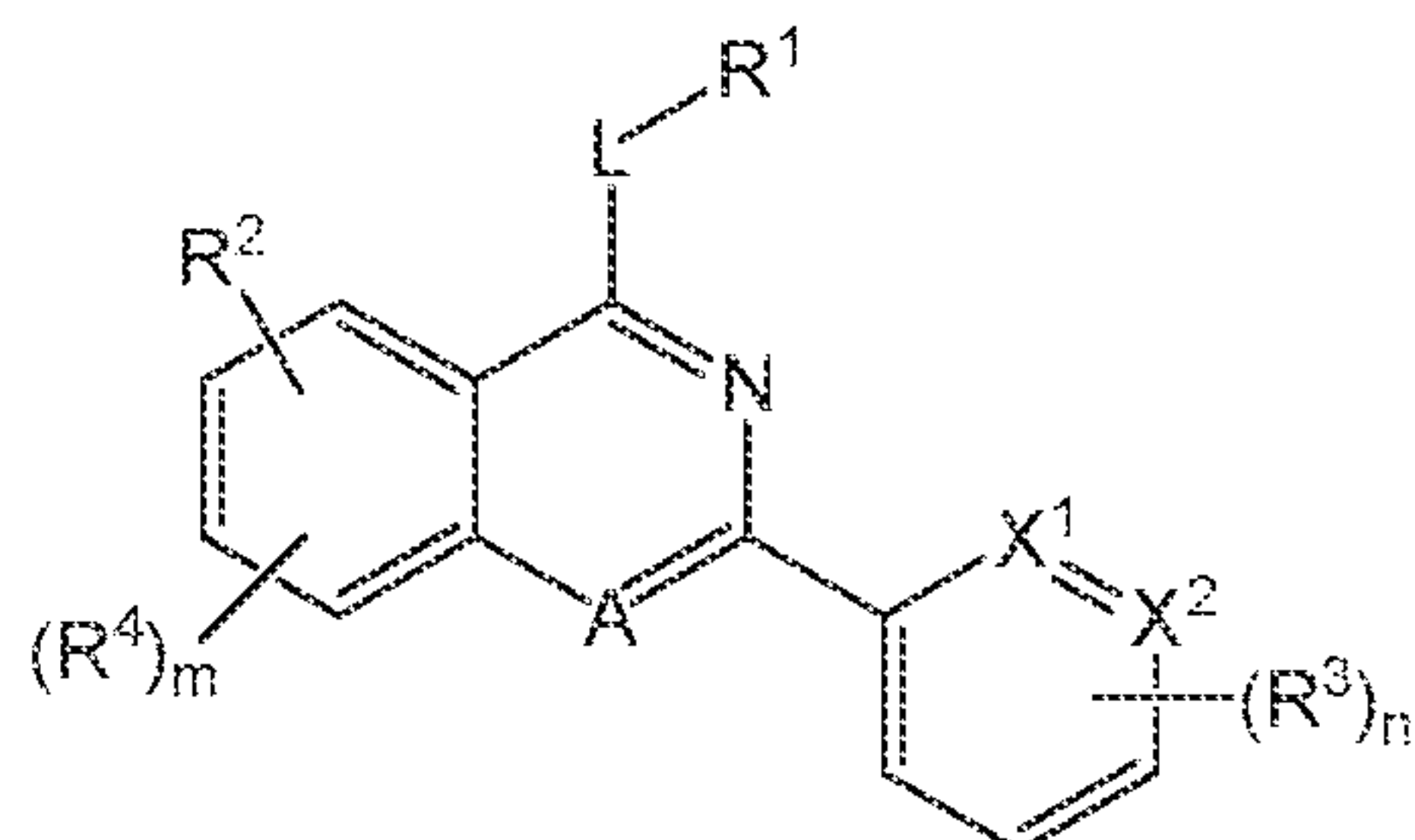
In some embodiments, m is 0.

In some embodiments, m is 1.

In some embodiments, R^4 is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, R^4 is $-\text{OR}^d$. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl). In some

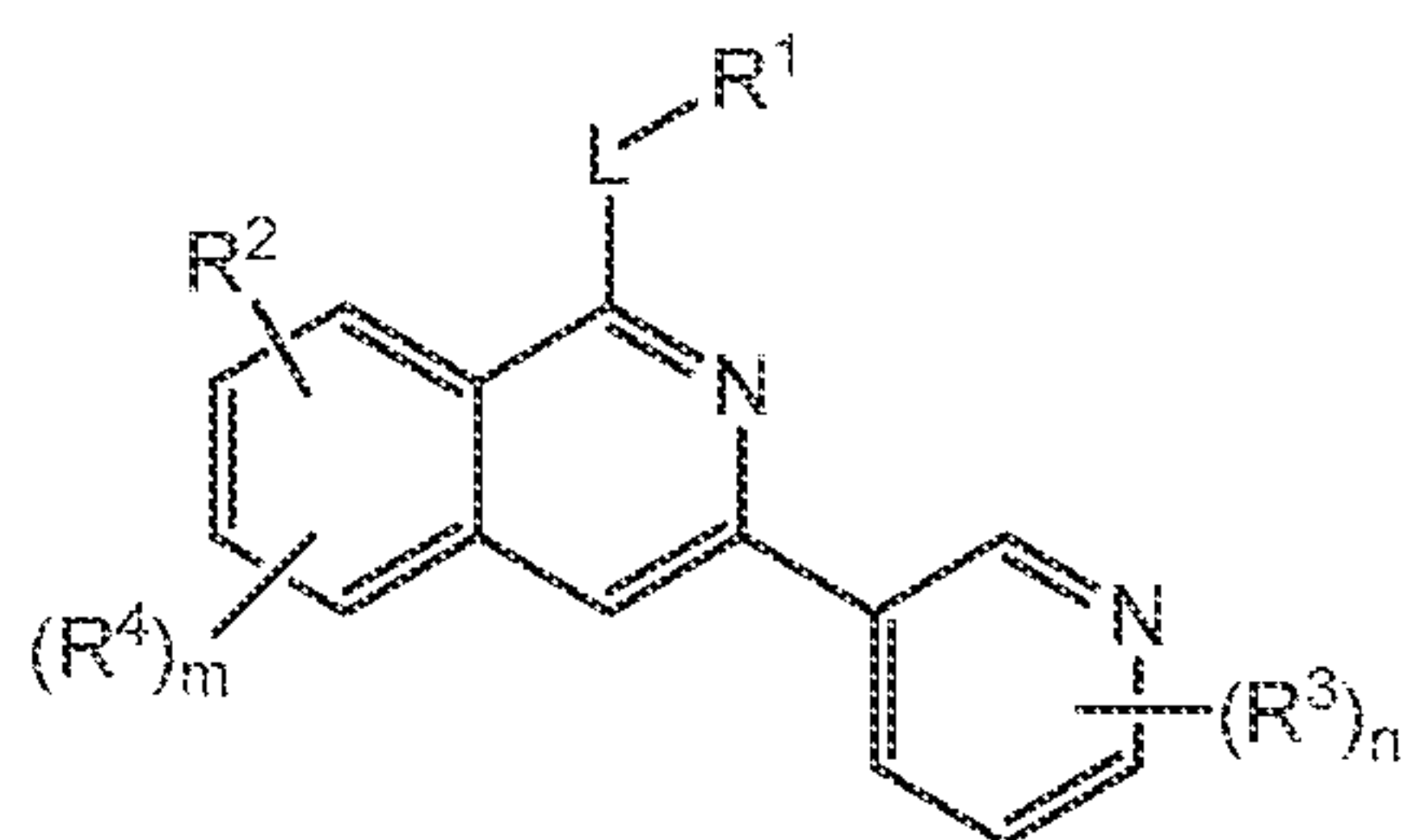
embodiments, R^4 is halo. In some embodiments, R^4 is methoxy. In some embodiments, R^d is C_1 - C_8 alkyl.

In some embodiments, the compound has the following structure:



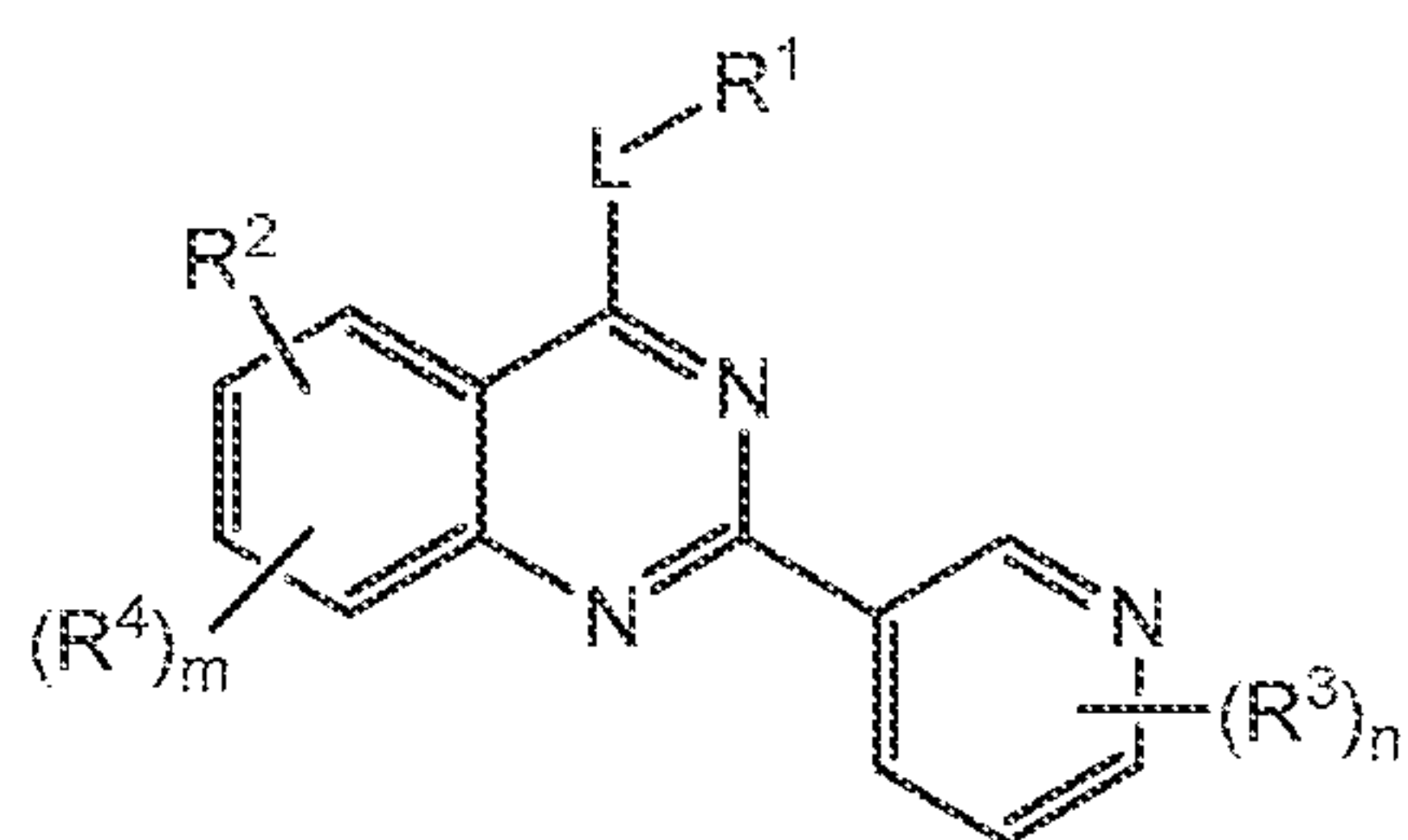
wherein one of X^1 and X^2 is N and the other is CH.

In some embodiments, X^1 is CH and X^2 is N. In some embodiments, X^1 is N and X^2 is CH. In some embodiments, the compound has the following structure:



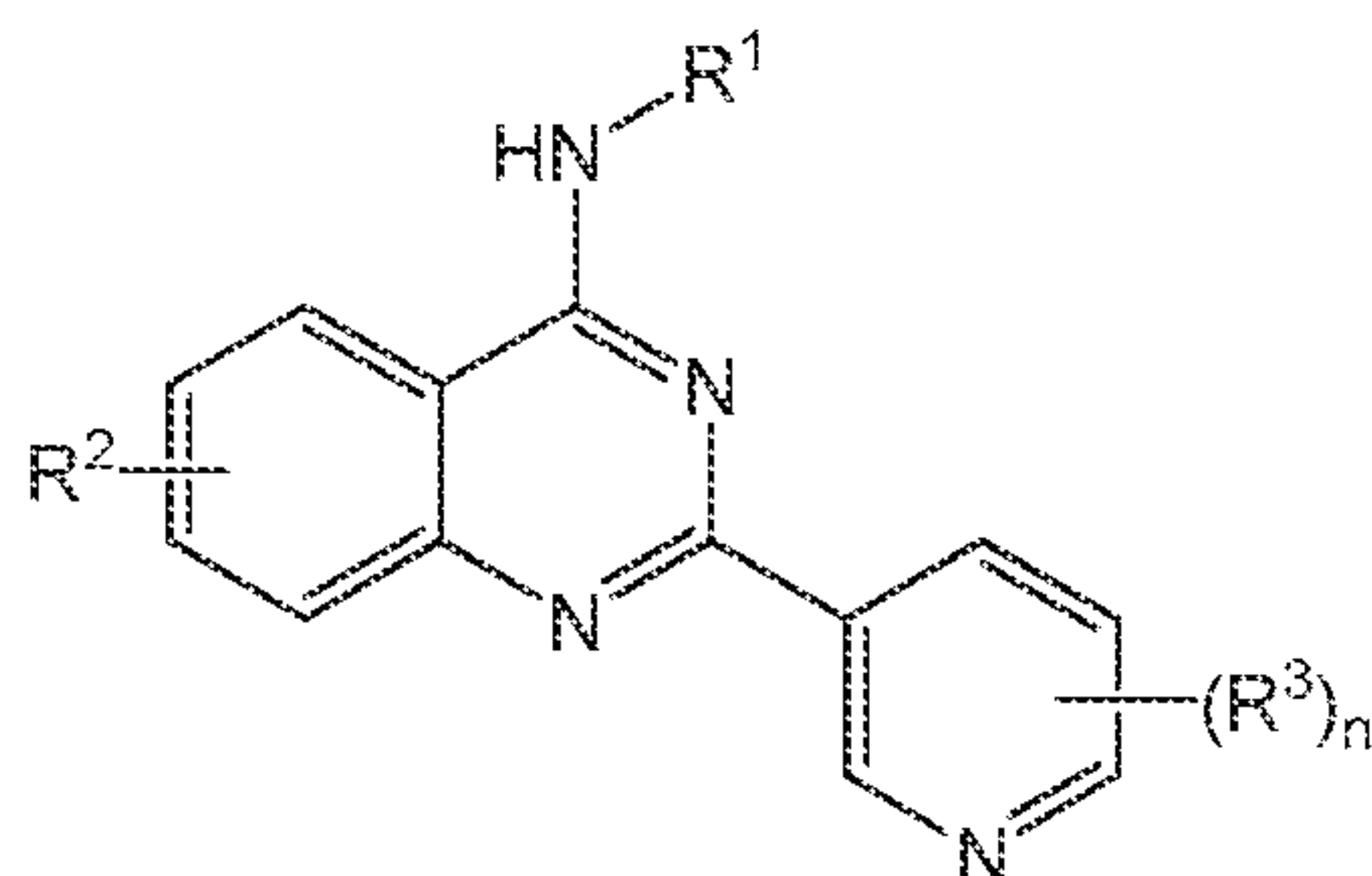
In some embodiments, R^2 is aryl. In some embodiments, R^2 is heteroaryl. In some embodiments, R^1 is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, the compound has the following structure:



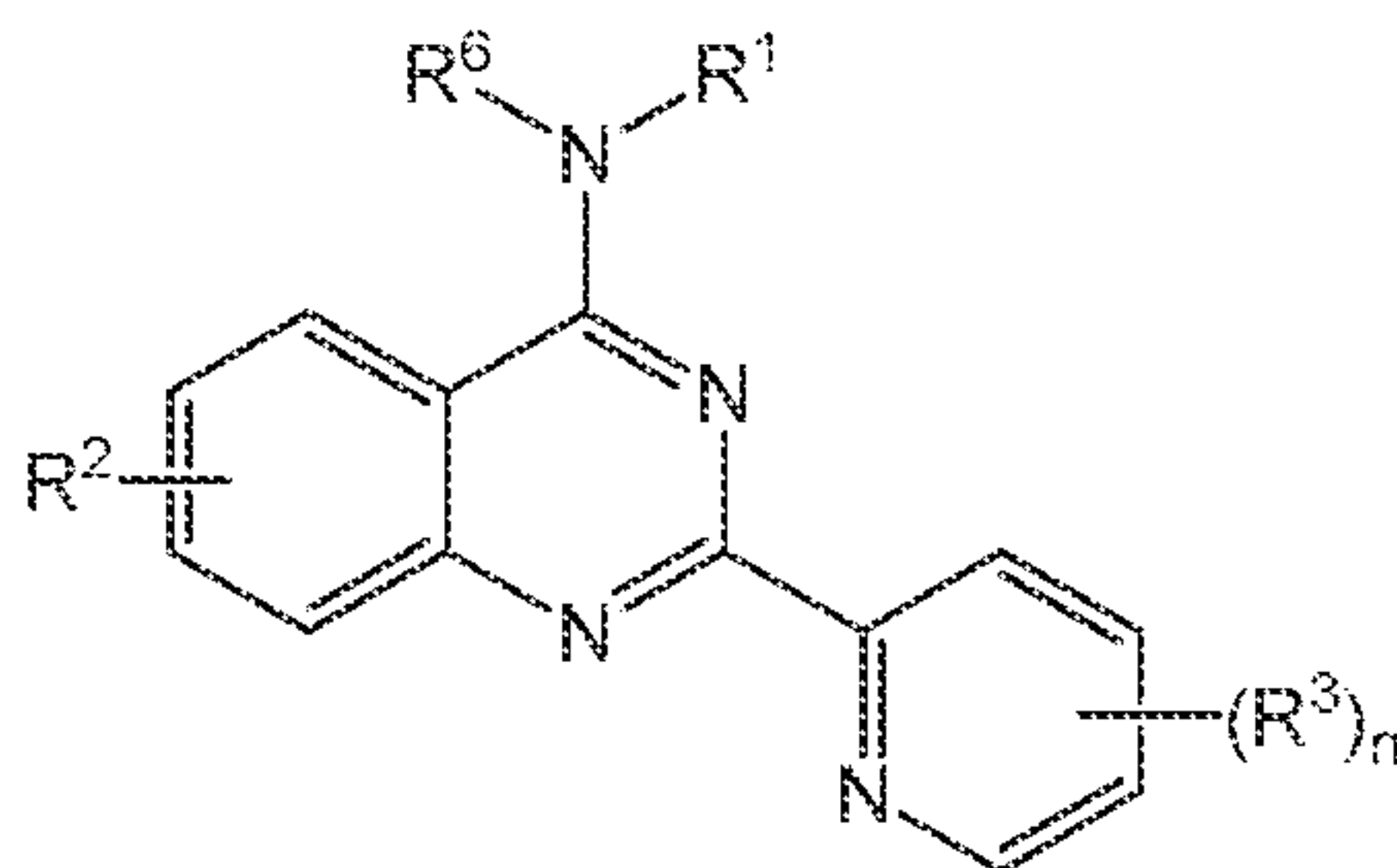
In some embodiments, R^2 is aryl. In some embodiments, R^2 is heteroaryl. In some embodiments, R^1 is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, the compound has the following structure:



In some embodiments, R^2 is aryl. In some embodiments, R^2 is heteroaryl. In some embodiments, R^1 is C_1 - C_8 alkyl (e.g., methyl).

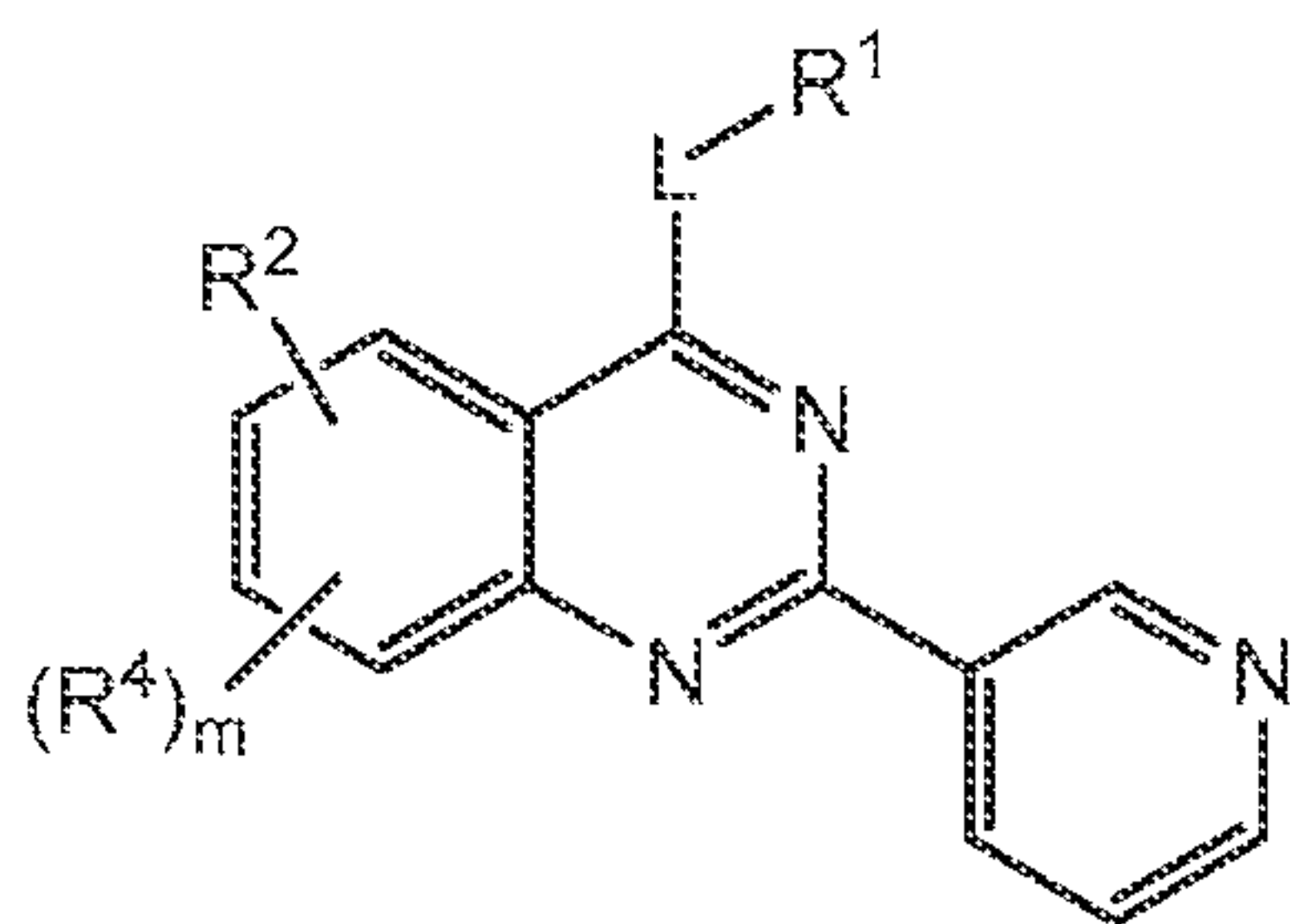
In some embodiments, the compound has the following structure:



wherein R^1 is C_1 - C_8 alkyl, which is optionally substituted with 1-3 R^7 .

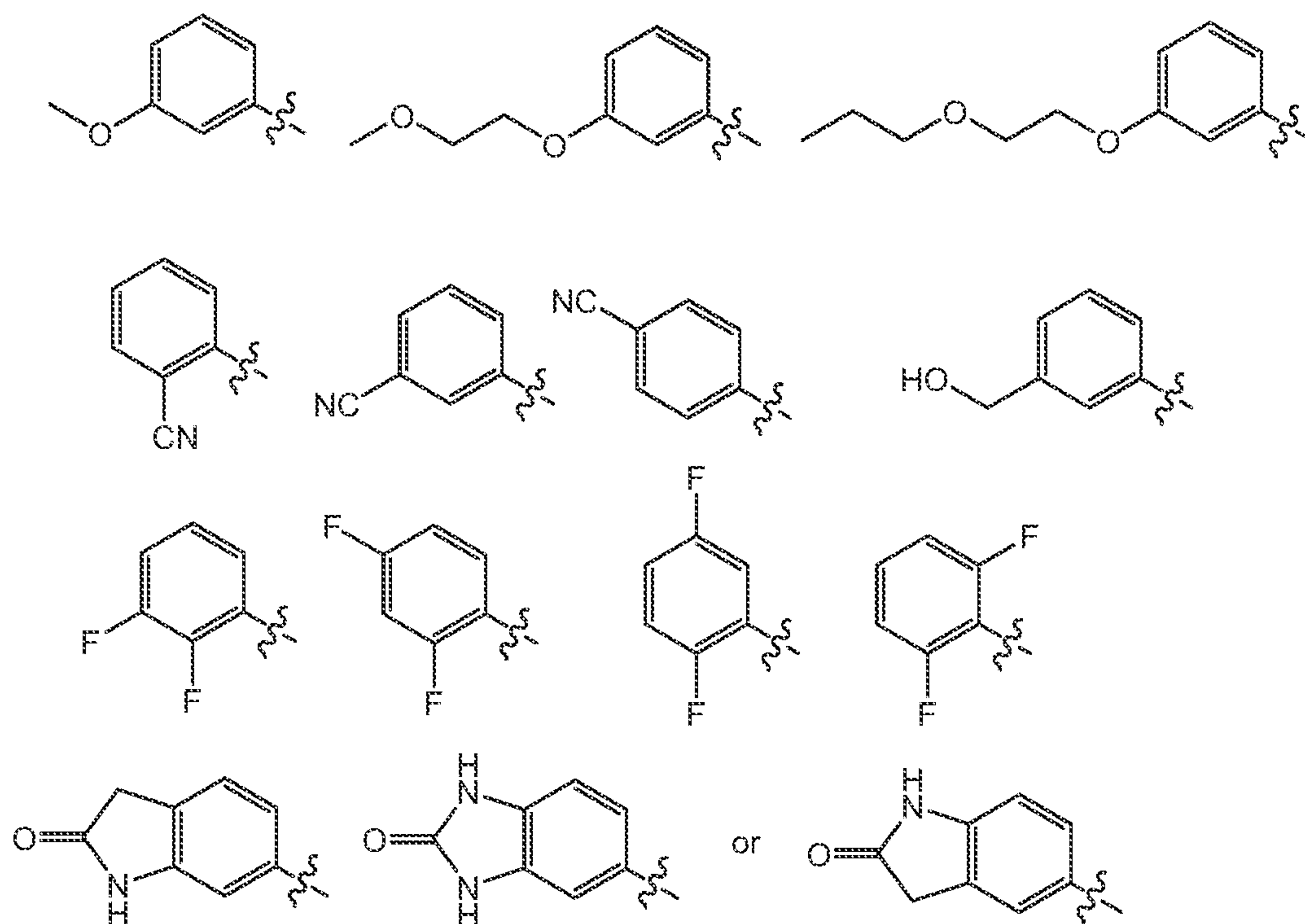
In some embodiments, R^2 is aryl. In some embodiments, R^2 is heteroaryl. In some embodiments, R^1 is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, the compound has the following structure:

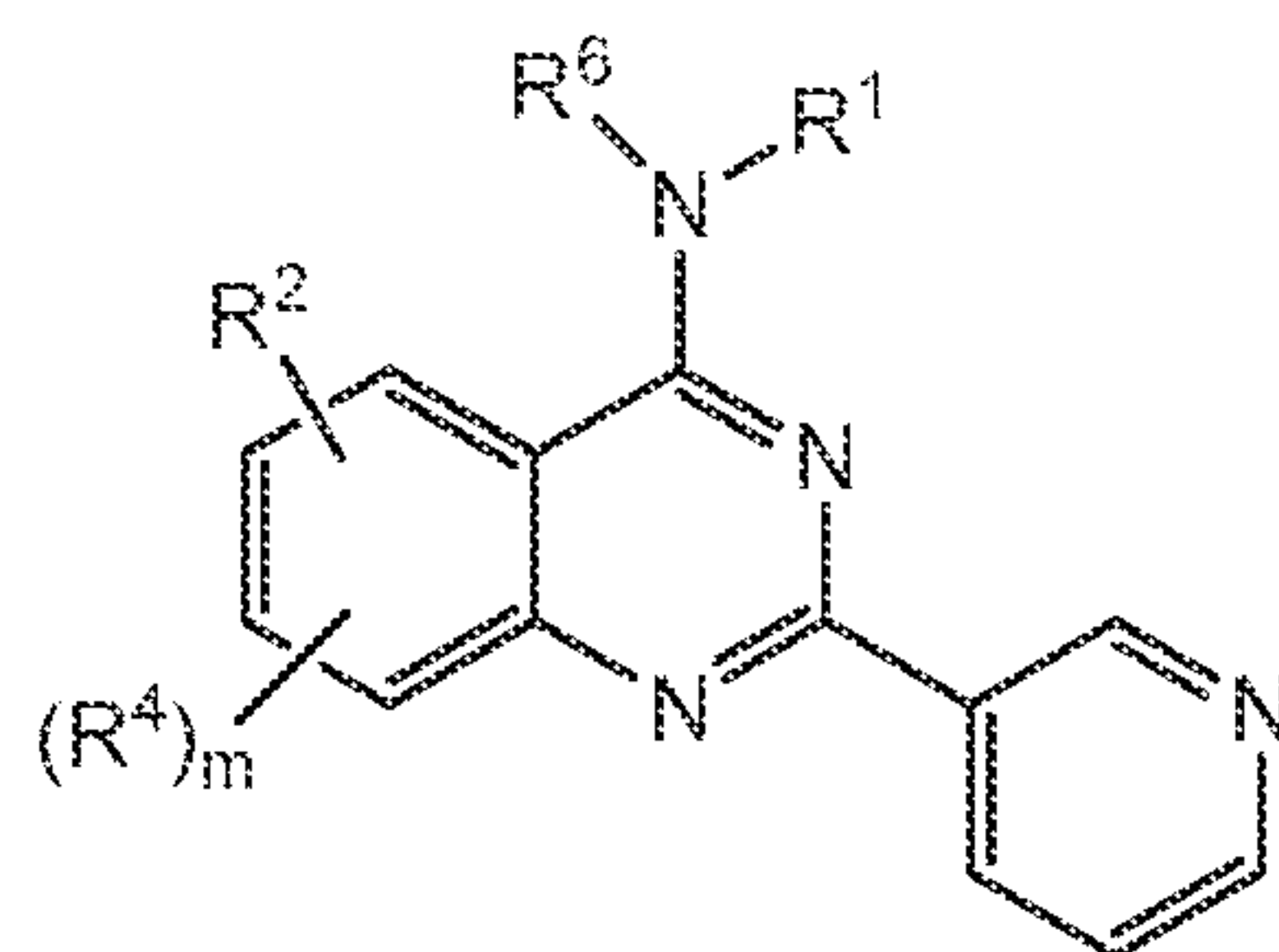


In some embodiments, R^2 is aryl. In some embodiments, R^2 is heteroaryl. In some embodiments, R^1 is C_1 - C_8 alkyl (e.g., methyl).

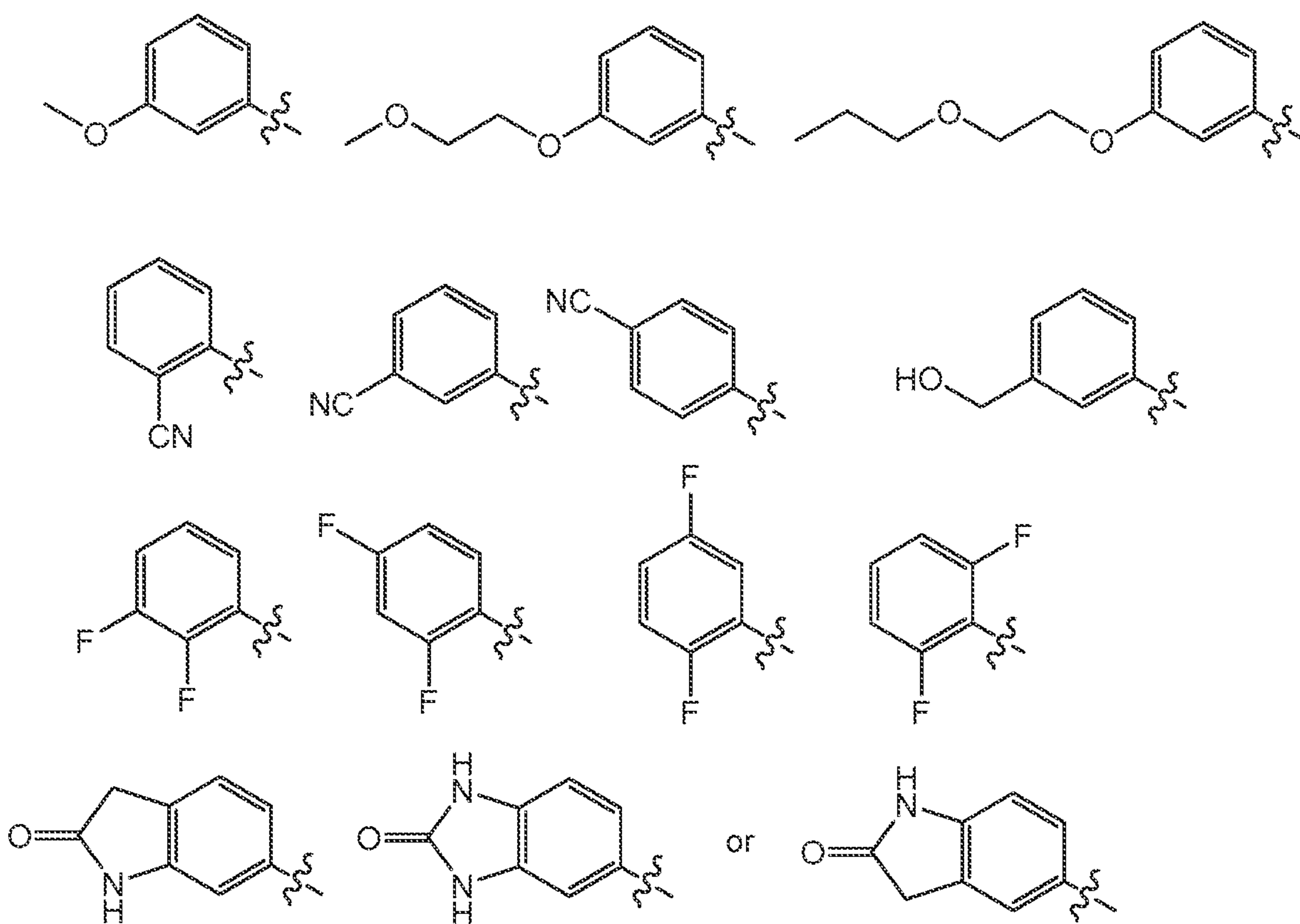
In some embodiments, R^2 is



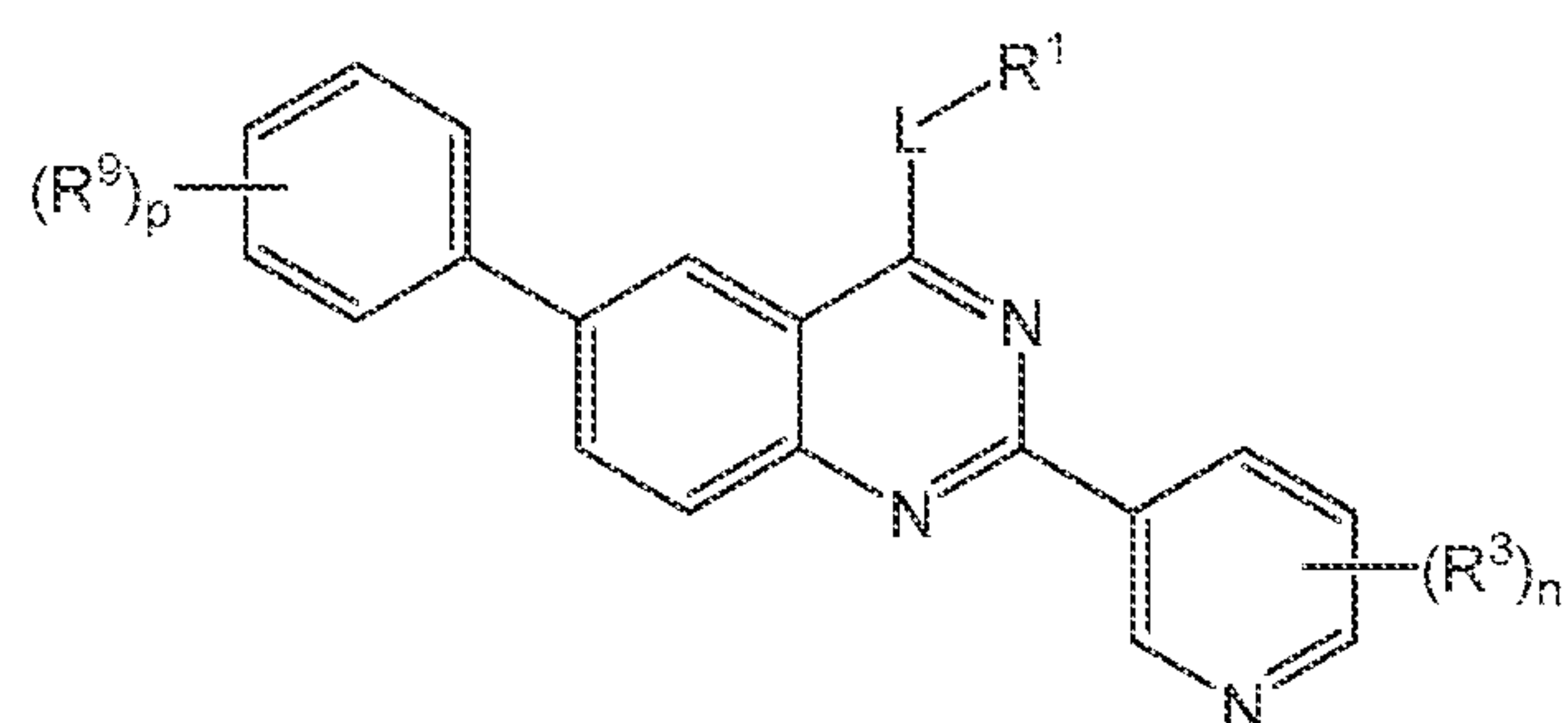
In some embodiments, the compound has the following structure:



In some embodiments, R^2 is aryl. In some embodiments, R^2 is heteroaryl. In some embodiments R^1 is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, R^2 is



In some embodiments, the compound has the following structure:



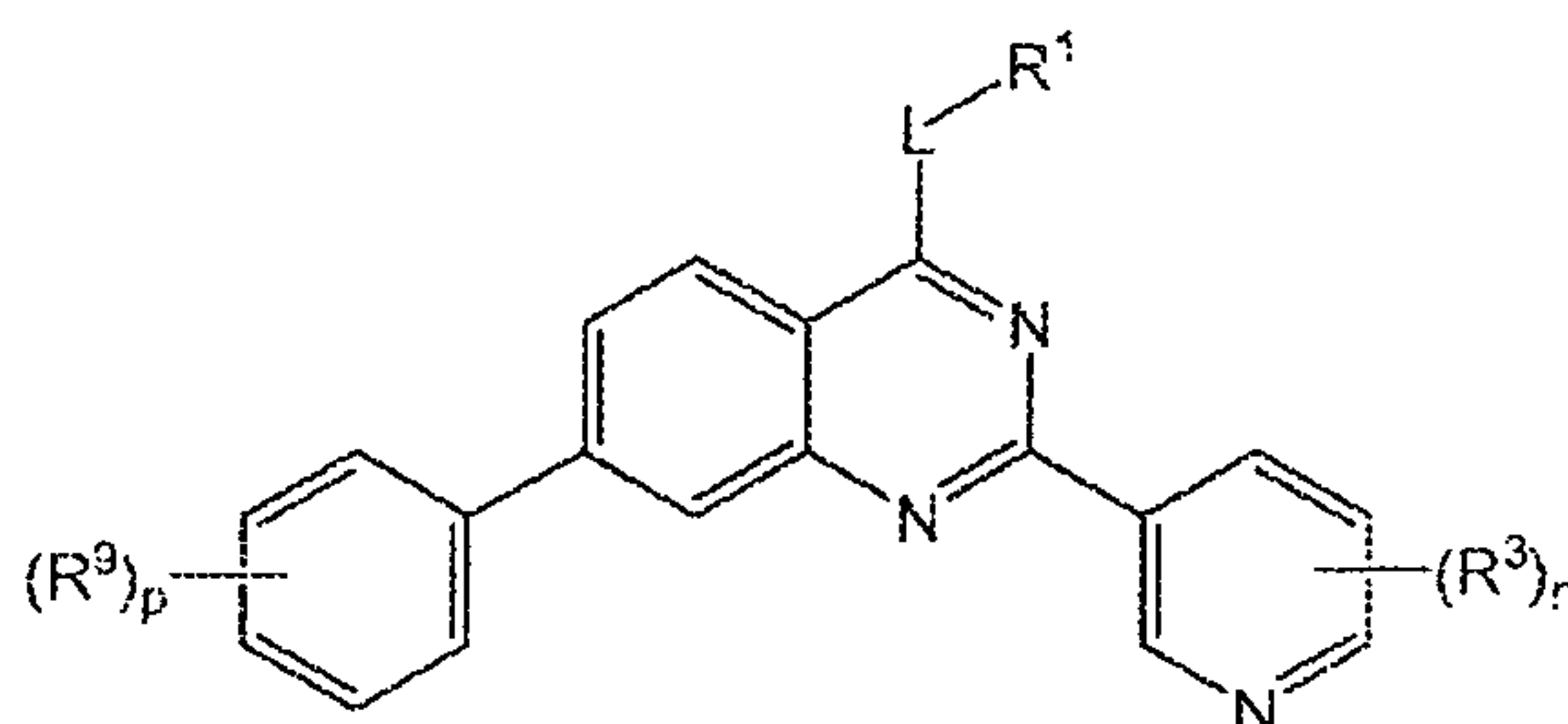
wherein p is 1, 2, 3, 4 or 5.

In some embodiments, L is NR^6 . In some embodiments, L is O . In some embodiments, R^1 is hydrogen or C_1 - C_8 alkyl. In some embodiments, R^1 is cyclyl or heterocyclyl. In some embodiments, R^1 is aralkyl or heteroaralkyl. In some

embodiments, R^1 is methyl, cyclohexyl, *t*-butyl, or . In some embodiments, R^6 is hydrogen or C_1 - C_8 alkyl.

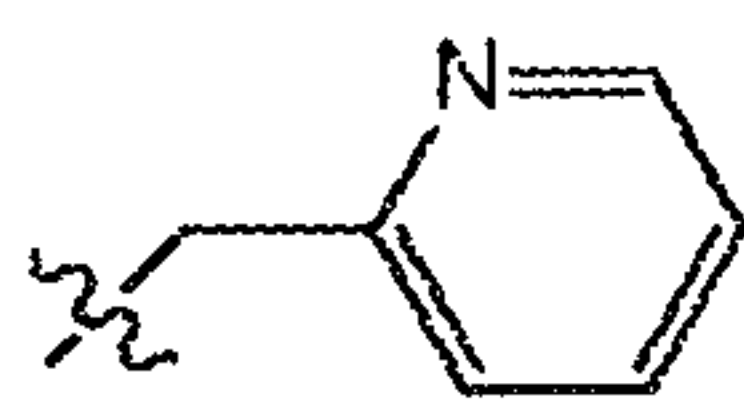
In some embodiments, R^9 is C_1 - C_8 alkyl, halo, -CN, or -OR^d. In some embodiments, R^3 is hydrogen.

In some embodiments, the compound has the following structure:



wherein p is 1, 2, 3, 4 or 5.

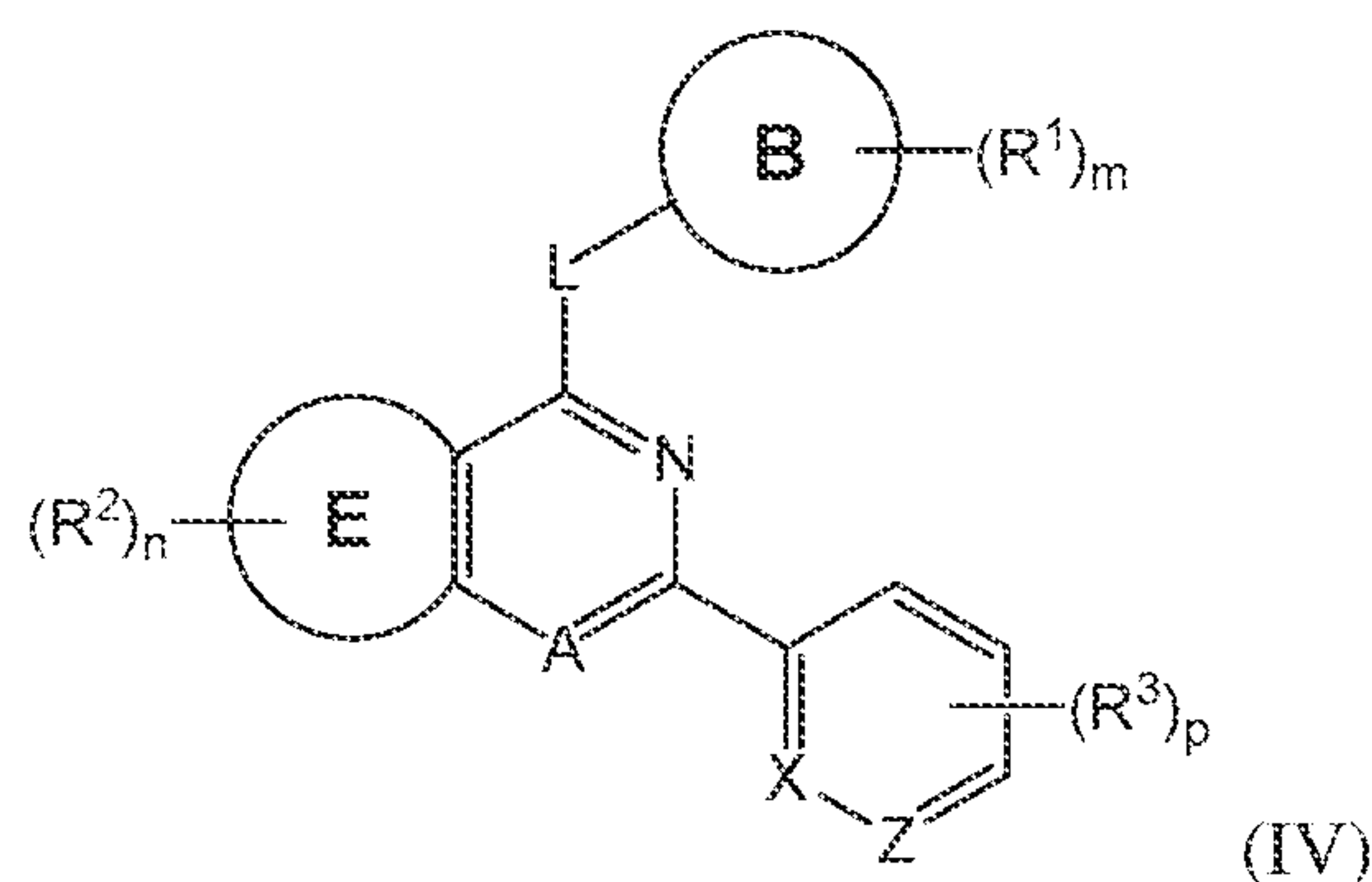
In some embodiments, L is NR⁶. In some embodiments, L is O. In some embodiments, R^1 is hydrogen or C_1 - C_8 alkyl. In some embodiments, R^1 is cyclyl or heterocyclyl. In some embodiments, R^1 is aralkyl or heteroaralkyl. In some

embodiments, R^1 is methyl, cyclohexyl, t-butyl, or . In some embodiments, R^6 is hydrogen or C_1 - C_8 alkyl. In some embodiments, R^9 is C_1 - C_8 alkyl, halo, -CN, or -OR^d. In some embodiments, R^3 is hydrogen.

Compounds of Formula (IV)

The following aspects and embodiments relate to compounds of formula (IV).

Item 38. A compound of formula (IV):



wherein:

A is CH, CR⁴ or N;

B is aryl or a 5- or 6-membered heteroaryl;

m is 0, 1, 2, 3, 4 or 5;

E is aryl or a 5-membered heteroaryl;

when E is aryl, n is 1, 2, 3 or 4; and when E is a 5-membered heteroaryl, n is 0, 1, 2 or 3;

L is NR⁵ or O;

one of X and Z is N and the other is CH;

p is 0, 1, 2, 3 or 4;

each R¹, R² and R³ is independently C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, -CN, -NO₂, -C(O)OR^a, -C(Y)NR^bR^{b'}, -NR^cC(Y)R^{c'}, -NR^bR^{b'}, -OC(O)NR^bR^{b'}, -NR^cC(O)OR^{c'}, -SO₂NR^bR^{b'}, -NR^cSO₂R^{c'}, -NR^cC(Y)NR^bR^{b'}, -OR^d, -SR^{d'}, -C(Y)R^e or -S(O)_qR^f, each of which may be optionally substituted with 1-3 R⁶; wherein two R¹, together with the atoms to which they are attached, may form an optionally substituted cyclyl, heterocyclyl, aryl or heteroaryl ring;

R⁴ is hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, -CN, -NO₂, -C(O)OR^a, -C(Y)NR^bR^{b'}, -NR^cC(Y)R^{c'}, -NR^bR^{b'}, -OC(O)NR^bR^{b'}, -NR^cC(O)OR^{c'}, -

$\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^{c'}$, $-\text{NR}^c\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^{d'}$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$, each of which may be optionally substituted with 1-3 R^6 ;

R^5 is hydrogen; or when m is not 0, R^5 and 1 R^1 may be taken together with the atoms to which they are attached to form an optionally substituted heteroaryl or heterocyclyl ring;

each R^6 is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, oxo, thiono, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^{c'}$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{O})\text{OR}^{c'}$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^{c'}$, $-\text{NR}^c\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^{d'}$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$, each of which may be optionally substituted with 1-3 R^7 ;

each R^7 is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, oxo, thiono, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^{c'}$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{O})\text{OR}^{c'}$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^{c'}$, $-\text{NR}^c\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^{d'}$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$;

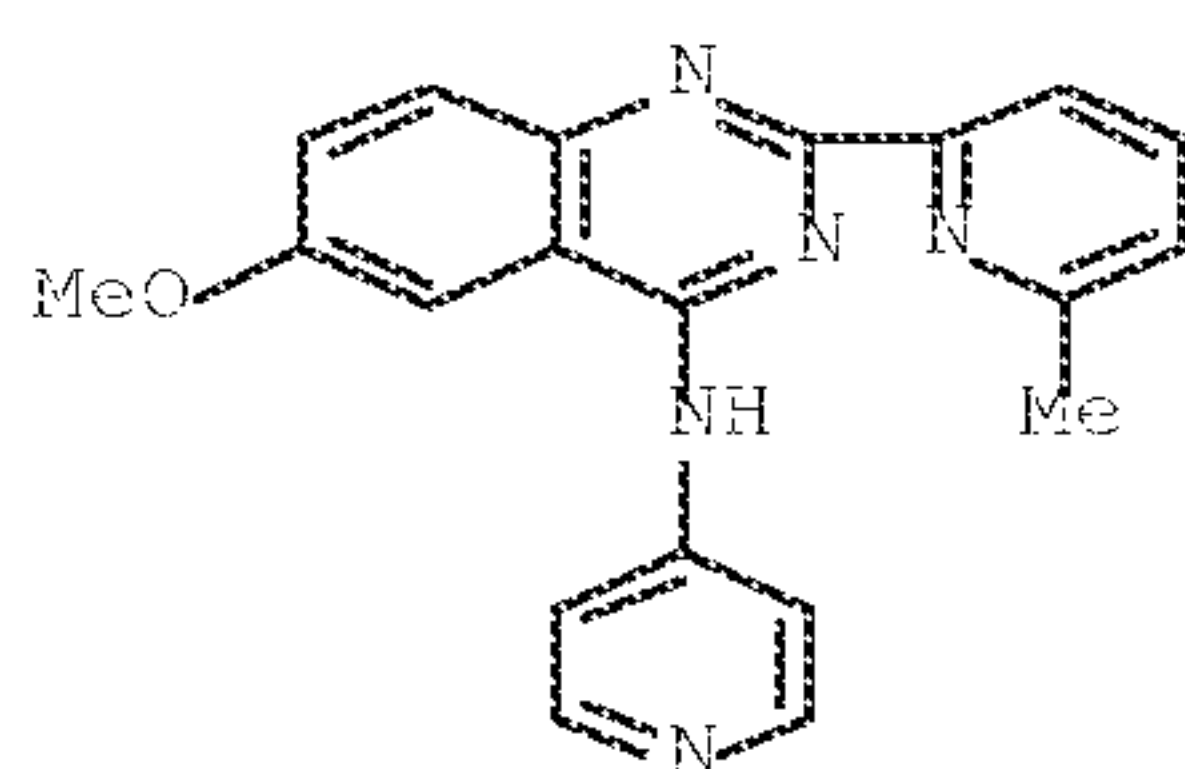
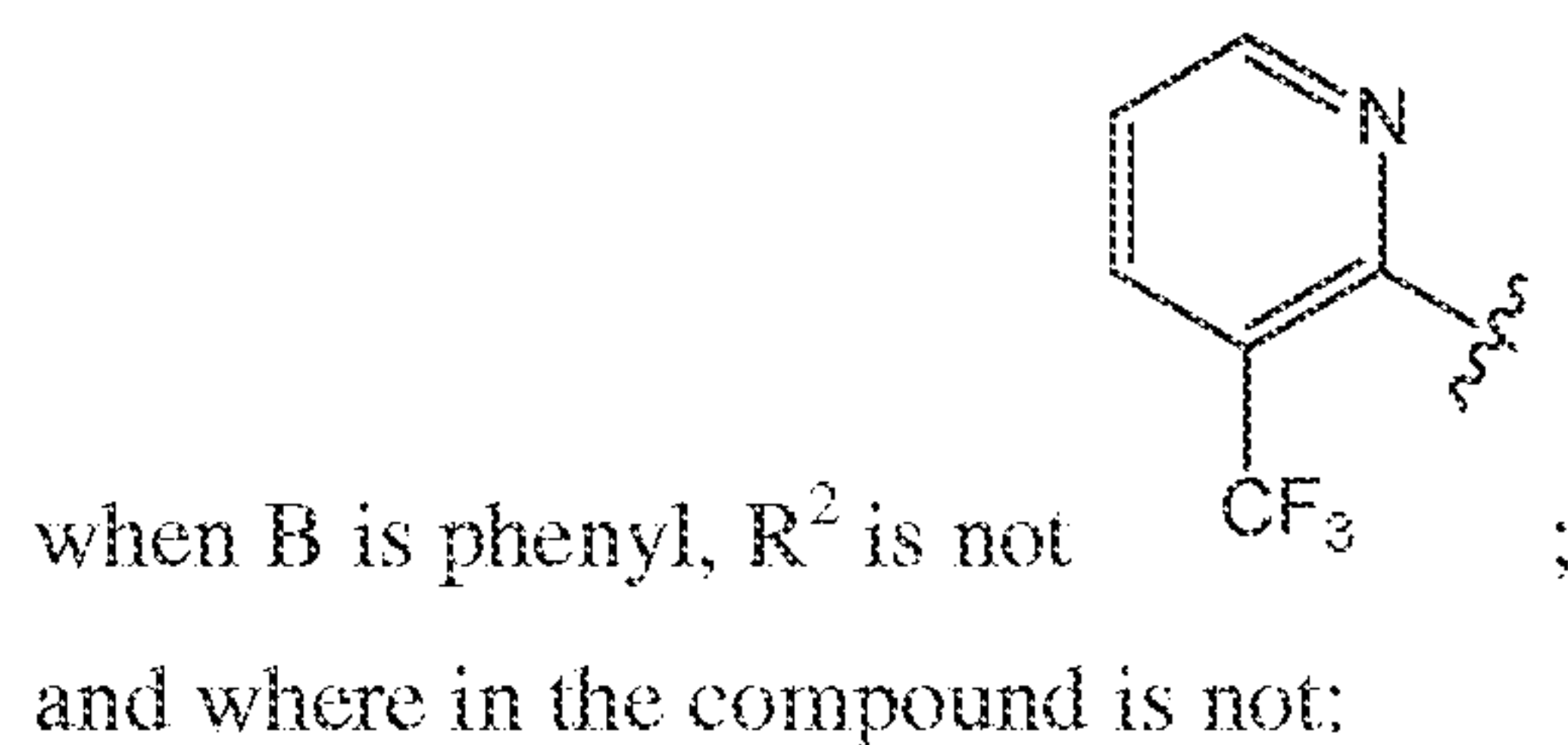
each Y is independently O or S ;

q is 1 or 2; and

each R^a , R^b , $\text{R}^{b'}$, R^c , $\text{R}^{c'}$, R^d , $\text{R}^{d'}$, R^e , $\text{R}^{e'}$ and R^f is independently selected from hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, acyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy and silylalkoxyalkyl, each of which may be optionally substituted with 1-3 R^6 , wherein R^b and $\text{R}^{b'}$, together with the atoms to which they are attached, may form an optionally substituted cyclyl or heterocyclyl ring;

or a pharmaceutically acceptable derivative or prodrug thereof,

wherein when B is phenyl, two R^1 are not taken together to form a pyrazole ring;



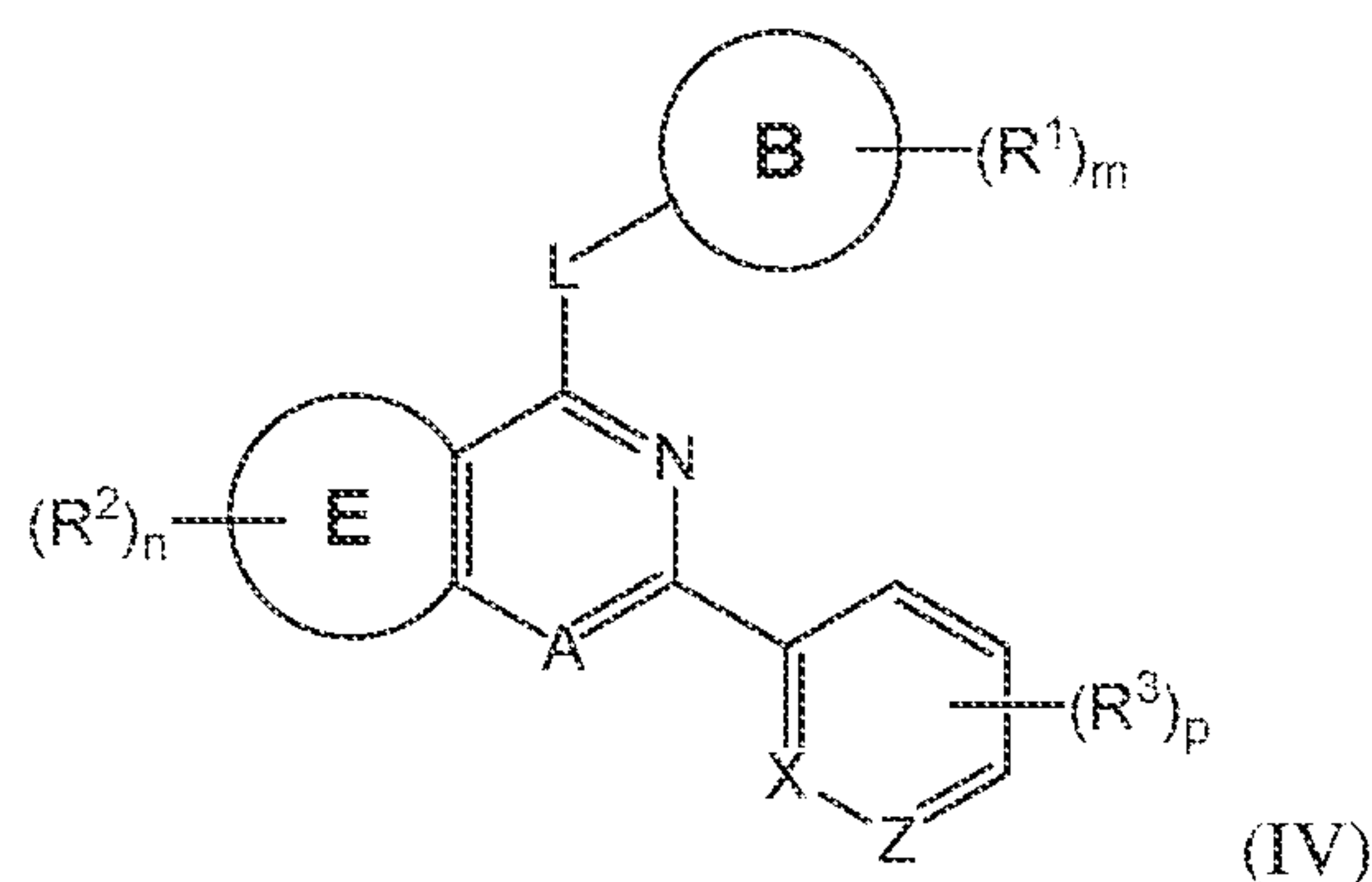
In some embodiments, when B is phenyl, R^2 is not a substituted pyridyl. In some embodiments, when B is phenyl and $n = 1$, R^2 is not a substituted pyridyl.

In some embodiments, when X is N, B is not 4-pyridyl.

In some embodiments, each R^a , R^b , $R^{b'}$, R^c , $R^{c'}$, R^d , $R^{d'}$, R^e , $R^{e'}$ and R^f is independently selected from hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, acyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy and silylalkoxyalkyl, each of which may be optionally substituted with 1-3 R^6 .

In some embodiments, B is aryl.

Item 39. A compound of formula (IV):



wherein:

A is CH, CR⁴ or N;

B is aryl or a 5-membered heteroaryl;

m is 0, 1, 2, 3, 4 or 5;

E is aryl or a 5-membered heteroaryl;

when E is aryl, n is 1, 2, 3 or 4; and when E is a 5-membered heteroaryl, n is 0, 1, 2 or 3;

L is NR⁵ or O;

one of X and Z is N and the other is CH;

p is 0, 1, 2, 3 or 4;

each R¹, R² and R³ is independently C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, -CN, -NO₂, -C(O)OR^a, -C(Y)NR^bR^{b'}, -NR^cC(Y)R^{c'}, -NR^bR^{b'}, -OC(O)NR^bR^{b'}, -NR^cC(O)OR^{c'}, -SO₂NR^bR^{b'}, -NR^cSO₂R^{c'}, -NR^cC(Y)NR^bR^{b'}, -OR^d, -SR^{d'}, -C(Y)R^e or -S(O)_qR^f, each of which may be optionally substituted with 1-3 R⁶; wherein two R¹, together with the atoms to which they are attached, may form an optionally substituted cyclyl, heterocyclyl, aryl or heteroaryl ring;

R⁴ is hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, -CN, -NO₂, -C(O)OR^a, -C(Y)NR^bR^{b'}, -NR^cC(Y)R^{c'}, -NR^bR^{b'}, -OC(O)NR^bR^{b'}, -NR^cC(O)OR^{c'}, -SO₂NR^bR^{b'}, -NR^cSO₂R^{c'}, -NR^cC(Y)NR^bR^{b'}, -OR^d, -SR^{d'}, -C(Y)R^e or -S(O)_qR^f, each of which may be optionally substituted with 1-3 R⁶;

R⁵ is hydrogen; or when m is not 0, R⁵ and 1 R¹ may be taken together with the atoms to which they are attached to form an optionally substituted heteroaryl or heterocyclyl ring;

each R⁶ is independently C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl,

hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, oxo, thiono, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^c$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{O})\text{OR}^c$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^c$, $-\text{NR}^c\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^{d'}$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$, each of which may be optionally substituted with 1-3 R^7 ;

each R^7 is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, oxo, thiono, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^c$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{O})\text{OR}^c$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^c$, $-\text{NR}^c\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^{d'}$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$;

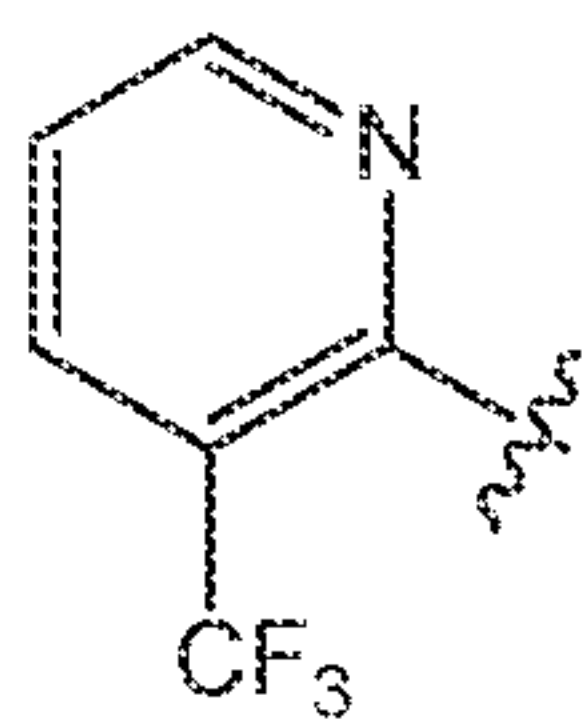
each Y is independently O or S;

q is 1 or 2; and

each R^a , R^b , $\text{R}^{b'}$, R^c , $\text{R}^{c'}$, R^d , $\text{R}^{d'}$, R^e , $\text{R}^{e'}$ and R^f is independently selected from hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, acyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy and silylalkoxyalkyl, each of which may be optionally substituted with 1-3 R^6 wherein R^b and $\text{R}^{b'}$, together with the atoms to which they are attached, may form an optionally substituted cyclyl or heterocyclyl ring;

or a pharmaceutically acceptable derivative or prodrug thereof,

wherein when B is phenyl, two R^1 are not taken together to form a pyrazole ring; and



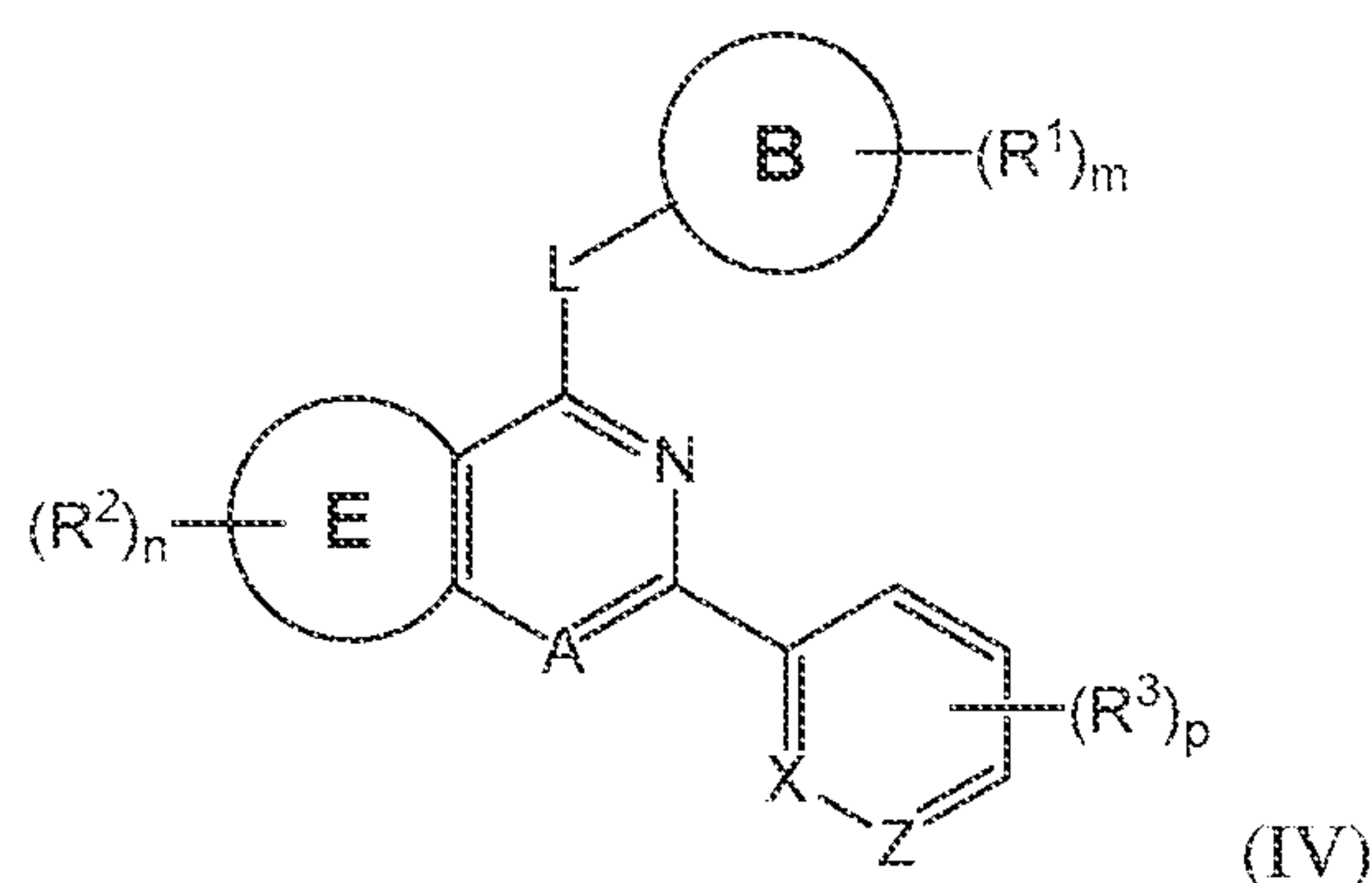
when B is phenyl, R^2 is not

In some embodiments, each R^a , R^b , $\text{R}^{b'}$, R^c , $\text{R}^{c'}$, R^d , $\text{R}^{d'}$, R^e , $\text{R}^{e'}$ and R^f is independently selected from hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, acyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl,

heterocyclalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy and silylalkoxyalkyl, each of which may be optionally substituted with 1-3 R^6 .

In some embodiments, when B is phenyl, R^2 is not a substituted pyridyl. In some embodiments, when B is phenyl and $n = 1$, R^2 is not a substituted pyridyl.

In one aspect, the invention features a compound of formula (IV):



wherein:

A is CH, CR^4 or N;

B is aryl or a 5-membered heteroaryl;

E is aryl or a 5-membered heteroaryl;

L is NR^5 or O;

one of X and Z is N and the other is CH;

m is 0, 1, 2, 3, 4 or 5;

n is 1, 2, 3 or 4;

p is 0, 1, 2, 3 or 4;

each R^1 and R^3 is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, $-CN$, $-NO_2$, $-C(O)OR^a$, $-C(Y)NR^bR^{b'}$, $-NR^cC(Y)R^{c'}$, $-NR^bR^{b'}$, $-OC(O)NR^bR^{b'}$, $-NR^cC(O)OR^{c'}$, $-SO_2NR^bR^{b'}$, $-NR^cSO_2R^{c'}$, $-NR^cC(Y)NR^bR^{b'}$, $-OR^d$, $-SR^d$, $-C(Y)R^e$ or $-S(O)_qR^f$, each of which may be optionally substituted with 1-3 R^6 ; wherein two R^1 , together with the atoms to which they are attached, may form an optionally substituted cyclyl, heterocyclyl, aryl or heteroaryl ring;

each R^2 is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, $-CN$, $-NO_2$, $-C(O)OR^a$, $-C(Y)NR^bR^{b'}$, $-NR^cC(Y)R^{c'}$, $-NR^bR^{b'}$, $-OC(O)NR^bR^{b'}$, $-NR^cC(O)OR^{c'}$, $-SO_2NR^bR^{b'}$, $-NR^cSO_2R^{c'}$, $-NR^cC(Y)NR^bR^{b'}$, $-OR^d$, $-SR^d$, $-C(Y)R^e$ or $-S(O)_qR^f$, each of which may be optionally substituted with 1-3 R^6 ; wherein two R^1 , together with the carbons to which they are attached, may form an optionally substituted cyclyl, heterocyclyl, aryl or heteroaryl ring;

R^4 is hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, $-CN$, $-NO_2$, $-C(O)OR^a$, $-C(Y)NR^bR^{b'}$, $-NR^cC(Y)R^{c'}$, $-NR^bR^{b'}$, $-OC(O)NR^bR^{b'}$, $-NR^cC(O)OR^{c'}$, $-SO_2NR^bR^{b'}$, $-NR^cSO_2R^{c'}$, $-NR^cC(Y)NR^bR^{b'}$, $-OR^d$, $-SR^d$, $-C(Y)R^e$ or $-S(O)_qR^f$, each of which may be optionally substituted with 1-3 R^6 ;

R^5 is hydrogen; or when m is not 0, R^5 and 1 R^1 may be taken together with the atoms to which they are attached to form an optionally substituted heteroaryl or heterocyclyl ring;

each R^6 is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, oxo, thiono, $-CN$, $-NO_2$, $-C(O)OR^a$, $-C(Y)NR^bR^{b'}$, $-NR^cC(Y)R^{c'}$, $-NR^bR^{b'}$, $-OC(O)NR^bR^{b'}$, $-NR^cC(O)OR^{c'}$, $-SO_2NR^bR^{b'}$, $-NR^cSO_2R^{c'}$, $-NR^cC(Y)NR^bR^{b'}$, $-OR^d$, $-SR^d$, $-C(Y)R^e$ or $-S(O)_qR^f$, each of which may be optionally substituted with 1-3 R^7 ;

each R^7 is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, oxo, thiono, $-CN$, $-NO_2$, $-C(O)OR^a$, $-C(Y)NR^bR^{b'}$, $-NR^cC(Y)R^{c'}$, $-NR^bR^{b'}$, $-$

$\text{OC(O)NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C(O)OR}^{c'}$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^{c'}$, $-\text{NR}^c\text{C(Y)NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^{d'}$, $-\text{C(Y)R}^e$ or $-\text{S(O)}_q\text{R}^f$;

Y is O or S;

q is 1 or 2; and

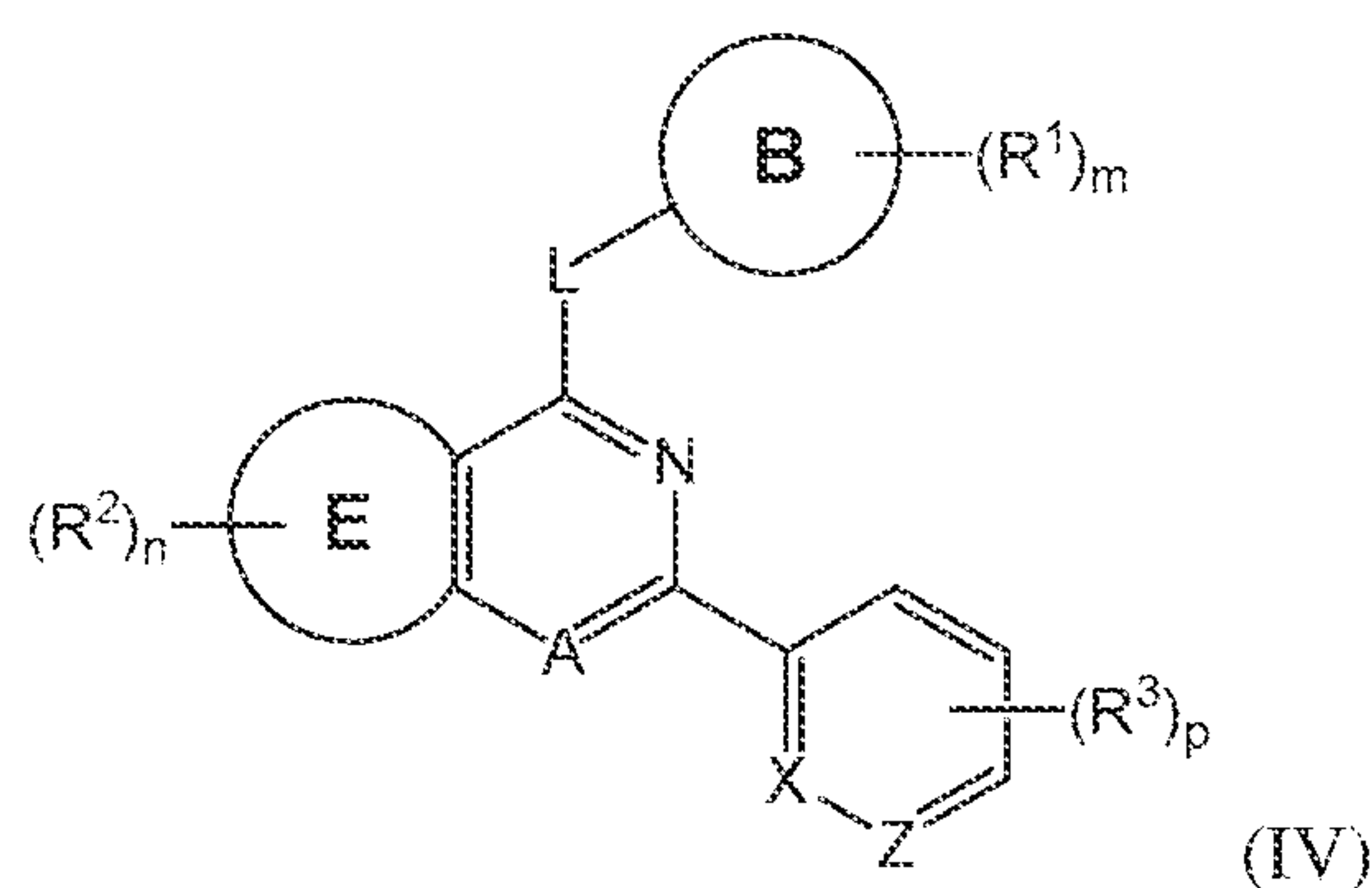
each R^a , R^b , $\text{R}^{b'}$, R^c , $\text{R}^{c'}$, R^d , $\text{R}^{d'}$, R^e , $\text{R}^{e'}$ and R^f is independently selected from hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, acyl, cyclyl, heterocyclyl, aryl, heteroaryl, cyclylalkyl, heterocyclylalkyl, aralkyl and heteroaralkyl, each of which may be optionally further substituted with 1-3 R^6 wherein R^b and $\text{R}^{b'}$, together with the atoms to which they are attached, may form an optionally substituted cyclyl or heterocyclyl ring;

or a pharmaceutically acceptable derivative or prodrug thereof,

wherein when B is phenyl, two R^1 are not taken together to form a pyrazole ring.

In some embodiments, each R^a , R^b , $\text{R}^{b'}$, R^c , $\text{R}^{c'}$, R^d , $\text{R}^{d'}$, R^e , $\text{R}^{e'}$ and R^f is independently selected from hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, acyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy and silylalkoxyalkyl, each of which may be optionally substituted with 1-3 R^6 .

In one aspect, the invention features a compound of formula (IV):



wherein:

A is CH, CR^4 or N;

B is aryl or a 5-membered heteroaryl;

E is aryl or a 5-membered heteroaryl;

L is NR⁵ or O;

one of X and Z is N and the other is CH;

m is 0, 1, 2, 3, 4 or 5;

n is 1, 2, 3 or 4;

p is 0, 1, 2, 3 or 4;

each R¹ and R³ is independently C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, -CN, -NO₂, -C(O)OR^a, -C(Y)NR^bR^{b'}, -NR^cC(Y)R^{c'}, -NR^bR^{b'}, -OC(O)NR^bR^{b'}, -NR^cC(O)OR^{c'}, -SO₂NR^bR^{b'}, -NR^cSO₂R^{c'}, -NR^cC(Y)NR^bR^{b'}, -OR^d, -SR^{d'}, -C(Y)R^e or -S(O)_qR^f, each of which may be optionally substituted with 1-3 R⁶; wherein two R¹, together with the atoms to which they are attached, may form an optionally substituted cyclyl, heterocyclyl, or aryl ring;

each R² is independently C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, aryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, -CN, -NO₂, -C(O)OR^a, -C(Y)NR^bR^{b'}, -NR^cC(Y)R^{c'}, -NR^bR^{b'}, -OC(O)NR^bR^{b'}, -NR^cC(O)OR^{c'}, -SO₂NR^bR^{b'}, -NR^cSO₂R^{c'}, -NR^cC(Y)NR^bR^{b'}, -OR^d, -SR^{d'}, -C(Y)R^e or -S(O)_qR^f, each of which may be optionally substituted with 1-3 R⁶; wherein two R¹, together with the carbons to which they are attached, may form an optionally substituted cyclyl, heterocyclyl, aryl or heteroaryl ring;

R⁴ is hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, -CN, -NO₂, -C(O)OR^a, -C(Y)NR^bR^{b'}, -NR^cC(Y)R^{c'}, -NR^bR^{b'}, -OC(O)NR^bR^{b'}, -NR^cC(O)OR^{c'}, -SO₂NR^bR^{b'}, -NR^cSO₂R^{c'}, -NR^cC(Y)NR^bR^{b'}, -OR^d, -SR^{d'}, -C(Y)R^e or -S(O)_qR^f, each of which may be optionally substituted with 1-3 R⁶;

R^5 is hydrogen; or when m is not 0, R^5 and 1 R^1 may be taken together with the atoms to which they are attached to form an optionally substituted heteroaryl or heterocyclyl ring;

each R^6 is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, oxo, thiono, $-CN$, $-NO_2$, $-C(O)OR^a$, $-C(Y)NR^bR^{b'}$, $-NR^cC(Y)R^c$, $-NR^bR^{b'}$, $-OC(O)NR^bR^{b'}$, $-NR^cC(O)OR^c$, $-SO_2NR^bR^{b'}$, $-NR^cSO_2R^c$, $-NR^cC(Y)NR^bR^{b'}$, $-OR^d$, $-SR^{d'}$, $-C(Y)R^e$ or $-S(O)_qR^f$, each of which may be optionally substituted with 1-3 R^7 ;

each R^7 is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, oxo, thiono, $-CN$, $-NO_2$, $-C(O)OR^a$, $-C(Y)NR^bR^{b'}$, $-NR^cC(Y)R^c$, $-NR^bR^{b'}$, $-OC(O)NR^bR^{b'}$, $-NR^cC(O)OR^c$, $-SO_2NR^bR^{b'}$, $-NR^cSO_2R^c$, $-NR^cC(Y)NR^bR^{b'}$, $-OR^d$, $-SR^{d'}$, $-C(Y)R^e$ or $-S(O)_qR^f$;

Y is O or S;

q is 1 or 2; and

each R^a , R^b , $R^{b'}$, R^c , R^c , R^d , $R^{d'}$, R^e , $R^{e'}$ and R^f is independently selected from hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, acyl, cyclyl, heterocyclyl, aryl, heteroaryl, cyclylalkyl, heterocyclylalkyl, aralkyl and heteroaralkyl, each of which may be optionally further substituted with 1-3 R^6 , wherein R^b and $R^{b'}$, together with the atoms to which they are attached, may form an optionally substituted cyclyl or heterocyclyl ring;

In some embodiments, A is N. In some embodiments, A is CH. In some embodiments, A is CR^4 .

In some embodiments, B is aryl (e.g., phenyl).

In some embodiments, m is 0.

In some embodiments, m is 1. In some embodiments, m is 2. In some embodiments, m is 3.

In some embodiments, R^1 is in the ortho position. In some embodiments, R^1 is in the meta position. In some embodiments, R^1 is in the para position.

In some embodiments, R^1 is C_1 - C_8 alkyl (e.g., methyl or tert-butyl). In some embodiments, R^1 is heteroaryl (e.g., oxazolyl, oxadiazolyl or quinazoliny).

In some embodiments, R^1 is heteroaryl substituted with 1-3 R^6 (e.g., 1 R^6).

In some embodiments, R^1 is oxadiazolyl substituted with 1 R^6 . In some embodiments, R^6 is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, R^1 is heteroaryl substituted with 2 R^6 . In some embodiments, R^1 is quinazoliny substituted with 2 R^6 . In some embodiments, one R^6 is halo (e.g., bromo) and the other is heteroaryl (e.g., pyridyl).

In some embodiments, m is 1 and R^1 is halo (e.g., fluoro, chloro or bromo). In some embodiments, m is 2 and each R^1 is halo (e.g., fluoro, chloro or bromo). In some embodiments, m is 3 and each R^1 is halo (e.g., fluoro, chloro or bromo). In some embodiments, R^1 is haloalkyl (e.g., trifluoromethyl). In some embodiments, R^1 is haloalkoxy (e.g., difluoromethoxy or trifluoromethoxy).

In some embodiments, R^1 is haloalkoxy substituted with 1 R^6 . In some embodiments, R^1 is $-O-CF_2-R^6$. In some embodiments, R^6 is $-C(Y)NR^bR^{b'}$. In some embodiments, Y is O, R^b is hydrogen and $R^{b'}$ is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, R^1 is $-O-CF_2-CH_2-R^6$. In some embodiments, R^6 is $-OR^d$. In some embodiments, R^d is hydrogen. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, R^6 is $-NR^bR^{b'}$. In some embodiments, R^b and $R^{b'}$ are each independently C_1 - C_8 alkyl (e.g., R^b and $R^{b'}$ are both methyl). In some embodiments, R^6 is heterocyclyl (e.g., morpholino).

In some embodiments, R^1 is aminoalkyl. In some embodiments, R^1 is $-CH_2NH_2$. In some embodiments, R^1 is alkylaminoalkyl. In some embodiments, R^1 is $-CH_2NHCH_2CH_2CH_3$. In some embodiments, R^1 is dialkylaminoalkyl. In some embodiments, R^1 is $-CH_2N(CH(CH_3)_2)_2$.

In some embodiments, R^1 is hydroxyalkyl. In some embodiments, R^1 is $-CH_2OH$.

In some embodiments, R^1 is $-CN$.

In some embodiments, R^1 is $-NO_2$.

In some embodiments, R^1 is $-C(O)OR^a$. In some embodiments, R^a is hydrogen. In some embodiments, R^a is C_1 - C_8 alkyl (e.g., methyl or ethyl).

In some embodiments, R^1 is $-NR^cC(Y)R^{c'}$. In some embodiments, one of R^c and $R^{c'}$ is hydrogen and the other is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, R^1 is $-OR^d$. In some embodiments, R^d is hydrogen. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl or ethyl).

In some embodiments, R^1 is $-SO_2NR^bR^{b'}$. In some embodiments, R^b and $R^{b'}$ are both hydrogen.

In some embodiments, R^1 is $-C(Y)R^e$. In some embodiments, Y is O . In some embodiments, R^e is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, R^e is heterocyclyl (e.g., pyrrolidinyl, piperidinyl or morpholino).

In some embodiments, R^1 is $-C(Y)NR^bR^{b'}$. In some embodiments, Y is S . In some embodiments, Y is O . In some embodiments, R^b and $R^{b'}$ are both hydrogen. In some embodiments, R^b is hydrogen. In some embodiments, R^b is hydrogen and $R^{b'}$ is aralkyl. In some embodiments, R^b is hydrogen and $R^{b'}$ is optionally substituted benzyl. In some embodiments, $R^{b'}$ is C_1 - C_8 alkyl, e.g., methyl, ethyl, C_3 alkyl (e.g., n-propyl or isopropyl), C_4 alkyl (e.g., n-butyl, sec-butyl or tert-butyl), C_5 alkyl (e.g., n-pentyl, isopentyl or pentan-3-yl), C_6 alkyl (e.g., n-hexyl or 3,3-dimethylbutan-2-yl), or C_7 alkyl (e.g., n-heptyl or 2-heptyl).

In some embodiments, $R^{b'}$ is C_1 - C_8 alkyl substituted with 1 R^6 . In some embodiments, R^6 is $-OR^d$. In some embodiments, R^d is aryl (e.g., phenyl). In some embodiments, $R^{b'}$ is C_2 - C_8 alkenyl, e.g., C_3 alkenyl (e.g., $-\text{CH}_2\text{-CH=CH}_2$). In some embodiments, $R^{b'}$ is C_2 - C_8 alkynyl, e.g., C_3 alkenyl (e.g., $-\text{CH}_2\text{-C}\equiv\text{CH}$).

In some embodiments, $R^{b'}$ is aryl (e.g., phenyl). In some embodiments, $R^{b'}$ is aryl substituted with 1 R^6 (e.g., phenyl substituted with 1 R^6). In some embodiments, R^6 is haloalkyl (e.g., trifluoromethyl). In some embodiments, $R^{b'}$ is cyclyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl). In some embodiments, $R^{b'}$ is cyclyl substituted with 1 R^6 (e.g., cyclopropyl substituted with 1 R^6 or cyclopentyl substituted with 1 R^6). In some embodiments, R^6 is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, R^6 is $-OR^d$. In some embodiments, R^d is aralkyl (e.g., benzyl).

In some embodiments, $R^{b'}$ is cyclohexyl substituted with 1 R^6 . In some embodiments, R^6 is $-C(O)OR^a$. In some embodiments, R^a is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, $R^{b'}$ is bicycyl (e.g., indanyl). In some embodiments, $R^{b'}$ is heterocyclyl, e.g., a 6-membered heterocyclyl. In some embodiments, $R^{b'}$ is a 6-membered oxygen-containing heterocyclyl (e.g., tetrahydropyranyl). In some embodiments, $R^{b'}$ is a 6-membered nitrogen-containing heterocyclyl (e.g., piperidiny).

In some embodiments, $R^{b'}$ is heterocyclyl substituted with 1 R^6 (e.g., piperidiny substituted with 1 R^6). In some embodiments, R^6 is $-C(O)OR^a$. In some embodiments, R^a is C_1 - C_8 alkyl (e.g., ethyl). In some embodiments, R^6 is $-C(Y)R^c$. In some embodiments, Y is O. In some embodiments, R^c is C_1 - C_8 alkyl (e.g., methyl or ethyl).

In some embodiments, $R^{b'}$ is aralkyl. In some embodiments, the alkyl is a C_1 - C_8 alkyl (e.g., C_1 , C_2 , C_3 or C_4 alkyl). In some embodiments, the alkyl is a straight-chain alkyl. In some embodiments, the alkyl is a branched alkyl. In some embodiments, the aryl is phenyl. In some embodiments, $R^{b'}$ is benzyl. In some embodiments, $R^{b'}$ is phenylethyl. In some embodiments, the aryl is substituted with 1 R^6 . In some embodiments, R^6 is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, R^6 is halo (e.g., fluoro or chloro). In some embodiments, R^6 is haloalkyl (e.g., trifluoromethyl). In some embodiments, R^6 is $-OR^d$. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, the aryl is substituted with 2 R^6 . In some embodiments, each R^6 is independently $-OR^d$. In some embodiments, each R^d is independently C_1 - C_8 alkyl (e.g., each R^d is methyl). In some embodiments, each R^6 is independently halo (e.g., each R^6 is fluoro).

In some embodiments, $R^{b'}$ is heteroaralkyl. In some embodiments, the alkyl is a C_1 - C_8 alkyl (e.g., C_1 , C_2 or C_3 alkyl). In some embodiments, the alkyl is a straight-chain alkyl. In some embodiments, the alkyl is a branched alkyl. In some embodiments, the heteroaryl is pyridyl. In some embodiments, the heteroaryl is furanyl. In some embodiments, the heteroaryl is thiazolyl. In some embodiments, the heteroaryl is thienyl. In some embodiments, the heteroaryl is substituted with 1 R^6 .

In some embodiments, R^6 is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, R^6 is haloalkyl (e.g., trifluoromethyl).

In some embodiments, $R^{b'}$ is cyclylalkyl. In some embodiments, the alkyl is a C_1 - C_8 alkyl (e.g., C_1 alkyl). In some embodiments, the cyclyl group is cyclopropyl. In some embodiments, the cyclyl group is cyclopentyl. In some embodiments, the cyclyl group is a bicyclic group. In some embodiments, the bicyclic group is indanyl. In some embodiments, $R^{b'}$ is cyclylalkyl substituted with 1 R^6 . In some embodiments, R^6 is aryl (e.g., phenyl).

In some embodiments, $R^{b'}$ is heterocyclylalkyl. In some embodiments, the alkyl is a C_1 - C_8 alkyl (e.g., C_1 alkyl). In some embodiments, the heterocyclyl group is tetrahydropyranyl.

In some embodiments, $R^{b'}$ is haloalkyl (e.g., fluoroethyl, difluoroethyl, trifluoroethyl or trifluoropropyl).

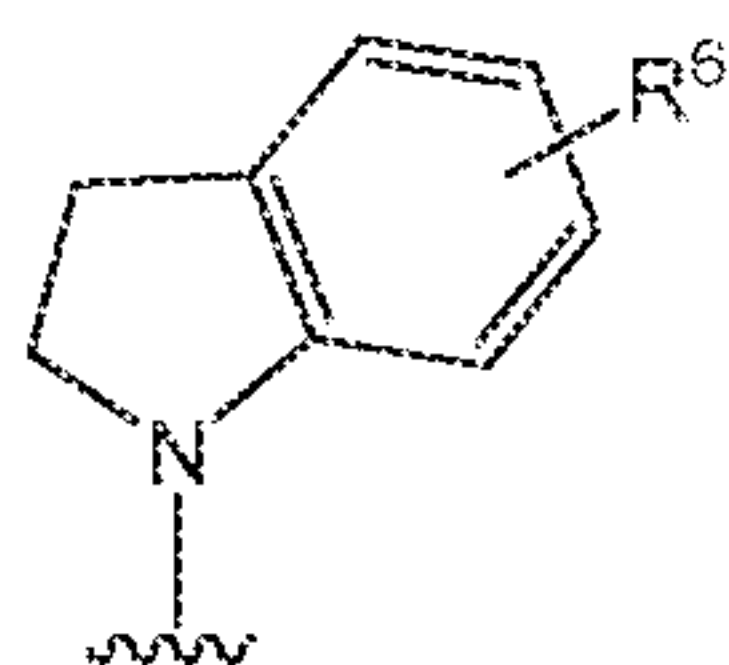
In some embodiments, $R^{b'}$ is alkoxyalkyl. In some embodiments, the alkyl is a C_1 - C_8 alkyl (e.g., C_1 , C_2 , C_3 or C_4 alkyl). In some embodiments, the alkyl is a straight-chain alkyl. In some embodiments, the alkyl is a branched alkyl. In some embodiments, the alkoxy is methoxy.

In some embodiments, R^b and $R^{b'}$ are each independently C_1 - C_8 alkyl (e.g., R^b and $R^{b'}$ are both methyl, both ethyl or both isopropyl).

In some embodiments, R^1 and R^5 , together with the atoms to which they are attached, form a heteroaryl ring (e.g., a substituted heteroaryl ring). In some embodiments, R^1 and R^5 , together with the atoms to which they are attached, form a heterocyclyl ring (e.g., a substituted heterocyclyl ring).

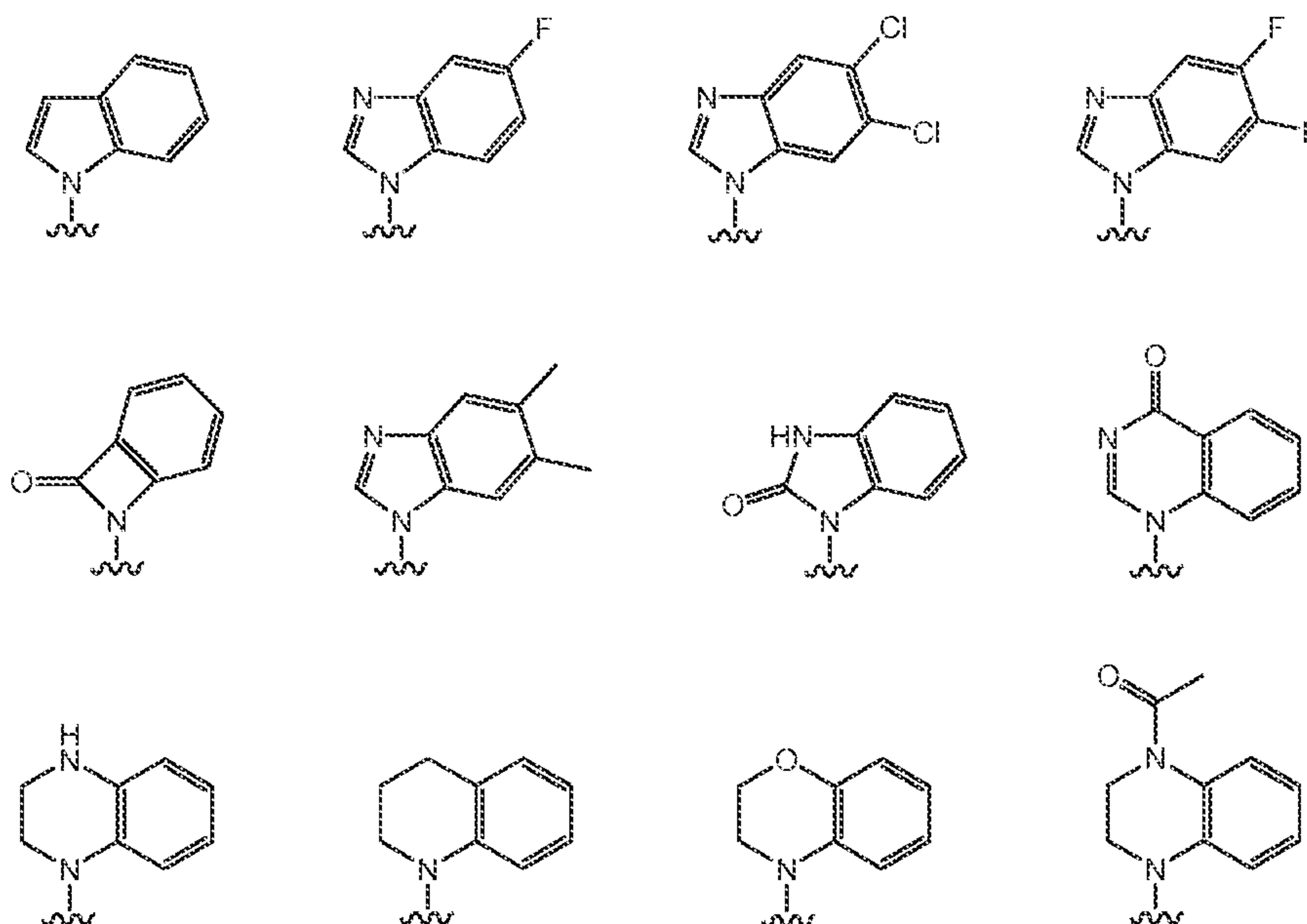
In some embodiments, R^1 , R^5 , B and L are taken together to form a bicyclic heteroaryl or heterocyclic ring.

In some embodiments, R^1 , R^5 , B and L are taken together to form



. In some embodiments, R^6 is halo. In some embodiments, R^6 is at the 6, 7, or 8 position.

In some embodiments, R^1 , R^5 , B and L are taken together to form a group selected from:



In some embodiments, R^2 is aryl.

In some embodiments, each R^1 is independently C_1 - C_8 alkyl (e.g., each R^1 is methyl). In some embodiments, each R^1 is independently halo (e.g., each R^1 is fluoro or each R^1 is chloro). In some embodiments, one R^1 is fluoro and the other is chloro. In some embodiments, one R^1 is chloro and the other is bromo.

In some embodiments, each R^1 is independently $-OR^d$. In some embodiments, each R^d is independently C_1 - C_8 alkyl (e.g., each R^d is methyl).

In some embodiments, one R^1 is halo (e.g., chloro) and the other is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, one R^1 is halo (e.g., fluoro) and the other is heterocyclylalkyl (e.g., $-CH_2$ -heterocyclyl). In some embodiments, the heterocyclyl is morpholino. In some embodiments, the heterocyclyl is pyrrolidinyl. In some embodiments, the heterocyclyl is piperazinyl. In some embodiments, the piperazinyl is substituted with 1 R^6 . In some embodiments, R^6 is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, one R^1 is halo (e.g., fluoro or chloro) and the other is haloalkyl (e.g., trifluoromethyl).

In some embodiments, one R^1 is halo (e.g., chloro) and the other is haloalkoxy (e.g., difluoromethoxy or trifluoromethoxy).

In some embodiments, one R^1 is halo (e.g., chloro) and the other is $-C(O)OR^a$. In some embodiments, R^a is hydrogen.

In some embodiments, one R^1 is halo (e.g., fluoro or chloro) and the other is $-C(Y)NR^bR^{b'}$. In some embodiments, Y is O. In some embodiments, R^b and $R^{b'}$ are both hydrogen. In some embodiments, one of R^b and $R^{b'}$ is hydrogen and the other is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, one R^1 is halo (e.g., chloro) and the other is $-NR^cC(Y)R^{c'}$. In some embodiments, Y is O. In some embodiments, R^c is hydrogen and $R^{c'}$ is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, one R^1 is halo (e.g., fluoro or chloro) and the other is $-OR^d$. In some embodiments, R^d is hydrogen. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, one R^1 is halo (e.g., fluoro or chloro) and the other is $-CN$.

In some embodiments, one R^1 is halo (e.g., chloro) and the other is $-NO_2$.

In some embodiments, one R^1 is $-C(O)OR^a$ and the other is $-NO_2$. In some embodiments, R^a is hydrogen.

In some embodiments, one R^1 is $-C(O)OR^a$ and the other is $-OR^d$. In some embodiments, each R^a and R^d is hydrogen.

In some embodiments, one R^1 is $-C(Y)NR^bR^{b'}$ and the other is haloalkyl (e.g., trifluoromethyl). In some embodiments, R^b and $R^{b'}$ are both hydrogen.

In some embodiments, one R^1 is $-C(Y)NR^bR^{b'}$ and the other is haloalkoxy (e.g., trifluoromethoxy). In some embodiments, R^b and $R^{b'}$ are both hydrogen.

In some embodiments, one R^1 is $-C(Y)NR^bR^{b'}$ and the other is $-S(O)_qR^f$. In some embodiments, R^b and $R^{b'}$ are both hydrogen. In some embodiments, R^f is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, one R^1 is $-C(Y)NR^bR^{b'}$ and the other is $-CN$. In some embodiments, R^b and $R^{b'}$ are both hydrogen.

In some embodiments, one R^1 is $-OR^d$ and the other is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, one R^1 is $-OR^d$ and the other is haloalkyl (e.g., trifluoromethyl). In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl).

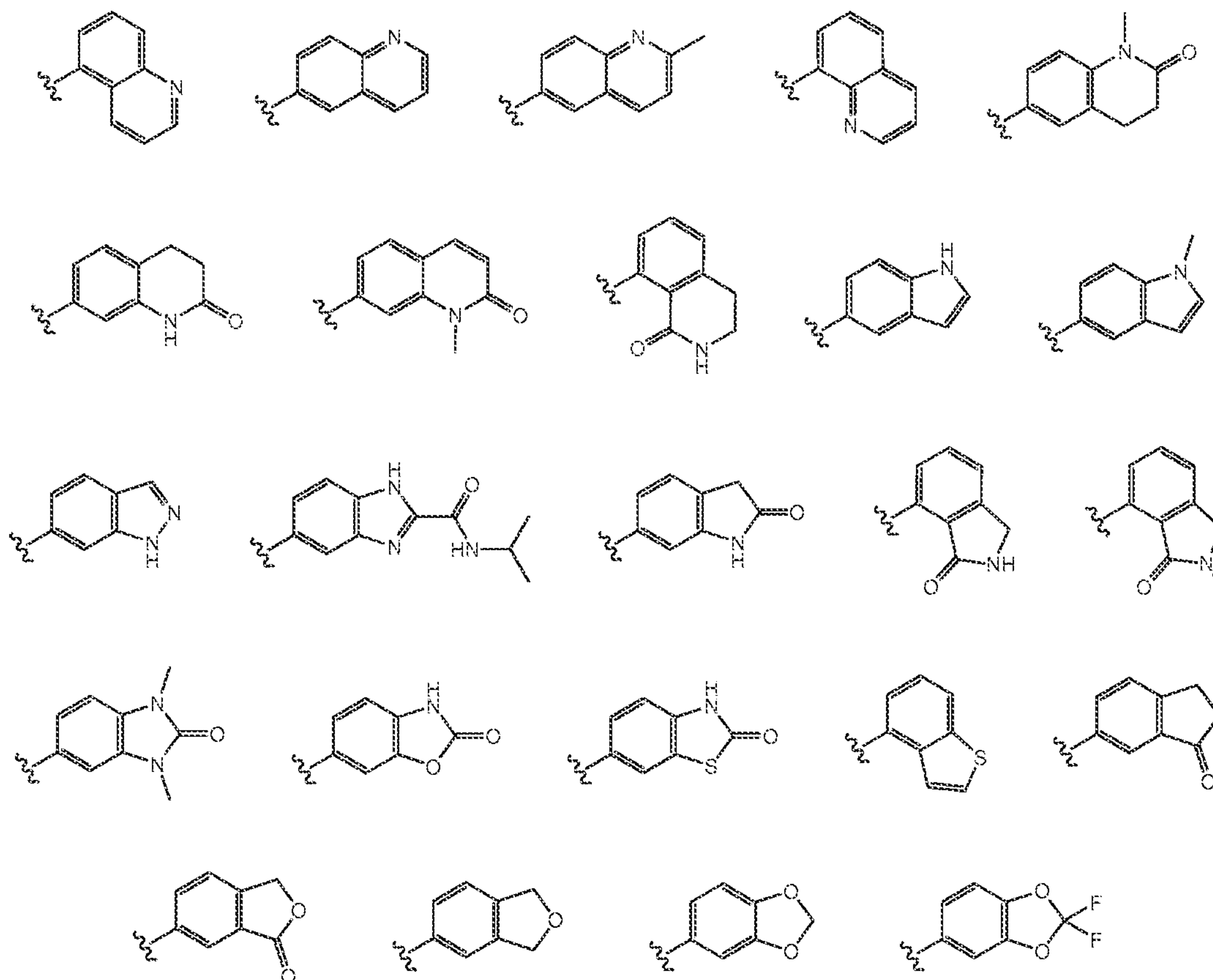
In some embodiments, one R^1 is $-OR^d$ and the other is $-C(O)OR^a$. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, R^a is hydrogen. In some embodiments, R^a is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, one R^1 is $-OR^d$ and the other is $-NR^cC(O)R^{c'}$. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, R^c is hydrogen and $R^{c'}$ is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, one R^1 is haloalkyl (e.g., trifluoromethyl) and the other is $-CN$.

In some embodiments, two R^1 , together with the atoms to which they are attached, are taken together to form a cyclyl ring (e.g., a substituted cyclyl ring). In some embodiments, two R^1 , together with the atoms to which they are attached, are taken together to form a heterocyclyl ring (e.g., a substituted heterocyclyl ring). In some embodiments, two R^1 , together with the atoms to which they are attached, are taken together to form a heteroaryl ring (e.g., a substituted heteroaryl ring).

In some embodiments, two R^1 and ring B are taken together to form a group selected from:



In some embodiments, R^2 is aryl.

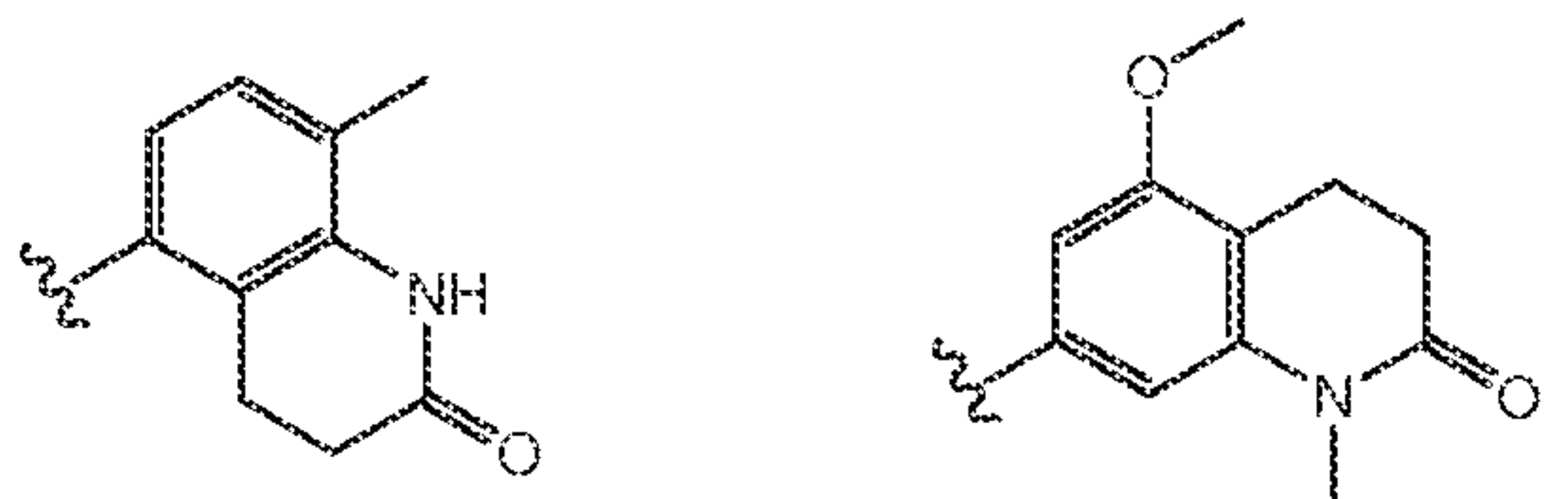
In some embodiments, each R^1 is independently halo (e.g., all three R^1 are fluoro or all three R^1 are chloro).

In some embodiments, two R^1 are independently halo (e.g., both are chloro) and the other is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, two R^1 are independently halo (e.g., both are chloro) and the other is heteroaryl (e.g., pyrrolyl). In some embodiments, two R^1 are independently halo (e.g., both are fluoro) and the other is $-C(Y)NR^bR^{b'}$ (e.g., $-C(O)NH_2$). In some embodiments, two R^1 are independently C_1 - C_8 alkyl (e.g., both are methyl) and the other is halo (e.g., chloro or bromo).

In some embodiments, one R^1 is C_1 - C_8 alkyl (e.g., methyl), and two R^1 , together with the atoms to which they are attached, are taken together to form a heterocyclyl ring.

In some embodiments, one R^1 is $-OR^d$, and two R^1 , together with the atoms to which they are attached, are taken together to form a heterocyclyl ring. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, three R^1 and ring B are taken together to form a group selected from:

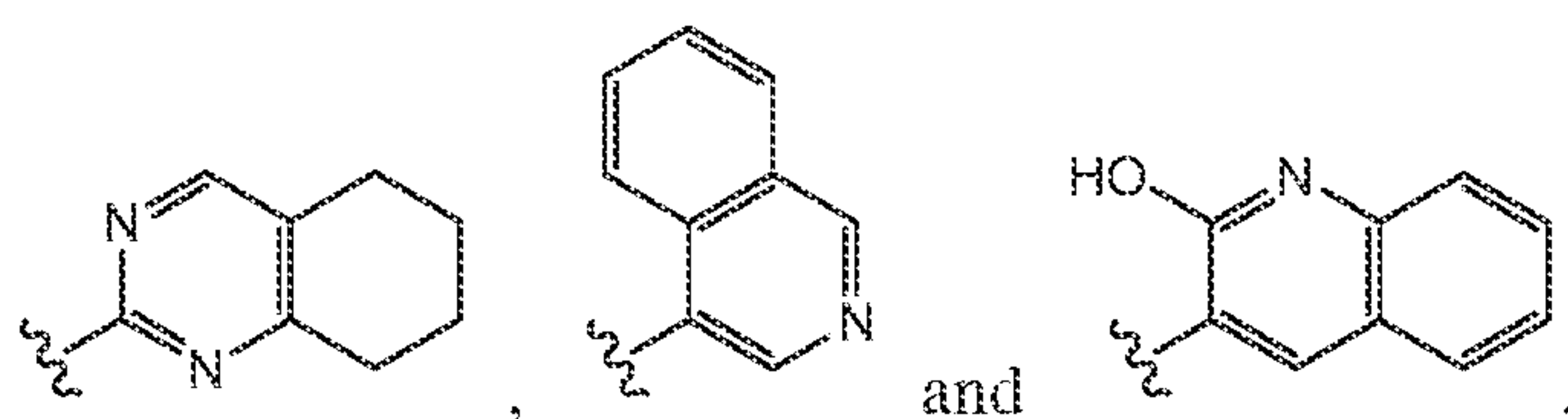


In some embodiments, B is a 6-membered heteroaryl.

In some embodiments, B is pyridyl. In some embodiments, B is 3-pyridyl. In some embodiments, m is 2. In some embodiments, two R^1 , together with the atoms to which they are attached, are taken together to form an aryl ring (e.g., a phenyl ring). In some embodiments, m is 3. In some embodiments, one R^1 is $-OR^d$, and two R^1 , together with the atoms to which they are attached, are taken together to form an aryl ring (e.g., a phenyl ring). In some embodiments, R^d is hydrogen.

In some embodiments, B is pyrazolyl. In some embodiments, m is 2. In some embodiments, two R^1 , together with the atoms to which they are attached, are taken together to form a cyclyl ring (e.g., a cyclohexyl ring).

In some embodiments, B is selected from:



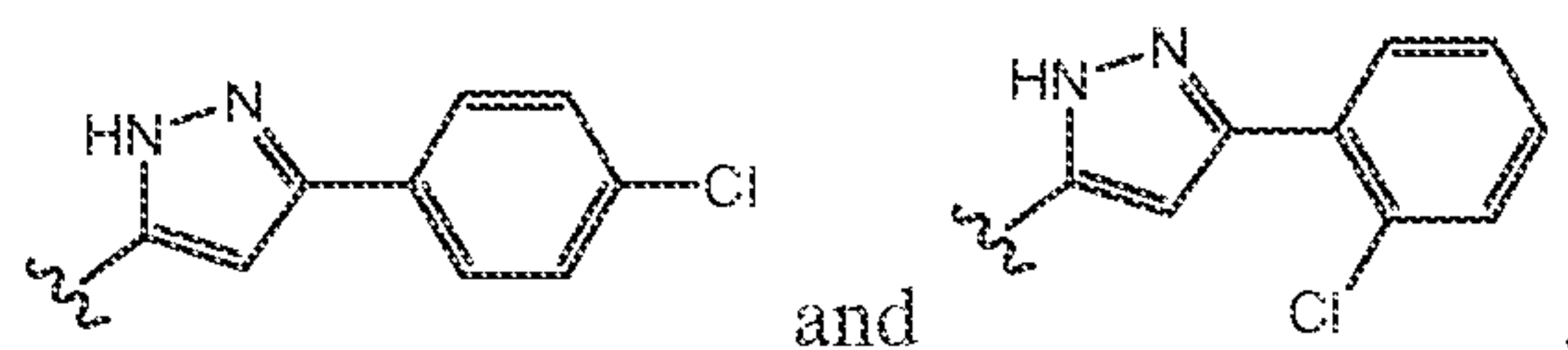
In some embodiments, B is a 5-membered heteroaryl (e.g., pyrazolyl).

In some embodiments, m is 1.

In some embodiments, R^1 is aryl (e.g., phenyl).

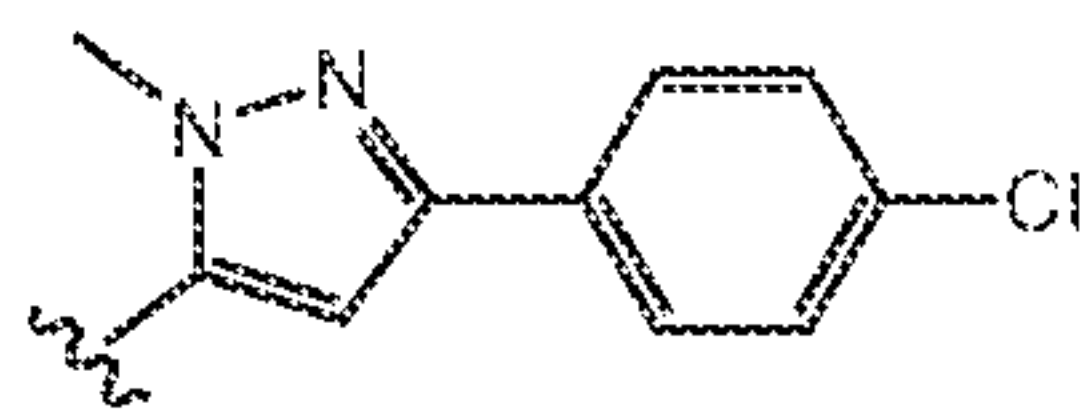
In some embodiments, R^1 is phenyl substituted with 1 R^6 .

In some embodiments, R^6 is halo (e.g., chloro). In some embodiments, R^1 is selected from:

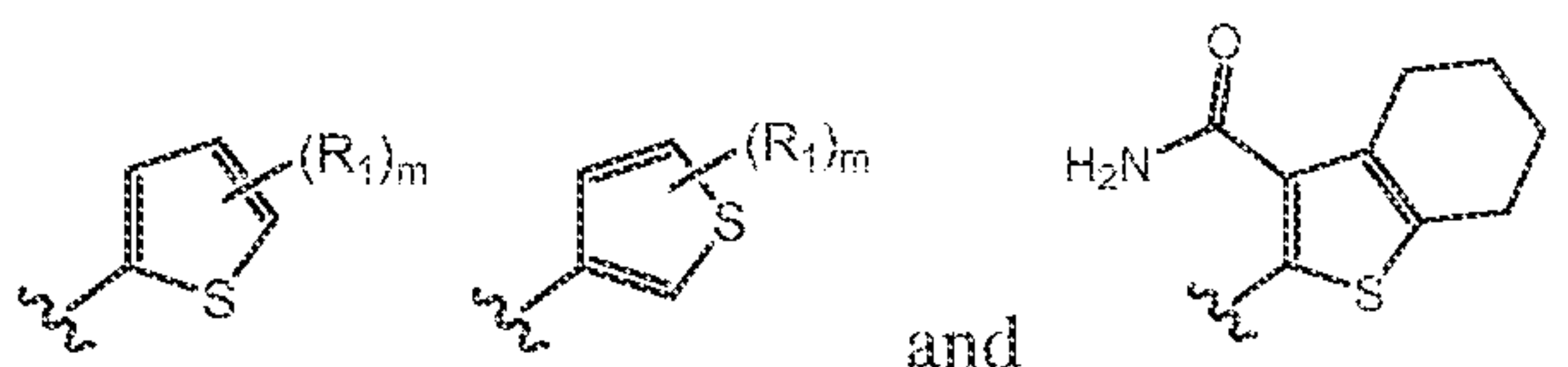


In some embodiments, m is 2.

In some embodiments, one R^1 is C_1 - C_8 alkyl (e.g., methyl) and the other is aryl (e.g., phenyl). In some embodiments, the aryl is phenyl substituted with 1 R^6 . In some embodiments, R^6 is halo (e.g., chloro). In some embodiments, R^1 is:



In some embodiments, B is thienyl. In some embodiments, B is selected from:



In some embodiments, m is 1. In some embodiments, m is 2. In some embodiments m is 2 and two R^1 , together with the atoms to which they are attached, form an optionally substituted cyclyl, heterocyclyl, aryl or heteroaryl ring

In some embodiments, R^1 is $-C(O)OR^a$. In some embodiments, R^a is C_1 - C_8 alkyl (e.g., ethyl).

In some embodiments, R^1 is $-C(Y)NR^bR^{b'}$. In some embodiments, Y is O. In some embodiments, R^b and $R^{b'}$ are both hydrogen.

In some embodiments, m is 2.

In some embodiments, one R^1 is C_1 - C_8 alkyl (e.g., methyl) and the other is $-C(Y)NR^bR^{b'}$. In some embodiments, Y is O. In some embodiments, R^b and $R^{b'}$ are both hydrogen.

In some embodiments, B is thiazolyl.

In some embodiments, m is 1.

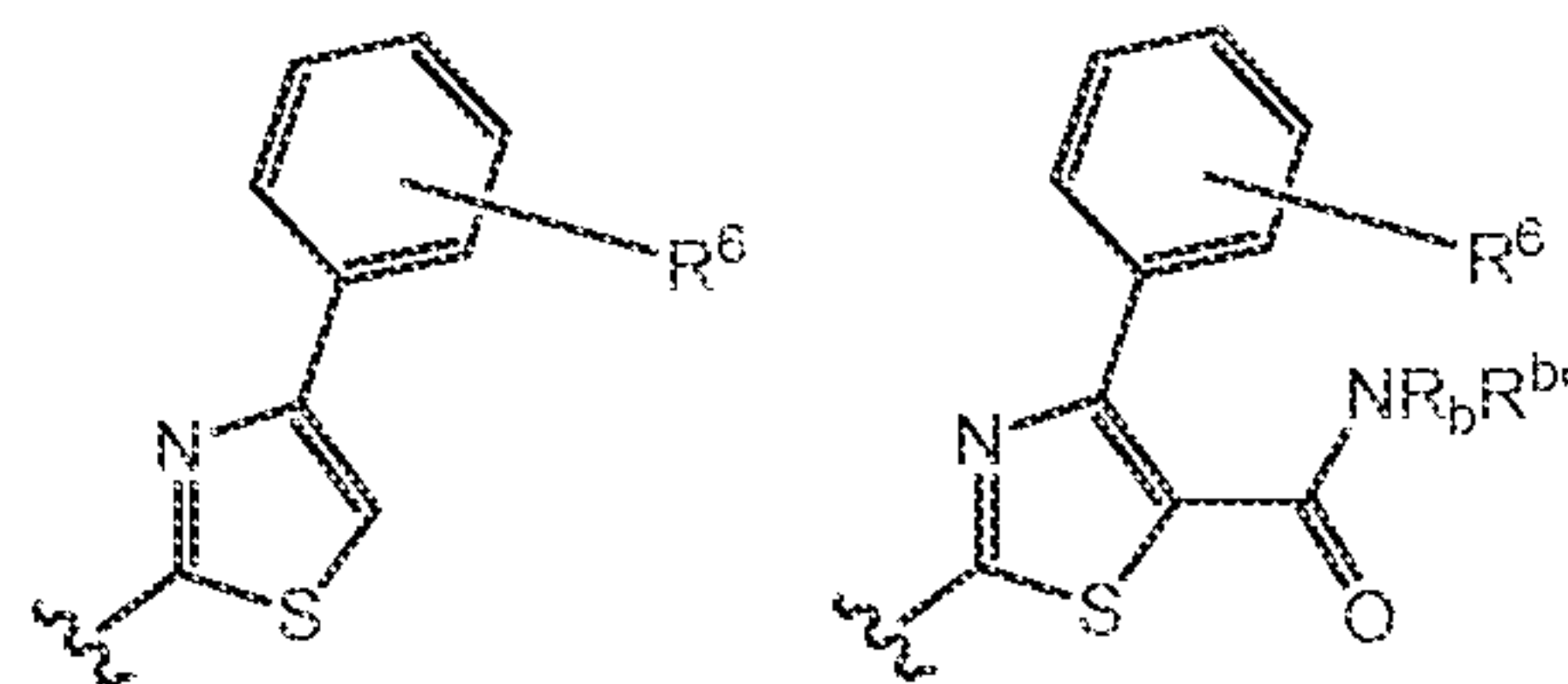
In some embodiments, R^1 is aryl (e.g., phenyl).

In some embodiments, m is 2.

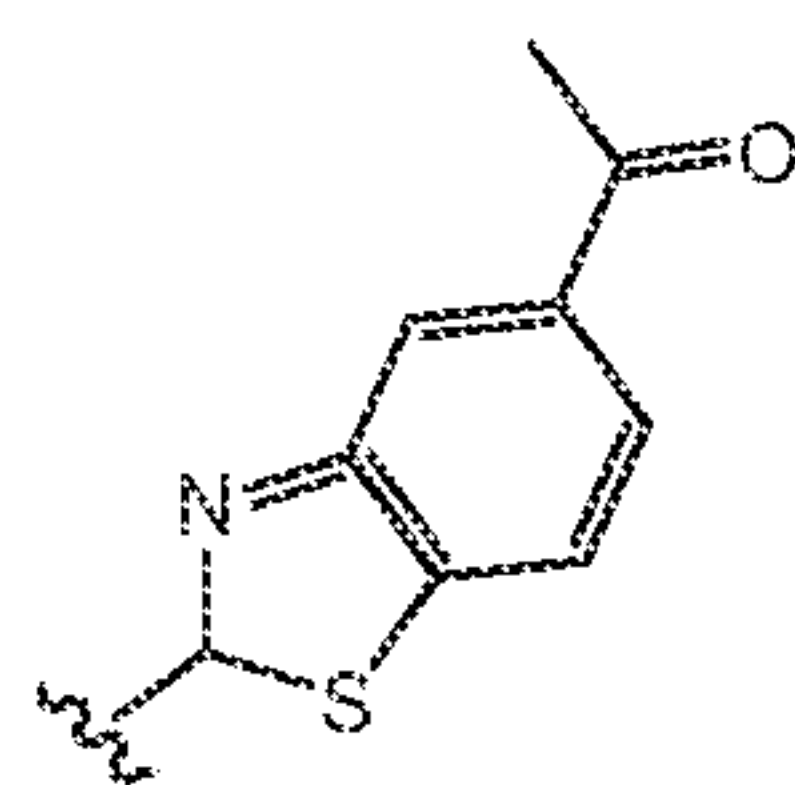
In some embodiments, two R^1 , together with the atoms to which they are attached, form an aryl ring. In some embodiments, the aryl ring is substituted with --

$C(Y)R^c$. In some embodiments, Y is O. In some embodiments, R^c is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, B is:



In some embodiments, B is:



In some embodiments, E is aryl (e.g., phenyl).

In some embodiments, n is 1.

In some embodiments, R^2 is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, R^2 is C_1 - C_8 alkyl substituted with 1-3 R^6 . In some embodiments, R^2 is C_1 alkyl substituted with 1 R^6 .

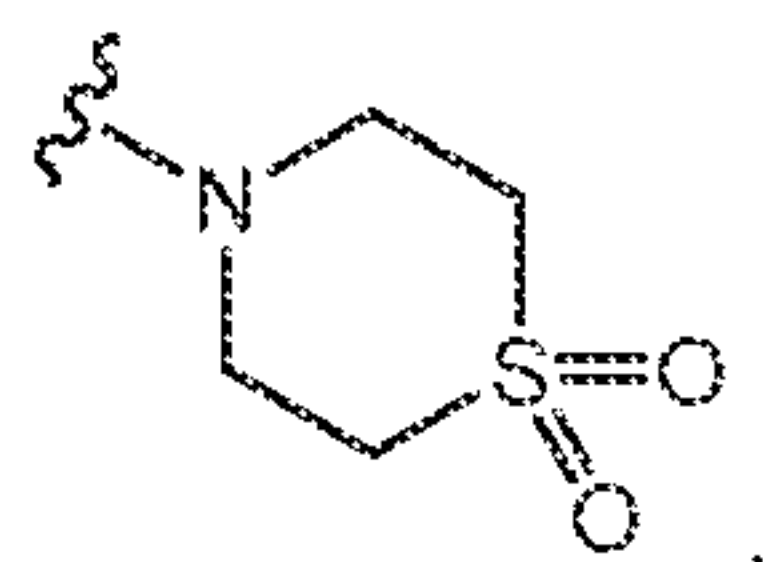
In some embodiments, R^6 is $-NR^b R^{b'}$. In some embodiments, R^b and $R^{b'}$ are each independently C_1 - C_8 alkyl (e.g., R^b and $R^{b'}$ are both methyl, or R^b and $R^{b'}$ are both ethyl). In some embodiments, one of R^b and $R^{b'}$ is hydrogen and the other is haloalkyl (e.g., trifluoroethyl).

In some embodiments, R^6 is $-OR^d$. In some embodiments, R^d is cyclyl (e.g., cyclopentyl). In some embodiments, R^d is heterocyclalkyl (e.g., $-CH_2$ -tetrahydropyranyl).

In some embodiments, R^2 is C_2 alkyl substituted with 1 R^6 .

In some embodiments, R^6 is $-C(Y)NR^b R^{b'}$. In some embodiments, Y is O. In some embodiments, R^b and $R^{b'}$ are both hydrogen. In some embodiments, R^b and $R^{b'}$ are each independently C_1 - C_8 alkyl (e.g., R^b and $R^{b'}$ are both methyl). In some embodiments, one of R^b and $R^{b'}$ is hydrogen and the other is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, R^6 is $-C(Y)R^e$. In some embodiments, Y is O. In some embodiments, R^e is heterocyclyl (e.g., morpholino or thiomorpholino). In some embodiments, R^e is thiomorpholino substituted with 2 R^6 . In some embodiments, each R^6 is oxo. In some embodiments, R^e is:



In some embodiments, R^2 is C_3 alkyl substituted with 1 R^6 .

In some embodiments, R^6 is $-C(Y)NR^bR^{b'}$. In some embodiments, Y is O. In some embodiments, R^b and $R^{b'}$ are both hydrogen. In some embodiments, R^b and $R^{b'}$ are each independently C_1 - C_8 alkyl (e.g., R^b and $R^{b'}$ are both methyl). In some embodiments, one of R^b and $R^{b'}$ is hydrogen and the other is C_1 - C_8 alkyl (e.g., methyl).

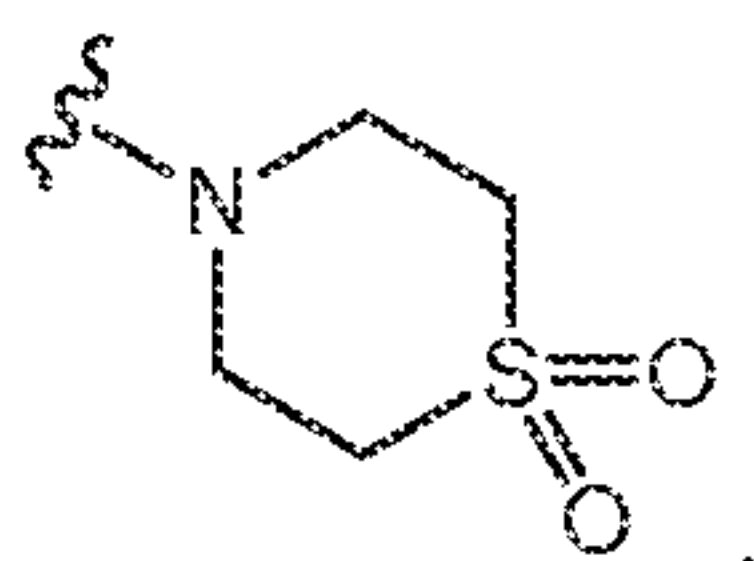
In some embodiments, R^6 is $-NR^cC(Y)R^{c'}$. In some embodiments, Y is O. In some embodiments, R^c and $R^{c'}$ are each independently C_1 - C_8 alkyl (e.g., R^c and $R^{c'}$ are both methyl).

In some embodiments, R^6 is $-OR^d$. In some embodiments, R^d is hydrogen. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, R^6 is silyloxy (e.g., tert-butyldimethylsilyloxy).

In some embodiments, R^6 is $-C(Y)R^e$. In some embodiments, Y is O. In some embodiments, R^e is heterocyclyl (e.g., morpholino).

In some embodiments, R^2 is C_2 - C_8 alkynyl. In some embodiments, R^2 is C_2 - C_8 alkynyl substituted with 1 R^6 (e.g., C_3 alkynyl substituted with 1 R^6). In some embodiments, R^2 is $-C\equiv C-CH_2-R^6$. In some embodiments, R^6 is $-NR^bR^{b'}$. In some embodiments, R^b and $R^{b'}$ are each independently C_1 - C_8 alkyl (e.g., R^b and $R^{b'}$ are both methyl). In some embodiments, R^6 is $-OR^d$. In some embodiments, R^d is hydrogen. In some embodiments, R^6 is silyloxy (e.g., tert-butyldimethylsilyloxy). In some embodiments, R^6 is heterocyclyl (e.g., morpholino or thiomorpholino). In some embodiments, R^6 is thiomorpholino substituted with 2 R^7 . In some embodiments, each R^7 is oxo. In some embodiments, R^6 is:



In some embodiments, R^2 is aryl (e.g., phenyl). In some embodiments, R^2 is unsubstituted phenyl.

In some embodiments, R^2 is phenyl substituted with 1 R^6 .

In some embodiments, R^6 is heterocyclalkyl (e.g., $-\text{CH}_2$ -morpholino). In some embodiments, R^6 is haloalkyl (e.g., trifluoromethyl). In some embodiments, R^6 is $-\text{CN}$. In some embodiments, R^6 is $-\text{OR}^d$. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, R^6 is $-\text{C}(\text{Y})\text{R}^e$. In some embodiments, Y is O. In some embodiments, R^e is heterocyclalkyl (e.g., morpholino).

In some embodiments, R^2 is phenyl substituted with 2 R^6 .

In some embodiments, each R^6 is independently $-\text{OR}^d$. In some embodiments, each R^d is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, one R^6 is halo (e.g., fluoro) and the other is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, one R^6 is $-\text{C}(\text{O})\text{OR}^a$ and the other is $-\text{OR}^d$. In some embodiments, R^a and R^d are each independently C_1 - C_8 alkyl (e.g., R^a and R^d are both methyl).

In some embodiments, R^2 is heteroaryl.

In some embodiments, R^2 is isoxazolyl. In some embodiments, R^2 is isoxazolyl substituted with 2 R^6 . In some embodiments, each R^6 is independently C_1 - C_8 alkyl (e.g., R^6 is methyl).

In some embodiments, R^2 is pyrazolyl. In some embodiments, R^2 is pyrazolyl substituted with 1 R^6 . In some embodiments, R^6 is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, R^2 is pyridyl. In some embodiments, R^2 is unsubstituted pyridyl. In some embodiments, R^2 is pyridyl substituted with 1 R^6 . In some embodiments, R^6 is halo (e.g., fluoro). In some embodiments, R^6 is $-\text{NR}^b\text{R}^{b'}$. In some embodiments, R^b and $R^{b'}$ are each hydrogen. In some embodiments, R^6 is $-\text{OR}^d$. In some embodiments, R^d is hydrogen. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, R^6 is heterocyclalkyl (e.g., morpholino or piperazinyl). In some embodiments, R^6 is piperazinyl substituted with 1 R^7 . In some embodiments, R^7 is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, R^2 is pyrimidinyl.

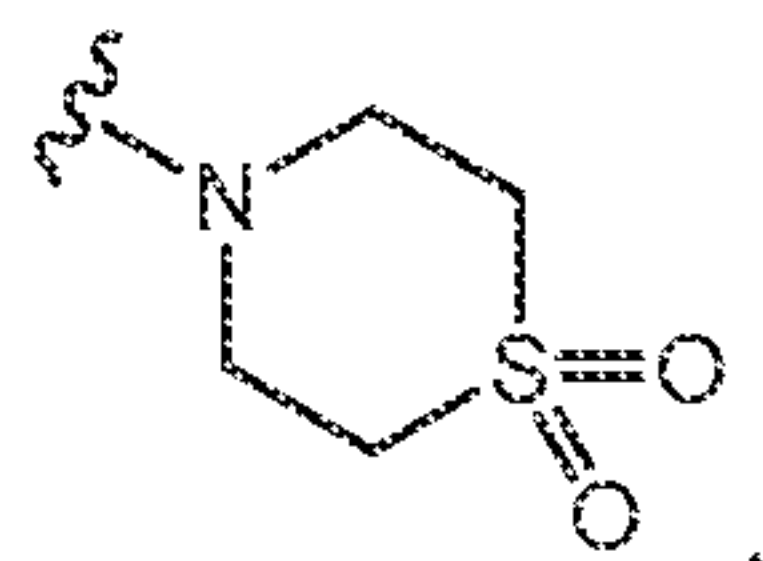
In some embodiments, R^2 is pyridazinyl.

In some embodiments, R^2 is cyclyl (e.g., cyclopropyl).

In some embodiments, R^2 is heterocyclyl (e.g., morpholino or pyrrolidinyl).

In some embodiments, R^2 is aralkyl (e.g., benzyl).

In some embodiments, R^2 is heterocyclylalkyl. In some embodiments, the alkyl is C_1 alkyl. In some embodiments, the alkyl is C_2 alkyl. In some embodiments, the alkyl is C_3 alkyl. In some embodiments, the heterocyclyl is piperidinyl. In some embodiments, the heterocyclyl is piperazinyl. In some embodiments, the heterocyclyl is piperazinyl substituted with 1 R^6 . In some embodiments, R^6 is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, the heterocyclyl is pyrrolidinyl. In some embodiments, the heterocyclyl is morpholino. In some embodiments, the heterocyclyl is thiomorpholino. In some embodiments, the heterocyclyl is thiomorpholino substituted with 2 R^6 . In some embodiments, each R^6 is oxo. In some embodiments, the heterocyclyl is:



In some embodiments, R^2 is halo (e.g., fluoro, chloro, bromo or iodo).

In some embodiments, R^2 is haloalkyl (e.g., trifluoromethyl).

In some embodiments, R^2 is haloalkoxy (e.g., trifluoromethoxy).

In some embodiments, R^2 is $-CN$.

In some embodiments, R^2 is $-NO_2$.

In some embodiments, R^2 is $-C(O)OR^a$. In some embodiments, R^a is hydrogen. In some embodiments, R^a is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, R^2 is $-C(Y)NR^bR^{b'}$. In some embodiments, Y is O . In some embodiments, R^b and $R^{b'}$ are each hydrogen. In some embodiments, R^b and $R^{b'}$ are each independently C_1 - C_8 alkyl (e.g., R^b and $R^{b'}$ are both methyl). In some embodiments, one of R^b and $R^{b'}$ is hydrogen and the other is C_1 - C_8 alkyl (e.g., methyl or ethyl). In some embodiments, the C_1 - C_8 alkyl is ethyl substituted with 2 R^6 . In some embodiments, each R^6 is independently $-OR^d$. In some embodiments, each R^d

is C₁-C₈ alkyl (e.g., each R^d is methyl). In some embodiments, one of R^b and R^{b'} is hydrogen and the other is heterocyclalkyl (e.g., -CH₂-CH₂-morpholino). In some embodiments, one of R^b and R^{b'} is hydrogen and the other is haloalkyl (e.g., trifluoroethyl).

In some embodiments, R² is -NR^bR^{b'}. In some embodiments, R^b and R^{b'} are both hydrogen. In some embodiments, R^b and R^{b'} are each independently C₁-C₈ alkyl (e.g., R^b and R^{b'} are both methyl). In some embodiments, one of R^b and R^{b'} is hydrogen and the other is C₁-C₈ alkyl (e.g., methyl). In some embodiments, one of R^b and R^{b'} is hydrogen and the other is heterocycl (e.g., tetrahydropyranyl). In some embodiments, one of R^b and R^{b'} is hydrogen and the other is heterocyclalkyl. In some embodiments, the alkyl is C₁ alkyl. In some embodiments, the alkyl is C₂ alkyl. In some embodiments, the alkyl is C₃ alkyl. In some embodiments, the heterocycl is morpholino. In some embodiments, the heterocycl is pyrrolidinyl. In some embodiments, the heterocycl is tetrahydrofuranyl. In some embodiments, the heterocycl is tetrahydropyranyl. In some embodiments, one of R^b and R^{b'} is hydrogen and the other is hydroxyalkyl. In some embodiments, the alkyl is C₂ alkyl. In some embodiments, one of R^b and R^{b'} is hydrogen and the other is alkoxyalkyl. In some embodiments, the alkyl is C₂ alkyl. In some embodiments, the alkyl is C₃ alkyl. In some embodiments, the alkoxy is methoxy. In some embodiments, one of R^b and R^{b'} is hydrogen and the other is -C(Y)R^e. In some embodiments, Y is O. In some embodiments, R^e is C₁-C₈ alkyl (e.g., methyl). In some embodiments, R^e is heterocycl. In some embodiments, R^e is tetrahydropyranyl.

In some embodiments, R² is -OR^d.

In some embodiments, R^d is hydrogen. In some embodiments, R^d is C₁-C₈ alkyl (e.g., methyl). In some embodiments, R^d is methyl substituted with 1 R⁶. In some embodiments, R⁶ is -C(Y)R^e. In some embodiments, Y is O. In some embodiments, R^e is heterocycl (e.g., morpholino). In some embodiments, R⁶ is -C(Y)NR^bR^{b'}. In some embodiments, Y is O. In some embodiments, R^b and R^{b'} are each independently C₁-C₈ alkyl (e.g., R^b and R^{b'} are both methyl or R^b and R^{b'} are both ethyl). In some embodiments, one of R^b and R^{b'} is hydrogen and the other is C₁-C₈ alkyl (e.g., methyl or ethyl).

In some embodiments, R^d is ethyl. In some embodiments, R^d is C_3 alkyl (e.g., isopropyl or n-propyl). In some embodiments, R^d is optionally substituted heteroaralkyl. In some embodiments, R^d is optionally substituted pyrindinalkyl.

In some embodiments, R^d is n-propyl substituted with 1 R^6 . In some embodiments, R^6 is $-NR^cC(Y)R^{c'}$. In some embodiments, Y is O. In some embodiments, R^c and $R^{c'}$ are each independently C_1 - C_8 alkyl (e.g., R^c and $R^{c'}$ are both methyl). In some embodiments, R^d is cyclyl (e.g., cyclopentyl).

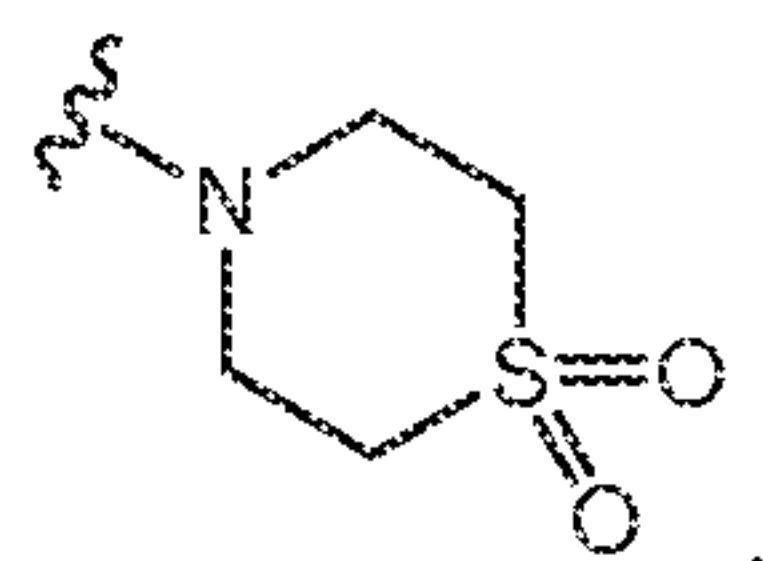
In some embodiments, R^d is heteroaralkyl (e.g., $-\text{CH}_2$ -pyridyl). In some embodiments, the pyridyl is substituted with 1 R^6 . In some embodiments, R^6 is alkyl (e.g., methyl) or haloalkyl (e.g., CF_3). In some embodiments, R^6 is $-\text{OR}^d$. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, R^d is heterocyclylalkyl. In some embodiments, the alkyl is C_1 alkyl. In some embodiments, the alkyl is C_2 alkyl. In some embodiments, the alkyl is C_3 alkyl. In some embodiments, the alkyl is C_4 alkyl. In some embodiments, the heterocyclyl is morpholino. In some embodiments, the heterocyclyl is piperidinyl. In some embodiments, the heterocyclyl is tetrahydrofuranyl. In some embodiments, R^d is cyclylalkyl (e.g., $-\text{CH}_2$ -cyclobutyl).

In some embodiments, R^d is alkoxyalkyl. In some embodiments, the alkyl is C_2 alkyl. In some embodiments, the alkyl is C_3 alkyl. In some embodiments, the alkoxy is methoxy.

In some embodiments, R^d is dialkylaminoalkyl. In some embodiments, the alkyl is C_2 alkyl. In some embodiments, the alkyl is C_3 alkyl. In some embodiments, the dialkylamino is dimethylamino.

In some embodiments, R^2 is $-\text{C}(Y)R^c$. In some embodiments, Y is O. In some embodiments, R^c is heterocyclyl. In some embodiments, R^c is piperidinyl. In some embodiments, R^c is pyrrolidinyl. In some embodiments, R^c is piperazinyl. In some embodiments, R^c is piperazinyl substituted with 1 R^6 . In some embodiments, R^6 is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, R^c is morpholino. In some embodiments, R^c is thiomorpholino. In some embodiments, R^c is thiomorpholino substituted with 2 R^6 . In some embodiments, each R^6 is oxo. In some embodiments, R^c is:



In some embodiments, n is 2.

In some embodiments, each R^2 is independently halo (e.g., each R^2 is chloro).

In some embodiments, each R^2 is independently $-OR^d$.

In some embodiments, each R^d is C_1 - C_8 alkyl.

In some embodiments, each R^2 is methoxy. In some embodiments, one R^2 is methoxy and the other is ethoxy. In some embodiments, one R^2 is methoxy and the other is propoxy. In some embodiments, one R^2 is methoxy and the other is isopropoxy.

In some embodiments, one R^2 is methoxy and the other is ethoxy substituted with 1 R^6 . In some embodiments, R^6 is $-NR^bR^{b'}$. In some embodiments, R^b and $R^{b'}$ are each independently C_1 - C_8 alkyl (e.g., R^b and $R^{b'}$ are both methyl). In some embodiments, R^6 is $-OR^d$. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, one R^2 is methoxy and the other is propoxy substituted with 1 R^6 . In some embodiments, R^6 is $-OR^d$. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, one R^2 is $-OR^d$ and the other is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl or ethyl).

In some embodiments, one R^2 is $-OR^d$ and the other is halo (e.g., chloro). In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, one R^2 is $-OR^d$ and the other is $-CN$. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, one R^2 is $-OR^d$ and the other is $-C(O)OR^a$. In some embodiments, R^d and R^a are both hydrogen.

In some embodiments, one R^2 is $-OR^d$ and the other is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, one R^2 is $-OR^d$ and the other is $-C(Y)R^e$. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, Y is O. In some embodiments, R^e is heterocyclyl (e.g., morpholino).

In some embodiments, one R^2 is halo (e.g., chloro or bromo) and the other is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, one R^2 is C_1 - C_8 alkyl (e.g., methyl) and the other is -CN.

In some embodiments, one R^2 is C_1 - C_8 alkyl (e.g., methyl) and the other is heteroaryl (e.g., pyridyl). In some embodiments, the pyridyl is substituted with 1 R^6 . In some embodiments, R^6 is $-OR^d$. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, one R^2 is C_1 - C_8 alkyl (e.g., methyl) and the other is heterocyclalkyl (e.g., $-CH_2$ -morpholino).

In some embodiments, p is 0.

In some embodiments, p is 1.

In some embodiments, R^3 is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, R^3 is halo (e.g., chloro). In some embodiments, R^3 is haloalkyl (e.g., trifluoromethyl). In some embodiments, R^3 is oxo.

In some embodiments, R^3 is $-OR^d$. In some embodiments, R^d is hydrogen. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, R^3 is $-NR^bR^{b'}$. In some embodiments, R^b and $R^{b'}$ are both hydrogen. In some embodiments, one of R^b and $R^{b'}$ is hydrogen and the other is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, R^3 is heterocycl (e.g., piperazinyl). In some embodiments, R^3 is piperazinyl substituted with 1 R^6 . In some embodiments, R^6 is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, E is a 5-membered heteroaryl ring.

In some embodiments, E is a thiophene ring.

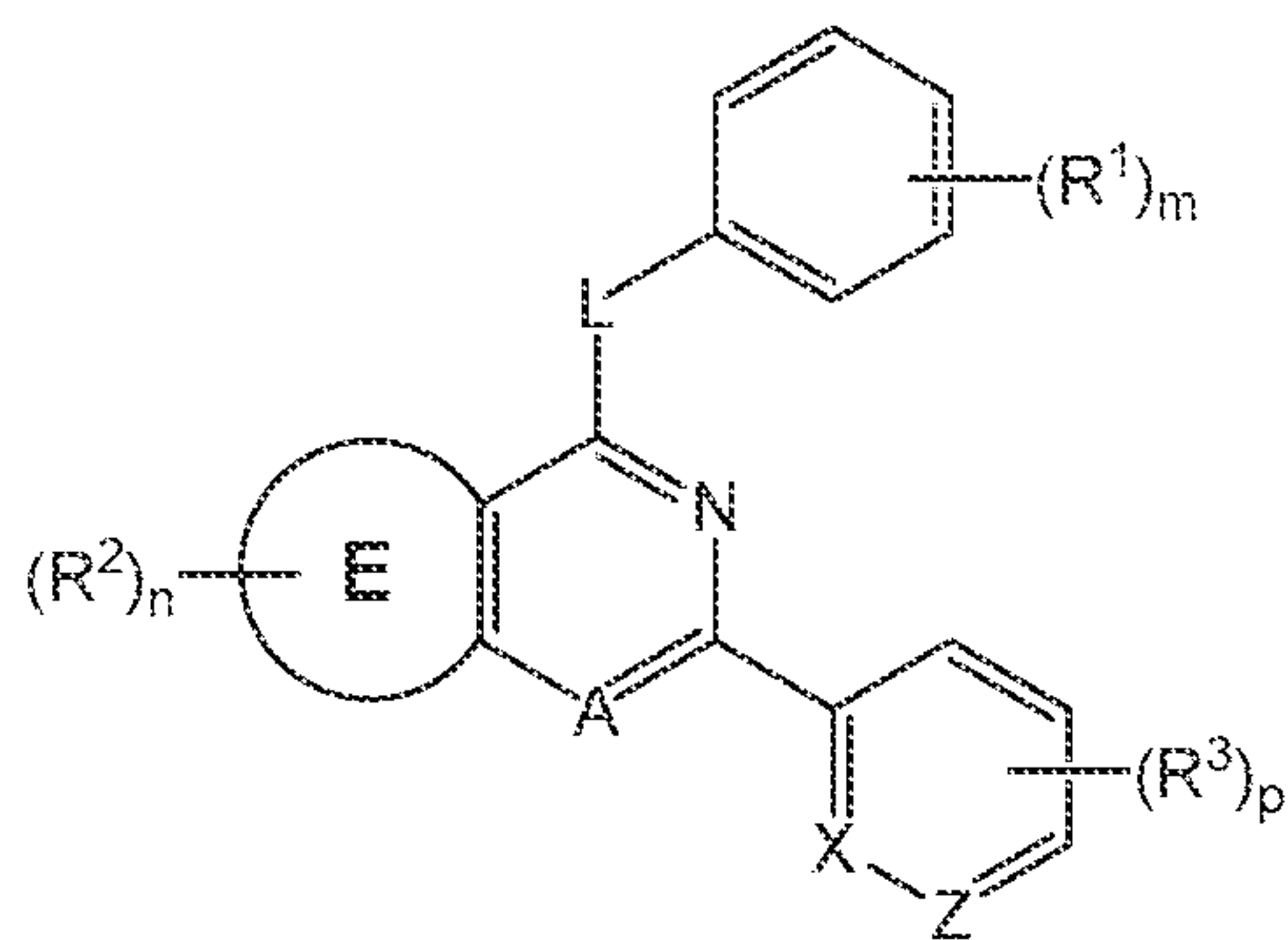
In some embodiments, E is a pyrrole ring.

In some embodiments, n is 1. In some embodiments, R^2 is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, E is an N-methylpyrrole ring.

In some embodiments, L is NR^5 . In some embodiments, R^5 is hydrogen.

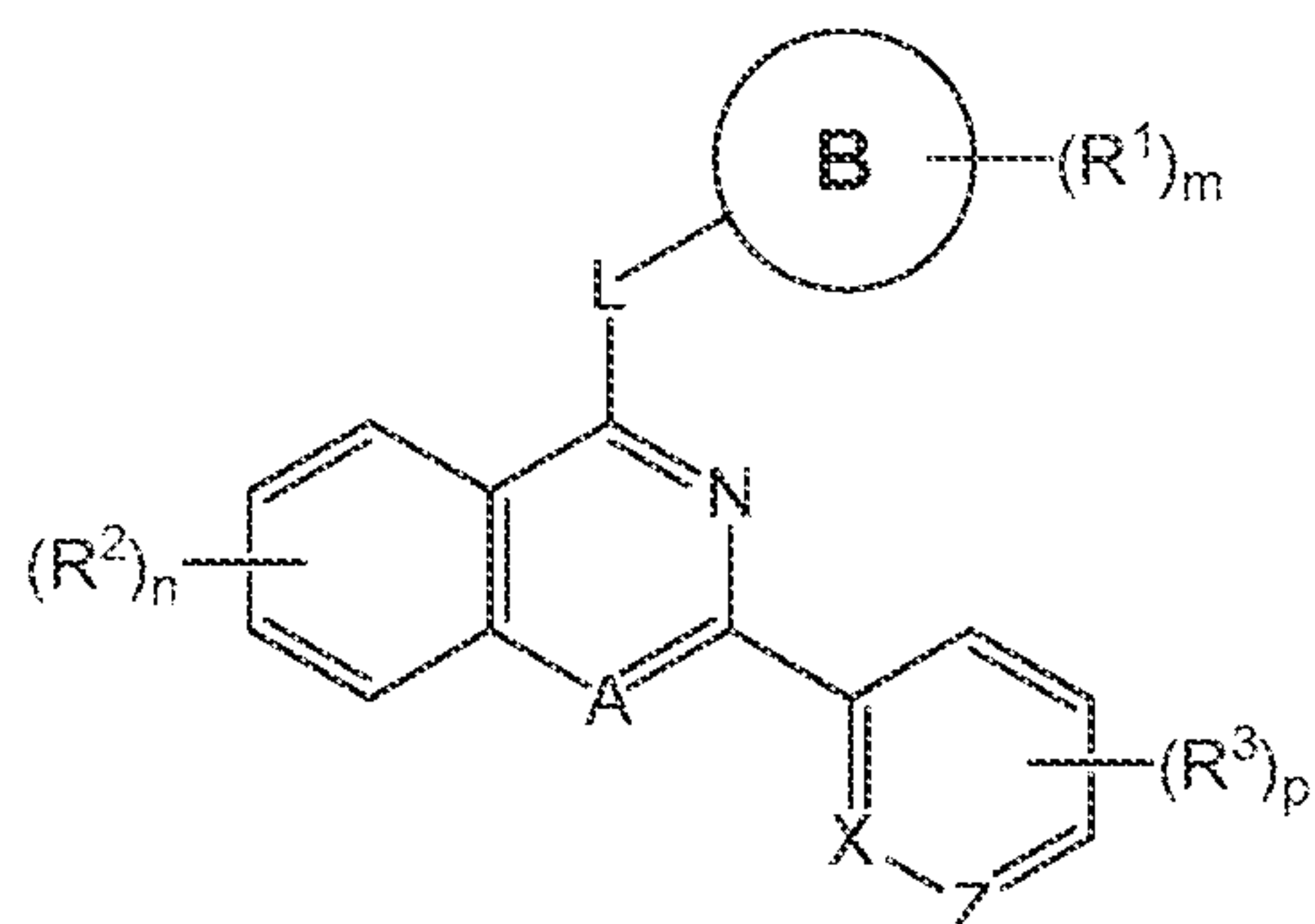
In some embodiments, L is O.

In some embodiments, the compound is:

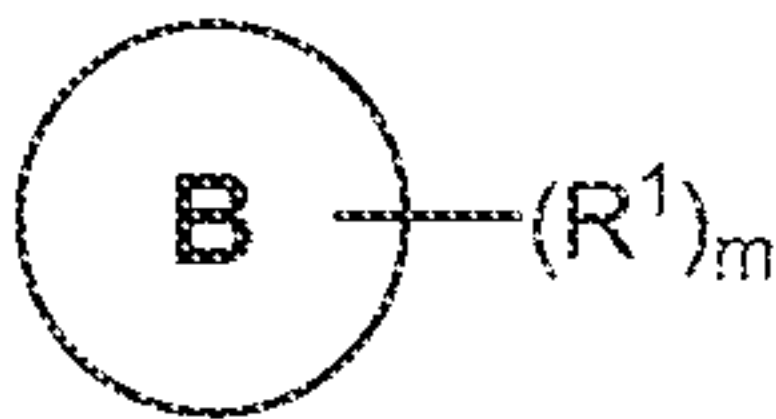
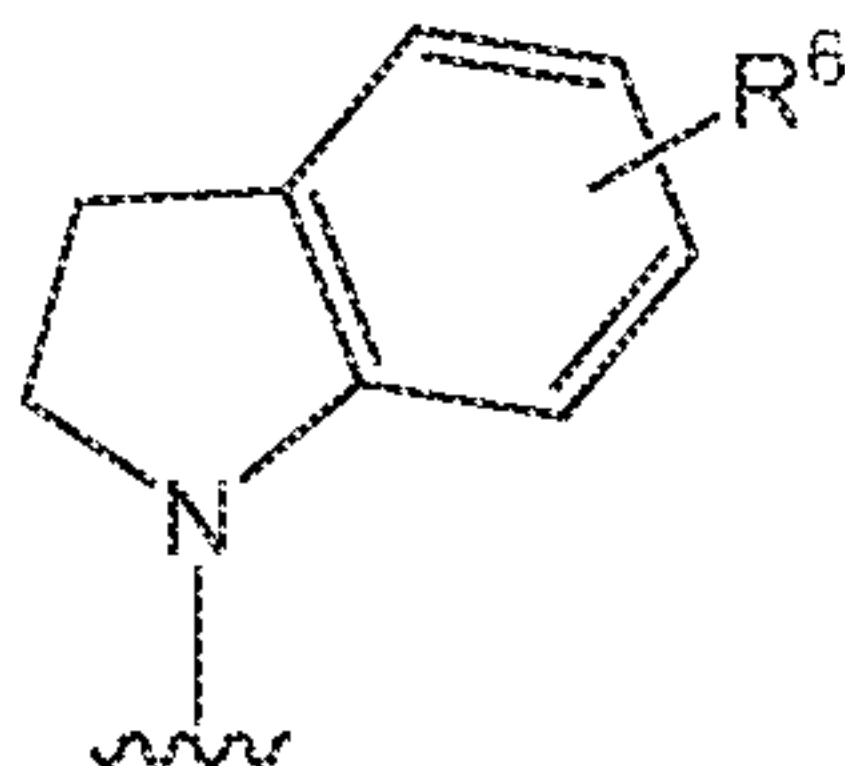


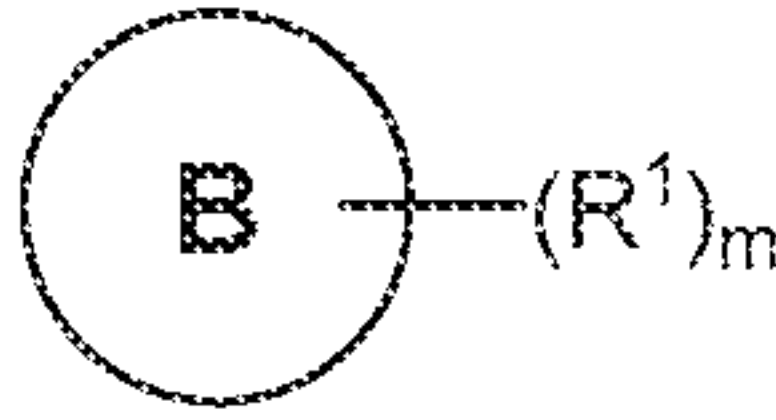
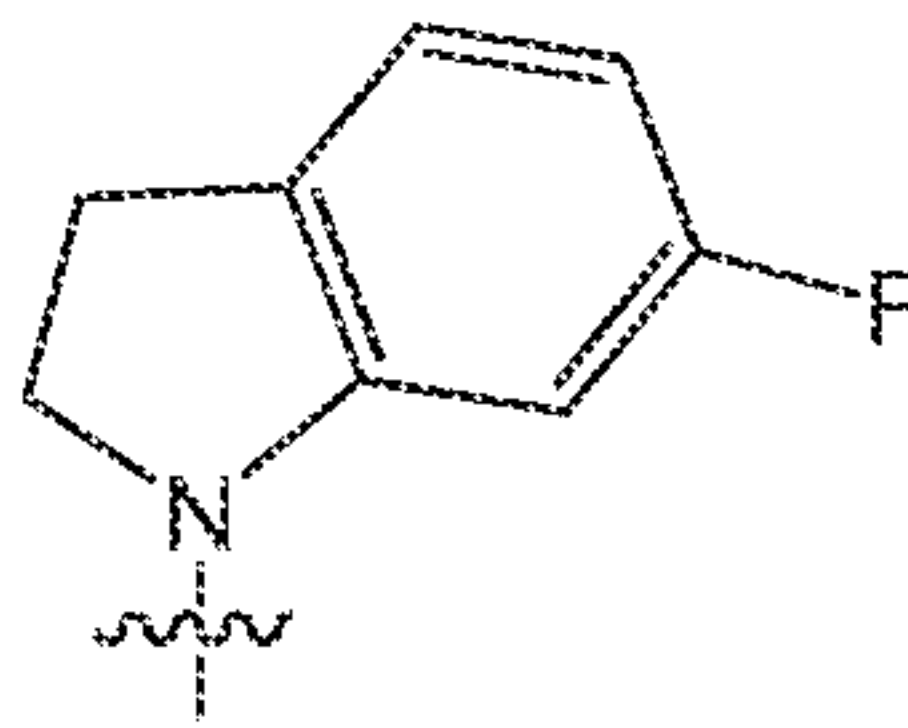
In some embodiments, R^2 is C_1 - C_4 alkoxy. In some embodiments, R^2 is halo. In some embodiments, R^1 is $-C(Y)NR^bR^{b'}$.

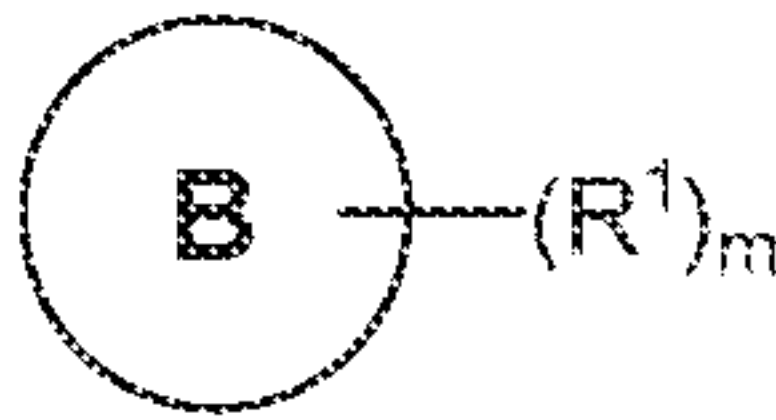
In some embodiments, the compound is:

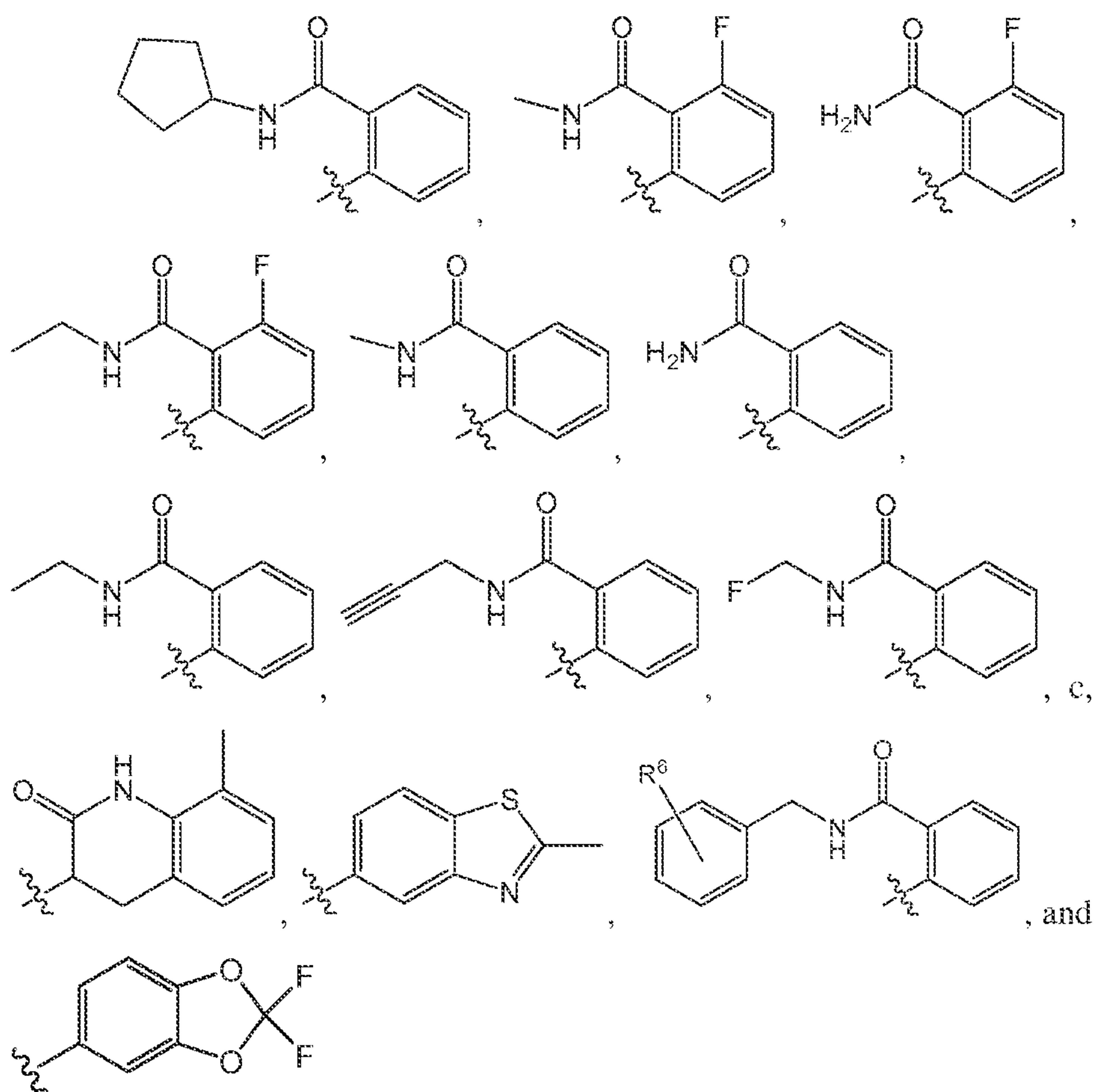


In some embodiments, R^2 is C_1 - C_4 alkoxy. In some embodiments, R^2 is halo. In some embodiments, R^1 is $-C(Y)NR^bR^{b'}$.

In some embodiments, L and  are . In some

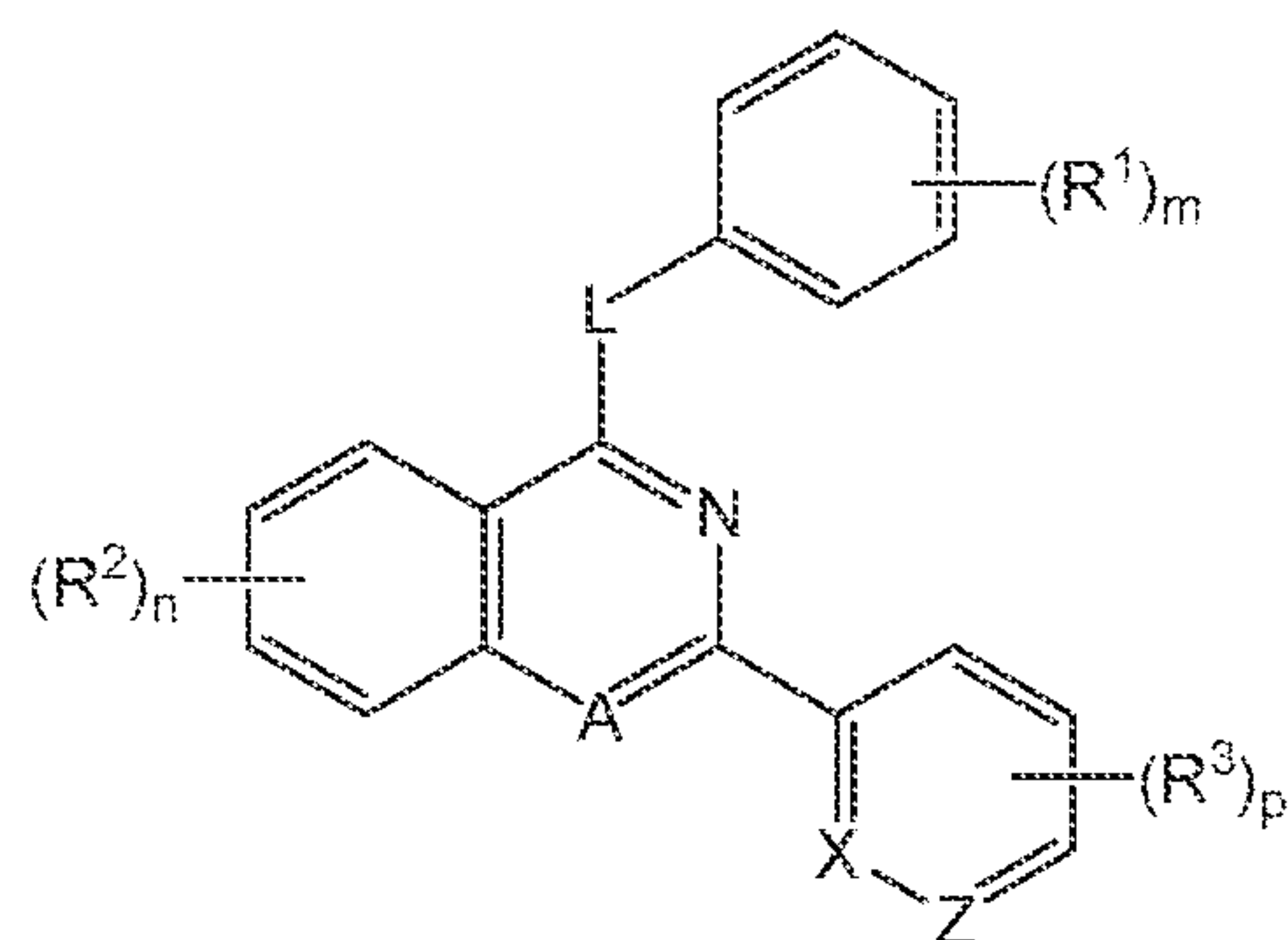
embodiments, L and  are . In some embodiments,

L is NH, and  is selected from



In some embodiments R^6 is halo. In some embodiments, R^b or $R^{b'}$ are disubstituted with R^6 (e.g., dichloro, 4-fluoro, 3-chloro, or difluoro).

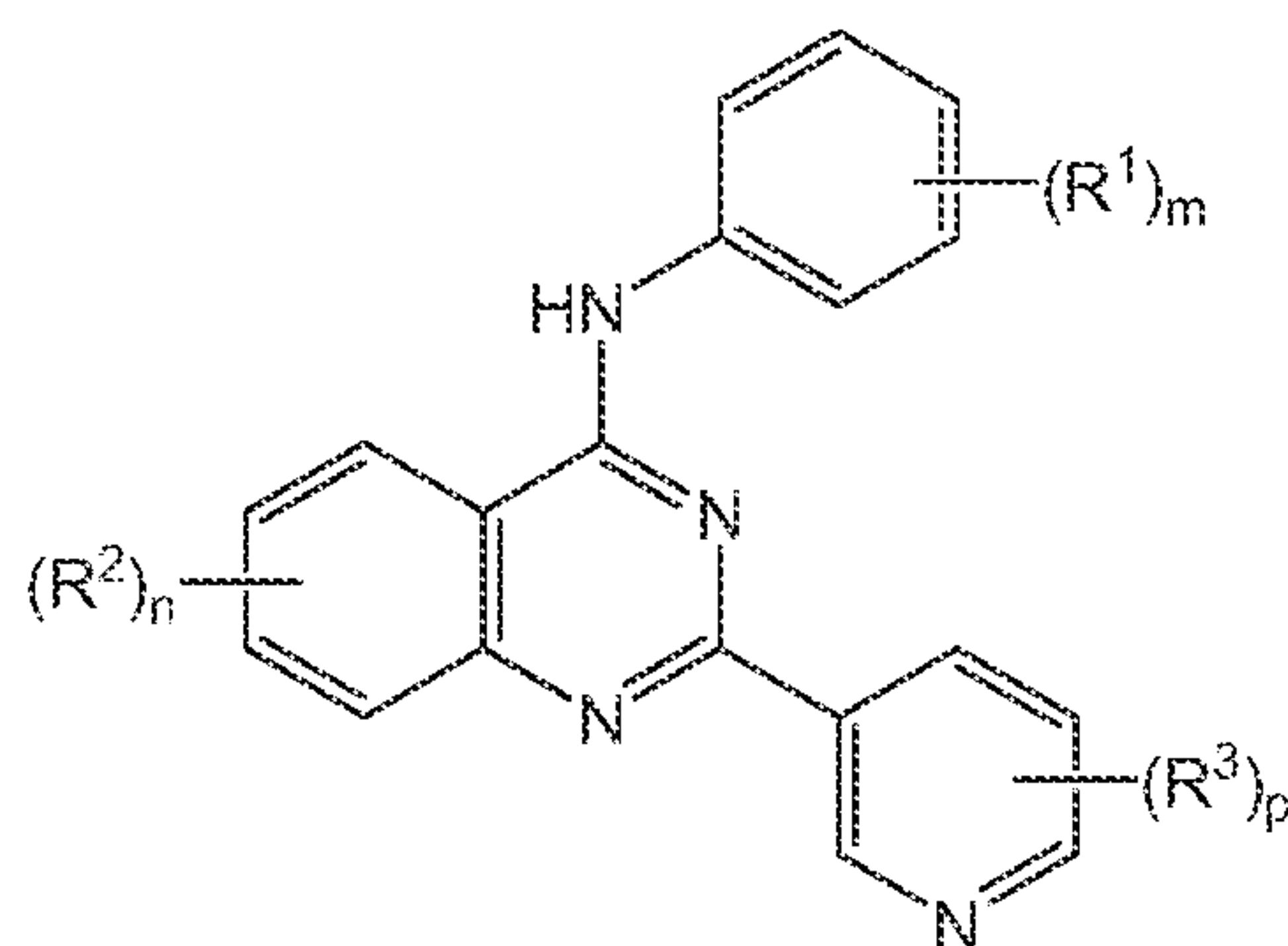
In some embodiments, the compound is:



In some embodiments, R^1 is $-C(Y)NR^bR^{b'}$. In some embodiments, R^1 is halo. In some embodiments, R^2 is C_1 - C_4 alkoxy. In some embodiments, R^2 is halo. In some

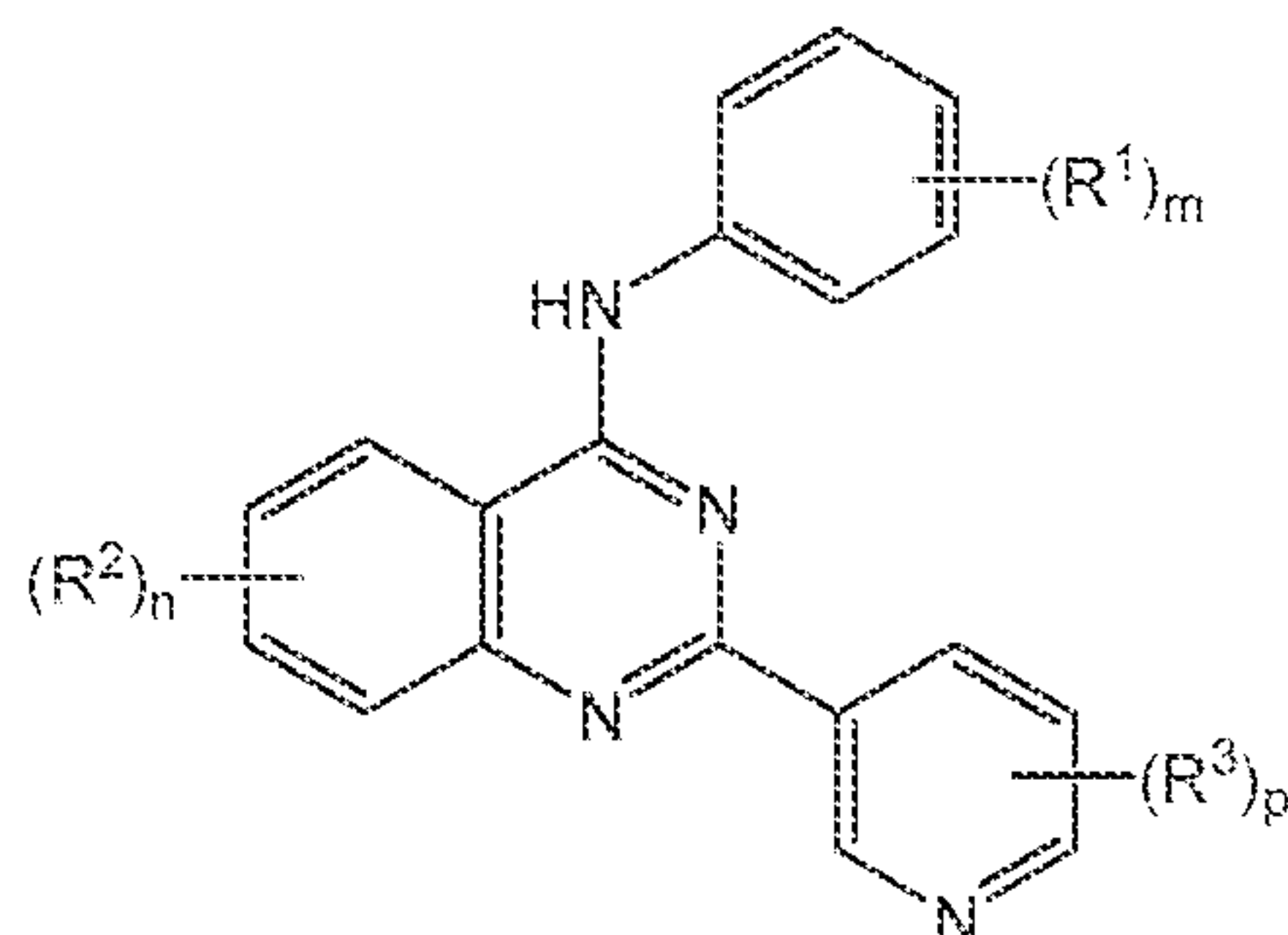
embodiments, m is 2 and two R^1 are 3,4-dichloro; 3,4-difluoro, 3,5- dichloro; 3,5-difluoro; 3-chloro,4-fluoro; or 3-chloro,5-fluoro. In some embodiments, R^2 is— $C(O)NR^bR^{b'}$ and R^3 is H. In some embodiments, R^b and $R^{b'}$ are H. In some embodiments, R^b and $R^{b'}$ are independently C_1 - C_4 alkyl or halo-substituted C_1 - C_4 alkyl. In some embodiments, R^b is methyl and $R^{b'}$ is trifluoroethyl. In some embodiments, R^1 is C_1 - C_4 alkoxy or halo-substituted C_1 - C_4 alkoxy. In some embodiments, n and p are zero.

In some embodiments, the compound is:



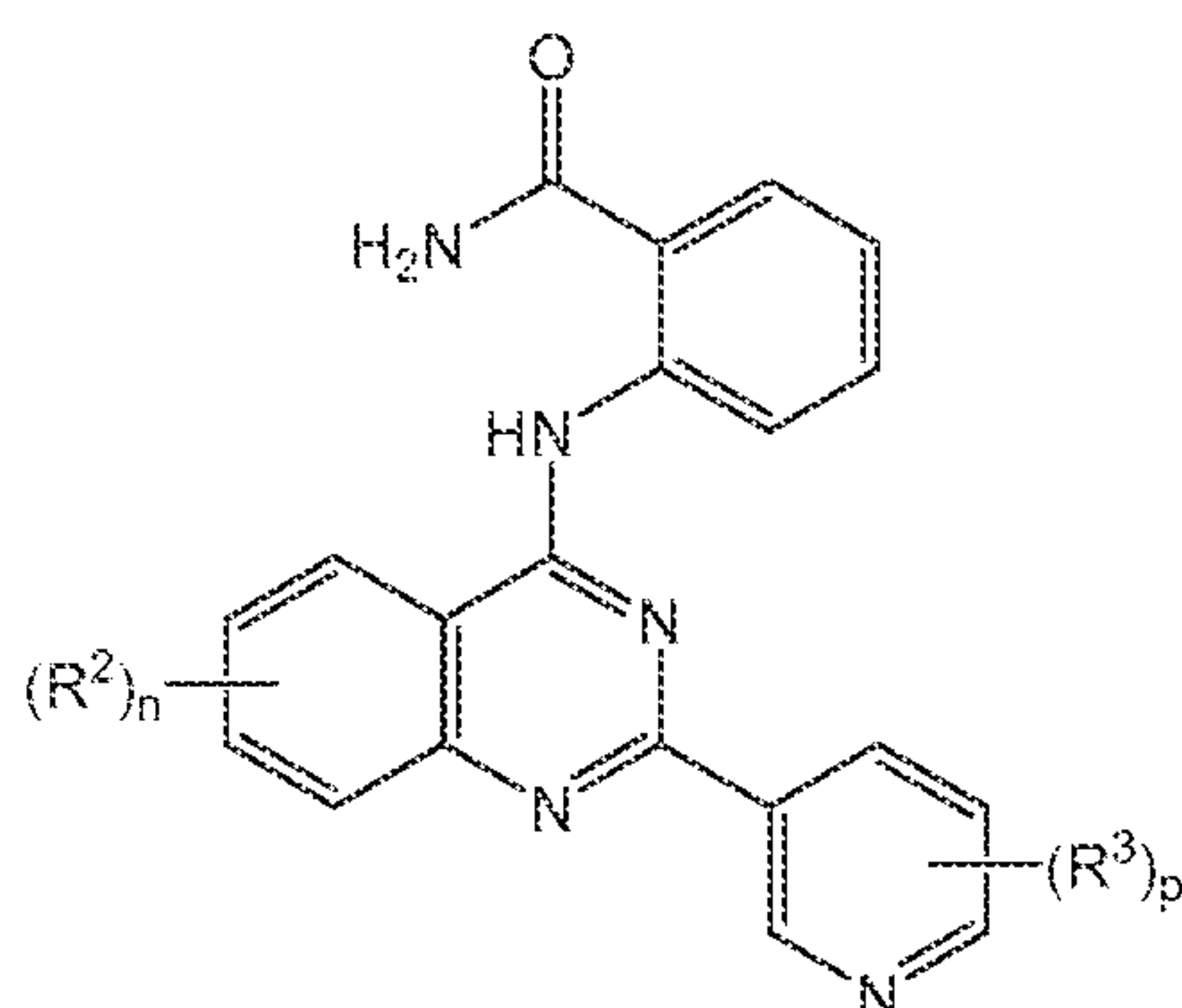
In some embodiments, R^1 is $-C(Y)NR^bR^{b'}$. In some embodiments, R^1 is halo. In some embodiments, R^2 is C_1 - C_4 alkoxy. In some embodiments, R^2 is halo. In some embodiments, m is 2 and two R^1 are 3,4-dichloro; 3,4-difluoro, 3,5- dichloro; 3,5-difluoro; 3-chloro,4-fluoro; or 3-chloro,5-fluoro. In some embodiments, R^2 is— $C(O)NR^bR^{b'}$ and R^3 is H. In some embodiments, R^b and $R^{b'}$ are H. In some embodiments, R^b and $R^{b'}$ are independently C_1 - C_4 alkyl or halo-substituted C_1 - C_4 alkyl. In some embodiments, R^b is methyl and $R^{b'}$ is trifluoroethyl. In some embodiments, R^1 is C_1 - C_4 alkoxy or halo-substituted C_1 - C_4 alkoxy. In some embodiments, n and p are zero.

In some embodiments, the compound is:



In some embodiments, R^1 is $-C(Y)NR^bR^{b'}$. In some embodiments, R^1 is halo. In some embodiments, R^2 is C_1 - C_4 alkoxy. In some embodiments, R^2 is halo. In some embodiments, m is 2 and two R^1 are 3,4-dichloro; 3,4-difluoro, 3,5- dichloro; 3,5-difluoro; 3-chloro,4-fluoro; or 3-chloro,5-fluoro. In some embodiments, R^2 is $-C(O)NR^bR^{b'}$ and R^3 is H. In some embodiments, R^b and $R^{b'}$ are H. In some embodiments, R^b and $R^{b'}$ are independently C_1 - C_4 alkyl or halo-substituted C_1 - C_4 alkyl. In some embodiments, R^b is methyl and $R^{b'}$ is trifluoroethyl. In some embodiments, R^1 is C_1 - C_4 alkoxy or halo-substituted C_1 - C_4 alkoxy. In some embodiments, n and p are zero.

In some embodiments, the compound is:



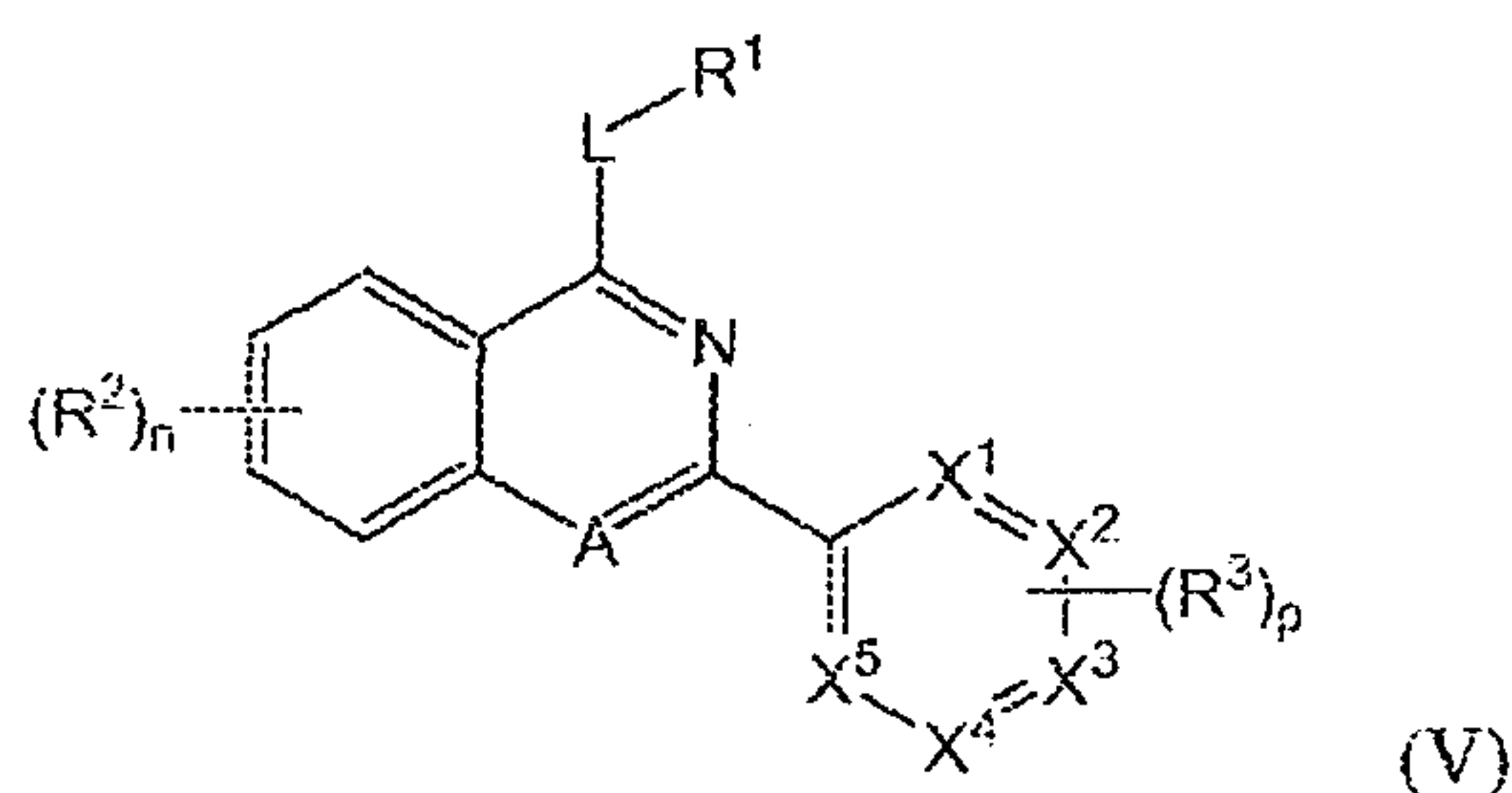
In some embodiments, R^1 is $-C(Y)NR^bR^{b'}$. In some embodiments, R^1 is halo. In some embodiments, R^2 is C_1 - C_4 alkoxy. In some embodiments, R^2 is halo. In some embodiments, m is 2 and two R^1 are 3,4-dichloro; 3,4-difluoro, 3,5- dichloro; 3,5-difluoro; 3-chloro,4-fluoro; or 3-chloro,5-fluoro. In some embodiments, R^2 is $-C(O)NR^bR^{b'}$ and R^3 is H. In some embodiments, R^b and $R^{b'}$ are H. In some embodiments, R^b and $R^{b'}$ are independently C_1 - C_4 alkyl or halo-substituted C_1 - C_4 alkyl. In some embodiments, R^b is methyl and $R^{b'}$ is trifluoroethyl. In some

embodiments, R^1 is C_1 - C_4 alkoxy or halo-substituted C_1 - C_4 alkoxy. In some embodiments, n and p are zero.

Compounds of Formula (V)

The following aspects and embodiments relate to compounds of formula (V).

Item 40. A compound of formula (V):



wherein:

L is CR^4R^5 , O , $C(O)$, $NR^6C(O)$, or NR^7 ;

A is CR^8 , CH or N ;

each X^1 , X^2 , X^3 , X^4 and X^5 is independently CH or N , provided that at least two of X^1 , X^2 , X^3 , X^4 and X^5 are N ;

n is 0, 1, 2, 3 or 4;

p is 0, 1, 2 or 3;

R^1 is C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl or heterocyclylalkyl, each of which may be optionally substituted with 1-5 R^9 ; wherein R^3 or R^9 may optionally be taken together with one of R^4 , R^5 , R^6 or R^7 , and the atoms to which they are attached, to form a cyclyl, heterocyclyl, aryl or heteroaryl ring that is optionally substituted with 1-3 R^{10} ;

each R^2 and R^3 is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl,

dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^{c'}$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{O})\text{OR}^{c'}$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^{c'}$, $-\text{NR}^c\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^{d'}$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$; each of which is optionally substituted with 1-3 R^{11} ;

each R^4 , R^5 , R^6 and R^7 is independently H, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^{c'}$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{O})\text{OR}^{c'}$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^{c'}$, $-\text{NR}^c\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^{d'}$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$;

each R^8 , R^9 , R^{10} and R^{11} is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, oxo, thiono, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^{c'}$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{O})\text{OR}^{c'}$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^{c'}$, $-\text{NR}^c\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^{d'}$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$, each of which may be optionally further substituted; wherein two R^8 , two R^9 , two R^{10} or two R^{11} may optionally be taken together with the atoms to which they are attached to form an optionally substituted cyclyl, heterocyclyl, aryl or heteroaryl ring;

each Y is independently O or S;

q is 1 or 2; and

each R^a , R^b , $\text{R}^{b'}$, R^c , $\text{R}^{c'}$, R^d , $\text{R}^{d'}$, R^e , $\text{R}^{e'}$ and R^f is independently selected from hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, acyl, cyclyl, heterocyclyl, aryl, heteroaryl, cyclylalkyl, heterocyclylalkyl, aralkyl and heteroaralkyl, each of which may be optionally substituted with 1-3 R^8 ,

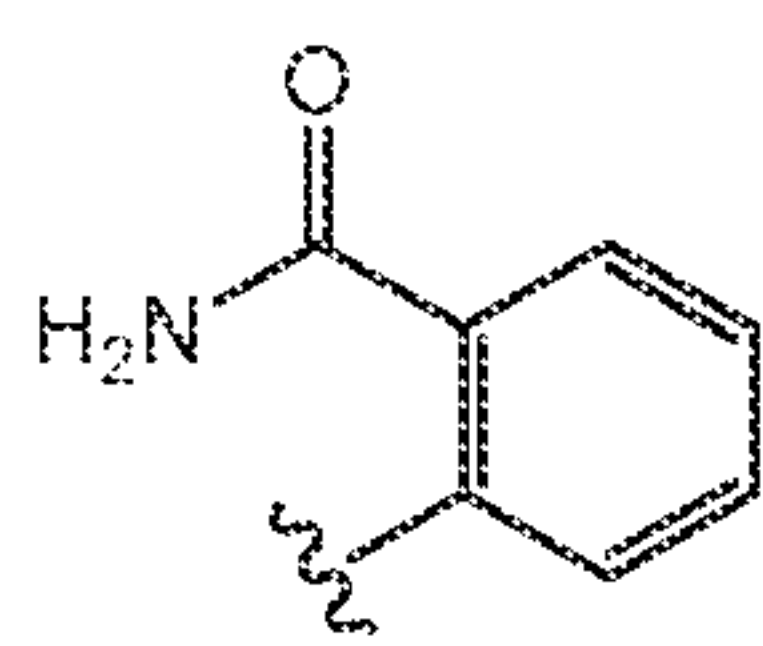
or a pharmaceutically acceptable derivative or prodrug thereof.

In some embodiments, A is CH. In some embodiments, A is N.

In some embodiments, L is NR^7 . In some embodiments, R^7 is H.

In some embodiments, R^1 is aryl (e.g., phenyl).

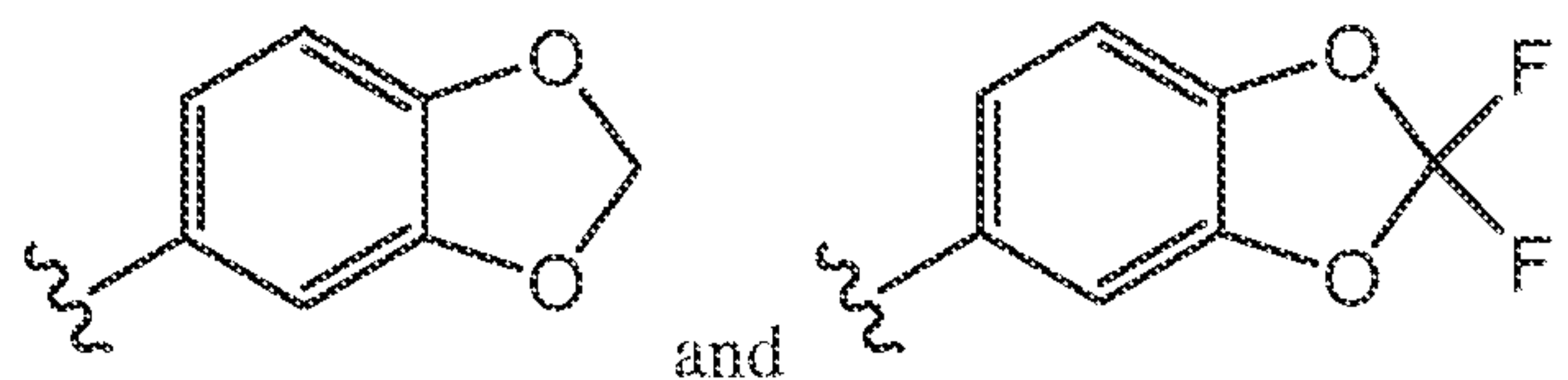
In some embodiments, R^1 is phenyl substituted with 1 R^9 . In some embodiments, R^1 is phenyl substituted with 1 R^9 in the ortho position. In some embodiments, R^1 is phenyl substituted with 1 R^9 in the meta position. In some embodiments, R^9 is haloalkoxy (e.g., difluoromethoxy or trifluoromethoxy). In some embodiments, R^9 is $-\text{CN}$. In some embodiments, R^9 is $-\text{C}(\text{O})\text{OR}^a$. In some embodiments, R^a is hydrogen. In some embodiments, R^9 is $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$. In some embodiments, Y is O. In some embodiments, R^b and $R^{b'}$ are both hydrogen. In some embodiments, R^1 is:



In some embodiments, one of R^b and $R^{b'}$ is hydrogen and the other is $\text{C}_1\text{-C}_8$ alkyl (e.g., methyl).

In some embodiments, R^1 is phenyl substituted with 2 R^9 . In some embodiments, each R^9 is independently halo (e.g., each R^9 is fluoro or each R^9 is chloro). In some embodiments, one R^9 is fluoro and the other is chloro. In some embodiments, one R^9 is halo (e.g., chloro) and the other is haloalkoxy (e.g., difluoromethoxy or trifluoromethoxy).

In some embodiments, 2 R^9 are taken together with the atoms to which they are attached to form a heterocyclyl ring, e.g., a 5-membered heterocyclyl ring (e.g., a dioxole ring). In some embodiments, the dioxole ring is unsubstituted. In some embodiments, the dioxole ring is substituted. In some embodiments, the dioxole ring is substituted with two fluoro substituents. In some embodiments, R^1 is selected from:



In some embodiments, R^1 is aralkyl (e.g., benzyl). In some embodiments, R^1 is aralkyl substituted with 2 R^9 (e.g., benzyl substituted with 2 R^9). In some

embodiments, 2 R^9 substituents are on the phenyl ring. In some embodiments, each R^9 is independently halo (e.g., each R^9 is chloro).

In some embodiments, R^1 is alkyl (e.g., methyl).

In some embodiments, n is 0.

In some embodiments, n is 1.

In some embodiments, R^2 is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, R^2 is C_1 - C_8 alkyl substituted with 1 R^{11} (e.g., methyl substituted with 1 R^{11}). In some embodiments, R^{11} is heterocyclyl (e.g., morpholino).

In some embodiments, R^2 is aryl (e.g., phenyl). In some embodiments, R^2 is phenyl substituted with 1 R^{11} . In some embodiments, R^{11} is $-CN$. In some embodiments, R^{11} is $-OR^d$. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, R^{11} is halo.

In some embodiments, R^2 is halo (e.g., fluoro, chloro, bromo or iodo).

In some embodiments, R^2 is $-NR^cC(Y)R^{c'}$. In some embodiments, R^c is hydrogen. In some embodiments, Y is O. In some embodiments, $R^{c'}$ is alkyl (e.g., methyl). In some embodiments, $R^{c'}$ is aryl (e.g., phenyl). In some embodiments, $R^{c'}$ is phenyl substituted with 1 R^8 . In some embodiments, R^8 is $-OR^d$. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, $R^{c'}$ is heteroaryl. In some embodiments, $R^{c'}$ is furanyl. In some embodiments, $R^{c'}$ is pyridyl. In some embodiments, $R^{c'}$ is pyridyl substituted with 1 R^8 . In some embodiments, R^8 is $-OR^d$. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, $R^{c'}$ is cyclyl (e.g., cyclohexyl). In some embodiments, $R^{c'}$ is cyclohexyl substituted with 1 R^8 . In some embodiments, R^8 is $-OR^d$. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, $R^{c'}$ is heterocyclyl (e.g., tetrahydropyranyl).

In some embodiments, R^2 is $-NR^bR^{b'}$. In some embodiments, R^b and $R^{b'}$ are both hydrogen. In some embodiments, R^b and $R^{b'}$ are each independently C_1 - C_8 alkyl (e.g., R^b and $R^{b'}$ are both methyl).

In some embodiments, R^2 is $-OR^d$. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl or ethyl). In some embodiments, R^d is ethyl substituted with 1 R^8 . In

some embodiments, R^8 is $-OR^d$. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, R^2 is $-OCH_2CH_2OCH_3$. In some embodiments, R^2 is $-OCH_2CH_2OCH_2CH_2CH_3$. In some embodiments, R^2 is $-OCH_2CH_2OCH_2CH_2OCH_3$.

In some embodiments, n is 2.

In some embodiments, one R^2 is C_1 - C_8 alkyl (e.g., methyl) and the other is halo (e.g., chloro).

In some embodiments, one R^2 is $-OR^d$ and the other is halo (e.g., chloro). In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl).

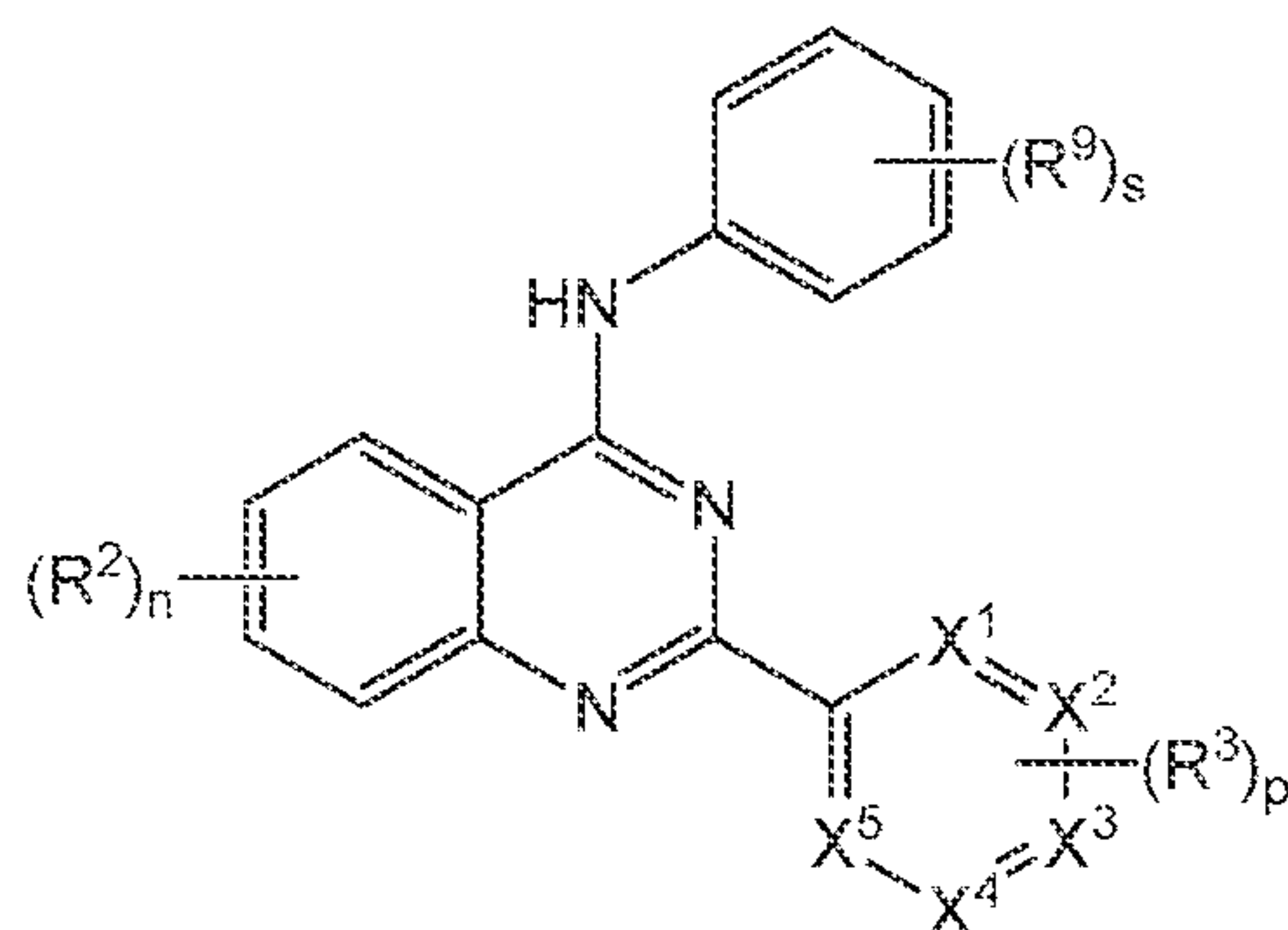
In some embodiments, X^1 and X^4 are N and X^2 , X^3 and X^5 are CH.

In some embodiments, X^1 and X^3 are N and X^2 , X^4 and X^5 are CH.

In some embodiments, X^2 and X^3 are N and X^1 , X^4 and X^5 are CH.

In some embodiments, X^2 and X^4 are N and X^1 , X^3 and X^5 are CH.

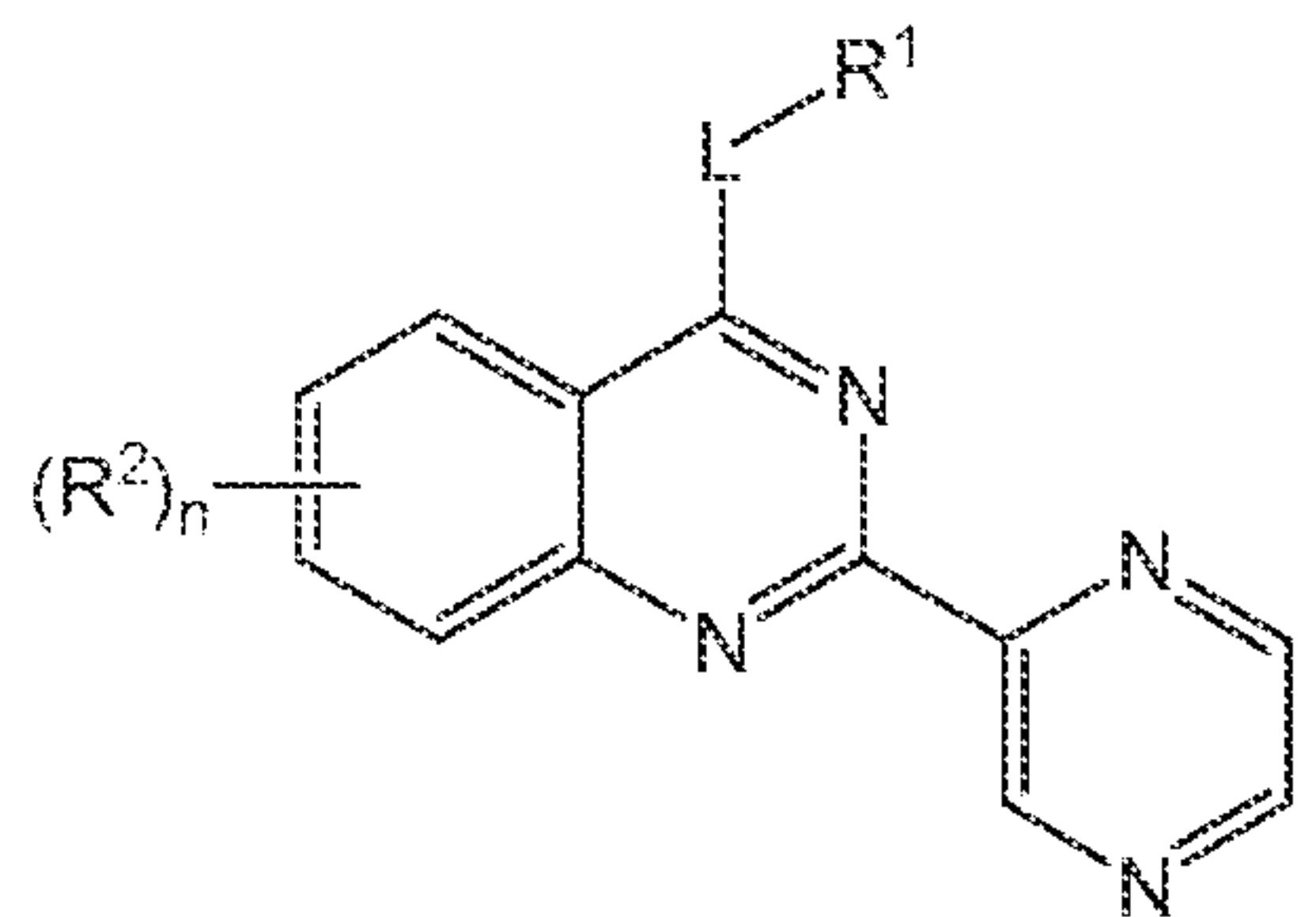
In some embodiments, the compound is:



wherein s is 0, 1, 2, 3 or 4.

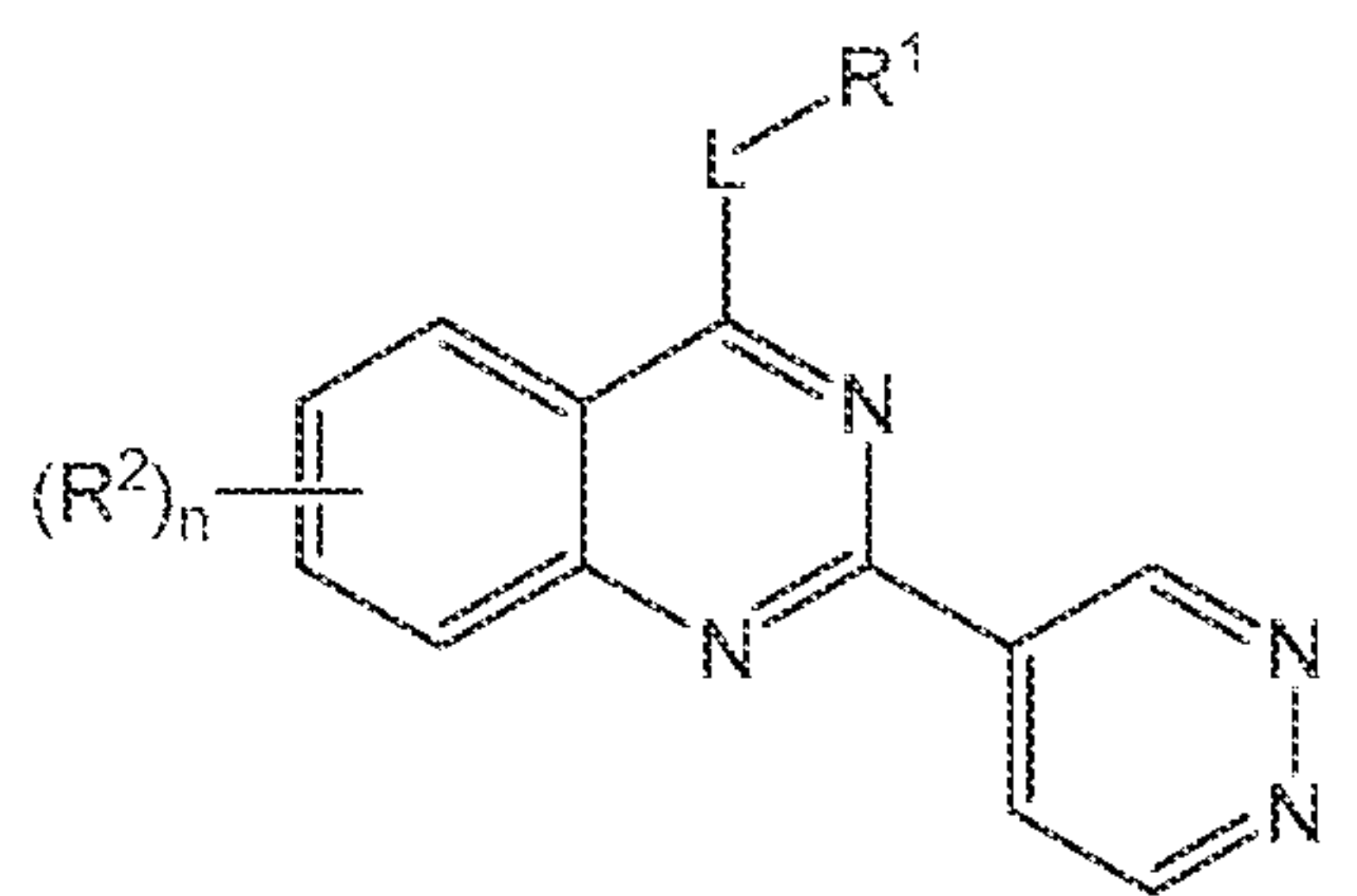
In some embodiments, R^9 is $-C(O)NH_2$, C_1 - C_4 alkoxy, or substituted C_1 - C_4 alkoxy. In some embodiments, R^9 is halo.

In some embodiments, the compound is:



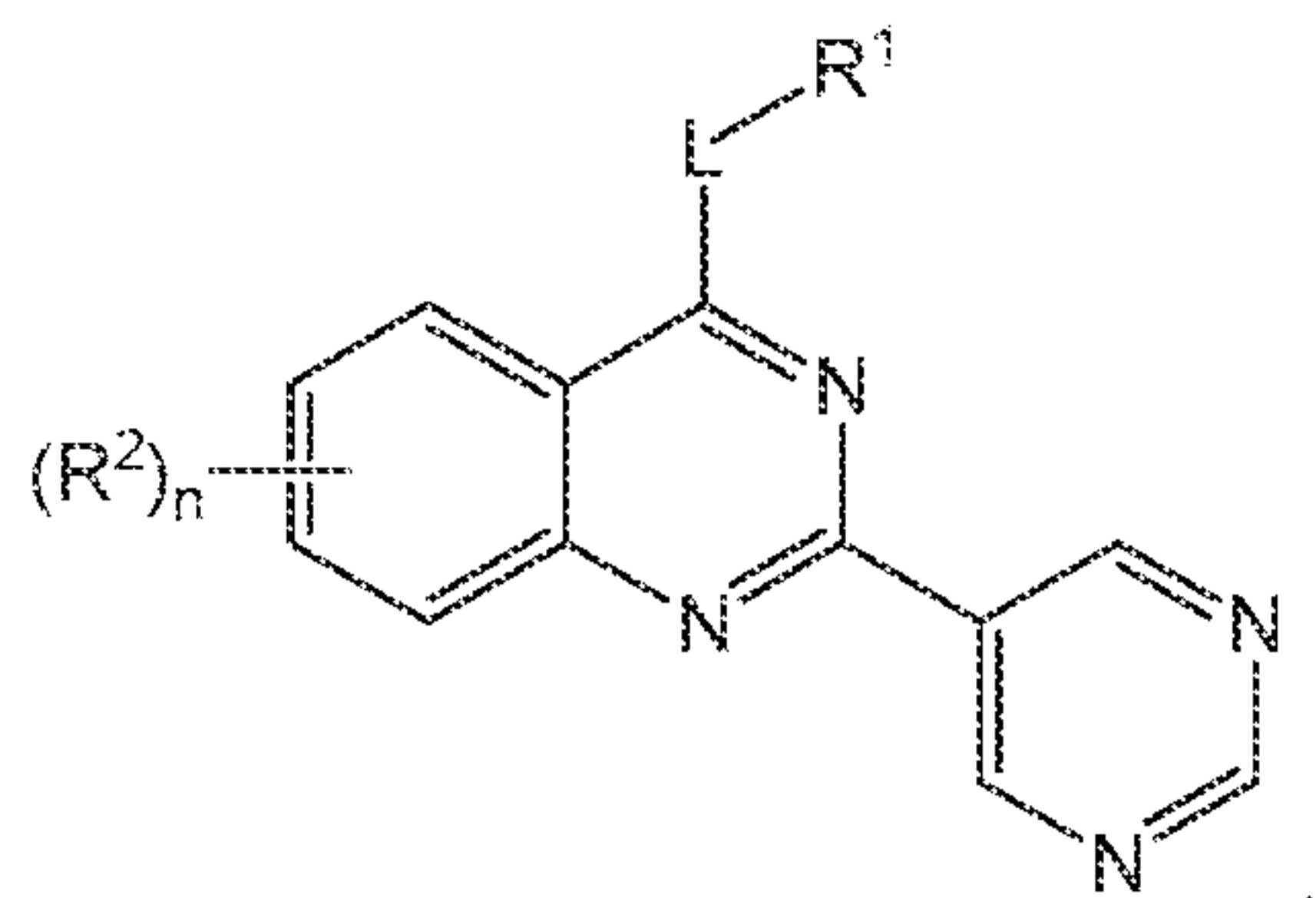
In some embodiments, R_1 is selected from methyl, cyclohexyl, t-butyl, and pyridinyl. In some embodiments, R_1 is heteroaralkyl (e.g., $-\text{CH}_2\text{-pyridyl}$). In some embodiments, LR^1 is $\text{NH}(\text{CH}_3)$.

In some embodiments, the compound is:



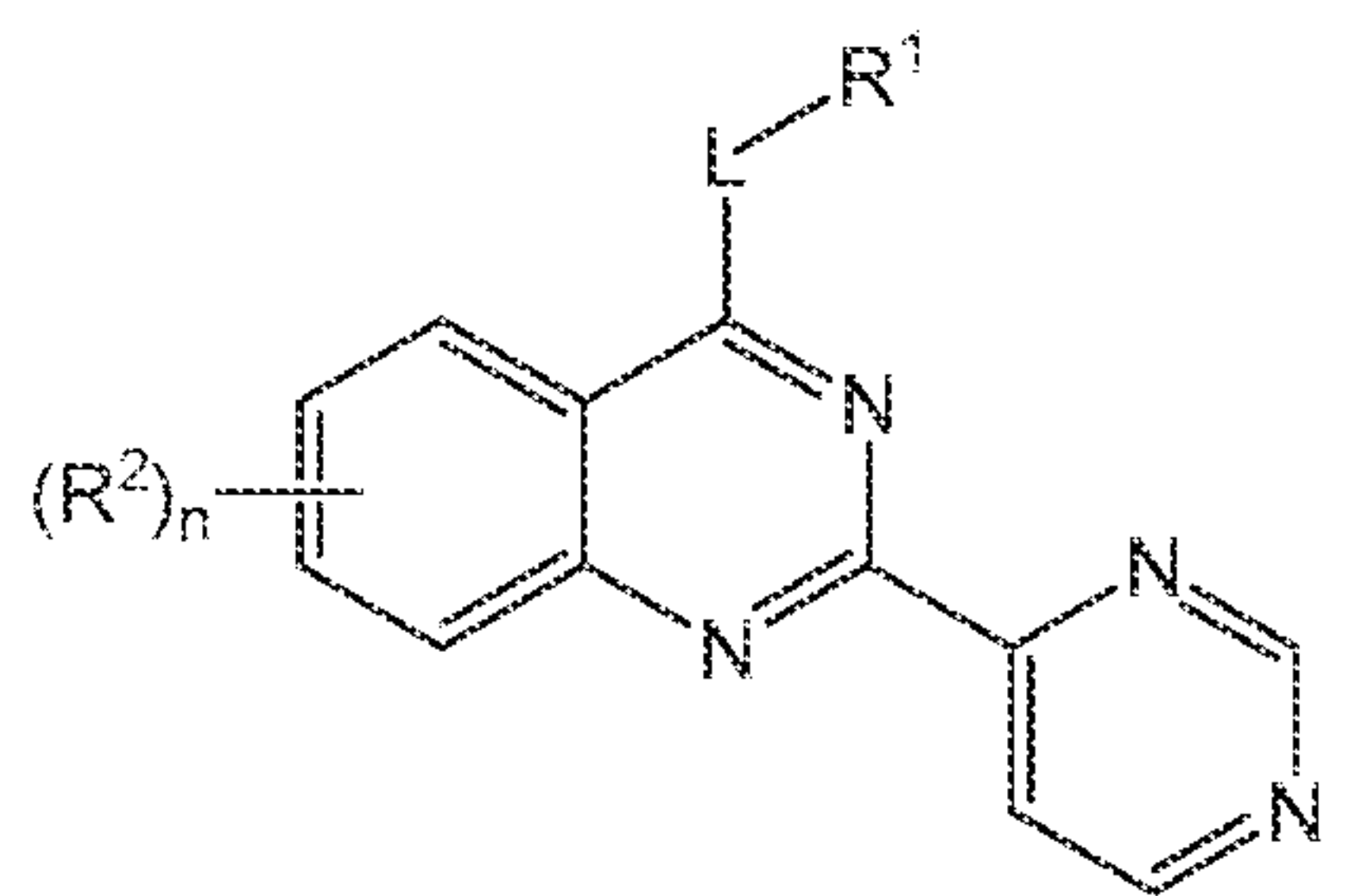
In some embodiments, R_1 is selected from methyl, cyclohexyl, t-butyl, and pyridinyl. In some embodiments, R_1 is heteroaralkyl (e.g., $-\text{CH}_2\text{-pyridyl}$). In some embodiments, LR^1 is $\text{NH}(\text{CH}_3)$.

In some embodiments, the compound is:



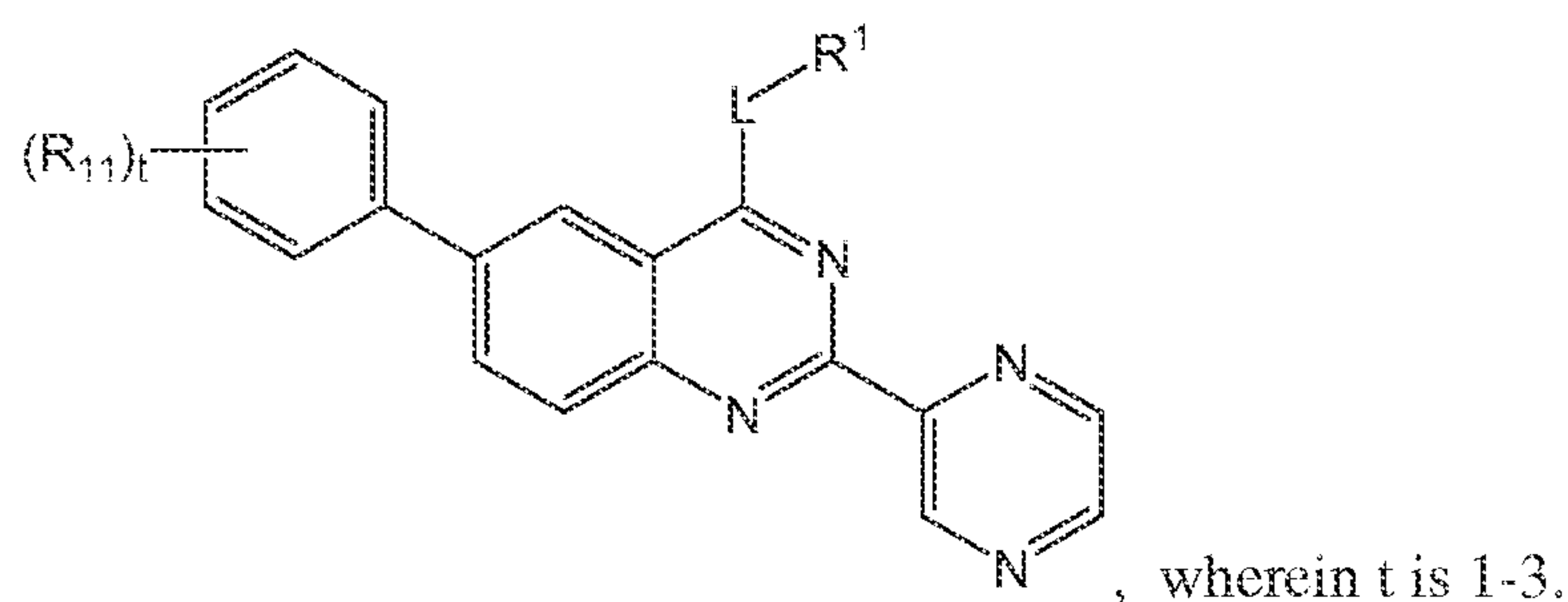
In some embodiments, R_1 is selected from methyl, cyclohexyl, t-butyl, and pyridinyl. In some embodiments, R_1 is heteroaralkyl (e.g., $-\text{CH}_2\text{-pyridyl}$). In some embodiments, LR^1 is $\text{NH}(\text{CH}_3)$.

In some embodiments, the compound is:



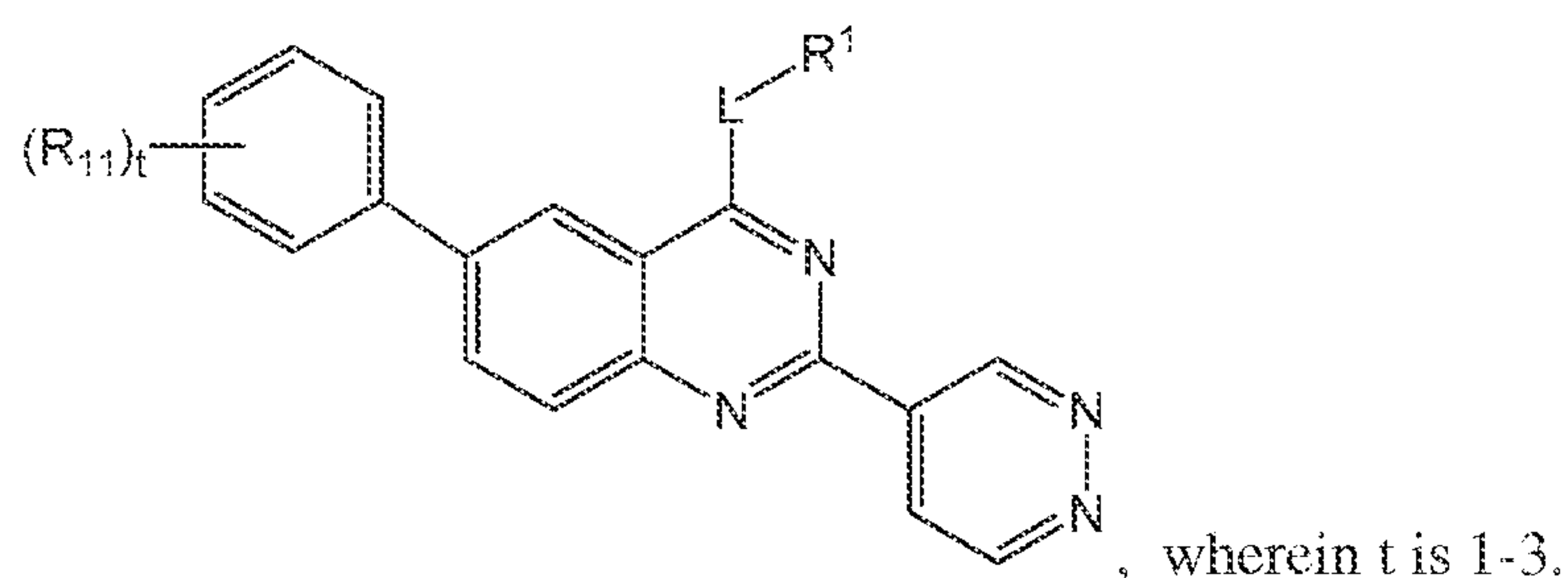
In some embodiments, R_1 is selected from methyl, cyclohexyl, t-butyl, and pyridinyl. In some embodiments, R_1 is heteroaralkyl (e.g., $-\text{CH}_2\text{-pyridyl}$). In some embodiments, LR^1 is $\text{NH}(\text{CH}_3)$.

In some embodiments, the compound is:



In some embodiments, R_1 is selected from methyl, cyclohexyl, t-butyl, and pyridinyl. In some embodiments, R_1 is heteroaralkyl (e.g., $-\text{CH}_2\text{-pyridyl}$). In some embodiments, LR^1 is $\text{NH}(\text{CH}_3)$. In some embodiments, R^{11} is independently halo, nitrile, $\text{C}_1\text{-C}_4$ alkoxy, $-\text{C}(\text{O})\text{NH}_2$, hydroxy, or $\text{C}_1\text{-C}_4$ hydroxyalkyl. In some embodiments, R^{11} is fluoro. In some embodiments, R^{11} is methoxy, ethoxy, or methoxyethoxy ether. In some embodiments, R^{11} is $-\text{OCH}_2\text{CH}_2\text{OCH}_3$. In some embodiments, R^{11} is $-\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CH}_3$. In some embodiments, R^{11} is $-\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$.

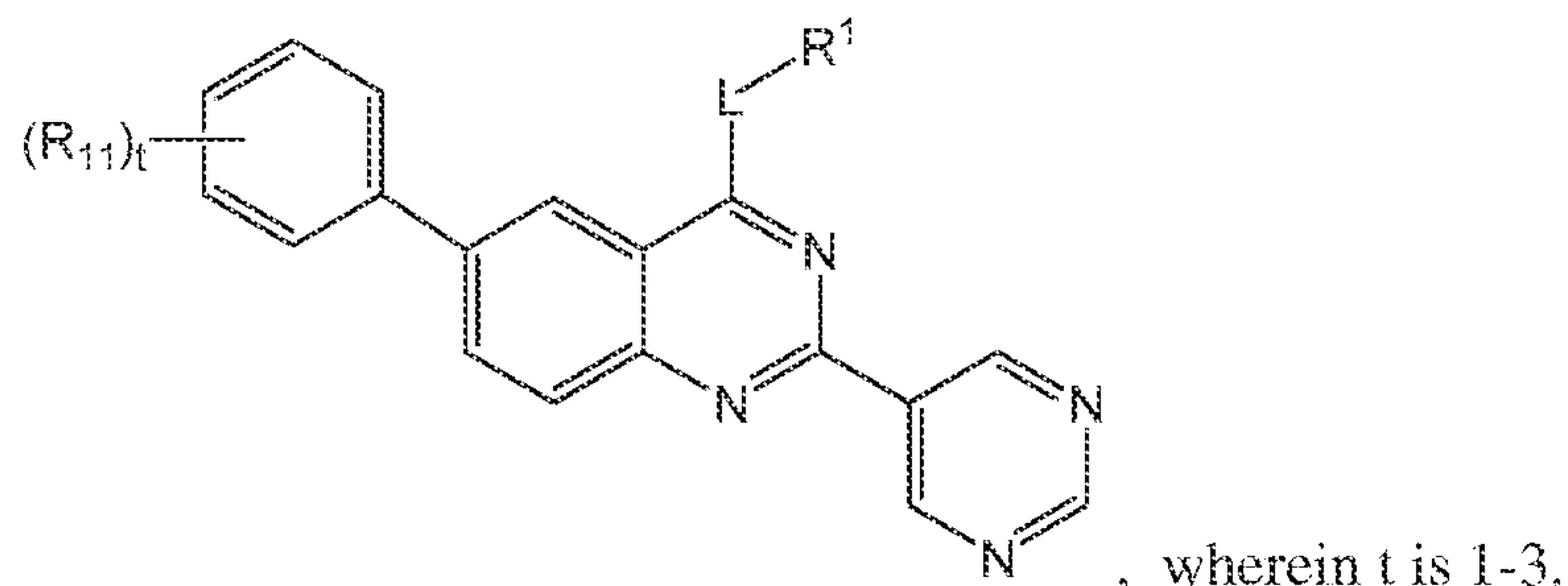
In some embodiments, the compound is:



In some embodiments, R_1 is selected from methyl, cyclohexyl, t-butyl, and pyridinyl. In some embodiments, LR^1 is $\text{NH}(\text{CH}_3)$. In some embodiments, R^{11} is independently halo, nitrile, $\text{C}_1\text{-C}_4$ alkoxy, $-\text{C}(\text{O})\text{NH}_2$, hydroxy, or $\text{C}_1\text{-C}_4$ hydroxyalkyl. In some embodiments, R^{11} is fluoro. In some embodiments, R^{11} is methoxy, ethoxy, or methoxyethoxy ether. In some embodiments, R^{11} is $-\text{OCH}_2\text{CH}_2\text{OCH}_3$. In some

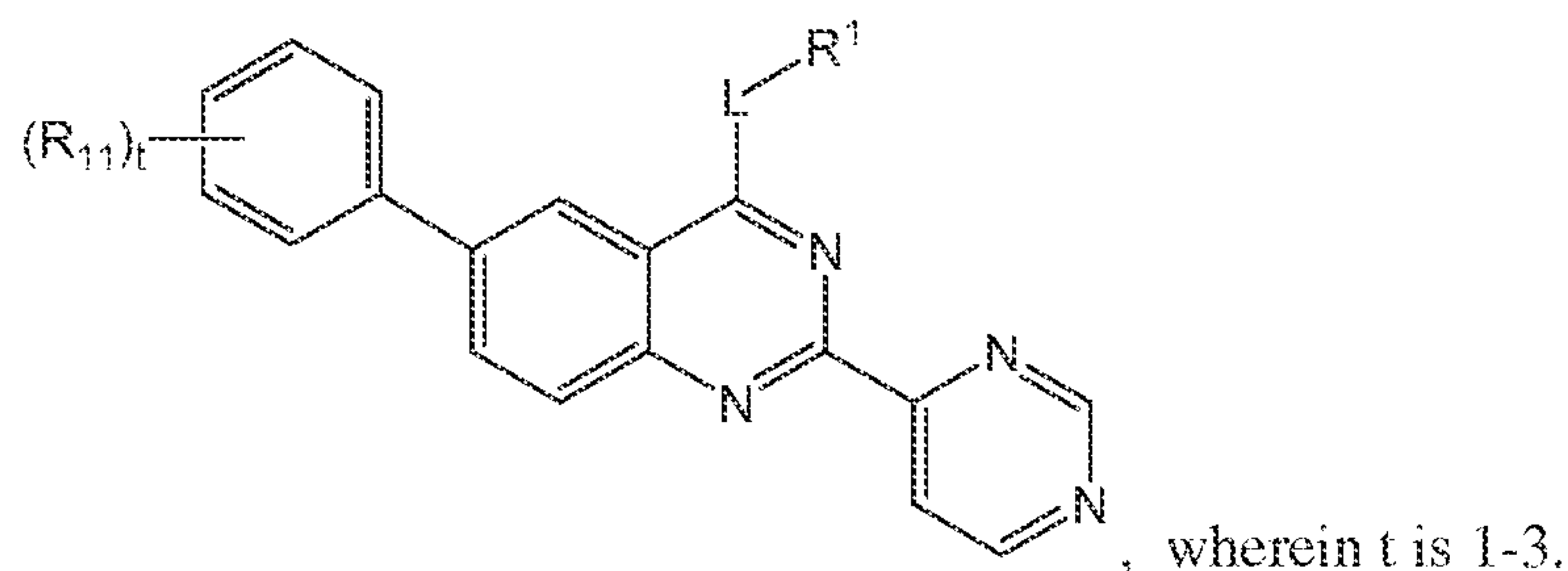
embodiments, R^{11} is $-\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CH}_3$. In some embodiments, R^{11} is $-\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$.

In some embodiments, the compound is:



In some embodiments, R_1 is selected from methyl, cyclohexyl, t-butyl, and pyridinyl. In some embodiments, LR^1 is $\text{NH}(\text{CH}_3)$. In some embodiments, R^{11} is independently halo, nitrile, C_1 - C_4 alkoxy, $-\text{C}(\text{O})\text{NH}_2$, hydroxy, or C_1 - C_4 hydroxyalkyl. In some embodiments, R^{11} is fluoro. In some embodiments, R^{11} is methoxy, ethoxy, or methoxyethoxy ether. In some embodiments, R^{11} is $-\text{OCH}_2\text{CH}_2\text{OCH}_3$. In some embodiments, R^{11} is $-\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CH}_3$. In some embodiments, R^{11} is $-\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$.

In some embodiments, the compound is:

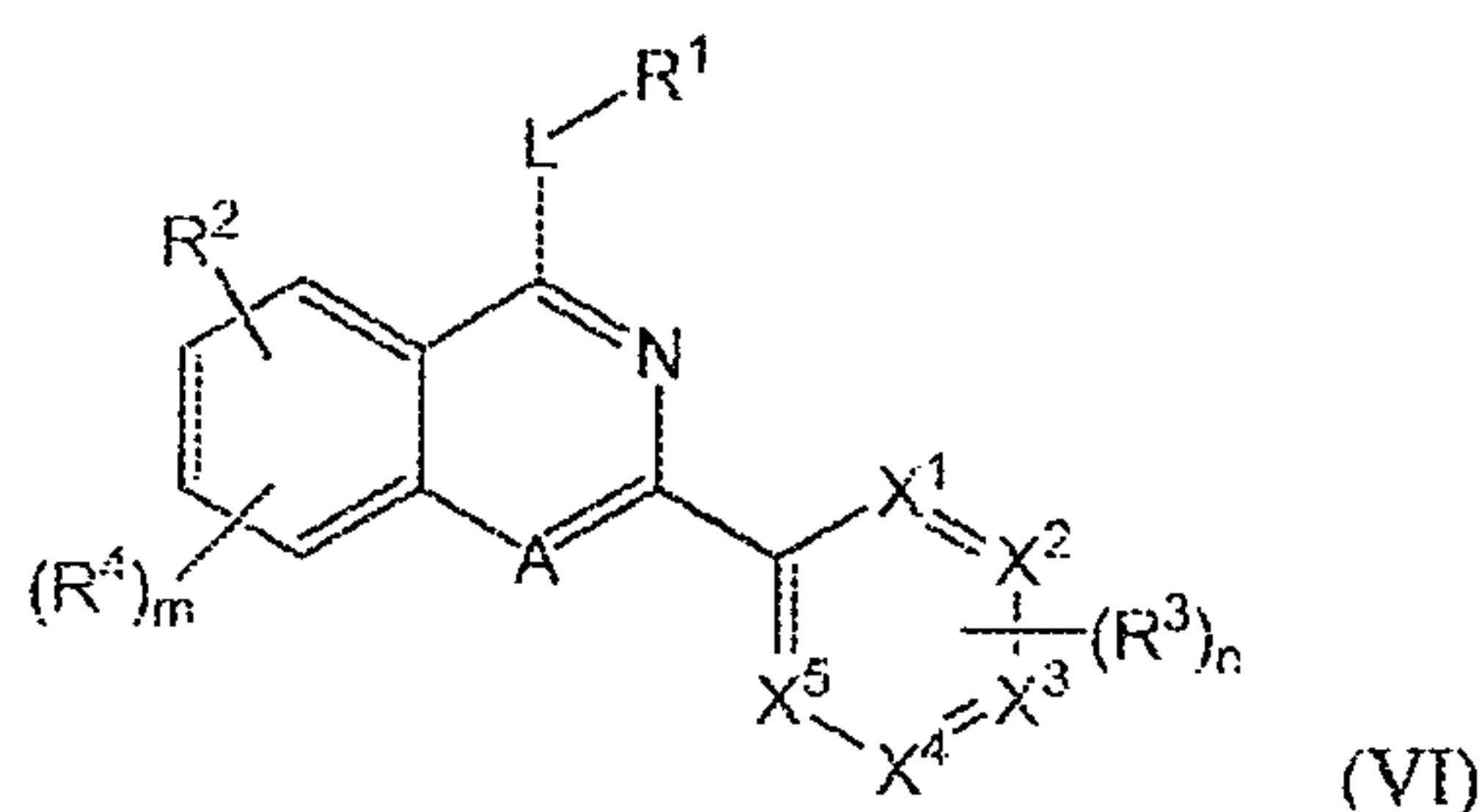


In some embodiments, R_1 is selected from methyl, cyclohexyl, t-butyl, and pyridinyl. In some embodiments, LR^1 is $\text{NH}(\text{CH}_3)$. In some embodiments, R^{11} is independently halo, nitrile, C_1 - C_4 alkoxy, $-\text{C}(\text{O})\text{NH}_2$, hydroxy, or C_1 - C_4 hydroxyalkyl. In some embodiments, R^{11} is fluoro. In some embodiments, R^{11} is methoxy, ethoxy, or methoxyethoxy ether. In some embodiments, R^{11} is $-\text{OCH}_2\text{CH}_2\text{OCH}_3$. In some embodiments, R^{11} is $-\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CH}_3$. In some embodiments, R^{11} is $-\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$.

Compounds of Formula (VI)

The following aspects and embodiments relate to compounds of formula (VI).

Item 41. A compound of formula (VI):



wherein:

A is CR⁵, CH or N;

L is O or NR⁶;

1, 2 or 3 of X¹, X², X³, X⁴ and X⁵ are N and the others are CH;

m is 0, 1, 2 or 3;

n is 0, 1, 2, 3 or 4;

R¹ is hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, cyclyl or heterocyclyl, each of which is optionally substituted with 1-3 R⁷; or when L is NR⁶, R¹ or R⁷ may be taken together with R⁶ and the atoms to which they are attached to form a heterocyclyl or heteroaryl ring that is optionally substituted with 1-3 R⁸;

R² is aryl or heteroaryl, each of which is optionally substituted with 1-5 R⁹;

each R³, R⁴ and R⁵ is independently C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclylalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, -CN, -NO₂, -C(O)OR^a, -C(Y)NR^bR^{b'}, -NR^cC(Y)R^{c'}, -NR^bR^{b'}, -OC(O)NR^bR^{b'}, -NR^cC(O)OR^{c'}, -SO₂NR^bR^{b'}, -NR^cSO₂R^{c'}, -NR^cC(Y)NR^bR^{b'}, -OR^d, -SR^{d'}, -C(Y)R^e or -S(O)_qR^f, each of which is optionally substituted with 1-3 R¹⁰;

R^6 is hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, cyclyl or heterocyclyl, each of which is optionally substituted with 1-3 R^{11} ;

each R^7 , R^8 , R^9 and R^{10} is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, oxo, thiono, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^{c'}$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{O})\text{OR}^{c'}$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^{c'}$, $-\text{NR}^c\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^d$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$, each of which is optionally substituted with 1-3 R^{12} ; wherein two R^7 , two R^8 , two R^9 or two R^{10} may optionally be taken together with the atoms to which they are attached to form an optionally substituted cyclyl, heterocyclyl, aryl or heteroaryl ring;

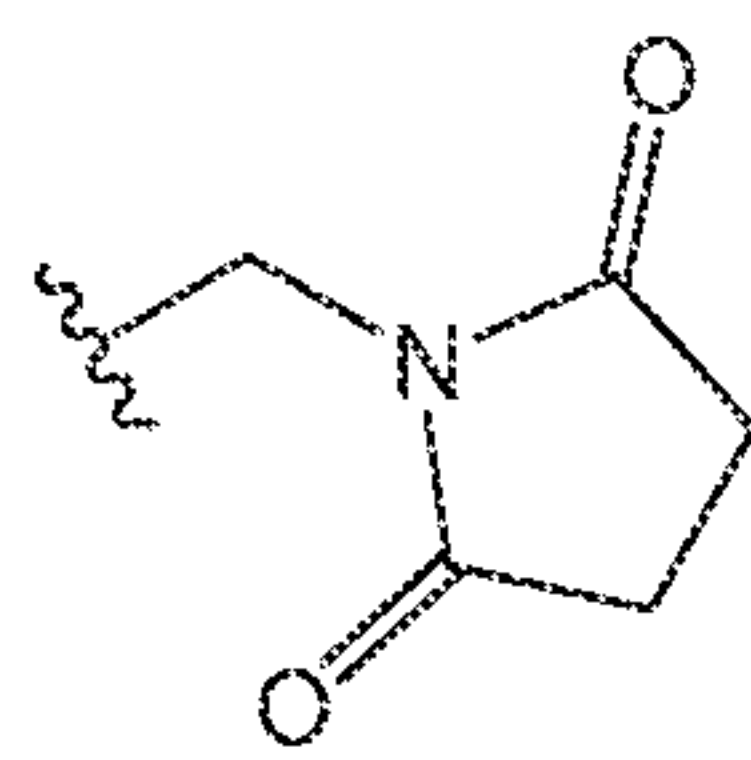
each R^{11} and R^{12} is independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, aryl, heteroaryl, cyclyl, heterocyclyl, aralkyl, heteroaralkyl, cyclylalkyl, heterocyclalkyl, halo, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxy, silyloxyalkyl, silylalkoxy, silylalkoxyalkyl, oxo, thiono, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{Y})\text{R}^{c'}$, $-\text{NR}^b\text{R}^{b'}$, $-\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{C}(\text{O})\text{OR}^{c'}$, $-\text{SO}_2\text{NR}^b\text{R}^{b'}$, $-\text{NR}^c\text{SO}_2\text{R}^{c'}$, $-\text{NR}^c\text{C}(\text{Y})\text{NR}^b\text{R}^{b'}$, $-\text{OR}^d$, $-\text{SR}^d$, $-\text{C}(\text{Y})\text{R}^e$ or $-\text{S}(\text{O})_q\text{R}^f$;

each Y is independently O or S;

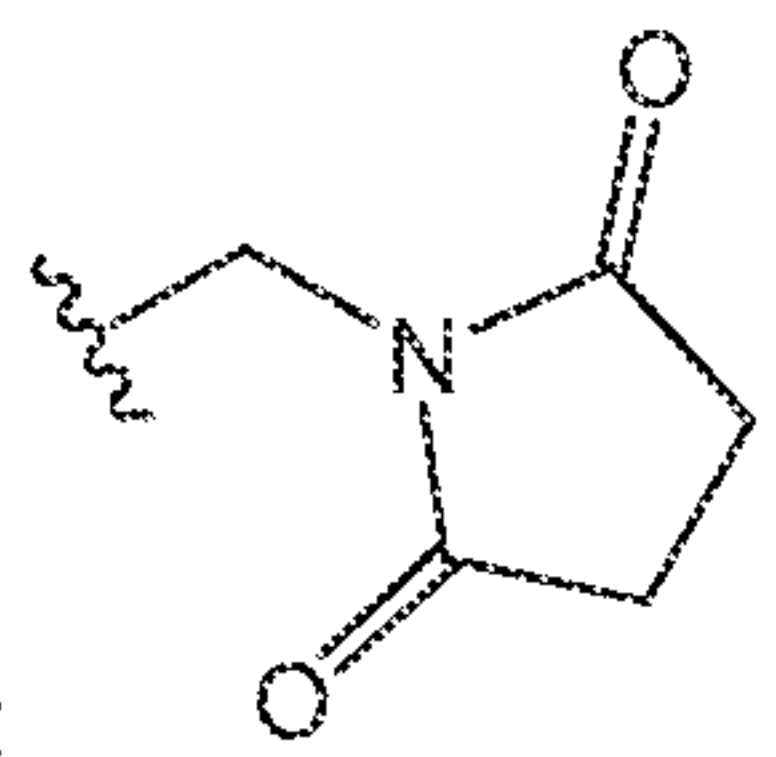
q is 1 or 2; and

each R^a , R^b , $R^{b'}$, R^c , $R^{c'}$, R^d , R^d , R^e , $R^{e'}$ and R^f is independently selected from hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, acyl, cyclyl, heterocyclyl, aryl, heteroaryl, cyclylalkyl, heterocyclalkyl, aralkyl and heteroaralkyl, each of which may be optionally substituted with 1-3 R^7 ;

or a pharmaceutically acceptable derivative or prodrug thereof,



wherein when R^1 is cyclopropyl, R^9 is not:



In some embodiments, R^9 is not:

In some embodiments, R^1 is C_1 - C_8 alkyl, which is optionally substituted with 1-3 R^7 ; or when L is NR^6 , R^1 and R^6 may be taken together with the atoms to which they are attached to form a heterocyclyl or heteroaryl ring that is optionally substituted with 1-3 R^8 .

In some embodiments, A is CH. In some embodiments, A is N.

In some embodiments, L is NR^6 . In some embodiments, R^6 is hydrogen.

In some embodiments, R^1 is C_1 - C_8 alkyl, e.g., methyl, ethyl, C_3 alkyl (e.g., n-propyl or isopropyl), C_4 alkyl (e.g., n-butyl, isobutyl or tert-butyl), or C_5 alkyl (e.g., pentan-3-yl).

In some embodiments, R^1 is C_1 - C_8 alkyl substituted with 1-3 R^7 (e.g., C_1 - C_8 alkyl substituted with 1 R^7). In some embodiments, R^1 is methyl substituted with 1 R^7 . In some embodiments, R^7 is cyclyl (e.g., cyclopropyl). In some embodiments, R^7 is aryl (e.g., phenyl).

In some embodiments, R^1 is ethyl substituted with 1 R^7 . In some embodiments, R^7 is aryl (e.g., phenyl). In some embodiments, R^7 is $-OR^d$. In some embodiments, R^d is aryl (e.g., phenyl).

In some embodiments, R^1 is n-propyl substituted with 1 R^7 . In some embodiments, R^7 is $-OR^d$. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., C_3 alkyl, e.g., n-propyl).

In some embodiments, R^1 is C_1 - C_8 alkyl substituted with 3 R^7 . In some embodiments, R^1 is ethyl substituted with 3 R^7 . In some embodiments, each R^7 is independently halo (e.g., each R^7 is fluoro). In some embodiments, R^1 is 2,2,2-trifluoroethyl.

In some embodiments, R^1 is C_2 - C_8 alkenyl, e.g., C_3 alkenyl (e.g., $-\text{CH}_2-\text{CH}=\text{CH}_2$).

In some embodiments, R^1 is C_2 - C_8 alkynyl, e.g., C_3 alkynyl (e.g., $-\text{CH}_2-\text{C}\equiv\text{CH}$).

In some embodiments, R^1 is cyclyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl). In some embodiments, the cyclyl group is a bicyclic group (e.g., indanyl).

In some embodiments, R^1 is heterocyclyl (e.g., piperidyl). In some embodiments, R^1 is piperidyl substituted with 1 R^7 . In some embodiments, R^7 is $-C(Y)R^e$. In some embodiments, Y is O. In some embodiments, R^e is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, R^7 is $-OR^d$.

In some embodiments, R^6 is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, R^1 and R^6 are taken together with the atoms to which they are attached to form a heterocyclyl ring (e.g., a pyrrolidine ring).

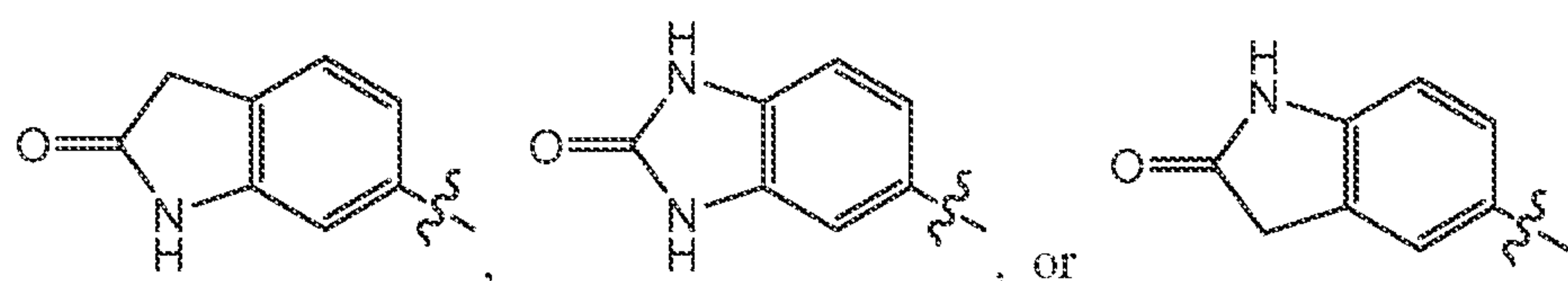
In some embodiments, R^1 and R^6 are taken together with the atoms to which they are attached to form a heteroaryl ring (e.g., an imidazole ring).

In some embodiments, L is O.

In some embodiments, R^1 is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, R^2 is aryl (e.g., phenyl). In some embodiments, R^2 is unsubstituted phenyl. In some embodiments, R^2 is phenyl substituted with 1-3 R^9 . In some embodiments, R^2 is phenyl substituted with 1 R^9 .

In some embodiments, R^2 is:



In some embodiments, R^9 is halo (e.g., fluoro or chloro). In some embodiments, R^9 is $-CN$. In some embodiments, R^9 is $-NO_2$. In some embodiments, R^9 is haloalkoxy (e.g., trifluoroethoxy). In some embodiments, R^9 is $-NR^bR^{b'}$. In some embodiments, R^b and $R^{b'}$ are each independently C_1 - C_8 alkyl (e.g., R^b and $R^{b'}$ are both methyl).

In some embodiments, R^9 is $-OR^d$. In some embodiments, R^9 is $-OCH_2CH_2OCH_3$. In some embodiments, R^9 is $-OCH_2CH_2OCH_2CH_2CH_3$. In some embodiments, R^9 is $-OCH_2CH_2OCH_2CH_2OCH_3$. In some embodiments, R^d is hydrogen. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl). In some

embodiments, R^d is methyl substituted with 1 R^7 . In some embodiments, R^7 is $-\text{CYNR}^b\text{R}^{b'}$. In some embodiments, Y is O and R^b and $R^{b'}$ are each independently C_1 - C_8 alkyl (e.g., R^b and $R^{b'}$ are both methyl). In some embodiments, R^d is ethyl. In some embodiments, R^d is ethyl substituted with 1 R^7 . In some embodiments, R^7 is $-\text{OR}^d$. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, R^7 is heterocyclyl (e.g., morpholino).

In some embodiments, R^9 is hydroxyalkyl (e.g., $-\text{CH}_2\text{OH}$). In some embodiments, R^9 is alkoxyalkyl (e.g., $-\text{CH}_2\text{-O-CH}_3$). In some embodiments, R^9 is $-\text{C(O)R}^e$. In some embodiments, R^e is heterocyclyl (e.g., morpholino). In some embodiments, R^9 is $-\text{S(O)}_q\text{R}^f$. In some embodiments, q is 1. In some embodiments, R^f is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, R^2 is phenyl substituted with 2 R^9 . In some embodiments, each R^9 is independently halo (e.g., each R^9 is fluoro). In some embodiments, each R^9 is independently $-\text{OR}^d$. In some embodiments, each R^d is independently C_1 - C_8 alkyl (e.g., each R^d is methyl).

In some embodiments, R^2 is heteroaryl. In some embodiments, R^2 is a 6-membered heteroaryl. In some embodiments, R^2 is a 6-membered nitrogen-containing heteroaryl, e.g., pyridyl. In some embodiments, R^2 is unsubstituted pyridyl.

In some embodiments, R^2 is pyridyl substituted with 1 R^9 . In some embodiments, R^9 is $-\text{OR}^d$. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl).

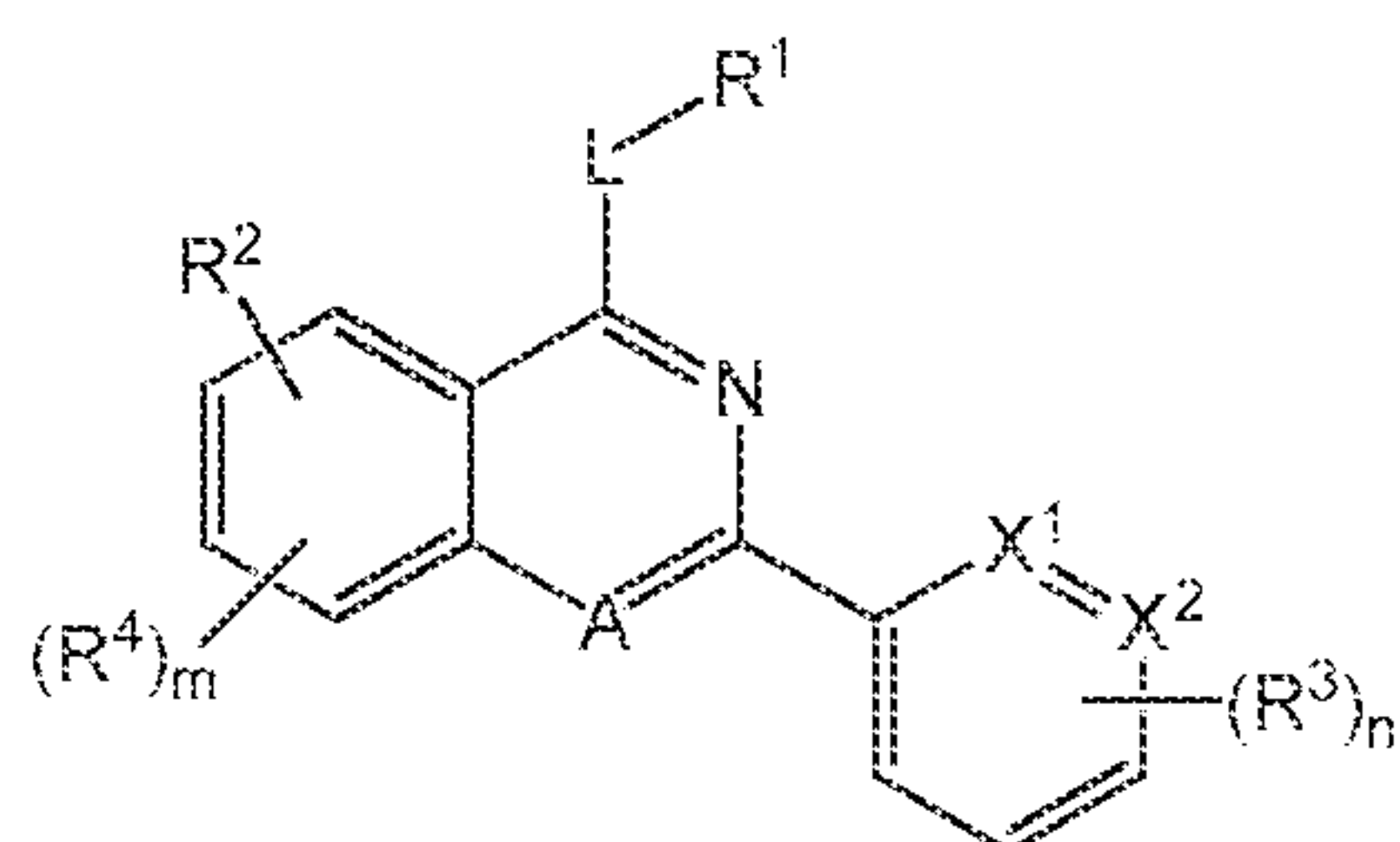
In some embodiments, R^2 is a 5-membered heteroaryl. In some embodiments, R^2 is a 5-membered nitrogen-containing heteroaryl (e.g., pyrrolyl or oxazolyl).

In some embodiments, m is 0.

In some embodiments, m is 1.

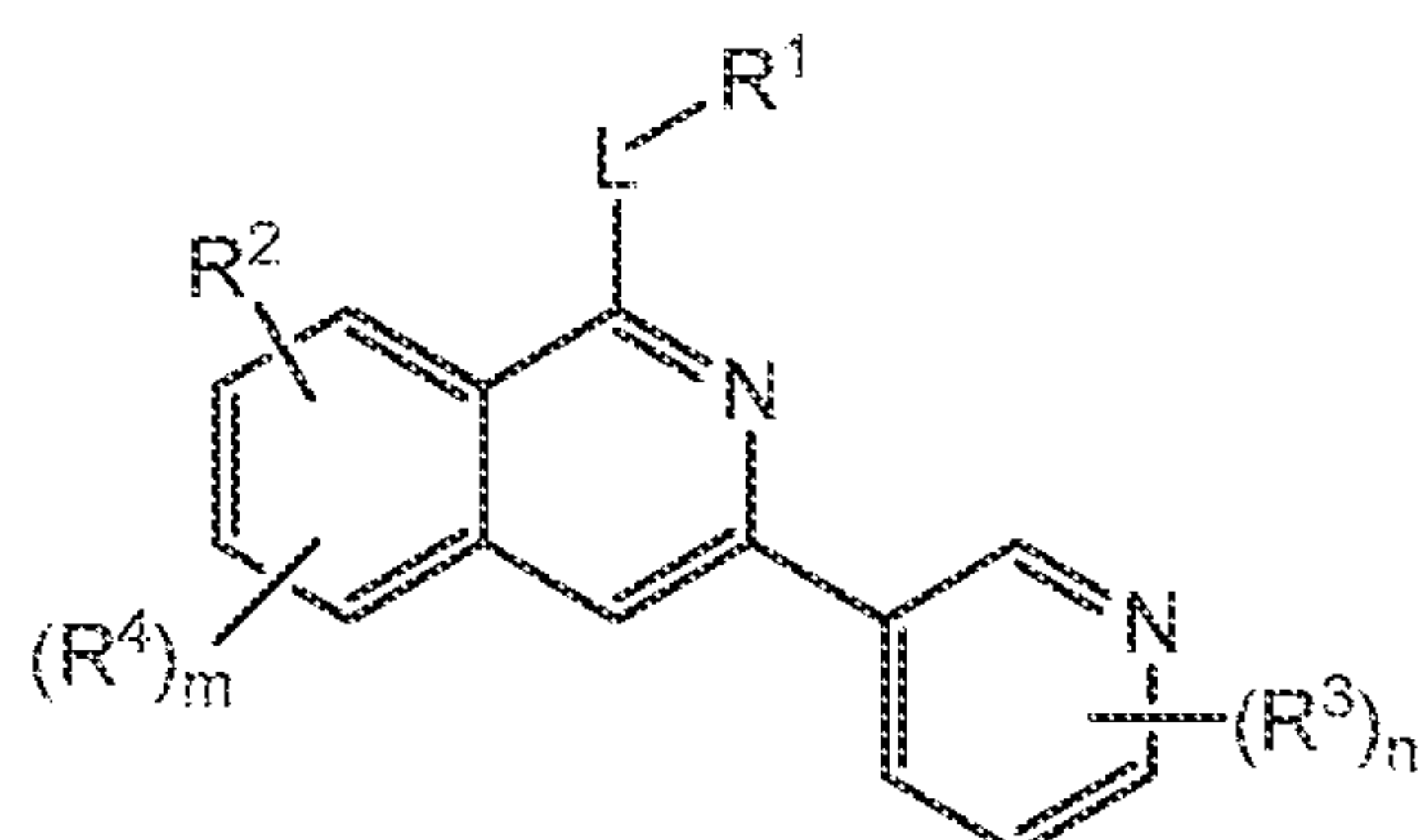
In some embodiments, R^4 is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, R^4 is $-\text{OR}^d$. In some embodiments, R^d is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, R^4 is halo. In some embodiments, R^4 is methoxy. In some embodiments, R^d is C_1 - C_8 alkyl.

In some embodiments, the compound has the following structure:



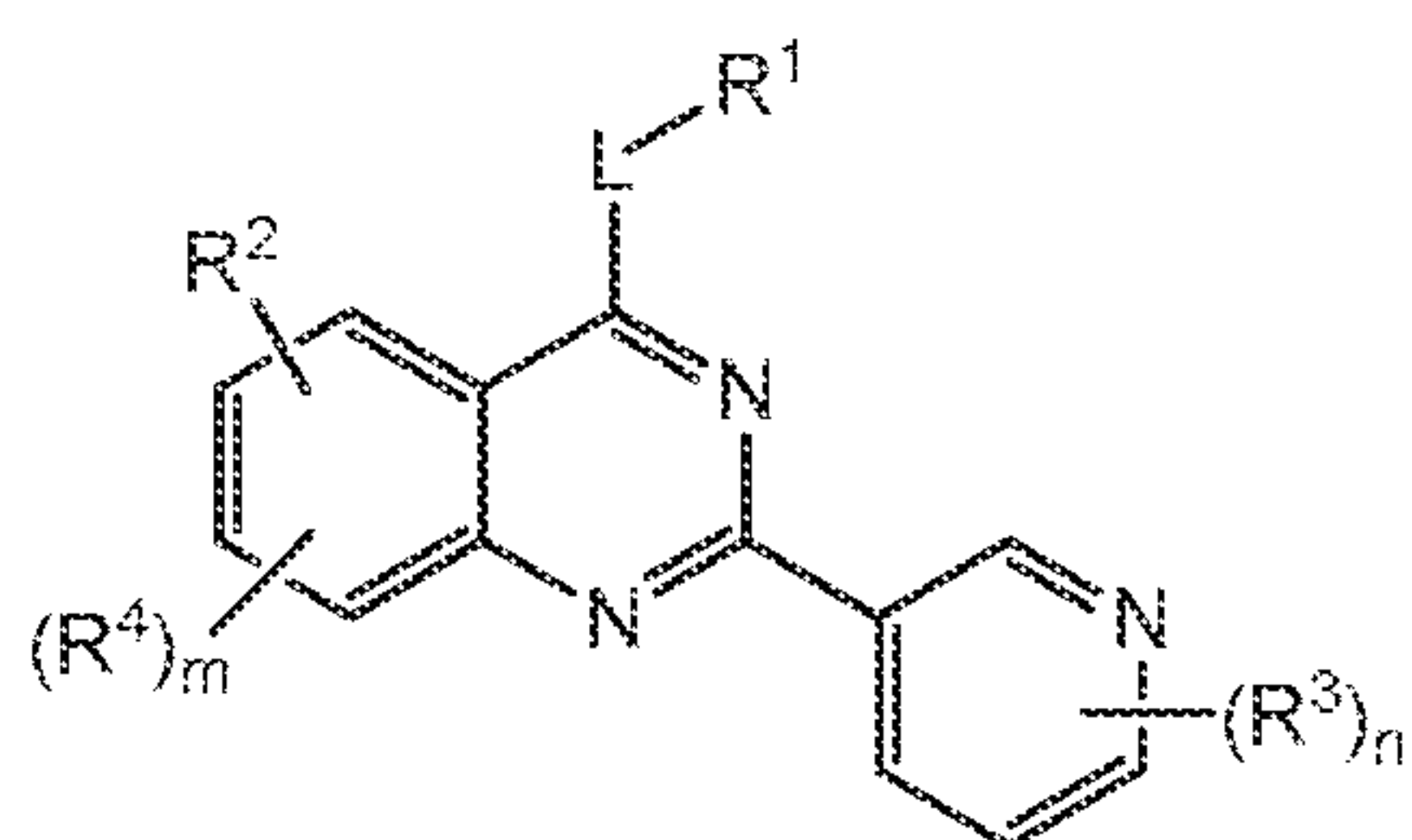
wherein one of X^1 and X^2 is N and the other is CH.

In some embodiments, X^1 is CH and X^2 is N. In some embodiments, X^1 is N and X^2 is CH. In some embodiments, the compound has the following structure:



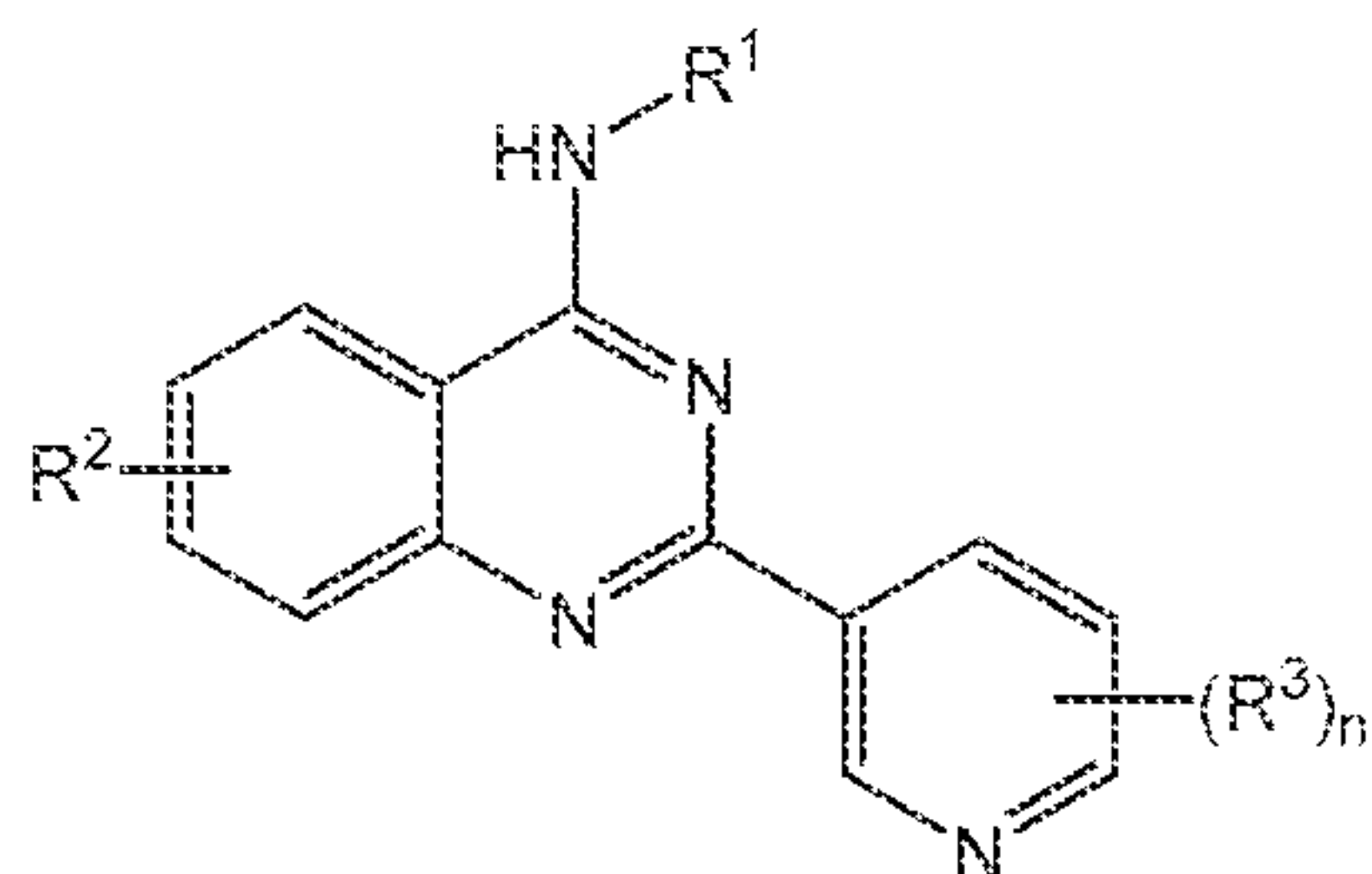
In some embodiments, R^2 is aryl. In some embodiments, R^2 is heteroaryl. In some embodiments, R^1 is C_1 - C_3 alkyl (e.g., methyl).

In some embodiments, the compound has the following structure:



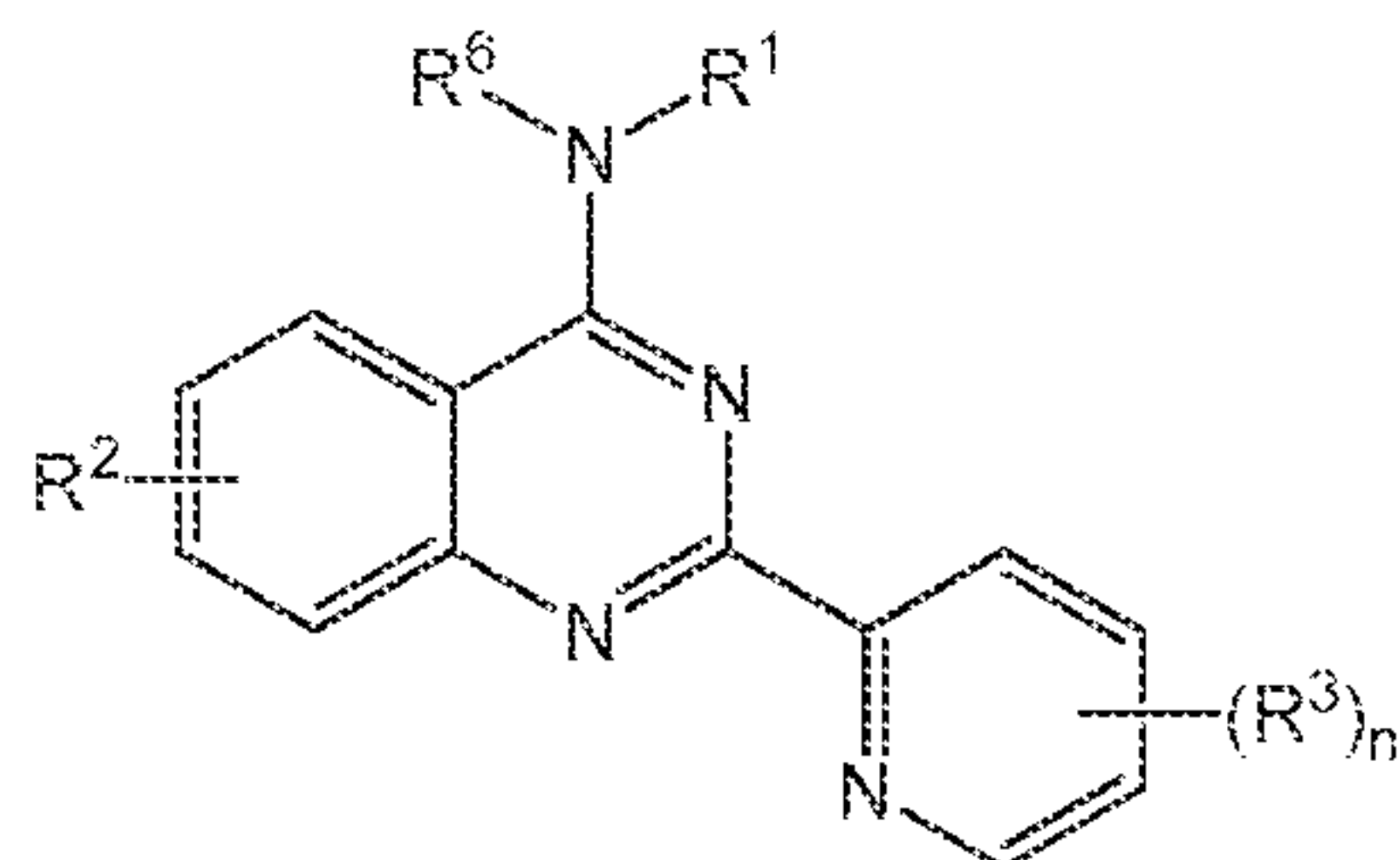
In some embodiments, R^2 is aryl. In some embodiments, R^2 is heteroaryl. In some embodiments, R^1 is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, the compound has the following structure:



In some embodiments, R^2 is aryl. In some embodiments, R^2 is heteroaryl. In some embodiments, R^1 is C_1 - C_8 alkyl (e.g., methyl).

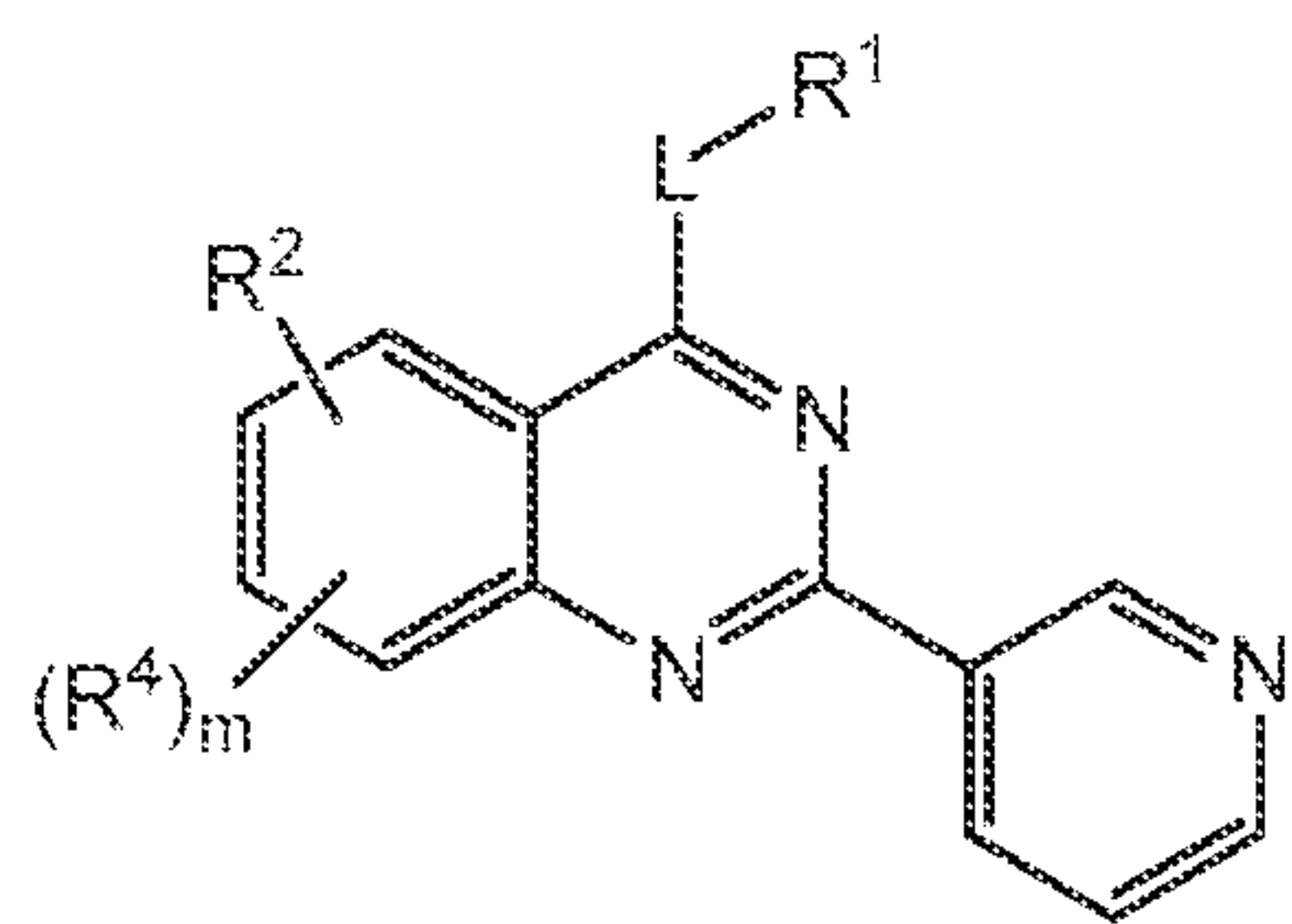
In some embodiments, the compound has the following structure:



wherein R^1 is C_1 - C_8 alkyl, which is optionally substituted with 1-3 R^7 .

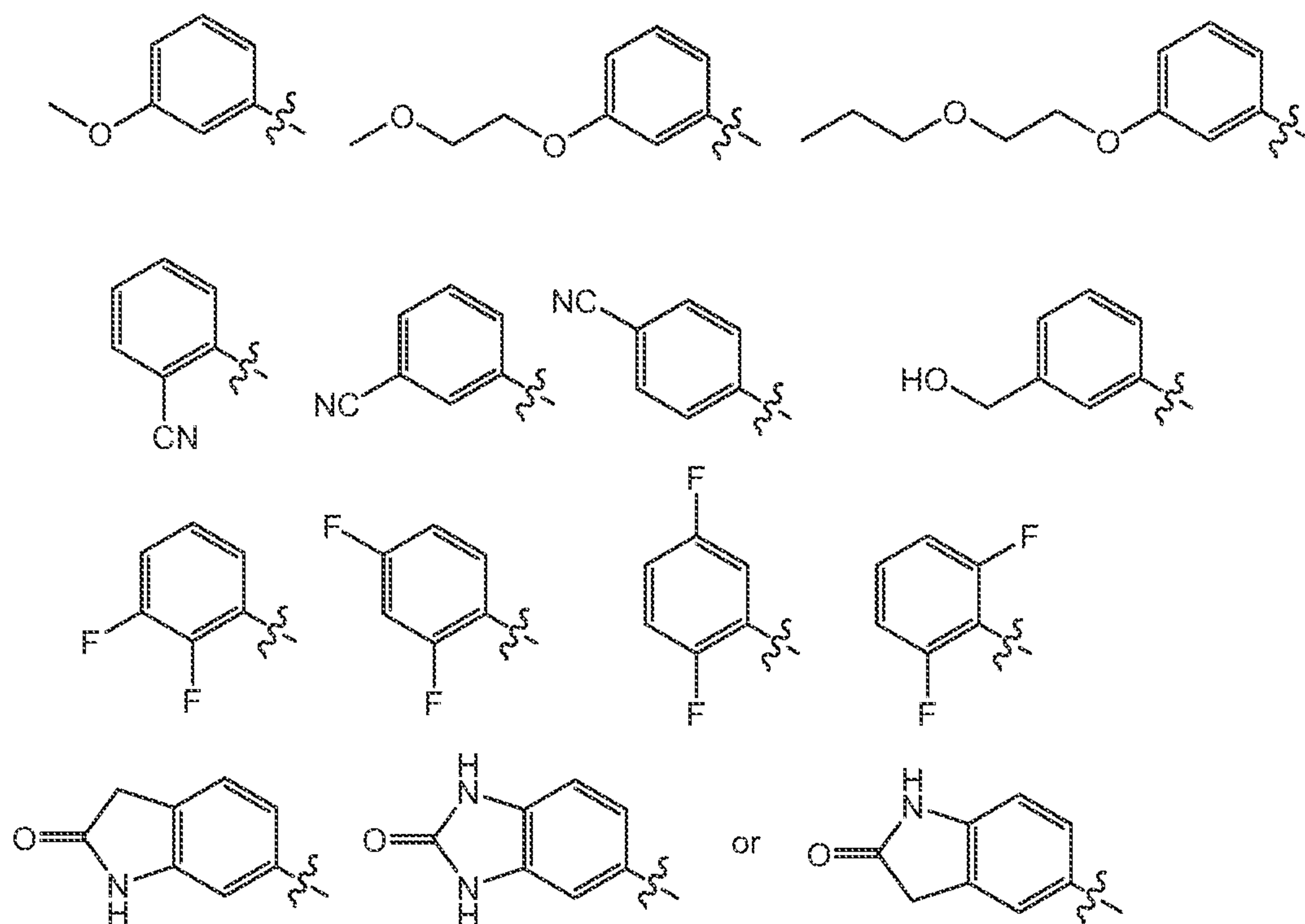
In some embodiments, R^2 is aryl. In some embodiments, R^2 is heteroaryl. In some embodiments, R^1 is C_1 - C_8 alkyl (e.g., methyl).

In some embodiments, the compound has the following structure:

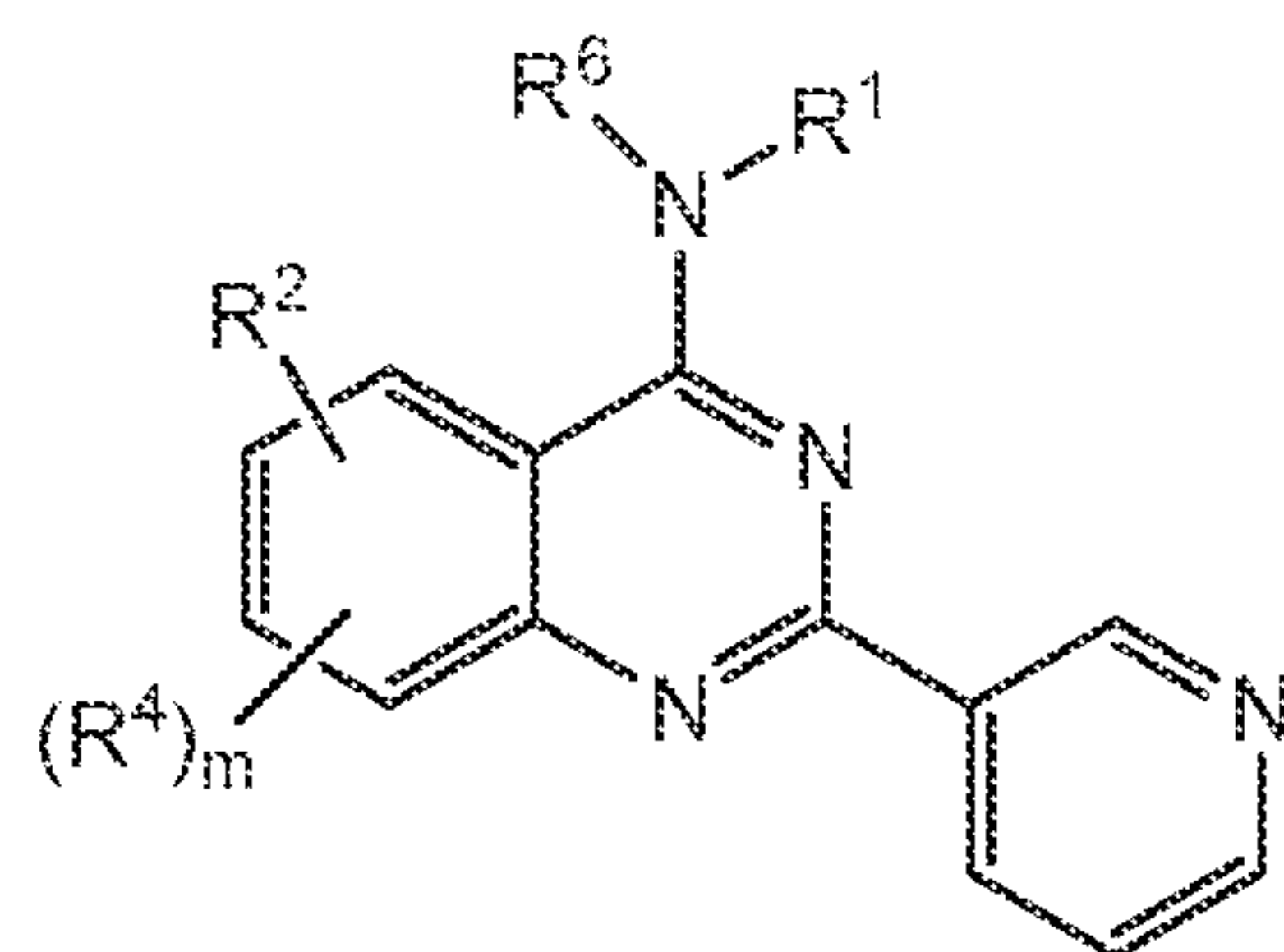


In some embodiments, R^2 is aryl. In some embodiments, R^2 is heteroaryl. In some embodiments, R^1 is C_1 - C_8 alkyl (e.g., methyl).

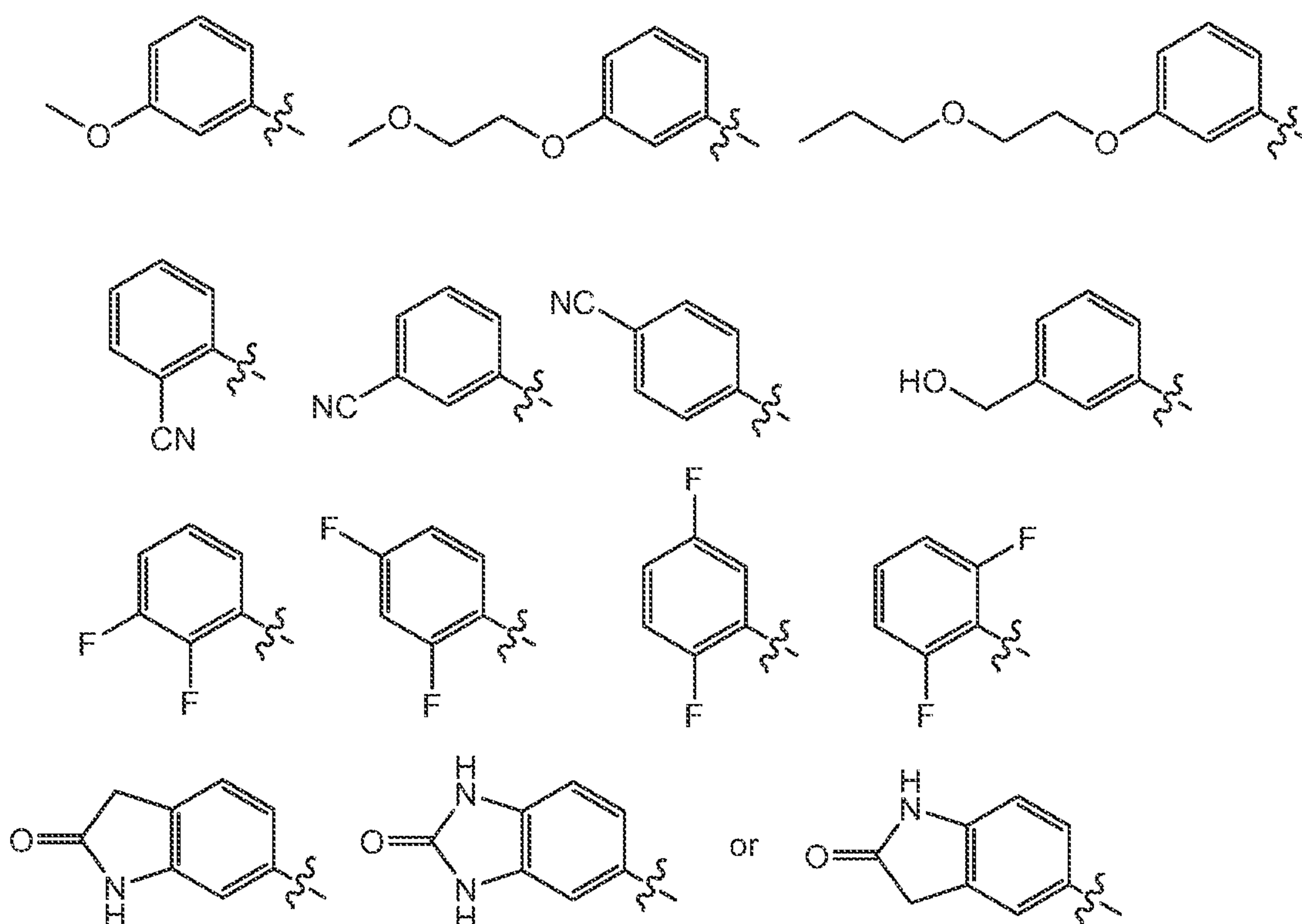
In some embodiments, R^2 is



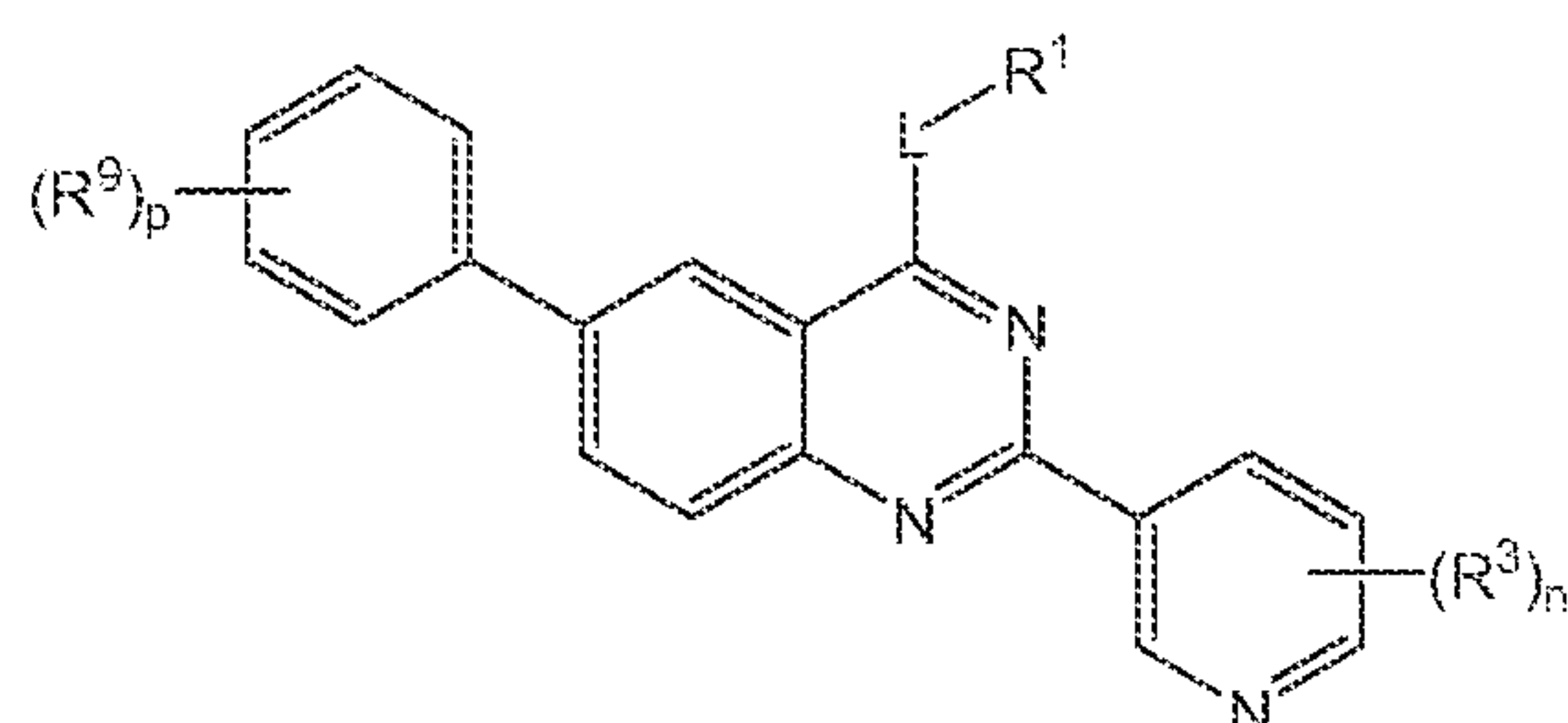
In some embodiments, the compound has the following structure:



In some embodiments, R^2 is aryl. In some embodiments, R^2 is heteroaryl. In some embodiments R^1 is C_1 - C_8 alkyl (e.g., methyl). In some embodiments, R^2 is

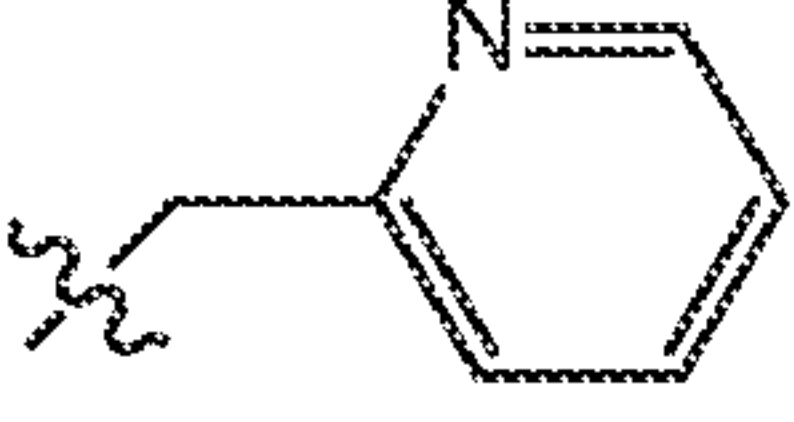


In some embodiments, the compound has the following structure:



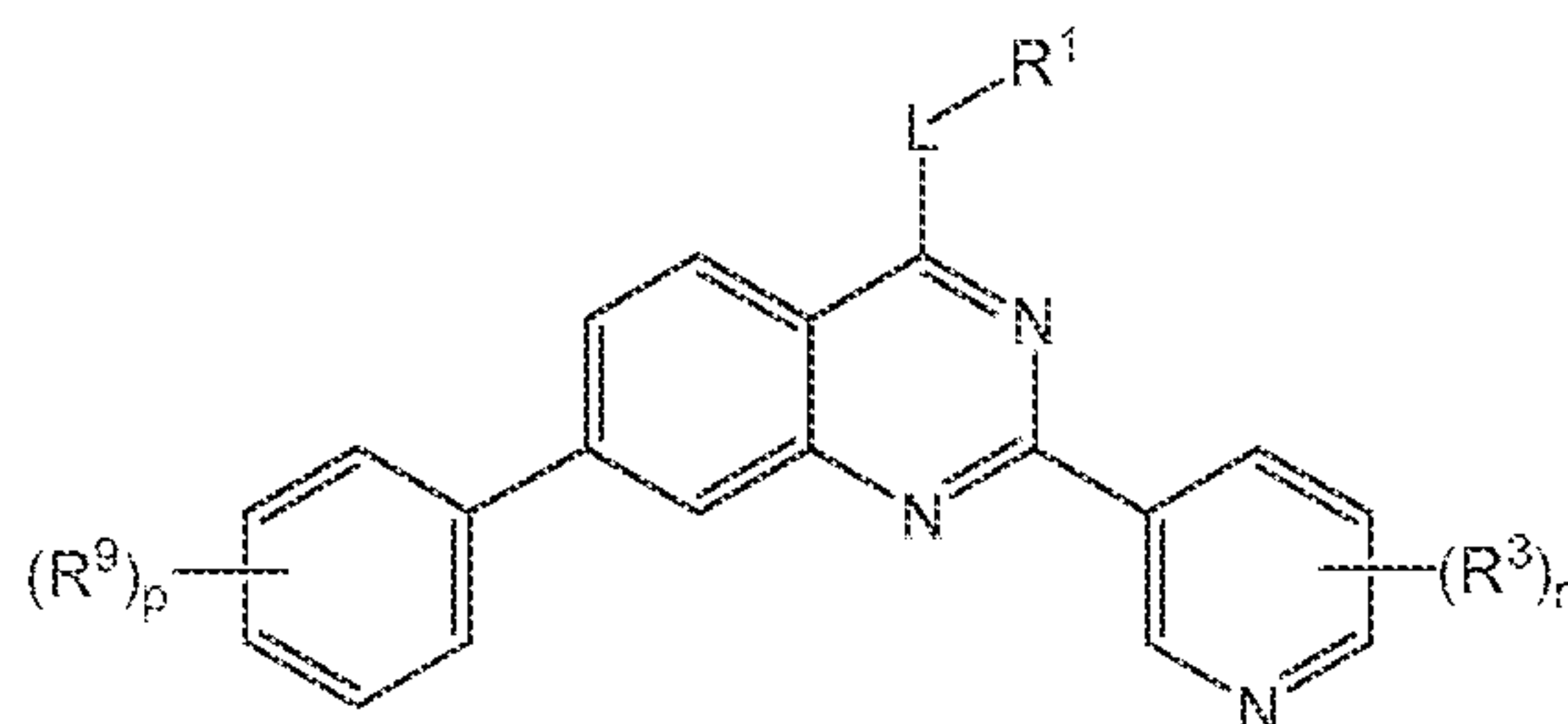
wherein p is 1, 2, 3, 4 or 5.

In some embodiments, L is NR^6 . In some embodiments, L is O. In some embodiments, R^1 is hydrogen or C_1 - C_8 alkyl. In some embodiments, R^1 is cyclyl or heterocyclyl. In some embodiments, R^1 is aralkyl or heteroaralkyl. In some

embodiments, R^1 is methyl, cyclohexyl, t-butyl, or . In some embodiments, R^6 is hydrogen or C_1 - C_8 alkyl.

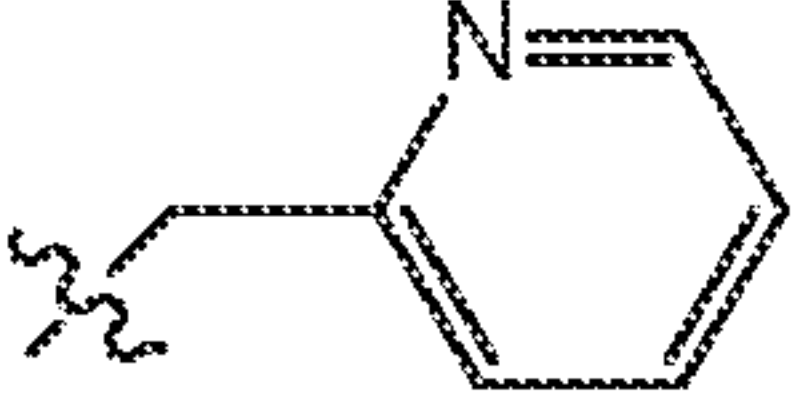
In some embodiments, R^9 is C_1 - C_8 alkyl, halo, -CN, or -OR^d. In some embodiments, R^3 is hydrogen.

In some embodiments, the compound has the following structure:



wherein p is 1, 2, 3, 4 or 5.

In some embodiments, L is NR^6 . In some embodiments, L is O . In some embodiments, R^1 is hydrogen or C_1 - C_8 alkyl. In some embodiments, R^1 is cyclyl or heterocyclyl. In some embodiments, R^1 is aralkyl or heteroaralkyl. In some

embodiments, R^1 is methyl, cyclohexyl, t -butyl, or . In some embodiments, R^6 is hydrogen or C_1 - C_8 alkyl. In some embodiments, R^9 is C_1 - C_8 alkyl, halo, -CN, or -OR^d. In some embodiments, R^3 is hydrogen.

Aspects and Embodiments of Compounds of Formulas (I), (II), (III), (IV), (V), and (VI)

In one aspect, the invention features a composition comprising a compound of formula (I), (II), (III), (IV), (V), or (VI) and an acceptable carrier.

In one aspect, the invention features a pharmaceutical composition comprising a compound of formula (I), (II), (III), (IV), (V), or (VI) and a pharmaceutically acceptable carrier.

In one aspect, the invention features a kit comprising a composition comprising a compound of formula (I), (II), (III), (IV), (V), or (VI) and an acceptable carrier.

In one aspect, the invention features a kit comprising a pharmaceutical composition comprising a compound of formula (I), (II), (III), (IV), (V), or (VI) and a pharmaceutically acceptable carrier.

In one aspect, the invention features a dosage form comprising a composition comprising a compound of formula (I), (II), (III), (IV), (V), or (VI) and an acceptable carrier.

In one aspect, the invention features a dosage form comprising a pharmaceutical composition comprising a compound of formula (I), (II), (III), (IV), (V), or (VI) and a pharmaceutically acceptable carrier.

In one aspect, the invention features a method of treating a disorder that would benefit by the modulation of STEP (e.g., by activation or inhibition of STEP) in a subject, the method comprising administering to a subject in need thereof a compound of formula (I), (II), (III), (IV), (V), or (VI). In one aspect, the invention features a method of treating a disorder that would benefit by the inhibition of STEP, the method comprising administering to a subject in need thereof a compound of formula (I), (II), (III), (IV), (V), or (VI). In some embodiments, the disorder is selected from schizophrenia, schizoaffective disorder, bipolar disorder, manic-depressive disorder, psychosis, mood and anxiety disorders, mania, drug or substance addiction, cognition disorders, learning disabilities, learning and memory disorders, aging and neurologic disorders associated with or linked with cognitive impairments; mild cognitive impairments (MCI), Alzheimer's disease, Alzheimer-related cognition disorders, Huntington's disease, Parkinson's disease, CADASIL syndrome (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), amnesia, Wernicke-Korsakoff syndrome, Korsakoff syndrome, mild traumatic head injury (MBTI), traumatic head injury (TBI), fragile X syndrome, stroke, attention-deficit and hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD), loss of concentration, autism, cerebral palsy, encephalopathy, and narcolepsy. In some embodiments, the disorder affects learning and memory, neurogenesis, neuronal plasticity, pain perception, mood and anxiety, or neuroendocrine regulation. In some embodiments, the disorder is a cognitive deficit disorder. In some embodiments, the disorder involves pain perception or neuroendocrine regulation. In some embodiments, the disorder affects the central nervous system. In some embodiments the disorder is selected from the group consisting of schizophrenia; refractory, intractable or chronic schizophrenia;

emotional disturbance; psychotic disorder; mood disorder; bipolar I type disorder; bipolar II type disorder; depression; endogenous depression; major depression; melancholy and refractory depression; dysthymic disorder; cyclothymic disorder; panic attack; panic disorder; agoraphobia; social phobia; obsessive-compulsive disorder; post-traumatic stress disorder; generalized anxiety disorder; acute stress disorder; hysteria; somatization disorder; conversion disorder; pain disorder; hypochondriasis; factitious disorder; dissociative disorder; sexual dysfunction; sexual desire disorder; sexual arousal disorder; erectile dysfunction; anorexia nervosa; bulimia nervosa; sleep disorder; adjustment disorder; alcohol abuse; alcohol intoxication; drug addiction; stimulant intoxication; narcotism; anhedonia; iatrogenic anhedonia; anhedonia of a psychic or mental cause; anhedonia associated with depression; anhedonia associated with schizophrenia; delirium; cognitive impairment; cognitive impairment associated with Alzheimer's disease, Parkinson's disease and other neurodegenerative diseases; cognitive impairment caused by Alzheimer's disease; Parkinson's disease and associated neurodegenerative diseases; cognitive impairment of schizophrenia; cognitive impairment caused by refractory, intractable or chronic schizophrenia; vomiting; motion sickness; obesity; migraine; pain (ache); mental retardation; autism disorder (autism); Tourette's disorder; tic disorder; attention-deficit/hyperactivity disorder; conduct disorder; and Down's syndrome.

In one aspect, the invention features a method of treating a condition that would benefit by the modulation of STEP (e.g., by activation or inhibition of STEP) in a subject, the method comprising administering to a subject in need thereof a compound of formula (I), (II), (III), (IV), (V), or (VI). In some embodiments, the condition is selected from decreased neurogenesis, cell resilience, or neuronal plasticity due to normal aging, neurodegenerative disorders of the CNS; Alzheimer's disease, Huntington's disease, fragile X syndrome, amyotrophic lateral sclerosis/Lou Gehrig's disease, stroke, Parkinson's disease, parkinsonism, dementia, Pick disease, Corticobasal degeneration, Multiple system atrophy, Progressive supranuclear palsy, traumatic brain injury, head trauma, mild traumatic head injury (MBTI), traumatic head injury (TBI), encephalopathy, intoxication related to ethanol, alcoholism, fetal alcohol syndrome, drug addiction or drug abuse.

In some embodiments, a compound of formula (I), (II), (III), (IV), (V), or (VI) is administered in combination with an additional therapeutic agent. In some embodiments, the additional therapeutic agent is an atypical antipsychotic. In some embodiments, the additional therapeutic agent is selected from the group consisting of aripiprazole, clozapine, ziprasidone, risperidone, quetiapine, olanzapine, amisulpride, asenapine, iloperidone, melperone, paliperidone, perospirone, sertindole and sulpiride. In some embodiments, the additional therapeutic agent is a typical antipsychotic. In some embodiments, the additional therapeutic agent is selected from the group consisting of haloperidol, molindone, loxapine, thioridazine, molindone, thiothixene, pimozide, fluphenazine, trifluoperazine, mesoridazine, chlorprothixene, chlorpromazine, perphenazine, triflupromazine and zuclopenthixol.

DETAILED DESCRIPTION

A compound or composition described herein can be used, e.g., in a method of treating schizophrenia or cognitive deficit. Many of the compounds described herein modulate STEP activity and can be used, e.g., to reduce or inhibit STEP activity, e.g., in a subject.

Definitions

The term “acyl” refers to an alkylcarbonyl, cycloalkylcarbonyl, arylcarbonyl, heterocyclylcarbonyl, or heteroarylcarbonyl substituent, any of which may be further substituted (e.g., by one or more substituents).

The term “alkenyl” refers to a straight or branched hydrocarbon chain containing 2-12 carbon atoms (unless otherwise noted) and having one or more double bonds. Examples of alkenyl groups include, but are not limited to, allyl, propenyl, 2-butenyl, 3-hexenyl and 3-octenyl groups. One of the double bond carbons may optionally be the point of attachment of the alkenyl substituent.

The term “alkenylene” refers to a divalent alkenyl, e.g. $-\text{CH}=\text{CH}-$, $-\text{CH}_2-\text{CH}=\text{CH}-$, and $-\text{CH}=\text{CH}-\text{CH}_2-$.

The term “alkynyl” refers to a straight or branched hydrocarbon chain containing 2-12 carbon atoms (unless otherwise noted) and characterized in having

one or more triple bonds. Examples of alkynyl groups include, but are not limited to, ethynyl, propargyl, and 3-hexynyl. One of the triple bond carbons may optionally be the point of attachment of the alkynyl substituent.

The term "alkynylene" refers to a divalent alkynyl, e.g., $-\text{CH}\equiv\text{CH}-$, $-\text{CH}_2-\text{CH}\equiv\text{CH}-$, and $-\text{CH}\equiv\text{CH}-\text{CH}_2-$.

The terms "alkoxyl" or "alkoxy" as used herein refers to an alkyl group, as defined below, having an oxygen radical attached thereto. Representative alkoxy groups include methoxy, ethoxy, propyloxy, tert-butoxy and the like. The term "alkoxyalkyl" refers to an alkyl in which one or more hydrogen atoms are replaced by an alkoxy group.

An "ether" is two hydrocarbons covalently linked by an oxygen.

The term "alkyl" refers to the radical of saturated aliphatic groups, including straight-chain alkyl groups, and branched-chain alkyl groups. In preferred embodiments, a straight chain or branched chain alkyl has 12 or fewer carbon atoms in its backbone (unless otherwise noted) e.g., from 1-12, 1-8, 1-6, or 1-4. Exemplary alkyl moieties include methyl, ethyl, propyl (e.g., n-propyl or isopropyl), butyl (e.g., n-butyl, isobutyl or t-butyl), pentyl (e.g., n-pentyl, isopentyl or pentan-3-yl), hexyl and heptyl.

The term "alkylene" refers to a divalent alkyl, e.g., $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, and $-\text{CH}_2\text{CH}_2\text{CH}_2-$.

The term "alkoxylene" refers to an alkylene wherein a CH_2 is substituted with an oxygen. For example, an aryl alkoxyene refers to a group with an alkylene attached to an aryl group through an oxygen, an optionally substituted heteroaryl alkoxyene refers to a group with an alkylene attached to a heteroaryl group through an oxygen.

The term "amino" refers to $-\text{NH}_2$.

The term "aminoalkyl" refers to an alkyl in which one or more hydrogen atoms are replaced by an amino group.

The terms "alkylamino" and "dialkylamino" refer to $-\text{NH}(\text{alkyl})$ and $-\text{N}(\text{alkyl})_2$ radicals respectively.

The term “aralkylamino” or “arylalkylamino” refers to a $-\text{NH}(\text{aralkyl})$ radical. The term “alkylaminoalkyl” refers to a $(\text{alkyl})\text{NH-alkyl-}$ radical; the term “dialkylaminoalkyl” refers to an $(\text{alkyl})_2\text{N-alkyl-}$ radical.

The term “amido” refers to a $-\text{NHC}(\text{O})-$ or $\text{C}(\text{O})\text{NH}_2$ substituent.

The term “aryl” refers to a 6-carbon monocyclic, 10-carbon bicyclic, or 14-carbon tricyclic aromatic ring system wherein 0, 1, 2, 3, or 4 atoms of each ring may be substituted by a substituent. Examples of aryl moieties include, but are not limited to, phenyl, naphthyl and the like. The term “arylalkyl” or “aralkyl” refers to alkyl substituted with an aryl. Exemplary aralkyls include but are not limited to benzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, 9-fluorenyl, benzhydryl, phenethyl, and trityl groups. The term “arylalkenyl” refers to an alkenyl substituted with an aryl. The term “arylalkynyl” refers to an alkynyl substituted with an aryl. Terms such as “arylC₂-C₆alkyl” are to be read as a further limitation on the size of the alkyl group. The term “arylalkoxy” refers to an alkoxy substituted with aryl. The term “arylenyl” refers to a divalent aryl (i.e., -Ar-).

The terms “cycloalkyl” or “cyclyl” as employed herein include saturated and partially unsaturated cyclic hydrocarbon groups having 3 to 12 carbons, preferably 3 to 8 carbons, and more preferably 3 to 6 carbons, wherein the cycloalkyl group may be optionally substituted. Exemplary cyclyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl. Cyclyl moieties also include both bridged and fused ring systems. Cyclyl groups also include those that are fused to additional ring systems, which may be saturated or unsaturated. A cyclyl group may thus be a bicyclic group in which one ring is saturated or partially unsaturated and the other is fully unsaturated (e.g., indanyl).

The term “cyclylalkyl” as used herein, refers to an alkyl group substituted with a cyclyl group. Cyclylalkyl includes groups in which more than one hydrogen atom of an alkyl group has been replaced by a cyclyl group.

The term “cycloalkylalkyl” as used herein, refers to an alkyl group substituted with a cycloalkyl group.

The term “halo” or “halogen” refers to any radical of fluorine, chlorine, bromine or iodine.

The term “haloalkyl” refers to an alkyl group that may have any number of hydrogens available on the group replaced with a halogen atom. Representative haloalkyl groups include but are not limited to: $-\text{CH}_2\text{Cl}$, $-\text{CH}_2\text{ClCF}_3$, $-\text{CHBr}_2$, $-\text{CF}_3$, $-\text{CH}_2\text{F}$, $-\text{CHF}_2$, and $-\text{CH}_2\text{CF}_3$. The term “fluoroalkyl” refers to an alkyl group that may have any number of hydrogens available on the group replaced with a fluorine atom. Representative fluoroalkyl groups include but are not limited to: $-\text{CH}_2\text{F}$, $-\text{CH}_2\text{FCF}_3$, $-\text{CHF}_2$ and $-\text{CF}_3$. The term “haloalkoxy” refers to an alkoxy group that may have any number of hydrogen atoms available on the alkyl group replaced with a halogen atom. Representative haloalkoxy groups include but are not limited to: $-\text{OCH}_2\text{Cl}$, $-\text{OCH}_2\text{ClCF}_3$, $-\text{OCHBr}_2$, $-\text{OCHF}_2$ or $-\text{OCF}_3$. The term “fluoroalkoxy” refers to an alkoxy group that may have any number of hydrogens available on the group replaced with a fluorine atom. Representative fluoroalkoxy groups include but are not limited to: $-\text{OCH}_2\text{F}$, $-\text{OCH}_2\text{FCF}_3$, $-\text{OCHF}_2$ or $-\text{OCF}_3$.

The term “heteroatom” as used herein means an atom of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, sulfur, phosphorus and silicon. A heteroatom may be present in any oxidation state (e.g., any oxidized form of nitrogen, sulfur, phosphorus or silicon) and any charged state (e.g., the quaternized form of any basic nitrogen), and includes a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidiny) or NR^+ (as in N-substituted pyrrolidiny).

The term “heteroaryl” refers to an aromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S (e.g., carbon atoms and 1-3, 1-6, or 1-9 heteroatoms of N, O, or S if monocyclic, bicyclic, or tricyclic, respectively), wherein 0, 1, 2, 3, or 4 atoms of each ring may be substituted by a substituent. Examples of heteroaryl groups include pyridyl, furyl or furanyl, imidazolyl, benzimidazolyl, pyrimidinyl, thiophenyl or thienyl, quinolinyl, indolyl, thiazolyl, oxazolyl and the like. The term “heteroarylalkyl” or the term “heteroaralkyl” refers to an alkyl

substituted with a heteroaryl. The term "heteroarylalkenyl" refers to an alkenyl substituted with a heteroaryl. The term "heteroarylalkynyl" refers to an alkynyl substituted with a heteroaryl. The term "heteroarylalkoxy" refers to an alkoxy substituted with heteroaryl.

The term "heteroaryl" refers to a group having 5 to 14 ring atoms, preferably 5, 6, 9, or 10 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to five heteroatoms. A heteroaryl group may be mono-, bi-, tri-, or polycyclic, preferably mono-, bi-, or tricyclic, more preferably mono- or bicyclic. When a heteroaryl is substituted by a hydroxy group, it also includes its corresponding tautomer. The term "heteroaryl," as used herein, also includes groups in which a heteroaromatic ring is fused to one or more aryl rings. Nonlimiting examples of heteroaryl groups include thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indoliziny, purinyl, naphthyridinyl, pteridinyl, indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 4H-quinoliziny, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinoliny, tetrahydroisoquinoliny, and pyrido[2,3-b]-1,4-oxazin-3(4H)-one. The term "heteroaryl" may be used interchangeably with the terms "heteroaryl ring", "heteroaryl group," or "heteroaromatic," any of which terms include rings that are optionally substituted. A ring nitrogen atom of a heteroaryl may be oxidized to form the corresponding N-oxide compound. A nonlimiting example of such a heteroaryl having an oxidized ring nitrogen atom is N-oxopyridyl.

The term "heteroarylalkyl" or "heteroaralkyl" refers to an alkyl group substituted by a heteroaryl. Heteroaralkyl includes groups in which more than one hydrogen atom has been replaced by a heteroaryl group.

As used herein, the terms "heterocycle," "heterocyclyl" and "heterocyclic ring" are used interchangeably and refer to a stable 3- to 8-membered monocyclic or 7-10-membered bicyclic heterocyclic moiety that is either saturated or partially unsaturated, and having, in addition to carbon atoms, one or more, preferably one to four,

heteroatoms, as defined above. When used in reference to a ring atom of a heterocycle, the term "nitrogen" includes a substituted nitrogen. As an example, in a saturated or partially unsaturated ring having 0-3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4-dihydro-2H-pyrrolyl), NH (as in pyrrolidinyl), or NR^+ (as in N-substituted pyrrolidinyl). A heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure and any of the ring atoms can be optionally substituted. Examples of such saturated or partially unsaturated heterocyclic radicals include, without limitation, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothienyl, piperidinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, and thiomorpholinyl. A heterocyclyl group may be mono-, bi-, tri-, or polycyclic, preferably mono-, bi-, or tricyclic, more preferably mono- or bicyclic. Additionally, a heterocyclic ring also includes groups in which the heterocyclyl ring is fused to one or more aryl, heteroaryl or cyclyl rings. A ring nitrogen atom of a heterocyclic ring also may be oxidized to form the corresponding N-hydroxy compound.

The term "heterocyclylalkyl" refers to an alkyl group substituted by a heterocyclyl. Heterocyclylalkyl includes groups in which more than one hydrogen atom has been replaced by a heterocyclyl group.

The terms "hetaralkyl" and "heteroaralkyl", as used herein, refers to an alkyl group substituted with a heteroaryl group. Exemplary heteroaralkyl groups include but are not limited to methylpyridyl or methylpyrimidyl.

The term "heterocyclyl" or "heterocyclylalkyl" refers to a nonaromatic 5-8 membered monocyclic, 5-12 membered bicyclic, or 11-14 membered tricyclic ring system having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S (e.g., carbon atoms and 1-3, 1-6, or 1-9 heteroatoms of N, O, or S if monocyclic, bicyclic, or tricyclic, respectively), wherein 0, 1, 2 or 3 atoms of each ring may be substituted by a substituent. Examples of heterocyclyl groups include piperazinyl, pyrrolidinyl, dioxanyl, morpholinyl, tetrahydrofuranyl, and include both bridged and fused ring

systems. The term “heterocyclalkyl” refers to an alkyl substituted with a heterocycl.

The term “heterocyclalkyl”, as used herein, refers to an alkyl group substituted with a heterocycle group.

The term “heteroalkyl,” as used herein, refers to a saturate or unsaturated, straight or branched chain aliphatic group, wherein one or more of the carbon atoms in the chain are independently replaced by a heteroatom. Exemplary hetero atoms include O, S, and N.

In the case of aralkyl, heteroaralkyl, cyclalkyl, heterocyclalkyl etc., groups described as optionally substituted, it is intended that either or both aryl, heteroaryl, cycl, heterocycl and alkyl moieties may be independently optionally substituted or unsubstituted.

The term “hydroxyalkyl” refers to an alkyl in which one or more hydrogen atoms are replaced by a hydroxy group.

The term “oxo” refers to an oxygen atom ($=O$), which forms a carbonyl when attached to carbon, an N-oxide when attached to nitrogen, and a sulfoxide or sulfone when attached to sulfur.

The term “thioalkyl” as used herein refers to an $-S(alkyl)$ group, where the point of attachment is through the sulfur atom and the alkyl group is as defined above.

The term “thiono” or “thioxo” refers to a sulfur atom ($=S$), which forms a thioketone when attached to carbon.

The term “substituted” refers to moieties having substituents replacing a hydrogen on one or more carbons of the backbone. It will be understood that “substitution” or “substituted with” includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. As used herein, the term “substituted” is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. The

permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms.

The term "substituent" refers to a group "substituted" on a moiety described herein. Any atom on any substituent can be substituted. Substituents can include any substituents described herein. Exemplary substituents include, without limitation, alkyl (e.g., C1, C2, C3, C4, C5, C6, C7, C8, C9, C10, C11, C12 straight or branched chain alkyl), cycloalkyl, haloalkyl (e.g., perfluoroalkyl such as CF₃), aryl, heteroaryl, aralkyl, heteroaralkyl, heterocyclyl, alkenyl, alkynyl, cycloalkenyl, heterocycloalkenyl, alkoxy, haloalkoxy (e.g., perfluoroalkoxy such as OCF₃), halo, hydroxy, carboxy, carboxylate, cyano, nitro, amino, alkylamino, SO₃H, sulfate, phosphate, methylenedioxy (-O-CH₂-O- wherein oxygens are attached to vicinal atoms), ethylenedioxy, oxo, thioxo (e.g., C=S), imino (alkyl, aryl, aralkyl), S(O)_nalkyl (where n is 0-2), S(O)_n aryl (where n is 0-2), S(O)_n heteroaryl (where n is 0-2), S(O)_n heterocyclyl (where n is 0-2), amine (mono-, di-, alkyl, cycloalkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, and combinations thereof), ester (alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl), amide (mono-, di-, alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, and combinations thereof), sulfonamide (mono-, di-, alkyl, aralkyl, heteroaralkyl, and combinations thereof). In one aspect, the substituents on a group are independently any one single, or any subset of the aforementioned substituents. In another aspect, a substituent may itself be substituted with any one of the above substituents.

As used herein, the phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted." In general, the term "substituted", whether preceded by the term "optionally" or not, means that a hydrogen radical of the designated moiety is replaced with the radical of a specified substituent, provided that the substitution results in a stable or chemically feasible compound. The term "substitutable", when used in reference to a designated atom, means that attached to the atom is a hydrogen radical, which hydrogen atom can be replaced with the radical of a suitable substituent. Unless otherwise indicated, an "optionally substituted" group

may have a substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds.

As used herein, the term “optionally substituted” means substituted or unsubstituted.

As used herein, the term “partially unsaturated” refers to a moiety that includes at least one double or triple bond between atoms. The term “partially unsaturated” encompasses rings, e.g., having one or more sites of unsaturation, but that are not completely unsaturated so as to be aryl or heteroaryl.

The term “chiral” refers to molecules which have the property of non-superimposability of the mirror image partner, while the term “achiral” refers to molecules which are superimposable on their mirror image partner. With respect to the nomenclature of a chiral center, terms “R” and “S” configuration are as defined by the IUPAC Recommendations. The term “enantiomers” refers to two stereoisomers of a compound which are non-superimposable mirror images of one another. An equimolar mixture of two enantiomers is called a “racemic mixture” or a “racemate.” The term “isomers” or “stereoisomers” refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space. For example, isomers include *cis*- and *trans*-isomers, *E*- and *Z*-isomers, *R*- and *S*-enantiomers, diastereomers, (D)-isomers, (L)-isomers, racemic mixtures thereof, and other mixtures thereof. The term “diastereomers” refers to stereoisomers with two or more centers of dissymmetry and whose molecules are not mirror images of one another.

The term “administration” or “administering” includes routes of introducing the compounds, or a composition thereof, of the invention to a subject to perform their intended function. Examples of routes of administration that may be used include injection (subcutaneous, intravenous, parenterally, intraperitoneally, intrathecal), oral, inhalation, rectal and transdermal. The pharmaceutical compositions may be given by

forms suitable for each administration route. For example, these compositions are administered in tablets or capsule form, by injection, inhalation, eye lotion, ointment, suppository, etc. administration by injection, infusion or inhalation; topical by lotion or ointment; and rectal by suppositories. Oral administration is preferred. The injection can be bolus or can be continuous infusion. Depending on the route of administration, a compound described herein can be coated with or disposed in a selected material to protect it from natural conditions which may detrimentally affect its ability to perform its intended function. A compound or composition described herein can be administered alone, or in conjunction with either another agent as described above or with a pharmaceutically-acceptable carrier, or both. A compound or composition described herein can be administered prior to the administration of the other agent, simultaneously with the agent, or after the administration of the agent. Furthermore, a compound described herein can also be administered in a pro-drug form which is converted into its active metabolite, or more active metabolite *in vivo*.

The language “biological activities” of a compound described herein includes all activities elicited by a compound described herein in a responsive subject or cell. It includes genomic and non-genomic activities elicited by these compounds.

The terms “inhibit” and “inhibitor” as used herein means an agent that measurably slows or stops the production of STriatal-Enriched tyrosine Phosphatase (STEP), or decreases or inactivates STEP, or interferes with STEP-mediated biological pathways. Inhibitors of STEP include compounds of the invention, e.g., compounds of Formulas (I), (II), or (III). A compound can be evaluated to determine if it is an inhibitor by measuring either directly or indirectly the activity of STEP in the presence of the compound suspected to inhibit STEP. Exemplary methods of measure STEP inhibition are described in the EXAMPLES herein.

An “effective amount” or “an amount effective” refers to an amount of the compound or composition which is effective, upon single or multiple dose administrations to a subject and for periods of time necessary, in treating a cell, or curing, alleviating, relieving or improving a symptom of a disorder, e.g., a disorder described herein. An effective amount of a compound described herein may vary according to factors such as the disease state, age, and weight of the subject, and the

ability of a compound described herein to elicit a desired response in the subject. Dosage regimens may be adjusted to provide the optimum therapeutic response. An effective amount is also one in which any toxic or detrimental effects (e.g., side effects) of a compound described herein are outweighed by the therapeutically beneficial effects. The term “effective amount” includes an amount effective, at dosages and for periods of time necessary, to achieve the desired result, e.g., modulate or regulate protein tyrosine phosphatases, e.g., STEP, in a subject and/or treat a disorder described herein such as a protein tyrosine phosphatase related disorder. Exemplary disorders include those related to cognition, learning and memory, neurogenesis. An effective amount may also affect neuronal plasticity, pain perception, mood and anxiety, and neuroendocrine regulation.

An effective amount of a compound described herein may vary according to factors such as the disease state, age, and weight of the subject, and the ability of a compound described herein to elicit a desired response in the subject. Dosage regimens may be adjusted to provide the optimum therapeutic response. An effective amount is also one in which any toxic or detrimental effects (e.g., side effects) of a compound described herein are outweighed by the therapeutically beneficial effects.

A therapeutically effective amount of a compound described herein (i.e., an effective dosage) may range from about 0.001 to 50 mg/kg body weight, preferably about 0.01 to 40 mg/kg body weight, more preferably about 0.1 to 35 mg/kg body weight, still more preferably about 1 to 30 mg/kg, and even more preferably about 10 to 30 mg/kg. The skilled artisan will appreciate that certain factors may influence the dosage required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of a compound described herein can include a single treatment or, preferably, can include a series of treatments. In one example, a subject is treated with a compound described herein in the range of between about 0.1 to 20 mg/kg body weight, one time per week for between about 1 to 10 weeks, preferably between 2 to 8 weeks, more preferably between about 3 to 7 weeks, and even more preferably for about 4, 5, or 6 weeks. It will also be appreciated that the effective

dosage of a compound described herein used for treatment may increase or decrease over the course of a particular treatment.

As used herein, an amount of a compound effective to prevent a disorder, or “a prophylactically effective amount” of the compound refers to an amount effective, upon single- or multiple-dose administration to the subject, in preventing or delaying the occurrence of the onset or recurrence of a disorder or a symptom of the disorder.

The language “improved biological properties” refers to any activity inherent in a compound described herein that enhances its effectiveness in vivo. In a preferred embodiment, this term refers to any qualitative or quantitative improved therapeutic property of a compound described herein, such as reduced off-target effects.

The term “modulate” refers to an increase or decrease, e.g., in the activity of an enzyme in response to exposure to a compound or composition described herein, e.g., the activation or inhibition of STEP, in at least a sub-population of cells in a subject such that a desired end result is achieved (e.g., a therapeutic result). In some embodiments, a compound as described herein inhibits a target described herein, e.g., STEP. In some embodiments, a compound as described herein is activates a target described herein, e.g., STEP.

As used herein, the term “subject” is intended to include human and non-human animals. Exemplary human subjects include a human patient having a disorder, e.g., a disorder described herein, or a normal subject. The term “non-human animals” includes all vertebrates, e.g., non-mammals (such as chickens, amphibians, reptiles) and mammals, such as non-human primates, domesticated and/or agriculturally useful animals, e.g., sheep, dog, cat, cow, pig, etc.

As used herein, the term “treat” or “treating” is defined as applying or administering a compound or composition, alone or in combination with a second compound or composition, to a subject, e.g., a patient, or applying or administering the compound or composition to an isolated tissue or cell, e.g., cell line, from a subject, e.g., a patient, who has a disorder (e.g., a disorder as described herein), a symptom of a disorder, or a predisposition toward a disorder, with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve or affect the disorder, one or more symptoms of the disorder or the predisposition toward the disorder (e.g., to

prevent at least one symptom of the disorder or to delay onset of at least one symptom of the disorder).

The phrases “parenteral administration” and “administered parenterally” as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

The term “prodrug” or “pro-drug” includes compounds with moieties that can be metabolized *in vivo*. Generally, the prodrugs are metabolized *in vivo* by esterases or by other mechanisms to active drugs. Examples of prodrugs and their uses are well known in the art (See, *e.g.*, Berge *et al.* (1977) “Pharmaceutical Salts”, *J. Pharm. Sci.* 66:1-19). The prodrugs can be prepared *in situ* during the final isolation and purification of the compounds, or by separately reacting the purified compound in its free acid form or hydroxyl with a suitable esterifying agent. Hydroxyl groups can be converted into esters *via* treatment with a carboxylic acid. Examples of prodrug moieties include substituted and unsubstituted, branch or unbranched lower alkyl ester moieties, (*e.g.*, propionoic acid esters), lower alkenyl esters, di-lower alkyl-amino lower-alkyl esters (*e.g.*, dimethylaminoethyl ester), acylamino lower alkyl esters (*e.g.*, acetyloxymethyl ester), acyloxy lower alkyl esters (*e.g.*, pivaloyloxymethyl ester), aryl esters (phenyl ester), aryl-lower alkyl esters (*e.g.*, benzyl ester), substituted (*e.g.*, with methyl, halo, or methoxy substituents) aryl and aryl-lower alkyl esters, amides, lower-alkyl amides, di-lower alkyl amides, and hydroxy amides. Preferred prodrug moieties are propionoic acid esters and acyl esters. Prodrugs which are converted to active forms through other mechanisms *in vivo* are also included.

The language “a prophylactically effective amount” of a compound refers to an amount of a compound described herein any formula herein or otherwise described herein which is effective, upon single or multiple dose administration to the patient, in preventing or treating a disease or condition.

The language “reduced off-target effects” is intended to include a reduction in any undesired side effect elicited by a compound described herein when administered

in vivo. In some embodiments, a compound described herein has little to no cardio and/or pulmonary toxicity (e.g., when administered to a subject). In some embodiments, a compound described herein has little to no hallucinogenic activity (e.g., when administered to a subject).

The term “selective” means a greater activity against a first target. In some embodiments a compound has a selectivity of at least 1.25-fold, at least 1.5 fold, at least 2-fold, at least 3-fold, at least 4-fold, at least 5-fold, at least 6-fold, at least 10-fold or at least 100-fold greater towards a first target relative to a second target. In some embodiments, a compound described herein, e.g., a compound of Formulas (I), (II), or (III) is selective toward STEP relative to one or more other protein tyrosine phosphatases.

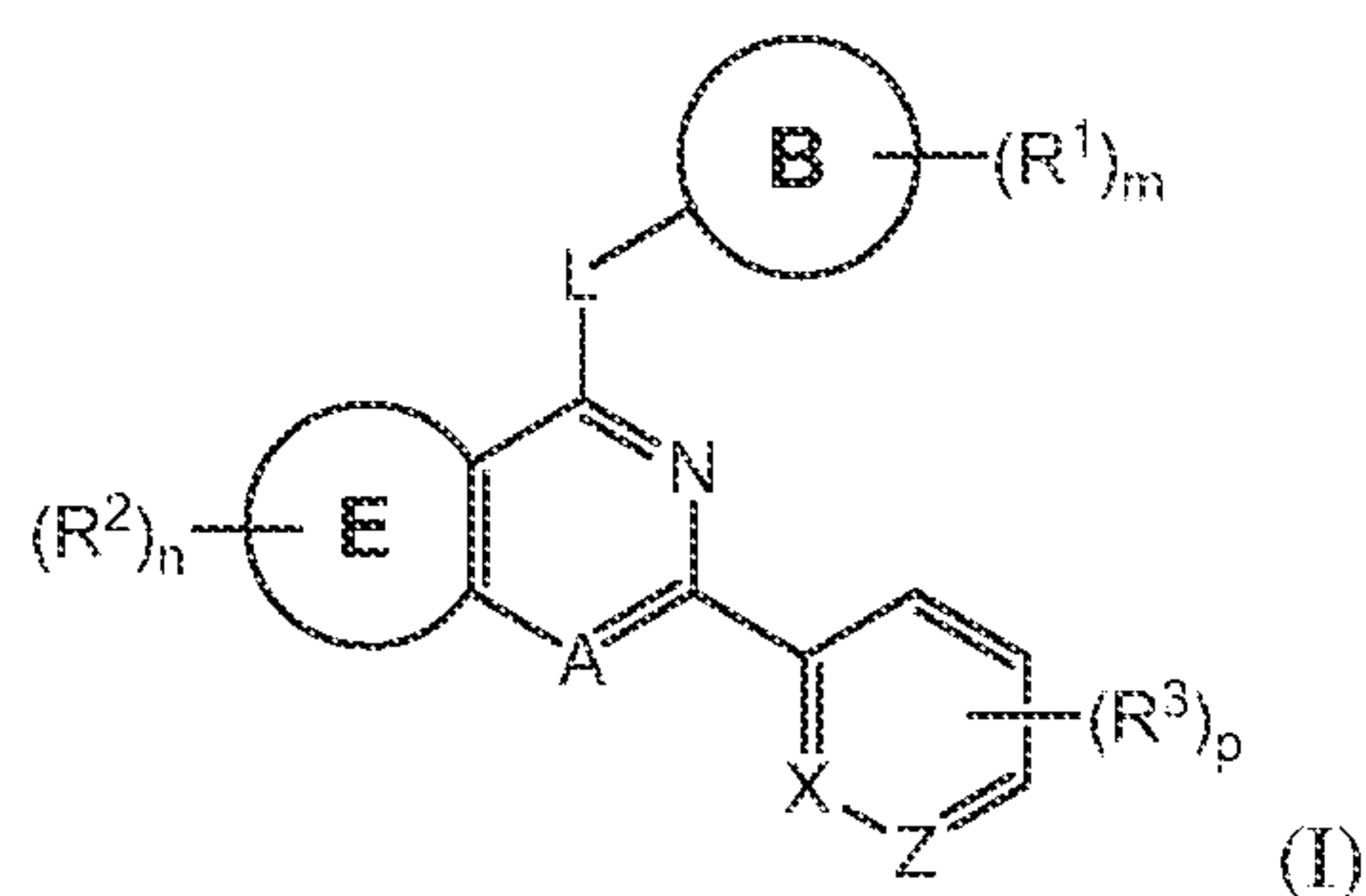
The term “subject” includes organisms which are capable of suffering from a serotonin-receptor-related disorder or who could otherwise benefit from the administration of a compound described herein of the invention, such as human and non-human animals. Preferred humans include human patients suffering from or prone to suffering from a serotonin-related disorder or associated state, as described herein. The term “non-human animals” of the invention includes all vertebrates, e.g., mammals, e.g., rodents, e.g., mice, and non-mammals, such as non-human primates, e.g., sheep, dog, cow, chickens, amphibians, reptiles, etc.

The phrases “systemic administration,” “administered systemically”, “peripheral administration” and “administered peripherally” as used herein mean the administration of a compound described herein(s), drug or other material, such that it enters the patient's system and, thus, is subject to metabolism and other like processes, for example, subcutaneous administration.

Compounds

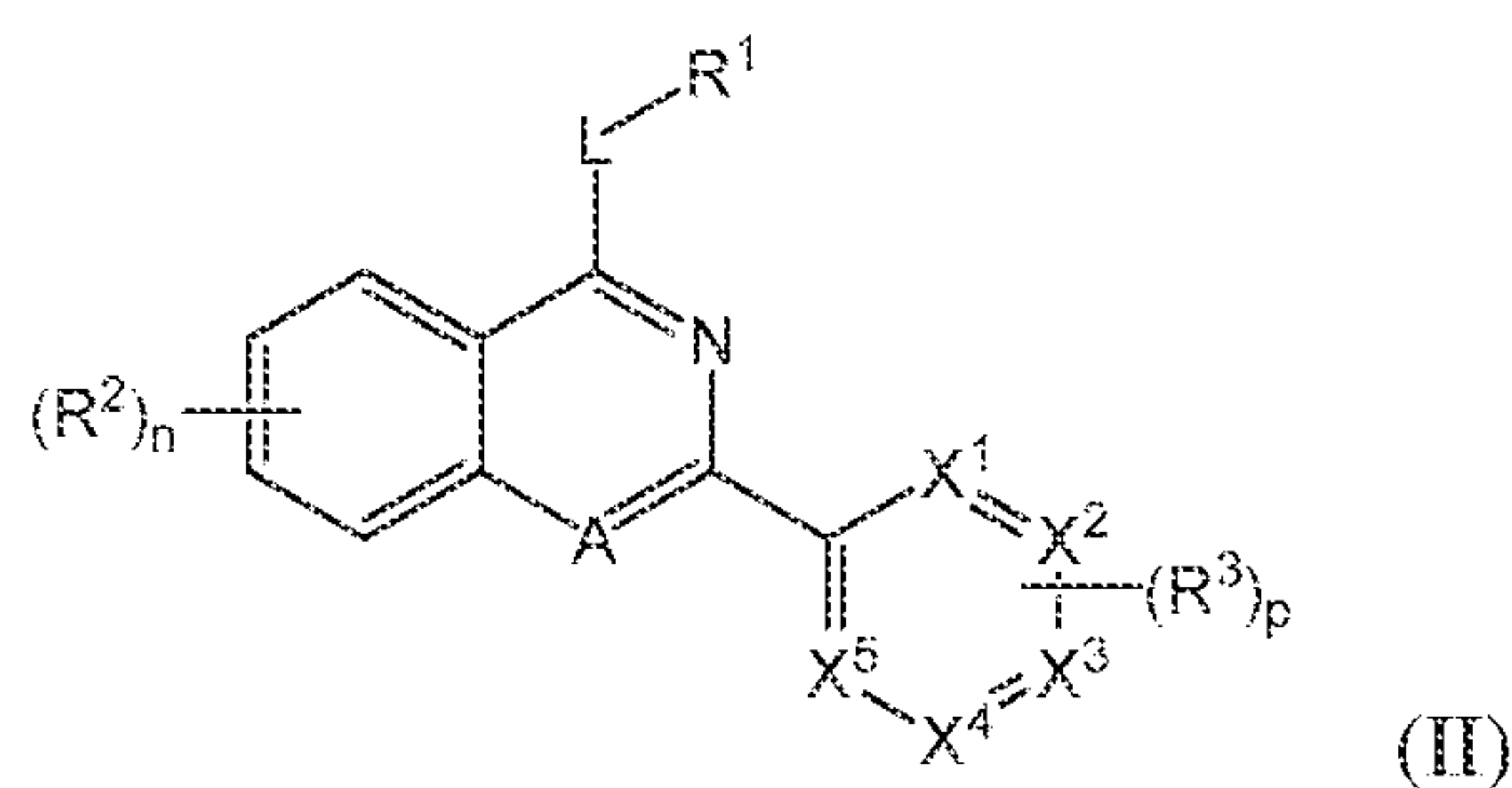
The compounds described herein can be used for a variety of purposes, e.g., therapeutic purposes. Many of the compounds modulate STEP activity and can be used, for example to inhibit STEP, e.g., in a subject.

Exemplary compounds include a compound of formula (I):



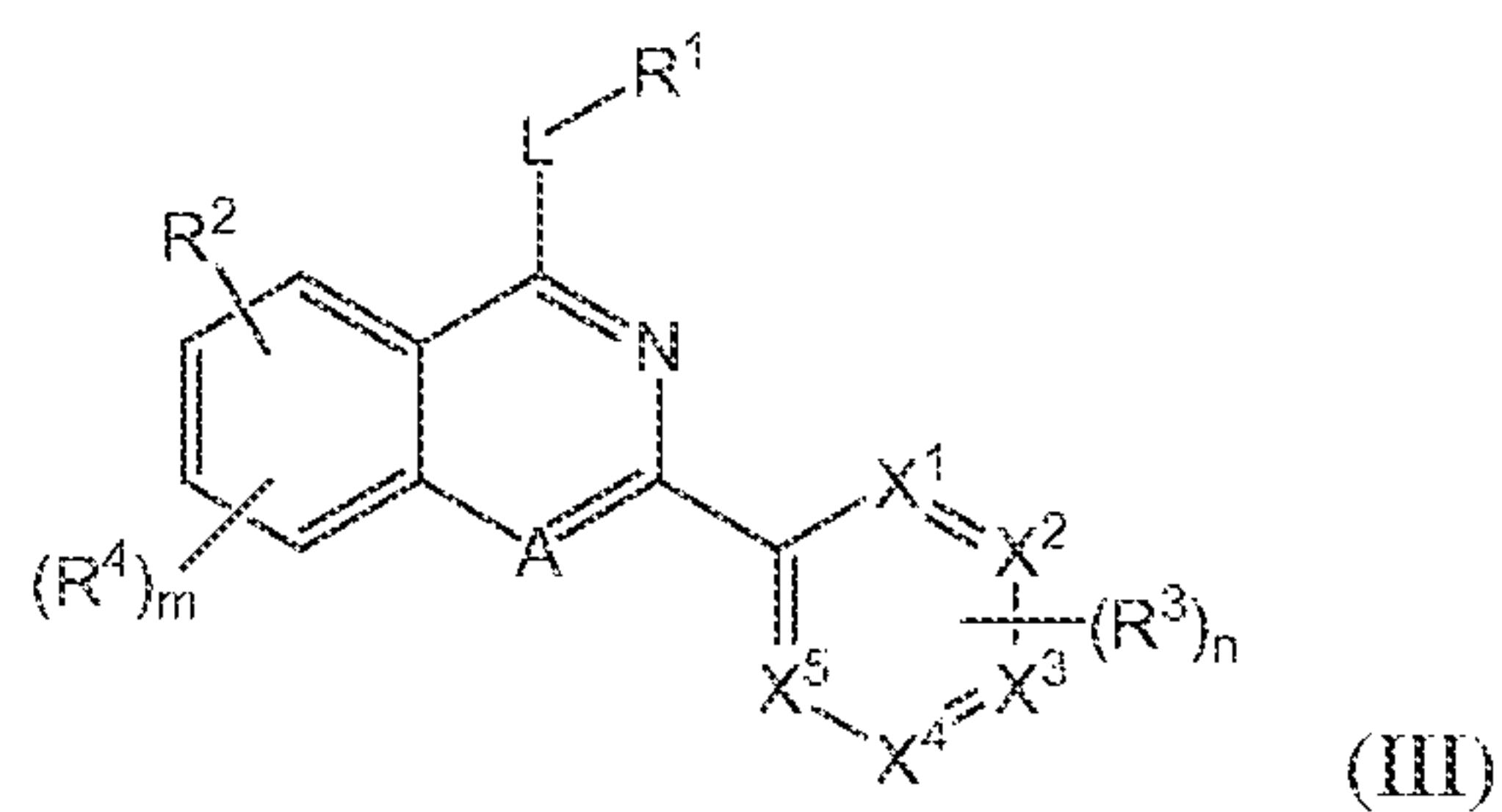
wherein A, B, E, L, X, Z, R^1 , R^2 , R^3 , m, n and p are as defined above in the section relating to compound of Formula (I). In preferred embodiments, L is NH, B is aryl (e.g., phenyl) that may be optionally substituted, E is aryl (e.g., phenyl), A is N, X is CH and Z is N.

Exemplary compounds include a compound of formula (II):



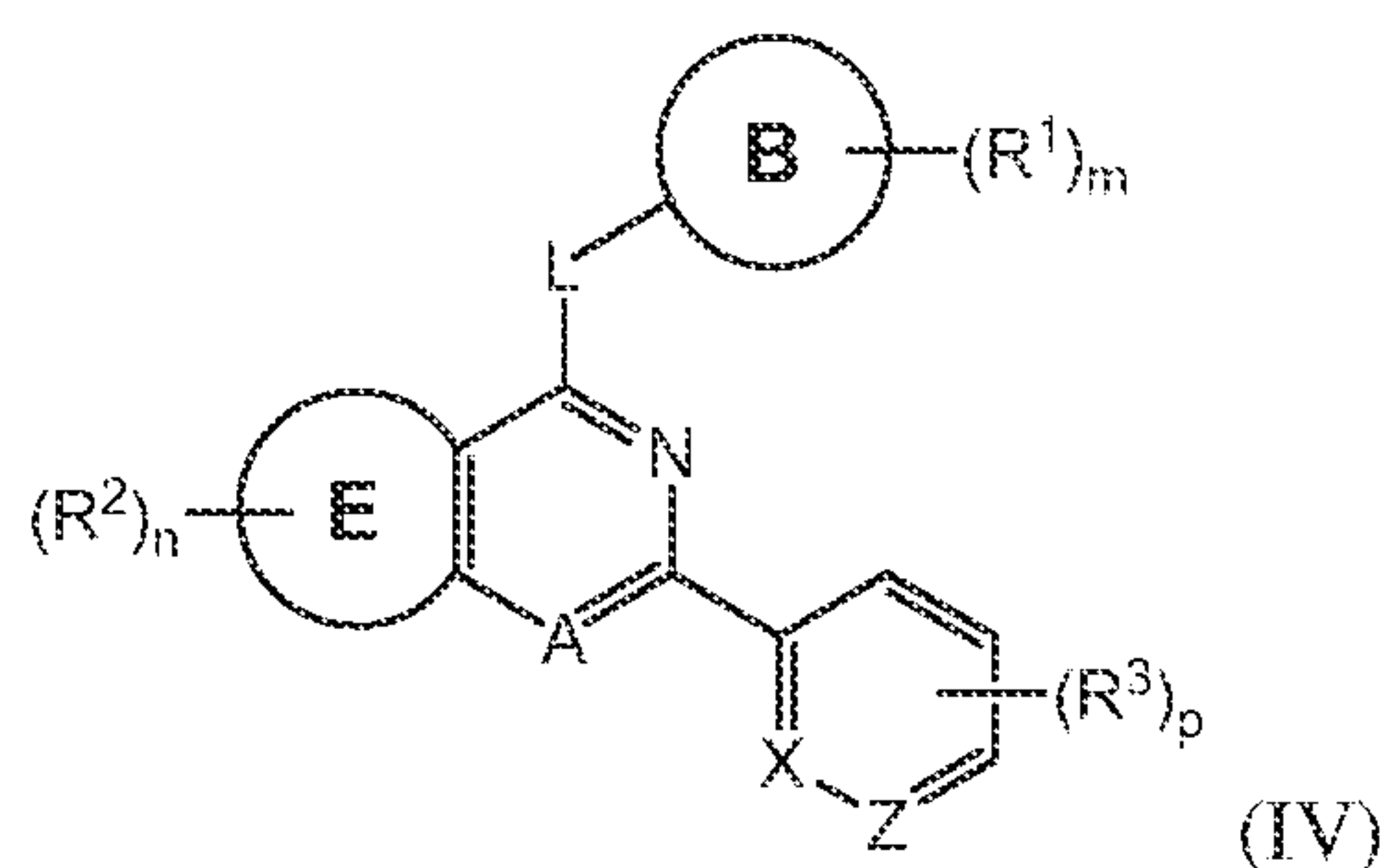
wherein A, L, X^1 , X^2 , X^3 , X^4 , X^5 , R^1 , R^2 , R^3 , n and p are as defined above in the section relating to compound of Formula (II).

Exemplary compounds include a compound of formula (III):



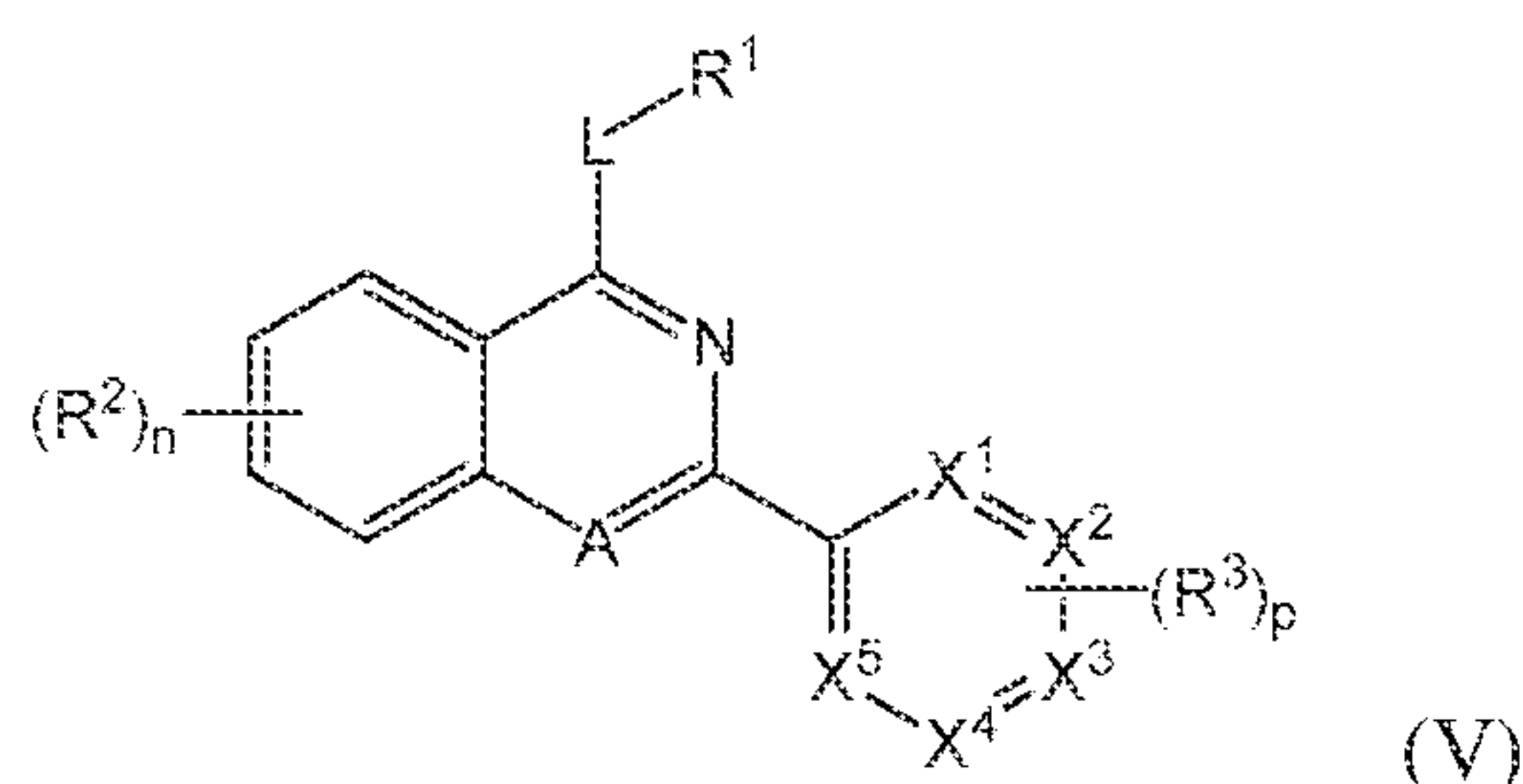
wherein A, L, X^1 , X^2 , X^3 , X^4 , X^5 , R^1 , R^2 , R^3 , R^4 , m, and n are as defined above in the section relating to compound of Formula (III).

Exemplary compounds include a compound of formula (IV):



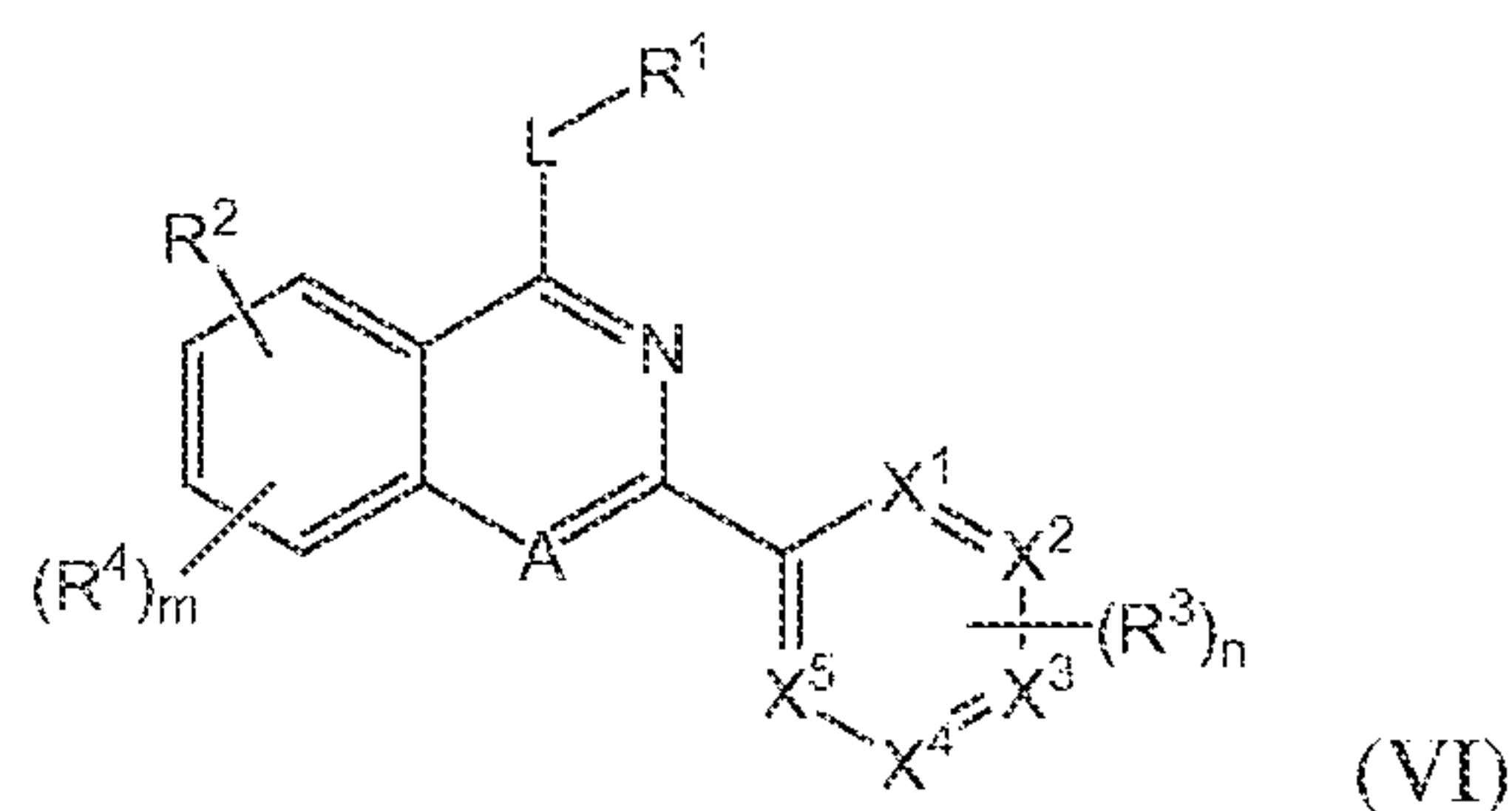
wherein A, B, E, L, X, Z, R^1 , R^2 , R^3 , m, n and p are as defined above in the section relating to compound of Formula (IV). In preferred embodiments, L is NH, B is aryl (e.g., phenyl) that may be optionally substituted, E is aryl (e.g., phenyl), A is N, X is CH and Z is N.

Exemplary compounds include a compound of formula (V):



wherein A, L, X^1 , X^2 , X^3 , X^4 , X^5 , R^1 , R^2 , R^3 , n and p are as defined above in the section relating to compound of Formula (V).

Exemplary compounds include a compound of formula (VI):



wherein A, L, X^1 , X^2 , X^3 , X^4 , X^5 , R^1 , R^2 , R^3 , R^4 , m, and n are as defined above in the section relating to compound of Formula (VI).

The present invention includes compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, the replacement of a carbon by a ^{13}C - or ^{14}C -enriched carbon, or the replacement of a

fluorine by a ^{19}F -enriched fluorine are within the scope of this invention. Such compounds are useful, for example, as analytical tools or probes in biological assays, or as bioactive agents.

In the compounds of the present invention, any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom unless otherwise stated (e.g., hydrogen, ^2H or deuterium and ^3H or tritium). The formulas described herein may or may not indicate whether atoms at certain positions are isotopically enriched. When a structural formula is silent with respect to whether a particular position is isotopically enriched, it is to be understood that the isotopes at that particular position are present in natural abundance or, that the particular position is isotopically enriched with one or more naturally occurring stable isotopes. For example, the formula $-\text{CH}_2-$ represents the following possible structures: $-\text{CH}_2-$, $-\text{CHD}-$ or $-\text{CD}_2-$.

The variable "D" is defined as deuterium.

The terms "compound" or "compounds," when referring to a compound of this invention or a compound described herein, refers to a collection of molecules having an identical chemical structure, except that there may be isotopic variation among the constituent atoms of the molecules. Thus, it will be clear to those of skill in the art that a compound represented by a particular chemical structure containing indicated hydrogen atoms will contain lesser amounts of isotopologues having deuterium atoms at one or more of the designated hydrogen positions in that structure. Alternatively, a compound represented by a particular chemical structure containing indicated deuterium atoms will contain lesser amounts of isotopologues having hydrogen atoms at one or more of the designated deuterium positions in that structure. The relative amount of such isotopologues in a compound of this invention will depend on a number of factors including isotopic purity of deuterated reagents used to make the compound and the efficiency of incorporation of deuterium in the various synthetic steps used to prepare the compound. The relative amount of such isotopologues in total will be less than 55% of the compound. In other embodiments, the relative amount of such isotopologues in total will be less than 50%, less than 45%, less than

40%, less than 35%, less than 35%, less than 15%, less than 10%, less than 5%, less than 1% or less than 0.5% of the compound.

The term "isotopologue" refers to a species that differs from a specific compound of this invention only in the isotopic composition thereof. Isotopologues can differ in the level of isotopic enrichment at one or more positions and/or in the position(s) of isotopic enrichment.

The compounds of this invention may contain one or more asymmetric centers and thus occur as racemates and racemic mixtures, single enantiomers, individual diastereomers and diastereomeric mixtures. Described herein are enantiomerically enriched compounds (e.g., a compound resolved to an enantiomeric excess of 60%, 70%, 80%, 85%, 90%, 95%, 99% or greater). All such isomeric forms of these compounds are expressly included in the present invention. The compounds of this invention may also contain linkages (e.g., carbon-carbon bonds) or substituents that can restrict bond rotation, e.g. restriction resulting from the presence of a ring or double bond. Accordingly, all *cis/trans* and *E/Z* isomers are expressly included in the present invention. The compounds of this invention may also be represented in multiple tautomeric forms, in such instances, the invention expressly includes all tautomeric forms of the compounds described herein, even though only a single tautomeric form may be represented (e.g., alkylation of a ring system may result in alkylation at multiple sites, the invention expressly includes all such reaction products). All such isomeric forms of such compounds are expressly included in the present invention. All crystal forms of the compounds described herein are expressly included in the present invention.

Naturally occurring or synthetic isomers can be separated in several ways known in the art. Methods for separating a racemic mixture of two enantiomers include chromatography using a chiral stationary phase (see, e.g., "Chiral Liquid Chromatography," W.J. Lough, Ed. Chapman and Hall, New York (1989)). Enantiomers can also be separated by classical resolution techniques. For example, formation of diastereomeric salts and fractional crystallization can be used to separate enantiomers. For the separation of enantiomers of carboxylic acids, the diastereomeric salts can be formed by addition of enantiomerically pure chiral bases

such as brucine, quinine, ephedrine, strychnine, and the like. Alternatively, diastereomeric esters can be formed with enantiomerically pure chiral alcohols such as menthol, followed by separation of the diastereomeric esters and hydrolysis to yield the free, enantiomerically enriched carboxylic acid. For separation of the optical isomers of amino compounds, addition of chiral carboxylic or sulfonic acids, such as camphorsulfonic acid, tartaric acid, mandelic acid, or lactic acid can result in formation of the diastereomeric salts. For example a compound can be resolved to an enantiomeric excess (e.g., 60%, 70%, 80%, 85%, 90%, 95%, 99% or greater) via formation of diastereomeric salts, e.g. with a chiral base, e.g., (+) or (-) α -methylbenzylamine, or via high performance liquid chromatography using a chiral column. In some embodiments a product is purified directly on a chiral column to provide enantiomerically enriched compound.

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., therapeutic administration to a subject).

Compounds of formulas (I), (II), (III), (IV), (V), and (VI) are described herein, for example as provided in the summary above. Exemplary compounds are shown in Tables 1-30 in the Examples section.

Synthetic Methods

A compound described herein may be prepared via a variety of synthetic methods. Representative syntheses are shown in the Examples section.

As can be appreciated by the skilled artisan, further methods of synthesizing the compounds of the formulae herein will be evident to those of ordinary skill in the art. Additionally, the various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the compounds described herein are known in the art and

include, for example, those such as described in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 2d. Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995), and subsequent editions thereof.

Additionally, the compounds disclosed herein can be prepared on a solid support. The term "solid support" refers a material to which a compound is attached to facilitate identification, isolation, purification, or chemical reaction selectivity of the compound. Such materials are known in the art and include, for example, beads, pellets, disks, fibers, gels, or particles such as cellulose beads, pore-glass beads, silica gels, polystyrene beads optionally cross-linked with divinylbenzene and optionally grafted with polyethylene glycol, poly-acrylamide beads, latex beads, dimethylacrylamide beads optionally cross-linked with N,N'-bis-acryloyl ethylene diamine, glass particles coated with hydrophobic polymer, and material having a rigid or semi-rigid surface. The solid supports optionally have functional groups such as amino, hydroxy, carboxy, or halo groups, (see, Obrecht, D. and Villalgrodo, J.M., *Solid-Supported Combinatorial and Parallel Synthesis of Small-Molecular-Weight Compound Libraries*, Pergamon-Elsevier Science Limited (1998)), and include those useful in techniques such as the "split and pool" or "parallel" synthesis techniques, solid-phase and solution-phase techniques, and encoding techniques (see, for example, Czarnik, A.W., *Curr. Opin. Chem. Bio.*, (1997) 1, 60).

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

Included herein are pharmaceutically acceptable derivatives or prodrugs of the compounds described herein. A "pharmaceutically acceptable derivative or prodrug" means any pharmaceutically acceptable salt, ester, salt of an ester, or other

derivative of a compound of this invention (for example an imide ester of an amide), which, upon administration to a recipient, is capable of providing (directly or indirectly) a compound described herein. Particularly favored derivatives and prodrugs are those that increase the bioavailability of the compounds of this invention when such compounds are administered to a mammal (e.g., by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to a biological compartment (e.g., the brain or lymphatic system) relative to the parent species. In an exemplary embodiment, the prodrug is a derivative including a group that enhances aqueous solubility or active transport through the gut membrane is appended to the structure of formulae described herein. In another exemplary embodiment, the prodrug is suitable for treatment or prevention of those diseases and conditions that require the drug molecule to cross the blood brain barrier. In a preferred embodiment, the prodrug enters the brain, where it is converted into the active form of the drug molecule.

Pharmaceutically acceptable salts of the compounds of this invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acid salts include acetate, adipate, benzoate, benzenesulfonate, butyrate, citrate, digluconate, dodecylsulfate, formate, fumarate, glycolate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, lactate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, palmoate, phosphate, picrate, pivalate, propionate, salicylate, succinate, sulfate, tartrate, tosylate and undecanoate. Salts derived from appropriate bases include alkali metal (e.g., sodium), alkaline earth metal (e.g., magnesium), ammonium and N-(alkyl)₄⁺ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersible products may be obtained by such quaternization.

Evaluating Compounds

A variety of methods can be used to evaluate a compound for ability to modulate STEP activity. Evaluation methods include *in vitro* assays (e.g., enzyme-based assays), *in vitro* cell-based signaling assays, and *in vivo* methods (e.g., testing in

animal models). The evaluation methods can evaluate binding activity, phosphatase activity, or an activity downstream of STEP, such as the activity of ERK.

For example, a compound described herein may be evaluated using a fluorescence-based phosphatase assay. A phosphate-containing reagent may be used in the assay which, upon dephosphorylation by a phosphatase, generates a fluorescent product that may be detected using a fluorometer or fluorescence plate reader. Data may be expressed as percentage (%) inhibition of enzyme activity. For compounds showing enzymatic activation, data may be represented as percentage of inhibition but with negative values.

Compositions and routes of administration

The invention also provides a pharmaceutical composition, comprising an effective amount of a compound described herein (e.g., a compound capable of treating or preventing a condition as described herein, e.g., a compound of any formula herein or otherwise described herein) and a pharmaceutically acceptable carrier.

The compositions delineated herein include the compounds delineated herein (e.g., a compound described herein), as well as additional therapeutic agents if present, in amounts effective for achieving a modulation of disease or disease symptoms, including those described herein.

The term “pharmaceutically acceptable carrier or adjuvant” refers to a carrier or adjuvant that may be administered to a patient, together with a compound of this invention, and which does not destroy the pharmacological activity thereof and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the compound.

Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as d- α -tocopherol polyethylene glycol 1000 succinate, surfactants used in pharmaceutical dosage forms such as Tweens™ or other similar polymeric delivery matrices, serum proteins, such as human serum albumin, buffer

substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat. Cyclodextrins such as α -, β -, and γ -cyclodextrin, or chemically modified derivatives such as hydroxyalkylcyclodextrins, including 2- and 3-hydroxypropyl- β -cyclodextrins, or other solubilized derivatives may also be advantageously used to enhance delivery of compounds of the formulae described herein.

The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir, preferably by oral administration or administration by injection. The pharmaceutical compositions of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability of the formulated compound or its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a

solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, or carboxymethyl cellulose or similar dispersing agents which are commonly used in the formulation of pharmaceutically acceptable dosage forms such as emulsions and or suspensions. Other commonly used surfactants such as Tweens or Spans and/or other similar emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, emulsions and aqueous suspensions, dispersions and solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions and/or emulsions are administered orally, the active ingredient may be suspended or dissolved in an oily phase is combined with emulsifying and/or suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

The pharmaceutical compositions of this invention may also be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

Topical administration of the pharmaceutical compositions of this invention is useful when the desired treatment involves areas or organs readily accessible by topical application. For application topically to the skin, the pharmaceutical

composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier with suitable emulsifying agents. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-transdermal patches are also included in this invention.

The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

When the compositions of this invention comprise a combination of a compound of the formulae described herein and one or more additional therapeutic agents, both the compound and the additional agent should be present at dosage levels of between about 1 to 100%, and more preferably between about 5 to 95% of the dosage normally administered in a monotherapy regimen. The additional agents may be administered separately, as part of a multiple dose regimen, from the compounds of this invention. Alternatively, those agents may be part of a single dosage form, mixed together with the compounds of this invention in a single composition.

The compounds described herein can, for example, be administered by injection, intravenously, intraarterially, subdermally, intraperitoneally, intramuscularly, or subcutaneously; or orally, buccally, nasally, transmucosally, topically, in an ophthalmic preparation, or by inhalation, with a dosage ranging from about 0.5 to about 100 mg/kg of body weight, alternatively dosages between 1 mg and

1000 mg/dose, every 4 to 120 hours, or according to the requirements of the particular drug. The methods herein contemplate administration of an effective amount of compound or compound composition to achieve the desired or stated effect. Typically, the pharmaceutical compositions of this invention will be administered from about 1 to about 6 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Alternatively, such preparations contain from about 20% to about 80% active compound.

Lower or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the disease, condition or symptoms, the patient's disposition to the disease, condition or symptoms, and the judgment of the treating physician.

Upon improvement of a patient's condition, a maintenance dose of a compound, composition or combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

Methods of treatment

The compounds and compositions described herein can be administered to cells in culture, e.g. *in vitro* or *ex vivo*, or to a subject, e.g., *in vivo*, to treat, prevent, and/or diagnose a variety of disorders, including those described herein below.

The compounds and compositions described herein can be administered to a subject, for example using a method described herein, who is suffering from a disorder described herein, e.g., a disorder that would benefit from the modulation of STEP (e.g., activating or inhibiting STEP). The compounds and compositions described herein can be administered to a subject, for example using a method described herein, who is at risk for a disorder described herein, e.g., a disorder that would benefit from the modulation of STEP (e.g., activating or inhibiting STEP).

Inhibitors of STEP may increase phosphorylation of an NMDA-R. Thus, in some embodiments, a compound described herein, e.g., a compound that inhibits STEP, may be useful for treating a disorder in which increasing phosphorylation of an NMDA-R would be beneficial.

Inhibitors of STEP may activate an ERK1 or ERK2 kinase, for example, in the CNS. Thus, in some embodiments, a compound described herein, e.g., a compound that inhibits STEP, may be useful for treating a disorder in which activate an ERK1 or ERK2 kinase would be beneficial.

Compounds described herein may be useful in treating a variety of disorders, including disorders of the CNS. Exemplary disorders include schizophrenia, schizoaffective disorders, major depression, bipolar disorder, cognitive deficit, mild cognitive impairment (MCI), Alzheimer's disease (AD), attention-deficit/hyperactivity disorder (ADHD), dementia, generalized anxiety disorders, panic disorders, obsessive-compulsive disorders, phobias, post-traumatic stress syndrome, anorexia nervosa, drug addiction, ischemic stroke, head trauma or brain injury, Huntington's disease, Parkinson's disease, spinocerebellar degeneration, motor neuron diseases, epilepsy, neuropathic pain, chronic pain, neuropathies, autism and autistic disorders.

Compounds described herein may be useful for treating or preventing central nervous system disorders selected from the group consisting of schizophrenia; refractory, intractable or chronic schizophrenia; emotional disturbance; psychotic disorder; mood disorder; bipolar I type disorder; bipolar II type disorder; depression; endogenous depression; major depression; melancholy and refractory depression; dysthymic disorder; cyclothymic disorder; panic attack; panic disorder; agoraphobia; social phobia; obsessive-compulsive disorder; post-traumatic stress disorder;

generalized anxiety disorder; acute stress disorder; hysteria; somatization disorder; conversion disorder; pain disorder; hypochondriasis; factitious disorder; dissociative disorder; sexual dysfunction; sexual desire disorder; sexual arousal disorder; erectile dysfunction; anorexia nervosa; bulimia nervosa; sleep disorder; adjustment disorder; alcohol abuse; alcohol intoxication; drug addiction; stimulant intoxication; narcotism; anhedonia; iatrogenic anhedonia; anhedonia of a psychic or mental cause; anhedonia associated with depression; anhedonia associated with schizophrenia; delirium; cognitive impairment; cognitive impairment associated with Alzheimer's disease, Parkinson's disease and other neurodegenerative diseases; cognitive impairment caused by Alzheimer's disease; Parkinson's disease and associated neurodegenerative diseases; cognitive impairment of schizophrenia; cognitive impairment caused by refractory, intractable or chronic schizophrenia; vomiting; motion sickness; obesity; migraine; pain (ache) ; mental retardation; autism disorder (autism); Tourette's disorder; tic disorder; attention-deficit/hyperactivity disorder; conduct disorder; and Down's syndrome.

Compounds described herein may be useful for treating or preventing disorders selected from schizophrenia, schizoaffective disorder, bipolar disorder, manic-depressive disorder, psychosis, mood and anxiety disorders, mania, drug or substance addiction, cognition disorders, learning disabilities, learning and memory disorders, aging and neurologic disorders associated with or linked with cognitive impairments; mild cognitive impairments (MCI), Alzheimer's disease, Alzheimer-related cognition disorders, Huntington's disease, Parkinson's disease, CADASIL syndrome (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), amnesia, Wernicke-Korsakoff syndrome, Korsakoff syndrome, mild traumatic head injury (MBTI), traumatic head injury (TBI), fragile X syndrome, stroke, attention-deficit and hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD), loss of concentration, autism, cerebral palsy, encephalopathy, and narcolepsy. The disorder may affect learning and memory, neurogenesis, neuronal plasticity, pain perception, mood and anxiety, or neuroendocrine regulation. The disorder may be a cognitive deficit disorder. The disorder may involve pain perception or neuroendocrine regulation.

Schizophrenia

In some embodiments, a compound or composition described herein can be used in the treatment of schizophrenia. Schizophrenia is a psychiatric diagnosis that describes a mental disorder characterized by abnormalities in the perception or expression of reality. Distortions in perception may affect all five senses, including sight, hearing, taste, smell and touch, but most commonly manifests as auditory hallucinations, paranoid or bizarre delusions, or disorganized speech and thinking with significant social or occupational dysfunction. Onset of symptoms typically occurs in young adulthood, with approximately 0.4–0.6% of the population affected. Diagnosis is based on the patient's self-reported experiences and observed behavior.

The disorder is thought to mainly affect cognition, but it also usually contributes to chronic problems with behavior and emotion. People with schizophrenia are likely to have additional (comorbid) conditions, including major depression and anxiety disorders. Social problems, such as long-term unemployment, poverty and homelessness, are common. Furthermore, the average life expectancy of people with the disorder is 10 to 12 years less than those without, due to increased physical health problems and a higher suicide rate.

The Diagnostic and Statistical Manual of Mental Disorders (DSM) contains five sub-classifications of schizophrenia. These include Paranoid type (where delusions and hallucinations are present but thought disorder, disorganized behavior, and affective flattening are absent); Disorganized type (also known as hebephrenic schizophrenia, where thought disorder and flat affect are present together); Catatonic type (the subject may be almost immobile or exhibit agitated, purposeless movement; symptoms can include catatonic stupor and waxy flexibility); Undifferentiated type (psychotic symptoms are present but the criteria for paranoid, disorganized, or catatonic types have not been met); and Residual type (where positive symptoms are present at a low intensity only).

The International Statistical Classification of Diseases and Related Health Problems (10th Revision) defines two additional subtypes. These include Post-schizophrenic depression (a depressive episode arising in the aftermath of a schizophrenic illness where some low-level schizophrenic symptoms may still be

present); and Simple schizophrenia (insidious and progressive development of prominent negative symptoms with no history of psychotic episodes.)

An agent for the treatment of schizophrenia may improve so-called positive symptoms in the acute period of schizophrenia such as hallucinations, delusions, excitations and the like. An agent for treating schizophrenia may also improve so-called negative symptoms that are observed in the chronic period of schizophrenia such as apathy, emotional depression, hyposychosis and the like.

Schizoaffective Disorder

Schizoaffective disorder is a psychiatric diagnosis that describes a mental disorder characterized by recurring episodes of elevated or depressed mood, or simultaneously elevated and depressed mood that alternate or occur together with distortions in perception. The perceptual distortion component of the disorder, called psychosis, may affect all five senses, including sight, hearing, taste, smell and touch, but most commonly manifest as auditory hallucinations, paranoid or bizarre delusions, or disorganized speech and thinking with significant social and occupational dysfunction. The elevated, depressed or simultaneously elevated and depressed mood episode components of the disorder, called mood disorder, are broadly recognized as depressive and bipolar types of the illness; the division is based on whether the individual has ever had a manic, hypomanic or mixed episode. Onset of symptoms usually begins in early adulthood and is rarely diagnosed in childhood (prior to age 13). The lifetime prevalence of the disorder is uncertain (due to studies using varying diagnostic criteria), although it is generally agreed to be less than 1 percent, and possibly in the range of 0.5 to 0.8 percent. Diagnosis is based on the patient's self-reported experiences and observed behavior. No laboratory test for schizoaffective disorder currently exists. As a group, people with schizoaffective disorder have a more favorable prognosis than people with schizophrenia, but a worse prognosis than those with mood disorders.

The disorder is thought to mainly affect cognition and emotion, but it also usually contributes to ongoing problems with behavior and motivation. People with schizoaffective disorder are likely to have additional (comorbid) conditions, including anxiety disorders and substance abuse. Social problems, such as long-term

unemployment, poverty and homelessness, are common. Furthermore, the average life expectancy of people with the disorder is shorter than those without the disorder, due to increased physical health problems and a higher suicide rate.

Cognitive Deficit

Treatment using a compound or composition described herein may improve a cognitive deficit associated with a cognition-related disorder. Cognitive deficit is an inclusive term to describe any characteristic that acts as a barrier to cognitive performance. The term may describe deficits in global intellectual performance, such as mental retardation, it may describe specific deficits in cognitive abilities (learning disorders, dyslexia), or it may describe drug-induced cognitive/memory impairment, such as that seen with alcohol and the benzodiazepines. Cognitive deficits may be congenital or caused by environmental factors such as brain injuries, neurological disorders, or mental illness.

Exemplary cognition-related disorders (e.g., cognitive dysfunction) include, without limitation, mild cognitive impairment (MCI), dementia, delirium, amnestic disorder, Alzheimer's disease, Parkinson's disease and Huntington's disease; memory disorders including memory deficits associated with depression, senile dementia, dementia of Alzheimer's disease; cognitive deficits or cognitive dysfunction associated with neurological conditions including, for example, Parkinson's disease (PD), Huntington's disease (HD), Alzheimer's disease, depression, schizophrenia and other psychotic disorders such as paranoia and manic-depressive illness; cognitive dysfunction in schizophrenia; disorders of attention and learning such as attention deficit disorders (e.g., attention deficit hyperactivity disorder (ADHD)) and dyslexia; cognitive dysfunction associated with developmental disorders such as Down's syndrome and Fragile X syndrome; loss of executive function; loss of learned information; vascular dementia; schizophrenia; cognitive decline; a neurodegenerative disorder; and other dementias, for example, dementia due to HIV disease, head trauma, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeldt-Jakob disease, or due to multiple etiologies. Cognition-related disorders also include, without limitation, cognitive dysfunction associated with MCI and dementias such as Lewy Body, vascular, and post stroke dementias. Cognitive dysfunction associated

with surgical procedures, traumatic brain injury or stroke may also be treated in accordance with the embodiments described herein.

Major Depression

Major depression (also known as clinical depression, major depressive disorder, unipolar depression, or unipolar disorder) is a mental disorder characterized by a pervasive low mood, low self-esteem, and loss of interest or pleasure in normally enjoyable activities. Types of Major depressive disorder include, e.g., Atypical depression, Melancholic depression, Psychotic depression, Catatonic depression, Postpartum depression, and Seasonal affective disorder.

Bipolar Disorder

Bipolar disorder, also known as manic depressive disorder, manic depressive psychosis, manic depression or bipolar affective disorder, is a psychiatric diagnosis that describes a category of mood disorders defined by the presence of one or more episodes of abnormally elevated mood clinically referred to as mania or, if milder, hypomania. Individuals who experience manic episodes also commonly experience depressive episodes or symptoms, or mixed episodes in which features of both mania and depression are present at the same time. These episodes are usually separated by periods of "normal" mood, but in some individuals, depression and mania may rapidly alternate, known as rapid cycling. Extreme manic episodes can sometimes lead to psychotic symptoms such as delusions and hallucinations. The disorder has been subdivided into bipolar I, bipolar II, cyclothymia, and other types, based on the nature and severity of mood episodes experienced; the range is often described as the bipolar spectrum.

Anxiety Disorders

Anxiety disorder is a blanket term covering several different forms of abnormal and pathological fear and anxiety. Current psychiatric diagnostic criteria recognize a wide variety of anxiety disorders. Recent surveys have found that as many as 18% of Americans may be affected by one or more of them.

Generalized anxiety disorder is a common chronic disorder characterized by long-lasting anxiety that is not focused on any one object or situation. Those suffering from generalized anxiety experience non-specific persistent fear and worry and

become overly concerned with everyday matters. Generalized anxiety disorder is the most common anxiety disorder to affect older adults.

In panic disorder, a person suffers from brief attacks of intense terror and apprehension, often marked by trembling, shaking, confusion, dizziness, nausea, difficulty breathing. These panic attacks, defined by the APA as fear or discomfort that abruptly arises and peaks in less than ten minutes, can last for several hours and can be triggered by stress, fear, or even exercise; although the specific cause is not always apparent. In addition to recurrent unexpected panic attacks, a diagnosis of panic disorder also requires that said attacks have chronic consequences: either worry over the attacks' potential implications, persistent fear of future attacks, or significant changes in behavior related to the attacks. Accordingly, those suffering from panic disorder experience symptoms even outside of specific panic episodes. Often, normal changes in heartbeat are noticed by a panic sufferer, leading them to think something is wrong with their heart or they are about to have another panic attack. In some cases, a heightened awareness (hypervigilance) of body functioning occurs during panic attacks, wherein any perceived physiological change is interpreted as a possible life threatening illness (i.e. extreme hypochondriasis).

Obsessive compulsive disorder is a type of anxiety disorder primarily characterized by repetitive obsessions (distressing, persistent, and intrusive thoughts or images) and compulsions (urges to perform specific acts or rituals). The OCD thought pattern may be likened to superstitions insofar as it involves a belief in a causative relationship where, in reality, one does not exist. Often the process is entirely illogical; for example, the compulsion of walking in a certain pattern may be employed to alleviate the obsession of impending harm. And in many cases, the compulsion is entirely inexplicable, simply an urge to complete a ritual triggered by nervousness. In a minority of cases, sufferers of OCD may only experience obsessions, with no overt compulsions; a much smaller number of sufferers experience only compulsions.

The single largest category of anxiety disorders is that of Phobia, which includes all cases in which fear and anxiety is triggered by a specific stimulus or situation. Sufferers typically anticipate terrifying consequences from encountering the

object of their fear, which can be anything from an animal to a location to a bodily fluid.

Post-traumatic stress disorder or PTSD is an anxiety disorder which results from a traumatic experience. Post-traumatic stress can result from an extreme situation, such as combat, rape, hostage situations, or even serious accident. It can also result from long term (chronic) exposure to a severe stressor, for example soldiers who endure individual battles but cannot cope with continuous combat. Common symptoms include flashbacks, avoidant behaviors, and depression.

Combination therapies

In some embodiments, the subject is being treated with an additional therapeutic agent. Such additional agents include atypical antipsychotics such as aripiprazole, clozapine, ziprasidone, risperidone, quetiapine, olanzapine, amisulpride, asenapine, iloperidone, melperone, paliperidone, perospirone, sertindole and sulpiride; and typical antipsychotics such as haloperidol, molindone, loxapine, thioridazine, molindone, thiothixene, pimozide, fluphenazine, trifluoperazine, mesoridazine, chlorprothixene, chlorpromazine, perphenazine, triflupromazine and zuclopenthixol.

Clinical outcomes

In some embodiments, treatment with a compound or composition described herein, for example, using a method described herein, improves one or more clinical outcomes. For example, in some embodiments, treatment with a compound or composition described herein may improve cognitive function. Elements of cognitive function include memory, orientation, attention, reasoning, language and praxis.

In some embodiments, clinical outcomes may be assessed using known methods. One such method is the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients.

In some embodiments, clinical outcomes may be assessed using the 7-point Clinical Global Impression (CGI) rating scale, a commonly used measure of symptom

severity, treatment response and the efficacy of treatments. The CGI reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient.

In some embodiments, clinical outcomes may be assessed using the 30-item Positive and Negative Symptoms Scale (PANSS). The name refers to the two types of symptoms in schizophrenia, as defined by the American Psychiatric Association: positive symptoms, which refer to an excess or distortion of normal functions (e.g. hallucinations and delusions), and negative symptoms, which represent a diminution or loss of normal functions.

In some embodiments, clinical outcomes may be assessed using the Scale for Assessing Negative Symptoms (SANS). SANS assesses five symptom complexes to obtain clinical ratings of negative symptoms in patients with schizophrenia. They are: affective blunting; alogia (impoverished thinking); avolition/apathy; anhedonia/asociality; and disturbance of attention. Assessments are conducted on a six-point scale.

The invention is further illustrated by the following examples which are intended to illustrate but not limit the scope of the invention.

EXAMPLES

Abbreviations:

DCM: Dichloromethane
EA, EtOAc or AcOEt: Ethyl acetate
PE: Petroleum ether
DIPEA: Diisopropylethylamine
TEA: Triethylamine
rt: Room temperature
SOCl₂: Thionyl chloride
POCl₃: Phosphorous oxychloride
THF: Tetrahydrofuran
NaOAc: Sodium acetate
MeOH: Methanol
i-AmOH: Isoamyl alcohol

NaH: Sodium hydride
 NaBH₃CN: Sodium cyanoborohydride
 n-BuLi: *n*-Butyl lithium
 LHMDs: Lithium bis(trimethylsilyl)amide
 LDA: Lithium diisopropylamide
 i-PrOH: Isopropyl alcohol
 Na₂SO₄: Sodium sulfate
 Mg₂SO₄: Magnesium sulfate
 MeCN: Acetonitrile
 NaOH: Sodium hydroxide
 EtOH: Ethanol
 CuI: Copper(I) iodide
 Pd(PPh₃)₂Cl₂: trans-Dichlorobis(triphenylphosphine)palladium(II)
 MsCl: Methanesulfonyl chloride
 BINAM: [1,1'-Binaphthalene]-2,2'-diamine
 Xphos: 2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
 Sphos: 2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
 DavePhos: 2-(Dicyclohexylphosphino)-2'-(N,N-dimethylamino)biphenyl
 Cs₂CO₃: Cesium carbonate
 K₂CO₃: Potassium carbonate
 Mwave or μW or mW: Microwave
t-BuOH: *tert*-Butanol
 K₃PO₄: Potassium phosphate
 Pd(APhos)₂Cl₂: Bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)dichloro palladium(II)
 Pd(PPh₃)₄: Tetrakis(triphenylphosphine)palladium (0)
 Pd(dppf)₂Cl₂: Dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II)
 PdOAc: Palladium(II) acetate
 Pd₂dba₃: Tris(dibenzylideneacetone)dipalladium (0)
 Pd-118: Dichloro[1,1'-bis(di-*t*-butylphosphino)ferrocene]palladium(II)
 Xantphos: 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene
 BINAP: (±)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene
 EDCI: 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide
 HOBt: Hydroxybenzotriazole
 NH₄OH: Ammonium hydroxide
 H₂O: Water
 Pd/C: Palladium on carbon
 DMF: *N,N*-Dimethylformamide
 KOCN: Potassium cyanate
 WSC-HCl or WSCDI: Water Soluble Carbodiimide hydrochloride
 HATU: O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
 HBTU: O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
 Py-Brop: Bromotripyrrolidinophosphonium hexafluorophosphate
 BOP: Benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluoro phosphate

DBU: diaza(1,3)bicyclo[5.4.0]undecene
 DMSO: Dimethyl sulfoxide
 LCMS: Liquid chromatography mass spectrometry
 HPLC: High performance liquid chromatography
 DMA: N,N-dimethylacetamide
 h: hour
 TLC: Thin layer chromatography
 TFA: Trifluoroacetic acid
 Et₃N: Triethylamine
 DIPEA: N,N-Diisopropylethylamine
 O.N: Overnight
 TBSO: tert-Butyldimethylsilyloxy
 DME: Dimethyl ether
 NMP: 1-methyl-2-pyrrolidinone
 PS-BEMP: 2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine supported on Polystyrene
 PBr₃ : Phosphorus tribromide
 NaOtBu: Sodium tert-butoxide
 KI : Potassium iodide
 PPh₃ : Triphenylphosphine
 NMM : *N*-Methylmorpholine
 HCHO: Formaldehyde
 PG: Protecting group
 ISCO: Teledyne ISCO purification systems
 BINAM: 1,1'-binaphthyl-2,2'-diamine.

General Experimental:

All exemplified target compounds are fully analyzed and characterized (TLC, LCMS, ¹H-NMR) prior to submission for biological evaluation. Thin-layer chromatography was carried out on native silica 254F plates. Visualization was accomplished with ultraviolet or phosphomolybdic acid. ¹H-NMR spectra were recorded on multiple NMR spectrometers, either on 400 MHz on a Avance III 400 Ultra shield-plus™ digital Spectrometer or on 300 MHz using a Varian™ Mercury 300Plus Spectrometer, designated by 400 MHz or 300 MHz, respectively. ¹H-NMR spectra were also recorded on a Bruker™ Spectrospin 300 MHz Spectrometer at 300.13 MHz in DMSO-d₆ with TMS as an internal standard and will be designated as Bruker 300 Hz. NMR assignments are based on a combination of the ¹H, ¹³C, ¹HCO¹³C, HMBC and HMQC spectra. Coupling constants are given in hertz (Hz). Anhydrous methylene chloride,

tetrahydrofuran, and dimethylformamide were obtained by distillation, and other materials are reagent grade.

LC-MS Methods are listed here:

Method A: Mobile phase: A = 0.1% TFA/H₂O, B = 0.01% TFA/MeCN; Gradient: B = 5%-95% in 1.5 min; Flow rate: 2.0 mL/min; Column: sunfire-C₁₈, 50 × 4.6 mm, 3.5 μm;

Method B: Mobile phase: A = 10mM NH₄HCO₃/H₂O, B = MeCN; Gradient: B = 5%-95% in 1.5 min; Flow rate: 2.0 mL/min; Column: Xbridge™-C₁₈, 50 × 4.6mm, 3.5 μm;

Method C: Mobile phase: A = 10 mM ammonium formate/H₂O/4.9% MeCN, B = MeCN; Gradient: B = 5%-100% in 2.0 min; Flow rate: 2.5 mL/min; Column: Atlantis T3 3μM 4.6x30mm

Method D: Mobile phase: A = 0.1% formic acid/H₂O/4.9% MeCN, B = MeCN; Gradient: B = 5%-100% in 2.0 min; Flow rate: 2.5 mL/min; Column: Atlantis T3 3μM 4.6x30mm

Method E: Mobile phase: A = 0.05% TFA/H₂O, B = 0.05% TFA/MeCN; Gradient: B = 5%-100% in 3.0 min; Flow rate: 0.8 mL/min; Column: CAPCELL PAK C18 (Shiseido, UG120, 3 mM, 2.0 mm I.D. x 50 mm).

Representative Conditions of PREP-HPLC are listed here:

PREP-HPLC Condition A (Basic Mobile Phase):

Instrument: Gilson 281

Mobile Phase: A = 0.01% NH₄HCO₃/H₂O, B = MeCN

Flow Rate: 40.0 mL/min

Column: AGT Venusil XBP C₁₈, 10.0 μm, 30 mm × 100 mm

PREP-HPLC Condition B (Basic Mobile Phase):

Instrument: Gilson 281

Mobile Phase: A = $\text{NH}_3\text{-H}_2\text{O}$, 10 mmol/L, B = MeCN

Flow Rate: 40.0 mL/min

Column: Waters X-Bridge, 5.0 μm , 30 mm $\times$ 150 mm**PREP-HPLC Condition C (Basic Mobile Phase):**

Instrument: Gilson 281

Mobile Phase: A = 0.01% $\text{NH}_4\text{HCO}_3/\text{H}_2\text{O}$, B = MeCN

Flow Rate: 30.0 mL/min

Column: Shimadzu PRC-ODS, 10.0 μm , 20 mm $\times$ 250 mm

Gradient: B = xx%-yy% 0.0 to 8.0 min

yy%-95% 8.0 to 8.2 min

95%-95% 8.2 to 11.0 min

The following table shows the relationship of representative value (xx%-yy%) of gradient and retention time on LC-MS of corresponding compound.

25%-30% 0.5-1.0 min

30%-50% 1.0-1.5 min

50%-70% 1.5-1.75 min

70%-90% 1.7-2.0 min

PREP-HPLC Condition D:

Instrument: Waters 600 pump, Waters 2996, Photodiode Array Detector, Waters MicromassTM ZQ, Gilson 215 Liquid Handler.

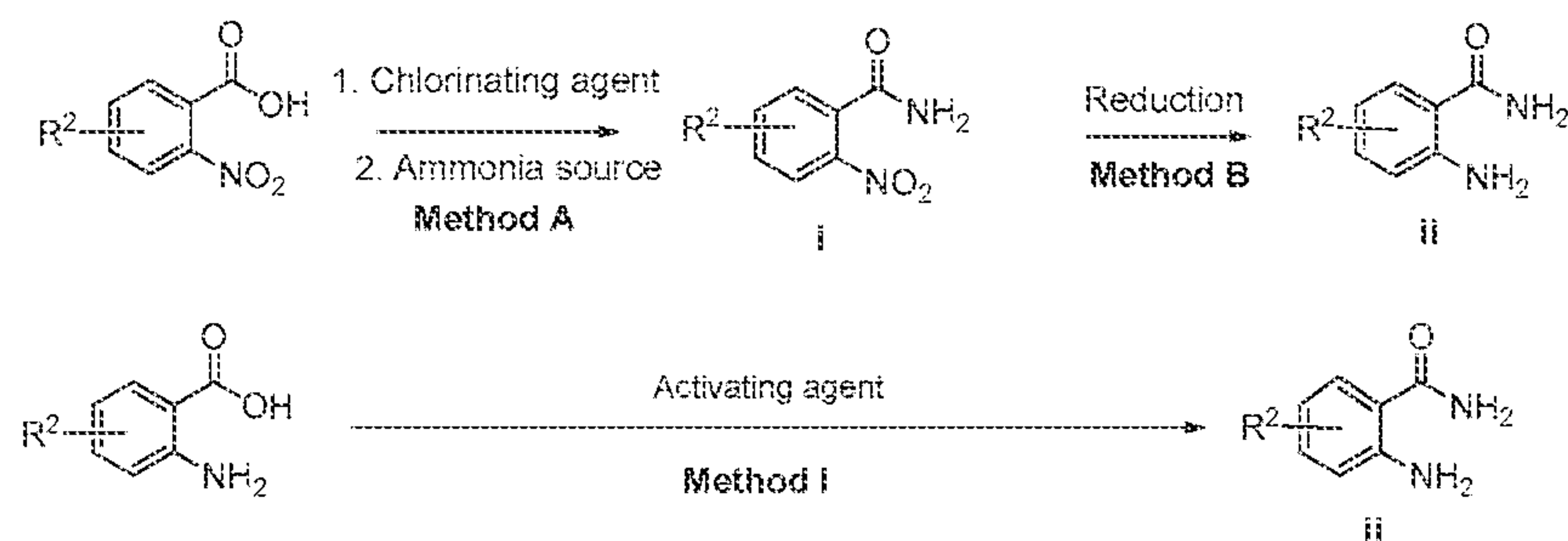
Mobile Phase: A = 0.05% TFA/ H_2O , B = MeCN

Flow Rate: 36.0 mL/min

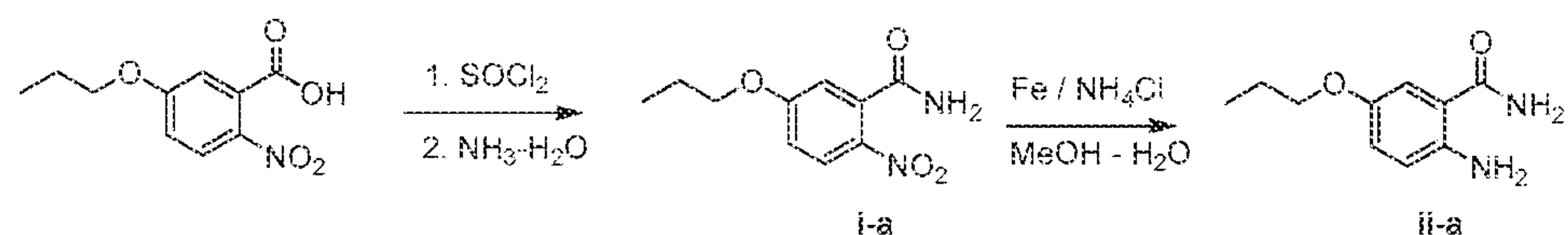
Column: Shiseido CAPCELL PAK C18, UG120, 5 μM , 20 mm I.D. $\times$ 50 mm

Gradient: B = 5%-100% 0.0 to 4.0 min

Scheme 1: General route for the synthesis of compounds with general formula ii



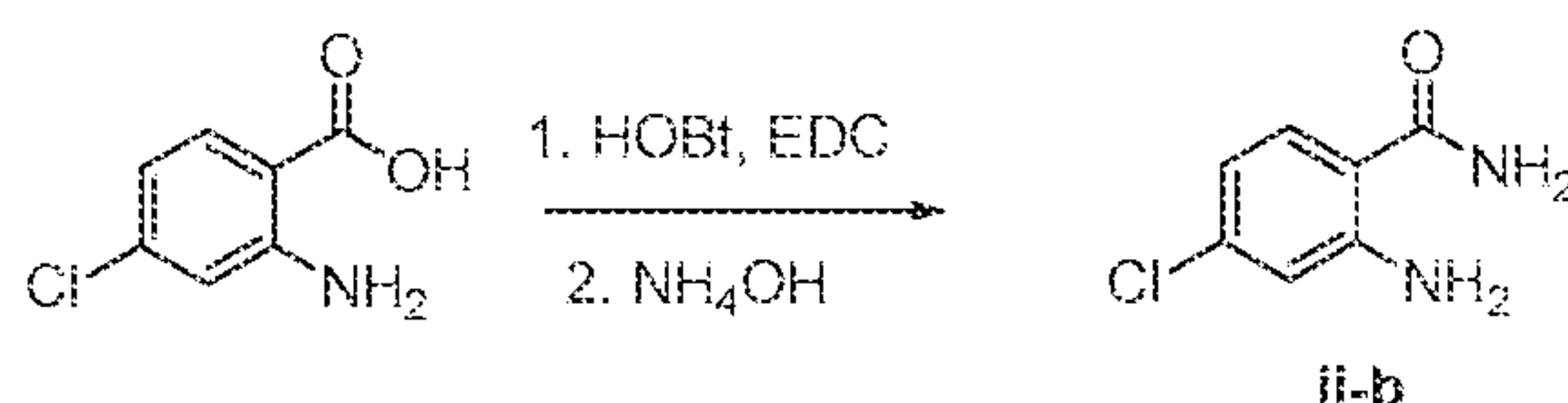
Scheme 2: Representative synthesis of compounds of formula ii (see Scheme 1)



Method A: 2-Nitro-5-propoxy-benzamide (i-a) A mixture of 2-nitro-5-propoxy-benzoic acid (1.97 g, 8.75 mmol) and DMF (0.1 mL) in SOCl_2 (20 mL) was stirred at 65 °C for 2 h. After the reaction was completed, the mixture was cooled to room temperature. SOCl_2 was removed *in vacuo* and the residue was dissolved in anhydrous CH_2Cl_2 (10 mL), which was added to $\text{NH}_3\text{-H}_2\text{O}$ (28%) dropwise. After 1 h, the precipitate was collected and dried *in vacuo* to give 1.68 g of **i-a** as a yellow solid (85.2%). LCMS m/z = 208.1 (M-16), 225.1 (M+1) (Method B) (retention time = 1.88 min).

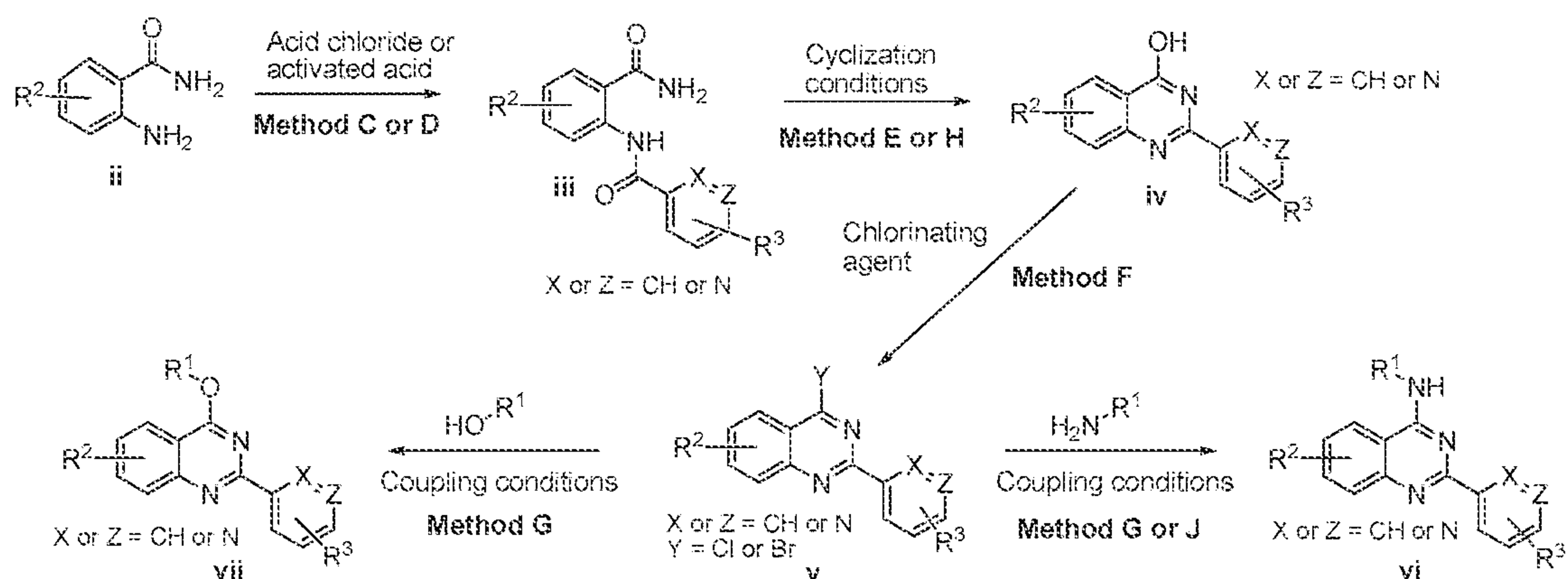
Method B: 2-Amino-5-propoxy-benzamide (ii-a) To a mixture of 2-nitro-5-propoxy-benzamide (1.20 g, 5.36 mmol) in $\text{MeOH-H}_2\text{O}$ (v/v, 3:1, 60 mL) was added NH_4Cl (2.84 g, 53.6 mmol) and Fe (2.99 g, 53.6 mmol). The resulting mixture was stirred at 60 °C for 3 h. After the reaction was completed, the mixture was cooled to room temperature and the iron was filtered off. The filtrate was concentrated to 15 mL and the formed precipitate was collected and dried *in vacuo* to give 1.02 g of **ii-a** as a pale yellow solid (98%). LCMS m/z = 178.1 (M-16), 195.1 (M+1) (Method B) (retention time = 1.46 min).

Scheme 3: Representative synthesis of compounds of formula ii by Method I (see Scheme 1)



Method I : 2-Amino-4-chlorobenzamide (ii-b) To a mixture of 2-amino-4-chlorobenzoic acid (3.42 g, 20 mmol) in DMF (45 mL) was added HOBt (2.70 g, 20 mmol). After stirring for 10 min, EDC hydrogen chloride (3.82 g, 20 mmol) was added to the mixture. The resulted mixture was stirred at room temperature for 2 h. NH_4OH (28%, 5 mL) was added at 0 °C with vigorous stirring. After addition, the mixture was stirred at room temperature for another 2 h. The reaction mixture was added to water (200 mL) dropwise with stirring, then a precipitate formed. The precipitate was collected and dried *in vacuo* to give 2.98 g of **ii-b** as a grey solid (87.6% yield). LCMS $m/z = 171.0$ ($M+1$), 173.0 ($M+3$) (Method B) (retention time = 1.39 min). ^1H NMR (400 MHz, DMSO-d_6): δ 7.27 (d, $J = 9.6$ Hz, 1H), 6.68 (d, $J = 2.4$ Hz, 1H), 6.60 (dd, $J = 8.4, 2.0$ Hz, 1H), 5.50 – 5.82 (m, 4H).

Scheme 4: General route for the synthesis of compounds with general formula vi and vii



Method F for Chlorinating Conditions

F1: POCl₃/N,N-dimethylbenzeneamine
F2: SOCl₂/DMF/80 °C
F3: SOCl₂ (4-8 equiv.)/DMF/DCM/rt-40 °C
F4: Phenylphosphinic dichloride/ 80-120 °C
F5: POCl₃/Δ
F6: POCl₃/Toluene/100 °C
F7: PBr₃/CH₂Cl₂/DMF/60 °C

Method G for Coupling Conditions

G1: *i*-PrOH/85-100 °C
G2: THF/reflux
G3: *i*-AmOH/100-130 °C

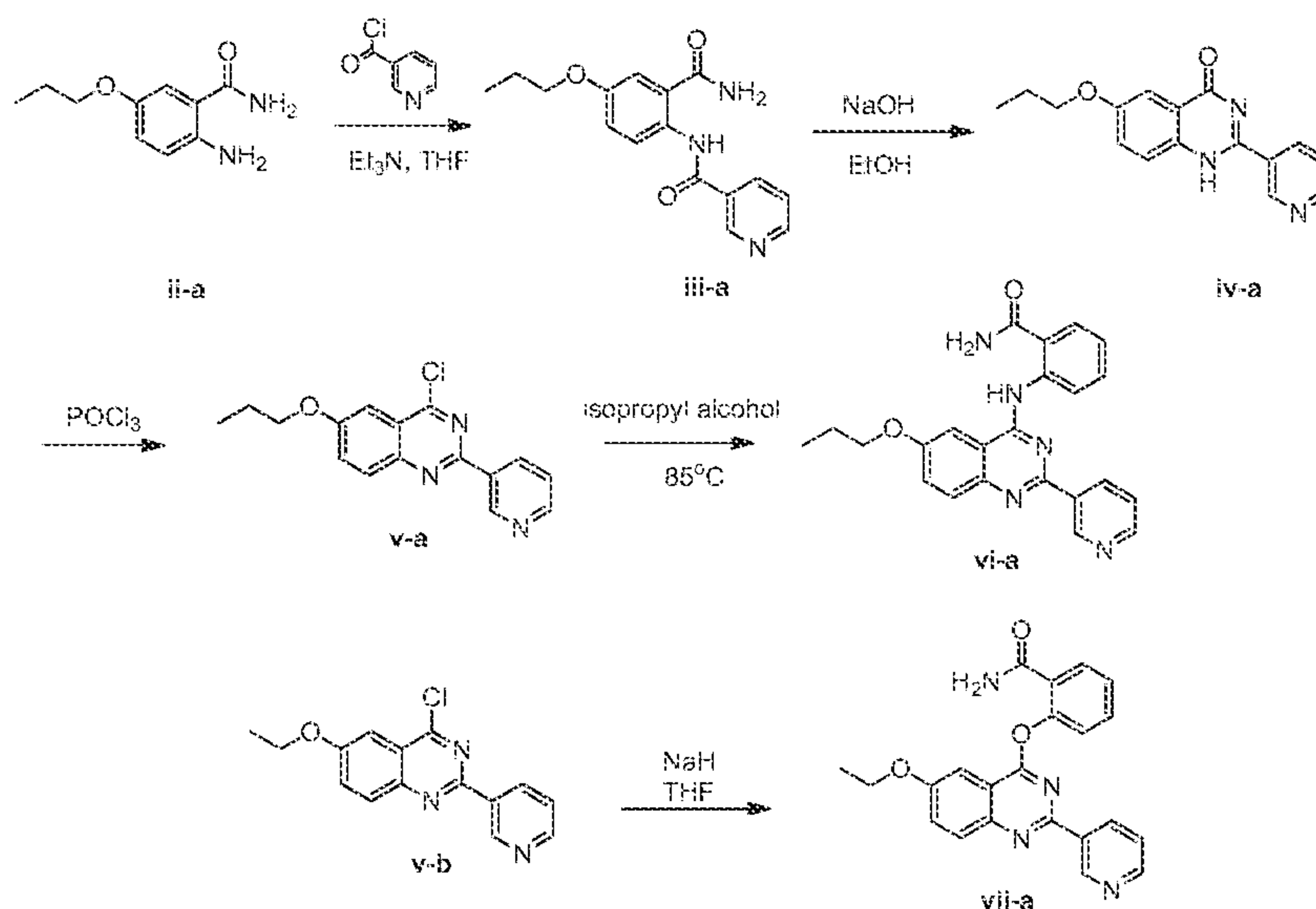
G4: MeOH/microwave/150 °C
G5: *i*-AmOH/ microwave/150 °C

G6: THF/Et₃N/reflux
G7: THF-H₂O/NaOAc/rt-60 °C
G8: NaH/THF
G9: *n*-BuLi/THF
G10: LHMDs/THF
G11: LDA/THF
G12: K₂CO₃/DMF/60 °C
G13: Cs₂CO₃/DMA/80 °C
G14: NaOtBu/DMF/Microwave/100 °C

Method J for Coupling Conditions

J1: Pd(PPh₃)₄/ *t*-BuOK/ Dioxane
J2: Pd₂(dba)₃/ Xantphos/ Cs₂CO₃/ Dioxane

Scheme 5: Representative synthesis of compounds of formula vi and vii (see Scheme 4)



Method C: N-(2-Carbamoyl-4-propoxy-phenyl)-nicotinamide (iii-a) To a solution of 2-amino-5-propoxy-benzamide (760 mg, 3.91 mmol) in THF (15 mL) and Et_3N (1 mL) was added nicotinoyl chloride (607 mg, 4.30 mmol) in anhydrous THF (15 mL) dropwise. The resulting mixture was stirred at room temperature for 3 h. After the reaction was completed, the volatiles were removed. The residue was washed with H_2O (10 mL). The pH was adjusted to approximately 5 by adding dilute HCl (2N in water). The resulting solid was collected and dried *in vacuo* to give 1.00 g of **iii-a** as a pale yellow solid (89.0%). LCMS $m/z = 300.1$ (M+1) (Method B) (retention time = 1.60 min).

Method D: 2-benzamido-5-methoxy-3-methylbenzamide (iii-b) A 50 mL round-bottom flask was charged with nicotinic acid (41 mg, 0.33 mmol, 1.0 eq.), 2-amino-5-methoxy-3-methylbenzamide (60 mg, 0.33 mmol, 1.0 eq.) and HBTU (190 mg, 0.50 mmol, 1.5 eq), which were suspended in 4 mL of DMF. DIPEA (86 mg, 0.66 mmol, 2.0 eq.) was added dropwise at room temperature and the reaction mixture was stirred overnight. The reaction mixture was added to water (10 mL) dropwise with stirring. The mixture was extracted with ethyl acetate. The ethyl acetate was evaporated and 55 mg of the orange solid (58.5% yield) was obtained. LCMS $m/z = 286.1$ (M+1) (Method B) (retention time = 1.24 min).

Method E: 6-Propoxy-2-pyridin-3-yl-1H-quinazolin-4-one (iv-a) A mixture of N-(2-carbamoyl-4-propoxy-phenyl)-nicotinamide (980 mg, 3.27 mmol) in EtOH (20 mL) was treated with NaOH (654 mg, 16.37 mmol). The resulting mixture was stirred at room temperature for 18 h. After the reaction was completed, the volatiles were removed *in vacuo*. The residue was partitioned between H₂O (50 mL) and ethyl acetate (50 mL). The aqueous layer was neutralized to pH 7 by slowly adding aq. citric acid and then a precipitate formed. The precipitate was collected and dried to give 1.00 g of **iv-a** as a grey solid (quantitative yield). LCMS *m/z* = 282.1 (M+1) (Method B) (retention time = 1.60 min).

Method F1: 4-Chloro-6-propoxy-2-pyridin-3-yl-quinazoline (v-a)

(This method is representative of method F1, F2, F3 and F4. These three methods can be implemented in a similar way except for substitution of the appropriate chlorinating reagent, solvent and temperature) To a mixture of 6-propoxy-2-pyridin-3-yl-1H-quinazolin-4-one (1.00 g, 3.56 mmol) in POCl₃ (10 mL) was added *N,N*-dimethylaniline (0.1 mL). The resulting mixture was stirred at 120 °C for 2 h. After the reaction was completed, POCl₃ was removed *in vacuo*, and the residue was added to ice-water slowly. The pH was adjusted to around 7 by slowly adding NaHCO₃ (sat.) at 0 °C. The resultant solid was collected and purified by chromatography on silica gel eluted with petroleum ether / ethyl acetate (v/ v = 4: 1 to 1: 1) to give 580 mg of **v-a** as a pale yellow solid (54.7%).

Method F5: 4-chloro-6-methoxy-2-(pyridin-3-yl)quinazoline (v-c) In a sealed tube, phosphorus oxychloride (11 mL, 120 mmol) was added to 6-methoxy-2-(pyridin-3-yl)quinazolin-4(3H)-one (2.70 g, 10.66 mmol). The mixture was refluxed at 120°C for 12 h. After cooling, the remaining phosphorus oxychloride was removed *in vacuo* to leave a tan solid. This residue was added to an ice-water mixture (100 mL) with cooling and allowed to stir. The pH of the suspension was adjusted to about pH 9 via dropwise addition of 28% ammonium hydroxide, and stirring was continued for 30 mins. The resulting solid was filtered to give the desired product as a tan solid

(2.55 g, 9.39 mmol, 88%). LC-MS m/z = 272.0 (M+1) (retention time = 2.05) ^1H NMR (300 MHz, DMSO) δ 9.55 (s, 1H), 8.81 – 8.64 (m, 2H), 8.09 (d, J = 9.2 Hz, 1H), 7.78 (dd, J = 9.2, 2.8 Hz, 1H), 7.61 (dd, J = 7.9, 4.8 Hz, 1H), 7.49 (d, J = 2.5 Hz, 1H), 4.00 (s, 3H).

Method F6: 6-Bromo-4-chloro-8-fluoro-2-(pyridin-3-yl)quinazoline (v-d) To a suspension of 6-bromo-8-fluoro-2-(pyridin-3-yl)quinazolin-4-ol (6.16 g, 0.0192 mol) in toluene (60 mL) was added phosphorus oxychloride (5.30 mL, 0.0579 mol) at room temperature. The mixture was refluxed for 3 h. The solvent was evaporated and water was added to the residue under cooling conditions. The suspension was stirred at room temperature for 30 min, the resulting precipitate was filtered and dried to give the title compound (6.5 g, quantitative). ^1H NMR (400 MHz, DMSO) δ 9.58 (d, J = 1.6 Hz, 1H), 8.82 (dd, J = 4.7, 1.5 Hz, 1H), 8.80 – 8.75 (m, 1H), 8.37 (dd, J = 9.7, 1.9 Hz, 1H), 8.34 – 8.29 (m, 1H), 7.67 (dd, J = 7.8, 4.6 Hz, 1H).

Method F7: 4-Bromo-6-methoxy-2-(pyridin-3-yl)quinazoline (v-e) To a sealed tube containing 6-methoxy-2-(pyridin-3-yl)quinazolin-4(3H)-one (1.30 g, 5.13 mmol) in dichloromethane (20 mL) was added 1 M phosphorus tribromide in dichloromethane (10.3 mL, 10.3 mmol) and DMF (2 mL). The reaction mixture was heated at 60°C for 4 h. After cooling, excess dichloromethane was evaporated leaving a tan residue. This solid was added to an ice-water mixture (100 mL) with cooling and allowed to stir. The pH of the suspension was adjusted to about pH 9 via dropwise addition of 28% ammonium hydroxide, and stirring was continued for 30 mins. The resulting solid was filtered to give the desired product as a tan solid (1.49 g, 4.71 mmol, 92%). LC-MS m/z = 318.3 (M+2) (retention time = 2.19).

Method G1: 2-(6-Propoxy-2-pyridin-3-yl-quinazolin-4-ylamino)-benzamide (vi-a) (This method is representative of method G1, G2, and G3. These three methods can be implemented in a similar way except for substitution of the appropriate solvent and temperature) A mixture of 4-chloro-6-propoxy-2-(pyridin-3-yl)quinazoline (90 mg, 0.3 mmol) and 2-aminobenzamide (52 mg, 0.4 mmol) in *i*-

PrOH (5 mL) was stirred at 85 °C for 18 h. The yellow precipitate was collected and washed with *i*-PrOH (10 mL). The solid was suspended in water (10 mL) and NH₃-H₂O (1 mL) was added. After filtration the solid was dried *in vacuo* to afford 31.0 mg of **vi-a** as a white solid (30.8%). LCMS *m/z* = 400.1 (M+1) (Method B) (retention time = 1.96 min). ¹H-NMR (400 MHz, DMSO-*d*₆): δ 9.59 (d, *J* = 2.0 Hz, 1H), 9.58 (d, *J* = 7.6 Hz, 1H), 8.69 – 8.74 (m, 2H), 8.48 (s, 1H), 7.97 (d, *J* = 6.8 Hz, 2H), 7.90 (d, *J* = 8.8 Hz 1H), 7.74 (t, *J* = 7.6 Hz, 1H), 7.56 – 7.61 (m, 3H), 7.20 (t, *J* = 7.2 Hz, 1H), 4.16 (t, *J* = 6.4 Hz, 2H), 1.86 (dd, *J* = 14.0, 6.8 Hz, 2H), 1.07 (t, *J* = 7.2 Hz, 3H).

Method G8: 2-(6-ethoxy-2-(pyridin-3-yl)quinazolin-4-yloxy)benzamide (vii-a)

(The method G8 is representative of method G6, G7, G9, G10 and G11. These six methods can be implemented in a similar way except for substitution of the appropriate base, solvent and temperature) To a 2.5 dram reaction vial was first added sodium hydride 60% (0.028 g, 0.700 mmol) and salicylamide (0.072 g, 0.525 mmol) in DMF (2 mL). The mixture was allowed to stir at room temperature for 1 h. Then, 4-chloro-6-ethoxy-2-(pyridin-3-yl)quinazoline (0.100 g, 0.350 mmol) was added to the mixture, and the reaction was allowed to proceed at room temperature overnight. LC-MS analysis of the crude mixture showed about 85% of product formed and 10% remaining starting material. Water (30 mL) was added to the mixture, and the product was extracted with chloroform (3 x 15 mL). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated. The crude product was purified via ISCO (silica gel, 97.5:2.5 CH₂Cl₂/MeOH; 12 g column) to afford 13.9 mg of the desired product as a white solid (10.3%) LCMS *m/z* = 387 (M+1) (Method C) (retention time = 2.05 min). ¹H NMR (300 MHz, DMSO) δ 11.47 (s, 2H), 9.39 (s, 1H), 8.66 (d, *J* = 2.8 Hz, 1H), 8.56 – 8.47 (m, 1H), 8.01 – 7.90 (m, 2H), 7.69 – 7.55 (m, 2H), 7.55 – 7.40 (m, 2H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.97 (d, *J* = 8.2 Hz, 1H), 4.23 (q, *J* = 6.9 Hz, 2H), 1.44 (t, *J* = 6.9 Hz, 3H).

Method G13: 4-(4-chlorophenyl)-N-(6-methoxy-2-(pyridin-3-yl)quinazolin-4-yl)thiazol-2-amine (vi-c) (The method G13 is representative of method G12 also.

This method can be implemented in a similar way except for substitution of the appropriate base, solvent and temperature) To a suspension of 4-chloro-6-methoxy-2-(pyridine-3-yl)quinazoline (645.2 mg, 2.375 mmol) and 2-amino-4-(4-chlorophenyl)thiazole (1050 mg, 4.98 mmol) in DMA (40 mL) was added Cs₂CO₃ (2430 mg, 7.46 mmol) at room temperature. The mixture was stirred at 80°C for 9.5 h. Water was added and a precipitate formed which was collected by filtration and washed with H₂O. Recrystallization from acetone/DMF/methanol gave 383.6 mg of the product in a 36% yield as yellow solid, >98% purity by ¹H NMR. ¹H NMR (400 MHz DMSO-d₆) δ 12.52 (s, 1H), 9.78 (d, J = 1.56 Hz, 1H), 8.91-8.88 (m, 1H), 8.74 (dd, J = 4.74, 1.60 Hz, 1H), 8.33 (brs, 1H), 8.06 (d, J = 8.56 Hz, 2H), 7.93 (d, J = 9.08 Hz, 1H), 7.89 (s, 1H), 7.66-7.59 (m, 2H), 7.55 (d, J = 8.56 Hz, 2H), 4.01 (s, 3H).

Method G14: 4-(6-methoxy-2-(pyridin-3-yl)quinazolin-4-ylamino)-1H-pyrazole-5-carboxamide, 2HCl (vi-d): (The method G14 is representative of method G4 and G5 also. This method can be implemented in a similar way except for substitution of the appropriate solvent and adjustment of the temperature)

To a microwave vial containing 4-bromo-6-methoxy-2-(pyridin-3-yl)quinazoline (150.0 mg, 0.47 mmol) in DMF (2 mL) was added 4-amino-1H-pyrazole-5-carboxamide (66.0 mg, 0.52 mmol) and sodium *tert*-butoxide (50 mg, 0.52 mmol). The reaction mixture was heated at 100°C for 15 mins by microwave irradiation. Water (50 mL) was added to the reaction mixture, and extracted with ethyl acetate (5 x 50 mL). The crude material was purified via ISCO (silica, 12 g column, 93% CH₂Cl₂ – 7% MeOH – 0.1% NH₄OH) giving the product as a yellow solid. The free base was then converted to the HCl salt to yield the final product as an orange solid (59.8 mg, 0.14 mmol, 22%). LC-MS m/z = 362.4 (M+1) (retention time = 1.57) ¹H NMR (300 MHz, DMSO) δ 11.28 (s, 1H), 9.62 (d, J = 1.7 Hz, 1H), 9.17 (d, J = 7.8 Hz, 1H), 8.93 (dd, J = 5.2, 1.3 Hz, 1H), 8.60 (s, 1H), 8.05 (s, 1H), 8.03 - 7.94 (m, 2H), 7.77 (s, 1H), 7.64 (dd, J = 9.2, 2.5 Hz, 1H), 7.40 (d, J = 2.6 Hz, 1H), 3.97 (s, 3H).

Method J1: 1-(6-Methoxy-2-(pyridin-3-yl)quinazolin-4-yl)-1H-benzo[d]imidazol-2(3H)-one (vi-b) To a 50-mL two-neck round bottom flask equipped with a reflux

condenser was added a mixture of 4-chloro-6-methoxy-2-(pyridin-3-yl)quinazoline (50 mg, 0.18 mmol, 1 eq.) and 1H-benzo[d]imidazol-2(3H)-one (27 mg, 0.21 mmol, 1.1 eq.) in 5 mL of dry 1,4-dioxane. Pd(PPh₃)₄ (10.6 mg, 0.009 mmol, 0.05 eq) and *t*-BuOK (41 mg, 0.36 mmol, 2 eq.) were added. The resulting mixture was stirred at 100 °C under N₂ atmosphere overnight. After cooling, 20 mL of methanol was added. The mixture was filtered, the filtrate was concentrated *in vacuo* and then was purified with chromatography on silica gel (ethyl acetate/ petroleum ether from 1:4 to 1:2) to give the crude product, which was further purified with reverse phase HPLC to afford 4.8 mg of **vi-e** as a pale yellow solid (7%). MS *m/z* = 370.1 (M+1) (Method B) (retention time = 1.680 min). ¹H NMR (400 MHz, DMSO-d₆): δ 11.51 (s, 1H), 8.78 (d, *J* = 8.0 Hz, 2H), 8.17 (d, *J* = 9.2 Hz, 1H), 7.80 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.70 – 7.64 (m, 1H), 7.46 (d, *J* = 2.8 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.20 (d, *J* = 4.0 Hz, 2H), 7.16 – 7.08 (m, 1H), 3.89 (s, 3H).

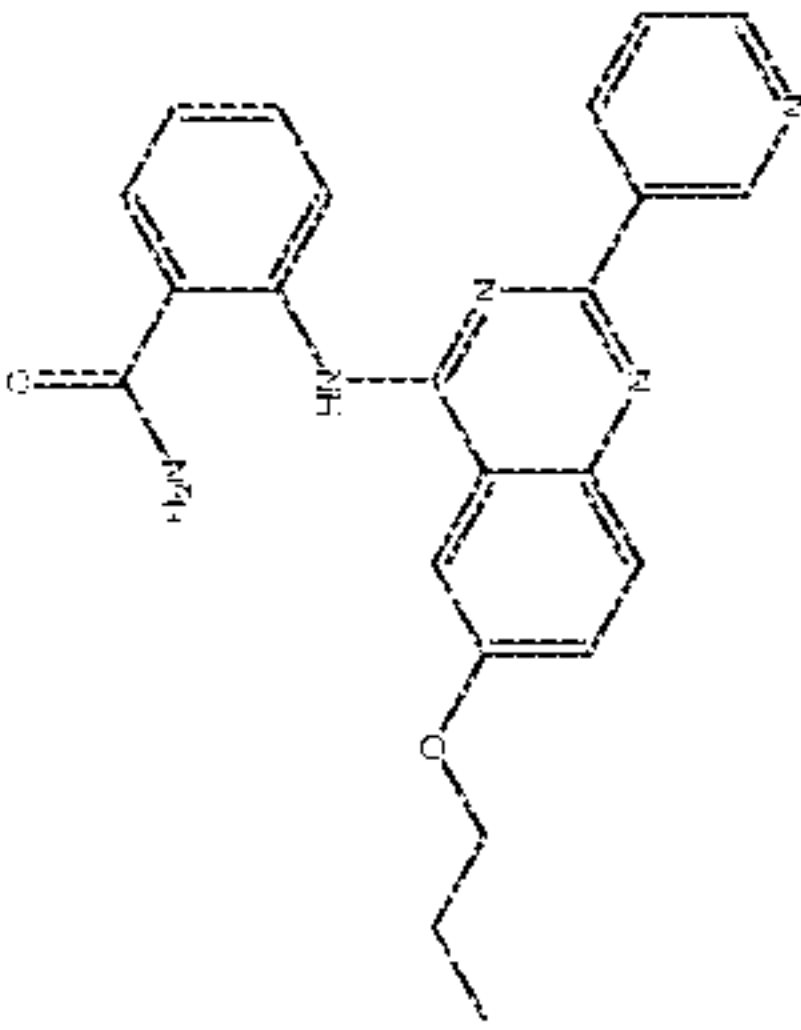
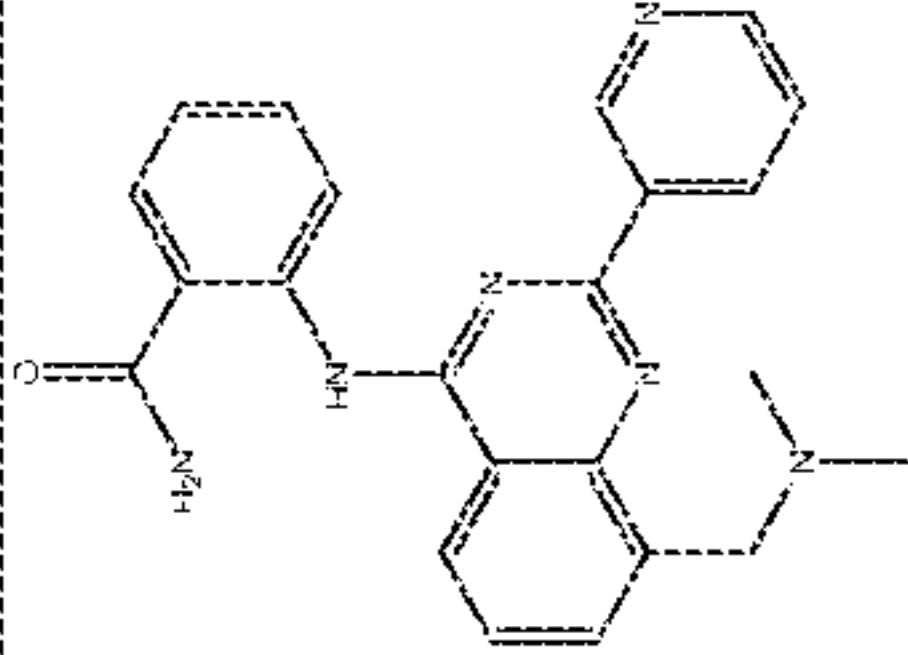
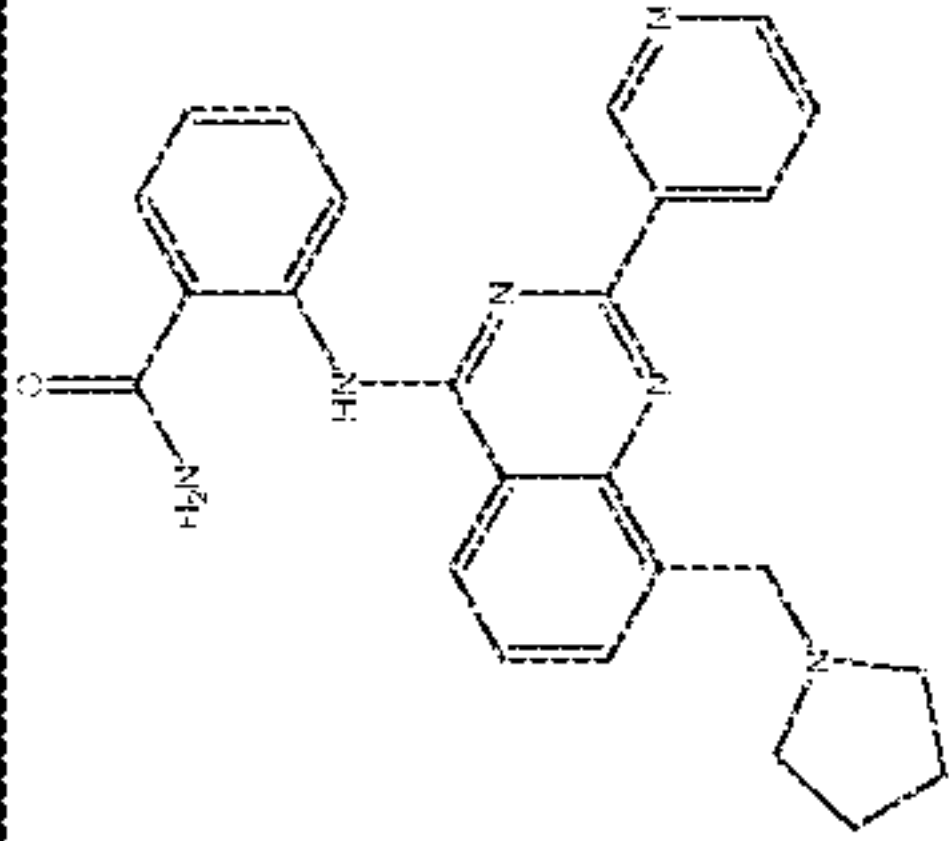
Method J2: 6-methoxy-N-(pyridin-2-yl)-2-(pyridin-3-yl)quinazolin-4-amine dihydrochloride (vi-e) To a suspension of 4-chloro-6-methoxy-2-(pyridine-3-yl)quinazoline (600 mg, 2.208 mmol) in dioxane (40 mL) under N₂, was added tris(dibenzylideneacetone)dipalladium(0) (103.1 mg, 0.113 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (132.2 mg, 0.228 mmol) and cesium carbonate (1.1289 g, 3.46 mmol) at room temperature. 2-Aminopyridine (229 mg, 2.43 mmol) was added and the mixture was stirred at 100°C for 2h 30 min. Water was added and then a precipitate formed. The solid was collected and washed with water. The solid was dissolved in CH₂Cl₂. Purification was carried out using NH-silica gel to give the free base (649.3 mg). The free base was converted to the HCl salt by dissolving the compound in CH₂Cl₂ / MeOH and 1.5 ml of 4N HCl in ethyl acetate was added and then a precipitate formed. The solid was collected and dried *in vacuo* (at 40 degrees on and 60 degrees for ca. 3 h) and then washed with methanol. The resulting solid was dried *in vacuo* at 60 degrees to give 682mg of the desired product as the HCl salt in a 77% yield as a pale yellow solid. ¹H NMR (DMSO-d₆) δ 11.14 (brs, 1H), 9.58 (s, 1H), 9.13 (dd, *J* = 7.96 Hz, 1H), 8.93 (d, *J* = 5.24 Hz, 1H), 8.54 (d, *J* = 4.72 Hz, 1H), 8.48 (d, *J* = 8.32 Hz, 1H), 8.28 (brs, 1H), 8.09 (brt, *J* = 7.16 Hz, 1H),

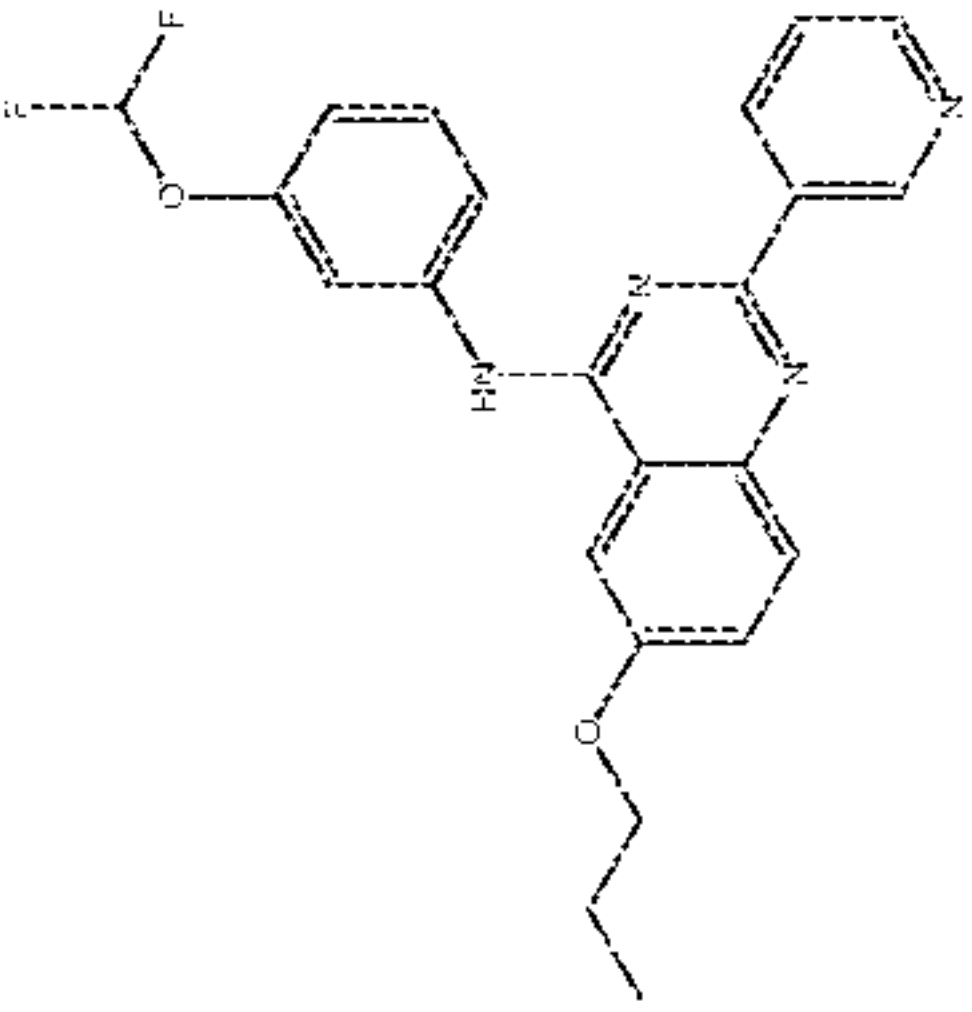
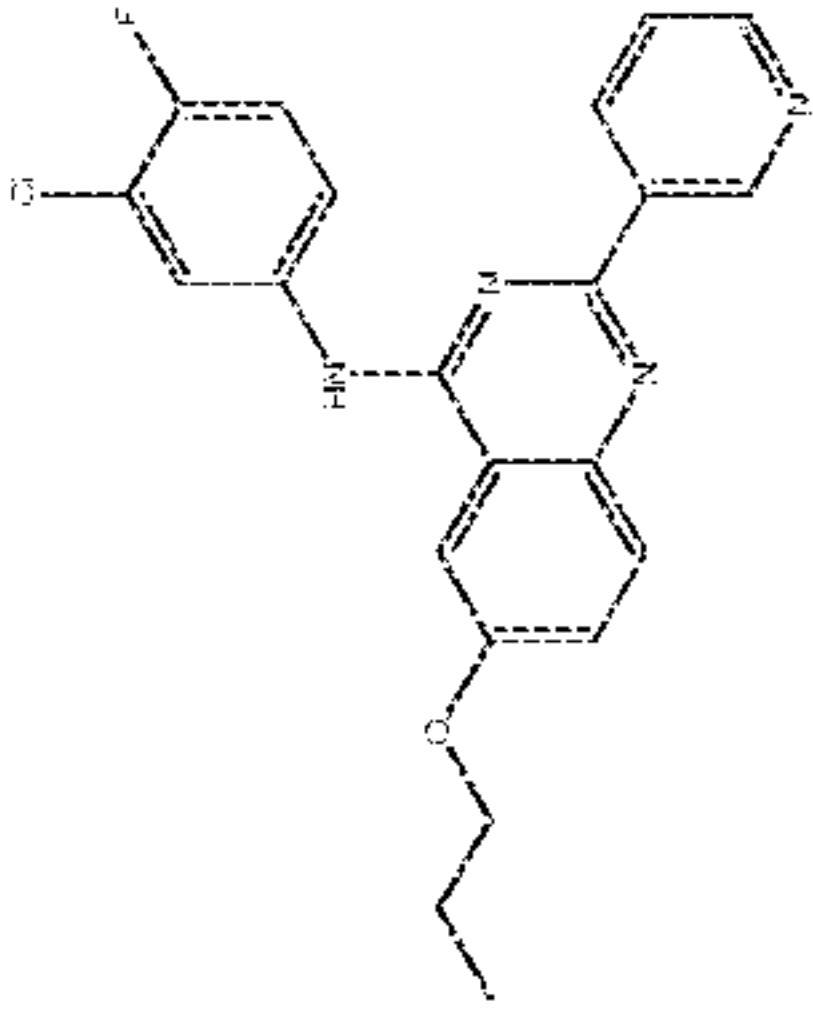
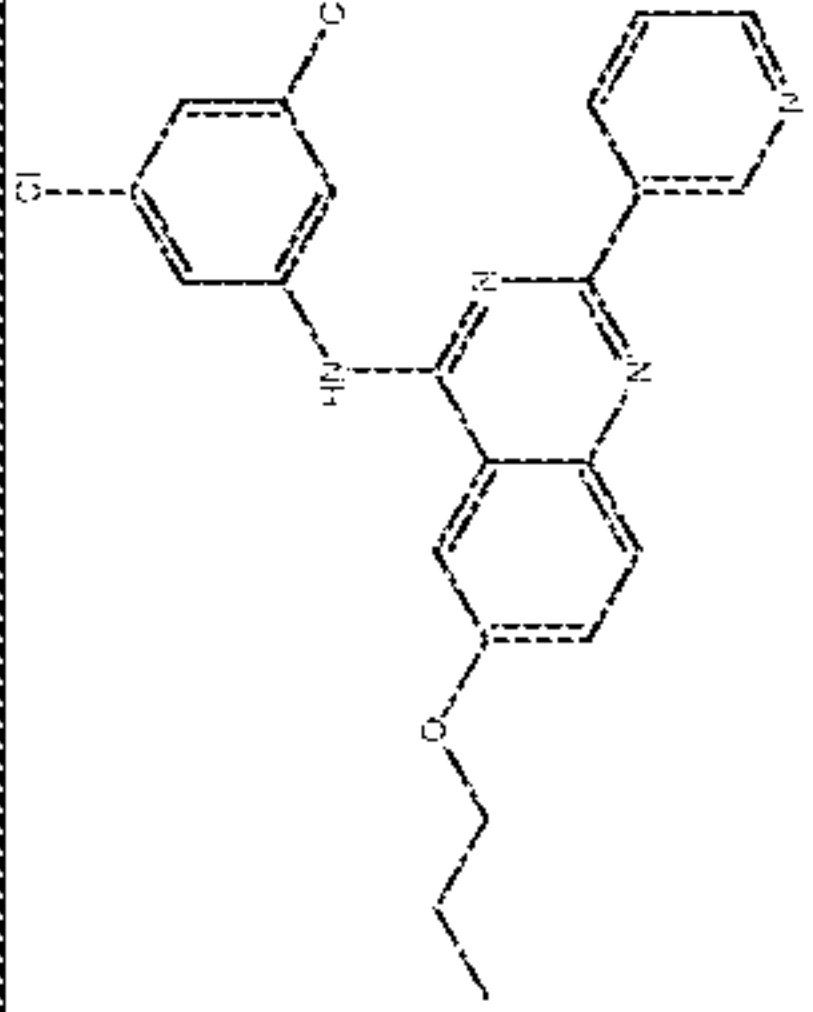
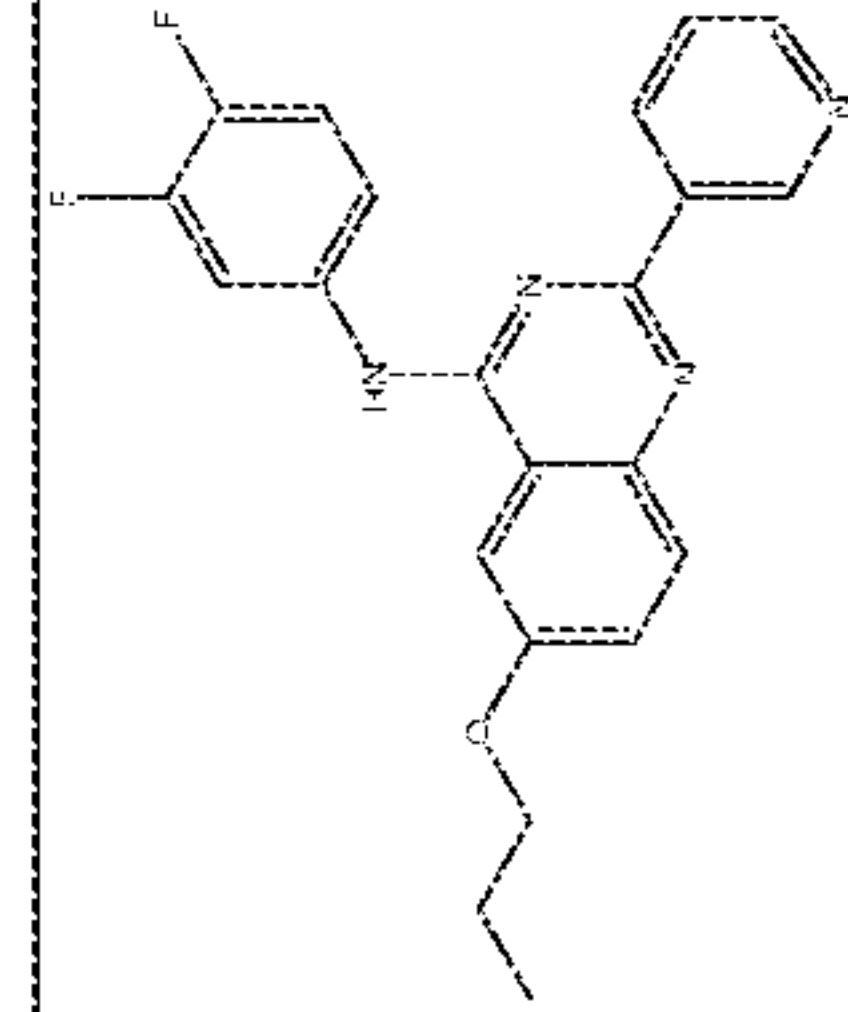
8.02-7.96 (m, 2H), 7.65 (dd, $J = 8.80, 2.48$ Hz, 1H), 7.34 (brt, $J = 6.52$ Hz, 1H), 4.01 (s, 3H). The 1H of 2HCl was not observed.

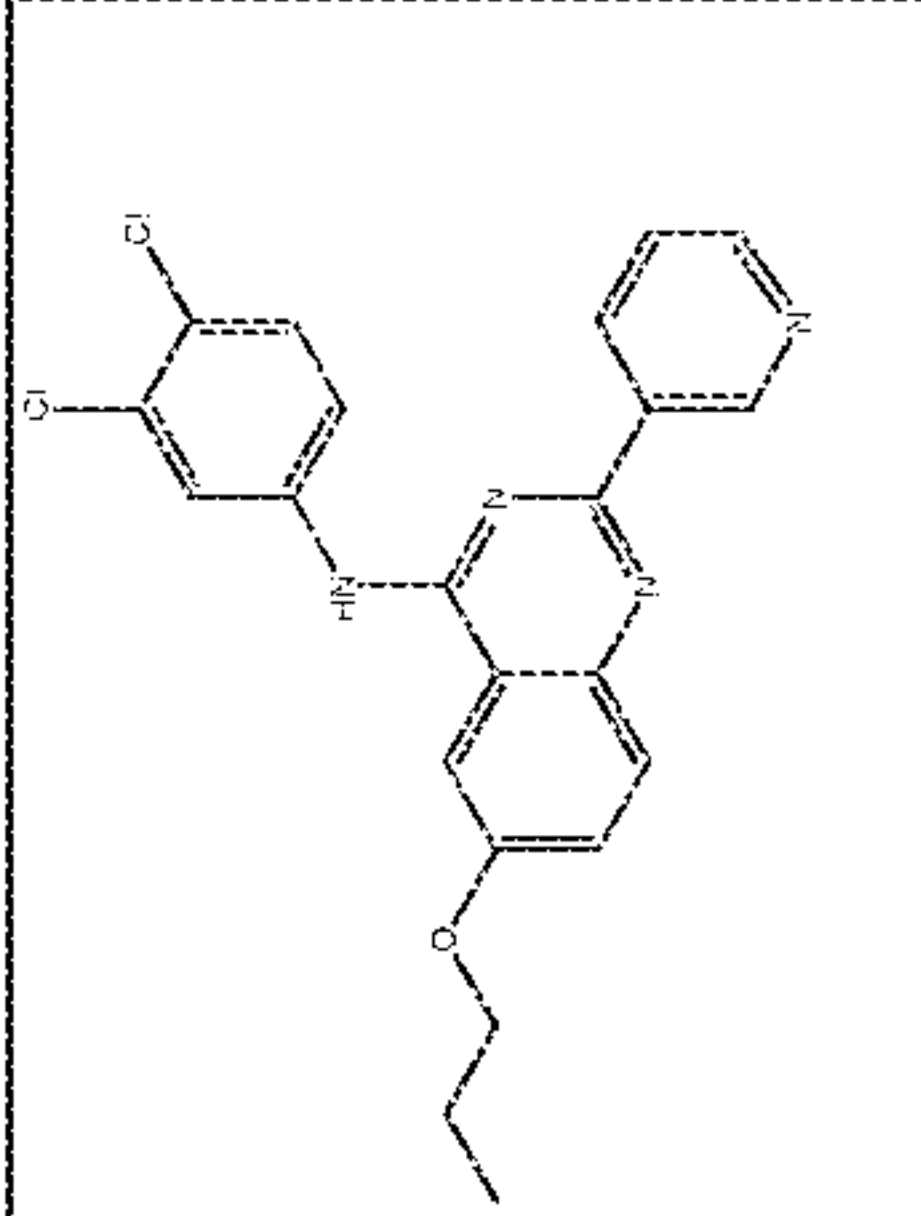
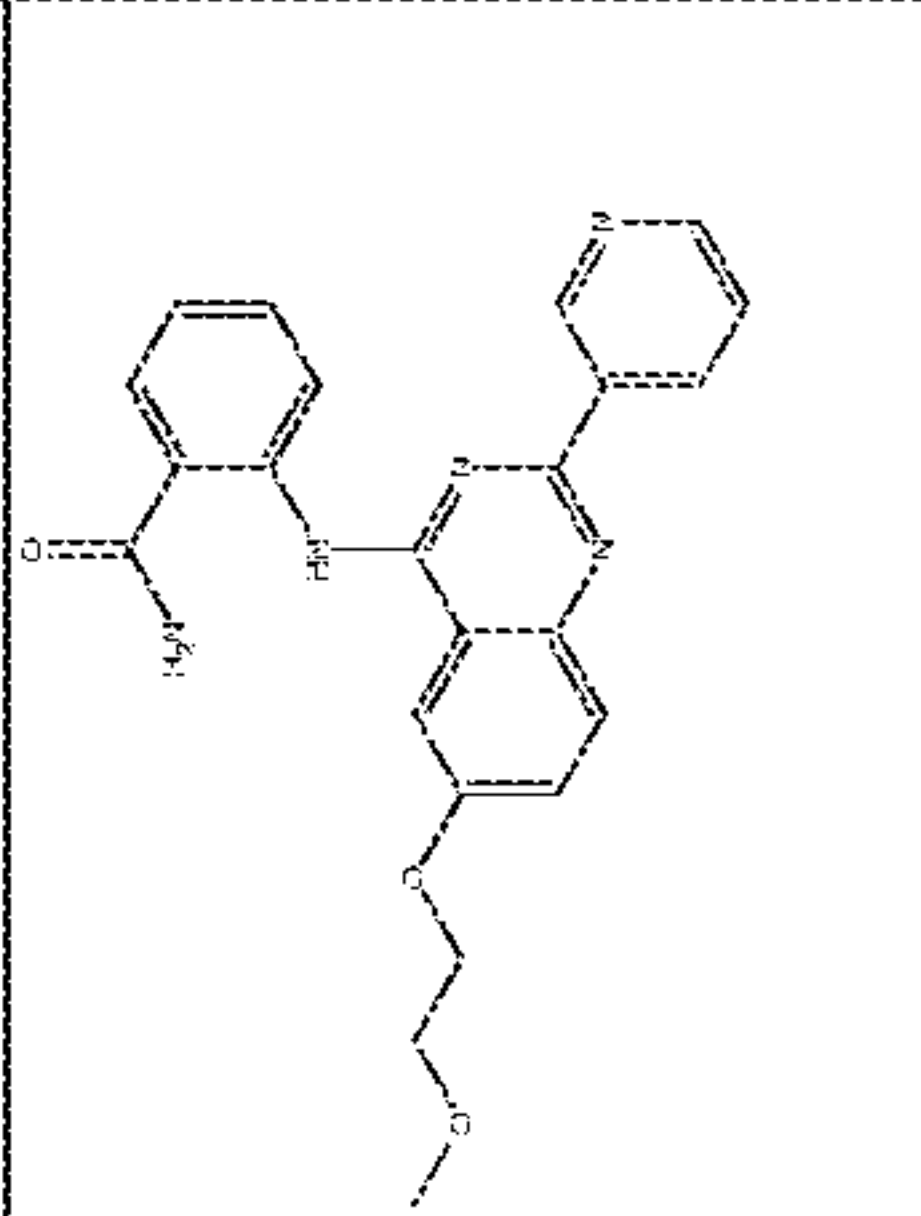
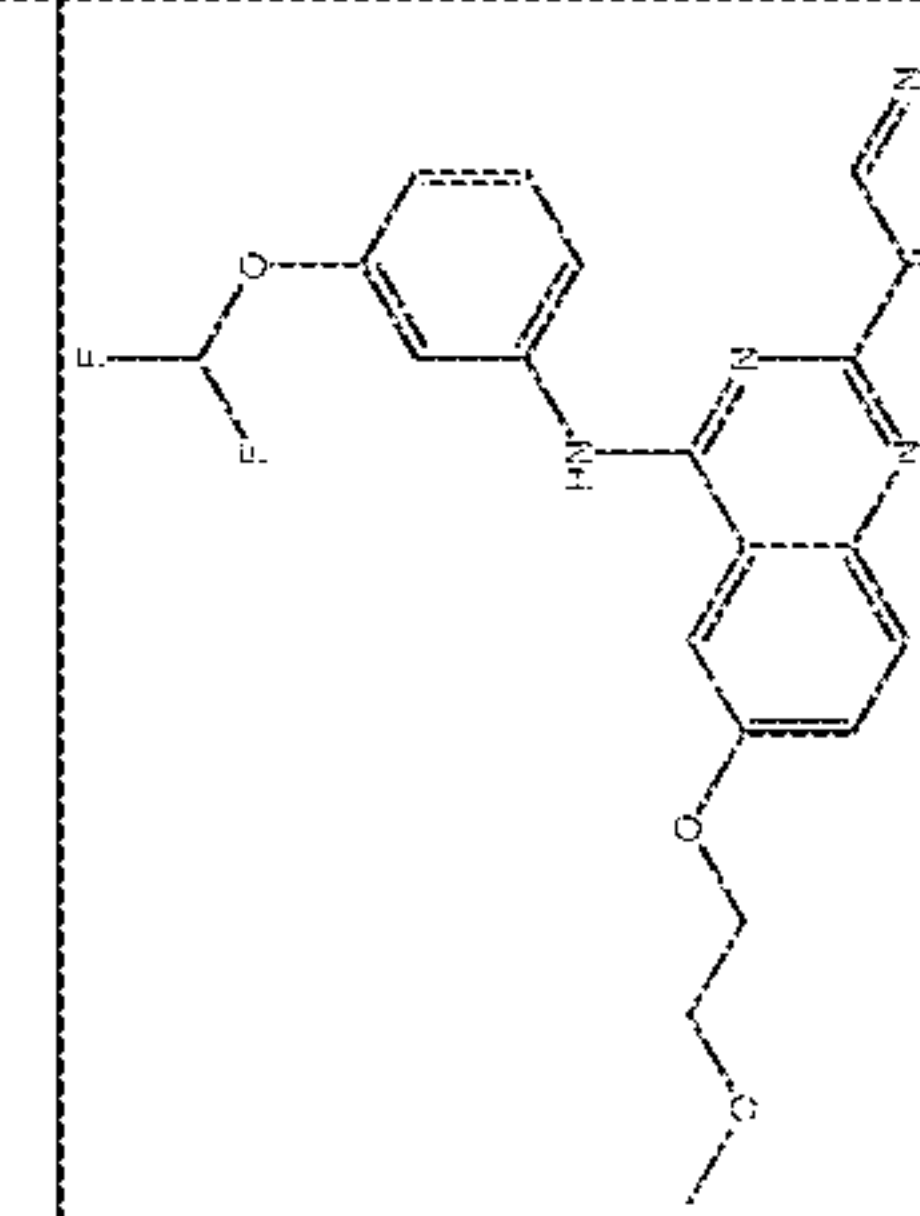
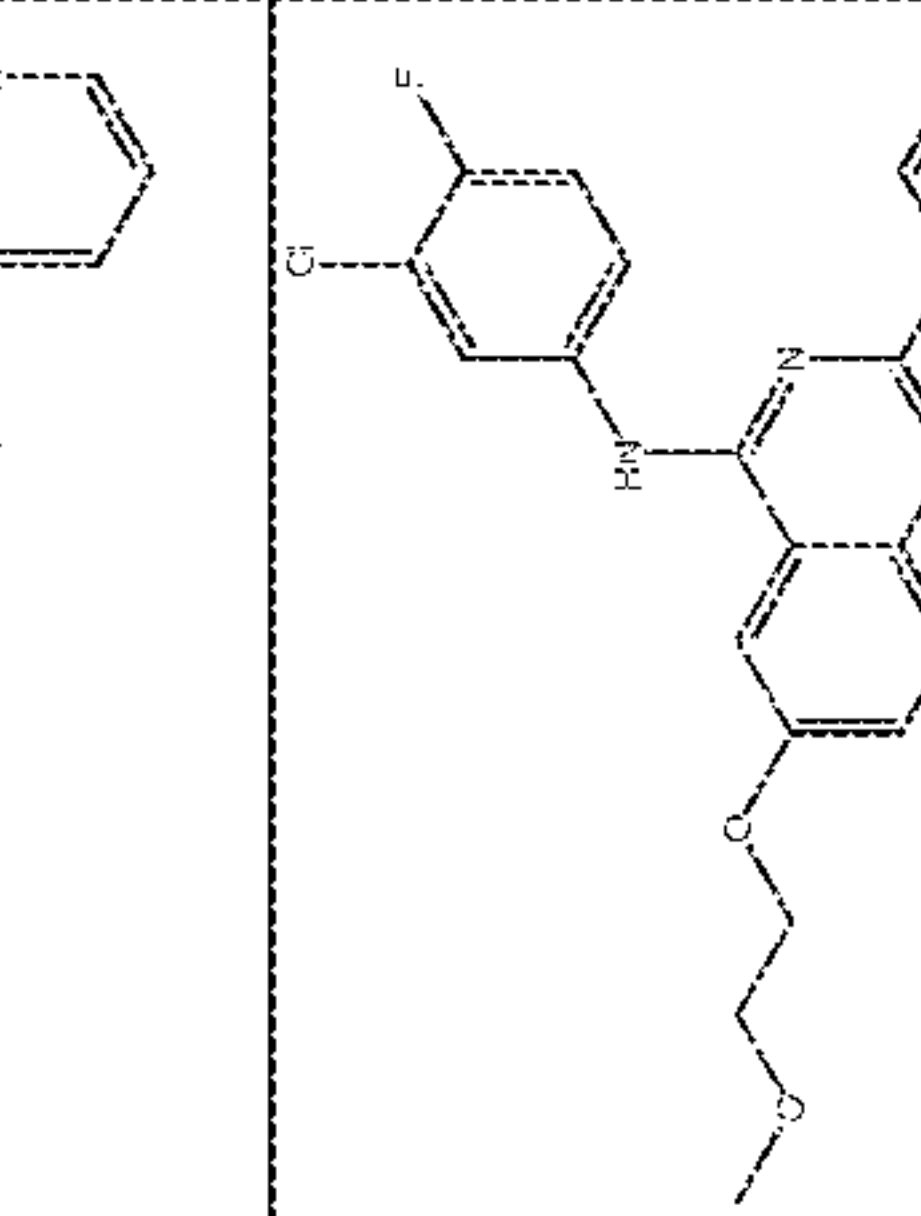
Method J3: N-(Biphenyl-4-yl)-6-methoxy-2-(pyridin-3-yl)quinazolin-4-amine hydrochloride (vi-f) To a suspension of N-(4-bromophenyl)-6-methoxy-2-(pyridin-3-yl)quinazolin-4-amine (548.7 mg, 1.347 mmol) and phenylboronic acid (270 mg, 2.21 mmol) in dioxane / H₂O (2/1) (30 mL) under N₂ was added Na₂CO₃ (485 mg, 4.58 mmol) and tetrakis(triphenylphosphine) palladium(0) (78 mg, 0.067 mmol) at room temperature. The mixture was stirred at 100°C for 1 h. Water was added and then a precipitate formed. The solid was dissolved in methanol/acetone at 60°C. The solution was filtrated through Celite™ to remove any extra palladium. The filtrate was concentrated down to give 493.4 mg of a solid residue in. The solid was added to CH₂Cl₂ followed by addition of 4N HCl in ethyl acetate (0.4 mL) at room temperature to form the HCl salt. The mixture was stirred at room temperature and the resulting solid was filtered and dried *in vacuo* to give 435.2 mg and a yield of 73% as the HCl salt. ¹H NMR (DMSO-d₆) δ 10.24 (br, 1H), 9.54 (s, 1H), 8.92 (d, $J = 7.52$ Hz, 1H), 8.82 (d, $J = 3.96$ Hz, 1H), 8.10 (d, $J = 2.44$ Hz, 1H), 8.03 (d, $J = 8.68$ Hz, 2H), 7.92 (d, $J = 9.08$ Hz, 1H), 7.84 (d, $J = 8.68$ Hz, 2H), 7.81 (m, 1H), 7.77-7.75 (m, 2H), 7.62 (dd, $J = 9.08, 2.44$ Hz, 1H), 7.50 (m, 2H), 7.38 (m, 1H), 4.01 (s, 3H). The 1H of HCl was not observed.

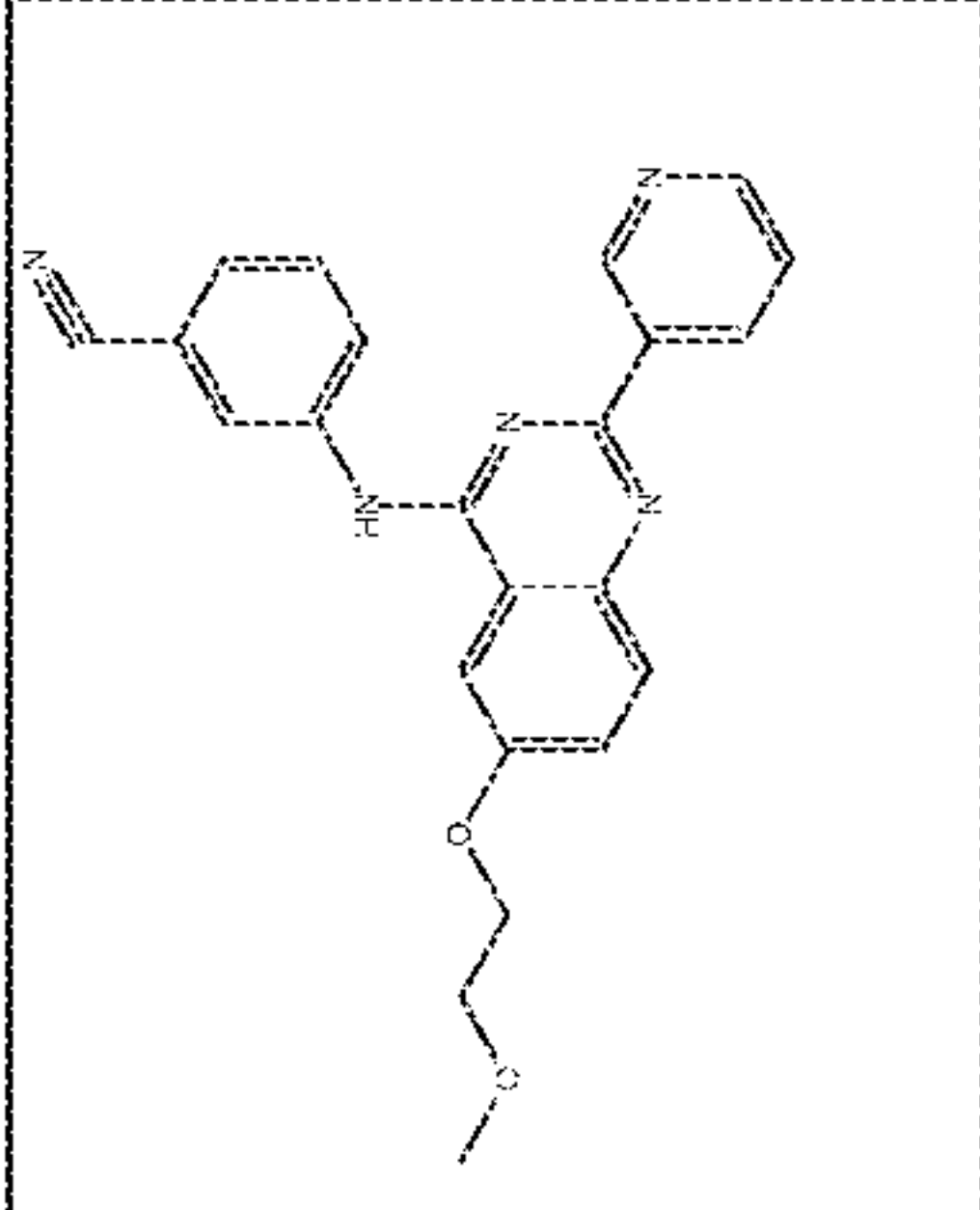
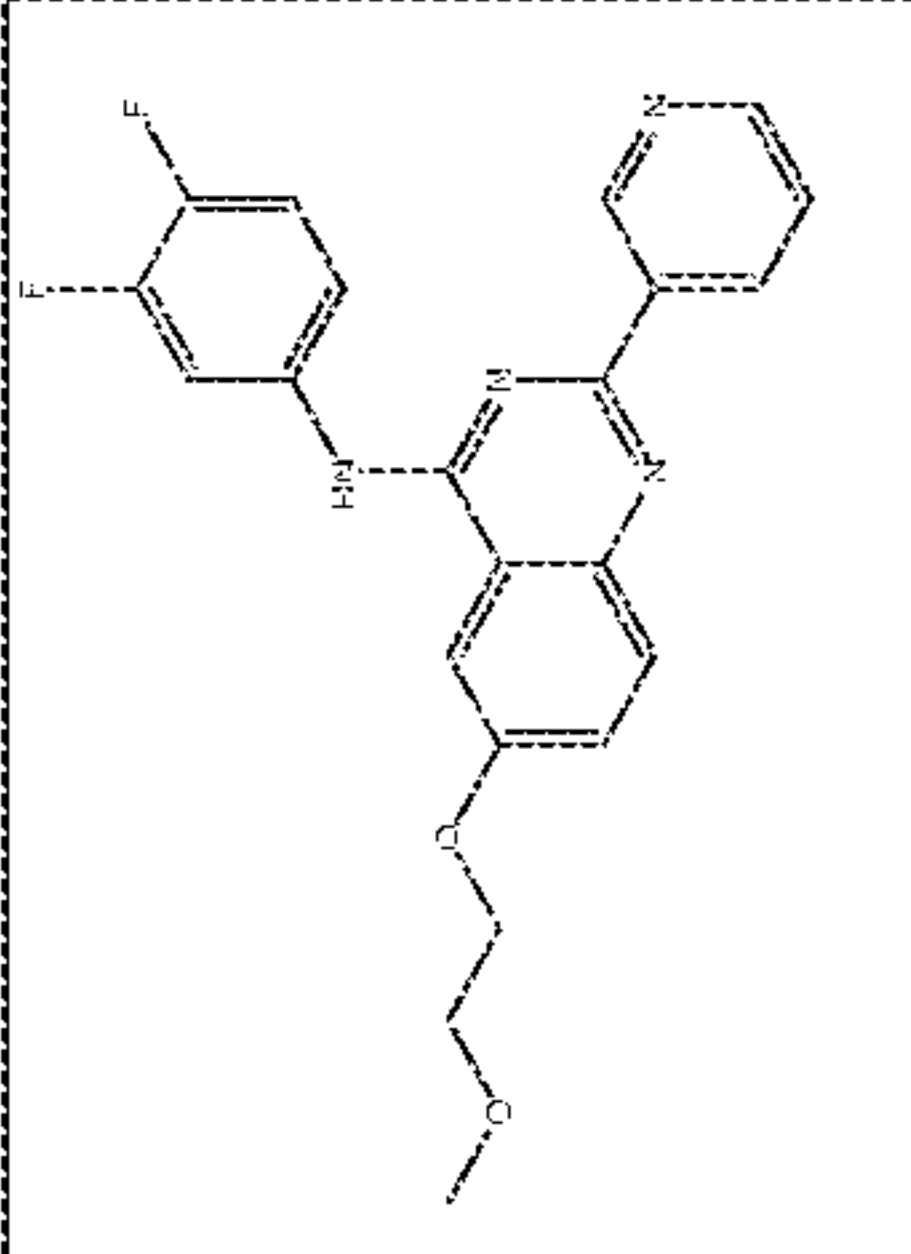
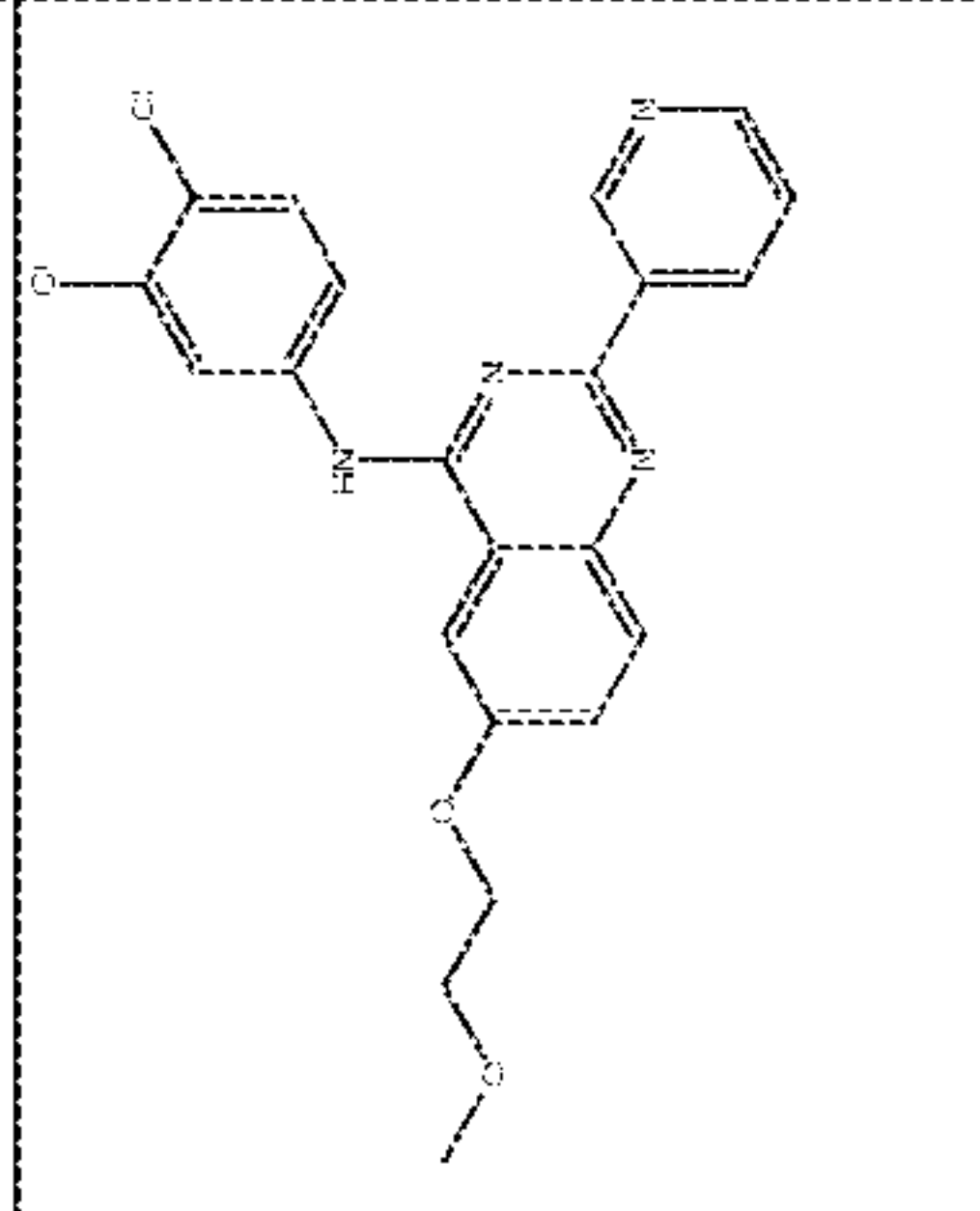
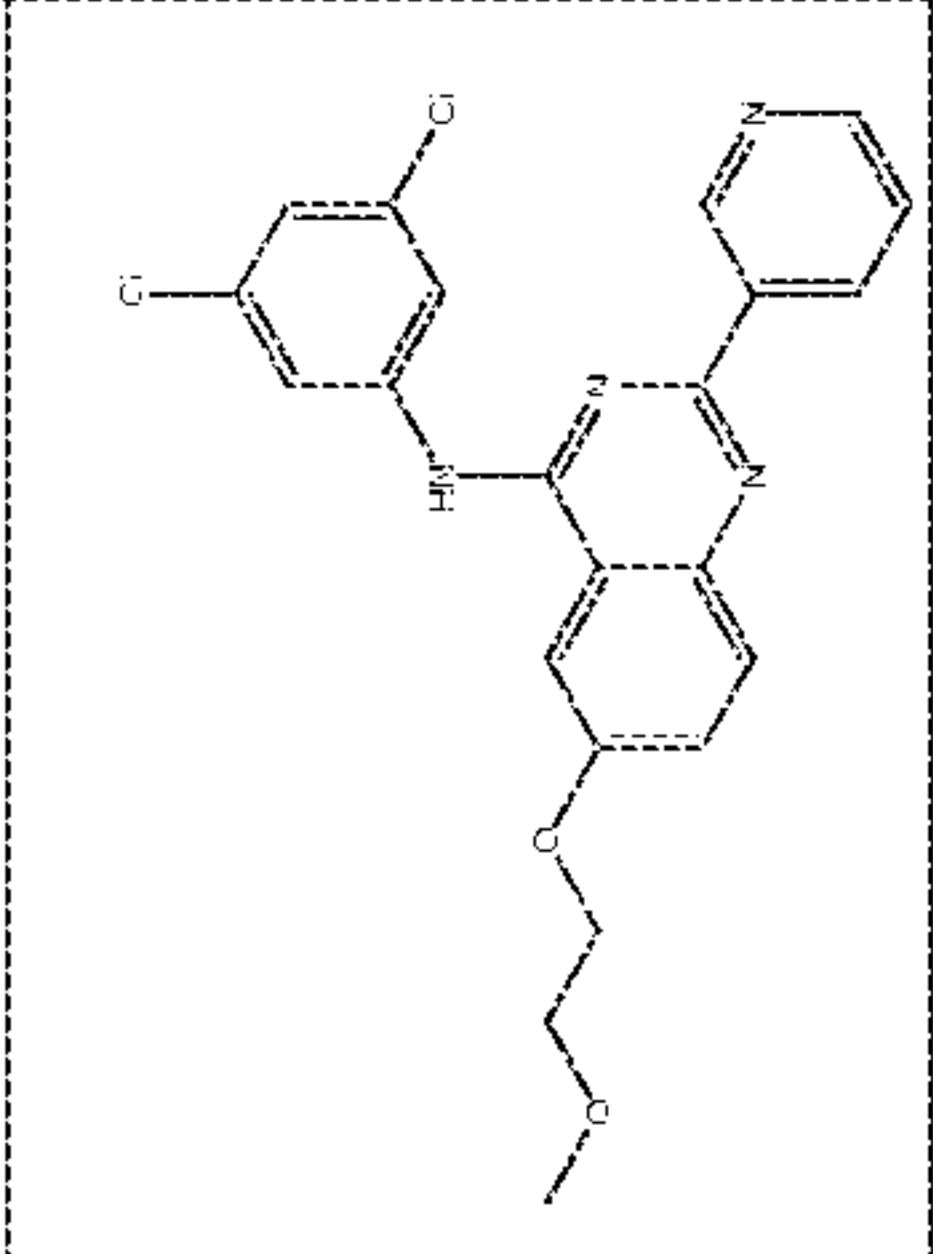
The compounds in the following table were prepared in a manner analogous to that described in Scheme 1 and 5 (prepared according to method procedure A - J as designated).

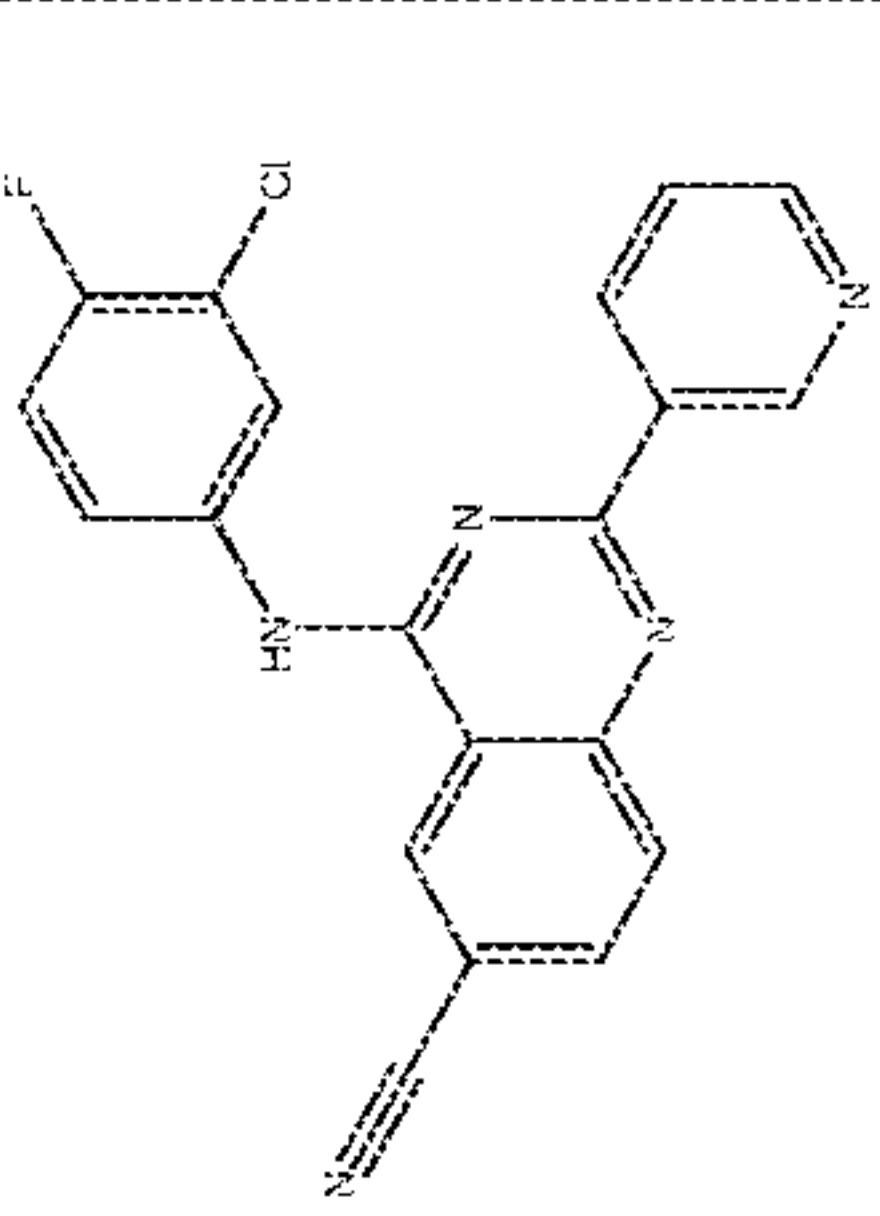
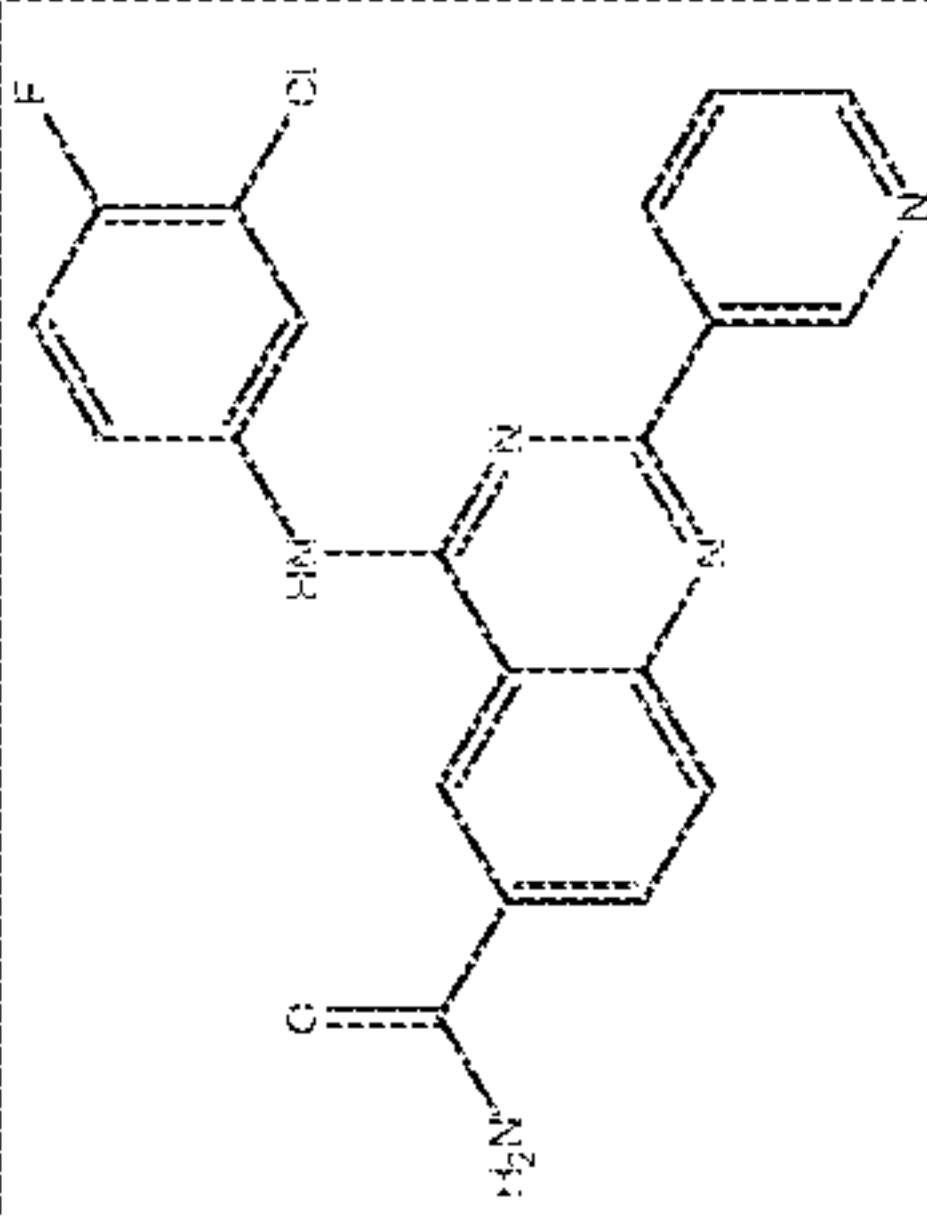
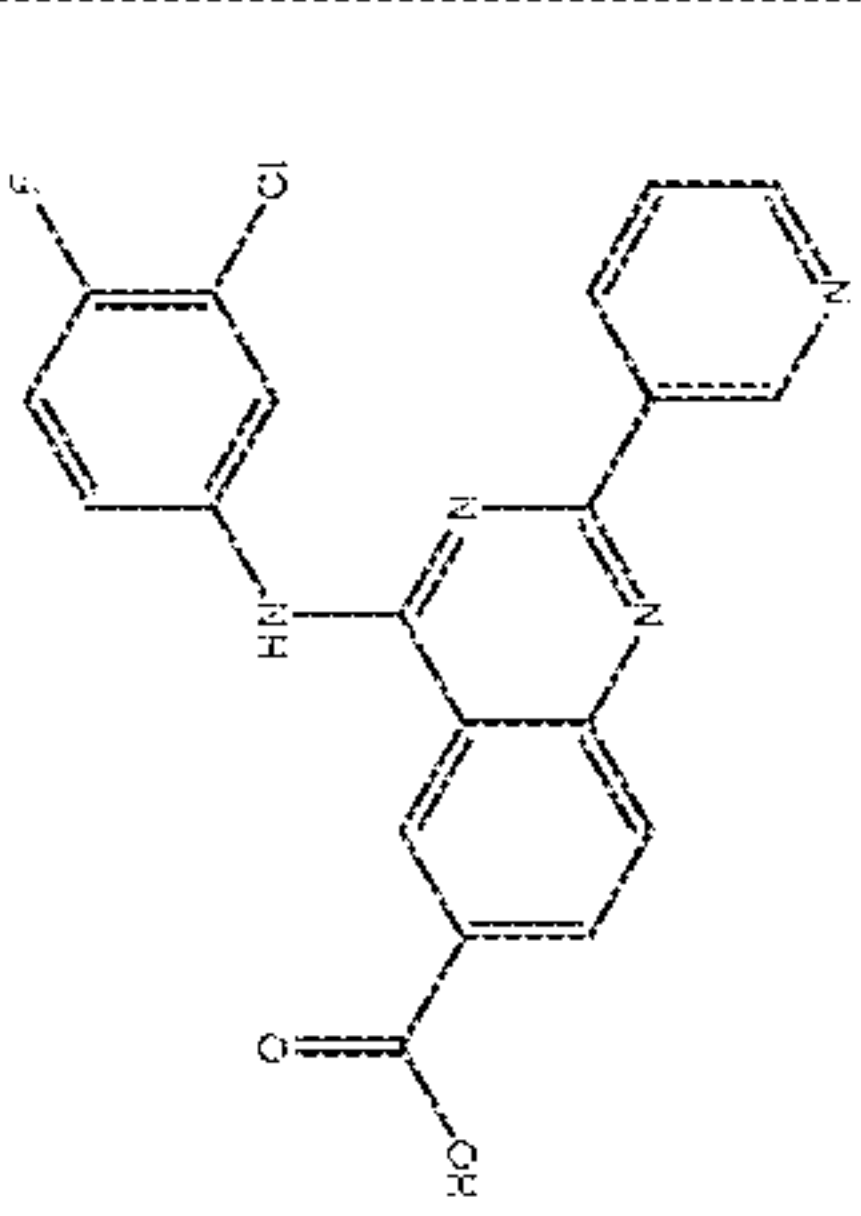
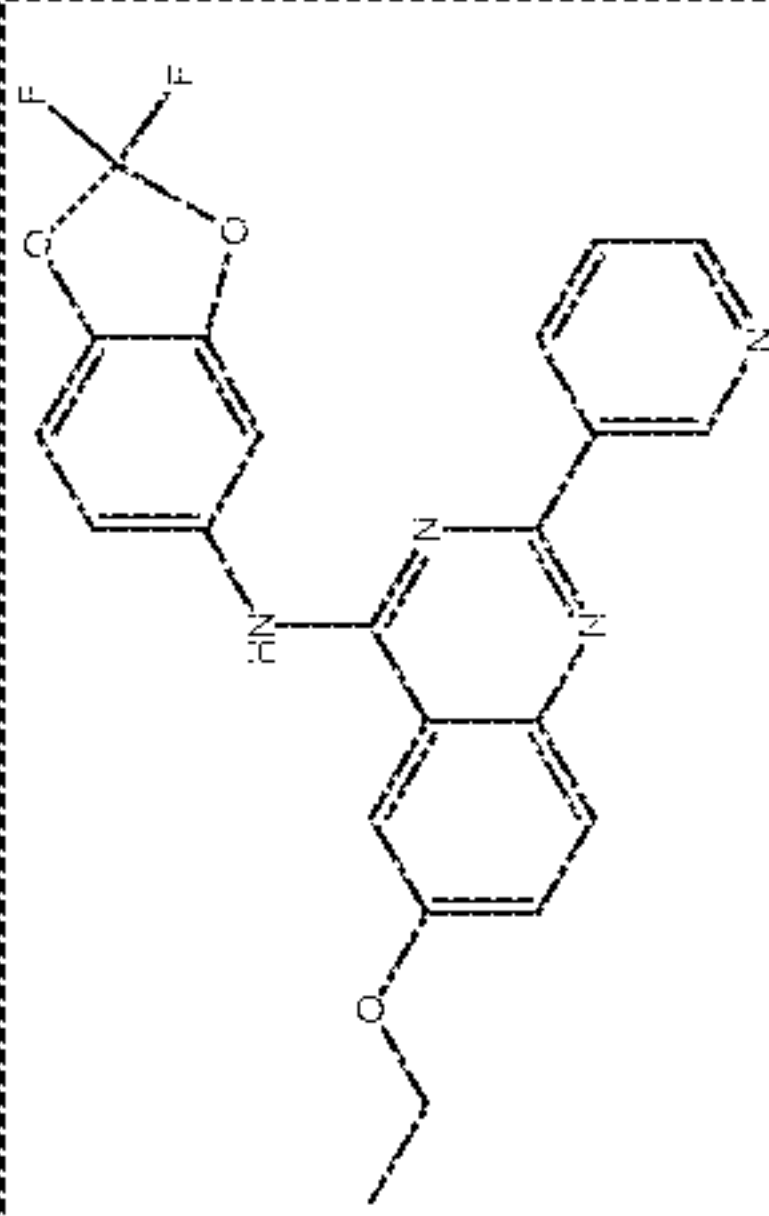
Table 1:

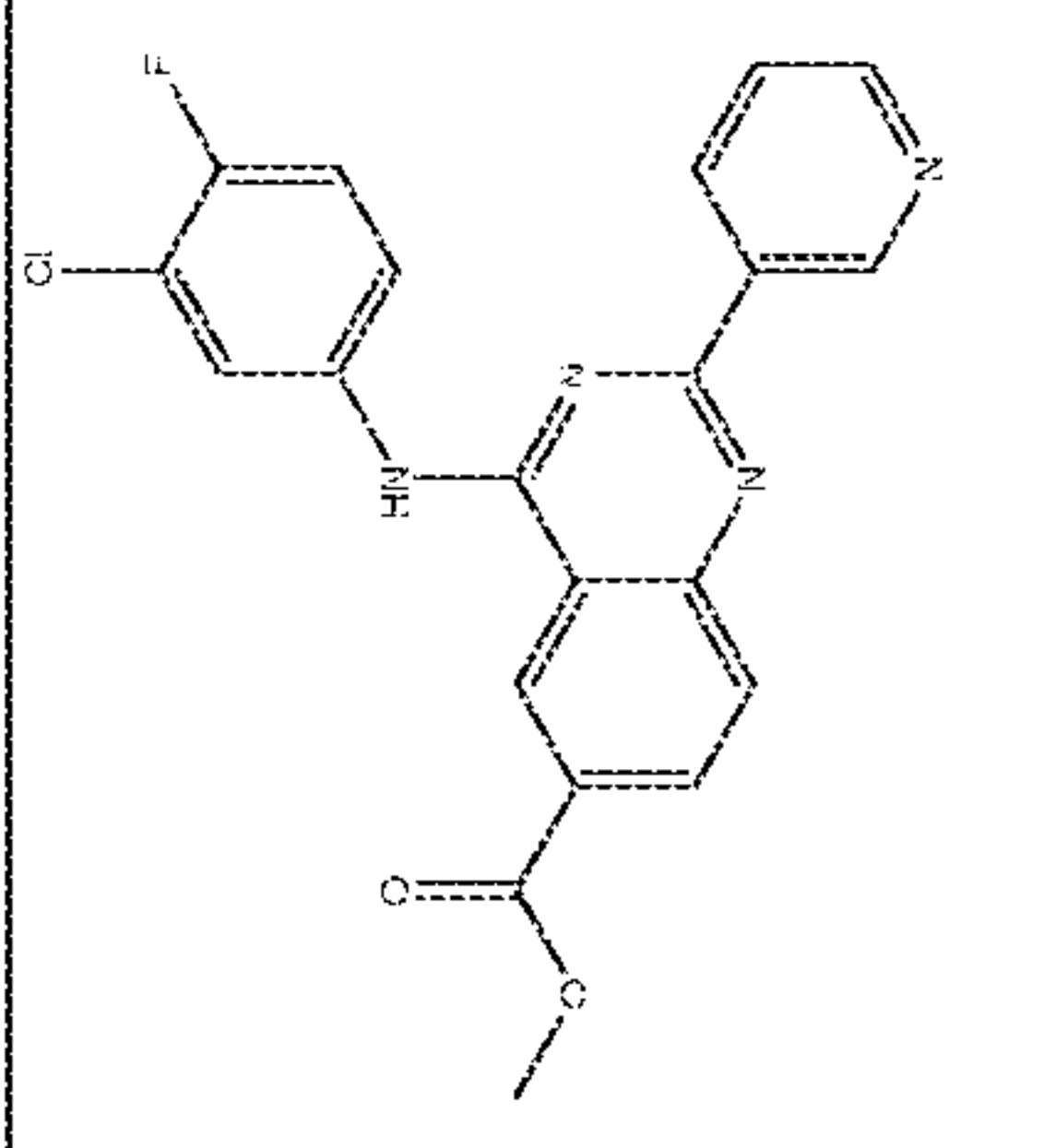
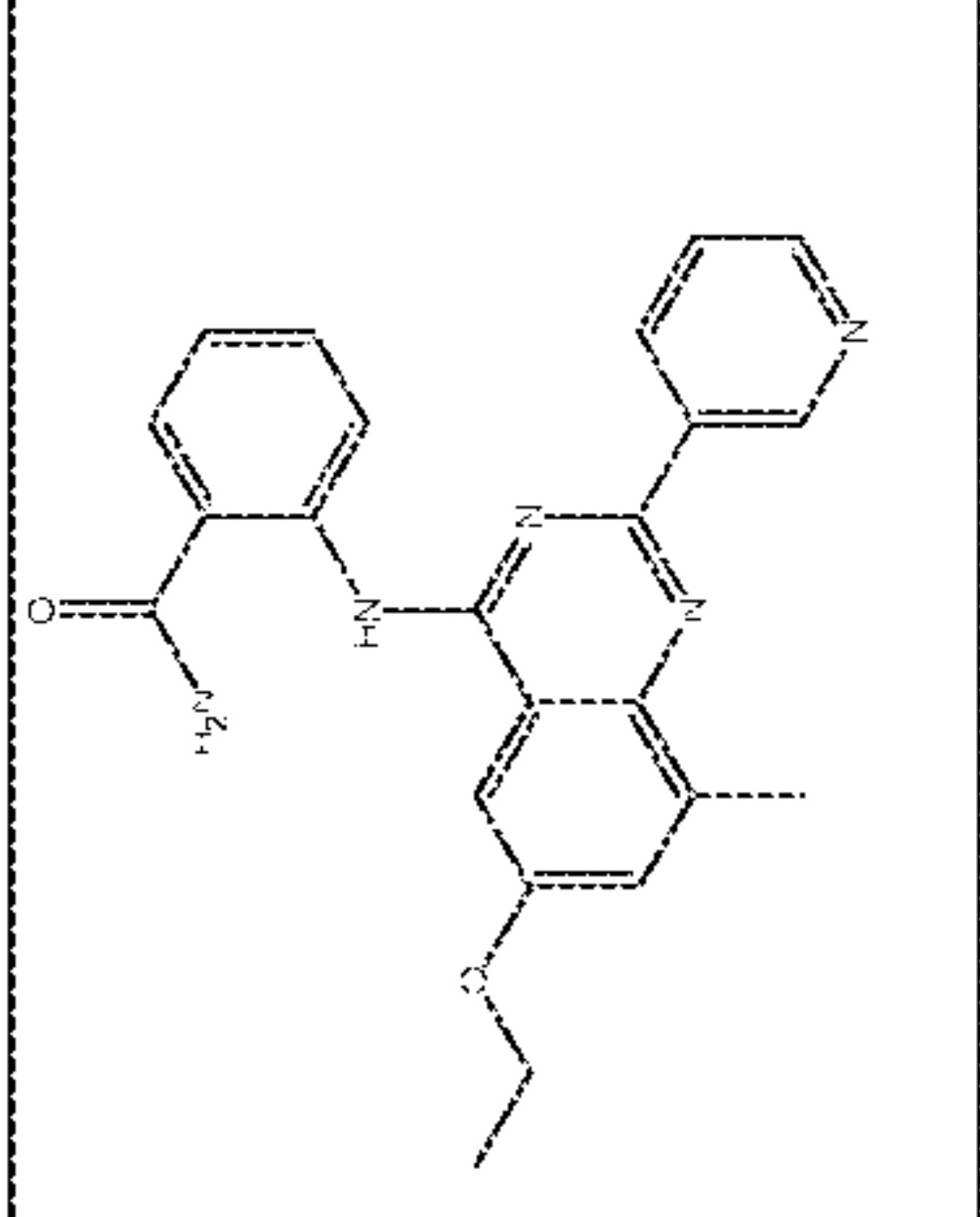
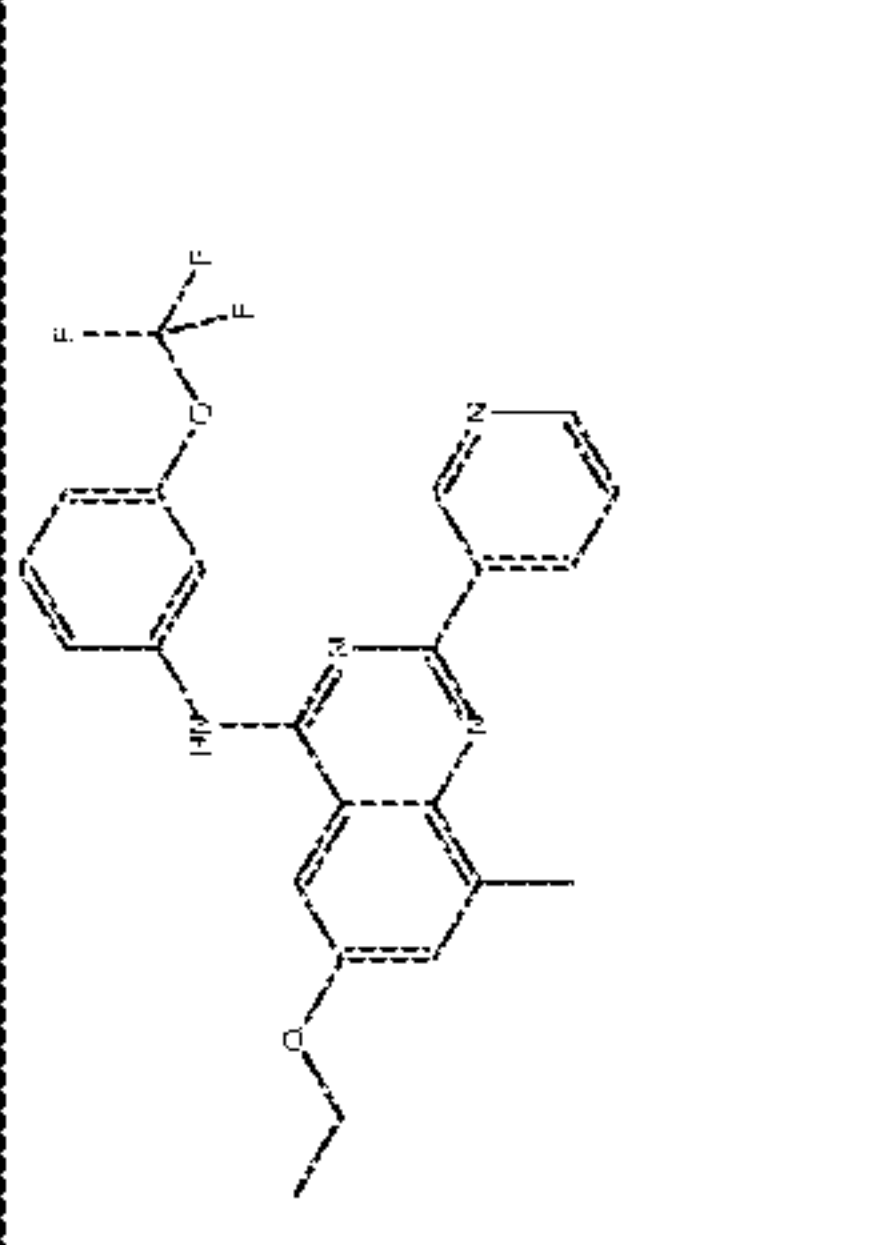
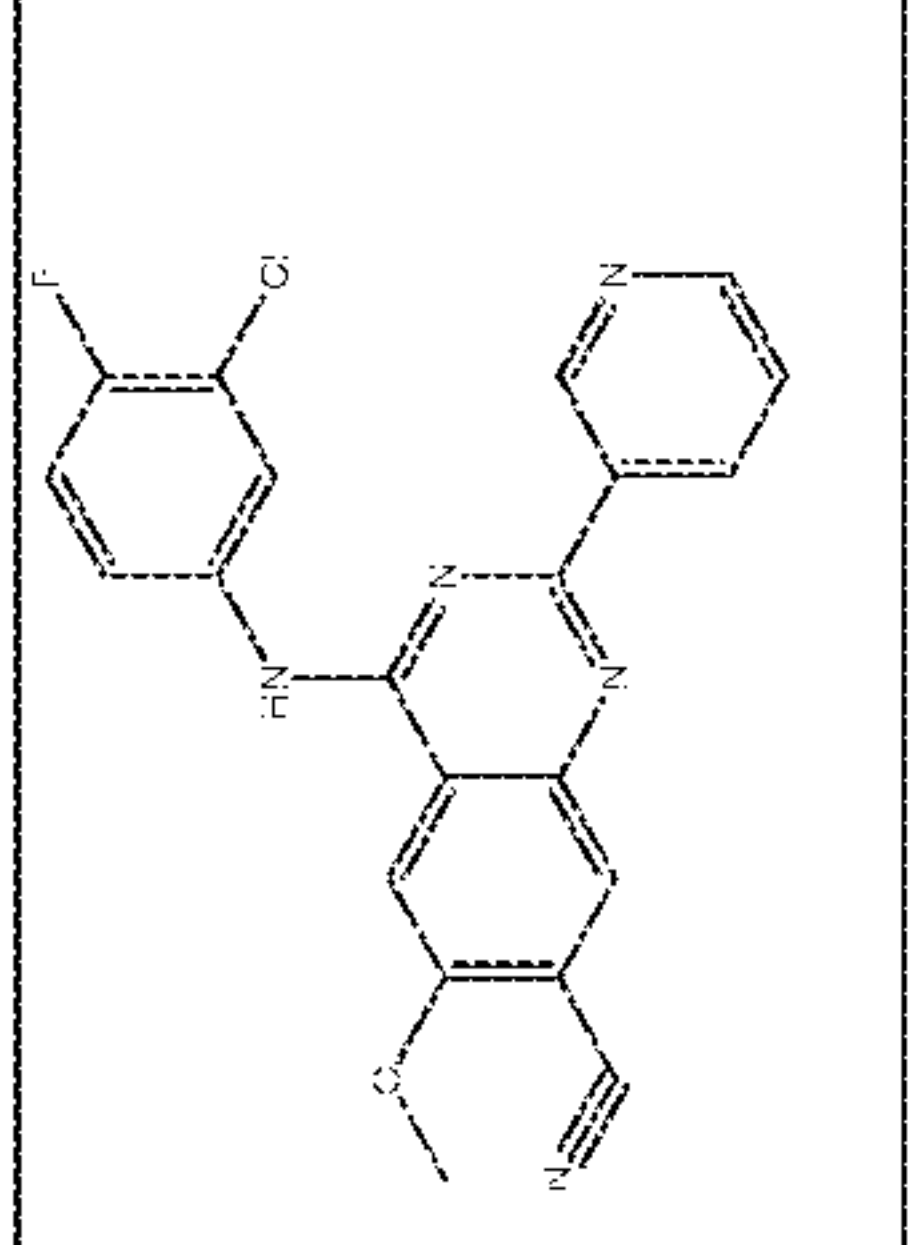
Number	Product	Salt type	Molecular Mass	¹ H-NMR	¹ H-NMR Solvent	LCMS	LCMS Protocol	Purity percent	Method for Coupling
1			399.45	¹ H-NMR (400 MHz, DMSO-d ₆): δ 9.59 (d, J = 2.0 Hz, 1H), 9.58 (d, J = 7.6 Hz, 1H), 8.69 – 8.74 (m, 2H), 8.48 (s, 1H), 7.97 (d, J = 6.8 Hz, 2H), 7.90 (d, J = 8.8 Hz, 1H), 7.74 (t, J = 7.6 Hz, 1H), 7.56 – 7.61 (m, 3H), 7.20 (t, J = 7.2 Hz, 1H), 4.16 (t, J = 6.4 Hz, 2H), 1.86 (dd, J = 7.2, 6.8 Hz, 2H), 1.07 (t, J = 7.2 Hz, 3H).	DMSO	400.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
2		HCl	396.46	¹ H-NMR (400 MHz, DMSO-d ₆): δ 13.20 (s, 1H), 9.79 (s, 1H), 9.02 – 9.08 (m, 2H), 8.87 (d, J = 3.2 Hz, 1H), 8.53 (s, 1H), 8.34 (d, J = 8.0 Hz, 1H), 8.19 (d, J = 6.8 Hz, 1H), 7.74 – 7.99 (m, 5H), 7.28 (t, J = 7.6 Hz, 1H), 4.92 (d, J = 4.0 Hz, 2H), 2.87 (d, J = 3.2 Hz, 6H).	DMSO	399.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
3		HCl	424.50	¹ H-NMR (400 MHz, DMSO-d ₆): δ 13.07 (s, 1H), 9.64 (d, J = 1.6 Hz, 1H), 9.15 (d, J = 8.0 Hz, 1H), 8.78 (ddd, J = 8.0, 4.0, 2.4 Hz, 1H), 8.73 (dd, J = 4.4, 1.2 Hz, 1H), 8.49 (s, 1H), 8.09 (d, J = 8.0 Hz, 1H), 7.92 – 7.69 (m, 3H), 7.67 – 7.74 (m, 2H), 7.62 (dd, J = 8.0, 4.8 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 4.29 (s, 2H), 2.61 (brs, 4H), 1.70 (brs, 4H).	DMSO	425.2 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1

4			422.43	¹ H-NMR (400 MHz, DMSO-d ₆): δ 9.87 (s, 1H), 9.52 (s, 1H), 8.67 (d, J = 5.6 Hz, 1H), 7.99 (d, J = 2.4 Hz, 1H), 7.94 (s, 1H), 7.86 (d, J = 9.2 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.50 – 7.58 (m, 3H), 7.30 (t, J = 34.0 Hz, 1H), 7.00 (dd, J = 8.4, 2.0 Hz, 1H), 4.16 (t, J = 6.4 Hz, 2H), 1.86 (dd, J = 7.2, 6.4 Hz, 2H), 1.07 (t, J = 7.2 Hz, 3H).	DMSO	423.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
5		HCl	408.86	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.28 (s, 1H), 9.48 (s, 1H), 8.93 (d, J = 6.4 Hz, 1H), 8.85 (d, J = 4.4 Hz, 1H), 8.18 (dd, J = 7.6, 2.4 Hz, 1H), 8.06 (d, J = 2.0 Hz, 1H), 7.85 – 7.93 (m, 3H), 7.62 (dd, J = 8.8, 6.4 Hz, 1H), 7.55 (t, J = 8.8 Hz, 1H), 4.17 (t, J = 6.4 Hz, 3H), 1.86 (dd, J = 7.6, 6.4 Hz, 2H), 1.06 (t, J = 7.6 Hz, 3H).	DMSO	409.1, 411.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
6			425.31	¹ H-NMR (400 MHz, DMSO-d ₆): δ 9.93 (s, 1H), 9.51 (s, 1H), 8.68 – 8.71 (m, 2H), 8.16 (d, J = 2.4 Hz, 1H), 7.94 (d, J = 2.0 Hz, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.56 – 7.60 (m, 2H), 7.37 (s, 1H), 4.14 (t, J = 6.4 Hz, 2H), 1.84 (dd, J = 10.4 Hz, 7.2 Hz, 2H), 1.07 (t, J = 7.6 Hz, 3H).	DMSO	425.0, 427.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
7			392.4	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.06 (s, 1H), 9.49 (s, 1H), 8.77 – 8.81 (m, 2H), 8.09 (ddd, J = 10.0, 7.6, 2.4 Hz, 1H), 7.88 (d, J = 9.2 Hz, 1H), 7.69 – 7.74 (m, 2H), 7.54 – 7.61 (m, 2H), 4.15 (t, J = 6.4 Hz, 2H), 1.86 (dd, J = 14.0, 7.6 Hz, 2H), 1.06 (t, J = 7.2 Hz, 3H).	DMSO	393.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1

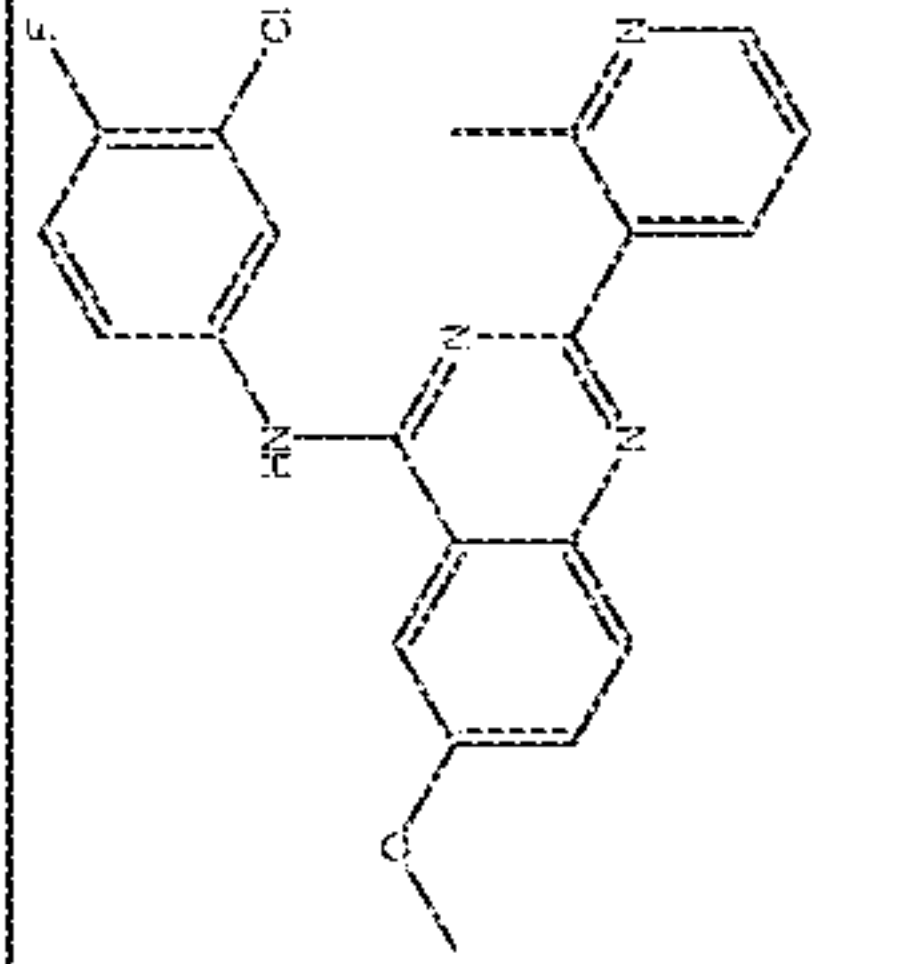
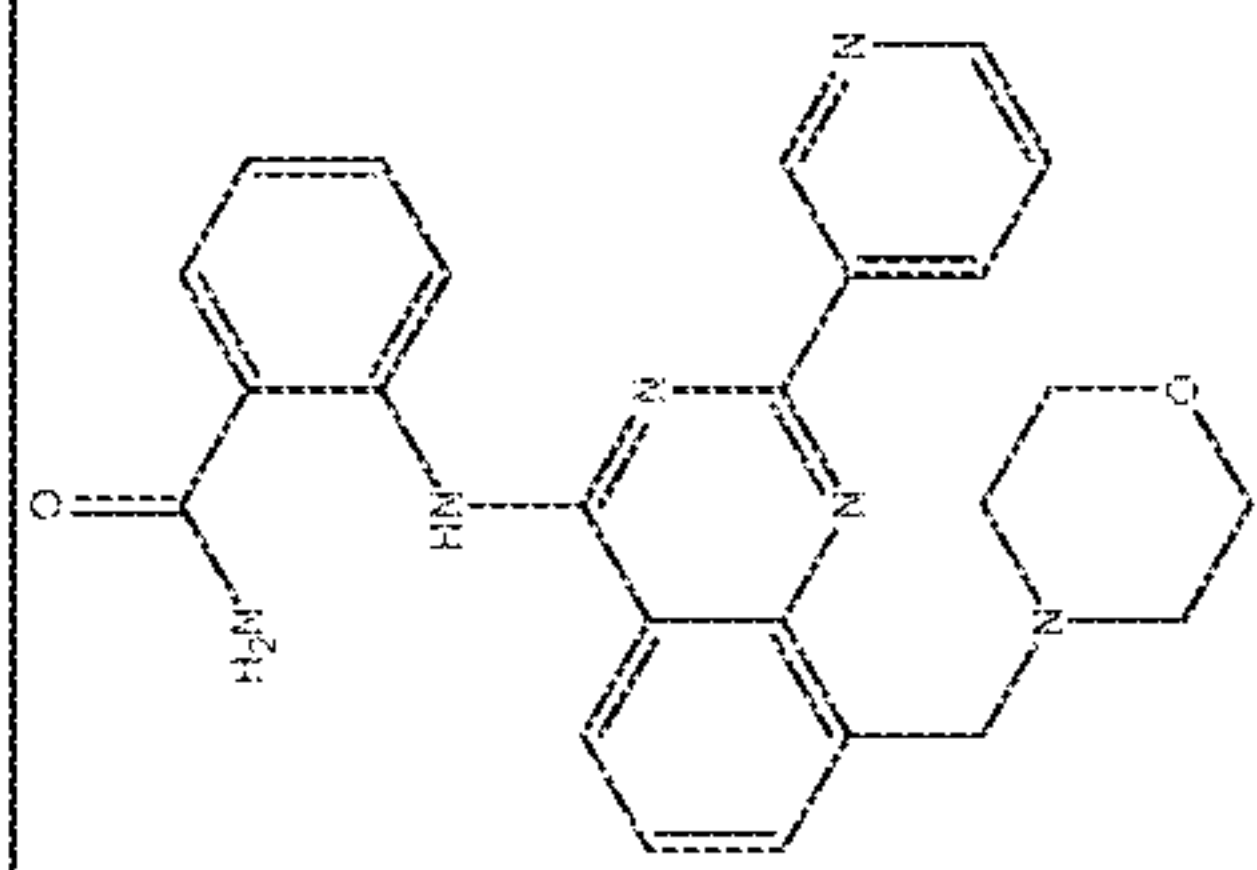
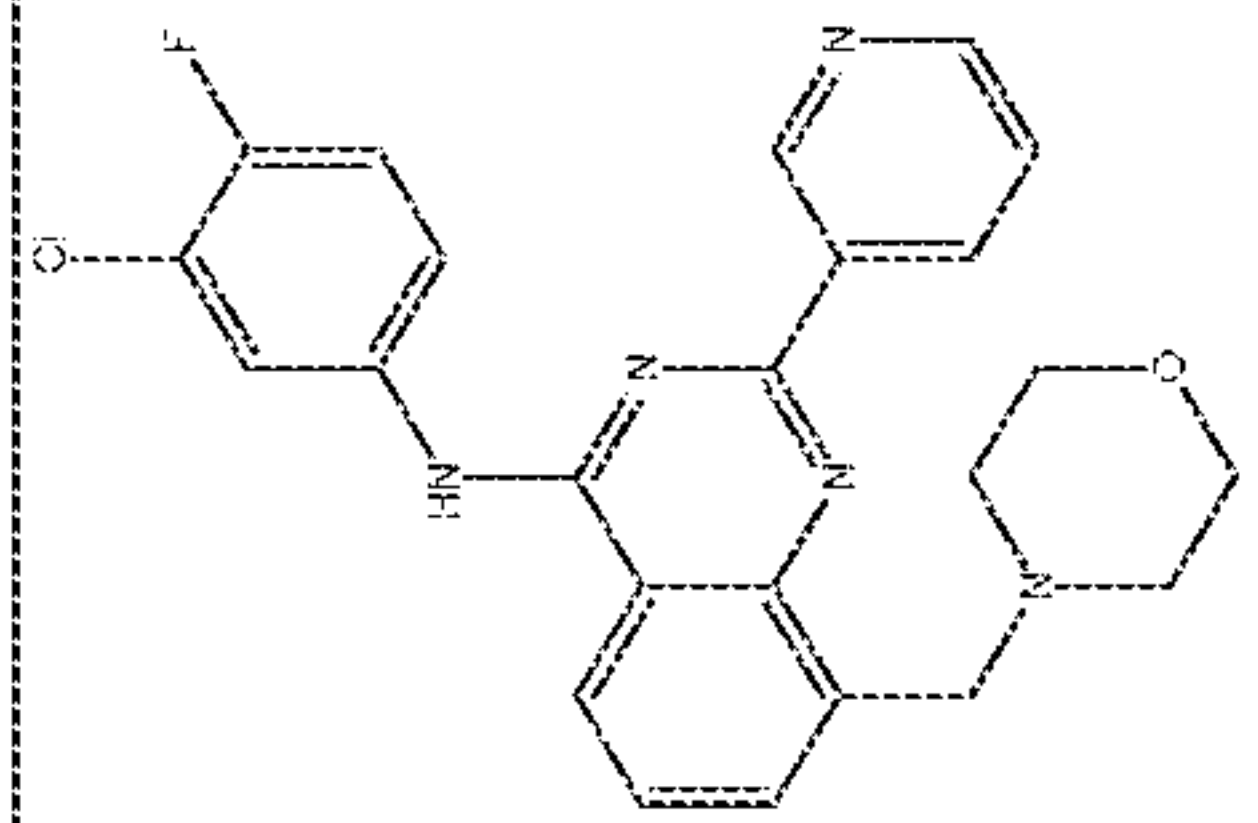
8			425.31	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.05 (s, 1H), 9.51 (s, 1H), 8.75 – 8.80 (m, 2H), 8.34 (d, J = 2.4 Hz, 1H), 7.96 – 8.00 (m, 2H), 7.88 (d, J = 9.2 Hz, 1H), 7.68 – 7.75 (m, 2H), 7.59 (dd, J = 9.2, 2.8 Hz, 1H), 4.15 (t, J = 6.4 Hz, 2H), 1.86 (dd, J = 7.2, 6.8 Hz, 2H), 1.06 (t, J = 7.6 Hz, 3H).	DMSO	425.0, 427.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
9			415.44	¹ H-NMR (400 MHz, DMSO-d ₆): δ 13.03 (s, 1H), 9.59 (d, J = 1.2 Hz, 1H), 9.15 (d, J = 8.4 Hz, 1H), 8.69 – 8.74 (m, 2H), 8.49 (s, 1H), 7.96 – 8.06 (m, 2H), 7.90 (d, J = 9.2 Hz, 1H), 7.56 – 7.63 (m, 3H), 7.20 (t, J = 8.0 Hz, 1H), 4.31 (t, J = 4.0 Hz, 2H), 3.79 (t, J = 4.8 Hz, 2H), 3.31 (s, 3H).	DMSO	416.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
10			438.43	¹ H-NMR (400 MHz, DMSO-d ₆): δ 9.86 (s, 1H), 9.53 (s, 1H), 8.66 – 8.68 (m, 2H), 8.02 (d, J = 2.8 Hz, 1H), 7.95 (t, J = 2.0 Hz, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.79 (d, J = 1.2 Hz, 1H), 7.48 – 7.60 (m, 3H), 7.30 (t, J = 74.4 Hz, 1H), 7.00 (dd, J = 8.0, 2.0 Hz, 1H), 4.33 (t, J = 4.8 Hz, 2H), 3.79 (t, J = 4.4 Hz, 2H), 3.37 (s, 3H).	DMSO	439.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
11		HCl	424.86	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.27 (s, 1H), 9.48 (s, 1H), 8.93 (d, J = 8.4 Hz, 1H), 8.85 (d, J = 4.8 Hz, 1H), 8.19 (dd, J = 6.8, 2.4 Hz, 1H), 8.10 (d, J = 2.4 Hz, 1H), 7.85 – 7.93 (m, 3H), 7.64 (dd, J = 9.2, 6.8 Hz, 1H), 7.55 (t, J = 8.8 Hz, 1H), 4.34 (t, J = 4.4 Hz, 2H), 3.78 (t, J = 4.4 Hz, 2H), 3.31 (s, 3H).	DMSO	425.1, 427.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1

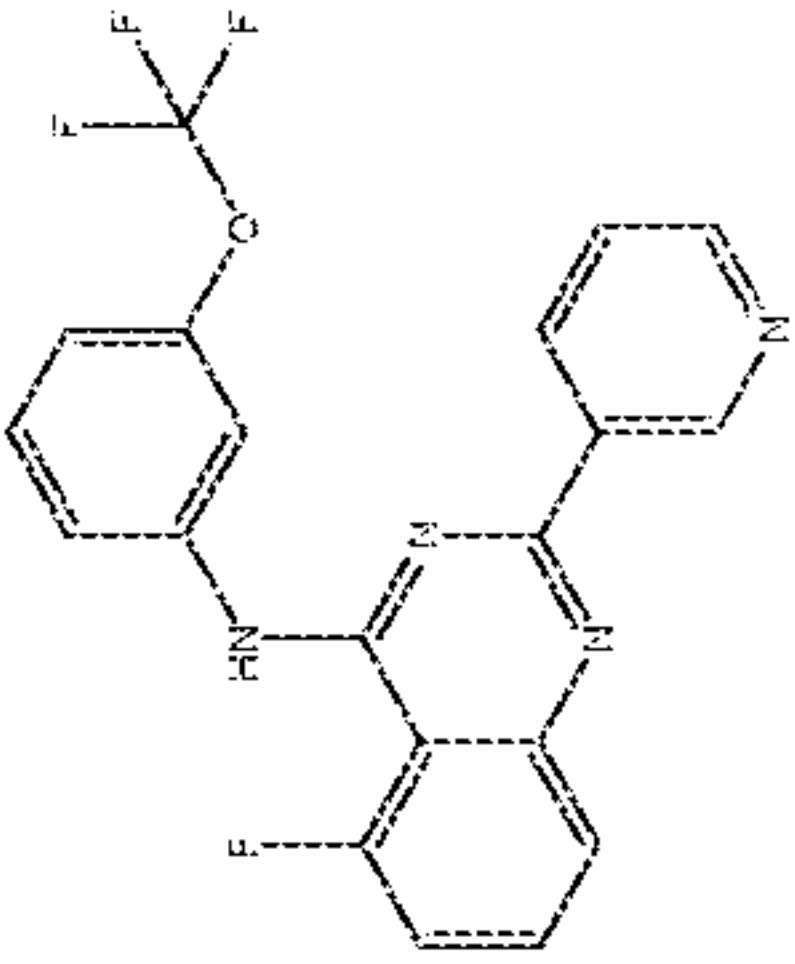
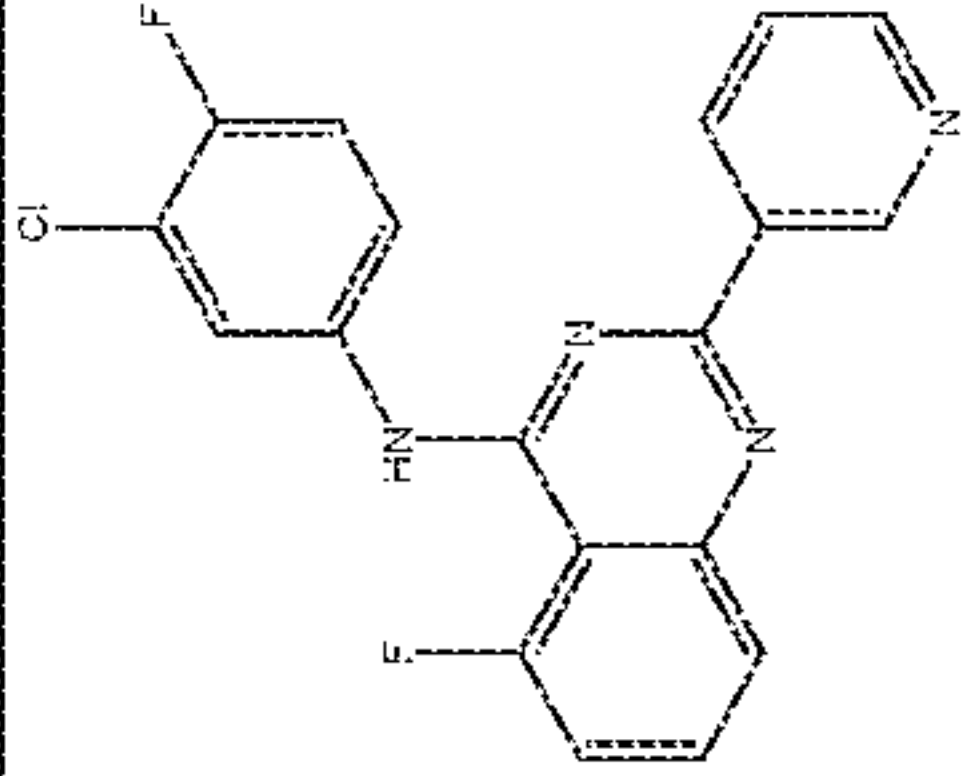
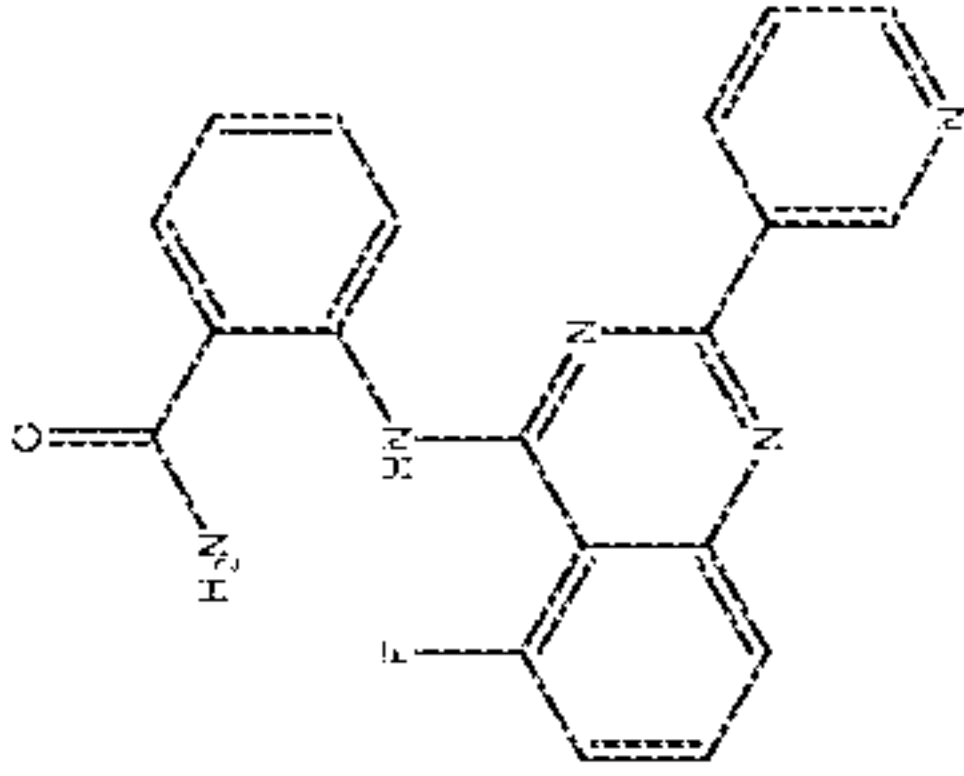
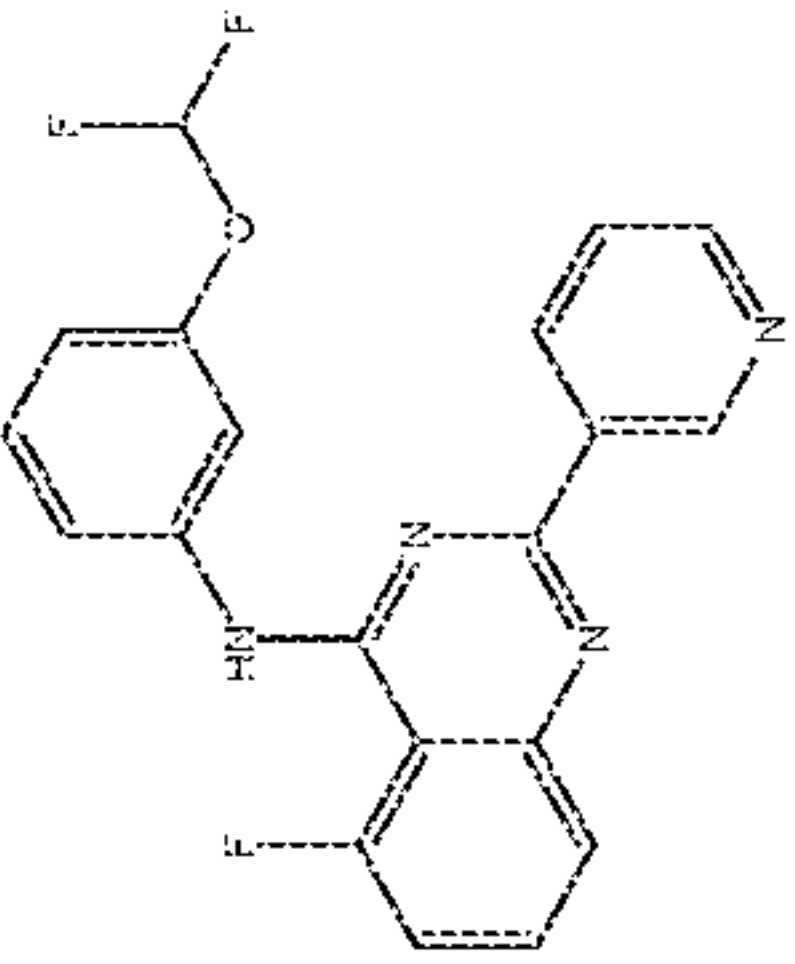
12			397.43	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.07 (s, 1H), 9.50 (s, 1H), 8.78 (dd, J = 17.6, 7.6 Hz, 1H), 8.39 (s, 1H), 8.26 (dd, J = 8.0, 2.0 Hz, 1H), 8.02 (d, J = 2.0 Hz, 1H), 7.90 (d, J = 9.2 Hz, 1H), 7.61 – 7.73 (m, 4H), 4.34 (t, J = 4.8 Hz, 2H), 3.79 (t, J = 4.4 Hz, 2H), 3.35 (s, 3H).	DMSO	398.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
13			408.4	¹ H-NMR (400 MHz, DMSO-d ₆): δ 9.86 (s, 1H), 9.50 (d, J = 1.6 Hz, 1H), 8.67 (dd, J = 4.8, 1.6 Hz, 1H), 8.64 (dt, J = 8.0, 1.6 Hz, 1H), 8.12 (ddd, J = 13.2, 7.2, 2.4 Hz, 1H), 7.98 (d, J = 2.8 Hz, 1H), 7.86 (d, J = 9.2, 1H), 7.69 – 7.72 (m, 1H), 7.52 – 7.60 (m, 3H), 4.31 (t, J = 4.0 Hz, 2H), 3.76 – 3.80 (m, 2H), 3.37 (s, 3H).	DMSO	409.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
14			441.31	¹ H-NMR (400 MHz, DMSO-d ₆): δ 9.90 (s, 1H), 9.52 (d, J = 1.2 Hz, 1H), 8.64 – 8.68 (m, 1H), 8.37 (d, J = 2.8 Hz, 1H), 7.98 (d, J = 2.4 Hz, 1H), 7.96 (dd, J = 10.6, 2.4 Hz, 1H), 7.86 (d, J = 9.2 Hz, 1H), 7.74 (d, J = 9.2 Hz, 1H), 7.59 (dd, J = 8.8, 2.4 Hz, 1H), 7.55 (dd, J = 8.0, 4.8 Hz, 1H), 4.31 (t, J = 4.08 Hz, 2H), 3.78 (t, J = 4.4 Hz, 2H), 3.37 (s, 3H).	DMSO	441.0, 443.0 (M+1), 221.9 (M/2 +1)	Method A (TFA)	95	Method C, G1
15			441.31	¹ H-NMR (400 MHz, DMSO-d ₆): δ 9.93 (s, 1H), 9.53 (d, J = 1.6 Hz, 1H), 8.66 – 8.70 (m, 2H), 8.18 (s, 1H), 8.17 (s, 1H), 7.99 (d, J = 2.4 Hz, 1H), 7.89 (d, J = 8.8 Hz, 1H), 7.61 (dd, J = 8.8, 2.4 Hz, 1H), 7.56 (dd, J = 7.6, 4.8 Hz, 1H), 7.39 (t, J = 2.0 Hz, 1H), 4.33 (t, J = 4.8 Hz, 2H), 3.79 (t, J = 4.4 Hz, 2H), 3.37 (s, 3H).	DMSO	441.1, 443.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1

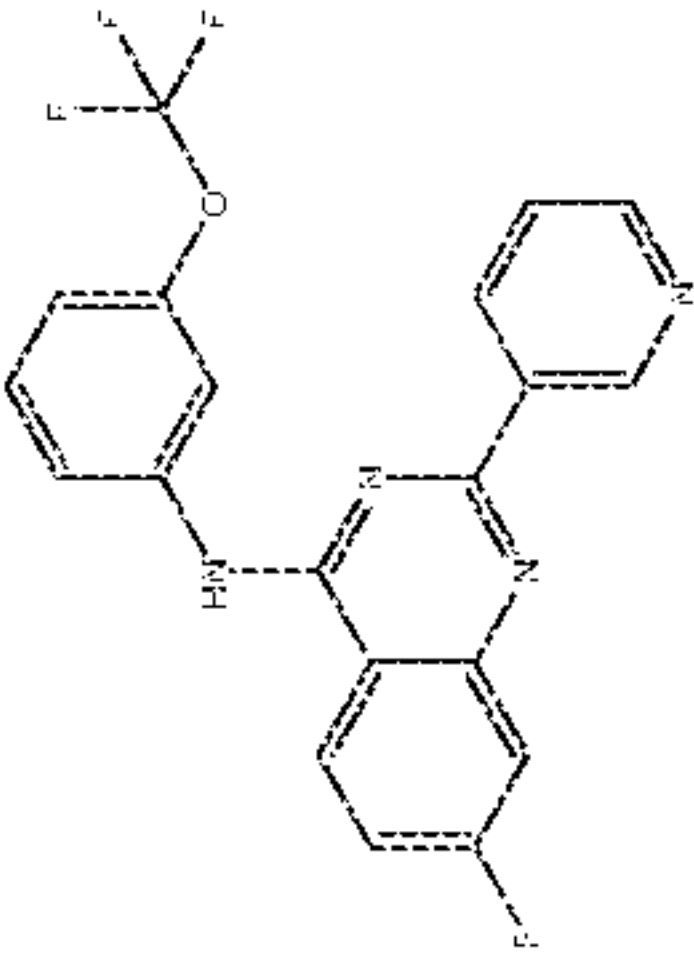
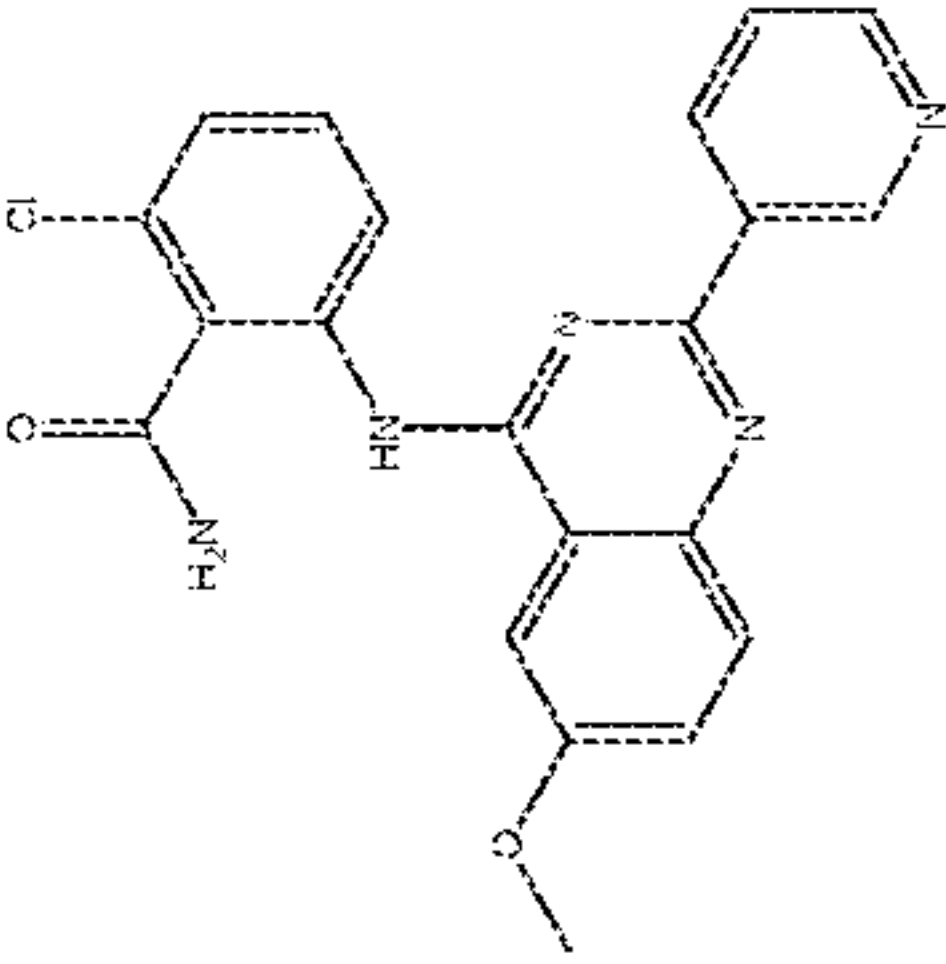
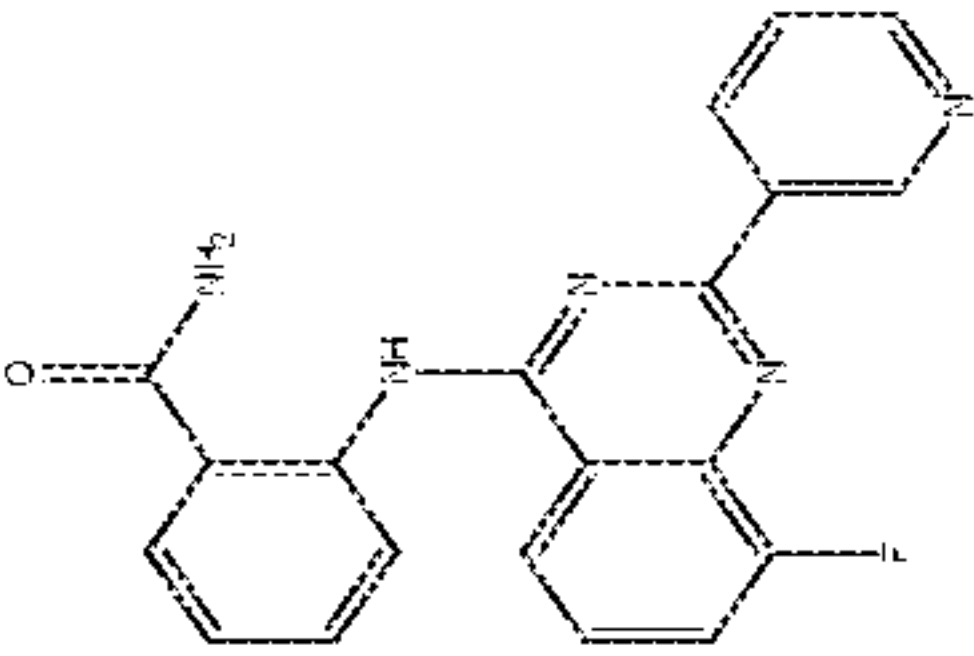
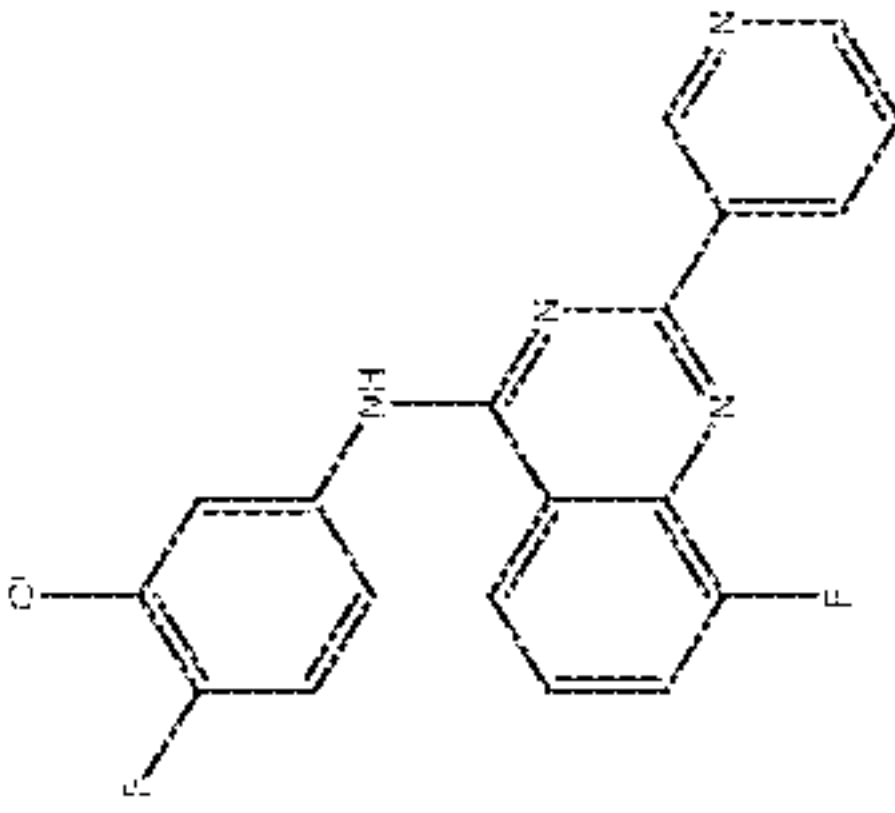
16		HCl	375.79	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.34 (s, 1H), 9.53 (d, J = 1.2 Hz, 1H), 9.16 (d, J = 1.2 Hz, 1H), 8.74 (dd, J = 4.0, 1.6 Hz, 1H), 8.66 – 8.69 (m, 2H), 8.20 – 8.28 (m, 2H), 8.00 (d, J = 8.4 Hz, 1H), 7.89 – 7.93 (m, 1H), 7.55 – 7.61 (m, 2H).	DMSO	376.0, 378.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
17			393.8	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.37 (s, 1H), 9.54 (d, J = 1.6 Hz, 1H), 9.09 (s, 1H), 8.69 (d, J = 10.0 Hz, 1H), 8.68 (d, J = 8.0 Hz, 1H), 8.23 – 8.27 (m, 2H), 8.11 (s, 1H), 8.78 (s, 2H), 7.50 – 7.58 (m, 3H).	DMSO	394.1, 396.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
18		HCl	394.79	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.81 (s, 1H), 9.48 (d, J = 0.8 Hz, 1H), 9.28 (d, J = 0.8 Hz, 1H), 8.69 (d, J = 10.0 Hz, 1H), 8.68 (d, J = 8.0 Hz, 1H), 8.23 – 8.27 (m, 2H), 8.11 (s, 1H), 8.78 (s, 2H), 7.50 – 7.58 (m, 3H).	DMSO	395.0, 397.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
19			422.38	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.11 (brs, 1H), 9.48 (s, 1H), 8.79 (d, J = 4.6 Hz, 1H), 8.83 (d, J = 8.0 Hz, 1H), 8.07 (d, J = 2.0 Hz, 1H), 8.02 (d, J = 2.4 Hz, 1H), 7.88 – 7.90 (m, 1H), 1.77 (d, J = 8.0 Hz, 1H), 7.52 – 7.62 (m, 3H), 4.27 (q, J = 7.2 Hz, 2H), 1.46 (t, J = 7.2 Hz, 3H).	DMSO	423.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1

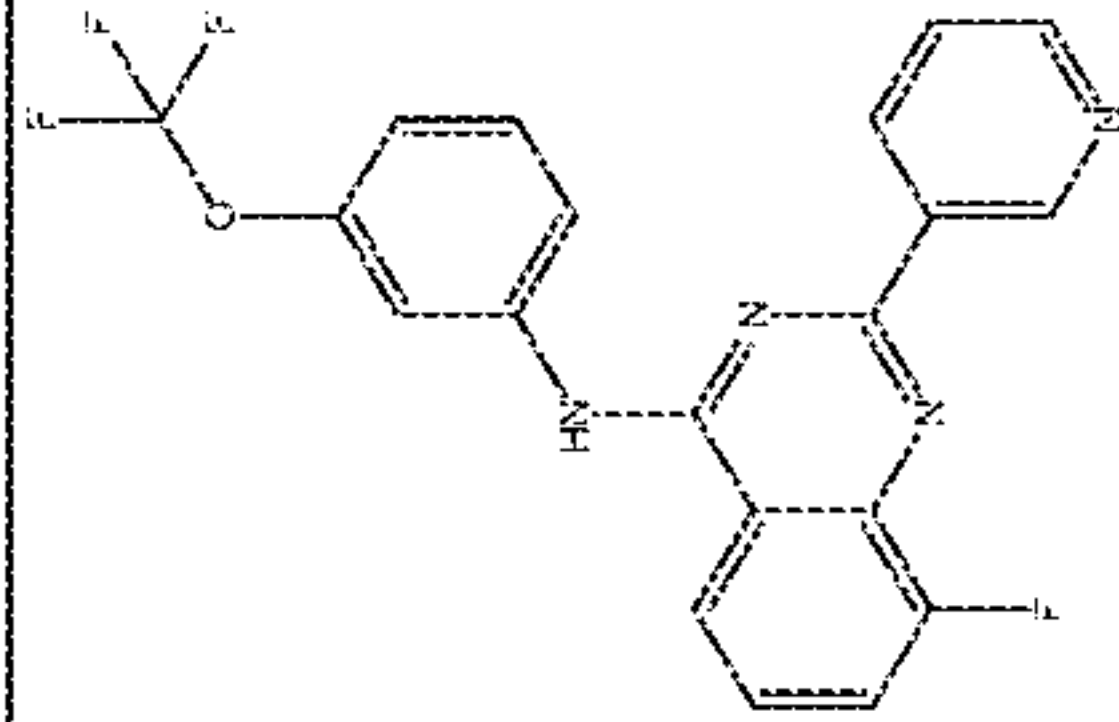
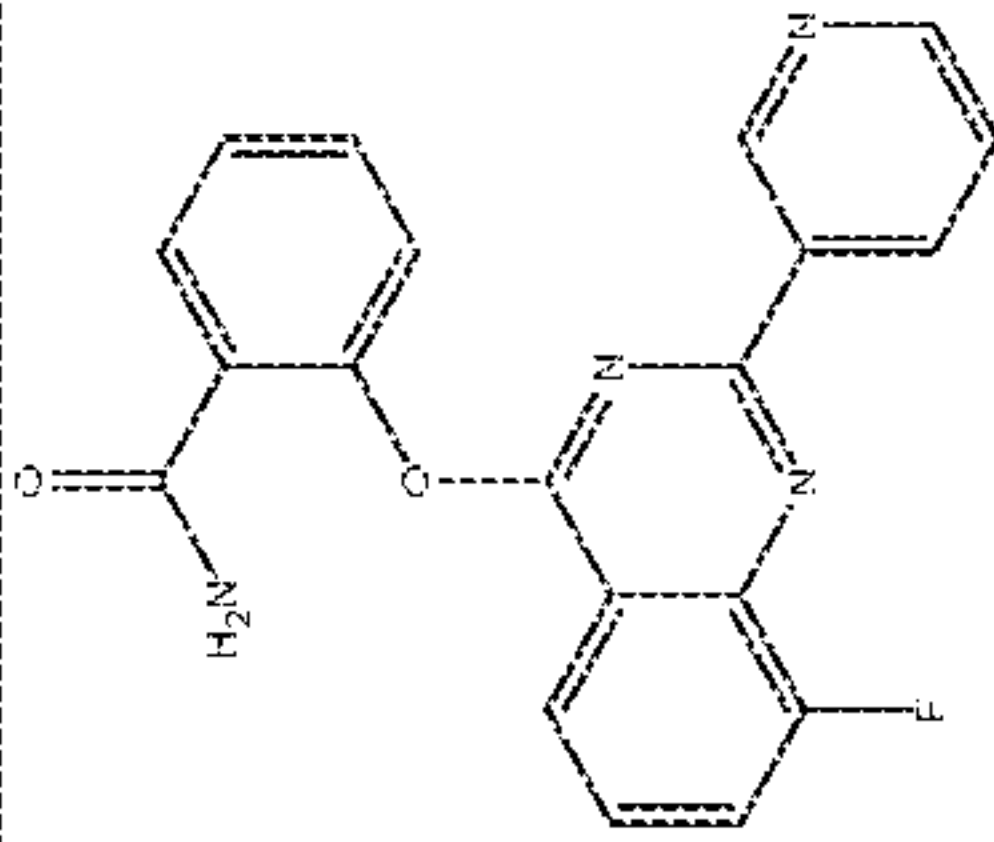
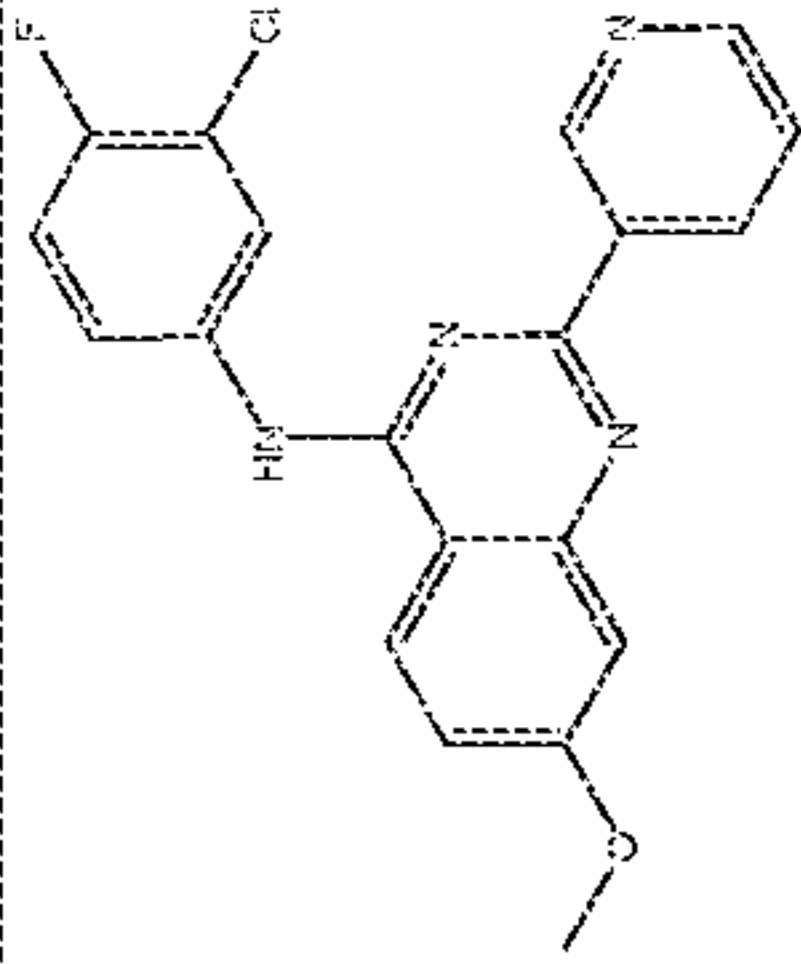
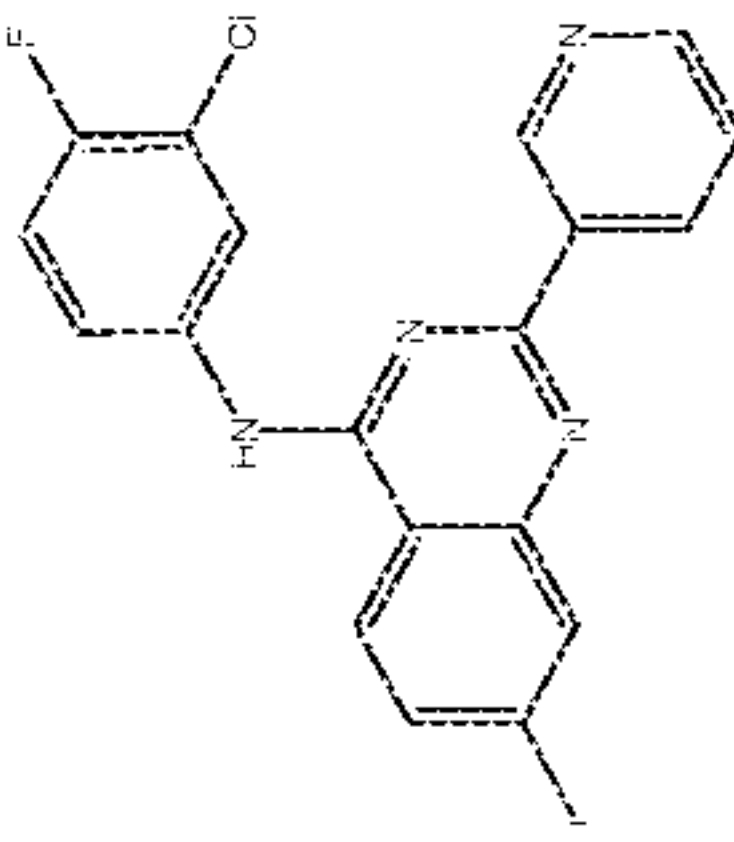
20		HCl	408.81	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.73 (s, 1H), 9.52 (d, J = 1.6 Hz, 1H), 9.32 (d, J = 1.6 Hz, 1H), 9.01 (d, J = 4.8 Hz, 1H), 8.91 (d, J = 5.2 Hz, 1H), 8.39 (dd, J = 8.4, 1.6 Hz, 1H), 8.17 (dd, J = 6.8, 2.0 Hz, 1H), 8.01 (d, J = 8.8 Hz, 1H), 7.90 – 7.95 (m, 2H), 7.55 (t, J = 9.2 Hz, 1H), 3.98 (s, 3H).	DMSO	409.1, 411.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
21			399.45	¹ H-NMR (400 MHz, DMSO-d ₆): δ 12.94 (s, 1H), 9.56 (s, 1H), 9.14 (d, J = 8.0 Hz, 1H), 8.83 – 8.66 (m, 2H), 8.48 (s, 1H), 8.06 – 7.91 (m, 2H), 7.76 – 7.58 (m, 2H), 7.35 (s, 1H), 7.27 (d, J = 2.0 Hz, 1H), 7.18 (t, J = 7.2 Hz, 1H), 4.15 (q, J = 6.8 Hz, 2H), 2.64 (s, 3H), 1.43 (t, J = 6.8 Hz, 1H).	DMSO	400.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method D, G1
22			440.42	¹ H-NMR (400 MHz, DMSO-d ₆): δ 9.84 (s, 1H), 9.55 (d, J = 1.2 Hz, 1H), 8.73 – 8.60 (m, 2H), 8.14 (s, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 2.4 Hz, 1H), 7.60 (t, J = 8.0 Hz, 1H), 7.53 (dd, J = 7.6, 4.8 Hz, 1H), 7.45 (d, J = 1.6 Hz, 1H), 7.16 (d, J = 8.4 Hz, 1H), 4.23 (q, J = 6.8 Hz, 2H), 2.70 (s, 3H), 1.44 (t, J = 6.8 Hz, 3H).	DMSO	440.9 (M+1)	Method A (TFA)	95	Method D, G1
23			405.81	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.08 (s, 1H), 9.42 (s, 1H), 8.68 (d, J = 3.6 Hz, 1H), 8.55 (d, J = 8.4 Hz, 1H), 8.32 (s, 1H), 8.15 (dd, J = 6.8, 2.4 Hz, 1H), 8.04 (s, 1H), 7.93 – 7.78 (m, 1H), 7.54 (td, J = 8.3, 6.9 Hz, 2H), 4.08 (s, 3H).	DMSO	406.1, 408.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1

24			493.92	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.00 (s, 1H), 9.49 – 9.51 (m, 1H), 8.62 – 8.70 (m, 2H), 8.21 (dd, <i>J</i> = 6.8, 2.8 Hz, 1H), 8.03 (s, 1H), 7.87 – 7.91 (m, 1H), 7.75 (s, 1H), 7.53 – 7.59 (m, 2H), 4.02 (s, 3H), 3.64 – 3.73 (m, 4H), 3.49 – 3.58 (m, 2H), 3.14 – 3.22 (m, 2H).	DMSO	494.1, 496.1 (M+1)	Method B (NH ₄ HCO ₄)	95	Method C, G1
25		TFA	369.38	¹ H-NMR (400 MHz, DMSO-d ₆): δ 11.51 (s, 1H), 8.78 (d, <i>J</i> = 8.0 Hz, 2H), 8.17 (d, <i>J</i> = 9.2 Hz, 1H), 7.80 (dd, <i>J</i> = 9.2, 2.8 Hz, 1H), 7.70 – 7.64 (m, 1H), 7.46 (d, <i>J</i> = 2.8 Hz, 1H), 7.41 (d, <i>J</i> = 8.0 Hz, 1H), 7.20 (d, <i>J</i> = 4.0 Hz, 2H), 7.16 – 7.08 (m, 1H), 3.89 (s, 3H).	DMSO	370.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, J1
26			408.4	¹ H-NMR (400 MHz, DMSO-d ₆): δ 9.87 (s, 1H), 8.53 (dd, <i>J</i> = 4.7, 1.5 Hz, 1H), 8.23 (d, <i>J</i> = 6.8 Hz, 1H), 8.00 (d, <i>J</i> = 2.6 Hz, 1H), 7.8 (t, <i>J</i> = 2.1 Hz, 1H), 7.84 (d, <i>J</i> = 9.1 Hz, 1H), 7.73 (dd, <i>J</i> = 8.2, 1.2 Hz, 1H), 7.58 (dd, <i>J</i> = 9.1, 2.6 Hz, 1H), 7.41 – 7.25 (m, 3H), 7.24 (t, <i>J</i> = 74.0 Hz, 1H), 6.96 (dd, <i>J</i> = 8.0, 2.2 Hz, 1H), 3.99 (s, 3H), 2.75 (s, 3H).	DMSO	409.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method D, G1
27			385.42	¹ H-NMR (400 MHz, DMSO-d ₆): δ 13.09 (s, 1H), 9.08 (d, <i>J</i> = 7.8 Hz, 1H), 8.55 (dd, <i>J</i> = 4.8, 1.6 Hz, 1H), 8.49 (s, 1H), 8.22 (dd, <i>J</i> = 7.8, 1.7 Hz, 1H), 8.01 (s, 1H), 7.95 (dd, <i>J</i> = 7.9, 1.2 Hz, 1H), 7.87 (d, <i>J</i> = 9.6 Hz, 1H), 7.66 – 7.58 (m, 3H), 7.40 (dd, <i>J</i> = 7.7, 4.8 Hz, 1H), 7.15 (dd, <i>J</i> = 11.5, 4.4 Hz, 1H), 3.99 (s, 3H), 2.77 (s, 3H).	DMSO	386.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method D, G1

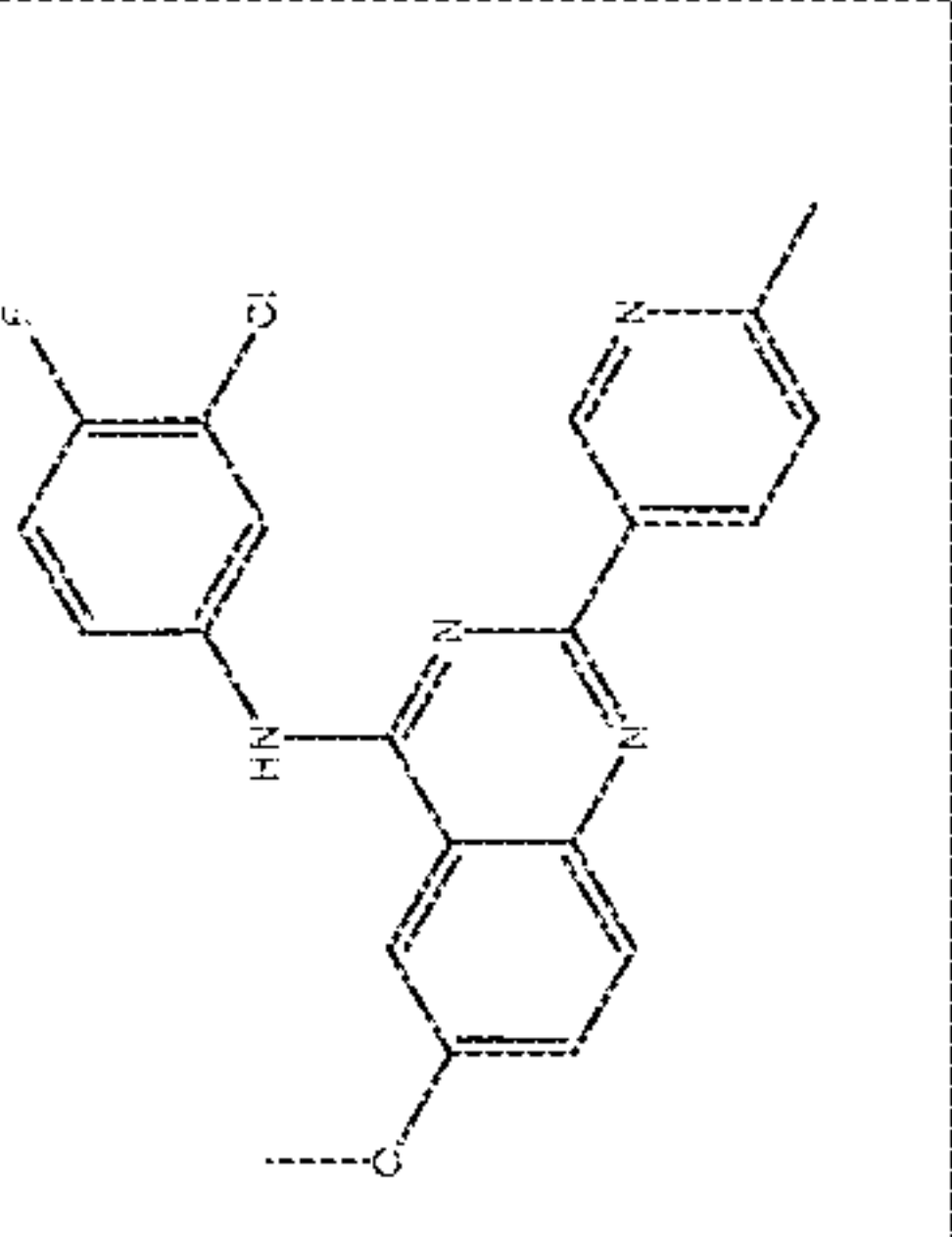
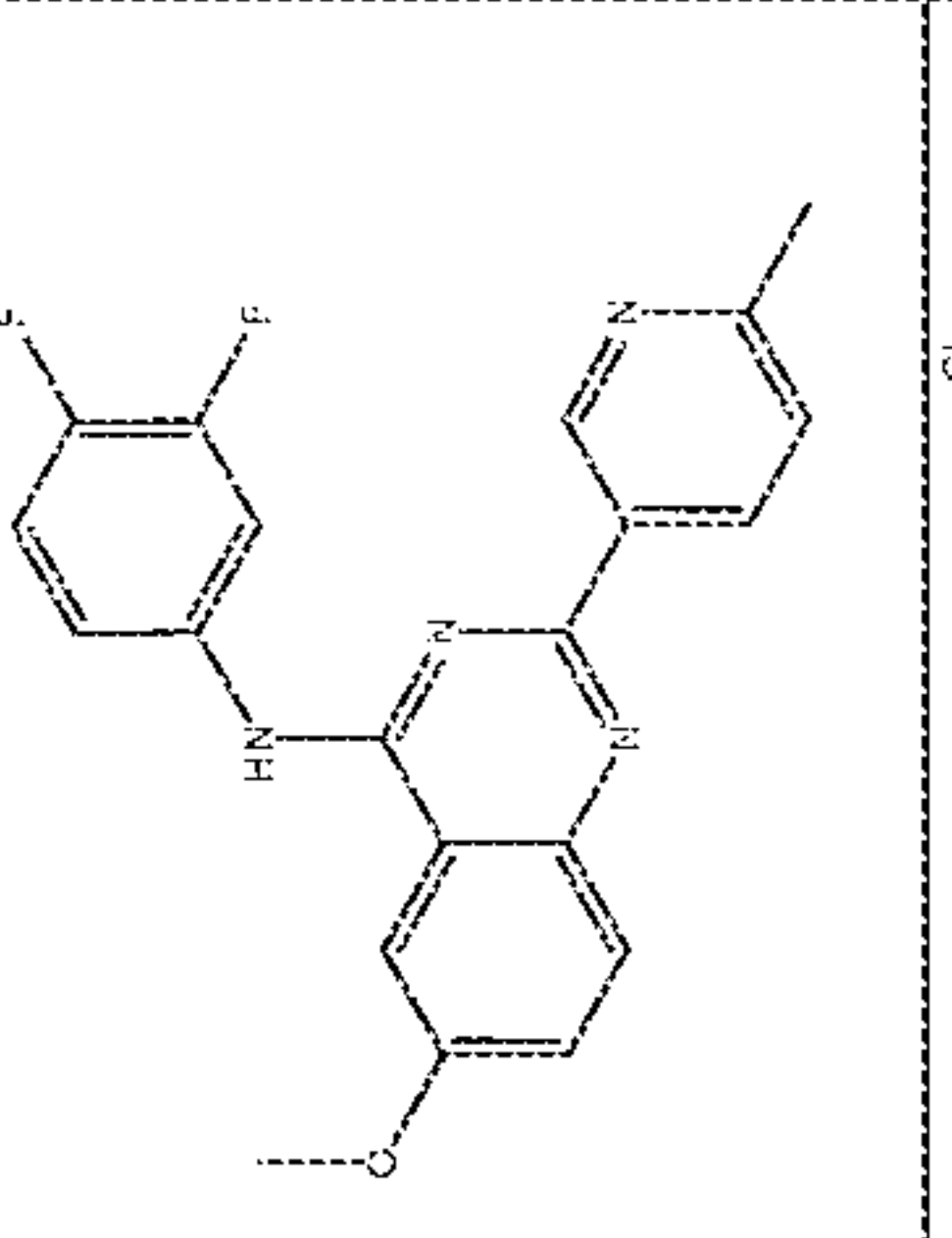
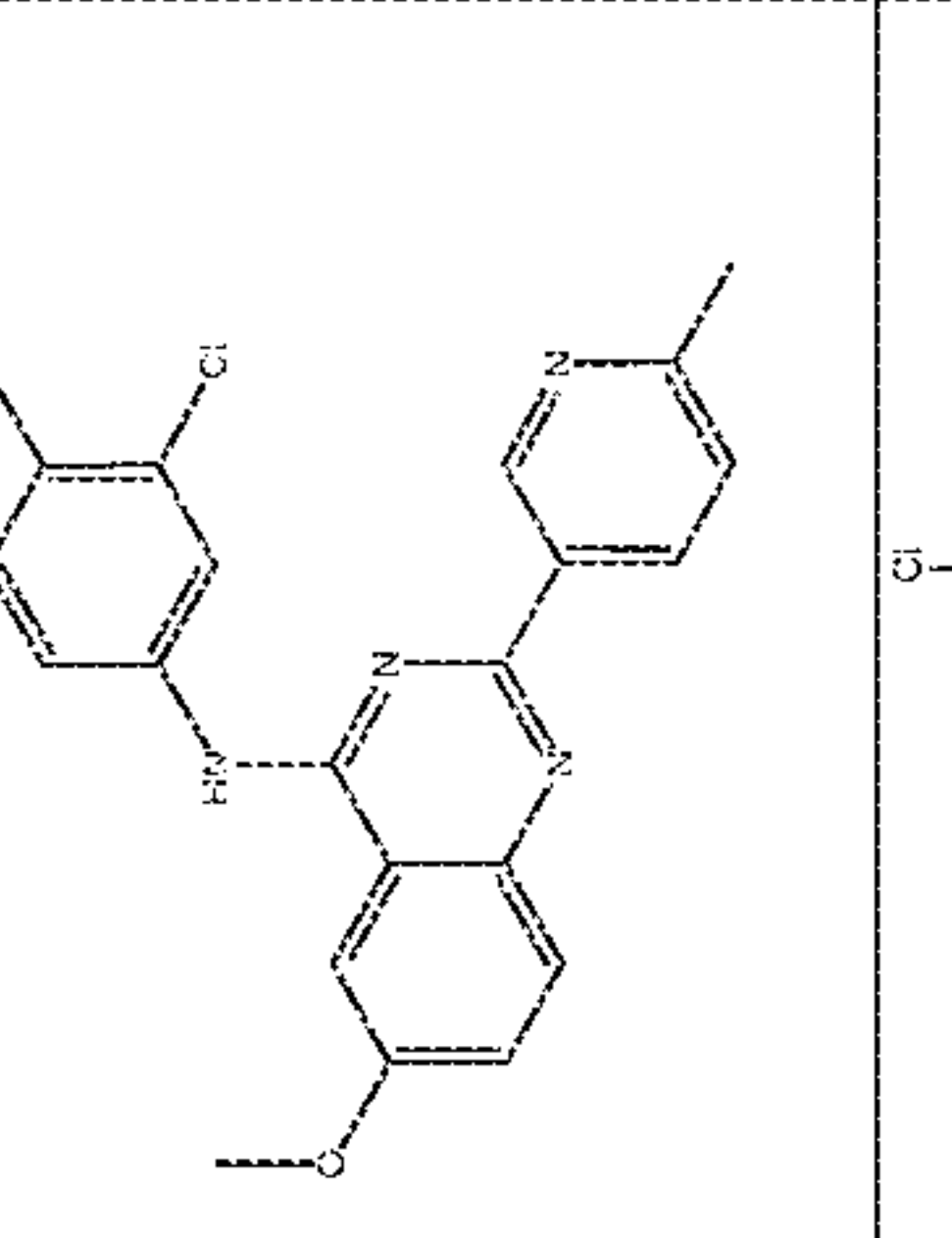
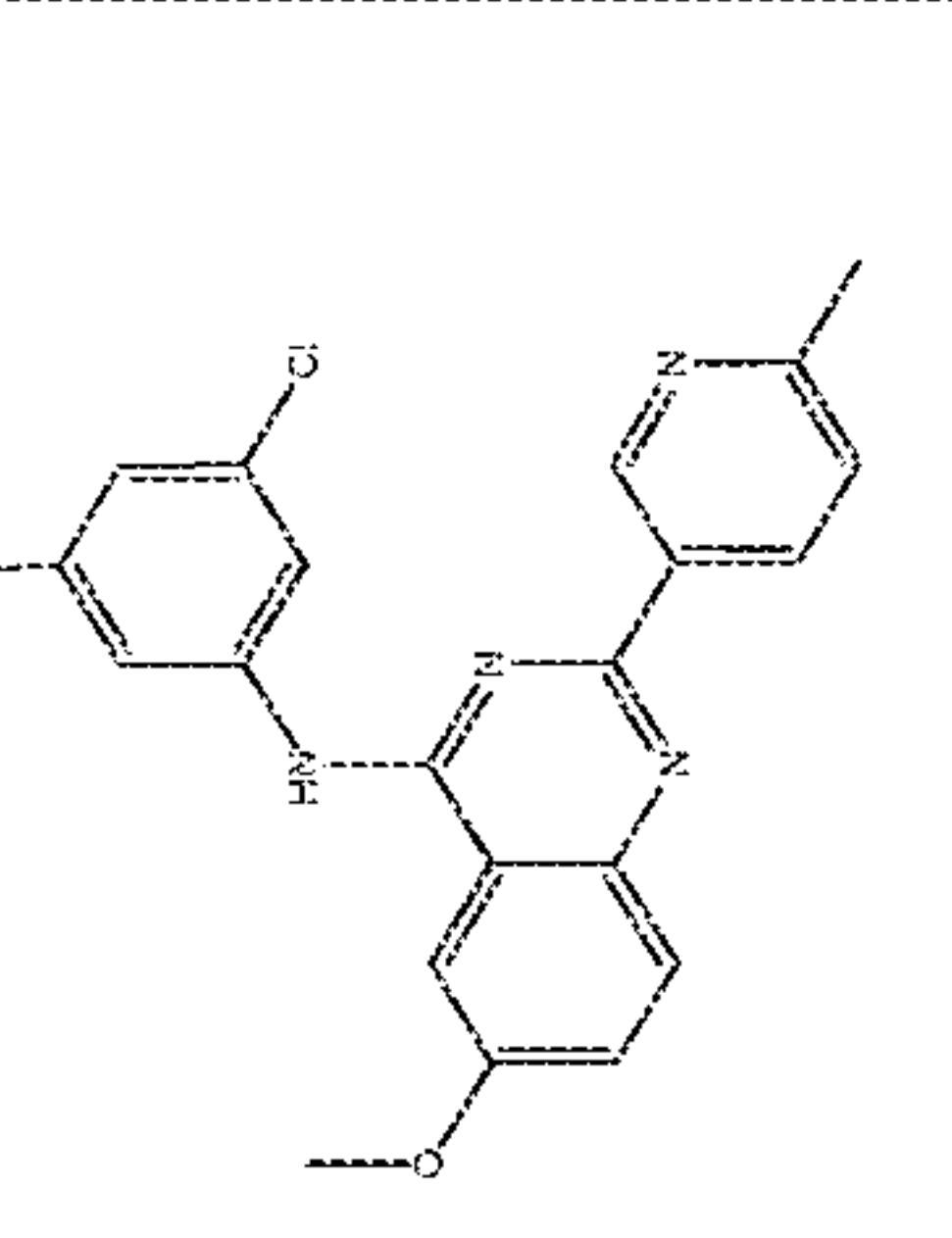
28			394.83	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.10 (s, 1H), 8.63 (d, J = 4.1 Hz, 1H), 8.43 (d, J = 7.6 Hz, 1H), 8.15 (dd, J = 6.8, 2.5 Hz, 1H), 8.03 (d, J = 2.3 Hz, 1H), 7.88 – 7.78 (m, 2H), 7.58 (ddd, J = 12.5, 8.3, 4.1 Hz, 2H), 7.49 (t, J = 9.1 Hz, 1H), 3.99 (s, 3H), 2.80 (s, 3H).	DMSO	395.1, 397.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method D, G1
29		HCl	440.5	¹ H-NMR (400 MHz, DMSO-d ₆): δ 13.19 (s, 1H), 11.12 – 10.93 (m, 1H), 9.83 (d, J = 1.5 Hz, 1H), 9.21 (d, J = 7.8 Hz, 1H), 9.01 (d, J = 7.8 Hz, 1H), 8.93 – 8.89 (m, 1H), 8.53 (s, 1H), 8.36 (dd, J = 11.8, 7.9 Hz, 2H), 8.02 – 7.73 (m, 6H), 7.29 (d, J = 8.02 Hz, 1H), 5.01 (s, 2H), 3.95 – 3.81 (m, 4H), 3.37 (s, 4H).	DMSO	441.2 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
30		HCl	449.91	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.05 (s, 1H), 9.56 (s, 1H), 8.73 – 8.66 (m, 2H), 8.47 (d, J = 8.1 Hz, 1H), 8.28 (dd, J = 6.8, 2.5 Hz, 1H), 7.99 – 7.90 (m, 2H), 7.67 – 7.50 (m, 3H), 4.16 (s, 2H), 3.62 (s, 4H), 2.53 (s, 4H).	DMSO	450.1, 452.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1

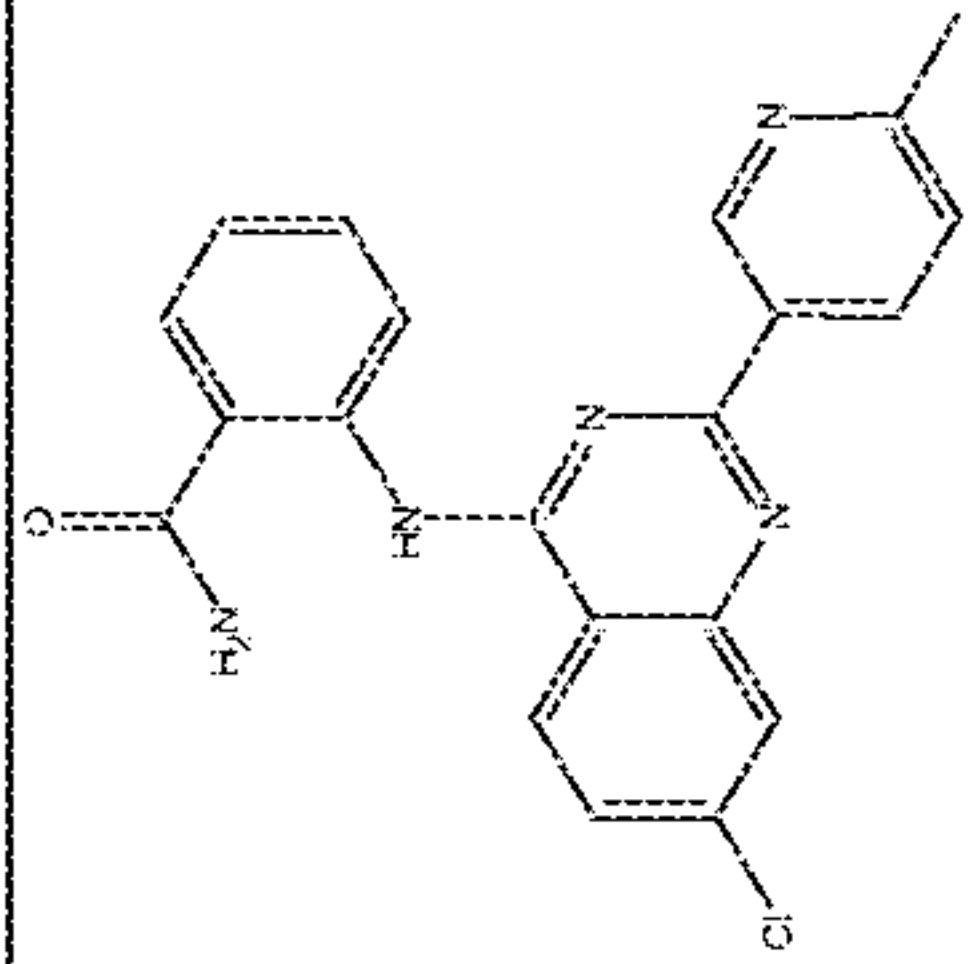
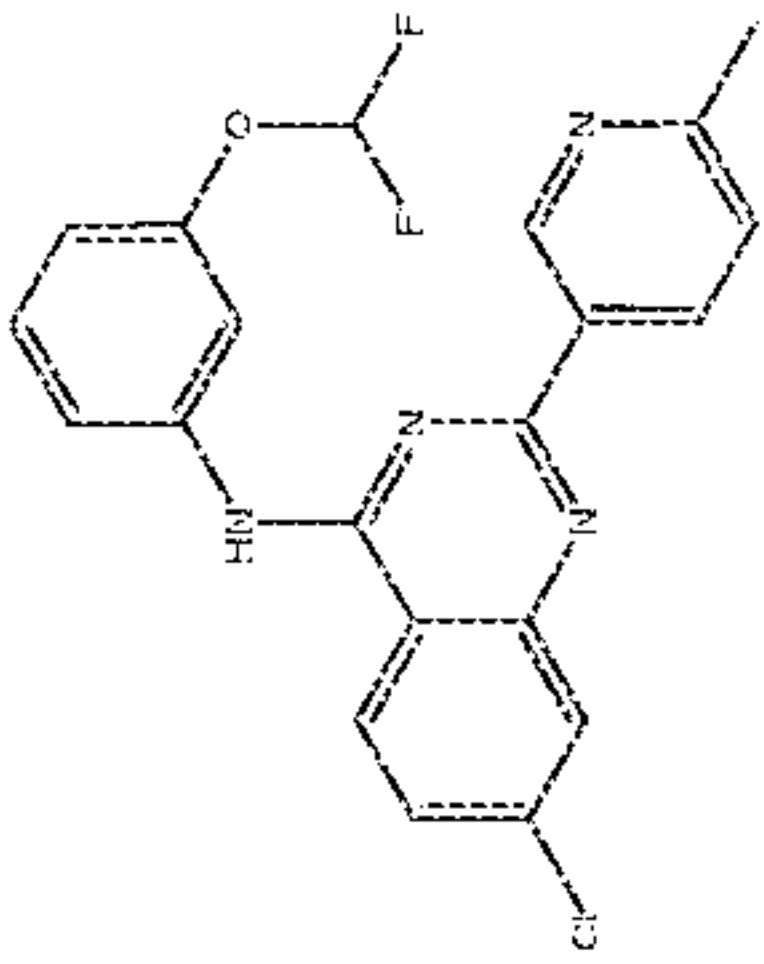
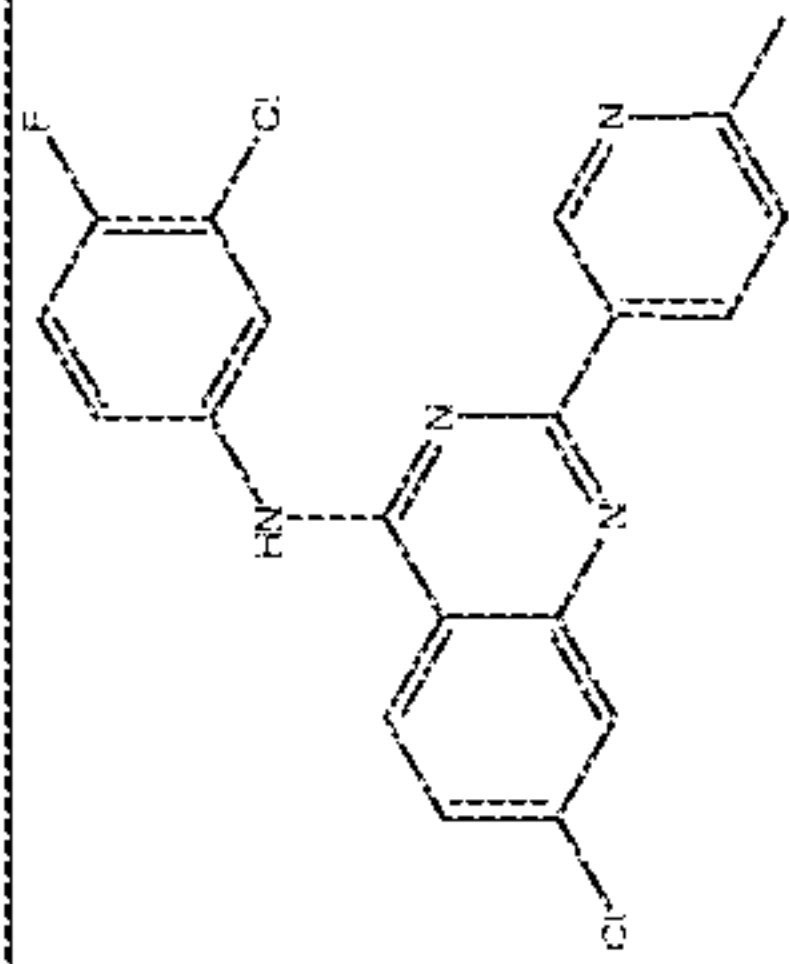
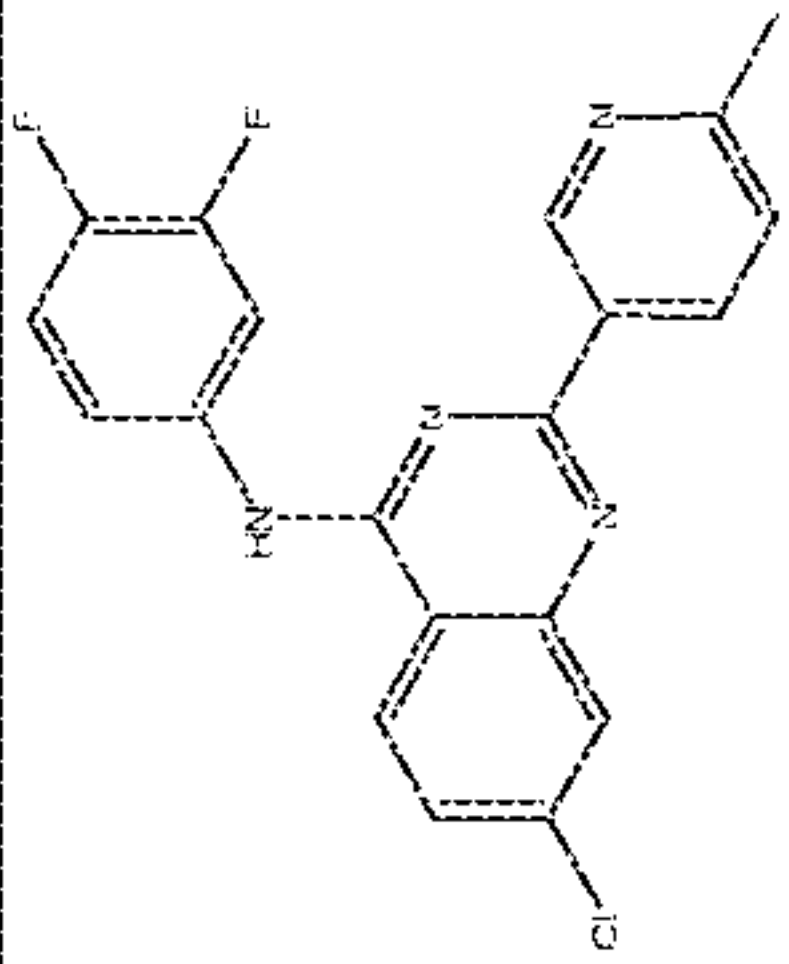
31			400.33	¹ H-NMR (400 MHz, DMSO-d ₆): δ 9.47 (d, <i>J</i> = 2.0 Hz, 2H), 8.70 (dd, <i>J</i> = 4.8, 1.6 Hz, 1H), 8.65 – 8.59 (m, 1H), 8.06 (s, 1H), 7.91 (dt, <i>J</i> = 8.1, 6.0 Hz, 1H), 7.82 (dd, <i>J</i> = 8.2, 1.2 Hz, 1H), 7.76 (d, <i>J</i> = 8.4 Hz, 1H), 7.59 (t, <i>J</i> = 8.2 Hz, 1H), 7.51 (ddd, <i>J</i> = 20.0, 10.0, 6.4 Hz, 2H), 7.21 (d, <i>J</i> = 8.4 Hz, 1H).	DMSO	401.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
32		HCl	368.77	¹ H-NMR (400 MHz, DMSO-d ₆): δ 9.53 (d, <i>J</i> = 11.3 Hz, 1H), 9.44 (d, <i>J</i> = 1.2 Hz, 1H), 8.84 – 8.79 (m, 2H), 8.09 (dd, <i>J</i> = 6.8, 2.6 Hz, 1H), 7.97 – 7.89 (m, 1H), 7.85 – 7.75 (m, 3H), 7.57 – 7.47 (m, 2H).	DMSO	369.1, 371.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
33		HCl	359.36	¹ H-NMR (400 MHz, DMSO-d ₆): δ 12.21 (d, <i>J</i> = 12.1 Hz, 1H), 9.53 (d, <i>J</i> = 1.2 Hz, 1H), 8.99 (d, <i>J</i> = 8.1 Hz, 1H), 8.89 (d, <i>J</i> = 4.2 Hz, 1H), 8.71 (d, <i>J</i> = 7.9 Hz, 1H), 8.36 (s, 1H), 7.97 – 7.76 (m, 5H), 7.72 – 7.65 (m, 1H), 7.50 (dd, <i>J</i> = 12.1, 7.5 Hz, 1H), 7.29 (t, <i>J</i> = 7.1 Hz, 1H).	DMSO	360.2 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
34			382.34	¹ H-NMR (400 MHz, DMSO-d ₆): δ 9.49 (d, <i>J</i> = 1.8 Hz, 1H), 9.42 (s, 1H), 8.71 (dd, <i>J</i> = 4.6, 1.3 Hz, 1H), 8.65 (d, <i>J</i> = 7.8 Hz, 1H), 7.90 (dd, <i>J</i> = 15.8, 9.7 Hz, 2H), 7.73 (dd, <i>J</i> = 19.0, 8.26 Hz, 2H), 7.56 – 7.12 (m, 4H), 7.04 (dd, <i>J</i> = 8.2, 1.8 Hz, 1H).	DMSO	383.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1

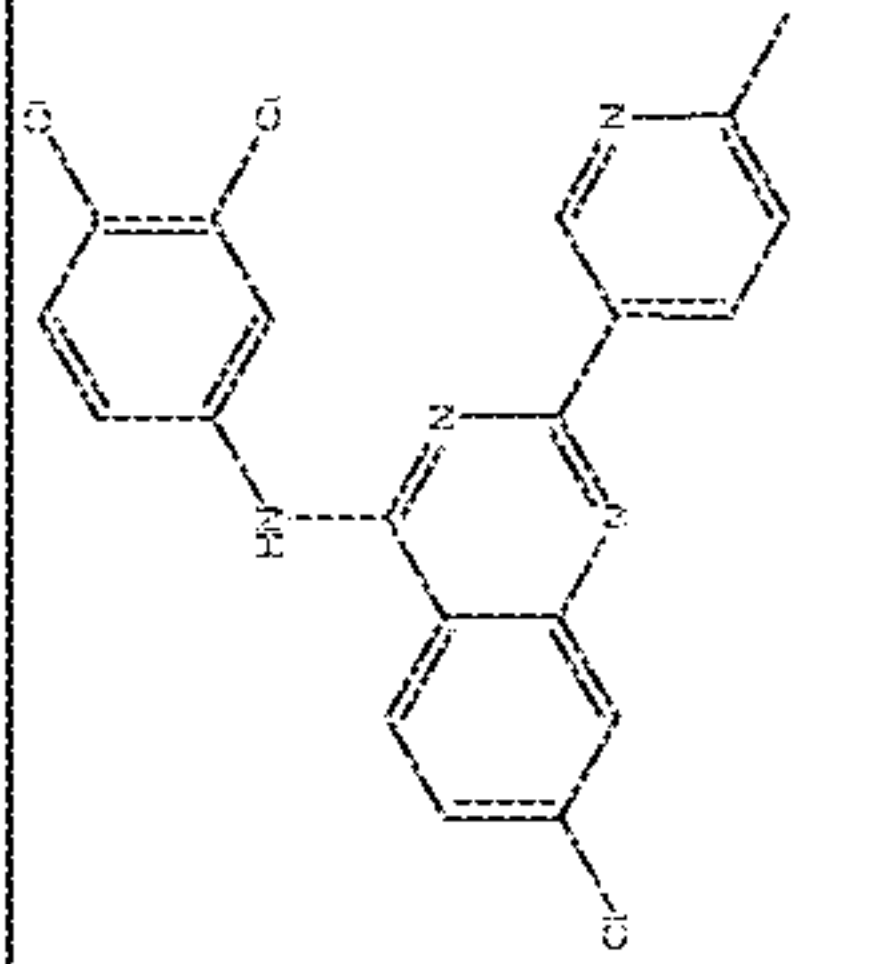
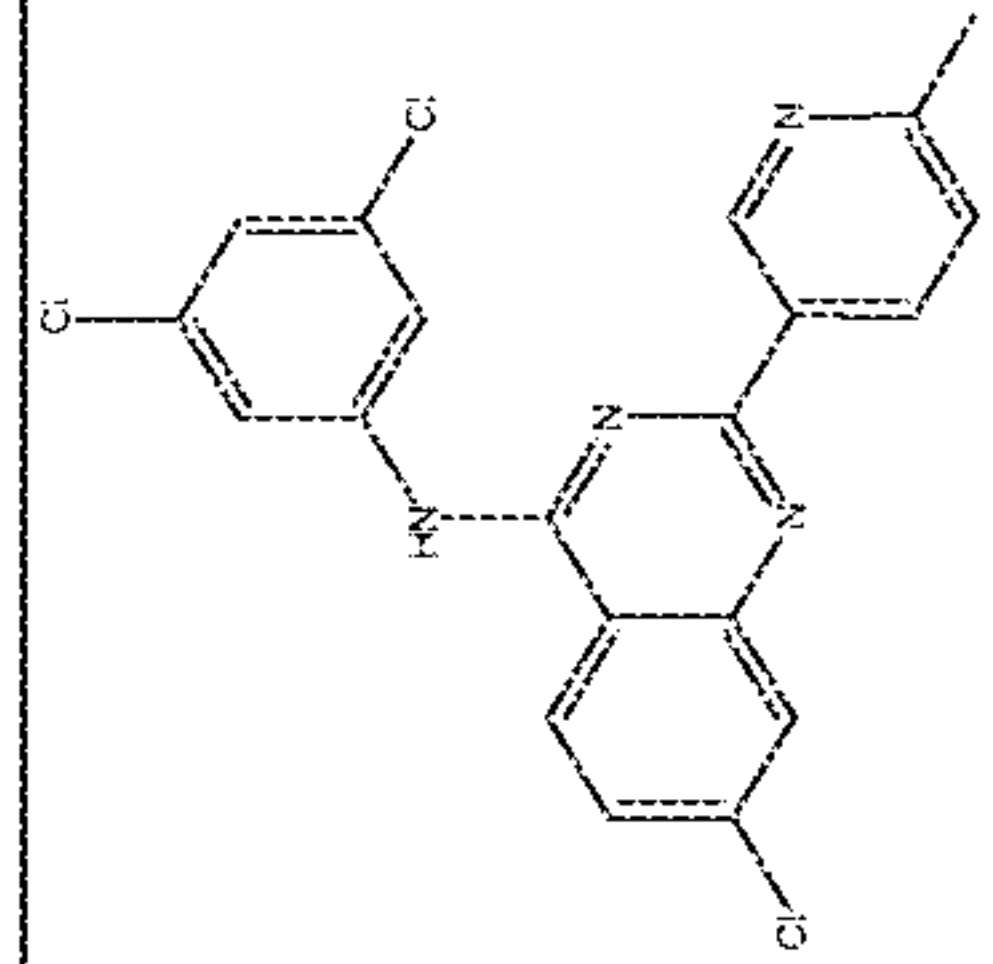
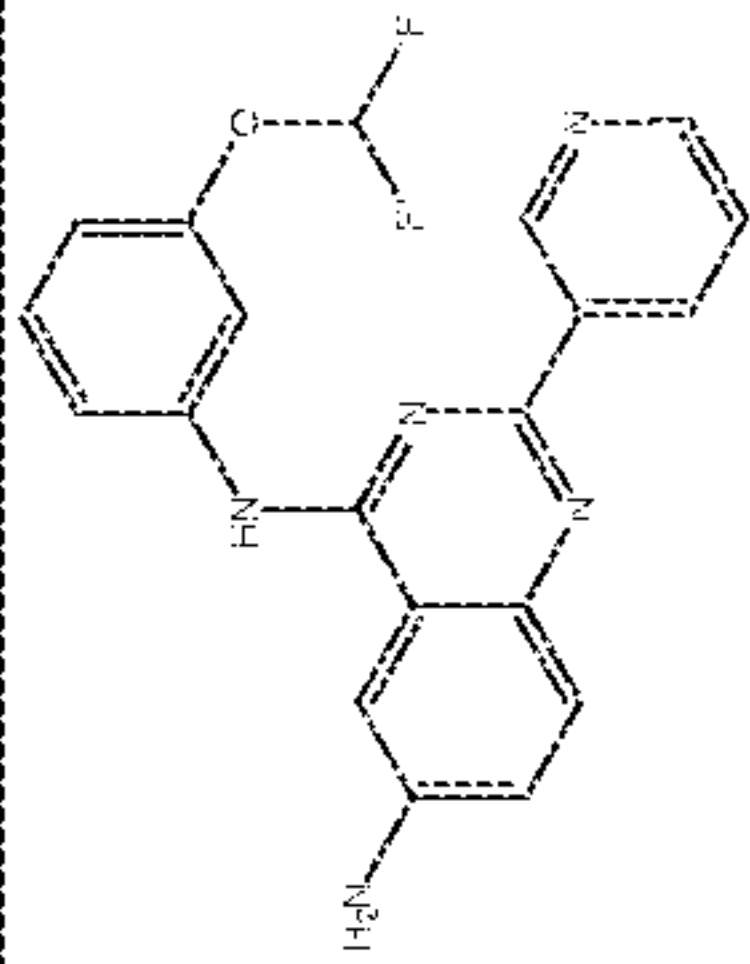
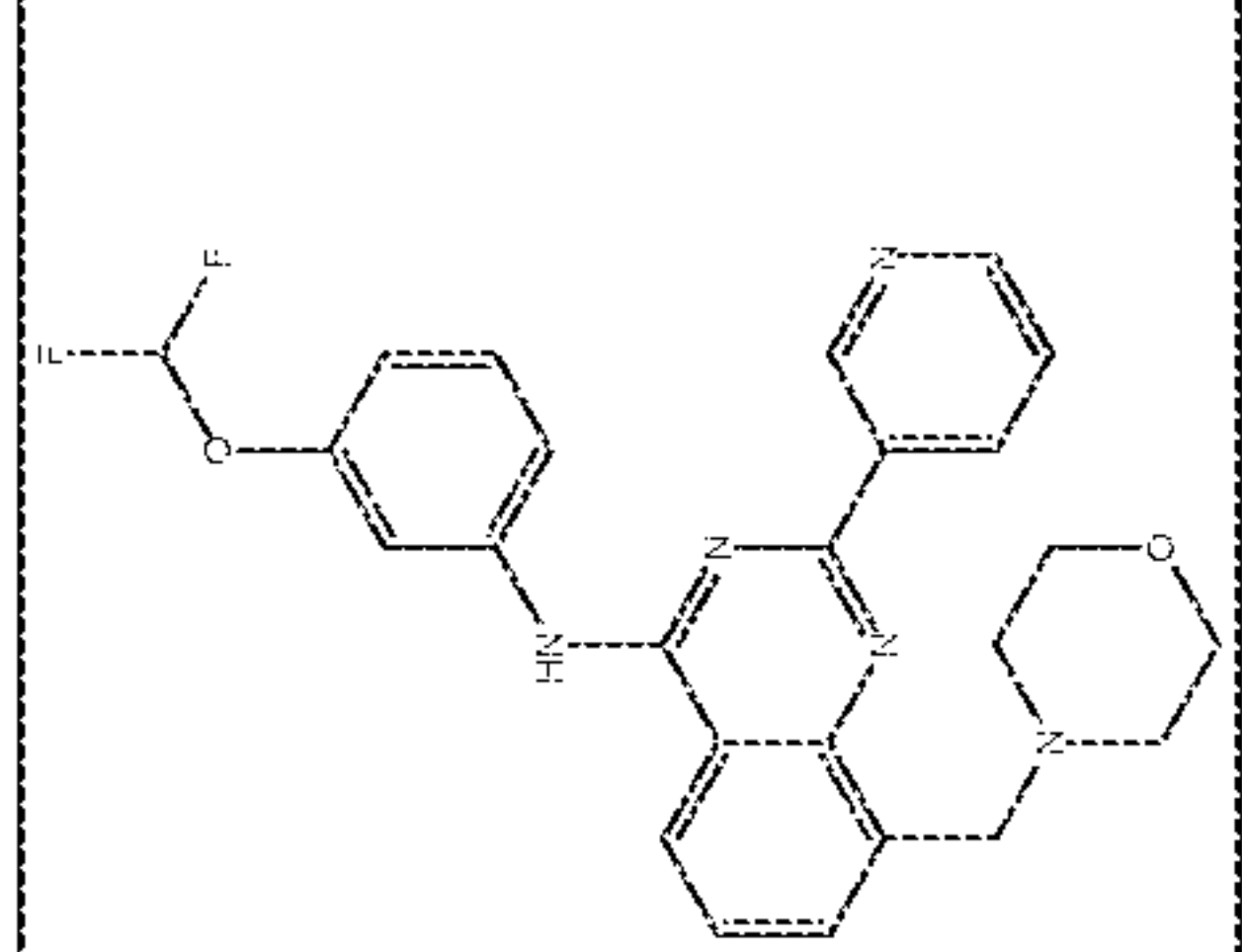
35		HCl	400.33	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.43 (s, 1H), 9.52 (s, 1H), 8.89 (d, J = 8.2 Hz, 1H), 8.85 (d, J = 4.2 Hz, 1H), 8.78 (dd, J = 9.2, 5.9 Hz, 1H), 8.09 (s, 1H), 7.95 (dd, J = 8.2, 1.2 Hz, 1H), 7.80 (dd, J = 7.9, 5.2 Hz, 1H), 7.72 – 7.58 (m, 3H), 7.21 (d, J = 8.4 Hz, 1H).	DMSO	401.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
36		HCl	405.84	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.74 – 10.48 (m, 1H), 9.36 (d, J = 1.6 Hz, 1H), 8.95 (d, J = 8.2 Hz, 1H), 8.89 – 8.85 (m, 1H), 8.06 (d, J = 1.7 Hz, 1H), 8.02 (d, J = 9.15 Hz, 1H), 7.93 – 7.86 (m, 2H), 7.73 – 7.63 (m, 3H), 7.60 – 7.52 (m, 2H), 3.98 (s, 3H).	DMSO	406.1, 408.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
37		HCl	359.36	¹ H-NMR (400 MHz, DMSO-d ₆): δ 9.61 (s, 1H), 9.00 (dd, J = 15.4, 8.2 Hz, 2H), 8.86 (d, J = 4.13 Hz, 1H), 8.52 (s, 1H), 8.04 – 7.94 (m, 3H), 7.86 – 7.70 (m, 4H), 7.26 (dd, J = 11.2, 4.2 Hz, 1H).	DMSO	360.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
38		HCl	368.77	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.22 (s, 1H), 9.52 (s, 1H), 8.73 (d, J = 3.6 Hz, 1H), 8.69 (td, J = 8.0, 1.8 Hz, 1H), 8.38 (d, J = 8.4 Hz, 1H), 8.25 (dd, J = 6.8, 2.6 Hz, 1H), 7.91 (ddd, J = 9.0, 4.2, 2.6 Hz, 1H), 7.79 (dd, J = 9.8, 7.9 Hz, 1H), 7.67 (dd, J = 8.2, 5.2 Hz, 1H), 7.61 – 7.53 (m, 2H).	DMSO	369.0, 371.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1

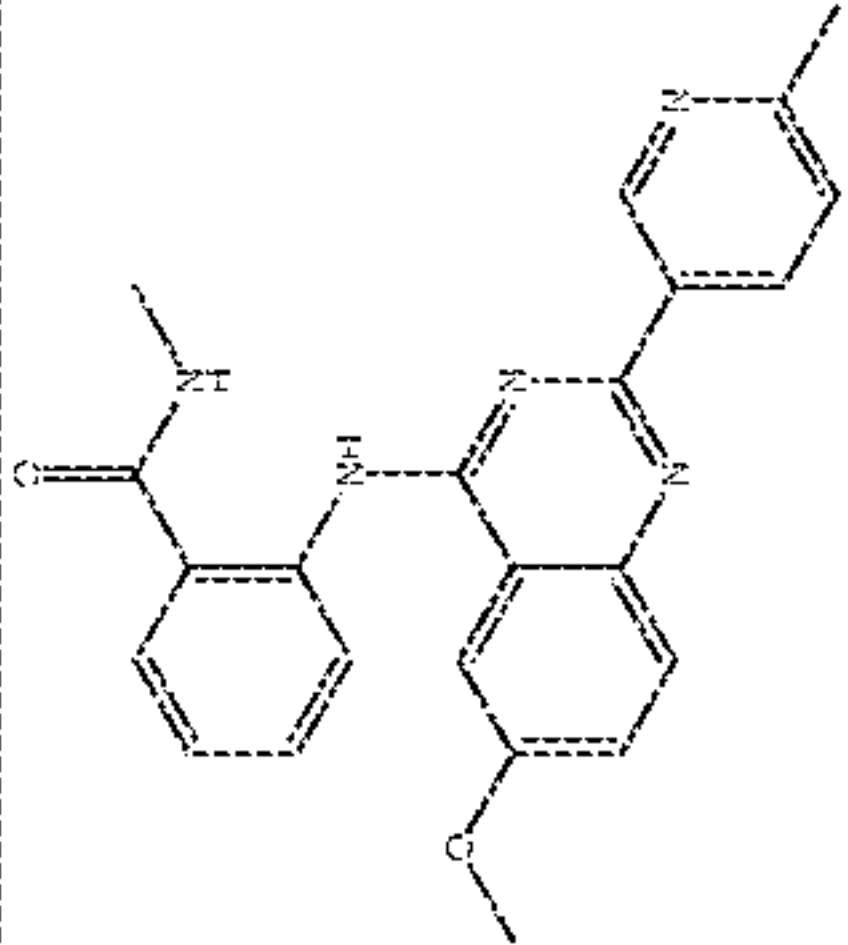
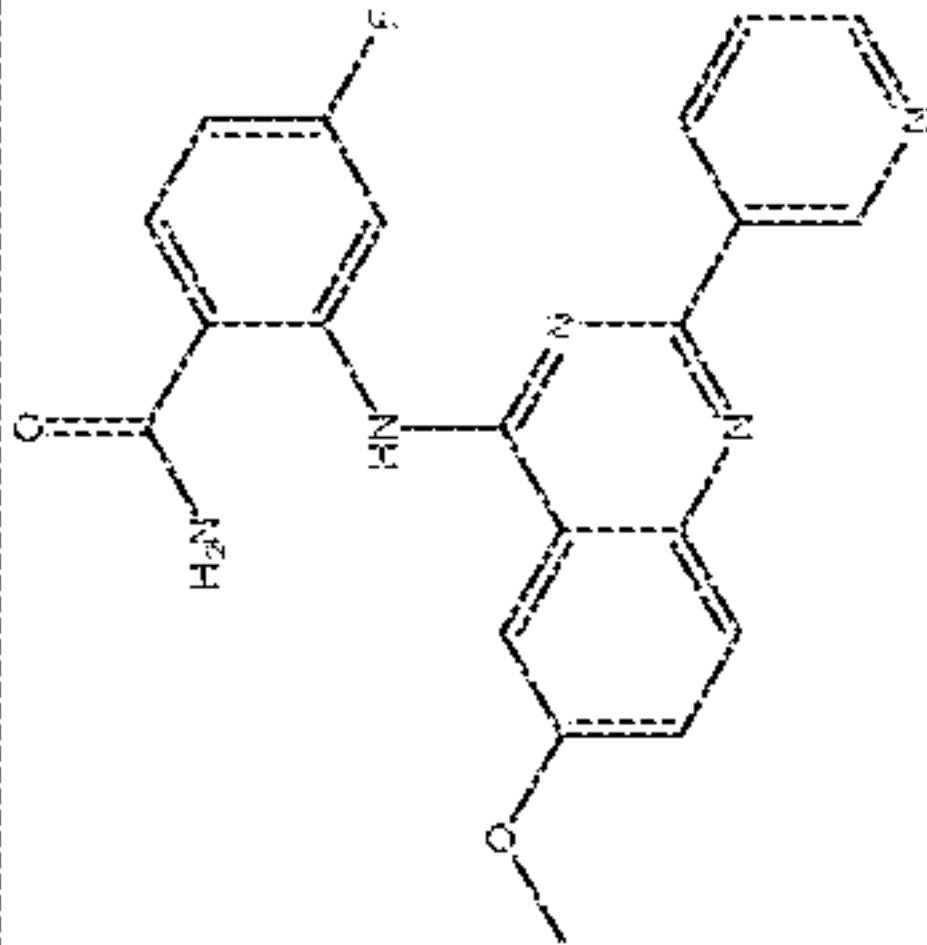
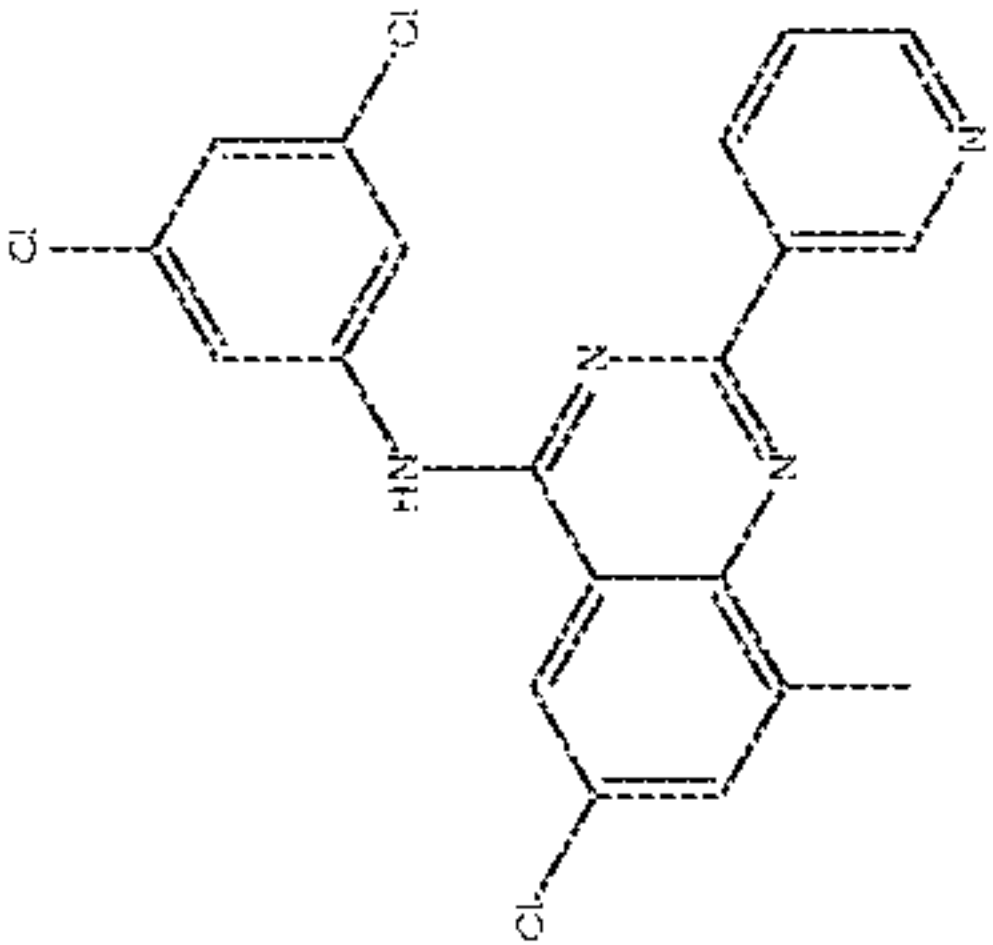
39		HCl	400.33	¹H-NMR (400 MHz, DMSO-d₆): δ 10.47 (s, 1H), 9.52 (d, J = 1.4 Hz, 1H), 9.04 (d, J = 8.0 Hz, 1H), 8.92 (dd, J = 5.2, 1.2 Hz, 1H), 8.52 (d, J = 8.4 Hz, 1H), 8.07 (s, 1H), 7.97 (d, J = 1.2 Hz, 2H), 7.86 – 7.80 (m, 1H), 7.74 – 7.68 (m, 1H), 7.62 (t, J = 8.2 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H).	DMSO	401.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
40			360.34	¹H-NMR (400 MHz, DMSO-d₆): δ 9.66 (d, J = 1.6 Hz, 1H), 8.82 (td, J = 7.9, 1.8 Hz, 1H), 8.71 (dd, J = 4.6, 1.6 Hz, 1H), 8.22 (d, J = 8.2 Hz, 1H), 7.87 (dd, J = 7.8, 1.9 Hz, 1H), 7.73 (dd, J = 9.2, 7.8 Hz, 1H), 7.59 (dt, J = 8.1, 5.0 Hz, 2H), 7.21 – 7.15 (m, 1H), 6.66 (d, J = 8.2 Hz, 1H), 6.54 (t, J = 7.4 Hz, 1H).	DMSO	360.9 (M+1), 382.9 (M+23)	Method B (NH ₄ HCO ₃)	95	Method C, G9
41			380.08	¹H-NMR (400 MHz, DMSO-d₆): δ 10.56 (brs, 1H), 9.62 (d, J = 1.2 Hz, 1H), 9.05 (d, J = 8.4 Hz, 1H), 9.00 (dd, J = 1.6, 4.8 Hz, 1H), 8.71 (d, J = 9.2 Hz, 1H), 8.31 (dd, J = 2.0, 7.2 Hz, 1H), 8.02 – 7.99 (m, 2H), 7.66 (t, J = 9.2 Hz, 1H), 7.54 (s, 1H), 7.50 (dd, J = 2.4, 9.2 Hz, 1H), 4.11 (s, 3H).	DMSO	381.1, 383.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
42			476.67	¹H-NMR (400 MHz, DMSO-d₆): δ 10.40 (s, 1H), 9.51 (s, 1H), 8.93 (d, J = 8.0 Hz, 1H), 8.88 (d, J = 4.8 Hz, 1H), 8.40 (d, J = 8.8 Hz, 1H), 8.35 (d, J = 1.6 Hz, 1H), 8.20 (dd, J = 4.4, 6.8 Hz, 1H), 8.04 (dd, J = 7.2, 8.8 Hz, 1H), 7.93 – 7.86 (m, 2H), 7.35 (t, J = 9.2 Hz, 1H).	DMSO	477.0, 499.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1

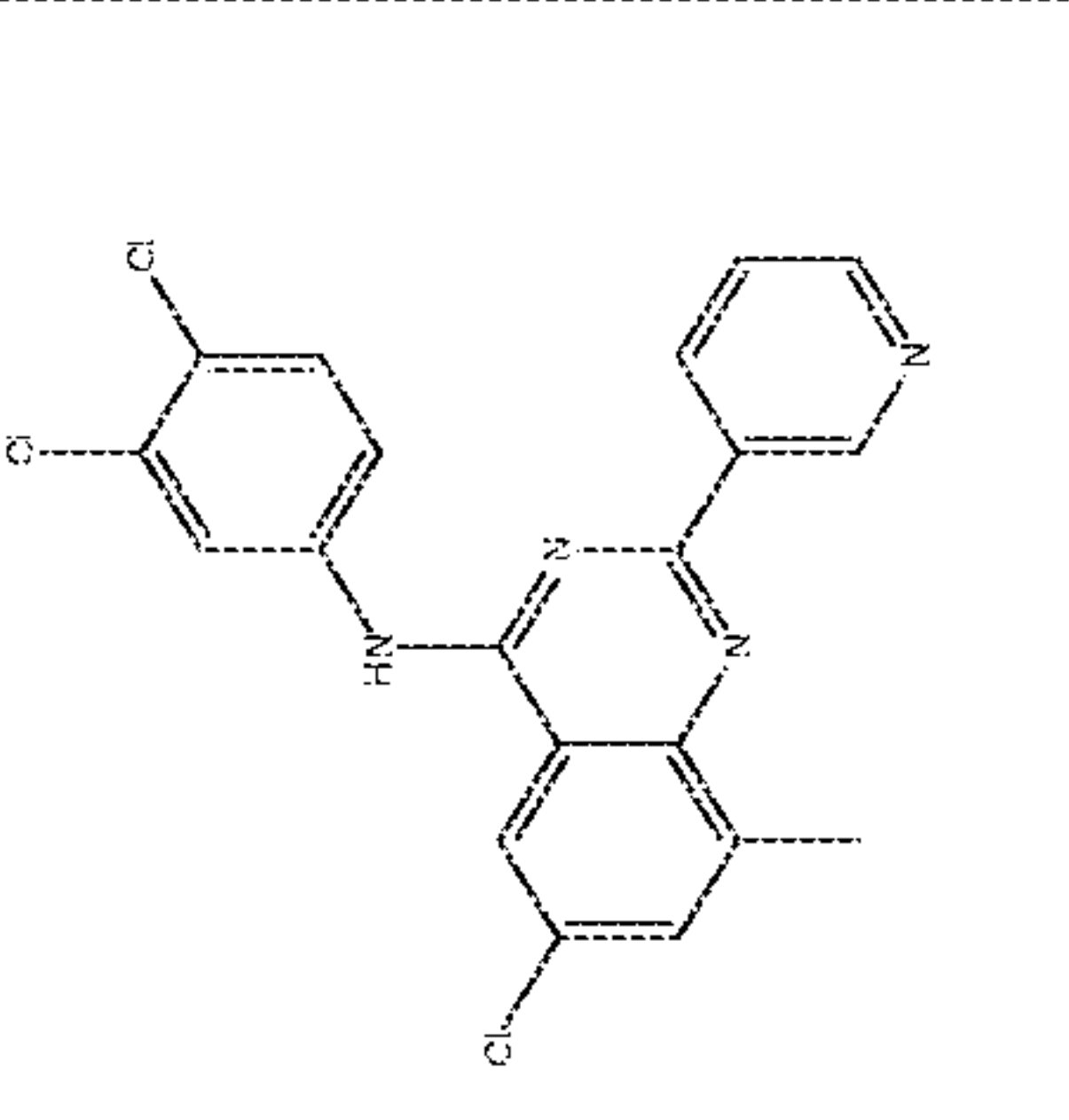
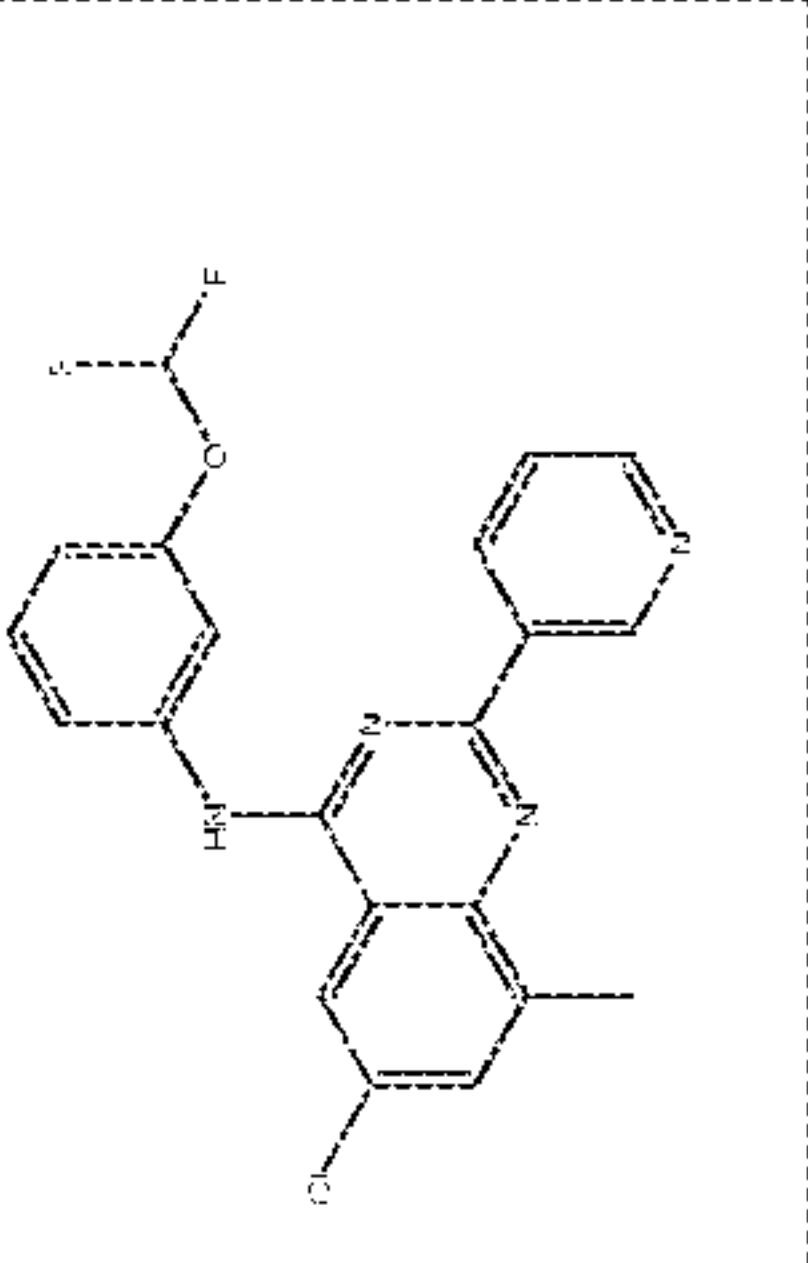
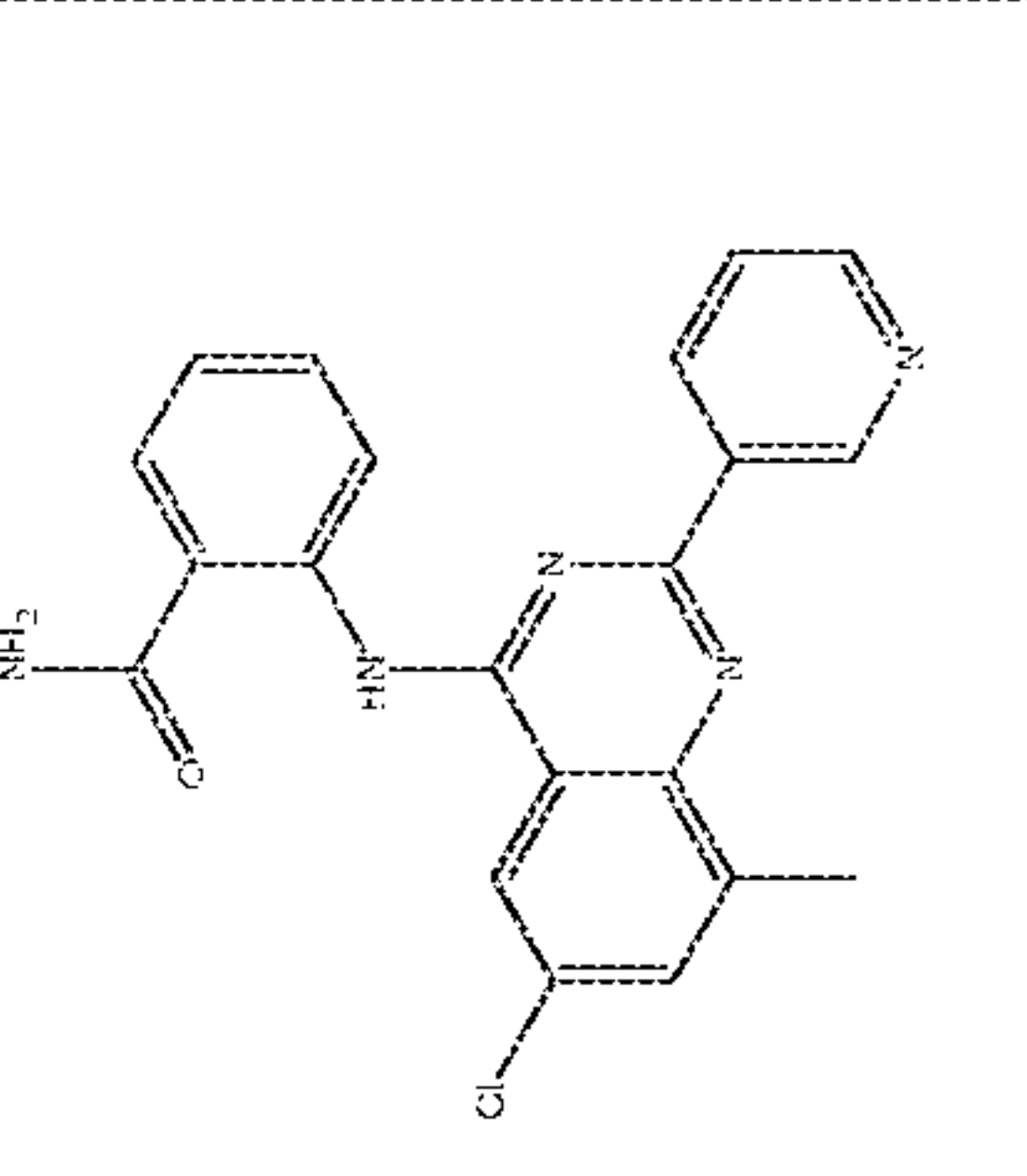
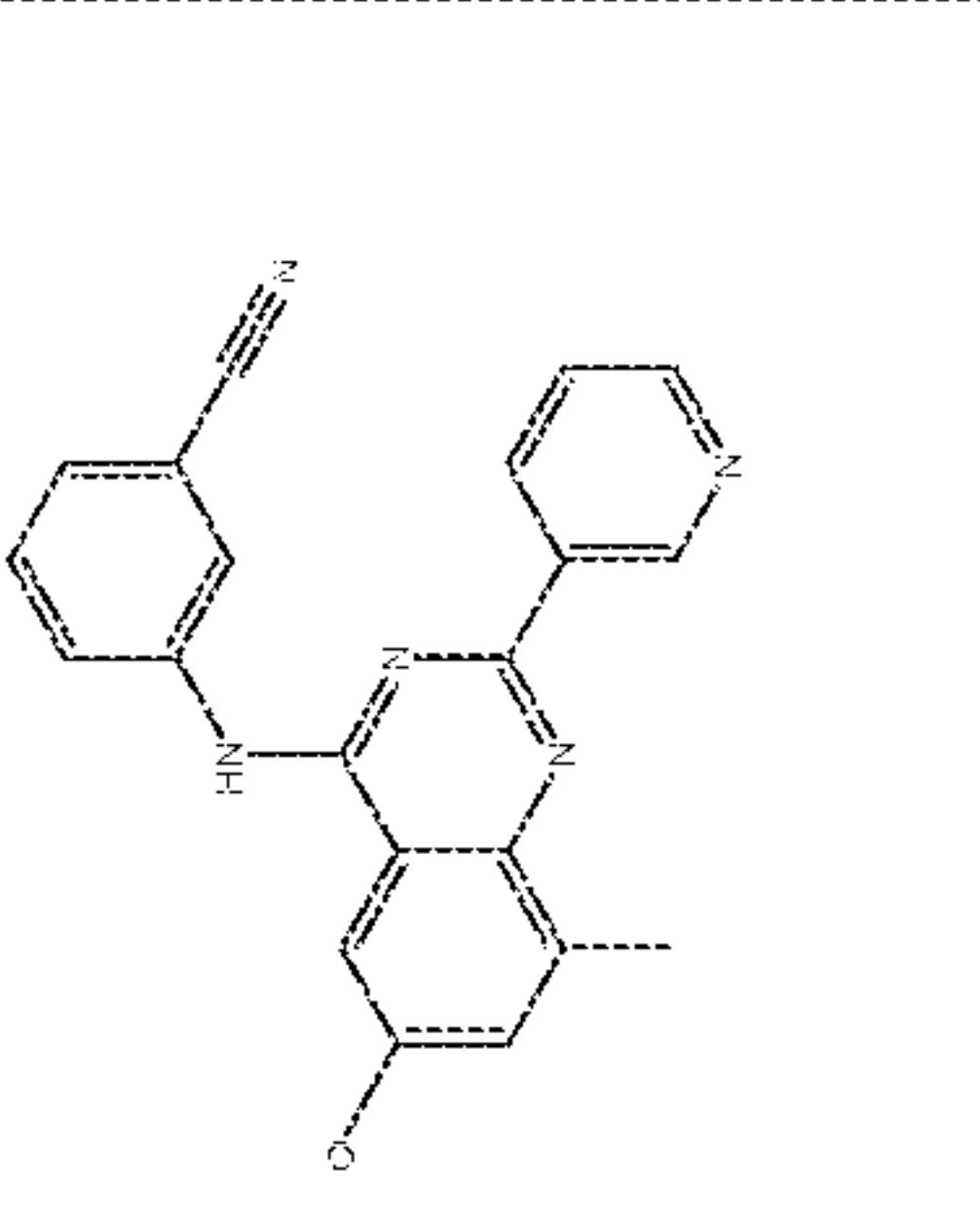
43			429.67	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.46 (s, 1H), 9.49 (s, 1H), 8.95 (d, J = 8.1 Hz, 1H), 8.89 (d, J = 4.97 Hz, 1H), 8.60 (d, J = 6.9 Hz, 1H), 8.19 (dd, J = 6.8, 2.6 Hz, 1H), 8.14 (d, J = 1.9 Hz, 1H), 7.96 – 7.83 (m, 3H), 7.53 (t, J = 9.0 Hz, 1H).	DMSO	429.0, 430.9, 433.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
44		HCl	385.42	¹ H-NMR (400 MHz, DMSO-d ₆): δ 13.05 (s, 1H), 9.44 (d, J = 1.7 Hz, 1H), 9.16 – 8.91 (m, 2H), 8.03 – 7.89 (m, 3H), 7.88 – 7.82 (m, 1H), 7.75 – 7.63 (m, 1H), 7.67 – 7.60 (m, 2H), 7.25 (t, J = 7.6 Hz, 1H), 4.00 (s, 3H), 2.74 (s, 3H).	DMSO	386.0 (M+1) 193.4 (M/2+1)	Method A (TFA)	95	Method C, G1
45		HCl	408.4	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.37 – 10.12 (m, 1H), 9.35 (d, J = 1.8 Hz, 1H), 8.95 (dd, J = 4.6, 3.4 Hz, 1H), 8.09 (d, J = 2.3 Hz, 1H), 7.92 (d, J = 9.1 Hz, 1H), 7.87 (s, 1H), 7.84 – 7.74 (m, 2H), 7.62 (dd, J = 9.1, 2.6 Hz, 1H), 7.54 (t, J = 8.2 Hz, 1H), 7.32 (t, J = 74.0 Hz, 1H), 7.05 (dd, J = 8.3, 1.9 Hz, 1H), 4.00 (s, 3H), 2.72 (s, 3H).	DMSO	409.0 (M+1) 205.0 (M/2+1)	Method A (TFA)	95	Method C, G1

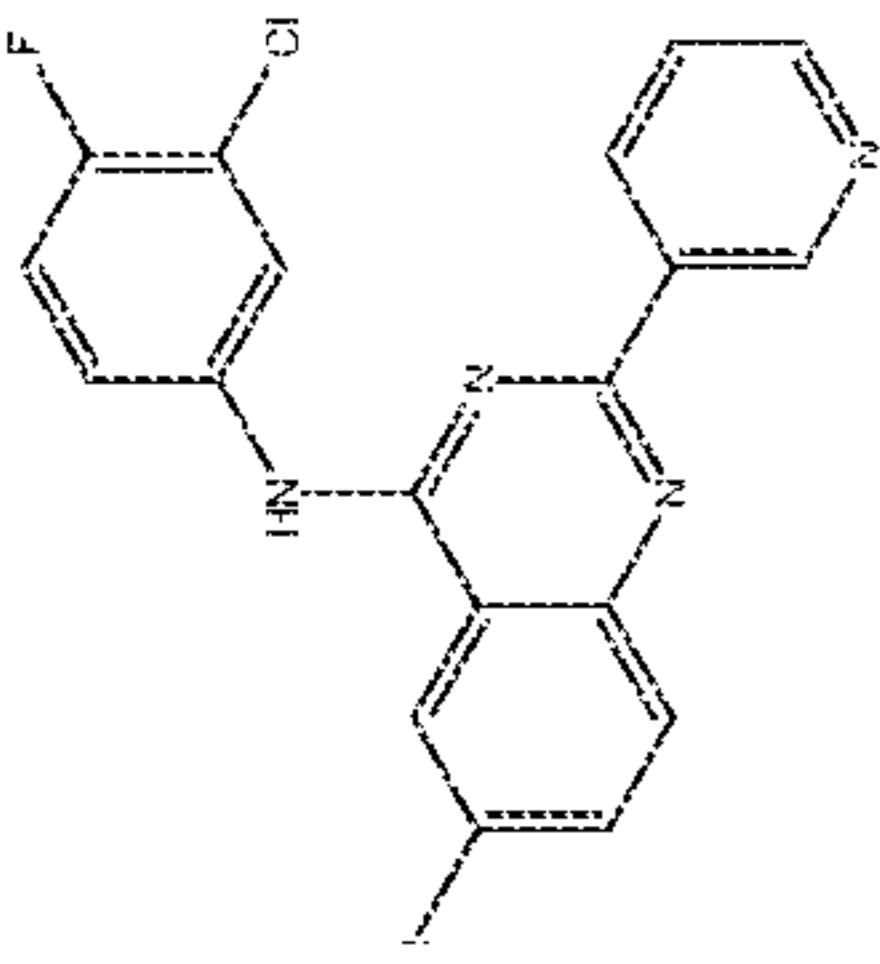
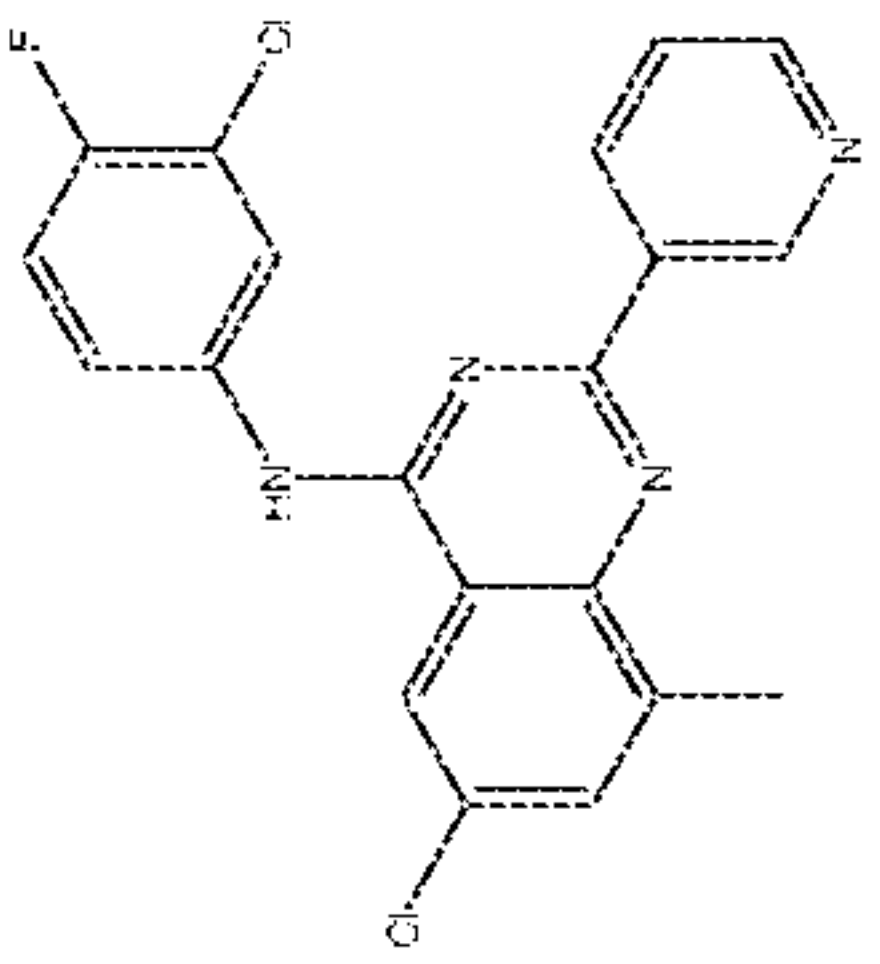
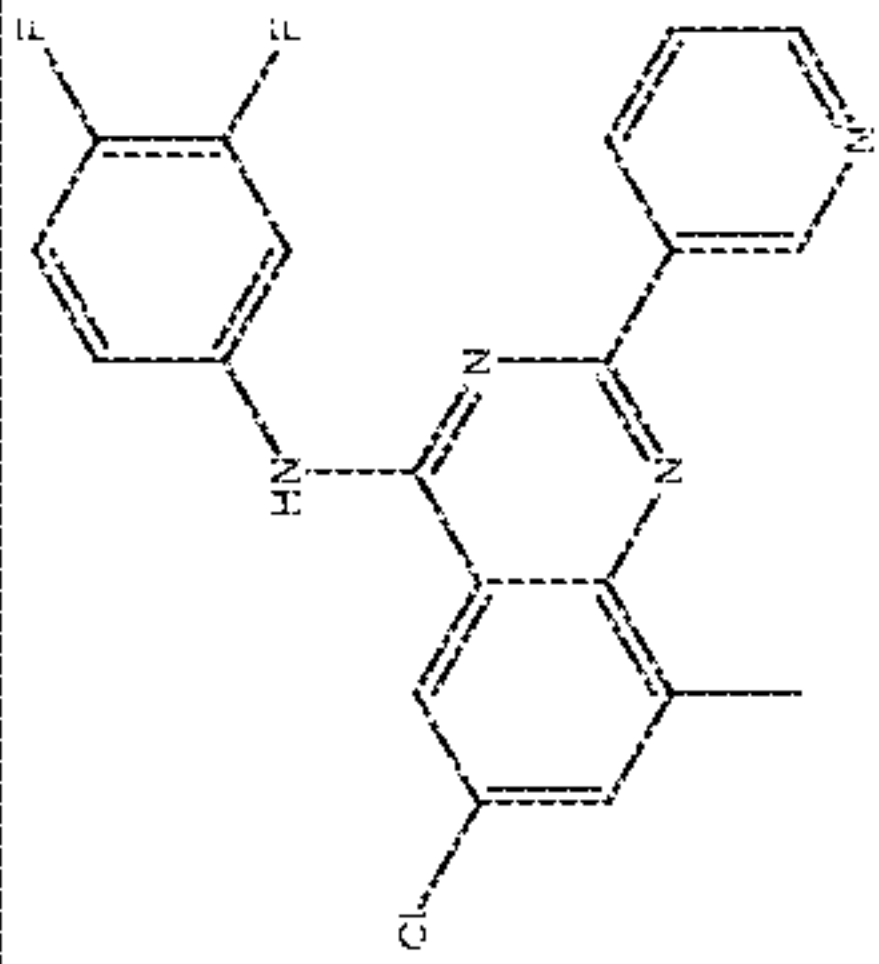
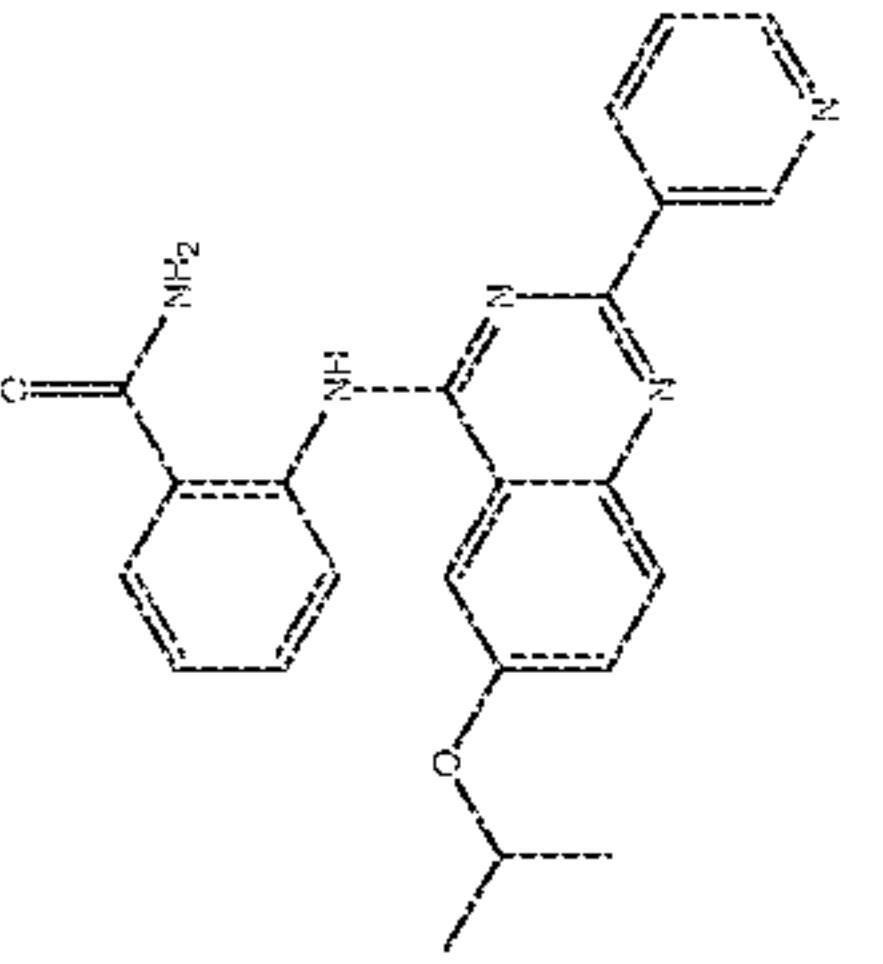
46		HCl	394.83	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.27 (brs, 1H), 9.32 (d, J = 1.7 Hz, 1H), 8.93 (d, J = 7.5 Hz, 1H), 8.19 (dd, J = 6.8, 2.5 Hz, 1H), 8.07 (d, J = 2.3 Hz, 1H), 7.88 - 7.92 (m, 2H), 7.64 (d, J = 8.1 Hz, 1H), 7.62 (dd, J = 9.2, 2.5 Hz, 1H), 7.54 (t, J = 9.1 Hz, 1H), 4.00 (s, 3H), 2.72 (s, 3H).	DMSO	395.0, 397.0 (M+1) 197.8, 198.8 (M/2+1)	Method A (TFA)	95	Method C, G1
47		HCl	378.37	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.58 - 10.30 (m, 1H), 9.32 (d, J = 1.9 Hz, 1H), 9.04 (d, J = 7.9 Hz, 1H), 8.17 - 8.04 (m, 2H), 7.95 (d, J = 9.0 Hz, 2H), 7.73 - 7.66 (m, 1H), 7.63 (dd, J = 9.2, 2.6 Hz, 1H), 7.60 - 7.50 (m, 1H), 4.01 (s, 3H), 2.76 (s, 3H).	DMSO	379.0 (M+1) 190.0 (M/2+1)	Method A (TFA)	95	Method C, G1
48		HCl	411.28	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.29 (s, 1H), 9.33 (d, J = 1.7 Hz, 1H), 9.04 - 8.89 (m, 1H), 8.31 (d, J = 2.4 Hz, 1H), 8.07 (d, J = 2.4 Hz, 1H), 7.97 (dd, J = 8.8, 2.5 Hz, 1H), 7.91 (d, J = 9.1 Hz, 1H), 7.85 (d, J = 8.6 Hz, 1H), 7.73 (d, J = 8.8 Hz, 1H), 7.62 (dd, J = 9.1, 2.5 Hz, 1H), 4.00 (s, 3H), 2.73 (s, 3H).	DMSO	411.0, 413.0 (M+1) 205.0, 206.9 (M/2+1)	Method A (TFA)	95	Method C, G1
49			411.28	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.30 (s, 1H), 9.31 (d, J = 1.5 Hz, 1H), 8.94 (d, J = 7.3 Hz, 1H), 8.13 (d, J = 1.7 Hz, 2H), 8.07 (d, J = 2.3 Hz, 1H), 7.90 (d, J = 9.2 Hz, 1H), 7.87 (d, J = 8.5 Hz, 1H), 7.61 (dd, J = 9.1, 2.6 Hz, 1H), 7.41 (d, J = 1.7 Hz, 1H), 4.00 (s, 3H), 2.72 (s, 3H).	DMSO	411.0, 413.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1

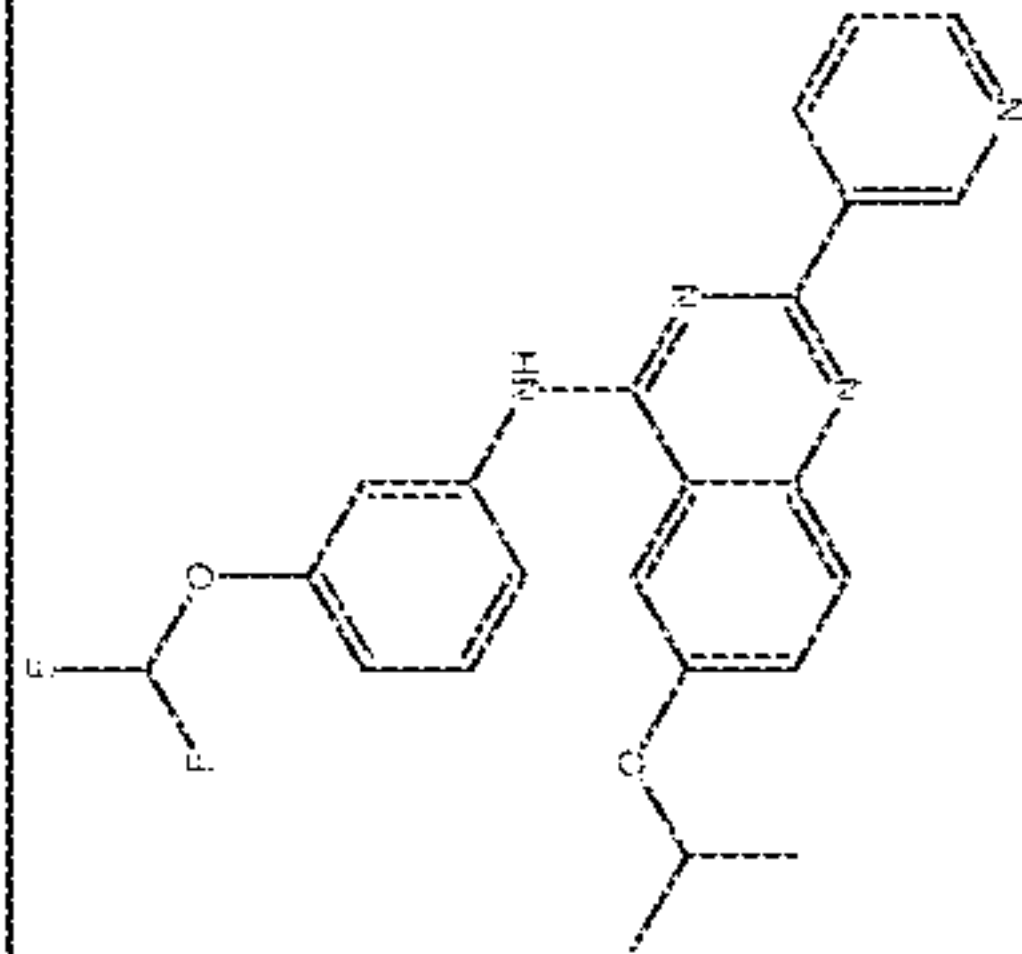
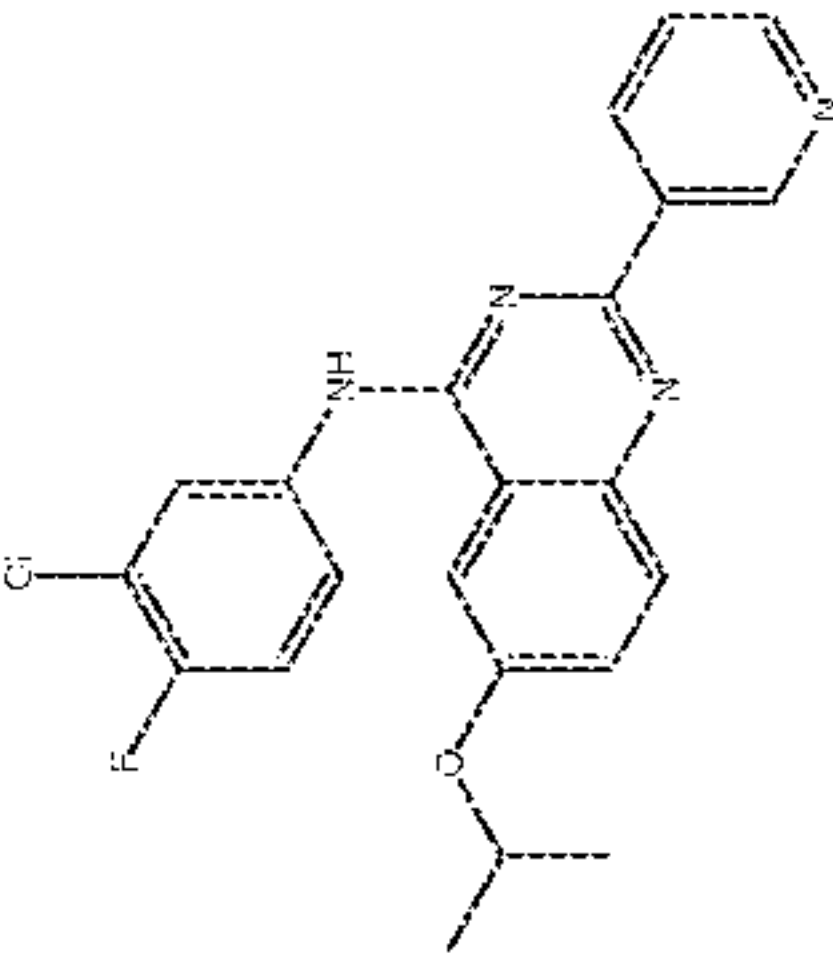
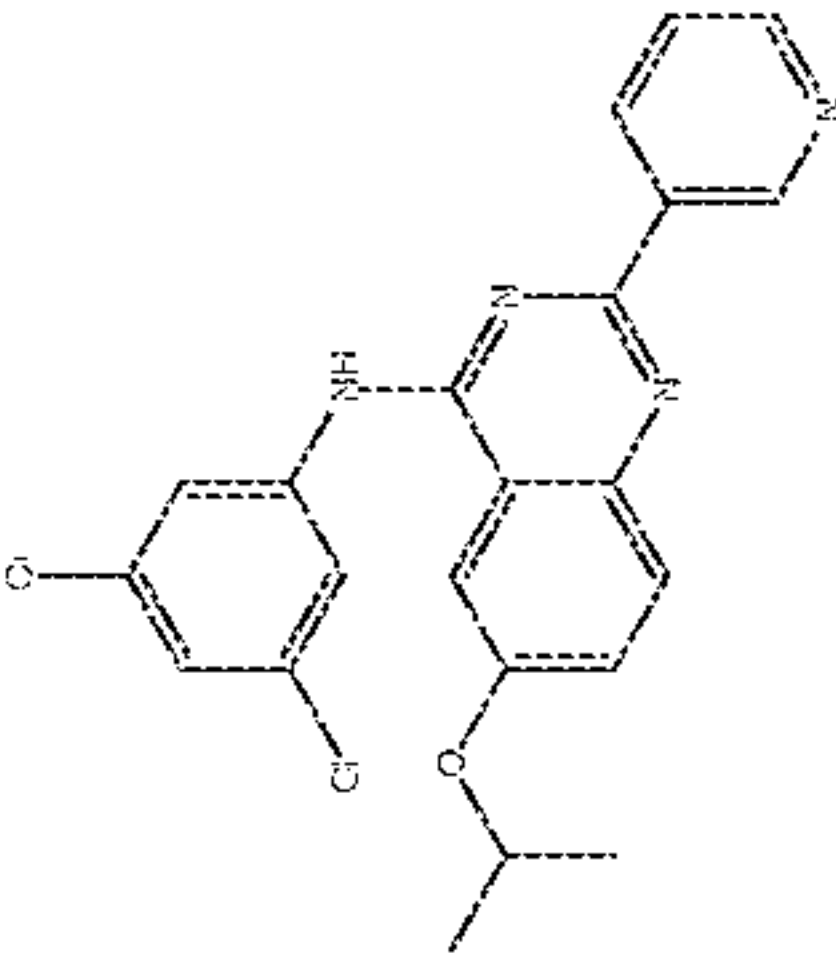
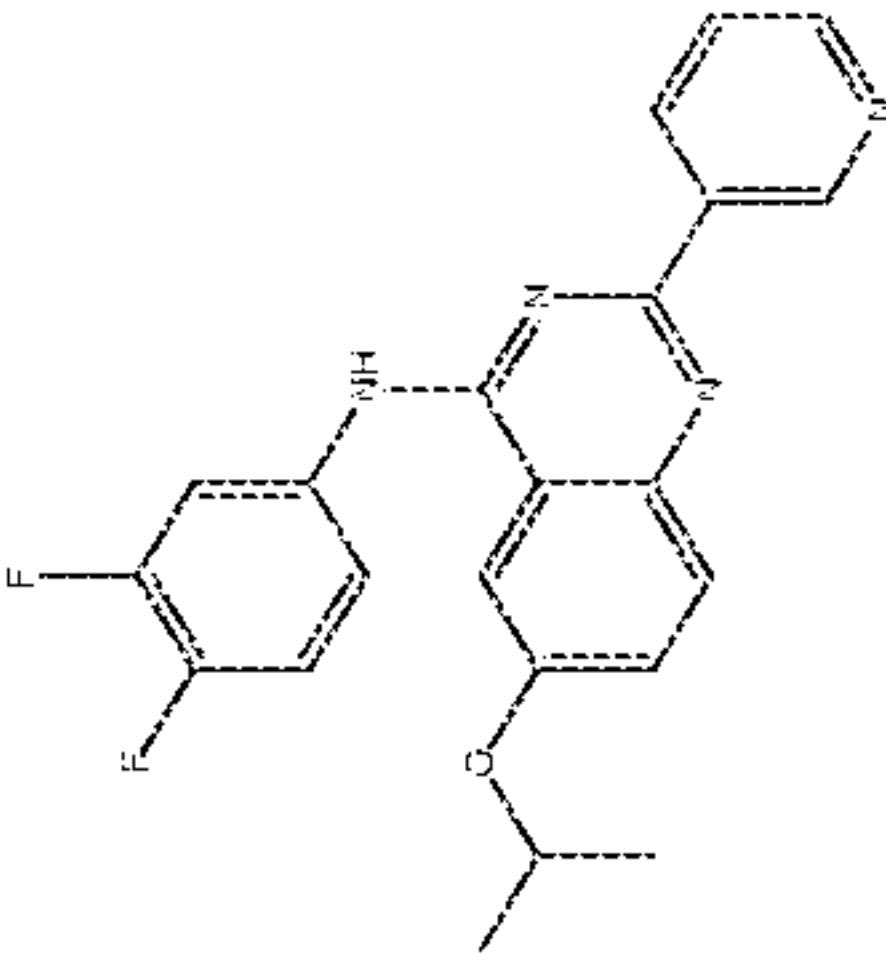
50		HCl	389.84	¹ H-NMR (400 MHz, DMSO-d ₆): δ 13.09 (s, 1H), 9.38 (s, 1H), 9.16 (d, <i>J</i> = 8.4 Hz, 1H), 8.83 (d, <i>J</i> = 8.3 Hz, 1H), 8.50 (s, 1H), 8.20 (d, <i>J</i> = 8.8 Hz, 1H), 8.05 – 7.99 (m, 2H), 7.97 (d, <i>J</i> = 7.9 Hz, 1H), 7.92 (s, 1H), 7.81 (dd, <i>J</i> = 8.8, 2.0 Hz, 1H), 7.68 (t, <i>J</i> = 7.8 Hz, 1H), 7.28 (t, <i>J</i> = 7.6 Hz, 1H), 2.82 (s, 3H).	DMSO	390.1, 392.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
51		HCl	412.82	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.49 (s, 1H), 9.35 (d, <i>J</i> = 1.7 Hz, 1H), 9.08 (dd, <i>J</i> = 8.3, 1.5 Hz, 1H), 8.75 (d, <i>J</i> = 9.0 Hz, 1H), 8.02 (d, <i>J</i> = 2.1 Hz, 1H), 7.97 (d, <i>J</i> = 6.3 Hz, 1H), 7.87 (s, 1H), 7.80 (dd, <i>J</i> = 9.0, 2.0 Hz, 2H), 7.53 (t, <i>J</i> = 8.2 Hz, 1H), 7.31 (t, <i>J</i> = 74.0 Hz, 1H), 7.06 (dd, <i>J</i> = 8.1, 2.0 Hz, 1H), 2.79 (s, 3H).	DMSO	413.0, 415.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
52			399.25	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.49 (s, 1H), 9.32 (d, <i>J</i> = 1.7 Hz, 1H), 9.00 (d, <i>J</i> = 8.4 Hz, 1H), 8.69 (d, <i>J</i> = 8.9 Hz, 1H), 8.20 (dd, <i>J</i> = 6.8, 2.6 Hz, 1H), 8.00 (d, <i>J</i> = 2.1 Hz, 1H), 7.96 – 7.86 (m, 2H), 7.80 (dd, <i>J</i> = 8.9, 2.1 Hz, 1H), 7.53 (t, <i>J</i> = 9.1 Hz, 1H), 2.76 (s, 3H).	DMSO	399.0, 401.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
53		HCl	382.79	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.55 (s, 1H), 9.32 (d, <i>J</i> = 1.7 Hz, 1H), 9.07 (dd, <i>J</i> = 8.2, 1.2 Hz, 1H), 8.73 (d, <i>J</i> = 8.9 Hz, 1H), 8.08 (ddd, <i>J</i> = 13.0, 7.5, 2.6 Hz, 1H), 8.00 (dd, <i>J</i> = 8.9, 5.2 Hz, 2H), 7.80 (dd, <i>J</i> = 8.9, 2.1 Hz, 1H), 7.71 (dd, <i>J</i> = 6.1, 2.9 Hz, 1H), 7.54 (dd, <i>J</i> = 19.7, 9.2 Hz, 1H), 2.78 (s, 3H).	DMSO	383.0, 385.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1

54		HCl	415.7	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.63 (s, 1H), 9.30 (d, J = 1.7 Hz, 1H), 9.07 (dd, J = 8.3, 1.8 Hz, 1H), 8.75 (d, J = 9.0 Hz, 1H), 8.29 (d, J = 2.4 Hz, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.99 (d, J = 2.1 Hz, 1H), 7.96 (dd, J = 8.9, 2.5 Hz, 1H), 7.77 (dd, J = 8.9, 2.1 Hz, 1H), 7.70 (d, J = 8.8 Hz, 1H), 2.81 (s, 3H).	DMSO	415.0, 417.0, 419.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
55		HCl	415.7	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.54 (s, 1H), 9.32 (s, 1H), 9.01 (dd, J = 8.0, 1.8 Hz, 1H), 8.72 (d, J = 9.0 Hz, 1H), 8.11 (d, J = 1.8 Hz, 2H), 8.01 (d, J = 2.0 Hz, 1H), 7.97 (d, J = 8.5 Hz, 1H), 7.80 (dd, J = 8.9, 2.0 Hz, 1H), 2.76 (s, 3H).	DMSO	415.0, 417.0, 419.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
56			379.36	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.16 (s, 1H), 9.47 (s, 1H), 8.79 (dd, J = 8.9, 7.1 Hz, 2H), 7.91 (s, 1H), 7.84 – 7.77 (m, 2H), 7.76 – 7.68 (m, 1H), 7.56 (d, J = 2.1 Hz, 1H), 7.51 (t, J = 8.2 Hz, 1H), 7.39 (dd, J = 8.9, 2.2 Hz, 1H), 7.29 (t, J = 74.0 Hz, 1H), 7.00 (dd, J = 8.1, 2.1 Hz, 1H), 4.23 (brs, 2H).	DMSO	380.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
57		HCl	463.48	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.43 – 10.20 (m, 2H), 9.72 (s, 1H), 8.89 – 8.67 (m, 3H), 8.29 – 8.21 (m, 1H), 7.97 (s, 1H), 7.87 – 7.80 (m, 1H), 7.81 – 7.73 (m, 1H), 7.63 – 7.46 (m, 2H), 7.30 (t, J = 74.0 Hz, 1H), 7.08 – 6.98 (m, 1H), 5.00 (s, 2H), 4.05 – 3.65 (m, 4H), 3.39 – 3.36 (m, 4H).	DMSO	464.2 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1

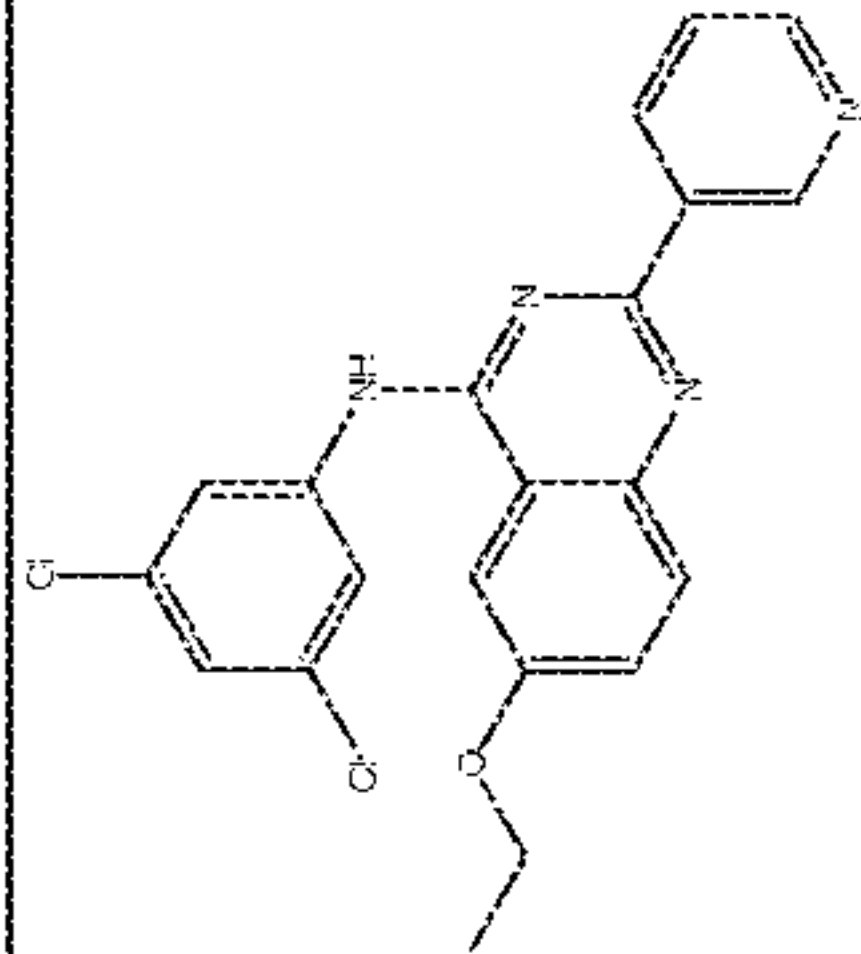
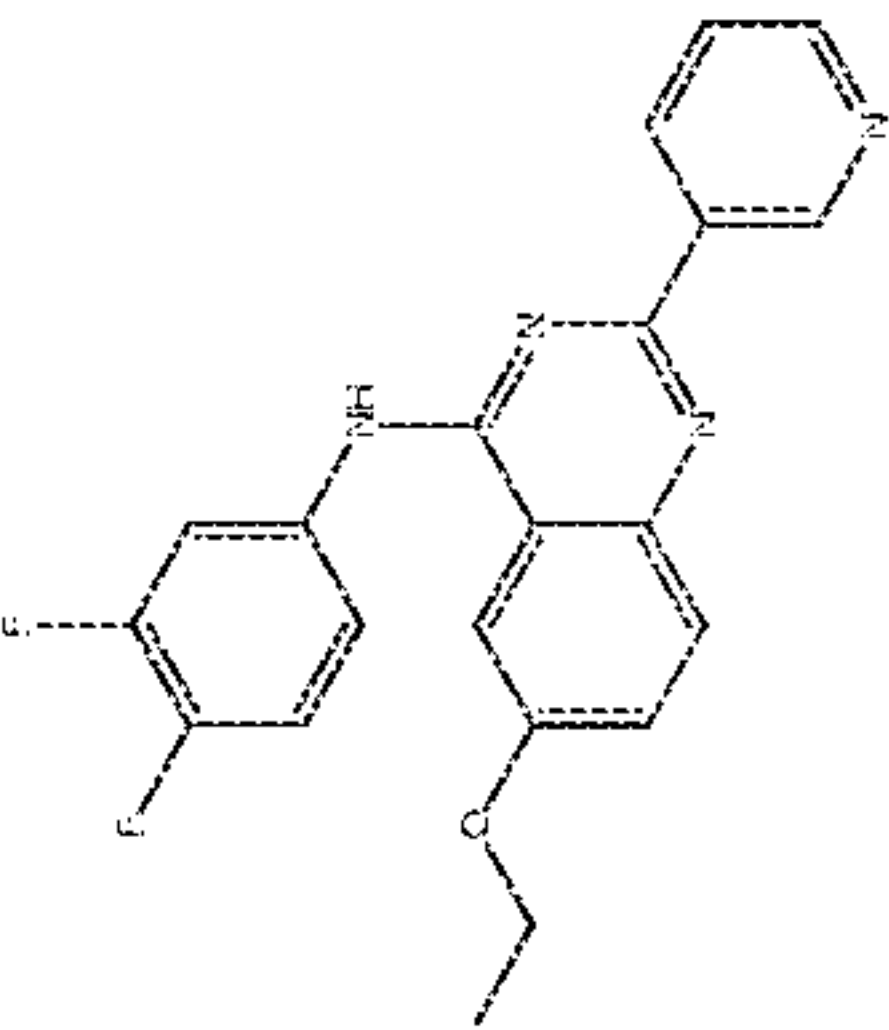
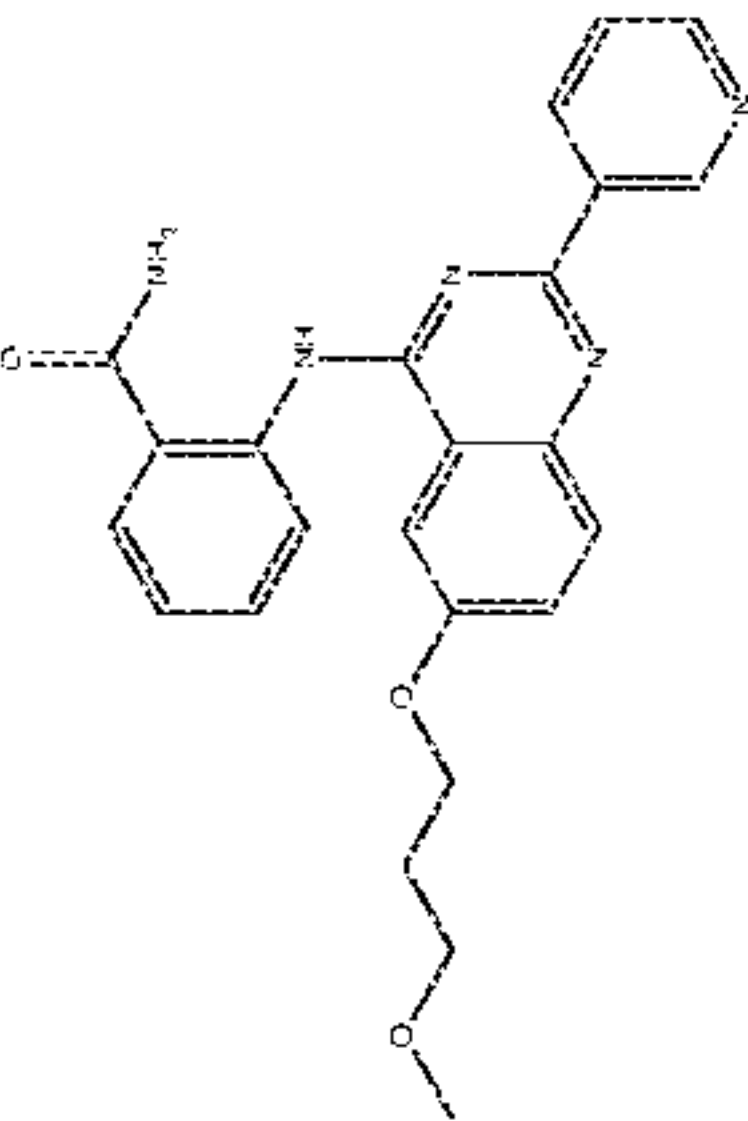
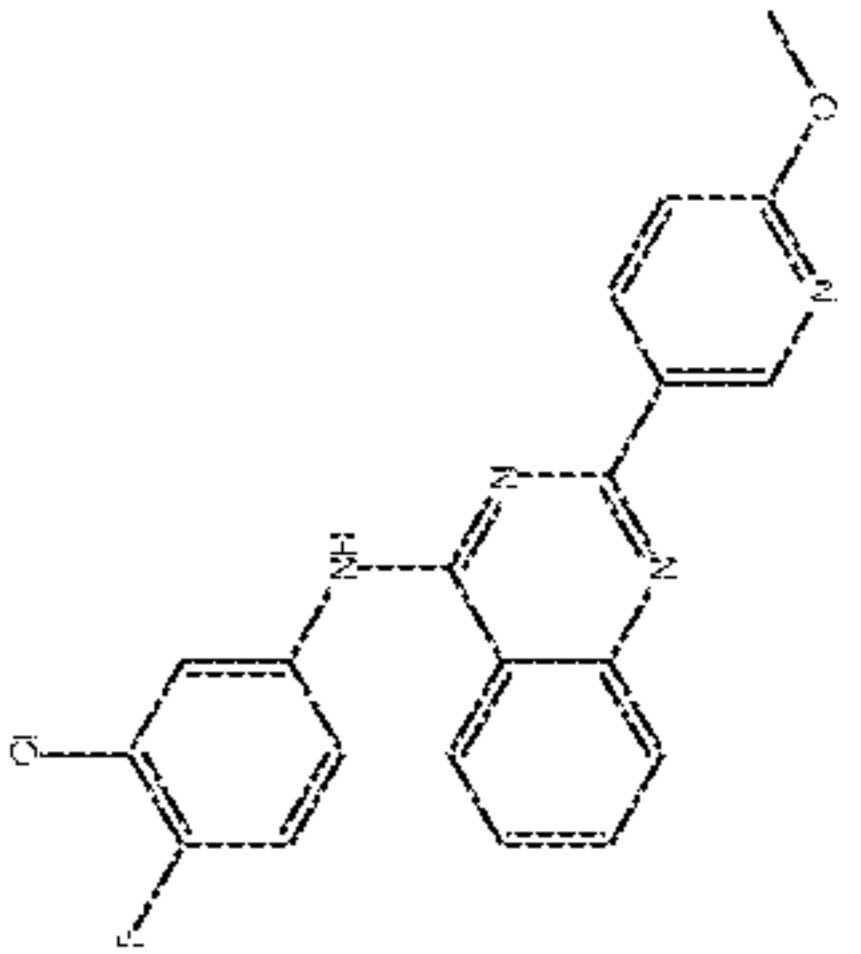
58		HCl	399.45	¹ H-NMR (400 MHz, DMSO-d ₆): δ 12.53 (s, 1H), 9.30 (d, J = 1.6 Hz, 1H), 9.03 – 8.96 (m, 1H), 8.94 – 8.88 (m, 1H), 8.71 (d, J = 8.4 Hz, 1H), 7.91 – 7.83 (m, 3H), 7.67 – 7.55 (m, 3H), 7.25 (t, J = 7.2 Hz, 1H), 3.98 (s, 3H), 2.80 – 2.74 (m, 6H).	DMSO	400.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method D, G1
59		HCl	389.38	¹ H-NMR (400 MHz, DMSO-d ₆): δ 13.27 (s, 1H), 9.23 (s, 1H), 8.98 (d, J = 5.2 Hz, 1H), 8.91 (d, J = 8.0 Hz, 1H), 8.54 (dd, J = 12.0, 2.6 Hz, 1H), 8.48 (s, 1H), 8.07 (dd, J = 8.0, 5.6 Hz, 1H), 7.97 – 7.93 (m, 2H), 7.66 (d, J = 9.0 Hz, 1H), 7.37 (dd, J = 9.0, 2.4 Hz, 1H), 7.13 (d, J = 2.0 Hz, 1H), 6.91 (dt, J = 8.4, 2.6 Hz, 1H), 3.80 (s, 3H).	DMSO	390.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
60			415.70	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.13 (s, 1H), 9.48 (s, 1H), 8.87 (dd, J = 14.0, 6.2 Hz, 2H), 8.54 (d, J = 1.7 Hz, 1H), 8.10 (d, J = 1.8 Hz, 2H), 7.89 – 7.78 (m, 2H), 7.37 (t, J = 1.8 Hz, 1H), 2.70 (s, 3H).	DMSO	414.9, 416.9, 419.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1

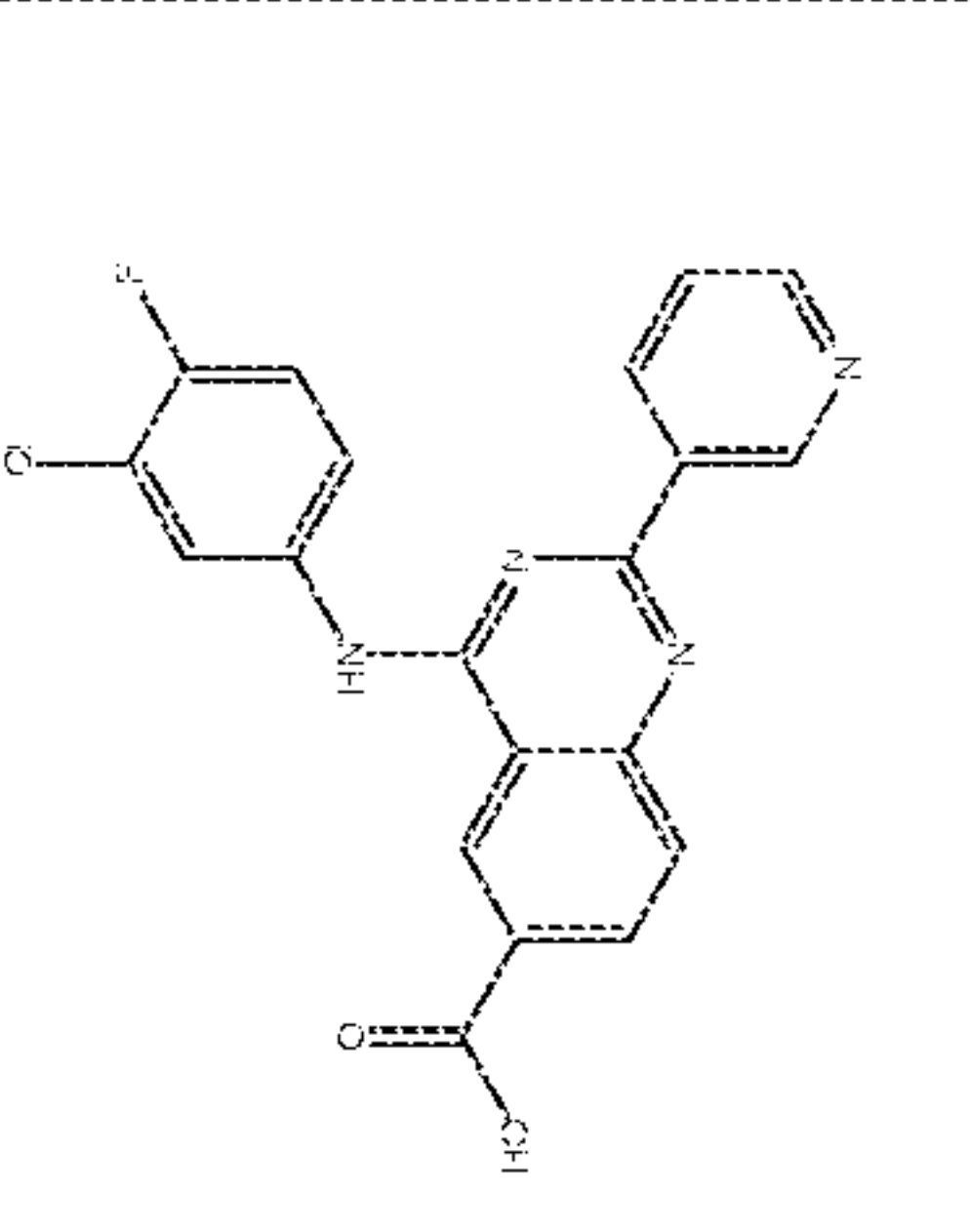
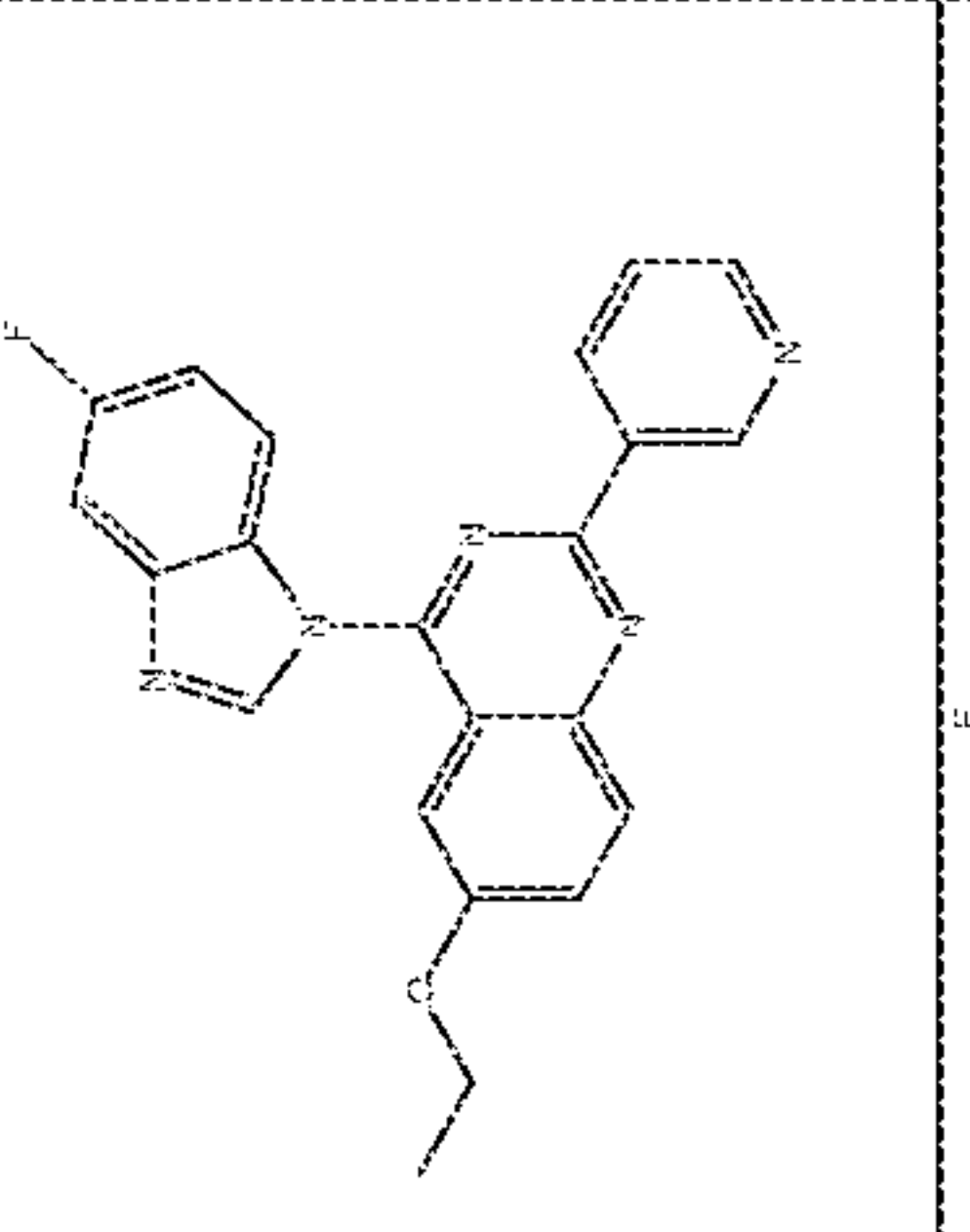
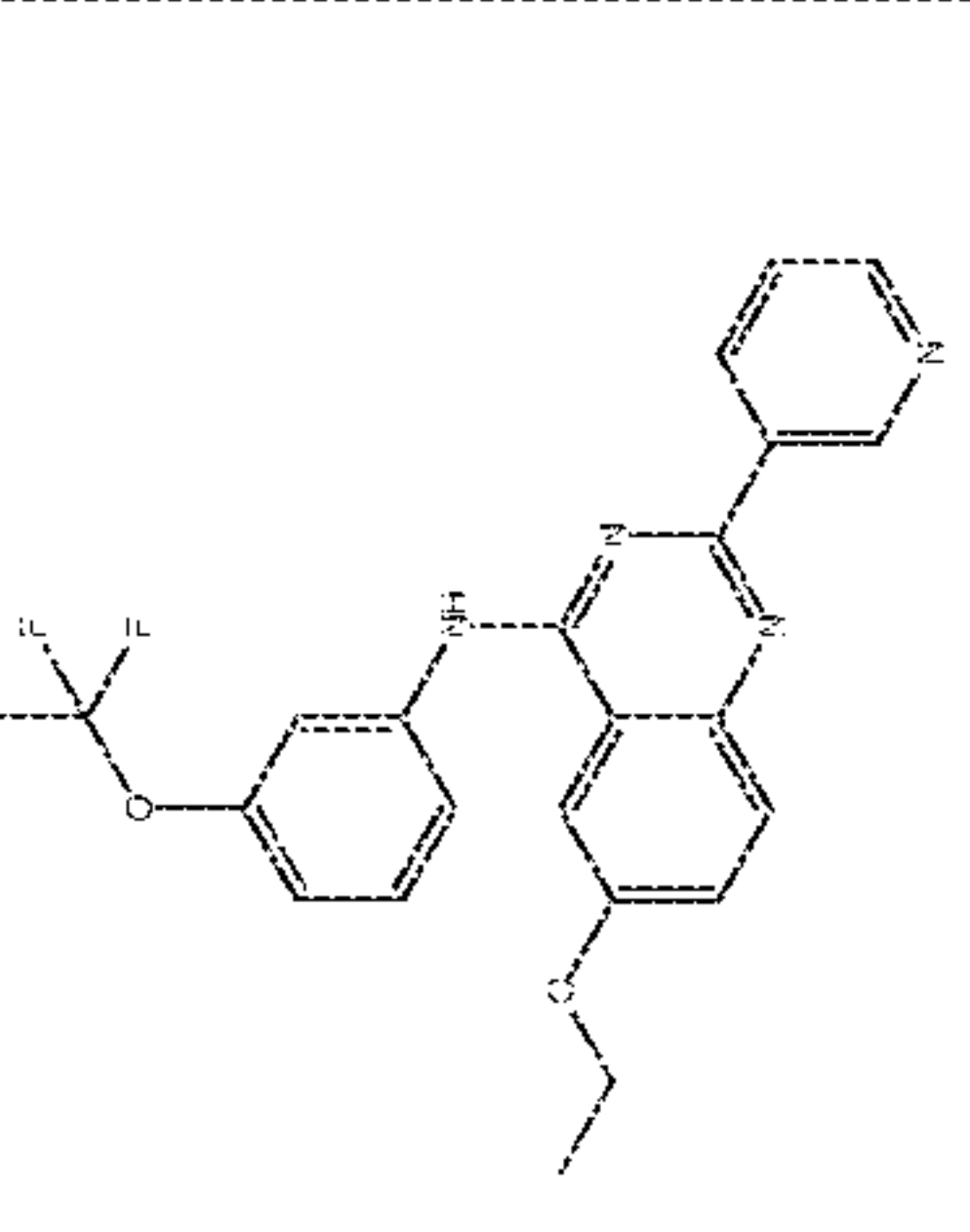
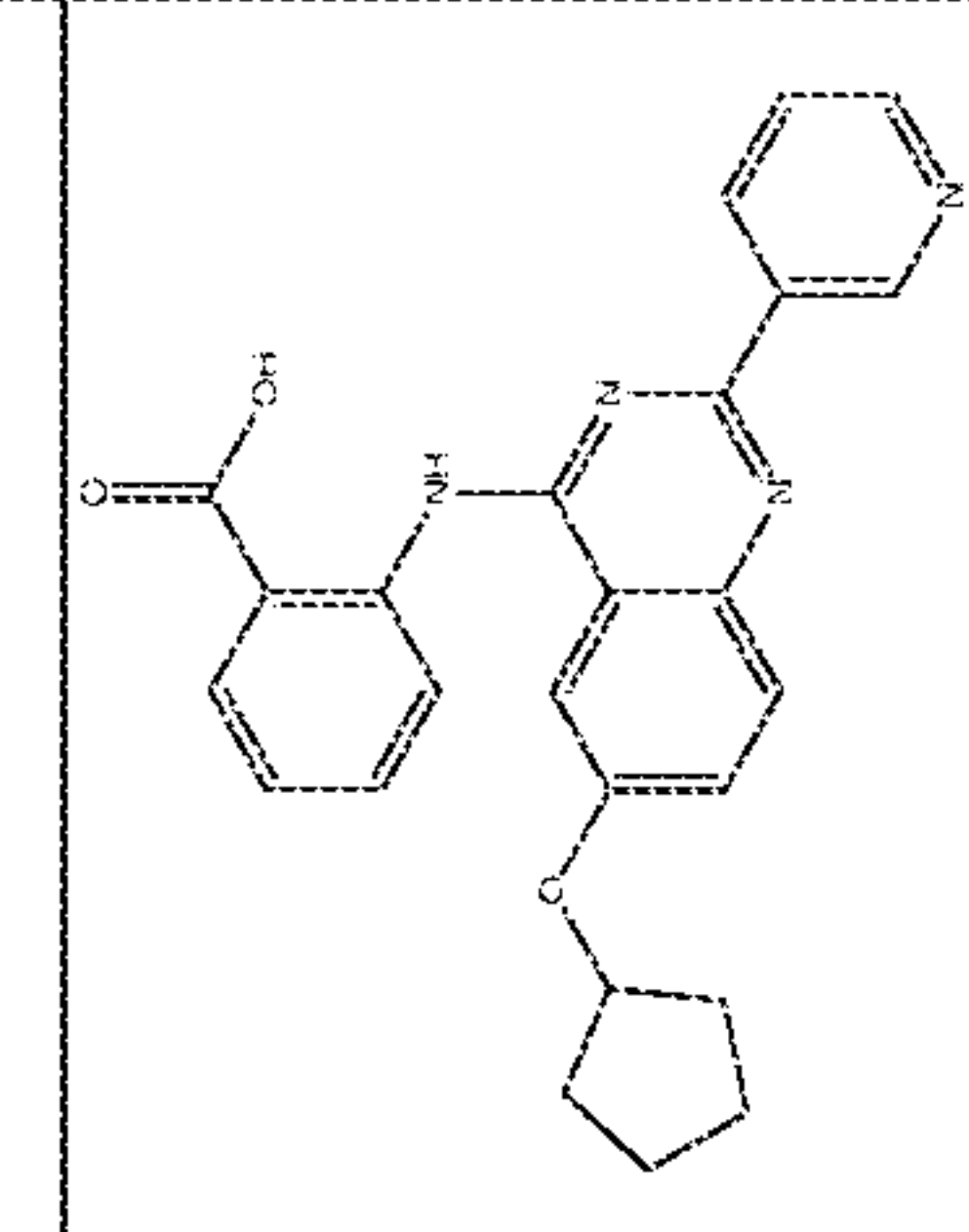
61			415.70	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.10 (s, 1H), 9.44 (s, 1H), 8.86 (d, J = 7.8 Hz, 1H), 8.79 (d, J = 4.5 Hz, 1H), 8.50 (d, J = 1.7 Hz, 1H), 8.23 (d, J = 2.4 Hz, 1H), 7.89 (dd, J = 8.8, 2.4 Hz, 1H), 7.83 – 7.71 (m, 2H), 7.62 (d, J = 8.8 Hz, 1H), 2.62 (s, 3H)	DMSO	414.9, 416.9, 418.9 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
62			412.82	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.02 (s, 1H), 9.56 (d, J = 1.8 Hz, 1H), 8.76 – 8.67 (m, 2H), 8.59 (d, J = 1.8 Hz, 1H), 7.96 (s, 1H), 7.82 (d, J = 6.6 Hz, 2H), 7.54 (ddd, J = 16.4, 10.0, 6.4 Hz, 2H), 7.30 (t, J = 74.0 Hz, 1H), 7.01 (dd, J = 8.0, 2.0 Hz, 1H), 2.74 (s, 3H).	DMSO	413.0, 415.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
63			389.84	¹ H-NMR (400 MHz, DMSO-d ₆): δ 13.15 (s, 1H), 9.58 (s, 1H), 9.03 (d, J = 0.8 Hz, 1H), 8.78 – 8.84 (m, 2H), 8.50 (s, 1H), 7.95 – 8.03 (m, 3H), 7.80 (s, 1H), 7.70 – 7.74 (m, 2H), 7.23 (d, J = 7.2 Hz, 1H), 2.70 (s, 3H).	DMSO	391.0, 392.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
64			371.82	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.31 (s, 1H), 9.48 (d, J = 1.2 Hz, 1H), 9.01 (d, J = 8.4 Hz, 1H), 8.90 (d, J = 4.0 Hz, 1H), 8.61 (d, J = 1.6 Hz, 1H), 8.33 (s, 1H), 8.27 (dd, J = 6.0, 2.0 Hz, 1H), 7.95 – 7.63 (m, 3H), 2.70 (s, 3H).	DMSO	372.0 373.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1

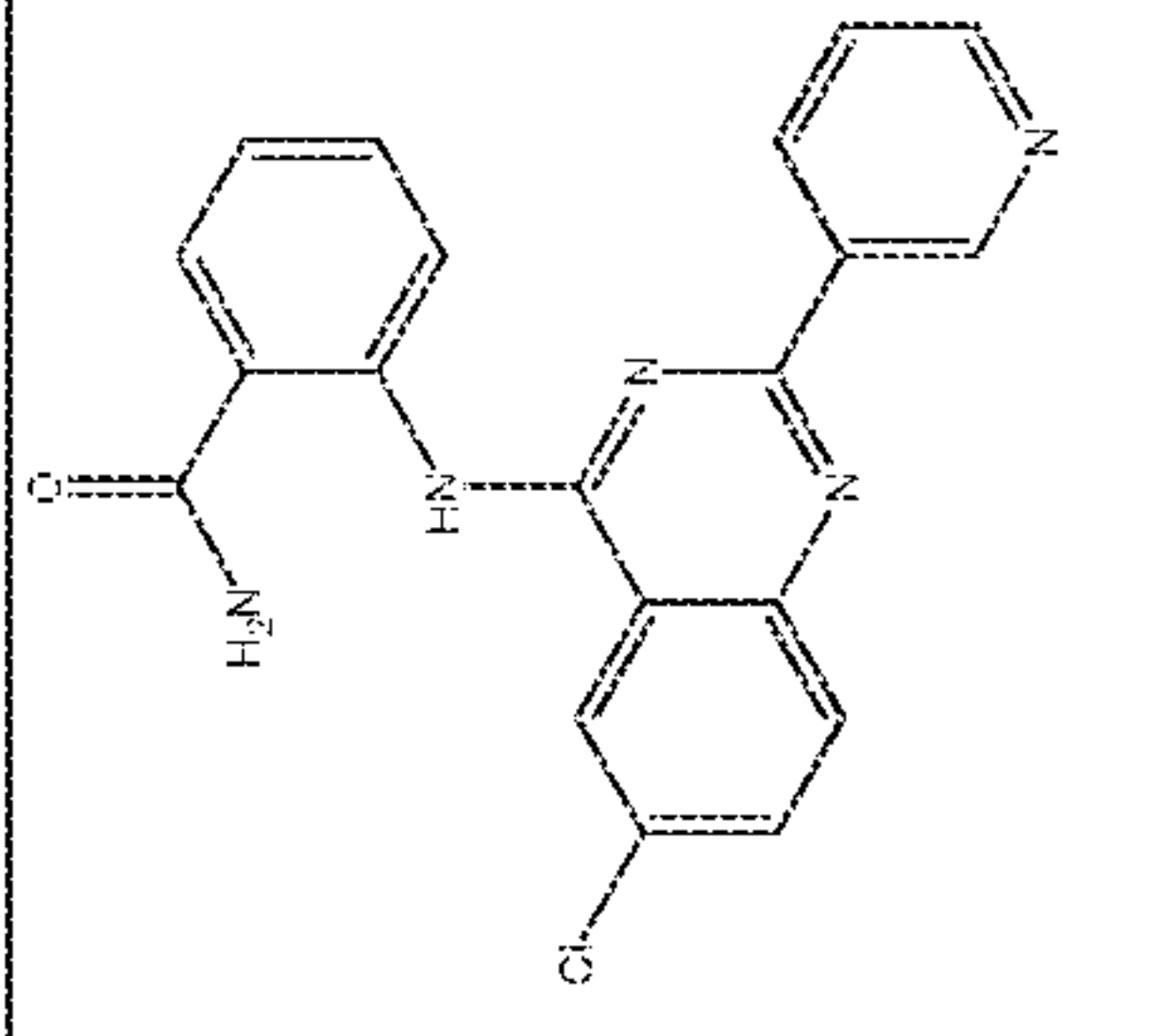
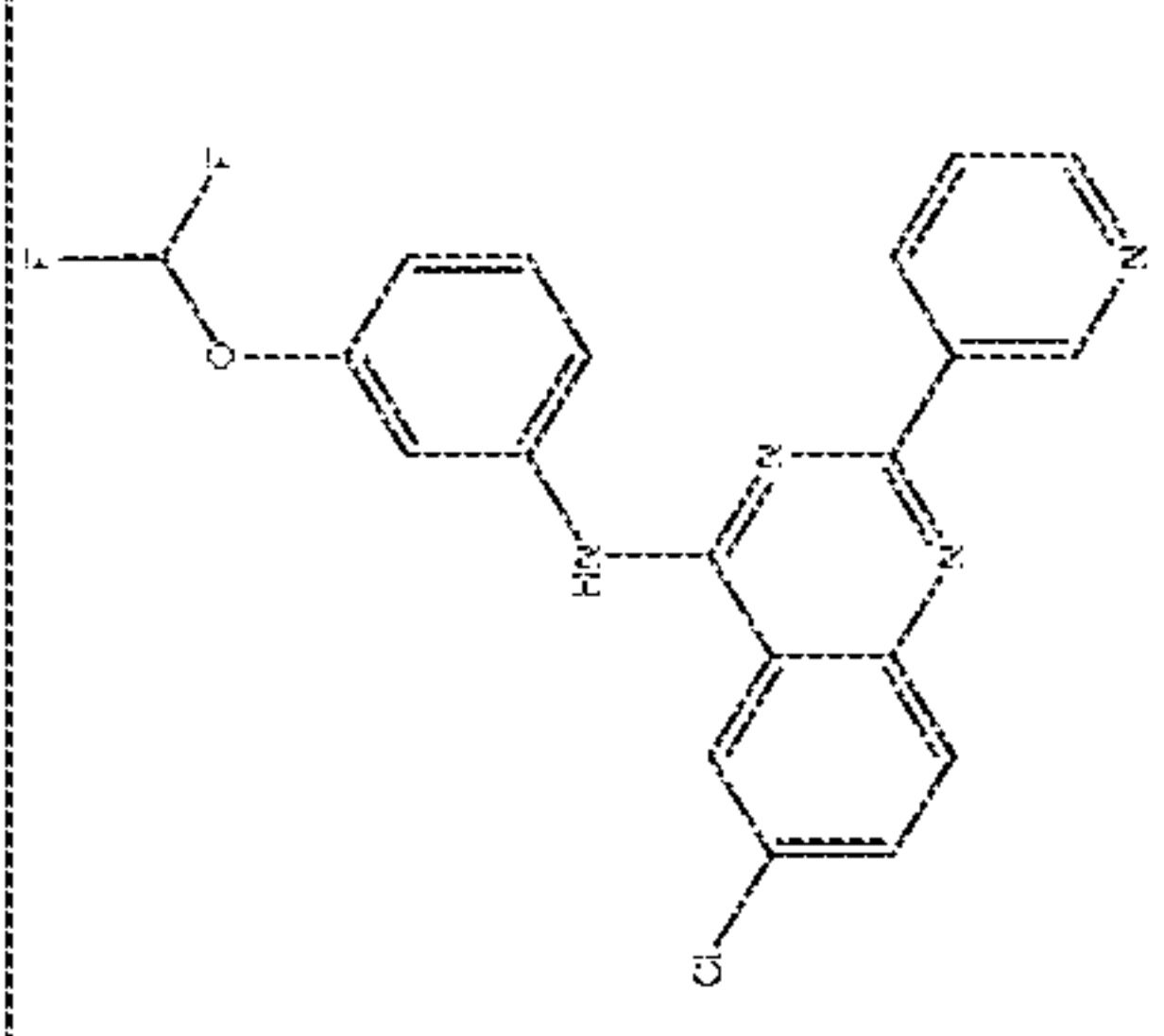
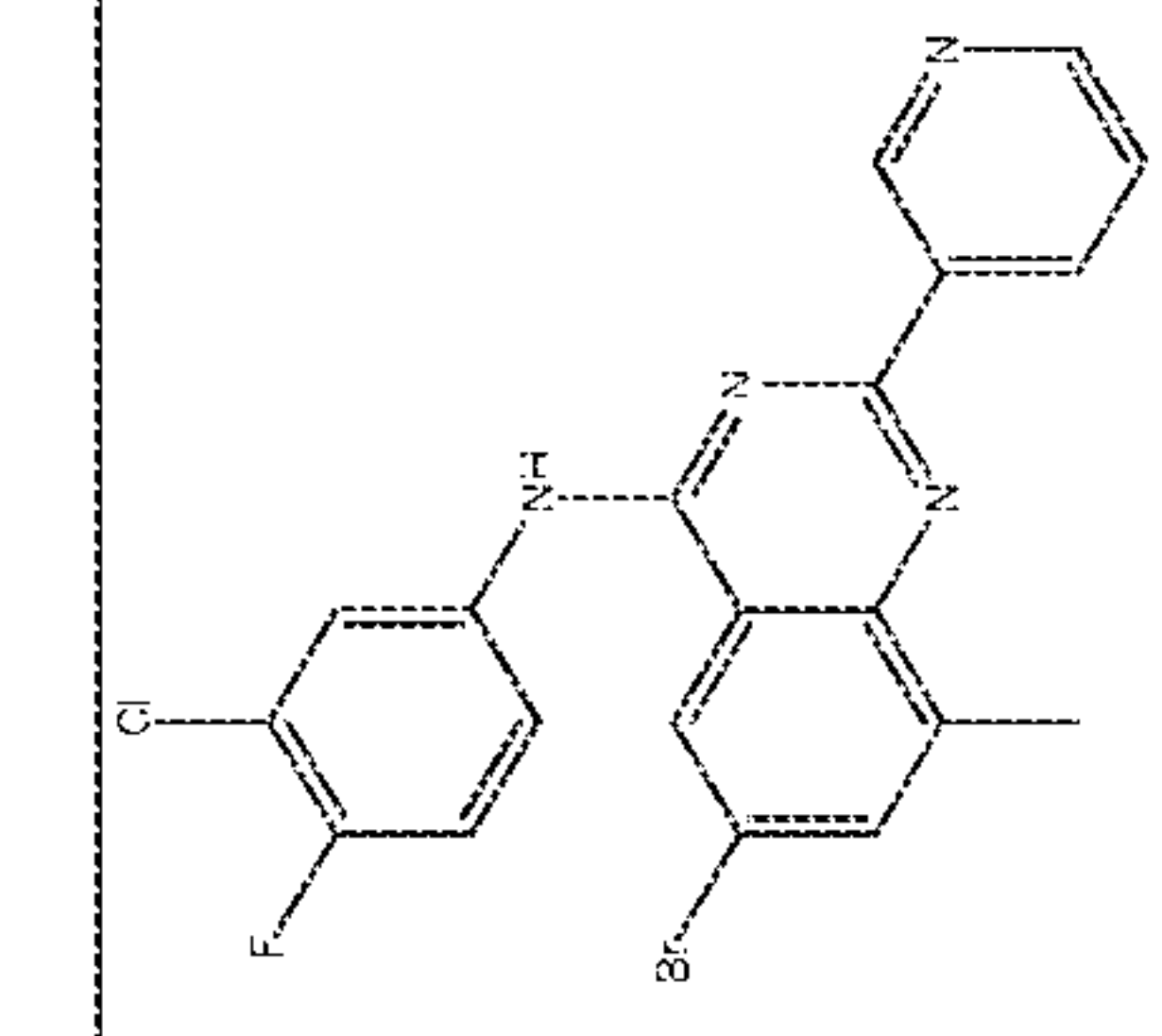
65			476.67	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.28 (s, 1H), 9.46 (d, J = 1.2 Hz, 1H), 9.01 (d, J = 1.2 Hz, 1H), 8.83 (dd, J = 8.4, 1.6 Hz, 2H), 8.19 – 8.14 (m, 2H), 7.89 – 7.49 (m, 2H).	DMSO	476.9, 478.9 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
66			399.25	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.03 (s, 1H), 8.54 (s, 1H), 8.71 – 8.67 (m, 2H), 8.53 (s, 1H), 8.26 (dd, J = 6.8 Hz, 2.4 Hz, 1H), 7.83 (s, 1H), 7.58 – 7.52 (m, 2H), 2.72 (s, 3H).	DMSO	399.0, 401.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
67			382.79	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.04 (s, 1H), 9.51 (d, J = 1.2 Hz, 1H), 8.72 – 8.69 (m, 2H), 8.53 (d, J = 2.0 Hz, 1H), 8.08 (ddd, J = 9.2, 7.6, 2.4 Hz, 1H), 7.79 – 7.48 (m, 4H), 2.69 (s, 3H).	DMSO	383.0, 385.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
68		HCl	399.45	¹ H-NMR (400 MHz, DMSO-d ₆): δ 13.02 (s, 1H), 9.59 (s, 1H), 9.09 (d, J = 8.0 Hz, 1H), 8.96 (d, J = 8.4 Hz, 1H), 8.91 (d, J = 4.61 Hz, 1H), 8.48 (s, 1H), 7.97 (dd, J = 8.0, 2.8 Hz, 4H), 7.72 (t, J = 7.6 Hz, 1H), 7.64 – 7.61 (m, 2H), 7.26 (t, J = 7.6 Hz, 1H), 4.88 – 4.82 (m, 1H), 1.43 (d, J = 6.0 Hz, 6H).	DMSO	400.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1

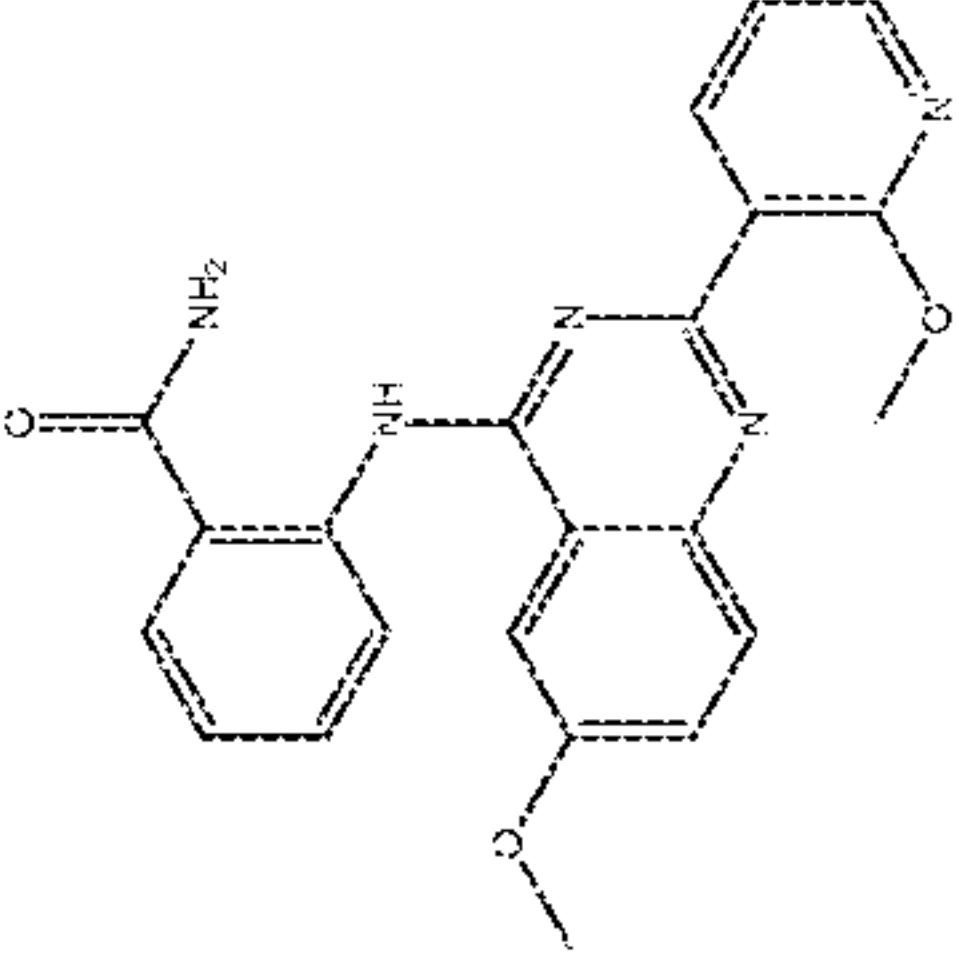
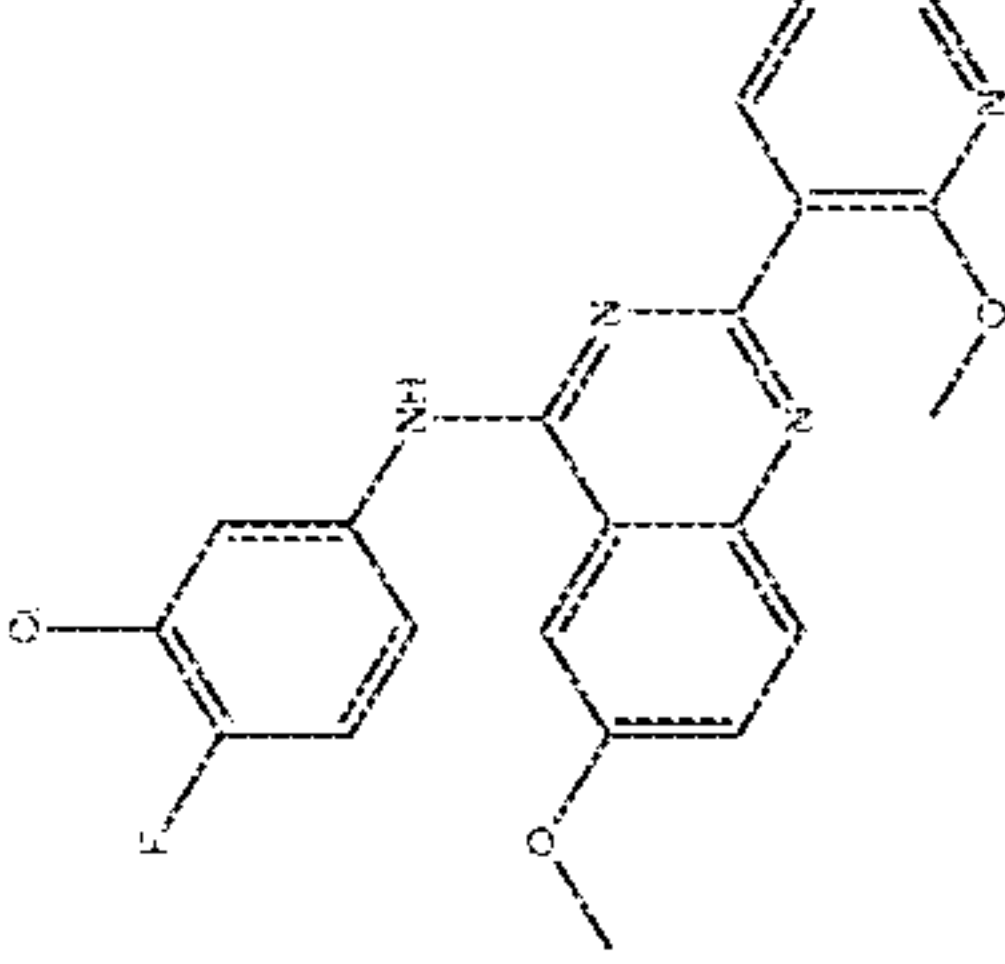
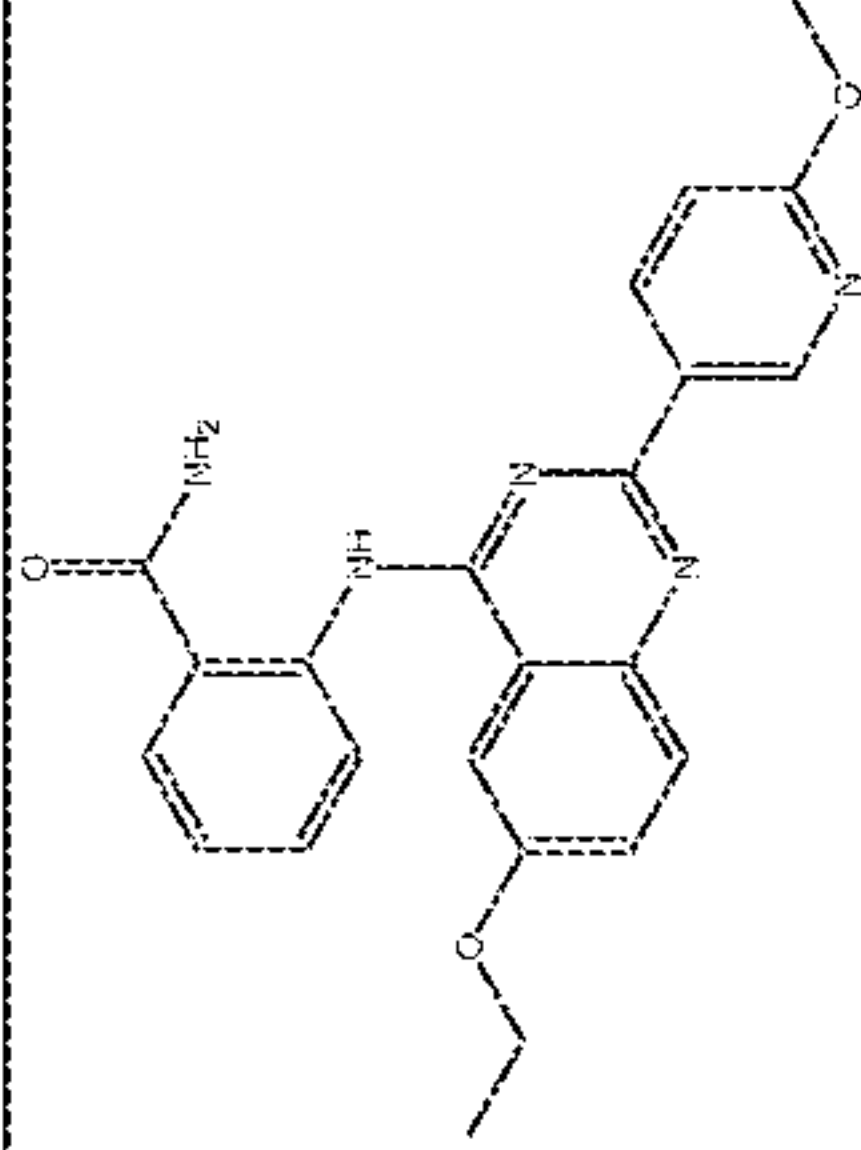
69		HCl	422.43	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.63 (s, 1H), 9.51 (s, 1H), 9.09 (d, J = 7.6 Hz, 1H), 8.91 (d, J = 7.6 Hz, 1H), 8.23 (s, 1H), 8.03 – 7.97 (m, 1H), 7.83 – 7.80 (m, 2H), 7.64 (dd, J = 9.2, 2.4 Hz, 1H), 7.55 (t, J = 8.1 Hz, 1H), 7.32 (t, J = 74.0 Hz, 1H), 7.08 (d, J = 7.4 Hz, 1H), 5.02 – 4.97 (m, 1H), 1.39 (d, J = 6.0 Hz, 6H).	DMSO	423.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
70		HCl	408.86	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.61 (s, 1H), 9.48 (s, 1H), 9.05 (d, J = 7.2 Hz, 1H), 8.93 (d, J = 5.2 Hz, 1H), 8.19 – 8.15 (m, 2H), 8.01 – 7.92 (m, 3H), 7.63 – 7.53 (m, 2H), 5.01 – 4.94 (m, 1H), 1.39 (d, J = 6.0 Hz, 6H).	DMSO	409.1, 411.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
71		HCl	425.31	¹ H-NMR (400 MHz, DMSO-d ₆): δ 9.92 (s, 1H), 9.52 (d, J = 1.2 Hz, 1H), 8.70 – 8.66 (m, 2H), 8.17 (d, J = 1.6 Hz, 2H), 7.98 (d, J = 2.4 Hz, 1H), 7.38 (d, J = 8.8 Hz, 1H), 7.60 – 7.56 (m, 2H), 7.39 (t, J = 1.8 Hz, 1H), 4.94 – 4.88 (m, 1H), 1.39 (d, J = 6.0 Hz, 6H).	DMSO	424.9, 426.9 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
72		HCl	392.4	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.26 (s, 1H), 9.49 (d, J = 1.2 Hz, 1H), 8.93 (d, J = 8.0 Hz, 1H), 8.86 – 8.84 (m, 1H), 8.10 – 8.05 (m, 2H), 7.93 – 7.85 (m, 2H), 7.71 – 7.69 (m, 2H), 7.61 – 7.52 (m, 1H), 4.97 – 4.91 (m, 1H), 1.39 (d, J = 6.0 Hz, 6H).	DMSO	393.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1

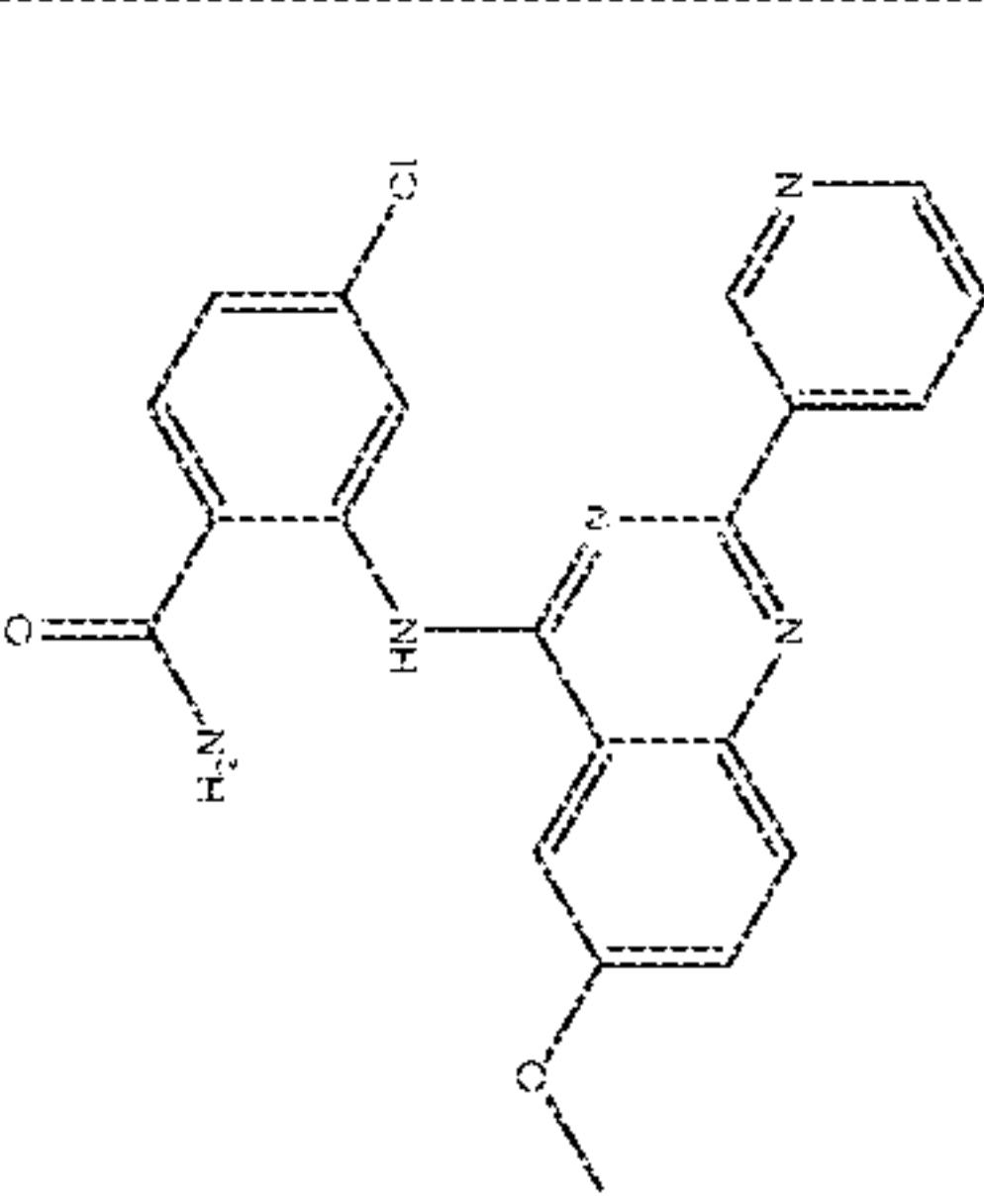
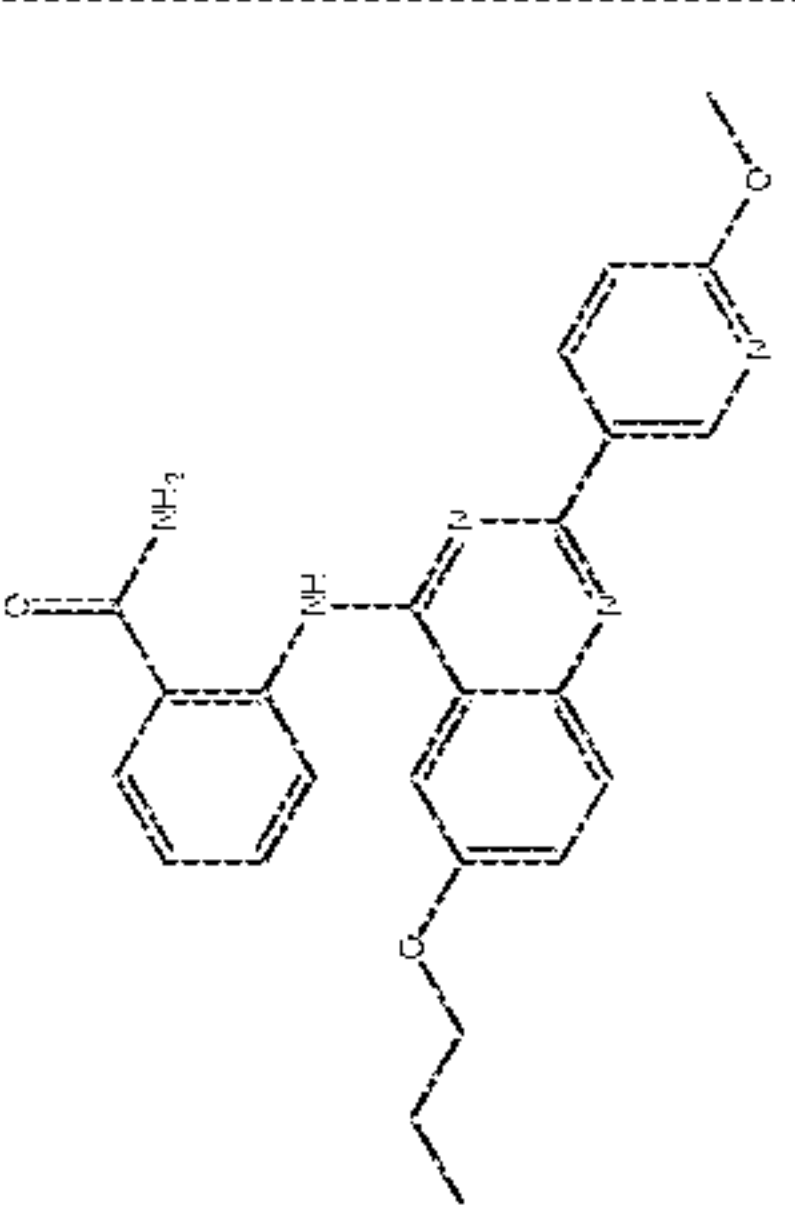
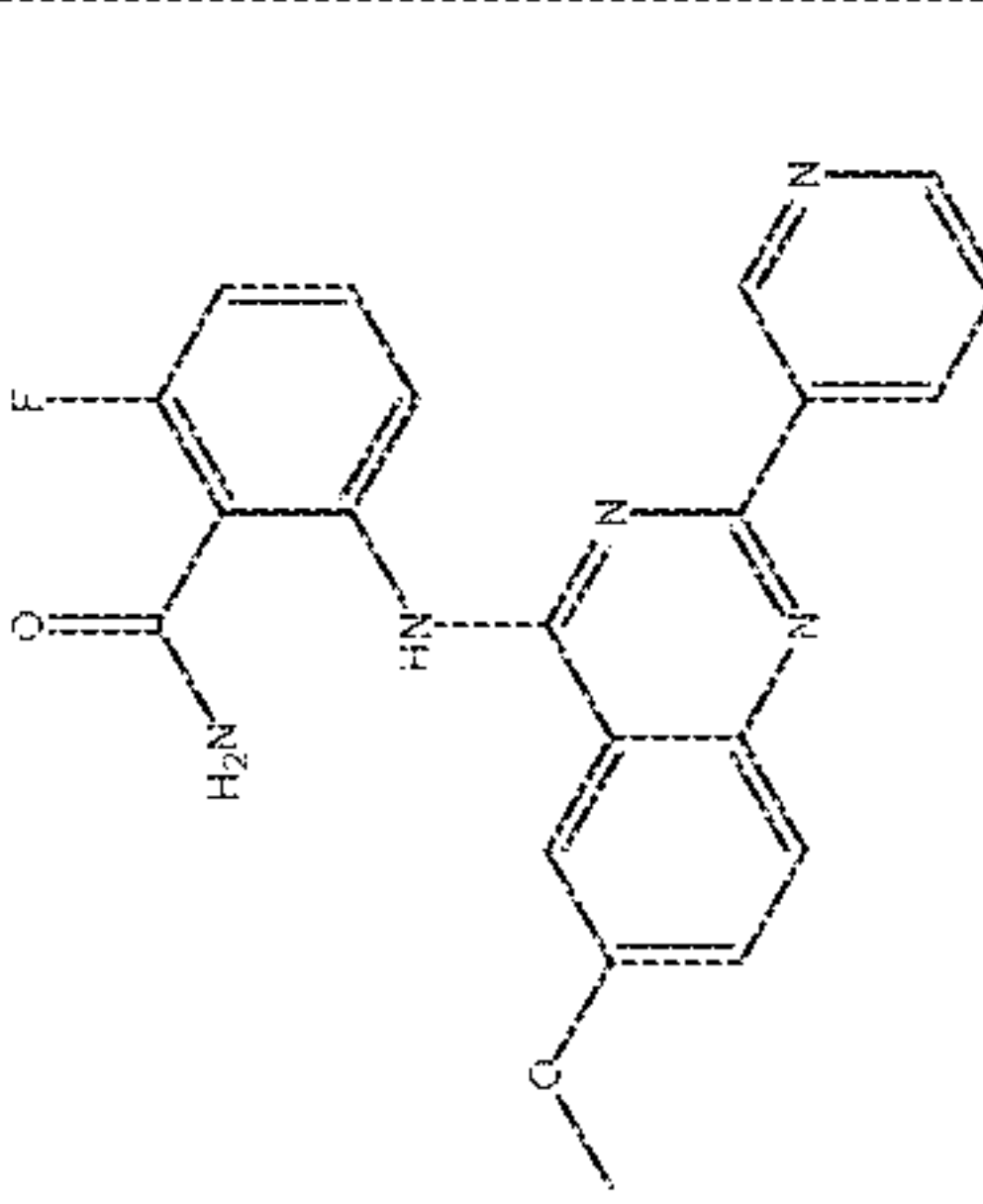
73		HCl	385.42	¹H-NMR (400 MHz, DMSO-d₆): δ 13.03 (s, 1H), 9.53 (d, <i>J</i> = 1.2 Hz, 1H), 9.10 (d, <i>J</i> = 8.4 Hz, 1H), 8.93 – 8.90 (m, 2H), 8.49 (s, 1H), 8.01 – 7.91 (m, 4H), 7.69 (t, <i>J</i> = 7.6 Hz, 1H), 7.59 – 7.54 (m, 2H), 7.24 (t, <i>J</i> = 7.6 Hz, 1H), 4.21 (q, <i>J</i> = 6.8 Hz, 2H), 1.46 (t, <i>J</i> = 6.9 Hz, 3H).	DMSO	386.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
74		HCl	367.4	¹H-NMR (400 MHz, DMSO-d₆): δ 10.35 (s, 1H), 9.49 (s, 1H), 8.95 (d, <i>J</i> = 7.6 Hz, 1H), 8.85 (d, <i>J</i> = 4.8 Hz, 1H), 8.37 (s, 1H), 8.28 (d, <i>J</i> = 7.6 Hz, 1H), 8.08 (s, 1H), 7.94 – 7.85 (m, 2H), 7.73 – 7.60 (m, 3H), 4.28 (q, <i>J</i> = 6.8 Hz, 2H), 1.46 (t, <i>J</i> = 6.8 Hz, 3H).	DMSO	368.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
75		HCl	394.83	¹H-NMR (400 MHz, DMSO-d₆): δ 10.64 (s, 1H), 9.44 (s, 1H), 8.99 (d, <i>J</i> = 8.4 Hz, 1H), 8.91 (d, <i>J</i> = 4.4 Hz, 1H), 8.17 (d, <i>J</i> = 3.2 Hz, 2H), 7.59 – 7.50 (m, 2H), 4.26 (q, <i>J</i> = 6.8 Hz, 2H), 1.44 (t, <i>J</i> = 6.8 Hz, 3H).	DMSO	395.1 397.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
76		HCl	411.28	¹H-NMR (400 MHz, DMSO-d₆): δ 10.48 (s, 1H), 9.47 (s, 1H), 9.02 (d, <i>J</i> = 7.6 Hz, 1H), 8.91 (d, <i>J</i> = 4.4 Hz, 1H), 8.28 (d, <i>J</i> = 1.6 Hz, 1H), 8.13 (s, 1H), 8.01 – 7.91 (m, 3H), 7.72 (d, <i>J</i> = 8.8 Hz, 1H), 7.59 – 7.57 (m, 1H), 4.26 (q, <i>J</i> = 6.8 Hz, 2H), 1.44 (t, <i>J</i> = 6.8 Hz, 3H).	DMSO	411.0 413.0 415.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1

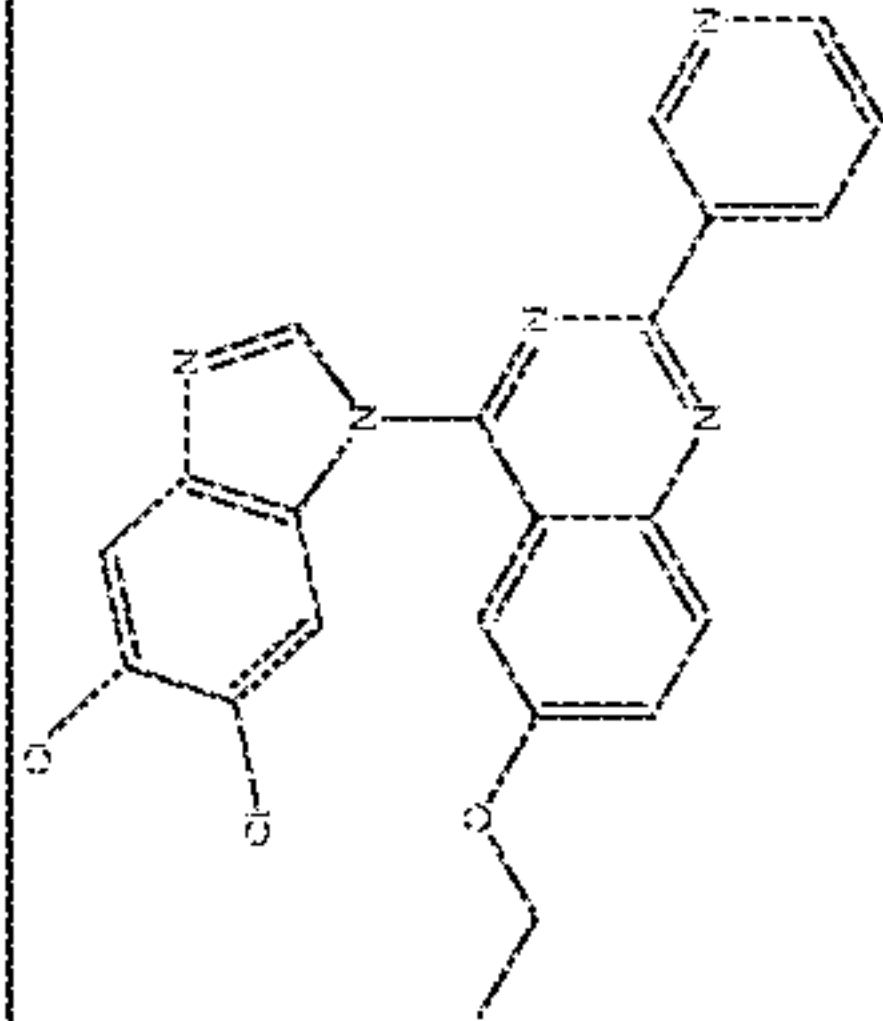
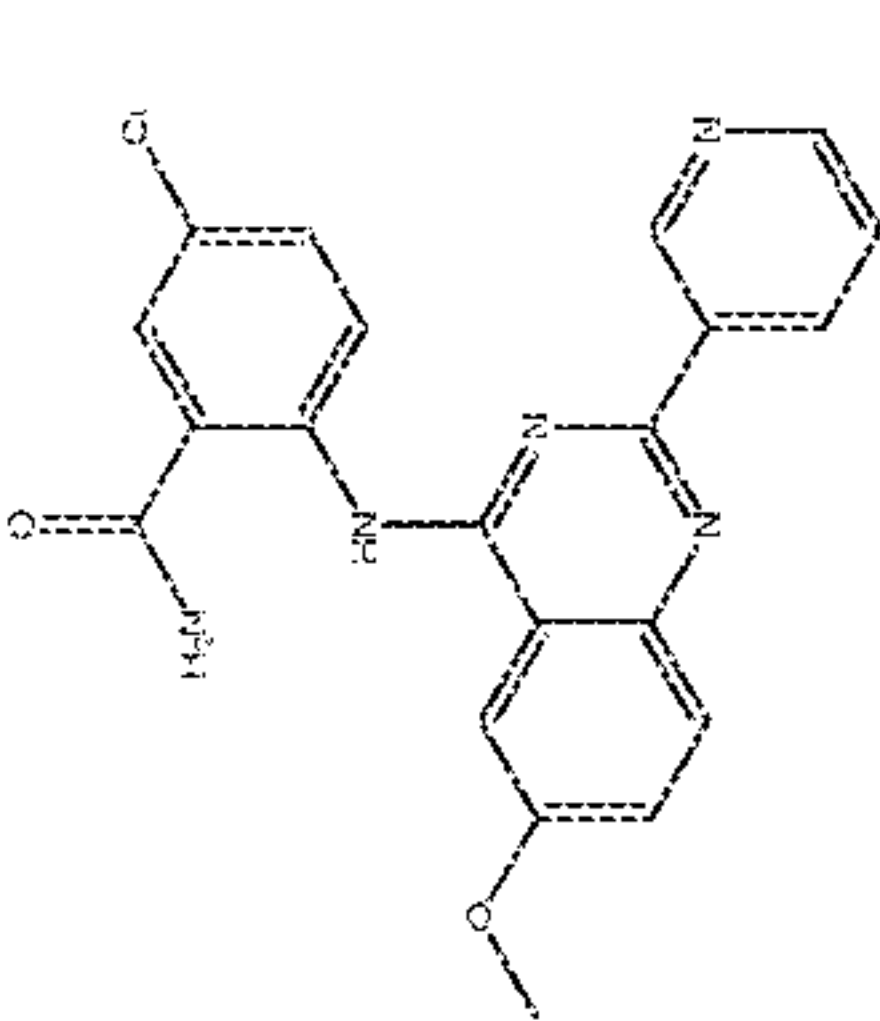
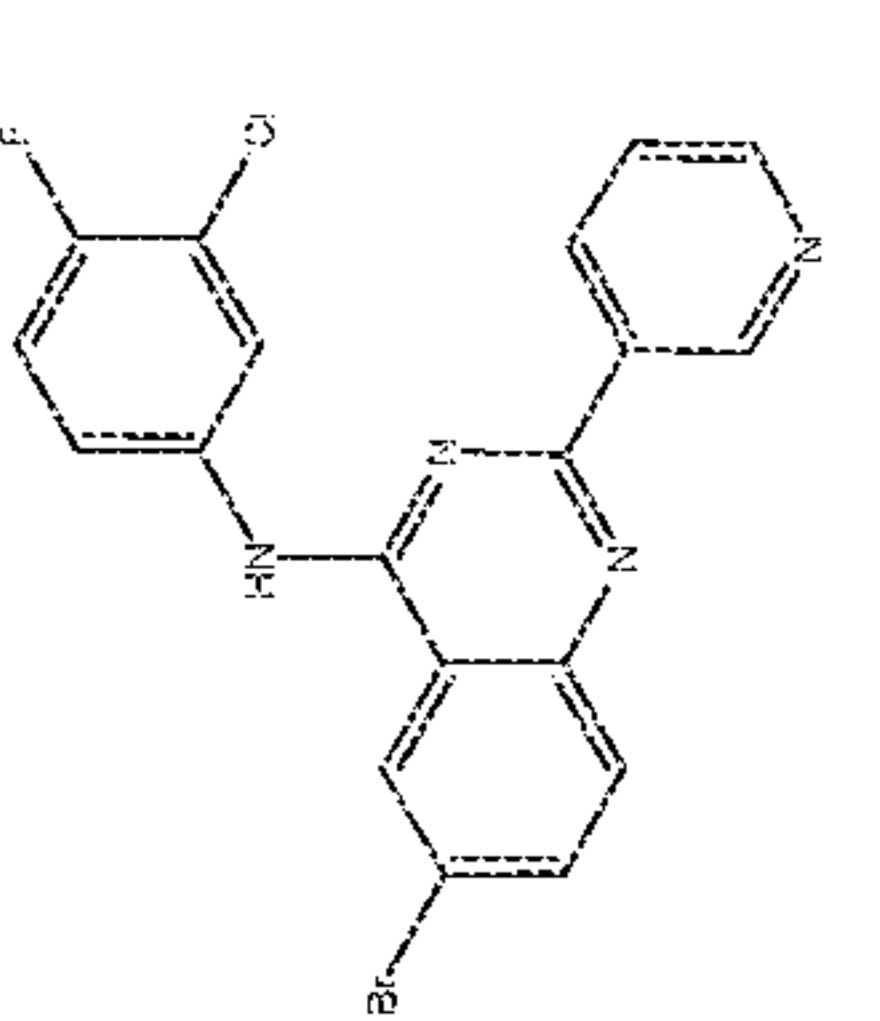
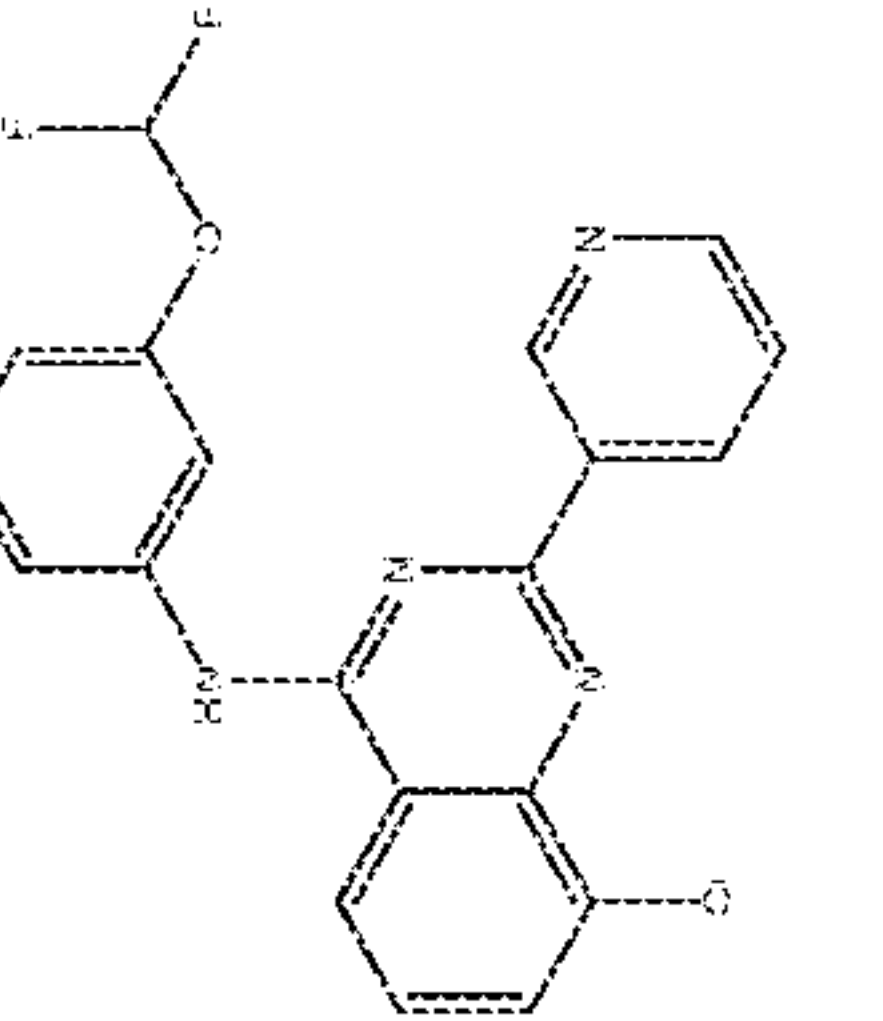
77		HCl	411.28	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.23 (s, 1H), 9.48 (s, 1H), 8.93 (d, J = 8.0 Hz, 1H), 8.85 (d, J = 4.8 Hz, 1H), 8.14 (s, 2H), 8.05 (d, J = 1.6 Hz, 1H), 7.92 – 7.85 (m, 2H), 7.61 (dd, J = 9.1, 1.8 Hz, 1H), 7.41 (s, 1H), 4.26 (q, J = 6.8 Hz, 2H), 1.45 (t, J = 6.8 Hz, 3H).	DMSO	411.0 413.1 415.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
78		HCl	378.37	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.39 (s, 1H), 9.49 (s, 1H), 8.98 (d, J = 8.0 Hz, 1H), 8.88 (d, J = 4.8 Hz, 1H), 8.11 – 8.05 (m, 2H), 7.95 – 7.91 (m, 2H), 7.72 – 7.52 (m, 3H), 4.28 (q, J = 6.8 Hz, 2H), 1.45 (t, J = 6.8 Hz, 3H).	DMSO	379.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
79		HCl	429.47	¹ H-NMR (400 MHz, DMSO-d ₆): δ 12.99 (s, 1H), 9.59 (d, J = 1.6 Hz, 1H), 9.14 (d, J = 7.6 Hz, 1H), 8.75 – 8.69 (m, 2H), 8.48 (s, 1H), 7.99 – 7.96 (m, 2H), 7.90 (d, J = 8.8 Hz, 1H), 7.76 – 7.72 (m, 1H), 7.61 – 7.56 (m, 3H), 7.22 – 7.19 (m, 1H), 4.24 (t, J = 6.0 Hz, 2H), 3.56 (t, J = 6.0 Hz, 2H), 3.28 (s, 3H), 2.11 – 2.04 (m, 2H).	DMSO	430.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
80		HCl	380.80	¹ H-NMR (400 MHz, DMSO-d ₆): δ 11.67 (s, 1H), 9.18 (d, J = 2.0 Hz, 1H), 8.90 (d, J = 8.4 Hz, 1H), 8.66 (dd, J = 8.8, 2.4 Hz, 1H), 8.35 (d, J = 8.4 Hz, 1H), 8.14 – 8.08 (m, 2H), 7.90 – 7.81 (m, 2H), 7.62 (t, J = 9.2 Hz, 1H), 7.09 (d, J = 8.8 Hz, 1H), 3.98 (s, 3H).	DMSO	380.9, 382.9 (M+1)	Method A (TFA)	95	Method C, G1

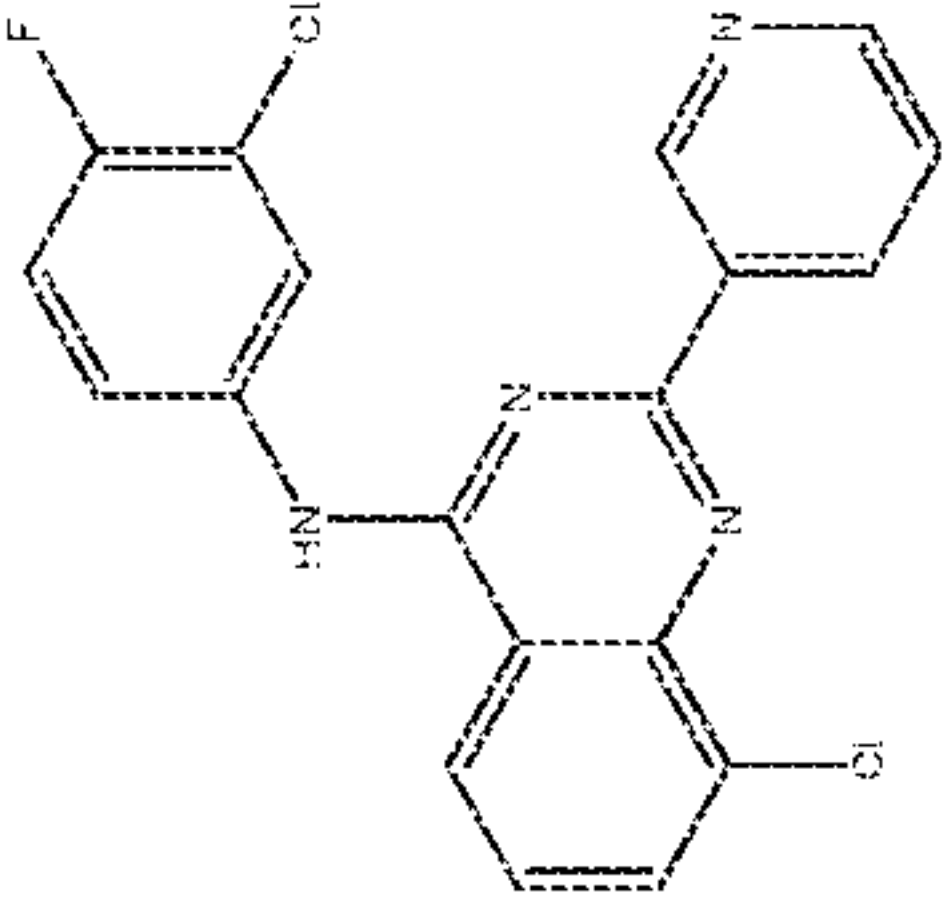
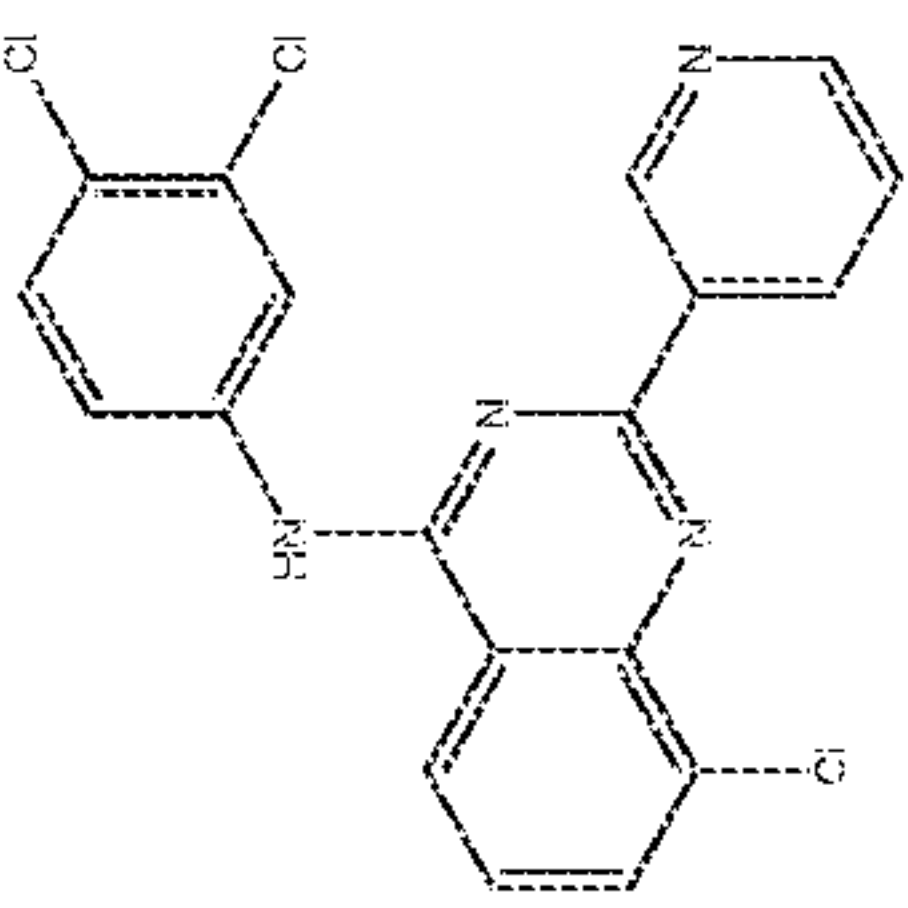
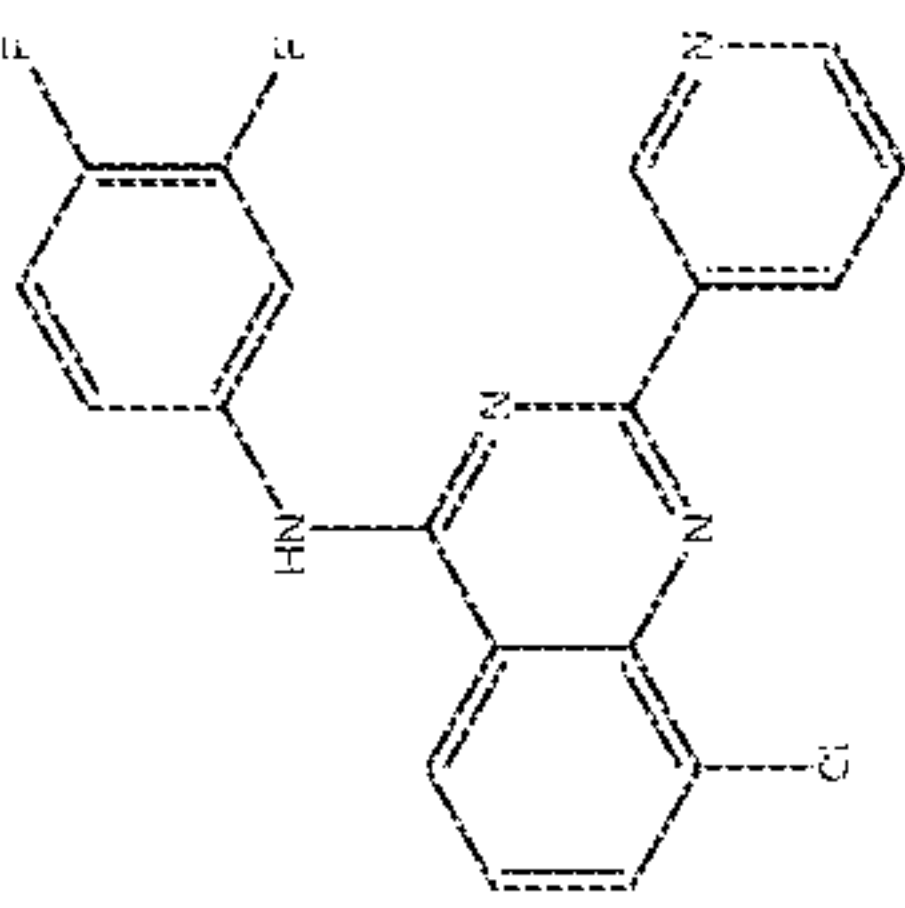
81		HCl	394.79	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.81 (s, 1H), 9.49 (d, J = 1.2 Hz, 1H), 9.28 (d, J = 0.8 Hz, 1H), 9.15 (d, J = 8.0 Hz, 1H), 9.02 (d, J = 5.2 Hz, 1H), 8.37 – 8.34 (m, 1H), 8.12 – 8.09 (m, 2H), 8.01 (d, J = 8.4 Hz, 1H), 7.95 – 7.91 (m, 1H), 7.53 (t, J = 9.0 Hz, 1H).	DMSO	395.0, 397.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
82			385.39	¹ H-NMR (400 MHz, DMSO-d ₆): δ 9.63 (d, J = 1.6 Hz, 1H), 9.13 (s, 1H), 8.80 – 8.75 (m, 2H), 8.21 (d, J = 9.2 Hz, 1H), 7.97 – 7.94 (m, 1H), 7.82 (dd, J = 9.2, 2.8 Hz, 1H), 7.73 (dd, J = 9.2, 2.4 Hz, 1H), 7.64 – 7.61 (m, 1H), 7.38 – 7.32 (m, 2H), 4.16 (q, J = 6.8 Hz, 2H), 3.19 (t, J = 7.0 Hz, 3H).	DMSO	386.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G10
83		HCl	426.39	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.43 (s, 1H), 9.49 (d, J = 1.6 Hz, 1H), 8.99 (d, J = 8.0 Hz, 1H), 8.89 (dd, J = 9.2, 1.6 Hz, 1H), 8.13 (d, J = 2.4 Hz, 1H), 8.05 (s, 1H), 7.97 – 7.89 (m, 3H), 7.65 – 7.61 (m, 2H), 7.23 (d, J = 8.4 Hz, 1H), 4.29 (q, J = 6.8 Hz, 2H), 1.46 (t, J = 7.2 Hz, 3H).	DMSO	427.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
84			426.47	¹ H-NMR (400 MHz, DMSO-d ₆): δ 12.00 (s, 1H), 9.55 (s, 1H), 9.12 (d, J = 8.0 Hz, 1H), 8.94 (d, J = 4.8 Hz, 1H), 8.84 (d, J = 8.4 Hz, 1H), 8.11 – 8.09 (m, 1H), 8.02 – 7.99 (m, 1H), 7.96 (d, J = 9.2 Hz, 1H), 7.82 – 7.11 (m, 1H), 7.65 (s, 1H), 7.62 – 7.59 (m, 1H), 7.30 (t, J = 7.2 Hz, 1H), 5.06 – 5.03 (m, 1H), 2.15 – 2.09 (m, 2H), 1.86 – 1.74 (m, 4H), 1.68 – 1.65 (m, 2H).	DMSO	427.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1

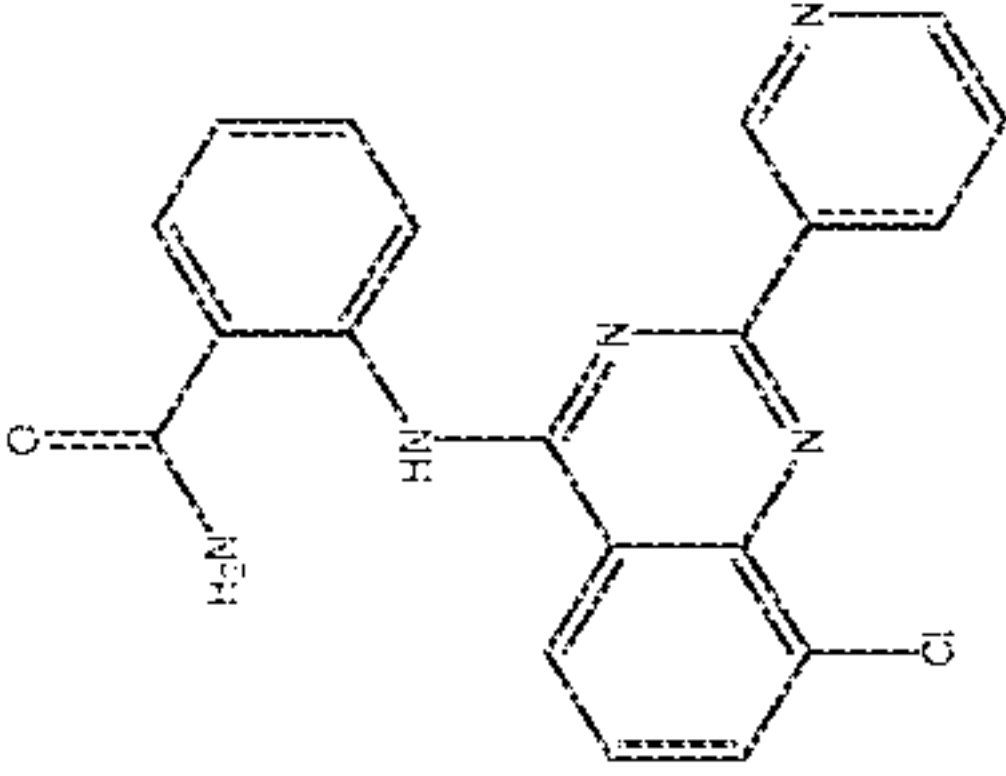
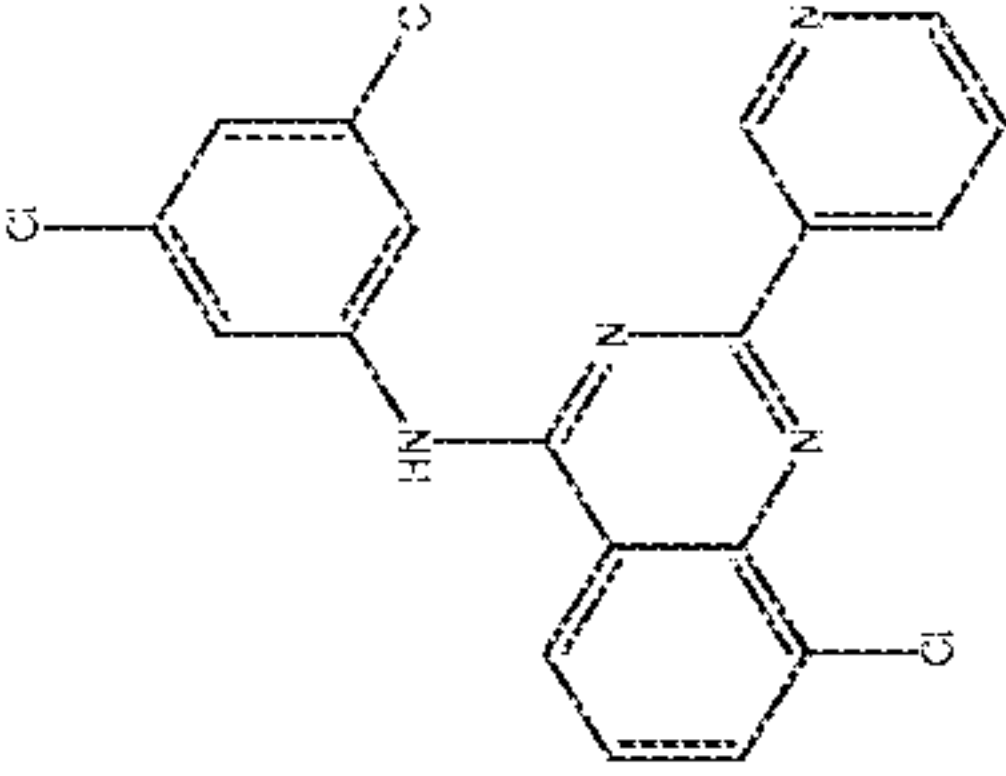
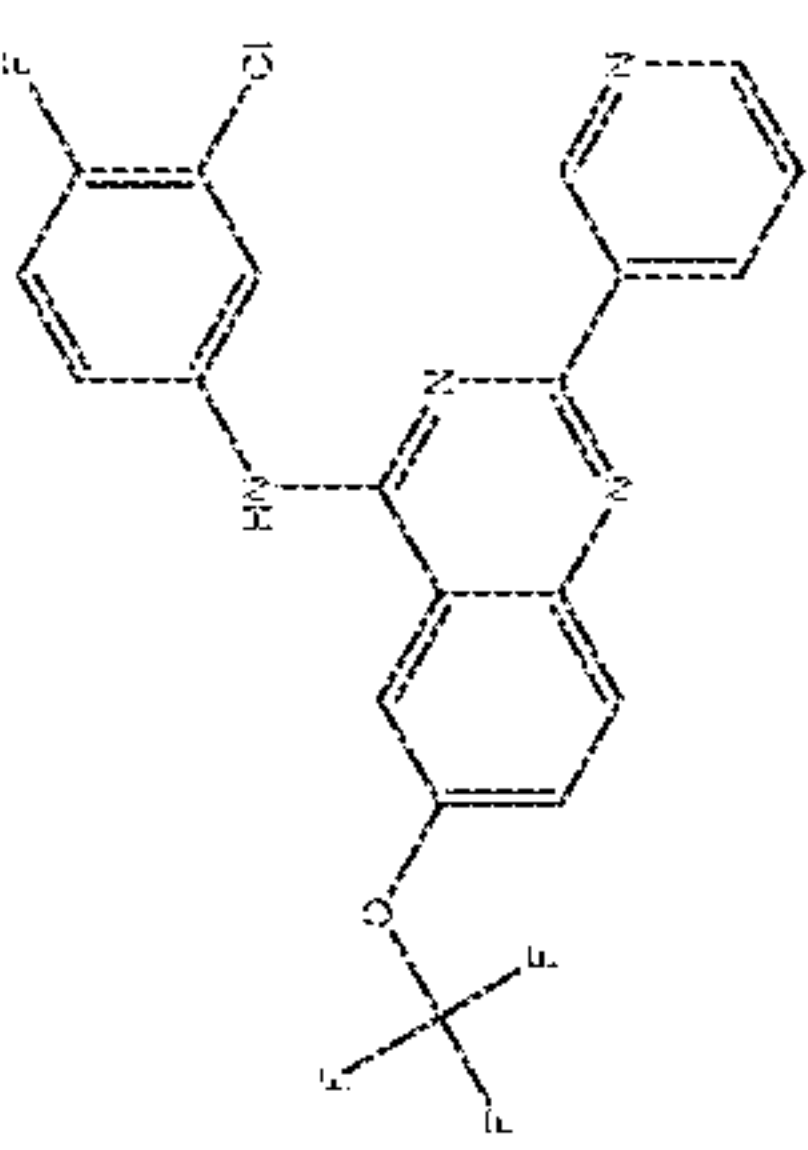
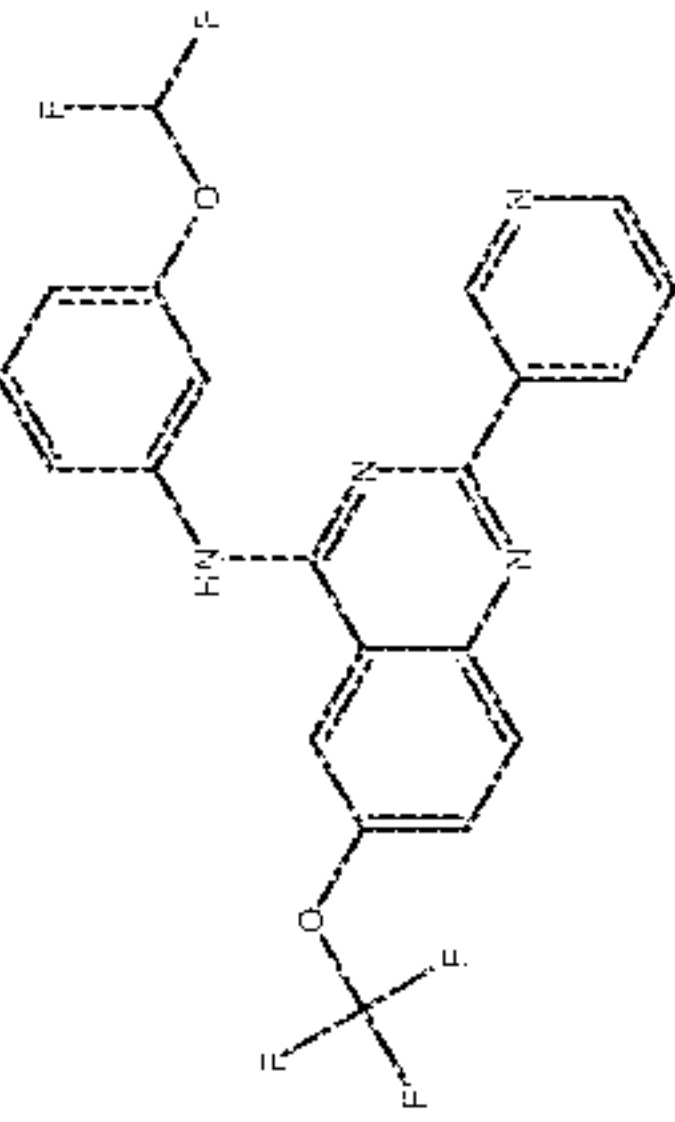
65			375.81	¹H-NMR (400 MHz, DMSO-d₆): δ 13.09 (s, 1H), 9.58 (s, 1H), 9.12 (d, J = 8.4 Hz, 1H), 8.94 (d, J = 4.4 Hz, 1H), 8.88 (d, J = 8.4 Hz, 1H), 8.50 (s, 1H), 8.25 (s, 1H), 8.01 – 7.96 (m, 5H), 7.71 (t, J = 8.0 Hz, 1H), 7.27 (t, J = 8.0 Hz, 1H).	DMSO	376.0, 378.0 (M+1) 397.9 (M+29) 188.4 (M/2+1)	Method A (TFA)	95	Method C, G1
66			398.79	¹H-NMR (400 MHz, DMSO-d₆): δ 10.10 (s, 1H), 9.54 (s, 1H), 8.78 (s, 1H), 8.71 – 8.67 (m, 2H), 7.96 (s, 1H), 7.91 (d, J = 8.0 Hz, 2H), 7.82 (d, J = 8.0 Hz, 1H), 7.56 – 7.51 (m, 2H), 7.30 (t, J = 74.0 Hz, 1H), 7.01 (dd, J = 2.0, 8.0 Hz, 1H).	DMSO	399.0, 401.0 (M+1) 199.9, 200.8 (M/2+1)	Method A (TFA)	95	Method C, G1
67			443.7	¹H-NMR (400 MHz, DMSO-d₆): δ 10.09 (s, 1H), 9.39 (s, 1H), 8.93 (d, J = 8.4 Hz, 1H), 8.90 (d, J = 5.6 Hz, 1H), 8.62 (d, J = 1.6 Hz, 1H), 8.11 (dd, J = 6.8, 2.4 Hz, 1H), 7.95 – 7.91 (m, 1H), 7.89 – 7.85 (m, 1H), 7.80 (s, 1H), 7.45 (t, J = 8.8 Hz, 1H), 2.66 (s, 3H).	DMSO	443.0, 445.0, 447.0 (M+1)	Method B (NH ₄ HCO ₃)	98	Method C, G1

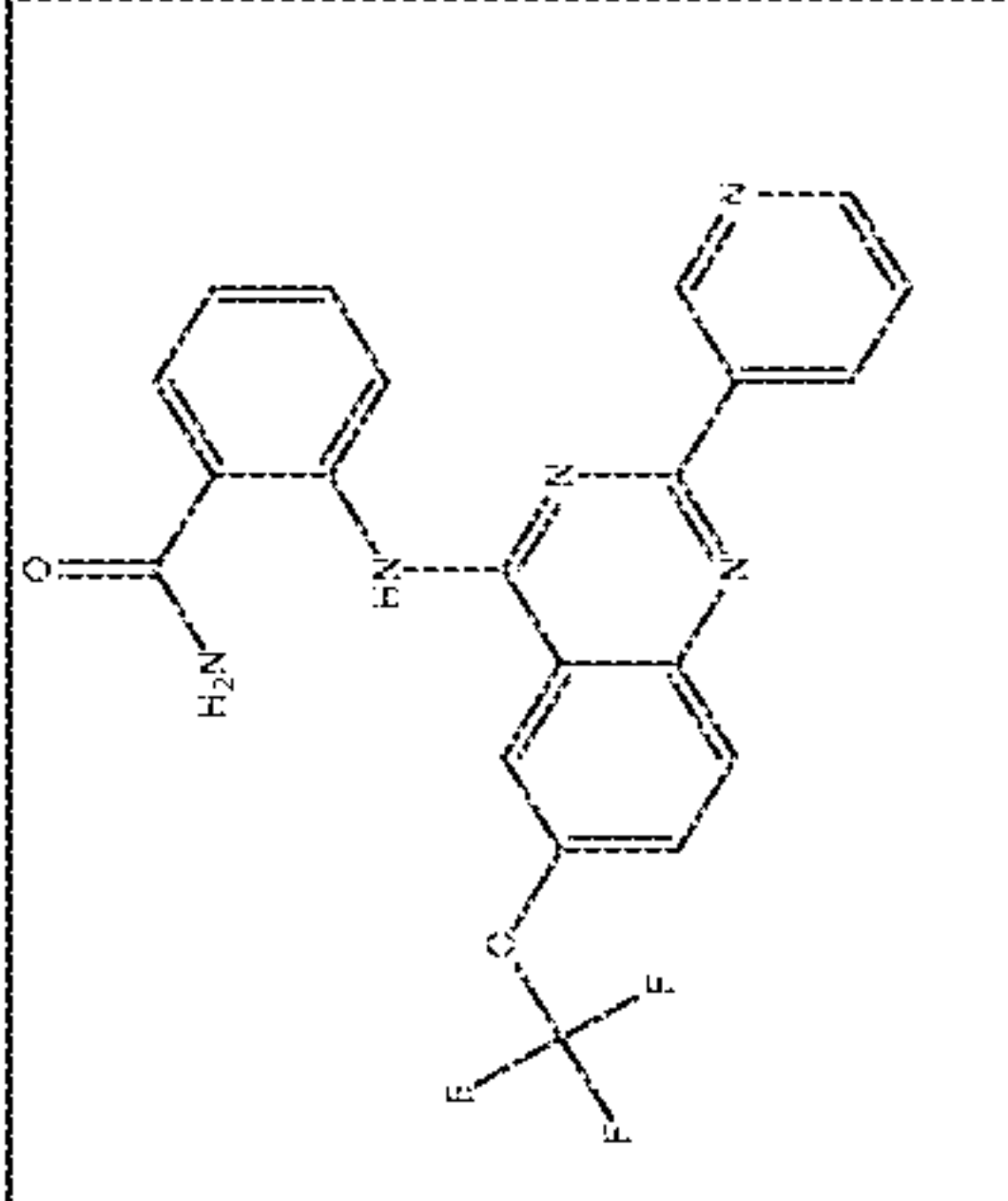
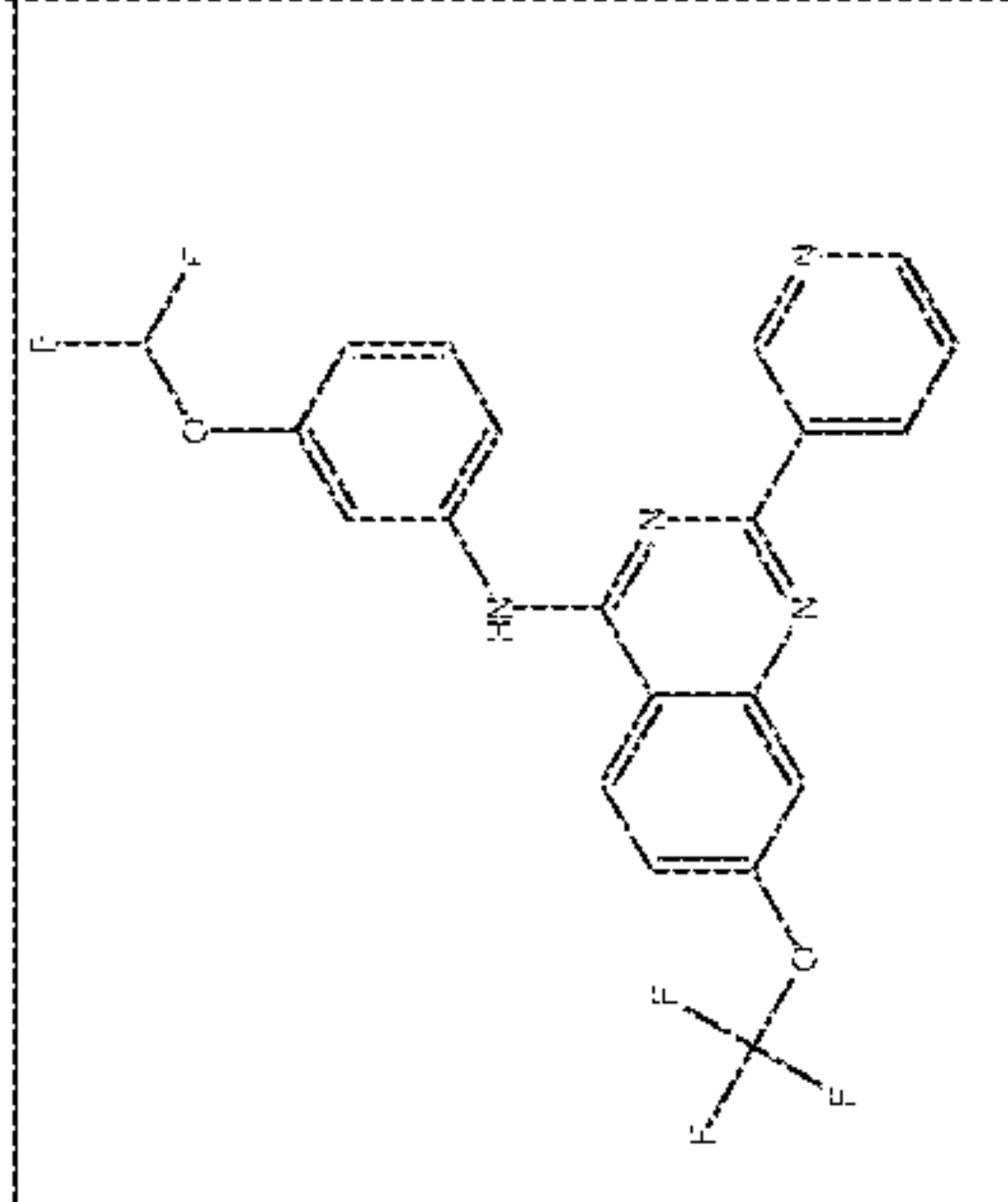
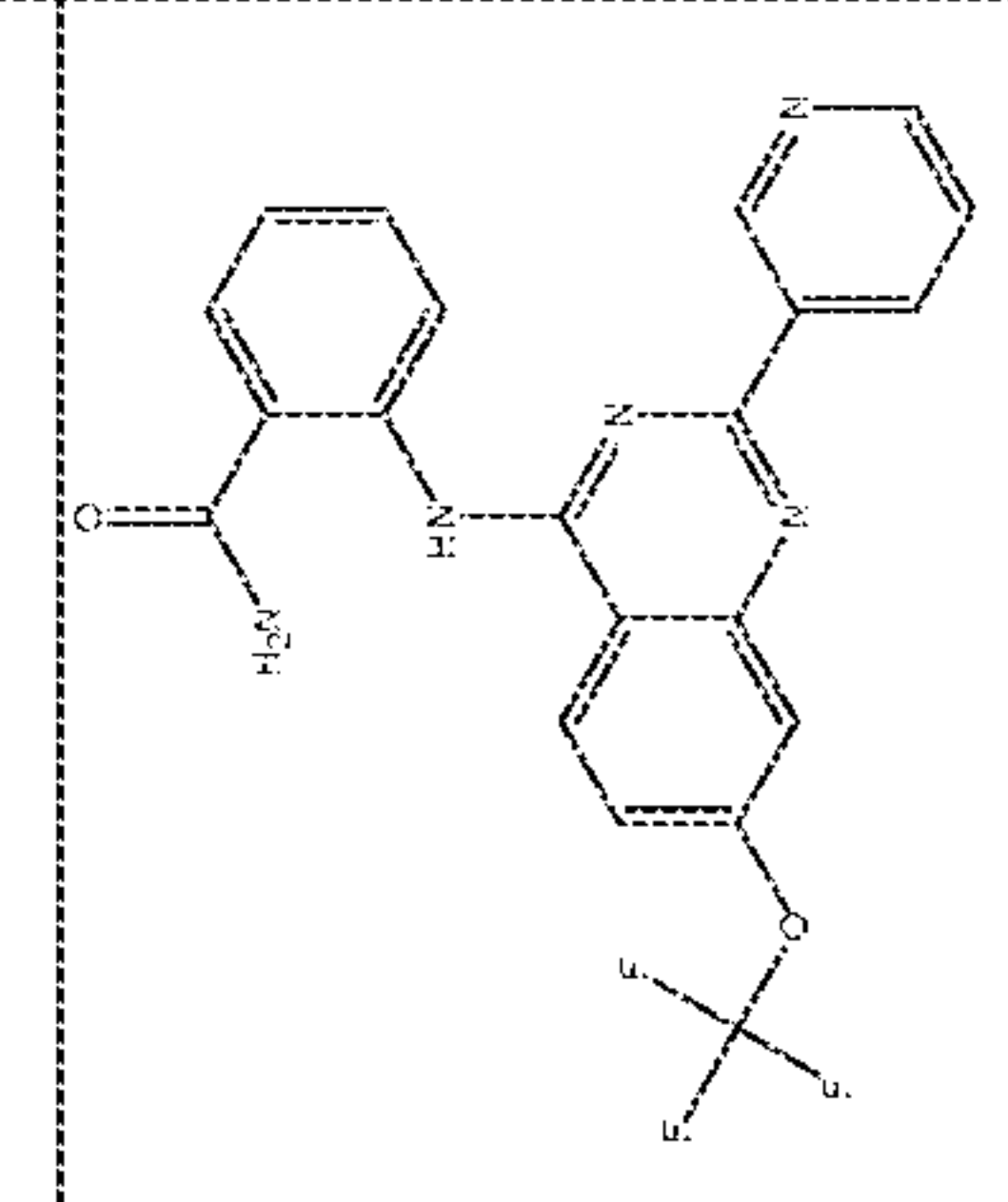
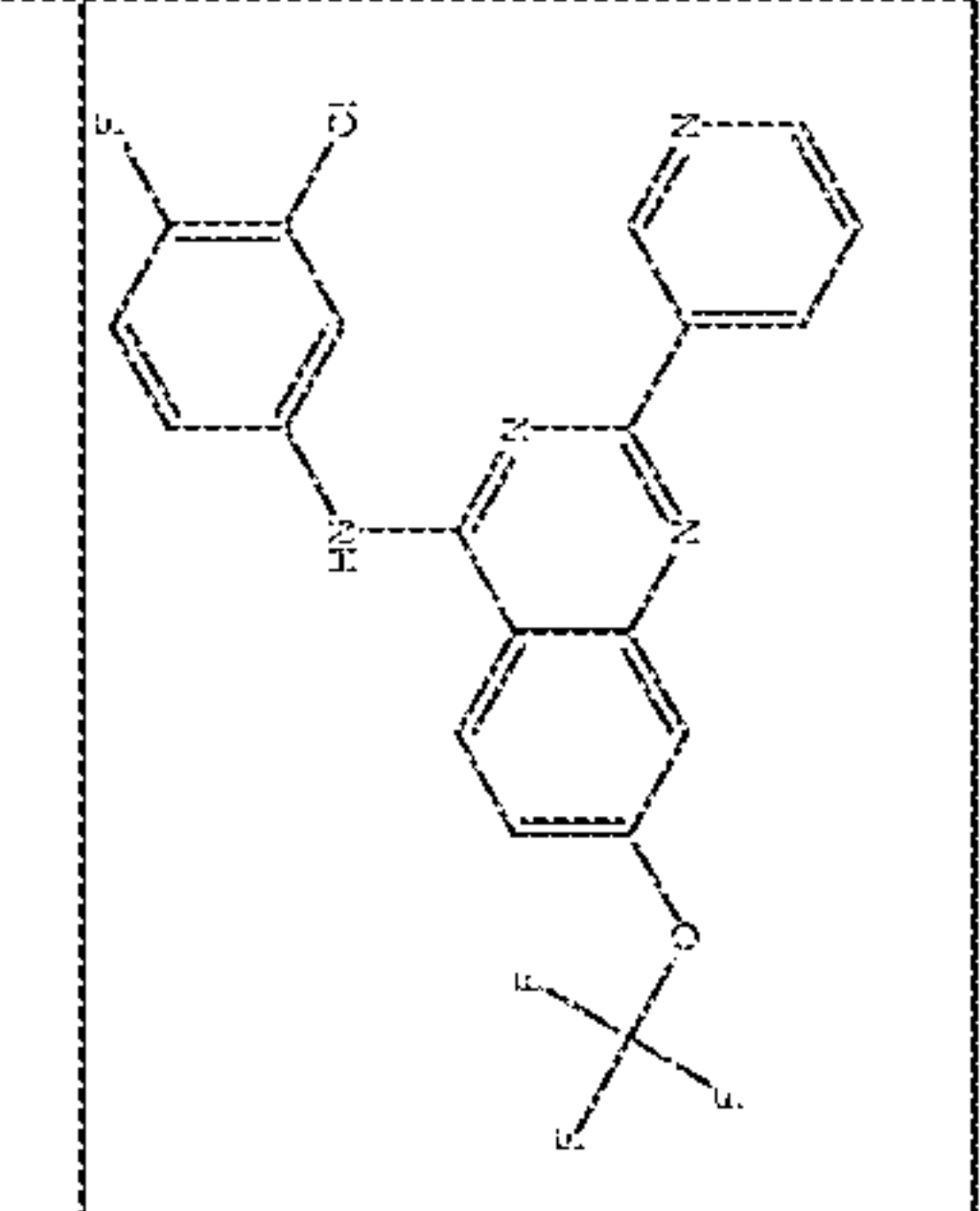
88			401.42	¹ H-NMR (400 MHz, DMSO-d ₆): δ 13.19 (s, 1H), 9.43 (d, J = 8.0 Hz, 1H), 8.53 (s, 1H), 8.31 (dd, J = 4.8, 1.6 Hz, 1H), 8.26 (dd, J = 1.6, 7.2 Hz, 1H), 8.03 (s, 1H), 7.96 – 7.89 (m, 1H), 7.86 (d, J = 9.2 Hz, 1H), 7.65 – 7.54 (m, 3H), 7.18 – 7.12 (m, 2H), 4.02 (s, 3H), 3.98 (s, 3H).	DMSO	402.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
89			410.83	¹ H-NMR (400 MHz, DMSO-d ₆): δ 9.79 (s, 1H), 8.52 (dd, J = 2.4, 7.2 Hz, 1H), 8.26 (dd, J = 5.6, 2.4 Hz, 1H), 8.12 (dd, J = 2.4, 5.2 Hz, 1H), 7.98 – 7.94 (m, 2H), 7.82 (d, J = 9.2 Hz, 1H), 7.56 (dd, J = 9.2, 2.8 Hz, 1H), 7.47 (t, J = 9.2 Hz, 1H), 7.14 – 7.11 (m, 1H), 4.00 (s, 3H), 3.99 (s, 3H).	DMSO	411.1, 413.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
90			415.44	¹ H-NMR (400 MHz, DMSO-d ₆): δ 13.03 (s, 1H), 9.21 (d, J = 2.2 Hz, 1H), 9.16 (d, J = 7.9 Hz, 1H), 8.67 (dd, J = 8.7, 2.4 Hz, 1H), 8.50 (s, 1H), 8.02 (s, 1H), 7.99 – 7.93 (m, 1H), 7.64 (d, J = 8.9 Hz, 1H), 7.78 – 7.72 (m, 1H), 7.56 (dd, J = 11.2, 2.1 Hz, 2H), 7.19 (t, J = 7.2 Hz, 1H), 6.99 (d, J = 8.8 Hz, 1H), 4.24 (q, J = 6.9 Hz, 2H), 3.96 (s, 3H), 1.46 (t, J = 6.9 Hz, 3H).	DMSO	416.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method D, G1

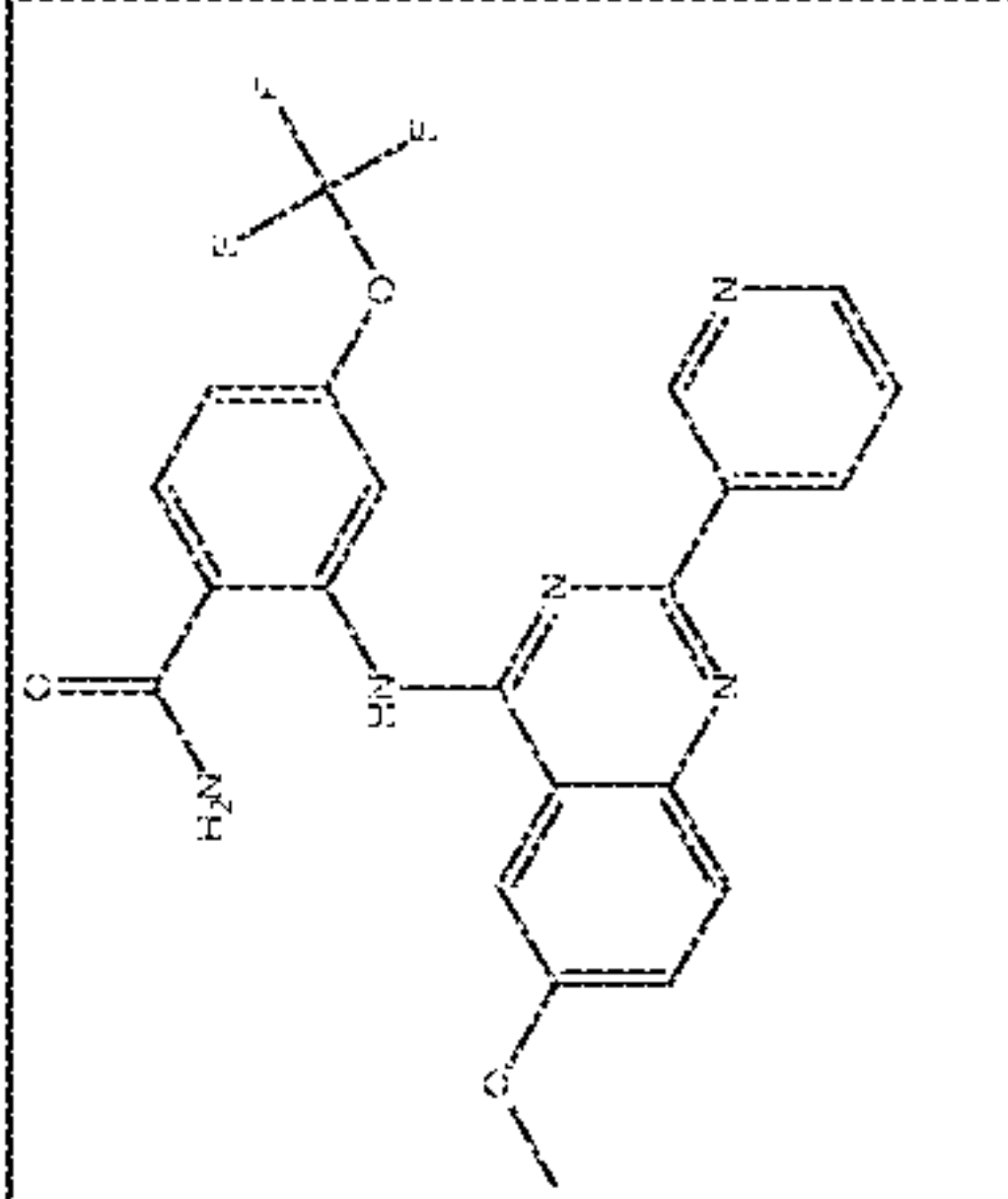
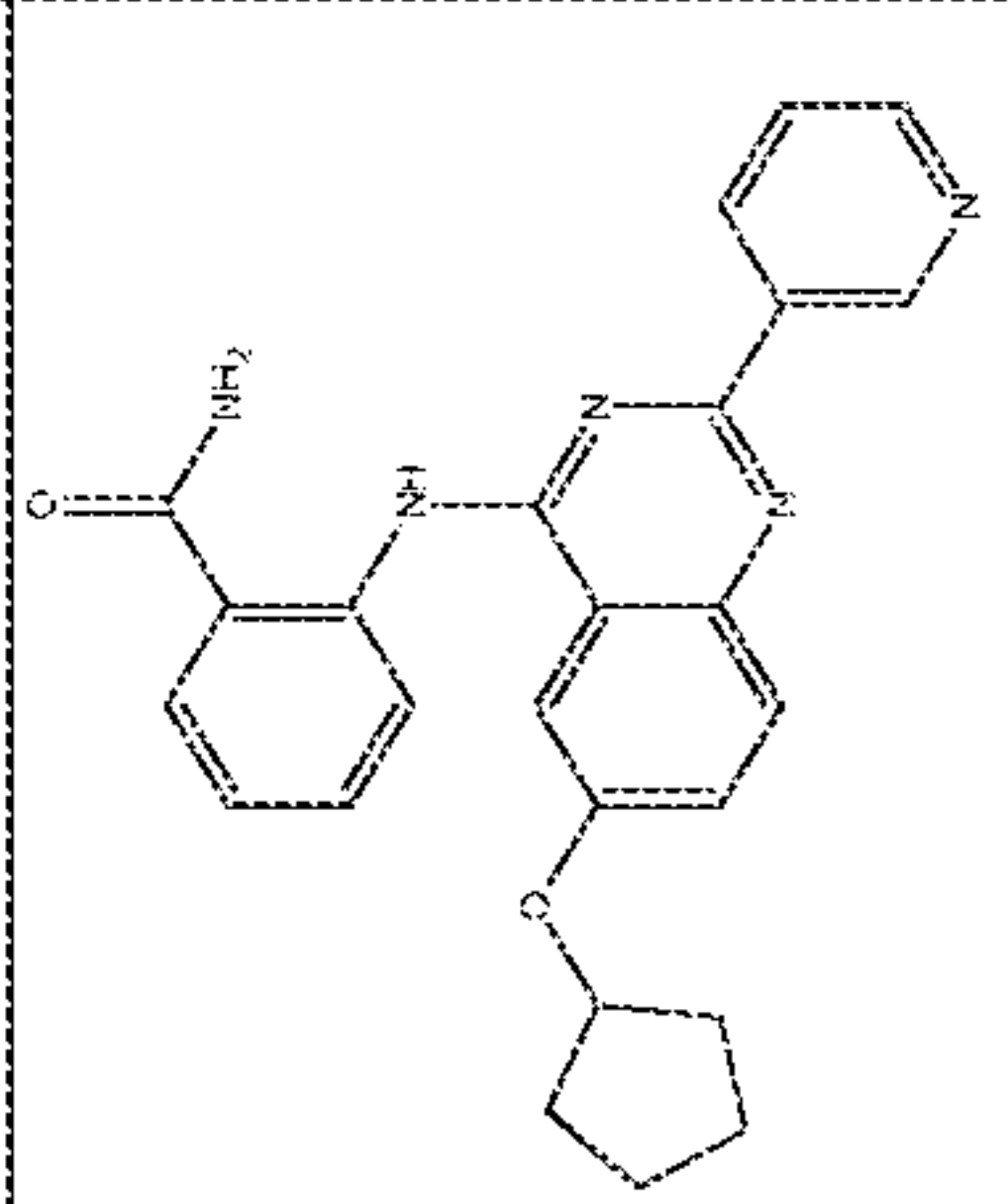
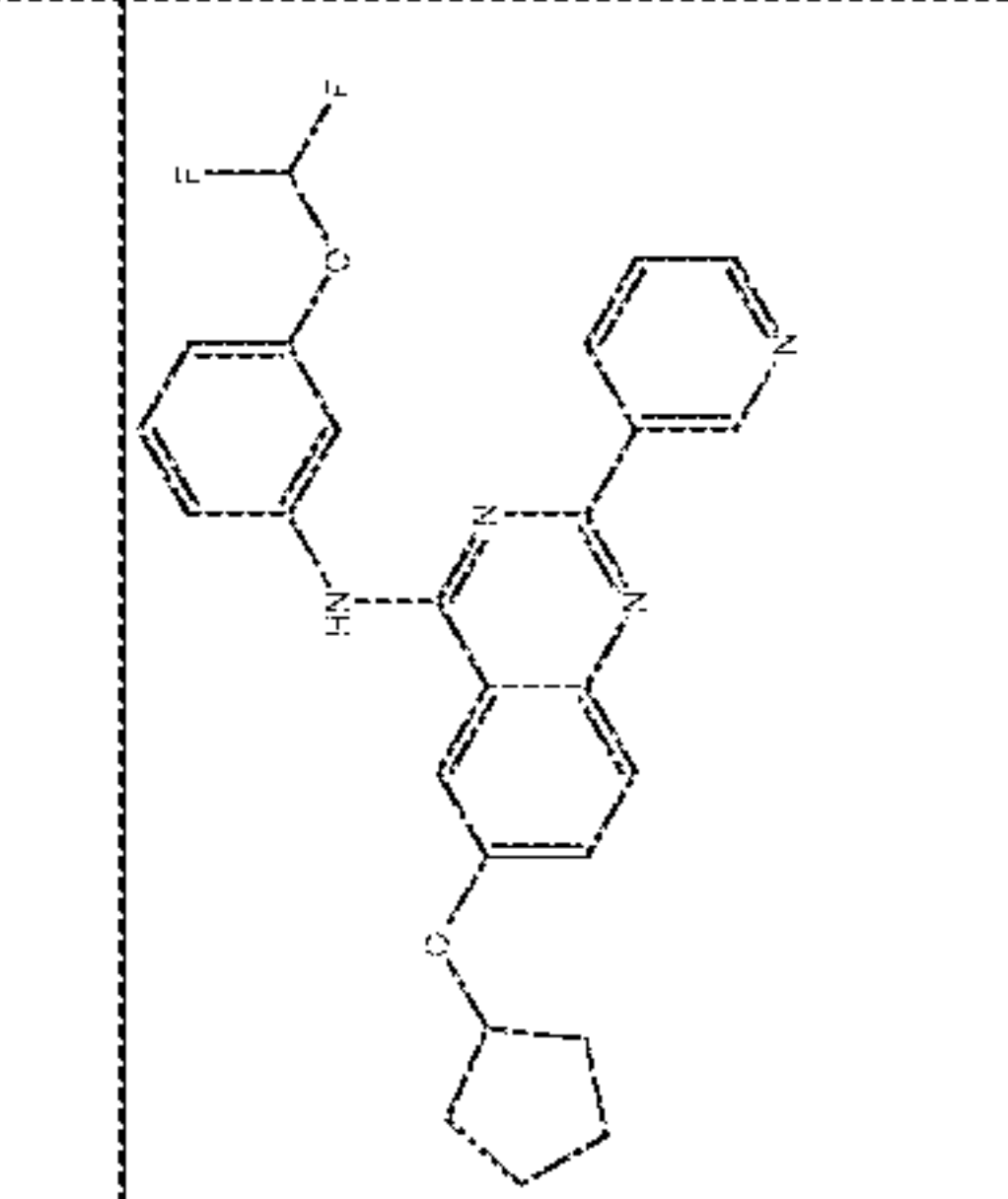
91		HCl	405.84	¹ H-NMR (400 MHz, DMSO-d ₆): δ 13.28 (s, 1H), 9.55 (d, J = 1.7 Hz, 1H), 9.31 (d, J = 2.1 Hz, 1H), 8.90 (d, J = 8.3 Hz, 1H), 8.63 (dd, J = 5.0, 1.4 Hz, 1H), 8.58 (s, 1H), 8.12 (s, 1H), 8.01 (d, J = 8.6 Hz, 1H), 7.93 (d, J = 9.1 Hz, 1H), 7.82 (dd, J = 7.9, 5.0 Hz, 1H), 7.63 (dd, J = 9.1, 2.6 Hz, 1H), 7.54 (d, J = 2.5 Hz, 1H), 7.30 (dd, J = 8.5, 2.2 Hz, 1H), 3.98 (s, 3H).	DMSO	406.0, 408.0 (M+1)	Method A (TFA)	95	Method C, G2
92			429.47	¹ H-NMR (400 MHz, DMSO-d ₆): δ 12.99 (s, 1H), 9.21 (d, J = 2.0 Hz, 1H), 9.14 (d, J = 8.4 Hz, 1H), 8.67 (dd, J = 8.7, 2.3 Hz, 1H), 8.49 (s, 1H), 8.05 – 7.90 (m, 2H), 7.85 (d, J = 9.0 Hz, 1H), 7.75 (t, J = 7.2 Hz, 1H), 7.67 – 7.47 (m, 2H), 7.20 (t, J = 7.5 Hz, 1H), 6.99 (d, J = 8.8 Hz, 1H), 4.15 (t, J = 6.3 Hz, 2H), 3.96 (s, 3H), 1.07 (t, J = 7.4 Hz, 3H), 1.86 (dd, J = 14.0, 6.7 Hz, 2H).	DMSO	430.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method D, G1
93		HCl	389.36	¹ H-NMR (400 MHz, DMSO-d ₆): δ 11.34 (s, 1H), 9.52 (d, J = 1.7 Hz, 1H), 8.99 (d, J = 7.8 Hz, 1H), 8.85 (dd, J = 5.2, 1.3 Hz, 1H), 8.22 (d, J = 8.1 Hz, 1H), 8.11 – 8.00 (m, 2H), 7.95 (d, J = 9.1 Hz, 1H), 7.87 (dd, J = 7.9, 5.3 Hz, 1H), 7.77 – 7.59 (m, 3H), 7.27 – 7.16 (m, 1H), 3.99 (s, 3H).	DMSO	390.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G3

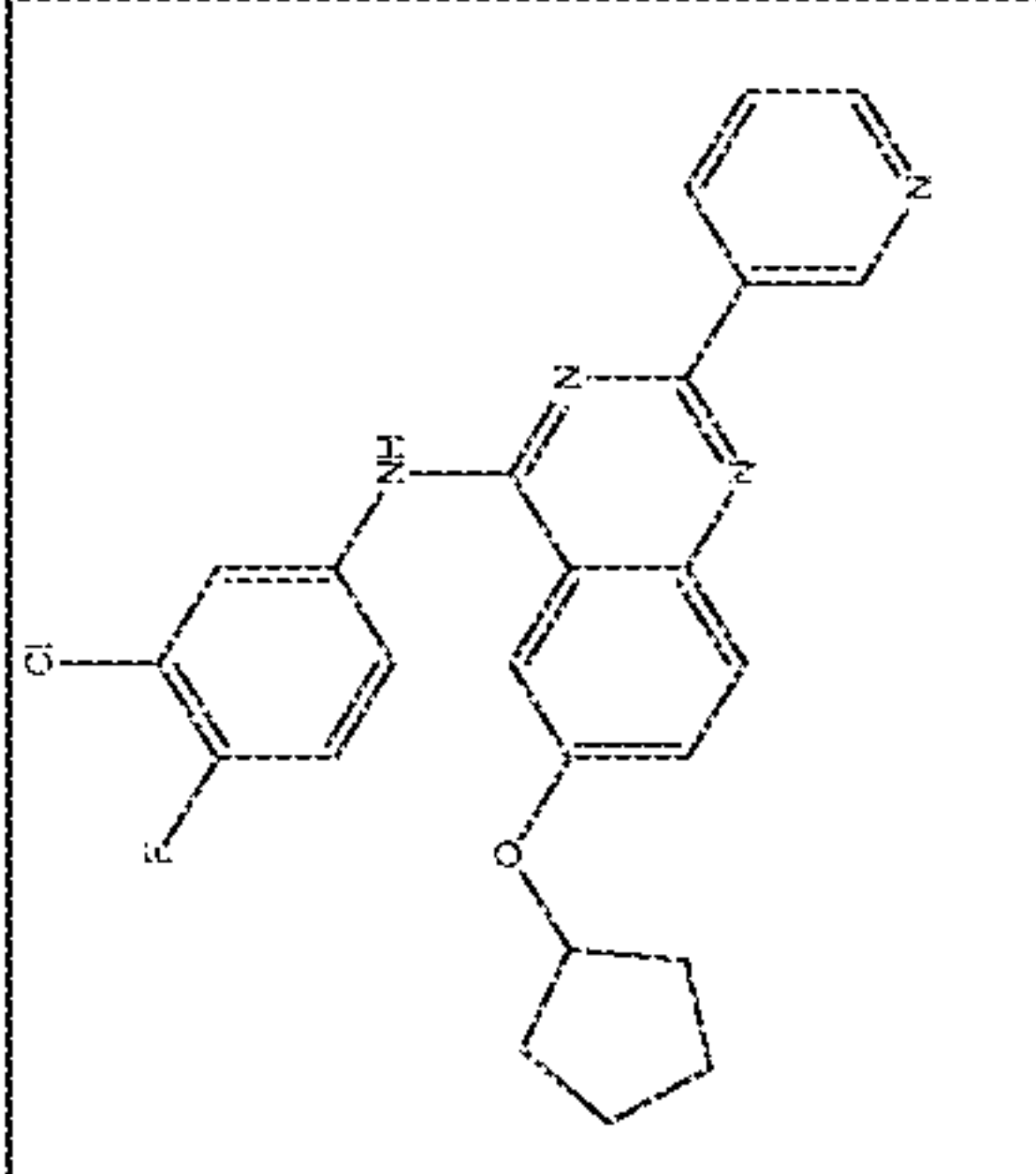
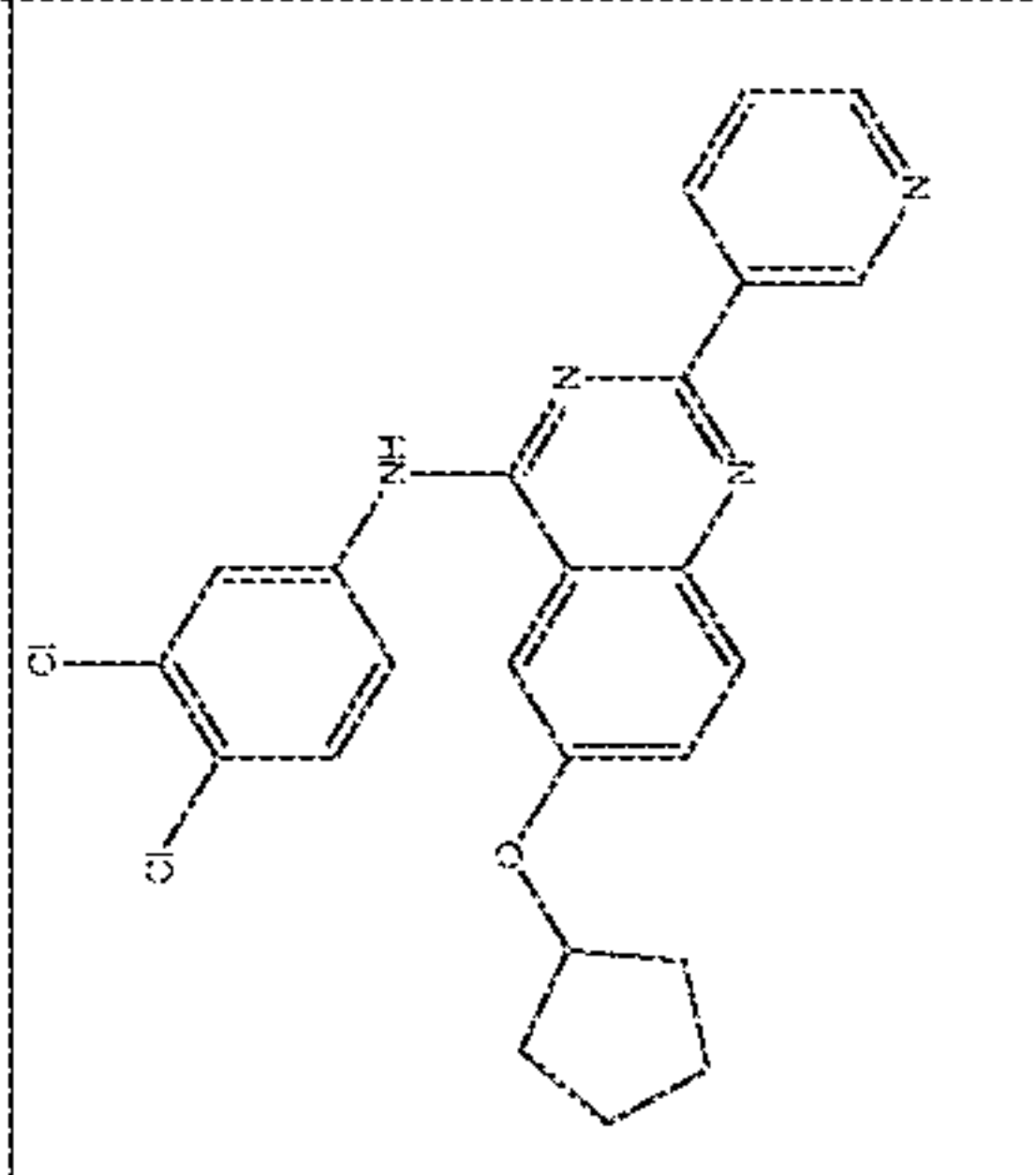
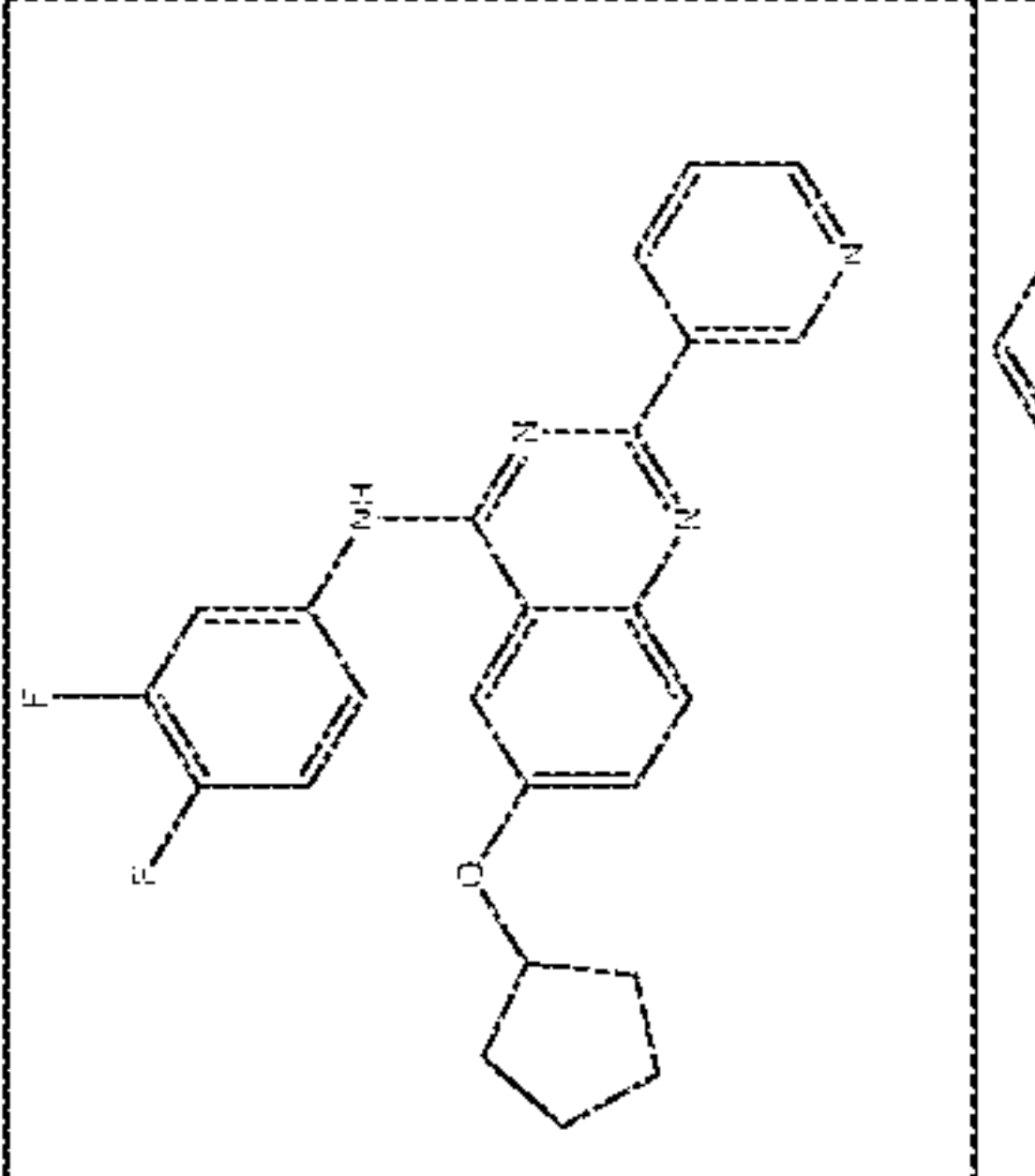
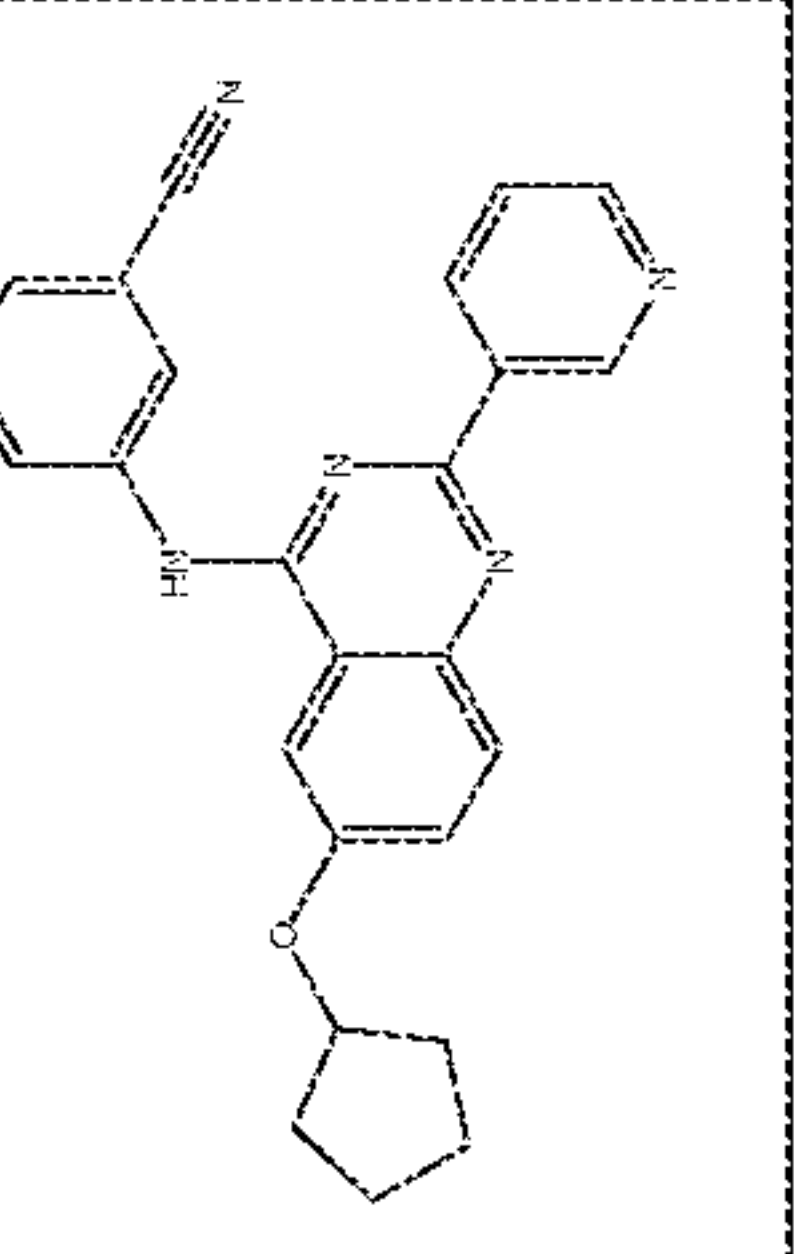
94			436.29	¹H-NMR (400 MHz, DMSO-d₆): δ 9.62 (s, 1H), 9.17 (s, 1H), 8.77 (d, J = 8.0 Hz, 1H), 8.76 (d, J = 4.0 Hz, 1H), 8.26 – 8.07 (m, 3H), 7.83 (dd, J = 9.1, 2.5 Hz, 1H), 7.63 (dd, J = 7.5, 5.0 Hz, 1H), 7.36 (d, J = 2.4 Hz, 1H), 4.18 (q, J = 6.8 Hz, 2H), 1.39 (t, J = 6.9 Hz, 3H).	DMSO	436.1, 438.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G10
95			405.84	¹H-NMR (400 MHz, DMSO-d₆): δ 12.93 (s, 1H), 9.58 (s, 1H), 9.16 (d, J = 9.0 Hz, 1H), 8.70 – 8.74 (m, 2H), 8.59 (s, 1H), 8.13 (s, 1H), 8.05 (d, J = 2.9 Hz, 1H), 7.92 (d, J = 9.1 Hz, 1H), 7.82 (dd, J = 8.9, 2.1 Hz, 1H), 7.65 – 7.49 (m, 3H), 3.98 (s, 3H).	DMSO	406.1, 408.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C,G3
96			429.67	¹H-NMR (400 MHz, DMSO-d₆): δ 10.45 (s, 1H), 9.47 (s, 1H), 9.02 – 8.92 (m, 3H), 8.18 – 8.16 (m, 1H), 8.06 – 8.04 (m, 1H), 7.96 – 7.84 (m, 3H), 7.54 – 7.50 (m, 1H).	DMSO	429.9, 431.0, 433.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C,G1
97			398.79	¹H-NMR (400 MHz, DMSO-d₆): δ 10.25 (s, 1H), 9.58 (s, 1H), 8.85 – 8.76 (m, 2H), 8.60 (d, J = 7.2 Hz, 1H), 8.12 – 8.10 (m, 1H), 7.92 (s, 1H), 7.83 – 7.80 (m, 1H), 7.71 – 7.64 (m, 2H), 7.56 – 7.52 (m, 1H), 7.30 (t, J = 74.0 Hz, 1H), 7.05 – 7.03 (m, 1H).	DMSO	399.0, 401.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C,G1

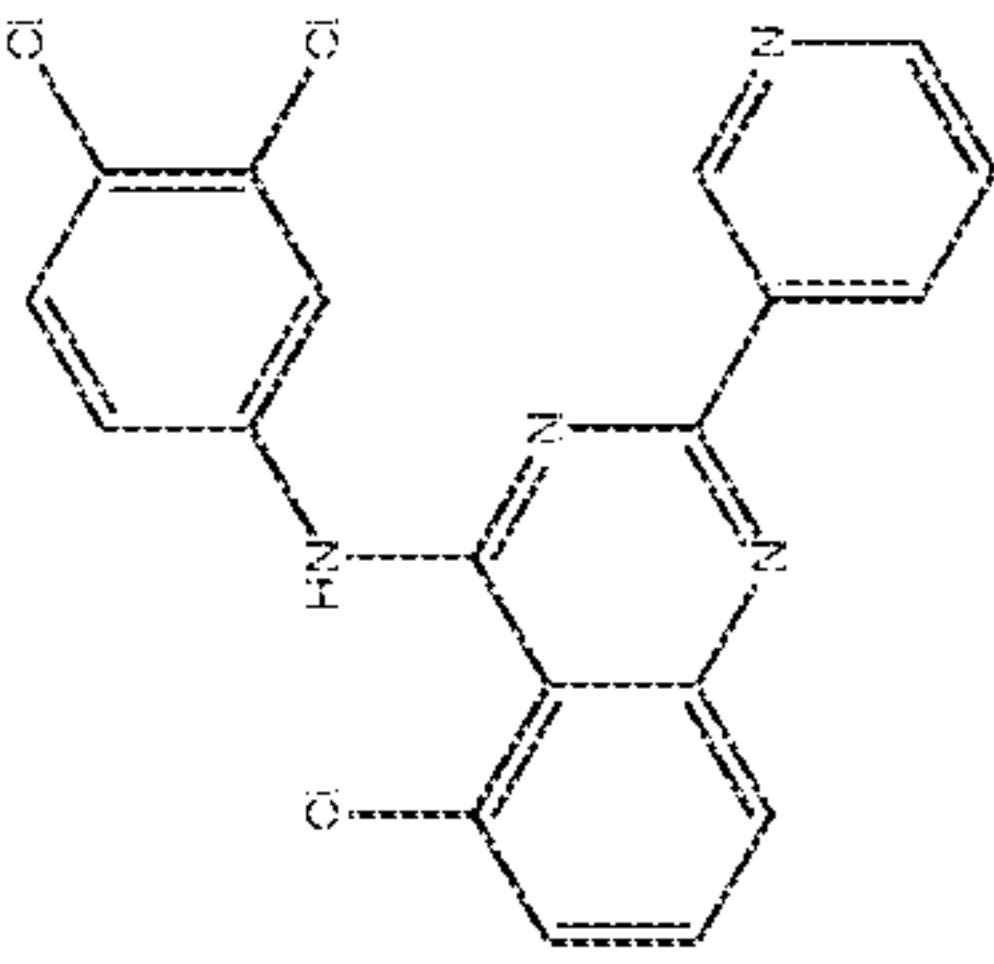
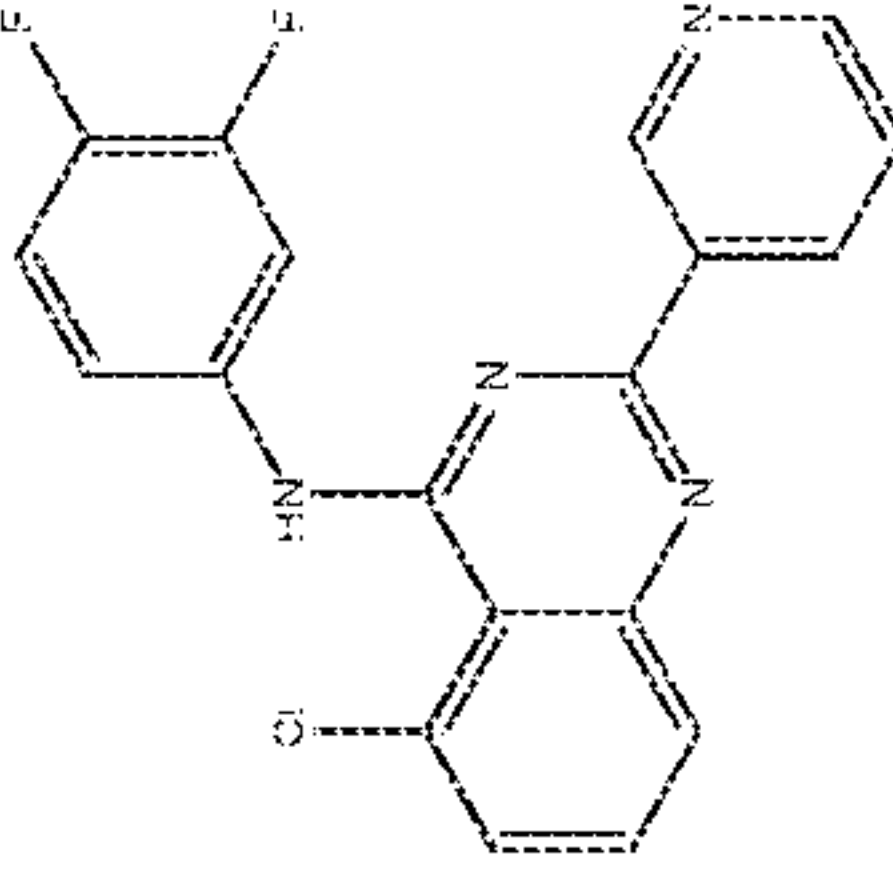
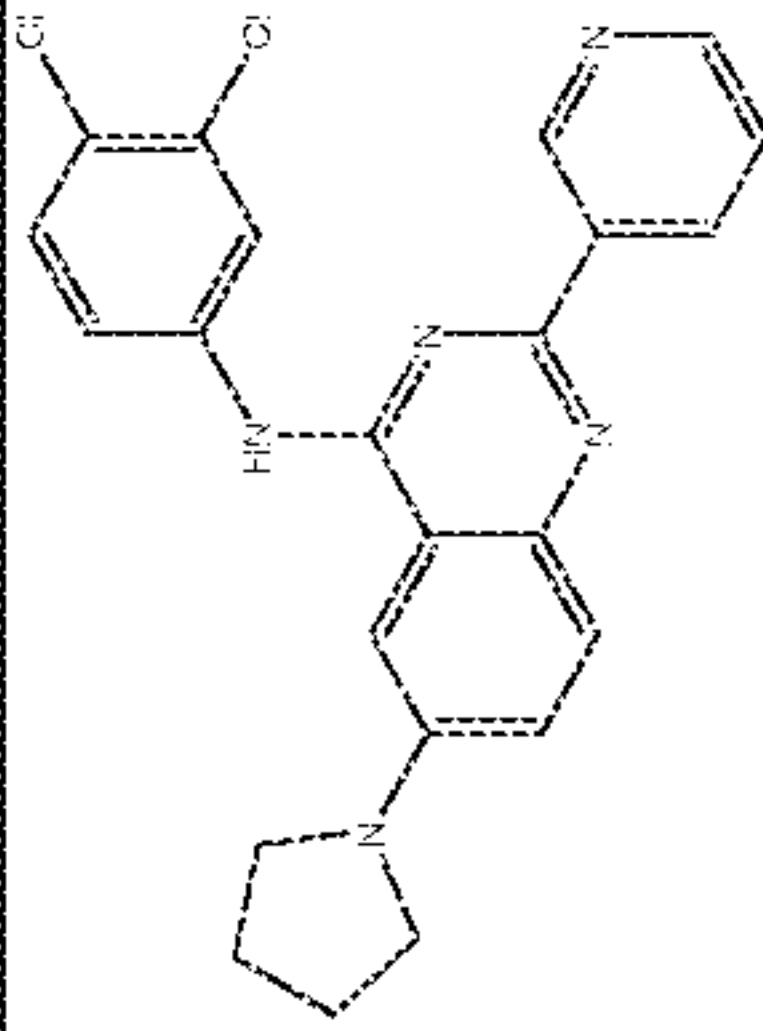
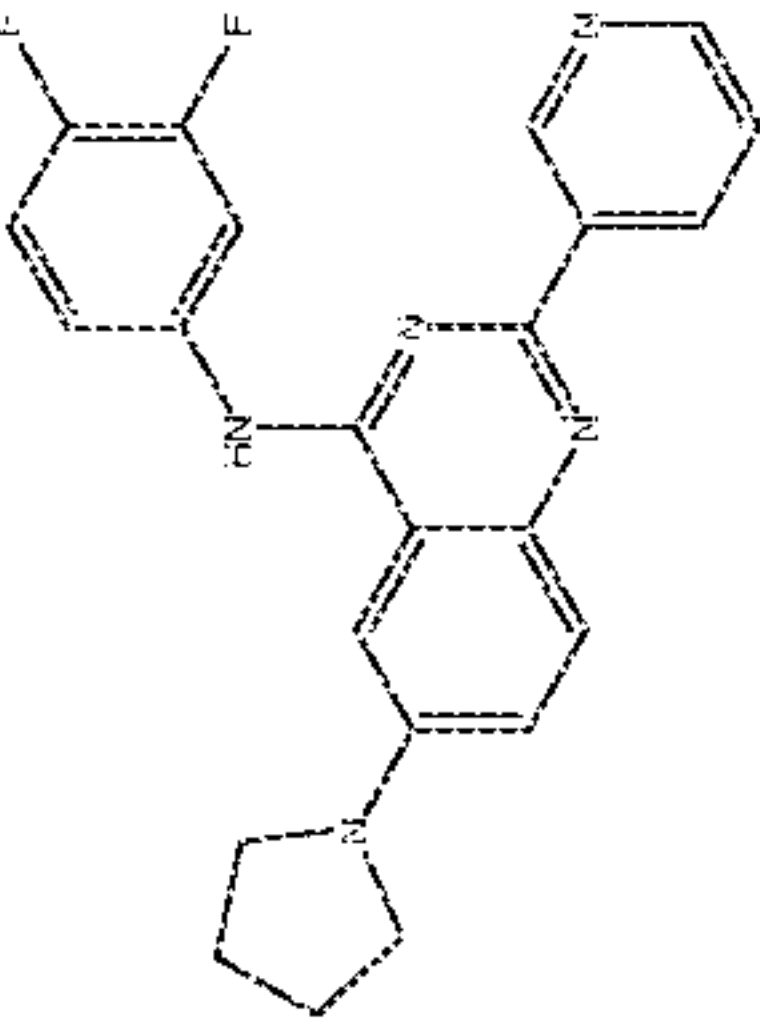
98			385.22	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.47 (s, 1H), 9.50 (s, 1H), 9.04 (d, <i>J</i> = 8.0 Hz, 1H), 8.93 (d, <i>J</i> = 5.2 Hz, 2H), 8.64 (d, <i>J</i> = 8.8 Hz, 1H), 8.20 – 8.18 (m, 1H), 8.11 (d, <i>J</i> = 8.4 Hz, 1H), 7.97 – 7.92 (m, 2H), 7.68 – 7.64 (m, 1H), 7.53 (t, <i>J</i> = 9.2 Hz, 1H).	DMSO	385.0, 386.9 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
99			401.68	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.42 (s, 1H), 9.55 (d, <i>J</i> = 1.6 Hz, 1H), 8.96 (d, <i>J</i> = 4.0 Hz, 1H), 8.88 – 8.87 (m, 1H), 8.61 (d, <i>J</i> = 7.6 Hz, 1H), 8.32 (d, <i>J</i> = 2.4 Hz, 1H), 8.14 – 8.12 (m, 1H), 7.99 – 7.95 (m, 1H), 7.88 (dd, <i>J</i> = 8.0, 5.2 Hz, 1H), 7.74 (d, <i>J</i> = 8.8 Hz, 1H), 7.70 – 7.67 (m, 1H).	DMSO	400.9, 402.9, 404.9 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
100			368.77	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.47 (s, 1H), 9.51 (d, <i>J</i> = 1.2 Hz, 1H), 9.04 (d, <i>J</i> = 8.0 Hz, 1H), 8.92 (d, <i>J</i> = 5.6 Hz, 1H), 8.65 (d, <i>J</i> = 8.0 Hz, 1H), 8.11 – 8.05 (m, 2H), 7.97 (dd, <i>J</i> = 8.0, 4.0 Hz, 1H), 7.75 – 7.73 (m, 1H), 7.66 (t, <i>J</i> = 8.0 Hz, 1H), 7.58 – 7.51 (m, 1H).	DMSO	369.0, 371.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1

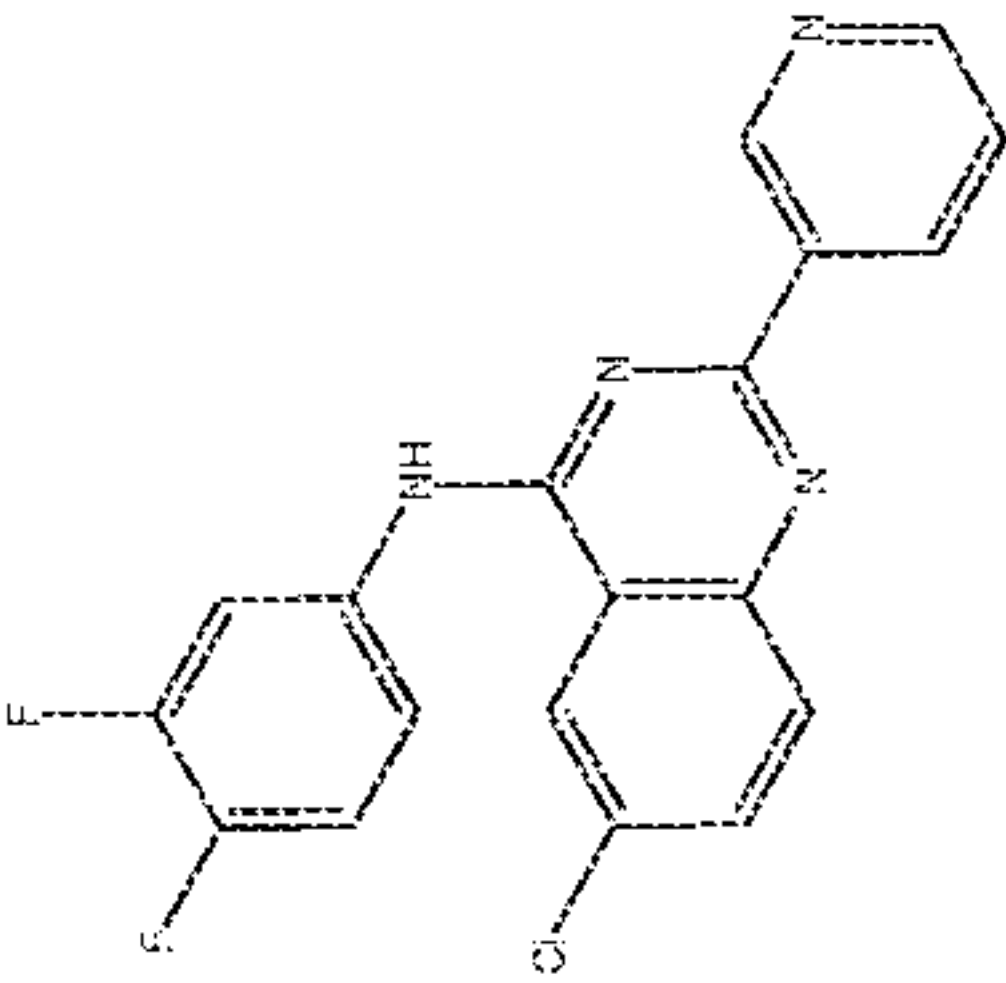
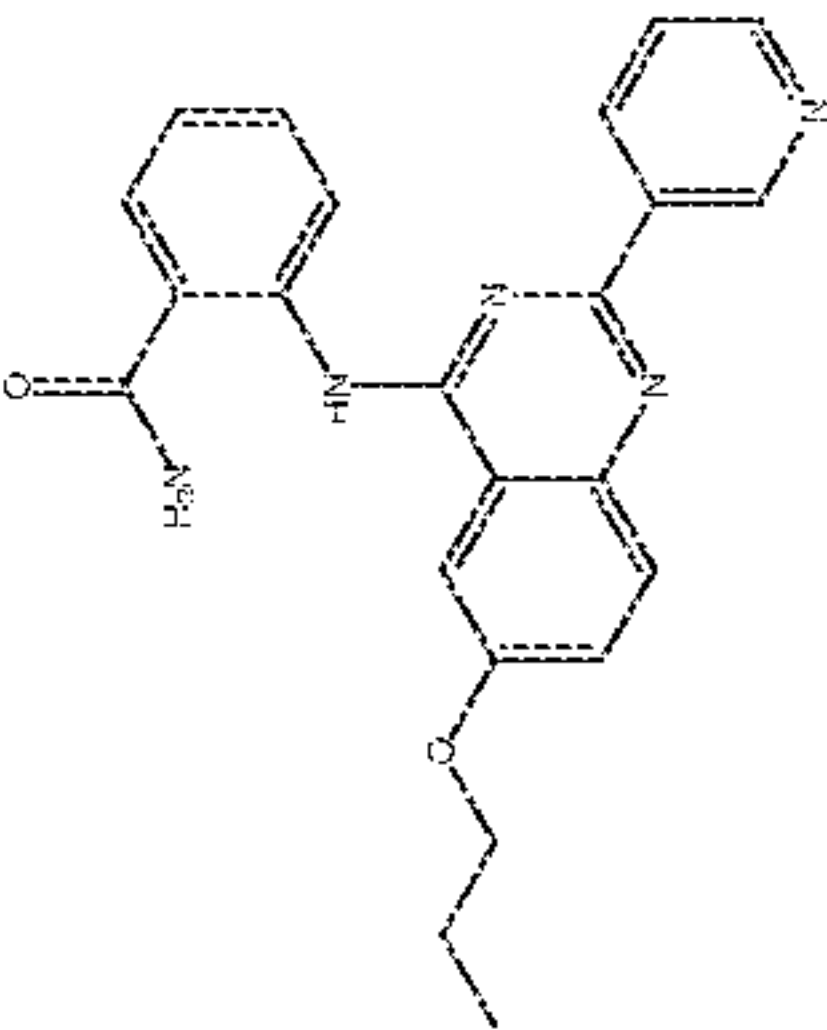
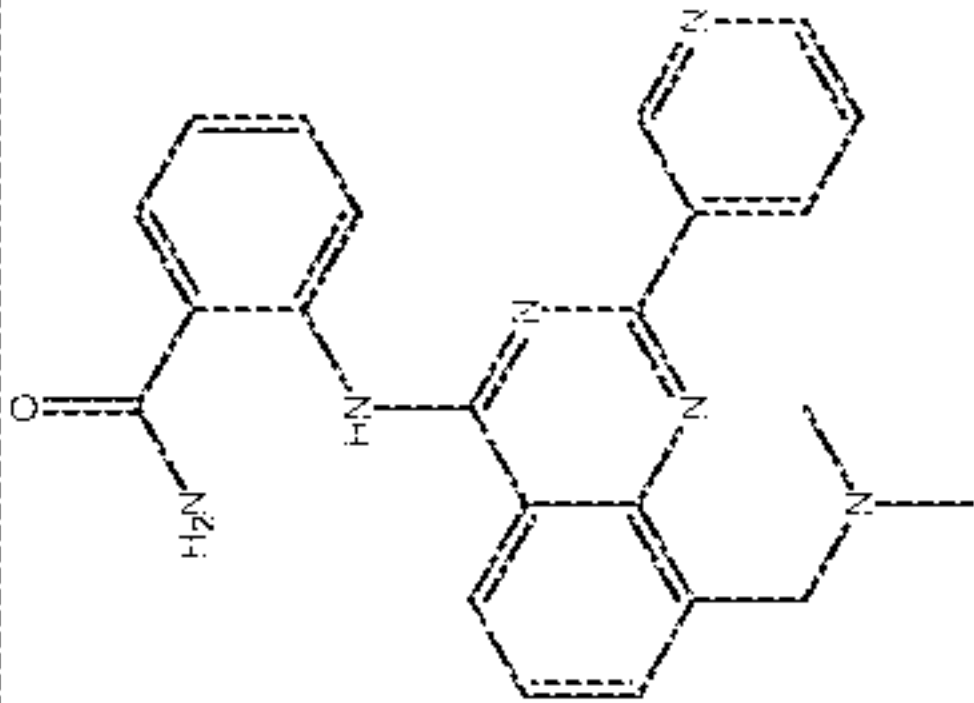
101			375.09	¹H-NMR (400 MHz, DMSO-d₆): δ 13.18 (s, 1H), 9.61 (s, 1H), 9.02 (d, J = 8.4 Hz, 1H), 8.93 (d, J = 8.4 Hz, 1H), 8.83 (d, J = 4.0 Hz, 1H), 8.52 (s, 1H), 8.16 – 8.08 (m, 2H), 7.98 – 7.94 (m, 2H), 7.80 – 7.67 (m, 3H), 7.26 (t, J = 7.6 Hz, 1H).	DMSO	376.0, 378.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
102			401.68	¹H-NMR (400 MHz, DMSO-d₆): δ 10.47 (s, 1H), 9.49 (d, J = 2.0 Hz, 1H), 9.00 – 8.98 (m, 1H), 8.91 (dd, J = 5.2, 1.6 Hz, 1H), 8.64 – 8.62 (m, 1H), 8.12 – 8.09 (m, 3H), 7.94 (dd, J = 8.0, 5.2 Hz, 1H), 7.67 (t, J = 8.0 Hz, 1H), 7.41 (t, J = 2.0 Hz, 1H).	DMSO	400.9, 402.9, 404.9 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
103			434.77	¹H-NMR (400 MHz, DMSO-d₆): δ 10.17 (d, J = 1.2 Hz, 1H), 9.51 (s, 1H), 8.71 – 8.62 (m, 3H), 8.25 – 8.22 (m, 1H), 8.04 – 8.00 (m, 1H), 7.92 – 7.87 (m, 2H), 7.58 – 7.53 (m, 2H).	DMSO	435.1, 437.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
104			448.35	¹H-NMR (400 MHz, DMSO-d₆): δ 10.16 (s, 1H), 9.55 (d, J = 1.2 Hz, 1H), 8.72 – 8.68 (m, 3H), 8.05 (d, J = 9.2 Hz, 1H), 7.92 – 7.95 (m, 2H), 7.80 (dd, J = 8.0, 1.2 Hz, 1H), 7.57 – 7.53 (m, 2H), 7.31 (t, J = 74.4 Hz, 1H), 7.03 (dd, J = 8.0, 1.2 Hz, 1H).	DMSO	449.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1

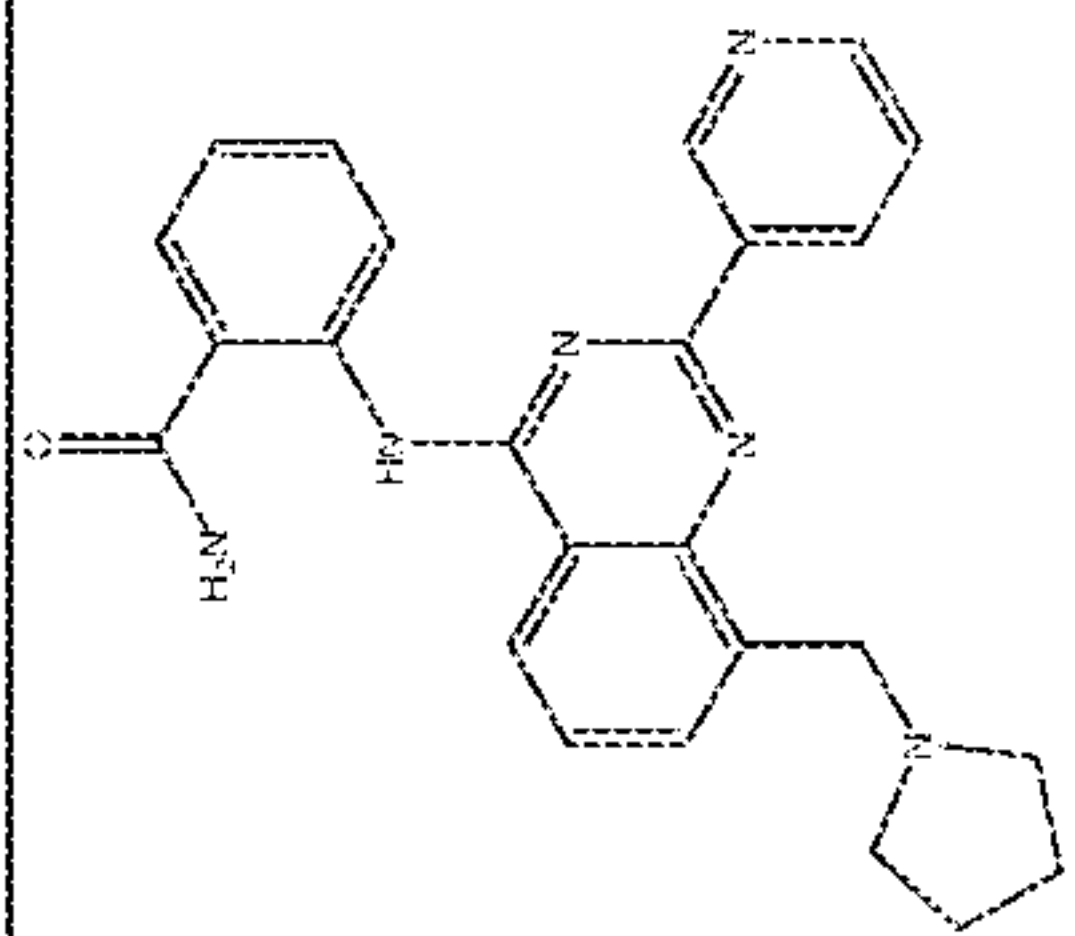
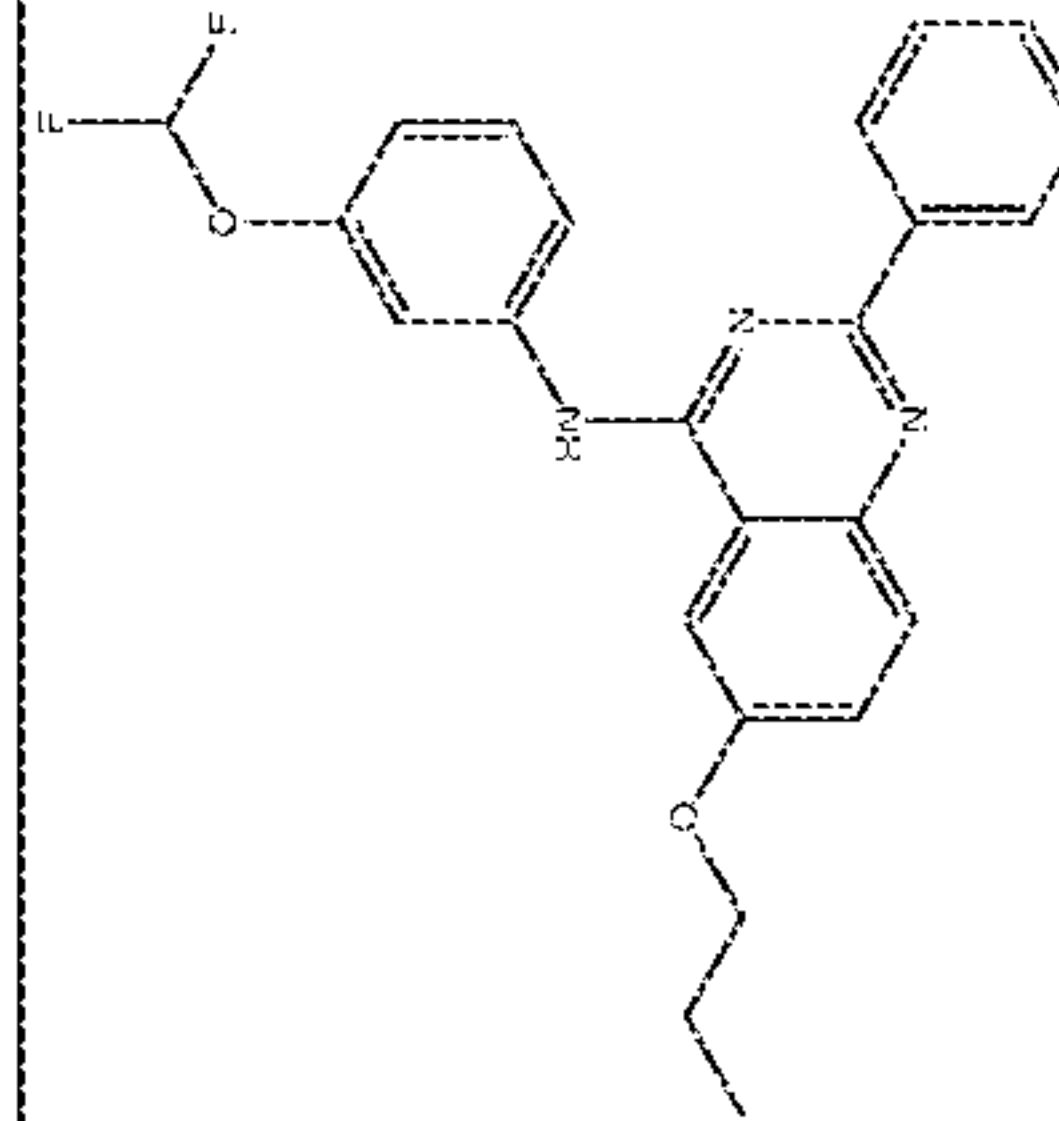
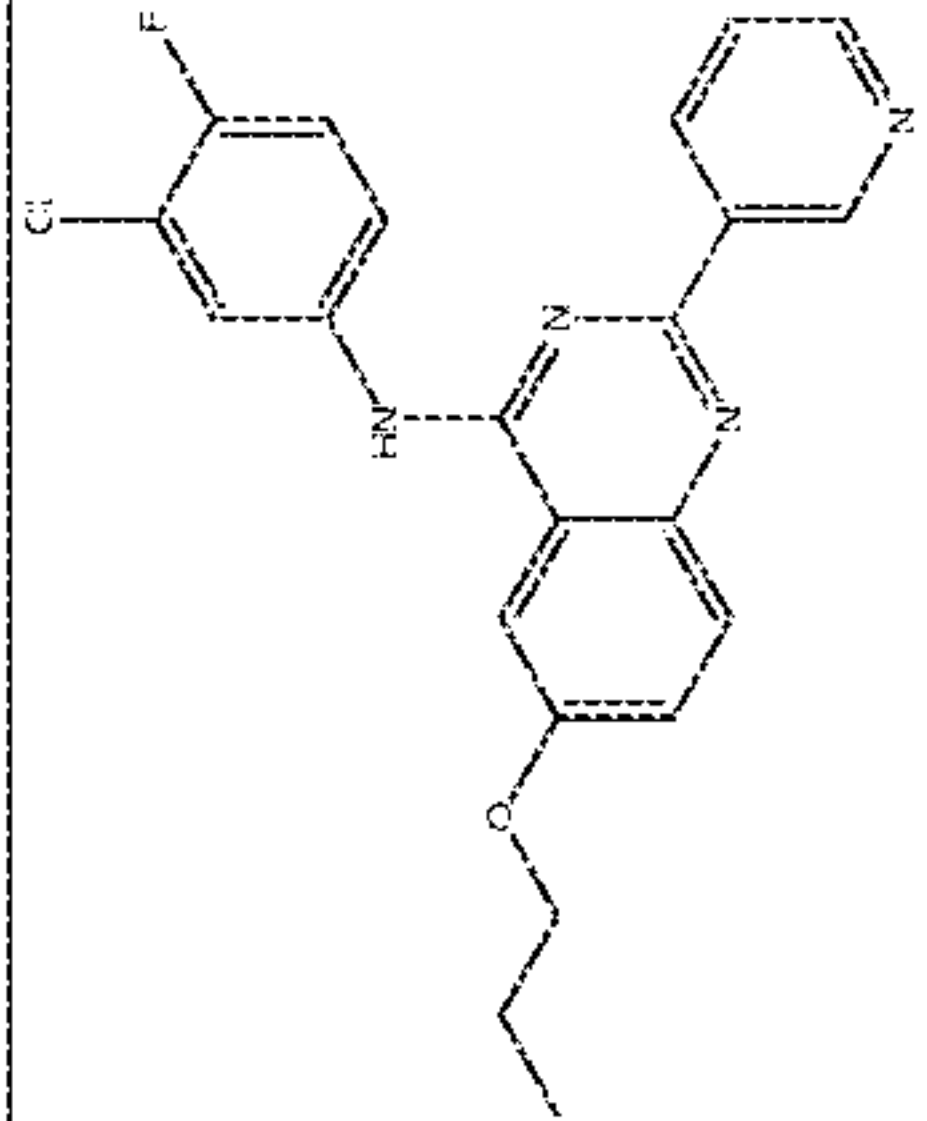
105			425.36	¹ H-NMR (400 MHz, DMSO-d ₆): δ 13.24 (s, 1H), 9.59 (s, 1H), 9.06 (d, J = 8.0 Hz, 1H), 8.74 – 8.73 (m, 2H), 8.54 (s, 1H), 8.10 – 7.91 (m, 5H), 7.77 – 7.73 (m, 1H), 7.61 – 7.58 (m, 1H), 7.26 (t, J = 7.6 Hz, 1H).	DMSO	426.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
106			448.35	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.23 (s, 1H), 9.55 (d, J = 1.6 Hz, 1H), 8.76 (d, J = 9.1 Hz, 1H), 8.74 – 8.67 (m, 2H), 7.94 (t, J = 2.0 Hz, 1H), 7.82 – 7.78 (m, J = 10.3 Hz, 2H), 7.68 (dd, J = 9.0, 1.8 Hz, 1H), 7.59 – 7.50 (m, 2H), 7.30 (t, J = 74.0 Hz, 1H), 7.03 (dd, J = 8.2, 2.2 Hz, 1H).	DMSO	449.0 (M+1) 225.0 (M/2+1)	Method A (TFA)	95	Method C, G1
107			425.36	¹ H-NMR (400 MHz, DMSO-d ₆): δ 13.17 (s, 1H), 9.59 (s, 1H), 9.04 (d, J = 8.0 Hz, 1H), 8.74 – 8.70 (m, 2H), 8.51 (s, 1H), 8.30 (d, J = 9.0 Hz, 1H), 8.02 – 7.90 (m, 2H), 7.86 – 7.69 (m, 3H), 7.65 – 7.56 (m, 1H), 7.25 (t, J = 9.8 Hz, 1H).	DMSO	426.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
108			434.77	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.26 (s, 1H), 9.52 (s, 1H), 8.81 – 8.59 (m, 3H), 8.24 (dd, J = 6.9, 2.5 Hz, 1H), 7.89 – 7.52 (m, 1H), 7.79 (s, 1H), 7.70 (d, J = 9.1 Hz, 1H), 7.65 – 7.50 (m, 2H).	DMSO	435.0, 437.0 (M+1) 218.1 (M/2+1)	Method A (TFA)	95	Method C, G1

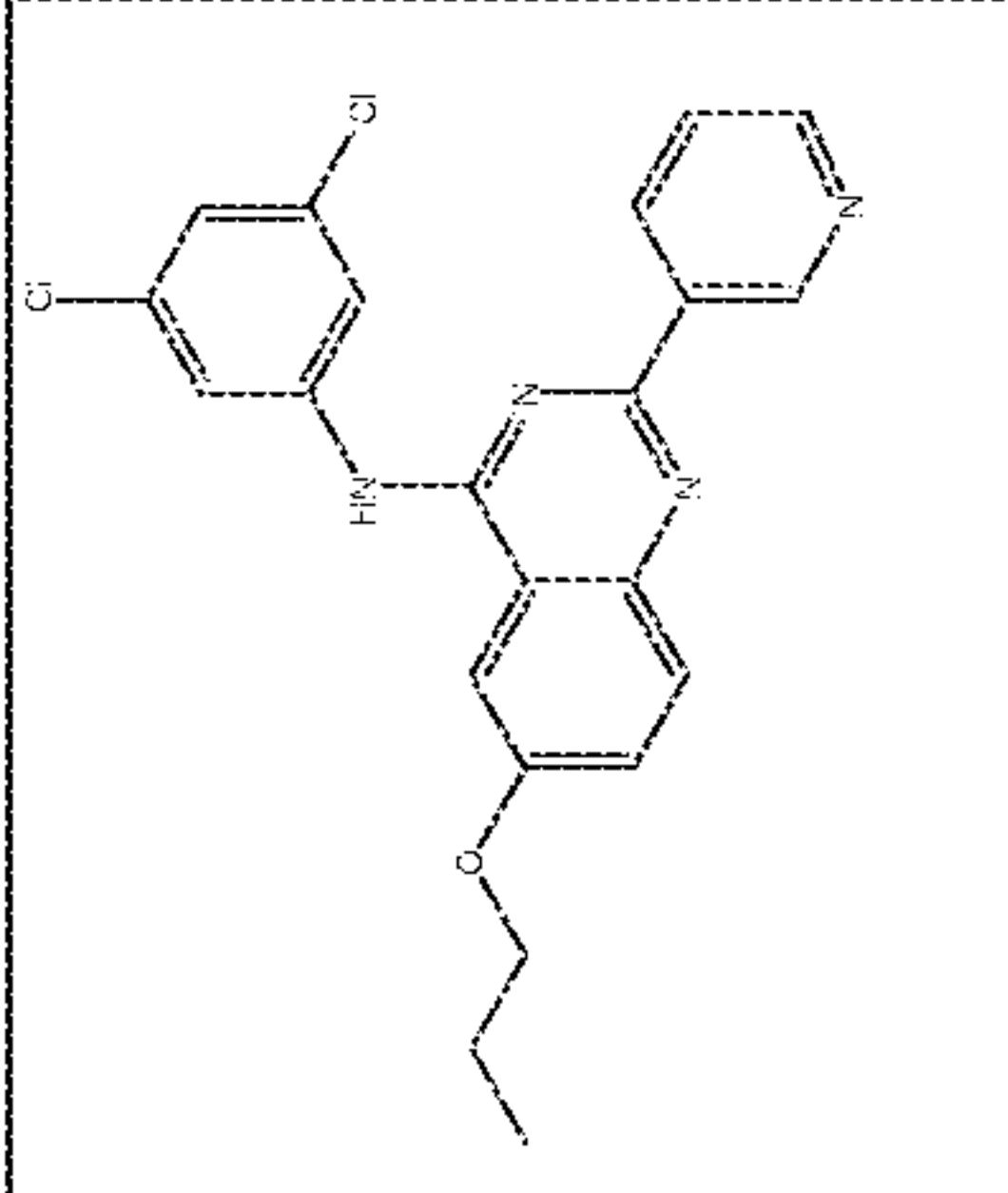
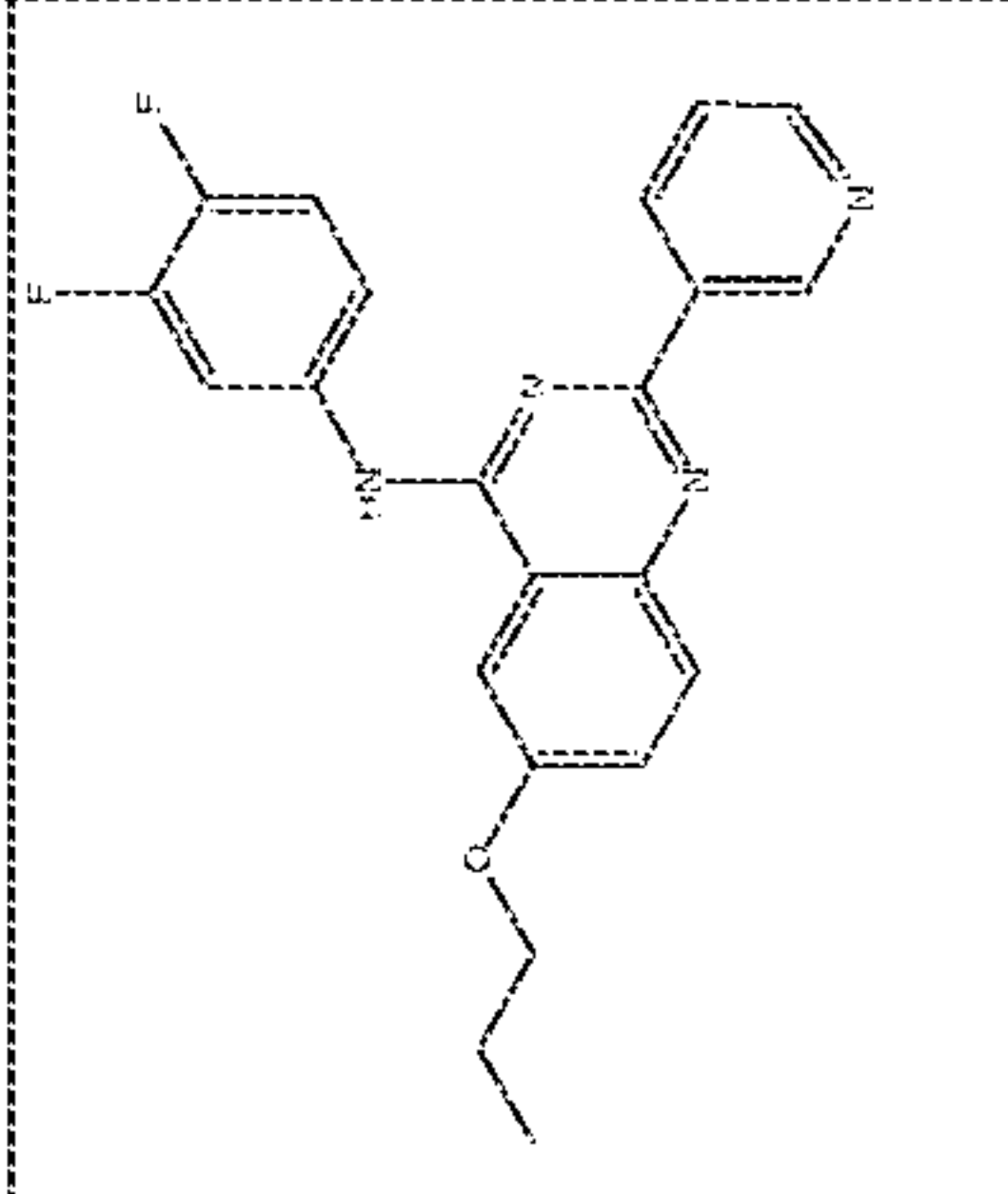
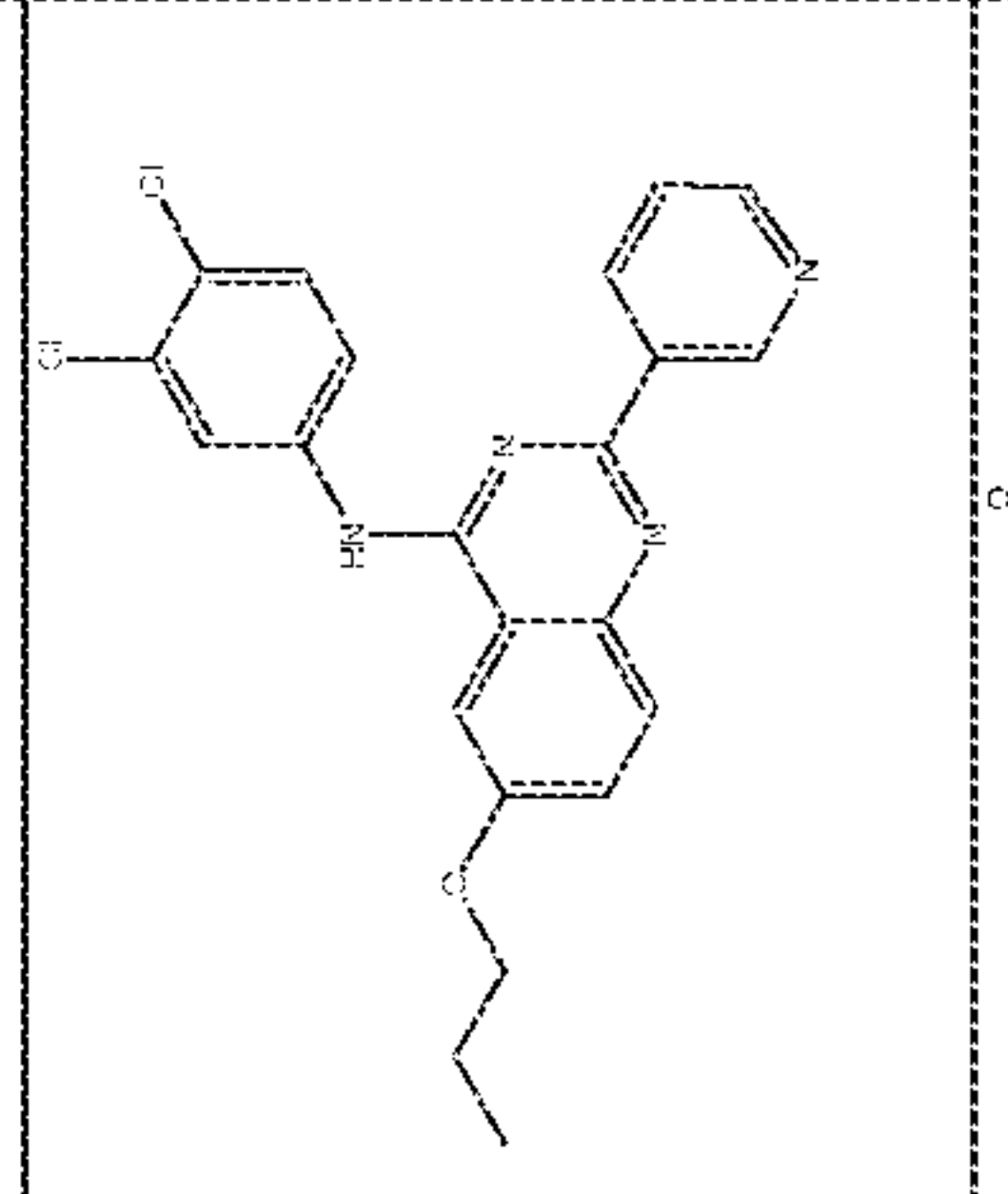
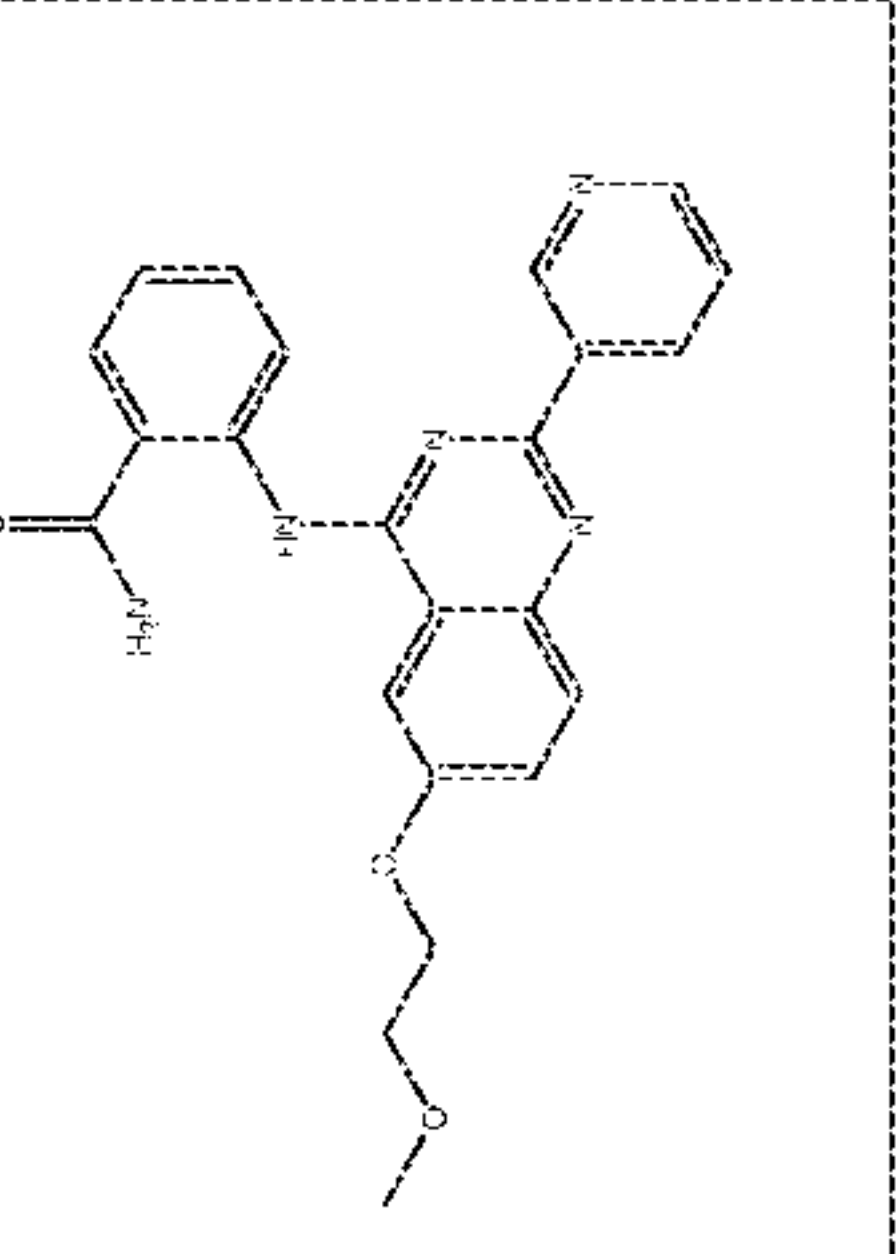
109			455.39	¹ H-NMR (400 MHz, DMSO-d ₆): δ 13.35 (s, 1H), 9.58 (s, 1H), 9.27 (s, 1H), 8.89 – 8.70 (m, 2H), 8.62 (s, 1H), 8.18 (s, 1H), 8.11 (d, J = 8.8 Hz, 1H), 7.92 (d, J = 9.1 Hz, 1H), 7.68 – 7.58 (m, 2H), 7.54 (d, J = 2.5 Hz, 1H), 7.19 (dd, J = 8.4, 2.17 Hz, 1H), 3.98 (s, 3H).	DMSO	456.0 (M+1) 228.5 (M/2+1)	Method A (TFA)	95	Method C, J1
110			425.48	¹ H-NMR (400 MHz, DMSO-d ₆): δ 13.08 (s, 1H), 9.59 (s, 1H), 9.07 (d, J = 7.6 Hz, 1H), 9.02 (d, J = 8.0 Hz, 1H), 8.89 (d, J = 4.0 Hz, 1H), 8.50 (s, 1H), 7.92 – 7.99 (m, 4H), 7.73 (t, J = 7.6 Hz, 1H), 7.59 – 7.60 (m, 2H), 7.25 (t, J = 7.6 Hz, 1H), 2.12 – 2.15 (m, 2H), 5.02 – 5.03 (m, 1H), 1.67 – 1.86 (m, 6H).	DMSO	426.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
111			448.46	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.26 (s, 1H), 9.50 (d, J = 1.6 Hz, 1H), 8.95 (d, J = 7.2 Hz, 1H), 8.55 (d, J = 4.4 Hz, 1H), 8.08 (s, 1H), 7.94 (d, J = 8.8 Hz, 1H), 7.85 (d, J = 9.6 Hz, 2H), 7.79 (d, J = 8.8 Hz, 1H), 7.60 – 7.63 (m, 1H), 7.55 (t, J = 8.0 Hz, 1H), 7.31 (t, J = 74.0 Hz, 1H), 7.05 (d, J = 8.4 Hz, 1H), 5.14 (s, 1H), 2.03 – 2.09 (m, 2H), 1.61 – 1.81 (m, 6H).	DMSO	449.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1

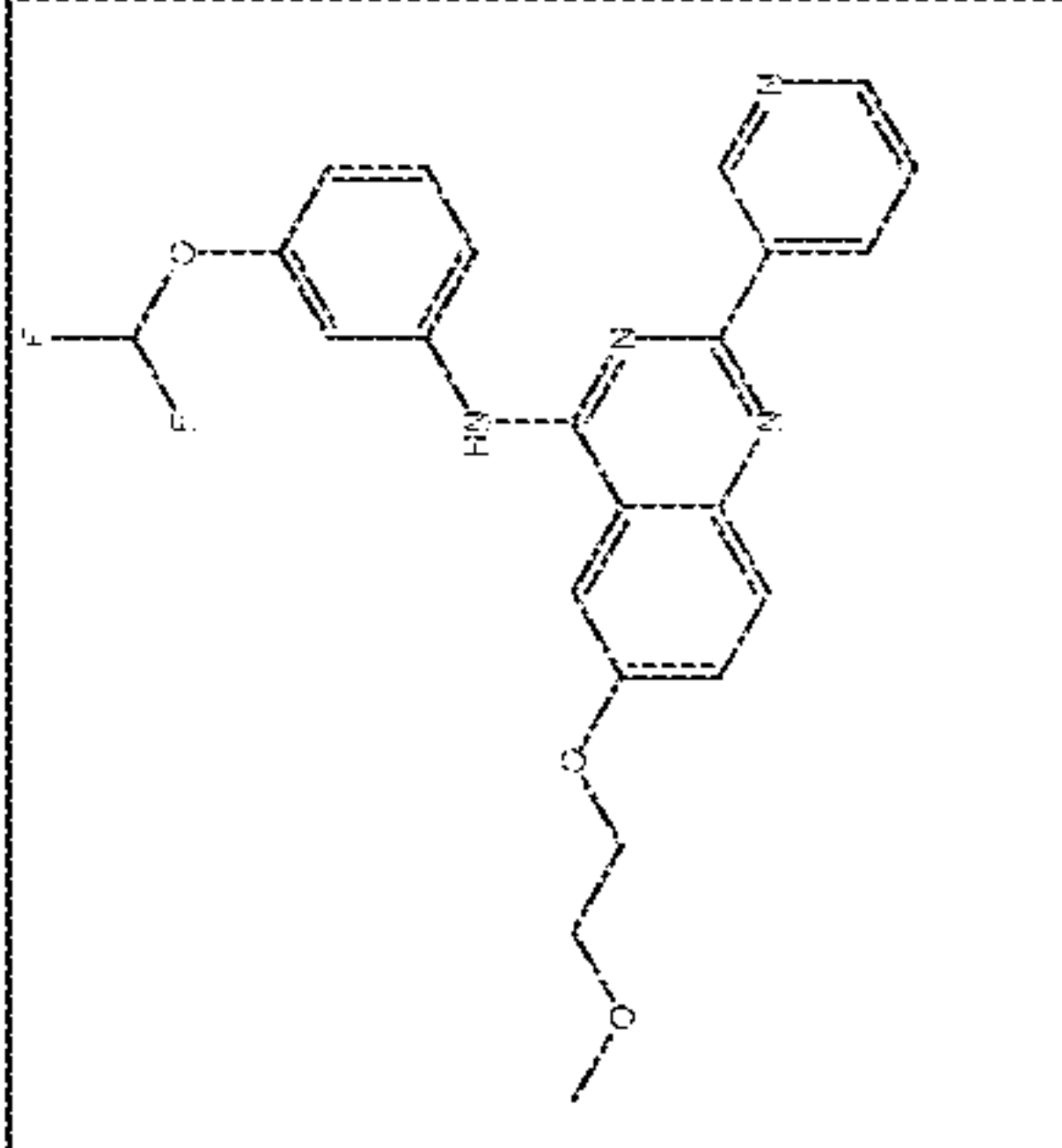
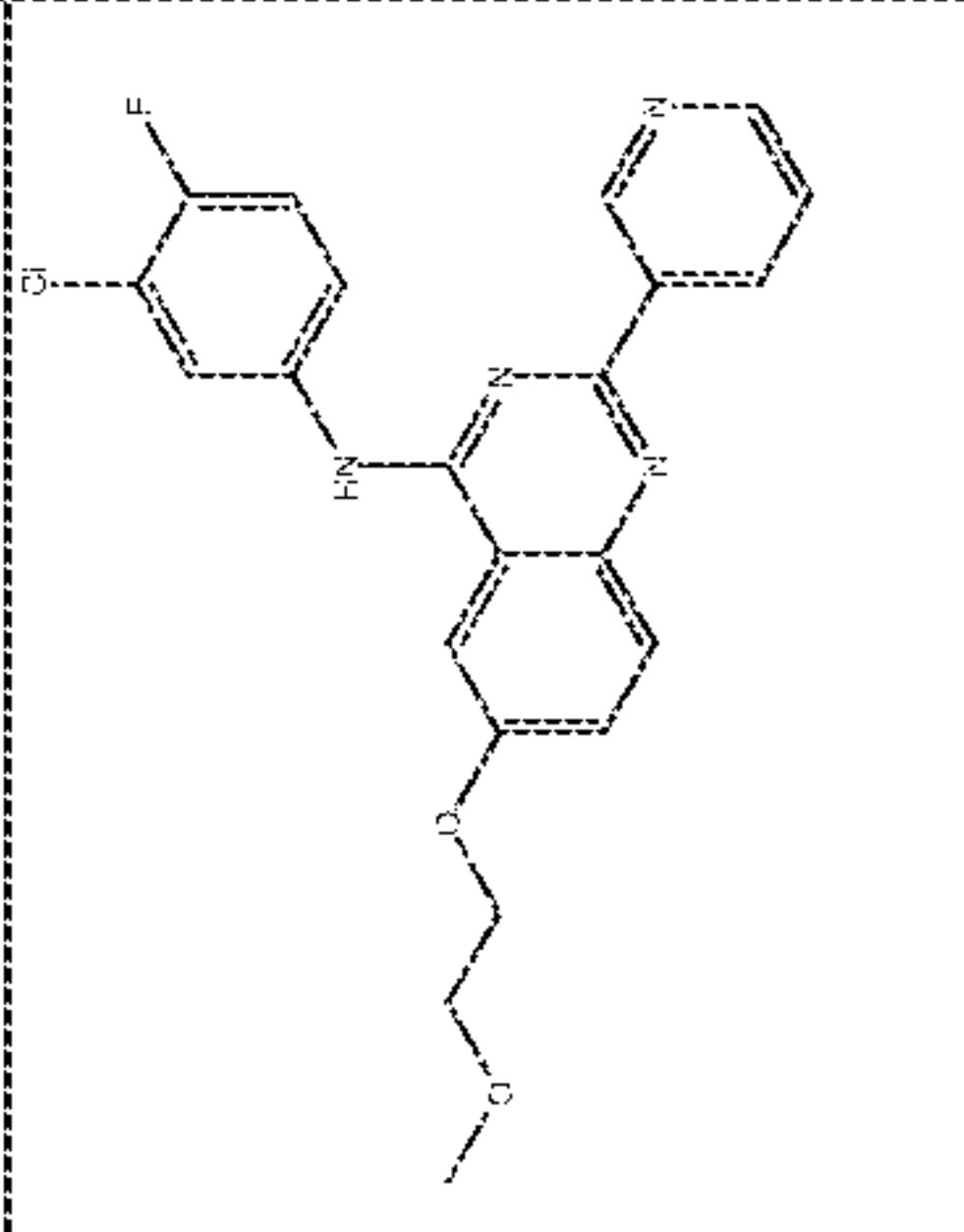
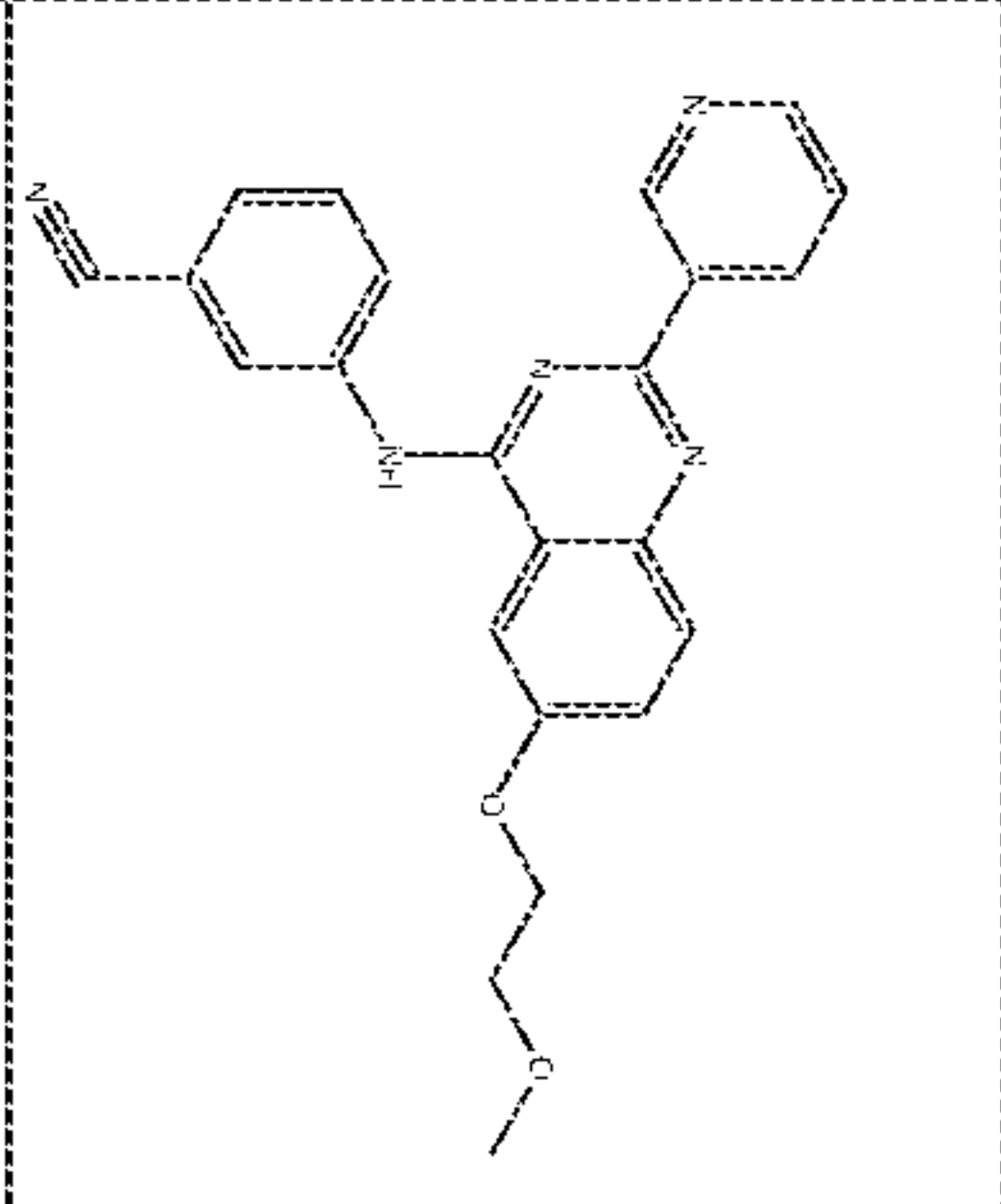
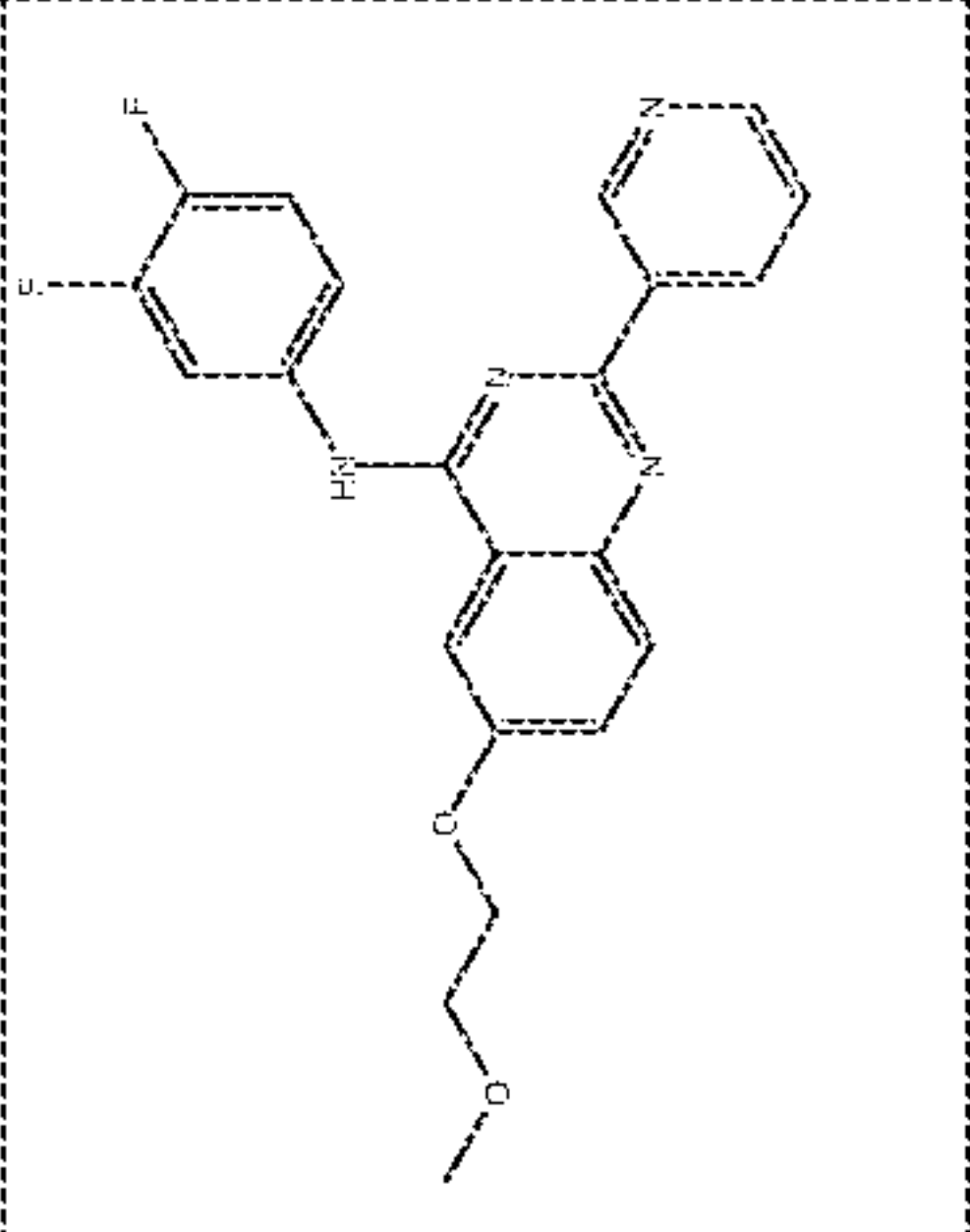
112			434.89	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.47 (s, 1H), 9.47 (s, 1H), 8.97 (d, J = 7.6 Hz, 1H), 8.89 (d, J = 4.4 Hz, 1H), 8.16 – 8.19 (m, 1H), 7.53 – 7.61 (m, 2H), 8.10 (s, 1H), 7.90 – 7.96 (m, 3H), 5.15 (s, 1H), 2.09 – 2.10 (m, 2H), 1.67 – 1.78 (m, 6H).	DMSO	435.0, 437.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
113			451.35	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.23 (s, 1H), 9.49 (s, 1H), 8.85 (d, J = 7.6 Hz, 1H), 8.80 (d, J = 4.0 Hz, 1H), 8.32 (s, 1H), 8.03 (s, 1H), 7.97 – 7.99 (m, 1H), 7.88 (d, J = 8.8 Hz, 1H), 7.77 – 7.79 (m, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.55 – 7.58 (m, 1H), 5.13 (s, 1H), 2.08 (d, J = 8.4 Hz, 2H), 1.79 (d, J = 9.6 Hz, 4H).	DMSO	451.0, 453.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
114			418.44	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.24 (s, 1H), 9.49 (s, 1H), 8.92 (d, J = 8.0 Hz, 1H), 8.40 (d, J = 6.4 Hz, 1H), 8.04 – 8.11 (m, 2H), 7.92 (d, J = 9.2 Hz, 1H), 7.84 – 7.91 (m, 1H), 7.69 – 7.71 (m, 1H), 7.52 – 7.61 (m, 2H), 5.13 (s, 1H), 2.06 – 2.11 (m, 2H), 1.65 – 1.81 (m, 6H).	DMSO	419.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
115			407.47	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.70 (s, 1H), 9.45 (s, 1H), 8.98 (d, J = 6.8 Hz, 1H), 8.89 (d, J = 6.0 Hz, 1H), 8.37 (s, 1H), 8.32 (d, J = 6.8 Hz, 1H), 8.18 (s, 1H), 7.93 (t, J = 9.2 Hz, 2H), 7.70 (t, J = 7.2 Hz, 2H), 7.56 (d, J = 8.8 Hz, 1H), 5.18 (s, 1H), 2.09 (s, 2H), 1.77 (m, 4H), 1.66 (m, 2H).	DMSO	408.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1

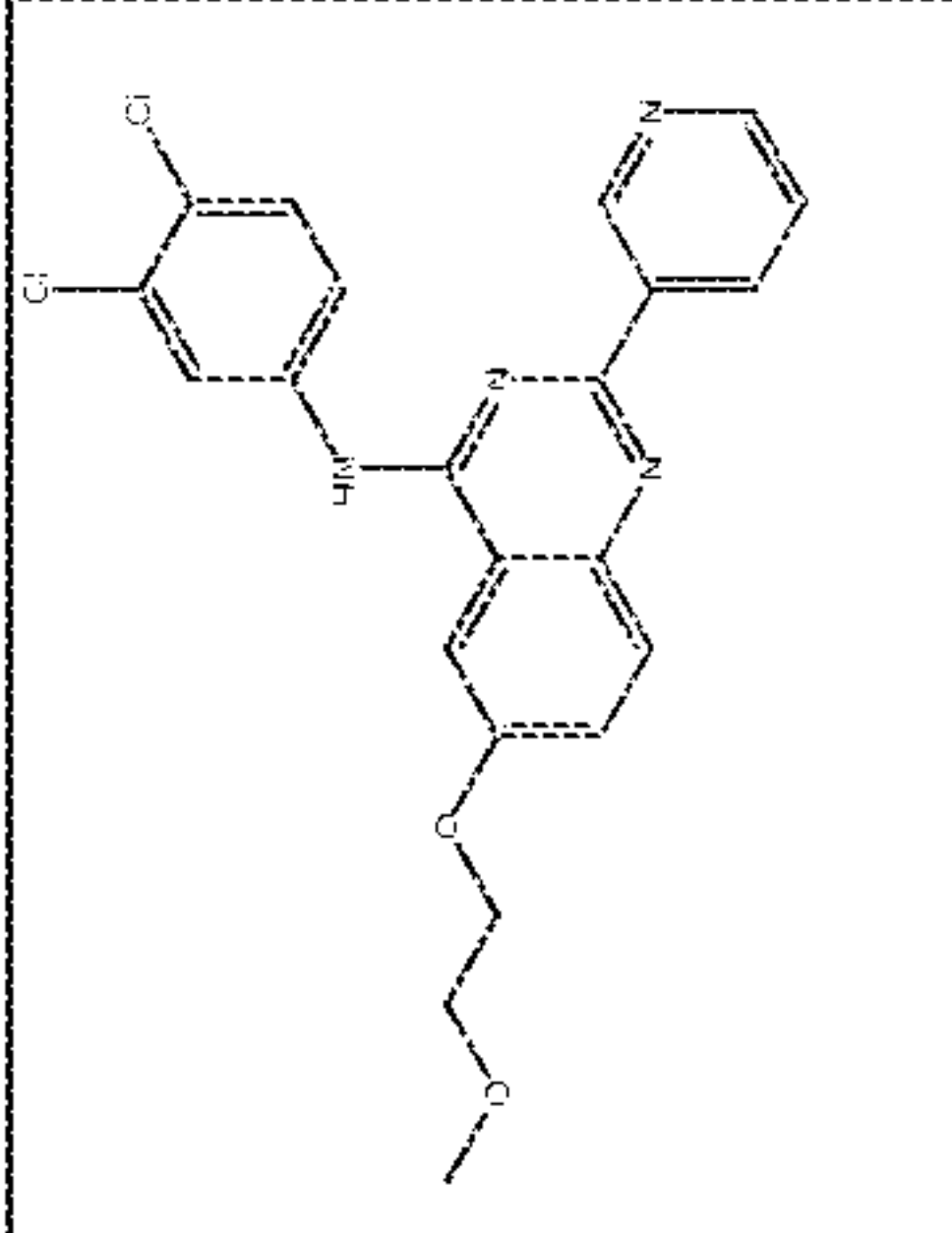
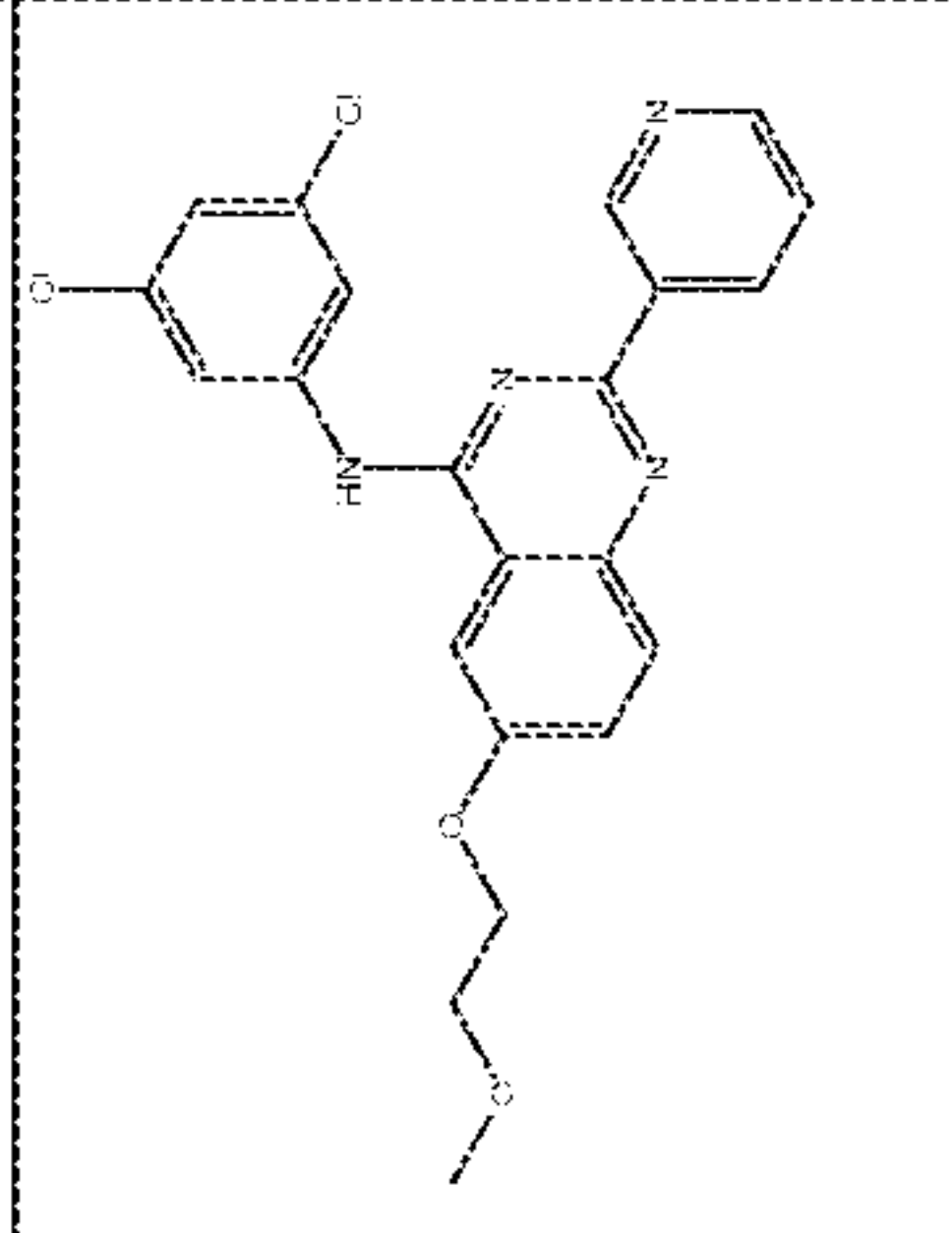
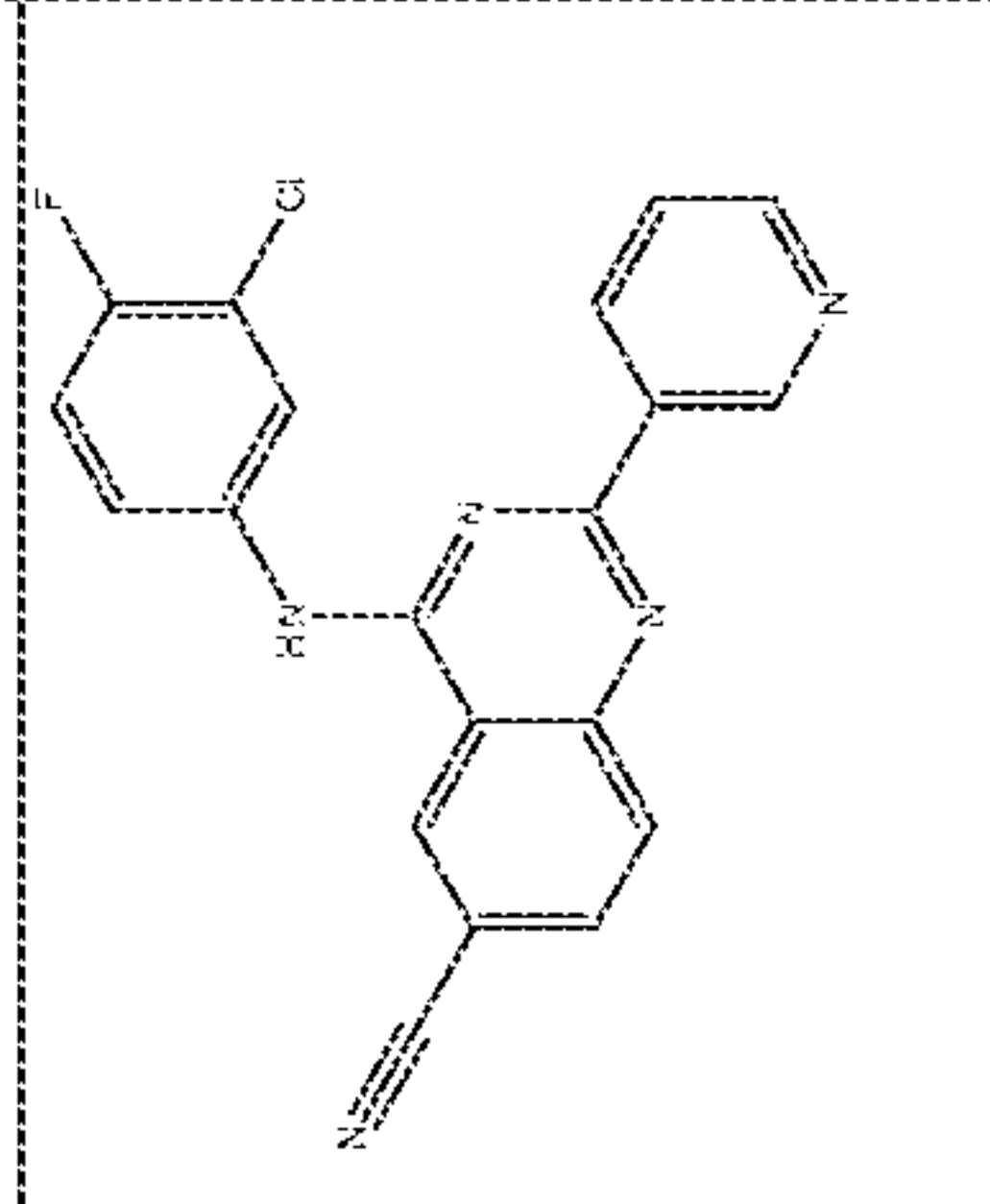
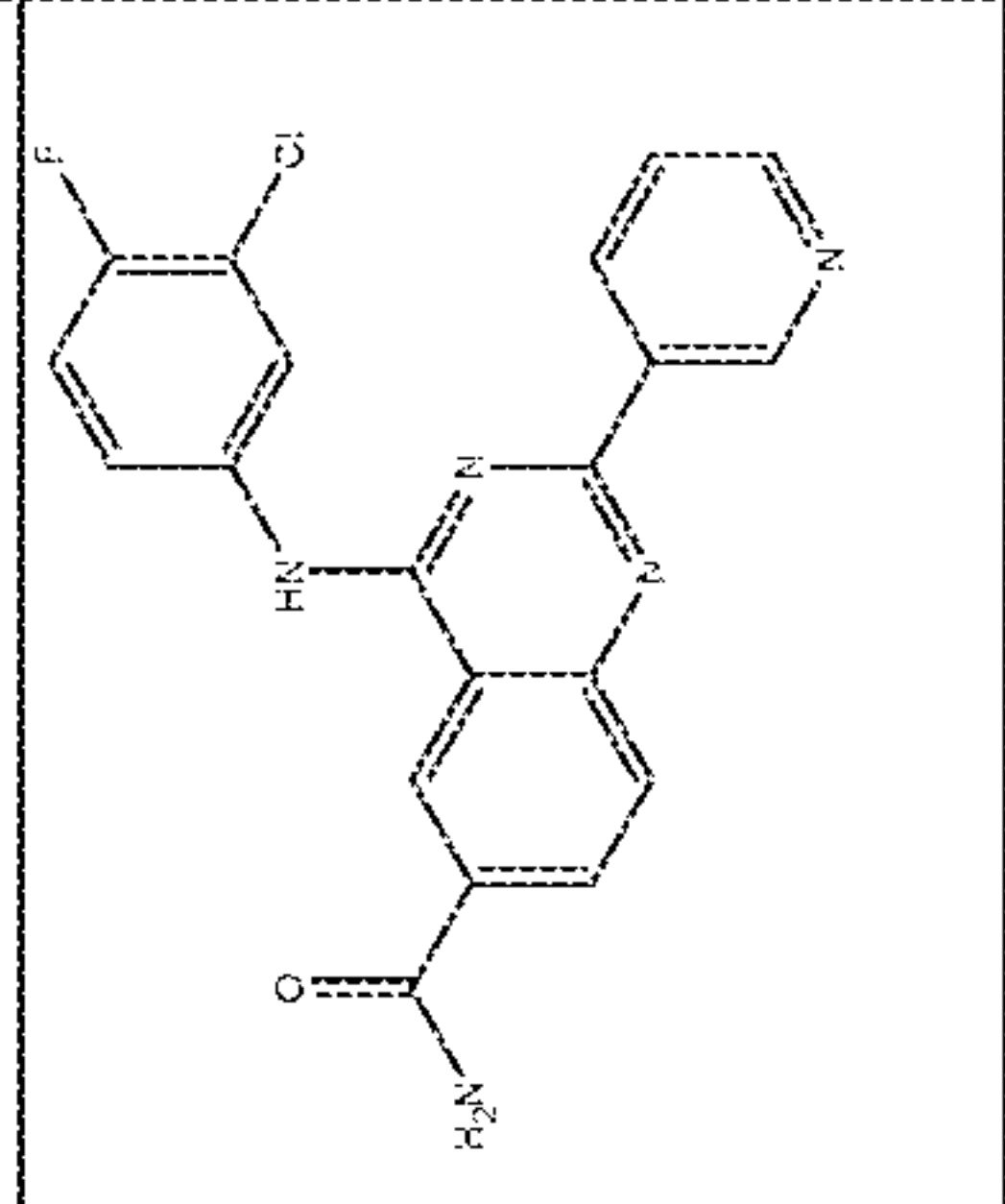
116			401.68	¹H-NMR (400 MHz, DMSO-d₆): δ 9.81 (s, 1H), 9.47 (s, 1H), 8.71 (d, J = 6.4 Hz, 1H), 8.62 (d, J = 7.6 Hz, 1H), 8.26 (s, 1H), 7.88 (t, J = 7.2 Hz, 3H), 7.75 – 7.73 (m, 2H), 7.57 – 7.56 (m, 1H).	DMSO	401.0, 403.0 405.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
117			368.77	¹H-NMR (400 MHz, DMSO-d₆): δ 9.74 (s, 1H), 9.45 (d, J = 1.2 Hz, 1H), 8.70 (dd, J = 4.4, 1.6 Hz, 1H), 8.60 (d, J = 8.0 Hz, 1H), 8.04 – 8.00 (m, 1H), 7.98 – 7.85 (m, 2H), 7.74 (dd, J = 8.4, 1.6 Hz, 1H), 7.65 – 7.63 (m, 1H), 7.57 – 7.56 (m, 2H).	DMSO	369.1, 371.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
118			436.34	¹H-NMR (400 MHz, DMSO-d₆): δ 10.33 (s, 1H), 8.87 – 8.20 (m, 2H), 8.27 (d, J = 1.6 Hz, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.90 – 7.72 (m, 3H), 7.39 – 7.36 (m, 2H), 3.44 (brs, 4H), 2.05 (brs, 4H).	DMSO	435.9, 437.9, 439.8 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
119			403.43	¹H-NMR (400 MHz, DMSO-d₆): δ 10.38 (s, 1H), 9.43 (d, J = 1.2 Hz, 1H), 8.85 – 8.80 (m, 2H), 8.07 – 8.05 (m, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.81 (t, J = 6.8 Hz, 1H), 7.69 – 7.67 (m, 1H), 7.58 – 7.83 (m, 1H), 7.43 – 7.41 (m, 2H), 3.45 (brs, 4H), 2.06 (brs, 4H).	DMSO	403.9 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1

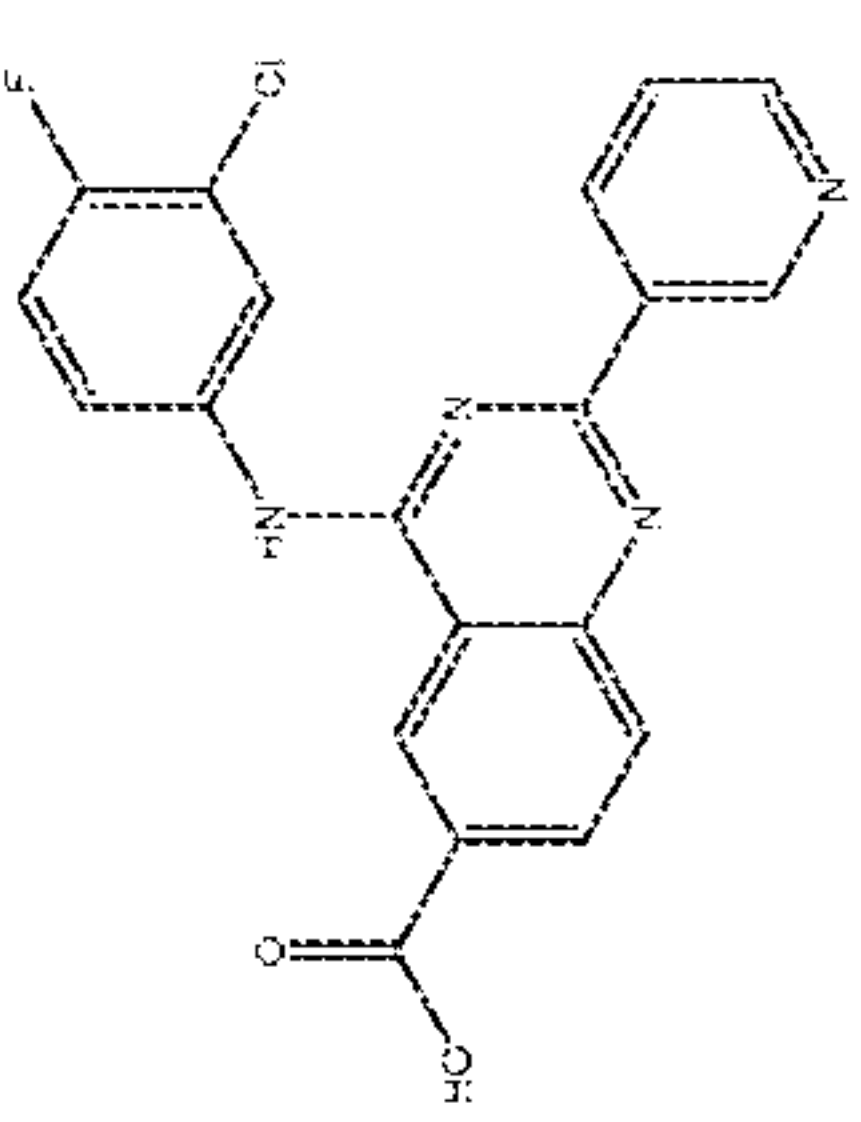
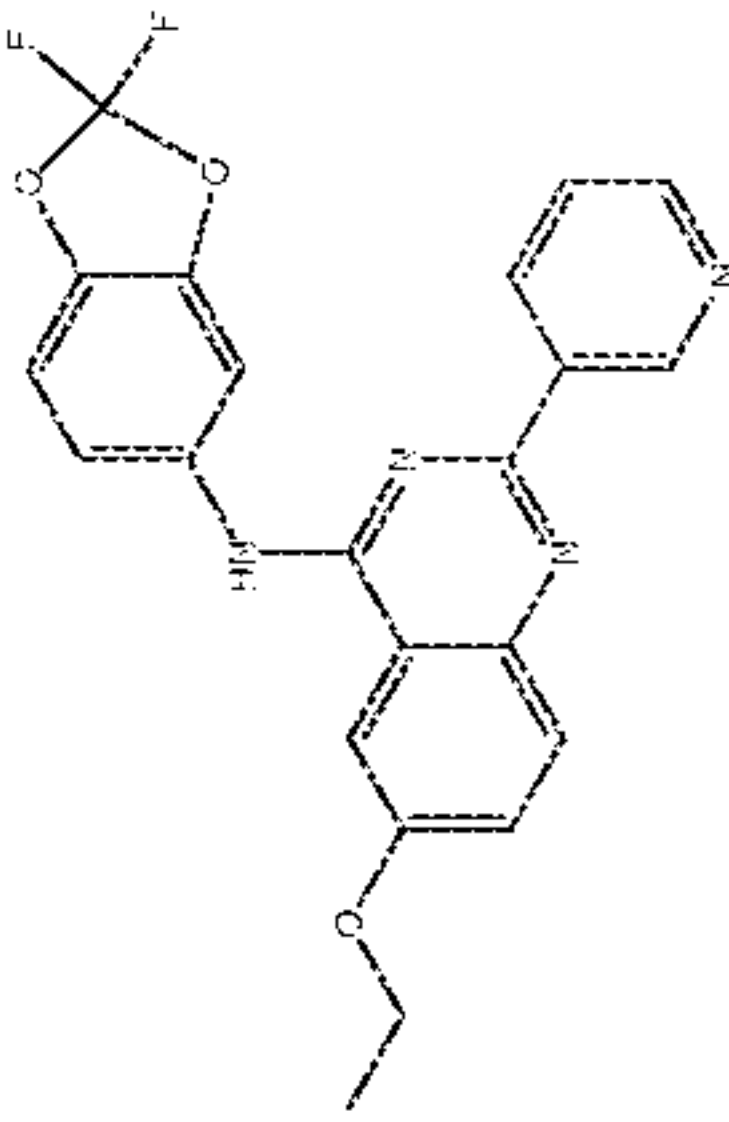
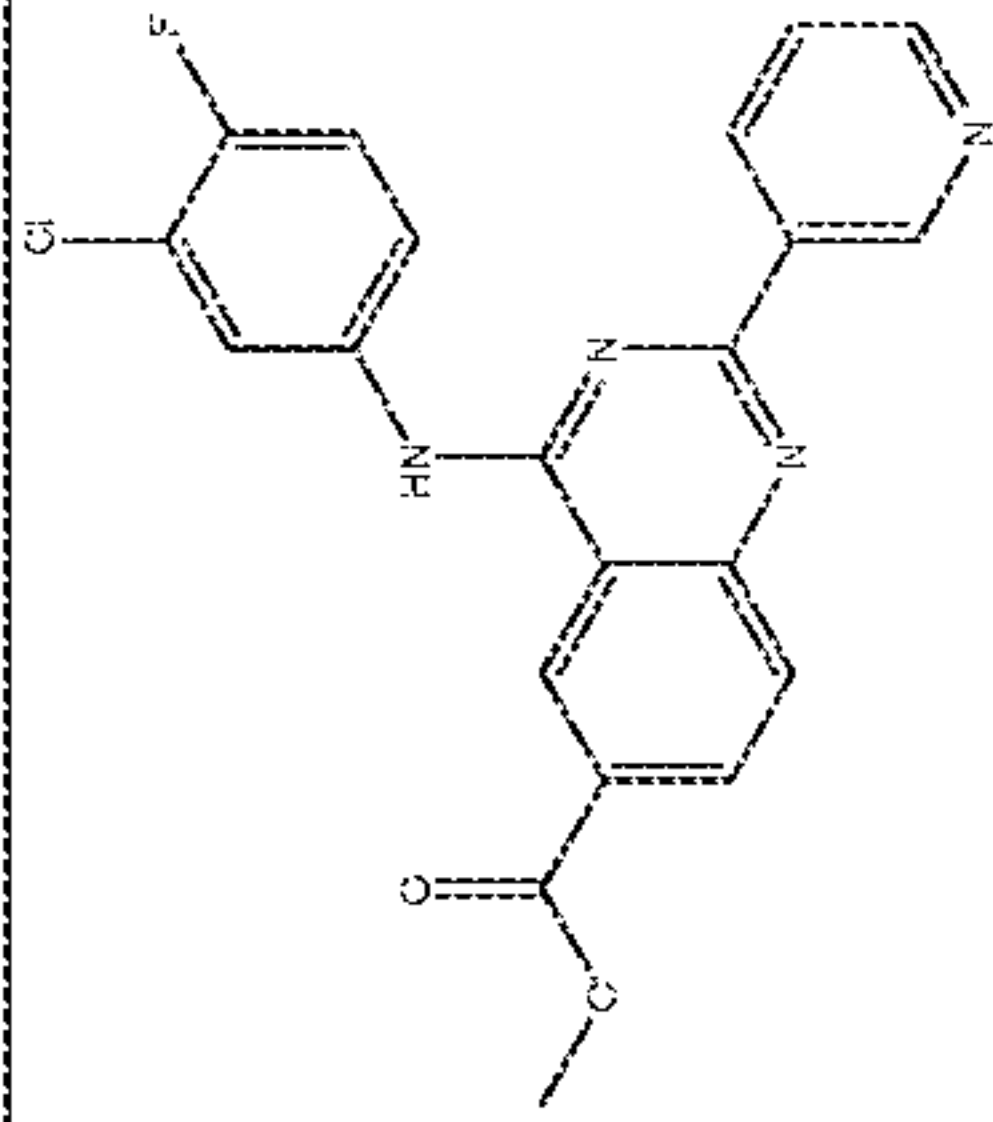
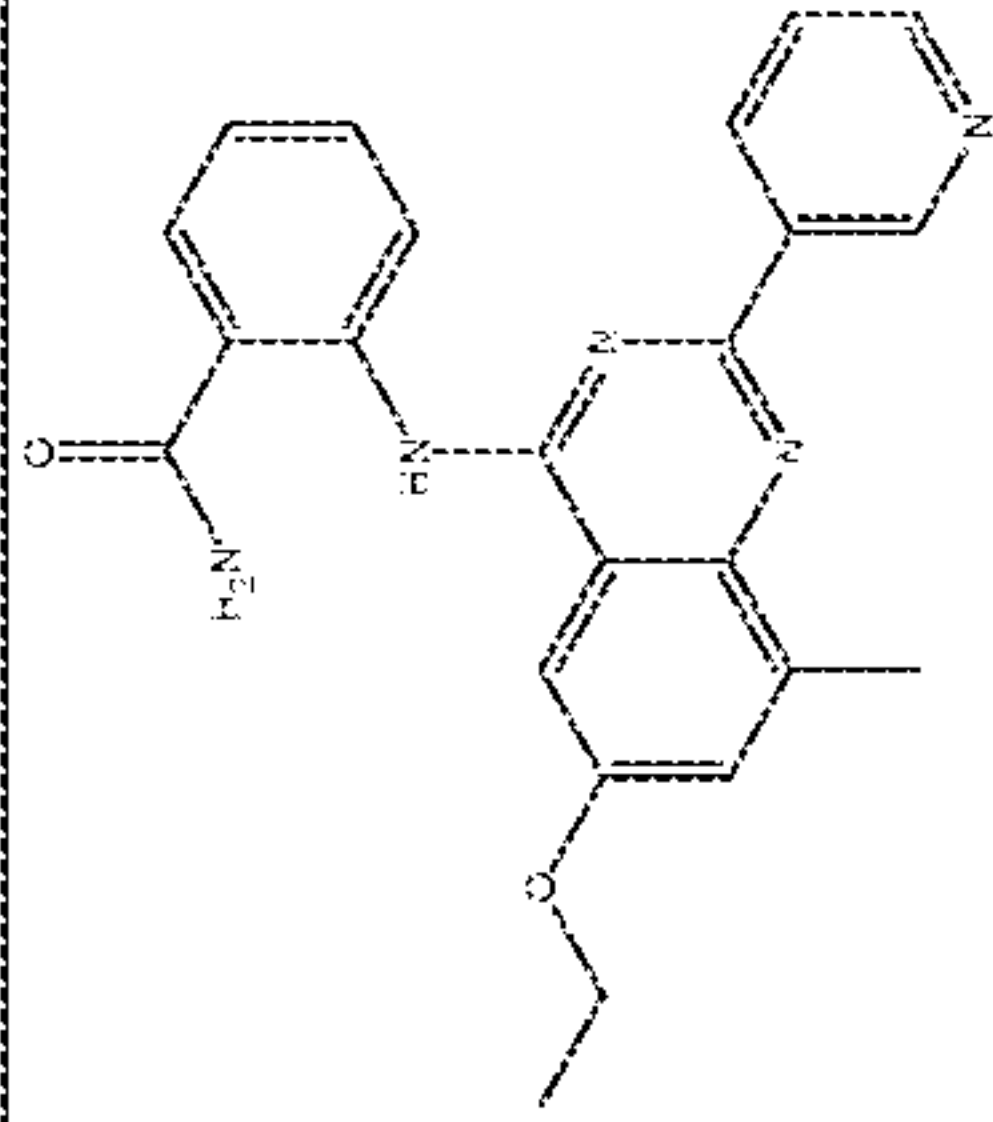
120			368.77	¹H-NMR (400 MHz, DMSO-d₆): δ 10.28 (s, 1H), 9.49 (s, 1H), 8.77 – 8.87 (m, 3H), 8.06 – 8.12 (m, 1H), 7.90 – 7.95 (m, 2H), 7.78 – 7.81 (m, 1H), 7.57 – 7.73 (m, 1H), 7.53 (dd, J = 19.6 Hz, 9.2 Hz, 1H).	DMSO	369.0, 371.1 (M+1)	Method A (TFA)	95	Method C, G1
121			401.68	¹H-NMR (400 MHz, DMSO-d₆): δ 10.37 (s, 1H), 9.52 (s, 1H), 8.95 (d, J = 3.2 Hz, 1H), 8.87 (m, 1H), 8.81 (s, 1H), 8.32 (d, J = 2.0 Hz, 1H), 7.95 – 7.99 (m, 3H), 7.87 – 7.89 (m, 1H), 7.72 (d, J = 8.8 Hz, 1H).	DMSO	401.0, 403.0, 405.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
122			385.22	¹H-NMR (400 MHz, DMSO-d₆): δ 10.09 (s, 1H), 9.50 (s, 1H), 8.69 (s, 2H), 8.64 (d, J = 8.0 Hz, 1H), 8.26 (dd, J = 10.6 Hz, 1.8 Hz, 1H), 7.89 – 7.90 (m, 3H), 7.51 – 7.57 (m, 2H).	DMSO	385.0, 387.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1

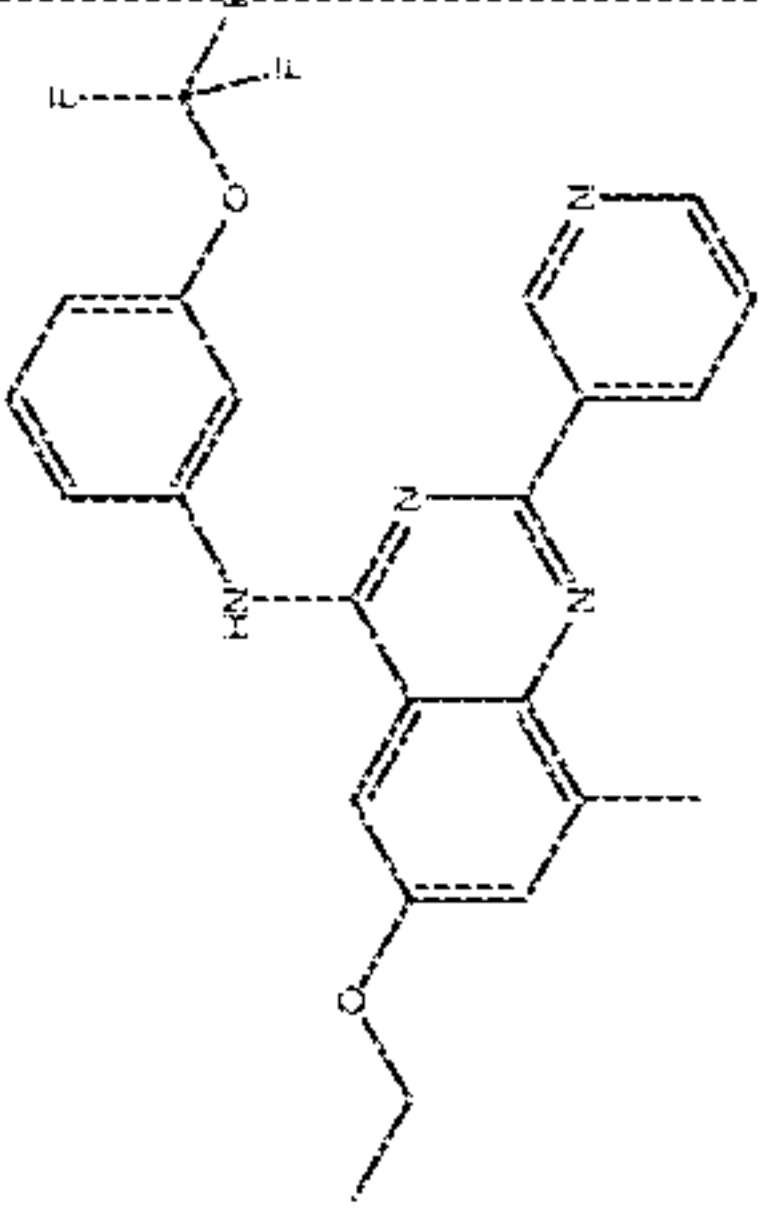
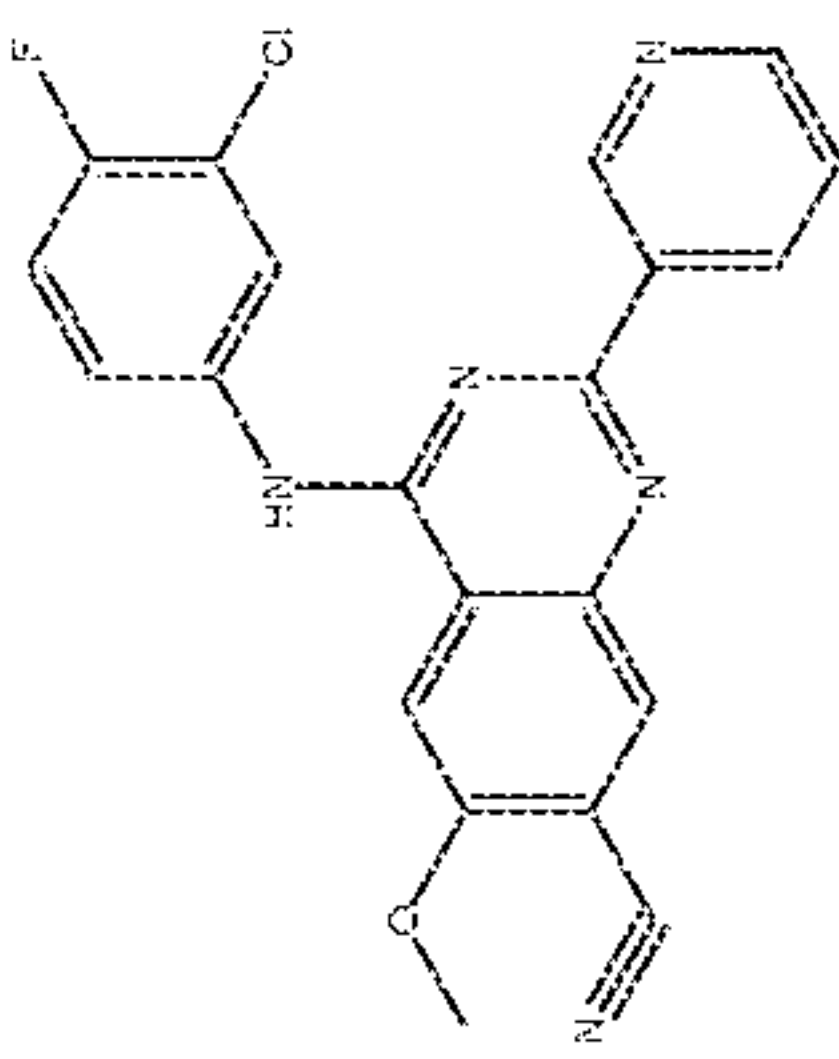
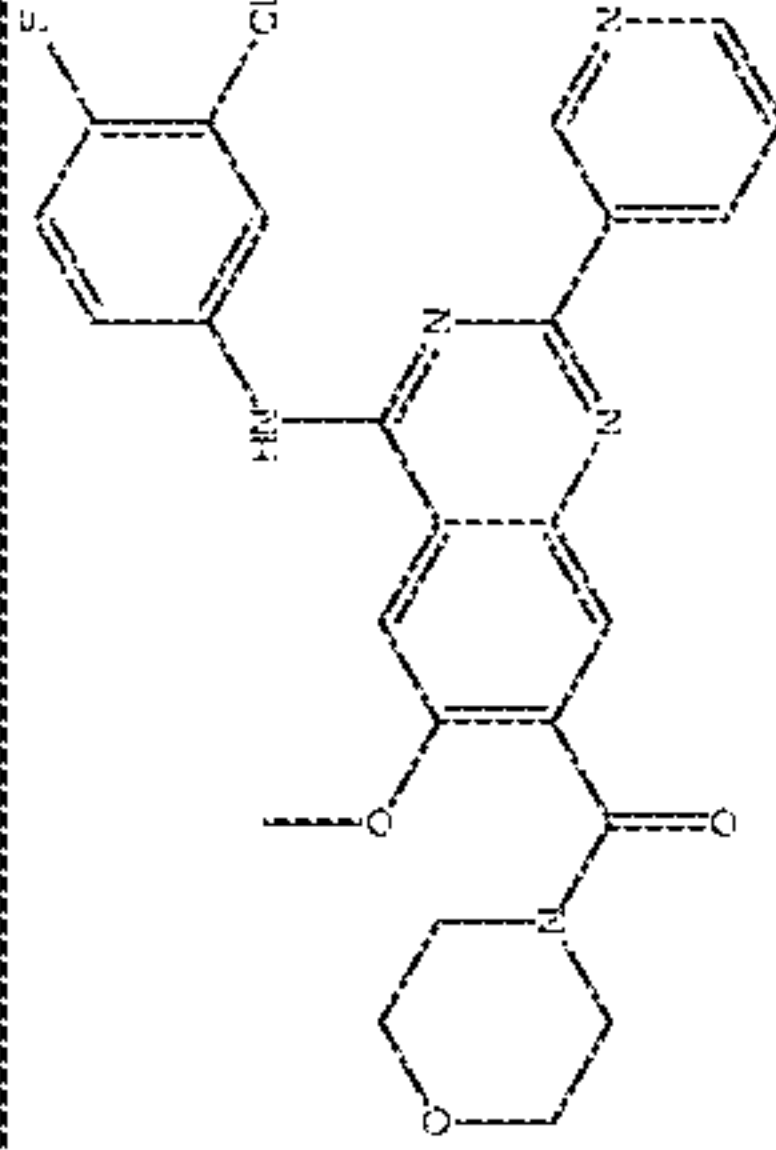
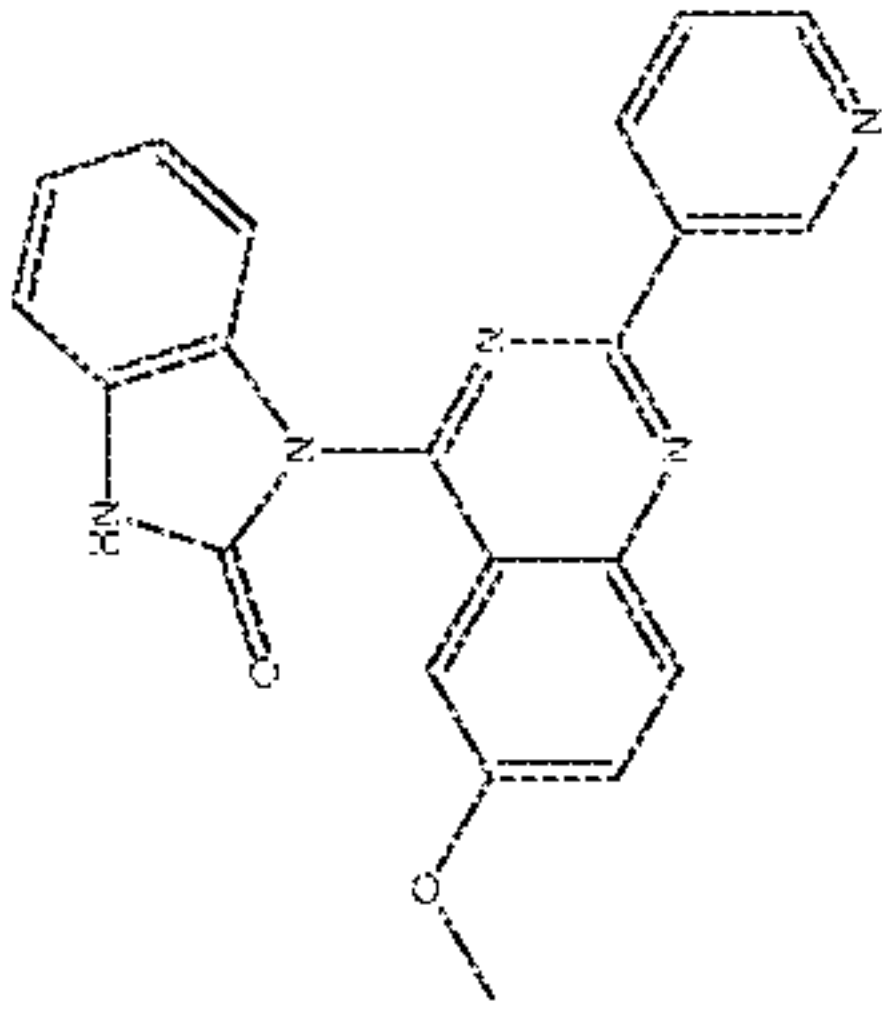
123			357.8	1H-NMR (400 MHz, DMSO-d6): δ 10.25 (s, 1H), 9.52 (s, 1H), 8.67 – 8.76 (m, 3H), 8.44 (s, 1H), 8.27 (m, 1H), 7.96 (s, 2H), 7.66 – 7.69 (m, 2H), 7.57 – 7.59 (m, 1H).	DMSO	358.0 (M+1)	Method A (TFA)	95	Method C, G1
124			411.86	1H-NMR (400 MHz, DMSO-d6): δ 10.53 (s, 1H), 9.54 (s, 1H), 9.08 (d, J = 8.4 Hz, 1H), 8.94 – 8.90 (m, 2H), 8.15 (d, J = 8.4 Hz, 2H), 8.00 – 7.93 (m, 5H), 7.39 (s, 2H).	DMSO	412.0, 414.0 (M+1)	Method A (TFA)	95	Method C, G1
125			411.86	1H-NMR (400 MHz, DMSO-d6): δ 10.64 (s, 1H), 9.54 (s, 1H), 9.22 (s, 1H), 8.92 – 8.98 (m, 2H), 8.70 (s, 1H), 8.10 (s, 1H), 8.03 – 8.05 (m, 1H), 7.95 (s, 2H), 7.69 (s, 2H), 7.53 (s, 2H).	DMSO	412.0, 414.0 (M+1)	Method A (TFA)	95	Method C, G1

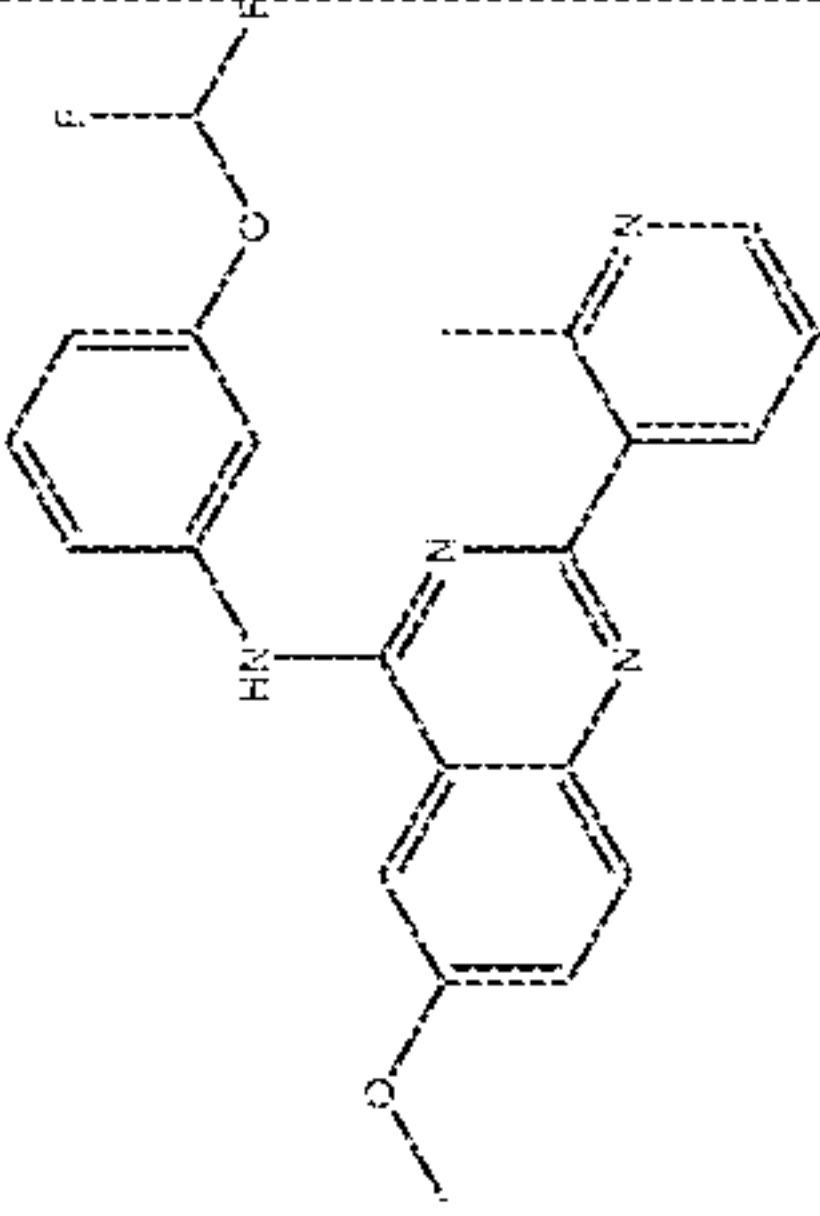
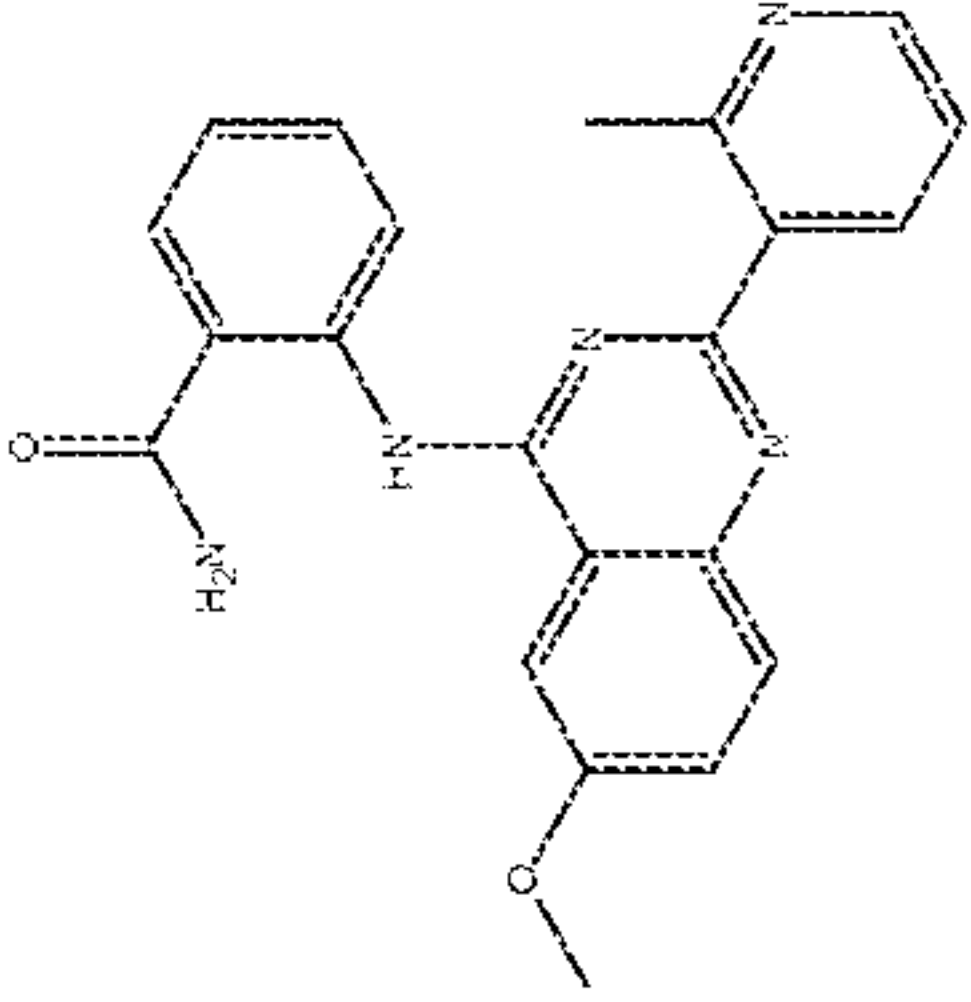
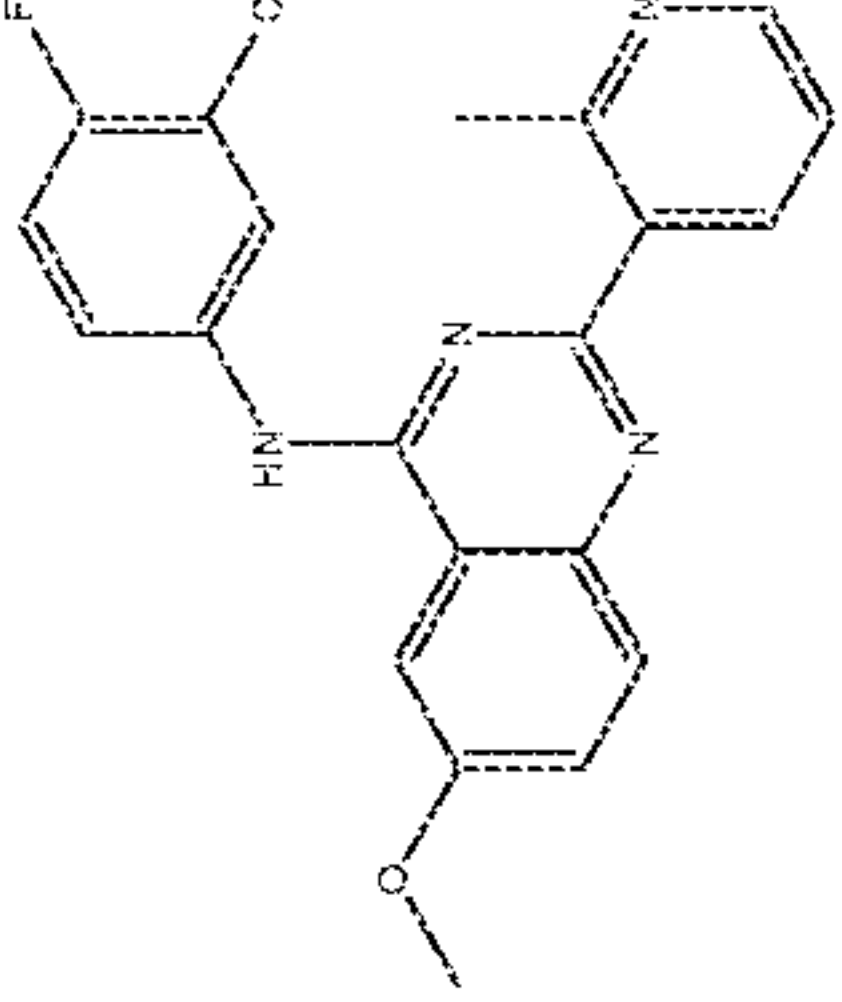
126			364.35	1H-NMR (400 MHz, DMSO-d6): δ 10.65 (s, 1H), 9.47 (s, 1H), 9.02 (d, J = 7.6 Hz, 1H), 8.92 (s, 1H), 8.21 (s, 1H), 8.08 – 8.10 (m, 1H), 7.95 – 7.97 (m, 2H), 7.74 – 7.75 (m, 1H), 7.54 – 7.62 (m, 2H), 4.00 (s, 3H).	DMSO	365.1 (M+1), 183.1 (M/2+1)	Method A (TFA)	95	Method C, G1
127			397.26	1H-NMR (400 MHz, DMSO-d6): δ 10.56 (s, 1H), 9.48 (s, 1H), 9.02 (d, J = 8.0 Hz, 1H), 8.91 – 8.92 (m, 1H), 8.28 (d, J = 2.4 Hz, 1H), 8.16 – 8.17 (m, 1H), 7.92 – 8.03 (m, 3H), 7.72 (d, J = 8.8 Hz, 1H), 7.58 – 7.61 (m, 1H), 4.00 (s, 3H).	DMSO	397.0, 399.0 (M+1), 200.1 (M/2+1)	Method A (TFA)	95	Method C, G1
128			407.45	1H-NMR (400 MHz, DMSO-d6): δ 10.32 (s, 1H), 9.55 (s, 1H), 8.92 – 8.84 (m, 2H), 8.16 – 8.09 (m, 3H), 7.95 – 7.89 (m, 3H), 7.83 – 7.79 (m, 1H), 7.62 – 7.58 (m, 1H), 7.36 (s, 2H), 3.40 (s, 3H).	DMSO	408.1 (M+1)	Method A (TFA)	95	Method C, G1
129			362.81	1H-NMR (400 MHz, DMSO-d6): δ 10.06 (s, 1H), 9.51 (s, 1H), 8.82 – 8.85 (m, 2H), 8.10 – 8.11 (m, 1H), 8.05 (d, J = 2.0 Hz, 1H), 7.98 – 7.93 (m, 2H), 7.75 – 7.77 (m, 1H), 7.59 – 7.61 (m, 1H), 7.52 (t, J = 8.0 Hz, 1H), 7.27 – 7.28 (m, 1H), 3.99 (s, 3H).	DMSO	363.0, 365.0 (M+1), 182.1 (M/2+1)	Method A (TFA)	95	Method C, G1

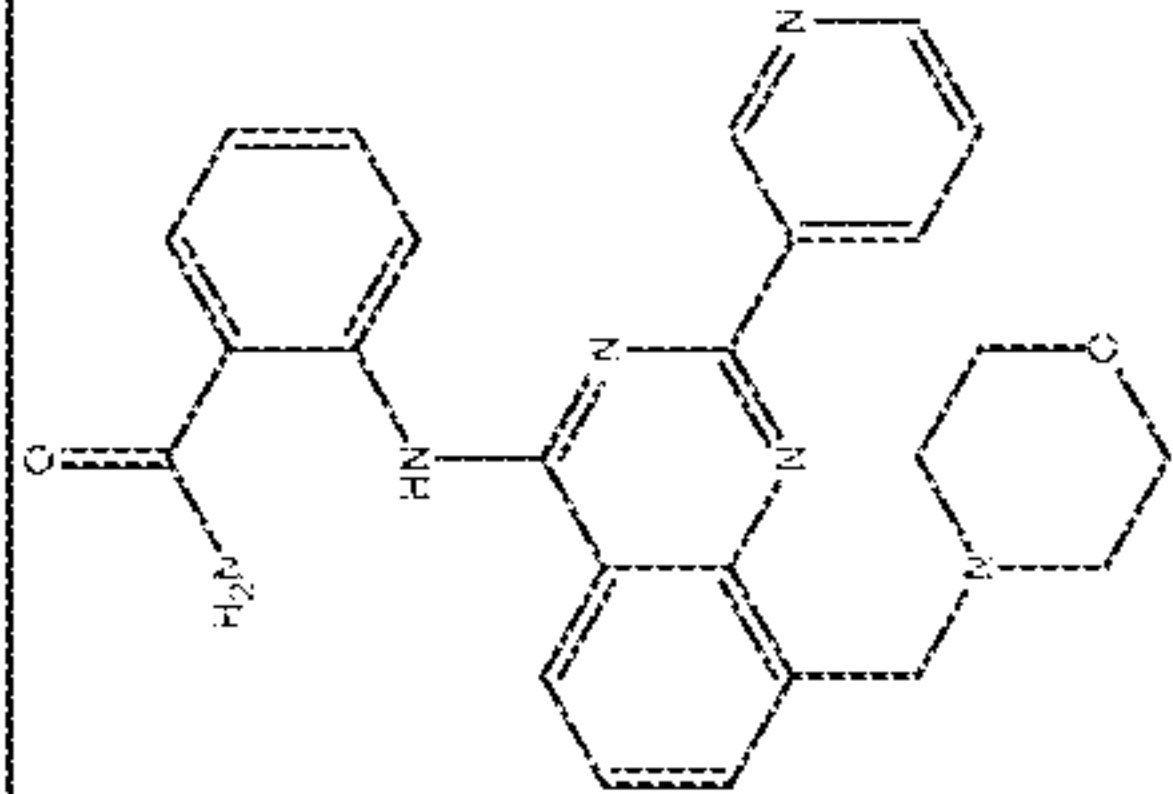
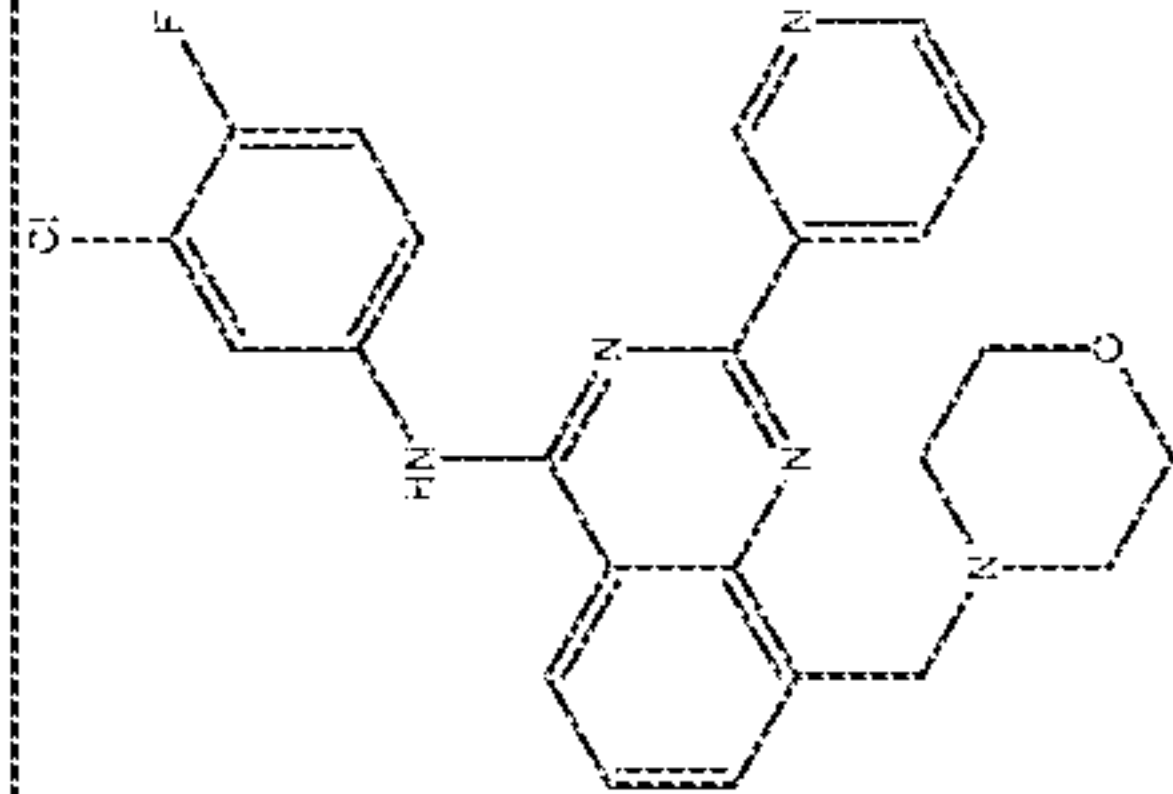
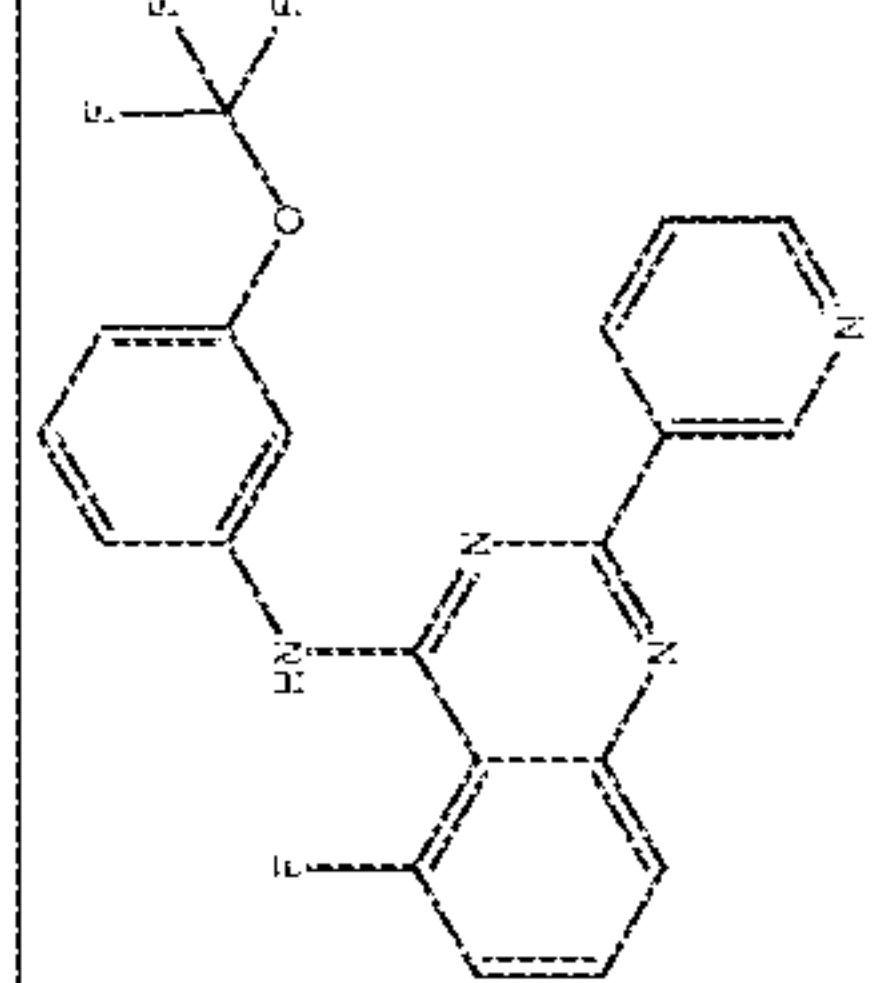
130			380.8	1H-NMR (300 MHz, DMSO-d6): δ 10.02 (s, 1H), 9.50 (s, 1H), 7.78 – 8.79 (m, 2H), 8.19 – 8.24 (m, 1H), 7.86 – 8.00 (m, 3H), 7.52 – 7.70 (m, 3H), 3.98 (s, 3H).	DMSO	381.1, 383.1 (M+1), 191.1 (M/2+1)	Method A (TFA)	95	Method C, G1
131			371.39	1H-NMR (300 MHz, DMSO-d6): δ 13.08 (s, 1H), 9.59 (s, 1H), 9.07 (d, J = 8.1 Hz, 1H), 8.96(d, J = 8.1 Hz, 1H), 8.83 (d, J = 3.9 Hz, 1H), 8.49(s, 1H), 7.89 – 7.99 (m, 3H), 7.80 – 7.84 (m, 1H), 7.72 (t, J = 7.8 Hz, 1H), 7.60 – 7.63 (m, 2H), 7.23 (t, J = 7.5 Hz, 1H), 3.98 (s, 3H).	DMSO	371.9 (M+1)	Method A (TFA)	95	Method C, G1
132			362.81	1H-NMR (400 MHz, DMSO-d6): δ 10.12 (s, 1H), 9.28 (s, 1H), 8.69 (d, J = 4.0 Hz, 1H), 8.59 (d, J = 8.4 Hz, 1H), 8.00 (d, J = 2.8 Hz, 1H), 7.87 (d, J = 9.2 Hz, 1H), 7.68 – 7.70 (m, 2H), 7.57 – 7.63 (m, 2H), 7.48 – 7.53 (m, 1H), 7.40 – 7.44 (m, 1H), 3.86 (s, 3H).	DMSO	363.0, 365.1 (M+1), 182.1 (M/2+1)	Method A (TFA)	95	Method C, G1
133			348.35	1H-NMR (400 MHz, DMSO-d6): δ 9.46 (s, 1H), 9.11 (s, 1H), 8.79 – 8.76 (m, 2H), 8.00 – 7.94 (m, 1H), 7.83 – 7.73 (m, 3H), 7.62 – 7.48 (m, 3H), 3.00 (s, 3H).	DMSO	349.1 (M+1), 175.1 (M/2+1)	Method A (TFA)	95	Method C, G1

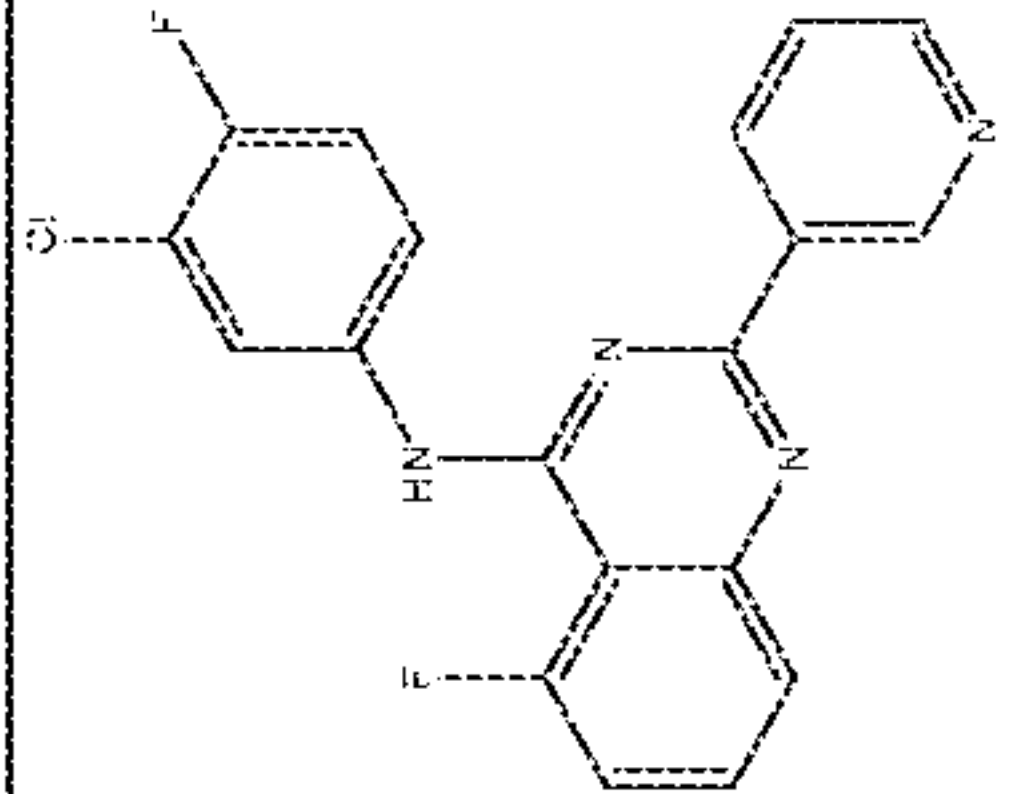
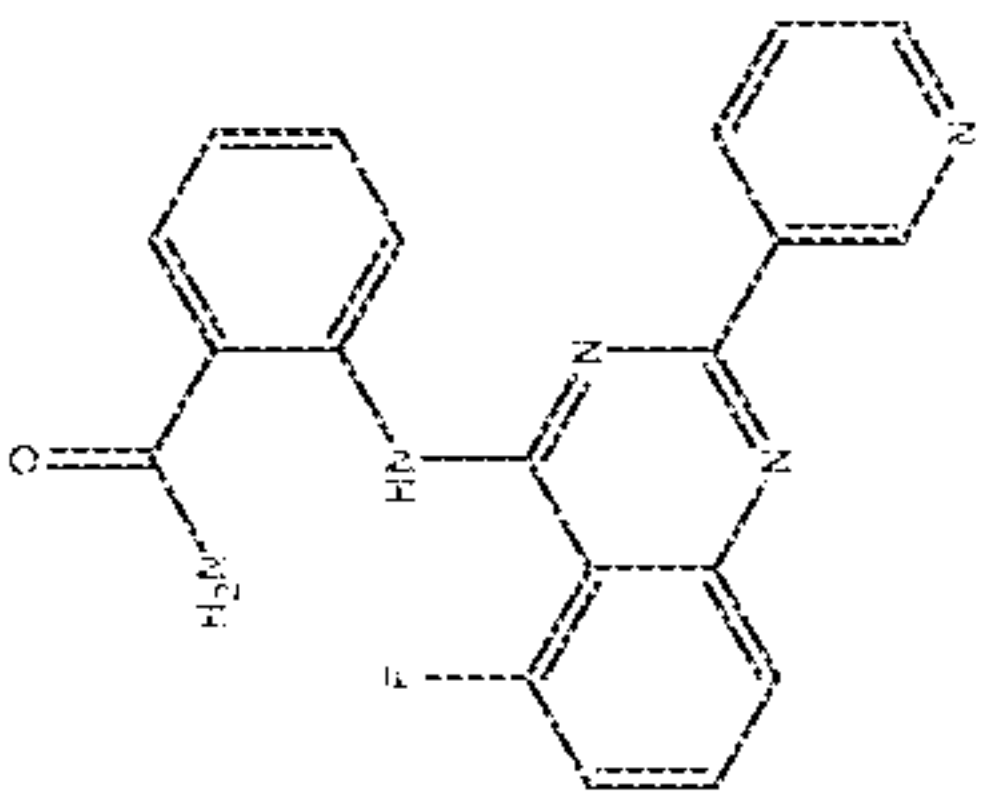
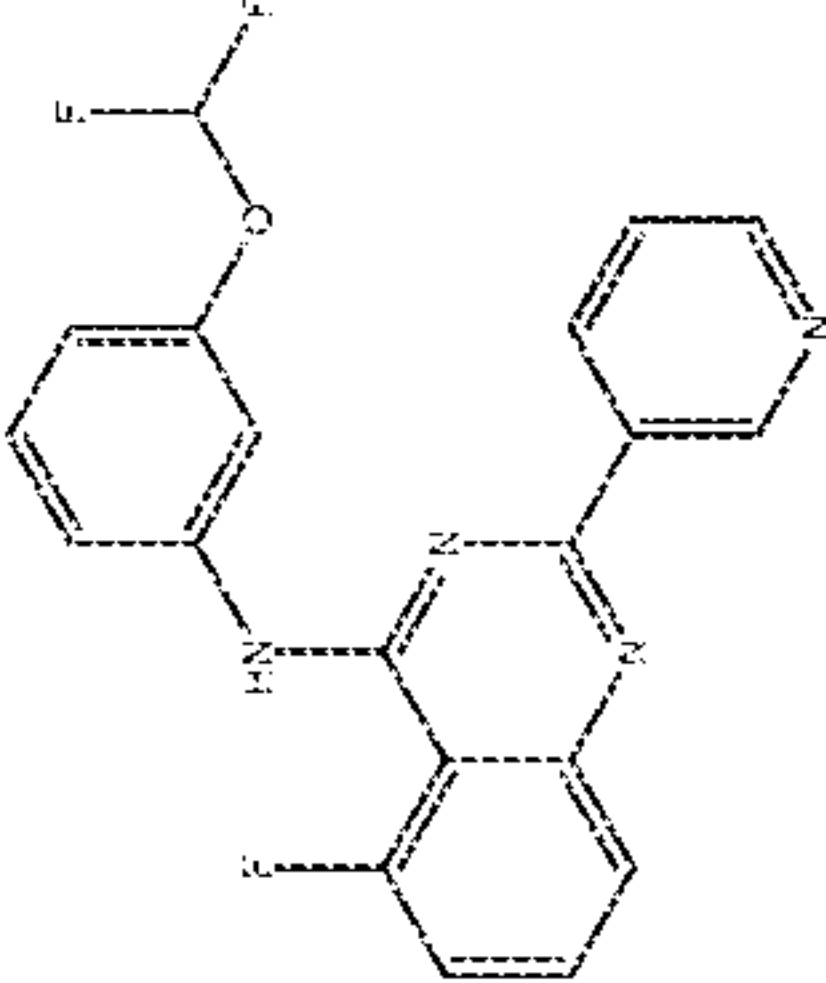
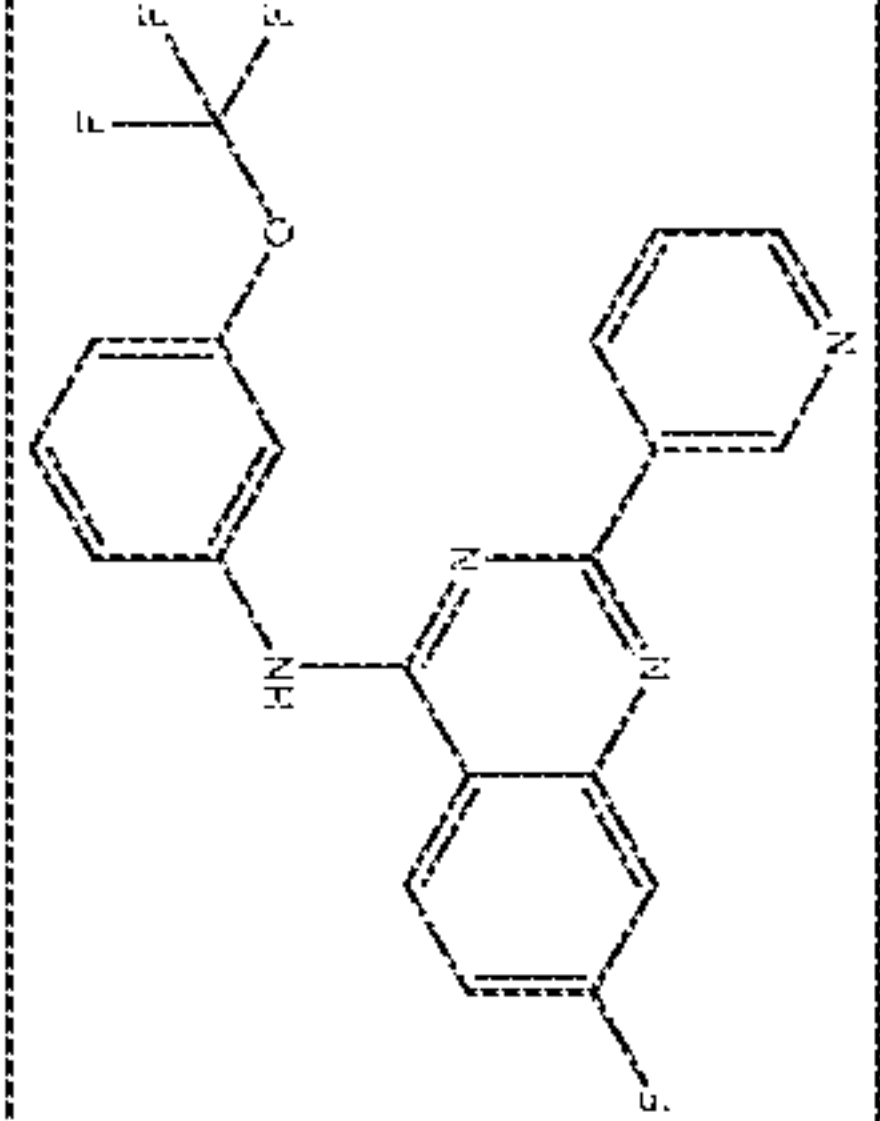
134			381.26	1H-NMR (400 MHz, DMSO-d6): δ 9.46 (s, 1H), 9.13 (s, 1H), 8.75 -- 8.77 (m, 2H), 8.18 (s, 1H), 7.72 -- 7.85 (m, 5H), 7.49 -- 7.50 (m, 1H), 3.00 (s, 3H).	DMSO	381.0, 363.0, 385.0 (M+1)	Method A (TFA)	95	Method C, G1
135			364.8	1H-NMR (400 MHz, DMSO-d6): δ 9.43 (m, 2H), 8.94 -- 8.89 (m, 2H), 8.08 -- 8.06 (m, 1H), 7.92 -- 7.81 (m, 4H), 7.57 -- 7.53 (m, 2H), 3.03 (s, 3H).	DMSO	365.0, 367.0 (M+1), 183.1 (M/2+1)	Method A (TFA)	95	Method C, G1
136			337.38	1H-NMR (400 MHz, DMSO-d6): δ 9.52 -- 9.44 (m, 2H), 8.98 (d, J = 8.0 Hz, 1H), 8.92 (d, J = 4.4 Hz, 1H), 8.36 -- 8.19 (m, 2H), 8.02 -- 7.84 (m, 3H), 7.73 -- 7.69 (m, 2H), 7.55 (d, J = 6.6 Hz, 1H), 3.04 (s, 3H).	DMSO	338.1 (M+1), 169.6 (M/2+1)	Method A (TFA)	95	Method C, G1
137			364.35	1H-NMR (400 MHz, DMSO-d6): δ 9.97 (s, 1H), 9.51 (s, 1H), 8.69 -- 8.66 (m, 2H), 8.16 -- 8.08 (m, 2H), 7.75 -- 7.73 (m, 1H), 7.61 -- 7.53 (m, 3H), 7.40 (d, J = 7.6 Hz, 1H), 4.01 (s, 3H).	DMSO	183.1 (M/2+1) 365.1 (M+1)	Method A (TFA)	95	Method C, G1

138			397.26	1H-NMR (400 MHz, DMSO-d6): δ 10.01 (s, 1H), 9.53 (s, 1H), 8.67 – 8.70 (m, 2H), 8.41 (d, J = 2.4 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.95 – 7.99 (m, 1H), 7.73 (d, J = 8.8 Hz, 1H), 7.56 – 7.63 (m, 2H), 7.42 (d, J = 8.4 Hz, 1H), 4.02 (s, 3H).	DMSO	397.0, 399.0 (M+1)	Method A (TFA)	95	Method C, G1
139			380.8	1H-NMR (400 MHz, DMSO-d6): δ 10.21 (s, 1H), 9.48 (s, 1H), 8.99 (d, J = 8.0 Hz, 1H), 8.89 (d, J = 4.8 Hz, 1H), 8.15 – 8.22 (m, 2H), 7.92 – 7.95 (m, 2H), 7.62 (t, J = 8.0 Hz, 1H), 7.52 (t, J = 8.8 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 4.02 (s, 3H).	DMSO	191.1 (M/2+1), 361.1, 383.1 (M+1)	Method A (TFA)	95	Method C, G1
140			401.68	1H-NMR (400 MHz, DMSO-d6): δ 10.11 (s, 1H), 8.50 (m, 1H), 8.63 – 8.70 (m, 3H), 8.14 (d, J = 2.0 Hz, 2H), 7.92 (m, 2H), 7.57 (m, 1H), 7.38 (t, J = 1.6 Hz, 1H).	DMSO	401.0, 403.0 (M+1)	Method B (NH4HCO3)	95	Method C, G1
141			348.35	1H-NMR (400 MHz, DMSO-d6): δ 9.46 (s, 1H), 9.11 (s, 1H), 8.76 – 8.70 (m, 2H), 7.95 – 7.99 (m, 1H), 7.78 – 7.60 (m, 3H), 7.54 – 7.44 (m, 3H), 3.00 (s, 3H).	DMSO	175.1 (M/2+1), 349.1 (M+1)	Method A (TFA)	95	Method C, G1

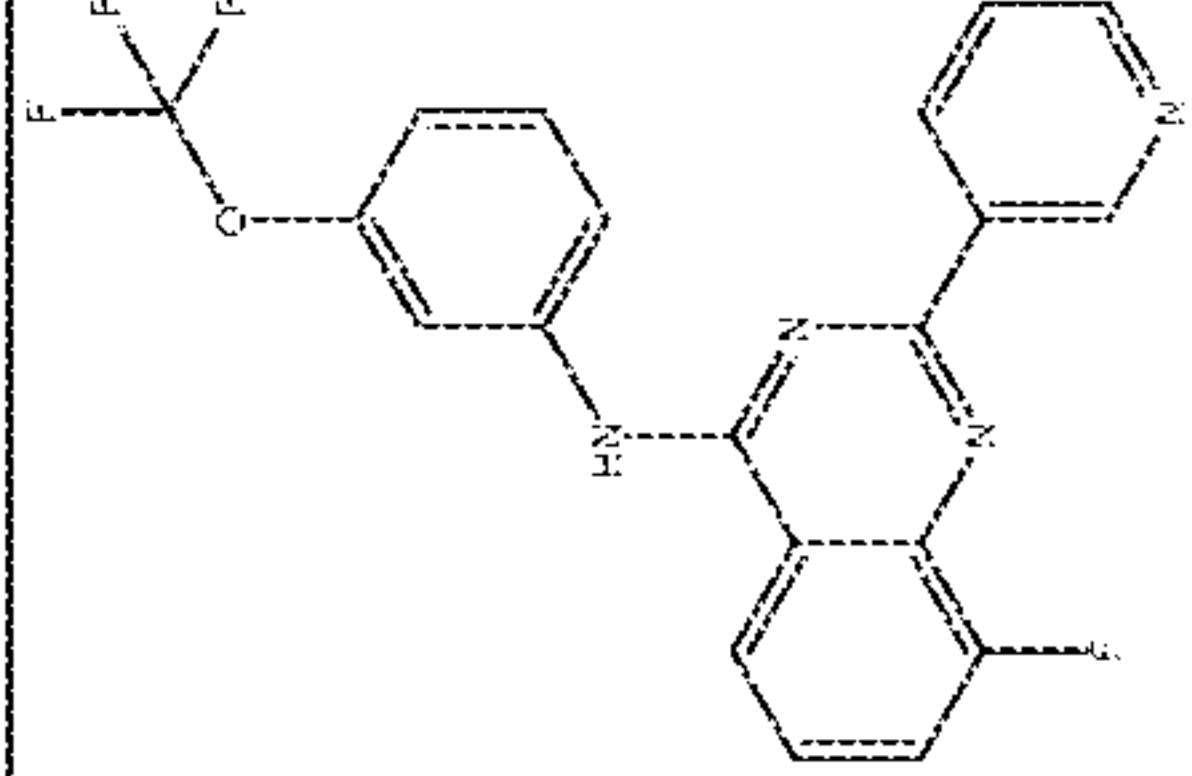
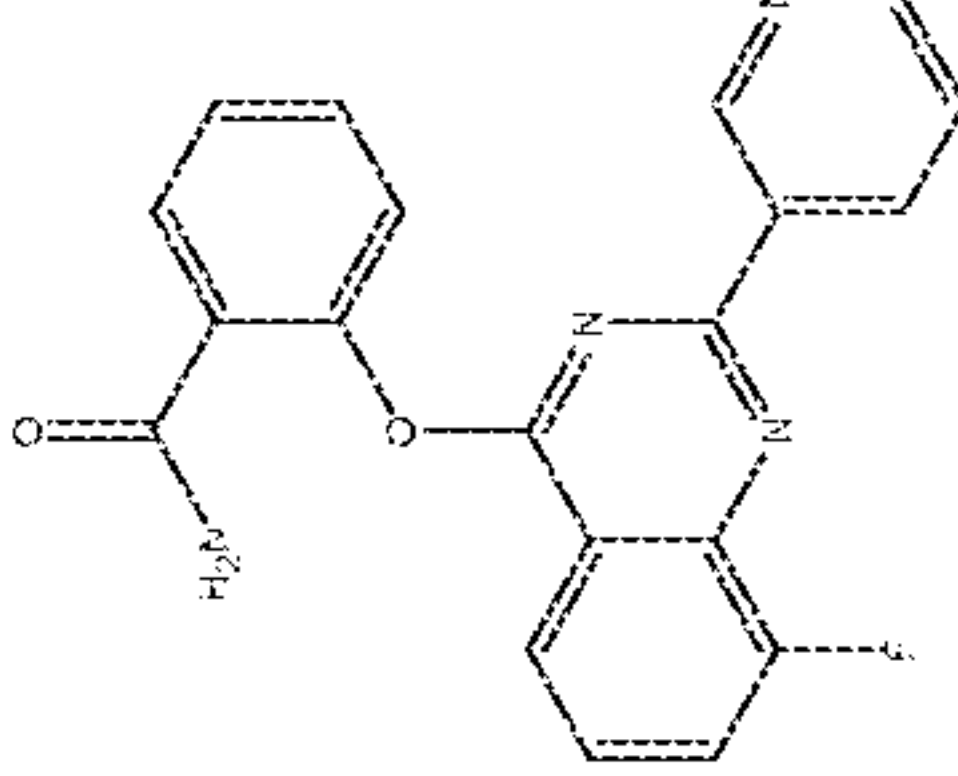
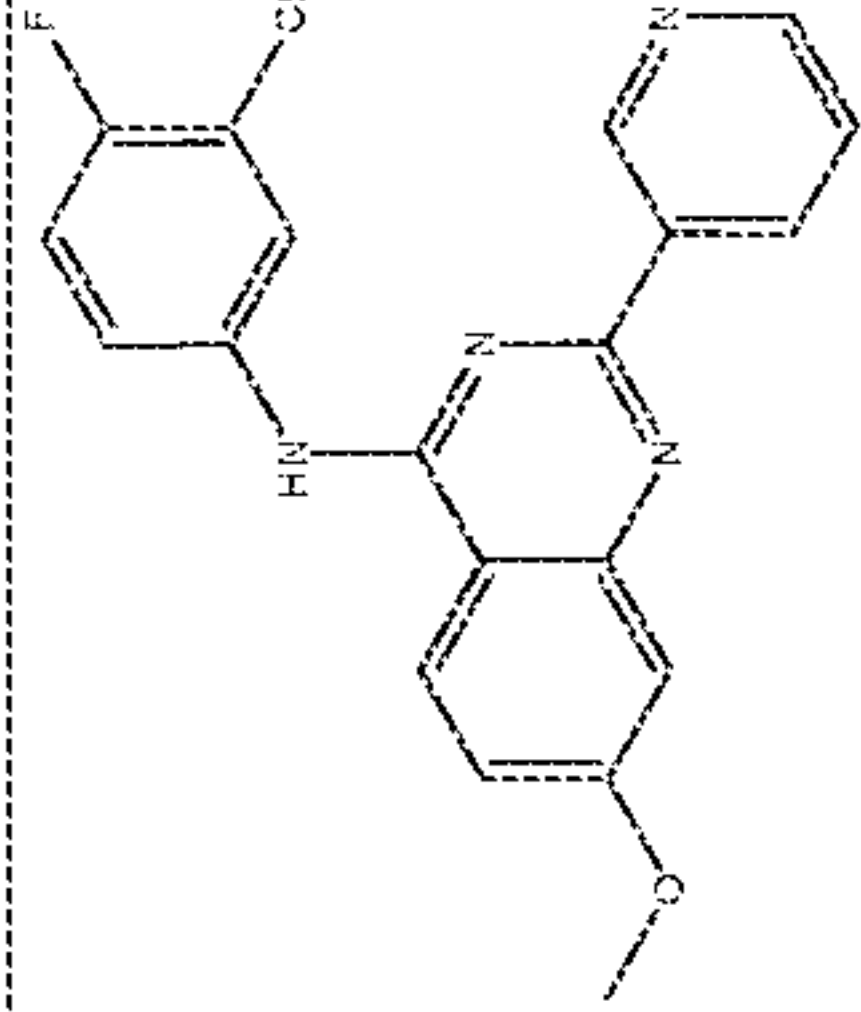
142			397.26	1H-NMR (400 MHz, DMSO-d6): δ 10.30 (s, 1H), 8.39 (s, 1H), 8.83 (s, 2H), 8.03 – 8.12 (m, 3H), 7.79 – 7.81 (m, 2H), 7.50 – 7.51 (m, 1H), 7.32 (s, 1H), 3.96 (s, 3H).	DMSO	397.0, 399.0, 401.0 (M+1)	Method B (NH4HCO3)	95	Method C, G1
143			452.34	1H-NMR (400 MHz, DMSO-d6): δ 9.86 (s, 1H), 9.51 (s, 1H), 8.65 – 8.66 (m, 2H), 8.34 – 8.35 (m, 1H), 7.95 – 7.96 (m, 1H), 7.72 – 7.80 (m, 4H), 7.54 (m, 1H), 3.84 (m, 4H), 3.56 (m, 4H).	DMSO	452.1, 454.0 (M+1)	Method B (NH4HCO3)	95	Method C, G1
144			435.88	1H-NMR (400 MHz, DMSO-d6): δ 9.83 (s, 1H), 9.49 (s, 1H), 8.62 – 8.65 (m, 2H), 8.21 – 8.23 (m, 1H), 7.89 – 7.91 (m, 1H), 7.78 – 7.81 (m, 1H), 7.72 – 7.73 (m, 2H), 7.51 – 7.54 (m, 2H), 3.84 (t, J = 4.0 Hz, 4H), 3.36 (m, 4H).	DMSO	436.1, 438.1 (M+1)	Method B (NH4HCO3)	95	Method C, G1
145			419.43	1H-NMR (400 MHz, DMSO-d6): δ 10.50 (s, 1H), 9.45 (s, 1H), 8.83 – 8.90 (m, 2H), 8.06 – 8.08 (m, 1H), 7.70-7.93 (m, 5H), 7.56 (dd, J = 19.6, 9.6 Hz, 1H), 3.82 – 3.83 (m, 4H), 3.39 – 3.41 (m, 4H).	DMSO	420.1 (M+1)	Method B (NH4HCO3)	95	Method C, G1

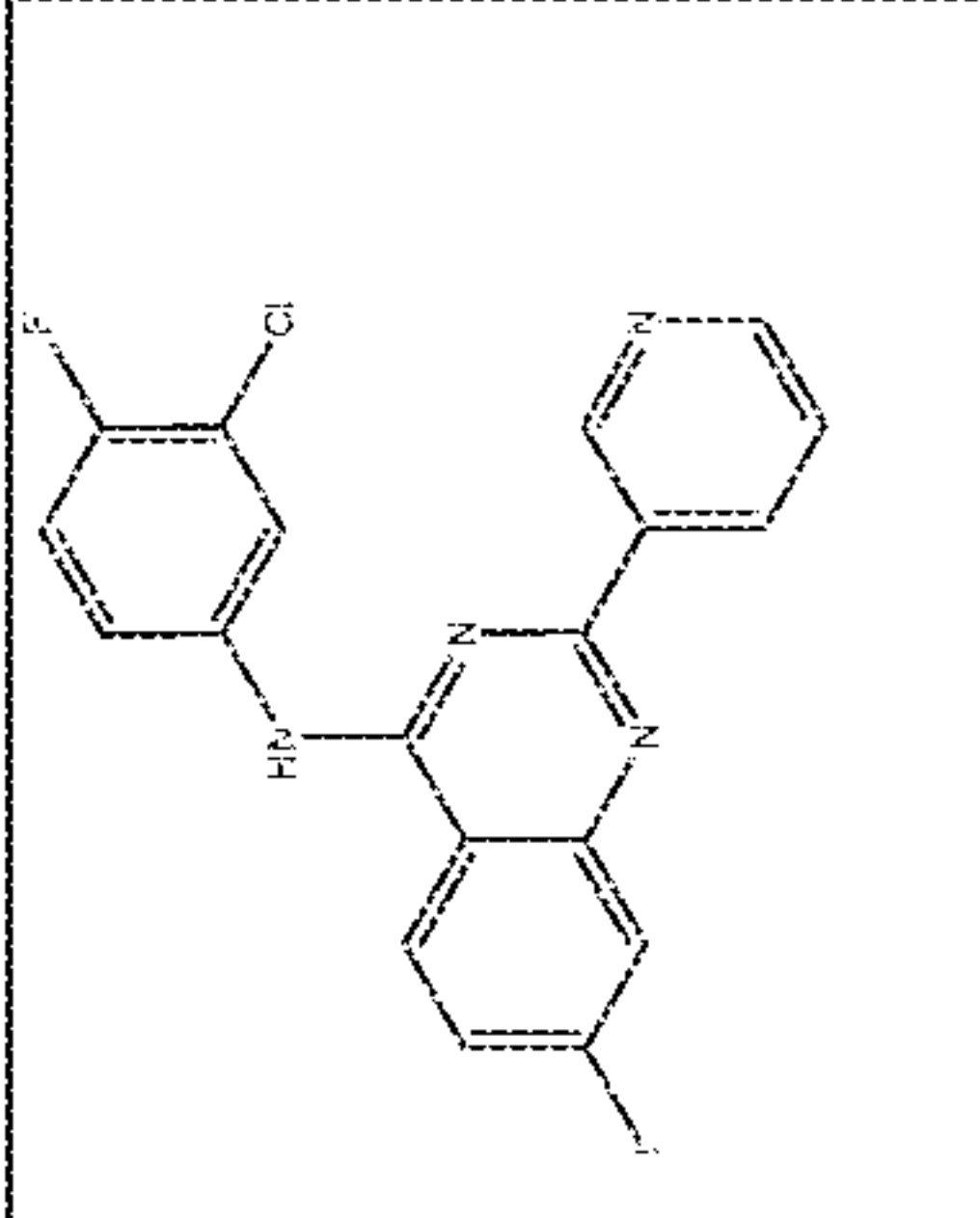
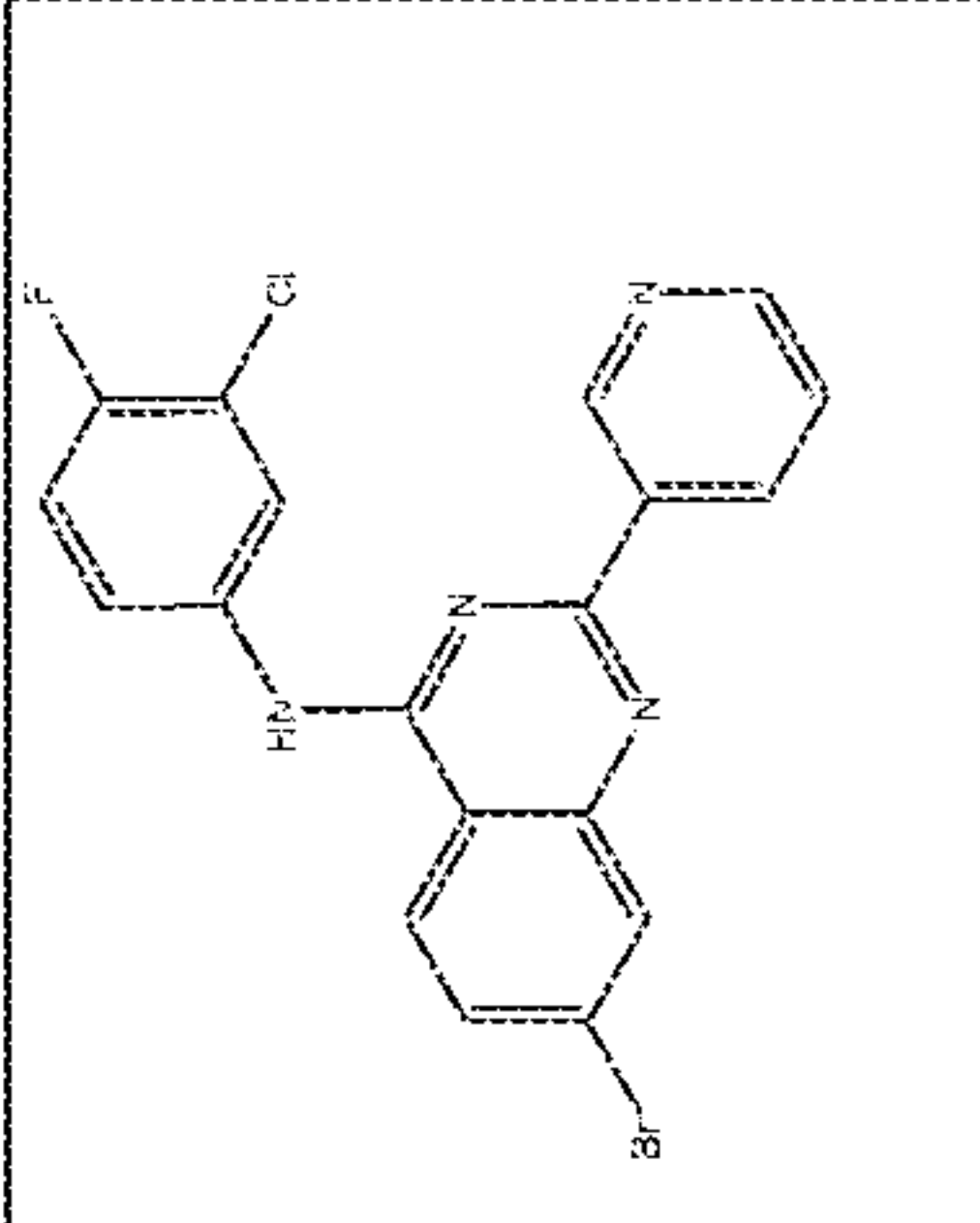
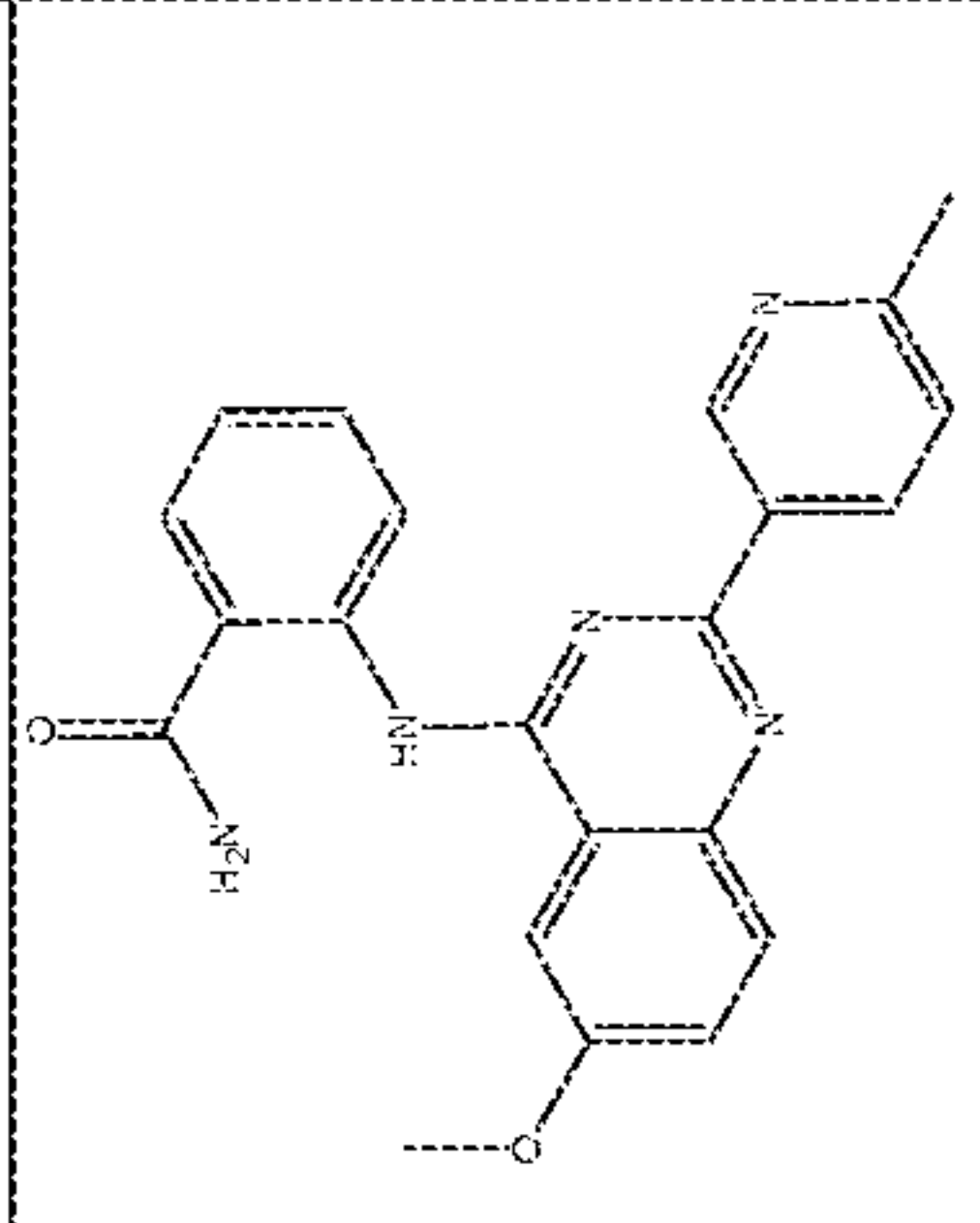
146		408.46	¹H-NMR (400 MHz, DMSO-d₆): δ 10.54 (s, 1H), 9.44 (s, 1H), 8.90 (d, J = 8.0 Hz, 1H), 8.84 (d, J = 4.4 Hz, 1H), 8.34 (s, 1H), 8.27 (d, J = 7.2 Hz, 1H), 7.67 – 7.92 (m, 6H), 3.82 – 3.83 (m, 4H), 3.39 – 3.40 (m, 4H).	DMSO	409.2 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
147		452.34	¹H-NMR (400 MHz, DMSO-d₆): δ 10.42 (s, 1H), 9.42 (s, 1H), 8.85 – 8.87 (m, 2H), 8.11 (s, 2H), 7.73 – 7.88 (m, 4H), 7.38 (s, 1H), 3.82 – 3.83 (m, 4H), 3.39 – 3.40 (m, 4H).	DMSO	452.1, 454.1, 456.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
148		426.47	¹H-NMR (400 MHz, DMSO-d₆): δ 12.93 (s, 1H), 9.57 (m, 1H), 9.12 (d, J = 8.4 Hz, 1H), 8.68 – 8.72 (m, 2H), 8.56 (s, 1H), 8.02 (d, J = 6.8 Hz, 1H), 7.96 (s, 1H), 7.72 – 7.84 (m, 3H), 7.56 – 7.57 (m, 1H), 7.40 (m, 1H), 7.19 (t, J = 8.0 Hz, 1H), 3.84 (t, J = 4.4 Hz, 4H), 3.35 (t, J = 4.4 Hz, 4H).	DMSO	427.2 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1

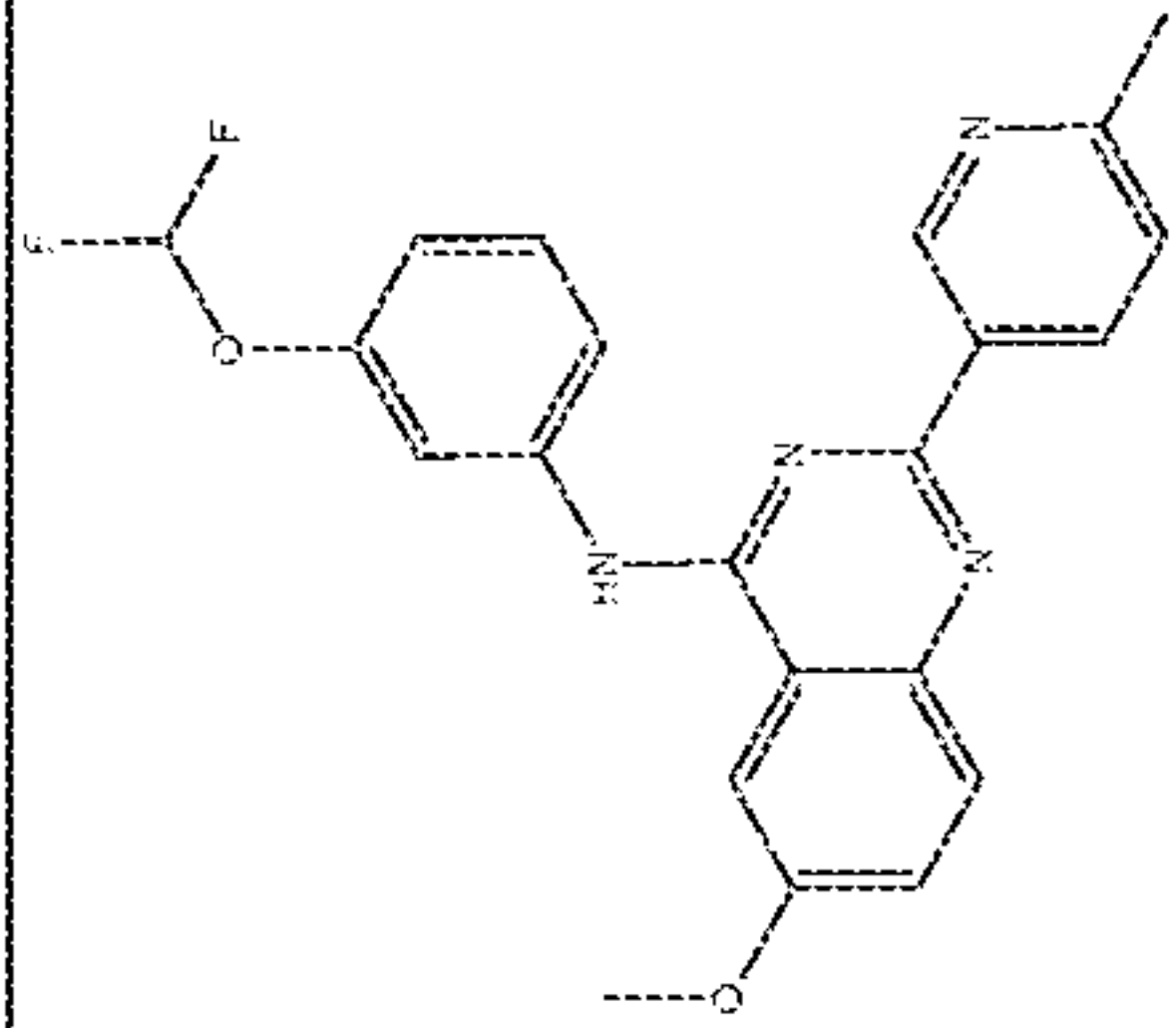
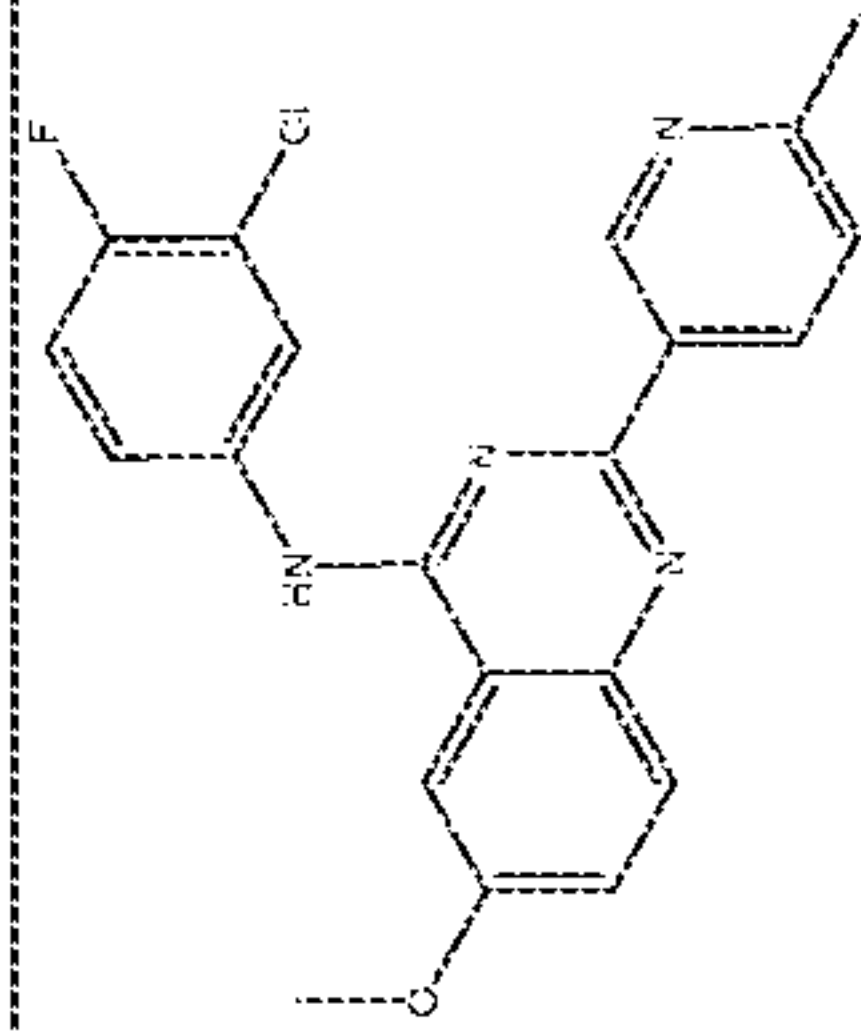
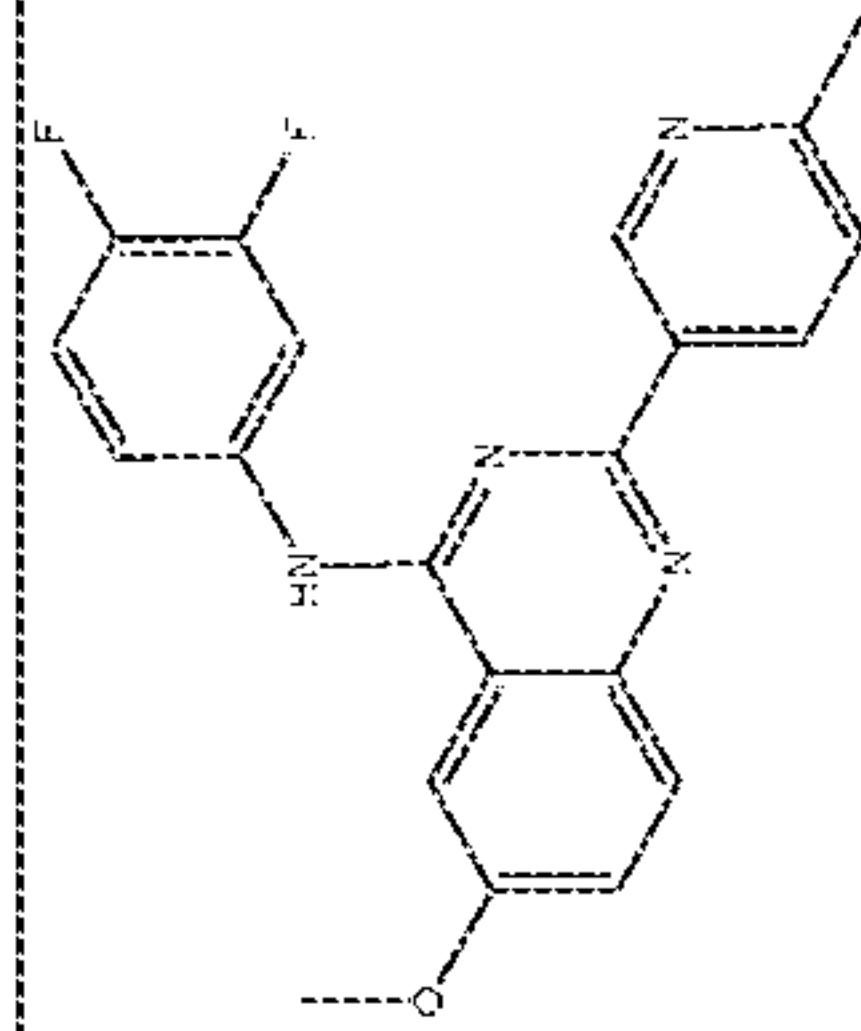
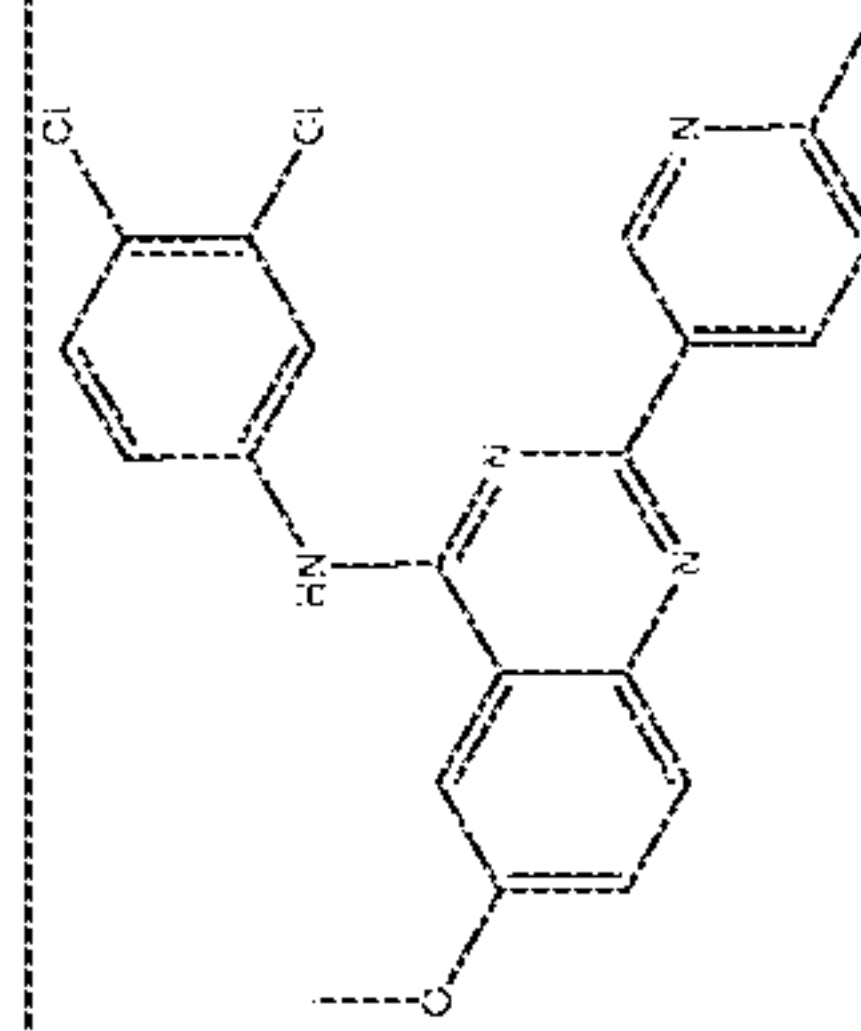
149			393.84	1H-NMR (400 MHz, DMSO-d6): δ 9.71 (s, 1H), 9.48 (s, 1H), 8.62 -- 8.63 (m, 2H), 8.23 (m, 1H), 7.92 (m, 1H), 7.77 (d, J = 9.6 Hz, 1H), 7.51 -- 7.56 (m, 3H), 7.42 (m, 1H), 3.12 (s, 6H).	DMSO	394.1, 396.1 (M+1)	Method B (NH4HCO3)	95	Method C, G1
150			377.39	1H-NMR (400 MHz, DMSO-d6): δ 9.72 (s, 1H), 9.48 (m, 1H), 8.60 -- 8.63 (m, 2H), 8.08 -- 8.14 (m, 1H), 7.77 (d, J = 9.2 Hz, 1H), 7.69 -- 7.71 (m, 1H), 7.50 -- 7.57 (m, 3H), 7.42 -- 7.43 (m, 1H), 3.12 (s, 6H).	DMSO	378.2 (M+1)	Method B (NH4HCO3)	95	Method C, G1
151			410.3	1H-NMR (400 MHz, DMSO-d6): δ 9.72 (s, 1H), 9.49 (s, 1H), 8.60 -- 8.64 (m, 2H), 8.17 (s, 2H), 7.76 (d, J = 8.8 Hz, 1H), 7.51 -- 7.53 (m, 2H), 7.37 (s, 1H), 7.32 (s, 1H), 3.11 (s, 6H).	DMSO	410.1, 412.0, 414.1 (M+1)	Method B (NH4HCO3)	95	Method C, G1

152			410.3	1H-NMR (400 MHz, DMSO-d6): δ 10.44 (s, 1H), 9.45 (s, 1H), 8.83 – 8.91 (m, 2H), 8.26 – 8.27 (m, 1H), 7.72 – 7.99 (m, 4H), 7.57 – 7.61 (m, 2H), 3.14 (s, 6H).	DMSO	410.1, 412.1, 414.0 (M+1)	Method B (NH4HCO3)	95	Method C, G1
153			366.42	1H-NMR (400 MHz, DMSO-d6): δ 9.82 (s, 1H), 9.48 (s, 1H), 8.55 – 8.64 (m, 2H), 8.41 (s, 1H), 8.28 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 9.6 Hz, 1H), 7.69 (t, J = 8.0 Hz, 1H), 7.50 – 7.61 (m, 3H), 7.43 (m, 1H), 3.12 (s, 6H).	DMSO	367.1 (M+1)	Method B (NH4HCO3)	95	Method C, G1
154			435.23	1H-NMR (400 MHz, DMSO-d6): δ 10.57 (s, 1H), 9.53 (s, 1H), 8.86 – 8.94 (m, 3H), 8.32 – 8.39 (m, 1H), 8.21 (s, 1H), 7.97 – 8.01 (m, 2H), 7.84 – 7.88 (m, 1H), 7.73 (d, J = 8.8 Hz, 1H).	DMSO	435.1, 437.1, 439.1 (M+1)	Method B (NH4HCO3)	95	Method C, G1
155			402.32	1H-NMR (400 MHz, DMSO-d6): δ 10.32 (s, 1H), 9.51 – 9.52 (m, 1H), 8.65 – 8.78 (m, 3H), 8.19 (s, 1H), 8.11 (m, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.71 (m, 1H), 7.55 – 7.59 (m, 2H).	DMSO	403.1 (M+1)	Method B (NH4HCO3)	95	Method C, G1

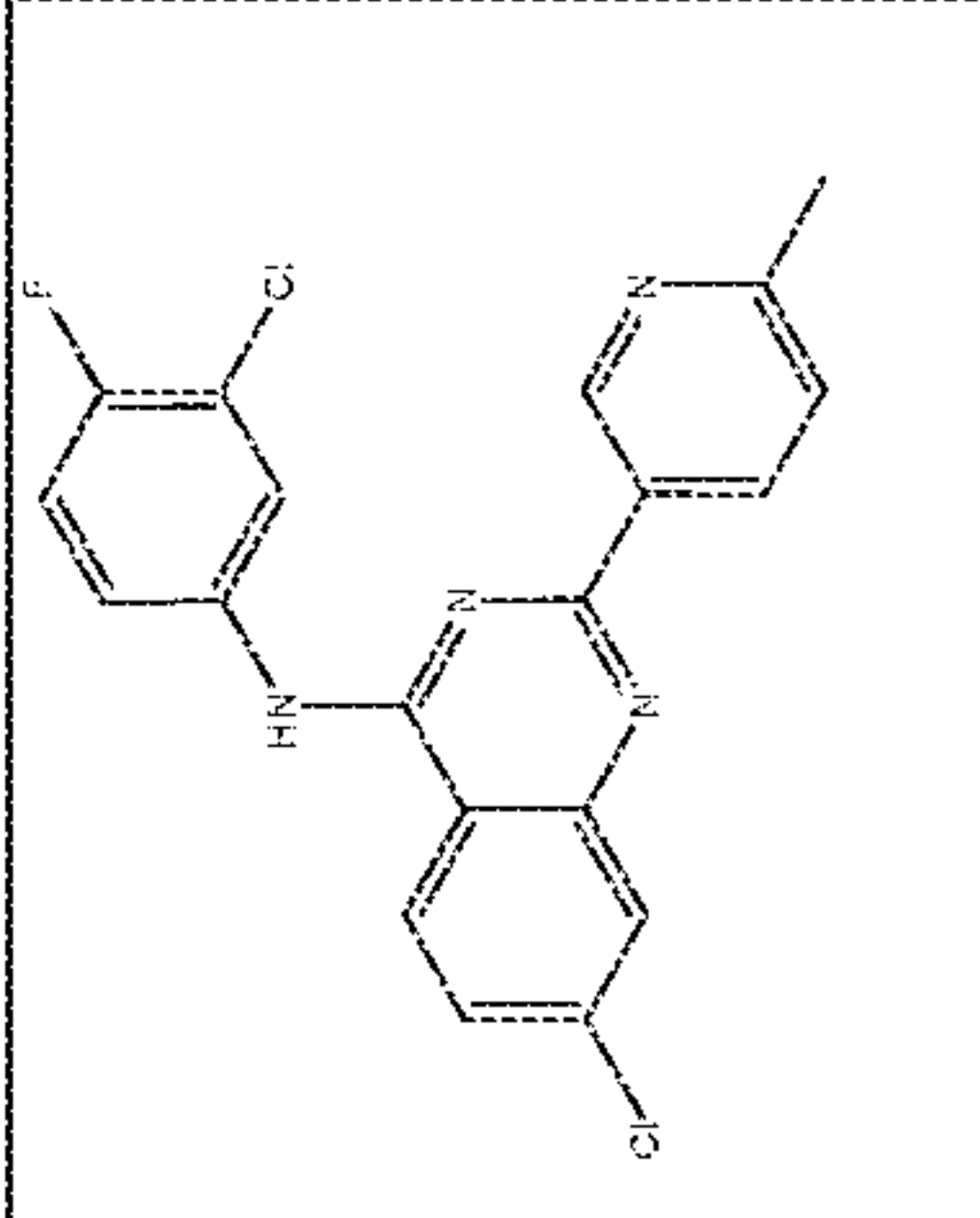
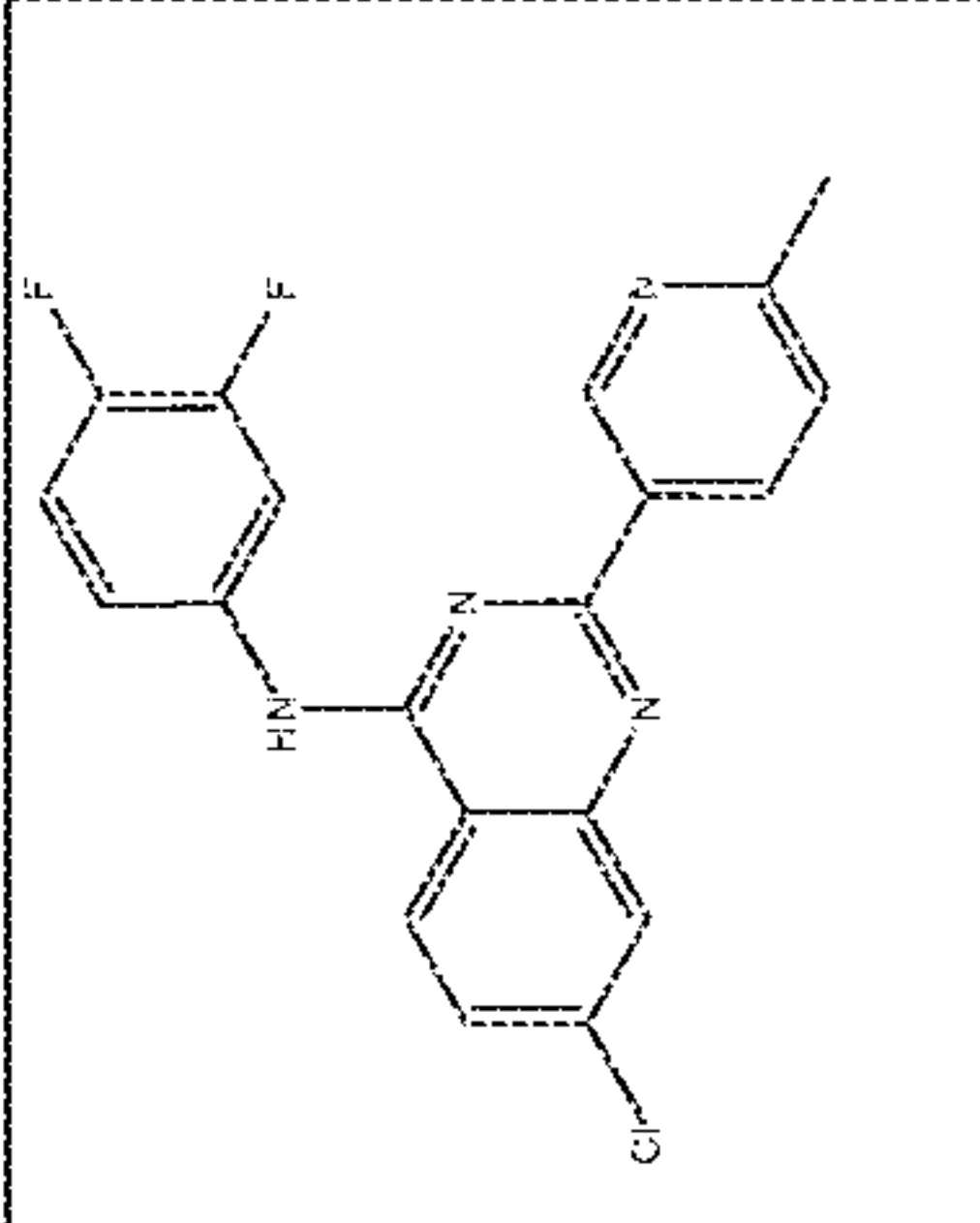
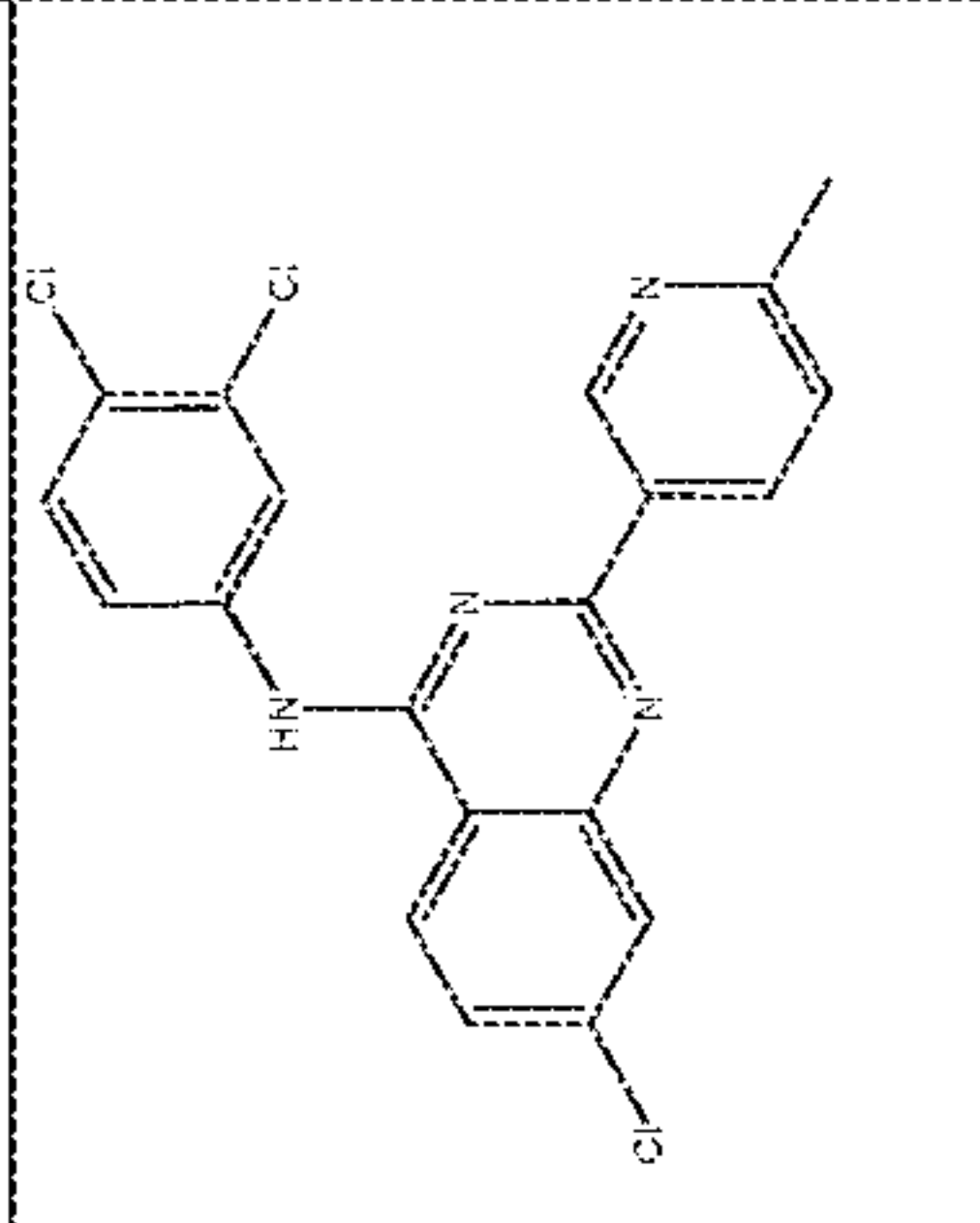
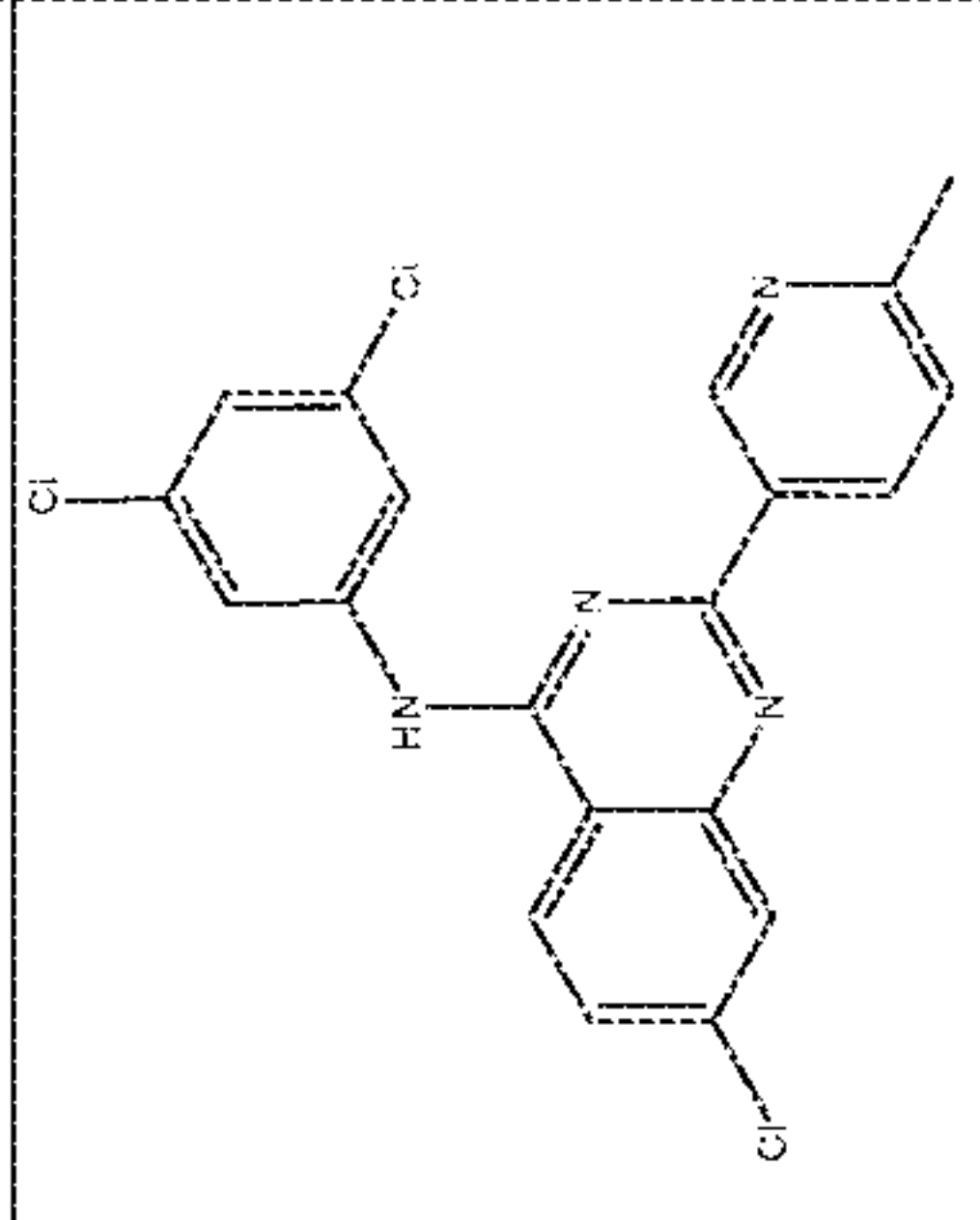
156			435.23	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.65 (s, 1H), 9.46 (s, 1H), 8.88 – 8.97 (m, 3H), 8.17 (s, 1H), 8.10 – 8.11 (m, 2H), 7.97 (s, 1H), 7.95 (s, 1H), 7.39 (s, 1H).	DMSO	435.1, 437.0, 439.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
157			418.77	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.62 (s, 1H), 9.52 (s, 1H), 8.99 (d, J = 8.0 Hz, 1H), 8.88 – 8.90 (m, 2H), 8.20 – 8.23 (m, 2H), 8.01 (d, J = 8.0 Hz, 1H), 7.92 – 7.95 (m, 2H), 7.54 (t, J = 9.2 Hz, 1H).	DMSO	419.1, 421.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G
158			409.36	¹ H-NMR (400 MHz, DMSO-d ₆): δ 13.24 (s, 1H), 9.56 (s, 1H), 9.10 (d, J = 8.4 Hz, 1H), 8.96 (s, 1H), 8.87 (d, J = 8.0 Hz, 1H), 8.54 (s, 1H), 8.33 (d, J = 8.8 Hz, 1H), 8.18 (s, 1H), 7.95 – 8.01 (m, 4H), 7.70 (t, J = 7.6 Hz, 1H), 7.27 (t, J = 7.2 Hz, 1H).	DMSO	410.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G

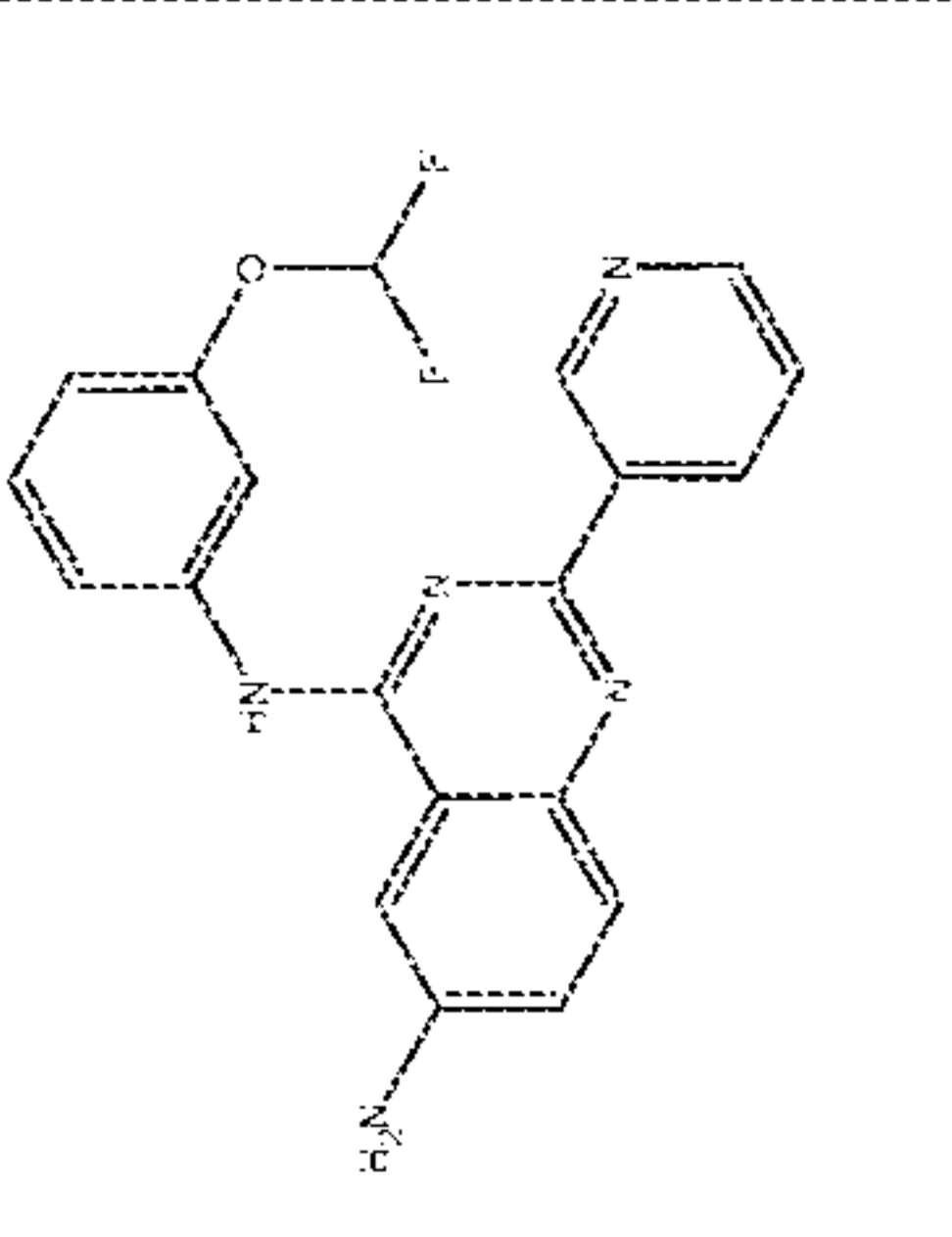
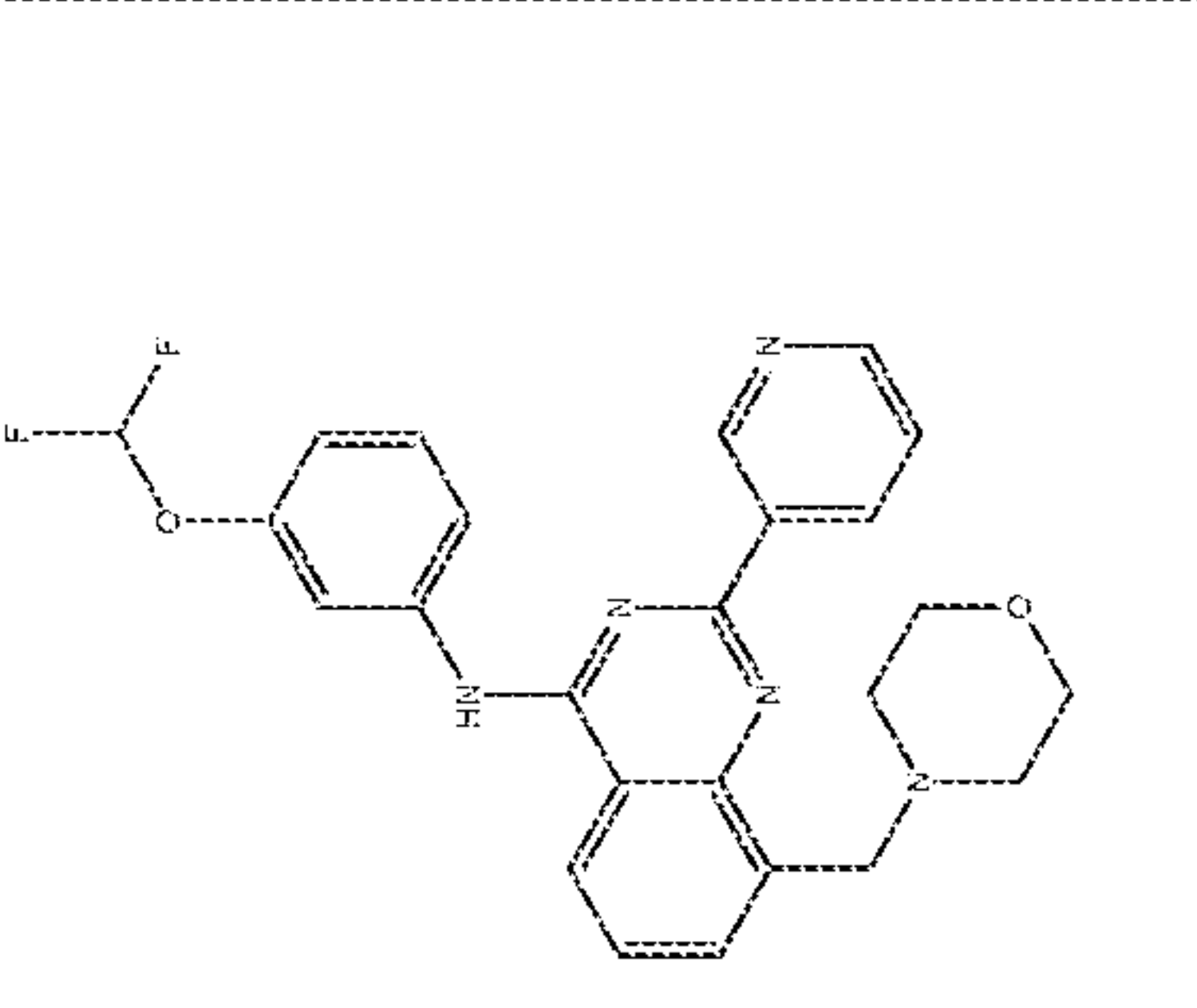
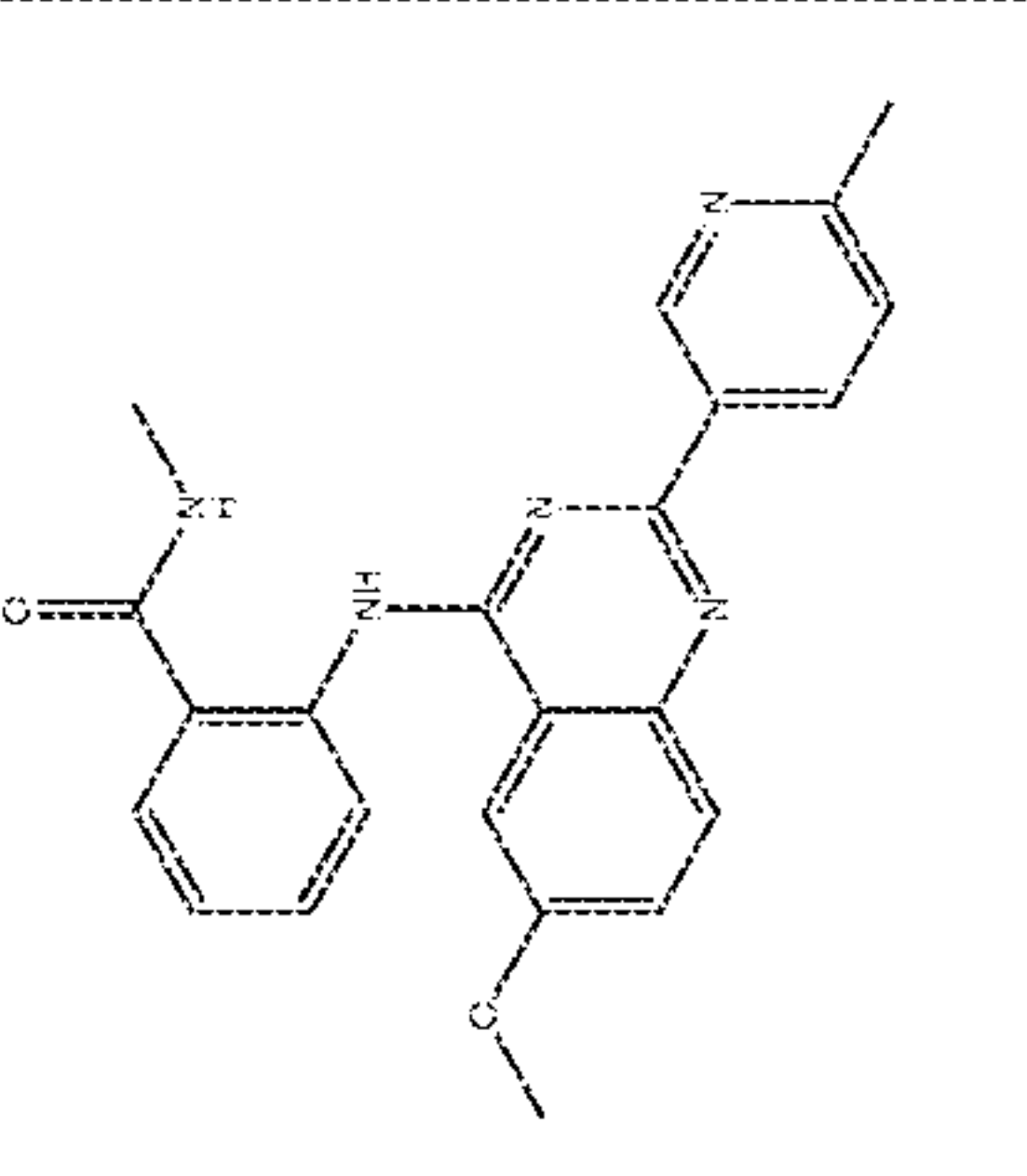
159			391.35	1H-NMR (400 MHz, DMSO-d6): δ 10.82 (s, 1H), 8.50 (s, 1H), 9.04 (d, J = 8.0 Hz, 1H), 8.96 (d, J = 8.6 Hz, 2H), 8.37 (s, 1H), 8.30 – 8.28 (m, 1H), 8.21 (s, 1H), 7.98 (d, J = 7.6 Hz, 2H), 7.68 – 7.69 (m, 2H).	DMSO	392.2 (M+1)	Method B (NH4HCO3)	95	Method C, G
160			450.34	1H-NMR (400 MHz, DMSO-d6): δ 10.40 (s, 1H), 9.54 – 9.55 (m, 1H), 8.82 – 8.84 (m, 1H), 8.67 – 8.73 (m, 2H), 8.16 – 8.21 (m, 2H), 7.93 – 8.00 (m, 2H), 7.54 – 7.64 (m, 2H), 7.21 (d, J = 8.0 Hz, 1H).	DMSO	451.1 (M+1)	Method B (NH4HCO3)	95	Method C, G
161			416.78	1H-NMR (400 MHz, DMSO-d6): δ 10.10 (s, 1H), 9.49 (s, 1H), 8.62 – 8.72 (m, 3H), 8.13 (s, 1H), 7.88 – 7.92 (m, 3H), 7.51 – 7.60 (m, 2H), 7.14 – 7.16 (m, 1H).	DMSO	417.1, 419.1 (M+1)	Method B (NH4HCO3)	95	Method C, G1

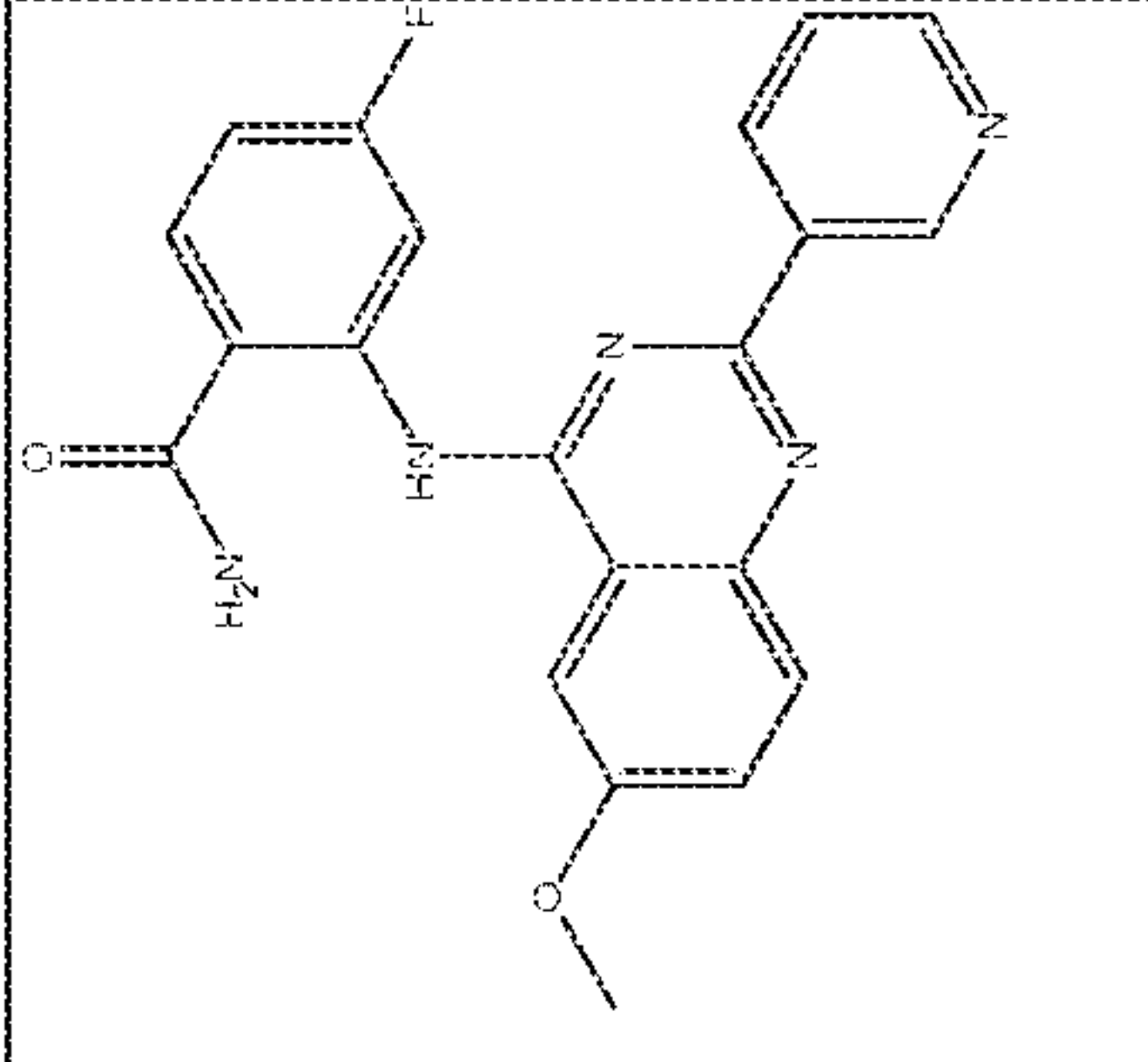
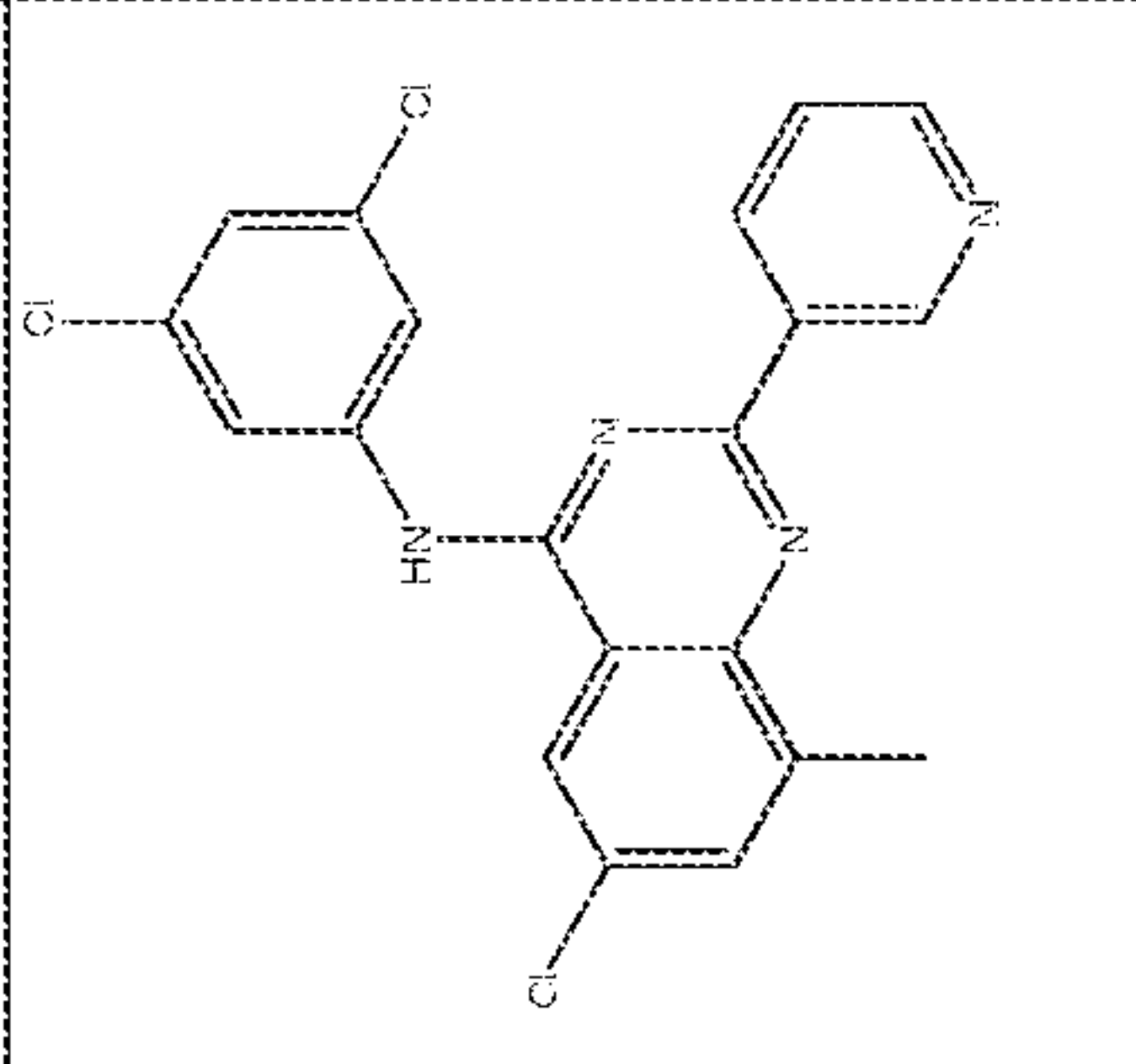
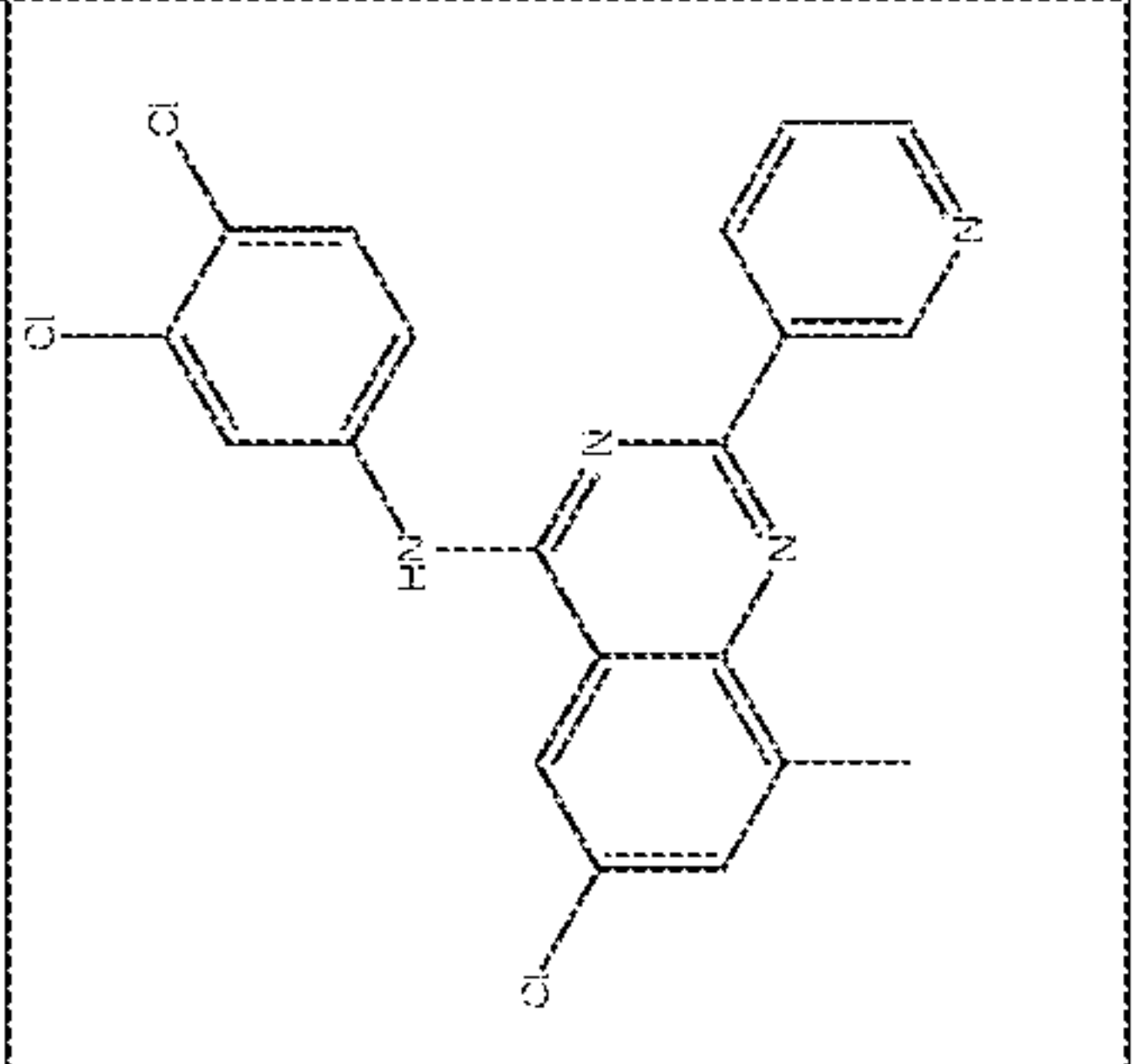
162			375.81	1H-NMR (400 MHz, DMSO-d6): δ 13.13 (s, 1H), 9.53 (s, 1H), 9.01 (d, J = 8.0 Hz, 1H), 8.68 – 8.72 (m, 2H), 8.50 (s, 1H), 8.10 (d, J = 8.8, 1H), 7.88 – 7.97 (m, 3H), 7.70 – 7.72 (m, 2H), 7.57 – 7.59 (m, 1H), 7.22 (t, J = 7.6, 1H).	DMSO	376.0, 378.0 (M+1)	Method B (NH4HCO3)	95	Method C, G1
163			376.8	1H-NMR (400 MHz, DMSO-d6): δ 12.07(s, 1H), 9.56 (s, 1H), 8.84 (d, J = 8.4 Hz, 1H), 8.71 – 8.73 (m, 2H), 8.34 (s, 1H), 7.96 – 8.09(m, 3H), 7.59 – 7.80 (m, 2H), 7.29 (t, J = 7.2 Hz, 1H).	DMSO	377.0, 379.0 (M+1)	Method B (NH4HCO3)	95	Method C, G1
164			394.37	1H-NMR (400 MHz, DMSO-d6): δ 9.90 (s, 1H), 9.53 (s, 1H), 8.67 (d, J = 5.2 Hz, 2H), 7.99 (d, J = 2.4 Hz, 1H), 7.94 (m, 1H), 7.87 (d, J = 9.2 Hz, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.49 – 7.59 (m, 3H), 7.31 (t, J = 74.0 Hz, 1H), 7.00 (d, J = 8.0 Hz, 1H), 3.99 (s, 3H).	DMSO	395.1 (M+1)	Method B (NH4HCO3)	95	Method C, G1

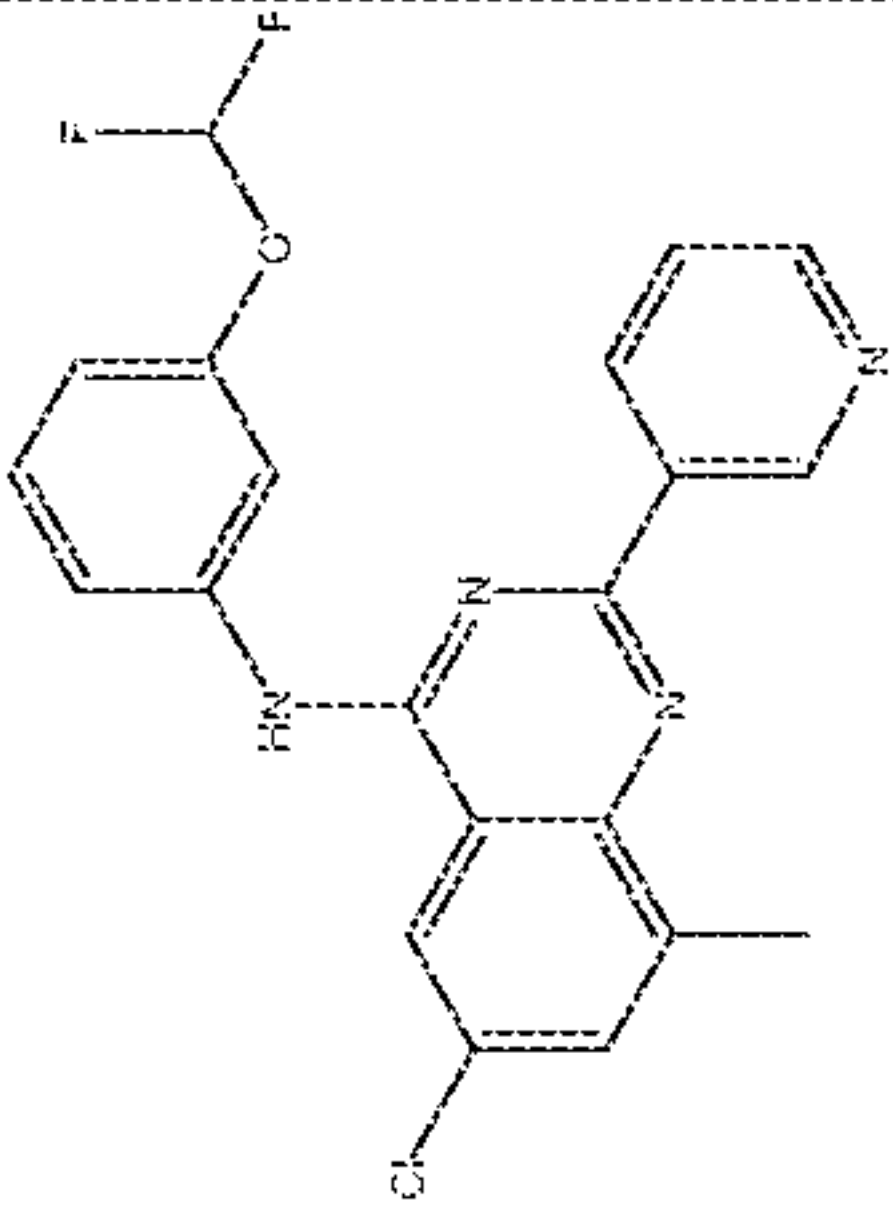
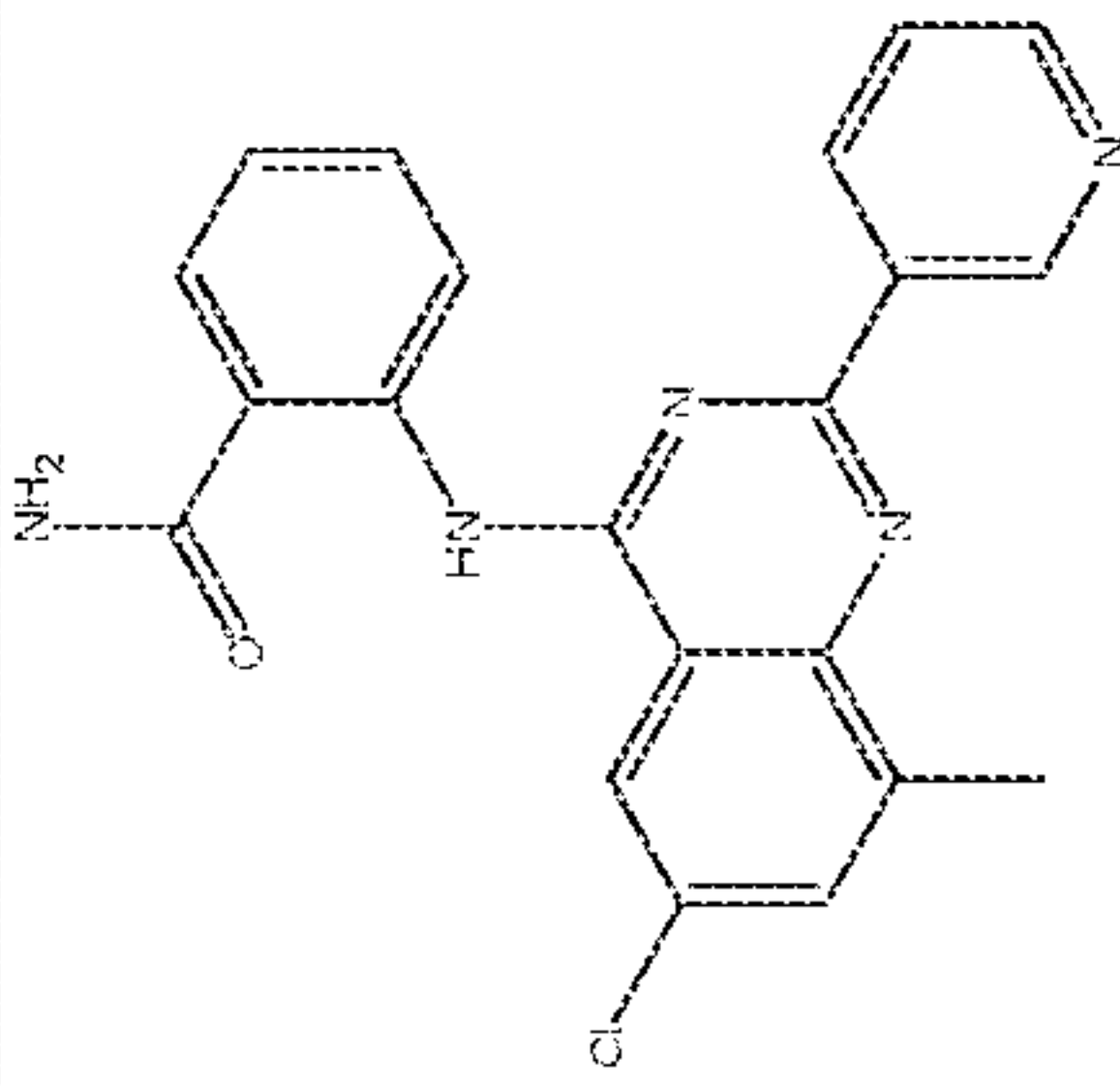
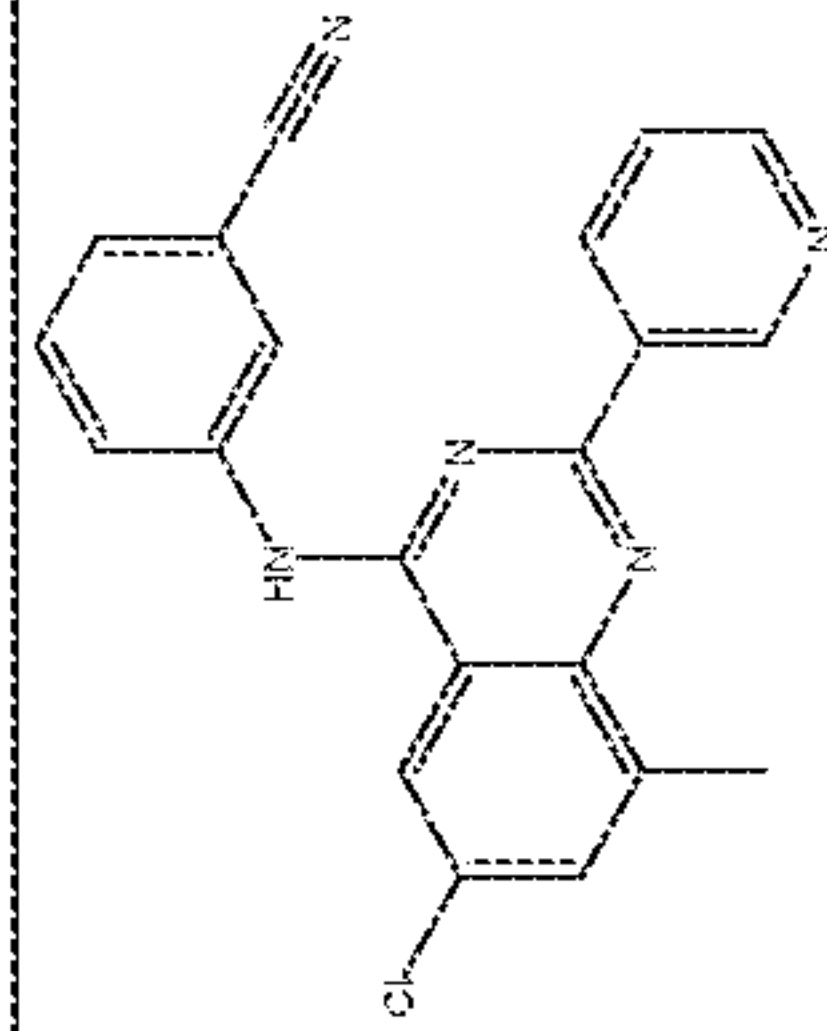
165		HCl	458.51	1H-NMR (400 MHz, DMSO-d6): δ 9.42 (s, 1H), 8.98 (d, J = 8.4 Hz, 1H), 8.68 – 8.71 (m, 2H), 7.94 (d, J = 7.6 Hz, 1H), 7.70 (t, J = 8.0 Hz, 1H), 7.57 (t, J = 5.6 Hz, 1H), 7.53 (s, 1H), 7.38 (s, 1H), 7.19 (t, J = 7.2 Hz, 1H), 4.52 (s, 2H), 4.00 (s, 3H), 3.63 (s, 2H), 2.89 (s, 6H).	DMSO	459.1 (M+1) 230.2 (M/2+1)	Method A (TFA)	95	Method C, G1
166			467.92	1H-NMR (400 MHz, DMSO-d6): δ 9.71 (s, 1H), 9.50 (d, J = 1.6 Hz, 1H), 8.62 – 8.67 (m, 2H), 8.20 (dd, J = 6.8, 2.4 Hz, 1H), 7.86 – 7.89 (m, 2H), 7.51 – 7.55 (m, 2H), 7.31 (s, 1H), 4.24 (t, J = 6.0 Hz, 2H), 3.98 (s, 3H), 2.77 (t, J = 5.6 Hz, 2H), 2.29 (s, 6H).	DMSO	468.1 (M+1) 234.6 (M/2+1)	Method B (NH4HCO3)	95	Method C, G1
167		HCl	428.82	1H-NMR (400 MHz, DMSO-d6): δ 10.41 (s, 1H), 9.50 (d, J = 1.6 Hz, 1H), 8.98 (d, J = 8.4 Hz, 1H), 8.88 (dd, J = 5.2, 1.6 Hz, 1H), 8.13 (d, J = 2.8 Hz, 1H), 8.00 (t, J = 2.0 Hz, 1H), 7.89 – 7.95 (m, 3H), 7.62 (dd, J = 9.2, 3.2 Hz, 1H), 7.36 (t, J = 73.6 Hz, 1H), 7.16 (d, J = 2.0 Hz, 1H), 4.01 (s, 3H).	DMSO	429.1, 431.1 (M+1)	Method B (NH4HCO3)	95	Method C, G1
168			385.42	1H-NMR (400 MHz, DMSO-d6): δ 13.03 (s, 1H), 9.62 (d, J = 1.6 Hz, 1H), 9.20 (d, J = 8.4 Hz, 1H), 8.74 – 8.77 (m, 1H), 8.70 (dd, J = 4.4, 1.6 Hz, 1H), 8.48 (s, 1H), 7.96 – 7.99 (m, 2H), 7.72 – 7.76 (m, 1H), 7.57 – 7.60 (m, 1H), 7.47 (m, 1H), 7.41 (m, 1H), 7.17 – 7.21 (m, 1H), 3.95 (s, 3H), 2.72 (s, 3H).	DMSO	386.1 (M+1)	Method B (NH4HCO3)	95	Method D, G1

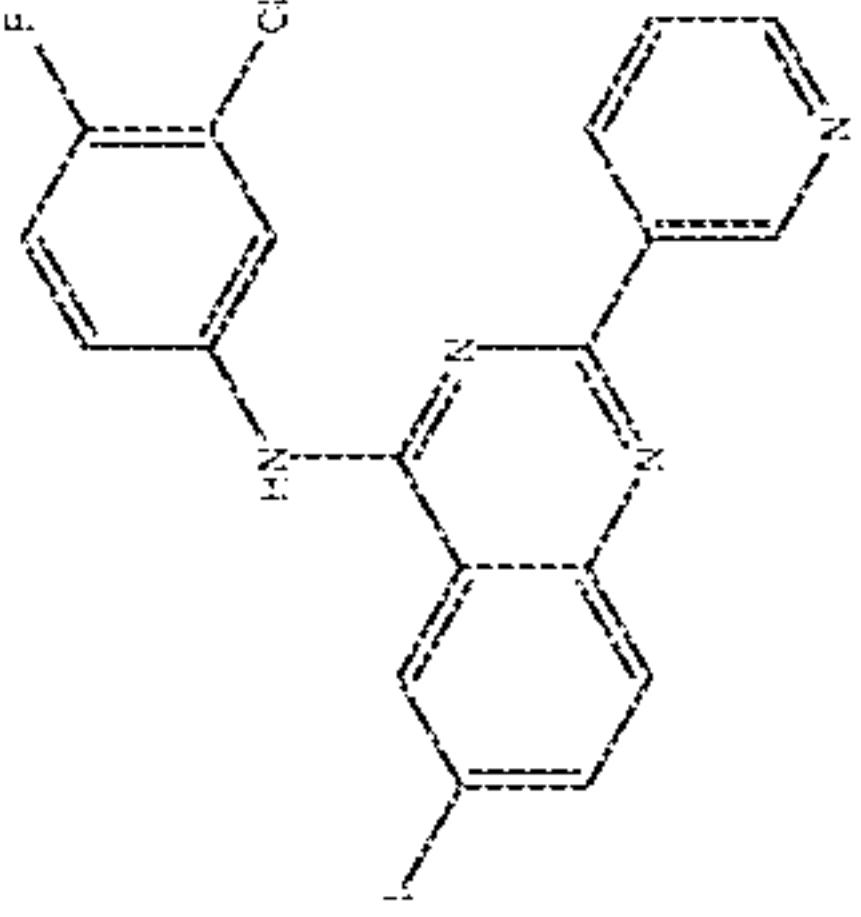
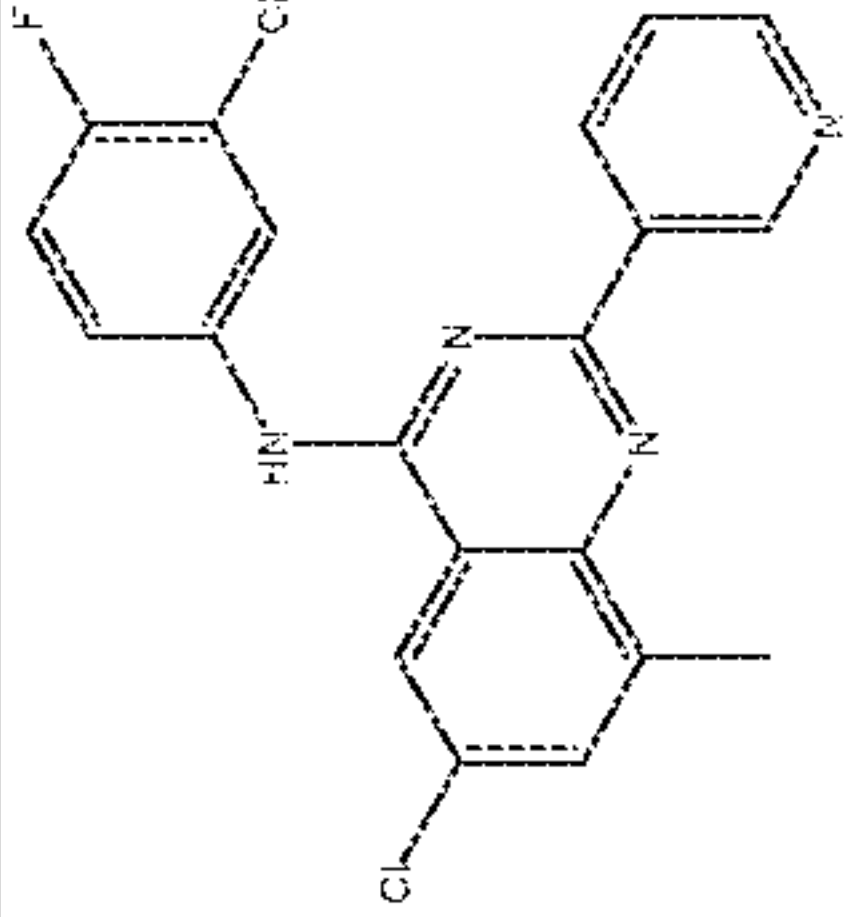
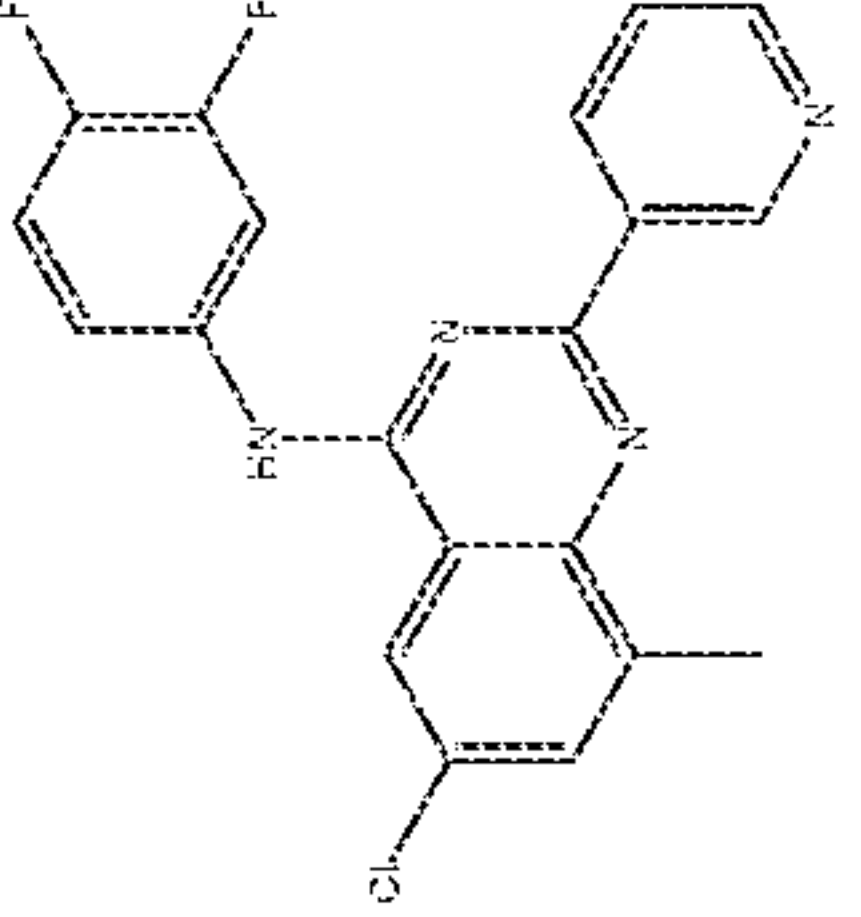
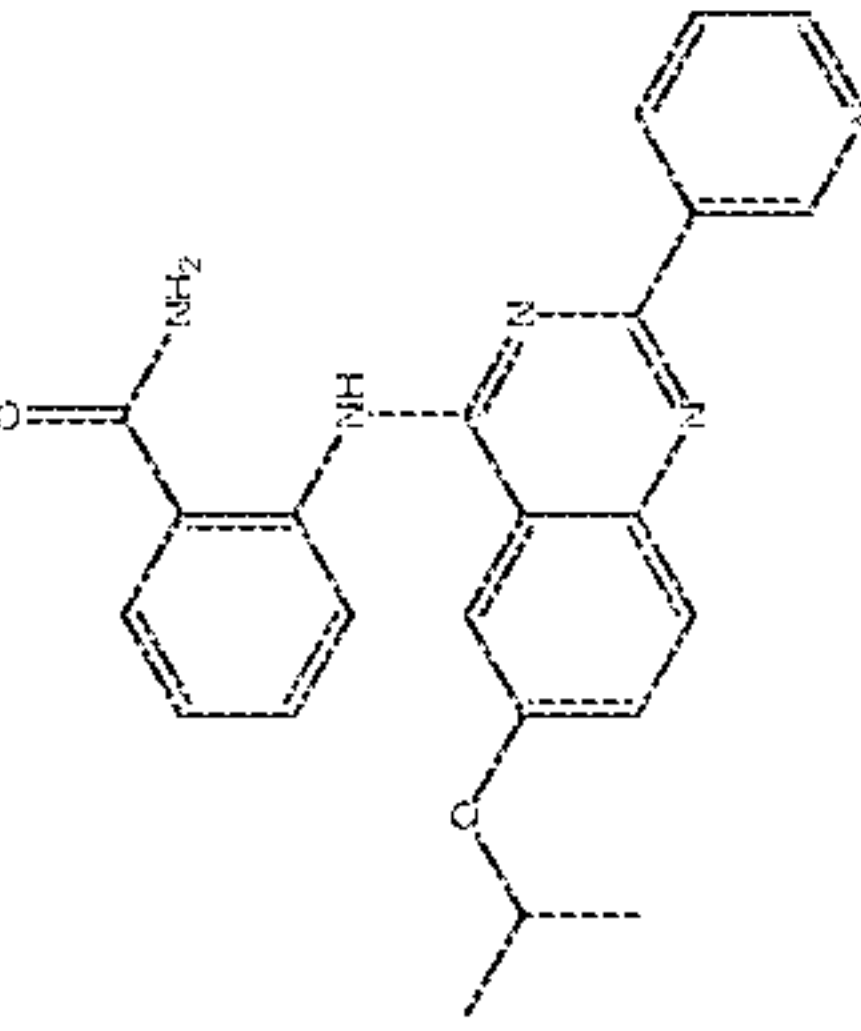
169		HCl	368.77	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.31 (s, 1H), 9.47 (s, 1H), 8.86 – 8.93 (m, 2H), 8.54 (dd, J = 10.0, 2.8 Hz, 1H), 8.21 (dd, J = 6.8, 2.4 Hz, 1H), 7.82 – 8.00 (m, 4H), 7.52 (t, J = 9.2 Hz, 1H).	DMSO	369.0, 371.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
170		HCl	400.33	¹ H-NMR (400 MHz, DMSO-d ₆): δ 10.35 (s, 1H), 9.53 (s, 1H), 8.99 (d, J = 8.0 Hz, 1H), 8.89 (d, J = 4.0 Hz, 1H), 8.60 (dd, J = 10.4, 3.2 Hz, 1H), 7.97 – 8.09 (m, 3H), 7.68 – 7.92 (m, 2H), 7.62 (t, J = 8.0 Hz, 1H), 7.21 (d, J = 8.0 Hz, 1H).	DMSO	401.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
171			359.36	¹ H-NMR (400 MHz, DMSO-d ₆): δ 13.06 (s, 1H), 9.58 (s, 1H), 9.07 (d, J = 8.4 Hz, 1H), 8.72 (d, J = 5.6 Hz, 2H), 8.52 (s, 1H), 7.96 – 8.02 (m, 3H), 7.83 – 7.87 (m, 2H), 7.74 (t, J = 8.0 Hz, 1H), 7.59 (t, J = 6.0 Hz, 1H), 7.23 (t, J = 7.6 Hz, 1H).	DMSO	360.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1

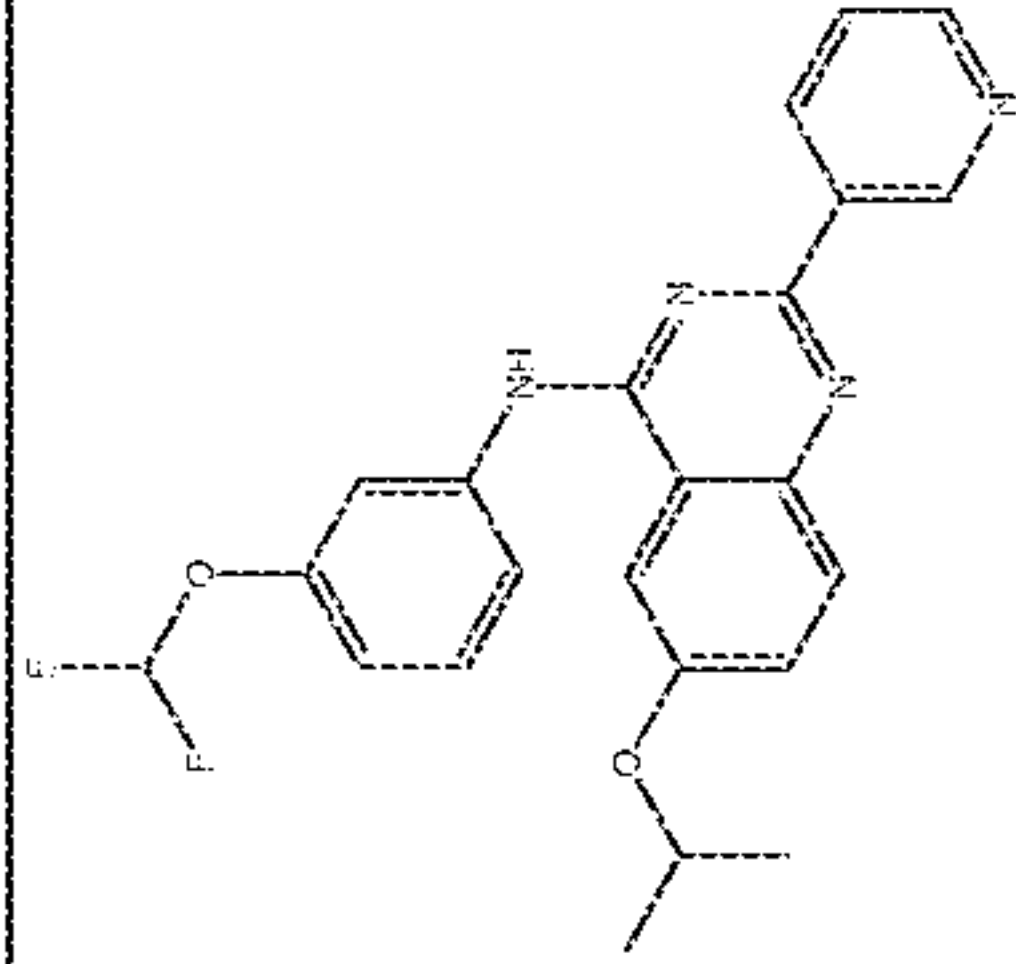
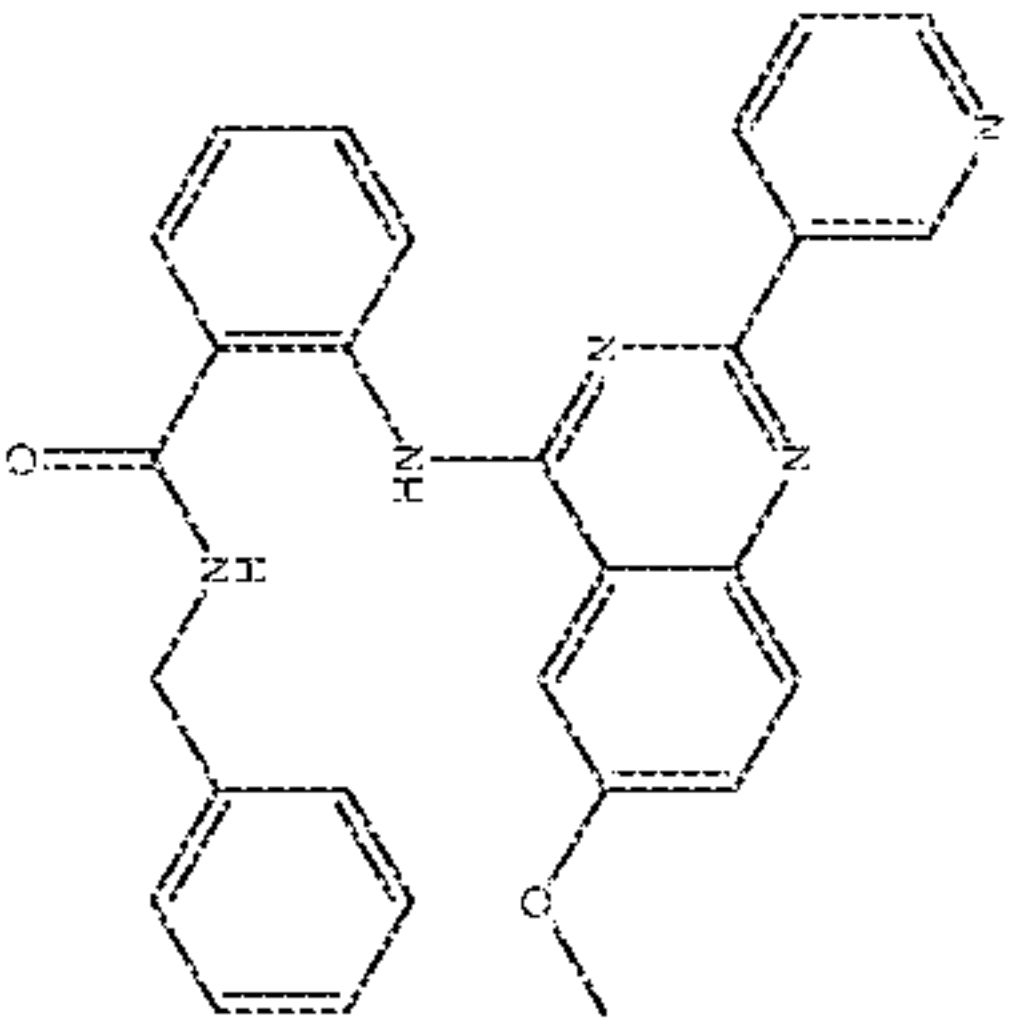
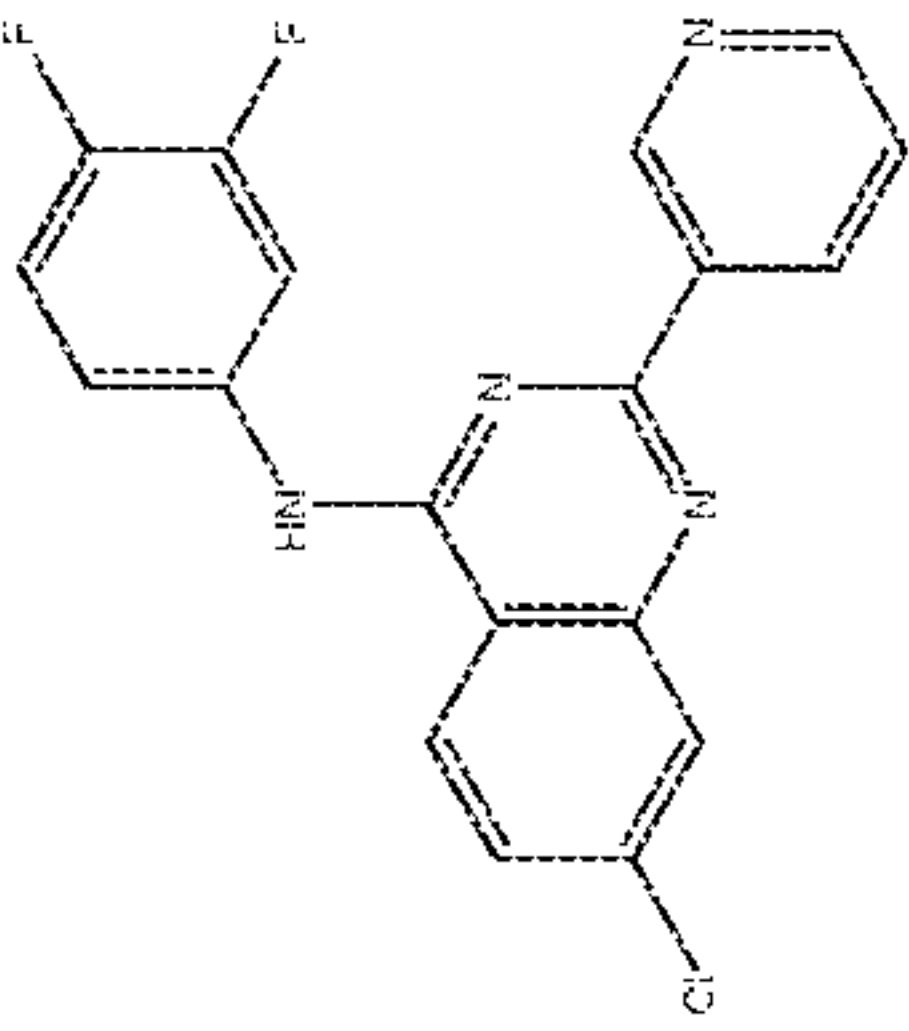
172		HCl	382.34	¹H-NMR (400 MHz, DMSO-d₆): δ 10.30 (s, 1H), 9.53 (d, J = 1.2 Hz, 1H), 8.98 (d, J = 8.0 Hz, 1H), 8.88 (d, J = 4.4 Hz, 1H), 8.62 (dd, J = 10.0, 2.8 Hz, 1H), 8.01 – 8.05 (m, 1H), 7.84 – 7.92 (m, 4H), 7.50 – 7.56 (m, 1H), 7.32 (t, J = 74.0 Hz, 1H), 7.03 (dd, J = 8.0, 2.0 Hz, 1H).	DMSO	383.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
173			348.35	¹H-NMR (400 MHz, DMSO-d₆): δ 10.09 (s, 1H), 9.51 (s, 1H), 8.79 – 8.76 (m, 2H), 8.38 (s, 1H), 8.16 – 8.11 (m, 1H), 7.86 – 7.66 (m, 4H), 7.59 – 7.50 (m, 1H), 2.57 (s, 3H).	DMSO	349.1 (M+1), 175.1 (M/2+1)	Method A (TFA)	95	Method C, G1
174			364.8	¹H-NMR (300 Hz, CD₃OD): δ 9.50 (d, J = 1.2 Hz, 1H), 9.14 (d, J = 8.4 Hz, 1H), 8.94 (d, J = 4.8 Hz, 1H), 8.35 (s, 1H), 8.09 – 7.99 (m, 2H), 7.93 (s, 2H), 7.78 – 7.73 (m, 1H), 7.39 (t, J = 9.0 Hz, 1H), 2.64 (s, 3H).	CD ₃ OD	365.1, 367.1 (M+1)	Method A (TFA)	95	Method C, G1
175			381.26	¹H-NMR (400 MHz, DMSO-d₆): δ 10.13 (s, 1H), 9.51 (s, 1H), 8.84 – 8.79 (m, 2H), 8.36 – 8.34 (m, 2H), 7.96 (dd, J = 8.8, 2.5 Hz, 1H), 7.85 – 7.70 (m, 4H), 2.55 (s, 3H).	DMSO	381.0, 383.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1

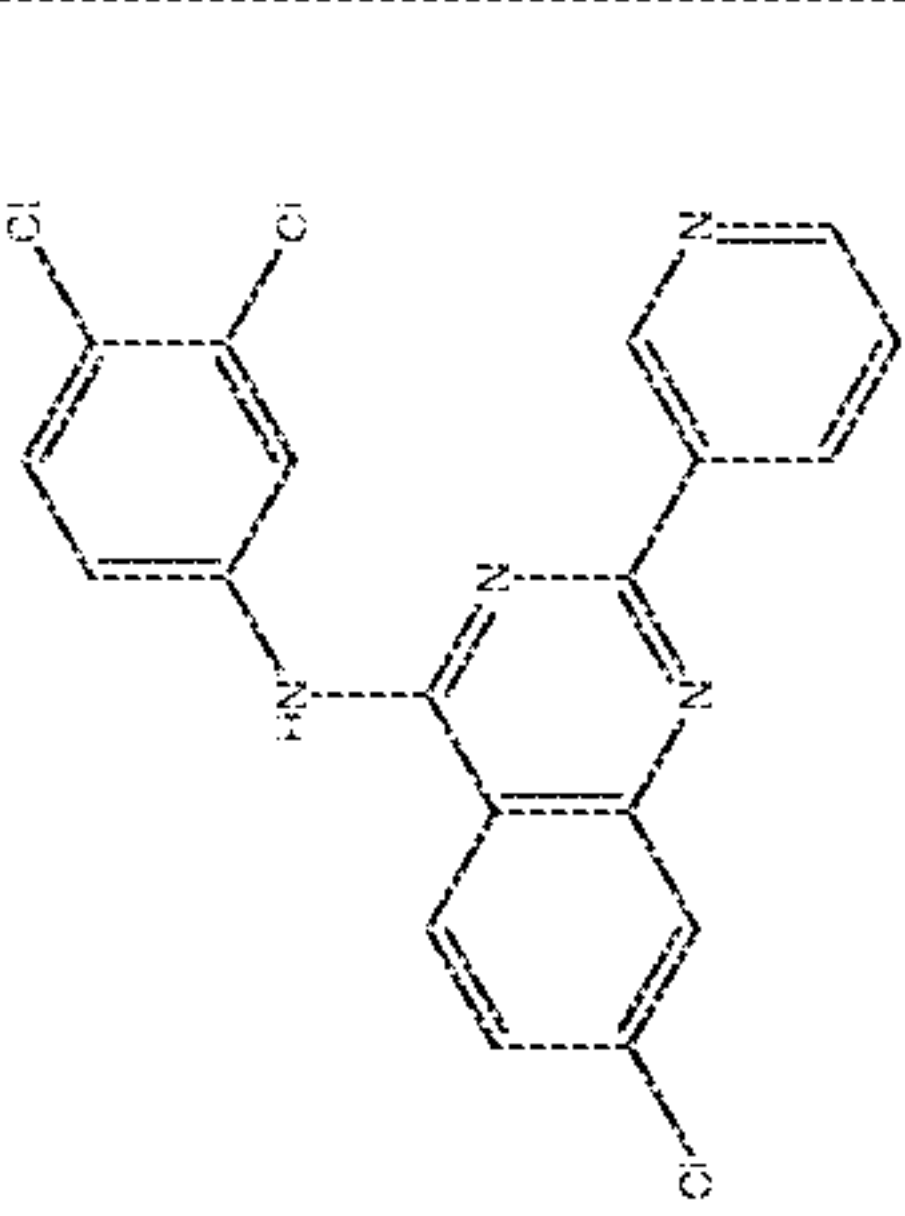
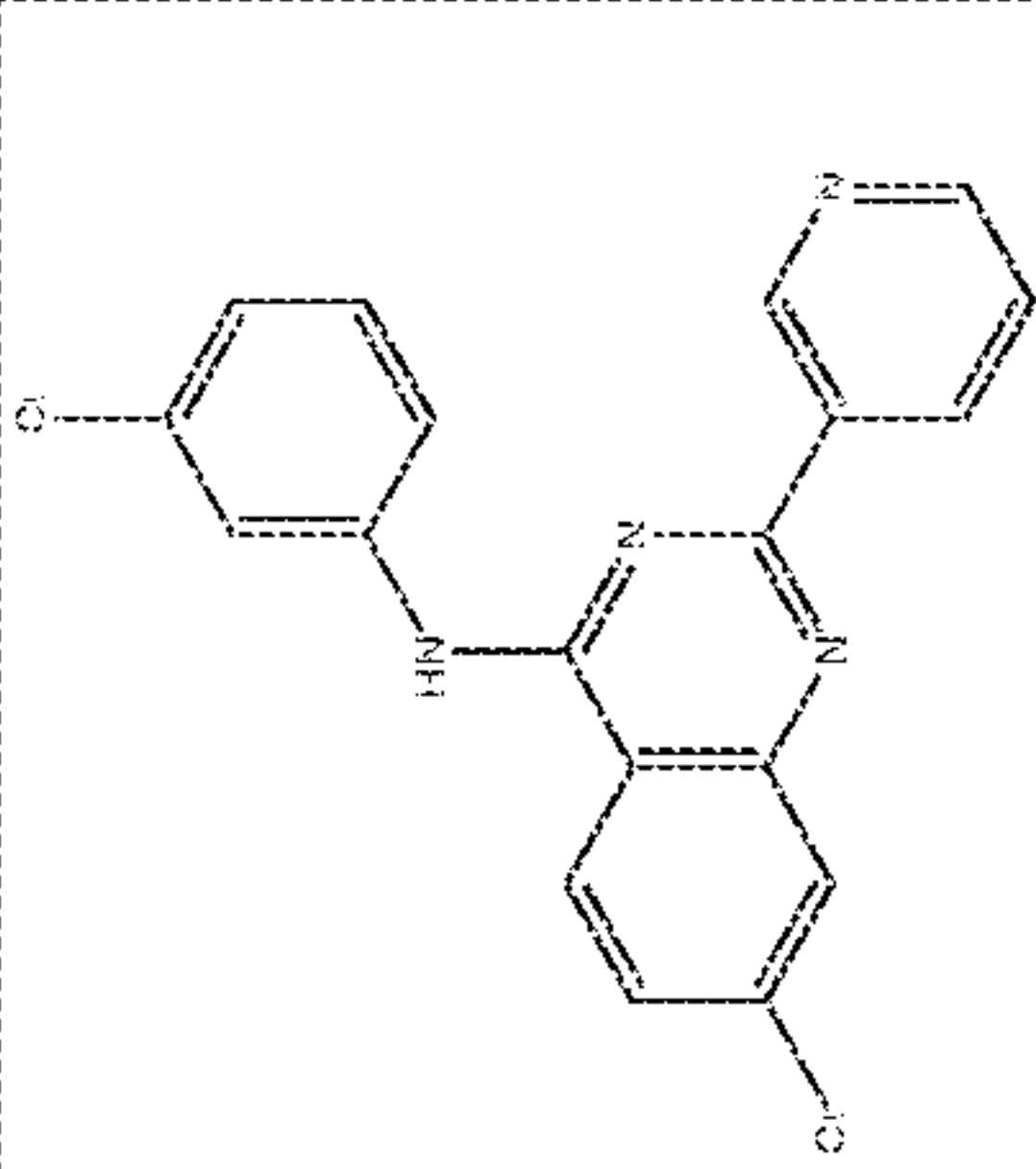
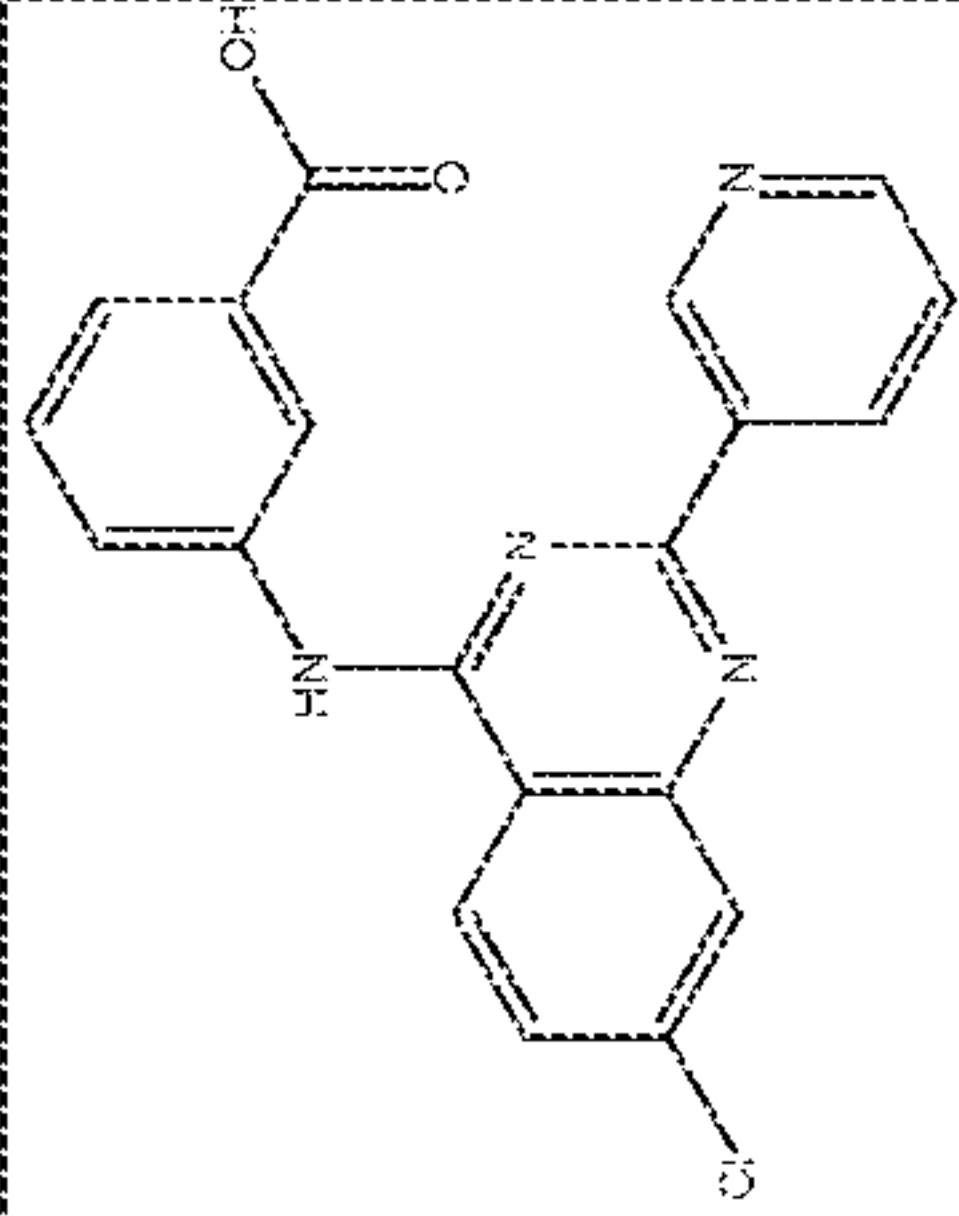
176			346.81	¹H-NMR (300 MHz, CD₃OD): δ 9.48 (d, J = 1.2 Hz, 1H), 8.99 – 8.95 (m, 1H), 8.82 – 8.80 (m, 1H), 8.30 – 8.29 (m, 1H), 7.90 – 7.81 (m, 5H), 7.52 – 7.46 (m, 2H), 2.62 (s, 3H).	CD ₃ OD	347.0, 349.1 (M+1)	Method A (TFA)	95	Method C, G1
177			346.81	¹H-NMR (400 MHz, DMSO-d₆): δ 10.12 (s, 1H), 9.52 (s, 1H), 8.84 – 8.78 (m, 2H), 8.42 (s, 1H), 8.16 – 8.15 (m, 1H), 7.94 – 7.91 (m, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.75 – 7.71 (m, 1H), 7.50 (t, J = 8.1 Hz, 1H), 7.27 – 7.23 (m, 1H), 2.56 (s, 3H).	DMSO	347.1, 349.1 (M+1)	Method A (TFA)	95	Method C, G1
178			360.37	¹H-NMR (400 MHz, DMSO-d₆): δ 10.60 (s, 1H), 9.50 (d, J = 2.1 Hz, 1H), 9.00 (d, J = 8.1 Hz, 1H), 8.90 (dd, J = 5.1, 1.2 Hz, 1H), 8.55 (s, 1H), 8.43 (s, 1H), 8.25 (d, J = 7.8 Hz, 1H), 7.96 – 7.90 (m, 2H), 7.84 (d, J = 8.1 Hz, 1H), 7.27 (t, J = 8.2 Hz, 1H), 7.57 (d, J = 7.8 Hz, 1H), 2.62 (s, 3H).	DMSO	381.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1

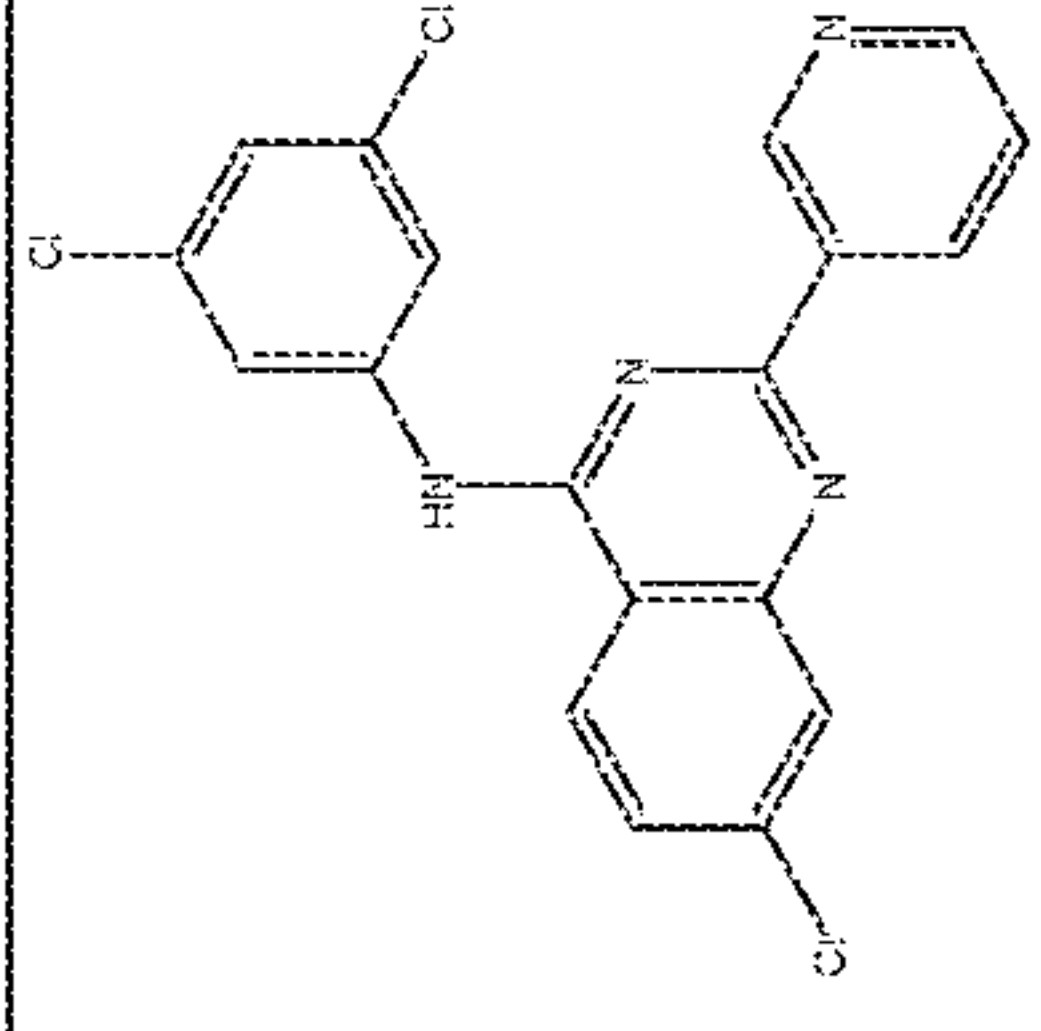
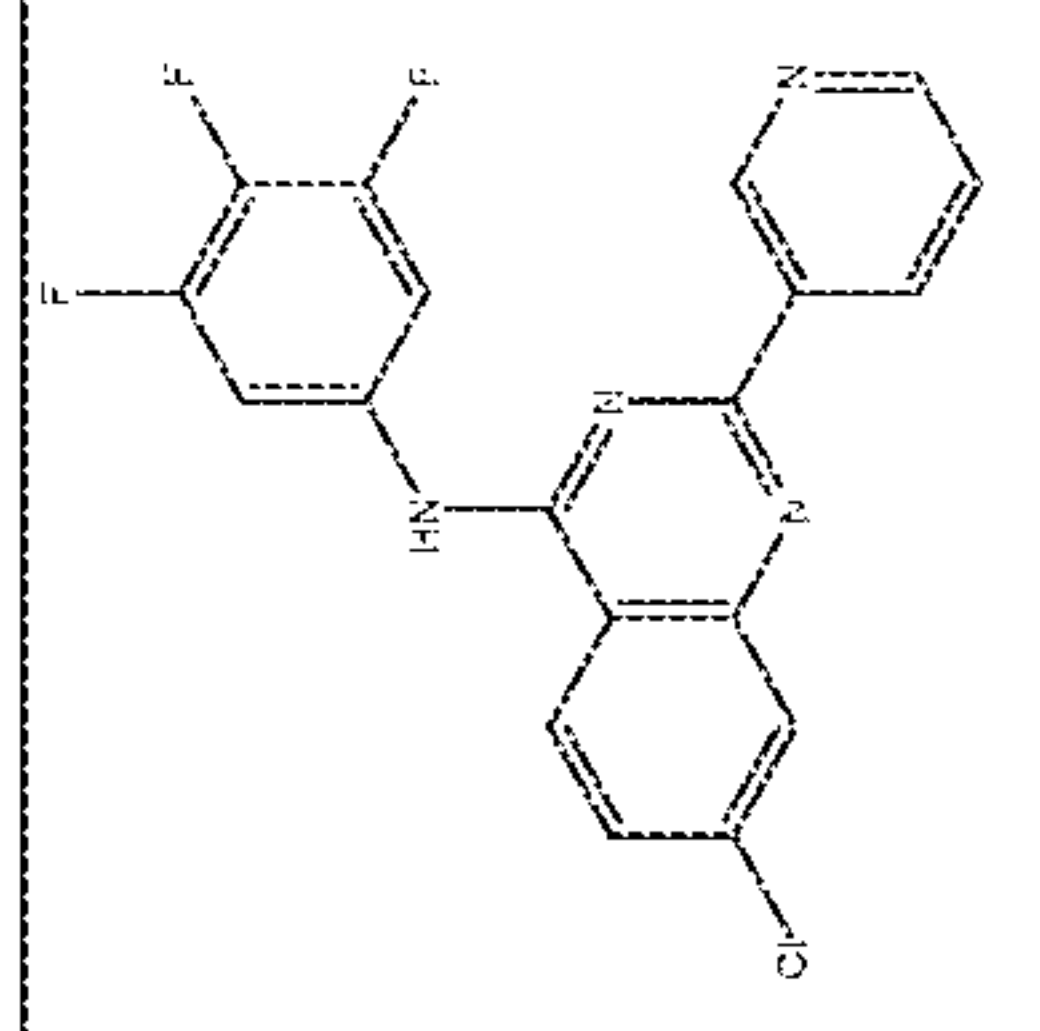
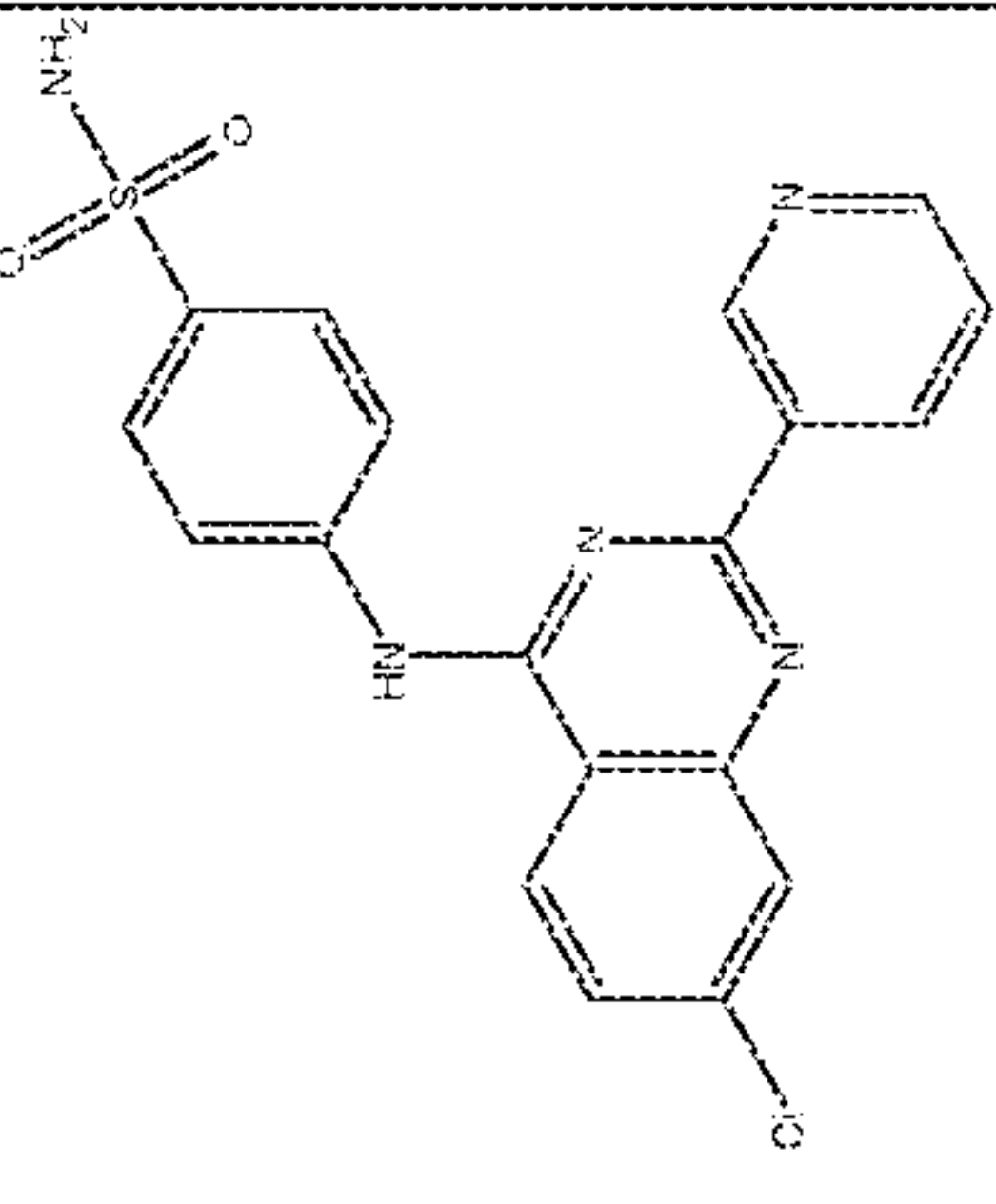
179			414.81	1H-NMR (400 MHz, DMSO-d6): δ 10.59 (s, 1H), 9.50 (s, 1H), 9.02 (d, J = 8.4 Hz, 1H), 8.92 (d, J = 5.2 Hz, 1H), 8.59 (d, J = 2.8 Hz, 1H), 8.54 (s, 1H), 8.34 (dd, J = 8.6, 2.6 Hz, 1H), 7.96 – 7.90 (m, 2H), 7.81 (d, J = 8.8 Hz, 2H), 2.56 (s, 3H).	DMSO	415.1, 417.1 (M+1)	Method B (NH4HCO3)	95	Method C, G1
180			401.37	1H-NMR (400 MHz, DMSO-d6): δ 13.91 (s, 1H), 10.38 (s, 1H), 9.59 (s, 1H), 8.79 – 8.76 (m, 1H), 8.73 (d, J = 4.8 Hz, 1H), 8.61 (d, J = 2.4 Hz, 1H), 8.44 (s, 1H), 8.33 (dd, J = 9.0, 2.6 Hz, 1H), 8.20 (d, J = 8.8 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.81 (dd, J = 8.4, 1.2 Hz, 1H), 7.60 – 7.57 (m, 1H), 2.58 (s, 3H).	DMSO	402.0 (M+1)	Method A (TFA)	95	Method C, G1
181			381.26	1H-NMR (400 MHz, DMSO-d6): δ 10.40 (s, 1H), 9.47 (s, 1H), 8.98 (d, J = 7.5 Hz, 1H), 8.91 (d, J = 4.5 Hz, 1H), 8.48 (s, 1H), 8.12 (d, J = 2.1 Hz, 2H), 7.97 – 7.93 (m, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.40 (s, 1H), 2.55 (s, 3H).	DMSO	381.0, 383.0 (M+1)	Method B (NH4HCO3)	95	Method C, G1

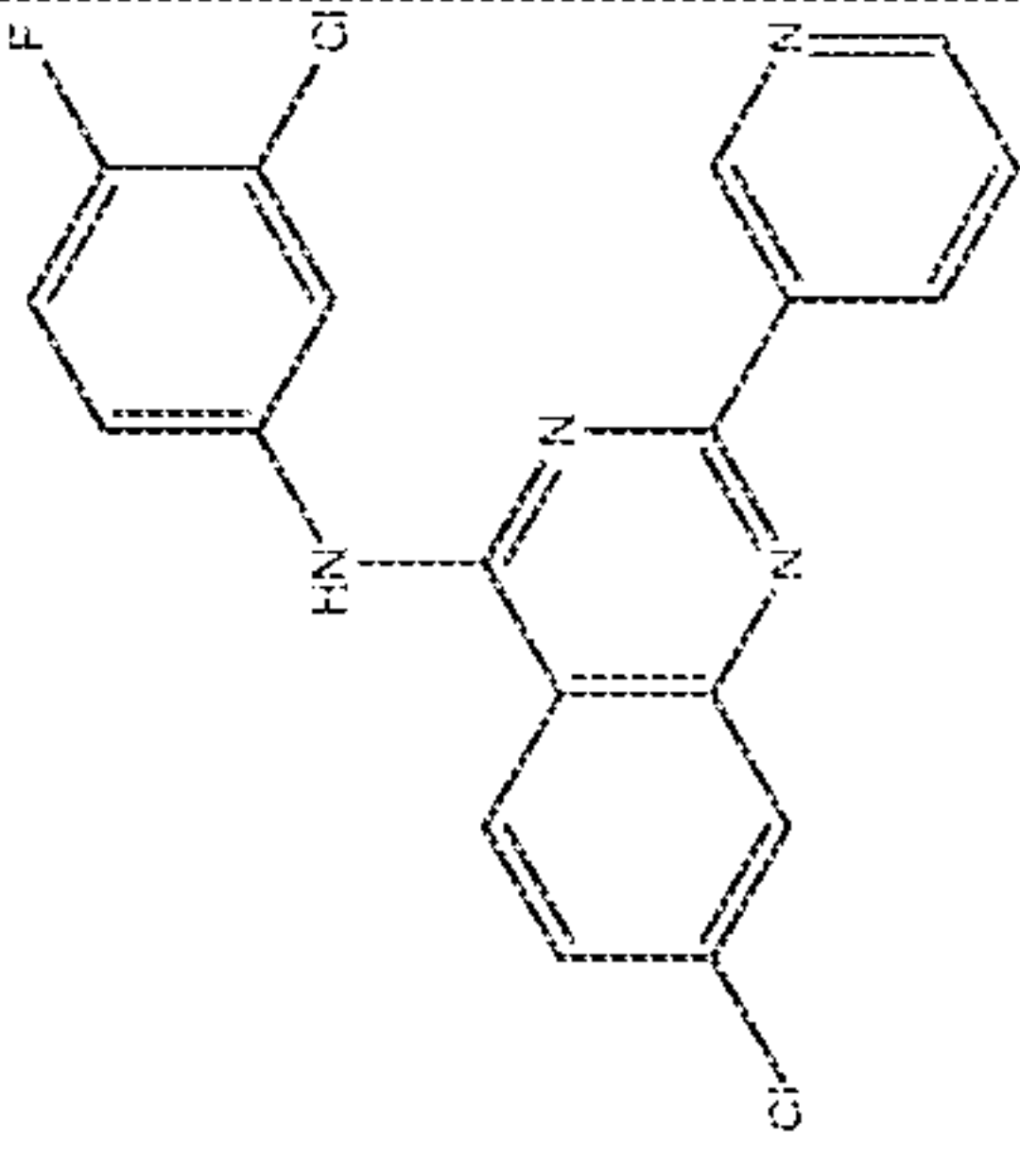
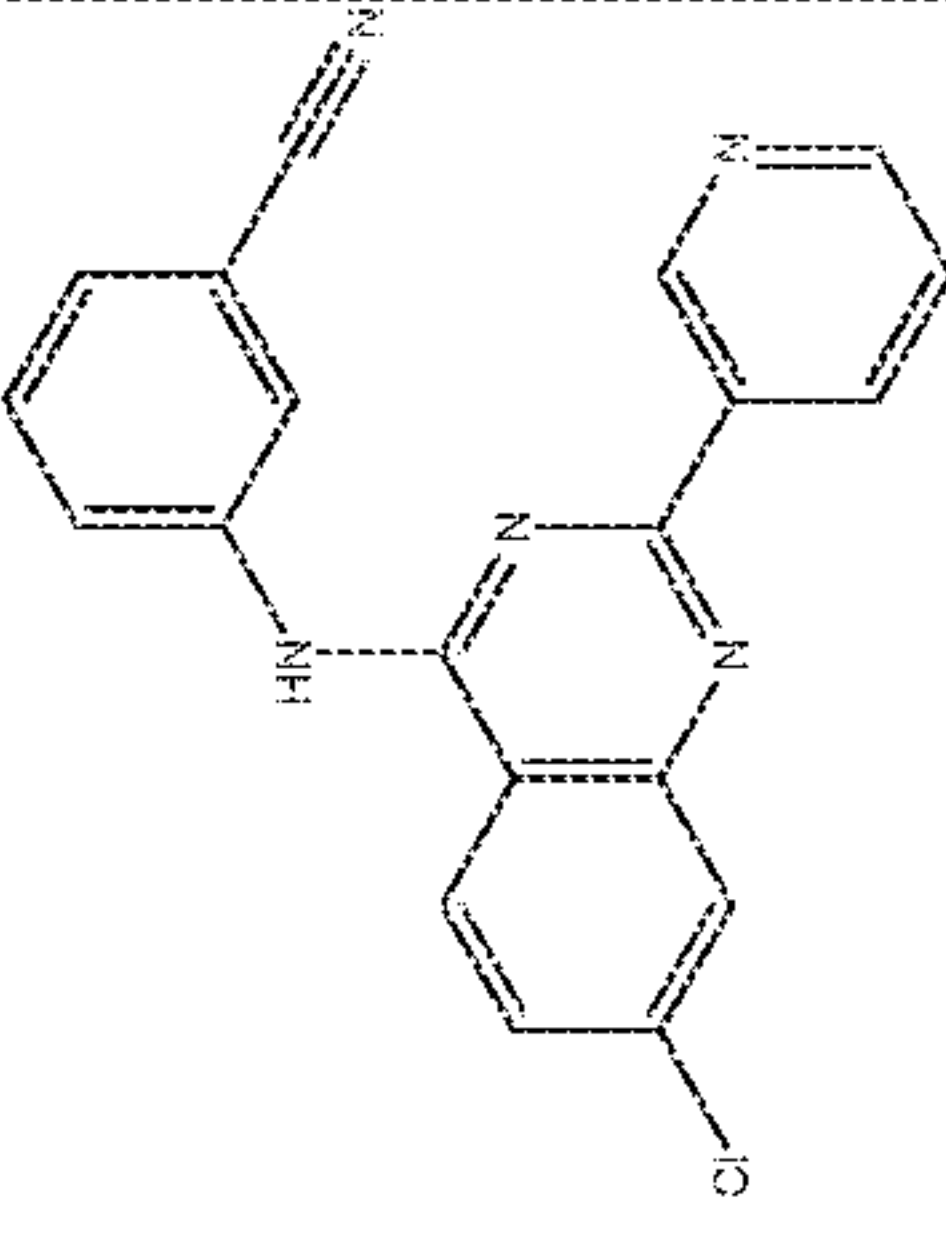
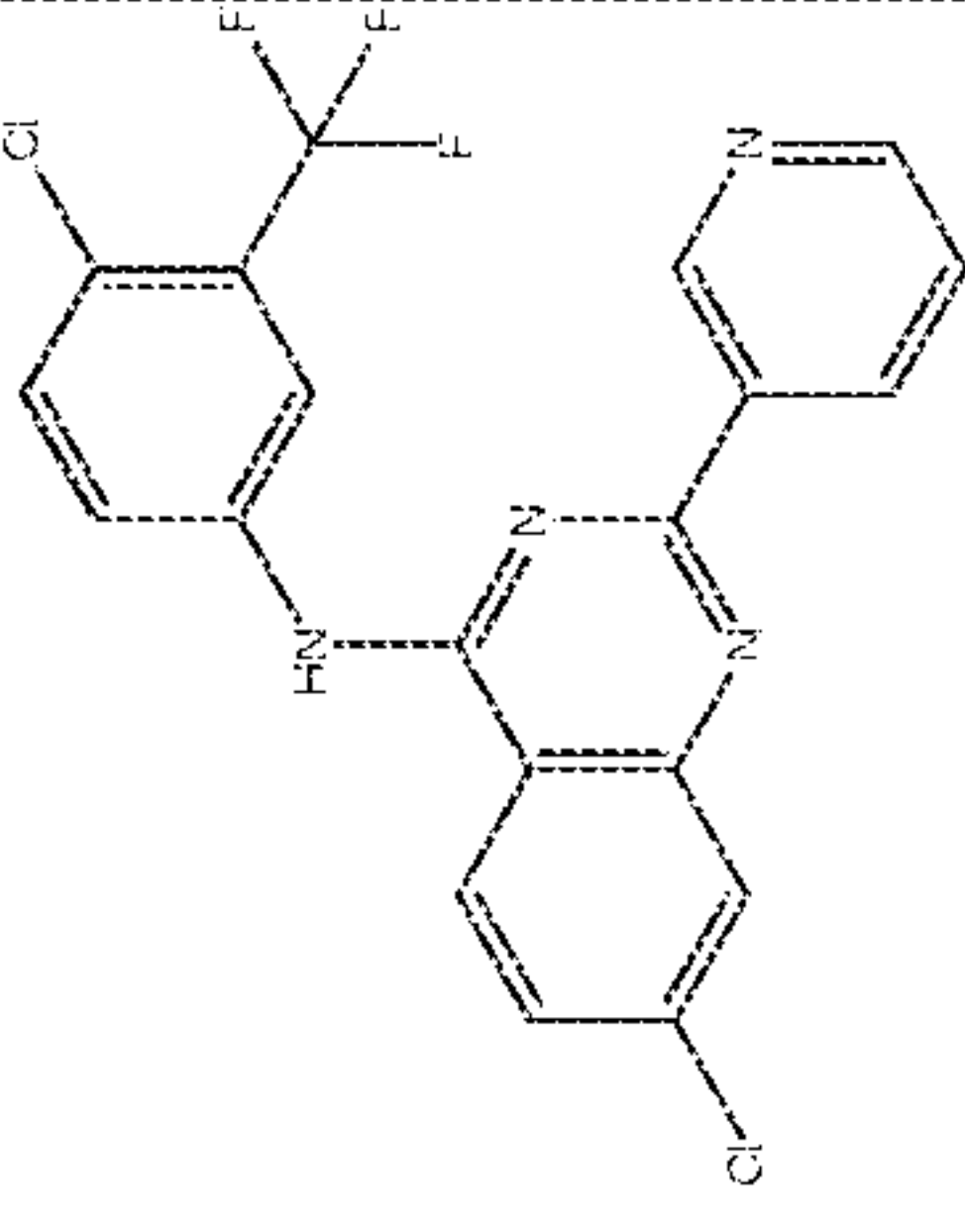
182			390.82	¹H-NMR (400 MHz, DMSO-d₆): δ 12.25 (s, 1H), 9.54 (s, 1H), 9.25 (s, 1H), 8.84 – 8.80 (m, 2H), 8.09 (d, J = 8.0 Hz, 1H), 7.96 (s, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 9.2 Hz, 1H), 7.77 – 7.75 (m, 1H), 7.29 (d, J = 8.4 Hz, 1H), 2.56 (s, 3H).	DMSO	391.1, 393.0 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
183			366.34	¹H-NMR (400 MHz, DMSO-d₆): δ 9.98 (s, 1H), 9.50 (d, J = 1.6 Hz, 1H), 8.69 (dd, J = 4.8, 1.6 Hz, 1H), 8.66 – 8.63 (m, 1H), 8.30 (s, 1H), 7.99 – 7.95 (m, 2H), 7.82 (d, J = 8.4 Hz, 1H), 7.76 (dd, J = 8.6, 1.4 Hz, 1H), 7.58 – 7.55 (m, 1H), 2.55 (s, 3H).	DMSO	367.1 (M+1), 184.1 (M/2+1)	Method A (TFA)	95	Method C, G1
184			415.7	¹H-NMR (400 MHz, DMSO-d₆): δ 10.09 (s, 1H), 9.51 (s, 1H), 8.75 – 8.72 (m, 2H), 8.38 (s, 2H), 8.32 (s, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.66 – 7.64 (m, 1H), 2.55 (s, 3H).	DMSO	414.8, 416.8 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1

185			354.4	¹H-NMR (400 MHz, DMSO-d₆): δ 10.26 (s, 1H), 9.56 (s, 1H), 8.93 (d, J = 8.0 Hz, 1H), 8.81 (d, J = 4.0 Hz, 1H), 8.65 (s, 1H), 8.48 (s, 1H), 8.21 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.88 – 7.89 (m, 3H), 7.65 (t, J = 7.6 Hz, 1H), 2.65 (s, 3H), 2.58 (s, 3H).	DMSO	355.1 (M+1), 178.1 (M/2+1)	Method A (TFA)	95	Method C, G1
186			356.38	¹H-NMR (400 MHz, DMSO-d₆): δ 12.18 (s, 1H), 9.57 (s, 1H), 9.07 (d, J = 8.4 Hz, 1H), 8.71 (d, J = 5.6 Hz, 2H), 8.10 (d, J = 8.0 Hz, 1H), 7.99 (s, 1H), 7.86 – 7.76 (m, 3H), 7.58 (t, J = 6.2 Hz, 1H), 7.23 (t, J = 7.4 Hz, 1H), 2.55 (s, 3H).	DMSO	357.1 (M+1)	Method A (TFA)	95	Method C, G1
187			337.38	¹H-NMR (400 MHz, DMSO-d₆): δ 10.10 (s, 1H), 9.51 (s, 1H), 8.65 – 8.70 (m, 2H), 8.45 (s, 1H), 8.38 (s, 1H), 8.28 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.69 (t, J = 7.8 Hz, 1H), 7.62 (d, J = 7.2 Hz, 1H), 7.54 – 7.57 (m, 1H), 2.56 (s, 3H).	DMSO	338.1 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1
188			355.39	¹H-NMR (400 MHz, DMSO-d₆): δ 13.11 (s, 1H), 9.61 (s, 1H), 9.09 (d, J = 8.8 Hz, 1H), 8.89 (d, J = 8.0 Hz, 1H), 8.81 (s, 1H), 8.50 (s, 1H), 8.01 – 7.98 (m, 2H), 7.96 (dd, J = 7.8, 1.0 Hz, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.76 – 7.72 (m, 3H), 7.23 (t, J = 7.4 Hz, 1H), 2.56 (s, 3H).	DMSO	356.2 (M+1)	Method B (NH ₄ HCO ₃)	95	Method C, G1

189			385.42	1H-NMR (400 MHz, DMSO-d6): δ 12.62 (s, 1H), 9.58 (s, 1H), 9.03 (d, J = 8.4 Hz, 1H), 8.92 (d, J = 4.0 Hz, 1H), 8.74 – 8.69 (m, 2H), 7.92 – 7.87 (m, 2H), 7.72 (t, J = 7.6 Hz, 1H), 7.66 – 7.56 (m, 3H), 7.23 (t, J = 7.6 Hz, 1H), 4.00 (s, 3H), 2.84 (d, J = 4.4 Hz, 3H).	DMSO	386.2 (M+1)	Method B (NH4HCO3)	95	Method C, G1
190			461.51	1H-NMR (400 MHz, DMSO-d6): δ 12.40 (s, 1H), 9.57 (d, J = 1.2 Hz, 1H), 9.48 (t, J = 6.0 Hz, 1H), 8.89 (d, J = 8.8 Hz, 1H), 8.73 – 8.68 (m, 2H), 7.96 (ddt, J = 8.0, 1.2 Hz, 1H), 7.89 (d, J = 8.8 Hz, 1H), 7.76 – 7.72 (m, 1H), 7.61 – 7.55 (m, 3H), 7.34 – 7.20 (m, 6H), 4.52 (d, J = 5.6 Hz, 2H), 3.93 (s, 3H).	DMSO	462.2 (M+1)	Method B (NH4HCO3)	95	Method C, G1
191			368.77	1H NMR (300 MHz, DMSO-d6): δ 10.32 (s, 1H), 9.55 – 9.45 (m, 1H), 8.93 – 8.76 (m, 2H), 8.63 (d, J = 8.9 Hz, 1H), 8.10 (ddd, J = 13.2, 7.5, 2.6 Hz, 1H), 7.97 (d, J = 2.1 Hz, 1H), 7.80 – 7.67 (m, 3H), 7.62 – 7.49 (m, 1H).	DMSO	369.0, 371.0 (M+1)	Method B (NH4HCO3)	97	Method C, G1

192			401.68	1H NMR (300 MHz, DMSO-d6): δ 10.36 (s, 1H), 9.58 – 9.43 (m, 1H), 8.90 – 8.79 (m, 2H), 8.65 (d, J = 9.0 Hz, 1H), 8.33 (d, J = 2.4 Hz, 1H), 8.01 – 7.90 (m, 2H), 7.82 – 7.68 (m, 3H).	DMSO	401.0, 403.0, 405.0 (M+1)	Method B (NH4HCO3)	97	Method C, G1
193			367.23	1H NMR (300 MHz, DMSO-d6): δ 10.19 (s, 1H), 9.53 (d, J = 2.1 Hz, 1H), 8.78 – 8.56 (m, 3H), 8.17 (t, J = 2.0 Hz, 1H), 7.96 (d, J = 2.1 Hz, 1H), 7.93 – 7.85 (m, 1H), 7.75 (dd, J = 8.9, 2.2 Hz, 1H), 7.58 (ddd, J = 8.0, 4.8, 0.7 Hz, 1H), 7.51 (t, J = 8.1 Hz, 1H), 7.26 (ddd, J = 8.0, 2.0, 0.6 Hz, 1H).	DMSO	367.0, 369.0 (M+1)	Method B (NH4HCO3)	98	Method C, G1
194			376.80	1H NMR (300 MHz, DMSO-d6): δ 13.11 (s, 1H), 10.27 (s, 1H), 9.58 (d, J = 2.1 Hz, 1H), 8.87 – 8.62 (m, 4H), 8.21 – 8.10 (m, 1H), 7.96 (d, J = 2.1 Hz, 1H), 7.82 – 7.68 (m, 2H), 7.64 – 7.53 (m, 2H).	DMSO	377.0, 379.0 (M+1)	Method A (TFA)	95	Method C, G1

195			401.68	1H NMR (300 MHz, DMSO-d6): δ 10.32 (s, 1H), 9.52 -- 9.49 (m, 1H), 8.85 -- 8.73 (m, 2H), 8.61 (d, J = 9.0 Hz, 1H), 8.18 -- 8.08 (m, 2H), 7.99 -- 7.95 (m, 1H), 7.77 (dd, J = 8.9, 2.2 Hz, 1H), 7.71 (dd, J = 7.8, 5.0 Hz, 1H), 7.42 -- 7.39 (m, 1H).	DMSO	401.0, 403.0, 405.0 (M+1)	Method B (NH4HCO3)	97	Method C, G1
196			386.76	1H-NMR (300 MHz, DMSO-d6): δ 10.43 (s, 1H), 9.49 (d, J = 1.9 Hz, 1H), 8.95 -- 8.82 (m, 2H), 8.64 (d, J = 9.0 Hz, 1H), 8.01 -- 7.82 (m, 4H), 7.78 (dd, J = 8.9, 2.2 Hz, 1H).	DMSO	387.0, 389.1 (M+1)	Method B (NH4HCO3)	97	Method C, G1
197			411.86	1H NMR (400 MHz, DMSO-d6): δ 10.50 (brs, 1H), 9.56 (s, 1H), 9.08 -- 8.93 (m, 1H), 8.92 -- 8.82 (m, 1H), 8.73 (d, J = 8.9 Hz, 1H), 8.21 -- 8.11 (m, 2H), 8.02 (d, J = 1.9 Hz, 1H), 7.98 -- 7.77 (m, 4H), 7.38 (s, 2H).	DMSO	412.1, 414.1 (M+1)	Method B (NH4HCO3)	97	Method C, G1

198			385.22	1H NMR (400 MHz, DMSO-d6): δ 10.25 (s, 1H), 9.51 (d, J = 1.4 Hz, 1H), 8.77 – 8.69 (m, 2H), 8.60 (d, J = 9.0 Hz, 1H), 8.27 – 8.20 (m, 1H), 7.97 (d, J = 2.1 Hz, 1H), 7.90 (ddd, J = 9.0, 4.3, 2.6 Hz, 1H), 7.76 (dd, J = 8.9, 2.1 Hz, 1H), 7.64 (dd, J = 8.0, 4.9 Hz, 1H), 7.55 (t, J = 9.1 Hz, 1H).	DMSO	385.0, 387.0 (M+1)	Method B (NH4HCO3)	100	Method C, G1
199			357.80	1H NMR (400 MHz, DMSO-d6): δ 10.36 (s, 1H), 9.53 – 9.49 (m, 1H), 8.81 – 8.70 (m, 2H), 8.64 (d, J = 8.9 Hz, 1H), 8.45 – 8.36 (m, 1H), 8.29 – 8.21 (m, 1H), 7.98 (d, J = 2.1 Hz, 1H), 7.77 (dd, J = 8.9, 2.1 Hz, 1H), 7.74 – 7.61 (m, 3H).	DMSO	357.9, 359.9 (M+1)	Method B (NH4HCO3)	99	Method C, G1
200			435.23	1H-NMR (400 MHz, DMSO-d6): δ 10.44 (s, 1H), 9.53 (s, 1H), 8.84 – 8.74 (m, 2H), 8.69 – 8.61 (m, 2H), 8.26 (dd, J = 8.8, 2.6 Hz, 1H), 7.99 (d, J = 2.1 Hz, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.78 (dd, J = 8.9, 2.1 Hz, 1H), 7.70 (dd, J = 7.7, 5.3 Hz, 1H).	DMSO	435.0, 437.0 (M+1)	Method B (NH4HCO3)	99	Method C, G1

DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS
COMPREND PLUS D'UN TOME.**

CECI EST LE TOME __1__ DE __3__

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

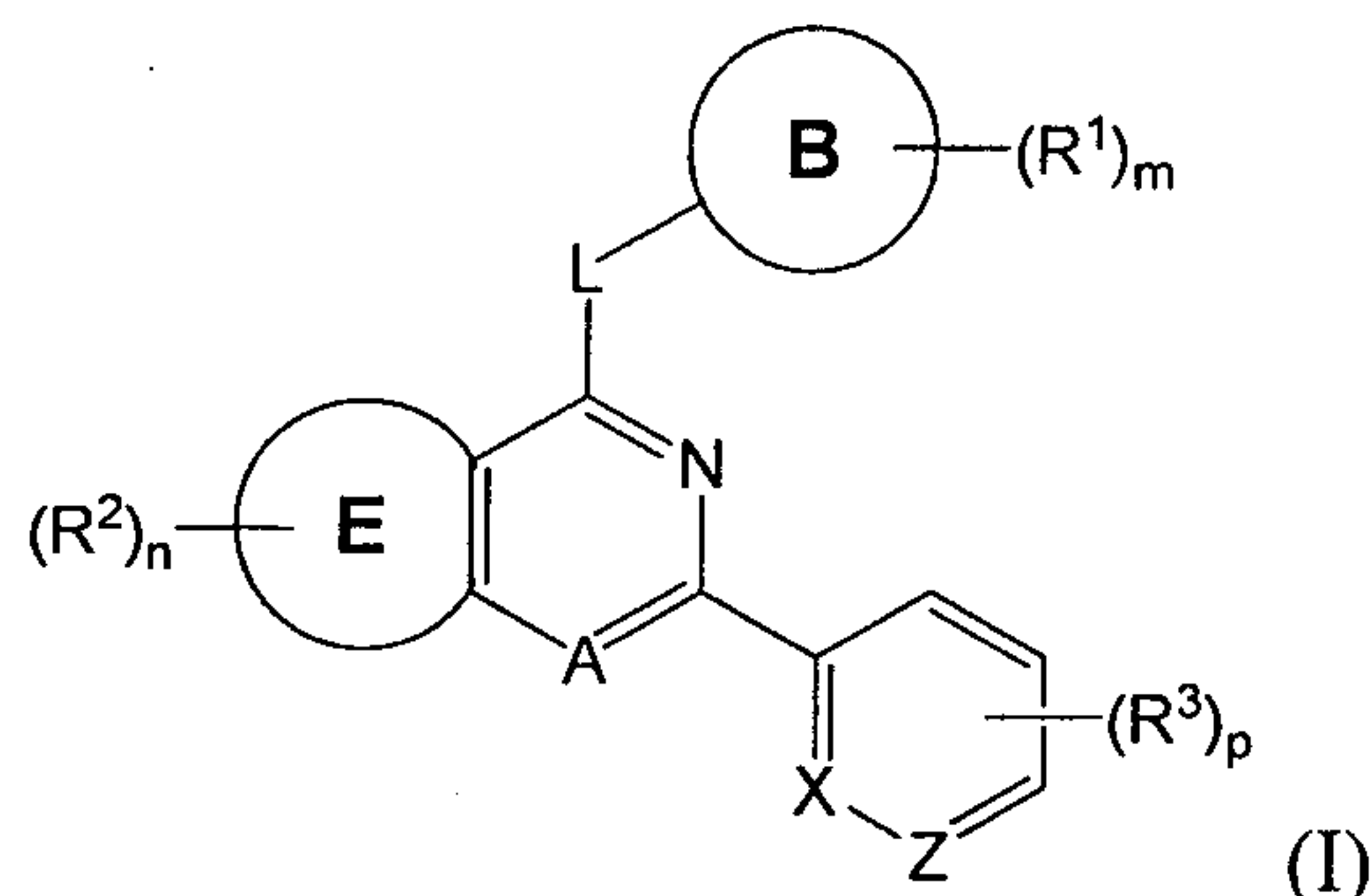
**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

THIS IS VOLUME __1__ OF __3__

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

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A compound of formula (I):



or a salt thereof,

wherein:

A is CH or N;

B is phenyl, dihydroindenyl, dihydrobenzoxazinyl, dihydrobenzodioxinyl, chromenyl, tetrahydroisoquinolyl, tetrahydroquinolyl, dihydroquinolyl, quinolyl, tetrahydroquinazolinyl, indolinyl, dihydrobenzothiazolyl, dihydrobenzimidazolyl, dihydrobenzoxazolyl, isoindolinyl, benzofuryl, benzothienyl, benzodioxolyl, indolyl, indazolyl, benzoimidazolyl, benzotriazolyl, benzisoxazolyl, benzoxazolyl, benzothiazolyl, benzoxadiazolyl, tetrahydrobenzothienyl, thienyl, thiazolyl, imidazolyl, pyrazolyl, thiadiazolyl or pyridyl;

m is 1, 2, 3, or 4;

E is phenyl, thienyl or pyrrolyl;

when E is phenyl, n is 1, or 2; and when E is thienyl or pyrrolyl, n is 0, or 1;

L is NR⁵;

one of X and Z is N and the other is CH;

p is 0, 1, or 2;

R¹ is C₁-C₈ alkyl, halo, haloalkyl, haloalkoxy, alkoxyalkyl, -CN, oxo, -NO₂, -C(Y)NR^bR^{b'}, -NR^cC(Y)R^{c'}, -SO₂NR^bR^{b'}, -OR^d, or -S(O)_qR^f;

R² is C₁-C₈ alkyl, C₃-C₈ cycloalkyl, thiomorpholinylalkyl, pyrrolidinylalkyl, morpholinylalkyl, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, silyloxyalkyl, -CN, -NO₂, -C(O)OR^a, -C(Y)NR^bR^{b'}, -NR^bR^{b'}, -OR^d, -C(Y)R^e or -S(O)_qR^f;

R^3 is C_1 - C_8 alkyl, halo, haloalkyl, $-NR^bR^{b'}$ or $-OR^d$

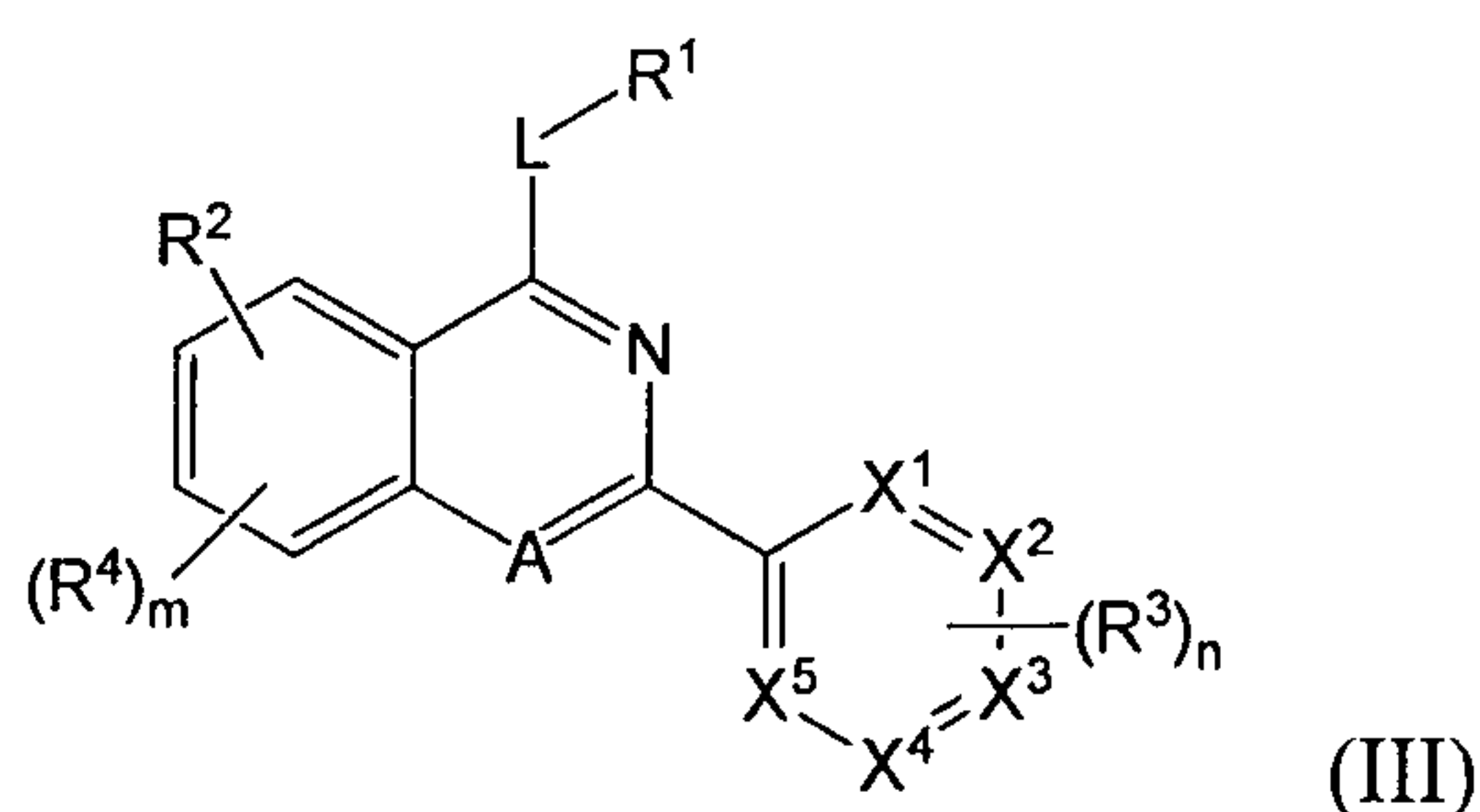
R^5 is hydrogen;

Y is O or S;

q is 1 or 2 and

each R^a , R^b , $R^{b'}$, R^c , $R^{c'}$, R^d , R^e and R^f is independently hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, C_3 - C_8 cycloalkyl, phenyl, dihydroindenyl, morpholinyl, tetrahydropyranyl, piperidyl, pyrrolidinyl, thiomorpholinyl, phenylalkyl, thienylalkyl, pyridylalkyl, tetrahydropyranylalkyl, dihydroindenylalkyl, tetrahydrofurylalkyl, hydroxyalkyl, morpholinylalkyl, pyrrolidinylalkyl, dialkylaminoalkyl, piperidylalkyl, benzodioxolylalkyl, dihydrobenzodioxinylalkyl, C_3 - C_8 cycloalkylalkyl, haloalkyl or alkoxyalkyl, or

a compound of formula (III) :



or a salt thereof,

wherein:

A is N;

L is NR^6 ;

one of X^1 , X^2 , X^3 , X^4 and X^5 is N and the others are CH;

m is 1;

n is 0 or 1;

R^1 is hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, alkoxyalkyl, hydroxyalkyl, imidazolyl, furylalkyl, pyridylalkyl, phenylalkyl, oxazolylalkyl, thienylalkyl, thiazolidinyl, isoindolyl, $-C(O)R^e$, dihydroindenyl, C_3 - C_8 cycloalkyl,

C_3 - C_8 cycloalkylalkyl, piperidyl, morpholinyl, pyrrolidinyl, azetidyl or piperazinyl, each of which is optionally substituted with 1-3 R^7 ;

R^2 is phenyl, naphthyl, benzofuryl, indazolyl, benzothienyl, pyridyl, pyrimidinyl, dihydrobenzodioxinyl, benzodioxolyl, benzoimidazolyl, isoxazolyl, pyrazolyl, indolinyl or benzisoxazolyl, each of which is optionally substituted with 1-5 R^9 ;

each R^3 or R^4 is independently hydrogen, C_1 - C_8 alkyl, halo, haloalkyl or $-OR^d$;

R^6 is hydrogen or C_1 - C_8 alkyl;

each R^7 and R^9 is independently C_1 - C_8 alkyl, phenyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, alkoxyalkyl, oxo, $-CN$, $-NO_2$, $-C(O)OR^a$, $-C(O)NR^bR^{b'}$, $-NR^bR^{b'}$, $-OR^d$, $-C(O)R^e$ or $-S(O)_qR^f$, each of which is optionally substituted with 1-3 R^{12} ;

R^{12} is independently C_1 - C_8 alkyl, oxo, halo, haloalkyl, $-CN$, $-C(O)NR^bR^{b'}$ or $-C(O)R^e$, each of which is optionally substituted with 1-3 R^{13} ;

R^{13} is independently C_1 - C_8 alkyl, halo or pyrrolidinyl;

q is 1 or 2; and

each R^a , R^b , $R^{b'}$, R^d , R^e and R^f is independently hydrogen, C_1 - C_8 alkyl, C_3 - C_8 cycloalkyl, pyrrolidinyl, piperidyl, morpholinyl, piperazinyl, tetrahydropyranyl, phenylalkyl, alkoxyalkyl, morpholinylalkyl, oxazolidinylalkyl, imidazolylalkyl, tetrahydropyranylalkyl, pyridylalkyl, pyrazolylalkyl, tetrazolylalkyl, thiazolylalkyl, pyrrolylalkyl, benzoxazolylalkyl, indazolylalkyl, dihydrobenzoxazinylalkyl, tetrahydrofurylalkyl, tetrahydrofuryl, alkylaminoalkyl, dialkylaminoalkyl or phenyl.

2. The compound according to claim 1 represented by general formula (I) or a salt thereof, wherein

A is N;

B is phenyl or pyridyl;

m is 1, 2 or 3;

E is phenyl;

n is 1, or 2; and

p is 0 or 1.

3. The compound according to claim 2 represented by general formula (I) or a salt thereof, wherein

m is 1 or 2;

p is 0;

R^1 is C_1 - C_8 alkyl, halo, haloalkyl, haloalkoxy, $-CN$, $-NO_2$, $-C(Y)NR^bR^{b'}$, $-NR^cC(Y)R^c$, $-SO_2NR^bR^{b'}$, $-OR^d$, or $-S(O)_qR^f$; and

R^2 is $-OR^d$.

4. The compound according to claim 3 represented by general formula (I) or a salt thereof, wherein

R^2 is $-OR^d$, in which R^d is C_1 - C_8 alkyl; and

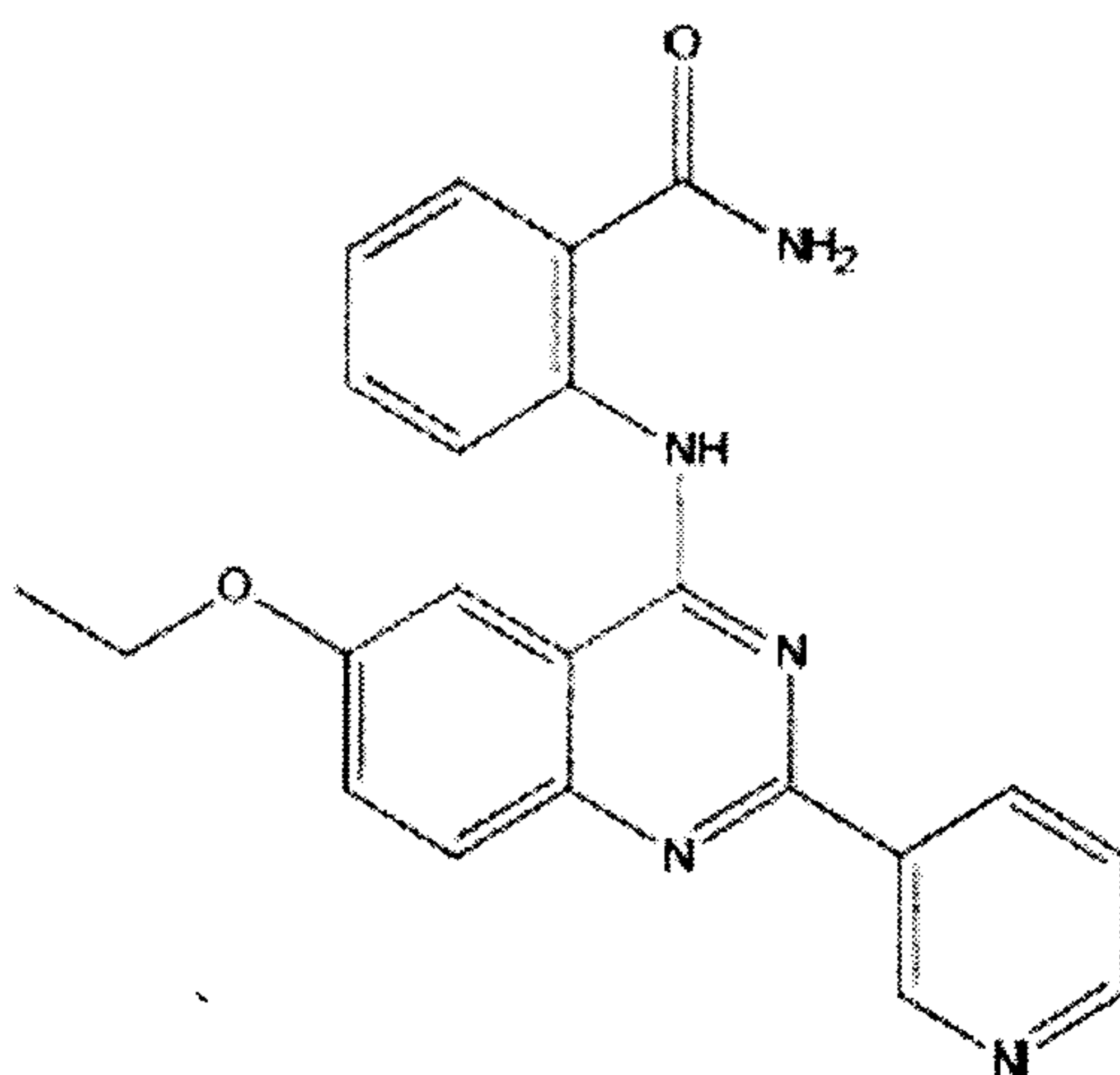
each R^b , $R^{b'}$, R^c , R^c , R^d and R^f is independently hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, C_3 - C_8 cycloalkyl, phenyl, dihydroindenyl, tetrahydropyranyl, phenylalkyl, thienylalkyl, tetrahydropyranylalkyl, dihydroindenylalkyl, or haloalkyl.

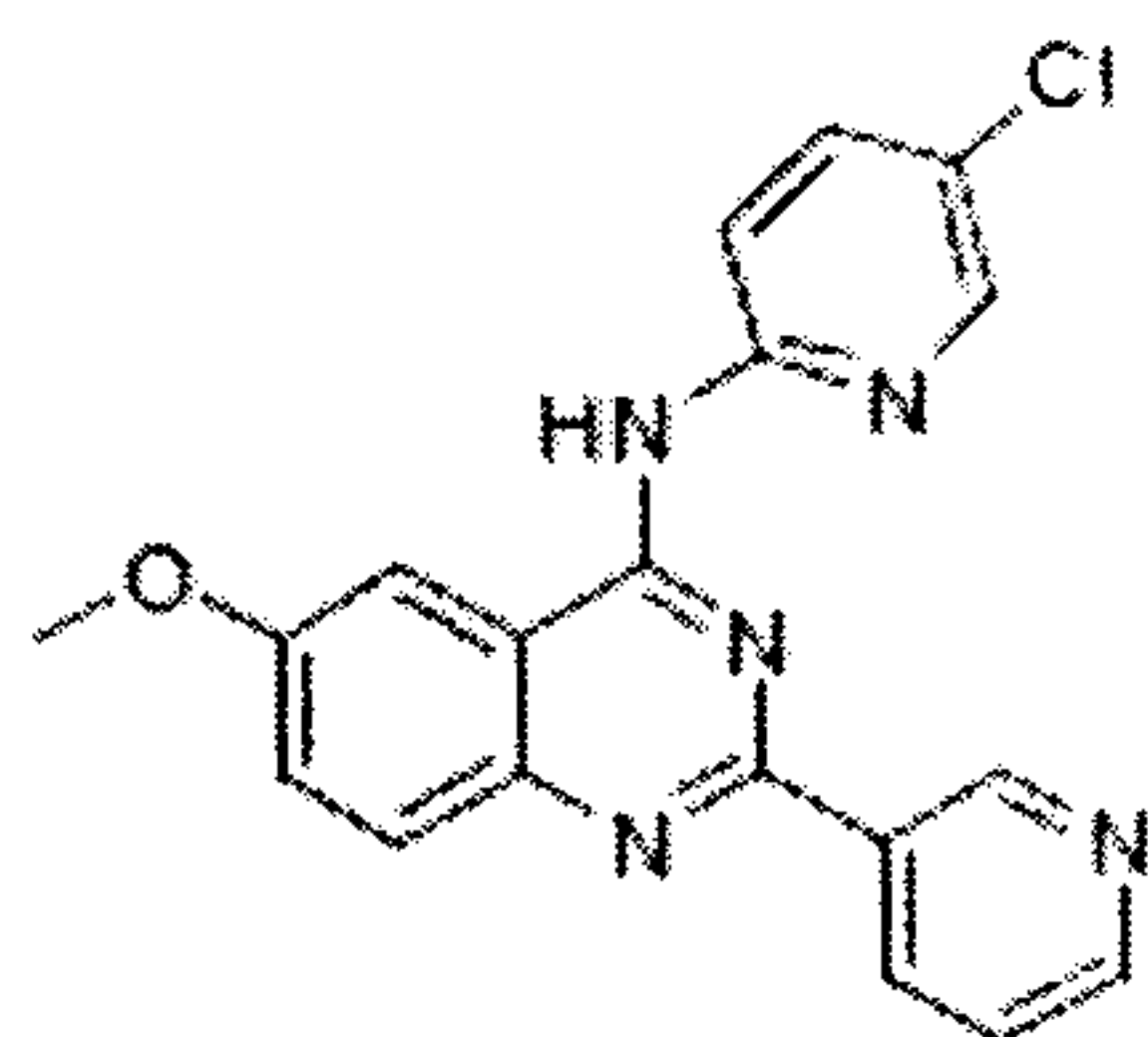
5. The compound according to claim 4 represented by general formula (I) or a salt thereof, wherein

R^1 is C_1 - C_8 alkyl, halo, haloalkyl, haloalkoxy, $-C(Y)NR^bR^{b'}$ or $-OR^d$; and

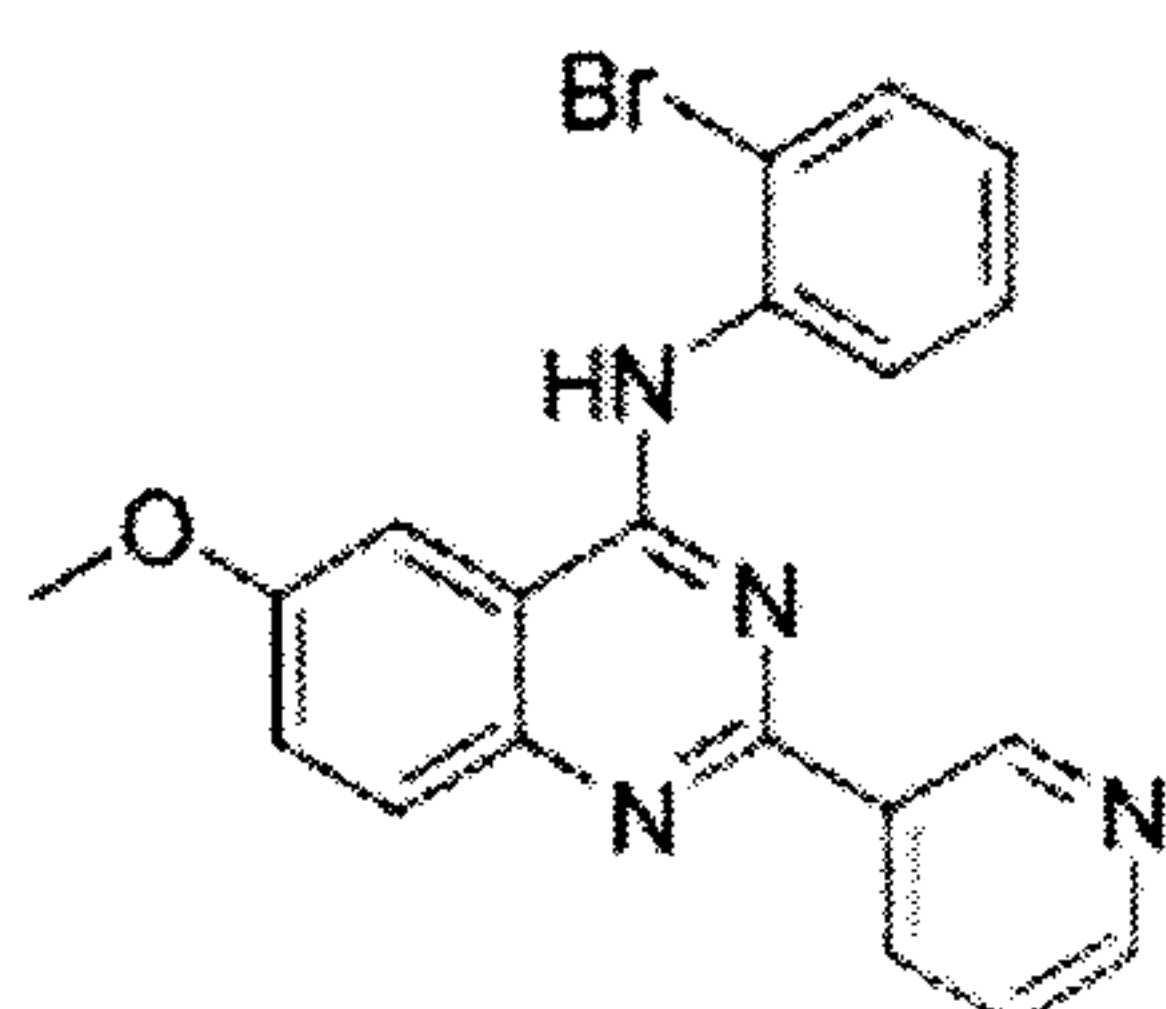
each R^b , $R^{b'}$, R^d and R^f is independently hydrogen, C_1 - C_8 alkyl, C_3 - C_8 cycloalkyl or haloalkyl.

6. The compound according to claim 1 represented by general formula (I) or a salt thereof, wherein the compound of formula (I) is:

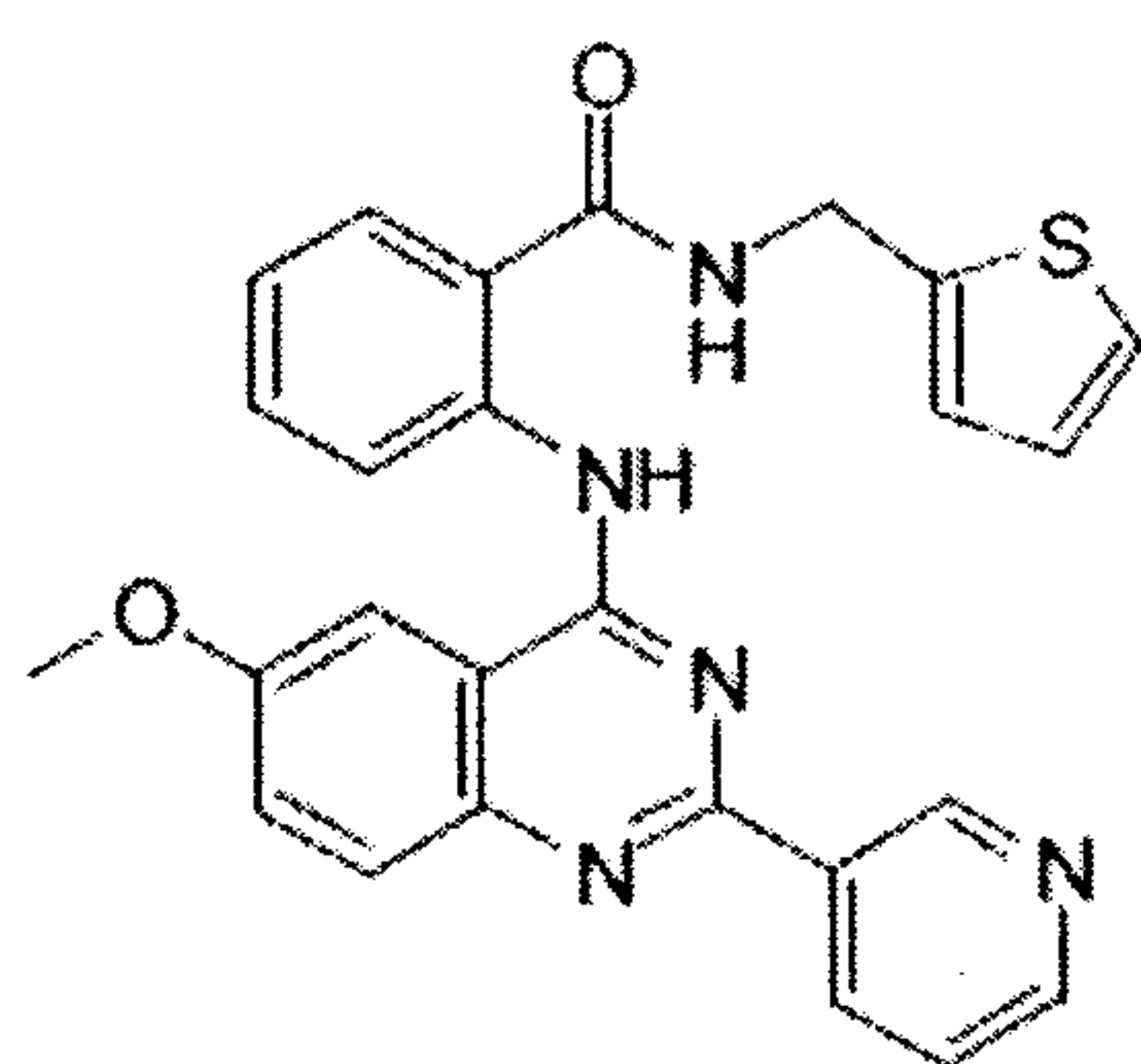




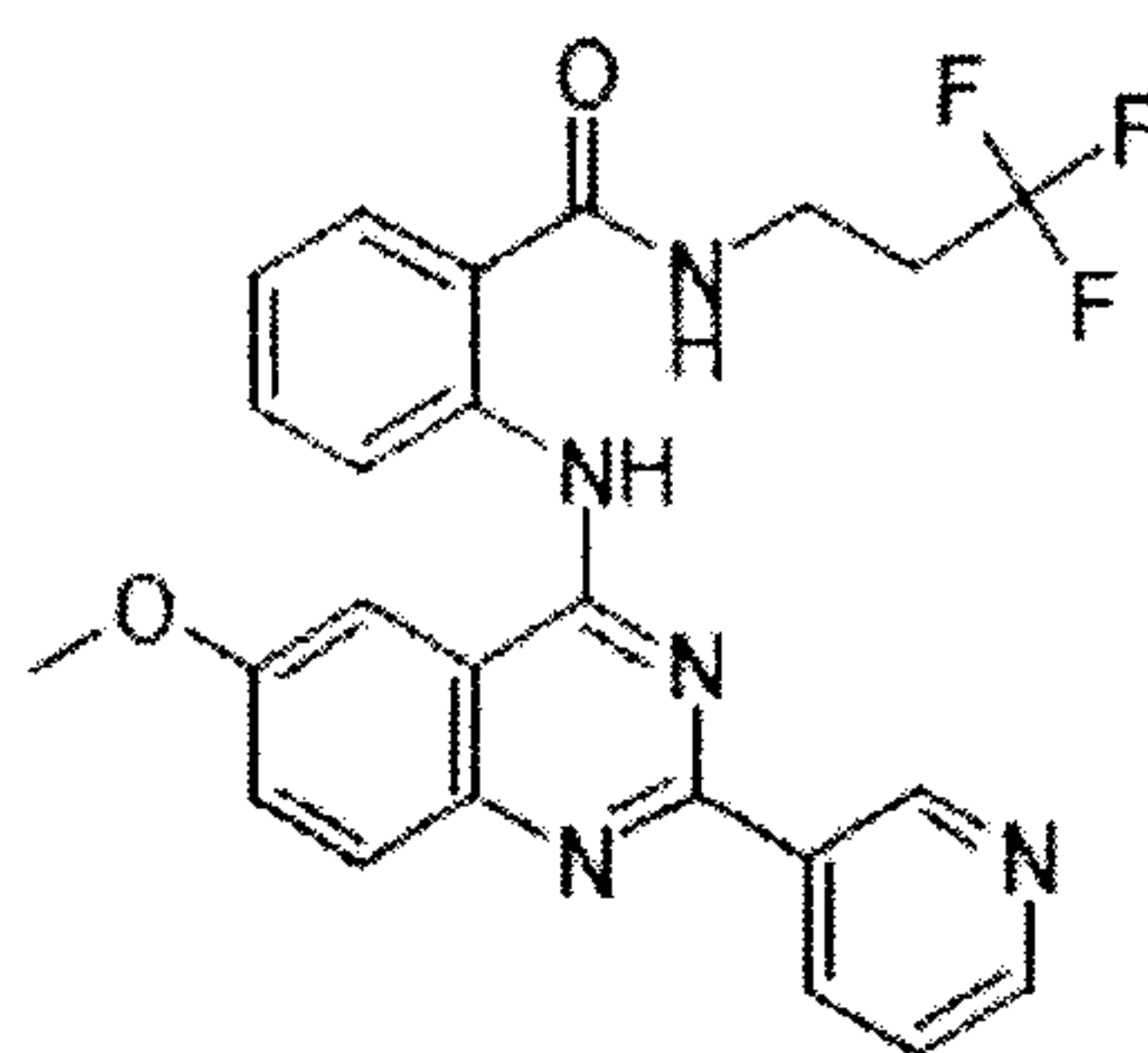
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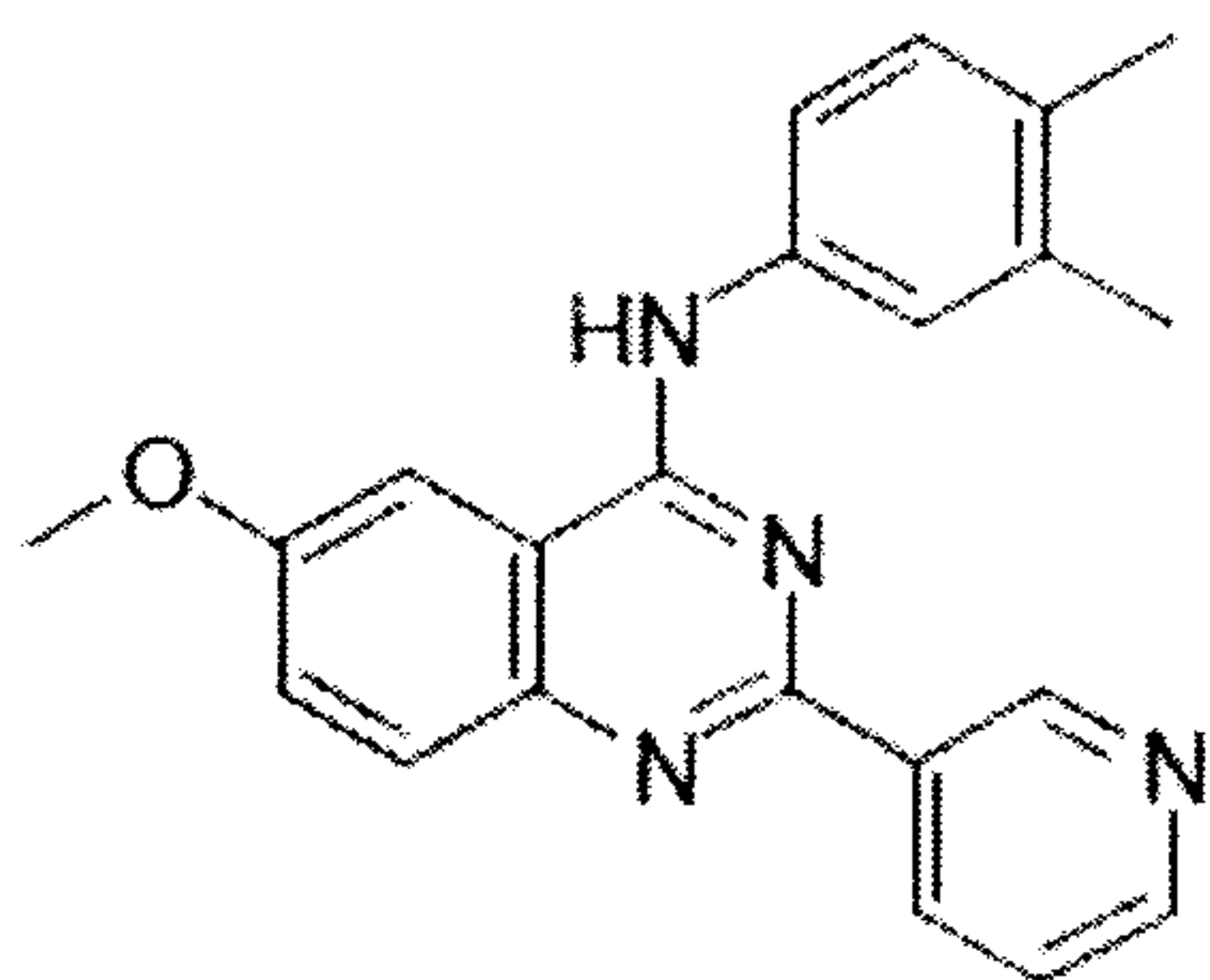
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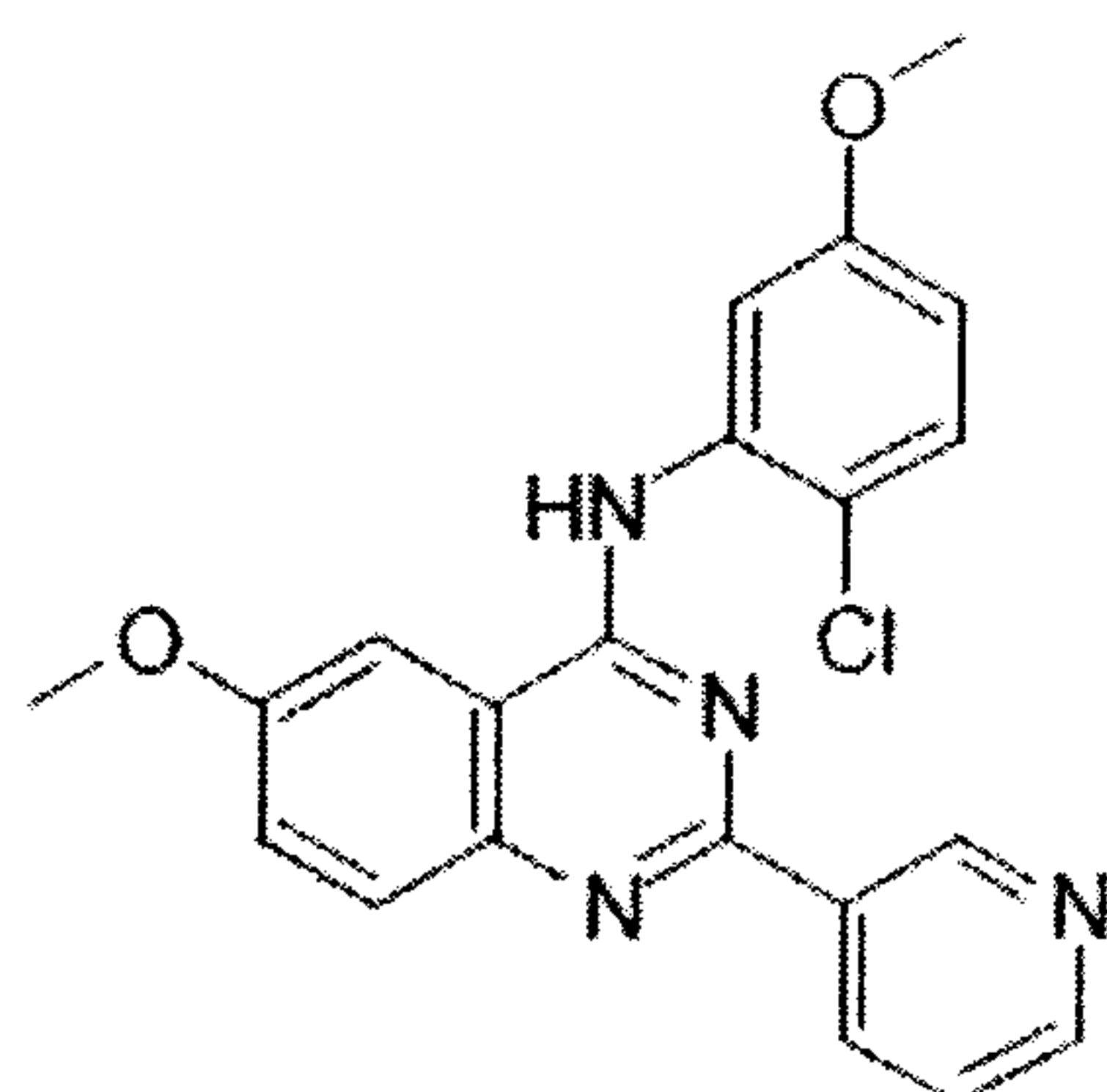
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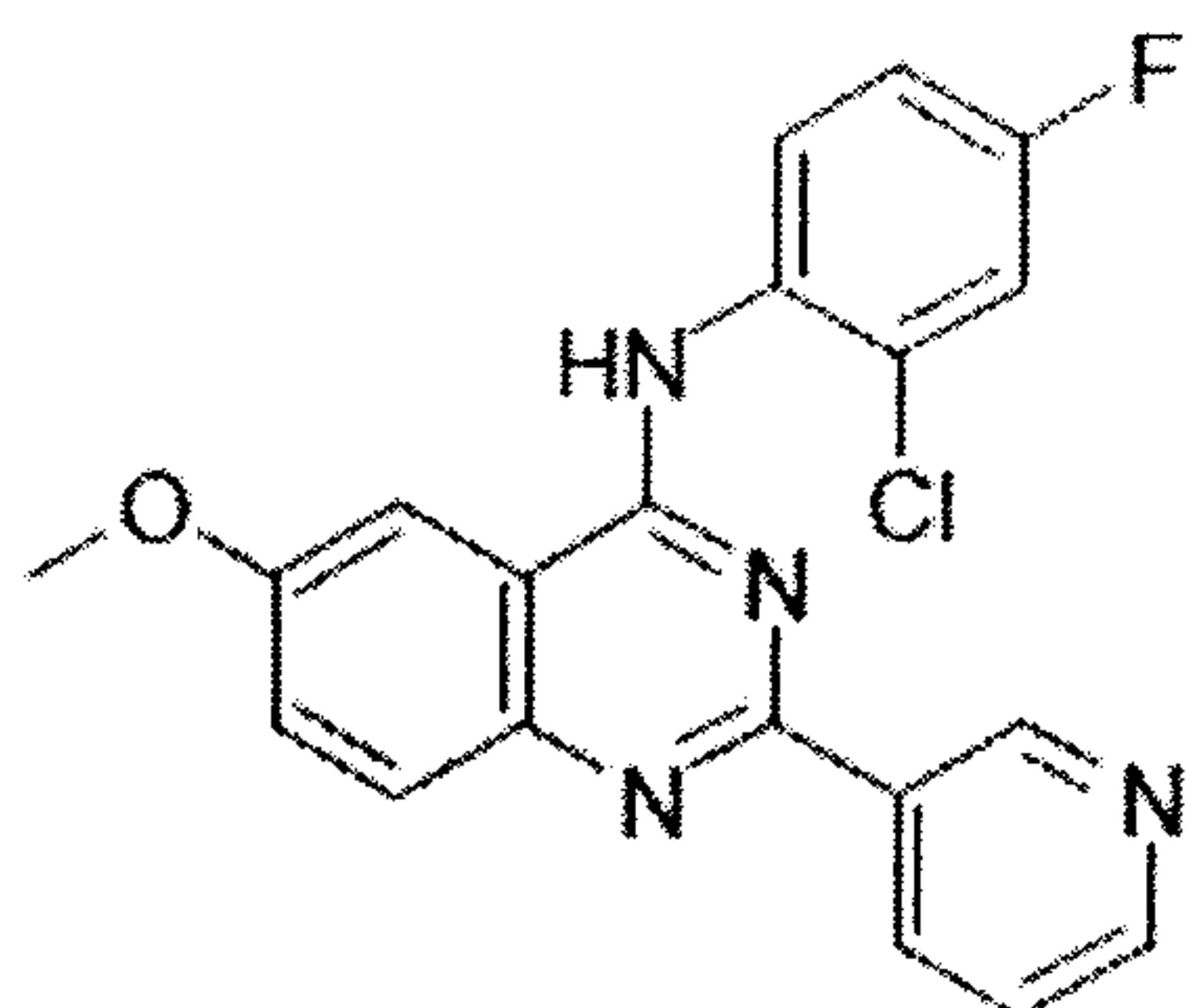
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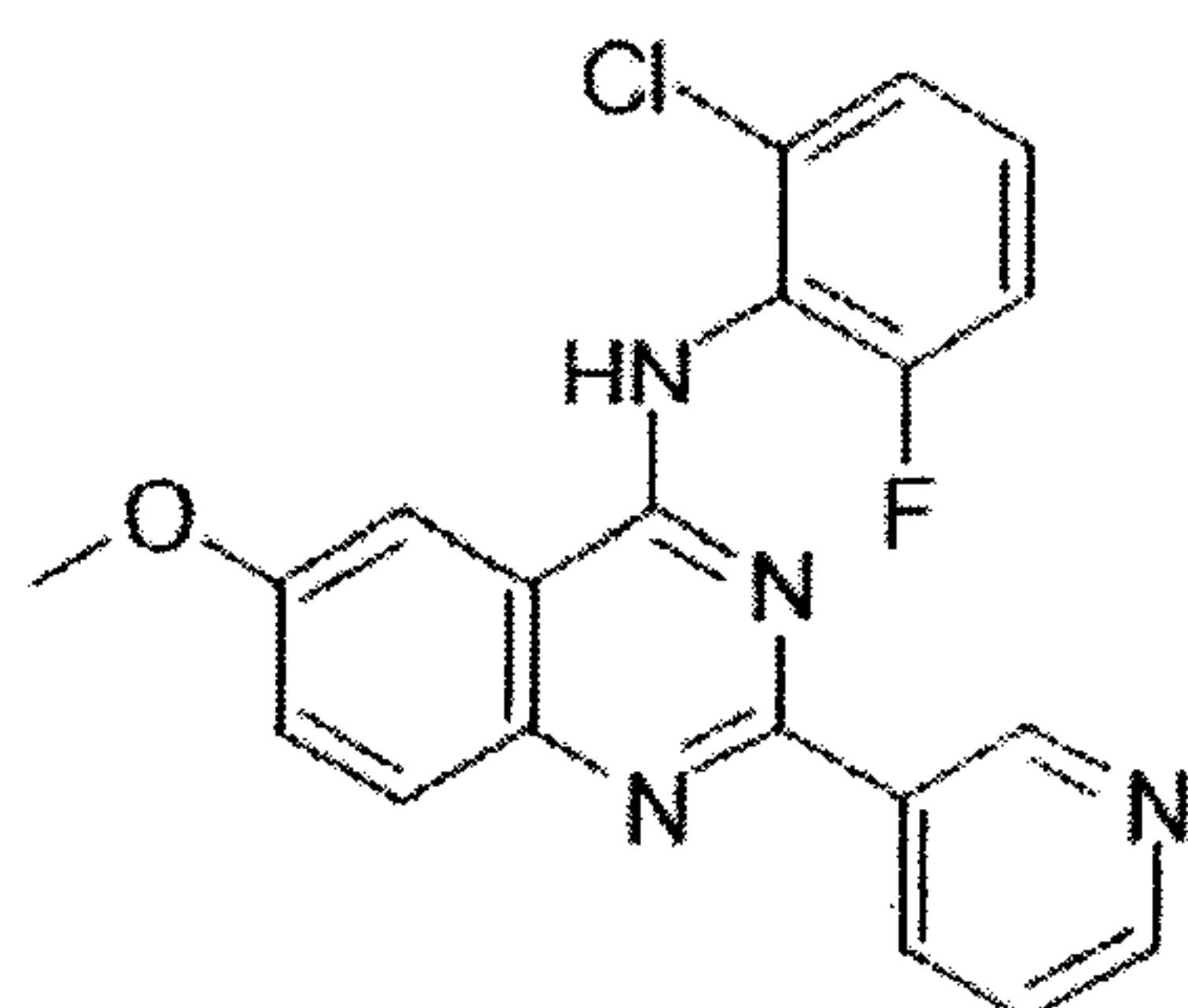
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, or



7. The compound according to claim 1 represented by general formula (III) or a salt thereof,
wherein:

R^3 is hydrogen, C_1 - C_8 alkyl, halo, haloalkyl, or $-OR^d$;

R^4 is hydrogen, C_1 - C_8 alkyl, halo, or $-OR^d$;

R^7 is C_1 - C_8 alkyl, phenyl, halo, haloalkyl, oxo, $-C(O)OR^a$, $-C(O)NR^bR^{b'}$ or $-OR^d$ each of which is optionally substituted with 1-3 R^{12} ; and

R^9 is C_1 - C_8 alkyl, phenyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, alkoxyalkyl, $-CN$, $-NO_2$, $-C(O)NR^bR^{b'}$, $-C(O)OR^a$, $-NR^bR^{b'}$, $-OR^d$, $-C(O)R^e$ or $-S(O)_qR^f$, each of which is optionally substituted with 1-3 R^{12} .

8. The compound according to claim 7 represented by general formula (III) or a salt thereof,

wherein:

R^7 is C_1 - C_8 alkyl, phenyl, halo, haloalkyl, oxo, $-C(O)OR^a$, $-C(O)NR^bR^{b'}$ or $-OR^d$; and

R^9 is C_1 - C_8 alkyl, phenyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, alkoxyalkyl, $-CN$, $-NO_2$, $-C(O)NR^bR^{b'}$, $-C(O)OR^a$, $-NR^bR^{b'}$, $-OR^d$, $-C(O)R^e$ or $-S(O)_qR^f$.

9. The compound according to claim 8 represented by general formula (III) or a salt thereof,

wherein:

R^2 is phenyl, which is optionally substituted with 1-5 R^9 ; and

each R^a , R^b , $R^{b'}$, R^d , R^e and R^f is independently hydrogen, C_1 - C_8 alkyl, pyrrolidinyl, morpholinyl, tetrahydropyranyl, alkoxyalkyl, morpholinylalkyl, tetrahydropyranylalkyl, pyridylalkyl, thiazolylalkyl, pyrrolylalkyl, tetrahydrofuryl, tetrahydrofurylalkyl, alkylaminoalkyl or phenyl.

10. The compound according to claim 9 represented by general formula (III) or a salt thereof,

wherein:

n is 0;

R^1 is hydrogen, C_1 - C_8 alkyl or pyridylalkyl, each of which is optionally substituted with 1-3 R^7 ;

R^7 is C_1 - C_8 alkyl or halo;

R^9 is C_1 - C_8 alkyl, phenyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, $-CN$, $-NO_2$, $-C(O)NR^bR^{b'}$, $-C(O)OR^a$, $-NR^bR^{b'}$, $-OR^d$, $-C(O)R^e$ or $-S(O)_qR^f$; and

each R^a , R^b , $R^{b'}$, R^c , $R^{c'}$, R^d , $R^{d'}$, R^e and R^f is independently hydrogen, C_1 - C_8 alkyl, pyrrolidinyl, morpholinyl, tetrahydropyranyl, alkoxyalkyl, morpholinylalkyl, tetrahydropyranylalkyl, pyridylalkyl, thiazolylalkyl, pyrrolylalkyl or tetrahydrofurylalkyl.

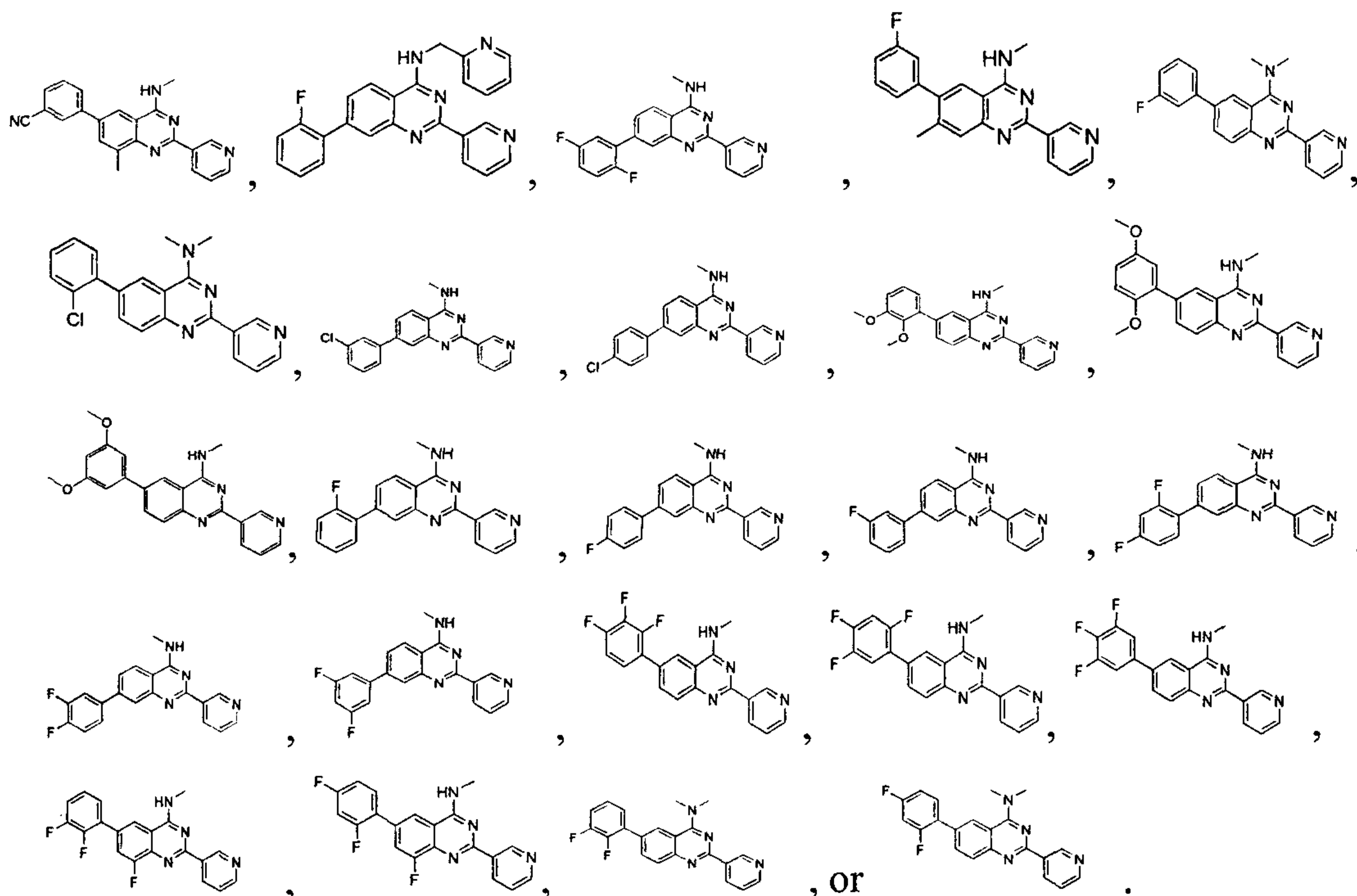
11. The compound according to claim 10 represented by general formula (III) or a salt thereof,

wherein:

R^9 is halo or $-OR^d$, and

R^d is C_1 - C_8 alkyl.

12. The compound according to claim 1 or a salt thereof, wherein the compound of formula (III) is:



13. A pharmaceutical composition comprising the compound as defined in any one of claims 1 to 12 or a salt thereof, and a pharmaceutically acceptable carrier.

14. The pharmaceutical composition according to claim 13 for use in preventing or

treating a central nervous system disease.

15. The pharmaceutical composition according to claim 13 for use in treating or preventing a central nervous system disorder which is: schizophrenia; refractory, intractable or chronic schizophrenia; emotional disturbance; psychotic disorder; mood disorder; bipolar I type disorder; bipolar II type disorder; depression; endogenous depression; major depression; melancholy or refractory depression; dysthymic disorder; cyclothymic disorder; panic attack; panic disorder; agoraphobia; social phobia; obsessive-compulsive disorder; post-traumatic stress disorder; generalized anxiety disorder; acute stress disorder; hysteria; somatization disorder; conversion disorder; pain disorder; hypochondriasis; factitious disorder; dissociative disorder; sexual dysfunction; sexual desire disorder; sexual arousal disorder; erectile dysfunction; anorexia nervosa; bulimia nervosa; sleep disorder; adjustment disorder; alcohol abuse; alcohol intoxication; drug addiction; stimulant intoxication; narcotism; anhedonia; iatrogenic anhedonia; anhedonia of a psychic or mental cause; anhedonia associated with depression; anhedonia associated with schizophrenia; delirium; cognitive impairment; cognitive impairment associated with a neurodegenerative disease; cognitive impairment caused by Alzheimer's disease or Parkinson's disease; Parkinson's disease and associated neurodegenerative diseases; cognitive impairment of schizophrenia; cognitive impairment caused by refractory, intractable or chronic schizophrenia; vomiting; motion sickness; obesity; migraine; aches or pain; mental retardation; autism or autism disorder; Tourette's disorder; tic disorder; attention-deficit/hyperactivity disorder; conduct disorder; or Down's syndrome.
16. A process for producing a pharmaceutical composition comprising mixing a compound or a salt thereof as defined in any one of claims 1 to 12 with a pharmaceutically acceptable carrier.
17. A compound or a salt thereof according to any one of claims 1 to 12 for use as an inhibitor of striatal-enriched tyrosine phosphatase (STEP).
18. A compound or a salt thereof according to any one of claims 1 to 12 for use in treating schizophrenia or cognitive deficit.

19. A combination of a compound or a salt thereof as defined in any one of claims 1 to 12 with an additional therapeutic agent for use in treating a disorder that would benefit by the modulation of striatal-enriched tyrosine phosphatase (STEP).
20. The combination for use according to claim 19, wherein the additional therapeutic agent is an atypical antipsychotic.
21. The combination for use according to claim 19, wherein the additional therapeutic agent is aripiprazole, clozapine, ziprasidone, risperidone, quetiapine, olanzapine, amisulpride, asenapine, iloperidone, melperone, paliperidone, perospirone, sertindole or sulpride.
22. The combination for use according to claim 19, wherein the additional therapeutic agent is a typical antipsychotic.
23. The combination for use according to claim 19, wherein the additional therapeutic agent is haloperidol, molindone, loxapine, thioridazine, thiothixene, pimozide, fluphenazine, trifluoperazine, mesoridazine, chlorprothixene, chlorpromazine, perphenazine, triflupromazine or zuclopenthixol.
24. A kit comprising a compound or a salt thereof as defined in any one of claims 1 to 12, and instructions for the use thereof to treat schizophrenia or cognitive deficit.
25. A kit comprising a pharmaceutical composition as defined in claim 13, and instructions for the use thereof to treat schizophrenia or cognitive deficit.
26. Use of a compound or a salt thereof as defined in any one of claims 1 to 12 in the preparation of a medicament for treating schizophrenia or cognitive deficit.

