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(54) **Titre : ANTAGONISTES SUBSTITUES DU RECEPTEUR NUCLEAIRE ORPHELIN LIE A L'ACIDE 2,3-DIHYDRO-1H-INDEN-1-ONE-RETINOIQUE POUR LE TRAITEMENT DE LA SCLEROSE EN PLAQUES**
(54) **Title: SUBSTITUTED 2, 3-DIHYDRO-1H-INDEN-1-ONE RETINOIC ACID-RELATED ORPHAN NUCLEAR RECEPTOR ANTAGONISTS FOR TREATING MULTIPLE SCLEROSIS**

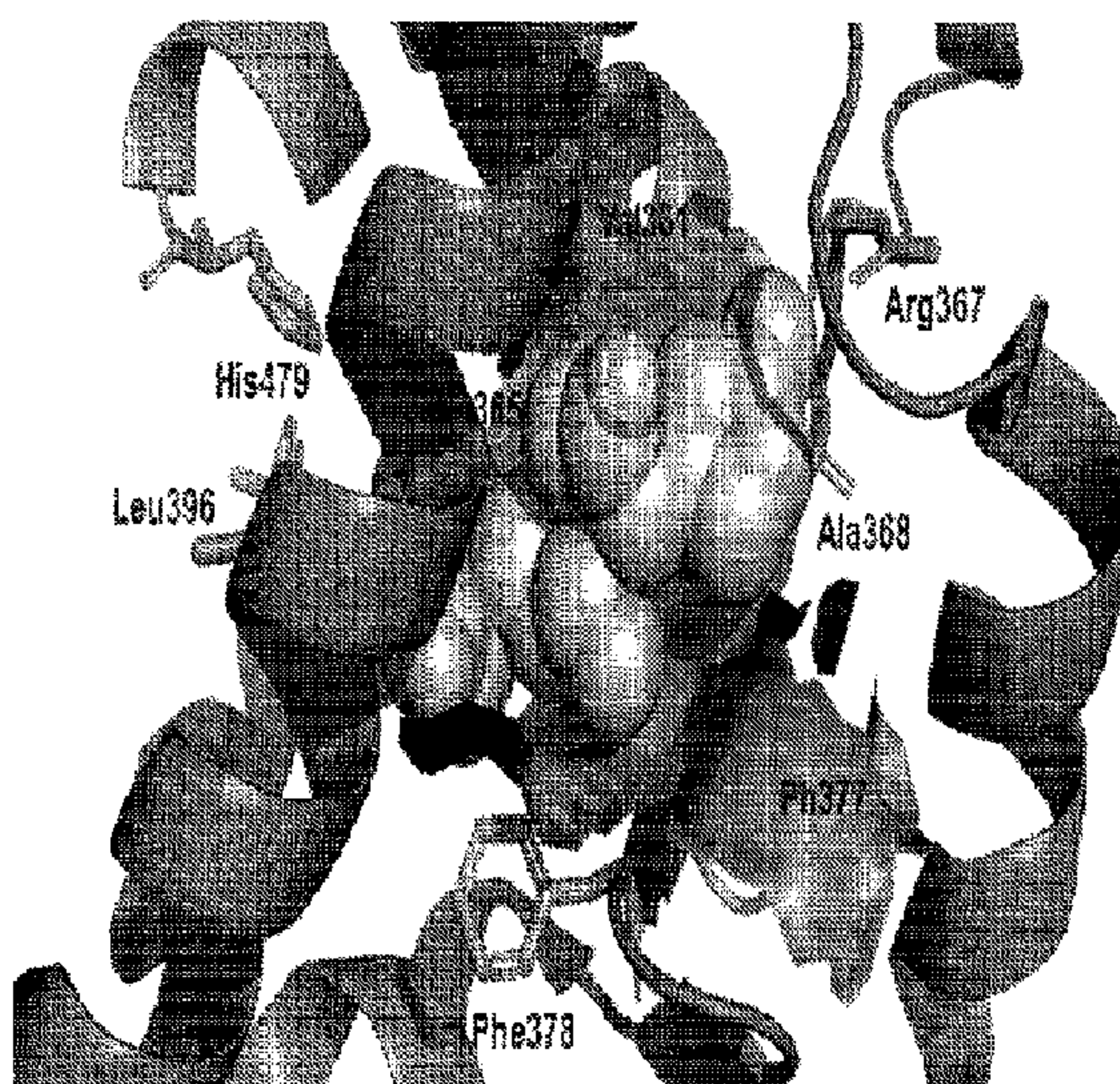


Figure 1

(57) **Abrégé/Abstract:**

The present invention is directed to compounds, their synthesis, and their use as antagonists, inverse agonists, modulators and or inhibitors of the Retinoic acid-related orphan nuclear receptor γ t (ROR γ t)/ROR γ . The compounds of the present invention are useful for modulating ROR γ t)/ROR γ activity and for treating diseases or conditions mediated by ROR γ t)/ROR γ such as for example, disease states associated with immunopathology of human autoimmune diseases such as Multiple Sclerosis (MS), Rheumatoid Arthritis (RA), Inflammatory Colitis, Psoriasis, COPD, Pain, Obesity, Diabetes, Dyslipidemia, Osteoporosis, Asthma, Neurodegenerative diseases and Cancer.

Abstract

The present invention is directed to compounds, their synthesis, and their use as antagonists, inverse agonists, modulators and or inhibitors of the Retinoic acid-related orphan nuclear receptor γ (ROR γ t)/ROR γ . The compounds of the present invention are useful for modulating ROR γ t)/ROR γ activity and for treating diseases or conditions mediated by ROR γ t)/ROR γ such as for example, disease states associated with immunopathology of human autoimmune diseases such as Multiple Sclerosis (MS), Rheumatoid Arthritis (RA), Inflammatory Colitis, Psoriasis, COPD, Pain, Obesity, Diabetes, Dyslipidemia, Osteoporosis, Asthma, Neurodegenerative diseases and Cancer.

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**SUBSTITUTED 2, 3-DIHYDRO-1*H*-INDEN-1-ONE RETINOIC ACID-RELATED
ORPHAN NUCLEAR RECEPTOR ANTAGONISTS FOR TREATING MULTIPLE
SCLEROSIS**

5 FIELD OF INVENTION

The present invention is directed to compounds, their synthesis, and their use as antagonists, inverse agonists, modulators and or inhibitors of the Retinoic acid-related Orphan nuclear Receptor γ t (ROR γ t)/ROR γ . In particular, the present invention is directed to substituted 2, 3-dihydro-1*H*-inden-1-one compounds that modulate (ROR γ t)/ROR γ . The compounds of the present invention are useful for modulating (ROR γ t)/ROR γ activity and for treating diseases or conditions mediated by (ROR γ t)/ROR γ such as, for example, disease states associated with immunopathology of human autoimmune diseases such as Multiple Sclerosis (MS), Rheumatoid Arthritis (RA), Inflammatory Colitis, Psoriasis, Chronic Obstructive Pulmonary Disease (COPD), Pain, Obesity, Diabetes, Dyslipidemia, Osteoporosis, Asthma, Neurodegenerative diseases and Cancer.

BACKGROUND OF THE INVENTION

Multiple Sclerosis (MS) is an autoimmune inflammatory demyelinating disease of the CNS (central nervous system) that damages the fatty myelin sheaths around the axons of the brain and spinal cord. This damage, destruction, and loss or scarring of the myelin sheaths (sclerosis or *plaques*) results in a broad spectrum of symptoms. MS is a chronic, disabling disease that affects about 400,000 people in the United States and nearly 2.5 million people worldwide. MS substantially and adversely affects the quality of life of each individual, with symptoms that include loss of muscle control and strength, fatigue, weakness, loss of vision, spasticity, balance, sensation, bladder and bowel problems, numbness, vision loss, tremors, and adverse mental function such as depression. In the United States alone MS care is estimated to cost nearly \$13 billion per year.

Inflammatory cytokines and its receptors have an important role in the progression of MS lesions, and pro- and anti-inflammatory cytokine levels have been found to correlate with changes in MS disease activity. Currently, available treatments usually focus on strategies to treat relapses (oral prednisone and i.v. methylprednisolone), manage symptoms and reduce the progress of the disease with Disease Modifying Drugs (DMDs). It includes relapsing-remitting MS (RRMS) drugs such as Immunomodulatory (β -interferons) therapeutics (Avonex, Betaseron, Rebif and Extavia), Monoclonal Antibodies (Tysabri, Lemtrada), other immunosuppressants (Mitoxantrone), Copaxone (glatiramer acetate injection) and oral agents; Teriflunomide, Fingolimod but none of these medications is a cure or prevent recurring symptoms. In addition

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to existing oral DMDs such as Fingolimod, and recently approved Tecfidera (BG-12 or Dimethyl Fumarate) and other experimental agents yet to be approved are in Phase III of clinical development such as Laquinimod, and Masitinib (oral immunomodulators) have been reported to cause opportunistic infections, antibody stimulation, liver and kidney toxicities. Target specific inhibitors or antagonists should promote myelination, neuronal repair, neuroprotection.

5 Inhibiting the disease and halting neurodegeneration should eliminate many of these adverse events.

Presently, oral DMT drugs such as Fingolimod, Cladribine, and Tecfidera – as well as about 46 other experimental agents in various stages of clinical development such as Laquinimode, and Masitinib – have been reported to cause serious adverse events including opportunistic infections, antibody stimulation, and liver and kidney toxicities. Thus, there is a continuing need for effective MS drugs with better toxicity profiles. Target specific inhibitors or antagonists should promote myelination, neuronal repair, halting neurodegeneration, and should eliminate many of these adverse events.

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The evidence supporting the risk-benefit profiles for available agents including emerging mAb (Alemtuzumab, Ocrelizumab and Daclizumab) DMTs is yet to fully emerge. Many of these approved and experimental agents yet to be approved create serious adverse events including opportunistic infections, antibody stimulation, and liver and kidney toxicities. Therefore, MS is still a significant target for innovative therapies that can have immunotherapeutic and/or neuroprotective effects on the disease. This opportunity has strengthened our research focus on clinically relevant ROR γ t, as an attractive target for the treatment of MS. ROR γ t as a nuclear hormone receptor that is a key regulator of T helper type 17 (Th17) cell differentiation. Th17 cells are normally produced in response to infection, but have been linked to the development of autoimmune diseases. A few pre-clinical stage lead ROR γ t and ROR γ inverse agonists have been reported. For example, azole-type fungicides, T0901317, SR1001, ursolic acid, VPR-66, digoxin, and hexafluoro-substituted sulphamoyl thiazoles had efficacy in autoimmune encephalomyelitis (EAE) mice models. At least dozen companies; Lycera/Merck, Karo Bio/Pfizer, Phenex/J&J, Orphagen/JT (OR-1050/T0901317, 5 μ M), Tempero/GSK (TMP-778, GSK-805), Exelixis/BMS, Teijin/Amgen, Cognoci (COG112), Innovimmune (INV-17), Visionary, 4SC Discovery and Genentech, have small molecule ROR γ t programs in preclinical stage of development. Identification of brain penetrant, ROR γ t specific antagonists that rescue myelin destruction, restore the axons of the brain and spinal cord following oral administration will be a significant approach for developing MS therapeutics. The substituted 2, 3-dihydro-1H-inden-1-one class of compounds claimed in Formula I discovered as

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potent, brain penetrant, orally available ROR γ t antagonist, and a small molecule candidate compounds as new drug entities for the treatment of such diseases claimed.

The present invention includes small molecule antagonists targeting Retinoic acid-related orphan nuclear receptor γ t (ROR γ t)/ROR γ . ROR γ t is the key transcription factor and is the master regulator of human Th17 (T helper 17) cells, a unique subset of CD4⁺T cells. ROR γ t controls cellular differentiation, function and InterleukinIL-17 (IL-17 producing T-helper lymphocytes) release by Th17 cells and helps mediate the immunopathology of human autoimmune diseases such as Multiple Sclerosis (MS), Rheumatoid Arthritis (RA), Inflammatory Colitis, Psoriasis, COPD, Pain, Obesity, Diabetes, Dyslipidemia, Osteoporosis, Asthma, Neurodegenerative diseases and Cancer.

In addition, the substituted 2, 3-dihydro-1*H*-inden-1-one Retinoic acid-related orphan nuclear receptor γ t (ROR γ t)/ROR γ antagonists of the present invention may be useful in the treatment of multiple cancers, includes gastric, colon cancers, chronic myelogenous leukemia (CML), acute myelogenous leukemia (AML), squamous cell, and bladder carcinomas, medulloblastoma, hepatocellular carcinoma, multiple myeloma, bladder, glioblastoma multiform (GBM), breast and ovarian cancers, Ewing's sarcoma and bone associated cancer diseases. The methods of treatment of the claims of Formula I and its associated claims in the application comprise of administering a safe and effective dose of a compounds according to Formula I or a pharmaceutically-acceptable salt, formulations thereof to a human patients.

Induction of autoimmune MS conditions in mice using Myelin Oligodendrocyte Glycoprotein (MOG) or Proteolipid Protein (PLP) immunization causes ROR γ t activation and differentiation of Th17 cells that recruit proinflammatory cytokines IL-17A (IL-17), IL-17F, IL-21 and IL-22 leads to sclerotic myelin and damaged oligodendrocytes. Mice with ROR γ t deficient T cells have attenuated disease and lack tissue-infiltrating Th17 cells. Hence, ROR γ t is a key regulator of immune homeostasis and is a potential therapeutic target for Multiple Sclerosis. Using proprietary internal company proprietary Fragment-Field Drug Design (FFDD) based technology and uniquely designed specific ROR γ t isoform assays a novel, potent small molecule substituted 2, 3-dihydro-1*H*-inden-1-one series and are specific ROR γ t antagonist (inverse agonist) and demonstrated its ROR γ t activity in an ROR γ t-activated IL-17A Prom/LUCPorter assay in HEK 293 cells, in IL-17 release from CD4⁺T cells assays, as well as inhibition of IL-17 production in vivo in BALB/c mouse experiments and the effect of substituted 2, 3-dihydro-1*H*-inden-1-one series of Formula I compounds on MOG₃₅₋₅₅ induced in C57/BL6 or BALB/c mice, PLP₁₃₉₋₁₅₁ (Proteolipid Protein) induced in SJL/J mice and Theiler's

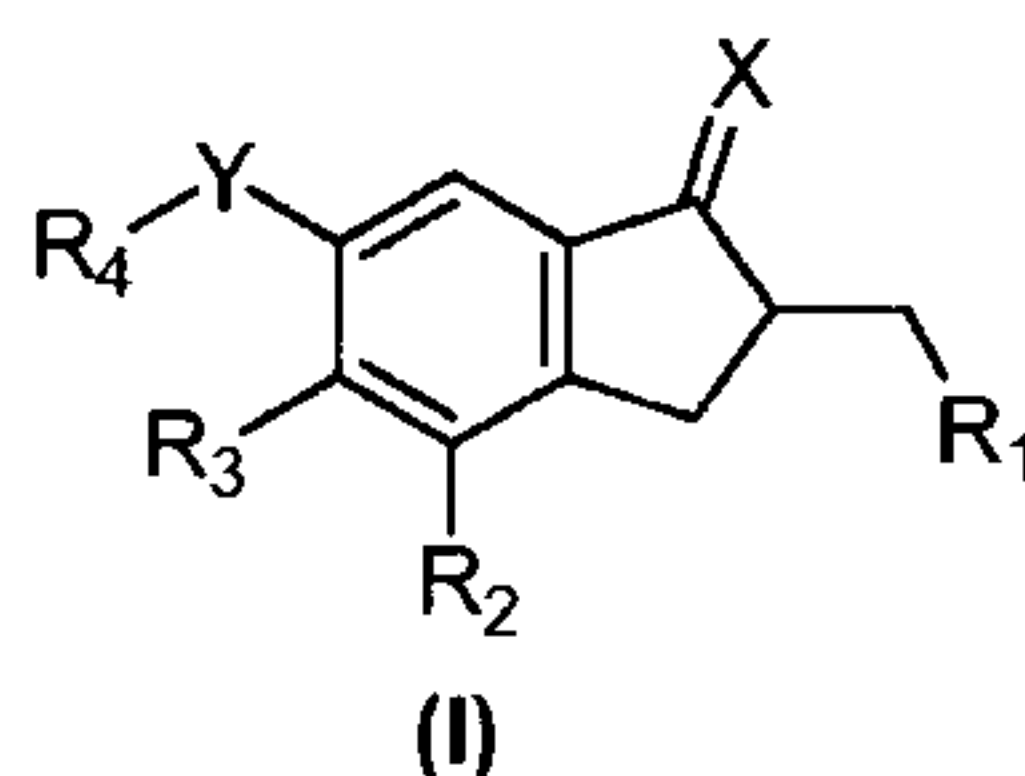
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Murine Encephalitis Virus-Induced Demyelinating Disease (TMEV-IDD) in female BALB/c mice induced Acute/Relapsing EAE model in female SJL/J mice is claimed in this application.

SUMMARY OF THE INVENTION

The present invention concerns compounds active on Nuclear hormone receptor superfamily, specifically ROR γ t and in general, including ROR α , - β , and - γ (NR1F1-3 or RORA-C), its two isoforms, γ 1 and γ 2 (ROR γ t/ROR- γ T) and any mutations of this Nuclear hormone receptor superfamily and the use thereof in treating disease and conditions associated with regulation of the activity of these Nuclear hormone receptor superfamily. More specifically the invention concerns compounds of Formula I as described below. Thus the invention provides novel use of compounds for therapeutic methods involving inhibition and or modulation of ROR α , - β , and - γ specifically ROR γ t as novel compounds that can be used for the therapeutic methods involving modulation of the immunopathology of human autoimmune diseases such as Multiple Sclerosis (MS), Rheumatoid Arthritis (RA), Inflammatory Colitis, Psoriasis, COPD, Pain, Obesity, Diabetes, Dyslipidemia, Osteoporosis, Asthma, Neurodegenerative diseases and Cancer.



The present invention relates to compounds according to Formulas I: to pharmaceutically acceptable composition, salts thereof, their synthesis and their use as ROR γ t and ROR γ inhibitors including such compounds and methods of their use in the treatment of various immunopathology of human autoimmune diseases such as Multiple Sclerosis (MS), Rheumatoid Arthritis (RA), Inflammatory Colitis, Psoriasis, COPD, Pain, Obesity, Diabetes, Dyslipidemia, Osteoporosis, Asthma, Neurodegenerative diseases and Cancer.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1: X-ray crystal structure ROR γ in complex with substituted 2, 3-dihydro-1H-inden-1-one containing ROR γ t antagonist.

Figure 2A: Effect of substituted 2, 3-dihydro-1H-inden-1-one series containing ROR γ antagonists on ROR γ t-mediated IL-17A promoter activity.

Figure 2B: ROR γ t-mediated IL-17A Dose-response curve.

Figure 3A: Effect of substituted 2, 3-dihydro-1H-inden-1-one series ROR γ antagonists on ROR γ t-mediated IL-17A promoter activity.

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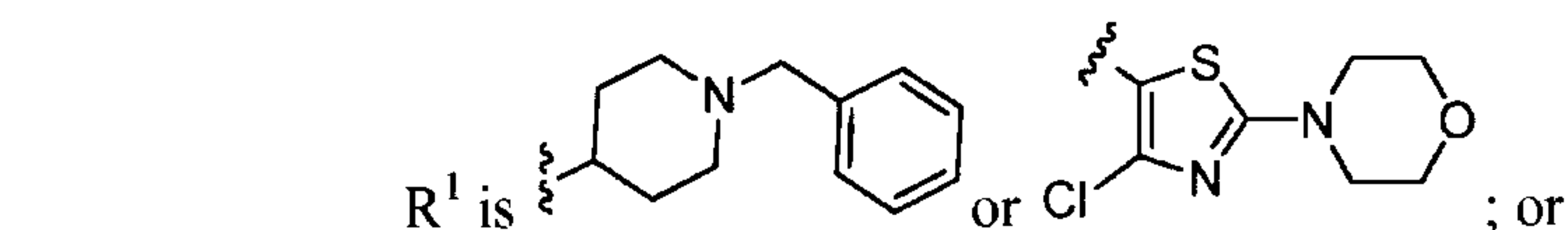
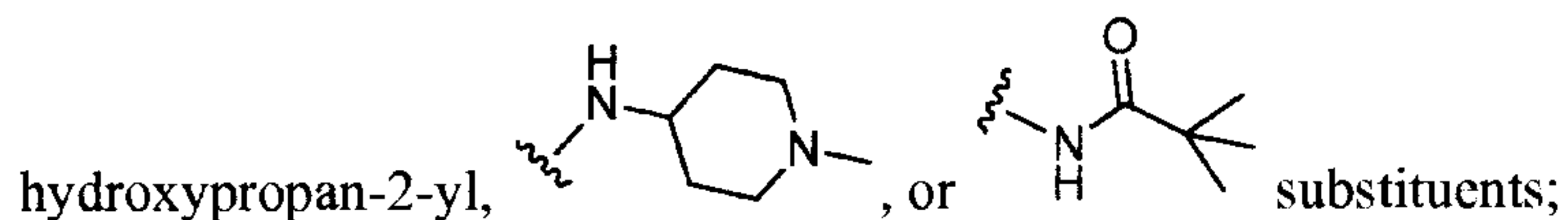
Figure 3B: ROR γ t-mediated IL-17A Dose-response curve.**Figure 4:** Cytokine IL-17 inhibition by substituted 2, 3-dihydro-1*H*-inden-1-one series.**Figure 5:** Effect of Test Compound on MOG35-55 Induced EAE in Female C57/BL6 Mice.**Figure 6:** Effect of Test Compound & Fingolimod Administration on Body Weight of EAE Mice (Female C57/BL6).**DETAILED DESCRIPTION OF THE INVENTION**

Compounds of the present invention are described by Formula I:



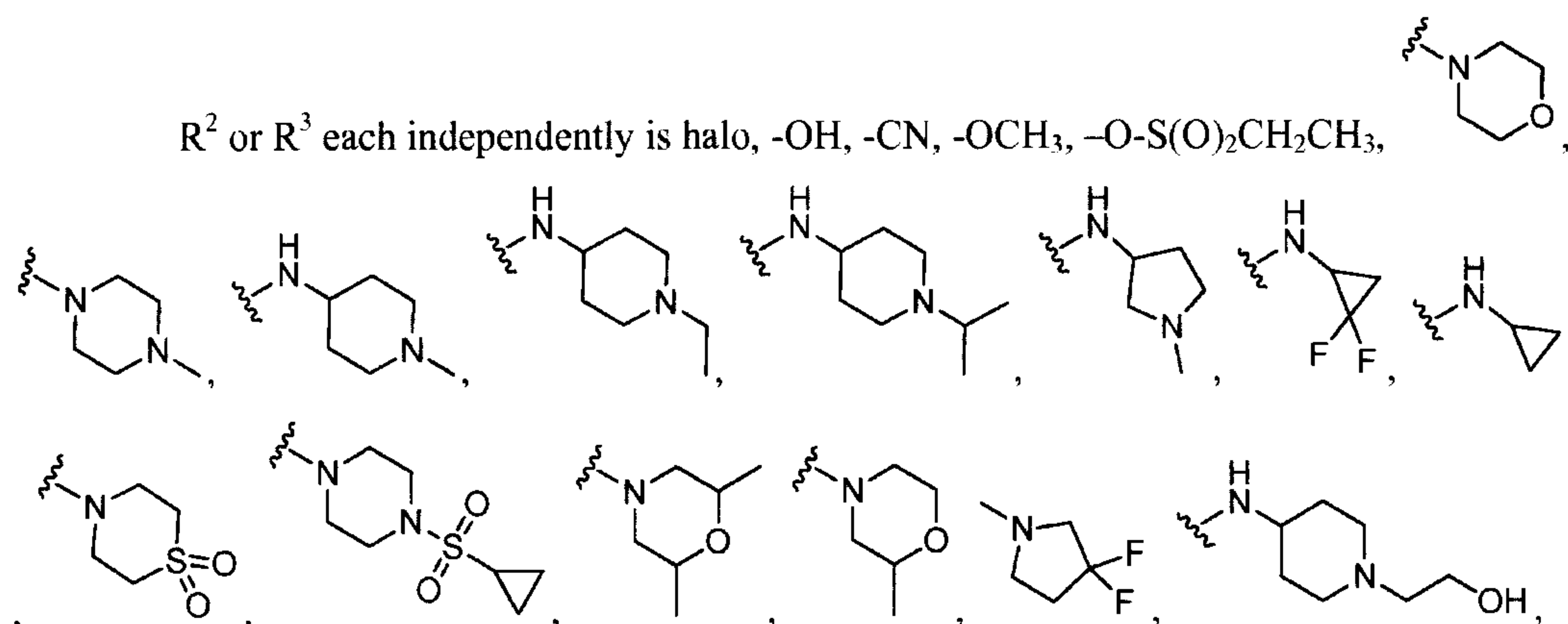
or pharmaceutically acceptable salts thereof, wherein:

X is O or S;

R¹ is C₁₋₄alkyl optionally substituted with 1-6 independent halo substituents; orR¹ is phenyl, pyridinyl, or pyrazolyl, each optionally substituted with 1-5 independent halo, trifluoromethyl, (trifluoromethyl)thio, trifluoromethoxy, 1,1,1,3,3,3,-hexafluoro-2-

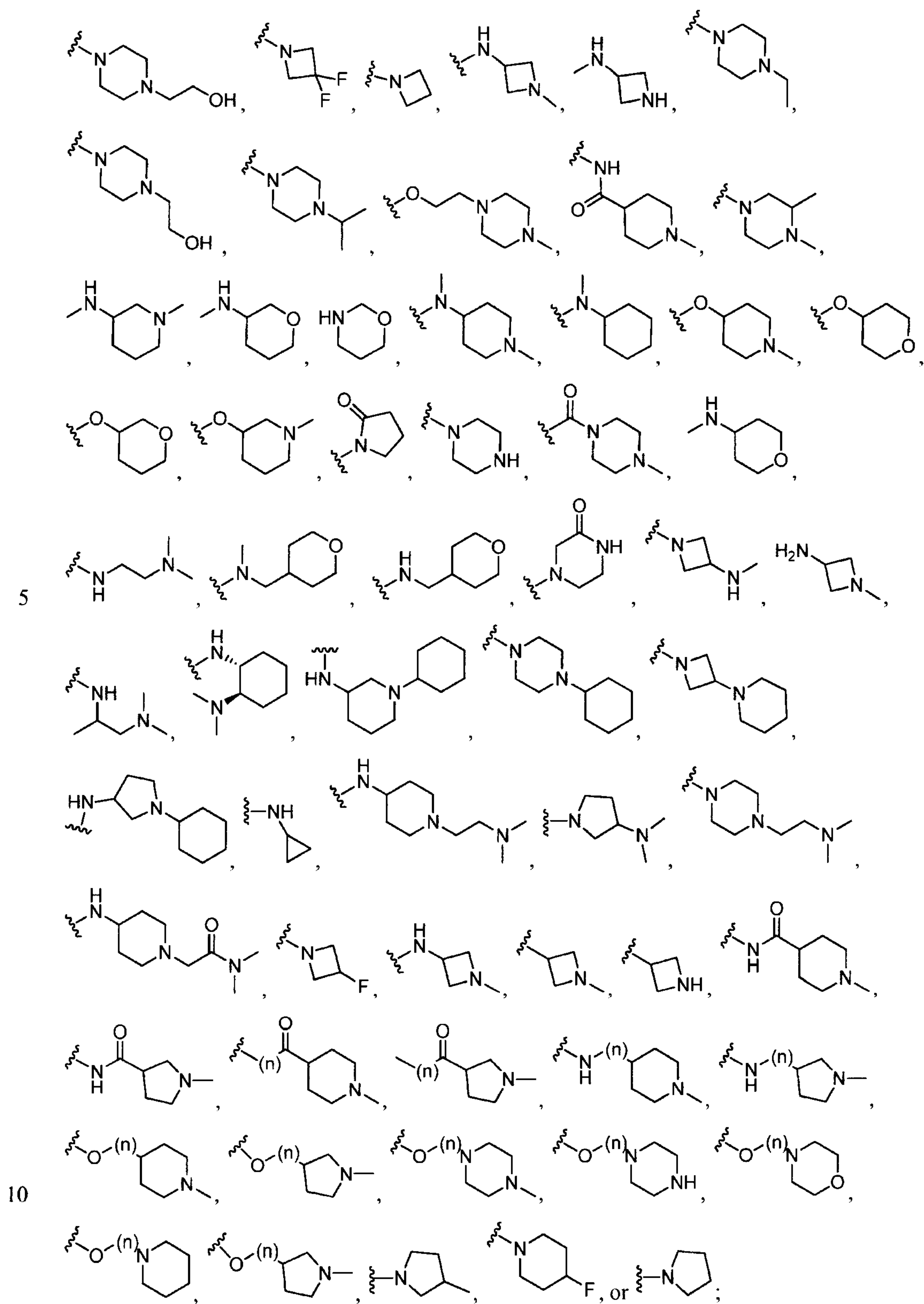
m is 0 or 1;

20 the dotted line indicates an optional double bond when m=1;



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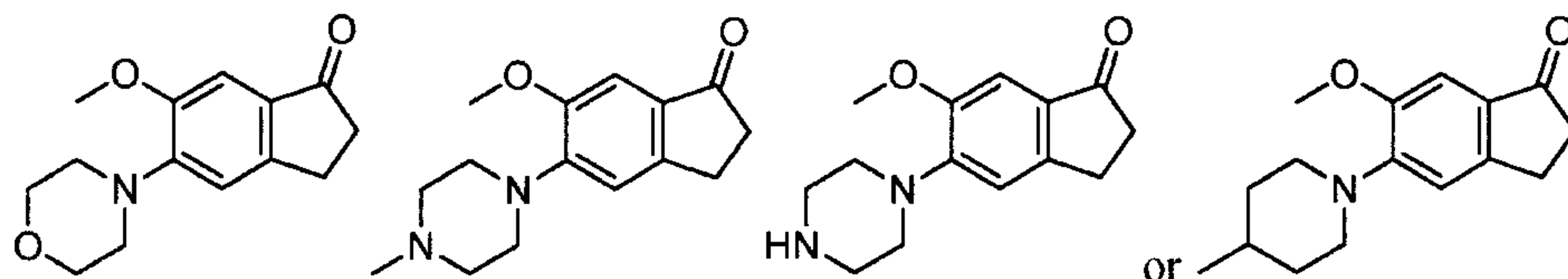


or R^2 or R^3 each independently is phenyl optionally substituted with 0-5 independent halo, trifluoromethoxy substituents;

n is 2 or 3 carbon chain; and

R⁴ is H, OH, OCH₃, or -O-S(O)₂CH₂CH₃.

Compounds of the present invention can be made using the compounds



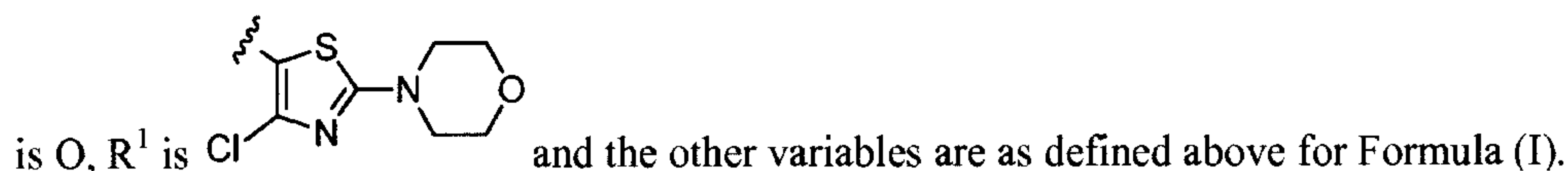
5 as an intermediate. Accordingly, the present invention includes these compounds.

In an aspect of the invention, compounds of the present invention are described by Formula (I) and pharmaceutically acceptable salts thereof, wherein X is O, and the other variables are as defined above for Formula (I).

10 In an embodiment of the aspect of the invention, compounds of the present invention are described by Formula (I) and pharmaceutically acceptable salts thereof, wherein X is O, R¹

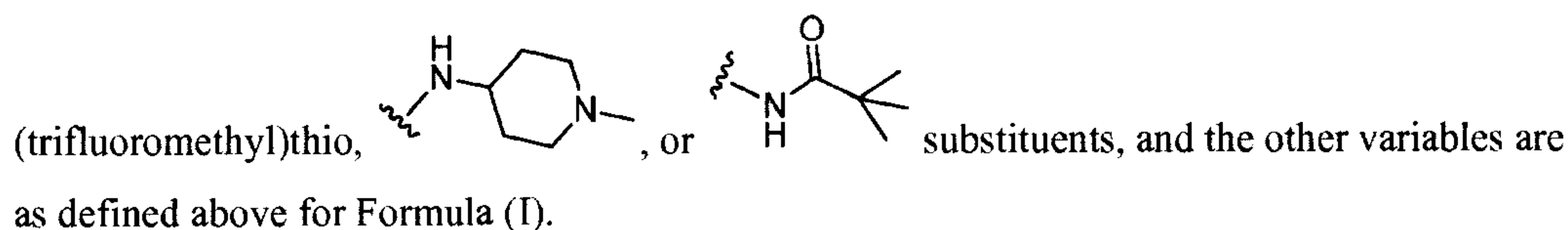


In another embodiment of the aspect of the invention, compounds of the present invention are described by Formula (I) and pharmaceutically acceptable salts thereof, wherein X



15 In yet another embodiment of the aspect of the invention, compounds of the present invention are described by Formula (I) and pharmaceutically acceptable salts thereof, wherein X is O, R¹ is C₁₋₄alkyl optionally substituted with 1-6 independent halo substituents and the other variables are as defined above for Formula (I).

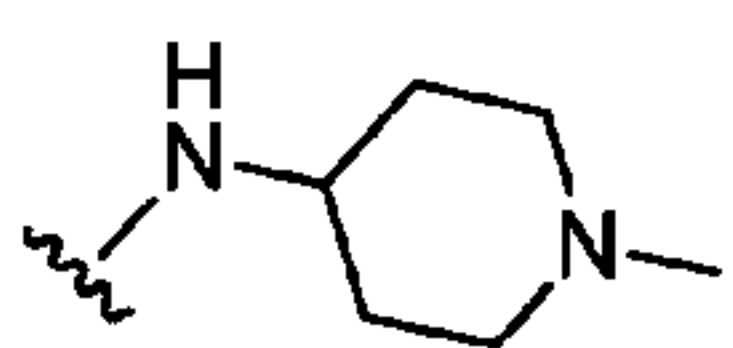
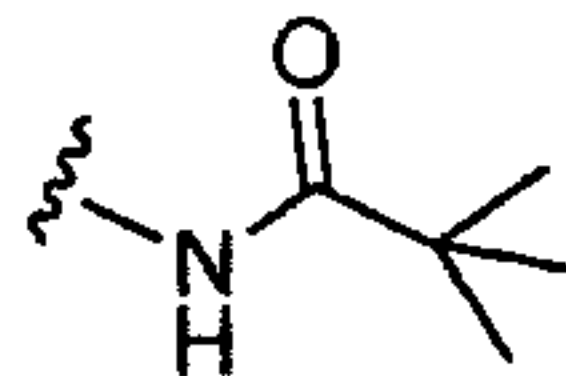
20 In still another embodiment of the aspect of the invention, compounds of the present invention are described by Formula (I) and pharmaceutically acceptable salts thereof, wherein X is O, R¹ is phenyl, optionally substituted with 1-5 independent halo, trifluoromethyl,



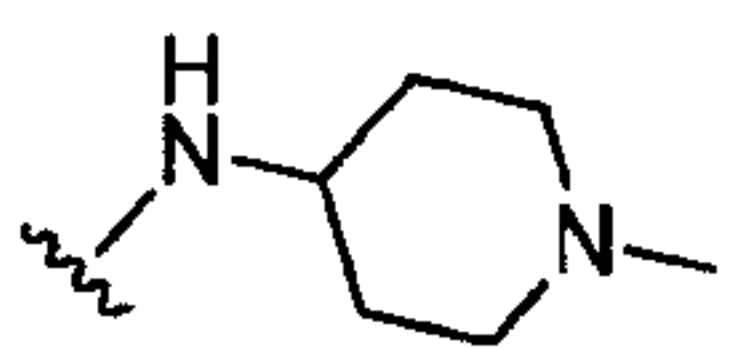
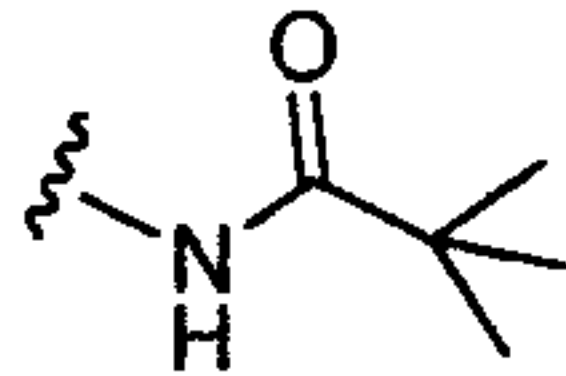
25 In another embodiment of the aspect of the invention, compounds of the present invention are described by Formula (I) and pharmaceutically acceptable salts thereof, wherein X is O, R¹ is pyridinyl, optionally substituted with 1-5 independent halo, trifluoromethyl,

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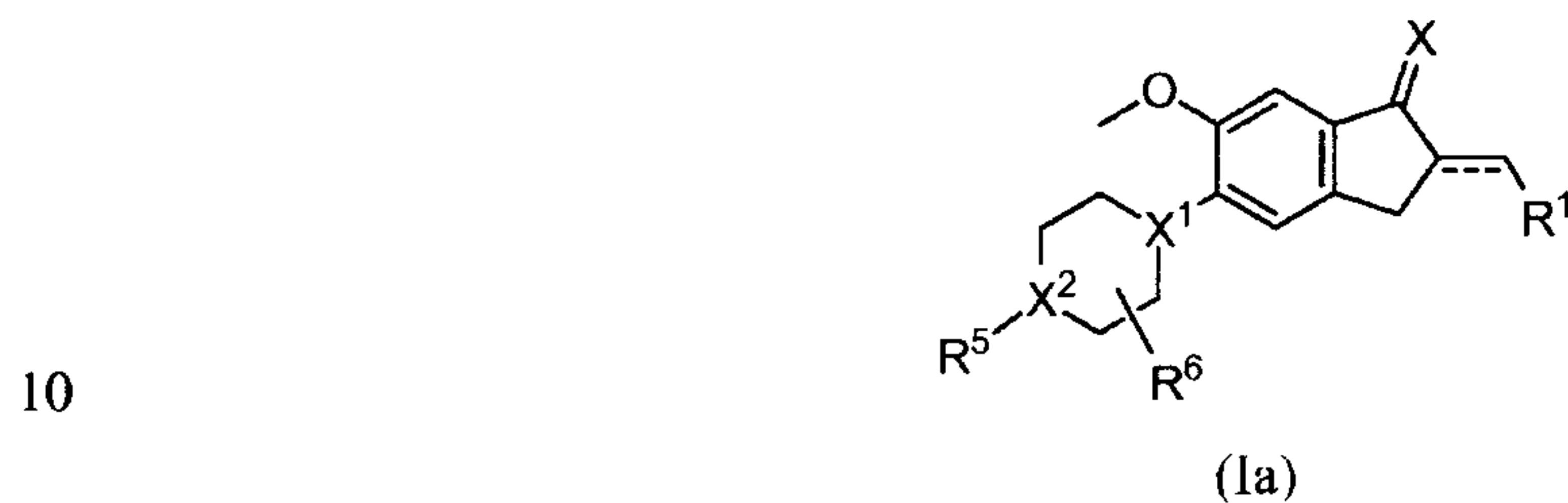
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(trifluoromethyl)thio, , or  substituents, and the other variables are as defined above for Formula (I).

In still another embodiment of the aspect of the invention, compounds of the present invention are described by Formula (I) and pharmaceutically acceptable salts thereof, wherein X is O, R¹ is pyrazolyl optionally substituted with 1-5 independent halo, trifluoromethyl,

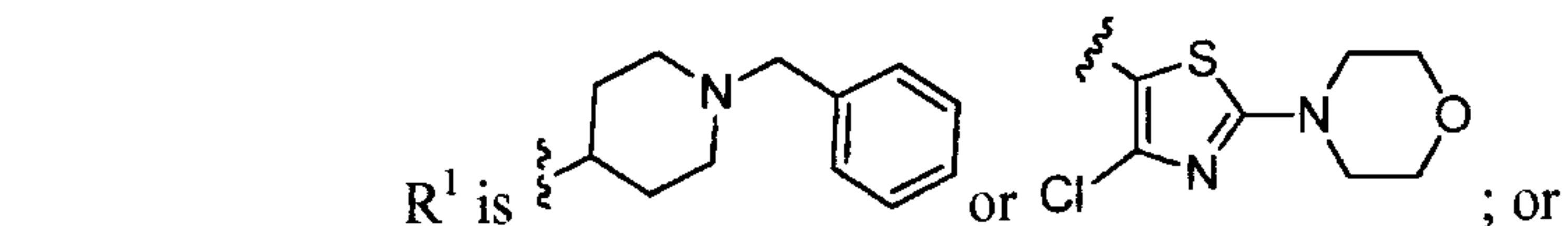
(trifluoromethyl)thio, , or  substituents, and the other variables are as defined above for Formula (I).

In an aspect of the present invention, compounds of the present invention are described by Formula (Ia) and pharmaceutically acceptable salts thereof,



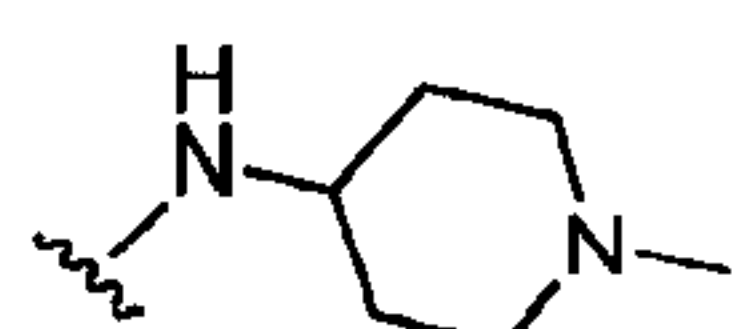
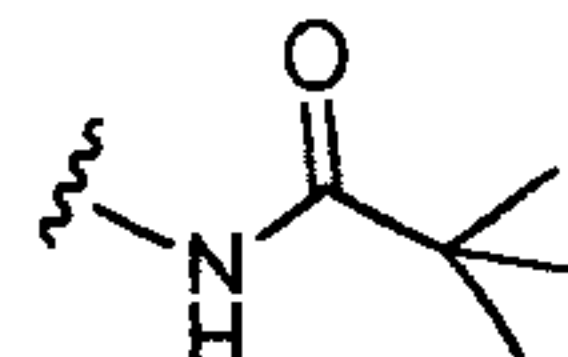
wherein

X is O or S;



R¹ is C₁₋₄alkyl optionally substituted with 1-6 independent halo substituents; or

R¹ is phenyl, pyridinyl, or pyrazolyl, each optionally substituted with 1-5 independent

halo, trifluoromethyl, (trifluoromethyl)thio, , or  substituents;

the dotted line indicates an optional double bond;

X¹ and X² are independently C, N, or O; wherein at least one is not C;

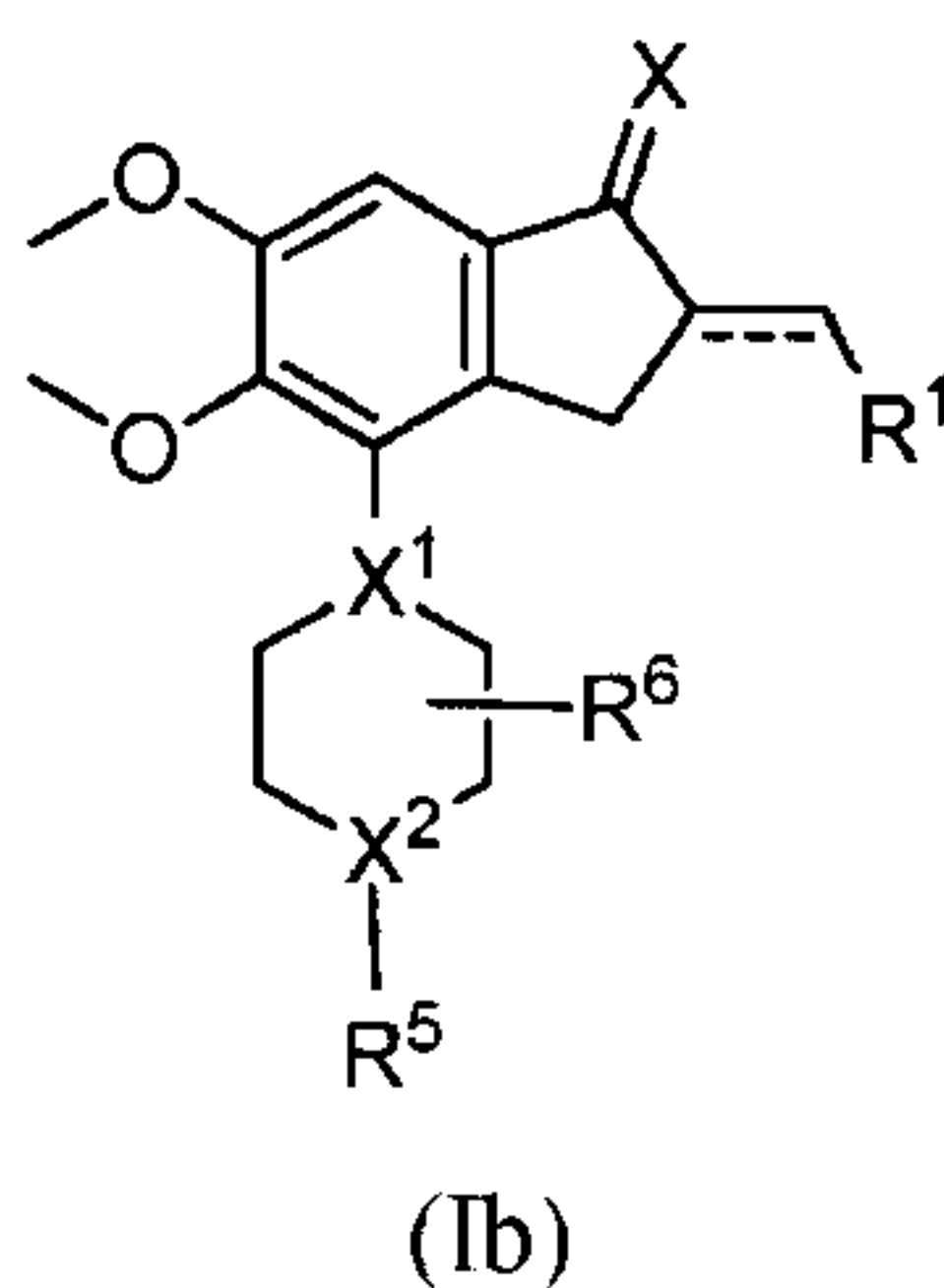
20 R⁵ is absent, halo, or C₀₋₄alkyl.

and R⁶ is halo, or C₀₋₄alkyl.

In an aspect of the present invention, compounds of the present invention are described by Formula (Ia) and pharmaceutically acceptable salts thereof,

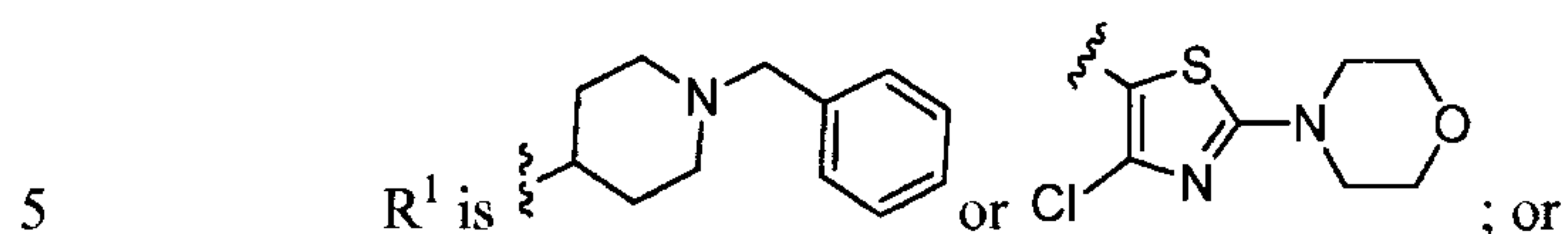
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wherein

X is O or S;



R^1 is C_{1-4} alkyl optionally substituted with 1-6 independent halo substituents; or

R^1 is phenyl, pyridinyl, or pyrazolyl, each optionally substituted with 1-5 independent

halo, trifluoromethyl, (trifluoromethyl)thio, , or substituents;

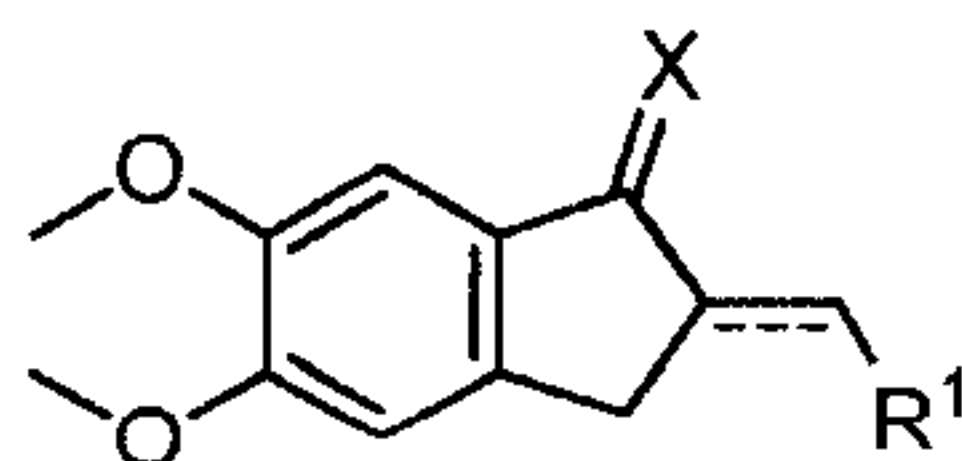
the dotted line indicates an optional double bond

10 X^1 and X^2 are independently C, N, or O; wherein at least one is not C;

R^5 is absent, halo, or C_{0-4} alkyl.

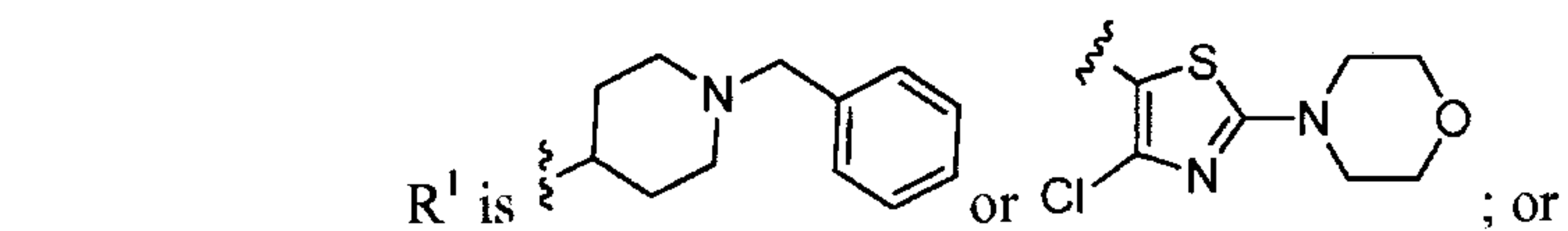
and R^6 is halo, or C_{0-4} alkyl.

15 In an aspect of the present invention, compounds of the present invention are described by Formula (Ia) and pharmaceutically acceptable salts thereof,



wherein

X is O or S;



R^1 is C_{1-4} alkyl optionally substituted with 1-6 independent halo substituents; or

R^1 is phenyl, pyridinyl, or pyrazolyl, each optionally substituted with 1-5 independent

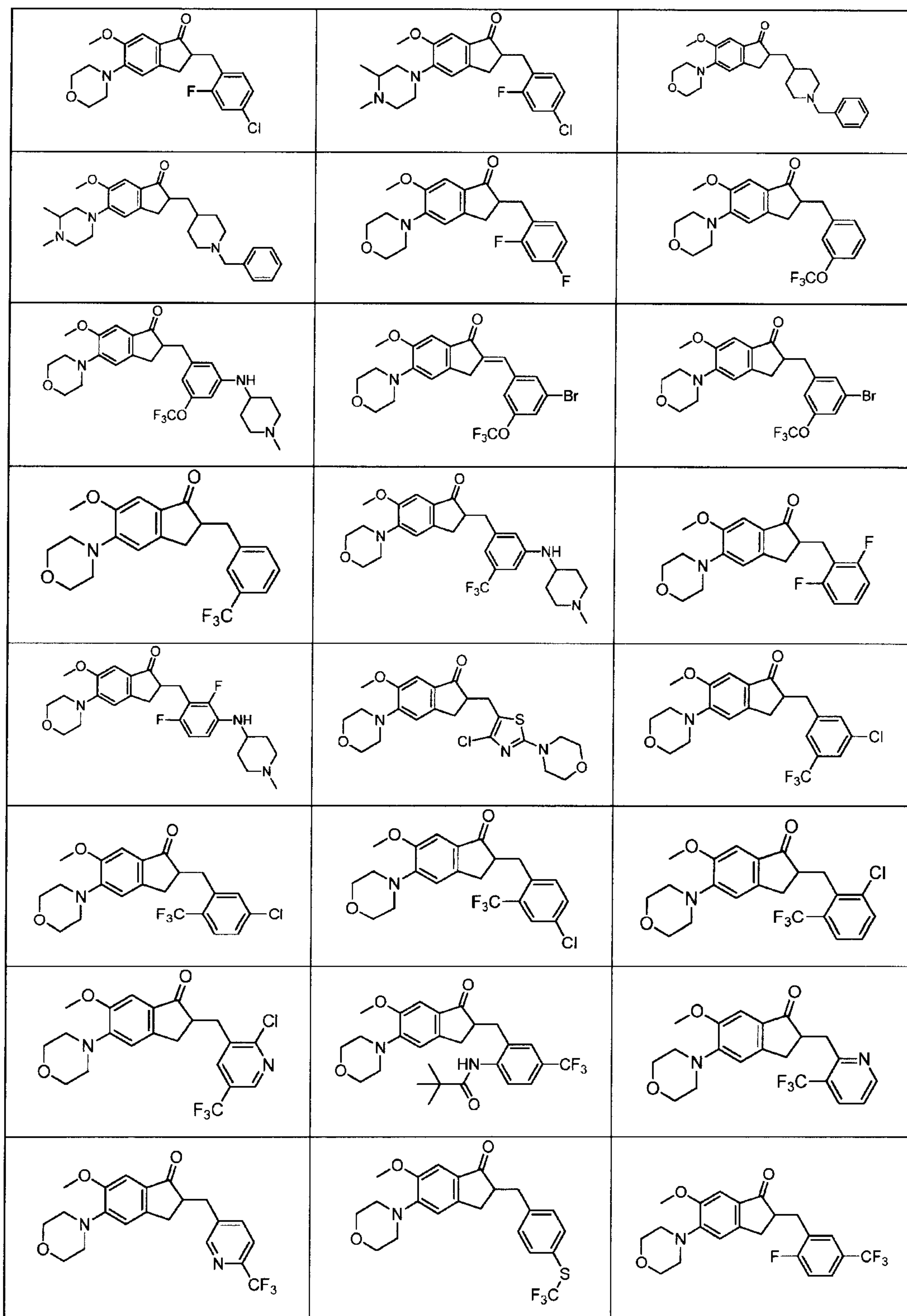
halo, trifluoromethyl, (trifluoromethyl)thio, , or substituents;

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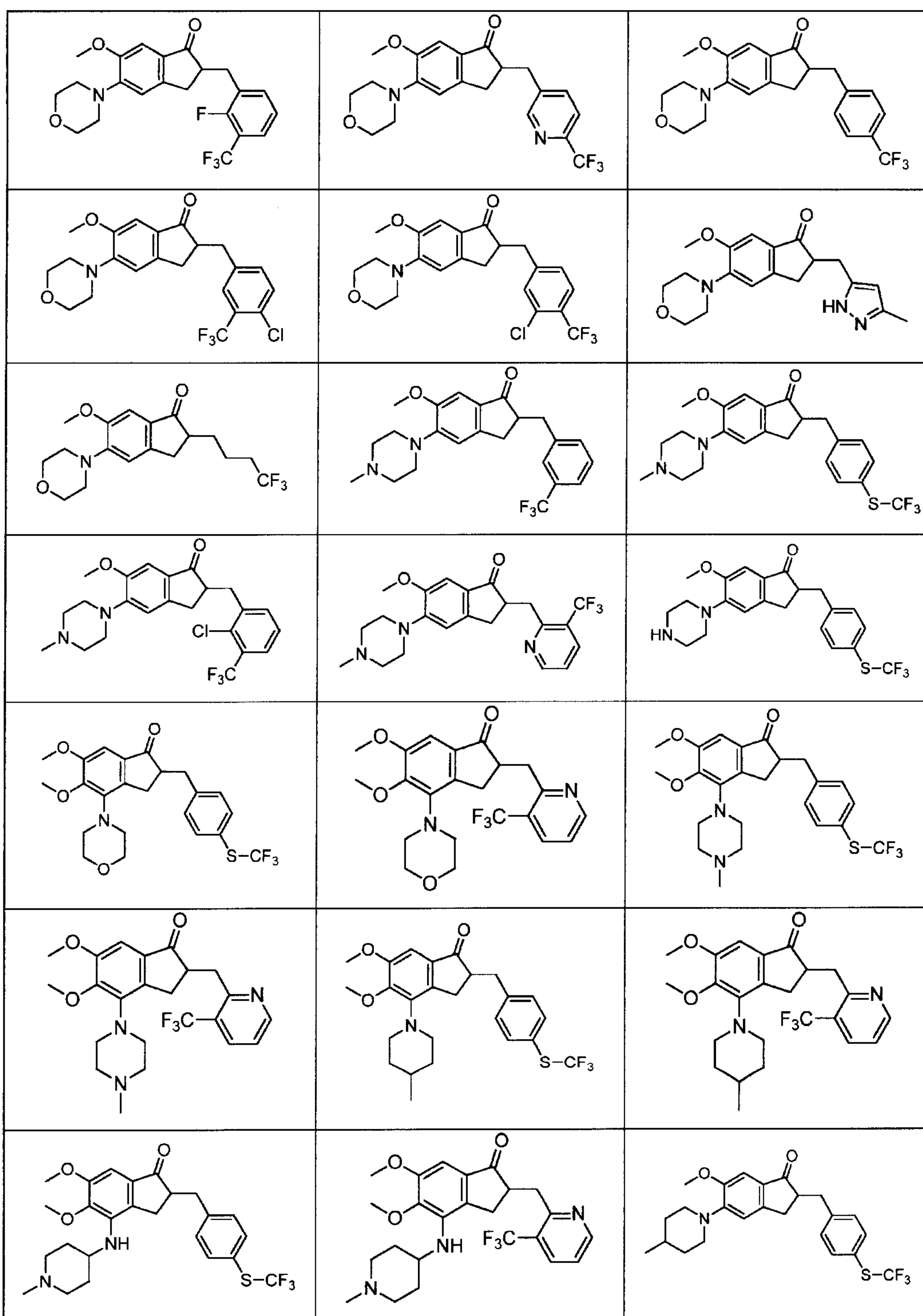
the dotted line indicates an optional double bond.

The compounds of the present invention include:



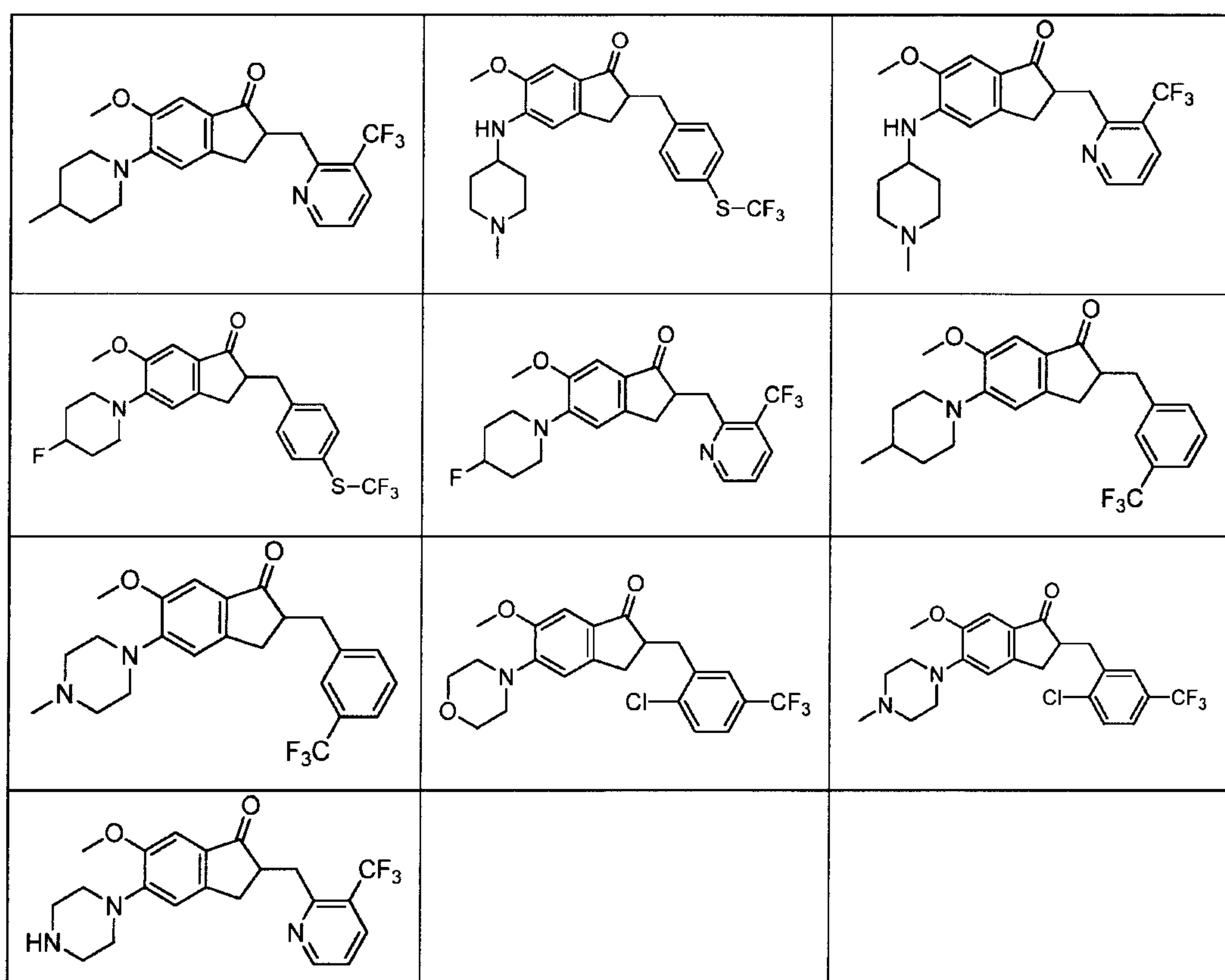
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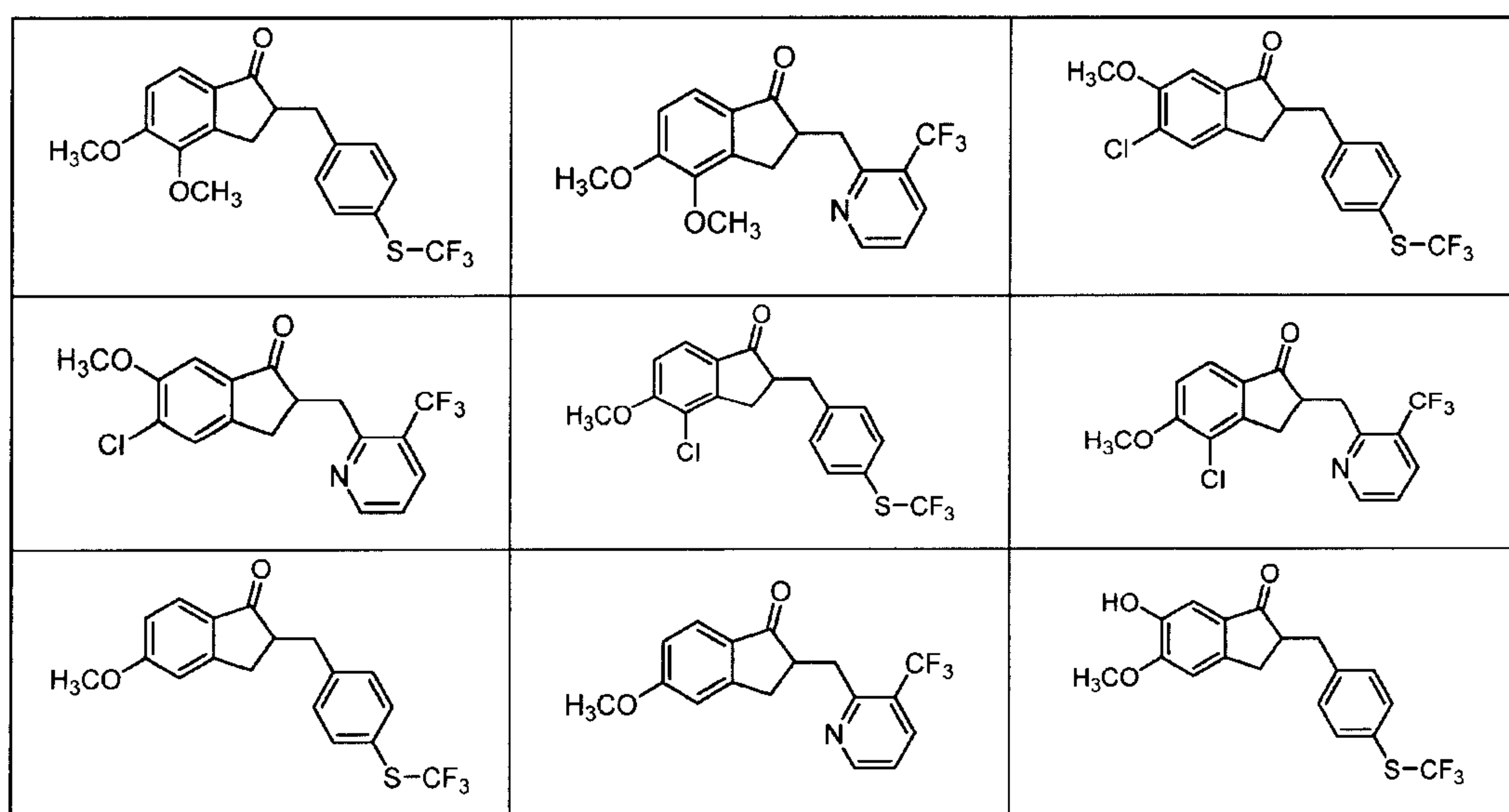


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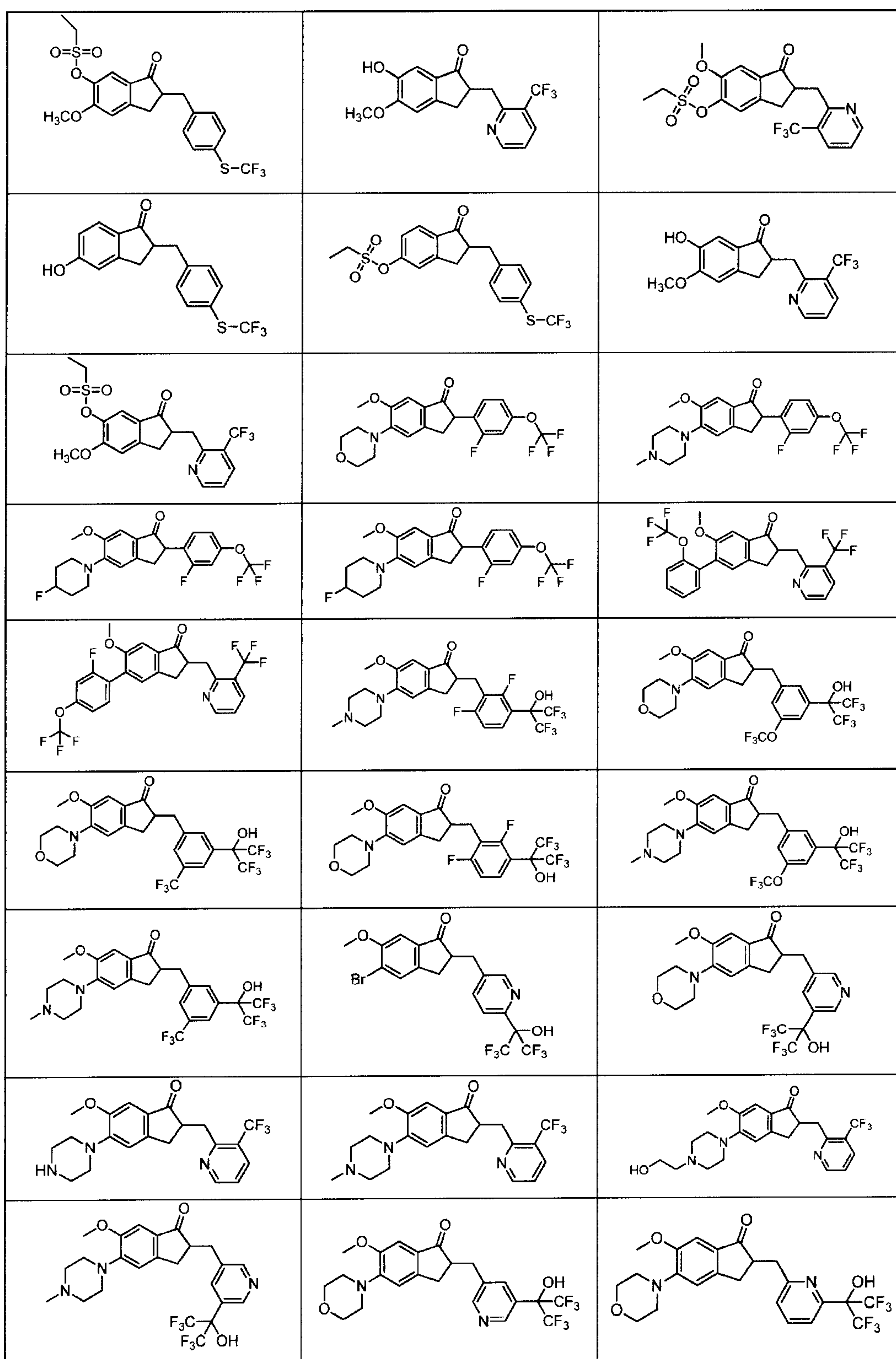


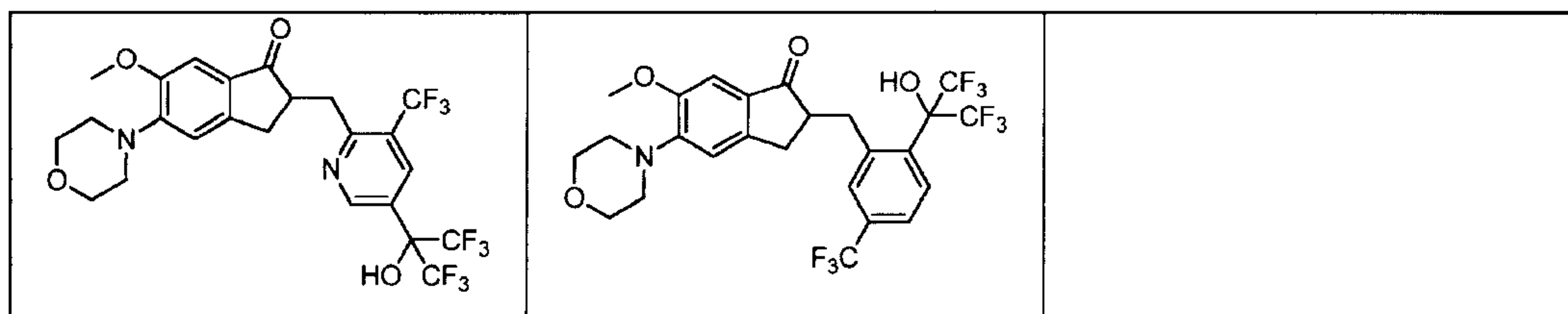
Compounds of the invention further include:



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Unless otherwise stated the following terms used in the specification and claims have the meanings discussed below:

"Alkyl" refers to a saturated straight or branched hydrocarbon radical of one to six carbon atoms, preferably one to four carbon atoms, e.g., methyl, ethyl, propyl, 2-propyl, n-butyl, iso-butyl, tert-butyl, pentyl, hexyl, and the like, preferably methyl, ethyl, propyl, or 2-propyl. Representative saturated straight chain alkyls include methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, and the like; while saturated branched alkyls include isopropyl, *sec*-butyl, isobutyl, *tert*-butyl, isopentyl, and the like. Cyclic alkyls are referred to herein as a "cycloalkyl."

Unsaturated alkyls contain at least one double or triple bond between adjacent carbon atoms (referred to as an "alkenyl" or "alkynyl", respectively.) Representative straight chain and branched alkenyls include ethylenyl, propylenyl, 1-butenyl, 2-butenyl, isobutylenyl, 1-pentenyl, 2-pentenyl, 3-methyl-1-butenyl, 2-methyl-2-butenyl, 2,3-dimethyl-2-butenyl, and the like; while representative straight chain and branched alkynyls include acetylenyl, propynyl, 1-butyne, 2-butyne, 1-pentyne, 2-pentyne, 3-methyl-1-butyne, and the like.

"C₀₋₄alkyl" refers to an alkyl with 0, 1, 2, 3, or 4 carbon atoms. C₀₋₄alkyl with 0 carbon atoms is a hydrogen atom when terminal and is a direct bond when linking.

"Alkylenc" means a linear saturated divalent hydrocarbon radical of one to six carbon atoms or a branched saturated divalent hydrocarbon radical of three to six carbon atoms, e.g., methylene, ethylene, 2,2-dimethylethylene, propylene, 2-methylpropylene, butylene, pentylene, and the like, preferably methylene, ethylene, or propylene.

"Cycloalkyl" refers to a saturated cyclic hydrocarbon radical of three to eight carbon atoms, e.g., cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

"Alkoxy" means a radical -OR_a where R_a is an alkyl as defined above, e.g., methoxy, ethoxy, propoxy, butoxy and the like.

"Halo" means fluoro, chloro, bromo, or iodo, preferably fluoro and chloro.

"Haloalkyl" means alkyl substituted with one or more, preferably one, two or three, same or different halo atoms, e.g., -CH₂Cl, -CF₃, -CH₂CF₃, -CH₂CCl₃, and the like.

"Haloalkoxy" means a radical -OR_b where R_b is an haloalkyl as defined above, e.g., trifluoromethoxy, trichloroethoxy, 2,2-dichloropropoxy, and the like.

"Acyl" means a radical -C(O)R_c where R_c is hydrogen, alkyl, or haloalkyl as defined herein, e.g., formyl, acetyl, trifluoroacetyl, butanoyl, and the like.

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"Aryl" refers to an all-carbon monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of carbon atoms) groups of 6 to 12 carbon atoms having a completely conjugated pi-electron system. Examples, without limitation, of aryl groups are phenyl, naphthyl and anthracenyl. The aryl group may be substituted or unsubstituted. Unless specifically stated
 5 otherwise, "substituted aryl" refers to the aryl group being substituted with one or more, more preferably one, two or three, even more preferably one or two substituents independently selected from the group consisting of alkyl (wherein the alkyl may be optionally substituted with one or two substituents), haloalkyl, halo, hydroxy, alkoxy, mercapto, alkylthio, cyano, acyl, nitro, phenoxy, heteroaryl, heteroaryloxy, haloalkyl, haloalkoxy, carboxy, alkoxycarbonyl,
 10 amino, alkylamino dialkylamino, aryl, heteroaryl, carbocycle or heterocycle (wherein the aryl, heteroaryl, carbocycle or heterocycle may be optionally substituted).

"Heteroaryl" refers to a monocyclic or fused ring (i.e., rings which share an adjacent pair of atoms) group of 5 to 12 ring atoms containing one, two, three or four ring heteroatoms selected from N, O, or S, the remaining ring atoms being C, and, in addition, having a
 15 completely conjugated pi-electron system. Examples, without limitation, of unsubstituted heteroaryl groups are pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrimidine, quinoline, isoquinoline, purine, triazole, tetrazole, triazine, and carbazole. The heteroaryl group may be unsubstituted or substituted, such as, for example, 5-methylthiazolyl. Unless specifically stated otherwise, "substituted heteroaryl" refers to the heteroaryl group being
 20 substituted with one or more, more preferably one, two or three, even more preferably one or two substituents independently selected from the group consisting of alkyl (wherein the alkyl may be optionally substituted with one or two substituents), haloalkyl, halo, hydroxy, alkoxy, mercapto, alkylthio, cyano, acyl, nitro, haloalkyl, haloalkoxy, carboxy, alkoxycarbonyl, amino, alkylamino dialkylamino, aryl, heteroaryl, carbocycle or heterocycle (wherein the aryl,
 25 heteroaryl, carbocycle or heterocycle may be optionally substituted).

"Carbocycle" refers to a saturated, unsaturated or aromatic ring system having 3 to 14 ring carbon atoms. The term "carbocycle", whether saturated or partially unsaturated, also refers to rings that are optionally substituted. The term "carbocycle" includes aryl. The term "carbocycle" also includes aliphatic rings that are fused to one or more aromatic or nonaromatic
 30 rings, such as in a decahydronaphthyl or tetrahydronaphthyl, where the radical or point of attachment is on the aliphatic ring. The carbocycle group may be substituted or unsubstituted. Unless specifically stated otherwise, "substituted carbocycle" refers to the carbocycle group being substituted with one or more, more preferably one, two or three, even more preferably one or two substituents independently selected from the group consisting of alkyl (wherein the alkyl
 35 may be optionally substituted with one or two substituents), haloalkyl, halo, hydroxy, alkoxy,

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mercapto, alkylthio, cyano, acyl, nitro, haloalkyl, haloalkoxy, carboxy, alkoxycarbonyl, amino, alkylamino dialkylamino, aryl, heteroaryl, carbocycle or heterocycle (wherein the aryl, heteroaryl, carbocycle or heterocycle may be optionally substituted).

"Heterocycle" refers to a saturated, unsaturated or aromatic cyclic ring system having 3 to 14 ring atoms in which one, two or three ring atoms are heteroatoms selected from N, O, or S(O)_m (where m is an integer from 0 to 2), the remaining ring atoms being C, where one or two C atoms may optionally be replaced by a carbonyl group. The term "heterocycle" includes heteroaryl. Unless specifically stated otherwise, "substituted heterocyclyl" refers to the heterocyclyl ring being substituted independently with one or more, preferably one, two, or three substituents selected from alkyl (wherein the alkyl may be optionally substituted with one or two substituents), haloalkyl, cycloalkylamino, cycloalkyl or cycloalkyl-alkyl, cycloalkyl-aminoalkyl, cycloalkyl-alkyl amino-alkyl, cyanoalkyl, halo, nitro, cyano, hydroxy, alkoxy, amino, alkylamino, dialkylamino, hydroxyalkyl, carboxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, carbocycle, heterocycle (wherein the aryl, heteroaryl, carbocycle or heterocycle may be optionally substituted), aralkyl, heteroaralkyl, saturated or unsaturated heterocycloamino, saturated or unsaturated heterocycloaminoalkyl, and -COR_d (where R_d is alkyl). More specifically the term heterocyclyl includes, but is not limited to, tetrahydropyranyl, 2,2-dimethyl-1,3-dioxolane, piperidino, N-methylpiperidin-3-yl, piperazino, N-methylpyrrolidin-3-yl, pyrrolidino, morpholino, 4-cyclopropylmethylpiperazino, thiomorpholino, thiomorpholino-1-oxide, thiomorpholino-1,1-dioxide, 4-ethyloxycarbonylpiperazino, 3-oxopiperazino, 2-imidazolidone, 2-pyrrolidinone, 2-oxohomopiperazino, tetrahydropyrimidin-2-one, and the derivatives thereof, including 2-methyl-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-c]pyridinyl. In certain embodiments, the heterocycle group is optionally substituted with one or two substituents independently selected from halo, alkyl, alkyl substituted with carboxy, ester, hydroxy, alkylamino, saturated or unsaturated heterocycloamino, saturated or unsaturated heterocycloaminoalkyl, or dialkylamino.

"Optional" or "optionally" means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "heterocyclic group optionally substituted with an alkyl group" means that the alkyl may but need not be present, and the description includes situations where the heterocycle group is substituted with an alkyl group and situations where the heterocycle group is not substituted with the alkyl group.

Lastly, unless specifically stated otherwise, the term "substituted" as used herein means any of the above groups (e.g., alkyl, aryl, heteroaryl, carbocycle, heterocycle, etc.) wherein at least one hydrogen atom is replaced with a substituent. In the case of an oxo

substituent (“=O”) two hydrogen atoms are replaced. “Substituents” within the context of this invention, if not specified, include halogen, hydroxy, oxo, cyano, nitro, amino, alkylamino, dialkylamino, alkyl, alkoxy, thioalkyl, haloalkyl (e.g., -CF₃), hydroxyalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl, substituted heterocyclealkyl, -NR_eR_f, -NR_eC(=O)R_f, -NR_eC(=O)NR_eR_f, -NR_eC(=O)OR_f, -NR_eSO₂R_f, -OR_e, -C(=O)R_e, -C(=O)OR_e, -C(=O)NR_eR_f, -OC(=O)NR_eR_f, -SH, -SR_e, -SOR_e, -S(=O)₂R_e, -OS(=O)₂R_e, -S(=O)₂OR_e, wherein R_e and R_f are the same or different and independently hydrogen, alkyl, haloalkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl or substituted heterocyclealkyl.

Compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers". Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers". When a compound has an asymmetric center, for example, it is bonded to four different groups; a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog (Cahn, R., Ingold, C., and Prelog, V. *Angew. Chem.* 78:413-47, 1966; *Angew. Chem. Internat. Ed. Eng.* 5:385-415, 511, 1966), or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture".

The compounds of this invention may possess one or more asymmetric centers; such compounds can therefore be produced as individual (R)- or (S)-stereoisomers or as mixtures thereof. Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (see discussion in Ch. 4 of *ADVANCED ORGANIC CHEMISTRY*, 4th edition, March, J., John Wiley and Sons, New York City, 1992).

The compounds of the present invention may exhibit the phenomena of tautomerism and structural isomerism. This invention encompasses any tautomeric or structural isomeric form and mixtures thereof which possess the ability to modulate (ROR_γt)/ROR_γ activity and is not limited to, any one tautomeric or structural isomeric form.

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It is contemplated that a compound of the present invention would be metabolized by enzymes in the body of the organism such as human being to generate a metabolite that can modulate the activity of the protein kinases. Such metabolites are within the scope of the present invention.

5 A compound of the present invention or a pharmaceutically acceptable salt thereof can be administered as such to a human patient or can be administered in pharmaceutical compositions in which the foregoing materials are mixed with suitable carriers or excipient(s). Techniques for formulation and administration of drugs may be found, for example, in REMINGTON'S PHARMACOLOGICAL SCIENCES, Mack Publishing Co., Easton, PA, latest edition.

10 A "pharmaceutical composition" refers to a mixture of one or more of the compounds described herein or pharmaceutically acceptable salts or prodrugs thereof, with other chemical components, such as pharmaceutically acceptable excipients. The purpose of a pharmaceutical composition is to facilitate administration of a compound to an organism.

 "Pharmaceutically acceptable excipient" refers to an inert substance added to a
15 pharmaceutical composition to further facilitate administration of a compound. Examples, without limitation, of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils and polyethylene glycols.

 "Pharmaceutically acceptable salt" refers to those salts which retain the biological effectiveness and properties of the parent compound. Such salts may include: (1) acid addition
20 salt which is obtained by reaction of the free base of the parent compound with inorganic acids such as hydrochloric acid, hydrobromic acid, nitric acid, phosphoric acid, sulfuric acid, and perchloric acid and the like, or with organic acids such as acetic acid, oxalic acid, (D)- or (L)-malic acid, maleic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, tartaric acid, citric acid, succinic acid or malonic acid and the like, preferably
25 hydrochloric acid or (L)-malic acid; or (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like.

 The compound of the present invention may also act, or be designed to act, as a
30 prodrug. A "prodrug" refers to an agent, which is converted into the parent drug *in vivo*. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. An example, without limitation, of a prodrug would be a compound of the

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present invention, which is, administered as an ester (the "prodrug"), phosphate, amide, carbamate, or urea.

"Therapeutically effective amount" refers to that amount of the compound being administered which will relieve to some extent one or more of the symptoms of the disorder being treated. In reference to the treatment of MS, a therapeutically effective amount refers to that amount which has the effect of: (1) ameliorating loss of muscle control and strength, (2) lessening fatigue or weakness, (3) stabilizing loss of vision, (4) decreasing spasticity, (5) increased balance, (6) lessening bladder and bowel problems, (7) decreasing numbness, or relieving one or more symptoms associated with MS.

The term "disease", as used herein, means any disease or other deleterious condition in which Retinoic acid-related orphan nuclear receptor γ t (ROR γ t)/ROR γ is known to play a role. The term "disease" also means those diseases or conditions that are alleviated by treatment with (ROR γ t)/ROR γ modulators.

The term "(ROR γ t)/ROR γ activity-mediated condition" or "disease", as used herein, means any disease or other deleterious condition in which (ROR γ t)/ROR γ activity is known to play a role. The term "(ROR γ t)/ROR γ activity-mediated condition" also means those diseases or conditions that are alleviated by treatment with a (ROR γ t)/ROR γ inhibitor.

As used herein, "administer" or "administration" refers to the delivery of an inventive compound or of a pharmaceutically acceptable salt thereof or of a pharmaceutical composition containing an inventive compound or a pharmaceutically acceptable salt thereof of this invention to an organism for the purpose of prevention or treatment of a (ROR γ t)/ROR γ related disorder.

Suitable routes of administration may include, without limitation, oral, rectal, transmucosal or intestinal administration or intramuscular, subcutaneous, intramedullary, intrathecal, direct intraventricular, intravenous, intravitreal, intraperitoneal, intranasal, or intraocular injections. In certain embodiments, the preferred routes of administration are oral and intravenous.

Pharmaceutical compositions of the present invention may be manufactured by processes well known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

Pharmaceutical compositions for use in accordance with the present invention may be formulated in any conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

For injection, the compounds of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

For oral administration, the compounds can be formulated by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, lozenges, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient. Pharmaceutical preparations for oral use can be made using a solid excipient, optionally grinding the resulting mixture, and processing the mixture of granules, after adding other suitable auxiliaries if desired, to obtain tablets or dragee cores. Useful excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol, cellulose preparations such as, for example, maize starch, wheat starch, rice starch and potato starch and other materials such as gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinyl-pyrrolidone (PVP). If desired, disintegrating agents may be added, such as cross-linked polyvinyl pyrrolidone, agar, or alginic acid. A salt such as sodium alginate may also be used.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical compositions which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, a binder such as starch, and/or a lubricant such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. Stabilizers may be added in these formulations, also. Pharmaceutical compositions which may also be used include hard gelatin capsules. The capsules or pills may be packaged into brown glass or plastic bottles to protect the active compound from light. The containers containing the active compound capsule formulation are preferably stored at controlled room temperature (15-30°C).

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For administration by inhalation, the compounds for use according to the present invention may be conveniently delivered in the form of an aerosol spray using a pressurized pack or a nebulizer and a suitable propellant, e.g., without limitation, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetra-fluoroethane or carbon dioxide. In the case of a
5 pressurized aerosol, the dosage unit may be controlled by providing a valve to deliver a metered amount. Capsules and cartridges of, for example, gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds may also be formulated for parenteral administration, e.g., by bolus
10 injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating materials such as suspending, stabilizing and/or dispersing agents.

15 Pharmaceutical compositions for parenteral administration include aqueous solutions of a water soluble form, such as, without limitation, a salt, of the active compound. Additionally, suspensions of the active compounds may be prepared in a lipophilic vehicle. Suitable lipophilic vehicles include fatty oils such as sesame oil, synthetic fatty acid esters such as ethyl oleate and triglycerides, or materials such as liposomes. Aqueous injection suspensions may contain
20 substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers and/or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

Alternatively, the active ingredient may be in powder form for constitution with a
25 suitable vehicle, e.g., sterile, pyrogen-free water, before use.

The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, using, e.g., conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds may also be
30 formulated as depot preparations. Such long acting formulations may be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. A compound of this invention may be formulated for this route of administration with suitable polymeric or hydrophobic materials (for instance, in an emulsion with a pharmacologically acceptable oil), with ion exchange resins, or as a sparingly soluble derivative such as, without
35 limitation, a sparingly soluble salt.

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A non-limiting example of a pharmaceutical carrier for the hydrophobic compounds of the invention is a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer and an aqueous phase such as the VPD cosolvent system. VPD is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant polysorbate 80, and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. The VPD cosolvent system (VPD: D5W) consists of VPD diluted 1:1 with a 5% dextrose in water solution. This cosolvent system dissolves hydrophobic compounds well, and itself produces low toxicity upon systemic administration. Naturally, the proportions of such a cosolvent system may be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the cosolvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of polysorbate 80, the fraction size of polyethylene glycol may be varied, other biocompatible polymers may replace polyethylene glycol, e.g., polyvinyl pyrrolidone, and other sugars or polysaccharides may substitute for dextrose.

Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. In addition, certain organic solvents such as dimethylsulfoxide also may be employed, although often at the cost of greater toxicity.

Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization may be employed.

The pharmaceutical compositions herein also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include, but are not limited to, calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

Many of the (ROR γ t)/ROR γ modulating compounds of the invention may be provided as physiologically acceptable salts wherein the claimed compound may form the negatively or the positively charged species. Examples of salts in which the compound forms the positively charged moiety include, without limitation, quaternary ammonium (defined elsewhere herein), salts such as the hydrochloride, sulfate, carbonate, lactate, tartrate, malate, maleate, succinate wherein the nitrogen atom of the quaternary ammonium group is a nitrogen of the selected compound of this invention which has reacted with the appropriate acid. Salts in which a

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compound of this invention forms the negatively charged species include, without limitation, the sodium, potassium, calcium and magnesium salts formed by the reaction of a carboxylic acid group in the compound with an appropriate base (e.g. sodium hydroxide (NaOH), potassium hydroxide (KOH), calcium hydroxide (Ca(OH)₂), etc).

5 Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an amount sufficient to achieve the intended purpose, e.g., the modulation of protein kinase activity and/or the treatment or prevention of a protein kinase-related disorder.

10 More specifically, a therapeutically effective amount means an amount of compound effective to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated.

Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

15 For any compound used in the methods of the invention, the therapeutically effective amount or dose can be estimated initially from cell culture assays. Then, the dosage can be formulated for use in animal models so as to achieve a circulating concentration range that includes the IC₅₀ as determined in cell culture (i.e., the concentration of the test compound which achieves a half-maximal inhibition of the (ROR γ t)/ROR γ , or surrogate marker activity). Such information can then be used to more accurately determine useful doses in humans.

20 Toxicity and therapeutic efficacy of the compounds described herein can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., by determining the IC₅₀ and the LD₅₀ (both of which are discussed elsewhere herein) for a subject compound. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage may vary depending upon
25 the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (See, e.g., GOODMAN & GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, Ch. 3, 9th ed., Ed. by Hardman, J., and Limbard, L., McGraw-Hill, New York City, 1996, p.46.)

30 Dosage amount and interval may be adjusted individually to provide plasma levels of the active species which are sufficient to maintain the kinase modulating effects. These plasma levels are referred to as minimal effective concentrations (MECs). The MEC will vary for each compound but can be estimated from *in vitro* data, e.g., the concentration necessary to achieve 50-90% inhibition of (ROR γ t)/ROR γ , or surrogate marker may be ascertained using the assays described herein. Dosages necessary to achieve the MEC will depend on individual

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characteristics and route of administration. HPLC assays or bioassays can be used to determine plasma concentrations.

Dosage intervals can also be determined using MEC value. Compounds should be administered using a regimen that maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90%.

At present, the therapeutically effective amounts of compounds of the present invention may range from approximately 2.5mg/m² to 1500mg/m² per day. Additional illustrative amounts range from 0.2-1000mg/qid, 2-500mg/qid, and 20-250mg/qid.

In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration, and other procedures known in the art may be employed to determine the correct dosage amount and interval.

The amount of a composition administered will, of course, be dependent on the subject being treated, the severity of the affliction, the manner of administration, the judgment of the prescribing physician, etc.

The compositions may, if desired, be presented in a pack or dispenser device, such as an FDA approved kit, which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accompanied by a notice associated with the container in a form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the compositions or of human or veterinary administration. Such notice, for example, may be of the labeling approved by the U.S. Food and Drug Administration for prescription drugs or of an approved product insert. Compositions comprising a compound of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition. Suitable conditions indicated on the label may include treatment of a tumor, inhibition of angiogenesis, treatment of fibrosis, diabetes, and the like.

As mentioned above, the compounds and compositions of the invention will find utility in a broad range of diseases and conditions mediated by protein kinases, including diseases and conditions mediated by (ROR γ t)/ ROR γ activity. Such diseases may include by way of example and not limitation, Multiple Sclerosis (MS), Rheumatoid Arthritis (RA), Inflammatory Colitis, Psoriasis, COPD, Pain, Obesity, Diabetes, Dyslipidemia, Osteoporosis, Asthma, Neurodegenerative diseases and Cancer.

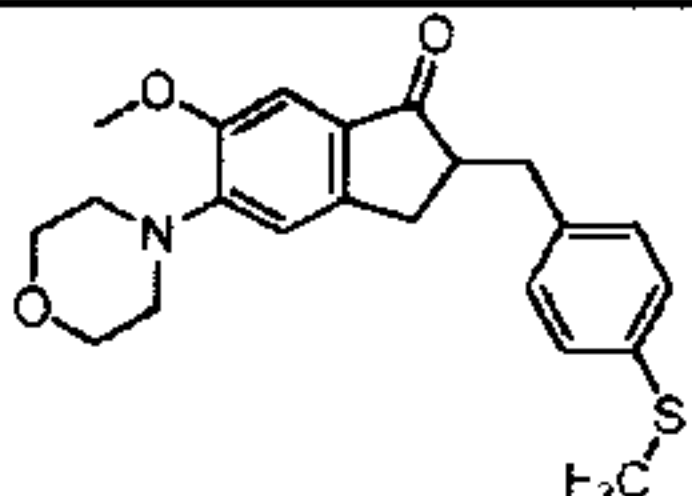
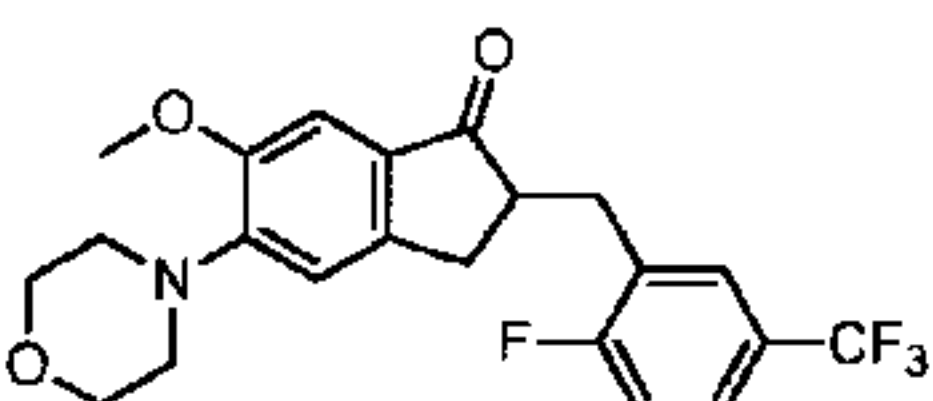
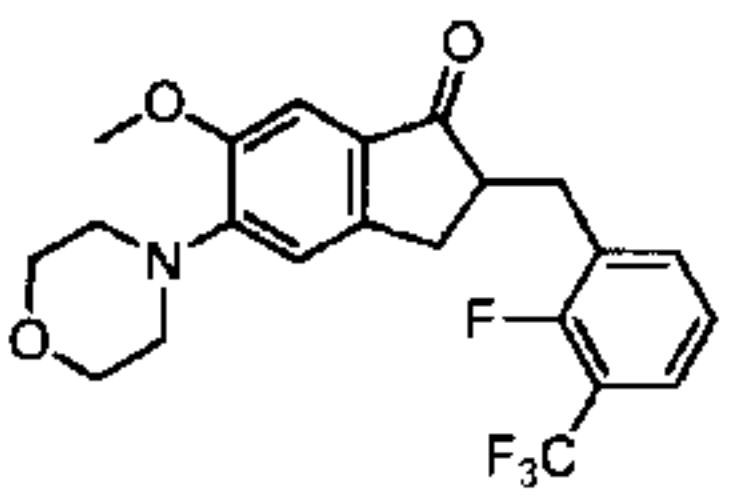
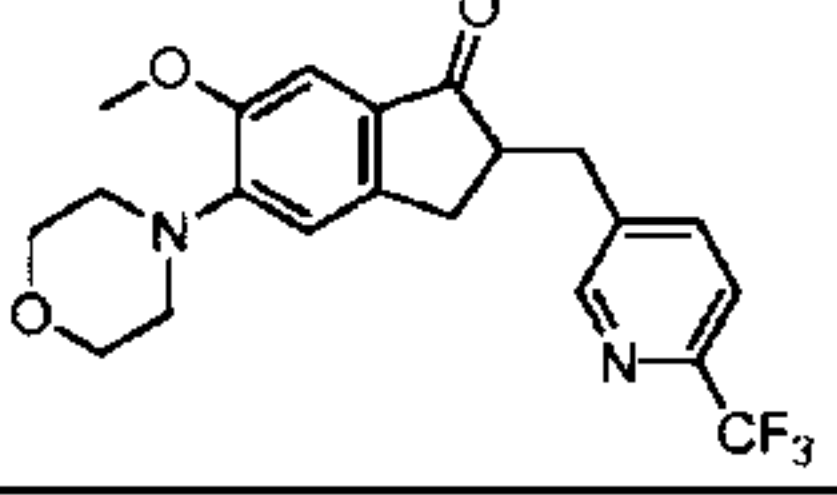
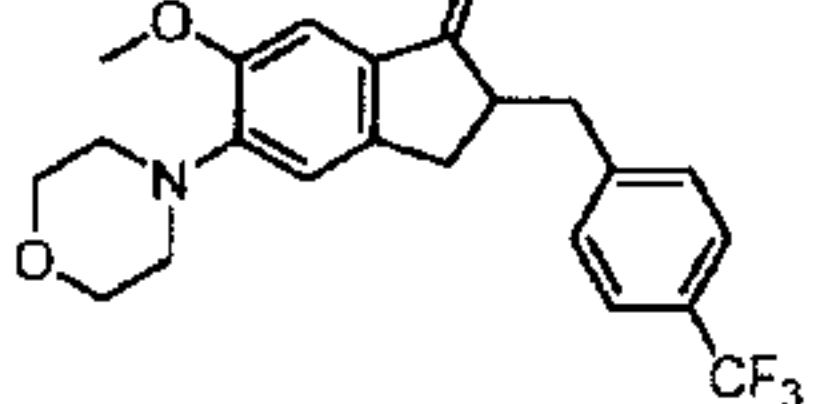
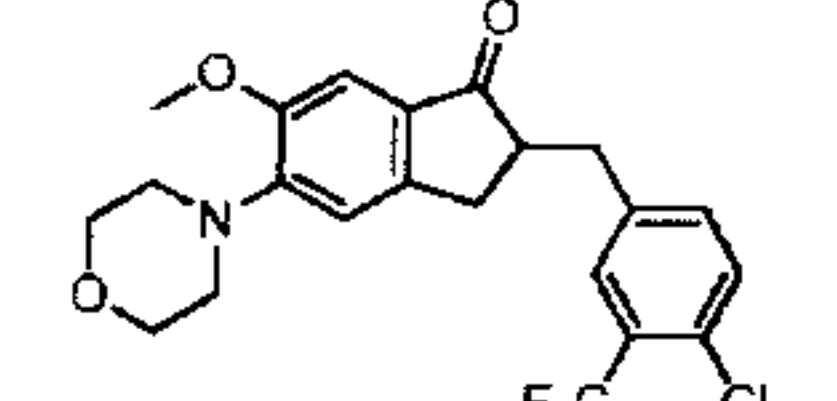
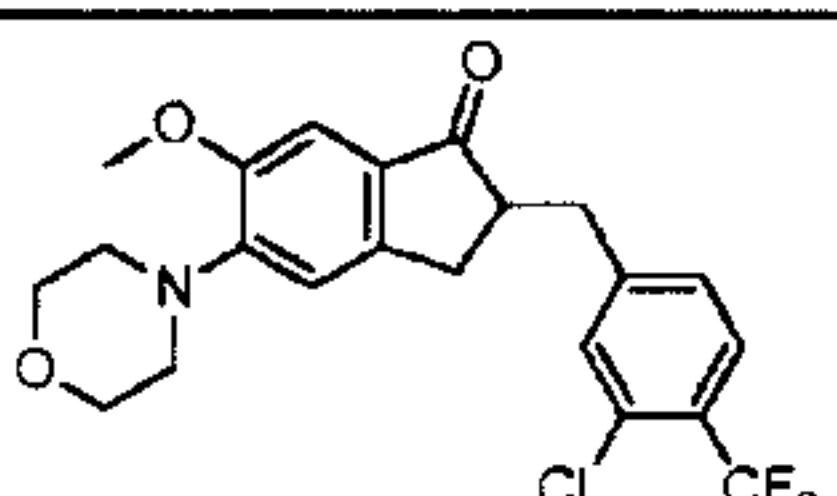
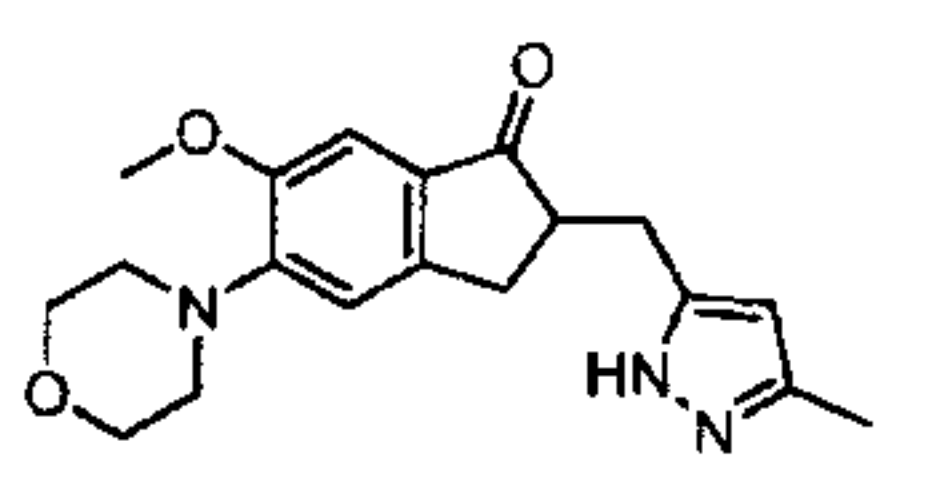
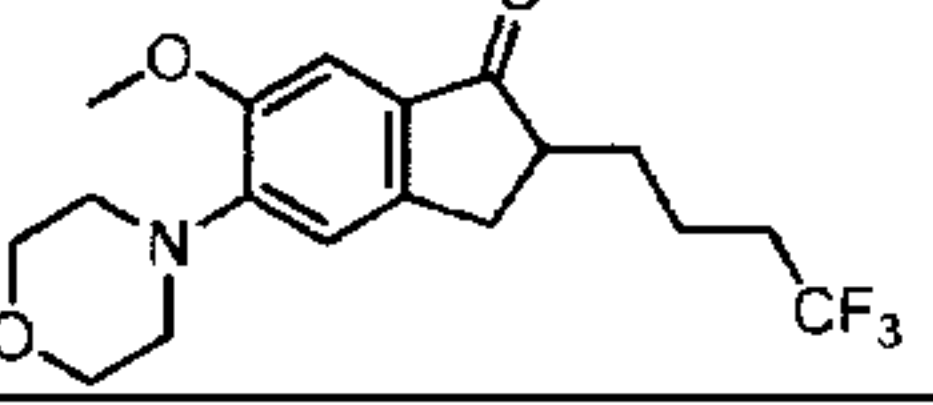
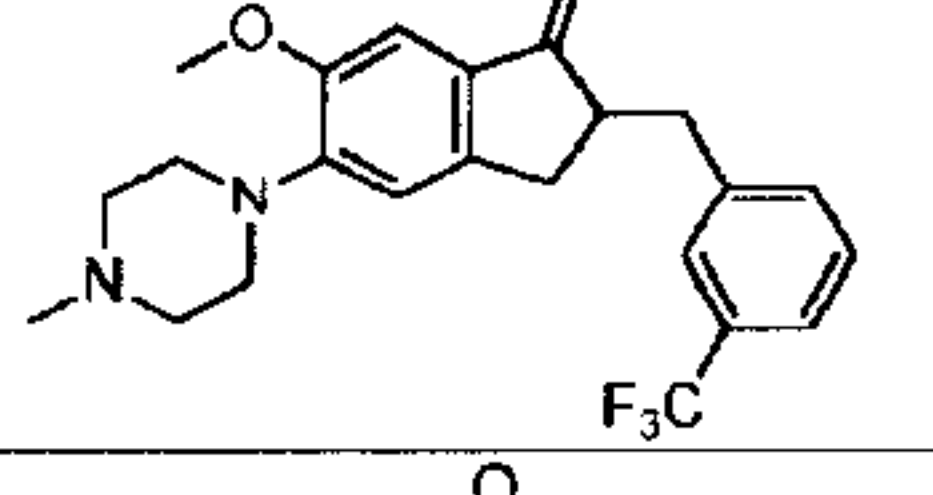
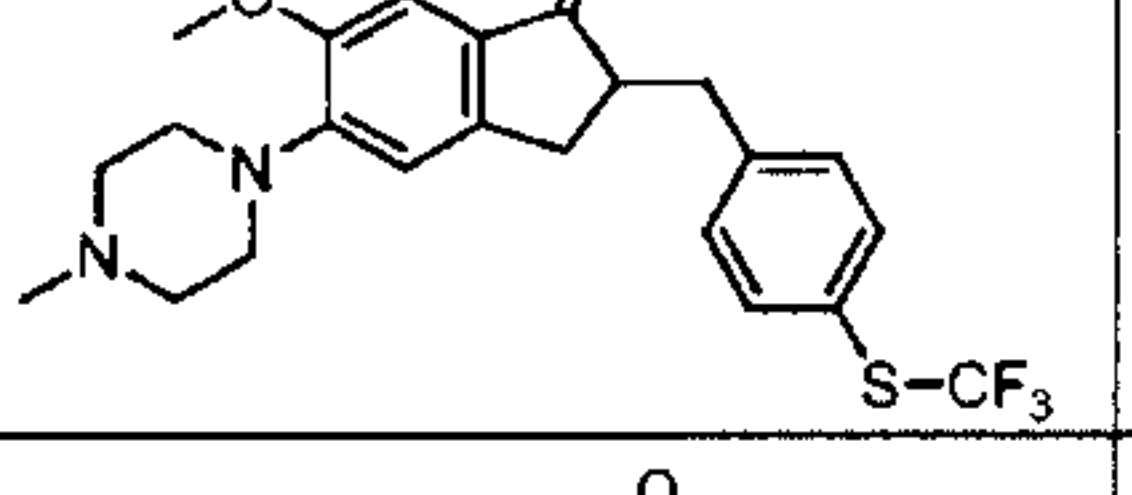
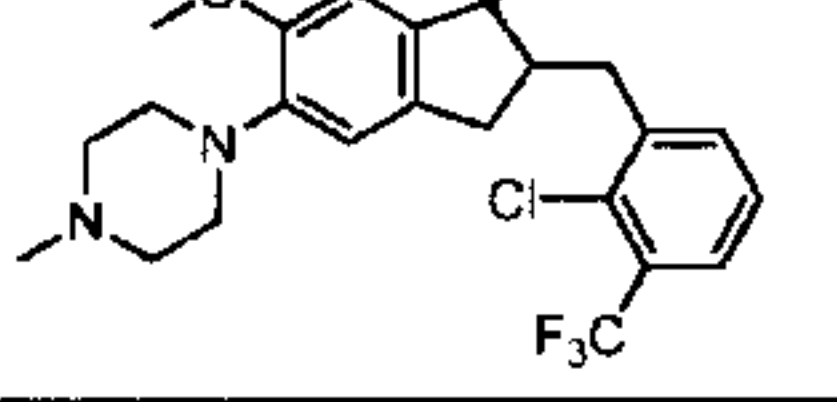
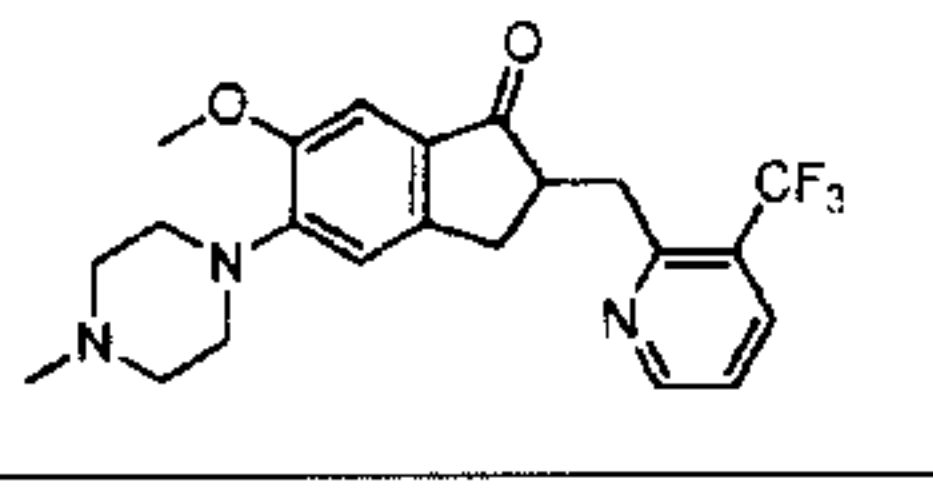
The invention will be further understood upon consideration of the following non-limiting Examples. In other aspects or embodiments include any of the compounds in TABLE

1A and 1B that fall within the scope of any of the embodiments described above of the compounds of Formula 1 or pharmaceutical acceptable salts thereof.

TABLE 1A: Substituted 2, 3-dihydro-1*H*-inden-1-one containing ROR γ Antagonists

Example ID	Structure	Name	MW
16		2-(4-chloro-2-fluorobenzyl)-6-methoxy-5-morpholino-2,3-dihydro-1 <i>H</i> -inden-1-one	389.8*
20		2-(4-chloro-2-fluorobenzyl)-5-(3,4-dimethylpiperazin-1-yl)-6-methoxy-2,3-dihydro-1 <i>H</i> -inden-1-one	414.9
23		2-((1-benzylpiperidin-4-yl)methyl)-6-methoxy-5-morpholino-2,3-dihydro-1 <i>H</i> -inden-1-one	435.2*
25		2-((1-benzylpiperidin-4-yl)methyl)-5-(3,4-dimethylpiperazin-1-yl)-6-methoxy-2,3-dihydro-1 <i>H</i> -inden-1-one	461.6
28		2-(2,4-difluorobenzyl)-6-methoxy-5-morpholino-2,3-dihydro-1 <i>H</i> -inden-1-one	373.9*
31		6-methoxy-5-morpholino-2-(3-(trifluoromethoxy)benzyl)-2,3-dihydro-1 <i>H</i> -inden-1-one	422.1*
34		6-methoxy-2-(3-((1-methylpiperidin-4-yl)amino)-5-(trifluoromethoxy)benzyl)-5-morpholino-2,3-dihydro-1 <i>H</i> -inden-1-one	533.2
30		(<i>E</i>)-2-(3-bromo-5-(trifluoromethoxy)benzylidene)-6-methoxy-5-morpholino-2,3-dihydro-1 <i>H</i> -inden-1-one	498.2
32		2-(3-bromo-5-(trifluoromethoxy)benzyl)-6-methoxy-5-morpholino-2,3-dihydro-1 <i>H</i> -inden-1-one	500.3
37		6-methoxy-5-morpholino-2-(3-(trifluoromethyl)benzyl)-2,3-dihydro-1 <i>H</i> -inden-1-one	406.0*

39		6-methoxy-2-(3-((1-methylpiperidin-4-yl)amino)-5-(trifluoromethyl)benzyl)-5-morpholino-2,3-dihydro-1H-inden-1-one	517.26
42		2-(2,6-difluorobenzyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one	374.0*
44		2-(2,6-difluoro-3-((1-methylpiperidin-4-yl)amino)benzyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one	485.25
47		2-((4-chloro-2-morpholinothiazol-5-yl)methyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one	463.98
50		2-(3-chloro-5-(trifluoromethyl)benzyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one	440.0*
53		2-(5-chloro-2-(trifluoromethyl)benzyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one	440.0*
56		2-(4-chloro-2-(trifluoromethyl)benzyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one	439.8
59		2-(2-chloro-6-(trifluoromethyl)benzyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one	439.8
62		2-((2-chloro-5-(trifluoromethyl)pyridin-3-yl)methyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one	440.8
65		N-(2-((6-methoxy-5-morpholino-1-oxo-2,3-dihydro-1H-inden-2-yl)methyl)-4-(trifluoromethyl)phenyl)pivalamide	504.5
68		6-methoxy-5-morpholino-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-2,3-dihydro-1H-inden-1-one	407.0*
71		6-methoxy-5-morpholino-2-((6-(trifluoromethyl)pyridin-3-yl)methyl)-2,3-dihydro-1H-inden-1-one	407.0*

74		6-methoxy-5-morpholino-2-(4-((trifluoromethyl)thio)benzyl)-2,3-dihydro-1H-inden-1-one	438.0*
77		2-(2-fluoro-5-(trifluoromethyl)benzyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one	424.0*
80		2-(2-fluoro-3-(trifluoromethyl)benzyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one	424.0
83		6-methoxy-5-morpholino-2-((6-(trifluoromethyl)pyridin-3-yl)methyl)-2,3-dihydro-1H-inden-1-one	406.4
86		6-methoxy-5-morpholino-2-(4-(trifluoromethyl)benzyl)-2,3-dihydro-1H-inden-1-one	406.0*
89		2-(4-chloro-3-(trifluoromethyl)benzyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one	439.9*
92		2-(3-chloro-4-(trifluoromethyl)benzyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one	440.0*
95		6-methoxy-2-((3-methyl-1H-pyrazol-5-yl)methyl)-5-morpholino-2,3-dihydro-1H-inden-1-one	342.0*
98		6-methoxy-5-morpholino-2-(4,4,4-trifluorobutyl)-2,3-dihydro-1H-inden-1-one	357.3
103		6-methoxy-5-(4-methylpiperazin-1-yl)-2-(3-(trifluoromethyl)benzyl)-2,3-dihydro-1H-inden-1-one	418.4
106		6-methoxy-5-(4-methylpiperazin-1-yl)-2-(3-((trifluoromethyl)thio)benzyl)-2,3-dihydro-1H-inden-1-one	451.0*
110		2-(2-chloro-3-(trifluoromethyl)benzyl)-6-methoxy-5-(4-methylpiperazin-1-yl)-2,3-dihydro-1H-inden-1-one	452.9
113		6-methoxy-5-(4-methylpiperazin-1-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-2,3-dihydro-1H-inden-1-one	419.4

		1-one	
117		6-methoxy-5-(piperazin-1-yl)-2-(4-((trifluoromethyl)thio)benzyl)-2,3-dihydro-1H-inden-1-one	436.5
120		5,6-dimethoxy-4-morpholino-2-(4-((trifluoromethyl)thio)benzyl)-2,3-dihydro-1H-inden-1-one	467.5
123		5,6-dimethoxy-4-morpholino-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-2,3-dihydro-1H-inden-1-one	436.4
125		5,6-dimethoxy-4-(4-methylpiperazin-1-yl)-2-(4-((trifluoromethyl)thio)benzyl)-2,3-dihydro-1H-inden-1-one	480.5
128		5,6-dimethoxy-4-(4-methylpiperazin-1-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-2,3-dihydro-1H-inden-1-one	449.4
131		5,6-dimethoxy-4-(4-methylpiperidin-1-yl)-2-(4-((trifluoromethyl)thio)benzyl)-2,3-dihydro-1H-inden-1-one	479.5
133		5,6-dimethoxy-4-(4-methylpiperidin-1-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-2,3-dihydro-1H-inden-1-one	448.5
136		5,6-dimethoxy-4-((1-methylpiperidin-4-yl)amino)-2-(4-((trifluoromethyl)thio)benzyl)-2,3-dihydro-1H-inden-1-one	494.5
138		5,6-dimethoxy-4-((1-methylpiperidin-4-yl)amino)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-2,3-dihydro-1H-inden-1-one	463.5
140		6-methoxy-5-(4-methylpiperidin-1-yl)-2-(4-((trifluoromethyl)thio)benzyl)-2,3-dihydro-1H-inden-1-one	450.1*
142		6-methoxy-5-(4-methylpiperidin-1-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-2,3-dihydro-1H-inden-1-one	418.4

144		6-methoxy-5-((1-methylpiperidin-4-yl)amino)-2-(4-((trifluoromethyl)thio)benzyl)-2,3-dihydro-1H-inden-1-one	464.5
146		6-methoxy-5-((1-methylpiperidin-4-yl)amino)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-2,3-dihydro-1H-inden-1-one	433.4
149		5-(4-fluoropiperidin-1-yl)-6-methoxy-2-(4-((trifluoromethyl)thio)benzyl)-2,3-dihydro-1H-inden-1-one	453.5
151		5-(4-fluoropiperidin-1-yl)-6-methoxy-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-2,3-dihydro-1H-inden-1-one	422.4
154		6-methoxy-5-(4-methylpiperidin-1-yl)-2-(3-(trifluoromethyl)benzyl)-2,3-dihydro-1H-inden-1-one	418.*
156		6-methoxy-5-(4-methylpiperazin-1-yl)-2-(3-(trifluoromethyl)benzyl)-2,3-dihydro-1H-inden-1-one	419.0*
158		2-(2-chloro-5-(trifluoromethyl)benzyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one	440.0*
161		2-(2-chloro-5-(trifluoromethyl)benzyl)-6-methoxy-5-(4-methylpiperazin-1-yl)-2,3-dihydro-1H-inden-1-one	452.9
164		6-methoxy-5-(piperazin-1-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-2,3-dihydro-1H-inden-1-one	405.4

* MS (ESI) m/z (M+H)

TABLE 1B: Substituted 2, 3-dihydro-1H-inden-1-one containing ROR γ Antagonists

Example ID	Structure	Name	MW
167		4,5-dimethoxy-2-(4-((trifluoromethyl)thio)benzyl)-2,3-dihydro-1H-inden-1-one	382.40

169		4,5-dimethoxy-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-2,3-dihydro-1H-inden-1-one	351.32
172		5-chloro-6-methoxy-2-(4-((trifluoromethyl)thio)benzyl)-2,3-dihydro-1H-inden-1-one	386.82
174		5-chloro-6-methoxy-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-2,3-dihydro-1H-inden-1-one	355.74
177		4-chloro-5-methoxy-2-(4-((trifluoromethyl)thio)benzyl)-2,3-dihydro-1H-inden-1-one	386.84
179		4-chloro-5-methoxy-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-2,3-dihydro-1H-inden-1-one	355.06
182		5-methoxy-2-(4-((trifluoromethyl)thio)benzyl)-2,3-dihydro-1H-inden-1-one	352.07
184		5-methoxy-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-2,3-dihydro-1H-inden-1-one	321.10
187		6-hydroxy-5-methoxy-2-(4-((trifluoromethyl)thio)benzyl)-2,3-dihydro-1H-inden-1-one	368.01
188		6-methoxy-3-oxo-2-(4-((trifluoromethyl)thio)benzyl)-2,3-dihydro-1H-inden-5-yl ethanesulfonate	460.06
190		6-hydroxy-5-methoxy-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-2,3-dihydro-1H-inden-1-one	337.09

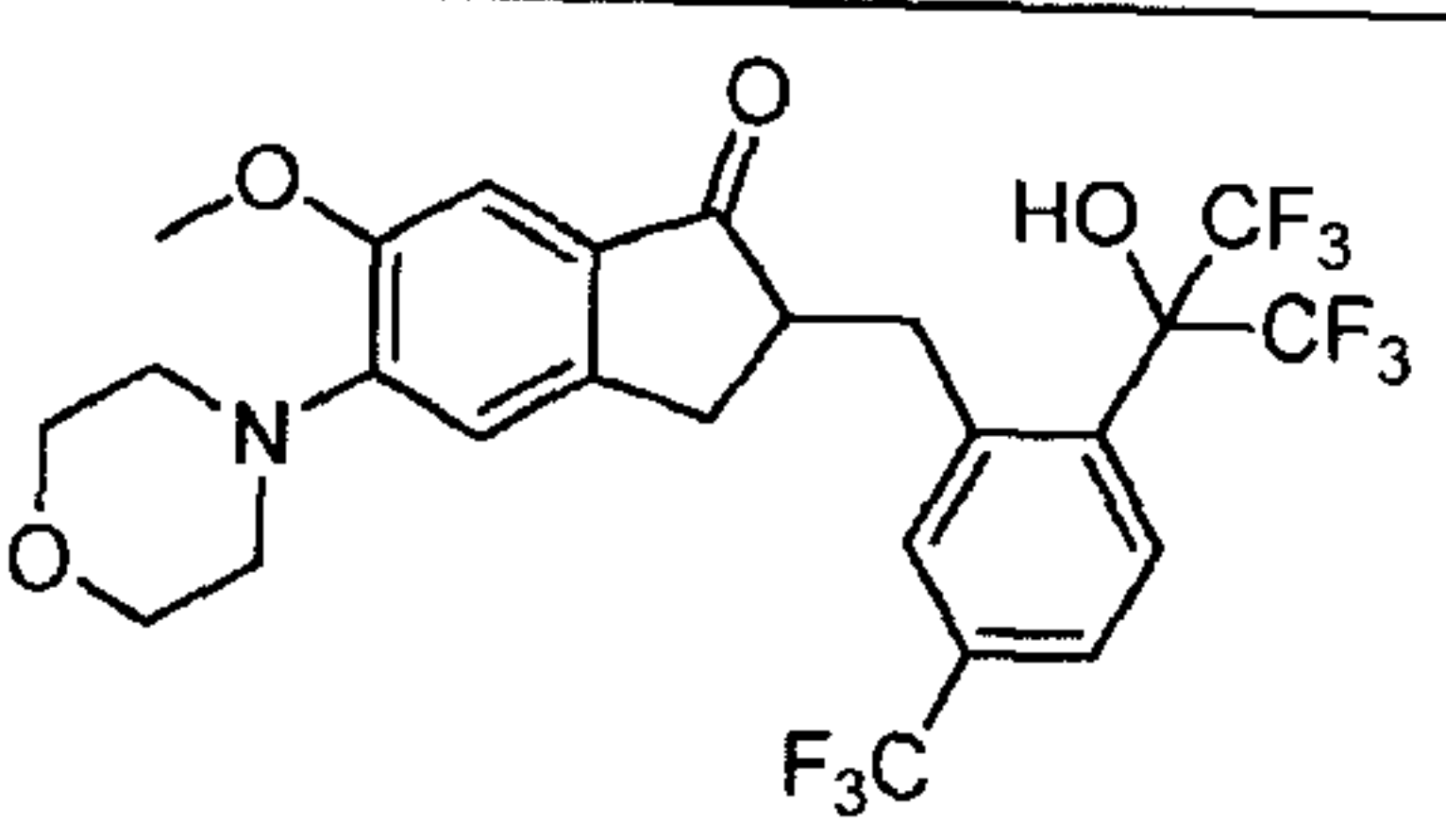
191		6-methoxy-3-oxo-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-2,3-dihydro-1H-inden-5-yl ethanesulfonate	429.09
193		5-hydroxy-2-(4-((trifluoromethyl)thio)benzyl)-2,3-dihydro-1H-inden-1-one	338.06
194		1-oxo-2-(4-((trifluoromethyl)thio)benzyl)-2,3-dihydro-1H-inden-5-yl ethanesulfonate	430.05
196		6-hydroxy-5-methoxy-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-2,3-dihydro-1H-inden-1-one	337.09
197		6-methoxy-3-oxo-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-2,3-dihydro-1H-inden-5-yl ethanesulfonate	429.09
200		2-(2-fluoro-4-(trifluoromethoxy)phenyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one	425.13
202		2-(2-fluoro-4-(trifluoromethoxy)phenyl)-6-methoxy-5-(4-methylpiperazin-1-yl)-2,3-dihydro-1H-inden-1-one	438.16
206		2-(2-fluoro-4-(trifluoromethoxy)phenyl)-5-(4-fluoropiperidin-1-yl)-6-methoxy-2,3-dihydro-1H-inden-1-one	441.14
209		2-(2-fluoro-4-(trifluoromethoxy)phenyl)-5-(4-fluoropiperidin-1-yl)-6-methoxy-2,3-dihydro-1H-inden-1-one	441.14
213		6-methoxy-5-(2-(2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-2,3-dihydro-1H-inden-1-one)-2-(trifluoromethoxy)phenyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-2,3-dihydro-1H-inden-1-one	481.11

216		5-(2-fluoro-4-(trifluoromethoxy)phenyl)-6-methoxy-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-2,3-dihydro-1H-inden-1-one	499.10
220		2-(2,6-difluoro-3-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)benzyl)-6-methoxy-5-(4-methylpiperazin-1-yl)-2,3-dihydro-1H-inden-1-one	552.17
225		2-(3-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-5-(trifluoromethoxy)benzyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one	587.14
229		2-(3-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-5-(trifluoromethyl)benzyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one	571.14
232		2-(2,6-difluoro-3-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)benzyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one	539.13
236		2-(3-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-5-(trifluoromethoxy)benzyl)-6-methoxy-5-(4-methylpiperazin-1-yl)-2,3-dihydro-1H-inden-1-one	600.17
240		2-(3-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-5-(trifluoromethyl)benzyl)-6-methoxy-5-(4-methylpiperazin-1-yl)-2,3-dihydro-1H-inden-1-one	584.17
242		5-bromo-2-(((6-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)pyridin-3-yl)methyl)-6-methoxy-2,3-dihydro-1H-inden-1-one	497.01

245		2-((6-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)pyridin-3-yl)methyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one	504.15
249		6-methoxy-5-(piperazin-1-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-2,3-dihydro-1H-inden-1-one	405.41
250		6-methoxy-5-(4-methylpiperazin-1-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-2,3-dihydro-1H-inden-1-one	419.18
251		5-(4-(2-hydroxyethyl)piperazin-1-yl)-6-methoxy-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-2,3-dihydro-1H-inden-1-one	449.19
256		2-((6-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)pyridin-3-yl)methyl)-6-methoxy-5-(4-methylpiperazin-1-yl)-2,3-dihydro-1H-inden-1-one	517.18
264		2-((5-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)pyridin-3-yl)methyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one	504.42
266		2-((5-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)pyridin-3-yl)methyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one	504.42
268		2-((5-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-3-(trifluoromethyl)pyridin-2-yl)methyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one	572.42

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270		2-(2-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-5-(trifluoromethyl)benzyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one	571.43
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* MS (ESI) m/z (M+H)

TABLE 2: List of abbreviation and meaning used through out this application

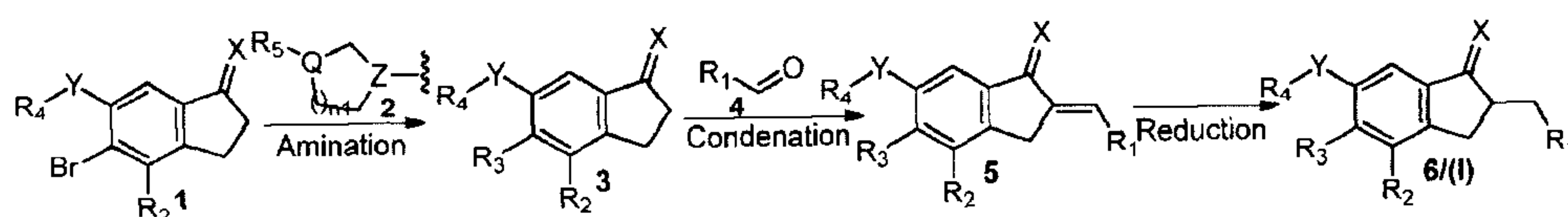
Abbreviation	Meaning
CHCl ₃	Chloroform – CHCl ₃
CDCl ₃	Chloroform deuterated solvent – CDCl ₃
DCM	Dichloromethane – CH ₂ Cl ₂
DME	1,2-Dimethoxyethane
DMF	<i>N,N</i> -Dimethylformamide
DMSO	Dimethylsulfoxide
DMSO-d ₆	Dimethylsulfoxide deuterated solvent
Pd2(pda) ₃	Tris(dibenzylideneacetone)dipalladium(0)
Pd(PH ₃) ₄	Tetrakis(trifluorophosphine)palladium(0)
PTSA	<i>p</i> -Toluene Sulfonic Acid
THF	Tetrahydrofuran
±BINAP	<i>rac</i> 2,2'-Bis(diphenylphosphino)-9,9-dimethylxanthene
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
Pd(dppf)Cl ₂ •CH ₂ Cl ₂	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium II DCM
Et	Ethyl
Me	Methyl
MeOH	Methanol
EtOH	Ethanol
EtOAc	Ethylacetate
AcCN/MeCN	Acetonitrile
DIPEA	Diisopropylethylamine
IP	Isopropanol
Na ₂ CO ₃	Sodium Carbonate
K ₂ CO ₃	Potassium Carbonate
Cs ₂ CO ₃	Cesium Carbonate
TFA	Trifluoroacetic acid
EDC HCl	<i>N</i> -Ethyl- <i>N'</i> -(3-dimethylaminopropyl)carbodiimide HCl
HOBT	1-Hydroxybenzotriazole hydrate
HOAc	Acetic Acid
Et	Ethyl
TMS	Trimethylsilyl
NBS	<i>N</i> -Bromosuccinamide
NCS	<i>N</i> -Chlorosuccinamide
PG	Protecting Group
g, gm	Gram(s)
mg	Milligram(s)
h, hr	Hour
min	Minute(s)

M	Molar, molarity
mM	Millimolar
μ M	Micromolar
nM	Nanomolar
L, l	Liter(s)
mL, mL	Milliliter(s)
μ L	Microliter(s)
RM	Reaction Mixture or Reaction Mass
SM	Starting Material
RT, rt	Room Temperature
HPLC	High-Performance Liquid Chromatography
LCMS	Liquid Chromatography Mass Spectrometry
MS or ms	Mass Spectrometry
NMR	Nuclear Magnetic Resonance Spectroscopy
TLC	Thin Layer Chromatography
UV	Ultra-Violet Spectrometry
s	Singlet
d, Dt, dt	Doublet, doublet of doublet
t, tr	Triplet
m	Multiplet

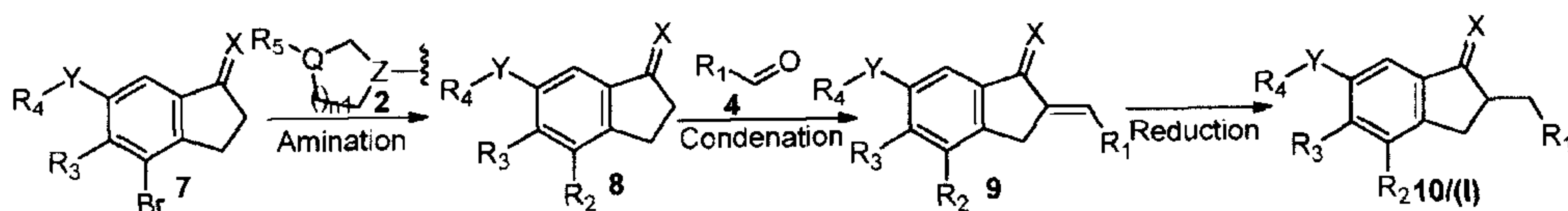
METHODS OF PREPARATION OF COMPOUNDS

In certain embodiments, the Examples below are compounds prepared according to general procedures given in the following sections. Although the synthetic methods and Schemes depict the syntheses of certain compounds of the present invention, the methods and other methods known to one of ordinary skill in the art can be applied to all the compounds of the genus, the genus sub-class and species of each of these compounds as described herein. Aspects of this invention can be understood from the following general Schemes 1 and 2. The following are exemplary and are not intended to limit the scope of the invention.

10 Scheme 1:



Scheme 2:



15

EXAMPLES

Experimental Details and Examples

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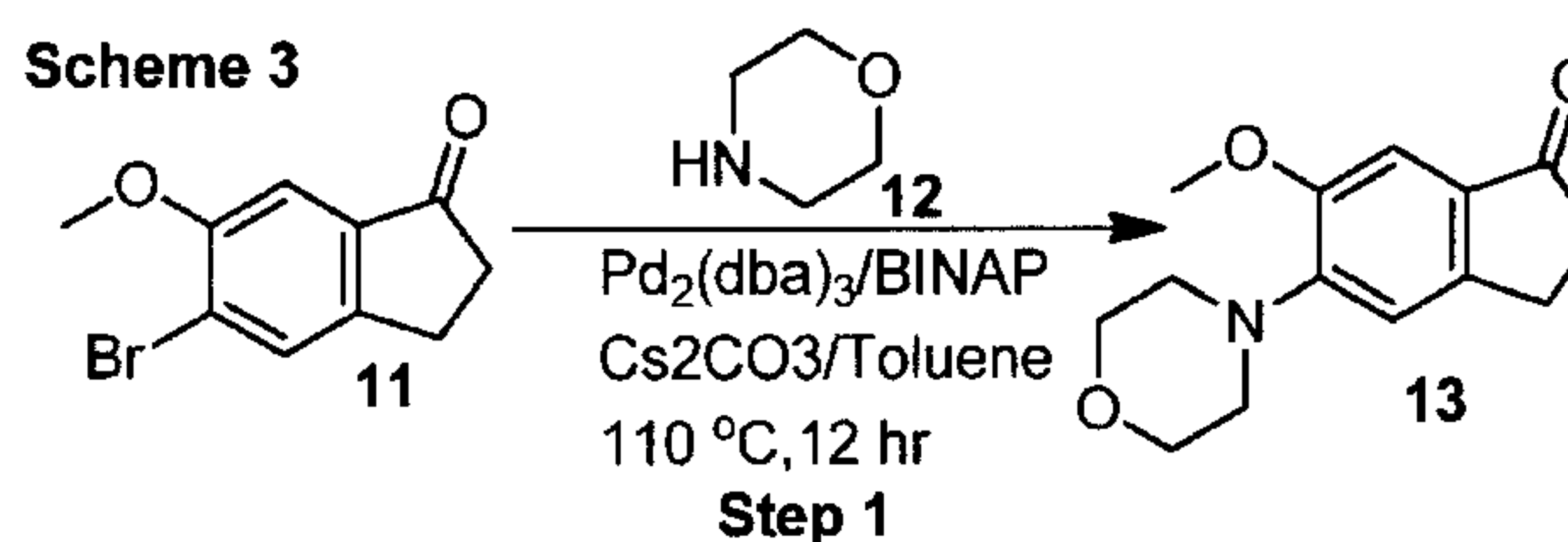
Melting points were determined in a MP-96 digital Polmon apparatus. ^1H NMR and ^{13}C NMR spectra were recorded at RT in CDCl_3 or $\text{DMSO}-d_6$ at Jeol 400-MHz NMR spectrophotometer using solvent peaks for CDCl_3 : 7.27 and $\text{DMSO}-d_6$ 2.50 (D) as internal references. The assignment of chemical shifts is based on standard NMR experiments (^1H , ^{13}C). Mass spectra were recorded on a Shimadzu LCMS LC-210EV spectrometer with an API-ES ionization source. Jasco-FTIR-4100 was used to record the IR spectra. TLC analyses were performed on silica F254 and detection by UV light at 254nm, or by spraying with phosphomolybdic- H_2SO_4 dyeing reagent, KMnO_4 or iodine. Column chromatography were performed on silica Gel 60 (230 mesh). Purifications and separations were performed on a standard silica flash chromatography system. The purity of the samples has been determined by HPLC for the % area peak corresponding to the retention of compound and elemental analysis for C, H, N and O was carried out using Perkin-Elmer 2400 elemental analyser and chloride analysis performed using calorimetric titration at the Intertek USA Inc., QTL.

General synthetic methodology

The compounds of this invention are prepared in general by methods such as those depicted in the Schemes below, and the preparative examples that follow.

PREPARATION OF EXAMPLES

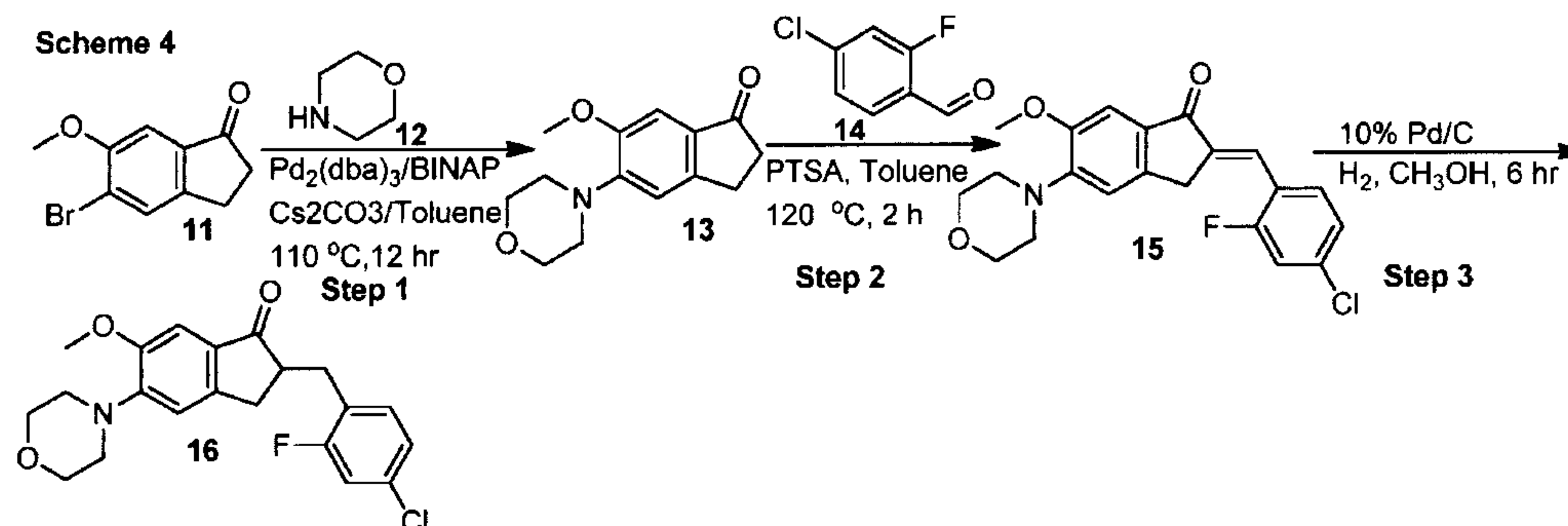
EXAMPLE 1: 6-methoxy-5-morpholino-2, 3-dihydro-1H-inden-1-one (**13**)



Step 1: A solution of 5-bromo-6-methoxy-2,3-dihydro-1H-inden-1-one (**11**) (1g, 4.149mmol) and morpholine (0.36g, 4.149mmol) in toluene 15mL was added cesium carbonate (2.69g, 8.298mmol). The reaction was degassed and purged with nitrogen for 10min. $\text{Pd}_2(\text{dba})_3$ (189.3mg, 0.207mmol) and BINAP (64.5mg, 0.103mmol) was added, degassed and purged and with nitrogen for another 10min. The reaction was heated to 110°C overnight under sealed microwave vial. After completion of the starting material, the reaction was diluted with chloroform and filtered through celite bed. The organic layer was concentrated to get the crude compound **13** and the resulting crude was purified through flash chromatography by using 100-200 mesh silica gel eluting the compound at 25% ethyl acetate in hexane as pale yellow coloured solid 6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one **13**. ^1H NMR (400 MHz, CDCl_3) δ ppm 7.70 (s, 1H), 7.20 (s, 1H), 3.93 (s, 3H), 3.06 (m, 2H), 2.72 (m, 2H); MS (ESI) m/z 247.9 (M+H).

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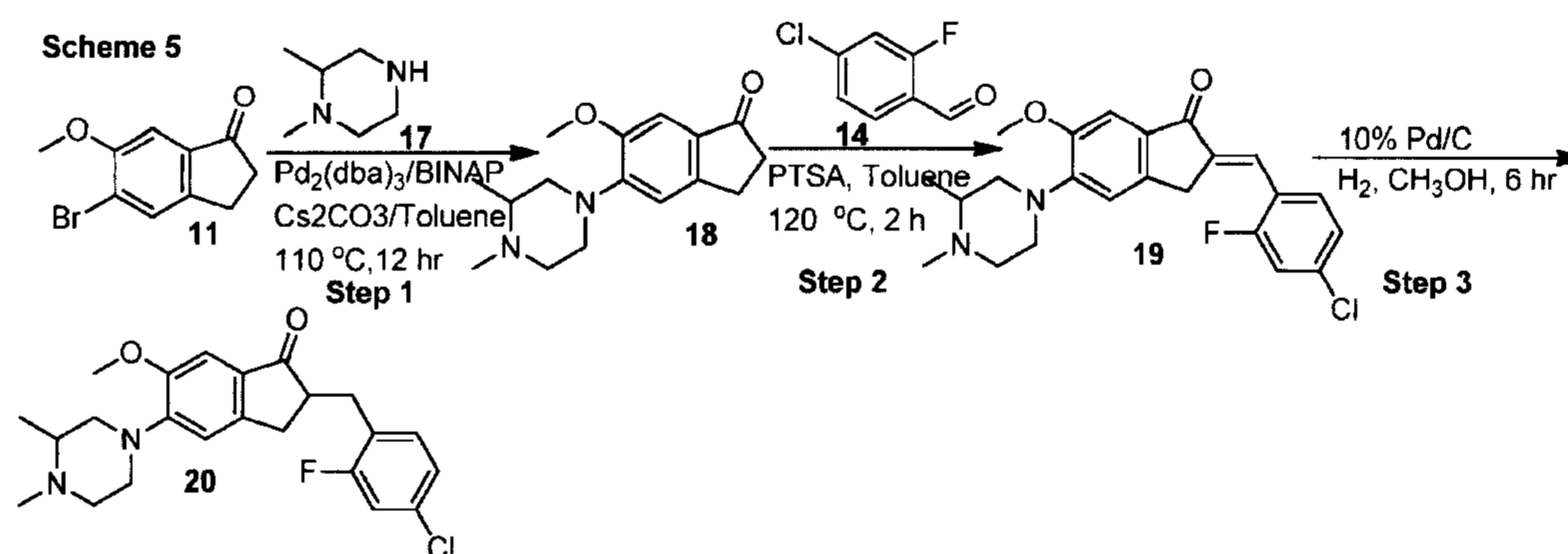
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EXAMPLE 2: 2-(4-chloro-2-fluorobenzyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one (**16**)

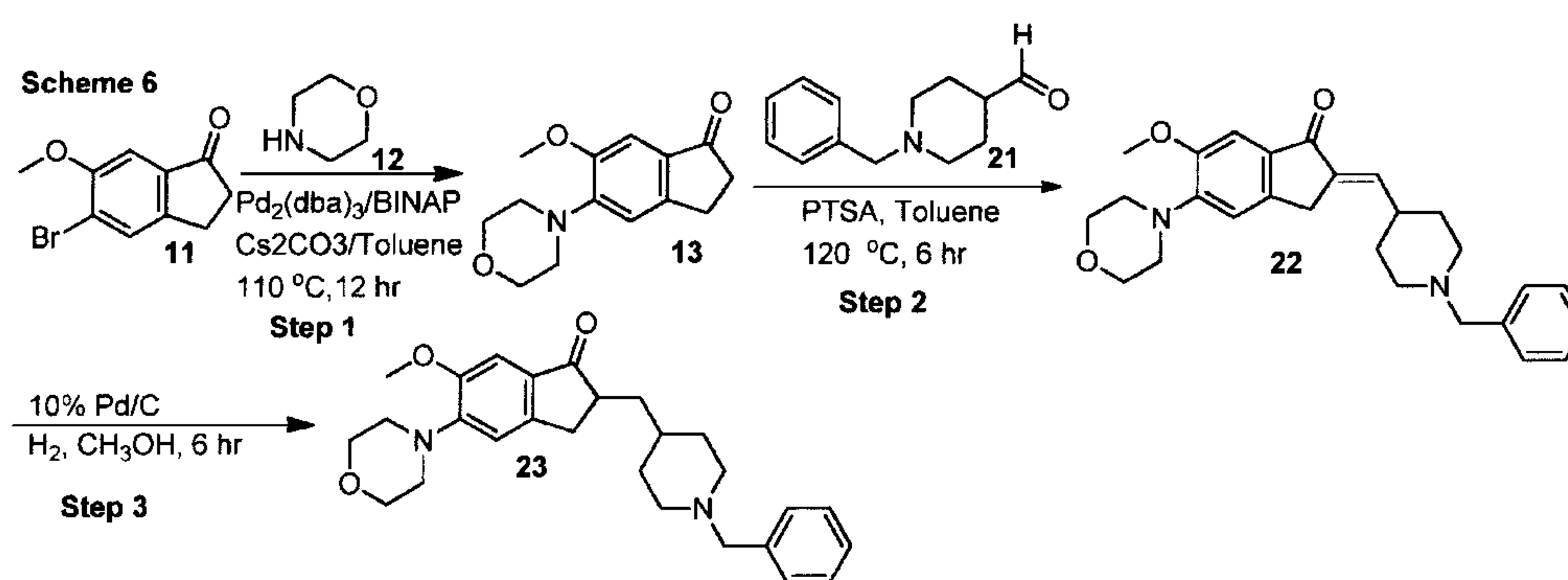
Step 2: To a solution of compound **13** (150mg, 0.607mmol) in toluene 15mL was added **14** (86.2mg, 0.607mmol). *p*-Toluene sulphonic acid (PTSA) (230.9mg, 1.214mmol) was added to the reaction mixture, and stirred at 120°C for 6h. The reaction mass was diluted with ethyl acetate and washed with water (3 x 25mL). The organic layer was dried over sodium sulphate and concentrated to get the crude compound **15**. The crude compound **15** was purified through flash chromatography by using 100-200 mesh silica gel. The compound (E)-2-(4-chloro-2-fluorobenzylidene)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one **15** was eluted at 28% ethyl acetate in hexane to afford a yellow coloured solid.

Step 3: Compound **15** (45mg, 0.121mmol) was dissolved in methanol and was added Pd/C 20mg and stirred the reaction under hydrogen balloon for 6h. The reaction was filtered through celite bed and washed with excess methanol. The organic layer was concentrated to get the crude compound **16**. The crude **16** was purified by flash chromatography using 100-200 mesh silica gel. Compound **16** was eluted at 23 % ethyl acetate in hexane as half white coloured solid 2-(4-chloro-2-fluorobenzyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one **16**. ¹HNMR (400 MHz, CDCl₃) δ ppm 7.18 (m, 2H), 6.82 (m, 3H), 3.88 (m, 3H), 3.86 (m, 4H), 3.31 (m, 1H), 3.16 (m, 4H), 3.06 (m, 1H), 2.95 (m, 1H), 2.73 (m, 2H); MS (ESI) m/z 389.8 (M+H).

EXAMPLE 3: 2-(4-chloro-2-fluorobenzyl)-5-(3,4-dimethylpiperazin-1-yl)-6-methoxy-2,3-dihydro-1H-inden-1-one (**20**)



EXAMPLE 4: 2-((1-benzylpiperidin-4-yl) methyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one (**23**)



5 **Step 1:** To a solution of **13** (150mg, 0.607mmol) in toluene 15mL was added 1-benzylpiperidine-4-carbaldehyde **21** (123.4mg, 0.607mmol). *p*-Toluene sulphonic acid (PTSA) (230.9mg, 1.214mmol) was added to the reaction mixture, and stirred at 120°C for 6h. The reaction mass was diluted with ethyl acetate and washed with water (3 x 25mL). The organic layer was dried over sodium sulphate and concentrated to get the crude material, which was

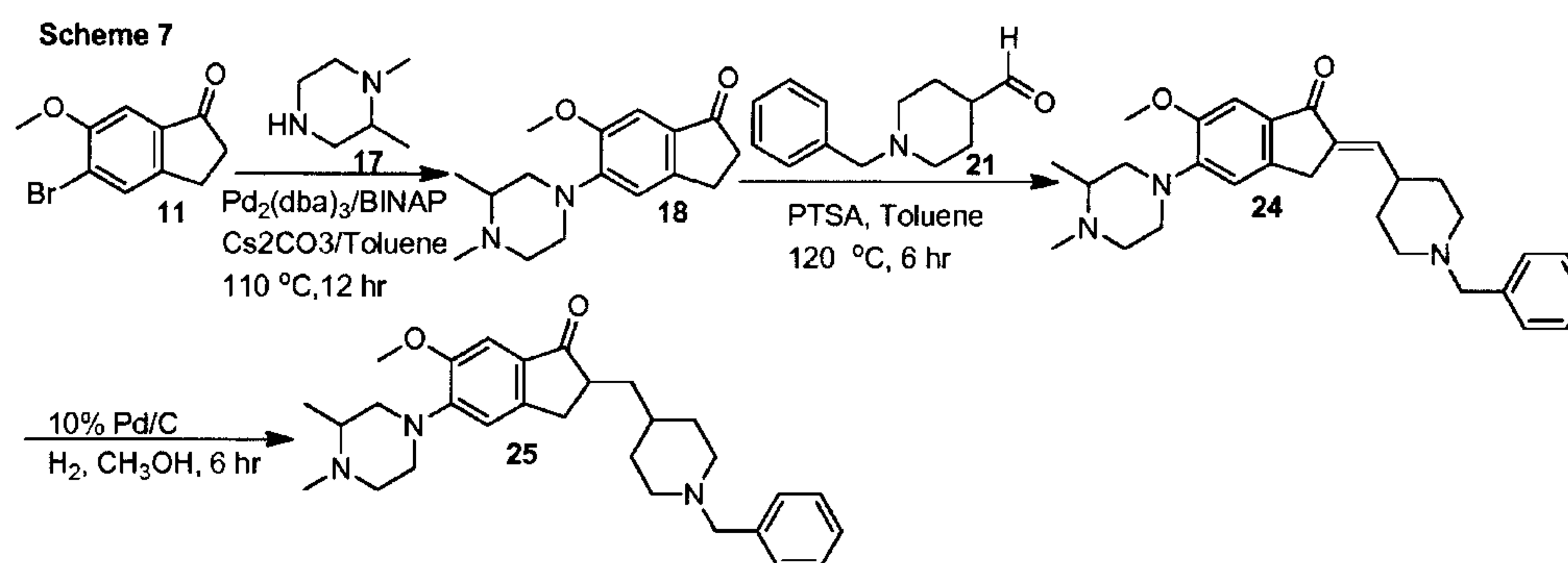
10 purified through flash chromatography using 100-200 mesh silica gel. Eluting at 30% ethyl acetate in hexane gave yellow coloured solid (E)-2-((1-benzylpiperidin-4-yl) methylene)-6-methoxy-5-morpholino-2, 3-dihydro-1H-inden-1-one **22**.

Step 2: Compound **22** (85mg, 0.195mmol) was dissolved in methanol 25mL, added Pd/C 40mg and stirred under hydrogen balloon for 6h. The reaction was filtered through celite

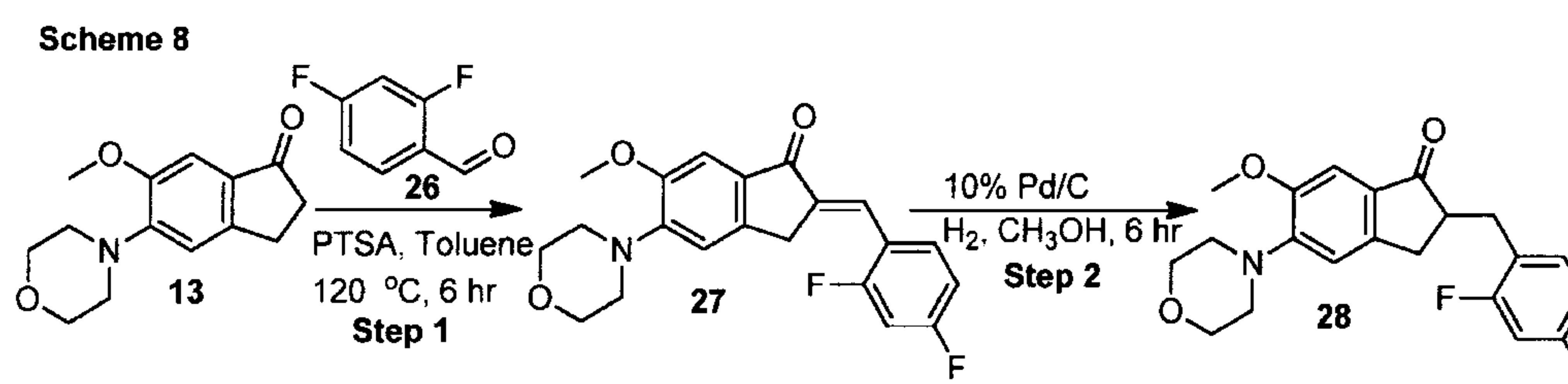
15 bed and washed with excess methanol. The organic layer was concentrated to get the crude compound **23**. The crude material was purified by flash chromatography using 100-200 mesh silica gel. The compound was eluted with 20% ethyl acetate in hexane to give half white coloured solid compound 2-((1-benzylpiperidin-4-yl)methyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one **23**. ^1H NMR (400 MHz, CDCl_3) δ ppm 7.31 (m, 5H), 7.15 (bs, 1H),

20 6.85 (bs, 1H), 3.88 (m, 7H), 3.51 (bs, 2H), 3.22 (m, 4H), 2.90 (m, 2H), 2.65 (m, 2H), 1.90 (m, 3H), 1.64 (m, 2H), 1.58 (bs, 4H); MS (ESI) m/z 435.2 (M+H).

EXAMPLE 5: 2-((1-benzylpiperidin-4-yl) methyl)-5-(3, 4-dimethylpiperazin-1-yl)-6-methoxy-2, 3-dihydro-1H-inden-1-one (**25**)



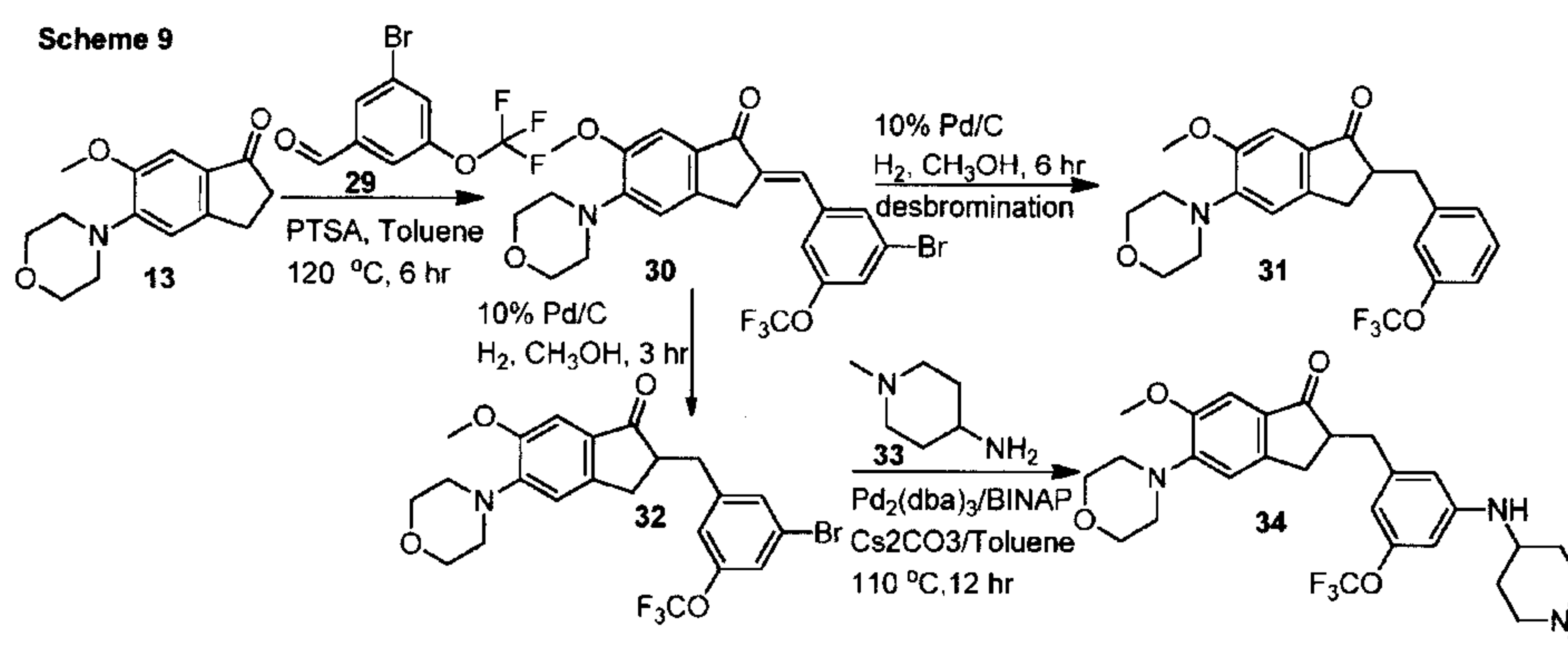
EXAMPLE 6: 2-(2, 4-difluorobenzyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one (**28**)



Step 1: To a solution of compound **13** (150mg, 0.607mmol) in toluene 15mL was added **26** (86.2mg, 0.607mmol), then PTSA (230.9mg, 1.214mmol) was added and stirred at 120°C for 6h. The resulting mixture was diluted with ethyl acetate and washed with water (3 x 25mL). The organic layer was dried over sodium sulphate and concentrated to get the crude compound **27**, which was purified through flash chromatography using 100-200 mesh silica gel. Eluting at 28% ethyl acetate in hexane gave yellow coloured solid compound (E)-2-(2,4-difluorobenzylidene)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one **27**.

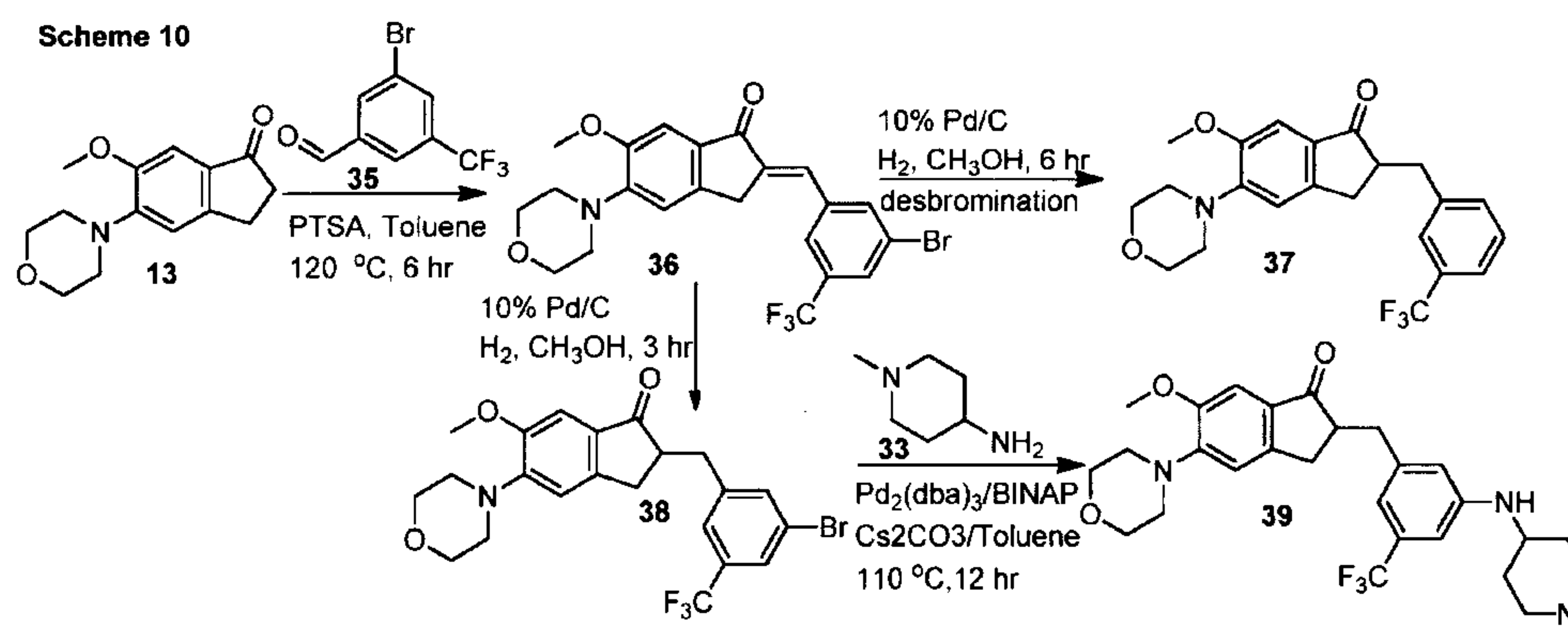
Step 2: To **27** (45mg, 0.121mmol), dissolved in methanol, was added Pd/C 20mg and stirred under hydrogen balloon for 6h. The reaction was filtered through celite bed and washed with excess methanol. The organic layer was concentrated to get the crude, which was purified by flash chromatography using 100-200 mesh silica gel. The compound was eluted at 23 % ethyl acetate in hexane as half white coloured solid compound 2-(2,4-difluorobenzyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one **28**. ¹HNMR (400 MHz, CDCl₃) δ ppm 7.18 (m, 2H), 6.82 (m, 3H), 3.88 (m, 3H), 3.86 (m, 4H), 3.31 (m, 1H), 3.16 (m, 4H), 3.06 (m, 1H), 2.95 (m, 1H), 2.73 (m, 2H); MS (ESI) m/z 373.9 (M+H).

EXAMPLE 7: 6-methoxy-5-morpholino-2-(3-(trifluoromethoxy) benzyl)-2, 3-dihydro-1H-inden-1-one (**31**)



To a solution of compound **13** (150mg, 0.607mmol) in toluene 15mL was added 3-bromo-5-(trifluoromethoxy) benzaldehyde **29** (115.4mg, 0.607mmol). PTSA (230.9mg, 1.214mmol) was added to the reaction mixture, then stirred at 120°C for 6h. The reaction mixture was diluted with ethyl acetate and washed with water (3 x 25mL). The organic layer was dried over sodium sulphate and concentrated to get the crude compound (E)-2-(3-bromo-5-(trifluoromethoxy) benzylidene)-6-methoxy-5-morpholino-2, 3-dihydro-1H-inden-1-one **30**, which was purified through flash chromatography by using 100-200 mesh silica gel. Compound **30** was eluted at 25% ethyl acetate in hexane to afford a yellow coloured solid. To **30** (45mg, 0.107mmol), dissolved in methanol 20mL, was added Pd/C 20mg and stirred under hydrogen balloon for 6h. The reaction was filtered through celite bed and washed with excess methanol. The organic layer was concentrated to get the crude des-brominated compound **31**. The crude **31** was purified by flash chromatography using 100-200 mesh silica gel. Compound **31** was eluted as des-brominated compound at 25% ethyl acetate in hexane as half white coloured solid compound 6-methoxy-5-morpholino-2-(3-(trifluoromethoxy)benzyl)-2,3-dihydro-1H-inden-1-one **31**. ¹HNMR (400 MHz, CDCl₃) δ ppm 7.43 (m, 4H), 7.18 (s, 1H), 6.81 (s, 1H), 3.89 (m, 3H), 3.87 (m, 4H), 3.43 (m, 1H), 3.17 (m, 4H), 3.06 (m, 1H), 2.97 (m, 1H), 2.69 (m, 2H); MS (ESI) m/z 422.1 (M+H).

EXAMPLE 8: 6-methoxy-5-morpholino-2-(3-(trifluoromethyl) benzyl)-2, 3-dihydro-1H-inden-1-one (**37**)



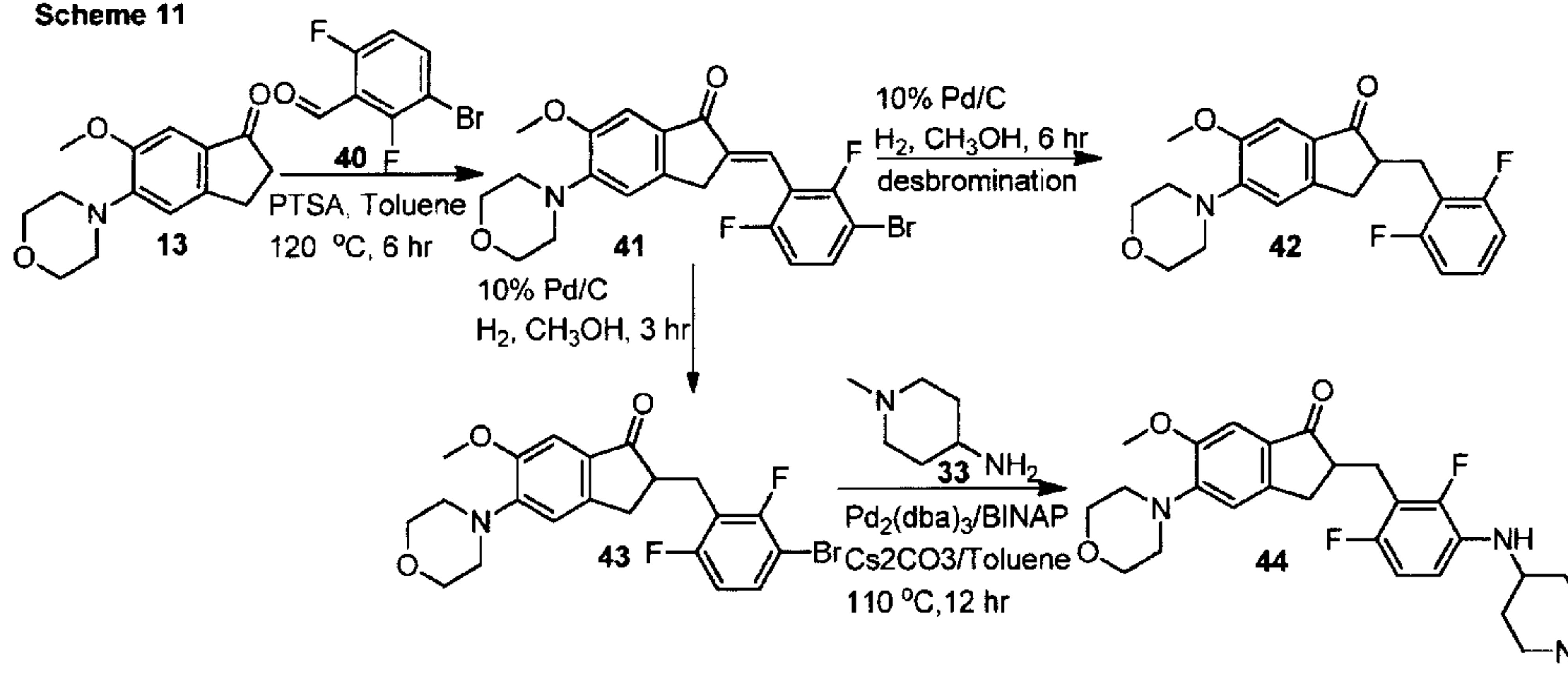
To a solution of **13** (450mg, 1.819mmol) in toluene 10mL was added 3-bromo-5-(trifluoromethyl) benzaldehyde **35** (316.8mg, 1.819mmol). PTSA (692.2mg, 3.639mmol) was added to the reaction mixture, then stirred at 120°C for 6h. The reaction mass was diluted with ethyl acetate and washed with water (3 x 25mL). The organic layer was dried over sodium sulphate and concentrated to get the crude **36**, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound (E)-2-(3-bromo-5-(trifluoromethyl)benzylidene)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one **36** was eluted at 30% ethyl acetate in hexane to afford yellow coloured solid.

The **36** (570mg, 1.413mmol) was dissolved in methanol and was added Pd/C (350mg), and stirred under hydrogen balloon for 6h. The reaction was filtered through celite bed and washed with excess methanol. The organic layer was concentrated to get the crude **37**, which was purified by flash chromatography using 100-200 mesh silica gel. The compound 6-methoxy-5-morpholino-2-(3-(trifluoromethyl)benzyl)-2,3-dihydro-1H-inden-1-one **37** was eluted as des-brominated compound at 28 % ethyl acetate in hexane as half white coloured solid. ¹HNMR (400 MHz, CDCl₃) δ ppm 7.47 (m, 4H), 7.18 (s, 1H), 6.81 (s, 1H), 3.89 (m, 3H), 3.87 (m, 3H), 3.40 (m, 1H), 3.17 (m, 4H), 3.06 (m, 1H), 2.97 (m, 1H), 2.69 (m, 2H); MS (ESI) m/z 406.0 (M+H).

EXAMPLE 9: 2-(2, 6-difluorobenzyl)-6-methoxy-5-morpholino-2, 3-dihydro-1H-inden-1-one

(42)

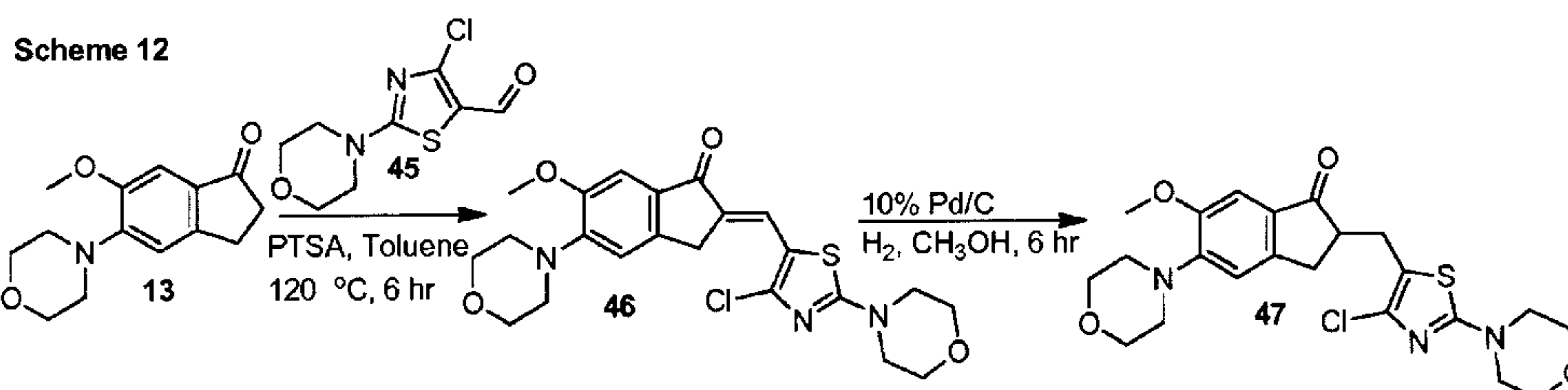
Scheme 11



To a solution of **13** (150mg, 0.607mmol) in toluene 15mL was added 3-bromo-2, 6-difluorobenzaldehyde **40** (81.4mg, 0.607mmol) and subsequently PTSA (230.9mg, 1.214mmol) was added, and stirred at 120°C for 6h. The reaction mass was diluted with ethyl acetate and washed with water (3 x 25mL). The organic layer was dried over sodium sulphate and concentrated to get the crude compound **41**. The crude **41** was purified through flash chromatography by using 100-200 mesh silica gel. The compound (E)-2-(3-bromo-2,6-difluorobenzylidene)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one **41** was eluted at 32% ethyl acetate in hexane to afford yellow coloured solid.

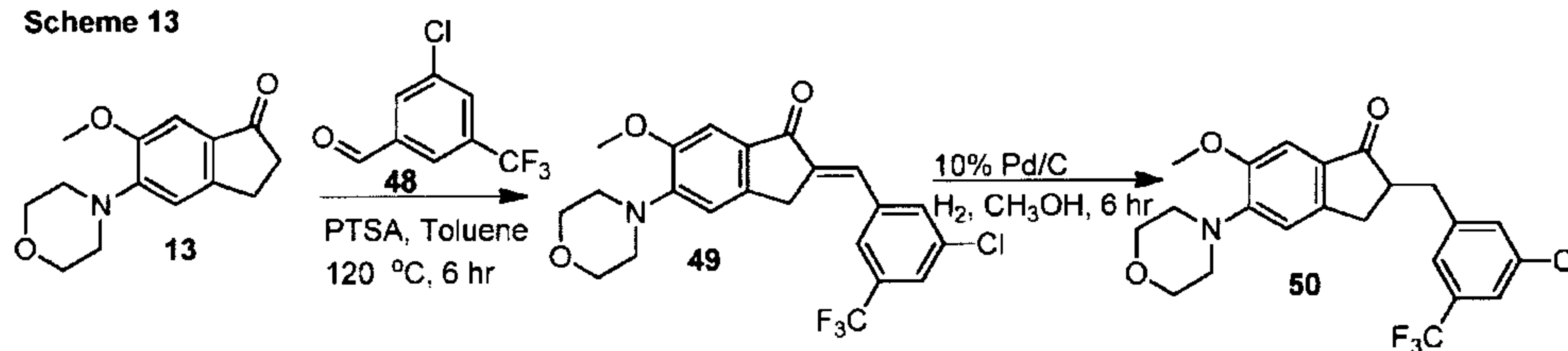
The **41** (40mg, 0.088mmol) was dissolved in methanol 15mL and added Pd/C 20mg and stirred under hydrogen balloon for 6h. The reaction was filtered through elite bed and washed with excess methanol. The organic layer was concentrated to get the crude compound **42**, which was purified by flash chromatography using 100-200 mesh silica gel. The compound 2-(2,6-difluorobenzyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one **42** was eluted as des-brominated compound at 26 % ethyl acetate in hexane as half white coloured solid. ¹HNMR (400 MHz, CDCl₃) δ ppm 7.17 (m, 2H), 6.89 (m, 3H), 3.89 (m, 7H), 3.35 (m, 1H), 3.19 (m, 4H), 3.06 (m, 2H), 2.76 (m, 2H); MS (ESI) m/z 374.0 (M+H).

EXAMPLE 10: 2-((4-chloro-2-morpholinothiazol-5-yl) methyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one (**47**)



EXAMPLE 11: 2-(3-chloro-5-(trifluoromethyl) benzyl)-6-methoxy-5-morpholino-2, 3-dihydro-1H-inden-1-one (**50**)

Scheme 13

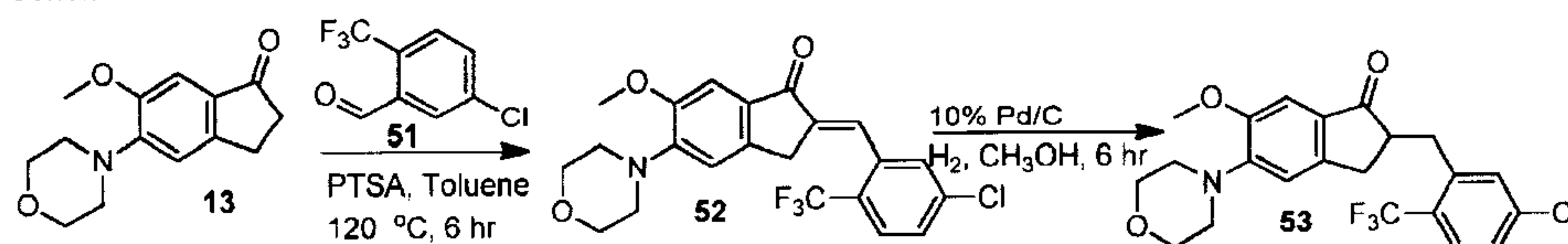


To a solution of **13** (100mg, 0.404mmol) in toluene 5mL was added 3-chloro-5-(trifluoromethyl) benzaldehyde **48** (84.4mg, 0.404mmol). PTSA (153.9mg, 0.809mmol) was added to the reaction mass, then stirred at 120°C for 6h. The reaction mass was diluted with ethyl acetate and washed with water (3 x 25mL). The organic layer was dried over sodium sulphate and concentrated to get the crude compound **49**, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound (E)-2-(3-chloro-5-(trifluoromethyl)benzylidene)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one **49** was eluted at 35 % ethyl acetate in hexane to afford yellow coloured solid.

The **49** (30mg, 0.068mmol) was dissolved in methanol 20mL, Pd/C 10mg added and stirred under hydrogen balloon for 6h. The reaction was filtered through celite bed and washed with excess methanol. The organic layer was concentrated to get the crude compound **50**. The crude **50** was purified by flash chromatography using 100-200 mesh silica gel. The compound 2-(3-chloro-5-(trifluoromethyl)benzyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one **50** was eluted at 28 % ethyl acetate in hexane as half white coloured solid. ¹HNMR (400 MHz, CDCl₃) δ ppm 7.43 (m, 3H), 7.18 (s, 1H), 6.82 (s, 1H), 3.90 (m, 3H), 3.87(m, 4H), 3.37(m, 1H), 3.17(m, 4H), 3.09 (m, 1H), 2.96 (m, 1H), 2.70 (m, 2H); MS (ESI) m/z 440.0 (M+H).

EXAMPLE 12: 2-(5-chloro-2-(trifluoromethyl) benzyl)-6-methoxy-5-morpholino-2, 3-dihydro-1H-inden-1-one (**53**)

Scheme 14



To a solution of **13** (100mg, 0.404mmol) in toluene 5mL was added 5-chloro-2-(trifluoromethyl) benzaldehyde **51** (84.4mg, 0.404mmol) and PTSA (153.9mg, 0.809mmol). The reaction was stirred at 120°C for 6h. The reaction mixture was diluted with ethyl acetate and washed with water (3 x 25mL). The organic layer was dried over sodium sulphate and concentrated to get the crude compound **52**. The crude **52** was purified through flash chromatography by using 100-200 mesh silica gel. The compound (E)-2-(5-chloro-2-(trifluoromethyl)benzylidene)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one **52** was eluted at 28% ethyl acetate in hexane to afford yellow coloured solid.

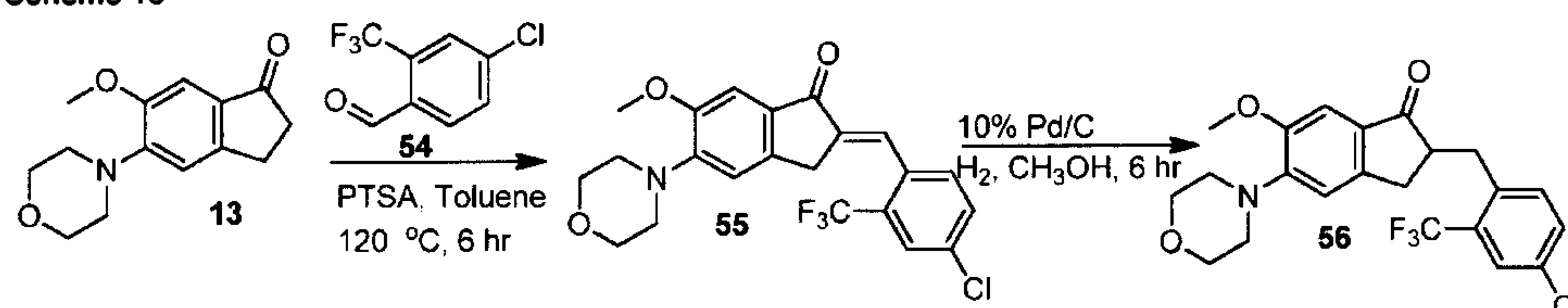
WO 2015/038350

PCT/US2014/053227

Compound **52** (50mg, 0.114mmol) was dissolved in methanol 30mL, Pd/C 17mg added and the reaction stirred under hydrogen balloon for 6h. The reaction was filtered through celite bed and washed with excess methanol. The organic layer was concentrated to get the crude, which was purified by flash chromatography using 100-200 mesh silica gel. The compound **53** was eluted at 24% ethyl acetate in hexane as half white coloured solid compound 2-(5-chloro-2-(trifluoromethyl)benzyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one **53**. ¹HNMR (400 MHz, CDCl₃) δ ppm 7.43 (m, 3H), 7.18 (s, 1H), 6.82 (s, 1H), 3.90 (m, 3H), 3.87 (m, 4H), 3.48 (d, 1H), 3.38 (m, 1H), 3.17 (m, 4H), 3.09 (m, 1H), 2.95 (m, 1H), 2.67 (m, 2H); MS (ESI) m/z 440.0 (M+H).

EXAMPLE 13: 2-(4-chloro-2-(trifluoromethyl) benzyl)-6-methoxy-5-morpholino-2, 3-dihydro-1H-inden-1-one (**56**)

Scheme 15

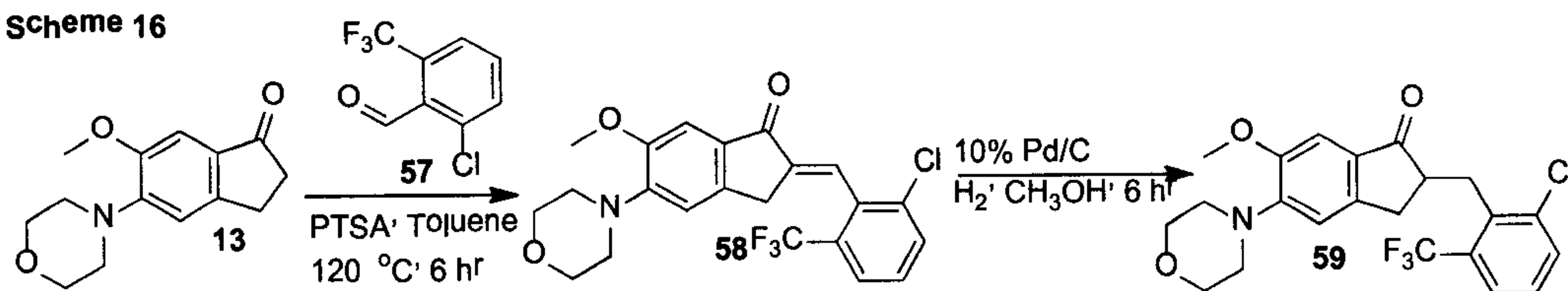


To a solution of **13** (100mg, 0.404mmol) in toluene 5mL was added compound 4-chloro-2-(trifluoromethyl)benzaldehyde **54** (84.4mg, 0.404mmol). PTSA (153.9mg, 0.809mmol) was added to the reaction mass and stirred at 120°C for 6h. The reaction mass was diluted with ethyl acetate and washed with water (3 x 25mL). The organic layer was dried over sodium sulphate and concentrated to get the crude compound **55**, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound **55** was eluted at 28% ethyl acetate in hexane to afford a yellow coloured solid.

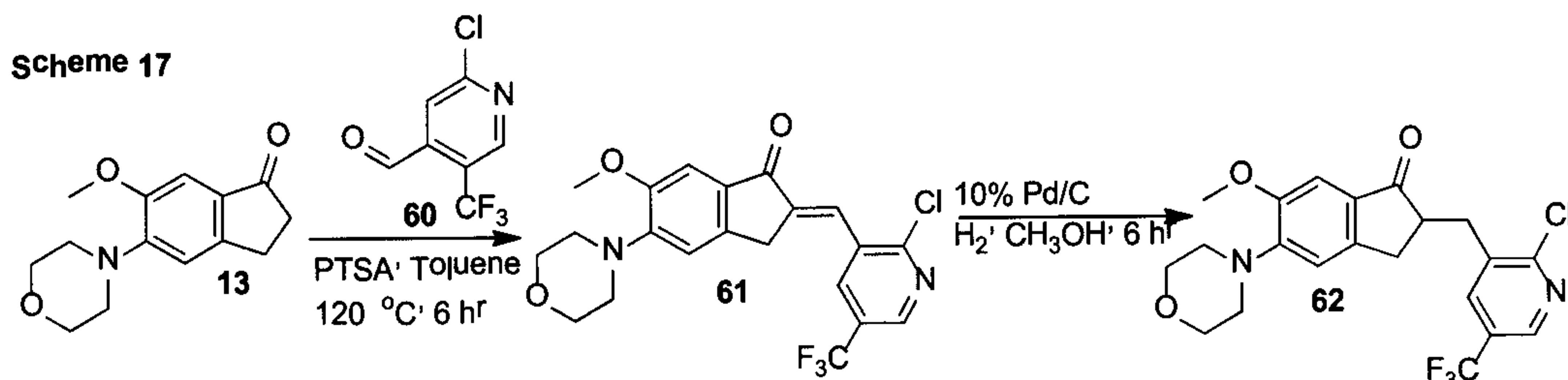
Compound **55** (40mg, 0.104mmol) was dissolved in methanol 30mL, Pd/C 14mg added and the reaction stirred under hydrogen balloon for 6h. The reaction was filtered through celite bed and washed with excess methanol. The organic layer was concentrated to get the crude **56**. Which was purified by flash chromatography using 100-200 mesh silica gel. The compound was eluted at 24% ethyl acetate in hexane as half white coloured solid 2-(4-chloro-2-(trifluoromethyl)benzyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one **56**. ¹HNMR (400 MHz, CDCl₃) δ ppm 7.64 (m, 1H), 7.44 (m, 2H), 7.19 (m, 2H), 6.81 (s, 1H), 4.00 (bs, 2H), 3.48 (d, 1H), 3.89 (m, 7H), 3.48 (m, 4H), 3.17 (m, 5H), 2.90 (m, 1H), 2.64 (m, 1H).

EXAMPLE 14: 2-(2-chloro-6-(trifluoromethyl) benzyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one (**59**)

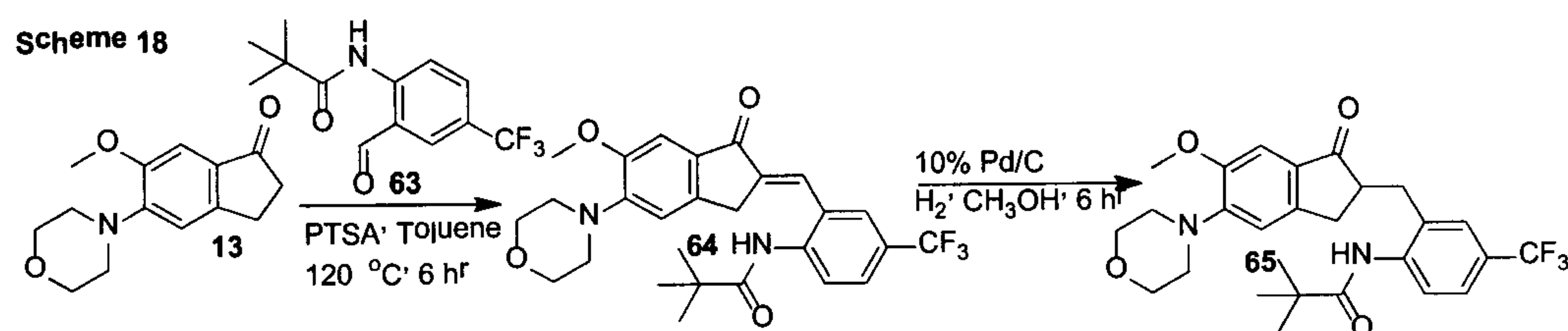
Scheme 16



EXAMPLE 15: 2-((2-chloro-5-(trifluoromethyl) pyridin-3-yl) methyl)-6-methoxy-5-morpholino-2, 3-dihydro-1H-inden-1-one (**62**)

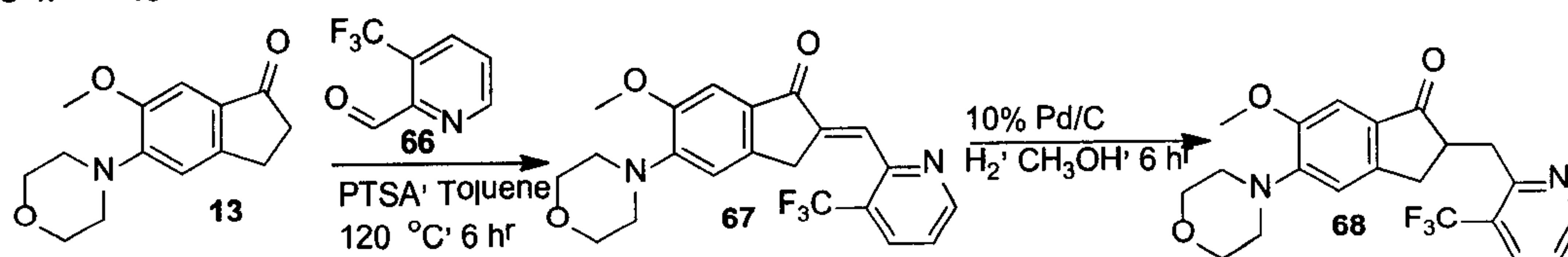


EXAMPLE 16: N-(2-((6-methoxy-5-morpholino-1-oxo-2, 3-dihydro-1H-inden-2-yl) methyl)-4-(trifluoromethyl) phenyl) pivalamide (**65**)



EXAMPLE 17: 6-methoxy-5-morpholino-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-2,3-dihydro-1H-inden-1-one (**68**)

Scheme 19



To a solution of **13** (250mg, 1.010mmol) in toluene 10mL was added 3-(trifluoromethyl)picolinaldehyde (177.0mg, 1.010mmol). PTSA (384.5mg, 2.021mmol) was added to the reaction mixture and stirred at 120°C for 6h. The reaction mass was diluted with ethyl acetate and washed with water (3 x 25mL). The organic layer was dried over sodium sulphate and concentrated to get the crude compound (E)-6-methoxy-5-morpholino-2-((3-(trifluoromethyl)pyridin-2-yl)methylene)-2,3-dihydro-1H-inden-1-one **67**. The compound **67** was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 34% ethyl acetate in hexane to afford yellow coloured solid.

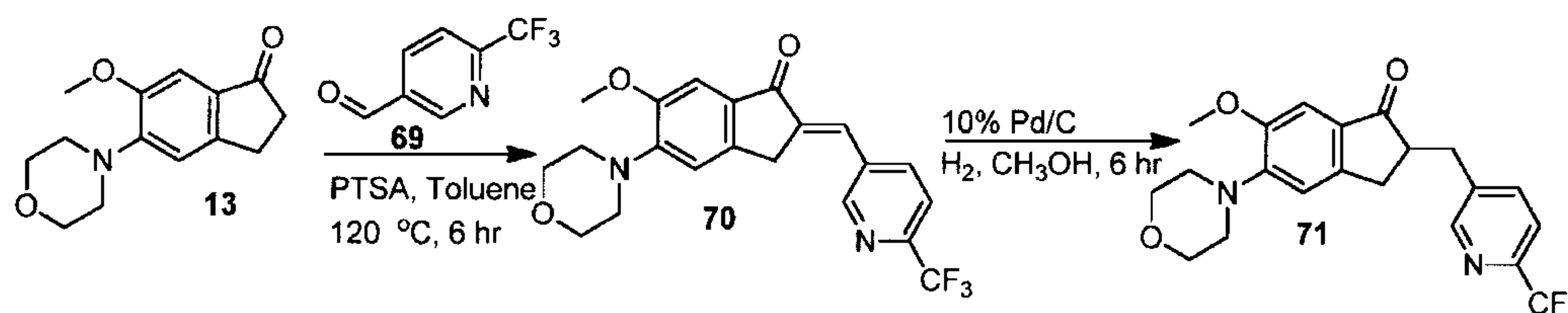
Compound **67** (80mg, 0.197mmol) was dissolved in methanol 15mL, Pd/C 50mg added, and the reaction stirred under hydrogen balloon for 6h. The reaction was filtered through

celite bed and washed with excess methanol. The organic layer was concentrated to get the crude. The crude was purified by flash chromatography using 100-200 mesh silica gel. The compound was eluted at 26 % ethyl acetate in hexane as half white coloured solid compound **68**.

¹HNMR (400 MHz, CDCl₃) δ ppm 8.64 (d, 1H), 7.91 (d, 1H), 7.22 (d, 2H), 6.83 (s, 1H), 3.89 (m, 7H), 3.65 (dd, 1H), 3.44 (m, 1H), 3.16 (m, 6H), 2.72 (dd, 1H); MS (ESI) m/z 407.0 (M+H).

EXAMPLE 18: 6-methoxy-5-morpholino-2-((6-(trifluoromethyl) pyridin-3-yl) methyl)-2,3-dihydro-1H-inden-1-one (**71**)

Scheme 20

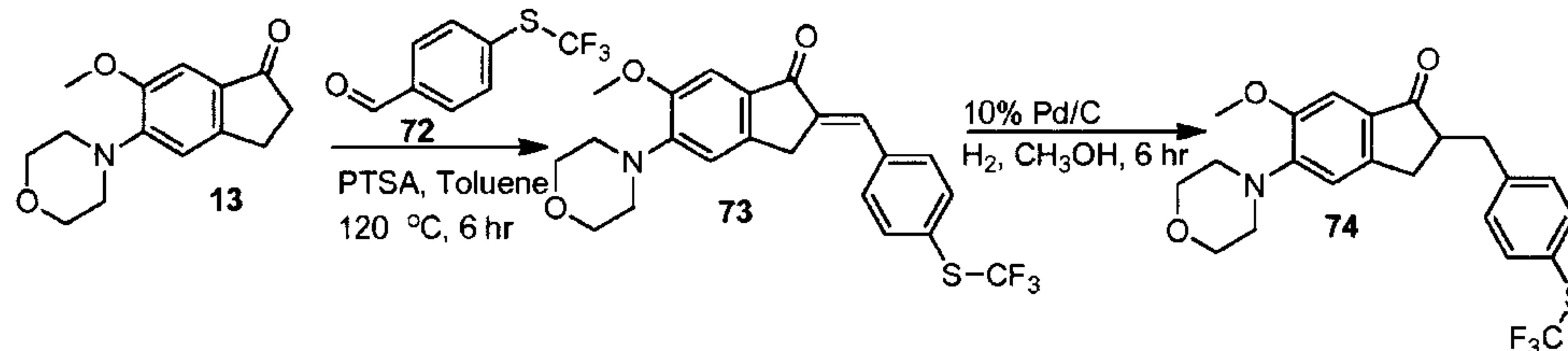


To a solution of **13** (100mg, 0.404mmol) in toluene 5ml was added 6-(trifluoromethyl) nicotinaldehyde **69** (70.8mg, 0.404mmol). PTSA (154mg, 0.808mmol) was added, and the reaction mixture stirred at 120°C for 6h. The reaction mass was diluted with ethyl acetate and washed with water (3 x 25mL). The organic layer was dried over sodium sulphate and concentrated to get the crude compound (E)-6-methoxy-5-morpholino-2-((6-(trifluoromethyl)pyridin-3-yl)methylene)-2,3-dihydro-1H-inden-1-one **70**. The crude **70** was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 32 % ethyl acetate in hexane to afford yellow coloured solid **70**.

Compound **70** (55mg, 0.136mmol) was dissolved in methanol 20mL, Pd/C 35mg added, and the reaction stirred under hydrogen balloon for 6h. The reaction was filtered through celite bed and washed with excess methanol. The organic layer was concentrated to get the crude compound **71**. The crude **71** was purified by flash chromatography using 100-200 mesh silica gel. The compound was eluted at 28 % ethyl acetate in hexane as half white coloured solid compound 6-methoxy-5-morpholino-2-((6-(trifluoromethyl)pyridin-3-yl)methyl)-2,3-dihydro-1H-inden-1-one **71**. ¹HNMR (400 MHz, CDCl₃) δ ppm 8.61 (s, 1H), 7.74 (d, 1H), 7.59 (d, 1H), 7.17 (s, 1H), 6.80 (s, 1H), 3.89 (m, 3H), 3.86 (m, 4H), 3.39 (dd, 1H), 3.17 (m, 4H), 3.11 (m, 1H), 2.98 (m, 1H), 2.83 (m, 1H), 2.71 (m, 1H); MS (ESI) m/z 407.0 (M+H).

EXAMPLE 19: 6-methoxy-5-morpholino-2-(4-((trifluoromethyl) thio) benzyl)-2, 3-dihydro-1H-inden-1-one (**74**)

Scheme 21

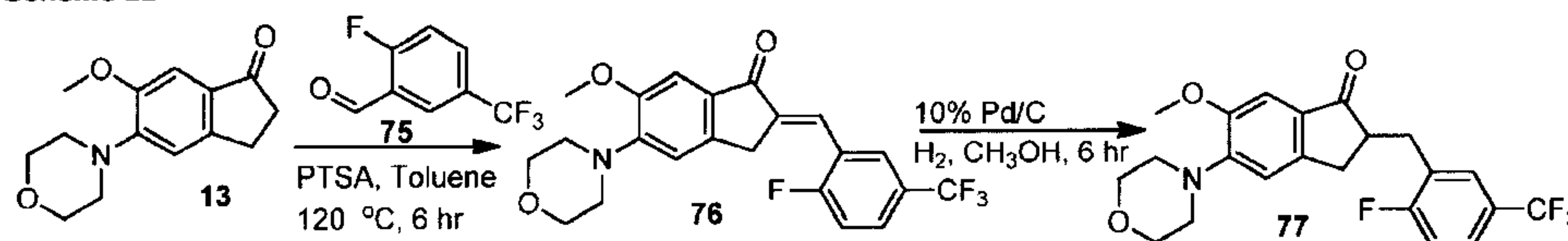


To a solution of **13** (1.2g, 4.858mmol) in toluene 40mL was added 4-((trifluoromethyl)thio)benzaldehyde **72** (1g, 4.858mmol). PTSA (1.84g, 9.716mmol) was added and the reaction mixture was stirred at 120°C for 6h. The reaction mass was diluted with ethyl acetate and washed with water (3 x 25mL). The organic layer was dried over sodium sulphate and concentrated to get the crude compound **73**, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound (E)-6-methoxy-5-morpholino-2-(4-((trifluoromethyl)thio)benzylidene)-2,3-dihydro-1H-inden-1-one **73** was eluted at 37 % ethyl acetate in hexane to afford yellow coloured solid.

Compound **73** (1.0 g, 2.296mmol) was dissolved in methanol 250mL, Pd/C 400mg was added, and the reaction was stirred under hydrogen balloon for 6h. The result was filtered through celite bed and washed with excess methanol. The organic layer was concentrated to get the crude compound **74**, which was purified by flash chromatography using 100-200 mesh silica gel. The compound was eluted at 30 % ethyl acetate in hexane as half white coloured solid 6-methoxy-5-morpholino-2-(4-((trifluoromethyl)thio)benzyl)-2,3-dihydro-1H-inden-1-one **74**. ¹HNMR (400 MHz, CDCl₃) δ ppm 7.56 (d, 2H), 7.28 (d, 2H), 7.18 (s, 1H), 6.81 (s, 1H), 3.89 (m, 3H), 3.87 (m, 4H), 3.37 (dd, 1H), 3.15 (m, 4H), 3.06 (m, 1H), 2.96 (m, 1H), 2.66 (m, 2H); MS (ESI) m/z 438.0 (M+H).

EXAMPLE 20: 2-(2-fluoro-5-(trifluoromethyl) benzyl)-6-methoxy-5-morpholino-2, 3-dihydro-1H-inden-1-one (**77**)

Scheme 22

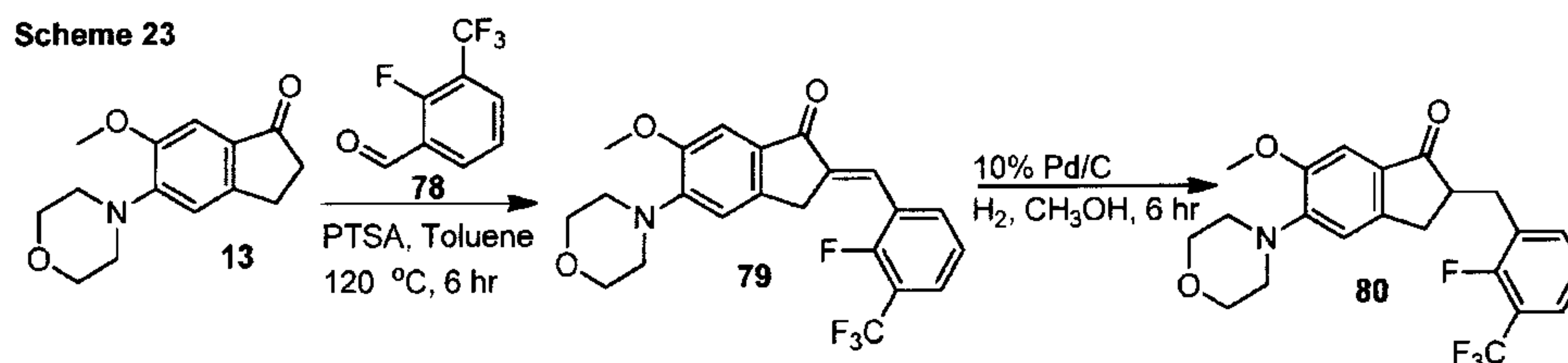


To a solution of **13** (100mg, 0.404mmol) in toluene 10mL was added 2-fluoro-5-(trifluoromethyl) benzaldehyde **75** (77.7mg, 0.404mmol). PTSA (153.8mg, 0.809mmol) was added and the reaction mixture stirred at 120°C for 6h. The reaction mass was diluted with ethyl acetate and washed with water (3 x 25mL). The organic layer was dried over sodium sulphate and concentrated to get the crude compound **76** which was purified through flash chromatography by using 100-200 mesh silica gel. The compound (E)-2-(2-fluoro-5-

(trifluoromethyl)benzylidene)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one **76** was eluted at 34 % ethyl acetate in hexane to afford yellow coloured solid.

Compound **76** (50mg, 0.118mmol) was dissolved in methanol 20mL, Pd/C 30.6mg added, and the reaction stirred under hydrogen balloon for 6h. The result was filtered through
 5 celite bed and washed with excess methanol. The organic layer was concentrated to get the crude which was purified by flash chromatography using 100-200 mesh silica gel. The compound was eluted at 26 % ethyl acetate in hexane as half white coloured solid compound 2-(2-fluoro-5-(trifluoromethyl)benzyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one **77**. ¹HNMR (400 MHz, CDCl₃) δ ppm 7.51 (dd, 1H), 7.48 (m, 1H), 7.15 (m, 2H), 6.82 (s, 1H), 3.89 (m, 3H),
 10 3.87 (m, 4H), 3.40 (m, 1H), 3.17 (m, 4H), 3.11 (m, 1H), 3.02 (m, 1H), 2.70 (m, 2H); MS (ESI) m/z 424.0 (M+H).

EXAMPLE 21: 2-(2-fluoro-5-(trifluoromethyl) benzyl)-6-methoxy-5-morpholino-2, 3-dihydro-1H-inden-1-one (**80**)



To a solution of **13** (100mg, 0.404mmol) in toluene 10mL was added 2-fluoro-3-(trifluoromethyl) benzaldehyde **78** (77.7mg, 0.404mmol). PTSA (153.8mg, 0.809mmol) was added to the reaction mixture and stirred at 120°C for 6h. The reaction mass was diluted with ethyl acetate and washed with water (3 x 25mL). The organic layer was dried over sodium sulphate and concentrated to get the crude compound **79** which was purified through flash
 20 chromatography by using 100-200 mesh silica gel. The compound (E)-2-(2-fluoro-3-(trifluoromethyl)benzylidene)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one **79** was eluted at 34 % ethyl acetate in hexane to afford yellow coloured.

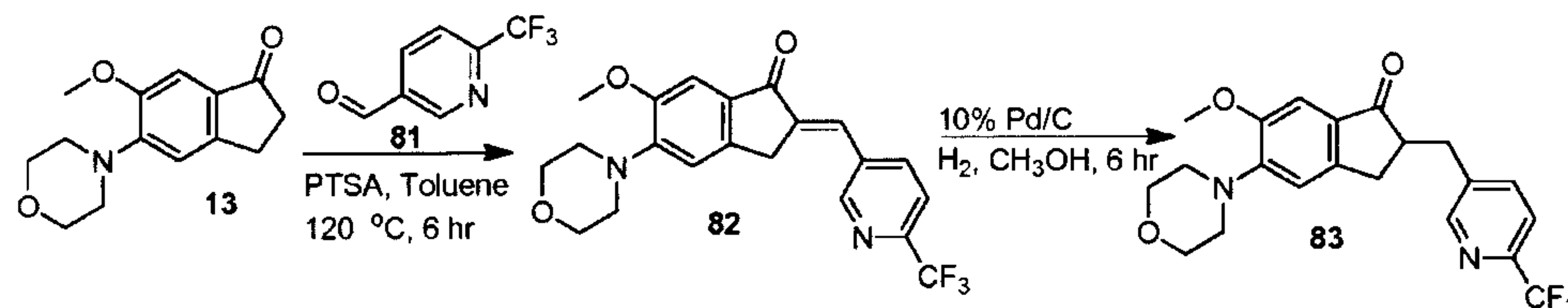
Compound **79** (40mg, 0.094mmol) was dissolved in methanol 15mL, Pd/C 25mg, added, and the reaction stirred under hydrogen balloon for 6h. The reaction was filtered through
 25 celite bed and washed with excess methanol. The organic layer was concentrated to get the crude **80** which was purified by flash chromatography using 100-200 mesh silica gel. The compound was eluted at 30 % ethyl acetate in hexane as half white coloured solid compound 2-(2-fluoro-3-(trifluoromethyl)benzyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one **80**. ¹HNMR (400 MHz, CDCl₃) δ ppm 7.48 (m, 2H), 7.33 (m, 1H), 7.15 (m, 1H), 6.82 (s, 1H), 3.88 (m, 3H),
 30 3.86 (m, 4H), 3.47 (dd, 1H), 3.14 (m, 4H), 3.08 (m, 1H), 2.83 (m, 1H), 2.55 (m, 2H); MS (ESI) m/z 424.0 (M+H).

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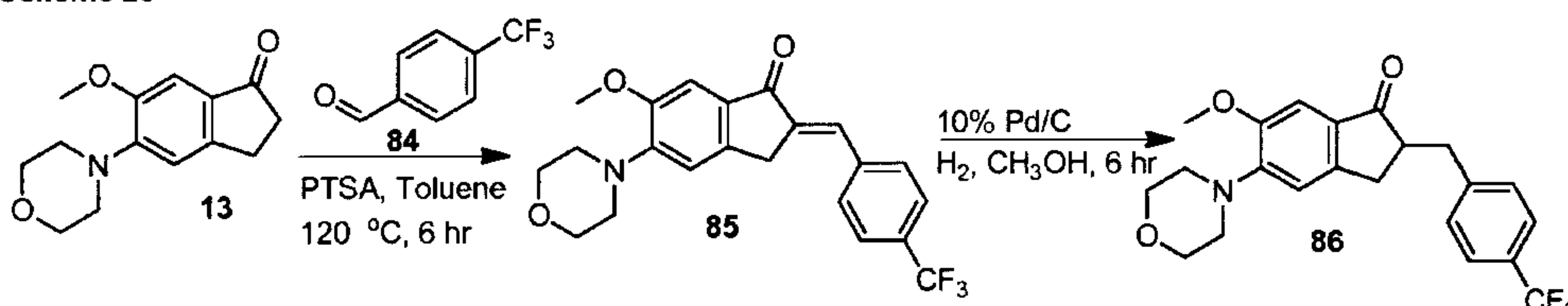
EXAMPLE 22: 6-methoxy-5-morpholino-2-((6-(trifluoromethyl) pyridin-3-yl) methyl)-2, 3-dihydro-1H-inden-1-one (**83**)

Scheme 24



EXAMPLE 23: 6-methoxy-5-morpholino-2-(4-(trifluoromethyl) benzyl)-2, 3-dihydro-1H-inden-1-one (**86**)

Scheme 25

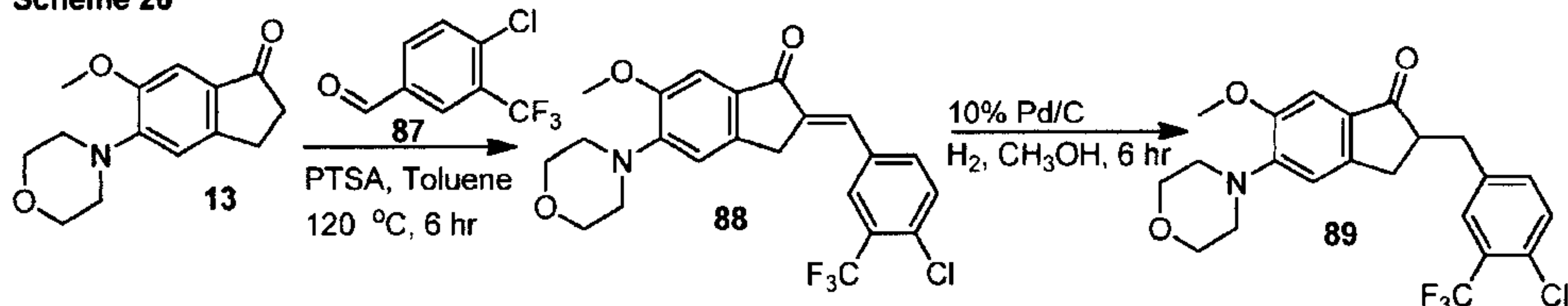


To a solution of **13** (100mg, 0.4048mmol) in toluene 10mL was added 4-(trifluoromethyl) benzaldehyde **84** (70.4mg, 0.404mmol). PTSA (153.9mg, 0.809mmol) was added to the reaction mass, then stirred at 120°C for 6h. The reaction mass was diluted with ethyl acetate and washed with water (3 x 25mL). The organic layer was dried over sodium sulphate and concentrated to get the crude **85** which was purified through flash chromatography by using 100-200 mesh silica gel. The compound **85** was eluted at 28 % ethyl acetate in hexane to afford yellow coloured solid compound (E)-6-methoxy-5-morpholino-2-(4-(trifluoromethyl)benzylidene)-2,3-dihydro-1H-inden-1-one **85**.

The **85** (50mg, 0.123mmol) was dissolved in methanol 20mL, Pd/C 20mg added, and the reaction stirred under hydrogen balloon for 6h, then filtered through celite bed and washed with excess methanol. The organic layer was concentrated to get the crude **86** which was purified by flash chromatography using 100-200 mesh silica gel. The compound **86** was eluted at 25 % ethyl acetate in hexane as half white coloured solid compound 6-methoxy-5-morpholino-2-(4-(trifluoromethyl)benzyl)-2,3-dihydro-1H-inden-1-one **86**. ¹HNMR (400 MHz, CDCl₃) δ ppm 7.53 (d, 2H), 7.34 (d, 2H), 7.18 (s, 1H), 6.80 (s, 1H), 3.89 (m, 3H), 3.86 (m, 4H), 3.38 (m, 1H), 3.15 (m, 4H), 3.08 (m, 1H), 2.96 (m, 1H), 2.68 (m, 2H); MS (ESI) m/z 406.0 (M+H).

EXAMPLE 24: 2-(4-chloro-3-(trifluoromethyl) benzyl)-6-methoxy-5-morpholino-2, 3-dihydro-1H-inden-1-one (**89**)

Scheme 26

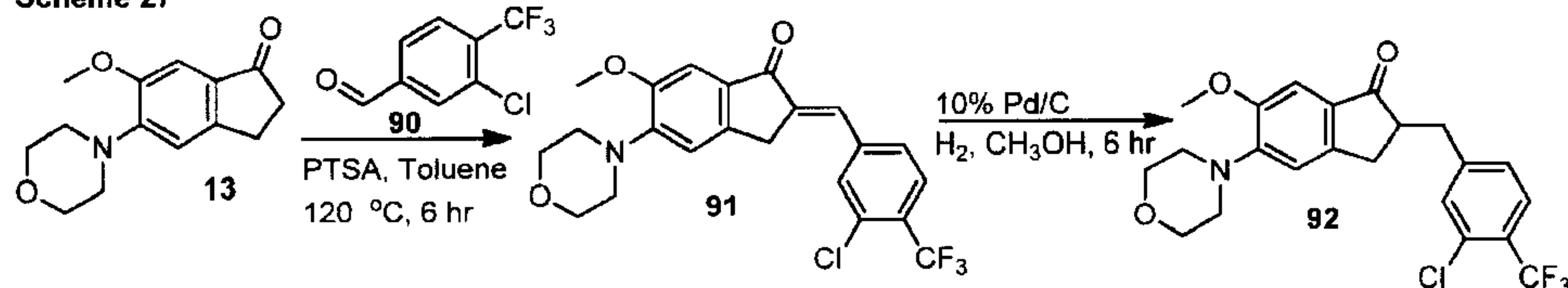


To a solution of **13** (100mg, 0.404mmol) in toluene 10mL was added 4-chloro-3-(trifluoromethyl) benzaldehyde **87** (84.4mg, 0.404mmol). PTSA (153.8mg, 0.808mmol) was added and the reaction was stirred at 120°C for 6h. The reaction mass was diluted with ethyl acetate and washed with water (3 x 25mL). The organic layer was dried over sodium sulphate and concentrated to get the crude **88** which was purified through flash chromatography by using 100-200 mesh silica gel. The compound (E)-2-(4-chloro-3-(trifluoromethyl)benzylidene)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one **88** was eluted at 31 % ethyl acetate in hexane to afford yellow coloured solid.

The **88** (65mg, 0.148mmol) was dissolved in ethyl acetate 50mL, Pd/C 15mg added, and the reaction stirred under hydrogen balloon for 6h, then filtered through celite bed and washed with excess methanol. The organic layer was concentrated to get the crude compound **89**. The crude was purified by flash chromatography using 100-200 mesh silica gel. The compound **89** was eluted at 25 % ethyl acetate in hexane as half white coloured solid compound **89**. ¹HNMR (400 MHz, CDCl₃) δ ppm 7.55 (d, 1H), 7.41 (d, 1H), 7.34 (dd, 1H), 7.17 (s, 1H), 6.81 (s, 1H), 3.87 (m, 7H), 3.33 (dd, 1H), 3.17 (m, 4H), 3.06 (m, 1H), 2.93 (m, 1H), 2.66 (m, 2H); MS (ESI) m/z 439.9 (M+H).

EXAMPLE 25: 2-(3-chloro-4-(trifluoromethyl) benzyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one (**92**)

Scheme 27



To a solution of **13** (550mg, 2.226mmol) in toluene 25mL was added 3-chloro-4-(trifluoromethyl) benzaldehyde **90** (464.2mg, 2.226mmol). PTSA (846.7mg, 4.452mmol) was added to the reaction, and stirred at 120°C for 6h, then diluted with ethyl acetate and washed with water (3 x 25mL). The organic layer was dried over sodium sulphate and concentrated to get the crude compound **91** which was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 30% ethyl acetate in hexane to afford yellow

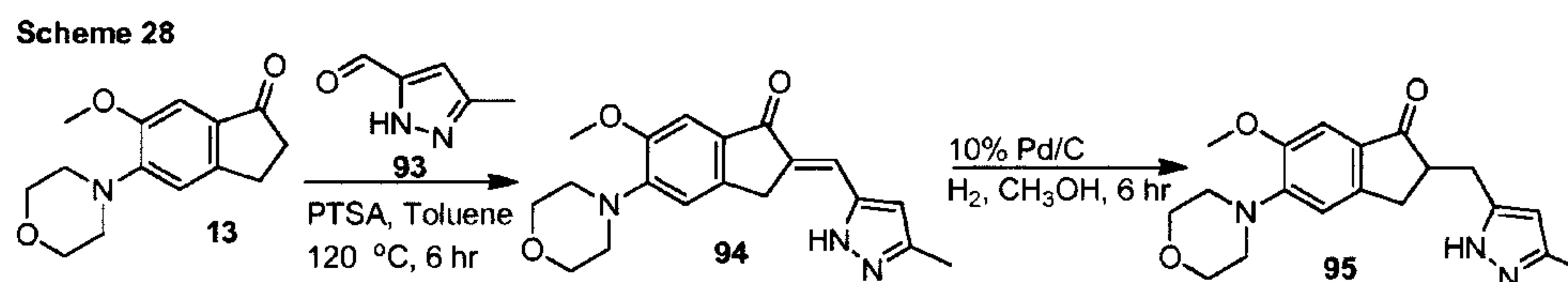
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coloured solid compound (E)-2-(3-chloro-4-(trifluoromethyl)benzylidene)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one **91**.

The **91** (220mg, 0.502mmol) was dissolved in ethyl acetate 150mL, Pd/C 100mg added, and the reaction stirred under hydrogen balloon for 6h, then filtered through celite bed and washed with excess methanol. The organic layer was concentrated to get the crude **92** which was purified by flash chromatography using 100-200 mesh silica gel. The compound was eluted at 28 % ethyl acetate in hexane as half white coloured solid compound 2-(3-chloro-4-(trifluoromethyl)benzyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one **92**. ¹HNMR (400 MHz, CDCl₃) δ ppm 7.59 (d, 1H), 7.49 (d, 1H), 7.31 (m, 1H), 7.19 (s, 1H), 6.83 (s, 1H), 3.89 (m, 3H), 3.87 (m, 4H), 3.53 (m, 1H), 3.17 (m, 4H), 3.07 (m, 2H), 2.91 (m, 1H), 2.73 (m, 1H); MS (ESI) m/z 440.0 (M+H).

EXAMPLE 26: 6-methoxy-2-((3-methyl-1H-pyrazol-5-yl) methyl)-5-morpholino-2, -dihydro-1H-inden-1-one (**95**)

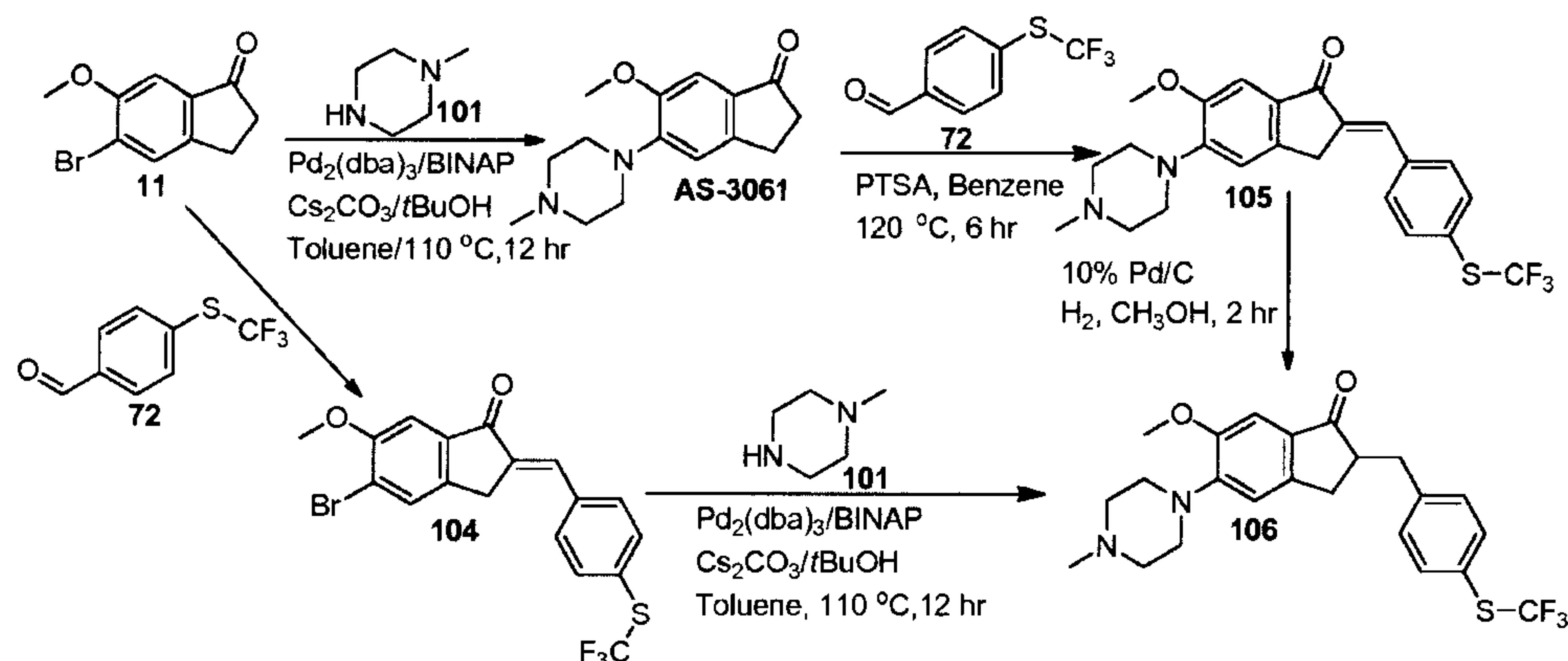


To a solution of **13** (100mg, 0.404mmol) in toluene 10mL was added 3-methyl-1H-pyrazole-5-carbaldehyde **93** (70.8mg, 0.404mmol). PTSA (153.8mg, 0.808mmol) was added to the reaction mass, then stirred at 120°C for 6h, diluted with ethyl acetate and washed with water (3 x 25mL). The organic layer was dried over sodium sulphate and concentrated to get the crude **94** and was purified through flash chromatography by using 100-200 mesh silica gel eluting at 2% MeOH in DCM to afford yellow coloured solid compound (E)-6-methoxy-2-((3-methyl-1H-pyrazol-5-yl) methylene)-5-morpholino-2, 3-dihydro-1H-inden-1-one **94**.

The **94** (85mg, 0.250mmol) was dissolved in methanol 50mL, Pd/C 55mg added, and the reaction stirred under hydrogen balloon for 6h, filtered through celite bed and washed with excess methanol. The organic layer was concentrated to get the crude **95** and was purified by flash chromatography using 100-200 mesh silica gel. The compound **95** was eluted at 2%MeOH in DCM as half white coloured solid compound 6-methoxy-2-((3-methyl-1H-pyrazol-5-yl)methyl)-5-morpholino-2,3-dihydro-1H-inden-1-one **95**. ¹HNMR (400 MHz, CDCl₃) δ ppm 7.17 (s, 1H), 6.82 (s, 1H), 5.86 (s, 1H), 3.88 (m, 3H), 3.86 (m, 4H), 3.18 (m, 6H), 2.97 (m, 1H), 2.81 (m, 1H), 2.77 (m, 1H); MS (ESI) m/z 342.0 (M+H).

EXAMPLE 29: 6-methoxy-5-(4-methylpiperazin-1-yl)-2-(4-((trifluoromethyl) thio)benzyl)-2,3-dihydro-1H-inden-1-one (**106**)

Scheme 31



To a solution of 5-bromo-6-methoxy-2,3-dihydro-1H-inden-1-one **11** (250mg, 1.04mol) and N-methylpiperazine (125mg, 1.248mol) in toluene 15mL was added cesium carbonate (677mg, 2.08mol). The reaction was degassed and purged with nitrogen for 10min.

5 Pd₂(dba)₃ (4.7mg, 0.052mol) and BINAP (6.4mg, 0.104mol) was added and again degassed and purged with nitrogen for another 10min. The reaction was heated to 110°C overnight under sealed conditions. The reaction was diluted with chloroform and filtered through celite bed. The organic layer was concentrated to get the crude compound **AS-3061** and was purified through flash chromatography by using 100-200 mesh silica gel eluting the compound at 2% methanol in

10 chloroform as pale yellow coloured solid compound 6-methoxy-5-(4-methylpiperazin-1-yl)-2,3-dihydro-1H-inden-1-one **AS-3061**. ¹HNMR (400 MHz, CDCl₃) δ ppm 7.24 (s, 1H), 7.16 (s, 1H), 6.90 (s, 1H), 4.06 (m, 1H), 3.92 (s, 3H), 3.89 (s, 1H), 3.70 (s, 3H), 3.50 (m, 2H), 3.29 (s, 4H), 3.01 (m, 4H), 2.62 (m, 6H), 2.42 (s, 3H); MS (ESI) m/z 260.9 (M+H).

To a solution of **11** (250mg, 1.04mol) in toluene 15mL was added 4-((trifluoromethyl)thio) benzaldehyde **72** (235mg, 1.144mol). PTSA (357mg, 2.08mol) was added to the reaction

15 mass, which was stirred at 120°C for 6h, diluted with ethyl acetate and washed with water (3 x 25mL). The organic layer was dried over sodium sulphate and concentrated to get the crude compound **104** which was purified through flash chromatography by using 100-200 mesh silica gel. The compound **104** was eluted at 10% ethyl acetate in hexane to afford yellow coloured

20 solid (E)-5-bromo-6-methoxy-2-(4-((trifluoromethyl)thio)benzylidene)-2,3-dihydro-1H-inden-1-one **104**.

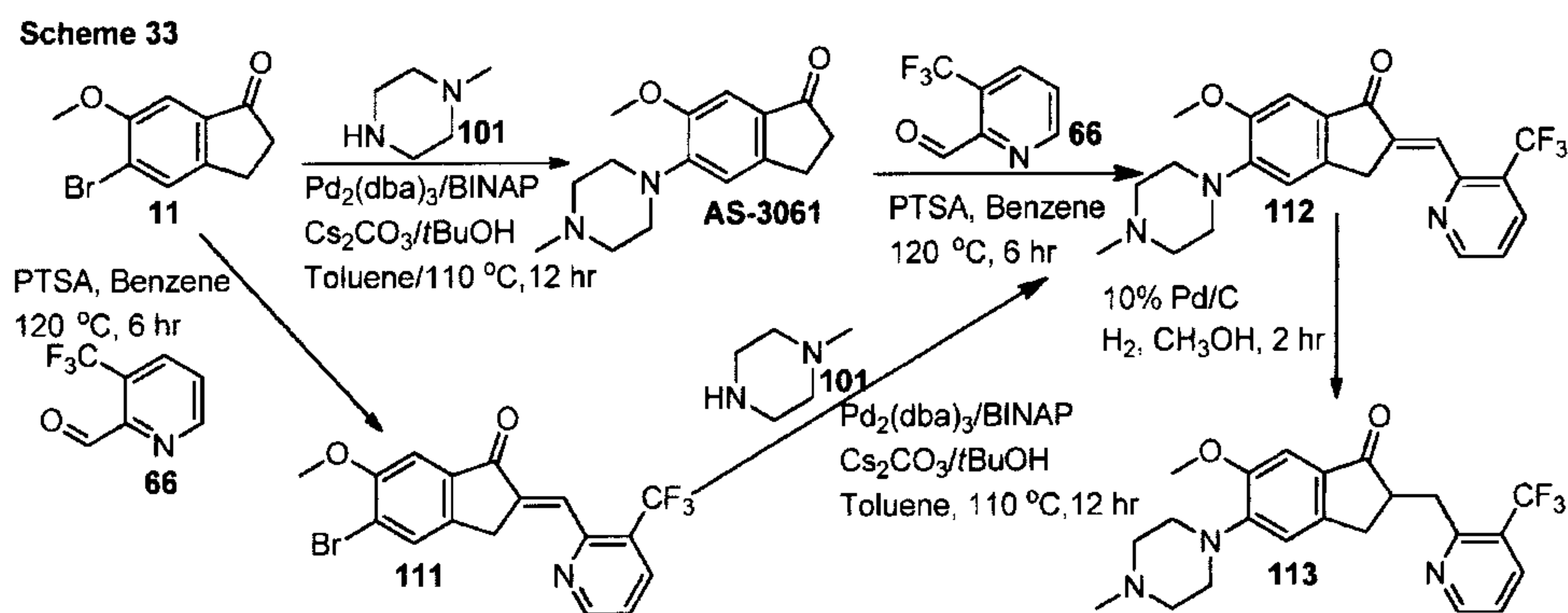
The **104** (125mg, 0.467mol) was dissolved in methanol 25mL, Pt/C 10mg added and the reaction stirred under hydrogen balloon for 6h, then filtered through celite bed and washed with excess methanol. The organic layer was concentrated to get the crude compound (E)-6-methoxy-5-(4-methylpiperazin-1-yl)-2-(4-((trifluoromethyl)thio)benzylidene)-2,3-dihydro-1H-

25 inden-1-one **105** and was purified by flash chromatography using 100-200 mesh silica gel. The

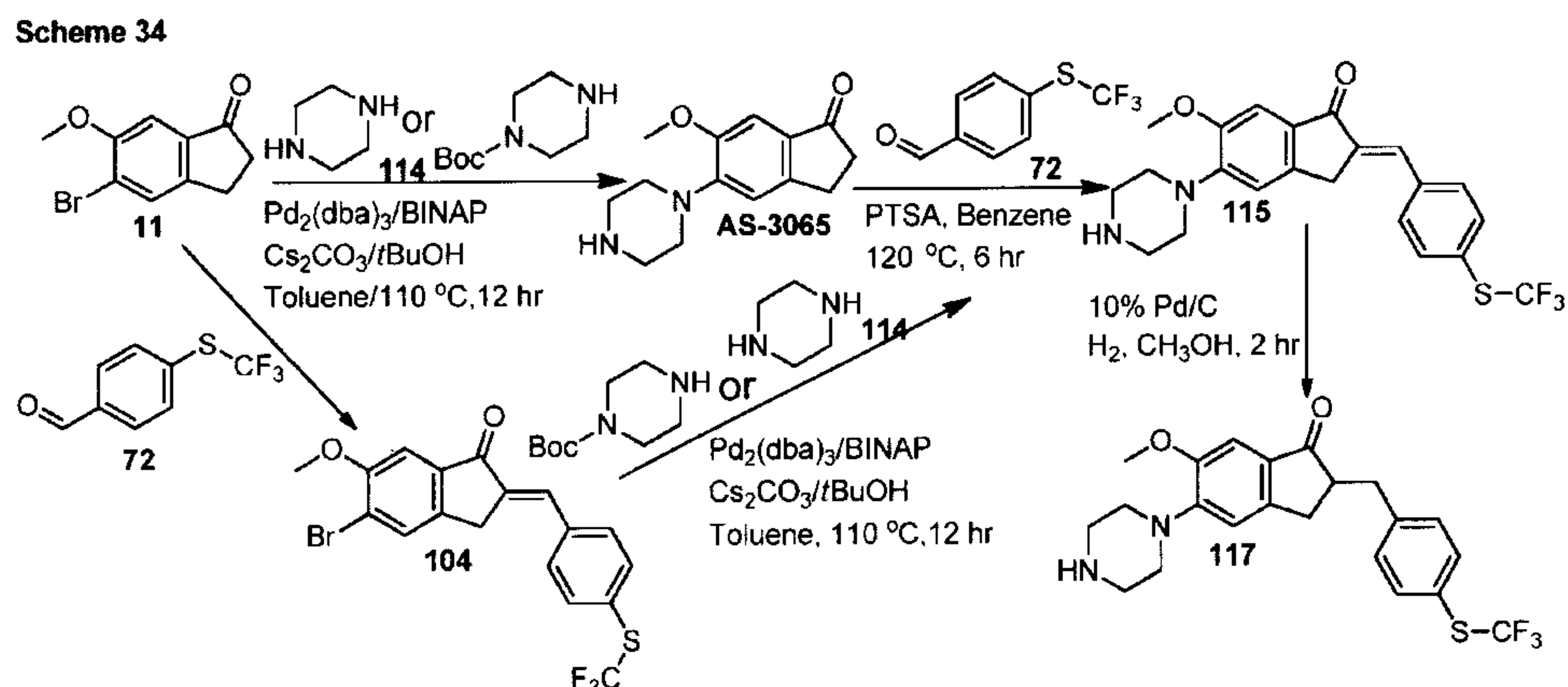
compound was eluted at 12% ethyl acetate in hexane as half white coloured solid compound **105**.

To a solution of **105** (75mg, 0.174mol) and N-methyl piperazine (20.9mg, 0.209mol) in toluene 15mL was added cesium carbonate (113.3mg, 0.348mol). The reaction was degassed and purged with nitrogen for 10min. Pd₂(dba)₃ (7.96mg, 0.0087mol) and BINAP (10.8mg, 0.0174mol) was added and again degassed and purged with nitrogen for another 10min. The reaction was heated to 110°C overnight under sealed conditions. The reaction was diluted with chloroform and filtered through celite bed. The organic layer was concentrated to get the crude compound **106** and was purified through flash chromatography by using 100-200 mesh silica gel eluting the compound at 5% methanol in chloroform as brown coloured solid 6-methoxy-5-(4-methylpiperazin-1-yl)-2-(4-((trifluoromethyl) thio)benzyl)-2,3-dihydro-1H-inden-1-one **106**.
¹HNMR (400 MHz, CDCl₃) δ ppm 7.57 (d, 2H), 7.28 (bs, 2H), 7.20 (s, 1H), 6.90 (s, 1H), 3.91 (s, 3H), 3.70 (bs, 4H), 3.35 (d, 2H), 2.99 (bs, 5H), 2.73 (bs, 3H); MS (ESI) m/z 451.0 (M+H).

EXAMPLE 31: 6-methoxy-5-(4-methylpiperazin-1-yl)-2-((3-(trifluoromethyl) pyridin-2-yl) methyl)-2, 3-dihydro-1H-inden-1-one (**113**)

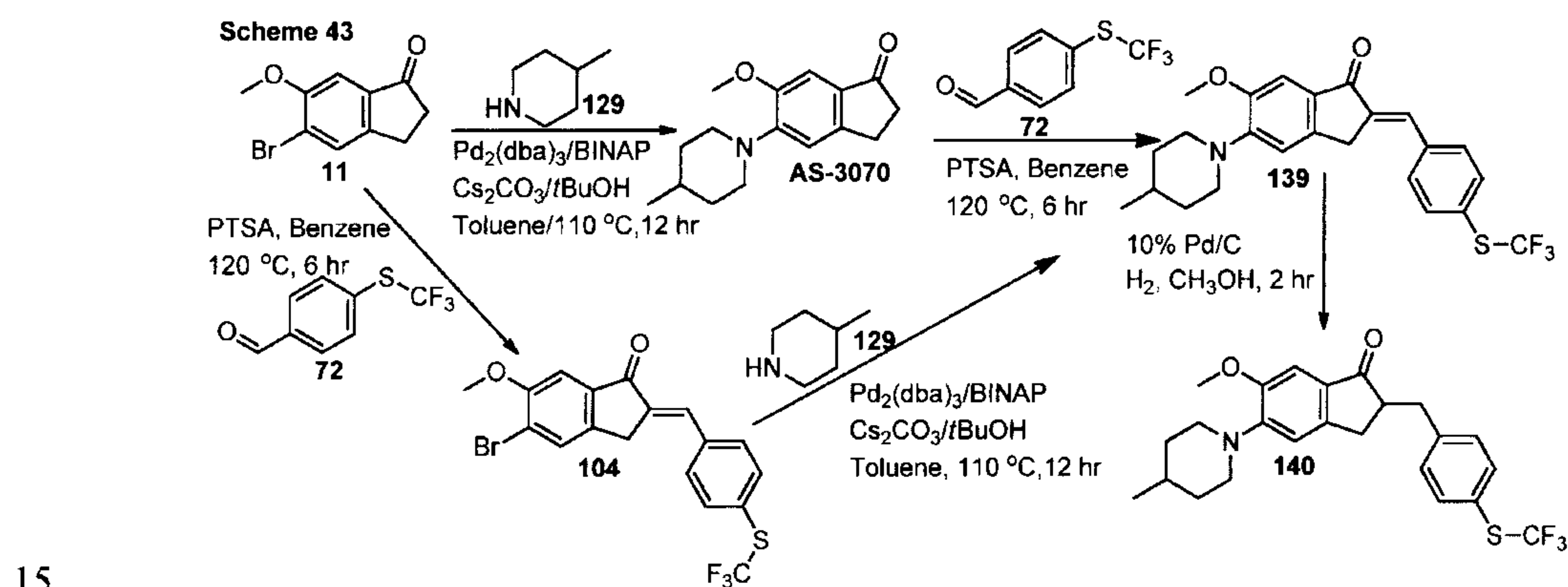


EXAMPLE 32: 6-methoxy-5-(piperazin-1-yl)-2-(4-((trifluoromethyl) thio) benzyl)-2, 3-dihydro-1H-inden-1-one (**117**)



To a solution of 5-bromo-6-methoxy-2,3-dihydro-1H-inden-1-one **11** (250mg, 1.04mol), piperazine (107mg, 1.248mol) and/or Boc-piperazine in toluene 15mL was added cesium carbonate (677mg, 2.08mol). The reaction was degassed and purged with nitrogen for 10min. Pd₂(dba)₃ (4.7mg, 0.052mol) and BINAP (6.4mg, 0.104mol) was added and again
 5 degassed and purged with nitrogen for another 10min. The reaction mixture was heated to 110°C overnight under sealed conditions. After completion, the reaction was diluted with chloroform and filtered through celite bed. The organic layer was concentrated to get the crude compound and was purified through flash chromatography by using 100-200 mesh silica gel eluting the compound **AS-3065** at 4% methanol in chloroform as pale yellow coloured solid compound 6-methoxy-5-(piperazin-1-yl)-2,3-dihydro-1H-inden-1-one **AS-3065**. ¹HNMR (400 MHz, CDCl₃)
 10 δ ppm 7.17 (s, 1H) , 6.90 (s, 1H), 3.89 (s, 3H), 3.21 (m, 4H), 3.15 (m, 4H), 3.035 (m, 2H), 2.67 (m, 2H).

EXAMPLE 41: 6-methoxy-5-(4-methylpiperidin-1-yl)-2-(4-((trifluoromethyl) thio) benzyl)-2,3-dihydro-1H-inden-1-one (**140**)



To a solution of compound 5-bromo-6-methoxy-2,3-dihydro-1H-inden-1-one **11** (250mg, 1.04mol) and 4-methylpiperidine **129** (120mg, 1.248mol) in toluene 15mL was added cesium carbonate (677mg, 2.08mol). The reaction was degassed and purged with nitrogen for 10min, Pd₂(dba)₃ (4.7mg, 0.052mol) and BINAP (6.7mg, 0.104mol) was added and again
 20 degassed and purged with nitrogen for another 10min. The reaction was heated to 110°C overnight under sealed conditions. After completion, the reaction was diluted with chloroform and filtered through celite bed. The organic layer was concentrated to get the crude compound **AS-3070** which was purified through flash chromatography by using 100-200 mesh silica gel eluting the compound at 25% ethyl acetate in hexane as pale yellow coloured solid 6-methoxy-
 25 5-(4-methylpiperidin-1-yl)-2,3-dihydro-1H-inden-1-one **AS-3070**. ¹HNMR (400 MHz, CDCl₃) δ ppm 7.14 (s, 1H), 6.90 (s, 1H), 3.88 (s, 3H), 3.60 (d, 2H), 3.00 (m, 2H), 2.64 (m, 4H), 1.73 (m, 2H), 1.41 (m, 3H), 0.99 (m, 3H).

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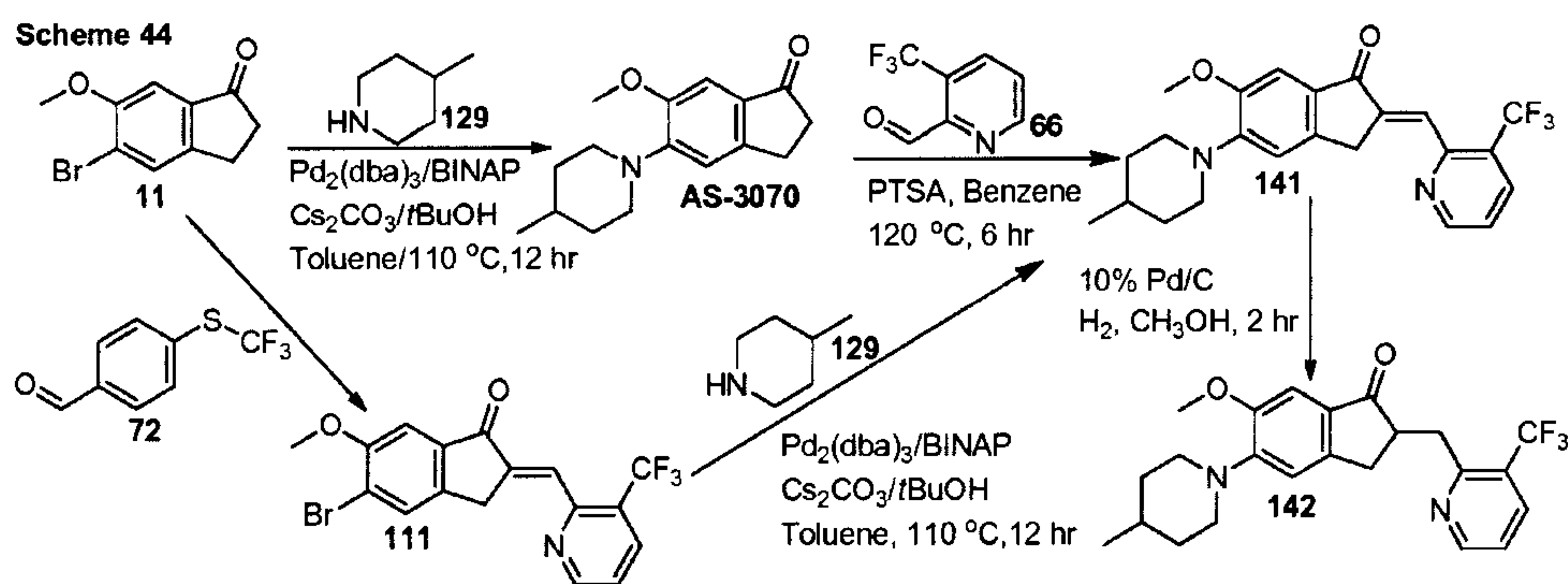
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To a solution of 5-bromo-6-methoxy-2, 3-dihydro-1H-inden-1-one **11** (250mg, 0.1037mmol) in benzene was added 4-((trifluoromethyl) thio) benzaldehyde **72** (213mg, 0.103mmol). PTSA (395mg, 0.207mmol) was added, the reaction mass was stirred at 120°C for 6h, then diluted with ethyl acetate and washed with water (3 x 25mL). The organic layer was dried over sodium sulphate and concentrated to get the crude compound **104** and was purified through flash chromatography by using 100-200 mesh silica gel. The compound **104** was eluted at 30% ethyl acetate in hexane to afford yellow coloured solid.

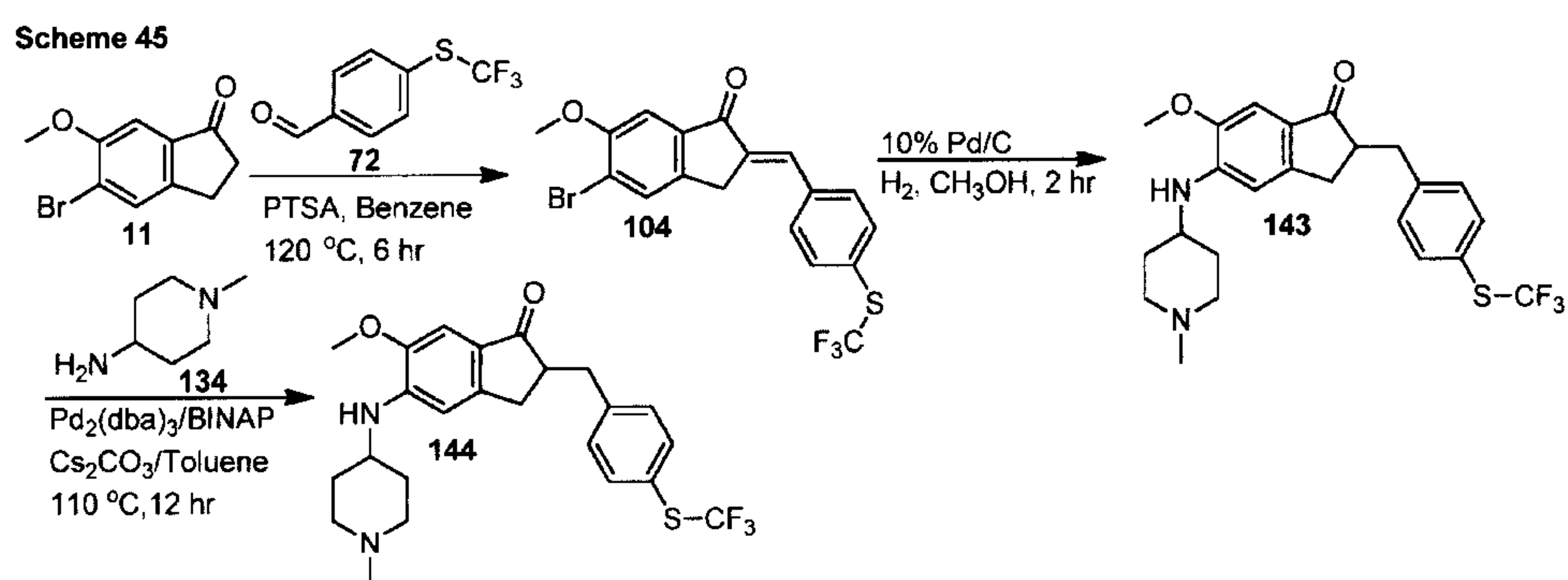
To a solution of **104** (150mg, 0.348mmol) and 4-methylpiperidine (69mg, 0.696mmol) in toluene and *t*BuOH (8:2, 10mL) was added cesium carbonate 228mg, 0.696). The reaction was degassed and purged with nitrogen for 10min. Pd₂(dba)₃ (15.9mg, 0.0174mmol) and BINAP (32.4mg, 0.15m.mol) was added and again degassed and purged with nitrogen for another 10min. The reaction was heated to 110°C for overnight under sealed condition. The reaction was diluted with chloroform and filtered through celite bed. The organic layer was concentrated to get the crude compound **139** which was purified through flash chromatography by using 100-200 mesh silica gel eluting the compound at 10% ethyl acetate in hexane as pale yellow coloured solid (E)-6-methoxy-5-(4-methylpiperidin-1-yl)-2-(4-((trifluoromethyl)thio)benzylidene)-2,3-dihydro-1H-inden-1-one **139**.

The **139** (80mg, 0.178mmol) was dissolved in methanol 50mL and Raney-Nickel (8mg) added and the reaction stirred under hydrogen balloon for 2h. The reaction was filtered through celite bed and washed with excess methanol. The organic layer was concentrated to get the crude compound **140** and purified by flash chromatography using 100-200 mesh silica gel. The compound **140** was eluted at 8% ethyl acetate in hexane as half white coloured solid compound 6-methoxy-5-(4-methylpiperidin-1-yl)-2-(4-((trifluoromethyl)thio)benzyl)-2,3-dihydro-1H-inden-1-one **140**. ¹HNMR (400 MHz, CDCl₃) δ ppm 7.27 (m, 3H), 7.11 (m, 4H), 6.81 (s, 1H), 3.89 (s, 3H), 3.60 (bs, 2H), 3.37 (dd, 1H), 2.94 (m, 2H), 2.59 (m, 4H), 0.94 (m, 3H), 0.86 (m, 4H); MS (ESI) m/z 450.1 (M+H).

EXAMPLE 42: 6-methoxy-5-(4-methylpiperidin-1-yl)-2-((3-(trifluoromethyl) pyridin-2-yl) methyl)-2, 3-dihydro-1H-inden-1-one (**142**)



EXAMPLE 43: 6-methoxy-5-((1-methylpiperidin-4-yl) amino)-2-(4-((trifluoromethyl) thio) benzyl)-2, 3-dihydro-1H-inden-1-one (**144**)



5 To a solution of **11** (250mg, 1.04mol) in toluene 15mL was added 4-((trifluoromethyl) thio) benzaldehyde **72** (235mg, 1.144mol). PTSA (357mg, 2.08mol) was added, the reaction mixture stirred at 120°C for 6h, diluted with ethyl acetate and washed with water (3 x 25mL). The organic layer was dried over sodium sulphate and concentrated to get the crude compound **104** and was purified through flash chromatography by using 100-200 mesh silica gel. The resulting compound (E)-5-bromo-6-methoxy-2-(4-((trifluoromethyl) thio)benzylidene)-2,3-dihydro-1H-inden-1-one **104** was eluted at 10% ethyl acetate in hexane to afford yellow coloured solid.

The **104** (125mg, 0.467mol) was dissolved in methanol 25mL, Pt/C 10mg added, the reaction stirred under hydrogen balloon for 6h, filtered through celite bed and washed with excess methanol. The organic layer was concentrated to get the crude compound **143** and was purified by flash chromatography using 100-200 mesh silica gel. The compound 5-bromo-6-methoxy-2-(4-((trifluoromethyl)thio)benzyl)-2,3-dihydro-1H-inden-1-one **143** was eluted at 12% ethyl acetate in hexane as half white coloured solid.

To a solution of **143** (75mg, 0.174mol) and 1-methylpiperidin-4-amine **134** (23.8mg, 0.0208mol) in toluene 15mL was added cesium carbonate (113.3mg, 0.348mol). The reaction was degassed and purged with nitrogen for 10min. Pd₂(dba)₃ (7.96mg, 0.0087mol) and BINAP (10.8mg, 0.0174mol) was added and again degassed and purged with nitrogen for another

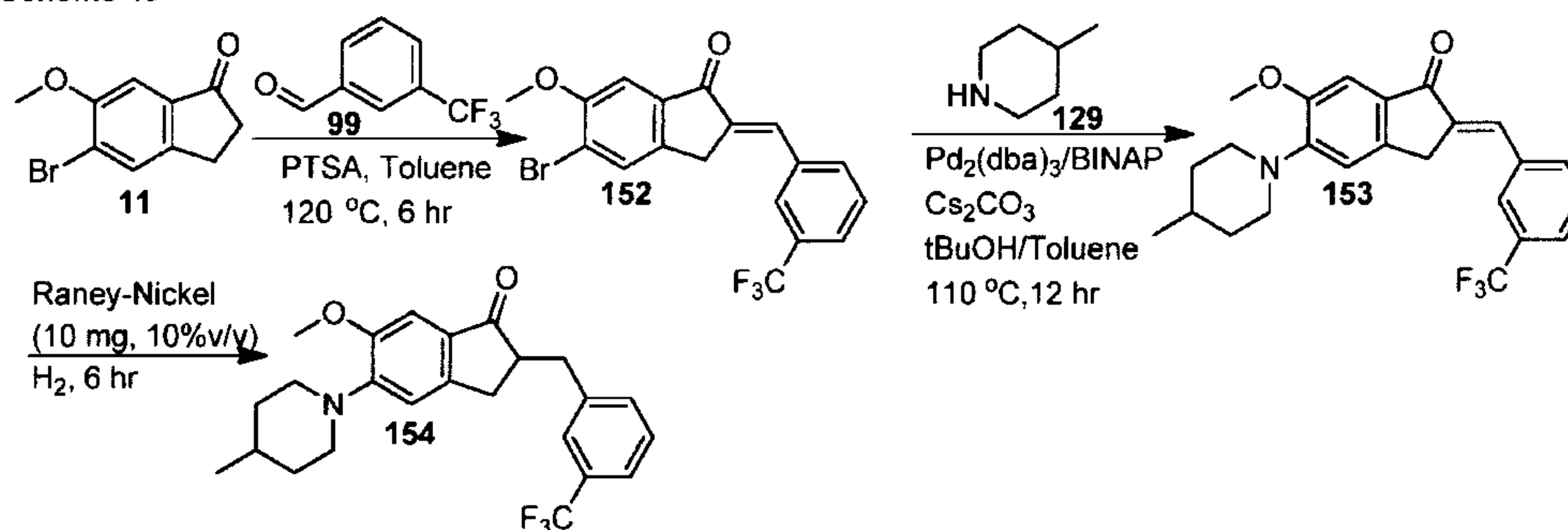
10min. The reaction was heated to 110°C overnight under sealed conditions. The reaction was diluted with chloroform and filtered through celite bed. The organic layer was concentrated to get the crude compound **144** and was purified through flash chromatography by using 100-200 mesh silica gel eluting the compound at 7.5% methanol in chloroform as brown coloured solid

5 6-methoxy-5-((1-methylpiperidin-4-yl) amino)-2-(4-((trifluoromethyl) thio) benzyl)-2, 3-dihydro-1H-inden-1-one **144**. ¹HNMR (400 MHz, CDCl₃) δ ppm 7.55 (bs, 2H), 7.28 (bs, 2H), 7.08 (s, 1H), 6.42 (s, 1H), 4.99 (s, 1H), 3.89 (s, 3H), 3.37 (m, 4H), 2.84 (m, 6H), 2.66 (m, 3H), 2.09 (m, 4H); MS (ESI) m/z 465.0 (M+H).

EXAMPLE 47: 6-methoxy-5-(4-methylpiperidin-1-yl)-2-(3-(trifluoromethyl) benzyl)-2, 3-dihydro-1H-inden-1-one (**146**)

10

Scheme 49



To a solution of **11** (200mg, 0.829mmol) in toluene was added 3-(trifluoromethyl) benzaldehyde **99** (158.86mg, 0.9128mmol). PTSA (285.5mg, 172.20mmol) was added to the reaction mass, then stirred at 120°C for 6h, diluted with ethyl acetate and washed with water (3 x

15 25mL). The organic layer was dried over sodium sulphate and concentrated to get the crude compound **152** which was purified through flash chromatography by using 100-200 mesh silica gel. The compound (E)-5-bromo-6-methoxy-2-(3-(trifluoromethyl)benzylidene)-2,3-dihydro-1H-inden-1-one **152** was eluted at 30% ethyl acetate in hexane to afford yellow coloured solid.

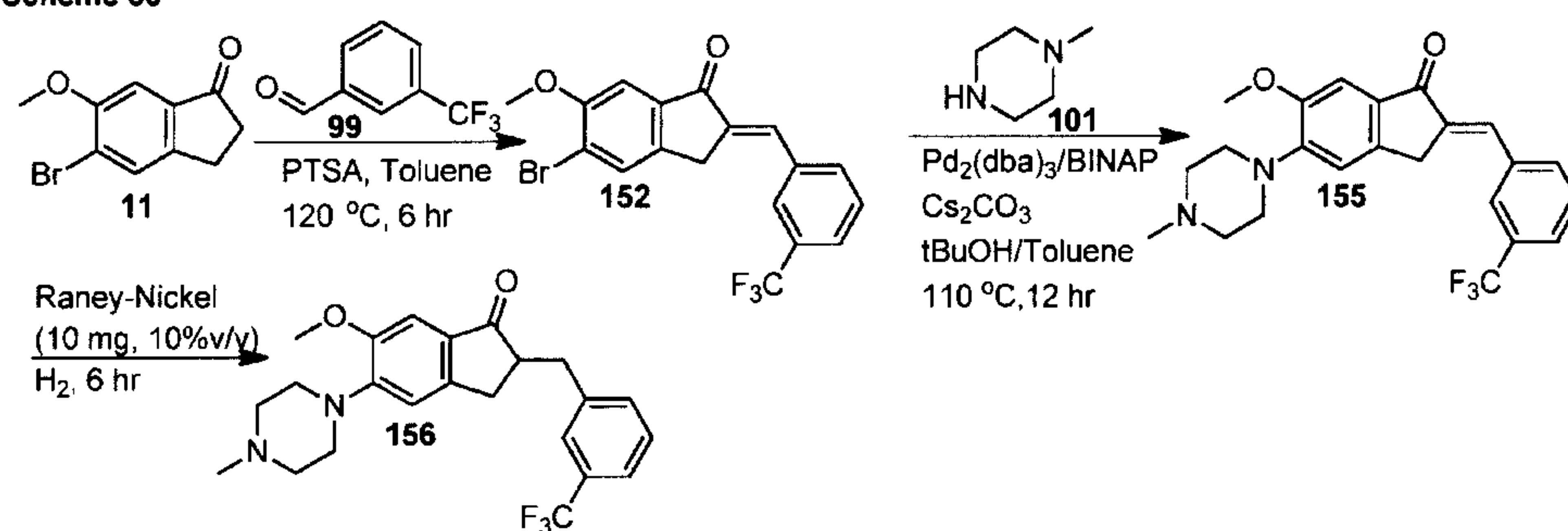
To a solution of **152** (120mg, 0.3007mmol) and 4-methylpiperidine **129** (60.2mg, 0.6015mmol) in toluene was added cesium carbonate (197.2mg, 0.6015mmol). The reaction was degassed and purged with nitrogen for 10min. Pd₂(dba)₃ (13.7mg, 0.0150mmol) and BINAP (28.1mg, 0.0451mmol) was added and again degassed and purged with nitrogen for another 10min. The reaction was heated to 110°C overnight under sealed conditions. The reaction was diluted with chloroform and filtered through celite bed. The organic layer was concentrated to

25 get the crude compound **153** which was purified through flash chromatography by using 100-200 mesh silica gel eluting the compound (E)-6-methoxy-5-(4-methylpiperidin-1-yl)-2-(3-(trifluoromethyl)benzylidene)-2,3-dihydro-1H-inden-1-one **153** at 25% ethyl acetate in hexane as pale yellow coloured solid.

The **153** (100mg, 0.240mmol) was dissolved in methanol and Raney-Nickel (10mg, 10%v/v) added and the reaction stirred under hydrogen balloon for 6h. The reaction was filtered through celite bed and washed with excess methanol. The organic layer was concentrated to get the crude compound **154** which was purified by flash chromatography using 100-200 mesh silica gel. The compound **154** was eluted at 20% ethyl acetate in hexane as half white coloured solid compound 6-methoxy-5-(4-methylpiperidin-1-yl)-2-(3-(trifluoromethyl) benzyl)-2,3-dihydro-1H-inden-1-one **154**. ¹HNMR (400 MHz, CDCl₃) δ ppm 7.40 (m, 4H), 7.15 (s, 1H), 6.82 (s, 1H), 3.89 (s, 3H), 3.60 (s, 2H), 3.41 (dd, 1H), 2.94 (m, 2H), 2.62 (m, 4H), 0.92 (m, 4H), 0.85 (m, 3H); MS (ESI) m/z 418.0 (M+H).

EXAMPLE 48: 6-methoxy-5-(4-methylpiperazin-1-yl)-2-(3-(trifluoromethyl) benzyl)-2, 3-dihydro-1H-inden-1-one (**156**)

Scheme 50



A solution of **11** (200mg, 0.829mmol) in toluene was added 3-(trifluoromethyl) benzaldehyde **99** (158.86mg, 0.9128mmol). PTSA (285.5mg, 172.20mmol) was added to the reaction mass. The reaction was stirred at 120°C for 6h. The reaction mass was diluted with ethyl acetate and washed with water (3 x 25mL). The organic layer was dried over sodium sulphate and concentrated to get the crude compound **152** which was purified through flash chromatography by using 100-200 mesh silica gel. The compound (E)-5-bromo-6-methoxy-2-(3-(trifluoromethyl)benzylidene)-2,3-dihydro-1H-inden-1-one **152** was eluted at 30% ethyl acetate in hexane to afford yellow coloured solid.

To a solution of **152** (120mg, 0.3009mmol) and 4-methylpiperazine (60.1mg, 0.6105mmol) in toluene was added cesium carbonate (197.2mg, 0.6015mmol). The reaction was degassed and purged with nitrogen for 10min. Pd₂(dba)₃ (13.7mg, 0.0150mmol) and BINAP (28.0mg, 0.0451mmol) was added and again degassed and purged with nitrogen for another 10min. The reaction was heated to 110°C overnight under sealed conditions. The reaction was diluted with chloroform and filtered through celite Bed. The organic layer was concentrated to get the crude compound **155** which was purified through flash chromatography by using 100-200 mesh silica gel eluting the compound at 25% ethyl acetate in hexane as pale yellow

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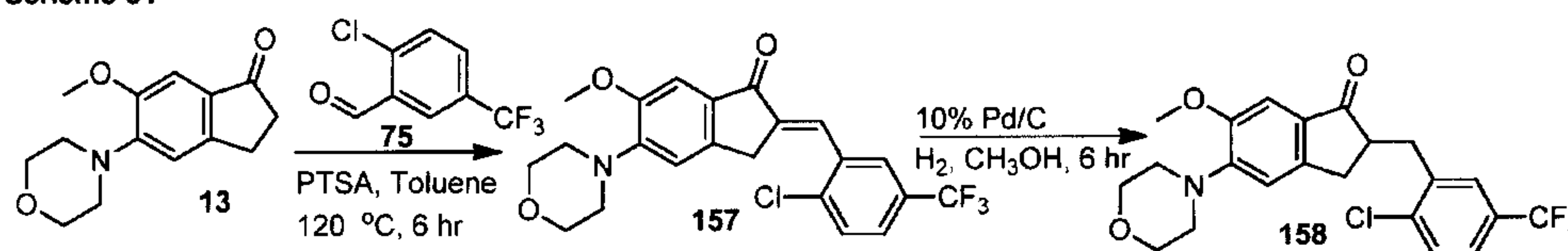
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coloured solid (E)-6-methoxy-5-(4-methylpiperazin-1-yl)-2-(3-(trifluoromethyl)benzylidene)-2,3-dihydro-1H inden-1-one **155**.

The **155** (100mg, 0.241mmol) was dissolved in methanol and Raney-Nickel (10mg, 10% v/v) added and the reaction stirred under hydrogen balloon for 6h. The reaction was filtered
5 through celite bed and washed with excess methanol. The organic layer was concentrated to get the crude product **156** which was purified by flash chromatography using 100-200 mesh silica gel. The compound **156** was eluted at 20% ethyl acetate in hexane as half white coloured solid 6-methoxy-5-(4-methylpiperazin-1-yl)-2-(3-(trifluoromethyl) benzyl)-2,3-dihydro-1H-inden-1-one **156**. ¹HNMR (400 MHz, CDCl₃) δ ppm 7.42 (m, 4H), 7.17 (s, 1H), 6.83 (s, 1H), 3.41 (dd, 1H),
10 3.21 (bs, 4H), 3.03 (m, 1H), 2.95 (m, 1H), 2.68 (m, 2H), 2.61 (bs, 4H), 2.35 (s, 3H); MS (ESI) m/z 419.0 (M+H).

EXAMPLE 49: 2-(2-chloro-5-(trifluoromethyl) benzyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one (**158**)

Scheme 51

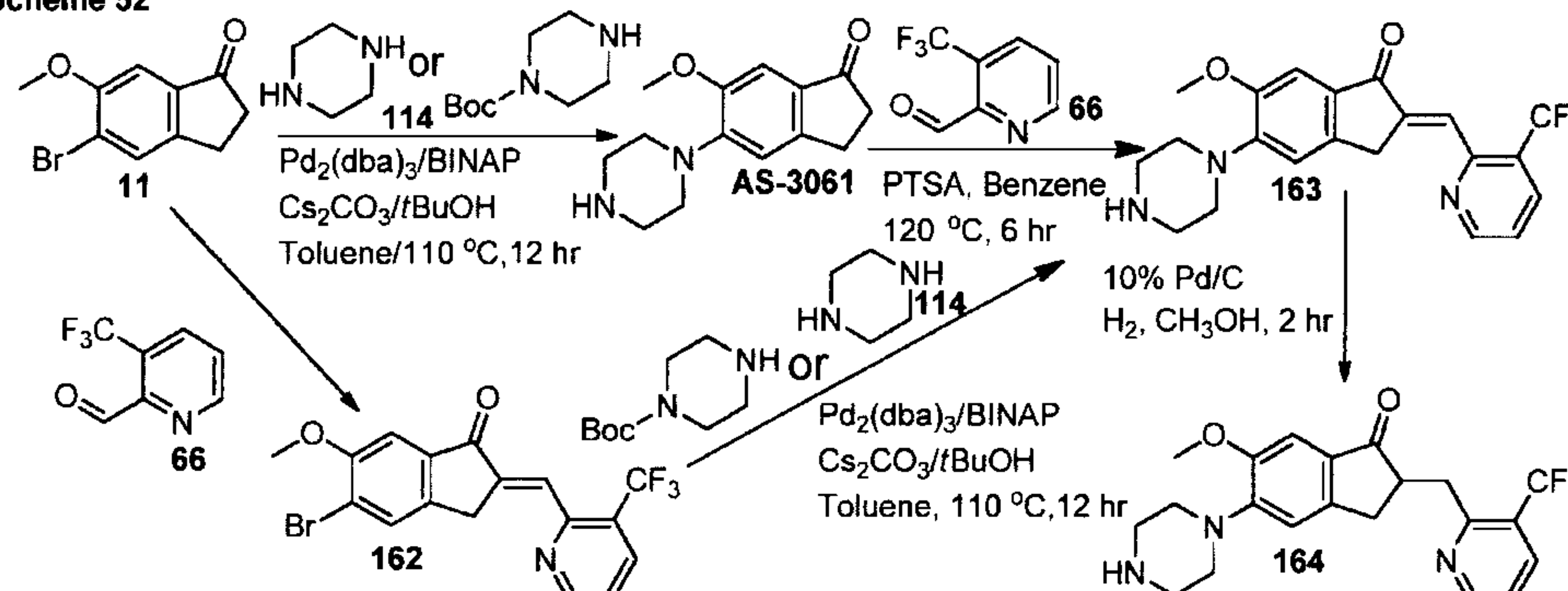


To a solution of 6-methoxy-5-morpholino-2, 3-dihydro-1H-inden-1-one **13** (0.120mg, 0.485mmol) in toluene (10mL) was added 2-chloro-5-(trifluoromethyl) benzaldehyde **75** (0.101mg, 0.485mmol). PTSA (0.184mg, 0.971mmol) was added to the reaction mass, reaction stirred at 100°C for 6h, diluted with ethyl acetate and washed with water (3 x 25mL). The organic layer was dried over sodium sulphate and concentrated to get the crude compound **157**
20 which was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 15 % ethyl acetate in hexane to afford yellow coloured solid (E)-2-(2-chloro-5-(trifluoromethyl) benzylidene)-6-methoxy-5-morpholino-2, 3-dihydro-1H-inden-1-one **157**.

The **157** (100mg, 0.228mmol) was dissolved in methanol and Pd/C (40mg) added, the
25 reaction stirred under hydrogen balloon for 6h, filtered through celite bed and washed with excess methanol. The organic layer was concentrated to get the crude compound **158** which was purified by flash chromatography using 100-200 mesh silica gel. The compound was eluted at 10% ethyl acetate in hexane as half white coloured solid 2-(2-chloro-5-(trifluoromethyl)benzyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one **158**. ¹HNMR (400 MHz, CDCl₃) δ ppm
30 7.43 (m, 3H), 7.20 (s, 1H), 6.84 (s, 1H), 3.89 (m, 7H), 3.54 (dd, 1H), 3.14 (m, 4H), 3.07 (m, 2H), 2.75 (m, 2H); MS (ESI) m/z 440.0 (M+H).

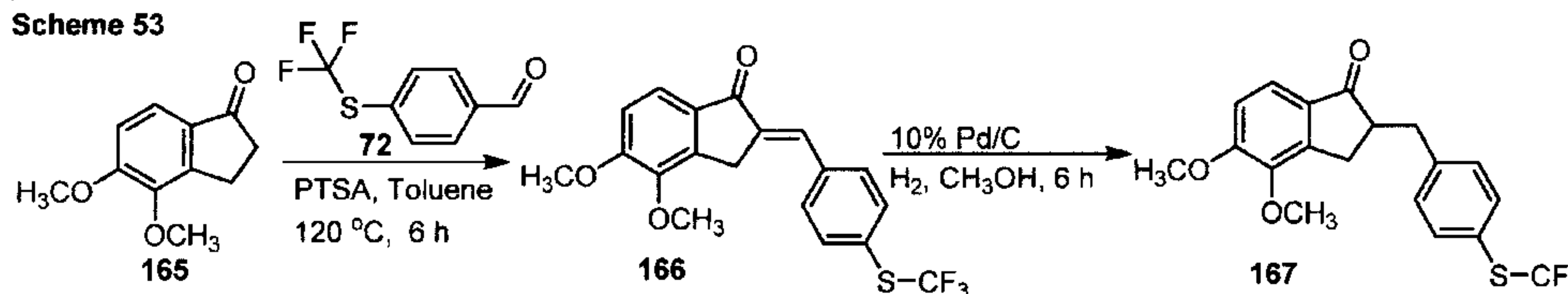
EXAMPLE 50: 6-methoxy-5-(piperazin-1-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-2,3-dihydro-1H-inden-1-one (**164**)

Scheme 52



EXAMPLE 51: 4,5-dimethoxy-2-(4-((trifluoromethyl)thio)benzyl)-2,3-dihydro-1H-inden-1-one (**167**)

Scheme 53



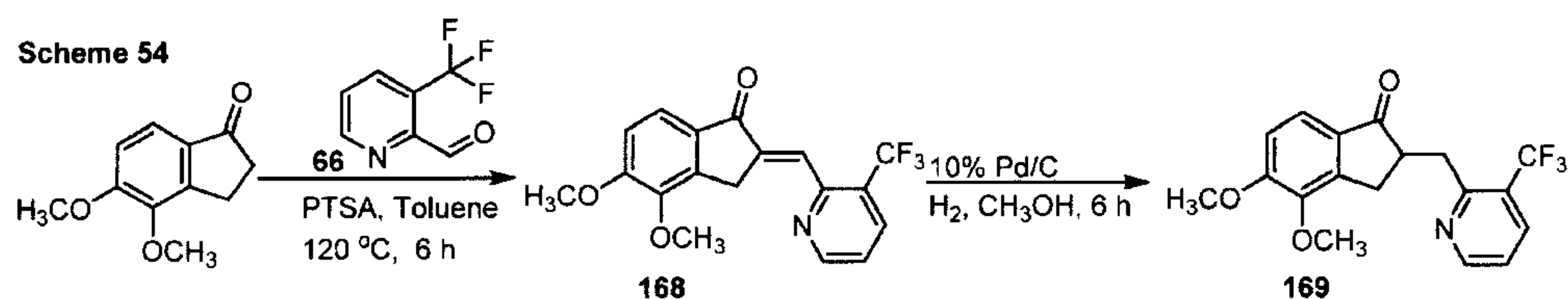
To a solution of 4,5-dimethoxy-2,3-dihydro-1H-inden-1-one (**165**) (100mg, 0.520mmol) in toluene 15mL was added 4-((trifluoromethyl)thio)benzaldehyde (**72**) (118.4mg, 0.572mmol) and PTSA (178.9mg, 1.414mmol). The reaction was stirred at 120°C for 6h. The resulting reaction mixture was diluted with ethyl acetate and washed with water (3x 25mL). The organic layer was dried over sodium sulphate and concentrated to get the crude, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 25% ethyl acetate in hexane to afford yellow coloured solid of (E)-4,5-dimethoxy-2-(4-((trifluoromethyl)thio)benzylidene)-2,3-dihydro-1H-inden-1-one intermediate **166**.

The **166** (85mg, 0.223mmol) was dissolved in methanol 25ml. Pd/C 20mg was added and the reaction stirred under H₂ balloon for 6h. The reaction was filtered through Celite bed and washed with excess methanol. The organic layer was concentrated to get the crude compound 4,5-dimethoxy-2-(4-((trifluoromethyl)thio)benzyl)-2,3-dihydro-1H-inden-1-one **167**, which was purified by flash chromatography using 100-200 mesh silica gel. The resulting compound **167** was eluted at 20% ethyl acetate in hexane as half white coloured solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.56 (m, 3H), 7.29 (m, 2H), 6.96 (d, 1H), 3.94 (s, 3H), 3.85 (s, 3H), 3.37 (m, 1H), 3.17 (m, 1H), 2.95 (m, 1H), 2.71 (m, 2H); MS (ESI) m/z 382.9 (M+H).

EXAMPLE 52: 4,5-dimethoxy-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-2,3-dihydro-1H-inden-1-one (**169**)

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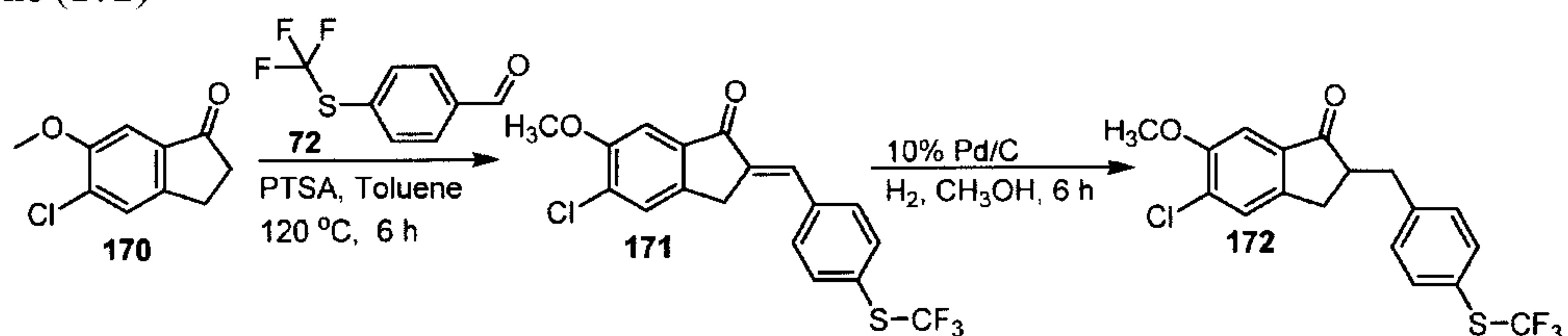
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To a solution of **165** (100mg, 0.518mmol) in toluene 15ml was added **66** (99.7mg, 0.569mmol). PTSA (196.8mg 1.03mmol) was added to the reaction mass, which was then stirred at 120°C for 12h. The reaction mass was diluted with ethyl acetate and washed with water (3 x 25 ml.). The organic layer was dried over sodium sulphate and concentrated to get the crude, which was used in the next step with out further purification.

The **168** (100mg) was dissolved in methanol 25ml, and Pd/C 15mg added, and the reaction stirred under H₂ balloon for 6h. The reaction was filtered through celite bed and washed with excess methanol. The organic layer was concentrated to get the crude **169** and was purified by flash chromatography using 100-200 mesh silica gel. The compound was eluted at 20% ethyl acetate in hexane as half white coloured solid **168**. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.64 (d, 1H), 7.91 (d, 1H), 7.56 (d, 1H), 6.97 (d, 1H), 7.11 (d, 1H), 3.86 (s, 6H), 3.66 (d, 1H), 3.43 (m, 1H), 3.32 (m, 1H), 3.17 (m, 1H), 2.74 (dd, 1H); MS-ES+351.9.

EXAMPLE 53: 5-chloro-6-methoxy-2-(4-((trifluoromethyl)thio)benzyl)-2,3-dihydro-1H-inden-1-one (**172**)



To a solution of 5-chloro-6-methoxy-2,3-dihydro-1H-inden-1-one **170** (100mg, 0.510mmol) in toluene 15mL was added 4-((trifluoromethyl)thio)benzaldehyde **72** (98.4mg, 0.561mmol). PTSA (175.9mg, 1.2mmol) was added to the reaction mass, which was stirred at 120°C for 6h. The reaction mass was diluted with ethyl acetate and washed with water (3 x 25mL). The organic layer was dried over sodium sulphate and concentrated to get the crude (E)-5-chloro-6-methoxy-2-(4-((trifluoromethyl)thio)benzylidene)-2,3-dihydro-1H-inden-1-one (**171**), which was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 22% ethyl acetate in hexane to afford yellow coloured solid.

The compound **171** (85mg, 0.195mmol) was dissolved in methanol 25mL and Pt/C (40mg) and the reaction stirred under H₂ balloon for 6h. The reaction was filtered through celite bed and washed with excess methanol. The organic layer was concentrated to get the crude. The crude was purified by flash chromatography using 100-200 mesh silica gel. The compound was eluted at 25% ethylacetate in hexane as half white coloured solid **172**. ¹H NMR (400 MHz,

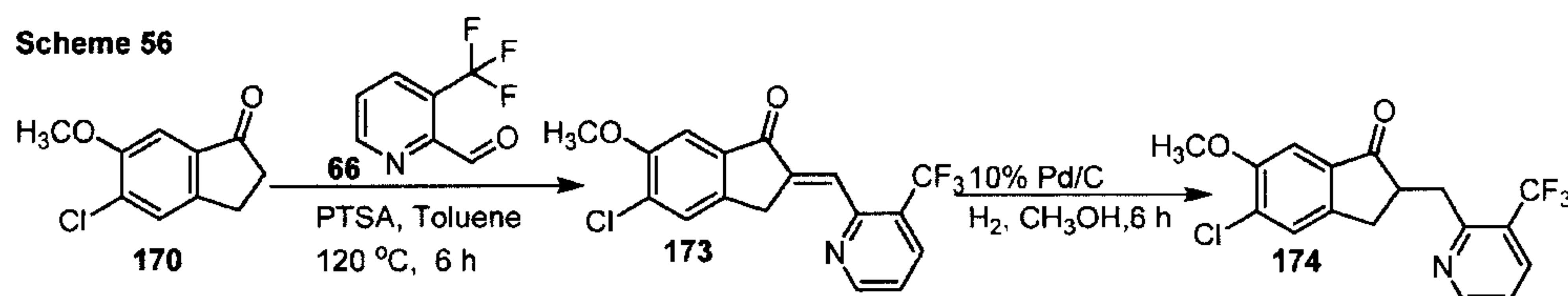
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CDCl₃) δ ppm 7.57 (d, 2H), 7.43 (s, 1H), 7.27(d, 2H), 7.25 (s, 1H), 3.94 (s, 3H), 3.37 (dd, 1H), 3.11 (m, 1H), 2.99 (m, 1H), 2.72 (m, 2H); MS-ES+386.8.

EXAMPLE 54: 5-chloro-6-methoxy-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-2,3-dihydro-1H-inden-1-one (**174**)

5

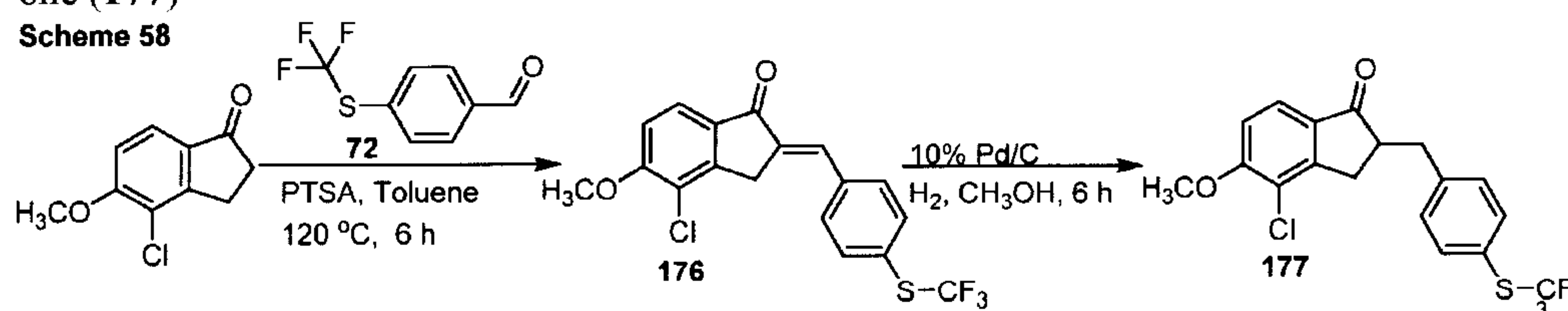


To a solution of **170** (150mg, 0.7769mmol) in toluene 15ml was added **66** (203.9mg, 1.165mmol). PTSA (443.06mg, 0.2337mmol) was added to the reaction mass, which was stirred at 120°C for 6h. The reaction mass was diluted with ethyl acetate and washed with water (3 x 25ml). The organic layer was dried over sodium sulphate and concentrated to get the crude, used for the next step without further purification.

The **173** (50mg) was dissolved in methanol 25ml. Pt/C 10mg was added and the reaction stirred under H₂ balloon for 6h. The reaction was filtered through celite bed and washed with excess methanol. The organic layer was concentrated to get the crude. The crude was purified by flash chromatography using 100-200 mesh silica gel. The compound **174** was eluted at 20% ethyl acetate in hexane as half white coloured solid **174**. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.57 (d, 1H), 7.91 (d, 1H), 7.43 (s, 1H), 7.29 (s, 1H), 7.23 (d, 1H), 3.95 (s, 3H), 3.64 (dd, 1H), 3.40 (m, 1H), 3.23 (m, 2H), 2.75 (dd, 1H); MS-ES+357.8.

EXAMPLE 55: 4-chloro-5-methoxy-2-(4-((trifluoromethyl)thio)benzyl)-2,3-dihydro-1H-inden-1-one (**177**)

20



To a solution of 4-chloro-5-methoxy-2,3-dihydro-1H-inden-1-one **175** (100mg, 0.510mmol) in toluene 15mL was added compound **72** (123.4mg, 0.607mmol). PTSA (230.9mg, 1.214mmol) was added to the reaction mass, and stirred at 120°C for 6h. The reaction mass was diluted with ethyl acetate and washed with water (3 x 25mL). The organic layer was dried over sodium sulphate and concentrated to get the crude **176**, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 24 % ethyl acetate in hexane to afford yellow coloured solid.

The (E)-4-chloro-5-methoxy-2-(4-((trifluoromethyl)thio)benzylidene)-2,3-dihydro-1H-inden-1-one **176** (75mg, 0.195mmol) was dissolved in methanol 25ml to which was added

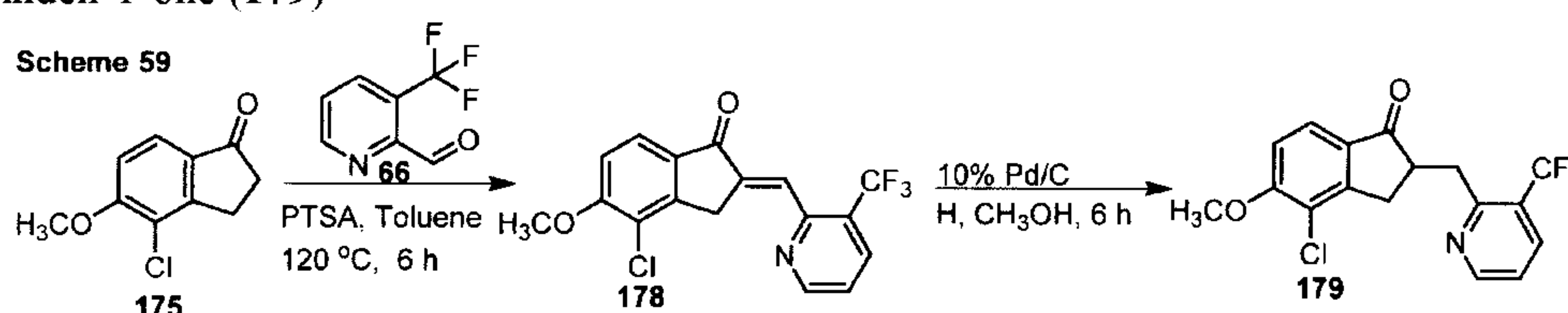
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Pt/c 40mg and the reaction stirred under H₂ balloon for 6h. The reaction was filtered through celite bed and washed with excess methanol. The organic layer was concentrated to get the crude, which was purified by flash chromatography using 100-200 mesh silica gel. The final compound **177** was eluted at 20% ethylacetate in hexane as half white coloured solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.69 (d, 1H), 7.58 (d, 2H), 7.29 (d, 2H), 6.98 (d, 1H), 3.99 (s, 3H), 3.38 (dd, 1H), 3.18 (dd, 1H), 2.99 (m, 1H), 2.73 (m, 1H); MS-ES+386.8.

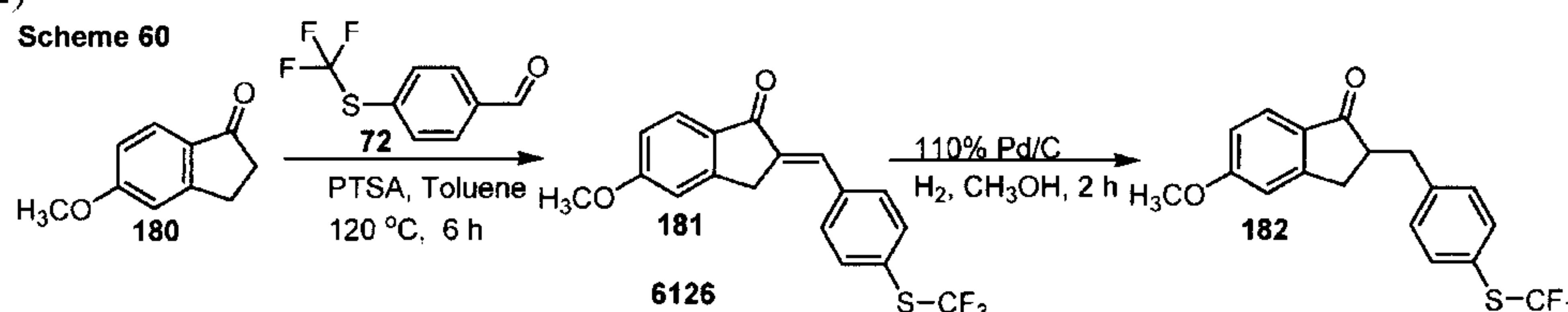
EXAMPLE 56: 4-chloro-5-methoxy-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-2,3-dihydro-1H-inden-1-one (**179**)



To a solution of **175** (100mg, 0.776mmol) in toluene 15ml was added **66** (203.9mg, 1.16mmol). PTSA (452mg, 2.303mmol) was added to the reaction mass and stirred at 120°C for 6h. The reaction mass was diluted with ethyl acetate and washed with water (3 x 25ml). The organic layer was dried over sodium sulphate and concentrated to get the crude **178**, used in the next step without further purification

The **178** (70mg) was dissolved in methanol 25ml, Pt/C 10mg added, and the reaction stirred under H₂ balloon for 6h. The reaction was filtered through celite bed and washed with excess methanol. The organic layer was concentrated to get the crude, which was purified by flash chromatography using 100-200 mesh silica gel. The compound **179** was eluted at 20% ethyl acetate in hexane as half white coloured solid **179**. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.60 (d, 1H), 7.91 (d, 1H), 7.72 (d, 1H), 7.24 (d, 1H), 6.99 (d, 1H), 4.00 (s, 3H), 3.66 (dd, 1H), 3.44 (m, 1H), 3.24 (m, 2H), 2.75 (dd, 1H); MS-ES+355.8.

EXAMPLE 57: 5-methoxy-2-(4-((trifluoromethyl)thio)benzyl)-2,3-dihydro-1H-inden-1-one (**182**)



To a solution of **180** (100mg, 0.617mmol) in toluene 15mL was added **72** (139.4mg, 0.6787mmol). PTSA (212.9mg, 1.234mmol) was added to the reaction mass, and stirred at 120°C for 6h. The reaction mass was diluted with ethyl acetate and washed with water (3 x 25mL). The organic layer was dried over sodium sulphate and concentrated to get the crude,

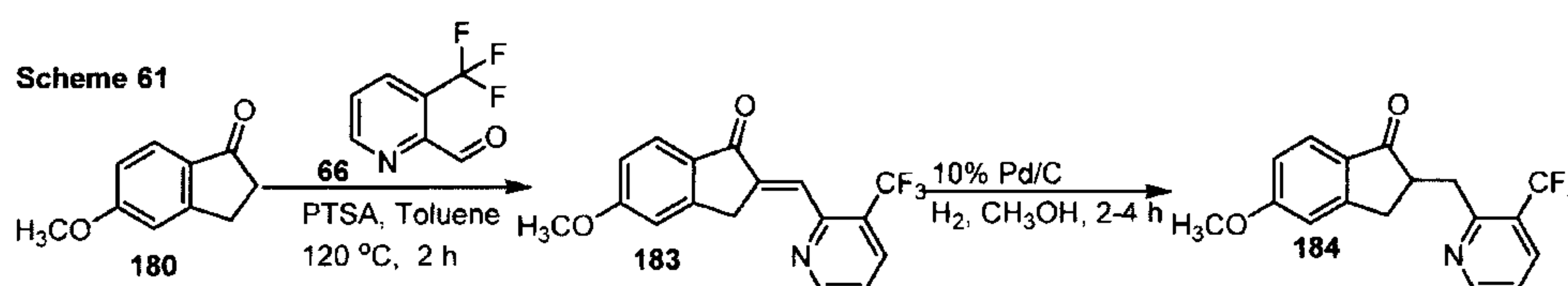
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which was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 15% ethyl acetate in hexane to afford **181** as a yellow solid.

The **181** (90mg, 0.270mmol) was dissolved in methanol 25mL, Pd/C 15mg added, and the reaction stirred under H₂ balloon for 6h. The reaction was filtered through celite bed and washed with excess methanol. The organic layer was concentrated to get the crude, which was purified by flash chromatography using 100-200 mesh silica gel. The compound was eluted at 20% ethyl acetate in hexane as half white coloured solid **182**. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.70 (d, 1H), 7.56 (d, 2H), 7.28 (d, 2H), 6.89 (m, 1H), 6.83 (m, 1H), 3.86 (s, 3H), 3.38 (dd, 1H), 3.13 (dd, 1H), 2.96 (m, 1H), 2.70 (m, 2H); MS-ES+352.9.

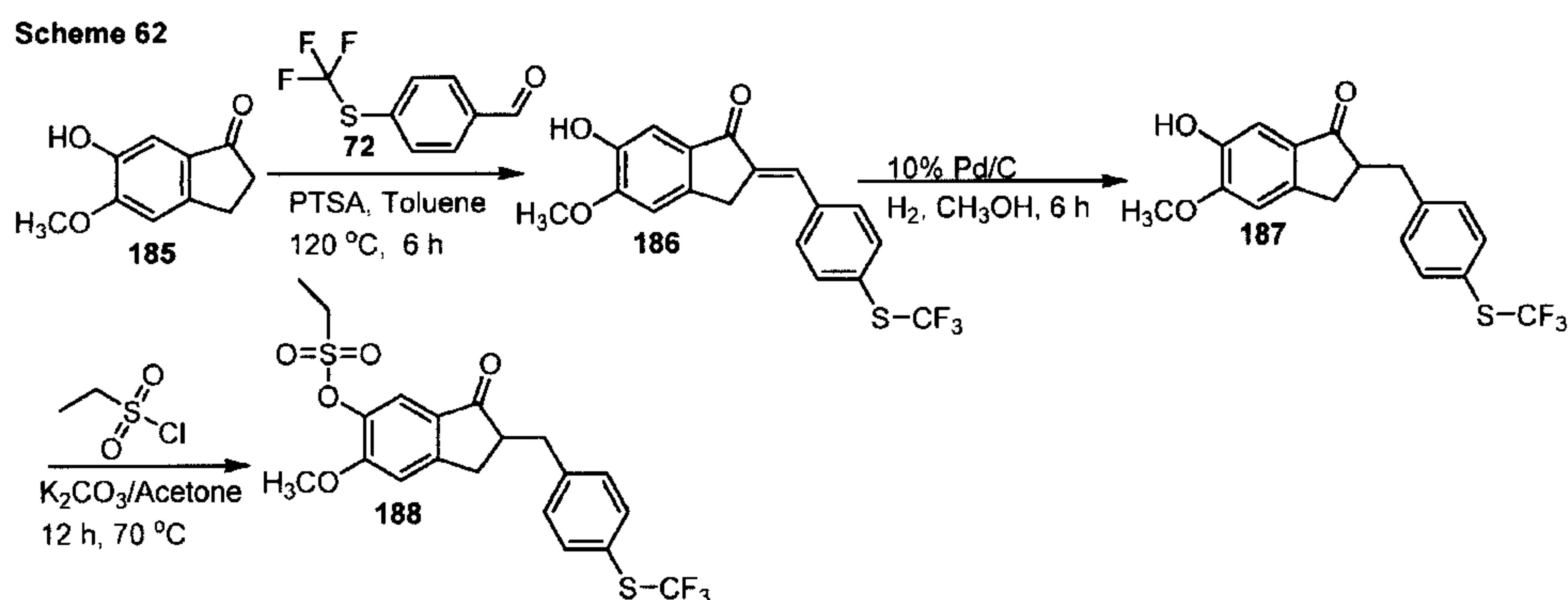
EXAMPLE 58: 5-methoxy-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-2,3-dihydro-1H-inden-1-one (**184**)



A solution of **180** (100mg, 0.617mmol) in toluene 15ml was added **66** (151.2mg, 0.864mmol). PTSA (234.5mg, 1.234mmol) was added to the reaction mass. The reaction was stirred at 120°C for 6h. The reaction mass was diluted with ethyl acetate and washed with water (3 x 25mL). The organic layer was dried over sodium sulphate and concentrated to get the crude **183**, used the next step without further purification.

The **183** (100mg) was dissolved in methanol 25ml, Pd/C 10mg added, and the reaction stirred under H₂ balloon for 6h. The reaction was filtered through celite bed and washed with excess methanol. The organic layer was concentrated to get the crude, which was purified by flash chromatography using 100-200 mesh silica gel. The compound **184** was eluted at 12% ethyl acetate in hexane as half white coloured solid **184**. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.64 (d, 1H), 7.91 (d, 1H), 7.72 (d, 1H), 6.90 (d, 1H), 6.85 (s, 1H), 3.87 (s, 3H), 3.65 (dd, 1H), 3.42 (m, 1H), 3.27 (m, 1H), 3.15 (m, 1H), 2.79 (dd, 1H); MS-ES+321.8.

EXAMPLE 59: 6-methoxy-3-oxo-2-(4-((trifluoromethyl)thio)benzyl)-2,3-dihydro-1H-inden-5-yl ethanesulfonate (**188**)

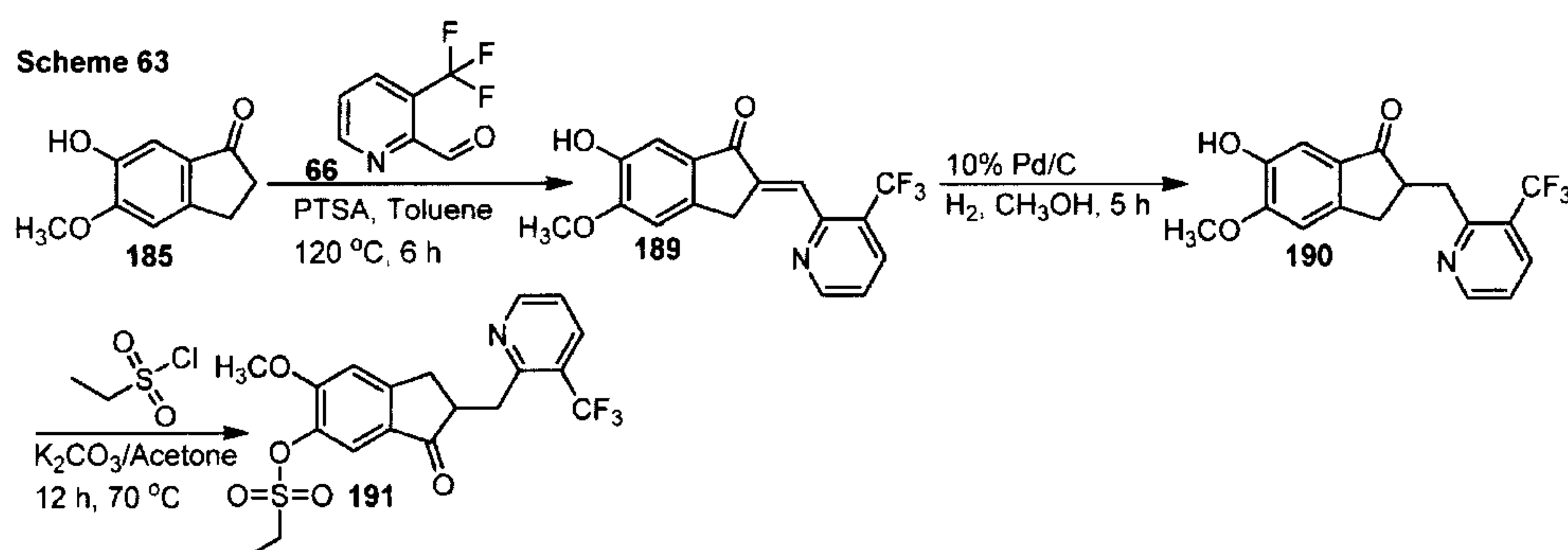


To a solution of **185** (50mg, 0.280mmol) in toluene 15mL was added **72** (34.4mg, 0.280mmol). PTSA (94.129mg, 0.561mmol) was added to the reaction mass and stirred at 120°C for 6h. The reaction mass was diluted with ethyl acetate and washed with water (3 x 25mL). The organic layer was dried over sodium sulphate and concentrated to get the crude, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound **186** was eluted at 30% ethyl acetate in hexane to afford yellow coloured solid.

The **186** (70mg 0.195mmol) was dissolved in methanol 25mL, Pd/C 30mg added, and the reaction stirred under H₂ balloon for 6h. The reaction was filtered through celite bed and washed with excess methanol. The organic layer was concentrated to get the crude **187** which was purified by flash chromatography using 100-200 mesh silica gel. The compound **187** was eluted at 20% ethyl acetate in hexane as half white coloured solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.56 (d, 2H), 7.28 (d, 2H), 6.80 (s, 1H), 5.67 (s, 1H), 3.96 (s, 3H), 3.36 (dd, 1H), 3.07 (dd, 1H), 2.94 (m, 1H), 2.70 (m, 2H); MS-ES+368.9.

The **187** (50mg, 0.1366mmol) was dissolved in acetone and K₂CO₃ (37.7mg, 0.2732mmol) added followed by ethane sulfonyl chloride (50mg, 0.1366mmol). The reaction was stirred for 12h at 70°C, then diluted with ethyl acetate and washed with water (3x50ml). The organic layer was concentrated to get the crude **188** which was purified by flash chromatography using 100-200mesh silica gel. The compound was eluted at 15% ethyl acetate in hexane as half white coloured solid **188**. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.65 (s, 1H), 7.57 (d, 2H), 7.27 (d, 2H), 6.94 (s, 1H), 3.95 (s, 3H), 3.35 (m, 3H), 3.14 (m, 1H), 2.99 (m, 1H), 2.71 (m, 2H), 1.57 (m, 3H); MS-ES+460.8.

EXAMPLE 60: 6-methoxy-3-oxo-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-2,3-dihydro-1H-inden-5-yl ethanesulfonate (**191**)

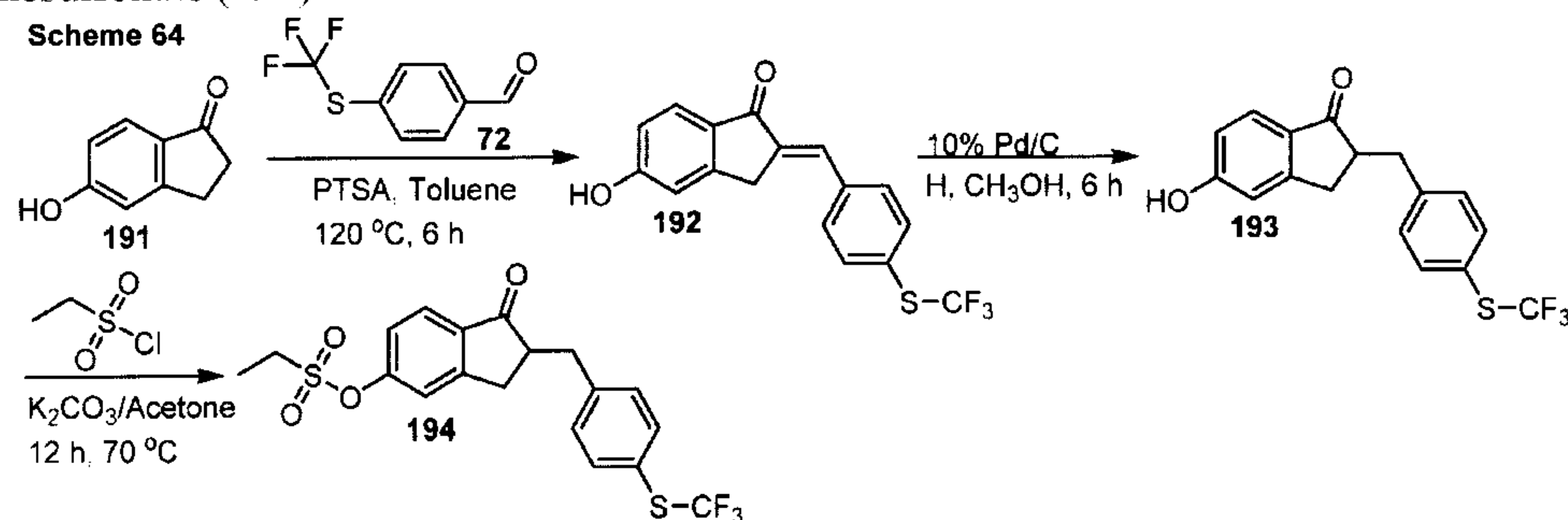


To a solution of **185** (50mg, 0.2808mmol) in toluene 15ml was added **66** (68.8mg, 0.393mmol). PTSA (106.7mg, 0.561mmol) was added to the reaction mass and stirred at 120°C for 6h. The reaction mass was diluted with ethyl acetate and washed with water (3 x 25ml.). The organic layer was dried over sodium sulphate and concentrated to get the crude **189**, which was used for next step without further purification.

The **189** (50mg) was dissolved in methanol 25ml, Pd/C 10mg added, and the reaction stirred under H₂ balloon for 6h. The reaction was filtered through celite bed and washed with excess methanol. The organic layer was concentrated to get the crude **190**, which was purified by flash chromatography using 100-200 mesh silica gel. The compound was eluted at 20% ethyl acetate in hexane as half white coloured solid **190**. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.64 (d, 1H), 7.91 (d, 1H), 7.29 (s, 1H), 6.82 (s, 1H), 3.97 (s, 3H), 3.64 (dd, 1H), 3.43 (m, 1H), 3.13 (m, 2H), 2.74 (dd, 1H); MS-ES+337.8.

The **190** (40mg, 0.108mmol) was dissolved in acetone, K₂CO₃ (29.9mg, 0.217mmol) added, followed by ethane sulfonyl chloride (16.6mg, 0.103mmol). The reaction was stirred for about 12h at 70°C. The reaction mass was diluted with ethyl acetate and washed with water (3 x 50mL). The organic layer was concentrated to get the crude **191**, which was purified by flash chromatography using 100-200 mesh silica gel. The compound was eluted at 14% ethyl acetate in hexane as half white coloured solid **191**. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.60 (d, 1H), 7.91 (d, 1H), 7.67 (s, 1H), 7.27 (s, 1H), 6.96 (s, 1H), 3.95 (s, 3H), 3.65 (dd, 1H), 3.42 (m, 2H), 3.20 (m, 2H), 2.82 (dd, 1H), 1.57 (m, 2H), 1.20 (m, 3H); MS-ES+ 429.8.

EXAMPLE 61: 1-oxo-2-(4-((trifluoromethyl)thio)benzyl)-2,3-dihydro-1H-inden-5-yl ethanesulfonate (**194**)



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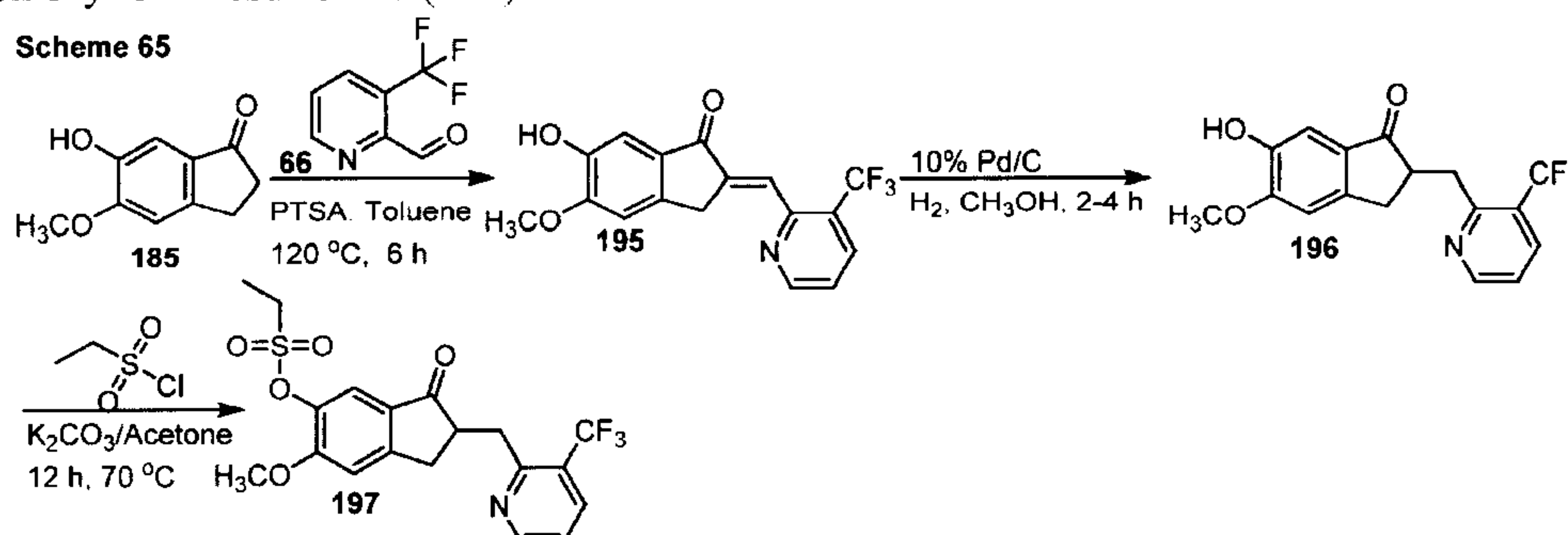
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To a solution of **191** (250mg, 1.688mmol) in toluene 15mL was added **72** (382.5mg, 1.858mmol). PTSA (641.7mg, 3.376mmol) was added to the reaction mass, then stirred at 120°C for 6h, diluted with ethyl acetate, and washed with water (3 x 25mL). The organic layer was dried over sodium sulphate and concentrated to get the crude, which was purified through
 5 flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 30% ethyl acetate in hexane to afford yellow coloured solid **192**.

The **192** (250mg, 0.744mmol) was dissolved in methanol 25mL, Pd/C 10mg added, and the reaction stirred under H₂ balloon for 6h. The reaction was filtered through celite bed and washed with excess methanol. The organic layer was concentrated to get the crude, which was
 10 purified by flash chromatography using 100-200 mesh silica gel. The compound was eluted at 20% ethylacetate in hexane as half white coloured solid **193**. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.69 (d, 1H), 7.56 (d, 2H), 7.28 (d, 2H), 6.79 (d, 2H), 5.46 (s, 1H), 3.38 (dd, 1H), 3.11 (dd, 1H), 2.97 (m, 1H), 2.70 (m, 2H); MS-ES+336.9.

The **193** (100mg, 0.295mmol) was dissolved in acetone and K₂CO₃ (62mg, 0.442mmol) added, followed by ethane sulfonyl chloride (42mg, 0.324mmol). The reaction was stirred for about 12h at 70°C. The reaction mass was diluted with acetate and washed with water (3 x 50mL). The organic layer was concentrated to get the crude, which was purified by flash chromatography using 100-200 mesh silica gel. The compound was eluted at 20% ethyl acetate in hexane as half white coloured solid **194**. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.81 (d, 1H), 7.58 (d, 2H), 7.34 (s, 1H) 7.26 (m, 3H), 3.33 (m, 3H), 3.21 (m, 2H), 3.02 (m, 1H), 2.75 (m, 2H), 1.56 (m, 4H), 1.28 (m, 3H); MS-ES+429.0.
 20

EXAMPLE 62: 6-methoxy-3-oxo-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-2,3-dihydro-1H-inden-5-yl ethanesulfonate (**197**)



To a solution of **185** (100mg, 0.6754mmol) in toluene 15mL was added **66** (130.09mg, 0.742mmol). PTSA for 6h. The reaction mass was diluted with ethyl acetate and washed with water (3 x 25mL). The organic layer was dried over sodium sulphate and concentrated to get the crude **195**, which was used for next step without further purification.
 25

The **195** (100mg) was dissolved in methanol 25ml, Pd/C 20mg added, and the
 30 reaction stirred under H₂ balloon for 6h. The reaction was filtered through celite bed and washed

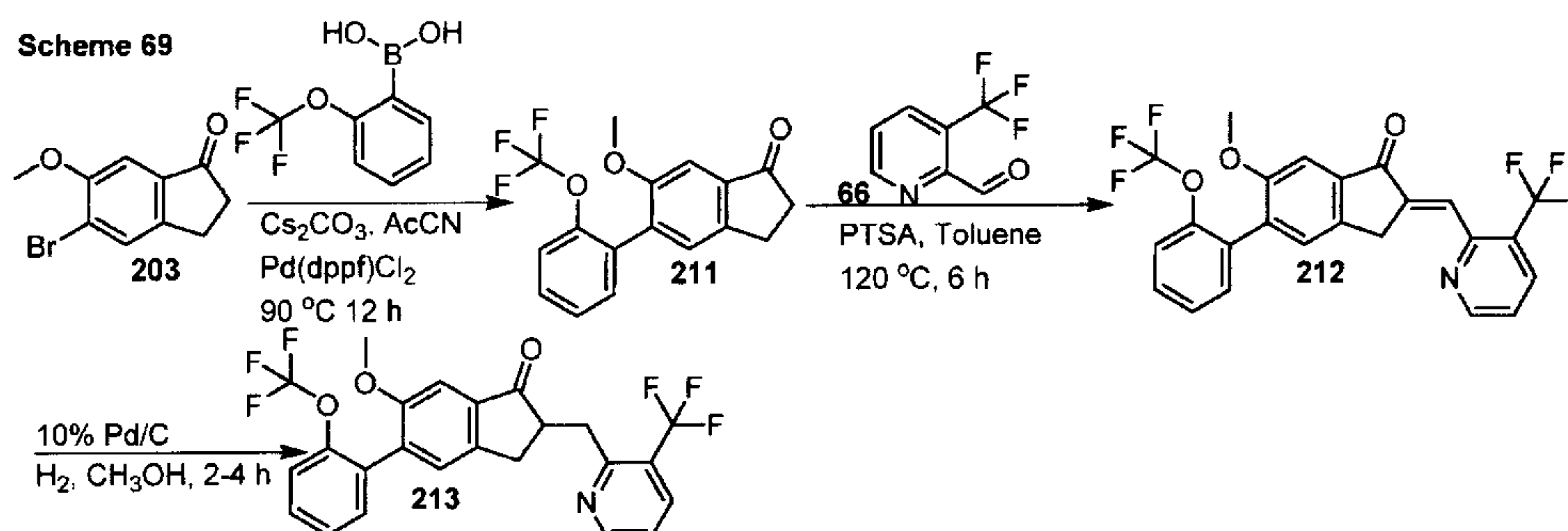
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with excess methanol. The organic layer was concentrated to get the crude **196**, which was purified by flash chromatography using 100-200 mesh silica gel. The compound **196** was eluted at 20% ethyl acetate in hexane as half white coloured solid **196**. ¹HNMR (400 MHz, CDCl₃) δ ppm 10.4 (s, 1H), 8.74 (d, 1H), 8.14 (d, 1H), 7.49 (m, 2H), 6.81 (m, 2H), 3.45 (dd, 1H), 3.18 (m, 2H), 3.01 (m, 1H), 2.77 (dd, 1H); MS-ES+ 307.8.

The **196** (40mg, 0.1299mmol) was dissolved in acetone, K₂CO₃ (35.7mg, 0.259mmol) added, followed by ethane sulfonyl chloride (33.1mg, 0.259mmol). The reaction was stirred for about 12h at 70°C. The reaction mass was diluted with acetate and washed with water (3x50ml).the organic layer was concentrated to get the crude **197**, which was purified by flash chromatography using 100-200 mesh silica gel. The compound was eluted at 20% ethyl acetate in hexane as half white coloured solid **197**. ¹HNMR (400 MHz, CDCl₃) δ ppm 8.56 (d, 1H), 7.91 (d, 1H), 7.83 (d, 1H), 7.35 (s, 1H), 7.27 (s, 1H), 3.64 (dd, 1H), 3.41 (m, 1H), 3.31 (m, 4H), 2.88 (m, 1H), 1.57 (m, 4H), 1.23 (m, 3H); MS-ES+ 399.9.

EXAMPLE 63: 6-methoxy-5-(2-(trifluoromethoxy)phenyl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-2,3-dihydro-1H-inden-1-one (**213**)



To a solution of **203** (100mg, 0.414mmol) and 2-(trifluoromethoxy)phenyl boronic acid (85.32mg, 0.414mmol) in acetonitrile was added cesium carbonate (271mg, 0.826mmol). The reaction was degassed and purged with N₂ for 10min. Pd(dppf)Cl₂ (16.88mg, 0.02mmol) was added to the reaction, then degassed and purged with nitrogen for another 10min. The reaction was heated to 90°C under sealed condition overnight. The reaction mixture was allowed to cool to rt, and diluted with chloroform. The organic layer was filtered through celite plug and concentrated to get the crude, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound **211** was eluted in 5% ethyl acetate in hexane as half white solid **211**.

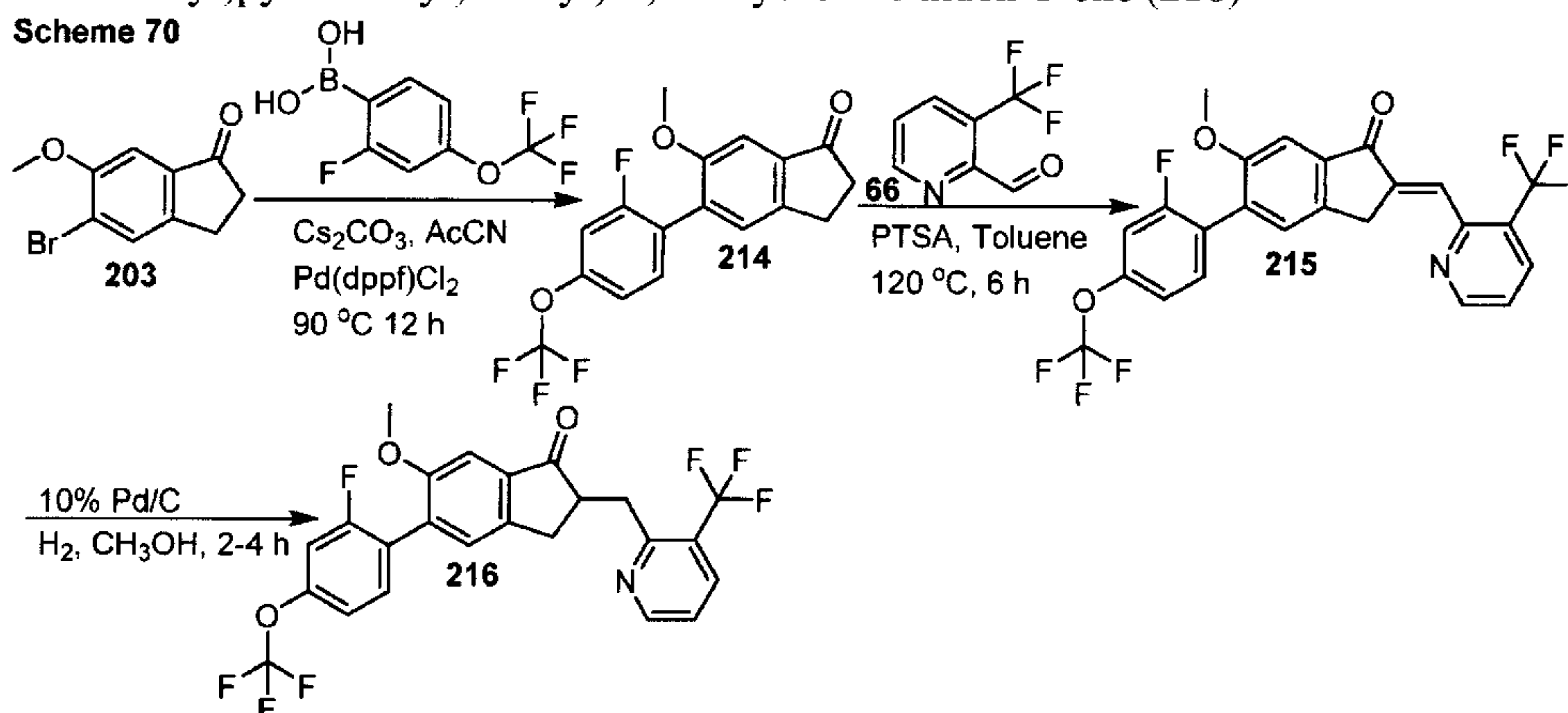
To a solution of **211** (150mg, 0.465mmol) and **66** (122mg, 0.698mmol) in toluene 15mL was added PTSA (177mg, 0.9314mmol). The reaction was stirred at 120°C for 6h, diluted with ethyl acetate and washed with water (3 x 25mL). The organic layer was dried over sodium sulphate and concentrated to get the crude **212**, which was purified through flash

chromatography by using 100-200 mesh silica gel. The compound **212** was eluted at 10% ethyl acetate in hexane to afford yellow coloured solid.

The **212** (70mg, 0.145mmol) was dissolved in methanol 25mL and Pd/C 10mg added. The reaction was stirred under H₂ balloon for 6h, then filtered through celite bed and washed with excess methanol. The organic layer was concentrated to get the crude **213** which was purified by flash chromatography using 100-200 mesh silica gel. The compound **213** was eluted at 12% ethyl acetate in hexane as half white coloured solid. ¹HNMR (400 MHz, CDCl₃) δ ppm 8.16 (d, 1H), 7.92 (d, 1H), 7.41 (m, 1H), 7.34 (m, 4H), 7.24 (m, 2H), 3.82 (s, 3H), 3.68 (dd, 1H), 3.49 (m, 1H), 3.26 (m, 1H), 2.79 (dd, 1H); MS-ES+ 482.0.

EXAMPLE 64: 5-(2-fluoro-4-(trifluoromethoxy)phenyl)-6-methoxy-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-2,3-dihydro-1H-inden-1-one (**216**)

Scheme 70

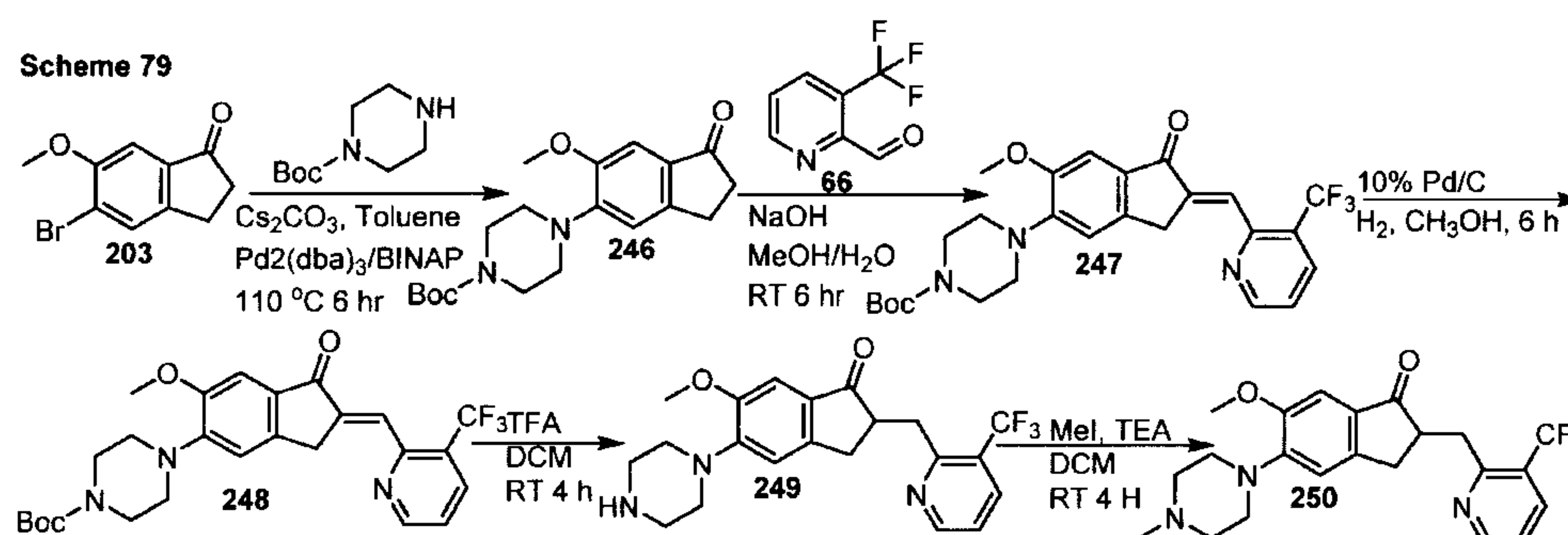


To a solution of **203** (100mg, 0.414mmol) and (2-fluoro-4-(trifluoromethoxy)phenyl)boronic acid (101.8mg, 0.456mmol) in acetonitrile was added cesium carbonate (272.1mg, 0.829mmol). The reaction was degassed and purged with nitrogen for 10min. Pd(dppf)Cl₂ (16.9mg, 0.020mmol) was added to the reaction, which was then degassed and purged with nitrogen for another 10min. The reaction was heated to 90°C under sealed condition overnight, then allowed to cool to rt, and diluted with chloroform. The organic layer was filtered through celite plug and concentrated to get the crude **214**, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted in 5% ethyl acetate in hexane as half white solid **214**.

To a solution of **214** (110mg, 0.322mmol) in toluene 15ml was added **66** (84.9mg, 0.483mmol). PTSA (122.4mg, 0.644mmol) was added to the reaction mass, which was stirred at 120°C for 6h. The reaction mass was diluted with ethyl acetate and washed with water (3 x 25mL). The organic layer was dried over sodium sulphate and concentrated to get the crude **215**, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 10% ethyl acetate in hexane to afford yellow coloured solid **215**.

The **215** (65mg, 0.130mmol) was dissolved in methanol 25mL, Pd/C 10mg added, and the reaction stirred under H₂ balloon for 6h, filtered through celite bed and washed with excess methanol. The organic layer was concentrated to get the crude **216**, which was purified by flash chromatography using 100-200 mesh silica gel. The compound **216** was eluted at 12% ethyl acetate in hexane as half white coloured solid. ¹HNMR (400 MHz, CDCl₃) δ ppm 8.63 (d, 1H), 7.92 (d, 1H), 7.36 (m, 2H), 7.28 (m, 2H), 7.06 (m, 2H), 3.86 (s, 3H), 3.68 (dd, 1H), 3.48 (m, 1H), 3.26 (m, 2H), 2.80 (dd, 1H); MS-ES+ 500.1.

EXAMPLE 65: 6-methoxy-5-(4-methylpiperazin-1-yl)-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-2,3-dihydro-1H-inden-1-one (**250**)



To a solution of **203** (1.0g, 0.0041mmol) and tert-butyl piperazine-1-carboxylate (960mg, 0.00518mmol) in toluene 15ml was added cesium carbonate (2.69g, 0.0082mmol). The reaction was degassed and purged with N₂ for 10min. Pd₂(dba)₃ (112mg, 0.000123mmol) and BINAP (153mg, 0.000246mmol) was added and again degassed and purged with nitrogen for another 10min. The reaction was heated to 110°C overnight under sealed condition, then diluted with chloroform and filtered through celite bed. The organic layer was concentrated to get the crude **246**, which was purified through flash chromatography by using 100-200 mesh silica gel eluting the compound at 25% Ethyl acetate in hexane as pale yellow coloured solid **246**.

To a solution of **246** (0.42g, 0.0012mmol) in MeOH/H₂O was added **66** (233mg, 0.00133mmol) and sodium hydroxide (96mg, 0.0024mmol). The reaction was stirred at RT for 6h, diluted with chloroform, and washed with water (3 x 25mL). The organic layer was dried over sodium sulphate and concentrated to get the crude, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound **247** was eluted at 30% ethyl acetate in hexane to afford yellow coloured solid **247**.

The **247** (400mg, 0.0009mmol) was dissolved in methanol 25mL and Pd/C 40mg added and the reaction stirred under H₂ balloon for 6h. The reaction was filtered through celite bed and washed with excess methanol. The organic layer was concentrated to get the crude **248**,

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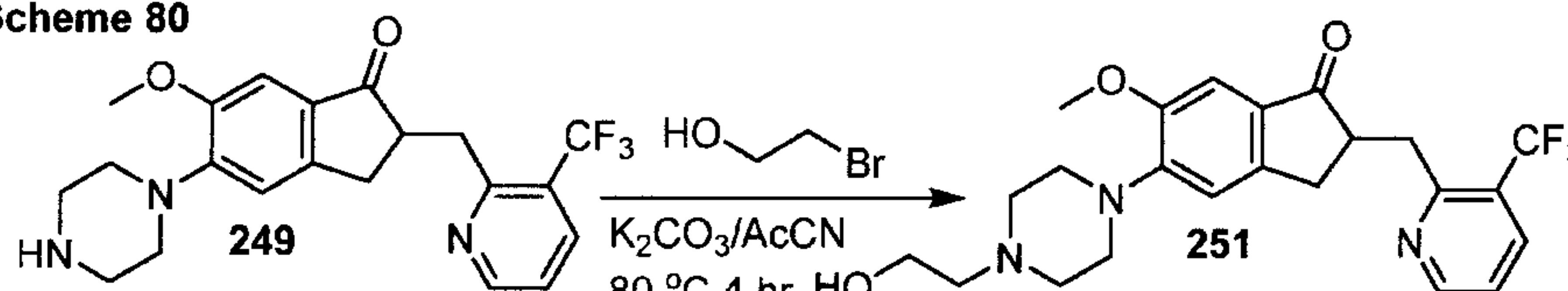
which was purified by flash chromatography using 100-200 mesh silica gel. The compound was eluted at 20% ethyl acetate in hexane as half white coloured solid **248**.

To a solution **248** (300mg, 0.0059mmol) in DCM was added trifluoroacetic acid 3ml and kept stirring for 4h at RT. After completion of the reaction, solvent was evaporated, and remainder diluted with water. The aqueous layer was washed with ethyl acetate and kept aside. The aqueous layer pH was adjusted to 9-10, then extracted with chloroform twice. The combined organic layer was dried over sodium sulphate and concentrated to get the crude **249**, which was titrated with hexane at 5°C to get pale yellow coloured solid **249**.

A solution of **249** (0.15g, 0.00037mmol) was dissolved in DCM. Triethyl amine (56mg, 0.00055mmol) was added to the reaction followed by methyl iodide (50mg, 0.00044mmol) and kept stirring at RT for 4h. After completion of the reaction, it was diluted with DCM and washed with water twice. The organic layer was dried over sodium sulphate and concentrated to get the crude **250**, which was purified through flash chromatography using neutral alumina eluting the compound at 2% MeOH in chloroform as thick sticky solid **250**.
¹HNMR (400 MHz, CDCl₃) δ ppm 8.65 (d, 1H), 7.91 (d, 1H), 7.27 (d, 1H), 7.20 (s, 1H), 6.90 (s, 1H), 3.90 (m, 4H), 3.64 (dd, 1H), 3.42 (m, 1H), 3.03 (m, 4H), 2.65 (m, 4H), 2.36 (m, 4H); MS-ES+420.0.

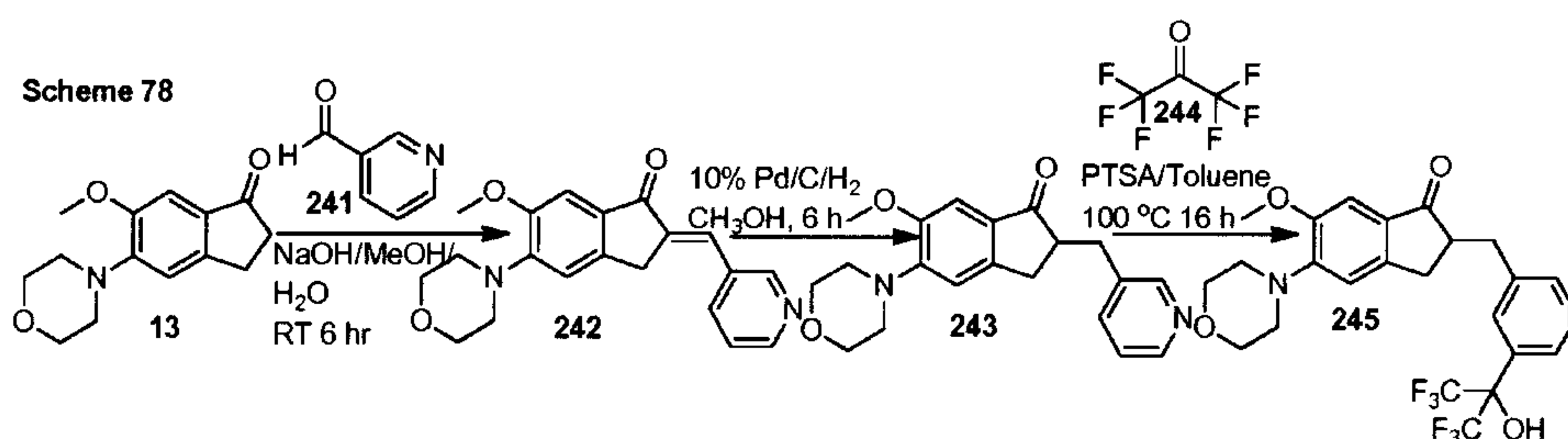
EXAMPLE 66: 5-(4-(2-hydroxyethyl)piperazin-1-yl)-6-methoxy-2-((3-(trifluoromethyl)pyridin-2-yl)methyl)-2,3-dihydro-1H-inden-1-one (**251**)

Scheme 80



To a stirred solution of **249** (150mg, 0.00037mmol) in acetonitrile was added potassium carbonate (100mg, 0.00074mmol) then 2-bromo ethanol (57mg, 0.00046mmol). The stirred reaction mixture was heated to 80 °C for 4h. After completion of the reaction, it was filtered through celite bed and washed with chloroform. The organic layer was concentrated to get the crude **251**, which was purified through flash chromatography using neutral alumina by eluting the compound at 2% methanol in chloroform to yield compound **251**.
¹HNMR (400 MHz, CDCl₃) δ ppm 8.65 (d, 1H), 7.91 (d, 1H), 7.20 (m, 2H), 6.84 (s, 1H), 3.89 (m, 5H), 3.66 (m, 4H), 3.43 (m, 1H), 3.12 (m, 4H), 3.03 (m, 1H), 2.72 (m, 4H), 2.63 (m, 3H); MS-ES+450.0.

EXAMPLE 67: 2-((5-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)pyridin-3-yl)methyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one (**245**)

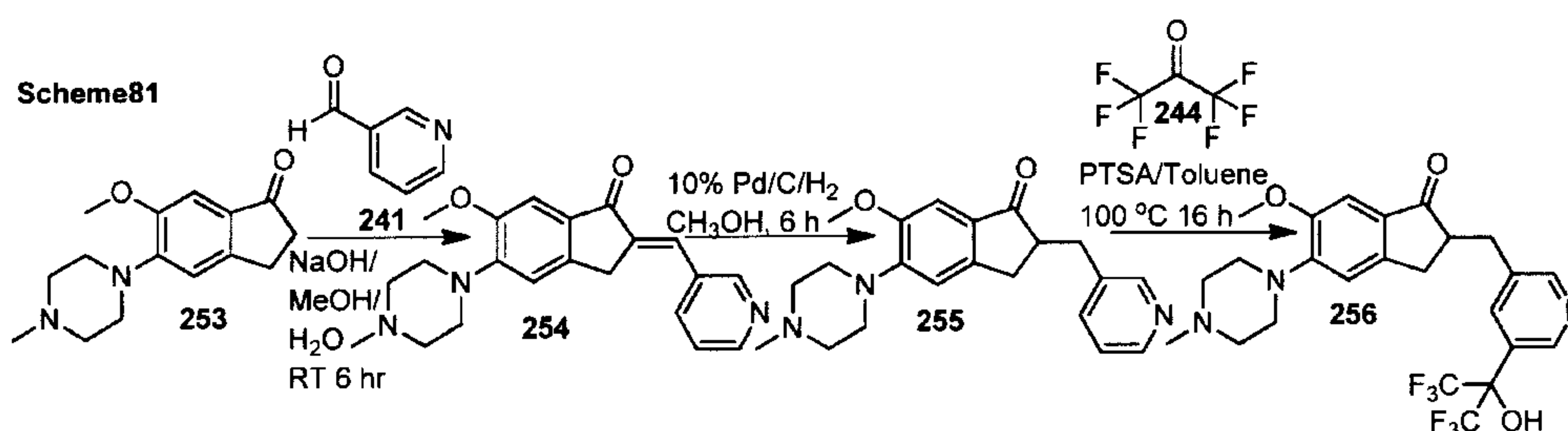


To a solution of **13** (0.1g, 0.404 mmol) in MeOH/H₂O (1:1) was added nicotinaldehyde **241** (0.052g, 0.484mmol) and NaOH (0.032g, 0.808mmol). The reaction was stirred at RT for 6h, diluted with chloroform and washed with water (3 x 25 mL). The organic layer was dried over sodium sulphate and concentrated to get the crude, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound **242** was eluted at 30% ethyl acetate in hexane to afford yellow coloured solid (E)-6-methoxy-5-morpholino-2-(pyridin-3-ylmethylene)-2,3-dihydro-1H-inden-1-one **242**.

The **242** (0.1g 0.297mmol) was dissolved in methanol 25ml and Pd/C 40mg added. The reaction was stirred under H₂ balloon for 6h. The reaction was filtered through celite bed and washed with excess methanol. The organic layer was concentrated to get the crude which was purified by flash chromatography using 100-200 mesh silica gel. The compound **243** was eluted at 20% ethyl acetate in hexane as half white coloured solid 6-methoxy-5-morpholino-2-(pyridin-3-ylmethyl)-2,3-dihydro-1H-inden-1-one **243**. ¹HNMR (400 MHz, CDCl₃) δ ppm 8.47 (m, 2H), 7.56 (d, 1H), 7.22 (m, 1H), 7.17 (s, 1H), 6.84 (s, 1H), 3.89 (m, 3H), 3.87 (m, 4H), 3.30 (dd, 1H), 3.07 (m, 4H), 2.99 (m, 1H), 2.95 (m, 1H), 2.70 (m, 2H).

To a stirred solution of **243** (0.08g, 0.236 mmol) in toluene was added PTSA (0.090g, 0.472mmol) and kept stirring at 120°C. Hexafluoroacetone **244** (0.129g, 0.590mmol) was added to the reaction and heated to 100°C for 16h. Reaction was cooled to RT, diluted with water, extracted with ethyl acetate twice, the organic layer dried over sodium sulphate and concentrated to get the crude, which was purified through flash chromatography by using 100-200 mesh silica gel eluting the compound at 30% ethyl acetate in hexane as thick sticky solid 2-((5-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)pyridin-3-yl)methyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one **245**. ¹HNMR (400 MHz, CDCl₃) δ ppm 7.06 (m, 2H), 6.88 (s, 1H), 6.90 (s, 1H), 6.123 (s, 1H), 3.88 (m, 7H), 3.49 (m, 1H), 3.08 (m, 2H), 3.03 (m, 6H), 2.29 (m, 2H).

EXAMPLE 68: 2-((5-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)pyridin-3-yl)methyl)-6-methoxy-5-(4-methylpiperazin-1-yl)-2,3-dihydro-1H-inden-1-one (**256**)



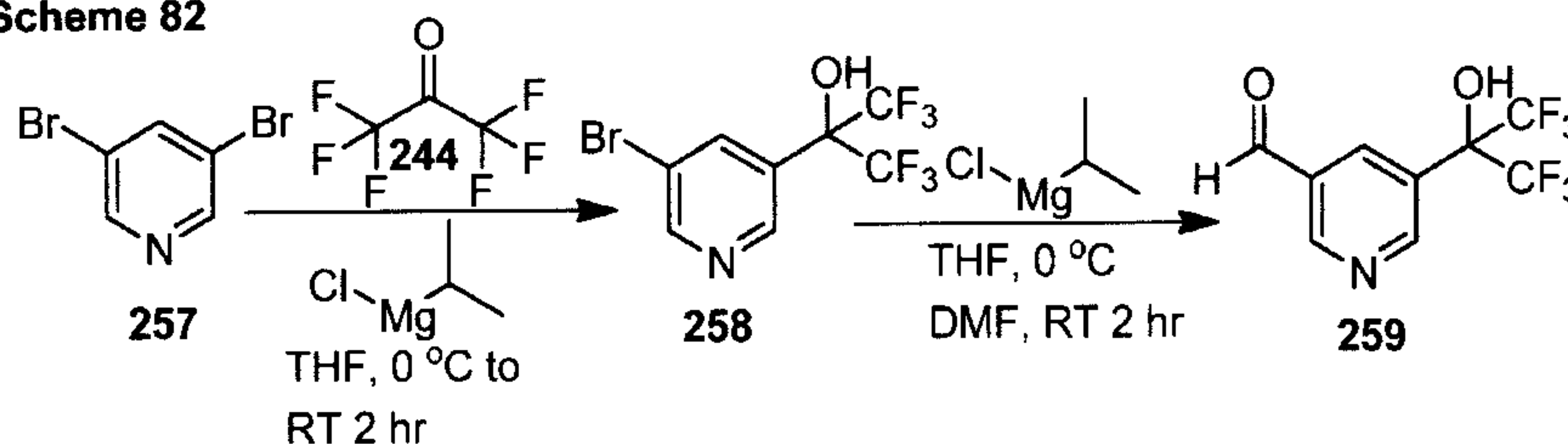
To a solution of 6-methoxy-5-(4-methylpiperazin-1-yl)-2,3-dihydro-1H-inden-1-one **253** (0.1g, 0.384mmol) in MeOH/H₂O (1:1) was added nicotinaldehyde (0.049g, 0.461mmol) and NaOH (0.03g, 0.768mmol) was added to the reaction mass, which was then stirred at RT for 6h. The reaction mass was diluted with chloroform and washed with water (3 x 25mL). The organic layer was dried over sodium sulphate and concentrated to get the crude, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 30% ethyl acetate in hexane to afford yellow coloured solid (E)-6-methoxy-5-(4-methylpiperazin-1-yl)-2-(pyridin-3-ylmethylene)-2,3-dihydro-1H-inden-1-one **254**.

The **254** (0.08g, 0.229mmol) was dissolved in methanol 25ml, Pd/C 20mg added and the reaction stirred under H₂ balloon for 6h. The reaction was filtered through celite bed and washed with excess methanol. The organic layer was concentrated to get the crude, which was purified by flash chromatography using 100-200 mesh silica gel. The compound was eluted at 20% ethyl acetate in hexane as half white coloured solid 6-methoxy-5-(4-methylpiperazin-1-yl)-2-(pyridin-3-ylmethyl)-2,3-dihydro-1H-inden-1-one **255**.

To a stirred solution of **255** (0.05g, 0.142mmol) in toluene was added PTSA (0.054g, 0.284mmol) and kept stirring at 120°C. Hexafluoroacetone **244** (0.078g, 0.356mmol) was added to the reaction and kept at temperature and stirred for 16h. Reaction was then cooled to RT, diluted with water, and extracted with ethyl acetate twice, The organic layer was dried over sodium sulphate and concentrated to get the crude, which was purified through flash chromatography by using 100-200 mesh silica gel and eluting the compound at 30% ethyl acetate in hexane as thick sticky solid 2-((5-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)pyridin-3-yl)methyl)-6-methoxy-5-(4-methylpiperazin-1-yl)-2,3-dihydro-1H-inden-1-one **256**.

EXAMPLE 69: 5-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)nicotinaldehyde (**259**)

Scheme 82



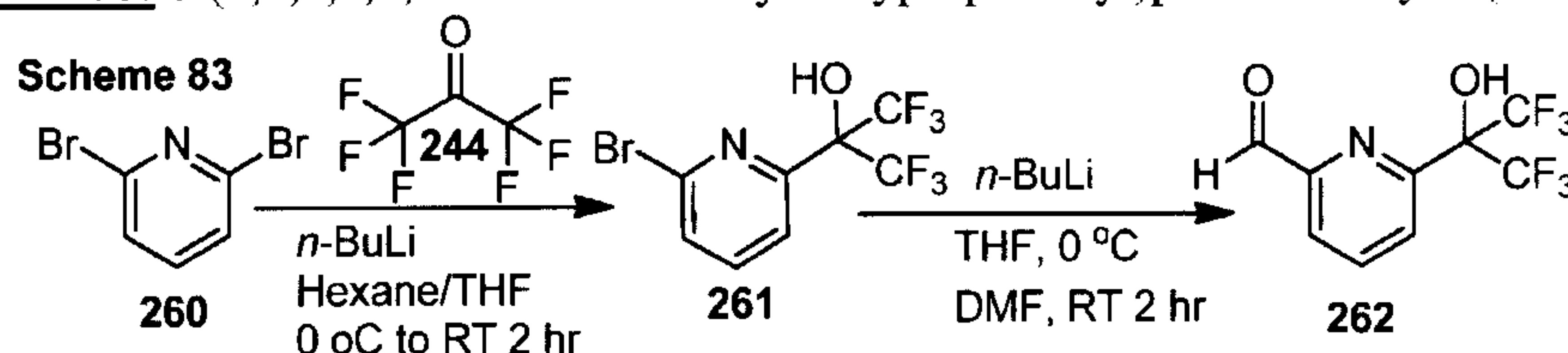
To a stirred solution of 3,5-dibromo pyridine **257** (1.09g, 4.60mmol) in dry THF cooled to 0°C, was added isopropyl magnesium chloride (2.4mL, 4.8mmol) drop wise while stirring for 10min. Hexafluoroacetone (CF₃-CO-CF₃) **244** was added to the resulting reaction and continued stirring for another 2h. After completion of the starting materials, the reaction was

5 quenched with saturated ammonium chloride solution. The organic layer was separated and aqueous phase was extracted again with diethyl ether, the combined organic layer was dried over sodium sulphate and concentrated to get the crude 2-(5-bromopyridin-3-yl)-1,1,1,3,3,3-hexafluoropropan-2-ol **258**. The crude was purified through silica gel by using 100-200 mesh silica gel by eluting the compound at 20:5 ethyl acetate in hexane as thick oil of compound **258**.

10 To a stirred solution of **258** (0.347g, 1.07mmol) in dry THF, cooled to 0°C, was added isopropyl magnesium chloride (1.2mL, 2.4mmol) drop wise and stirred for 10min followed by the addition of DMF (0.015ml, 1.94mmol) to the reaction and stirred for additional 2h. After completion of the reaction, it was quenched with saturated ammonium chloride solution. The organic layer was separated and aqueous phase was extracted again with diethyl ether, the

15 combined organic layer was dried over sodium sulphate and concentrated to get the crude compound 5-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)nicotinaldehyde **259** used directly to proceed for the next step.

EXAMPLE 70: 6-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)picolinaldehyde (**262**)



20 To a stirred solution of 2,6-dibromo pyridine **260** (2.37g, 10mmol) in dry THF, cooled to 0°C, *n*-BuLi 1.4mmol in hexane (7.9ml, 11mmol) was added drop wise, and stirred for 10min. Then hexafluoroacetone (CF₃-CO-CF₃) **244** was added to the reaction mixture and continued stirring for another 2h. After completion of the reaction, it was quenched with saturated ammonium chloride solution. The organic layer was separated and aqueous phase was extracted

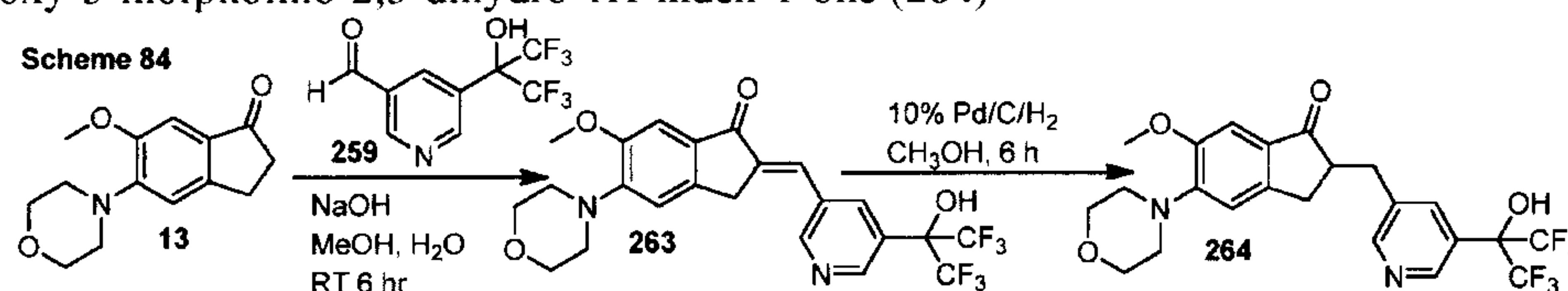
25 again with diethyl ether, the combined organic layer was dried over sodium sulphate and concentrated to get the crude compound 2-(6-bromopyridin-2-yl)-1,1,1,3,3,3-hexafluoropropan-2-ol **261**, which was purified through 100-200 mesh silica gel by eluting the compound at 15 % Ethylacetate in hexane to get the thick oil compound **261**.

To a stirred solution of **261** (0.5g, 1.54mmol) in dry THF, cooled to 0°C, *n*-BuLi

30 (0.118g, 1.85mmol) was added drop wise and continued stirring for 10min. Then DMF (0.224g, 3.08mmol) was added to the reaction mixture while stirring for another 2h. After completion of the reaction, it was quenched with saturated ammonium chloride solution. The organic layer was

separated and aqueous phase was extracted again with diethyl ether, the combined organic layer was dried over sodium sulphate and concentrated to get the crude compound 6-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)picolinaldehyde **262**.

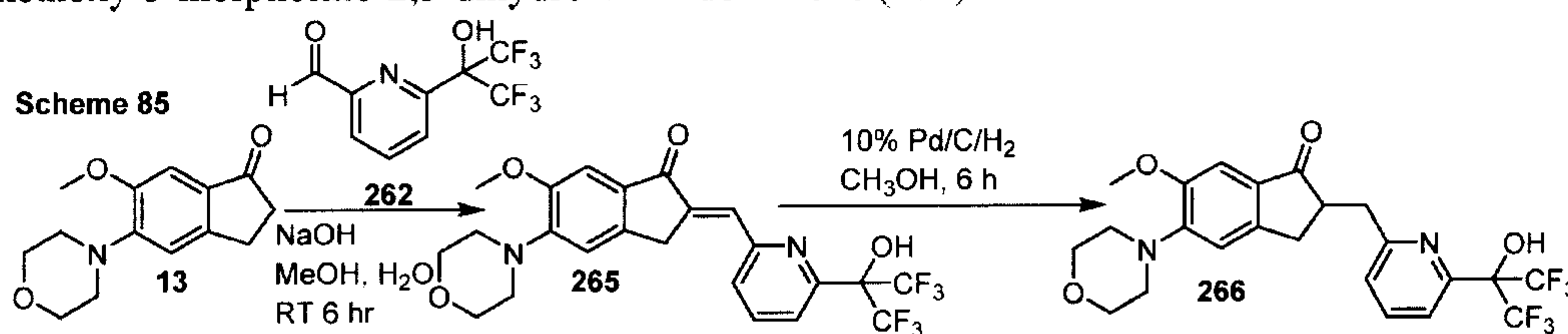
EXAMPLE 71: 2-((5-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)pyridin-3-yl)methyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one (**264**)



To a solution of **13** (0.1g, 0.40mmol), MeOH/H₂O (1:1), was added 5-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)nicotinaldehyde **259** (0.132g, 0.485mmol) and NaOH (0.032g, 0.80mmol). The reaction was stirred at RT for 6h. The reaction mass was diluted with chloroform and washed with water (3 x 25ml). The organic layer was dried over sodium sulphate and concentrated to get the crude **263**, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 30% ethyl acetate in hexane to afford yellow coloured solid (E)-2-((5-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)pyridin-3-yl)methylene)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one **263**.

The **263** (50mg, 0.090mmol) was dissolved in methanol 25ml, Pd/C 40mg added, and the reaction stirred under H₂ balloon for 6h. The reaction was filtered through celite bed and washed with excess methanol. The organic layer was concentrated to get the crude, which was purified by flash chromatography using 100-200 mesh silica gel. The crude compound **264** was eluted at 20% ethyl acetate in hexane as half white coloured solid 2-((5-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)pyridin-3-yl)methyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one **264**.

EXAMPLE 72: 2-((6-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)pyridin-2-yl)methyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one (**266**)



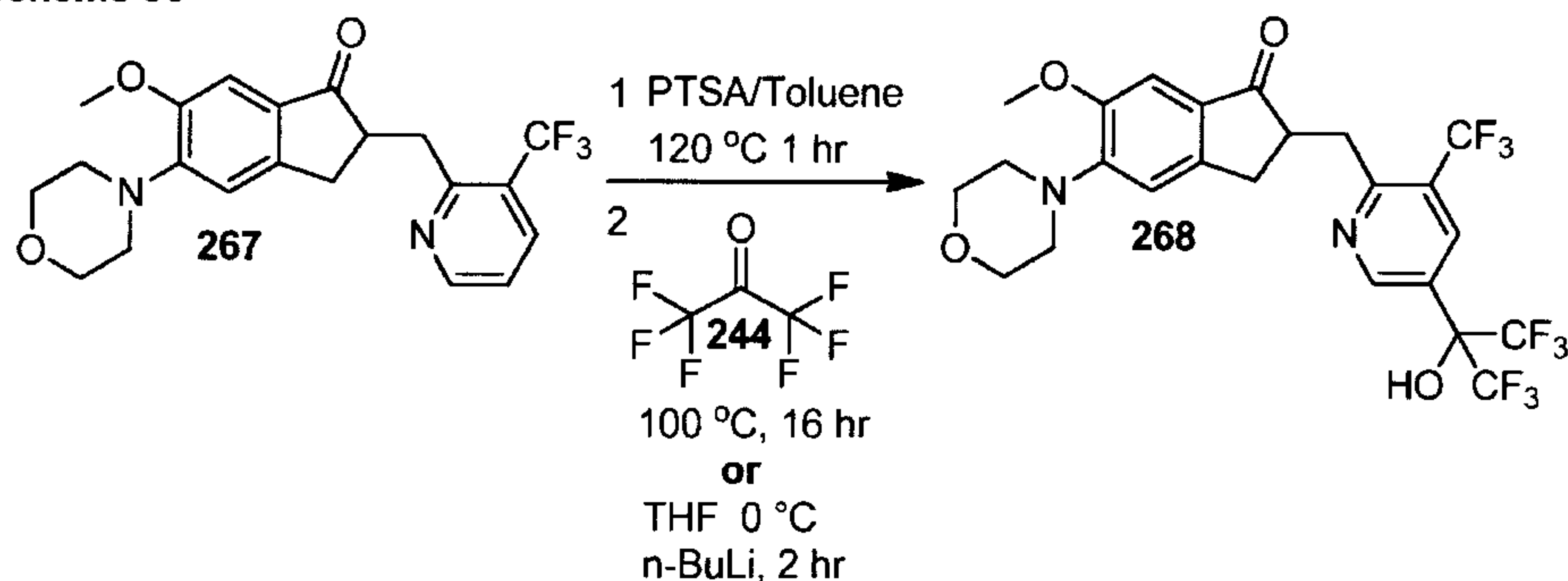
To a solution of **13** (0.1g, 0.40mmol) in MeOH/H₂O (1:1) was added 6-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)picolinaldehyde **262** (0.132g, 0.485mmol), NaOH (0.032g, 0.80mmol), and the reaction stirred at RT for 6h. The reaction mass was diluted with chloroform and washed with water (3 x 25 ml). The organic layer was dried over sodium sulphate and concentrated to get the crude, which was purified through flash chromatography by using 100-

200 mesh silica gel. The compound **265** was eluted at 30% ethyl acetate in hexane to afford yellow coloured solid (E)-2-((6-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)pyridin-2-yl)methylene)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one **265**.

The **265** (50mg 0.1mmol) was dissolved in methanol 25ml, Pd/C 40mg added, and the reaction stirred under H₂ balloon for 6h. The reaction was filtered through celite bed and washed with excess methanol. The organic layer was concentrated to get the crude **266** and was purified by flash chromatography using 100-200 mesh silica gel. The **266** compound was eluted at 20% ethyl acetate in hexane as half white coloured solid 2-((6-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)pyridin-2-yl)methyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one **266**.

EXAMPLE 73: 2-((5-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-3-(trifluoromethyl)pyridin-2-yl)methyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one (**268**)

Scheme 86



15

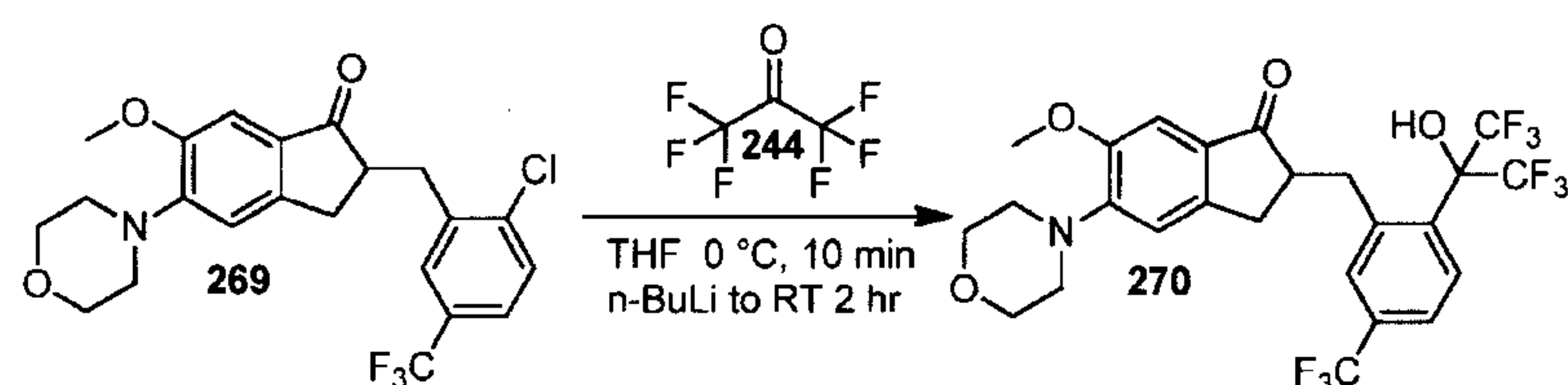
To a stirred solution of **267** (0.1g, 0.245mmol) in toluene was added PTSA (0.094g, 0.490mmol) and kept stirring at 120°C for 1h. After the addition of hexafluoroacetone **244** (0.134g, 0.614mmol), the reaction was heated to 100°C for 16h. After completion of the reaction, it was cooled to RT, diluted with water, and extracted with ethyl acetate twice. The organic layer was dried over sodium sulphate and concentrated to get the crude compound **268**, which was purified through flash chromatography by using 100-200 mesh silica gel eluting the compound at 30% ethyl acetate in hexane as thick sticky solid compound 2-((5-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-3-(trifluoromethyl)pyridin-2-yl)methyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one **268**.

20

EXAMPLE 74: 2-(2-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-5-(trifluoromethyl)benzyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one (**270**)

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To a stirred solution of 2-(2-chloro-5-(trifluoromethyl)benzyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one **269** (0.1g, 0.226mmol) in dry THF, cooled to 0°C, n-BuLi (0.021g, 0.339mmol) was added drop wise and the solution stirred for 10min. Then

5 hexafluoroacetone **244** (0.10g, 0.453mmol) was added to the reaction and stirred for another 2h. After completion of the reaction, it was quenched with saturated ammonium chloride solution. The organic layer was separated and aqueous phase was extracted again with diethyl ether, the combined organic layer was dried over sodium sulphate and concentrated to get the crude **270**, which was purified through 100-200 mesh silica gel by eluting with 15 % ethyl acetate in

10 hexane to give 20 mg of compound 2-(2-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-5-(trifluoromethyl)benzyl)-6-methoxy-5-morpholino-2,3-dihydro-1H-inden-1-one **270**.

ADDITIONAL EXAMPLES OF USAGE METHOD

EXAMPLE 75:

15 **Structural Modelling of ROR γ t**: The compounds of Formula **I** provided in **TABLE 1A & 1B** were designed using a crystal structures of ROR γ t. Nuclear hormone receptor superfamily ROR α/γ contains a signature type II zinc finger DNA binding motif and a ligand binding hydrophobic pocket. Three subtypes; ROR α , - β , and - γ (NR1F1-3 or RORA-C), have been identified with unique tissue distributions and biological function. In the thymus, ROR α

20 and two isoforms, γ 1 and γ 2 (ROR γ t/ROR- γ T), have been identified with ROR γ t distinct from the ROR γ 1 isoform in that it lacks the amino terminus of ROR γ 1. A sequence of ROR- γ t (NP_001001523, 1-497) search with in the rcsb.org provided the 6 homologues X-ray crystal structure templates and 3B0W is selected for FFDD strategy lead to the discovery of substituted 2, 3-dihydro-1*H*-inden-1-one containing ROR γ antagonists depicted in **Figure 1** and its

25 analogues.

IN VITRO INHIBITION ASSAYS

EXAMPLE 76:

TR-FRET ROR γ t Binding Assay: ROR γ -LBD contains a 6-His and GST tag peptide from SRC1-2 an aminoterminal biotinyl-CPSSHSSLTERHKILHRLQLQEGSPS was employed

30 and the 6-His-(GST) ROR γ -LBD was used which expressed and purified from baculovirus infected Sf-21 insect cells from Invitrogen and purified using glutathione sepharose. The assay

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protocol included 50 μ L of TR-FRET buffer 50mM KCl, 50mM TRIS, 1mM Na-EDTA, 0.1mM DTT, (pH 7.0); 10nM of 6-His(GST)ROR γ -LBD, 1nM Anti-6-His-Eu , 0.1 μ M of SRC1_2 peptide and Strep-APC 10nM. The peptide binding due to dose-curves of compounds was added the 0.1 % DMSO. Fluorescence at wavelength 340nm was read in each well of 94 well plates
 5 using an Envision fluorescence reader in Time Resolved mode after overnight incubation at 4°C. Dose-response data and IC₅₀ values are provided in the TABLE 3.

EXAMPLE 77:**Effects of the test compounds on the ROR γ -activated IL-17A**

Prom/LUCPorter™ HEK 293 cells: Antagonistic (or inverse agonistic) effects of the test
 10 compounds on the ROR γ -activated IL-17A Prom/LUCPorter™ HEK 293 cells were analyzed and IC₅₀ of each compound was evaluated. The IL-17A Prom/LUCPorter™ HEK 293 cell line (IMGENEX, IML-301) was plated in 96-well white plates at 0.75×10^5 cells per well for overnight. Cells were transfected with the ROR γ plasmid (IMGENEX, IMP-122) for 6h. Cells were treated with a series of 8 point concentrations of each compound (100, 33.33, 11.11, 3.70,
 15 1.23, 0.41, 0.14 and 0.0457 μ M) for 16h. Luciferase activity was analyzed using the luciferase reporter assay reagent (IMGENEX, LS100). The data were analyzed using Excel and Prism software. Percent activity was defined as $100 \times (1 - (\text{Well} - \text{Control A}) / (\text{Control B} - \text{Control A}))$, where Control A was the wells containing cells transfected with ROR γ and Control B was the wells containing non-transfected cells. Both Controls A and B were treated with vehicle
 20 alone.

IC₅₀ evaluation of selected compound from the TABLE 1 on ROR γ -mediated IL-17A promoter activity and its 10 dose-response curve is given in **Figure 2 and 3**.

EXAMPLE 78:

Cytokine IL-17 estimation by HTRF: The assay was designed to assess the potency
 25 of test compounds on IL-17 cytokine release from CD4+ T cells. In order to aid in the identification of potent inhibitors, the IC₅₀'s determined for the test compounds IL-17 release from CD4+ T cells through the generation of 10 point Dose Response Curves (DRC). Assay methods used to quantify IL-17 secretion is HTRF (Homogenous Time Resolved Fluorescence). IL-17 secreted is detected by anti-IL-17 MAb labeled with XL665, the second MAb labeled with
 30 Cryptate, which binds to specific epitopes of human IL-17. Upon close proximity of both acceptor and donor energy transfer (FRET) occurs. This technique has been further enhanced by using long-lived labels combined with the detection on a time-resolved fluorescence basis, allowing maximization of prompt fluorescence interferences.

The assay was performed according to manufacturer's instruction. All the reagents were reconstituted according to instructions provided. The reagents were dispensed into a half area 96-well plate in the following order: 10µL standard or sample, IL-17 MAbXL665 and 5µL IL-17 Cryptate. For the negative control, the standard or sample is replaced by 10µL of diluent.

5 The plate is covered with a plate sealer and incubated at rt for 2h. Following incubation, the plate sealer is removed and the plate is read using HTRF protocol on Envision Microplate reader. All of the data analysis was carried out using Microsoft Excel (2010) and IC₅₀ was determined using GraphPad Prism 4 software. %Inhibition of the test compounds were determined utilizing the following formula:

10
$$\% \text{Inhibition} = 100 - (100 * (\text{Average Test Compound Counts} - \text{Average Negative Control Counts}) / (\text{Average Positive Control Counts} - \text{Average Negative Control Counts}))$$
. Dose-response data and IC₅₀ values are provided in the **TABLE 3**.

15 **TABLE 3:** List of substituted 2, 3-dihydro-1*H*-inden-1-one containing compounds and corresponding RORyt antagonistic, cellular and IL-17 inhibition results*

Example ID	RORyt Binding	RORyt Cell Specific	IL-17 Inhibition
16	**	**	**
20	**	*	**
23	***	**	***
25	NA	*	NA
28	**	*	**
31	**	*	**
34	NA	NA	NA
30	*	*	**
32	***	***	**
37	***	***	***
39	NA	NA	NA
42	**	NA	**
44	NA	NA	*
47	**	**	**
50	***	**	**
53	**	**	**
56	**	**	**
59	**	*	**
62	**	**	***
65	*	**	**
68	***	***	***
71	*	*	**
74	*	*	**
77	**	**	**
80	**	**	**
83	**	**	**

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86	**	**	**
89	**	**	***
92	**	**	**
95	**	**	**
98	NA	NA	NA
103	***	**	**
106	***	**	**
110	***	***	**
113	***	***	**
117	***	**	**
120	NA	NA	NA
123	**	**	**
125	**	**	**
128	**	**	**
131	**	**	**
133	**	**	**
136	NA	NA	NA
138	NA	NA	NA
140	***	**	*
142	**	**	***
144	**	**	**
146	**	**	***
149	***	*	**
151	**	**	**
154	**	**	***
156	*	***	**
158	***	**	***
161	**	***	**
164	***	**	***
167	**	**	***
169	**	**	***
172	**	**	***
174	**	**	***
177	***	**	***
179	***	**	***
182	**	**	***
184	***	**	***
187	**	**	***
188	***	**	***
190	***	**	***
191	***	***	***
193	***	***	***
194	***	***	***
196	***	**	**
197	***	***	***
200	NA	NA	NA
202	NA	NA	NA
206	NA	NA	NA
209	NA	NA	NA
213	***	**	***

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216	**	**	***
220	NA	NA	NA
225	NA	NA	NA
229	***	***	***
232	***	***	***
236	**	**	***
240	***	***	***
242	***	***	***
245	**	***	**
249	**	***	**
250	**	***	**
251	***	***	***
256	***	***	***
264	***	***	***
266	***	***	***
268	***	***	***
270	NA	NA	NA

*ROR γ t antagonistic, cellular and IL-17 inhibition activity result for selected compounds

*** <0.5 μ M, ** >1.0 μ M, * >10 μ M

NA = Not Available

5 IN VIVO MODELS EXPERIMENT

EXAMPLE 79:

Efficacy of substituted 2, 3-dihydro-1*H*-inden-1-one containing selected compounds on Inhibition of Anti-CD3e Antibody induced CD4⁺T cell Cytokine-IL-17 Production in Male BALB/c Mice

- 10 **In Vivo Mice Cytokine IL-17 by ELISA Method:** A quantitative analysis of mouse IL-17 sandwich ELISA was conducted from the collected serum samples (Mouse IL-17 ELISA Ready-DuoSet ELISA kit, from R&D Systems, USA). The serum samples tested were collected from mice after 1.5 h of anti-CD3e antibody challenge, before antibody challenge, the mice were treated with different doses of test compounds or Dexamethasone as mentioned above in
- 15 experimental design. The capture antibody was diluted in coating buffer (1X PBS) and transferred into each well. The plate was sealed and incubated overnight at RT. The following day the wells of the plate were aspirated and washed (3 times), allowing a one minute soak time in each step. The plate was blocked using 1% BSA in PBS, sealed, and incubated in ambient conditions for not less than one hour. After the incubation period, the plate was washed as
- 20 described above, and the standards and serum samples were added to the appropriate wells and incubated for two hours at RT. The samples were diluted in a 1:10 ratio with 1% BSA in PBS (reagent diluent). After two hours, well were washed as mentioned above three times and added the detection antibody and incubated for two hours. After washing (as mentioned above), the HRP enzyme is added and incubated for 20min and washed again and added substrate according

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to the manufacturer's instructions and incubated for 30min/until blue color develops. The plate was read at 450/570 nm using the Microplate Absorbance Reader (SpectraMax; M3). **Statistics:** One-Way ANOVA was performed followed by Dunnett's multiple comparison test. Per cent inhibition of cytokine production was calculated for all groups compared to positive control.

5 **IL-17 production:** Intravenous administration of 5 ug/animal anti-CD3e antibody to each mice resulted in significant elevation of IL-17 production at 1.5 h time point compared to negative control group. Oral administration of test compounds 10mg/kg, 20mins prior to antibody administration resulted in 50% respectively. Dexamethasone treatment showed 94%, respectively, reduction in IL-17 production when compared to positive control group. Data is
10 shown in **Figure 4**.

EXAMPLE 80:

Pharmacokinetic Experiments: The bio-availability and pharmacokinetics of some compounds of the present invention were examined in male Sprague Dawley rats. A total of 6
15 male rats were used in the study. The study was performed using parallel design (n=3) with serial sampling.

 Dose formulations were prepared on the day of doing. Blood samples were collected at 0.083 (only IV), 0.25, 0.5, 1, 2, 4, 8 and 24 h post-dose. At each time point, approximately 0.2mL of blood was withdrawn from each cannulated rat through jugular vein and transferred to
20 a pre-labeled microfuge tube containing 20 µL of 200mm K2EDTA per mL of blood. Following collection of blood sample, equal volume of heparinized saline was flushed into jugular vein of rat. The blood samples were centrifuged at 5000g for 5min at $4 \pm 2^{\circ}\text{C}$. The plasma was separated within 30min of scheduled time and stored below -60°C until bio-analysis. The plasma samples were analyzed for selected test EXAMPLES using a fixed-for purpose liquid
25 chromatographic tandem mass spectrometric detection (LC-MS/MS) method with a lower limit of quantification of 2.21ng/mL. The pharmacokinetic parameters for select EXAMPLES were calculated using the non-compartmental analysis tool of validated WinNonlin® software (Version 5.2).

 Pharmacokinetic parameters (mean $\pm$ SD; n = 3) of 7 following intravenous bolus and
30 oral gavage administration of 7 solution in male Sprague Dawley rats are shown in **TABLE 4** below:

TABLE 4: Rat PK: The pharmacokinetic profiles of substituted 2, 3-dihydro-1*H*-inden-1-one containing compounds following intravenous bolus administration and oral gavage in male
35 Sprague Dawley rats.

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Formulation	Group	Route/Dose (mg/kg)	T _{max} (h)	C _{max} (ng/mL)	AUC _{last} (ng.h/mL)	AUC _{inf} (ng.h/mL)	CL (mL/min/kg)	V ₃₅ (L/kg)	T _{1/2} (h)	F ^a
Solution	1	IV/2	n/a	1937.82 ±481.94	571.57 ±57.37	589.36 ±63.88	56.98 ±5.85	7.18 ± 2.00	6.63 ± 4.92	19
	2	PO/10	2.00 ^c (1.00- 2.00)	176.16 ±22.73	552.65 ±123.98	557.70 ±124.96	n/a	n/a	n/a	

^aAUC_{inf} and nominal doses were used for bioavailability (F) calculation; ^bback extrapolated concentration at time zero; ^cT_{max} reported as median (min-max); n/a: not applicable

EXAMPLE 81: Assessment of the potency of test compounds on IL-17 release from CD4⁺ T cells: We have established robust *in vitro* cell-based HTRF assay for the activation and stimulation of CD4⁺ T lymphocytes to T helper 17 (Th17) cell differentiation and IL-17 production. The test compounds are selective small-molecule inhibitors of ROR γ t, was found to inhibit IL-17 production, with an IC₅₀ of 220 nM to 1.2 μ M. The assay quantification was performed using a standard Dex and SB203589 reported to inhibit IL-17, with an IC₅₀ of 14 & 37 nM respectively. These series of compounds dose dependently inhibited CD4⁺ T cell pool and exhausted IL-17 release from mouse splenocytes.

EXAMPLE 82: Efficacy of dihydro-1*H*-inden-1-one class analogues in MOG₃₅₋₅₅ Induced EAE in Female C57BL/6 mice: To establish the *in vivo* proof-of-concept in chronic mouse MOG EAE model, the lead dihydro-1*H*-inden-1-one class analogues was administered orally for QD 28 days as a prophylactic treatment where the disease severity was successfully controlled for dihydro-1*H*-inden-1-one class analogues and control Fingolimod (**Figure 5**). The cumulative EAE scores (Scale: 0-3.5) of 0.2, 0.0, 0.4, 0.7, 0.1 on days 9-18 (p=0.001) and reached to 0 on day 18 to until day 28th (p=0.001) for dihydro-1*H*-inden-1-one class analogues and similar scores observed for Fingolimod as well (**Figure 6**). The results are striking for this study, whereas the positive control (disease mice) with an EAE score of >3.0 (>95% disease incidence). The dihydro-1*H*-inden-1-one class treated mice was well tolerated through put the study with optimal body conditions and had no signs of Clinical Chemistry changes or toxicity events observed throughout the study. All the mice in the treatment groups are similar body weights to that of vehicle treated group. Oral dihydro-1*H*-inden-1-one class analogues treatment from this study provided a compelling evidence of its ROR γ t antagonistic activity, translating cellular efficacy in to *in vivo* further supports these series of compounds for MS and other indications claimed. All references are incorporated by reference herein in their entireties.

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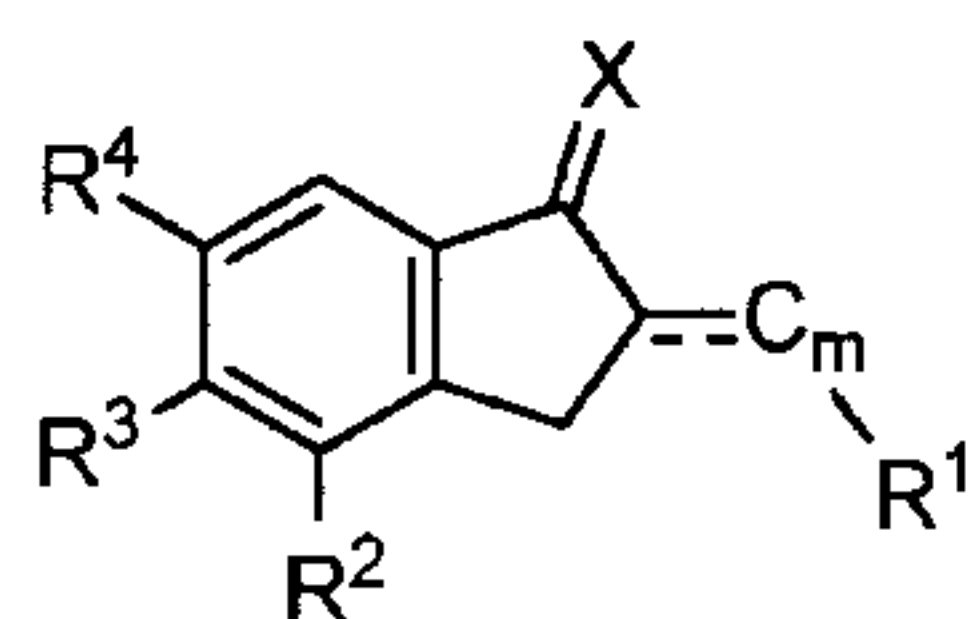
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What is claimed is:

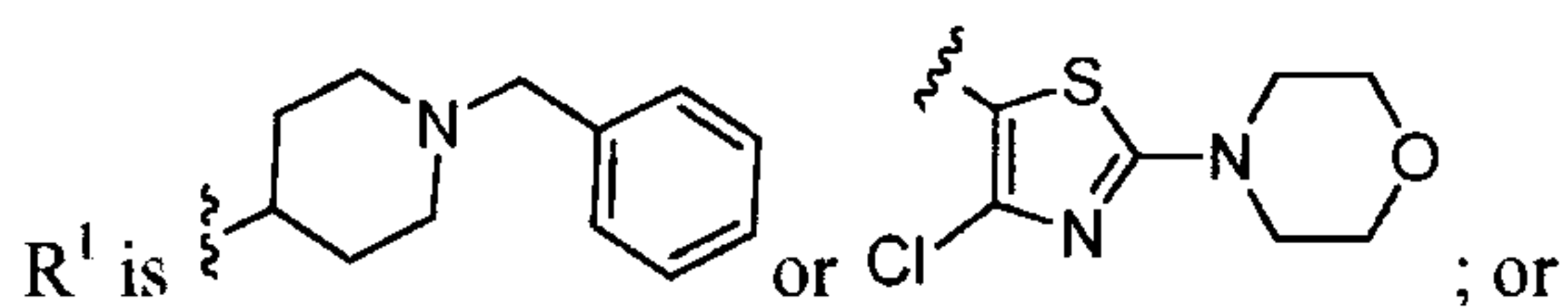
Claim 1. A compound according to Formula I:



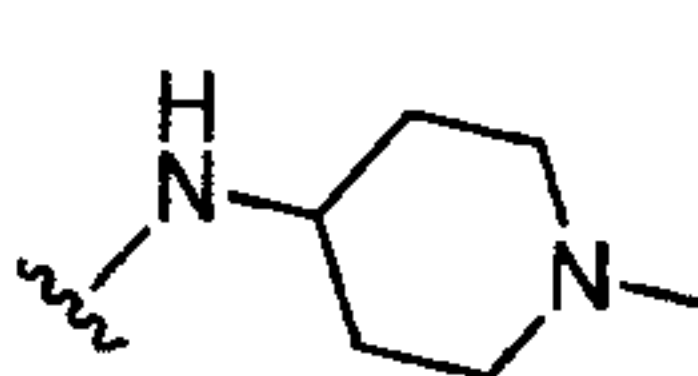
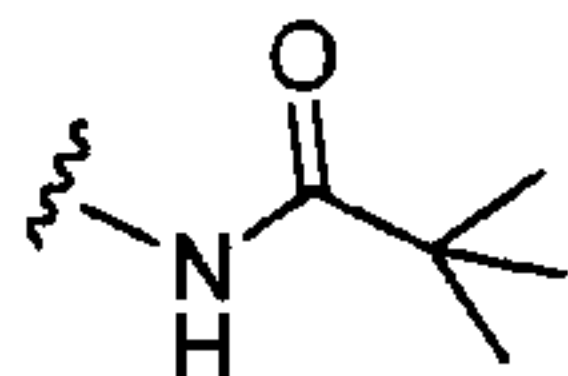
(I)

or pharmaceutically acceptable salts thereof, wherein:

X is O or S;



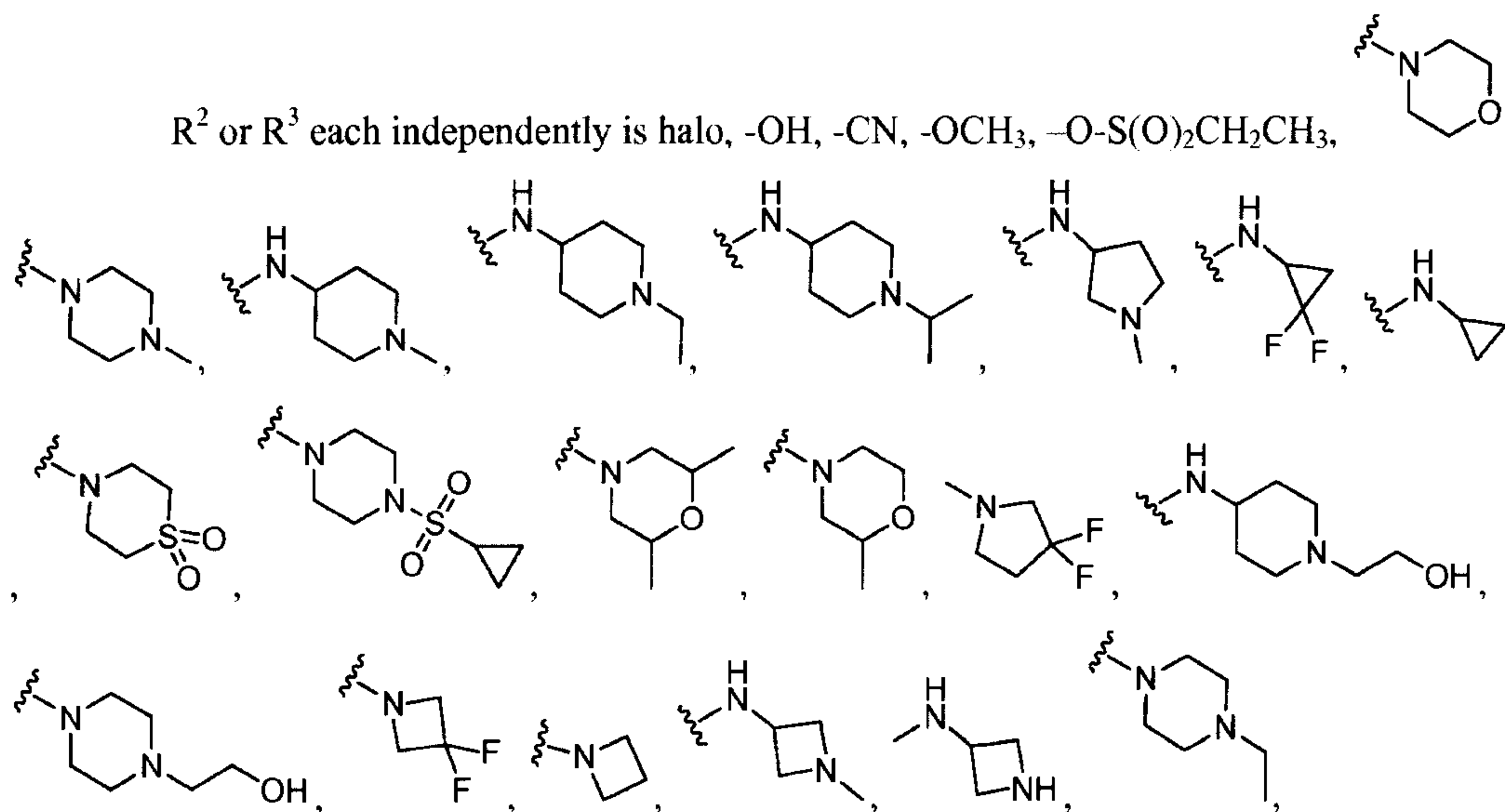
R^1 is C_{1-4} alkyl optionally substituted with 1-6 independent halo substituents; or
 R^1 is phenyl, pyridinyl, or pyrazolyl, each optionally substituted with 1-5 independent halo, trifluoromethyl, (trifluoromethyl)thio, trifluoromethoxy, 1,1,1,3,3,3-hexafluoro-2-

hydroxypropan-2-yl, , or  substituents;

m is 0 or 1;

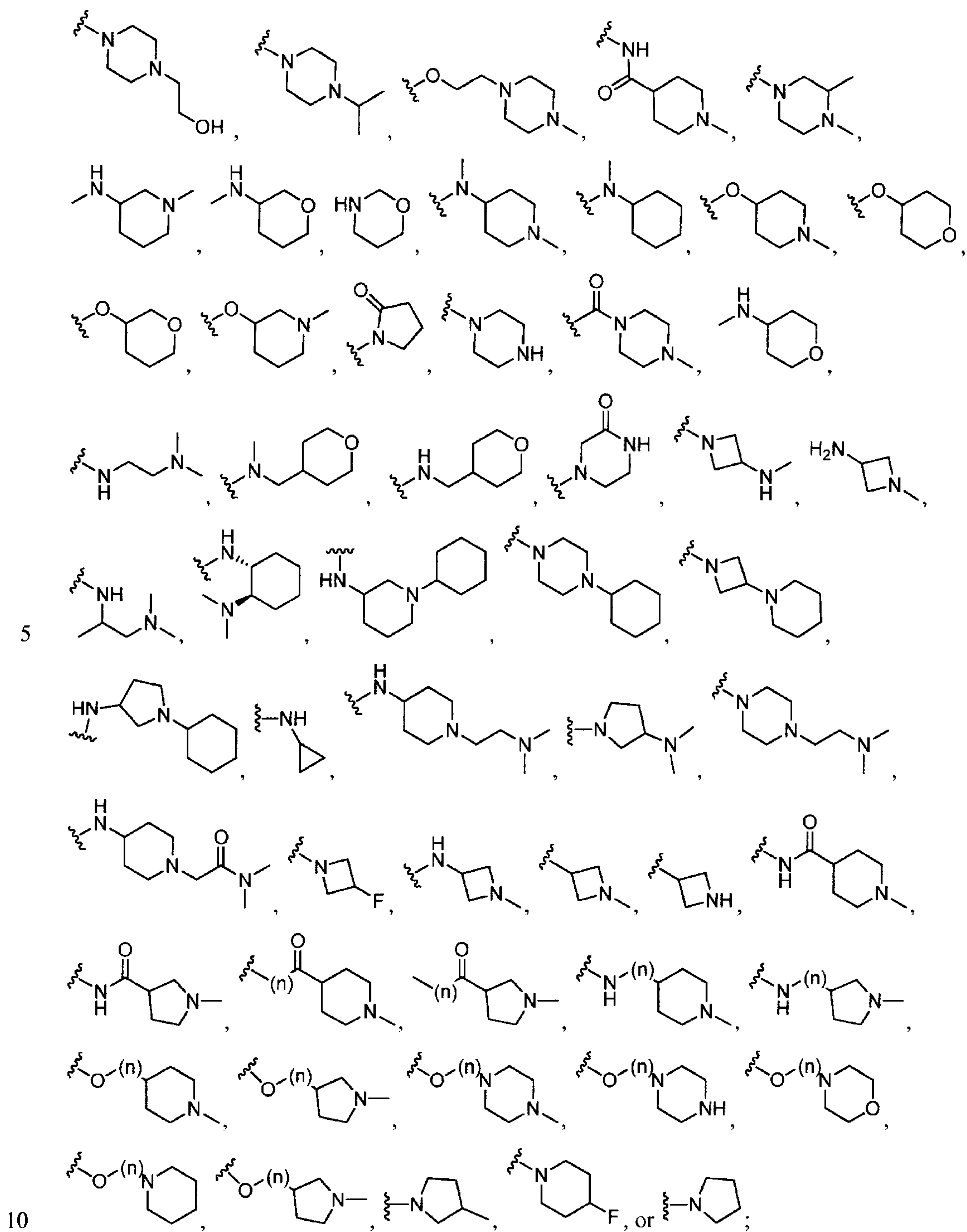
the dotted line indicates an optional double bond when $m=1$;

R^2 or R^3 each independently is halo, -OH, -CN, -OCH₃, -O-S(O)₂CH₂CH₃,



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or R^2 or R^3 each independently is phenyl optionally substituted with 0-5 independent halo, trifluoromethoxy substituents;

n is 2 or 3 carbon chain; and

R^4 is H, OH, OCH_3 , or $-O-S(O)_2CH_2CH_3$.

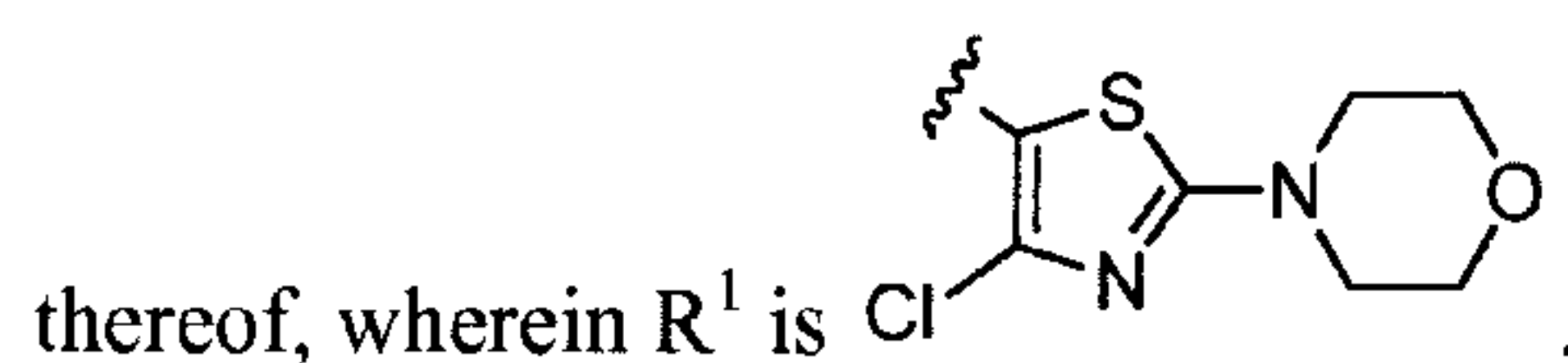
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Claim 2. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein X is O.

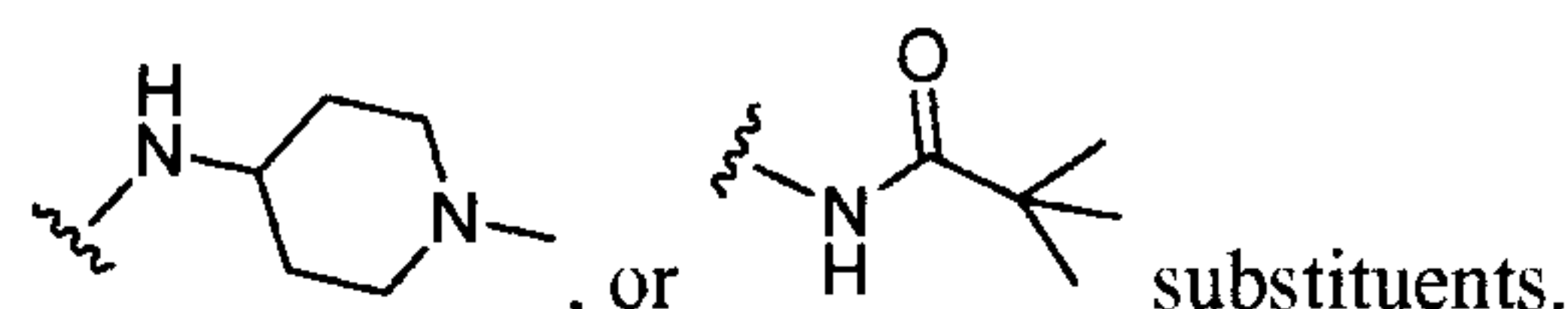
Claim 3. The compound according to claim 2, or a pharmaceutically acceptable salt thereof, wherein R¹ is.

Claim 4. The compound according to claim 2, or a pharmaceutically acceptable salt

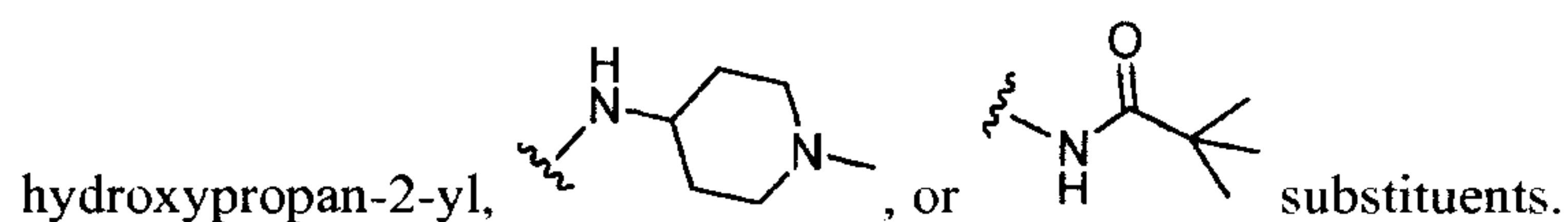


Claim 5. The compound according to claim 2, or a pharmaceutically acceptable salt thereof, wherein R¹ is C₁₋₄alkyl optionally substituted with 1-6 independent halo substituents.

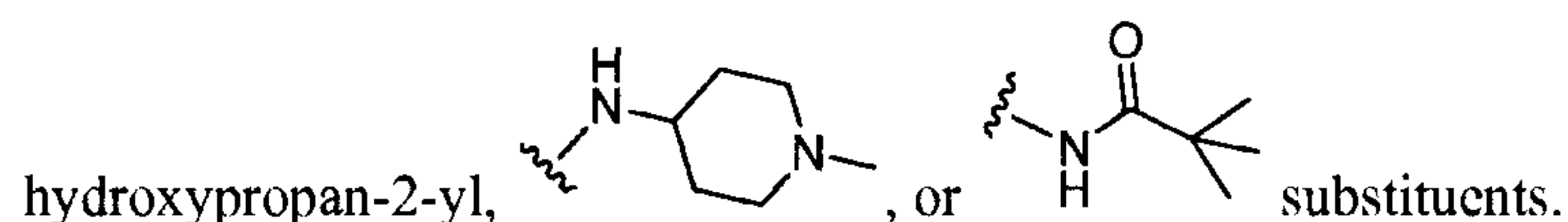
Claim 6. The compound according to claim 2, or a pharmaceutically acceptable salt thereof, wherein R¹ is phenyl, optionally substituted with 1-5 independent halo, trifluoromethyl, (trifluoromethyl)thio, trifluoromethoxy, 1,1,1,3,3,3,-hexafluoro-2-hydroxypropan-2-yl,



Claim 7. The compound according to claim 2, or a pharmaceutically acceptable salt thereof, wherein R¹ is pyridinyl, optionally substituted with 1-5 independent halo, trifluoromethyl, (trifluoromethyl)thio, trifluoromethoxy, 1,1,1,3,3,3,-hexafluoro-2-



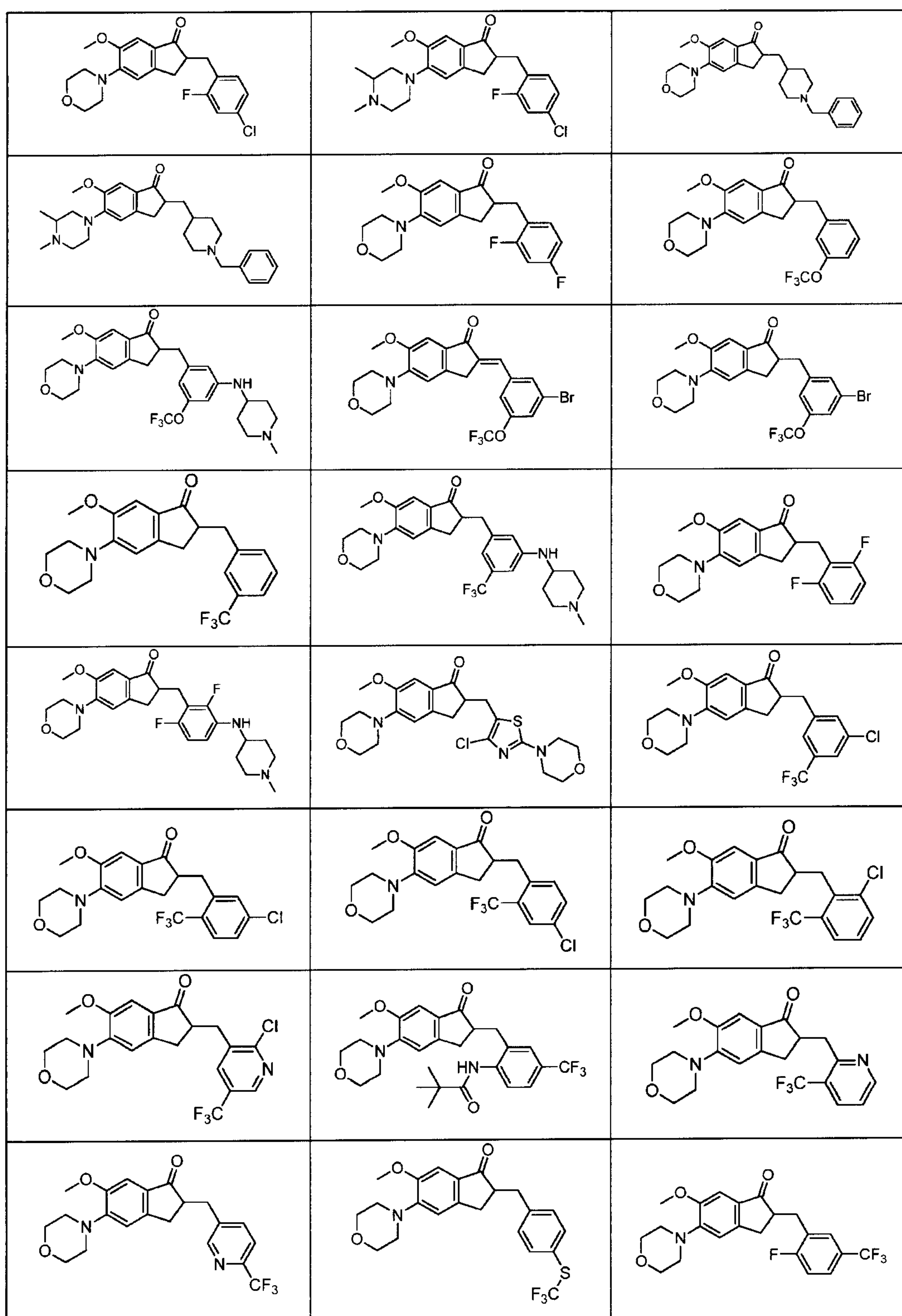
Claim 8. The compound according to claim 2, or a pharmaceutically acceptable salt thereof, wherein R¹ is pyrazolyl optionally substituted with 1-5 independent halo, trifluoromethyl, (trifluoromethyl)thio, trifluoromethoxy, 1,1,1,3,3,3,-hexafluoro-2-



Claim 9. The compound according to claim 1 consisting of a compound selected from:

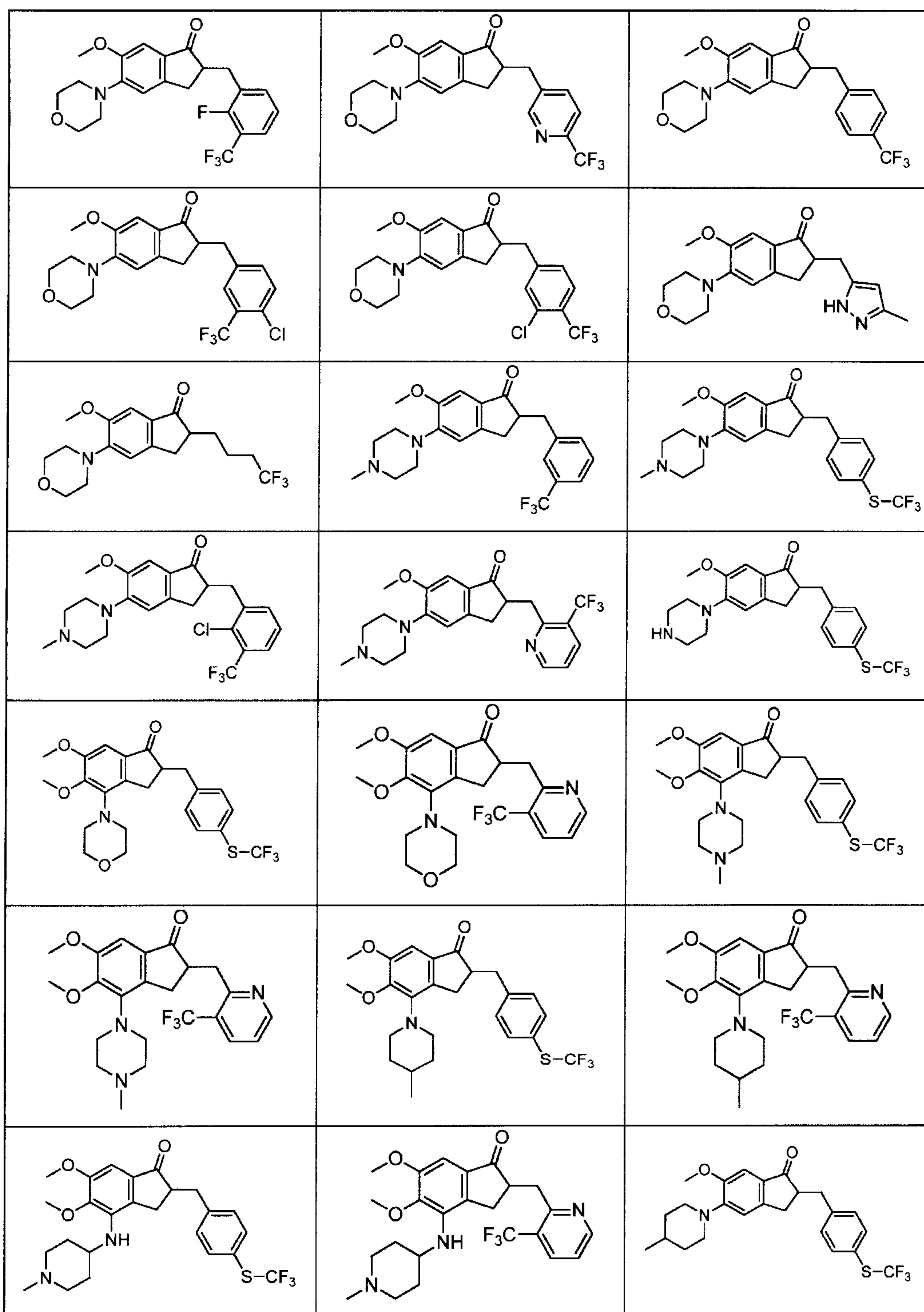
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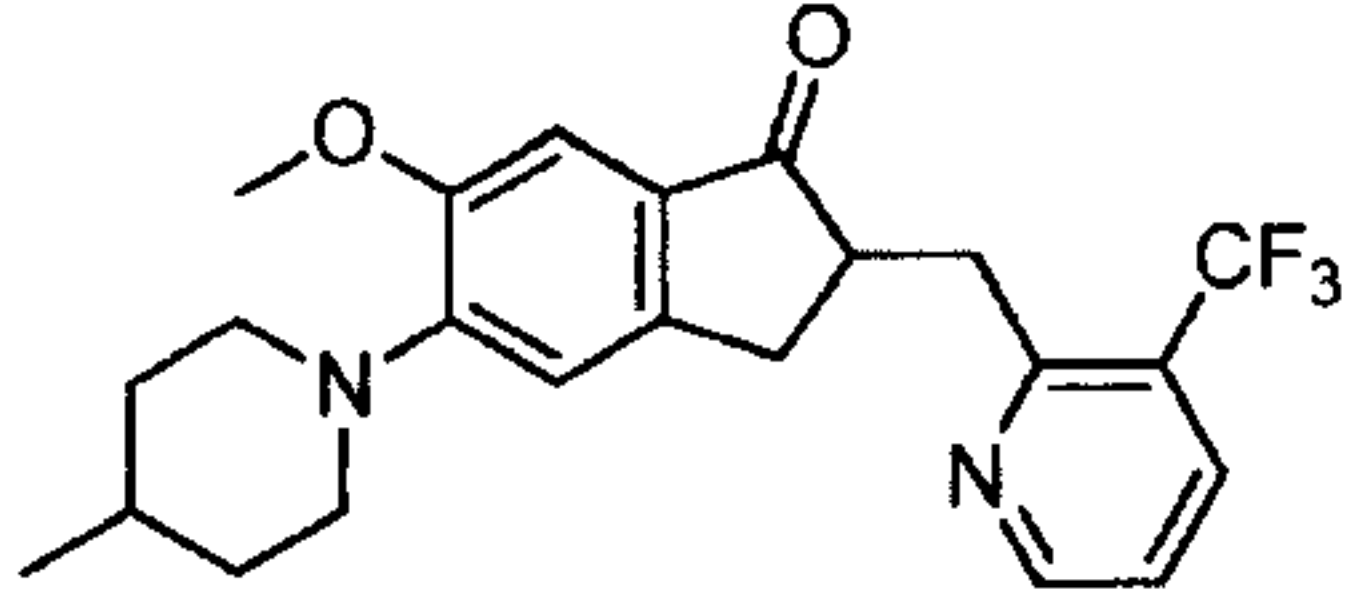
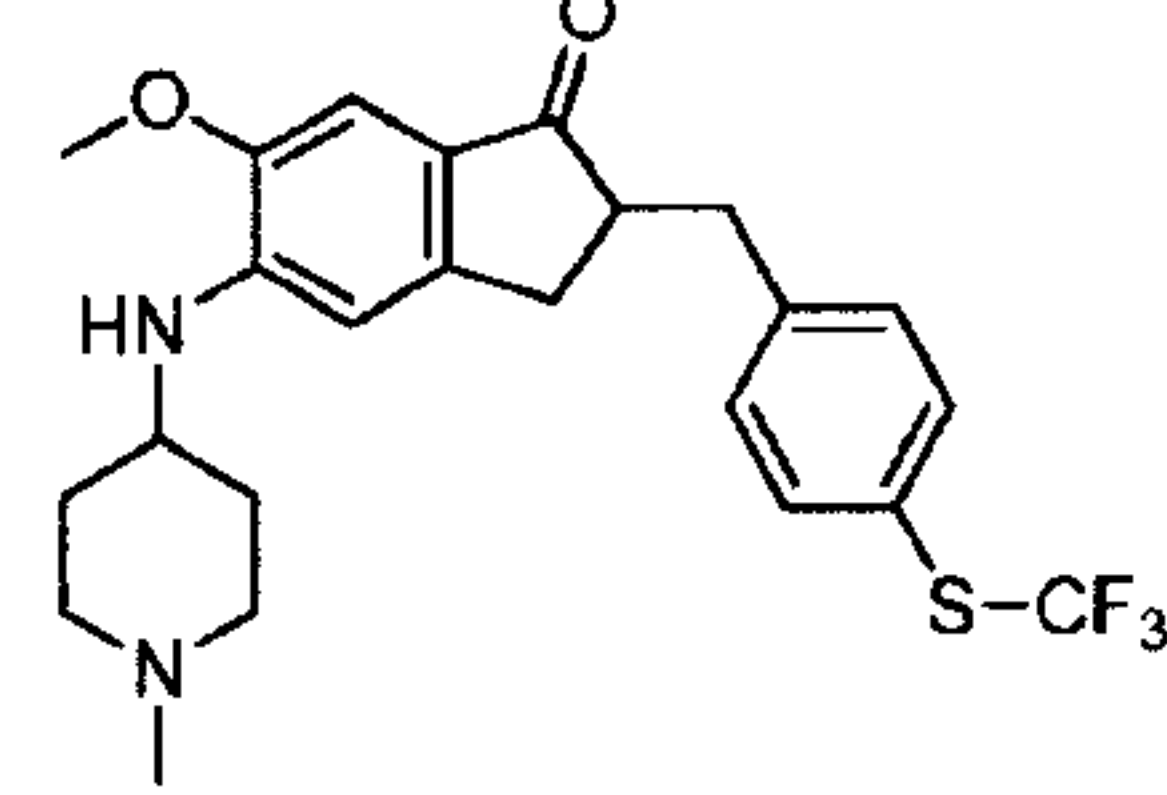
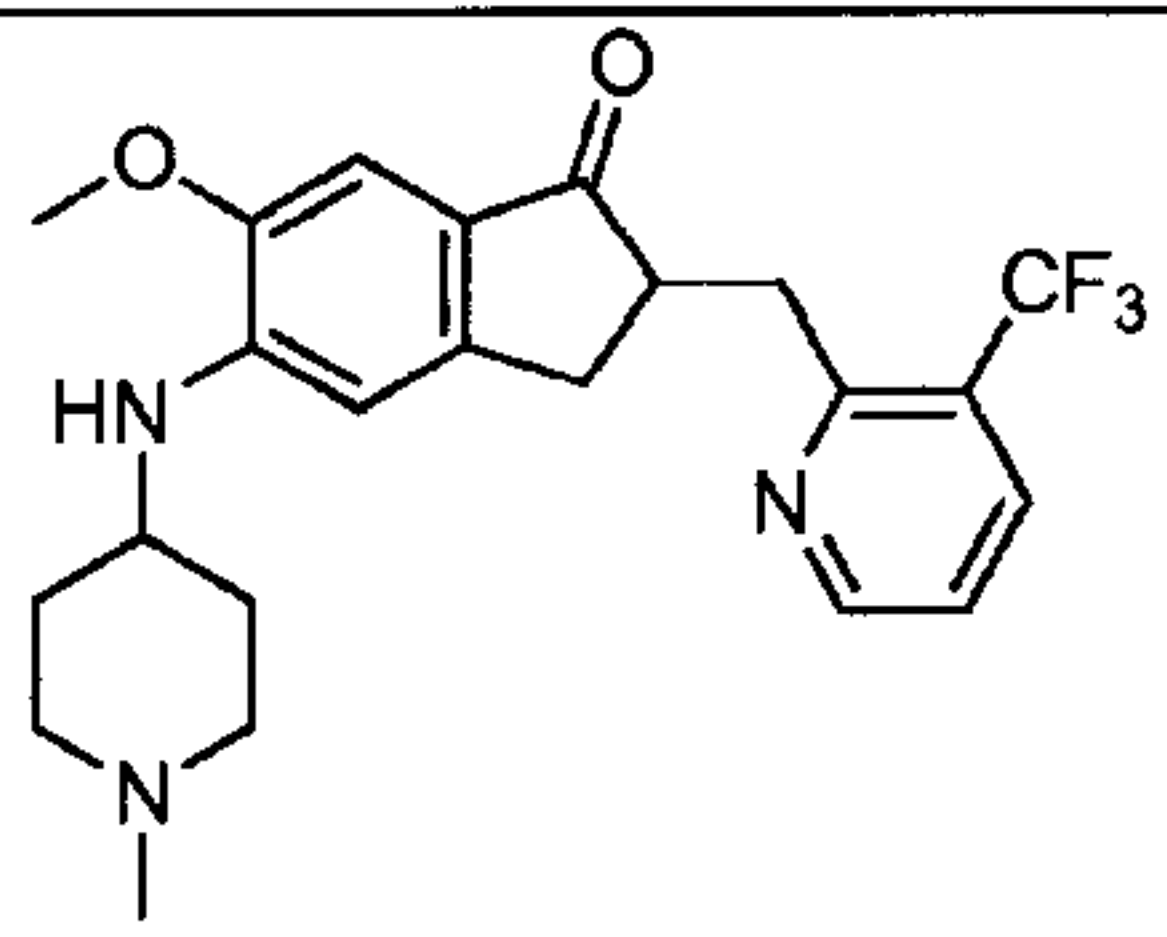
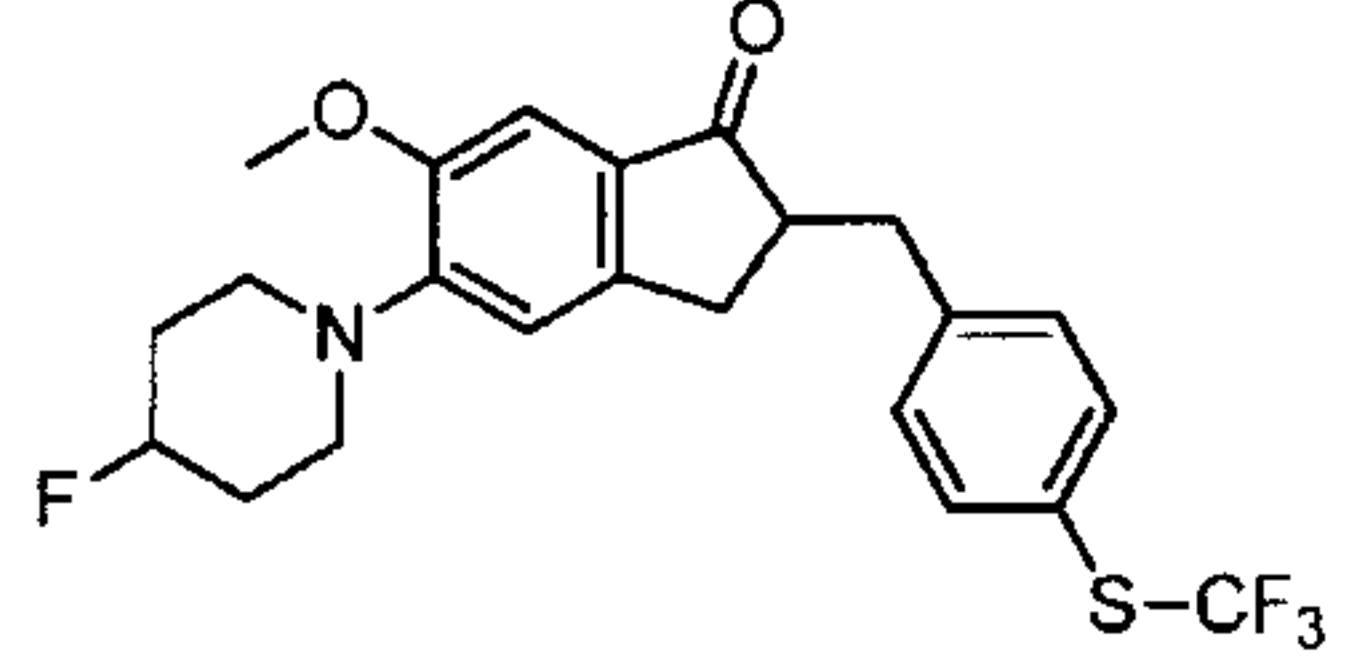
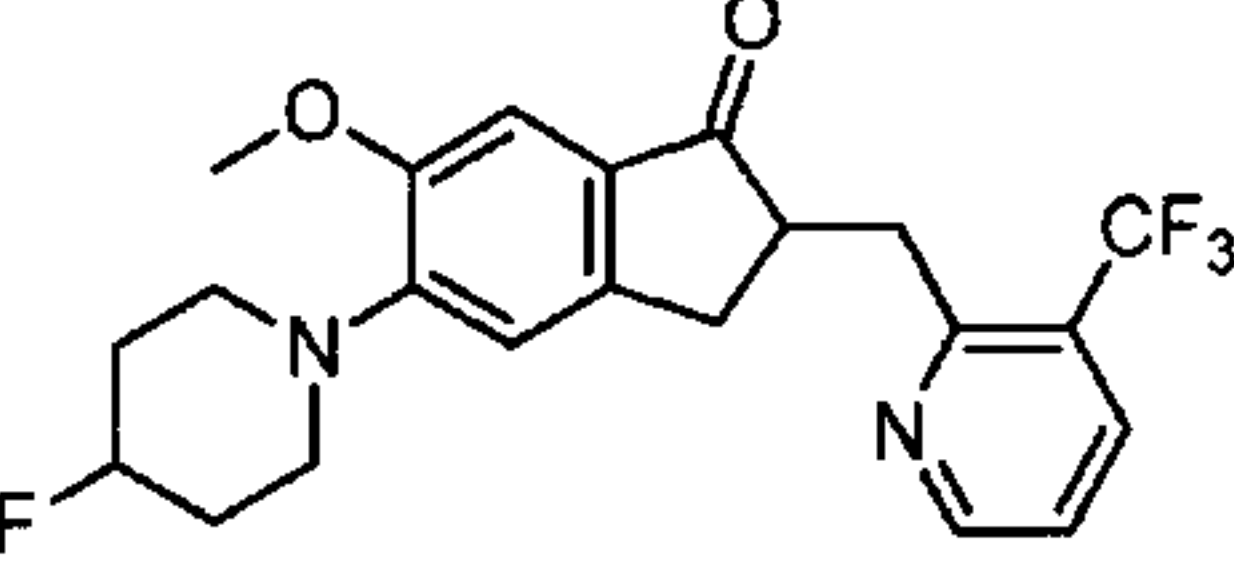
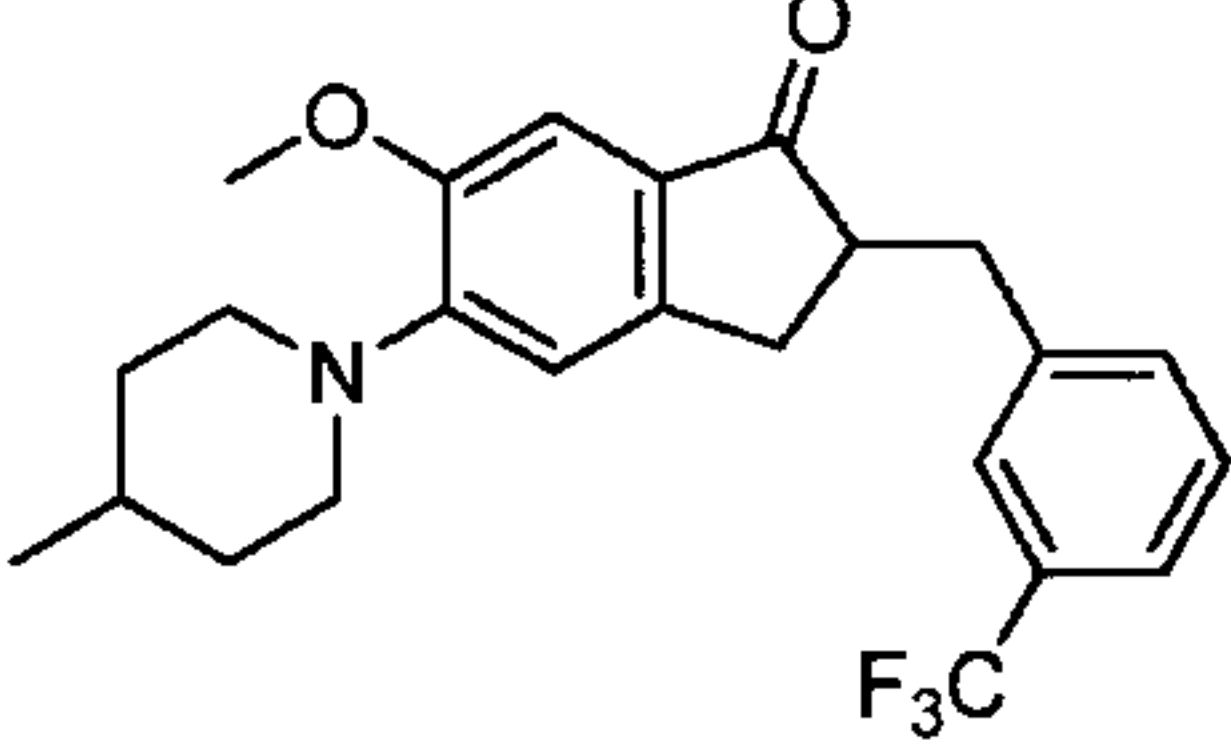
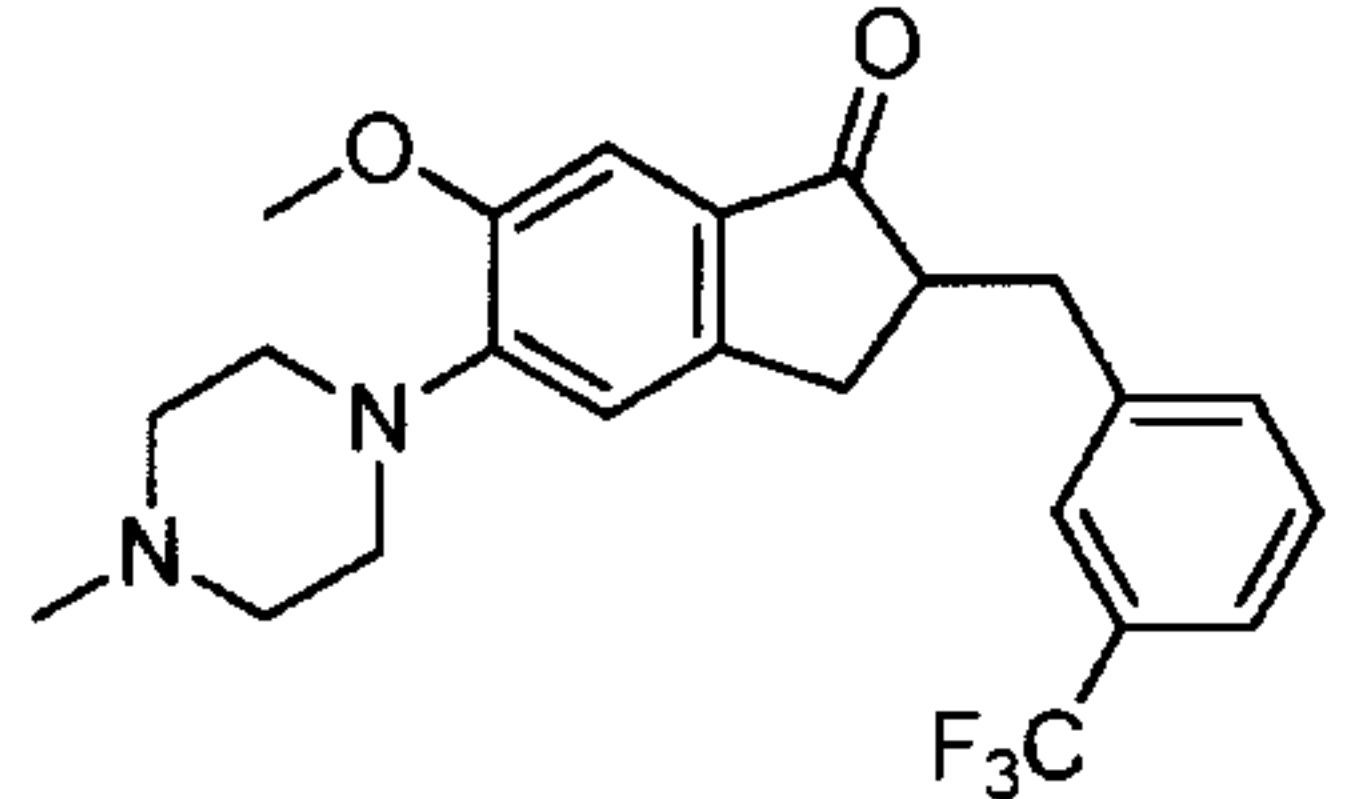
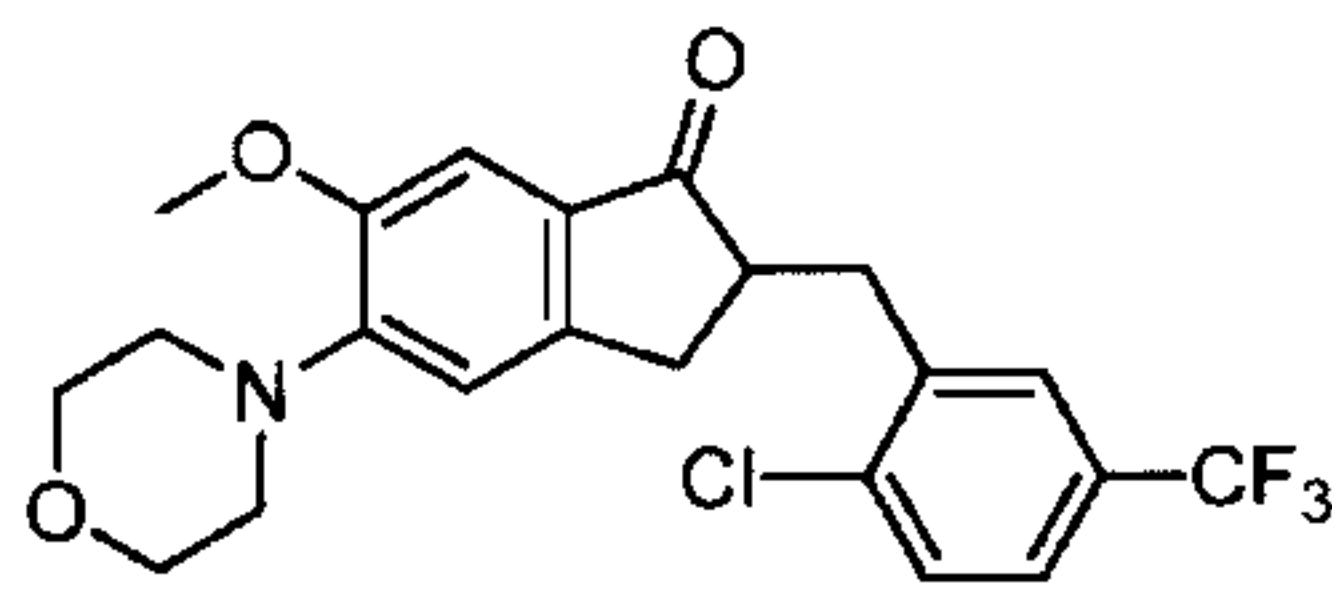
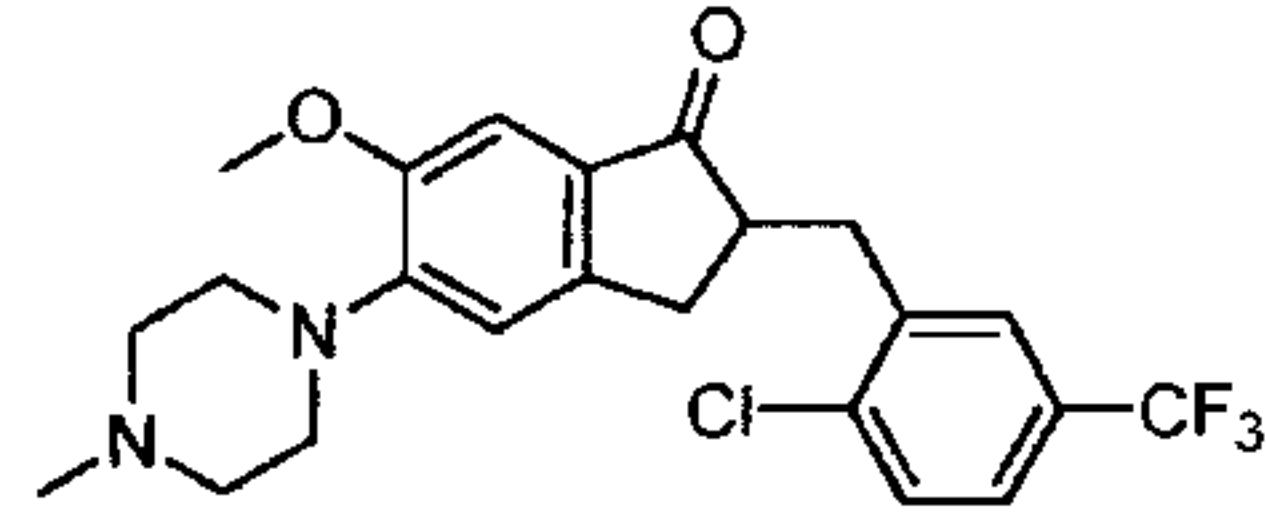
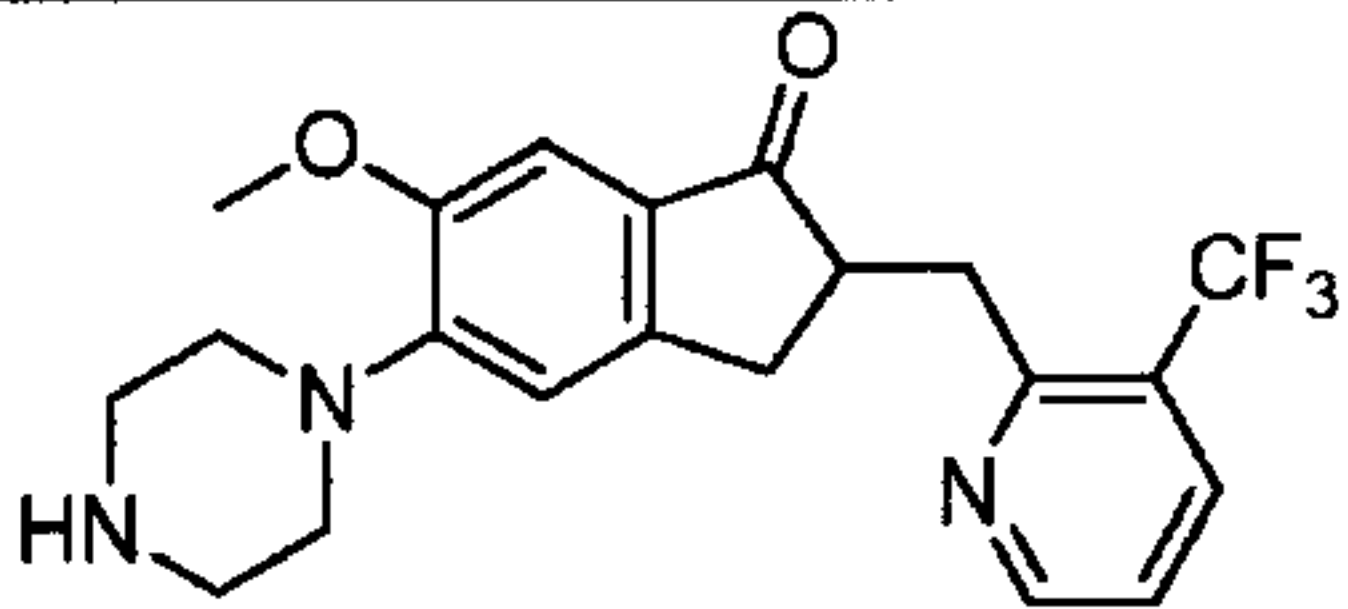
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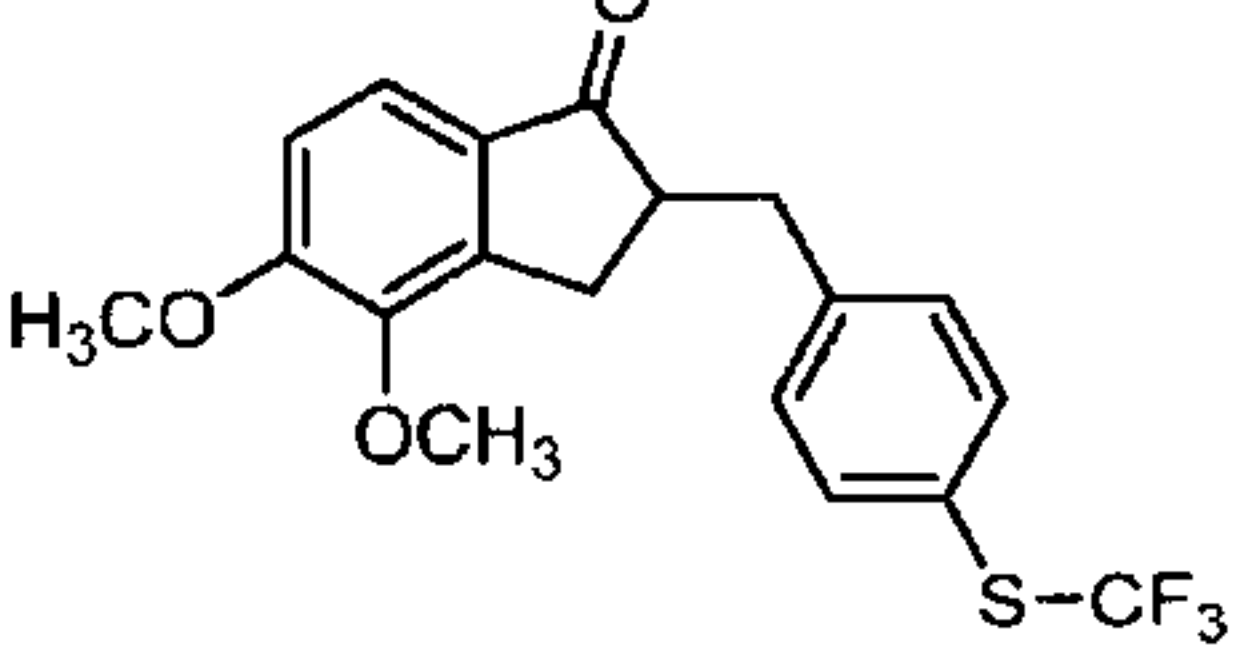
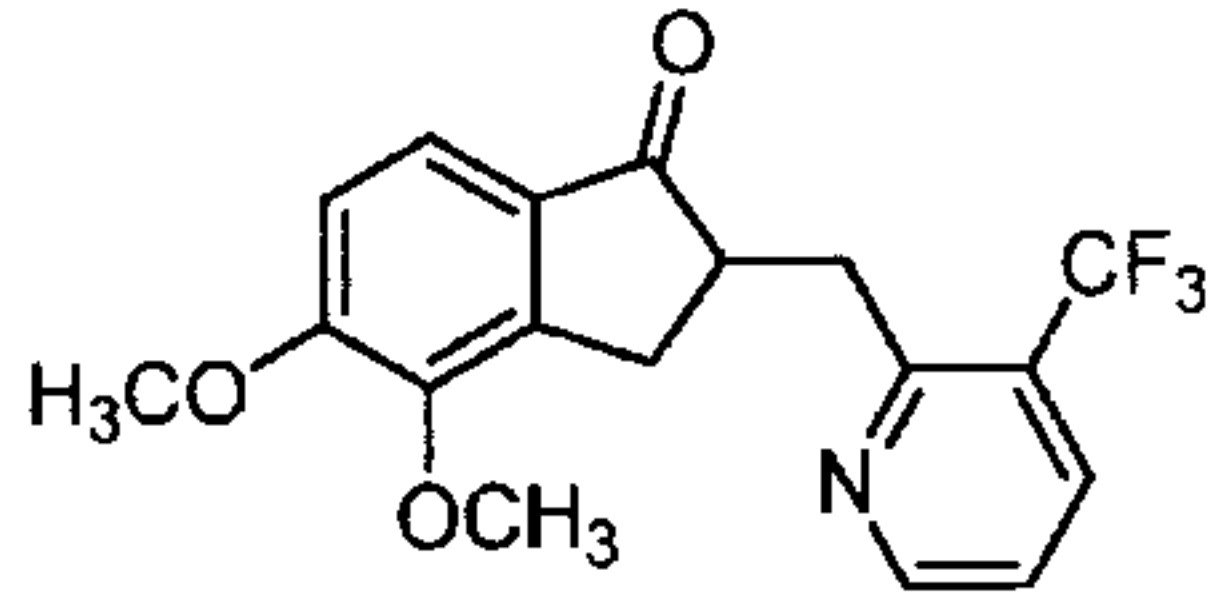
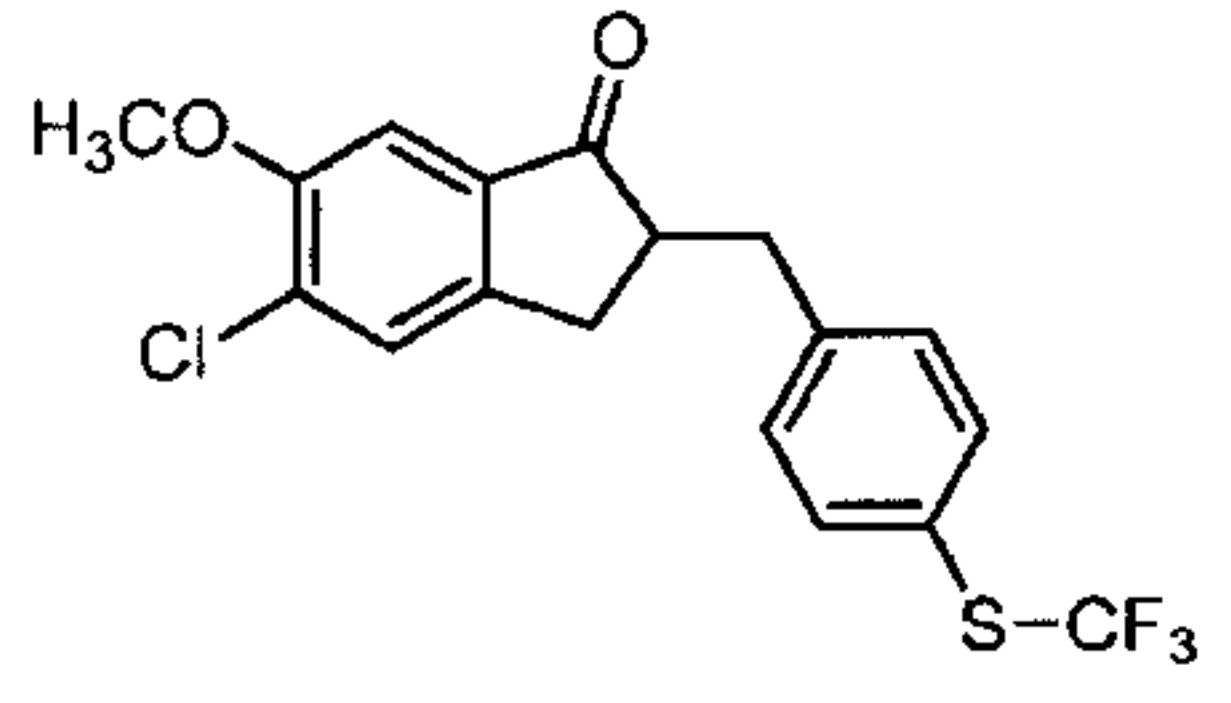
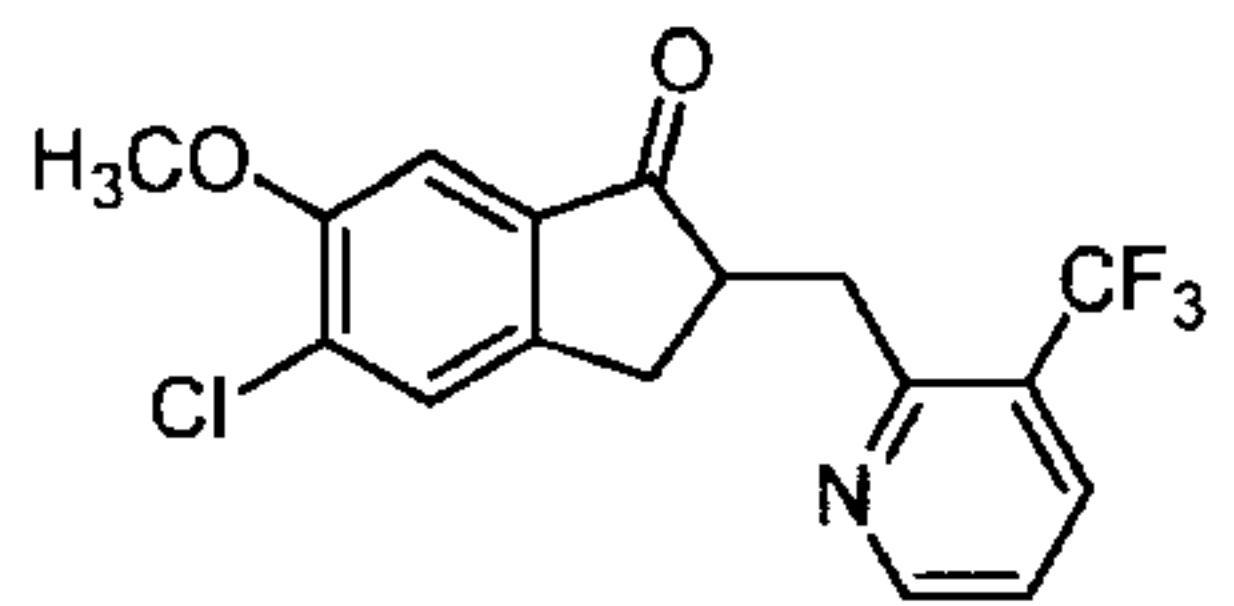
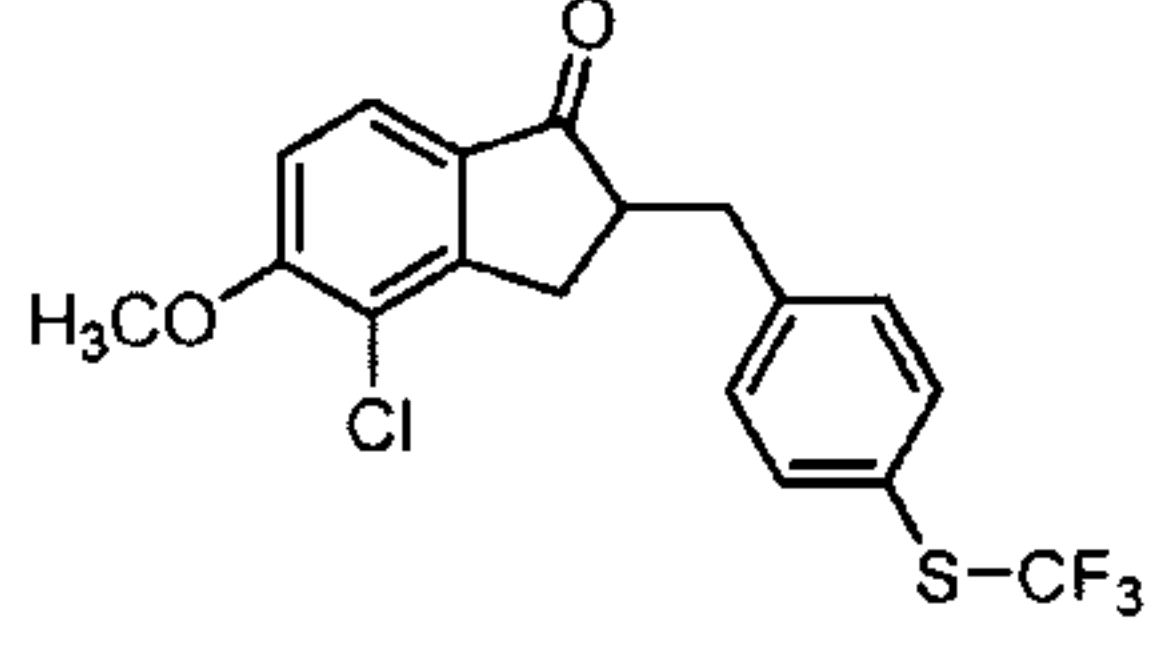
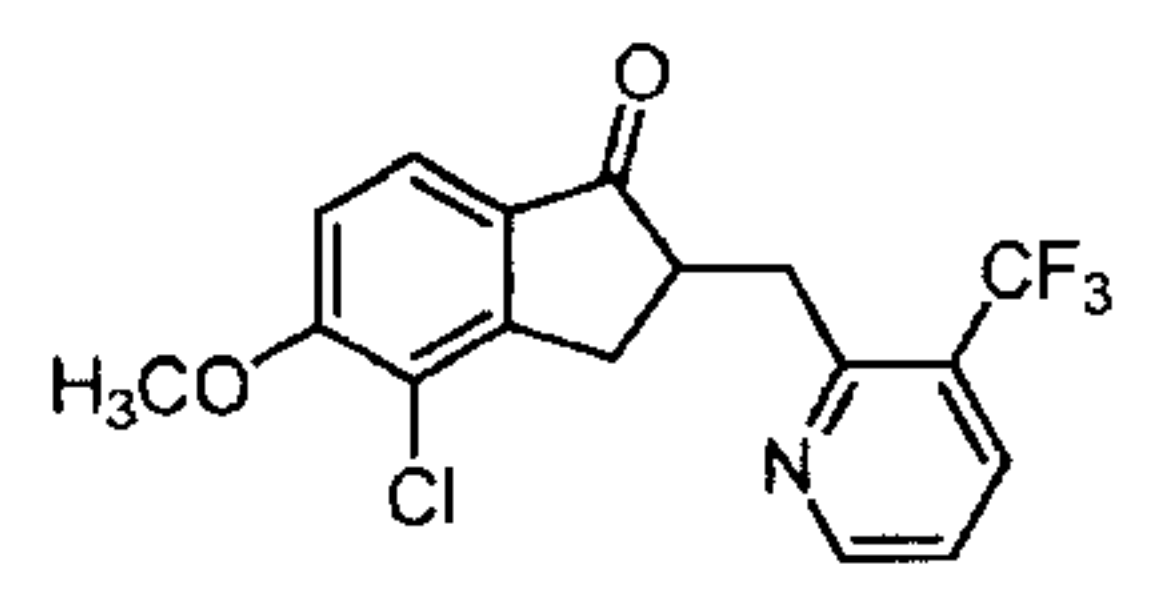
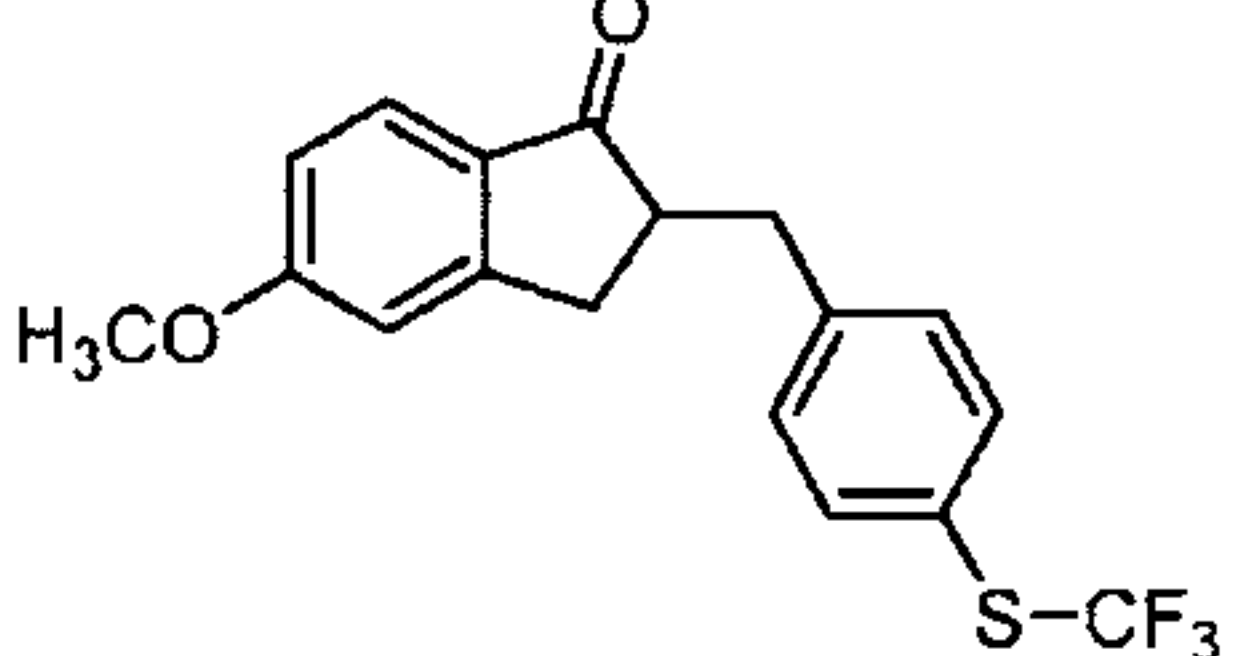
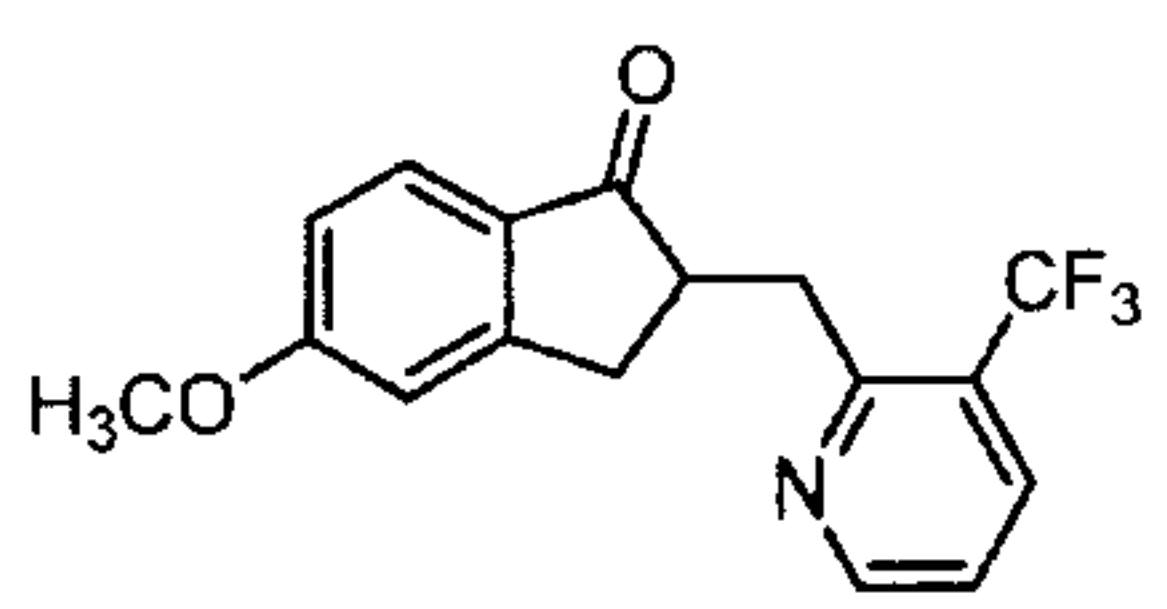
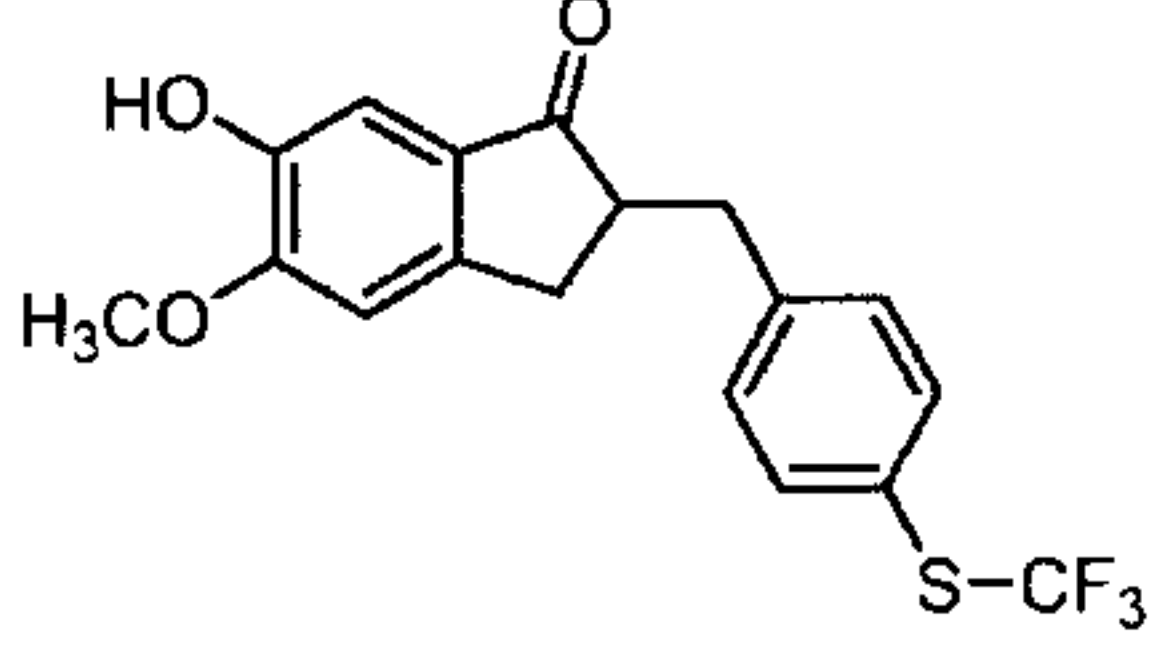
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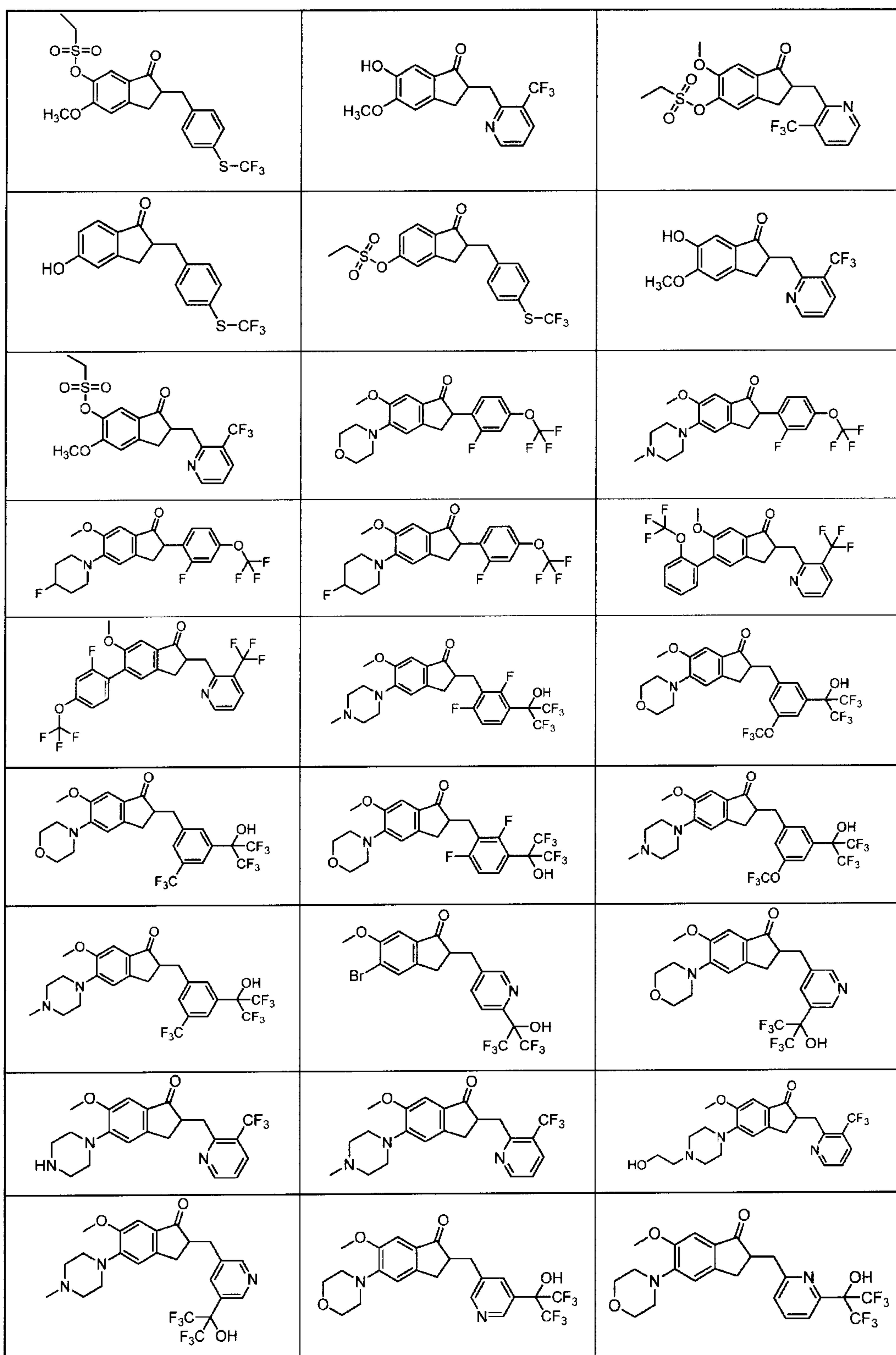
or a pharmaceutically acceptable salt thereof.

Claim 10. The compound according to claim 1 consisting of a compound selected from:

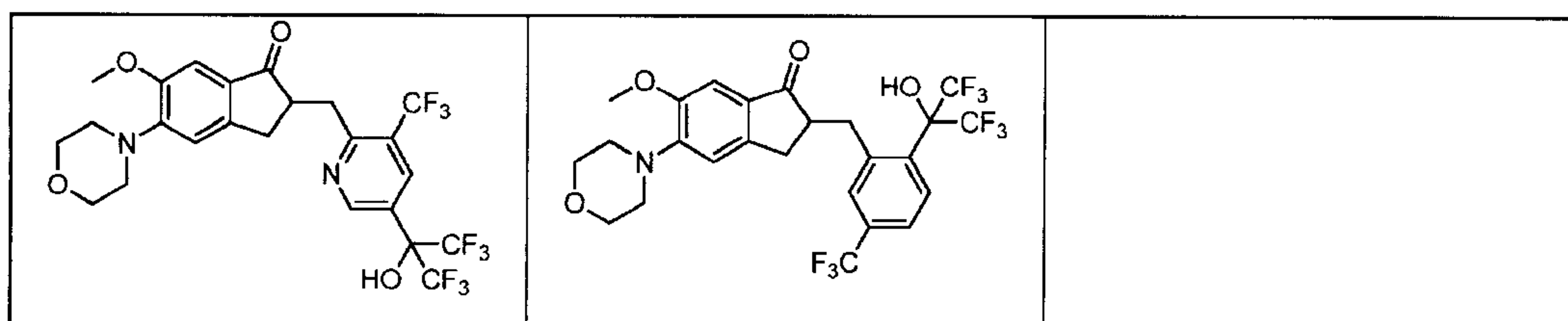
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or a pharmaceutically acceptable salt thereof.

Claim 11. A method of treatment of multiple sclerosis comprising the step of administering to a patient in need thereof an effective amount of a compound according to claim 1.

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Claim 12. A method of treatment of human autoimmune diseases comprising the step of administering to a patient in need thereof an effective amount of a compound according to claim 1.

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Claim 13. The method according to claim 12 wherein the human autoimmune disease is Multiple Sclerosis (MS), Rheumatoid Arthritis (RA), Inflammatory Colitis, Psoriasis, Chronic Obstructive Pulmonary Disease (COPD), Pain, Obesity, Diabetes, Dyslipidemia, Osteoporosis, Asthma, Neurodegenerative diseases or Cancer.

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Claim 14. The method according to claim 13 wherein the cancer is gastric cancer, colon cancer, chronic myelogenous leukemia (CML), acute myelogenous leukemia (AML), squamous cell or bladder carcinomas, medulloblastoma, hepatocellular carcinoma, multiple myeloma, bladder cancer, glioblastoma multiform (GBM), breast and ovarian cancers, Ewing's sarcoma or bone associated cancer diseases.

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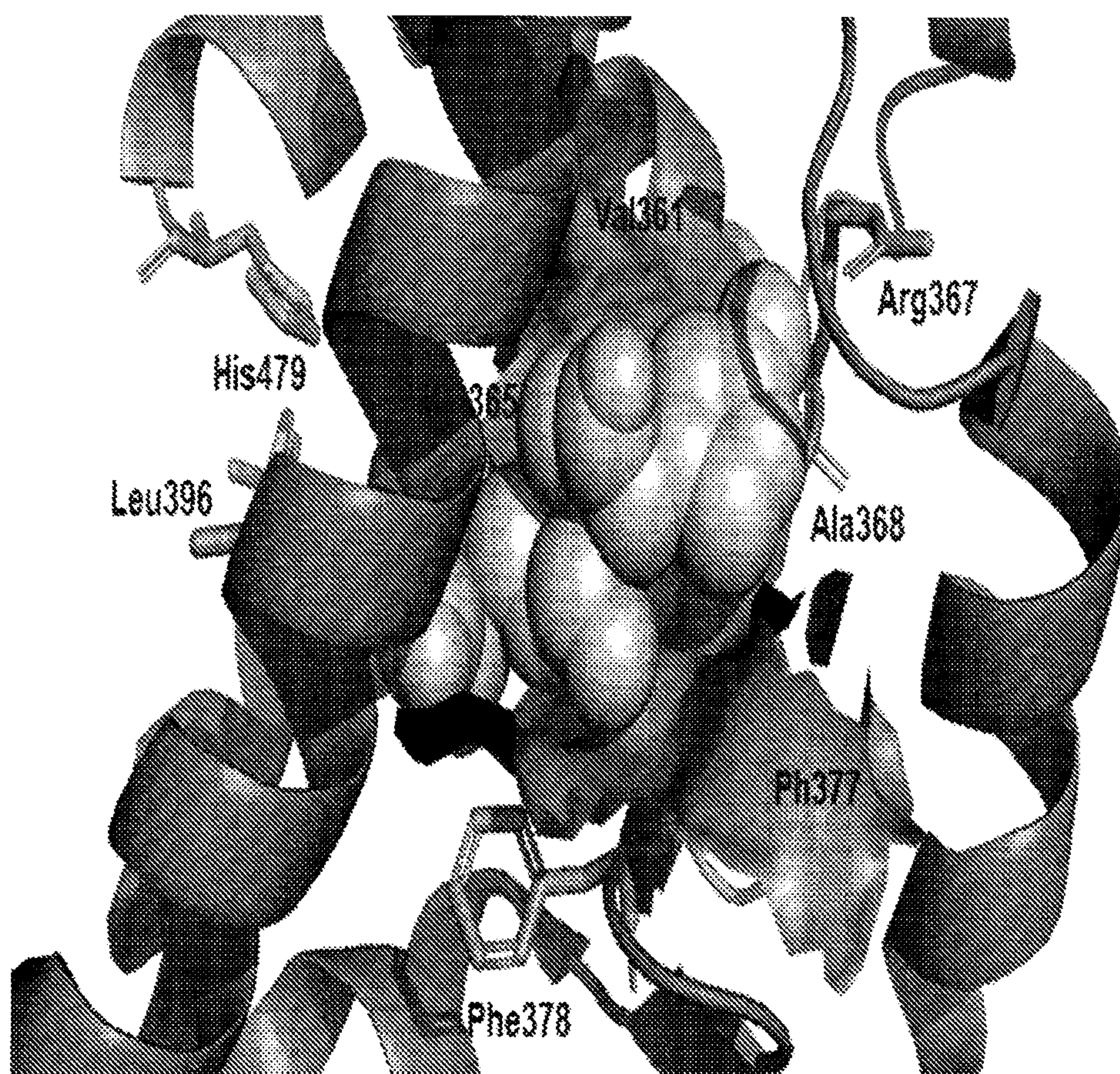


Figure 1

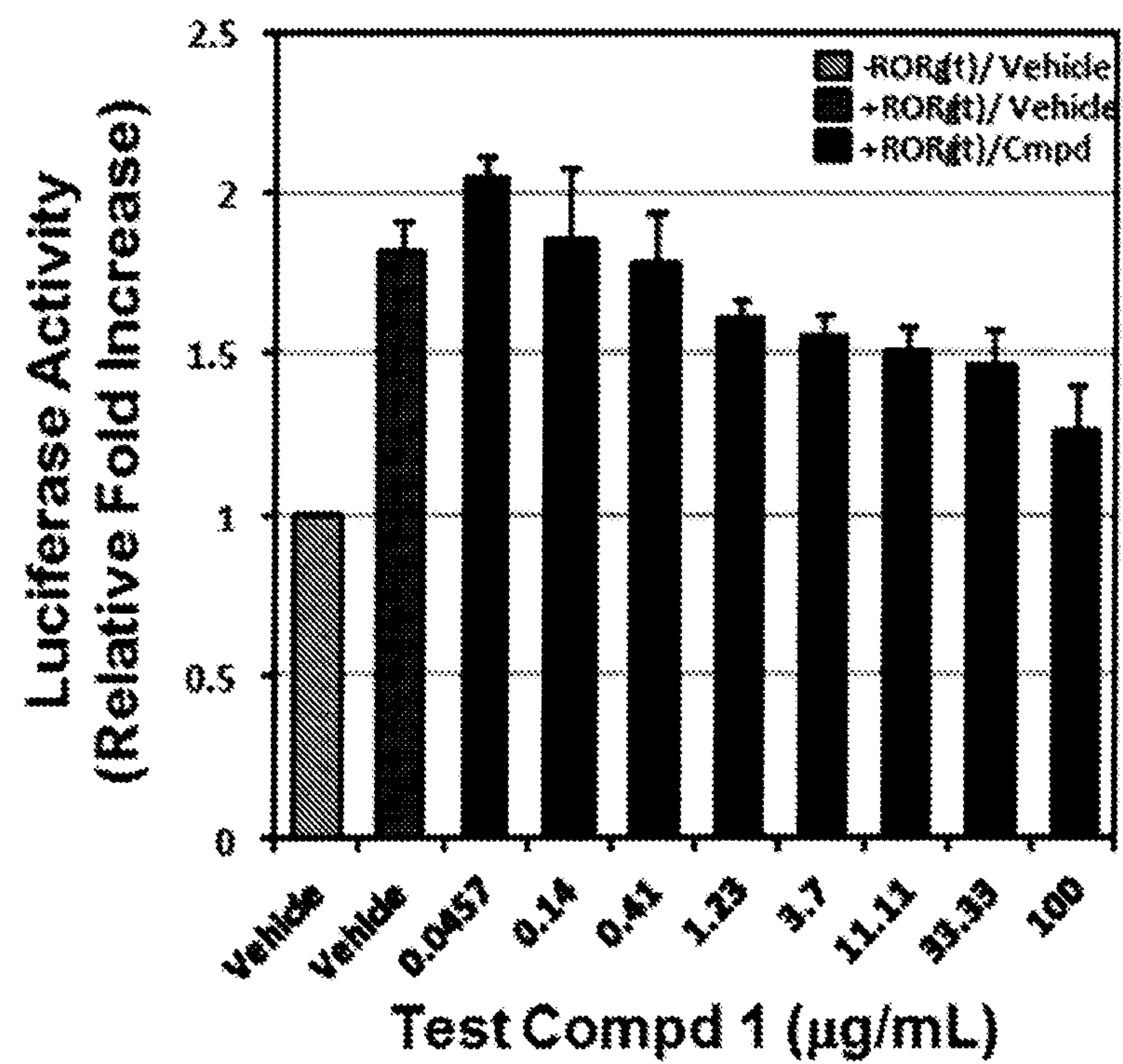


Figure 2A

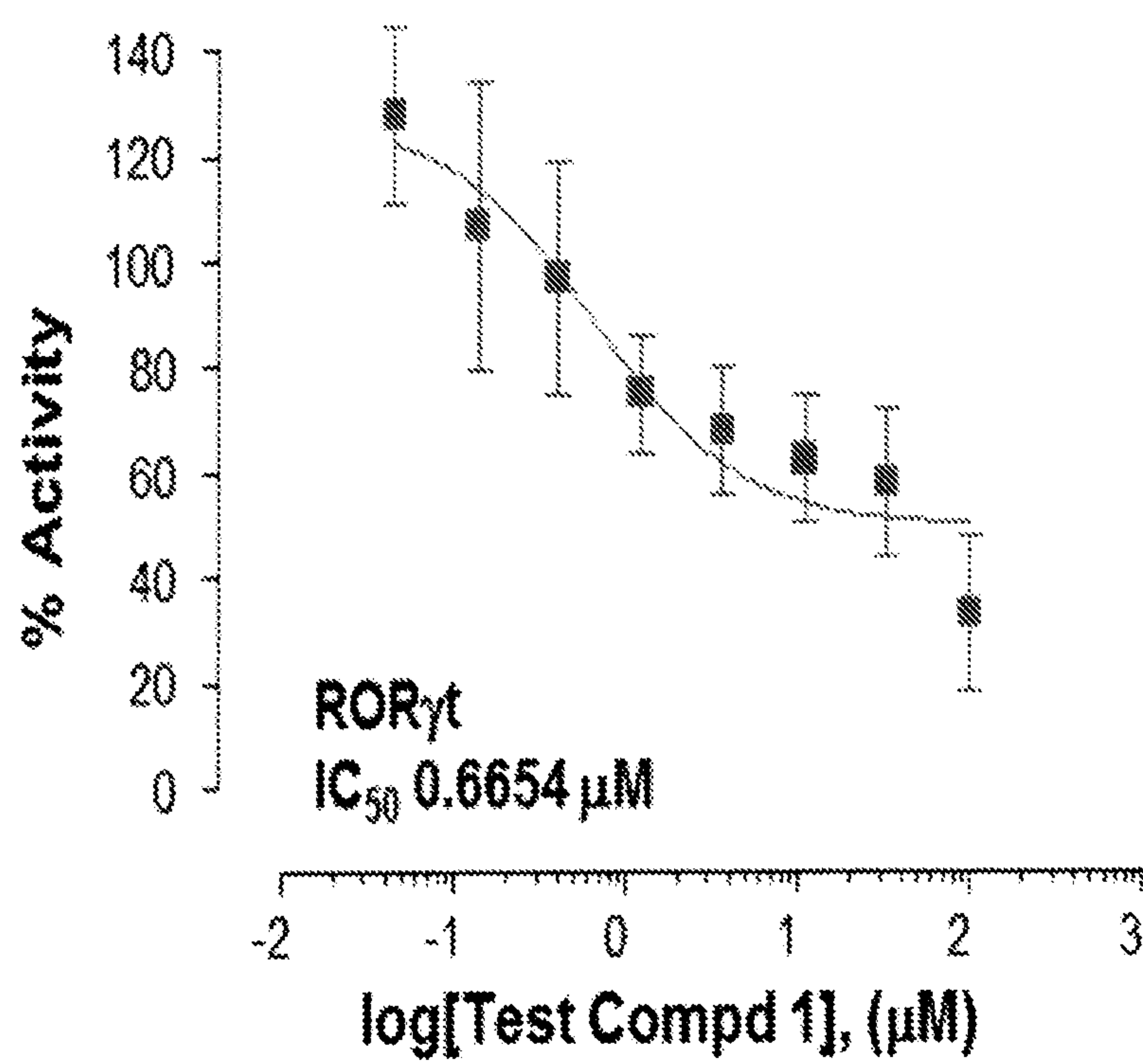


Figure 2B

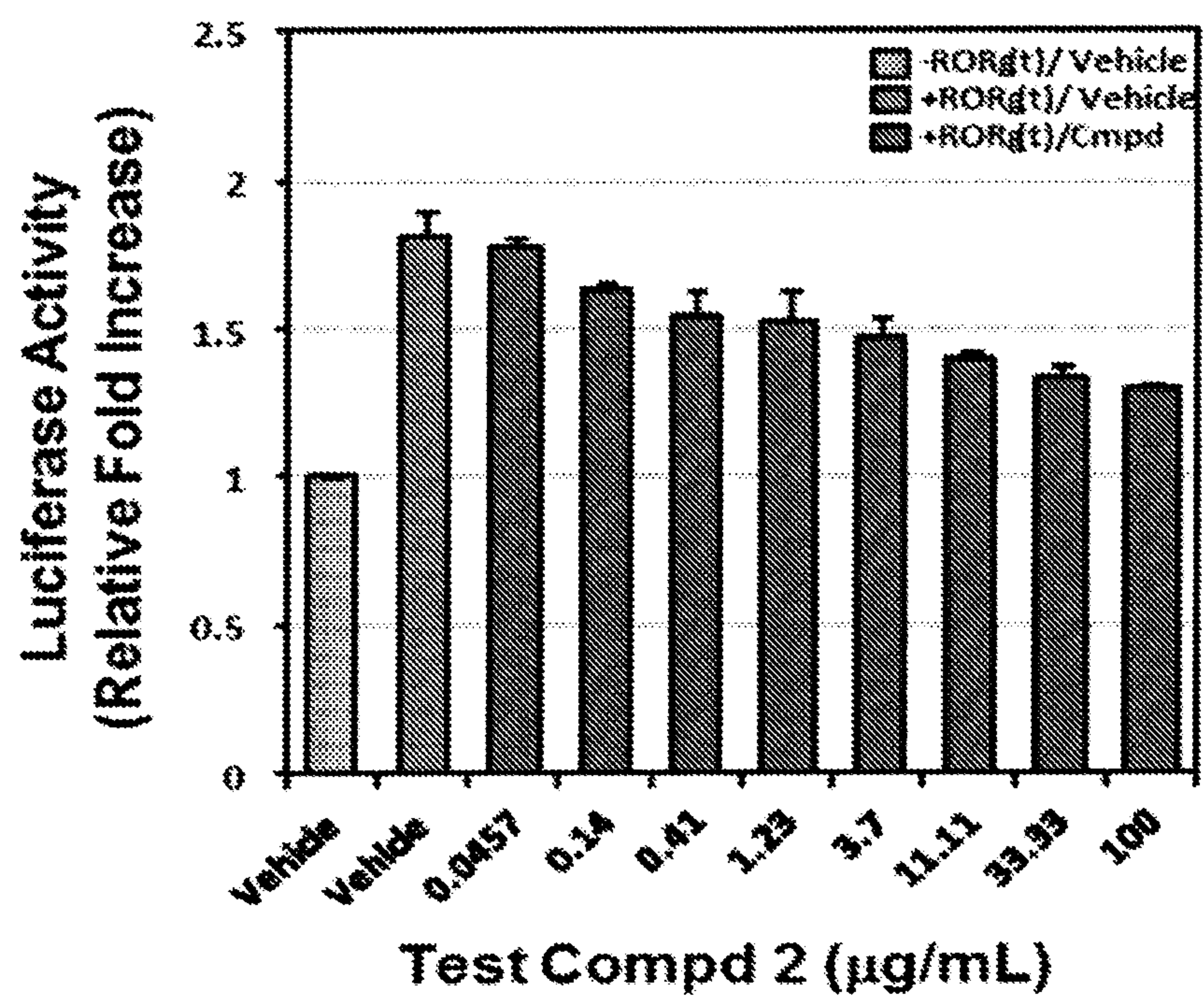
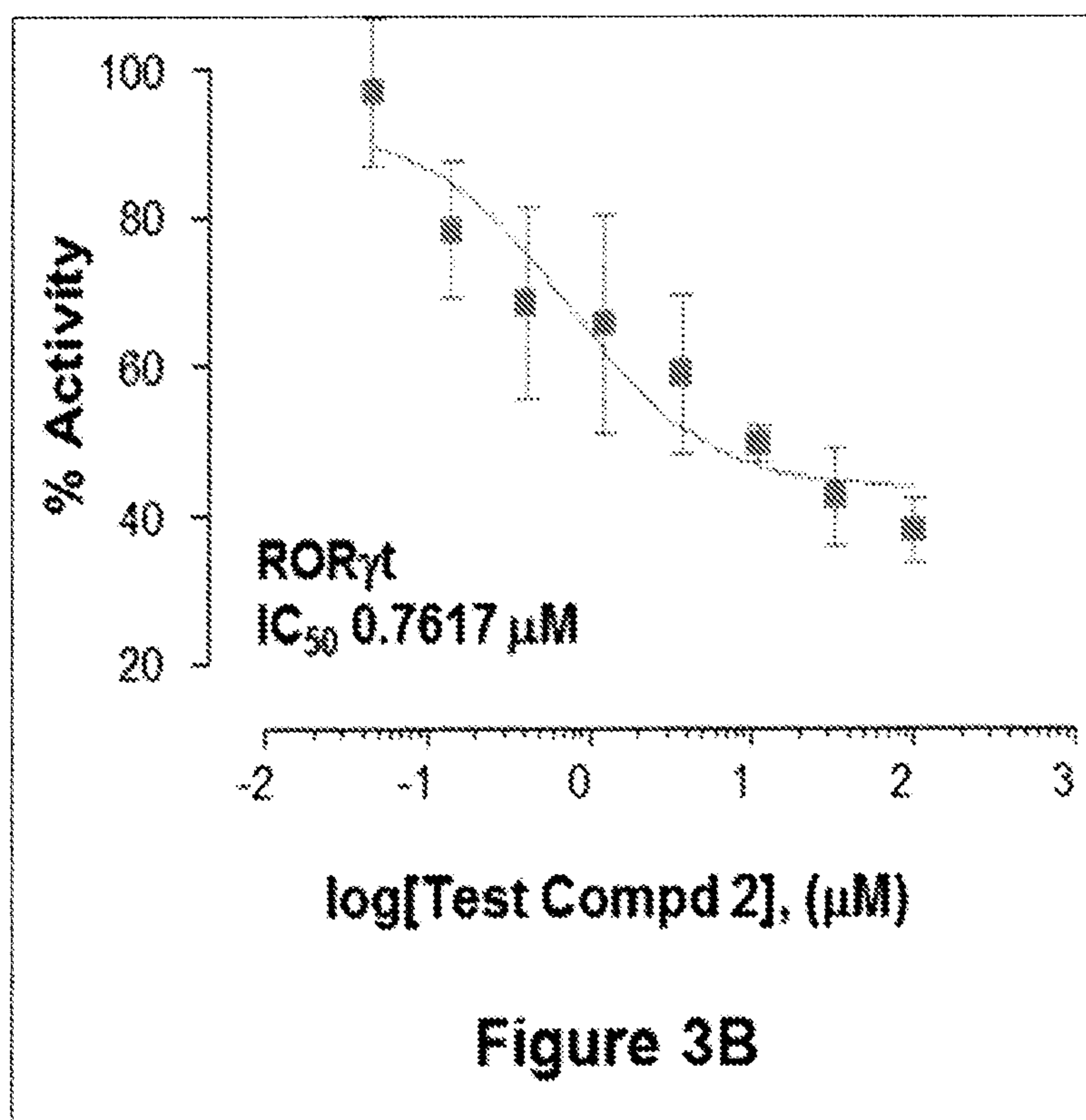
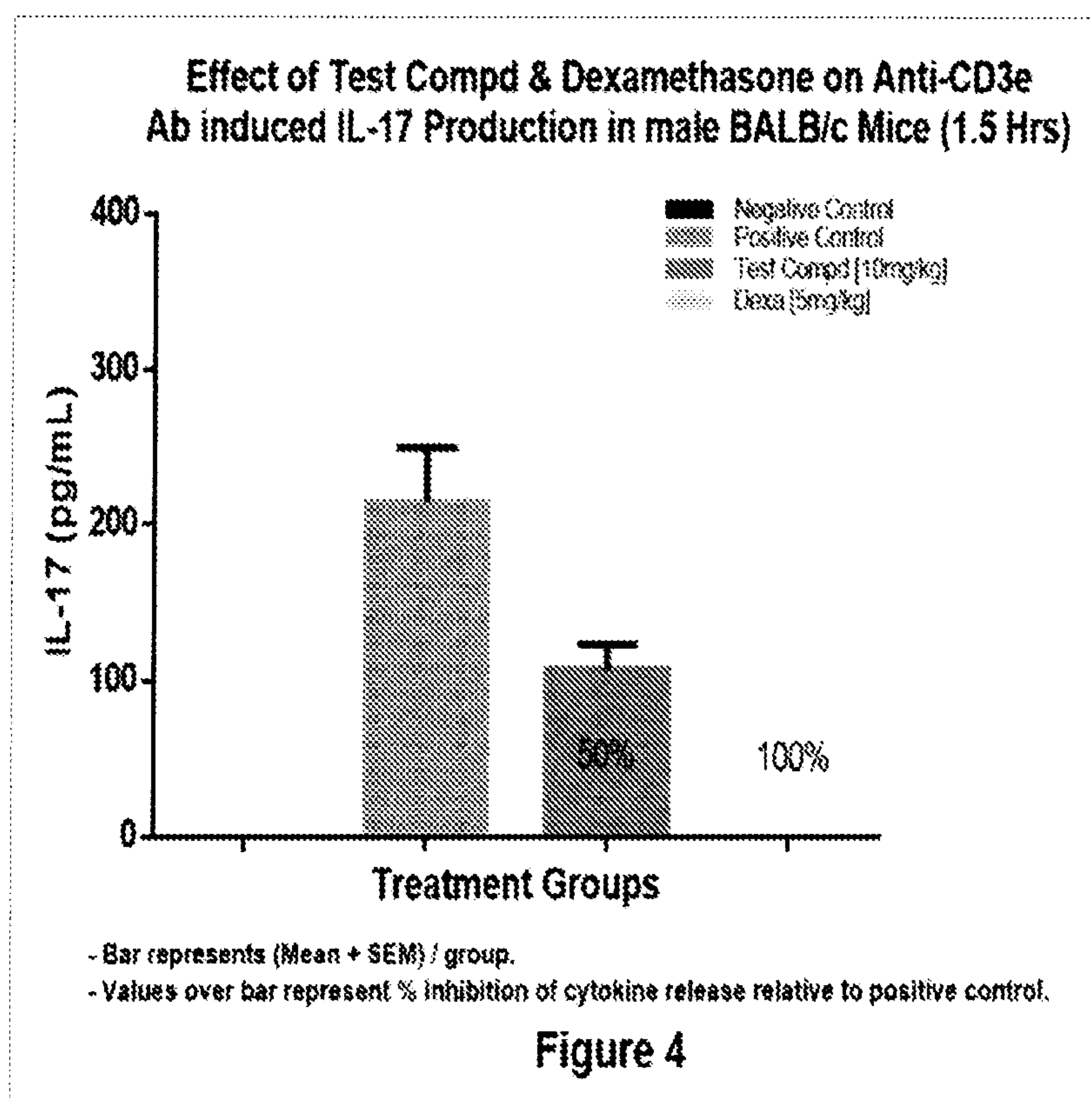
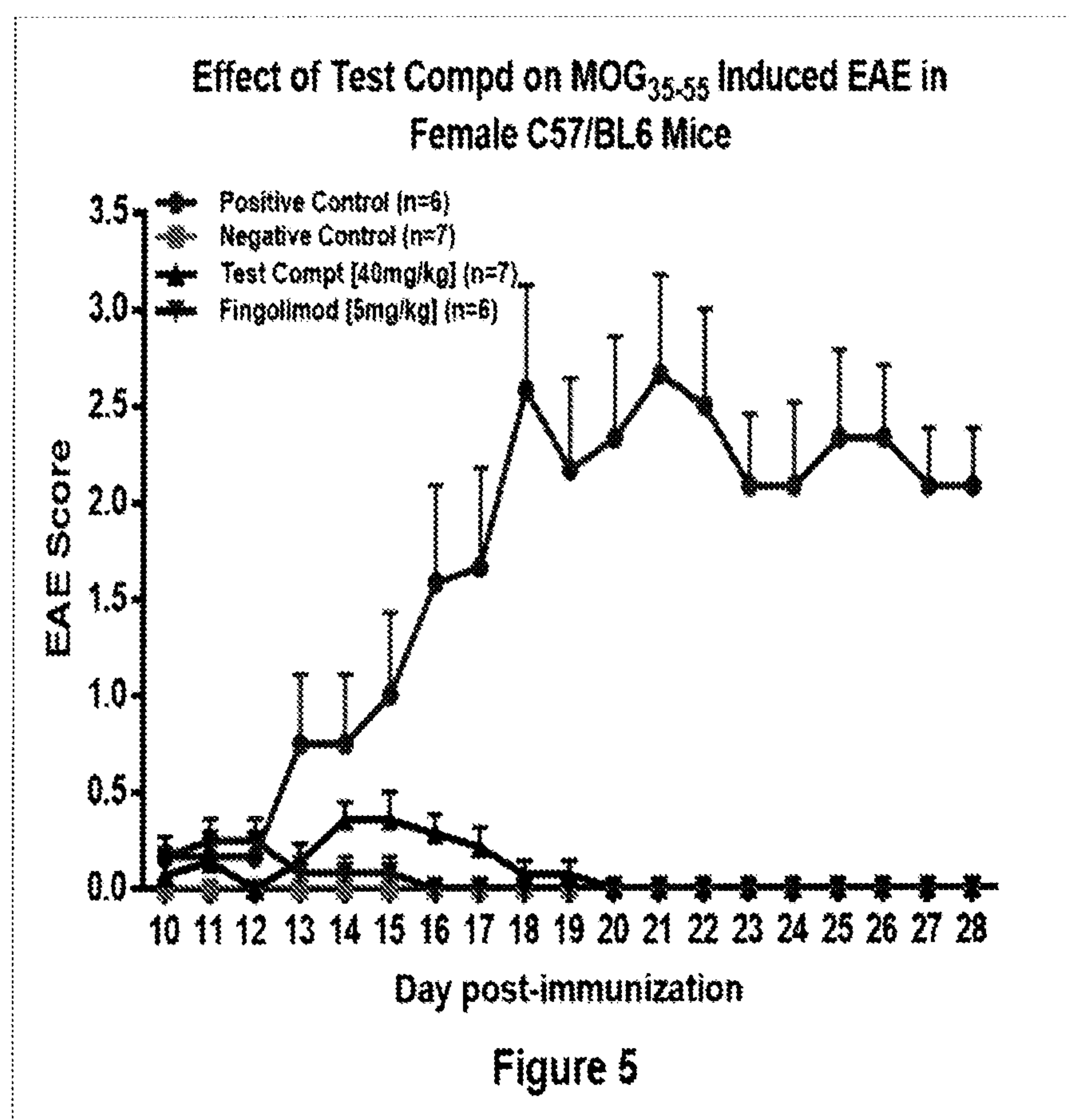
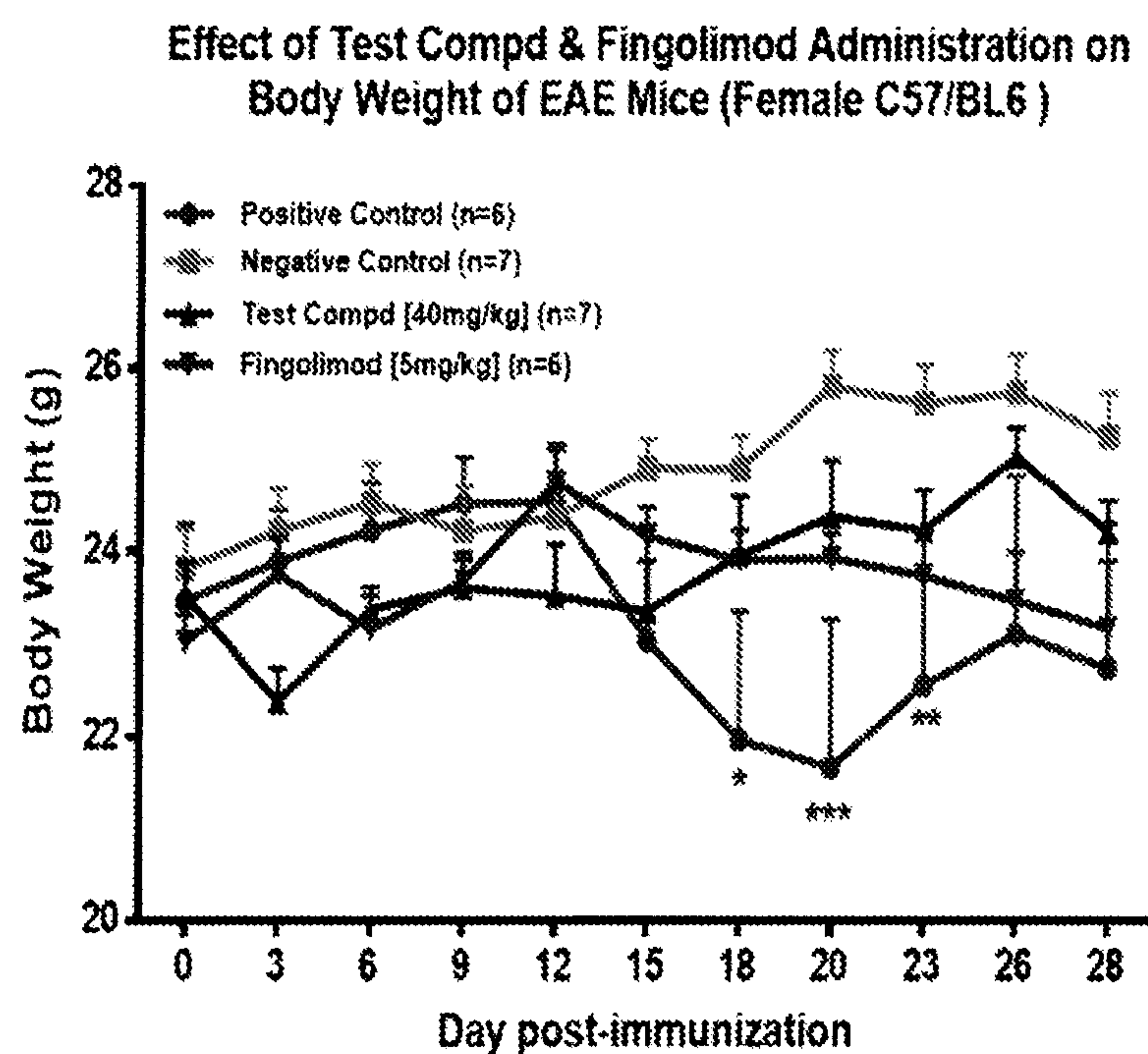


Figure 3A









Each data point represent mean+SEM of the group, on the day.
^{*}P<0.05, ^{**}P<0.01, ^{***}P<0.001, Two way RM ANOVA followed by Bonferroni
 post test, in comparison to Negative control

Figure 6

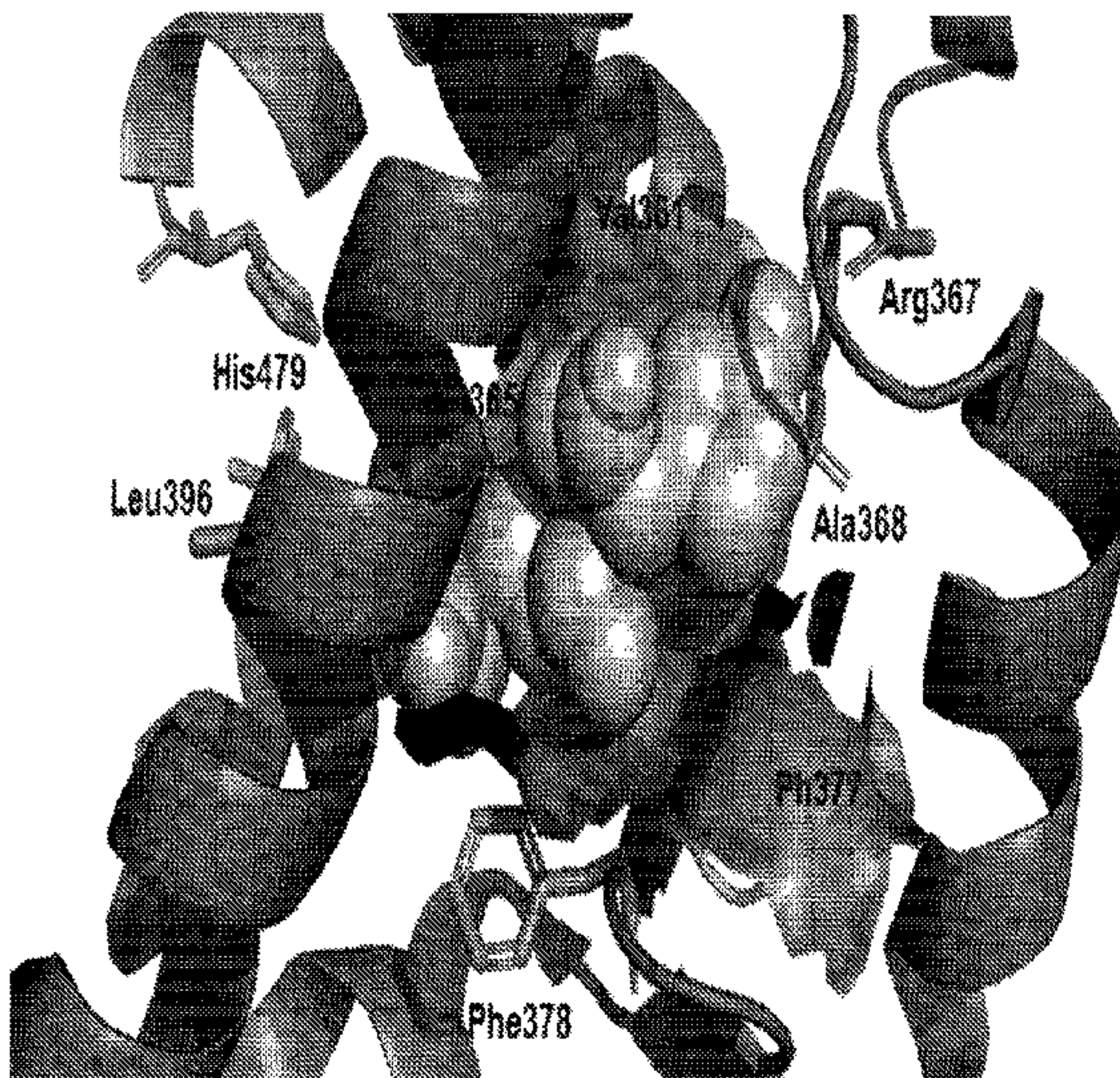


Figure 1