



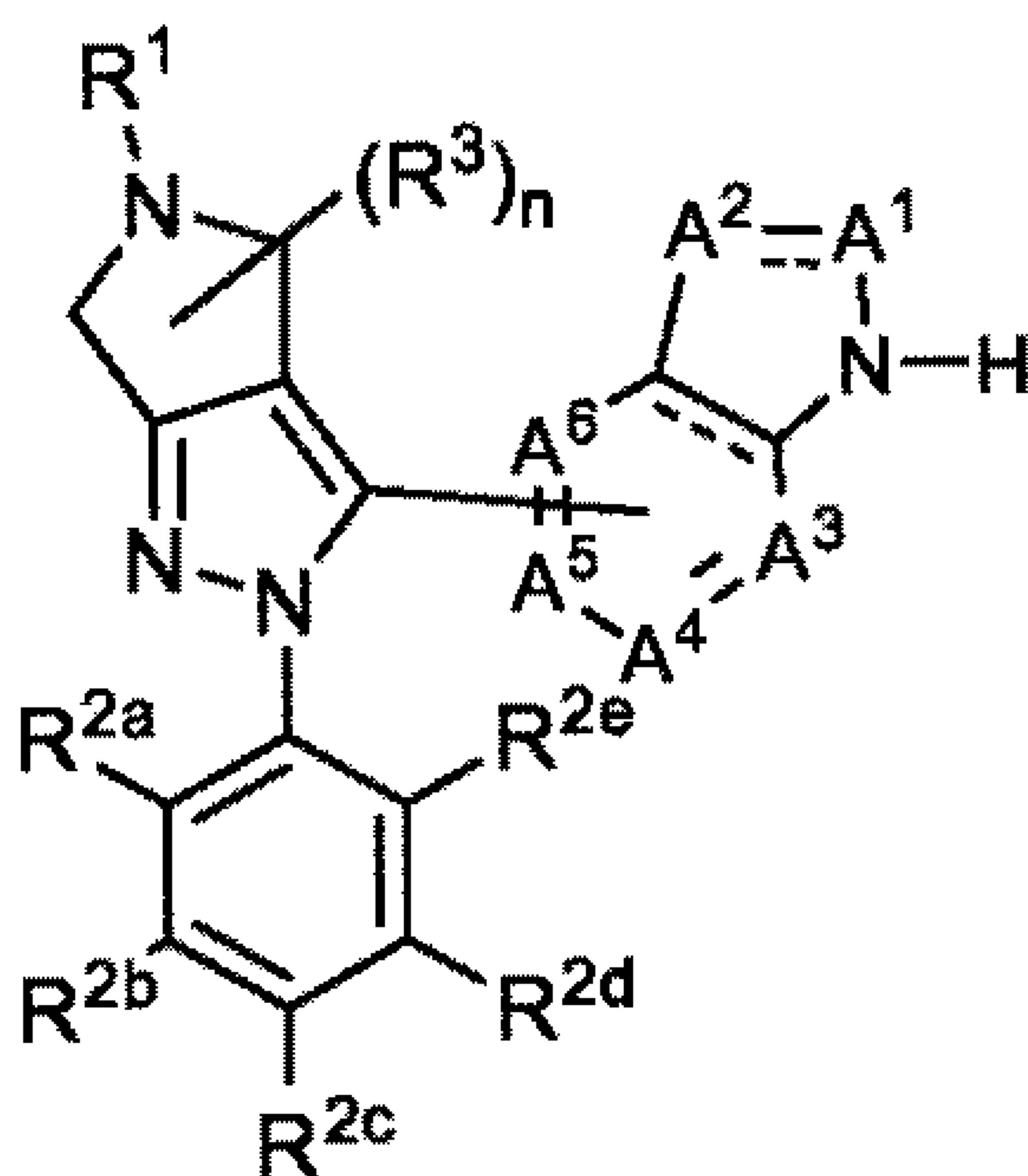
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(54) Titre : CYCLES 5-5 FUSIONNES UTILISES EN TANT QU'INHIBITEURS DE C5A
(54) Title: 5-5 FUSED RINGS AS C5A INHIBITORS



(I)

(57) Abrégé/Abstract:

The present disclosure provides, inter alia, Compounds of Formula (I) (I) or pharmaceutically acceptable salts thereof that are modulators of the C5a receptor. Also provided are pharmaceutical compositions and methods of use including the treatment of diseases or disorders involving pathologic activation from C5a and non-pharmaceutical applications.

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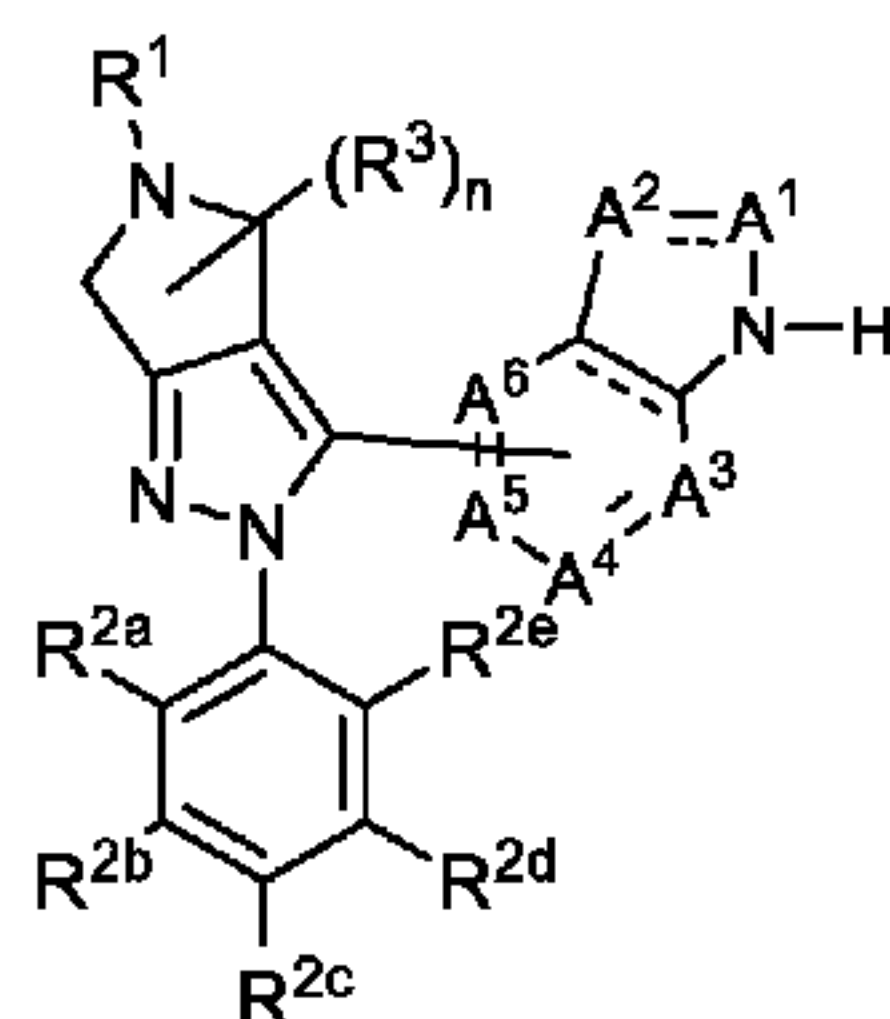
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(54) Title: 5-5 FUSED RINGS AS C5a INHIBITORS



(I)

(57) Abstract: The present disclosure provides, inter alia, Compounds of Formula (I) (I) or pharmaceutically acceptable salts thereof that are modulators of the C5a receptor. Also provided are pharmaceutical compositions and methods of use including the treatment of diseases or disorders involving pathologic activation from C5a and non-pharmaceutical applications.

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5-5 FUSED RINGS AS C5a INHIBITORS

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application is an application claiming benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application No. 62/513,025 filed May 31, 2017, which is herein incorporated by
5 reference in its entirety.

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

[0002] NOT APPLICABLE

REFERENCE TO A "SEQUENCE LISTING," A TABLE, OR A COMPUTER 10 PROGRAM LISTING APPENDIX SUBMITTED ON A COMPACT DISK

[0003] NOT APPLICABLE

BACKGROUND OF THE INVENTION

[0004] The complement system plays a central role in the clearance of immune complexes and in immune responses to infectious agents, foreign antigens, virus infected cells and tumor cells.
15 Inappropriate or excessive activation of the complement system can lead to harmful, and even potentially life-threatening consequences due to severe inflammation and resulting tissue destruction. These consequences are clinically manifested in various disorders including septic shock; myocardial, as well as, intestinal ischemia/reperfusion injury; graft rejection; organ failure; nephritis; pathological inflammation; and autoimmune diseases.

20 [0005] The complement system is composed of a group of proteins that are normally present in the serum in an inactive state. Activation of the complement system encompasses mainly three distinct pathways, *i.e.*, the classical, the alternative, and the lectin pathway (V. M. Holers, *In Clinical Immunology: Principles and Practice*, ed. R. R. Rich, Mosby Press; 1996, 363-391): 1) The classical pathway is a calcium/magnesium-dependent cascade, which is normally activated
25 by the formation of antigen-antibody complexes. It can also be activated in an antibody-independent manner by the binding of C-reactive protein, complexed with ligand, and by many

pathogens including gram-negative bacteria. 2) The alternative pathway is a magnesium-dependent cascade which is activated by deposition and activation of C3 on certain susceptible surfaces (*e.g.* cell wall polysaccharides of yeast and bacteria, and certain biopolymer materials). 3) The lectin pathway involves the initial binding of mannose-binding lectin and the subsequent
 5 activation of C2 and C4, which are common to the classical pathway (Matsushita, M. *et al.*, *J. Exp. Med.* 176: 1497-1502 (1992); Suankratay, C. *et al.*, *J. Immunol.* 160: 3006-3013 (1998)).

[0006] The activation of the complement pathway generates biologically active fragments of complement proteins, *e.g.* C3a, C4a and C5a anaphylatoxins and C5b-9 membrane attack complexes (MAC), all which mediate inflammatory responses by affecting leukocyte
 10 chemotaxis; activating macrophages, neutrophils, platelets, mast cells and endothelial cells; and increasing vascular permeability, cytolysis and tissue injury.

[0007] Complement C5a is one of the most potent proinflammatory mediators of the complement system. (The anaphylactic C5a peptide is 100 times more potent, on a molar basis, in eliciting inflammatory responses than C3a.) C5a is the activated form of C5 (190 kD,
 15 molecular weight). C5a is present in human serum at approximately 80 ng/ml (Kohler, P. F. *et al.*, *J. Immunol.* 99: 1211-1216 (1967)). It is composed of two polypeptide chains, α and β , with approximate molecular weights of 115 kD and 75 kD, respectively (Tack, B. F. *et al.*, *Biochemistry* 18: 1490-1497 (1979)). Biosynthesized as a single-chain promolecule, C5 is enzymatically cleaved into a two-chain structure during processing and secretion. After
 20 cleavage, the two chains are held together by at least one disulphide bond as well as noncovalent interactions (Ooi, Y. M. *et al.*, *J. Immunol.* 124: 2494-2498(1980)).

[0008] C5 is cleaved into the C5a and C5b fragments during activation of the complement pathways. The convertase enzymes responsible for C5 activation are multi-subunit complexes of C4b, C2a, and C3b for the classical pathway and of (C3b)₂, Bb, and P for the alternative pathway
 25 (Goldlust, M. B. *et al.*, *J. Immunol.* 113: 998-1007 (1974); Schreiber, R. D. *et al.*, *Proc. Natl. Acad. Sci.* 75: 3948-3952 (1978)). C5 is activated by cleavage at position 74-75 (Arg-Leu) in the α -chain. After activation, the 11.2 kD, 74 amino acid peptide C5a from the amino-terminus portion of the α -chain is released. Both C5a and C3a are potent stimulators of neutrophils and monocytes (Schindler, R. *et al.*, *Blood* 76: 1631-1638 (1990); Haeffner-Cavaillon, N. *et al.*, *J.*
 30 *Immunol.* 138: 794-700 (1987); Cavaillon, J. M. *et al.*, *Eur. J. Immunol.* 20: 253-257 (1990)).

[0009] In addition to its anaphylatoxic properties, C5a induces chemotactic migration of neutrophils (Ward, P. A. *et al.*, *J. Immunol.* 102: 93-99 (1969)), eosinophils (Kay, A. B. *et al.*, *Immunol.* 24: 969-976 (1973)), basophils (Lett-Brown, M. A. *et al.*, *J. Immunol.* 117: 246-252 (1976)), and monocytes (Snyderman, R. *et al.*, *Proc. Soc. Exp. Biol. Med.* 138: 387-390 (1971)).

5 Both C5a and C5b-9 activate endothelial cells to express adhesion molecules essential for sequestration of activated leukocytes, which mediate tissue inflammation and injury (Foreman, K. E. *et al.*, *J. Clin. Invest.* 94: 1147-1155 (1994); Foreman, K. E. *et al.*, *Inflammation* 20: 1-9 (1996); Rollins, S. A. *et al.*, *Transplantation* 69: 1959-1967 (2000)). C5a also mediates inflammatory reactions by causing smooth muscle contraction, increasing vascular permeability, 10 inducing basophil and mast cell degranulation and inducing release of lysosomal proteases and oxidative free radicals (Gerard, C. *et al.*, *Ann. Rev. Immunol.* 12: 775-808 (1994)). Furthermore, C5a modulates the hepatic acute-phase gene expression and augments the overall immune response by increasing the production of TNF- α , IL-1 β , IL-6, IL-8, prostaglandins and leukotrienes (Lambris, J. D. *et al.*, *In: The Human Complement System in Health and Disease*, 15 Volanakis, J. E. ed., Marcel Dekker, New York, pp. 83-118).

[0010] The anaphylactic and chemotactic effects of C5a are believed to be mediated through its interaction with the C5a receptor. The human C5a receptor (C5aR) is a 52 kD membrane bound G protein-coupled receptor, and is expressed on neutrophils, monocytes, basophils, eosinophils, hepatocytes, lung smooth muscle and endothelial cells, and renal glomerular tissues 20 (Van-Epps, D. E. *et al.*, *J. Immunol.* 132: 2862-2867 (1984); Haviland, D. L. *et al.*, *J. Immunol.* 154:1861-1869 (1995); Wetsel, R. A., *Immunol. Leff.* 44: 183-187 (1995); Buchner, R. R. *et al.*, *J. Immunol.* 155: 308-315 (1995); Chenoweth, D. E. *et al.*, *Proc. Natl. Acad. Sci.* 75: 3943-3947 (1978); Zwirner, J. *et al.*, *Mol. Immunol.* 36:877-884 (1999)). The ligand-binding site of C5aR is complex and consists of at least two physically separable binding domains. One binds the C5a 25 amino terminus (amino acids 1-20) and disulfide-linked core (amino acids 21-61), while the second binds the C5a carboxy-terminal end (amino acids 62-74) (Wetsel, R. A., *Curr. Opin. Immunol.* 7: 48-53 (1995)).

[0011] C5a plays important roles in inflammation and tissue injury. In cardiopulmonary bypass and hemodialysis, C5a is formed as a result of activation of the alternative complement 30 pathway when human blood makes contact with the artificial surface of the heart-lung machine

or kidney dialysis machine (Howard, R. J. *et al.*, *Arch. Surg.* 123: 1496-1501 (1988); Kirklin, J. K. *et al.*, *J. Cardiovasc. Surg.* 86: 845-857 (1983); Craddock, P. R. *et al.*, *N. Engl. J. Med.* 296: 769-774 (1977)). C5a causes increased capillary permeability and edema, bronchoconstriction, pulmonary vasoconstriction, leukocyte and platelet activation and infiltration to tissues, in particular the lung (Czermak, B. J. *et al.*, *J. Leukoc. Biol.* 64: 40-48 (1998)). Administration of an anti-C5a monoclonal antibody was shown to reduce cardiopulmonary bypass and cardioplegia-induced coronary endothelial dysfunction (Tofukuji, M. *et al.*, *J. Thorac. Cardiovasc. Surg.* 116: 1060-1068 (1998)).

[0012] C5a is also involved in acute respiratory distress syndrome (ARDS), Chronic Obstructive Pulmonary Disorder (COPD) and multiple organ failure (MOF) (Hack, C. E. *et al.*, *Am. J. Med.* 1989; 86: 20-26; Hammerschmidt DE *et al.* *Lancet* 1980; 1: 947-949; Heideman M. *et al.* *J. Trauma* 1984; 4: 1038-1043; Marc, MM, *et al.*, *Am. J. Respir. Cell and Mol. Biol.*, 2004; 31: 216-219). C5a augments monocyte production of two important pro-inflammatory cytokines, TNF- and IL-1. C5a has also been shown to play an important role in the development of tissue injury, and particularly pulmonary injury, in animal models of septic shock (Smedegard G *et al.* *Am. J. Pathol.* 1989; 135: 489-497; Markus, S., *et al.*, *FASEB Journal* (2001), 15: 568-570). In sepsis models using rats, pigs and non-human primates, anti-C5a antibodies administered to the animals before treatment with endotoxin or E. coli resulted in decreased tissue injury, as well as decreased production of IL-6 (Smedegard, G. *et al.*, *Am. J. Pathol.* 135: 489-497 (1989); Hopken, U. *et al.*, *Eur. J. Immunol.* 26: 1103-1109 (1996); Stevens, J. H. *et al.*, *J. Clin. Invest.* 77: 1812-1816 (1986)). More importantly, blockade of C5a with anti-C5a polyclonal antibodies has been shown to significantly improve survival rates in a caecal ligation/puncture model of sepsis in rats (Czermak, B.J. *et al.*, *Nat. Med.* 5: 788-792 (1999)). This model share many aspects of the clinical manifestation of sepsis in humans. (Parker, S.J. *et al.*, *Br. J. Surg.* 88: 22-30 (2001)). In the same sepsis model, anti-C5a antibodies were shown to inhibit apoptosis of thymocytes (Guo, R.F. *et al.*, *J. Clin. Invest.* 106: 1271-1280 (2000)) and prevent MOF (Huber-Lang, M. *et al.*, *J. Immunol.* 166: 1193-1199 (2001)). Anti-C5a antibodies were also protective in a cobra venom factor model of lung injury in rats, and in immune complex-induced lung injury (Mulligan, M. S. *et al.* *J. Clin. Invest.* 98: 503-512 (1996)). The importance of C5a in immune complex-mediated lung injury was later confirmed in mice (Bozic, C. R. *et al.*, *Science* 26: 1103-1109 (1996)).

[0013] C5a is found to be a major mediator in myocardial ischemia-reperfusion injury.

Complement depletion reduced myocardial infarct size in mice (Weisman, H. F. *et al.*, *Science* 249: 146-151 (1990)), and treatment with anti-C5a antibodies reduced injury in a rat model of hindlimb ischemia-reperfusion (Bless, N. M. *et al.*, *Am. J. Physiol.* 276: L57-L63 (1999)).

5 Reperfusion injury during myocardial infarction was also markedly reduced in pigs that were retreated with a monoclonal anti-C5a IgG (Amsterdam, E. A. *et al.*, *Am. J. Physiol.* 268:H448-H457 (1995)). A recombinant human C5aR antagonist reduces infarct size in a porcine model of surgical revascularization (Riley, R. D. *et al.*, *J. Thorac. Cardiovasc. Surg.* 120: 350-358 (2000)).

10 [0014] C5a driven neutrophils also contribute to many bullous diseases (e.g., bullous pemphigoid, pemphigus vulgaris and pemphigus foliaceus). These are chronic and recurring inflammatory disorders clinically characterized by sterile blisters that appear in the sub-epidermal space of the skin and mucosa. While autoantibodies to keratinocytes located at the cutaneous basement membranes are believed to underlie the detachment of epidermal basal
15 keratinocytes from the underlying basement membrane, blisters are also characterized by accumulation of neutrophils in both the upper dermal layers and within the blister cavities. In experimental models a reduction of neutrophils or absence of complement (total or C5-selective) can inhibit formation of sub-epidermal blisters, even in the presence of high auto-antibody titers.

[0015] Complement levels are elevated in patients with rheumatoid arthritis (Jose, P. J. *et al.*,
20 *Ann. Rheum. Dis.* 49: 747-752 (1990); Grant, E.P., *et al.*, *J. of Exp. Med.*, 196(11): 1461-1471, (2002)), lupus nephritis (Bao, L., *et al.*, *Eur. J. of Immunol.*, 35(8), 2496-2506, (2005)) and systemic lupus erythematosus (SLE) (Porcel, J. M. *et al.*, *Clin. Immunol. Immunopathol.* 74: 283-288 (1995)). C5a levels correlate with the severity of the disease state. Collagen-induced arthritis in mice and rats resembles the rheumatoid arthritic disease in human. Mice deficient in
25 the C5a receptor demonstrated a complete protection from arthritis induced by injection of monoclonal anti-collagen Abs (Banda, N.K., *et al.*, *J. of Immunol.*, 2003, 171: 2109-2115). Therefore, inhibition of C5a and/or C5a receptor (C5aR) could be useful in treating these chronic diseases.

[0016] The complement system is believed to be activated in patients with inflammatory bowel
30 disease (IBD) and is thought to play a role in the disease pathogenesis. Activated complement

products were found at the luminal face of surface epithelial cells, as well as in the muscularis mucosa and submucosal blood vessels in IBD patients (Woodruff, T.M., *et al.*, *J of Immunol.*, 2003, 171: 5514-5520).

[0017] C5aR expression is upregulated on reactive astrocytes, microglia, and endothelial cells
 5 in an inflamed human central nervous system (Gasque, P. *et al.*, *Am. J. Pathol.* 150: 31-41 (1997)). C5a might be involved in neurodegenerative diseases, such as Alzheimer disease (Mukherjee, P. *et al.*, *J. Neuroimmunol.* 105: 124-130 (2000); O'Barr, S. *et al.*, *J. Neuroimmunol.* (2000) 105: 87-94; Farkas, I., *et al. J. Immunol.* (2003) 170:5764-5771), Parkinson s disease, Pick disease and transmissible spongiform encephalopathies. Activation of neuronal C5aR may
 10 induce apoptosis (Farkas I *et al. J. Physiol.* 1998; 507: 679-687). Therefore, inhibition of C5a and/or C5aR could also be useful in treating neurodegenerative diseases.

[0018] There is some evidence that C5a production worsens inflammation associated with atopic dermatitis (Neuber, K., *et al.*, *Immunology* 73:83-87, (1991)), and chronic urticaria (Kaplan, A.P., *J. Allergy Clin. Immunol.* 114; 465-474, (2004).

15 [0019] Psoriasis is now known to be a T cell-mediated disease (Gottlieb, E. L. *et al.*, *Nat. Med.* 1: 442-447 (1995)). However, neutrophils and mast cells may also be involved in the pathogenesis of the disease (Terui, T. *et al.*, *Exp. Dermatol.* 9: 1-10; 2000); Werfel, T. *et al.*, *Arch. Dermatol. Res.* 289: 83-86 (1997)). Neutrophil accumulation under the stratum corneum is observed in the highly inflamed areas of psoriatic plaques, and psoriatic lesion (scale) extracts
 20 contain highly elevated levels of C5a and exhibit potent chemotactic activity towards neutrophils, an effect that can be inhibited by addition of a C5a antibody. T cells and neutrophils are chemo-attracted by C5a (Nataf, S. *et al.*, *J. Immunol.* 162: 4018-4023 (1999); Tsuji, R. F. *et al.*, *J. Immunol.* 165: 1588-1598 (2000); Cavaillon, J. M. *et al.*, *Eur. J. Immunol.* 20: 253-257 (1990)). Additionally expression of C5aR has been demonstrated in plasmacytoid dendritic cells
 25 (pDC) isolated from lesions of cutaneous lupus erythematosus and these cells were shown to display chemotactic behavior towards C5a, suggesting that blockade of C5aR on pDC might be efficacious in reducing pDC infiltration into inflamed skin in both SLE and psoriasis. Therefore C5a could be an important therapeutic target for treatment of psoriasis.

[0020] Immunoglobulin G-containing immune complexes (IC) contribute to the pathophysiology in a number of autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, Sjogren's disease, Goodpasture's syndrome, and hypersensitivity pneumonitis (Madaio, M. P., *Semin. Nephrol.* 19: 48-56 (1999); Korganow, A. S. *et al.*, *Immunity* 10: 451-459 (1999); Bolten, W. K., *Kidney Int.* 50: 1754-1760 (1996); Ando, M. *et al.*, *Curr. Opin. Pulm. Med.* 3: 391-399 (1997)). These diseases are highly heterogeneous and generally affect one or more of the following organs: skin, blood vessels, joints, kidneys, heart, lungs, nervous system and liver (including cirrhosis and liver fibrosis). The classical animal model for the inflammatory response in these IC diseases is the Arthus reaction, which features the infiltration of polymorphonuclear cells, hemorrhage, and plasma exudation (Arthus, M., *C.R. Soc. Biol.* 55: 817-824 (1903)). Recent studies show that C5aR deficient mice are protected from tissue injury induced by IC (Kohl, J. *et al.*, *Mol. Immunol.* 36: 893-903 (1999); Baumann, U. *et al.*, *J. Immunol.* 164: 1065-1070 (2000)). The results are consistent with the observation that a small peptidic anti-C5aR antagonist inhibits the inflammatory response caused by IC deposition (Strachan, A. J. *et al.*, *J. Immunol.* 164: 6560-6565 (2000)). Together with its receptor, C5a plays an important role in the pathogenesis of IC diseases. Inhibitors of C5a and C5aR could be useful to treat these diseases.

Description of Related Art:

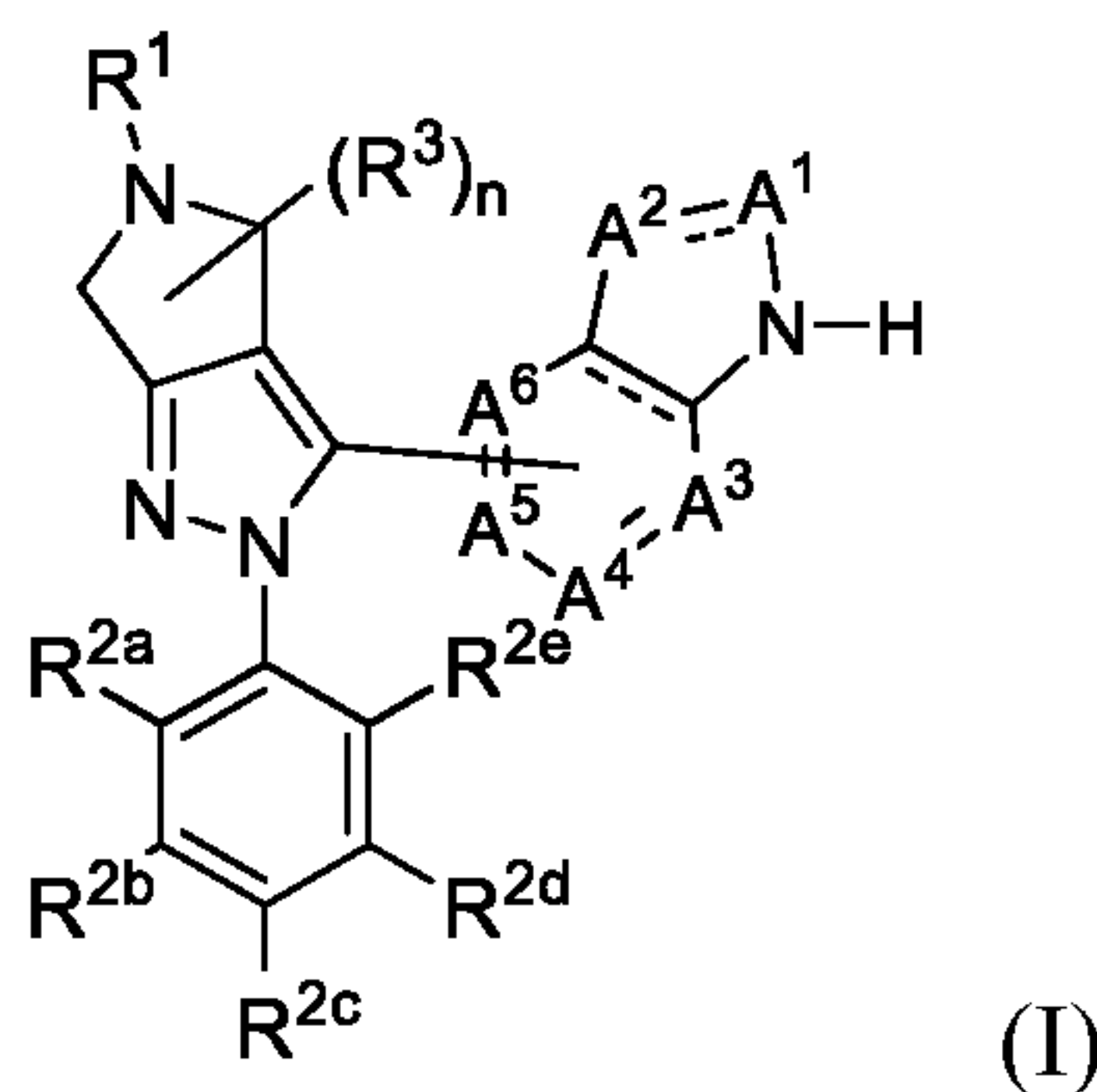
[0021] Non-peptide based C5a receptor antagonist have been reported as being effective for treating endotoxic shock in rats (Strachan, A.J., *et al.*, *J. of Immunol.* (2000), 164(12): 6560-6565); and for treating IBD in a rat model (Woodruff, T.M., *et al.*, *J of Immunol.*, 2003, 171: 5514-5520). Non-peptide based C5a receptor modulators also have been described in the patent literature by Neurogen Corporation, (*e.g.*, WO2004/043925, WO2004/018460, WO2005/007087, WO03/082826, WO03/08828, WO02/49993, WO03/084524); Dompe S.P.A. (WO02/029187); The University of Queensland (WO2004/100975); and ChemoCentryx (WO2010/075257).

[0022] There is considerable experimental evidence in the literature that implicates increased levels of C5a with a number of diseases and disorders, in particular in autoimmune and inflammatory diseases and disorders. Thus, there remains a need in the art for new small organic molecule modulators, *e.g.*, agonists, preferably antagonists, partial agonists, of the C5a receptor

(C5aR) that are useful for inhibiting pathogenic events, *e.g.*, chemotaxis, associated with increased levels anaphylatoxin activity. The present invention fulfills this and other needs.

BRIEF SUMMARY OF THE INVENTION

[0023] In one aspect, the present invention provide compounds of Formula (I):



or a pharmaceutically acceptable salt thereof, wherein,

ring vertex A¹ is selected from the group consisting of N, CH, C(O) and C(R⁴);

ring vertex A² is selected from the group consisting of N, CH, and C(R⁴);

each of ring vertices A³, A⁴, A⁵ and A⁶ is independently selected from the group
consisting of CH and C(R⁴);

each of the dashed bonds independently indicate a single or double bond;

R¹ is selected from the group consisting of -C₁₋₈ alkylene heteroaryl, -C₁₋₈ alkylene-C₆₋₁₀ aryl, C₁₋₈ alkyl, C₁₋₈ haloalkyl, -C(O)-C₁₋₈ alkyl, -C(O)-C₆₋₁₀ aryl, -C(O)-heteroaryl, -C(O)-C₃₋₆ cycloalkyl, -C(O)-heterocycloalkyl, -C(O)NR^{1a}R^{1b}, -SO₂-C₆₋₁₀ aryl, -SO₂-heteroaryl, -C(O)-C₁₋₈ alkylene-O-heteroaryl, -C(O)-C₁₋₈ alkylene-O-C₆₋₁₀ aryl, -C(O)-C₁₋₈ alkylene-O- heterocycloalkyl, -C(O)-C₁₋₈ alkylene-O- C₃₋₆ cycloalkyl, -C(O) C₁₋₈ alkylene heteroaryl, -C(O) C₁₋₈ alkylene C₆₋₁₀ aryl, -C(O) C₁₋₈ alkylene heterocycloalkyl, -C(O) C₁₋₈ alkylene C₃₋₆ cycloalkyl and CO₂R^{1a}; the heterocycloalkyl is a 4 to 8 membered ring having from 1 to 3

heteroatoms as ring vertices selected from N, O and S; and the heteroaryl group is a 5 to 10 membered aromatic ring having from 1 to 3 heteroatoms as ring vertices selected from N, O and S;

wherein R^{1a} and R^{1b} are each independently selected from the group consisting of hydrogen, C_{1-8} alkyl, and C_{1-8} haloalkyl;

wherein R^1 is optionally substituted with 1 to 5 R^5 substituents;

R^{2a} and R^{2e} are each independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, $-O-C_{1-6}$ haloalkyl, $-S-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl- $O-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl- $S-C_{1-6}$ alkyl, CN, and halogen;

R^{2b} , R^{2c} , and R^{2d} are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, $-O-C_{1-6}$ haloalkyl, $-S-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl- $O-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl- $S-C_{1-6}$ alkyl, cyano, and halogen;

each R^3 is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, halogen and hydroxyl, and optionally two R^3 groups on the same carbon atom are combined to form oxo ($=O$) or to form a three to five membered cycloalkyl ring;

each R^4 is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} hydroxyalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, $-O-C_{1-6}$ haloalkyl, halogen, cyano, hydroxyl, $-S-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl- $O-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl- $S-C_{1-6}$ alkyl, $-NR^{4a}R^{4b}$, $-CONR^{4a}R^{4b}$, $-CO_2R^{4a}$, $-COR^{4a}$, $-OC(O)NR^{4a}R^{4b}$, $-NR^{4a}C(O)R^{4b}$, $-NR^{4a}C(O)_2R^{4b}$, and $NR^{4a}-C(O)NR^{4a}R^{4b}$;

each R^{4a} and R^{4b} is independently selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{1-4} haloalkyl;

each R^5 is independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} haloalkyl, C_{1-8} haloalkoxy, C_{1-8} hydroxyalkyl, $-C_{1-8}$ alkylene-heterocycloalkyl, $-C_{1-8}$ alkylene- C_{3-6} cycloalkyl, C_{3-6} cycloalkyl, heterocycloalkyl, halogen, OH, C_{2-8} alkenyl, C_{2-8} alkynyl, CN, $C(O)R^{5a}$, $-NR^{5b}C(O)R^{5a}$, $-CONR^{5a}R^{5b}$, $-NR^{5a}R^{5b}$, $-C_{1-8}$ alkylene $NR^{5a}R^{5b}$, $-S-C_{1-6}$ alkyl, $-C_{1-6}$ alkylene- $O-C_{1-6}$ alkyl, $-C_{1-6}$ alkylene- $S-C_{1-6}$ alkyl, $-OC(O)NR^{5a}R^{5b}$, $-NR^{5a}C(O)_2R^{5b}$, $-NR^{5a}-C(O)NR^{5b}R^{5b}$, and CO_2R^{5a} , wherein the heterocycloalkyl group is a 4 to 8 membered ring having from 1 to 3 heteroatoms as ring vertices selected from N, O, and S;

wherein each R^{5a} and R^{5b} is independently selected from the group consisting of hydrogen, C_{1-8} alkyl, and C_{1-8} haloalkyl, or when R^{5a} and R^{5b} are attached to the same nitrogen atom they are combined with the nitrogen atom to form a 5 or 6-

membered ring having from 0 to 1 additional heteroatoms as ring vertices selected from N, O, or S; and
the subscript n is 0, 1, 2 or 3.

[0024] In addition to the compounds provided herein, the present invention further provides pharmaceutical compositions containing one or more of these compounds, as well as methods for the use of these compounds in therapeutic methods, primarily to treat diseases associated C5a signaling activity.

[0025] In yet another aspect, the present invention provides methods of diagnosing disease in an individual. In these methods, the compounds provided herein are administered in labeled form to a subject, followed by diagnostic imaging to determine the presence or absence of C5aR and/or the localization of cells expressing a C5aR receptor. In a related aspect, a method of diagnosing disease is carried out by contacting a tissue or blood sample with a labeled compound as provided herein and determining the presence, absence, amount, or localization of C5aR in the sample.

BRIEF DESCRIPTION OF THE DRAWINGS

[0026] Not Applicable.

DETAILED DESCRIPTION OF THE INVENTION

I. Abbreviation and Definitions

[0027] The term "alkyl", by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain hydrocarbon radical, having the number of carbon atoms designated (*i.e.* C₁₋₈ means one to eight carbons). Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. The term "alkenyl" refers to an unsaturated alkyl group having one or more double bonds. Similarly, the term "alkynyl" refers to an unsaturated alkyl group having one or more triple bonds. Examples of such unsaturated alkyl groups include vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), isobutenyl, 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butylnyl, and the higher homologs and isomers.

The term "cycloalkyl" refers to hydrocarbon rings having the indicated number of ring atoms (*e.g.*, C₃₋₆cycloalkyl) and being fully saturated or having no more than one double bond between ring vertices. "Cycloalkyl" is also meant to refer to bicyclic and polycyclic hydrocarbon rings such as, for example, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, etc. The term "heterocycloalkyl" refers to a cycloalkyl group that contain from one to five heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. The heterocycloalkyl may be a monocyclic, a bicyclic or a polycyclic ring system. Non limiting examples of heterocycloalkyl groups include pyrrolidine, imidazolidine, pyrazolidine, butyrolactam, valerolactam, imidazolidinone, hydantoin, dioxolane, phthalimide, piperidine, 1,4-dioxane, morpholine, thiomorpholine, thiomorpholine-S-oxide, thiomorpholine-S,S-oxide, piperazine, pyran, pyridone, 3-pyrroline, thiopyran, pyrone, tetrahydrofuran, tetrahydrothiophene, quinuclidine, and the like. A heterocycloalkyl group can be attached to the remainder of the molecule through a ring carbon or a heteroatom.

[0028] The term "alkylene" by itself or as part of another substituent means a divalent radical derived from an alkane, as exemplified by -CH₂CH₂CH₂CH₂-. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the present invention. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having four or fewer carbon atoms. Similarly, "alkenylene" and "alkynylene" refer to the unsaturated forms of "alkylene" having double or triple bonds, respectively.

[0029] The term heteroalkyl, by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, consisting of the stated number of carbon atoms and from one to three heteroatoms selected from the group consisting of O, N, Si and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S may be placed at any interior position of the heteroalkyl group. The heteroatom Si may be placed at any position of the heteroalkyl group, including the position at which the alkyl group is attached to the remainder of the

molecule. Examples include $-\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_3)-\text{CH}_3$, $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{S}(\text{O})-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{S}(\text{O})_2-\text{CH}_3$, $-\text{CH}=\text{CH}-\text{O}-\text{CH}_3$, $-\text{Si}(\text{CH}_3)_3$, $-\text{CH}_2-\text{CH}=\text{N}-\text{OCH}_3$, and $-\text{CH}=\text{CH}-\text{N}(\text{CH}_3)-\text{CH}_3$. Up to two heteroatoms may be consecutive, such as, for example, $-\text{CH}_2-\text{NH}-\text{OCH}_3$ and $-\text{CH}_2-\text{O}-\text{Si}(\text{CH}_3)_3$. Similarly, the

5 terms heteroalkenyl and heteroalkynyl by itself or in combination with another term, means, unless otherwise stated, an alkenyl group or alkynyl group, respectively, that contains the stated number of carbons and having from one to three heteroatoms selected from the group consisting of O, N, Si and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s)

10 O, N and S may be placed at any interior position of the heteroalkyl group.

[0030] The term heteroalkylene by itself or as part of another substituent means a divalent radical, saturated or unsaturated or polyunsaturated, derived from heteroalkyl, as exemplified by $-\text{CH}_2-\text{CH}_2-\text{S}-\text{CH}_2\text{CH}_2-$ and $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-$, $-\text{O}-\text{CH}_2-\text{CH}=\text{CH}-$, $-\text{CH}_2-\text{CH}=\text{C}(\text{H})\text{CH}_2-\text{O}-\text{CH}_2-$ and $-\text{S}-\text{CH}_2-\text{C}\equiv\text{C}-$. For heteroalkylene

15 groups, heteroatoms can also occupy either or both of the chain termini (*e.g.*, alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like).

[0031] The terms "alkoxy," "alkylamino" and "alkylthio" (or thioalkoxy) are used in their conventional sense, and refer to those alkyl groups attached to the remainder of the molecule via an oxygen atom, an amino group, or a sulfur atom, respectively. Additionally, for dialkylamino groups, the alkyl portions can be the same or different and can also be combined to form a 3-7 membered ring with the nitrogen atom to which each is attached. Accordingly, a group represented as $-\text{NR}^a\text{R}^b$ is meant to include piperidinyl, pyrrolidinyl, morpholinyl, azetidiny and the like.

[0032] The term "hydroxyalkyl" is used in its conventional sense, and refers to branched or straight chain alkyl group substituted with at least one hydroxyl group. The hydroxyl group may be at any position in the alkyl group. For example, the term "C₁₋₄hydroxyalkyl" is meant to include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxyisopropyl, and the like.

[0033] The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl," are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "C₁₋₄ haloalkyl" is mean to include trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0034] The term "aryl" means, unless otherwise stated, a polyunsaturated, typically aromatic, hydrocarbon group which can be a single ring or multiple rings (up to three rings) which are fused together or linked covalently. The term "heteroaryl" refers to aryl groups (or rings) that contain from one to five heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a heteroatom. Non-limiting examples of aryl groups include phenyl, naphthyl and biphenyl, while non-limiting examples of heteroaryl groups include pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, triazinyl, quinoliny, quinoxaliny, quinazolinyl, cinnoliny, phthalazinyl, benzotriazinyl, purinyl, benzimidazolyl, benzopyrazolyl, benzooxazolyl, benzotriazolyl, benzisoxazolyl, isobenzofuryl, isoindolyl, indoliziny, benzotriazinyl, thienopyridinyl, thienopyrimidinyl, pyrazolopyrimidinyl, pyrrolopyridyl, imidazopyridines, benzothiazolyl, benzofuranyl, benzothienyl, indolyl, quinolyl, isoquinolyl, isothiazolyl, pyrazolyl, indazolyl, pteridinyl, imidazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiadiazolyl, pyrrolyl, thiazolyl, furyl, thienyl and the like. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below.

[0035] The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of salts derived from pharmaceutically-acceptable inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous,

lithium, magnesium, manganic, manganous, potassium, sodium, zinc and the like. Salts derived from pharmaceutically-acceptable organic bases include salts of primary, secondary and tertiary amines, including substituted amines, cyclic amines, naturally-occurring amines and the like, such as arginine, betaine, caffeine, choline, N,N -dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperadine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge, S.M., et al, *Pharmaceutical Salts* , *Journal of Pharmaceutical Science*, **1977**, 66, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0036] The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

[0037] In addition to salt forms, the present invention provides compounds which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the

present invention. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

[0038] Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

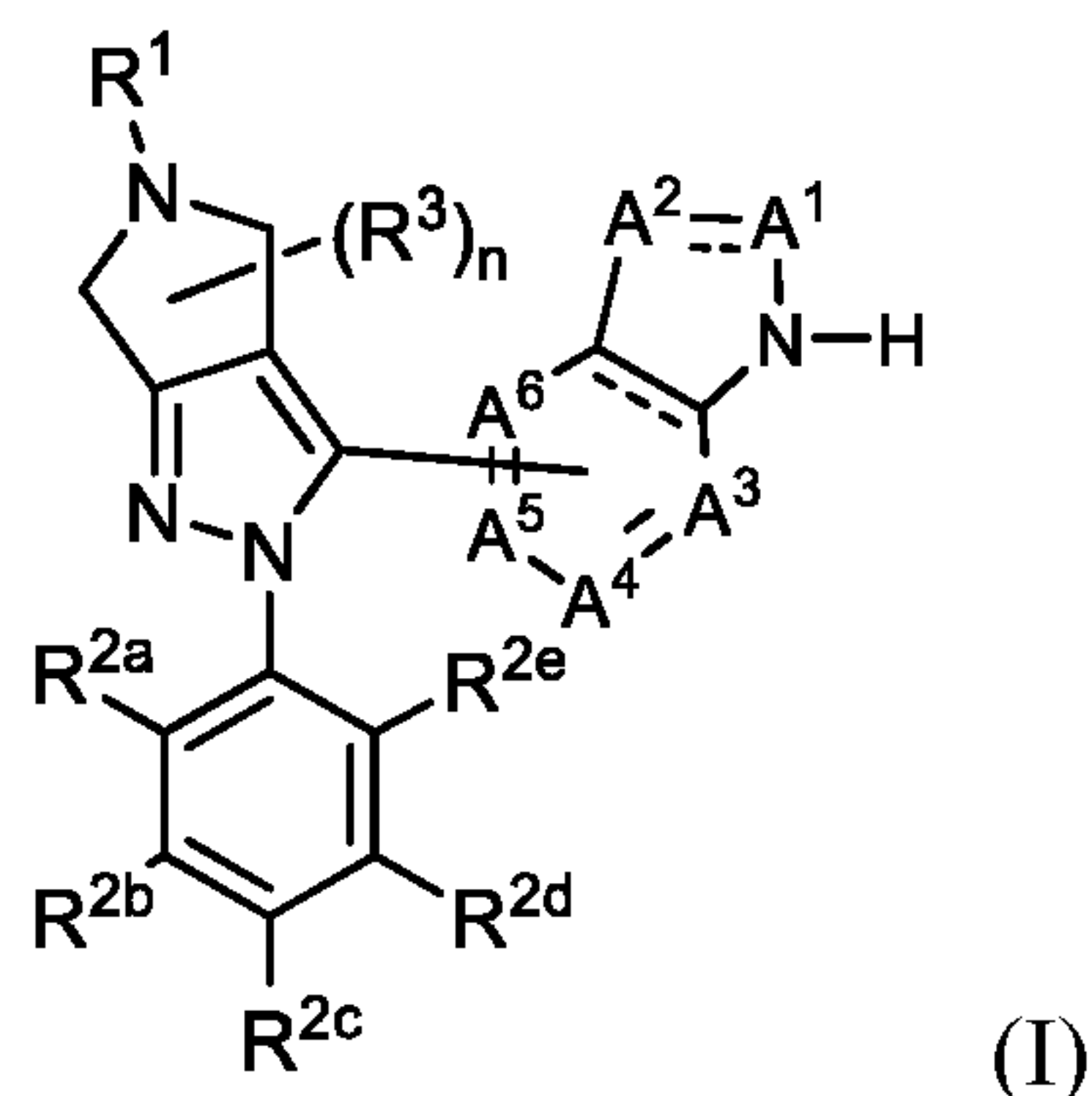
[0039] Certain compounds of the present invention possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers, regioisomers and individual isomers (*e.g.*, separate enantiomers) are all intended to be encompassed within the scope of the present invention. The compounds of the present invention may also contain
5 unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^3H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are intended to be encompassed within the scope of the present invention.

10 [0040] As used herein, a wavy line, " $\sim$ ", that intersects a single, double or triple bond in any chemical structure depicted herein, represent the point attachment of the single, double, or triple bond to the remainder of the molecule.

II. Description of the Embodiments

A. Compounds

[0041] In one aspect, the present invention provides compounds of Formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein,

ring vertex A^1 is selected from the group consisting of N, CH, C(O) and $C(R^4)$;

ring vertex A^2 is selected from the group consisting of N, CH, and $C(R^4)$;

5 each of ring vertices A^3 , A^4 , A^5 and A^6 is independently selected from the group consisting of CH and $C(R^4)$;

each of the dashed bonds independently indicate a single or double bond;

R^1 is selected from the group consisting of $-C_{1-8}$ alkylene heteroaryl, $-C_{1-8}$ alkylene- C_{6-10}

aryl, C_{1-8} alkyl, C_{1-8} haloalkyl, $-C(O)-C_{1-8}$ alkyl, $-C(O)-C_{6-10}$ aryl,

10 $-C(O)$ -heteroaryl, $-C(O)-C_{3-6}$ cycloalkyl, $-C(O)$ -heterocycloalkyl, $-C(O)NR^{1a}R^{1b}$,

$-SO_2-C_{6-10}$ aryl, $-SO_2$ -heteroaryl, $-C(O)-C_{1-8}$ alkylene-O-heteroaryl, $-C(O)-C_{1-8}$

alkylene-O- C_{6-10} aryl, $-C(O)-C_{1-8}$ alkylene-O- heterocycloalkyl, $-C(O)-C_{1-8}$

alkylene-O- C_{3-6} cycloalkyl, $-C(O)$ C_{1-8} alkylene heteroaryl,

$-C(O)$ C_{1-8} alkylene C_{6-10} aryl, $-C(O)$ C_{1-8} alkylene heterocycloalkyl,

15 $-C(O)$ C_{1-8} alkylene C_{3-6} cycloalkyl and CO_2R^{1a} ; the heterocycloalkyl is a 4 to 8

membered ring having from 1 to 3 heteroatoms as ring vertices selected from N, O

and S; and the heteroaryl group is a 5 to 10 membered aromatic ring having from

1 to 3 heteroatoms as ring vertices selected from N, O and S;

wherein R^{1a} and R^{1b} are each independently selected from the group consisting of

20 hydrogen, C_{1-8} alkyl, and C_{1-8} haloalkyl;

wherein R^1 is optionally substituted with 1 to 5 R^5 substituents;

R^{2a} and R^{2e} are each independently selected from the group consisting of C_{1-6} alkyl, C_{1-6}

alkoxy, C_{1-6} haloalkyl, $-O-C_{1-6}$ haloalkyl, $-S-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl-O- C_{1-6} alkyl, $-C_{1-6}$

alkyl-S- C_{1-6} alkyl, CN, and halogen;

R^{2b} , R^{2c} , and R^{2d} are each independently selected from the group consisting of hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, -O-C₁₋₆ haloalkyl, -S-C₁₋₆ alkyl, -C₁₋₆ alkyl-O-C₁₋₆ alkyl, -C₁₋₆ alkyl-S-C₁₋₆ alkyl, cyano, and halogen;

each R^3 is independently selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, halogen and hydroxyl, and optionally two R^3 groups on the same carbon atom are combined to form oxo (=O) or to form a three to five membered cycloalkyl ring;

each R^4 is independently selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ hydroxyalkyl, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, -O-C₁₋₆ haloalkyl, halogen, cyano, hydroxyl, -S-C₁₋₆ alkyl, -C₁₋₆ alkyl-O-C₁₋₆ alkyl, -C₁₋₆ alkyl-S-C₁₋₆ alkyl, -NR^{4a}R^{4b}, -CONR^{4a}R^{4b}, -CO₂R^{4a}, -COR^{4a}, -OC(O)NR^{4a}R^{4b}, -NR^{4a}C(O)R^{4b}, -NR^{4a}C(O)₂R^{4b}, and NR^{4a}-C(O)NR^{4a}R^{4b};

each R^{4a} and R^{4b} is independently selected from the group consisting of hydrogen, C₁₋₄ alkyl, and C₁₋₄ haloalkyl;

each R^5 is independently selected from the group consisting of C₁₋₈ alkyl, C₁₋₈ alkoxy, C₁₋₈ haloalkyl, C₁₋₈ haloalkoxy, C₁₋₈ hydroxyalkyl, -C₁₋₈ alkylene-heterocycloalkyl, -C₁₋₈ alkylene-C₃₋₆ cycloalkyl, C₃₋₆ cycloalkyl, heterocycloalkyl, halogen, OH, C₂₋₈ alkenyl, C₂₋₈ alkynyl, CN, C(O)R^{5a}, -NR^{5b}C(O)R^{5a}, -CONR^{5a}R^{5b}, -NR^{5a}R^{5b}, -C₁₋₈ alkylene NR^{5a}R^{5b}, -S-C₁₋₆ alkyl, -C₁₋₆ alkylene-O-C₁₋₆ alkyl, -C₁₋₆ alkylene-S-C₁₋₆ alkyl, -OC(O)NR^{5a}R^{5b}, -NR^{5a}C(O)₂R^{5b}, -NR^{5a}-C(O)NR^{5b}R^{5b}, and CO₂R^{5a};

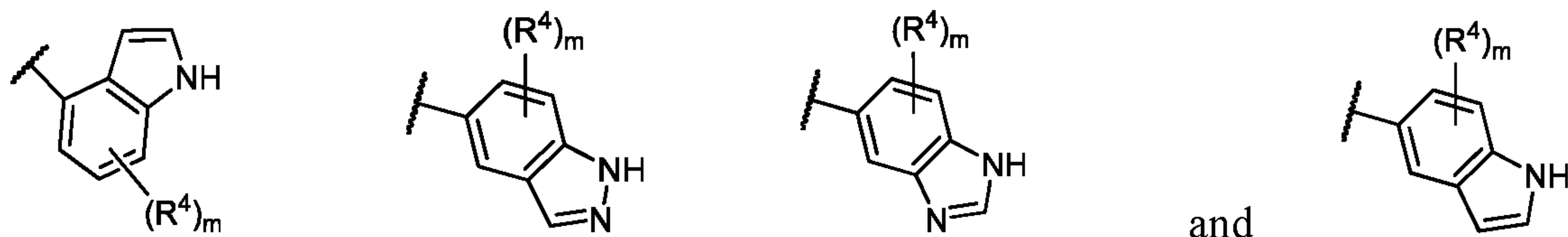
wherein the heterocycloalkyl group is a 4 to 8 membered ring having from 1 to 3 heteroatoms as ring vertices selected from N, O, and S;

wherein each R^{5a} and R^{5b} is independently selected from the group consisting of hydrogen, C₁₋₈ alkyl, and C₁₋₈ haloalkyl, or when R^{5a} and R^{5b} are attached to the same nitrogen atom they are combined with the nitrogen atom to form a 5 or 6-membered ring having from 0 to 1 additional heteroatoms as ring vertices selected from N, O, or S; and

the subscript n is 0, 1, 2 or 3.

[0042] Focusing on the ring portion having A¹, A², A³, A⁴, A⁵, and A⁶ as ring vertices, in some embodiments, the ring portion having A¹, A², A³, A⁴, A⁵, and A⁶ as ring vertices is a bicyclic

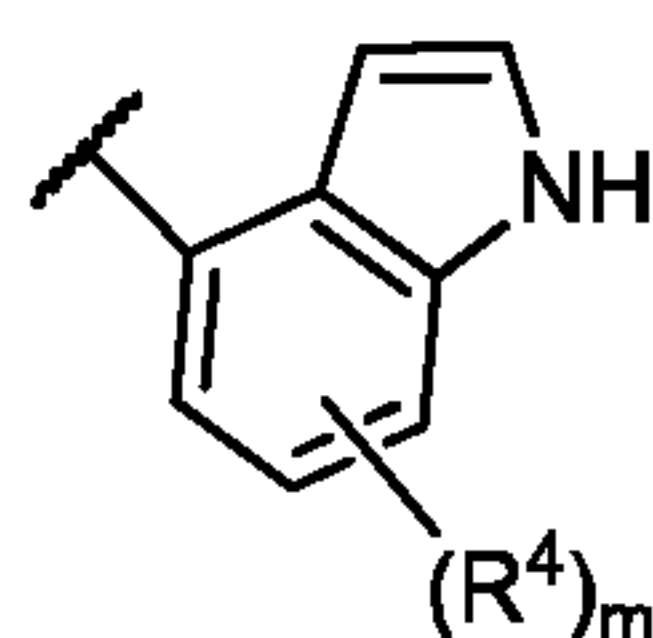
heteroaryl selected from



and

wherein m is 0, 1, 2 or 3; and wherein the R^4 substituents may be attached to any suitable carbon ring vertex of the bicyclic heteroaryl.

[0043] In some embodiments, the ring portion having A^1 , A^2 , A^3 , A^4 , A^5 , and A^6 as ring vertices is



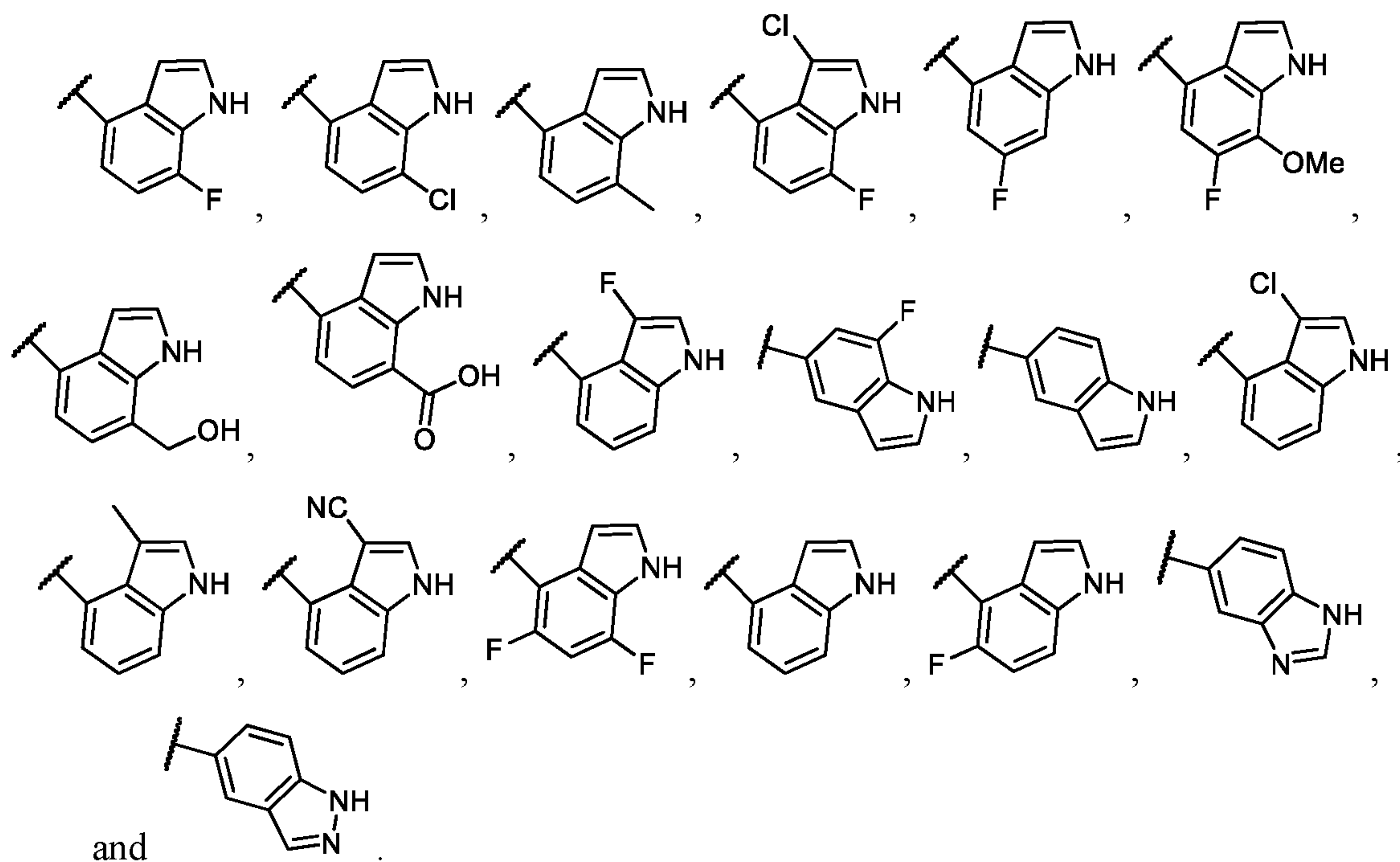
wherein m is 0, 1, 2, or 3; wherein the R^4 substituents may be attached to any suitable carbon ring vertex of the bicyclic heteroaryl.

[0044] In some embodiments, each R^4 is independently C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-6}

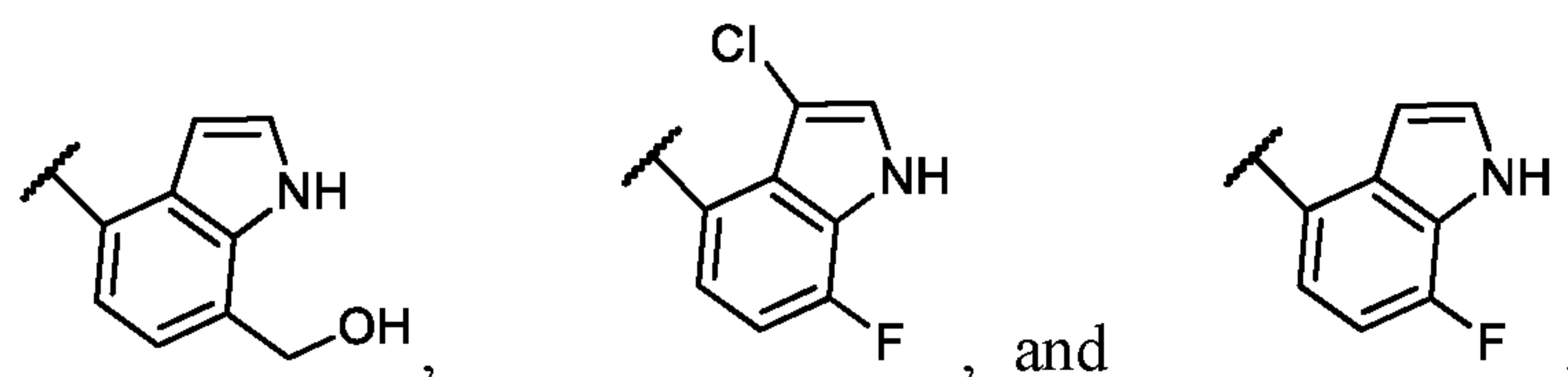
hydroxyalkyl, halogen, cyano, and $-CO_2R^{4a}$, wherein R^{4a} is as defined above, and wherein the R^4 substituents may be attached to any suitable carbon ring vertex of the bicyclic heteroaryl

[0045] A person of skill in the art will recognize that particular carbon atoms of the ring portion having A^1 , A^2 , A^3 , A^4 , A^5 , and A^6 cannot be substituted with R^4 . For example, the carbon atom linking the bicyclic heteroaryl moiety (i.e. the ring portion having A^1 , A^2 , A^3 , A^4 , A^5 , and A^6) to the remainder of the molecule and the carbon atoms that are members of both ring systems in the fused bicyclic heteroaryl moiety (i.e. the two carbon atoms that are ring vertices in both the benzene and five-membered ring system) cannot be substituted with R^4 because an additional substituent will exceed the valence of these carbon atoms.

[0046] In some embodiments, the ring portion having A^1 , A^2 , A^3 , A^4 , A^5 , and A^6 as ring vertices is selected from the group consisting of:



- 5 [0047] In some embodiments, the ring portion having A¹, A², A³, A⁴, A⁵, and A⁶ as ring vertices is selected from the group consisting of:



- [0048] Turning to R¹ and optional substituent(s), R⁵, in some embodiments, R¹ is -C₁₋₈ alkylene heteroaryl, -C₁₋₈alkylene C₆₋₁₀ aryl, C₁₋₈ alkyl, C₁₋₈ haloalkyl, -C(O)-C₁₋₈ alkyl, -C(O)-
 10 C₆₋₁₀ aryl, -C(O)-heteroaryl, -C(O)-C₃₋₈ cycloalkyl, C(O)NR^{1a}R^{1b}, -SO₂-C₆₋₁₀ aryl, -C(O)-C₁₋₈ alkylene-O-C₆₋₁₀ aryl, or CO₂R^{1a}; wherein R^{1a} and R^{1b}, heterocycloalkyl, and the heteroaryl are as defined above, and wherein R¹ is optionally substituted with 1 to 5 R⁵ substituents.

- [0049] In some embodiments, heterocycloalkyl groups of R¹ or R⁵ are from 4 to 6 membered rings having from 1 to 3 heteroatoms as ring vertices selected from N, O, and S. In some
 15 embodiments, the heteroaryl groups of R¹ or R⁵ are 5 to 6 membered aromatic rings having from 1 to 3 heteroatoms as ring vertices selected from N, O, and S. In some embodiments, the C₆₋₁₀ aryl group of R¹ is phenyl.

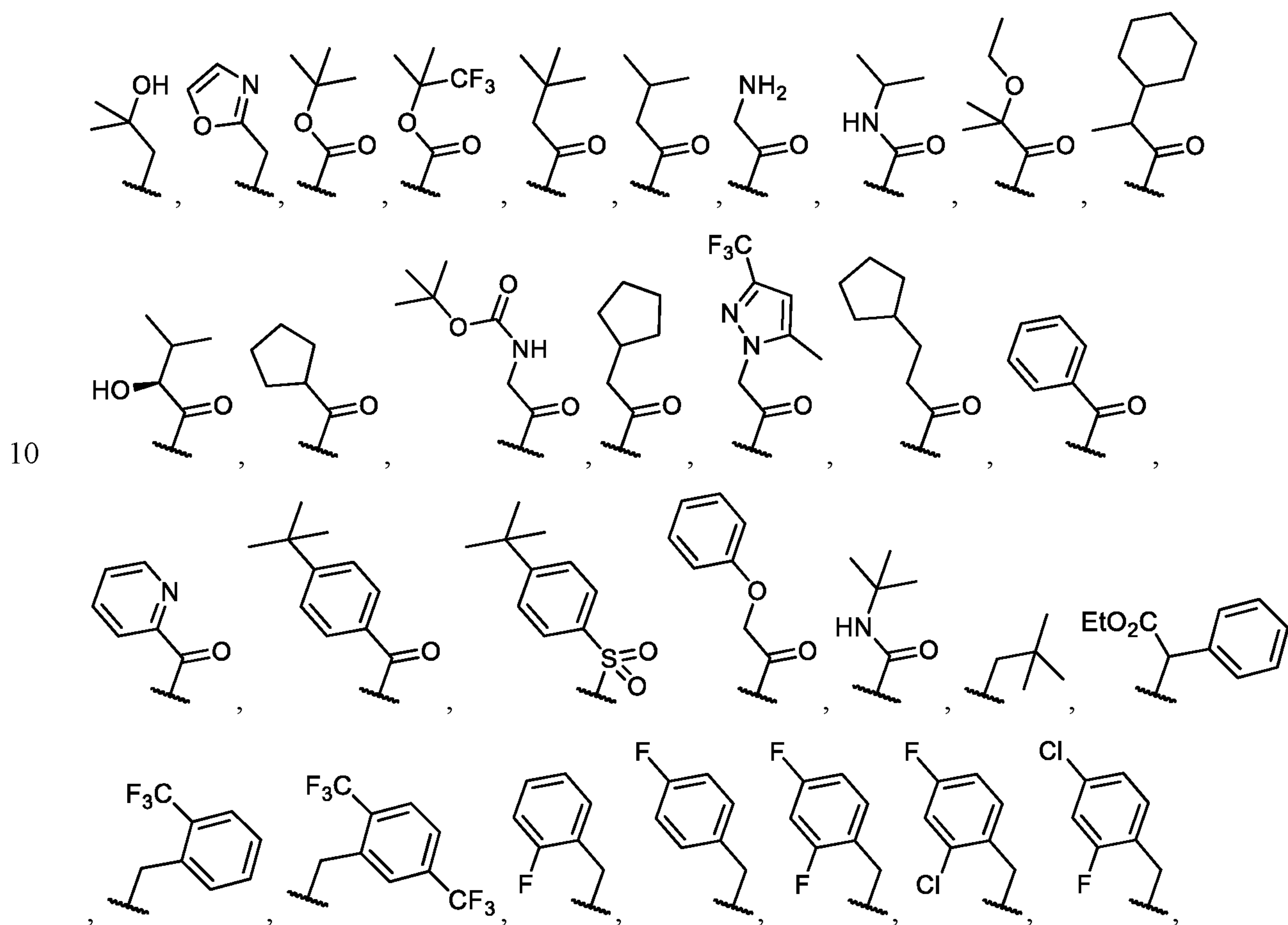
- [0050] In some embodiments, R¹ is -CH₂-phenyl optionally substituted by 1 to 3 R⁵.

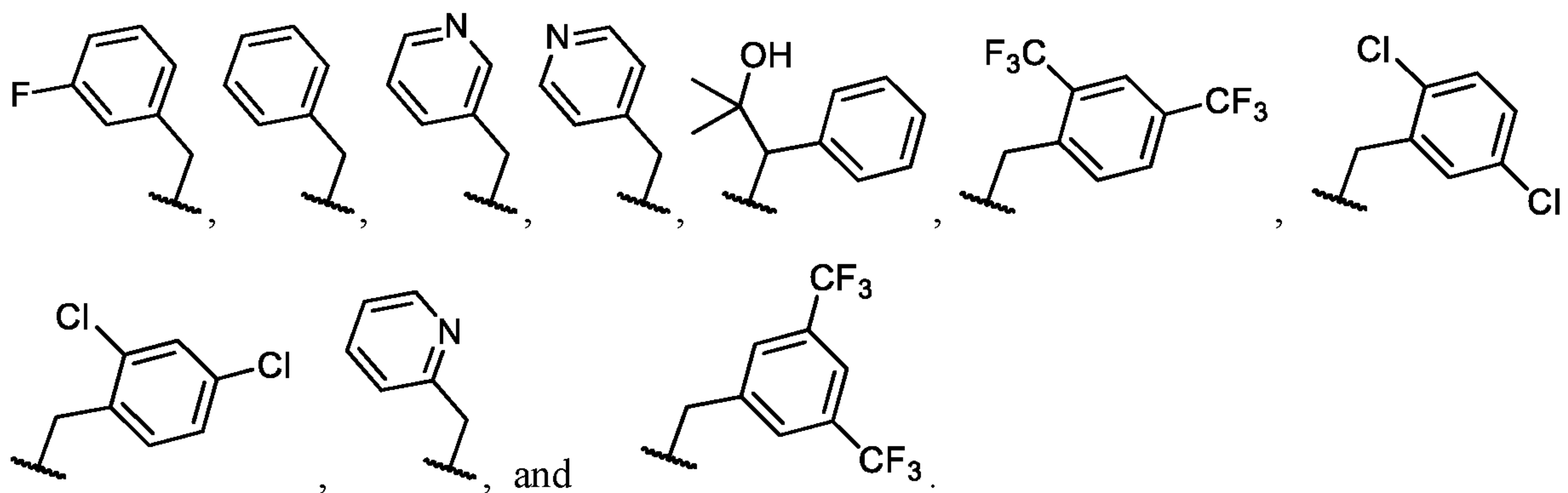
[0051] In some embodiments, each R⁵ is independently of C₁₋₈ alkyl, C₁₋₈ alkoxy, C₁₋₈ haloalkyl, C₁₋₈ haloalkoxy, C₁₋₈ hydroxyalkyl, C₃₋₆ cycloalkyl, halogen, OH, -NR^{5a}R^{5b}, or CO₂R^{5a}, wherein each R^{5a} and R^{5b} is independently selected from the group consisting of hydrogen, C₁₋₈ alkyl, and C₁₋₈ haloalkyl.

5 **[0052]** In some embodiments, R¹ is -CH₂-phenyl substituted by 1 or 2 R⁵, wherein each R⁵ is independently C₁₋₄ haloalkyl.

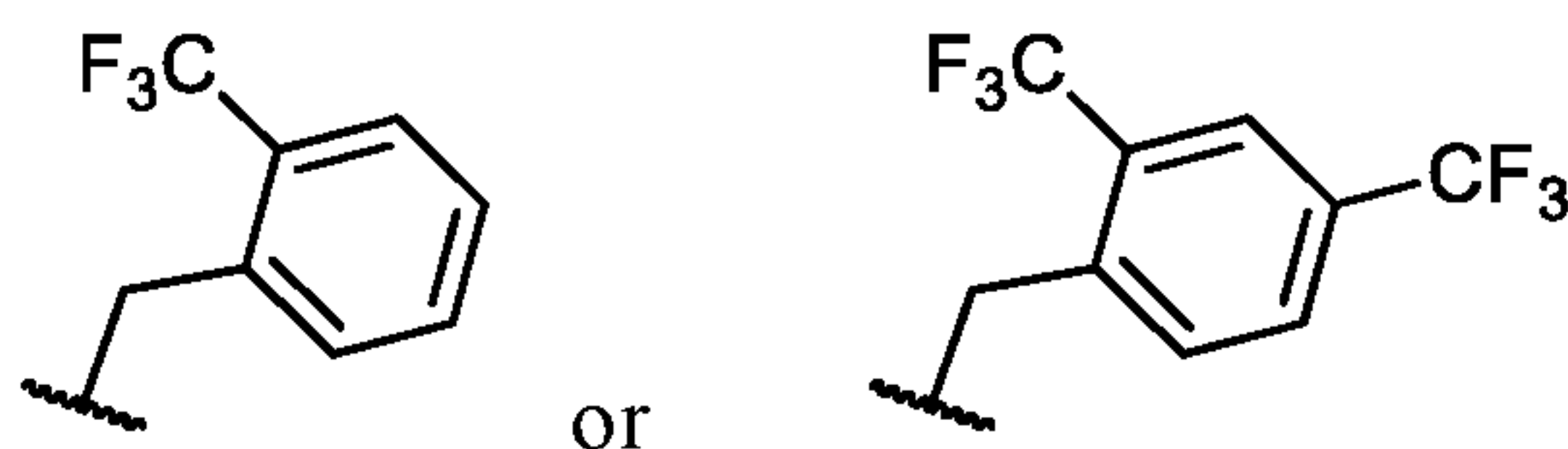
[0053] In some embodiments, R¹ is -CH₂-phenyl substituted by 1 or 2 CF₃.

[0054] In some embodiments, R^1 is selected from the group consisting of





[0055] In some embodiments R^1 is



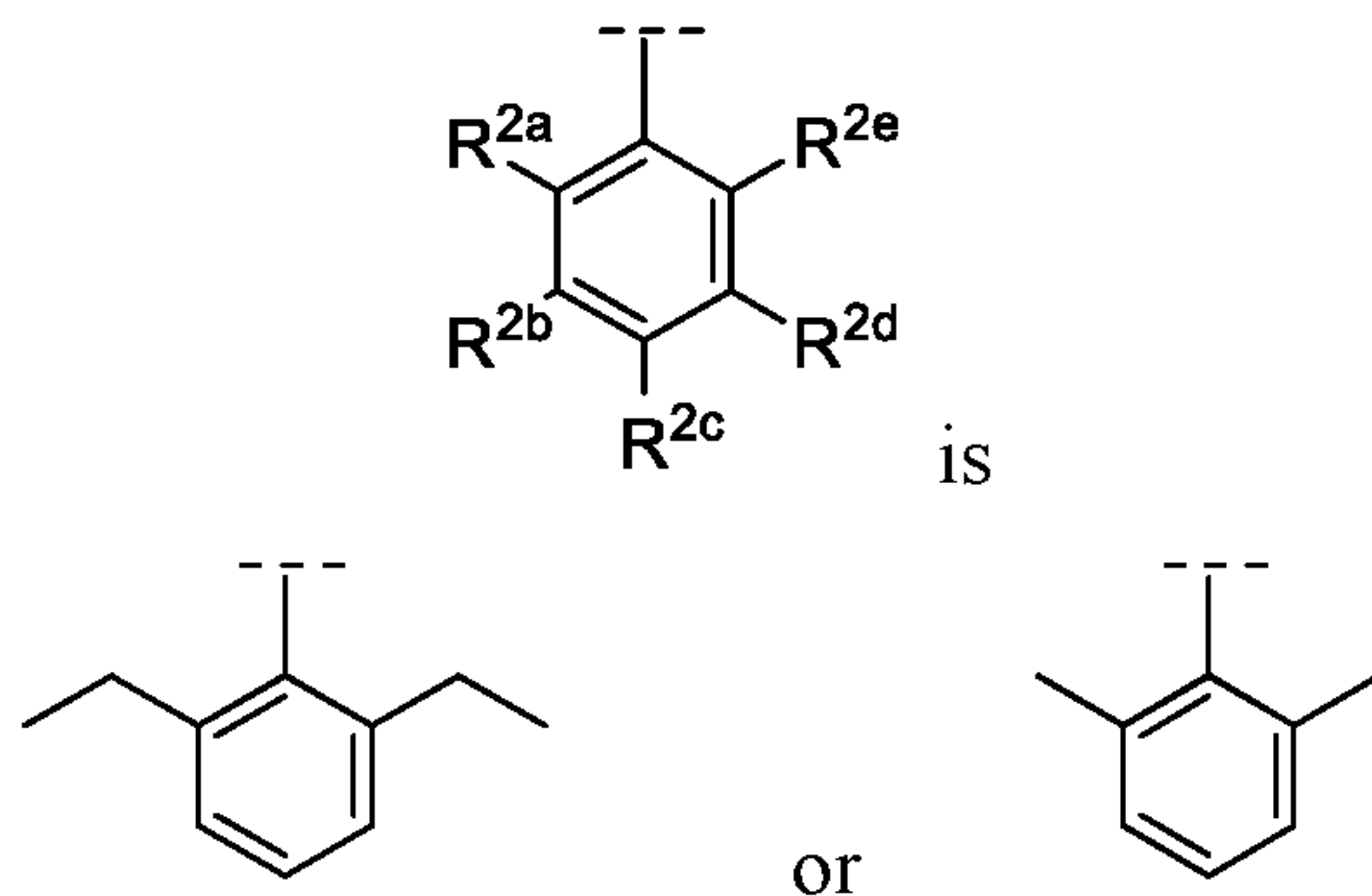
- 5 [0056] Returning to Formula I and substituents R^{2a} , R^{2b} , R^{2c} , R^{2d} , and R^{2e} , in some embodiments, R^{2a} and R^{2e} are each independently C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, $-O-C_{1-6}$ haloalkyl, or halogen. In some embodiments, R^{2b} , R^{2c} , and R^{2d} are independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, or halogen.

[0057] In some embodiments, R^{2b} , R^{2c} , and R^{2d} are each H.

- 10 [0058] In some embodiments, R^{2a} and R^{2e} are each independently C_{1-6} alkyl or C_{1-6} haloalkyl.

[0059] In some embodiments, R^{2a} and R^{2e} are each independently methyl or ethyl. In some embodiments, R^{2a} and R^{2e} are both methyl or are both ethyl.

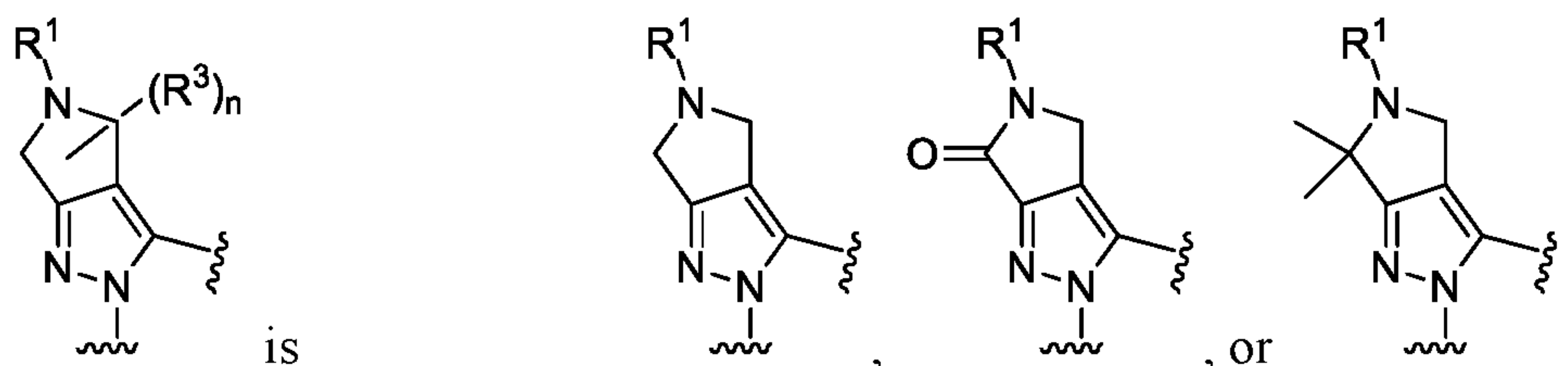
[0060] In some embodiments, the portion of Formula I represented by



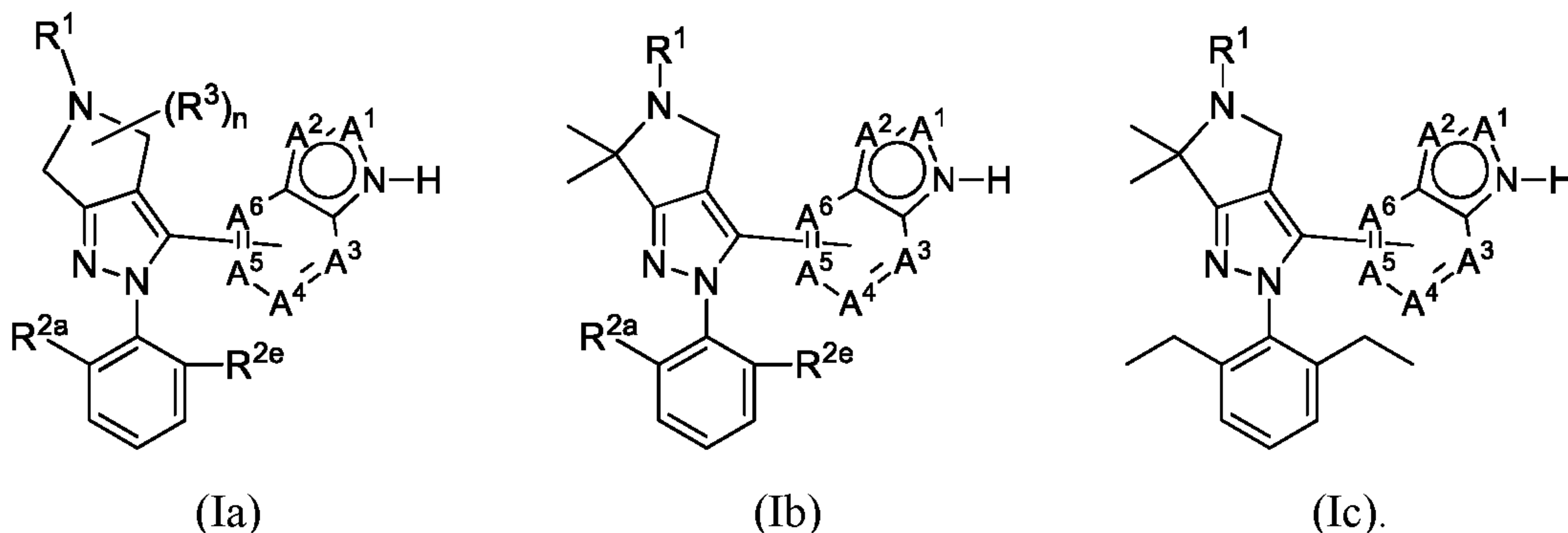
[0061] Each R^3 of Formula I, in some embodiments, is independently C_{1-6} alkyl, C_{1-6} haloalkyl, or halogen. In some embodiments, each R^3 is independently C_{1-4} alkyl.

[0062] In some embodiments, n , the subscript of R^3 , is 0, 1, or 2. In some embodiments, n is 0. In some embodiments, n is 2.

5 [0063] In some embodiments, the portion of Formula I represented by



[0064] In some embodiments, the compound of Formula I is represented by Formula (Ia), (Ib), or (Ic).

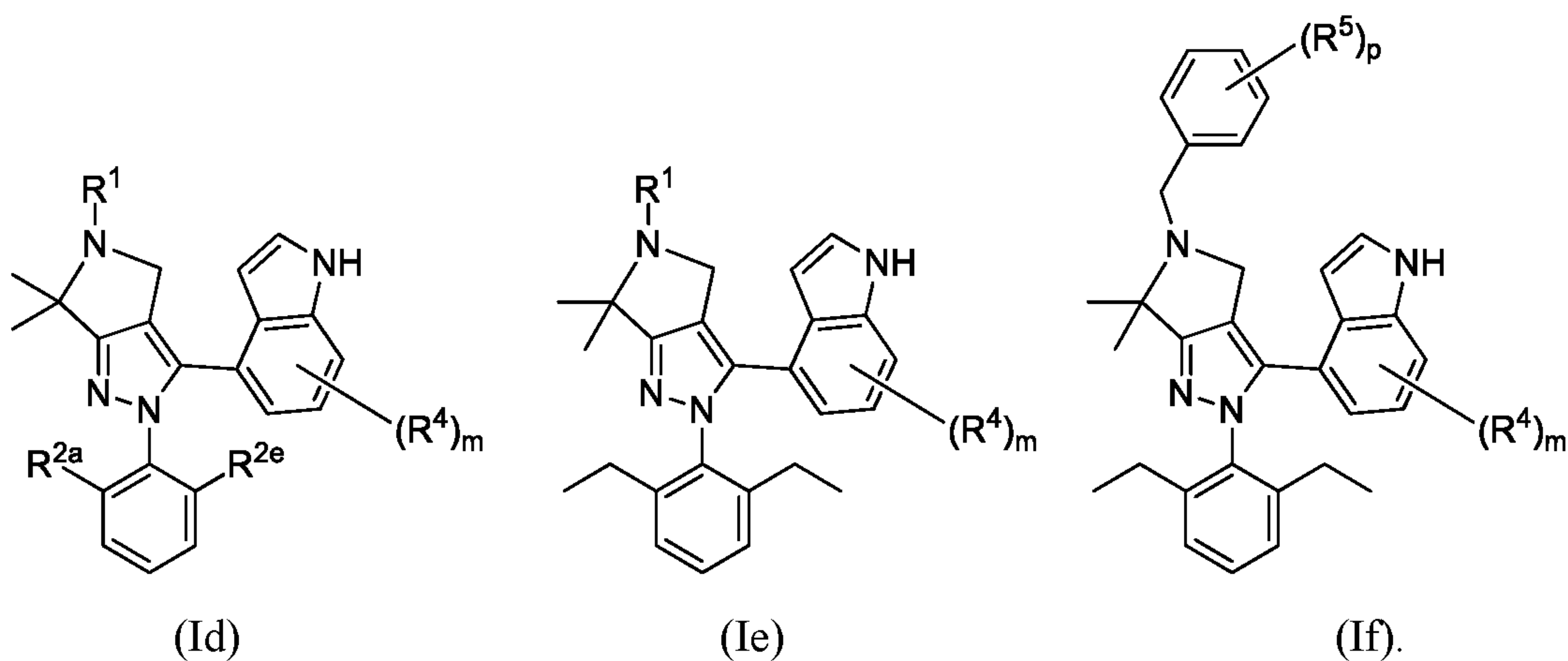


[0065] In embodiments where the compound of Formula (I) is represented by Formula (Ia), R^1 , R^3 , n , R^{2a} , R^{2e} , and the ring portion having A^1 , A^2 , A^3 , A^4 , A^5 , and A^6 as ring vertices are as defined above for Formula (I).

15 [0066] In embodiments where the compound of Formula (I) is represented by Formula (Ib), R^1 , R^{2a} , R^{2e} , and the ring portion having A^1 , A^2 , A^3 , A^4 , A^5 , and A^6 as ring vertices are as defined above for Formula (I).

[0067] In embodiments where the compound of Formula (I) is represented by Formula (Ic), R^1 and the ring portion having A^1 , A^2 , A^3 , A^4 , A^5 , and A^6 as ring vertices are as defined above for Formula (I).

[0068] In some embodiments, the compound of Formula (I) is represented by Formula (Id), (Ie), or (If)

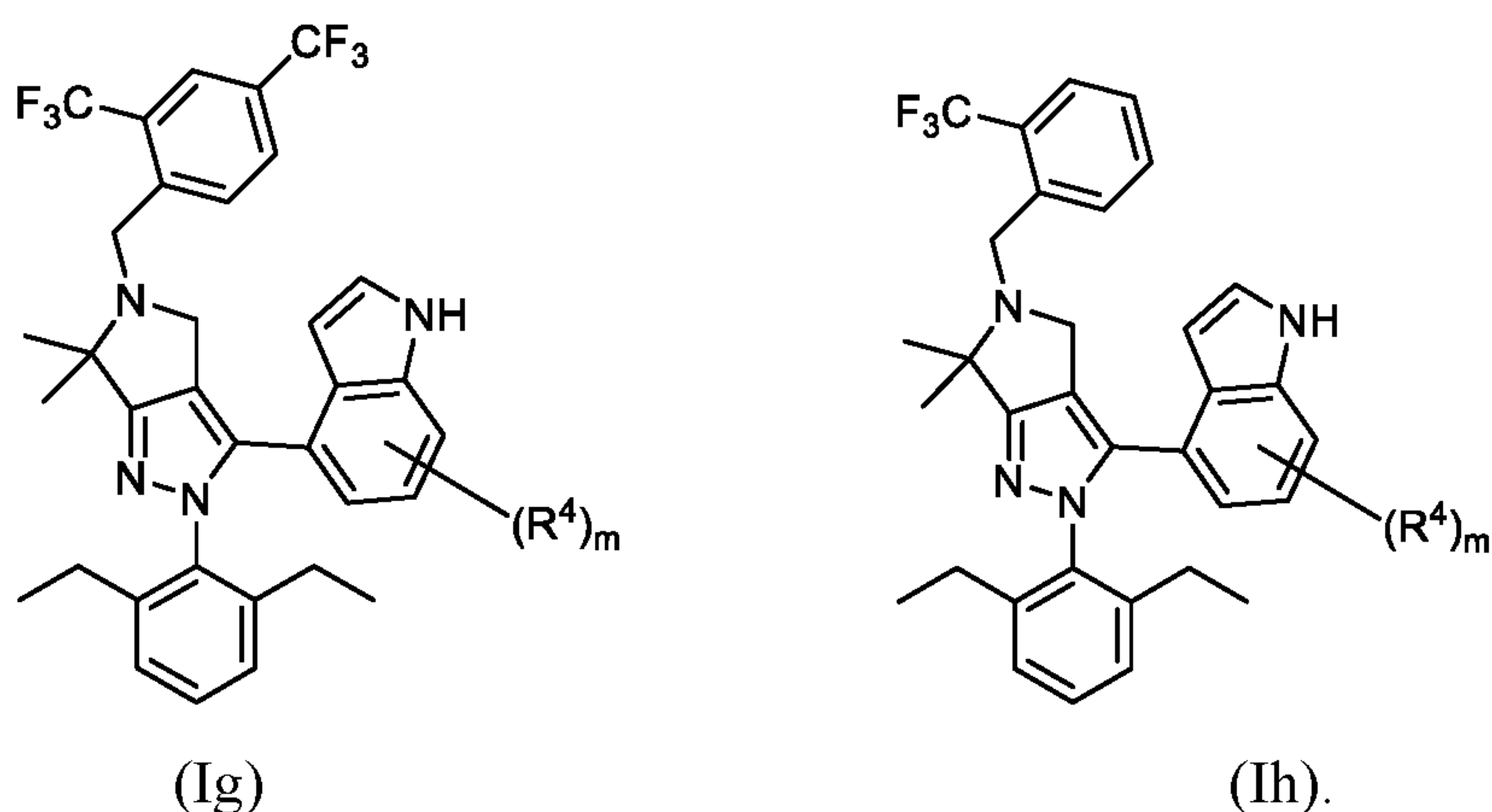


5 [0069] In embodiments where the compound of Formula (I) is represented by Formula (Id), R^1 , R^4 , m , R^{2a} , and R^{2e} are as defined above for Formula (I).

[0070] In embodiments where the compound of Formula (I) is represented by Formula (Ie), R^1 , R^4 , and m are as defined above for Formula (I).

10 [0071] In embodiments where the compound of Formula (I) is represented by Formula (If), R^5 , R^4 , and m are as defined above for Formula (I), and p is 0, 1, or 2.

[0072] In some embodiments, the compound of Formula (I) is represented by Formula (Ig) or (Ih)



15 [0073] In embodiments where the compound of Formula (I) is represented by Formula (Ig) or (Ih), R^4 and m are as defined above for Formula (I).

[0074] In some embodiments, the compound of Formula (I) is a compound described in the Examples section.

Preparation of Compounds

[0075] Certain compounds of the invention can be prepared following methodology as described in the Examples section of this document. In addition, the syntheses of certain intermediate compounds that are useful in the preparation of compounds of the invention are also described.

B. Pharmaceutical Compositions

[0076] In addition to the compounds provided above, compositions for modulating C5a activity in humans and animals will typically contain a pharmaceutical carrier or diluent.

10 [0077] The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

15 [0078] The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy and drug delivery. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases.

25 [0079] The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions and self emulsifications as described in U.S. Patent Application 2002-0012680, hard or soft capsules, syrups, elixirs, solutions, buccal patch, oral

gel, chewing gum, chewable tablets, effervescent powder and effervescent tablets. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents, antioxidants and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as cellulose, silicon dioxide, aluminum oxide, calcium carbonate, sodium carbonate, glucose, mannitol, sorbitol, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example PVP, cellulose, PEG, starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated, enterically or otherwise, by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the U.S. Pat. Nos. 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

[0080] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil. Additionally, emulsions can be prepared with a non-water miscible ingredient such as oils and stabilized with surfactants such as mono-diglycerides, PEG esters and the like.

[0081] Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxy-ethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylenoxycetanol,

or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more
5 flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

[0082] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard
10 paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[0083] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting
15 agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[0084] The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a
20 mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The
25 emulsions may also contain sweetening and flavoring agents.

[0085] Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. Oral solutions can be prepared in combination with, for example, cyclodextrin, PEG and surfactants.

[0086] The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension
5 in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are 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. In addition, fatty acids such as oleic acid
10 find use in the preparation of injectables.

[0087] The compounds of the present invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug.
15 Such materials include cocoa butter and polyethylene glycols. Additionally, the compounds can be administered via ocular delivery by means of solutions or ointments. Still further, transdermal delivery of the subject compounds can be accomplished by means of iontophoretic patches and the like. For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of the present invention are employed. As used herein, topical application is also
20 meant to include the use of mouth washes and gargles.

[0088] The compounds of this invention may also be coupled a carrier that is a suitable polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxyethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the
25 compounds of the invention may be coupled to a carrier that is a class of biodegradable polymers useful in achieving controlled release of a drug, for example polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels. Polymers and semipermeable polymer matrices
30 may be formed into shaped articles, such as valves, stents, tubing, prostheses and the like. In one

embodiment of the invention, the compound of the invention is coupled to a polymer or semipermeable polymer matrix that is formed as a stent or stent-graft device.

[0089] The pharmaceutical compositions of the present disclosure may be formulated with one or more additional therapeutic agents. The one or more additional therapeutic agents can include
5 corticosteroids, steroids, immunosuppressants, or CD 20 inhibitors. In some embodiments, the one or more additional therapeutic agents include obinutuzumab, rituximab, ocrelizumab, cyclophosphamide, prednisone, hydrocortisone, hydrocortisone acetate, cortisone acetate, tixocortol pivalate, prednisolone, methylprednisolone, triamcinolone acetonide, triamcinolone alcohol, mometasone, amcinonide, budesonide, desonide, fluocinonide, fluocinolone acetonide,
10 halcinonide, betamethasone, betamethasone sodium phosphate, dexamethasone, dexamethasone sodium phosphate, fluocortolone, hydrocortisone-17-valerate, halometasone, alclometasone dipropionate, beclomethasone, betamethasone valerate, betamethasone dipropionate, prednicarbate, clobetasone-17-butyrate, clobetasol-17-propionate, fluocortolone caproate, fluocortolone pivalate, fluprednidene acetate, hydrocortisone-17-butyrate, hydrocortisone-17-
15 aceponate, hydrocortisone-17-buteprate, ciclesonide and prednicarbate. Further discussions of combination therapy are included in the Methods of Use section of this application.

C. Methods of Use

[0090] The compounds of the invention may be used as agonists, (preferably) antagonists, partial agonists, inverse agonists, of C5a receptors in a variety of contexts, both *in vitro* and *in*
20 *vivo*. In one embodiment, the compounds of the invention are C5aR antagonist that can be used to inhibit the binding of C5a receptor ligand (*e.g.*, C5a) to C5a receptor *in vitro* or *in vivo*. In general, such methods comprise the step of contacting a C5a receptor with a sufficient amount of one or more C5a receptor modulators as provided herein, in the presence of C5a receptor ligand in aqueous solution and under conditions otherwise suitable for binding of the ligand to C5a
25 receptor. The C5a receptor may be present in suspension (*e.g.*, in an isolated membrane or cell preparation), in a cultured or isolated cell, or in a tissue or organ.

[0091] Preferably, the amount of C5a receptor modulator contacted with the receptor should be sufficient to inhibit C5a binding to C5a receptor *in vitro* as measured, for example, using a radioligand binding assay, calcium mobilization assay, or chemotaxis assay as described herein.

[0092] In one embodiment of the invention, the C5a modulators of the invention are used to modulate, preferably inhibit, the signal-transducing activity of a C5a receptor, for example, by contacting one or more compound(s) of the invention with a C5a receptor (either *in vitro* or *in vivo*) under conditions suitable for binding of the modulator(s) to the receptor. The receptor may be present in solution or suspension, in a cultured or isolated cell preparation or within a patient. Any modulation of the signal transducing activity may be assessed by detecting an effect on calcium ion calcium mobilization or by detecting an effect on C5a receptor-mediated cellular chemotaxis. In general, an effective amount of C5a modulator(s) is an amount sufficient to modulate C5a receptor signal transducing activity *in vitro* within a calcium mobilization assay or C5a receptor-mediated cellular chemotaxis within a migration assay.

[0093] When compounds of the invention are used to inhibit C5a receptor-mediated cellular chemotaxis, preferably leukocyte (*e.g.*, neutrophil) chemotaxis, in an *in vitro* chemotaxis assay, such methods comprise contacting white blood cells (particularly primate white blood cells, especially human white blood cells) with one or more compounds of the invention. Preferably the concentration is sufficient to inhibit chemotaxis of white blood cells in an *in vitro* chemotaxis assay, so that the levels of chemotaxis observed in a control assay are significantly higher, as described above, than the levels observed in an assay to which a compound of the invention has been added.

[0094] In another embodiment, the compounds of the present invention further can be used for treating patients suffering from conditions that are responsive to C5a receptor modulation. As used herein, the term "treating" or "treatment" encompasses both disease-modifying treatment and symptomatic treatment, either of which may be prophylactic (*i.e.*, before the onset of symptoms, in order to prevent, delay or reduce the severity of symptoms) or therapeutic (*i.e.*, after the onset of symptoms, in order to reduce the severity and/or duration of symptoms). As used herein, a condition is considered "responsive to C5a receptor modulation" if modulation of C5a receptor activity results in the reduction of inappropriate activity of a C5a receptor. As used herein, the term "patients" include primates (especially humans), domesticated companion animals (such as dogs, cats, horses, and the like) and livestock (such as cattle, pigs, sheep, and the like), with dosages as described herein.

Conditions that can be treated by C5a modulation:

[0095] Autoimmune disorders-- *e.g.*, Rheumatoid arthritis, systemic lupus erythematosus, Guillain-Barre syndrome, pancreatitis, lupus nephritis, lupus glomerulonephritis, psoriasis, Crohn's disease, vasculitis, irritable bowel syndrome, dermatomyositis, multiple sclerosis, bronchial asthma, dense deposit disease, pemphigus, pemphigoid, scleroderma, myasthenia
 5 gravis, autoimmune hemolytic and thrombocytopenic states, Goodpasture's syndrome (and associated glomerulonephritis and pulmonary hemorrhage), C3-glomerulopathy, C3-glomerulonephritis, membranoproliferative glomerulonephritis, Kawasaki disease, IGs nephropathy, immunovascularitis, tissue graft rejection, graft versus host disease, hyperacute rejection of transplanted organs; and the like.

10 [0096] Inflammatory disorders and related conditions-- *e.g.*, Neutropenia, sepsis, septic shock, Alzheimer's disease, multiple sclerosis, neutrophilia, stroke, inflammatory bowel disease (IBD), inflammation associated with severe burns, lung injury, and ischemia-reperfusion injury, osteoarthritis, as well as acute (adult) respiratory distress syndrome (ARDS), chronic pulmonary
 15 obstructive disorder (COPD), systemic inflammatory response syndrome (SIRS), atopic dermatitis, psoriasis, chronic urticaria and multiple organ dysfunction syndrome (MODS) Hemolytic uremic syndrome, atypical hemolytic uremic syndrome (aHUS). Also included are pathologic sequelae associated with insulin-dependent diabetes mellitus (including diabetic retinopathy), lupus nephropathy, Heyman nephritis, membranous nephritis and other forms of glomerulonephritis, contact sensitivity responses, and inflammation resulting from contact of
 20 blood with artificial surfaces that can cause complement activation, as occurs, for example, during extracorporeal circulation of blood (*e.g.*, during hemodialysis or via a heart-lung machine, for example, in association with vascular surgery such as coronary artery bypass grafting or heart valve replacement), or in association with contact with other artificial vessel or container
 25 surfaces (*e.g.*, ventricular assist devices, artificial heart machines, transfusion tubing, blood storage bags, plasmapheresis, plateletpheresis, and the like). Also included are diseases related to ischemia/reperfusion injury, such as those resulting from transplants, including solid organ transplant, and syndromes such as ischemic reperfusion injury, ischemic colitis and cardiac ischemia. Compounds of the instant invention may also be useful in the treatment of age-related macular degeneration (Hageman et al, *P.N.A.S.* **102**: 7227-7232, 2005).

[0097] Cardiovascular and Cerebrovascular Disorders--*e.g.*, myocardial infarction, coronary thrombosis, vascular occlusion, post-surgical vascular reocclusion, atherosclerosis, traumatic central nervous system injury, and ischemic heart disease. In one embodiment, an effective amount of a compound of the invention may be administered to a patient at risk for myocardial infarction or thrombosis (*i.e.*, a patient who has one or more recognized risk factor for myocardial infarction or thrombosis, such as, but not limited to, obesity, smoking, high blood pressure, hypercholesterolemia, previous or genetic history of myocardial infarction or thrombosis) in order to reduce the risk of myocardial infarction or thrombosis.

[0098] Oncologic Diseases or Disorders--*e.g.*, melanoma, lung cancer, lymphoma, sarcoma, carcinoma, fibrosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, angiosarcoma, lymphangiosarcoma, synovioma, mesothelioma, meningioma, leukemia, lymphoma, leiomyosarcoma, rhabdomyosarcoma, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, papillary carcinoma, cystadenocarcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatocellular carcinoma, transitional cell carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, wilm's tumor, pleomorphic adenoma, liver cell papilloma, renal tubular adenoma, cystadenoma, papilloma, adenoma, leiomyoma, rhabdomyoma, hemangioma, lymphangioma, osteoma, chondroma, lipoma and fibroma.

[0099] Diseases of Vasculitis Vasculitic diseases are characterized by inflammation of the vessels. Infiltration of leukocytes leads to destruction of the vessel walls, and the complement pathway is believed to play a major role in initiating leukocyte migration as well as the resultant damage manifested at the site of inflammation (Vasculitis, Second Edition, Edited by Ball and Bridges, Oxford University Press, pp 47-53, 2008). The compounds provided in the present invention can be used to treat leukoclastic vasculitis, Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis, immune vasculitis Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome, Henoch-Schonlein purpura, polyarteritis nodosa, Rapidly Progressive Glomerulonephritis (RPGN), cryoglobulinaemia, giant cell arteritis (GCA), Behcet's disease and Takayasu's arteritis (TAK).

[0100] HIV infection and AIDS -- C5a receptor modulators provided herein may be used to inhibit HIV infection, delay AIDS progression or decrease the severity of symptoms or HIV infection and AIDS.

[0101] Neurodegenerative disorders and related diseases-- Within further aspects, C5a antagonists provided herein may be used to treat Alzheimer's disease, multiple sclerosis, and cognitive function decline associated with cardiopulmonary bypass surgery and related procedures.

5 [0102] In one embodiment of the invention, the compounds of the invention can be used for the treatment of diseases selected from the group consisting of sepsis (and associated disorders), COPD, rheumatoid arthritis, lupus nephritis and multiple sclerosis.

[0103] Treatment methods provided herein include, in general, administration to a patient an effective amount of one or more compounds provided herein. Suitable patients include those
10 patients suffering from or susceptible to (*i.e.*, prophylactic treatment) a disorder or disease identified herein. Typical patients for treatment as described herein include mammals, particularly primates, especially humans. Other suitable patients include domesticated companion animals such as a dog, cat, horse, and the like, or a livestock animal such as cattle, pig, sheep and the like.

15 [0104] In general, treatment methods provided herein comprise administering to a patient an effective amount of a compound one or more compounds provided herein. In a preferred embodiment, the compound(s) of the invention are preferably administered to a patient (*e.g.*, a human) orally or topically. The effective amount may be an amount sufficient to modulate C5a receptor activity and/or an amount sufficient to reduce or alleviate the symptoms presented by
20 the patient. Preferably, the amount administered is sufficient to yield a plasma concentration of the compound (or its active metabolite, if the compound is a pro-drug) high enough to detectably inhibit white blood cell (*e.g.*, neutrophil) chemotaxis *in vitro*. Treatment regimens may vary depending on the compound used and the particular condition to be treated; for treatment of most disorders, a frequency of administration of 4 times daily or less is preferred. In general, a dosage
25 regimen of 2 times daily is more preferred, with once a day dosing particularly preferred. It will be understood, however, that the specific dose level and treatment regimen 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, sex, diet, time of administration, route of administration, rate of excretion, drug combination (*i.e.*, other drugs being administered to the
30 patient) and the severity of the particular disease undergoing therapy, as well as the judgment of

the prescribing medical practitioner. In general, the use of the minimum dose sufficient to provide effective therapy is preferred. Patients may generally be monitored for therapeutic effectiveness using medical or veterinary criteria suitable for the condition being treated or prevented.

5 [0105] Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment or preventions of conditions involving pathogenic C5a activity (about 0.5 mg to about 7 g per human patient per day). 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. Dosage unit forms
10 will generally contain between from about 1 mg to about 500 mg of an active ingredient. For compounds administered orally, transdermally, intravenously, or subcutaneously, it is preferred that sufficient amount of the compound be administered to achieve a serum concentration of 5 ng (nanograms)/mL-10 g (micrograms)/mL serum, more preferably sufficient compound to achieve a serum concentration of 20 ng-1 g/ml serum should be administered, most preferably
15 sufficient compound to achieve a serum concentration of 50 ng/ml-200 ng/ml serum should be administered. For direct injection into the synovium (for the treatment of arthritis) sufficient compounds should be administered to achieve a local concentration of approximately 1 micromolar.

[0106] Frequency of dosage may also vary depending on the compound used and the particular
20 disease treated. However, for treatment of most disorders, a dosage regimen of 4 times daily, three times daily, or less is preferred, with a dosage regimen of once daily or 2 times daily being particularly preferred. It will be understood, however, that the specific dose level 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, sex, diet, time of administration, route of administration, and rate of excretion, drug combination (*i.e.*, other drugs being
25 administered to the patient), the severity of the particular disease undergoing therapy, and other factors, including the judgment of the prescribing medical practitioner.

Combination Therapy

[0107] The presently disclosed compounds may be used in combination with one or more additional therapeutic agents that are used in the treatment, prevention, suppression or amelioration of the diseases or conditions for which compounds and compositions of the present invention are useful. Such one or more additional therapeutic agents may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound or composition of the present invention. When a compound or composition of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound or composition of the present invention is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients or therapeutic agents, in addition to a compound or composition of the present invention.

[0108] Examples of the one or more additional therapeutic agents that may be combined with a compound or composition of the present invention, either administered separately or in the same pharmaceutical compositions, include, but are not limited to: (a) VLA-4 antagonists, (b) steroids and corticosteroids, such as beclomethasone, betamethasone (including betamethasone sodium phosphate, betamethasone valerate, betamethasone dipropionate) prednisone, prednisolone, methylprednisolone, mometasone, dexamethasone (including dexamethasone sodium phosphate), fluticasone, cortisone (including cortisone acetate) hydrocortisone (including hydrocortisone acetate, hydrocortisone-17-valerate, hydrocortisone-17-butyrate, hydrocortisone-17-aceponate, hydrocortisone-17-buteprate), budesonide, desonide, fluocinonide (including fluocinolone acetonide), triamcinolone (including triamcinolone acetonide and triamcinolone alcohol), tixocortol (including tixocortol pivalate) fluocortolone (including fluocortolone caproate and fluocortolone pivalate), amcinonide, halcinonide, halometasone, fluprednidene acetate, salmeterol, salmeterol, salbutamol, ciclesonide, formeterol, alclometasone (including alclometasone dipropionate), prednicarbate, clobetasone (including clobetasone-17-butyrate), clobetasol (including clobetasol-17-propionate); (c) immunosuppressants such as cyclosporine (cyclosporine A, Sandimmune®, Neoral®), tacrolimus (FK-506, Prograf®), rapamycin (sirolimus, Rapamune®) and other FK-506 type immunosuppressants, and mycophenolate, e.g., mycophenolate mofetil (CellCept®); (d) antihistamines (H1-histamine antagonists) such as bromopheniramine, chlorpheniramine, dexchlorpheniramine, triprolidine, clemastine, diphenhydramine, diphenylpyraline, tripeleminamine, hydroxyzine, methdilazine, promethazine,

trimeprazine, azatadine, cyproheptadine, antazoline, pheniramine pyrilamine, astemizole, terfenadine, loratadine, cetirizine, fexofenadine, descarboethoxyloratadine, and the like; (e) non steroidal anti asthmatics (e.g., terbutaline, metaproterenol, fenoterol, isoetharine, albuterol, bitolterol and pirbuterol), theophylline, cromolyn sodium, atropine, ipratropium bromide,

5 leukotriene antagonists (e.g., zafmlukast, montelukast, pranlukast, iralukast, pobilukast and SKB-106,203), leukotriene biosynthesis inhibitors (zileuton, BAY-1005); (f) non steroidal anti-inflammatory agents (NSAIDs) such as propionic acid derivatives (e.g., alminoprofen, benoxaprofen, bucloxic acid, carprofen, fenbufen, fenoprofen, fluprofen, flurbiprofen, ibuprofen, indoprofen, ketoprofen, miroprofen, naproxen, oxaprozin, pirprofen, pranoprofen, suprofen,

10 tiaprofenic acid and tioxaprofen), acetic acid derivatives (e.g., indomethacin, acemetacin, alclofenac, clidanac, diclofenac, fenclofenac, fenclozic acid, fentiazac, furofenac, ibufenac, isoxepac, oxpinac, sulindac, tiopinac, tolmetin, zidometacin and zomepirac), fenamic acid derivatives (e.g., flufenamic acid, meclofenamic acid, mefenamic acid, niflumic acid and tolfenamic acid), biphenylcarboxylic acid derivatives (e.g., diflunisal and flufenisal), oxicams

15 (e.g., isoxicam, piroxicam, sudoxicam and tenoxicam), salicylates (e.g., acetyl salicylic acid and sulfasalazine) and the pyrazolones (e.g., apazone, bezpiperylon, feprazone, mofebutazone, oxyphenbutazone and phenylbutazone); (g) cyclooxygenase-2 (COX-2) inhibitors such as celecoxib (Celebrex®) and rofecoxib (Vioxx®); (h) inhibitors of phosphodiesterase type IV (PDE IV); (i) gold compounds such as auranofin and aurothioglucose, (j) etanercept (Enbre10),

20 (k) cyclophosphamide, (l) antibody therapies such as orthoclone (OKT3), daclizumab (Zenapax®), basiliximab (Simulect®) and infliximab (Remicade®), (m) antibody therapies targeting CD20 such as obinutuzumab, rituximab, or ocrelizumab; (n) chemotherapeutic agents such anthracyclines (e.g., daunorubicin (daunomycin; rubidomycin), doxorubicin, epirubicin, idarubicin, and valrubicin), mitoxantrone, and pixantrone; platinum-based agents (e.g., cisplatin, carboplatin, oxaliplatin, satraplatin, picoplatin, nedaplatin, triplatin, and lipoplatin); tamoxifen

25 and metabolites thereof such as 4-hydroxytamoxifen (afimoxifene) and N-desmethyl-4-hydroxytamoxifen (endoxifen); taxanes such as paclitaxel (taxol) and docetaxel; alkylating agents (e.g., nitrogen mustards such as mechlorethamine (HN2), cyclophosphamide, ifosfamide, melphalan (L-sarcolysin), and chlorambucil); ethylenimines and methylmelamines (e.g.,

30 hexamethylmelamine, thiotepa, alkyl sulphonates such as busulfan, nitrosoureas such as carmustine (BCNU), lomustine (CCNLJ), semustine (methyl-CCN-U), and streptozoein

(streptozotocin), and triazenes such as decarbazine (DTIC; dimethyltriazenoimidazolecarboxamide)); antimetabolites (*e.g.*, folic acid analogues such as methotrexate (amethopterin), pyrimidine analogues such as fluorouracil (5-fluorouracil; 5-FU), floxuridine (fluorodeoxyuridine; FUdR), and cytarabine (cytosine arabinoside), and purine analogues and related inhibitors such as mercaptopurine (6-mercaptopurine; 6-MP), thioguanine (6-thioguanine; 6-TG), and pentostatin (2'-deoxycofonnycin)); (o) other antagonists of the chemokine receptors, especially CXCR2, CXCR3, CCR2, CCR3, CCR4, CCR7, CX3CR1 and CXCR6.

[0109] The disease or disorder being treated will determine which additional therapeutic agent or therapeutic agents are most appropriately administered in combination with the compounds of the present invention such determination can be made by a person of skill in the art.

[0110] The weight ratio of the compound of the present invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with an NSAID the weight ratio of the compound of the present invention to the NSAID will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

Non-Pharmaceutical Applications

[0111] In another aspect of the invention, the compounds of the invention can be used in a variety of non-pharmaceutical *in vitro* and *in vivo* application. For example, the compounds of the invention may be labeled and used as probes for the detection and localization of C5a receptor (cell preparations or tissue sections samples). The compounds of the invention may also be used as positive controls in assays for C5a receptor activity, *i.e.*, as standards for determining the ability of a candidate agent to bind to C5a receptor, or as radiotracers for positron emission tomography (PET) imaging or for single photon emission computerized tomography (SPECT). Such methods can be used to characterize C5a receptors in living subjects. For example, a C5a receptor modulator may be labeled using any of a variety of well known techniques (*e.g.*,

radiolabeled with a radionuclide such as tritium), and incubated with a sample for a suitable incubation time (*e.g.*, determined by first assaying a time course of binding). Following incubation, unbound compound is removed (*e.g.*, by washing), and bound compound detected using any method suitable for the label employed (*e.g.*, autoradiography or scintillation counting for radiolabeled compounds; spectroscopic methods may be used to detect luminescent groups and fluorescent groups). As a control, a matched sample containing labeled compound and a greater (*e.g.*, 10-fold greater) amount of unlabeled compound may be processed in the same manner. A greater amount of detectable label remaining in the test sample than in the control indicates the presence of C5a receptor in the sample. Detection assays, including receptor autoradiography (receptor mapping) of C5a receptor in cultured cells or tissue samples may be performed as described by Kuhar in sections 8.1.1 to 8.1.9 of Current Protocols in Pharmacology (1998) John Wiley & Sons, New York.

[0112] The compounds provided herein may also be used within a variety of well known cell separation methods. For example, modulators may be linked to the interior surface of a tissue culture plate or other support, for use as affinity ligands for immobilizing and thereby isolating, C5a receptors (*e.g.*, isolating receptor-expressing cells) *in vitro*. In one preferred application, a modulator linked to a fluorescent marker, such as fluorescein, is contacted with the cells, which are then analyzed (or isolated) by fluorescence activated cell sorting (FACS).

III. Examples

[0113] The following examples are offered to illustrate, but not to limit the claimed invention.

[0114] Reagents and solvents used below can be obtained from commercial sources such as Aldrich Chemical Co. (Milwaukee, Wisconsin, USA). ¹H-NMR spectra were recorded on a Varian Mercury 400 MHz NMR spectrometer. Significant peaks are provided relative to TMS and are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet) and number of protons. Mass spectrometry results are reported as the ratio of mass over charge, followed by the relative abundance of each ion (in parenthesis). In the examples, a single m/e value is reported for the M+H (or, as noted, M-H) ion containing the most common atomic isotopes. Isotope patterns correspond to the expected formula in all

cases. Electrospray ionization (ESI) mass spectrometry analysis was conducted on a Hewlett-Packard MSD electrospray mass spectrometer using the HP1100 HPLC for sample delivery. Normally the analyte was dissolved in methanol at 0.1 mg/mL and 1 microliter was infused with the delivery solvent into the mass spectrometer, which scanned from 100 to 1500 daltons. All compounds could be analyzed in the positive ESI mode, using acetonitrile / water with 1% formic acid as the delivery solvent. The compounds provided below could also be analyzed in the negative ESI mode, using 2 mM NH₄OAc in acetonitrile / water as delivery system.

[0115] The following abbreviations are used in the Examples and throughout the description of the invention:

EtOH: Ethanol

EtONa: Sodium ethoxide

THF: Tetrahydrofuran

TLC: Thin layer chromatography

MeOH: Methanol

[0116] Compounds within the scope of this invention can be synthesized as described below, using a variety of reactions known to the skilled artisan. One skilled in the art will also recognize that alternative methods may be employed to synthesize the target compounds of this invention, and that the approaches described within the body of this document are not exhaustive, but do provide broadly applicable and practical routes to compounds of interest.

[0117] Certain molecules claimed in this patent can exist in different enantiomeric and diastereomeric forms and all such variants of these compounds are claimed.

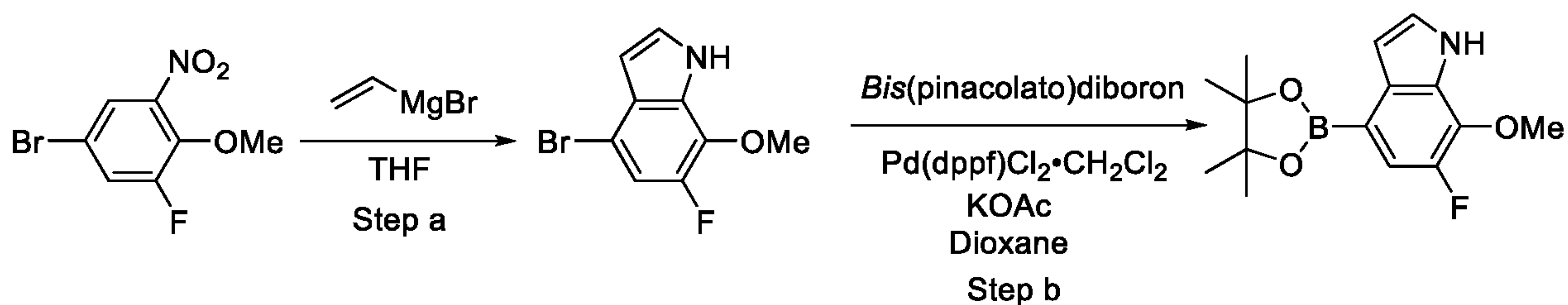
[0118] The detailed description of the experimental procedures used to synthesize key compounds in this text lead to molecules that are described by the physical data identifying them as well as by the structural depictions associated with them.

[0119] Those skilled in the art will also recognize that during standard work up procedures in organic chemistry, acids and bases are frequently used. Salts of the parent compounds are

sometimes produced, if they possess the necessary intrinsic acidity or basicity, during the experimental procedures described within this patent.

Example 1

Synthesis of intermediate 6-fluoro-7-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole

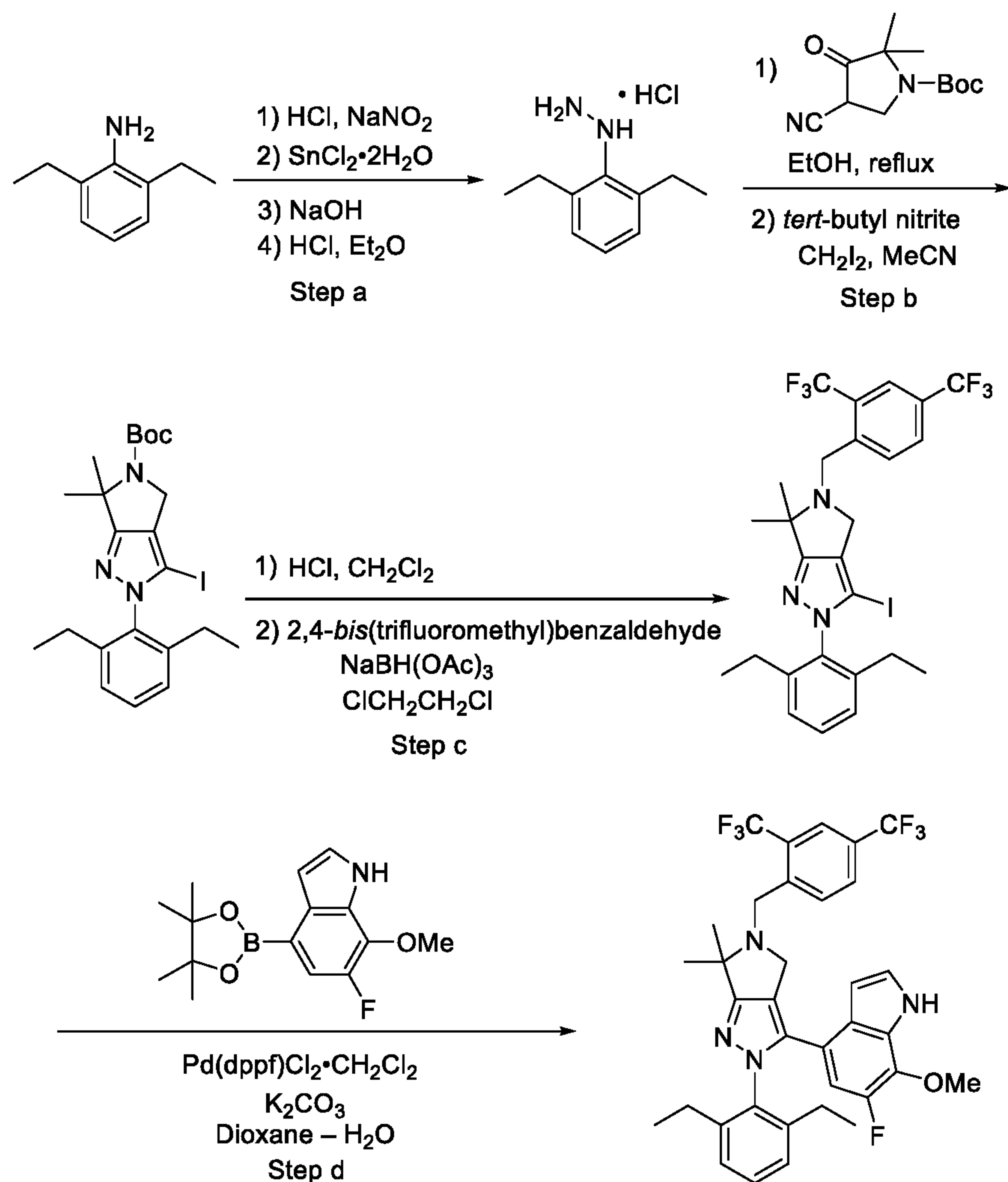


[0120] Step a: Vinylmagnesium bromide solution in THF (1.0 M, 70 mL, 70 mmol) was added to a solution of 4-bromo-2-fluoro-6-nitroanisole (5.0 g, 20 mmol) in anhydrous THF (70 mL) under N₂ at 50 °C. The reaction mixture was stirred at the same temperature and allowed to warm to 30 °C over 1.5 h. The reaction mixture was quenched with saturated aqueous NH₄Cl solution and allowed to warm up to room temperature over 1 h. The reaction mixture was diluted with EtOAc, washed with brine and dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography (0 to 100% EtOAc in hexanes) to yield 4-bromo-6-fluoro-7-methoxy-1H-indole. MS: (ES) *m/z* calculated for C₉H₈BrFNO [M + H]⁺ 243.9, found 243.9.

[0121] Step b: To a suspension of 4-bromo-6-fluoro-7-methoxy-1H-indole (900 mg, 3.68 mmol), *bis*(pinacolato)diboron (1.21 g, 4.8 mmol) and KOAc (1.08 g, 11 mmol) in dioxane (16 mL) was added Pd(dppf)Cl₂ complex with dichloromethane (400 mg, 0.49 mmol). The reaction mixture was degassed with N₂ for 2 min and stirred at 100 °C for 2 h. The reaction mixture was diluted with EtOAc and filtered through Celite. The solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography (0 to 100% EtOAc in hexanes) to give 6-fluoro-7-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole. MS: (ES) *m/z* calculated for C₁₅H₂₀BFNO₃ [M + H]⁺ 292.1, found 292.1.

Example 2

Synthesis of 4-(5-(2,4-bis(trifluoromethyl)benzyl)-2-(2,6-diethylphenyl)-6,6-dimethyl-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-yl)-6-fluoro-7-methoxy-1H-indole



[0122] Step a: To a 250 mL flask containing 90 mL of concentrated hydrochloric acid with magnetic stirring was added 2,6-diethylaniline (10 g, 67 mmol). The resulting mixture was stirred for 30 min and cooled with an ice/salt bath until the internal temperature reached 5 °C. A solution of sodium nitrite (5.5 g, 80 mmol) in water (60 mL) was added slowly to the above mixture while maintaining the internal temperature below 5 °C.

[0123] Separately, tin(II) chloride dihydrate (31.6 g, 140 mmol) was added to a 500 mL 3-neck round bottom flask containing concentrated hydrochloric acid (60 mL) with mechanical stirring. The resulting solution was then cooled with an ice bath.

[0124] The diazonium slurry was then filtered into the 500 mL flask containing the vigorously stirred and cold tin chloride solution. After 90 min, the reaction mixture was transferred to a 500 mL Erlenmeyer flask and the flask was rinsed with water (20 mL) and chloroform (8 mL). The combined mixture was stirred overnight at room temperature. The liquid was decanted to give a wet solid. The solid was dried *in vacuo* for one day and then transferred to a 500 mL 3-neck round bottom flask equipped with a mechanical stirrer and stirred with ether (180 mL). The resulting mixture was cooled in an ice bath and 10 N NaOH solution (30 mL) was added slowly to the mixture while maintaining the internal temperature below 12 °C. After the addition, the mixture was allowed to stand for 2 h on ice. The ether layer was decanted into a 500 mL flask and a stream of hydrogen chloride gas was bubbled into the stirred ether solution. The resulting precipitate was collected by filtration to afford (2,6-diethylphenyl)hydrazine hydrochloride. MS: (ES) *m/z* calculated for C₁₀H₁₇N₂ [M + H]⁺ 165.1, found 165.1.

[0125] Step b: Pyridine (4 mL, 49.5 mmol) was added to a mixture of (2,6-diethylphenyl)hydrazine hydrochloride (5 g, 24.91 mmol), *tert*-butyl 4-cyano-2,2-dimethyl-3-oxopyrrolidine-1-carboxylate (5 g, 20.98 mmol) and EtOH (60 mL) in a 250 mL round bottom flask under magnetic stirring. The resulting mixture was stirred at 70 °C for 24 h. The solvent was removed under reduced pressure and the residue was diluted with EtOAc and washed with aqueous citric acid solution, aqueous NaHCO₃ solution, brine, and dried over MgSO₄. The solvent was removed under reduced pressure and the residue was crystallized from cyclohexane to give *tert*-butyl 3-amino-2-(2,6-diethylphenyl)-6,6-dimethyl-2,6-dihydropyrrolo[3,4-*c*]pyrazole-5(4*H*)-carboxylate. MS: (ES) *m/z* calculated for C₂₂H₃₃N₄O₂ [M + H]⁺ 385.2, found 385.2.

[0126] *Tert*-butyl nitrite (0.5 mL, 3.8 mmol) was added slowly at room temperature to a mixture of *tert*-butyl 3-amino-2-(2,6-diethylphenyl)-6,6-dimethyl-2,6-dihydropyrrolo[3,4-*c*]pyrazole-5(4*H*)-carboxylate (1 g, 2.6 mmol), diiodomethane (1.5 mL, 18.6 mmol) and MeCN (15 mL) in a 100 mL round bottom flask under magnetic stirring. The resulting mixture was stirred at 45 °C for 3 h before it was diluted with toluene, washed with saturated NH₄Cl solution/NH₄OH (3:1), brine, and dried over MgSO₄. The solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography (2 to 25% EtOAc in hexanes) to give *tert*-butyl 2-(2,6-diethylphenyl)-3-iodo-6,6-dimethyl-2,6-dihydropyrrolo[3,4-

c]pyrazole-5(4*H*)-carboxylate. MS: (ES) *m/z* calculated for C₂₂H₃₁IN₃O₂ [M + H]⁺ 496.1, found 496.2.

[0127] Step c: The above *tert*-butyl 2-(2,6-diethylphenyl)-3-iodo-6,6-dimethyl-2,6-dihydropyrrolo[3,4-*c*]pyrazole-5(4*H*)-carboxylate was dissolved in dichloromethane (10 mL) and charged with HCl in dioxane (4 N, 5 mL). The resulting mixture was stirred at room temperature for 12 h. Upon completion, the solvent was evaporated *in vacuo* to give 2-(2,6-diethylphenyl)-3-iodo-6,6-dimethyl-2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazole hydrochloride. MS: (ES) *m/z* calculated for C₁₇H₂₃IN₃ [M + H]⁺ 396.1, found 396.2.

[0128] *N,N*-diisopropylethylamine (0.3 mL, 1.73 mmol) was added to a suspension of 2-(2,6-diethylphenyl)-3-iodo-6,6-dimethyl-2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazole hydrochloride (680 mg, 1.57 mmol), and 2,4-*bis*(trifluoromethyl)benzaldehyde (800 mg, 3.3 mmol) in 1,2-dichloroethane (10 mL) under magnetic stirring. After stirring at room temperature for 10 min, NaBH(OAc)₃ (800 mg, 3.77 mmol) was added in portions. The resulting mixture was stirred at 45 °C for 2 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc, washed with aqueous NaHCO₃ solution, brine and dried over MgSO₄. The solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography (2 to 25% EtOAc in hexanes) to give 5-(2,4-*bis*(trifluoromethyl)benzyl)-2-(2,6-diethylphenyl)-3-iodo-6,6-dimethyl-2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazole. MS: (ES) *m/z* calculated for C₂₆H₂₇F₆IN₃ [M + H]⁺ 622.1, found 622.1.

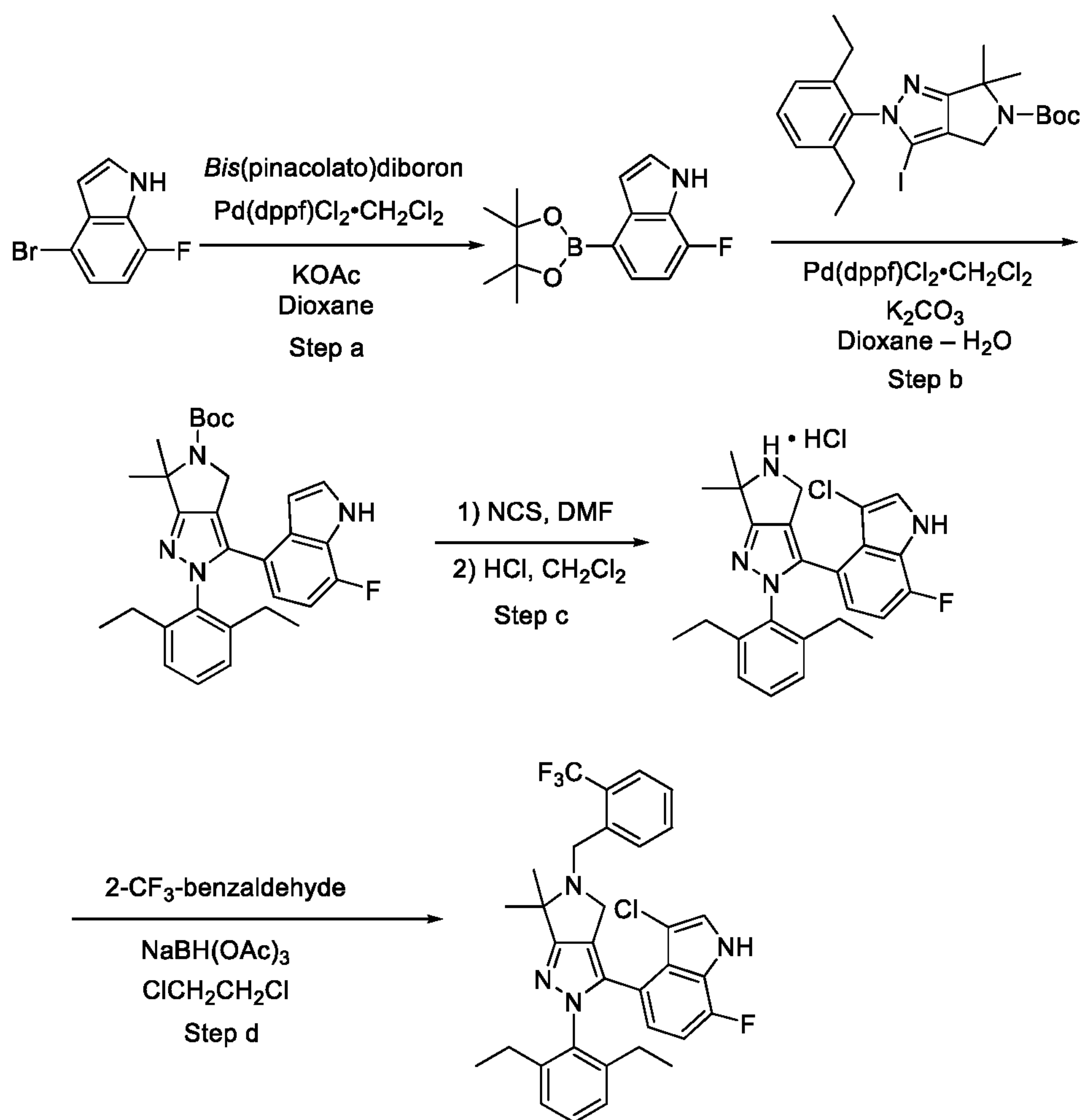
[0129] Step d: To a suspension of 5-(2,4-*bis*(trifluoromethyl)benzyl)-2-(2,6-diethylphenyl)-3-iodo-6,6-dimethyl-2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazole (250 mg, 0.40 mmol), 6-fluoro-7-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (100 mg, 0.34 mmol) and K₂CO₃ (445 mg, 1.81 mmol) in dioxane (6 mL) and water (1 mL) was added Pd(dppf)Cl₂ complex with dichloromethane (50 mg, 0.06 mmol). The reaction mixture was degassed with N₂ for 2 min and stirred under N₂ at 100 °C for 2.5 h. The reaction mixture was diluted with EtOAc, washed with aqueous NaHCO₃ and dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography (3 to 35% EtOAc in hexanes) followed by HPLC (MeCN/H₂O, with 1% TFA) to give 4-(5-(2,4-*bis*(trifluoromethyl)benzyl)-2-(2,6-diethylphenyl)-6,6-dimethyl-2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazol-3-yl)-6-fluoro-7-methoxy-1*H*-indole. ¹H NMR (400 MHz, CDCl₃) 8.37 (br s, 1H),

8.19 (d, $J = 12$ Hz, 1H), 7.86 (s, 1H), 7.76 (d, $J = 12$ Hz, 1H), 7.07–7.33 (m, 4H), 6.41 (dd, $J = 2.2, 3.2$ Hz, 1H), 6.33 (d, $J = 13.8$ Hz, 1H), 4.14 (s, 2H), 4.01 (s, 3H), 3.70 (s, 2H), 2.23–2.37 (m, 4H), 1.55 (s, 6H), 1.02 (t, $J = 7.6$ Hz, 6H). MS: (ES) m/z calculated for $C_{35}H_{34}F_7N_4O$ $[M + H]^+$ 659.2, found 659.2.

5

Example 3

Synthesis of 3-chloro-4-(2-(2,6-diethylphenyl)-6,6-dimethyl-5-(2-(trifluoromethyl)benzyl)-2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazol-3-yl)-7-fluoro-1*H*-indole



[0130] Step a: To a suspension of 4-bromo-7-fluoro-1*H*-indole (1.00 g, 4.67 mmol),
 10 *bis*(pinacolato)diboron (1.31 g, 5.14 mmol) and KOAc (1.15 g, 11.7 mmol) in dioxane (15 mL) was added $Pd(dppf)Cl_2$ complex with dichloromethane (416 mg, 0.51 mmol). The reaction mixture was degassed with N_2 for 2 min and stirred at 100 °C for 2 h. The reaction mixture was

cooled to room temperature, diluted with EtOAc, and filtered through Celite. The solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography (0 to 30% EtOAc in hexanes) to give 7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole. MS: (ES) m/z calculated for $C_{14}H_{18}BFNO_2$ $[M + H]^+$ 262.1, found 262.1.

- 5 [0131] Step b: To a suspension of *tert*-butyl 2-(2,6-diethylphenyl)-3-iodo-6,6-dimethyl-2,6-dihydropyrrolo[3,4-*c*]pyrazole-5(4*H*)-carboxylate (540 mg, 1.09 mmol), 7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (350 mg, 1.34 mmol), and K_2CO_3 (830 mg, 6.78 mmol) in dioxane (10 mL) and water (2mL) was added $Pd(dppf)Cl_2$ complex with dichloromethane (200 mg, 0.32 mmol). The reaction mixture was degassed with N_2 for 2 min
10 and stirred under N_2 at 100 °C for 2 h. The reaction mixture was cooled to room temperature, diluted with EtOAc, washed with aqueous $NaHCO_3$, and dried over Na_2SO_4 . The solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography (5 to 25% EtOAc in hexanes) to give *tert*-butyl 2-(2,6-diethylphenyl)-3-(7-fluoro-1*H*-indol-4-yl)-6,6-dimethyl-2,6-dihydropyrrolo[3,4-*c*]pyrazole-5(4*H*)-carboxylate. MS: (ES) m/z calculated for
15 $C_{30}H_{36}FN_4O_2$ $[M + H]^+$ 503.2, found 503.3.

- [0132] Step c: The above *tert*-butyl 2-(2,6-diethylphenyl)-3-(7-fluoro-1*H*-indol-4-yl)-6,6-dimethyl-2,6-dihydropyrrolo[3,4-*c*]pyrazole-5(4*H*)-carboxylate (200 mg, 0.40 mmol) was dissolved in DMF (5 mL) and charged with *N*-chlorosuccinimide (100 mg, 0.75 mmol). The resulting mixture was stirred at room temperature for 12 h. The reaction mixture was diluted
20 with EtOAc, washed with aqueous $Na_2S_2O_3$ solution, brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography (2 to 25% EtOAc in hexanes) to give *tert*-butyl 3-(3-chloro-7-fluoro-1*H*-indol-4-yl)-2-(2,6-diethylphenyl)-6,6-dimethyl-2,6-dihydropyrrolo[3,4-*c*]pyrazole-5(4*H*)-carboxylate. MS: (ES) m/z calculated for $C_{30}H_{33}ClFN_4O_2$ $[M - H]^-$ 535.2, found 535.2.

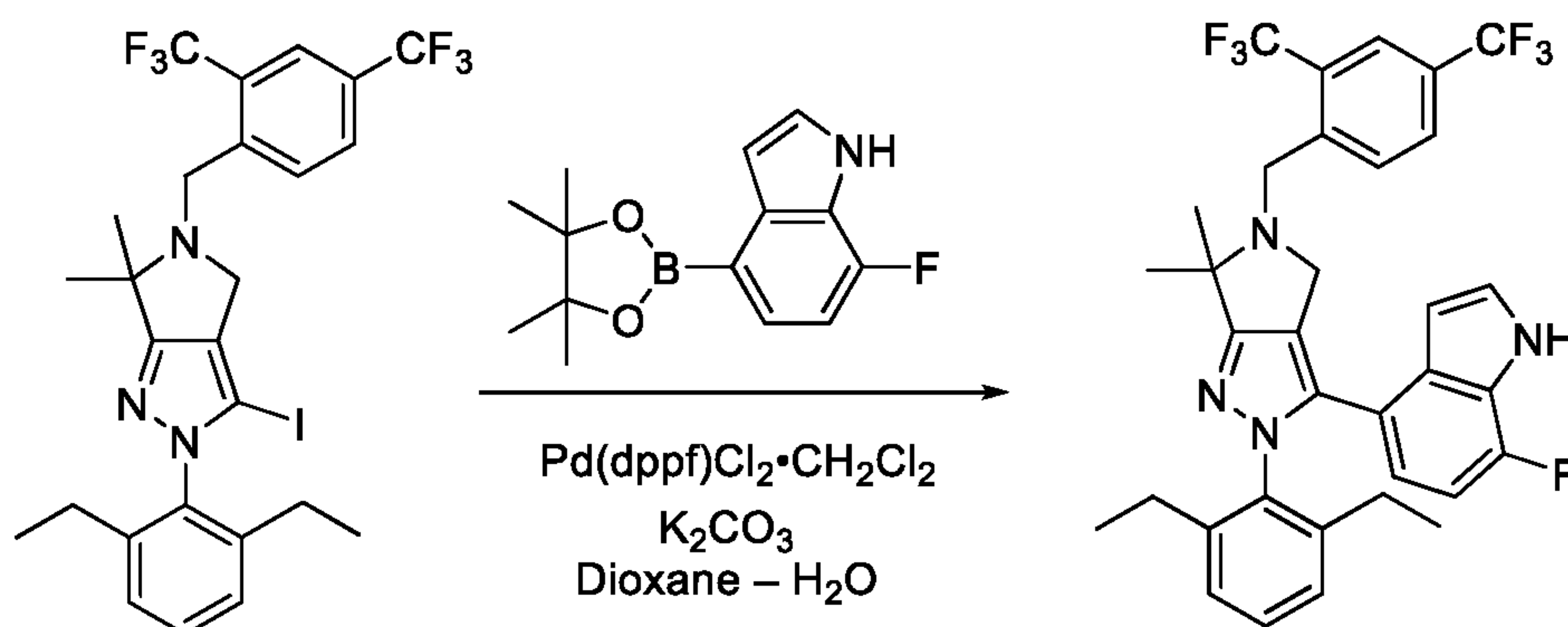
- 25 [0133] The above *tert*-butyl 3-(3-chloro-7-fluoro-1*H*-indol-4-yl)-2-(2,6-diethylphenyl)-6,6-dimethyl-2,6-dihydropyrrolo[3,4-*c*]pyrazole-5(4*H*)-carboxylate was dissolved in dichloromethane (6 mL) and charged with HCl in dioxane (4 N, 5 mL). The resulting mixture was stirred at room temperature for 12 h. After the reaction was complete, the solvent was evaporated *in vacuo* to give 3-chloro-4-(2-(2,6-diethylphenyl)-6,6-dimethyl-2,4,5,6-

tetrahydropyrrolo[3,4-*c*]pyrazol-3-yl)-7-fluoro-1*H*-indole hydrochloride. MS: (ES) *m/z* calculated for C₂₅H₂₇ClFN₄ [M + H]⁺ 437.2, found 437.2.

[0134] Step d: *N,N*-diisopropylethylamine (0.2 mL, 1.15 mmol) was added to a suspension of 3-chloro-4-(2-(2,6-diethylphenyl)-6,6-dimethyl-2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazol-3-yl)-7-fluoro-1*H*-indole hydrochloride (75 mg, 0.16 mmol), and 2-trifluoromethylbenzaldehyde (120 mg, 0.69 mmol) in 1,2-dichloroethane (6 mL) under magnetic stirring. After stirring at room temperature for 10 min, NaBH(OAc)₃ (150 mg, 0.71 mmol) was added to the reaction mixture. The resulting mixture was stirred at 40 °C for 1 h, then cooled to room temperature, diluted with EtOAc, washed with brine, and dried over MgSO₄. The solvent was removed under reduced pressure and the residue was purified by preparative TLC (40% EtOAc in hexanes) followed by HPLC (MeCN/H₂O, with 1% TFA) to give 3-chloro-4-(2-(2,6-diethylphenyl)-6,6-dimethyl-5-(2-(trifluoromethyl)benzyl)-2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazol-3-yl)-7-fluoro-1*H*-indole. ¹H NMR (400 MHz, CD₃OD) 7.92–7.99 (m, 1H), 7.52–7.66 (m, 2H), 7.34–7.38 (m, 2H), 7.24–7.29 (m, 2H), 6.94–6.98 (m, 1H), 6.66 (dd, *J* = 8.2, 10.8 Hz, 1H), 6.50 (dd, *J* = 4.5, 8.2 Hz, 1H), 4.88 (br, 1H), 4.09 (s, 2H), 3.82 (d, *J* = 11.5 Hz, 1H), 3.43 (d, *J* = 11.5 Hz, 1H), 2.53 (dq, *J* = 7.5, 15 Hz, 1H), 2.37–2.46 (m, 2H), 2.07 (dq, *J* = 7.5, 15 Hz, 1H), 1.54 (s, 3H), 1.51 (s, 3H), 1.33 (t, *J* = 7.6 Hz, 3H), 0.76 (t, *J* = 7.6 Hz, 3H). MS: (ES) *m/z* calculated for C₃₃H₃₂ClF₄N₄ [M + H]⁺ 595.2, found 595.2.

Example 4

20 **Synthesis of 4-(5-(2,4-bis(trifluoromethyl)benzyl)-2-(2,6-diethylphenyl)-6,6-dimethyl-2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazol-3-yl)-7-fluoro-1*H*-indole**

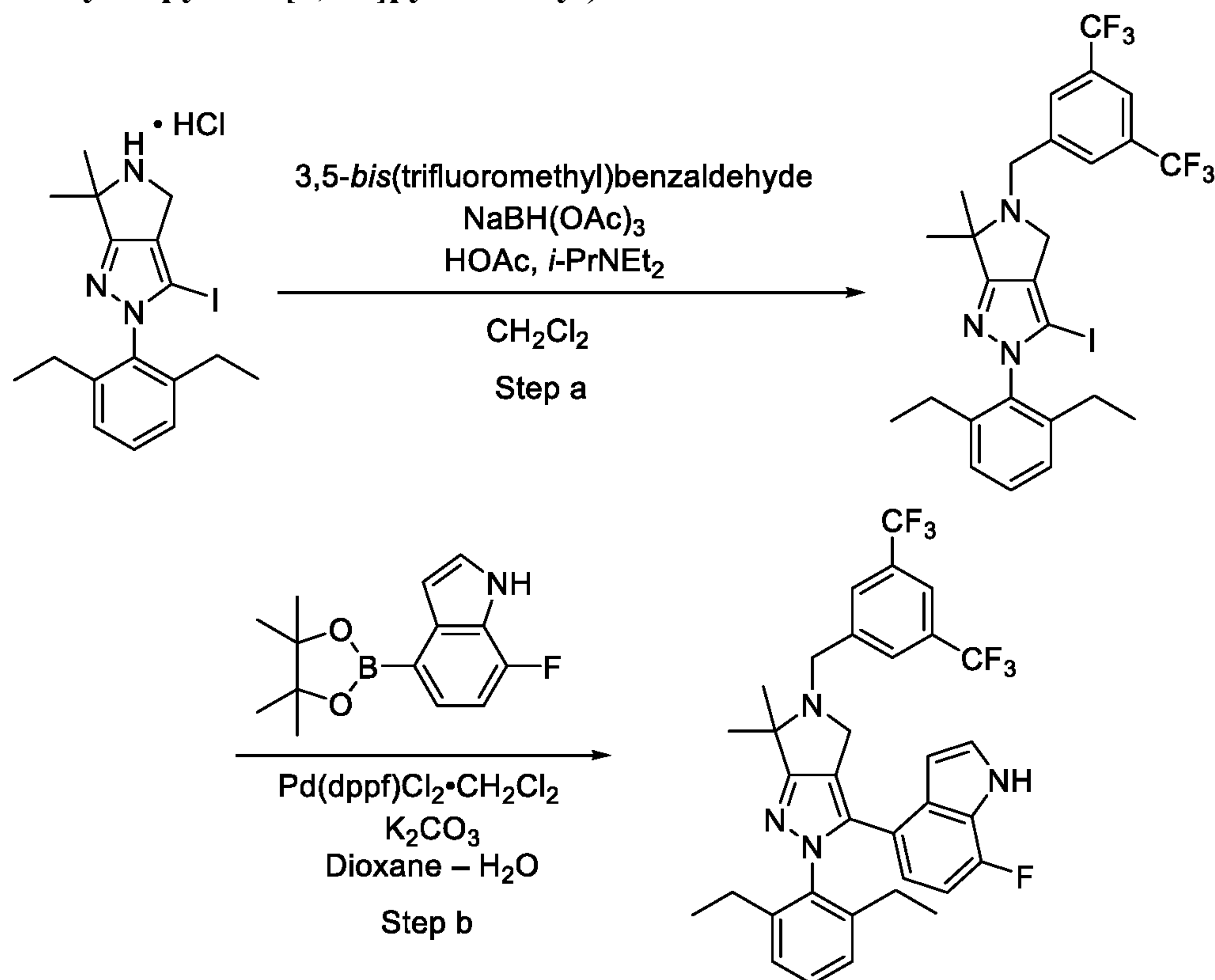


[0135] A mixture of 5-(2,4-bis(trifluoromethyl)benzyl)-3-iodo-2-(2,6-diethylphenyl)-6,6-dimethyl-2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazole (200 mg, 0.32 mmol), 7-fluoro-4-(4,4,5,5-

tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (150 mg, 0.57 mmol), K₂CO₃ (276 mg, 2.0 mmol) and Pd(dppf)Cl₂ complex with dichloromethane (60 mg, 0.07 mmol) in dioxane (6 mL) and water (1 mL) was stirred at 100 °C for 5 h under N₂. The mixture was cooled to room temperature, diluted with EtOAc, and filtered through a plug of Celite. The filtrate was collected, concentrated *in vacuo* and the residue was purified by silica gel flash chromatography (0 to 50% EtOAc in hexanes) to yield 4-(5-(2,4-bis(trifluoromethyl)benzyl)-2-(2,6-diethylphenyl)-6,6-dimethyl-2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazol-3-yl)-7-fluoro-1*H*-indole. ¹H NMR (400 MHz, CDCl₃) 8.44 (s, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 7.86 (s, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.22 (m, 2H), 7.07 (d, *J* = 7.6 Hz, 2H), 6.61 (m, 1H), 6.47 (m, 2H), 4.15 (s, 2H), 3.71 (s, 2H), 2.37 (m, 2H), 2.22 (m, 2H), 1.56 (s, 6H), 1.00 (t, *J* = 7.6 Hz, 6H). MS: (ES) *m/z* calculated for C₃₄H₃₂F₇N₄ [M + H]⁺ 629.2, found 629.2.

Example 5

Synthesis of 4-(5-(3,5-bis(trifluoromethyl)benzyl)-2-(2,6-diethylphenyl)-6,6-dimethyl-2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazol-3-yl)-7-fluoro-1*H*-indole



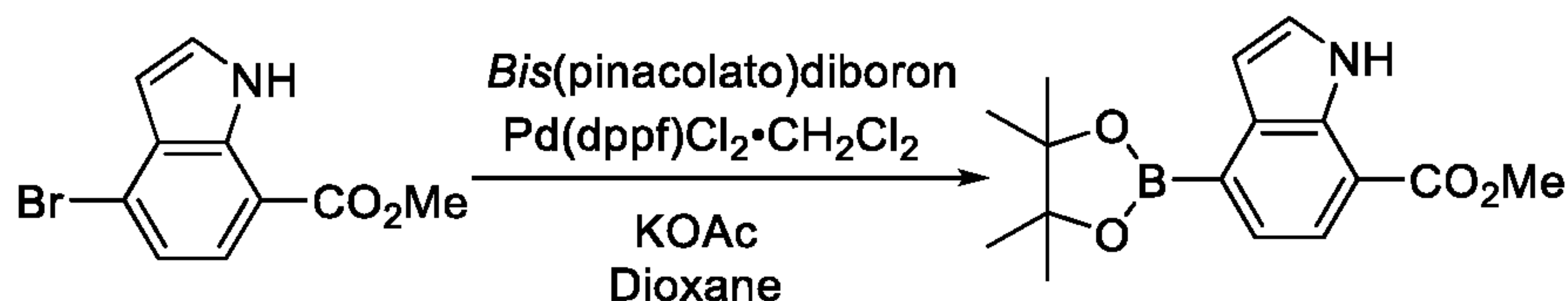
[0136] Step a: A mixture of 2-(2,6-diethylphenyl)-3-iodo-6,6-dimethyl-2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazole hydrochloride (2.20 g, 5.1 mmol), 3,5-

bis(trifluoromethyl)benzaldehyde (1.85 g, 7.6 mmol), NaBH(OAc)₃ (3.24 g, 15.3 mmol), *i*PrNEt₂ (0.84 mL, 5.1 mmol) and acetic acid (0.49 mL, 7.6 mmol) in DCM (30 mL) was stirred at room temperature for 1.5 h. It was then quenched with aqueous NaHCO₃ and extracted with EtOAc. The organic layer was separated, dried over Na₂SO₄, concentrated *in vacuo*, and the residue was purified by silica gel flash chromatography (0 to 30% EtOAc in hexanes) to give 5-(3,5-bis(trifluoromethyl)benzyl)-2-(2,6-diethylphenyl)-3-iodo-6,6-dimethyl-2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazole. MS: (ES) *m/z* calculated for C₂₆H₂₇FIN₃ [M + H]⁺ 622.1, found 622.1.

[0137] Step b: A mixture of 5-(3,5-bis(trifluoromethyl)benzyl)-2-(2,6-diethylphenyl)-3-iodo-6,6-dimethyl-2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazole (1.50 g, 2.4 mmol), 7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (817 mg, 3.1 mmol), K₂CO₃ (0.830 g, 6.0 mmol) and Pd(dppf)Cl₂ complex with dichloromethane (30 mg, 0.36 mmol) in dioxane (12 mL) and water (1.5 mL) was stirred at 100 °C for 2 h under N₂. The reaction mixture was cooled to room temperature and partitioned between EtOAc and aqueous NaHCO₃. The organic layer was separated, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (0 to 50% EtOAc in hexanes) followed by HPLC (MeCN/H₂O, with 1% TFA) to give 4-(5-(3,5-bis(trifluoromethyl)benzyl)-2-(2,6-diethylphenyl)-6,6-dimethyl-2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazol-3-yl)-7-fluoro-1*H*-indole. ¹H NMR (400 MHz, CDCl₃) 8.48 (s, 1H), 7.92 (s, 2H), 7.14 (s, 1H), 7.24 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.20 (d, *J* = 2.8 Hz, 1H), 7.07 (dd, *J* = 7.6, 7.6 Hz, 2H), 6.61 (m, 1H), 6.47 (m, 2H), 4.03 (s, 2H), 3.65 (s, 2H), 2.37 (m, 2H), 2.22 (m, 2H), 1.56 (s, 6H), 1.00 (t, *J* = 7.6 Hz, 6H). MS: (ES) *m/z* calculated for C₃₄H₃₂F₇N₄ [M + H]⁺ 629.2, found 629.2.

Example 6

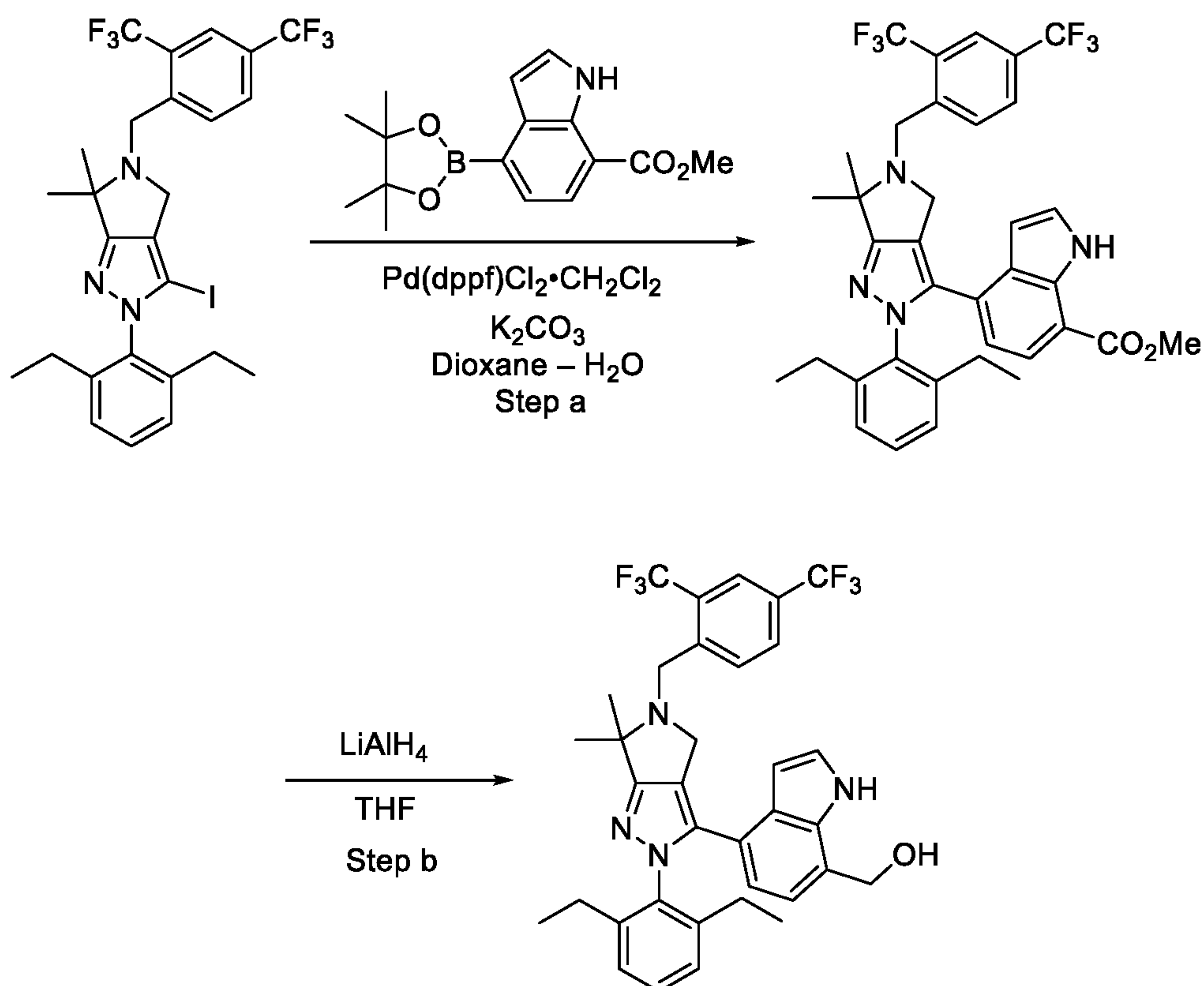
Synthesis of intermediate methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole-7-carboxylate



[0138] Step a: To a suspension of methyl 4-bromo-1*H*-indole-7-carboxylate (300 mg, 1.18 mmol), *bis*(pinacolato)diboron (330 mg, 1.30 mmol), and KOAc (290 mg, 2.96 mmol) in dioxane (8 mL) was added Pd(dppf)Cl₂ complex with dichloromethane (100 mg, 0.12 mmol). The reaction mixture was degassed with N₂ for 2 min and stirred at 100 °C for 1 h. The reaction mixture was diluted with EtOAc, filtered through Celite. The solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography (5 to 30% EtOAc in hexanes) to give methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole-7-carboxylate. MS: (ES) *m/z* calculated for C₁₆H₂₁BNO₄ [M + H]⁺ 302.2, found 302.2.

Example 7

10 Synthesis of (4-(5-(2,4-*bis*(trifluoromethyl)benzyl)-2-(2,6-diethylphenyl)-6,6-dimethyl-2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazol-3-yl)-1*H*-indol-7-yl)methanol



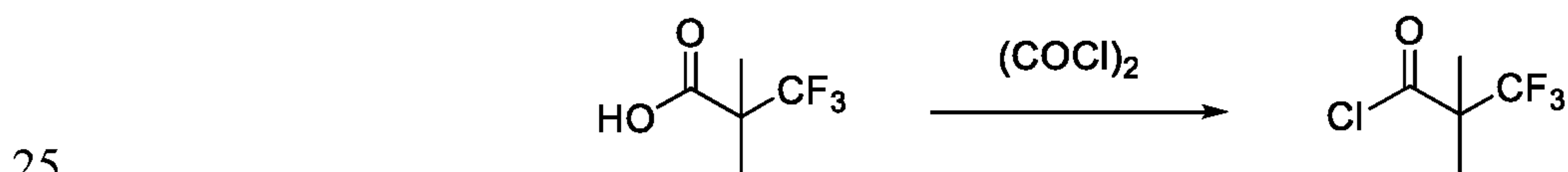
[0139] Step a: A mixture of 5-(2,4-*bis*(trifluoromethyl)benzyl)-2-(2,6-diethylphenyl)-3-iodo-6,6-dimethyl-2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazole (100 mg, 0.16 mmol), methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole-7-carboxylate (78 mg, 0.26 mmol), K₂CO₃ (150 mg, 1.1 mmol) and Pd(dppf)Cl₂ complex with dichloromethane (90 mg, 0.11 mmol) in dioxane

(4 mL) and water (0.7 mL) was stirred at 100 °C for 2 h under N₂. The reaction mixture was cooled to room temperature and partitioned between EtOAc and aqueous NaHCO₃. The organic layer was separated, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (0 to 40% EtOAc in hexanes) to give methyl 4-(5-(2,4-
 5 *bis*(trifluoromethyl)benzyl)-2-(2,6-diethylphenyl)-6,6-dimethyl-2,4,5,6-tetrahydropyrrolo[3,4-
c]pyrazol-3-yl)-1*H*-indole-7-carboxylate. MS: (ES) *m/z* calculated for C₃₆H₃₅F₆N₄O₂ [M + H]⁺ 669.3, found 669.3.

[0140] Step b: To a solution of methyl 4-(5-(2,4-*bis*(trifluoromethyl)benzyl)-2-(2,6-diethylphenyl)-6,6-dimethyl-2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazol-3-yl)-1*H*-indole-7-
 10 carboxylate (25 mg, 0.037 mmol) in THF (1.5 mL) at 0 °C was added a solution of LiAlH₄ in ether (1.0 M, 0.20 mL, 0.20 mmol). After 1 h at 0 °C, the reaction mixture was quenched with water and partitioned between EtOAc and aqueous NaHCO₃. The organic layer was separated, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by HPLC (MeCN/H₂O, with 1% TFA) followed by silica gel flash chromatography (0 to 60% EtOAc in hexanes) to give
 15 (4-(5-(2,4-*bis*(trifluoromethyl)benzyl)-2-(2,6-diethylphenyl)-6,6-dimethyl-2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazol-3-yl)-1*H*-indol-7-yl)methanol. ¹H NMR (400 MHz, CDCl₃) 8.99 (s, 1H), 8.18 (d, *J* = 8.0 Hz, 1H), 7.86 (s, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.24 (m, 2H), 7.06 (d, *J* = 7.6 Hz, 2H), 6.70 (d, *J* = 7.4 Hz, 1H), 6.49 (d, *J* = 7.4 Hz, 1H), 6.48 (d, *J* = 2.6 Hz, 1H), 4.92 (d, *J* = 5.6 Hz, 2H), 4.15 (s, 2H), 3.72 (s, 2H), 2.39 (m, 2H), 2.26 (m, 2H), 1.83 (t, *J* = 5.8
 20 Hz, 1H), 1.56 (s, 6H), 1.02 (t, *J* = 7.6, 6H). MS: (ES) *m/z* calculated for C₃₅H₃₅F₆N₄O [M + H]⁺ 641.3, found 641.3.

Example 8

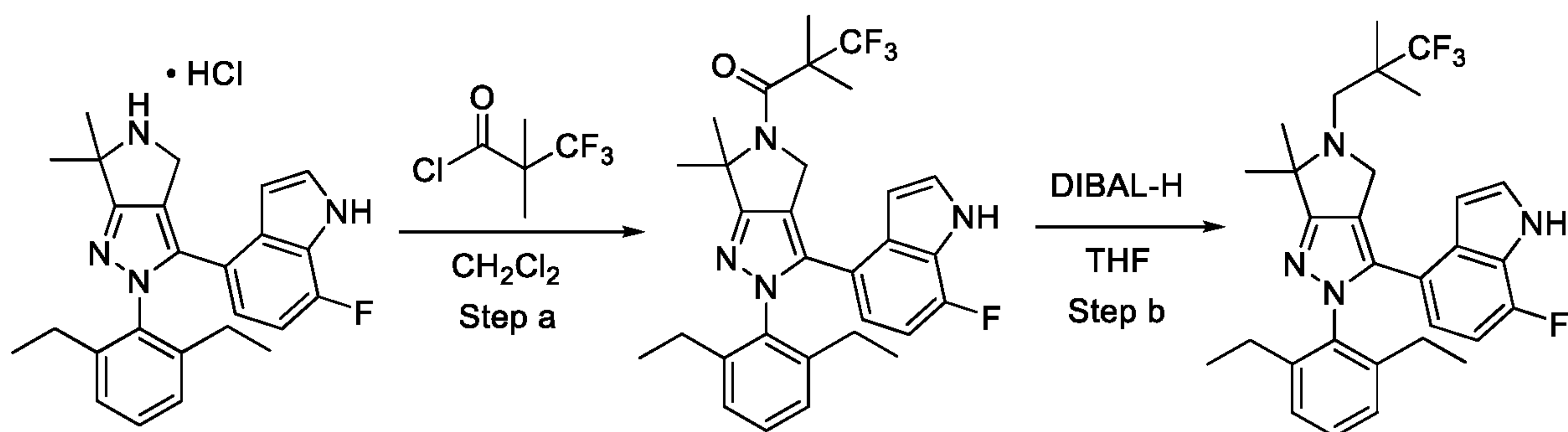
Synthesis of intermediate 3,3,3-trifluoro-2,2-dimethylpropanoyl chloride



[0141] A mixture of 3,3,3-trifluoro-2,2-dimethylpropanoic acid (0.312 g, 2.0 mmol), oxalyl chloride (0.17 mL, 2.0 mmol) and DMF (2 drops) in DCM (6.7 mL) was stirred at room temperature for 30 min. The reaction mixture containing 3,3,3-trifluoro-2,2-dimethylpropanoyl chloride was directly used in the subsequent step without further purification.

Example 9

Synthesis of 4-(2-(2,6-diethylphenyl)-6,6-dimethyl-5-(3,3,3-trifluoro-2,2-dimethylpropyl)-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-yl)-7-fluoro-1H-indole



5 [0142] Step a: A mixture of 4-(2-(2,6-diethylphenyl)-6,6-dimethyl-2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazol-3-yl)-7-fluoro-1*H*-indole hydrochloride (78 mg, 0.18 mmol), 3,3,3-trifluoro-2,2-dimethylpropanoyl chloride (~2 mmol) and NEt₃ (0.13 mL, 0.89 mmol) in DCM (3 mL) was stirred for 1 h at room temperature. The mixture was then partitioned between EtOAc and aqueous NaHCO₃. The organic layer was separated, dried over Na₂SO₄, and

10 concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (0 to 15% EtOAc in DCM) to give 1-(2-(2,6-diethylphenyl)-3-(7-fluoro-1*H*-indol-4-yl)-6,6-dimethyl-2,6-dihydropyrrolo[3,4-*c*]pyrazol-5(4*H*)-yl)-3,3,3-trifluoro-2,2-dimethylpropan-1-one. MS: (ES) *m/z* calculated for C₃₀H₃₃F₄N₄O [M + H]⁺ 541.3, found 541.2.

[0143] Step b: To a solution of 1-(2-(2,6-diethylphenyl)-3-(7-fluoro-1*H*-indol-4-yl)-6,6-dimethyl-2,6-dihydropyrrolo[3,4-*c*]pyrazol-5(4*H*)-yl)-3,3,3-trifluoro-2,2-dimethylpropan-1-one (35 mg, 0.064 mmol) in THF (2 mL) was added a solution of DIBAL-H in DCM (1.0 M, 1.5 mL, 1.5 mmol). After 1 h at room temperature, the reaction mixture was quenched with aqueous NaHCO₃, and partitioned between EtOAc and aqueous NaHCO₃. The organic layer was

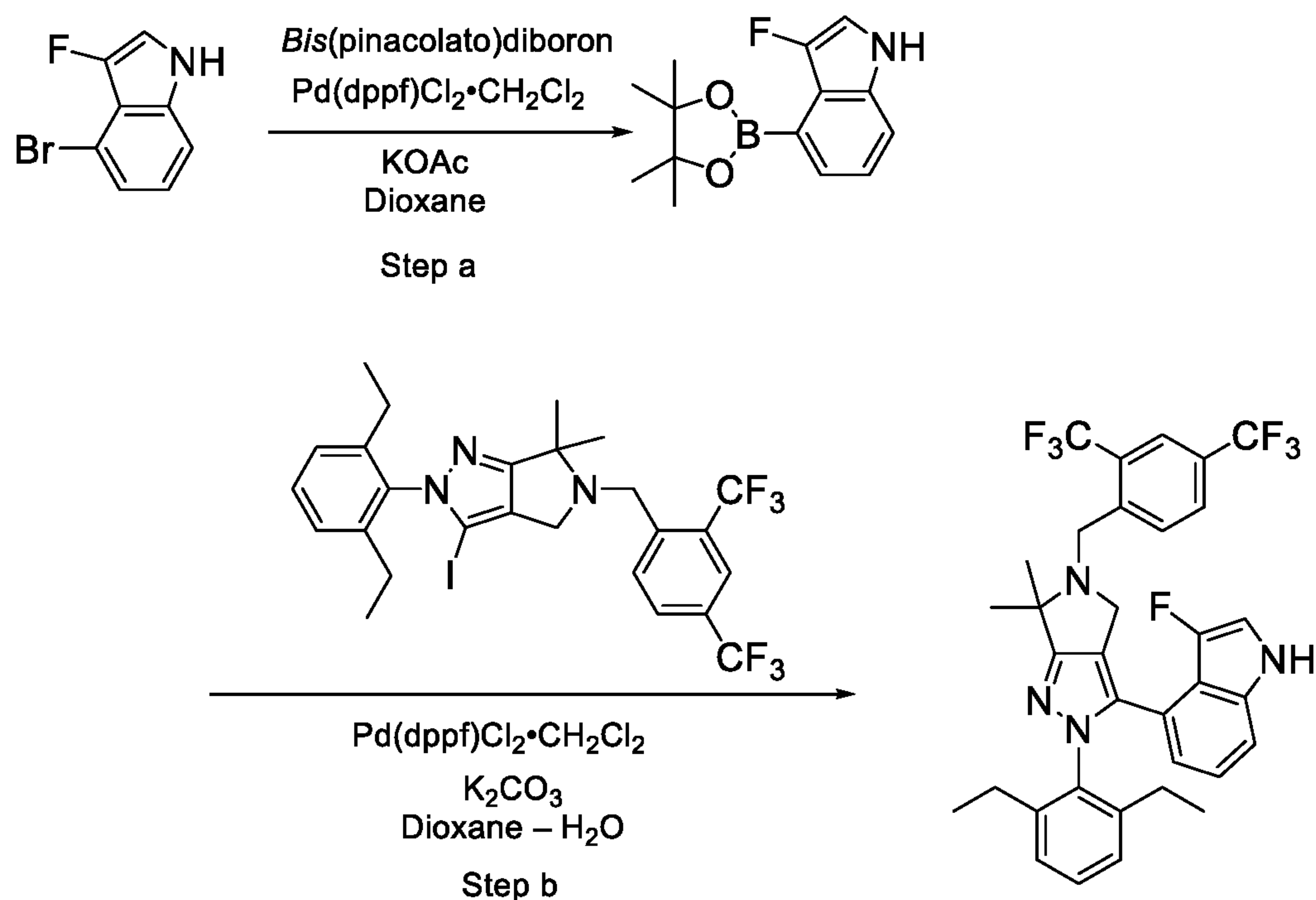
15 separated, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by silica gel

20 flash chromatography (0 to 10% EtOAc in DCM) to give 4-(2-(2,6-diethylphenyl)-6,6-dimethyl-5-(3,3,3-trifluoro-2,2-dimethylpropyl)-2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazol-3-yl)-7-fluoro-1*H*-indole. ¹H NMR (400 MHz, CDCl₃) 8.49 (s, 1H), 7.27 (dd, *J* = 2.4, 2.4 Hz, 1H), 7.23 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.06 (d, *J* = 7.2 Hz, 2H), 6.63 (m, 1H), 6.56 (m, 1H), 6.47 (m, 1H), 3.93 (s, 2H), 2.84 (s, 2H), 2.35 (m, 2H), 2.20 (m, 2H), 1.41 (s, 6H), 1.19 (s, 6H), 0.98 (t, *J* = 7.6 Hz, 6H).

25 MS: (ES) *m/z* calculated for C₃₀H₃₅F₄N₄ [M + H]⁺ 527.3, found 527.2.

Example 10

Synthesis of 4-(5-(2,4-bis(trifluoromethyl)benzyl)-2-(2,6-diethylphenyl)-6,6-dimethyl-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-yl)-3-fluoro-1H-indole



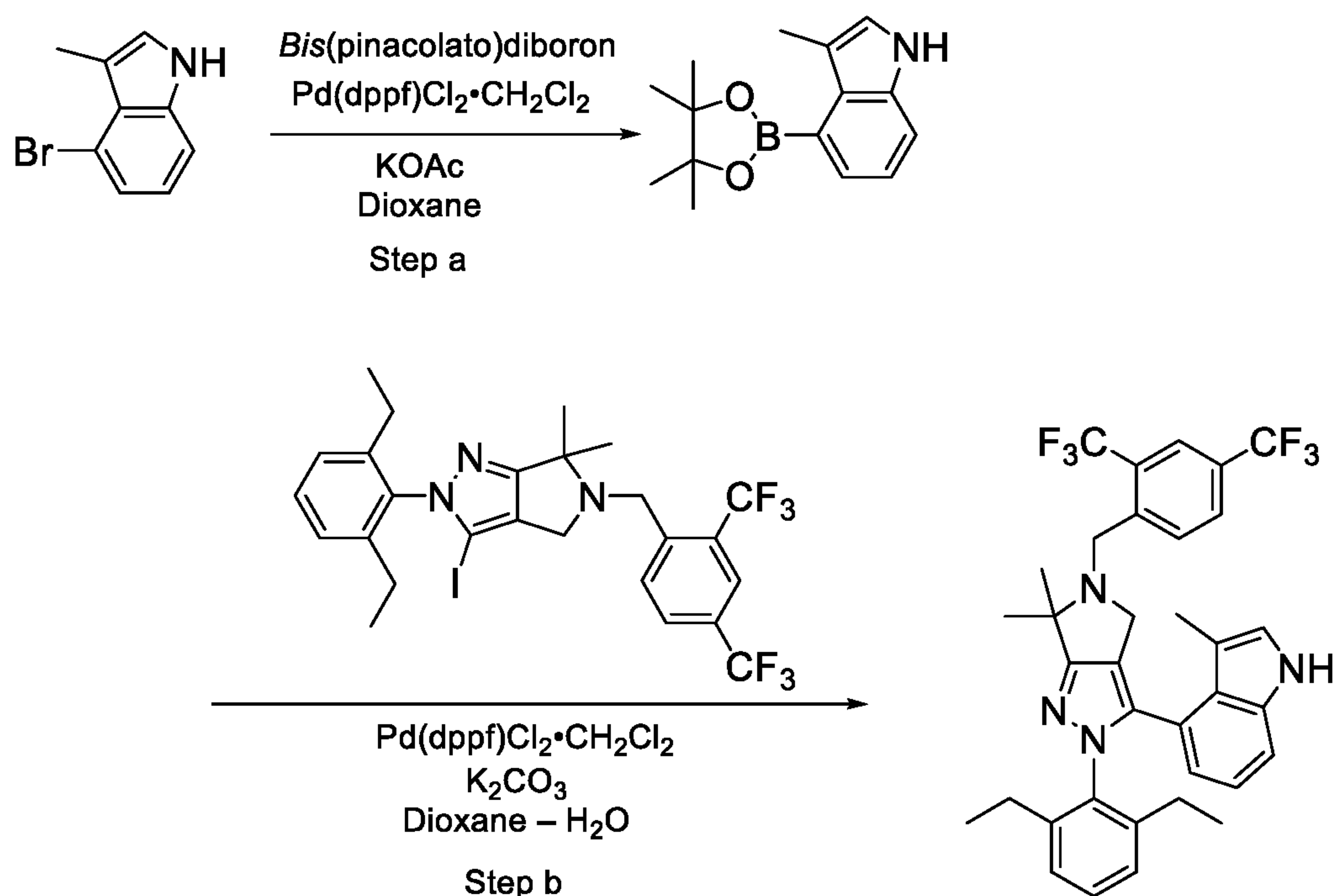
- 5 [0144] Step a: To a suspension of 4-bromo-3-fluoro-1H-indole (240 mg, 1.1 mmol), bis(pinacolato)diboron (420 mg, 1.7 mmol) and KOAc (320 mg, 3.3 mmol) in dioxane (5 mL) was added Pd(dppf)Cl₂ complex with dichloromethane (140 mg, 0.17 mmol). The reaction mixture was degassed with N₂ for 2 min and stirred at 90 °C for 2 h. The reaction mixture was adsorbed onto silica gel and purified by silica gel flash chromatography (0 to 100% EtOAc in hexanes) to give 3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole. MS: (ES) *m/z* calculated for C₁₄H₁₈BFNO₂ [M + H]⁺ 262.1, found 261.2.

- 15 [0145] Step b: To a suspension of 5-(2,4-bis(trifluoromethyl)benzyl)-2-(2,6-diethylphenyl)-3-iodo-6,6-dimethyl-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole (74 mg, 0.12 mmol), 3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (64 mg, 0.25 mmol) and K₂CO₃ (169 mg, 1.2 mmol) in dioxane (6 mL) and water (1 mL) was added Pd(dppf)Cl₂ complex with dichloromethane (49 mg, 0.060 mmol). The reaction mixture was degassed with N₂ for 2 min and stirred under N₂ at 90 °C for 16 h. The reaction mixture was adsorbed onto silica gel and

purified by silica gel flash chromatography (0 to 30% MTBE in hexanes) followed by HPLC (MeCN/H₂O, with 1% TFA), and preparative TLC (EtOAc in toluene) to give 4-(5-(2,4-*bis*(trifluoromethyl)benzyl)-2-(2,6-diethylphenyl)-6,6-dimethyl-2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazol-3-yl)-3-fluoro-1*H*-indole. ¹H NMR (400 MHz, CD₃OD) 8.25 (d, *J* = 8.4 Hz, 1H), 7.89–7.94 (m, 2H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.20 (dd, *J* = 8.0, 2.6 Hz, 1H), 7.09–7.15 (m, 3H), 6.85 (t, *J* = 8.4 Hz, 1H), 6.51 (d, *J* = 7.2 Hz, 1H), 4.19 (s, 2H), 3.65 (s, 2H), 2.19–2.50 (m, 4H), 1.54 (s, 6H), 0.87–1.21 (m, 6H). MS: (ES) *m/z* calculated for C₃₄H₃₂F₇N₄ [M + H]⁺ 629.3, found 629.3.

Example 11

10 Synthesis of 4-(5-(2,4-*bis*(trifluoromethyl)benzyl)-2-(2,6-diethylphenyl)-6,6-dimethyl-2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazol-3-yl)-3-methyl-1*H*-indole



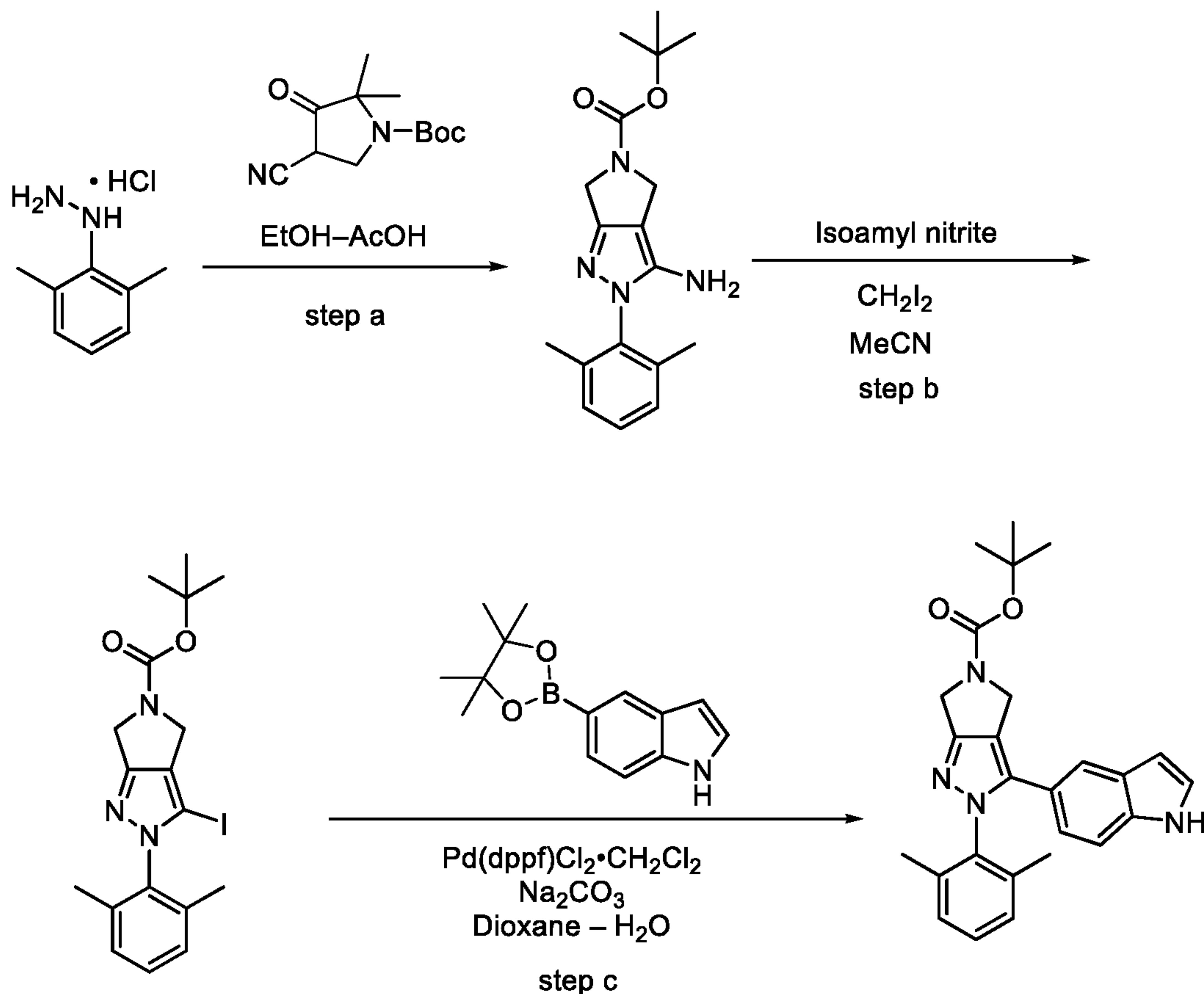
[0146] Step a: To a suspension of 4-bromo-3-methyl-1*H*-indole (240 mg, 1.1 mmol), *bis*(pinacolato)diboron (910 mg, 3.6 mmol) and KOAc (710 mg, 7.2 mmol) in dioxane (6 mL) was added Pd(dppf)Cl₂ complex with dichloromethane (290 mg, 0.36 mmol). The reaction mixture was degassed (N₂) for 2 min and stirred at 90 °C for 4 h. The reaction mixture was adsorbed onto silica gel and purified by silica gel flash chromatography (0 to 25% MTBE in

hexanes) to give 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole. MS: (ES) m/z calculated for $C_{15}H_{21}BNO_2$ $[M + H]^+$ 258.2, found 258.1.

[0147] Step b: To a suspension of 5-(2,4-*bis*(trifluoromethyl)benzyl)-2-(2,6-diethylphenyl)-3-iodo-6,6-dimethyl-2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazole (65 mg, 0.10 mmol), 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (127 mg, 0.49 mmol) and K_2CO_3 (256 mg, 1.9 mmol) in dioxane (6 mL) and water (1 mL) was added $Pd(dppf)Cl_2$ complex with dichloromethane (51 mg, 0.062 mmol). The reaction mixture was degassed with N_2 for 2 min and stirred under N_2 at 90 °C for 2 h. The reaction mixture was adsorbed onto silica gel and purified by silica gel flash chromatography (0 to 100% MTBE in hexanes) followed by HPLC (MeCN/ H_2O , with 1% TFA) and preparative TLC (40% acetone in hexanes) to give 4-(5-(2,4-*bis*(trifluoromethyl)benzyl)-2-(2,6-diethylphenyl)-6,6-dimethyl-2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazol-3-yl)-3-methyl-1*H*-indole. 1H NMR (400 MHz, CD_3OD) δ 8.25–8.18 (m, 1H), 7.92 (d, $J = 9.0$ Hz, 2H), 7.29–7.17 (m, 3H), 7.04 (d, $J = 1.2$ Hz, 1H), 6.97–6.90 (m, 1H), 6.77 (dd, $J = 8.2, 7.3$ Hz, 1H), 6.44 (dd, $J = 7.4, 0.9$ Hz, 1H), 4.25–4.10 (m, 2H), 3.66 (d, $J = 11.6$ Hz, 1H), 3.51 (d, $J = 11.6$ Hz, 1H), 2.28–2.58 (m, 3H), 2.17 (s, 3H), 2.00–2.11 (m, 1H), 1.55 (s, 3H), 1.53 (s, 3H), 1.34 (t, $J = 7.6$ Hz, 3H), 0.77 (t, $J = 7.6$ Hz, 3H). MS: (ES) m/z calculated for $C_{35}H_{35}F_6N_4$ $[M + H]^+$ 625.3, found 625.3.

Example 12

Synthesis of *tert*-butyl 2-(2,6-dimethylphenyl)-3-(1*H*-indol-5-yl)-4,6-dihydropyrrolo[3,4-*c*]pyrazole-5-carboxylate



[0148] Step a: To *tert*-butyl 3-cyano-4-oxo-pyrrolidine-1-carboxylate (19.5 g, 92.54 mmol) and (2,6-dimethylphenyl)hydrazine hydrochloride (16 g, 92.65 mmol) were added EtOH (160 mL) and AcOH (40 mL). The resulting suspension was stirred at 50 °C overnight. Upon completion, the reaction mixture was quenched with 1N NaOH aqueous solution and extracted with EtOAc (2 x 100 mL), dried (MgSO₄), and concentrated *in vacuo*. The crude product was then purified by silica gel flash chromatography (50% EtOAc in hexanes) to obtain *tert*-butyl 3-amino-2-(2,6-dimethylphenyl)-4,6-dihydropyrrolo[3,4-*c*]pyrazole-5-carboxylate. MS: (ES) *m/z* calculated for C₁₈H₂₅N₄O₂ [M + H]⁺ 329.2, found 329.2.

[0149] Step b: Isoamyl nitrite (11.74 mL, 87.5 mmol) was added slowly at room temperature to a mixture of *tert*-butyl 3-amino-2-(2,6-dimethylphenyl)-4,6-dihydropyrrolo[3,4-*c*]pyrazole-5-carboxylate (14.35 g, 43.75 mmol), diiodomethane (14 mL, 175 mmol) and MeCN (180 mL). The resulting reaction mixture was stirred at room temperature for 2 h. The reaction mixture was adsorbed onto silica gel and purified by silica gel flash chromatography (30% EtOAc in hexanes)

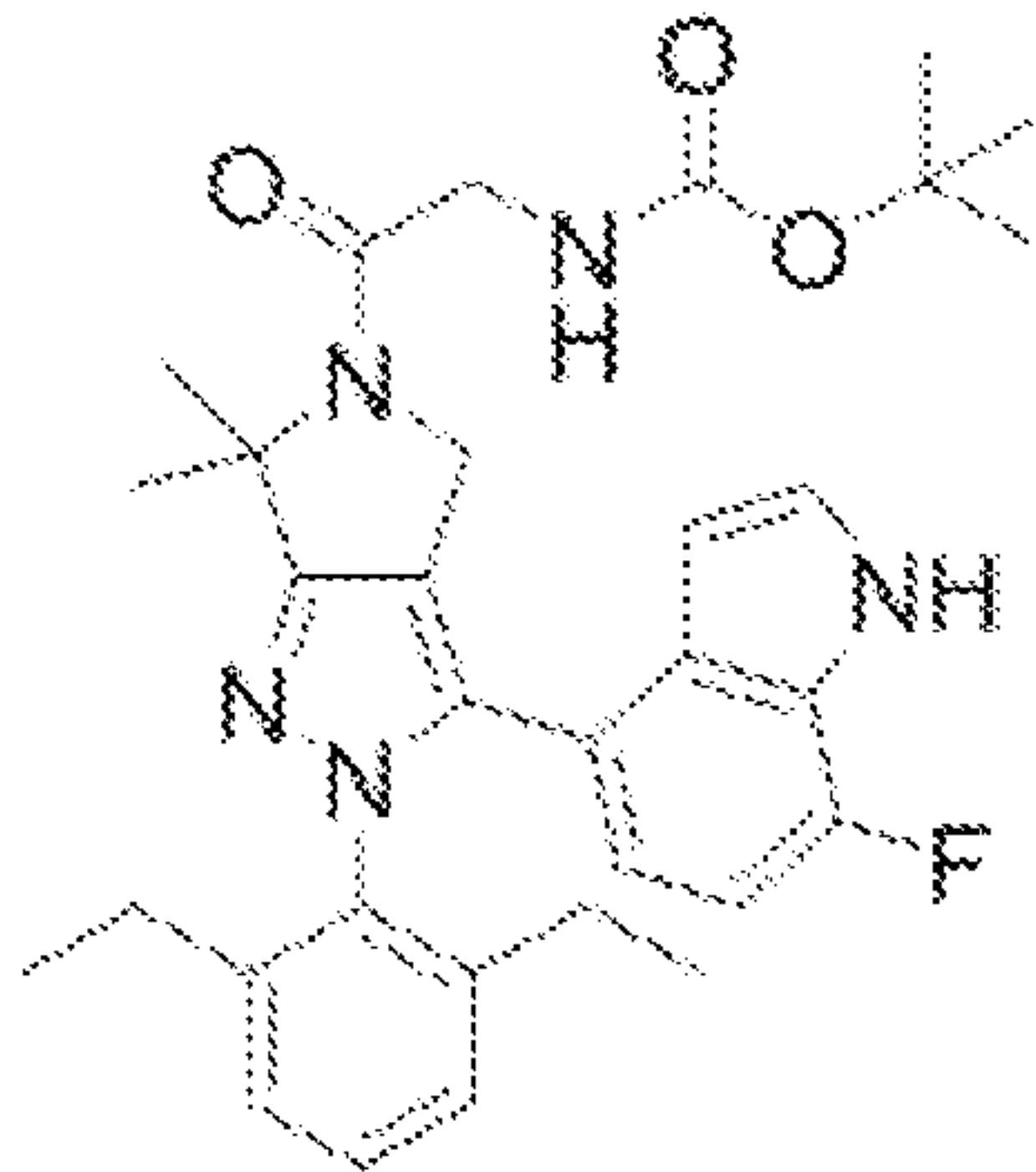
to obtain *tert*-butyl 2-(2,6-dimethylphenyl)-3-iodo-4,6-dihydropyrrolo[3,4-*c*]pyrazole-5-carboxylate. MS: (ES) *m/z* calculated for C₁₈H₂₃IN₃O₂ [M + H]⁺ 440.1, found 440.2.

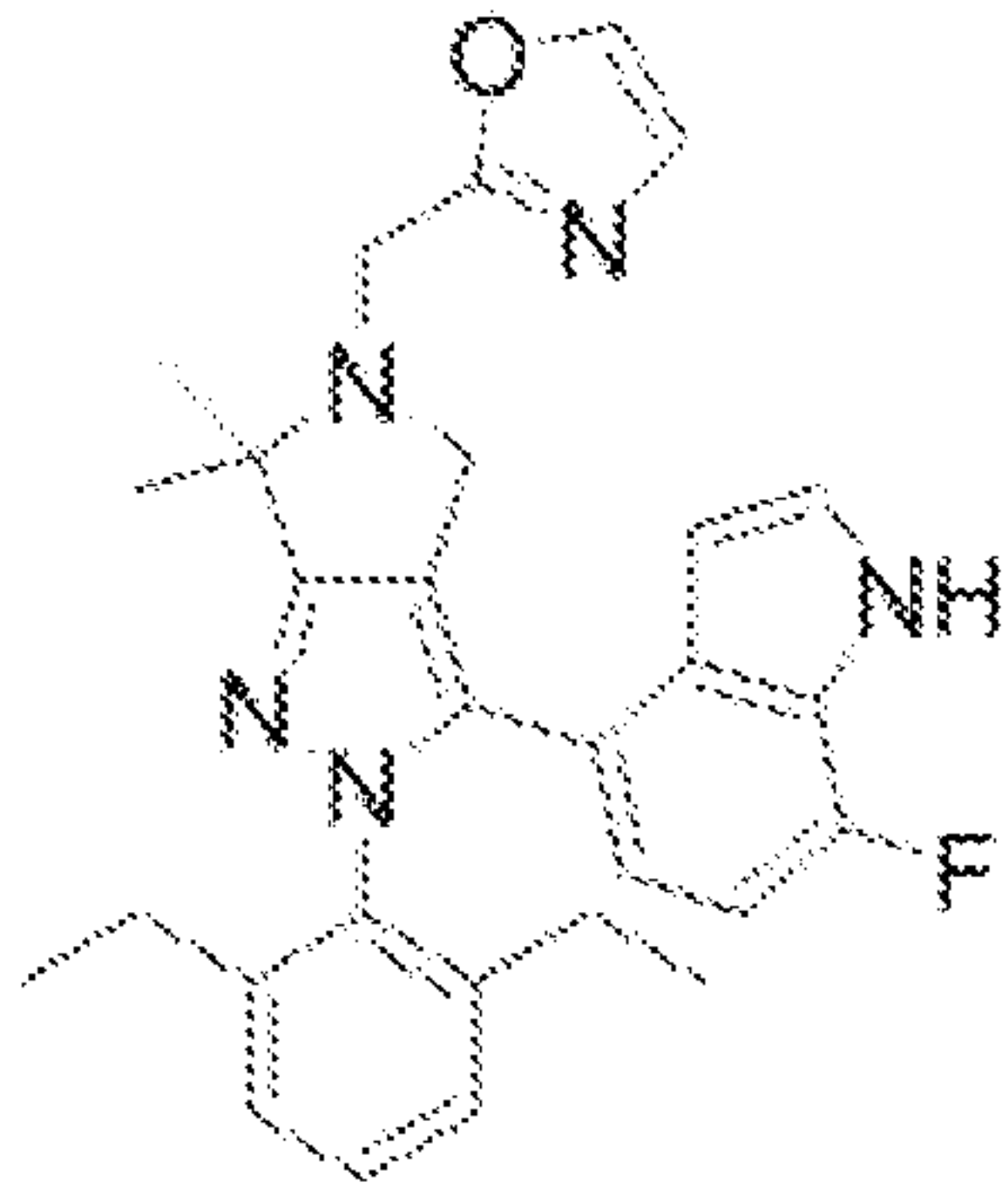
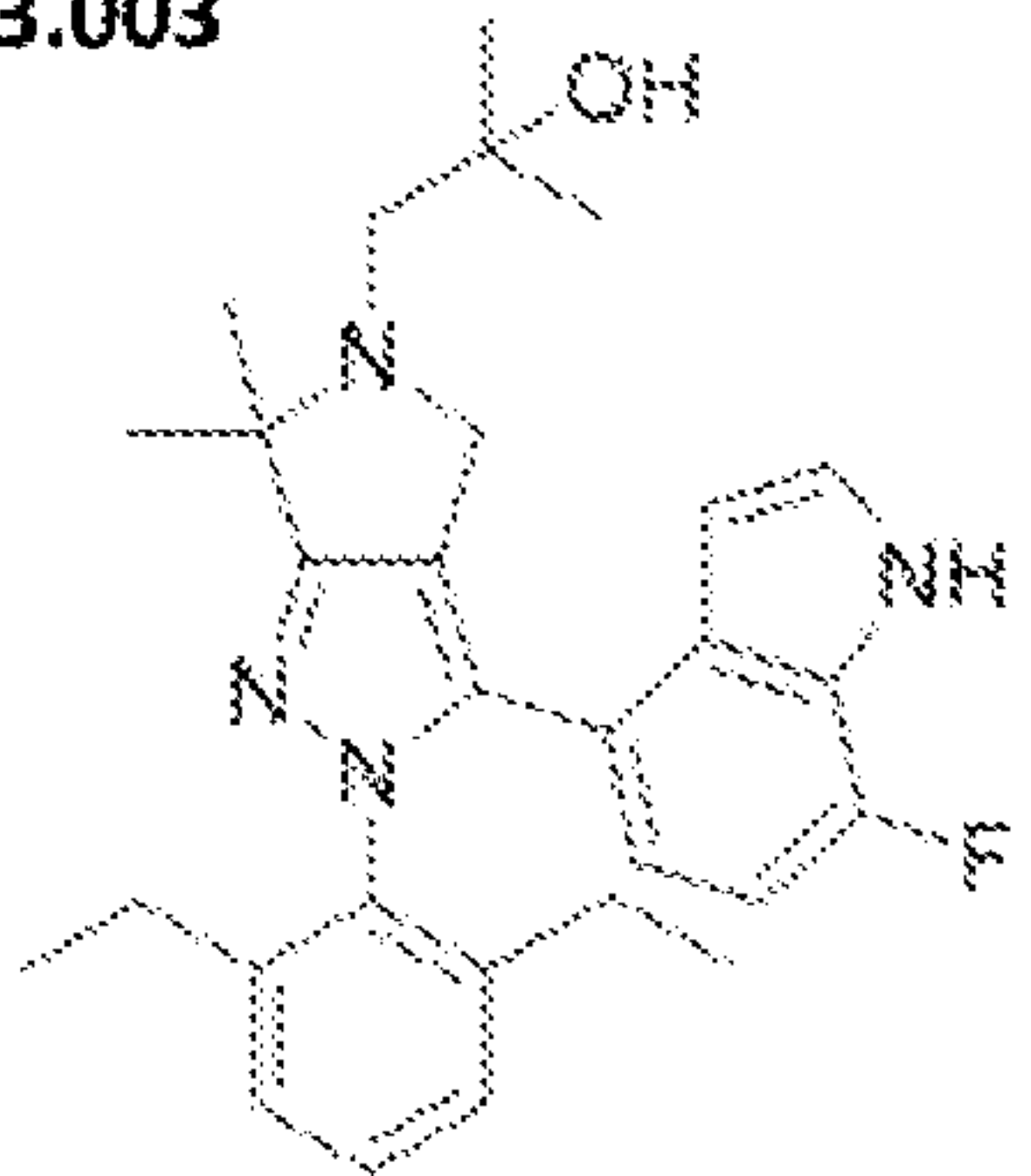
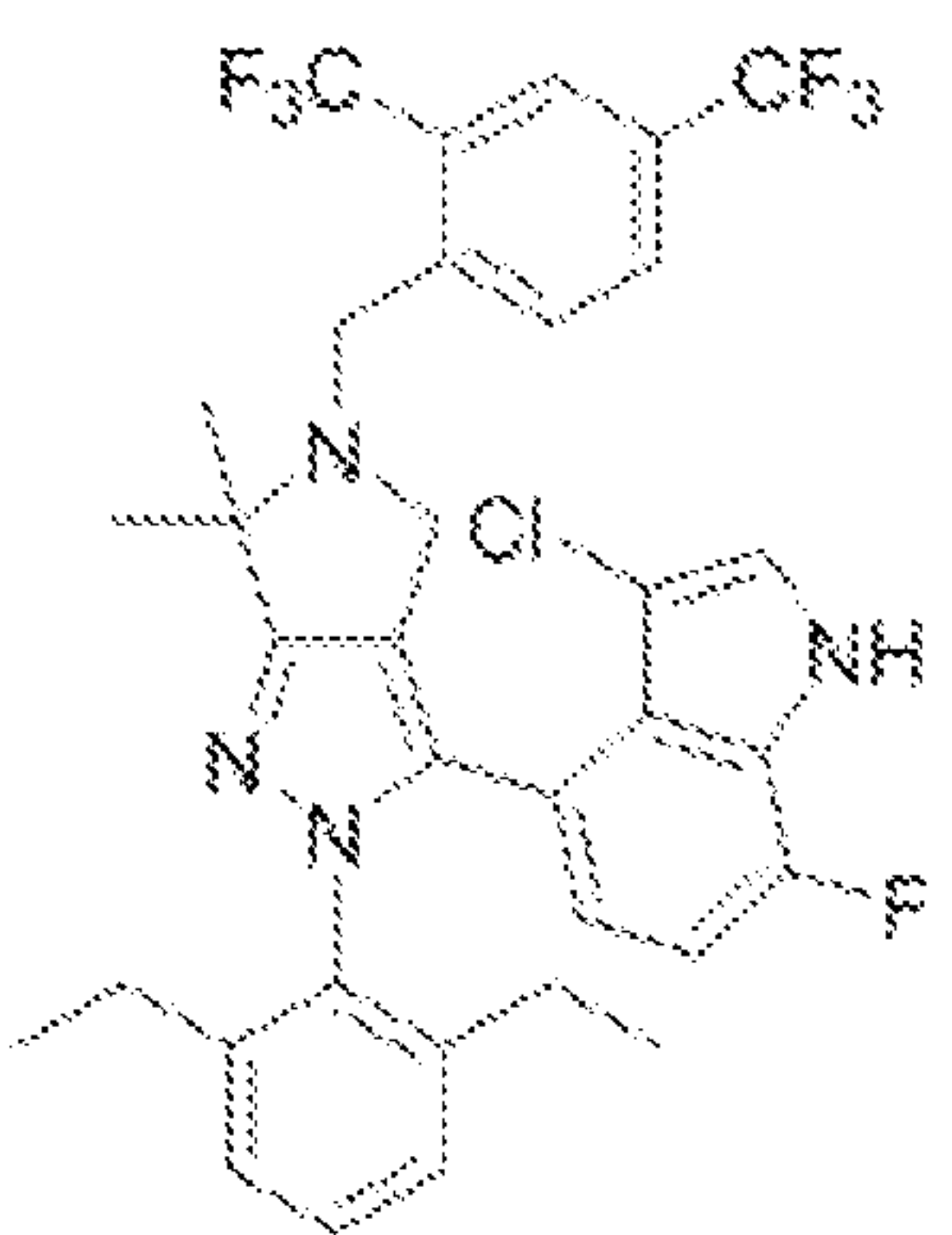
[0150] Step c: To a suspension of *tert*-butyl 2-(2,6-dimethylphenyl)-3-iodo-4,6-dihydropyrrolo[3,4-*c*]pyrazole-5-carboxylate (878 mg, 2 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (729 mg, 3 mmol) and Na₂CO₃ (530 g, 5 mmol) in dioxane (8 mL) and water (2 mL) was added Pd(dppf)Cl₂ complex with dichloromethane (163 mg, 0.2 mmol). The reaction mixture was degassed with N₂ for 2 min and stirred at 90 °C for 2 h. The reaction mixture was diluted with EtOAc and filtered through Celite. The solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography (0 to 100% EtOAc in hexanes) to give *tert*-butyl 2-(2,6-dimethylphenyl)-3-(1*H*-indol-5-yl)-4,6-dihydropyrrolo[3,4-*c*]pyrazole-5-carboxylate. MS: (ES) *m/z* calculated for C₂₆H₂₉N₄O₂ [M + H]⁺ 429.2, found 429.2.

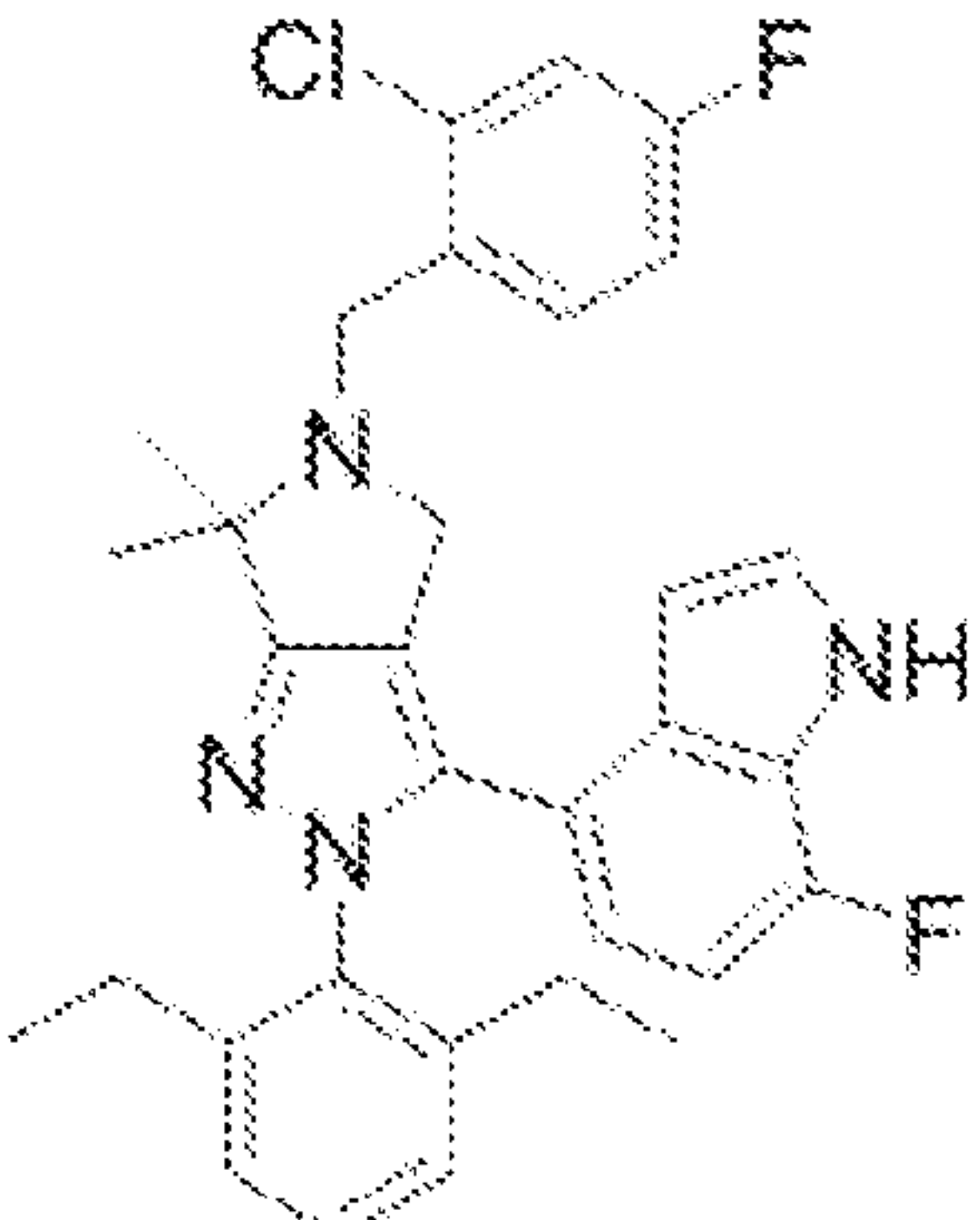
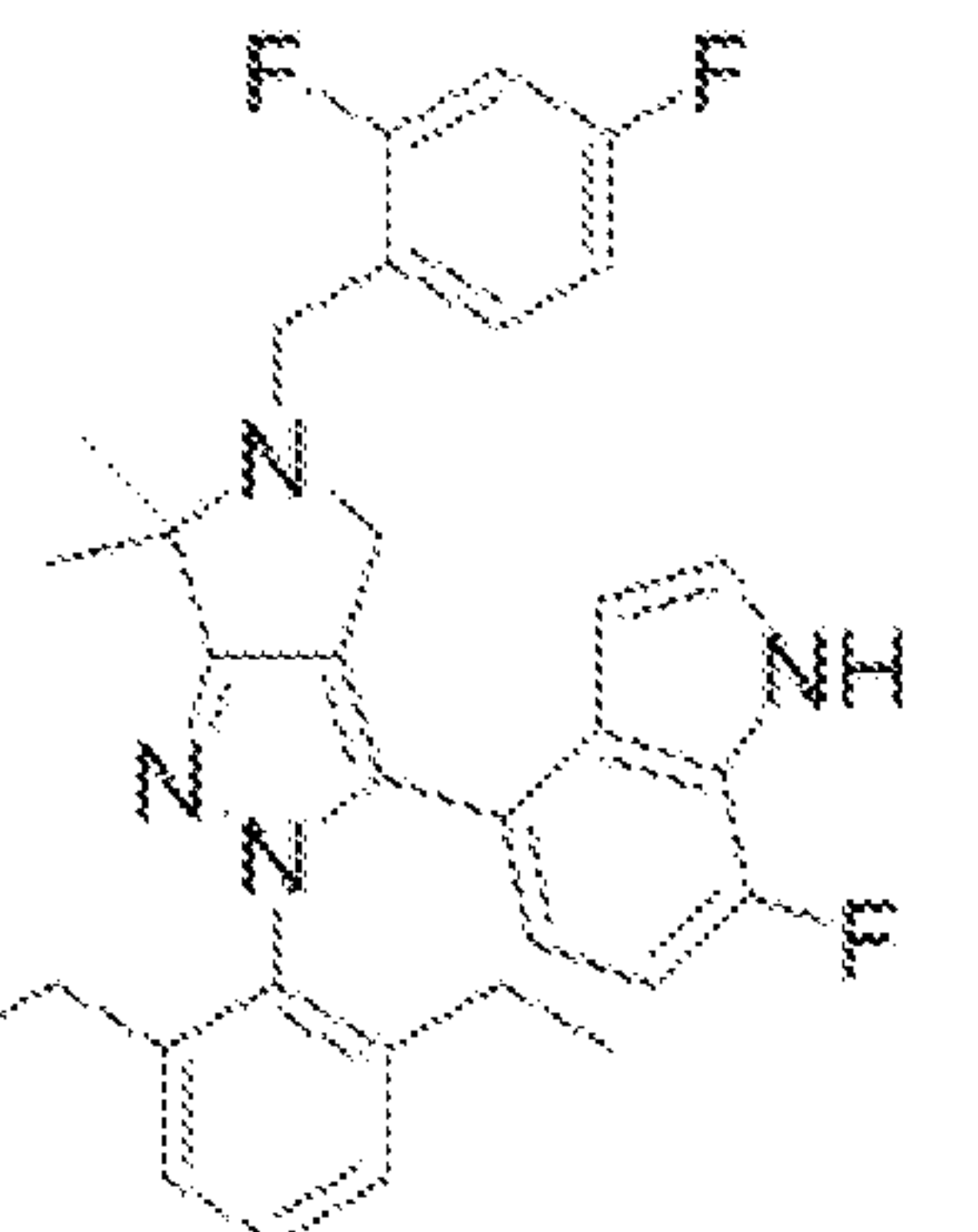
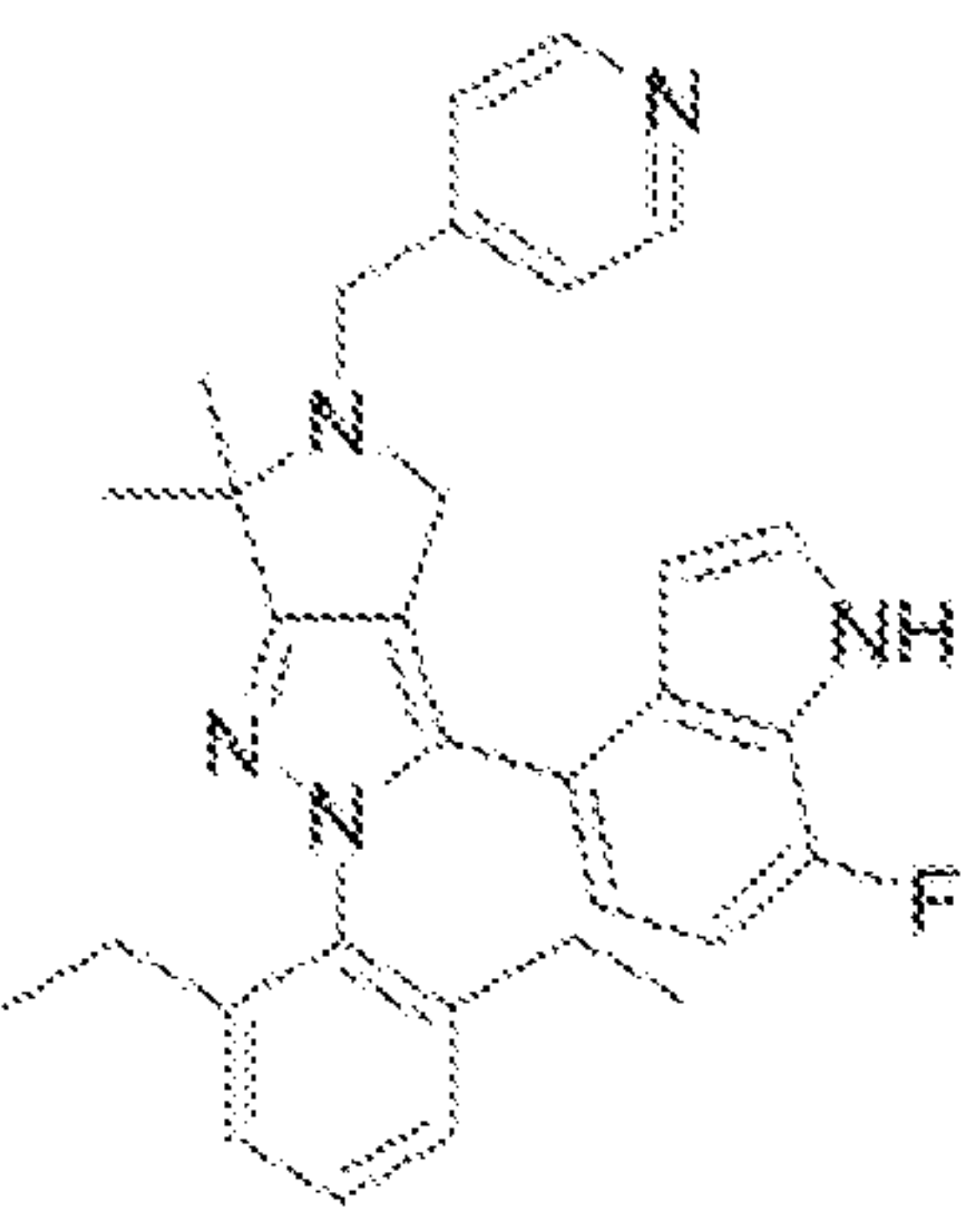
Example 13

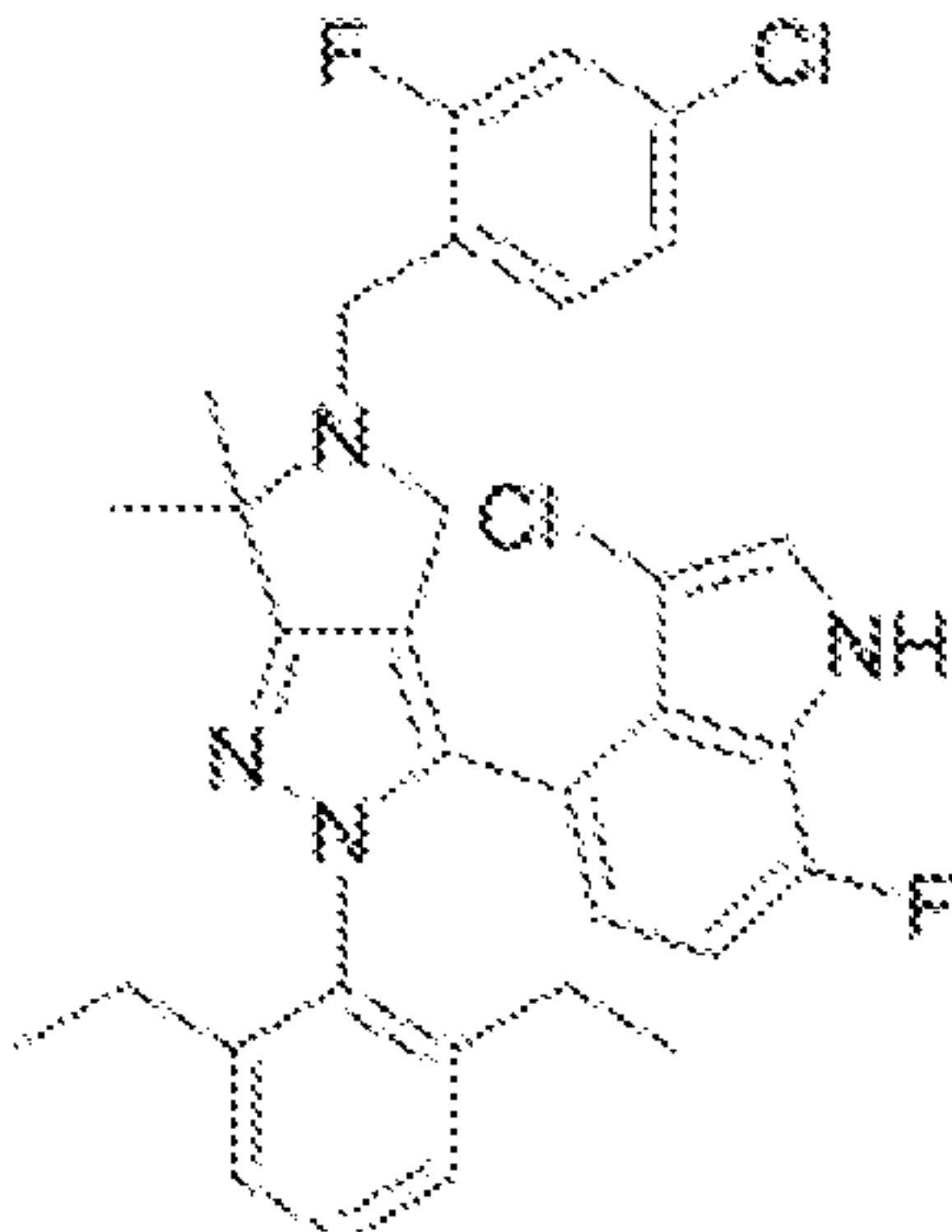
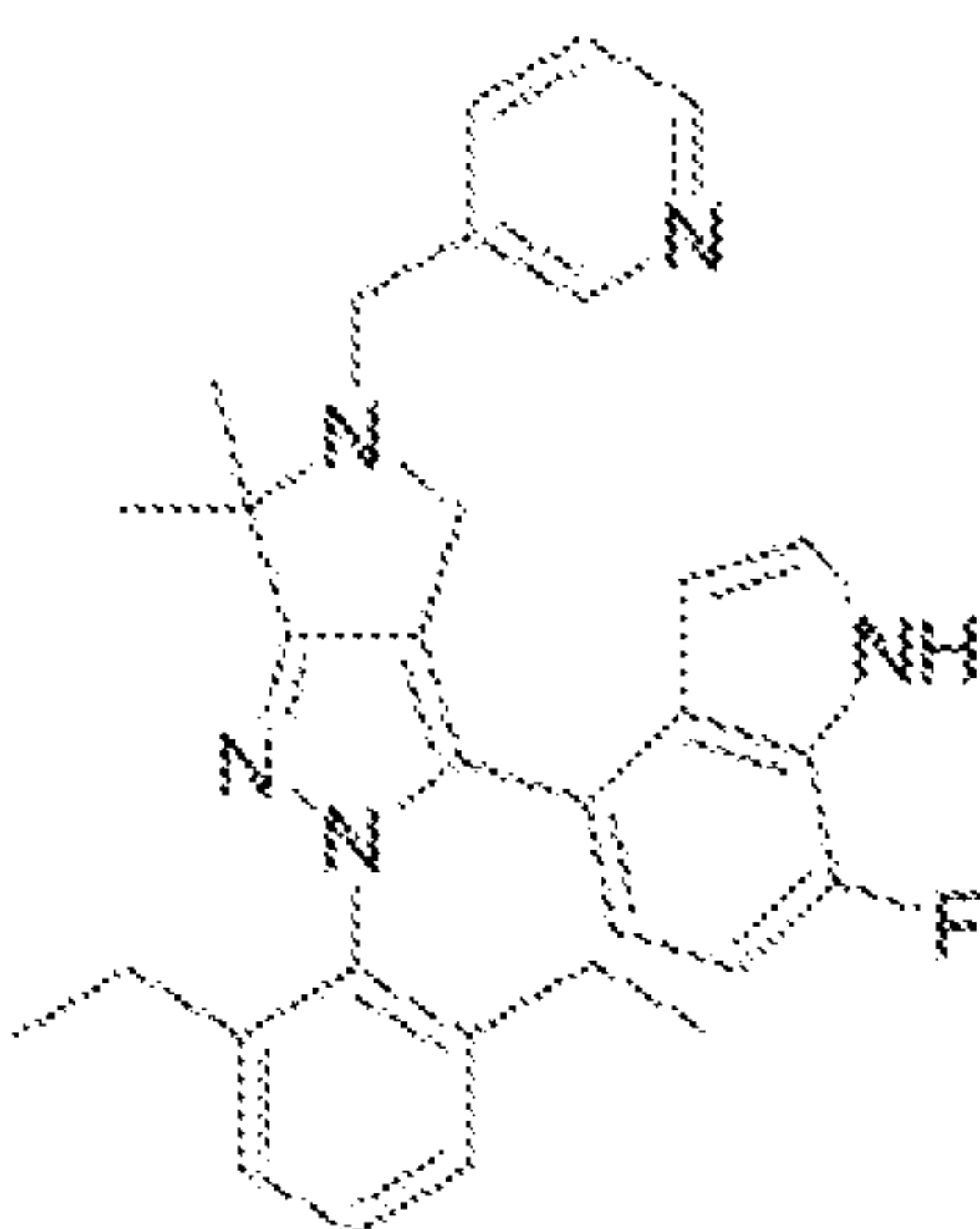
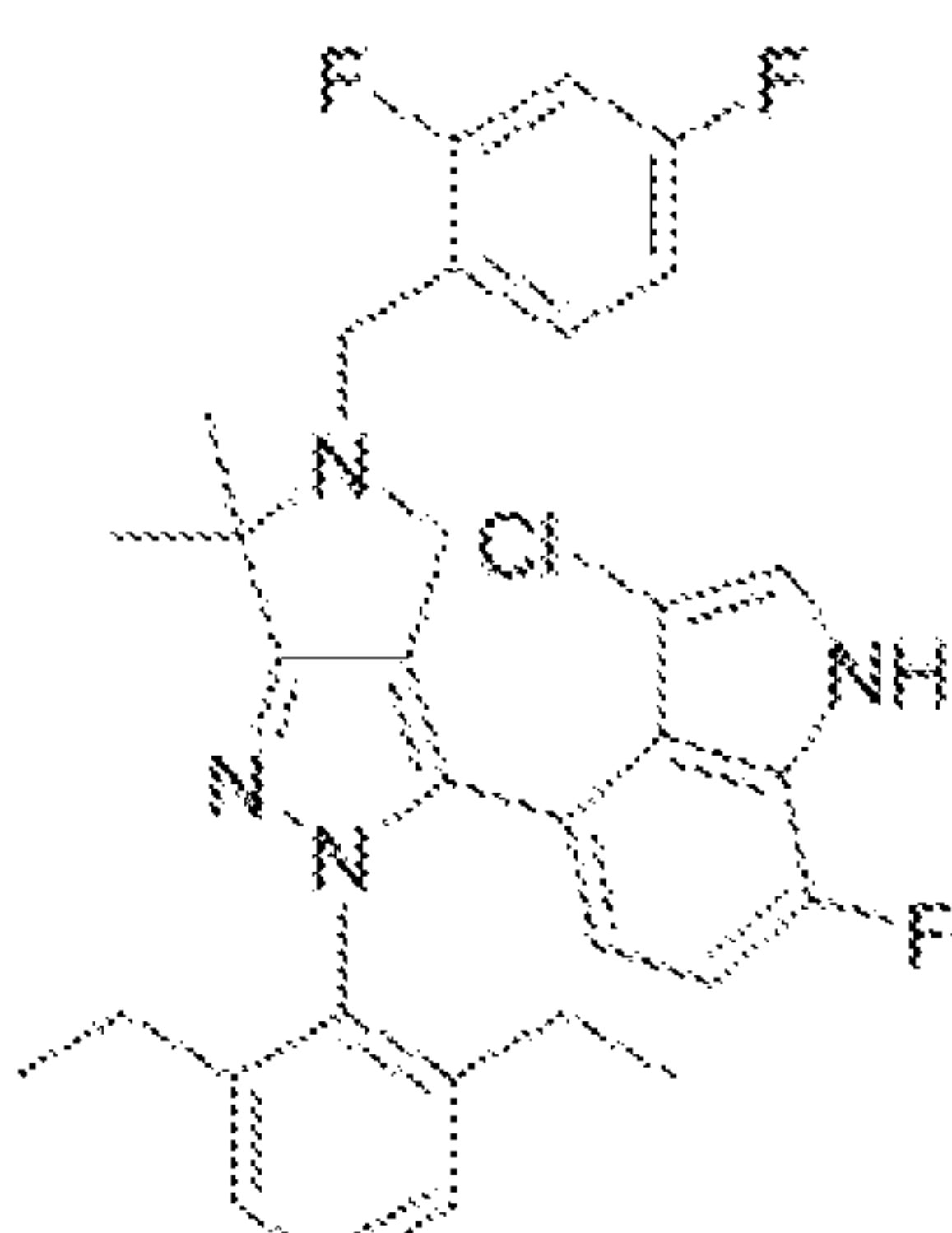
[0151] The compounds in Table 1 and Table 2, below, were prepared using the methods described above. Characterization data (MS and/or NMR) is provided for each compound listed.

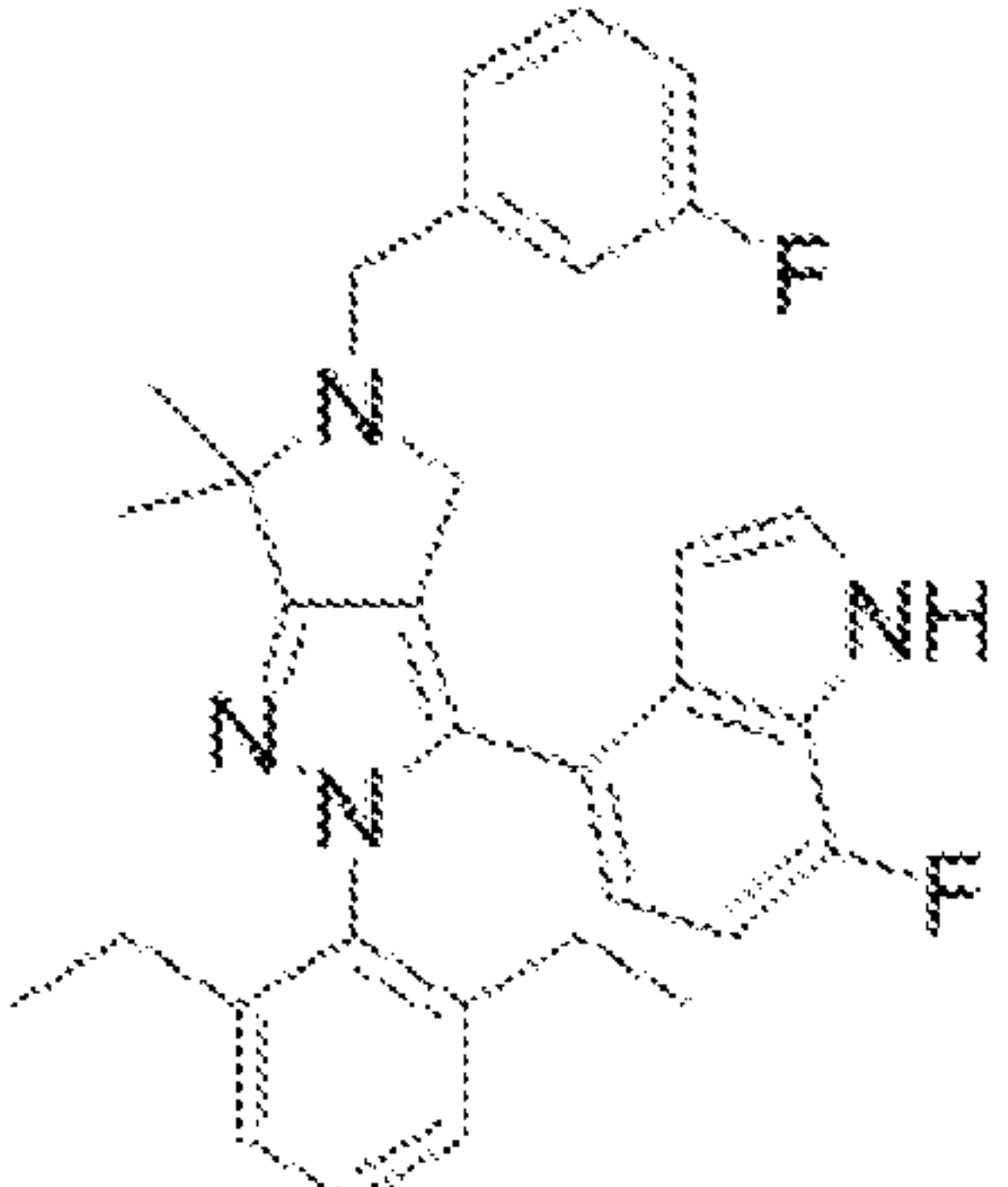
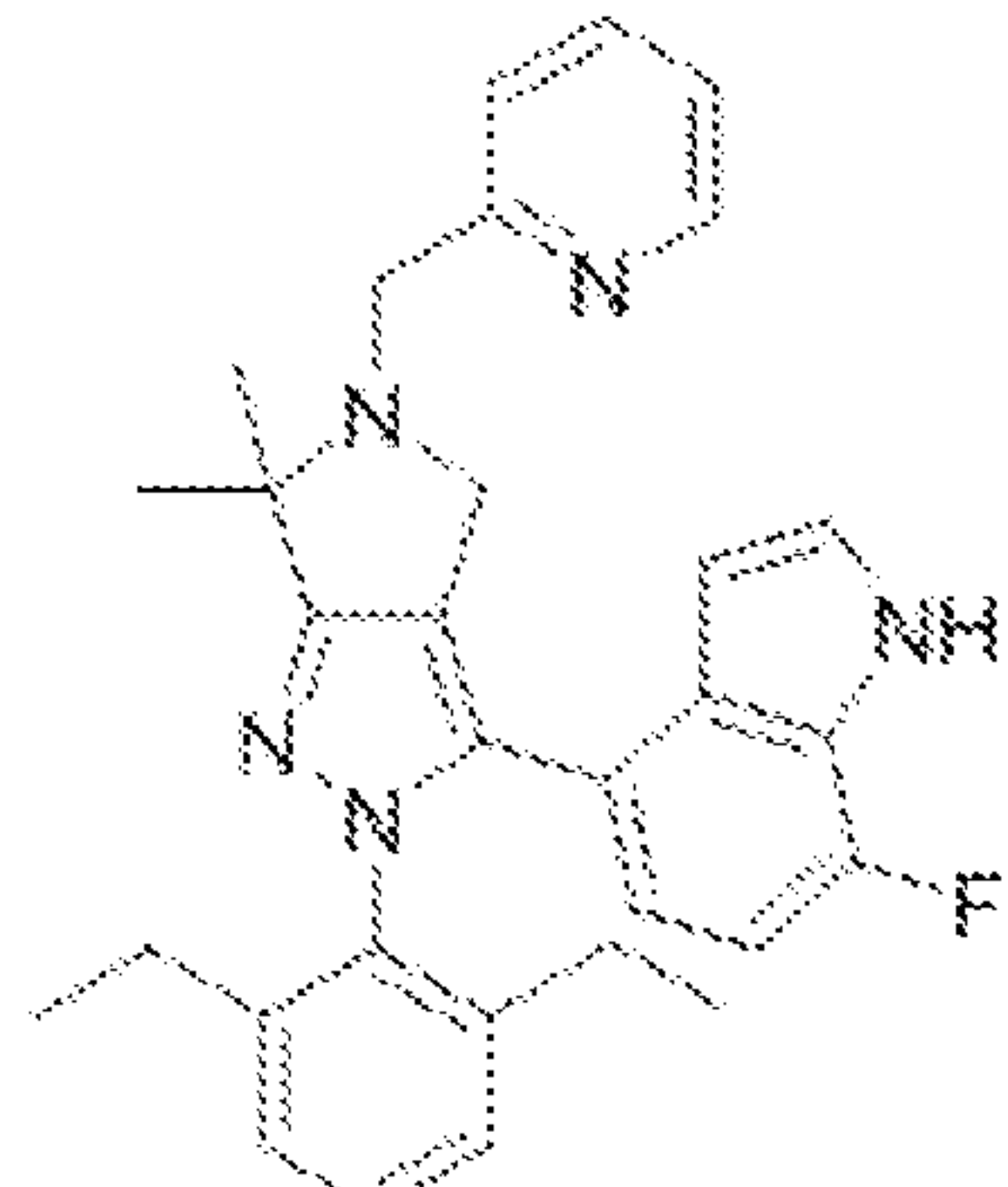
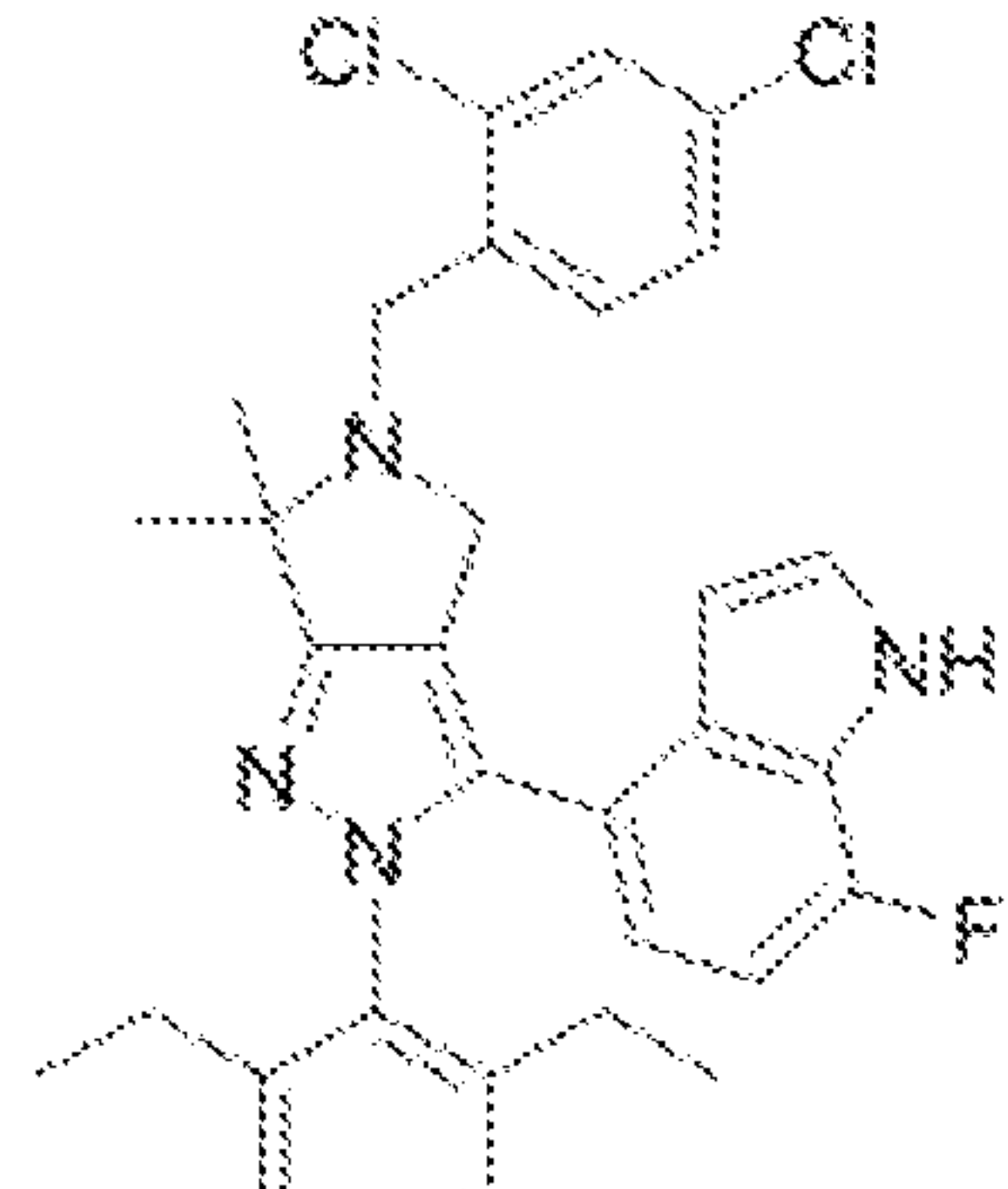
Table 1: Structure & NMR/ MS Characterization Data of Specific Embodiments

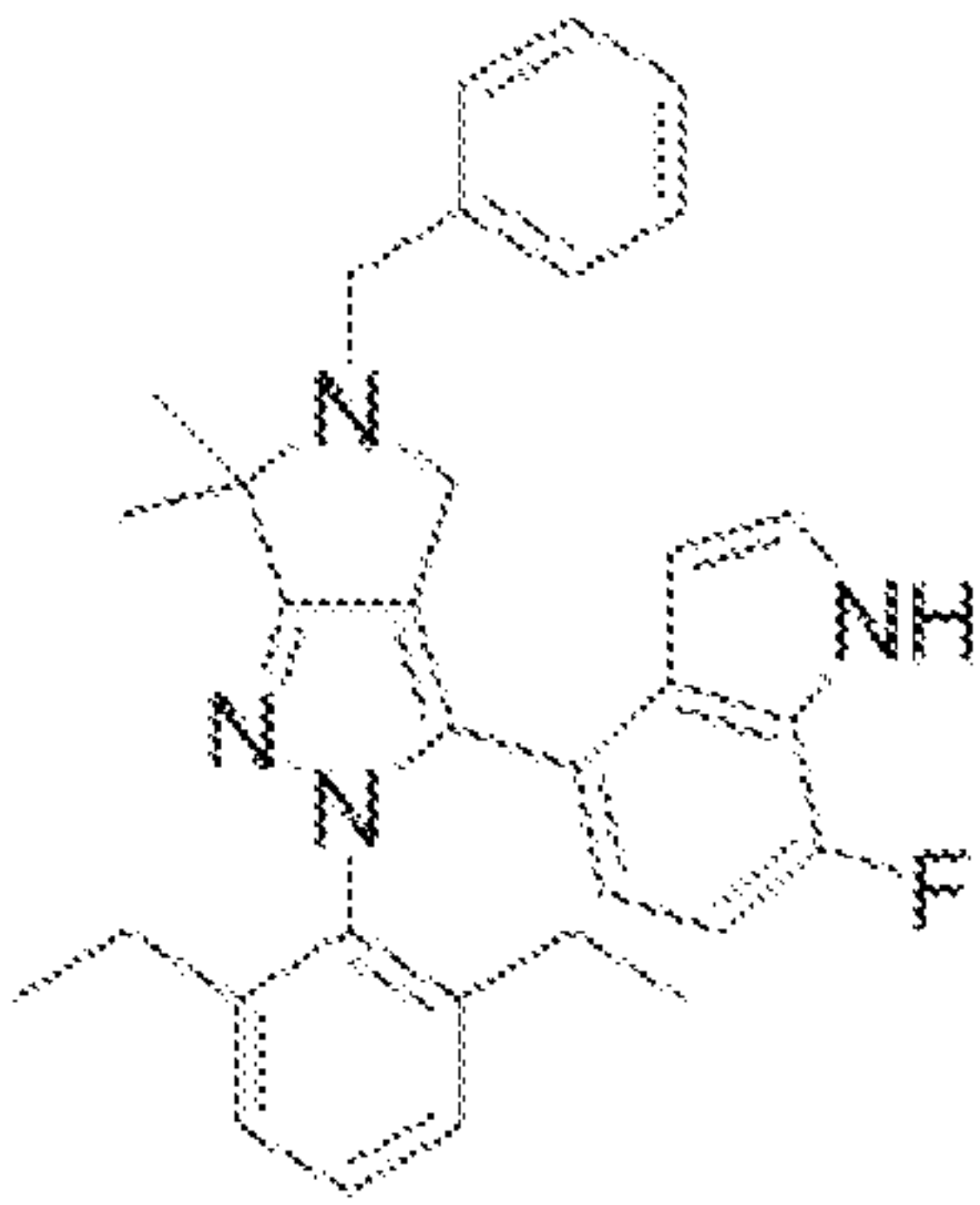
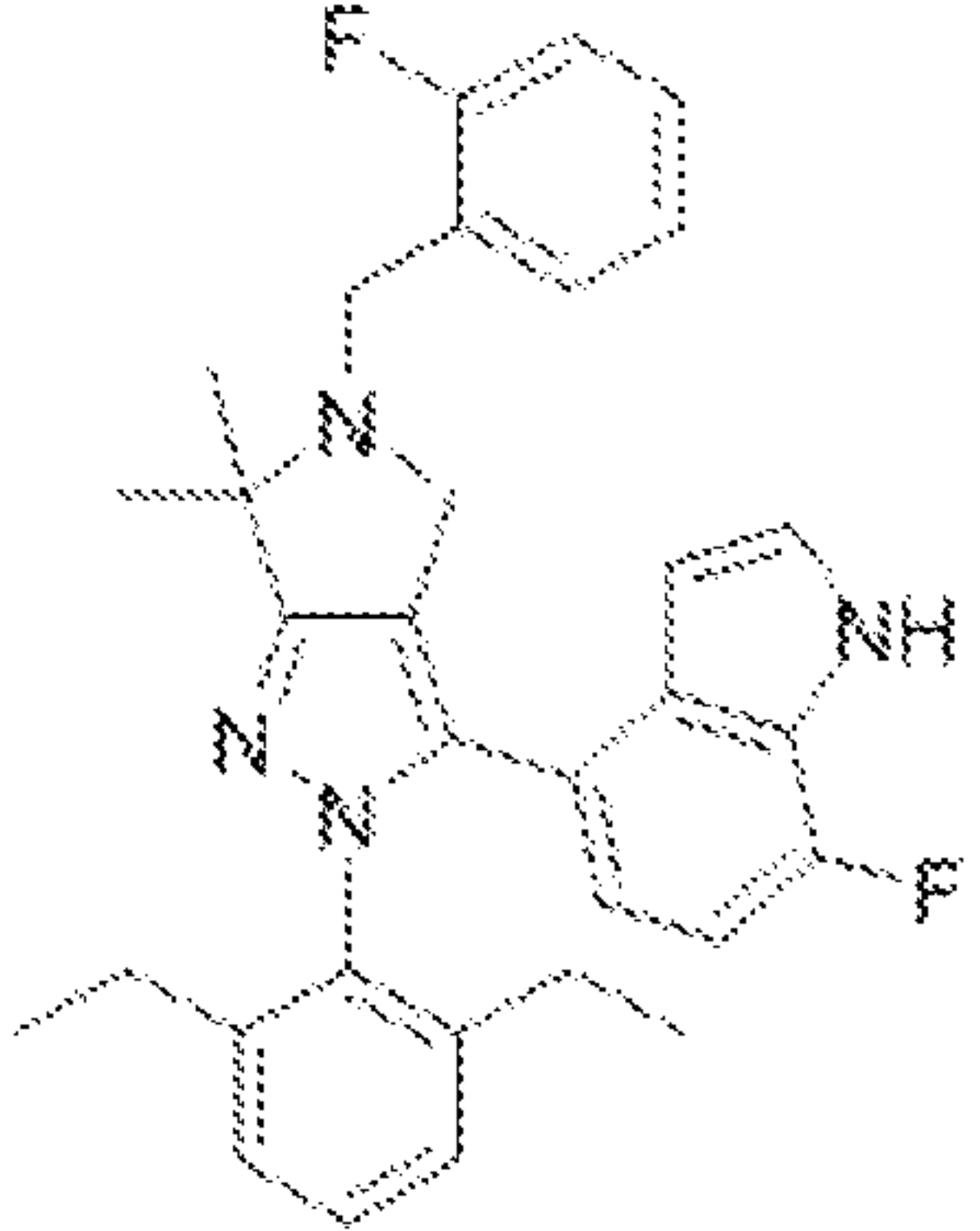
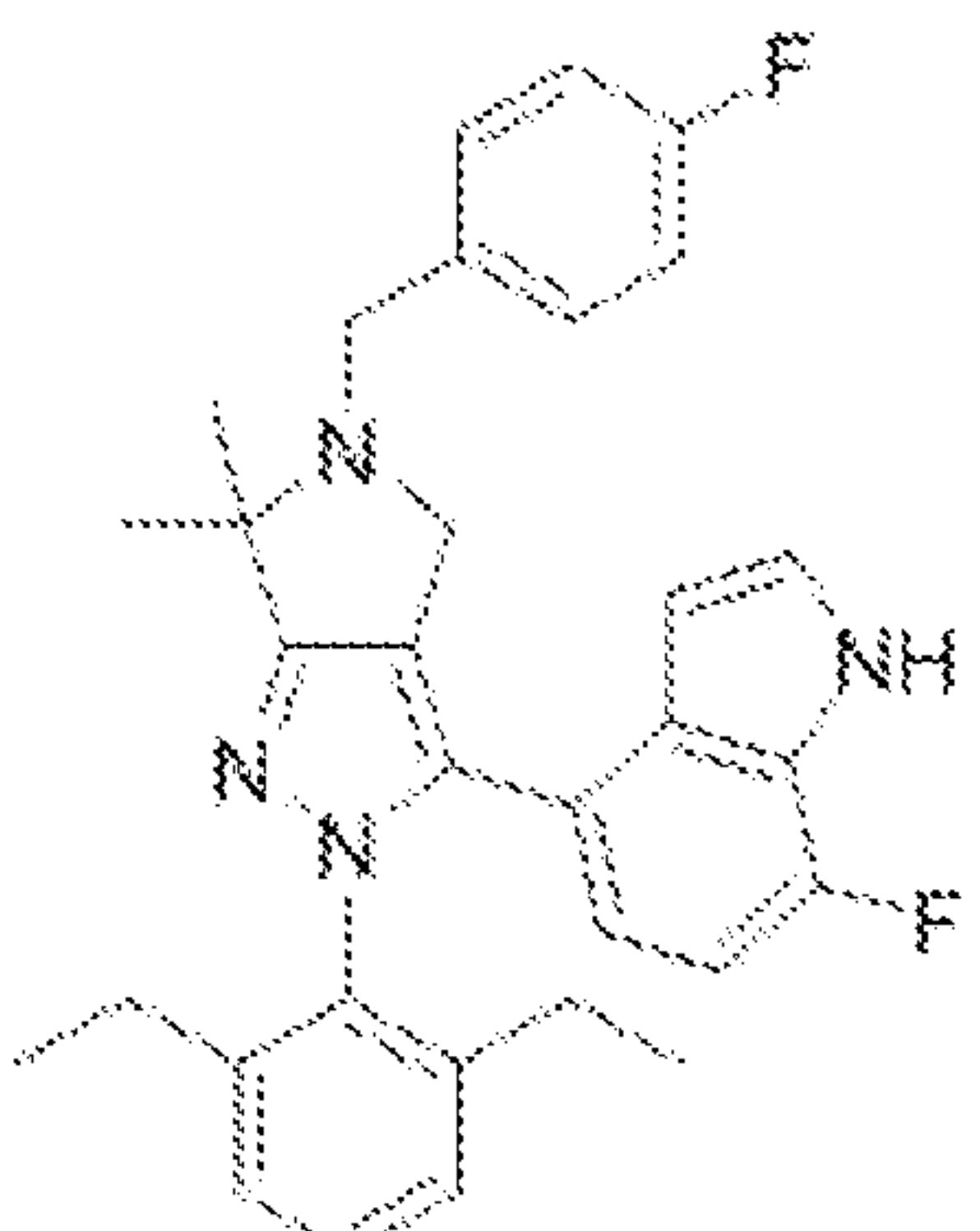
Structure	¹ H NMR	MS
Ex. 13.001 	¹ H NMR (400 MHz, CD ₃ OD) δ 7.44 (d, <i>J</i> = 3.1 Hz, 1H), 7.32 (t, <i>J</i> = 8.0 Hz, 1H), 7.16 (d, <i>J</i> = 7.6 Hz, 2H), 6.59–6.65 (m, 1H), 6.53–6.56 (m, 1H), 6.45–6.50 (m, 1H), 4.72 (s, 2H), 3.88 (s, 2H), 2.19–2.37 (m, 4H), 1.87 (s, 6H), 1.46 (s, 9H), 0.99 (t, <i>J</i> = 7.6 Hz, 6H).	MS: (ES) <i>m/z</i> calculated for C ₃₂ H ₃₉ FN ₅ O ₃ [M + H] ⁺ 560.3, found 560.3.

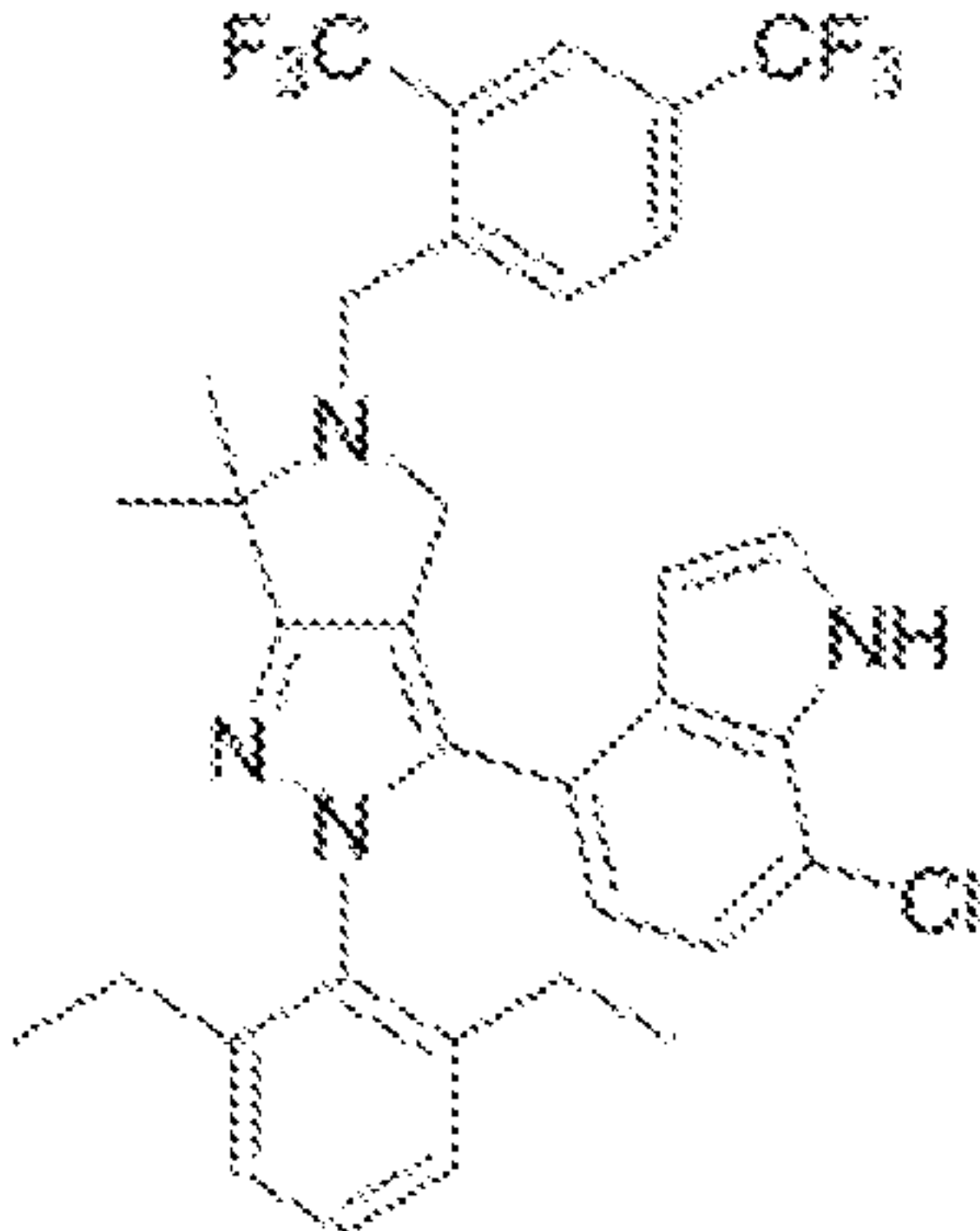
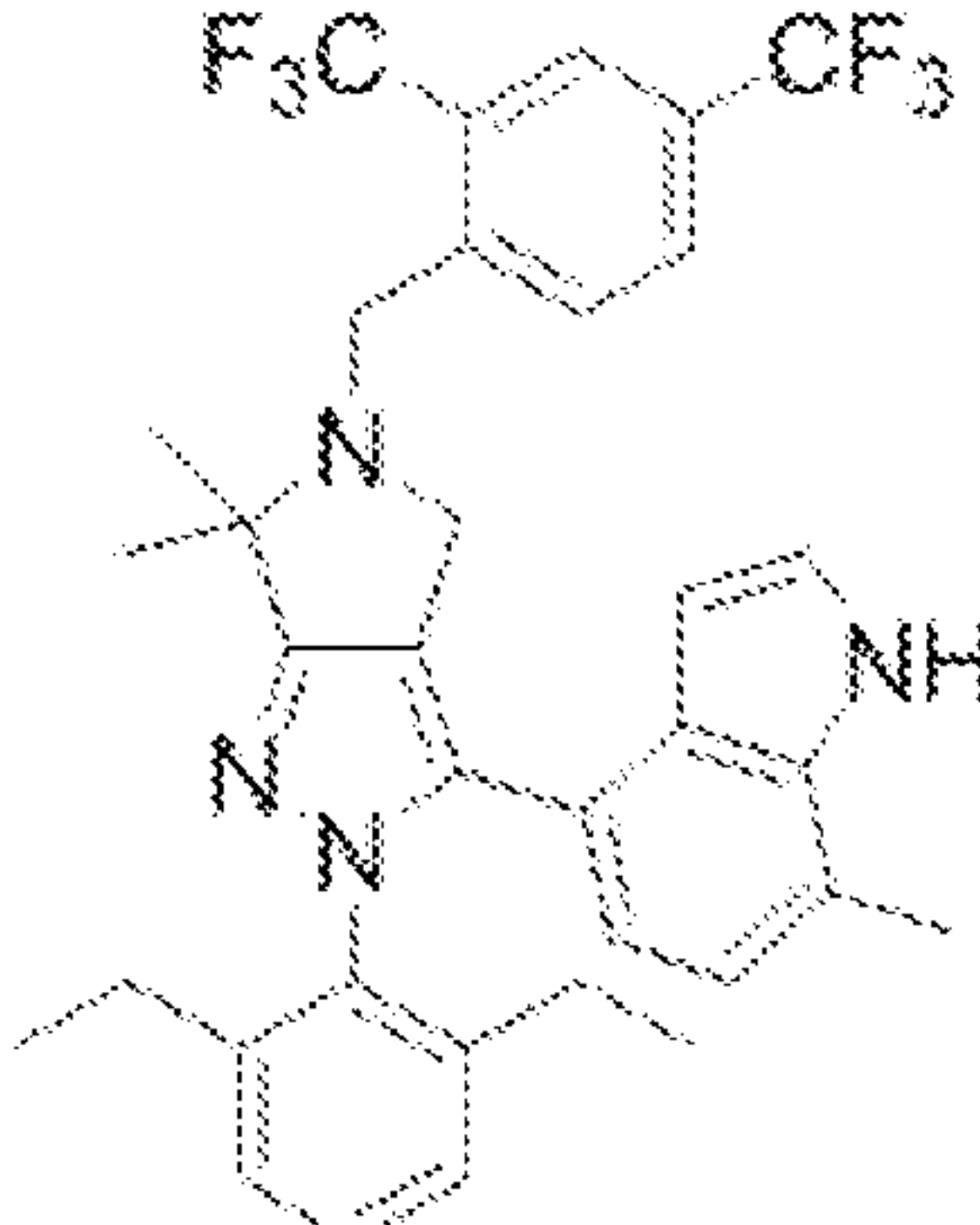
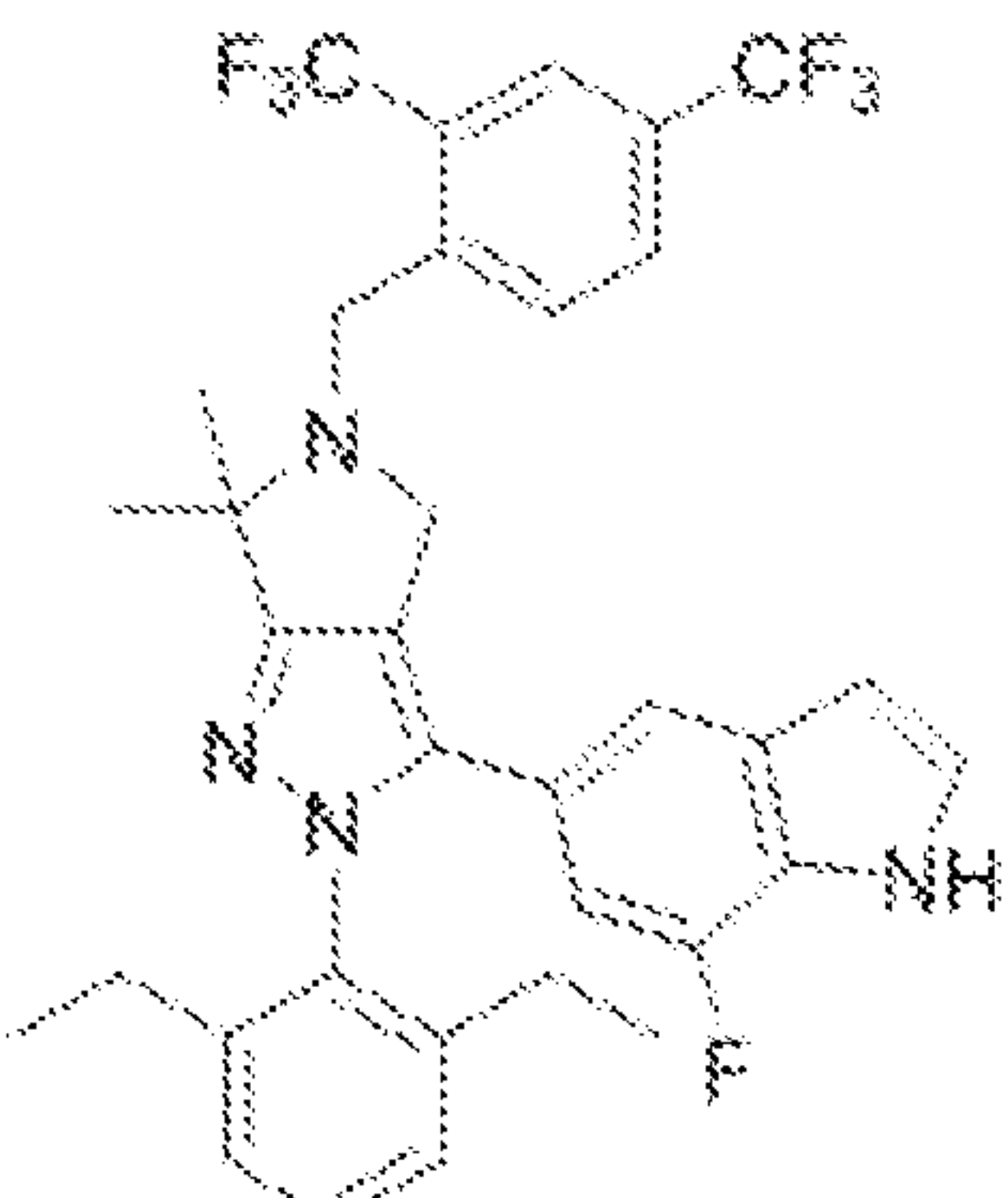
Ex. 13.002 	^1H NMR (400 MHz, CD_3OD) δ 7.89 (br s, 1H), 7.37 (d, J = 3.2 Hz, 1H), 7.31 (t, J = 8.0 Hz, 1H), 7.12–7.15 (m, 3H), 6.54–6.60 (m, 1H), 6.50–6.53 (m, 1H), 6.39–6.43 (m, 1H), 4.12 (s, 2H), 3.90 (s, 2H), 2.15–2.37 (m, 4H), 1.50 (s, 6H), 0.97 (t, J = 7.6 Hz, 6H).	MS: (ES) m/z calculated for $\text{C}_{29}\text{H}_{31}\text{FN}_5\text{O}$ $[\text{M} + \text{H}]^+$ 484.3, found 484.3.
Ex. 13.003 	^1H NMR (400 MHz, CDCl_3) δ 8.53 (s, 1H), 7.27 (dd, J = 2.6, 2.6 Hz, 1H), 7.23 (dd, J = 7.6, 7.6 Hz, 1H), 7.06 (d, J = 7.6, 2H), 6.63 (m, 1H), 6.56 (m, 1H), 6.48 (m, 1H), 3.99 (s, 2H), 2.70 (s, 2H), 2.39 (m, 2H), 2.23 (m, 2H), 1.62 (br s, 1H), 1.43 (s, 6H), 1.25 (s, 6H), 0.99 (t, J = 7.6 Hz, 6H).	MS: (ES) m/z calculated for $\text{C}_{29}\text{H}_{36}\text{FN}_4\text{O}$ $[\text{M} + \text{H}]^+$ 475.3, found 475.3.
Ex. 13.004 	^1H NMR (400 MHz, CD_3OD) δ 8.20–8.27 (m, 1H), 7.89–7.92 (m, 2H), 7.38 (s, 1H), 7.22–7.32 (m, 2H), 6.95–6.98 (m, 1H), 6.66 (dd, J = 8.2, 10.8 Hz, 1H), 6.50 (dd, J = 4.5, 8.2 Hz, 1H), 4.88 (br, 1H), 4.18 (s, 2H), 3.84 (d, J = 11.4 Hz, 1H), 3.49 (d, J = 11.4 Hz, 1H), 2.47 (dq, J = 7.5, 15 Hz, 1H), 2.37–2.46 (m, 2H), 2.07 (dq, J = 7.5, 15 Hz, 1H), 1.54 (s, 3H), 1.52 (s, 3H), 1.33 (t, J = 7.6 Hz, 3H), 0.76 (t, J = 7.6 Hz, 3H).	MS: (ES) m/z calculated for $\text{C}_{34}\text{H}_{31}\text{ClF}_7\text{N}_4$ $[\text{M} + \text{H}]^+$ 663.2, found 663.2.

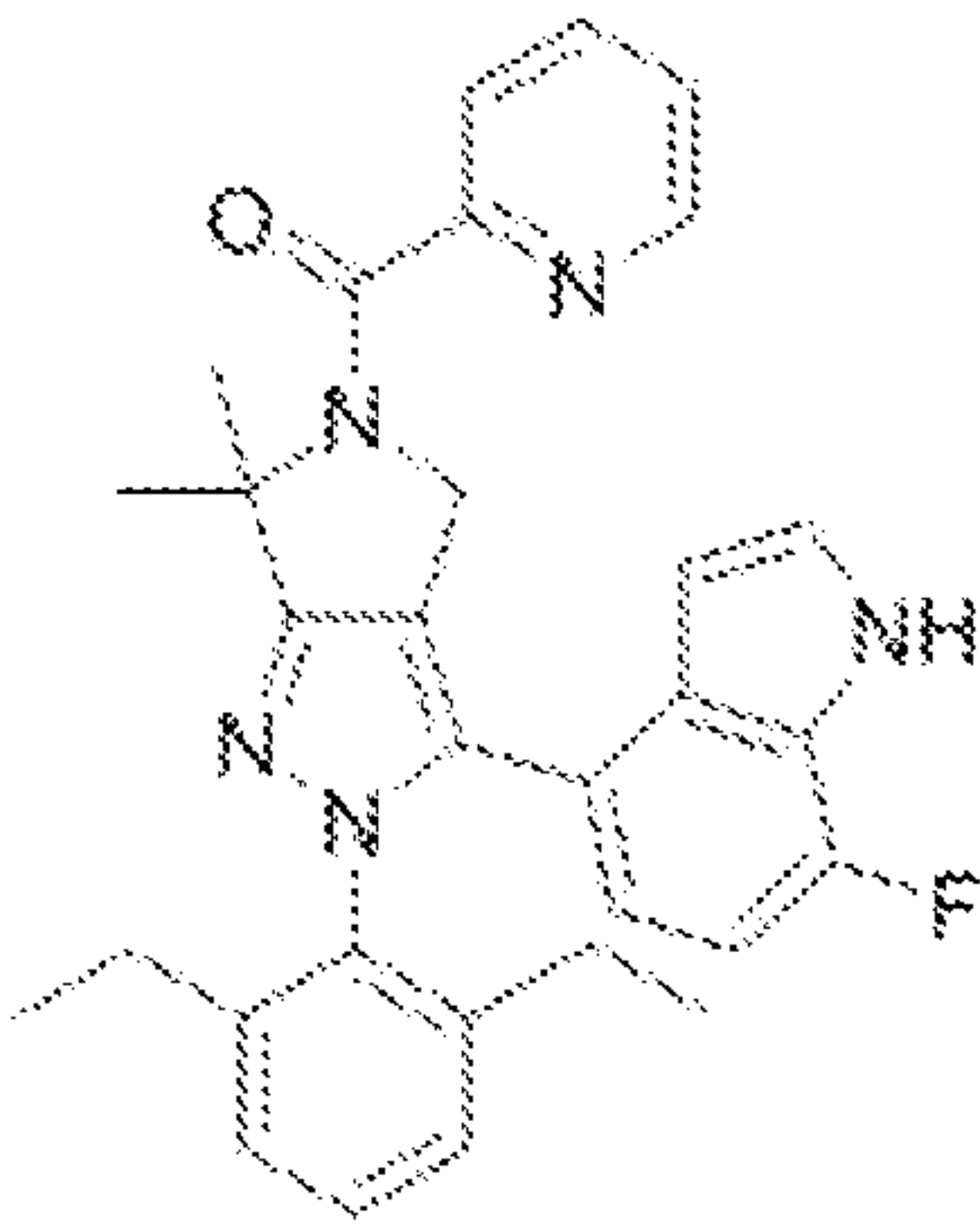
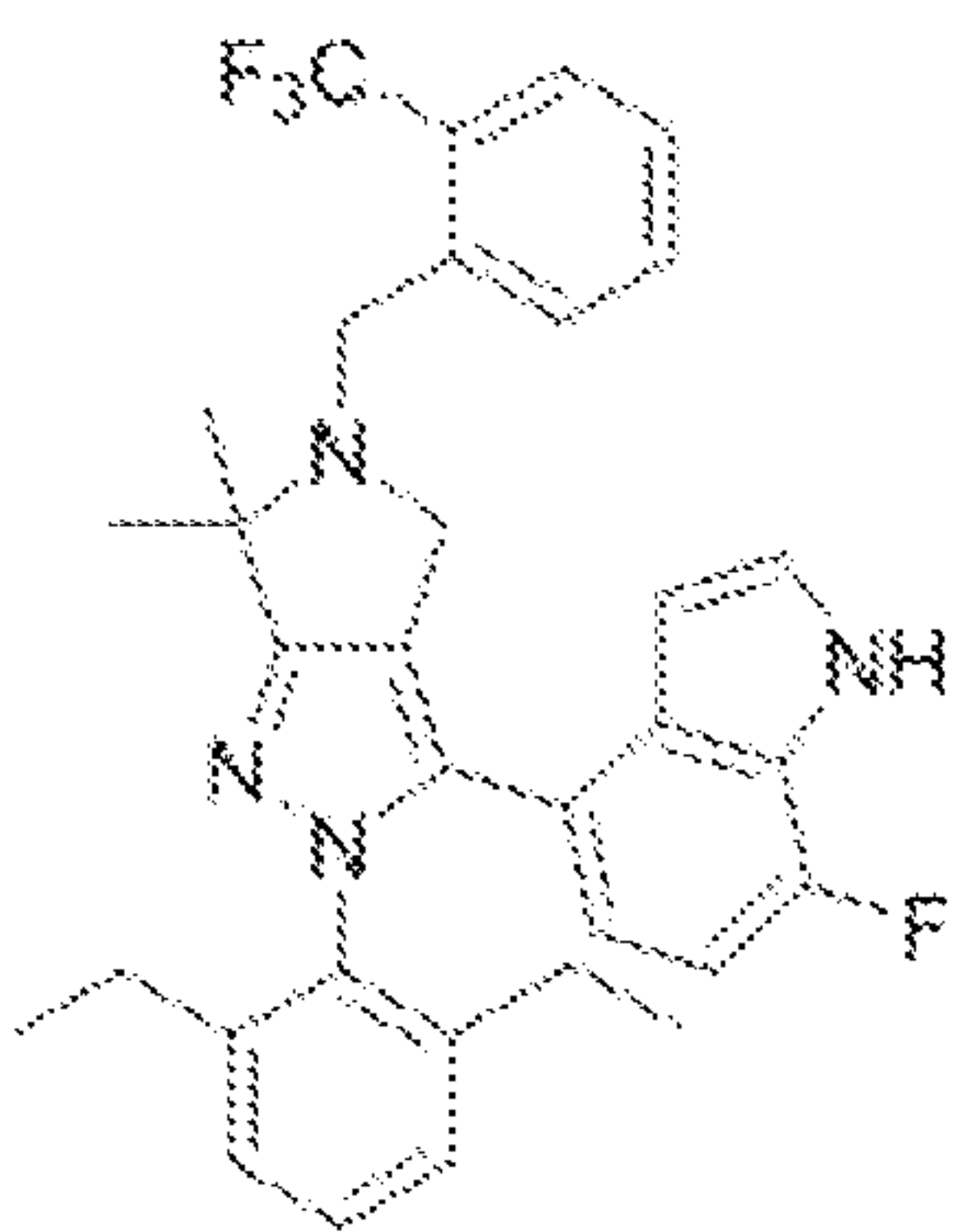
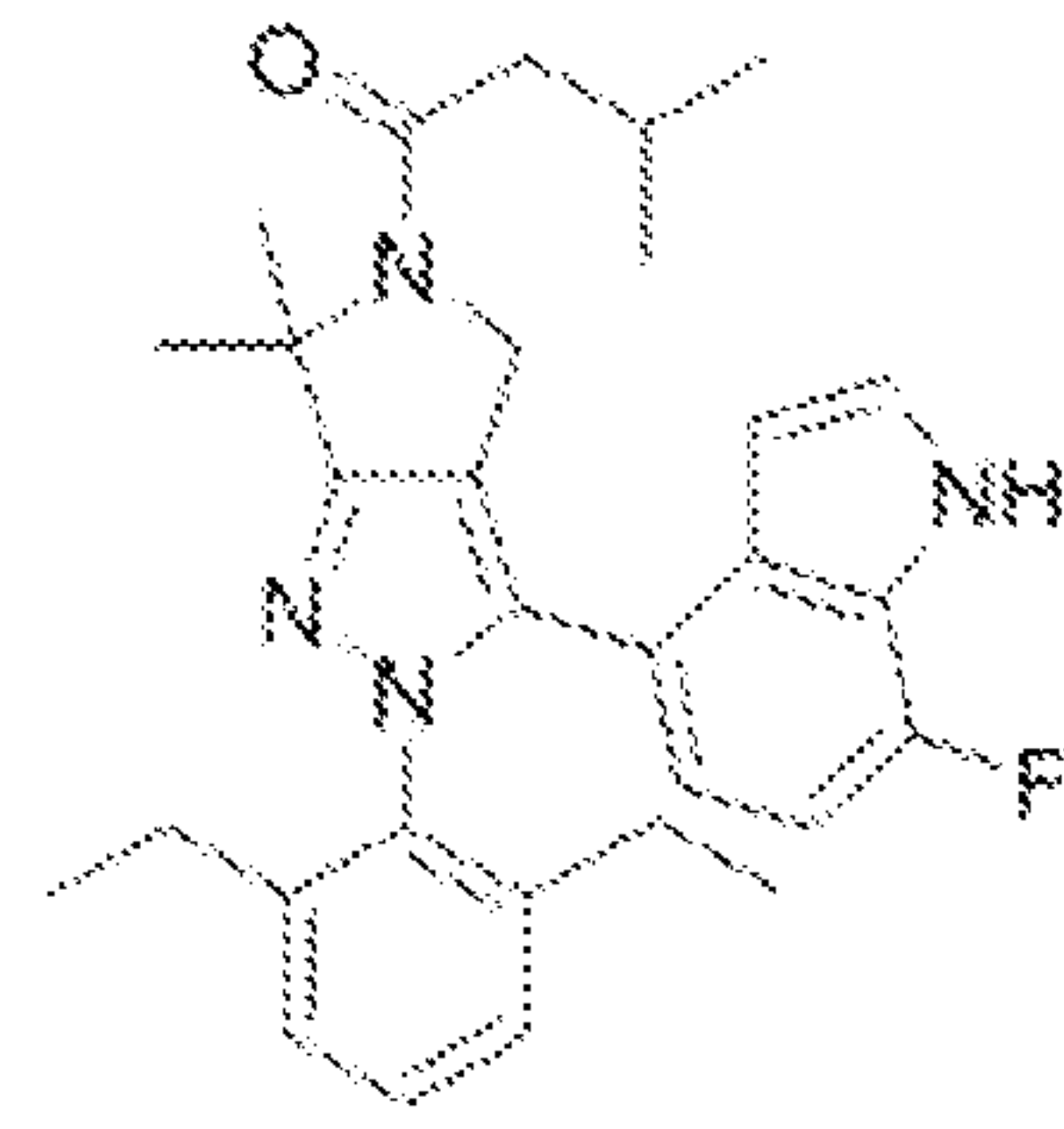
Ex. 13.005 	¹H NMR (400 MHz, CD₃OD) δ 7.56–7.61 (m, 1H), 7.34 (d, <i>J</i> = 3.0 Hz, 1H), 7.30 (t, <i>J</i> = 7.6 Hz, 1H), 7.18–7.22 (m, 1H), 7.14 (d, <i>J</i> = 8.0 Hz, 2H), 7.01–7.07 (m, 1H), 6.53–6.58 (m, 1H), 6.45 (t, <i>J</i> = 3.1 Hz, 1H), 6.38–6.42 (m, 1H), 4.04 (s, 2H), 3.73 (s, 2H), 2.15–2.38 (m, 4H), 1.57 (s, 6H), 0.98 (t, <i>J</i> = 7.2 Hz, 6H).	MS: (ES) <i>m/z</i> calculated for C₃₂H₃₂ClF₂N₄ [M + H]⁺ 545.2, found 545.2.
Ex. 13.006 	¹H NMR (400 MHz, CD₃OD) δ 7.50 (m, 1H), 7.37 – 7.26 (m, 2H), 7.14 (d, <i>J</i> = 7.7 Hz, 2H), 6.91 (t, <i>J</i> = 8.7 Hz, 2H), 6.55 (dd, <i>J</i> = 10.9, 8.2 Hz, 1H), 6.48 – 6.36 (m, 2H), 3.96 (s, 2H), 3.73 (s, 2H), 2.26 (m, 4H), 1.56 (s, 6H), 0.97 (t, <i>J</i> = 7.6 Hz, 6H).	MS: (ES) <i>m/z</i> calculated for C₃₂H₃₂F₃N₄ [M + H]⁺ 529.3, found 529.3.
Ex. 13.007 	¹H NMR TFA salt (400 MHz, CD₃OD) δ 11.41 (s, 1H), 8.75 (d, <i>J</i> = 5.6 Hz, 2H), 7.94 (d, <i>J</i> = 6.4 Hz, 2H), 7.39 (dd, <i>J</i> = 2.6, 2.6 Hz, 1H), 7.34 (dd, <i>J</i> = 7.6, 7.6 Hz, 1H), 7.16 (d, <i>J</i> = 7.6 Hz, 2H), 6.60 (m, 1H), 6.45 (m, 2H), 4.67 (s, 2H), 4.39 (s, 2H), 2.25 (m, 4H), 1.88 (s, 6H), 0.98 (t, <i>J</i> = 7.6 Hz, 6H).	MS: (ES) <i>m/z</i> calculated for C₃₁H₃₃FN₅ [M + H]⁺ 494.3, found 494.3.

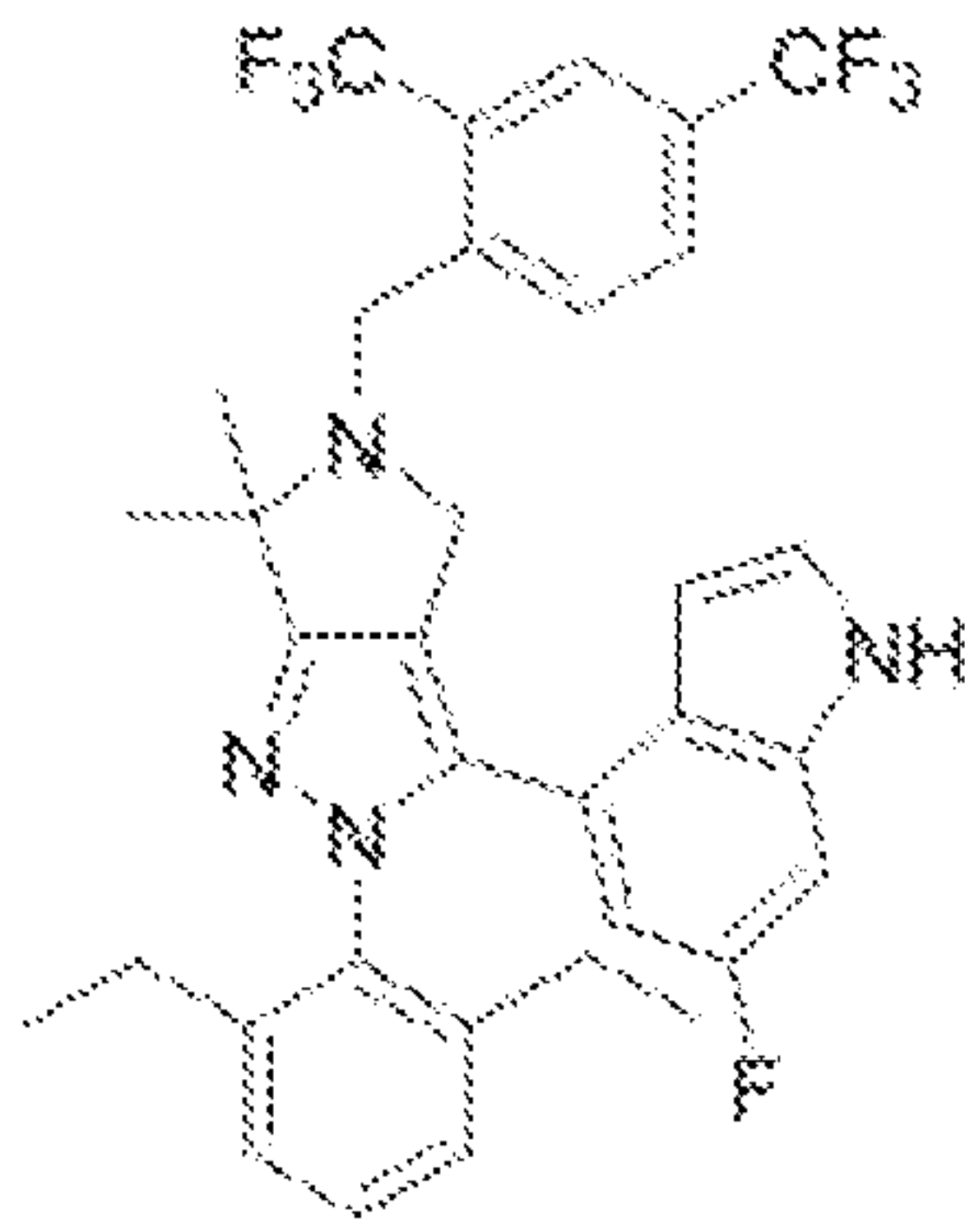
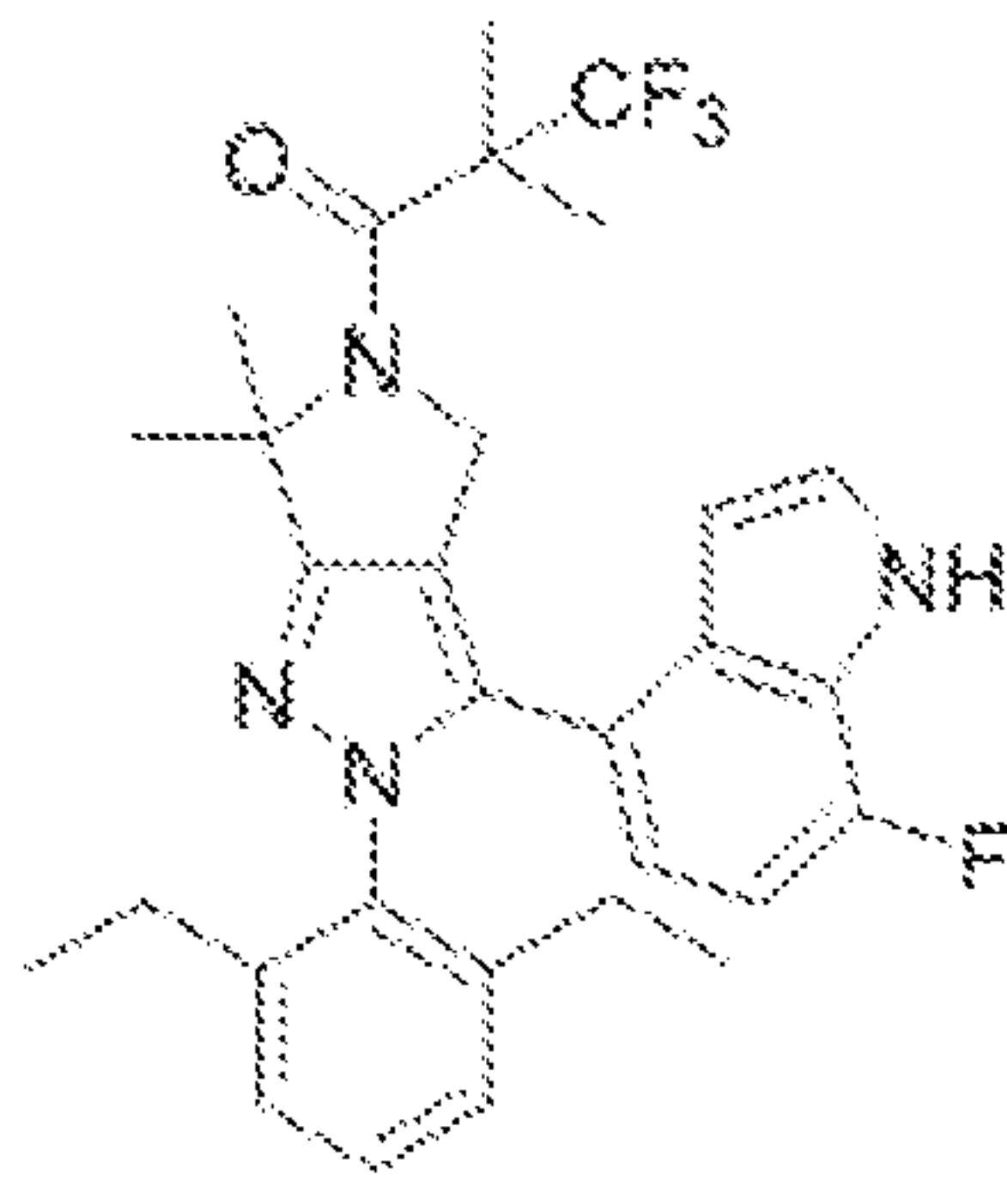
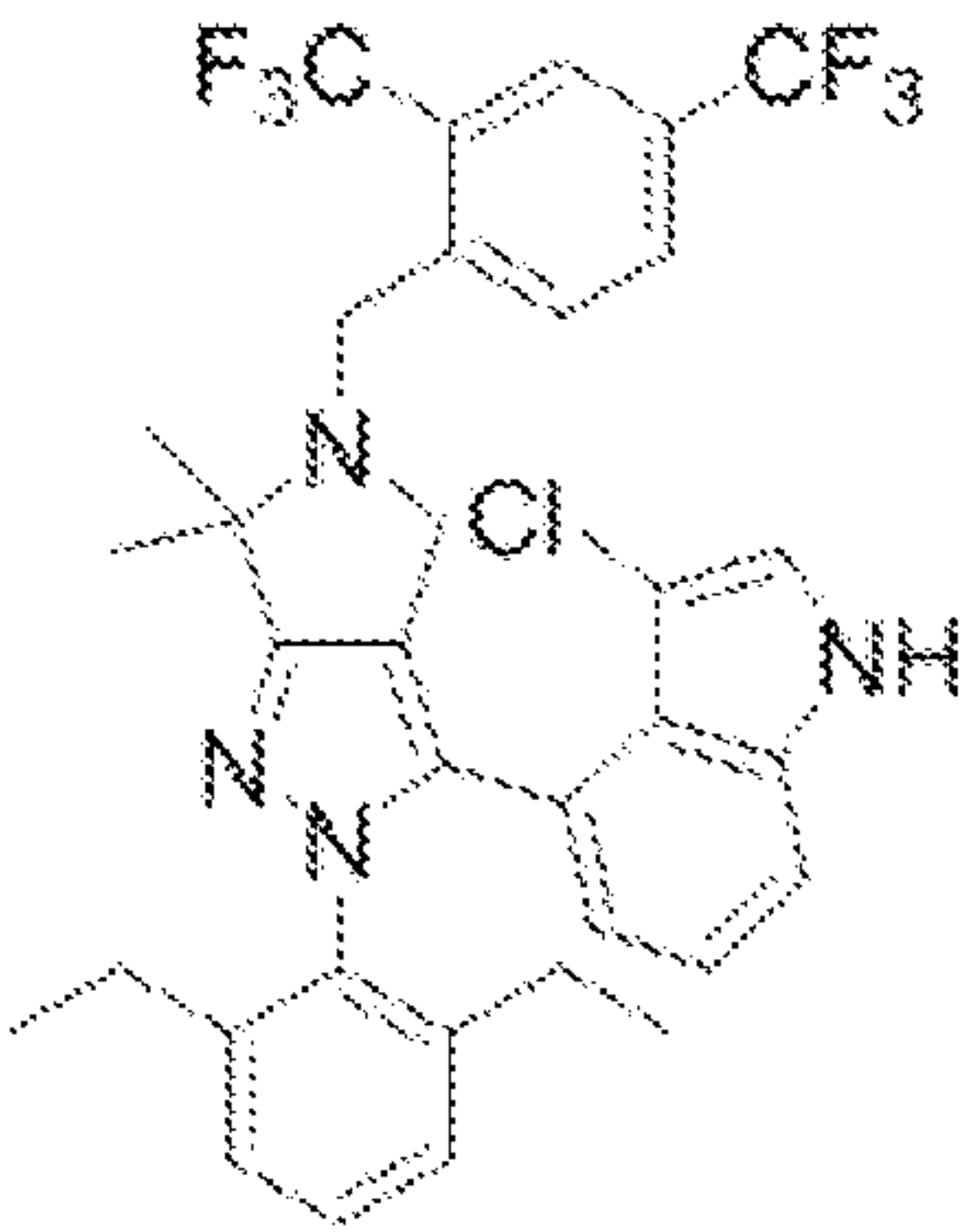
Ex. 13.008 	¹H NMR (400 MHz, CD₃OD) δ 7.47–7.57 (m, 1H), 7.39 (s, 1H), 7.23–7.28 (m, 2H), 7.12–7.16 (m, 2H), 6.95–6.98 (m, 1H), 6.66 (dd, <i>J</i> = 8.2, 10.8 Hz, 1H), 6.50 (dd, <i>J</i> = 4.5, 8.2 Hz, 1H), 4.88 (br, 1H), 4.00 (d, <i>J</i> = 11.4 Hz, 1H), 3.81–3.90 (m, 2H), 3.50 (d, <i>J</i> = 11.4 Hz, 1H), 2.33–2.46 (m, 3H), 2.00–2.13 (m, 1H), 1.56 (s, 3H), 1.49 (s, 3H), 1.31 (t, <i>J</i> = 7.6 Hz, 3H), 0.75 (t, <i>J</i> = 7.6 Hz, 3H).	MS: (ES) <i>m/z</i> calculated for C₃₂H₃₁Cl₂F₂N₄ [M + H]⁺ 579.2, found 579.2.
Ex. 13.009 	¹H NMR TFA salt (400 MHz, CD₃OD) δ 11.46 (s, 1H), 8.87 (d, <i>J</i> = 1.0 Hz, 1H), 8.71 (d, <i>J</i> = 5.2 Hz, 1H), 8.26 (d, <i>J</i> = 7.6 Hz, 1H), 7.68 (m, 1H), 7.41 (dd, <i>J</i> = 2.8, 2.8 Hz, 1H), 7.35 (dd, <i>J</i> = 7.8, 7.8 Hz, 1H), 7.18 (d, <i>J</i> = 8.0 Hz, 2H), 6.61 (m, 1H), 6.45 (m, 2H), 4.75 (s, 2H), 4.53 (s, 2H), 2.25 (m, 4H), 1.97 (s, 6H), 0.97 (t, <i>J</i> = 7.6 Hz, 6H).	MS: (ES) <i>m/z</i> calculated for C₃₁H₃₃FN₅ [M + H]⁺ 494.3, found 494.3.
Ex. 13.010 	¹H NMR (400 MHz, CD₃OD) δ 7.46–7.52 (m, 1H), 7.39 (s, 1H), 7.23–7.28 (m, 2H), 6.82–7.00 (m, 3H), 6.66 (dd, <i>J</i> = 8.2, 10.8 Hz, 1H), 6.50 (dd, <i>J</i> = 4.5, 8.2 Hz, 1H), 4.88 (br, 1H), 4.00 (d, <i>J</i> = 11.6 Hz, 1H), 3.81–3.90 (m, 2H), 3.50 (d, <i>J</i> = 11.6 Hz, 1H), 2.30–2.58 (m, 3H), 2.00–2.12 (m, 1H), 1.57 (s, 3H), 1.49 (s, 3H), 1.31 (t, <i>J</i> = 7.6 Hz, 3H), 0.75 (t, <i>J</i> = 7.6 Hz, 3H).	MS: (ES) <i>m/z</i> calculated for C₃₂H₃₁ClF₃N₄ [M + H]⁺ 563.2, found 563.2.

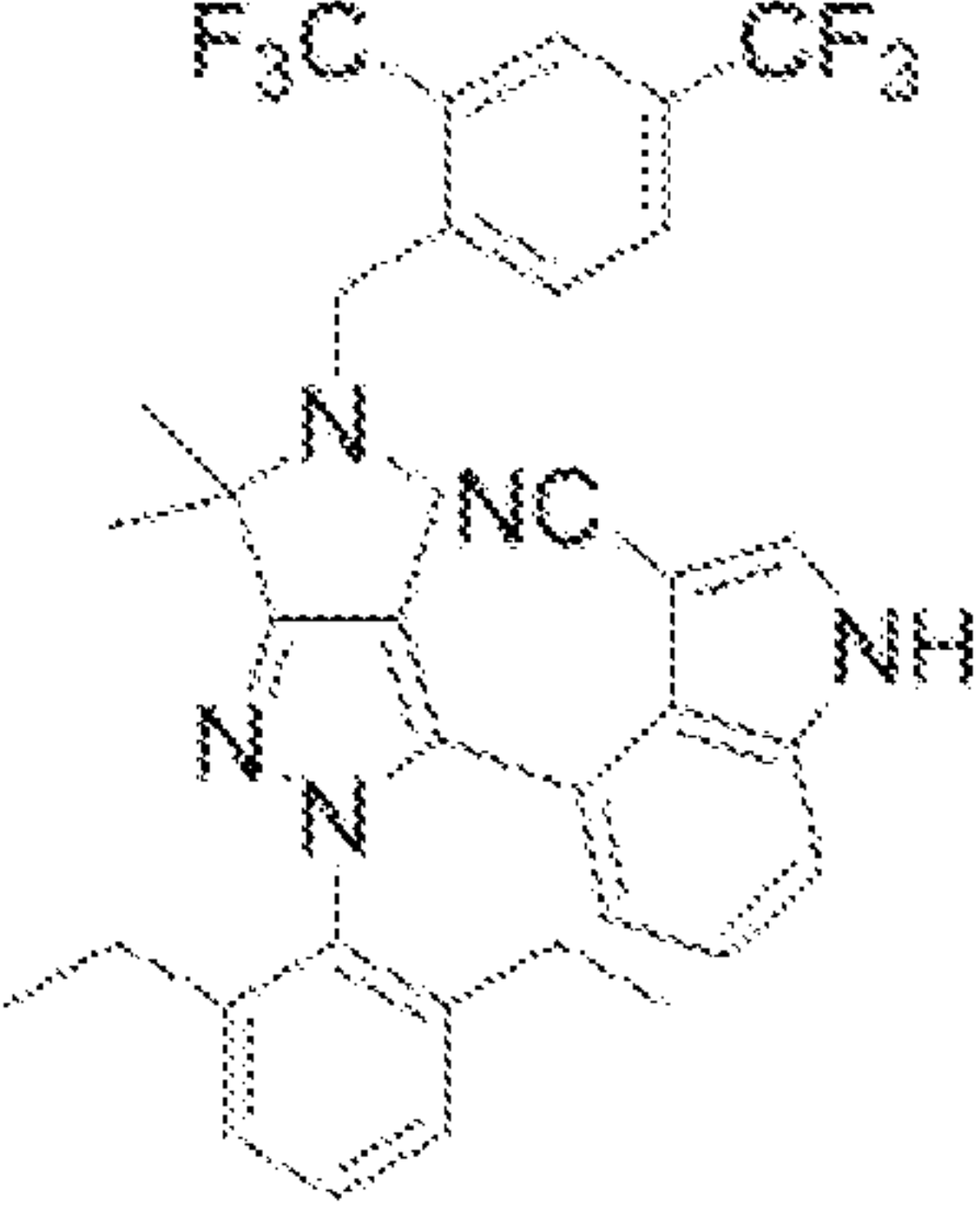
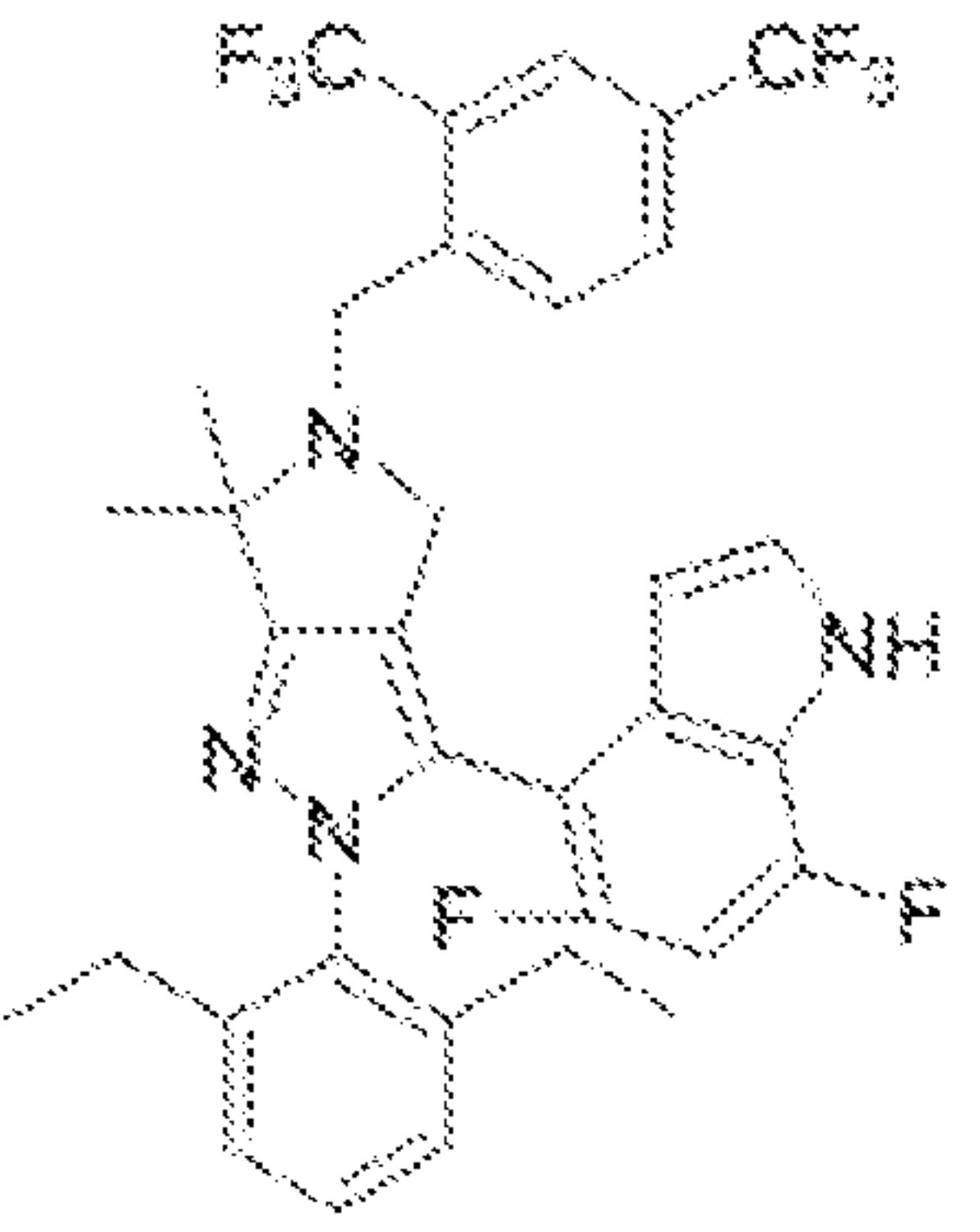
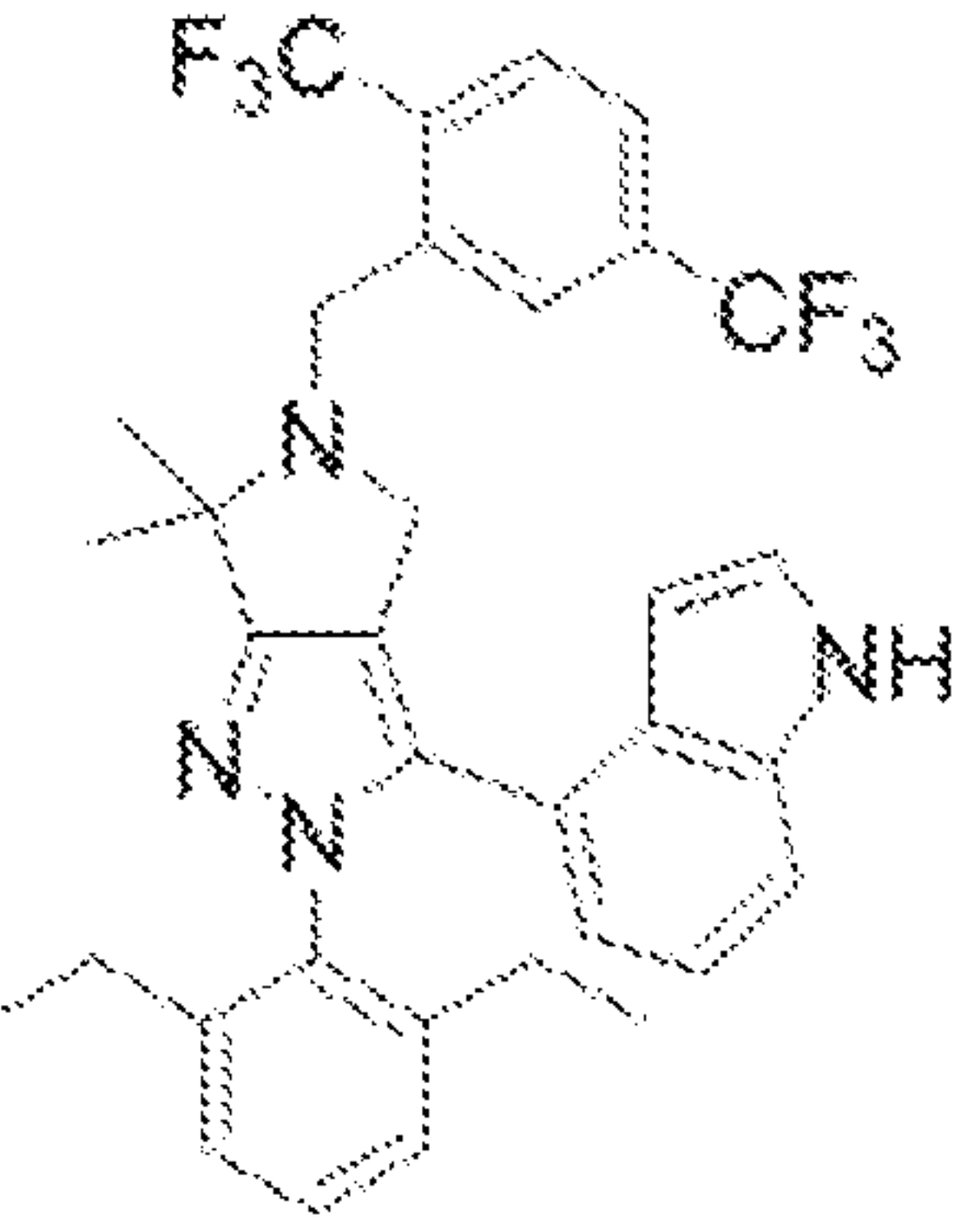
Ex. 13.011 	¹H NMR (400 MHz, CD₃OD) δ 7.26–7.34 (m, 3H), 7.16 – 7.25 (m, 2H), 7.13 (d, <i>J</i> = 7.2 Hz, 2H), 6.90–7.00 (m, 1H), 6.55 (dd, <i>J</i> = 10.9, 8.1 Hz, 1H), 6.36–6.46 (m, 2H), 5.46–5.51 (m, 1H), 3.93 (s, 2H), 3.67 (s, 2H), 2.05–2.45 (m, 4H), 1.54 (s, 6H), 0.98 (t, <i>J</i> = 7.6 Hz, 6H).	MS: (ES) <i>m/z</i> calculated for C₃₂H₃₃F₂N₄ [M + H]⁺ 511.3, found 511.3.
Ex. 13.012 	¹H NMR TFA salt (400 MHz, CD₃OD) δ 11.46 (s, 1H), 8.68 (d, <i>J</i> = 4.8 Hz, 1H), 7.92 (dd, <i>J</i> = 1.6, 7.6 Hz, 1H), 7.62 (d, <i>J</i> = 8.0, 1H), 7.45 (m, 2H), 7.38 (dd, <i>J</i> = 7.6, 7.6 Hz, 1H), 7.18 (d, <i>J</i> = 7.6 Hz, 2H), 6.62 (m, 1H), 6.53 (m, 1H), 6.45 (m, 1H), 4.79 (s, 2H), 4.64 (s, 2H), 2.27 (m, 4H), 1.92 (s, 6H), 0.98 (t, <i>J</i> = 7.6 Hz, 6H).	MS: (ES) <i>m/z</i> calculated for C₃₁H₃₃FN₅ [M + H]⁺ 494.3, found 494.3.
Ex. 13.013 	¹H NMR (400 MHz, CD₃OD) δ 7.57 (d, <i>J</i> = 8.2 Hz, 1H), 7.44 (d, <i>J</i> = 2.1 Hz, 1H), 7.26–7.37 (m, 3H), 7.14 (d, <i>J</i> = 7.7 Hz, 2H), 6.66 (dd, <i>J</i> = 8.2, 10.8 Hz, 1H), 6.39–6.46 (m, 2H), 4.88 (br, 1H), 4.04 (s, 2H), 3.74 (s, 2H), 2.03–2.33 (m, 4H), 1.56 (s, 6H), 0.98 (t, <i>J</i> = 7.6 Hz, 6H).	MS: (ES) <i>m/z</i> calculated for C₃₂H₃₂Cl₂FN₄ [M + H]⁺ 561.2, found 561.2.

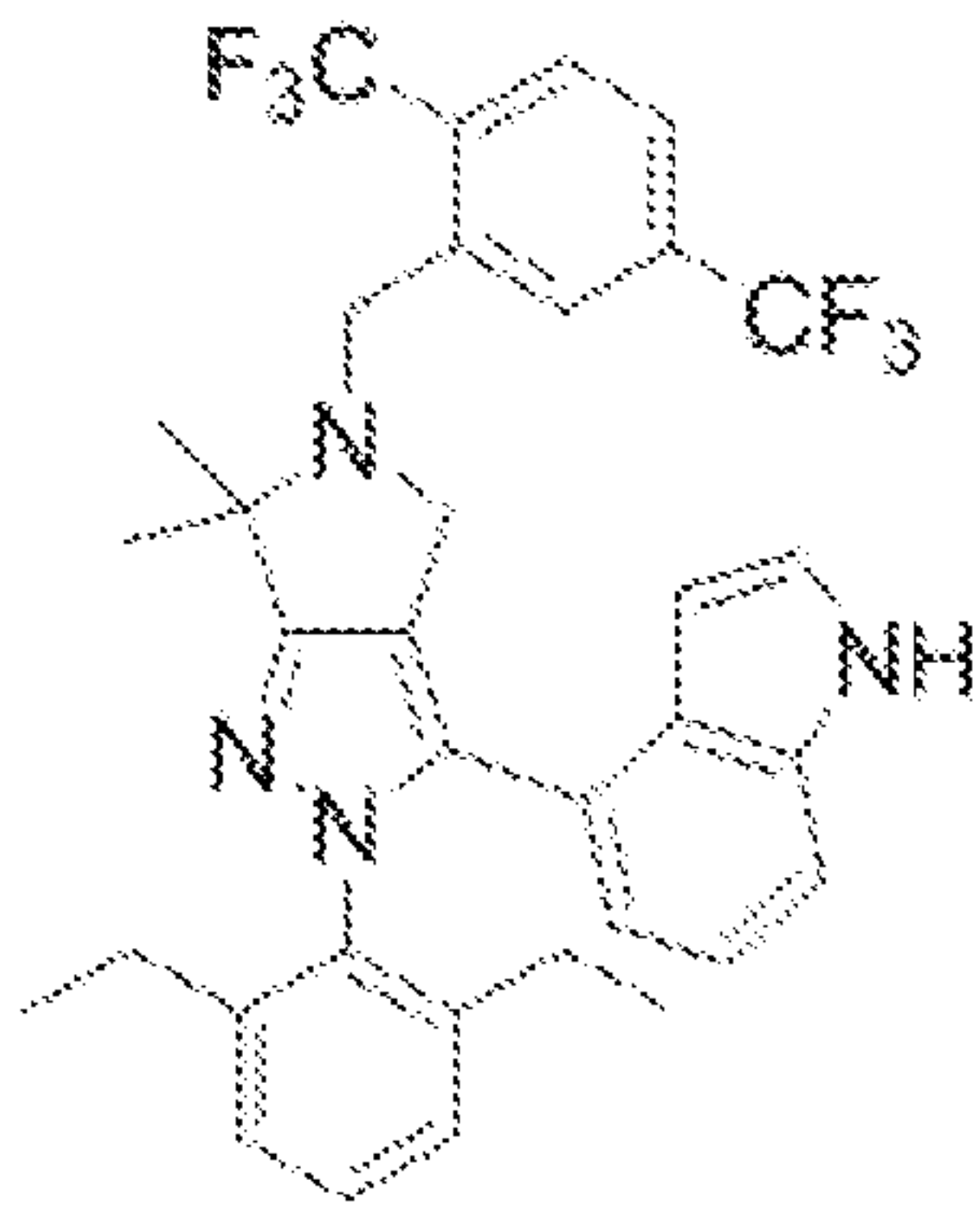
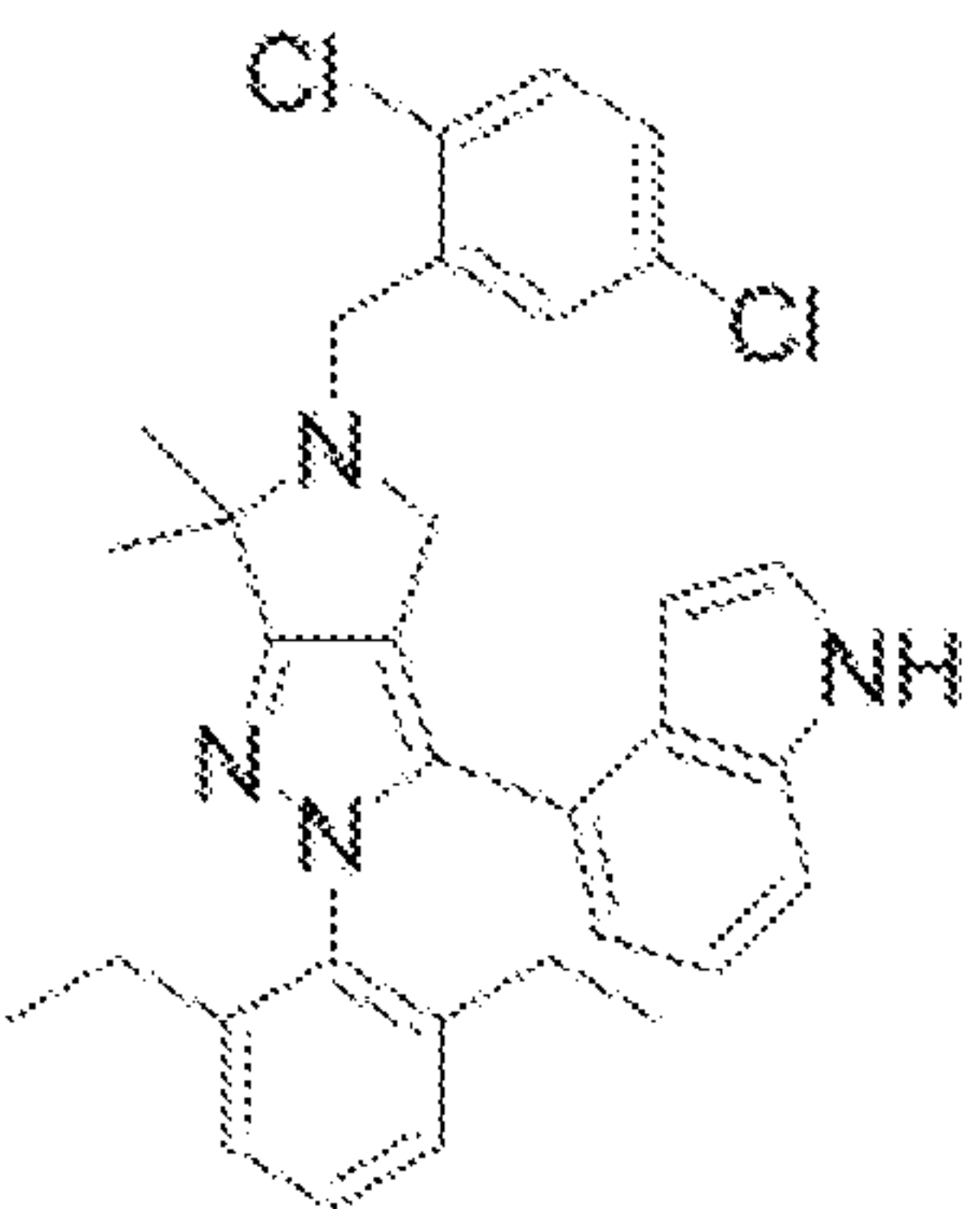
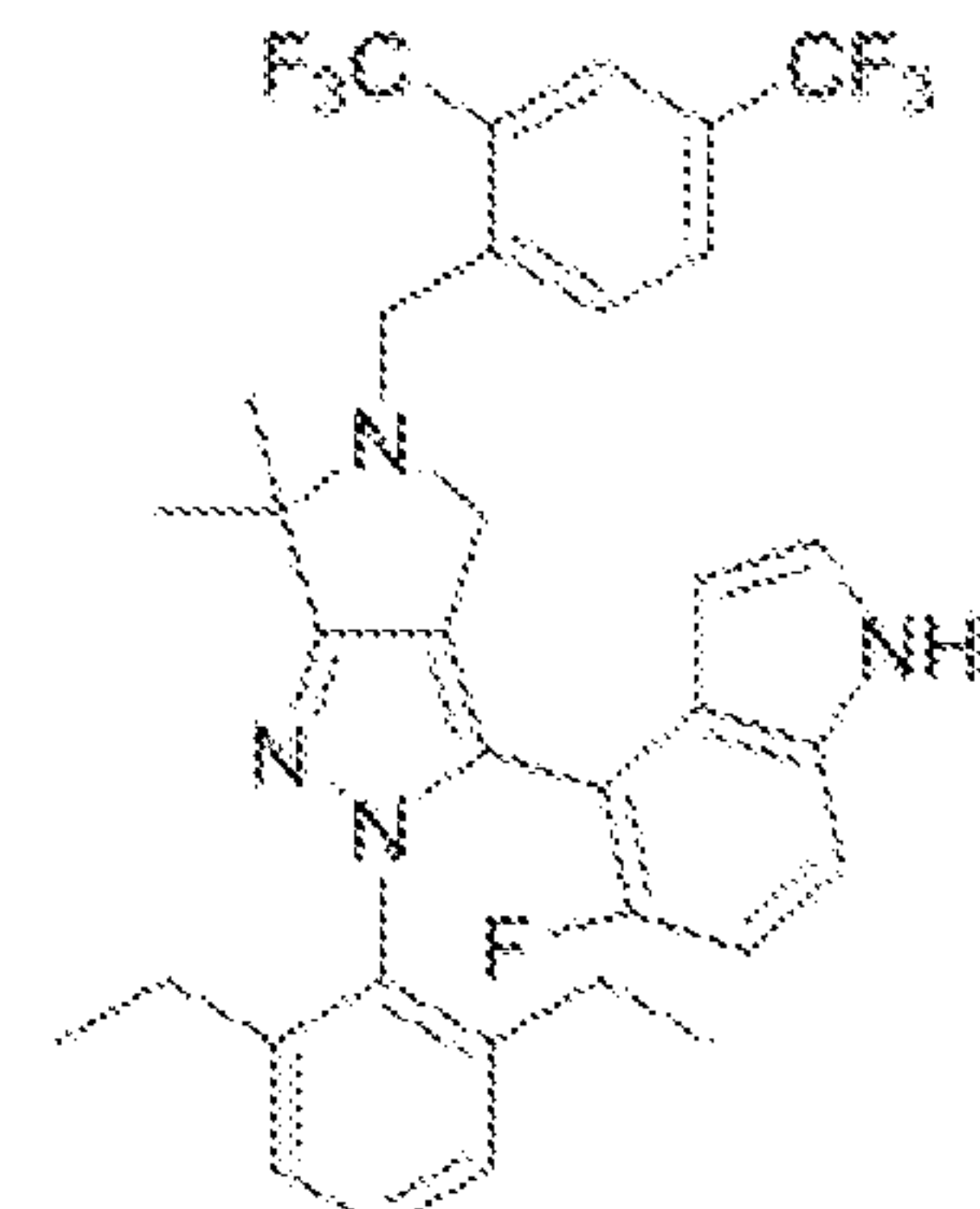
Ex. 13.014 	¹H NMR (400 MHz, CD₃OD) δ 7.42 (d, <i>J</i> = 8.4 Hz, 2H), 7.28–7.34 (m, 4H), 7.20–7.26 (m, 1H), 7.14 (d, <i>J</i> = 7.7 Hz, 2H), 6.55 (dd, <i>J</i> = 8.2, 11.0 Hz, 1H), 6.47–6.35 (m, 2H), 3.93 (s, 2H), 3.68 (s, 2H), 2.12–2.39 (m, 4H), 1.56 (s, 6H), 0.97 (t, <i>J</i> = 7.6 Hz, 6H).	MS: (ES) <i>m/z</i> calculated for C₃₂H₃₄FN₄ [M + H]⁺ 493.3, found 493.3.
Ex. 13.015 	¹H NMR (400 MHz, CD₃OD) δ 7.32–7.49 (m, 1H), 7.25–7.34 (m, 3H), 7.04–7.14 (m, 4H), 6.53–6.57 (m, 1H), 6.38–6.46 (m, 2H), 4.88 (br, 1H), 3.99 (s, 2H), 3.74 (s, 2H), 2.17–2.36 (m, 4H), 1.57 (s, 6H), 0.97 (t, <i>J</i> = 7.6 Hz, 6H).	MS: (ES) <i>m/z</i> calculated for C₃₂H₃₃F₂N₄ [M + H]⁺ 511.3, found 511.3.
Ex. 13.016 	¹H NMR (400 MHz, CD₃OD) δ 7.39–7.45 (m, 2H), 7.26–7.36 (m, 2H), 7.14 (d, <i>J</i> = 8.2 Hz, 2H), 6.98–7.04 (m, 2H), 6.55 (dd, <i>J</i> = 8.2, 11.0 Hz, 1H), 6.35–6.46 (m, 2H), 4.88 (br, 1H), 3.91 (s, 2H), 3.66 (s, 2H), 2.17–2.36 (m, 4H), 1.55 (s, 6H), 0.97 (t, <i>J</i> = 7.6 Hz, 6H).	MS: (ES) <i>m/z</i> calculated for C₃₂H₃₃F₂N₄ [M + H]⁺ 511.3, found 511.3.

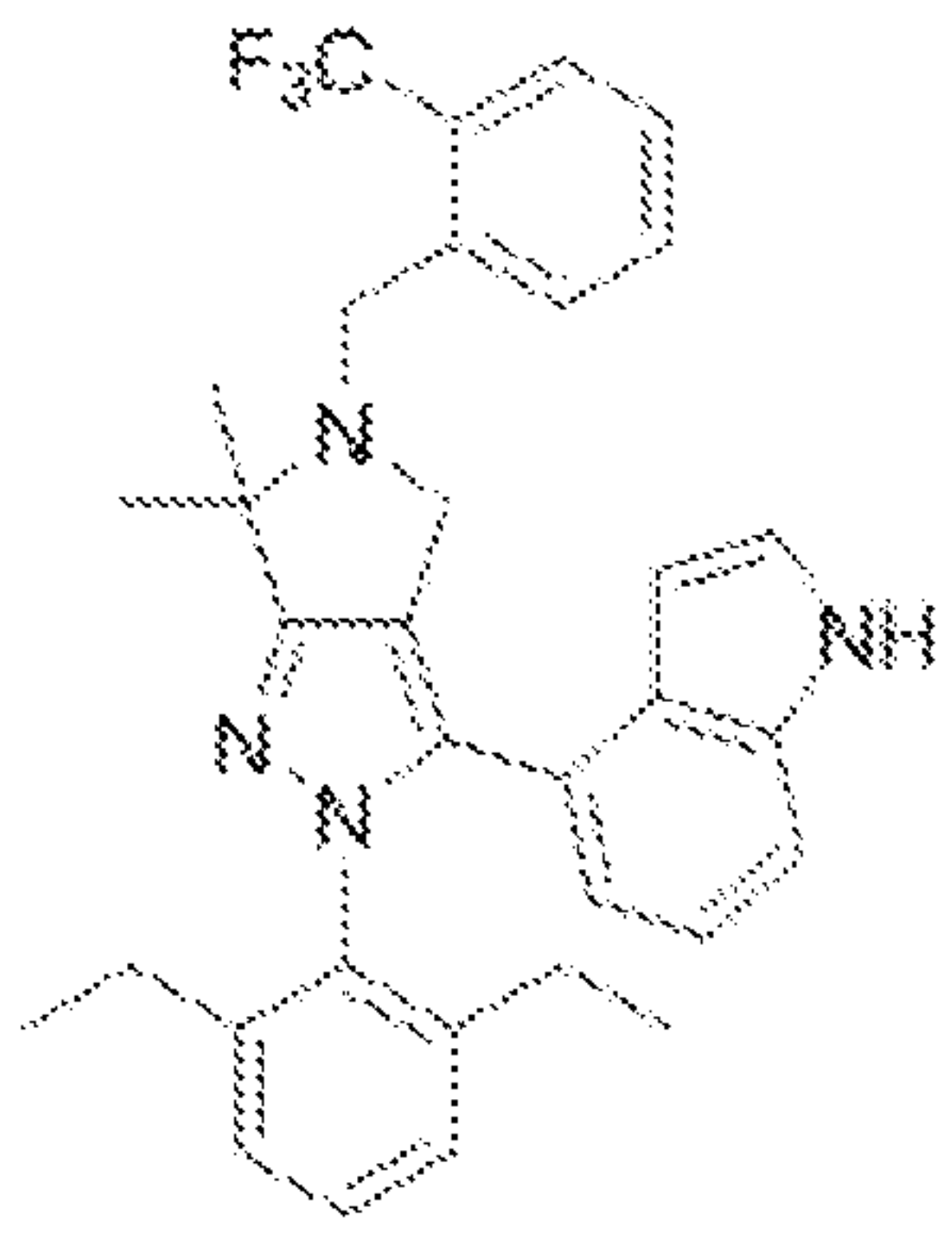
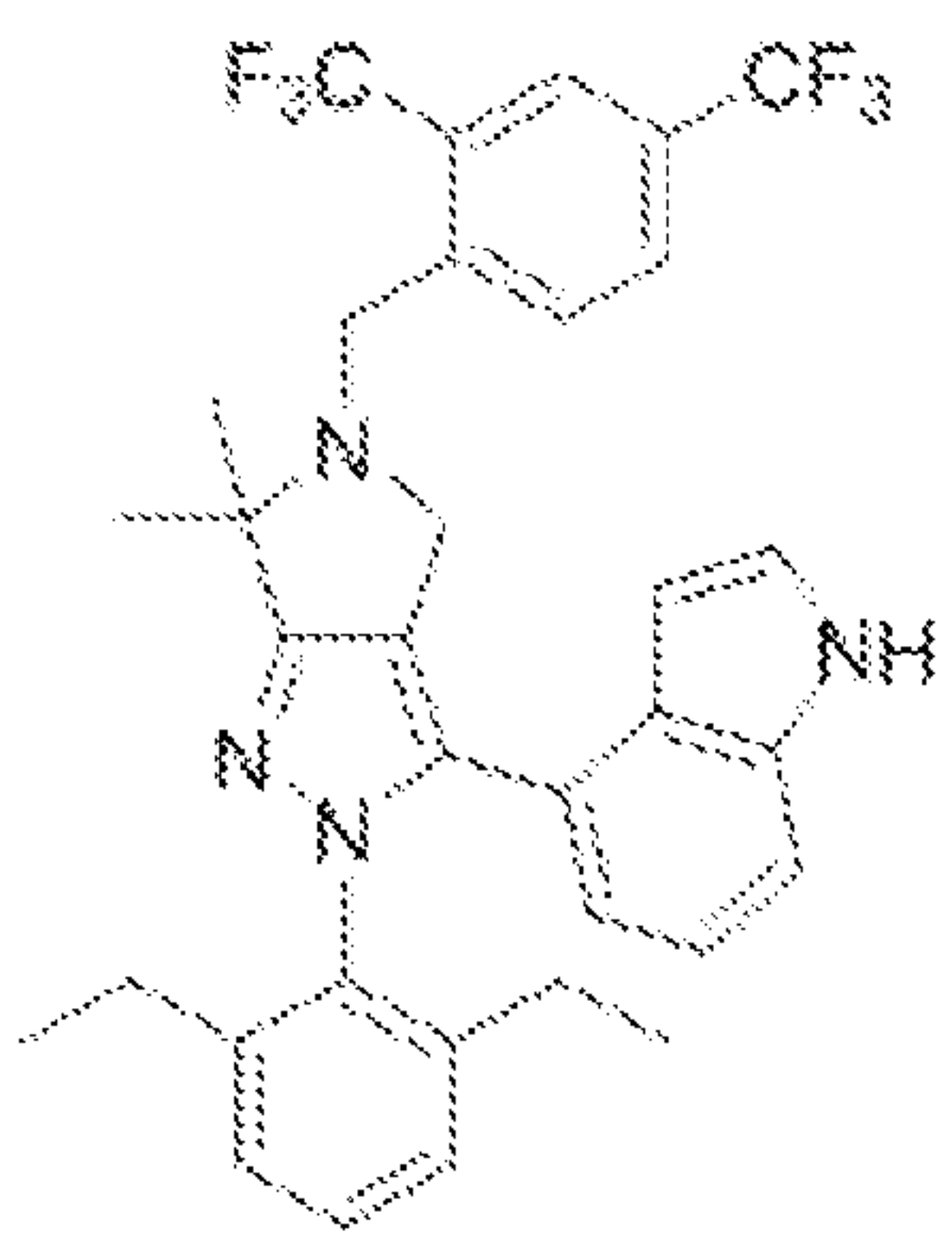
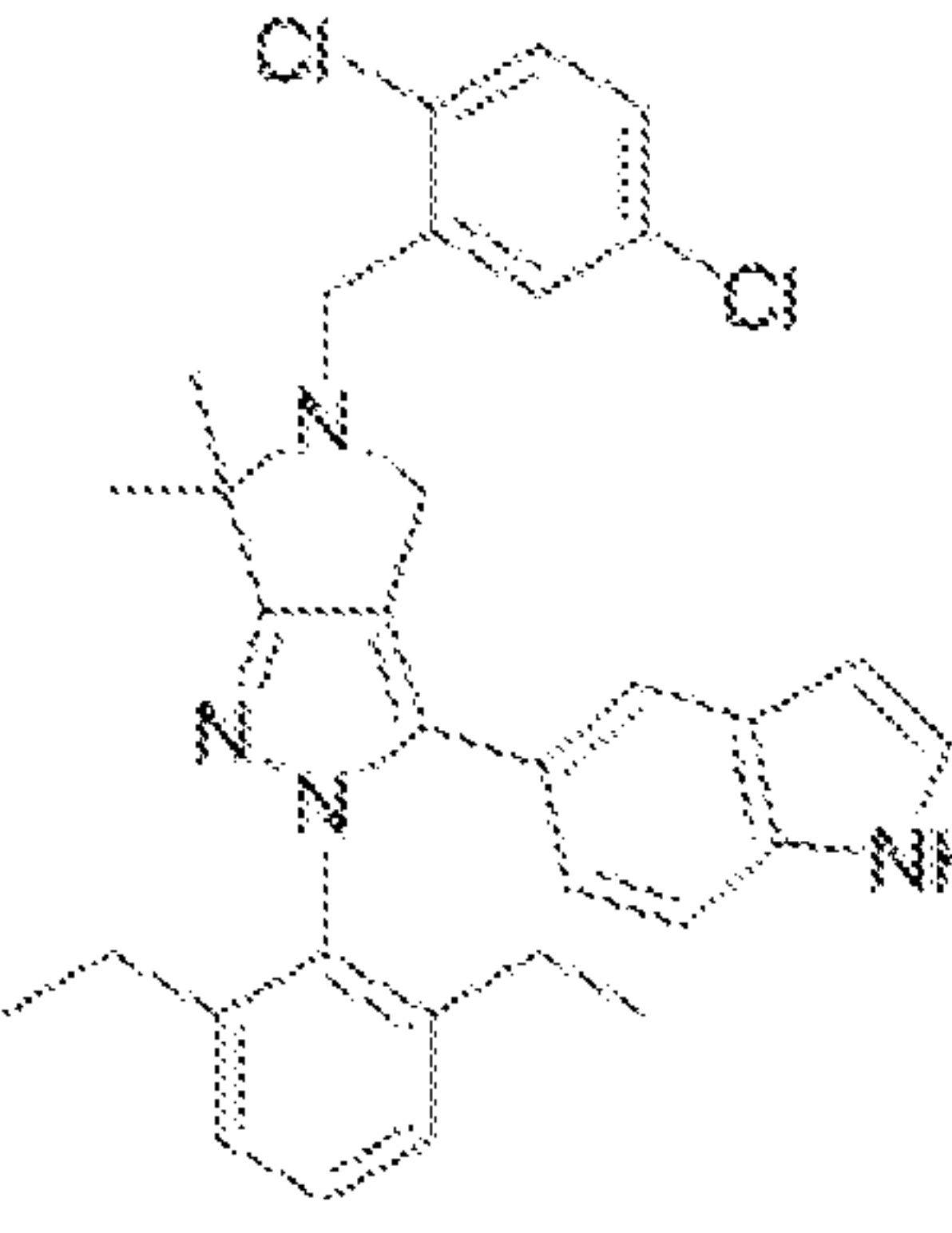
Ex. 13.017 	¹H NMR (400 MHz, CD₃OD) δ 8.23 (d, <i>J</i> = 8.2 Hz, 1H), 7.92–7.93 (m, 2H), 7.27–7.39 (m, 2H), 7.15 (d, <i>J</i> = 7.7 Hz, 2H), 6.83 (d, <i>J</i> = 7.7 Hz, 1H), 6.42–6.48 (m, 2H), 4.88 (br, 1H), 4.22 (s, 2H), 3.66 (s, 2H), 2.20–2.36 (m, 4H), 1.56 (s, 6H), 1.00 (t, <i>J</i> = 7.6 Hz, 6H).	MS: (ES) <i>m/z</i> calculated for C₃₄H₃₂ClF₆N₄ [M + H]⁺ 645.2, found 645.2.
Ex. 13.018 	¹H NMR (400 MHz, CD₃OD) δ 8.24 (d, <i>J</i> = 8.6 Hz, 1H), 7.89–7.95 (m, 2H), 7.24–7.34 (m, 2H), 7.13 (d, <i>J</i> = 7.7 Hz, 2H), 6.60 (d, <i>J</i> = 7.2 Hz, 1H), 6.33–6.42 (m, 2H), 4.22 (s, 2H), 3.73 (s, 2H), 2.16–2.42 (m, 7H), 1.56 (s, 6H), 0.99 (t, <i>J</i> = 7.6 Hz, 6H).	MS: (ES) <i>m/z</i> calculated for C₃₅H₃₅F₆N₄ [M + H]⁺ 625.3, found 625.3.
Ex. 13.019 	¹H NMR (400 MHz, CD₃OD) δ 8.25–8.29 (m, 1H), 7.95–7.97 (m, 2H), 7.21–7.29 (m, 4H), 7.07 (d, <i>J</i> = 1.4 Hz, 1H), 6.47 (dd, <i>J</i> = 1.4, 12.6 Hz, 1H), 6.33–6.35 (m, 1H), 4.88 (br, 1H), 4.25 (s, 2H), 3.93 (s, 2H), 2.26–2.35 (m, 4H), 1.53 (s, 6H), 1.04 (t, <i>J</i> = 7.6 Hz, 6H).	MS: (ES) <i>m/z</i> calculated for C₃₄H₃₂F₇N₄ [M + H]⁺ 629.2, found 629.3.

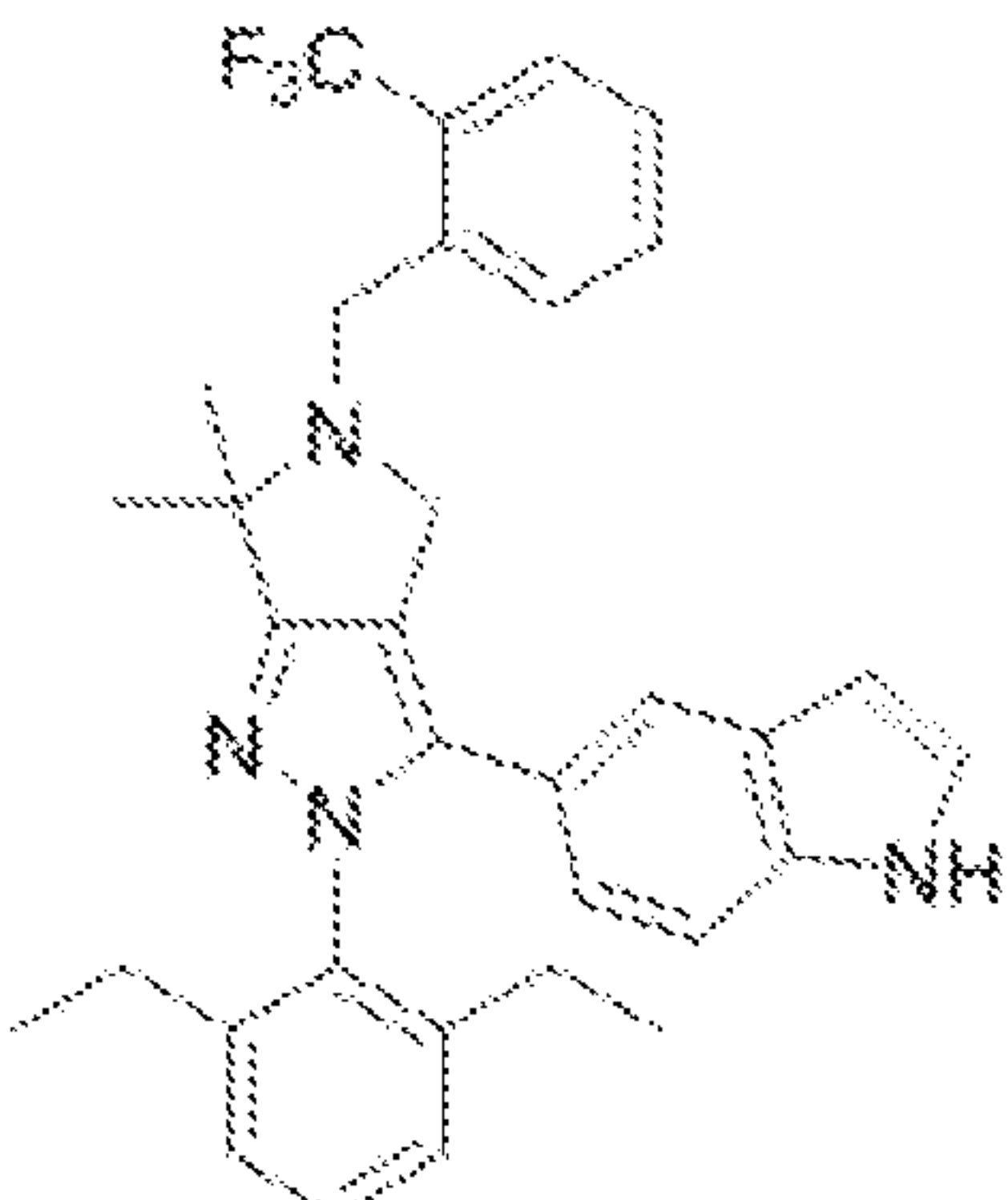
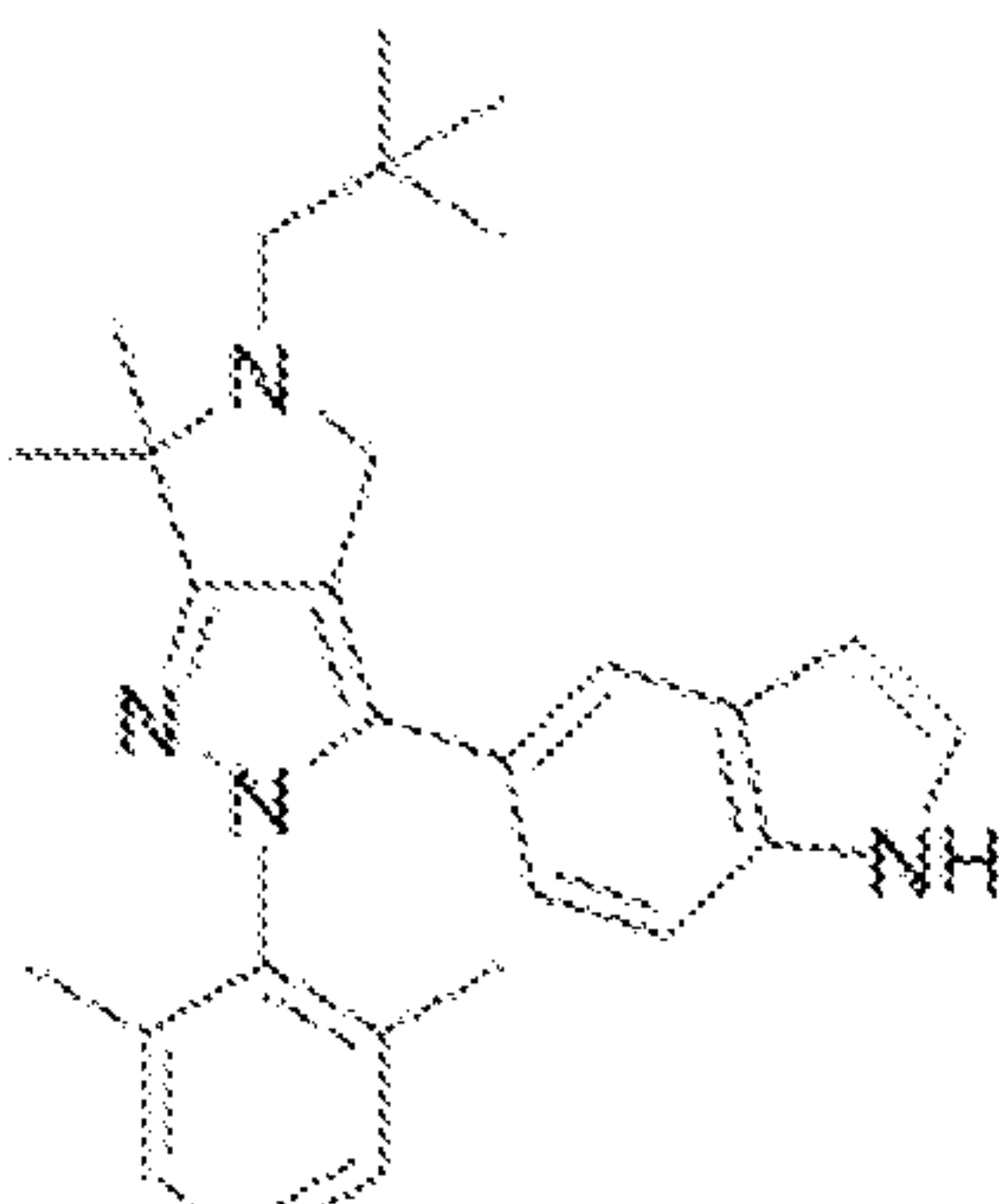
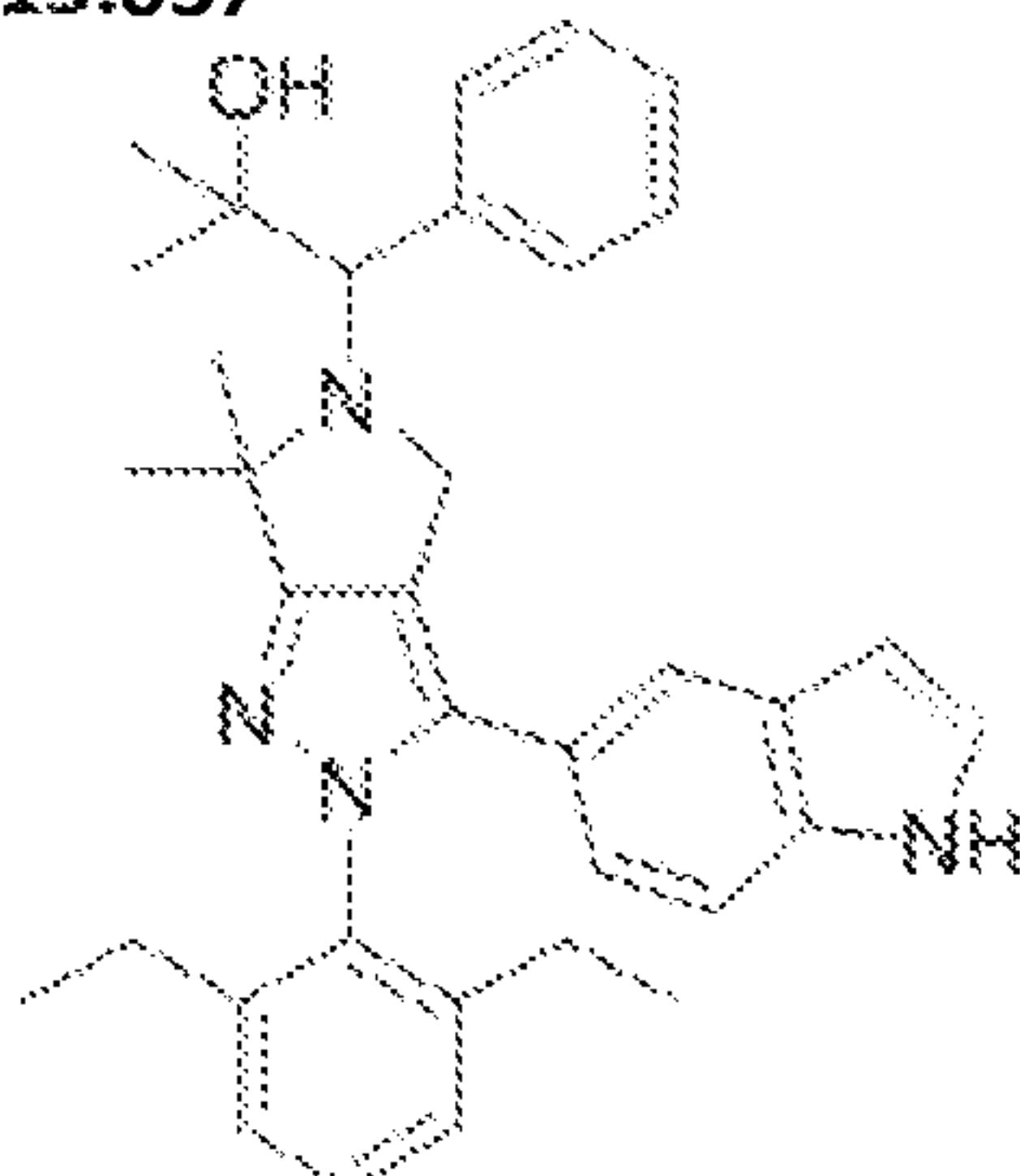
Ex. 13.020 	¹H NMR TFA salt (400 MHz, CD₃OD) δ 11.31 (s, 1H), 8.56 (d, <i>J</i> = 4.4 Hz, 1H), 7.99 (dd, <i>J</i> = 1.6, 7.2 Hz, 1H), 7.73 (d, <i>J</i> = 7.6 Hz, 1H), 7.50 (m, 1H), 7.32 (m, 2H), 7.15 (d, <i>J</i> = 7.6 Hz, 2H), 6.58 (m, 1H), 6.44 (m, 1H), 6.39 (m, 1H), 4.71 (s, 2H), 2.28 (m, 4H), 2.03 (s, 6H), 0.99 (t, <i>J</i> = 7.6 Hz, 6H).	MS: (ES) <i>m/z</i> calculated for C₃₁H₃₁FN₅O [M + H]⁺ 508.2, found 508.2.
Ex. 13.021 	¹H NMR (400 MHz, CDCl₃) δ 8.30 (s, 1H), 7.91 (d, <i>J</i> = 7.6 Hz, 1H), 7.51 (d, <i>J</i> = 8.0 Hz, 1H), 7.40 (dd, <i>J</i> = 7.6, 7.6 Hz, 1H), 7.14 (m, 3H), 6.97 (d, <i>J</i> = 7.6 Hz, 2H), 6.51 (m, 1H), 6.41 (m, 1H), 6.36 (m, 1H), 4.00 (s, 2H), 3.62 (s, 2H), 2.28 (m, 2H), 2.12 (m, 2H), 1.47 (s, 6H), 0.90 (t, <i>J</i> = 7.4 Hz, 6H).	MS: (ES) <i>m/z</i> calculated for C₃₃H₃₃F₄N₄ [M + H]⁺ 561.3, found 561.3.
Ex. 13.022 	¹H NMR (400 MHz, CDCl₃) δ 8.54 (s, 1H), 7.26 (dd, <i>J</i> = 2.8, 2.8 Hz, 1H), 7.16 (dd, <i>J</i> = 7.6, 7.6 Hz, 1H), 6.99 (d, <i>J</i> = 7.6 Hz, 2H), 6.59 (m, 1H), 6.43 (m, 2H), 4.53 (s, 2H), 2.20 (m, 6H), 1.84 (s, 6H), 0.91 (m, 13H).	MS: (ES) <i>m/z</i> calculated for C₃₀H₃₆FN₄O [M + H]⁺ 487.3, found 487.3.

Ex. 13.023 	^1H NMR (400 MHz, CDCl_3) δ 8.19 (s, 1H), 8.11 (d, $J = 8.0$ Hz, 1H), 7.78 (s, 1H), 7.67 (d, $J = 8.4$ Hz, 1H), 7.17 (dd, $J = 7.8, 7.8$ Hz, 1H), 7.09 (dd, $J = 2.8, 2.8$ Hz, 1H), 7.01 (d, $J = 7.6$ Hz, 2H), 6.81 (dd, $J = 2.0, 8.8$ Hz, 1H), 6.35 (m, 1H), 6.25 (dd, $J = 2.0, 10.8$ Hz, 1H), 4.06 (s, 2H), 3.64 (s, 2H), 2.28 (m, 2H), 2.15 (m, 2H), 1.48 (s, 6H), 0.92 (t, $J = 7.6$ Hz, 6H).	MS: (ES) m/z calculated for $\text{C}_{34}\text{H}_{32}\text{F}_7\text{N}_4$ $[\text{M} + \text{H}]^+$ 629.2, found 629.2.
Ex. 13.024 	^1H NMR (400 MHz, CDCl_3) δ 8.54 (s, 1H), 7.34 (dd, $J = 2.8, 2.8$ Hz, 1H), 7.26 (m, 1H), 7.07 (d, $J = 7.6$ Hz, 2H), 6.68 (m, 1H), 6.49 (m, 2H), 4.85 (s, 2H), 2.84 (s, 2H), 2.32 (m, 2H), 2.20 (m, 2H), 1.91 (s, 6H), 1.54 (s, 6H), 1.00 (t, $J = 7.6$ Hz, 6H).	MS: (ES) m/z calculated for $\text{C}_{30}\text{H}_{33}\text{F}_4\text{N}_4\text{O}$ $[\text{M} + \text{H}]^+$ 541.3, found 541.2.
Ex. 13.025 	^1H NMR (400 MHz, CD_3OD) δ 8.21 (d, $J = 8.4$ Hz, 1H), 7.90 (br s, 2H), 7.24 – 7.31 (m, 4H), 6.92 – 6.95 (m, 1H), 6.88 (t, $J = 8.4$ Hz), 6.55 (dd, $J = 0.76, 7.6$ Hz, 1H), 4.18 (s, 2H), 3.86 (d, $J = 12$ Hz, 1H), 3.48 (d, $J = 11.6$ Hz, 1H), 2.03 – 2.61 (m, 4H), 1.54 (s, 3H), 1.53 (s, 3H), 1.35 (t, $J = 7.6$ Hz, 3H), 0.75 (t, $J = 7.6$ Hz, 3H).	MS: (ES) m/z calculated for $\text{C}_{34}\text{H}_{32}\text{ClF}_6\text{N}_4$ $[\text{M} + \text{H}]^+$ 645.2, found 645.2.

Ex. 13.026 	¹H NMR (400 MHz, CD₃OD) δ 8.38 (d, <i>J</i> = 8.7 Hz, 1H), 8.06 (s, 1H), 7.88 (d, <i>J</i> = 4.5 Hz, 2H), 7.41 (dd, <i>J</i> = 8.3, 0.8 Hz, 1H), 7.23 – 7.33 (m, 2H), 6.93 – 7.08 (m, 2H), 6.68–6.75 (m, 1H), 4.21 (s, 2H), 3.99 (d, <i>J</i> = 11.3 Hz, 1H), 3.51 (d, <i>J</i> = 11.4 Hz, 1H), 2.46–2.68 (m, 2H), 2.30 – 2.40 (m, 1H), 1.98 – 2.06 (m, 1H), 1.57 (s, 3H), 1.55 (s, 3H), 1.36 (t, <i>J</i> = 7.5 Hz, 3H), 0.77 (t, <i>J</i> = 7.6 Hz, 3H).	MS: (ES) <i>m/z</i> calculated for C₃₅H₃₂F₆N₅ [M + H]⁺ 636.3, found 636.3.
Ex. 13.027 	¹H NMR (400 MHz, CDCl₃) δ 8.42 (s, 1H), 8.20 (d, <i>J</i> = 8.4 Hz, 1H), 7.86 (s, 1H), 7.77 (d, <i>J</i> = 8.0 Hz, 1H), 7.21 (m, 2H), 7.03 (br s, 2H), 6.51 (t, <i>J</i> = 10.4 Hz, 1H), 6.38 (m, 1H), 4.14 (s, 2H), 3.63 (s, 2H), 2.38 (br s, 4H), 1.56 (s, 6H), 1.00 (br s, 6H).	MS: (ES) <i>m/z</i> calculated for C₃₄H₃₁F₈N₄ [M + H]⁺ 647.2, found 647.2.
Ex. 13.028 	¹H NMR (400 MHz, CD₃OD) δ 8.34 (s, 1H), 7.89 (d, <i>J</i> = 8.2 Hz, 1H), 7.69 – 7.77 (m, 1H), 7.22 – 7.35 (m, 3H), 7.14 (d, <i>J</i> = 7.7 Hz, 2H), 6.80 (t, <i>J</i> = 7.8 Hz, 1H), 6.49 (m, 1H), 6.34 (m, 1H), 4.22 (s, 2H), 3.71 (s, 2H), 2.20 – 2.50 (m, 4H), 1.56 (s, 6H), 0.99 (m, 6H).	MS: (ES) <i>m/z</i> calculated for C₃₄H₃₃F₆N₄ [M + H]⁺ 611.3, found 611.3.

Ex. 13.029 	¹H NMR (400 MHz, CD₃OD) δ 7.38 (d, <i>J</i> = 3.0 Hz, 1H), 7.24–7.35 (m, 4H), 7.15 (d, <i>J</i> = 7.6 Hz, 2H), 6.90–7.01 (m, 3H), 6.85 (t, <i>J</i> = 7.6 Hz, 1H), 6.54 (d, <i>J</i> = 7.2 Hz, 1H), 6.48 (d, <i>J</i> = 3.1 Hz, 1H), 4.82 (s, 2H), 2.18–2.42 (m, 4H), 1.91 (s, 6H), 0.99 (t, <i>J</i> = 7.6 Hz, 6H).	MS: (ES) <i>m/z</i> calculated for C₃₃H₃₅N₄O₂ [M + H]⁺ 519.3, found 519.3.
Ex. 13.030 	¹H NMR (400 MHz, CD₃OD) δ 7.63 (d, <i>J</i> = 2.7 Hz, 1H), 7.20–7.40 (m, 5H), 7.13 (d, <i>J</i> = 7.7 Hz, 2H), 6.76–6.85 (m, 1H), 6.49 (dt, <i>J</i> = 7.5, 0.7 Hz, 1H), 6.40 (dd, <i>J</i> = 3.2, 0.8 Hz, 1H), 4.06 (s, 2H), 3.76 (s, 2H), 3.31 (s, 2H), 2.15–2.45 (m, 4H), 1.57 (s, 6H), 0.94 (t, <i>J</i> = 7.6 Hz, 6H).	MS: (ES) <i>m/z</i> calculated for C₃₂H₃₃Cl₂N₄ [M + H]⁺ 543.2, found 543.2.
Ex. 13.031 	¹H NMR (400 MHz, CD₃OD) δ 8.23 (d, <i>J</i> = 8.2 Hz, 1H), 7.92–7.93 (m, 2H), 7.22–7.39 (m, 3H), 7.07 (br, 2H), 6.65 (dd, <i>J</i> = 8.2, 10.8, 1H), 6.23–6.27 (m, 1H), 4.87 (br, 1H), 4.21 (s, 2H), 3.67 (s, 2H), 2.20–2.36 (br, 4H), 1.57 (s, 6H), 0.88–1.02 (br, 6H).	MS: (ES) <i>m/z</i> calculated for C₃₄H₃₂F₇N₄ [M + H]⁺ 629.2, found 629.3.

Ex. 13.032 	¹H NMR (400 MHz, CD₃OD) δ 8.24 (d, <i>J</i> = 7.9 Hz, 1H), 7.54–7.64 (m, 2H), 7.23–7.42 (m, 4H), 7.13 (d, <i>J</i> = 7.7 Hz, 2H), 6.80 (t, <i>J</i> = 7.7 Hz, 1H), 6.35–6.49 (m, 2H), 4.86 (br, 1H), 4.13 (s, 2H), 3.70 (s, 2H), 2.17–2.42 (m, 4H), 1.55 (s, 6H), 0.99 (t, <i>J</i> = 7.6 Hz, 6H).	MS: (ES) <i>m/z</i> calculated for C₃₃H₃₄F₃N₄ [M + H]⁺ 543.3, found 543.6.
Ex. 13.033 	¹H NMR (400 MHz, CD₃OD) δ 8.24 (d, <i>J</i> = 8.2 Hz, 1H), 7.90–7.93 (m, 2H), 7.26–7.32 (m, 3H), 7.14 (d, <i>J</i> = 7.7 Hz, 2H), 6.80 (t, <i>J</i> = 7.7 Hz, 1H), 6.35–6.49 (m, 2H), 4.88 (br, 1H), 4.22 (s, 2H), 3.74 (s, 2H), 2.20–2.36 (m, 4H), 1.56 (s, 6H), 0.99 (t, <i>J</i> = 7.6 Hz, 6H).	MS: (ES) <i>m/z</i> calculated for C₃₄H₃₃F₆N₄ [M + H]⁺ 611.3, found 611.6.
Ex. 13.034 	¹H NMR (400 MHz, CD₃OD) δ 7.68 (s, 1H), 7.37–7.46 (m, 2H), 7.14–7.32 (m, 5H), 7.07 (d, <i>J</i> = 1.4 Hz, 1H), 6.84–6.86 (m, Hz, 1H), 6.25–6.26 (m, 1H), 4.86 (br, 1H), 4.08 (s, 2H), 3.94 (s, 2H), 2.26–2.35 (m, 4H), 1.53 (s, 6H), 1.03 (t, <i>J</i> = 7.6 Hz, 6H).	MS: (ES) <i>m/z</i> calculated for C₃₂H₃₃Cl₂N₄ [M + H]⁺ 543.2, found 543.5.

Ex. 13.035 	¹H NMR (400 MHz, CD₃OD) δ 8.01 (d, <i>J</i> = 8.0 Hz, 1H), 7.58–7.73 (m, 2H), 7.42 (t, <i>J</i> = 7.7 Hz, 2H), 7.13–7.28 (m, 5H), 6.82 (dd, <i>J</i> = 1.7, 8.0 Hz, 1H), 6.23–6.24 (m, 1H), 4.88 (br, 1H), 4.16 (s, 2H), 3.88 (s, 2H), 2.20–2.36 (m, 4H), 1.52 (s, 6H), 1.03 (t, <i>J</i> = 7.6 Hz, 6H).	MS: (ES) <i>m/z</i> calculated for C₃₃H₃₄F₃N₄ [M + H]⁺ 543.3, found 543.5.
Ex. 13.036 	¹H NMR (400 MHz, CDCl₃) δ 8.13 (br, 1H), 7.32–7.37 (m, 1H), 7.15–7.22 (m, 4H), 7.06 (d, <i>J</i> = 7.6 Hz, 1H), 6.91 (dd, <i>J</i> = 1.7, 8.5 Hz, 1H), 6.43–6.44 (m, 1H), 4.08 (s, 2H), 2.50 (s, 2H), 2.00 (s, 6H), 1.36 (s, 6H), 1.00 (s, 9H).	MS: (ES) <i>m/z</i> calculated for C₂₈H₃₅N₄ [M + H]⁺ 427.3, found 427.5.
Ex. 13.037 	¹H NMR (400 MHz, CD₃OD) δ 7.55–7.63 (m, 2H), 7.10–7.39 (m, 9H), 6.82–6.90 (m, 1H), 6.23–6.24 (m, 1H), 4.82 (br, 2H), 4.64 (d, <i>J</i> = 11.5 Hz, 1H), 4.33 (d, <i>J</i> = 11.5 Hz, 1H), 3.87 (s, 1H), 2.06–2.39 (m, 4H), 1.59 (s, 3H), 1.35 (s, 3H), 1.19 (s, 3H), 1.05 (s, 3H), 0.83–1.03 (m, 6H).	MS: (ES) <i>m/z</i> calculated for C₃₅H₄₁N₄O [M + H]⁺ 533.3, found 533.7.

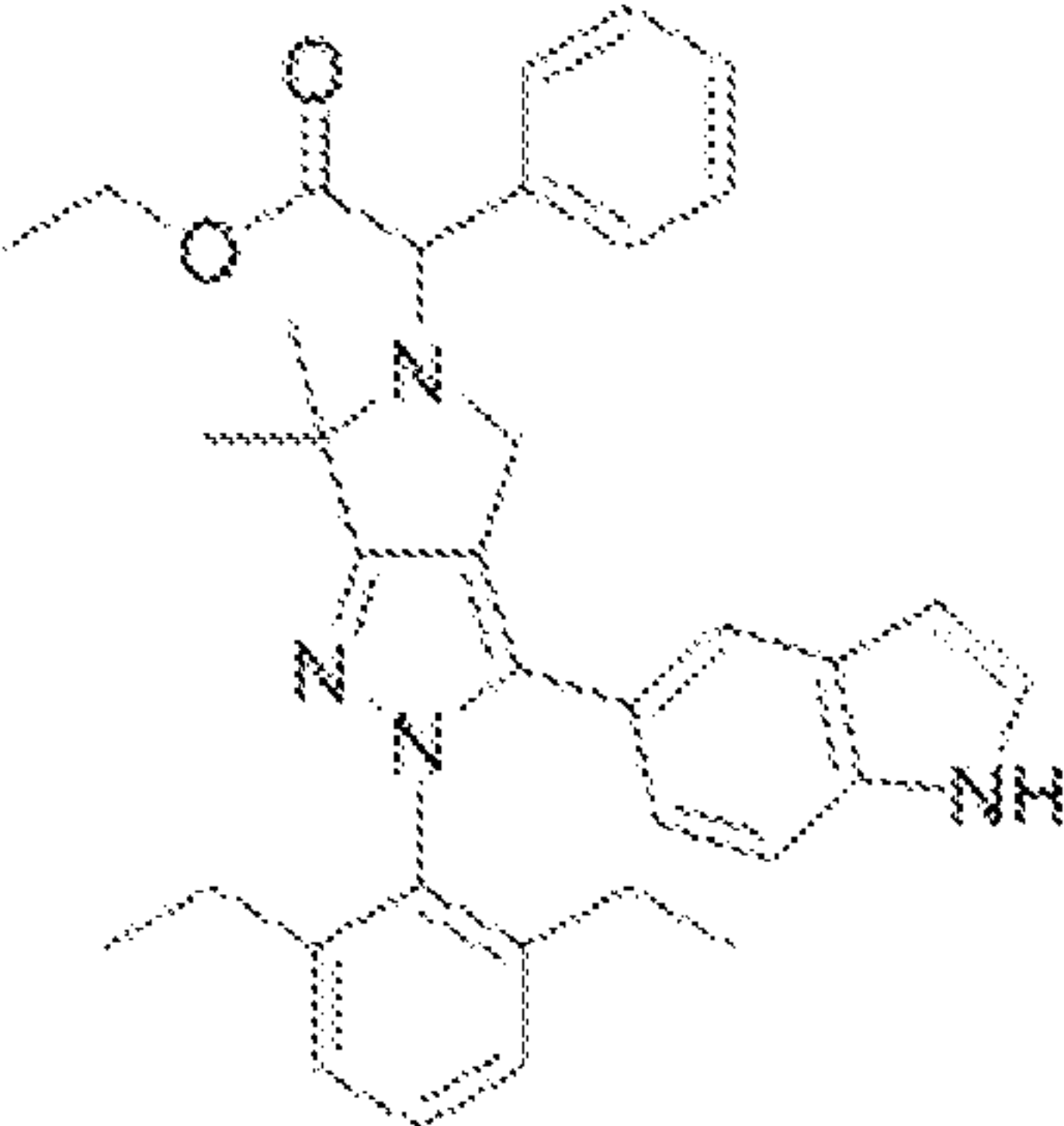
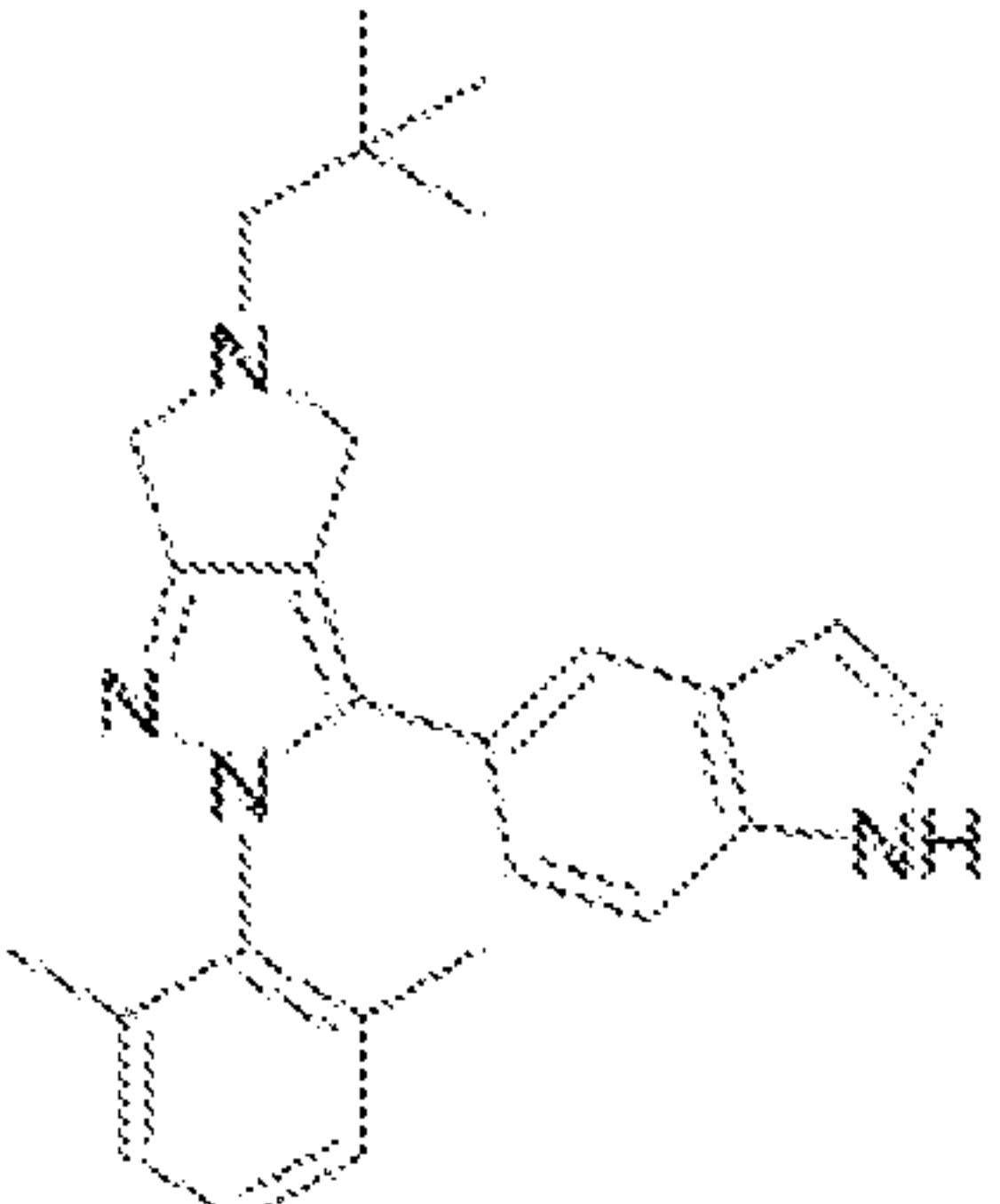
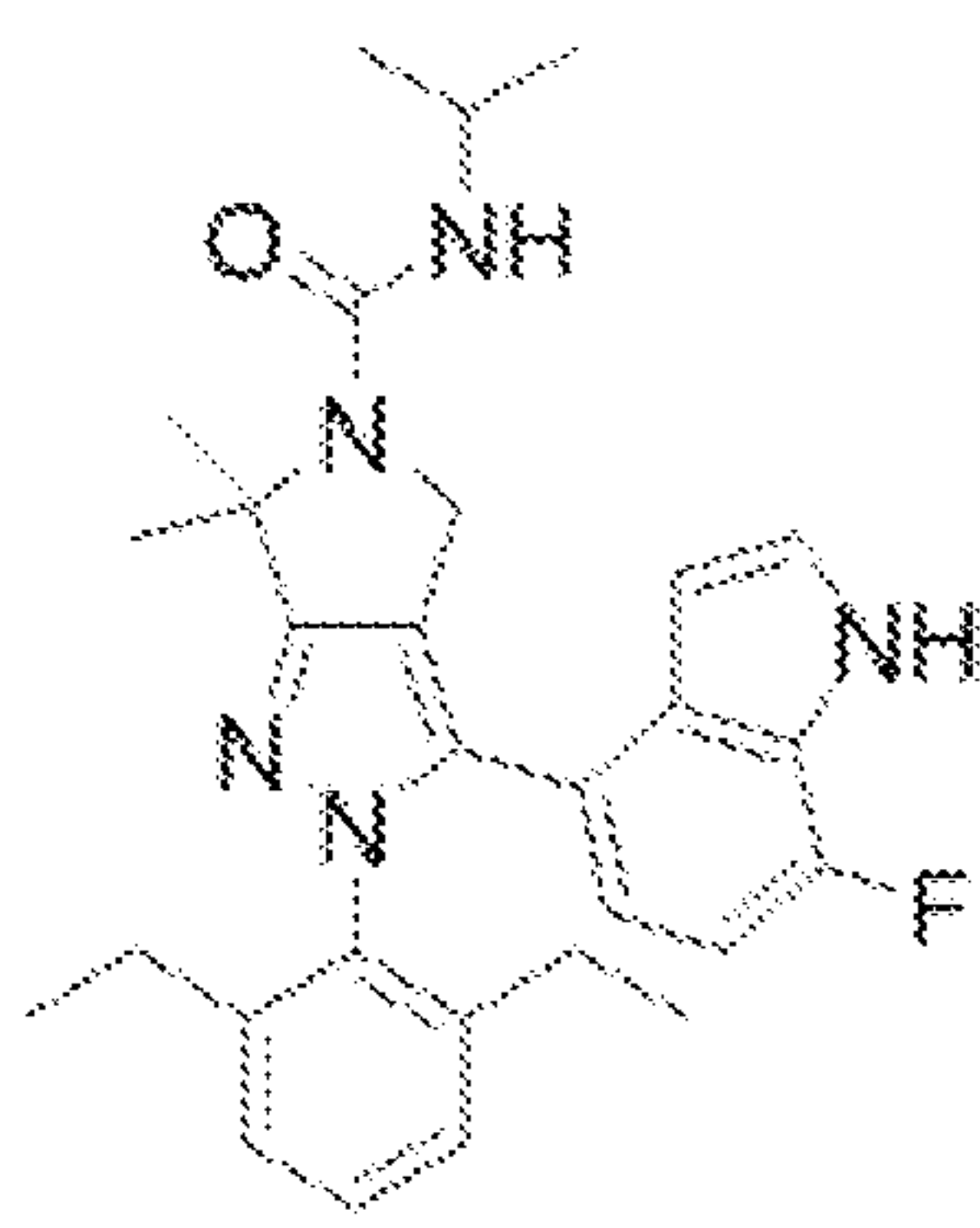
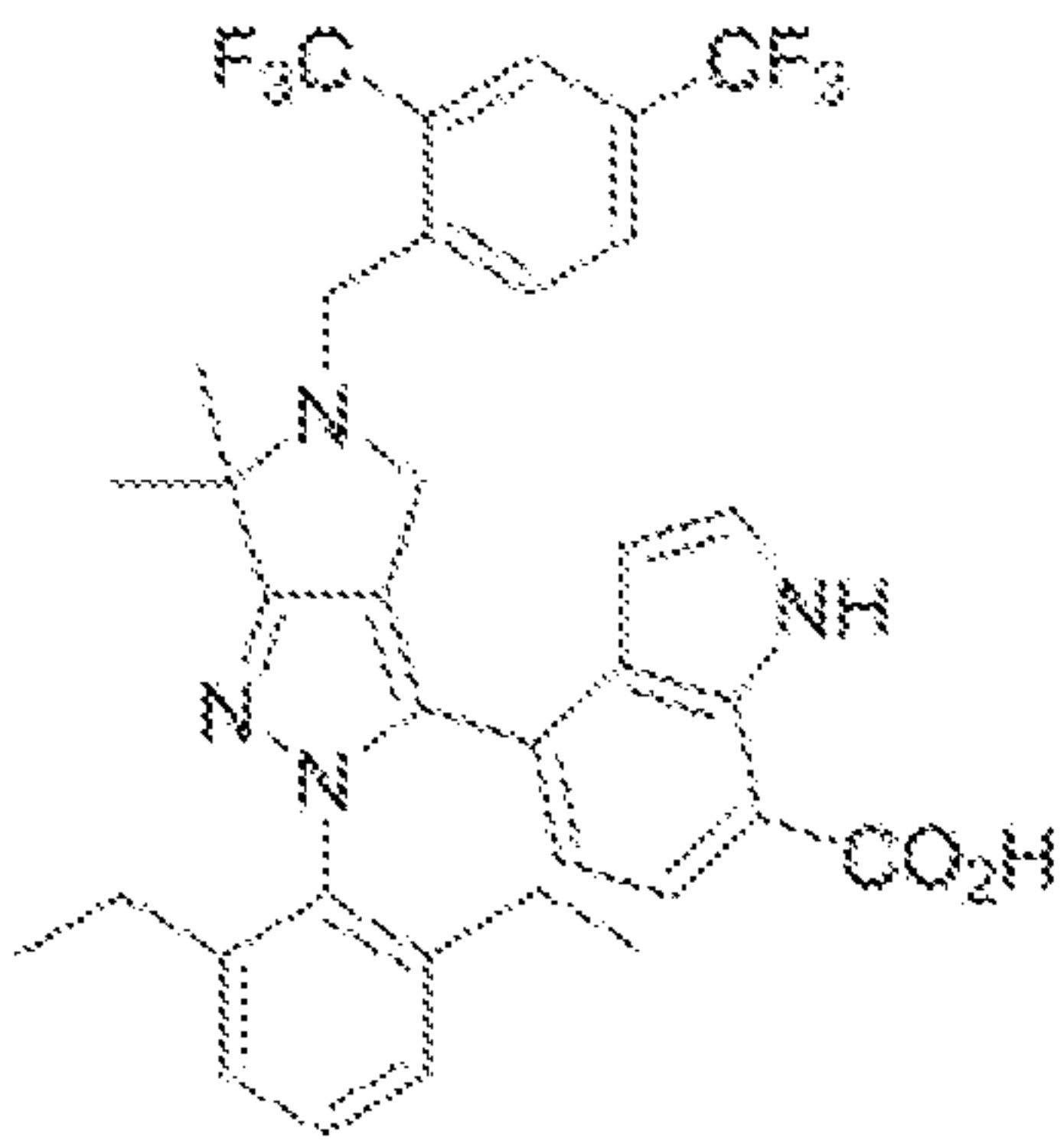
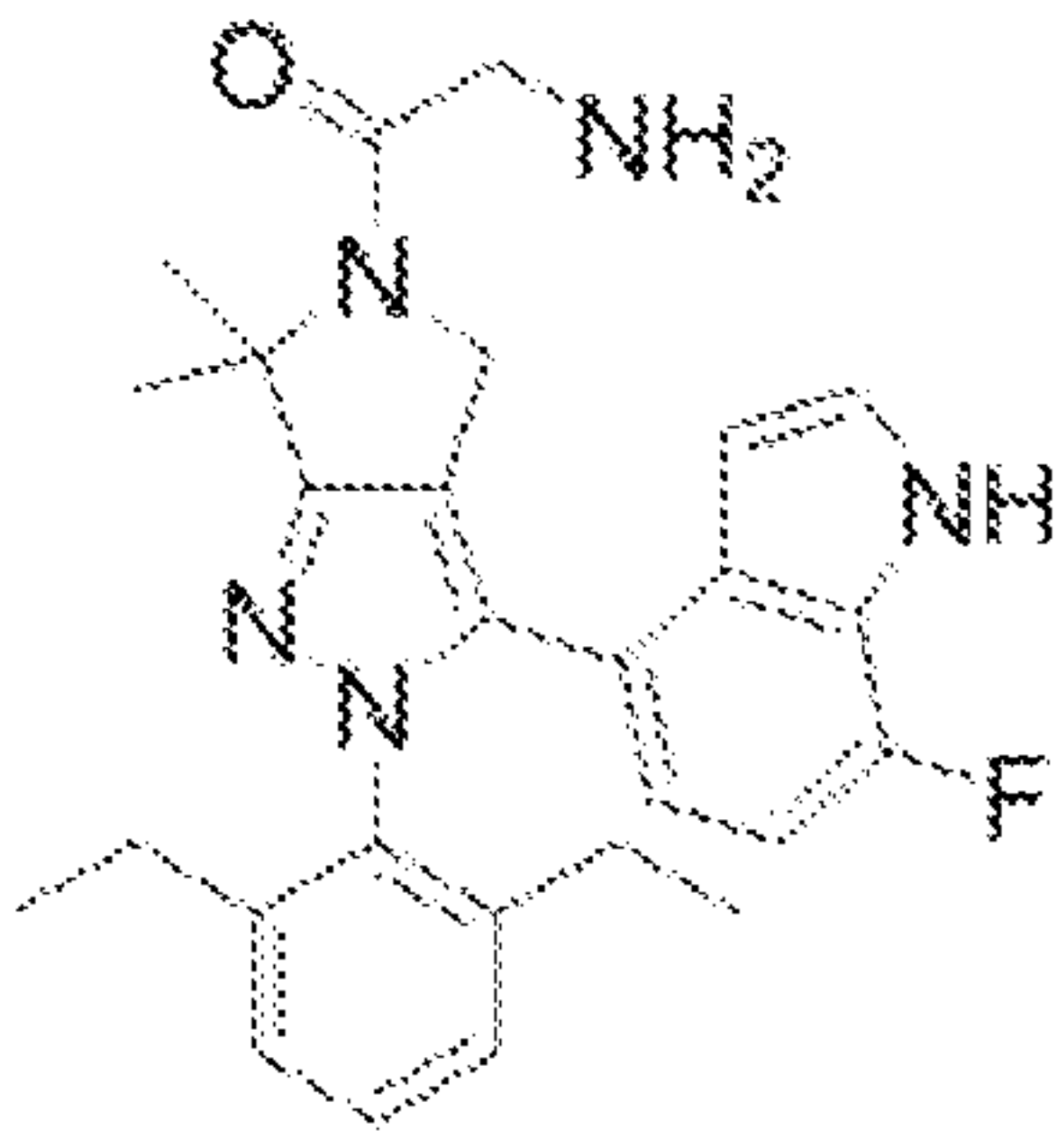
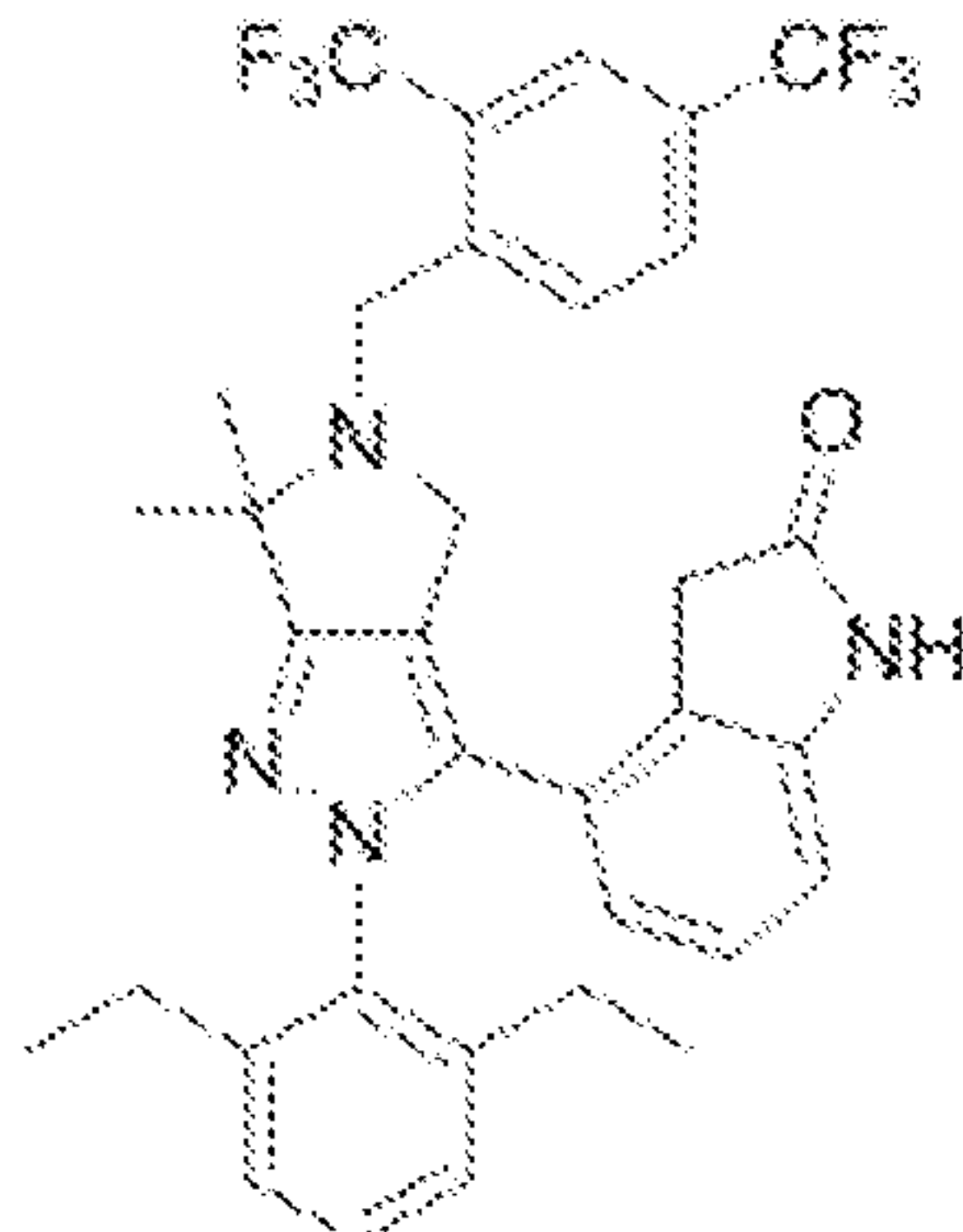
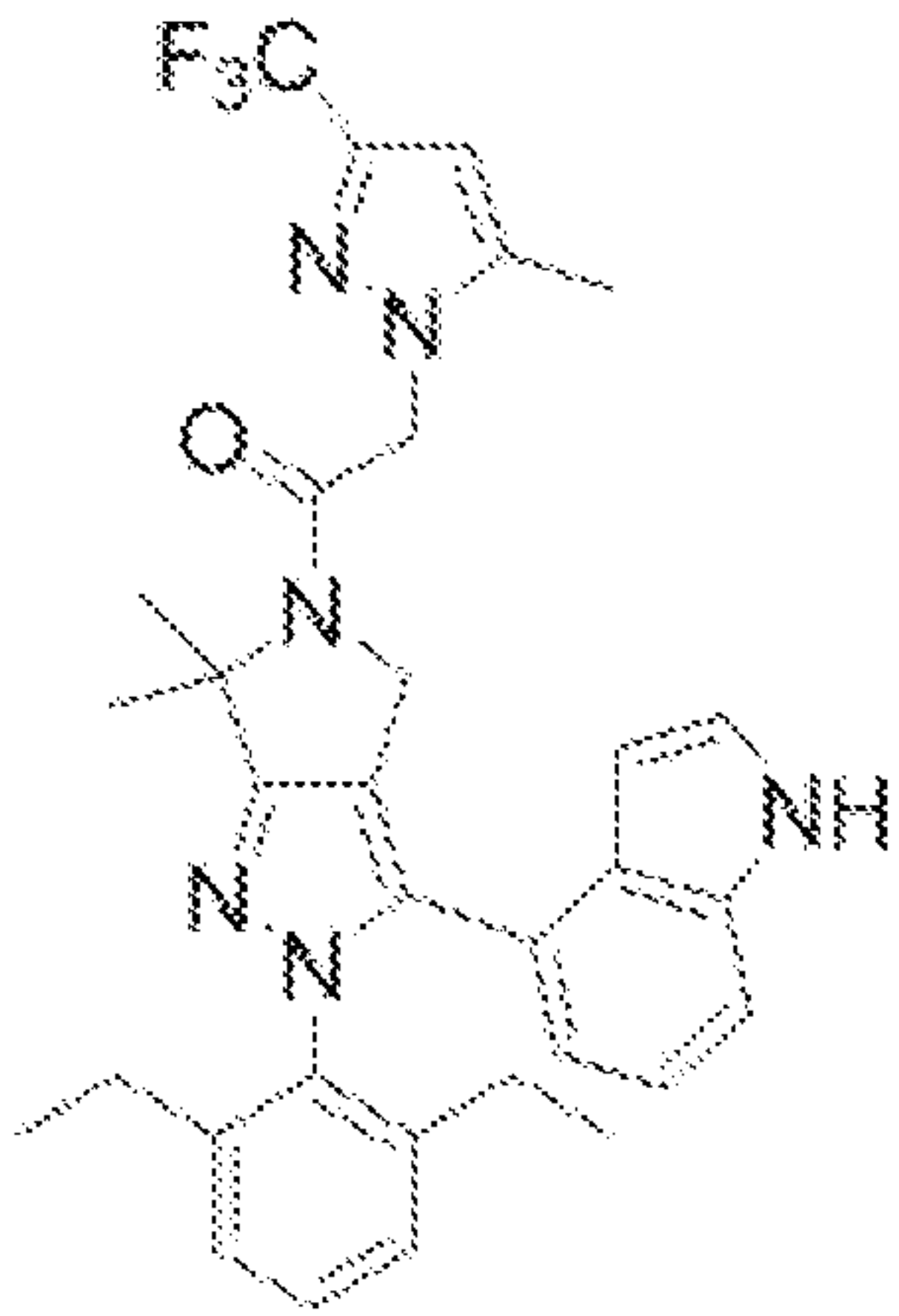
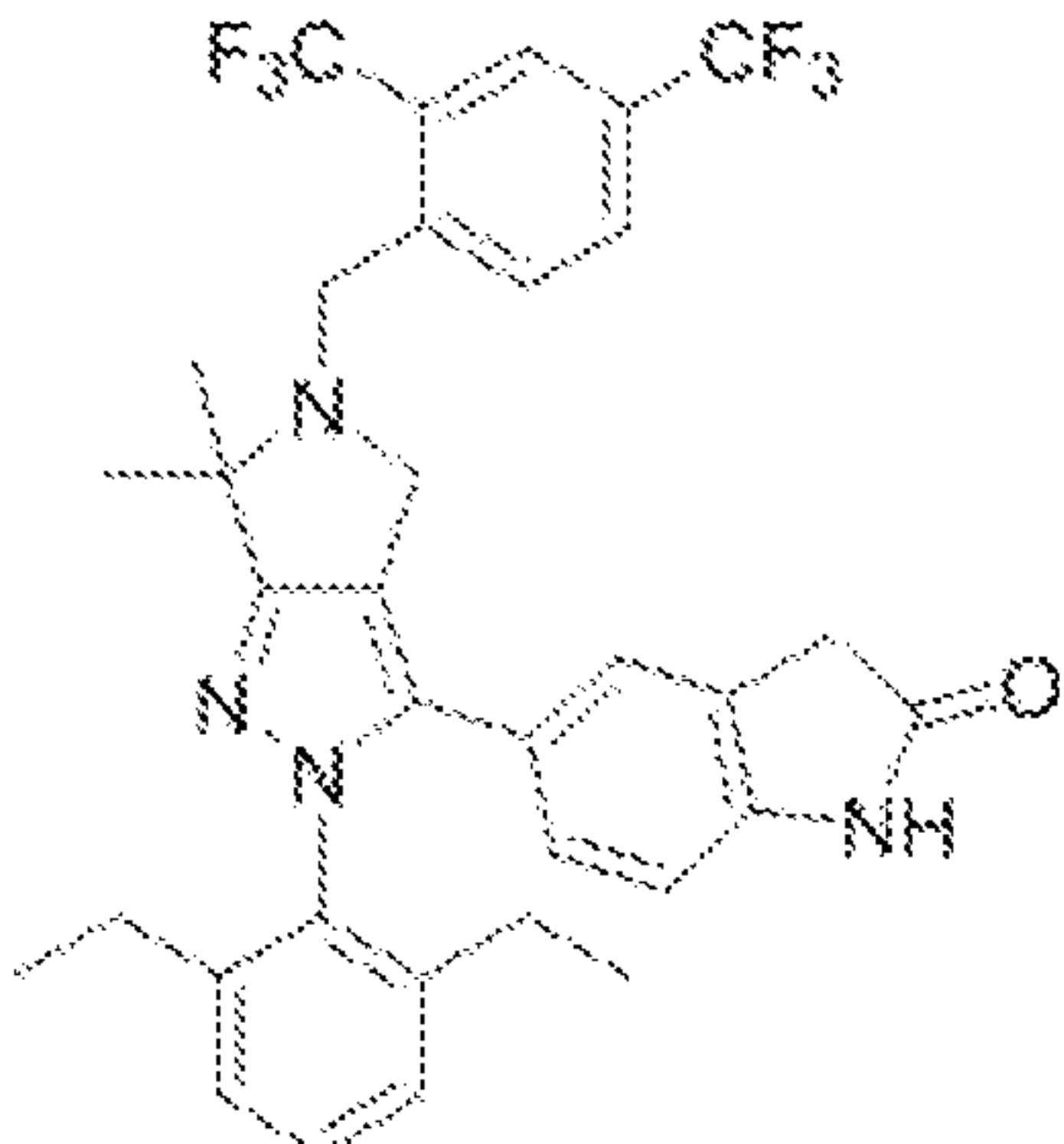
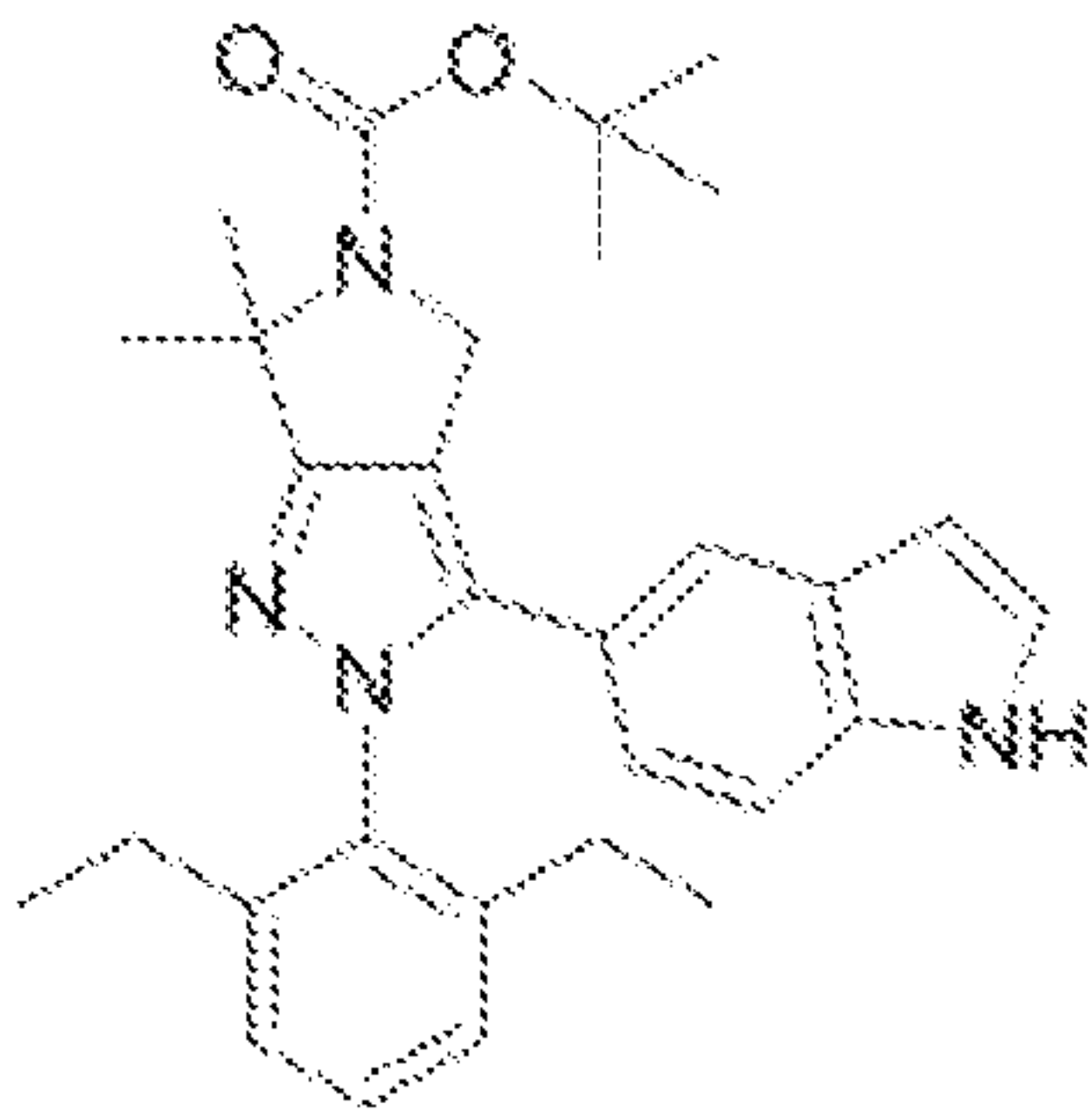
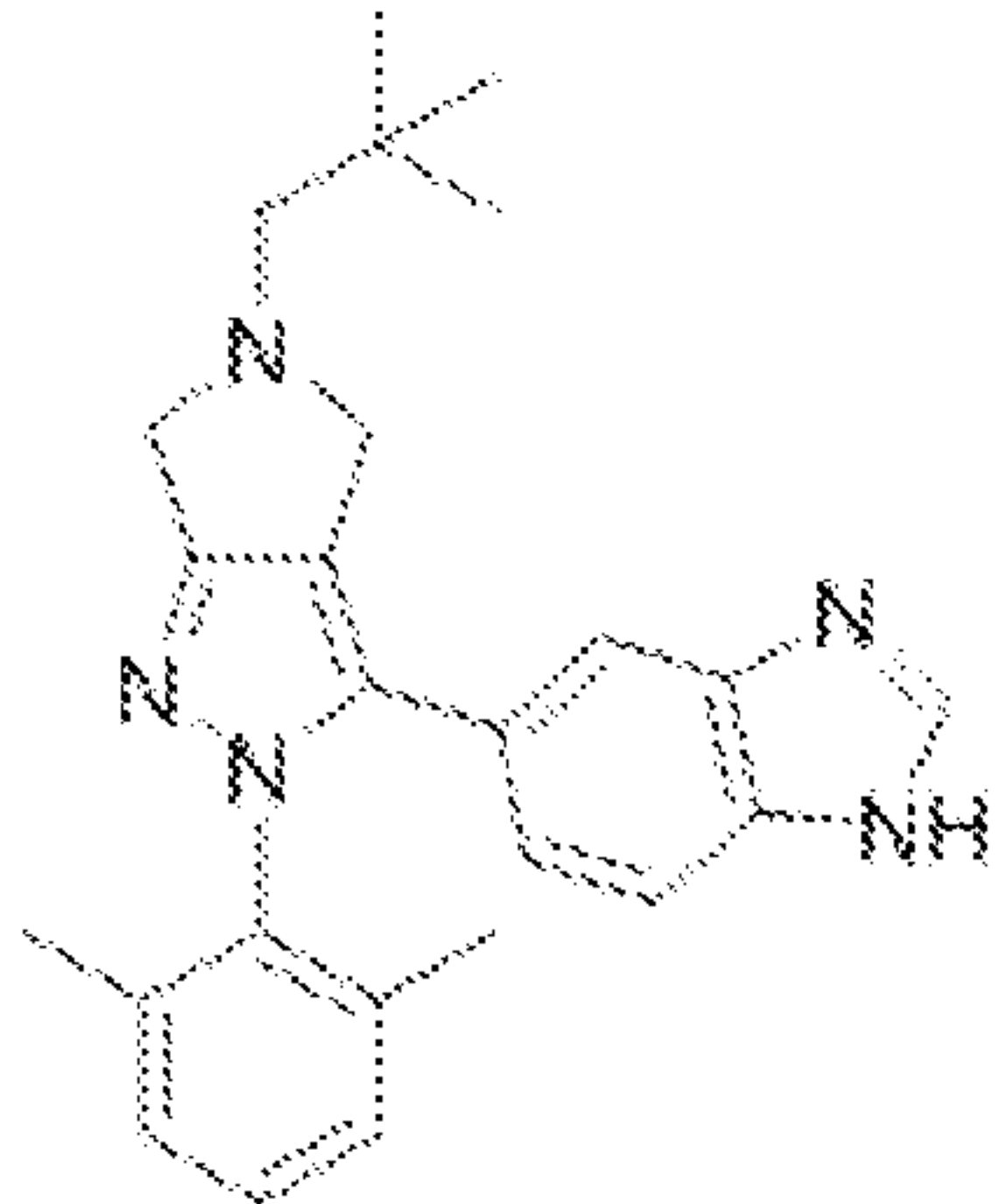
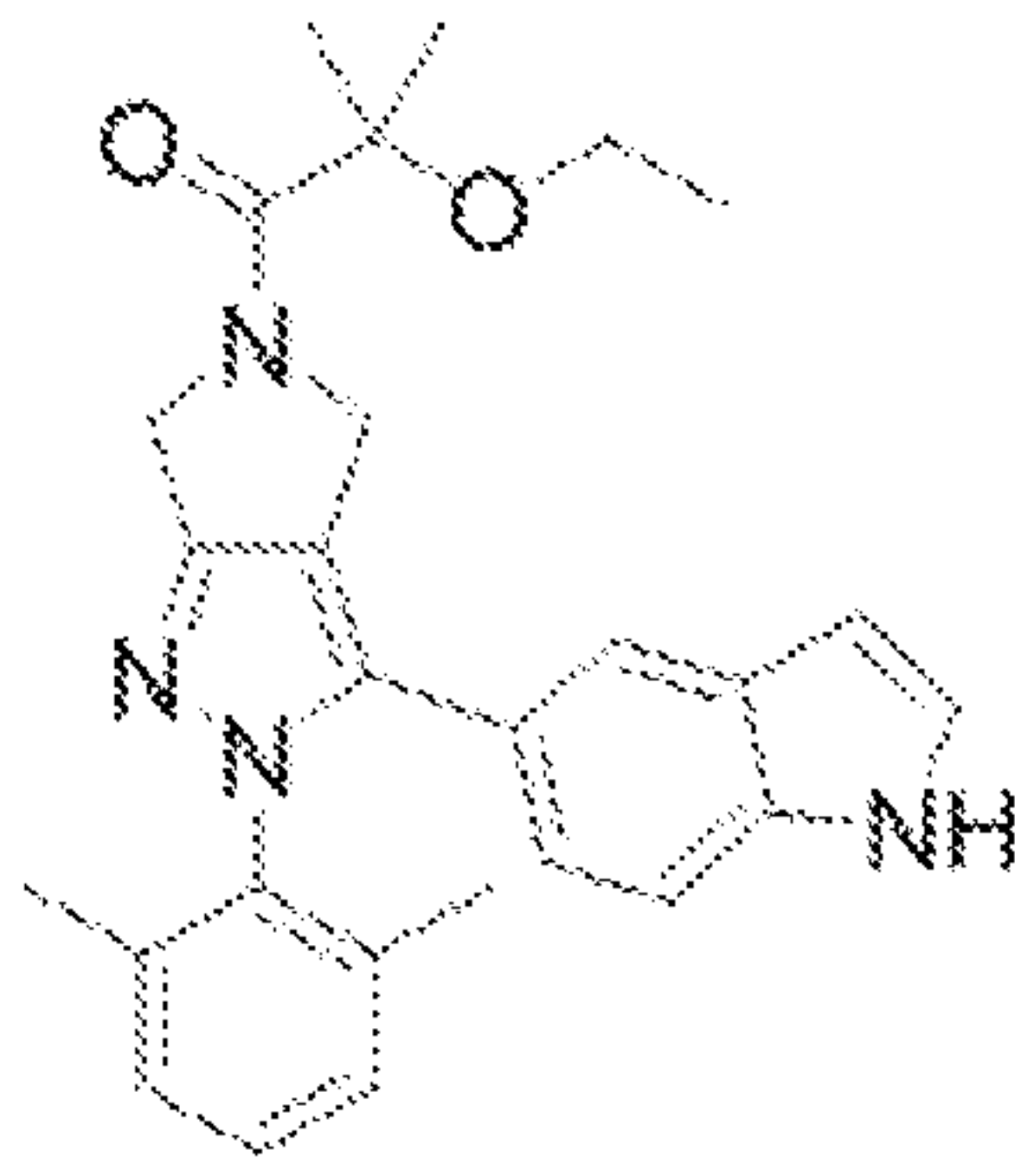
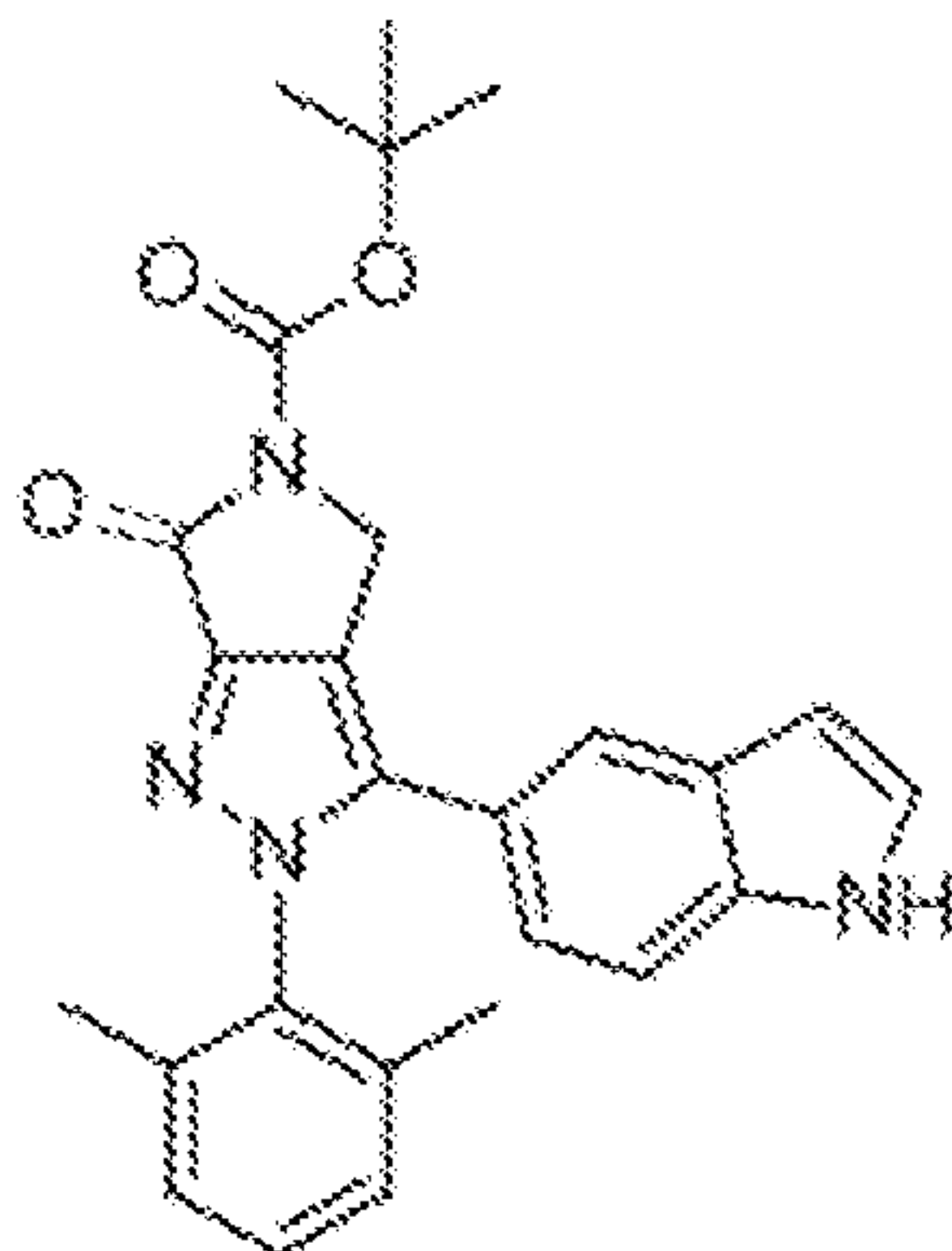
Ex. 13.038 	¹H NMR (400 MHz, CDCl₃) δ 8.15 (br, 1H), 7.48–7.56 (m, 2H), 7.24–7.44 (m, 5H), 7.08–7.20 (m, 4H), 6.83 (dd, <i>J</i> = 1.7, 8.6 Hz, 1H), 6.36–6.37 (m, 1H), 4.93 (s, 1H), 4.69 (d, <i>J</i> = 11.4 Hz, 1H), 4.18–4.35 (m, 4H), 3.94 (d, <i>J</i> = 11.4 Hz, 1H), 2.14–2.43 (m, 4H), 1.58 (s, 3H), 1.51 (s, 3H), 1.19–1.34 (m, 6H), 0.96–1.07 (m, 6H).	MS: (ES) <i>m/z</i> calculated for C₃₅H₃₉N₄O₂ [M + H]⁺ 547.3, found 547.5.
Ex. 13.039 	¹H NMR (400 MHz, CDCl₃) δ 8.17 (br, 1H), 7.13–7.37 (m, 4H), 7.03–7.06 (m, 2H), 6.89 (dd, <i>J</i> = 1.1, 8.5 Hz, 1H), 6.42–6.44 (m, 1H), 4.18 (s, 2H), 4.06 (s, 2H), 2.69 (s, 2H), 2.00 (s, 6H), 1.01 (s, 9H).	MS: (ES) <i>m/z</i> calculated for C₂₆H₃₁N₄ [M + H]⁺ 399.3, found 399.5.

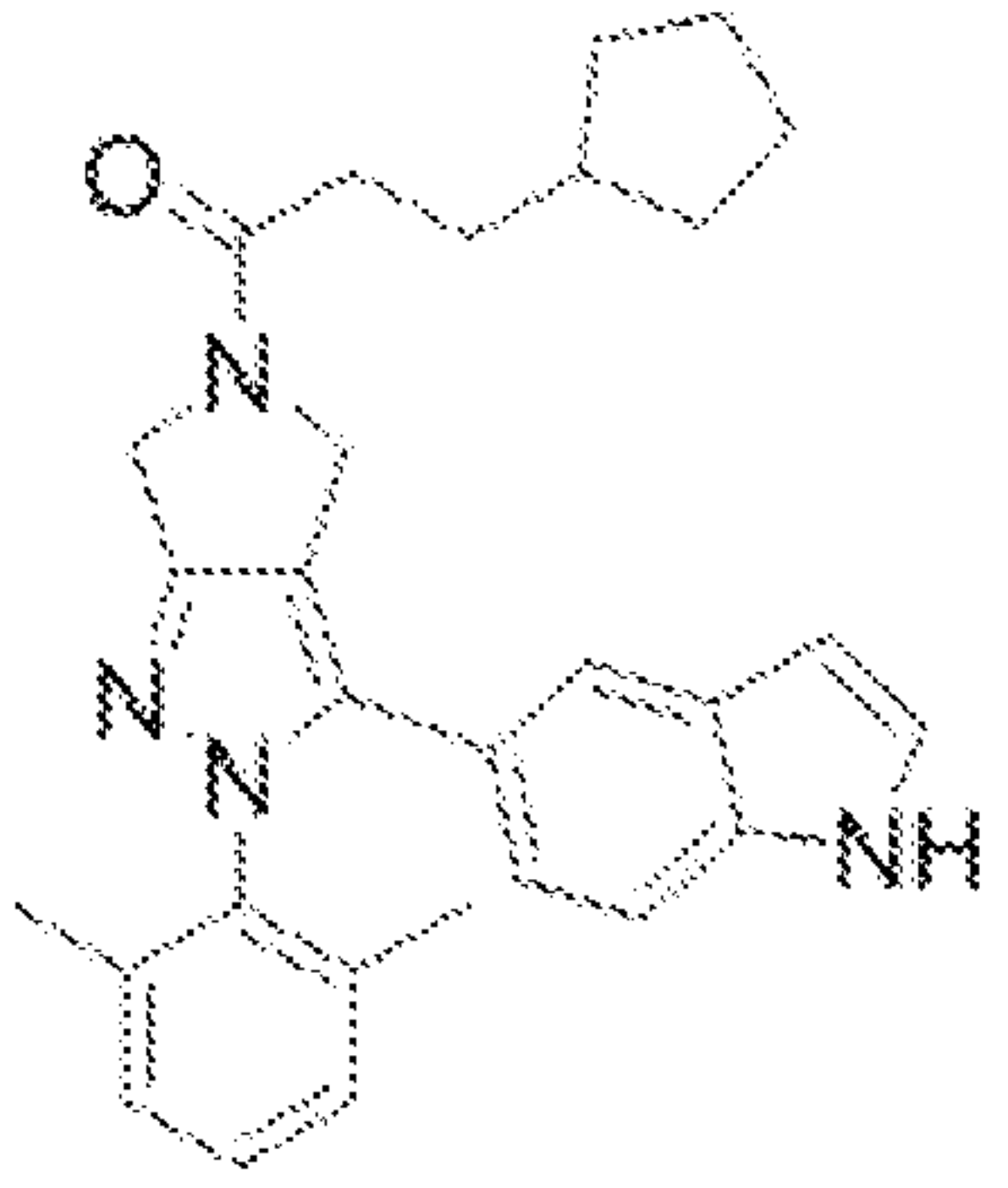
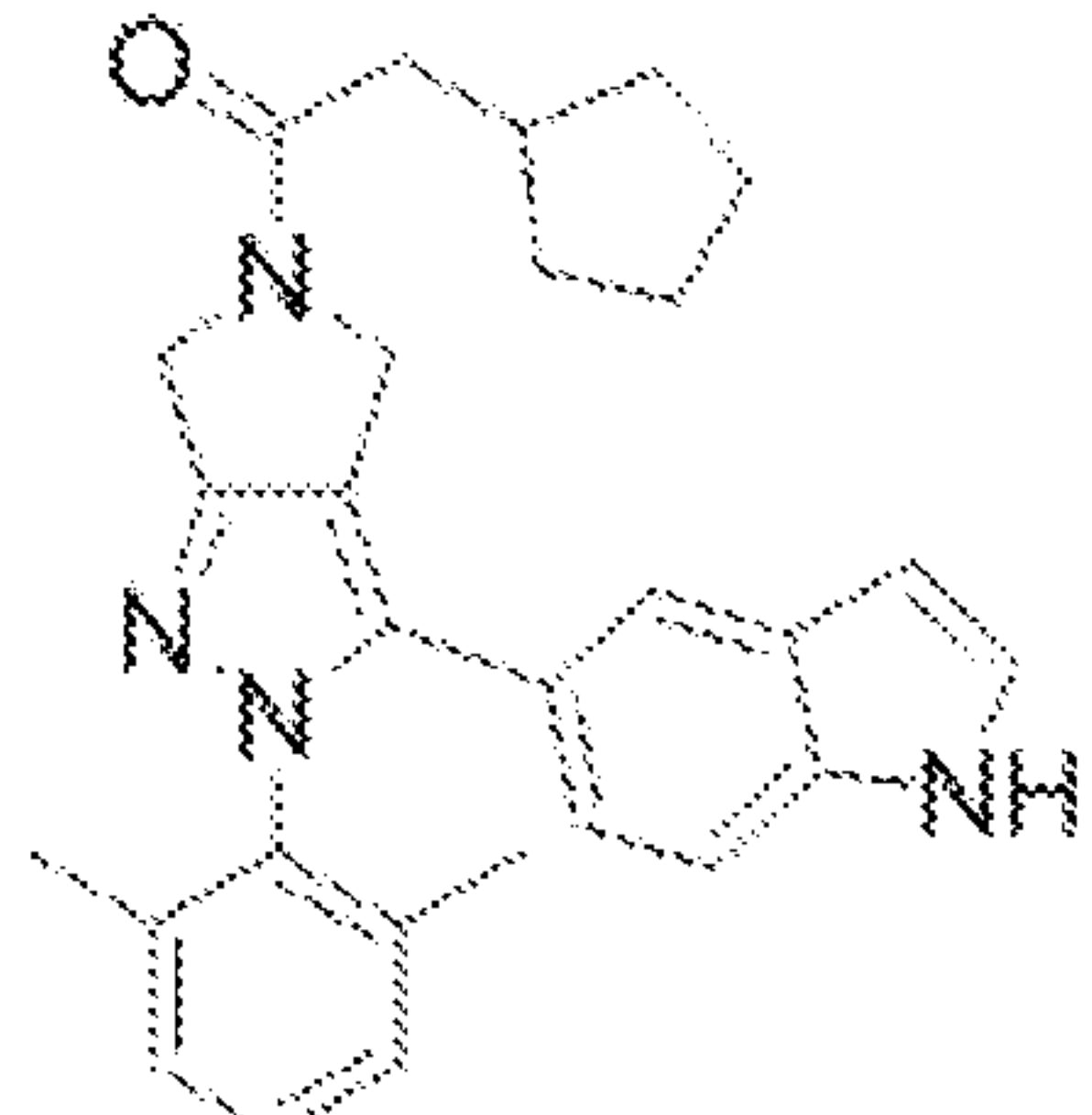
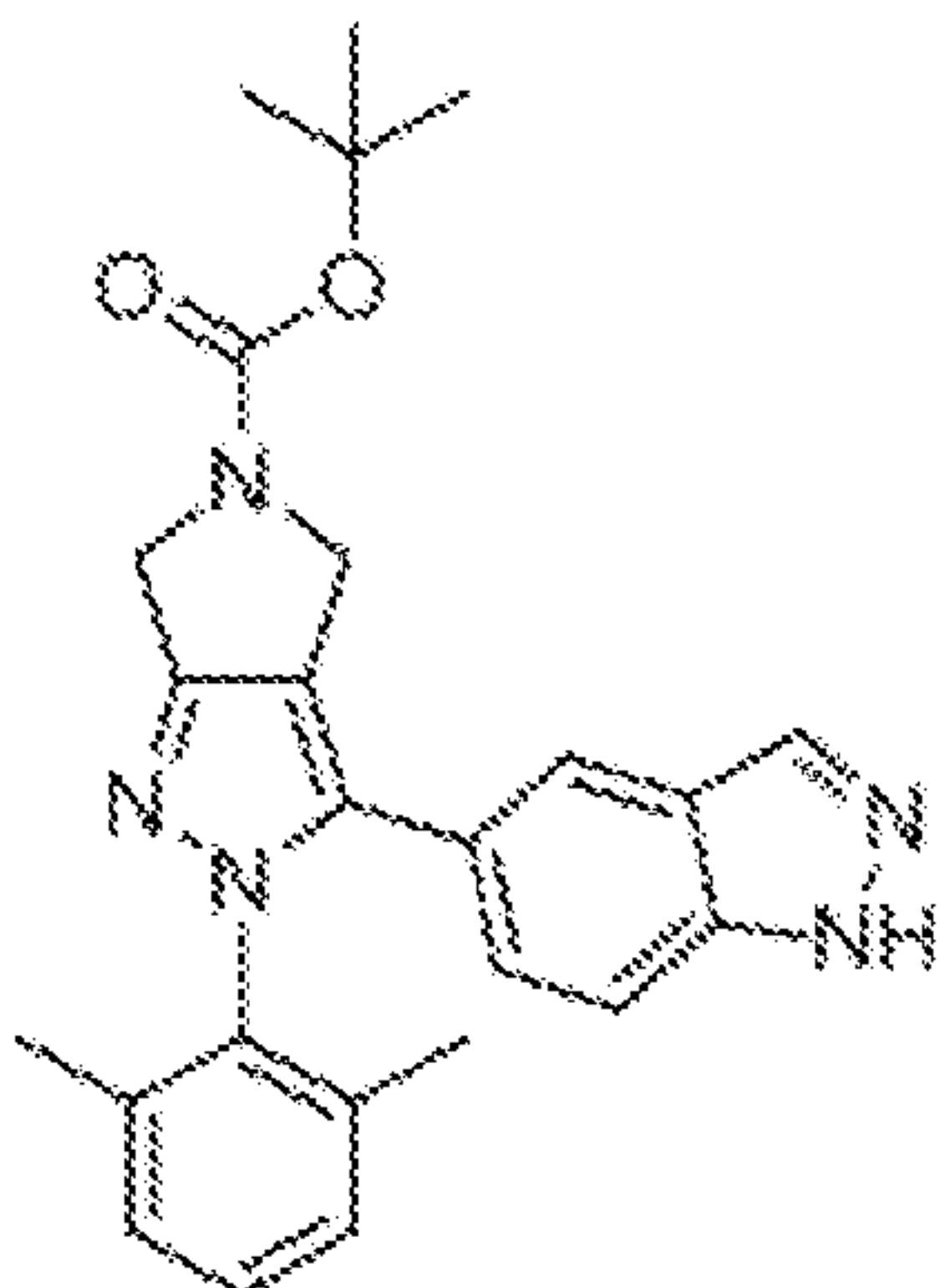
Table 2: Structure & MS Characterization Data of Specific Embodiments

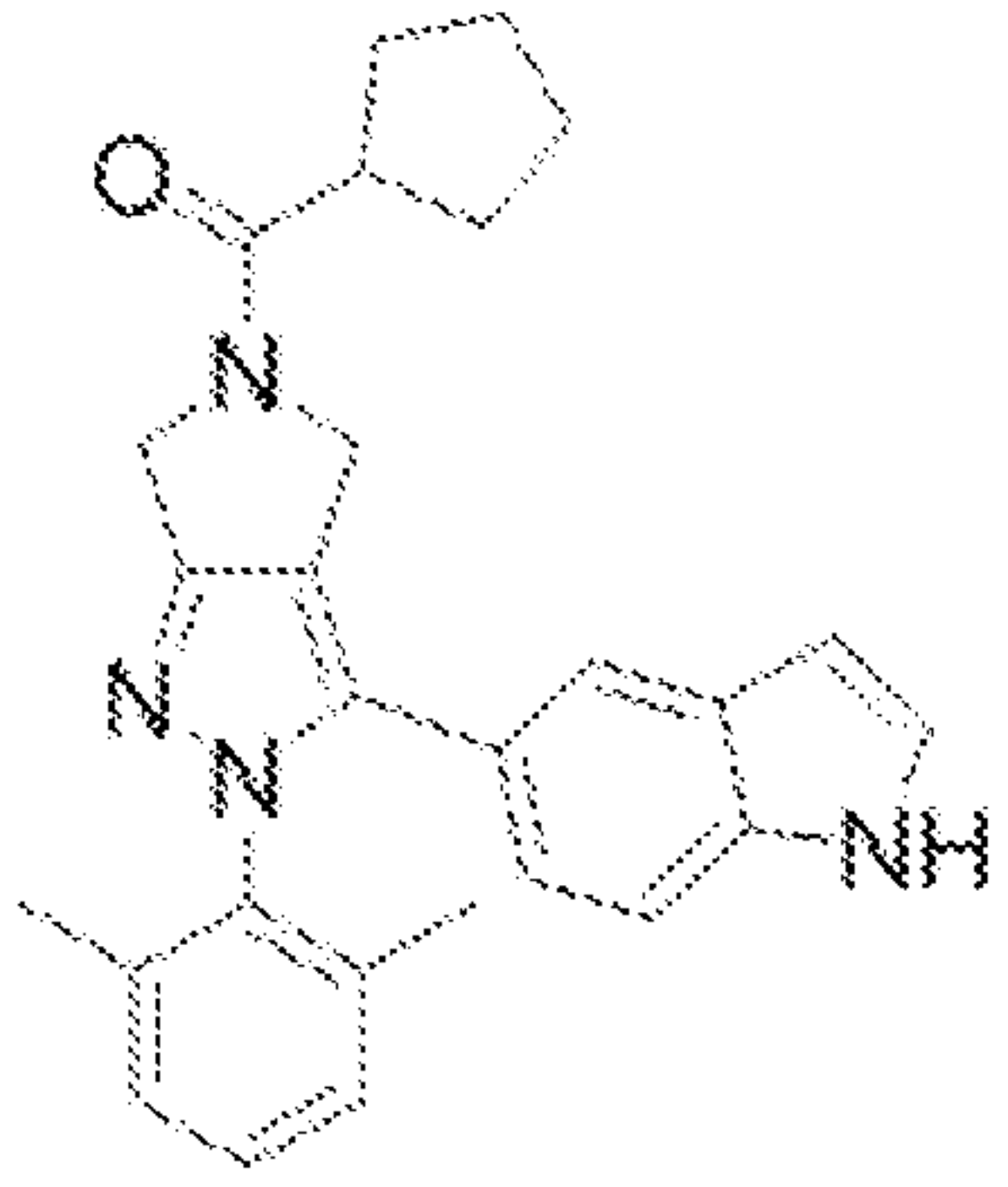
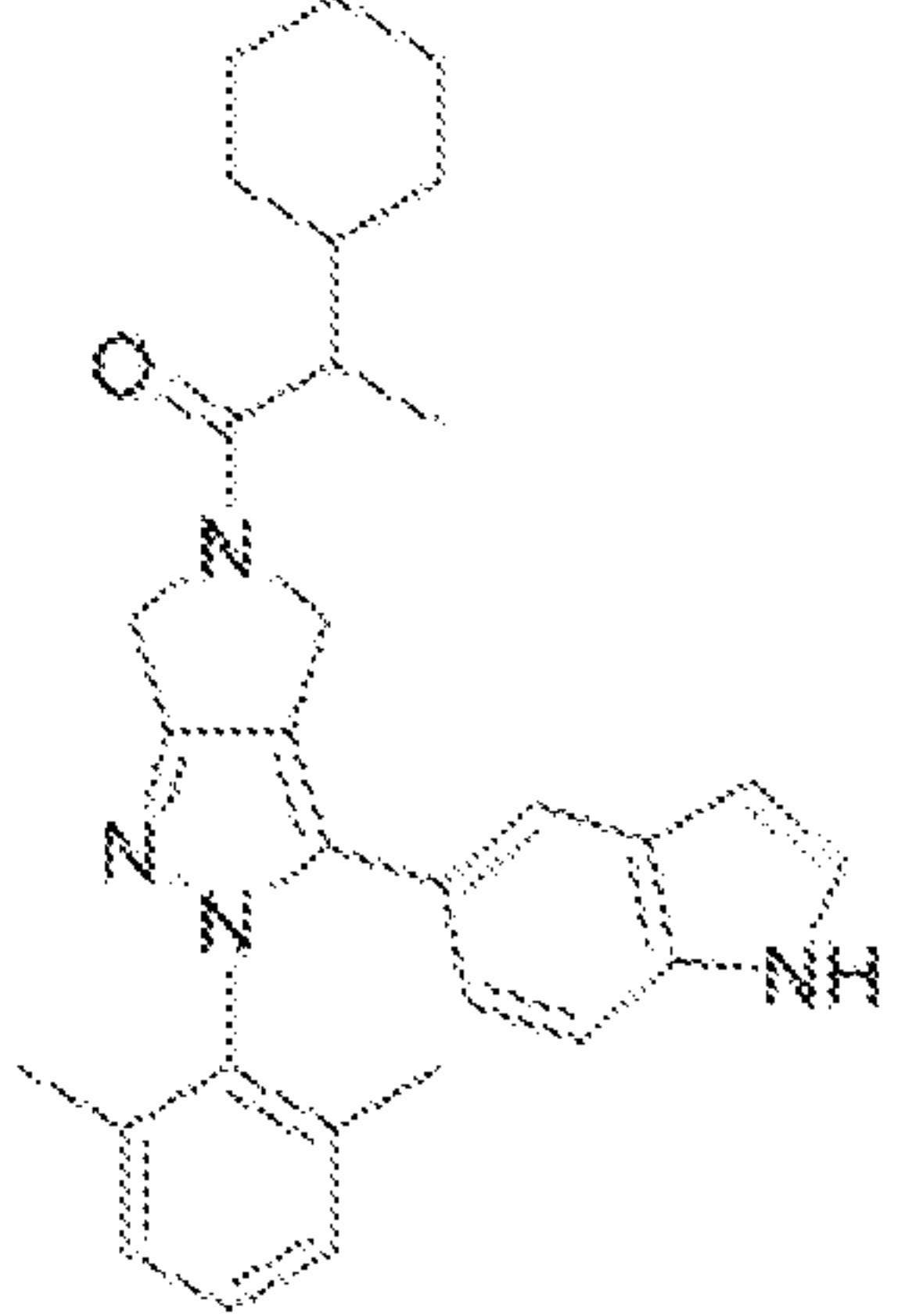
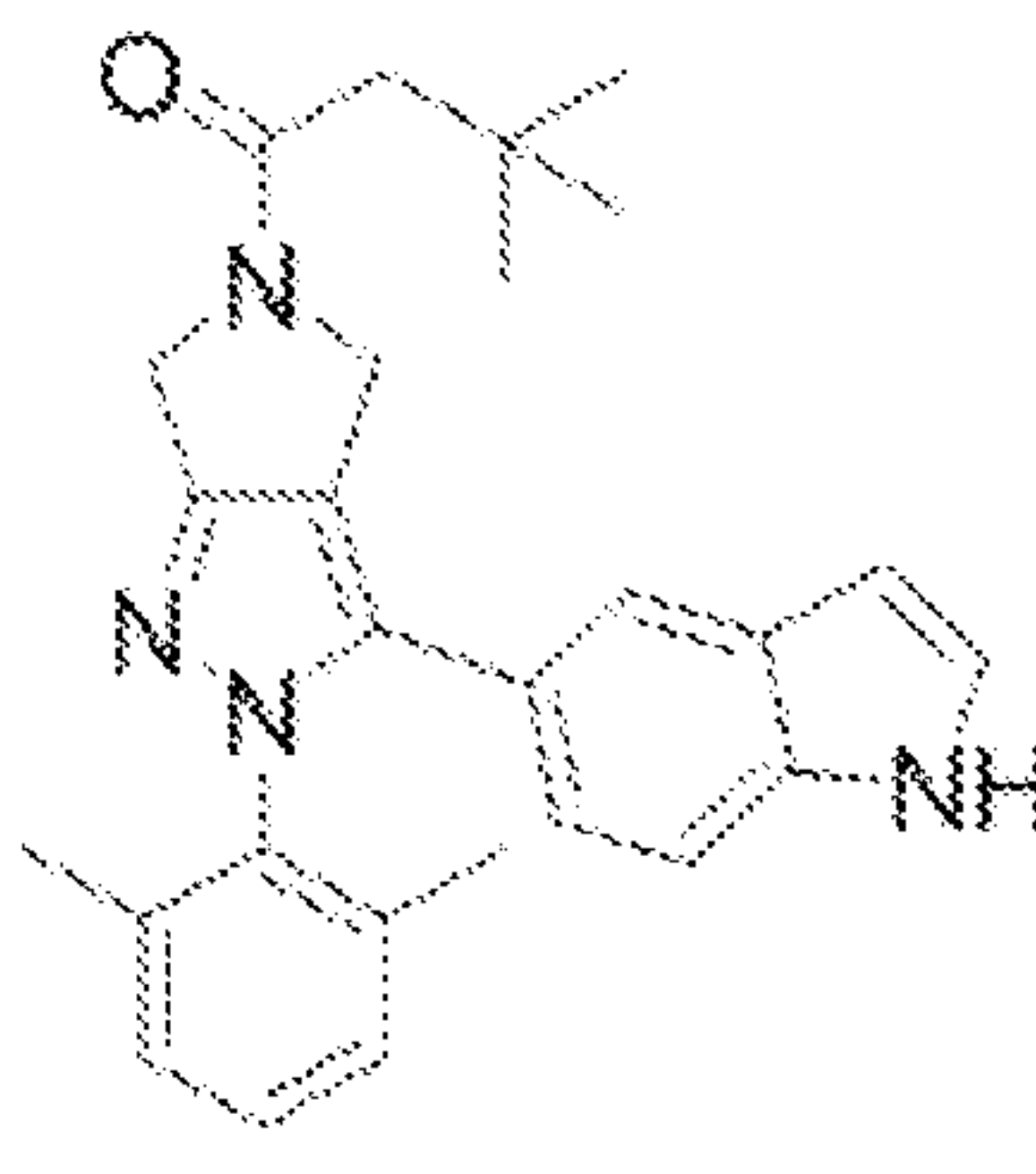
Structure	MS
Ex. 13.040 	MS: (ES) <i>m/z</i> calculated for C₂₉H₃₅FN₅O [M + H]⁺ 488.3, found 488.3.

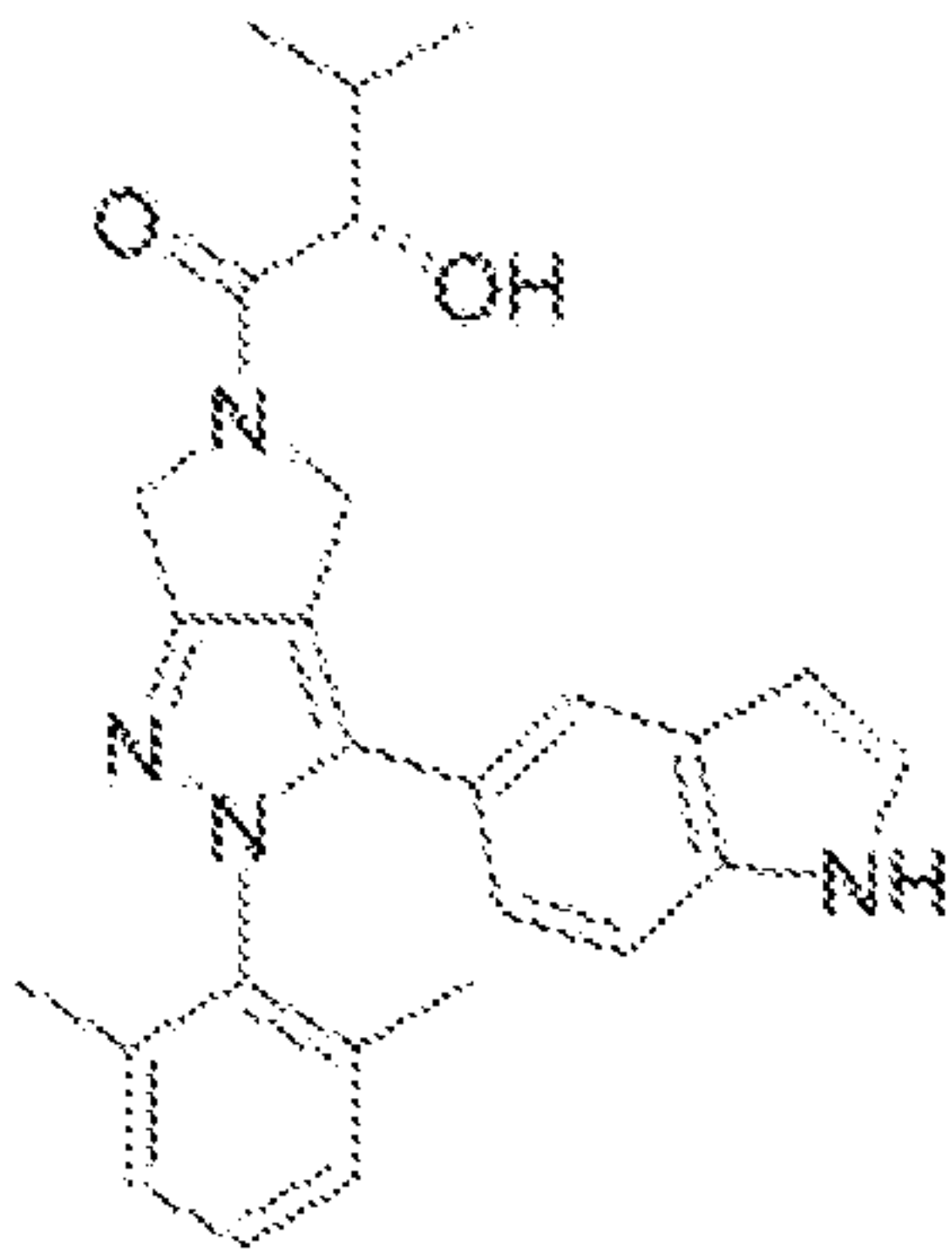
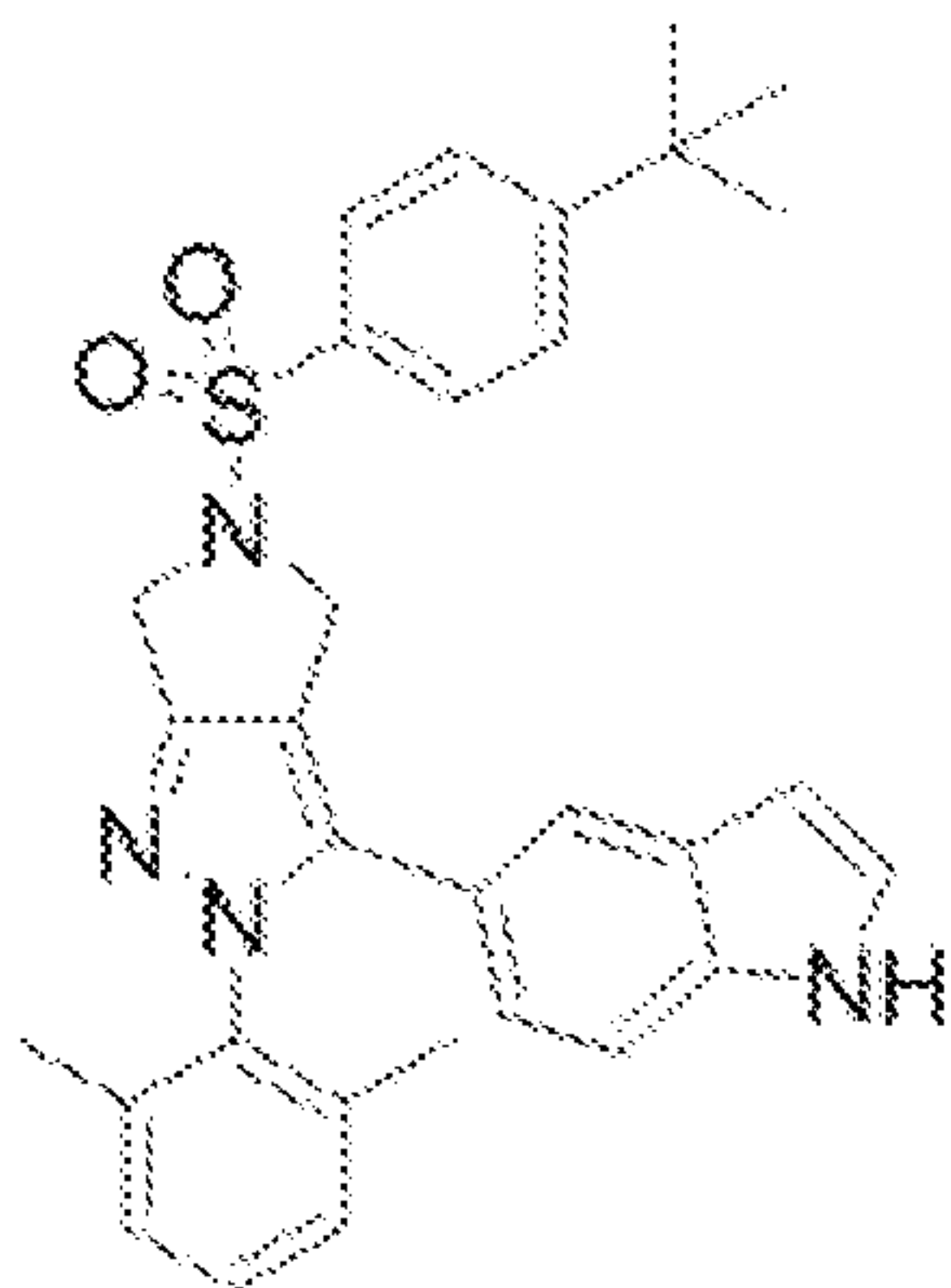
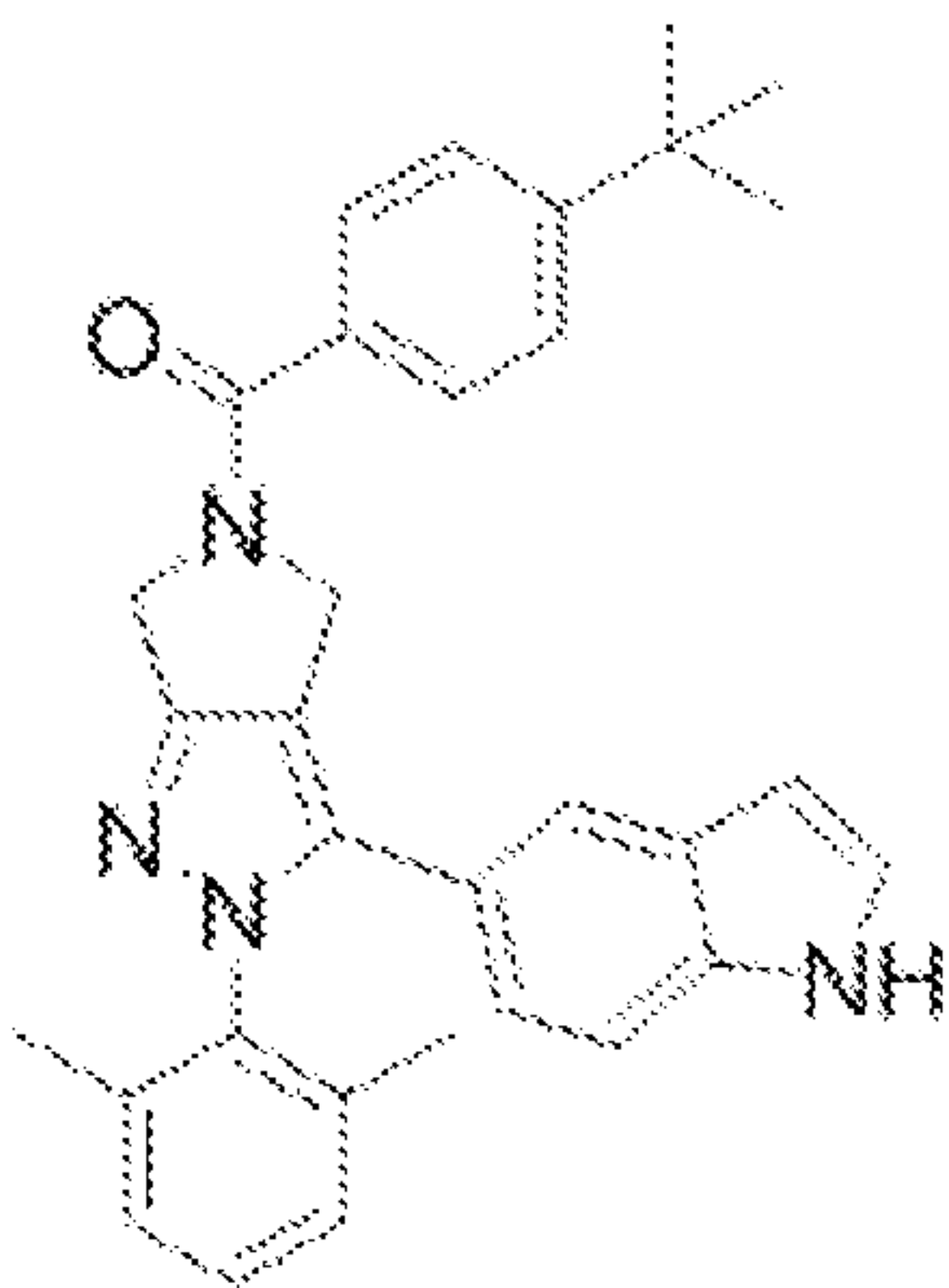
Ex. 13.041 	MS: (ES) <i>m/z</i> calculated for C₃₅H₃₂F₆N₄O₂ [M + H]⁺ 655.2, found 655.2.
Ex. 13.042 	MS: (ES) <i>m/z</i> calculated for C₂₇H₃₁FN₅O [M + H]⁺ 460.3, found 460.3.
Ex. 13.043 	MS: (ES) <i>m/z</i> calculated for C₃₄H₃₃F₆N₄O [M + H]⁺ 627.3, found 627.3.

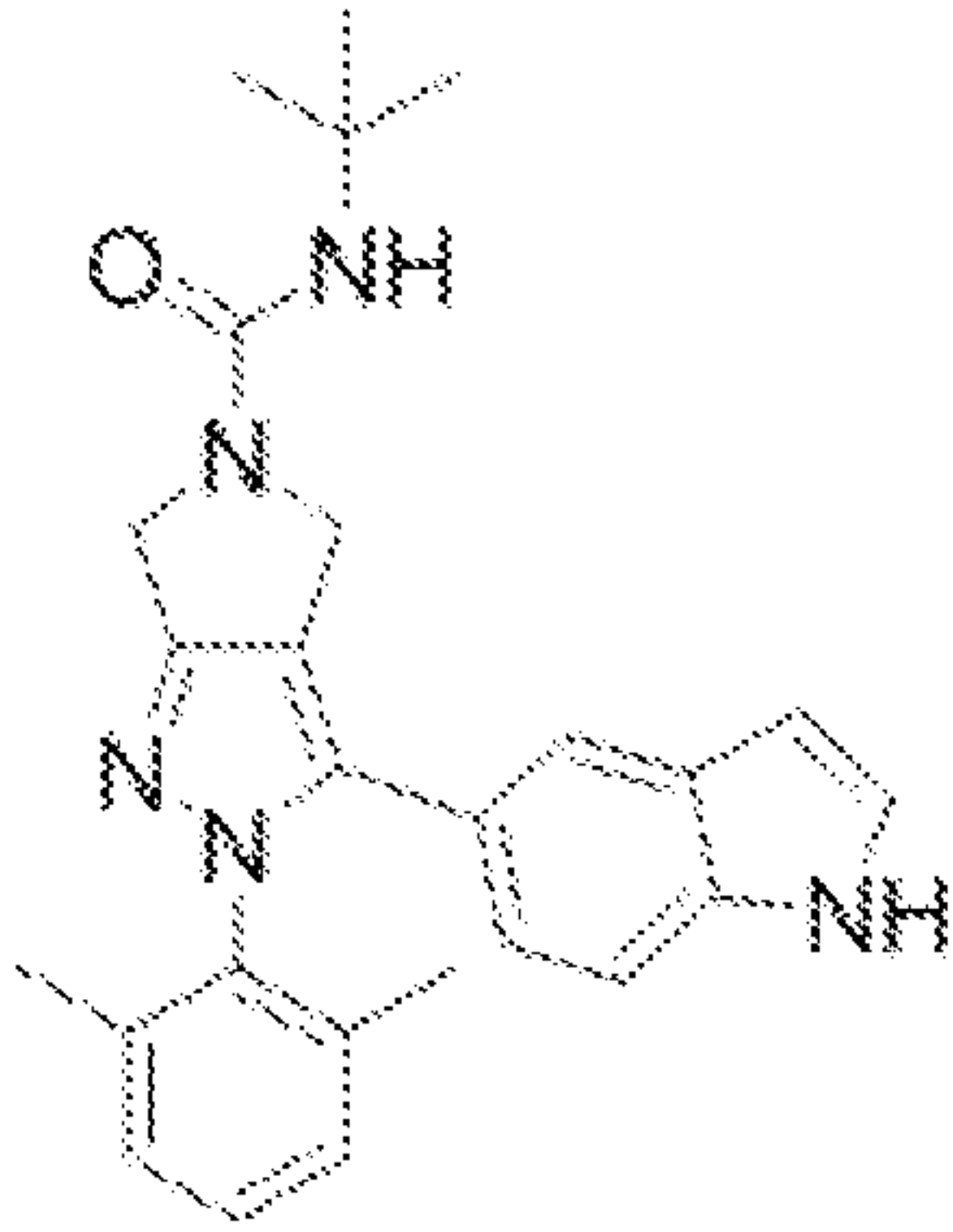
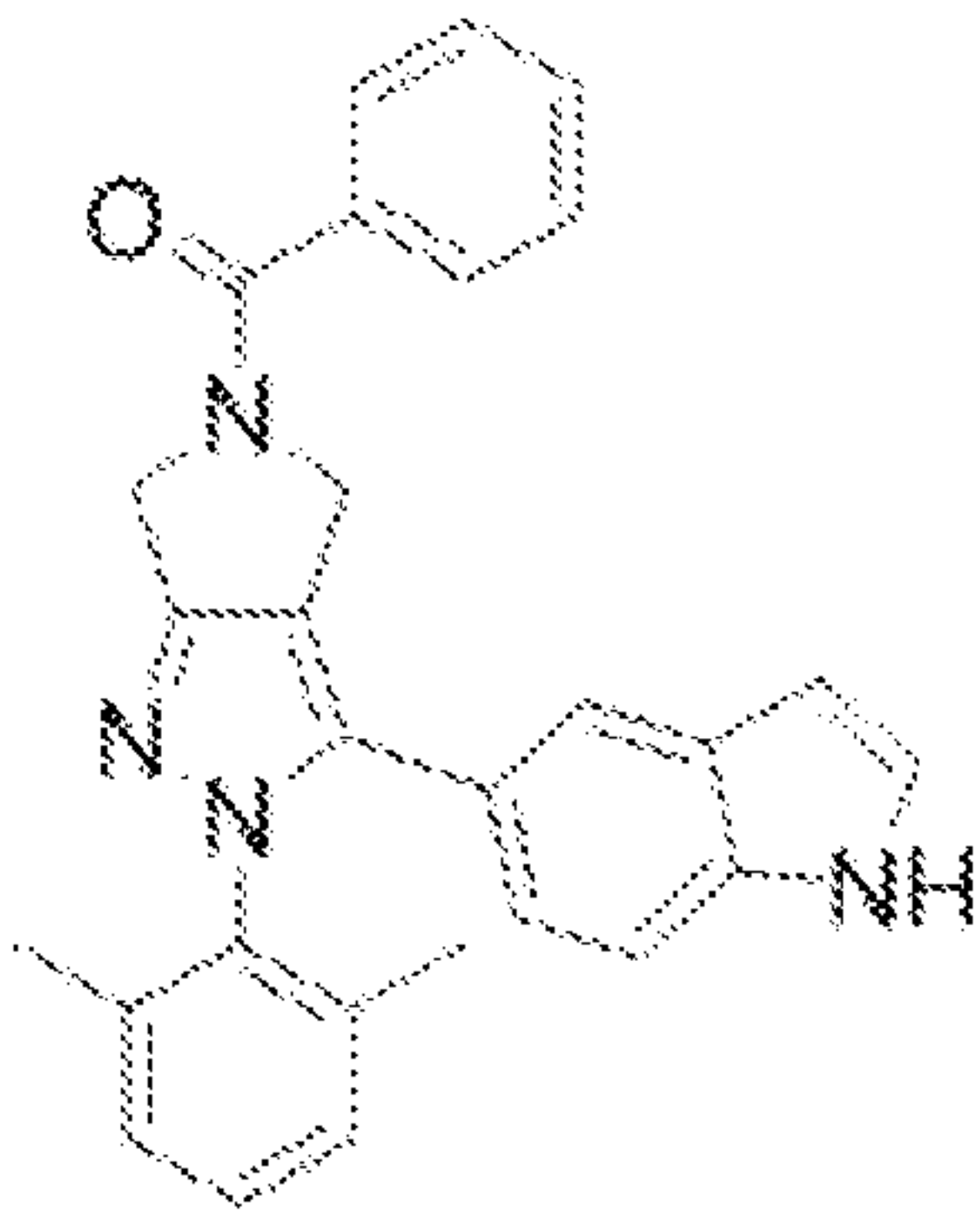
Ex. 13.044 	MS: (ES) <i>m/z</i> calculated for $C_{32}H_{34}F_3N_6O$ $[M + H]^+$ 575.3, found 575.3.
Ex. 13.045 	MS: (ES) <i>m/z</i> calculated for $C_{34}H_{33}F_6N_4O$ $[M + H]^+$ 627.3, found 627.3.
Ex. 13.046 	MS: (ES) <i>m/z</i> calculated for $C_{30}H_{37}N_4O_2$ $[M + H]^+$ 485.3, found 485.5.

Ex. 13.047 	MS: (ES) <i>m/z</i> calculated for C ₂₅ H ₃₀ N ₅ [M + H] ⁺ 400.2, found 400.5.
Ex. 13.048 	MS: (ES) <i>m/z</i> calculated for C ₂₇ H ₃₁ N ₄ O ₂ [M + H] ⁺ 443.2, found 443.2.
Ex. 13.049 	MS: (ES) <i>m/z</i> calculated for C ₂₆ H ₂₇ N ₄ O ₃ [M + H] ⁺ 443.2, found 443.2.

Ex. 13.050 	MS: (ES) <i>m/z</i> calculated for $C_{29}H_{33}N_4O$ $[M + H]^+$ 453.2, found 453.2.
Ex. 13.051 	MS: (ES) <i>m/z</i> calculated for $C_{28}H_{31}N_4O$ $[M + H]^+$ 439.2, found 439.2.
Ex. 13.052 	MS: (ES) <i>m/z</i> calculated for $C_{25}H_{28}N_5O_2$ $[M + H]^+$ 430.2, found 430.2.

Ex. 13.053 	MS: (ES) <i>m/z</i> calculated for $C_{27}H_{29}N_4O$ $[M + H]^+$ 425.2, found 425.2.
Ex. 13.054 	MS: (ES) <i>m/z</i> calculated for $C_{30}H_{35}N_4O$ $[M + H]^+$ 467.3, found 467.5.
Ex. 13.055 	MS: (ES) <i>m/z</i> calculated for $C_{27}H_{31}N_4O$ $[M + H]^+$ 427.2, found 427.2.

Ex. 13.056 	MS: (ES) <i>m/z</i> calculated for C ₂₆ H ₂₉ N ₄ O ₂ [M + H] ⁺ 429.2, found 429.5.
Ex. 13.057 	MS: (ES) <i>m/z</i> calculated for C ₃₁ H ₃₃ N ₄ O ₂ S [M + H] ⁺ 525.2, found 525.2.
Ex. 13.058 	MS: (ES) <i>m/z</i> calculated for C ₃₂ H ₃₃ N ₄ O [M + H] ⁺ 489.3, found 489.3.

Ex. 13.059 	MS: (ES) <i>m/z</i> calculated for $C_{26}H_{30}N_5O$ $[M + H]^+$ 428.2, found 428.2.
Ex. 13.060 	MS: (ES) <i>m/z</i> calculated for $C_{28}H_{25}N_4O$ $[M + H]^+$ 433.2, found 433.2.

Example 14

[0152] This example illustrates the evaluation of the biological activity associated with specific compounds of the invention.

MATERIALS AND METHODS

5 A. Cells

1. C5a receptor expressing cells

a) *U937 Cells*

[0153] U937 cells are a monocytic cell line which express C5aR, and are available from ATCC (VA). These cells were cultured as a suspension in RPMI-1640 medium supplemented with 2
10 mM L-glutamine, 1.5 g/L sodium bicarbonate, 4.5 g/L glucose, 10 mM HEPES, 1 mM sodium

pyruvate, and 10% FBS. Cells were grown under 5% CO₂/95% air, 100% humidity at 37°C and subcultured twice weekly at 1:6 (cells were cultured at a density range of 1 x 10⁵ to 2 x 10⁶ cells/mL) and harvested at 1 x 10⁶ cells/mL. Prior to assay, cells are treated overnight with 0.5 mM of cyclic AMP (Sigma, OH) and washed once prior to use. cAMP treated U937 cells can be used in C5aR ligand binding and functional assays.

b) Isolated human neutrophils

[0154] Optionally, human or murine neutrophils can be used to assay for compound activity. Neutrophils may be isolated from fresh human blood using density separation and centrifugation. Briefly, whole blood is incubated with equal parts 3% dextran and allowed to separate for 45 minutes. After separation, the top layer is layered on top of 15 mls of Ficoll (15 mls of Ficoll for every 30 mls of blood suspension) and centrifuged for 30 minutes at 400 x g with no brake. The pellet at the bottom of the tube is then isolated and resuspended into PharmLyse RBC Lysis Buffer (BD Biosciences, San Jose, CA) after which the sample is again centrifuged for 10 minutes at 400 x g with brake. The remaining cell pellet is resuspended as appropriate and consists of isolated neutrophils.

B. Assays

1. Inhibition of C5aR ligand binding

[0155] cAMP treated U937 cells expressing C5aR were centrifuged and resuspended in assay buffer (20 mM HEPES pH 7.1, 140 mM NaCl, 1 mM CaCl₂, 5 mM MgCl₂, and with 0.1% bovine serum albumin) to a concentration of 3 x 10⁶ cells/mL. Binding assays were set up as follows. 0.1 mL of cells was added to the assay plates containing 5 µL of the compound, giving a final concentration of ~2-10 µM each compound for screening (or part of a dose response for compound IC₅₀ determinations). Then 0.1 mL of ¹²⁵I labeled C5a (obtained from Perkin Elmer Life Sciences, Boston, MA) diluted in assay buffer to a final concentration of ~50 pM, yielding ~30,000 cpm per well, was added, the plates sealed and incubated for approximately 3 hours at 4°C on a shaker platform. Reactions were aspirated onto GF/B glass filters pre-soaked in 0.3% polyethyleneimine (PEI) solution, on a vacuum cell harvester (Packard Instruments; Meriden, CT). Scintillation fluid (40 µl; Microscint 20, Packard Instruments) was added to each well, the

plates were sealed and radioactivity measured in a Topcount scintillation counter (Packard Instruments). Control wells containing either diluent only (for total counts) or excess C5a (1 µg/mL, for non-specific binding) were used to calculate the percent of total inhibition for compound. The computer program Prism from GraphPad, Inc. (San Diego, Ca) was used to
5 calculate IC₅₀ values. IC₅₀ values are those concentrations required to reduce the binding of radiolabeled C5a to the receptor by 50%. (For further descriptions of ligand binding and other functional assays, see Dairaghi, *et al.*, *J. Biol. Chem.* **274**:21569-21574 (1999), Penfold, *et al.*, *Proc. Natl. Acad. Sci. USA.* **96**:9839-9844 (1999), and Dairaghi, *et al.*, *J. Biol. Chem.* **272**:28206-28209 (1997)).

10 2. Calcium mobilization

[0156] Optionally, compounds may be further assayed for their ability to inhibit calcium flux in cells. To detect the release of intracellular stores of calcium, cells (e.g., cAMP stimulated U937 or neutrophils) are incubated with 3 µM of INDO-1AM dye (Molecular Probes; Eugene, OR) in cell media for 45 minutes at room temperature and washed with phosphate buffered
15 saline (PBS). After INDO-1AM loading, the cells are resuspended in flux buffer (Hank's balanced salt solution (HBSS) and 1% FBS). Calcium mobilization is measured using a Photon Technology International spectrophotometer (Photon Technology International; New Jersey) with excitation at 350 nm and dual simultaneous recording of fluorescence emission at 400 nm and 490 nm. Relative intracellular calcium levels are expressed as the 400 nm/490 nm emission
20 ratio. Experiments are performed at 37°C with constant mixing in cuvettes each containing 10⁶ cells in 2 mL of flux buffer. The chemokine ligands may be used over a range from 1 to 100 nM. The emission ratio is plotted over time (typically 2-3 minutes). Candidate ligand blocking compounds (up to 10 µM) are added at 10 seconds, followed by chemokines at 60 seconds (*i.e.*, C5a; R&D Systems; Minneapolis, MN) and control chemokine (*i.e.*, SDF-1 ; R&D Systems;
25 Minneapolis, MN) at 150 seconds.

3. Chemotaxis assays

[0157] Optionally, compounds may be further assayed for their ability to inhibit chemotaxis in cells. Chemotaxis assays are performed using 5 µm pore polycarbonate, polyvinylpyrrolidone-coated filters in 96-well chemotaxis chambers (Neuroprobe; Gaithersburg, MD) using

chemotaxis buffer (Hank's balanced salt solution (HBSS) and 1% FBS). C5aR ligands (*i.e.*, C5a, R&D Systems; Minneapolis, MN) are used to evaluate compound mediated inhibition of C5aR mediated migration. Other chemokines (*i.e.*, SDF-1 α ; R&D Systems; Minneapolis, MN) are used as specificity controls. The lower chamber is loaded with 29 μ l of chemokine (*i.e.*, 0.03 nM C5a) and varying amounts of compound; the top chamber contains 100,000 U937 or neutrophil cells in 20 μ l. The chambers are incubated 1.5 hours at 37°C, and the number of cells in the lower chamber quantified either by direct cell counts in five high powered fields per well or by the CyQuant assay (Molecular Probes), a fluorescent dye method that measures nucleic acid content and microscopic observation.

C. Identification of inhibitors of C5aR

1. Assay

[0158] To evaluate small organic molecules that prevent the C5a receptor from binding ligand, an assay was employed that detected radioactive ligand (*i.e.*, C5a) binding to cells expressing C5aR on the cell surface (for example, cAMP stimulated U937 cells or isolated human neutrophils). For compounds that inhibited binding, whether competitive or not, fewer radioactive counts are observed when compared to uninhibited controls.

[0159] Equal numbers of cells were added to each well in the plate. The cells were then incubated with radiolabeled C5a. Unbound ligand was removed by washing the cells, and bound ligand was determined by quantifying radioactive counts. Cells that were incubated without any organic compound gave total counts; non-specific binding was determined by incubating the cells with unlabeled ligand and labeled ligand. Percent inhibition was determined by the equation:

$$\% \text{ inhibition} = (1 - [(\text{sample cpm}) - (\text{nonspecific cpm})] / [(\text{total cpm}) - (\text{nonspecific cpm})]) \times 100.$$

2. Dose Response Curves

[0160] To ascertain a candidate compound's affinity for C5aR as well as confirm its ability to inhibit ligand binding, inhibitory activity was titrated over a 1×10^{-10} to 1×10^{-4} M range of compound concentrations. In the assay, the amount of compound was varied; while cell number and ligand concentration were held constant.

D. **In Vivo Efficacy Models**

[0161] The compounds of interest can be evaluated for potential efficacy in treating a C5a mediated conditions by determining the efficacy of the compound in an animal model. In addition to the models described below, other suitable animal models for studying the compound of interest can be found in Mizuno, M. *et al.*, *Expert Opin. Investig. Drugs* (2005), 14(7), 807-821, which is incorporated herein by reference in its entirety.

1. **Models of C5a induced Leukopenia**

a) **C5a induced Leukopenia in a Human C5aR knock-in Mouse Model**

[0162] To study the efficacy of compounds of the instant invention in an animal model, a recombinant mouse can be created using standard techniques, wherein the genetic sequence coding for the mouse C5aR is replaced with sequence coding for the human C5aR, to create a hC5aR-KI mouse. In this mouse, administration of hC5a leads to upregulation of adhesion molecules on blood vessel walls which bind blood leukocytes, sequestering them from the blood stream. Animals are administered 20ug/kg of hC5a and 1 minute later leukocytes are quantified in peripheral blood by standard techniques. Pretreatment of mice with varying doses of the present compounds can almost completely block the hC5a induced leukopenia.

b) **C5a induced Leukopenia in a Cynomolgus Model**

[0163] To study the efficacy of compounds of the instant invention in a non-human primate model, C5a induced leukopenia is studied in a cynomolgus model. In this model administration of hC5a leads to upregulation of adhesion molecules on blood vessel walls which

bind blood leukocytes, hence sequestering them from the blood stream. Animals are administered 10ug/kg of hC5a and 1 minute later leukocytes are quantified in peripheral blood.

Mouse model of ANCA induced Vasculitis

[0164] On day 0 hC5aR-KI mice are intravenously injected with 50mg/kg purified antibody to myeloperoxidase (Xiao et al, *J. Clin. Invest.* **110**: 955-963 (2002)). Mice are further dosed with oral daily doses of compounds of the invention or vehicle for seven days, then mice are sacrificed and kidneys collected for histological examination. Analysis of kidney sections can show significantly reduced number and severity of crescentic and necrotic lesions in the glomeruli when compared to vehicle treated animals.

2. Mouse Model of Choroidal Neovascularization

[0165] To study the efficacy of compounds of the instant invention in treatment of age related macular degeneration (AMD) the bruch membrane in the eyes of hC5aR-KI mice are ruptured by laser photocoagulation (Nozika et al, *PNAS* **103**: 2328-2333 (2006). Mice are treated with vehicle or a daily oral or appropriate intra-vitreous dose of a compound of the invention for one to two weeks. Repair of laser induced damage and neovascularization are assessed by histology and angiography.

3. Rheumatoid Arthritis Models

a) Rabbit model of destructive joint inflammation

[0166] To study the effects of candidate compounds on inhibiting the inflammatory response of rabbits to an intra-articular injection of the bacterial membrane component lipopolysaccharide (LPS), a rabbit model of destructive joint inflammation is used. This study design mimics the destructive joint inflammation seen in arthritis. Intra-articular injection of LPS causes an acute inflammatory response characterized by the release of cytokines and chemokines, many of which have been identified in rheumatoid arthritic joints. Marked increases in leukocytes occur in synovial fluid and in synovium in response to elevation of these chemotactic mediators. Selective antagonists of chemokine receptors have shown efficacy in this model (see Podolin, *et al.*, *J. Immunol.* 169(11):6435-6444 (2002)).

[0167] A rabbit LPS study is conducted essentially as described in Podolin, et al. *ibid.*, female New Zealand rabbits (approximately 2 kilograms) are treated intra-articularly in one knee with LPS (10 ng) together with either vehicle only (phosphate buffered saline with 1% DMSO) or with addition of candidate compound (dose 1 = 50 μ M or dose 2 = 100 μ M) in a total volume of 1.0 mL. Sixteen hours after the LPS injection, knees are lavaged and cells counts are performed. Beneficial effects of treatment were determined by histopathologic evaluation of synovial inflammation. Inflammation scores are used for the histopathologic evaluation: 1 - minimal, 2 - mild, 3 - moderate, 4 - moderate-marked.

b) *Evaluation of a compound in a rat model of collagen induced arthritis*

[0168] A 17 day developing type II collagen arthritis study is conducted to evaluate the effects of a candidate compound on arthritis induced clinical ankle swelling. Rat collagen arthritis is an experimental model of polyarthritis that has been widely used for preclinical testing of numerous anti-arthritic agents (see Trentham, et al., *J. Exp. Med.* **146(3)**:857-868 (1977), Bendele, et al., *Toxicologic Pathol.* **27**:134-142 (1999), Bendele, et al., *Arthritis Rheum.* **42**:498-506 (1999)). The hallmarks of this model are reliable onset and progression of robust, easily measurable polyarticular inflammation, marked cartilage destruction in association with pannus formation and mild to moderate bone resorption and periosteal bone proliferation.

[0169] Female Lewis rats (approximately 0.2 kilograms) are anesthetized with isoflurane and injected with Freund's Incomplete Adjuvant containing 2 mg/mL bovine type II collagen at the base of the tail and two sites on the back on days 0 and 6 of this 17 day study. A candidate compound is dosed daily in a sub-cutaneous manner from day 0 till day 17 at a efficacious dose. Caliper measurements of the ankle joint diameter were taken, and reducing joint swelling is taken as a measure of efficacy.

4. Rat model of Sepsis

[0170] To study the effect of compounds of interest on inhibiting the generalized inflammatory response that is associated with a sepsis like disease, the Cecal Ligation and Puncture (CLP) rat model of sepsis is used. A Rat CLP study is conducted essentially as described in Fujimura N, et al. (*American Journal Respiratory Critical Care Medicine* 2000; 161: 440-446). Briefly

described here, Wistar Albino Rats of both sexes weighing between 200-250 g are fasted for twelve hours prior to experiments. Animals are kept on normal 12 hour light and dark cycles and fed standard rat chow up until 12 hours prior to experiment. Then animals are split into four groups; (i) two sham operation groups and (ii) two CLP groups. Each of these two groups (i.e., (i) and (ii)) is split into vehicle control group and test compound group. Sepsis is induced by the CLP method. Under brief anesthesia a midline laparotomy is made using minimal dissection and the cecum is ligated just below the ileocaecal valve with 3-0 silk, so the intestinal continuity is maintained. The antimesenteric surface of the cecum is perforated with an 18 gauge needle at two locations 1 cm apart and the cecum is gently squeezed until fecal matter is extruded. The bowel is then returned to the abdomen and the incision is closed. At the end of the operation, all rats are resuscitated with saline, 3 ml/100 g body weight, given subcutaneously. Postoperatively, the rats are deprived of food, but have free access to water for the next 16 hours until they are sacrificed. The sham operated groups are given a laparotomy and the cecum is manipulated but not ligated or perforated. Beneficial effects of treatment are measured by histopathological scoring of tissues and organs as well as measurement of several key indicators of hepatic function, renal function, and lipid peroxidation. To test for hepatic function aspartate transaminase (AST) and alanine transaminase (ALT) are measured. Blood urea nitrogen and creatinine concentrations are studied to assess renal function. Pro-inflammatory cytokines such as TNF-alpha and IL-1beta are also assayed by ELISA for serum levels.

5. Mouse SLE model of experimental lupus nephritis.

[0171] To study the effect of compounds of interest on a Systemic Lupus Erythematosus (SLE), the MRL/*lpr* murine SLE model is used. The MRL/Mp-*Tmfrsf6*^{*lpr/lpr*} strain (MRL/*lpr*) is a commonly used mouse model of human SLE. To test compounds efficacy in this model male MRL/*lpr* mice are equally divided between control and C5aR antagonists groups at 13 weeks of age. Then over the next 6 weeks compound or vehicle is administered to the animals via osmotic pumps to maintain coverage and minimize stress effects on the animals. Serum and urine samples are collected bi-weekly during the six weeks of disease onset and progression. In a minority of these mice glomerulosclerosis develops leading to the death of the animal from renal failure. Following mortality as an indicator of renal failure is one of the measured criteria and successful treatment will usually result in a delay in the onset of sudden death among the test

groups. In addition, the presence and magnitude of renal disease may also be monitored continuously with blood urea nitrogen (BUN) and albuminuria measurements. Tissues and organs were also harvested at 19 weeks and subjected to histopathology and immunohistochemistry and scored based on tissue damage and cellular infiltration.

5 6. Rat model of COPD

[0172] Smoke induced airway inflammation in rodent models may be used to assess efficacy of compounds in Chronic Obstructive Pulmonary Disease (COPD). Selective antagonists of chemokines have shown efficacy in this model (*see*, Stevenson, et al., *Am. J. Physiol Lung Cell Mol Physiol.* 288 L514-L522, (2005)). An acute rat model of COPD is conducted as described
10 by Stevenson et al. A compound of interest is administered either systemically via oral or IV dosing; or locally with nebulized compound. Male Sprague-Dawley rats (350-400 g) are placed in Perspex chambers and exposed to cigarette smoke drawn in via a pump (50 mL every 30 seconds with fresh air in between). Rats are exposed for a total period of 32 minutes. Rats are sacrificed up to 7 days after initial exposure. Any beneficial effects of treatment are assessed by
15 a decrease inflammatory cell infiltrate, decreases in chemokine and cytokine levels.

[0173] In a chronic model, mice or rats are exposed to daily tobacco smoke exposures for up to 12 months. Compound is administered systemically via once daily oral dosing, or potentially locally via nebulized compound. In addition to the inflammation observed with the acute model (Stevensen et al.), animals may also exhibit other pathologies similar to that seen in human
20 COPD such as emphysema (as indicated by increased mean linear intercept) as well as altered lung chemistry (see Martorana et al, *Am. J. Respir. Crit Care Med.* 172(7): 848-53.

7. Mouse EAE Model of Multiple Sclerosis

[0174] Experimental autoimmune encephalomyelitis (EAE) is a model of human multiple sclerosis. Variations of the model have been published, and are well known in the field. In a
25 typical protocol, C57BL/6 (Charles River Laboratories) mice are used for the EAE model. Mice are immunized with 200ug myelin oligodendrocyte glycoprotein (MOG) 35 55 (Peptide International) emulsified in Complete Freund s Adjuvant (CFA) containing 4 mg/ml Mycobacterium tuberculosis (Sigma-Aldrich) s.c. on day 0. In addition, on day 0 and day 2 animals are given 200 ng of pertussis toxin (Calbiochem) i.v. Clinical scoring is based on a scale

of 0-5: 0, no signs of disease; 1, flaccid tail; 2, hind limb weakness; 3, hind limb paralysis; 4, forelimb weakness or paralysis; 5, moribund. Dosing of the compounds of interest to be assessed can be initiated on day 0 (prophylactic) or day 7 (therapeutic, when histological evidence of disease is present but few animals are presenting clinical signs) and dosed once or more per day at concentrations appropriate for their activity and pharmacokinetic properties, e.g. 100 mg/kg s.c. Efficacy of compounds can be assessed by comparisons of severity (maximum mean clinical score in presence of compound compared to vehicle), or by measuring a decrease in the number of macrophages (F4/80 positive) isolated from spinal cords. Spinal cord mononuclear cells can be isolated via discontinuous Percoll-gradient. Cells can be stained using rat anti-mouse F4/80-PE or rat IgG2b-PE (Caltag Laboratories) and quantitated by FACS analysis using 10 ul of Polybeads per sample (Polysciences).

8. Mouse Model of Kidney Transplantation

[0175] Transplantation models can be performed in mice, for instance a model of allogeneic kidney transplant from C57BL/6 to BALB/c mice is described in Faikah Gueler et al, JASN Express, Aug 27th, 2008. Briefly, mice are anesthetized and the left donor kidney attached to a cuff of the aorta and the renal vein with a small caval cuff, and the ureters removed en block. After left nephrectomy of the recipient, the vascular cuffs are anastomosed to the recipient abdominal aorta and vena cava, respectively, below the level of the native renal vessels. The ureter is directly anastomosed into the bladder. Cold ischemia time is 60 min, and warm ischemia time is 30 min. The right native kidney can be removed at the time of allograft transplantation or at posttransplantation day 4 for long-term survival studies. General physical condition of the mice is monitored for evidence of rejection. Compound treatment of animals can be started before surgery or immediately after transplantation, eg by sub cut injection once daily. Mice are studied for renal function and survival. Serum creatinine levels are measured by an automated method (Beckman Analyzer, Krefeld, Germany).

9. Mouse Model of Ischemia/Reperfusion

[0176] A mouse model of ischemia/reperfusion injury can be performed as described by Xiufen Zheng et al, *Am. J. Pathol*, Vol 173:4, Oct, 2008. Briefly, CD1 mice aged 6-8 weeks are anesthetized and placed on a heating pad to maintain warmth during surgery. Following

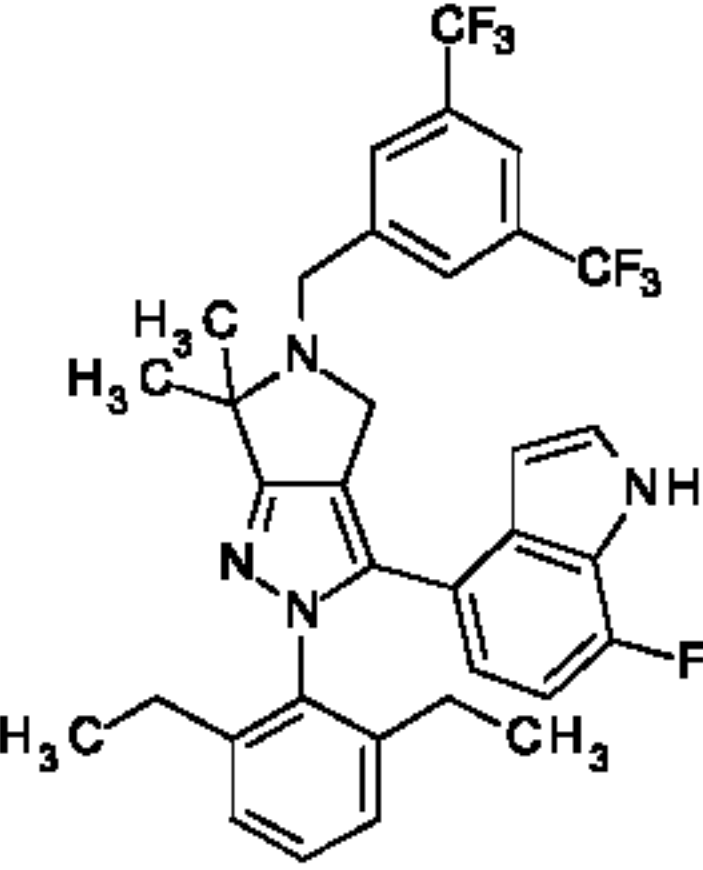
abdominal incisions, renal pedicles are bluntly dissected and a microvascular clamp placed on the left renal pedicle for 25-30 minutes. Following ischemia the clamps are removed along with the right kidney, incisions sutured, and the animals allowed to recover. Blood is collected for serum creatinine and BUN analysis as an indicator of kidney health. Alternatively animal survival is monitored over time. Compound can be administered to animals before and/or after the surgery and the effects on serum creatinine, BUN or animal survival used as indicators of compound efficacy.

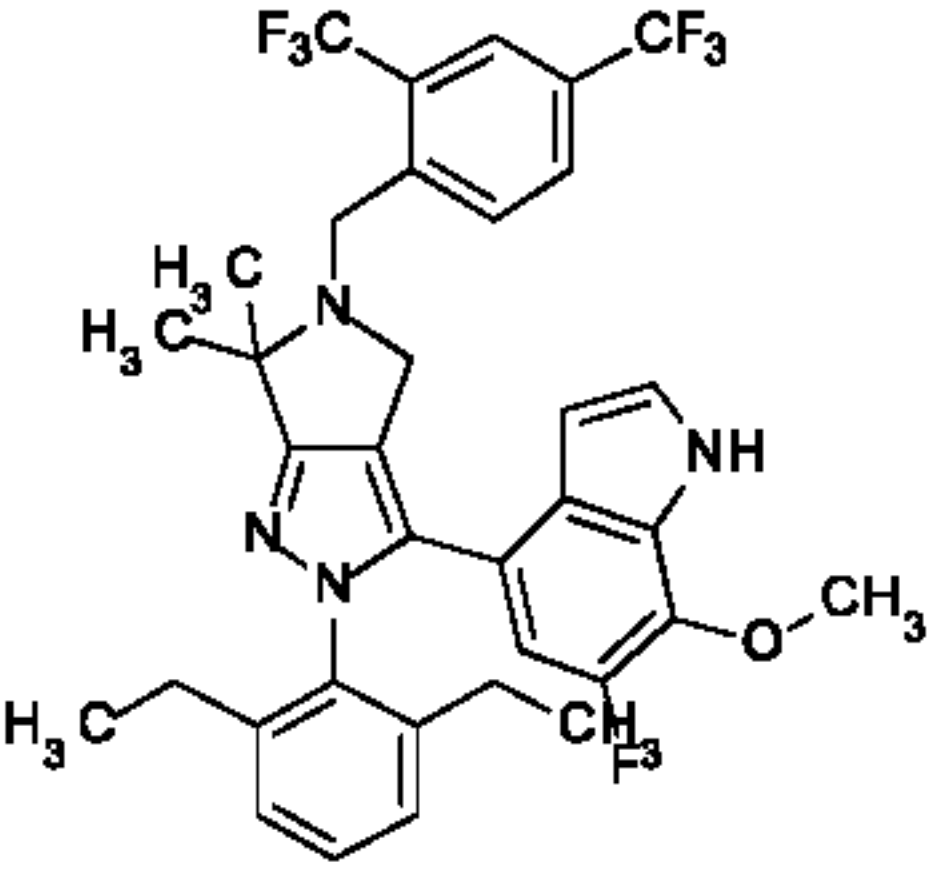
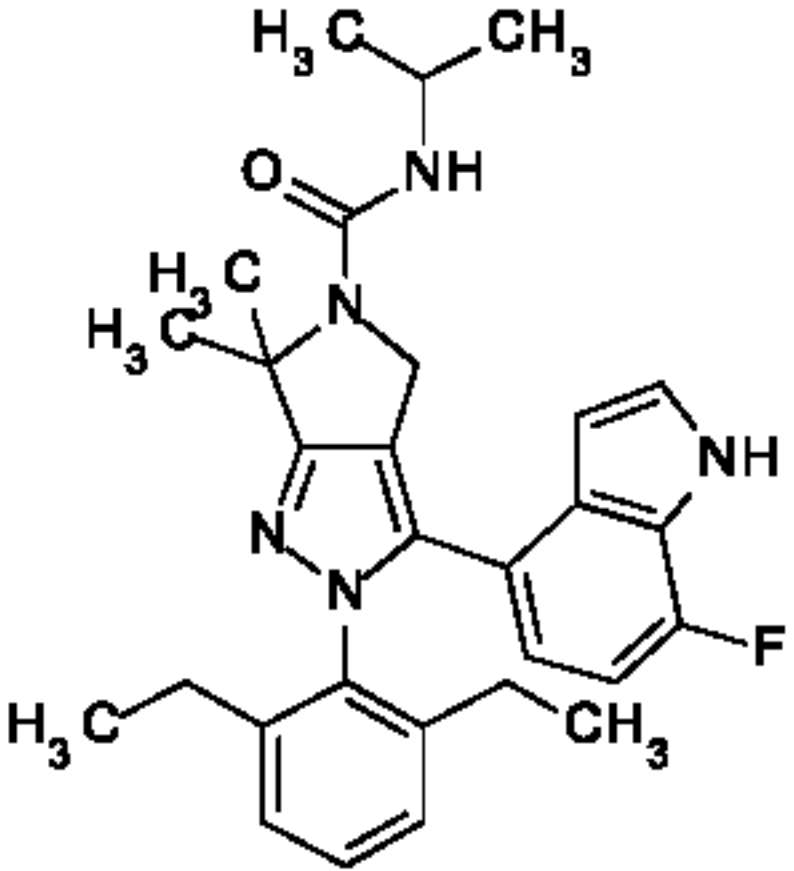
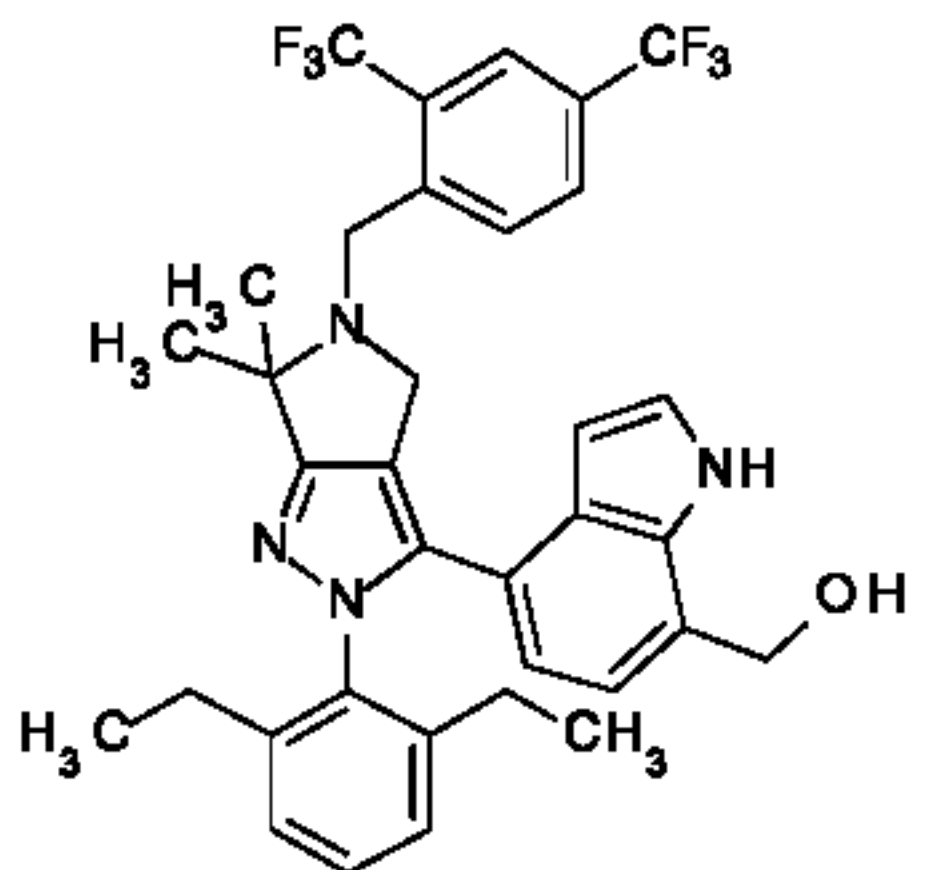
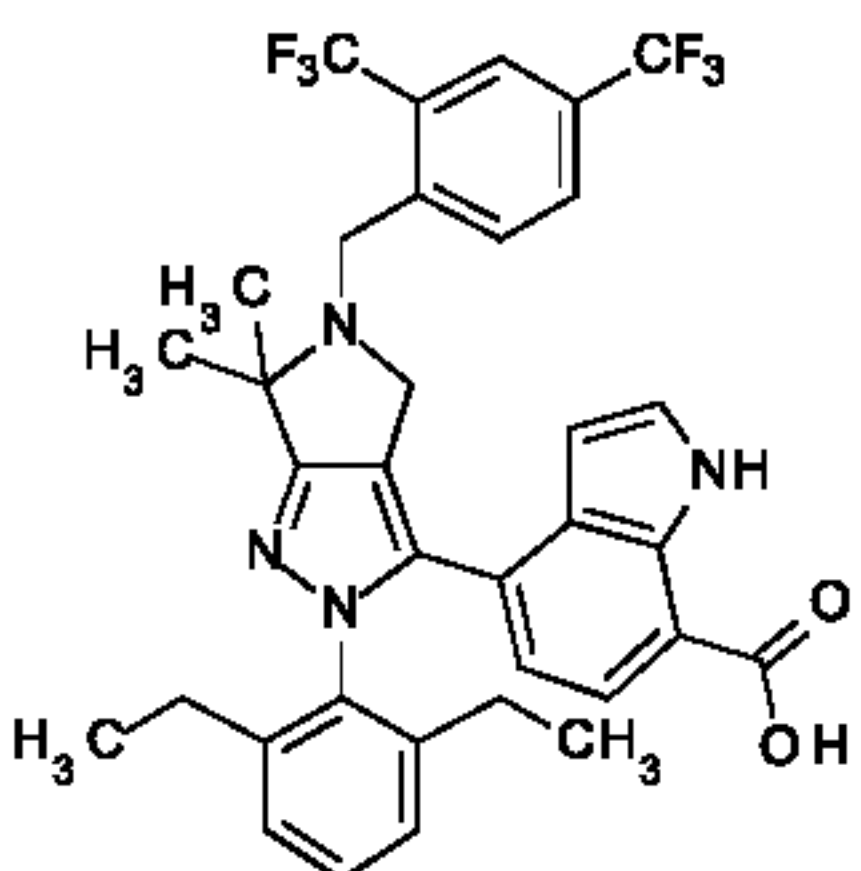
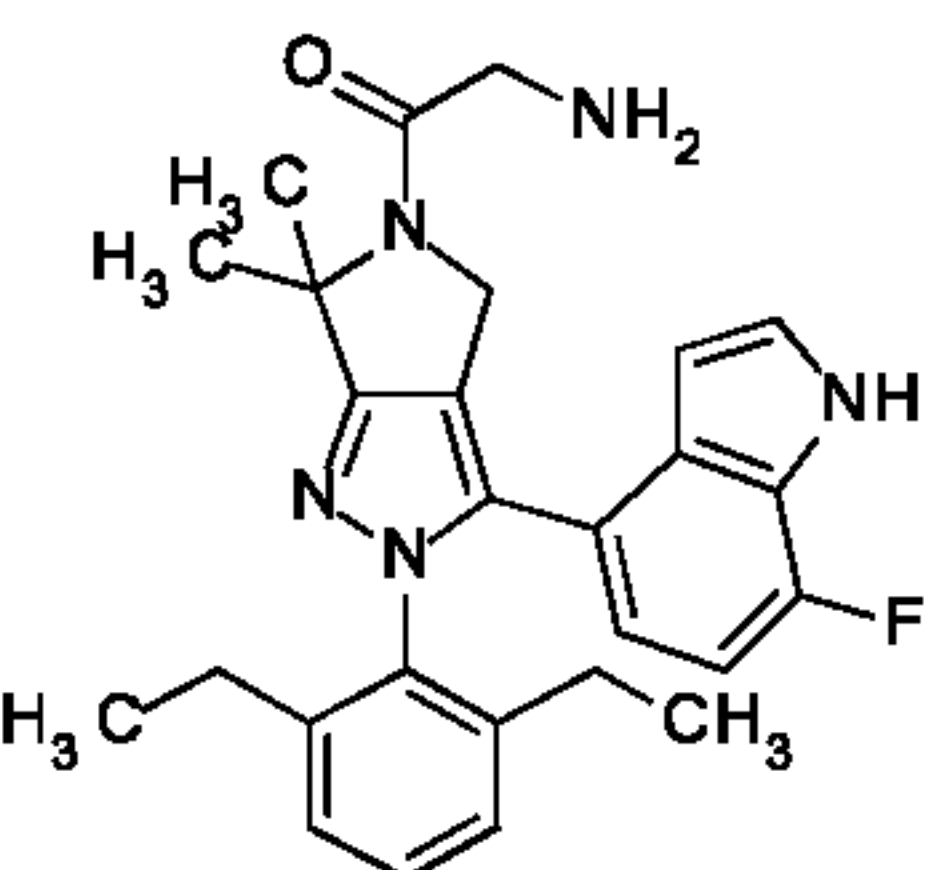
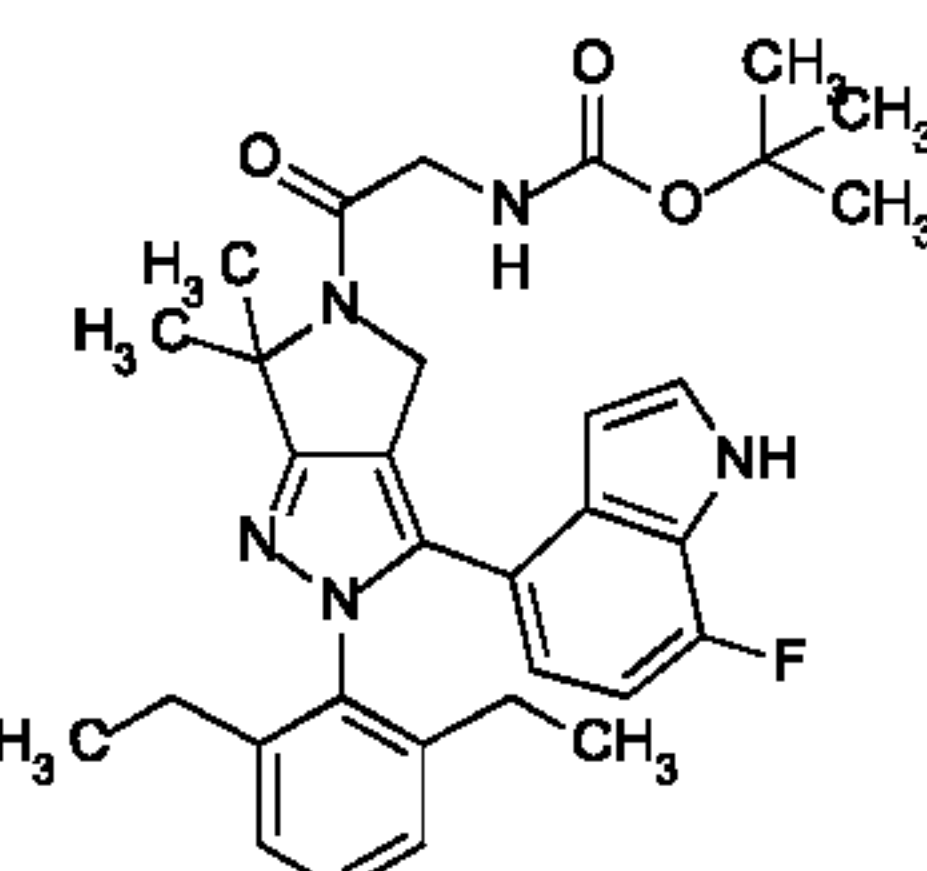
10. Mouse Model of Tumor Growth

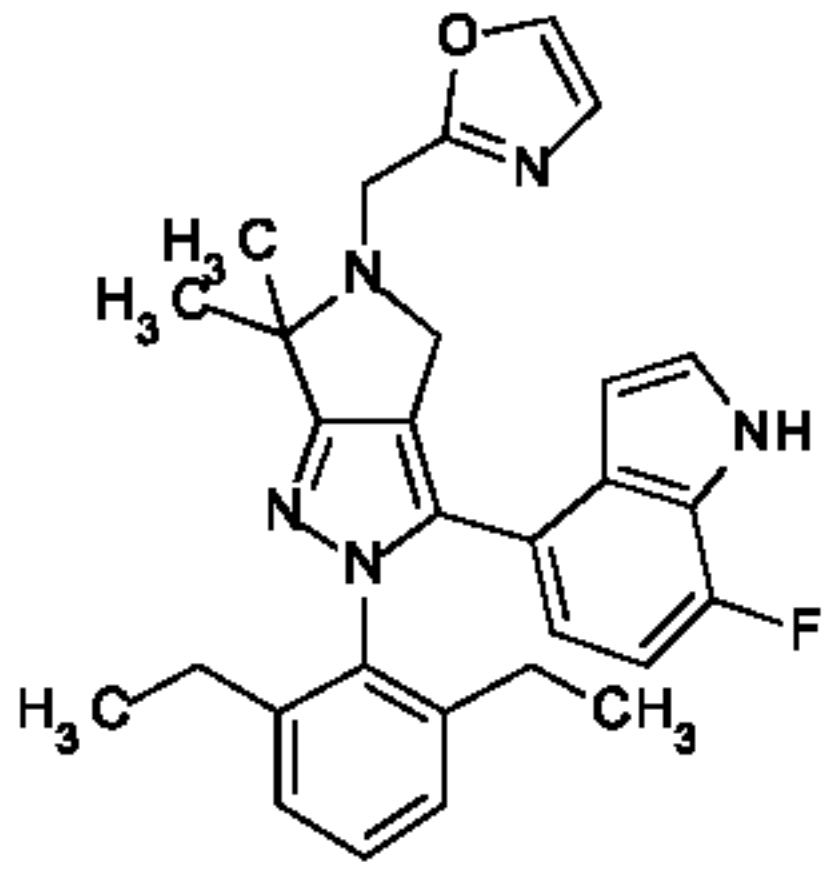
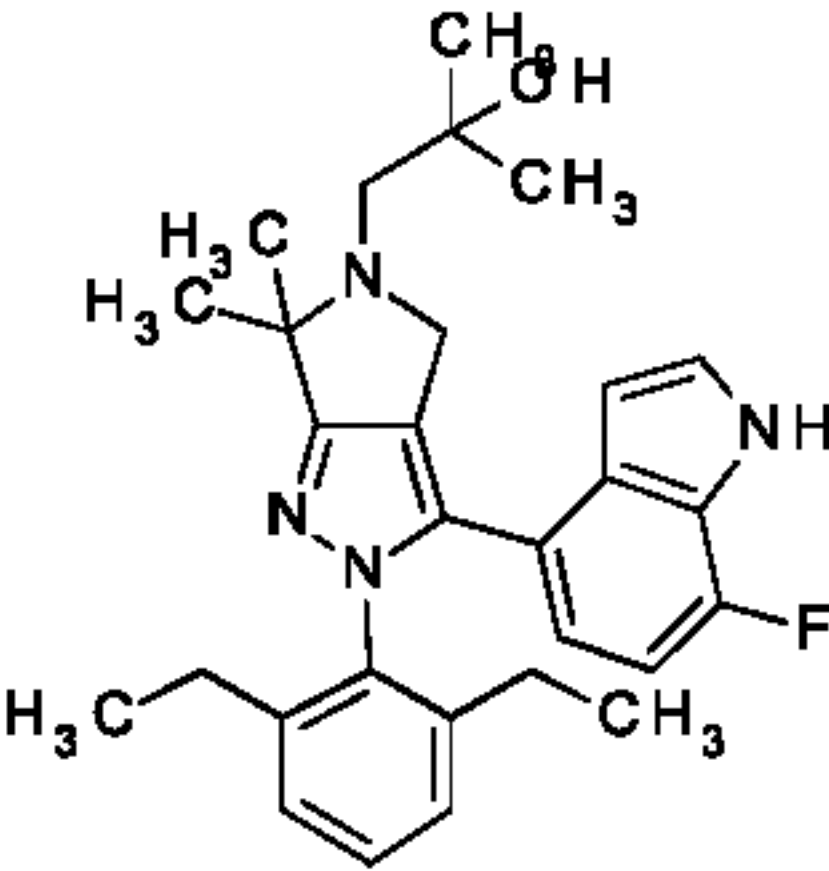
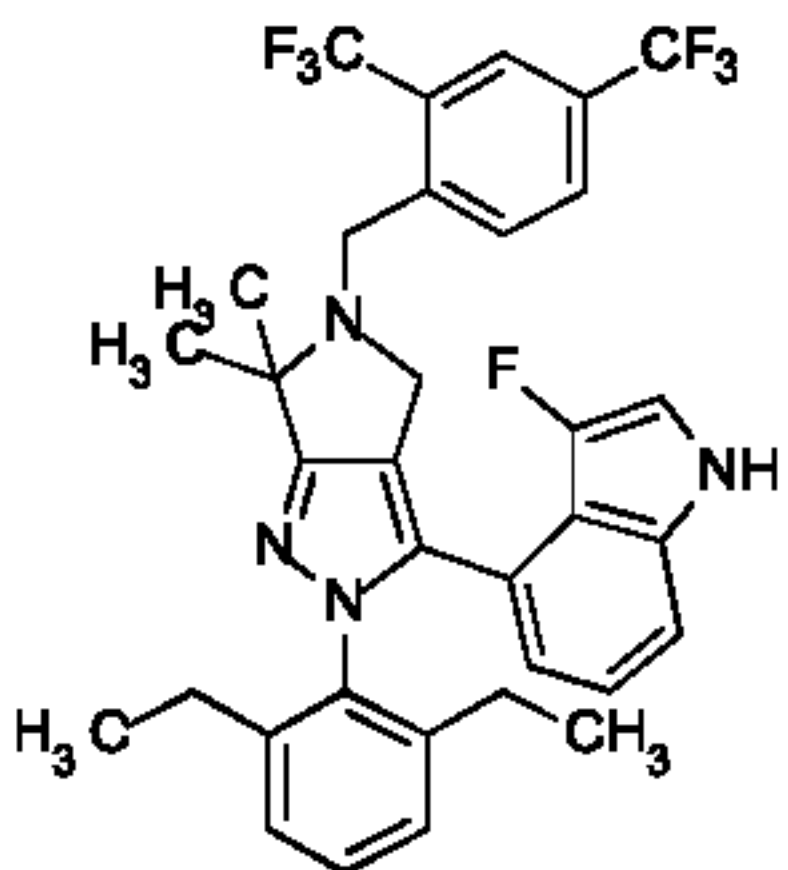
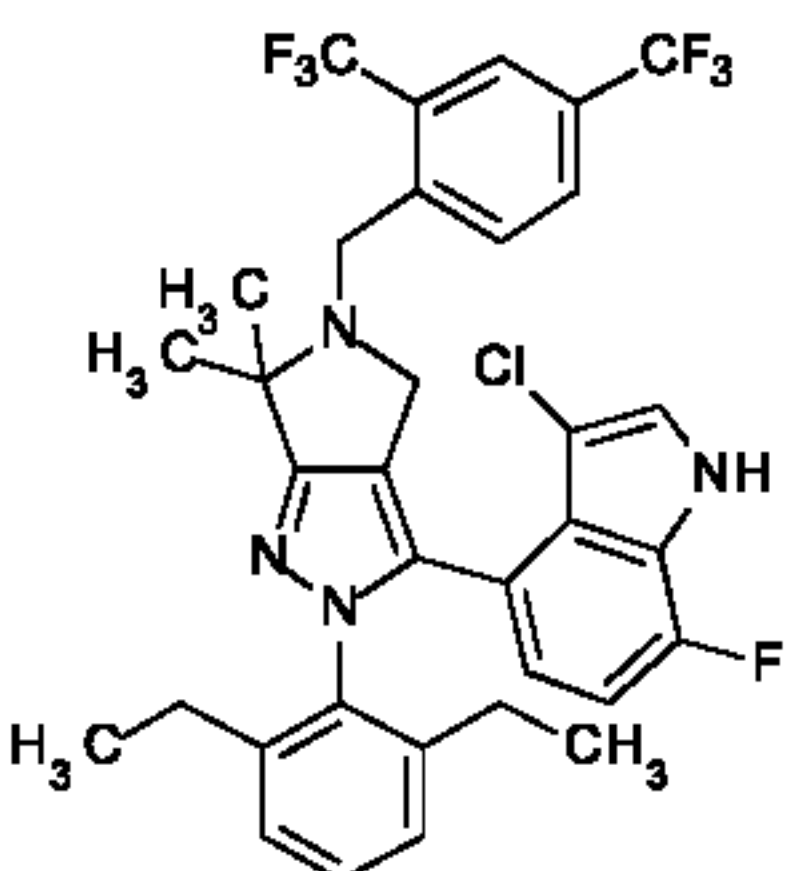
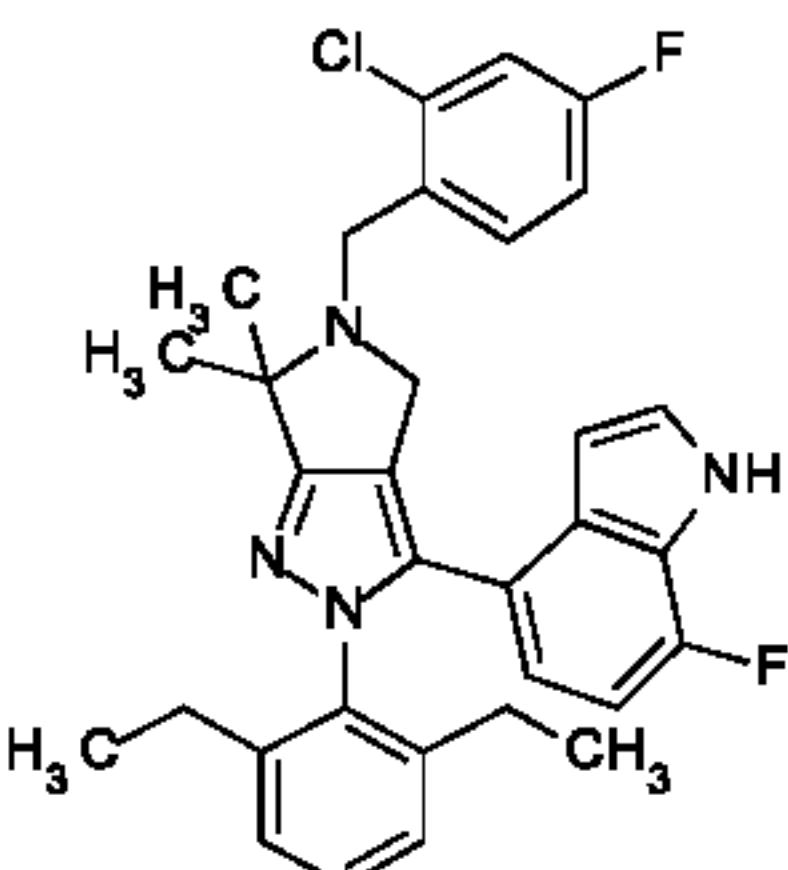
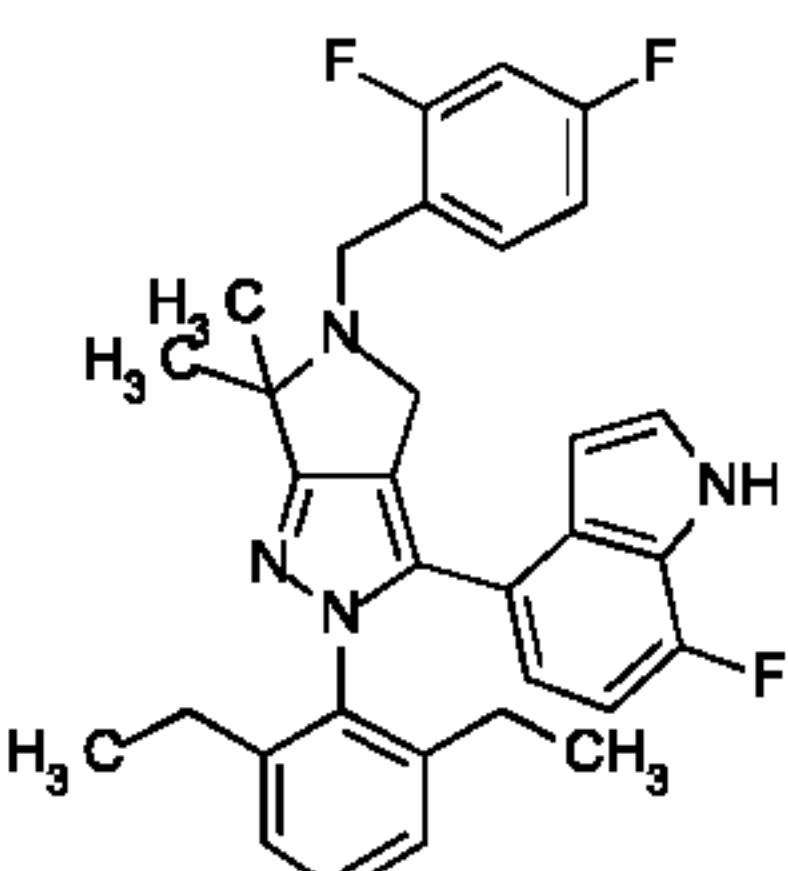
[0177] C57BL/6 mice 6-16 weeks of age are injected subcutaneously with 1x10⁵ TC-1 cells (ATCC, VA) in the right or left rear flank. Beginning about 2 weeks after cell injection, tumors are measured with calipers every 2-4 d until the tumor size required the mice are killed. At the time of sacrifice animals are subjected to a full necropsy and spleens and tumors removed. Excised tumors are measured and weighed. Compounds may be administered before and/or after tumor injections, and a delay or inhibition of tumor growth used to assess compound efficacy.

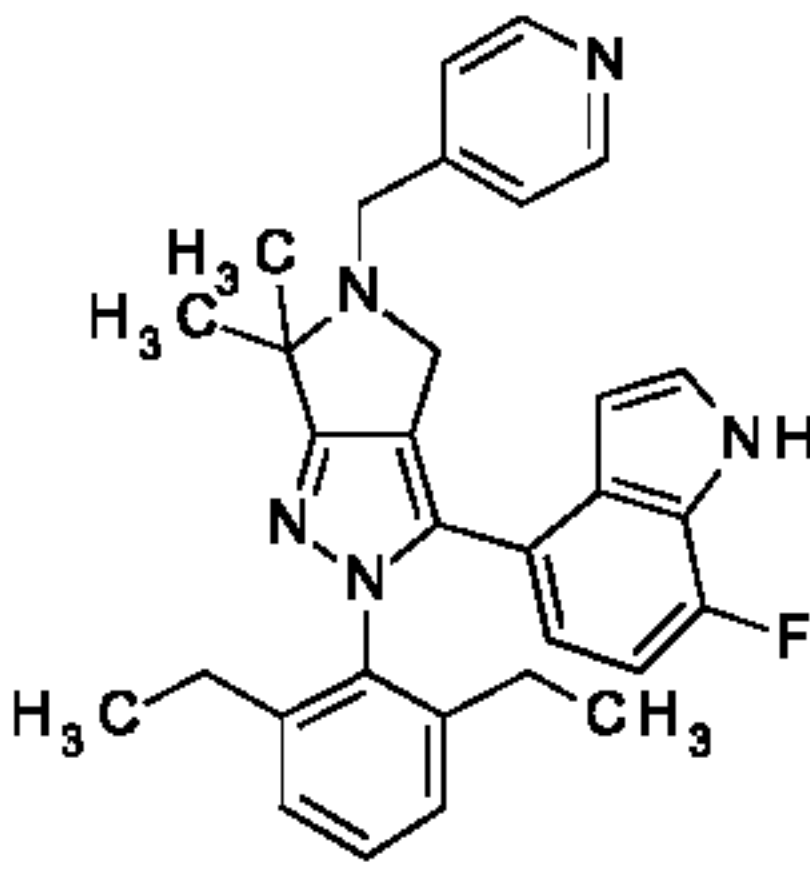
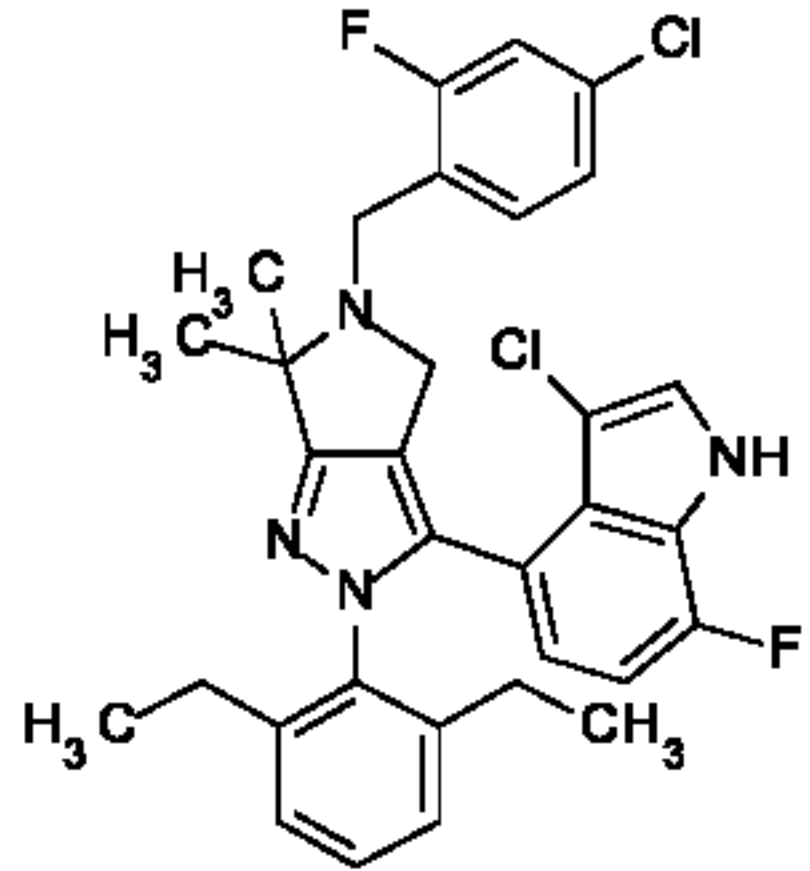
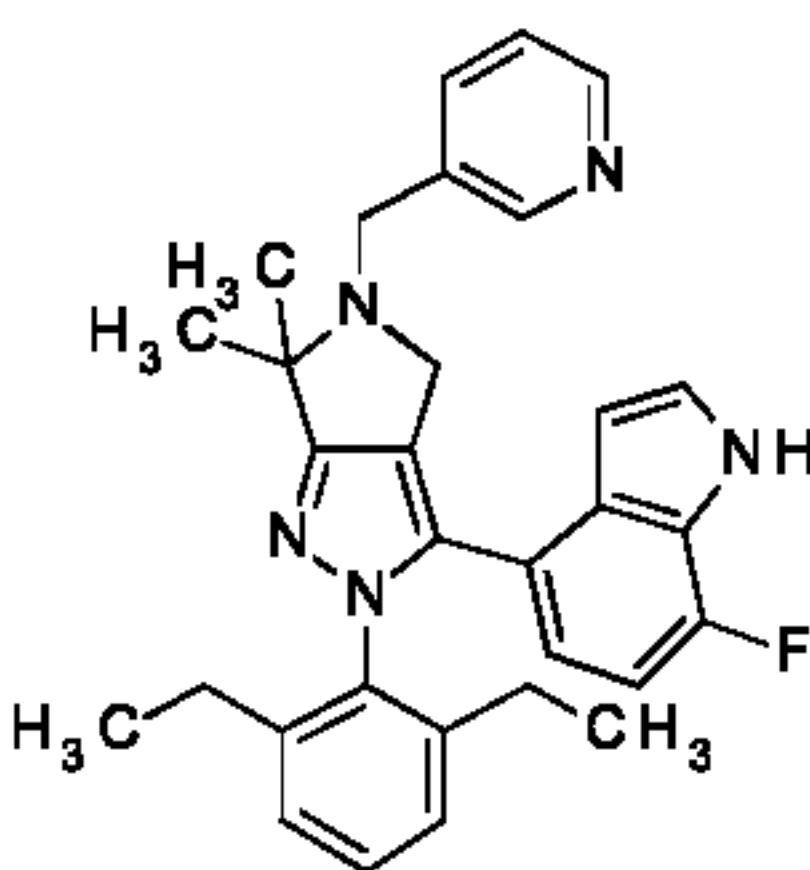
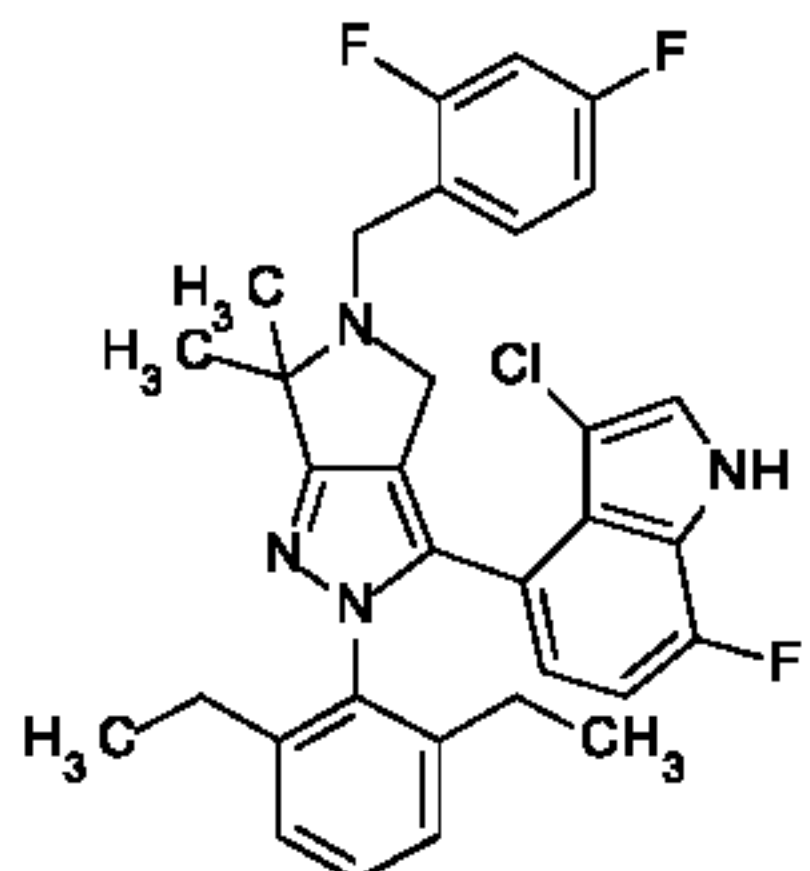
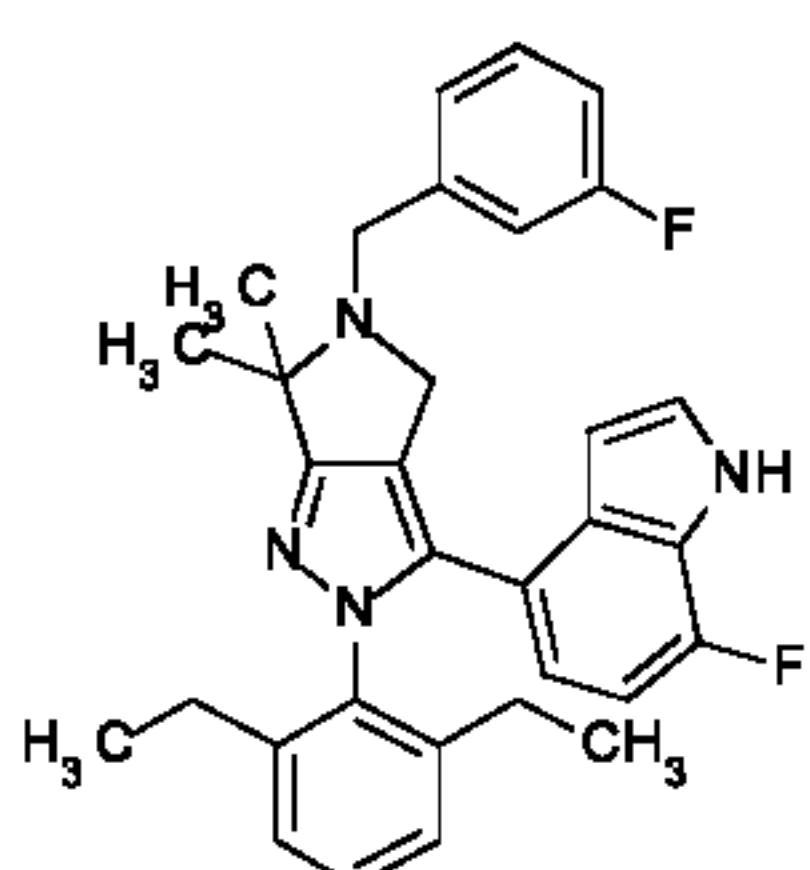
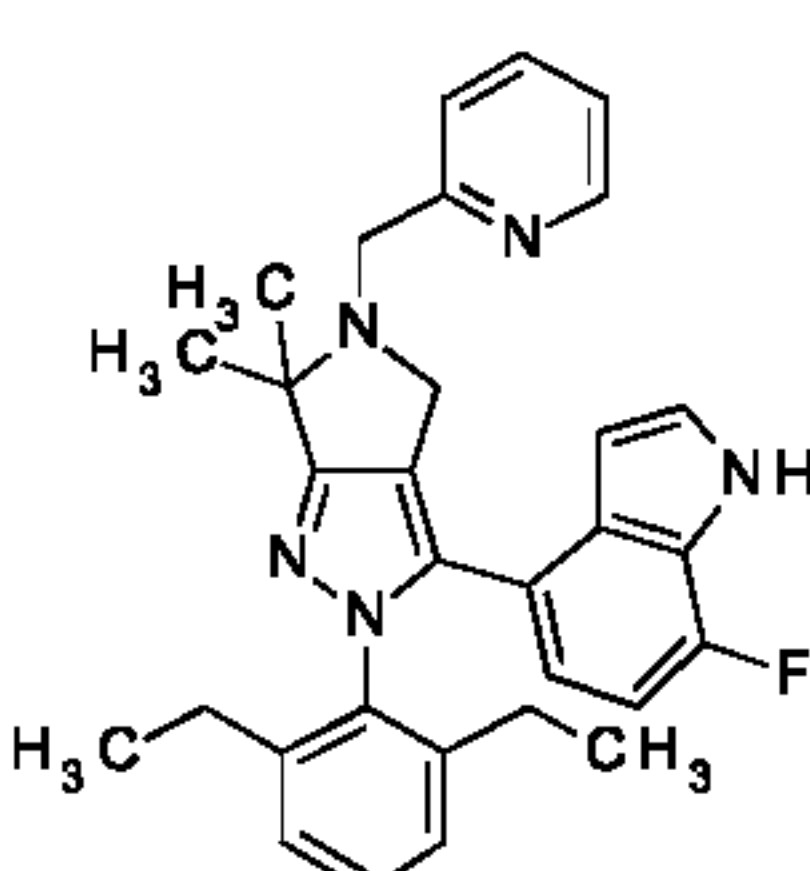
[0178] In **Table 3**, below, structures and activity are provided for representative compounds described herein. Activity is provided as follows for inhibition in the chemotaxis assay (see Example 14 B.3) as described herein: +, 500 nM ≤ IC₅₀; ++, 50 nM ≤ IC₅₀ < 500 nM; +++, 5 nM ≤ IC₅₀ < 50 nM; and +++, IC₅₀ < 5 nM.

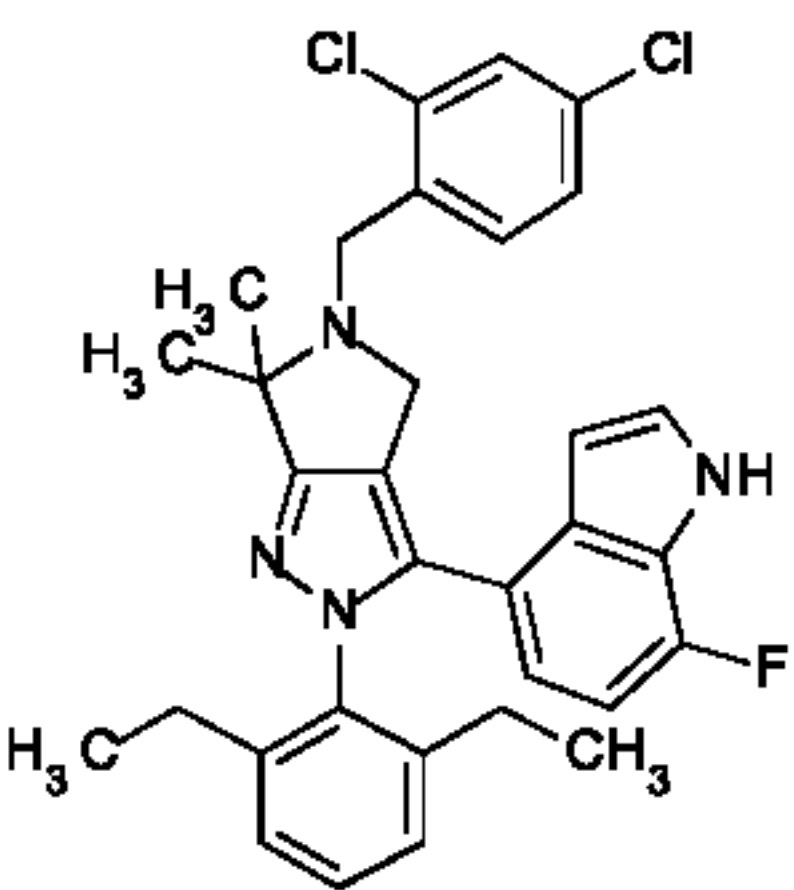
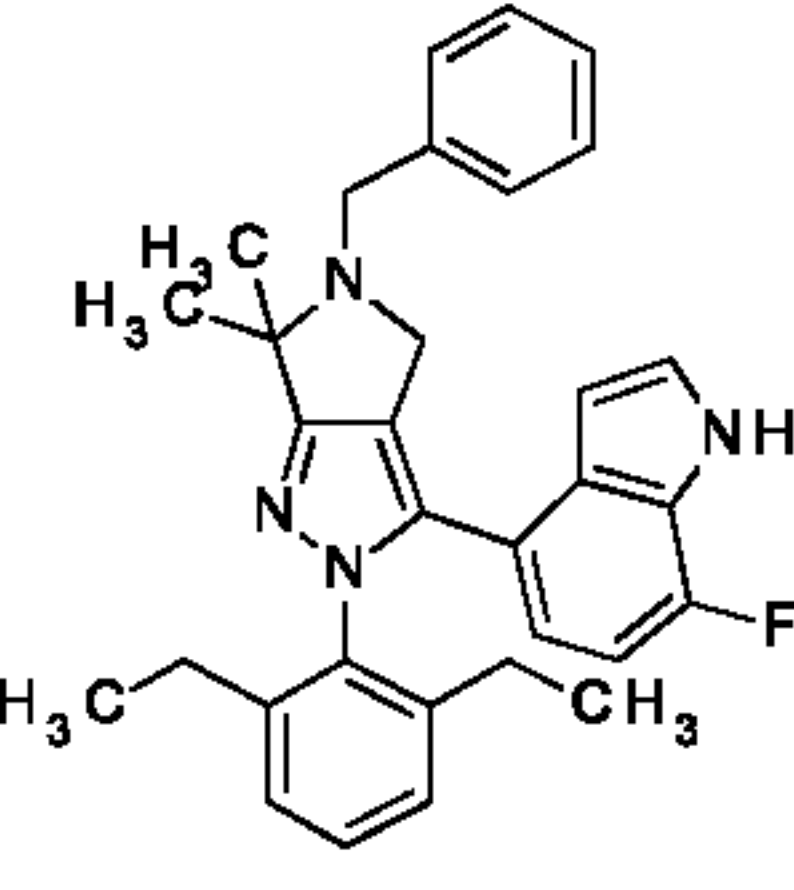
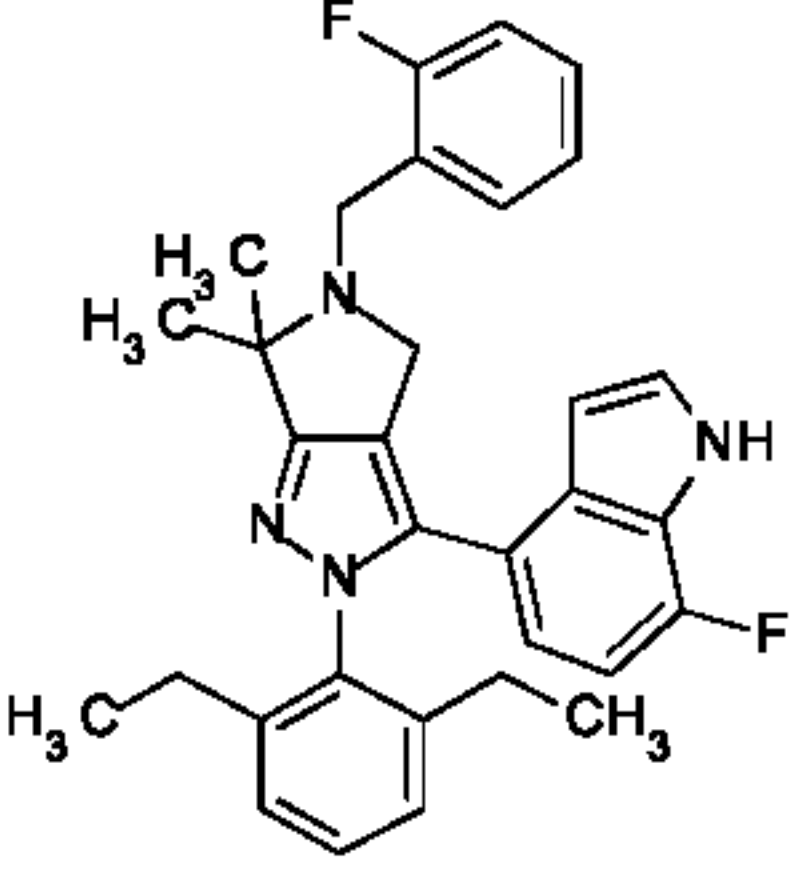
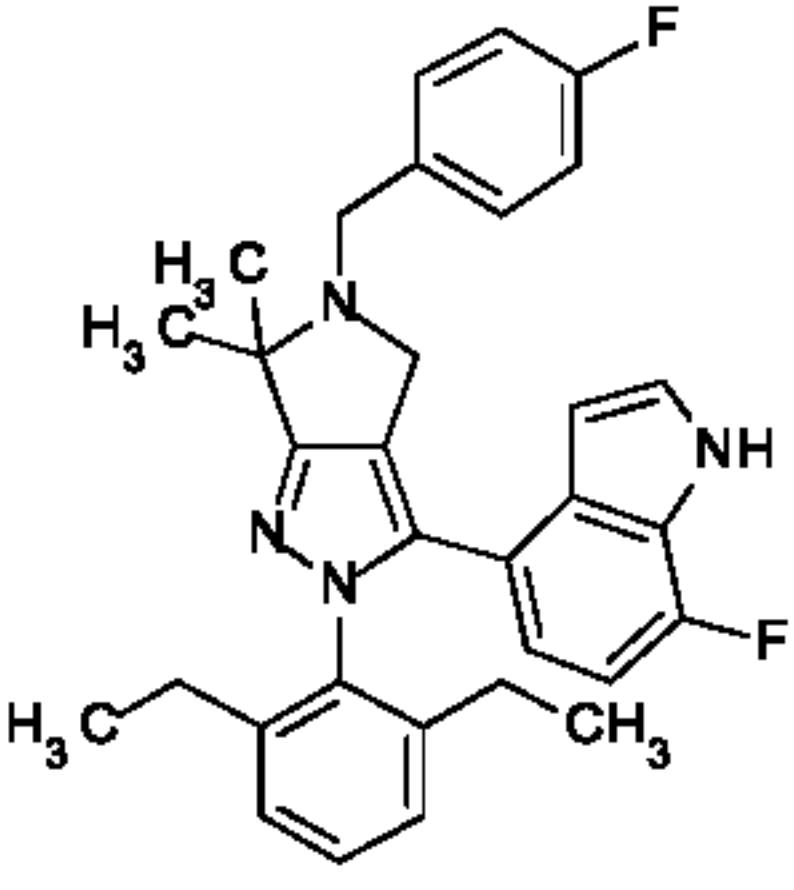
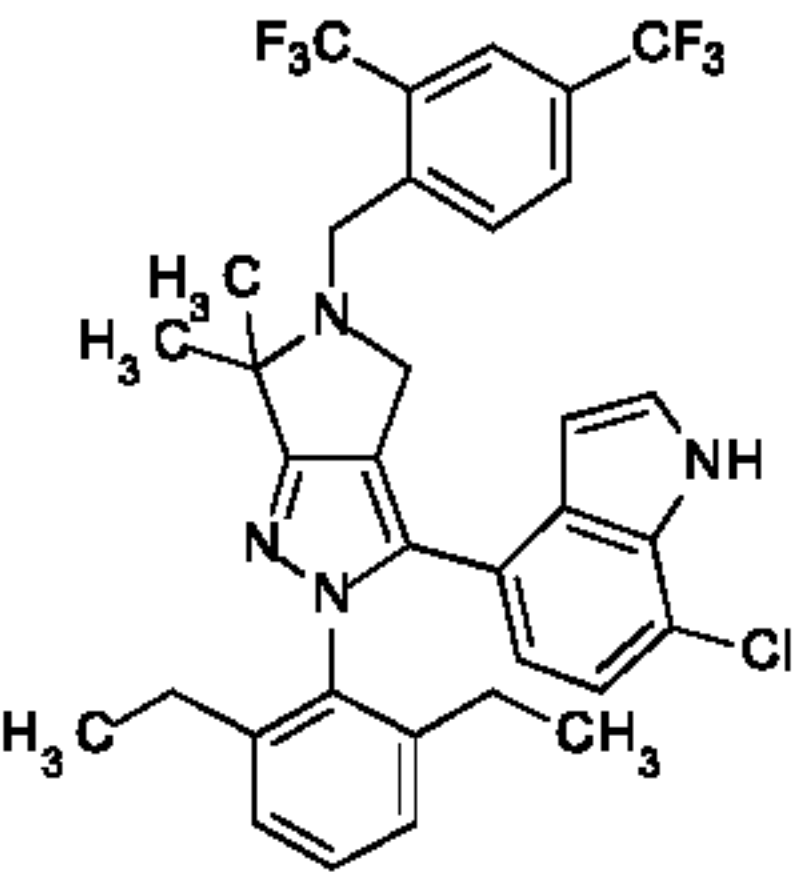
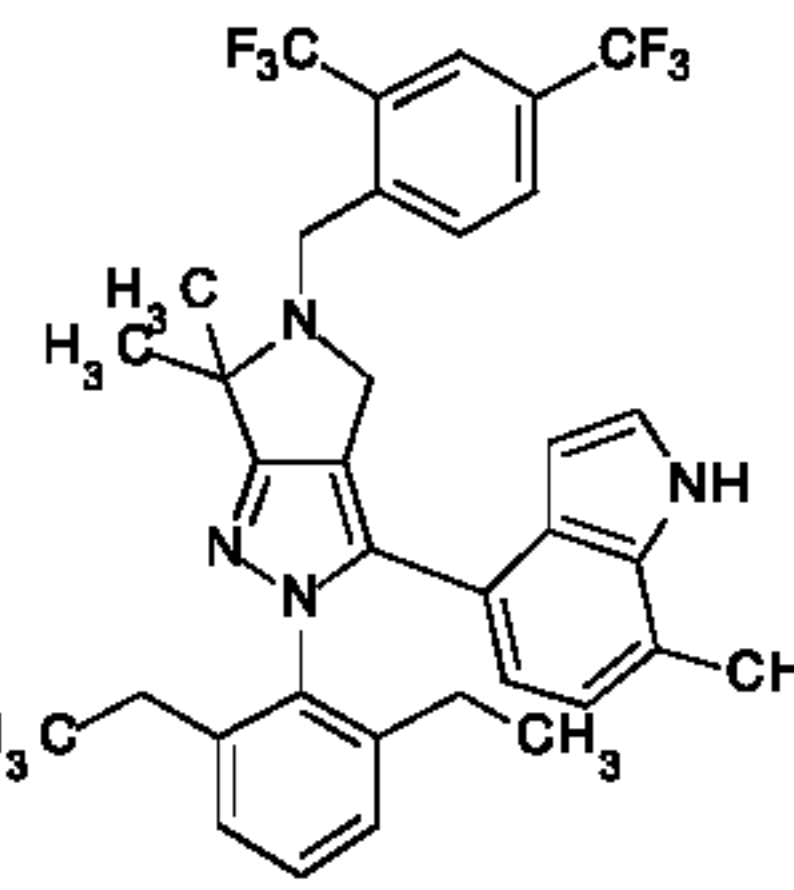
Table 3: Structure & Biological Activity of Specific Embodiments

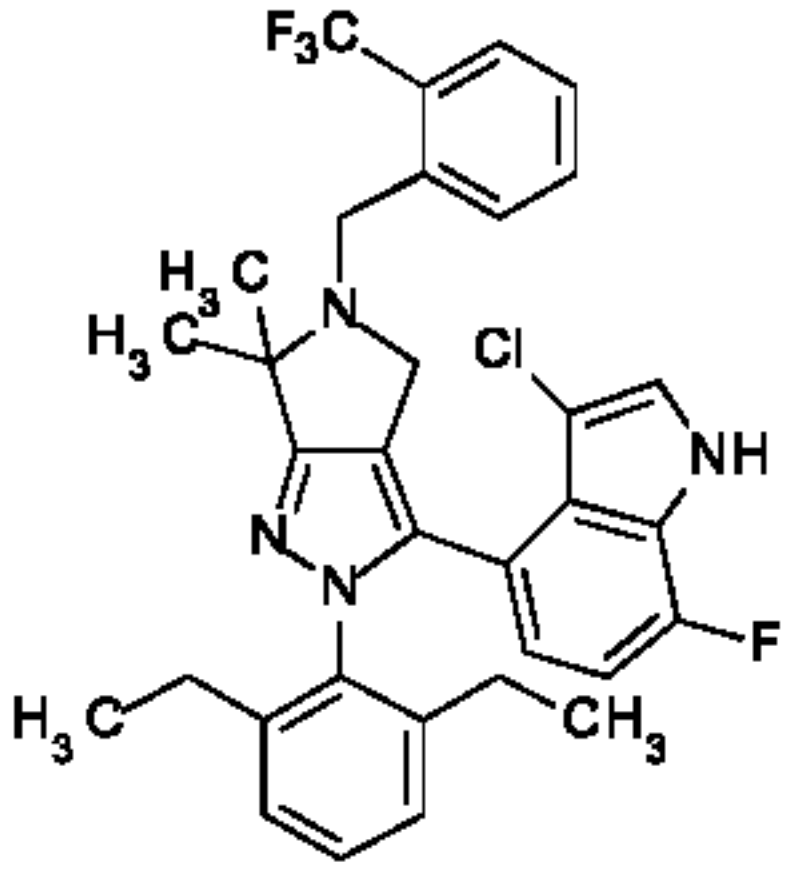
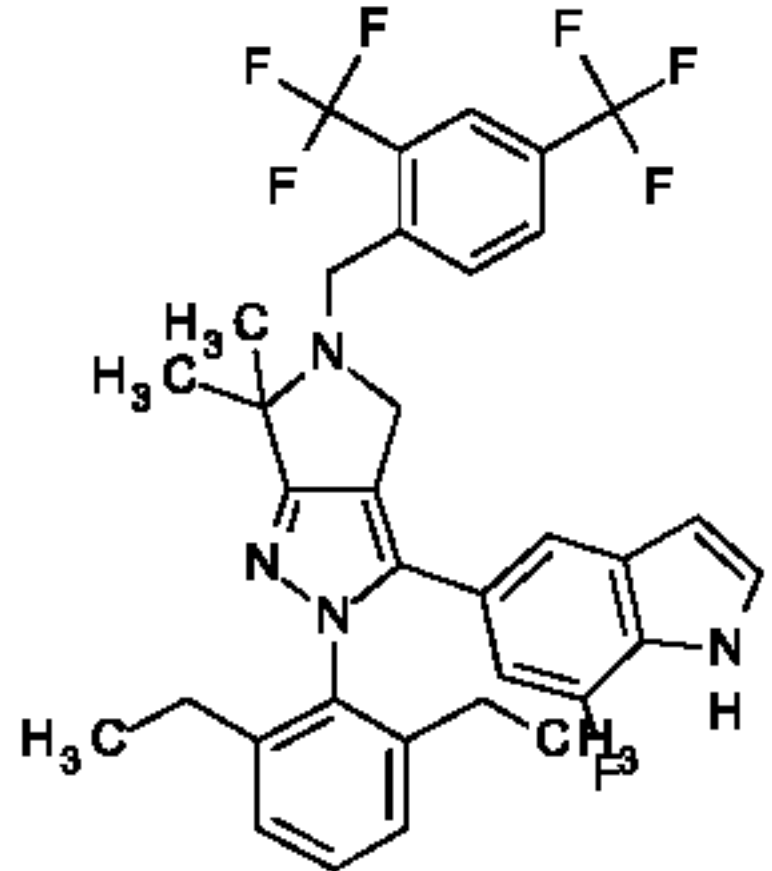
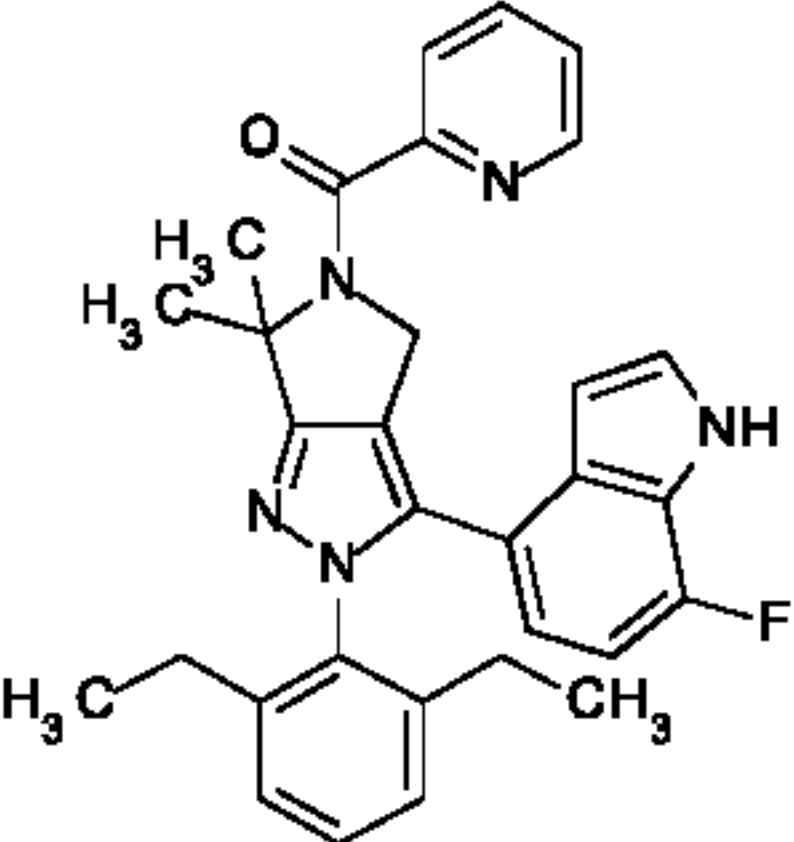
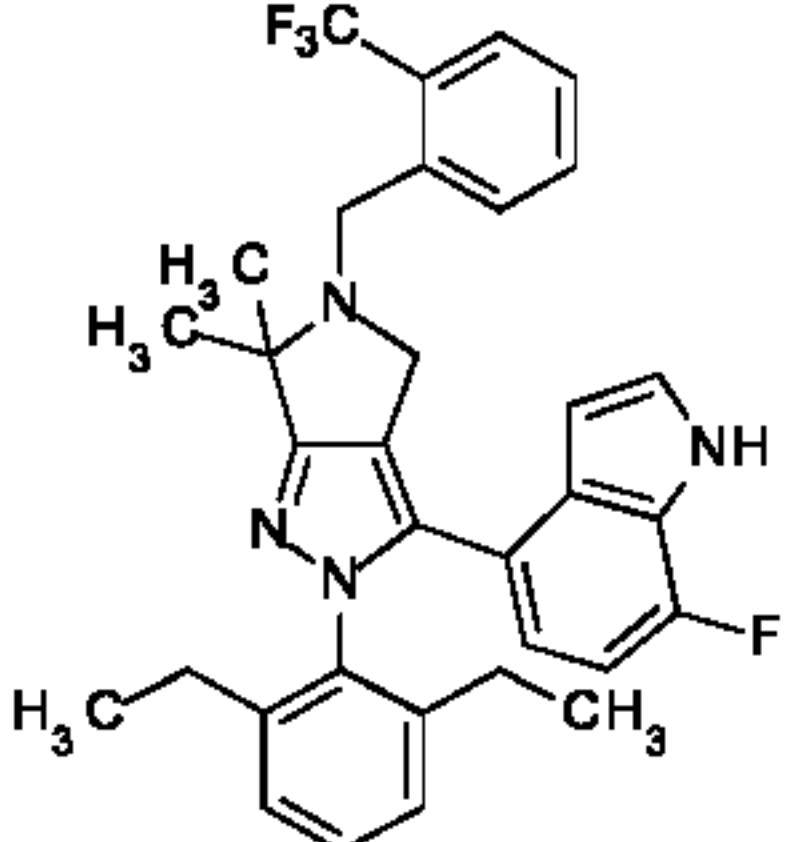
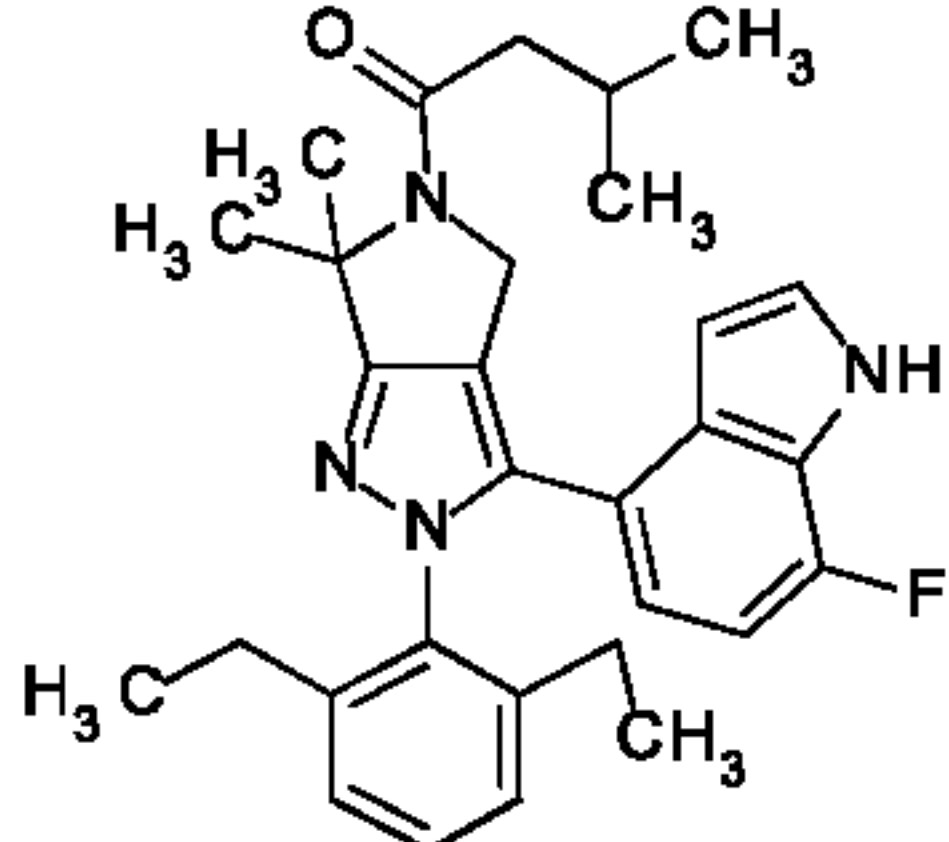
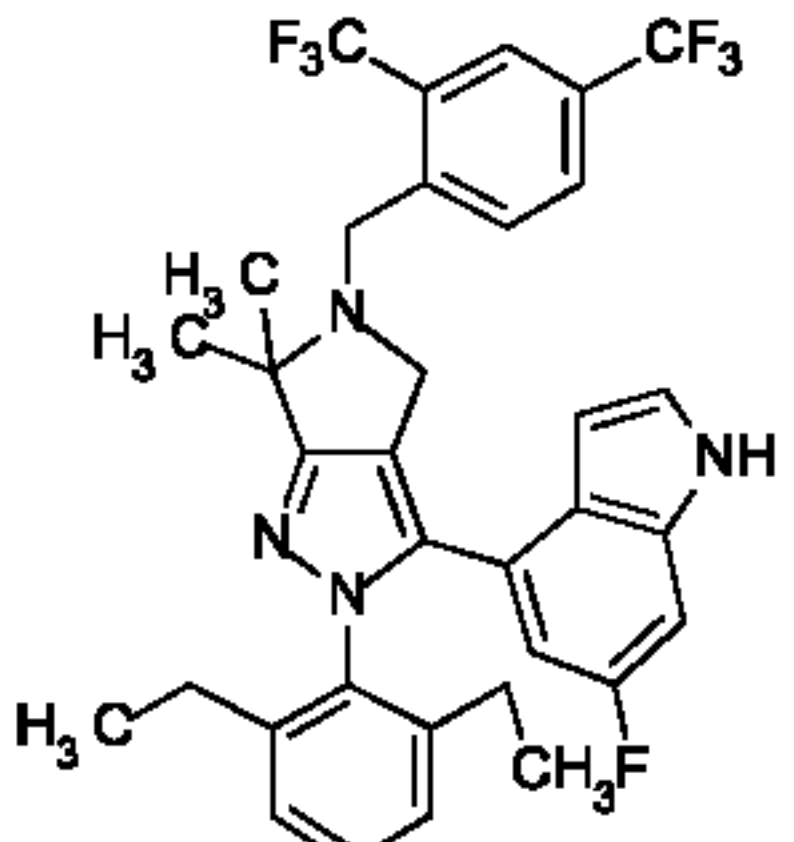
Compound	Structure	IC50 (nM)
1.001		+++

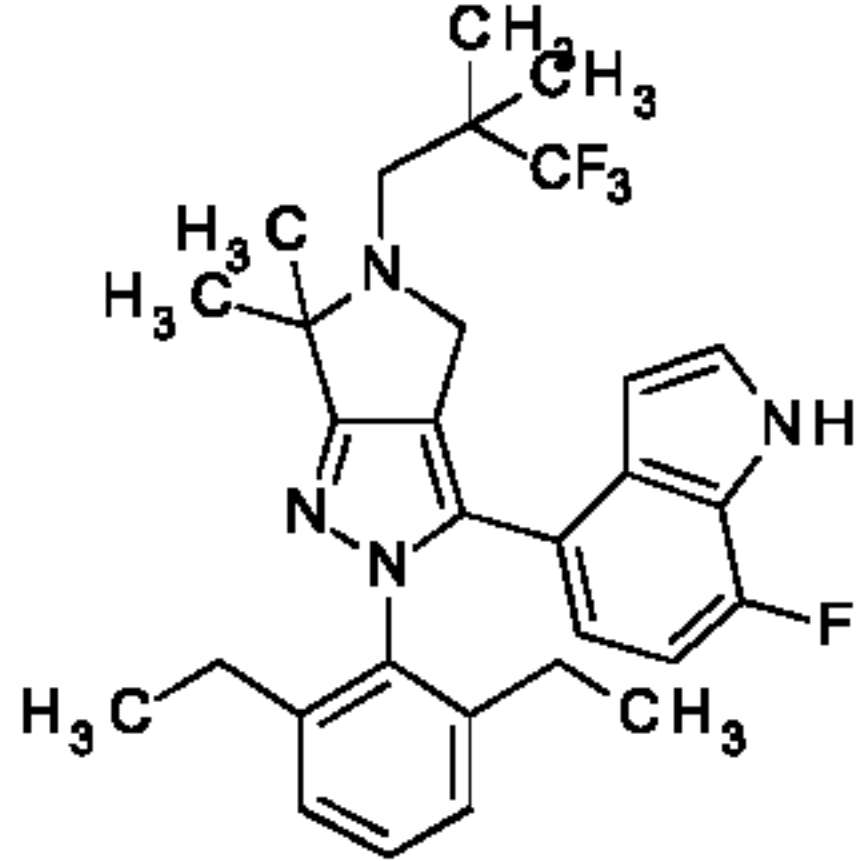
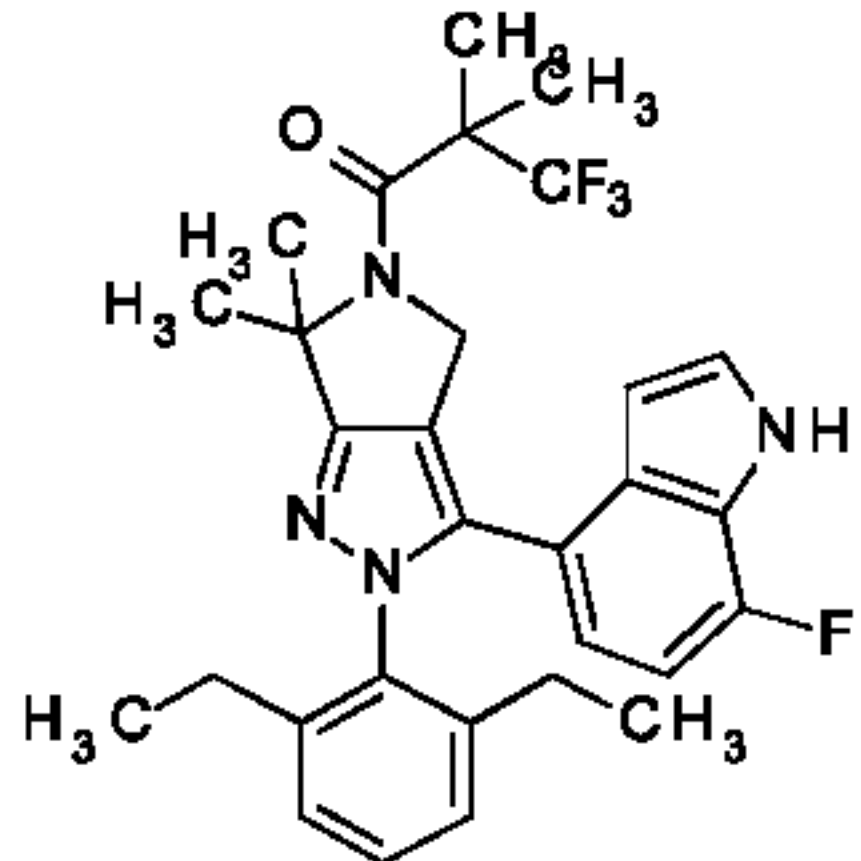
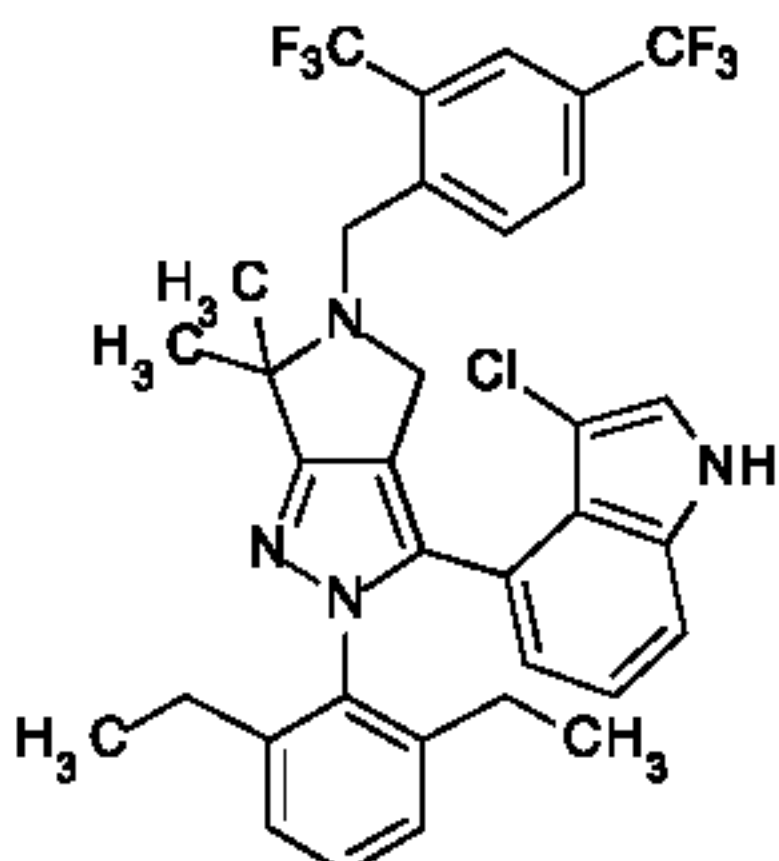
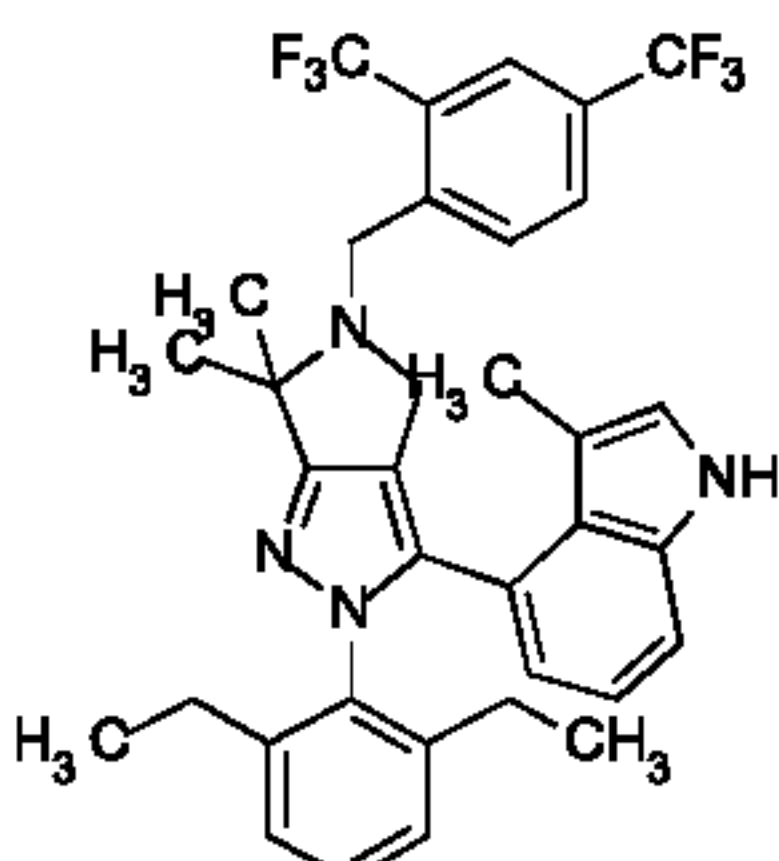
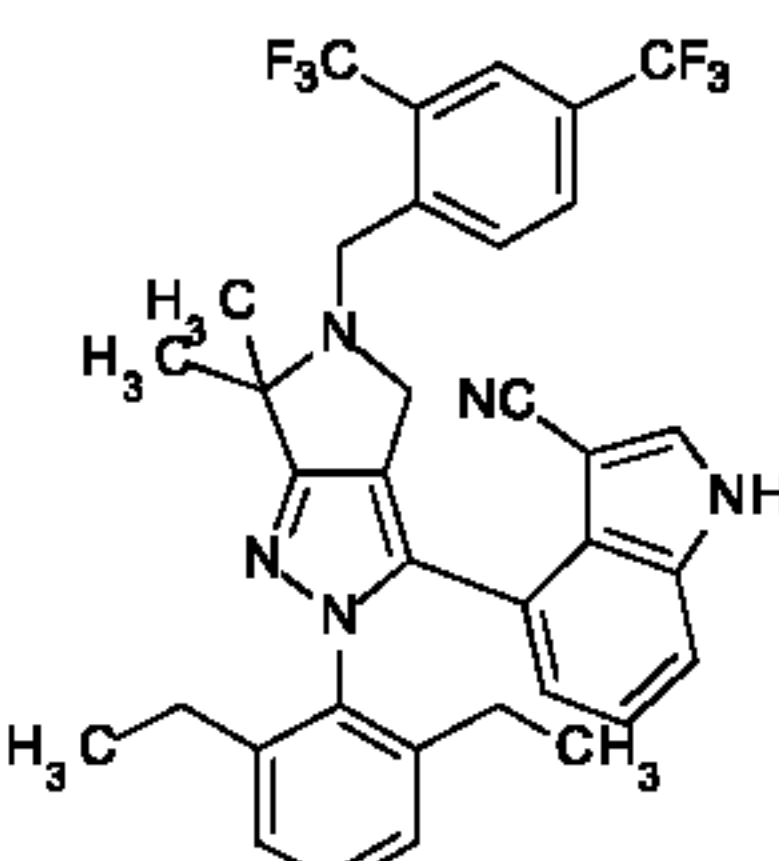
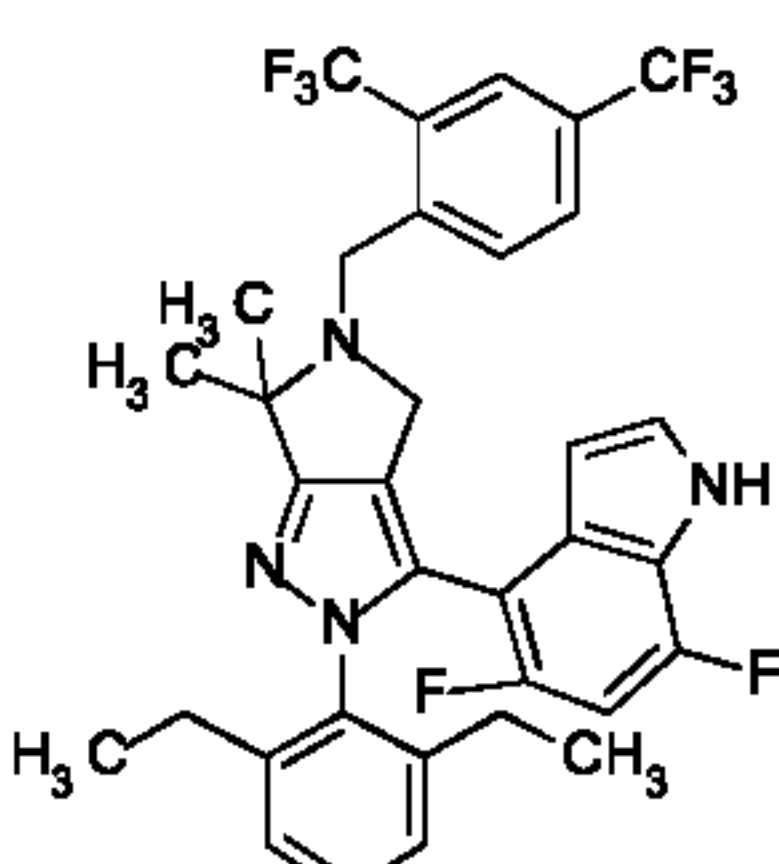
1.002		++++
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1.004		++++
1.005		+
1.006		+
1.007		++

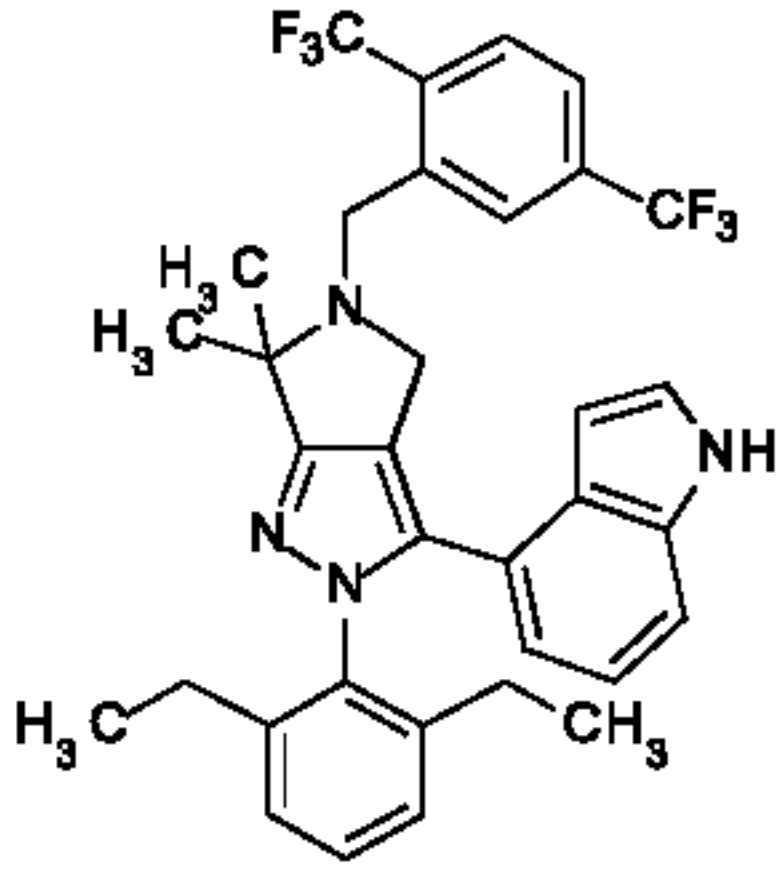
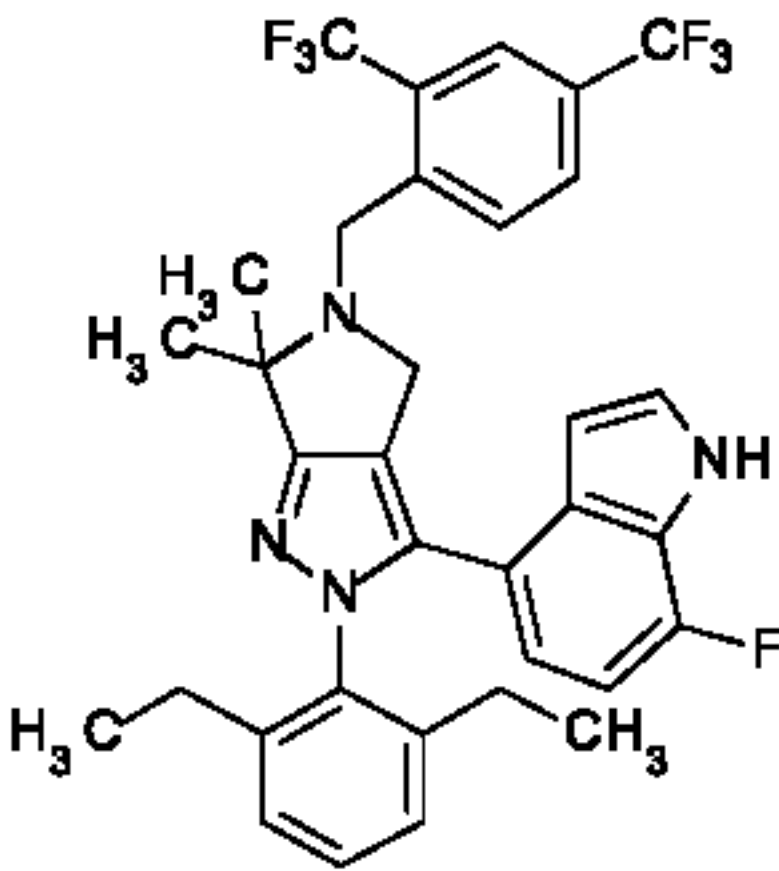
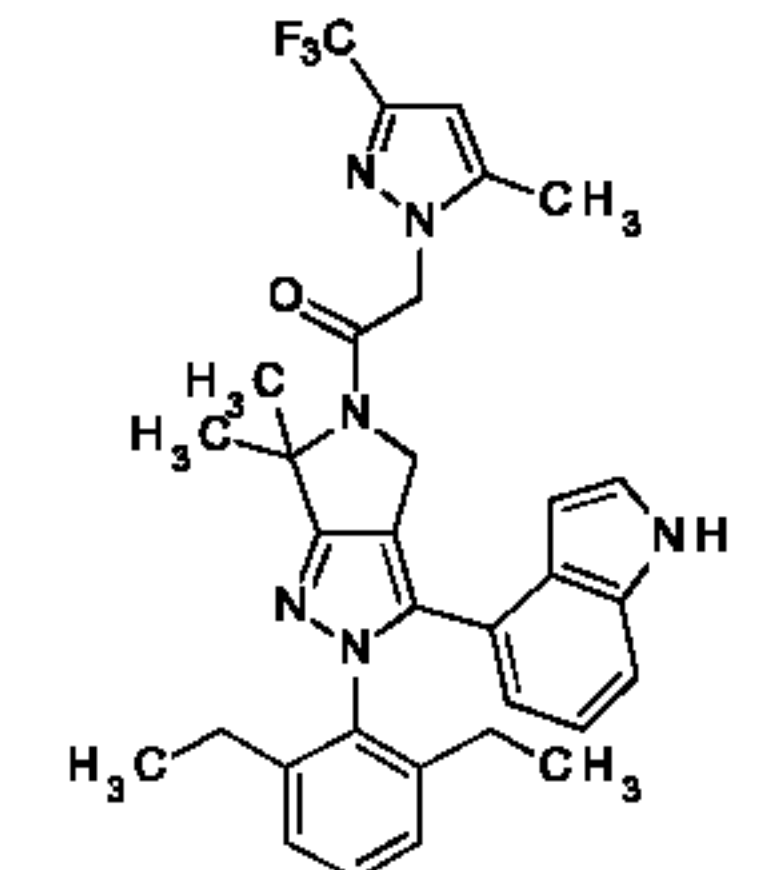
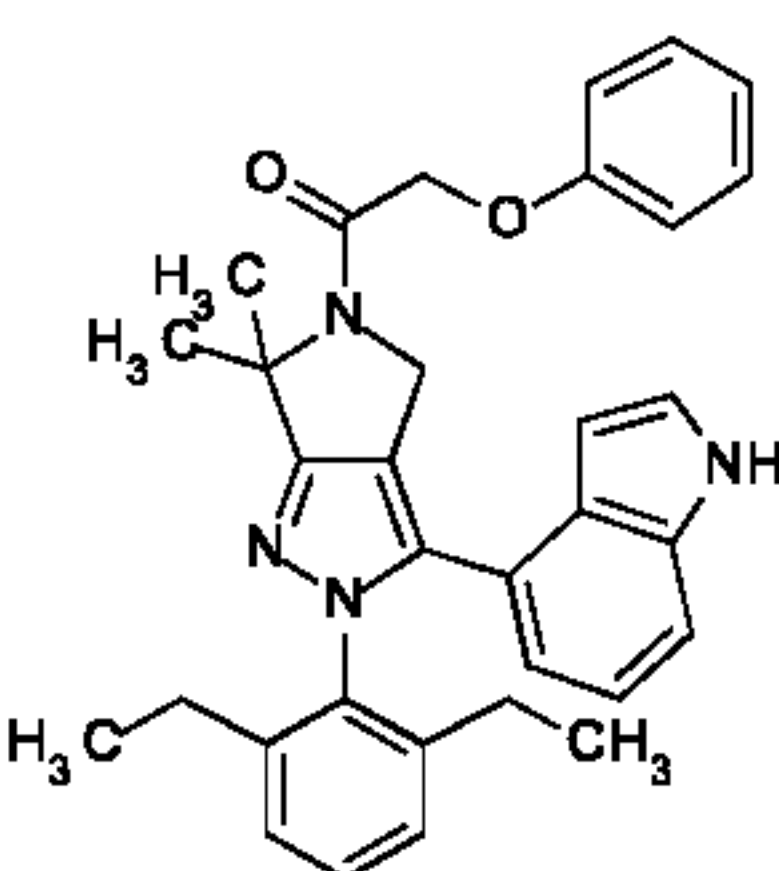
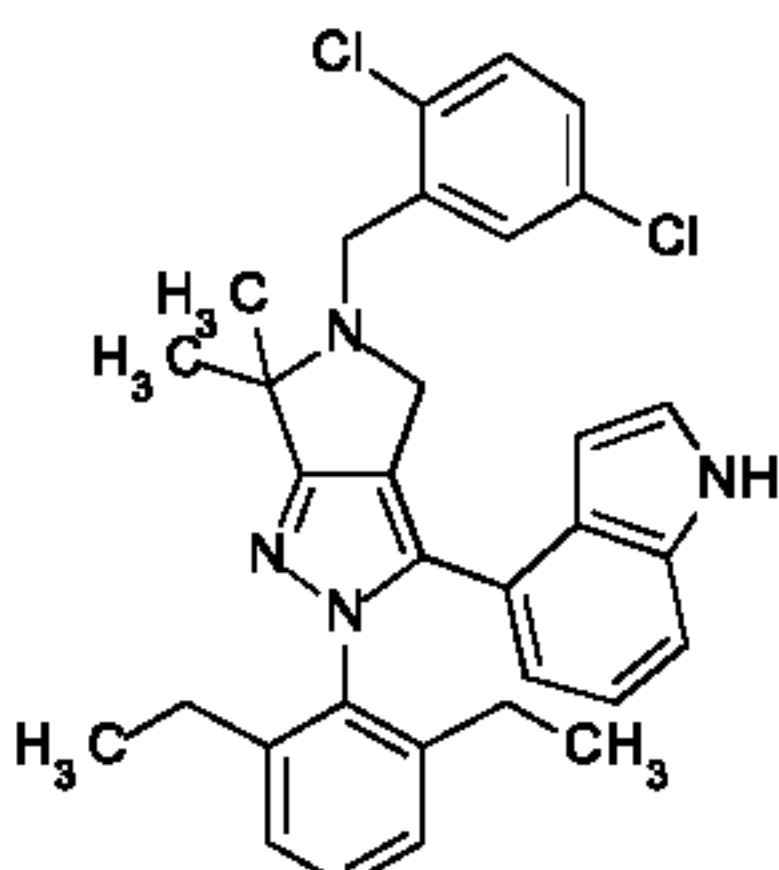
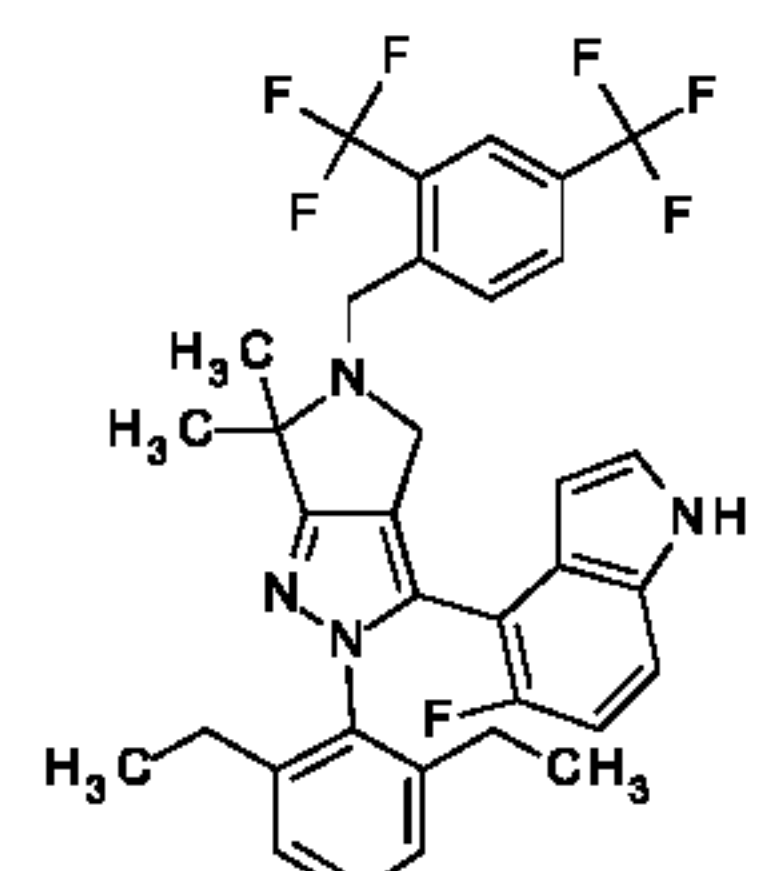
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1.009		++
1.010		+++
1.011		+++
1.012		+++
1.013		+++

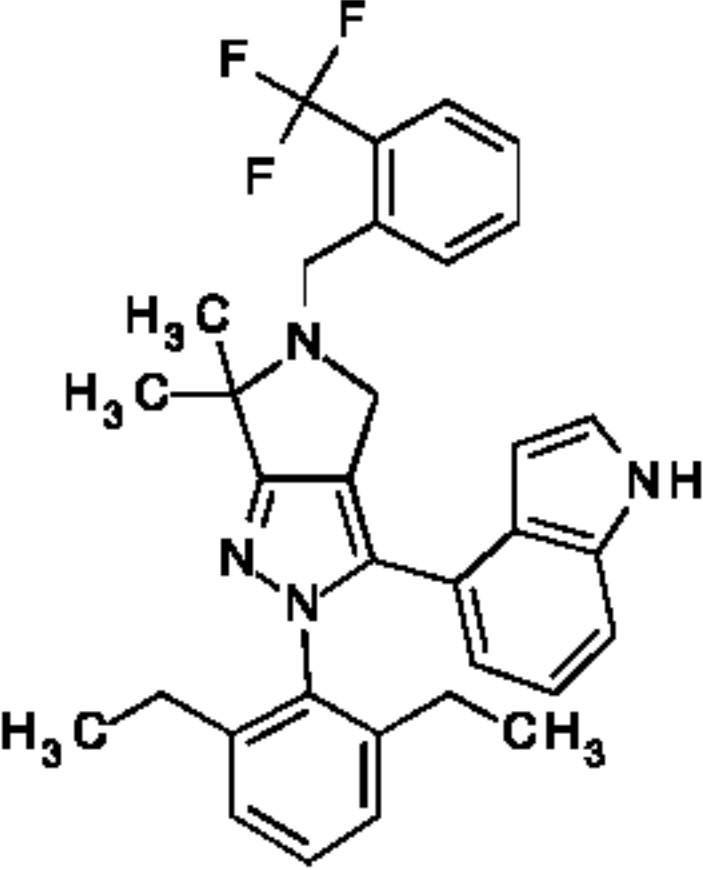
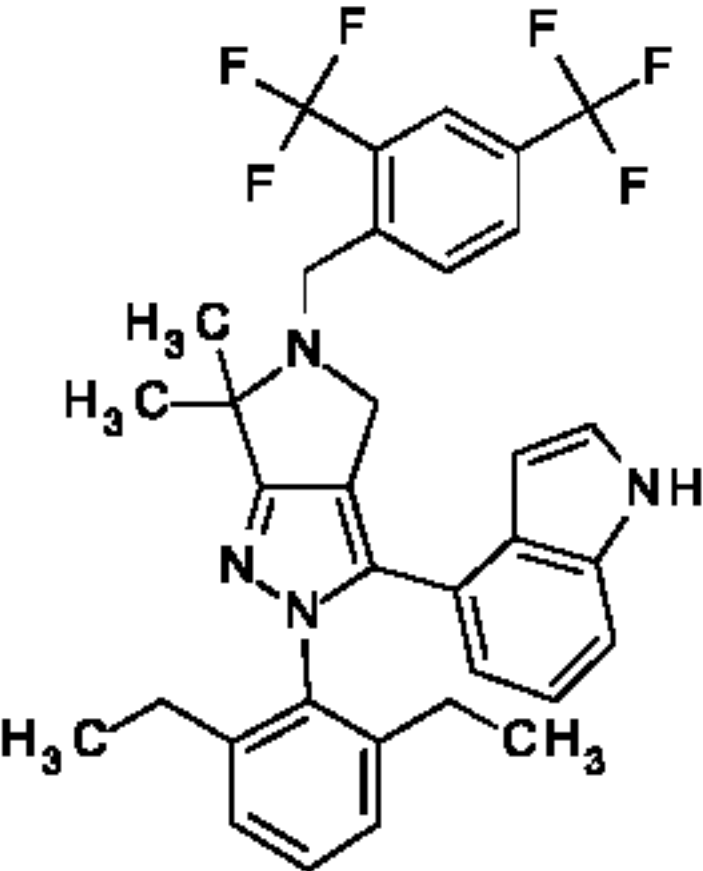
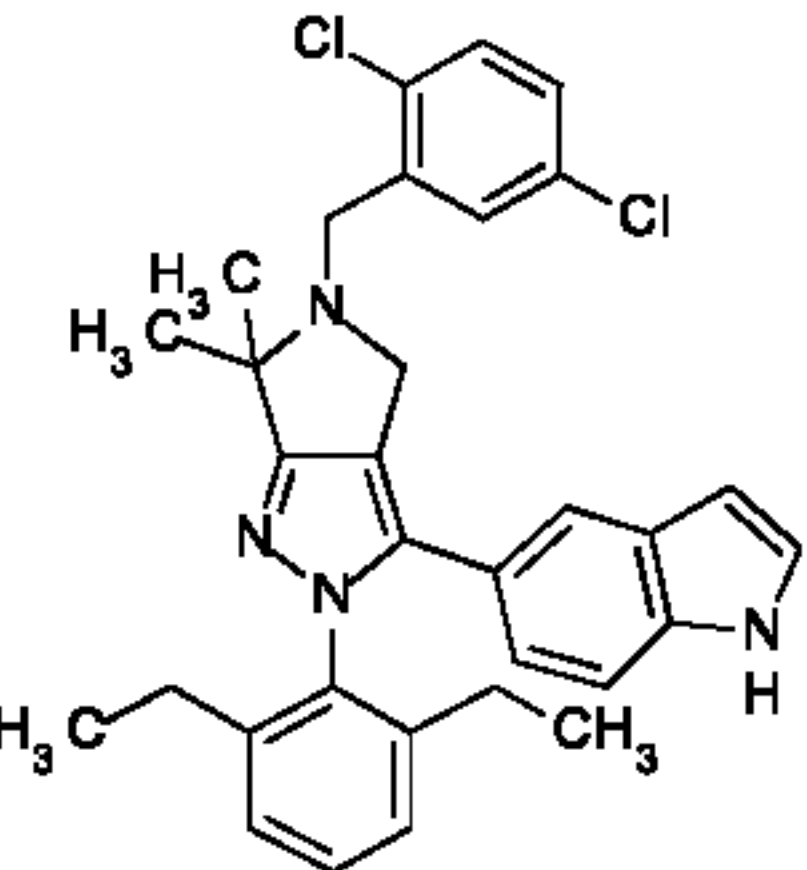
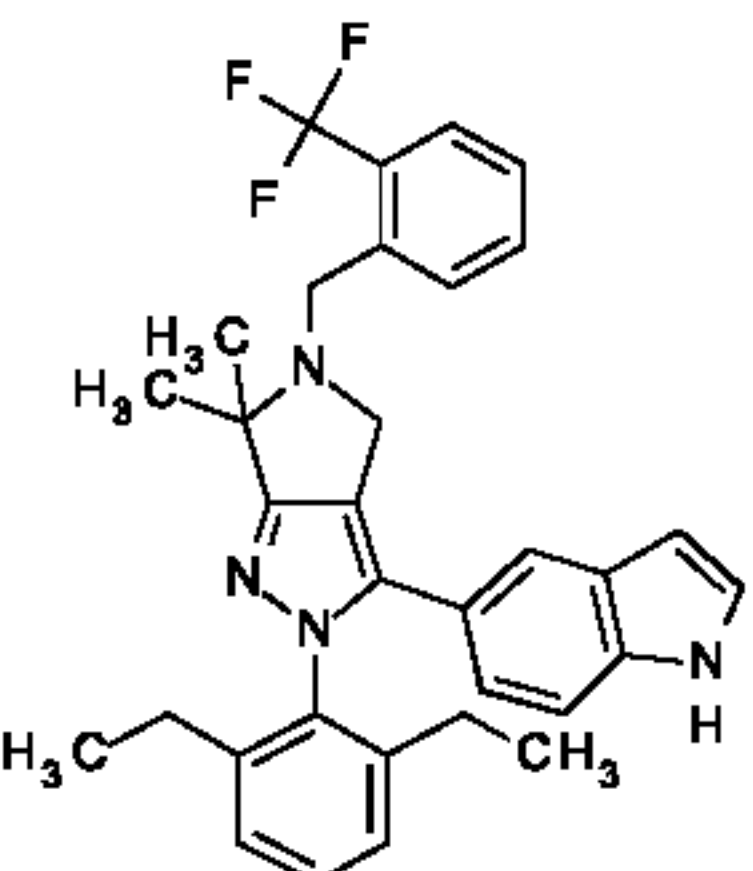
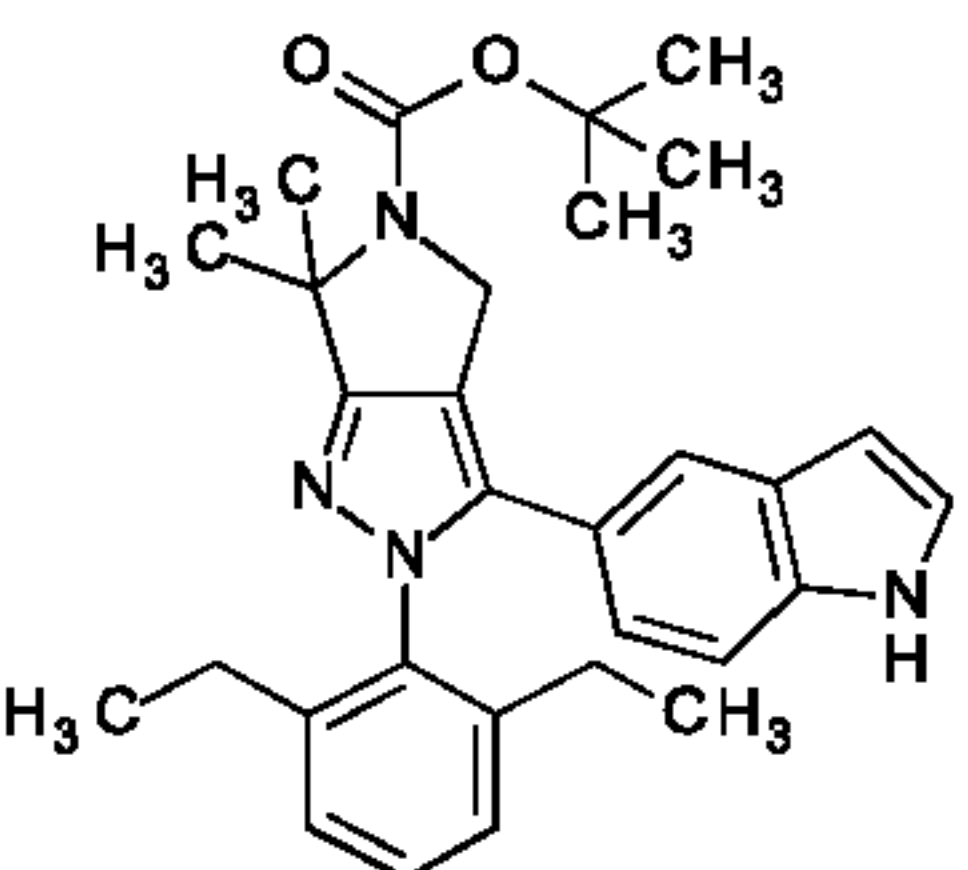
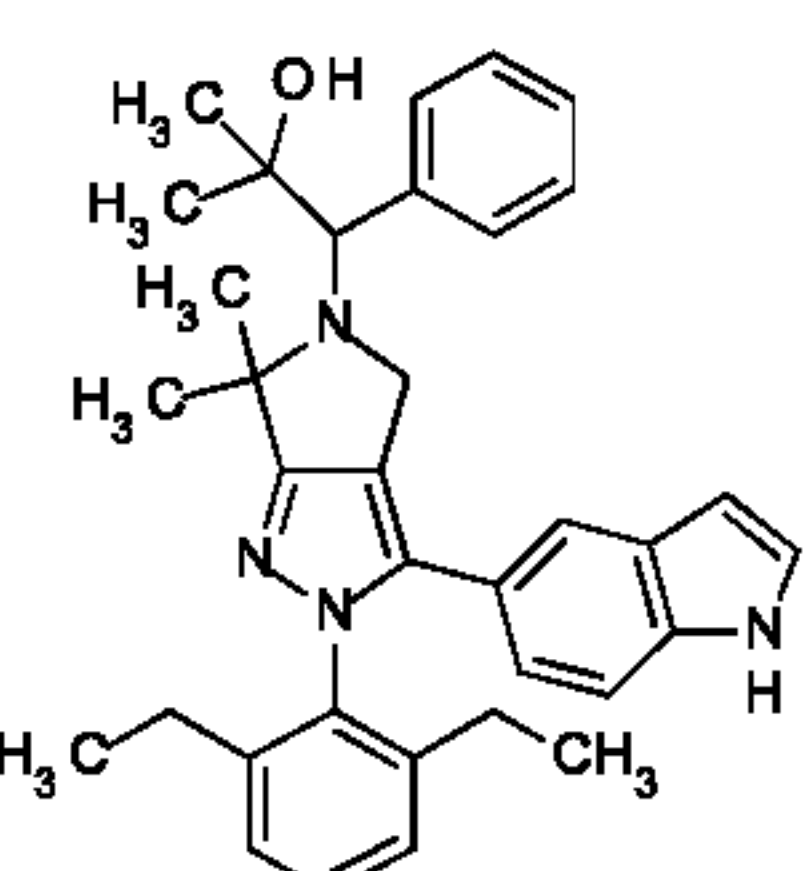
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1.015		+++
1.016		++
1.017		++++
1.018		+++
1.019		+++

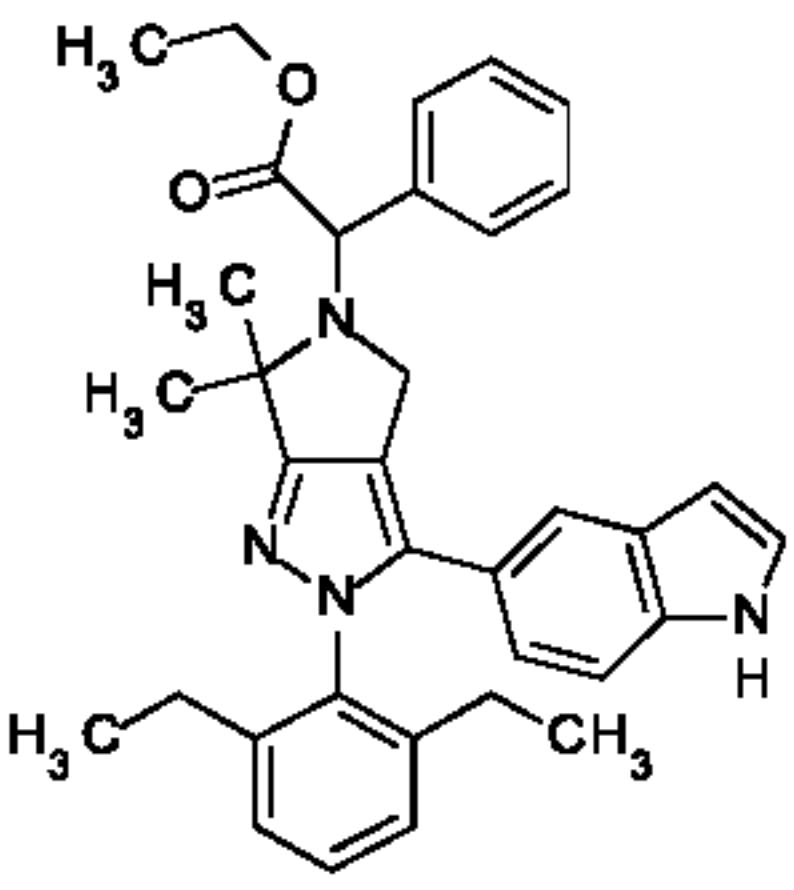
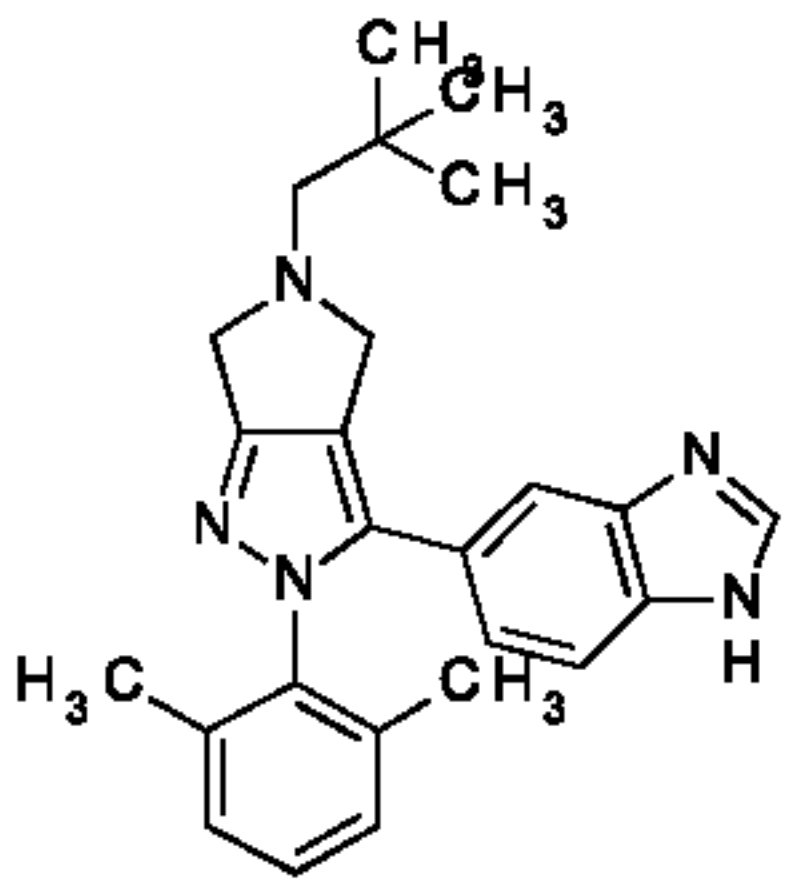
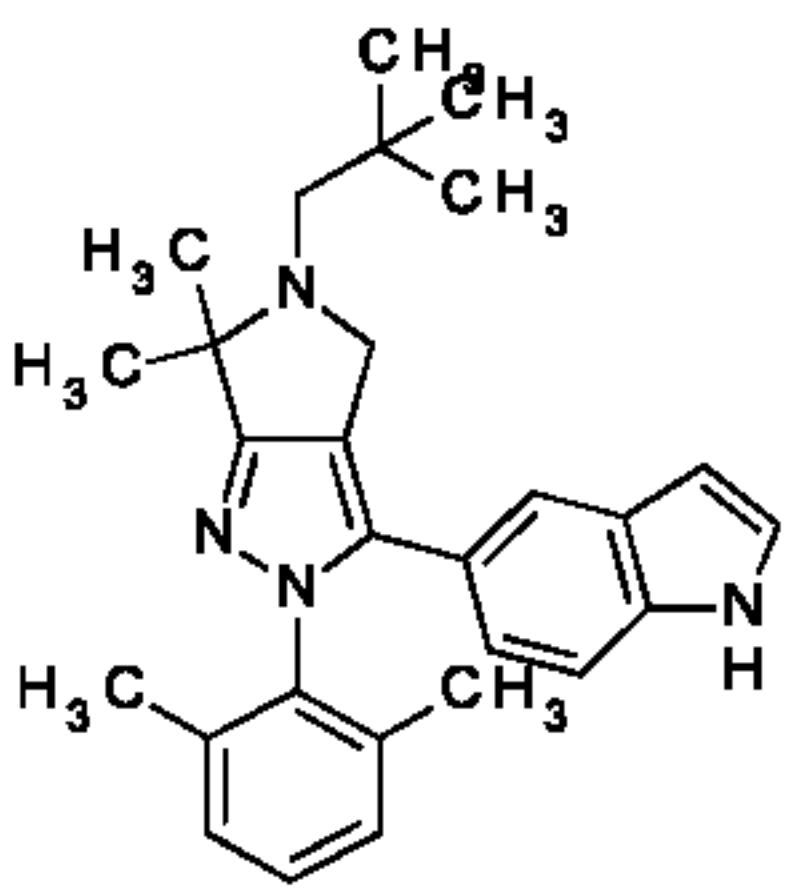
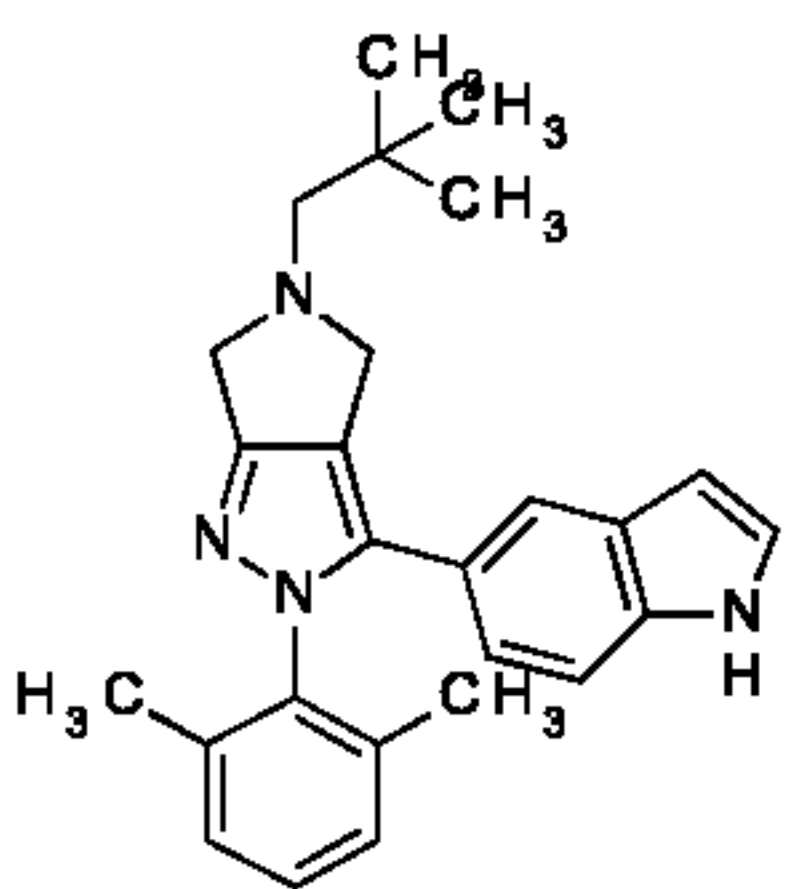
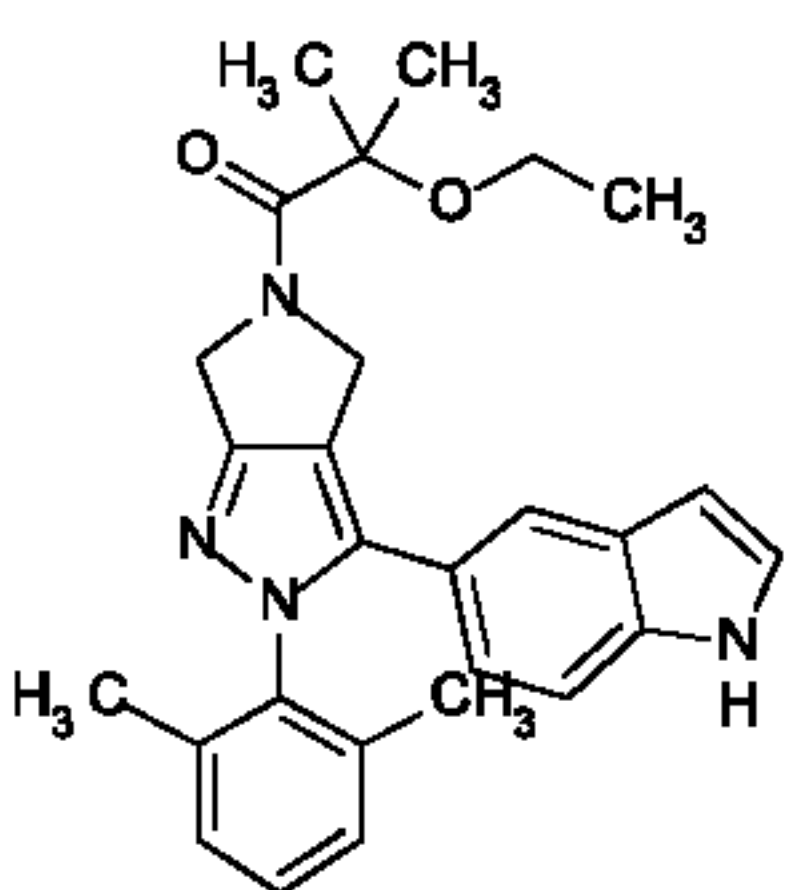
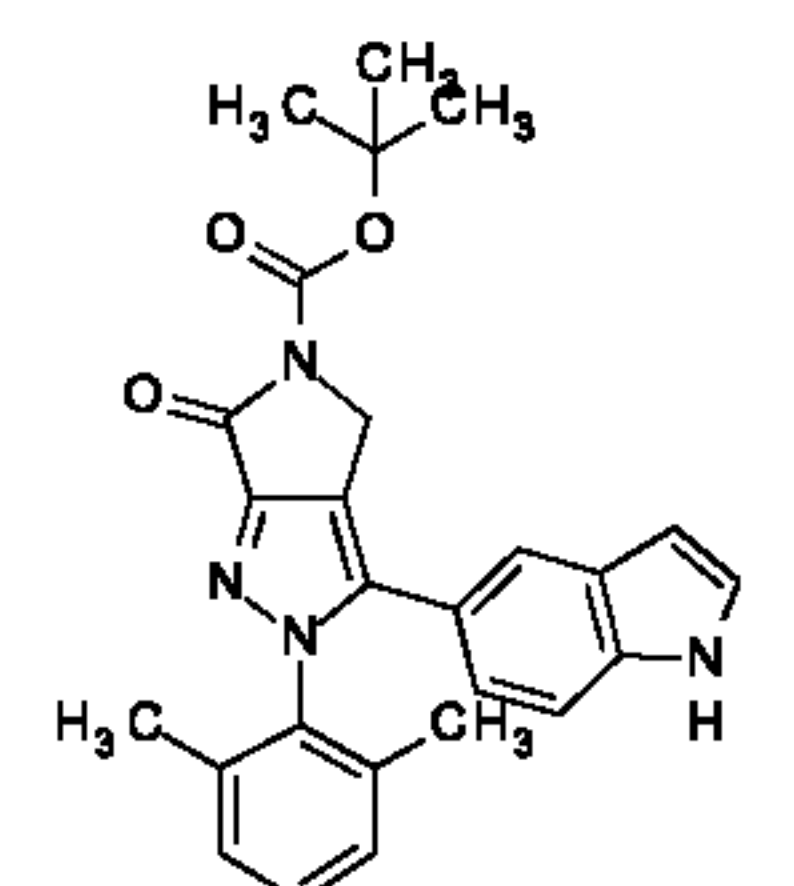
1.020		+++
1.021		++++
1.022		+++
1.023		++++
1.024		++++
1.025		++++

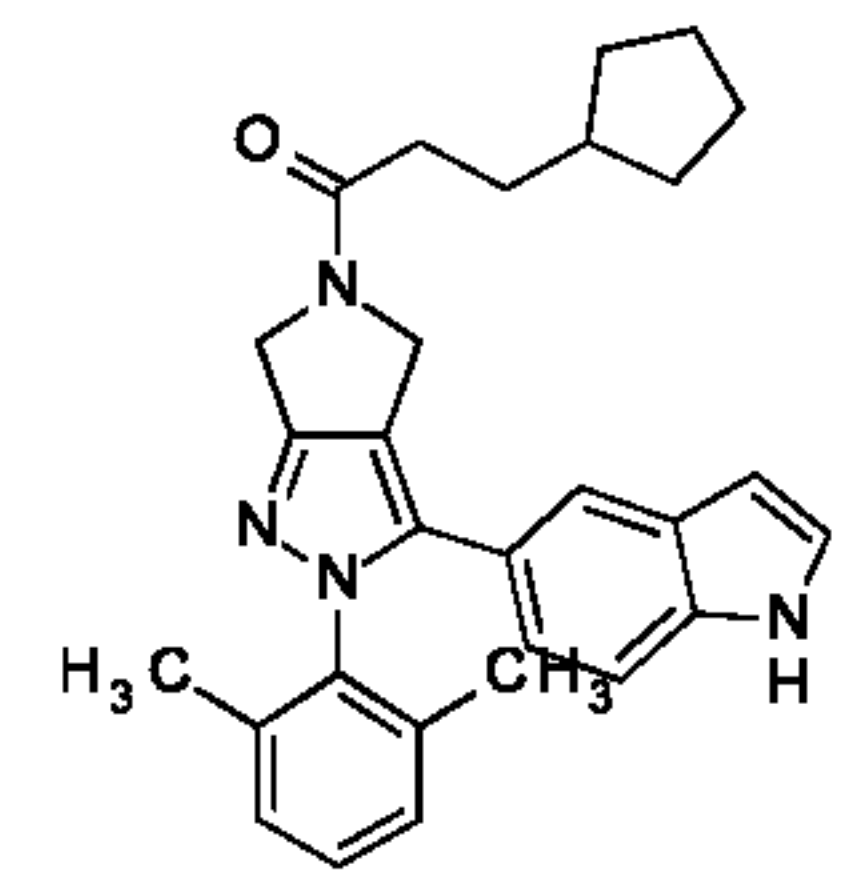
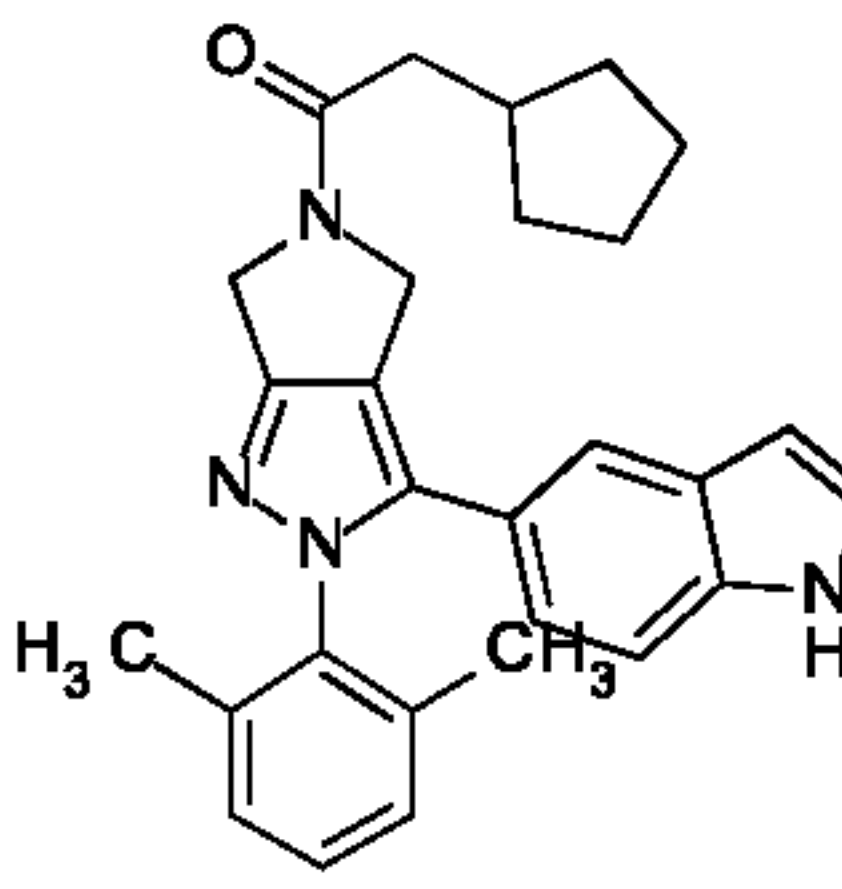
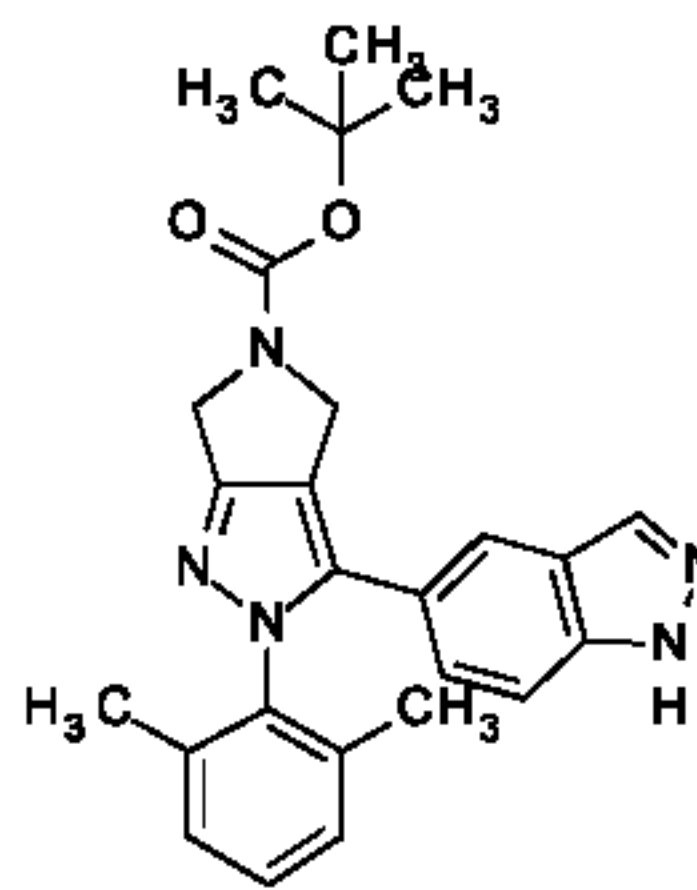
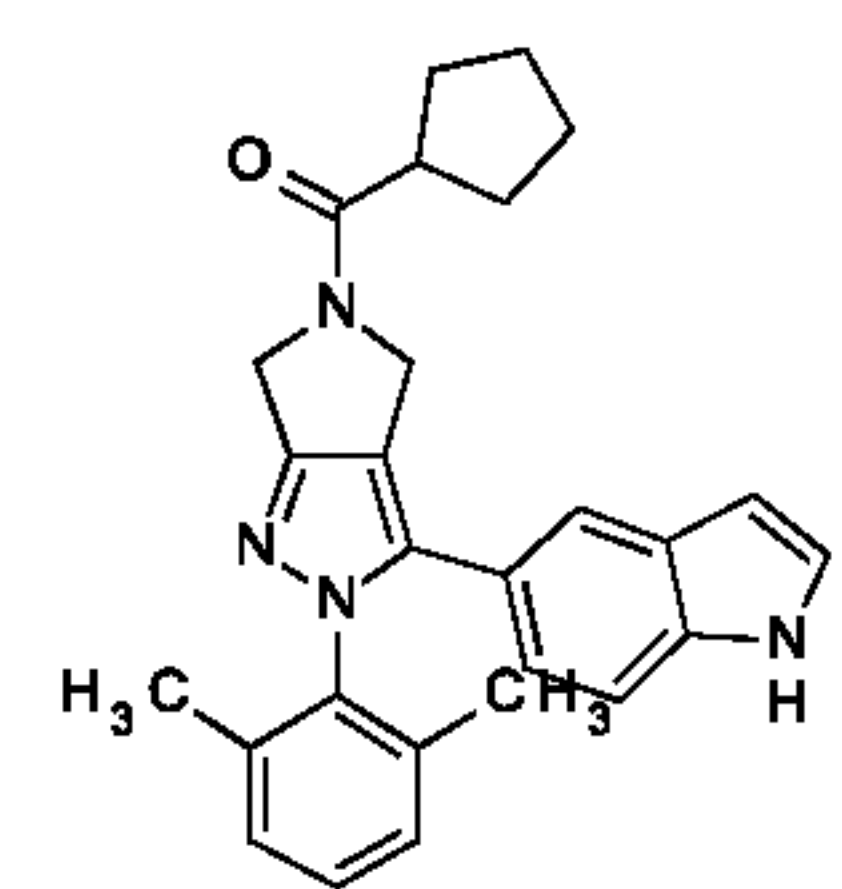
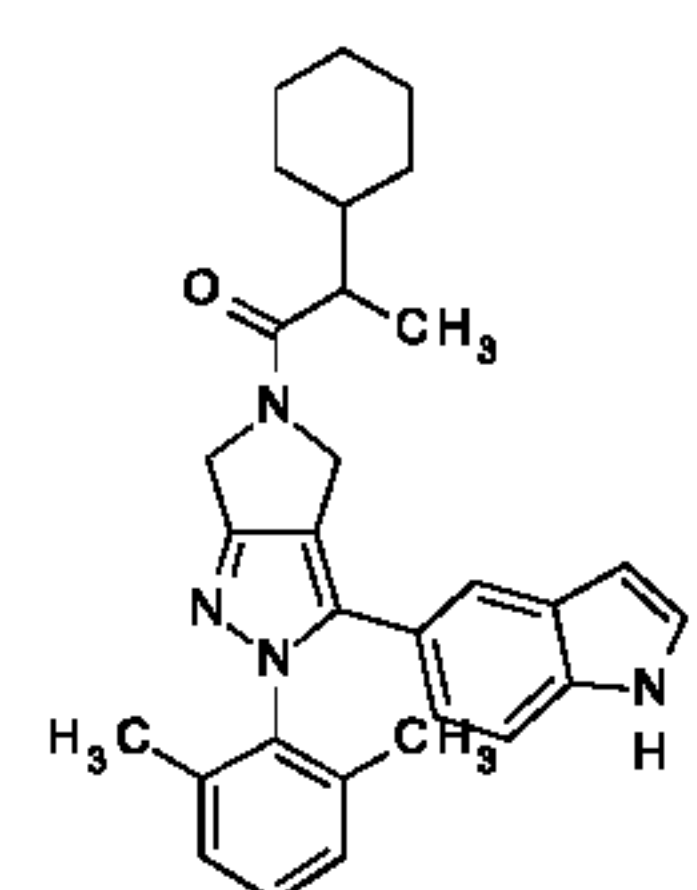
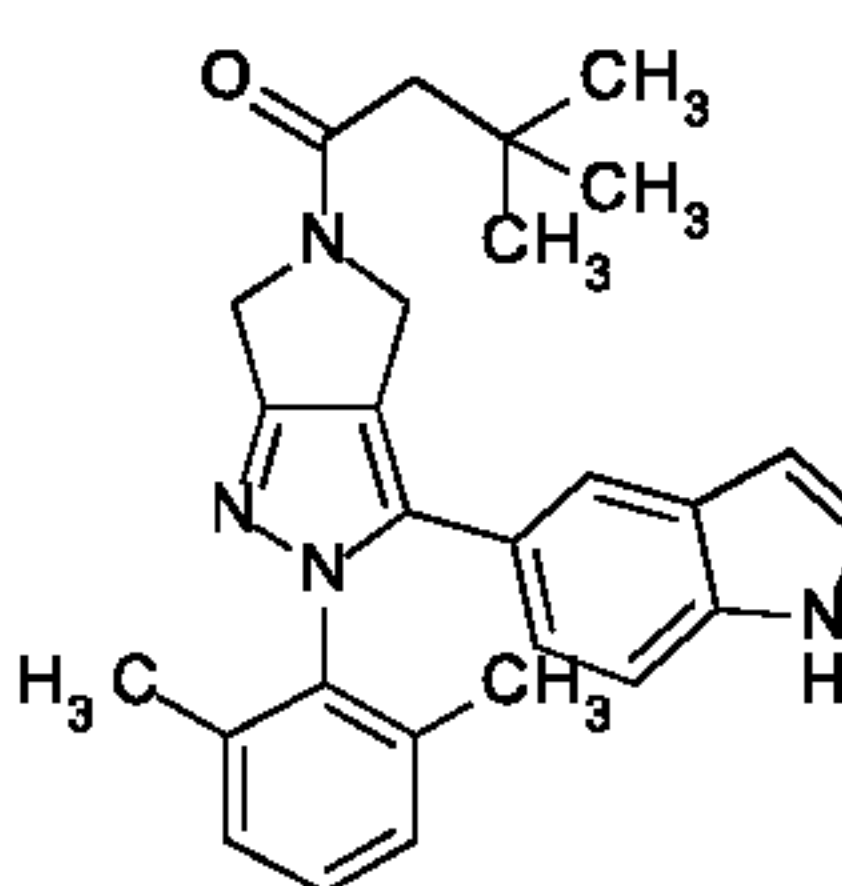
1.026		++++
1.027		+++
1.028		++
1.029		+++
1.030		+++
1.031		+++

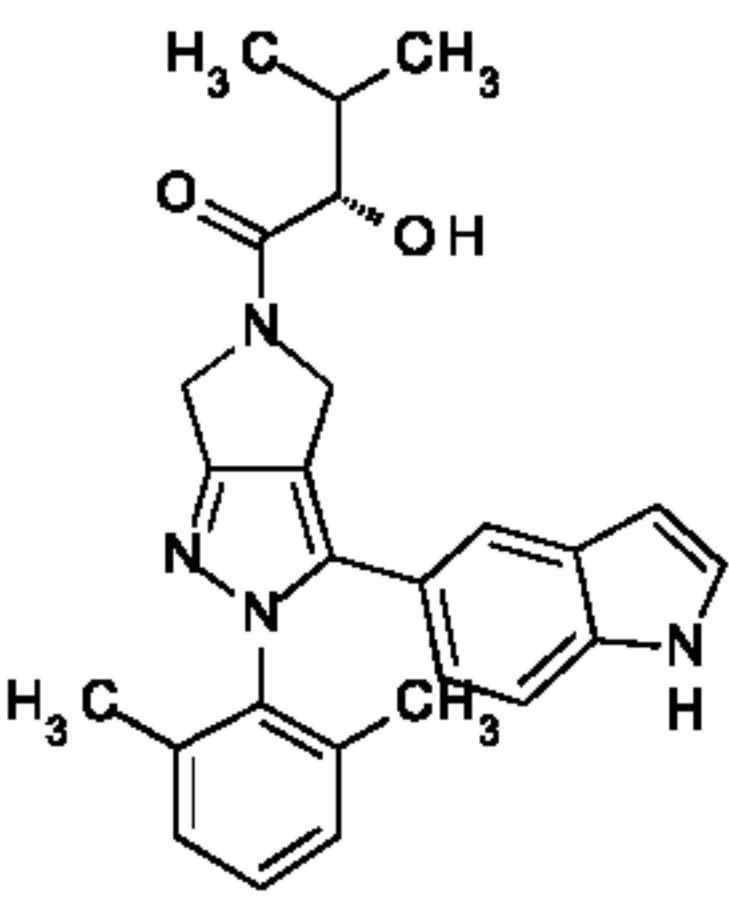
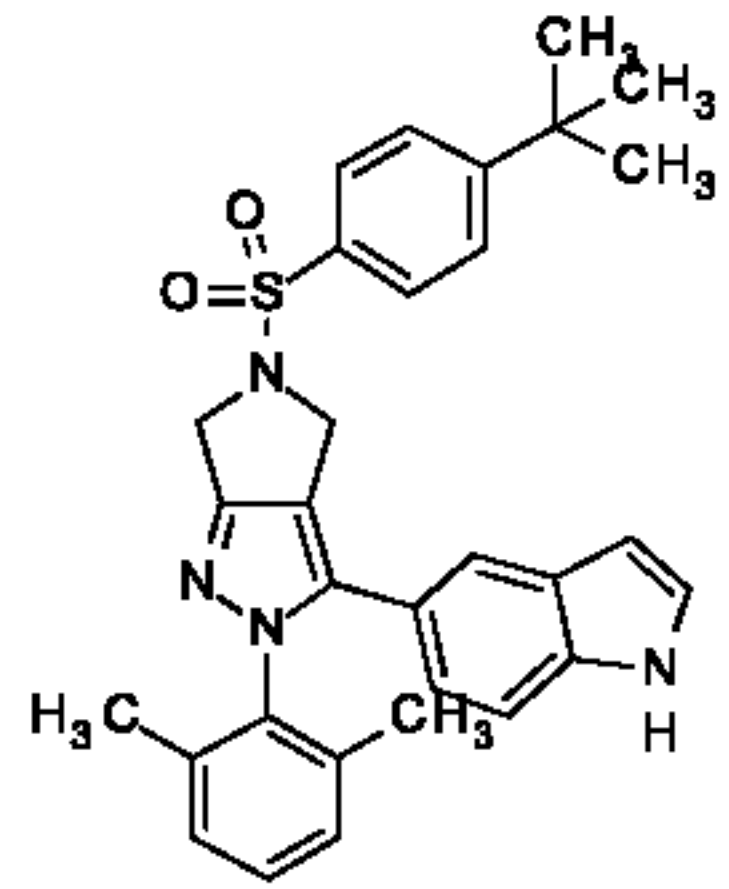
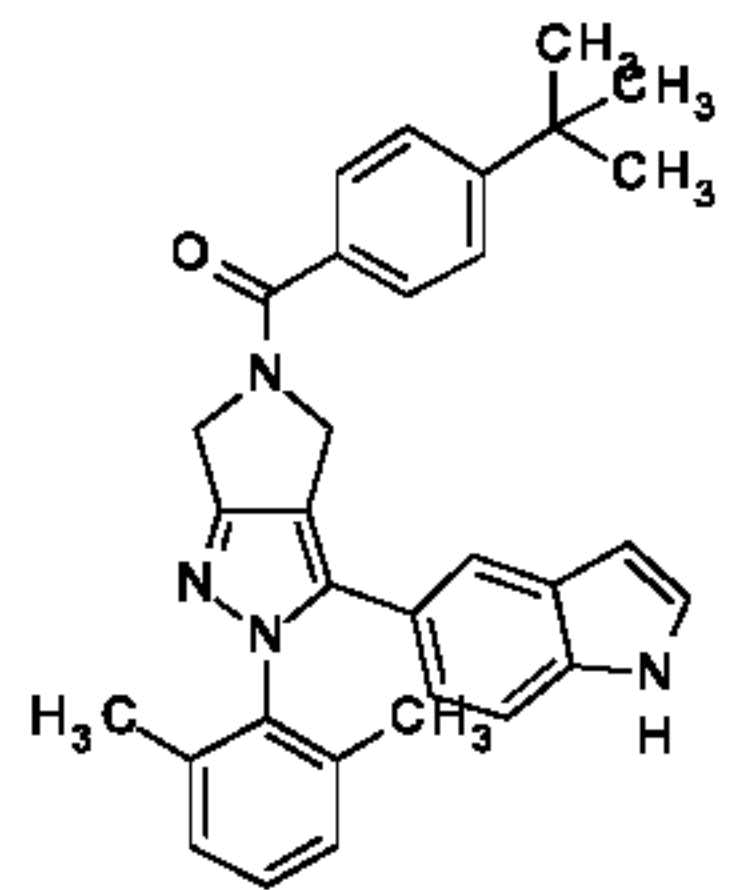
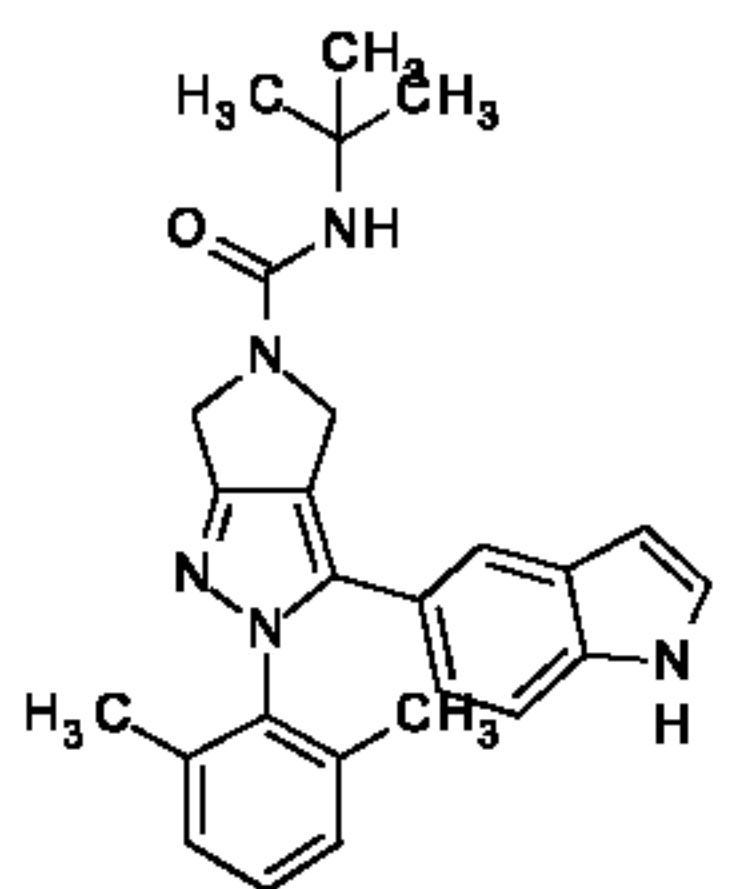
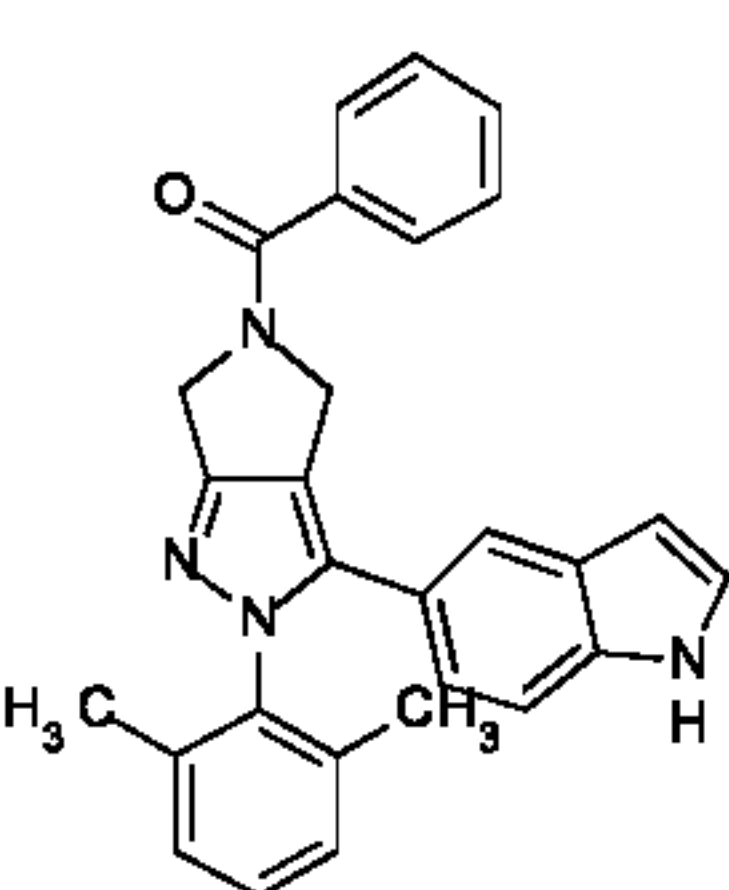
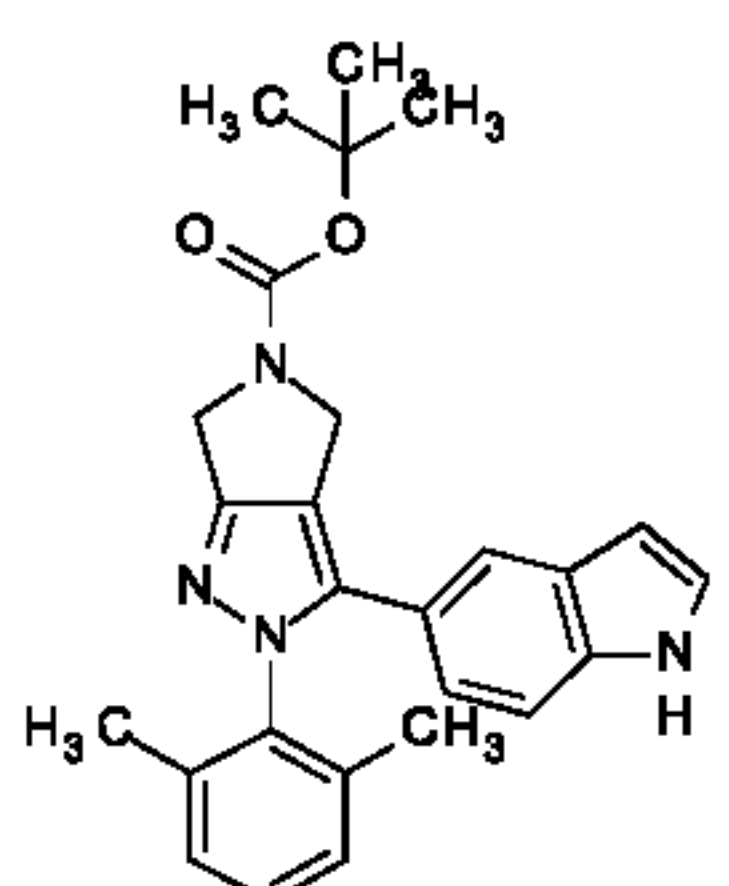
1.032		++++
1.033		+++
1.034		+++
1.035		+++
1.036		+++
1.037		++++

1.038		+++
1.039		+++
1.040		+
1.041		++
1.042		+++
1.043		+++

1.044		+++
1.045		+++
1.046		+++
1.047		+++
1.048		+++
1.049		++

1.050		+++
1.051		+
1.052		+++
1.053		++
1.054		+
1.055		+

1.056		+
1.057		+
1.058		+
1.059		+
1.060		++
1.061		+

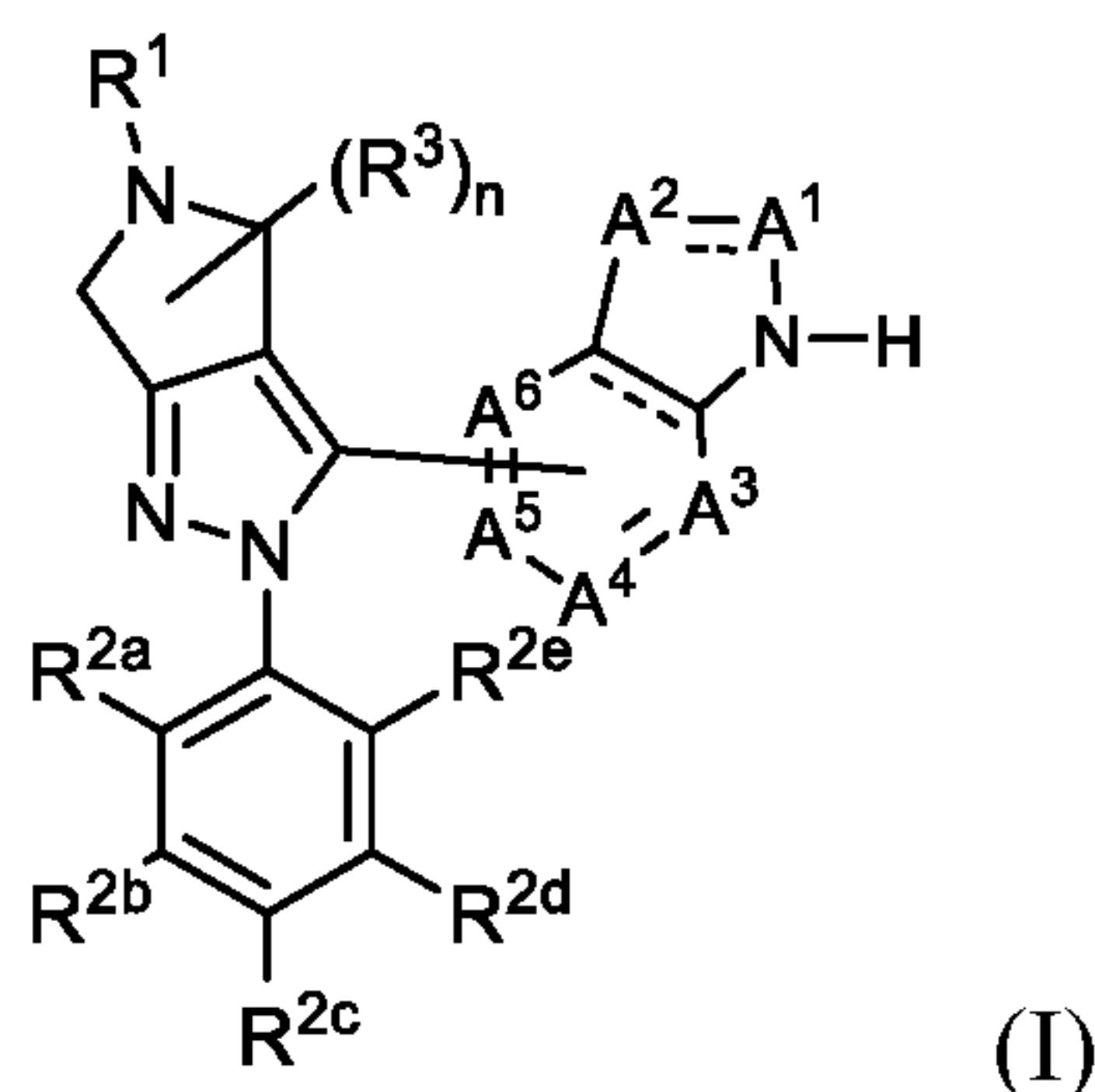
1.062		+
1.063		+
1.064		+
1.065		+
1.066		+
1.067		++

[0179] While particular embodiments of this invention are described herein, upon reading the description, variations of the disclosed embodiments may become apparent to individuals working in the art, and it is expected that those skilled artisans may employ such variations as appropriate. Accordingly, it is intended that the invention be practiced otherwise than as specifically described herein, and that the invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

10 [0180] All publications, patent applications, accession numbers, and other references cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference.

WHAT IS CLAIMED IS:

1. A compound of Formula (I)



or a pharmaceutically acceptable salt thereof, wherein,

ring vertex A¹ is selected from the group consisting of N, CH, C(O) and C(R⁴);

ring vertex A² is selected from the group consisting of N, CH, and C(R⁴);

each of ring vertices A³, A⁴, A⁵ and A⁶ is independently selected from the group consisting of CH and C(R⁴);

each of the dashed bonds independently indicate a single or double bond;

R¹ is selected from the group consisting of -C₁₋₈ alkylene heteroaryl, -C₁₋₈ alkylene-C₆₋₁₀ aryl, C₁₋₈ alkyl, C₁₋₈ haloalkyl, -C(O)-C₁₋₈ alkyl, -C(O)-C₆₋₁₀ aryl, -C(O)-heteroaryl, -C(O)-C₃₋₆ cycloalkyl, -C(O)-heterocycloalkyl, -C(O)NR^{1a}R^{1b}, -SO₂-C₆₋₁₀ aryl, -SO₂-heteroaryl, -C(O)-C₁₋₈ alkylene-O-heteroaryl, -C(O)-C₁₋₈ alkylene-O-C₆₋₁₀ aryl, -C(O)-C₁₋₈ alkylene-O- heterocycloalkyl, -C(O)-C₁₋₈ alkylene-O- C₃₋₆ cycloalkyl, -C(O) C₁₋₈ alkylene heteroaryl, -C(O) C₁₋₈ alkylene C₆₋₁₀ aryl, -C(O) C₁₋₈ alkylene heterocycloalkyl, -C(O) C₁₋₈ alkylene C₃₋₆ cycloalkyl and CO₂R^{1a}; the heterocycloalkyl is a 4 to 8 membered ring having from 1 to 3 heteroatoms as ring vertices selected from N, O and S; and the heteroaryl group is a 5 to 10 membered aromatic ring having from 1 to 3 heteroatoms as ring vertices selected from N, O and S;

wherein R^{1a} and R^{1b} are each independently selected from the group consisting of hydrogen, C₁₋₈ alkyl, and C₁₋₈ haloalkyl;

wherein R¹ is optionally substituted with 1 to 5 R⁵ substituents;

R^{2a} and R^{2e} are each independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, $-O-C_{1-6}$ haloalkyl, $-S-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl- $O-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl- $S-C_{1-6}$ alkyl, CN, and halogen;

R^{2b} , R^{2c} , and R^{2d} are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, $-O-C_{1-6}$ haloalkyl, $-S-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl- $O-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl- $S-C_{1-6}$ alkyl, cyano, and halogen;

each R^3 is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, halogen and hydroxyl, and optionally two R^3 groups on the same carbon atom are combined to form oxo ($=O$) or to form a three to five membered cycloalkyl ring;

each R^4 is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} hydroxyalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, $-O-C_{1-6}$ haloalkyl, halogen, cyano, hydroxyl, $-S-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl- $O-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl- $S-C_{1-6}$ alkyl, $-NR^{4a}R^{4b}$, $-CONR^{4a}R^{4b}$, $-CO_2R^{4a}$, $-COR^{4a}$, $-OC(O)NR^{4a}R^{4b}$, $-NR^{4a}C(O)R^{4b}$, $-NR^{4a}C(O)_2R^{4b}$, and $NR^{4a}-C(O)NR^{4a}R^{4b}$;

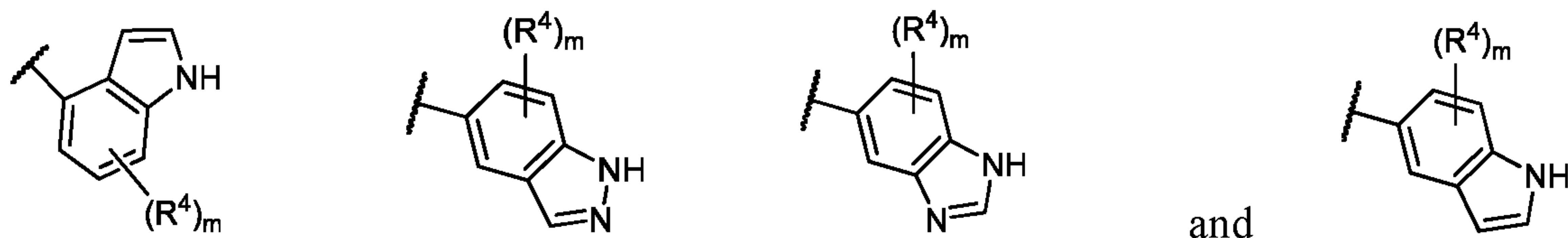
each R^{4a} and R^{4b} is independently selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{1-4} haloalkyl;

each R^5 is independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} haloalkyl, C_{1-8} haloalkoxy, C_{1-8} hydroxyalkyl, $-C_{1-8}$ alkylene-heterocycloalkyl, $-C_{1-8}$ alkylene- C_{3-6} cycloalkyl, C_{3-6} cycloalkyl, heterocycloalkyl, halogen, OH, C_{2-8} alkenyl, C_{2-8} alkynyl, CN, $C(O)R^{5a}$, $-NR^{5b}C(O)R^{5a}$, $-CONR^{5a}R^{5b}$, $-NR^{5a}R^{5b}$, $-C_{1-8}$ alkylene $NR^{5a}R^{5b}$, $-S-C_{1-6}$ alkyl, $-C_{1-6}$ alkylene- $O-C_{1-6}$ alkyl, $-C_{1-6}$ alkylene- $S-C_{1-6}$ alkyl, $-OC(O)NR^{5a}R^{5b}$, $-NR^{5a}C(O)_2R^{5b}$, $-NR^{5a}-C(O)NR^{5b}R^{5b}$, and CO_2R^{5a} ; wherein the heterocycloalkyl group is a 4 to 8 membered ring having from 1 to 3 heteroatoms as ring vertices selected from N, O, and S;

wherein each R^{5a} and R^{5b} is independently selected from the group consisting of hydrogen, C_{1-8} alkyl, and C_{1-8} haloalkyl, or when R^{5a} and R^{5b} are attached to the same nitrogen atom they are combined with the nitrogen atom to form a 5 or 6-membered ring having from 0 to 1 additional heteroatoms as ring vertices selected from N, O, or S; and

the subscript n is 0, 1, 2 or 3.

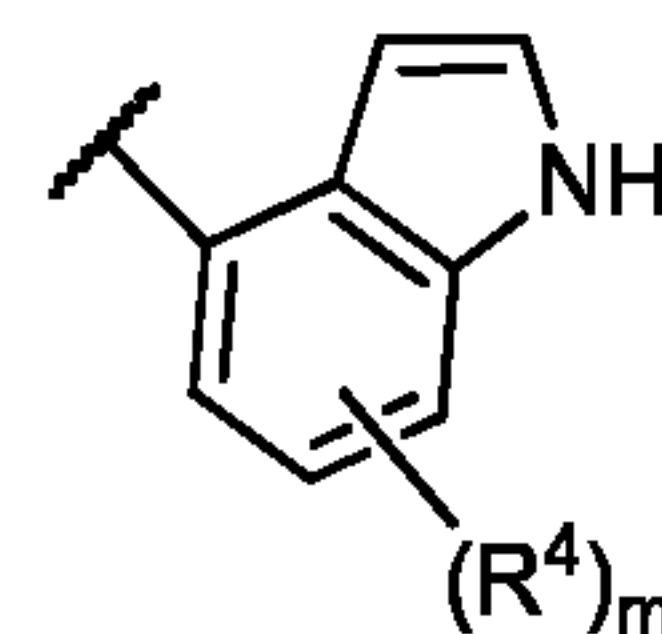
2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the ring portion having A¹, A², A³, A⁴, A⁵, and A⁶ as ring vertices is a bicyclic heteroaryl selected from the group consisting of



wherein m is 0, 1, 2 or 3; and wherein the R⁴ substituents may be attached to any suitable carbon ring vertex of the bicyclic heteroaryl.

3. The compound of any one of claims 1 or 2, or a pharmaceutically acceptable salt thereof, wherein the ring portion having A¹, A², A³, A⁴, A⁵, and A⁶ as ring

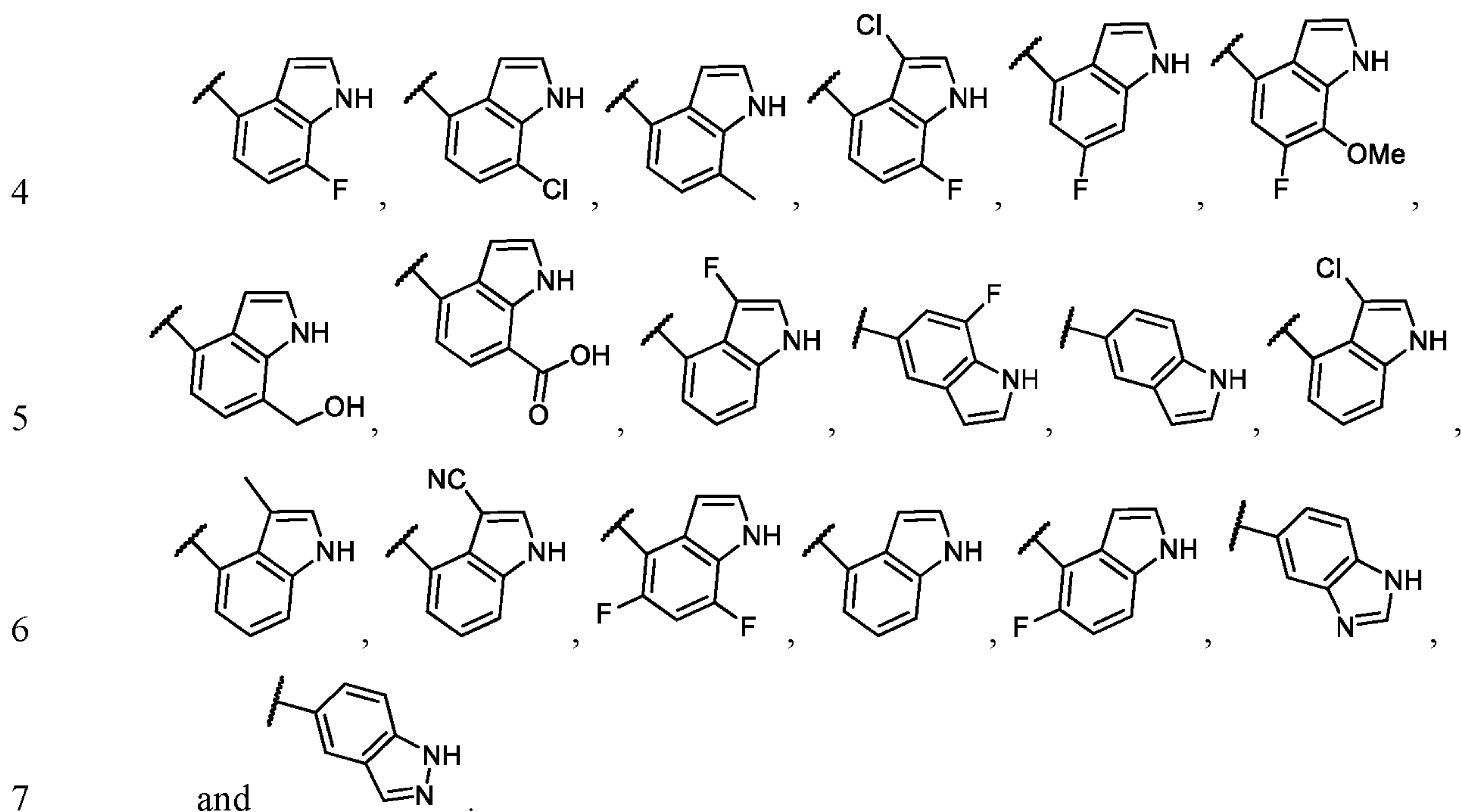
vertices is a bicyclic heteroaryl represented by the structure



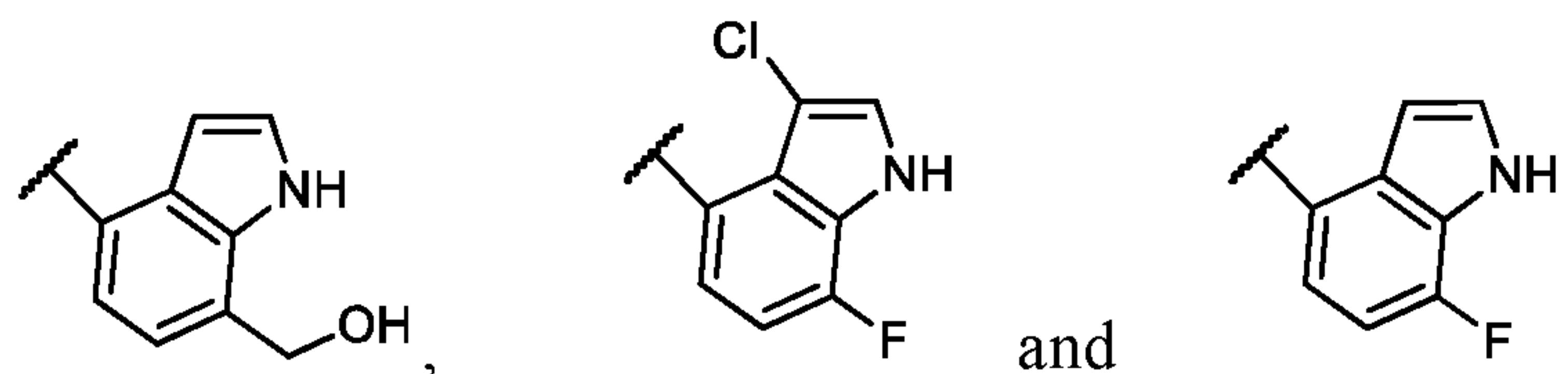
wherein m is 0, 1, 2, or 3; and wherein the R⁴ substituents may be attached to any suitable carbon ring vertex of the bicyclic heteroaryl.

4. The compound of any one of claims 1 or 3, or a pharmaceutically acceptable salt thereof, wherein each R⁴ is independently selected from the group consisting of C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₆ hydroxyalkyl, halogen, cyano, and -CO₂R^{4a}; and wherein the R⁴ substituents may be attached to any suitable carbon ring vertex of the bicyclic heteroaryl.

5. The compound of any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein the ring portion having A¹, A², A³, A⁴, A⁵, and A⁶ as ring vertices is a bicyclic heteroaryl selected from the group consisting of:



6. The compound of any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein the ring portion having A¹, A², A³, A⁴, A⁵, and A⁶ as ring vertices is a bicyclic heteroaryl selected from the group consisting of:



7. The compound of claim any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein R¹ is selected from the group consisting of -C₁₋₈ alkylene heteroaryl, -C₁₋₈alkylene C₆₋₁₀ aryl, C₁₋₈ alkyl, C₁₋₈ haloalkyl, -C(O)-C₁₋₈ alkyl, -C(O)-C₆₋₁₀ aryl, -C(O)-heteroaryl, -C(O)-C₃₋₈ cycloalkyl, C(O)NR^{1a}R^{1b}, -SO₂-C₆₋₁₀ aryl, -C(O)-C₁₋₈ alkylene-O-C₆₋₁₀ aryl, and CO₂R^{1a}; wherein the heterocycloalkyl is a 4 to 8 membered ring having from 1 to 3 heteroatoms as ring vertices selected from N, O and S; and the heteroaryl group is a 5 to 10 membered aromatic ring having from 1 to 3 heteroatoms as ring vertices selected from N, O and S; and wherein R^{1a} and R^{1b} are each independently selected from the group consisting of hydrogen, C₁₋₈ alkyl, and C₁₋₈ haloalkyl; and R¹ is optionally substituted with 1 to 5 R⁵ substituents.

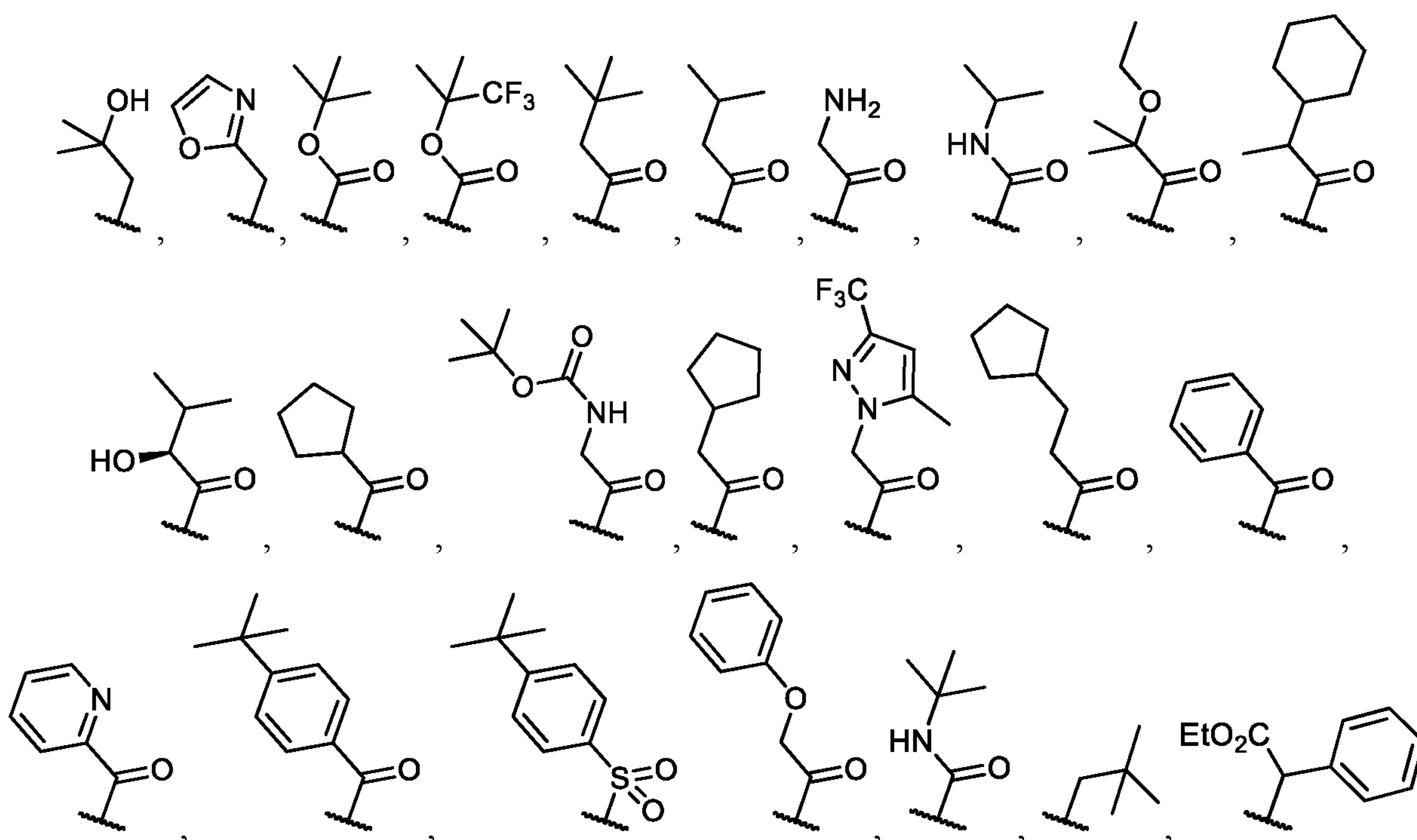
8. The compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein each R^5 is independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} haloalkyl, C_{1-8} haloalkoxy, C_{1-8} hydroxyalkyl, C_{3-6} cycloalkyl, halogen, OH, $-NR^{5a}R^{5b}$, and CO_2R^{5a} , wherein each R^{5a} and R^{5b} is independently selected from the group consisting of hydrogen, C_{1-8} alkyl, and C_{1-8} haloalkyl.

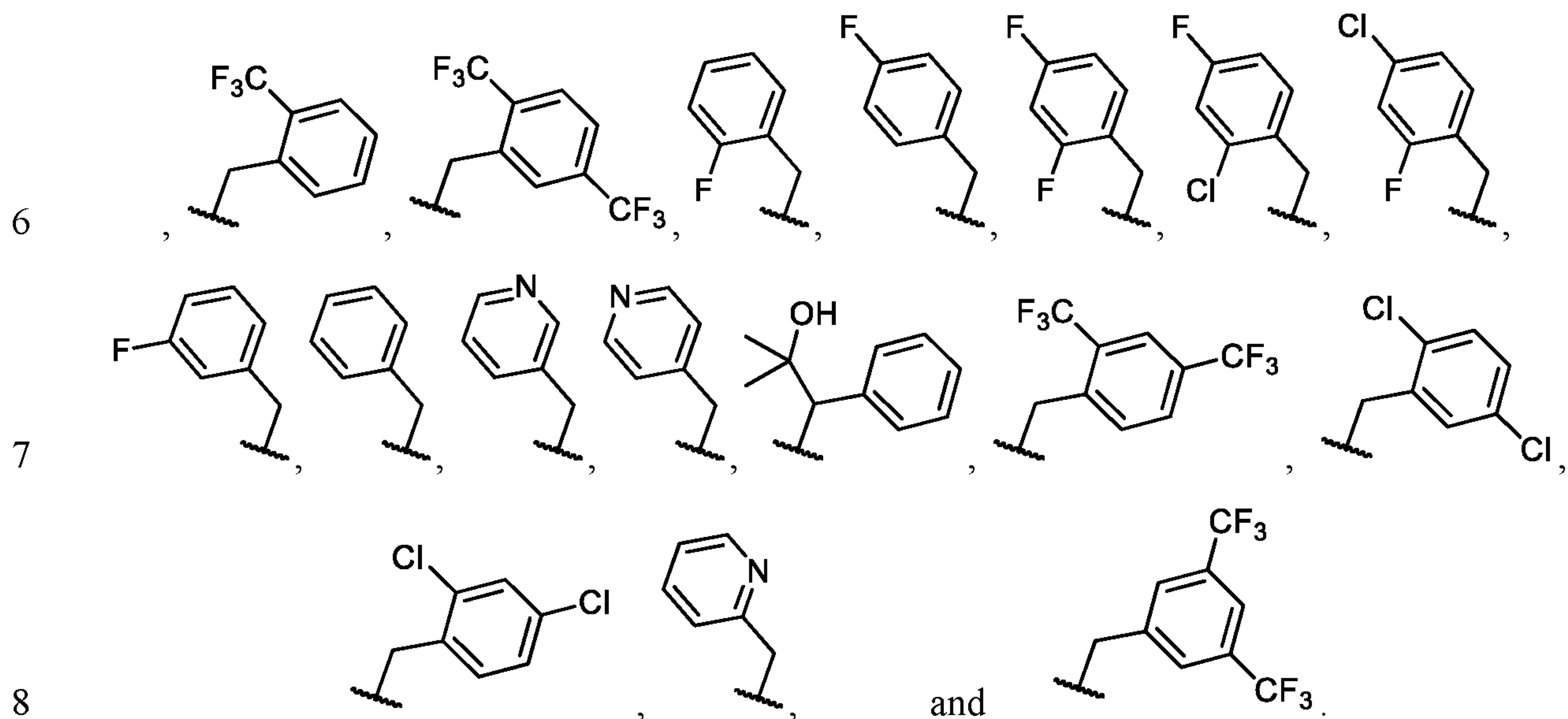
9. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein R^1 is $-CH_2$ -phenyl optionally substituted by 1 to 3 R^5 .

10. The compound of any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein R^1 is $-CH_2$ -phenyl substituted by 1 or 2 R^5 , wherein each R^5 is independently C_{1-4} haloalkyl.

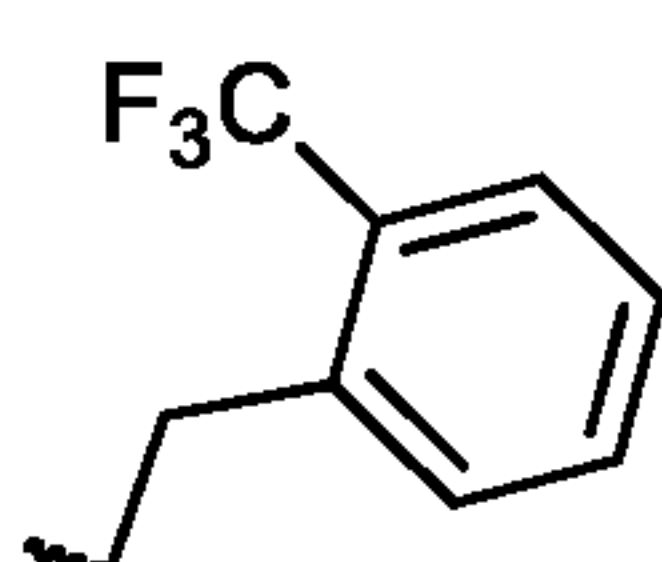
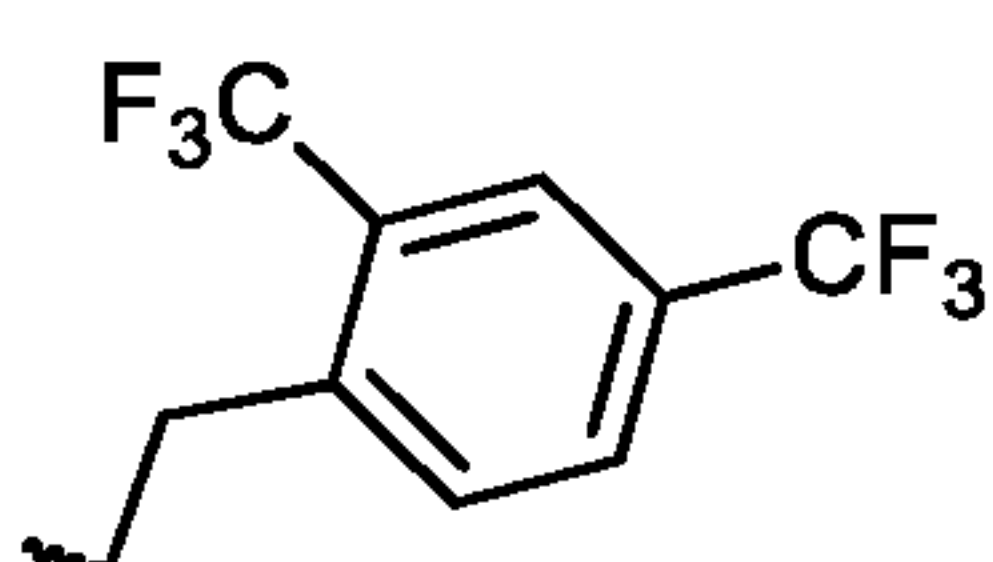
11. The compound of any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein R^1 is $-CH_2$ -phenyl substituted by 1 or 2 CF_3 .

12. The compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from the group consisting of





1 **13.** The compound of any one of claims **1** to **12**, or a pharmaceutically

2 acceptable salt thereof, wherein R^1 is  or .

1 **14.** The compound of any one of claims **1** to **13**, or a pharmaceutically

2 acceptable salt thereof, wherein R^{2b} , R^{2c} , and R^{2d} are each H.

1 **15.** The compound of any one of claims **1** to **14**, or a pharmaceutically

2 acceptable salt thereof, wherein R^{2a} and R^{2e} are each independently selected from the group

3 consisting of C_{1-6} alkyl and C_{1-6} haloalkyl.

1 **16.** The compound of any one of claims **1** to **15**, or a pharmaceutically

2 acceptable salt thereof, wherein R^{2a} and R^{2e} are each independently C_{1-6} alkyl.

1 **17.** The compound of any one of claims **1** to **16**, or a pharmaceutically

2 acceptable salt thereof, wherein R^{2a} and R^{2e} are each independently selected from the group

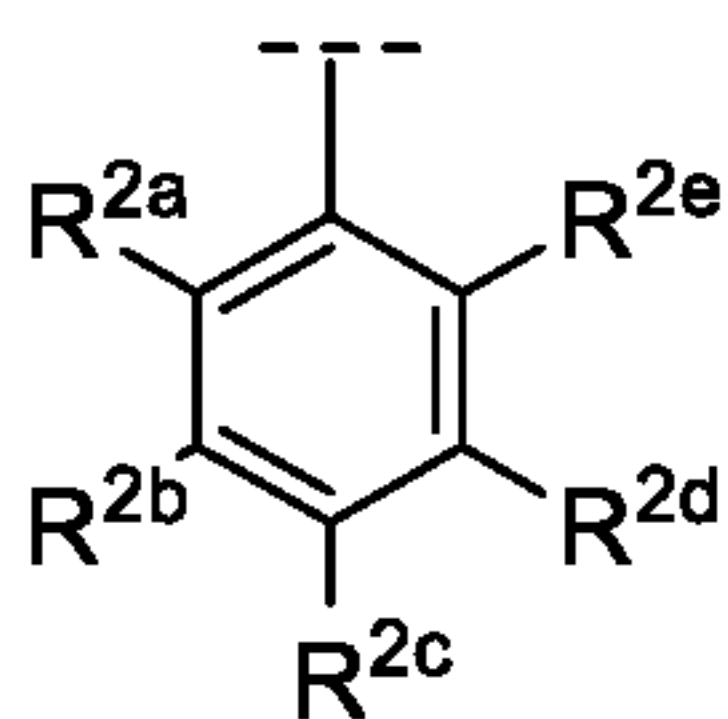
3 consisting of methyl and ethyl.

1 **18.** The compound of any one of claims **1** to **17**, or a pharmaceutically

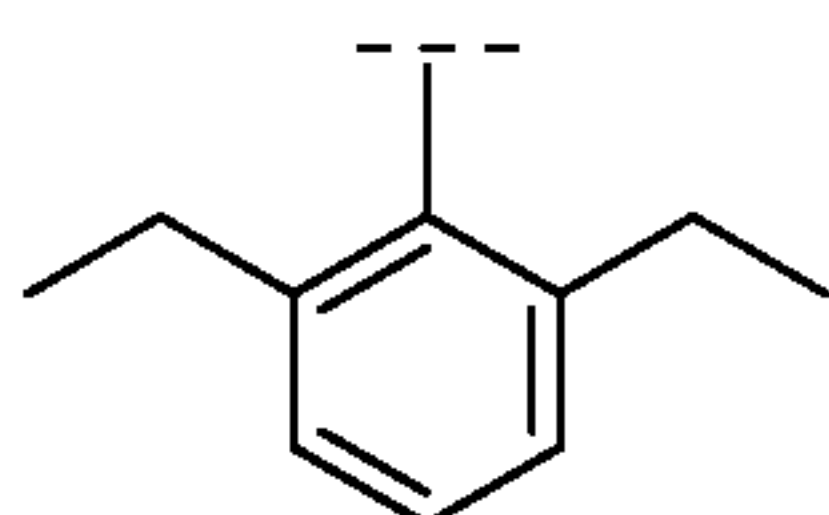
2 acceptable salt thereof, wherein R^{2a} and R^{2e} are both methyl or are both ethyl.

1 **19.** The compound of any one of claims **1** to **18**, or a pharmaceutically

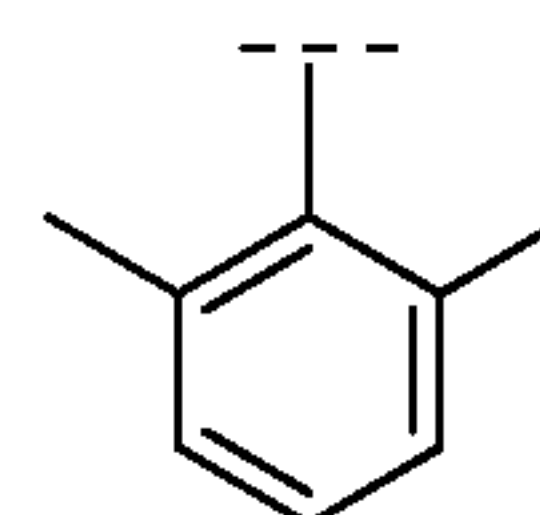
2 acceptable salt thereof, wherein



is selected from the group consisting of



and



1 **20.** The compound of any one of claims **1** to **19**, or a pharmaceutically

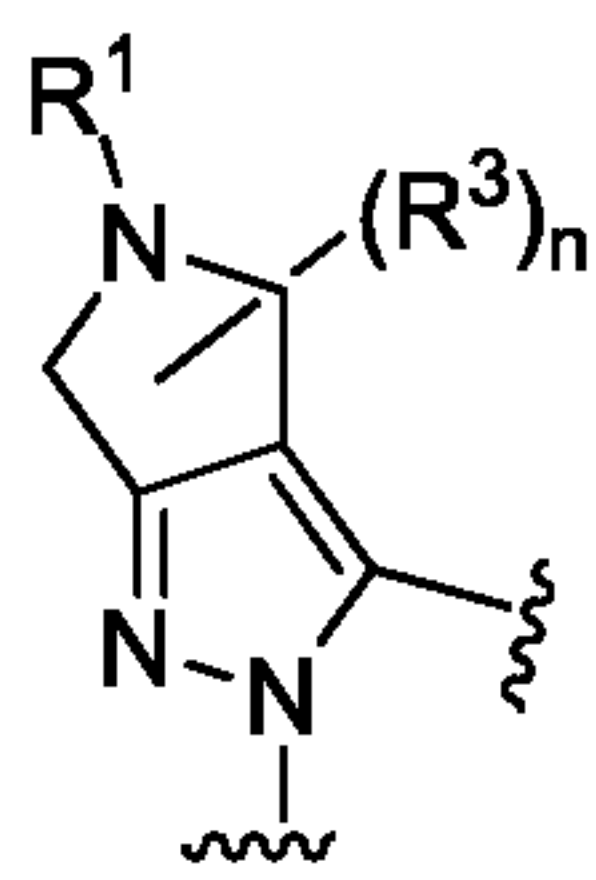
2 acceptable salt thereof, wherein n is 0, 1 or 2.

1 **21.** The compound of any one of claims **1** to **20**, or a pharmaceutically

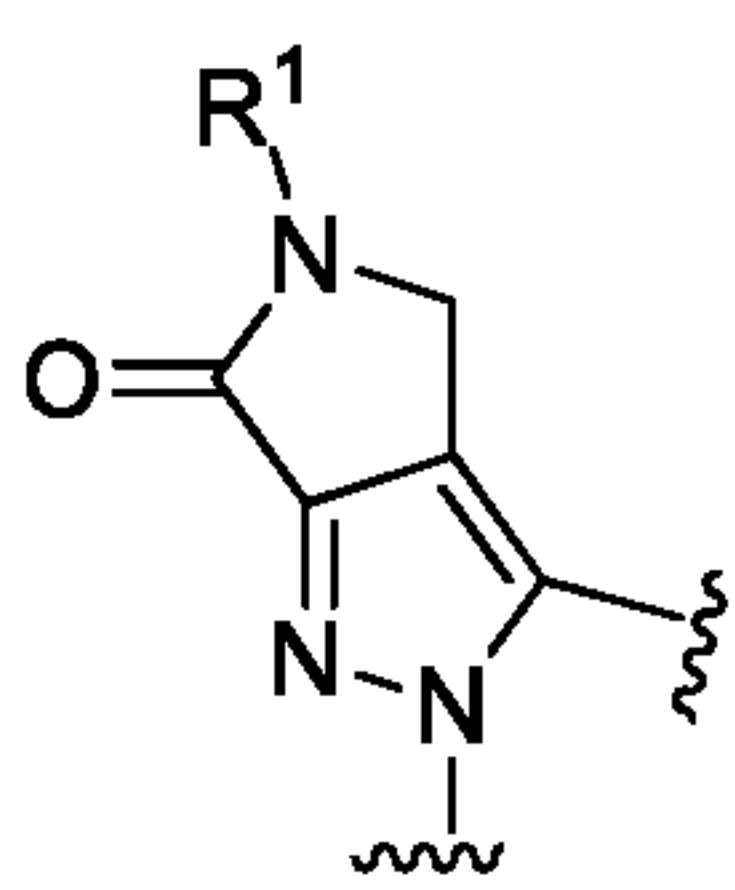
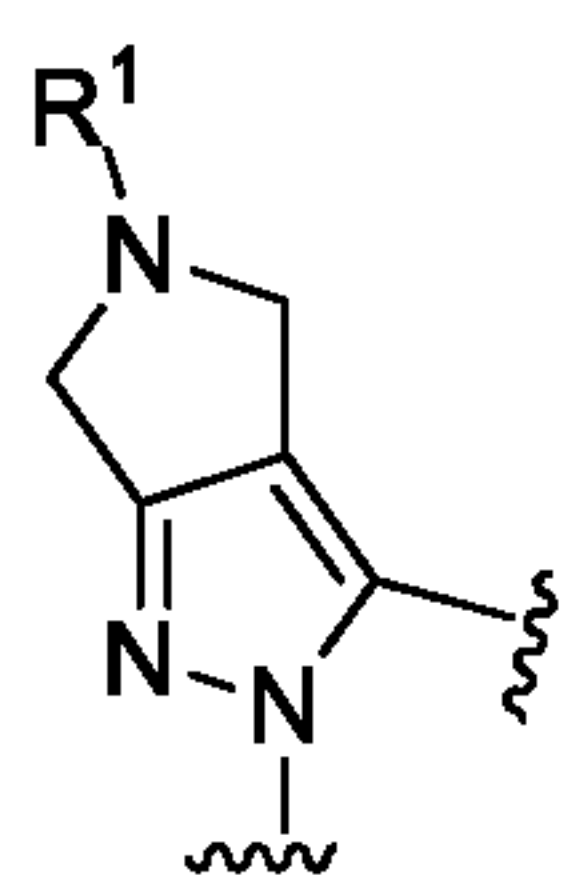
2 acceptable salt thereof, wherein each R^3 is independently C_{1-4} alkyl.

1 **22.** The compound of any one of claims **1** to **20**, or a pharmaceutically

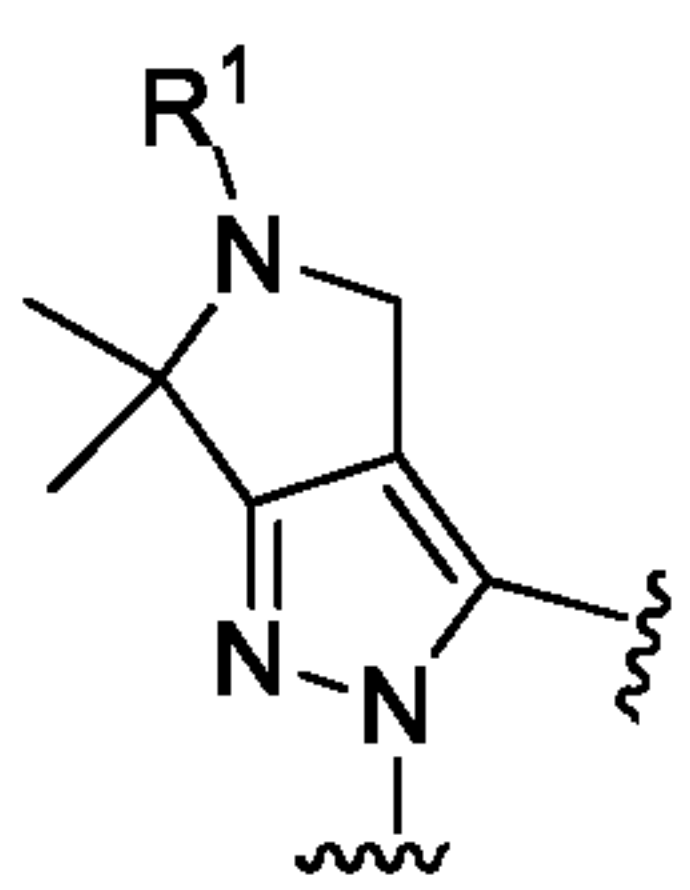
2 acceptable salt thereof, wherein



is selected from the group consisting of

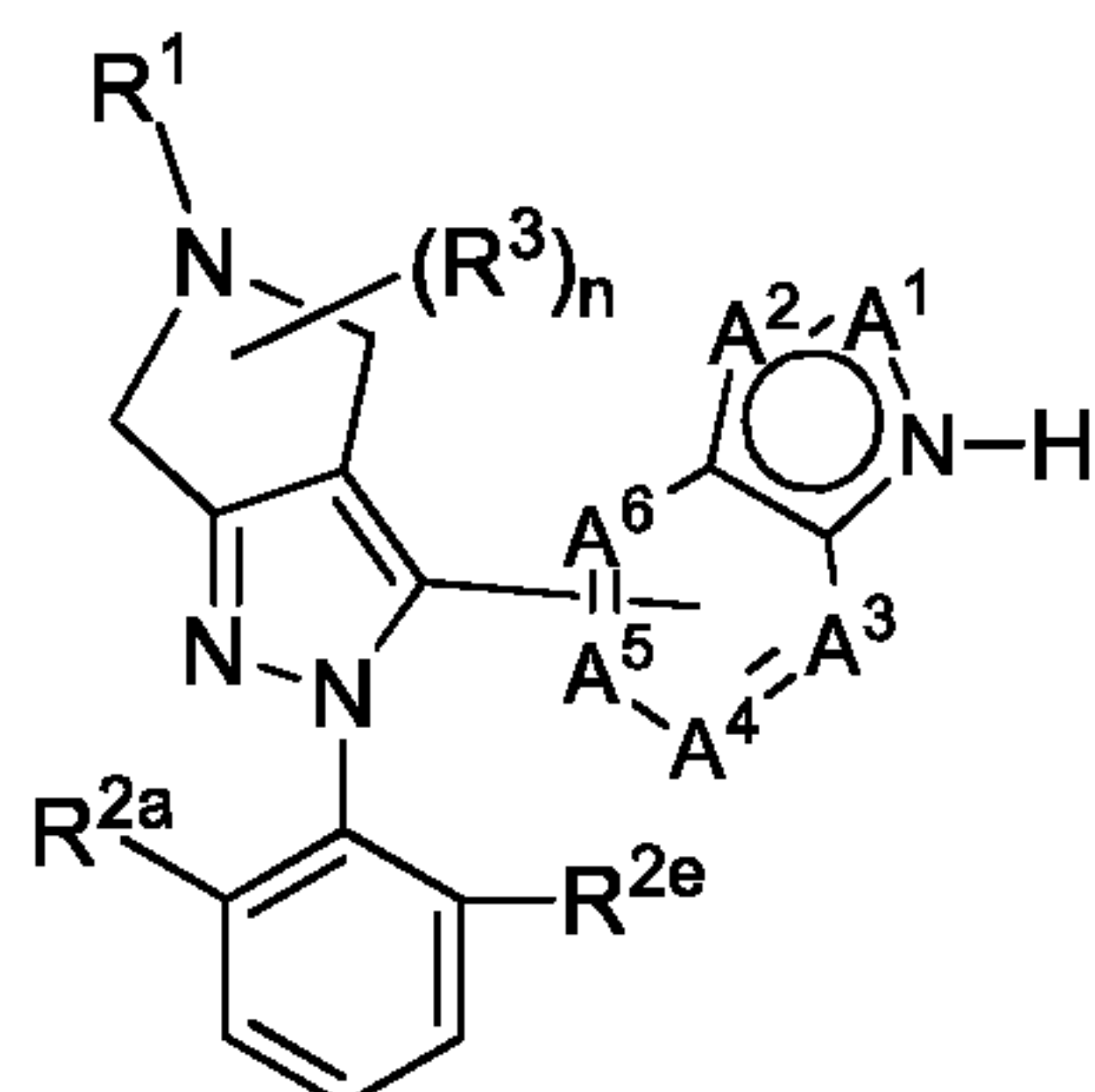


and

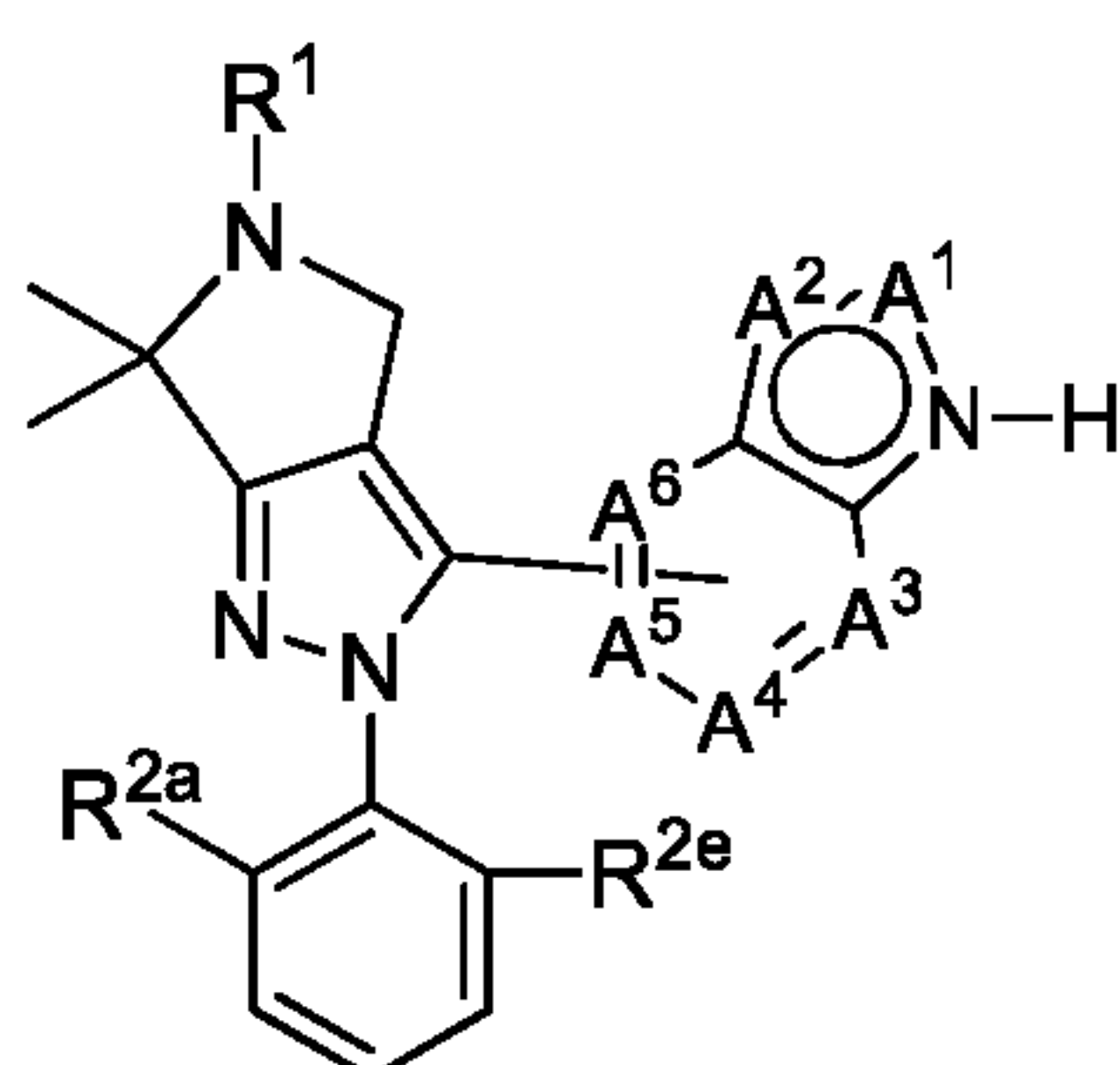


1 **23.** The compound of claim **1**, or a pharmaceutically acceptable salt thereof,

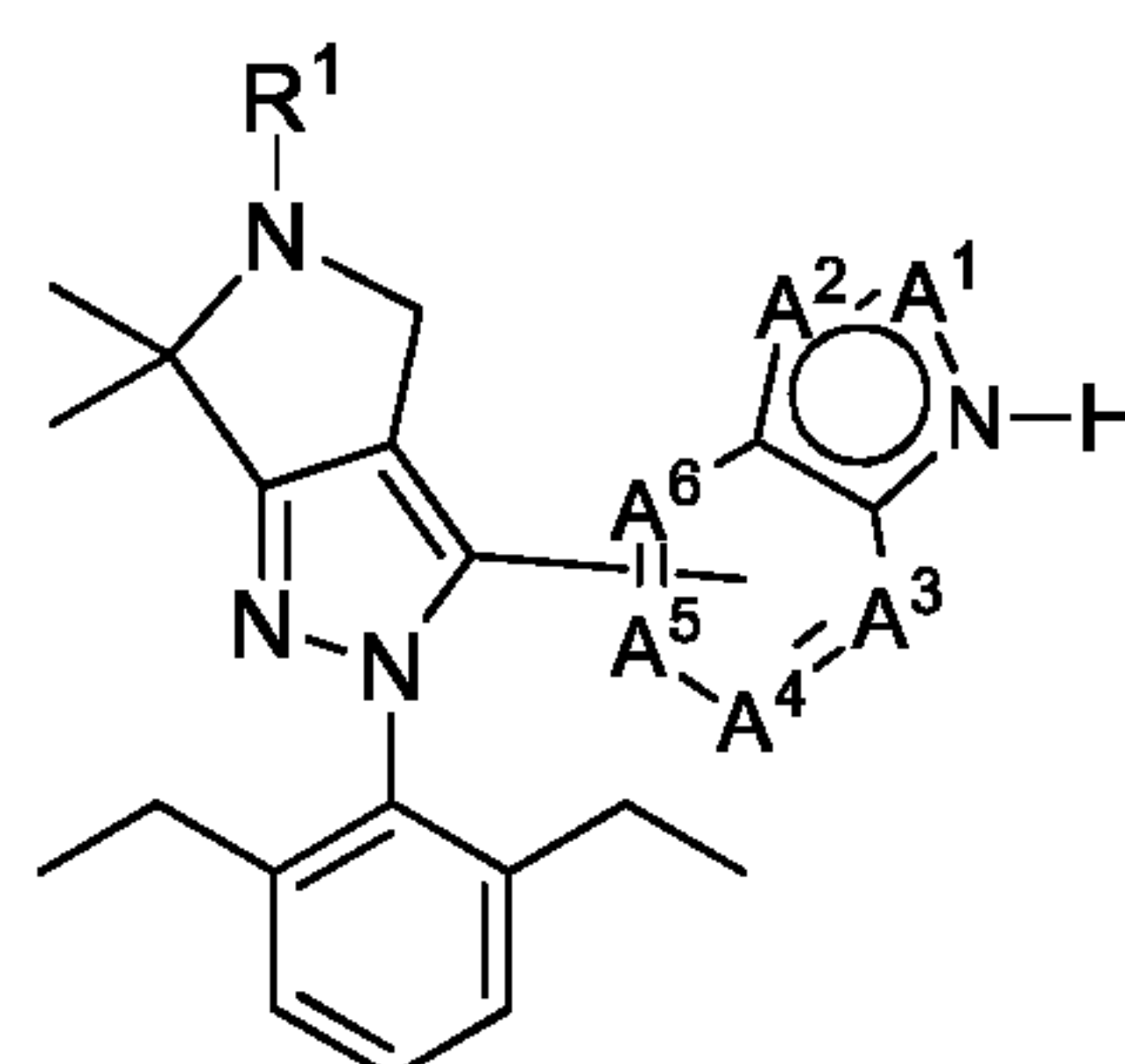
2 having a structure represented by Formula (Ia), (Ib) or (Ic):



(Ia)

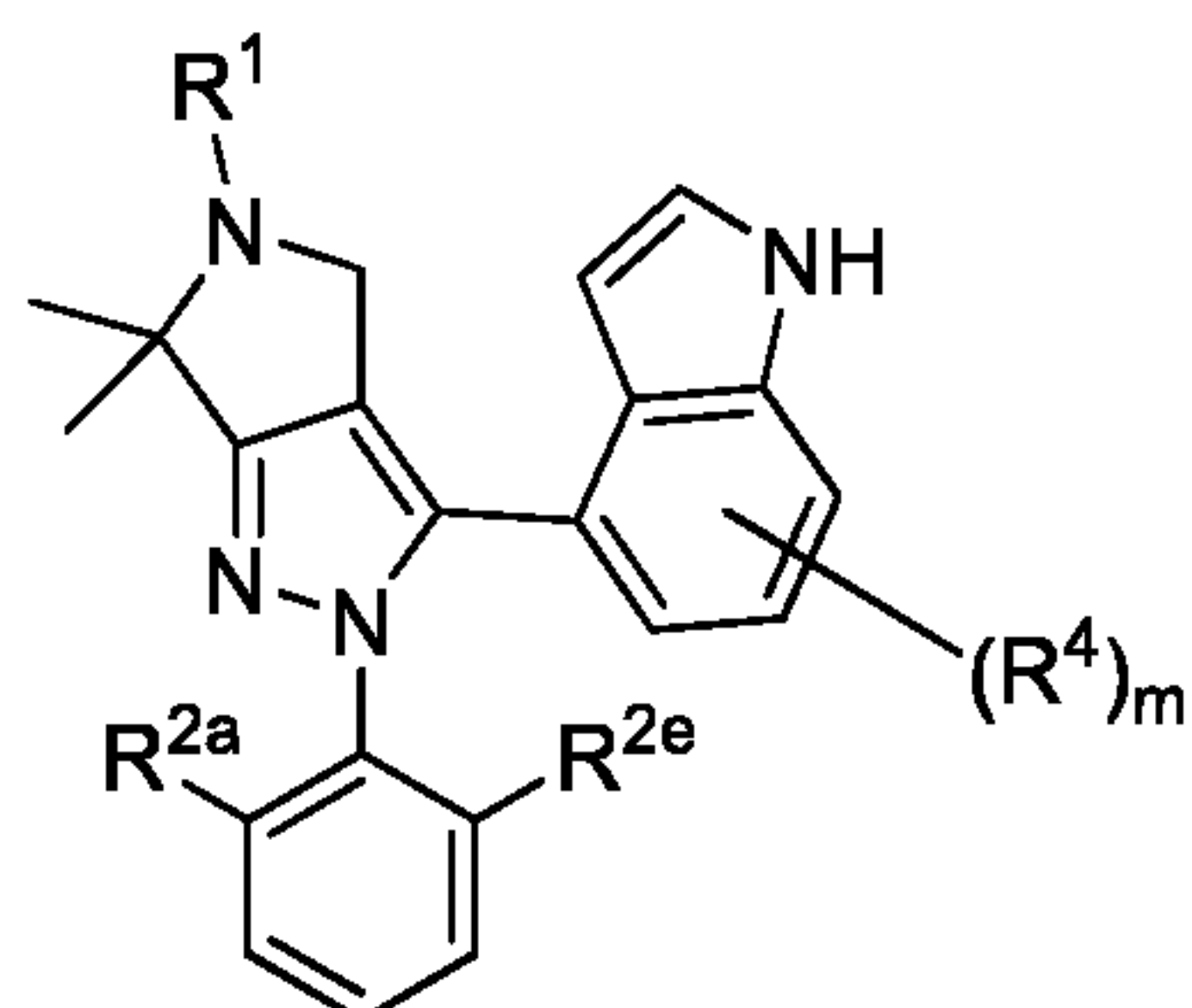


(Ib)

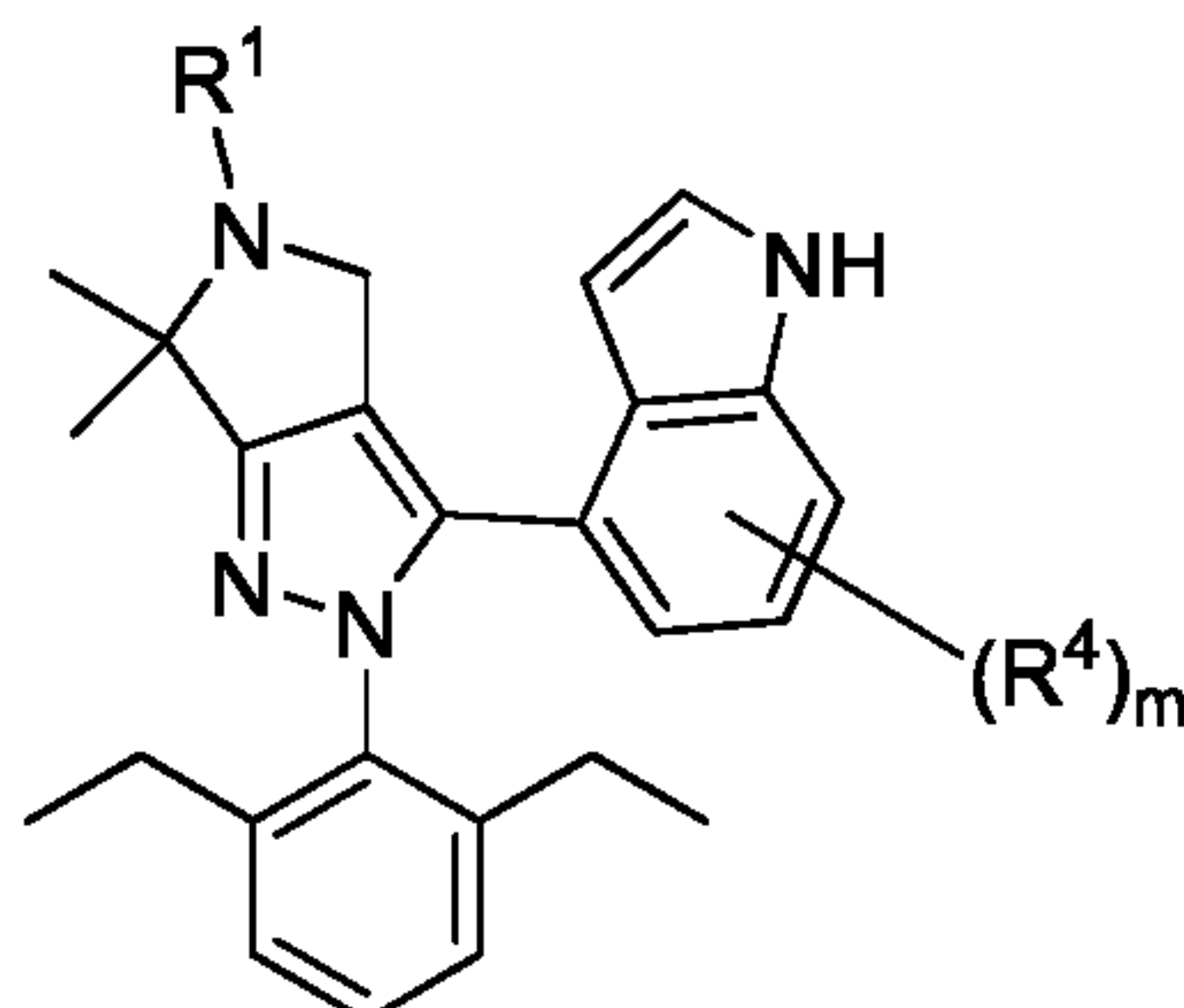


(Ic).

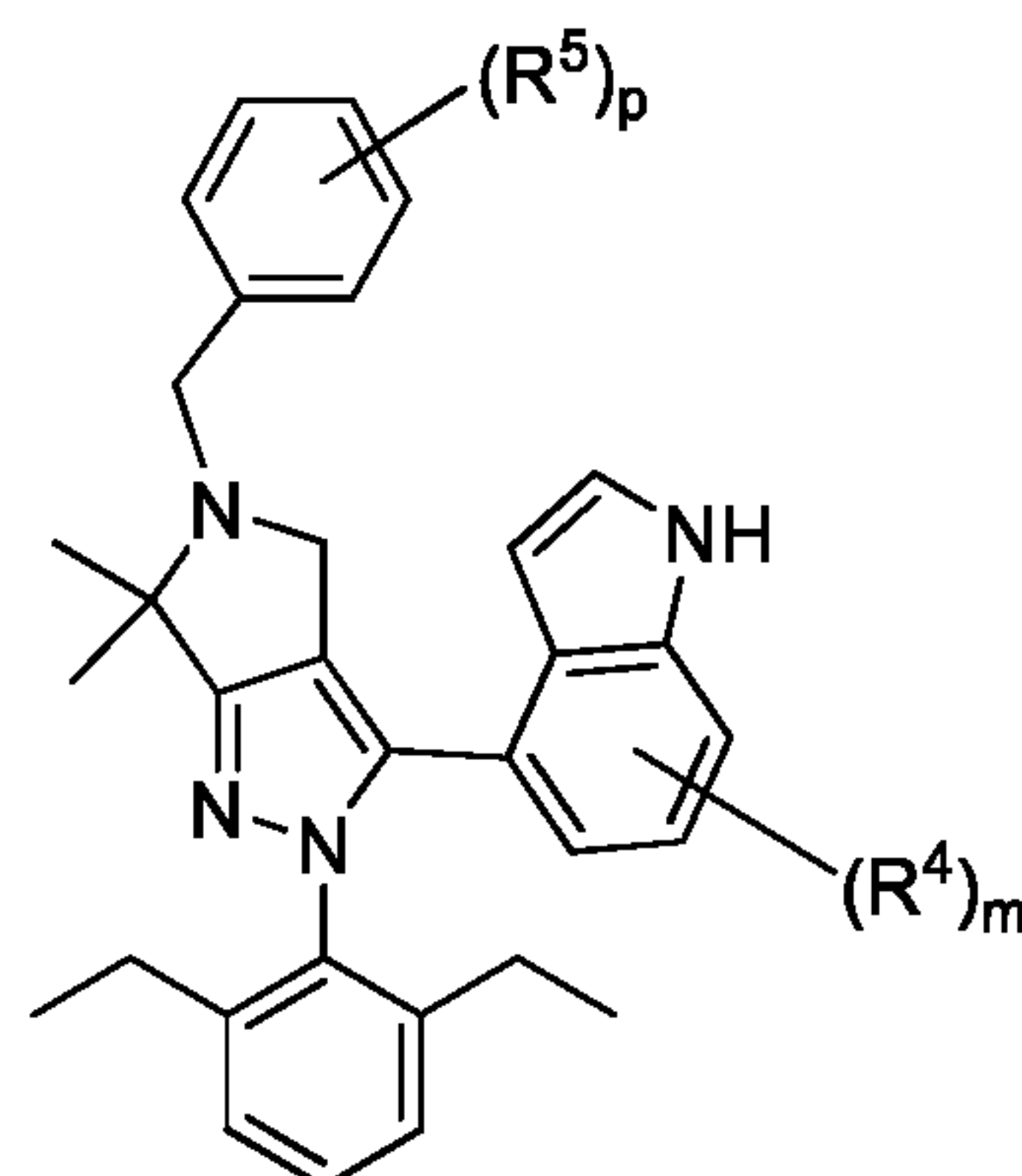
24. The compound of claim 2, or a pharmaceutically acceptable salt thereof, having a structure represented by Formula (Id), (Ie), or (If):



(Id)



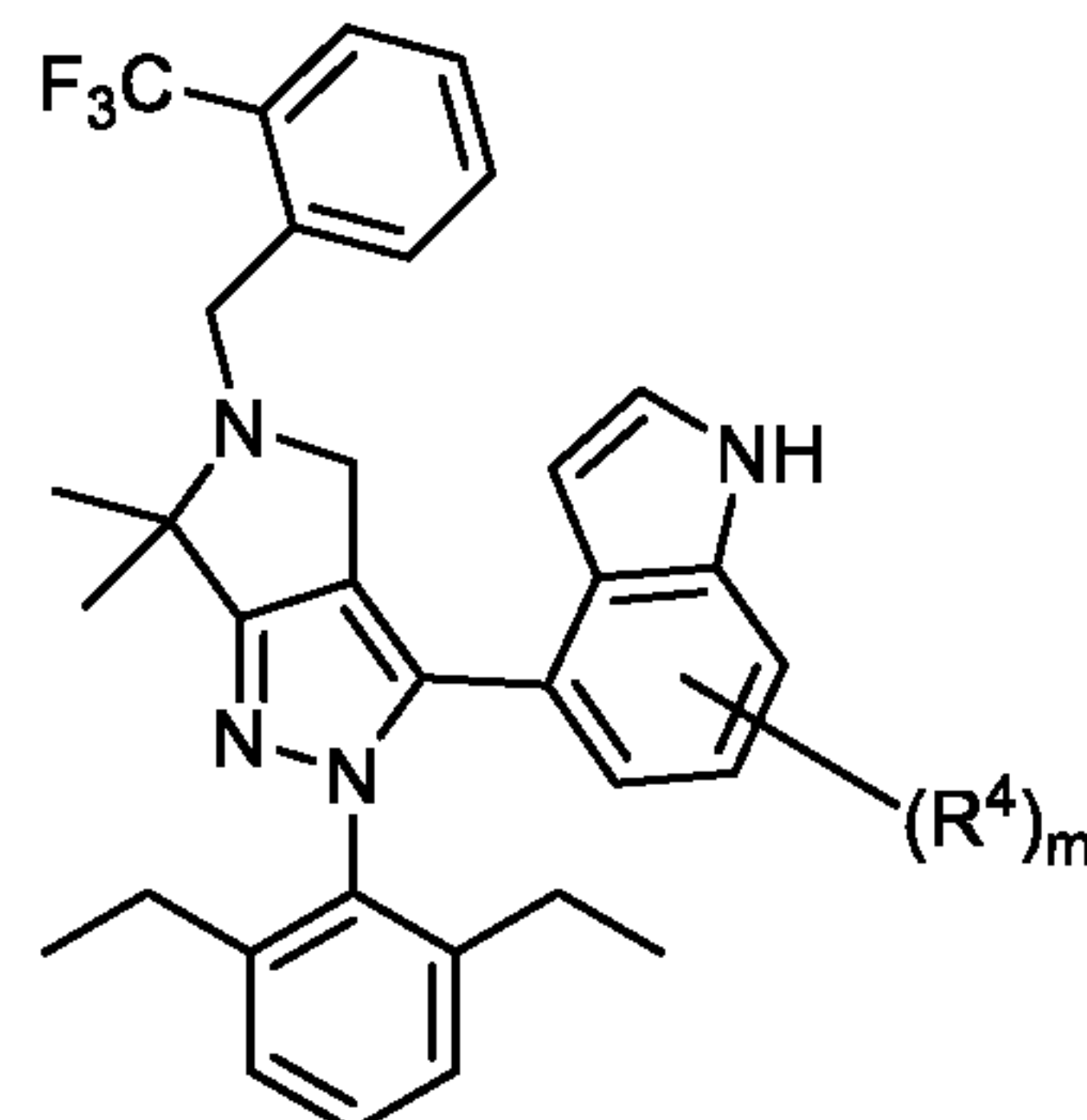
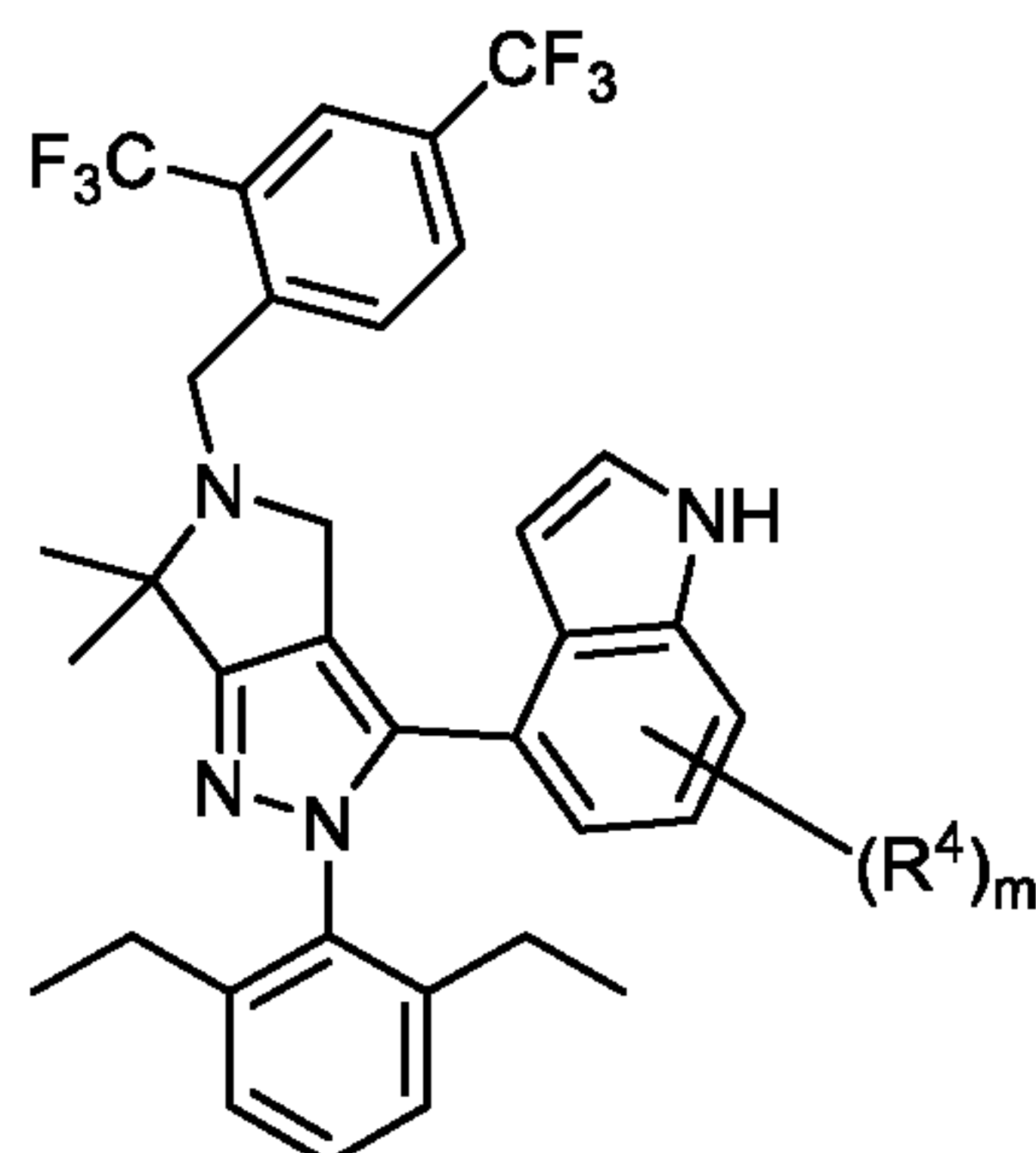
(Ie)



(If)

wherein m is 0, 1 or 2; wherein the R⁴ substituents may be attached to any suitable carbon ring vertex of the bicyclic heteroaryl; and wherein p is 0, 1 or 2.

25. The compound of claim 2, or a pharmaceutically acceptable salt thereof, having a structure represented by Formula (Ig) or (Ih):



4 (Ig) (Ih)
 5 wherein m is 0, 1 or 2 and wherein the R⁴ substituents may be attached to any
 6 suitable carbon ring vertex of the indole heteroaryl.

1 **26.** The compound of any one of claims **1** to **25**, or a pharmaceutically
 2 acceptable salt thereof, wherein said compound is selected from the group in **Table 3** having
 3 ++ or +++ activity.

1 **27.** A pharmaceutical composition comprising a compound of any one of
 2 claims **1** to **26** or a pharmaceutically acceptable salt thereof and a pharmaceutically
 3 acceptable carrier.

1 **28.** The pharmaceutical composition of claim **27**, further comprising one or
 2 more additional therapeutic agents.

1 **29.** The pharmaceutical composition of claim **28** wherein the one or more
 2 additional therapeutic agent is selected from the group consisting of corticosteroids, steroids,
 3 immunosuppressants, and CD20 inhibitors.

1 **30.** The pharmaceutical composition of claim **28**, wherein the one or more
 2 additional therapeutic agent is selected from the group consisting of obinutuzumab,
 3 rituximab, ocrelizumab, cyclophosphamide, prednisone, hydrocortisone, hydrocortisone
 4 acetate, cortisone acetate, tixocortol pivalate, prednisolone, methylprednisolone,
 5 triamcinolone acetonide, triamcinolone alcohol, mometasone, amcinonide, budesonide,
 6 desonide, fluocinonide, fluocinolone acetonide, halcinonide, betamethasone, betamethasone
 7 sodium phosphate, dexamethasone, dexamethasone sodium phosphate, fluocortolone,
 8 hydrocortisone-17-valerate, halometasone, alclometasone dipropionate, beclomethasone,
 9 betamethasone valerate, betamethasone dipropionate, prednicarbate, clobetasone-17-
 10 butyrate, clobetasol-17-propionate, fluocortolone caproate, fluocortolone pivalate,
 11 fluprednidene acetate, hydrocortisone-17-butyrate, hydrocortisone-17-aceponate,
 12 hydrocortisone-17-buteprate, ciclesonide.

1 **31.** A method for treating a mammal suffering from or susceptible to a
2 disease or disorder involving pathologic activation from C5a, comprising administering to
3 the mammal an effective amount of a compound of any one of claims **1** to **26**, or a
4 pharmaceutically acceptable salt thereof, or a composition of any one of claims **27** to **30**.

1 **32.** A method of inhibiting C5a mediated cellular chemotaxis comprising
2 contacting mammalian white blood cells with a C5a modulatory amount of a compound of
3 any one of claims **1** to **26**, or a pharmaceutically acceptable salt thereof.

1 **33.** The method of claim **31**, wherein the disease or disorder is an
2 inflammatory disease or disorder, a cardiovascular or cerebrovascular disorder, an
3 autoimmune disorder, or an oncologic disease or disorder.

1 **34.** The method of claim **31**, wherein the disease or disorder is selected
2 from the group consisting of neutropenia, neutrophilia, C3-glomerulopathy, C3-
3 glomerulonephritis, dense deposit disease, membranoproliferative glomerulonephritis,
4 Kawasaki disease, hemolytic uremic syndrome, atypical hemolytic uremic syndrome
5 (aHUS), tissue graft rejection, hyperacute rejection of transplanted organs, rheumatoid
6 arthritis, systemic lupus erythematosus, lupus nephritis, lupus glomerulonephritis, vasculitis,
7 ANCA associated vasculitis, Wegener s granulomatosis, microscopic polyangiitis,
8 autoimmune hemolytic and thrombocytopenic states, immuno vasculitis, graft versus host
9 disease, lupus nephropathy, Heyman nephritis, membranous nephritis, glomerulonephritis,
10 and IGA nephropathy.

1 **35.** The method of claim **31**, wherein the disease or disorder is selected
2 from the group consisting of melanoma, lung cancer, lymphoma, sarcoma, carcinoma,
3 fibrosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, angiosarcoma,
4 lymphangiosarcoma, synovioma, mesothelioma, meningioma, leukemia, lymphoma,
5 leiomyosarcoma, rhabdomyosarcoma, squamous cell carcinoma, basal cell carcinoma,
6 adenocarcinoma, papillary carcinoma, cystadenocarcinoma, bronchogenic carcinoma, renal
7 cell carcinoma, hepatocellular carcinoma, transitional cell carcinoma, choriocarcinoma,

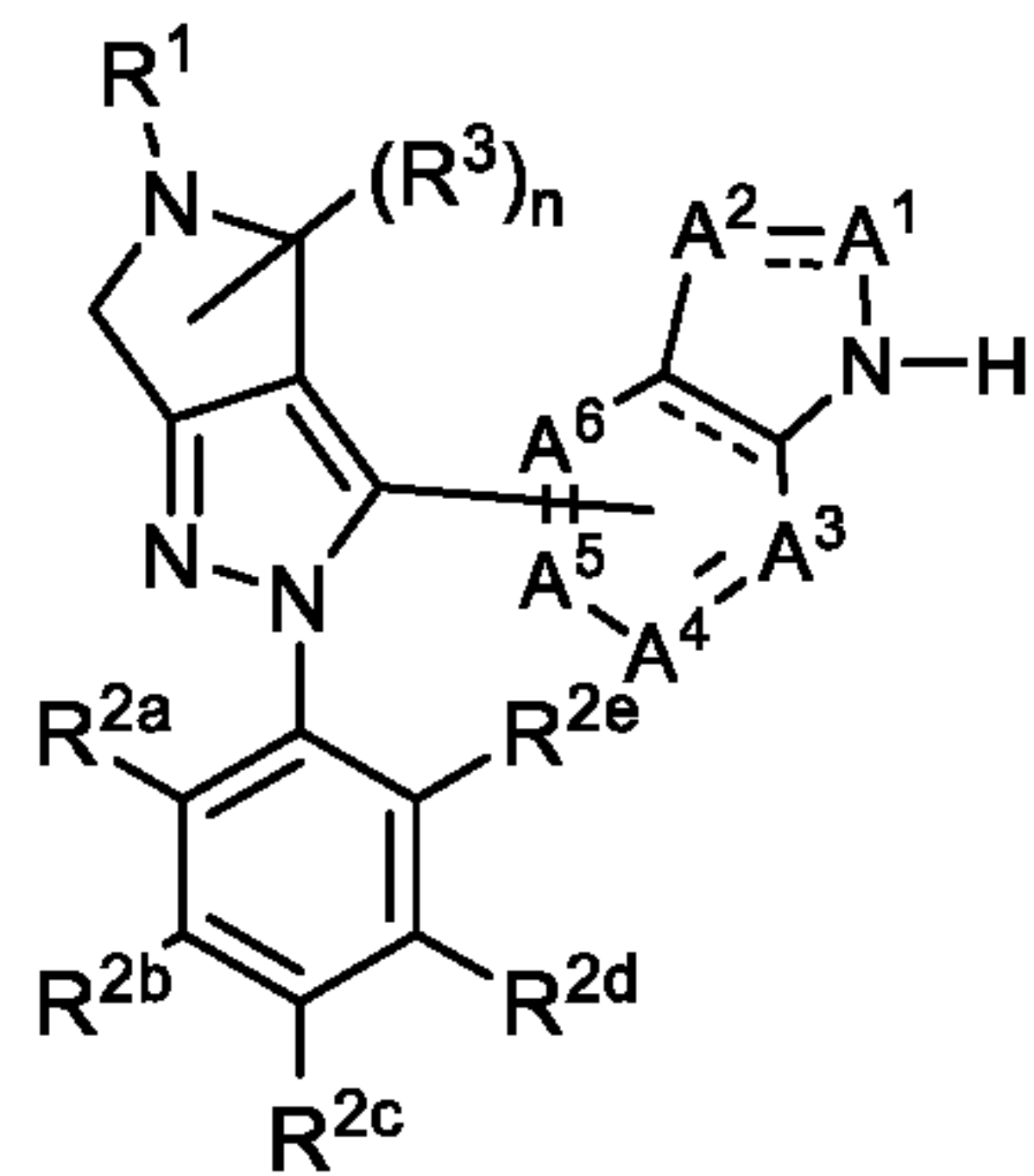
8 seminoma, embryonal carcinoma, wilm's tumor, pleomorphic adenoma, liver cell papilloma,
9 renal tubular adenoma, cystadenoma, papilloma, adenoma, leiomyoma, rhabdomyoma,
10 hemangioma, lymphangioma, osteoma, chondroma, lipoma and fibroma.

1 **36.** The method of any one of claims **31** to **35**, further comprising
2 administering to the human a therapeutically effective amount of one or more additional
3 therapeutic agents.

1 **37.** The method of claim **36** wherein the one or more additional therapeutic
2 agent is selected from the group consisting of corticosteroids, steroids, immunosuppressants,
3 and CD20 inhibitors.

1 **38.** The method of claim **36** wherein the one or more additional therapeutic
2 agent is selected from the group consisting of obinutuzumab, rituximab, ocrelizumab,
3 cyclophosphamide, prednisone, hydrocortisone, hydrocortisone acetate, cortisone acetate,
4 tixocortol pivalate, prednisolone, methylprednisolone, triamcinolone acetonide,
5 triamcinolone alcohol, mometasone, amcinonide, budesonide, desonide, fluocinonide,
6 fluocinolone acetonide, halcinonide, betamethasone, betamethasone sodium phosphate,
7 dexamethasone, dexamethasone sodium phosphate, fluocortolone, hydrocortisone-17-
8 valerate, halometasone, alclometasone dipropionate, beclomethasone, betamethasone
9 valerate, betamethasone dipropionate, prednicarbate, clobetasone-17-butyrate, clobetasol-17-
10 propionate, fluocortolone caproate, fluocortolone pivalate, fluprednidene acetate,
11 hydrocortisone-17-butyrate, hydrocortisone-17-aceponate, hydrocortisone-17-buteprate,
12 ciclesonide and prednicarbate.

1



(I)