



(86) Date de dépôt PCT/PCT Filing Date: 2003/03/05
(87) Date publication PCT/PCT Publication Date: 2003/09/18
(85) Entrée phase nationale/National Entry: 2004/08/16
(86) N° demande PCT/PCT Application No.: US 2003/006749
(87) N° publication PCT/PCT Publication No.: 2003/075921
(30) Priorité/Priority: 2002/03/05 (60/361,983) US

(51) Cl.Int.⁷/Int.Cl.⁷ A61K 31/4184, A61K 31/4164,
A61P 3/10, C07D 235/12, C07D 235/08, C07D 405/04,
C07D 403/14, C07D 401/14, C07D 403/12,
C07D 401/12, C07D 233/64, C07D 235/30,
C07D 235/18, C07D 401/04, C07D 453/02

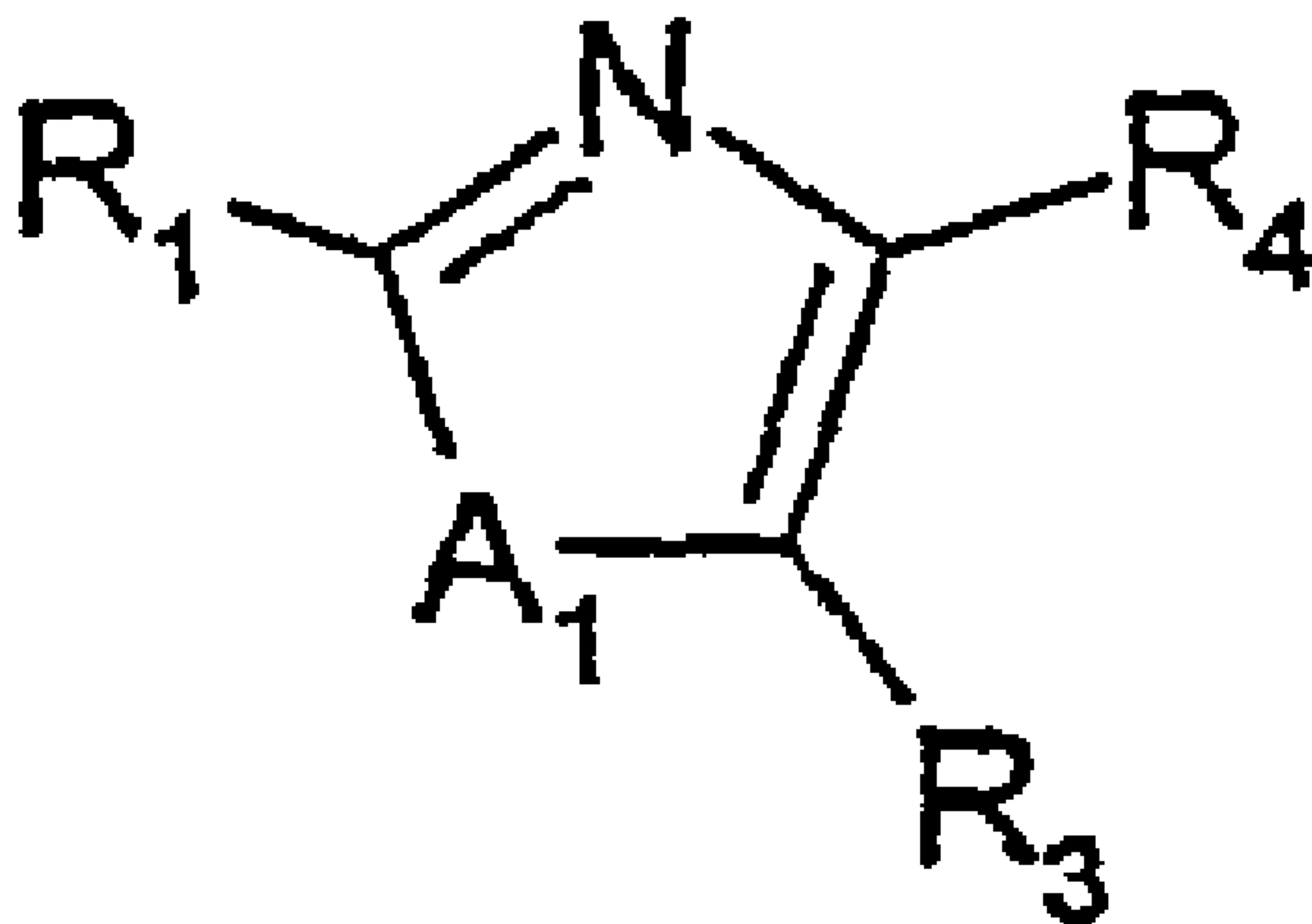
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(54) Titre : DERIVES DE L'AZOLE ET DERIVES BICYCLIQUES FUSIONNES DE L'AZOLE, AGENTS
THERAPEUTIQUES

(54) Title: MONO- AND BICYCLIC AZOLE DERIVATIVES THAT INHIBIT THE INTERACTION OF LIGANDS WITH RAGE



(I)

(57) Abrégé/Abstract:

This invention provides certain compounds of formula I wherein A₁ is O, S or -N(R²)-, methods of their preparation, pharmaceutical compositions comprising the compounds, and their use in treating human or animal disorders. The compounds of the invention are useful as modulators of the interaction between the receptor for advanced glycated end products (RAGE) and its ligands, such as advanced glycated end products (AGEs), S100/calgranulin/EN-RAGE, β-amyloid and amphoterin, and for the management, treatment, control, or as an adjunct treatment for diseases in humans caused by RAGE. Such diseases or disease states include acute and chronic inflammation, the development of diabetic late complications such as increased vascular permeability, nephropathy, atherosclerosis, and retinopathy, the development of Alzheimer's disease, erectile dysfunction, and tumor invasion and metastasis.

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ABSTRACT

This invention provides certain compounds of formula I wherein A1 is O, S or -N(R2)-, and methods of their preparation, pharmaceutical compositions comprising the compounds, and their use in treating human or animal disorders. The compounds of the invention are useful as modulators of the interaction between the receptor for advanced glycated end products (RAGE) and its ligands, such as advanced glycated end products (AGEs), S100/calgranulin/EN-RAGE, $\beta\beta$ -amyloid and amphoterin, and for the management, treatment, control, or as an adjunct treatment for diseases in humans caused by RAGE. Such diseases or disease states include acute and chronic inflammation, the development of diabetic late complications such as increased vascular permeability, nephropathy, atherosclerosis, and retinopathy, the development of Alzheimer's disease, erectile dysfunction, and tumor invasion and metastasis.

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NOTE POUR LE TOME / VOLUME NOTE:

MONO- AND BICYCLIC AZOLE DERIVATIVES THAT INHIBIT THE INTERACTION OF LIGANDS WITH RAGE

Statement of Related Application

The present application claims priority under 35 USC 119(e) from the following US
5 Provisional Application: Serial Number 60/361,983, filed March 5, 2002, entitled "Azole
Derivatives as Therapeutic Agents," the entirety of which is herein incorporated by reference.

Field of the Invention

This invention relates to compounds which are modulators of the receptor for
advanced glycated end products (RAGE) and interaction with its ligands such as advanced
10 glycated end products (AGEs), S100/calgranulin/EN-RAGE, β -amyloid and amphoterin, for
the management, treatment, control, or as an adjunct treatment of diseases caused by
RAGE.

Background of the Invention

Incubation of proteins or lipids with aldose sugars results in nonenzymatic glycation
15 and oxidation of amino groups on proteins to form Amadori adducts. Over time, the adducts
undergo additional rearrangements, dehydrations, and cross-linking with other proteins to
form complexes known as Advanced Glycosylation End Products (AGEs). Factors which
promote formation of AGEs included delayed protein turnover (e.g. as in amyloidoses),
accumulation of macromolecules having high lysine content, and high blood glucose levels
20 (e.g. as in diabetes) (Hori *et al.*, *J. Biol. Chem.* **270**: 25752-761, (1995)). AGEs have
implicated in a variety of disorders including complications associated with diabetes and
normal aging.

AGEs display specific and saturable binding to cell surface receptors on endothelial
cells of the microvasculature, monocytes and macrophages, smooth muscle cells, mesengial
25 cells, and neurons. The Receptor for Advanced Glycated Endproducts (RAGE) is a member
of the immunoglobulin super family of cell surface molecules. The extracellular (N-terminal)
domain of RAGE includes three immunoglobulin-type regions, one V (variable) type domain
followed by two C-type (constant) domains (Neeper *et al.*, *J. Biol. Chem.* **267**:14998-15004
(1992)). A single transmembrane spanning domain and a short, highly charged cytosolic tail
30 follow the extracellular domain. The N-terminal, extracellular domain can be isolated by
proteolysis of RAGE to generate soluble RAGE (sRAGE) comprised of the V and C
domains.

RAGE is expressed in most tissues, and in particular, is found in cortical neurons
during embryogenesis (Hori *et al.*, *J. Biol. Chem.* **270**:25752-761 (1995)). Increased levels

of RAGE are also found in aging tissues (Schleicher *et al.*, *J. Clin. Invest.* **99** (3): 457-468 (1997)), and the diabetic retina, vasculature and kidney (Schmidt *et al.*, *Nature Med.* **1**:1002-1004 (1995)). Activation of RAGE in different tissues and organs leads to a number of pathophysiological consequences. RAGE has been implicated in a variety of conditions including: acute and chronic inflammation (Hofmann *et al.*, *Cell* **97**:889-901 (1999)), the development of diabetic late complications such as increased vascular permeability (Wautier *et al.*, *J. Clin. Invest.* **97**:238-243 (1995)), nephropathy (Teillet *et al.*, *J. Am. Soc. Nephrol.* **11**:1488-1497 (2000)), atherosclerosis (Vlassara *et al.*, *The Finnish Medical Society DUODECIM, Ann. Med.* **28**:419-426 (1996)), and retinopathy (Hammes *et al.*, *Diabetologia* **42**:603-607 (1999)). RAGE has also been implicated in Alzheimer's disease (Yan *et al.*, *Nature* **382**: 685-691, (1996)), erectile dysfunction, and in tumor invasion and metastasis (Taguchi *et al.*, *Nature* **405**: 354-357, (2000)).

In addition to AGEs, other compounds can bind to, and modulate RAGE. In normal development, RAGE interacts with amphoterin, a polypeptide which mediates neurite outgrowth in cultured embryonic neurons (Hori *et al.*, 1995). RAGE has also been shown to interact with EN-RAGE, a protein having substantial similarity to calgranulin (Hofmann *et al.*, *Cell* **97**:889-901 (1999)). RAGE has also been shown to interact with β -amyloid (Yan *et al.*, *Nature* **389**:589-595, (1997); Yan *et al.*, *Nature* **382**:685-691 (1996); Yan *et al.*, *Proc. Natl.Acad. Sci.*, **94**:5296-5301 (1997)).

Binding of ligands such as AGEs, S100/calgranulin/EN-RAGE, β -amyloid, CML (N^ε-Carboxymethyl lysine), and amphoterin to RAGE has been shown to modify expression of a variety of genes. For example, in many cell types interaction between RAGE and its ligands generates oxidative stress, which thereby results in activation of the free radical sensitive transcription factor NF- κ B, and the activation of NF- κ B regulated genes, such as the cytokines IL-1 β , TNF- α , and the like. In addition, several other regulatory pathways, such as those involving p21ras, MAP kinases, ERK1 and ERK2, have been shown to be activated by binding of AGEs and other ligands to RAGE. In fact, transcription of RAGE itself is regulated at least in part by NF- κ B. Thus, an ascending, and often detrimental, spiral is fueled by a positive feedback loop initiated by ligand binding. Antagonizing binding of physiological ligands to RAGE, therefore, is our target for down-regulation of the pathophysiological changes brought about by excessive concentrations of AGEs and other ligands for RAGE.

Thus, there is a need for the development of compounds that antagonize binding of physiological ligands to the RAGE receptor.

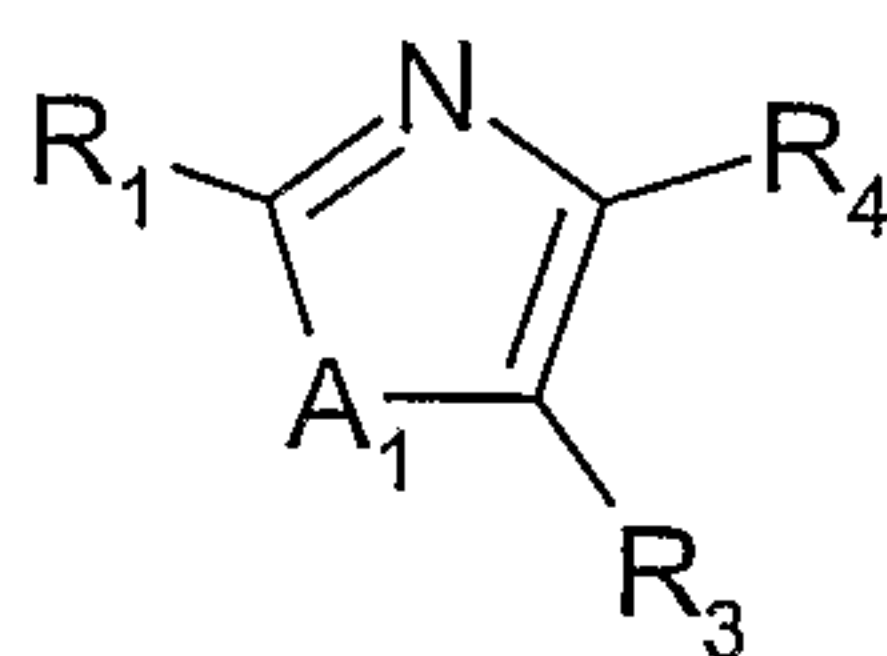
Summary of the Invention

This invention provides substituted benzimidazole compounds. Embodiments of the present invention provide compounds of Formula (I) as depicted below, methods of their preparation, pharmaceutical compositions comprising the compounds, and methods for their use in treating human or animal disorders. Compounds of the invention are useful as modulators of the interaction of the receptor for advanced glycated end products (RAGE) with its ligands such as advanced glycated end products (AGEs), S100/calgranulin/EN-RAGE, β -amyloid and amphoterin. The compounds are useful in a variety of applications including the management, treatment, control, and/or as an adjunct of diseases in humans caused by RAGE. Such diseases or disease states include acute and chronic inflammation, the development of diabetic late complications such as increased vascular permeability, nephropathy, atherosclerosis, and retinopathy, the development of Alzheimer's disease, erectile dysfunction, and tumor invasion and metastasis.

Detailed Description of the Invention

In a first aspect, the present invention provides certain substituted azole compounds. Such compounds are useful in the modulation, preferably in the inhibition, of the interaction of RAGE with its physiological ligands, as will be discussed in more detail below.

In a second aspect, the present invention provides compounds of Formula (I):



(I)

wherein

R_1 comprises -hydrogen, -aryl, -heteroaryl, -cycloalkyl, -heterocyclyl, -alkyl, -alkenyl, -alkynyl, -alkylene-aryl, -alkylene-heteroaryl, -alkylene-heterocyclyl, -alkylene-cycloalkyl, -fused cycloalkylaryl, -fused cycloalkylheteroaryl, -fused heterocyclaryl, -fused heterocyclheteroaryl, -alkylene-fused cycloalkylaryl, -alkylene-fused

cycloalkylheteroaryl, -alkylene-fused heterocyclylaryl, -alkylene-fused heterocyclylheteroaryl, or -G₁-G₂-G₃-R₅

wherein

G₁ and G₃ independently comprise alkylene, alkenylene, alkynylene, cycloalkylene, heterocyclylene, arylene, heteroarylene, (aryl)alkylene, (heteroaryl) alkylene, (aryl)alkenylene, (heteroaryl)alkenylene, or a direct bond;

G₂ comprises -O-, -S-, -S(O)-, -N(R₆)-, -S(O)₂-, -C(O)-, -O-C(O)-, -C(O)-O-, -C(O)N(R₆)-, -N(R₆)C(O)-, -S(O₂)N(R₆)-, N(R₆)S(O₂)-, -O-alkylene-C(O)-, -(O)C-alkylene-O-, -O-alkylene-, -alkylene-O-, alkylene, alkenylene, alkynylene, cycloalkylene, heterocyclylene, arylene, heteroarylene, fused cycloalkylarylene, fused cycloalkylheteroarylene, fused heterocyclylarylene, fused heterocyclylheteroarylene, or a direct bond, wherein R₆ comprises hydrogen, aryl, alkyl, -alkylene-aryl, alkoxy, or -alkylene-O-aryl; and

R₅ comprises hydrogen, aryl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, alkenyl, alkynyl, -alkylene-aryl, -alkylene-heteroaryl, -alkylene-heterocyclyl, -alkylene-cycloalkyl, fused cycloalkylaryl, fused cycloalkylheteroaryl, fused heterocyclylaryl, fused heterocyclylheteroaryl, -alkylene-fused cycloalkylaryl, -alkylene-fused cycloalkylheteroaryl, -alkylene-fused heterocyclylaryl, or -alkylene-fused heterocyclylheteroaryl;

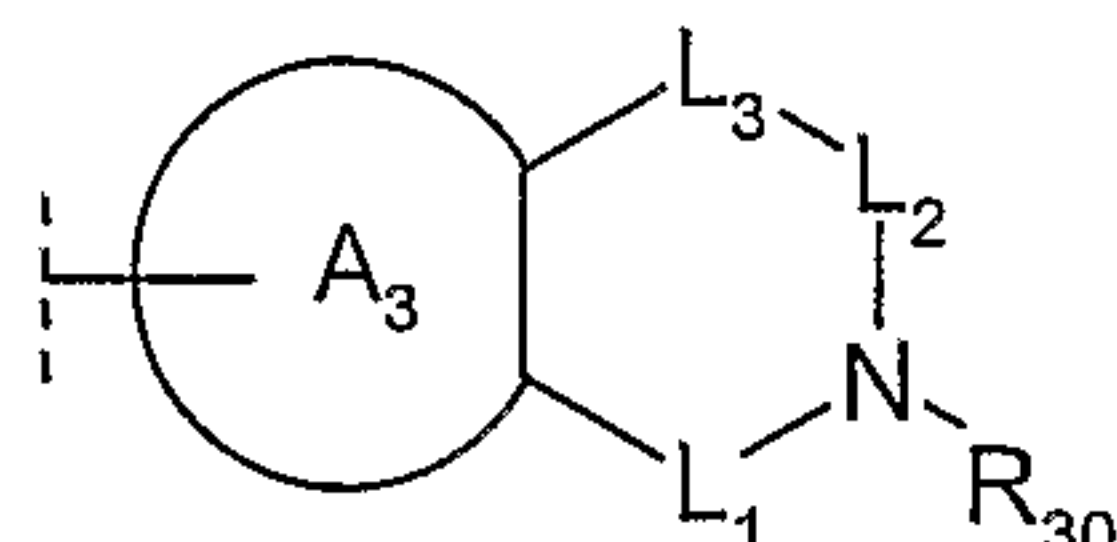
A₁ comprises O, S, or -N(R₂)-;

wherein

R₂ comprises

- a) -H;
- b) -aryl;
- c) -heteroaryl;
- d) -cycloalkyl
- e) heterocyclyl;
- f) -alkyl;
- g) -alkenyl;
- h) -alkynyl;
- i) -alkylene-aryl,
- j) -alkylene-heteroaryl,
- k) -alkylene-heterocyclyl,
- l) -alkylene-cycloalkyl;

- m) -fused cycloalkylaryl,
 n) -fused cycloalkylheteroaryl,
 o) -fused heterocyclylaryl,
 p) -fused heterocyclylheteroaryl;
 5 q) -alkylene-fused cycloalkylaryl,
 r) -alkylene-fused cycloalkylheteroaryl,
 s) -alkylene-fused heterocyclylaryl,
 t) -alkylene-fused heterocyclylheteroaryl; or
 u) a group of the formula

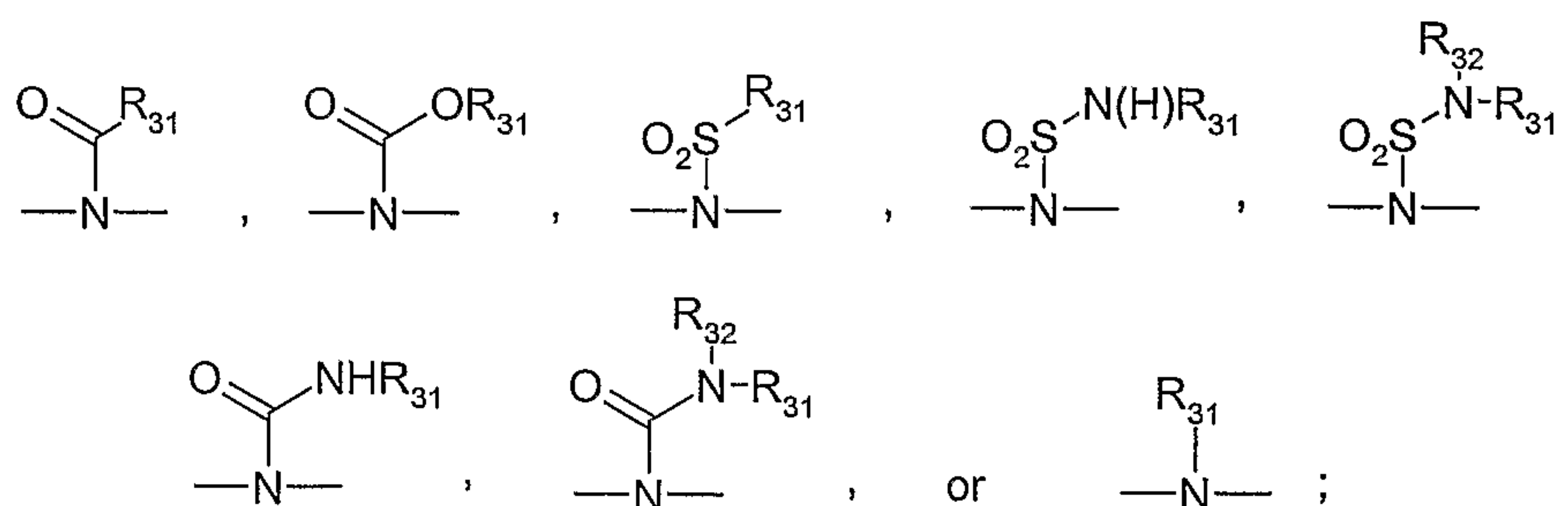


wherein

A_3 comprises an aryl or heteroaryl group;

L_1 and L_2 independently comprise alkylene or alkenylene; and

L_3 comprises a direct bond, alkylene, -O-, -S-, -S(O₂)-, -C(O)-,
 15 -CON(H)-, -NHC(O)-, -NHCON(H)-, -NHSO₂-, -SO₂N(H)-, -C(O)-O-
 , -O-C(O)-, -NHSO₂NH-,



wherein R_{30} , R_{31} , and R_{32} independently comprise hydrogen,
 aryl, heteroaryl, alkyl, alkylene-aryl, or -alkylene-heteroaryl;

R_3 and R_4 independently comprise

- a) -hydrogen,
 b) -halogen,
 c) -hydroxyl,
 25 d) -cyano,
 e) -carbamoyl,
 f) -carboxyl,
 g) -aryl,

- h) -heteroaryl,
- i) -cycloalkyl,
- j) -heterocyclyl,
- k) -alkyl,
- 5 l) -alkenyl,
- m) -alkynyl,
- n) -alkylene-aryl,
- o) -alkylene-heteroaryl,
- p) -alkylene-heterocyclyl,
- 10 q) -alkylene-cycloalkyl,
- r) -fused cycloalkylaryl,
- s) -fused cycloalkylheteroaryl,
- t) -fused heterocyclylaryl,
- u) -fused heterocyclylheteroaryl,
- 15 v) -alkylene-fused cycloalkylaryl,
- w) -alkylene-fused cycloalkylheteroaryl,
- x) -alkylene-fused heterocyclylaryl,
- y) -alkylene-fused heterocyclylheteroaryl;
- z) -C(O)-O-alkyl;
- 20 aa) -C(O)-O-alkylene-aryl;
- bb) -C(O)-NH-alkyl;
- cc) -C(O)-NH-alkylene-aryl;
- dd) -SO₂-alkyl;
- ee) -SO₂-alkylene-aryl;
- 25 ff) -SO₂-aryl;
- gg) -SO₂-NH-alkyl;
- hh) -SO₂-NH-alkylene-aryl;
- ii) -C(O)-alkyl;
- jj) -C(O)-alkylene-aryl;
- 30 kk) -G₄-G₅-G₆-R₇;
- ll) -Y₁-alkyl;
- mm) -Y₁-aryl;
- nn) -Y₁-heteroaryl;
- oo) -Y₁-alkylene-aryl;
- 35 pp) -Y₁-alkylene-heteroaryl;
- qq) -Y₁-alkylene-NR₉R₁₀; or
- rr) -Y₁-alkylene-W₁-R₁₁;

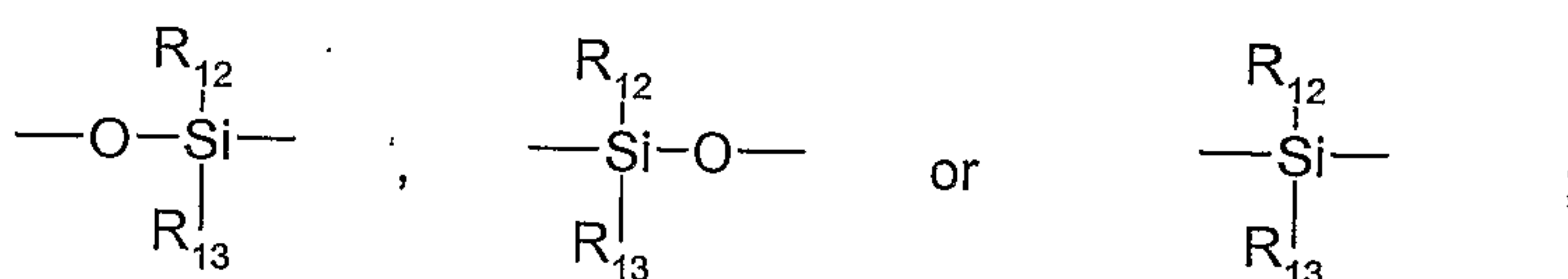
wherein

G₄ and G₆ independently comprise alkylene, alkenylene, alkynylene, cycloalkylene, heterocyclylene, arylene, heteroarylene, (aryl)alkylene, (heteroaryl)alkylene, (aryl)alkenylene, (heteroaryl)alkenylene, or a direct bond;

G₅ comprises -O-, -S-, -N(R₈)-, -S(O)-, -S(O)₂-, -C(O)-, -O-C(O)-, -C(O)-O-, -C(O)N(R₈)-, N(R₈)C(O)-, -S(O₂)N(R₈)-, N(R₈)S(O₂)-, -O-alkylene-C(O)-, -(O)C-alkylene-O-, -O-alkylene-, -alkylene-O-, alkylene, alkenylene, alkynylene, cycloalkylene, heterocyclylene, arylene, heteroarylene, fused cycloalkylarylene, fused cycloalkylheteroarylene, fused heterocyclylarylene, fused heterocyclylheteroarylene, or a direct bond, wherein R₈ comprises -hydrogen, -aryl, -alkyl, -alkylene-aryl, or -alkylene-O-aryl;

R₇ comprises hydrogen, aryl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, alkenyl, alkynyl, alkylene-aryl, -alkylene-heteroaryl, -alkylene-heterocyclyl, -alkylene-cycloalkyl, fused cycloalkylaryl, fused cycloalkylheteroaryl, fused heterocyclylaryl, fused heterocyclylheteroaryl, alkylene-fused cycloalkylaryl, -alkylene-fused cycloalkylheteroaryl, -alkylene-fused heterocyclylaryl, or -alkylene-fused heterocyclylheteroaryl;

Y₁ and W₁ independently comprise -CH₂-, -O-, -N(H)-, -S-, SO₂-, -CON(H)-, -NHC(O)-, -NHCON(H)-, -NHSO₂-, -SO₂N(H)-, -C(O)-O-, -NHSO₂NH-, -O-CO-



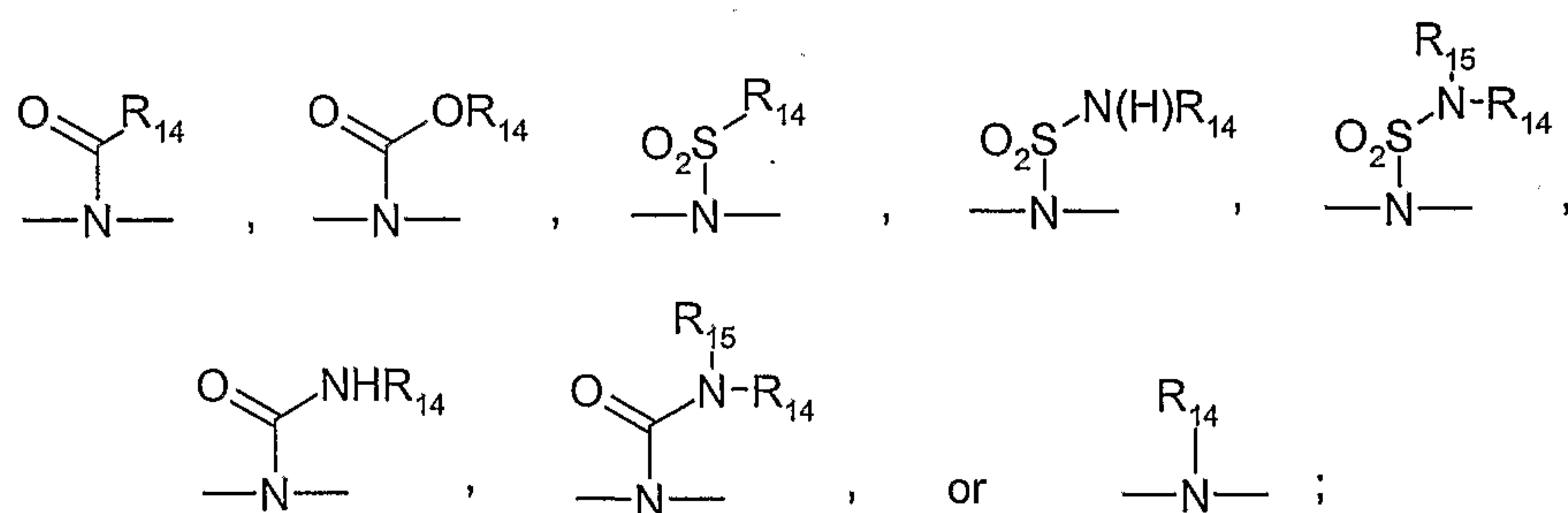
wherein R₁₂ and R₁₃ independently comprise aryl, alkyl, -alkylene-aryl, alkoxy, or -alkylene-O-aryl; and

R₉, R₁₀, and R₁₁ independently comprise aryl, heteroaryl, alkyl, -alkylene-heteroaryl, or -alkylene-aryl; and R₉ and R₁₀ may be taken together to form a ring having the formula -(CH₂)_o-X₁-(CH₂)_p- bonded to the nitrogen atom to which R₉ and R₁₀ are attached,

wherein

o and p are, independently, 1, 2, 3, or 4; and

X₁ comprises a direct bond, -CH₂-, -O-, -S-, -S(O₂)-, -C(O)-, -CON(H)-, -NHC(O)-, -NHCON(H)-, -NHSO₂-, -SO₂N(H)-, -C(O)-O-, -O-C(O)-, -NHSO₂NH-,



wherein R_{14} and R_{15} independently hydrogen, aryl, heteroaryl, alkyl, -alkylene-aryl, or -alkylene-heteroaryl;

5

wherein

the aryl and/or alkyl group(s) in R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , and R_{15} may be optionally substituted 1-4 times with a substituent group, wherein said substituent group(s) or the term substituted refers to a group comprising:

10

a) -H,

b) -halogen,

c) -hydroxyl,

d) -cyano,

e) -carbamoyl,

15

f) -carboxyl,

g) $-Y_2$ -alkyl;

h) $-Y_2$ -aryl;

i) $-Y_2$ -heteroaryl;

j) $-Y_2$ -alkylene-heteroarylaryl;

20

k) $-Y_2$ -alkylene-aryl;

l) $-Y_2$ -alkylene- W_2 - R_{18} ;

m) $-Y_3$ - Y_4 - $NR_{23}R_{24}$,

n) $-Y_3$ - Y_4 - $NH-C(=NR_{25})NR_{23}R_{24}$,

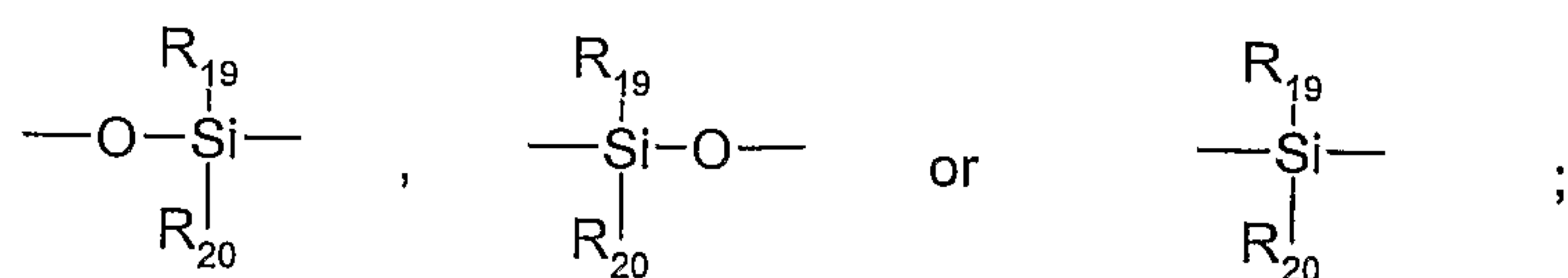
o) $-Y_3$ - Y_4 - $C(=NR_{25})NR_{23}R_{24}$, or

25

p) $-Y_3$ - Y_4 - Y_5 - A_2 ,

wherein

Y_2 and W_2 independently comprise -CH₂-, -O-, -N(H)-, -S-, SO₂-, -CON(H)-, -NHC(O)-, -NHCON(H)-, -NHSO₂-, -SO₂N(H)-, -C(O)-O-, -NHSO₂NH-, -O-S(O)₂-, -O-CO-,



wherein;

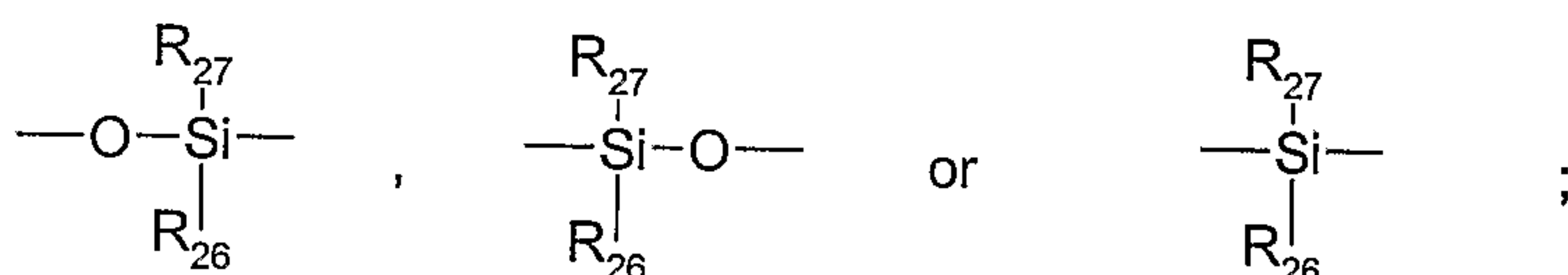
R₁₉ and R₂₀ independently comprise hydrogen, aryl, alkyl, -alkylene-aryl, alkoxy, or -alkylene-O-aryl; and

5

R₁₈ comprises aryl, alkyl, -alkylene-aryl, -alkylene-heteroaryl, and -alkylene-O-aryl;

10

Y₃ and Y₅ independently comprise a direct bond, -CH₂-, -O-, -N(H), -S-, SO₂-, -C(O)-, -CON(H)-, -NHC(O)-, -NHCON(H)-, -NHSO₂-, -SO₂N(H)-, -C(O)-O-, -NHSO₂NH-, -O-CO-,



wherein R₂₇ and R₂₆ independently comprise aryl, alkyl, -alkylene-aryl, alkoxy, or -alkyl-O-aryl;

15

Y₄ comprises

20

- a) -alkylene;
- b) -alkenylene;
- c) -alkynylene;
- d) -arylene;
- e) -heteroarylene;
- f) -cycloalkylene;
- g) -heterocyclylene;
- h) -alkylene-arylene;
- i) -alkylene-heteroarylene;
- j) -alkylene-cycloalkylene;
- k) -alkylene-heterocyclylene;
- l) -arylene-alkylene;
- m) -heteroarylene-alkylene;
- n) -cycloalkylene-alkylene;
- o) -heterocyclylene-alkylene;
- p) -O-;
- q) -S-;

25

30

r) $-\text{S}(\text{O}_2)-$; or

s) $-\text{S}(\text{O})-$;

wherein said alkylene groups may optionally contain one or more O, S, $\text{S}(\text{O})$, or SO_2 atoms;

5

A_2 comprises

a) heterocyclyl, fused arylheterocyclyl, or fused heteroarylheterocyclyl, containing at least one basic nitrogen atom,

b) -imidazolyl, or

c) -pyridyl; and

10

R_{23} , R_{24} , and R_{25} independently comprise hydrogen, aryl, heteroaryl, -alkylene-heteroaryl, alkyl, -alkylene-aryl, -alkylene-O-aryl, or -alkylene-O-heteroaryl; and R_{23} and R_{24} may be taken together to form a ring having the formula $-(\text{CH}_2)_s-\text{X}_3-(\text{CH}_2)_t-$ bonded to the nitrogen atom to which R_{23} and R_{24} are attached

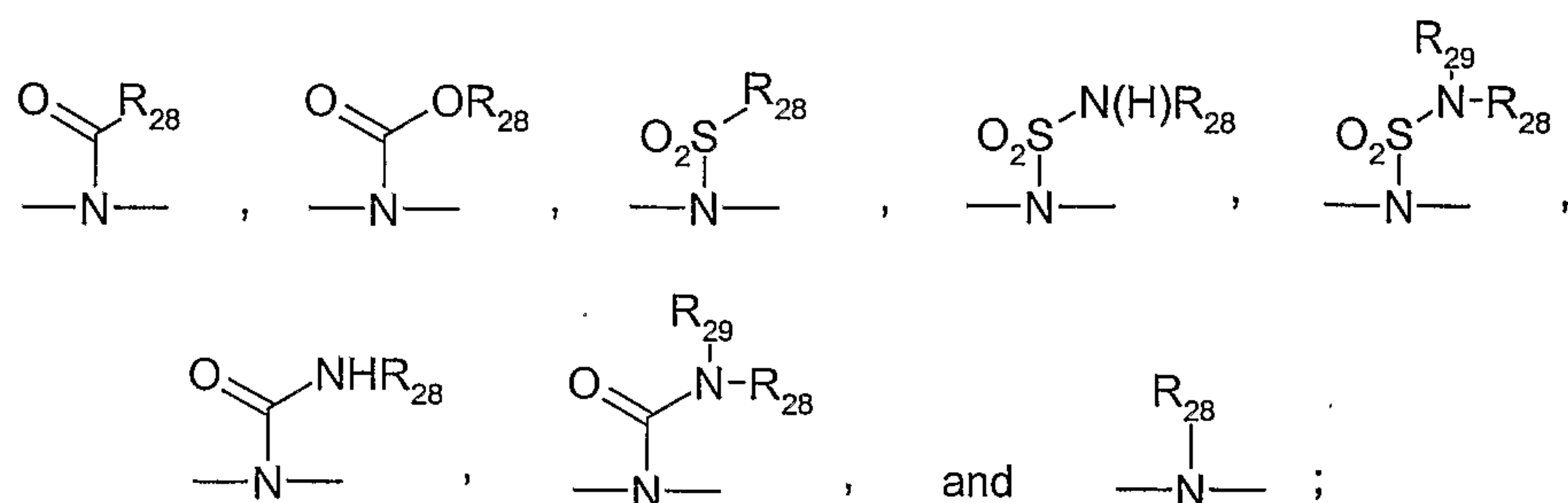
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wherein

s and t are, independently, 1, 2, 3, or 4;

X_3 comprises a direct bond, $-\text{CH}_2-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O}_2)-$, $-\text{C}(\text{O})-$, $-\text{CON}(\text{H})-$, $-\text{NHC}(\text{O})-$, $-\text{NHCON}(\text{H})-$, $-\text{NHSO}_2-$, $-\text{SO}_2\text{N}(\text{H})-$, $-\text{C}(\text{O})-\text{O}-$, $-\text{O}-\text{C}(\text{O})-$, $-\text{NHSO}_2\text{NH}-$,

20



wherein R_{28} and R_{29} independently comprise hydrogen, aryl, heteroaryl, alkyl, -alkylene-aryl, or -alkylene-heteroaryl;

25

wherein

either

at least one of the groups R_1 , R_2 , R_3 and R_4 are substituted with at least one group of the formula $-\text{Y}_3-\text{Y}_4-\text{NR}_{23}\text{R}_{24}$, $-\text{Y}_3-\text{Y}_4-\text{NH}-\text{C}(=\text{NR}_{25})\text{NR}_{23}\text{R}_{24}$, $-\text{Y}_3-\text{Y}_4-$

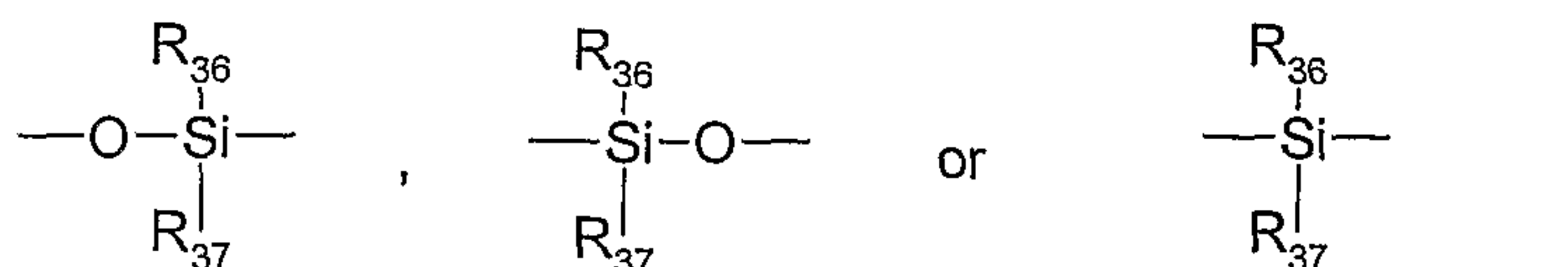
or

Chemical structure of a substituted benzene ring. A benzene ring is shown with a substituent A_3 at the para position. The ring is connected to a nitrogen atom (N) which is bonded to R_{30} . The nitrogen atom is also bonded to two other groups, L_1 and L_2 , which are connected to a third group L_3 . The text "and" follows the structure.

one of R₃ and R₄, R₃ and R₂, or R₁ and R₂ may be taken together to constitute, together with the atoms to which they are bonded, an aryl, heteroaryl, fused arylcycloalkyl, fused arylheterocyclyl, fused heteroaryl cycloalkyl, or fused heteroaryl heterocyclyl ring system, wherein

a) $-Y_5-Y_6-NR_{33}R_{34}$;
 b) $-Y_5-Y_6-NH-C(=NR_{35})NR_{33}R_{34}$;
 c) $-Y_5-Y_6-C(=NR_{35})NR_{33}R_{34}$; or
 d) $-Y_5-Y_6-Y_7-A_4$;

Y₅ and Y₇ independently comprise a direct bond, -CH₂-, -O-, -N(H)-, -S-, SO₂-,
-CON(H)-, -NHC(O)-, -NHCON(H)-, -NHSO₂-, -SO₂N(H)-, -C(O)-O-, -
NH₂SO₂NH-, -O-CO-,



Y_6 comprises

- a) alkylene;
- b) alkenylene;
- c) alkynylene;
- d) arylene;
- e) heteroarylene;
- f) cycloalkylene;
- g) heterocyclylene;

- h) alkylene-arylene;
- i) alkylene-heteroarylene;
- j) alkylene-cycloalkylene;
- k) alkylene-heterocyclylene;
- l) arylene-alkylene;
- m) heteroarylene-alkylene;
- n) cycloalkylene-alkylene;
- o) heterocyclylene-alkylene;
- p) -O-;
- q) -S-;
- r) -S(O₂)-; or
- s) -S(O)-;

wherein said alkylene groups may optionally contain one or more O, S, S(O), or SO₂ atoms;

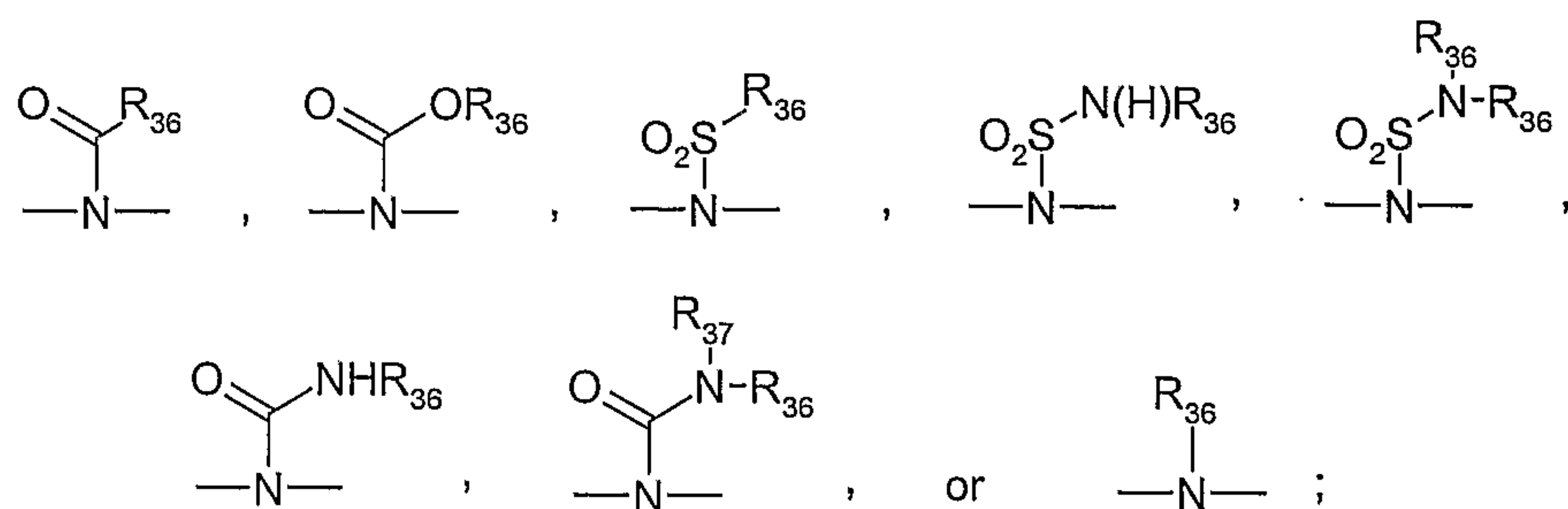
A₄ comprises

- a) heterocyclyl, fused arylheterocyclyl, or fused heteroarylheterocyclyl, containing at least one basic nitrogen atom,
- b) -imidazolyl, or
- c) -pyridyl; and

R₃₃, R₃₄ and R₃₅ independently comprise hydrogen, aryl, heteroaryl, alkyl, -alkylene-aryl, or -alkylene-O-aryl; with the proviso that no two of R₃₃, R₃₄ and R₃₅ are aryl and/or heteroaryl; and R₃₃ and R₃₄ may be taken together to form a ring having the formula -(CH₂)_u-X₄-(CH₂)_v- bonded to the nitrogen atom to which R₃₃ and R₃₄ are attached, wherein

u and v are, independently, 1, 2, 3, or 4;

X₄ comprises a direct bond, -CH₂-, -O-, -S-, -S(O₂)-, -C(O)-, -CON(H)-, -NHC(O)-, -NHCON(H)-, -NHSO₂-, -SO₂N(H)-, -C(O)-O-, -O-C(O)-, -NHSO₂NH-,



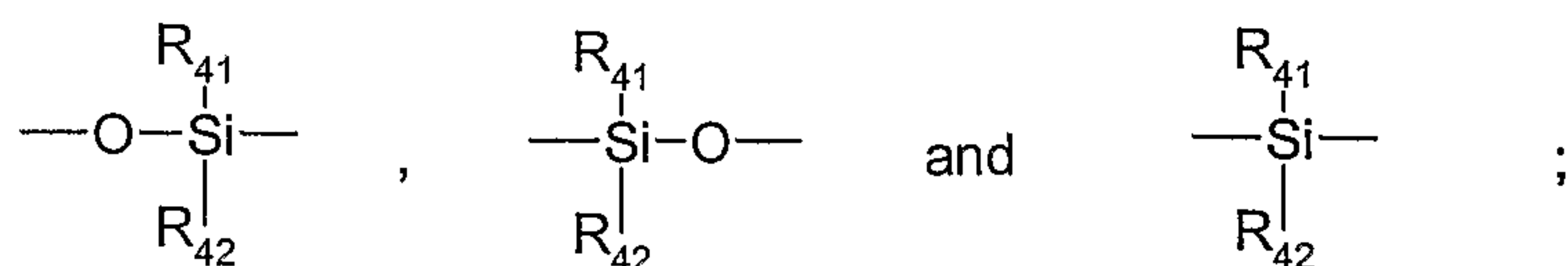
wherein R₃₆ and R₃₇ independently comprise hydrogen, aryl, heteroaryl, alkyl, -alkylene-aryl, or -alkylene-heteroaryl; and

wherein said ring system is optionally substituted with substituents comprising

- 5 a) -H;
- b) -halogen;
- c) -hydroxyl;
- d) -cyano;
- e) -carbamoyl;
- 10 f) -carboxyl;
- g) -Y₈-alkyl;
- h) -Y₈-aryl;
- i) -Y₈-heteroaryl;
- j) -Y₈-alkylene-aryl;
- 15 k) -Y₈-alkylene-heteroaryl;
- l) -Y₈-alkylene-NR₃₈R₃₉; or
- m) -Y₈-alkylene-W₃-R₄₀;

wherein

20 Y₈ and W₃ independently comprise -CH₂-, -O-, -N(H)-, -S-, SO₂-, -CON(H)-, -NHC(O)-, -NHCON(H)-, -NHSO₂-, -SO₂N(H)-, -C(O)-O-, -NHSO₂NH-, -O-CO-,

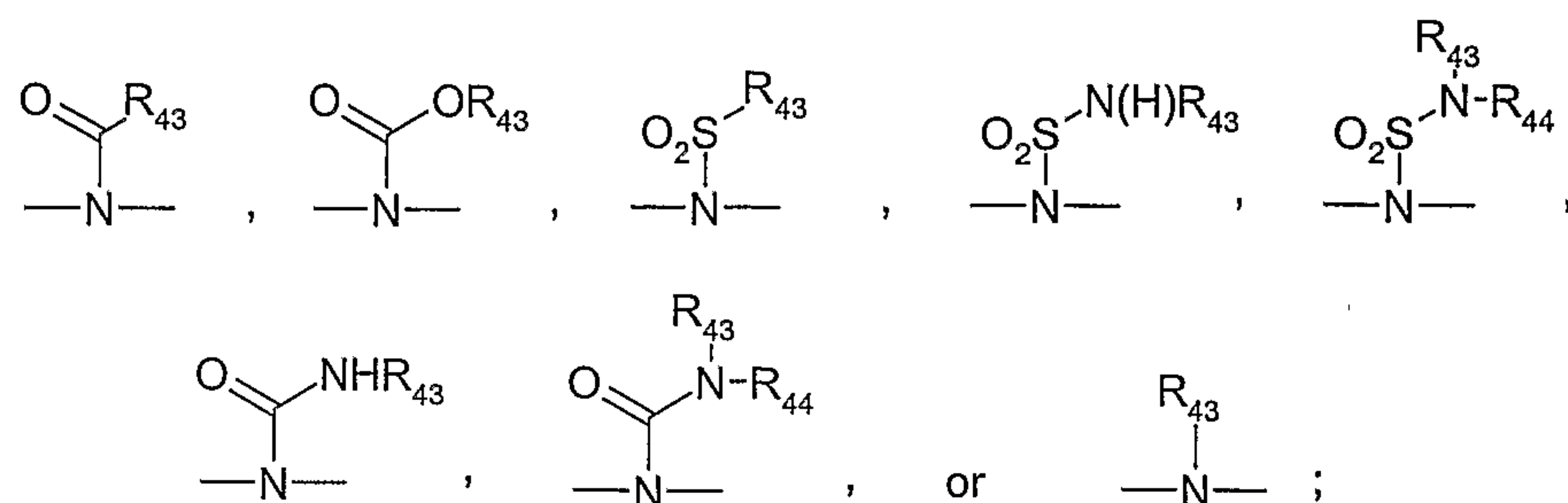


wherein R₄₁ and R₄₂ independently comprise aryl, alkyl, -alkylene-aryl, alkoxy, or -alkyl-O-aryl; and

25 R₃₈, R₃₉, and R₄₀ independently comprise hydrogen, aryl, alkyl, -alkylene-aryl, -alkylene-heteroaryl, and -alkylene-O-aryl; and R₃₈ and R₃₉ may be taken together to form a ring having the formula -(CH₂)_w-X₇-(CH₂)_x- bonded to the nitrogen atom to which R₃₈ and R₃₉ are attached wherein

w and x are, independently, 1, 2, 3, or 4;

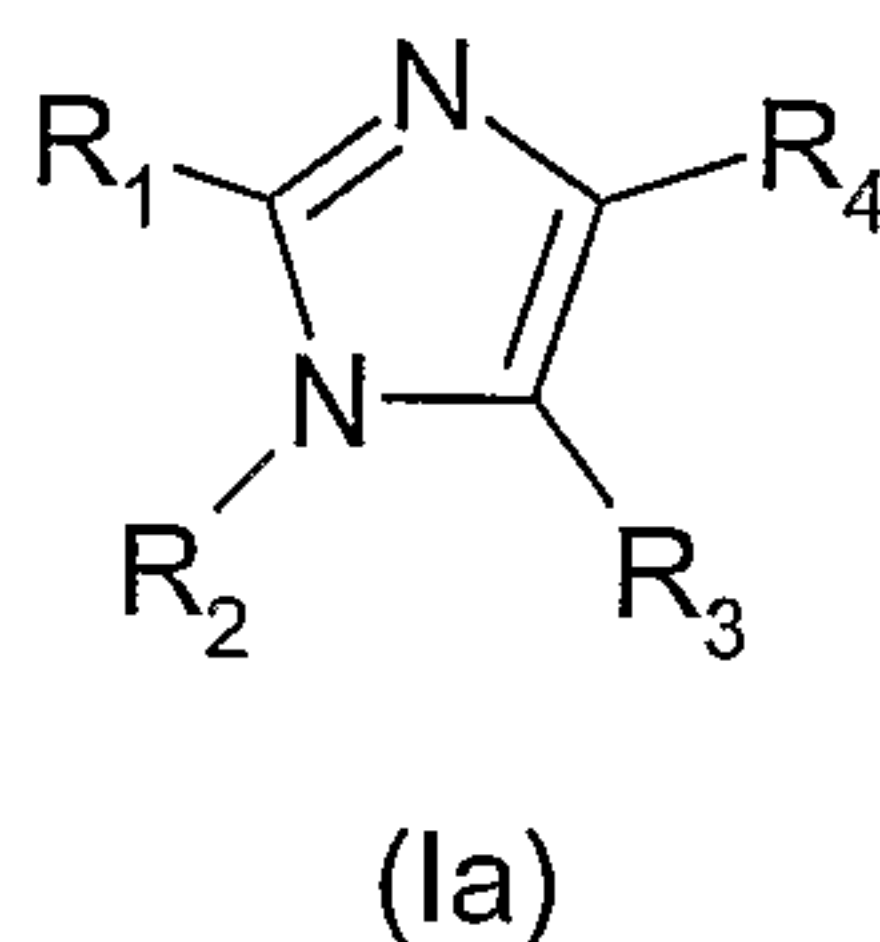
X₇ comprises a direct bond, -CH₂-, -O-, -S-, -S(O₂)-, -C(O)-, -CON(H)-, -NHC(O)-, -NHCON(H)-, -NHSO₂-, -SO₂N(H)-, -C(O)-O-, -O-C(O)-, -NHSO₂NH-,



wherein R₄₃ and R₄₄ independently comprise hydrogen, aryl, heteroaryl, alkyl, -alkylene-aryl, or -alkylene-heteroaryl;

or a pharmaceutically acceptable salt thereof.

In a preferred embodiment, the compound of Formula (I) comprises a compound of the Formula (Ia)



wherein

R₁ comprises -hydrogen, -aryl, -heteroaryl, -cycloalkyl, -heterocyclyl, -alkyl, -alkylene-aryl, -alkylene-heteroaryl, -alkylene-heterocyclyl, -alkylene-cycloalkyl, or -G₁-G₂-G₃-R₅ wherein

G₁ and G₃ independently comprise alkylene or a direct bond;

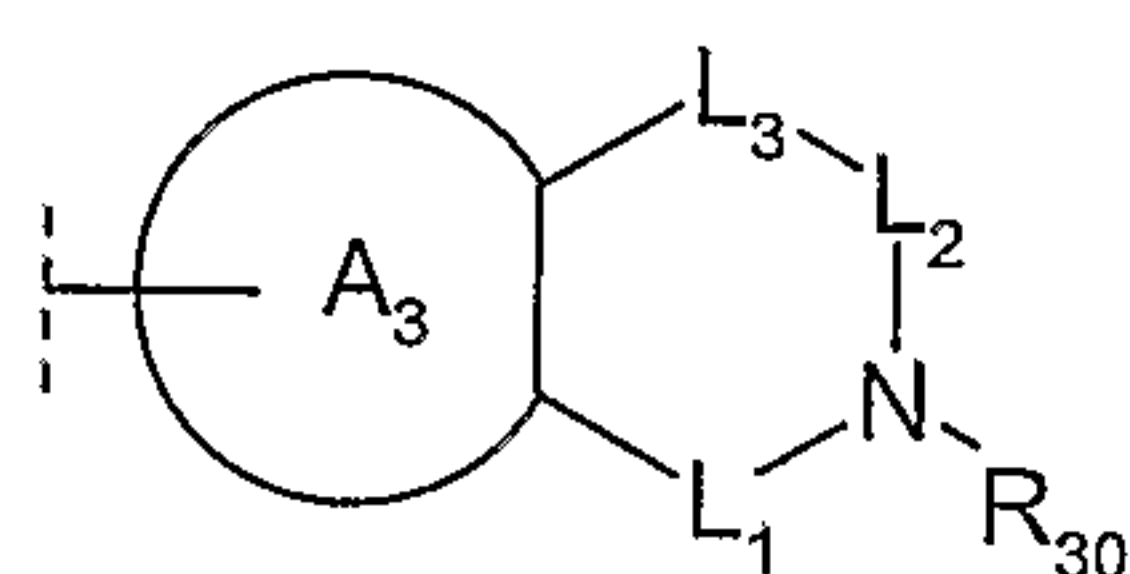
G₂ comprises -O-, -CO₂-, or a direct bond; and

R₅ comprises hydrogen, aryl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, alkenyl, alkynyl, -alkylene-aryl, -alkylene-heteroaryl, -alkylene-heterocyclyl, or -alkylene-cycloalkyl.

R₂ comprises

a) -hydrogen,

- b) -aryl,
 c) -heteroaryl,
 d) -heterocyclyl,
 e) -alkyl,
 5 f) -alkylene-aryl,
 g) -alkylene-heteroaryl,
 h) -alkylene-heterocyclyl,
 i) -fused cycloalkylaryl,
 j) -fused cycloalkylheteroaryl,
 10 k) -fused heterocyclylaryl,
 l) -fused heterocyclylheteroaryl;
 m) -alkylene-fused cycloalkylaryl,
 n) -alkylene-fused cycloalkylheteroaryl,
 o) -alkylene-fused heterocyclylaryl,
 15 p) -alkylene-fused heterocyclylheteroaryl; or
 q) a group of the formula

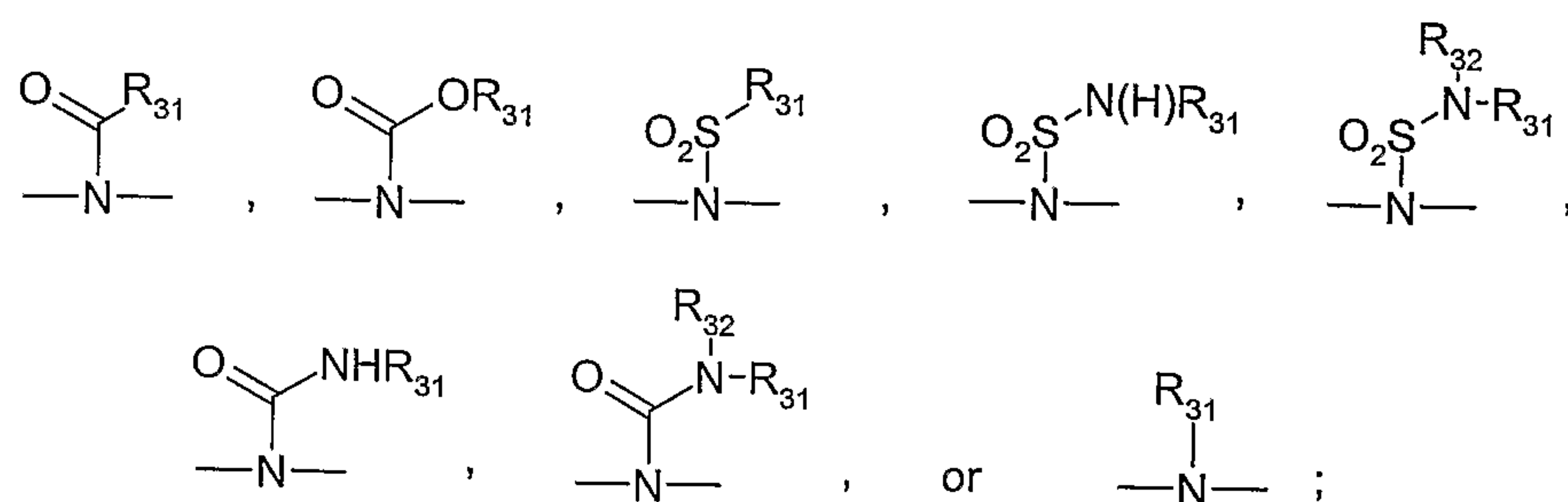


wherein

A₃ comprises an aryl or heteroaryl group;

20 L₁ and L₂ independently comprise alkylene or alkenylene;

L₃ comprises a direct bond, alkylene, -O-, -S-, -S(O₂)-, -C(O)-, -CON(H)-, -NHC(O)-, -NHCON(H)-, -NHSO₂-, -SO₂N(H)-, -C(O)-O-, -O-C(O)-, -NHSO₂NH-,



25 wherein R₃₀, R₃₁, and R₃₂ independently comprise hydrogen, aryl, heteroaryl, alkyl, alkylene-aryl, or -alkylene-heteroaryl;

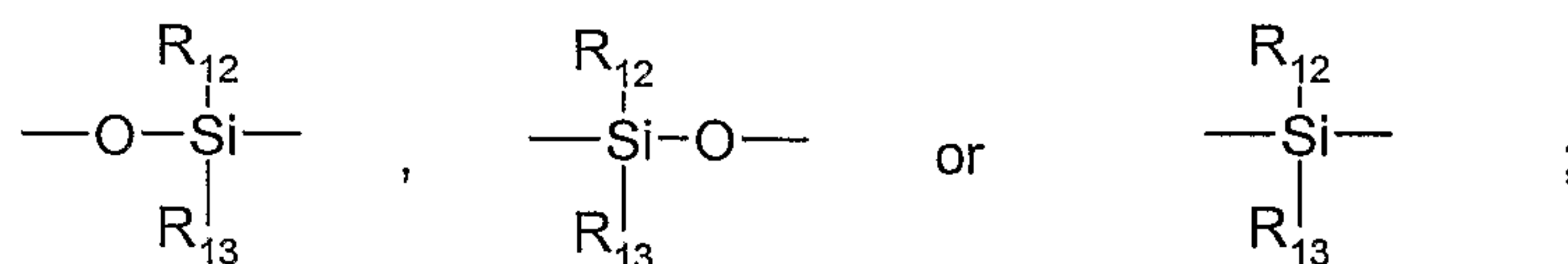
R₃ and R₄ independently comprise

- a) -hydrogen;
- b) -halogen,
- c) -hydroxyl,
- d) -cyano,
- 5 e) -carbamoyl,
- f) -carboxyl;
- g) -aryl,
- h) -heteroaryl,
- i) -cycloalkyl,
- 10 j) -heterocyclyl,
- k) -alkyl,
- l) -alkenyl,
- m) -alkynyl,
- n) -alkylene-aryl,
- 15 o) -alkylene-heteroaryl,
- p) -alkylene-heterocyclyl,
- q) -alkylene-cycloalkyl,
- r) -fused cycloalkylaryl,
- s) -fused cycloalkylheteroaryl,
- 20 t) -fused heterocyclylaryl,
- u) -fused heterocyclylheteroaryl,
- v) -alkylene-fused cycloalkylaryl,
- w) -alkylene-fused cycloalkylheteroaryl,
- x) -alkylene-fused heterocyclylaryl,
- 25 y) -alkylene-fused heterocyclylheteroaryl;
- z) -C(O)-O-alkyl;
- aa) -C(O)-O-alkylene-aryl;
- bb) -C(O)-NH-alkyl;
- cc) -C(O)-NH-alkylene-aryl;
- 30 dd) -SO₂-alkyl;
- ee) -SO₂-alkylene-aryl;
- ff) -SO₂-aryl;
- gg) -SO₂-NH-alkyl;
- hh) -SO₂-NH-alkylene-aryl
- 35 ii) -C(O)-alkyl;
- jj) -C(O)-alkylene-aryl;
- kk) -G₄-G₅-G₆-R₇

- ll) $-Y_1$ -alkyl;
 mm) $-Y_1$ -aryl;
 nn) $-Y_1$ -heteroaryl;
 oo) $-Y_1$ -alkylene-aryl;
 5 pp) $-Y_1$ -alkylene-heteroaryl;
 qq) $-Y_1$ -alkylene- NR_9R_{10} ; and
 rr) $-Y_1$ -alkylene- W_1-R_{11} ;

wherein

- 10 G_4 and G_6 independently comprise alkylene, alkenylene, alkynylene, cycloalkylene, heterocyclylene, arylene, heteroarylene, (arylalkylene, (heteroaryl) alkylene, (aryl)alkenylene, (heteroaryl)alkenylene, or a direct bond;
- 15 G_5 comprises $-O-$, $-S-$, $-N(R_8)-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)N(R_8)-$, $N(R_8)C(O)-$, $-S(O_2)N(R_8)-$, $N(R_8)S(O_2)-$, $-O$ -alkylene- $C(O)-$, $-(O)C$ -alkylene- $O-$, $-O$ -alkylene-, $-alkylene-O-$, alkylene, alkenylene, alkynylene, cycloalkylene, heterocyclylene, arylene, heteroarylene, fused cycloalkylaryl, fused cycloalkylheteroaryl, fused heterocyclylaryl, fused heterocyclylheteroaryl, or a direct bond, wherein R_8 comprises $-hydrogen$, $-aryl$, $-alkyl$, $-alkylene-aryl$, or $-alkylene-O-aryl$;
- 20 R_7 comprises hydrogen; aryl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, alkenyl, alkynyl, alkylene-aryl, $-alkylene-heteroaryl$, $-alkylene-heterocyclyl$, $-alkylene-cycloalkyl$, fused cycloalkylaryl, fused cycloalkylheteroaryl, fused heterocyclylaryl, fused heterocyclylheteroaryl, alkylene-fused cycloalkylaryl, $-alkylene-fused$ cycloalkylheteroaryl, $-alkylene-fused$ heterocyclylaryl, or
- 25 $-alkylene-fused$ heterocyclylheteroaryl;
- Y_1 and W_1 independently comprise $-CH_2-$, $-O-$, $-N(H)-$, $-S-$, SO_2- , $-CON(H)-$, $-NHC(O)-$, $-NHCON(H)-$, $-NHSO_2-$, $-SO_2N(H)-$, $-C(O)-O-$, $-NHSO_2NH-$, $-O-CO-$,



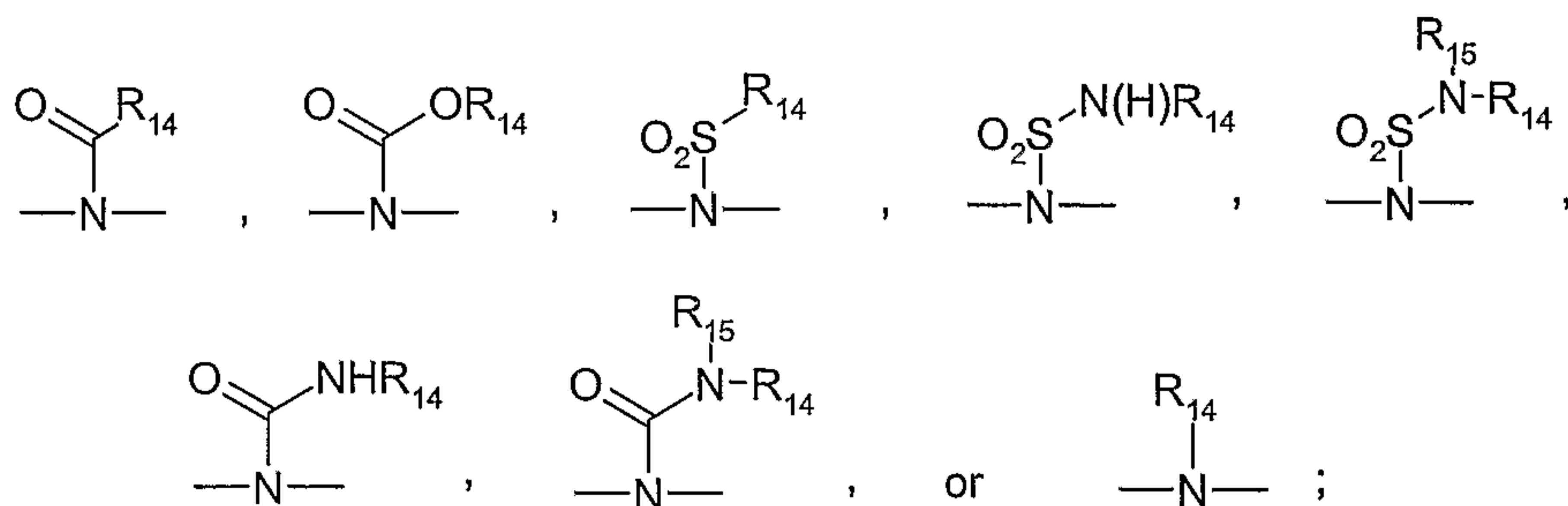
- 30 wherein R_{12} and R_{13} independently comprise aryl, alkyl, $-alkylene-aryl$, alkoxy, or $-alkylene-O-aryl$;
- R_9 , R_{10} , and R_{11} independently comprise aryl, heteroaryl, alkyl, $-alkylene-heteroaryl$, or $-alkylene-aryl$; and R_9 and R_{10} may be taken together to form a

ring having the formula $-(CH_2)_o-X_1-(CH_2)_p-$ bonded to the nitrogen atom to which R_9 and R_{10} are attached,

wherein

o and p are, independently, 1, 2, 3, or 4;

5 X_1 comprises a direct bond, $-CH_2-$, $-O-$, $-S-$, $-S(O_2)-$, $-C(O)-$, $-CON(H)-$, $-NHC(O)-$, $-NHCON(H)-$, $-NHSO_2-$, $-SO_2N(H)-$, $-C(O)-O-$, $-O-C(O)-$, $-NHSO_2NH-$,



10 with the proviso that R_3 and R_4 can not both be hydrogen.

In one group of preferred embodiments of Formula (Ia), R_1 comprises a hydrogen, methyl, ethyl, propyl, butyl, iso-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 3-butenyl, tert-butyl, 3-cyclohexyl-propyl, 3-phenoxy-propyl, methoxymethyl, 4-fluoro-phenyl, 3-
15 (4-chlorophenoxy)-propyl, 2,4,4-trimethyl-pentyl, 1-ethyl-propyl, 1-propyl-butyl, benzyloxymethyl, 2-cyclopropyl-ethyl, 2-phenyl-ethyl, 4-tert-butylphenoxy-methyl, 4-tert-butylcyclohexyl, 4-butylcyclohexyl, 4-ethylcyclohexyl, 3-methoxycarbonyl-1-propyl, or 2-(pyridin-3-yl)-ethyl group.

In another group of preferred embodiments of Formula (Ia), R_2 comprises a phenyl or
20 1,2,3,4-tetrahydroisoquinoline group, wherein the phenyl group is substituted with at least one substituent comprising

- a) $-Y_2$ -alkyl;
- b) $-Y_2$ -aryl;
- c) $-Y_2$ -heteroaryl;
- 25 d) $-Y_2$ -alkylene-heteroarylaryl;
- e) $-Y_2$ -alkylene-aryl;
- f) $-Y_2$ -alkylene- W_2-R_{18} ;
- g) $-Y_3-Y_4-NR_{23}R_{24}$;

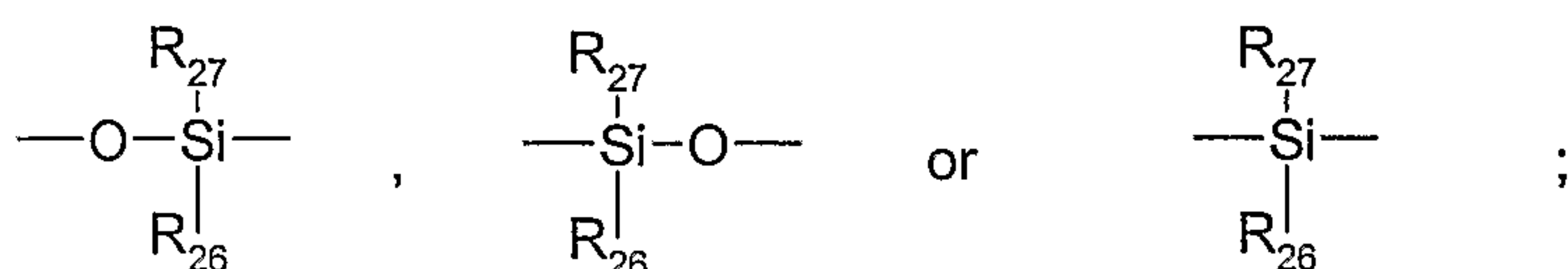
- h) $-Y_3-Y_4-NH-C(=NR_{25})NR_{23}R_{24}$;
 i) $-Y_3-Y_4-C(=NR_{25})NR_{23}R_{24}$; or
 j) $-Y_3-Y_4-Y_5-A_2$;

wherein

5 Y_2 and W_2 independently comprise $-CH_2-$ or $-O-$, and

R_{18} comprises aryl, alkyl, -alkylene-aryl, -alkylene-heteroaryl, or -alkylene-O-aryl;

10 Y_3 and Y_5 independently comprise a direct bond, $-CH_2-$, $-O-$, $-N(H)$, $-S-$, SO_2- , $-C(O)-$, $-CON(H)-$, $-NHC(O)-$, $-NHCON(H)-$, $-NHSO_2-$, $-SO_2N(H)-$, $-C(O)-O-$, $-NHSO_2NH-$, $-O-CO-$,



wherein R_{27} and R_{26} independently comprise aryl, alkyl, -alkylene-aryl, alkoxy, or -alkyl-O-aryl;

Y_4 comprises

- 15 a) -alkylene;
 b) -alkenylene;
 c) -alkynylene;
 d) -arylene;
 e) -heteroarylene;
 20 f) -cycloalkylene;
 g) -heterocyclylene;
 h) -alkylene-arylene;
 i) -alkylene-heteroarylene;
 j) -alkylene-cycloalkylene;
 25 k) -alkylene-heterocyclylene;
 l) -arylene-alkylene;
 m) -heteroarylene-alkylene;
 n) -cycloalkylene-alkylene;
 t) -heterocyclylene-alkylene;
 30 u) $-O-$;
 v) $-S-$;
 w) $-S(O_2)-$; or
 x) $-S(O)-$;

wherein said alkylene groups may optionally contain one or more O, S, S(O), or SO₂ atoms;

A₂ comprises

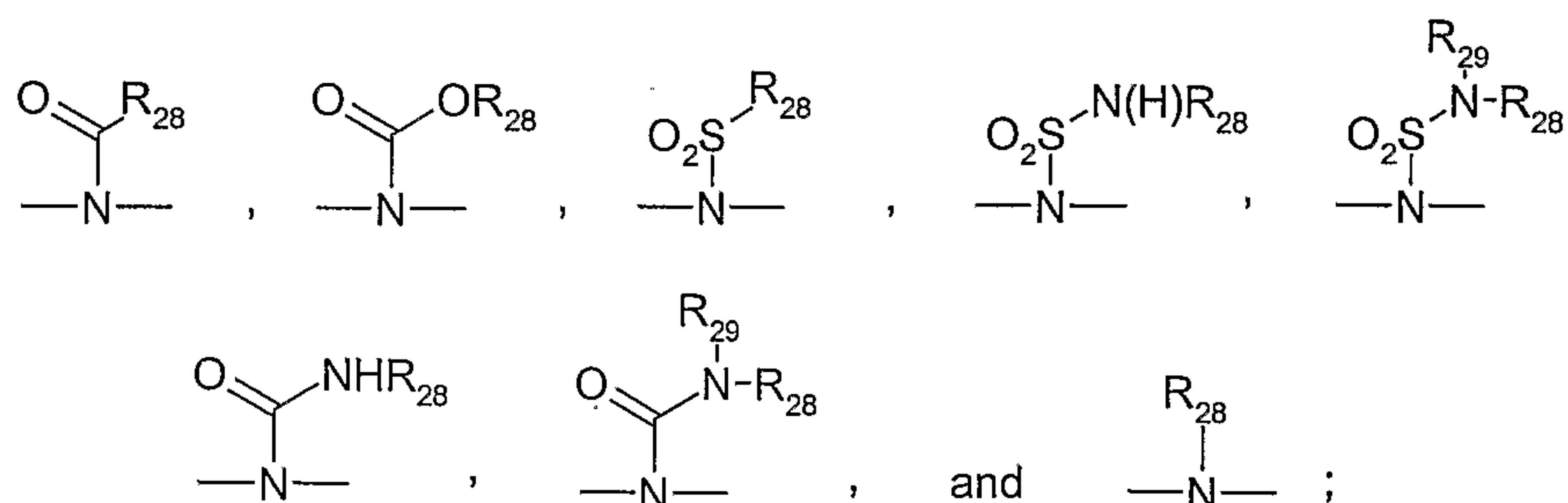
- 5 a) heterocyclyl, fused arylheterocyclyl, or fused heteroarylheterocyclyl, containing at least one basic nitrogen atom,
b) -imidazolyl, or
c) -pyridyl; and

10 R₂₃, R₂₄, and R₂₅ independently comprise hydrogen, aryl, heteroaryl, -alkylene-heteroaryl, alkyl, -alkylene-aryl, -alkylene-O-aryl, or -alkylene-O-heteroaryl; and R₂₃ and R₂₄ may be taken together to form a ring having the formula -(CH₂)_s-X₃-(CH₂)_t- bonded to the nitrogen atom to which R₂₃ and R₂₄ are attached

wherein

15 s and t are, independently, 1, 2, 3, or 4;

X₃ comprises direct bond, -CH₂-, -O-, -S-, -S(O₂)-, -C(O)-, -CON(H)-, -NHC(O)-, -NHCON(H)-, -NHSO₂-, -SO₂N(H)-, -C(O)-O-, -O-C(O)-, -NHSO₂NH-,



20

wherein R₂₈ and R₂₉ independently comprise hydrogen, aryl, heteroaryl, alkyl, -alkylene-aryl, or -alkylene-heteroaryl.

25 In another group of preferred embodiments of compounds of Formula (Ia), R₂ comprises 4-[3-(N,N'-diethylamino)-propoxy]-phenyl, 4-[3-(N,N'-dimethylamino)-propoxy]-phenyl, 3-[3-(N,N'-diethylamino)-propoxy]-phenyl, 4-(3-fluoro-4-trifluoromethyl-phenoxy)-phenyl, 4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl, 4-(4-trifluoromethoxy-phenoxy)-phenyl, 4-(3,4-dichloro-phenoxy)-phenyl, 4-(3,5-bis-trifluoromethyl-phenoxy)-phenyl, 4-benzyloxy-phenyl, 4-(4-methyloxy-phenoxy)-phenyl, 4-(2-hexyl-4-chloro-phenoxy)-phenyl, 4-(4-phenyl-phenoxy)-phenyl, 4-(4-acetamido-phenoxy)-phenyl, 4-(4-methyl-phenoxy)-phenyl,

30

4-(4-fluoro-phenoxy)-phenyl, 4-(4-bromo-phenoxy)-phenyl, 4-(4-chloro-phenoxy)-phenyl, 4-(4-amino-phenoxy)-phenyl, 4-(3-ethyl-4-chloro-phenoxy)-phenyl, 4-[2-(N-ethylamino)-ethoxy]-phenyl, 4-[2,2'-dimethyl-3-(N,N'-dimethylamino)-propoxy]-phenyl, 1,2,3,4-tetrahydroisoquinolin-7-yl, 4-(4-benzamido-phenoxy)-phenyl, 4-(4-isonicotinamido-phenoxy)-phenyl, 4-[2-(N-methyl-N'-pyrid-4-yl)-ethoxy]-phenyl, 4-[3-(diethylmethyl ammonium)-propoxy]-phenyl, 4-(2,5-di-fluoro-benzyloxy)-phenyl, 4-(2,4-dichloro-phenoxy)-phenyl, 4-(naphthalen-2-yloxy)-phenyl, 4-(6-methoxy-naphthalen-2-yloxy)-phenyl, 4-(4-methoxy-naphthalen-2-yloxy)-phenyl, 4-(6-hydroxy-naphthalen-2-yloxy)-phenyl, 4-(dibenzofuran-2-yloxy)-phenyl, 4-[2-(1-methyl-pyrrolidin-2-yl)-ethoxy]-phenyl, 4-[2-(piperazin-1-yl)-ethoxy]-phenyl, or 4-(4-tert-butyl-phenoxy)-phenyl.

In another group of preferred embodiments of Formula (Ia), R₃ comprises hydrogen; and R₄ comprises a phenyl group, wherein the phenyl group is substituted with at least one substituent comprising

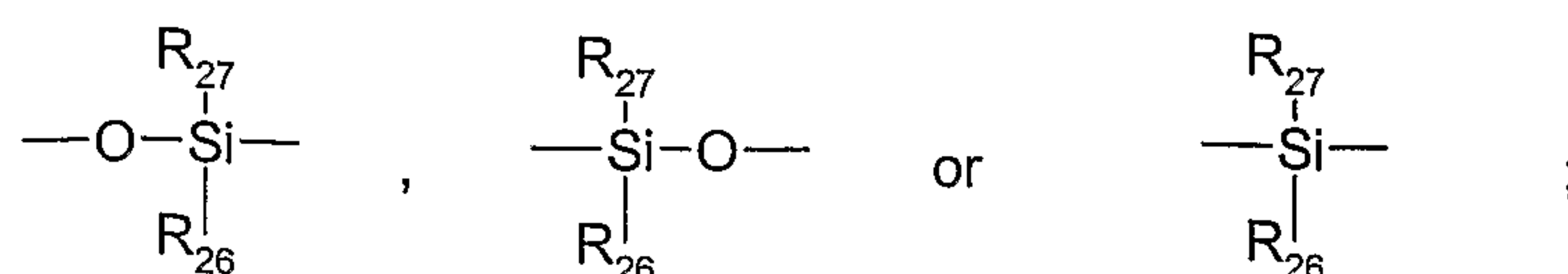
- a) -Y₂-alkyl;
- b) -Y₂-aryl;
- c) -Y₂-heteroaryl;
- d) -Y₂-alkylene-heteroaryl;
- e) -Y₂-alkylene-aryl;
- f) -Y₂-alkylene-W₂-R₁₈;
- g) -Y₃-Y₄-NR₂₃R₂₄;
- h) -Y₃-Y₄-NH-C(=NR₂₅)NR₂₃R₂₄;
- i) -Y₃-Y₄-C(=NR₂₅)NR₂₃R₂₄; or
- j) -Y₃-Y₄-Y₅-A₂;

wherein

Y₂ and W₂ independently comprise -CH₂- or -O-;

R₁₈ comprises aryl, alkyl, -alkylene-aryl, -alkylene-heteroaryl, or -alkylene-O-aryl;

Y₃ and Y₅ independently comprise a direct bond, -CH₂-, -O-, -N(H), -S-, SO₂-, -C(O)-, -CON(H)-, -NHC(O)-, -NHCON(H)-, -NHSO₂-, -SO₂N(H)-, -C(O)-O-, -NHSO₂NH-, -O-CO-,



wherein R_{27} and R_{26} independently comprise aryl, alkyl, -alkylene-aryl, alkoxy, or -alkyl-O-aryl;

Y_4 comprises

- a) -alkylene;
- b) -alkenylene;
- c) -alkynylene;
- d) -arylene;
- e) -heteroarylene;
- f) -cycloalkylene;
- g) -heterocyclylene;
- h) -alkylene-arylene;
- i) -alkylene-heteroarylene;
- j) -alkylene-cycloalkylene;
- k) -alkylene-heterocyclylene;
- l) -arylene-alkylene;
- m) -heteroarylene-alkylene;
- n) -cycloalkylene-alkylene;
- o) -heterocyclylene-alkylene;
- p) -O-;
- q) -S-;
- r) -S(O₂)-; or
- s) -S(O)-;

wherein said alkylene groups may optionally contain one or more O, S, S(O), or SO₂ atoms;

A_2 comprises

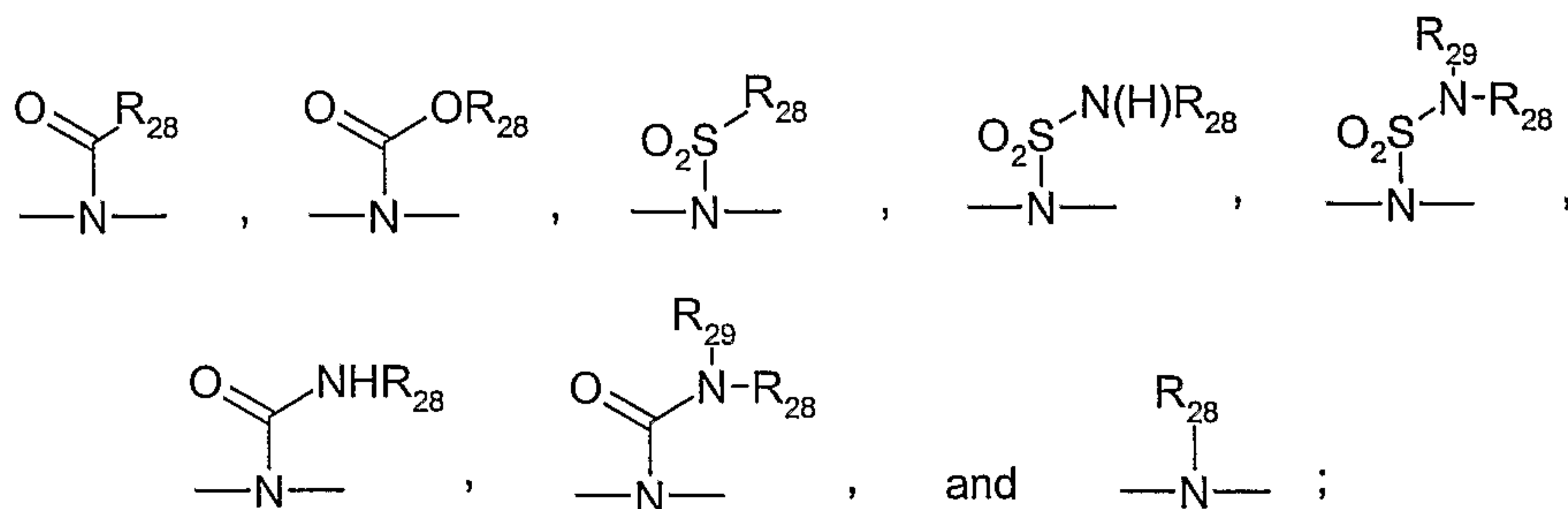
- a) heterocyclyl, fused arylheterocyclyl, or fused heteroarylheterocyclyl, containing at least one basic nitrogen atom,
- b) -imidazolyl, or
- c) -pyridyl;

R_{23} , R_{24} , and R_{25} independently comprise hydrogen, aryl, heteroaryl, -alkylene-heteroaryl, alkyl, -alkylene-aryl, -alkylene-O-aryl, or -alkylene-O-heteroaryl; and R_{23} and R_{24} may be taken together to form a ring having the formula $-(CH_2)_s-X_3-(CH_2)_t-$ bonded to the nitrogen atom to which R_{23} and R_{24} are attached

wherein

s and t are, independently, 1, 2, 3, or 4;

X₃ comprises direct bond, -CH₂-, -O-, -S-, -S(O₂)-, -C(O)-, -CON(H)-, -NHC(O)-, -NHCON(H)-, -NHSO₂-, -SO₂N(H)-, -C(O)-O-, -O-C(O)-, -NHSO₂NH-,



5

wherein R₂₈ and R₂₉ independently comprise hydrogen, aryl, heteroaryl, alkyl, -alkylene-aryl, or -alkylene-heteroaryl.

10 In a more preferred group of compounds of Formula (Ia), R₃ comprises hydrogen and R₄ comprises 4-{2-[(4-chlorophenyl)-ethoxy]}-phenyl, 4-[3-(N,N'-diethylamino)-propoxy]-phenyl, 4-(2-amino-ethoxy)-phenyl, 4-[2-(N-methyl-N'-pyridin-4-yl-amino)-ethoxy]-phenyl, 4-[2-(N-ethyl-N'-pyridin-4-yl-amino)-ethoxy]-phenyl, 4-[2-(N-pyridin-4-yl-amino)-ethoxy]-phenyl, 4-(4-amino-pyridin-3-yl-oxy)-phenyl, 4-[(pyridin-4-yl)-amino]-phenyl, 4-[2-(N,N'-bis-pyridin-2-ylmethyl-amino)-ethoxy]-phenyl, 4-[2-(guanidiny)-ethoxy]-phenyl, 4-{2-[4-(pyridin-4-yl)-piperazin-1-yl]-2-oxo-ethoxy}-phenyl, 4-[2-(N-methyl-N'-3-methylpyridin-4-yl-amino)-ethoxy]-phenyl, 4-(4-hydroxy-pyrrolidin-2-ylmethoxy)-phenyl, 4-(4-amino-3,5-dimethyl-pyrrolidin-2-ylmethoxy)-phenyl, dibenzofuran-2-yl, 4-[3-(piperazin-1-yl)-propoxy]-phenyl, 4-(piperazin-4-yl)-phenyl, 4-[5-(piperazin-1-yl)-pentoxy]-phenyl, 4-[3-(N,N'-dimethylamino)-propoxy]-phenyl, 4-(3-fluoro-4-trifluoromethyl-phenoxy)-phenyl, 4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl, 4-(4-phenyl-phenoxy)-phenyl, 4-(3-trifluoromethoxy-phenoxy)-phenyl, 4-(4-trifluoromethyl-benzyloxy)-phenyl, 4-(3,4-dichloro-phenoxy)-phenyl, 4-(2,4-dichloro-phenoxy)-phenyl, 4-(1-ethyl-piperidin-3-yloxy)-phenyl, 4-benzyloxy-phenyl, 4-[(1-ethyl-piperidin-3-yl)-methoxy]-phenyl, 4-(4-phenoxy-benzyloxy)-phenyl, 4-(4-benzyloxy-benzyloxy)-phenyl, 4-(2-benzenesulfonylmethyl-benzyloxy)-phenyl, 4-(3,4,5-trimethoxybenzyloxy)-phenyl, 4-[2-(pyrrolidin-1-yl)-ethoxy]-phenyl, 4-[2-(piperidin-1-yl)-ethoxy]-phenyl, 4-[2,2'-dimethyl-3-(N,N'-dimethylamino)-propoxy]-phenyl, 4-[2-(N,N'-diisopropylamino)-ethoxy]-phenyl, 4-(adamantan-1-ylmethoxy)-phenyl, 3-[(2,6-dichlorophenyl)-4-methyl-isoxazol-5-ylmethoxy]-phenyl, 4-(4-bromo-benzyloxy)-phenyl, 4-(4-chlorophenoxy)-phenyl, 4-[4-[(1-ethyl-piperidin-4-yl)-methylamino]-phenoxy]-phenyl, 4-(3,3-diphenylpropoxy)-phenyl, 4-[3,3-Bis-(4-fluorophenyl)-propoxy]-phenyl, 4-[3,3-Bis-(4-

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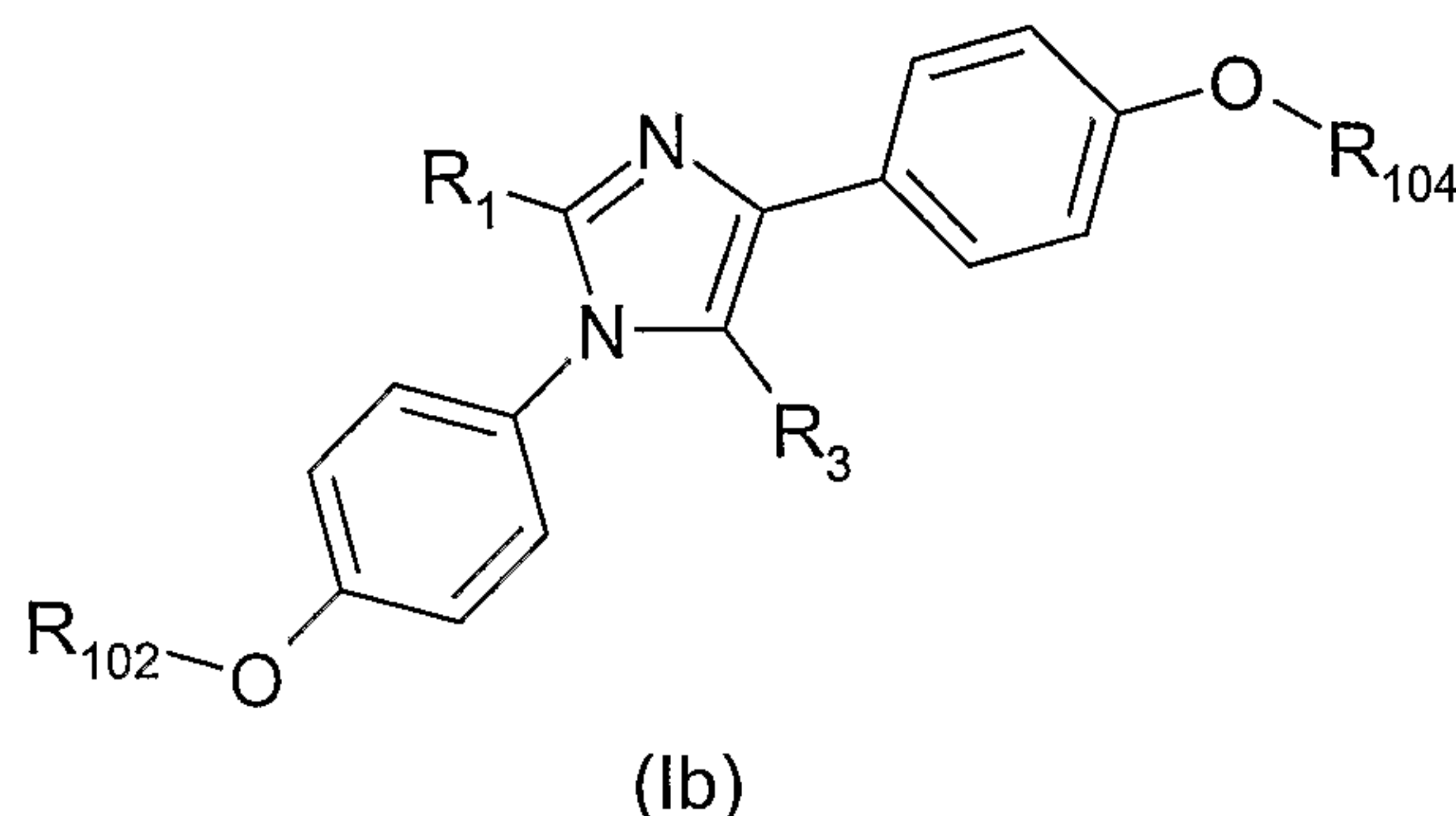
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chlorophenyl)-allyloxy]-phenyl, 4-(4-chlorophenoxy)-naphthalenyl, 4-[2-(biphenyl-4-yl)-acetamido]-phenyl, 4-(2-(9H-carbazole)-ethoxy)-phenyl, 4-[4-methoxyphenoxy]-phenyl, 4-(4-tert-butyl-phenoxy)-phenyl, or 4-(naphthylen-2-ylmethoxy)-phenyl.

5 In another preferred embodiment, the compound Formula (I) comprises the compound of Formula (Ib),



10 wherein

R_1 comprises -hydrogen, -aryl, -heteroaryl, -cycloalkyl, -heterocyclyl, -alkyl, -alkenyl, -alkylene-aryl, -alkylene-heteroaryl, -alkylene-heterocyclyl, -alkylene-cycloalkyl, -fused cycloalkylaryl, -fused cycloalkylheteroaryl, -fused heterocyclaryl, -fused heterocyclheteroaryl, -alkylene-fused cycloalkylaryl, -alkylene-fused cycloalkylheteroaryl, -alkylene-fused heterocyclaryl, -alkylene-fused heterocyclheteroaryl, or $-G_1-G_2-G_3-R_5$

wherein

G_1 and G_3 independently comprise alkylene, alkenylene, alkynylene, cycloalkylene, heterocyclylene, arylene, heteroarylene, (aryl)alkylene, (heteroaryl) alkylene, (aryl)alkenylene, (heteroaryl)alkenylene, or a direct bond;

G_2 comprises -O-, -S-, -S(O)-, -N(R_6)-, -S(O)₂-, -C(O)-, -CO₂-, -C(O)N(R_6)-, N(R_6)C(O)-, -S(O₂)N(R_6)-, N(R_6)S(O₂)-, -O-alkylene-C(O)-, -(O)C-alkylene-O-, -O-alkylene-, -alkylene-O-, alkylene, alkenylene, alkynylene, cycloalkylene, heterocyclylene, arylene, heteroarylene, fused cycloalkylaryl, fused cycloalkylheteroaryl, fused heterocyclaryl, fused heterocyclheteroaryl, or a direct bond, wherein R_6 comprises hydrogen, aryl, alkyl, -alkylene-aryl, alkoxy, or -alkylene-O-aryl; and

R₅ comprises hydrogen, aryl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, alkenyl, alkynyl, -alkylene-aryl, -alkylene-heteroaryl, -alkylene-heterocyclyl, -alkylene-cycloalkyl, fused cycloalkylaryl, fused cycloalkylheteroaryl, fused heterocyclylaryl, fused heterocyclylheteroaryl; -alkylene-fused cycloalkylaryl, -alkylene-fused cycloalkylheteroaryl, -alkylene-fused heterocyclylaryl, or -alkylene-fused heterocyclylheteroaryl;

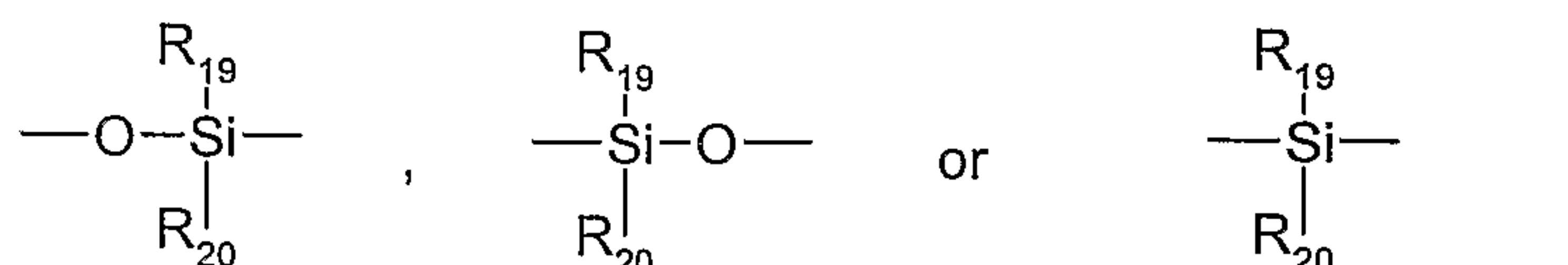
R₃ comprises hydrogen or an alkyl group; and

R₁₀₂ and R₁₀₄ independently comprise

- a) -H;
- b) -alkyl;
- c) -aryl;
- d) -heteroaryl;
- e) -alkylene-heteroarylaryl;
- f) -alkylene-aryl;
- g) -alkylene-W₂-R₁₈;
- h) -Y₄ -NR₂₃R₂₄;
- i) -Y₄ -NH-C(=NR₂₅)NR₂₃R₂₄;
- j) -Y₄ -C(=NR₂₅)NR₂₃R₂₄; or
- k) -Y₄ -Y₅-A₂;

wherein

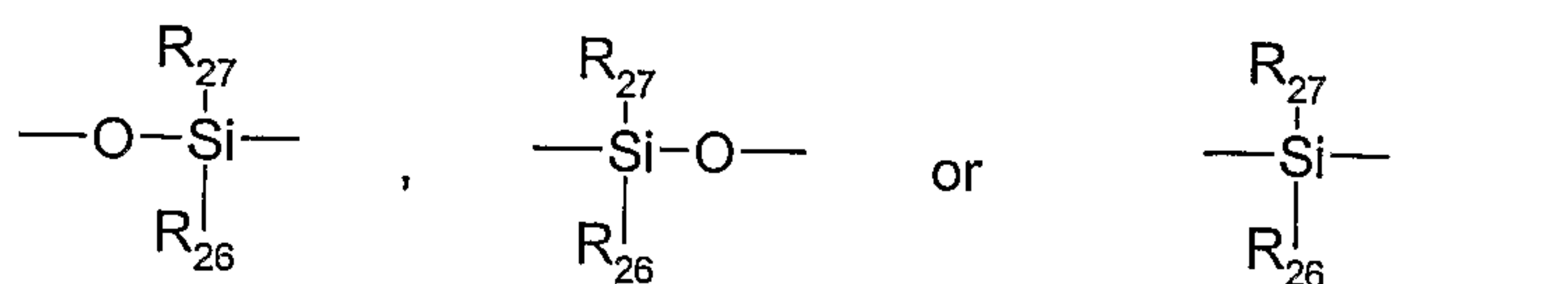
W₂ comprises -CH₂-, -O-, -N(H)-, -S-, SO₂-, -CON(H)-, -NHC(O)-, -NHCON(H)-, -NHCO₂-, -SO₂N(H)-, -C(O)-O-, -NHCO₂NH-, -O-S(O)₂-, -O-CO-,



wherein R₁₉ and R₂₀ independently comprise hydrogen, aryl, alkyl, -alkylene-aryl, alkoxy, or -alkylene-O-aryl; and

R₁₈ comprises aryl, alkyl, -alkylene-aryl, -alkylene-heteroaryl, and -alkylene-O-aryl;

Y₅ comprises a direct bond, -CH₂-, -O-, -N(H)-, -S-, SO₂-, -C(O)-, -CON(H)-, -NHC(O)-, -NHCON(H)-, -NHCO₂-, -SO₂N(H)-, -C(O)-O-, -NHCO₂NH-, -O-CO-,



wherein R_{27} and R_{26} independently comprise aryl, alkyl, -alkylene-aryl, alkoxy, or -alkyl-O-aryl;

Y_4 comprises

- 5 a) -alkylene;
b) -alkenylene;
c) -alkynylene;
d) -arylene;
e) -heteroarylene;
10 f) -cycloalkylene;
g) -heterocyclylene;
h) -alkylene-arylene;
i) -alkylene-heteroarylene;
j) -alkylene-cycloalkylene;
15 k) -alkylene-heterocyclylene;
l) -arylene-alkylene;
m) -heteroarylene-alkylene;
n) -cycloalkylene-alkylene;
o) -heterocyclylene-alkylene;
20 p) -O-;
q) -S-;
r) -S(O₂)-; or
s) -S(O)-;
- 25 wherein said alkylene groups may optionally contain one or more O, S, S(O), or SO₂ atoms;

A_2 comprises

- 30 a) heterocyclyl, fused arylheterocyclyl, or fused heteroarylheterocyclyl, containing at least one basic nitrogen atom,
b) -imidazolyl, or
c) -pyridyl;

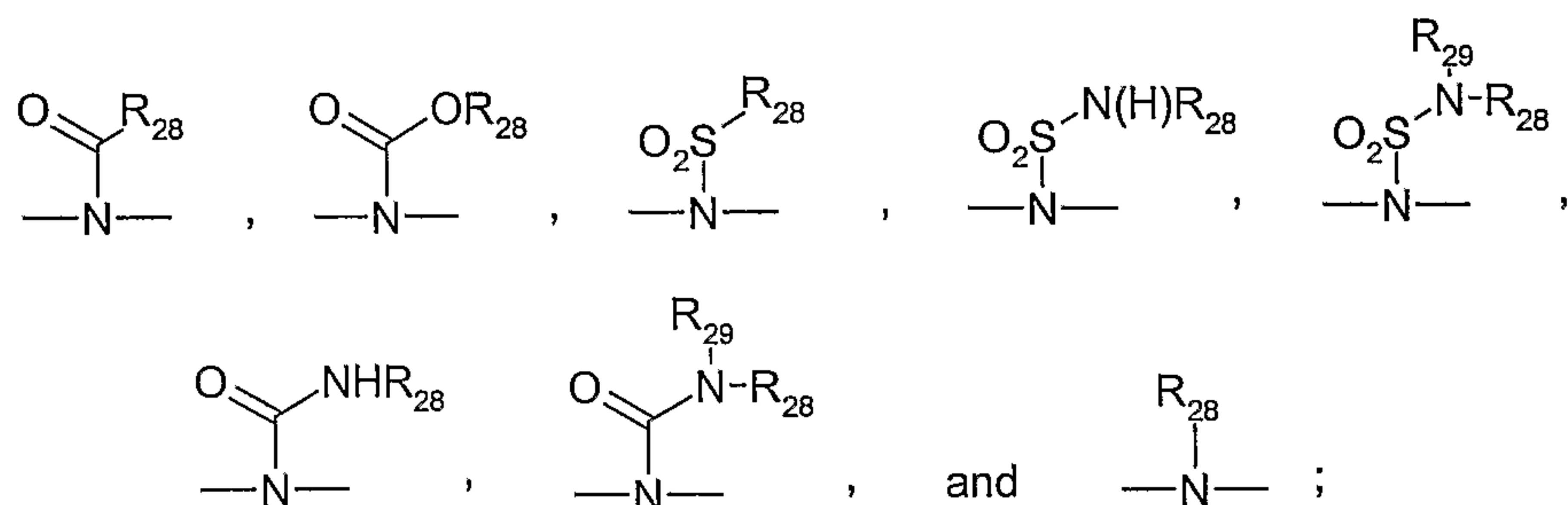
R_{23} , R_{24} , and R_{25} independently comprise hydrogen, aryl, heteroaryl, -alkylene-heteroaryl, alkyl, -alkylene-aryl, -alkylene-O-aryl, or -alkylene-O-heteroaryl; and R_{23} and R_{24} may be taken together to form a ring having

the formula $-(CH_2)_s-X_3-(CH_2)_t-$ bonded to the nitrogen atom to which R_{23} and R_{24} are attached

wherein

s and t are, independently, 1, 2, 3, or 4;

5 X_3 comprises direct bond, $-CH_2-$, $-O-$, $-S-$, $-S(O_2)-$, $-C(O)-$, $-CON(H)-$, $-NHC(O)-$, $-NHCON(H)-$, $-NHSO_2-$, $-SO_2N(H)-$, $-C(O)-O-$, $-O-C(O)-$, $-NHSO_2NH-$,



10 wherein R_{28} and R_{29} independently comprise hydrogen, aryl, heteroaryl, alkyl, -alkylene-aryl, or -alkylene-heteroaryl;

wherein

the alkyl and/or aryl groups of R_{102} and R_{104} may be optionally substituted 1-4 times with a substituent group, wherein said substituent group(s) or the term substituted refers to a group comprising:

- 15 a) halogen;
b) perhaloalkyl;
c) alkyl;
d) cyano;
20 e) alkyloxy;
f) aryl; or
g) aryloxy.

25 In a group of preferred embodiments of the compound of Formula (Ib), R_1 comprises comprises a hydrogen, methyl, ethyl, propyl, butyl, iso-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 3-butenyl, tert-butyl, 3-cyclohexyl-propyl, 3-phenoxy-propyl, methoxymethyl, 4-fluoro-phenyl, 3-(4-chlorophenoxy)-propyl, 2,4,4-trimethyl-pentyl, 1-ethyl-propyl, 1-propyl-butyl, benzyloxymethyl, 2-cyclopropyl-ethyl, 2-phenyl-ethyl, 4-tert-butylphenoxy-methyl, 4-tert-butylcyclohexyl, 4-ethylcyclohexyl, 4-butylcyclohexyl, 3-methoxycarbonyl-1-propyl, or 2-(pyridin-3-yl)-ethyl group, and R_3 comprises hydrogen.

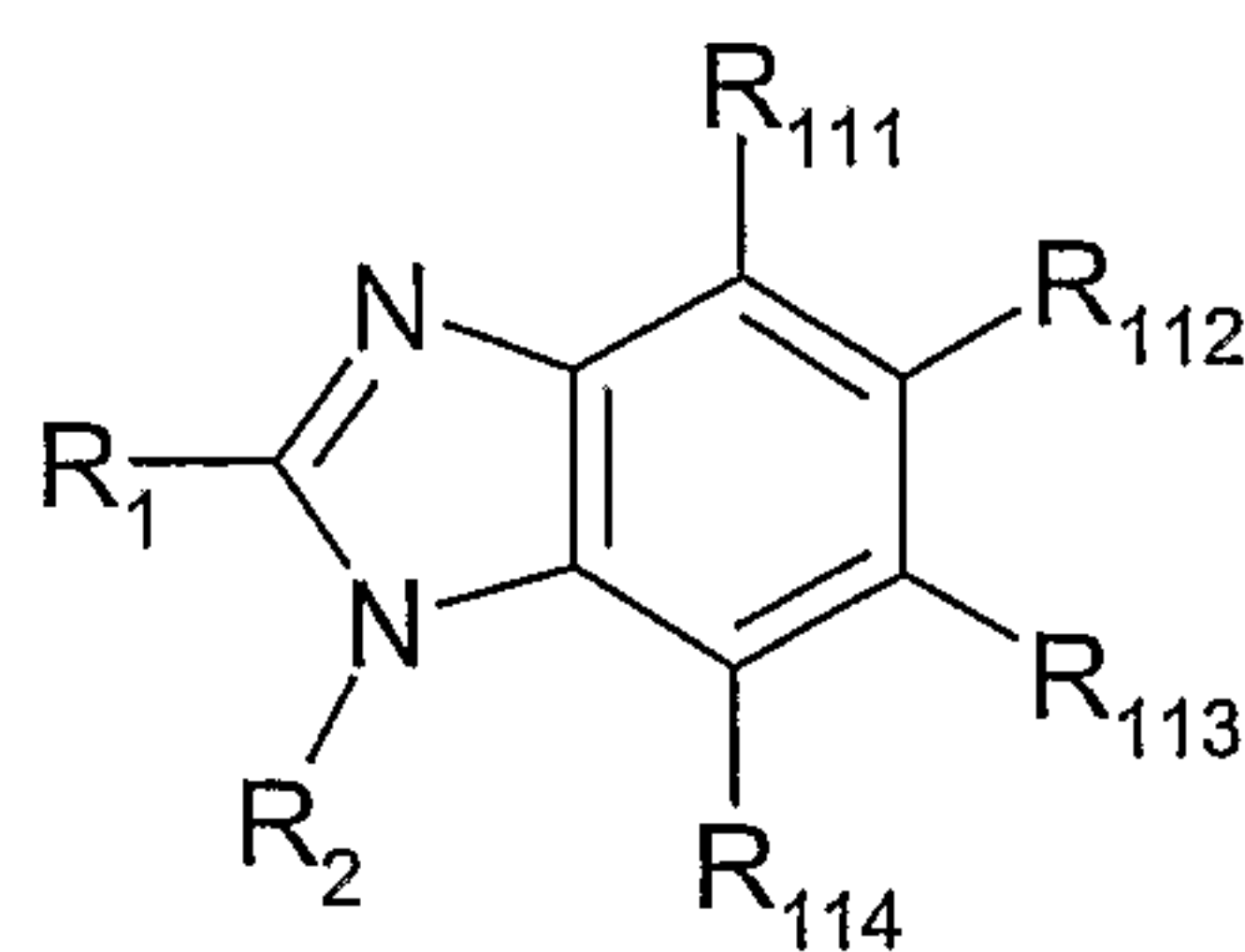
30

In another group of preferred embodiments of the compound of Formula (Ib), R_{102} and R_{104} independently comprise 2-(4-chlorophenyl)-ethyl, 3-(N,N'-diethylamino)-propyl, 2-amino-ethyl, 2-(N-methyl-N'-pyridin-4-yl-amino)-ethyl, 2-(N-ethyl-N'-pyridin-4-yl-amino)-ethyl, 2-(N-pyridin-4-yl-amino)-ethoxy, 4-(4-amino-pyridin-3-yl-oxy), 4-(pyridin-4-yl)-amino, 2-(N,N'-bis-pyridin-2-ylmethyl-amino)-ethyl, 2-(guanidiny)-ethyl, 2-[4-(pyridin-4-yl)-piperazin-1-yl]-2-oxo-ethyl, 2-(N-methyl-N'-3-methylpyridin-4-yl-amino)-ethyl, 4-hydroxy-pyrrolidin-2-ylmethyl, 4-amino-3,5-dimethyl-pyrrolidin-2-ylmethyl, dibenzofuran-2-yl, 3-(piperazin-1-yl)-propyl, piperazin-4-yl, 5-(piperazin-1-yl)-pentyl, 3-(N,N'-dimethylamino)-propyl, 3-fluoro-4-trifluoromethyl-phenyl, 4-fluoro-3-trifluoromethyl-phenyl, 4-phenyl-phenyl, 3-trifluoromethoxy-phenyl, 4-trifluoromethyl-benzyl, 3,4-dichloro-phenyl, 2,4-dichloro-phenyl, 1-ethyl-piperidin-3-yl, benzyl, (1-ethyl-piperidin-3-yl)-methyl, 4-phenoxy-benzyl, 4-benzyloxy-benzyl, 2-benzenesulfonylmethyl-benzyl, 3,4,5-trimethoxybenzyl, 2-(pyrrolidin-1-yl)-ethyl, 2-(piperidin-1-yl)-ethyl, 2,2'-dimethyl-3-(N,N'-dimethylamino)-propyl, 2-(N,N'-diisopropylamino)-ethyl, 3-(2,6-dichlorophenyl)-4-methyl-isoxazol-5-ylmethyl, 4-bromo-benzyl, 4-chlorophenyl, 4-[(1-ethyl-piperidin-4-yl)-methylamino]-phenyl, 3,3-diphenylpropyl, 3,3-Bis-(4-fluorophenyl)-propyl, 3,3-Bis-(4-chlorophenyl)-allyl, 4-(4-chlorophenoxy)-naphthalenyl, 4-[2-(biphenyl-4-yl)-acetamido]-phenyl, 2-(9H-carbazole)-ethyl, 4-methoxyphenyl, 4-tert-butyl-phenyl, or naphthyl-2-ylmethyl.

In another group of preferred embodiments of the compound of Formula (Ib), R_1 comprises -alkyl, -alkylene-cycloalkylene-alkyl, -cycloalkyl, -heterocyclyl, -alkylene-cycloalkyl, -alkylene-heteroaryl, -alkylene-heterocyclyl, or -alkylene-heterocyclylene-alkyl; R_3 comprises hydrogen; R_{102} comprises -aryl or -alkylene-aryl substituted with at least one of a halogen, a perhaloalkyl, or an alkoxy group; and R_{104} comprises $-Y_4-NR_{23}R_{24}$ or $-Y_4-Y_5-A_2$.

In another group of preferred embodiments of the compound of Formula (Ib), R_1 comprises -heterocyclyl, heterocyclylene-heteroaryl, -alkylene-cycloalkyl, -alkylene-heteroaryl, -alkylene-heterocyclyl, or -alkylene-heterocyclylene-alkyl; R_3 comprises hydrogen; and R_{102} and R_{104} independently comprise -aryl or -alkylene-aryl, wherein the alkyl or aryl groups are optionally substituted with at least one of a halogen, a perhaloalkyl, or an alkoxy group, and wherein at least one of R_{102} and R_{104} comprise $-Y_4-NR_{23}R_{24}$ or $-Y_4-Y_5-A_2$, wherein Y_4 comprises alkylene.

In a preferred embodiment, the compound of Formula (I) comprises a compound of the Formula (Ic)



(Ic)

wherein

- 5 R_1 comprises -hydrogen, -aryl, -heteroaryl, -cycloalkyl, -heterocyclyl, -alkyl, -alkenyl, -alkynyl, -alkylene-aryl, -alkylene-heteroaryl, -alkylene-heterocyclyl, -alkylene-cycloalkyl, -fused cycloalkylaryl, -fused cycloalkylheteroaryl, -fused heterocyclylaryl, -fused heterocyclylheteroaryl, -alkylene-fused cycloalkylaryl, -alkylene-fused cycloalkylheteroaryl, -alkylene-fused heterocyclylaryl, -alkylene-fused heterocyclylheteroaryl, or $-G_1-G_2-G_3-R_5$
- 10

wherein

- G_1 and G_3 independently comprise alkylene, alkenylene, alkynylene, cycloalkylene, heterocyclylene, arylene, heteroarylene, (aryl)alkylene, (heteroaryl) alkylene, (aryl)alkenylene, (heteroaryl)alkenylene, or a direct
- 15 bond;
- G_2 comprises -O-, -S-, -S(O)-, -N(R_6)-, -S(O)₂-, -C(O)-, -CO₂-, -C(O)N(R_6)-, N(R_6)C(O)-, -S(O₂)N(R_6)-, N(R_6)S(O₂)-, -O-alkylene-C(O)-, -(O)C-alkylene-O-, -O-alkylene-, -alkylene-O-, alkylene, alkenylene, alkynylene, cycloalkylene, heterocyclylene, arylene, heteroarylene, fused cycloalkylaryl, fused
- 20 cycloalkylheteroaryl, fused heterocyclylaryl, fused heterocyclylheteroaryl, or a direct bond, wherein R_6 comprises hydrogen, aryl, alkyl, -alkylene-aryl, alkoxy, or -alkylene-O-aryl; and
- R_5 comprises hydrogen, aryl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, alkenyl, alkynyl, -alkylene-aryl, -alkylene-heteroaryl, -alkylene-heterocyclyl, -alkylene-cycloalkyl, fused cycloalkylaryl, fused cycloalkylheteroaryl, fused
- 25 heterocyclylaryl, fused heterocyclylheteroaryl; -alkylene-fused cycloalkylaryl, -alkylene-fused cycloalkylheteroaryl, -alkylene-fused heterocyclylaryl, or -alkylene-fused heterocyclylheteroaryl;

R₂ comprises

- a) -hydrogen,
- b) -aryl,
- c) -heteroaryl,
- 5 d) -cycloalkyl,
- e) -heterocyclyl;
- f) -alkyl,
- g) -alkenyl,
- h) -alkynyl,
- 10 i) -alkylene-aryl,
- j) -alkylene-heteroaryl,
- k) -alkylene-heterocyclyl,
- l) -alkylene-cycloalkyl;
- m) fused cycloalkylaryl,
- 15 n) fused cycloalkylheteroaryl,
- o) fused heterocyclylaryl,
- p) fused heterocyclylheteroaryl;
- q) -alkylene-fused cycloalkylaryl,
- r) -alkylene-fused cycloalkylheteroaryl,
- 20 s) -alkylene-fused heterocyclylaryl, or
- t) -alkylene-fused heterocyclylheteroaryl,

R₁₁₁, R₁₁₂, R₁₁₃ and R₁₁₄ independently comprise

- a) -hydrogen,
- 25 b) -halogen,
- c) -hydroxyl,
- d) -cyano,
- e) -carbamoyl,
- f) -carboxyl,
- 30 g) -Y₈-alkyl,
- h) -Y₈-aryl,
- i) -Y₈-heteroaryl,
- j) -Y₈-alkylene-aryl,
- k) -Y₈-alkylene-heteroaryl,
- 35 l) -Y₈-alkylene-W₃-R₄₀,
- m) -Y₅-Y₆-NR₃₃R₃₄,

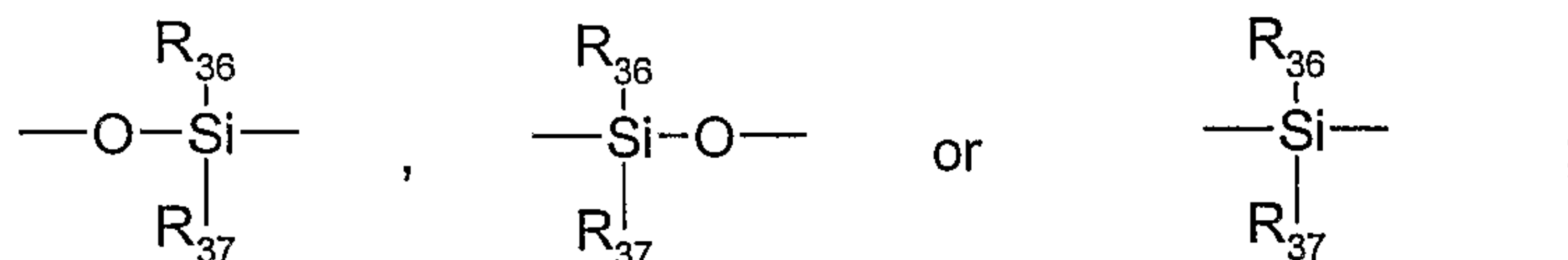
n) $-Y_5-Y_6-NH-C(=NR_{35})NR_{33}R_{34}$,

o) $-Y_5-Y_6-C(=NR_{35})NR_{33}R_{34}$, or

p) $-Y_5-Y_6-Y_7-A_4$;

wherein

5 Y_5 and Y_7 independently comprise a direct bond, $-CH_2-$, $-O-$, $-N(H)-$, $-S-$, SO_2- , $-CON(H)-$, $-NHC(O)-$, $-NHCON(H)-$, $-NHSO_2-$, $-SO_2N(H)-$, $-C(O)-O-$, $-NHSO_2NH-$, $-O-CO-$,



10 wherein R_{36} and R_{37} independently comprise aryl, alkyl, $-alkylene-aryl$, alkoxy, or $-alkyl-O-aryl$;

Y_6 comprises

a) alkylene;

b) alkenylene;

c) alkynylene;

15 d) arylene;

e) heteroarylene;

f) cycloalkylene;

g) heterocyclylene;

h) alkylene-arylene;

20 i) alkylene-heteroarylene;

j) alkylene-cycloalkylene;

k) alkylene-heterocyclylene;

l) arylene-alkylene;

m) heteroarylene-alkylene;

25 n) cycloalkylene-alkylene;

o) heterocyclylene-alkylene;

p) $-O-$;

q) $-S-$;

r) $-S(O_2)-$; or

30 s) $-S(O)-$;

wherein said alkylene groups may optionally contain one or more O, S, S(O), or SO_2 atoms;

A_4 comprises

- a) heterocyclyl, fused arylheterocyclyl, or fused heteroarylheterocyclyl, containing at least one basic nitrogen atom,
 b) -imidazolyl, or
 c) -pyridyl;

5

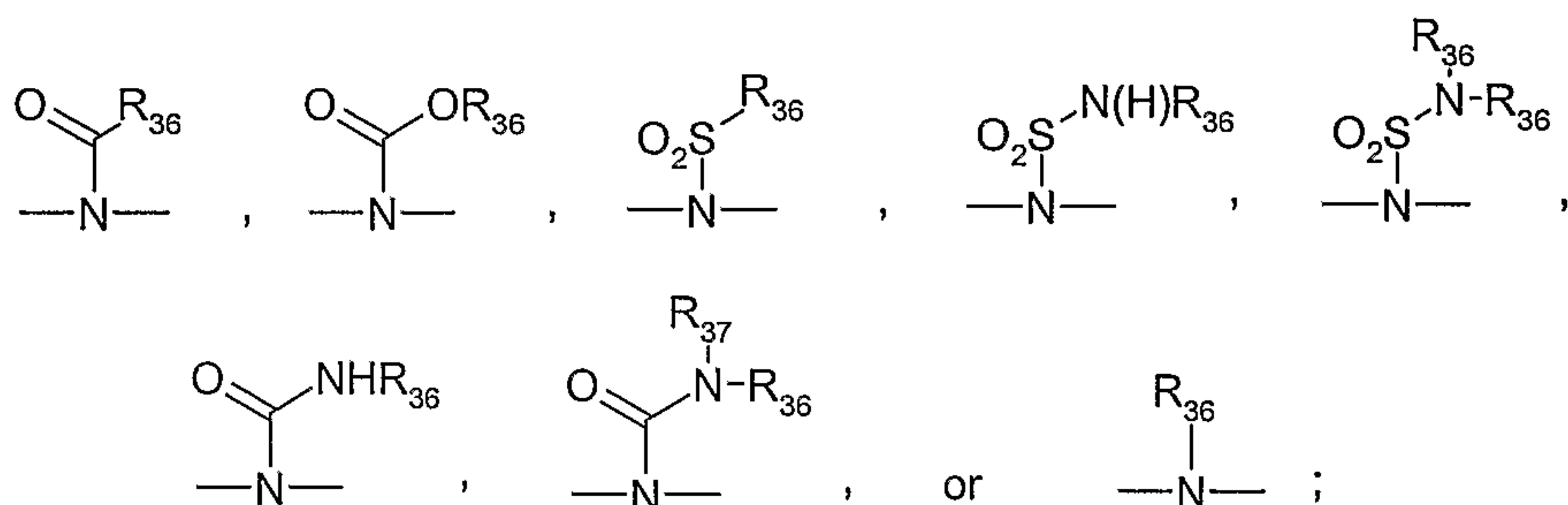
R_{33} , R_{34} and R_{35} independently comprise hydrogen, aryl, heteroaryl, alkyl, -alkylene-aryl, or -alkylene-O-aryl; and R_{33} and R_{34} may be taken together to form a ring having the formula $-(CH_2)_u-X_4-(CH_2)_v-$ bonded to the nitrogen atom to which R_{33} and R_{34} are attached,

10

wherein

u and v are, independently, 1, 2, 3, or 4;

X_4 comprises a direct bond, $-CH_2-$, $-O-$, $-S-$, $-S(O_2)-$, $-C(O)-$, $-CON(H)-$, $-NHC(O)-$, $-NHCON(H)-$, $-NHSO_2-$, $-SO_2N(H)-$, $-C(O)-O-$, $-O-C(O)-$, $-NHSO_2NH-$,

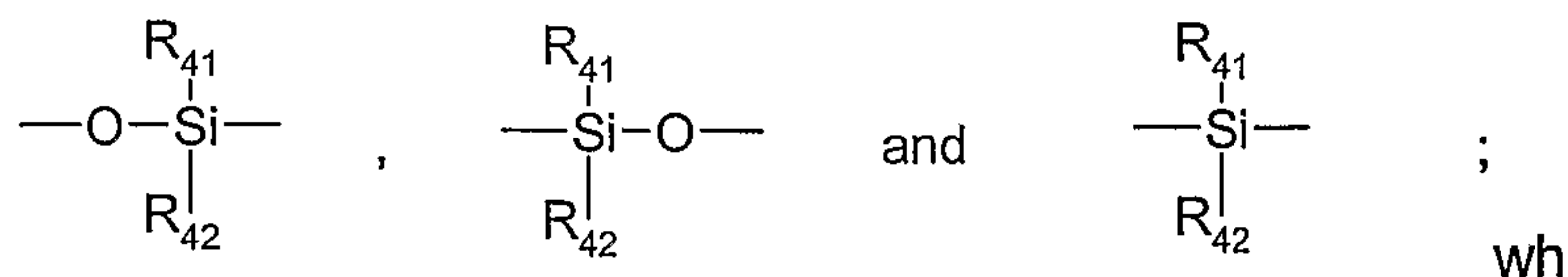


15

wherein R_{36} and R_{37} independently comprise hydrogen, aryl, heteroaryl, alkyl, -alkylene-aryl, or -alkylene-heteroaryl;

Y_8 and W_3 independently comprise $-CH_2-$, $-O-$, $-N(H)-$, $-S-$, SO_2- , $-CON(H)-$, $-NHC(O)-$, $-NHCON(H)-$, $-NHSO_2-$, $-SO_2N(H)-$, $-C(O)-O-$, $-NHSO_2NH-$, $-O-CO-$,

20



wh

wherein R_{41} and R_{42} independently comprise aryl, alkyl, -alkylene-aryl, alkoxy, or -alkyl-O-aryl; and

R_{40} comprises hydrogen, aryl, alkyl, -alkylene-aryl, -alkylene-heteroaryl, and -alkylene-O-aryl;

25

wherein at least one of R_{111} , R_{112} , R_{113} , and R_{114} comprise a group of the formula $-Y_5-Y_6-NR_{33}R_{34}$, $-Y_5-Y_6-NH-C(=NR_{35})NR_{33}R_{34}$, $-Y_5-Y_6-C(=NR_{35})NR_{33}R_{34}$, or $-Y_5-Y_6-Y_7-A_4$.

In one group of preferred embodiments of the compound of Formula (Ic), R₂ comprises hydrogen or alkyl.

In another group of preferred embodiments of the compound of Formula (Ic), R₁ comprises a phenyl group substituted by one or more substituents comprising

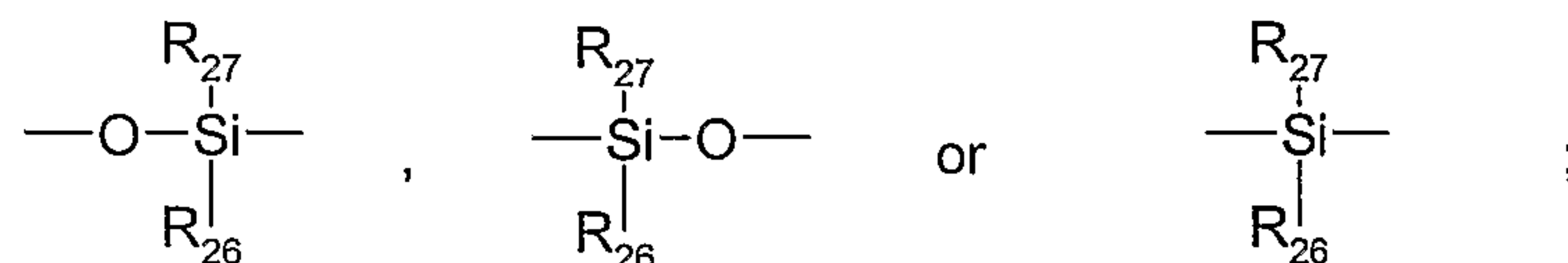
- a) -Y₂-alkyl;
- b) -Y₂-aryl;
- c) -Y₂-heteroaryl;
- d) -Y₂-alkylene-heteroarylaryl;
- e) -Y₂-alkylene-aryl;
- f) -Y₂-alkylene-W₂-R₁₈;
- g) -Y₃-Y₄-NR₂₃R₂₄
- h) -Y₃-Y₄-NH-C(=NR₂₅)NR₂₃R₂₄
- i) -Y₃-Y₄-C(=NR₂₅)NR₂₃R₂₄
- j) -Y₃-Y₄-Y₅-A₂

wherein

Y₂ and W₂ independently comprise -CH₂-, -O-, and

R₁₈ comprises aryl, alkyl, -alkylene-aryl, -alkylene-heteroaryl, or -alkylene-O-aryl;

Y₃ and Y₅ independently comprise a direct bond, -CH₂-, -O-, -N(H), -S-, SO₂-, -C(O)-, -CON(H)-, -NHC(O)-, -NHCON(H)-, -NHSO₂-, -SO₂N(H)-, -C(O)-O-, -NHSO₂NH-, -O-CO-,



wherein R₂₇ and R₂₆ independently comprise aryl, alkyl, -alkylene-aryl, alkoxy, or -alkyl-O-aryl;

Y₄ comprises

- a) -alkylene;
- b) -alkenylene;
- c) -alkynylene;
- d) -arylene;
- e) -heteroarylene;
- f) -cycloalkylene;
- g) -heterocyclylene;

- h) -alkylene-arylene;
 i) -alkylene-heteroarylene;
 j) -alkylene-cycloalkylene;
 k) -alkylene-heterocyclylene;
 l) -arylene-alkylene;
 m) -heteroarylene-alkylene;
 n) -cycloalkylene-alkylene;
 o) -heterocyclylene-alkylene;
 p) -O-;
 q) -S-;
 r) -S(O₂)-; or
 s) -S(O)-;

wherein said alkylene groups may optionally contain one or more O, S, S(O), or SO₂ atoms;

A₂ comprises

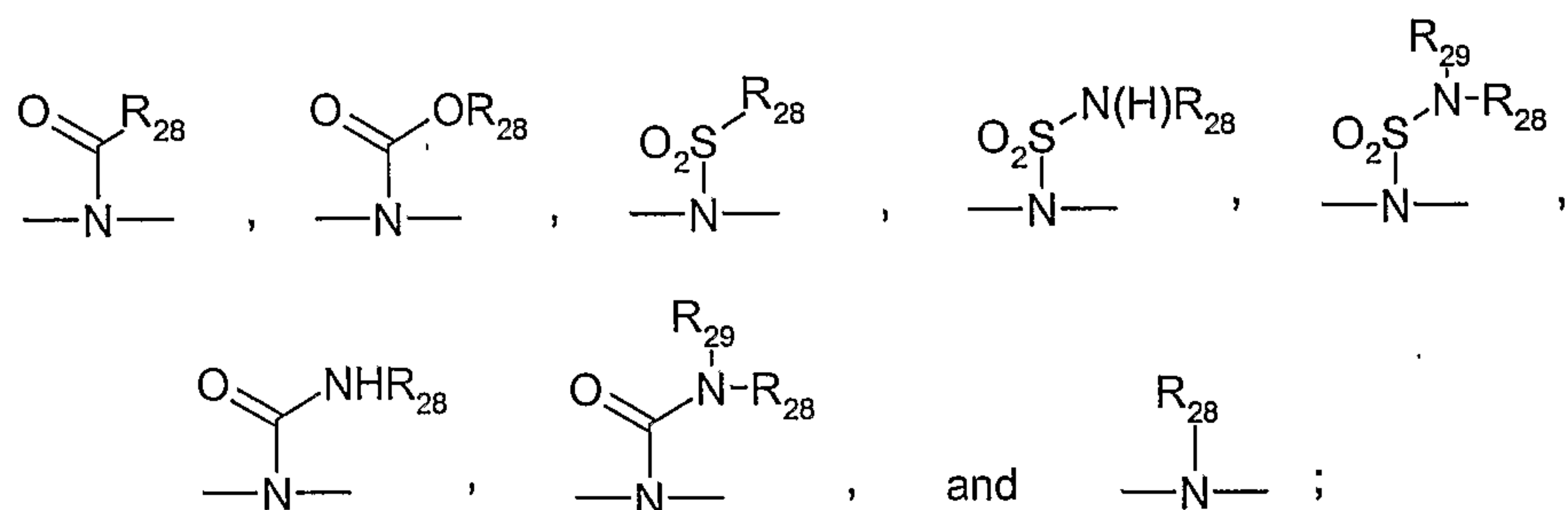
- a) heterocyclyl, fused arylheterocyclyl, or fused heteroarylheterocyclyl, containing at least one basic nitrogen atom,
 b) -imidazolyl, or
 c) -pyridyl;

R₂₃, R₂₄, and R₂₅ independently comprise hydrogen, aryl, heteroaryl, -alkylene-heteroaryl, alkyl, -alkylene-aryl, -alkylene-O-aryl, or -alkylene-O-heteroaryl; and R₂₃ and R₂₄ may be taken together to form a ring having the formula -(CH₂)_s-X₃-(CH₂)_t- bonded to the nitrogen atom to which R₂₃ and R₂₄ are attached

wherein

s and t are, independently, 1, 2, 3, or 4;

X₃ comprises direct bond, -CH₂-, -O-, -S-, -S(O₂)-, -C(O)-, -CON(H)-, -NHC(O)-, -NHCON(H)-, -NHSO₂-, -SO₂N(H)-, -C(O)-O-, -O-C(O)-, -NHSO₂NH-,



wherein R₂₈ and R₂₉ independently comprise hydrogen, aryl, heteroaryl, alkyl, -alkylene-aryl, or -alkylene-heteroaryl.

5

In another group of preferred embodiments of the compound of Formula (Ic), R₁ comprises 2-methoxy-3,5-dimethoxy-phenyl, 3-(4-tert-butyl-phenoxy)-phenyl, 4-[3-(N,N'-diethylamino)-propoxy]-phenyl, 4-[3-(N,N'-dimethylamino)-propoxy]-phenyl, 4-[(pyrrolidin-1-yl)-ethoxy]-phenyl, 3-[(pyrrolidin-1-yl)-ethoxy]-phenyl, 2-[(pyrrolidin-1-yl)-ethoxy]-phenyl, 3-(naphthalen-2-yloxy)-phenyl, 4-biphenyl, 3-(3,3-dimethylbutoxy)-phenyl, 3-(phenoxy)-phenyl, 3-(3,4-dichloro-phenoxy)-phenyl, 3-(3,5-dichloro-phenoxy)-phenyl, 4-tert-butyl-phenyl, 4-(dibutylamino)-phenyl, 4-[2-(4-methoxy-phenyl)-ethoxy]-phenyl, 2-naphthyl, 2-benzofuranyl, 3-(3-trifluoromethyl-phenoxy)-phenyl, 4-chloro-phenyl, 2-benzhydryl, 4-isopropoxy-phenyl, 3-(4-tertbutyl-phenoxy)-phenyl, 4-[2-(4-chloro-phenyl)-ethoxy]-phenyl, 3-[2-(4-chloro-phenyl)-ethoxy]-phenyl, 2-{3-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-ethyl, 2-{4-[2-(4-methoxy-phenyl)-ethoxy]-phenyl}-ethyl, or 2-[3-(N,N-diethylamino)-propoxy]-4-[2-(4-chloro-phenyl)-ethoxy]-phenyl.

In another group of preferred embodiments of the compound of Formula (Ic), R₁ comprises 4-[2-(4-chloro-phenyl)-ethoxy]-phenyl, 3-[2-(4-chloro-phenyl)-ethoxy]-phenyl, 2-{3-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-ethyl, 2-{4-[2-(4-methoxy-phenyl)-ethoxy]-phenyl}-ethyl, or 2-[3-(N,N-diethylamino)-propoxy]-4-[2-(4-chloro-phenyl)-ethoxy]-phenyl.

In another group of preferred embodiments of the compound of Formula (Ic), R₁₁₁, R₁₁₂ and R₁₁₄ comprise hydrogen; and R₁₁₃ comprises -Y₃-Y₄-NR₂₃R₂₄, or -Y₃-Y₄-Y₅-A₂.

In another group of preferred embodiments of the compound of Formula (Ic), R₁ comprises 4-[2-(4-chloro-phenyl)-ethoxy]-phenyl, 3-[2-(4-chloro-phenyl)-ethoxy]-phenyl, 2-{3-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-ethyl, 2-{4-[2-(4-methoxy-phenyl)-ethoxy]-phenyl}-ethyl, or 2-[3-(N,N-diethylamino)-propoxy]-4-[2-(4-chloro-phenyl)-ethoxy]-phenyl; R₂ comprises alkyl; R₁₁₂ and R₁₁₄ comprise hydrogen; and R₁₁₁ and R₁₁₃ comprise -Y₃-Y₄-NR₂₃R₂₄, or -Y₃-Y₄-Y₅-A₂.

5 In the compounds of Formula (I), the various functional groups represented should be understood to have a point of attachment at the functional group having the hyphen. In other words, in the case of $-C_{1-6}$ alkylaryl, it should be understood that the point of attachment is the alkyl group; an example would be benzyl. In the case of a group such as $-C(O)-NH-C_{1-6}$ alkylaryl, the point of attachment is the carbonyl carbon.

10 Also included within the scope of the invention are the individual enantiomers of the compounds represented by Formula (I) above as well as any wholly or partially racemic mixtures thereof. The present invention also covers the individual enantiomers of the compounds represented by the Formula above as mixtures with diastereoisomers thereof in which one or more stereocenters are inverted.

15 Compounds of the present invention preferred for their high biological activity are listed by name below in Table 1.

Table 1

Ex.	Structure	Name
1		1-butyl-2-(3-cyclohexylmethoxy-phenyl)-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
2		{3-[3-butyl-2-(3,5-di-tert-butyl-2-methoxy-phenyl)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
3		(2-{3-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-3H-benzimidazol-5-yloxy}-ethyl)-diisopropyl-amine
4		(3-{4-[1-butyl-6-(4-tert-butyl-phenoxy)-1H-benzimidazol-2-yl]-phenoxy}-propyl)-diethyl-amine

Ex.	Structure	Name
5		1-butyl-6-(4-tert-butyl-phenoxy)-2-[3-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1H-benzimidazole
6		1-butyl-6-(4-tert-butyl-phenoxy)-2-[2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1H-benzimidazole
7		1-butyl-2-[3-(naphthalen-2-yloxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
8		2-biphenyl-4-yl-1-butyl-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
9		1-butyl-6-(4-tert-butyl-phenoxy)-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1H-benzimidazole
10		1-butyl-2-[3-(3,3-dimethyl-butoxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
11		1-butyl-6-(4-fluoro-3-trifluoromethyl-phenoxy)-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1H-benzimidazole

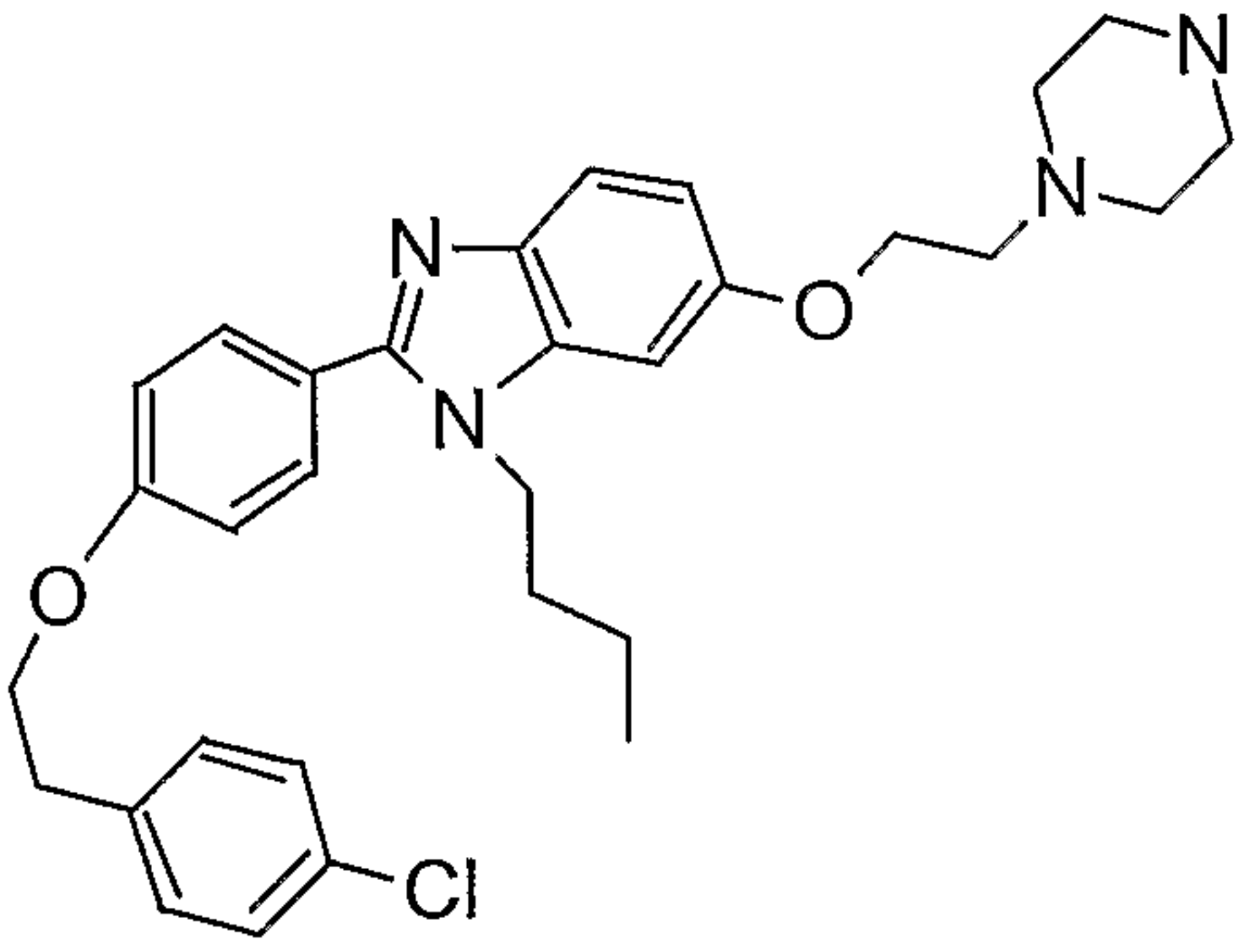
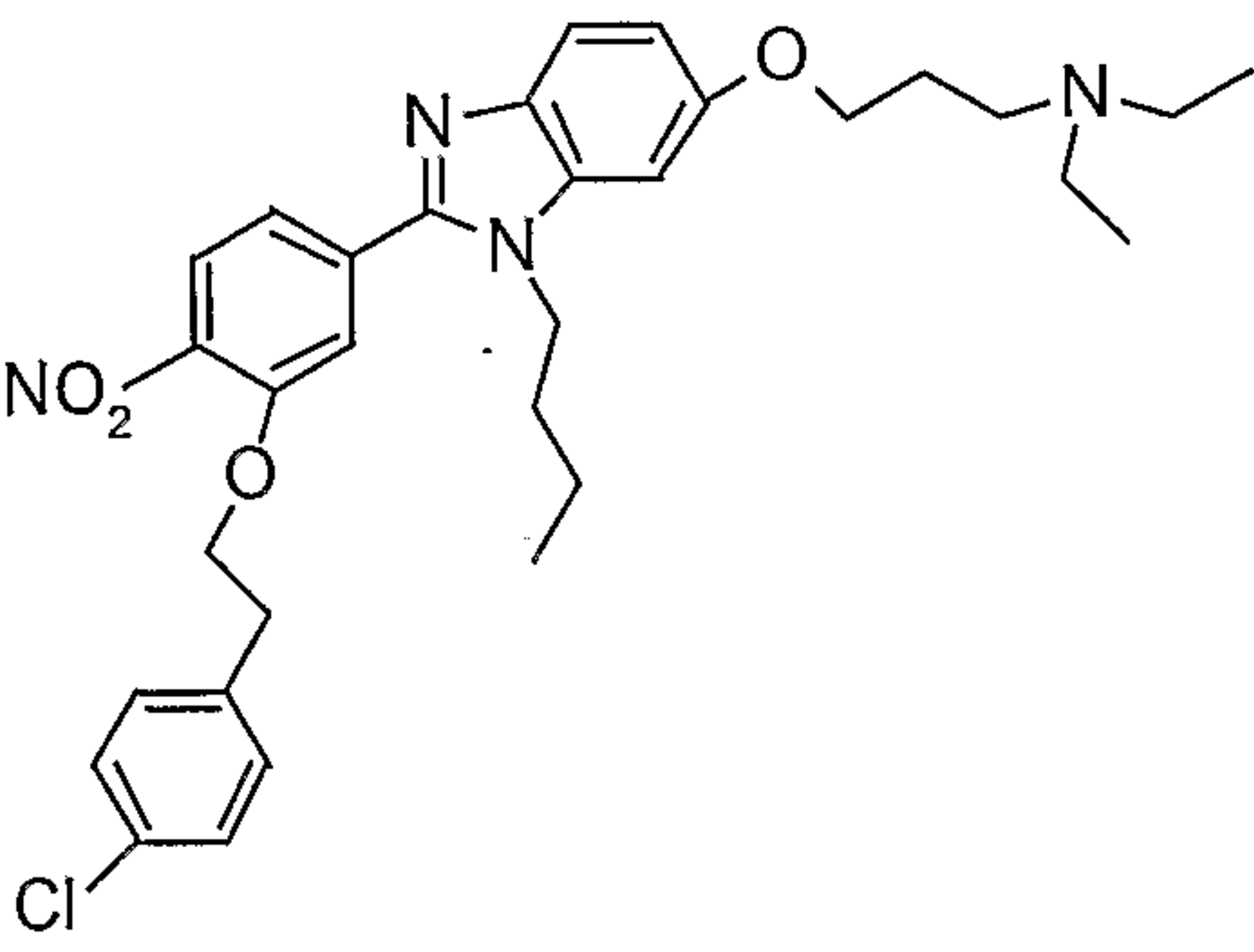
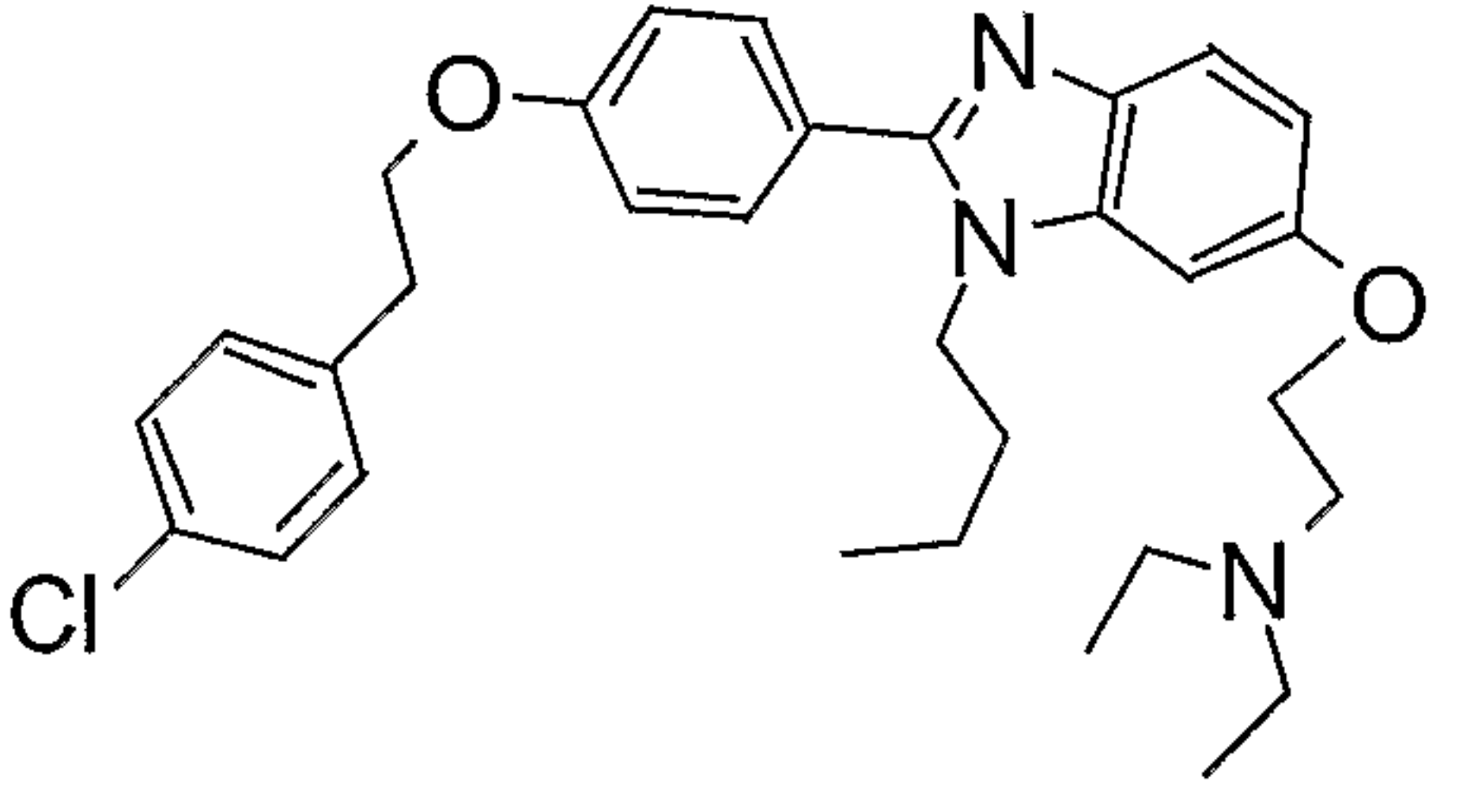
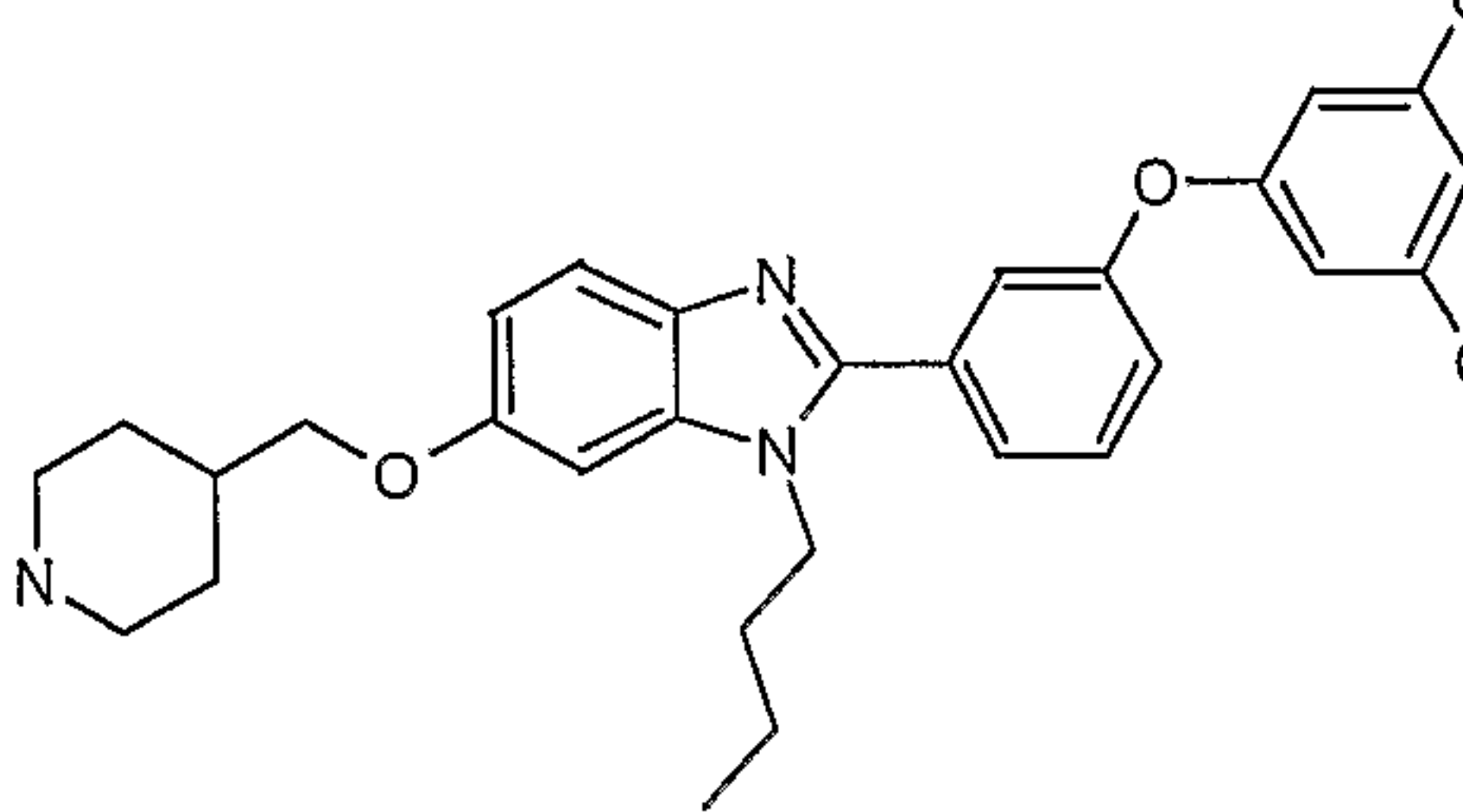
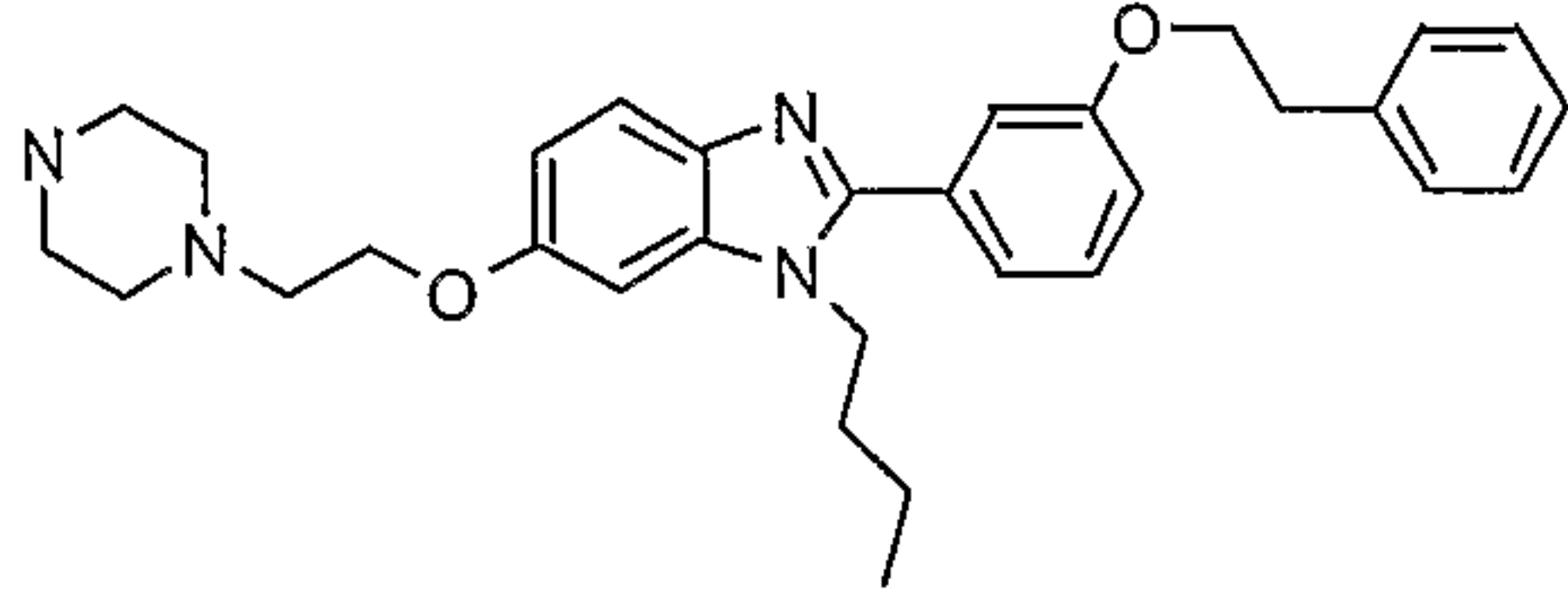
Ex.	Structure	Name
12		1-butyl-2-(3-phenoxy-phenyl)-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
13		1-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-6-(2-piperidin-1-yl-ethoxy)-1H-benzimidazole
14		1-butyl-2-[3-(3,4-dichloro-phenoxy)-phenyl]-6-(2-piperidin-1-yl-ethoxy)-1H-benzimidazole
15		1-butyl-6-[2-(4-chloro-phenyl)-ethoxy]-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1H-benzimidazole
16		1-butyl-2-[3-(3,5-dichloro-phenoxy)-phenyl]-6-(2-piperidin-1-yl-ethoxy)-1H-benzimidazole

Ex.	Structure	Name
17		1-butyl-2-(4-tert-butyl-phenyl)-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
18		dibutyl-{4-[1-butyl-6-(3-diethylamino-propoxy)-1H-benzimidazol-2-yl]-phenyl}-amine
19		(2-{3-butyl-2-[3-(3,5-dichlorophenoxy)-phenyl]-3H-benzimidazol-5-yloxy}-ethyl)-diisopropyl-amine
20		{3-[3-butyl-2-(4-tert-butyl-phenyl)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
21		1-butyl-2-(3,5-di-tert-butyl-2-methoxy-phenyl)-6-(2-piperazin-1-ylethoxy)-1H-benzimidazole
22		{3-[3-butyl-2-(3-{4-[2-(4-methoxy-phenyl)-ethoxy]-phenyl}-propyl)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine

Ex.	Structure	Name
23		1-butyl-2-naphthalen-2-yl-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
24		(2-{3-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-3H-benzimidazol-5-yloxy}-ethyl)-dimethyl-amine
25		2-benzofuran-2-yl-1-butyl-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
26		1-butyl-6-(2-piperazin-1-yl-ethoxy)-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazole
27		2-benzhydryl-1-butyl-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
28		1-Butyl-2-(4-chloro-phenyl)-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole

Ex.	Structure	Name
29		{3-[3-Butyl-2-(4-isopropoxy-phenyl)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
30		1-Butyl-6-(2-piperazin-1-yl-ethoxy)-2-[3-(4,4,4-trifluoro-butoxy)-phenyl]-1H-benzimidazole
31		{3-[3-Butyl-2-(2,4,4-trimethyl-pentyl)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
32		Diethyl-{2-[2-piperidin-3-yl-3-(4-pyrrolidin-1-yl-butyl)-3H-benzimidazol-5-yloxy]-ethyl}-amine
33		Diethyl-{2-[2-piperidin-4-yl-3-(4-pyrrolidin-1-yl-butyl)-3H-benzimidazol-5-yloxy]-ethyl}-amine

Ex.	Structure	Name
34		{3-[1-Butyl-6-(3-diethylamino-propoxy)-2-piperidin-4-yl-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
35		{3-[3-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-7-(2-pyrrolidin-1-yl-ethoxy)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
36		1-Butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
37		1-butyl-2-[3-(3-tert-butyl-phenoxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
38		2-[3-(biphenyl-4-yloxy)-phenyl]-1-butyl-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole

Ex.	Structure	Name
39		1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
40		[3-(3-butyl-2-{3-[2-(4-chloro-phenyl)-ethoxy]-4-nitro-phenyl}-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
41		[2-(3-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-3H-benzimidazol-5-yloxy)-ethyl]-diethyl-amine
42		1-butyl-2-[3-(3,5-dichloro-phenoxy)-phenyl]-6-(piperidin-4-ylmethoxy)-1H-benzimidazole
43		1-butyl-2-{3-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole

Ex.	Structure	Name
44		{3-[3-butyl-2-(2-{4-[2-(4-chlorophenyl)-ethoxy]-phenyl}-ethyl)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
45		1-butyl-2-[3-(3,5-dichloro-phenoxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
46		1-butyl-6-[2-(4-butyl-piperazin-1-yl)-ethoxy]-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazole
47		{3-[3-butyl-2-(2-{4-[2-(4-methoxyphenyl)-ethoxy]-phenyl}-ethyl)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
48		(3-{3-butyl-2-[3-(4-methoxy-phenoxy)-phenyl]-3H-benzimidazol-5-yloxy}-propyl)-diethyl-amine

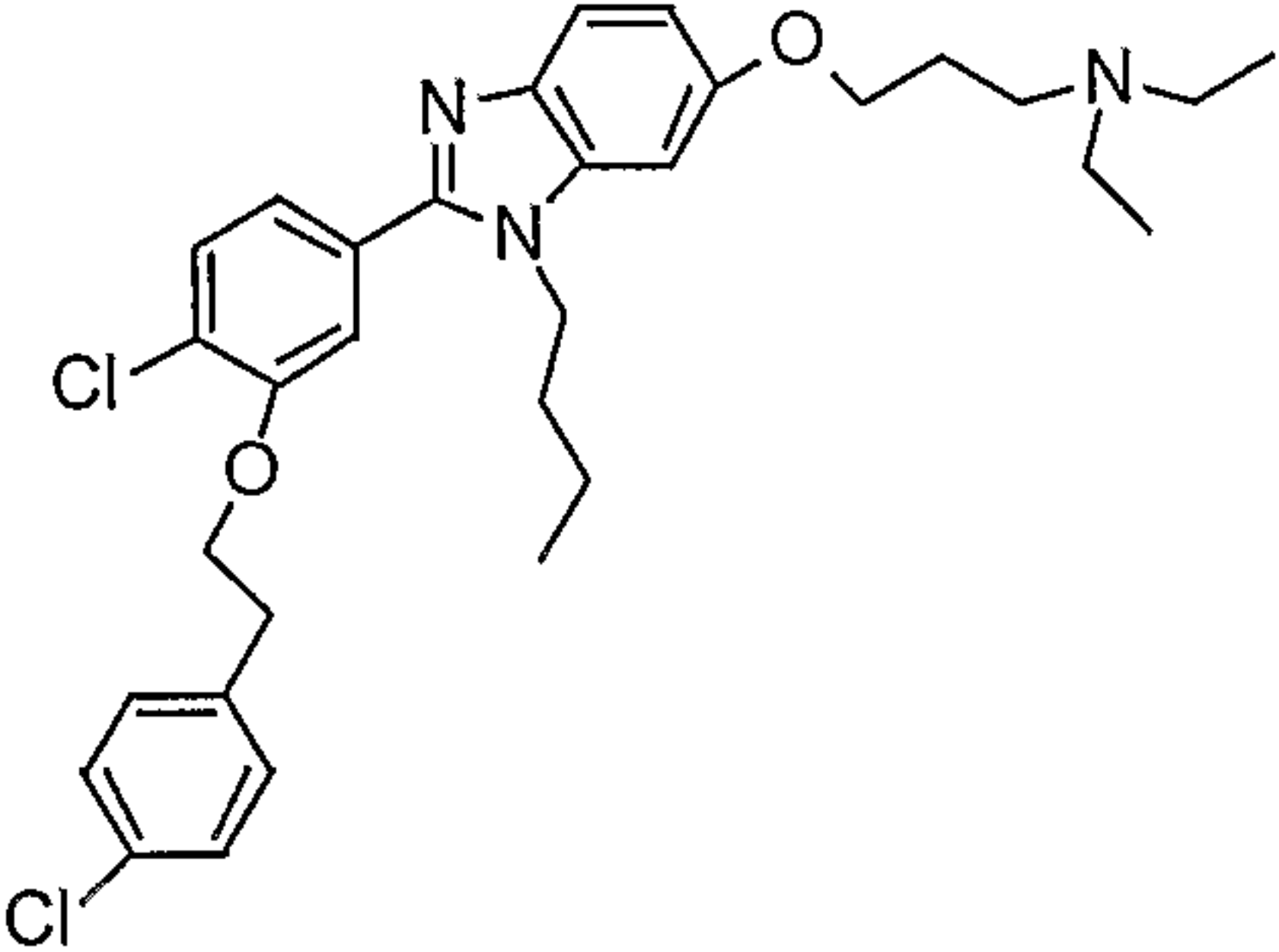
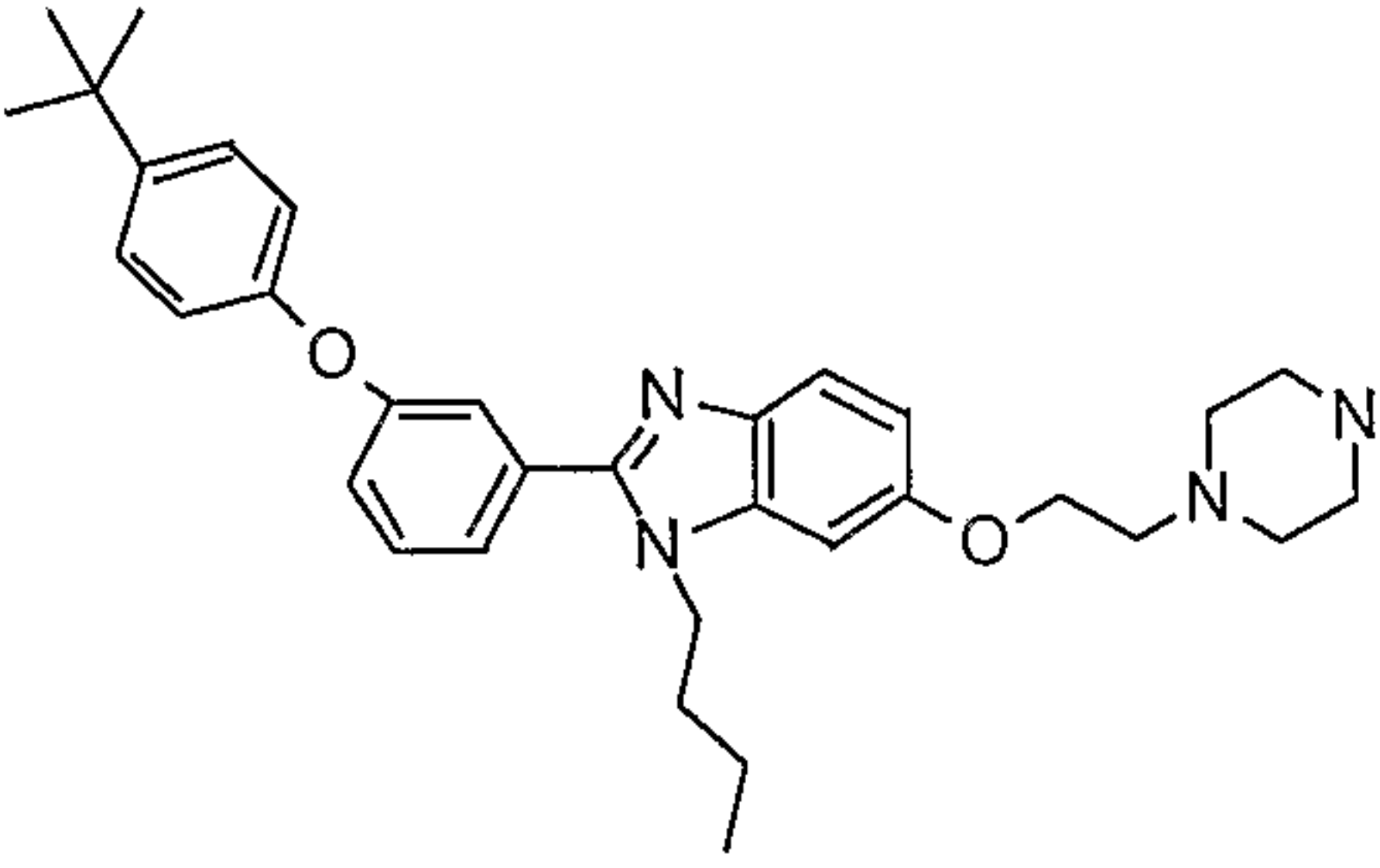
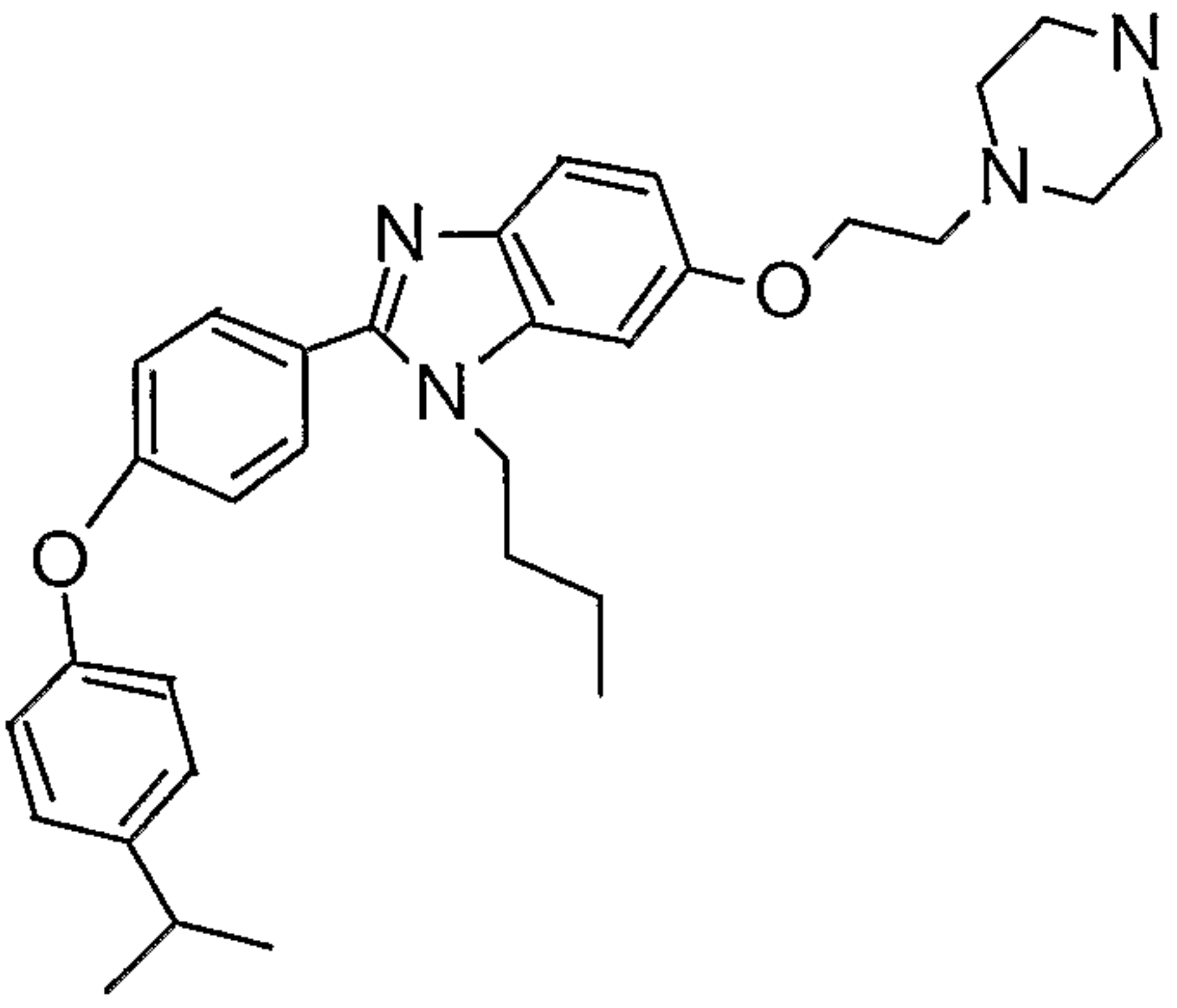
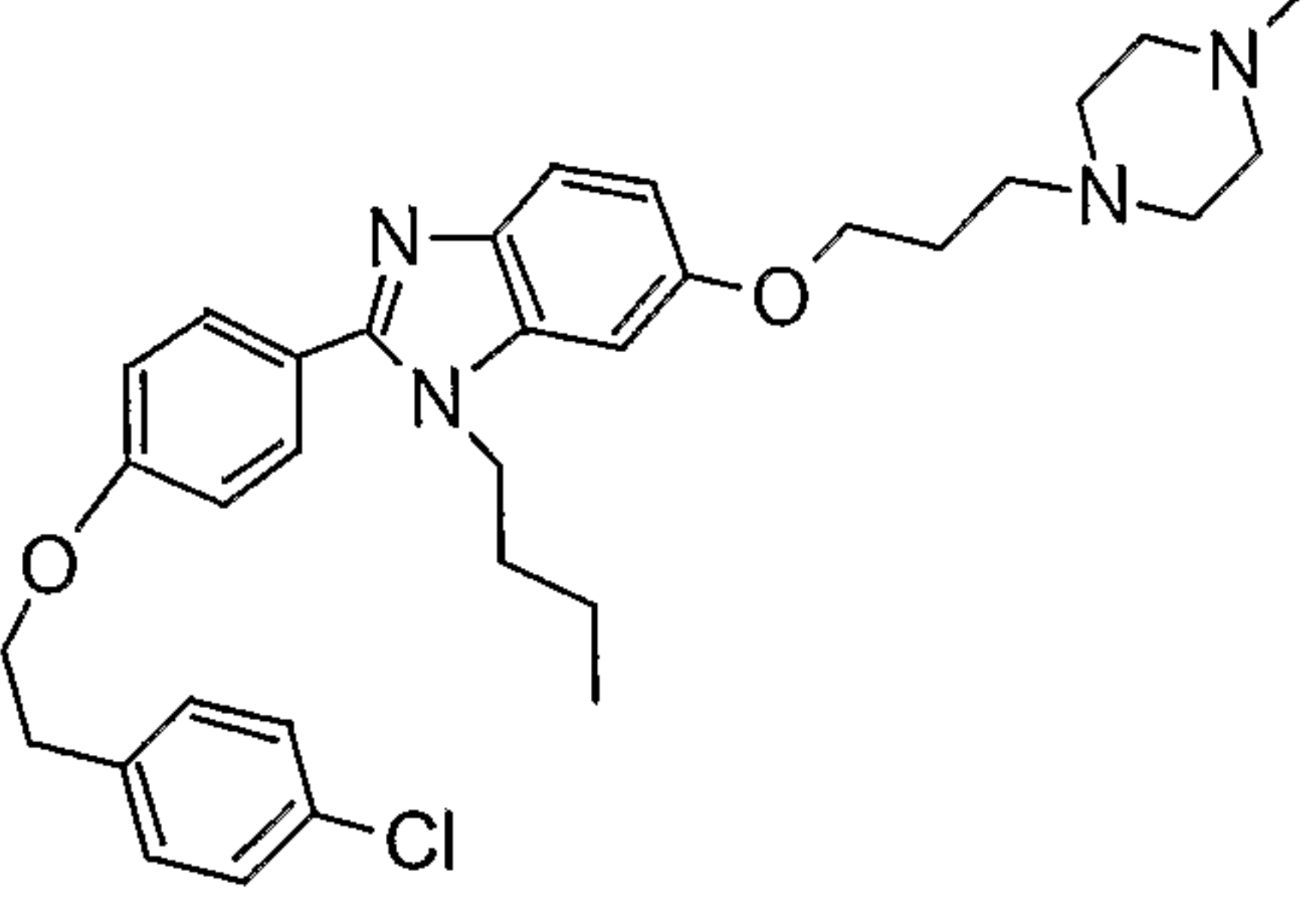
Ex.	Structure	Name
49		{3-[2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(2-diethylaminoethoxy)-benzimidazol-1-yl]-propyl}-diethyl-amine
50		[3-(1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-1H-benzimidazol-4-yloxy)-propyl]-diethyl-amine
51		[3-(1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-1H-benzimidazol-5-yl)-propyl]-diethyl-amine
52		1-butyl-2-[3-(2-isopropyl-phenoxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzoimidazole
53		{3-[3-butyl-2-(2-{4-[3-(4-methoxy-phenyl)-propoxy]-phenyl}-ethyl)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
54		{3-[3-butyl-2-(2-{4-[4-(4-methoxy-phenyl)-butoxy]-phenyl}-ethyl)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
55		[3-(3-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-3-ethoxy-phenyl}-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine

Ex.	Structure	Name
56		(3-{3-butyl-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-3H-benzimidazol-5-yloxy}-propyl)-diethyl-amine
57		1-butyl-2-[3-(4-chloro-phenoxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
58		1-butyl-2-[3-(3,4-dichloro-phenoxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
59		1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(piperidin-4-yloxy)-1H-benzimidazole
60		3-(3-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-3H-benzimidazol-5-yloxy)-1-aza-bicyclo[2.2.2]octane
61		1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(2,2,6,6-tetramethyl-piperidin-4-yloxy)-1H-benzimidazole
62		2-[3-(4-butoxy-phenoxy)-phenyl]-1-butyl-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole

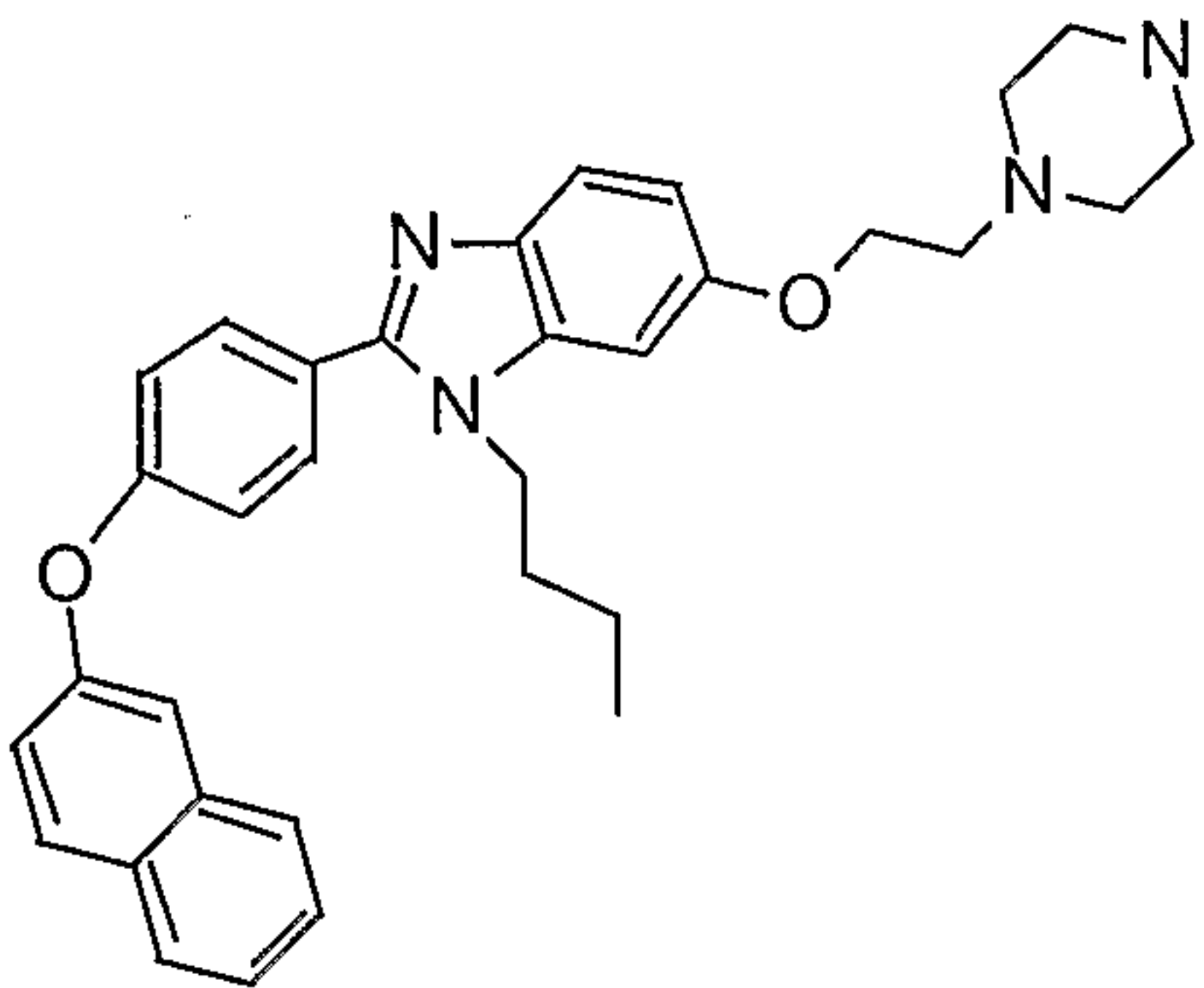
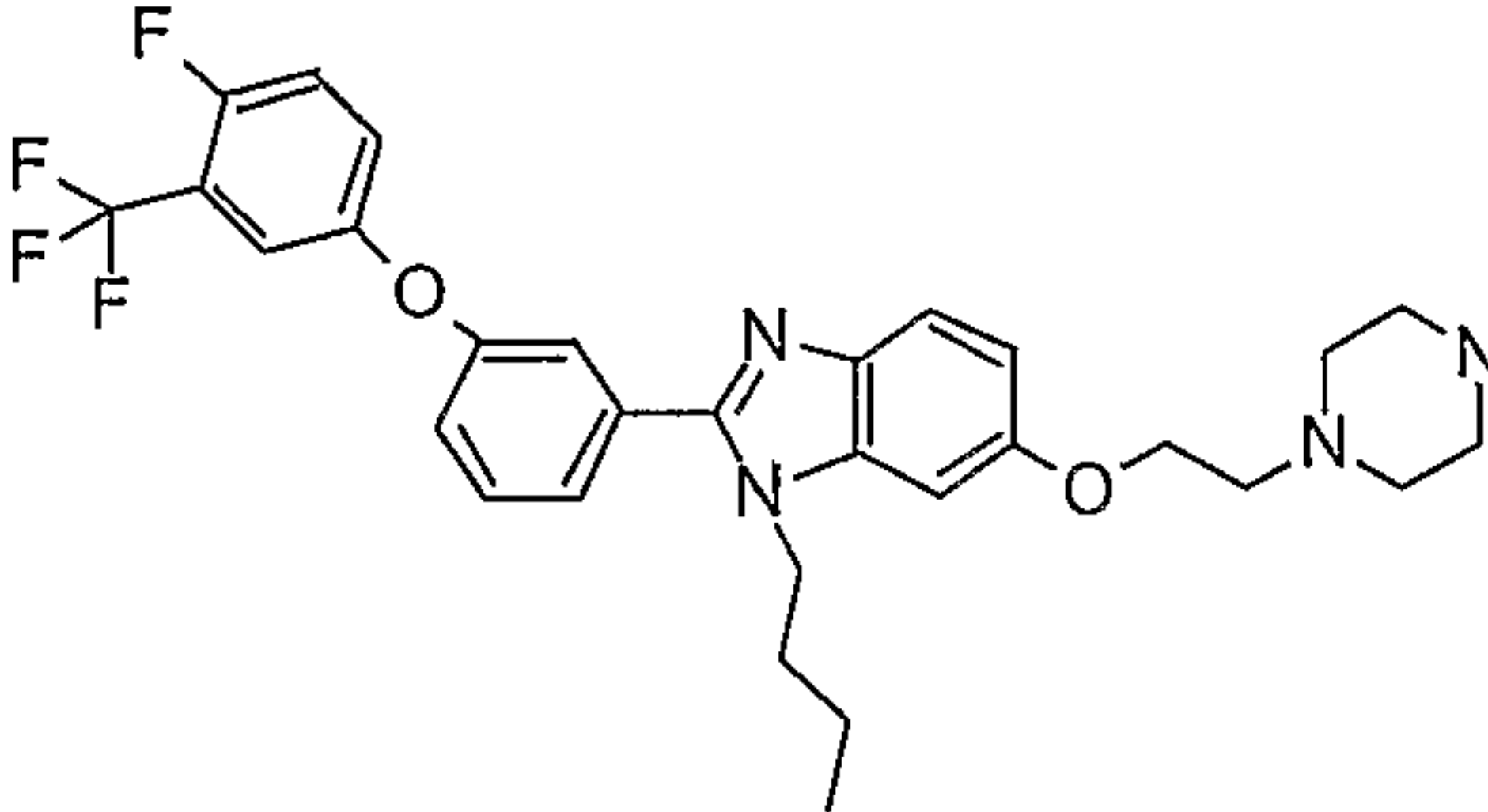
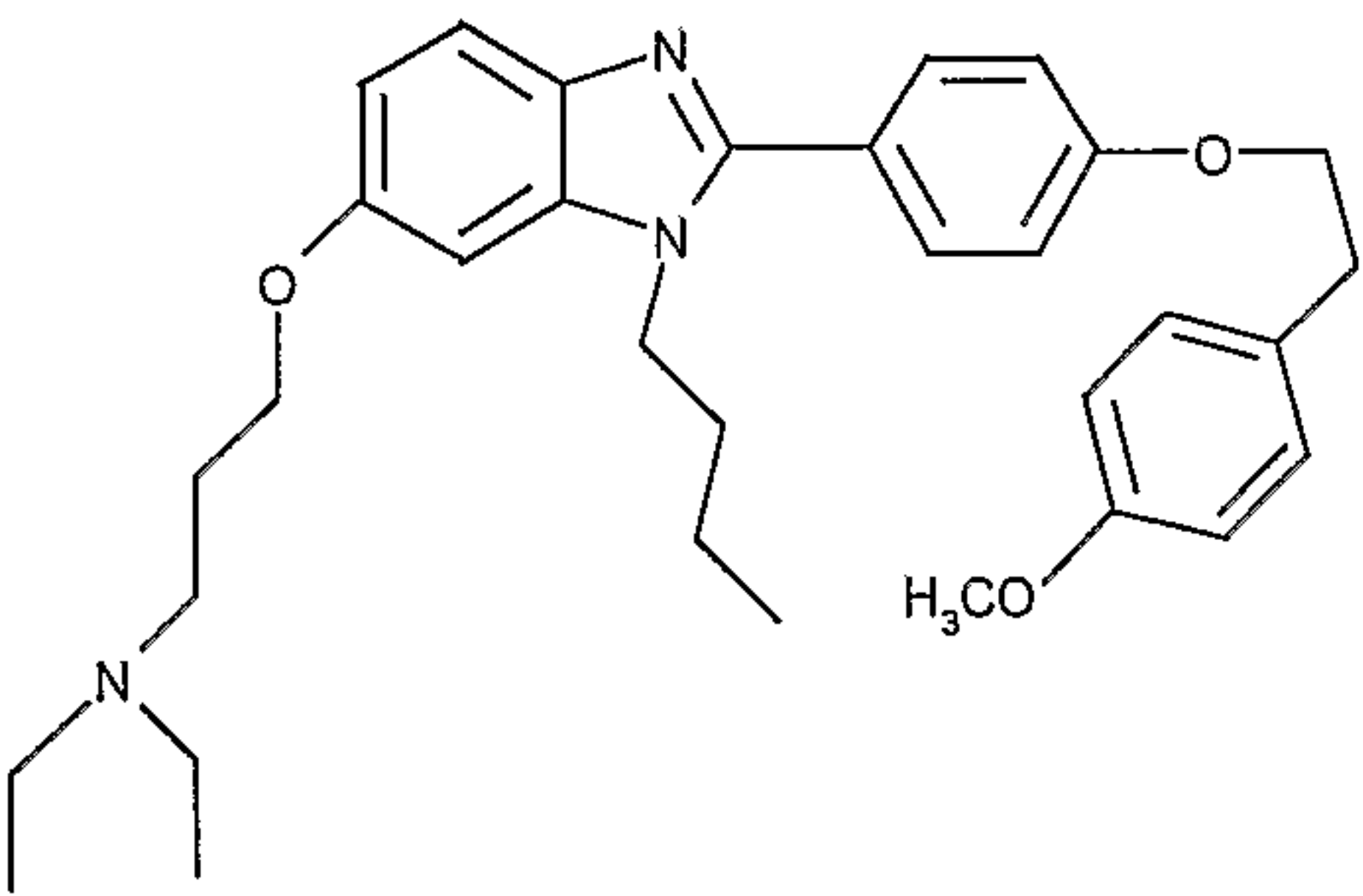
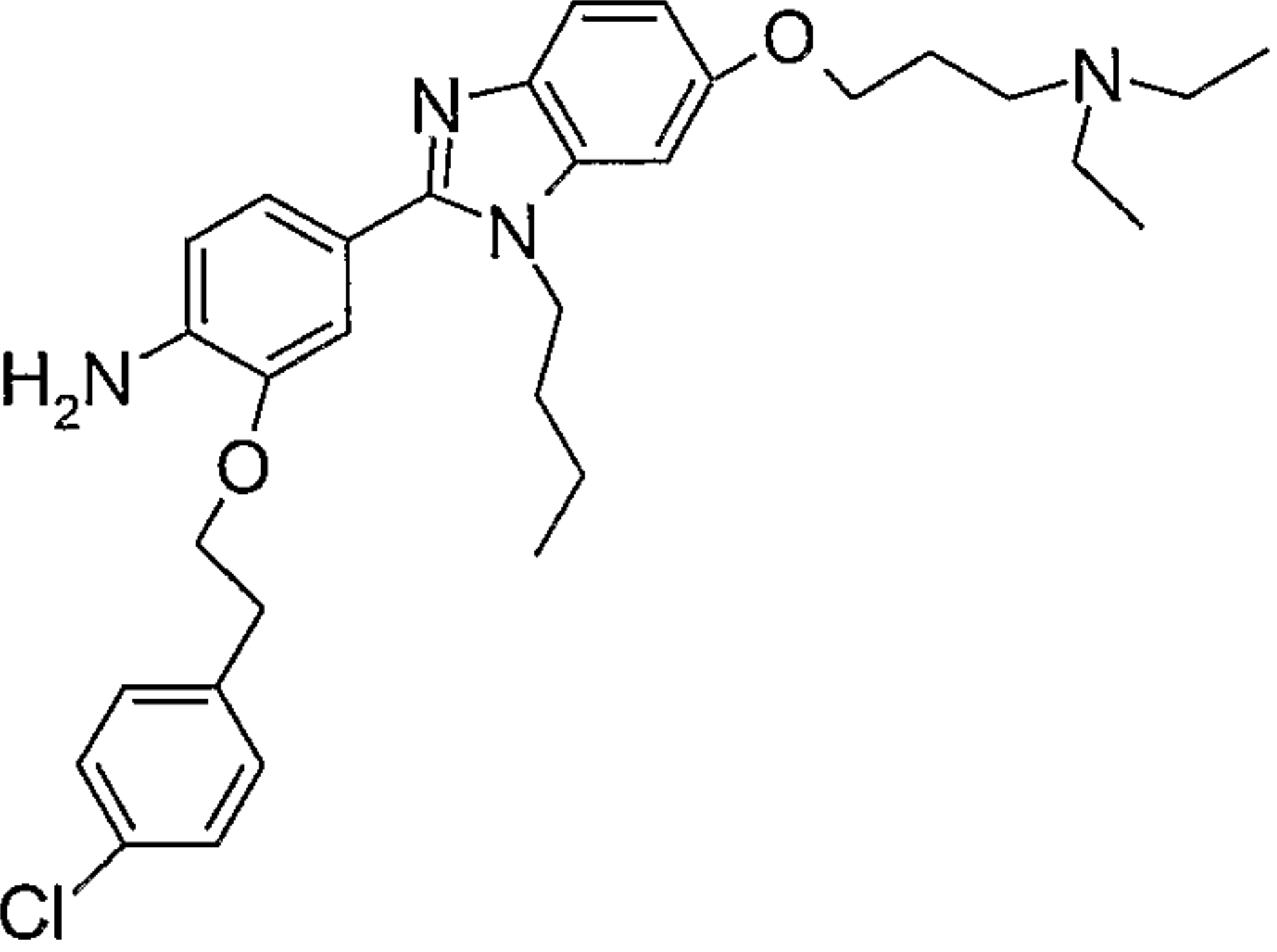
Ex.	Structure	Name
63		[3-(3-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
64		{3-[2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-3-(3-methyl-butyl)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
65		[3-(2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-3-hexyl-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
66		{3-[2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(2-diethylaminoethoxy)-benzimidazol-1-yl]-propyl}-dimethyl-amine
67		1-butyl-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-6-(2-piperazin-1-ylethoxy)-1H-benzimidazole
68		[3-(3-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
69		{3-[2-(4-benzyloxy-3,5-dimethyl-phenyl)-3-butyl-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
70		{3-[3-butyl-2-[3-(3,4-dichloro-phenoxy)-phenyl]-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine

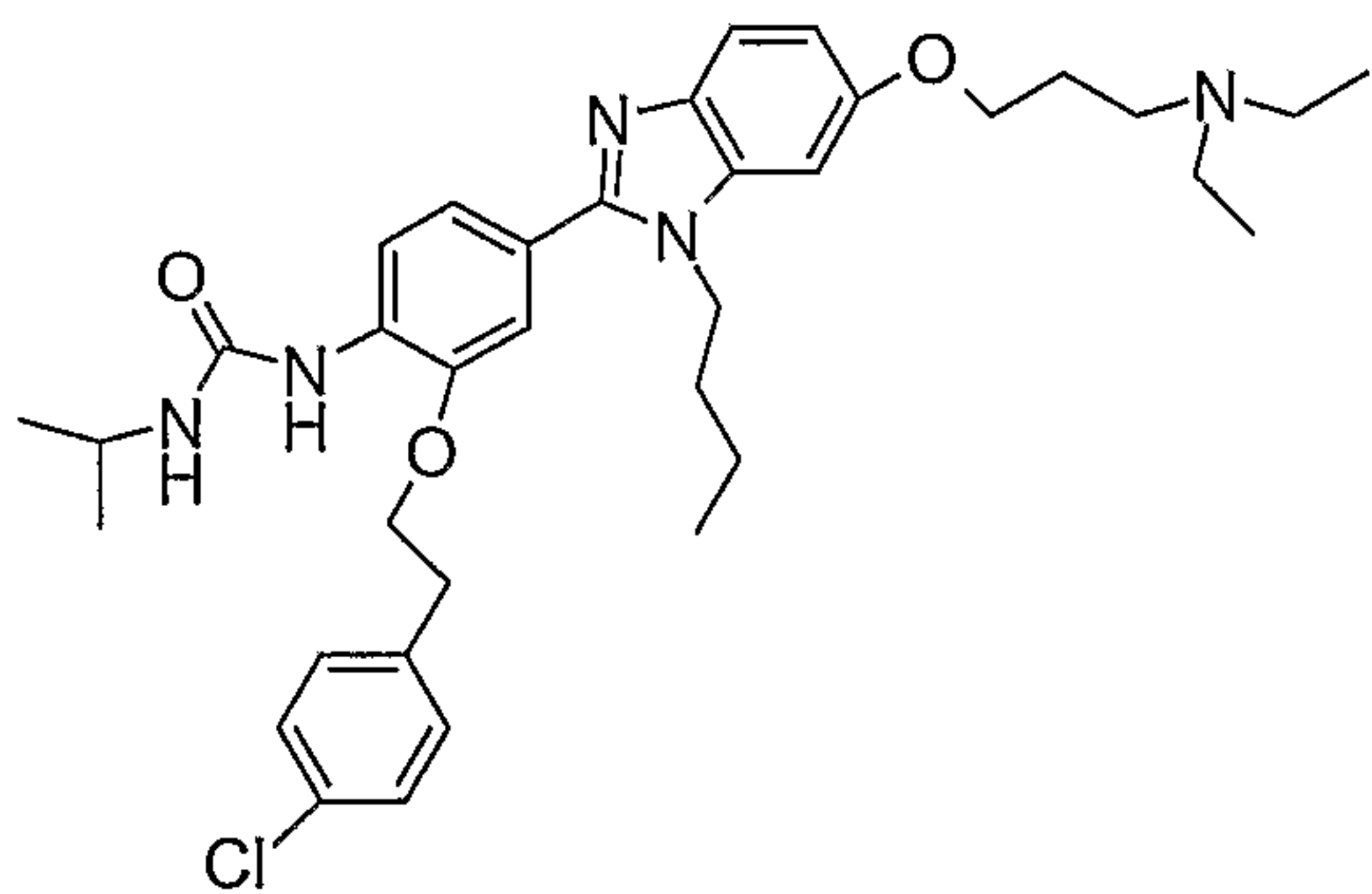
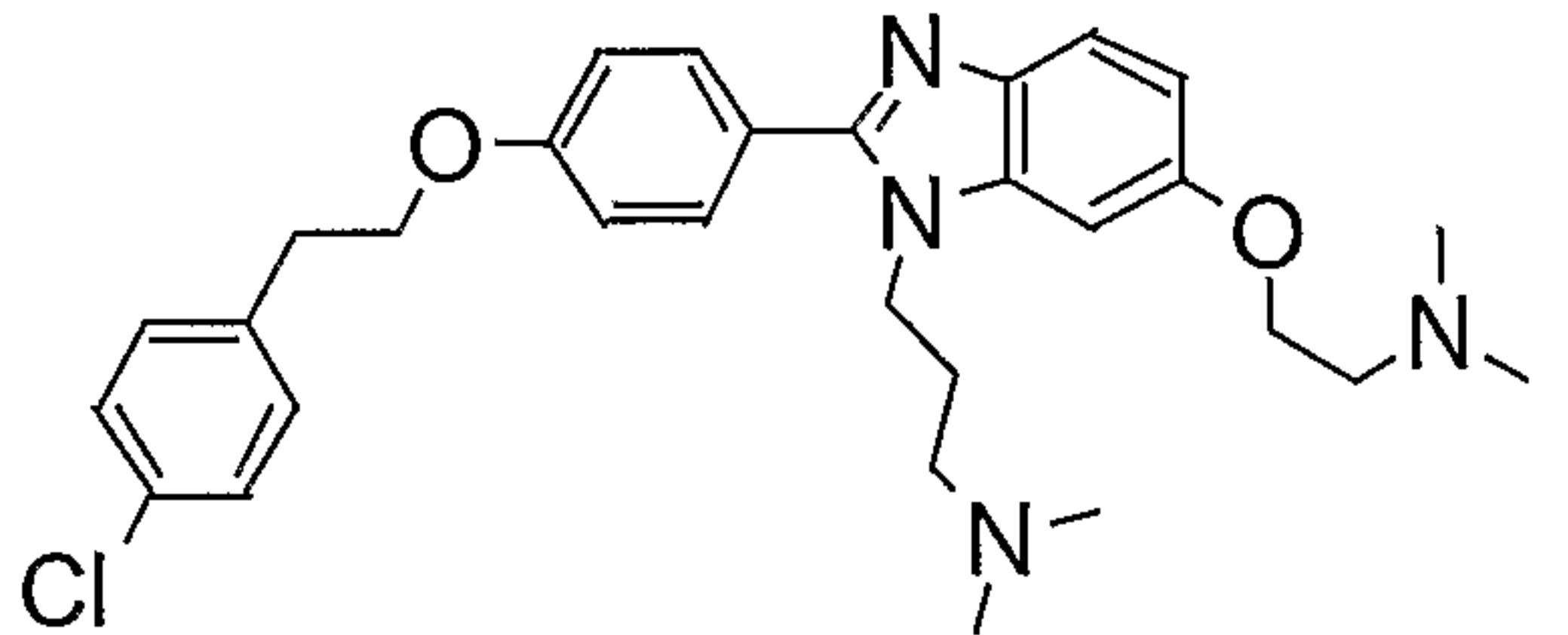
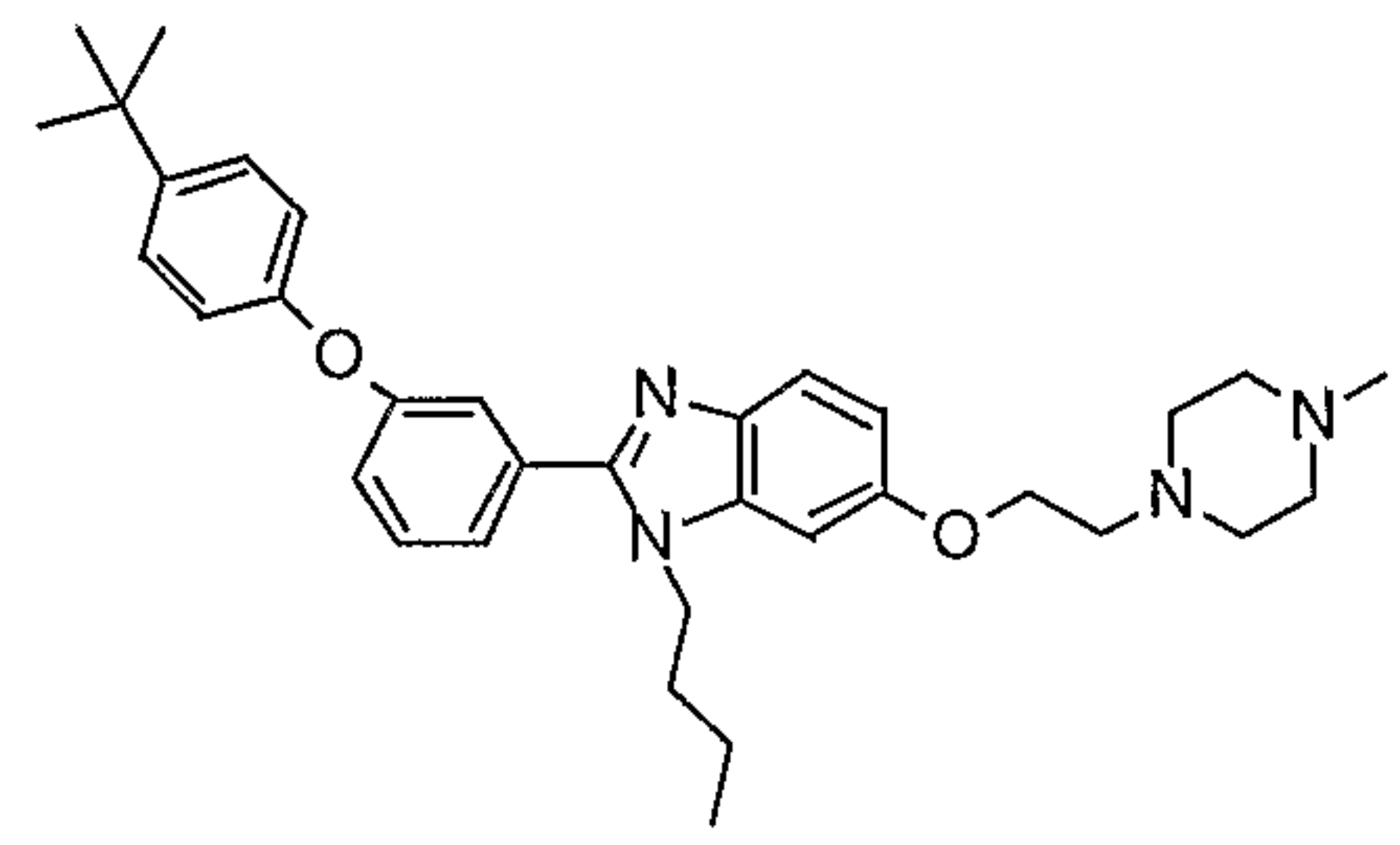
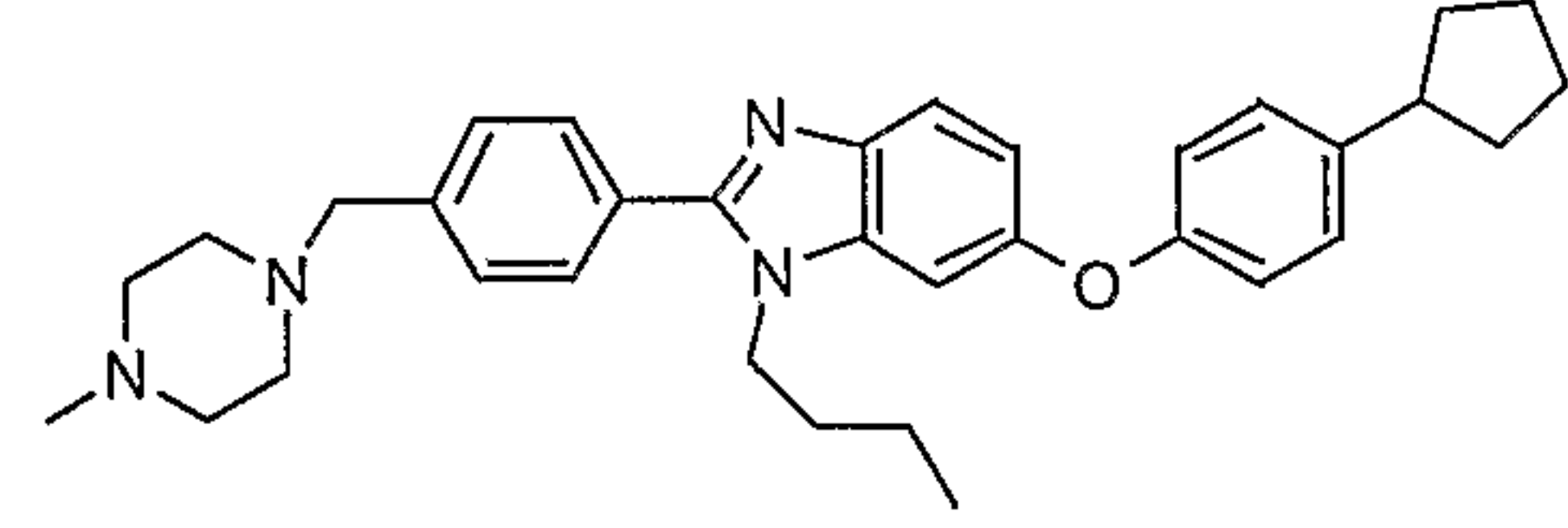
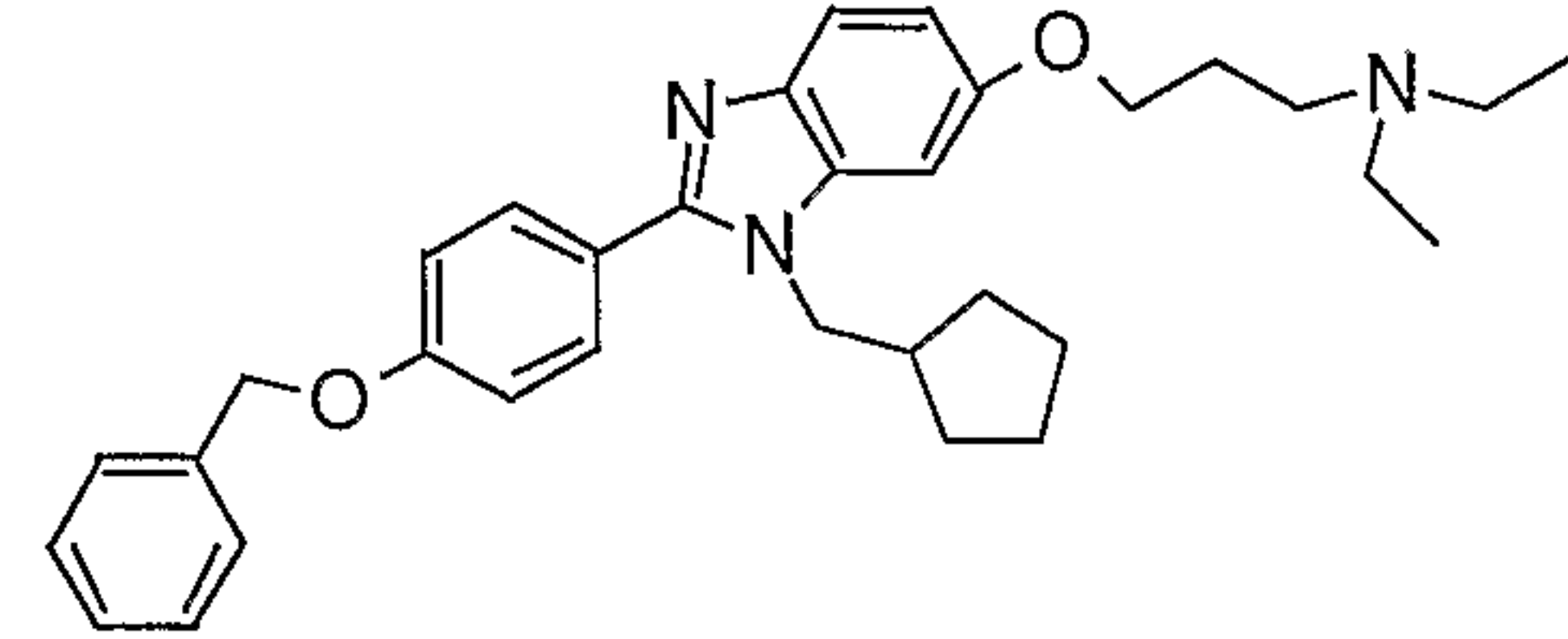
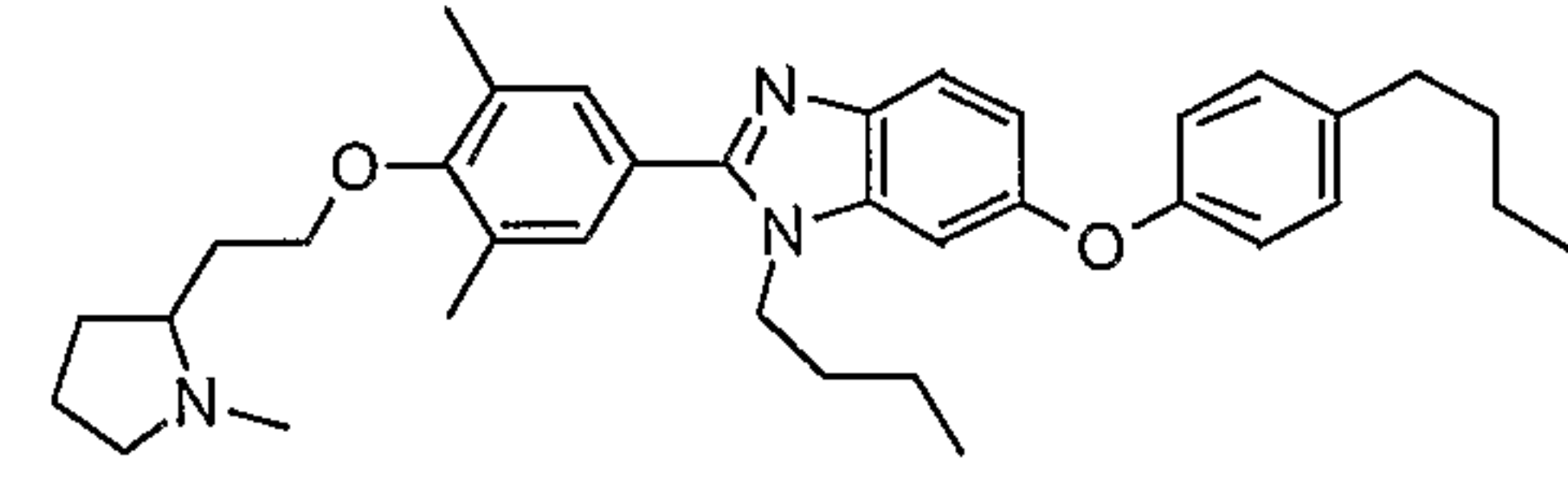
Ex.	Structure	Name
71		1-butyl-6-[2-(4-methyl-piperazin-1-yl)-ethoxy]-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazole
72		1-butyl-6-[2-(4-isopropyl-piperazin-1-yl)-ethoxy]-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzoimidazole
73		1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(3-piperazin-1-yl-propoxy)-1H-benzoimidazole
74		(3-{3-butyl-2-[3-(3,4-dichloro-phenoxy)-phenyl]-3H-benzimidazol-5-yloxy}-propyl)-diethyl-amine
75		1-butyl-2-[3-(3,4-dimethoxy-phenoxy)-phenyl]-6-(2-piperidin-4-yloxy)-1H-benzoimidazole
76		1-butyl-2-[3-(4-chloro-benzyloxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzoimidazole
77		1-butyl-2-[3-(3,5-dichloro-phenoxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzoimidazole

Ex.	Structure	Name
78		(3-{2-[2-(4-benzyloxy-phenyl)-ethyl]-3-butyl-3H-benzimidazol-5-yloxy}-propyl)-diethyl-amine
79		(3-{3-butyl-2-[2-(4-phenethyloxy-phenyl)-ethyl]-3H-benzimidazol-5-yloxy}-propyl)-diethyl-amine
80		{3-[3-butyl-2-(2-{4-[2-(4-fluoro-phenyl)-ethoxy]-phenyl}-ethyl)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
81		[3-(3-butyl-2-{2-[4-(4-chloro-benzyloxy)-phenyl]-ethyl}-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
82		(3-{3-butyl-2-[4-(4-fluoro-benzyloxy)-phenyl]-3H-benzimidazol-5-yloxy}-propyl)-diethyl-amine
83		{3-[2-(3-benzyloxy-phenyl)-3-butyl-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine

Ex.	Structure	Name
84		[3-(3-butyl-2-{4-chloro-3-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
85		1-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
86		1-butyl-2-[4-(4-isopropyl-phenoxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzoimidazole
87		1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-[3-(4-methyl-piperazin-1-yl)-propoxy]-1H-benzoimidazole

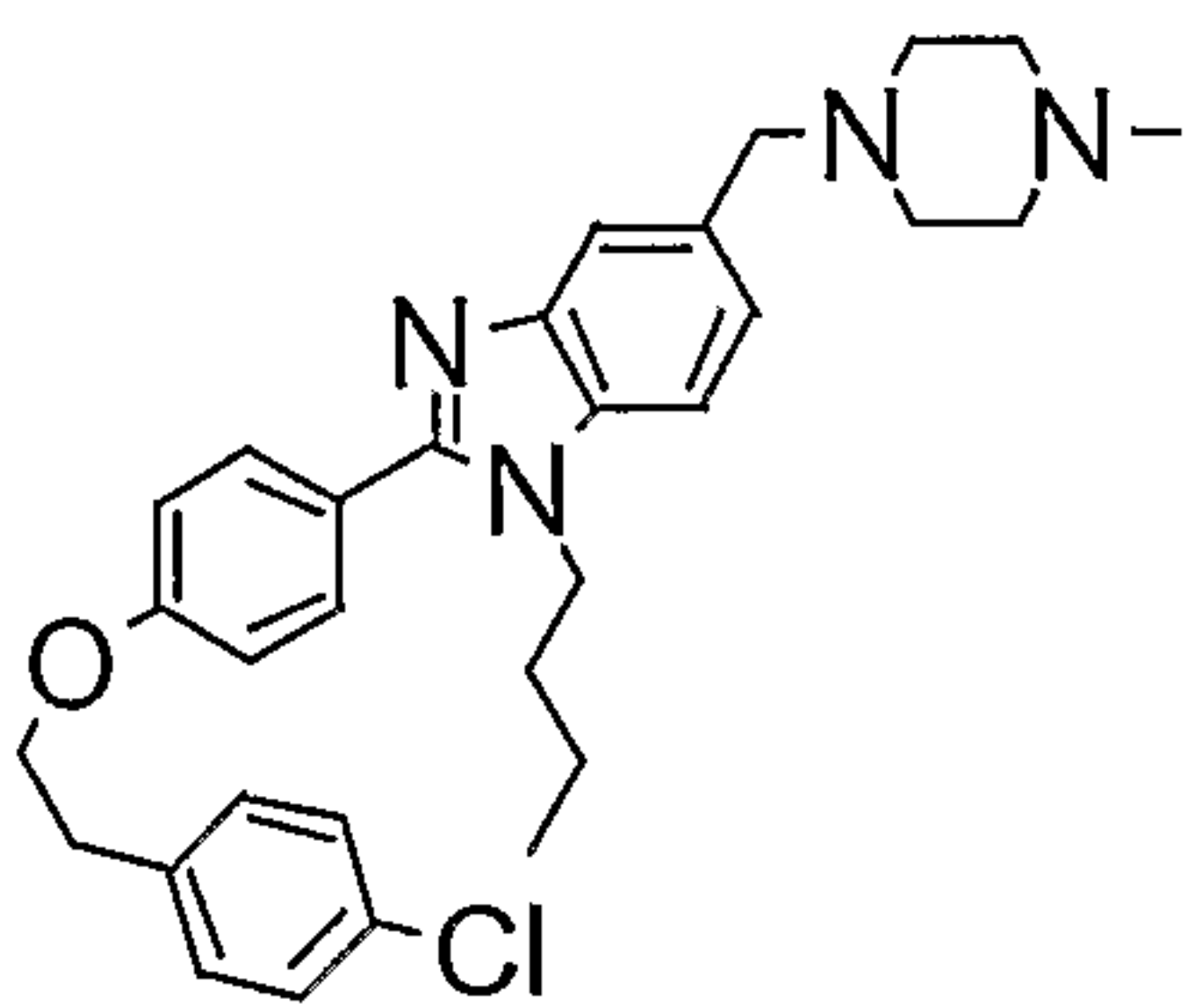
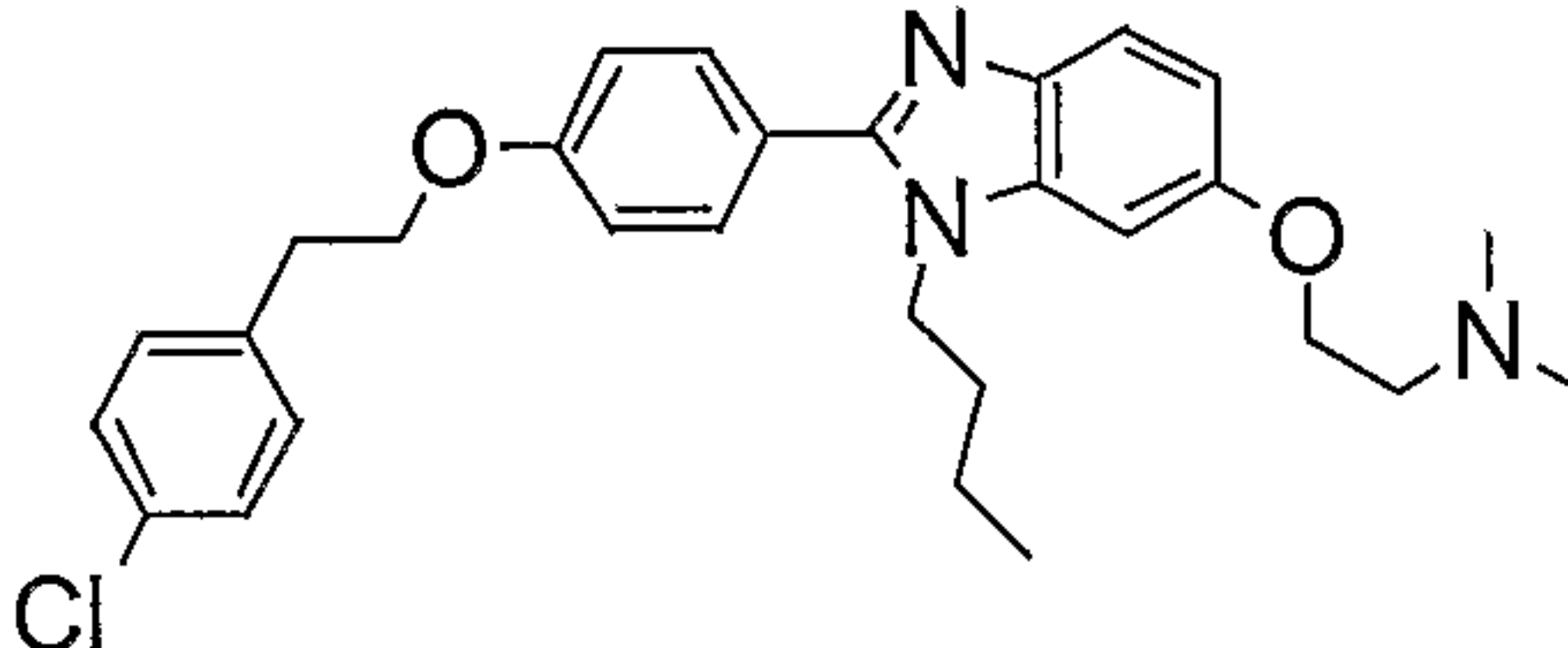
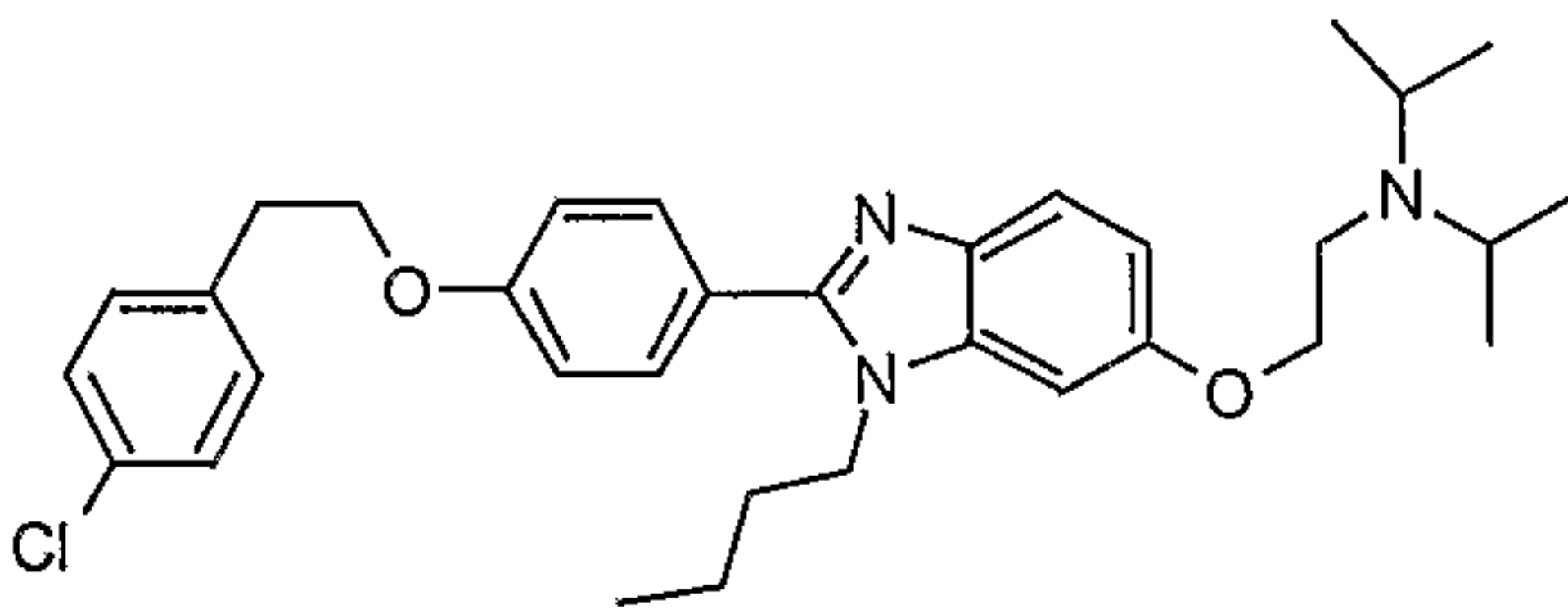
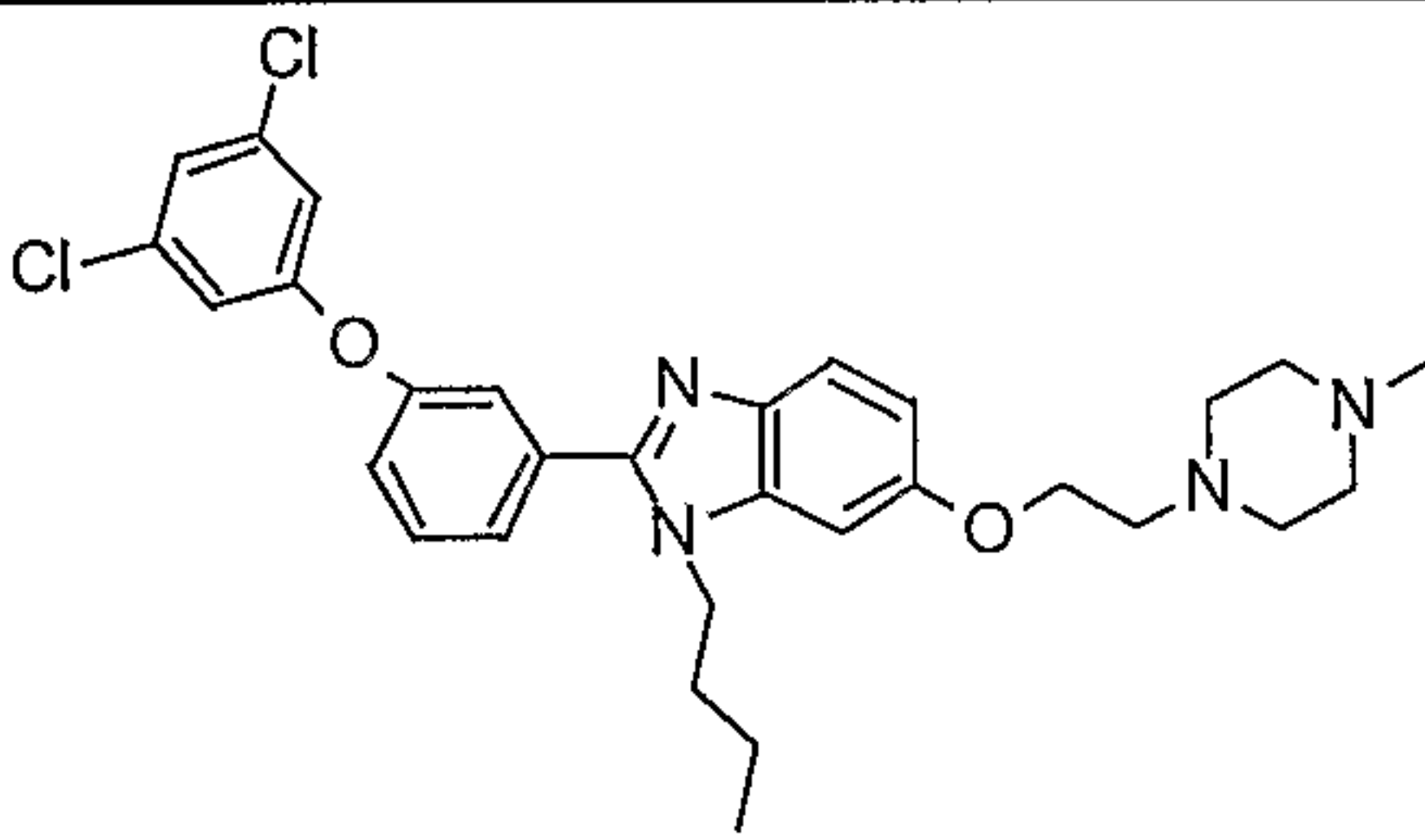
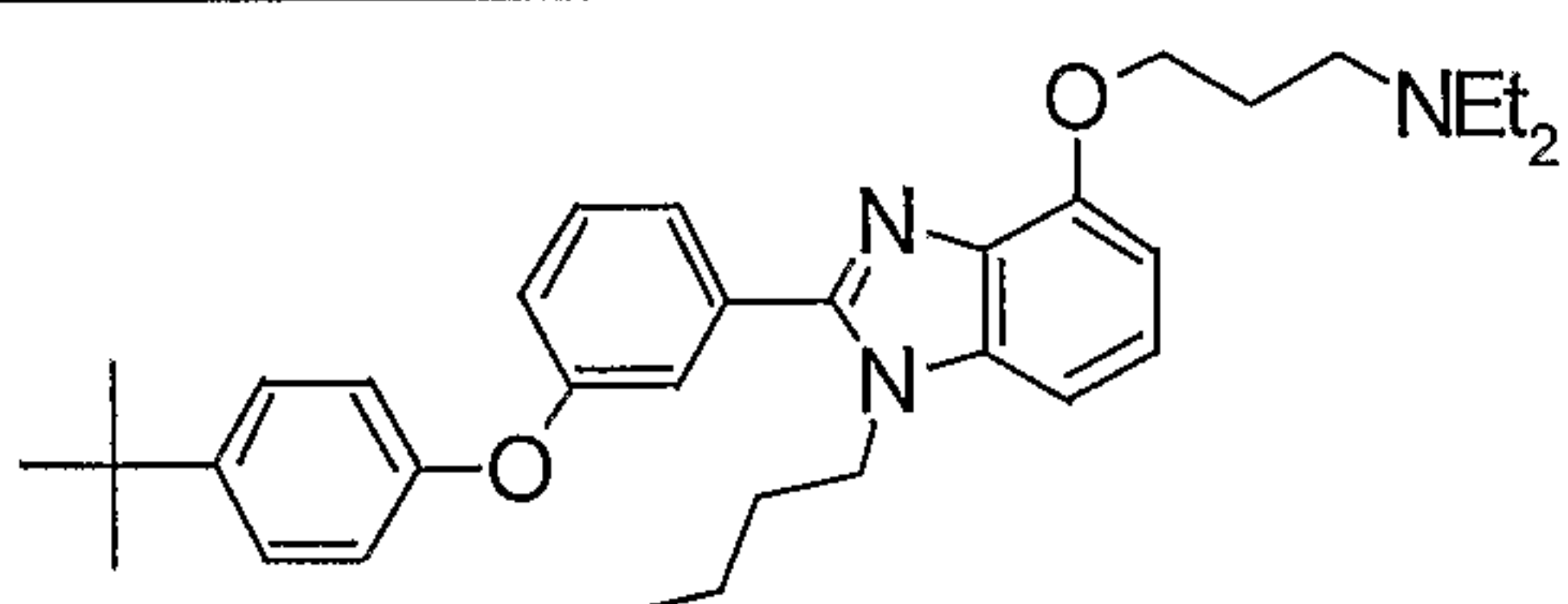
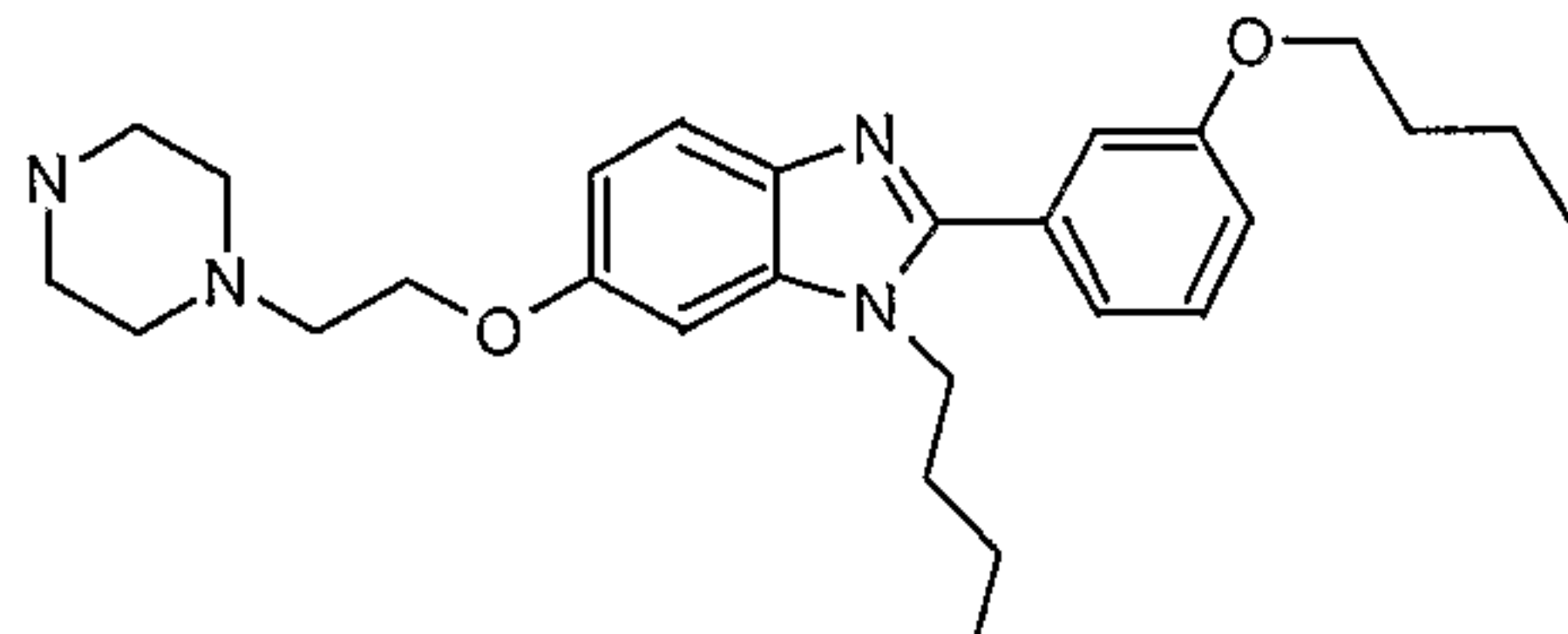
Ex.	Structure	Name
88		1-butyl-6-[2-(4-butyl-piperazin-1-yl)-ethoxy]-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-1H-benzimidazole
89		1-butyl-2-[3-(3,4-dimethoxy-phenoxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
90		1-butyl-2-[4-(4-tert-butyl-benzyl)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
91		N-{4-[1-butyl-6-(3-diethylamino-propoxy)-1H-benzimidazol-2-yl]-2-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2,2-dimethyl-propionamide
92		(3-{3-butyl-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-3H-benzimidazol-5-yloxy}-propyl)-diethyl-amine

Ex.	Structure	Name
93		1-butyl-2-[4-(naphthalen-2-yloxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
94		1-butyl-2-[3-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
95		[3-(3-butyl-2-{4-[2-(4-methoxy-phenyl)-ethoxy]-phenyl}-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
96		4-[1-butyl-6-(3-diethylamino-propoxy)-1H-benzimidazol-2-yl]-2-[2-(4-chloro-phenyl)-ethoxy]-phenylamine

Ex.	Structure	Name
97		1-{4-[1-butyl-6-(3-diethylamino-propoxy)-1H-benzimidazol-2-yl]-2-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-3-isopropyl-urea
98		{3-[2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(2-dimethylamino-ethoxy)-benzimidazol-1-yl]-propyl}-dimethyl-amine
99		1-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-6-[2-(4-methyl-piperazin-1-yl)-ethoxy]-1H-benzimidazole
100		1-butyl-6-(4-cyclopentyl-phenoxy)-2-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-benzimidazole
101		{3-[2-(4-benzyloxy-phenyl)-3-cyclopentylmethyl-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
102		1-butyl-6-(4-butyl-phenoxy)-2-{3,5-dimethyl-4-[2-(1-methyl-pyrrolidin-2-yl)-ethoxy]-phenyl}-1H-benzimidazole

Ex.	Structure	Name
103		1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(3-pyrrolidin-1-yl-propoxy)-1H-benzimidazole
104		{3-[2-(4-benzyloxy-phenyl)-3-isobutyl-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
105		[3-(3-butyl-2-{3-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
106		1-butyl-6-(1-butyl-piperidin-4-yloxy)-2-[3-(3,5-dichloro-phenoxy)-phenyl]-1H-benzimidazole
107		1-butyl-2-[3-(3,5-dichloro-phenoxy)-phenyl]-6-(1-ethyl-piperidin-4-yloxy)-1H-benzimidazole
108		1-butyl-6-(4-fluoro-3-trifluoromethyl-phenoxy)-2-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-benzimidazole

Ex.	Structure	Name
109		diethyl-{3-[3-isobutyl-2-(2-{4-[2-(4-methoxy-phenyl)-ethoxy]-phenyl}-ethyl)-3H-benzimidazol-5-yloxy]-propyl}-amine
110		{3-[2-(2-{4-[2-(4-chlorophenyl)-ethoxy]-phenyl}-ethyl)-3-isobutyl-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
111		1-butyl-6-(2-piperazin-1-yl-ethoxy)-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazole
112		1-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
113		1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-[2-(4-methyl-piperazin-1-yl)-ethoxy]-1H-benzimidazole
114		{3-[2-(4-benzyloxy-phenyl)-3-cyclopentyl-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine

Ex.	Structure	Name
115		1-Butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-5-(4-methyl-piperazin-1-ylmethyl)-1H-benzimidazole
116		[2-(3-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-3H-benzimidazol-5-yloxy)-ethyl]-dimethyl-amine
117		[2-(3-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-3H-benzimidazol-5-yloxy)-ethyl]-diisopropyl-amine
118		1-butyl-2-[3-(3,5-dichloro-phenoxy)-phenyl]-6-[2-(4-methyl-piperazin-1-yl)-ethoxy]-1H-benzimidazole
119		(3-{1-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine
120		2-(3-butoxy-phenyl)-1-butyl-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole

Ex.	Structure	Name
121		1-butyl-2-[3-(4-methanesulfonyl-benzyloxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
122		4'[{3-[1-butyl-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazol-2-yl]-phenoxy}]biphenyl-4-carbonitrile
123		{3-[2-(4-benzyloxy-phenyl)-3-butyl-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
124		1-Butyl-2-[4-(3-chloro-phenoxy)-phenyl]-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
125		1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-[2-(4-isopropyl-piperazin-1-yl)-ethoxy]-1H-benzimidazole

Ex.	Structure	Name
126		{3-[2-(3-benzyloxy-4-methoxy-phenyl)-3-butyl-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
127		(3-{3-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-3H-benzimidazol-5-yloxy}-propyl)-diethyl-amine
128		{3-[3-butyl-2-(3-phenoxy-phenyl)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
129		1-butyl-2-[3-(3,5-dichloro-phenoxy)-phenyl]-6-[2-(4-ethyl-piperazin-1-yl)-ethoxy]-1H-benzimidazole
130		1-butyl-2-[4-(2,3-di-methoxy-phenoxy)-phenyl]-6-(2-piperazin-1-ylethoxy)-1H-benzimidazole

Ex.	Structure	Name
131		[3-(3-butyl-2-{2-[4-(4-chloro-benzyloxy)-phenyl]-ethyl}-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
132		(3-{3-butyl-2-[3-(4-chloro-phenoxy)-phenyl]-3H-benzimidazol-5-yloxy}-propyl)-diethyl-amine
133		{3-[2-(4-benzyloxy-phenyl)-3-isopropyl-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
134		(2-{3-butyl-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-3H-benzimidazol-5-yloxy}-ethyl)-diisopropyl-amine
135		1-butyl-6-[2-(4-ethyl-piperazin-1-yl)-ethoxy]-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazole
136		{3-[3-butyl-2-[3-(3,5-dichloro-phenoxy)-phenyl]-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine

Ex.	Structure	Name
137		(3-{2-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-3H-benzimidazol-5-yloxy}-ethyl)-cyclohexyl-methyl-amine
138		1-butyl-6-[2-(4-propyl-piperazin-1-yl)-ethoxy]-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazole
139		1-butyl-6-(4-butyl-phenoxy)-2-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-benzimidazole
140		1-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-6-(2-morpholin-4-yl-ethoxy)-1H-benzimidazole
141		4-[1-butyl-6-(3-diethylamino-propoxy)-1H-benzimidazol-2-yl]-2-phenethyloxy-phenylamine
142		{2-[2-(4-benzyloxy-phenyl)-3-phenethyl-3H-benzimidazol-5-yloxy]-ethyl}-diethyl-amine

Ex.	Structure	Name
143		{3-[3-butyl-2-(4-phenoxy-phenyl)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
144		3-[4-(2-{3-butyl-2-[3-(3,4-dichlorophenoxy)-phenyl]-3H-benzimidazol-5-yloxy}-ethyl)-piperazin-1-yl]-propan-1-ol
145		1-butyl-6-(2-pyrrolidin-1-yl-ethoxy)-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazole
146		{2-[2-[4-[2-(4-chloro-phenyl)-ethoxy]-phenyl]-6-(2-diethylamino-ethoxy)-benzimidazol-1-yl]-ethyl}-dimethyl-amine
147		1-butyl-6-(2-morpholin-4-yl-ethoxy)-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazole
148		1-butyl-2-[3-(3,5-dichloro-phenoxy)-phenyl]-6-(1-methyl-piperidin-4-yloxy)-1H-benzoimidazole

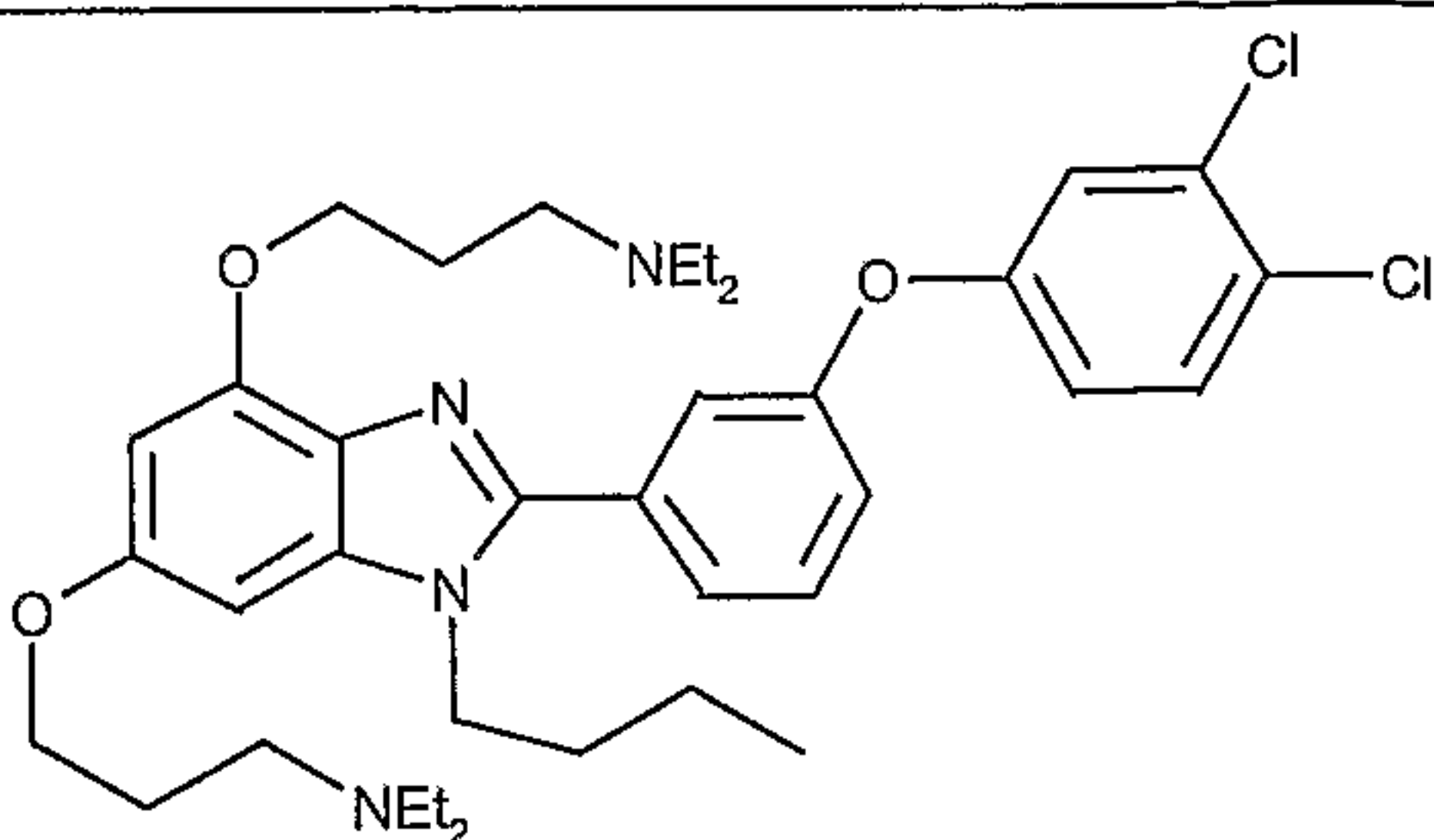
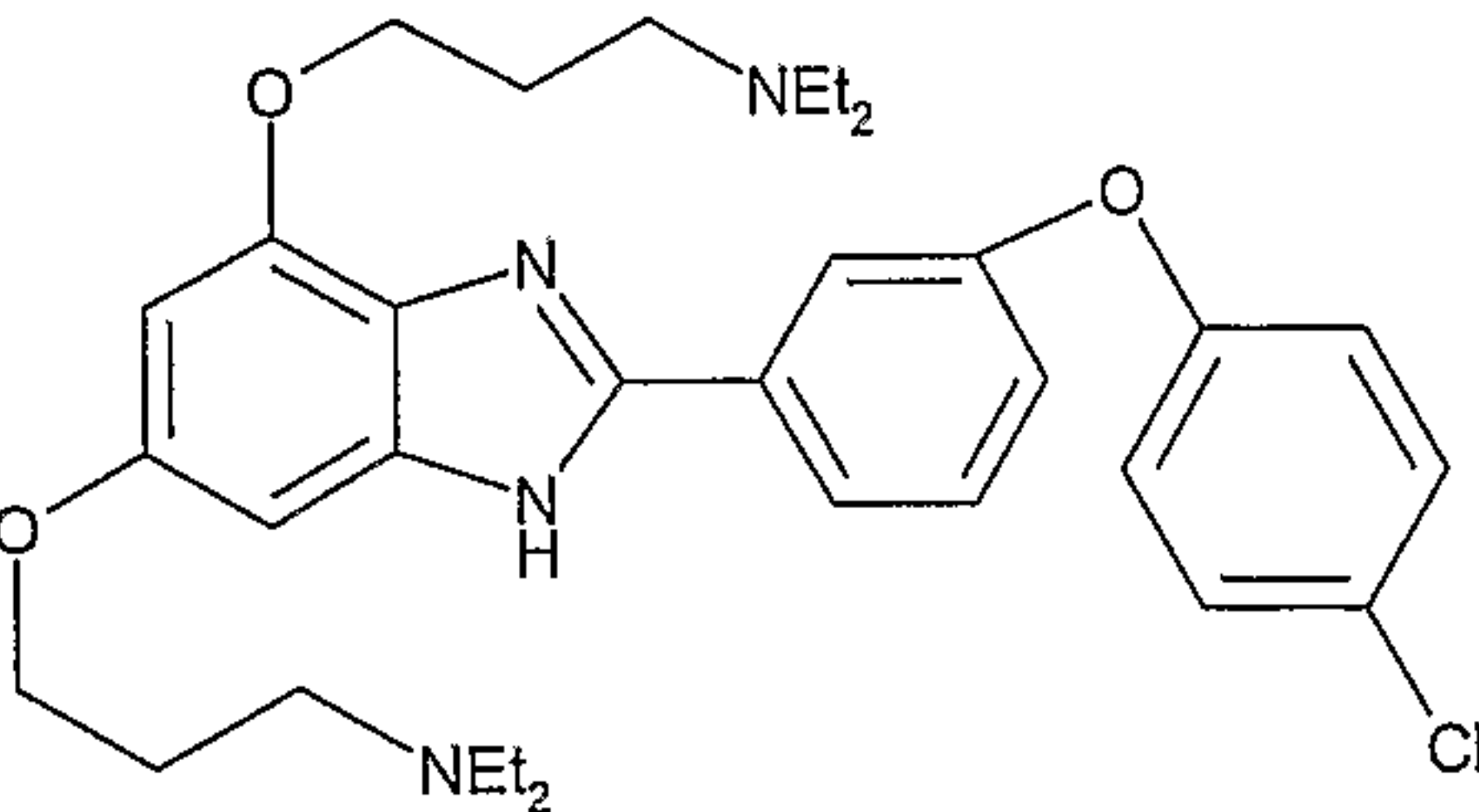
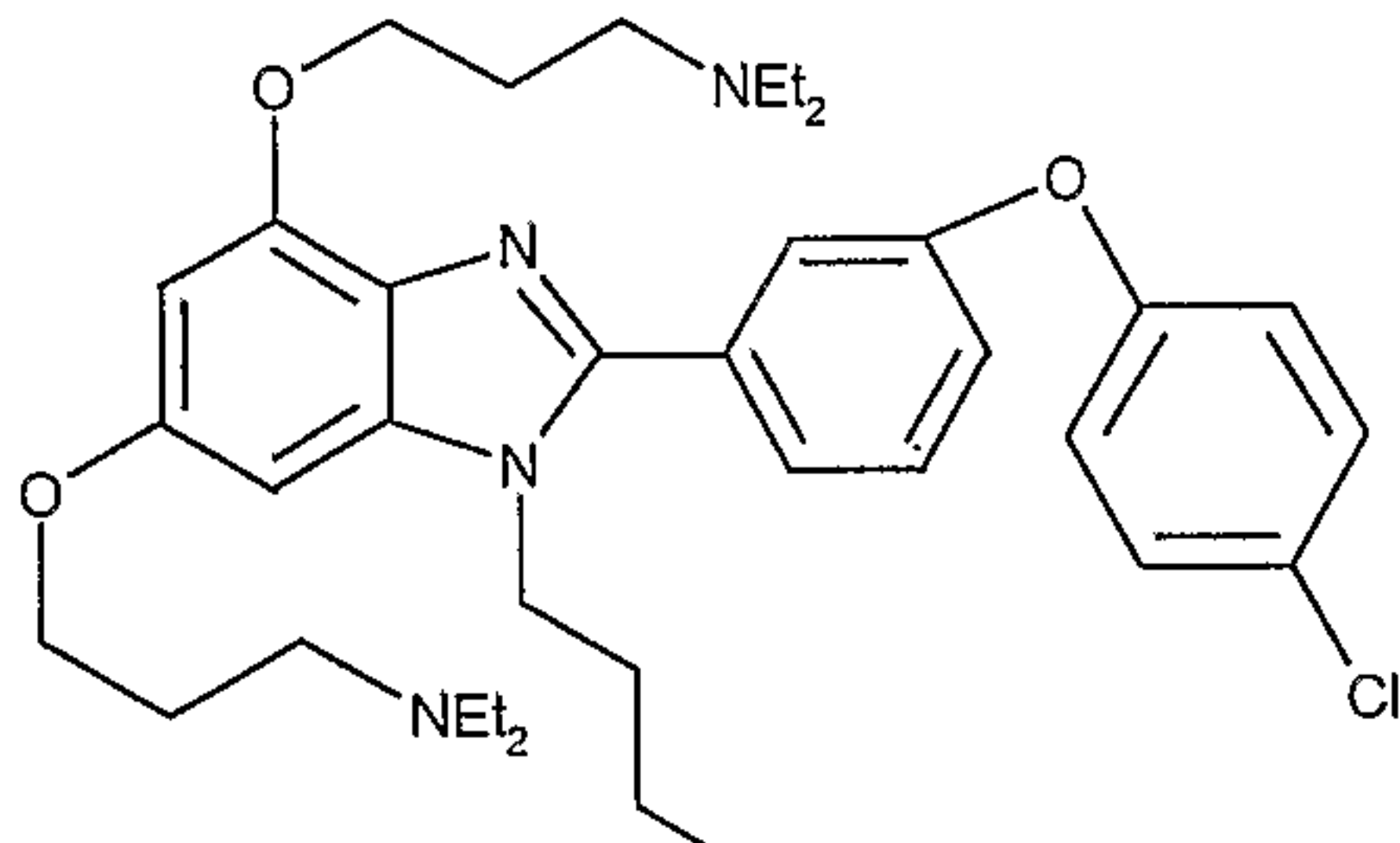
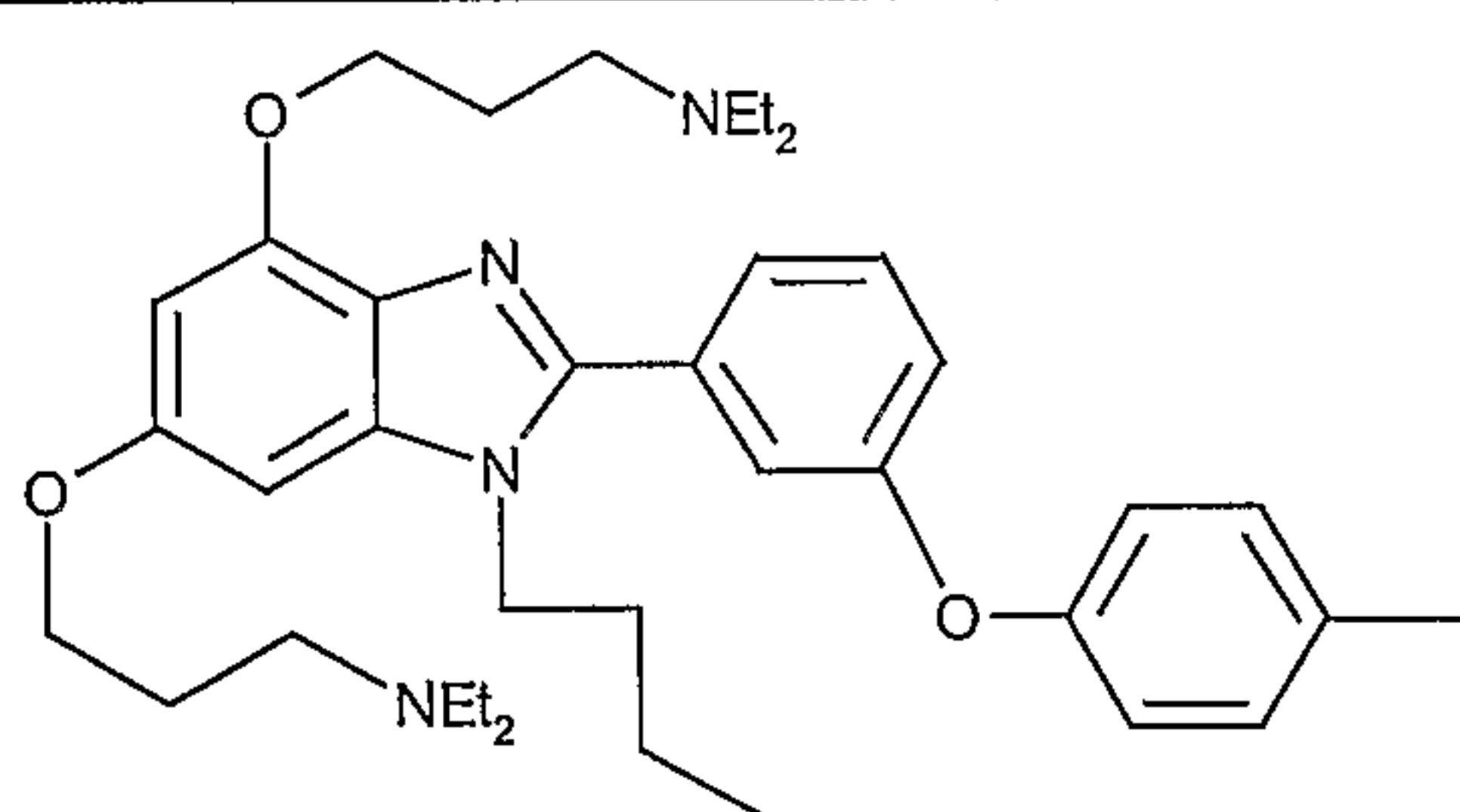
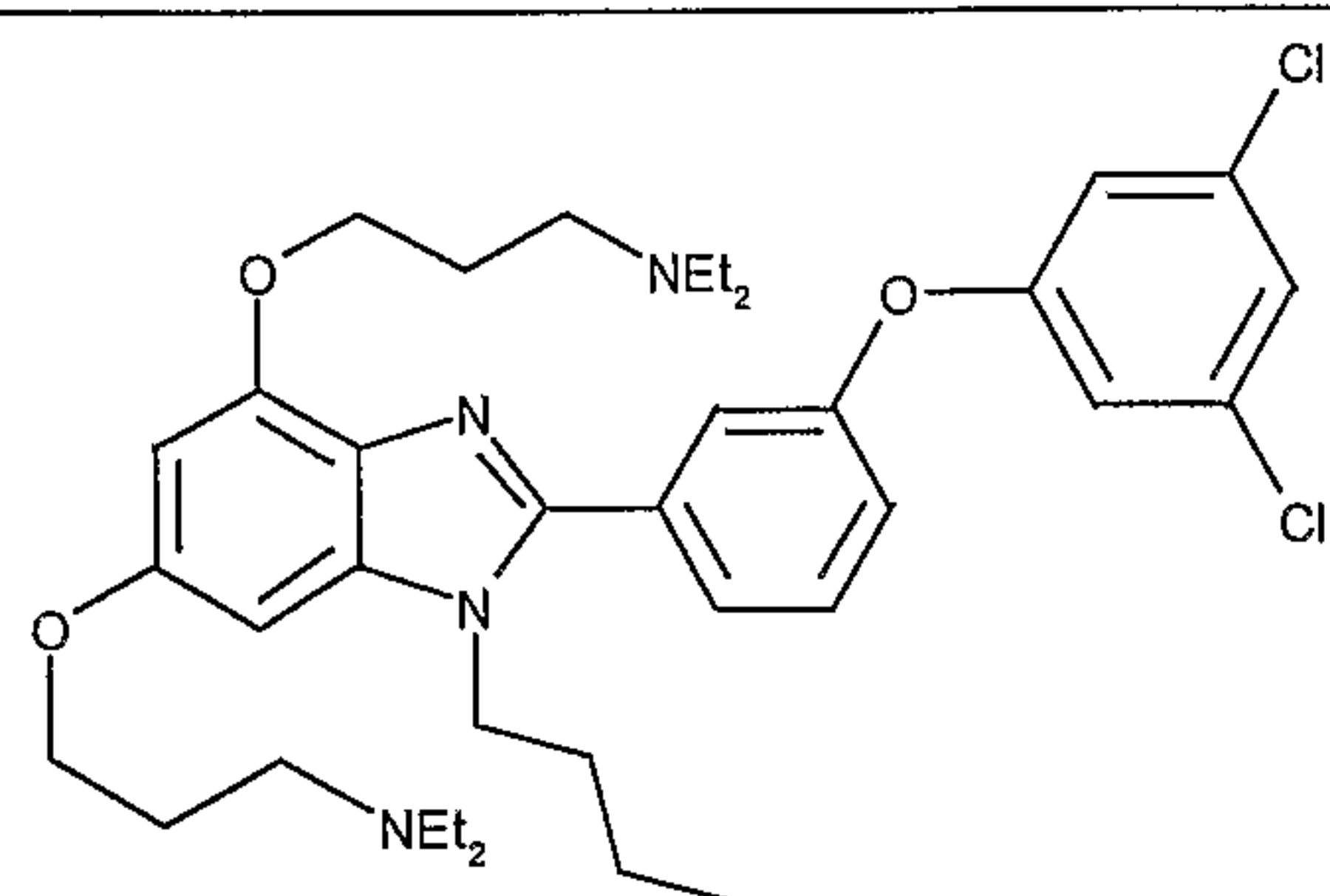
Ex.	Structure	Name
149		N'-[3-butyl-2-(2-{4-[2-(4-chlorophenyl)-ethoxy]-phenyl}-ethyl)-3H-benzimidazol-5-yl]-N,N-diethylpropane-1,3-diamine
150		1-butyl-2-[3-(2,4-dichlorophenoxy)-phenyl]-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
151		1-butyl-2-{4-[2-(4-chlorophenyl)-ethoxy]-phenyl}-6-(2-morpholin-4-yl-ethoxy)-1H-benzimidazole
152		1-butyl-6-(2-piperazin-1-yl-ethoxy)-2-[4-(4-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazole
153		2-[4-(biphenyl-4-yloxy)-phenyl]-1-butyl-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole

Ex.	Structure	Name
154		1-butyl-2-[3-(3,5-dichloro-phenoxy)-phenyl]-6-(2-morpholin-4-yl-ethoxy)-1H-benzimidazole
155		1-butyl-2-[3-(3,4-dimethoxy-phenoxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
156		1-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-5-(1H-imidazol-4-ylmethoxy)-1H-benzimidazole
157		{3-[2-(2-benzyloxy-phenyl)-3-butyl-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
158		{3-[1-Butyl-6-(3-diethylamino-propoxy)-2-piperidin-4-yl-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine

Ex.	Structure	Name
159		(2-{2-[2-(4-Benzyloxy-phenyl)-ethyl]-3-phenethyl-3H-benzoimidazol-5-yloxy}-ethyl)-diethyl-amine
160		[3-(3-Butyl-2-{3-[4-(4-fluorobenzyloxy)-phenyl]-propyl}-3H-benzoimidazol-5-yloxy)-propyl]-diethyl-amine
161		[3-(4-Benzyloxy-phenyl)-propyl]-[1-butyl-6-(3-diethylamino-propoxy)-1H-benzoimidazol-2-yl]-amine
162		{3-[3-Butyl-2-(3-{4-[2-(4-chlorophenyl)-ethoxy]-phenyl}-propyl)-3H-benzoimidazol-5-yloxy]-propyl}-diethyl-amine
163		1-Butyl-2-[3-(3,5-dichloro-phenoxy)-phenyl]-6-(2-imidazol-1-yl-ethoxy)-1H-benzimidazole
164		1-[4-(2-{3-Butyl-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-3H-benzoimidazol-5-yloxy}-ethyl)-piperazin-1-yl]-ethanone

Ex.	Structure	Name
165		N-[3-Butyl-2-(2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-ethyl)-3H-benzimidazol-5-yl]-N-(3-diethylamino-propyl)-N',N'-diethyl-propane-1,3-diamine
166		{3-[1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yl]-propyl}-diethyl-amine
167		{3-[1-Butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
168		{3-[2-(2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-ethyl)-6-(3-diethylamino-propoxy)-3H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
169		{3-[1-Butyl-2-[4-(4-chloro-3-trifluoromethyl-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine

Ex.	Structure	Name
170		(3-{1-Butyl-6-(3-diethylamino-propoxy)-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-benzoimidazol-4-yloxy}-propyl)-diethyl-amine
171		{3-[2-[3-(3,5-Dichloro-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
172		1-Butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
173		{3-[2-[3-(3,4-Dichloro-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
174		(3-{6-(3-diethylamino-propoxy)-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine

Ex.	Structure	Name
175		{3-[1-Butyl-2-[3-(3,4-dichloro-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
176		{3-[2-[3-(4-Chloro-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
177		{3-[1-Butyl-2-[3-(4-chloro-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
178		{3-[1-Butyl-6-(3-diethylamino-propoxy)-2-(3-p-tolyloxy-phenyl)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
179		{3-[1-Butyl-2-[3-(3,5-dichloro-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine

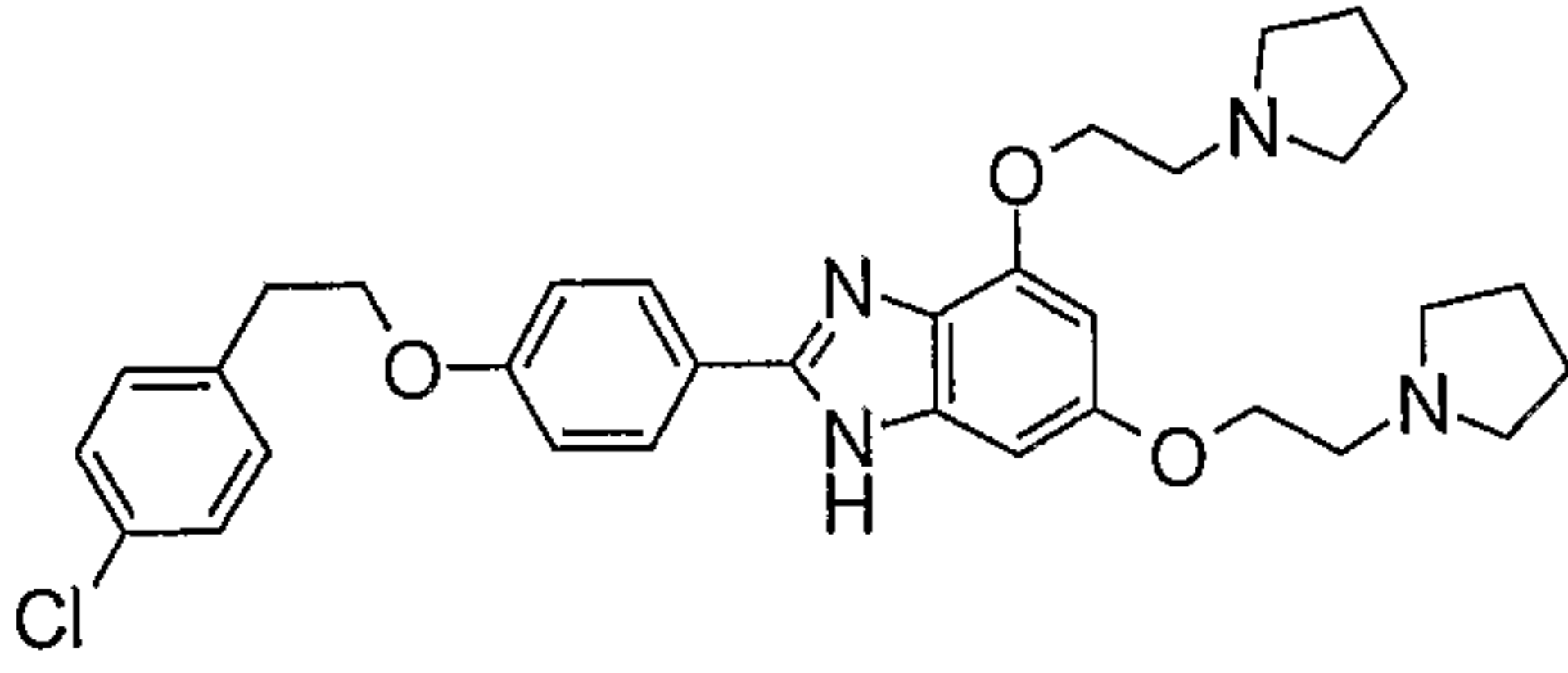
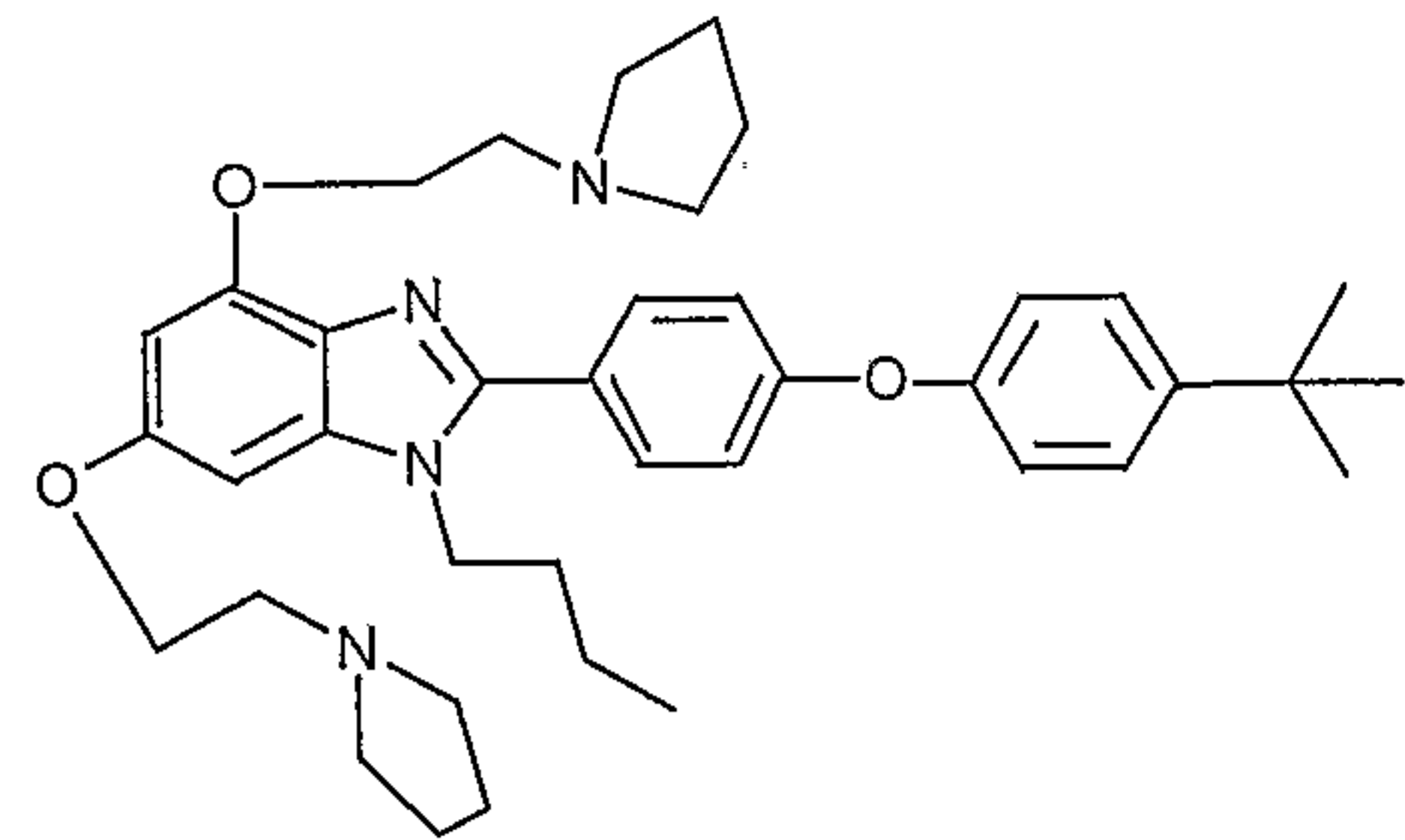
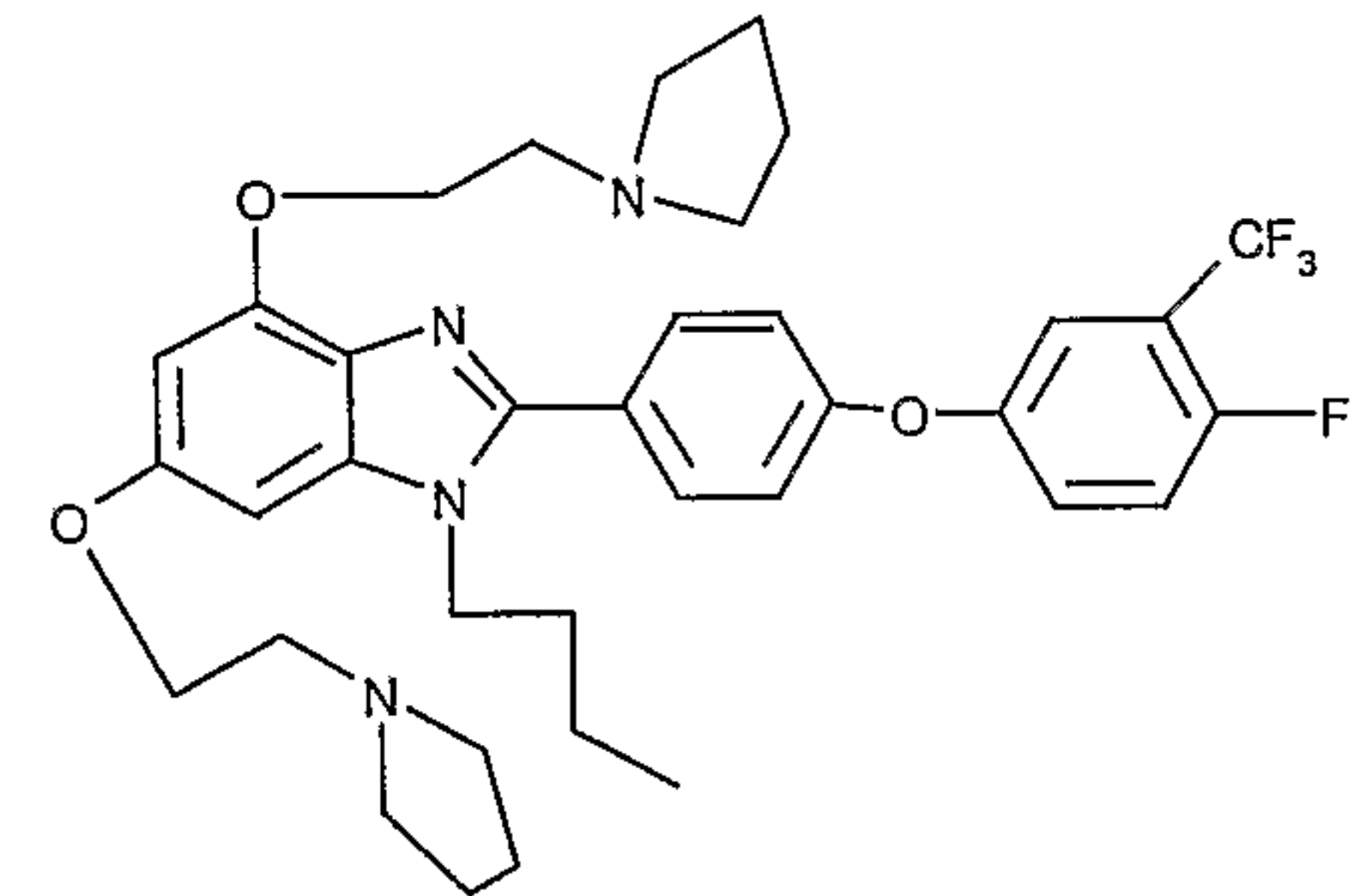
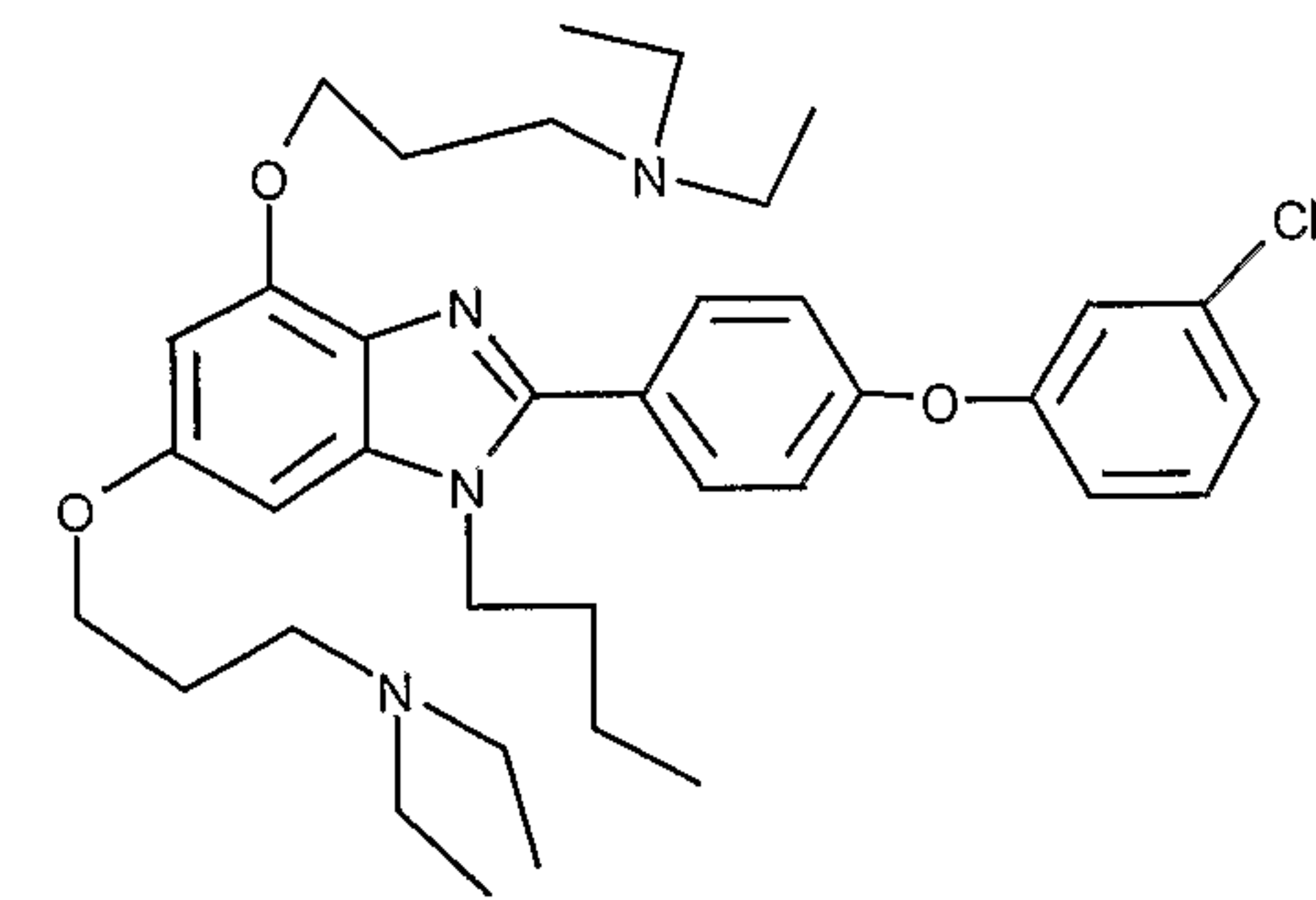
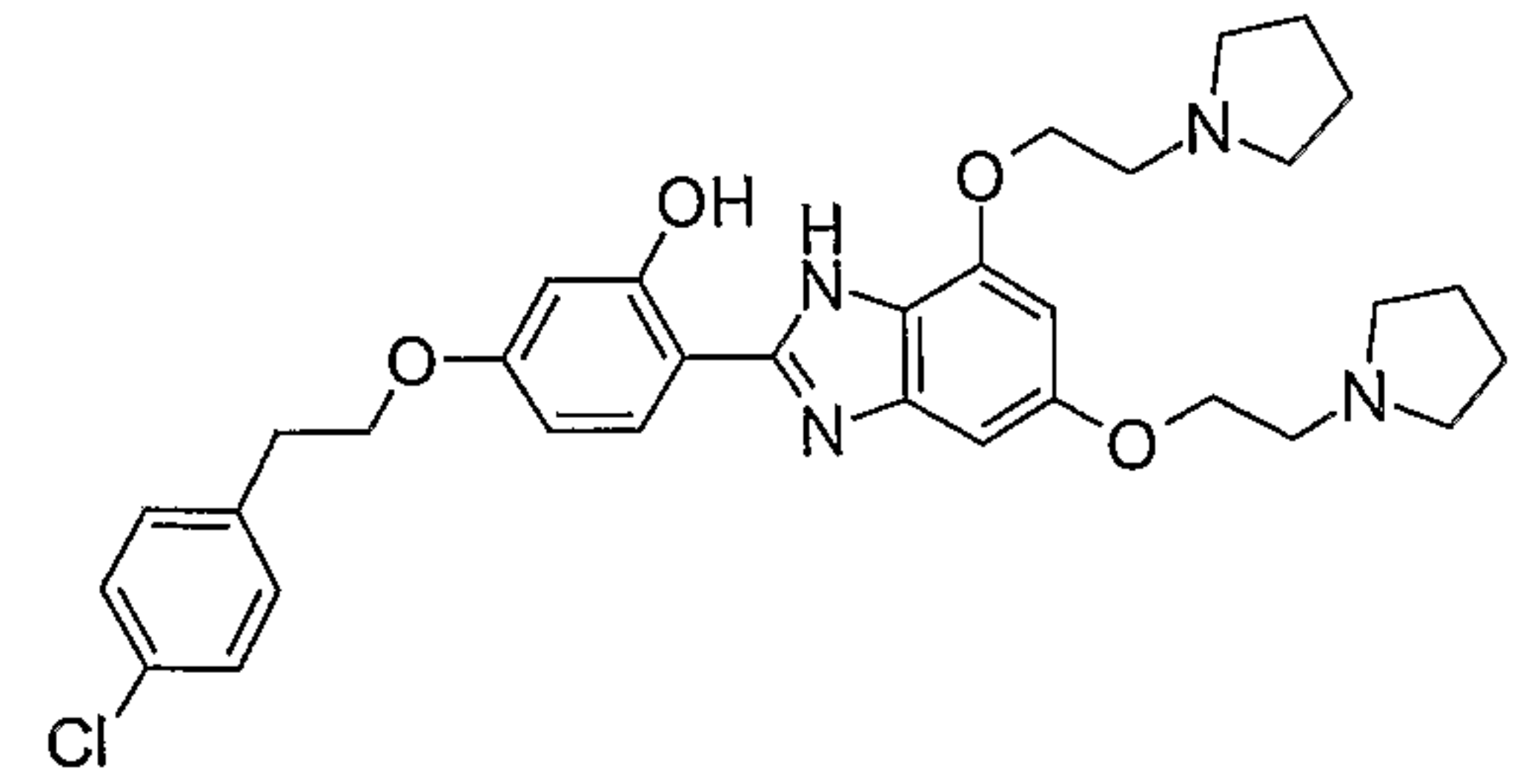
Ex.	Structure	Name
180		1-Butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
181		{3-[3-Butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-7-(2-pyrrolidin-1-yl-ethoxy)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
182		(3-{1-butyl-6-(3-diethylamino-propoxy)-2-[4-(3-fluoro-phenoxy)-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine
183		{3-[2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(3-diethylamino-propoxy)-1-isopropyl-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
184		{3-[1-Butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine

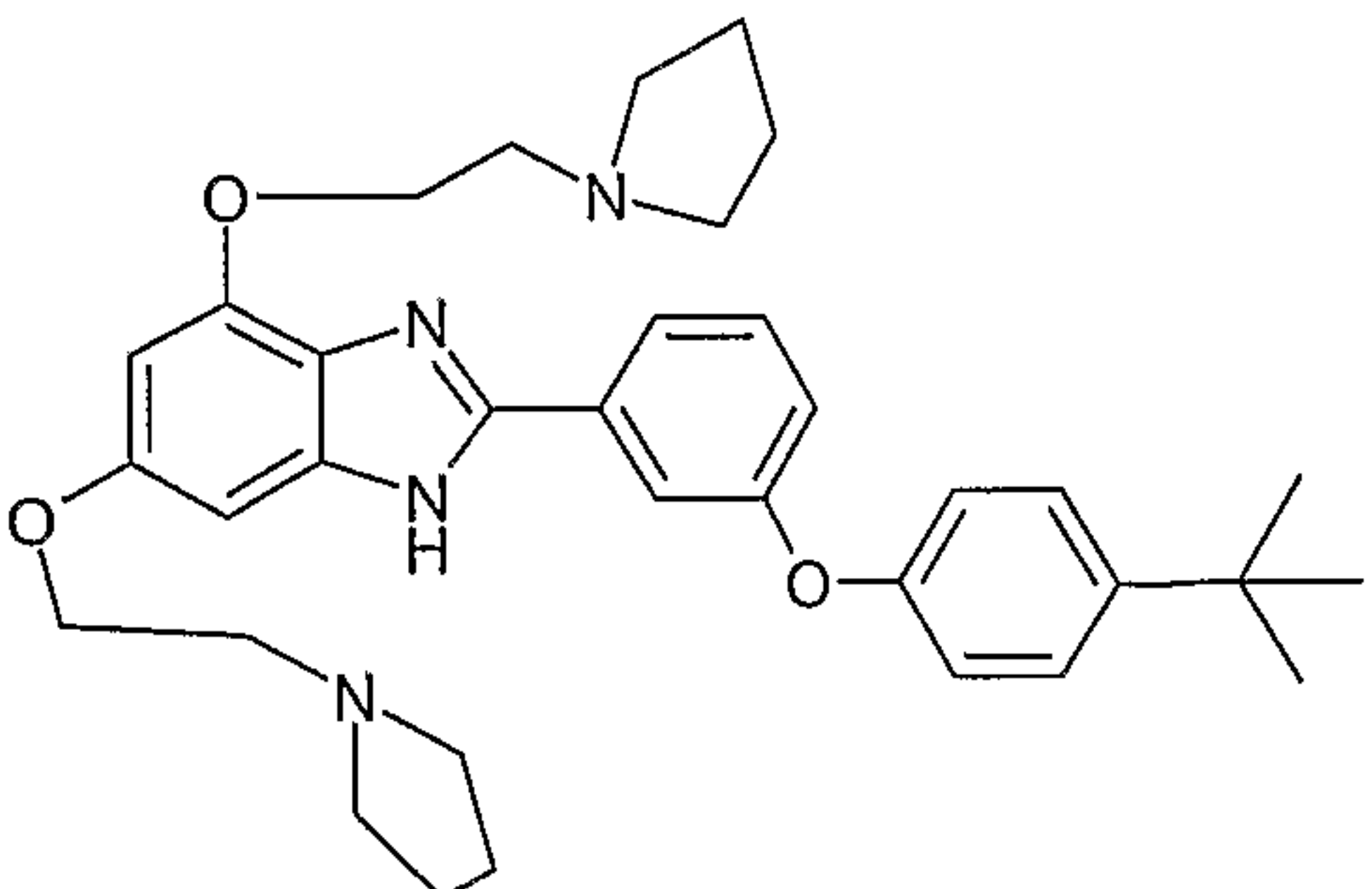
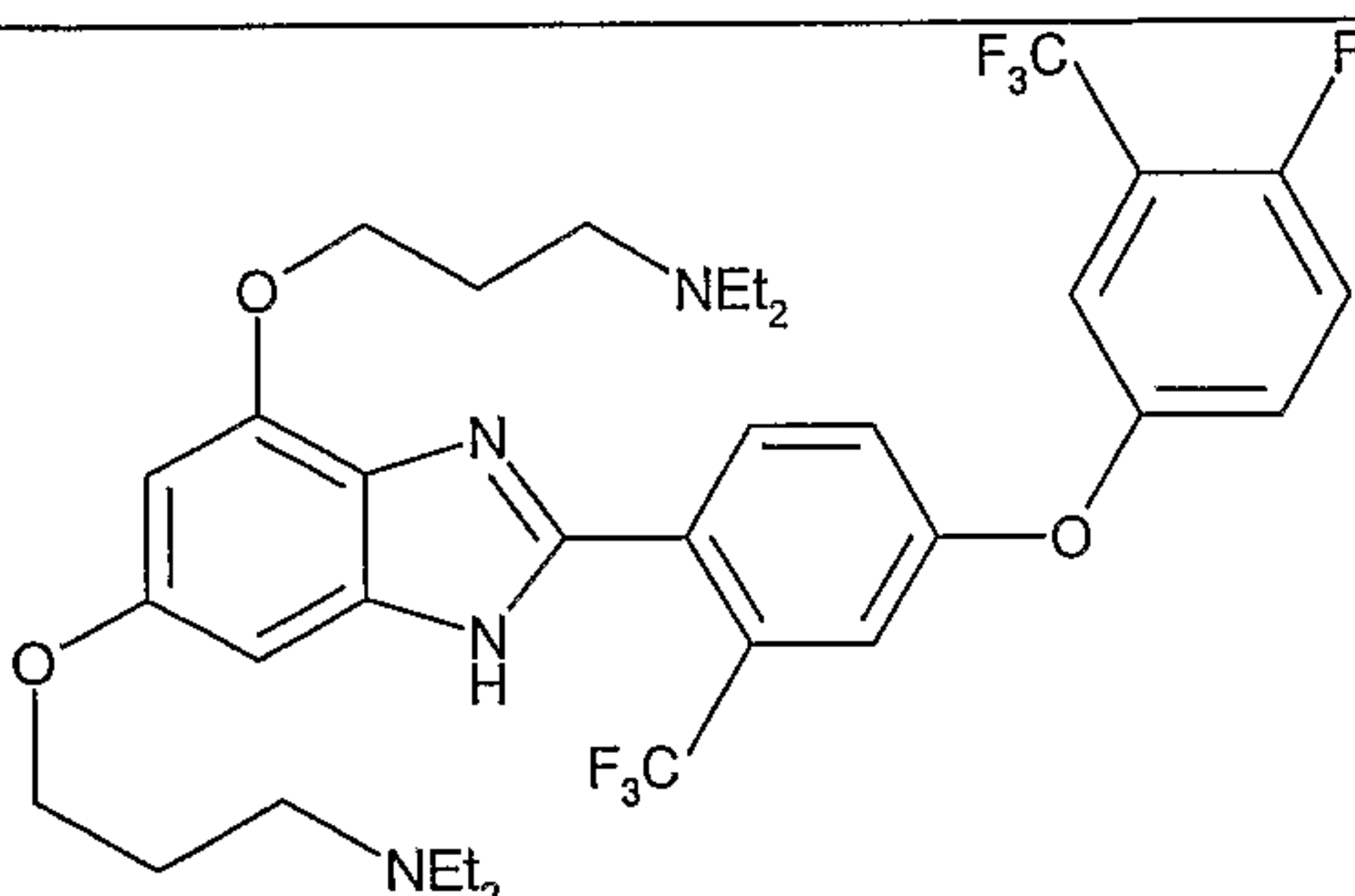
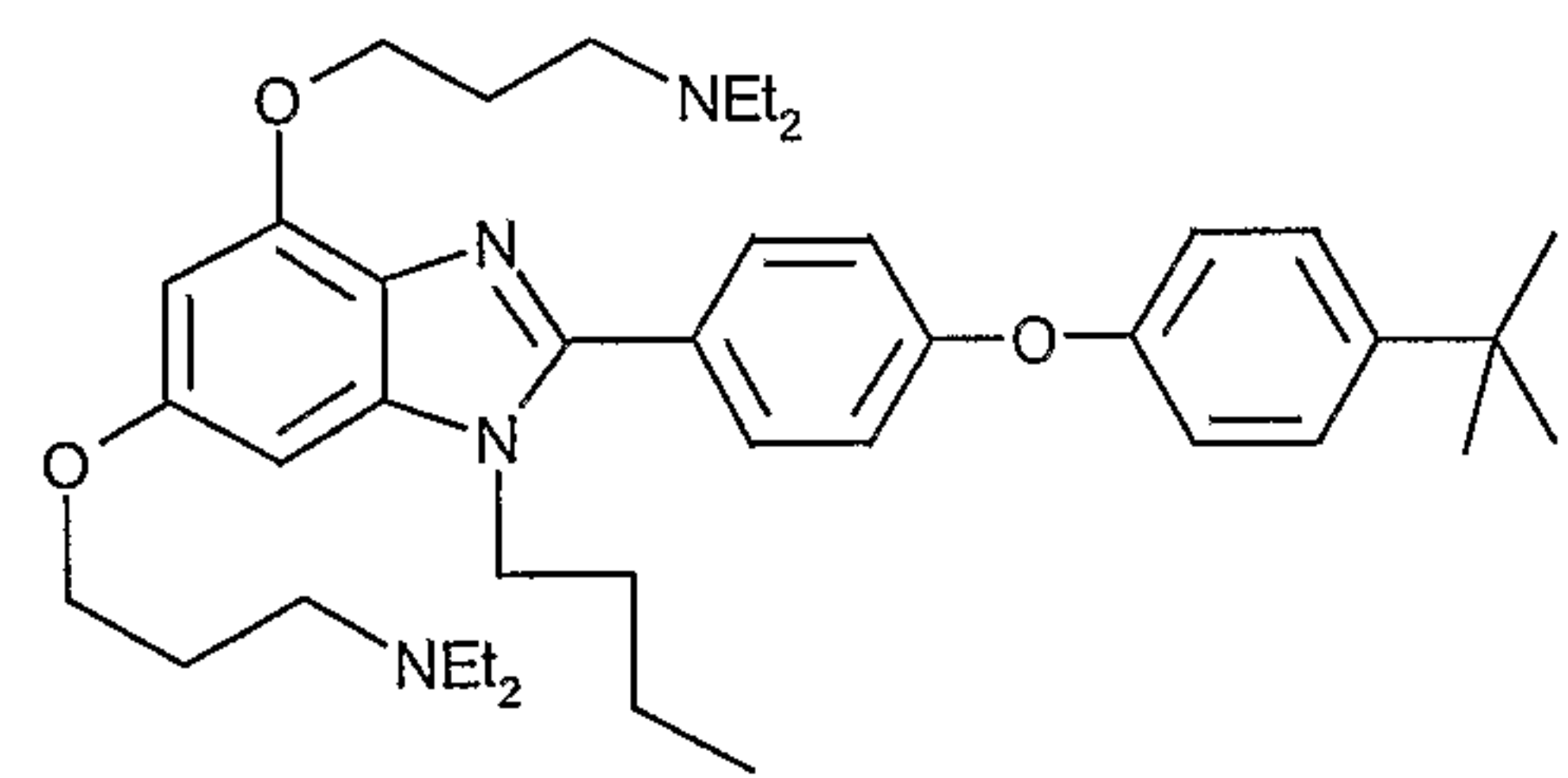
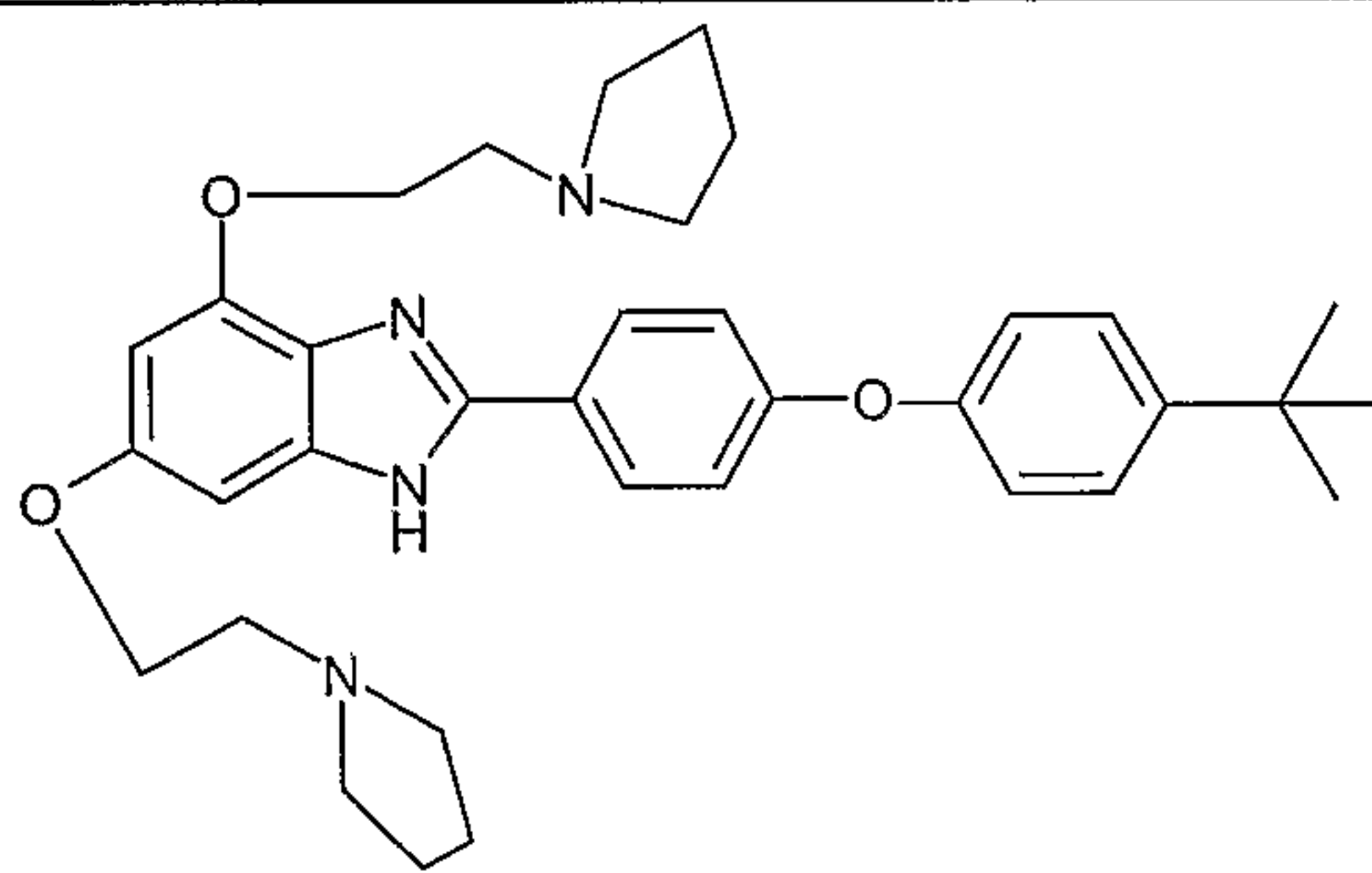
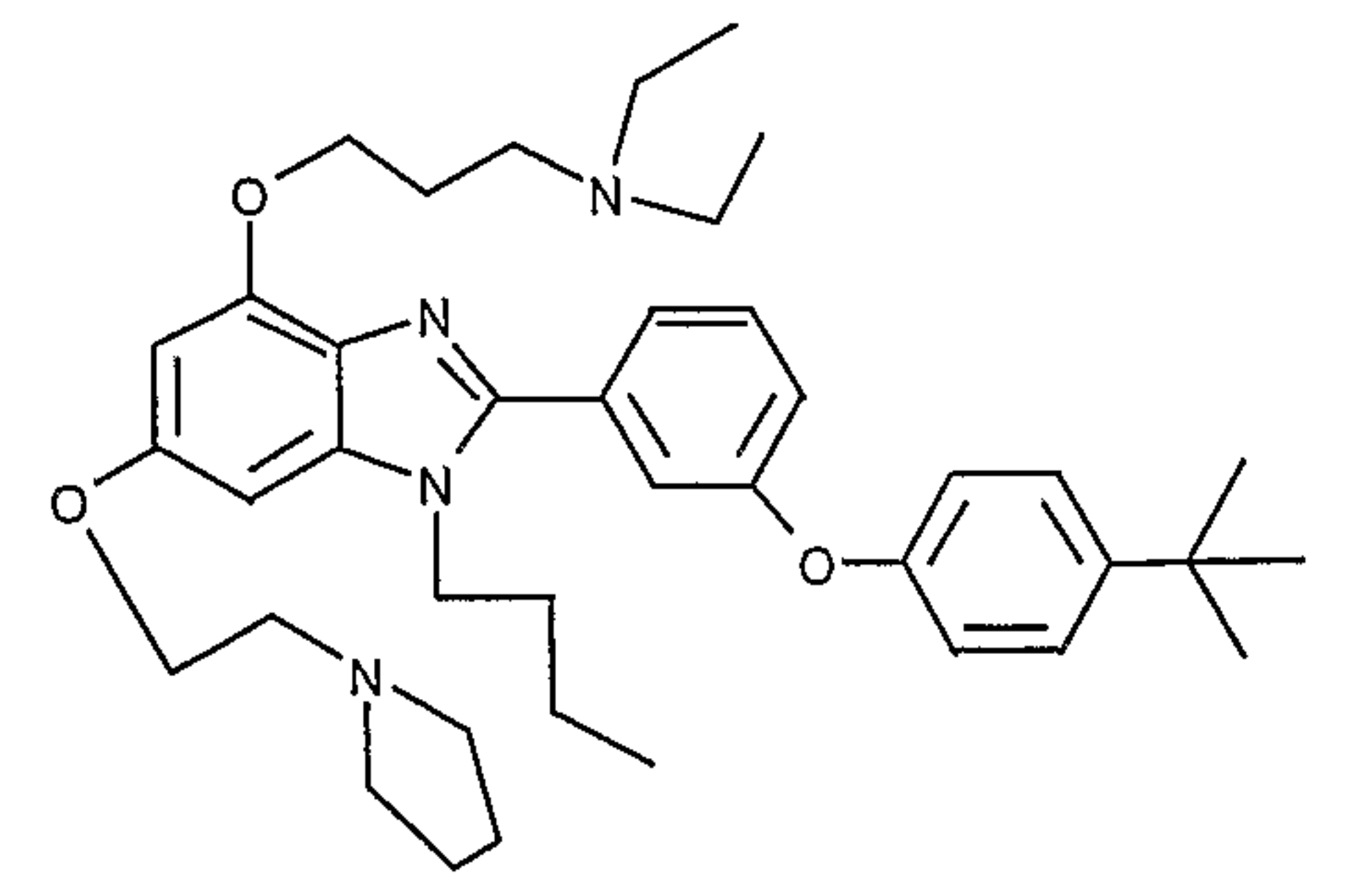
Ex.	Structure	Name
185		2-{4-[1-butyl-4,6-bis-(3-diethylamino-propoxy)-1H-benzimidazol-2-yl-phenoxy]-benzoic acid methyl ester
186		{3-[2-[4-(biphenyl-4-yloxy)-phenyl]-1-butyl-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
187		{3-[2-[4-(3,5-Bis-trifluoromethyl-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
188		{3-[1-butyl-2-[4-(4-chloro-benzylsulfanyl)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
189		{3-[2-[4-[2-(4-chloro-phenyl)-ethoxy]-phenyl]-6-(3-diethylamino-propoxy)-3H-benzimidazol-4-yloxy]-propyl}-diethyl-amine

Ex.	Structure	Name
190		(3-{1-butyl-6-(3-diethylamino-propoxy)-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine
191		[3-(1-butyl-6-(3-diethylamino-propoxy)-2-{4-[2-(4-fluoro-phenyl)-ethoxy]-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine
192		(3-{1-butyl-6-(3-diethylamino-propoxy)-2-[4-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine
193		{3-[2-[3-(4-tert-Butyl-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
194		(3-{1-Butyl-6-(3-diethylamino-propoxy)-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-2-trifluoromethyl-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine

Ex.	Structure	Name
195		{3-[1-Butyl-2-[4-chloro-2-(4-chloro-3-trifluoromethyl-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
196		2-[3-(4-Chloro-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
197		1-Butyl-2-[3-(4-chloro-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
198		{3-[3-butyl-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-7-(2-pyrrolidin-1-yl-ethoxy)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine

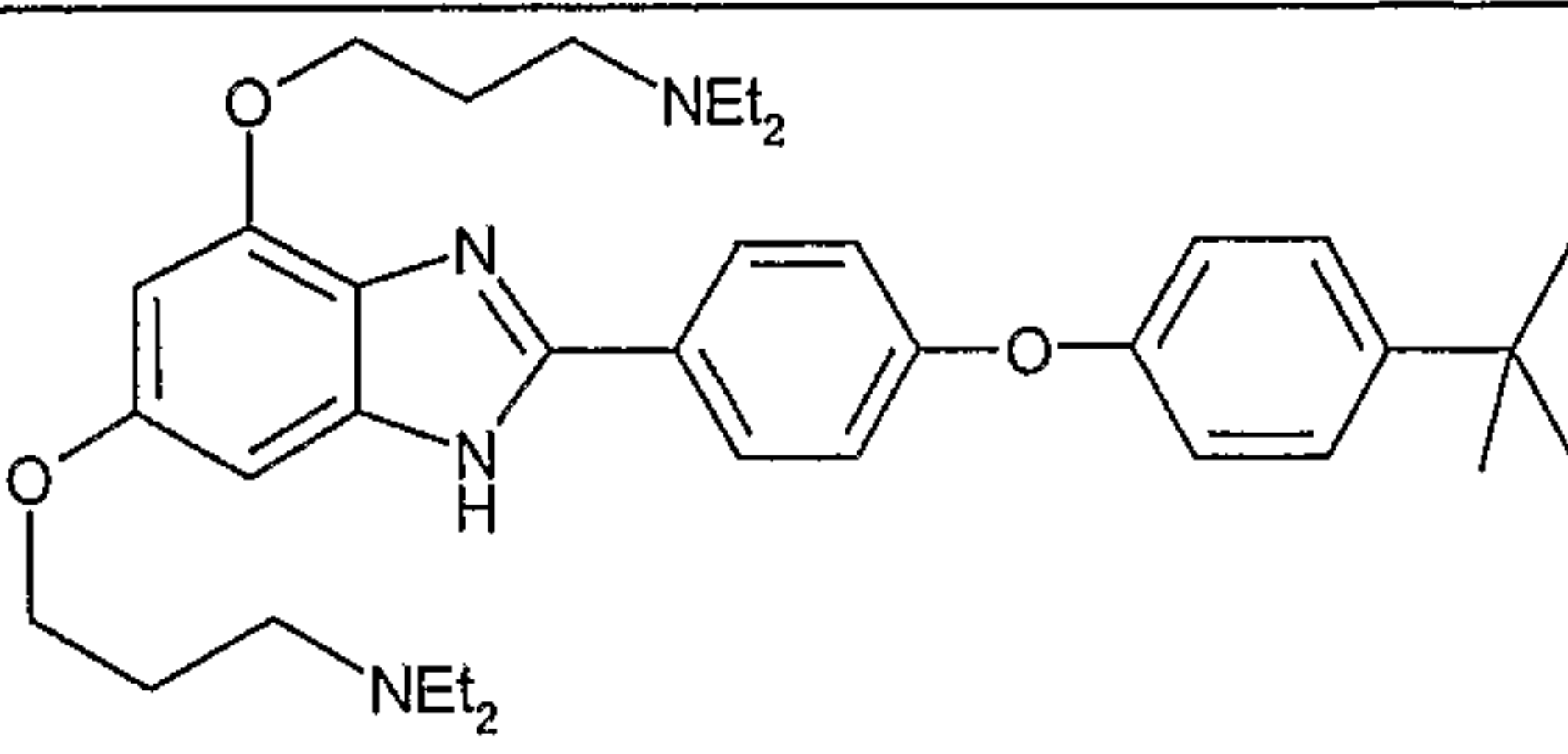
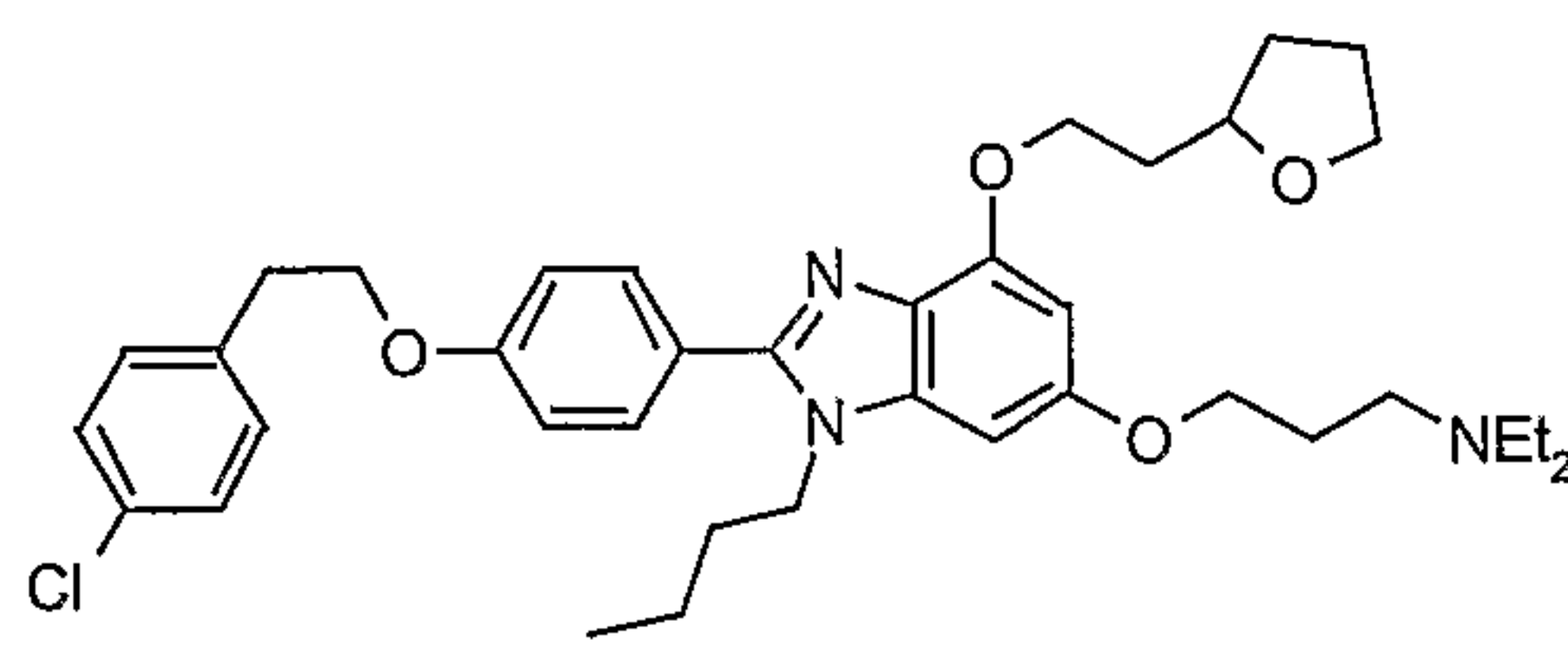
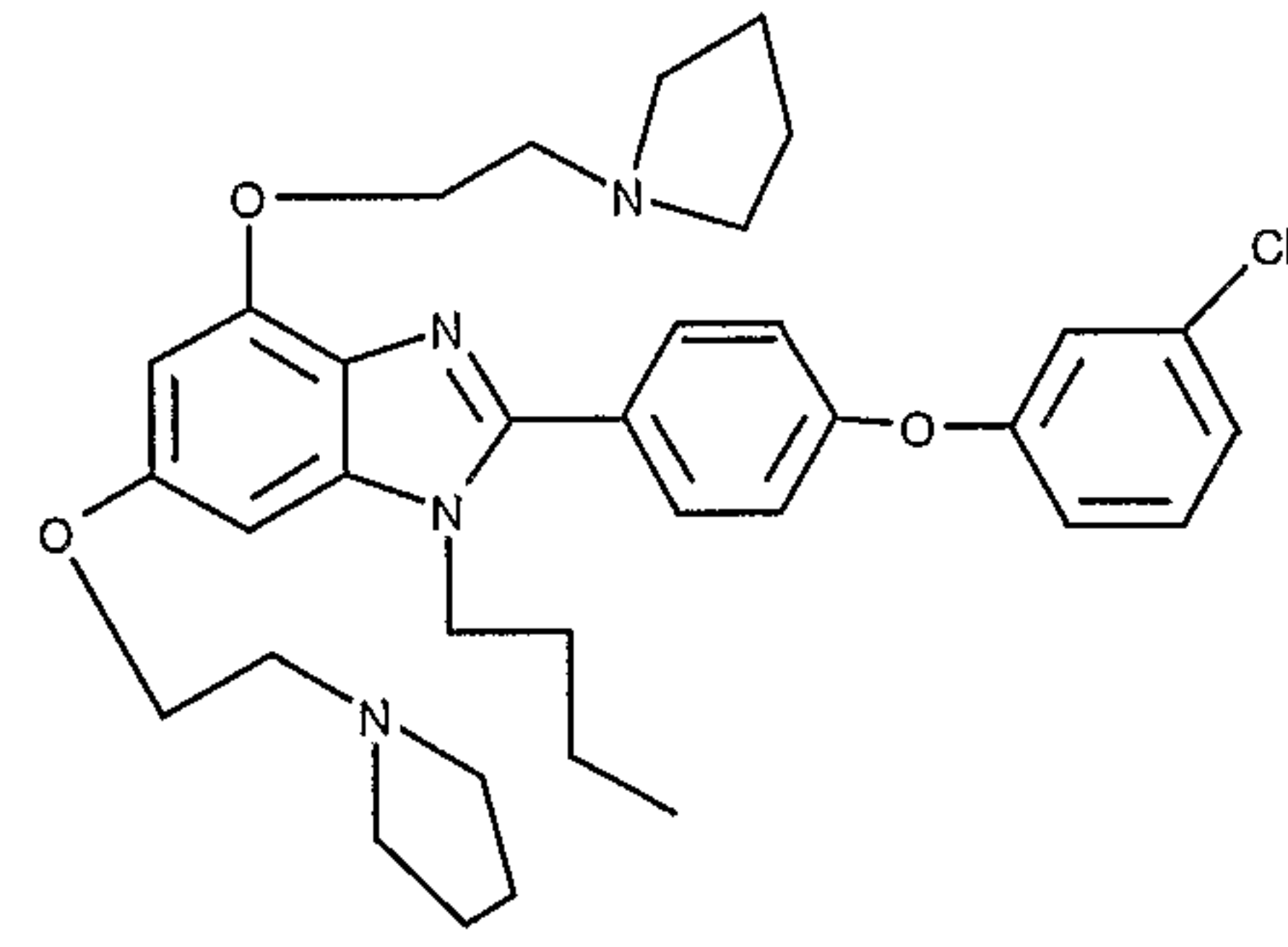
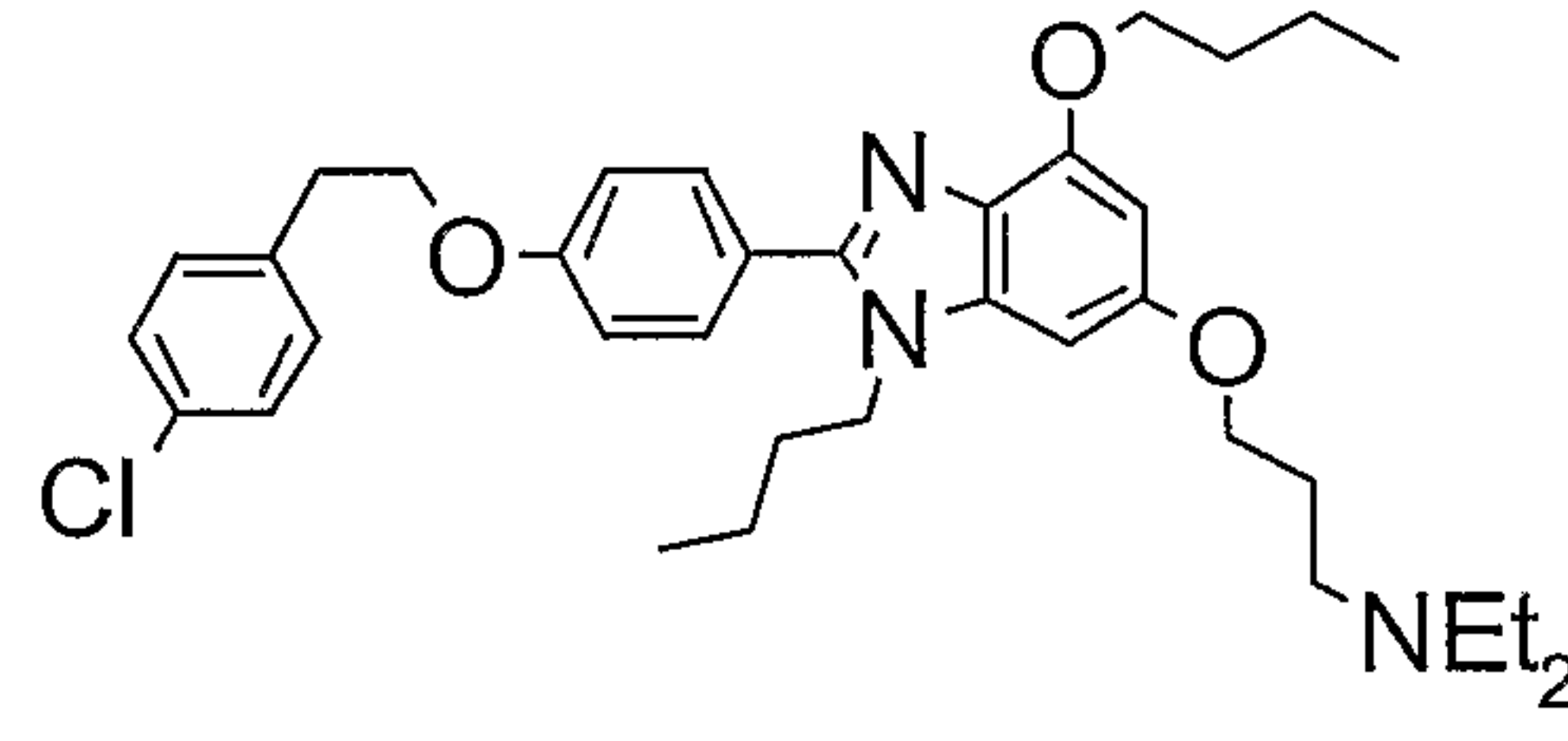
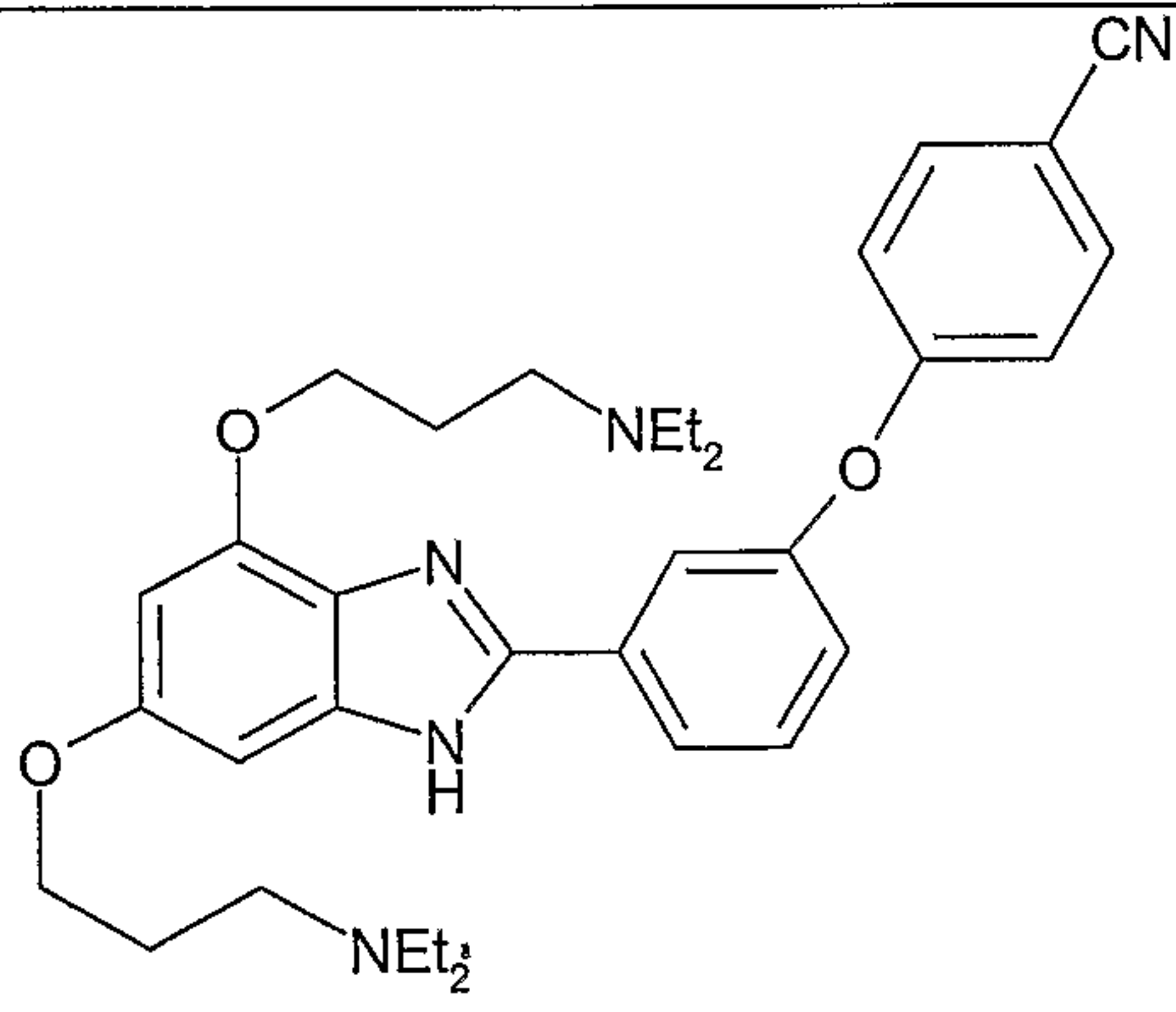
Ex.	Structure	Name
199		{2-[1-butyl-2-[3-(4-tert-butylphenoxy)-phenyl]-6-(2-diisopropylamino-ethoxy)-1H-benzimidazol-4-yloxy]-ethyl}-diethyl-amine
200		{3-[2-[4-(3,5-Bis-trifluoromethyl-phenoxy)-phenyl]-1-butyl-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
201		{3-[2-[4-(3,5-Bis-trifluoromethyl-phenoxy)-phenyl]-1-butyl-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
202		(3-{1-butyl-6-(3-diethylamino-propoxy)-2-[4-(4-methoxy-phenoxy)-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine
203		1-Butyl-2-[4-(4-chloro-3-trifluoromethyl-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole

Ex.	Structure	Name
204		2-{4-[2-(4-Chloro-phenyl)-ethoxy]-phenyl}-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
205		1-Butyl-2-[4-(4-tert-butyl-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
206		1-Butyl-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
207		{3-[1-Butyl-2-[4-(3-chloro-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
208		2-[5,7-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazol-2-yl]-5-[2-(4-chloro-phenyl)-ethoxy]-phenol

Ex.	Structure	Name
209		2-[3-(4-tert-butyl-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
210		(3-{6-(3-Diethylamino-propoxy)-2-[2-(1,1-difluoro-ethyl)-4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-benzoimidazol-4-yloxy}-propyl)-diethyl-amine
211		{3-[1-Butyl-2-[4-(4-tert-butyl-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
212		2-[4-(4-tert-Butyl-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole
213		{3-[1-Butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine

Ex.	Structure	Name
214		[3-(3-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-diethylaminomethyl-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
215		(3-{6-(3-Diethylamino-propoxy)-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-benzoimidazol-4-yloxy}-propyl)-diethyl-amine
216		(3-{1-butyl-6-(3-diethylamino-propoxy)-2-[4-(4-trifluoromethyl-pyrimidin-2-ylsulfanyl)-phenyl]-1H-benzoimidazol-4-yloxy}-propyl)-diethyl-amine
217		{3-[6-(3-Diethylamino-propoxy)-2-(3-p-tolyloxy-phenyl)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
218		4-{3-[1-Butyl-4,6-bis-(3-diethylamino-propoxy)-1H-benzoimidazol-2-yl]-phenoxy}-benzonitrile
219		[3-(3-Butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-7-pyrrolidin-1-yl-3H-benzoimidazol-5-yloxy)-propyl]-diethyl-amine

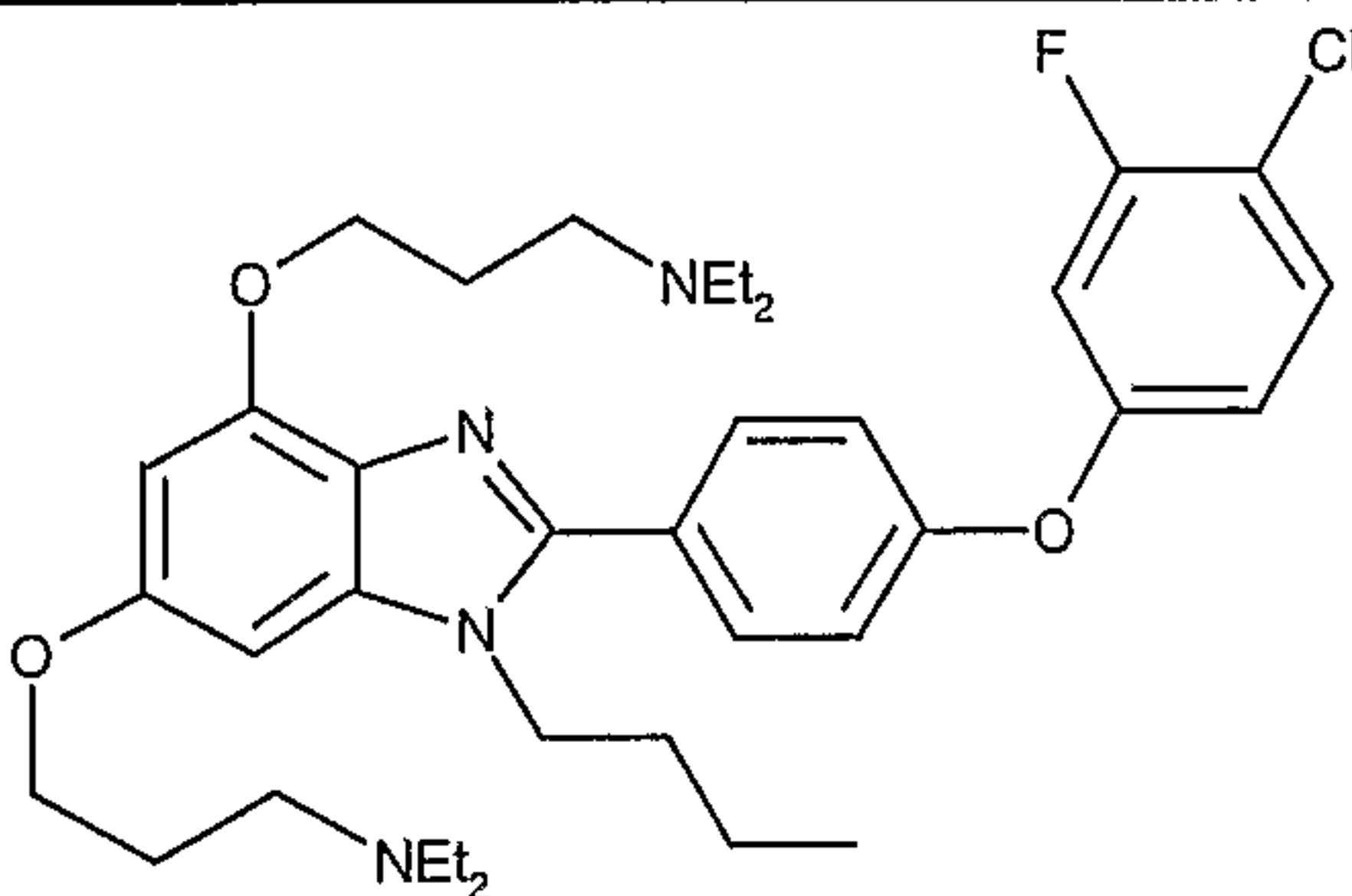
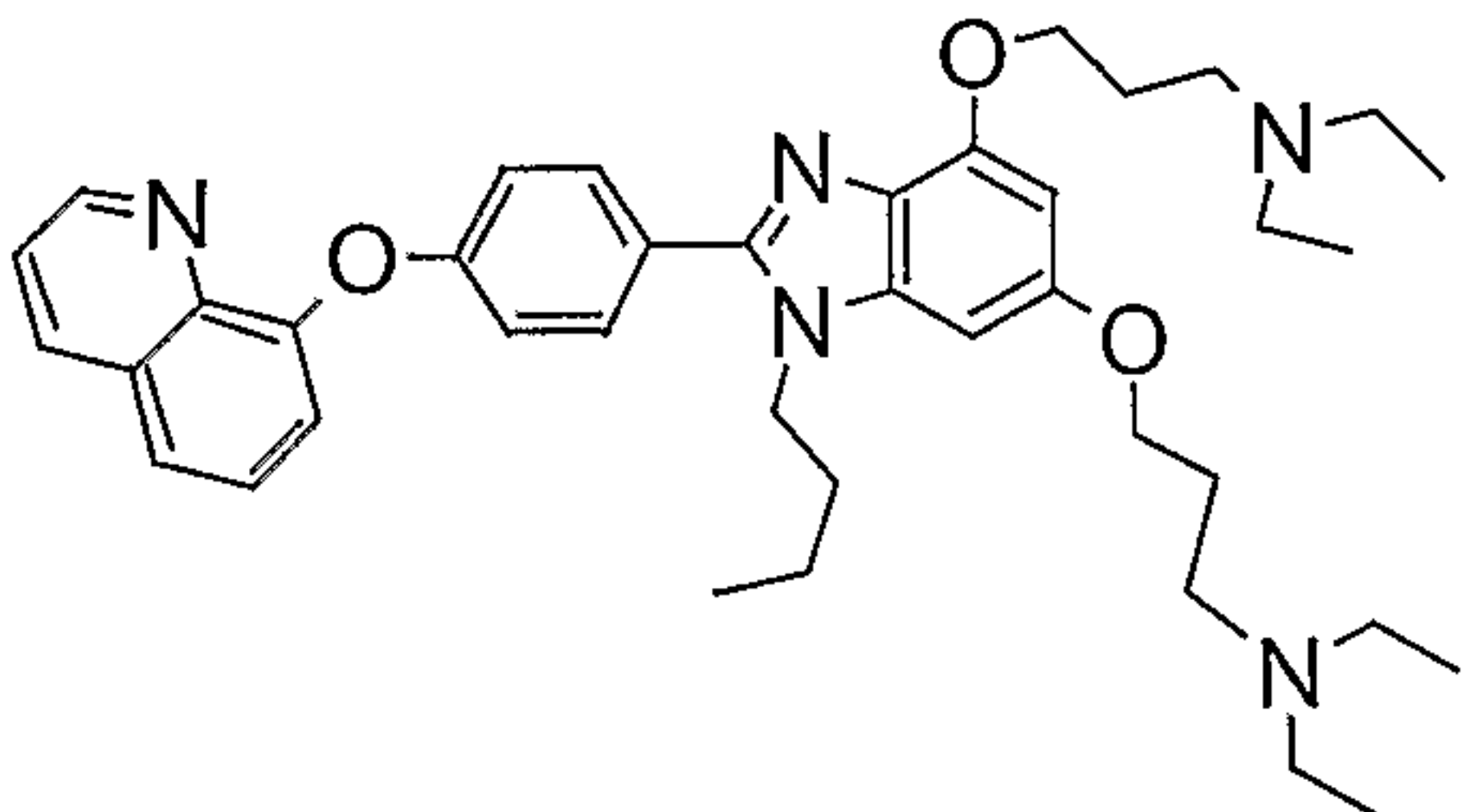
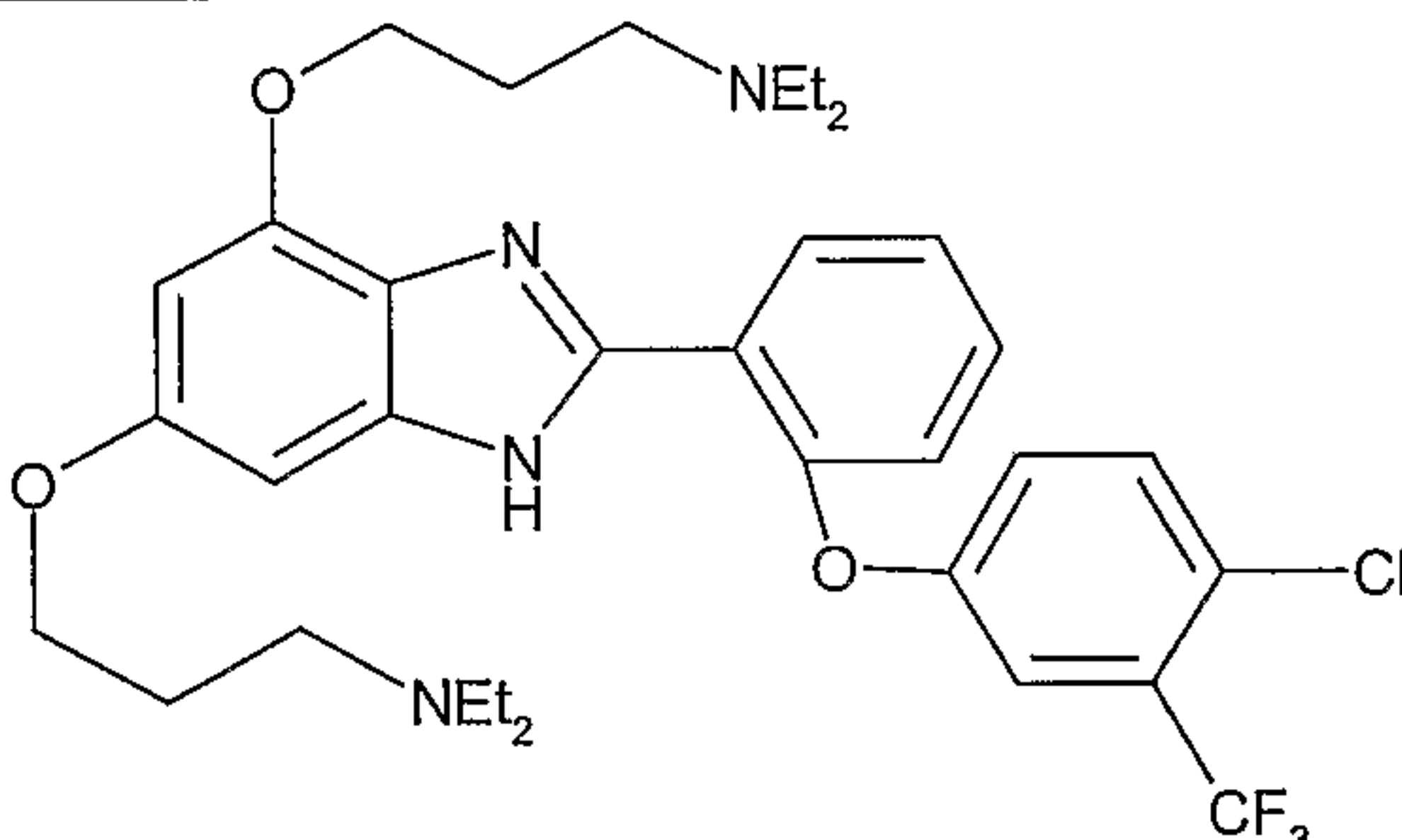
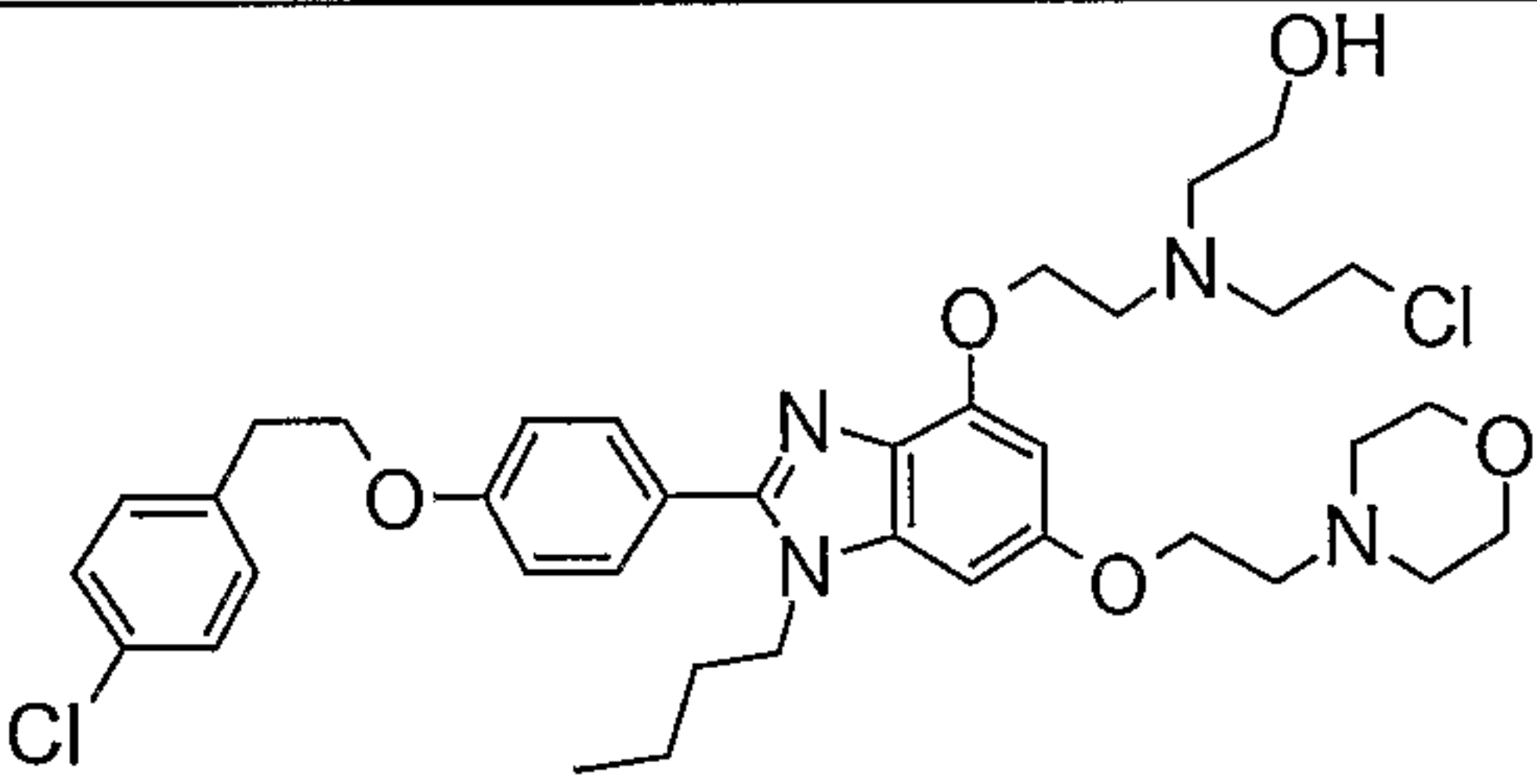
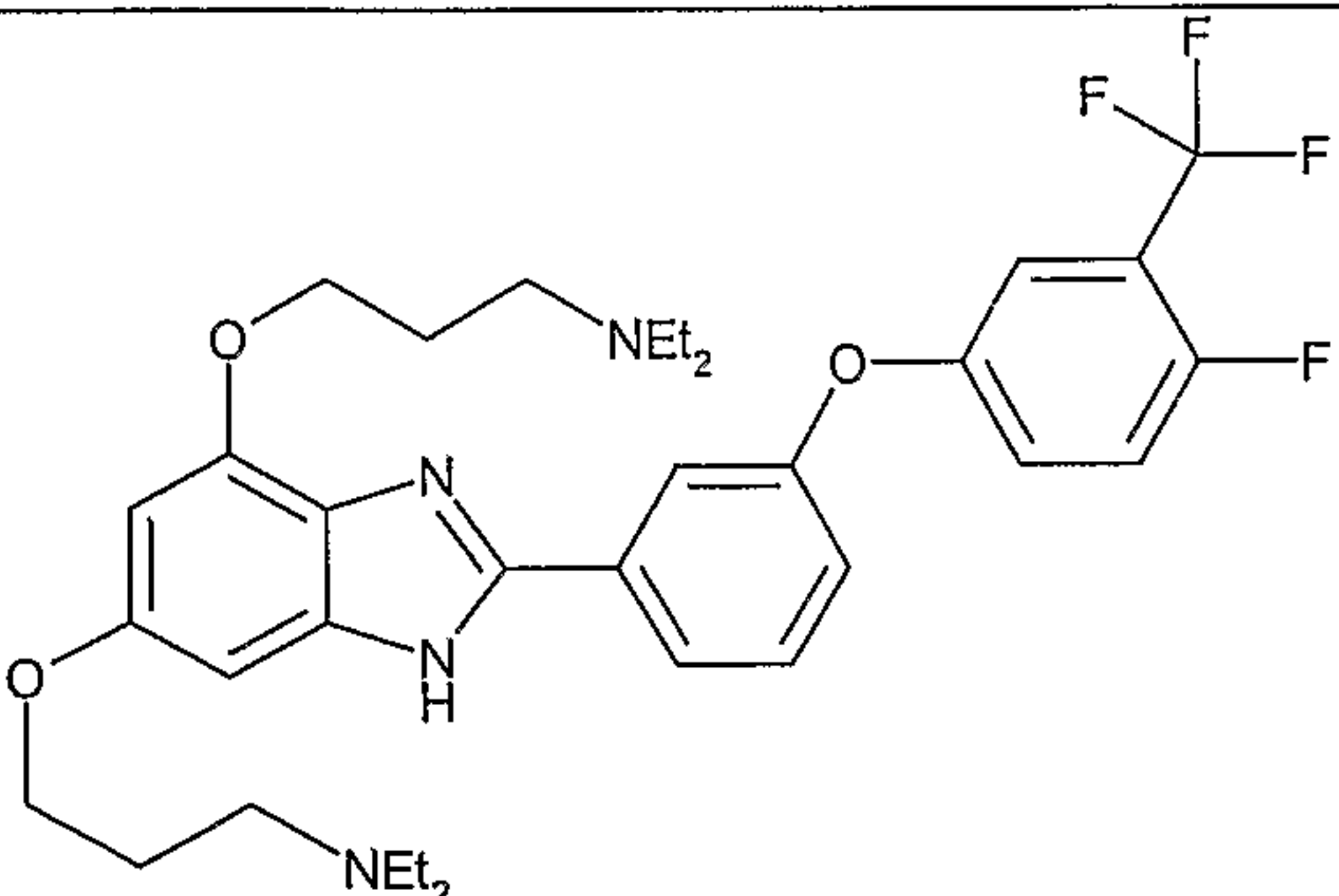
Ex.	Structure	Name
220		{3-[1-butyl-2-[4-(4-chloro-phenylmethanesulfinyl)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
221		(3-{1-butyl-6-(3-diethylamino-propoxy)-2-[4-(naphthalen-2-yloxy)-phenyl]-1H-benzimidazole-4-yloxy}-propyl)-diethyl-amine
222		(3-{6-(3-diethylamino-propoxy)-2-[4-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine
223		(3-{1-butyl-6-(3-diethylamino-propoxy)-2-[3-(4-methoxy-phenoxy)-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine
224		2-[3-(3,4-Dichloro-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole

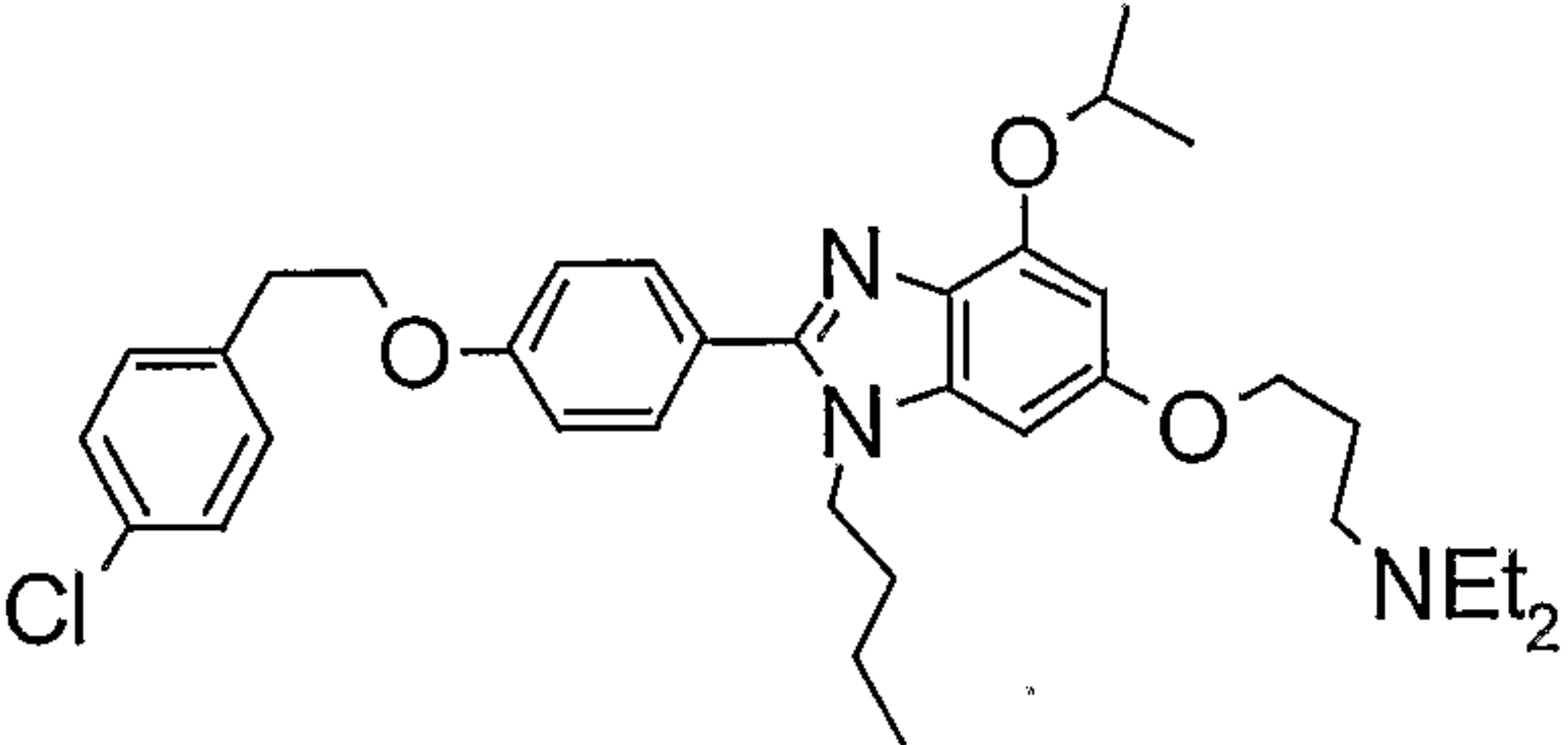
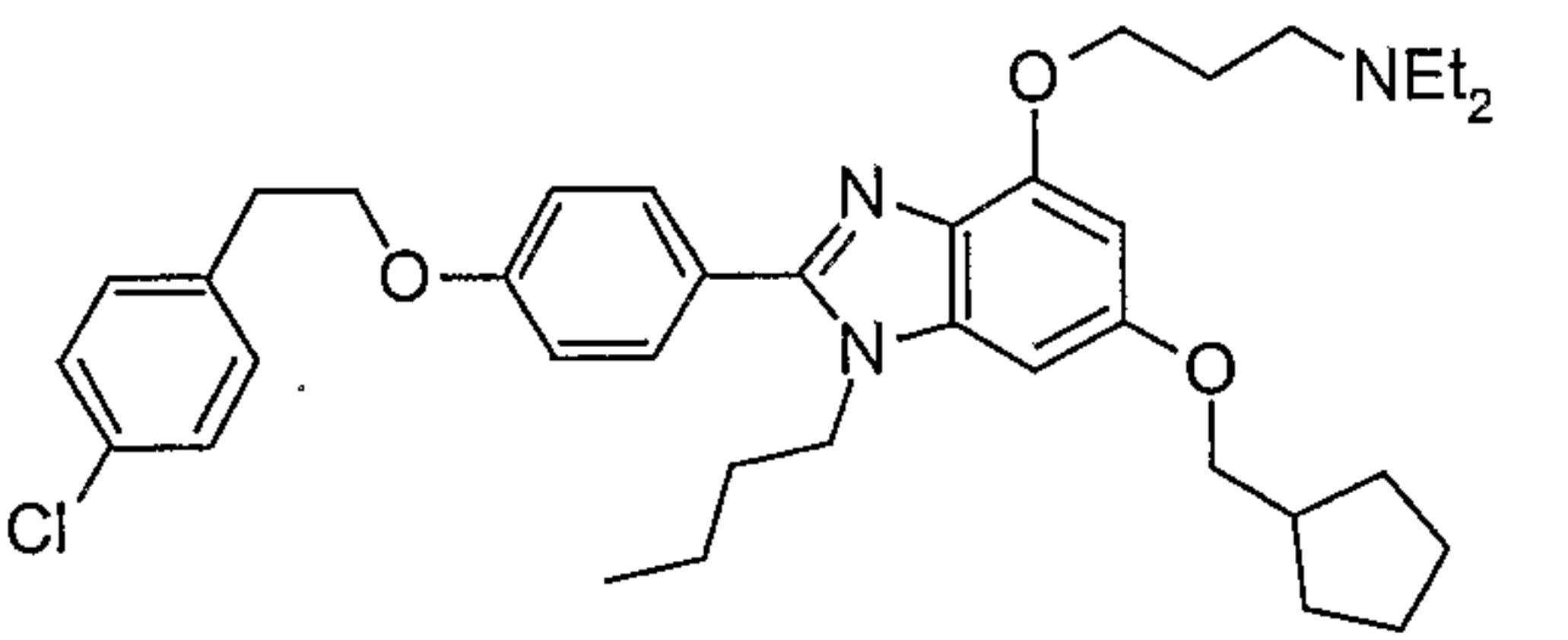
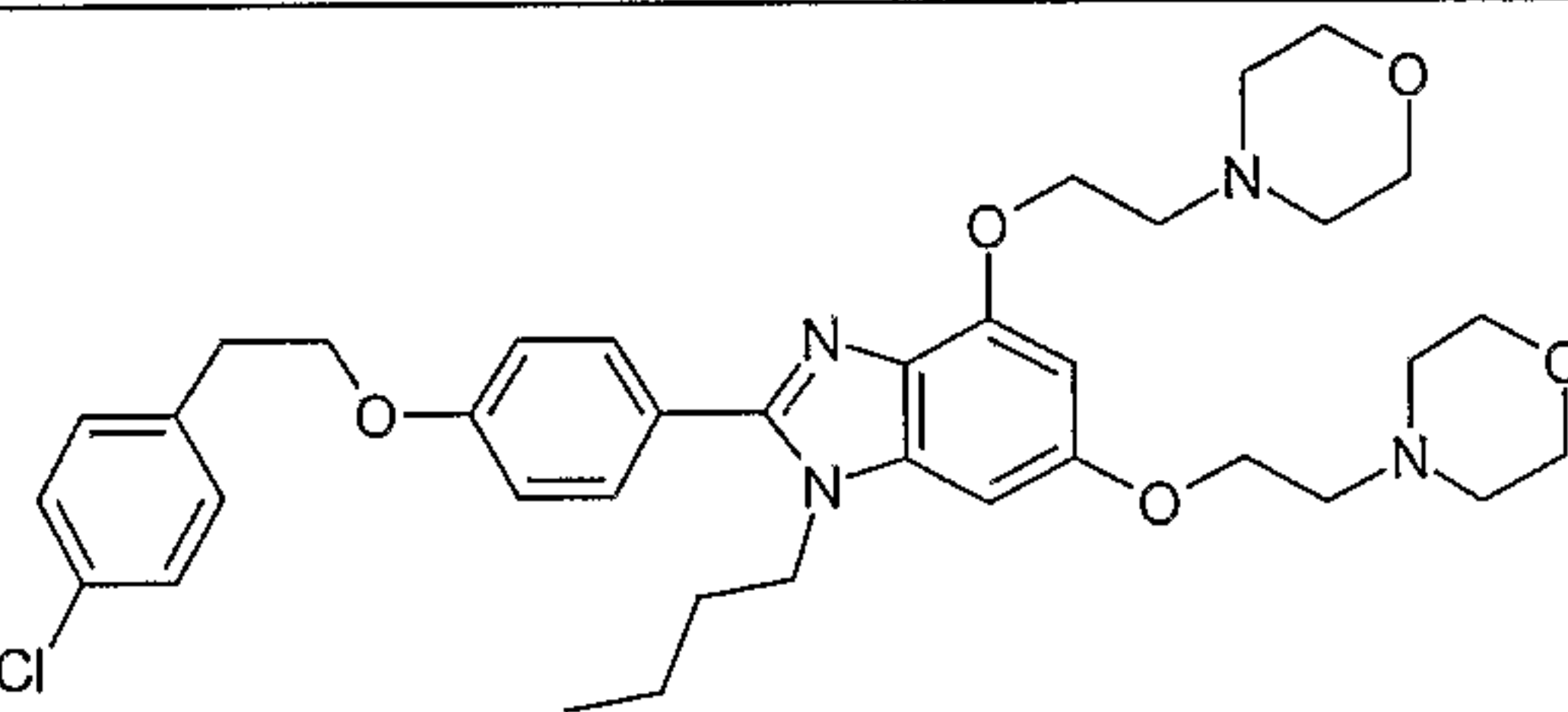
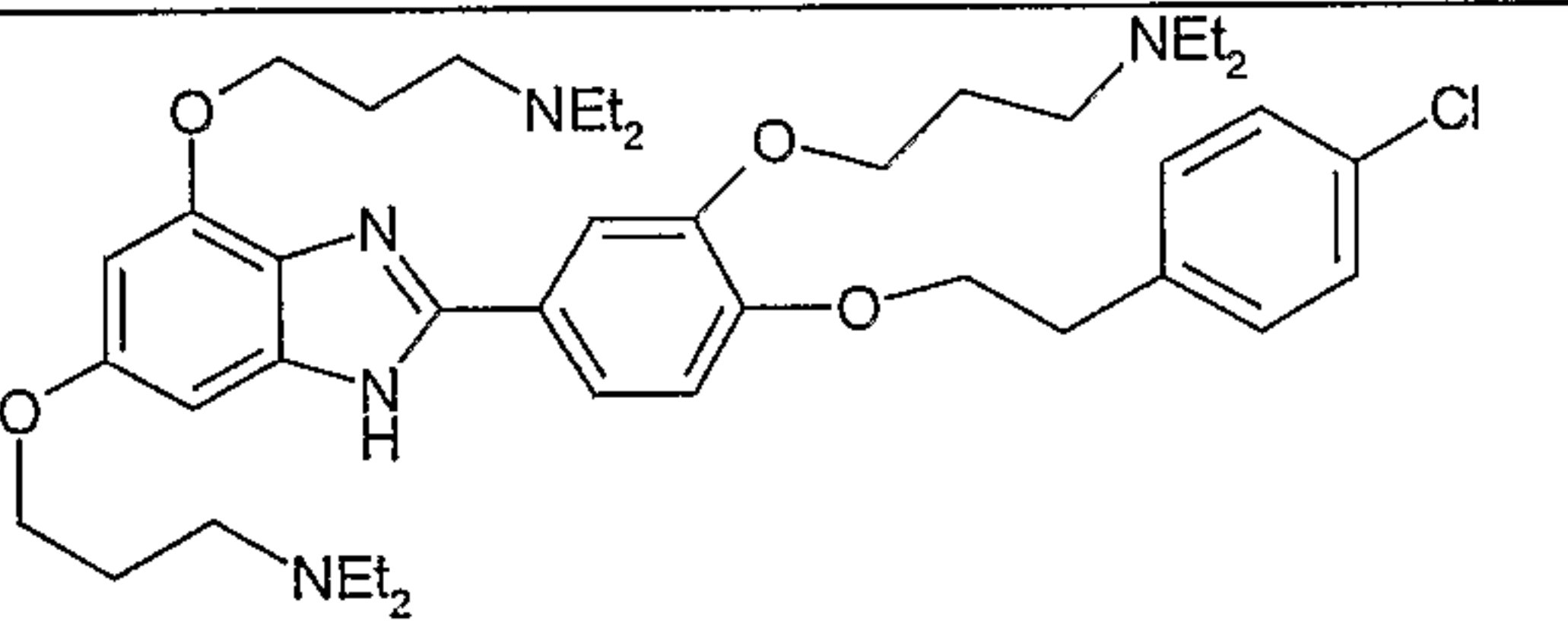
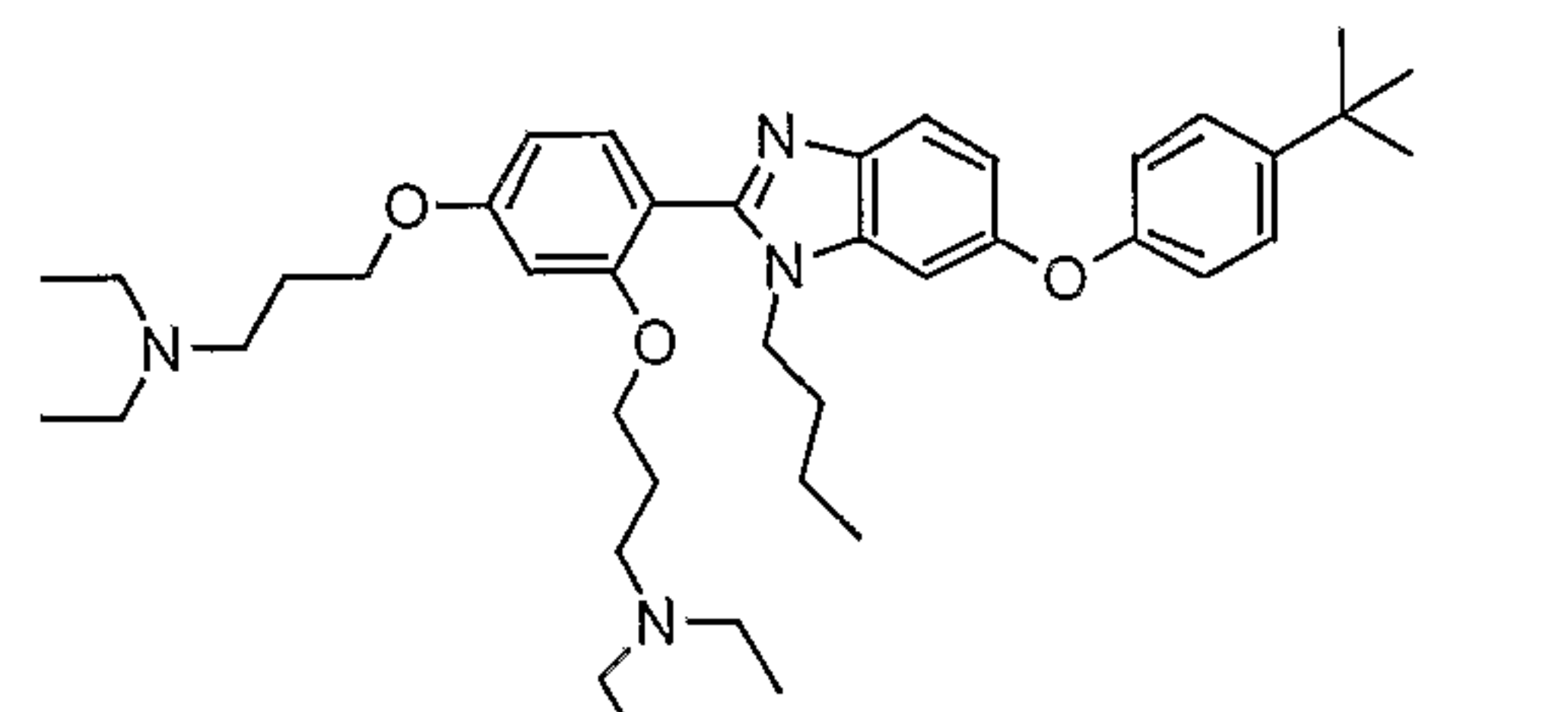
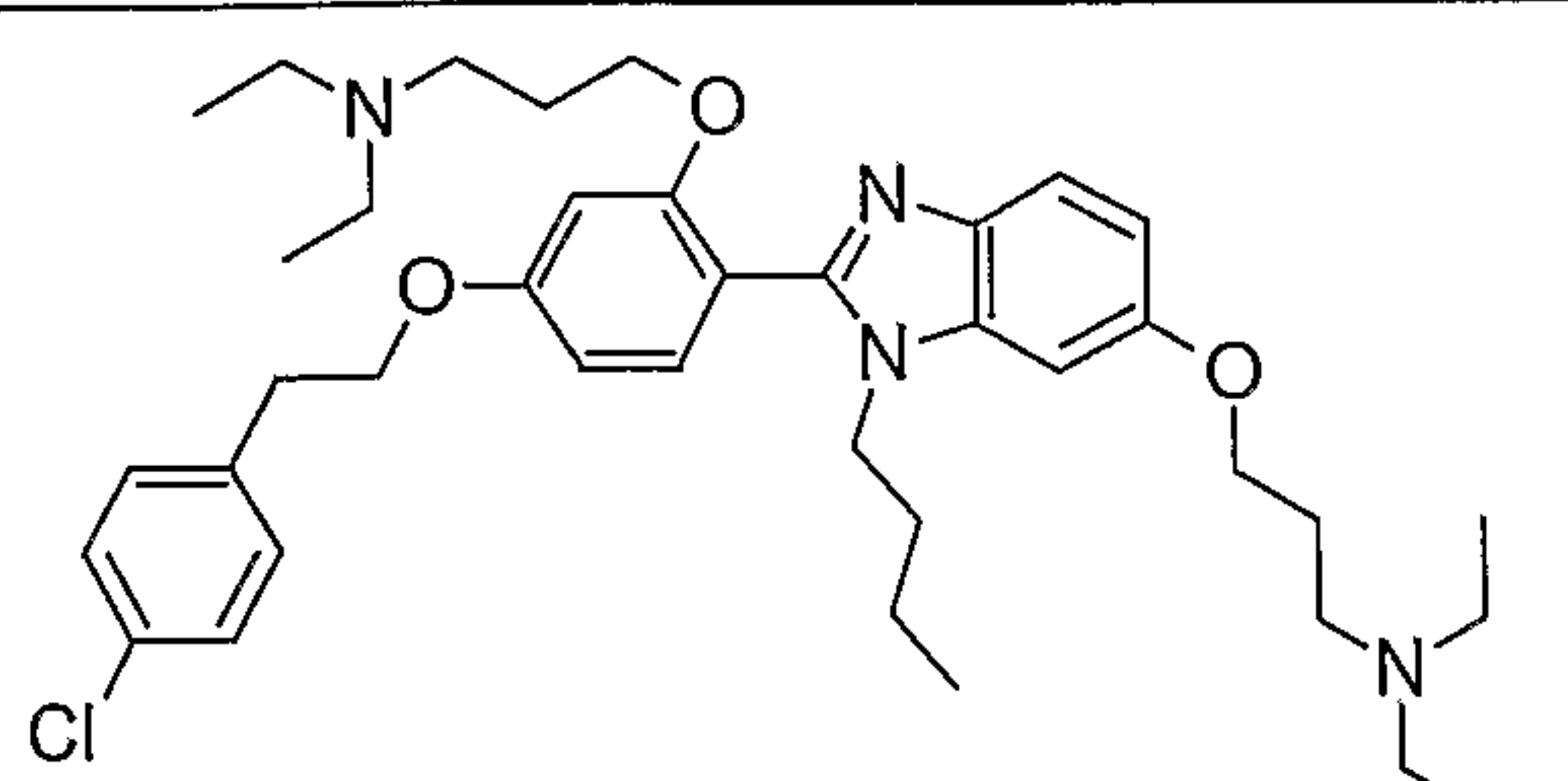
Ex.	Structure	Name
225		{3-[2-[4-(4-tert-Butyl-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
226		{3-[3-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-7-[2-(tetrahydrofuran-2-yl)-ethoxy]-3H-benzimidazol-5-yloxy}-propyl}-diethyl-amine
227		1-Butyl-2-[4-(3-chloro-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
228		[3-(7-Butoxy-3-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
229		4-{3-[4,6-Bis-(3-diethylamino-propoxy)-1H-benzimidazol-2-yl]-phenoxy}-benzonitrile

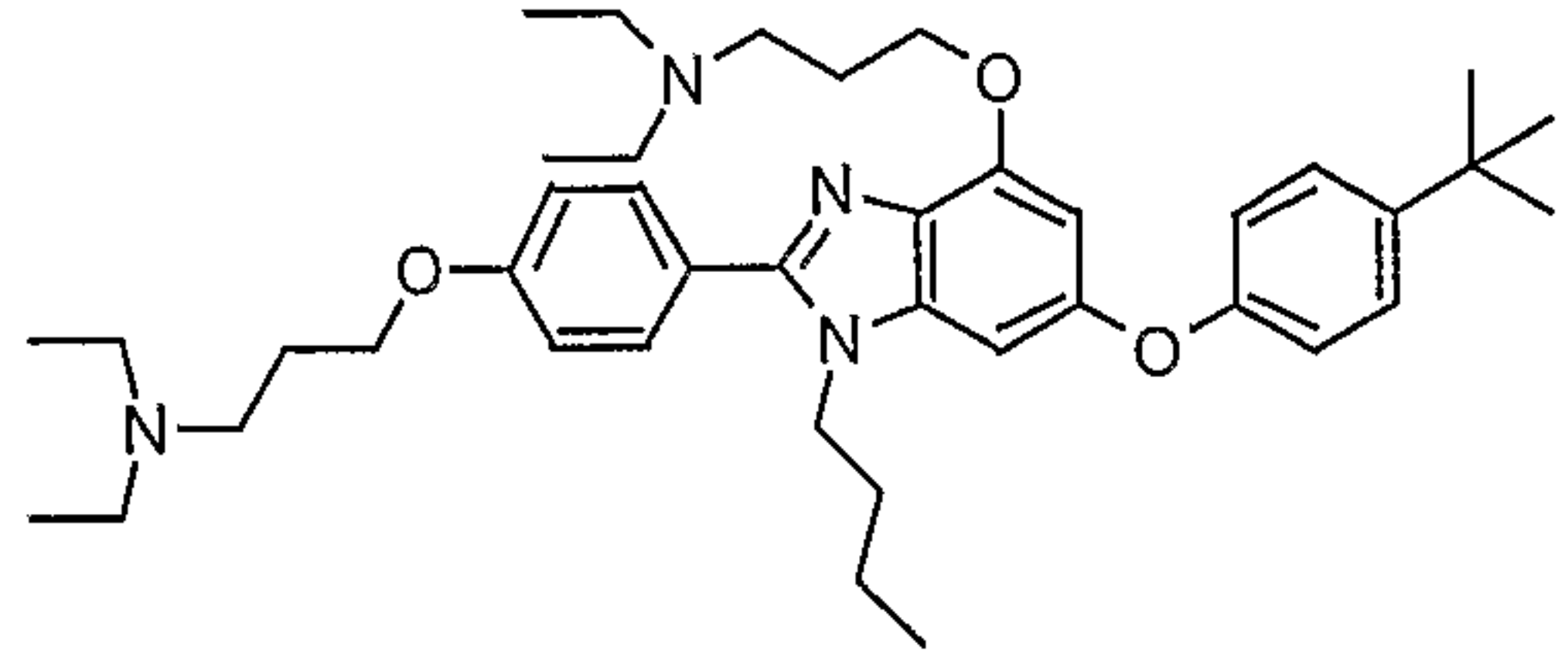
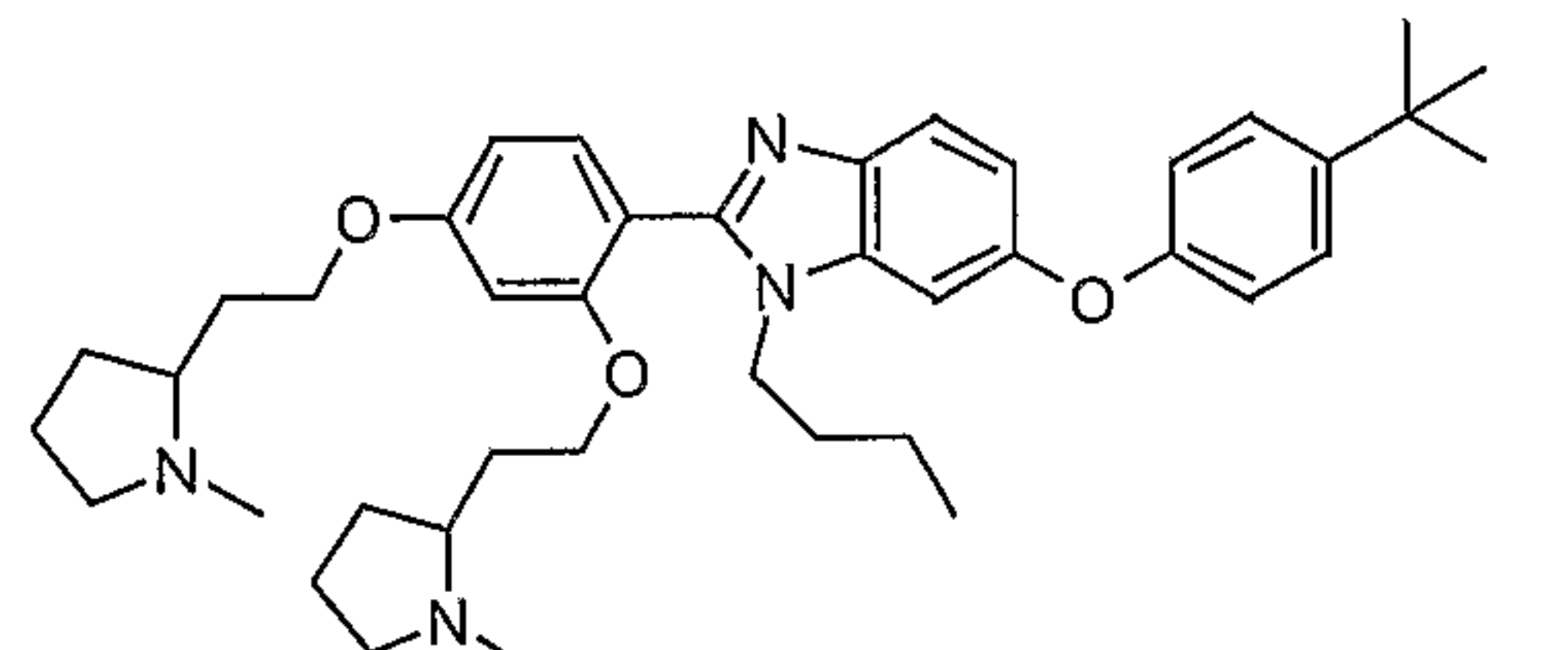
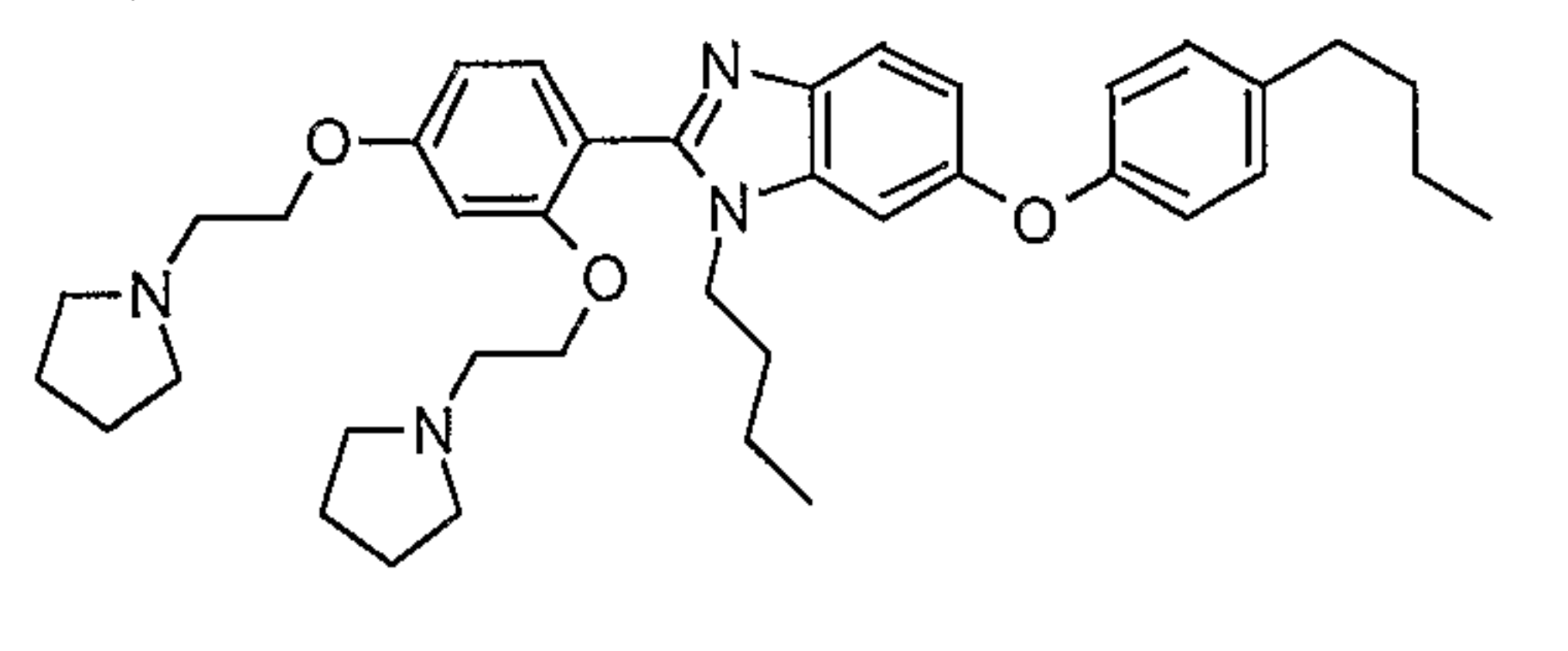
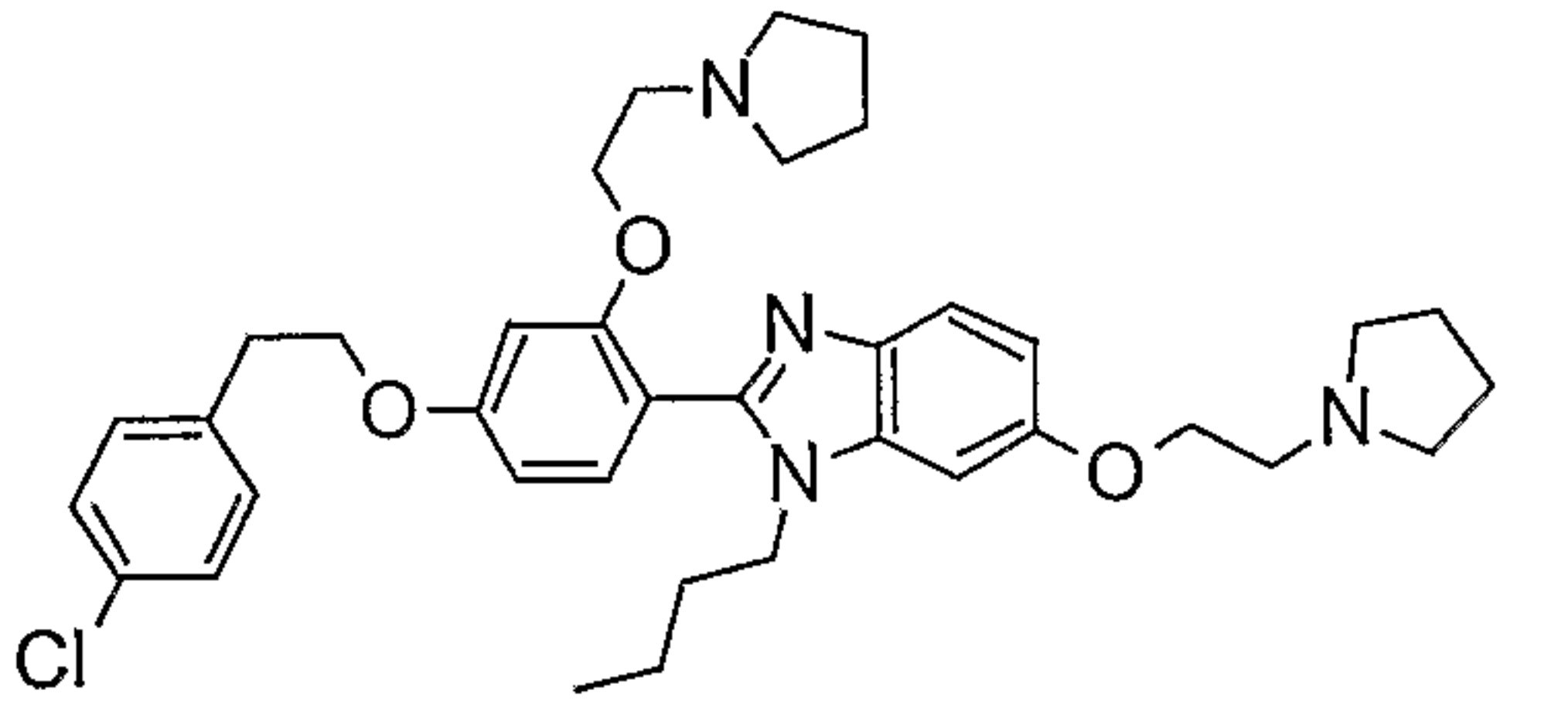
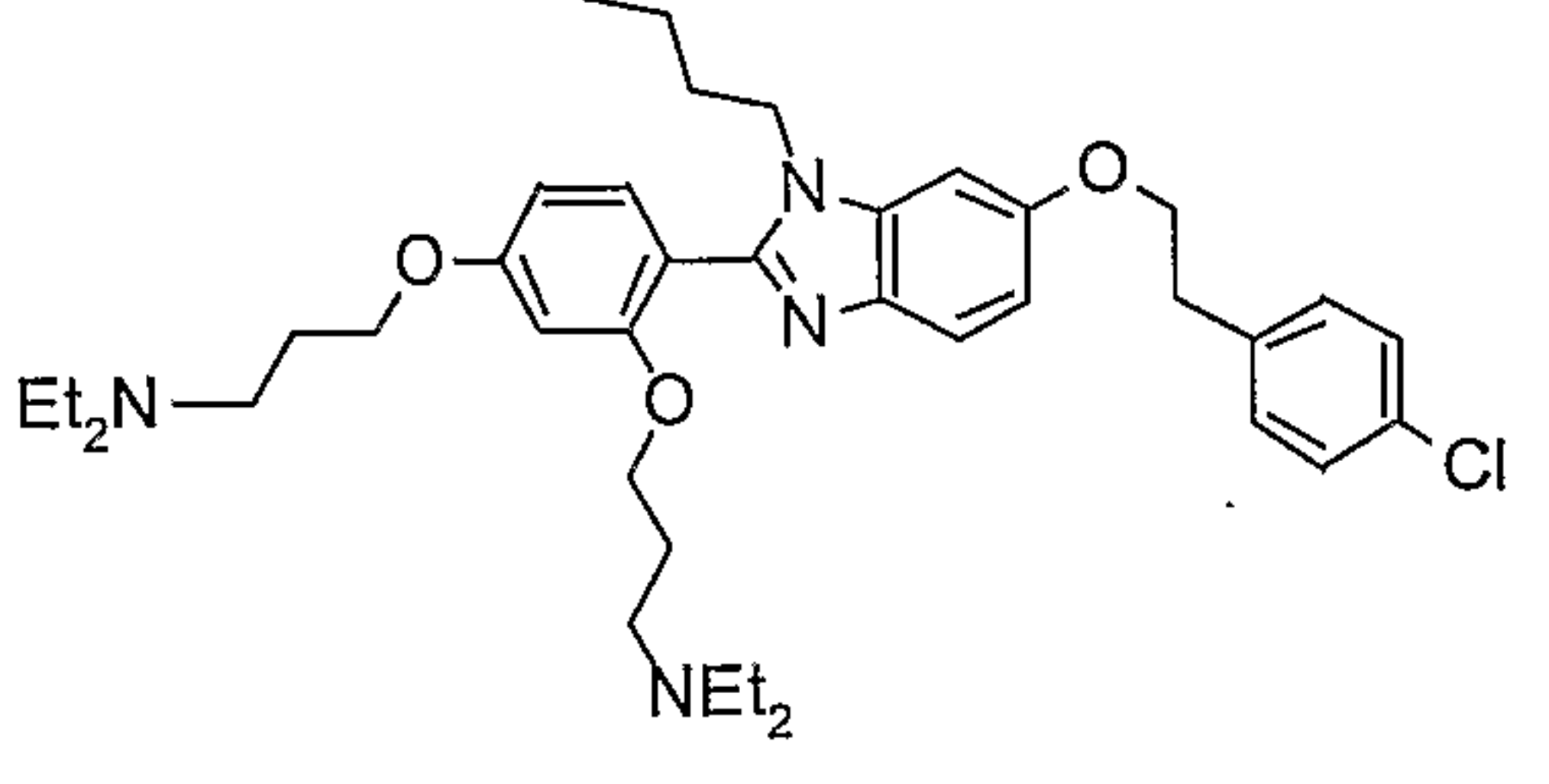
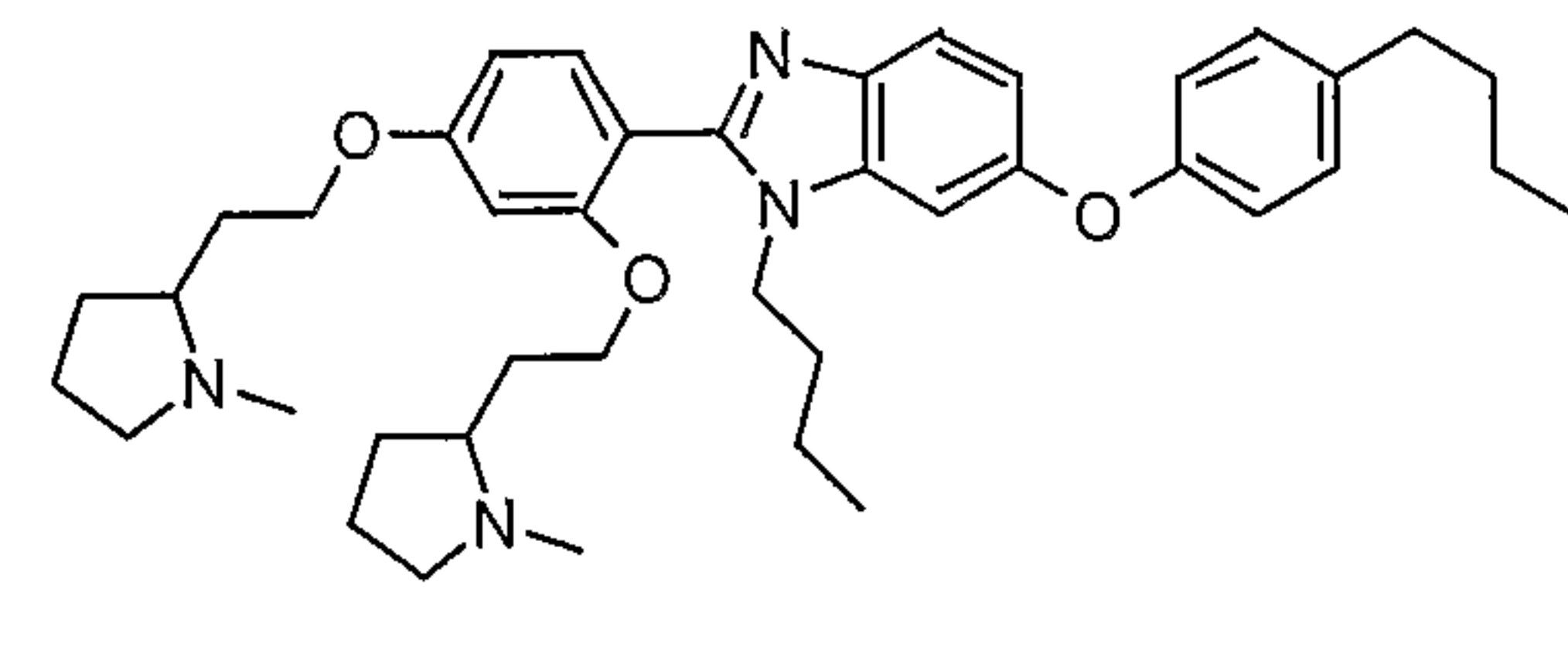
Ex.	Structure	Name
230		2-[3-(3,5-Dichloro-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
231		{3-[1-butyl-2-(2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-ethyl)-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
232		{3-[1-butyl-6-(3-diethylamino-propoxy)-2-(3-phenoxy-phenyl)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
233		{3-[1-Butyl-2-[2-(4-chloro-3-trifluoromethyl-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
234		2-[4-(4-Chloro-3-trifluoromethyl-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole

Ex.	Structure	Name
235		{3-[1-Butyl-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
236		[3-(3-butyl-2-[4-[2-(4-chloro-phenyl)-ethoxy]-phenyl]-6-methyl-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
237		{3-[1-butyl-6-(3-diethylamino-propoxy)-2-(4-phenoxy-phenyl)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
238		5-[4,6-bis-(3-diethylamino-propoxy)-1H-benzimidazol-2-yl]-2-[2-(4-chloro-phenyl)-ethoxy]-phenol
239		[3-(6-Butoxy-1-butyl-2-[4-[2-(4-chloro-phenyl)-ethoxy]-phenyl]-1H-benzimidazol-4-yloxy)-propyl]-diethyl-amine
240		{3-[2-[4-Chloro-2-(4-chloro-3-trifluoromethyl-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine

Ex.	Structure	Name
241		1-butyl-4-(4-chloro-benzyloxy)-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
242		4-{4-[1-butyl-4,6-bis-(3-diethylamino-propoxy)-1H-benzimidazol-2-yl]-phenoxy}-benzonitrile
243		[3-(1-Butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-fluoro-1H-benzimidazol-4-yloxy)-propyl]-diethyl-amine
244		(3-{6-(3-diethylamino-propoxy)-2-[3-(4-methoxy-phenoxy)-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine
245		(3-{6-(3-diethylamino-propoxy)-2-[4-(4-methoxy-phenoxy)-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine

Ex.	Structure	Name
246		{3-[1-butyl-2-[4-(4-chloro-3-fluoro-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yl]-propyl}-diethyl-amine
247		(3-{1-butyl-6-(3-diethylamino-propoxy)-2-[4-(quinolin-8-yloxy)-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine
248		{3-[2-[2-(4-chloro-3-trifluoromethyl-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
249		2-[[2-[1-Butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl]-6-(2-morpholin-4-yl-ethoxy)-1H-benzimidazol-4-yloxy]-ethyl]-2-chloro-ethyl]-amino]-ethanol
250		(3-{6-(3-Diethylamino-propoxy)-2-[3-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine

Ex.	Structure	Name
251		[3-(3-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-7-isopropoxy-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
252		[3-(1-Butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-cyclopentylmethoxy-1H-benzimidazol-4-yloxy)-propyl]-diethyl-amine
253		1-Butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-4,6-bis-(2-morpholin-4-yl-ethoxy)-1H-benzimidazole
254		{3-[2-[4-[2-(4-Chloro-phenyl)-ethoxy]-3-(3-diethylamino-propoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
255		{3-[2-[1-butyl-6-(4-tert-butyl-phenoxy)-1H-benzimidazol-2-yl]-5-(3-diethylamino-propoxy)-phenoxy]-propyl}-diethyl-amine
256		(3-{2-[1-butyl-6-(3-diethylamino-propoxy)-1H-benzimidazol-2-yl]-5-[2-(4-chloro-phenyl)-ethoxy]-phenoxy}-propyl)-diethyl-amine

Ex.	Structure	Name
257		(3-{1-butyl-6-(4-tert-butyl-phenoxy)-2-[4-(3-diethylamino-propoxy)-phenyl]-1H-benzoimidazol-4-yloxy}-propyl)-diethyl-amine
258		2-{2,4-bis-[2-(1-methyl-pyrrolidin-2-yl)-ethoxy]-phenyl}-1-butyl-6-(4-tert-butyl-phenoxy)-1H-benzoimidazole
259		2-[2,4-bis-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1-butyl-6-(4-butyl-phenoxy)-1H-benzoimidazole
260		1-butyl-2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole
261		{3-[2-{1-butyl-6-[2-(4-chloro-phenyl)-ethoxy]-1H-benzimidazol-2-yl]-5-(3-diethylamino-propoxy)-phenoxy]-propyl}-diethyl-amine
262		2-{2,4-bis-[2-(1-methyl-pyrrolidin-2-yl)-ethoxy]-phenyl}-1-butyl-6-(4-butyl-phenoxy)-1H-benzoimidazole

Ex.	Structure	Name
263		1-Butyl-2-[3-(3,5-dichloro-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
264		2-[2,4-bis-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1-butyl-6-(4-cyclopentyl-phenoxy)-1H-benzimidazole
265		2-[2,4-bis-[2-(1-methyl-pyrrolidin-2-yl)-ethoxy]-phenyl]-1-butyl-6-(4-cyclopentyl-phenoxy)-1H-benzimidazole
266		2-[2,4-bis-[2-(1-methyl-pyrrolidin-2-yl)-ethoxy]-phenyl]-1-butyl-6-(4-cyclopentyl-phenoxy)-1H-benzimidazole
267		2-[2,4-bis-[2-(1-methyl-pyrrolidin-2-yl)-ethoxy]-phenyl]-1-butyl-6-(4-cyclopentyl-phenoxy)-1H-benzimidazole

Ex.	Structure	Name
268		(2-{1-butyl-6-(2-dimethylamino-ethylsulfanyl)-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1H-benzimidazol-4-ylsulfanyl}-ethyl)-dimethyl-amine
269		2-[2,4-bis-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1-butyl-6-(4-tert-butyl-phenoxy)-1H-benzimidazole
270		{3-[2-[1-butyl-6-(4-butyl-phenoxy)-1H-benzimidazol-2-yl]-5-(3-diethylamino-propoxy)-phenoxy]-propyl}-diethyl-amine
271		{3-[2-[1-butyl-6-(4-fluoro-3-trifluoromethyl-phenoxy)-1H-benzimidazol-2-yl]-5-(3-diethylamino-propoxy)-phenoxy]-propyl}-diethyl-amine
272		2-[2,4-bis-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1-butyl-6-(4-isopropyl-phenoxy)-1H-benzimidazole
273		1-Butyl-2-[3-(3,4-dichloro-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole

Ex.	Structure	Name
274		(3-{3-Butyl-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-3H-benzimidazol-5-yloxy}-propyl)-diethyl-amine
275		{3-[2-[1-butyl-6-(4-cyclopentyl-phenoxy)-1H-benzimidazol-2-yl]-5-(3-diethylamino-propoxy)-phenoxy]-propyl}-diethyl-amine
276		{3-[2-[1-butyl-4-(4-tert-butyl-phenoxy)-1H-benzimidazol-2-yl]-5-(3-diethylamino-propoxy)-phenoxy]-propyl}-diethyl-amine
277		2-{2,4-bis-[2-(1-methyl-pyrrolidin-2-yl)-ethoxy]-phenyl}-1-butyl-6-(4-isopropyl-phenoxy)-1H-benzimidazole
278		(3-{5-[2-(4-chloro-phenyl)-ethoxy]-2-[6-(3-diethylamino-propoxy)-1-isopropyl-1H-benzimidazol-2-yl]-phenoxy}-propyl)-diethyl-amine

Ex.	Structure	Name
279		1-Butyl-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole
280		1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-4,6-bis-(1-methyl-piperidin-4-yloxy)-1H-benzimidazole
281		{3-[2-[6-(4-tert-butyl-phenoxy)-1H-benzimidazol-2-yl]-5-(3-diethylamino-propoxy)-phenoxy]-propyl}-diethyl-amine
282		1-butyl-2-[3-(3,4-dichloro-phenoxy)-phenyl]-4,6-bis-(1-methyl-pyrrolidin-2-ylmethoxy)-1H-benzoimidazole
283		(3-{3-butyl-2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(2-diethylamino-ethoxy)-phenyl]-3H-benzimidazol-5-yloxy}-propyl)-diethyl-amine

Ex.	Structure	Name
284		(3-{2-[1-Butyl-6-(2-imidazol-1-yl-ethoxy)-1H-benzoimidazol-2-yl]-5-[2-(4-chloro-phenyl)-ethoxy]-phenoxy}-propyl)-diethyl-amine
285		(3-{2-[1-Butyl-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazol-2-yl]-5-[2-(4-chloro-phenyl)-ethoxy]-phenoxy}-propyl)-diethyl-amine
286		{3-[2-(3,5-bis-benzyloxy-phenyl)-3-butyl-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
287		4,6-bis-(2-azepan-1-yl-ethoxy)-1-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-1H-benzimidazole
288		1-butyl-2-[3-(4-butyl-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole

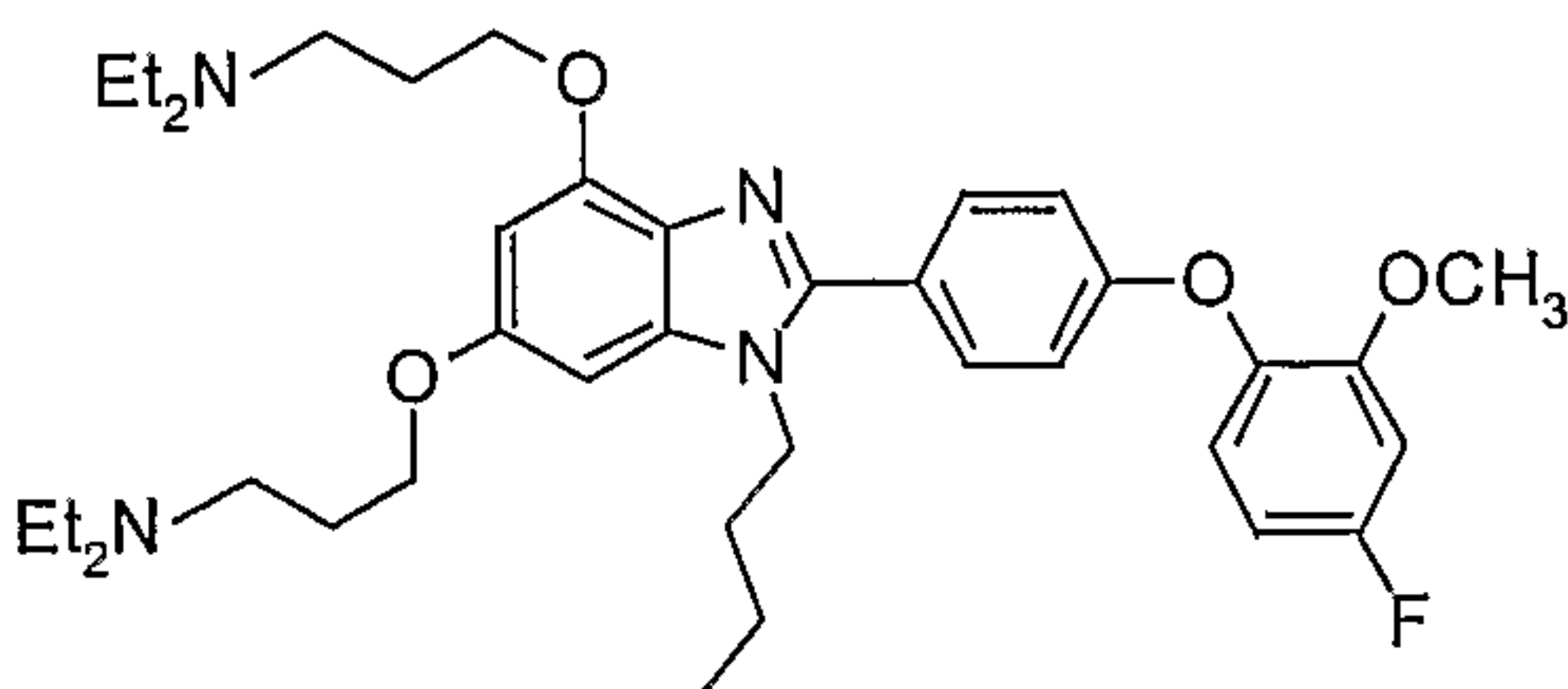
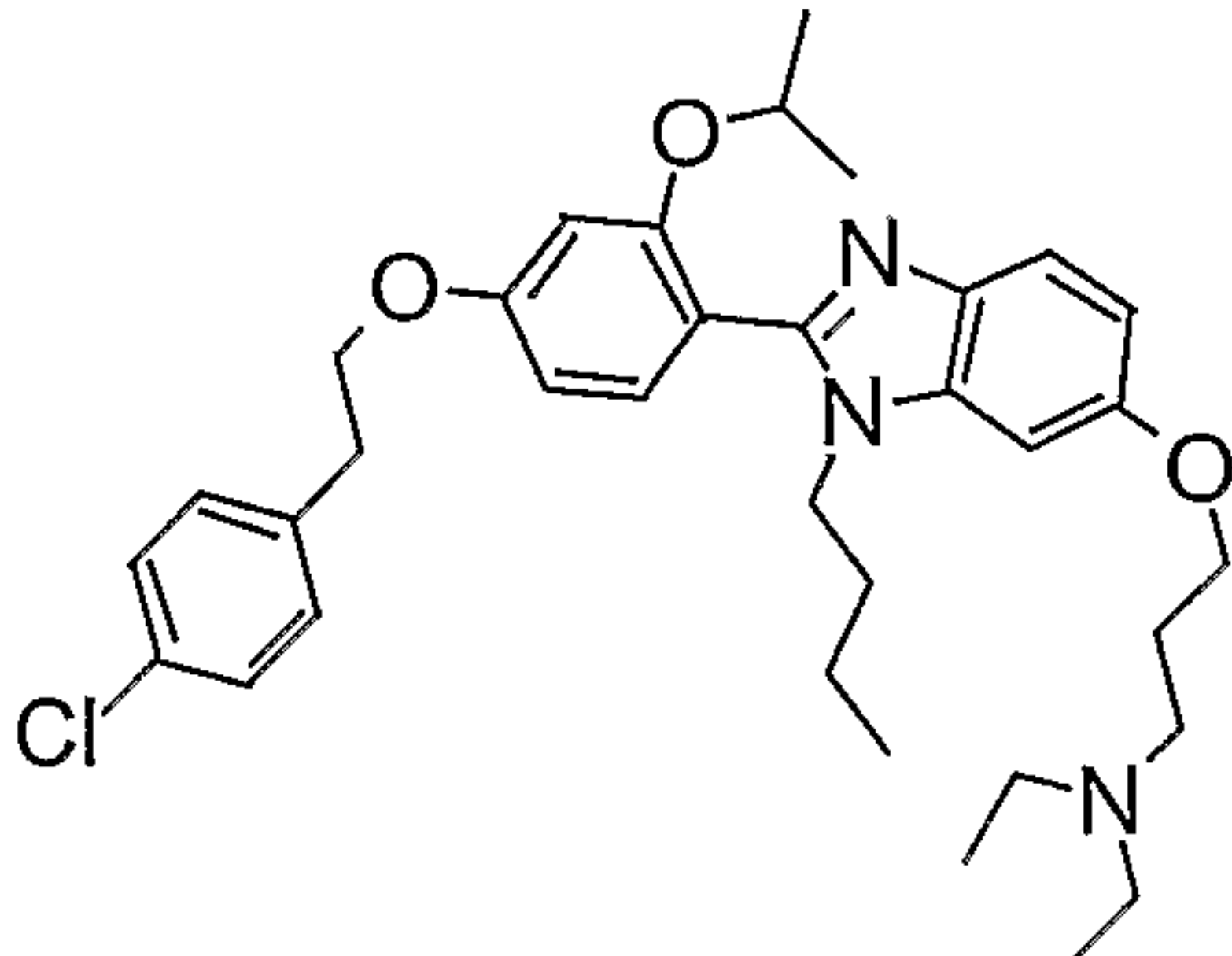
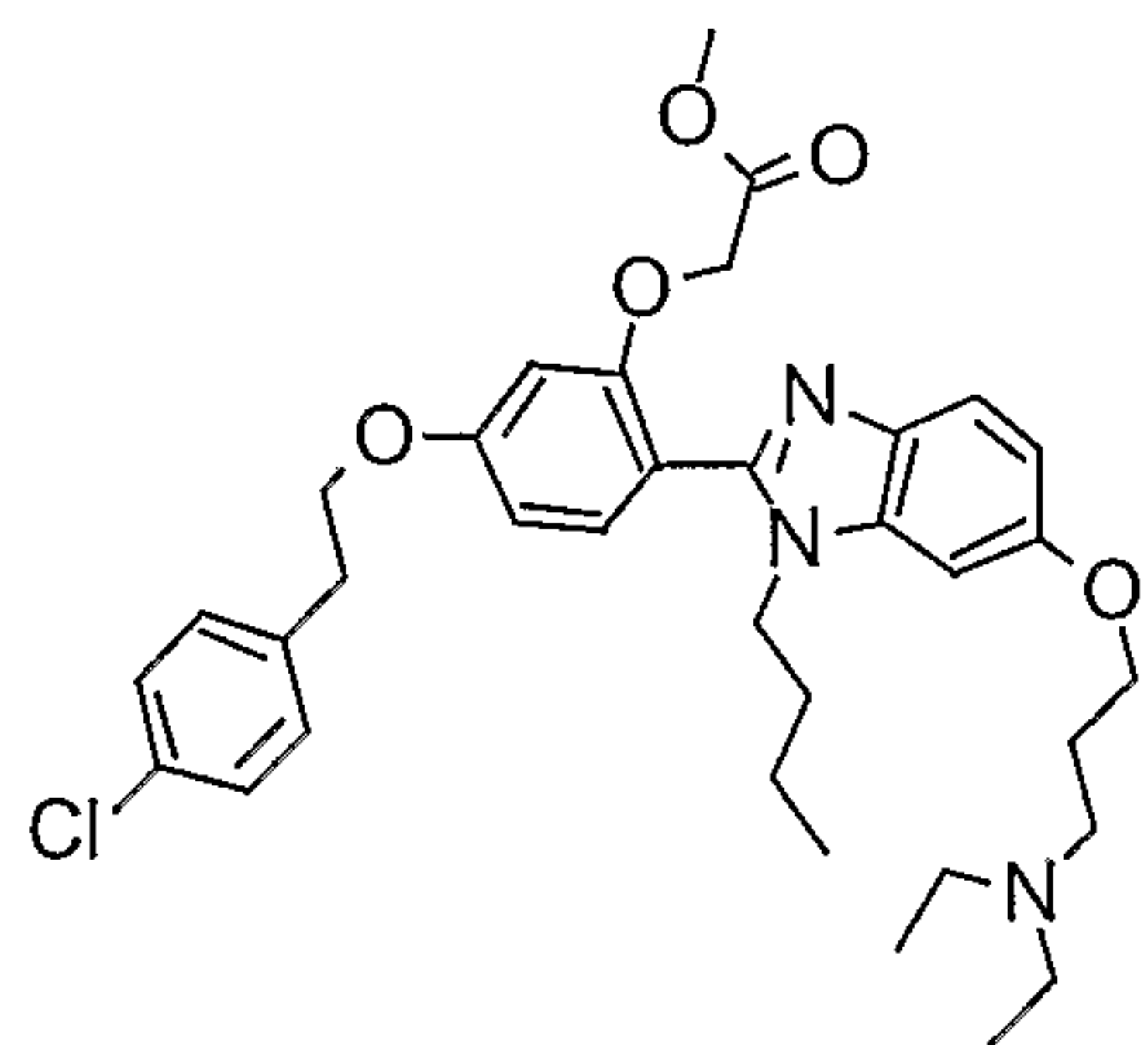
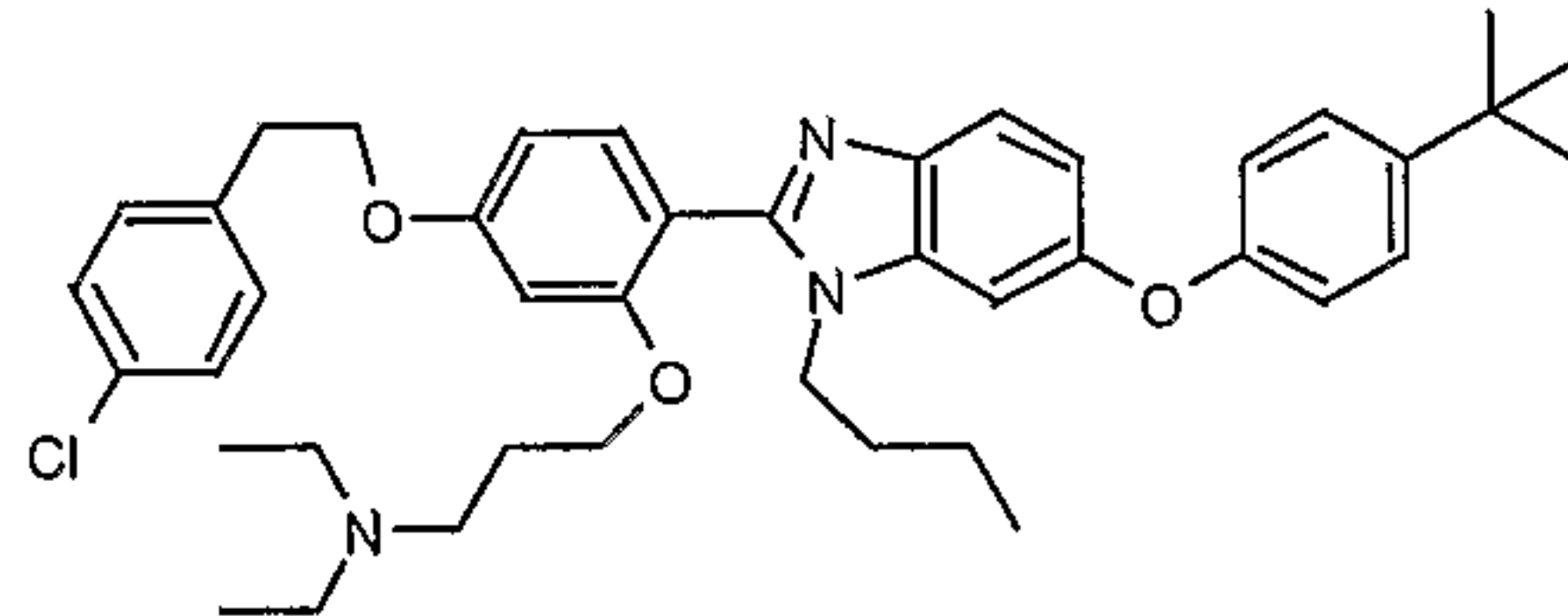
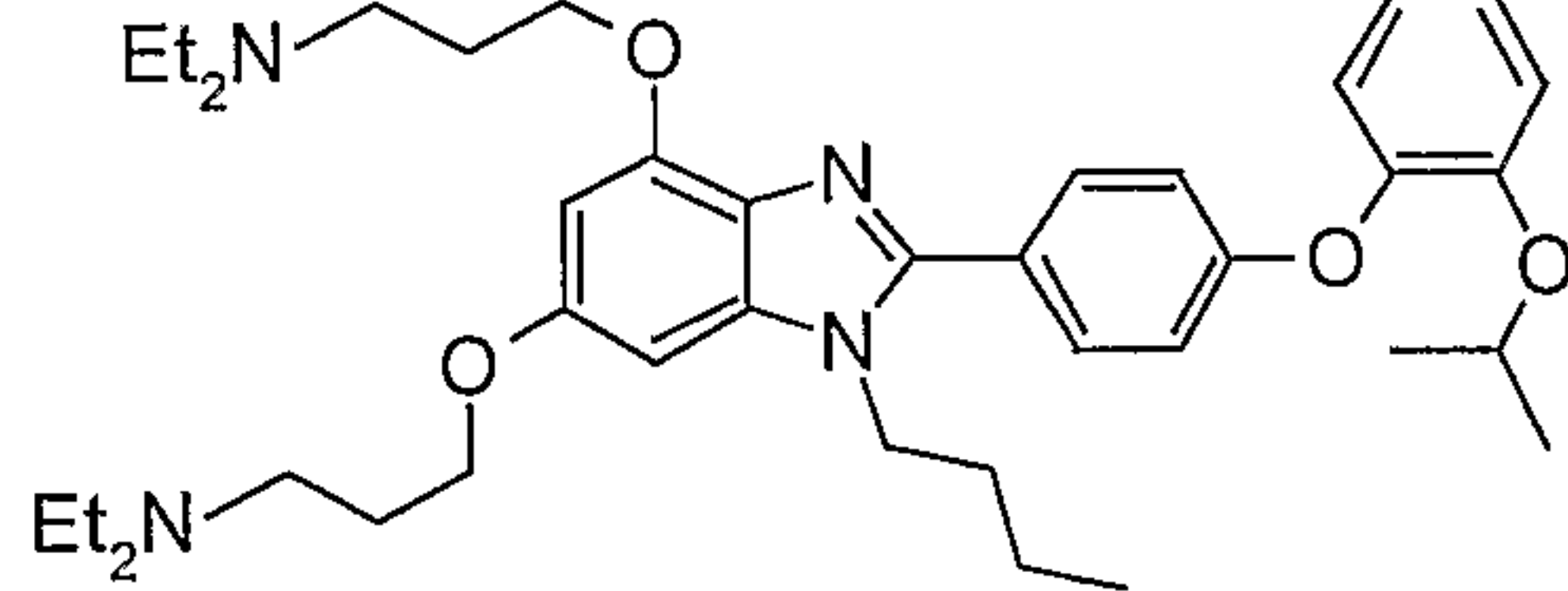
Ex.	Structure	Name
289		1-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-4,6-bis-(1-methyl-pyrrolidin-2-ylmethoxy)-1H-benzoimidazole
290		(2-{1-butyl-6-(2-dimethylamino-ethylsulfanyl)-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzoimidazole-4-ylsufanyl}-ethyl)-dimethyl-amine
291		(3-{1-butyl-6-(3-diethylamino-propoxy)-2-[4-(4-isopropyl-phenoxy)-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine
292		4,6-bis-(2-azepan-1-yl-ethoxy)-1-butyl-2-[3-(3,5-dichlorophenoxy)-phenyl]-1H-benzoimidazole
293		1-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-4,6-bis-[2-(cyclohexyl-methyl-amino)-ethoxy]-1H-benzoimidazole

Ex.	Structure	Name
294		{3-[1-butyl-2-[3-(3,5-dichloro-phenoxy)-phenyl]-6-(2-imidazol-1-yl-ethoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
295		[3-(2-{3,4-bis-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-3-butyl-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
296		1-butyl-4,6-bis-(1-methyl-piperidin-4-yloxy)-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazole
297		4,6-bis-(2-azepan-1-yl-ethoxy)-1-butyl-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazole

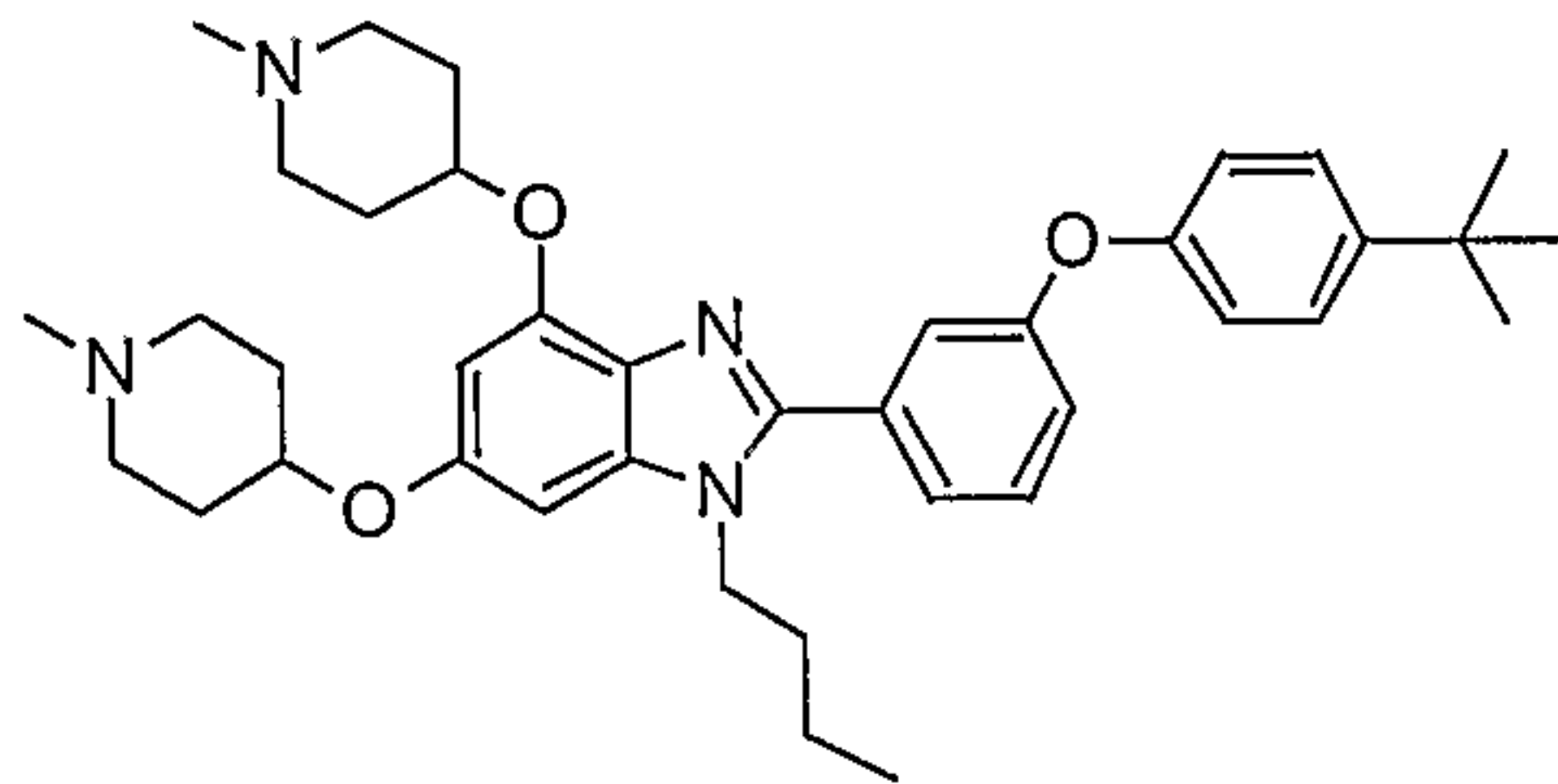
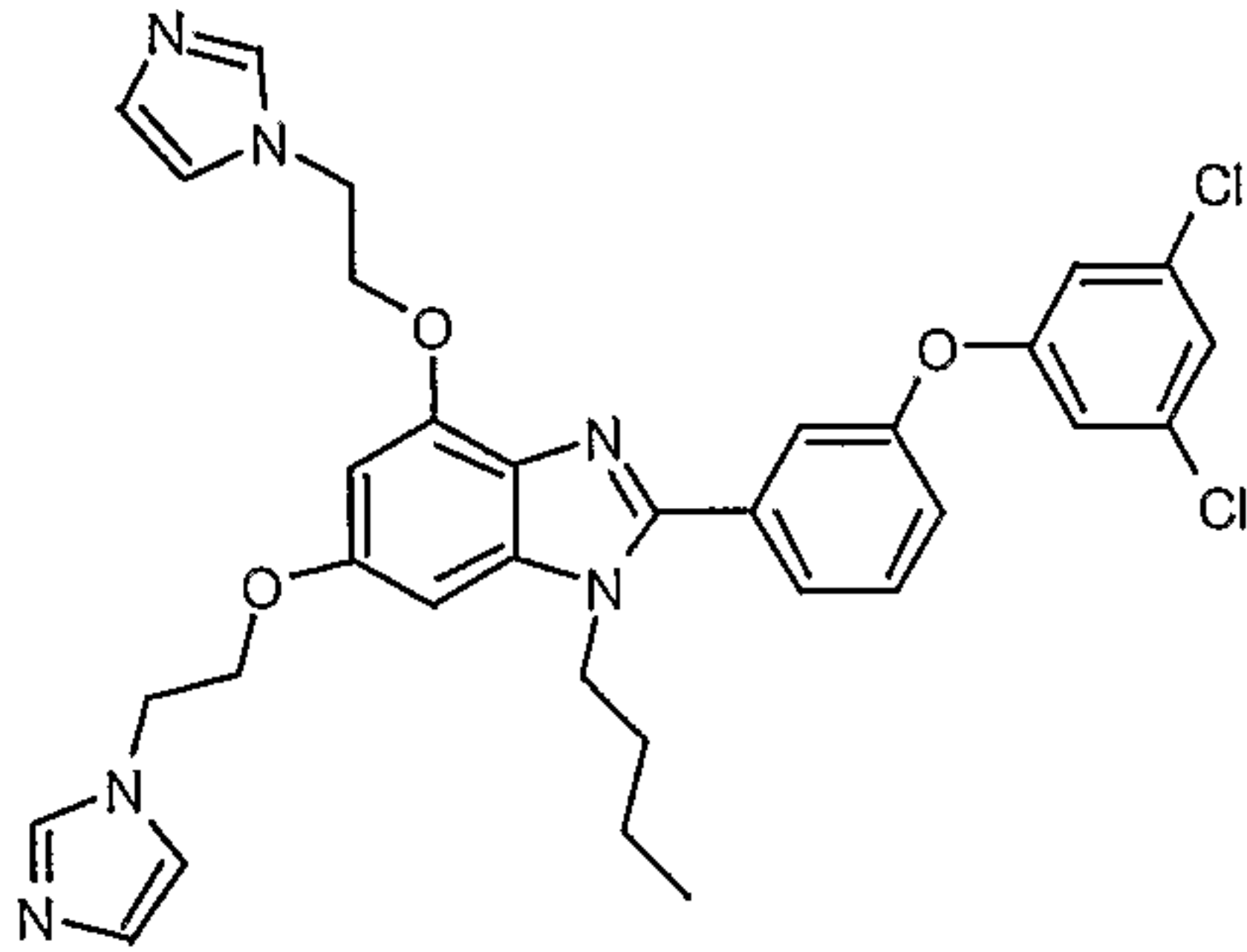
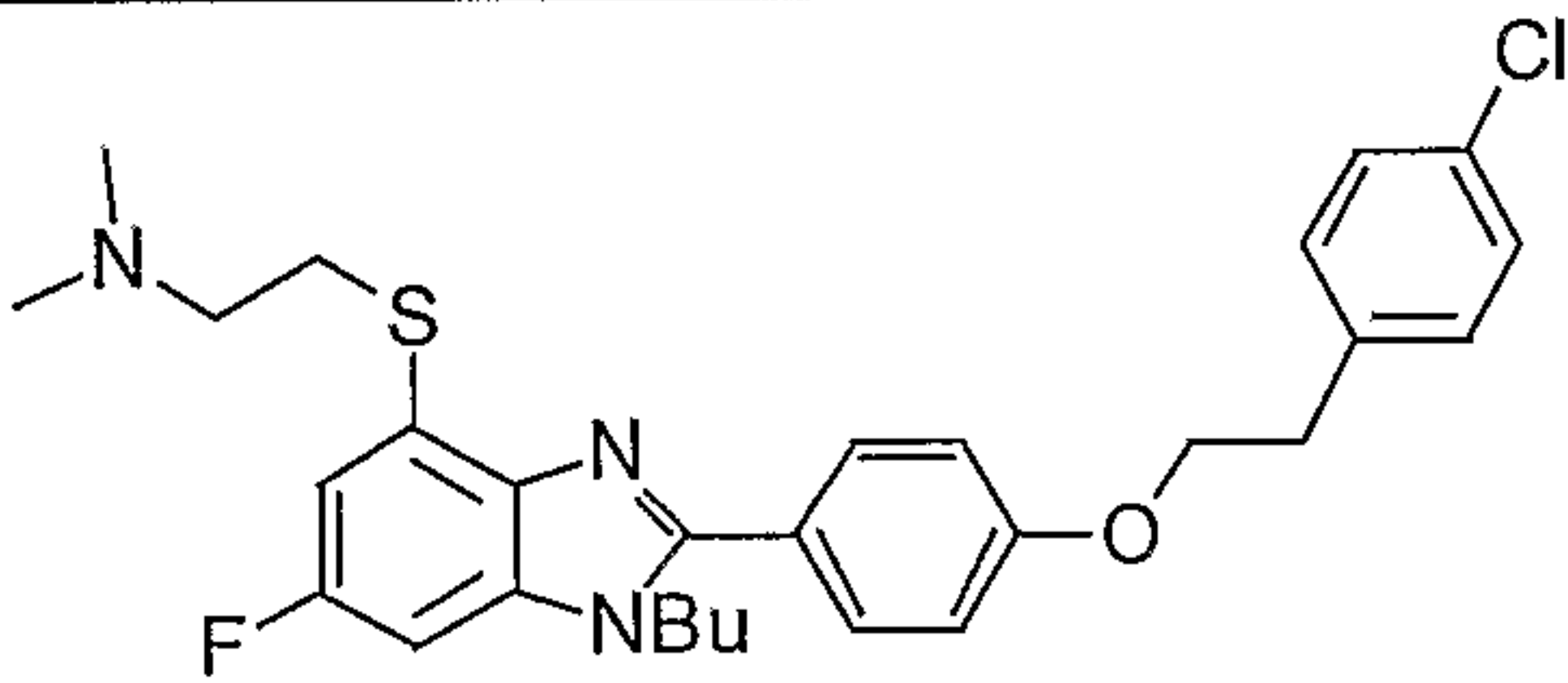
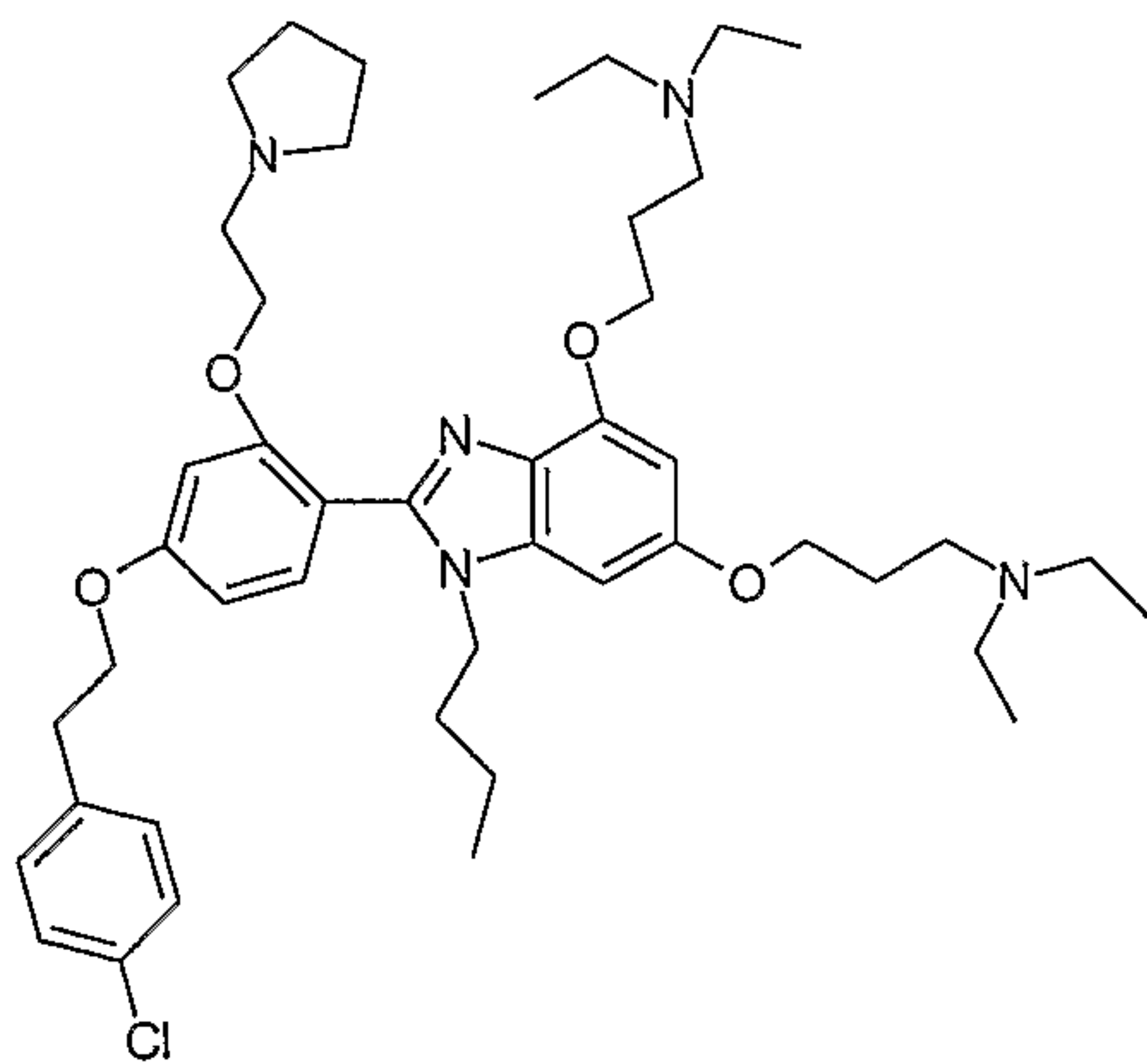
Ex.	Structure	Name
298		1-butyl-2-[3-(3,4-dichloro-phenoxy)-phenyl]-4,6-bis-(1-ethyl-pyrrolidin-2-ylmethoxy)-1H-benzimidazole
299		[3-(2-{2-benzyloxy-4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-3-butyl-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
300		{3-[2-[1-Butyl-6-(3-diethylamino-propoxy)-1H-benzimidazol-2-yl]-5-(4-fluoro-3-trifluoromethyl-phenoxy)-phenoxy]-propyl}-diethyl-amine
301		{3-[2-[1-Butyl-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazol-2-yl]-5-(4-fluoro-3-trifluoromethyl-phenoxy)-phenoxy]-propyl}-diethyl-amine

Ex.	Structure	Name
302		1-butyl-2-[3-(3,4-dimethoxyphenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
303		(2-{1-butyl-2-{4-[2-(4-chlorophenyl)ethoxy]-phenyl}-6-(2-dimethylaminoethylsulfanyl)-1H-benzimidazol-4-ylsulfanyl}-ethyl)-dimethyl-amine
304		1-butyl-2-[3-(4-tert-butylphenoxy)-phenyl]-4,6-bis-(1-ethylpyrrolidin-3-yloxy)-1H-benzimidazole
305		{3-[2-[3-(3,4-bis-benzyloxyphenyl)-3-butyl-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
306		(3-{5-[2-(4-chlorophenyl)ethoxy]-2-[6-(3-diethylamino-propoxy)-1H-benzimidazol-2-yl]-phenoxy}-propyl)-diethyl-amine

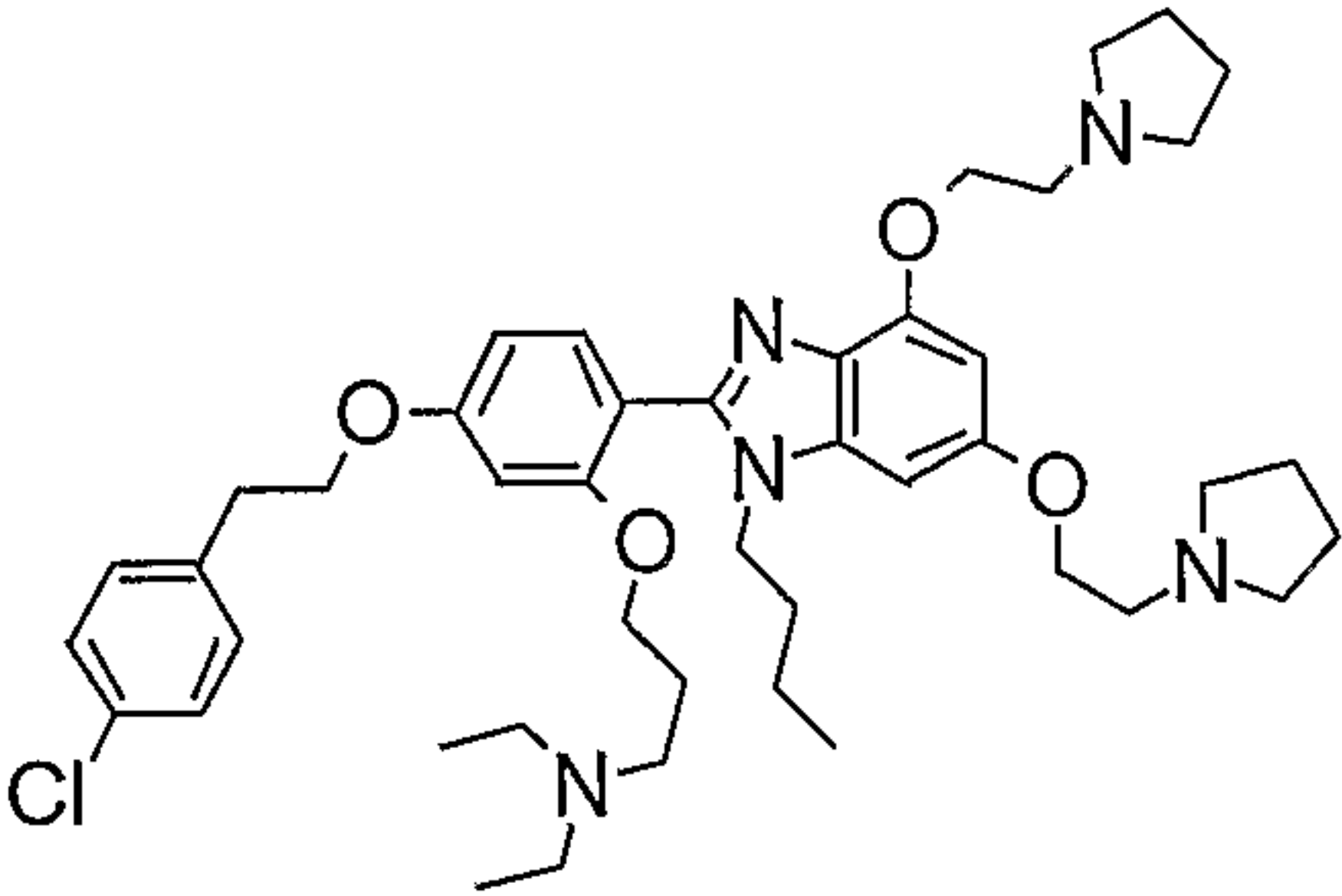
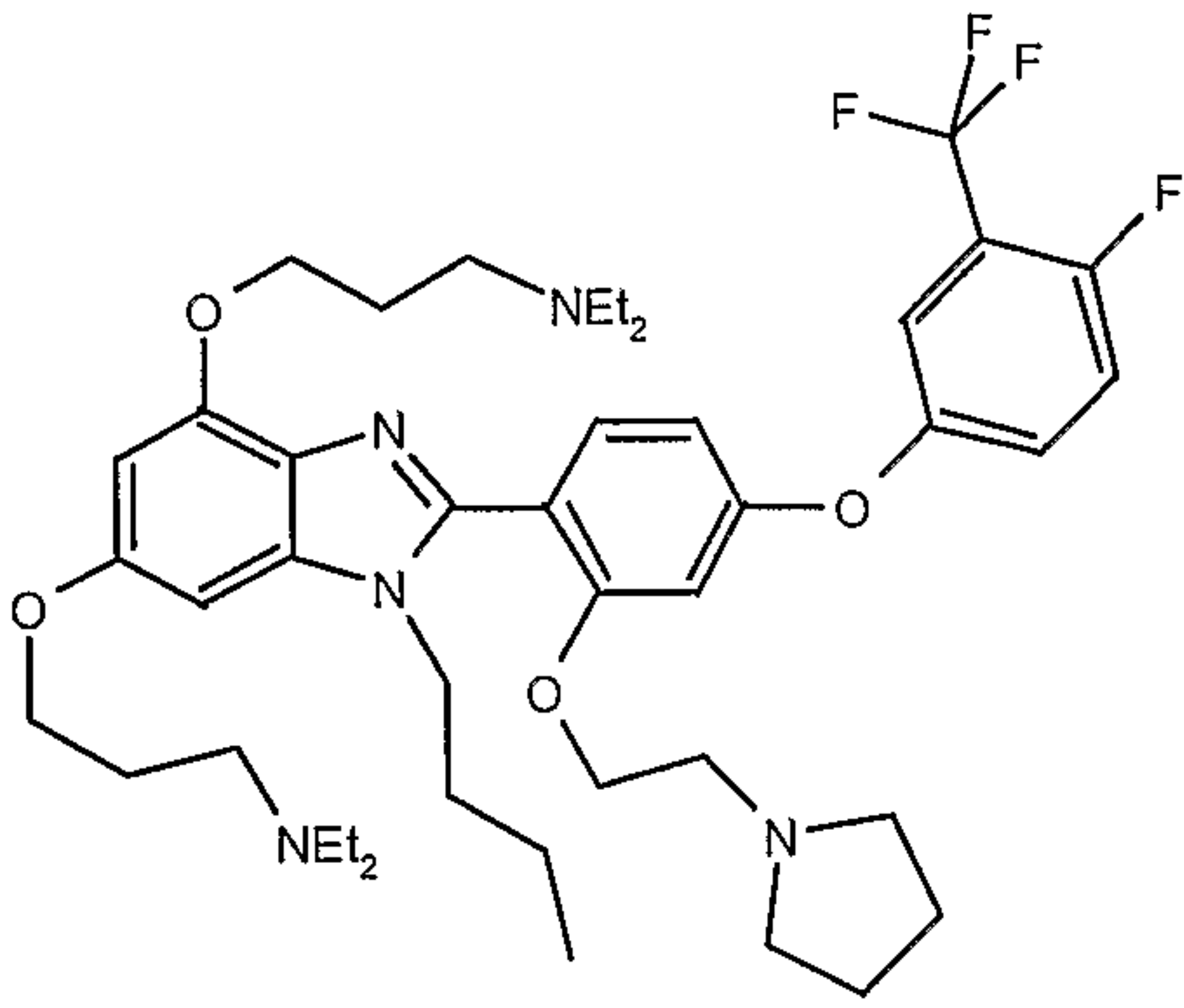
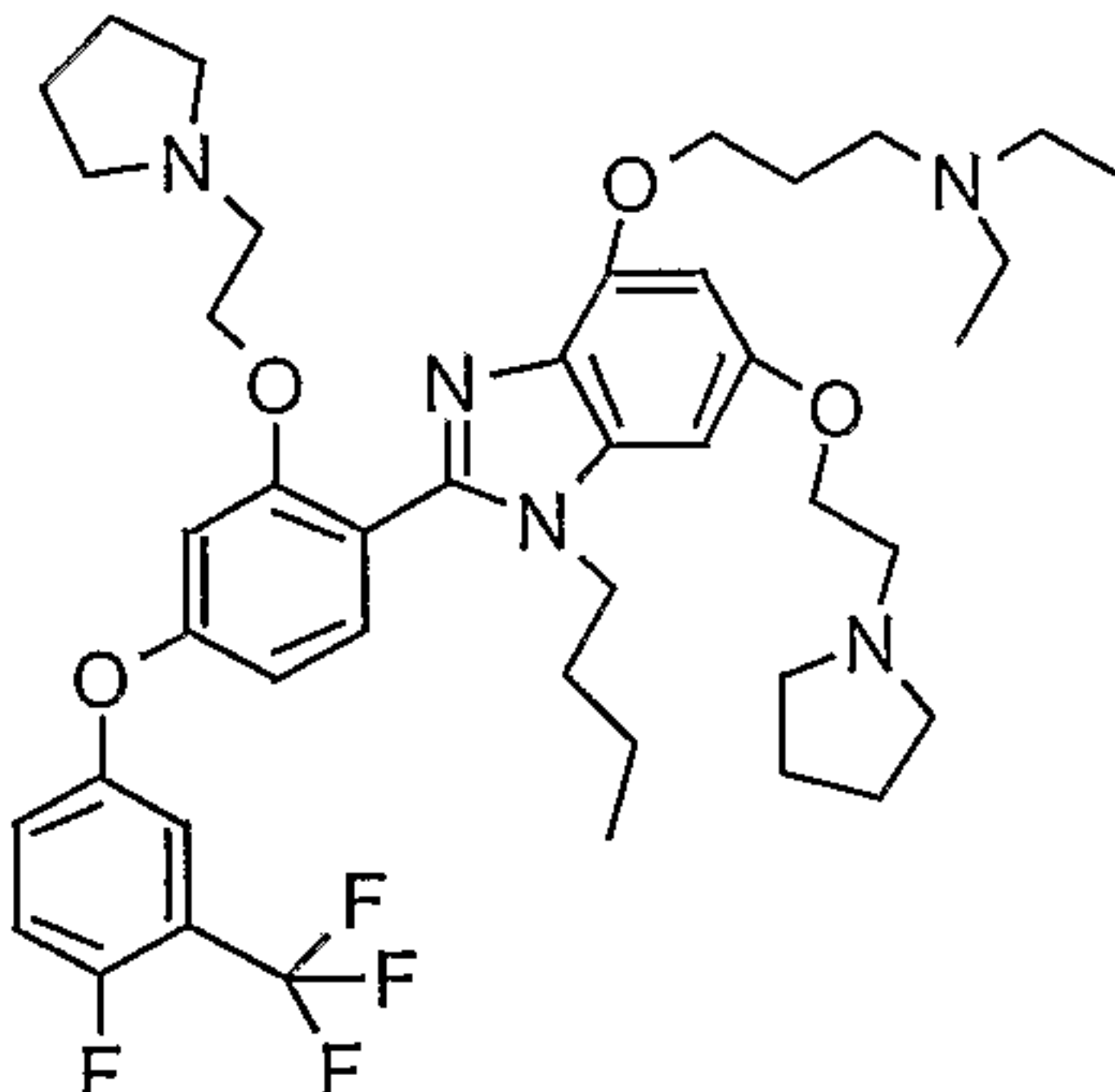
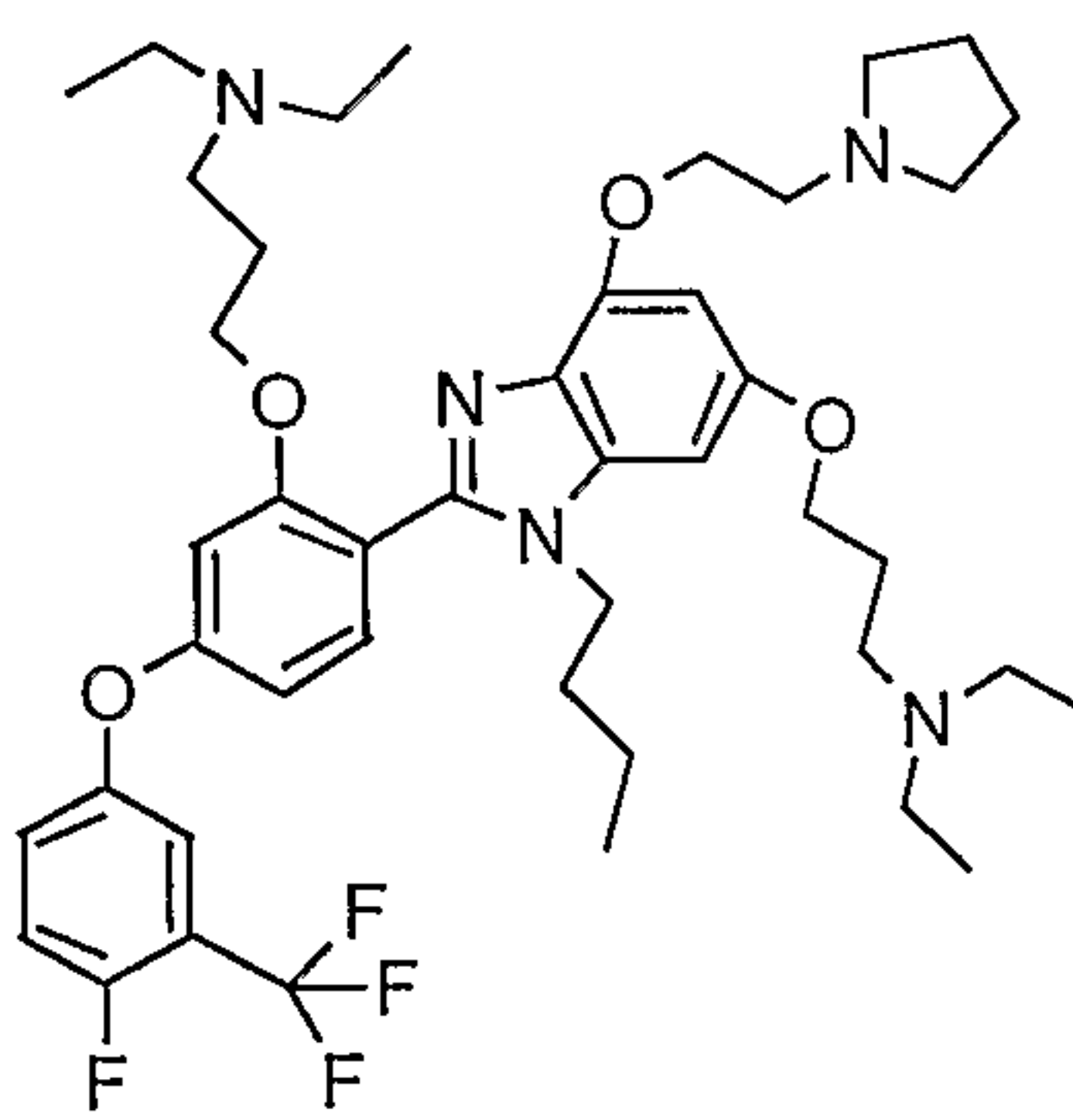
Ex.	Structure	Name
307		1-butyl-2-[4-(2-diethylamino-ethoxy)-phenyl]-4,6-bis-[2-(methyl-phenyl-amino)-ethoxy]-1H-benzimidazole
308		{3-[3-butyl-2-{4-[2-(4-chlorophenyl)-ethoxy]-phenyl}-7-(pyridin-3-yloxy)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
309		{2-[1-butyl-2-[3-(3,4-dichloro-phenoxy)-phenyl]-6-(2-diisopropylamino-ethoxy)-1H-benzimidazol-4-yloxy]-ethyl}-diethyl-amine
310		{3-[3-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-7-(pyridin-3-ylmethoxy)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
311		2-[1-butyl-6-(3-diethylamino-propoxy)-1H-benzoimidazol-2-yl]-5-[2-(4-chloro-phenyl)-ethoxy]-phenol
312		{3-[3-butyl-2-[2-(4-chloro-phenylsulfanyl)-phenyl]-7-(3-diethylamino-propoxy)-3H-benzimidazol-4-yloxy]-propyl}-diethyl-amine

Ex.	Structure	Name
313		(3-{1-butyl-6-(3-diethylamino-propoxy)-2-[4-(4-fluoro-2-methoxy-phenoxy)-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine
314		[3-(3-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-2-isopropoxy-phenyl}-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
315		{2-[1-butyl-6-(3-diethylamino-propoxy)-1H-benzimidazol-2-yl]-5-[2-(4-chloro-phenyl)-ethoxy]-phenoxy}-acetic acid methyl ester
316		(3-{2-[1-butyl-6-(4-tert-butyl-phenoxy)-1H-benzimidazol-2-yl]-5-[2-(4-chloro-phenyl)-ethoxy]-phenoxy}-propyl)-diethyl-amine
317		(3-{1-butyl-6-(3-diethylamino-propoxy)-2-[4-(2-isopropoxy-phenoxy)-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine

Ex.	Structure	Name
318		(3-{1-butyl-6-(3-diethylamino-propoxy)-2-[4-(2,3-dimethoxy-phenoxy)-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine
319		(3-{3-Butyl-2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-3H-benzoimidazol-5-yloxy}-propyl)-diethyl-amine
320		(2-{1-butyl-6-fluoro-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzoimidazole-4-ylsufanyl}-ethyl)-dimethyl-amine
321		Methanesulfonic acid 5-[2-(4-chloro-phenyl)-ethoxy]-2-[6-(3-diethylamino-propoxy)-1H-benzoimidazol-2-yl]-phenyl ester
322		5-[2-(4-Chloro-phenyl)-ethoxy]-2-[6-(3-diethylamino-propoxy)-1H-benzoimidazol-2-yl]-phenol
323		{3-[1-butyl-6-(3-diethylamino-propoxy)-2-(4-pyrrolidin-1-yl-phenyl)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine

Ex.	Structure	Name
324		1-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-4,6-bis-(1-methyl-piperidin-4-yloxy)-1H-benzimidazole
325		1-butyl-2-[3-(3,5-dichloro-phenoxy)-phenyl]-4,6-bis-(2-imidazol-1-yl-ethoxy)-1H-benzimidazole
326		[2-(1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-fluoro-1H-benzimidazol-4-ylsulfanyl)-ethyl]-dimethyl-amine
327		{3-[1-Butyl-2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(2-(pyrrolidin-1-yl-ethoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine

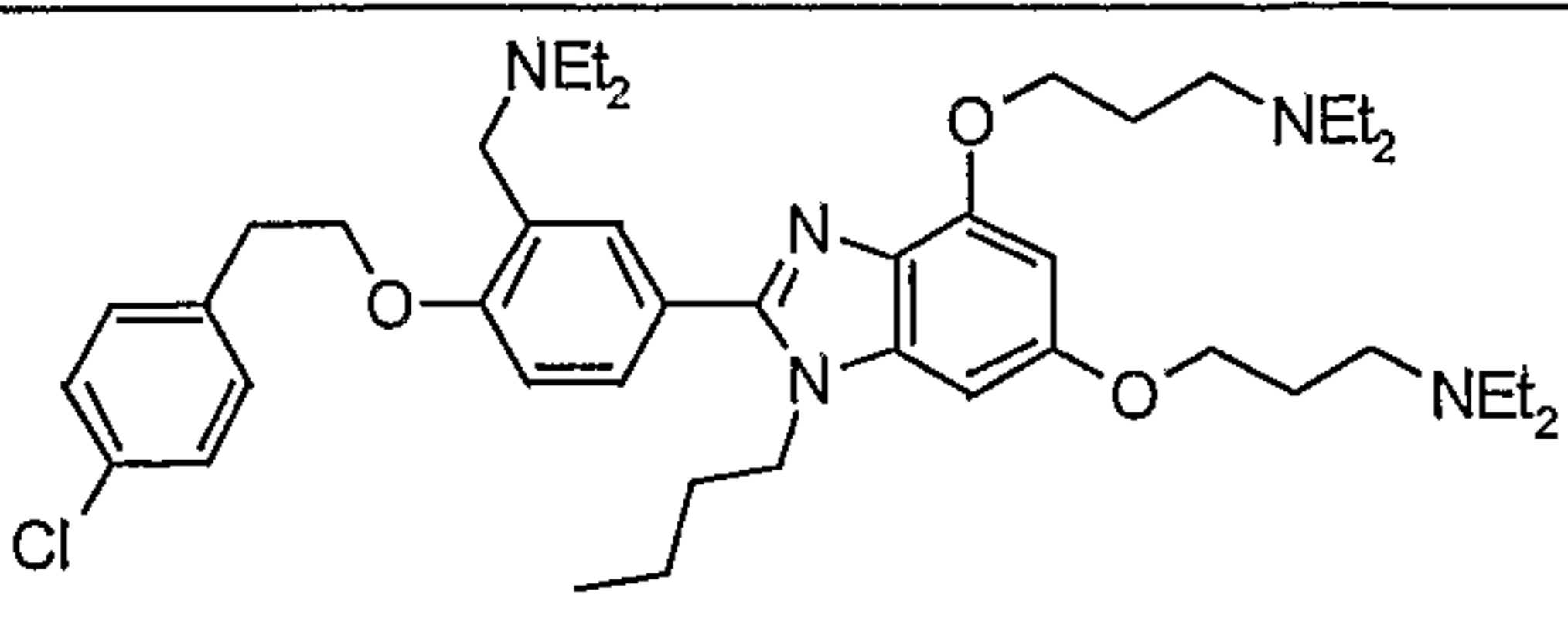
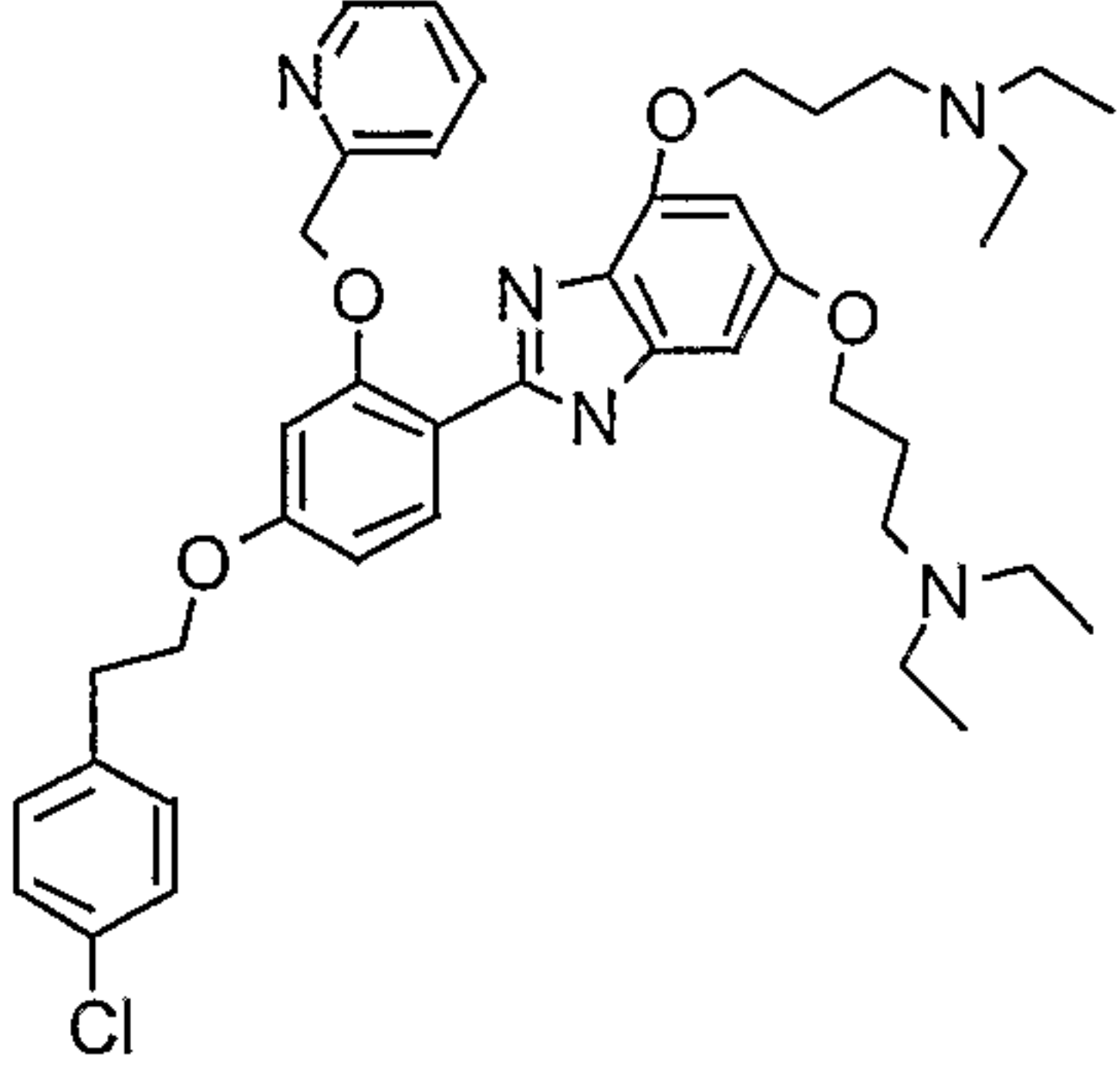
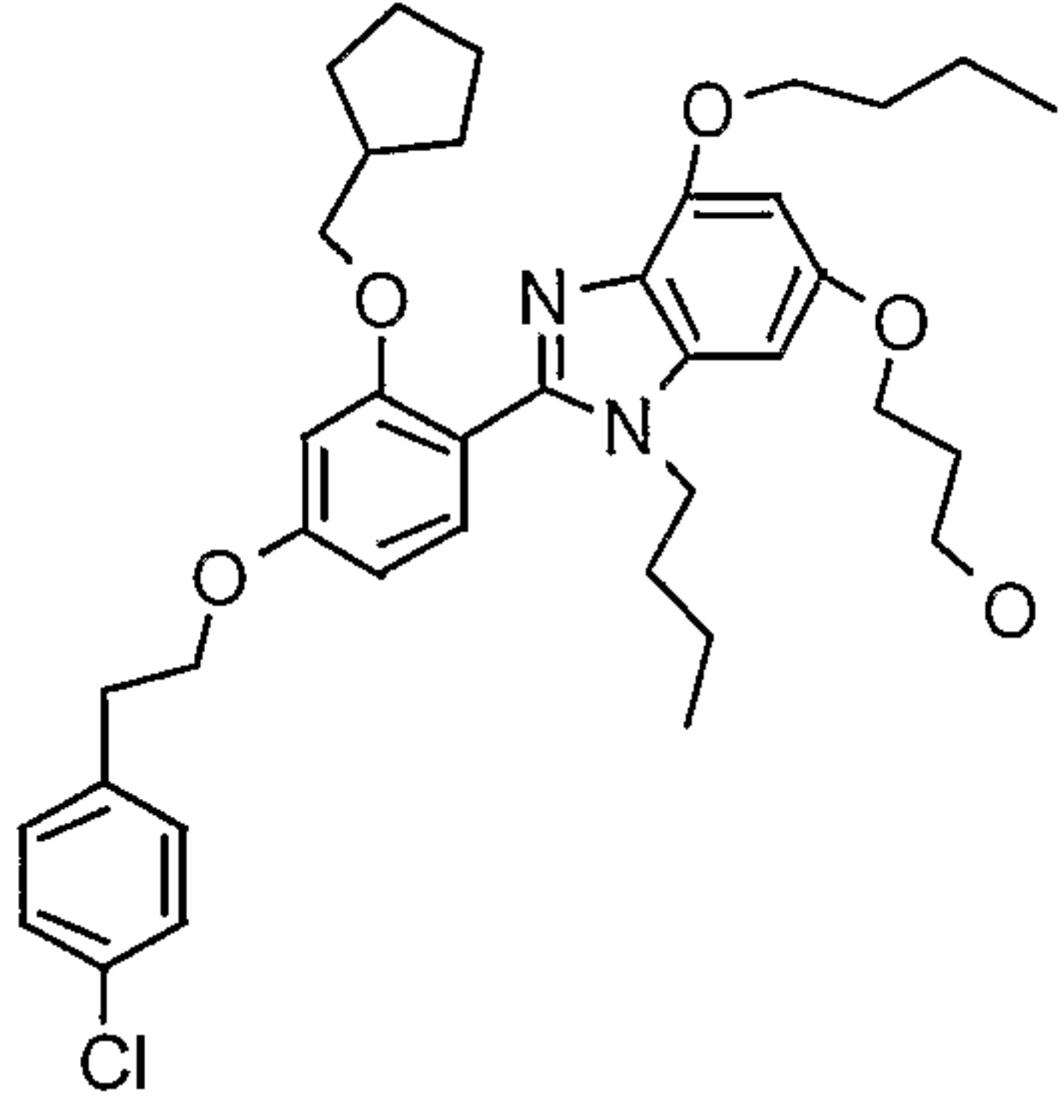
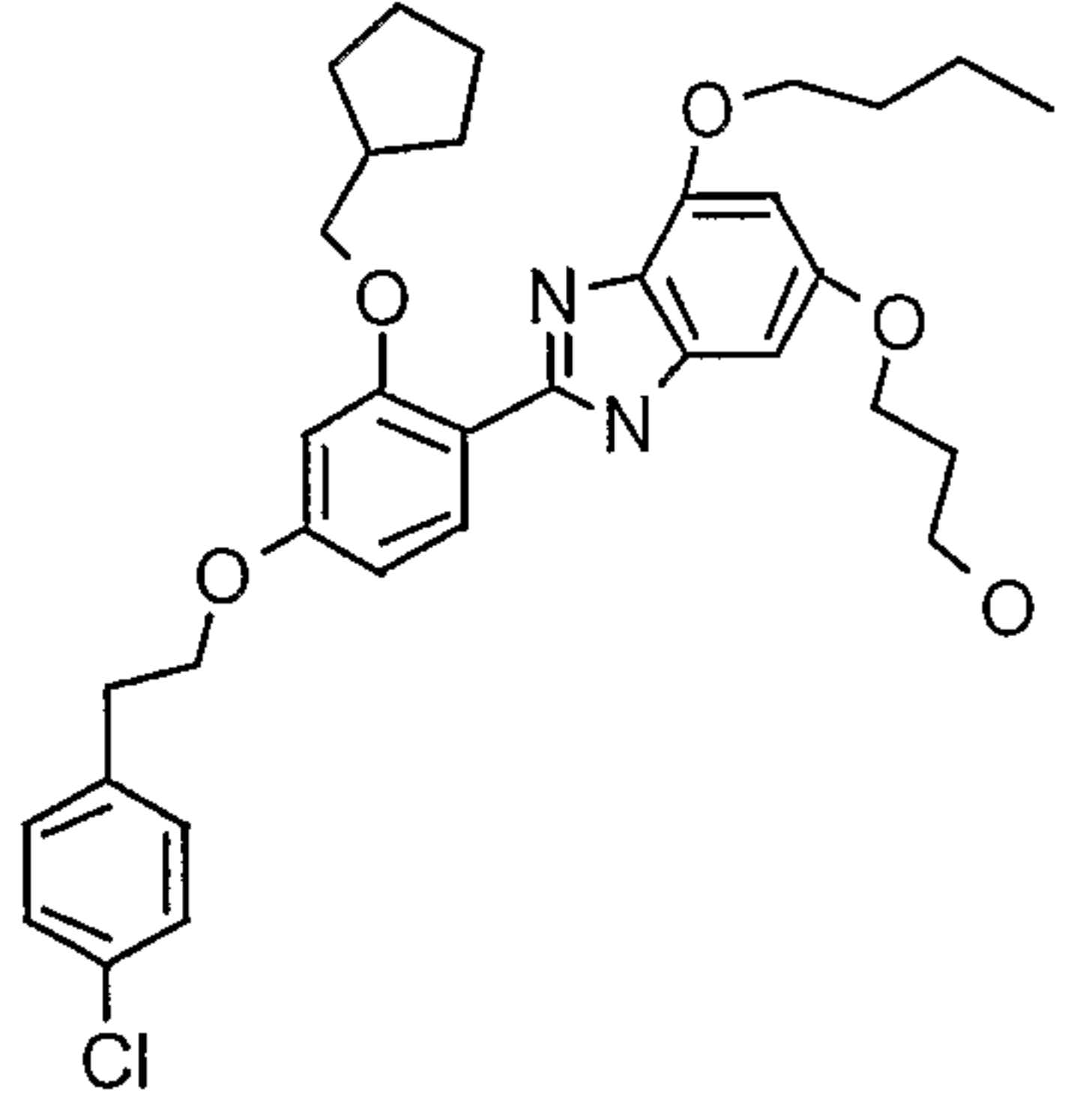
Ex.	Structure	Name
328		1-Butyl-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole
329		1-Butyl-2-[4-(4-chloro-3-trifluoromethyl-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole
330		(3-{2-[1-butyl-6-(3-diethylamino-propoxy)-4-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazol-2-yl]-5-[2-(4-chloro-phenyl)-ethoxy]-phenoxy}-propyl)-diethyl-amine
331		(3-{2-[1-butyl-4,6-bis-(3-diethylamino-propoxy)-1H-benzimidazol-2-yl]-5-[2-(4-chloro-phenyl)-ethoxy]-phenoxy}-propyl)-diethyl-amine

Ex.	Structure	Name
332		(3-{2-[1-Butyl-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazol-2-yl]-5-[2-(4-chloro-phenyl)-ethoxy]-phenoxy}-propyl)-diethyl-amine
333		(3-{1-Butyl-6-(3-diethylamino-propoxy)-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine
334		{3-[1-Butyl-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
335		{3-[2-[1-Butyl-6-(3-diethylamino-propoxy)-4-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazol-2-yl]-5-(4-fluoro-3-trifluoromethyl-phenoxy)-phenoxy]-propyl}-diethyl-amine

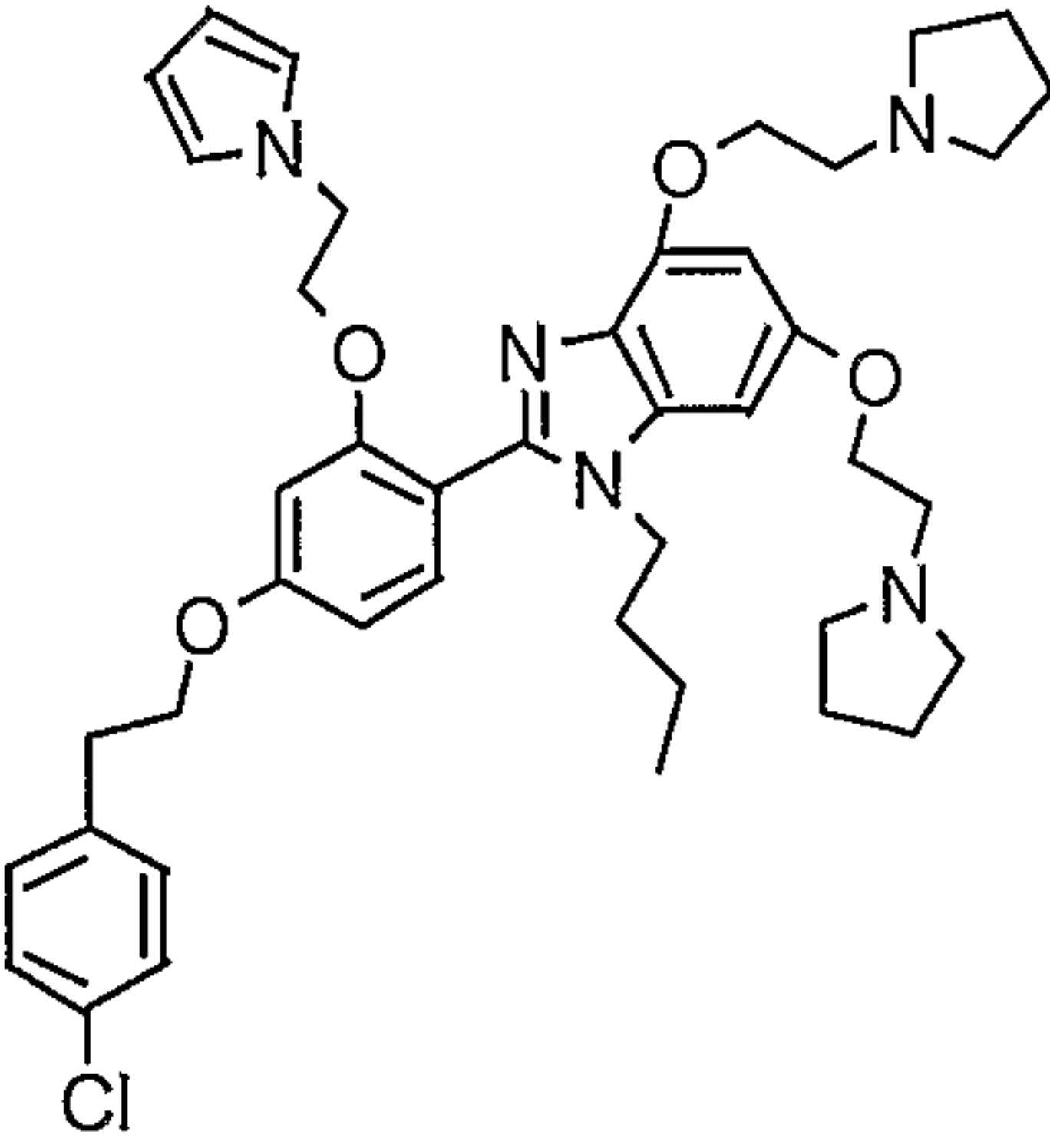
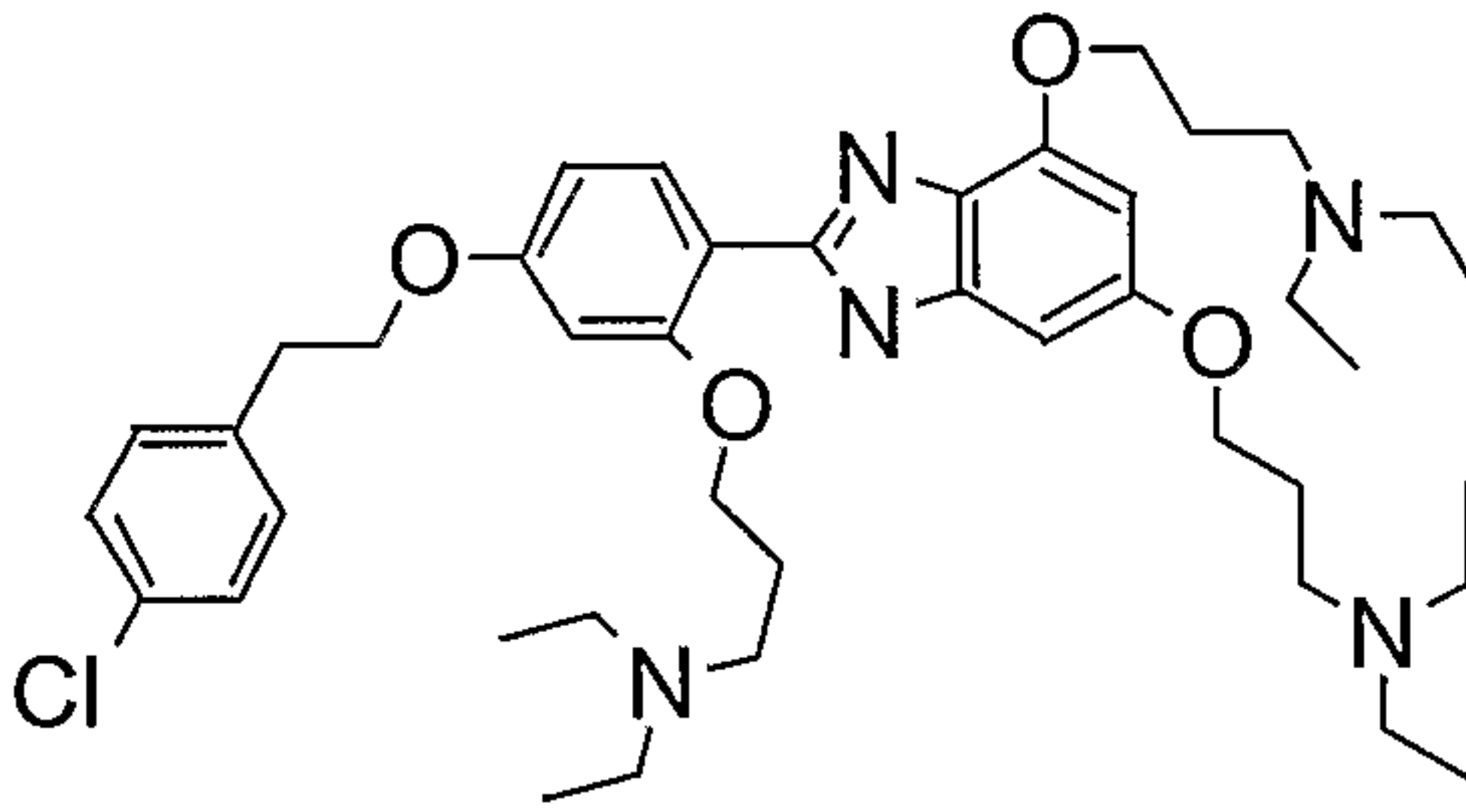
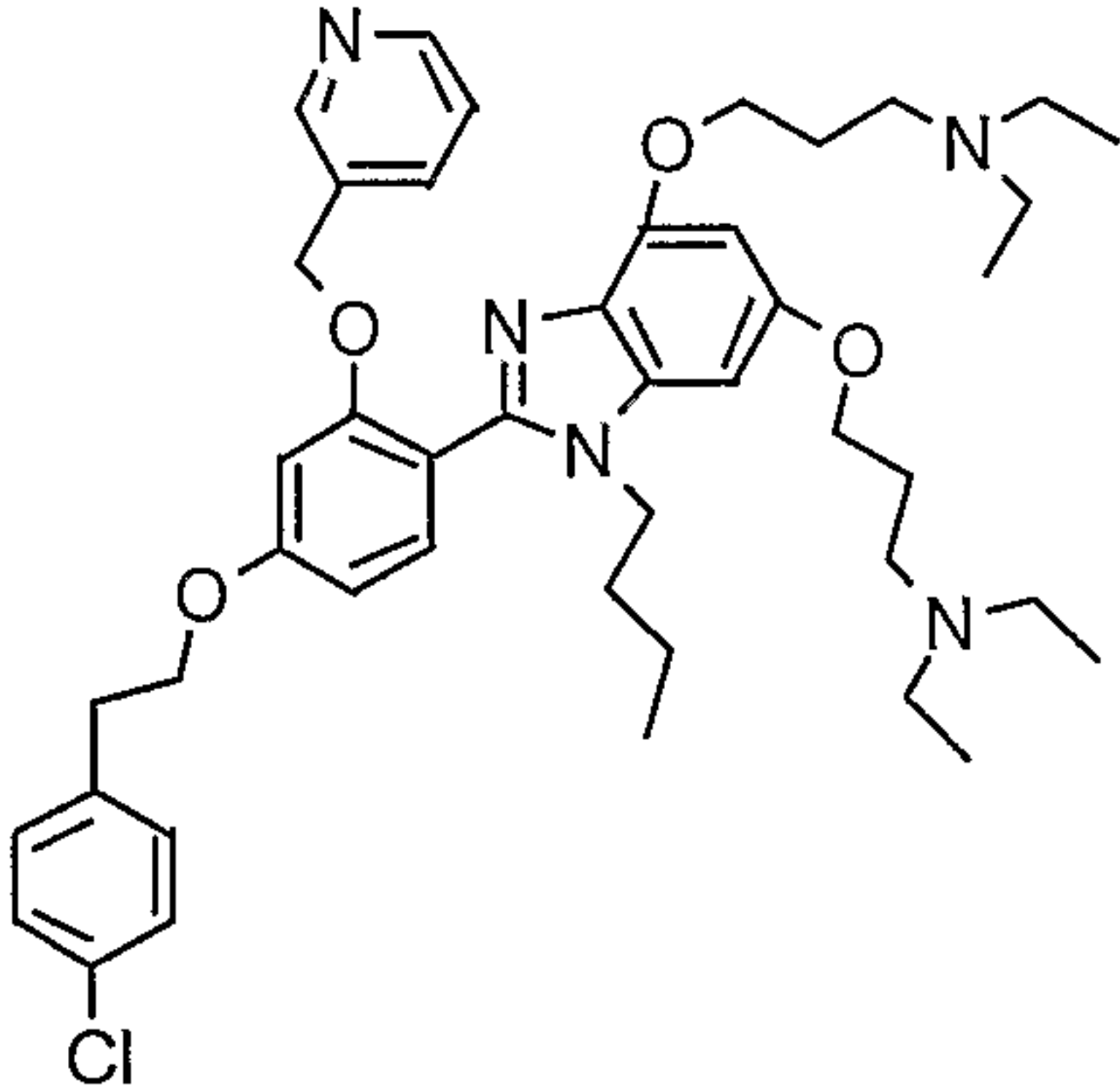
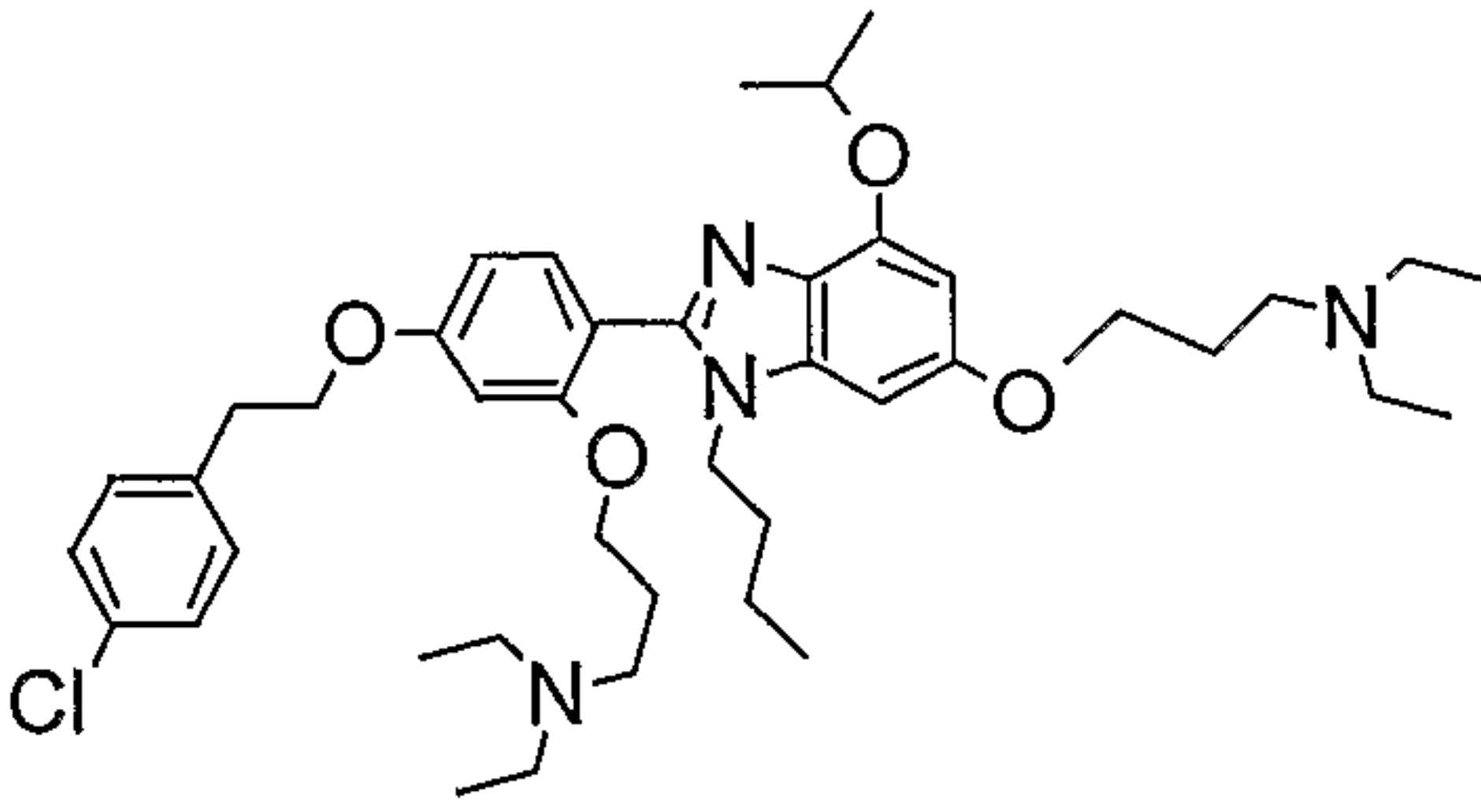
Ex.	Structure	Name
336		{3-[2-[1-Butyl-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazol-2-yl]-5-(4-fluoro-3-trifluoromethyl-phenoxy)-phenoxy]-propyl}-diethyl-amine
337		{3-[3-butyl-2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-7-(2-pyrrolidin-1-yl-ethoxy)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
338		(3-{2-[1-Butyl-4-(3-diethylamino-propoxy)-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazol-2-yl]-5-[2-(4-chloro-phenyl)-ethoxy]-phenoxy}-propyl)-diethyl-amine
339		{3-[1-butyl-2-[4-(3,4-dichloro-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
340		{3-[2-[2,4-bis-(3-diethylamino-propoxy)-phenyl]-1-butyl-6-(4-tert-butyl-phenoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine

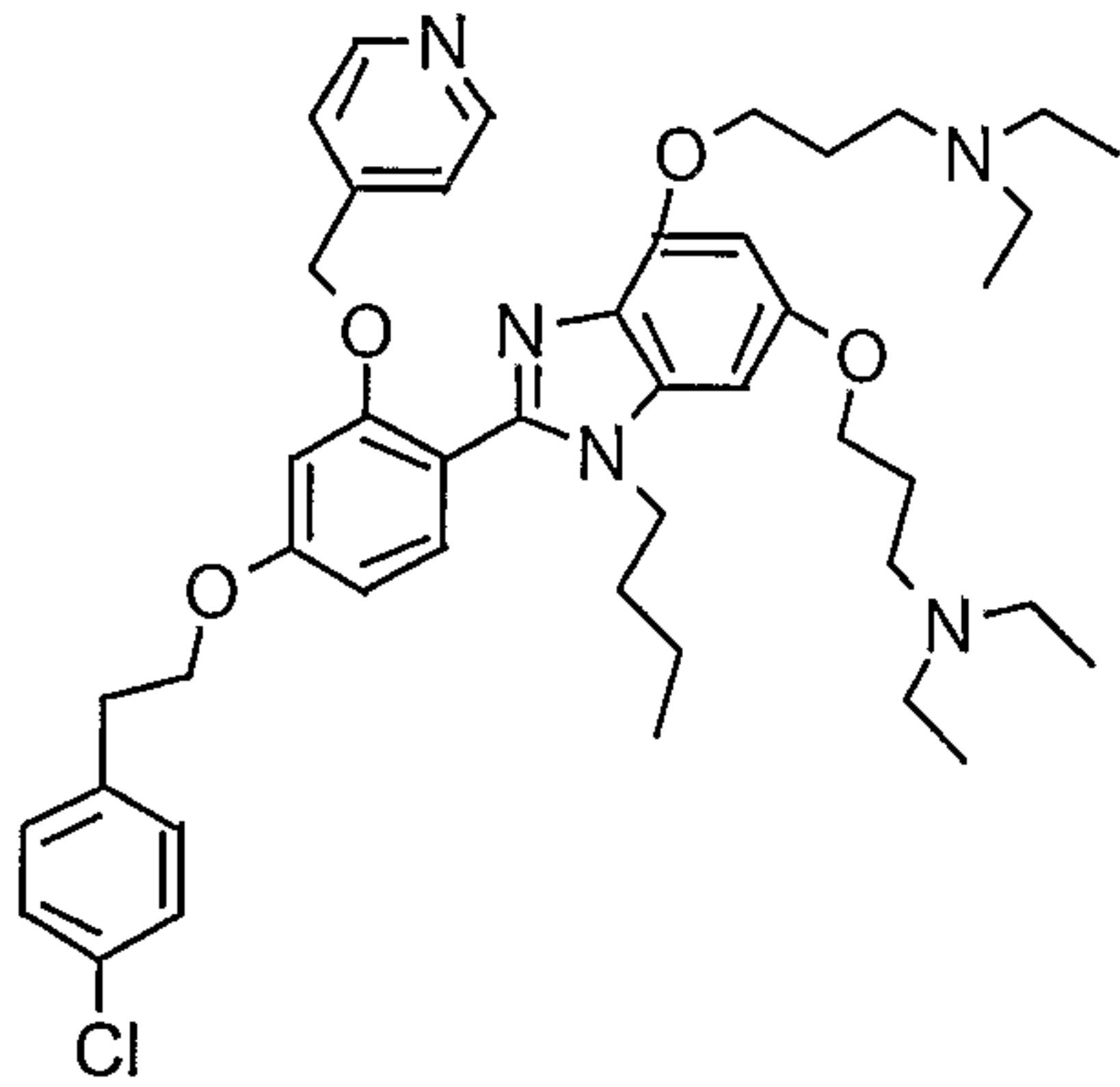
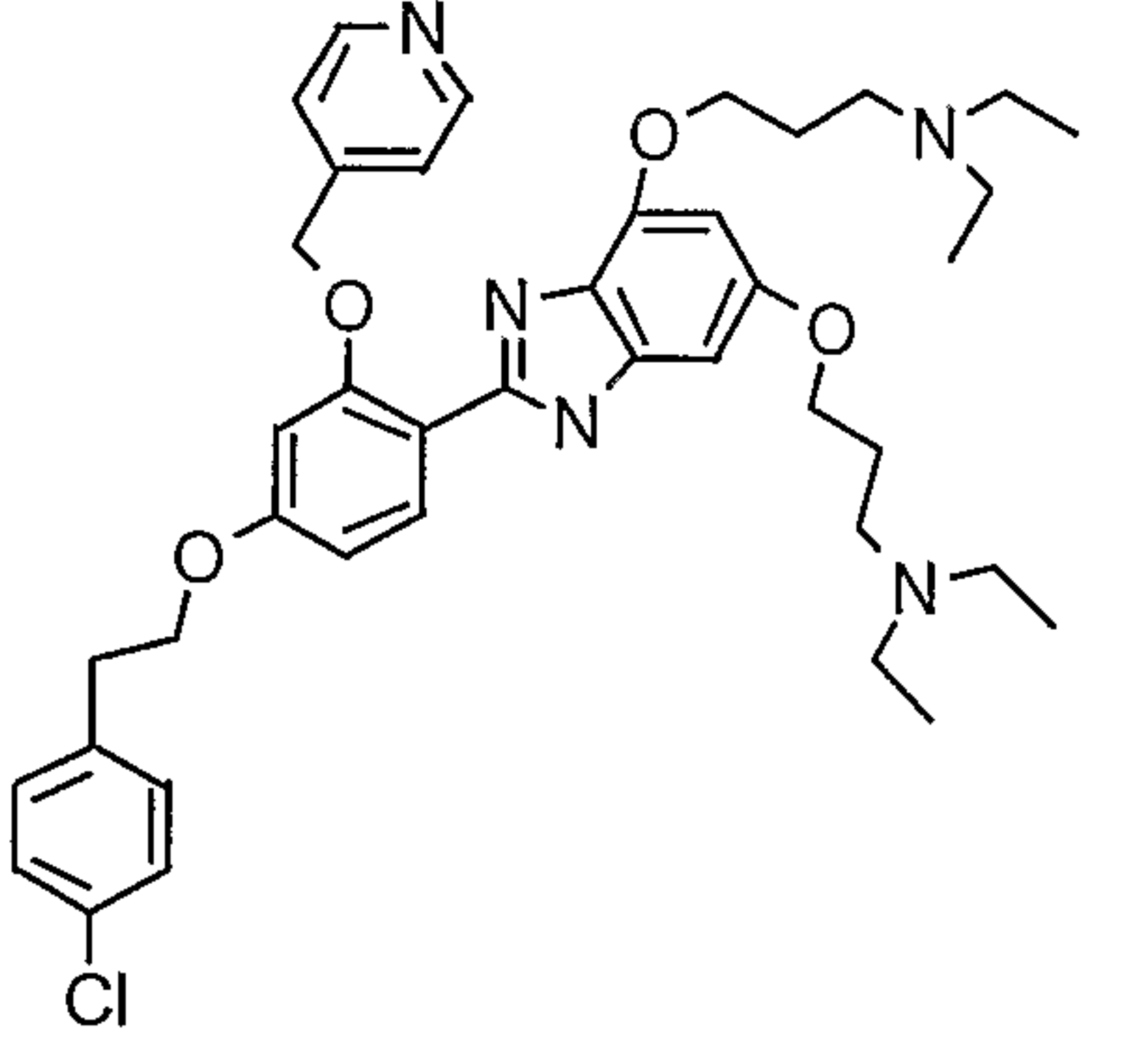
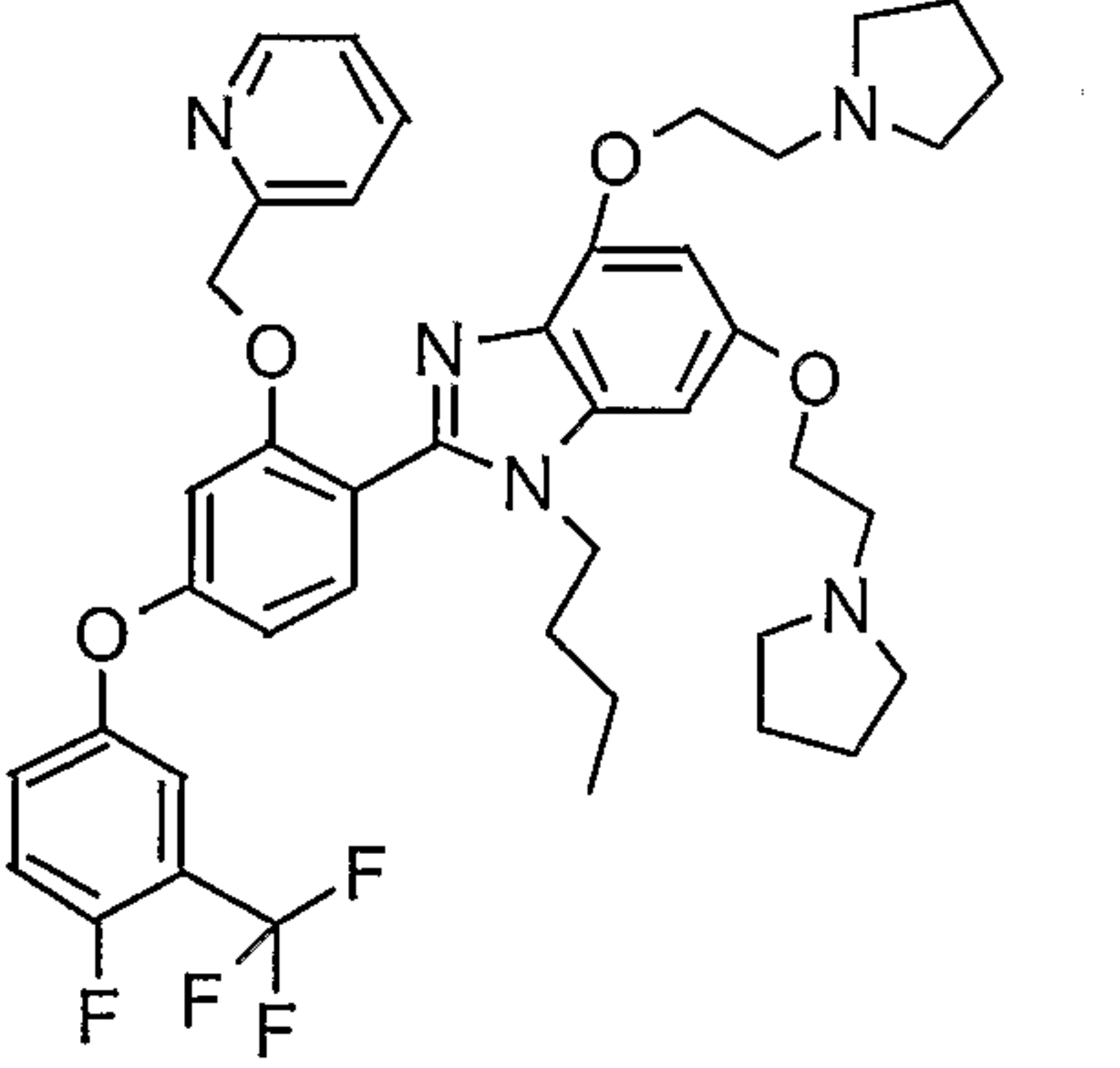
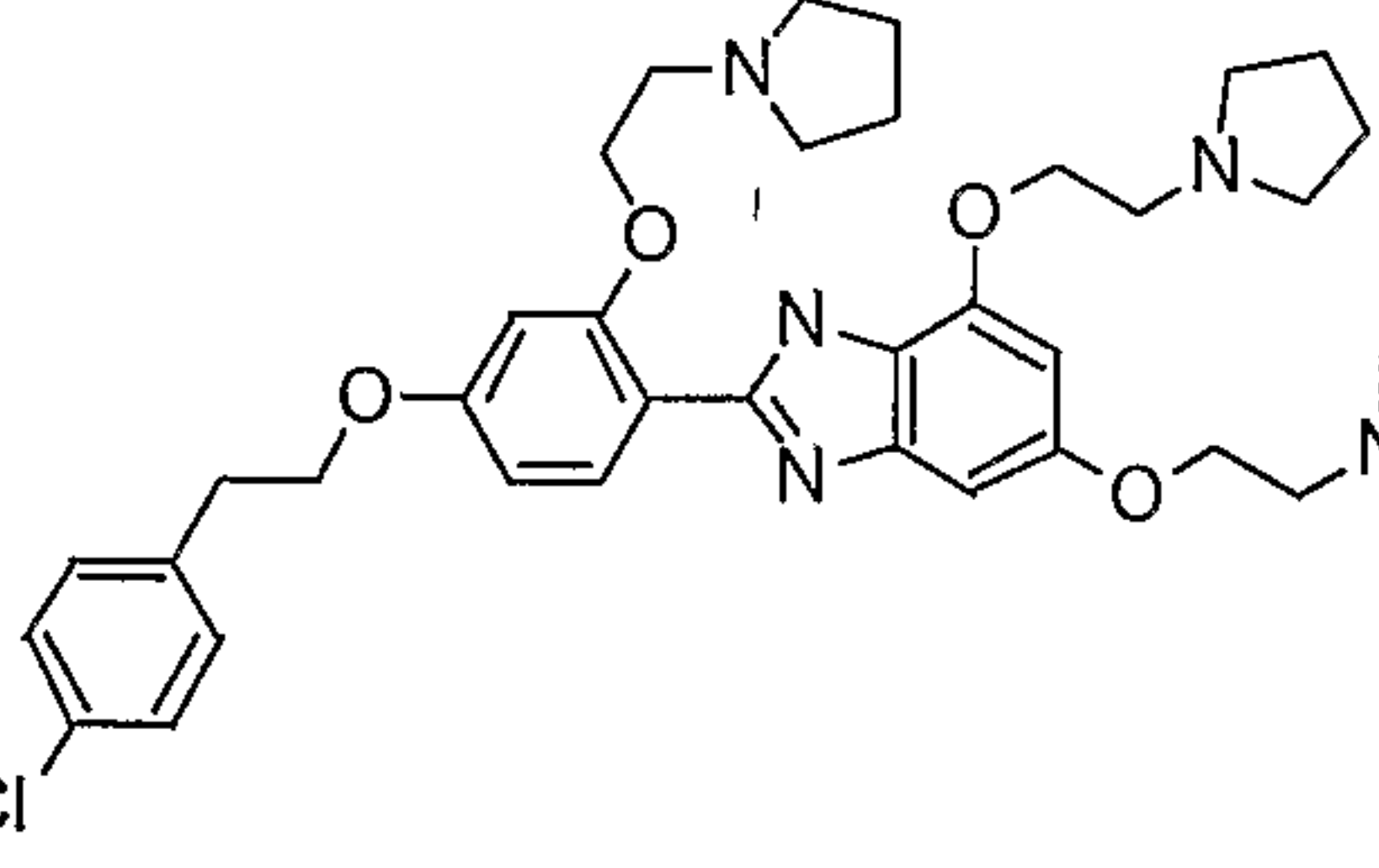
Ex.	Structure	Name
341		{3-[1-butyl-2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(pyridin-2-ylmethoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yl]-phenyl}-diethyl-amine
342		{3-[2-[4-[2-(4-Chloro-phenyl)-ethoxy]-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
343		1-Butyl-2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole
344		{3-[1-Butyl-2-[4-(4-chloro-3-trifluoromethyl-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
345		(3-{6-(3-Diethylamino-propoxy)-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1H-benzoimidazol-4-yloxy}-propyl)-diethyl-amine

Ex.	Structure	Name
346		{3-[2-[1-Butyl-4-(3-diethylamino-propoxy)-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazol-2-yl]-5-(4-fluoro-3-trifluoromethyl-phenoxy)-phenoxy]-propyl}-diethyl-amine
347		{3-[3-Butyl-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-7-(2-pyrrolidin-1-yl-ethoxy)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
348		{3-[1-butyl-2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
349		{3-[2-[1-butyl-4,6-bis-(2-pyrrolodin-1-yl-ethoxy)-1H-benzimidazol-2-yl]-5-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-propyl}-diethyl-amine

Ex.	Structure	Name
350		{3-[1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-3-diethylaminomethyl-phenyl}-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
351		{3-[2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(pyridin-2-ylmethoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yl]-propyl}-diethyl-amine
352		3-(7-Butoxy-3-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-2-cyclopentylmethoxy-phenyl}-3H-benzimidazol-5-yloxy)-propan-1-ol
353		3-(7-Butoxy-2-{4-[2-(4-chloro-phenyl)-ethoxy]-2-cyclopentylmethoxy-phenyl}-3H-benzimidazol-5-yloxy)-propan-1-ol

Ex.	Structure	Name
354		(3-{1-Butyl-6-(3-diethylamino-propoxy)-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-2-(pyridin-2-ylmethoxy)-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine
355		{3-[2-[1-Butyl-4,6-bis-(3-diethylamino-propoxy)-1H-benzimidazol-2-yl]-5-(4-fluoro-3-trifluoromethyl-phenoxy)-phenoxy]-propyl}-diethyl-amine
356		2-(3,5-bis-benzyloxy-phenyl)-1-butyl-4,6-bis-(2-pyrrolodin-1-ylethoxy)-1H-benzimidazole
357		{3-[2-[1-butyl-4,6-bis-(3-diethylamino-propoxy)-1H-benzimidazol-2-yl]-5-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-propyl}-diethyl-amine

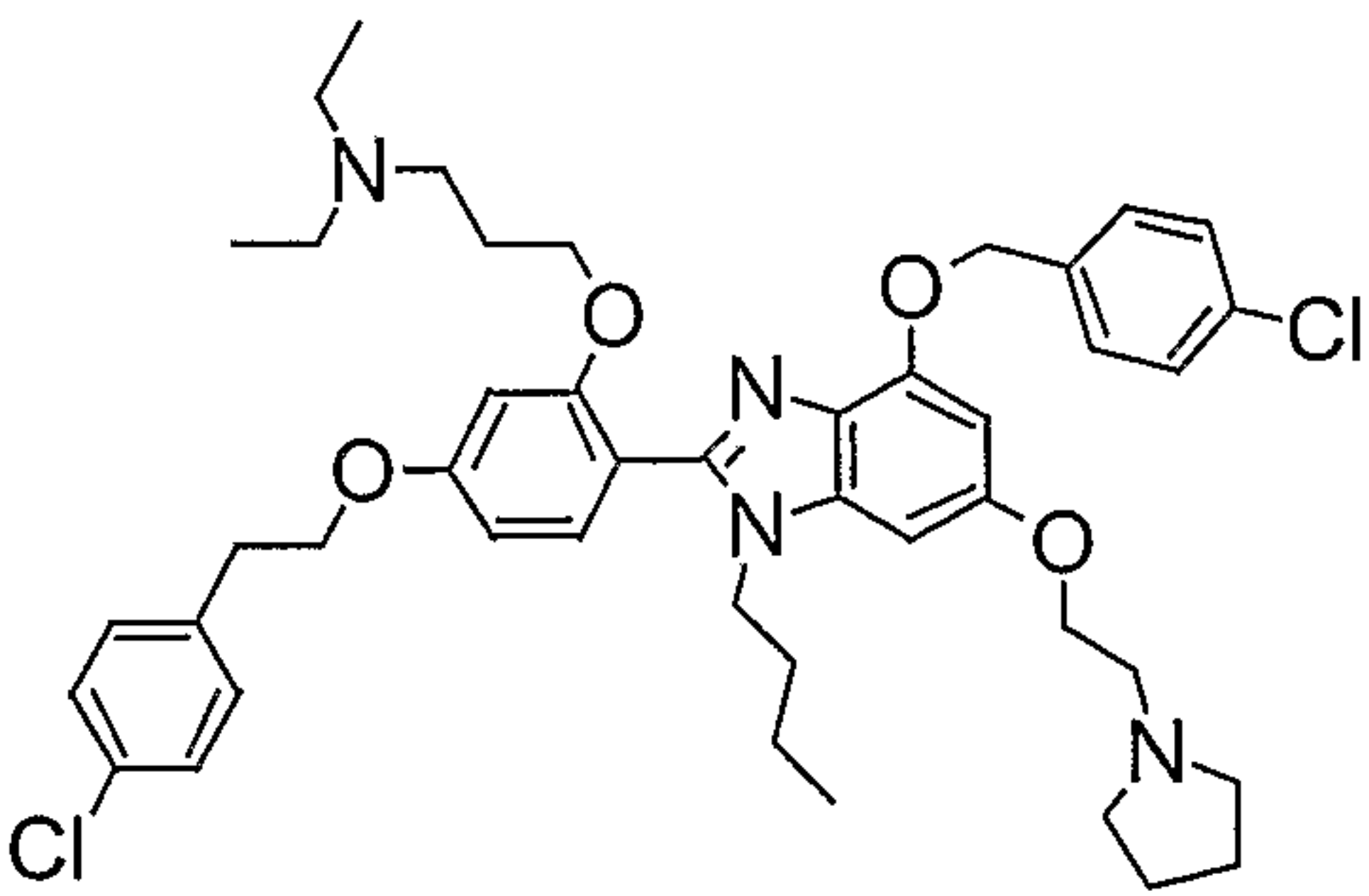
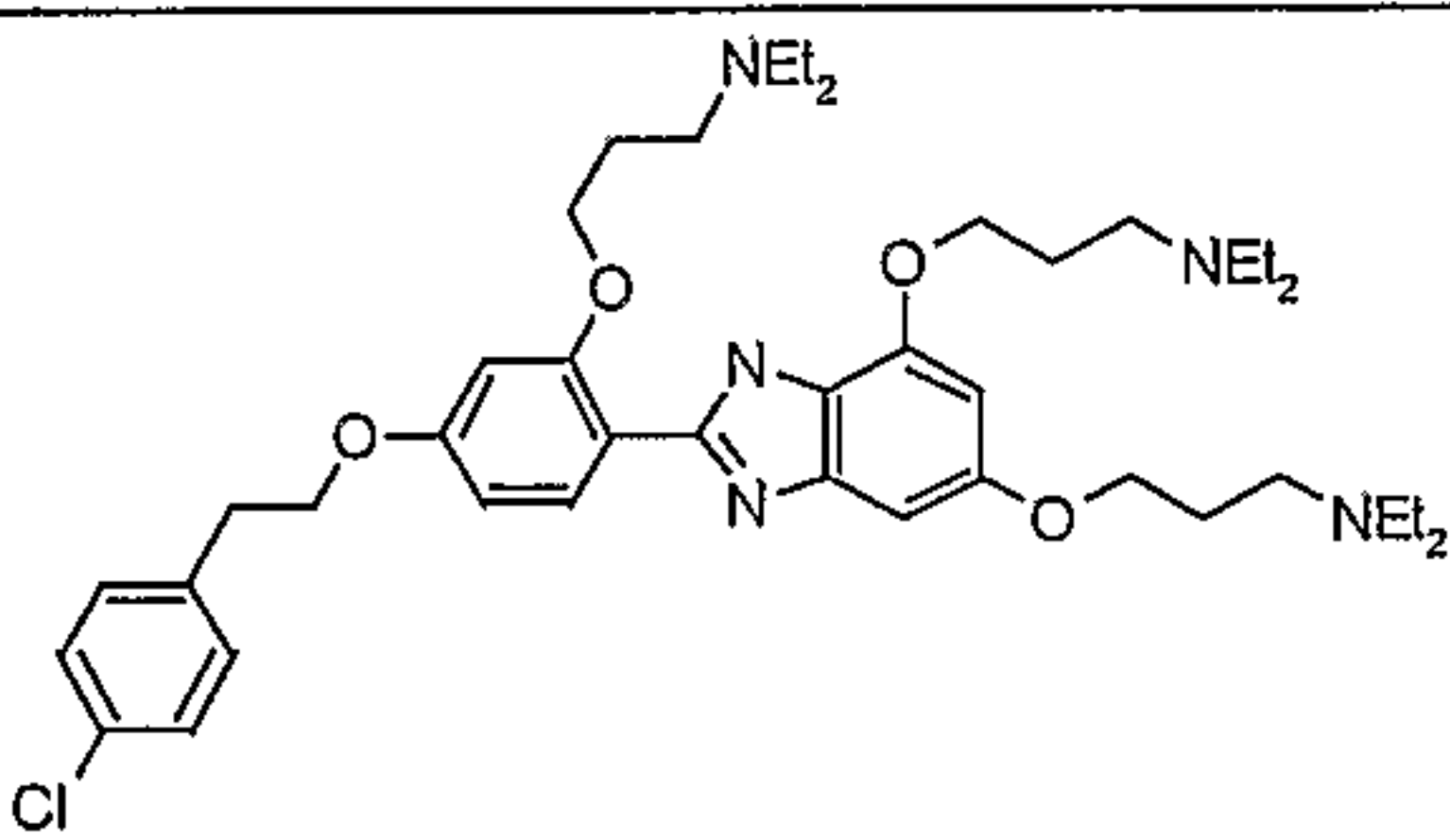
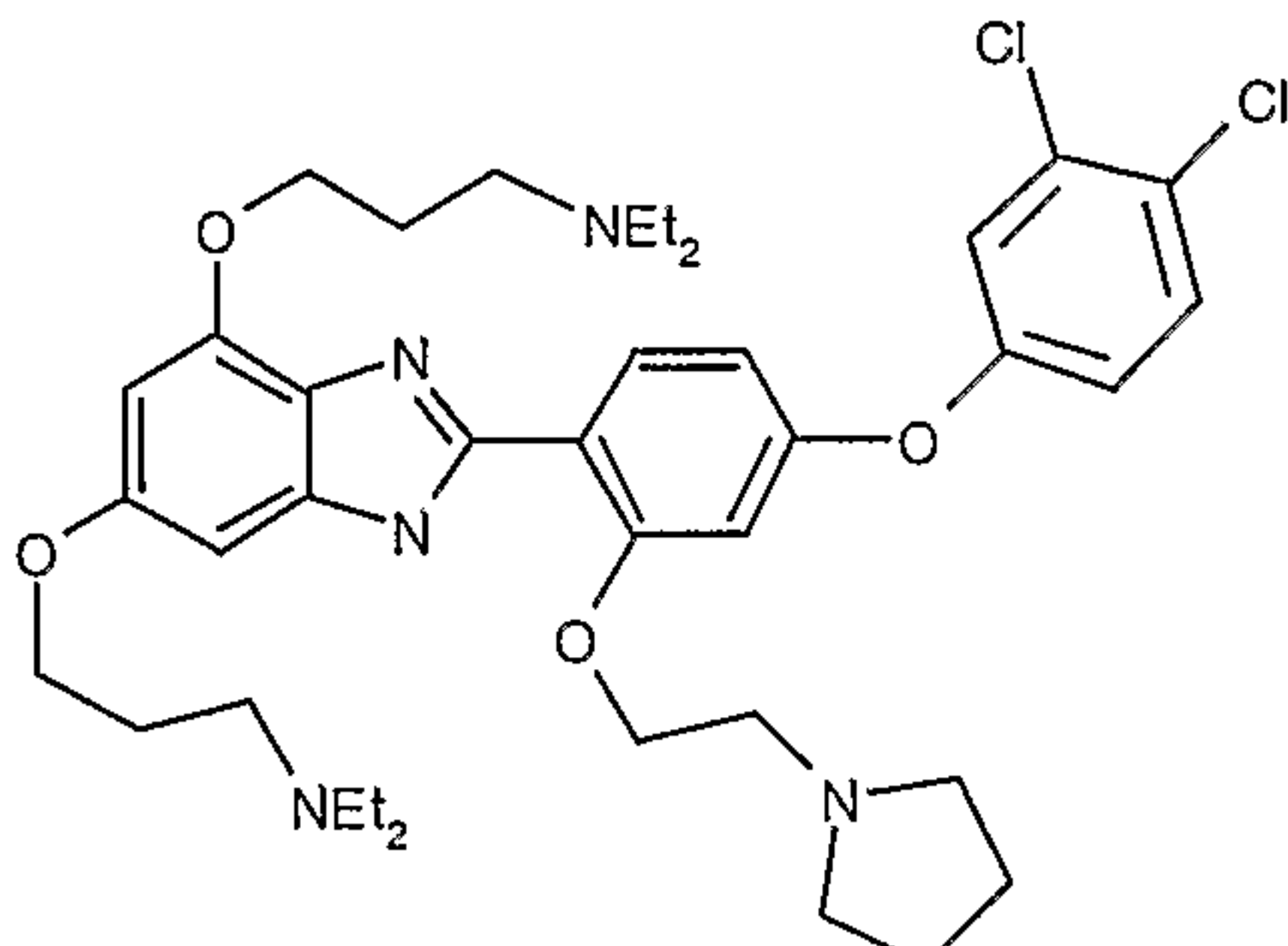
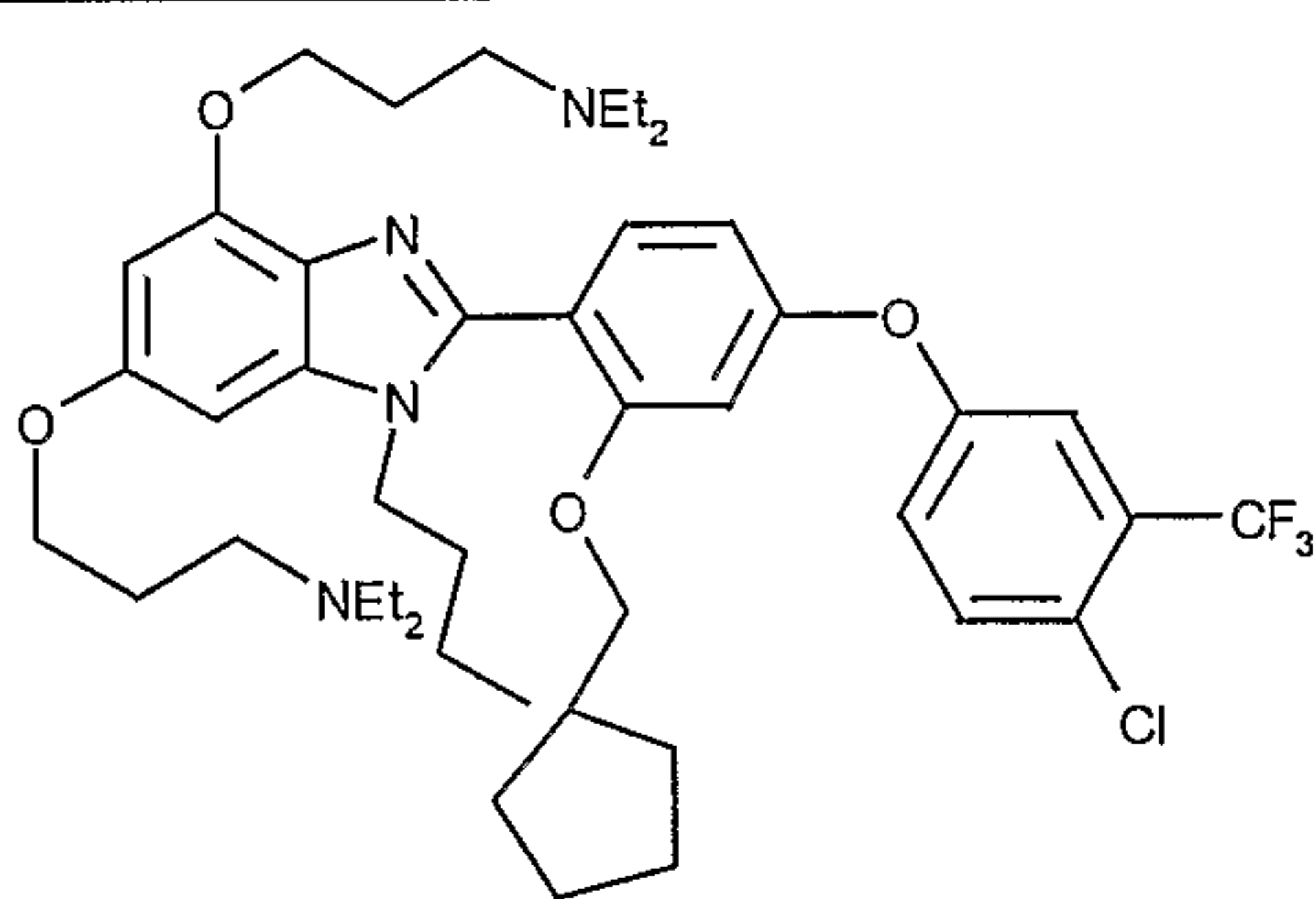
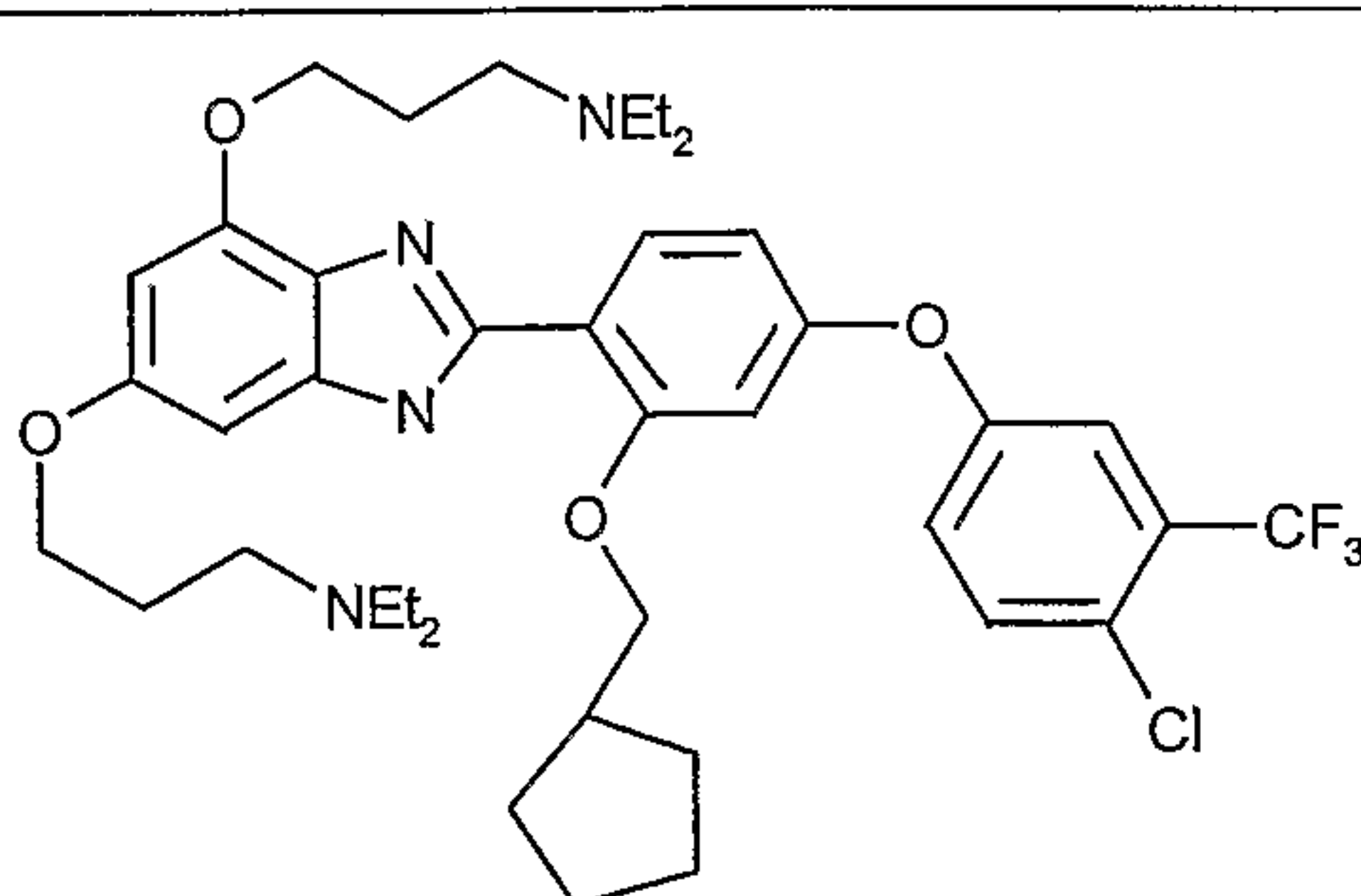
Ex.	Structure	Name
358		1-butyl-2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(2-pyrrol-1-yl-ethoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
359		{3-[2-{4-[2-(4-chloro-phenyl)-ethoxy]-2-(3-diethylamino-propoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
360		{3-[1-Butyl-2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(pyridin-3-ylmethoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
361		(3-{3-Butyl-2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(3-diethylamino-propoxy)-phenyl]-7-isopropoxy-3H-benzimidazol-5-yloxy}-propyl)-diethyl-amine

Ex.	Structure	Name
362		{3-[1-Butyl-2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(pyridin-4-ylmethoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
363		{3-[2-[4-[2-(4-Chloro-phenyl)-ethoxy]-2-(pyridin-4-ylmethoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
364		1-Butyl-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-2-(pyridin-2-ylmethoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
365 correct		2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,7-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole

Ex.	Structure	Name
366		{3-[1-Butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-2-methoxy-phenyl}-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
367		{3-[2-{4-[2-(4-Chloro-phenyl)-ethoxy]-2-methoxy-phenyl}-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
368		(3-{1-Butyl-2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(3-diethylamino-propoxy)-phenyl]-6-isopropoxy-1H-benzoimidazol-4-yloxy}-propyl)-diethyl-amine
369		{3-[1-Butyl-2-[4-(4-chloro-3-methyl-phenoxy)-2-(pyridin-2-ylmethoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine

Ex.	Structure	Name
370		1-Butyl-2-[4-(4-chloro-3-trifluoromethyl-phenoxy)-2-cyclopentylmethoxy-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole
371		(2-{1-butyl-6-(2-dimethylamino-ethoxy)-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1H-benzoimidazole-4-yloxy}-ethyl)-dimethyl-amine
372		2-[1-butyl-4,6-bis-(3-diethylamino-propoxy)-1H-benzimidazol-2-yl]-5-[2-(4-chloro-phenyl)-ethoxy]-phenol
373		1-Butyl-2-[4-(4-chloro-3-methyl-phenoxy)-2-(pyridin-2-ylmethoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole

Ex.	Structure	Name
374		2-[4-(4-Chloro-3-trifluoromethylphenoxy)-2-cyclopentylmethoxyphenyl]-4,6-bis-(2-pyrrolidin-1-ylethoxy)-1H-benzimidazole
375		2-[4-(4-Fluoro-3-trifluoromethylphenoxy)-2-(2-pyrrolidin-1-ylethoxy)phenyl]-4,6-bis-(2-pyrrolidin-1-ylethoxy)-1H-benzimidazole
376		{3-[2-(3,5-bis-benzyloxyphenyl)-1-butyl-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
377		(3-{1-butyl-6-(3-dimethylamino-propoxy)-2-[4-(3-fluorophenoxy)-2-(2-pyrrolidin-1-ylethoxy)phenyl]-1H-benzimidazole-4-yloxy}-propyl)-diethyl-amine

Ex.	Structure	Name
378		{3-[2-{1-butyl-4-(4-chlorobenzyloxy)-6-(2-pyrrolidin-1-ylethoxy)-1H-benzimidazol-2-yl]-5-[2-(4-chlorophenyl)-ethoxy]-phenoxy]-propyl}-diethyl-amine
379		{3-[2-{4-[2-(4-chlorophenyl)-ethoxy]-2-(3-diethylamino-propoxy)-phenyl]-6-(3-diethylamino-propoxy)-3H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
380		{3-[2-[4-(3,4-dichlorophenoxy)-2-(2-pyrrolidin-1-ylethoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
381		{3-[1-Butyl-2-[4-(4-chloro-3-trifluoromethylphenoxy)-2-cyclopentylmethoxyphenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
382		{3-[2-[4-(4-chloro-3-trifluoromethylphenoxy)-2-cyclopentylmethoxyphenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine

Ex.	Structure	Name
383		(3-{1-butyl-6-(4-tert-butyl-phenoxy)-2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(3-diethylamino-propoxy)-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine
384		2-{2,4-bis-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-1-butyl-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
385		(2-{1-butyl-6-(2-dimethylamino-ethoxy)-2-[4-(3-fluoro-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1H-benzimidazole-4-yloxy}-ethyl)-dimethyl-amine
386		{3-[2-[4-(3,5-bis-trifluoromethyl-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1-butyl-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine

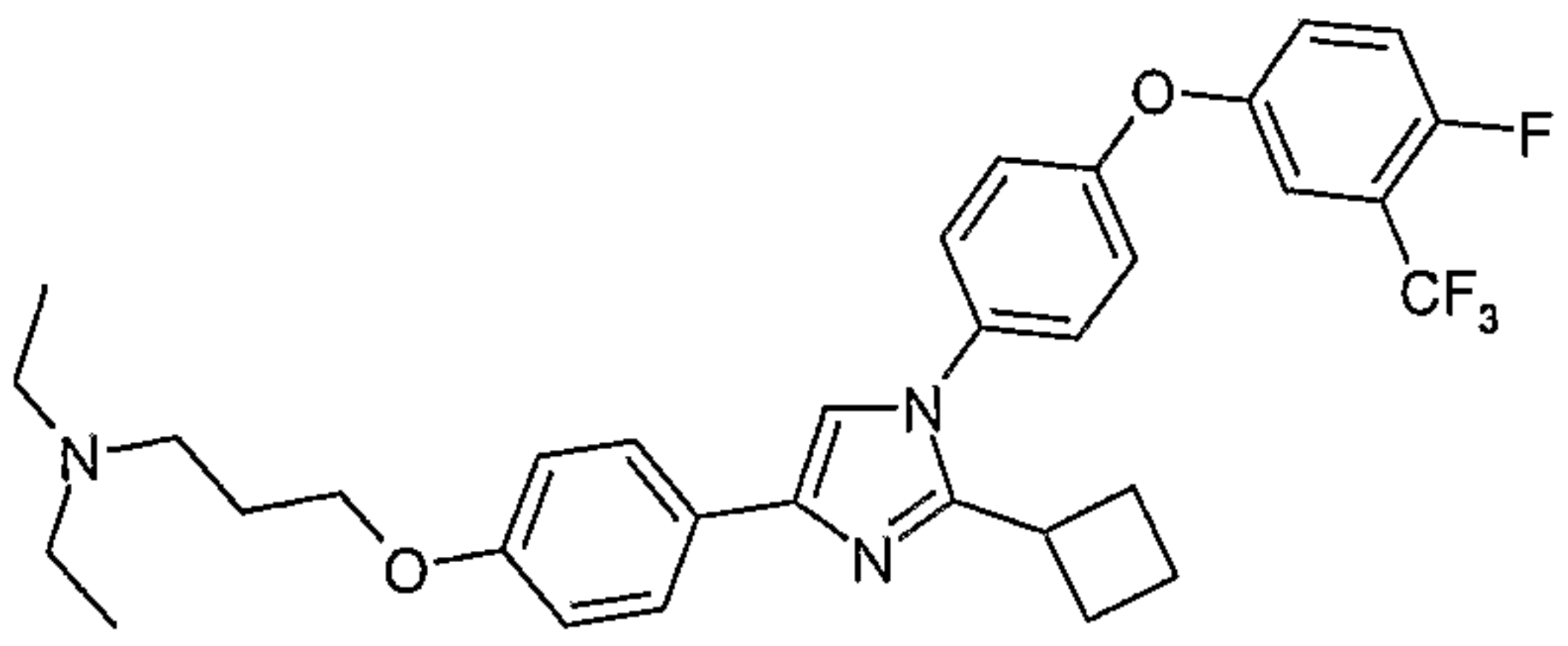
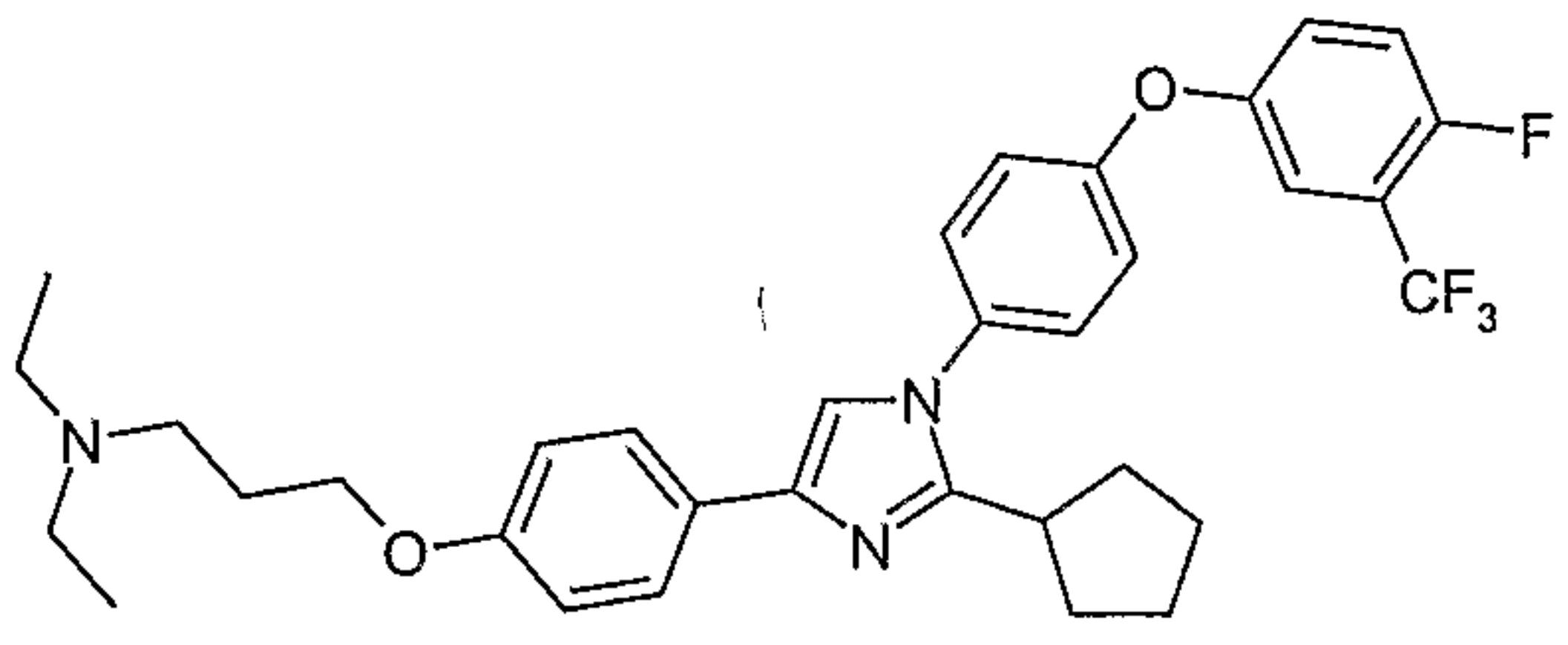
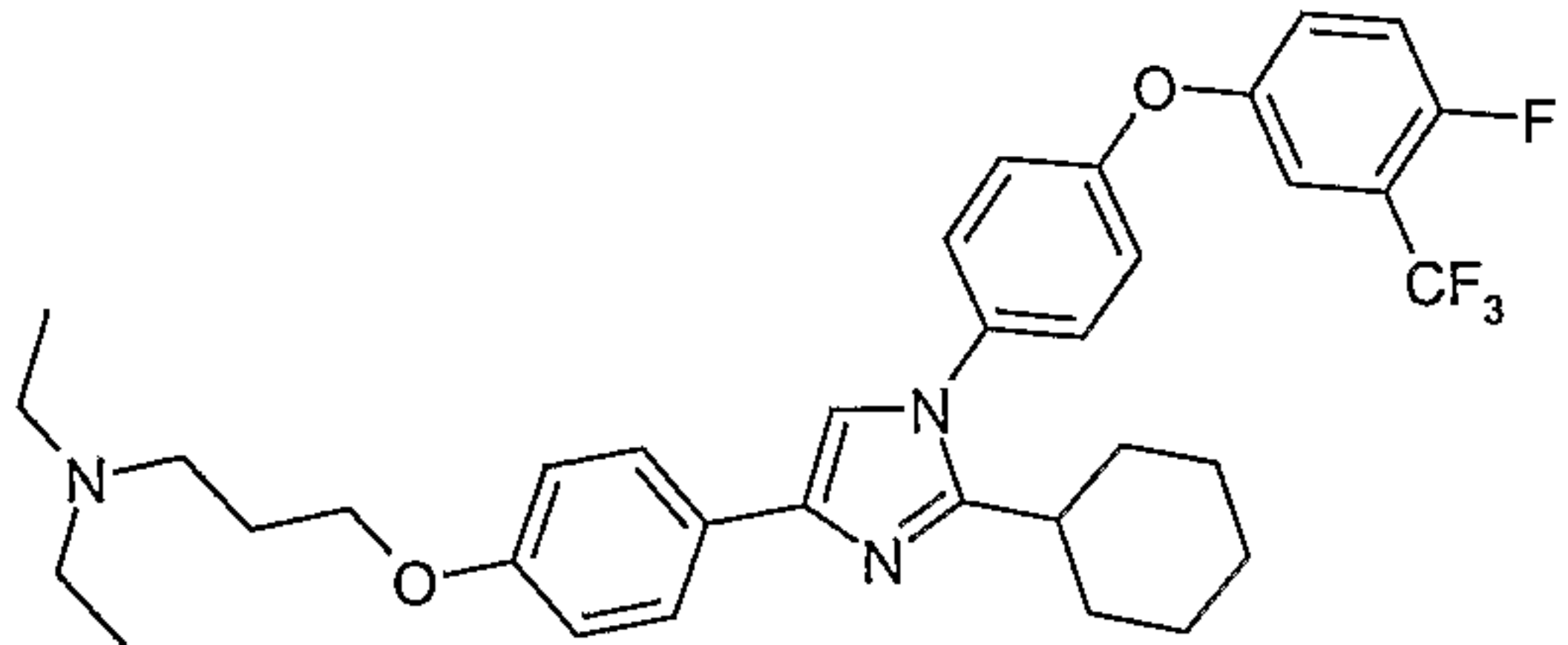
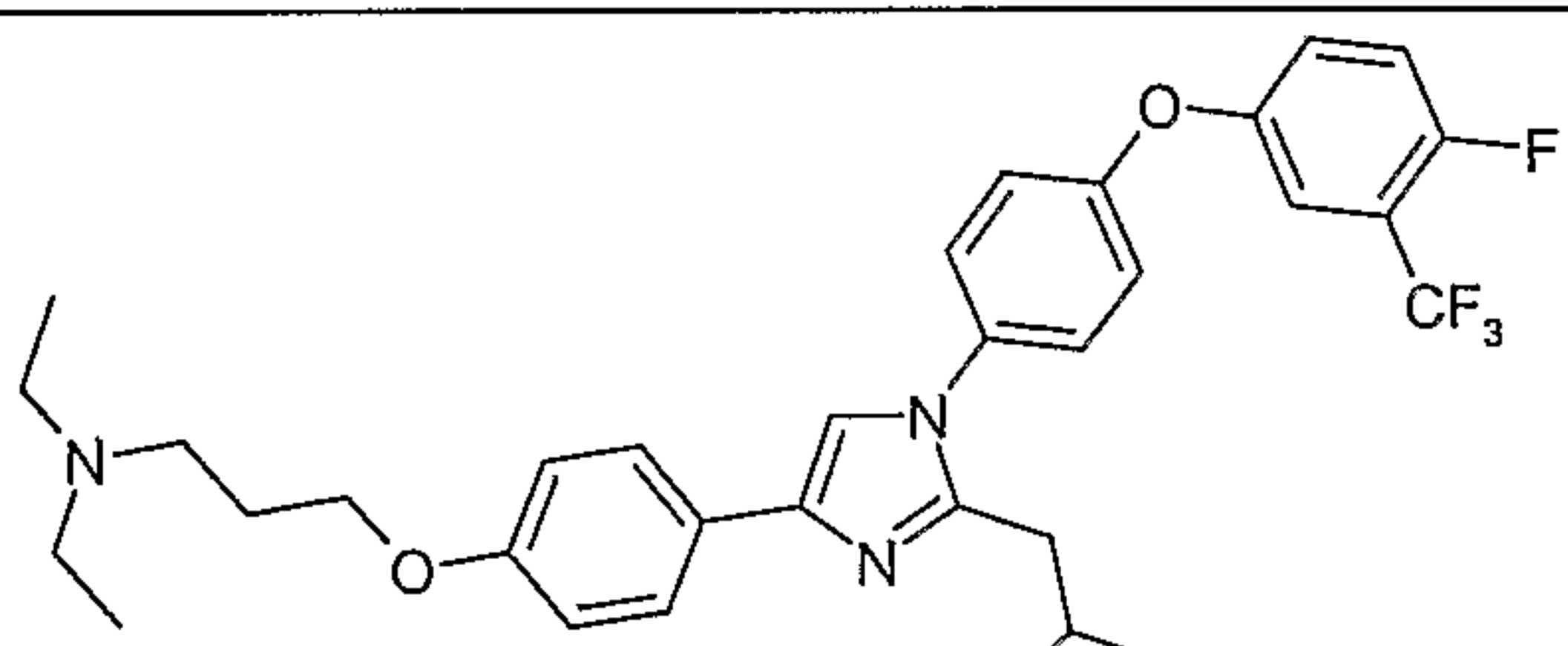
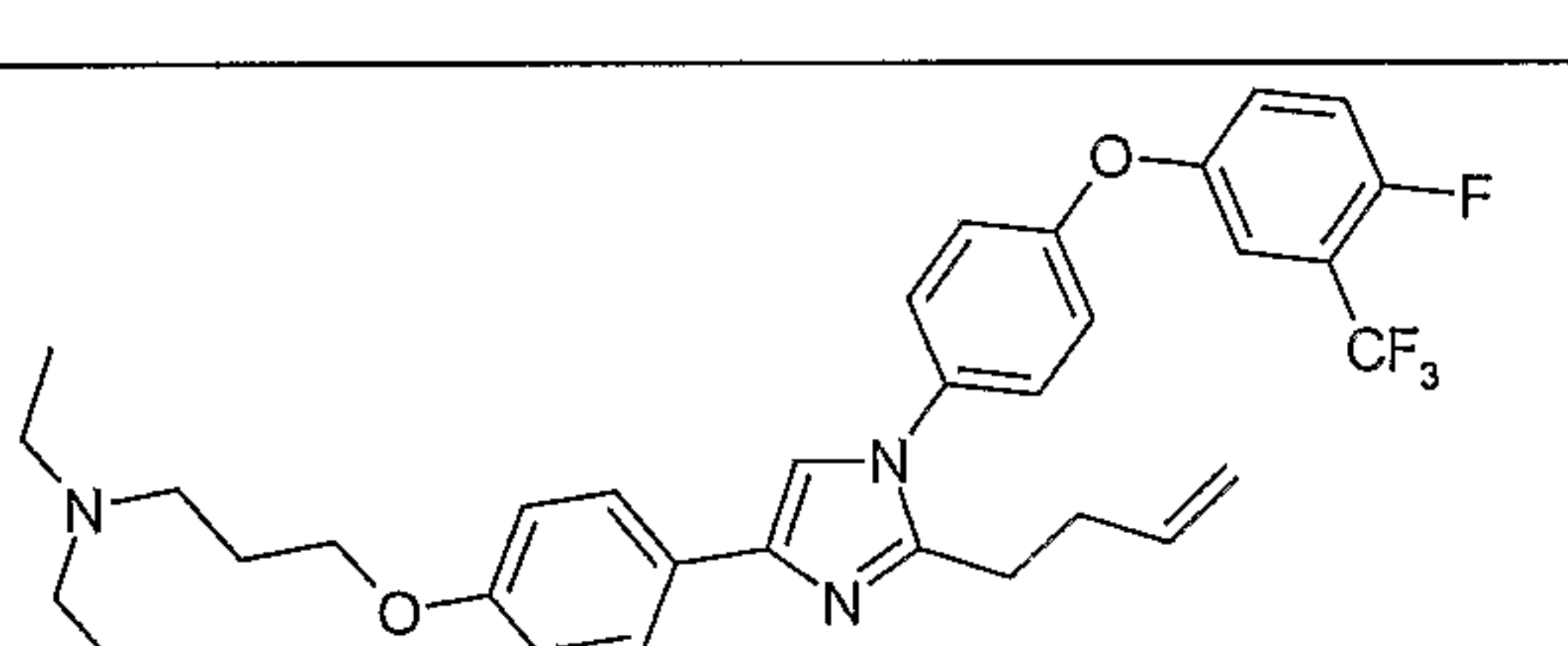
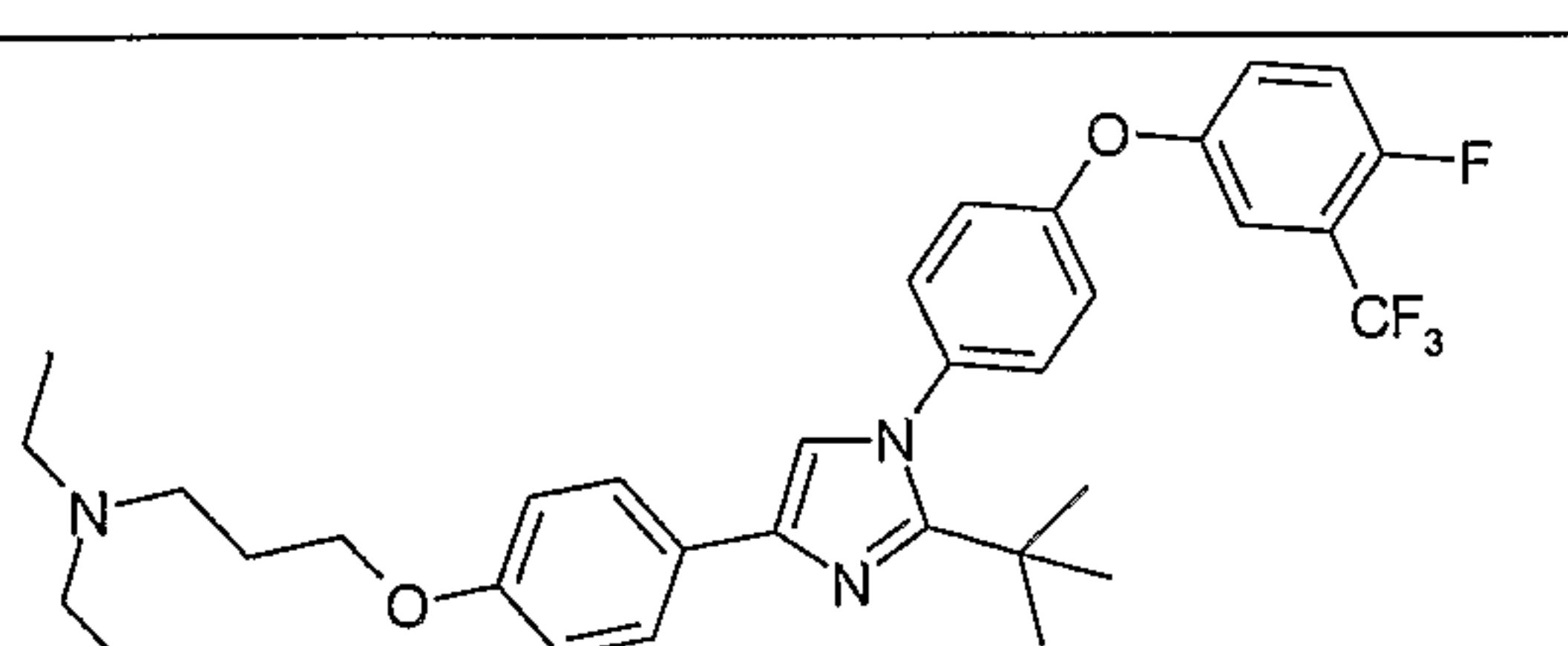
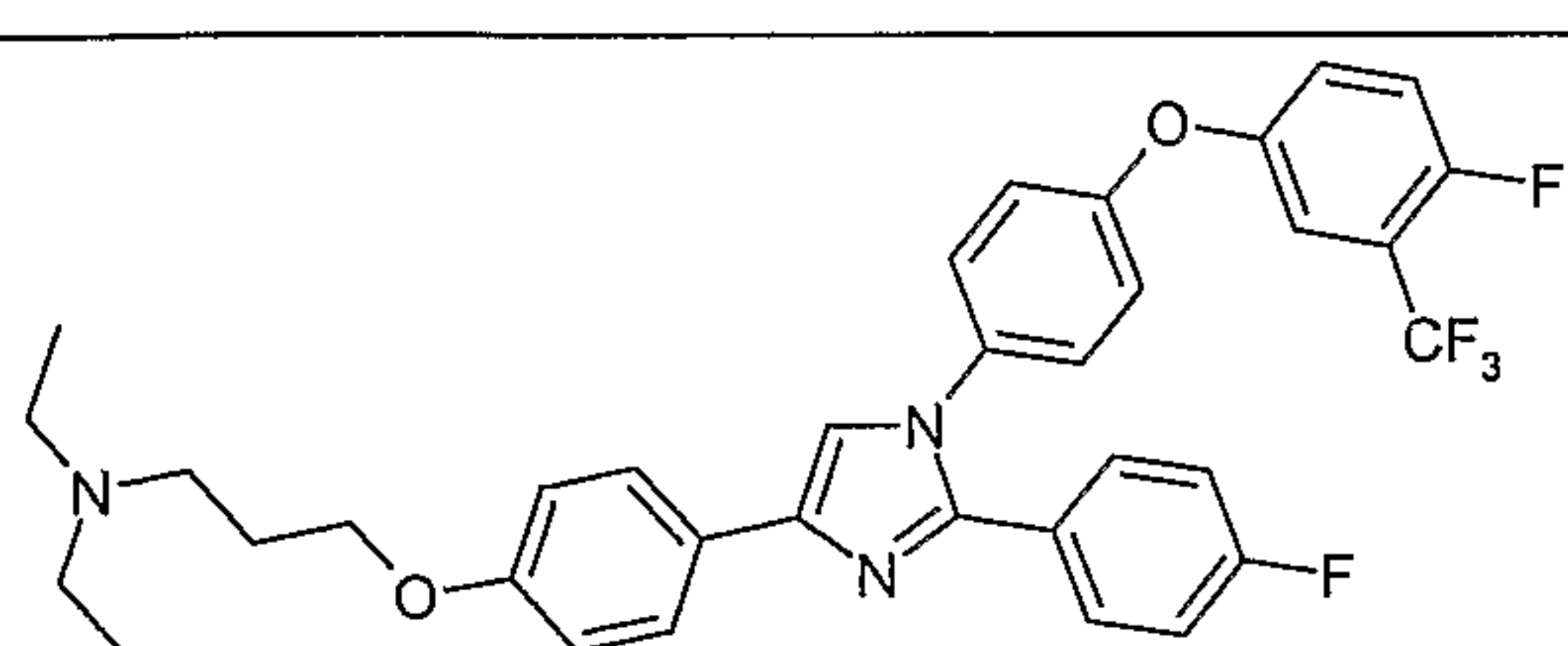
Ex.	Structure	Name
387		{3-[1-butyl-2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
388		(3-{2-(1-Butyl-4,6-diisopropoxy-1H-benzoimidazol-2-yl)-5-[2-(4-chloro-phenyl)-ethoxy]-phenoxy}-propyl)-diethyl-amine
389		{3-[1-butyl-2-{3-[2-(4-chloro-phenyl)-ethoxy]-4-diethylaminomethyl-phenyl}-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
390		(3-{1-Butyl-6-(3-diethylamino-propoxy)-2-[4-fluoro-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1H-benzoimidazol-4-yloxy}-propyl)-diethyl-amine
391		(2-{1-butyl-6-fluoro-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1H-benzoimidazol-4-ylsulfanyl}-ethyl)-dimethyl-amine

Ex.	Structure	Name
392		{3-[1-Butyl-2-[4-[2-(4-chloro-phenyl)-ethoxy]-3-(3-diethylamino-propoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
393		(4-benzyloxy-benzyl)-[1-butyl-6-(3-diethylamino-propoxy)-1H-benzimidazol-2-ylmethyl]-hexyl-amine
394		(4-benzyloxy-benzyl)-[1-butyl-6-(3-diethylamino-propoxy)-1H-benzimidazol-2-ylmethyl]-isobutyl-amine
395		[3-(2-[(4-benzyloxy-benzyl)-cyclopentylmethyl-amino]-methyl)-3-butyl-3H-benzimidazol-5-yloxy]-propyl]-diethyl-amine
396		N-(4-benzyloxy-benzyl)-N-[1-butyl-6-(3-diethylamino-propoxy)-1H-benzimidazol-2-ylmethyl]-benzamide
397		(3-{3-butyl-2-[(dibenzylamino)-methyl]-3H-benzimidazol-5-yloxy}-propyl)-diethyl-amine

Ex.	Structure	Name
398		(3-{2-[(4-benzyloxy-benzylamino)-methyl]-3-butyl-3H-benzimidazol-5-yloxy}-propyl)-diethyl-amine
399		N-(4-benzyloxy-benzyl)-N-[1-butyl-6-(3-diethylamino-propoxy)-1H-benzimidazol-2-ylmethyl]-methanesulfonamide
400		N-(4-benzyloxy-benzyl)-N-[1-butyl-6-(3-diethylamino-propoxy)-1H-benzimidazol-2-ylmethyl]-acetamide
401		{3-[3-butyl-2-({4-[2-(4-chloro-phenyl)-ethoxy]-benzylamino}-methyl)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
402		[3-(2-{[Bis-(4-benzyloxy-benzyl)-amino]-methyl}-3-butyl-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
403		[3-(2-{[Benzyl-(4-benzyloxy-benzyl)-amino]-methyl}-3-butyl-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine

Ex.	Structure	Name
404		{3-[4-(2-butyl-4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine
405		{3-[4-(4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-isobutyl-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine
406		[3-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
407		1-[4-(4-{2-butyl-1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-butyl]-piperazine
408		4-(4-{2-butyl-1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-1-methyl-piperidine
409		1-[5-(4-{2-butyl-1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-pentyl]-piperazine

Ex.	Structure	Name
410		{3-[4-(4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine
411		{3-[3-(4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine
412		[3-(4-{1-[4-(4-tert-butyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
413		[3-(4-{2-butyl-1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
414		diethyl-[3-(4-{1-[4-(4-trifluoromethoxy-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-amine
415		[3-(4-{2-butyl-1-[4-(3,4-dichloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine

Ex.	Structure	Name
416		[3-(4-{2-cyclobutyl-1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
417		[3-(4-{2-cyclopentyl-1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
418		[3-(4-{2-cyclohexyl-1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
419		diethyl-[3-(4-{1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxy)-propyl]-amine
420		[3-(4-{2-but-3-enyl-1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
421		[3-(4-{2-tert-butyl-1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
422		diethyl-[3-(4-{2-(4-fluoro-phenyl)-1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-amine

Ex.	Structure	Name
423		[3-(4-{1-[4-(3,5-bis-trifluoromethyl-phenoxy)-phenyl]-2-butyl-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
424		(3-{4-[1-(4-benzyloxy-phenyl)-2-butyl-1H-imidazol-4-yl]-phenoxy}-propyl)-diethyl-amine
425		{3-[4-(2-tert-butyl-4-{4-[2-(4-chlorophenyl)-ethoxy]-phenyl}-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine
426		[3-(4-{2-butyl-1-[4-(3-fluoro-4-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
427		diethyl-[3-(4-{4-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-imidazol-1-yl}-phenoxy)-propyl]-amine

Ex.	Structure	Name
428		(3-{4-[4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-(4-fluoro-phenyl)-imidazol-1-yl]-phenoxy}-propyl)-diethyl-amine
429		{3-[4-(4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-cyclopropyl-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine
430		{3-[4-(4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-cyclopentyl-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine
431		[3-(4-{4-[4-(biphenyl-4-yloxy)-phenyl]-imidazol-1-yl}-phenoxy)-propyl]-diethyl-amine
432		diethyl-[3-(4-{4-[4-(3-trifluoromethyl-phenoxy)-phenyl]-imidazol-1-yl}-phenoxy)-propyl]-amine
433		[3-(4-{4-[4-(3,4-dichloro-phenoxy)-phenyl]-imidazol-1-yl}-phenoxy)-propyl]-diethyl-amine

Ex.	Structure	Name
434		[3-(4-{2-butyl-1-[4-(4-methoxyphenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
435		1-[2-(4-{2-butyl-1-[4-(3-fluoro-4-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-ethyl]-piperazine
436		{3-[4-(4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-imidazol-1-yl)-phenoxy]-propyl}-dimethyl-amine
437		4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-1-{4-[2-(1-methyl-pyrrolidin-2-yl)-ethoxy]-phenyl}-1H-imidazole
438		1-{2-[4-(4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-imidazol-1-yl)-phenoxy]-ethyl}-piperazine
439		[3-(4-{2-(3-cyclohexyl-propyl)-1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
440		diethyl-(3-{4-[1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-2-(3-phenoxy-propyl)-1H-imidazol-4-yl]-phenoxy}-propyl)-amine

Ex.	Structure	Name
441		{3-[4-(4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-methyl-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine
442		3-(4-{2-butyl-1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-1-ethyl-piperidine
443		diethyl-[3-(4-{1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-2-methyl-1H-imidazol-4-yl}-phenoxy)-propyl]-amine
444		(3-{4-[4-(4-benzyloxy-phenyl)-2-butyl-imidazol-1-yl]-phenoxy}-propyl)-diethyl-amine
445		[3-(4-{2-butyl-1-[4-(2,5-difluorobenzyloxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
446		3-(S)-(4-{2-butyl-1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)methyl)-1-ethyl-piperidine
447		(3-{4-[4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-(2,4,4-trimethyl-pentyl)-imidazol-1-yl]-phenoxy}-propyl)-diethyl-amine

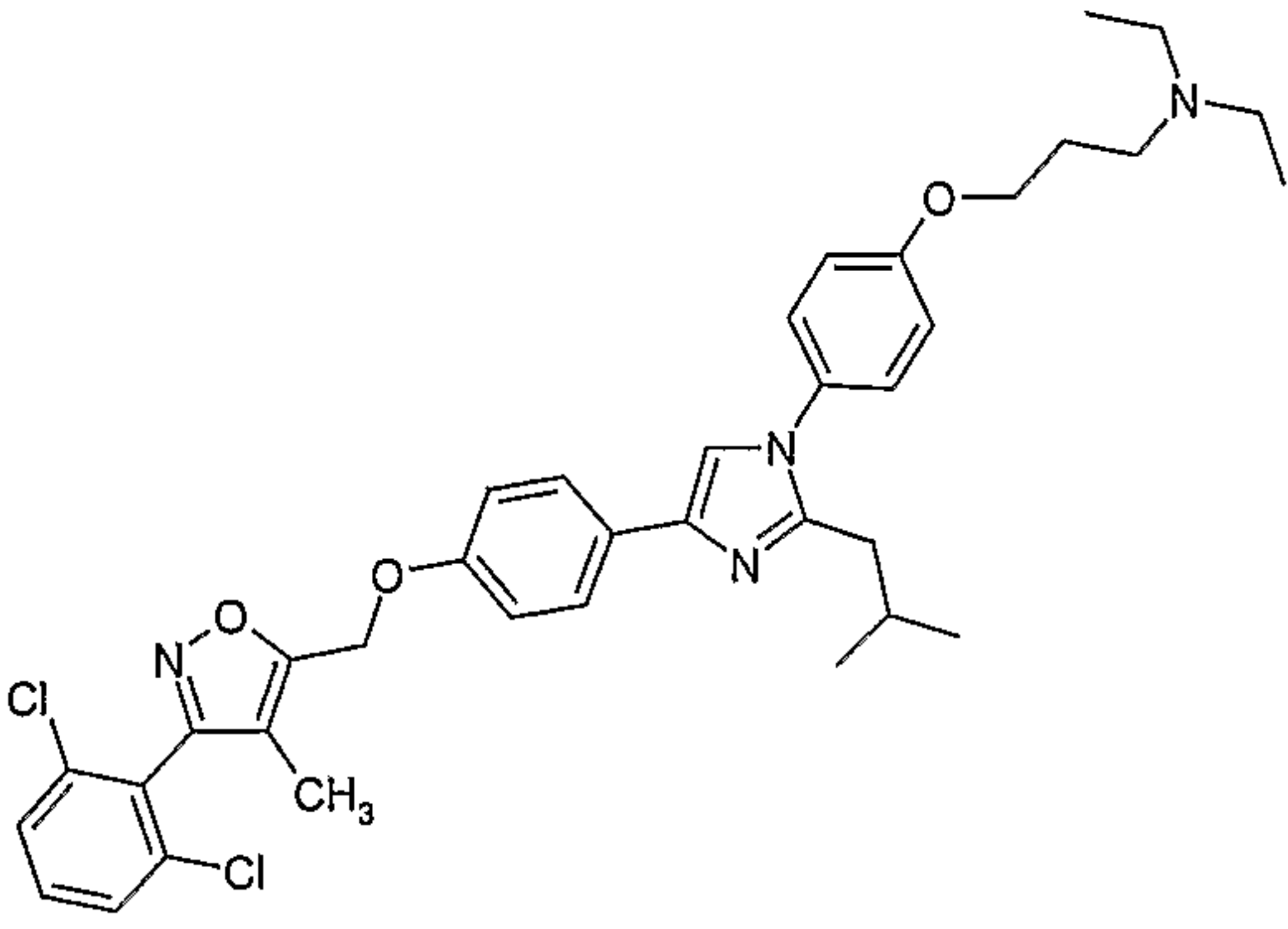
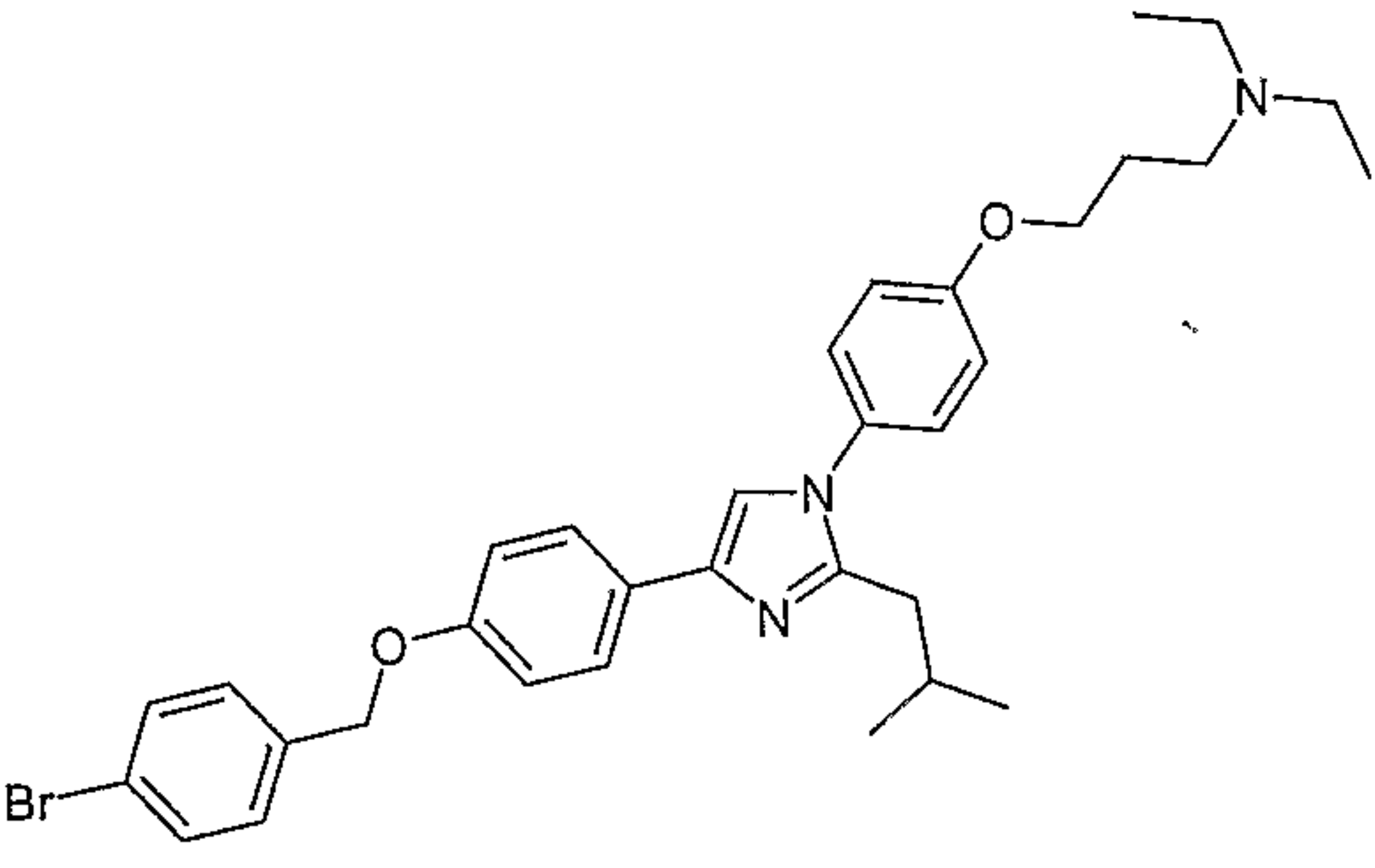
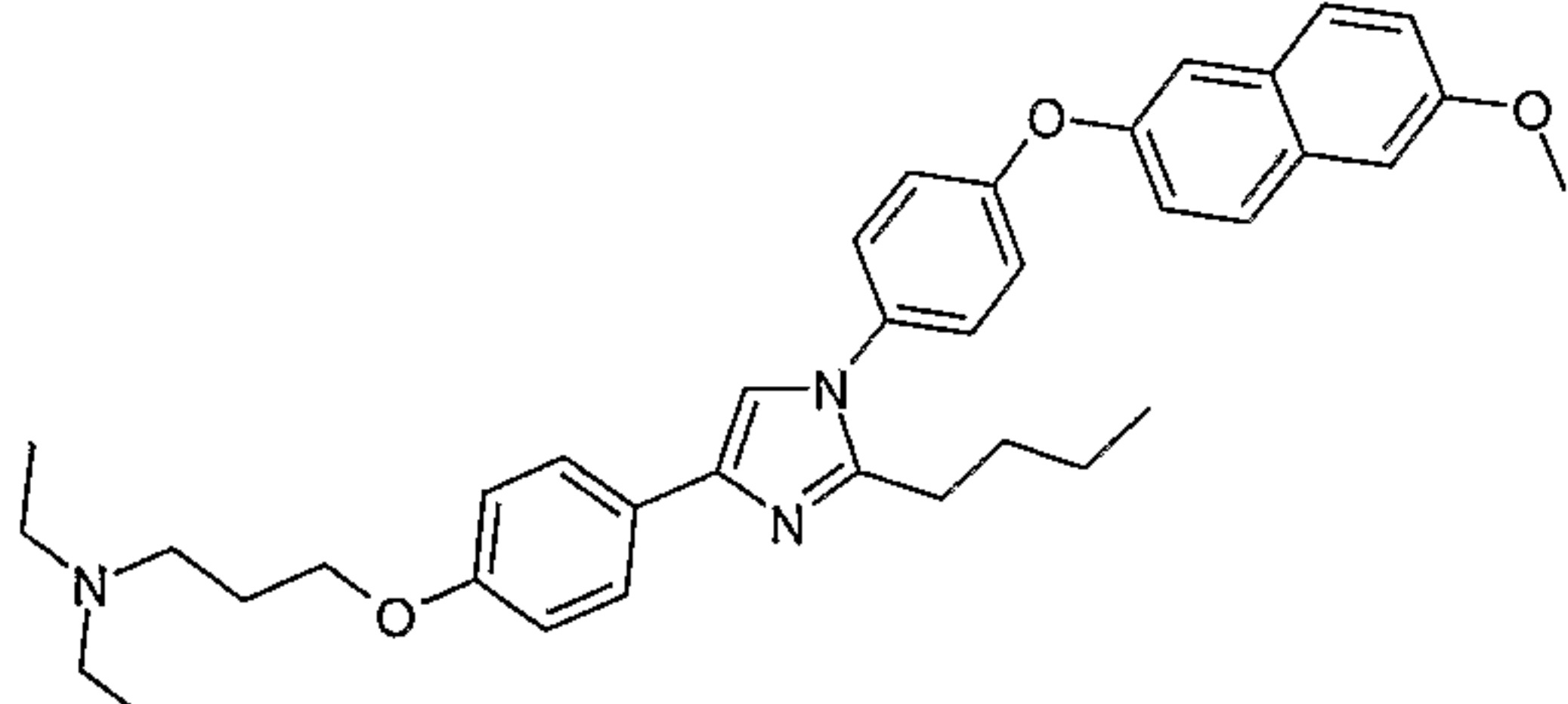
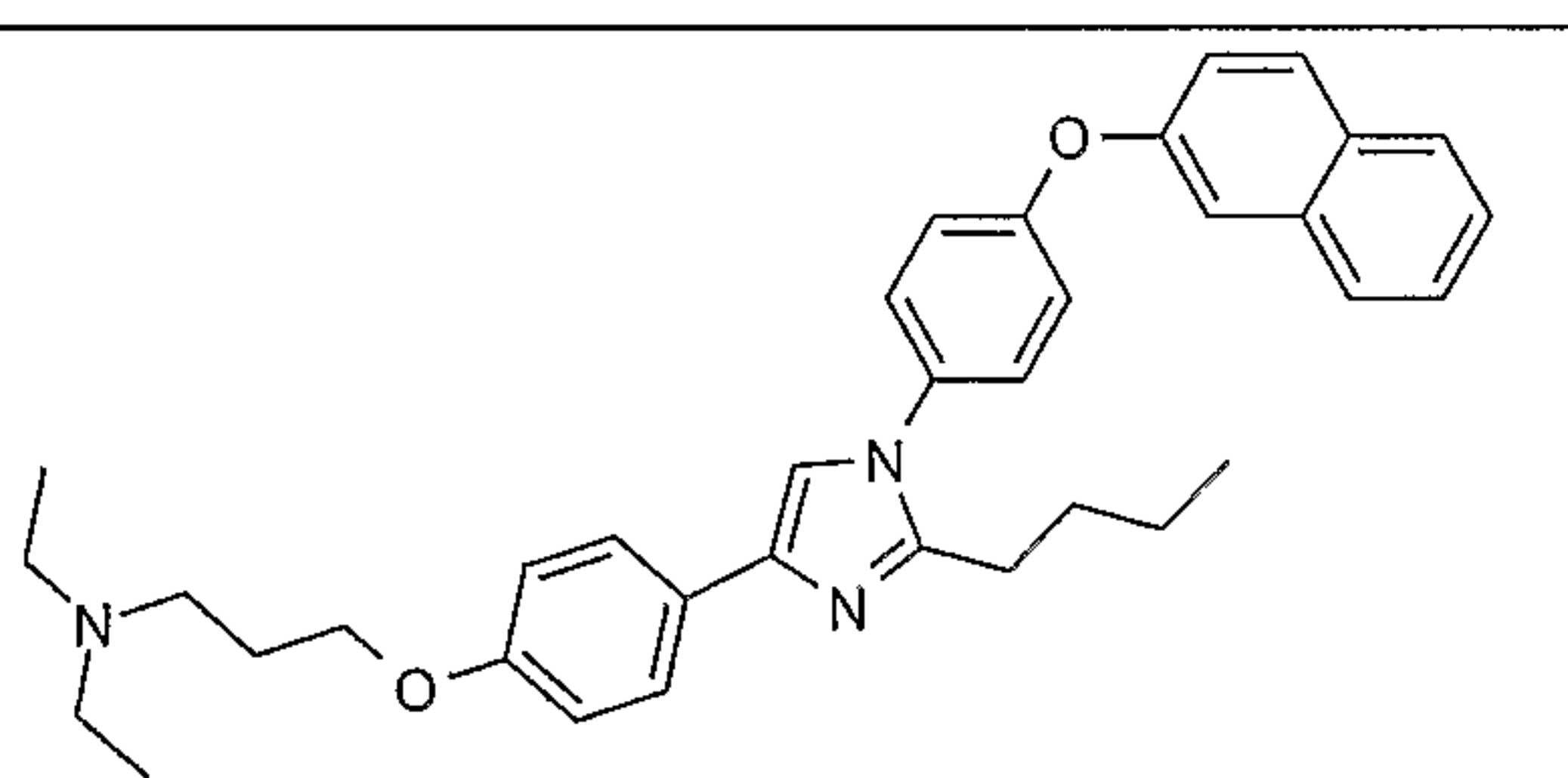
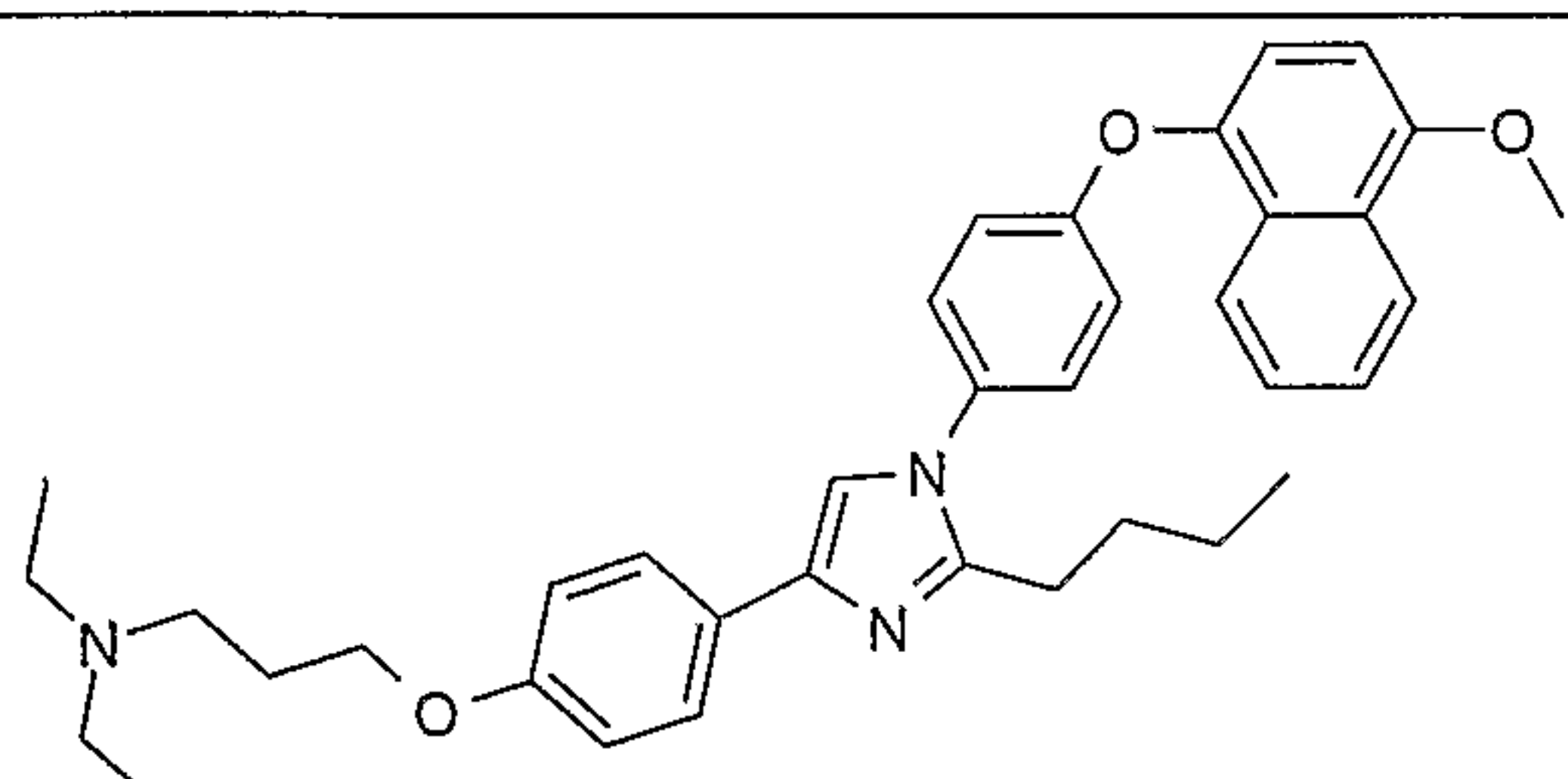
Ex.	Structure	Name
448		3-(R)-(4-{2-butyl-1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)methyl)-1-ethyl-piperidine
449		[3-(4-{2-butyl-1-[4-(3-tert-butyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
450		{3-[4-(4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-methoxymethyl-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine
451		(3-{4-[4-(4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-(1-ethyl-propyl)-imidazol-1-yl]-phenoxy}-propyl)-diethyl-amine
452		(3-{4-[4-(4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-(3-phenoxy-propyl)-imidazol-1-yl]-phenoxy}-propyl)-diethyl-amine
453		(3-{4-[4-(4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-(1-propyl-butyl)-imidazol-1-yl]-phenoxy}-propyl)-diethyl-amine

Ex.	Structure	Name
454		{3-[4-(2-(4-chloro-phenoxy)methyl)-4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine
455		{3-[4-(2-benzyloxymethyl-4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine
456		{3-[4-(4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-isobutyl-5-methyl-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine
457		{3-[4-(4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-isobutyl-5-propyl-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine
458		{3-[4-(5-butyl-4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-isobutyl-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine
459		{4-[4-{2-(4-chloro-phenyl)-ethoxy]-phenyl}-1-[4-(3-diethylamino-propoxy)-phenyl]-1H-imidazol-2-yl]-MeOH

Ex.	Structure	Name
460		diethyl-[3-(4-{2-isobutyl-4-[4-(4-phenoxy-benzyloxy)-phenyl]-imidazol-1-yl}-phenoxy)-propyl]-amine
461		[3-(4-{4-[4-(4-benzyloxy-benzyloxy)-phenyl]-2-isobutyl-imidazol-1-yl}-phenoxy)-propyl]-diethyl-amine
462		[3-(4-{4-[4-(2-benzenesulfonylmethyl-benzyloxy)-phenyl]-2-isobutyl-imidazol-1-yl}-phenoxy)-propyl]-diethyl-amine
463		diethyl-[3-(4-{2-isobutyl-4-[4-(3,4,5-trimethoxy-benzyloxy)-phenyl]-imidazol-1-yl}-phenoxy)-propyl]-amine
464		[3-(4-{1-[4-(4-chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
465		[3-(4-{1-[4-(4-chloro-phenoxy)-phenyl]-2-(2-cyclopentyl-ethyl)-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine

Ex.	Structure	Name
466		[3-(4-{1-[4-(4-chloro-phenoxy)-phenyl]-2-phenethyl-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
467		[3-(4-{2-(4-tert-butyl-phenoxy)methyl)-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
468		[3-(4-{2-butyl-1-[4-(2,4-dichloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
469		[3-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-5-methyl-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
470		[3-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-5-propyl-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
471		[3-(4-{2,5-dibutyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine

Ex.	Structure	Name
472		[3-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-5-ethyl-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
473		2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-4-[4-(2-pyrrolidin-1-ylethoxy)-phenyl]-1H-imidazole
474		1-[2-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-ethyl]-piperidine
475		[3-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-2,2-dimethyl-propyl]-dimethyl-amine
476		[2-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-ethyl]-diisopropyl-amine
477		[3-(4-{4-[4-(adamantan-1-ylmethoxy)-phenyl]-2-isobutyl-imidazol-1-yl}-phenoxy)-propyl]-diethyl-amine

Ex.	Structure	Name
478		{3-[4-(4-{4-[3-(2,6-dichloro-phenyl)-4-methyl-isoxazol-5-ylmethoxy]-phenyl}-2-isobutyl-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine
479		[3-(4-{4-[4-(4-bromo-benzyloxy)-phenyl]-2-isobutyl-imidazol-1-yl}-phenoxy)-propyl]-diethyl-amine
480		[3-(4-{2-butyl-1-[4-(6-methoxy-naphthalen-2-yloxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
481		[3-(4-{2-butyl-1-[4-(naphthalen-2-yloxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
482		[3-(4-{2-butyl-1-[4-(4-methoxy-naphthalen-1-yloxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine

Ex.	Structure	Name
483		[3-(4-{2-butyl-1-[4-(dibenzofuran-2-yloxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
484		6-(4-{2-butyl-4-[4-(3-diethylaminopropoxy)-phenyl]-imidazol-1-yl}-phenoxy)-naphthalen-2-ol
485		[3-(4-{2-butyl-4-[4-(4-chlorophenoxy)-phenyl]-imidazol-1-yl}-phenoxy)-propyl]-diethyl-amine
486		[3-(4-{2-(4-tert-butyl-cyclohexyl)-1-[4-(4-chlorophenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
487		[3-{4-[1-[4-(4-chlorophenoxy)-phenyl]-2-(trans-4-ethyl-cyclohexyl)-1H-imidazol-4-yl]-phenoxy}-propyl]-diethyl-amine
488		[4-(4-{2-butyl-1-[4-(4-chlorophenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-phenyl]-(1-ethyl-piperidin-4-ylmethyl)-amine

Ex.	Structure	Name
489		[4-{1-[4-(4-chloro-phenoxy)-phenyl]-4-[4-(3-diethylaminopropoxy)-phenyl]-1H-imidazol-2-yl}-butyric acid methyl ester
490		[3-(4-{2-butyl-1-[4-(4-chloro-2-cyclohexyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
491		[3-(4-{1-[4-(biphenyl-4-yloxy)-phenyl]-2-butyl-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
492		[3-(4-{1-[4-(4-bromo-phenoxy)-phenyl]-2-butyl-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
493		N-[4-(4-{2-butyl-4-[4-(3-diethylamino-propoxy)-phenyl]-imidazol-1-yl}-phenoxy)-phenyl]-acetamide
494		(3-{4-[2-butyl-1-(4-p-tolyloxy-phenyl)-1H-imidazol-4-yl]-phenoxy}-propyl)-diethyl-amine

Ex.	Structure	Name
495		[3-(4-{2-butyl-1-[4-(4-fluorophenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
496		[3-(4-{2-butyl-1-[4-(4-chloro-3-ethylphenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
497		{2-[4-(2-butyl-4-{4-[2-(4-chlorophenyl)-ethoxy]-phenyl}-imidazol-1-yl)-phenoxy]-ethyl}-ethyl-amine
498		[3-(4-{5-butyl-4-[4-(3,3-diphenylpropoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxy)-2,2-dimethyl-propyl]-dimethyl-amine
499		[3-(4-{4-[4-(3,3-diphenylpropoxy)-phenyl]-2-isobutyl-imidazol-1-yl}-phenoxy)-propyl]-diethyl-amine
500		7-{2-butyl-4-[4-(4-chlorophenoxy)-naphthalen-1-yl]-imidazol-1-yl}-1,2,3,4-tetrahydro-isoquinoline

Ex.	Structure	Name
501		2-biphenyl-4-yl-N-{4-[2-butyl-1-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-1H-imidazol-4-yl]-phenyl}-acetamide
502		7-{2-butyl-4-[4-(2,4-dichlorophenoxy)-phenyl]-imidazol-1-yl}-1,2,3,4-tetrahydro-isoquinoline
503		7-(2-butyl-4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-isobutyl-imidazol-1-yl)-1,2,3,4-tetrahydro-isoquinoline
504		7-[4-(4-benzyloxy-phenyl)-2-butyl-imidazol-1-yl]-1,2,3,4-tetrahydro-isoquinoline hydrochloride
505		9-(2-{4-[2-butyl-1-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-1H-imidazol-4-yl]-phenoxy}-ethyl)-9H-carbazole
506		7-{2-butyl-4-[4-(4-methoxyphenoxy)-phenyl]-imidazol-1-yl}-1,2,3,4-tetrahydro-isoquinoline

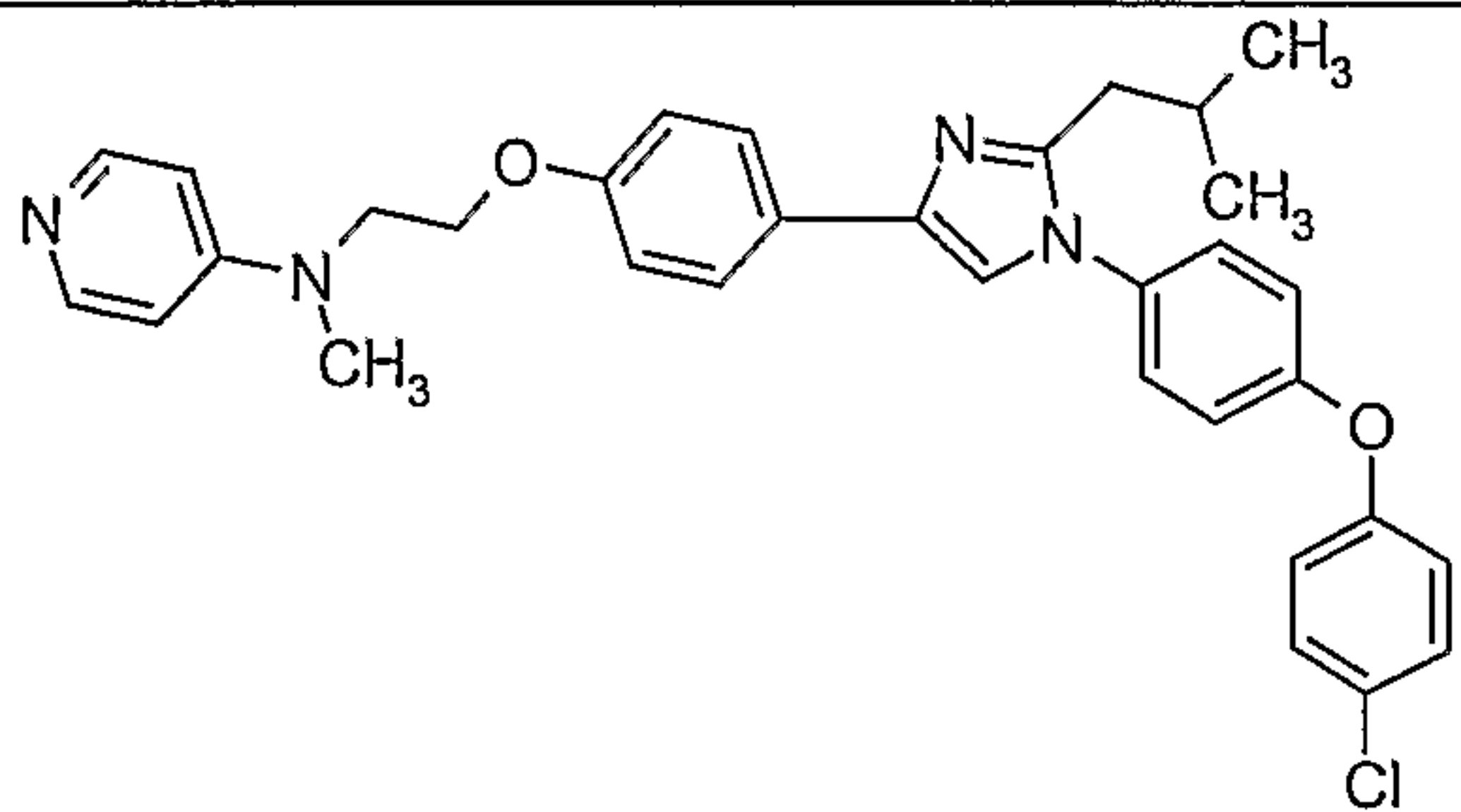
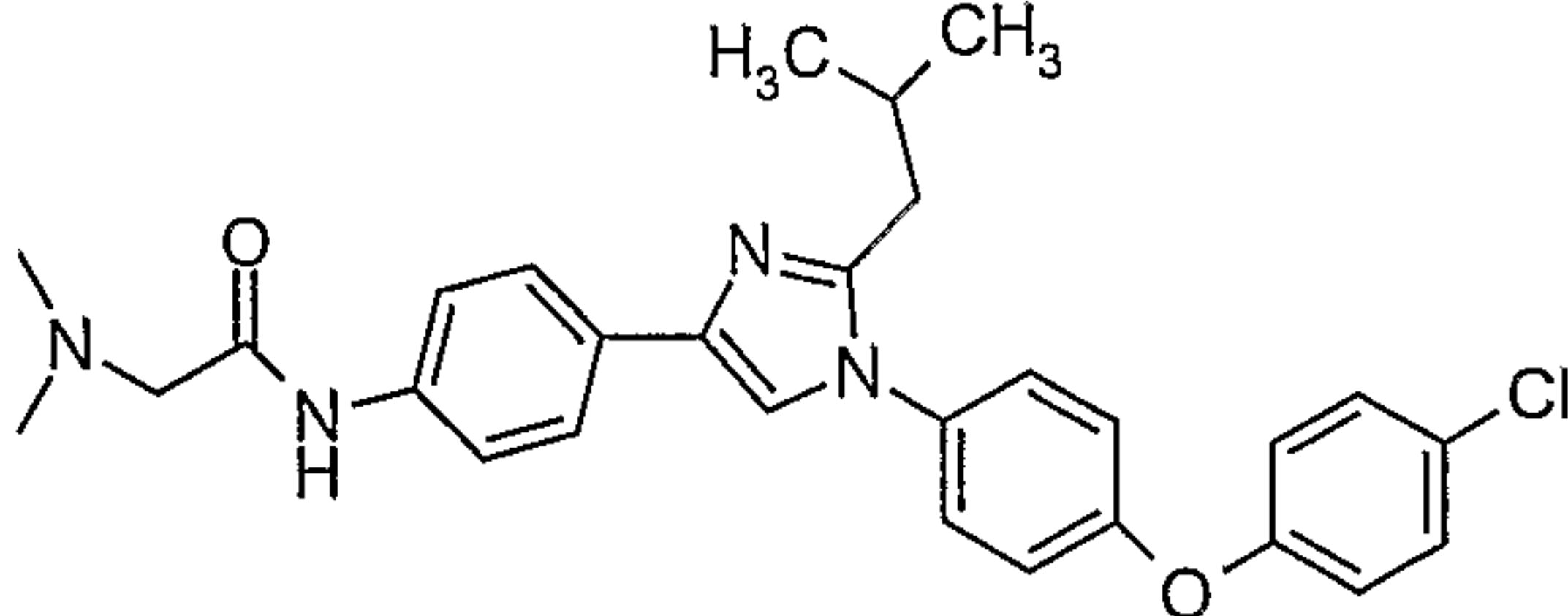
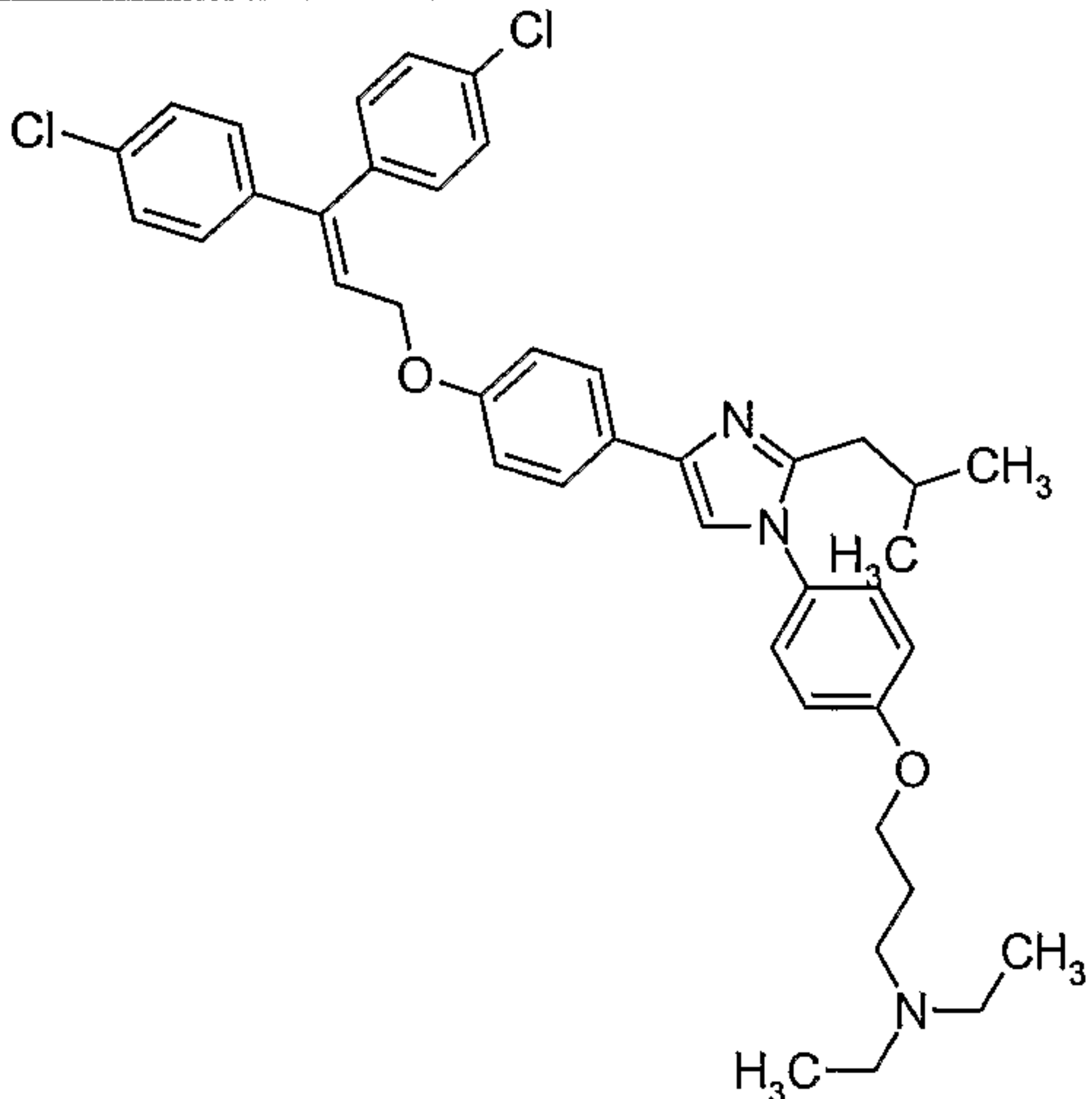
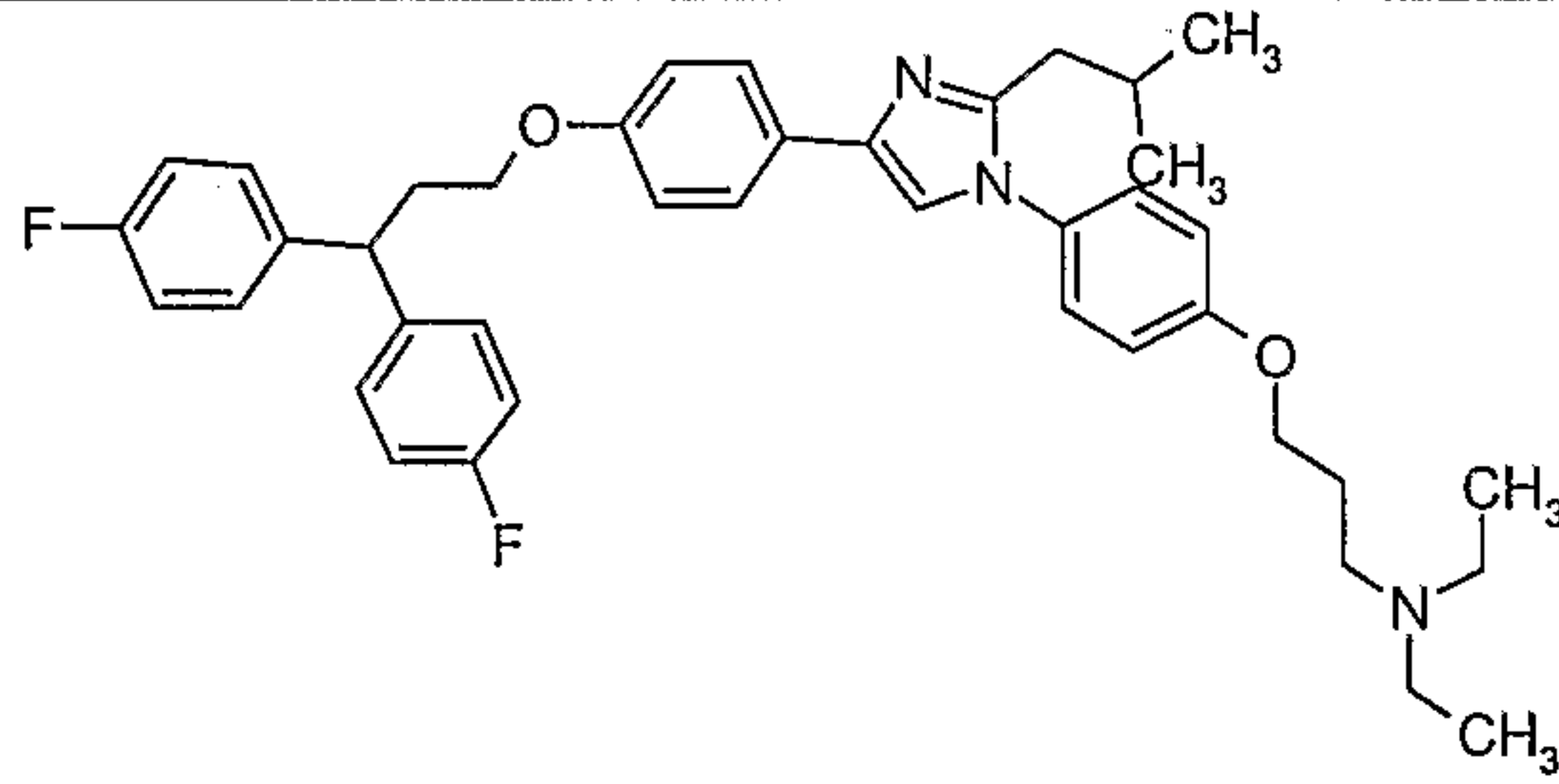
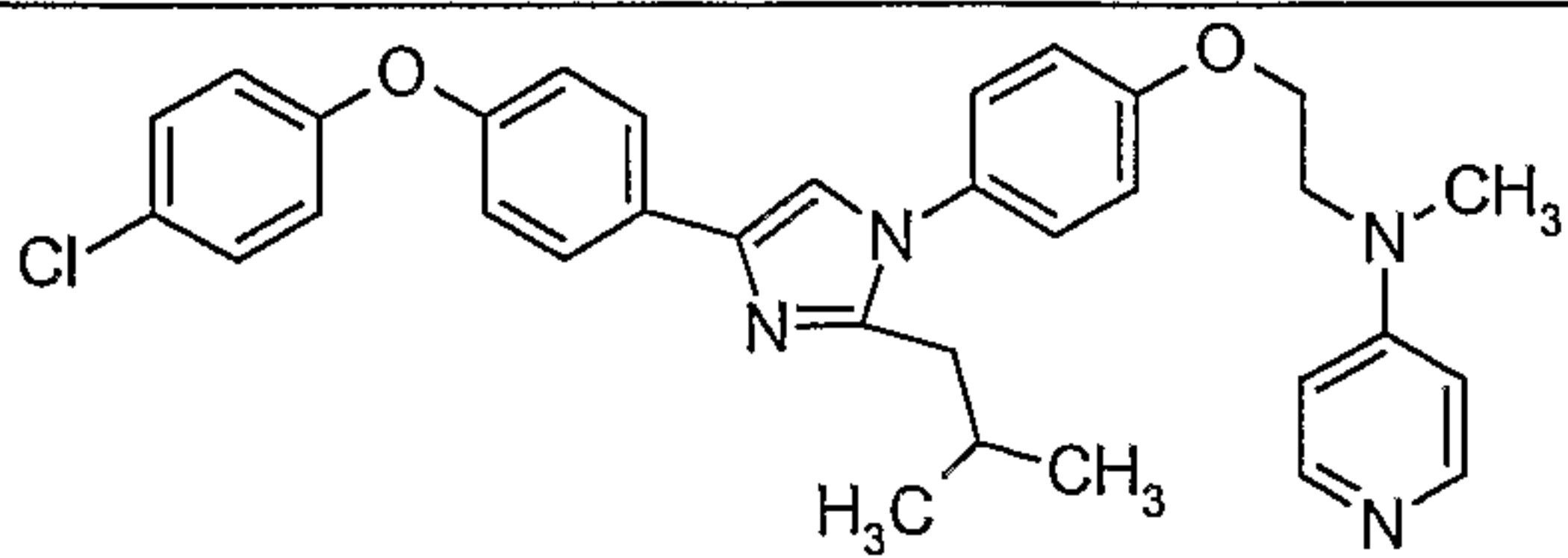
Ex.	Structure	Name
507		7-(2-butyl-4-{4-[2-(4-tert-butyl-phenyl)-ethoxy]-phenyl}-imidazol-1-yl)-1,2,3,4-tetrahydro-isoquinoline hydrochloride
508		7-{2-butyl-4-[4-(naphthalen-2-ylmethoxy)-phenyl]-imidazol-1-yl}-1,2,3,4-tetrahydro-isoquinoline hydrochloride
509		7-{2-butyl-4-[4-(4-trifluoromethyl-phenoxy)-phenyl]-imidazol-1-yl}-1,2,3,4-tetrahydro-isoquinoline hydrochloride
510		7-(2-butyl-4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-imidazol-1-yl)-1,2,3,4-tetrahydro-isoquinoline
511		[3-(4-{2-(4-Butyl-cyclohexyl)-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
512		2-(4-{1-[4-(4-Chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxy)-ethylamine

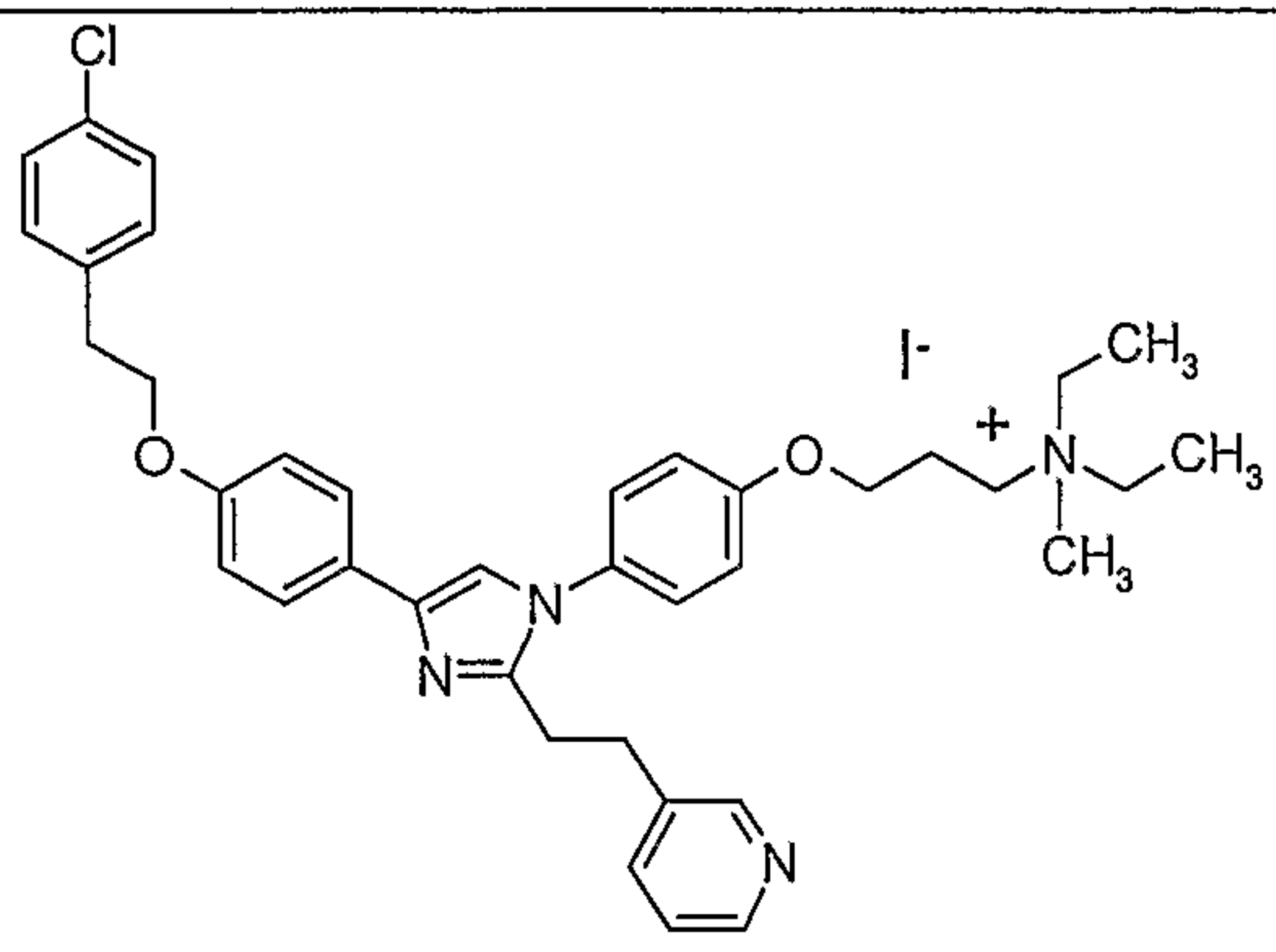
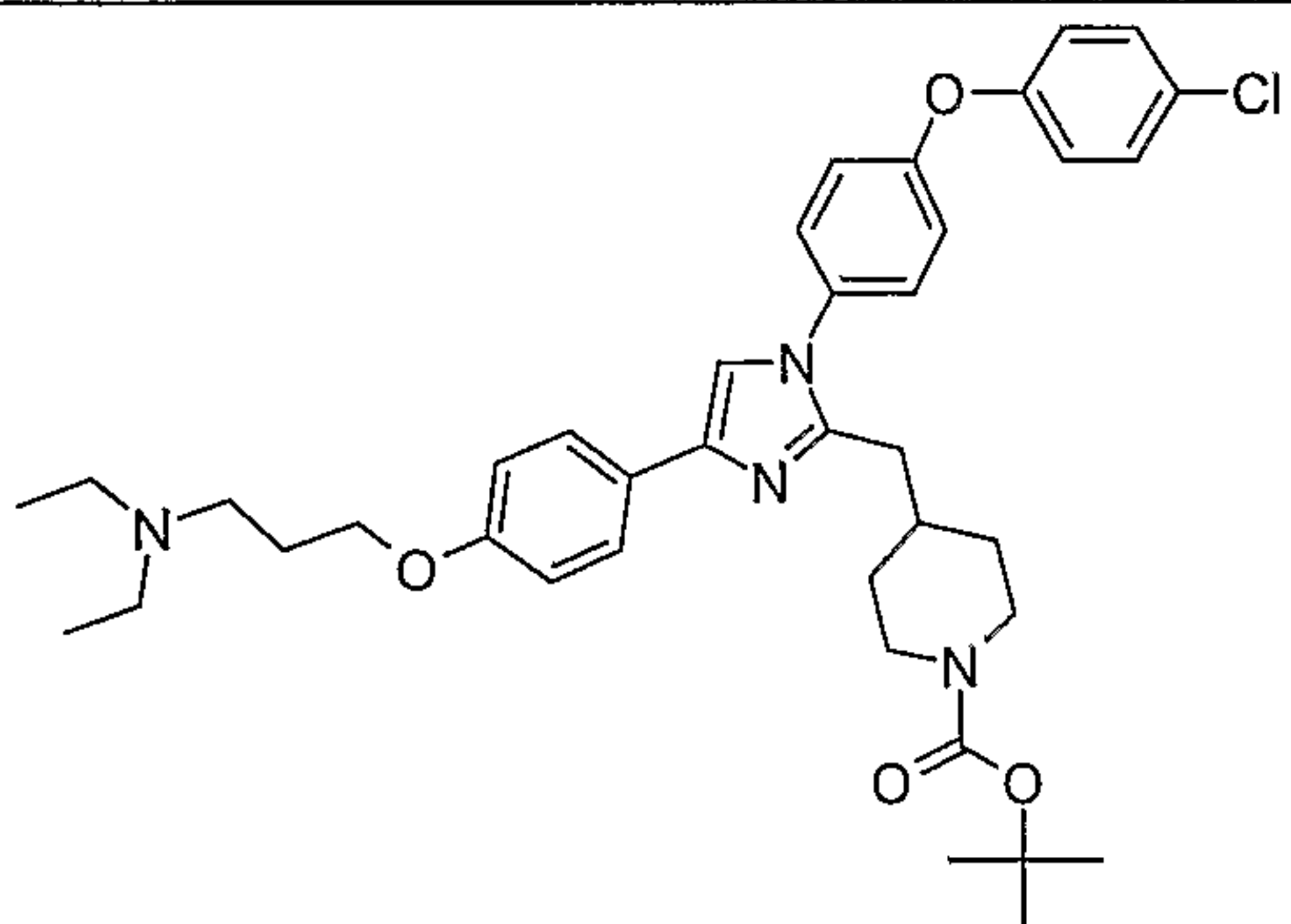
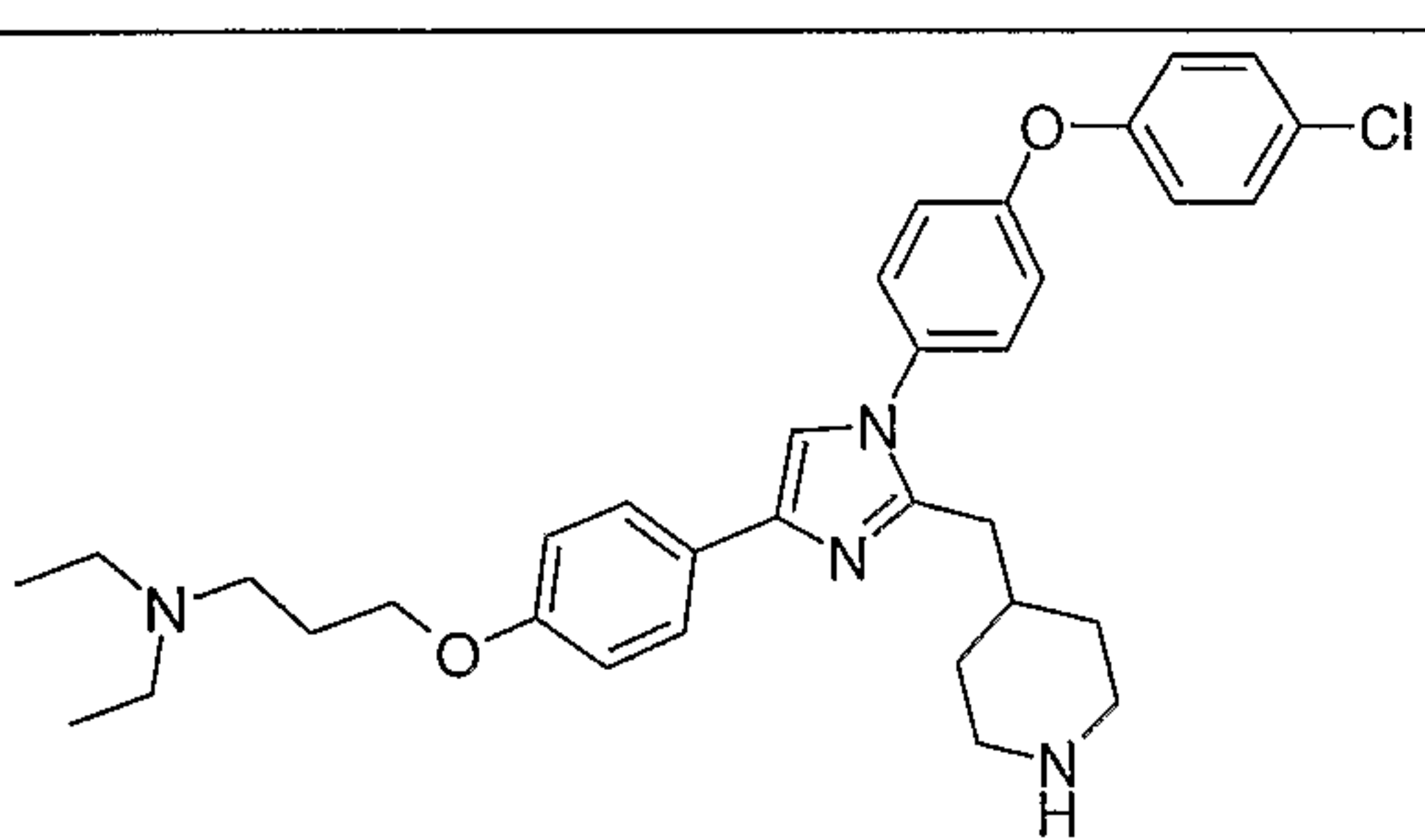
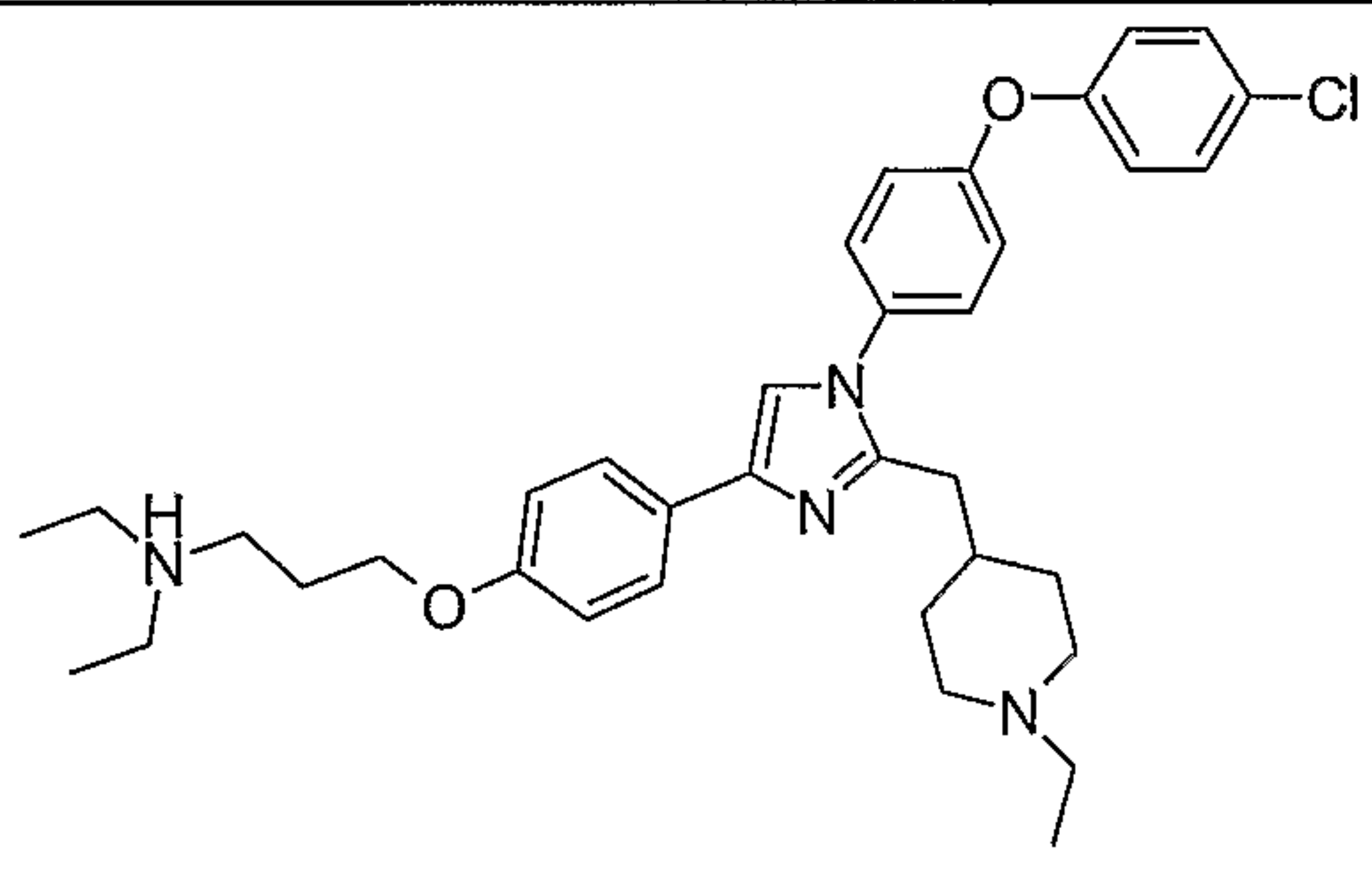
Ex.	Structure	Name
513		[3-(4-{2-(trans-4-tert-Butyl-cyclohexyl)-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
514		[3-(4-{2-(cis-4-tert-Butyl-cyclohexyl)-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
515		[2-(4-{2-Butyl-1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-ethyl]-methyl-pyridin-4-yl-amine
516		[2-(4-{1-[4-(4-Fluoro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxy)-ethyl]-methyl-pyridin-4-yl-amine
517		[2-(4-{1-[4-(4-Fluoro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxy)-ethyl]-methyl-(3-methyl-pyridin-4-yl)-amine
518		[2-(4-{1-[4-(4-Chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxy)-ethyl]-ethyl-pyridin-4-yl-amine

Ex.	Structure	Name
519		[2-(4-{1-[4-(4-Chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxy)-ethyl]-pyridin-4-yl-amine
520		[2-(4-{1-[4-(4-Chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxy)-ethyl]-bis-pyridin-2-ylmethyl-amine
521		N-[2-(4-{1-[4-(4-Chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxy)-ethyl]-guanidine

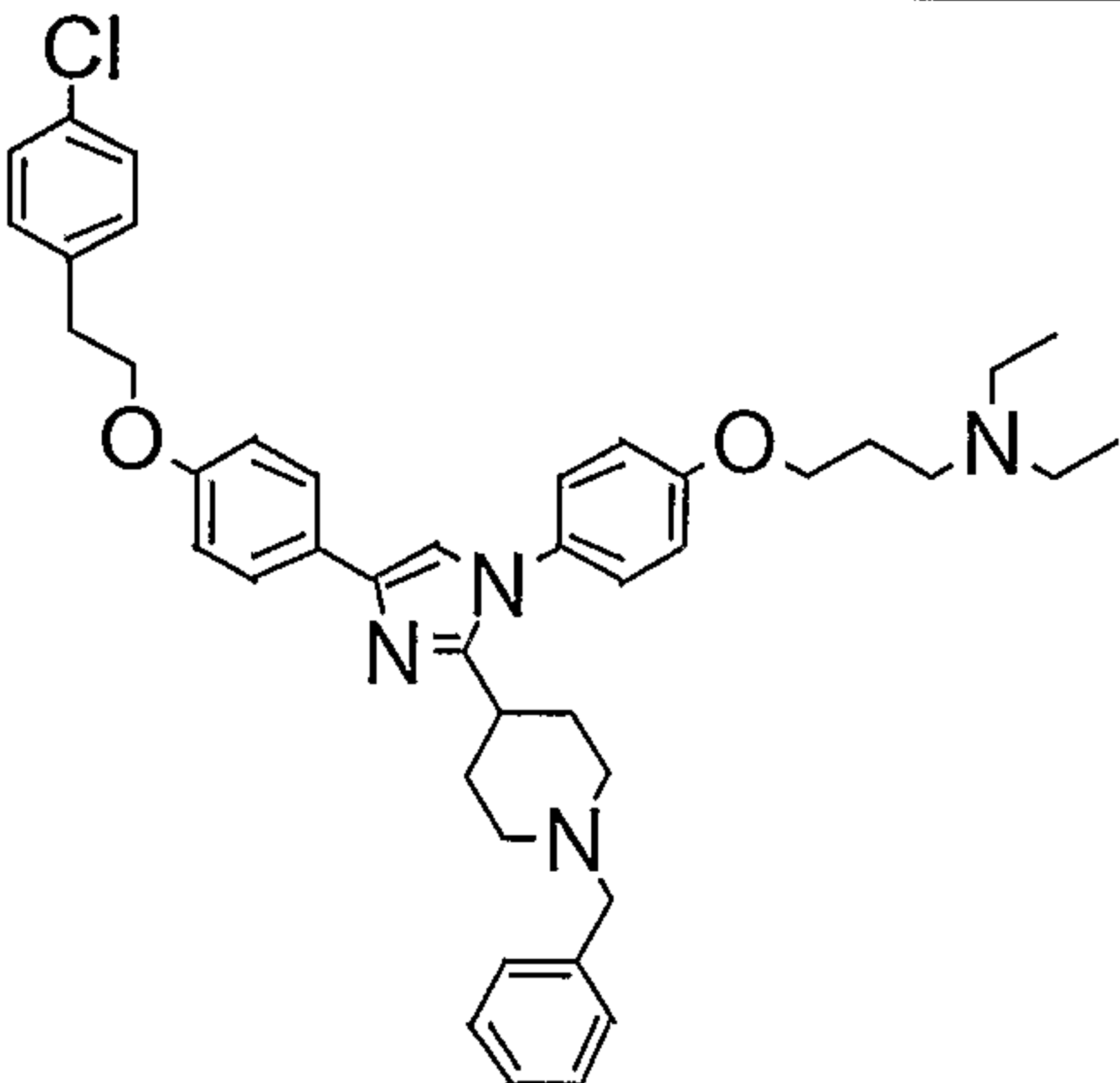
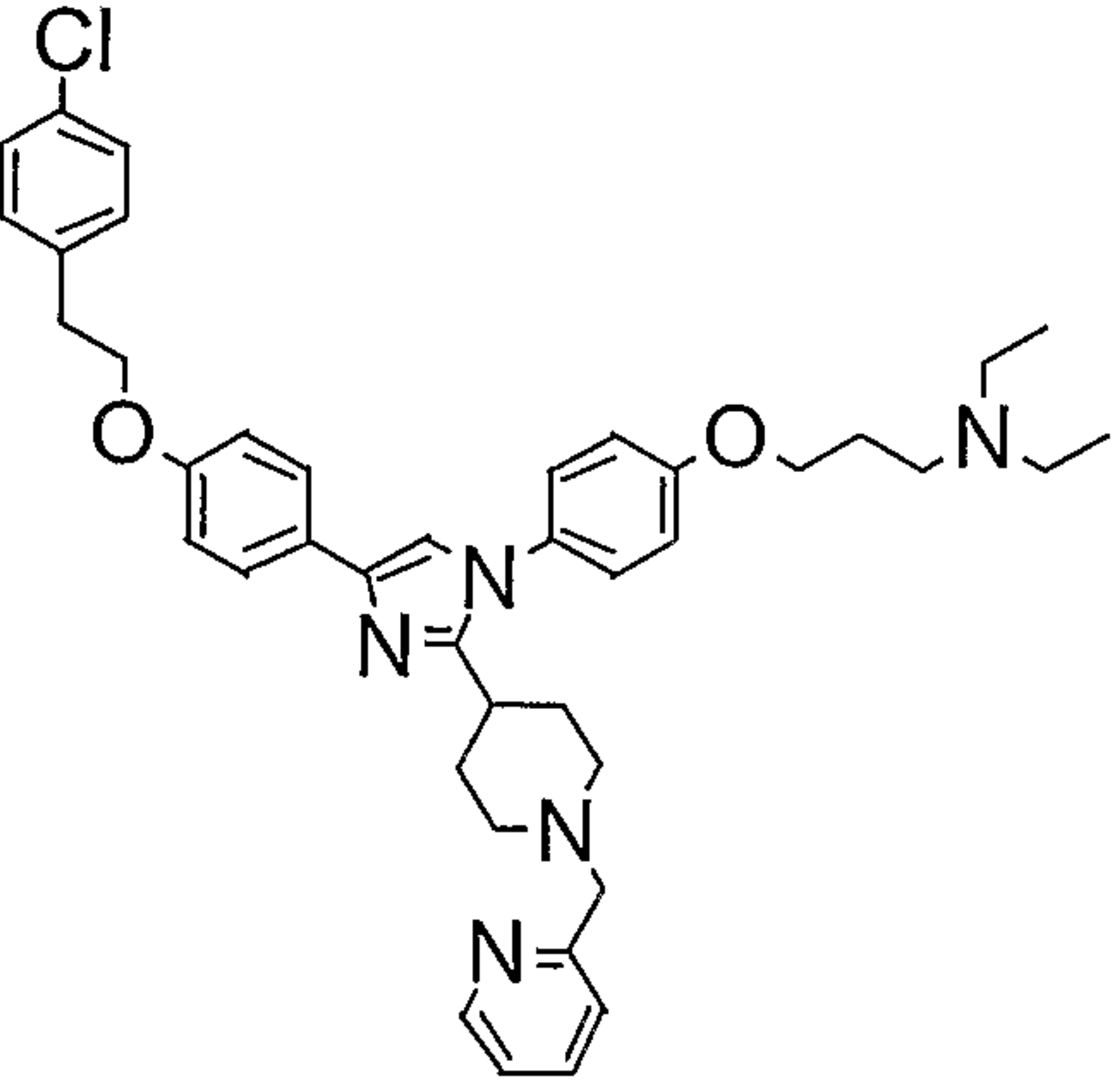
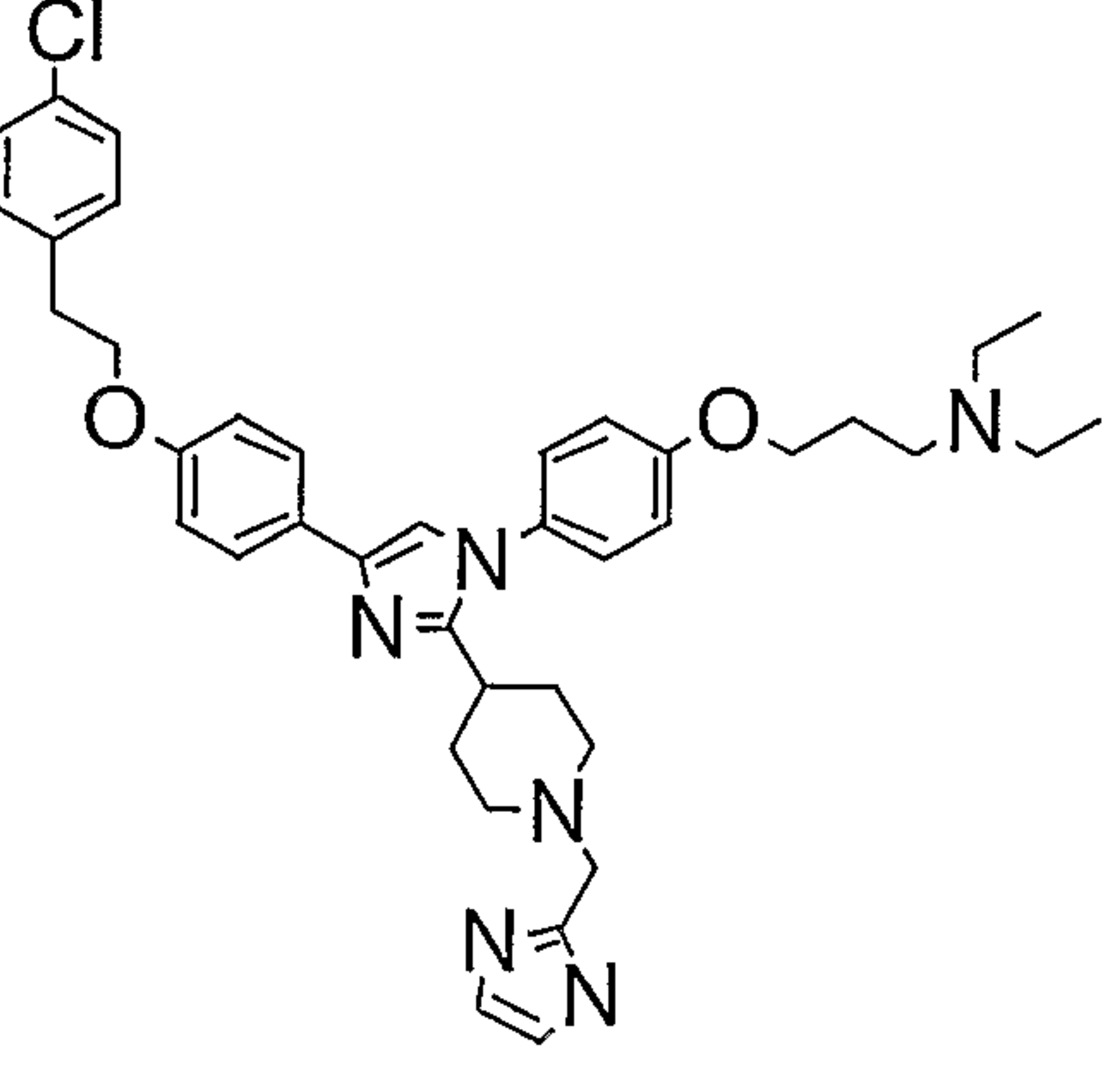
Ex.	Structure	Name
522		2-(4-{1-[4-(4-Chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxy)-1-(4-pyridin-4-yl-piperazin-1-yl)-ethanone
523		5-(4-{1-[4-(4-Chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxy)methyl)-pyrrolidin-3-ol
524		3-(4-{1-[4-(4-Fluoro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxy)-pyridin-4-ylamine
525		(4-{1-[4-(4-Chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenyl)-pyridin-4-yl-amine

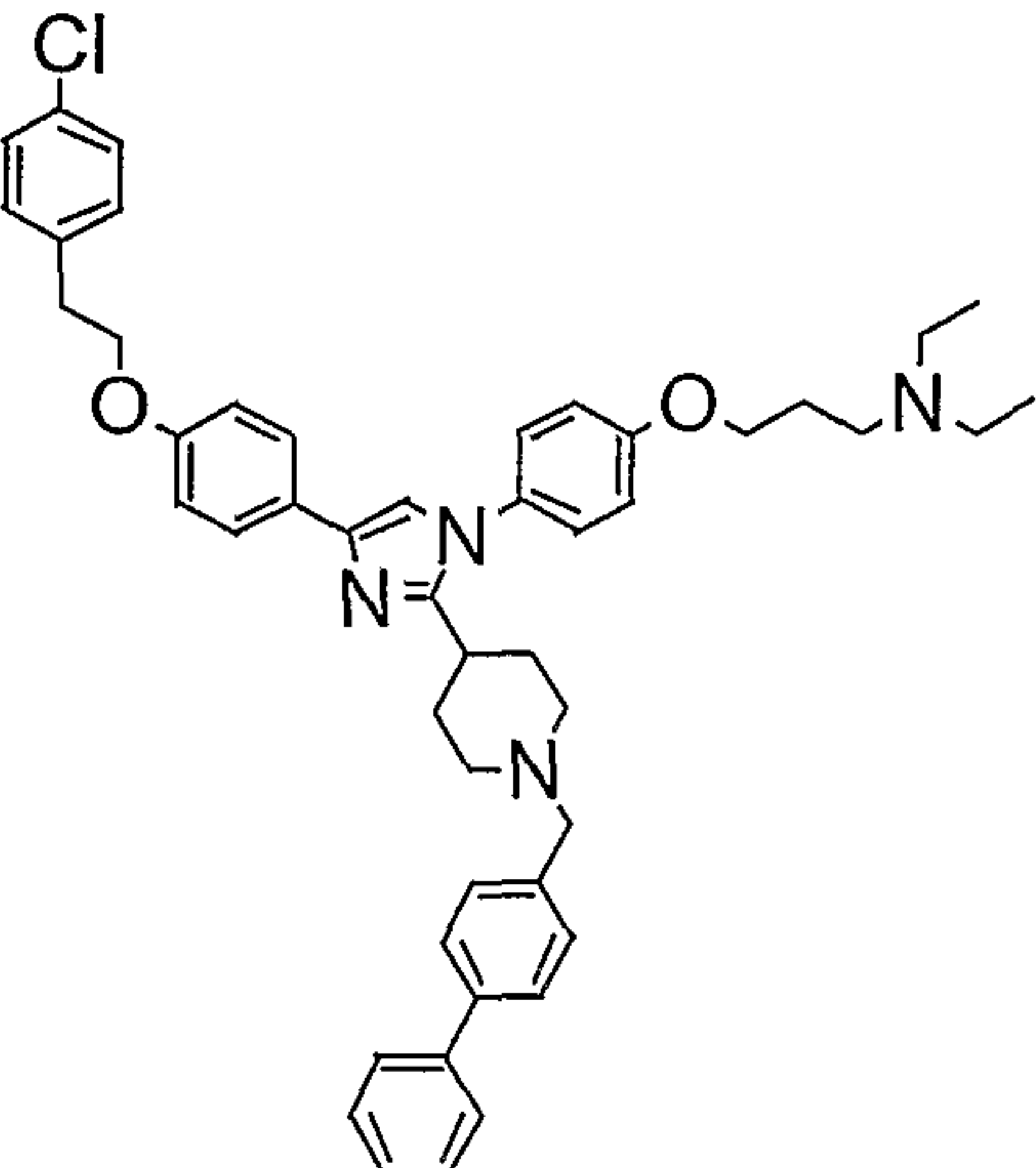
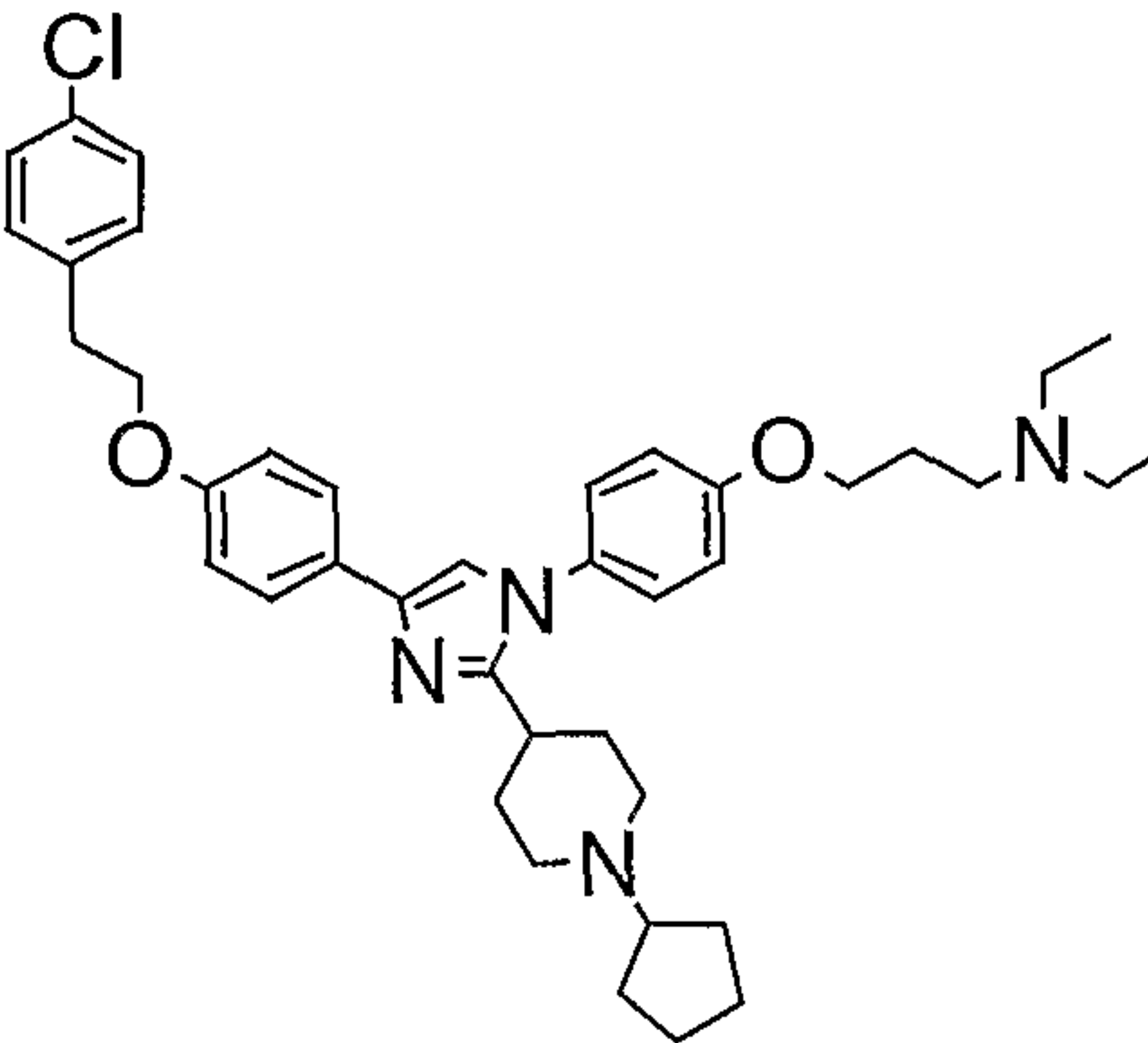
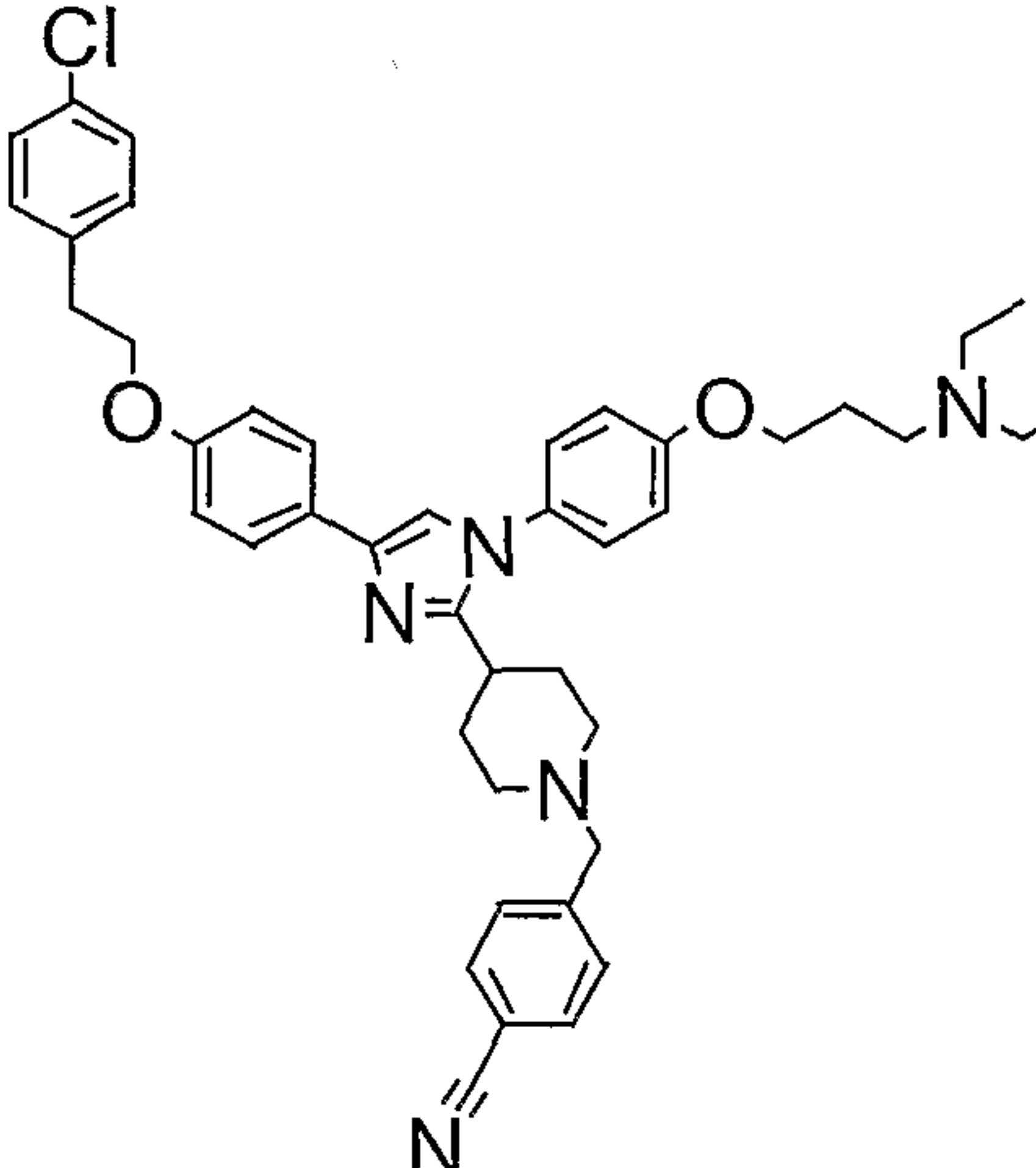
Ex.	Structure	Name
526		2-(4-{1-[4-(4-Fluoro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxy)methyl)-3,5-dimethyl-pyridin-4-ylamine
527		1-[2-(4-{1-[4-(4-Chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxy)-ethyl]-4-pyridin-4-yl-piperazine
528		4-(4-{2-Butyl-4-[4-(3-diethylamino-propoxy)-phenyl]-imidazol-1-yl}-phenoxy)-phenylamine
529		{3-[4-(2-Butyl-4-dibenzofuran-2-yl-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine
530		N-[4-(4-{2-Butyl-4-[4-(3-diethylamino-propoxy)-phenyl]-imidazol-1-yl}-phenoxy)-phenyl]-benzamide
531		N-[4-(4-{2-Butyl-4-[4-(3-diethylamino-propoxy)-phenyl]-imidazol-1-yl}-phenoxy)-phenyl]-isonicotinamide

Ex.	Structure	Name
532		[2-(4-{1-[4-(4-Chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxy)-ethyl]-methyl-pyridin-4-yl-amine
533		N-(4-{1-[4-(4-Chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenyl)-2-dimethylamino-acetamide
534		{3-[4-(4-{4-[3,3-Bis-(4-chloro-phenyl)-allyloxy]-phenyl}-2-isobutyl-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine
535		{3-[4-(4-{4-[3,3-Bis-(4-fluoro-phenyl)-propoxy]-phenyl}-2-isobutyl-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine
536		[2-(4-{4-[4-(4-Chloro-phenoxy)-phenyl]-2-isobutyl-imidazol-1-yl}-phenoxy)-ethyl]-methyl-pyridin-4-yl-amine

Ex.	Structure	Name
537		[3-(4-{4-{4-[2-(4-Chloro-phenyl)-ethoxy]-phenyl}-2-[2-(1-methyl-pyridin-3-yl)-ethyl]-imidazol-1-yl}-phenoxy)-propyl]-diethylmethyl ammonium iodide
538		[3-(4-{2-(N-BOC-piperidine-4-ylmethyl)-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
539		[3-(4-{2-(Piperidine-4-ylmethyl)-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
540		[3-(4-{2-(N-ethyl-piperidine-4-ylmethyl)-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine

Ex.	Structure	Name
541		[3-(4-{2-(piperidine-4-ylmethyl)-4-[4-(4-chloro-phenoxy)-phenyl]-imidazol-1-yl}-phenoxy)-propyl]-diethyl-amine
542		[3-(4-{2-(N-ethylpiperidine-4-ylmethyl)-4-[4-(4-chloro-phenoxy)-phenyl]-imidazol-1-yl}-phenoxy)-propyl]-diethyl-amine
543		[3-(4-{2-(N-acetylpiperidine-4-yl)-4-[4-(4-chloro-phenoxy)-phenyl]-imidazol-1-yl}-phenoxy)-propyl]-diethyl-amine
544		[3-(4-{2-(piperidine-4-yl)-4-[4-(4-chloro-phenoxy)-phenyl]-imidazol-1-yl}-phenoxy)-propyl]-diethyl-amine

Ex.	Structure	Name
545		[3-(4-{2-(N-Benzylpiperidine-4-yl)-4-[4-(4-chloro-phenoxy)-phenyl]-imidazol-1-yl}-phenoxy)-propyl]-diethyl-amine
546		[3-(4-{2-(N-(2-Pyridylmethyl)piperidine-4-yl)-4-[4-(4-chloro-phenoxy)-phenyl]-imidazol-1-yl}-phenoxy)-propyl]-diethyl-amine
547		[3-(4-{2-(N-(2-Imidazolylmethyl)piperidine-4-yl)-4-[4-(4-chloro-phenoxy)-phenyl]-imidazol-1-yl}-phenoxy)-propyl]-diethyl-amine

Ex.	Structure	Name
548		[3-(4-{2-(N-(4-biphenyl)methylpiperidine-4-yl)-4-[4-(4-chloro-phenoxy)-phenyl]-imidazol-1-yl}-phenoxy)-propyl]-diethyl-amine
549		[3-(4-{2-(N-Cyclohexylpiperidine-4-yl)-4-[4-(4-chloro-phenoxy)-phenyl]-imidazol-1-yl}-phenoxy)-propyl]-diethyl-amine
550		[3-(4-{2-(N-(4-Cyanobenzyl)piperidine-4-yl)-4-[4-(4-chloro-phenoxy)-phenyl]-imidazol-1-yl}-phenoxy)-propyl]-diethyl-amine

Ex.	Structure	Name
551		[3-(4-{2-(N-Ethylpiperidine-4-yl)-4-[4-(4-chloro-phenoxy)-phenyl]-imidazol-1-yl}-phenoxy)-propyl]-diethyl-amine

5

Definitions of Terms

As used herein, the term "lower" refers to a group having between one and six carbons.

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As used herein, the term "alkyl" refers to a straight or branched chain hydrocarbon having from one to ten carbon atoms, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, silyloxy optionally substituted by alkoxy, alkyl, or aryl, silyl optionally substituted by alkoxy, alkyl, or aryl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Such an "alkyl" group may containing one or more O, S, S(O), or S(O)₂ atoms. Examples of "alkyl" as used herein include, but are not limited to, methyl, n-butyl, t-butyl, n-pentyl, isobutyl, and isopropyl, and the like.

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As used herein, the term "alkylene" refers to a straight or branched chain divalent hydrocarbon radical having from one to ten carbon atoms, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, silyloxy optionally substituted by alkoxy, alkyl,

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or aryl, silyl optionally substituted by alkoxy, alkyl, or aryl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Such an "alkylene" group may containing one or more O, S, S(O), or S(O)₂ atoms. Examples of "alkylene" as used herein include, but are not limited to, methylene, ethylene, and the like.

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As used herein, the term "alkylene" refers to a straight or branched chain trivalent hydrocarbon radical having from one to ten carbon atoms, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, silyloxy optionally substituted by alkoxy, alkyl, or aryl, silyl optionally substituted by alkoxy, alkyl, or aryl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Examples of "alkylene" as used herein include, but are not limited to, methine, 1,1,2-ethylene, and the like.

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As used herein, the term "alkenyl" refers to a hydrocarbon radical having from two to ten carbons and at least one carbon - carbon double bond, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, silyloxy optionally substituted by alkoxy, alkyl, or aryl, silyl optionally substituted by alkoxy, alkyl, or aryl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Such an "alkenyl" group may containing one or more O, S, S(O), or S(O)₂ atoms.

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As used herein, the term "alkenylene" refers to a straight or branched chain divalent hydrocarbon radical having from two to ten carbon atoms and one or more carbon - carbon double bonds, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, silyloxy optionally substituted by alkoxy, alkyl, or aryl, silyl optionally substituted by alkoxy, alkyl, or aryl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Such an "alkenylene" group may containing one or more O, S, S(O), or S(O)₂ atoms. Examples of "alkenylene" as used herein include, but are not limited to, ethene-1,2-diyl, propene-1,3-diyl, methylene-1,1-diyl, and the like.

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As used herein, the term "alkynyl" refers to a hydrocarbon radical having from two to ten carbons and at least one carbon - carbon triple bond, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, silyloxy optionally substituted by alkoxy, alkyl, or aryl, silyl optionally substituted by alkoxy, alkyl, or aryl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Such an "alkynyl" group may containing one or more O, S, S(O), or S(O)₂ atoms.

As used herein, the term "alkynylene" refers to a straight or branched chain divalent hydrocarbon radical having from two to ten carbon atoms and one or more carbon - carbon triple bonds, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, silyloxy optionally substituted by alkoxy, alkyl, or aryl, silyl optionally substituted by alkoxy, alkyl, or aryl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Such an "alkynylene" group may containing one or more O, S, S(O), or S(O)₂ atoms. Examples of "alkynylene" as used herein include, but are not limited to, ethyne-1,2-diyl, propyne-1,3-diyl, and the like.

As used herein, "cycloalkyl" refers to an alicyclic hydrocarbon group optionally possessing one or more degrees of unsaturation, having from three to twelve carbon atoms, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. "Cycloalkyl" includes by way of example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl, and the like.

As used herein, the term "cycloalkylene" refers to an non-aromatic alicyclic divalent hydrocarbon radical having from three to twelve carbon atoms and optionally possessing one or more degrees of unsaturation, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy,

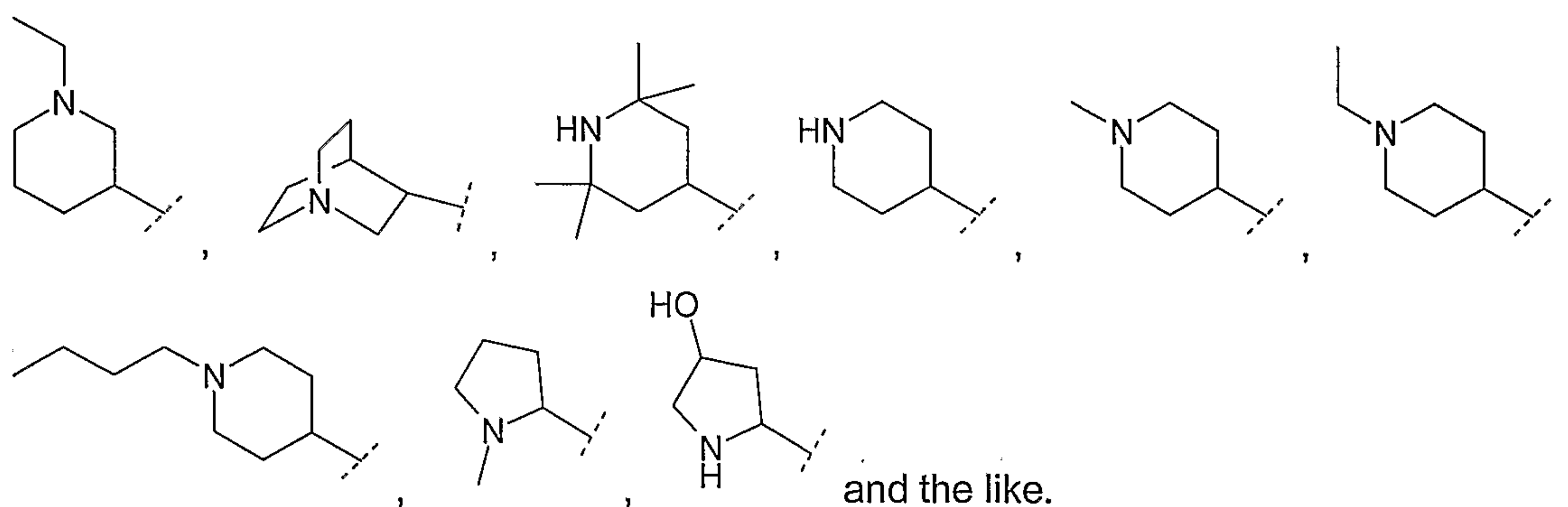
carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed.

Examples of "cycloalkylene" as used herein include, but are not limited to, cyclopropyl-1,1-diyl, cyclopropyl-1,2-diyl, cyclobutyl-1,2-diyl, cyclopentyl-1,3-diyl, cyclohexyl-1,4-diyl, cycloheptyl-1,4-diyl, or cyclooctyl-1,5-diyl, and the like.

As used herein, the term "heterocyclic" or the term "heterocyclyl" refers to a three to twelve-membered heterocyclic ring optionally possessing one or more degrees of unsaturation, containing one or more heteroatomic substitutions selected from S, SO, SO₂, O, or N, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Such a ring may be optionally fused to one or more of another "heterocyclic" ring(s) or cycloalkyl ring(s). Examples of "heterocyclic" include, but are not limited to, tetrahydrofuran, 1,4-dioxane, 1,3-dioxane, piperidine, pyrrolidine, morpholine, piperazine, and the like.

As used herein, the term "heterocyclyl containing at least one basic nitrogen atom" refers to a "heterocyclic" "heterocyclyl" group as defined above,

wherein said heterocyclyl group contains at least one nitrogen atom flanked by hydrogen, alkyl, alkylene, or alkylyne groups, wherein said alkyl and/or alkylene groups are not substituted by oxo. Examples of "heterocyclyl containing at least one basic nitrogen atom" include, but are not limited to, piperazine-2-yl, pyrrolidine-2-yl, azepine-4-yl,



As used herein, the term "heterocyclylene" refers to a three to twelve-membered heterocyclic ring diradical optionally having one or more degrees of unsaturation containing

one or more heteroatoms selected from S, SO, SO₂, O, or N, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Such a ring may be optionally fused to one or more benzene rings or to one or more of another "heterocyclic" rings or cycloalkyl rings. Examples of "heterocyclylene" include, but are not limited to, tetrahydrofuran-2,5-diyl, morpholine-2,3-diyl, pyran-2,4-diyl, 1,4-dioxane-2,3-diyl, 1,3-dioxane-2,4-diyl, piperidine-2,4-diyl, piperidine-1,4-diyl, pyrrolidine-1,3-diyl, morpholine-2,4-diyl, piperazine-1,4-diyl, and the like.

As used herein, the term "aryl" refers to a benzene ring or to an optionally substituted benzene ring system fused to one or more optionally substituted benzene rings, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy optionally substituted by acyl, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, silyloxy optionally substituted by alkoxy, alkyl, or aryl, silyl optionally substituted by alkoxy, alkyl, or aryl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Examples of aryl include, but are not limited to, phenyl, 2-naphthyl, 1-naphthyl, 1-anthracenyl, and the like.

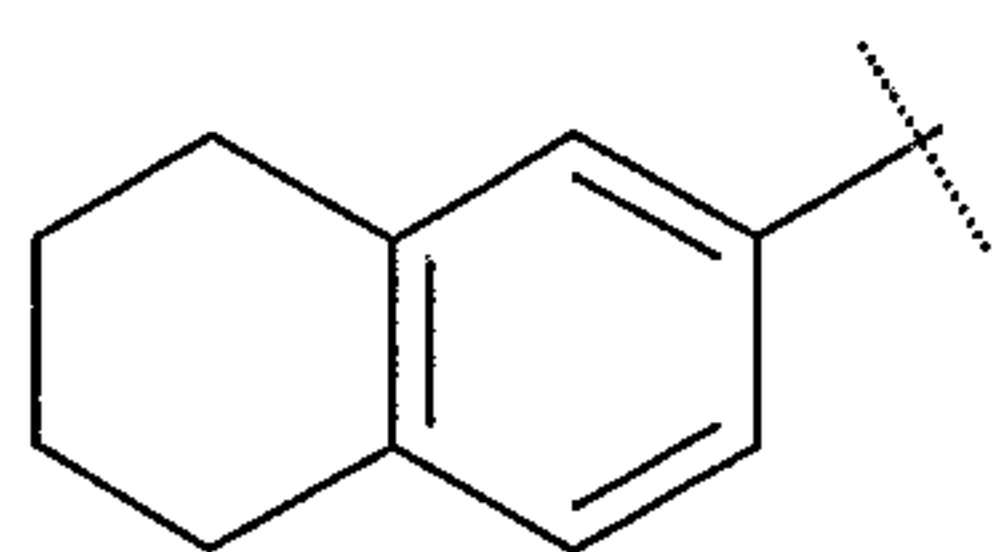
As used herein, the term "arylene" refers to a benzene ring diradical or to a benzene ring system diradical fused to one or more optionally substituted benzene rings, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, silyloxy optionally substituted by alkoxy, alkyl, or aryl, silyl optionally substituted by alkoxy, alkyl, or aryl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Examples of "arylene" include, but are not limited to, benzene-1,4-diyl, naphthalene-1,8-diyl, and the like.

As used herein, the term "heteroaryl" refers to a five - to seven - membered aromatic ring, or to a polycyclic heterocyclic aromatic ring, containing one or more nitrogen, oxygen,

or sulfur heteroatoms, where N-oxides and sulfur monoxides and sulfur dioxides are permissible heteroaromatic substitutions, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, silyloxy optionally substituted by alkoxy, alkyl, or aryl, silyl optionally substituted by alkoxy, alkyl, or aryl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. For polycyclic aromatic ring systems, one or more of the rings may contain one or more heteroatoms. Examples of "heteroaryl" used herein are furan, thiophene, pyrrole, imidazole, pyrazole, triazole, tetrazole, thiazole, oxazole, isoxazole, oxadiazole, thiadiazole, isothiazole, pyridine, pyridazine, pyrazine, pyrimidine, quinoline, isoquinoline, quinazoline, benzofuran, benzothiophene, indole, and indazole, and the like.

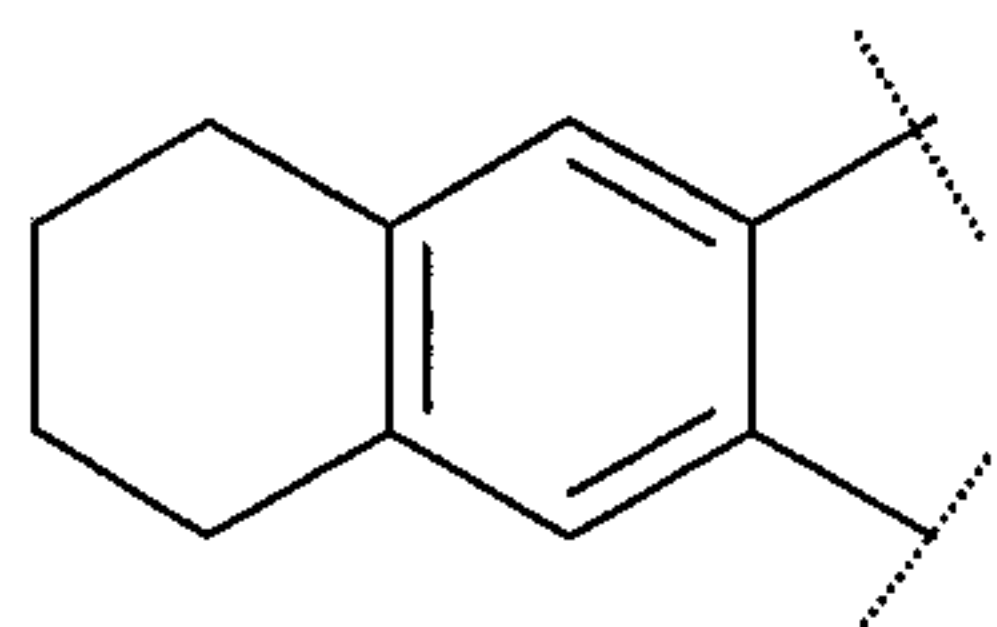
As used herein, the term "heteroarylene" refers to a five - to seven - membered aromatic ring diradical, or to a polycyclic heterocyclic aromatic ring diradical, containing one or more nitrogen, oxygen, or sulfur heteroatoms, where N-oxides and sulfur monoxides and sulfur dioxides are permissible heteroaromatic substitutions, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, silyloxy optionally substituted by alkoxy, alkyl, or aryl, silyl optionally substituted by alkoxy, alkyl, or aryl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. For polycyclic aromatic ring system diradicals, one or more of the rings may contain one or more heteroatoms. Examples of "heteroarylene" used herein are furan-2,5-diyl, thiophene-2,4-diyl, 1,3,4-oxadiazole-2,5-diyl, 1,3,4-thiadiazole-2,5-diyl, 1,3-thiazole-2,4-diyl, 1,3-thiazole-2,5-diyl, pyridine-2,4-diyl, pyridine-2,3-diyl, pyridine-2,5-diyl, pyrimidine-2,4-diyl, quinoline-2,3-diyl, and the like.

As used herein, the term "fused cycloalkylaryl" refers to one or more cycloalkyl groups fused to an aryl group, the aryl and cycloalkyl groups having two atoms in common, and wherein the aryl group is the point of substitution. Examples of "fused cycloalkylaryl" used herein include 5-indanyl, 5,6,7,8-tetrahydro-2-naphthyl,



, and the like.

As used herein, the term "fused cycloalkylarylene" refers to a fused cycloalkylaryl, wherein the aryl group is divalent. Examples include

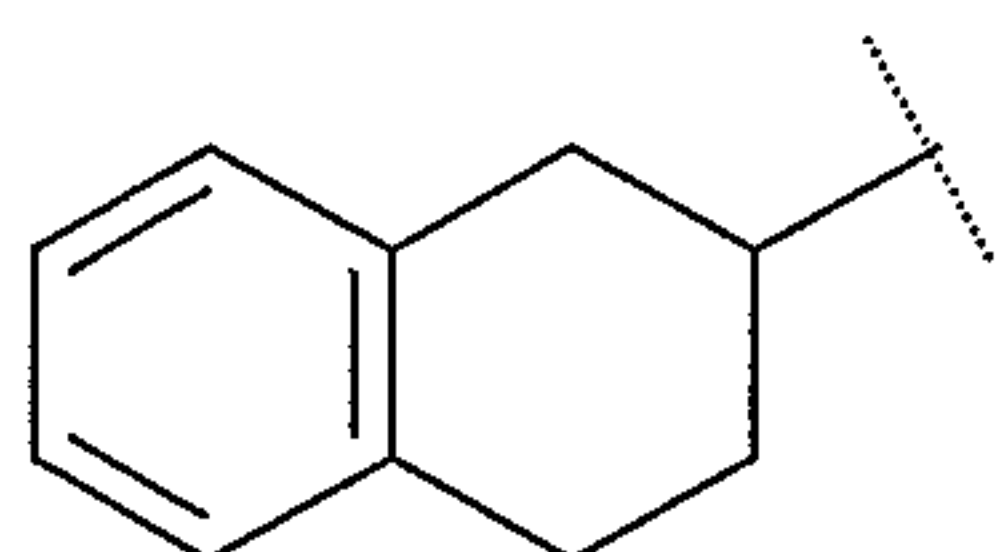


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, and the like.

As used herein, the term "fused arylcycloalkyl" refers to one or more aryl groups fused to a cycloalkyl group, the cycloalkyl and aryl groups having two atoms in common, and wherein the cycloalkyl group is the point of substitution. Examples of "fused arylcycloalkyl" used herein include 1-indanyl, 2-indanyl, 9-fluorenyl, 1-(1,2,3,4-tetrahydronaphthyl),

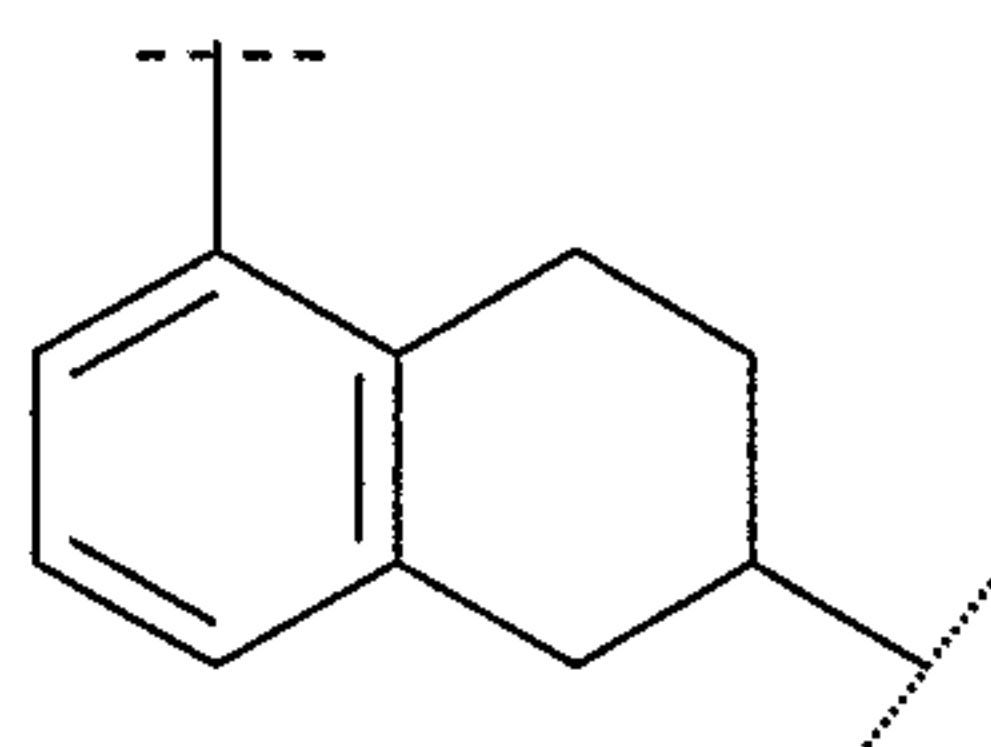
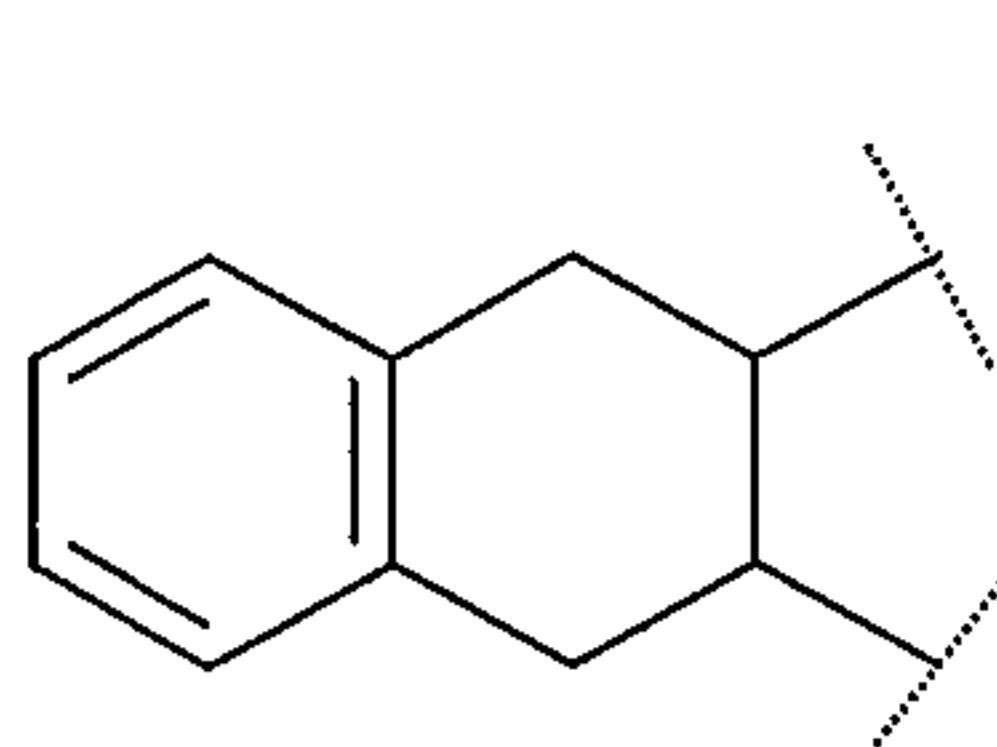
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, and the like.

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As used herein, the term "fused arylcycloalkylene" refers to a fused arylcycloalkyl, wherein the cycloalkyl group is divalent. Examples include 9,1-fluorenylene,

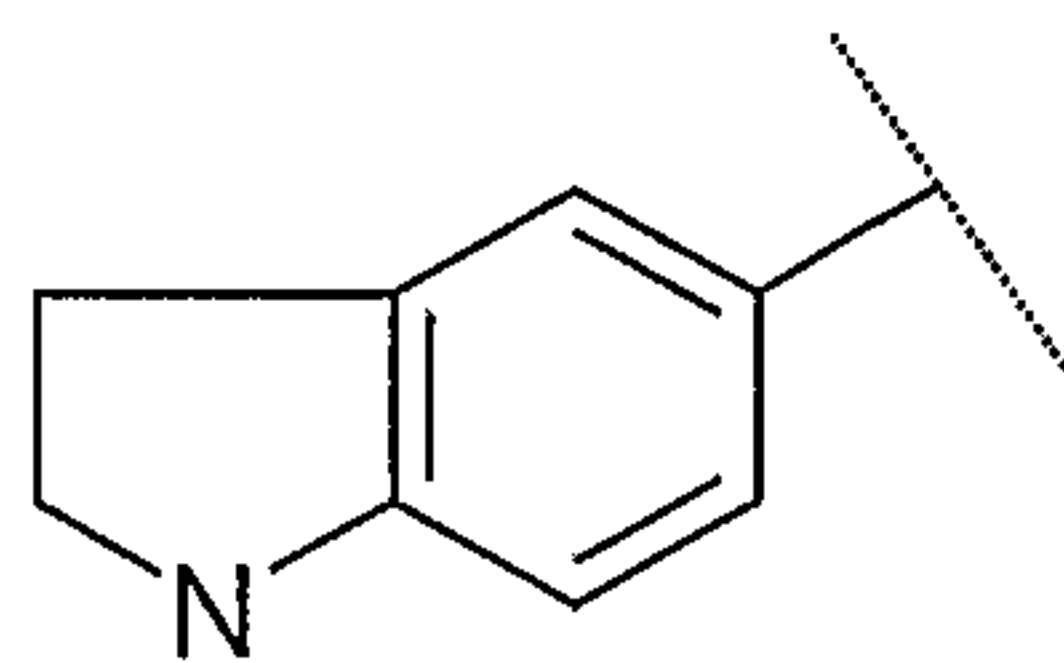


, and the like.

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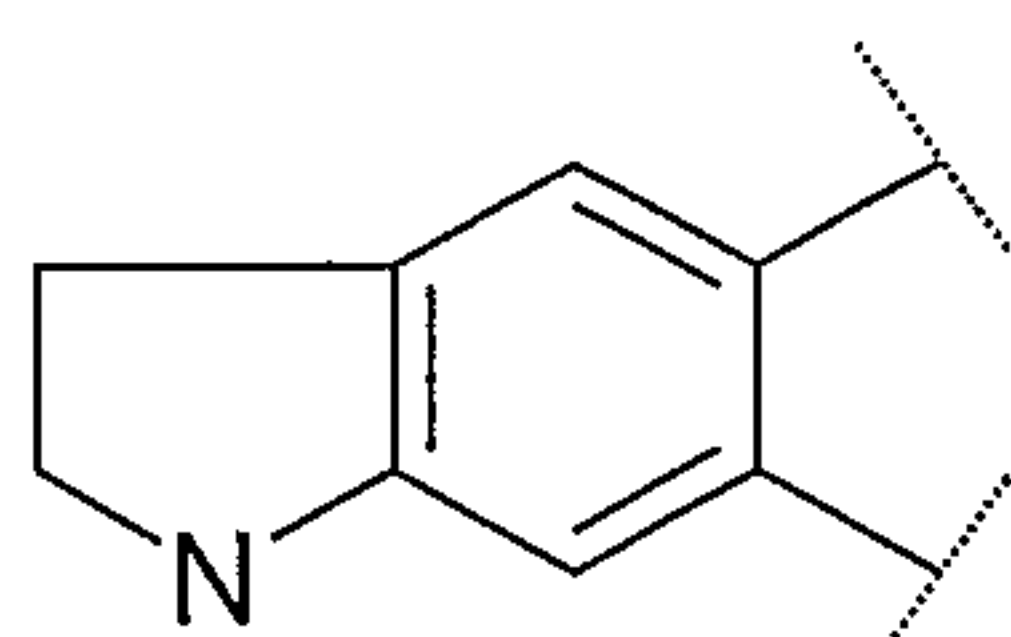
As used herein, the term "fused heterocyclaryl" refers to one or more heterocyclaryl groups fused to an aryl group, the aryl and heterocyclaryl groups having two atoms in common, and wherein the aryl group is the point of substitution. Examples of "fused

heterocyclaryl" used herein include 3,4-methylenedioxy-1-phenyl,



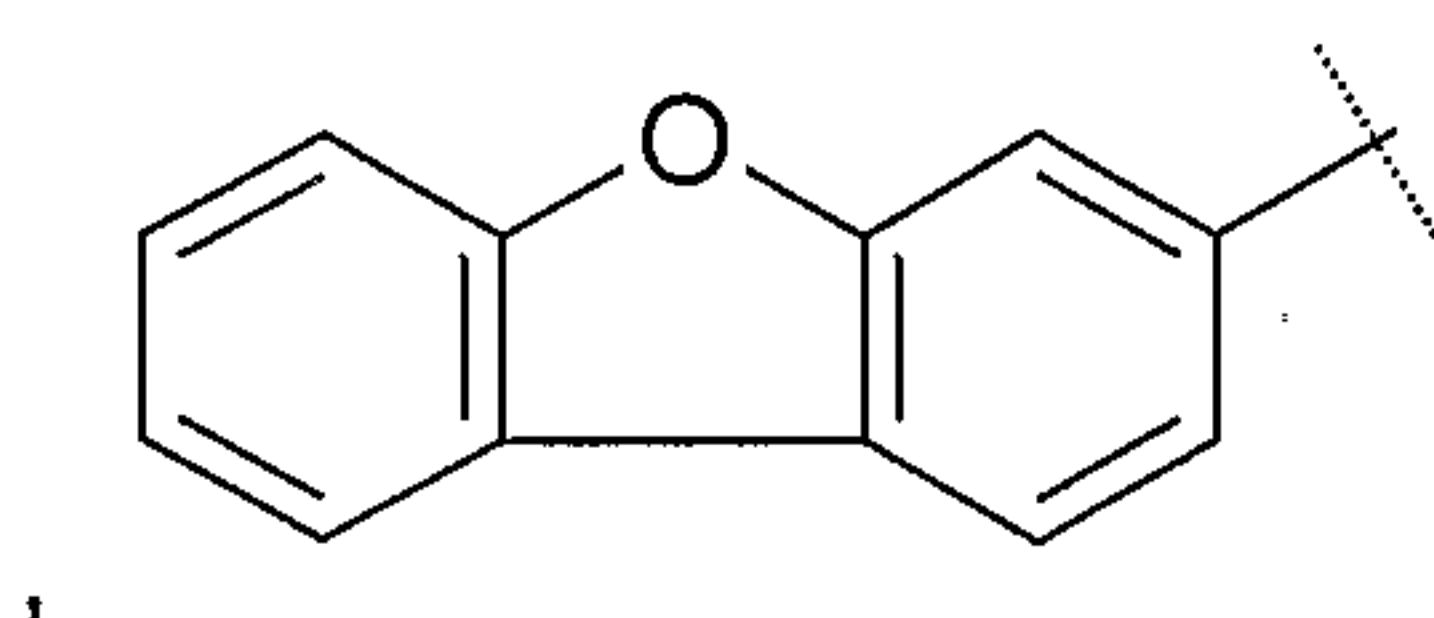
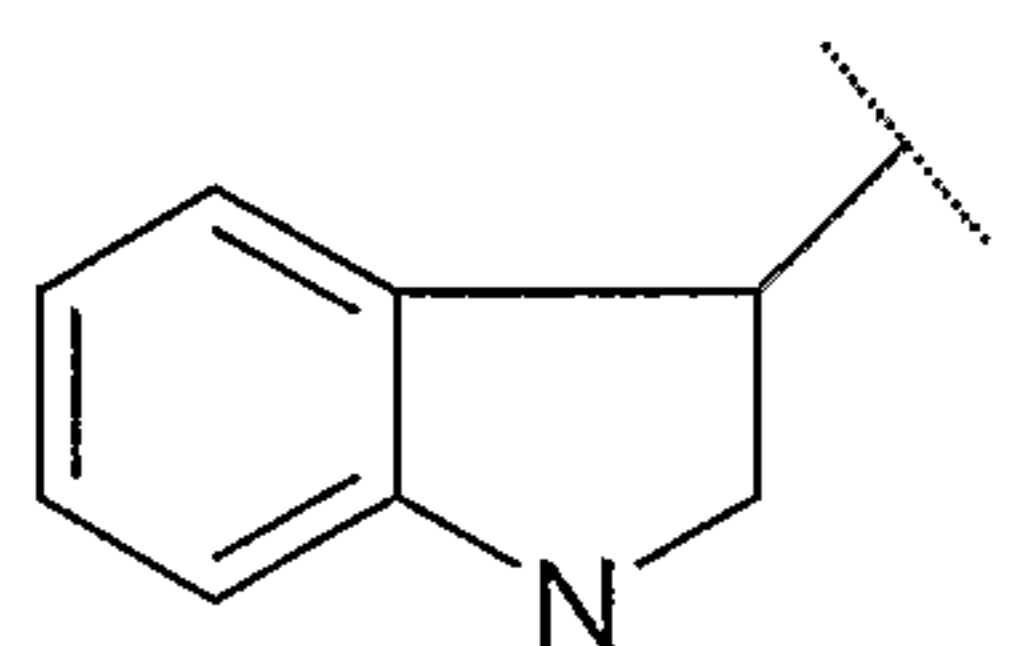
, and the like

5 As used herein, the term "fused heterocyclarylene" refers to a fused heterocyclaryl, wherein the aryl group is divalent. Examples include



, and the like.

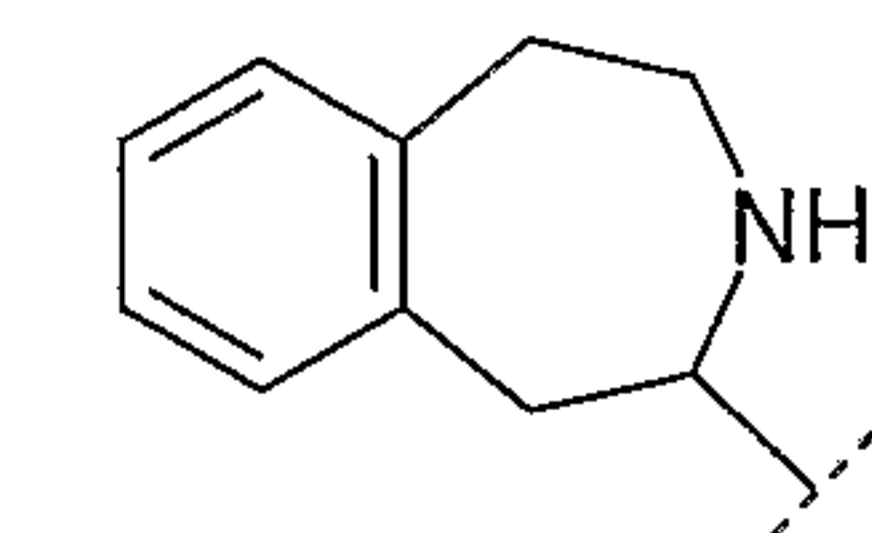
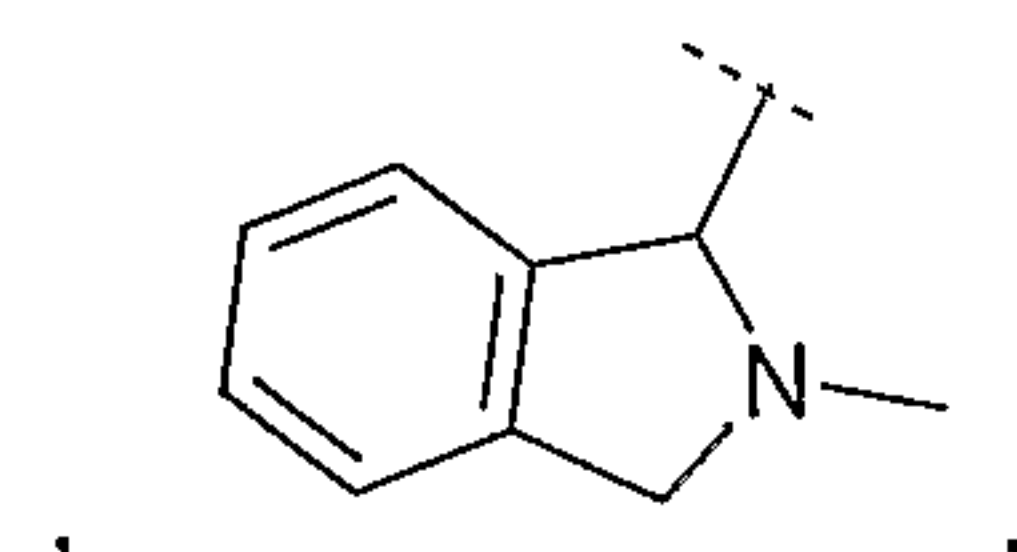
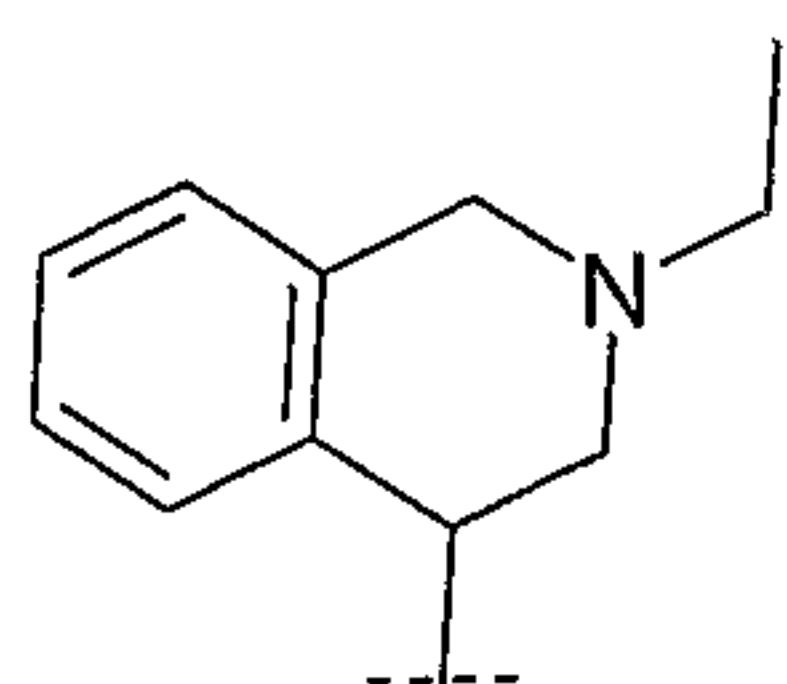
10 As used herein, the term "fused arylheterocycl" refers to one or more aryl groups fused to a heterocycl group, the heterocycl and aryl groups having two atoms in common, and wherein the heterocycl group is the point of substitution. Examples of "fused arylheterocycl" used herein include 2-(1,3-benzodioxolyl),



, and the like.

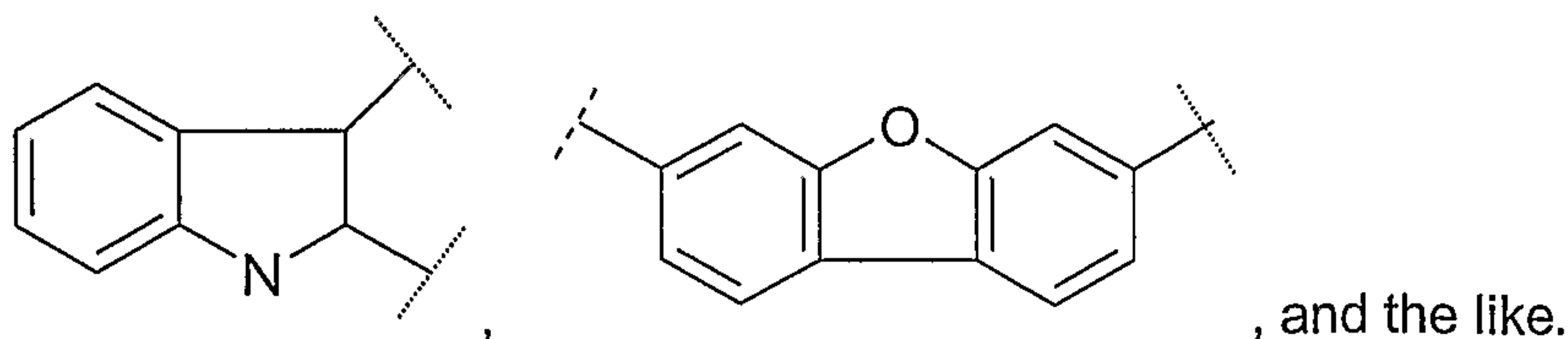
15 As used herein, the term "fused arylheterocycl containing at least one basic nitrogen atom" refers to a "fused arylheterocycl" group as defined above,

wherein said heterocycl group contains at least one nitrogen atom flanked by hydrogen, alkyl, alkylene, or alkylne groups, wherein said alkyl and/or alkylene groups are not substituted by oxo. Examples of "fused arylheterocycl containing at least one basic nitrogen atom" include, but are not limited to,

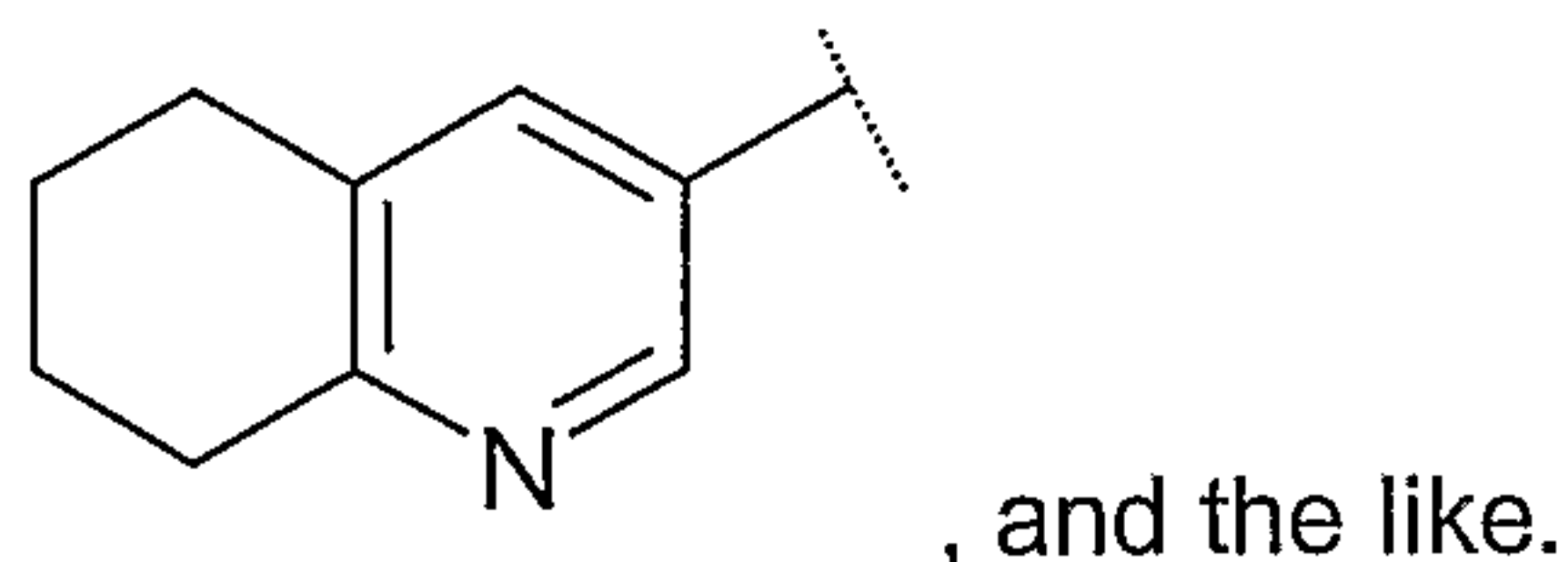


, and the like.

As used herein, the term "fused arylheterocyclylene" refers to a fused arylheterocyclyl, wherein the heterocyclyl group is divalent. Examples include

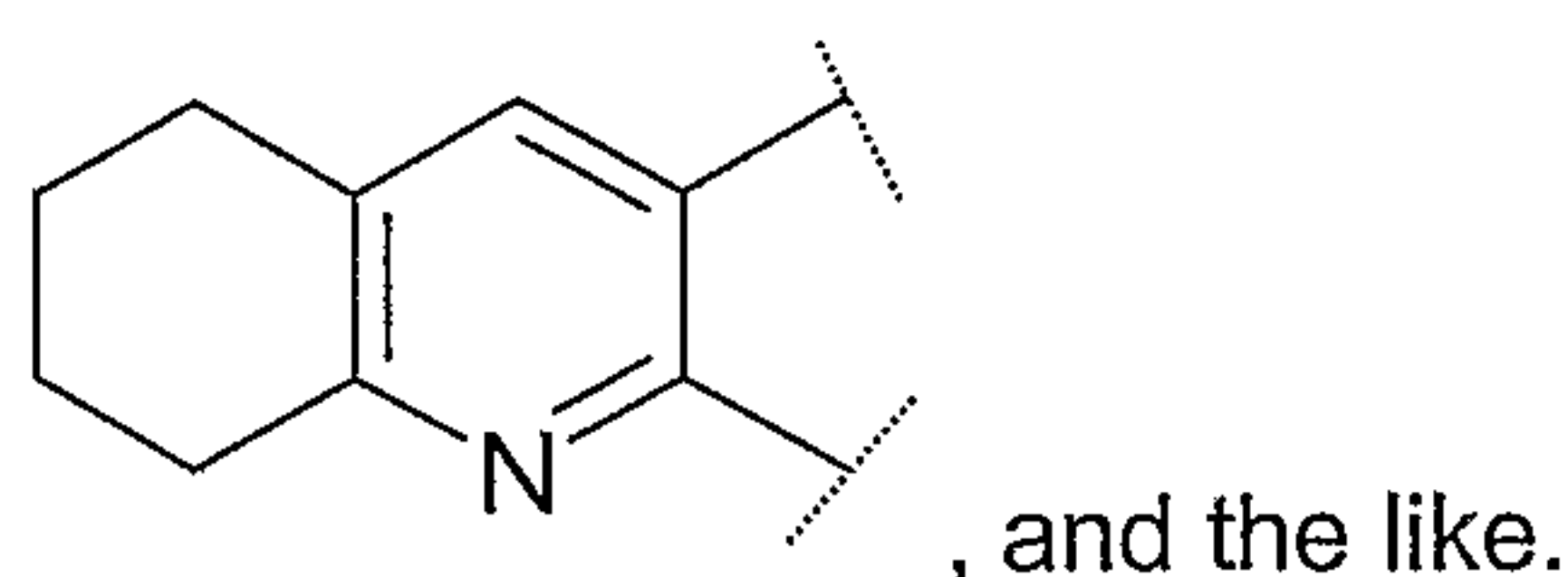


5 As used herein, the term "fused cycloalkylheteroaryl" refers to one or more cycloalkyl groups fused to a heteroaryl group, the heteroaryl and cycloalkyl groups having two atoms in common, and wherein the heteroaryl group is the point of substitution. Examples of "fused cycloalkylheteroaryl" used herein include 5-aza-6-indanyl,

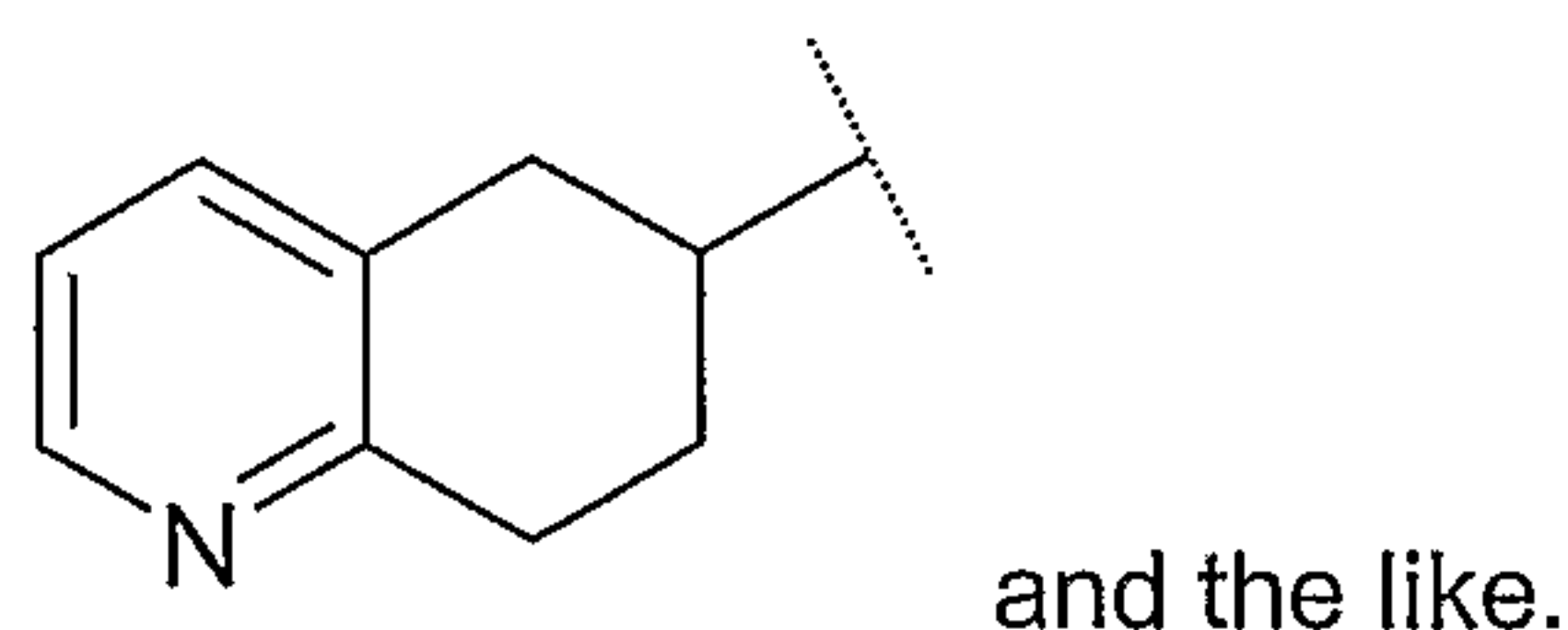


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As used herein, the term "fused cycloalkylheteroarylene" refers to a fused cycloalkylheteroaryl, wherein the heteroaryl group is divalent. Examples include

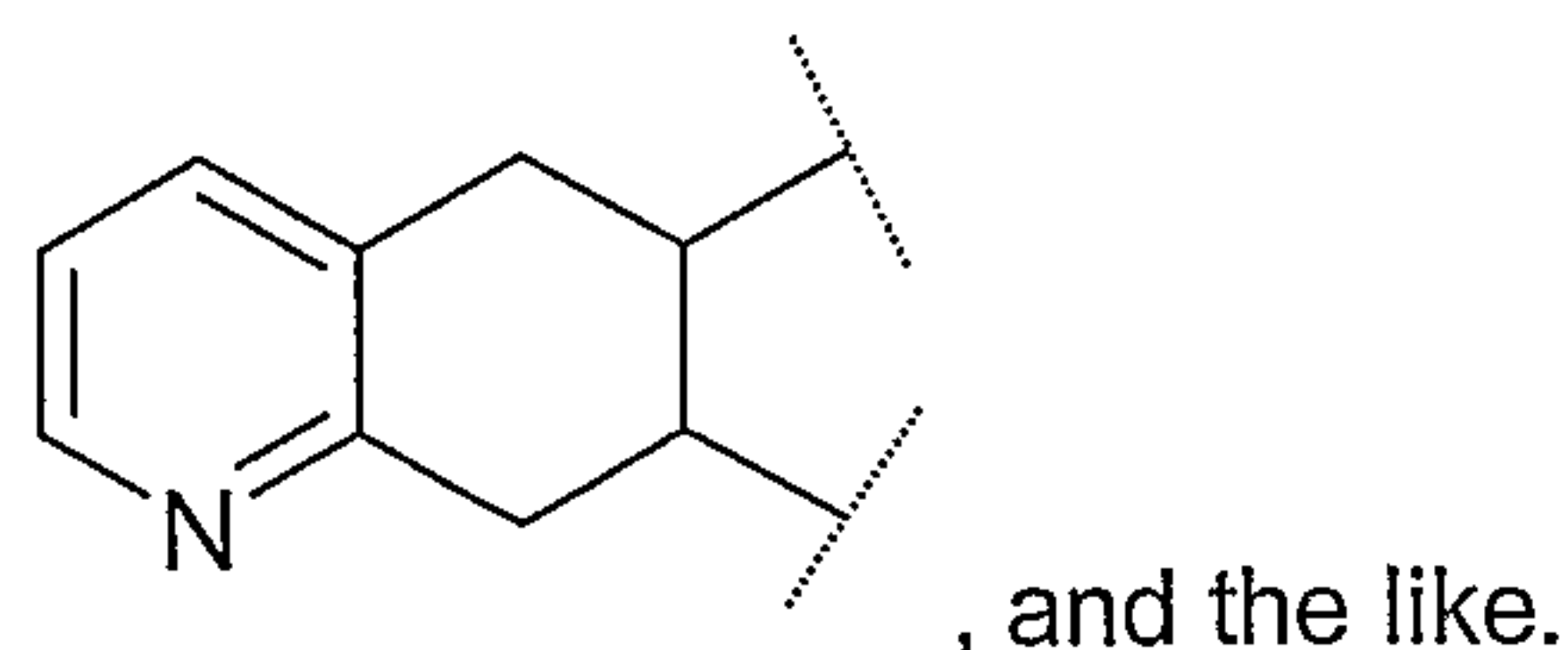


15 As used herein, the term "fused heteroarylcycloalkyl" refers to one or more heteroaryl groups fused to a cycloalkyl group, the cycloalkyl and heteroaryl groups having two atoms in common, and wherein the cycloalkyl group is the point of substitution. Examples of "fused heteroarylcycloalkyl" used herein include 5-aza-1-indanyl,

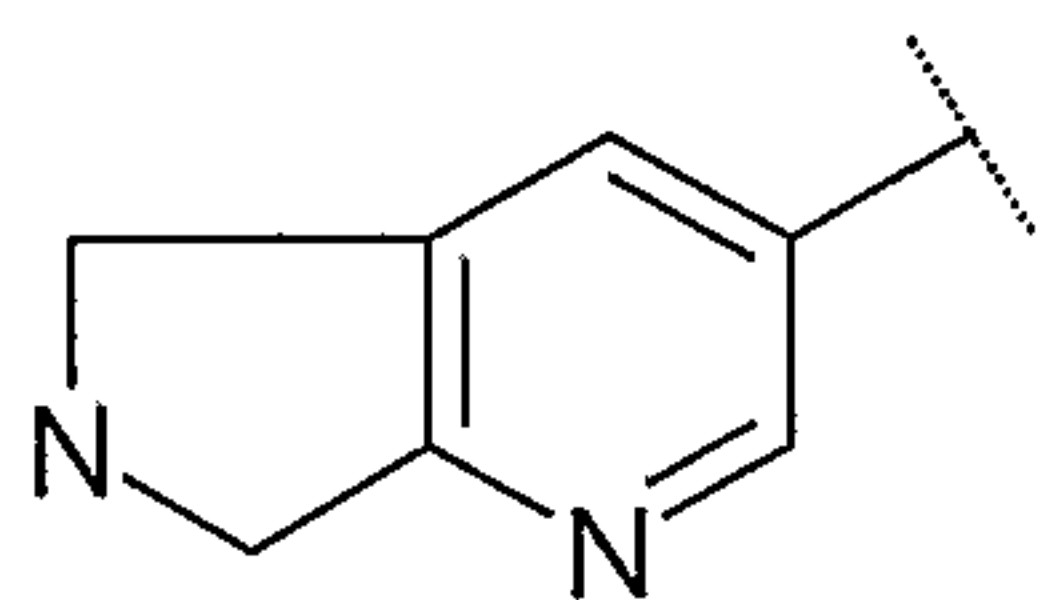


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As used herein, the term "fused heteroarylcycloalkylene" refers to a fused heteroarylcycloalkyl, wherein the cycloalkyl group is divalent. Examples include

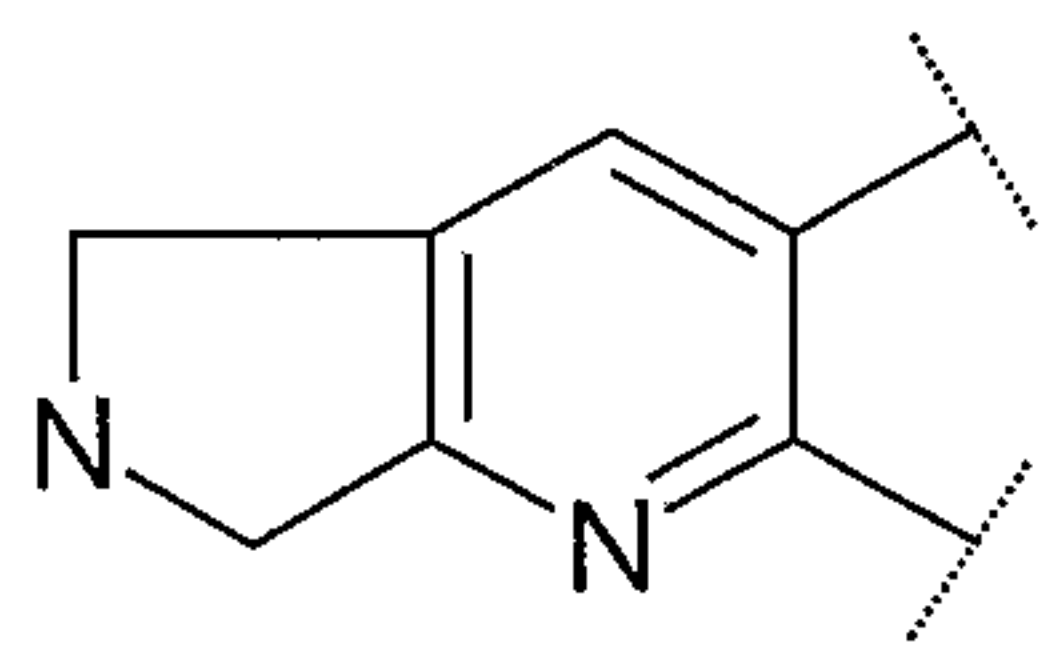


As used herein, the term "fused heterocyclylheteroaryl" refers to one or more heterocyclyl groups fused to a heteroaryl group, the heteroaryl and heterocyclyl groups having two atoms in common, and wherein the heteroaryl group is the point of substitution. Examples of "fused heterocyclylheteroaryl" used herein include 1,2,3,4-tetrahydro-beta-carbolin-8-yl,



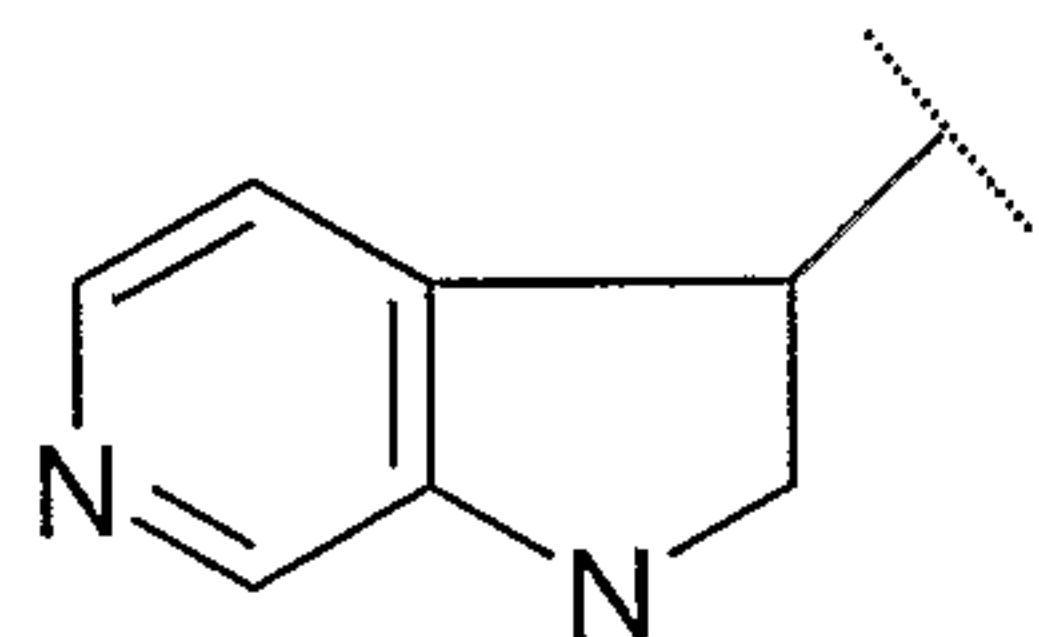
and the like.

As used herein, the term "fused heterocyclylheteroarylene" refers to a fused heterocyclylheteroaryl, wherein the heteroaryl group is divalent. Examples include



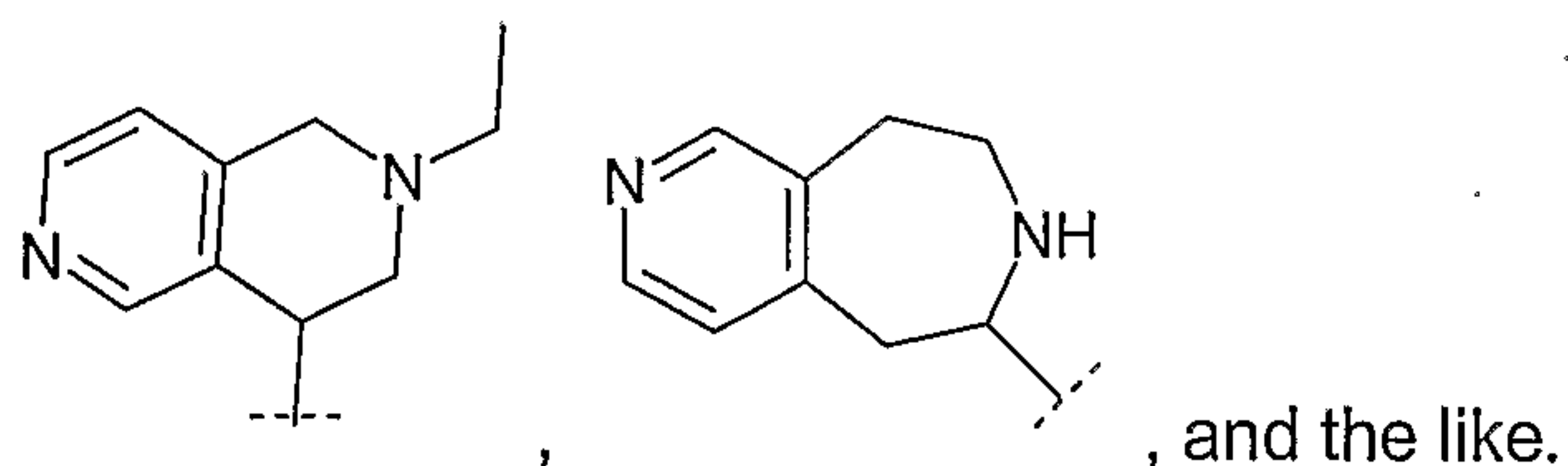
, and the like.

As used herein, the term "fused heteroarylheterocyclyl" refers to one or more heteroaryl groups fused to a heterocyclyl group, the heterocyclyl and heteroaryl groups having two atoms in common, and wherein the heterocyclyl group is the point of substitution. Examples of "fused heteroarylheterocyclyl" used herein include -5-aza-2,3-dihydrobenzofuran-2-yl,

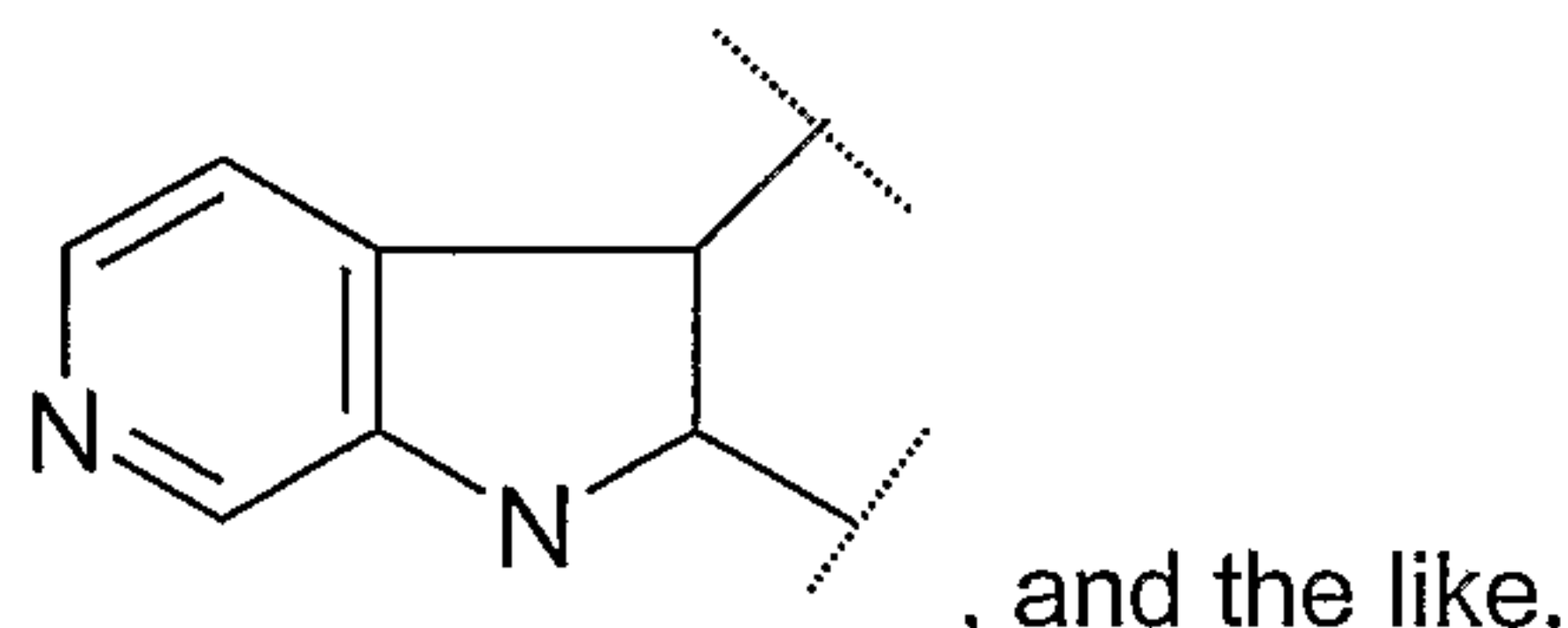


, and the like.

As used herein, the term "fused heteroarylheterocyclyl containing at least one basic nitrogen atom" refers to a "fused heteroarylheterocyclyl" group as defined above, wherein said heterocyclyl group contains at least one nitrogen atom flanked by hydrogen, alkyl, alkylene, or alkylyne groups, wherein said alkyl and/or alkylene groups are not substituted by oxo. Examples of "fused heteroarylheterocyclyl containing at least one basic nitrogen atom" include, but are not limited to,



As used herein, the term "fused heteroarylheterocyclylene" refers to a fused heteroarylheterocyclyl, wherein the heterocyclyl group is divalent. Examples include



As used herein, the term "acid isostere" refers to a substituent group which will ionize at physiological pH to bear a net negative charge. Examples of such "acid isosteres" include but are not limited to heteroaryl groups such as but not limited to isoxazol-3-ol-5-yl, 1H-tetrazole-5-yl, or 2H-tetrazole-5-yl. Such acid isosteres include but are not limited to heterocyclyl groups such as but not limited to imidazolidine-2,4-dione-5-yl, imidazolidine-2,4-dione-1-yl, 1,3-thiazolidine-2,4-dione-5-yl, or 5-hydroxy-4H-pyran-4-on-2-yl.

As used herein, the term "direct bond", where part of a structural variable specification, refers to the direct joining of the substituents flanking (preceding and succeeding) the variable taken as a "direct bond". Where two or more consecutive variables are specified each as a "direct bond", those substituents flanking (preceding and succeeding) those two or more consecutive specified "direct bonds" are directly joined.

As used herein, the term "alkoxy" refers to the group R_aO- , where R_a is alkyl.

As used herein, the term "alkenyloxy" refers to the group R_aO- , where R_a is alkenyl.

As used herein, the term "alkynyloxy" refers to the group R_aO- , where R_a is alkynyl.

As used herein, the term "alkylsulfanyl" refers to the group R_aS- , where R_a is alkyl.

As used herein, the term "alkenylsulfanyl" refers to the group R_aS- , where R_a is alkenyl.

As used herein, the term "alkynylsulfanyl" refers to the group R_aS- , where R_a is alkynyl.

5 As used herein, the term "alkylsulfenyl" refers to the group $R_aS(O)-$, where R_a is alkyl.

As used herein, the term "alkenylsulfenyl" refers to the group $R_aS(O)-$, where R_a is alkenyl.

10 As used herein, the term "alkynylsulfenyl" refers to the group $R_aS(O)-$, where R_a is alkynyl.

As used herein, the term "alkylsulfonyl" refers to the group R_aSO_2- , where R_a is alkyl.

15 As used herein, the term "alkenylsulfonyl" refers to the group R_aSO_2- , where R_a is alkenyl.

As used herein, the term "alkynylsulfonyl" refers to the group R_aSO_2- , where R_a is alkynyl.

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As used herein, the term "acyl" refers to the group $R_aC(O)-$, where R_a is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, or heterocyclyl.

As used herein, the term "aroyl" refers to the group $R_aC(O)-$, where R_a is aryl.

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As used herein, the term "heteroaroyl" refers to the group $R_aC(O)-$, where R_a is heteroaryl.

As used herein, the term "alkoxycarbonyl" refers to the group $R_aOC(O)-$, where R_a is alkyl.

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As used herein, the term "acyloxy" refers to the group $R_aC(O)O-$, where R_a is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, or heterocyclyl.

As used herein, the term "alkoxycarbonyl" refers to the group $R_aOC(O)-$, where R_a is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, or heterocyclyl.

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As used herein, the term "aryloxycarbonyl" refers to the group $R_aOC(O)-$, where R_a is aryl or heteroaryl.

As used herein, the term "aroxyloxy" refers to the group $R_aC(O)O-$, where R_a is aryl.

As used herein, the term "heteroaroxyloxy" refers to the group $R_aC(O)O-$, where R_a is heteroaryl.

As used herein, the term "optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s) which occur and events that do not occur.

As used herein, the term "substituted" refers to substitution with the named substituent or substituents, multiple degrees of substitution being allowed unless otherwise stated.

As used herein, the terms "contain" or "containing" can refer to in-line substitutions at any position along the above defined alkyl, alkenyl, alkynyl or cycloalkyl substituents with one or more of any of O, S, SO, SO_2 , N, or N-alkyl, including, for example, $-CH_2-O-CH_2-$, $-CH_2-SO_2-CH_2-$, $-CH_2-NH-CH_3$ and so forth.

Whenever the terms "alkyl" or "aryl" or either of their prefix roots appear in a name of a substituent (e.g. arylalkoxyaryloxy) they shall be interpreted as including those limitations given above for "alkyl" and "aryl". Alkyl or cycloalkyl substituents shall be recognized as being functionally equivalent to those having one or more degrees of unsaturation. Designated numbers of carbon atoms (e.g. C_{1-10}) shall refer independently to the number of carbon atoms in an alkyl, alkenyl or alkynyl or cyclic alkyl moiety or to the alkyl portion of a larger substituent in which the term "alkyl" appears as its prefix root.

As used herein, the term "oxo" shall refer to the substituent $=O$.

As used herein, the term "halogen" or "halo" shall include iodine, bromine, chlorine and fluorine.

As used herein, the term "mercapto" shall refer to the substituent $-SH$.

As used herein, the term "carboxy" shall refer to the substituent $-COOH$.

As used herein, the term "cyano" shall refer to the substituent -CN.

As used herein, the term "aminosulfonyl" shall refer to the substituent -SO₂NH₂.

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As used herein, the term "carbamoyl" shall refer to the substituent -C(O)NH₂.

As used herein, the term "sulfanyl" shall refer to the substituent -S-.

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As used herein, the term "sulfenyl" shall refer to the substituent -S(O)-.

As used herein, the term "sulfonyl" shall refer to the substituent -S(O)₂-.

15

As used herein, the term "solvate" is a complex of variable stoichiometry formed by a solute (in this invention, a compound of Formula (I)) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Solvents may be, by way of example, water, ethanol, or acetic acid.

20

As used herein, the term "biohydrolyzable ester" is an ester of a drug substance (in this invention, a compound of Formula (I)) which either a) does not interfere with the biological activity of the parent substance but confers on that substance advantageous properties *in vivo* such as duration of action, onset of action, and the like, or b) is biologically inactive but is readily converted *in vivo* by the subject to the biologically active principle. The advantage is that, for example, the biohydrolyzable ester is orally absorbed from the gut and is transformed to (I) in plasma. Many examples of such are known in the art and include by way of example lower alkyl esters (e.g., C₁-C₄), lower acyloxyalkyl esters, lower alkoxyacyloxyalkyl esters, alkoxyacyloxy esters, alkyl acylamino alkyl esters, and choline esters.

25

30

As used herein, the term "biohydrolyzable amide" is an amide of a drug substance (in this invention, a compound of general Formula (I)) which either a) does not interfere with the biological activity of the parent substance but confers on that substance advantageous properties *in vivo* such as duration of action, onset of action, and the like, or b) is biologically inactive but is readily converted *in vivo* by the subject to the biologically active principle. The advantage is that, for example, the biohydrolyzable amide is orally absorbed from the gut and is transformed to (I) in plasma. Many examples of such are known in the art and include

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by way of example lower alkyl amides, α -amino acid amides, alkoxyacyl amides, and alkylaminoalkylcarbonyl amides.

As used herein, the term "prodrug" includes biohydrolyzable amides and
5 biohydrolyzable esters and also encompasses a) compounds in which the biohydrolyzable
functionality in such a prodrug is encompassed in the compound of Formula (I): for example,
the lactam formed by a carboxylic group in R₂ and an amine in R₄, and b) compounds which
may be oxidized or reduced biologically at a given functional group to yield drug substances
of Formula (I). Examples of these functional groups include, but are not limited to, 1,4-
10 dihydropyridine, N-alkylcarbonyl-1,4-dihydropyridine, 1,4-cyclohexadiene, tert-butyl, and the
like.

The term "pharmacologically effective amount" or shall mean that amount of a drug
or pharmaceutical agent that will elicit the biological or medical response of a tissue, animal
15 or human that is being sought by a researcher or clinician. This amount can be a
therapeutically effective amount. The term "therapeutically effective amount" shall mean that
amount of a drug or pharmaceutical agent that will elicit the therapeutic response of an
animal or human that is being sought.

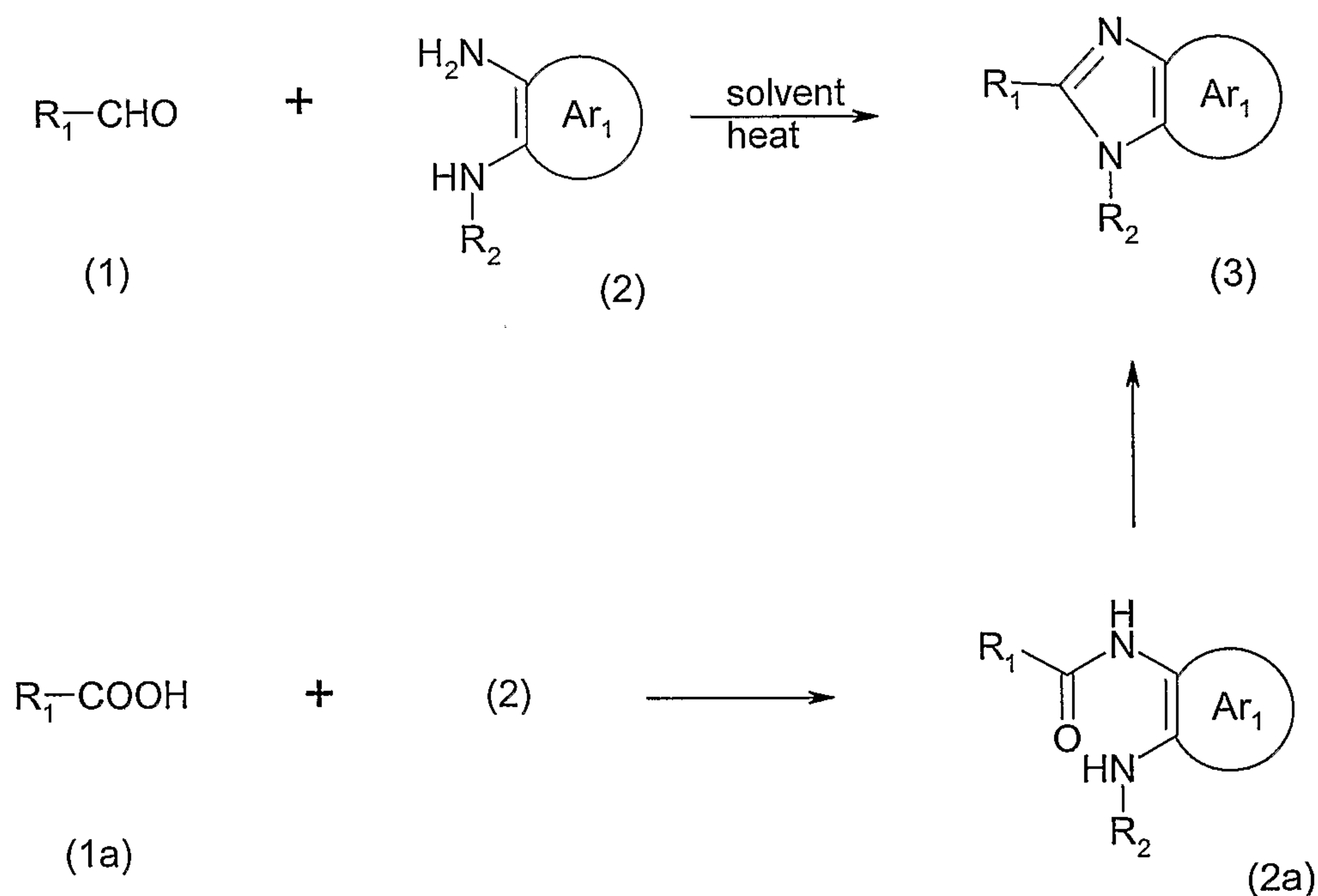
20 The term "treatment" or "treating" as used herein, refers to the full spectrum of
treatments for a given disorder from which the patient is suffering, including alleviation of
one, most of all symptoms resulting from that disorder, to an outright cure for the particular
disorder or prevention of the onset of the disorder.

25

The present invention also provides a method for the synthesis of compounds useful as intermediates in the preparation of compounds of Formula (I) along with methods for the preparation of compounds of Formula (I). Unless otherwise indicated, variables refer to those for Formula (I).

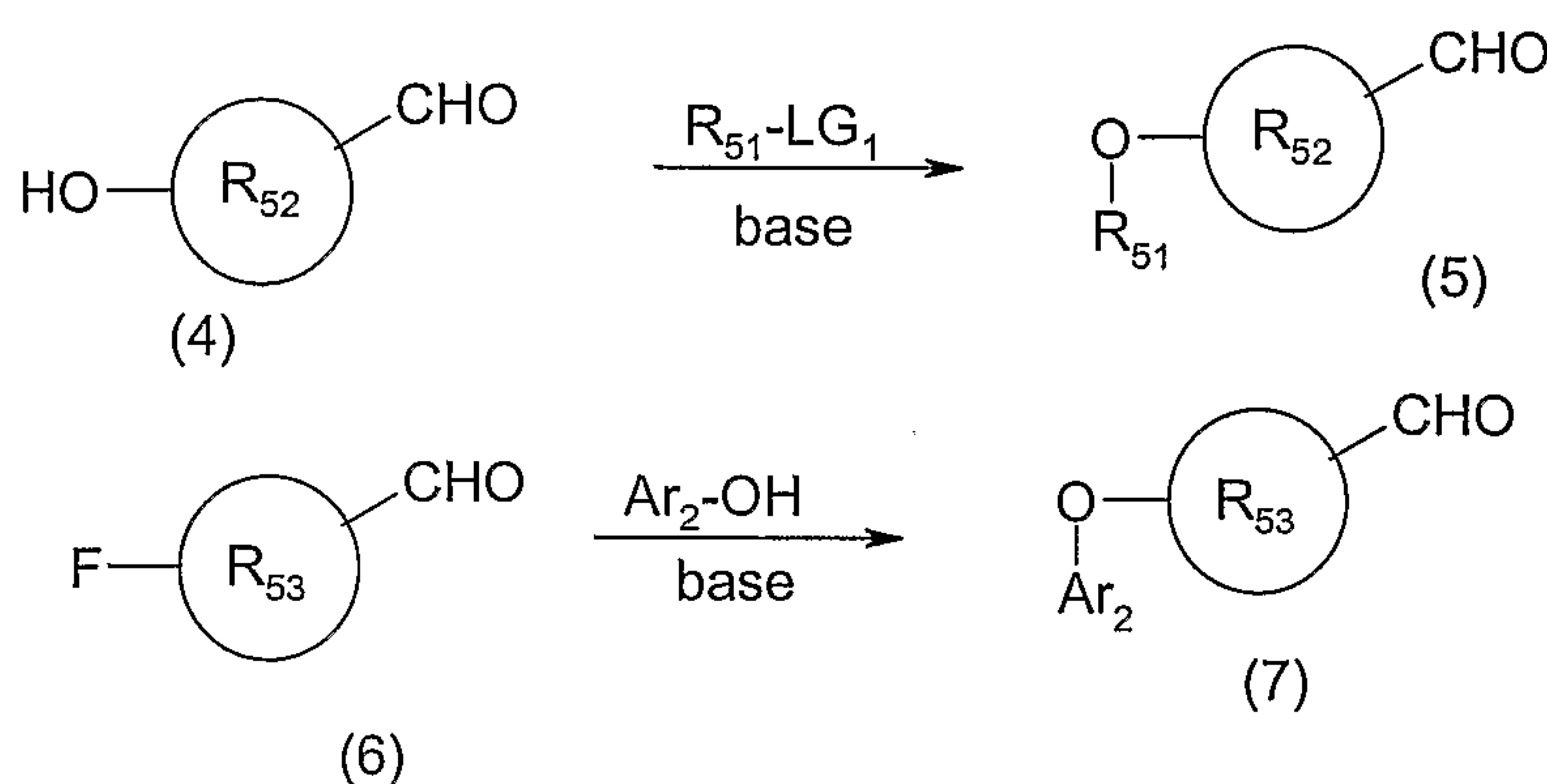
An aldehyde (1) (Scheme 1) may be condensed with a diamine compound (2) in a solvent such as ethanol at a temperature of from 25 to 100 degrees Celsius, to obtain the product benzimidazole (3), where the intermediate adduct undergoes spontaneous oxidation. Alternately, the acid (1a) may be coupled with the diamine compound (2) employing a reagent such as HBTU to afford (2a). The reaction may also afford some of the compound where the carboxylic acid has coupled to the secondary aniline nitrogen. Either product (2a) may be cyclized to (3). One nonlimiting method is to heat (2a) in a solvent such as acetic acid at a temperature of from 25 to 100 degrees Celsius, to obtain the cyclized product (3). Ar₁ is a group such as but not limited to an optionally substituted aryl or heteroaryl ring system.

Scheme 1



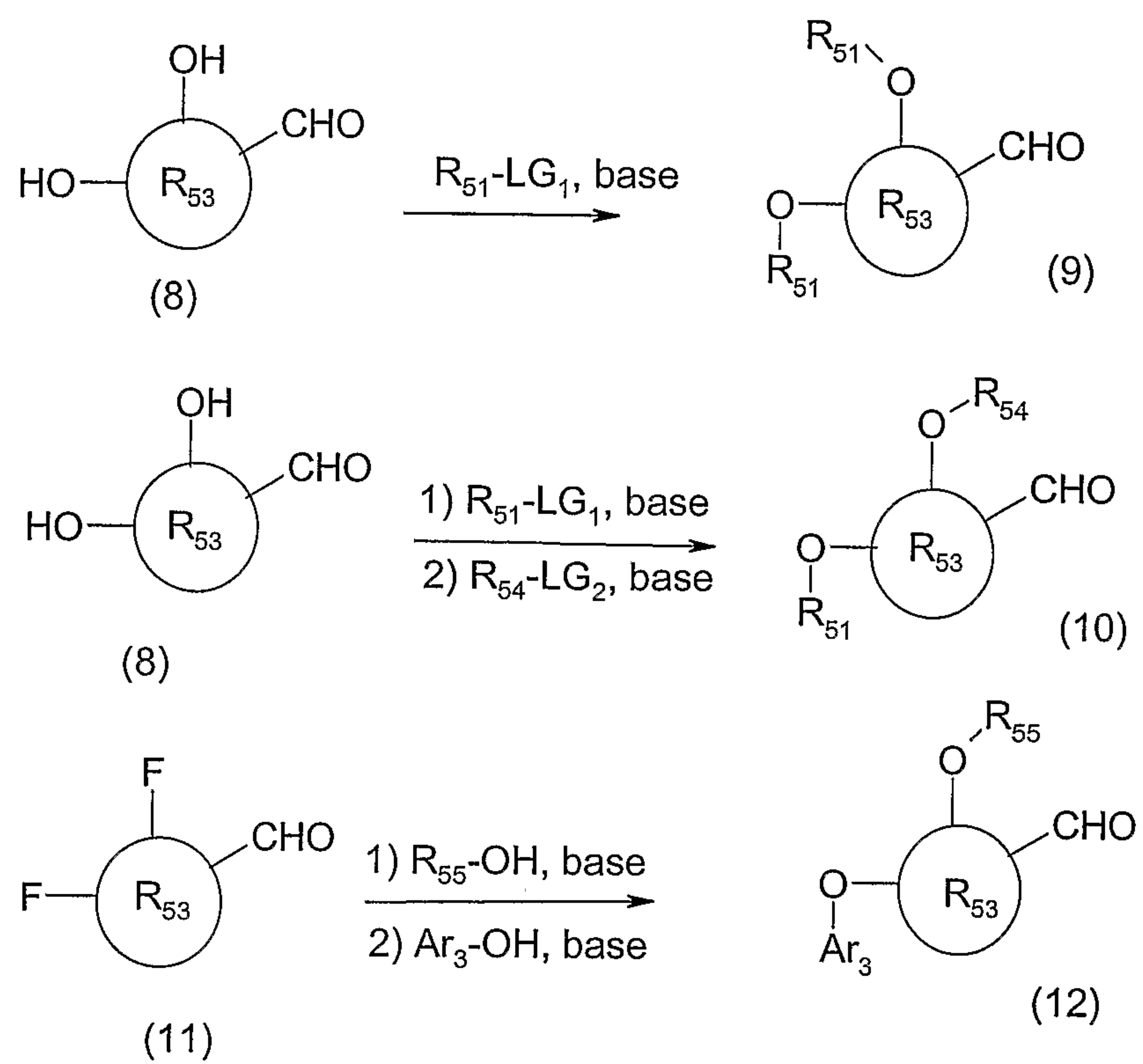
Where R_{52} is aryl, heteroaryl, or contains an aryl or heteroaryl group possessing a phenolic substituent, or where R_{52} possesses a free hydroxyl group, an aldehyde of formula (4) (Scheme 2) may be treated with an optionally substituted alkyl halide R_{51} -LG₁ and a base such as potassium carbonate, in a solvent such as DMF, at a temperature of from 0 to 120 °C, to afford (5). LG₁ represents a nucleofugal group such as iodide, bromide, methanesulfonate, or toluenesulfonate (Scheme 2). Where R_{53} in (6) represents an aryl or heteroaryl ring system, direct treatment of (6) in the presence of a base such as DIEA or TEA with an aryl or heteroaryl phenol Ar_2 -OH provides (7), where the Ar_2 -O- substituent is bonded to the same atom as the F in (6).

Scheme 2



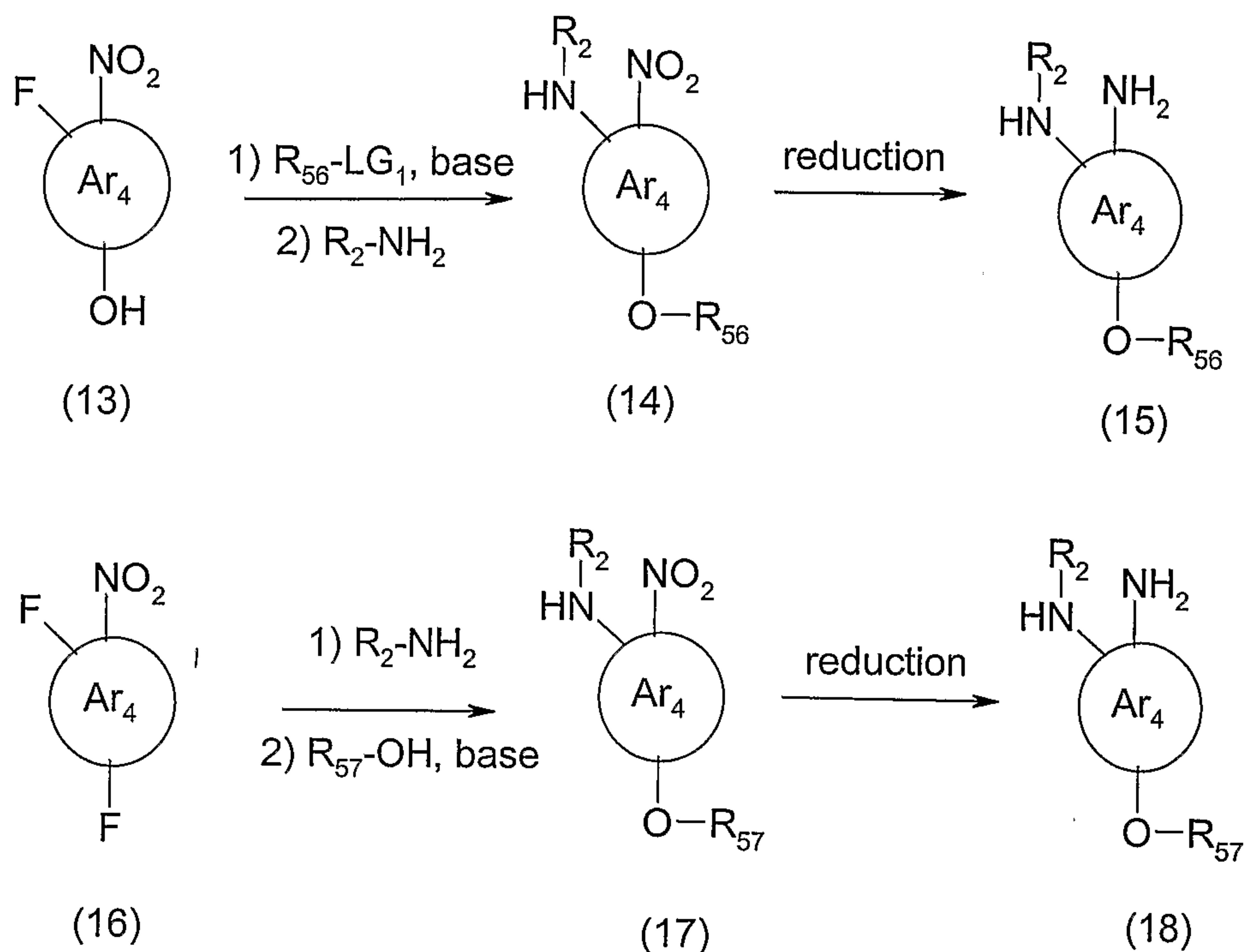
In Scheme 3, an aldehyde (8) possessing two free hydroxyl groups, two free phenolic groups, or a combination of phenolic and hydroxyl groups may be treated with two equivalents of an alkylating agent R_{51} -LG₁, in the presence of a suitable base such as potassium carbonate or DIEA, in a solvent such as DMF, to afford (9). Alternately, where R_{53} is an aryl ring possessing ortho and para hydroxyl groups relative to the aldehyde group, treatment of (8) with one equivalent of base and an alkylating agent R_{51} -LG₁ in the presence of a suitable base such as DIEA or potassium carbonate, followed by treatment with a second alkylating agent R_{54} -LG₂ in the presence of base, affords (10). The ortho, para difluoro aldehyde (11), where R_{53} is a heteroaryl or aryl ring, may be treated with an alcohol R_{55} -OH in the presence of base such as DIEA, followed by treatment with a phenol Ar_3 -OH in the presence of a base such as DIEA or potassium carbonate, to afford (12).

Scheme 3



Scheme 4 describes the synthesis of substituted arylenediamines.

Scheme 4



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In Scheme 4, an ortho-fluoro nitrophenol such as (13) may be alkylated with an alkyl halide or other alkylating agent $R_{56}\text{-LG}_1$, in the presence of an alkali metal carbonate as base in a solvent such as DMF or acetonitrile. LG_1 may represent a nucleofugal group such as iodide, bromide, methanesulfonate, and the like. In this transformation, R_{56} is a group such as but not limited to alkyl. The intermediate may be treated with an amine $R_2\text{-NH}_2$ in the presence or absence of a tertiary amine base, in a solvent such as THF, at a temperature of from 0 °C to 100 °C, to afford (14). Reduction of the nitro group in (14) may be accomplished by treatment of (14) in acidic or neutral ethanol with stannous chloride at a temperature of from 25 °C to 100 °C to afford the aniline (15). Alternately, (14) may be reduced by treatment of (14) with a noble metal catalyst such as palladium on charcoal and a hydrogen source such as gaseous hydrogen or ammonium formate, in a solvent such as ethanol, at a temperature of from 25 °C to 80 °C, to afford (15). The difluoronitroaromatic compound (16) may be employed in similar manner, where in (16), one fluoro is ortho to the nitro group. Treatment of (16) with the one equivalent of amine $R_2\text{-NH}_2$ gives preferential substitution of the ortho fluorine. The second fluorine in the intermediate may be substituted by an alcohol $R_{57}\text{-OH}$ to afford (17). In this instance, R_{57} may also be aryl. Reduction of

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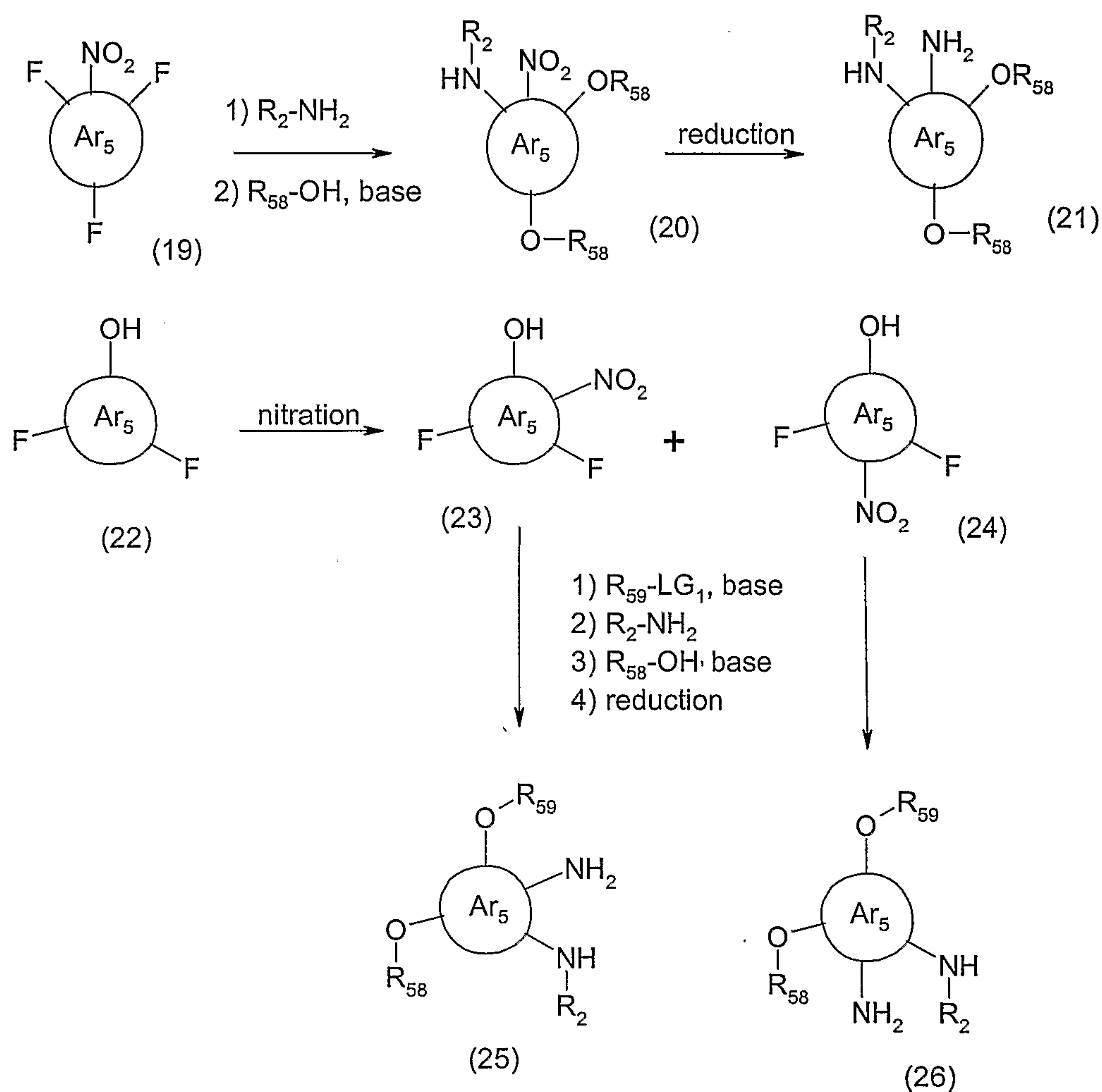
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the nitro group in (17) as before with stannous chloride provides (18). Ar₄ represents a group such as but not limited to aryl or heteroaryl.

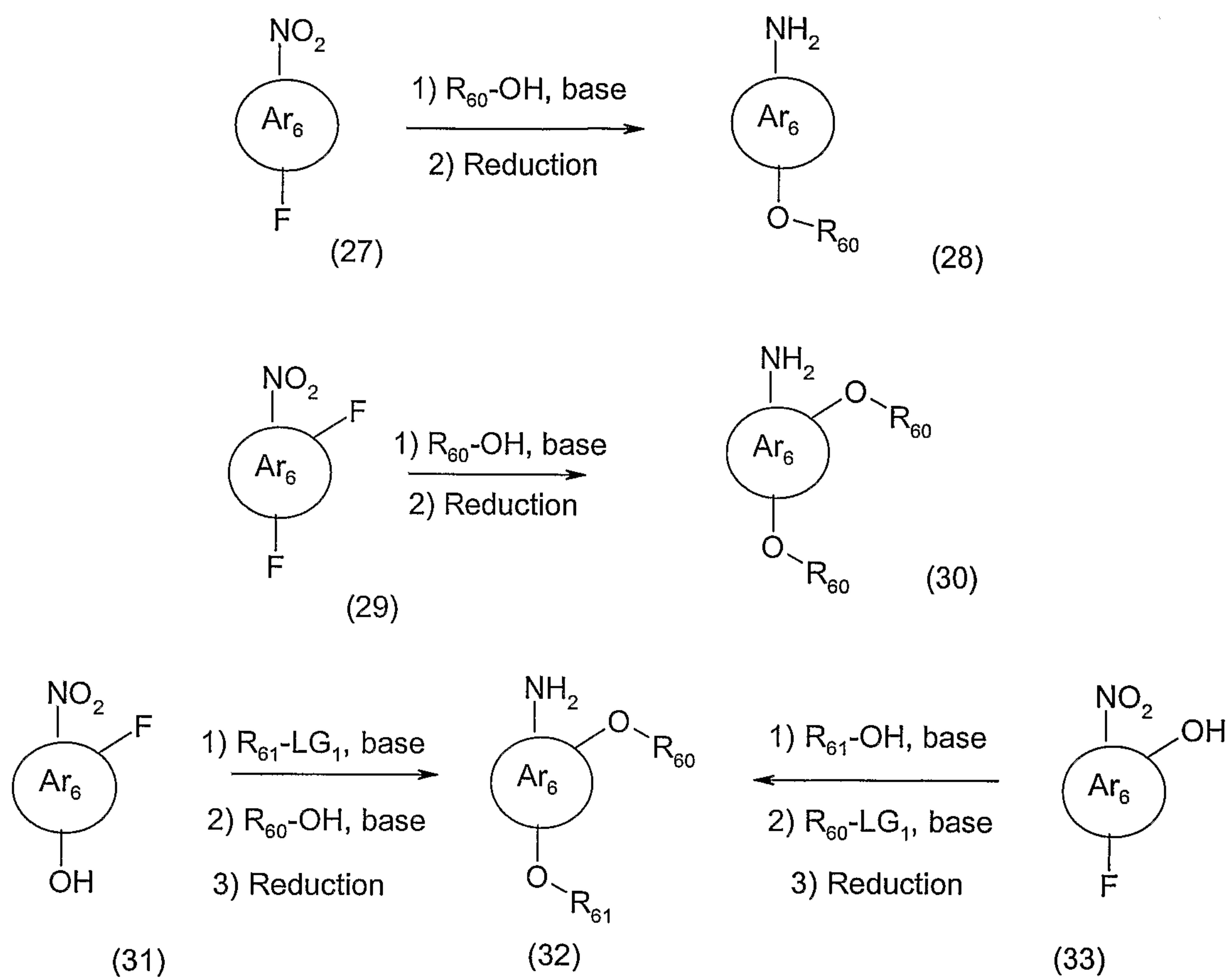
Scheme 5 describes synthesis of aryl diamines. The 2,4,6-trifluoronitroaromatic compound (19) may be treated with one equivalent of an amine R₂-NH₂ to afford the product of substitution at one ortho fluoro; excess R₅₈-OH may then be employed in the presence of a base such as potassium tert-butoxide or sodium hydride to afford (20). Reduction of the nitro group as for Scheme 4 affords the aniline (21). Similarly, a 3,5-difluorophenolic aromatic compound (22) may be nitrated under strong nitrating conditions, e.g. fuming nitric acid, to afford the ortho nitro phenol (23) along with the para nitrophenol (24). Each individually may be processed by sequential phenol alkylation, ortho fluoro displacement by R₂-NH₂, and para or ortho fluorodisplacement by R₅₈-OH, to afford (25) and (26) after reduction, following chemistries in the preceding general procedures. Ar₅ represents a group such as but not limited to aryl or heteroaryl.

Scheme 5



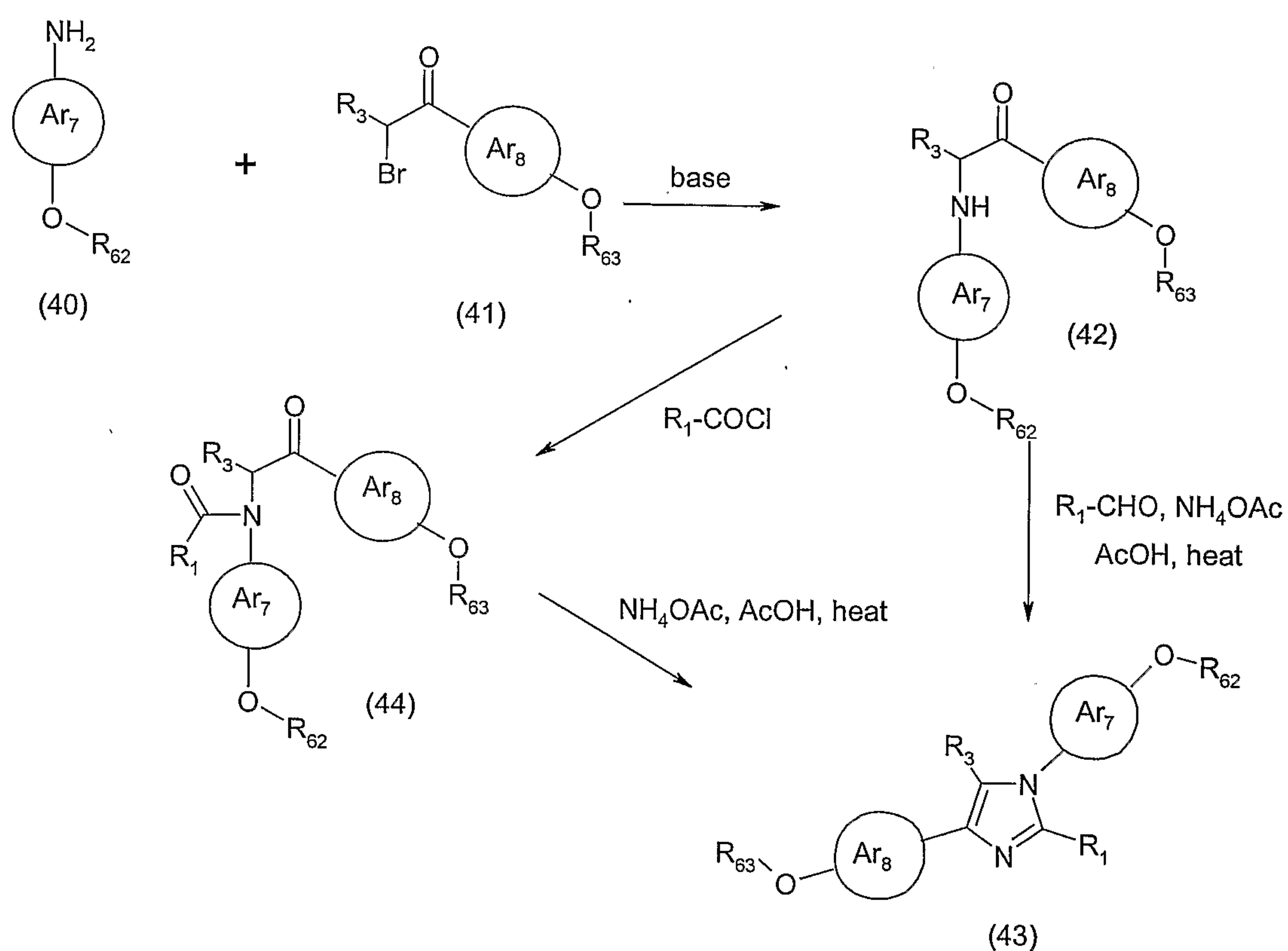
- 5 Scheme 6 describes the synthesis of mono and di alkoxy – substituted aminoaryl and aminoheteroaryl compounds. A fluoronitroaromatic (27), where F is preferably ortho or para to the nitro, may be treated with an alcohol or phenol $\text{R}_{60}\text{-OH}$ and a base such as potassium tert-butoxide or sodium hydride, to afford the ipso adduct. Reduction of the nitro group to amino following preceding methods affords (28). Similarly, displacement of the fluoro groups in (29) with $\text{R}_{60}\text{-OH}$ followed by reduction as before give (30). The nitro compound (31) may be treated with a base and $\text{R}_{61}\text{-LG}_1$ to afford the alkylation product, then treated with $\text{R}_{60}\text{-OH}$ and a base, then reduced as above to give (32). Alternately, (33) may be processed similarly to give (32). Ar_6 represents a group such as but not limited to aryl or heteroaryl.
- 10

Scheme 6



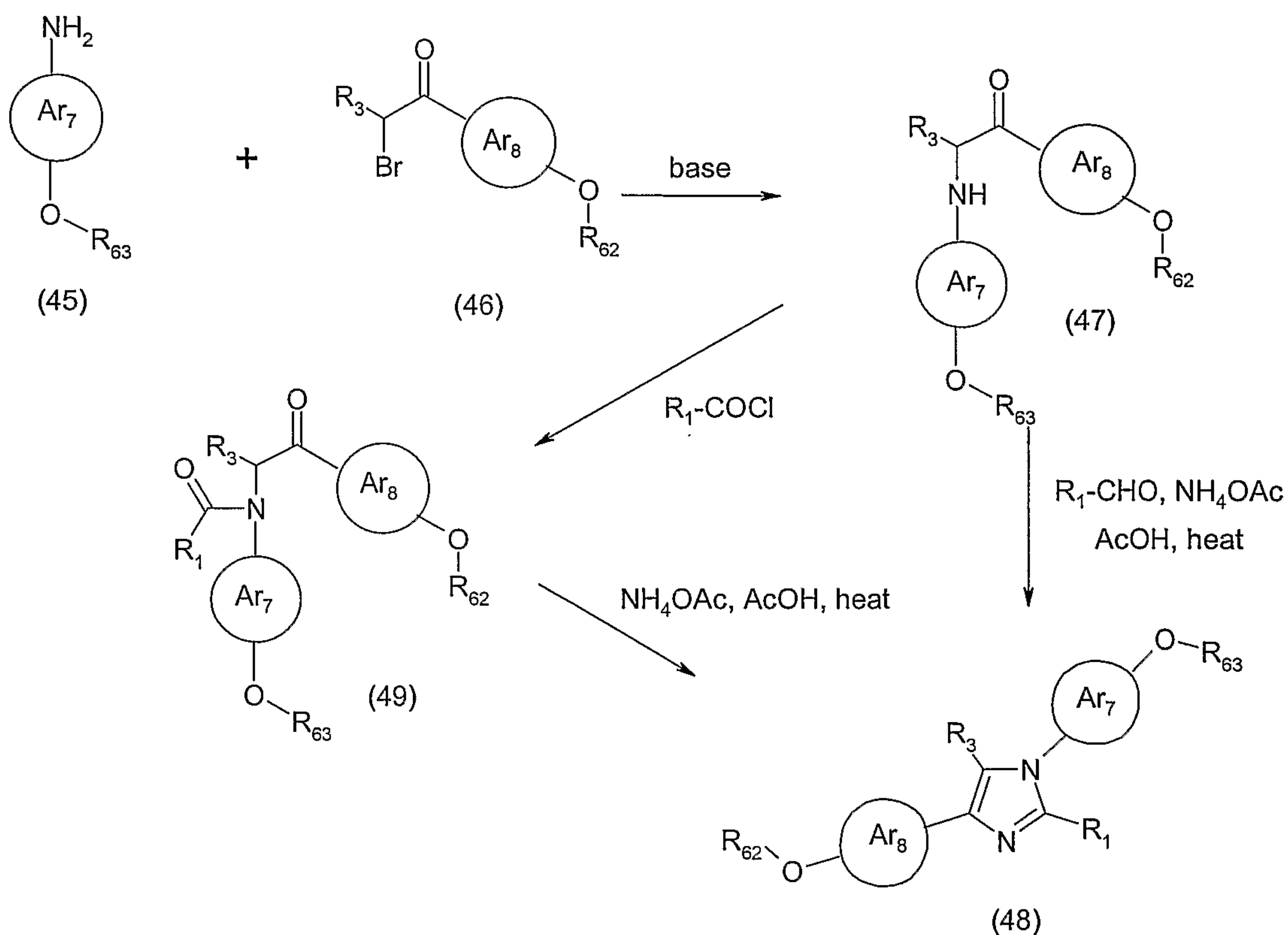
Scheme 7 describes a general synthesis of imidazoles. An aniline containing a basic side chain ($-\text{O}-\text{R}_{62}$) (40) may be coupled with a bromoketone containing a non-basic side chain ($-\text{O}-\text{R}_{63}$) (41) to give the aminoketone (42), which may then be treated with acetic acid, heat, an aldehyde $\text{R}_1\text{-CHO}$, and ammonium acetate to afford (43). Alternately, (42) may be treated with an acid chloride $\text{R}_1\text{-COCl}$ to afford (44), which may subsequently be treated with ammonium acetate, acetic acid and heat to afford (43). Ar_7 and Ar_8 represent groups such as but not limited to aryl or heteroaryl.

Scheme 7



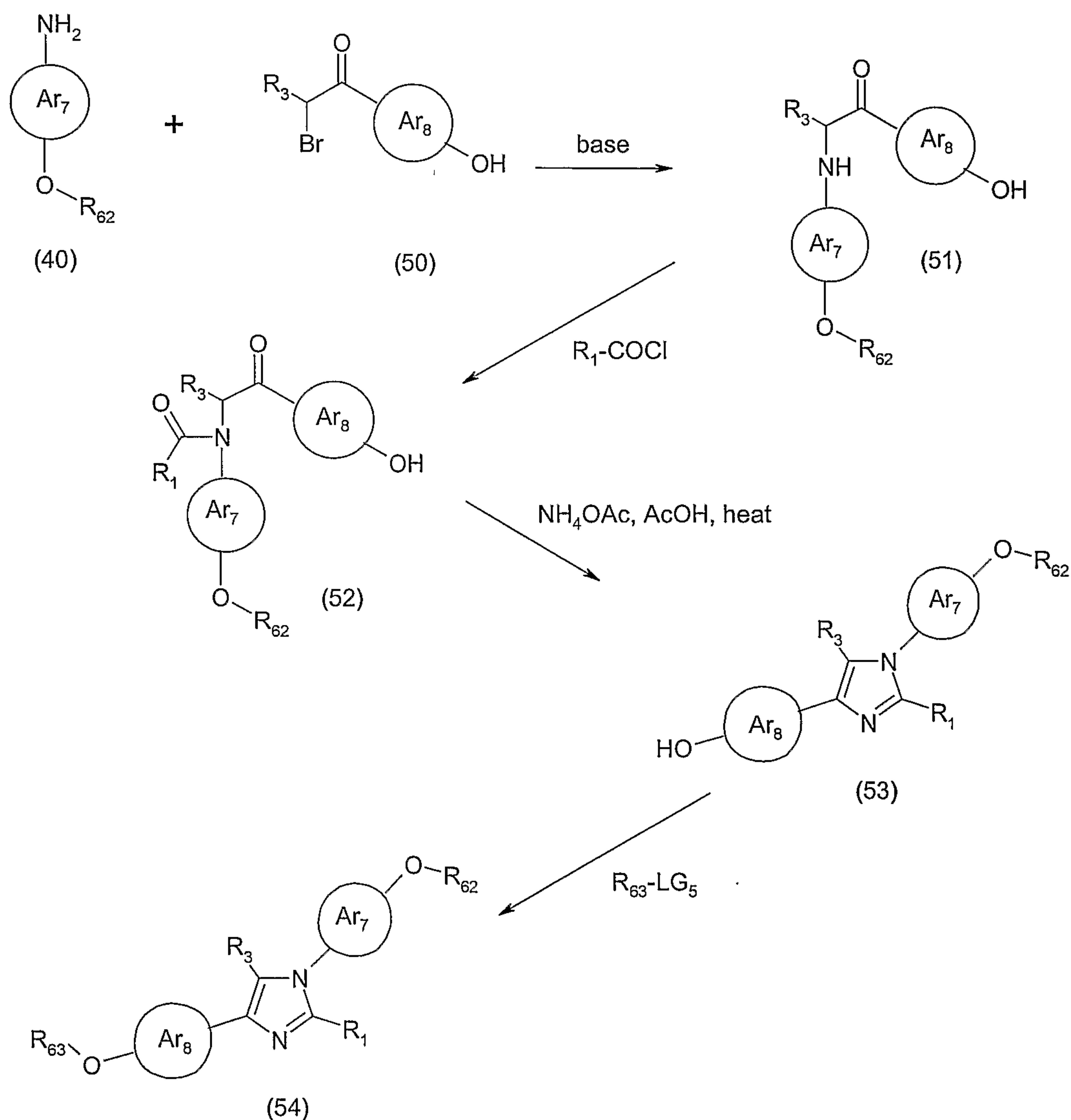
Scheme 8 describes another general synthesis of imidazoles. An aniline containing a non-basic side chain (45) may be coupled with a bromoketone containing a basic side chain (46) to give the aminoketone (47), which may then be treated with acetic acid, heat, an aldehyde R_1 -CHO, and ammonium acetate to afford (48). Alternately, (47) may be treated with an acid chloride R_1 -COCl to afford (49), which may subsequently be treated with ammonium acetate, acetic acid and heat to afford (48). Ar_7 and Ar_8 represent groups such as but not limited to aryl or heteroaryl.

Scheme 8



Scheme 9 describes another general synthesis of imidazoles. An aniline containing a basic side chain (40) may be coupled with a bromoketone (50) to give the aminoketone (51), which may then be treated with an acid chloride $R_1\text{-COCl}$ to afford (52), which may subsequently be treated with ammonium acetate, acetic acid and heat to afford (53). The phenol is then alkylated with an alkylating agent $R_{63}\text{-LG}_5$ to generate the desired imidazole (54). R_{63} is a group such as but not limited to substituted alkyl, and LG_5 is a leaving group such as iodide or methanesulfonate. Ar_7 and Ar_8 represent groups such as but not limited to aryl or heteroaryl.

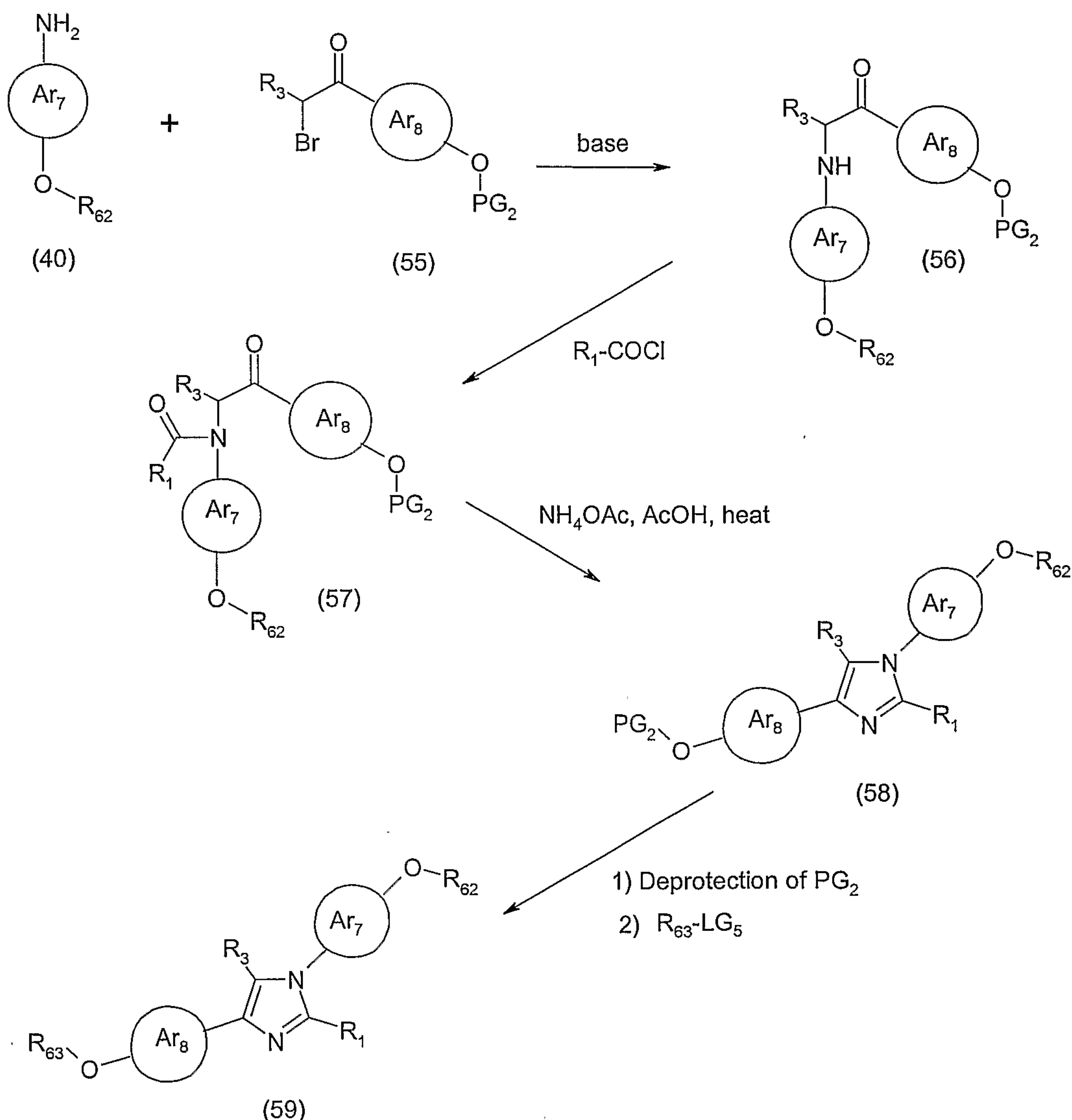
Scheme 9



Scheme 10 describes another general synthesis of imidazoles. An aniline containing a hydrophobic side chain (40) may be coupled with a bromoketone (55) to give the aminoketone (56), which may then be treated with an acid chloride $R_1\text{-COCl}$ to afford (57), which may subsequently be treated with ammonium acetate, acetic acid and heat to afford (58). The phenol is then deprotected; PG_1 may be a group such as but not limited to benzyl, which may be removed with treatment with hydrogen over palladium on carbon. The free phenolic group is subsequently alkylated with an alkylating agent $R_{63}\text{-LG}_5$ to generate the desired imidazole (59). R_{63} is a group such as but not limited to substituted alkyl, and LG_5 is a leaving group such as iodide or methanesulfonate.

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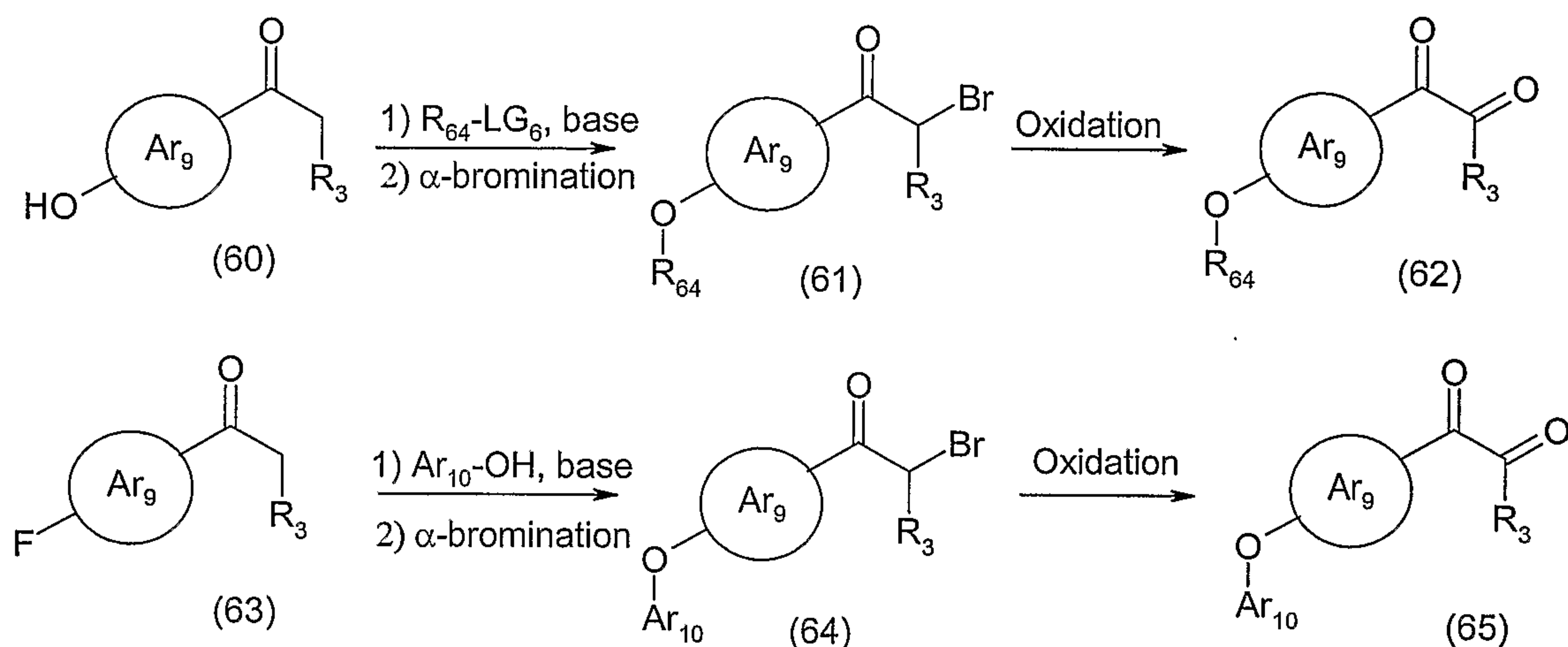
Scheme 10



Scheme 11 describes the symnthesis of diones, or bromoketones. A aryl ketone (60) may be treated with base and an alkylating agent $R_{64}\text{-LG}_6$ to generate the phenyl ether. R_{64} is a

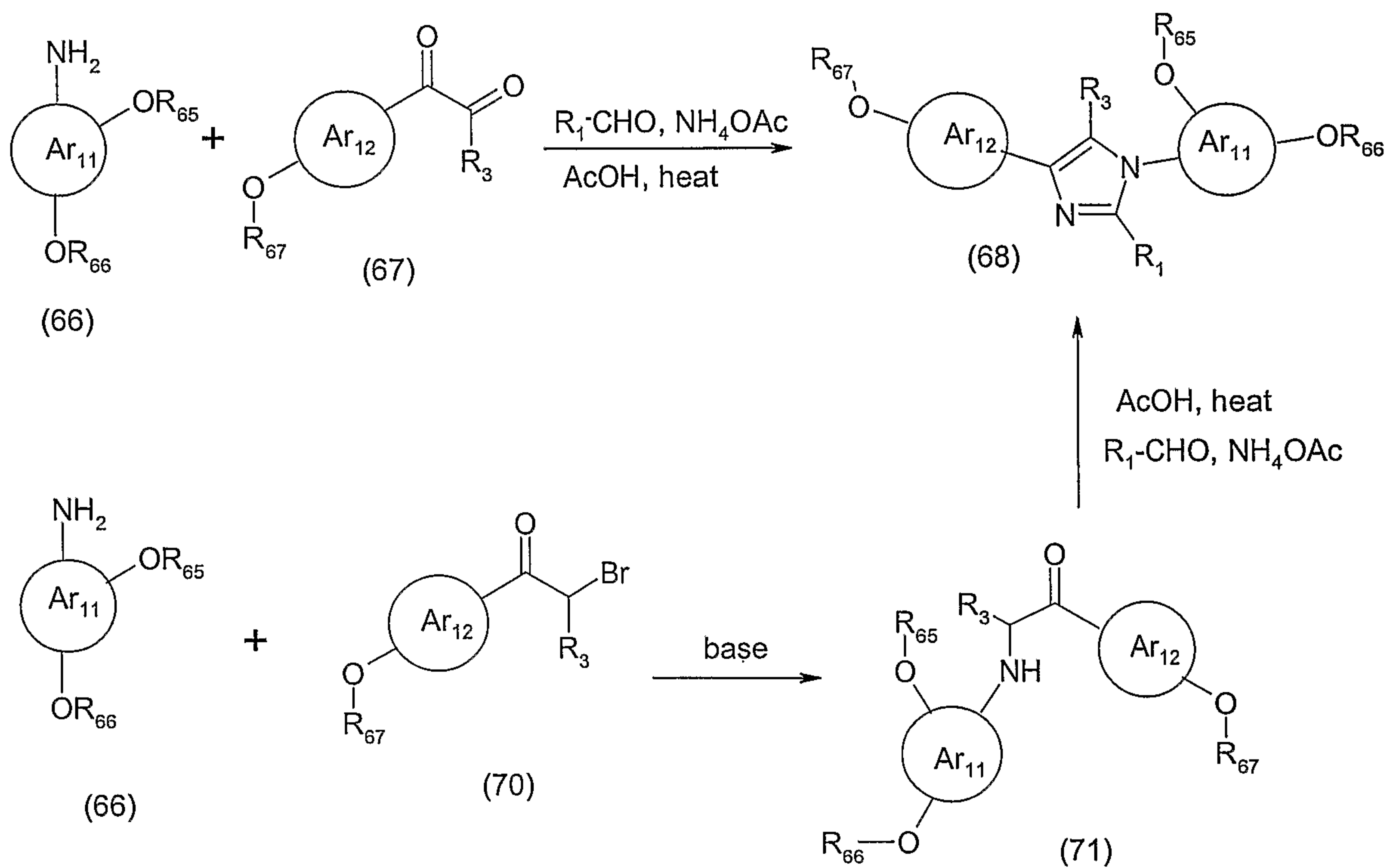
group such as but not limited to substituted alkyl, and LG₆ is a leaving group such as iodide or methanesulfonate. The product may be brominated with a reagent such as but not limited to pyrrolidinium hydrotribromide, to (61) and the bromide may be oxidized by treatment with DMSO to afford (62). (63) may be treated with Ar₁₀-OH and base, followed by bromination, to afford (64). Oxidation as before gives the dione (65). Ar₉ is a group such as but not limited to aryl or heteroaryl.

Scheme 11



Scheme 12 describes the synthesis of imidazoles. (66) may be treated with (67) and an aldehyde R₁-CHO to afford (68). Alternately, (66) may be coupled with the bromoketone (70) to give the aminoketone (71), which may be treated with acetic acid, heat, an aldehyde R₁-CHO, and ammonium acetate to afford (68). Ar₁₁ and Ar₁₂ are groups such as but not limited to aryl or heteroaryl.

Scheme 12

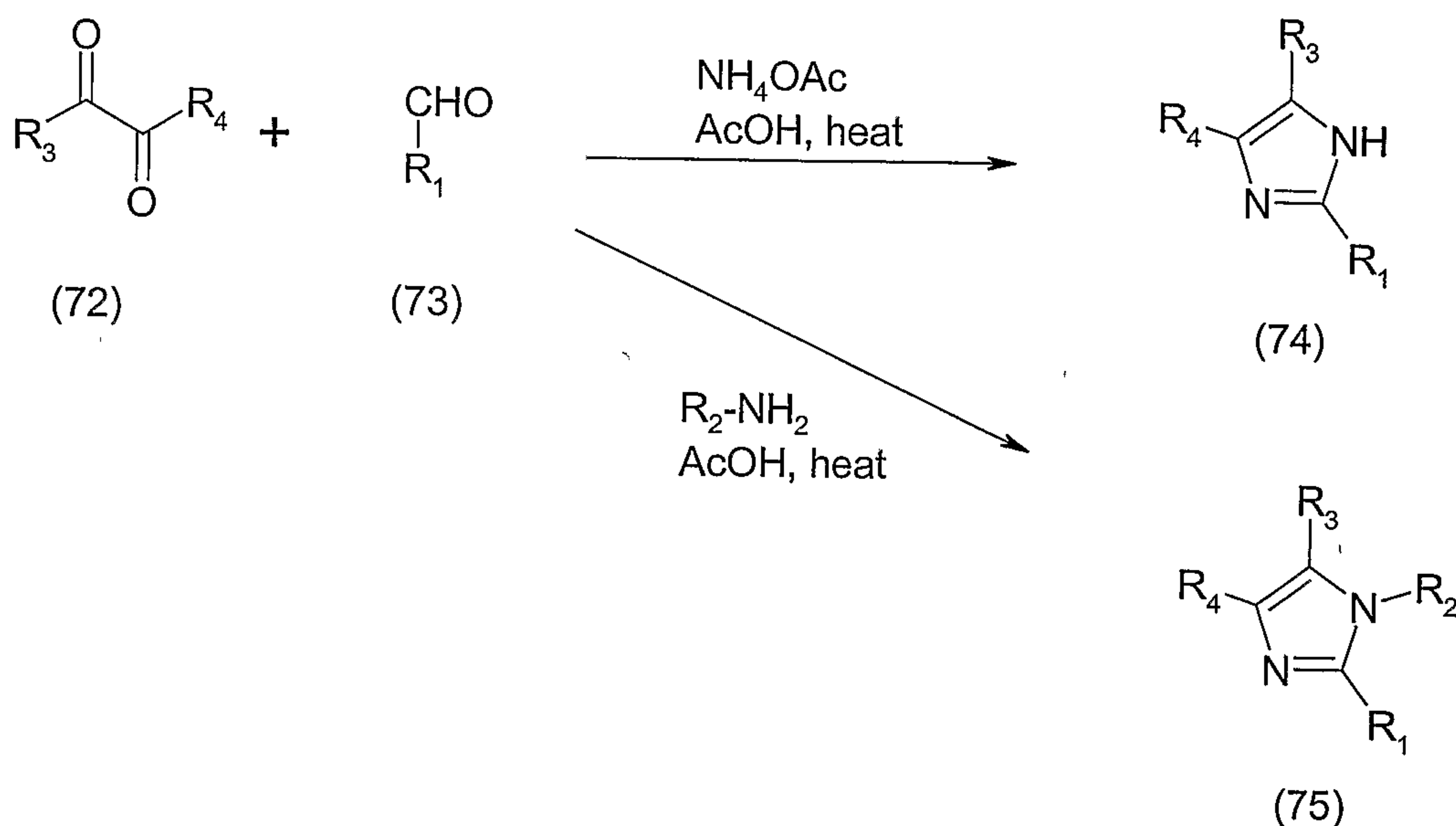


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Scheme 13 describes the synthesis of imidazoles. A dione (72) may be treated with $\text{R}_1\text{-CHO}$ and ammonium acetate – acetic acid to afford (74). Alternately, an amine $\text{R}_2\text{-NH}_2$ may be used in place of ammonium acetate to give (75).

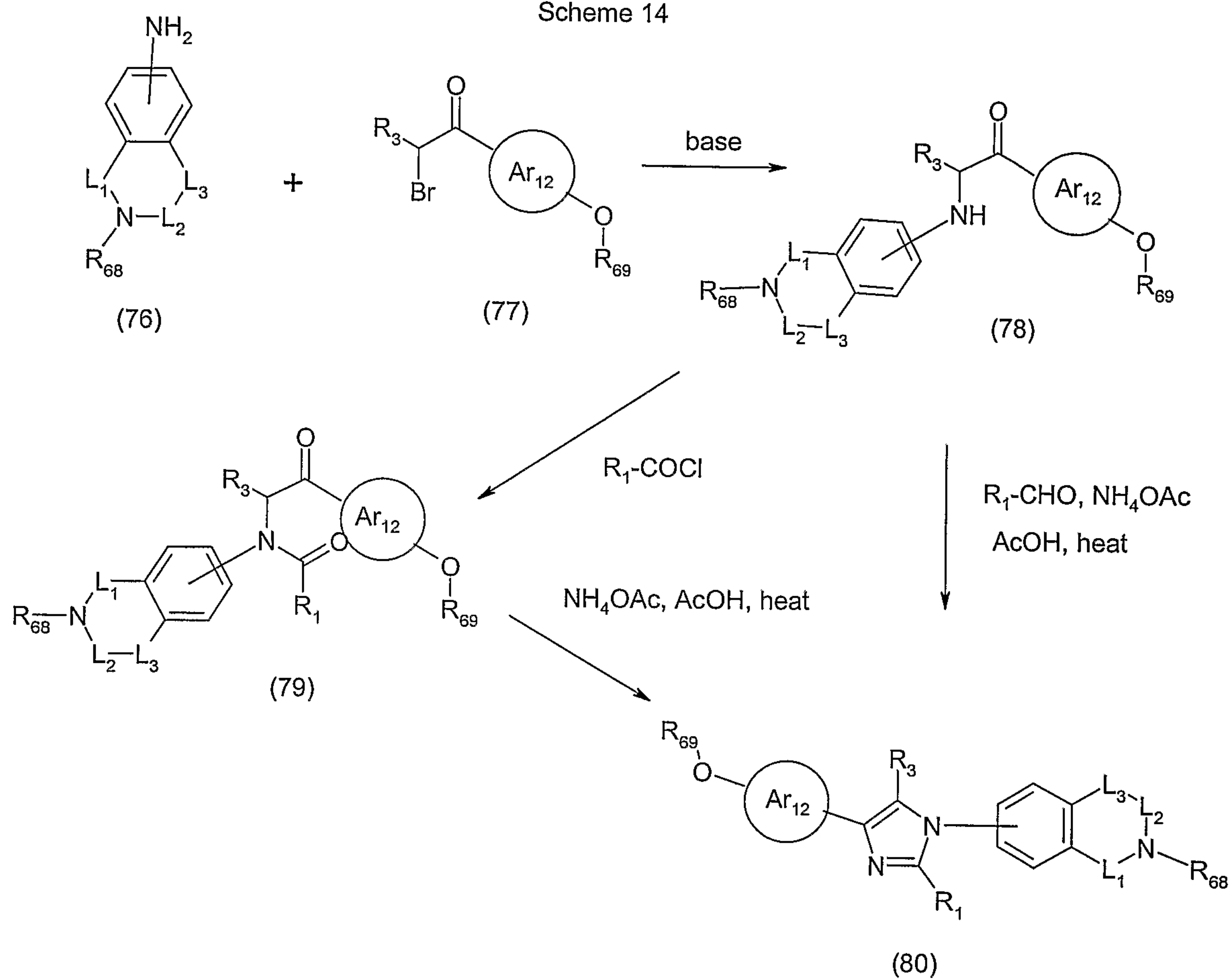
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Scheme 13

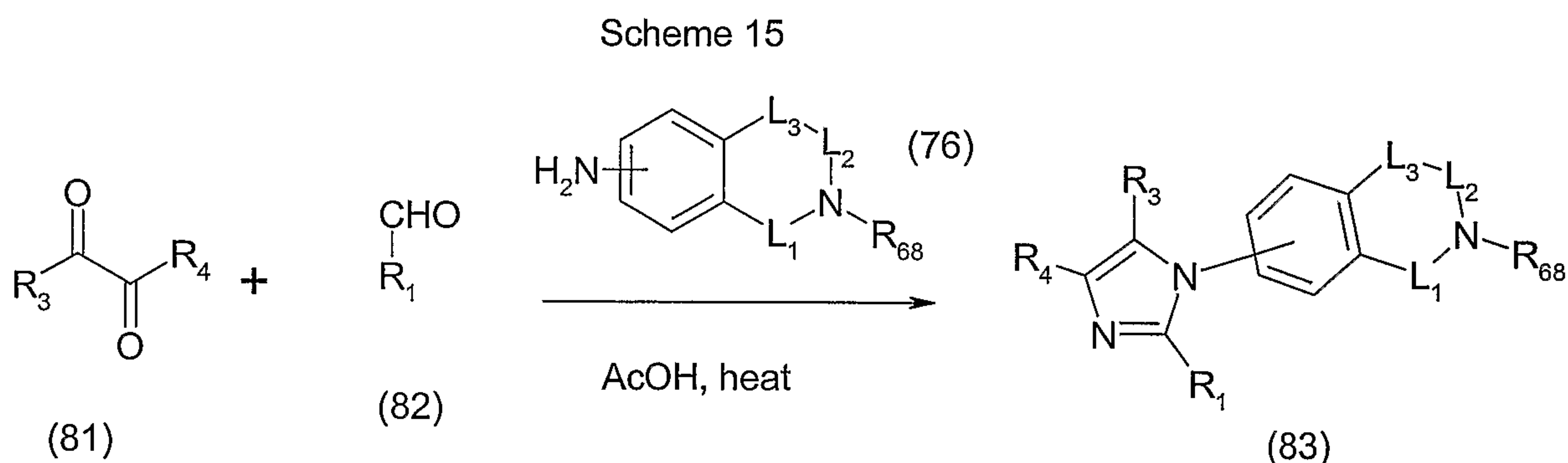


10 Scheme 14 describes another synthesis of imidazoles. (76) may be coupled with the
 bromoketone (77) to give the aminoketone (78), which may be treated with acetic acid, heat,
 an aldehyde $\text{R}_1\text{-CHO}$, and ammonium acetate to afford (80). Alternately, (78) may be
 treated with an acid chloride $\text{R}_1\text{-COCl}$ to afford (79), which may subsequently be treated with
 ammonium acetate, acetic acid and heat to afford (80). The group R_{68} may be an amino
 protecting group, such as BOC, which may be removed by treatment of (80)
 15 with TFA. The amine may be directly alkylated or reductively alkylated by methods known
 in the art. For example, treatment of the NH compound with acetaldehyde and sodium
 cyanoborohydride in a solvent such as acetic acid affords (80) where R_{68} is ethyl. Ar_{12} is a
 group such as but not limited to aryl or heteroaryl.

Scheme 14



Scheme 15 describes the synthesis of imidazoles. A dione (81) may be treated with R_1 -CHO and an amine (76) in acetic acid, in the presence of ammonium acetate, at a temperature of from 50 to 140 °C, to afford (83). If the group R_{68} is an amine protecting group, then said protecting group may be removed and the nitrogen alkylated as described in Scheme 14.



The term "amino protecting group" as used herein refers to substituents of the amino group commonly employed to block or protect the amino functionality while reacting other functional groups on the compound. Examples of such amino-protecting groups include the formyl group, the trityl group, the phthalimido group, the trichloroacetyl group, the chloroacetyl, bromoacetyl and iodoacetyl groups, urethane-type blocking groups such as benzyloxycarbonyl, 4-phenylbenzyloxycarbonyl, 2-methylbenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 4-fluorobenzyloxycarbonyl, 4-chlorobenzyloxycarbonyl, 3-chlorobenzyloxycarbonyl, 2-chlorobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 3-bromobenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-cyanobenzyloxy-carbonyl, 2-(4-xenyl)iso-propoxycarbonyl, 1,1-diphenyleth-1-yloxycarbonyl, 1,1-diphenylprop-1-yloxycarbonyl, 2-phenylprop-2-yloxycarbonyl, 2-(p-toluy)prop-2-yloxycarbonyl, cyclopentanyloxycarbonyl, 1-methylcyclopentanyloxycarbonyl, cyclohexanyloxycarbonyl, 1-methylcyclohexanyloxycarbonyl, 2-methylcyclohexanyloxycarbonyl, 2-(4-toluylsulfonyl)ethoxycarbonyl, 2(methylsulfonyl)ethoxycarbonyl, 2-(triphenylphosphino)ethoxycarbonyl, 9-fluorenylmethoxycarbonyl ("Fmoc"), t-butoxycarbonyl ("BOC"), 2-(trimethylsilyl)ethoxycarbonyl, allyloxycarbonyl, 1-(trimethylsilylmethyl)prop-1-enyloxycarbonyl, 5-benzisoxalylmethoxycarbonyl, 4-acetoxybenzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-ethynyl-2-propoxycarbonyl, cyclopropylmethoxycarbonyl, 4-

(decyloxy)benzyloxycarbonyl, isobornyloxycarbonyl, 1-piperidyloxycarbonyl and the like; the benzoylmethylsulfonyl group, the 2-(nitro)phenylsulfenyl group, the diphenylphosphine oxide group and like amino-protecting groups. The species of amino-protecting group employed is not critical so long as the derivatized amino group is stable to the condition of subsequent reaction(s) on other positions of the compound of Formula (I) and can be removed at the desired point without disrupting the remainder of the molecule. Preferred amino-protecting groups are the allyloxycarbonyl, the t-butoxycarbonyl, 9-fluorenylmethoxycarbonyl, and the trityl groups. Similar amino-protecting groups used in the cephalosporin, penicillin and peptide art are also embraced by the above terms. Further examples of groups referred to by the above terms are described by J. W. Barton, "Protective Groups In Organic Chemistry", J. G. W. McOmie, Ed., Plenum Press, New York, N.Y., 1973, and T. W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, N.Y., 1981. The related term "protected amino" or "protected amino group" defines an amino group substituted with an amino-protecting group discussed above.

The term "hydroxyl protecting group" as used herein refers to substituents of the alcohol group commonly employed to block or protect the alcohol functionality while reacting other functional groups on the compound. Examples of such alcohol -protecting groups include the 2-tetrahydropyranyl group, 2-ethoxyethyl group, the trityl group, the trichloroacetyl group, urethane-type blocking groups such as benzyloxycarbonyl, and the trialkylsilyl group, examples of such being trimethylsilyl, tert-butyldimethylsilyl, phenyldimethylsilyl, triisopropylsilyl and hexyldimethylsilyl. The choice of alcohol-protecting group employed is not critical so long as the derivatized alcohol group is stable to the condition of subsequent reaction(s) on other positions of the compound of the formulae and can be removed at the desired point without disrupting the remainder of the molecule. Further examples of groups referred to by the above terms are described by J. W. Barton, "Protective Groups In Organic Chemistry", J. G. W. McOmie, Ed., Plenum Press, New York, N.Y., 1973, and T. W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, N.Y., 1981. The related term "protected hydroxyl" or "protected alcohol" defines a hydroxyl group substituted with a hydroxyl - protecting group as discussed above.

The term "carboxyl protecting group" as used herein refers to substituents of the carboxyl group commonly employed to block or protect the -OH functionality while reacting other functional groups on the compound. Examples of such alcohol -protecting groups include the 2-tetrahydropyranyl group, 2-ethoxyethyl group, the trityl group, the allyl group, the trimethylsilylethoxymethyl group, the 2,2,2-trichloroethyl group, the benzyl group, and the trialkylsilyl group, examples of such being trimethylsilyl, tert-butyldimethylsilyl,

phenyldimethylsilyl, triisopropylsilyl and t-butyldimethylsilyl. The choice of carboxyl protecting group employed is not critical so long as the derivatized alcohol group is stable to the condition of subsequent reaction(s) on other positions of the compound of the formulae and can be removed at the desired point without disrupting the remainder of the molecule.

5 Further examples of groups referred to by the above terms are described by J. W. Barton, "Protective Groups In Organic Chemistry", J. G. W. McOmie, Ed., Plenum Press, New York, N.Y., 1973, and T. W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, N.Y., 1981. The related term "protected carboxyl" defines a carboxyl group substituted with a carboxyl -protecting group as discussed above.

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The general procedures used in the methods of the present invention are described below.

Methods

5 LC-MS data is obtained using gradient elution on a Waters 600 controller equipped with a 2487 dual wavelength detector and a Leap Technologies HTS PAL Autosampler using an YMC Combiscreen ODS-A 50x4.6 mm column. A three minute gradient is run from 25% B (97.5%acetonitrile, 2.5% water, 0.05% TFA) and 75% A (97.5% water, 2.5% acetonitrile, 0.05% TFA) to 100% B. The mass spectrometer used is a Micromass ZMD instrument. All
 10 data is obtained in the positive mode unless otherwise noted. ¹H NMR and ¹³C NMR data is obtained on a Varian 400 MHz spectrometer.

Abbreviations used in the Examples are as follows:

15 APCI = atmospheric pressure chemical ionization
 BOC = tert-butoxycarbonyl
 BOP= (1-benzotriazolyloxy)tris(dimethylamino)phosphonium hexafluorophosphate
 d = day
 DIAD = diisopropyl azodicarboxylate
 20 DCC = dicyclohexylcarbodiimide
 DCM = dichloromethane
 DIC = diisopropylcarbodiimide
 DIEA = diisopropylethylamine
 DMA = N, N-dimethylacetamide
 25 DMAP = dimethylaminopyridine
 DME = 1,2 dimethoxyethane
 DMF = N, N-dimethylformamide
 DMPU = 1,3-dimethypropylene urea
 DMSO = dimethylsulfoxide
 30 Et = ethyl
 iPr = isopropyl
 Bn = benzyl
 Me = methyl
 tBu = tert-butyl
 35 Pr = propyl
 Bu = butyl
 iBu = isobutyl

	EDC	=1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride
	EDTA	= ethylenediamine tetraacetic acid
	ELISA	= enzyme - linked immunosorbent assay
	ESI	= electrospray ionization
5	ether	= diethyl ether
	EtOAc	= ethyl acetate
	FBS	= fetal bovine serum
	g	= gram
	h	= hour
10	HBTU	= O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate
	HMPA	= hexamethylphosphoric triamide
	HOBt	=1-hydroxybenzotriazole
	Hz	= hertz
	i.v.	= intravenous
15	kD	= kiloDalton
	L	= liter
	LAH	= lithium aluminum hydride
	LDA	= lithium diisopropylamide
	LPS	= lipopolysaccharide
20	M	= molar
	<i>m/z</i>	= mass to charge ratio
	mbar	= millibar
	MeOH	= methanol
	mg	= milligram
25	min	= minute
	mL	= milliliter
	mM	= millimolar
	mmol	= millimole
	mol	= mole
30	mp	= melting point
	MS	= mass spectrometry
	N	= normal
	NMM	= N-methylmorpholine, 4-methylmorpholine
	NMR	= nuclear magnetic resonance spectroscopy
35	p.o.	= per oral
	PS-carbodiimide	= N-cyclohexylcarbodiimide-N'-propyloxymethyl polystyrene
	PBS	= phosphate buffered saline solution

PMA = phorbol myristate acetate

ppm = parts per million

psi = pounds per square inch

R_f = relative TLC mobility

5 rt = room temperature

s.c. = subcutaneous

SPA = scintillation proximity assay

TEA = triethylamine

TFA = trifluoroacetic acid

10 THF = tetrahydrofuran

THP = tetrahydropyranyl

TLC = thin layer chromatography

TMSBr = bromotrimethylsilane, trimethylsilylbromide

T_r = retention time

15

General synthesis of monoalkoxybenzaldehydes:

General Procedure A

20 To a stirred solution of a 2-, 3-, or 4-hydroxybenzaldehyde (2 mmol) in DMF (6 mL) at rt solid K₂CO₃ (4 mmol) is added. An alkyl halide or mesylate (prepared from the corresponding alcohol and methanesulfonyl chloride) (2.2 mmol) is added to the reaction mixture and heated to 80 °C until the reaction is complete as indicated by TLC or HPLC. After cooling to rt, the reaction mixture is poured into EtOAc (20ml) and washed with water (2X10 ml) and brine (15 ml). The organic layer is dried over magnesium sulfate and after removal of the

25 drying agent, the solvent is removed under high vacuum to afford the desired product. The crude product may be used for further transformation without any purification or after purifying using silica gel column chromatography.

General synthesis of monoaryloxybenzaldehydes:

30 General Procedure B

To a stirred solution of a 2-, 3-, or 4-fluorobenzaldehyde (2 mmol) in DMF (6 mL) at rt requisite phenol (2.2) is added followed by solid K₂CO₃ (3 mmol). The reaction mixture is heated to 100 °C until the reaction is complete as indicated by TLC or HPLC. After cooling to rt, the reaction mixture is poured into EtOAc (20ml) and washed with water (2X10 ml) and

35 brine (15 ml). The organic layer is dried over magnesium sulfate and after removal of the drying agent, the solvent is removed under high vacuum to afford the desired product. The

crude product may be used for further transformation without any purification or after purifying using silica gel column chromatography.

General synthesis of homosubstituted 2,4-dialkoxybenzaldehydes:

5 General Procedure C

To a stirred solution of 2,4-dihydroxybenzaldehyde (2 mmol) in DMF (8 mL) at rt solid Cs_2CO_3 (6 mmol) is added. An alkyl halide or mesylate (prepared from the corresponding alcohol and methanesulfonyl chloride, see General Procedure P2) (4.4 mmol) is added to the reaction mixture and heated to 80 °C until the reaction is complete as indicated by TLC or HPLC. After cooling to rt, the reaction mixture is poured into EtOAc (20ml) and washed with water (2X10 ml) and brine (15 ml). The organic layer is dried over magnesium sulfate and after removal of the drying agent, the solvent is removed under high vacuum to afford the desired product. The crude product may be used for further transformation without any purification or after purifying using silica gel column chromatography.

15

General synthesis of heterosubstituted 2,4-dialkoxybenzaldehydes:

General Procedure D1

To a stirred solution of 2,4-dihydroxybenzaldehyde (2.2 mmol) in DMF (5 mL) at rt solid KHCO_3 (2.2 mmol) is added. An alkyl halide or mesylate (prepared from the corresponding alcohol and methanesulfonyl chloride, see General Procedure P2) (2.0 mmol) is added to the reaction mixture and heated at 130°C for 4h. After cooling to rt, the reaction mixture is treated with cold H_2O (15 mL), and extracted with EtOAc (2X10 mL). The combined organic layers is washed with brine, and dried over sodium sulfate. The crude product is purified by flash chromatography to provide the 2-hydroxy-4-alkoxybenzaldehyde intermediate.

25

General Procedure D2

To a stirred solution of aforementioned 2-hydroxy-4-alkoxybenzaldehyde intermediate (2 mmol) in DMSO (5 mL) at rt solid Cs_2CO_3 (3 mmol) is added. An alkyl halide or mesylate (prepared from the corresponding alcohol and methanesulfonyl chloride, see General Procedure P2) (3 mmol) is added to the reaction mixture and heated to 90 °C until the reaction is complete as indicated by TLC or HPLC. After cooling to rt, the reaction mixture is treated with cold H_2O (15 mL), and extracted with EtOAc (2X10 mL). The combined organic layers is washed with H_2O (10 mL) and brine (10 mL) and dried over sodium sulfate. After removal of the drying agent, the solvent is removed under high vacuum to afford the desired product. The crude product may be used for further transformation without any purification or after purifying using silica gel column chromatography.

35

General synthesis of 2-alkoxy-4-aryloxybenzaldehydes:

General Procedure E

5 A solution of 2,4-difluorobenzaldehyde (2 mmol) in DMF (2 mL) is added dropwise to a precooled (0 °C) solution of sodium alkoxide (2mmol) in DMF (6 ml) [prepared by stirring a mixture of sodium hydride (2 mmol), and the corresponding alcohol (2 mmol) in DMF]. The resulting reaction mixture is warmed to rt and stirred for an additional 3 h. To the same reaction vessel, solid potassium carbonate (2 mmol) and requisite phenol (2 mmol)) is introduced and the reaction mixture is heated at 90 °C in an oil bath for 24. After cooling to rt, the reaction mixture is poured into EtOAc (20ml) and washed with water (2X10 ml) and
10 brine (15 ml). The organic layer is dried over magnesium sulfate and after removal of the drying agent, the solvent is removed under high vacuum to afford the desired product. The crude product may be used for further transformation without any purification or after purifying using silica gel column chromatography.

15 General synthesis of monoalkoxy ortho-phenylenediamines:

Method A

General Procedure F1

20 To a stirred solution of 3-fluoro-4-nitrophenol (4 mmol) in DMF (6 mL) at rt solid K₂CO₃ (8 mmol) is added. An alkyl halide or mesylate (prepared from the corresponding alcohol and methanesulfonyl chloride, see General Procedure P2) (4.4 mmol) is added to the reaction mixture and heated to 80 °C until the reaction is complete as indicated by TLC or HPLC. After cooling to rt, the reaction mixture is poured into EtOAc (40ml) and washed with water
25 (2X20 ml) and brine (30 ml). The organic layer is dried over magnesium sulfate and after removal of the drying agent, the solvent is removed under vacuum to afford the desired product. The crude product may be used for further transformation without any purification or after purifying using silica gel column chromatography.

30 General Procedure F2

To a stirred solution of 2-fluoro-4-alkoxynitrobenzene (2 mmol) obtained above, TEA (4 mmol) in DMF (5 mL) is added dropwise a solution of requisite alkylamine (2.2 mmol) in DMF (2 mL) at rt within 15 min, and then stirred at rt for 5h. The reaction mixture is treated with cold H₂O (10 mL), and extracted with EtOAc (2x15 mL), The combined organic layers is
35 washed with H₂O (10 mL) and brine (10 mL) and dried over sodium sulfate. After removal of the drying agent, the solvent is removed under high vacuum to afford the desired 2-alkylamino-4-alkoxynitrobenzene intermediate. The crude product may be used for further

transformation without any purification or after purifying using silica gel column chromatography.

Method B

5 General Procedure G1

To a stirred solution of 2,4-difluoronitrobenzene (2 mmol), TEA (4 mmol) in DMF (5 mL) is added dropwise a solution of requisite alkylamine (2.2 mmol) in DMF (2 mL) at rt within 15 min, and then stirred at rt for 5h. The reaction mixture is treated with cold H₂O (10 mL), and extracted with EtOAc (2x15 mL). The combined organic layers is washed with H₂O (10 mL) and brine (10 mL) and dried over sodium sulfate. After removal of the drying agent, the solvent is removed under high vacuum to afford the desired 2-alkylamino-4-fluoronitrobenzene. The crude product may be used for further transformation without any purification or after purifying using silica gel column chromatography.

15 General Procedure G2

To a stirred solution of 2-alkylamino-4-fluoronitrobenzene as obtained above (2.0 mmol) in anhydrous THF (4 mL), an alcohol (2.4 mmol) is added followed by powdered KOBu^t (2.4 mmol) in one portion at rt and under the N₂ stream. The reaction mixture is then refluxed until the reaction is complete as indicated by TLC or HPLC. After cooling to rt, the reaction mixture is treated with cold H₂O (15 mL), and extracted with EtOAc (2X10 mL). The combined organic layers is washed with brine, and dried over sodium sulfate. Evaporation of the solvent in vacuo afforded 2-alkylamino-4-alkoxynitrobenzene intermediate. The crude product may be used for further transformation without any purification or after purifying using silica gel column chromatography.

25

Reduction of monoalkoxy nitrobenzenes:

General Procedure H

The nitro intermediate (2 mmol) obtained above as in *Method A or B* is dissolved in MeOH (10 mL) and hydrogenated in the presence of 10% Pd/C (10 mg) until the reaction is complete as indicated by TLC or HPLC. The reaction mixture is then filtered through a celite pad to remove the catalyst. The solvent is removed under high vacuum to afford the desired diamine, which is used directly for further transformation without further purification.

30

General Procedure I

35 To a stirred solution of afforded 2-alkylamino-4-alkoxynitrobenzene intermediate [as obtained in (b)](2 mmol) in EtOH (20 mL), SnCl₂.2H₂O (8 mmol) is added and the mixture is

refluxed until the reaction is complete as indicated by TLC or HPLC. After completion of the reduction, the solvent is removed in vacuo, and the residue is treated with saturated NaHCO₃ to pH~8. The resulting yellow suspension is extracted with DCM (2x20 mL), washed with brine, and dried. The solvent is removed under high vacuum to afford the
5 desired diamine, which is used directly for further transformation without further purification.

General synthesis of homo disubstituted dialkoxy ortho-phenylenediamines:

General Procedure J1

To a stirred solution of 2,4,6-trifluoronitrobenzene (3.0 mmol) and triethylamine (6.0 mmol) in
10 DMF (6 mL), a solution of alkyl amine (3.0 mmol) in DMF (2 mL) is added dropwise at rt within 15 min, and then stirred at rt for 5h. The reaction mixture is treated with cold H₂O (10 mL), and extracted with EtOAc (2x15 mL). The combined organic layers is washed with H₂O (10 mL) and brine (10 mL) and dried over sodium sulfate. After removal of the drying agent, the solvent is removed under high vacuum to afford the desired 2-alkylamino-4,6-
15 difluoronitrobenzene. The crude product may be used for further transformation without any purification or after purifying using silica gel column chromatography.

General Procedure J2

To a stirred solution of 2-alkylamino-4,6-difluoronitrobenzene as obtained above (2.0 mmol)
20 in anhydrous THF (4 mL), an alcohol (4.4 mmol) is added followed by powdered KOBu^t (4.4 mmol) in one portion at rt and under the N₂ stream. The reaction mixture is then refluxed until the reaction is complete as indicated by TLC or HPLC. After cooling to rt, the reaction mixture is treated with cold H₂O (15 mL), and extracted with EtOAc (2X15 mL). The combined organic layers is washed with brine, and dried over sodium sulfate. Evaporation of
25 the solvent in vacuo afforded 2-alkylamino-4,6-dialkoxynitrobenzene intermediate. The crude product may be used for further transformation without any purification or after purifying using silica gel column chromatography.

The nitro intermediate (2 mmol) obtained may be reduces to the amino compound
30 employing general procedures H or I.

General synthesis of hetero disubstituted dialkoxy ortho-phenylenediamines:

General Procedure J3

To a stirred solution of 3,5-difluorophenol (3g; 17 mmol) in dichloromethane (30 mL) at 0 °C,
35 conc. HNO₃ (2.5 mL) is added dropwise over 10 min. The reaction mixture is then stirred at 0 °C for 60 min at which the nitration is complete as indicated by TLC. After the reaction is complete cold H₂O (30 mL) is added to the reaction flask and stirred. The contents are then

5 poured into a separatory funnel and the layers removed. The aqueous layer is then extracted with EtOAc (2x30 mL) and the combined organic layers are dried over magnesium sulfate. After removal of the drying agent, the solvent is removed under vacuum to the crude product mixture is purified using silica gel column chromatography to provide the nitrodifluorophenol.

General Procedure J4

10 To a stirred solution of 3,5-difluoro-4-nitrophenol (4 mmol) in DMF (6 mL) at rt solid K₂CO₃ (8 mmol) is added. An alkyl halide or mesylate (prepared from the corresponding alcohol and methanesulfonyl chloride, see General Procedure P2) (4.4 mmol) is added to the reaction mixture and heated to 80 °C until the reaction is complete as indicated by TLC or HPLC. After cooling to rt, the reaction mixture is poured into EtOAc (40ml) and washed with water (2X20 ml) and brine (30 ml). The organic layer is dried over magnesium sulfate and after removal of the drying agent, the solvent is removed under vacuum to afford the desired product. The crude product may be used for further transformation without any purification or after purifying using silica gel column chromatography.

General Procedure J5

20 To a stirred solution of 2,6-difluoro-4-alkoxynitrobenzene obtained above (3.0 mmol) and triethylamine (6.0 mmol) in DMF (6 mL), a solution of alkyl amine (3.0 mmol) in DMF (2 mL) is added dropwise at rt within 15 min, and then stirred at rt for 5h. The reaction mixture is treated with cold H₂O (10 mL), and extracted with EtOAc (2x15 mL). The combined organic layers is washed with H₂O (10 mL) and brine (10 mL) and dried over sodium sulfate. After removal of the drying agent, the solvent is removed under high vacuum to afford the desired 2-alkylamino-4-alkoxy-6-fluoronitrobenzene. The crude product may be used for further transformation without any purification or after purifying using silica gel column chromatography.

General Procedure J6

30 To a stirred solution of 2-alkylamino-4-alkoxy-6-fluoronitrobenzene as obtained above (2.0 mmol) in anhydrous THF (5 mL) at 0 °C, a 1M solution of an alkoxide (2.2 mmol) in THF (may be generated by adding the corresponding alcohol to a 1M solution of KOBu^t in THF) is added dropwise and under the N₂ stream. The reaction mixture is maintained at 0 °C until the reaction is complete as indicated by TLC or HPLC. The reaction mixture is then treated with cold H₂O (15 mL), and extracted with EtOAc (2X15 mL). The combined organic layers is washed with brine, and dried over sodium sulfate. Evaporation of the solvent in vacuo afforded the desired hetero dialkoxy substituted nitro intermediate. The crude product may

35

be used for further transformation without any purification or after purifying using silica gel column chromatography.

General Procedure J7

The nitro intermediate (2 mmol) obtained above is dissolved in MeOH (10 mL) and hydrogenated in the presence of 10% Pd/C (10 mg) until the reaction is complete as indicated by TLC or HPLC. The reaction mixture is then filtered through a celite pad to remove the catalyst. The solvent is removed under high vacuum to afford the desired hetero disubstituted dialkoxy ortho-phenylenediamine.

General Procedure for synthesis of benzimidazoles:

General Procedure K

A solution of an ortho phenylenediamine (2 mmol) and an appropriate aryl aldehyde in ethanol is refluxed until the reaction is complete as indicated by TLC or HPLC. The solvent is removed in vacuo and the residue obtained is purified by silica gel column chromatography to afford the desired 2-arylbenzimidazole.

General Procedure for Synthesis of monoalkoxyanilines:

Method A:

General Procedure L1

To a stirred solution of 4-fluoronitrobenzene (2.0 mmol) in anhydrous THF (5 mL) at 0 °C, a 1M solution of a potassium alkoxide (2.2 mmol) in THF (may be generated by adding the corresponding alcohol to a 1M solution of KOBu^t in THF) is added dropwise and under the N₂ stream. The reaction mixture is stirred at 0 °C until completion, as indicated by TLC or HPLC. The reaction mixture is then treated with cold H₂O (15 mL), and extracted with EtOAc (2x15 mL). The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of the solvent *in vacuo* afforded the desired 4-alkoxynitrobenzene. The crude product could be used directly for further transformation without any purification, or after purifying using silica gel column chromatography.

Method B:

General Procedure M1

To a stirred solution of 4-nitrophenol (2 mmol) in DMF (6 mL) at rt, solid potassium carbonate (4 mmol) is added. An alkyl halide or mesylate (prepared from the corresponding alcohol and methanesulfonyl chloride, see General Procedure P2) (2.2 mmol) is then added to the reaction mixture and heated to 80 °C until completion, as indicated by TLC or HPLC.

After cooling to rt, the reaction mixture is then treated with cold H₂O (15 mL), and extracted with EtOAc (2x15 mL). The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of the solvent *in vacuo* afforded the desired 4-alkoxynitrobenzene. The crude product could be used directly for further transformation without any purification, or after purifying using silica gel column chromatography.

General Procedure for Synthesis of homo disubstituted alkoxy-anilines:

Method C

General Procedure N1

To a stirred solution of 2,4-difluoronitrobenzene (2.0 mmol) in anhydrous THF (4 mL) at 0 °C, an alcohol (4.4 mmol) is added followed by powdered potassium t-butoxide (4.4 mmol) in one portion under a N₂ stream. The reaction mixture is then warmed to rt and heated under reflux until completion, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture is treated with cold H₂O (15 mL), and extracted with EtOAc (2x15 mL). The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of the solvent *in vacuo* afforded the 2,4-dialkoxynitrobenzene. The crude product could then be used for further transformation without any purification, or after purifying using silica gel column chromatography.

General Procedure for Synthesis of alkoxy-anilines:

General Procedure O2

To a stirred solution of 4-alkoxy-2-fluoronitrobenzene obtained above (2.0 mmol) in anhydrous THF (5 mL) at 0 °C, a 1M solution of an alkoxide (2.2 mmol) in THF (may be generated by adding the corresponding alcohol to a 1M solution of potassium t-butoxide in THF) is added dropwise and under a N₂ stream. The reaction mixture is maintained at 0°C until completion, as indicated by TLC or HPLC. The reaction mixture is then treated with cold H₂O (15 mL), and extracted with EtOAc (2X15 mL). The combined organic layers were washed with brine, and dried over sodium sulfate. Evaporation of the solvent *in vacuo* afforded the desired hetero-substituted dialkoxynitrobenzene. The crude product may be used for further transformation without any purification or after purifying using silica gel column chromatography.

Method E:

General Procedure P1

To a stirred solution of a 2-nitro-5-fluorophenol (2.0 mmol) in anhydrous THF (4 mL) at 0°C, an alcohol (2.2 mmol) is added followed by powdered potassium t-butoxide (4.2 mmol) in one portion under a N₂ stream. The reaction mixture is then warmed up to rt and heated under reflux until completion, as indicated by TLC or HPLC. After cooling to rt, the crude reaction mixture is treated with an alkyl halide or mesylate (2.2 mmol, prepared from the corresponding alcohol and methanesulfonyl chloride) and heated under reflux until completion, as indicated by TLC or HPLC. The reaction mixture is then cooled to rt, treated with cold H₂O (15 mL), and extracted with EtOAc (2X15 mL). The combined organic layers were washed with brine, and dried over sodium sulfate. Evaporation of the solvent *in vacuo* afforded the hetero-substituted dilkoxy nitrobenzene. The crude product may be used for further transformation without any purification or after purifying using silica gel column chromatography.

General Procedure P2

A primary or secondary alcohol (20 mmol, 1eq) is dissolved in DCM (25 mL), TEA (40 mmol, 2 eq) is added and the mixture is cooled to 0 °C. To this mixture, methanesulfonyl chloride (30 mmol, 1.5 eq) is added slowly with stirring and the reaction mixture is stirred at 0°C for an hour and at rt for another hour (until the reaction is complete by HPLC). The solvent is removed and to this saturated aqueous sodium bicarbonate is added. The product is extracted with EtOAc (3 x) and washed with sodium bicarbonate and water. The solvent is removed *in vacuo* to afford the product methanesulfonate.

General Procedure for Synthesis of alkyl phenones;

Method F

General Procedure Q1

To a stirred solution of 4'-hydroxyacetophenone (1.2 mmol) in DMF (10 mL) at rt, solid potassium carbonate (3.0 mmol) is added. An alkyl halide or mesylate (prepared from the corresponding alcohol and methanesulfonyl chloride, see General Procedure P2) (1.0 mmol) is added to the reaction mixture and heated to 80 °C until completion, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture is quenched by removing solvent *in vacuo* and treating the residue with saturated sodium bicarbonate. The aqueous layer is poured into EtOAc (20ml) and washed with H₂O (2X10 ml) and brine (15 ml). The organic layer is dried over magnesium sulfate, and the solvent is removed *in vacuo* to afford the desired product. The crude alkylated product may be used for further transformation without any purification or after purifying using silica gel column chromatography.

Method G

General Procedure Q2

To a stirred solution of an alcohol (75 mmol) in DMSO (80 mL) at rt, solid cesium carbonate (150 mmol) is added. 4'-fluoro-alkylphenone (50 mmol) is added to the reaction mixture and heated to 90°C until completion, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture is treated with saturated sodium bicarbonate (150 ml). The aqueous layer is extracted with diethyl ether (4X100ml). The organic layer is washed with H₂O (2X10 ml) and brine (15 ml). The organic layer is dried over magnesium sulfate, and the solvent is removed *in vacuo* to afford the desired alkoxy acetophenone. The crude alkylated acetophenone may be used for further transformation without any purification or after purifying using silica gel column chromatography.

General Procedure for N-aryl imidazoles:

Method H

General Procedure R1

To a stirred solution of alkoxyacetophenone (2 mmol) in anhydrous MeOH (5 mL) at 0°C, pyrrolidone hydrotribromide (1.2eq.) is added. The reaction mixture is stirred under nitrogen at 0°C for 1h and is allowed to warm to ambient temperature until completion, as indicated by TLC or HPLC. The solvent is then removed *in vacuo* and the crude alpha-bromoacetophenone is used for further transformation.

General Procedure R2

To a stirred solution of an alkoxy aniline (1.2 eq., 2 mmol) in anhydrous DMF (5 mL) diisopropylethylamine (3 eq. 6 mmol) is added, followed by a slow addition of the alpha-bromoacetophenone described above (1.6 mmol). The reaction mixture is stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture is then diluted with cold H₂O and the product is isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline is purified by chromatography (Silica gel). Pure product obtained from 2-4% MeOH/DCM (yield ~50-60%).

General Procedure R3

To a stirred solution of alkylated aniline described above (2 mmol) in anhydrous DCM (5 mL) at 0°C, TEA (3eq., 6 mmol) is added, followed by a slow addition of an acid chloride or anhydride (3 eq., 6 mmol). The reaction mixture is stirred under nitrogen at 0°C for 1h and allowed to warm to ambient temperature until completion, as indicated by TLC or HPLC. The solvent is removed *in vacuo*, and the crude amide is used for further transformation.

General Procedure R4

To a stirred solution of the amide described above (2 mmol) in AcOH (2 mL), ammonium acetate (excess, ~20 eq.) is added. The reaction mixture is stirred at 90°C overnight. The reaction mixture is then cooled down and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which is purified by column chromatography (Silica gel). Pure product is obtained from 4-6% MeOH/DCM (yield 40-50%).

General Procedure S1

To a stirred solution of an alkoxy aniline (2 mmol) in DCM (4 mL) at rt, TEA (2.5 mmol) is added followed by an acid chloride or anhydride (2.5 mmol). The reaction mixture is stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture is treated with saturated aqueous sodium bicarbonate solution (5 mL), then extracted with EtOAc (2X15 mL). The combined organic layers were washed with H₂O (2x15 mL) and brine, and dried over sodium sulfate. Evaporation of the solvent *in vacuo* afforded the anilide. The crude product is used for further transformation.

General Procedure S2

To a stirred solution of the anilide (2 mmol) obtained as above in anhydrous THF (4 mL) solid sodium hydride (60% dispersion in oil; 2.2 mmol) is added in portions. After the addition, a solution of a bromo-acetophenone (2.2 mmol) (prepared as described earlier) in anhydrous THF (2 mL) is added to the reaction mixture. The reaction is then allowed to proceed at rt or heated under reflux as needed. Upon completion of the reaction, EtOAc (20 mL) is added to the reaction mixture followed by H₂O (10 mL). The organic layer is washed with H₂O (2x15 mL) and brine, and dried over sodium sulfate. Evaporation of the solvent *in vacuo* afforded the N-alkylated anilide. The crude product may be used for further transformation.

General Procedure S3

To a stirred solution of the N-alkylated anilide (1 mmol) obtained as above in AcOH (3 mL), solid NH₄OAc (20 mmol) is added in one portion. The reaction mixture is then heated to 100 °C overnight. The reaction mixture is cooled to rt, and treated with saturated aqueous sodium bicarbonate solution while stirring to until the pH is 7-8. The contents were extracted with EtOAc (2X15 mL). The combined organic layers is washed with H₂O (2x15 mL) and brine, and dried over sodium sulfate. Evaporation of the solvent *in vacuo* afforded the

desired N-aryl imidazole. The crude product is purified using silica gel column chromatography.

5

General Procedure T1

4N hydrogen chloride in dioxane solution (4 mmol) is added to a mixture of BOC –amino compound (1 mmol) in anhydrous DCM (5 mL), and the mixture is stirred at rt until complete. Evaporation of the solvents *in vacuo* afforded deprotected amine hydrochloride.

10

General Procedure T2

A benzyl alkyl ether, benzyl ester, or a benzyl phenyl ether is dissolved in MeOH and hydrogenated in the presence of 10% Pd/C catalyst until the reaction is complete. reaction mixture is then filtered through a celite pad to remove the catalyst. Evaporation of the solvent *in vacuo* afforded the alcohol, carboxylic acid, or phenol, respectively.

15

General Procedure T3

A phenol (0.2 mmol) in anhydrous DMF (5 mL) is alkylated by a bromide or a mesylate (0.3 mmol) at rt (for a bromide, 60% NaH as base) or at 90°C (for a mesylate, K₂CO₃ as base).

20

The reaction is quenched by adding sat. NaHCO₃. The resulting mixture is extracted with EtOAc washed with brine and dried. The crude product is purified by silica gel column chromatography if desired.

25

5 **Example 1**

1-Butyl-2-(3-cyclohexylmethoxy-phenyl)-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole

Hydroxy benzimidazole was formed employing 1-BOC-4-[2-(4-amino-3-butylamino-phenoxy)-ethyl]-piperazine (synthesized via General Procedures G1 and G2 and H) (2.92 g; 10 mmol) and 3-hydroxybenzaldehyde (1.34 g, 11 mmol) in ethanol (20 mL) following the
10 general procedure K. The crude product was purified by silica gel column chromatography using 2% MeOH in DCM (3.2g).

MS m/z 396 (M+H)⁺

A solution of above mentioned hydroxybenzimidazole compound (39.4 mg, 0.1
15 mmol) in THF (2ml) was added cyclohexylmethyl bromide (19.5 mg, 0.11 mmol) and NaH (0.8 mg, 60% , 0.12 mmol) at 0° C. The resulting reaction mixture was warmed to rt and stirred for additional 12 h. The mixture was quenched with brine and extracted into EtOAc (2 X 10 mL). Combined organic EtOAc extracts were dried over sodium sulfate and concentrated to give compound which was purified by silica gel column chromatography
20 using dichloromethane and 2% methanol in dichloromethane as eluent, to give N-BOC compound, which was subjected to General Procedure T1 affording 1-butyl-2-(3-cyclohexylmethoxy-phenyl)-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole as a hydrochloride salt, 36.8 mg.

MS m/z 491 (M+H)⁺

25

Example 2

(3-(3-butyl-2-(3-,5-di-tert-butyl-2-methoxy-phenyl)-3H-benzimidazol-5-yloxy-propyl)-diethyl-amine

30 This compound was prepared according to the general procedure K by refluxing a mixture of 3,5-di-t-butyl-5-methoxybenzaldehyde (100 mg) and N²-Butyl-4-(3-diethylamino-propoxy)-benzene-1,2-diamine (synthesized via General Procedures G1 and G2 and H) (50 mg) in ethanol overnight. Ethanol was removed in vacuo and the residue was purified by silica gel chromatography using 5% MeOH in DCM to give (3-(3-butyl-2-(3-,5-di-tert-butyl-2-methoxy-phenyl)-3H-benzimidazol-5-yloxy-propyl)-diethyl-amine (45.0 mg).

35

MS: m/z 522 (M+H)⁺

Example 3

(2-(3-butyl-2-(3-(4-tert-butyl-phenoxy)-phenyl)-3H-benzimidazol-5-yloxy-ethyl)-diisopropyl-amine

- 5 A solution of 2-(n-butylamino)-4-(2-diisopropylaminoethoxy)aniline (synthesized via General Procedures G1 and G2 and H) (61.4mg, 0.2 mmol) and (3-(4-tert-butyl-phenoxy)-benzaldehyde (synthesized via General Procedure B) (56mg, 0.22 mmol) in ethanol (2 mL) was condensed following General Procedure K. The crude product was purified by silica gel column chromatography using 10% MeOH in DCM with a gradual increment of triethylamine (0.2 to 1.0%) as eluent to afford (2-(3-butyl-2-(3-(4-tert-butyl-phenoxy)-phenyl)-3H-benzimidazol-5-yloxy-ethyl)-diisopropyl-amine (54 mg).
MS m/z 542 (M+H)⁺

Example 4

(3-{4-[1-butyl-6-(4-tert-butyl-phenoxy)-1H-benzimidazol-2-yl]-phenoxy}-propyl)-diethyl-amine

- To a stirred solution of 4-hydroxybenzaldehyde (20 mmol) in DMSO (80 mL) at rt, solid Cs₂CO₃ (50 mmol) was added. A mesylate (prepared from 3-diethylamino-1-propanol and methanesulfonyl chloride, General Procedure P2) (30 mmol) was added to the reaction mixture and heated to 90 °C until the reaction was complete as indicated by LC-MS (10h).
After cooling to rt, the reaction was quenched by cold H₂O (100 mL), and the resulting mixture was extracted with EtOAc (3×100 mL). The combined EtOAc extracts were washed with brine (3×50 mL) and dried (anhydrous Na₂SO₄). The solvent was removed *in vacuo*, and the crude product was purified by silica gel column chromatography, eluting with 10% MeOH in DCM + 0.5% Et₃N, giving the desired 4-(3-diethylaminopropoxy)benzaldehyde.

- A solution of 2-*t*-butylamino-4-(4-*n*-butylphenoxy)aniline (synthesized via General Procedures G1 and G2 and H) (130 mg, 0.4 mmol) and 4-(3-diethylaminopropoxy)benzaldehyde obtained above (70 mg, 0.3 mmol) in MeOH (10 mL) was subjected to General Procedure K. The solvent was removed *in vacuo* and the residue was purified by silica gel column chromatography, eluting with 10% MeOH in DCM with a gradual increment of Et₃N (0.5 to 1%), affording the desired benzimidazole (120 mg).
MS m/z 528 (M+H)⁺

- ¹H NMR (400 MHz, CDCl₃): δ 0.84 (t, 3H), 1.05 (t, 6H), 1.24 (m, 2H), 1.31 (s, 9H), 1.75 (m, 2H), 1.98 (m, 2H), 2.58 (q, 4H), 2.66 (t, 2H), 4.09 (t, 2H), 4.13 (t, 2H), 6.93 (d, 2H), 7.00 (dd, 1H), 7.02 (d, 2H), 7.07 (d, 1H), 7.33 (d, 2H), 7.62 (d, 2H), 7.72 (d, 1H) ppm.

Example 5

1-butyl-6-(4-tert-butyl-phenoxy)-2-[3-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1H-benzimidazole

To a stirred solution of 3-hydroxybenzaldehyde (20 mmol) in DMSO (50 mL) at rt, solid
 5 Cs₂CO₃ (60 mmol) was added. 1-(2-chloroethyl)pyrrolidine hydrochloride (30 mmol) was
 added to the reaction mixture and heated to 90 °C for 9h. After cooling to rt, the reaction
 was quenched by cold H₂O (50 mL), and the resulting mixture was extracted with EtOAc
 (3×100 mL). The combined EtOAc extracts were washed with brine (3X50 mL) and dried
 (anhydrous Na₂SO₄). The solvent was removed *in vacuo* to afford crude 3-(2-pyrrolidin-1-yl-
 10 ethoxy)benzaldehyde.

A solution of 2-*t*-butylamino-4-(4-*n*-butylphenoxy)aniline (synthesized via General
 Procedures G1 and G2 and H) (130 mg, 0.4 mmol) and 3-(2-pyrrolidin-1-yl-
 ethoxy)benzaldehyde obtained above (70 mg, ~0.3 mmol) in MeOH (10 mL) was subjected
 15 to General Procedure K. The solvent was removed *in vacuo* and the residue was purified by
 silica gel column chromatography, eluting with 10% MeOH in DCM with a gradual increment
 of Et₃N (0.5 to 1%), to afford the desired benzimidazole (100 mg).

MS m/z 512 (M+H)⁺

¹H NMR (400 MHz, CDCl₃): δ 0.83 (t, 3H), 1.22 (m, 2H), 1.29 (s, 9H), 1.74 (m, 2H), 1.87 (m,
 20 4H), 2.78 (m, 4H), 3.03 (m, 2H), 4.16 (t, 2H), 4.25 (m, 2H), 6.94 (d, 2H), 7.01 (br d, 1H), 7.07
 (m, 2H), 7.26 (m, 2H), 7.33 (d, 2H), 7.41 (t, 1H), 7.74 (d, 1H) ppm.

The following Examples were synthesized according to the Methods employed for
 25 Examples 1-5;

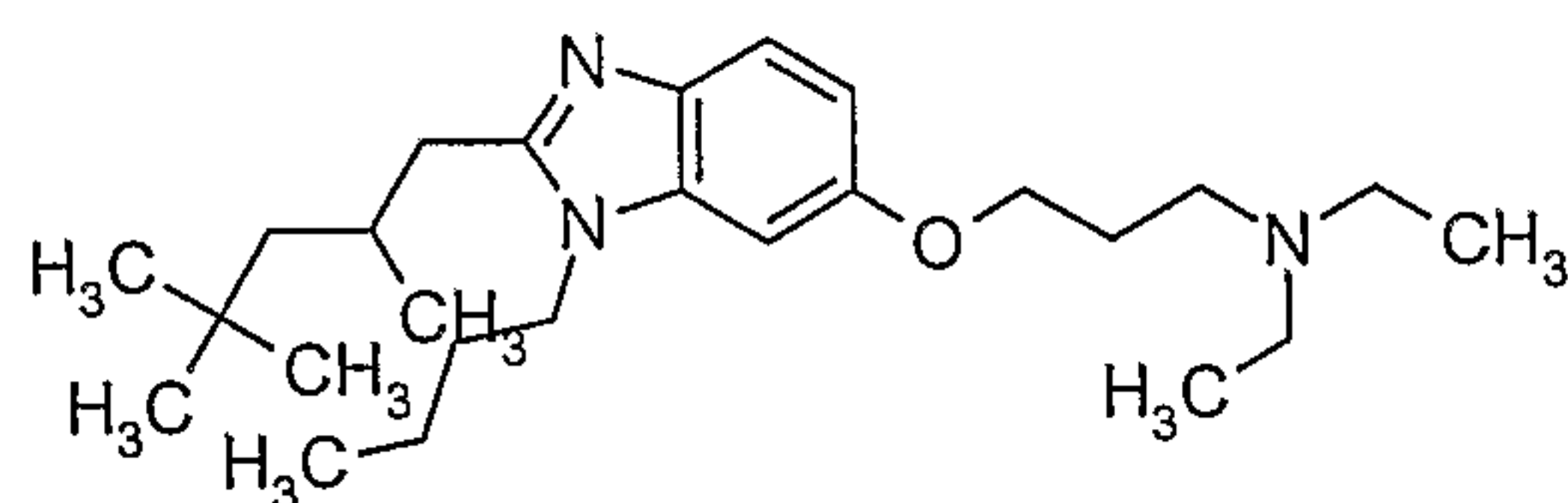
Example	Name
6	1-butyl-6-(4-tert-butyl-phenoxy)-2-[2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1H-benzimidazole
7	1-butyl-2-[3-(naphthalen-2-yloxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzoimidazole
8	2-biphenyl-4-yl-1-butyl-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
9	1-butyl-6-(4-tert-butyl-phenoxy)-2-[4-(2-pyrrolidin-1-yl-ethoxy)-

Example	Name
	phenyl]-1H-benzimidazole
10	1-butyl-2-[3-(3,3-dimethyl-butoxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
11	1-butyl-6-(4-fluoro-3-trifluoromethyl-phenoxy)-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1H-benzimidazole
12	1-butyl-2-(3-phenoxy-phenyl)-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
13	1-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-6-(2-piperidin-1-yl-ethoxy)-1H-benzimidazole
14	1-butyl-2-[3-(3,4-dichloro-phenoxy)-phenyl]-6-(2-piperidin-1-yl-ethoxy)-1H-benzimidazole
15	1-butyl-6-[2-(4-chloro-phenyl)-ethoxy]-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1H-benzimidazole
16	1-butyl-2-[3-(3,5-dichloro-phenoxy)-phenyl]-6-(2-piperidin-1-yl-ethoxy)-1H-benzimidazole
17	1-butyl-2-(4-tert-butyl-phenyl)-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
18	dibutyl-{4-[1-butyl-6-(3-diethylamino-propoxy)-1H-benzimidazol-2-yl]-phenyl}-amine
19	(2-{3-butyl-2-[3-(3,5-dichloro-phenoxy)-phenyl]-3H-benzimidazol-5-yloxy}-ethyl)-diisopropyl-amine
20	{3-[3-butyl-2-(4-tert-butyl-phenyl)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
21	1-butyl-2-(3,5-di-tert-butyl-2-methoxy-phenyl)-6-(2-piperazin-1-ylethoxy)-1H-benzimidazole
22	{3-[3-butyl-2-(3-{4-[2-(4-methoxy-phenyl)-ethoxy]-phenyl}-propyl)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
23	1-butyl-2-naphthalen-2-yl-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
24	(2-{3-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-3H-benzimidazol-5-yloxy}-ethyl)-dimethyl-amine
25	2-benzofuran-2-yl-1-butyl-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
26	1-butyl-6-(2-piperazin-1-yl-ethoxy)-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazole

Example	Name
27	2-benzhydryl-1-butyl-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
28	1-Butyl-2-(4-chloro-phenyl)-6-(2-piperazin-1-yl-ethoxy)-1H-benzoimidazole
29	{3-[3-Butyl-2-(4-isopropoxy-phenyl)-3H-benzoimidazol-5-yloxy]-propyl}-diethyl-amine
30	1-Butyl-6-(2-piperazin-1-yl-ethoxy)-2-[3-(4,4,4-trifluoro-butoxy)-phenyl]-1H-benzoimidazole

5 Example 31

(2-(3-butyl-2-(2,4,4-trimethylpentyl)-3H-benzimidazol-5-yloxy-propyl)-diethyl-amine



10 A solution of 2-(n-butylamino)-4-(3-diethylaminopropoxy)aniline (synthesized via General Procedures G1 and G2 and H) (58.6mg, 0.2 mmol) and 3,5,5-trimethylhexanal (31.2mg, 0.22 mmol) in ethanol (2 mL) was subjected to General Procedure K. The crude product was purified by silica gel column chromatography using 10% MeOH in DCM with a gradual increment of triethylamine (0.2 to 1.0%) as eluent to afford (2-(3-butyl-2-(2,4,4-trimethylpentyl)-3H-benzimidazol-5-yloxy-propyl)-diethyl-amine (41.0 mg). MS m/z 416 (M+H)⁺

15

Example 32

1-[(5-pyrrolidin-1-yl)pentyl]-6-[(3-diethylaminopropoxy)-2-piperidin-3-yl]-1H-benzimidazole

20 A solution of 1-(t-butyloxycarbonyl)piperidine-3-carboxaldehyde (235 mg; 1.1 mmol) and 2-[(5-pyrrolidin-1-yl)pentylamino]-4-(3-diethylaminopropoxy)-4-(2-diethylaminoethoxy)aniline (synthesized via General Procedures G1 and G2 and H) (362 mg; 1 mmol) in ethanol (5 mL) was subjected to General Procedure K. The crude product was purified by silica gel column chromatography using 10% MeOH in DCM with a gradual increment of triethylamine (0.2 to 1.0%) as eluent to afford 410 mg of *tert*-butyl 3-[[1-(5-pyrrolidin-1-yl)pentyl]-6-(3-diethylaminopropoxy)-1H-benzimidazol-2-yl]piperidine-1-carboxylate.

25

A solution of *tert*-butyl 3-[[1-(5-pyrrolidin-1-yl)pentyl]-6-(3-diethylaminopropoxy)-1*H*-benzimidazol-2-yl]piperidine-1-carboxylate (271 mg; 0.5 mmol) in DCM (2 mL) was subjected to General Procedure T1. The resulting mixture was stirred for 4-5 h and the solvent was removed *in vacuo*. The residue obtained was washed with ether twice and dried under vacuum to afford 1-[(5-pyrrolidin-1-yl)pentyl]-6-(3-diethylaminopropoxy)-2-piperidin-3-yl-1*H*-benzimidazole trihydrochloride (210 mg).

MS *m/z* 442 (*M*+*H*)⁺

10 Example 33

1-[(5-pyrrolidin-1-yl)pentyl]-6-(3-diethylaminopropoxy)-2-piperidin-4-yl-1*H*-benzimidazole

A solution of 1-(*t*-butyloxycarbonyl)piperidine-4-carboxaldehyde (235 mg; 1.1 mmol) and 2-[(5-pyrrolidin-1-yl)pentylamino]-4-(3-diethylaminopropoxy)-4-(2-diethylaminoethoxy)aniline (362 mg; 1 mmol) in ethanol (5 mL) was subjected to General Procedure K. The crude product was purified by silica gel column chromatography using 10% MeOH in DCM with a gradual increment of triethylamine (0.2 to 1.0%) as eluent to afford 430 mg of *tert*-butyl 4-[[1-(5-pyrrolidin-1-yl)pentyl]-6-(3-diethylaminopropoxy)-1*H*-benzimidazol-2-yl]piperidine-1-carboxylate.

A solution of *tert*-butyl 4-[[1-(5-pyrrolidin-1-yl)pentyl]-6-(3-diethylaminopropoxy)-1*H*-benzimidazol-2-yl]piperidine-1-carboxylate (271 mg; 0.5 mmol) in DCM (2 mL) was subjected to General Procedure T1. The resulting mixture was stirred for 4-5 h and the solvent was removed *in vacuo*. The residue obtained was washed with ether twice and dried under vacuum to afford 1-[(5-pyrrolidin-1-yl)pentyl]-6-(3-diethylaminopropoxy)-2-piperidin-4-yl-1*H*-benzimidazole trihydrochloride (220 mg).

MS *m/z* 442 (*M*+*H*)⁺

30 Example 34

{1-butyl-[4,6-di(3-diethylaminopropoxy)]-2-piperidin-4-yl}-1*H*-benzimidazole

A solution of 1-(*t*-butyloxycarbonyl)piperidine-4-carboxaldehyde (235 mg; 1.1 mmol) and 2-butylamino-4,6-di(3-diethylaminopropoxy)aniline (synthesized via General Procedures J1 and J2 and I) (424 mg; 1 mmol) in ethanol (5 mL) was subjected to General Procedure K. The crude product was purified by silica gel column chromatography using 10% MeOH in DCM with a gradual increment of triethylamine (0.2 to 1.0%) as eluent to afford 425 mg of

tert-butyl {4-[1-butyl-4,6-di(3-diethylaminopropoxy)-1*H*-benzimidazol-2-yl]}piperidine-1-carboxylate.

A solution of *tert*-butyl 4-[1-butyl-4,6-di(3-diethylaminopropoxy)-1*H*-benzimidazol-2-yl]piperidine-1-carboxylate (308 mg; 0.5 mmol) in DCM (2 mL) was subjected to General Procedure T1. The resulting mixture was stirred for 4-5 h and the solvent was removed *in vacuo*. The residue obtained was washed with ether twice and dried under vacuum to afford {1-butyl-[4,6-di(3-diethylaminopropoxy)]-2-piperidin-4-yl}-1*H*-benzimidazole trihydrochloride (260 mg).

MS *m/z* 516 (M+H)⁺

Example 35

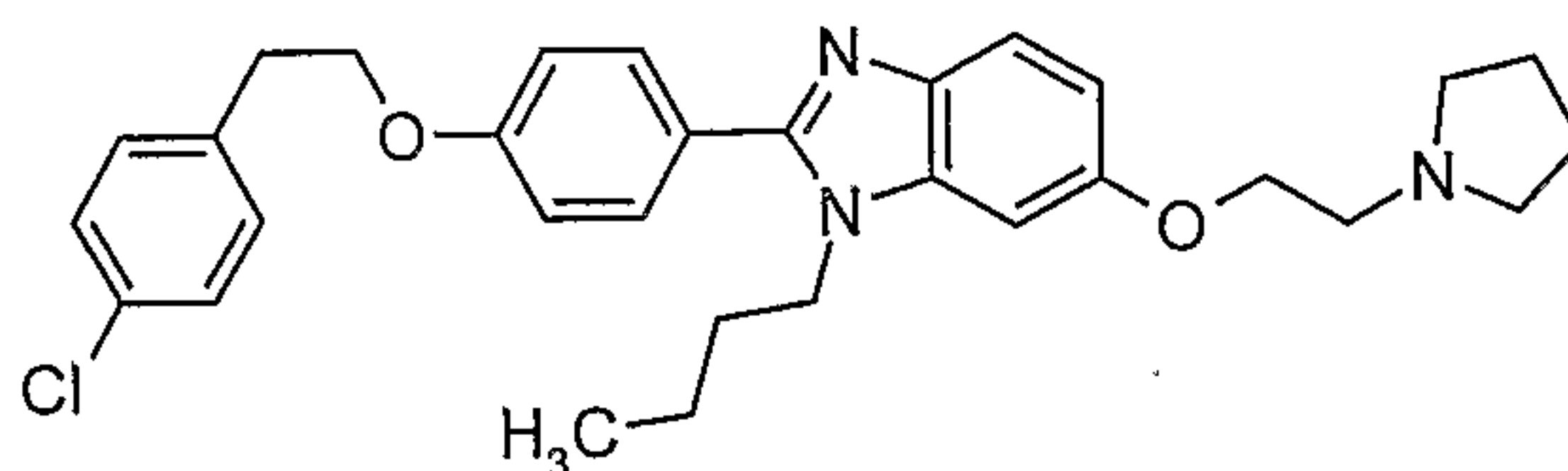
(3-(3-butyl-2-(3-(4-*tert*-butyl-phenoxy)-phenyl)-7-(2-pyrrolidin-1-yl-ethoxy)-3*H*-benzimidazol-5-yloxy-propyl)-diethyl-amine

Example 35 was formed employing 3-(4-*t*-butyl-phenoxy)benzaldehyde (synthesized via General Procedure B) (50 mg; 0.20 mmol) and 2-butylamino-4-(3-diethylaminopropoxy)-6-(2-pyrrolidin-1-yl-ethoxy)aniline (synthesized via General Procedures J3-J7) (39 mg; 0.20 mmol) in ethanol (1 mL) according to General Procedure K. The crude product was purified by silica gel column chromatography using 10% MeOH in DCM with a gradual increment of triethylamine (0.2 to 1.0%) as eluent to afford 40 mg of Example 243.

MS *m/z* 641 (M+H)⁺

Example 36

1-butyl-2-{4-[2-(4-chlorophenyl)ethoxy]-phenyl}-6-(2-pyrrolidin-1-yl-ethoxy)-1*H*-benzimidazole



This compound was prepared according to the General Procedure K by refluxing a mixture of 4-[2-(4-chloro-phenyl)-ethoxy]-bezaldehyde (synthesized via General Procedure A) (100 mg) and N²-Butyl-4-(2-pyrrolidin-1-ylethoxy)-benzene-1,2-diamine (synthesized via General Procedures G1 and G2 and H) (50 mg) in ethanol overnight. Ethanol was removed *in vacuo* and the residue was purified by silica gel chromatography using 5% MeOH in DCM to give

pure 1-butyl-2-{4-[2-(4-chlorophenyl)ethoxy]-phenyl}-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole (37.0 mg, 40%).

MS: m/z 518 (M+H)⁺

5 **Example 37**

1-butyl-2-{3-[3-tert-butyl-phenoxy]-phenyl}-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole

10 A mixture of 1-BOC-4-[2-(4-amino-3-butylamino-phenoxy)-ethyl]-piperazine (synthesized via General Procedures G1 and G2 and H) (0.130 g, 0.512 mmol) and 3-(3-tert-butylphenoxy) benzaldehyde was subjected to General Procedure K. Reaction was concentrated and purified on silica gel chromatography using DCM-2%MeOH/DCM. The BOC-group was removed employing General Procedure T1 to give 1-butyl-2-{3-[3-tert-butyl-phenoxy]-phenyl}-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole (0.10 g).

MS (m/z): 527 (M+H)⁺

15

Example 38

1-butyl-2-{3-[biphenyl-4-yloxy]-phenyl}-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole

20 A mixture of 3-bromobenzaldehyde (1.05 g) and 1-BOC-4-[2-(4-amino-3-butylamino-phenoxy)-ethyl]-piperazine (1.85g) was subjected to General Procedure K. The ethanol was removed in vacuo and the residue purified on silica gel using 1-2% MeOH/DCM.

25 To a solution of the aryl bromide (0.07 mmol) in pyridine (1 mL) was added copper powder (0.14 mmol) followed by K₂CO₃ (0.35 mmol) and the respective substituted phenol (0.14 mmol). The mixture was heated at 110 °C overnight, then diluted with water (2 mL) and extracted with EtOAc (3 x 2mL). The combined organic extract was dried over Na₂SO₄, filtered and concentrated to an oil, which was purified by column chromatography on silica gel. The pure product was obtained from 1-6% methanol/DCM (yield 28-42%). The BOC-group was removed via General Procedure T1 to give 1-butyl-2-{3-[biphenyl-4-yloxy]-phenyl}-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole.

30

MS (m/z): 547 (M+H)⁺

Example 39

35 1-butyl-2-{4-[2-(4-chlorophenyl)ethoxy]-phenyl}-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole

A mixture of 4-[2-(4-chloro-phenyl)-ethoxy]-benzaldehyde (0.08 g) and 1-BOC-4-[2-(4-amino-3-butylamino-phenoxy)-ethyl]-piperazine (0.10g) was subjected to General Procedure K. Ethanol was removed in vacuo and the residue purified on silica gel with 1-2%MeOH/DCM. The BOC-group was removed employing General Procedure T1 to give 1-butyl-2-{4-[2-(4-chlorophenyl)ethoxy]-phenyl}-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole (0.081 g).
MS (m/z): 533 (M+H)⁺

The following Examples were synthesized according to the Methods employed for Examples 35-39;

Example	Name
40	[3-(3-butyl-2-{3-[2-(4-chloro-phenyl)-ethoxy]-4-nitro-phenyl}-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
41	[2-(3-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-3H-benzimidazol-5-yloxy)-ethyl]-diethyl-amine
42	1-butyl-2-[3-(3,5-dichloro-phenoxy)-phenyl]-6-(piperidin-4-ylmethoxy)-1H-benzimidazole
43	1-butyl-2-{3-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
44	{3-[3-butyl-2-(2-{4-[2-(4-chlorophenyl)-ethoxy]-phenyl}-ethyl)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
45	1-butyl-2-[3-(3,5-dichloro-phenoxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
46	1-butyl-6-[2-(4-butyl-piperazin-1-yl)-ethoxy]-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazole
47	{3-[3-butyl-2-(2-{4-[2-(4-chlorophenyl)-ethoxy]-phenyl}-ethyl)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
48	(3-{3-butyl-2-[3-(4-methoxy-phenoxy)-phenyl]-3H-benzimidazol-5-yloxy}-propyl)-diethyl-amine
49	{3-[2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(2-diethylamino-ethoxy)-benzimidazol-1-yl]-propyl}-diethyl-amine
50	[3-(1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-1H-benzimidazol-4-yloxy)-propyl]-diethyl-amine
51	[3-(1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-1H-benzimidazol-5-yl)-propyl]-diethyl-amine
52	1-butyl-2-[3-(2-isopropyl-phenoxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
53	{3-[3-butyl-2-(2-{4-[3-(4-methoxy-phenyl)-propoxy]-phenyl}-ethyl)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
54	{3-[3-butyl-2-(2-{4-[4-(4-methoxy-phenyl)-butoxy]-phenyl}-ethyl)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
55	[3-(3-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-3-ethoxy-phenyl}-3H-

Example	Name
	benzimidazol-5-yloxy)-propyl]-diethyl-amine
56	(3-{3-butyl-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-3H-benzimidazol-5-yloxy}-propyl)-diethyl-amine
57	1-butyl-2-[3-(4-chloro-phenoxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzoimidazole
58	1-butyl-2-[3-(3,4-dichloro-phenoxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzoimidazole
59	1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(piperidin-4-yloxy)-1H-benzoimidazole
60	3-(3-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-3H-benzoimidazol-5-yloxy)-1-aza-bicyclo[2.2.2]octane
61	1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(2,2,6,6-tetramethyl-piperidin-4-yloxy)-1H-benzoimidazole
62	2-[3-(4-butoxy-phenoxy)-phenyl]-1-butyl-6-(2-piperazin-1-yl-ethoxy)-1H-benzoimidazole
63	[3-(3-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
64	{3-[2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-3-(3-methyl-butyl)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
65	[3-(2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-3-hexyl-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
66	{3-[2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(2-diethylamino-ethoxy)-benzimidazol-1-yl]-propyl}-dimethyl-amine
67	1-butyl-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-6-(2-piperazin-1-ylethoxy)-1H-benzoimidazole
68	[3-(3-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
69	{3-[2-(4-benzyloxy-3,5-dimethyl-phenyl)-3-butyl-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
70	{3-[3-butyl-2-[3-(3,4-dichloro-phenoxy)-phenyl]-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
71	1-butyl-6-[2-(4-methyl-piperazin-1-yl)-ethoxy]-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazole
72	1-butyl-6-[2-(4-isopropyl-piperazin-1-yl)-ethoxy]-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzoimidazole
73	1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(3-piperazin-1-yl-propoxy)-1H-benzoimidazole
74	(3-{3-butyl-2-[3-(3,4-dichloro-phenoxy)-phenyl]-3H-benzimidazol-5-yloxy}-propyl)-diethyl-amine
75	1-butyl-2-[3-(3,4-dimethoxy-phenoxy)-phenyl]-6-(2-piperidin-4-yloxy)-1H-benzoimidazole
76	1-butyl-2-[3-(4-chloro-benzyloxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-

Example	Name
	1H-benzoimidazole
77	1-butyl-2-[3-(3,5-dichloro-phenoxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzoimidazole
78	(3-{2-[2-(4-benzyloxy-phenyl)-ethyl]-3-butyl-3H-benzimidazol-5-yloxy}-propyl)-diethyl-amine
79	(3-{3-butyl-2-[2-(4-phenethyloxy-phenyl)-ethyl]-3H-benzimidazol-5-yloxy}-propyl)-diethyl-amine
80	{3-[3-butyl-2-(2-{4-[2-(4-fluoro-phenyl)-ethoxy]-phenyl}-ethyl)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
81	[3-(3-butyl-2-{2-[4-(4-chloro-benzyloxy)-phenyl]-ethyl}-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
82	(3-{3-butyl-2-[4-(4-fluoro-benzyloxy)-phenyl]-3H-benzimidazol-5-yloxy}-propyl)-diethyl-amine
83	{3-[2-(3-benzyloxy-phenyl)-3-butyl-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
84	[3-(3-butyl-2-{4-chloro-3-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
85	1-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
86	1-butyl-2-[4-(4-isopropyl-phenoxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzoimidazole
87	1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-[3-(4-methyl-piperazin-1-yl)-propoxy]-1H-benzoimidazole
88	1-butyl-6-[2-(4-butyl-piperazin-1-yl)-ethoxy]-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-1H-benzoimidazole
89	1-butyl-2-[3-(3,4-dimethoxy-phenoxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzoimidazole
90	1-butyl-2-[4-(4-tert-butyl-benzyl)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzoimidazole
91	N-{4-[1-butyl-6-(3-diethylamino-propoxy)-1H-benzimidazol-2-yl]-2-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2,2-dimethyl-propionamide
92	(3-{3-butyl-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-3H-benzimidazol-5-yloxy}-propyl)-diethyl-amine
93	1-butyl-2-[4-(naphthalen-2-yloxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzoimidazole
94	1-butyl-2-[3-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzoimidazole
95	[3-(3-butyl-2-{4-[2-(4-methoxy-phenyl)-ethoxy]-phenyl}-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
96	4-[1-butyl-6-(3-diethylamino-propoxy)-1H-benzimidazol-2-yl]-2-[2-(4-chloro-phenyl)-ethoxy]-phenylamine
97	1-{4-[1-butyl-6-(3-diethylamino-propoxy)-1H-benzimidazol-2-yl]-2-[2-

Example	Name
	(4-chloro-phenyl)-ethoxy]-phenyl]-3-isopropyl-urea
98	{3-[2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(2-dimethylamino-ethoxy)-benzimidazol-1-yl]-propyl}-dimethyl-amine
99	1-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-6-[2-(4-methyl-piperazin-1-yl)-ethoxy]-1H-benzimidazole
100	1-butyl-6-(4-cyclopentyl-phenoxy)-2-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-benzoimidazole
101	{3-[2-(4-benzyloxy-phenyl)-3-cyclopentylmethyl-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
102	1-butyl-6-(4-butyl-phenoxy)-2-{3,5-dimethyl-4-[2-(1-methyl-pyrrolidin-2-yl)-ethoxy]-phenyl}-1H-benzoimidazole
103	1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(3-pyrrolidin-1-yl-propoxy)-1H-benzoimidazole
104	{3-[2-(4-benzyloxy-phenyl)-3-isobutyl-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
105	[3-(3-butyl-2-{3-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
106	1-butyl-6-(1-butyl-piperidin-4-yloxy)-2-[3-(3,5-dichloro-phenoxy)-phenyl]-1H-benzoimidazole
107	1-butyl-2-[3-(3,5-dichloro-phenoxy)-phenyl]-6-(1-ethyl-piperidin-4-yloxy)-1H-benzoimidazole
108	1-butyl-6-(4-fluoro-3-trifluoromethyl-phenoxy)-2-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-benzoimidazole
109	diethyl-{3-[3-isobutyl-2-(2-{4-[2-(4-methoxy-phenyl)-ethoxy]-phenyl}-ethyl)-3H-benzimidazol-5-yloxy]-propyl}-amine
110	{3-[2-(2-{4-[2-(4-chlorophenyl)-ethoxy]-phenyl}-ethyl)-3-isobutyl-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
111	1-butyl-6-(2-piperazin-1-yl-ethoxy)-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazole
112	1-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
113	1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-[2-(4-methyl-piperazin-1-yl)-ethoxy]-1H-benzimidazole
114	{3-[2-(4-benzyloxy-phenyl)-3-cyclopentyl-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
115	1-Butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-5-(4-methyl-piperazin-1-ylmethyl)-1H-benzoimidazole
116	[2-(3-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-3H-benzimidazol-5-yloxy)-ethyl]-dimethyl-amine
117	[2-(3-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-3H-benzimidazol-5-yloxy)-ethyl]-diisopropyl-amine
118	1-butyl-2-[3-(3,5-dichloro-phenoxy)-phenyl]-6-[2-(4-methyl-piperazin-

Example	Name
	1-yl)-ethoxy]-1H-benzimidazole
119	(3-{1-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine
120	2-(3-butoxy-phenyl)-1-butyl-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
121	1-butyl-2-[3-(4-methanesulfonyl-benzyloxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzoimidazole
122	4'{3-[1-butyl-6-(2-piperazin-1-yl-ethoxy)-1H-benzoimidazol-2-yl]-phenoxy}-biphenyl-4-carbonitrile
123	{3-[2-(4-benzyloxy-phenyl)-3-butyl-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
124	1-Butyl-2-[4-(3-chloro-phenoxy)-phenyl]-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole
125	1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-[2-(4-isopropyl-piperazin-1-yl)-ethoxy]-1H-benzoimidazole
126	{3-[2-(3-benzyloxy-4-methoxy-phenyl)-3-butyl-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
127	(3-{3-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-3H-benzimidazol-5-yloxy}-propyl)-diethyl-amine
128	{3-[3-butyl-2-(3-phenoxy-phenyl)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
129	1-butyl-2-[3-(3,5-dichloro-phenoxy)-phenyl]-6-[2-(4-ethyl-piperazin-1-yl)-ethoxy]-1H-benzimidazole
130	1-butyl-2-[4-(2,3-di-methoxy-phenoxy)-phenyl]-6-(2-piperazin-1-ylethoxy)-1H-benzoimidazole
131	[3-(3-butyl-2-{2-[4-(4-chloro-benzyloxy)-phenyl]-ethyl}-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
132	(3-{3-butyl-2-[3-(4-chloro-phenoxy)-phenyl]-3H-benzimidazol-5-yloxy}-propyl)-diethyl-amine
133	{3-[2-(4-benzyloxy-phenyl)-3-isopropyl-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
134	(2-{3-butyl-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-3H-benzoimidazol-5-yloxy}-ethyl)-diisopropyl-amine
135	1-butyl-6-[2-(4-ethyl-piperazin-1-yl)-ethoxy]-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazole
136	{3-[3-butyl-2-[3-(3,5-dichloro-phenoxy)-phenyl]-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
137	(3-{2-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-3H-benzimidazol-5-yloxy}-ethyl)-cyclohexyl-methyl-amine
138	1-butyl-6-[2-(4-propyl-piperazin-1-yl)-ethoxy]-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazole
139	1-butyl-6-(4-butyl-phenoxy)-2-[4-(4-methyl-piperazin-1-ylmethyl)-

Example	Name
	phenyl]-1H-benzimidazole
140	1-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-6-(2-morpholin-4-yl-ethoxy)-1H-benzimidazole
141	4-[1-butyl-6-(3-diethylamino-propoxy)-1H-benzimidazol-2-yl]-2-phenethyloxy-phenylamine
142	{2-[2-(4-benzyloxy-phenyl)-3-phenethyl-3H-benzimidazol-5-yloxy]-ethyl}-diethyl-amine
143	{3-[3-butyl-2-(4-phenoxy-phenyl)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
144	3-[4-(2-{3-butyl-2-[3-(3,4-dichloro-phenoxy)-phenyl]-3H-benzimidazol-5-yloxy}-ethyl)-piperazin-1-yl]-propan-1-ol
145	1-butyl-6-(2-pyrrolidin-1-yl-ethoxy)-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazole
146	{2-[2-[4-[2-(4-chloro-phenyl)-ethoxy]-phenyl]-6-(2-diethylamino-ethoxy)-benzimidazol-1-yl]-ethyl}-dimethyl-amine
147	1-butyl-6-(2-morpholin-4-yl-ethoxy)-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazole
148	1-butyl-2-[3-(3,5-dichloro-phenoxy)-phenyl]-6-(1-methyl-piperidin-4-yloxy)-1H-benzimidazole
149	N'-[3-butyl-2-(2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-ethyl)-3H-benzimidazol-5-yl]-N,N-diethyl-propane-1,3-diamine
150	1-butyl-2-[3-(2,4-dichloro-phenoxy)-phenyl]-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
151	1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(2-morpholin-4-yl-ethoxy)-1H-benzimidazole
152	1-butyl-6-(2-piperazin-1-yl-ethoxy)-2-[4-(4-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazole
153	2-[4-(biphenyl-4-yloxy)-phenyl]-1-butyl-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
154	1-butyl-2-[3-(3,5-dichloro-phenoxy)-phenyl]-6-(2-morpholin-4-yl-ethoxy)-1H-benzimidazole
155	1-butyl-2-[3-(3,4-dimethoxy-phenoxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
156	1-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-5-(1H-imidazol-4-ylmethoxy)-1H-benzimidazole
157	{3-[2-(2-benzyloxy-phenyl)-3-butyl-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
158	{3-[1-Butyl-6-(3-diethylamino-propoxy)-2-piperidin-4-yl-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
159	(2-{2-[2-(4-Benzyloxy-phenyl)-ethyl]-3-phenethyl-3H-benzimidazol-5-yloxy}-ethyl)-diethyl-amine
160	[3-(3-Butyl-2-{3-[4-(4-fluoro-benzyloxy)-phenyl]-propyl}-3H-

Example	Name
	benzoimidazol-5-yloxy)-propyl]-diethyl-amine
161	[3-(4-Benzoyloxy-phenyl)-propyl]-[1-butyl-6-(3-diethylamino-propoxy)-1H-benzoimidazol-2-yl]-amine
162	{3-[3-Butyl-2-(3-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-propyl)-3H-benzoimidazol-5-yloxy]-propyl}-diethyl-amine
163	1-Butyl-2-[3-(3,5-dichloro-phenoxy)-phenyl]-6-(2-imidazol-1-yl-ethoxy)-1H-benzoimidazole
164	1-[4-(2-{3-Butyl-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-3H-benzoimidazol-5-yloxy}-ethyl)-piperazin-1-yl]-ethanone
165	N-[3-Butyl-2-(2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-ethyl)-3H-benzoimidazol-5-yl]-N-(3-diethylamino-propyl)-N',N'-diethyl-propane-1,3-diamine

Example 166

5 (3-(1-Butyl-2-{4-[2-(4-chlorophenyl)-ethoxy]-phenyl}-6--(3-diethylaminopropoxy)-1H-benzimidazole-4-yloxy)-propyl)diethyl-amine

10 This compound was prepared according to General Procedure K by refluxing a mixture of 4-[2-(4-chloro-phenyl)-ethoxy]-benzaldehyde (300 mg) and N¹-Butyl-3,5-bis-(3-diethylamino-propoxy)-benzene-1,2-diamine (synthesized via General Procedures J1 and J2 and I) (200 mg) in ethanol overnight. Ethanol was removed in vacuo and the residue was purified by silica gel chromatography using 5% MeOH in DCM to give pure (3-(1-Butyl-2-{4-[2-(4-chlorophenyl)-ethoxy]-phenyl}-6--(3-diethylaminopropoxy)-1H-benzimidazole-4-yloxy)-propyl)diethyl-amine (100 mg).

15 MS: *m/z* 663 (M+H)⁺

Example 167

20 {3-[1-Butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-6--(3-diethylaminopropoxy)-1H-benzimidazole-4-yloxy]-propyl}diethyl-amine

25 {3-[1-Butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-6--(3-diethylaminopropoxy)-1H-benzimidazole-4-yloxy]-propyl}diethyl-amine was formed employing 3(4-t-butyl-phenoxy)benzaldehyde (127 mg; 0.50 mmol) and 2-butylamino-4,6-di(3-diethylaminopropoxy)aniline (synthesized via General Procedures J1 and J2 and I) (1.6mg;

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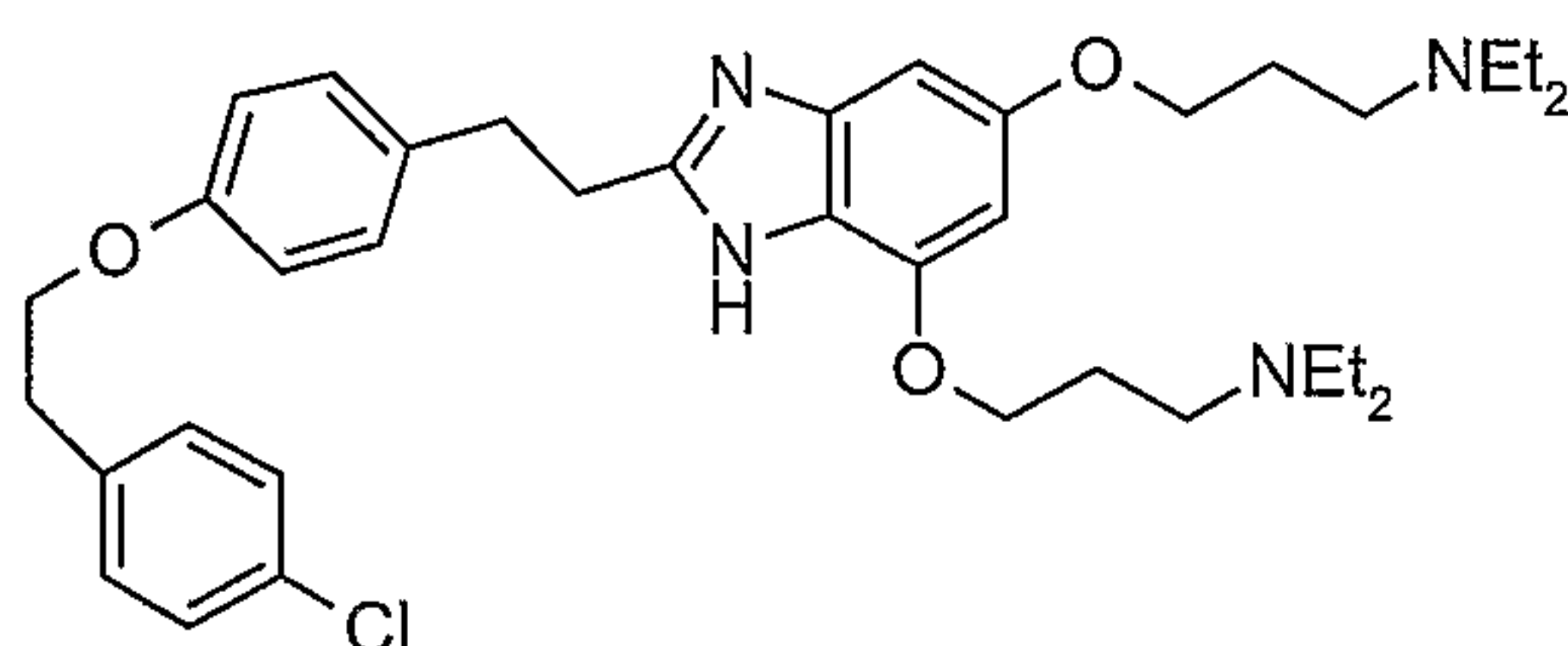
PCT/US03/06749

0.25 mmol) in ethanol (1 mL) following General Procedure K. The crude product was purified by silica gel column chromatography using 10% MeOH in DCM with a gradual increment of triethylamine (0.2 to 1.0%) as eluent to afford 145 mg (76%) of {3-[1-Butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-6--(3-diethylaminopropoxy)-1H-benzimidazole-4-yloxy]-propyl}diethyl-amine.

MS: m/z 657 (M+H)⁺

Example 168

{3-[2-(2-[4-[2-(4-chloro-phenyl)-ethoxy]]-phenyl)-ethyl]-6--(3-diethylaminopropoxy)-3H-benzimidazole-4-yloxy]-propyl}diethyl-amine



This compound was prepared according to the General Procedure K by refluxing a mixture of 3-{4-[2-(4-chloro-phenyl)-ethoxy]-propionaldehyde (100 mg) and 3,5-Bis-(3-diethylaminopropoxy)-benzene-1,2-diamine (synthesized via General Procedures J1 and J2 and I) (50 mg) in ethanol overnight. Ethanol was removed in vacuo and the residue was purified by silica gel chromatography using 10% MeOH in DCM to give {3-[2-(2-[4-[2-(4-chloro-phenyl)-ethoxy]]-phenyl)-ethyl]-6--(3-diethylaminopropoxy)-3H-benzimidazole-4-yloxy]-propyl}diethyl-amine (30 mg).

MS: m/z 635 (M+H)⁺

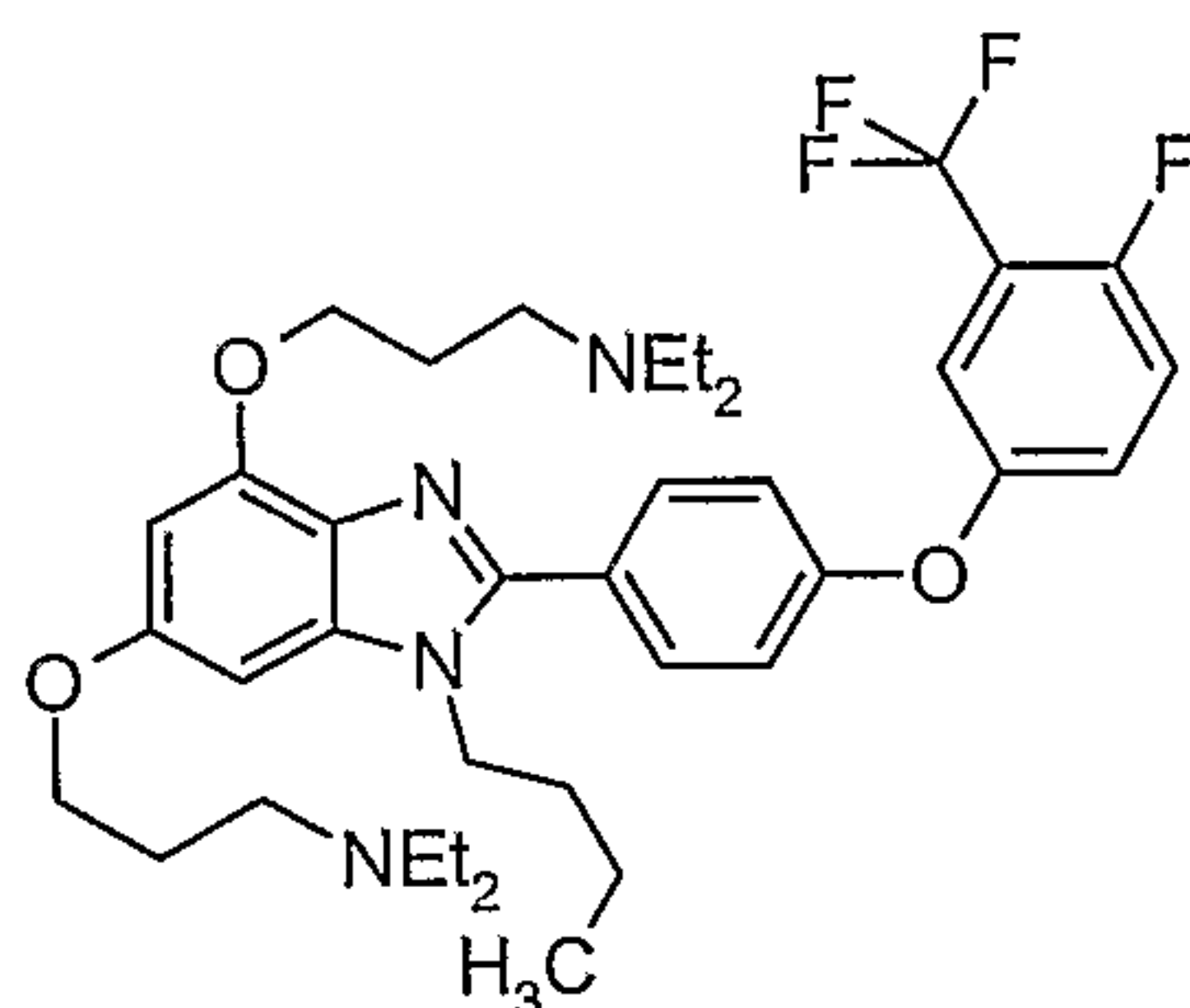
Example 169

(3-(1-Butyl-6-(3-diethylaminopropoxy)-2-[4-(4-chloro-3-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazole-4-yloxy)-propyl)diethyl-amine

4-(4-Chloro-3-trifluoromethyl)phenoxybenzaldehyde (synthesized employing General Procedure B) (150 mg) and 2-butylamino-4,6-di(3-diethylaminopropoxy)aniline (synthesized via General Procedures J1 and J2 and I) 106 mg; 0.25 mmol) in ethanol (1 mL) were condensed employing General Procedure K. The crude product was purified by silica gel column chromatography using 10% MeOH in DCM with a gradual increment of triethylamine (0.2 to 1.0%) as eluent to afford 160 mg of (3-(1-Butyl-6-(3-diethylaminopropoxy)-2-[4-(4-chloro-3-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazole-4-yloxy)-propyl)diethyl-amine.

MS: m/z 703 (M+H)⁺**Example 170**

(3-(1-Butyl-6-(3-diethylaminopropoxy)-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-



5 benzimidazole-4-yloxy)-propyl)diethyl-amine

A solution of 2-butylamino-4,6-di(3-diethylaminopropoxy)aniline (synthesized via General Procedures J1 and J2 and I) (84.4mg, 0.2 mmol) and 4-(4-fluoro-3-trifluoromethyl)phenoxybenzaldehyde (synthesized employing General Procedure B) (62.5mg, 0.2 mmol) in ethanol (2 mL) was heated to reflux following the General Procedure K.. The crude product was purified by silica gel column chromatography using 10% MeOH in DCM with a gradual increment of triethylamine (0.2 to 1.0%) as eluent to afford 3-(1-Butyl-6-(3-diethylaminopropoxy)-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazole-4-yloxy)-propyl)diethyl-amine (62 mg).

15 MS m/z 687 (M+H)

The following Examples were synthesized according to the Methods employed for Examples 166-170;

Example	Name
171	{3-[2-[3-(3,5-Dichloro-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
172	1-Butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
173	{3-[2-[3-(3,4-Dichloro-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
174	(3-{6-(3-diethylamino-propoxy)-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine
175	{3-[1-Butyl-2-[3-(3,4-dichloro-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
176	{3-[2-[3-(4-Chloro-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-

Example	Name
	benzoimidazol-4-yloxy]-propyl}-diethyl-amine
177	{3-[1-Butyl-2-[3-(4-chloro-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
178	{3-[1-Butyl-6-(3-diethylamino-propoxy)-2-(3-p-tolyloxy-phenyl)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
179	{3-[1-Butyl-2-[3-(3,5-dichloro-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
180	1-Butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
181	{3-[3-Butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-7-(2-pyrrolidin-1-yl-ethoxy)-3H-benzoimidazol-5-yloxy]-propyl}-diethyl-amine
182	(3-{1-butyl-6-(3-diethylamino-propoxy)-2-[4-(3-fluoro-phenoxy)-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine
183	{3-[2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(3-diethylamino-propoxy)-1-isopropyl-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
184	{3-[1-Butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
185	2-{4-[1-butyl-4,6-bis-(3-diethylamino-propoxy)-1H-benzimidazol-2-yl-phenoxy]-benzoic acid methyl ester
186	{3-[2-[4-(biphenyl-4-yloxy)-phenyl]-1-butyl-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
187	{3-[2-[4-(3,5-Bis-trifluoromethyl-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
188	{3-[1-butyl-2-[4-(4-chloro-benzylsulfanyl)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
189	{3-[2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(3-diethylamino-propoxy)-3H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
190	(3-{1-butyl-6-(3-diethylamino-propoxy)-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine
191	[3-(1-butyl-6-(3-diethylamino-propoxy)-2-{4-[2-(4-fluoro-phenyl)-ethoxy]-phenyl}-1H-benzimidazol-4-yloxy)-propyl]-diethyl-amine
192	(3-{1-butyl-6-(3-diethylamino-propoxy)-2-[4-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine
193	{3-[2-[3-(4-tert-Butyl-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
194	(3-{1-Butyl-6-(3-diethylamino-propoxy)-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-2-trifluoromethyl-phenyl]-1H-benzoimidazol-4-yloxy}-propyl)-diethyl-amine
195	{3-[1-Butyl-2-[4-chloro-2-(4-chloro-3-trifluoromethyl-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
196	2-[3-(4-Chloro-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-

Example	Name
	benzoimidazole
197	1-Butyl-2-[3-(4-chloro-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole
198	{3-[3-butyl-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-7-(2-pyrrolidin-1-yl-ethoxy)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
199	{2-[1-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-6-(2-diisopropylamino-ethoxy)-1H-benzimidazol-4-yloxy]-ethyl}-diethyl-amine
200	{3-[2-[4-(3,5-Bis-trifluoromethyl-phenoxy)-phenyl]-1-butyl-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
201	{3-[2-[4-(3,5-Bis-trifluoromethyl-phenoxy)-phenyl]-1-butyl-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
202	(3-{1-butyl-6-(3-diethylamino-propoxy)-2-[4-(4-methoxy-phenoxy)-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine
203	1-Butyl-2-[4-(4-chloro-3-trifluoromethyl-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole
204	2-{4-[2-(4-Chloro-phenyl)-ethoxy]-phenyl}-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole
205	1-Butyl-2-[4-(4-tert-butyl-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole
206	1-Butyl-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole
207	{3-[1-Butyl-2-[4-(3-chloro-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
208	2-[5,7-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazol-2-yl]-5-[2-(4-chloro-phenyl)-ethoxy]-phenol
209	2-[3-(4-tert-butyl-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
210	(3-{6-(3-Diethylamino-propoxy)-2-[2-(1,1-difluoro-ethyl)-4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-benzoimidazol-4-yloxy}-propyl)-diethyl-amine
211	{3-[1-Butyl-2-[4-(4-tert-butyl-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
212	2-[4-(4-tert-Butyl-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole
213	{3-[1-Butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
214	[3-(3-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-diethylaminomethyl-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
215	(3-{6-(3-Diethylamino-propoxy)-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-benzoimidazol-4-yloxy}-propyl)-diethyl-amine
216	(3-{1-butyl-6-(3-diethylamino-propoxy)-2-[4-(4-trifluoromethyl-

Example	Name
	pyrimidin-2-ylsulfanyl)-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine
217	{3-[6-(3-Diethylamino-propoxy)-2-(3-p-tolyloxy-phenyl)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
218	4-{3-[1-Butyl-4,6-bis-(3-diethylamino-propoxy)-1H-benzimidazol-2-yl]-phenoxy}-benzonitrile
219	[3-(3-Butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-7-pyrrolidin-1-yl-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
220	{3-[1-butyl-2-[4-(4-chloro-phenylmethanesulfinyl)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
221	(3-{1-butyl-6-(3-diethylamino-propoxy)-2-[4-(naphthalen-2-yloxy)-phenyl]-1H-benzimidazole-4-yloxy}-propyl)-diethyl-amine
222	(3-{6-(3-diethylamino-propoxy)-2-[4-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine
223	(3-{1-butyl-6-(3-diethylamino-propoxy)-2-[3-(4-methoxy-phenoxy)-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine
224	2-[3-(3,4-Dichloro-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
225	{3-[2-[4-(4-tert-Butyl-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
226	{3-[3-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-7-[2-(tetrahydrofuran-2-yl)-ethoxy]-3H-benzimidazol-5-yloxy]-propyl)-diethyl-amine
227	1-Butyl-2-[4-(3-chloro-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
228	[3-(7-Butoxy-3-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
229	4-{3-[4,6-Bis-(3-diethylamino-propoxy)-1H-benzimidazol-2-yl]-phenoxy}-benzonitrile
230	2-[3-(3,5-Dichloro-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
231	{3-[1-butyl-2-(2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-ethyl)-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
232	{3-[1-butyl-6-(3-diethylamino-propoxy)-2-(3-phenoxy-phenyl)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
233	{3-[1-Butyl-2-[2-(4-chloro-3-trifluoromethyl-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
234	2-[4-(4-Chloro-3-trifluoromethyl-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
235	{3-[1-Butyl-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-

Example	Name
	amine
236	[3-(3-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-methyl-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
237	{3-[1-butyl-6-(3-diethylamino-propoxy)-2-(4-phenoxy-phenyl)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
238	5-[4,6-bis-(3-diethylamino-propoxy)-1H-benzoimidazol-2-yl]-2-[2-(4-chloro-phenyl)-ethoxy]-phenol
239	[3-(6-Butoxy-1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-1H-benzoimidazol-4-yloxy)-propyl]-diethyl-amine
240	{3-[2-[4-Chloro-2-(4-chloro-3-trifluoromethyl-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
241	1-butyl-4-(4-chloro-benzyloxy)-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
242	4-{4-[1-butyl-4,6-bis-(3-diethylamino-propoxy)-1H-benzimidazol-2-yl]-phenoxy}-benzonitrile
243	[3-(1-Butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-fluoro-1H-benzoimidazol-4-yloxy)-propyl]-diethyl-amine
244	(3-{6-(3-diethylamino-propoxy)-2-[3-(4-methoxy-phenoxy)-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine
245	(3-{6-(3-diethylamino-propoxy)-2-[4-(4-methoxy-phenoxy)-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine
246	{3-[1-butyl-2-[4-(4-chloro-3-fluoro-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yl]-propyl}-diethyl-amine
247	(3-{1-butyl-6-(3-diethylamino-propoxy)-2-[4-(quinolin-8-yloxy)-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine
248	{3-[2-[2-(4-chloro-3-trifluoromethyl-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
249	2-[[2-[1-Butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(2-morpholin-4-yl-ethoxy)-1H-benzoimidazol-4-yloxy]-ethyl]-(2-chloro-ethyl)-amino]-ethanol
250	(3-{6-(3-Diethylamino-propoxy)-2-[3-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-benzoimidazol-4-yloxy}-propyl)-diethyl-amine
251	[3-(3-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-7-isopropoxy-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
252	[3-(1-Butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-cyclopentylmethoxy-1H-benzoimidazol-4-yloxy)-propyl]-diethyl-amine
253	1-Butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-4,6-bis-(2-morpholin-4-yl-ethoxy)-1H-benzoimidazole
254	{3-[2-[4-[2-(4-Chloro-phenyl)-ethoxy]-3-(3-diethylamino-propoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine

5 **Example 255**

{3-[2-[1-butyl-6-(4-tert-butyl-phenoxy)-1H-benzimidazol-2-yl]-5-(3-diethylamino-propoxy)-phenoxy]-propyl}-diethyl-amine

10 To a stirred solution of 2,4-dihydroxybenzaldehyde (10 mmol) in DMSO (50 mL) at rt, solid Cs_2CO_3 (45 mmol) was added. A mesylate (prepared from 3-diethylamino-1-propanol and methanesulfonyl chloride, General Procedure P2) (25 mmol) was added to the reaction mixture and heated to 90 °C until the reaction was complete as indicated by LC-MS (~10h). After cooling to rt, the reaction was quenched by cold H_2O (100 mL), and the resulting mixture was extracted with EtOAc (3×100 mL). The combined EtOAc extracts were washed
15 with brine (3X50 mL) and dried (anhydrous Na_2SO_4). The solvent was removed *in vacuo* to afford the desired 2,4-bis(3-diethylaminopropoxy)benzaldehyde which was used for further transformation.

20 To a stirred solution of 2,4-difluoronitrobenzene (50 mmol), Et_3N (100 mmol) and DMF (80 mL) was added dropwise a solution of *n*-butylamine (51 mmol) in DMF (20 mL) at rt, and the mixture was stirred at rt for 5h. The reaction was quenched by cold H_2O (100 mL), and the resulting mixture was extracted with EtOAc (4×100 mL). The combined EtOAc extracts were washed with brine (3X60 mL) and dried (anhydrous Na_2SO_4). The solvent was removed *in vacuo* to afford the desired 2-*n*-butylamino-4-fluoronitrobenzene which was used for further
25 transformation.

A mixture of 2-*n*-butylamino-4-fluoronitrobenzene (10 mmol), 4-*t*-butylphenol (13 mmol), solid K_2CO_3 (30 mmol) and DMF (30 mL) was heated with stirring at 90°C for 10h. The reaction was quenched by cold H_2O (50 mL), and the resulting mixture was extracted with
30 EtOAc (3×100 mL). The combined EtOAc extracts were washed with brine (2X50 mL) and dried (anhydrous Na_2SO_4). The solvent was removed *in vacuo*, and the crude products were purified by silica gel column chromatography (eluting with 10% EtOAc in hexane), giving 2-*n*-butylamino-4-(4-*t*-butylphenoxy)nitrobenzene.

35 The nitro intermediate (2 mmol) obtained above was dissolved in MeOH (10 mL) and hydrogenated in the presence of 10% Pd/C (50 mg) until completion as indicated by LC-MS

(~4h). The reaction mixture was then filtered through a celite pad to remove the catalyst. The MeOH solution containing 2-*n*-butylamino-4-(4-*t*-butylphenoxy)aniline was used directly for further transformation.

A solution of 2-*n*-butylamino-4-(4-*t*-butylphenoxy)aniline (130 mg, 0.4 mmol) and 2,4-bis(3-diethylaminopropoxy)benzaldehyde obtained above (110 mg, 0.3 mmol) in MeOH (10 mL) was refluxed until the reaction was complete. The solvent was removed *in vacuo* and the residue was purified by silica gel column chromatography, eluting with 10% MeOH in DCM with a gradual increment of Et₃N (0.5 to 1%), to afford the desired benzimidazole (100 mg).

MS m/z 657 (M+H)⁺

¹H NMR (400 MHz, CDCl₃) of HCl salt of the benzimidazole: δ 0.80 (t, 3H), 1.19 (m, 2H), 1.26 (t, 6H), 1.32 (s, 9H), 1.41 (t, 6H), 1.74 (m, 2H), 2.44 (m, 4H), 3.12-3.39 (m, 12H), 4.21 (t, 2H), 4.29 (m, 4H), 6.68 (br d, 1H), 6.79 (br s, 1H), 6.98 (d, 2H), 7.17 (d, 1H), 7.22 (dd, 1H), 7.35 (d, 1H), 7.40 (d, 2H), 8.06 (d, 1H), 11.4 (br, N.HCl), 11.9 (br, N.HCl) ppm.

Example 256

(3-{2-[1-butyl-6-(3-diethylamino-propoxy)-1H-benzimidazol-2-yl]-5-[2-(4-chloro-phenyl)-ethoxy]-phenoxy}-propyl)-diethylamine

A solution of 2-(3-diethylaminopropoxy)-4-[2-(4-chlorophenyl)ethoxy]benzaldehyde (synthesized via General Procedures D1 and D2) (429 mg; 1.1 mmol) and 2-(*n*-butylamino)-4-(3-diethylaminopropoxy)aniline (synthesized via General Procedures G1 and G2 and I) (293 mg; 1 mmol) in ethanol (5 mL) was heated to reflux following General Procedure K. The crude product was purified by silica gel column chromatography using 10% MeOH in DCM with a gradual increment of triethylamine (0.2 to 1.0%) as eluent to afford of (3-{2-[1-butyl-6-(3-diethylamino-propoxy)-1H-benzimidazol-2-yl]-5-[2-(4-chloro-phenyl)-ethoxy]-phenoxy}-propyl)-diethylamine (430 mg).

MS m/z 663 (M+H)⁺

Example 257

(3-{1-butyl-6-(4-*tert*-butyl-phenoxy)-2-[4-(3-diethylamino-propoxy)-phenyl]-1H-benzimidazol-4-yloxy}propyl)-diethyl-amine

To a stirred solution of 4-hydroxybenzaldehyde (20 mmol) in DMSO (80 mL) at rt, solid Cs₂CO₃ (50 mmol) was added. The mesylate prepared from 3-diethylamino-1-propanol and methanesulfonyl chloride, General Procedure P2 (30 mmol) was added to the reaction

mixture and heated to 90 °C until the reaction was complete. After cooling to rt, the reaction was quenched by cold H₂O (100 mL), and the resulting mixture was extracted with EtOAc (3×100 mL). The combined EtOAc extracts were washed with brine (3X50 mL) and dried (anhydrous Na₂SO₄). The solvent was removed *in vacuo*, and the crude product was purified by silica gel column chromatography (eluting with 10% MeOH in DCM + 0.5% Et₃N) to afford 4-(3-diethylaminopropoxy)benzaldehyde.

To a stirred solution of 6-(3-diethylaminopropoxy)-2,4-difluoronitrobenzene (11 mmol) and triethylamine (22 mmol) in DMF (20 mL), a solution of *n*-butylamine (11 mmol) in DMF (8 mL) was added dropwise at rt, and the mixture was stirred at rt for 10h. The reaction was quenched by cold H₂O (50 mL), and the resulting mixture was extracted with EtOAc (3×100 mL). The combined EtOAc extracts were washed with brine (3X50 mL) and dried (anhydrous Na₂SO₄). The solvent was removed *in vacuo* to afford the desired 2-*n*-butylamino-6-(3-diethylaminopropoxy)-4-fluoronitrobenzene which was used for further transformation.

A mixture of 2-*n*-butylamino-6-(3-diethylaminopropoxy)-4-fluoronitrobenzene obtained above (3 mmol), 4-*t*-butylphenol (4 mmol), solid K₂CO₃ (9 mmol) and DMF (15 mL) was heated with stirring at 90°C for 15h. The reaction was quenched by cold H₂O (30 mL), and the resulting mixture was extracted with EtOAc (3×100 mL). The combined EtOAc extracts were washed with brine (2X50 mL) and dried (anhydrous Na₂SO₄). The solvent was removed *in vacuo*, and the crude products were purified by silica gel column chromatography (eluting with 10% MeOH in DCM), giving 2-*n*-butylamino-4-(4-*t*-butylphenoxy)-6-(3-diethylaminopropoxy)nitrobenzene.

The nitro intermediate (1 mmol) obtained above was dissolved in MeOH (10 mL) and hydrogenated in the presence of 10% Pd/C (40 mg) until completion as indicated by LC-MS (~4h). The reaction mixture was then filtered to remove the catalyst. The MeOH solution containing 2-*n*-butylamino-4-(4-*t*-butylphenoxy)-6-(3-diethylaminopropoxy)aniline was used directly for further transformation.

A solution of 2-*n*-butylamino-4-(4-*t*-butylphenoxy)-6-(3-diethylaminopropoxy)-aniline (90 mg, 0.2 mmol) and 4-(3-diethylaminopropoxy)benzaldehyde obtained above (65 mg, 0.25 mmol) in MeOH (10 mL) was refluxed until the reaction was complete as indicated by LC-MS (~10h). The solvent was removed *in vacuo* and the residue was purified by silica gel column chromatography, eluting with 10% MeOH in DCM with a gradual increment of Et₃N (0.5 to 1%), to afford the desired benzimidazole (80 mg).
MS m/z 657 (M+H)⁺

¹H NMR (400 MHz, CDCl₃) of HCl salt of the benzimidazole: δ 0.80 (t, 3H), 1.21 (m, 2H), 1.31 (s, 9H), 1.40 (m, 12H), 1.74 (m, 2H), 2.39 (m, 2H), 2.52 (m, 2H), 3.17-3.27 (m, 12H), 3.80 (m, 2H), 4.18 (m, 4H), 6.60 (br s, 1H), 6.62 (br s, 1H), 6.95 (d, 2H), 7.14 (br, 2H), 7.39 (d, 1H), 7.80 (br, 2H), 11.17 (br, N.HCl), 11.83 (br, N.HCl) ppm.

5

Example 258

2-{2,4-bis-[2-(1-methyl-pyrrolidin-2-yl)-ethoxy]-phenyl}-1-butyl-6-(4-tert-butyl-phenoxy)-1H-benzimidazole

10 A solution of 2-*n*-butylamino-4-(4-*t*-butylphenoxy)aniline (synthesized via General Procedures J3 –J7) (100 mg, 0.3 mmol) and 2,4-bis[2-(1-methyl-2-pyrrolidin-2-yl)-ethoxy]benzaldehyde (synthesized via General Procedure C) (55mg, 0.15 mmol) in MeOH (10 mL) was subjected to General Procedure K. The solvent was removed *in vacuo* and the residue was purified by silica gel column chromatography, eluting with 10% MeOH in DCM with a gradual increment of Et₃N (0.5 to 1%), to afford the desired benzimidazole (50 mg).
15 MS m/z 653 (M+H)⁺

¹H NMR (400 MHz, CDCl₃): δ 0.73 (t, 3H), 1.10-2.53 (m, 22H), 1.32 (s, 9H), 2.20 (s, 3H), 2.39 (s, 3H), 3.94-3.99 (m, 6H), 6.50 (m, 2H), 6.92 (d, 2H), 6.98 (m, 1H), 7.05 (d, 1H), 7.32 (d, 2H), 7.42 (d, 1H), 7.70 (d, 1H) ppm.

20

Example 259

2-[2,4-bis-(2-pyrrolidin-1-yl)-ethoxy]-phenyl]-1-butyl-6-(4-butyl-phenoxy)-1H-benzimidazole

25 A solution of 2-*n*-butylamino-4-(4-*n*-butylphenoxy)aniline (synthesized via General Procedures G1 and G2 and I) (80 mg, 0.25 mmol) and 2,4-bis(2-pyrrolidin-1-yl-ethoxy)benzaldehyde (synthesized via General Procedure C) (50 mg, 0.15 mmol) was subjected to General procedure K. The solvent was removed *in vacuo* and the residue was purified by silica gel column chromatography, eluting with 10% MeOH in DCM with a gradual increment of Et₃N (0.5 to 1%), to afford the desired benzimidazole (80 mg).

30 MS m/z 625 (M+H)⁺

¹H NMR (400 MHz, CDCl₃): δ 0.73 (t, 3H), 0.92 (t, 3H), 1.10 (m, 2H), 1.35 (m, 2H), 1.55-1.60 (m, 4H), 1.64 (m, 4H), 1.83 (m, 4H), 2.39 (m, 4H), 2.58 (t, 2H), 2.65 (m, 4H), 2.73 (t, 2H), 2.93 (t, 2H), 3.96 (t, 2H), 4.07 (t, 2H), 4.16 (t, 2H), 6.60 (br s, 1H), 6.62 (dd, 1H), 6.92 (d, 2H), 6.96 (dd, 1H), 7.04 (d, 1H), 7.12 (d, 2H), 7.40 (d, 1H), 7.70 (d, 1H) ppm.

35

The following Examples were synthesized according to the Methods employed for Examples 255-259;

Example	Name
260	1-butyl-2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(2-pyrrolodin-1-yl-ethoxy)-phenyl]-6-(2-pyrrolodin-1-yl-ethoxy)-1H-benzoimidazole
261	{3-[2-[1-butyl-6-[2-(4-chloro-phenyl)-ethoxy]-1H-benzimidazol-2-yl]-5-(3-diethylamino-propoxy)-phenoxy]-propyl}-diethyl-amine
262	2-{2,4-bis-[2-(1-methyl-pyrrolidin-2-yl)-ethoxy]-phenyl}-1-butyl-6-(4-butyl-phenoxy)-1H-benzoimidazole
263	{3-[2-[1-butyl-5-(4-tert-butyl-phenoxy)-1H-benzimidazol-1-yl]-5-(3-diethylamino-propoxy)-phenoxy]-propyl}-diethyl-amine
264	1-Butyl-2-[3-(3,5-dichloro-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole
265	2-[2,4-bis-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1-butyl-6-(4-cyclopentyl-phenoxy)-1H-benzoimidazole
266	2-{2,4-bis-[2-(1-methyl-pyrrolidin-2-yl)-ethoxy]-phenyl}-1-butyl-6-(4-cyclopentyl-phenoxy)-1H-benzoimidazole
267	{3-[2-[1-butyl-6-(4-iospropyl-phenoxy)-1H-benzimidazol-2-yl]-5-(3-diethylamino-propoxy)-phenoxy]-propyl}-diethyl-amine
268	(2-{1-butyl-6-(2-dimethylamino-ethylsulfanyl)-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1H-benzoimidazol-4-ylsulfanyl}-ethyl)-dimethyl-amine
269	2-[2,4-bis-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1-butyl-6-(4-tert-butyl-phenoxy)-1H-benzimidazole
270	{3-[2-[1-butyl-6-(4-butyl-phenoxy)-1H-benzimidazol-2-yl]-5-(3-diethylamino-propoxy)-phenoxy]-propyl}-diethyl-amine
271	{3-[2-[1-butyl-6-(4-fluoro-3-trifluoromethyl-phenoxy)-1H-benzimidazol-2-yl]-5-(3-diethylamino-propoxy)-phenoxy]-propyl}-diethyl-amine
272	2-[2,4-bis-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1-butyl-6-(4-isopropyl-phenoxy)-1H-benzoimidazole
273	1-Butyl-2-[3-(3,4-dichloro-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole
274	(3-{3-Butyl-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-3H-benzoimidazol-5-yloxy}-propyl)-diethyl-amine
275	{3-[2-[1-butyl-6-(4-cyclopentyl-phenoxy)-1H-benzimidazol-2-yl]-5-(3-diethylamino-propoxy)-phenoxy]-propyl}-diethyl-amine
276	{3-[2-[1-butyl-4-(4-tert-butyl-phenoxy)-1H-benzimidazol-2-yl]-5-(3-diethylamino-propoxy)-phenoxy]-propyl}-diethyl-amine
277	2-{2,4-bis-[2-(1-methyl-pyrrolidin-2-yl)-ethoxy]-phenyl}-1-butyl-6-(4-isopropyl-phenoxy)-1H-benzoimidazole
278	(3-{5-[2-(4-chloro-phenyl)-ethoxy]-2-[6-(3-diethylamino-propoxy)-1-isopropyl-1H-benzimidazol-2-yl]-phenoxy}-propyl)-diethyl-amine

Example	Name
279	1-Butyl-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole
280	1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-4,6-bis-(1-methyl-piperidin-4-yloxy)-1H-benzimidazole
281	{3-[2-[6-(4-tert-butyl-phenoxy)-1H-benzimidazol-2-yl]-5-(3-diethylamino-propoxy)-phenoxy]-propyl}-diethyl-amine
282	1-butyl-2-[3-(3,4-dichloro-phenoxy)-phenyl]-4,6-bis-(1-methyl-pyrrolidin-2-ylmethoxy)-1H-benzoimidazole
283	(3-{3-butyl-2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(2-diethylamino-ethoxy)-phenyl]-3H-benzimidazol-5-yloxy}-propyl)-diethyl-amine
284	(3-{2-[1-Butyl-6-(2-imidazol-1-yl-ethoxy)-1H-benzoimidazol-2-yl]-5-[2-(4-chloro-phenyl)-ethoxy]-phenoxy}-propyl)-diethyl-amine
285	(3-{2-[1-Butyl-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazol-2-yl]-5-[2-(4-chloro-phenyl)-ethoxy]-phenoxy}-propyl)-diethyl-amine
286	{3-[2-(3,5-bis-benzyloxy-phenyl)-3-butyl-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
287	4,6-bis-(2-azepan-1-yl-ethoxy)-1-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-1H-benzoimidazole
288	1-butyl-2-[3-(4-butyl-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole
289	1-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-4,6-bis-(1-methyl-pyrrolidin-2-ylmethoxy)-1H-benzoimidazole
290	(2-{1-butyl-6-(2-dimethylamino-ethylsulfanyl)-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzoimidazole-4-ylsufanyl}-ethyl)-dimethyl-amine
291	(3-{1-butyl-6-(3-diethylamino-propoxy)-2-[4-(4-isopropyl-phenoxy)-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine
292	4,6-bis-(2-azepan-1-yl-ethoxy)-1-butyl-2-[3-(3,5-dichlorophenoxy)-phenyl]-1H-benzoimidazole
293	1-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-4,6-bis-[2-(cyclohexyl-methyl-amino)-ethoxy]-1H-benzoimidazole
294	{3-[1-butyl-2-[3-(3,5-dichloro-phenoxy)-phenyl]-6-(2-imidazol-1-yl-ethoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
295	[3-(2-{3,4-bis-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-3-butyl-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
296	1-butyl-4,6-bis-(1-methyl-piperidin-4-yloxy)-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzoimidazole
297	4,6-bis-(2-azepan-1-yl-ethoxy)-1-butyl-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzoimidazole
298	1-butyl-2-[3-(3,4-dichloro-phenoxy)-phenyl]-4,6-bis-(1-ethyl-pyrrolidin-2-ylmethoxy)-1H-benzoimidazole
299	[3-(2-{2-benzyloxy-4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-3-butyl-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine

Example	Name
300	{3-[2-[1-Butyl-6-(3-diethylamino-propoxy)-1H-benzoimidazol-2-yl]-5-(4-fluoro-3-trifluoromethyl-phenoxy)-phenoxy]-propyl}-diethyl-amine
301	{3-[2-[1-Butyl-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazol-2-yl]-5-(4-fluoro-3-trifluoromethyl-phenoxy)-phenoxy]-propyl}-diethyl-amine
302	1-butyl-2-[3-(3,4-dimethoxy-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
303	(2-{1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(2-dimethylamino-ethylsulfanyl)-1H-benzoimidazol-4-ylsulfanyl}-ethyl)-dimethyl-amine
304	1-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-4,6-bis-(1-ethyl-pyrrolidin-3-yloxy)-1H-benzoimidazole
305	{3-[2-[3-(3,4-bis-benzyloxy-phenyl)-3-butyl-3H-benzimidazol-5-yloxy]-propyl]-diethyl-amine
306	(3-{5-[2-(4-chloro-phenyl)-ethoxy]-2-[6-(3-diethylamino-propoxy)-1H-benzimidazol-2-yl]-phenoxy}-propyl)-diethyl-amine
307	1-butyl-2-[4-(2-diethylamino-ethoxy)-phenyl]-4,6-bis-[2-(methyl-phenyl-amino)-ethoxy]-1H-benzimidazole
308	{3-[3-butyl-2-{4-[2-(4-chlorophenyl)-ethoxy]-phenyl}-7-(pyridin-3-yloxy)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
309	{2-[1-butyl-2-[3-(3,4-dichloro-phenoxy)-phenyl]-6-(2-diisopropylamino-ethoxy)-1H-benzimidazol-4-yloxy]-ethyl}-diethyl-amine
310	{3-[3-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-7-(pyridin-3-ylmethoxy)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
311	2-[1-butyl-6-(3-diethylamino-propoxy)-1H-benzoimidazol-2-yl]-5-[2-(4-chloro-phenyl)-ethoxy]-phenol
312	{3-[3-butyl-2-[2-(4-chloro-phenylsulfanyl)-phenyl]-7-(3-diethylamino-propoxy)-3H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
313	(3-{1-butyl-6-(3-diethylamino-propoxy)-2-[4-(4-fluoro-2-methoxy-phenoxy)-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine
314	[3-(3-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-2-isopropoxy-phenyl}-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
315	{2-[1-butyl-6-(3-diethylamino-propoxy)-1H-benzoimidazol-2-yl]-5-[2-(4-chloro-phenyl)-ethoxy]-phenoxy}-acetic acid methyl ester
316	(3-{2-[1-butyl-6-(4-tert-butyl-phenoxy)-1H-benzimidazol-2-yl]-5-[2-(4-chloro-phenyl)-ethoxy]-phenoxy}-propyl)-diethyl-amine
317	(3-{1-butyl-6-(3-diethylamino-propoxy)-2-[4-(2-isopropoxy-phenoxy)-phenyl]-1H-benzoimidazol-4-yloxy}-propyl)-diethyl-amine
318	(3-{1-butyl-6-(3-diethylamino-propoxy)-2-[4-(2,3-dimethoxy-phenoxy)-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine
319	(3-{3-Butyl-2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-3H-benzoimidazol-5-yloxy}-propyl)-diethyl-amine
320	(2-{1-butyl-6-fluoro-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzoimidazole-4-ylsufanyl}-ethyl)-dimethyl-amine

Example	Name
321	Methanesulfonic acid 5-[2-(4-chloro-phenyl)-ethoxy]-2-[6-(3-diethylamino-propoxy)-1H-benzimidazol-2-yl]-phenyl ester
322	5-[2-(4-Chloro-phenyl)-ethoxy]-2-[6-(3-diethylamino-propoxy)-1H-benzimidazol-2-yl]-phenol
323	{3-[1-butyl-6-(3-diethylamino-propoxy)-2-(4-pyrrolidin-1-yl-phenyl)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
324	1-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-4,6-bis-(1-methyl-piperidin-4-yloxy)-1H-benzimidazole
325	1-butyl-2-[3-(3,5-dichloro-phenoxy)-phenyl]-4,6-bis-(2-imidazol-1-yl-ethoxy)-1H-benzimidazole
326	[2-(1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-fluoro-1H-benzimidazol-4-ylsulfanyl)-ethyl]-dimethyl-amine

Example 327

{3-[1-Butyl-2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(2-(pyrrolidin-1-yl-ethoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine

4-[2-(4-chloro-phenyl)-ethoxy]-[2-(2-pyrrolidin-1-yl-ethoxy)-benzaldehyde (synthesized via General Procedures D1 and D2) (0.030g, 0.080mM) and N-butyl-3,5-bis (3-dimethylamino-propoxy) benzene-1,2-diamine (0.035g, 0.080mM) were subjected to General Procedure K. After removal of ethanol, the residue was purified on silica gel using 10%MeOH/DCM with 0.1-0.4%Et₃N, yield 0.025 g .LC/MS (m/z): 776 (M+H)⁺

Example 328

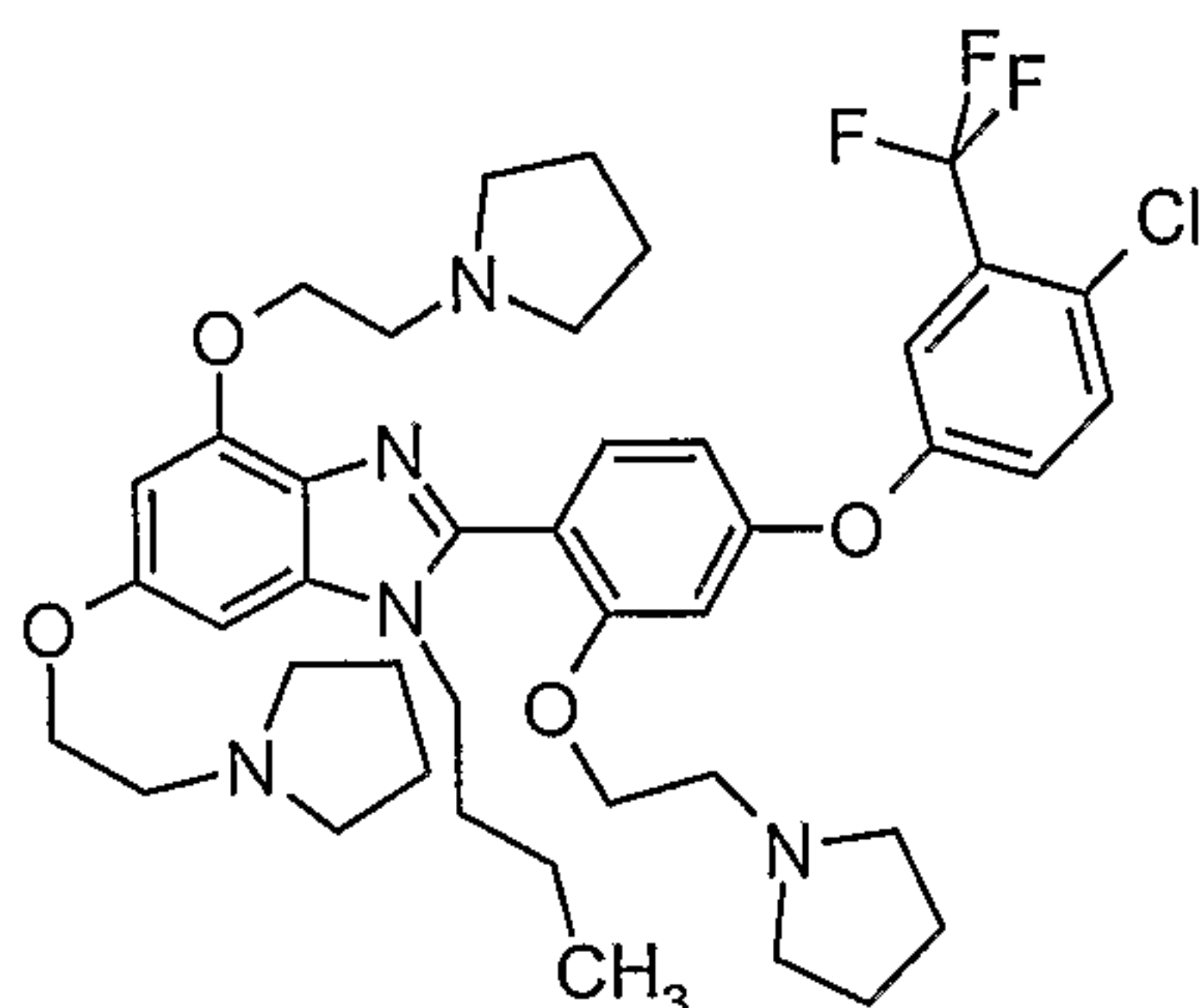
1-Butyl-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole

A solution of 2-butylamino-4,6-bis(2-pyrrolidinyl-1-ethoxy)aniline (synthesized via General Procedures G1 and G2 and H) (78.4mg, 0.2 mmol) and 2-pyrrolidin-1-yl-ethoxy-4-(4-fluoro-3-trifluoromethyl)phenoxybenzaldehyde (synthesized via General Procedure E) (91mg, 0.22 mmol) was subjected to General Procedure K. The crude product was purified by silica gel column chromatography using 10% MeOH in DCM with a gradual increment of triethylamine (0.2 to 1.0%) as eluent to afford Example 328 (62mg).

MS m/z 768 (M+H)⁺.

Example 329

1-Butyl-2-[4-(4-Chloro-3-trifluoromethyl-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole



- 5 A solution of 2-butylamino-4,6-bis(2-pyrrolidinyl-1-ethoxy)aniline (synthesized via General Procedures G1 and G2 and H) (78.4mg, 0.2 mmol) and 2-pyrrolidin-1-yl-ethoxy-4-(4-chloro-3-trifluoromethyl)phenoxybenzaldehyde (synthesized via General Procedure E) (91mg, 0.22 mmol) in ethanol (2 mL) was subjected to General Procedure K. The crude product was purified by silica gel column chromatography using 10% MeOH in DCM with a gradual increment of triethylamine (0.2 to 1.0%) as eluent to afford Example 329 (62.5mg)
- 10 MS m/z 784 (M+H)⁺

Example 330

- 15 (3-{2-[1-butyl-6-(3-diethylamino-propoxy)-4-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazol-2-yl]-5-[2-(4-chloro-phenyl)-ethoxy]-phenoxy}-propyl)-diethyl-amine

- A solution of 2-(3-diethylaminopropoxy)-4-[2-(4-chlorophenyl)ethoxy]benzaldehyde (synthesized via General Procedure E) (858; 2.2 mmol) and 2-(n-butylamino)-4-(N,N-diethylaminopropoxy)-6-(N-pyrrolidineethoxy)aniline (synthesized via General Procedures J3-J7) (816 mg; 2mmol) in ethanol (5 mL) was subjected to General Procedure K. The crude product was purified by silica gel column chromatography using 10% MeOH in DCM with a gradual increment of triethylamine (0.2 to 1.0%) as eluent to afford 520 mg (34%) of Example 330.
- 20
- 25 MS m/z 776 (M+H)⁺

Example 331

(3-{2-[1-butyl-4,6-bis-(3-diethylamino-propoxy)-1H-benzimidazol-2-yl]-5-[2-(4-chloro-phenyl)-ethoxy]-phenoxy}-propyl)-diethyl-amine

To a stirred solution of 2-(4-chlorophenyl)ethanol (20.0 mL, 148 mmol), TEA (31.0 mL, 222 mmol) in anhydrous DCM (100 mL) was added dropwise MsCl (12.0 mL, 156 mmol) at 0°C within 8 min, and stirred at the same temperature for 2h. The resulting yellow suspension
5 was diluted with DCM (200 mL), washed with cold H₂O and brine, and dried. Removal of the solvent afforded the mesylate (33.0g).

A mixture of the mesylate obtained as above (23.6 g, 100 mmol), 2,4-dihydroxybenzaldehyde (16.6g, 120 mmol) and KHCO₃ (12.0g, 120 mmol) in anhydrous
10 DMF (150 mL) was heated at 130°C for 4h following the general procedure described for disubstituted benzaldehydes. The crude products were purified by flash chromatography (eluting with 10% EtOAc in hexanes), giving 4-(4-chlorophenyl)ethoxysalicylaldehyde (12.5g) as a white solid.

Methanesulfonyl chloride, General Procedure P2 (2.90 mL, 37.5 mmol) was added dropwise
15 at 0°C to a stirred solution of 3-diethylaminopropanol (5.75 mL, 38.8 mmol), TEA (7.0 mL, 50.0 mmol) in anhydrous DCM (25 mL), and the mixture was stirred at the same temperature for 1h, and at rt for an additional 1h. After the removal of the solvent in vacuo, the solid residue was mixed with the aldehyde formed above (7.0g, 25.0 mmol), Cs₂CO₃ (20.4g, 62.5
20 mmol) and anhydrous DMSO (100 mL), and the whole mixture was heated at 90°C for 6h. following the general procedure described for disubstituted benzaldehydes to obtain oily 2-(3-diethylaminopropoxy)-4-[2-(4-chlorophenyl)ethoxy]benzaldehyde (11.0g, ~100% yield), which solidified upon standing.

To a stirred solution of 2,4,6-trifluoronitrobenzene (5.31g, 30 mmol), TEA (8.37 mL, 60
25 mmol) and DMF (50 mL) was added dropwise a solution of n-butylamine (2.96 mL, 30 mmol) in DMF (20 mL) at rt following General Procedure G1 to obtain crude 2-butylamino-4,6-difluoronitrobenzene (9.0g). This product was mixed with 3-diethylaminopropanol (11.1 mL, 75 mmol) and anhydrous THF (150 mL), and then powdered KOBu^t (8.5g, 75 mmol) was
30 added following General Procedure G2 to afford crude 2-butylamino-4,6-di(3-diethylaminopropoxy)nitrobenzene (15.5g).

The nitro compound formed above (6.8g, 15 mmol) dissolved in MeOH (90 mL) was
35 hydrogenated following general procedure H and 2-butylamino-4,6-di(3-diethylaminopropoxy)aniline obtained was used directly for the next step.

Example 331 was formed employing phenylenediamine formed above (848 mg; 2 mmol) and 2-(3-diethylaminopropoxy)-4-[2-(4-chlorophenyl)ethoxy]benzaldehyde (858; 2.2 mmol) in ethanol (5 mL) following the general procedure K. The crude product was purified by silica gel column chromatography using 10% MeOH in DCM with a gradual increment of triethylamine (0.2 to 1.0%) to afford 400 mg of Example 331.

MS m/z 792 (M+H)⁺

Example 332

(3-{2-[1-Butyl-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazol-2-yl]-5-[2-(4-chlorophenyl)-ethoxy]-phenoxy}-propyl)-diethyl-amine

2-butylamino-4,6-difluoronitrobenzene (9.0g) was mixed with 1-pyrrolidineethanol (8.81 mL, 75 mmol) and anhydrous THF (150 mL), and then powdered KOBu^t (8.5g, 75 mmol) was added following general procedures G1 and G2 described for homo disubstituted phenylenediamine to afford crude 2-butylamino-4,6-di(pyrrolidineethoxy)nitrobenzene (13.5g).

The nitro compound formed above (6.3 g, 15 mmol) dissolved in MeOH (90 mL) was hydrogenated following general procedure H and 2-butylamino-4,6-di(pyrrolidineethoxy)aniline obtained was used directly for the next step.

Example 332 was formed employing phenylenediamine formed above (784 mg; 2 mmol) and 2-(3-diethylaminopropoxy)-4-[2-(4-chlorophenyl)ethoxy]benzaldehyde (858; 2.2 mmol) in ethanol (5 mL) following the general procedure K. The crude product was purified by silica gel column chromatography using 10% MeOH in DCM with a gradual increment of triethylamine (0.2 to 1.0%) as eluent to afford 380 mg of Example 332.

MS m/z 760 (M+H)⁺

Example 333

(3-{1-Butyl-6-(3-diethylamino-propoxy)-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1H-benzoimidazol-4-yloxy}-propyl)-diethyl-amine

A solution of 2,4-difluorobenzaldehyde (2.13 g, 15.0 mmol) in DMF (10ml) was added dropwise to a precooled (0 °C) solution of sodium 2-pyrrolidinoethoxide in DMF (50 ml), which was made by stirring a mixture of sodium hydride (600 mg, 15.0 mmol, 60 % in mineral oil) and N-(2-hydroxyethyl)pyrrolidine (1.72 g, 15.0 mmol). The resulting reaction

mixture was warmed to rt and stirred for additional 3 h. To the same reaction flask was introduced potassium carbonate (2.10g, 15.0 mmol) and 3-fluoro-4-trifluoromethylphenol (2.7g, 15.0 mmol) and the reaction mixture was heated at 90 °C as described in the General Procedure E for 2-alkoxy-4-aryloxybenzaldehydes. The crude product was purified by silica gel column chromatography using dichloromethane and 5% methanol in dichloromethane as eluent, to give 2-(2-pyrrolidineethoxy)-4-(3-fluoro-4-trifluoromethyl)phenoxybenzaldehyde (2 g) as a brown oil.

MS m/z 399 (M+H)⁺

Example 333 was formed employing the aldehyde formed above (873 mg; 2.2 mmol) and 2-butylamino-4,6-di(3-diethylaminopropoxy)aniline (848; 2.0 mmol) following the general procedure K. The crude product was purified by silica gel column chromatography using 10% MeOH in DCM with a gradual increment of triethylamine (0.2 to 1.0%) as eluent to afford 390 mg of Example 333.

MS m/z 800 (M+H)⁺

Example 334

{3-[1-Butyl-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine

MsCl (1.4 mL, 18.0 mmol) was added dropwise at 0°C to a stirred solution of pyrrolidineethanol (1.90 mL, 16.0 mmol), TEA (2.8 mL, 20.0 mmol) in anhydrous DCM (20 mL), and the mixture was stirred at rt for 1h. After the removal of the solvent in vacuo, the solid residue was mixed with 3,5-difluoro-4-nitrophenol (1.75 g; 10 mmol) and K₂CO₃ (5.5 g; 40 mmol) following General Procedure F1. The product, 2,6-difluoro-4-(N-pyrrolidineethoxy)nitrobenzene (1.5 g) was used directly

To a stirred solution of 2,6-difluoro-4-(N-pyrrolidineethoxy)nitrobenzene obtained above (1.4 g; 5.1 mmol) and triethylamine (1.4 mL; 10.0 mmol) in DMF (10 mL), a solution of n-butylamine (505 µL; 5.1 mmol) in DMF (3 mL) was added according to General Procedure G1. The crude product, 2-(n-butylamino)-4-(N-pyrrolidineethoxy)-6-fluoronitrobenzene (1.5 g) was used for further transformation without any purification.

A solution of 3-diethylaminopropanol (652 μ L; 4.4 mmol) in anhydrous THF 4.4 mL was added with powdered KOBu^t (493 mg; 4.4 mmol) and stirred at rt for 5 min. This solution was added dropwise to a stirred solution of 2-(n-butylamino)-4-(N-pyrrolidineethoxy)-6-fluoronitrobenzene (1.32 g; 4.0 mmol) in anhydrous THF (10 mL) according to General Procedure G2. The crude product, 2-(n-butylamino)-4-(N-pyrrolidineethoxy)-6-(N,N-diethylaminopropoxy)nitrobenzene (1.5 g) was used directly.

The nitro compound formed above (1.31 g, 4 mmol) dissolved in MeOH (20 mL) was hydrogenated following general procedure H. The product obtained (1.15 g) was used directly for the next step.

Example 334 was formed employing phenylenediamine formed above (816 mg; 2 mmol) and 2-(2-pyrrolidineethoxy)-4-(3-fluoro-4-trifluoromethyl)phenoxybenzaldehyde (873 mg; 2.2 mmol) in ethanol (5 mL) following general procedure K. The crude product was purified by silica gel column chromatography using 10% MeOH in DCM with a gradual increment of triethylamine (0.2 to 1.0%) as eluent to afford 375 mg of Example 334.

MS m/z 784 (M+H)⁺

Example 335

{3-[2-[1-Butyl-6-(3-diethylamino-propoxy)-4-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazol-2-yl]-5-(4-fluoro-3-trifluoromethyl-phenoxy)-phenoxy]-propyl}-diethyl-amine

A solution of 2,4-difluorobenzaldehyde (2.13 g, 15.0 mmol) in DMF (10 mL) was added dropwise to a precooled (0 °C) solution of sodium 3-diethylaminopropoxide in DMF (50 mL), which was made by stirring a mixture of sodium hydride (600 mg, 15.0 mmol, 60 % in mineral oil) and 3-diethylaminopropanol (1.97 g, 15.0 mmol). The resulting reaction mixture was warmed to rt and stirred for additional 3 h. To the same reaction flask was introduced potassium carbonate (2.10 g, 15.0 mmol) and 3-fluoro-4-trifluoromethylphenol (2.7 g, 15.0 mmol) and the reaction mixture was heated at 90 °C as described general procedure E. The crude product was purified by silica gel column chromatography using dichloromethane and 5% methanol in dichloromethane as eluent, to give 2-(3-diethylaminopropoxy)-4-(3-fluoro-4-trifluoromethyl)phenoxybenzaldehyde (2.2 g).

Methanesulfonyl chloride (General Procedure P2) (1.55 mL, 20.0 mmol) was added dropwise at 0 °C to a stirred solution of 3-diethylaminopropanol (2.70 mL, 18.0 mmol), TEA (2.8 mL, 20.0 mmol) in anhydrous DCM (30 mL), and the mixture was stirred at rt for 1h. After the

removal of the solvent in vacuo, the solid residue was mixed with 3,5-difluoro-4-nitrophenol (2.65 g; 15 mmol) and K_2CO_3 (6.9 g; 50 mmol) according to General Procedure F1. The crude product, 2,6-difluoro-4-(3-diethylaminopropoxy)nitrobenzene (3.9 g) was used for further transformation.

5

To a stirred solution of 2,6-difluoro-4-(3-diethylaminopropoxy)nitrobenzene obtained above (1.9 g; 6.6 mmol) and triethylamine (1.4 mL; 10.0 mmol) in DMF (12 mL), a solution of n-butylamine (656 μ L; 6.6 mmol) in DMF (4 mL) was added dropwise at rt within 15 min, and the rest was followed as described in the general methods. The crude product, 2-(n-butylamino)-4-(3-diethylaminopropoxy)-6-fluoronitrobenzene (2.0 g) was used for further transformation without any purification.

10

A solution of 3-diethylaminopropanol (516 μ L; 4.4 mmol) in anhydrous THF 4.4 mL was added with powdered $KOBu^t$ (493 mg; 4.4 mmol) and stirred at roomtemperature for 5 min. This solution was added dropwise to a stirred solution of 2-(n-butylamino)-4-(3-diethylaminopropoxy)-6-fluoronitrobenzene (1.37 g; 4.0 mmol) in anhydrous THF (10 mL) at 0 °C under a N_2 stream. The reaction mixture was maintained at 0 °C for 1 h at which time the reaction was complete the rest was followed as described in the general methods. The crude product, 2-(n-butylamino)-4-(3-diethylaminopropoxy)-6-(N-pyrrolidineethoxy)nitrobenzene (1.6 g) was used for further transformation without any purification.

15

20

The nitro compound formed above (1.31 g, 4 mmol) dissolved in MeOH (20 mL) was hydrogenated following the general procedure and 2-(n-butylamino)-4-(N-pyrrolidineethoxy)-6-(N,N-diethylaminopropoxy)aniline (1.15 g) obtained was used directly for the next step reaction without further purification.

25

Example 335 was formed employing phenylenedimaine formed above (816 mg; 2 mmol) and 2-(3-diethylaminopropoxy)-4-(3-fluoro-4-trifluoromethyl)phenoxybenzaldehyde (910 mg; 2.2 mmol) in ethanol (5 mL) following the general procedure. The crude product was purified by silica gel column chromatography using 10% MeOH in DCM with a gradual increment of triethylamine (0.2 to 1.0%) as eluent to afford 380 mg of Example 335.

30

MS m/z 800 (M+H)⁺

35

Example 336

{3-[2-[1-Butyl-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazol-2-yl]-5-(4-fluoro-3-trifluoromethyl-phenoxy)-phenoxy]-propyl}-diethyl-amine

A solution of 2,4-difluorobenzaldehyde (2.13 g, 15.0 mmol) in DMF (10ml) was added dropwise to a precooled (0 °C) solution of sodium 3-dimethylaminopropoxide in DMF (50 ml), which was made by stirring a mixture of sodium hydride (600 mg, 15.0 mmol, 60 % in mineral oil) and 3-dimethylaminopropanol (1.55g, 15.0 mmol). The resulting reaction mixture was warmed to rt and stirred for additional 3 h. To the same reaction flask was introduced potassium carbonate (2.10g, 15.0 mmol) and 3-fluoro-4-trifluoromethylphenol (2.7g, 15.0 mmol) and the reaction mixture was heated at 90 °C as described in General Procedure E for 2-alkoxy-4-aryloxybenzaldehydes. The crude product was purified by silica gel column chromatography using dichloromethane and 5% methanol in dichloromethane as eluent, to give 2-(3-dimethylaminopropoxy)-4-(3-fluoro-4-trifluoromethyl)phenoxybenzaldehyde (2.0 g).

Example 336 was formed employing the aldehyde formed above (823 mg; 2.2 mmol) and 2-butylamino-4,6-di(pyrrolidineethoxy)aniline (784; 2.0 mmol) in ethanol (5 mL) following General Procedure K. The crude product was purified by silica gel column chromatography using 10% MeOH in DCM with a gradual increment of triethylamine (0.2 to 1.0%) as eluent to afford 380 mg of Example 336.

MS m/z 784 (M+H)⁺

Example 337

{3-[3-butyl-2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-7-(2-pyrrolidin-1-yl-ethoxy)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine

A solution of 2,4-difluorobenzaldehyde (2.13 g, 15.0 mmol) in DMF (10ml) was added dropwise to a precooled (0 °C) solution of sodium 3-dimethylaminopropoxide in DMF (50 ml), which was made by stirring a mixture of sodium hydride (600 mg, 15.0 mmol, 60 % in mineral oil) and 3-dimethylaminopropanol (1.55g, 15.0 mmol). The resulting reaction mixture was warmed to rt and stirred for additional 3 h. To the same reaction flask was introduced potassium carbonate (2.10g, 15.0 mmol) and 3-fluoro-4-trifluoromethylphenol (2.7g, 15.0 mmol) and the reaction mixture was heated at 90 °C as described in General Procedure E for 2-alkoxy-4-aryloxybenzaldehydes. The crude product was purified by silica gel column chromatography using dichloromethane and 5% methanol in dichloromethane as eluent, to give 2-(3-dimethylaminopropoxy)-4-(3-fluoro-4-trifluoromethyl)phenoxybenzaldehyde (2.0 g).

Example 337 was formed employing the aldehyde formed above (823 mg; 2.2 mmol) and 2-butylamino-4,6-di(pyrrolidineethoxy)aniline (784; 2.0 mmol) in ethanol (5 mL) following General Procedure K. The crude product was purified by silica gel column chromatography using 10% MeOH in DCM with a gradual increment of triethylamine (0.2 to 1.0%) as eluent to afford 380 mg of Example 337.

MS m/z 759 (M+H)⁺

Example 338

(3-{2-[1-Butyl-4-(3-diethylamino-propoxy)-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazol-2-yl]-5-[2-(4-chloro-phenyl)-ethoxy]-phenoxy}-propyl)-diethyl-amine

2-(3-diethylaminopropoxy)-4-[2-(4-chlorophenyl)ethoxy]benzaldehyde (858; 2.2 mmol) and 2-(n-butylamino)-4-(N-pyrrolidineethoxy)-6-(N,N-diethylaminopropoxy)aniline (816 mg; 2mmol) were condensed to form the benzimidazole following General Procedure K. The crude product was purified by silica gel column chromatography using 10% MeOH in DCM with a gradual increment of triethylamine (0.2 to 1.0%) as eluent to afford 390 mg of Example 338.

MS m/z 776 (M+H)⁺

The following Examples were synthesized according to the Methods employed for Examples 327-338;

Example	Name
339	{3-[1-butyl-2-[4-(3,4-dichloro-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
340	{3-[2-[2,4-bis-(3-diethylamino-propoxy)-phenyl]-1-butyl-6-(4-tert-butyl-phenoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
341	{3-[1-butyl-2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(pyridin-2-ylmethoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yl]-phenyl}-diethyl-amine
342	{3-[2-[4-[2-(4-Chloro-phenyl)-ethoxy]-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
343	1-Butyl-2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole
344	{3-[1-Butyl-2-[4-(4-chloro-3-trifluoromethyl-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine

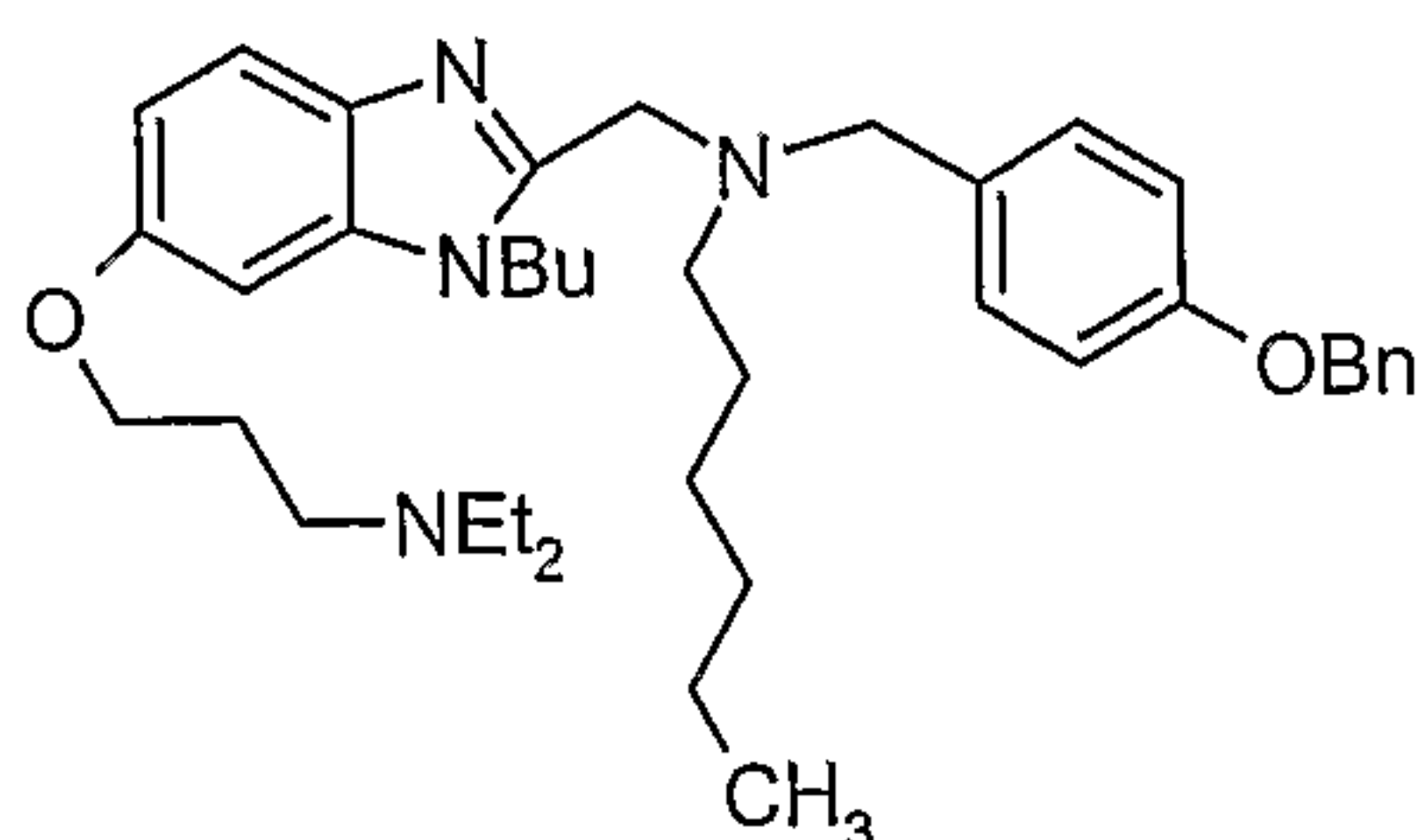
Example	Name
345	(3-{6-(3-Diethylamino-propoxy)-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1H-benzoimidazol-4-yloxy}-propyl)-diethyl-amine
346	{3-[2-[1-Butyl-4-(3-diethylamino-propoxy)-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazol-2-yl]-5-(4-fluoro-3-trifluoromethyl-phenoxy)-phenoxy]-propyl}-diethyl-amine
347	{3-[3-Butyl-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-7-(2-pyrrolidin-1-yl-ethoxy)-3H-benzoimidazol-5-yloxy]-propyl}-diethyl-amine
348	{3-[1-butyl-2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
349	{3-[2-[1-butyl-4,6-bis-(2-pyrrolodin-1-yl-ethoxy)-1H-benzimidazol-2-yl]-5-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-propyl}-diethyl-amine
350	{3-[1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-3-diethylaminomethyl-phenyl}-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
351	{3-[2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(pyridin-2-ylmethoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yl]-propyl}-diethyl-amine
352	3-(7-Butoxy-3-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-2-cyclopentylmethoxy-phenyl}-3H-benzoimidazol-5-yloxy)-propan-1-ol
353	3-(7-Butoxy-2-{4-[2-(4-chloro-phenyl)-ethoxy]-2-cyclopentylmethoxy-phenyl}-3H-benzoimidazol-5-yloxy)-propan-1-ol
354	(3-{1-Butyl-6-(3-diethylamino-propoxy)-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-2-(pyridin-2-ylmethoxy)-phenyl]-1H-benzoimidazol-4-yloxy}-propyl)-diethyl-amine
355	{3-[2-[1-Butyl-4,6-bis-(3-diethylamino-propoxy)-1H-benzoimidazol-2-yl]-5-(4-fluoro-3-trifluoromethyl-phenoxy)-phenoxy]-propyl}-diethyl-amine
356	2-(3,5-bis-benzyloxy-phenyl)-1-butyl-4,6-bis-(2-pyrrolodin-1-yl-ethoxy)-1H-benzimidazole
357	{3-[2-[1-butyl-4,6-bis-(3-diethylamino-propoxy)-1H-benzimidazol-2-yl]-5-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-propyl}-diethyl-amine
358	1-butyl-2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(2-pyrrol-1-yl-ethoxy)-phenyl]-4,6-bis-(2-pyrrolodin-1-yl-ethoxy)-1H-benzoimidazole
359	{3-[2-{4-[2-(4-chloro-phenyl)-ethoxy]-2-(3-diethylamino-propoxy)-phenyl}-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
360	{3-[1-Butyl-2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(pyridin-3-ylmethoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
361	(3-{3-Butyl-2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(3-diethylamino-propoxy)-phenyl]-7-isopropoxy-3H-benzoimidazol-5-yloxy}-propyl)-diethyl-amine
362	{3-[1-Butyl-2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(pyridin-4-ylmethoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-

Example	Name
	diethyl-amine
363	{3-[2-[4-[2-(4-Chloro-phenyl)-ethoxy]-2-(pyridin-4-ylmethoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
364	1-Butyl-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-2-(pyridin-2-ylmethoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
365	2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,7-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
366	{3-[1-Butyl-2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-methoxy-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
367	{3-[2-[4-[2-(4-Chloro-phenyl)-ethoxy]-2-methoxy-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
368	(3-{1-Butyl-2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(3-diethylamino-propoxy)-phenyl]-6-isopropoxy-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine
369	{3-[1-Butyl-2-[4-(4-chloro-3-methyl-phenoxy)-2-(pyridin-2-ylmethoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
370	1-Butyl-2-[4-(4-chloro-3-trifluoromethyl-phenoxy)-2-cyclopentylmethoxy-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
371	(2-{1-butyl-6-(2-dimethylamino-ethoxy)-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1H-benzimidazole-4-yloxy}-ethyl)-dimethyl-amine
372	2-[1-butyl-4,6-bis-(3-diethylamino-propoxy)-1H-benzimidazol-2-yl]-5-[2-(4-chloro-phenyl)-ethoxy]-phenol
373	1-Butyl-2-[4-(4-chloro-3-methyl-phenoxy)-2-(pyridin-2-ylmethoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
374	2-[4-(4-Chloro-3-trifluoromethyl-phenoxy)-2-cyclopentylmethoxy-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
375	2-[4-(4-Fluoro-3-trifluoromethyl-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
376	{3-[2-(3,5-bis-benzyloxy-phenyl)-1-butyl-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
377	(3-{1-butyl-6-(3-dimethylamino-propoxy)-2-[4-(3-fluoro-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1H-benzimidazole-4-yloxy}-propyl)-diethyl-amine
378	{3-[2-{1-butyl-4-(4-chloro-benzyloxy)-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazol-2-yl]-5-[2-(4-chloro-phenyl)-ethoxy]-phenoxy}-propyl)-diethyl-amine
379	{3-[2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(3-diethylamino-propoxy)-phenyl]-6-(3-diethylamino-propoxy)-3H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
380	{3-[2-[4-(3,4-dichloro-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine

Example	Name
381	{3-[1-Butyl-2-[4-(4-chloro-3-trifluoromethyl-phenoxy)-2-cyclopentylmethoxy-phenyl]-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
382	{3-[2-[4-(4-chloro-3-trifluoromethyl-phenoxy)-2-cyclopentylmethoxy-phenyl]-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
383	(3-{1-butyl-6-(4-tert-butyl-phenoxy)-2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(3-diethylamino-propoxy)-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine
384	2-{2,4-bis-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-1-butyl-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
385	(2-{1-butyl-6-(2-dimethylamino-ethoxy)-2-[4-(3-fluoro-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1H-benzoimidazole-4-yloxy}-ethyl)-dimethyl-amine
386	{3-[2-[4-(3,5-bis-trifluoromethyl-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1-butyl-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
387	{3-[1-butyl-2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
388	(3-{2-(1-Butyl-4,6-diisopropoxy-1H-benzoimidazol-2-yl)-5-[2-(4-chloro-phenyl)-ethoxy]-phenoxy}-propyl)-diethyl-amine
389	{3-[1-butyl-2-{3-[2-(4-chloro-phenyl)-ethoxy]-4-diethylaminomethyl-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
390	(3-{1-Butyl-6-(3-diethylamino-propoxy)-2-[4-fluoro-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1H-benzoimidazol-4-yloxy}-propyl)-diethyl-amine
391	(2-{1-butyl-6-fluoro-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1H-benzoimidazol-4-ylsulfanyl}-ethyl)-dimethyl-amine
392	{3-[1-Butyl-2-[4-[2-(4-chloro-phenyl)-ethoxy]-3-(3-diethylamino-propoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine

Example 393

- 5 (4-benzyloxy-benzyl)-[1-butyl-6-(3-diethylaminopropoxy)-1-H-benzimidazol-2-ylmethyl]-hexyl-amine



To 2-butylamino-4-(3-diethylaminopropoxy)aniline (3.44 g; 11.7 mmol) and BOC-glycine (2.46 g, 14.1 mmol) in DCM (20 mL) was added DCC (2.90 g, 14.1 mmol) and the reaction mixture was stirred for 4 h. The solid was removed by filtration and the filtrate was concentrated to afford the desired product. The crude product was used for further transformation without any purification.

To the product (11.7 mmol) obtained above in dioxane (7.5 mL) was added acetic acid (2.5 mL) and the reaction mixture was heated at 80 °C until the reaction was complete. Saturated sodium bicarbonate was added and the mixture was extracted with EtOAc. The combined organic layer was washed with water and brine, dried over sodium sulfate. Evaporation of the solvent in vacuo afforded desired 1-butyl-2-boc-aminomethyl-6-(3-diethylaminopropoxy)-1-H-benzimidazole. The product obtained was treated with 4 N HCl in dioxane according to General Procedure H to give 1-butyl-2-aminomethyl-6-(3-diethylaminopropoxy)-1-H-benzimidazole hydrochloride.

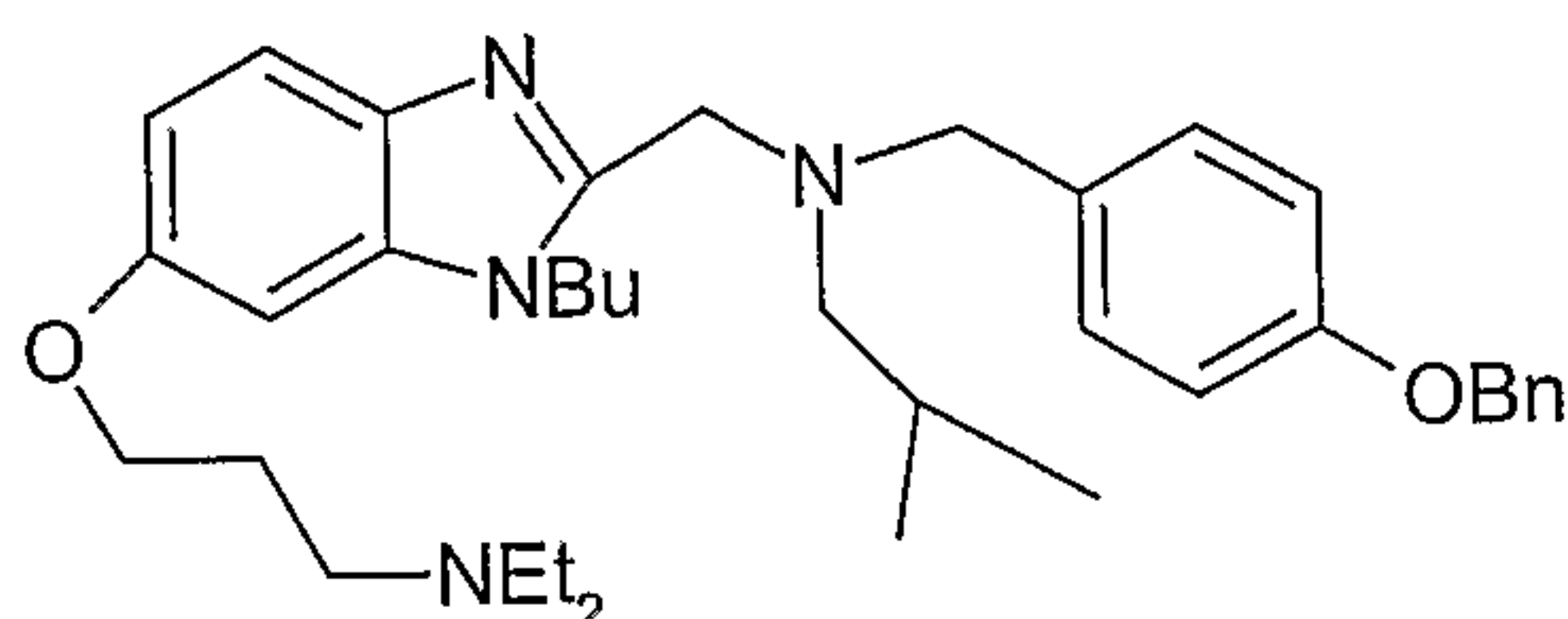
To 1-butyl-2-aminomethyl-6-(3-diethylaminopropoxy)-1-H-benzimidazole (1.0 mmol) in DCM (8 mL) were added Et₃N (3.0 mmol) and 4-benzyloxybenzaldehyde (1.0 mmol) and the mixture was stirred for 4h, then NaBH(OAc)₃ (4.0 mmol) was added and stirred for another 4 h, then sodium bicarbonate was added and the mixture was extracted with EtOAc. The combined organic layer was washed with brine, and dried over sodium sulfate. The crude product was purified by silica gel column chromatography using DCM with a gradual increment of MeOH (1% to 10%) as eluent to afford 1-butyl-2-(4-benzyloxy-benzyl)-aminomethyl-6-(3-diethylaminopropoxy)-1-H-benzimidazole.

To 1-butyl-2-(4-benzyloxy-benzyl)-aminomethyl-6-(3-diethylaminopropoxy)-1-H-benzimidazole (16 mg, 0.03 mmol) in DCM (2 mL) were added hexanal (8.3 mg, 0.083 mmol) and the mixture was stirred for 10 min, then NaBH(OAc)₃ (32 mg, 0.15 mmol) was added and stirred for 3 h, then sodium bicarbonate was added and the mixture was extracted with EtOAc (3X10 mL). The combined organic layer was washed with brine, and dried over sodium sulfate. The crude product was purified by silica gel column chromatography using DCM with a gradual increment of MeOH (1% to 5%) as eluent to afford 14 mg of Example 393.

MS m/z 613 [M+H]⁺

Example 394

5 (4-benzyloxy-benzyl)-[1-butyl-6-(3-diethylaminopropoxy)-1-H-benzimidazol-2-ylmethyl]-isobutyl-amine

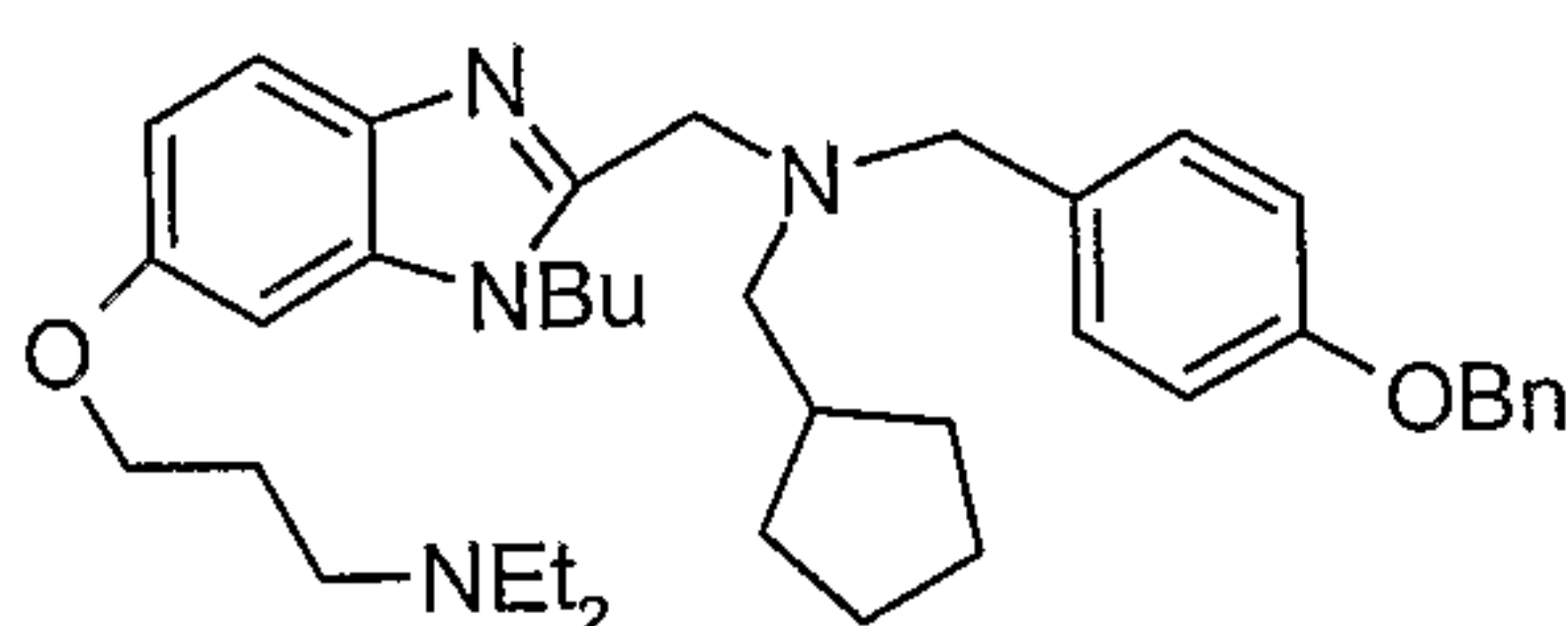


To 1-butyl-2-(4-benzyloxy-benzyl)-aminomethyl-6-(3-diethylaminopropoxy)-1-H-benzimidazole (16 mg, 0.03 mmol) in DCM (2 mL) were added isobutrylaldehyde (8.6 mg, 0.10 mmol) and the mixture was stirred for 10 min, then NaBH(OAc)₃ (32 mg, 0.15 mmol) was added and stirred for 3 h, then sodium bicarbonate was added and the mixture was extracted with EtOAc. The combined organic layer was washed with brine, and dried over sodium sulfate. The crude product was purified by silica gel column chromatography using DCM with a gradual increment of MeOH (1% to 5%) as eluent to afford 12 mg of Example 394.

15 MS m/z 585 [M+H]⁺

Example 395

20 [3-(2-[(4-benzyloxy-benzyl)-cyclopentylmethyl-amino]-methyl)-3-butyl-3-H-benzimidazol-5-yloxy)-propyl]-diethylamine



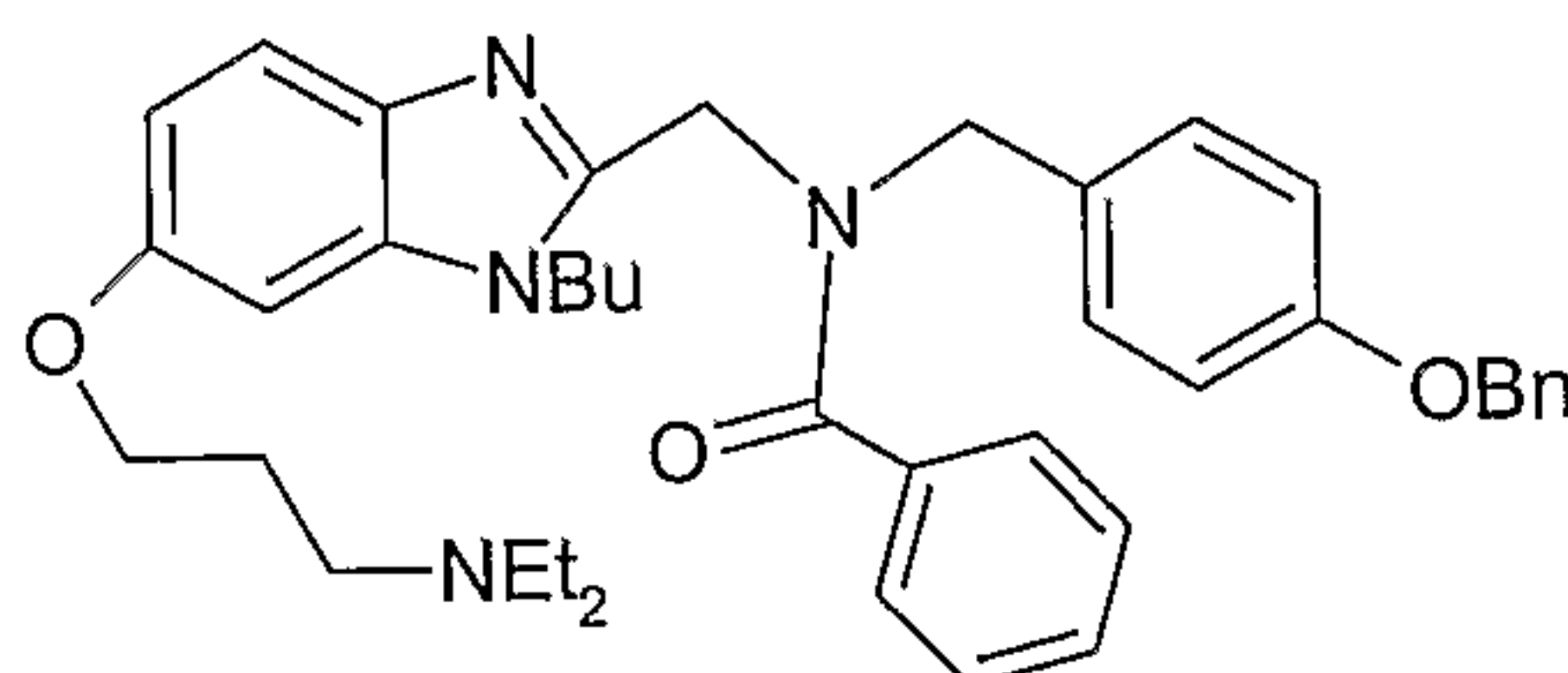
To 1-butyl-2-(4-benzyloxy-benzyl)-aminomethyl-6-(3-diethylaminopropoxy)-1-H-benzimidazole (16 mg, 0.03 mmol) in DCM (2 mL) were added cyclopentyl carboxaldehyde (11 mg, 0.10 mmol) and the mixture was stirred for 10 min, then NaBH(OAc)₃ (32 mg, 0.15 mmol) was added and stirred for 3 h, then sodium bicarbonate was added and the mixture was extracted with EtOAc (3X10 mL). The combined organic layer was washed with brine, and dried over sodium sulfate. The crude product was purified by silica gel column

chromatography using DCM with a gradual increment of MeOH (1% to 5%) as eluent to afford 8.0 mg of Example 395.

MS m/z 611 [M+H]⁺

5 Example 396

N-(4-benzyloxy-benzyl)-N-[1-butyl-6-(3-diethylaminopropoxy)-1-H-benzimidazol-2-ylmethyl]-benzamide

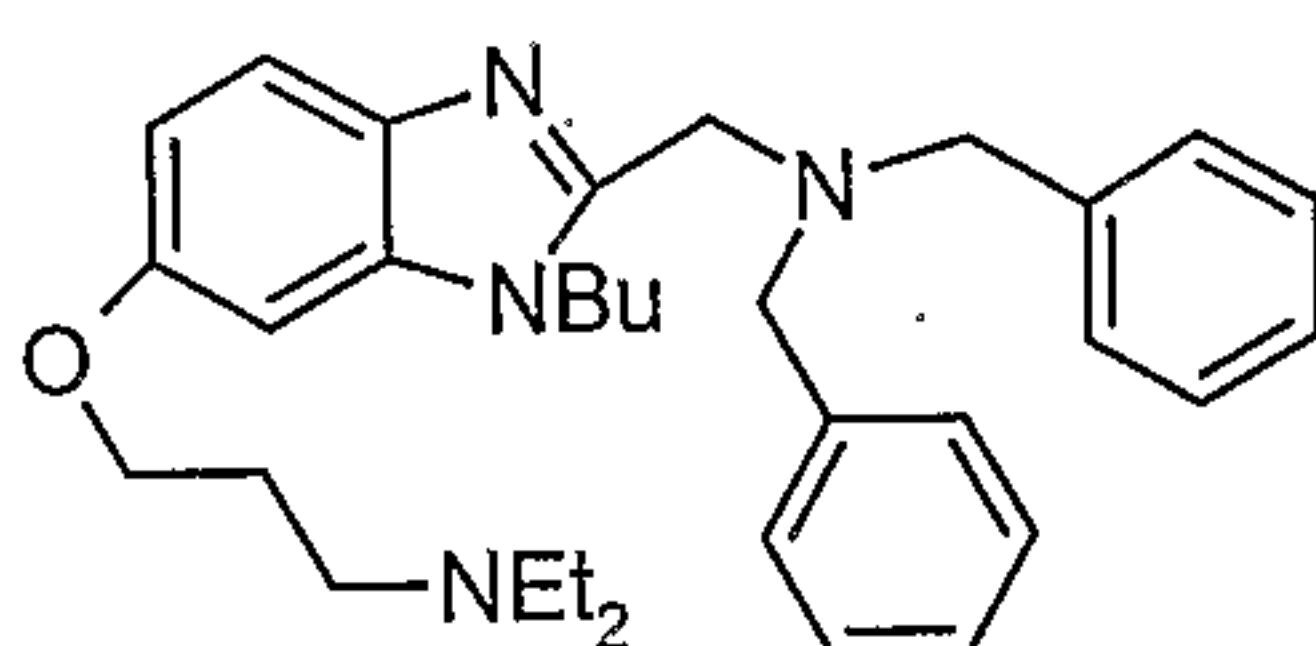


To 1-butyl-2-(4-benzyloxy-benzyl)-aminomethyl-6-(3-diethylaminopropoxy)-1-H-benzimidazole (32 mg, 0.06 mmol) in DCM (3 mL) were added benzoyl chloride (34 mg, 0.24 mmol), TEA (24 mg, 0.24 mmol), DMAP (catalytic amount) and the mixture was stirred for 12 h, then sodium bicarbonate was added and the mixture was extracted with EtOAc (3X10 mL). The combined organic layer was washed with brine, and dried over sodium sulfate. The crude product was purified by silica gel column chromatography using DCM with a gradual increment of MeOH (0 to 1%) as eluent to afford 30 mg of Example 396.

MS m/z 633 [M+H]⁺

20 Example 397

(3-{3-butyl-2-[(dibenzylamino)-methyl]-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine



To 1-butyl-2-aminomethyl-6-(3-diethylaminopropoxy)-1-H-benzimidazole (15 mg, 0.034 mmol) in DCM (2 mL) were added Et₃N (0.10 mmol) and benzaldehyde (180 mg, 0.17 mmol) and the mixture was stirred for 10 min, then NaBH(OAc)₃ (72 mg, 0.34 mmol) was added and stirred for 3 h, then sodium bicarbonate was added and the mixture was extracted with EtOAc. The combined organic layer was washed with brine, and dried over sodium sulfate. The crude product was purified by silica gel column chromatography using DCM with a gradual increment of MeOH (1% to 2%) as eluent to afford 10 mg of Example 397.

MS m/z 513 [M+H]⁺

The following Examples were synthesized according to the Methods employed for Examples 393-397;

5

Example	Name
398	(3-{2-[(4-benzyloxy-benzylamino)-methyl]-3-butyl-3H-benzimidazol-5-yloxy}-propyl)-diethyl-amine
399	N-(4-benzyloxy-benzyl)-N-[1-butyl-6-(3-diethylamino-propoxy)-1H-benzimidazol-2-ylmethyl]-methanesulfonamide
400	N-(4-benzyloxy-benzyl)-N-[1-butyl-6-(3-diethylamino-propoxy)-1H-benzimidazol-2-ylmethyl]-acetamide
401	{3-[3-butyl-2-({4-[2-(4-chloro-phenyl)-ethoxy]-benzylamino}-methyl)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
402	[3-(2-{[Bis-(4-benzyloxy-benzyl)-amino]-methyl}-3-butyl-3H-benzoimidazol-5-yloxy)-propyl]-diethyl-amine
403	[3-(2-{[Benzyl-(4-benzyloxy-benzyl)-amino]-methyl}-3-butyl-3H-benzoimidazol-5-yloxy)-propyl]-diethyl-amine

Example 404

{3-[4-(2-butyl-4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-imidazol-1-yl)-phenoxy]-propyl}-
5 diethyl-amine

To a stirred solution of 4-fluoronitrobenzene (2.0 mmol) in anhydrous THF (5 mL) at 0°C, a
1M solution of a potassium diethylaminopropoxide (2.2 mmol) in THF was added dropwise
and under a nitrogen stream, according to General Procedure L1. The reaction mixture was
stirred at 0°C for 1 h and allowed to warm to rt until completion, as indicated by TLC or
10 HPLC. The reaction mixture was then treated with cold H₂O and extracted with EtOAc. The
combined organic layers were washed with brine and dried over sodium sulfate.
Evaporation of the solvent *in vacuo* afforded the desired 4-alkoxynitrobenzene.

The N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (2 mmol) obtained above was dissolved
in MeOH (10 mL) and hydrogenated in the presence of 10% Pd/C (10 mg), according to
15 General Procedure H. The reaction mixture was then filtered to remove the catalyst. The
solvent was removed *in vacuo* to afford the desired 4-alkoxyaniline, which was used
directly for further transformation without further purification.

To a stirred solution of 4'-hydroxyacetophenone (2.2 mmol) in DMF (5 mL) at rt, solid
potassium carbonate (9.0 mmol) was added. 4-chlorophenethyl mesylate (2.0 mmol) was
20 added to the reaction mixture and heated to 80°C until completion, according to General
Procedure Q1. After cooling to rt, the reaction mixture was quenched using cold water (20
ml) and the product was isolated in EtOAc (2X20 ml). The combined organic layers were
washed with saturated sodium bicarbonate (2X10 ml), water (2X10 ml) and brine (15 ml).
The organic layer was dried over magnesium sulfate, and the solvent was removed *in*
25 *vacuo* to afford the desired 1-{4-[2-(4-chlorophenyl)ethoxy]phenyl}ethanone.

To a stirred solution of the 1-{4-[2-(4-chlorophenyl)ethoxy]phenyl}ethanone (2 mmol) in
anhydrous MeOH (5 mL) at 0°C, pyrrolidone hydrotribromide (1.2 eq., 2.2 mmol) was added,
according to General Procedure R1. The reaction mixture was stirred under nitrogen at 0°C
for 1h and was allowed to warm to rt until completion, as indicated by TLC or HPLC. The
30 solvent was then removed *in vacuo* and the residue was treated with saturated sodium
bicarbonate. The aqueous layer was poured into EtOAc (20 ml) and the product was
isolated in EtOAc (2X20 ml). The combined organic layers were washed with saturated
sodium bicarbonate (2X10 ml), and brine (15 ml). The organic layer was dried over

magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired product. The crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was purified by chromatography (Silica gel).

To a stirred solution of the N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (1.2 eq., 2 mmol) in anhydrous DMF (5 mL) DIEA (3 eq. 6 mmol) was added, followed by slow addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone described above (1.6 mmol), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was used for further transformation .

To a stirred solution of 1-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-[4-(3-diethylamino-propoxy)-phenylamino]-ethanone described above (1.6 mmol) in anhydrous DCM (5 mL) at 0°C, TEA (3 eq., 4.8 mmol) was added, followed by slow addition of valeryl chloride (2 eq., 3.2 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in DCM. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (1.6 mmol) in acetic acid (4 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled to rt and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography on silica gel (yield: 270 mg).

MS m/z 561 (M+H)⁺:

¹H NMR: δ 7.85 (s, 1H), 7.71 (d, 2H), 7.56 (d, 2H), 7.32 (m, 4H), 7.24 (d, 2H), 7.06 (d, 2H), 4.25 (t, 2H), 3.43 (t, 2H), 3.35 (m, 6H), 3.12 (t, 2H), 2.97 (t, 2H), 2.31 (m, 2H), 1.65 (m, 2H), 1.41 (t, 6H), 1.37 (m, 2H), 0.85 (t, 3H) ppm.

Example 405

{3-[4-(4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-isobutyl-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine

To a stirred solution of 4-fluoronitrobenzene (2.0 mmol) in anhydrous THF (5 mL) at 0°C, a 1M solution of a potassium diethylaminopropoxide (2.2 mmol) in THF was added dropwise and under a nitrogen stream, according to General Procedure L1. The reaction mixture was stirred at 0°C until completion, as indicated by TLC or HPLC. The reaction mixture was then treated with cold H₂O (15 mL), and extracted with EtOAc (2x15 mL). The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of the solvent *in vacuo* afforded the desired 4-alkoxynitrobenzene. The crude product was used directly for further transformation without any purification, or after purifying using silica gel column chromatography.

The N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (2 mmol) obtained above was dissolved in MeOH (10 mL) and hydrogenated in the presence of 10% Pd/C (10 mg) until completion as indicated by TLC or HPLC, according to General Procedure H. The reaction mixture was then filtered to remove the catalyst. The solvent was removed *in vacuo* to afford the desired 4-alkoxyaniline, which was used directly for further transformation without further purification.

To a stirred solution of 4'-hydroxyacetophenone (1.2 mmol) in DMF (10 mL) at rt, solid potassium carbonate (3.0 mmol) was added. 4-chlorophenethyl mesylate (1.0 mmol) was added to the reaction mixture and heated to 80°C until completion according to General Procedure Q1, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was quenched by removing solvent *in vacuo* and treating the residue with saturated sodium bicarbonate. The aqueous layer was poured into EtOAc (20ml) and washed with H₂O (2X10 ml) and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired 1-{4-[2-(4-chlorophenyl)ethoxy]phenyl}ethanone. The crude alkylated acetophenone was used for further transformation without any purification or after purifying using silica gel column chromatography.

To a stirred solution of the 1-{4-[2-(4-chlorophenyl)ethoxy]phenyl}ethanone (2 mmol) in anhydrous MeOH (5 mL) at 0°C, pyrrolidone hydrotribromide (1.2 eq) was added, according to General Procedure R1. The reaction mixture was stirred under nitrogen at 0°C for 1h and was allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was then removed *in vacuo* and the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was used for further transformation.

To a stirred solution of the N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (1.2 eq, 2 mmol) in anhydrous DMF (5 mL) DIEA (3 eq 6 mmol) was added, followed by a slow addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone described above (1.6 mmol), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold H₂O and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product was obtained from 2-4% MeOH/DCM.

To a stirred solution of 1-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-[4-(3-diethylamino-propoxy)-phenylamino]-ethanone described above (2 mmol) in anhydrous DCM (5 mL) at 0°C, TEA (3eq, 6 mmol) was added, followed by a slow addition of isovaleryl chloride (3 eq, 6 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (2 mmol) in acetic acid (2 mL), ammonium acetate (excess, ~20 eq) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled down and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained from 4-6% MeOH/DCM (Yield: 390 mg).

MS m/z 560 (M+H)⁺

¹H NMR: δ 7.86 (s, 1H), 7.65 (d, 2H), 7.59 (d, 2H), 7.31 (m, 4H), 7.23 (d, 2H), 7.13 (d, 2H), 4.51 (m, 2H), 3.42 (t, 2H), 3.31 (m, 6H), 3.05 (t, 2H), 2.87 (t, 2H), 2.31 (m, 2H), 1.95 (m, 1H), 1.49 (t, 6H), 0.86 (d, 6H) ppm.

Example 406

[3-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethylamine

3-Diethylaminopropanol (20mmol, 1eq) was dissolved in DCM (25mL), TEA (40mmol, 2 eq) was added and the mixture was cooled to 0°C. To this mixture, methanesulfonyl chloride

(30mmol, 1.5 eq) was added slowly with stirring and the reaction mixture stirred at 0°C for an hour and at rt for another hour (until the reaction was complete by HPLC). The solvent was removed and saturated aqueous sodium bicarbonate was added. The product was extracted with EtOAc (3 x) and washed with sodium bicarbonate and water. The solvent was removed
5 *in vacuo*.

The mesylate from the previous step (20mmol, 1 eq) was dissolved in anhydrous DMF (25mL), and 4-hydroxyacetophenone (20mmol, 1 eq) and potassium carbonate (60mmol, 3 eq) were added. The mixture was heated under reflux at 85°C for 18 h (until the reaction was complete by HPLC), after which it was cooled to rt. Saturated aqueous sodium bicarbonate
10 was added to the mixture, which was then transferred to a separatory funnel. The product 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was extracted with EtOAc and washed with sodium bicarbonate and water. The solvent was removed *in vacuo* and the product was purified by flash chromatography (going by increasing gradient up to 10% MeOH in DCM). T

To a stirred solution of 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone (5 mmol) in
15 anhydrous MeOH (10 mL) at 0°C, pyrrolidone hydrotribromide (6 mmol, 1.2 eq) was added, according to General Procedure R1. The reaction mixture was stirred under nitrogen at 0°C for 1h and was allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was then removed *in vacuo* and the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was used for further transformation.

To a solution of 4-chlorophenoxy aniline (1 eq, 5 mmol) in anhydrous DMF (10 mL), DIEA (3
20 eq 15 mmol) was added, followed by addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone described above (5 mmol), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the
25 product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product obtained from 2-4% MeOH/DCM.

To a stirred solution of 2-[4-(4-chlorophenoxy)-phenylamino]-1-[4-(3-diethylamino-propoxy)-
30 phenyl]-ethanone (2 mmol) in anhydrous DCM (8 mL) at 0°C, TEA (3eq, 6 mmol) was added, followed by a slow addition of valeryl chloride (3 eq, 6 mmol). The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion as indicated by TLC or HPLC, according to General Procedure R3. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (2 mmol) in acetic acid (8 mL), ammonium acetate (20 eq) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled to rt and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography on silica gel elutiopn with 4-6% MeOH/DCM) (yield 424 mg).

MS m/z 532 (M+H)⁺:

¹H NMR (CDCl₃): δ 7.68 (d, 2H), 7.34 (d, 2H), 7.28 (d, 2H), 7.14 (s, 1H), 7.07 (d, 2H), 7.01 (d, 2H), 6.89 (d, 2H) 4.04 (t, 2H), 2.64-2.78 (m, 8H), 1.99 (m, 2H), 1.64 (m, 2H), 1.30 (m, 2H), 1.09 (t, 6H), 0.83 (t, 3H) ppm.

Example 407

1-[4-(4-{2-butyl-1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-butyl]-piperazine

To a stirred solution of 4-benzyloxyacetophenone (7.0 mmol) in anhydrous DCM (30.0 mL) and MeOH (5.0mL) at rt, pyridinium bromide perbromide (1.1eq.) was added. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC. The mixture was diluted with EtOAc (100 ml) and washed with H₂O (2X50 ml), brine (30 ml) and dried with magnesium sulfate. The solvent was then removed *in vacuo* to give a white solid. The alpha-bromoacetophenone was used for further transformation without further purification.

To a stirred solution of 4-(4-fluoro-3-trifluoromethyl-phenoxy)-aniline (1.64 mmol) in anhydrous DMF (30 mL) DIEA (3 eq) was added, followed by slow addition of the alpha-bromoacetophenone described above (2 eq), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC and HPLC. The reaction mixture was then diluted with cold H₂O and the product was isolated in Et₂O. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was purified by chromatography on silica gel (elution with 5-20% EtOAc/Hexane).

To a stirred solution of alkylated aniline described above (1.0 mmol) in anhydrous THF (20 mL) at 0°C, TEA (3 eq, 3 mmol) was added, followed by slow addition of valeryl chloride (3 eq, 3.0 mmol). The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to

warm to ambient temperature until completion as indicated by TLC and HPLC, according to General Procedure R3. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (1.0 mmol) in acetic acid (2 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled down and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography on silica gel (elution with 5-15% EtOAc/Hexane). MS: m/z 562 ($M+H$)⁺

The benzyl imidazole from above was dissolved in MeOH (20 mL), and Pd/C (100 mg) was added and the heterogeneous mixture was stirred overnight under hydrogen atmosphere using a balloon, according to General Procedure H. The catalyst was removed by filtration. The solvent was removed *in vacuo*, and the crude phenol (MS: m/z 472 ($M+H$)⁺) was used directly.

To a stirred solution of the phenol (0.16 mmol) obtained above in anhydrous DMF (5 mL) solid sodium hydride (60% dispersion in oil; 1.0mmol) was added in portions. After the addition, a solution of 4-bromobutyl methanesulfonate (0.2 mmol) (prepared as described earlier) in anhydrous THF (2 mL) was added to the reaction mixture. The reaction was then allowed to proceed at rt. Upon completion of the reaction, piperazine (5.0 eq) was added. The mixture was stirred overnight. Et₂O (30 mL) was added to the reaction mixture followed by H₂O (10 mL). The organic layer was washed with H₂O (2x15 mL) and brine, and dried over sodium sulfate. The solvent was removed *in vacuo*. Product was purified by column chromatography on silica gel (elution with 5-10% MeOH/DCM) (yield 54.0 mg) MS m/z 612 ($M+H$)⁺:

Example 408

4-(4-{2-butyl-1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-1-methyl-piperidine

To a stirred solution of 4-benzyloxyacetophenone (7.0 mmol) in anhydrous DCM (30.0 mL) and MeOH (5.0mL) at rt, pyridinium bromide perbromide (1.1eq.) was added, according to General Procedure R1. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC. The mixture was diluted with EtOAc (100 ml) and washed with H₂O (2X50 ml), brine (30 ml) and dried with magnesium sulfate. The solvent was then removed

in vacuo to give a white solid. The alpha-bromoacetophenone was used for further transformation without further purification.

To a stirred solution of 4-(4-fluoro-3-trifluoromethyl-phenoxy)-aniline (1.64 mmol) in anhydrous DMF (30 mL) DIEA (3 eq) was added, followed by slow addition of the alpha-bromoacetophenone described above (2 eq), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC and HPLC. The reaction mixture was then diluted with cold H₂O and the product was isolated in Et₂O. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was purified by chromatography on silica gel (elution with 5-20% EtOAc/Hexane).

To a stirred solution of alkylated aniline described above (1.0 mmol) in anhydrous THF (20 mL) at 0°C, TEA (3eq, 3 mmol) was added, followed by slow addition of valeryl chloride (3 eq, 3.0 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (1.0 mmol) in acetic acid (2 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled down and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography on silica gel (elution with 5-15 % EtOAc/Hexane).

MS: *m/z* 562 (M+H)⁺

The above product was dissolved in MeOH (20 mL), and Pd/C (100 mg) was added and the heterogeneous mixture was stirred overnight under hydrogen atmosphere using a balloon, according to General Procedure T2. The Pd/C was removed by filtration. The solvent was removed *in vacuo*, and the crude 4-(1-{4-[4-fluoro-3-(trifluoromethyl)phenoxy]phenyl}-2-butyl-1H-imidazol-4-yl)phenol (MS: *m/z* 472 (M+H)⁺) was used directly.

A stirred solution of the 4-(1-{4-[4-fluoro-3-(trifluoromethyl)phenoxy]phenyl}-2-butyl-1H-imidazol-4-yl)phenol (1.0 eq) in anhydrous DMF (5.0 mL) was treated with solid sodium hydride (60% dispersion in oil; 1.0 mmol), added in portions. The mesylate of 1-methylpiperidin-4-ol (1.5-2.0eq) was then added to the reaction mixture, which was heated at 90 °C overnight, according to General Procedure T3. After cooling the mix to rt, Et₂O (30 mL) was added to the reaction mixture followed by H₂O (10 mL). The organic layer was

washed with H₂O (2x15 mL) and brine, and dried over sodium sulfate. The solvent was removed *in vacuo*. Pure imidazole was obtained from chromatography in 5-10% MeOH/DCM (yield 14 mg).

MS m/z value (M+H)⁺: 569

5 ¹H NMR (CDCl₃): δ7.70 (d, 2H), 7.20-7.35 (m, 5H), 7.14 (s, 1H), 7.08 (d, 2H), 6.92 (d, 2H), 4.4 (bs, 1H), 1.0-3.05 (m, 17H) ppm.

Example 409

10 1-[5-(4-{2-butyl-1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-pentyl]-piperazine

15 To a stirred solution of 4-benzyloxyacetophenone (7.0 mmol) in anhydrous DCM (30.0 mL) and MeOH (5.0 mL) at rt, pyridinium bromide perbromide (1.1 eq.) was added. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC. The mixture was diluted with EtOAc (100 mL) and washed with H₂O (2X50 mL), brine (30 mL) and dried with magnesium sulfate. The solvent was then removed *in vacuo* to give a white solid. The alpha-bromoacetophenone was used for further transformation without further purification.

20 To a stirred solution of 4-(4-fluoro-3-trifluoromethyl-phenoxy)-aniline (1.64 mmol) in anhydrous DMF (30 mL) DIEA (3 eq) was added, followed by slow addition of the alpha-bromoacetophenone described above (2 eq), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC and HPLC. The reaction mixture was then diluted with cold H₂O and the product was isolated in Et₂O. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product was obtained from 5-20% EtOAc/Hexane.

25 To a stirred solution of alkylated aniline described above (1.0 mmol) in anhydrous THF (20 mL) at 0°C, TEA (3 eq, 3 mmol) was added, followed by slow addition of valeryl chloride (3 eq, 3.0 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to ambient temperature until completion, as indicated by TLC and HPLC. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (1.0 mmol) in acetic acid (2 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled down and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained from 5-15 % EtOAc/Hexane. MS: m/z 562 ($M+H$)⁺

The above product was dissolved in MeOH (20 mL), and Pd/C (100 mg) was added and the heterogeneous mixture was stirred overnight under hydrogen atmosphere using a balloon, according to General Procedure H. The Pd/C was removed by filtration. The solvent was removed *in vacuo*, and the crude phenol (MS: m/z 472 ($M+H$)⁺) was used for further transformation.

To a stirred solution of the imidazole (0.16 mmol) obtained above in anhydrous DMF (5 mL) solid sodium hydride (60% dispersion in oil; 1.0mmol) was added in portions. After the addition, a solution of 5-bromopentyl methanesulfonate (0.2 mmol) anhydrous THF (2 mL) was added to the reaction mixture. The reaction was then allowed to proceed at rt. Upon completion of the reaction, piperazine (100 mg) added. The mixture was stirred overnight. Et₂O (30 mL) was added to the reaction mixture followed by H₂O (10 mL). The organic layer was washed with H₂O (2x15 mL) and brine, and dried over sodium sulfate. The solvent was removed *in vacuo*. Pure product was obtained after chromatography on silica gel (elution with 5-10% MeOH/DCM) (yield 36.0 mg).

MS m/z 626 ($M+H$)⁺:

Example 410

{3-[4-(4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine

To a stirred solution of 4-fluoronitrobenzene (2.0 mmol) in anhydrous THF (5 mL) at 0°C, a 1M solution of a potassium diethylaminopropoxide (2.2 mmol) in THF was added dropwise and under a nitrogen stream, according to General Procedure L1. The reaction mixture was stirred at 0°C until completion, as indicated by TLC or HPLC. The reaction mixture was then treated with cold H₂O (15 mL), and extracted with EtOAc (2x15 mL). The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of the solvent *in vacuo* afforded the desired 4-alkoxynitrobenzene. The crude product was used directly for

further transformation without any purification, or after purifying using silica gel column chromatography.

5 The N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (2 mmol) obtained above was dissolved in MeOH (10 mL) and hydrogenated in the presence of 10% Pd/C (10 mg) until completion as indicated by TLC or HPLC, according to General Procedure H. The reaction mixture was then filtered to remove the catalyst. The solvent was removed *in vacuo* to afford the desired N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine, which was used directly for further transformation without further purification.

10 To a stirred solution of 4'-hydroxyacetophenone (1.2 mmol) in DMF (10 mL) at rt, solid potassium carbonate (3.0 mmol) was added. 4-chlorophenethyl mesylate (1.0 mmol) was added to the reaction mixture and heated to 80°C until completion according to General Procedure Q1, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was quenched by removing solvent *in vacuo* and treating the residue with saturated sodium bicarbonate. The aqueous layer was poured into EtOAc (20ml) and washed with H₂O (2X10
15 ml) and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired 1-{4-[2-(4-chlorophenyl)ethoxy]phenyl}ethanone. The crude alkylated acetophenone was used for further transformation.

20 To a stirred solution of the 1-{4-[2-(4-chlorophenyl)ethoxy]phenyl}ethanone (2 mmol) in anhydrous MeOH (5 mL) at 0°C, pyrrolidinone hydrotribromide (1.2 eq) was added, according to General Procedure R1. The reaction mixture was stirred under nitrogen at 0°C for 1h and was allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was then removed *in vacuo* and the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was used for further transformation.

25 To a stirred solution of the N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (1.2 eq, 2 mmol) in anhydrous DMF (5 mL) DIEA (3 eq 6 mmol) was added, followed by a slow addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone described above (1.6 mmol), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with
30 cold H₂O and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product was obtained from 2-4% MeOH/DCM .

The 1-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-[4-(3-diethylamino-propoxy)-phenylamino]-ethanone obtained as above (1 mmol) was dissolved in formic acid (2 mL) and treated with ammonium formate (20 mmol). The resulting mixture was heated to 90°C overnight. The reaction mixture was then cooled to rt and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography on silica gel (elution with 4-6% MeOH/DCM) (yield 161 mg).

MS m/z 504 (M+H)⁺:

¹H NMR (CDCl₃): δ 7.77 (s, 1H), 7.73 (d, 2H), 7.38 (s, 1H), 7.10–7.35 (m, 6H), 6.97 (d, 2H), 6.92 (d, 2H), 4.17 (t, 2H), 4.06 (broad t, 2H), 3.07 (t, 2H), 2.81 (broad q, 4H) 1.95–2.15 (broad m, 4H), 1.17 (t, 6H) ppm.

Example 411

{3-[3-(4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine

To a stirred solution of 3-nitrophenol (2 mmol) in DMF (6 mL) at rt, solid potassium carbonate (4 mmol) was added. A solution of the mesylate of N,N-diethylaminopropanol (2.2 mmol) in DMF (2 mL) was then added to the reaction mixture and heated to 80°C until completion, according to General Procedure Q1, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was then treated with cold H₂O (15 mL), and extracted with EtOAc (2x15 mL). The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of the solvent *in vacuo* afforded the desired N,N-diethyl-N-[3-(3-nitrophenoxy)propyl]amine. The crude product was used directly for further transformation.

The N,N-diethyl-N-[3-(3-nitrophenoxy)propyl]amine (1 mmol) was dissolved in MeOH (5 mL) and hydrogenated in the presence of 10% Pd/C (50 mg) until completion as indicated by TLC or HPLC, according to General Procedure H. The reaction mixture was then filtered to remove the catalyst. The solvent was removed *in vacuo* to afford the desired N-[3-(3-aminophenoxy)propyl]-N,N-diethylamine, which was used directly for further transformation without further purification.

To a stirred solution of N-[3-(3-aminophenoxy)propyl]-N,N-diethylamine (1 mmol) in anhydrous DMF (3 mL), DIEA (3 mmol) was added followed by a slow addition of 1-bromo-

4'-(4-chlorophenoxy)acetophenone (0.8 mmol), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold H₂O and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was purified by chromatography on silica gel (elution with 2-4% MeOH/DCM).

The 1-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-[4-(3-diethylamino-propoxy)-phenylamino]-ethanone obtained as above (0.5 mmol) was dissolved in formic acid (1 mL) and treated with ammonium formate (10 mmol). The resulting mixture was heated to 90°C overnight. The reaction mixture was then cooled down and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography on silica gel (elution with 4-6% MeOH/DCM).

MS m/z value (M+H)⁺: 504

¹H NMR (CDCl₃): δ 7.89 (s, 1H), 7.74 (d, 2H), 7.47 (s, 1H), 7.30–7.10 (m, 7H), 6.92 (d, 2H), 6.85 (t, 1H), 4.10–4.20 (m, 4H), 3.00–3.20 (m, 6H), 2.31 (broad, 2H), 1.36 (t, 6H) ppm.

Example 412

[3-(4-{1-[4-(4-tert-butyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine

To a stirred solution of 4-fluoronitrobenzene (2.0 mmol) in anhydrous THF (5 mL) at 0°C, a 1M solution of potassium 4-tert-butyl-phenoxy (2.2 mmol) in THF (may be generated by adding the corresponding alcohol to a 1M solution of KOBu^t in THF) was added dropwise and under a nitrogen stream, according to General Procedure L1. The reaction mixture was stirred at 0°C until completion, as indicated by TLC or HPLC. The solvent was then removed *in vacuo* and the reaction mixture was treated with cold H₂O (15 mL), and extracted with EtOAc (2x15 mL). The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of the solvent *in vacuo* afforded the desired 4-alkoxynitrobenzene. The crude product was used directly for further transformation.

The nitro intermediate (2 mmol) obtained above was dissolved in MeOH (10 mL) and hydrogenated in the presence of 10% Pd/C (10 mg) until completion, as indicated by TLC or HPLC, according to General Procedure H. The reaction mixture was then filtered. The solvent was removed *in vacuo* to afford the desired 4-alkoxyaniline, which was used directly for further transformation without further purification.

To a stirred solution of 4'-hydroxyacetophenone (2.2 mmol) in DMF (10 mL) at rt, solid K₂CO₃ (8.0 mmol) was added. The mesylate of N,N-diethyaminopropanol (prepared from the corresponding alcohol and methanesulfonyl chloride, 2.0 mmol) was added to the reaction mixture and heated to 80°C until completion according to General Procedure Q1, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was diluted with H₂O and the product was isolated in EtOAc. The combined organic layers were washed with saturated sodium bicarbonate (2X15 ml), water (2X15 ml) and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired product. The crude 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was purified using silica gel column chromatography (elution with 2-3% MeOH/DCM).

To a stirred solution of the 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone (1 mmol) described above 48% HBr (3eq, 3 mmol) in DMSO (4 mL) was added. The reaction mixture was heated to 80°C until completion, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was neutralized with 2N sodium hydroxide solution and the product was isolated in EtOAc. The combined organic layers were washed with H₂O (2X15 ml) and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired product. The crude ketoaldehyde was used for further transformation.

To a stirred solution of the ketoaldehyde (1 mmol) in AcOH (5 mL) 4-tert-butyl-phenoxy aniline (1.2 eq., 1.2 mmol), formaldehyde (excess, ~30eq.) and ammonium acetate (excess, ~30 eq.) were added, according to General Procedure R4. The reaction mixture was heated to 80°C until completion, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was neutralized with saturated sodium bicarbonate solution and the product was isolated in EtOAc. Usual extractive work up gave the desired product, which was purified by column chromatography on silica gel (elution with 3-4% MeOH/DCM) (Yield 150 mg).

MS: *m/z* 498 (M+H)⁺

¹H NMR (CDCl₃): δ 7.64 (s, 1H), 7.39 (d, 2H), 7.12 (s, 1H), 7.06 (d, 2H) 7.02 (d, 2H) 6.97 (m, 2H) 6.79 (d, 2H), 3.98 (t, 2H), 2.66 (m, 6H), 2.02 (m, 2H), 1.31 (s, 9H), 1.08 (t, 6H) ppm.

Example 413

[3-(4-{2-butyl-1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine

To a stirred solution of 4-fluoronitrobenzene (2.0 mmol) in anhydrous THF (5 mL) at 0°C, a 1M solution of a potassium 4-fluoro-3-trifluoromethyl-phenoxide (2.2 mmol) in THF (may be generated by adding the corresponding alcohol to a 1M solution of potassium *t*-butoxide in THF) was added dropwise and under a nitrogen stream, according to General Procedure L1.

5 The reaction mixture was stirred at 0°C until completion, as indicated by TLC or HPLC. The solvent was then removed *in vacuo* and the reaction mixture was treated with cold H₂O (15 mL), and extracted with EtOAc (2x15 mL). The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of the solvent *in vacuo* afforded the desired 1-fluoro-4-(4-nitrophenoxy)-2-(trifluoromethyl)benzene. The crude product could be
10 used directly for further transformation .

The 1-fluoro-4-(4-nitrophenoxy)-2-(trifluoromethyl)benzene (2 mmol) obtained above was dissolved in MeOH (10 mL) and hydrogenated in the presence of 10% Pd/C (10 mg) until completion, as indicated by TLC or HPLC, according to General Procedure H. The reaction mixture was then filtered. The solvent was removed *in vacuo* to afford the desired 4-
15 alkoxyaniline, which was used directly for further transformation without further purification.

To a stirred solution of 4'-hydroxyacetophenone (2.2 mmol) in DMF (10 mL) at rt, solid potassium carbonate (8.0 mmol) was added. The mesylate of N,N-diethylaminopropanol (prepared from the corresponding alcohol and methanesulfonyl chloride) (2.0 mmol) was added to the reaction mixture and heated to 80°C until completion according to General
20 Procedure Q1, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was diluted with water and the product was isolated in EtOAc. The combined organic layers were washed with saturated sodium bicarbonate (2X15 ml), water (2X15 ml) and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired product. The crude 1-{4-[3-
25 (diethylamino)propoxy]phenyl}ethanone was purified using silica gel column chromatography. Pure product was obtained after elution with 2-3% MeOH/DCM. (yield 50-60%)

To a stirred solution of the 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone described above (1 mmol) in anhydrous MeOH (5 mL) at 0°C, pyrrolidone hydrotribromide (1.2 eq, 1.2 mmol)
30 was added, according to General Procedure R1. The reaction mixture was stirred under nitrogen at 0°C for 1h and was allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was then removed *in vacuo* and the residue was treated with saturated sodium bicarbonate and the product was isolated in EtOAc. The combined organic layers were washed with water (2X15 ml) and brine (15 ml). The organic layer was dried over
35 magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired product.

The crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was used for further transformation.

To a stirred solution of the 4-fluoro-3-trifluoromethyl-phenoxy aniline (1.2 eq., 1.2 mmol) in anhydrous DMF (5 mL) DIEA (3 eq. 3 mmol) was added, followed by slow addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone described above (1.0 mmol), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was used for further transformation.

To a stirred solution of alkylated aniline described above (1.0 mmol) in anhydrous DCM (5 mL) at 0°C, TEA (3eq., 3 mmol) was added, followed by slow addition of valeryl chloride (2 eq., 2.0 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with water and the product was isolated in DCM. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (1 mmol) in acetic acid (2 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled to rt and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained after elution with 4-6% MeOH/DCM (Yield 175 mg).

MS m/z 584 (M+H)⁺

Example 414

diethyl-[3-(4-{1-[4-(4-trifluoromethoxy-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-amine

To a stirred solution of 4-fluoronitrobenzene (2.0 mmol) in anhydrous THF (5 mL) at 0 °C, a 1M solution of potassium 4-trifluoromethoxy-phenoxy (2.2 mmol) in THF (may be generated by adding the corresponding alcohol to a 1M solution of KOBu^t in THF) was added dropwise under a nitrogen stream, according to General Procedure L1. The reaction

mixture was stirred at 0°C until completion, as indicated by TLC or HPLC. The solvent was then removed *in vacuo* and the reaction mixture was treated with cold H₂O (15 mL), and extracted with EtOAc (2x15 mL). The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of the solvent *in vacuo* afforded the desired 4-alkoxynitrobenzene. The crude product was used directly for further transformation .

The nitro intermediate (2 mmol) obtained above was dissolved in MeOH (10 mL) and hydrogenated in the presence of 10% Pd/C (10 mg) until completion, as indicated by TLC or HPLC, according to General Procedure H. The reaction mixture was then filtered to remove the catalyst. The solvent was removed *in vacuo* to afford the desired 4-alkoxyaniline, which was used directly for further transformation without further purification.

To a stirred solution of 4'-hydroxyacetophenone (2.2 mmol) in DMF (10 mL) at rt, solid K₂CO₃ (8.0 mmol) was added. The mesylate of N,N-diethylaminopropanol (prepared from the corresponding alcohol and methanesulfonyl chloride, 2.0 mmol) was added to the reaction mixture and heated to 80°C until completion according to General Procedure Q1, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was diluted with H₂O and the product was isolated in EtOAc. The combined organic layers were washed with saturated sodium bicarbonate (2X15 ml), H₂O (2X15 ml) and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired product. The crude 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was purified using silica gel column chromatography. Pure product was obtained with 2-3% MeOH/DCM.

To a stirred solution of the 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone (1 mmol) described above 48% HBr (3eq, 3 mmol) in DMSO (4 mL) was added. The reaction mixture was heated to 80°C until completion, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was neutralized with saturated sodium bicarbonate solution and the product was isolated in EtOAc. The combined organic layers were washed with water (2X15 ml) and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired product. The crude ketoaldehyde was used for further transformation.

To a stirred solution of the ketoaldehyde (1 mmol) in AcOH (5 mL), 4-trifluoromethoxyphenoxy-aniline (1.2 eq., 1.2 mmol), formaldehyde (excess, ~30eq.) and ammonium acetate (excess, ~30 eq.) were added, according to General Procedure R4. The reaction mixture was heated to 80°C until completion, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was neutralized with saturated sodium bicarbonate solution and the product was isolated in EtOAc. Usual extractive work up with EtOAc gave the desired product,

which was purified by column chromatography on silica gel, elution with 3-4% MeOH/DCM)
(Yield 130 mg).

MS: m/z 526 ($M+H$)⁺

¹H NMR (CDCl₃): δ 7.91 (s, 1H), 7.41 (d, 2H), 7.28 (d, 2H), 7.05 (d, 2H), 6.98 (m, 4H) 6.81 (d, 2H) 3.99 (t, 2H), 2.96 (m, 6H), 2.18 (m, 2H), 1.22 (t, 6H) ppm.

Example 415

[3-(4-{2-butyl-1-[4-(3,4-dichloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine

10 3-Diethylaminopropanol (20mmol, 1eq) was dissolved in DCM (25mL), TEA (40mmol, 2 eq) was added and the mixture was cooled to 0°C. To this mixture, methanesulfonyl chloride (30mmol, 1.5 eq) was added slowly with stirring and the reaction mixture was stirred at 0°C for an hour and at rt for another hour (until the reaction was complete by HPLC). The solvent was removed and saturated aqueous sodium bicarbonate was added. The product
15 was extracted with EtOAc (3 x) and washed with sodium bicarbonate and water. The solvent was removed *in vacuo*.

The product from the previous step (20mmol, 1 eq) was dissolved in anhydrous DMF (25mL) to which 4-hydroxyacetophenone (20mmol, 1 eq) and potassium carbonate (60mmol, 3 eq) were added. The mixture was heated under reflux at 85°C for 18 h (until the reaction was
20 complete by HPLC), after which it was cooled to rt. Saturated aqueous sodium bicarbonate was added to the mixture, which was then transferred to a separatory funnel. The product was extracted with EtOAc and washed with sodium bicarbonate and water. The solvent was removed *in vacuo* and the 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was purified by flash chromatography (going by increasing gradient up to 10% MeOH in DCM).

25 3,4-Dichlorophenol (10 mmol) was dissolved in 15 ml of anhydrous DMF and potassium carbonate (30 mmol) was added with stirring at rt. 4-Fluoronitrobenzene (10 mmol) was added to this mixture, which was then heated under reflux at 80°C for 18 h. The reaction was quenched with 30 ml of water and 30 ml of sodium bicarbonate, extracted with EtOAc (3 x 50 ml) and washed with sodium bicarbonate and water. The EtOAc layer was dried over
30 anhydrous sodium sulfate and filtered, after which the solvent was removed *in vacuo*.

The nitro intermediate (10 mmol) obtained above was dissolved in EtOH (30mL) and hydrogenated in the presence of 10% Pd/C (10 mg) until completion as indicated by TLC or HPLC, according to General Procedure H. The reaction mixture was then filtered to remove the catalyst. The solvent was removed *in vacuo* to afford the desired 4-(3,4-dichlorophenoxy)aniline, which was used directly for further transformation without further purification

To a stirred solution of 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone (2 mmol) in anhydrous MeOH (6 mL) at 0°C, pyrrolidone hydrotribromide (2.4 mmol, 1.2 eq) was added, according to General Procedure R1. The reaction mixture was stirred under nitrogen at 0°C for 1h and was allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was then removed *in vacuo* and the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was used for further transformation.

To a solution of 4-(3,4-dichlorophenoxy) aniline (1 eq, 2 mmol) in anhydrous DMF (6 mL), DIEA (3 eq 6 mmol) was added, followed by addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone described above (2 mmol), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product obtained from 2-4% MeOH/DCM.

To a stirred solution of alkylated aniline described above (1mmol) in anhydrous DCM (4 mL) at 0°C, TEA (3eq, 3 mmol) was added, followed by a slow addition of valeryl chloride (3 eq, 3 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (1 mmol) in acetic acid (4 mL), ammonium acetate (excess, ~20 eq) was added according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled to rt and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography on silica gel (elution with 4-6% MeOH/DCM) (yield 170 mg).

MS m/z 567 (M+H)⁺:

¹H NMR (400 MHz, CDCl₃): δ 7.7 (d, 2H), 7.3 (m, 3H), 6.9-7.1 (m, 7H), 4.0 (t, 2H), 2.7 (m, 8H), 2.0 (m, 2H), 1.6 (m, 2H), 1.3 (m, 2H), 1.1 (t, 6H), 0.8 (t, 3H) ppm.

Example 416

5 [3-(4-{2-cyclobutyl-1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine

To a stirred solution of 4-fluoronitrobenzene (20 mmol), 4-fluoro-3-trifluoromethylphenol (22 mmol) in DMF (50 mL) at rt, solid potassium carbonate (60 mmol) was added and the reaction mixture was heated to 90°C for 5h (monitored by TLC), according to General
10 Procedure L1. After cooling to rt, the reaction mixture was poured into cold H₂O (60 mL). The resulting mixture was extracted with EtOAc (3×100 mL). The combined EtOAc extracts were washed with H₂O (2×40 mL) and brine (50 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* to afford the desired 1-fluoro-4-(4-nitrophenoxy)-2-(trifluoromethyl)benzene. The crude product was used directly for further
15 transformation without further purification.

The nitro intermediate (2 mmol) obtained above was dissolved in MeOH (10 mL) and hydrogenated in the presence of 10% Pd/C (50 mg) until completion as indicated by TLC or LC-MS, according to General Procedure H. The reaction mixture was then filtered to remove the catalyst. The solvent was removed *in vacuo* to afford 4-(4'-fluoro-3'-trifluoromethyl-phenoxy)aniline, which was used directly for further transformation without
20 purification (overall yield: 95%).

To a stirred solution of ice-cold 3-diethylaminopropanol (63 mmol) and TEA (80 mmol) dissolved in anhydrous DCM (50 mL), methanesulfonyl chloride (60 mmol) was added dropwise and the reaction mixture was stirred for 2h at 0°C, followed by additional 1h at rt.
25 After the removal of the solvents *in vacuo*, the crude mesylate was dissolved in DMF (100 mL). 4-Hydroxyacetophenone (40 mmol) and cesium carbonate (100 mmol) were added, and the mixture was heated with stirring at 90°C for 18 h (monitored by LC-MS). After cooling to rt, the reaction was quenched with cold H₂O (100 mL), and the resulting mixture was extracted with EtOAc (4×100 mL). The combined EtOAc extracts were washed with
30 brine (3×60 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*, and the crude 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was purified by silica gel column chromatography eluting with 10% MeOH in EtOAc + 0.2% TEA (yield: 75%).

To a stirred solution of 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone (4 mmol) in MeOH (10 mL) at rt, pyrrolidone hydrotribromide (4.8 mmol) was added, according to General Procedure R1. The reaction mixture was stirred at rt for 1h (monitored by LC-MS). The solvent was then removed *in vacuo* and the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was directly used for further transformation.

To a stirred solution of 4-(4'-fluoro-3'-trifluoromethyl-phenoxy)aniline (4.8 mmol) dissolved in anhydrous DMF (10 mL), DIEA (12 mmol) was added followed by a slow addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone obtained above (~4 mmol), according to General Procedure R2. The reaction mixture was stirred at rt and under nitrogen until completion (~5h), as indicated by LC-MS. The reaction was quenched with saturated sodium bicarbonate (50 mL), and the resulting mixture was extracted with EtOAc (3×100 mL). The combined EtOAc extracts were washed with brine (3×40 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*, and the crude product was purified by silica gel column chromatography eluting with 10% MeOH in EtOAc + 0.2% TEA (yield: 64%).

To a stirred solution of the alkylated aniline described above (0.2 mmol) in anhydrous DCM (5 mL) at 0°C, TEA (1.2 mmol, 6 eq) was added followed by a slow addition of cyclobutanecarbonyl chloride (0.6 mmol, 3 eq), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by LC-MS. The solvent was removed *in vacuo*, and the crude amide was used directly for further transformation.

To a stirred solution of the amide described above (~0.2 mmol) in acetic acid (2 mL), ammonium acetate (excess, ~30 eq) was added according to General Procedure R4. The reaction mixture was stirred at 100°C for 2-5 h (as monitored by LC-MS). The reaction mixture was then cooled to rt and neutralized with saturated sodium bicarbonate. The resulting mixture was extracted with EtOAc (3×50 mL). The combined EtOAc extracts were washed with brine (3×20 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*, and the pure product was obtained by silica gel column chromatography eluting with 10% MeOH in EtOAc + 0.2% TEA (yield 64 mg).

MS m/z 582 (M+H)⁺:

¹H NMR (400 MHz, CDCl₃): δ 1.05 (t, 6H), 1.90-2.20 (m, 6H), 2.56 (m, 2H), 2.58 (q, 4H), 2.66 (t, 2H), 3.44 (m, 1H), 4.02 (t, 2H), 6.91 (d, 2H), 7.05 (d, 2H), 7.14 (s, 1H), 7.22-7.26 (m, 3H), 7.31 (d, 2H), 7.72 (d, 2H) ppm.

Example 417

[3-(4-{2-cyclopentyl-1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine

5 To a stirred solution of 4-fluoronitrobenzene (20 mmol), 4-fluoro-3-trifluoromethylphenol (22 mmol) in DMF (50 mL) at rt, solid potassium carbonate (60 mmol) was added, and the reaction mixture was heated to 90°C for 5h (monitored by TLC), according to General Procedure L1. After cooling to rt, the reaction mixture was poured into cold H₂O (60 mL). The resulting mixture was extracted with EtOAc (3×100 mL). The combined EtOAc extracts
10 were washed with H₂O (2×40 mL) and brine (50 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* to afford the desired 1-fluoro-4-(4-nitrophenoxy)-2-(trifluoromethyl)benzene. The crude product was used directly for further transformation without further purification.

The nitro intermediate (2 mmol) obtained above was dissolved in MeOH (10 mL) and
15 hydrogenated in the presence of 10% Pd/C (50 mg) until completion as indicated by TLC or LC-MS, according to General Procedure H. The reaction mixture was then filtered to remove the catalyst. The solvent was removed *in vacuo* to afford 4-(4'-fluoro-3'-trifluoromethyl-phenoxy)aniline, which was used directly for further transformation without purification (overall yield: 95%).

20 To a stirred solution of ice-cold 3-diethylaminopropanol (63 mmol) and TEA (80 mmol) dissolved in anhydrous DCM (50 mL) was added dropwise methanesulfonyl chloride (60 mmol), and the reaction mixture was stirred for 2h at 0°C and followed by additional 1h at rt. After the removal of the solvents *in vacuo*, the crude mesylate was dissolved in DMF (100 mL). 4-Hydroxyacetophenone (40 mmol) and cesium carbonate (100 mmol) were added,
25 and the mixture was heated with stirring at 90°C for 18 h (monitored by LC-MS). After cooling to rt, the reaction was quenched with cold H₂O (100 mL), and the resulting mixture was extracted with EtOAc (4×100 mL). The combined EtOAc extracts were washed with brine (3×60 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*, and the crude 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was purified by silica
30 gel column chromatography eluting with 10% MeOH in EtOAc + 0.2% TEA (yield: 75%).

To a stirred solution of 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone (4 mmol) in MeOH (10 mL) at rt, pyrrolidone hydrotribromide (4.8 mmol) was added, according to General Procedure R1. The reaction mixture was stirred at rt for 1h (monitored by LC-MS). The

solvent was then removed *in vacuo* and the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was directly used for further transformation.

5 To a stirred solution of 4-(4'-fluoro-3'-trifluoromethyl-phenoxy)aniline (4.8 mmol) dissolved in anhydrous DMF (10 mL), DIEA (12 mmol) was added, followed by a slow addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone obtained above (~4 mmol), according to General Procedure R2. The reaction mixture was stirred at rt and under nitrogen until completion (~5h), as indicated by LC-MS. The reaction was quenched with saturated sodium bicarbonate (50 mL), and the resulting mixture was extracted with EtOAc (3×100 mL). The combined EtOAc extracts were washed with brine (3×40 mL), and dried over
10 anhydrous sodium sulfate. The solvent was removed *in vacuo*, and the crude product was purified by silica gel column chromatography eluting with 10% MeOH in EtOAc + 0.2% TEA (yield: 64%).

15 To a stirred solution of the alkylated aniline described above (0.2 mmol) in anhydrous DCM (5 mL) at 0°C, TEA (1.2 mmol, 6 eq) was added, followed by a slow addition of cyclopentanecarbonyl chloride (0.6 mmol, 3 eq), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by LC-MS. The solvent was removed *in vacuo*, and the crude amide was used directly for further transformation.

20 To a stirred solution of the amide described above (~0.2 mmol) in acetic acid (2 mL), ammonium acetate (excess, ~30 eq) was added, according to General Procedure R4. The reaction mixture was stirred at 100°C for 2-5h (as monitored by LC-MS). The reaction mixture was then cooled down and neutralized with saturated sodium bicarbonate. The resulting mixture was extracted with EtOAc (3×50 mL). The combined EtOAc extracts were washed with brine (3×20 mL), and dried over anhydrous sodium sulfate. The solvent was
25 removed *in vacuo*, and the pure product was obtained by silica gel column chromatography eluting with 10% MeOH in EtOAc + 0.2% TEA (overall yield: 60-70%) (yield 77 mg).

MS m/z 596 (M+H)⁺:

¹H NMR (400 MHz, CDCl₃): δ 1.03-2.00 (m, 11H), 1.07 (t, 6H), 2.59 (q, 4H), 2.65 (t, 2H), 4.03 (t, 2H), 6.91 (d, 2H), 7.08 (d, 2H), 7.14 (s, 1H), 7.24-7.27 (m, 3H), 7.33 (d, 2H), 7.71 (d,
30 2H) ppm.

Example 418

[3-(4-{2-cyclohexyl-1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine

To a stirred solution of 4-fluoronitrobenzene (20 mmol), 4-fluoro-3-trifluoromethylphenol (22 mmol) in DMF (50 mL) at rt, solid potassium carbonate (60 mmol) was added, and the reaction mixture was heated to 90°C for 5h (monitored by TLC), according to General Procedure L1. After cooling to rt, the reaction mixture was poured into cold H₂O (60 mL). The resulting mixture was extracted with EtOAc (3×100 mL). The combined EtOAc extracts were washed with H₂O (2×40 mL) and brine (50 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* to afford the desired 1-fluoro-4-(4-nitrophenoxy)-2-(trifluoromethyl)benzene. The crude product was used directly for further transformation without further purification.

The nitro intermediate (2 mmol) obtained above was dissolved in MeOH (10 mL) and hydrogenated in the presence of 10% Pd/C (50 mg) until completion as indicated by TLC or LC-MS, according to General Procedure H. The reaction mixture was then filtered to remove the catalyst. The solvent was removed *in vacuo* to afford 4-(4'-fluoro-3'-trifluoromethyl-phenoxy)aniline, which was used directly for further transformation without purification.

To a stirred solution of ice-cold 3-diethylaminopropanol (63 mmol) and TEA (80 mmol) dissolved in anhydrous DCM (50 mL) was added dropwise methanesulfonyl chloride (60 mmol), and the reaction mixture was stirred for 2h at 0°C and followed by additional 1h at rt. After the removal of the solvents *in vacuo*, the crude mesylate was dissolved in DMF (100 mL). 4-Hydroxyacetophenone (40 mmol) and cesium carbonate (100 mmol) were added, and the mixture was heated with stirring at 90°C for 18 h (monitored by LC-MS). After cooling to rt, the reaction was quenched with cold H₂O (100 mL), and the resulting mixture was extracted with EtOAc (4×100 mL). The combined EtOAc extracts were washed with brine (3×60 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*, and the crude 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was purified by silica gel column chromatography eluting with 10% MeOH in EtOAc + 0.2% TEA.

To a stirred solution of 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone (4 mmol) in MeOH (10 mL) at rt, pyrrolidone hydrotribromide (4.8 mmol) was added, according to General Procedure R1. The reaction mixture was stirred at rt for 1h (monitored by LC-MS). The solvent was then removed *in vacuo* and the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was directly used for further transformation.

To a stirred solution of 4-(4'-fluoro-3'-trifluoromethyl-phenoxy)aniline (4.8 mmol) dissolved in anhydrous DMF (10 mL), DIEA (12 mmol) was added, followed by a slow addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone obtained above (~4 mmol), according to General Procedure R2. The reaction mixture was stirred at rt and under nitrogen until completion (~5h), as indicated by LC-MS. The reaction was quenched with saturated sodium bicarbonate (50 mL), and the resulting mixture was extracted with EtOAc (3×100 mL). The combined EtOAc extracts were washed with brine (3×40 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*, and the crude product was purified by silica gel column chromatography eluting with 10% MeOH in EtOAc + 0.2% TEA.

To a stirred solution of the alkylated aniline described above (0.2 mmol) in anhydrous DCM (5 mL) at 0°C, TEA (1.2 mmol, 6 eq) was added, followed by a slow addition of cyclohexanecarbonyl chloride (0.6 mmol, 3 eq), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by LC-MS. The solvent was removed *in vacuo*, and the crude amide was used directly for further transformation.

To a stirred solution of the amide described above (~0.2 mmol) in acetic acid (2 mL), ammonium acetate (excess, ~30 eq) was added, according to General Procedure R4. The reaction mixture was stirred at 100°C for 2-5h (as monitored by LC-MS). The reaction mixture was then cooled down and neutralized with saturated sodium bicarbonate. The resulting mixture was extracted with EtOAc (3×50 mL). The combined EtOAc extracts were washed with brine (3×20 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*, and the pure product was obtained by silica gel column chromatography eluting with 10% MeOH in EtOAc + 0.2% TEA (yield 74 mg).

MS m/z 610 (M+H)⁺:

¹H NMR (400 MHz, CDCl₃): δ 1.02-2.00 (m, 13H), 1.06 (t, 6H), 2.60 (q, 4H), 2.67 (t, 2H), 4.02 (t, 2H), 6.90 (d, 2H), 7.07 (d, 2H), 7.09 (s, 1H), 7.22-7.26 (m, 3H), 7.30 (d, 2H), 7.69 (d, 2H) ppm.

Example 419

diethyl-[3-(4-{1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxy)-propyl]-amine

To a stirred solution of 4-fluoronitrobenzene (20 mmol), 4-fluoro-3-trifluoromethylphenol (22 mmol) in DMF (50 mL) at rt, solid potassium carbonate (60 mmol) was added, and the reaction mixture was heated to 90°C for 5h (monitored by TLC), according to General Procedure L1. After cooling to rt, the reaction mixture was poured into cold H₂O (60 mL).

5 The resulting mixture was extracted with EtOAc (3×100 mL). The combined EtOAc extracts were washed with H₂O (2×40 mL) and brine (50 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* to afford the desired 1-fluoro-4-(4-nitrophenoxy)-2-(trifluoromethyl)benzene. The crude product was used directly for further transformation without further purification.

10 The nitro intermediate (2 mmol) obtained above was dissolved in MeOH (10 mL) and hydrogenated in the presence of 10% Pd/C (50 mg) until completion as indicated by TLC or LC-MS, according to General Procedure H. The reaction mixture was then filtered to remove the catalyst. The solvent was removed *in vacuo* to afford 4-(4'-fluoro-3'-trifluoromethyl-phenoxy)aniline, which was used directly for further transformation without
15 purification (overall yield: 95%).

To a stirred solution of ice-cold 3-diethylaminopropanol (63 mmol) and TEA (80 mmol) dissolved in anhydrous DCM (50 mL) was added dropwise methanesulfonyl chloride (60 mmol), and the reaction mixture was stirred for 2h at 0°C and followed by additional 1h at rt. After the removal of the solvents *in vacuo*, the crude mesylate was dissolved in DMF (100
20 mL). 4-Hydroxyacetophenone (40 mmol) and cesium carbonate (100 mmol) were added, and the mixture was heated with stirring at 90°C for 18 h (monitored by LC-MS). After cooling to rt, the reaction was quenched with cold H₂O (100 mL), and the resulting mixture was extracted with EtOAc (4×100 mL). The combined EtOAc extracts were washed with brine (3×60 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in*
25 *vacuo*, and the crude 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was purified by silica gel column chromatography eluting with 10% MeOH in EtOAc + 0.2% TEA.

To a stirred solution of 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone (4 mmol) in MeOH (10 mL) at rt, pyrrolidone hydrotribromide (4.8 mmol) was added, according to General Procedure R1. The reaction mixture was stirred at rt for 1h (monitored by LC-MS). The
30 solvent was then removed *in vacuo* and the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was directly used for further transformation.

To a stirred solution of 4-(4'-fluoro-3'-trifluoromethyl-phenoxy)aniline (4.8 mmol) dissolved in anhydrous DMF (10 mL), DIEA (12 mmol) was added, followed by a slow addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone obtained above (~4 mmol), according

to General Procedure R2. The reaction mixture was stirred at rt and under nitrogen until completion (~5h), as indicated by LC-MS. The reaction was quenched with saturated sodium bicarbonate (50 mL), and the resulting mixture was extracted with EtOAc (3×100 mL). The combined EtOAc extracts were washed with brine (3×40 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*, and the crude product was purified by silica gel column chromatography eluting with 10% MeOH in EtOAc + 0.2% TEA.

To a stirred solution of the alkylated aniline described above (0.2 mmol) in anhydrous DCM (5 mL) at 0°C, TEA (1.2 mmol, 6 eq) was added, followed by a slow addition of isovaleryl chloride (0.6 mmol, 3 eq), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by LC-MS. The solvent was removed *in vacuo*, and the crude amide was used directly for further transformation.

To a stirred solution of the amide described above (~0.2 mmol) in acetic acid (2 mL), ammonium acetate (excess, ~30 eq) was added, according to General Procedure R4. The reaction mixture was stirred at 100°C for 2-5h (as monitored by LC-MS). The reaction mixture was then cooled down and neutralized with saturated sodium bicarbonate. The resulting mixture was extracted with EtOAc (3×50 mL). The combined EtOAc extracts were washed with brine (3×20 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*, and the pure product was obtained by silica gel column chromatography eluting with 10% MeOH in EtOAc + 0.2% TEA (yield 70 mg).

MS m/z 584 (M+H)⁺:

¹H NMR (400 MHz, CDCl₃): δ 0.86 (d, 6H) 1.07 (t, 6H), 1.97 (m, 2H), 2.04 (m, 1H), 2.55 (d, 2H), 2.61 (q, 4H), 2.69 (t, 2H), 4.03 (t, 2H), 6.90 (d, 2H), 7.07 (d, 2H), 7.14 (s, 1H), 7.22-7.25 (m, 3H), 7.30 (d, 2H), 7.70 (d, 2H) ppm.

Example 420

[3-(4-{2-but-3-enyl-1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine

To a stirred solution of 4-fluoronitrobenzene (20 mmol), 4-fluoro-3-trifluoromethylphenol (22 mmol) in DMF (50 mL) at rt, solid potassium carbonate (60 mmol) was added, and the reaction mixture was heated to 90°C for 5h (monitored by TLC), according to General

Procedure L1. After cooling to rt, the reaction mixture was poured into cold H₂O (60 mL). The resulting mixture was extracted with EtOAc (3×100 mL). The combined EtOAc extracts were washed with H₂O (2×40 mL) and brine (50 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* to afford the desired 1-fluoro-4-(4-nitrophenoxy)-2-(trifluoromethyl)benzene. The crude product was used directly for further transformation without further purification.

The nitro intermediate (2 mmol) obtained above was dissolved in MeOH (10 mL) and hydrogenated in the presence of 10% Pd/C (50 mg) until completion as indicated by TLC or LC-MS, according to General Procedure H. The reaction mixture was then filtered to remove the catalyst. The solvent was removed *in vacuo* to afford 4-(4'-fluoro-3'-trifluoromethyl-phenoxy)aniline, which was used directly for further transformation without purification (overall yield: 95%).

To a stirred solution of ice-cold 3-diethylaminopropanol (63 mmol) and TEA (80 mmol) dissolved in anhydrous DCM (50 mL) was added dropwise methanesulfonyl chloride (60 mmol), and the reaction mixture was stirred for 2h at 0°C and followed by additional 1h at rt. After the removal of the solvents *in vacuo*, the crude mesylate was dissolved in DMF (100 mL). 4-Hydroxyacetophenone (40 mmol) and cesium carbonate (100 mmol) were added, and the mixture was heated with stirring at 90°C for 18 h (monitored by LC-MS). After cooling to rt, the reaction was quenched with cold H₂O (100 mL), and the resulting mixture was extracted with EtOAc (4×100 mL). The combined EtOAc extracts were washed with brine (3×60 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*, and the crude 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was purified by silica gel column chromatography eluting with 10% MeOH in EtOAc + 0.2% TEA (yield: 75%).

To a stirred solution of 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone (4 mmol) in MeOH (10 mL) at rt, pyrrolidone hydrotribromide (4.8 mmol) was added, according to General Procedure R1. The reaction mixture was stirred at rt for 1h (monitored by LC-MS). The solvent was then removed *in vacuo* and the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was directly used for further transformation.

To a stirred solution of 4-(4'-fluoro-3'-trifluoromethyl-phenoxy)aniline (4.8 mmol) dissolved in anhydrous DMF (10 mL), DIEA (12 mmol) was added, followed by a slow addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone obtained above (~4 mmol), according to General Procedure R2. The reaction mixture was stirred at rt and under nitrogen until completion (~5h), as indicated by LC-MS. The reaction was quenched with saturated sodium bicarbonate (50 mL), and the resulting mixture was extracted with EtOAc (3×100

mL). The combined EtOAc extracts were washed with brine (3×40 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*, and the crude product was purified by silica gel column chromatography eluting with 10% MeOH in EtOAc + 0.2% TEA (yield: 64%).

5 To a stirred solution of the alkylated aniline described above (0.2 mmol) in anhydrous DCM (5 mL) at 0°C, TEA (1.2 mmol, 6 eq) was added, followed by a slow addition of pent-4-enoyl chloride (0.6 mmol, 3 eq), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by LC-MS. The solvent was removed *in vacuo*, and the crude amide was used directly for
10 further transformation.

To a stirred solution of the amide described above (~0.2 mmol) in acetic acid (2 mL), ammonium acetate (excess, ~30 eq) was added, according to General Procedure R4. The reaction mixture was stirred at 100°C for 2-5h (as monitored by LC-MS). The reaction mixture was then cooled down and neutralized with saturated sodium bicarbonate. The
15 resulting mixture was extracted with EtOAc (3×50 mL). The combined EtOAc extracts were washed with brine (3×20 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*, and the pure product was obtained by silica gel column chromatography eluting with 10% MeOH in EtOAc + 0.2% TEA (yield 58 mg).

MS m/z 582+H)⁺:

20 ¹H NMR (400 MHz, CDCl₃): δ 1.12 (t, 6H), 2.03 (m, 2H), 2.45 (t, 2H), 2.63 (t, 2H), 2.73 (q, 4H), 2.77 (t, 2H), 4.04 (t, 2H), 4.94 (dd, 1H), 5.00 (dd, 1H), 5.79 (m, 1H), 6.90 (d, 2H), 7.07 (d, 2H), 7.15 (s, 1H), 7.24-7.25 (m, 3H), 7.32 (d, 2H), 7.70 (d, 2H) ppm.

Example 421

25 [3-(4-{2-tert-butyl-1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine

To a stirred solution of 4-fluoronitrobenzene (20 mmol), 4-fluoro-3-trifluoromethylphenol (22 mmol) in DMF (50 mL) at rt, solid potassium carbonate (60 mmol) was added, and the reaction mixture was heated to 90°C for 5h (monitored by TLC), according to General
30 Procedure L1. After cooling to rt, the reaction mixture was poured into cold H₂O (60 mL). The resulting mixture was extracted with EtOAc (3×100 mL). The combined EtOAc extracts were washed with H₂O (2×40 mL) and brine (50 mL), and dried over anhydrous sodium

sulfate. The solvent was removed *in vacuo* to afford the desired 1-fluoro-4-(4-nitrophenoxy)-2-(trifluoromethyl)benzene. The crude product was used directly for further transformation without further purification.

The nitro intermediate (2 mmol) obtained above was dissolved in MeOH (10 mL) and hydrogenated in the presence of 10% Pd/C (50 mg) until completion as indicated by TLC or LC-MS, according to General Procedure H. The reaction mixture was then filtered to remove the catalyst. The solvent was removed *in vacuo* to afford 4-(4'-fluoro-3'-trifluoromethyl-phenoxy)aniline, which was used directly for further transformation without purification (overall yield: 95%).

To a stirred solution of ice-cold 3-diethylaminopropanol (63 mmol) and TEA (80 mmol) dissolved in anhydrous DCM (50 mL) was added dropwise methanesulfonyl chloride (60 mmol), and the reaction mixture was stirred for 2h at 0°C and followed by additional 1h at rt. After the removal of the solvents *in vacuo*, the crude mesylate was dissolved in DMF (100 mL). 4-Hydroxyacetophenone (40 mmol) and cesium carbonate (100 mmol) were added, and the mixture was heated with stirring at 90°C for 18 h (monitored by LC-MS). After cooling to rt, the reaction was quenched with cold H₂O (100 mL), and the resulting mixture was extracted with EtOAc (4×100 mL). The combined EtOAc extracts were washed with brine (3×60 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*, and the crude 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was purified by silica gel column chromatography eluting with 10% MeOH in EtOAc + 0.2% TEA.

To a stirred solution of 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone (4 mmol) in MeOH (10 mL) at rt, pyrrolidone hydrotribromide (4.8 mmol) was added, according to General Procedure R1. The reaction mixture was stirred at rt for 1h (monitored by LC-MS). The solvent was then removed *in vacuo* and the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was directly used for further transformation.

To a stirred solution of 4-(4'-fluoro-3'-trifluoromethyl-phenoxy)aniline (4.8 mmol) dissolved in anhydrous DMF (10 mL), DIEA (12 mmol) was added, followed by a slow addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone obtained above (~4 mmol), according to General Procedure R2. The reaction mixture was stirred at rt and under nitrogen until completion (~5h), as indicated by LC-MS. The reaction was quenched with saturated sodium bicarbonate (50 mL), and the resulting mixture was extracted with EtOAc (3×100 mL). The combined EtOAc extracts were washed with brine (3×40 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*, and the crude product was purified by silica gel column chromatography eluting with 10% MeOH in EtOAc + 0.2% TEA.

To a stirred solution of the alkylated aniline described above (0.2 mmol) in anhydrous DCM (5 mL) at 0°C, TEA (1.2 mmol, 6 eq) was added, followed by a slow addition of pivaloyl chloride (0.6 mmol, 3 eq), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by LC-MS. The solvent was removed *in vacuo*, and the crude amide was used directly for further transformation.

To a stirred solution of the amide described above (~0.2 mmol) in acetic acid (2 mL), ammonium acetate (excess, ~30 eq) was added, according to General Procedure R4. The reaction mixture was stirred at 100°C for 2-5h (as monitored by LC-MS). The reaction mixture was then cooled down and neutralized with saturated sodium bicarbonate. The resulting mixture was extracted with EtOAc (3×50 mL). The combined EtOAc extracts were washed with brine (3×20 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*, and the pure product was obtained by silica gel column chromatography eluting with 10% MeOH in EtOAc + 0.2% TEA (yield 76 mg).

MS m/z 584 (M+H)⁺

¹H NMR (400 MHz, CDCl₃): δ 1.09 (t, 6H), 1.24 (s, 9H), 1.99 (m, 2H), 2.64 (q, 4H), 2.72 (t, 2H), 4.02 (t, 2H), 6.89 (d, 2H), 7.02 (s, 1H), 7.03 (d, 2H), 7.23-7.25 (m, 3H), 7.35 (d, 2H), 7.69 (d, 2H) ppm.

Example 422

diethyl-[3-(4-{2-(4-fluoro-phenyl)-1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-amine

To a stirred solution of 4-fluoronitrobenzene (20 mmol), 4-fluoro-3-trifluoromethylphenol (22 mmol) in DMF (50 mL) at rt, solid potassium carbonate (60 mmol) was added, and the reaction mixture was heated to 90°C for 5h (monitored by TLC), according to General Procedure L1. After cooling to rt, the reaction mixture was poured into cold H₂O (60 mL). The resulting mixture was extracted with EtOAc (3×100 mL). The combined EtOAc extracts were washed with H₂O (2×40 mL) and brine (50 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* to afford the desired 1-fluoro-4-(4-nitrophenoxy)-2-(trifluoromethyl)benzene. The crude product was used directly for further transformation without further purification.

The nitro intermediate (2 mmol) obtained above was dissolved in MeOH (10 mL) and hydrogenated in the presence of 10% Pd/C (50 mg) until completion as indicated by TLC or LC-MS, according to General Procedure H. The reaction mixture was then filtered to remove the catalyst. The solvent was removed *in vacuo* to afford 4-(4'-fluoro-3'-trifluoromethyl-phenoxy)aniline, which was used directly for further transformation without purification (overall yield: 95%).

To a stirred solution of ice-cold 3-diethylaminopropanol (63 mmol) and TEA (80 mmol) dissolved in anhydrous DCM (50 mL) was added dropwise methanesulfonyl chloride (60 mmol), and the reaction mixture was stirred for 2h at 0°C and followed by additional 1h at rt. After the removal of the solvents *in vacuo*, the crude mesylate was dissolved in DMF (100 mL). 4-Hydroxyacetophenone (40 mmol) and cesium carbonate (100 mmol) were added, and the mixture was heated with stirring at 90°C for 18 h (monitored by LC-MS). After cooling to rt, the reaction was quenched with cold H₂O (100 mL), and the resulting mixture was extracted with EtOAc (4×100 mL). The combined EtOAc extracts were washed with brine (3×60 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*, and the crude 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was purified by silica gel column chromatography eluting with 10% MeOH in EtOAc + 0.2% TEA (yield: 75%).

To a stirred solution of 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone (4 mmol) in MeOH (10 mL) at rt, pyrrolidone hydrotribromide (4.8 mmol) was added, according to General Procedure R1. The reaction mixture was stirred at rt for 1h (monitored by LC-MS). The solvent was then removed *in vacuo* and the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was directly used for further transformation.

To a stirred solution of 4-(4'-fluoro-3'-trifluoromethyl-phenoxy)aniline (4.8 mmol) dissolved in anhydrous DMF (10 mL), DIEA (12 mmol) was added, followed by a slow addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone obtained above (~4 mmol), according to General Procedure R2. The reaction mixture was stirred at rt and under nitrogen until completion (~5h), as indicated by LC-MS. The reaction was quenched with saturated sodium bicarbonate (50 mL), and the resulting mixture was extracted with EtOAc (3×100 mL). The combined EtOAc extracts were washed with brine (3×40 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*, and the crude product was purified by silica gel column chromatography eluting with 10% MeOH in EtOAc + 0.2% TEA (yield: 64%).

To a stirred solution of the alkylated aniline described above (0.2 mmol) in anhydrous DCM (5 mL) at 0°C, TEA (1.2 mmol, 6 eq) was added, followed by a slow addition of 4-

fluorobenzoyl chloride (0.6 mmol, 3 eq), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by LC-MS. The solvent was removed *in vacuo*, and the crude amide was used directly for further transformation.

- 5 To a stirred solution of the amide described above (~0.2 mmol) in acetic acid (2 mL), ammonium acetate (excess, ~30 eq) was added, according to General Procedure R4. The reaction mixture was stirred at 100°C for 2-5h (as monitored by LC-MS). The reaction mixture was then cooled down and neutralized with saturated sodium bicarbonate. The resulting mixture was extracted with EtOAc (3×50 mL). The combined EtOAc extracts were
10 washed with brine (3×20 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*, and the pure product was obtained by silica gel column chromatography eluting with 10% MeOH in EtOAc + 0.2% TEA (overall yield: 60-70%) (yield 75 mg).

MS m/z 622 (M+H)⁺:

- 15 ¹H NMR (400 MHz, CDCl₃): δ 1.11 (t, 6H), 2.01 (m, 2H), 2.67 (q, 4H), 2.75 (t, 2H), 4.05 (t, 2H), 6.93 (d, 2H), 6.98-7.26 (m, 7H), 7.01 (d, 2H), 7.33 (s, 1H), 7.43 (d, 2H), 7.44 (d, 1H), 7.78 (d, 2H) ppm.

Example 423

- 20 [3-(4-{1-[4-(3,5-bis-trifluoromethyl-phenoxy)-phenyl]-2-butyl-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine

- 3-Diethylaminopropanol (20mmol, 1eq) was dissolved in DCM (25mL), TEA (40mmol, 2 eq) was added and the mixture was cooled to 0°C. To this mixture, methanesulfonyl chloride (30mmol, 1.5 eq) was added slowly with stirring and the reaction mixture was stirred at 0°C for an hour and at rt for another hour (until the reaction was complete by HPLC). The
25 solvent was removed and saturated aqueous sodium bicarbonate was added. The product was extracted with EtOAc (3 x) and washed with sodium bicarbonate and water. The solvent was removed *in vacuo*.

- The mesylate from the previous step (20mmol, 1 eq) was dissolved in anhydrous DMF (25mL) to which 4-hydroxyacetophenone (20mmol, 1 eq) and potassium carbonate (60mmol, 3 eq) were added. The mixture was heated under reflux at 85°C for 18 h (until the
30 reaction was complete by HPLC), after which it was cooled to rt. Saturated aqueous sodium

bicarbonate was added to the mixture, which was then transferred to a separatory funnel. The product was extracted with EtOAc and washed with sodium bicarbonate and water. The solvent was removed *in vacuo* and the 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was purified by flash chromatography (going by increasing gradient up to 10% MeOH in DCM).

5 The overall yield was 60%.

3,5-bis-trifluoromethylphenol (10 mmol) was dissolved in 15 ml of anhydrous DMF and potassium carbonate (30 mmol) was added with stirring at rt. 4-Fluoronitrobenzene (10 mmol) was added to this mixture, which was then heated under reflux at 80°C for 18 h. The reaction was quenched with 30 ml of water and 30 ml of sodium bicarbonate, extracted with EtOAc (3 x 50 ml) and washed with sodium bicarbonate and water. The EtOAc layer was dried over anhydrous sodium sulfate and filtered, after which the solvent was removed *in vacuo*.

10 The nitro intermediate (10 mmol) obtained above was dissolved in EtOH (30mL) and hydrogenated in the presence of 10% Pd/C (10 mg) until completion as indicated by TLC or HPLC, according to General Procedure H. The reaction mixture was then filtered to remove the catalyst. The solvent was removed *in vacuo* to afford the desired 4-(3,5-bis-trifluoromethyl)phenoxyaniline, which was used directly for further transformation without further purification (yield 80%).

20 To a stirred solution of 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone (2 mmol) in anhydrous MeOH (6 mL) at 0°C, pyrrolidone hydrotribromide (1.2 eq) was added, according to General Procedure R1. The reaction mixture was stirred under nitrogen at 0°C for 1h and was allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was then removed *in vacuo* and the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was used for further transformation.

25 To a solution of 4-(3,5-bis-trifluoromethyl)phenoxyaniline (1 eq, 2 mmol) in anhydrous DMF (6mL), DIEA (3 eq 6 mmol) was added, followed by addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone described above (2 mmol), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Removal of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product obtained from 2-4% MeOH/DCM (yield 50%).

To a stirred solution of alkylated aniline described above (1 mmol) in anhydrous DCM (4 mL) at 0°C, TEA (3eq, 3 mmol) was added, followed by a slow addition of valeryl chloride (3 eq, 3 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (1 mmol) in acetic acid (4 mL), ammonium acetate (20 eq) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled to rt and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained from 4-6% MeOH/DCM (yield 139mg).

MS m/z 635 (M+H)⁺:

¹H NMR (400 MHz, CDCl₃): δ 7.7 (d, 2H), 7.3 (m, 3H), 7.1 (m, 5H), 6.9 (d, 2H), 4.0 (t, 2H), 2.6-2.8 (m, 8H), 2.0 (m, 2H), 1.6 (m, 2H), 1.3 (m, 2H), 1.1 (t, 6H), 0.8 (t, 3H) ppm.

Example 424

(3-{4-[1-(4-benzyloxy-phenyl)-2-butyl-1H-imidazol-4-yl]-phenoxy}-propyl)-diethyl-amine

3-Diethylaminopropanol (20mmol, 1eq) was dissolved in DCM (25mL), TEA (40mmol, 2 eq) was added and the mixture was cooled to 0°C. To this mixture, methanesulfonyl chloride (30mmol, 1.5 eq) was added slowly with stirring and the reaction mixture was stirred at 0°C for an hour and at rt for another hour (until the reaction was complete by HPLC). The solvent was removed and saturated aqueous sodium bicarbonate was added. The product was extracted with EtOAc (3 x) and washed with sodium bicarbonate and water. The solvent was removed *in vacuo*.

The mesylate from the previous step (20mmol, 1 eq) was dissolved in anhydrous DMF (25mL) to which 4-hydroxyacetophenone (20mmol, 1 eq) and potassium carbonate (60mmol, 3 eq) were added. The mixture was heated under reflux at 85°C for 18 h (until the reaction was complete by HPLC), after which it was cooled to rt. Saturated aqueous sodium bicarbonate was added to the mixture, which was then transferred to a separatory funnel.

The product was extracted with EtOAc and washed with sodium bicarbonate and water. The

solvent was removed *in vacuo* and the product was purified by flash chromatography (going by increasing gradient up to 10% MeOH in DCM). The overall yield was 60%.

To a stirred solution of 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone (2 mmol) in anhydrous MeOH (6 mL) at 0°C, pyrrolidone hydrotribromide (1.2 eq) was added, according to General Procedure R1. The reaction mixture was stirred under nitrogen at 0°C for 1h and was allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was then removed *in vacuo* and the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was used for further transformation.

To a solution of 4-benzyloxyaniline (1 eq, 2 mmol) in anhydrous DMF (6 mL), DIEA (3 eq 6 mmol) was added, followed by addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone described above (2 mmol), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product obtained from 2-4% MeOH/DCM (yield 56%).

To a stirred solution of alkylated aniline described above (1 mmol) in anhydrous DCM (4 mL) at 0°C, TEA (3eq, 3 mmol) was added, followed by a slow addition of valeryl chloride (3 eq, 3 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (1 mmol) in acetic acid (4 mL), ammonium acetate (20 eq) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled to rt and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained from 4-6% MeOH/DCM (yield 205 mg).

MS m/z 513 (M+H)⁺;

¹H NMR (CDCl₃): δ 7.68 (d, 2H), 7.40 (m, 5H), 7.23 (d, 2H), 7.11 (s, 1H), 7.05 (d, 2H), 6.89 (d, 2H), 5.12 (s, 2H), 4.02 (t, 2H), 2.62-2.73 (m, 8H), 1.98 (m, 2H), 1.63 (m, 2H), 1.28 (m, 2H), 1.07 (t, 6H), 0.82 (t, 3H) ppm.

Example 425

{3-[4-(2-tert-butyl-4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine

- 5 To a stirred solution of 4-fluoronitrobenzene (2.0 mmol) in anhydrous THF (5 mL) at 0°C, a 1M solution of a potassium diethylaminopropoxide (2.2 mmol) in THF was added dropwise and under a nitrogen stream, according to General Procedure L1. The reaction mixture was stirred at 0°C for 1 h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The reaction mixture was then treated with cold H₂O (15 mL), and extracted with EtOAc (2x15 mL). The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of the solvent *in vacuo* afforded the desired 4-alkoxynitrobenzene. The crude product was used directly for further transformation .

- 15 The N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (2 mmol) obtained above was dissolved in MeOH (10 mL) and hydrogenated in the presence of 10% Pd/C (10 mg) until completion as indicated by TLC or HPLC, according to General Procedure H. The reaction mixture was then filtered to remove the catalyst. The solvent was removed *in vacuo* to afford the desired 4-alkoxyaniline, which was used directly for further transformation without further purification.

- 20 To a stirred solution of 4'-hydroxyacetophenone (2.2 mmol) in DMF (5 mL) at rt, solid potassium carbonate (9.0 mmol) was added. 4-chlorophenethyl mesylate (2.0 mmol) was added to the reaction mixture and heated to 80°C until completion according to General Procedure Q1, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was quenched using cold water (20 ml) and the product was isolated in EtOAc (2X20 ml). The combined organic layers were washed with saturated sodium bicarbonate (2X10 ml), water (2X10 ml) and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired 1-{4-[2-(4-chlorophenyl)ethoxy]phenyl}ethanone. The crude alkylated acetophenone was used for further transformation .

- 30 To a stirred solution of the 1-{4-[2-(4-chlorophenyl)ethoxy]phenyl}ethanone (2 mmol) in anhydrous MeOH (5 mL) at 0°C, pyrrolidone hydrotribromide (1.2 eq., 2.2 mmol) was added, according to General Procedure R1. The reaction mixture was stirred under nitrogen at 0°C for 1h and was allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was then removed *in vacuo* and the residue was treated with saturated sodium

bicarbonate. The aqueous layer was poured into EtOAc (20 ml) and the product was isolated in EtOAc (2X20 ml). The combined organic layers were washed with saturated sodium bicarbonate (2X10 ml), and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired product.

5 The crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was purified by chromatography (Silica gel). Pure product was obtained from 20-30% EtOAc/hexane (yield ~70-75%).

10 To a stirred solution of the N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (1.2 eq., 2 mmol) in anhydrous DMF (5 mL) DIEA (3 eq. 6 mmol) was added, followed by slow addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone described above (1.6 mmol), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was used for further transformation .

20 To a stirred solution of 1-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-[4-(3-diethylamino-propoxy)-phenylamino]-ethanone described above (1.6 mmol) in anhydrous DCM (5 mL) at 0°C, TEA (3eq., 4.8 mmol) was added, followed by slow addition of pivaloyl chloride (2 eq., 3.2 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in DCM. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

25 To a stirred solution of the amide described above (1.6 mmol) in acetic acid (4 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled to rt and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained from 4-6% MeOH/DCM (yield: 270 mg).

30 MS m/z 561 (M+H)⁺:

¹H NMR (400 MHz, CDCl₃): δ7.69 (d, 2H), 7.23-7.25 (m, 6H), 6.98 (s, 1H), 6.84 (m 4H), 4.15 (t, 2H), 4.08 (t, 2H), 3.05 (t, 2H), 2.85 (m, 6H), 2.16 (s, 9H), 2.05 (m, 2H), 1.19 (t, 6H) ppm.

Example 426

[3-(4-{2-butyl-1-[4-(3-fluoro-4-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine

To a stirred solution of 4-benzyloxyacetophenone (7.0 mmol) in anhydrous DCM (30.0 mL) and MeOH (5.0mL) at rt, pyridinium bromide perbromide (1.1eq.) was added. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC. The mixture was diluted with EtOAc (100 ml) and washed with H₂O (2X50 ml), brine (30 ml) and dried with magnesium sulfate. The solvent was then removed *in vacuo* to give a white solid. The alpha-bromoacetophenone was used for further transformation without further purification.

To a stirred solution of 4-(3-fluoro-4-trifluoromethyl-phenoxy)-aniline (1.64 mmol) in anhydrous DMF (30 mL) DIEA (3 eq) was added, followed by slow addition of the alpha-bromoacetophenone described above (2 eq), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC and HPLC. The reaction mixture was then diluted with cold H₂O and the product was isolated in Et₂O. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product was obtained from 5-20% EtOAc/Hexane (yield ~50-60%).

To a stirred solution of alkylated aniline described above (1.0 mmol) in anhydrous THF (20 mL) at 0°C, TEA (3eq, 3 mmol) was added, followed by slow addition of valeryl chloride (3 eq, 3.0 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to ambient temperature until completion, as indicated by TLC and HPLC. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (1.0 mmol) in acetic acid (2 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled down and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained from 5-15 % EtOAc/Hexane (yield 80%).(MS: *m/z* 562 (M+H)⁺)

The above product was dissolved in MeOH (20 mL), and Pd/C (100 mg) was added and the heterogeneous mixture was stirred overnight under hydrogen atmosphere using a balloon,

according to General Procedure H. The Pd/C was removed by filtration. The solvent was removed *in vacuo*, and the crude phenol (MS: m/z 472 (M+H)⁺) was used for further transformation.

To a stirred solution of the phenol (1.0 eq) obtained above in anhydrous DMF (5.0 mL) solid sodium hydride (60% dispersion in oil; 1.0mmol) was added in portions. After the addition, the requisite alkylhalide or the mesylate (prepared from the corresponding alcohol and methanesulfonyl chloride) (1.5-2.0eq) was added to the reaction mixture. The reaction mixture was heated at 90 °C overnight. After cooling the mix to rt, Et₂O (30 mL) was added to the reaction mixture followed by H₂O (10 mL). The organic layer was washed with H₂O (2x15 mL) and brine, and dried over sodium sulfate. The solvent was removed *in vacuo*. Pure product was obtained from 5-10% MeOH/DCM (yield 65.0 mg).

MS m/z 557 (M+H)⁺:

¹H NMR (CDCl₃): δ 7.70 (d, 2H), 7.20-7.35 (m, 5H), 7.14 (s, 1H), 7.08 (d, 2H), 6.92 (d, 2H), 4.02 (t, 2H), 2.66 (t, 2H), 2.47 (t, 2H), 2.26 (s, 6H), 1.96 (m, 2H), 1.64 (m, 2H), 1.29 (m, 2H) 0.9 (t, 3H) ppm.

Example 427

diethyl-[3-(4-{4-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-imidazol-1-yl}-phenoxy)-propyl]-amine

To a stirred solution of N-[3-(4-aminophenoxy)propyl]-N,N-diethylamine (1.2 eq, 2 mmol) in anhydrous DMF (5 mL) DIEA (3 eq 6 mmol) was added, followed by a slow addition of 2-bromo-1-(4-bromophenyl)ethanone (1.6 mmol), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold H₂O and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product was obtained from 2-4% MeOH/DCM (yield ~50-60%).

To a stirred solution of 1-(4-bromophenyl)-2-({4-[3-(diethylamino)propoxy]phenyl}amino)ethanone (2 mmol) in acetic acid (2 mL), ammonium acetate (excess, ~20 eq) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled down and

neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained from 4-6% MeOH/DCM (yield 40-50%).

To a solution of N-(3-{4-[4-(4-bromophenyl)-1H-imidazol-1-yl]phenoxy}propyl)-N,N-diethylamine (0.07 mmol) in pyridine (1 mL), copper powder was added (0.14 mmol), followed by potassium carbonate (0.35 mmol) and 4-fluoro-3-methylphenol (0.14 mmol). The mixture was heated at 110°C overnight, then diluted with H₂O (2 mL) and extracted with EtOAc (3 x 2mL). The combined organic extract was dried over sodium sulfate, filtered and concentrated to an oil, which was purified by column chromatography (Silica gel). The pure product was obtained from 1-6% MeOH/DCM.

MS m/z 528 (M+H)⁺:

¹H NMR (400 MHz, CDCl₃): δ 7.86-7.78 (m, 3H), 7.54-7.44 (m, 2H), 7.38-7.34 (m, 2H), 7.28-7.24 (m, 1H), 7.20-7.16 (m, 2H), 7.06-6.80 (m, 3H), 4.10 (t, 2H), 2.80-2.60 (m, 6H), 2.10-2.00 (m, 2H), 1.30 (t, 3H), 1.10 (t, 3H) ppm.

Example 428

(3-{4-[4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-(4-fluoro-phenyl)-imidazol-1-yl]-phenoxy}-propyl)-diethyl-amine

To a stirred solution of 4-fluoronitrobenzene (2.0 mmol) in anhydrous THF (5 mL) at 0°C, a 1M solution of a potassium diethylaminopropoxide (2.2 mmol) in THF was added dropwise and under a nitrogen stream, according to General Procedure L1. The reaction mixture was stirred at 0°C for 1 h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The reaction mixture was then treated with cold H₂O (15 mL), and extracted with EtOAc (2x15 mL). The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of the solvent *in vacuo* afforded the desired 4-alkoxynitrobenzene. The crude product was used directly for further transformation .

The N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (2 mmol) obtained above was dissolved in MeOH (10 mL) and hydrogenated in the presence of 10% Pd/C (10 mg) until completion as indicated by TLC or HPLC, according to General Procedure H. The reaction mixture was then filtered to remove the catalyst. The solvent was removed *in vacuo* to afford the desired 4-alkoxyaniline, which was used directly for further transformation without further purification.

To a stirred solution of 4'-hydroxyacetophenone (2.2 mmol) in DMF (5 mL) at rt, solid potassium carbonate (9.0 mmol) was added. 4-chlorophenethyl mesylate (2.0 mmol) was added to the reaction mixture and heated to 80°C until completion according to General Procedure Q1, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was quenched using cold water (20 ml) and the product was isolated in EtOAc (2X20 ml). The combined organic layers were washed with saturated sodium bicarbonate (2X10 ml), water (2X10 ml) and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired 1-{4-[2-(4-chlorophenyl)ethoxy]phenyl}ethanone. The crude alkylated acetophenone was used for further transformation .

To a stirred solution of the 1-{4-[2-(4-chlorophenyl)ethoxy]phenyl}ethanone (2 mmol) in anhydrous MeOH (5 mL) at 0°C, pyrrolidone hydrotribromide (1.2 eq., 2.2 mmol) was added, according to General Procedure R1. The reaction mixture was stirred under nitrogen at 0°C for 1h and was allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was then removed *in vacuo* and the residue was treated with saturated sodium bicarbonate. The aqueous layer was poured into EtOAc (20 ml) and the product was isolated in EtOAc (2X20 ml). The combined organic layers were washed with saturated sodium bicarbonate (2X10 ml), and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired product. The crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was purified by chromatography (Silica gel). Pure product was obtained from 20-30% EtOAc/hexane (yield ~70-75%).

To a stirred solution of the N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (1.2 eq., 2 mmol) in anhydrous DMF (5 mL) DIEA (3 eq. 6 mmol) was added, followed by slow addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone described above (1.6 mmol), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was used for further transformation .

To a stirred solution of 1-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-[4-(3-diethylamino-propoxy)-phenylamino]-ethanone described above (1.6 mmol) in anhydrous DCM (5 mL) at 0°C, TEA (3eq., 4.8 mmol) was added, followed by slow addition of 4-fluorobenzoyl chloride (2 eq., 3.2 mmol), according to General Procedure R3. The reaction mixture was stirred

under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in DCM. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

5 To a stirred solution of the amide described above (1.6 mmol) in acetic acid (4 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled to rt and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica
10 gel). Pure product was obtained from 4-6% MeOH/DCM (yield: 334 mg).

MS m/z 598 (M+H)⁺:

¹H NMR (400 MHz, CDCl₃): δ 7.76 (d, 2H), 7.41 (m, 2H), 7.26 (m, 2H), 7.21 (d, 2H), 7.16 (d, 2H), 7.01 (m, 7H), 4.16 (t, 2H), 4.05 (t, 2H), 3.05 (t, 2H), 2.97 (m, 6H), 2.18 (m, 2H), 1.24 (t, 6H) ppm

15

Example 429

{3-[4-(4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-cyclopropyl-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine

To a stirred solution of 4-fluoronitrobenzene (2.0 mmol) in anhydrous THF (5 mL) at 0°C, a
20 1M solution of a potassium diethylaminopropoxide (2.2 mmol) in THF was added dropwise and under a nitrogen stream, according to General Procedure L1. The reaction mixture was stirred at 0°C for 1 h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The reaction mixture was then treated with cold H₂O (15 mL), and extracted with EtOAc (2x15 mL). The combined organic layers were washed with brine and dried over
25 sodium sulfate. Evaporation of the solvent *in vacuo* afforded the desired 4-alkoxynitrobenzene. The crude product was used directly for further transformation .

The N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (2 mmol) obtained above was dissolved in MeOH (10 mL) and hydrogenated in the presence of 10% Pd/C (10 mg) until completion as indicated by TLC or HPLC, according to General Procedure H. The reaction mixture was
30 then filtered to remove the catalyst. The solvent was removed *in vacuo* to afford the desired 4-alkoxyaniline, which was used directly for further transformation without further purification.

To a stirred solution of 4'-hydroxyacetophenone (2.2 mmol) in DMF (5 mL) at rt, solid potassium carbonate (9.0 mmol) was added. 4-chlorophenethyl mesylate (2.0 mmol) was added to the reaction mixture and heated to 80°C until completion according to General Procedure Q1, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was quenched using cold water (20 ml) and the product was isolated in EtOAc (2X20 ml). The combined organic layers were washed with saturated sodium bicarbonate (2X10 ml), water (2X10 ml) and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired 1-{4-[2-(4-chlorophenyl)ethoxy]phenyl}ethanone. The crude alkylated acetophenone was used for further transformation .

To a stirred solution of the 1-{4-[2-(4-chlorophenyl)ethoxy]phenyl}ethanone (2 mmol) in anhydrous MeOH (5 mL) at 0°C, pyrrolidone hydrotribromide (1.2 eq., 2.2 mmol) was added, according to General Procedure R1. The reaction mixture was stirred under nitrogen at 0°C for 1h and was allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was then removed *in vacuo* and the residue was treated with saturated sodium bicarbonate. The aqueous layer was poured into EtOAc (20 ml) and the product was isolated in EtOAc (2X20 ml). The combined organic layers were washed with saturated sodium bicarbonate (2X10 ml), and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired product. The crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was purified by chromatography (Silica gel). Pure product was obtained from 20-30% EtOAc/hexane.

To a stirred solution of the N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (1.2 eq., 2 mmol) in anhydrous DMF (5 mL) DIEA (3 eq. 6 mmol) was added, followed by slow addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone described above (1.6 mmol), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was used for further transformation .

To a stirred solution of 1-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-[4-(3-diethylamino-propoxy)-phenylamino]-ethanone described above (1.6 mmol) in anhydrous DCM (5 mL) at 0°C, TEA (3eq., 4.8 mmol) was added, followed by slow addition of cyclopropanecarbonyl chloride (2 eq., 3.2 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated

by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in DCM. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (1.6 mmol) in acetic acid (4 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled to rt and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained from 4-6% MeOH/DCM (yield: 260 mg).

MS m/z 544 (M+H)⁺:

¹H NMR (400 MHz, CDCl₃): δ 7.65 (d, 2H), 7.31 (m, 4H), 7.21 (d, 2H), 7.18 (s, 1H), 6.98 (d, 2H), 6.88 (d, 2H), 4.18 (t, 2H), 4.08 (t, 2H), 3.07 (t, 2H), 3.12 (m, 1H), 2.78 (m, 6H), 2.57 (m, 4H), 2.06 (m, 2H), 1.12 (t, 6H) ppm

Example 430

{3-[4-(4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-cyclopentyl-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine

To a stirred solution of 4-fluoronitrobenzene (2.0 mmol) in anhydrous THF (5 mL) at 0°C, a 1M solution of a potassium diethylaminopropoxide (2.2 mmol) in THF was added dropwise and under a nitrogen stream, according to General Procedure L1. The reaction mixture was stirred at 0°C for 1 h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The reaction mixture was then treated with cold H₂O (15 mL), and extracted with EtOAc (2x15 mL). The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of the solvent *in vacuo* afforded the desired 4-alkoxynitrobenzene. The crude product was used directly for further transformation.

The N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (2 mmol) obtained above was dissolved in MeOH (10 mL) and hydrogenated in the presence of 10% Pd/C (10 mg) until completion as indicated by TLC or HPLC, according to General Procedure H. The reaction mixture was then filtered to remove the catalyst. The solvent was removed *in vacuo* to afford the desired 4-alkoxyaniline, which was used directly for further transformation without further purification.

To a stirred solution of 4'-hydroxyacetophenone (2.2 mmol) in DMF (5 mL) at rt, solid potassium carbonate (9.0 mmol) was added. 4-chlorophenethyl mesylate (2.0 mmol) was added to the reaction mixture and heated to 80°C until completion according to General Procedure Q1, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was quenched using cold water (20 ml) and the product was isolated in EtOAc (2X20 ml). The combined organic layers were washed with saturated sodium bicarbonate (2X10 ml), water (2X10 ml) and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired 1-{4-[2-(4-chlorophenyl)ethoxy]phenyl}ethanone. The crude alkylated acetophenone was used for further transformation .

To a stirred solution of the 1-{4-[2-(4-chlorophenyl)ethoxy]phenyl}ethanone (2 mmol) in anhydrous MeOH (5 mL) at 0°C, pyrrolidone hydrotribromide (1.2 eq., 2.2 mmol) was added, according to General Procedure R1. The reaction mixture was stirred under nitrogen at 0°C for 1h and was allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was then removed *in vacuo* and the residue was treated with saturated sodium bicarbonate. The aqueous layer was poured into EtOAc (20 ml) and the product was isolated in EtOAc (2X20 ml). The combined organic layers were washed with saturated sodium bicarbonate (2X10 ml), and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired product. The crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was purified by chromatography (Silica gel). Pure product was obtained from 20-30% EtOAc/hexane (yield ~70-75%).

To a stirred solution of the N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (1.2 eq., 2 mmol) in anhydrous DMF (5 mL) DIEA (3 eq. 6 mmol) was added, followed by slow addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone described above (1.6 mmol), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was used for further transformation .

To a stirred solution of 1-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-[4-(3-diethylamino-propoxy)-phenylamino]-ethanone described above (1.6 mmol) in anhydrous DCM (5 mL) at 0°C, TEA (3eq., 4.8 mmol) was added, followed by slow addition of cyclopentanecarbonyl chloride (2 eq., 3.2 mmol), according to General Procedure R3. The reaction mixture was

stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in DCM. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

- 5 To a stirred solution of the amide described above (1.6 mmol) in acetic acid (4 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled to rt and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained from 4-6% MeOH/DCM (yield: 366 mg)
- 10

MS m/z 572 (M+H)⁺:

Example 431

[3-(4-{4-[4-(biphenyl-4-yloxy)-phenyl]-imidazol-1-yl}-phenoxy)-propyl]-diethyl-amine

- 15 To a stirred solution of N-[3-(4-aminophenoxy)propyl]-N,N-diethylamine (1.2 eq, 2 mmol) in anhydrous DMF (5 mL) DIEA (3 eq 6 mmol) was added, followed by a slow addition of the 2-bromo-1-(4-bromophenyl)ethanone described above (1.6 mmol), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold H₂O and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product.
- 20 The crude alkylated aniline was purified by chromatography (Silica gel). Pure product was obtained from 2-4% MeOH/DCM (yield ~50-60%).

- To a stirred solution of 1-(4-bromophenyl)-2-({4-[3-(diethylamino)propoxy]phenyl}amino)ethanone (2 mmol) in acetic acid (2 mL), ammonium acetate (excess, ~20 eq) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled down and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained from 4-6% MeOH/DCM (yield 40-50%).
- 25
- 30

To a solution of the N-(3-{4-[4-(4-bromophenyl)-1H-imidazol-1-yl]phenoxy}propyl)-N,N-diethylamine (0.07 mmol) in pyridine (1 mL), copper powder was added (0.14 mmol),

5 followed by potassium carbonate (0.35 mmol) and 1,1'-biphenyl-4-ol (0.14 mmol). The mixture was heated at 110°C overnight, then diluted with H₂O (2 mL) and extracted with EtOAc (3 x 2mL). The combined organic extract was dried over sodium sulfate, filtered and concentrated to an oil, which was purified by column chromatography (Silica gel). The pure product was obtained from 1-6% MeOH/DCM (yield 11 mg).

MS m/z 518 (M+H)⁺:

¹H NMR (400 MHz, CDCl₃): δ 7.83-7.79 (m, 3H), 7.59-7.57 (m, 4H), 7.45-7.43 (m, 4H), 7.42-7.34 (m, 4H), 7.11 (d, 2H), 7.05 (d, 3H), 4.10 (t, 2H), 2.80-2.60 (m, 6H), 2.00-2.10 (m, 2H), 1.30 (t, 3H), 1.10 (t, 3H) ppm.

Example 432

diethyl-[3-(4-{4-[4-(3-trifluoromethyl-phenoxy)-phenyl]-imidazol-1-yl}-phenoxy)-propyl]-amine

To a stirred solution of N-[3-(4-aminophenoxy)propyl]-N,N-diethylamine (1.2 eq, 2 mmol) in anhydrous DMF (5 mL) DIEA (3 eq 6 mmol) was added, followed by a slow addition of 2-bromo-1-(4-bromophenyl)ethanone (1.6 mmol), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold H₂O and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product was obtained from 2-4% MeOH/DCM (yield ~50-60%).

To a stirred solution of 1-(4-bromophenyl)-2-({4-[3-(diethylamino)propoxy]phenyl}amino)ethanone (2 mmol) in acetic acid (2 mL), ammonium acetate (excess, ~20 eq) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled down and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained from 4-6% MeOH/DCM (yield 40-50%).

To a solution of N-(3-{4-[4-(4-bromophenyl)-1H-imidazol-1-yl]phenoxy}propyl)-N,N-diethylamine (0.07 mmol) in pyridine (1 mL), copper powder was added (0.14 mmol), followed by potassium carbonate (0.35 mmol) and 3-(trifluoromethyl)phenol (0.14 mmol).

The mixture was heated at 110°C overnight, then diluted with H₂O (2 mL) and extracted with EtOAc (3 x 2mL). The combined organic extract was dried over sodium sulfate, filtered and concentrated to an oil, which was purified by column chromatography (Silica gel). The pure product was obtained from 1-6% MeOH/DCM (yield 10 mg).

5 MS m/z 510 (M+H)⁺:

Example 433

[3-(4-{4-[4-(3,4-dichloro-phenoxy)-phenyl]-imidazol-1-yl}-phenoxy)-propyl]-diethyl-amine

10 To a stirred solution of N-[3-(4-aminophenoxy)propyl]-N,N-diethylamine (1.2 eq, 2 mmol) in anhydrous DMF (5 mL) DIEA (3 eq 6 mmol) was added, followed by a slow addition of 2-bromo-1-(4-bromophenyl)ethanone (1.6 mmol), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold H₂O and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate.

15 Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product was obtained from 2-4% MeOH/DCM (yield ~50-60%).

20 To a stirred solution of 1-(4-bromophenyl)-2-({4-[3-(diethylamino)propoxy]phenyl}amino)ethanone (2 mmol) in acetic acid (2 mL), ammonium acetate (excess, ~20 eq) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled down and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained from 4-6% MeOH/DCM (yield 40-50%).

25 To a solution of N-(3-{4-[4-(4-bromophenyl)-1H-imidazol-1-yl]phenoxy}propyl)-N,N-diethylamine (0.07 mmol) in pyridine (1 mL), copper powder was added (0.14 mmol) followed by potassium carbonate (0.35 mmol), and 3,4-dichlorophenol (0.14 mmol). The mixture was heated at 110°C overnight, then diluted with H₂O (2 mL) and extracted with EtOAc (3 x 2mL). The combined organic extract was dried over sodium sulfate, filtered and

30 concentrated to an oil, which was purified by column chromatography (Silica gel). The pure product was obtained from 1-6% MeOH/DCM (yield 15 mg).

MS m/z 510 (M+H)⁺:

Example 434

5 [3-(4-{2-butyl-1-[4-(4-methoxy-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine

3-Diethylaminopropanol (20mmol, 1 eq) was dissolved in DCM (25mL), TEA (40mmol, 2 eq) was added and the mixture was cooled to 0°C. To this mixture, methanesulfonyl chloride (30mmol, 1.5 eq) was added slowly with stirring and the reaction mixture was stirred at 0°C for an hour and at rt for another hour (until the reaction was complete by HPLC). The solvent was removed and to this saturated aqueous sodium bicarbonate was added. The product was extracted with EtOAc (3 x) and washed with sodium bicarbonate and water. The solvent was removed *in vacuo*.

15 The mesylate from the previous step (20mmol, 1 eq) was dissolved in anhydrous DMF (25mL) to which 4-hydroxyacetophenone (20mmol, 1 eq) and potassium carbonate (60mmol, 3 eq) were added. The mixture was heated under reflux at 85°C for 18 h (until the reaction was complete by HPLC), after which it was cooled to rt. Saturated aqueous sodium bicarbonate was added to the mixture, which was then transferred to a separatory funnel. The product was extracted with EtOAc and washed with sodium bicarbonate and water. The solvent was removed *in vacuo* and the 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was purified by flash chromatography (going by increasing gradient up to 10% MeOH in DCM). The overall yield was 60%.

25 4-Methoxyphenol (10 mmol) was dissolved in 15 ml of anhydrous DMF and potassium carbonate (30 mmol) was added with stirring at rt. 4-Fluoronitrobenzene (10 mmol) was added to this mixture, which was then heated under reflux at 80°C for 18 h. The reaction was quenched with 30 ml of water and 30 ml of sodium bicarbonate, extracted with EtOAc (3 x 50 ml) and washed with sodium bicarbonate and water. The EtOAc layer was dried over anhydrous sodium sulfate and filtered, after which the solvent was removed *in vacuo*.

30 The nitro intermediate (10 mmol) obtained above was dissolved in EtOH (30mL) and hydrogenated in the presence of 10% Pd/C (10 mg) until completion as indicated by TLC or HPLC, according to General Procedure H. The reaction mixture was then filtered to remove the catalyst. The solvent was removed *in vacuo* to afford the desired 4-(4-

methoxyphenoxy)aniline, which was used directly for further transformation without further purification (yield 80%).

To a stirred solution of 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone (2 mmol) in anhydrous MeOH (6 mL) at 0°C, pyrrolidone hydrotribromide (1.2 eq) was added, according to General Procedure R1. The reaction mixture was stirred under nitrogen at 0°C for 1h and was allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was then removed *in vacuo* and the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was used for further transformation.

To a solution of 4-(4-methoxyphenoxy) aniline (1 eq, 2 mmol) in anhydrous DMF (6 mL), DIEA (3 eq 6 mmol) was added, followed by addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone described above (2 mmol), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product obtained from 2-4% MeOH/DCM (yield 52%).

To a stirred solution of alkylated aniline described above (1 mmol) in anhydrous DCM (4 mL) at 0°C, TEA (3eq, 3 mmol) was added, followed by a slow addition of valeryl chloride (3 eq, 3 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (1 mmol) in acetic acid (4 mL), ammonium acetate (20 eq) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled to rt and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained from 4-6% MeOH/DCM (yield 190 mg).

MS m/z 529 (M+H)⁺:

¹H NMR (CDCl₃): δ7.7 (d, 2H), 7.2 (d, 2H), 7.16 (s, 1H), 6.8-7.1 (m, 8H), 4.0 (t, 2H), 3.8 (s, 3H), 2.8-3.0 (m, 8H), 2.6 (m, 2H), 2.2 (m, 2H), 1.6(m, 2H), 1.2 (t, 6H), 0.8 (t, 3H) ppm.

Example 435

1-[2-(4-{2-butyl-1-[4-(3-fluoro-4-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-ethyl]-piperazine

To a stirred solution of 4-benzyloxyacetophenone (7.0 mmol) in anhydrous DCM (30.0 mL) and MeOH (5.0 mL) at rt, pyridinium bromide perbromide (1.1 eq.) was added. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC. The mixture was diluted with EtOAc (100 ml) and washed with H₂O (2X50 ml), brine (30 ml) and dried with magnesium sulfate. The solvent was then removed *in vacuo* to give a white solid. The alpha-bromoacetophenone was used for further transformation without further purification.

To a stirred solution of 4-(3-fluoro-4-trifluoromethyl-phenoxy)-aniline (1.64 mmol) in anhydrous DMF (30 mL) DIEA (3 eq) was added, followed by slow addition of the alpha-bromoacetophenone described above (2 eq), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC and HPLC. The reaction mixture was then diluted with cold H₂O and the product was isolated in Et₂O. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product was obtained from 5-20% EtOAc/Hexane (yield ~50-60%).

To a stirred solution of alkylated aniline described above (1.0 mmol) in anhydrous THF (20 mL) at 0°C, TEA (3eq, 3 mmol) was added, followed by slow addition of valeryl chloride (3 eq, 3.0 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to ambient temperature until completion, as indicated by TLC and HPLC. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (1.0 mmol) in acetic acid (2 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled down and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained from 5-15 % EtOAc/Hexane (yield 80%). (MS: *m/z* 562 (M+H)⁺)

The above product was dissolved in MeOH (20 mL), and Pd/C (100 mg) was added and the heterogeneous mixture was stirred overnight under hydrogen atmosphere using a balloon,

according to General Procedure H. The Pd/C was removed by filtration. The solvent was removed *in vacuo*, and the crude phenol (MS: m/z 472 (M+H)⁺) was used for further transformation.

To a stirred solution of the phenol (0.16 mmol) obtained above in anhydrous DMF (5 mL) solid sodium hydride (60% dispersion in oil; 1.0mmol) was added in portions. After the addition, 4-(2-methanesulfonyloxy)-piperazine-1-carboxylic acid tertbutylester (2.0 mmol) was added to the reaction mixture. The reaction mixture was heated at 90°C overnight. After cooling the mix to rt, Et₂O (30 mL) was added to the reaction mixture followed by H₂O (10 mL). The organic layer was washed with H₂O (2x15 mL) and brine, and dried over sodium sulfate. The solvent was removed *in vacuo*. Pure product was obtained from 5-10% MeOH/DCM (yield ~45%).

This product was dissolved in DCM (10 mL) and HCl (4.0 M in dioxane, 1.0 mL) was added and stirrings continued overnight until reaction completed as indicated by HPLC. EtOAc (40 ml) added, followed by sodium bicarbonate (sat, 15mL). The organic layer was washed with brine (10 mL) and dried with magnesium sulfate. The solvent was removed in *in vacuo* to give the title compound as white solid (yield 37 mg).

MS m/z 584 (M+H)⁺:

¹H NMR (CDCl₃): δ7.70 (d, 2H), 7.20-7.35 (m, 5H), 7.14 (s, 1H), 7.08 (d, 2H), 6.92 (d, 2H), 4.05 (t, 2H), 3.0 (m, 4H), 2.8 (t, 2H), 3.4 (m, 6H), 1.6 (m, 2H), 1.3 (m, 3H), 0.9 (t, 3H) ppm.

Example 436

{3-[4-(4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-imidazol-1-yl)-phenoxy]-propyl}-dimethyl-amine

To a stirred solution of 4-aminophenol (4.8 mmol) in MeOH (20 mL), 1-bromo-4'-(4-chlorophenethoxy)acetophenone (4 mmol) was added at rt. The resulting mixture was then heated to reflux for 45 min. The reaction mixture was then cooled to rt and the solvent was removed *in vacuo*. The resulting solid was dissolved in EtOAc (30 mL), washed with H₂O (2X20 mL) and brine (20 mL) and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired 1-(4-hydroxyphenyl)amino-4'-(4-chlorophenethoxy)acetophenone, which was used for further transformation .

The aminoacetophenone obtained as above (3 mmol) was dissolved in formic acid (3 mL) and added with ammonium formate (60 mmol). The resulting mixture was heated to 90°C overnight. The reaction mixture was then cooled down and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product, 4-{4-[2-(4-chlorophenyl)ethoxy]phenyl}-1-[(4-hydroxy)phenyl]-1H-imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained from 4-6% MeOH/DCM (yield ~50%).

To a solution of the product obtained above (0.5 mmol) in anhydrous THF (2 mL), NaH (60% dispersion in oil; 1 mmol) was added at 0°C. The resulting mixture was added with a solution of the mesylate of N,N-dimethylpropanol (0.6 mmol) in THF (1 mL). The reaction mixture was then heated to 70°C overnight. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained from 4-6% MeOH/DCM.

MS m/z 476 (M+H)⁺:

¹H NMR (CDCl₃): δ 7.76 (s, 1H), 7.73 (d, 2H), 7.38 (s, 1H), 7.31 (d, 2H), 7.25 (AB_q, 4H), 6.99 (d, 2H), 6.92 (d, 2H), 4.18 (t, 2H), 4.05 (t, 2H), 3.07 (t, 2H), 2.49 (t, 2H), 2.28 (s, 6H), 1.99 (q, 2H) ppm.

Example 437

4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-1-{4-[2-(1-methyl-pyrrolidin-2-yl)-ethoxy]-phenyl}-1H-imidazole

To a stirred solution of 4-aminophenol (4.8 mmol) in MeOH (20 mL), 1-bromo-4'-(4-chlorophenethoxy)acetophenone (4 mmol) was added at rt. The resulting mixture was then heated to reflux for 45 min. The reaction mixture was then cooled to rt and the solvent was removed *in vacuo*. The resulting solid was dissolved in EtOAc (30 mL), washed with H₂O (2X20 mL) and brine (20 mL) and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired 1-(4-hydroxyphenyl)amino-4'-(4-chlorophenethoxy)acetophenone, which was used for further transformation.

The aminoacetophenone obtained as above (3 mmol) was dissolved in formic acid (3 mL) and added with ammonium formate (60 mmol). The resulting mixture was heated to 90°C overnight. The reaction mixture was then cooled down and neutralized with saturated

sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product, 4-{4-[2-(4-chlorophenyl)ethoxy]phenyl}-1-[(4-hydroxy)phenyl]-1H-imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained from 4-6% MeOH/DCM (yield ~50%).

- 5 To a solution of the product obtained above (0.5 mmol) in anhydrous THF (2 mL), NaH (60% dispersion in oil; 1 mmol) was added at 0°C. The resulting mixture was added with a solution of the mesylate of 2-(N-methylpyrrolidin-2-yl)ethanol (0.6 mmol) in THF (1 mL). The reaction mixture was then heated to 70°C overnight. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product
10 was by obtained by elution with 4-6% MeOH/DCM (yield 125 mg)

MS m/z 503 (M+H)⁺:

¹H NMR (CDCl₃): δ7.75 (s, 1H), 7.72 (d, 2H), 7.38 (s, 1H), 7.31 (d, 2H), 7.26 (AB_q, 4H), 6.95 (d, 2H), 6.92 (d, 2H), 4.17 (t, 2H), 3.04 (t, 2H), 2.90-2.50 (m, 4H), 2.43 (s, 3H), 2.30-1.50 (m, 7H) ppm.

15

Example 438

1-{2-[4-(4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-imidazol-1-yl)-phenoxy]-ethyl}-piperazine

- To a stirred solution of 4-aminophenol (4.8 mmol) in MeOH (20 mL), 1-bromo-4'-(4-chlorophenethoxy)acetophenone (4 mmol) was added at rt. The resulting mixture was then
20 heated to reflux for 45 min. The reaction mixture was then cooled to rt and the solvent was removed *in vacuo*. The resulting solid was dissolved in EtOAc (30 mL), washed with H₂O(2X20 mL) and brine (20 mL) and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired 1-(4-hydroxyphenyl)amino-4'-(4-chlorophenethoxy)acetophenone, which was used for further transformation .

- 25 The aminoacetophenone obtained as above (3 mmol) was dissolved in formic acid (3 mL) and added with ammonium formate (60 mmol). The resulting mixture was heated to 90°C overnight. The reaction mixture was then cooled down and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product, 4-{4-[2-(4-chlorophenyl)ethoxy]phenyl}-1-[(4-hydroxy)phenyl]-1H-imidazole, which was purified by
30 column chromatography (Silica gel). Pure product was obtained by elution with 4-6% MeOH/DCM (yield ~50%).

To a solution of the product obtained above (0.5 mmol) in anhydrous THF (2 mL), NaH (60% dispersion in oil; 1 mmol) was added at 0°C. The resulting mixture was added with a solution of the mesylate of 1-(*t*-butyloxycarbonyl)-2-(2-hydroxy)ethylpiperazine (0.6 mmol) in THF (1 mL). The reaction mixture was then heated to 70°C overnight. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained by elution with 4-6% MeOH/DCM (yield ~50%).

The product obtained above was treated with 4M HCl in dioxane (1 mL) and the resulting mixture was stirred at rt for 4h. Evaporation of the solvent, repeated washing of the hydrochloride salt thus obtained with diethyl ether and subsequent drying *in vacuo* afforded the desired product.

MS *m/z* 503 (M+H)⁺:

¹H NMR (CD₃OD): δ9.47 (s, 1H), 8.28(s, 1H), 7.76 (d, 2H), 7.72 (d, 2H), 7.33 (d, 2H), 7.29 (s, 4H), 7.06 (d, 2H), 4.58 (broad t, 2H), 4.22 (t, 2H), 3.83 (broad t, 4H), 3.74 (broad t, 6H), 3.06 (t, 2H) ppm.

Example 439

[3-(4-{2-(3-cyclohexyl-propyl)-1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine

To a stirred solution of 4-fluoronitrobenzene (20 mmol), 4-fluoro-3-trifluoromethylphenol (22 mmol) in DMF (50 mL) at rt, solid potassium carbonate (60 mmol) was added, and the reaction mixture was heated to 90°C for 5h (monitored by TLC), according to General Procedure L1. After cooling to rt, the reaction mixture was poured into cold H₂O (60 mL). The resulting mixture was extracted with EtOAc (3×100 mL). The combined EtOAc extracts were washed with H₂O (2×40 mL) and brine (50 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* to afford the desired 1-fluoro-4-(4-nitrophenoxy)-2-(trifluoromethyl)benzene. The crude product was used directly for further transformation without further purification.

The nitro intermediate (2 mmol) obtained above was dissolved in MeOH (10 mL) and hydrogenated in the presence of 10% Pd/C (50 mg) until completion as indicated by TLC or LC-MS, according to General Procedure H. The reaction mixture was then filtered to remove the catalyst. The solvent was removed *in vacuo* to afford 4-(4'-fluoro-3'-

trifluoromethyl-phenoxy)aniline, which was used directly for further transformation without purification (overall yield: 95%).

To a stirred solution of ice-cold 3-diethylaminopropanol (63 mmol) and TEA (80 mmol) dissolved in anhydrous DCM (50 mL) was added dropwise methanesulfonyl chloride (60 mmol), and the reaction mixture was stirred for 2h at 0°C and followed by additional 1h at rt. After the removal of the solvents *in vacuo*, the crude mesylate was dissolved in DMF (100 mL). 4-Hydroxyacetophenone (40 mmol) and cesium carbonate (100 mmol) were added, and the mixture was heated with stirring at 90°C for 18 h (monitored by LC-MS). After cooling to rt, the reaction was quenched with cold H₂O (100 mL), and the resulting mixture was extracted with EtOAc (4×100 mL). The combined EtOAc extracts were washed with brine (3×60 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*, and the crude 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was purified by silica gel column chromatography eluting with 10% MeOH in EtOAc + 0.2% TEA (yield: 75%).

To a stirred solution of 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone (4 mmol) in MeOH (10 mL) at rt, pyrrolidone hydrotribromide (4.8 mmol) was added, according to General Procedure R1. The reaction mixture was stirred at rt for 1h (monitored by LC-MS). The solvent was then removed *in vacuo* and the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was directly used for further transformation.

To a stirred solution of 4-(4'-fluoro-3'-trifluoromethyl-phenoxy)aniline (4.8 mmol) dissolved in anhydrous DMF (10 mL), DIEA (12 mmol) was added, followed by a slow addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone obtained above (~4 mmol), according to General Procedure R2. The reaction mixture was stirred at rt and under nitrogen until completion (~5h), as indicated by LC-MS. The reaction was quenched with saturated sodium bicarbonate (50 mL), and the resulting mixture was extracted with EtOAc (3×100 mL). The combined EtOAc extracts were washed with brine (3×40 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*, and the crude product was purified by silica gel column chromatography eluting with 10% MeOH in EtOAc + 0.2% TEA (yield: 64%).

To a stirred solution of the alkylated aniline described above (0.2 mmol) in anhydrous DCM (5 mL) at 0°C, TEA (1.2 mmol, 6 eq) was added, followed by a slow addition of 4-cyclohexylbutanoyl chloride (0.6 mmol, 3 eq), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by LC-MS. The solvent was removed *in vacuo*, and the crude amide was used directly for further transformation.

To a stirred solution of the amide described above (~0.2 mmol) in acetic acid (2 mL), ammonium acetate (excess, ~30 eq) was added, according to General Procedure R4. The reaction mixture was stirred at 100°C for 2-5h (as monitored by LC-MS). The reaction mixture was then cooled down and neutralized with saturated sodium bicarbonate. The resulting mixture was extracted with EtOAc (3×50 mL). The combined EtOAc extracts were washed with brine (3×20 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*, and the pure product was obtained by silica gel column chromatography eluting with 10% MeOH in EtOAc + 0.2% TEA (overall yield: 60-70%) (yield 78 mg).

MS m/z 652 (M+H)⁺:

¹H NMR (400 MHz, CDCl₃): δ 0.75-1.65 (m, 15H), 1.07 (t, 6H), 1.97 (m, 2H), 2.62 (q, 4H), 2.63-2.70 (m, 4H), 4.02 (t, 2H), 6.90 (d, 2H), 7.07 (d, 2H), 7.14 (s, 1H), 7.22 (br s, 1H), 7.23 (br d, 1H), 7.25 (d, 1H), 7.31 (d, 2H), 7.69 (d, 2H) ppm.

Example 440

diethyl-(3-{4-[1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-2-(3-phenoxy-propyl)-1H-imidazol-4-yl]-phenoxy}-propyl)-amine

To a stirred solution of 4-fluoronitrobenzene (20 mmol), 4-fluoro-3-trifluoromethylphenol (22 mmol) in DMF (50 mL) at rt, solid potassium carbonate (60 mmol) was added, and the reaction mixture was heated to 90°C for 5h (monitored by TLC), according to General Procedure L1. After cooling to rt, the reaction mixture was poured into cold H₂O (60 mL). The resulting mixture was extracted with EtOAc (3×100 mL). The combined EtOAc extracts were washed with H₂O (2×40 mL) and brine (50 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* to afford the desired 1-fluoro-4-(4-nitrophenoxy)-2-(trifluoromethyl)benzene. The crude product was used directly for further transformation without further purification.

The nitro intermediate (2 mmol) obtained above was dissolved in MeOH (10 mL) and hydrogenated in the presence of 10% Pd/C (50 mg) until completion as indicated by TLC or LC-MS, according to General Procedure H. The reaction mixture was then filtered to remove the catalyst. The solvent was removed *in vacuo* to afford 4-(4'-fluoro-3'-trifluoromethyl-phenoxy)aniline, which was used directly for further transformation without purification (overall yield: 95%).

To a stirred solution of ice-cold 3-diethylaminopropanol (63 mmol) and TEA (80 mmol) dissolved in anhydrous DCM (50 mL) was added dropwise methanesulfonyl chloride (60 mmol), and the reaction mixture was stirred for 2h at 0°C and followed by additional 1h at rt. After the removal of the solvents *in vacuo*, the crude mesylate was dissolved in DMF (100 mL). 4-Hydroxyacetophenone (40 mmol) and cesium carbonate (100 mmol) were added, and the mixture was heated with stirring at 90°C for 18 h (monitored by LC-MS). After cooling to rt, the reaction was quenched with cold H₂O (100 mL), and the resulting mixture was extracted with EtOAc (4×100 mL). The combined EtOAc extracts were washed with brine (3×60 ml), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*, and the crude 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was purified by silica gel column chromatography eluting with 10% MeOH in EtOAc + 0.2% TEA (yield: 75%).

To a stirred solution of 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone (4 mmol) in MeOH (10 mL) at rt, pyrrolidone hydrotribromide (4.8 mmol) was added, according to General Procedure R1. The reaction mixture was stirred at rt for 1h (monitored by LC-MS). The solvent was then removed *in vacuo* and the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was directly used for further transformation.

To a stirred solution of 4-(4'-fluoro-3'-trifluoromethyl-phenoxy)aniline (4.8 mmol) dissolved in anhydrous DMF (10 mL), DIEA (12 mmol) was added, followed by a slow addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone obtained above (~4 mmol), according to General Procedure R2. The reaction mixture was stirred at rt and under nitrogen until completion (~5h), as indicated by LC-MS. The reaction was quenched with saturated sodium bicarbonate (50 mL), and the resulting mixture was extracted with EtOAc (3×100 mL). The combined EtOAc extracts were washed with brine (3×40 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*, and the crude product was purified by silica gel column chromatography eluting with 10% MeOH in EtOAc + 0.2% TEA (yield: 64%).

To a stirred solution of the alkylated aniline described above (0.2 mmol) in anhydrous DCM (5 mL) at 0°C, TEA (1.2 mmol, 6 eq) was added, followed by a slow addition of 4-phenoxybutanoyl chloride (0.6 mmol, 3 eq), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by LC-MS. The solvent was removed *in vacuo*, and the crude amide was used directly for further transformation.

To a stirred solution of the amide described above (~0.2 mmol) in acetic acid (2 mL), ammonium acetate (excess, ~30 eq) was added, according to General Procedure R4. The reaction mixture was stirred at 100°C for 2-5h (as monitored by LC-MS). The reaction mixture was then cooled down and neutralized with saturated sodium bicarbonate. The resulting mixture was extracted with EtOAc (3×50 mL). The combined EtOAc extracts were washed with brine (3×20 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*, and the pure product was obtained by silica gel column chromatography eluting with 10% MeOH in EtOAc + 0.2% TEA (yield 73 mg).

MS m/z 662 (M+H)⁺:

¹H NMR (400 MHz, CDCl₃): δ 1.06 (t, 6H), 1.97 (m, 2H), 2.24 (m, 2H), 2.60 (q, 4H), 2.67 (t, 2H), 2.88 (t, 2H), 3.99 (t, 2H), 4.03 (t, 2H), 6.80 (d, 2H), 6.90-7.25 (m, 8H), 7.01 (d, 2H), 7.15 (s, 1H), 7.28 (d, 1H), 7.70 (d, 2H) ppm.

Example 441

{3-[4-(4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-methyl-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine

To a stirred solution of 4-fluoronitrobenzene (2.0 mmol) in anhydrous THF (5 mL) at 0°C, a 1M solution of a potassium diethylaminopropoxide (2.2 mmol) in THF was added dropwise and under a nitrogen stream, according to General Procedure L1. The reaction mixture was stirred at 0°C for 1 h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The reaction mixture was then treated with cold H₂O (15 mL), and extracted with EtOAc (2×15 mL). The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of the solvent *in vacuo* afforded the desired 4-alkoxynitrobenzene. The crude product was used directly for further transformation .

The N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (2 mmol) obtained above was dissolved in MeOH (10 mL) and hydrogenated in the presence of 10% Pd/C (10 mg) until completion as indicated by TLC or HPLC, according to General Procedure H. The reaction mixture was then filtered to remove the catalyst. The solvent was removed *in vacuo* to afford the desired 4-alkoxyaniline, which was used directly for further transformation without further purification.

To a stirred solution of 4'-hydroxyacetophenone (2.2 mmol) in DMF (5 mL) at rt, solid potassium carbonate (9.0 mmol) was added. 4-chlorophenethyl mesylate (2.0 mmol) was added to the reaction mixture and heated to 80°C until completion according to General Procedure Q1, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was quenched using cold water (20 ml) and the product was isolated in EtOAc (2X20 ml). The combined organic layers were washed with saturated sodium bicarbonate (2X10 ml), water (2X10 ml) and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired 1-{4-[2-(4-chlorophenyl)ethoxy]phenyl}ethanone. The crude alkylated acetophenone was used for further transformation .

To a stirred solution of the 1-{4-[2-(4-chlorophenyl)ethoxy]phenyl}ethanone (2 mmol) in anhydrous MeOH (5 mL) at 0°C, pyrrolidone hydrotribromide (1.2eq., 2.2 mmol) was added, according to General Procedure R1. The reaction mixture was stirred under nitrogen at 0°C for 1h and was allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was then removed *in vacuo* and the residue was treated with saturated sodium bicarbonate. The aqueous layer was poured into EtOAc (20 ml) and the product was isolated in EtOAc (2X20 ml). The combined organic layers were washed with saturated sodium bicarbonate (2X10 ml), and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired product. The crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was purified by chromatography (Silica gel). Pure product was obtained by elution with 20-30% EtOAc/hexane (yield ~70-75%).

To a stirred solution of the N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (1.2 eq., 2 mmol) in anhydrous DMF (5 mL) DIEA (3 eq. 6 mmol) was added, followed by slow addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone described above (1.6 mmol), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was used for further transformation .

To a stirred solution of 1-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-[4-(3-diethylamino-propoxy)-phenylamino]-ethanone described above (1.6 mmol) in anhydrous DCM (5 mL) at 0°C, TEA (3eq., 4.8 mmol) was added, followed by slow addition of acetyl chloride (2 eq., 3.2 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen

at 0°C for 1h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in DCM. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (1.6 mmol) in acetic acid (4 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled to rt and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained by elution with 4-6% MeOH/DCM (yield: 250 mg).

MS m/z 519 (M+H)⁺:

¹H NMR (400 MHz, CDCl₃): δ 7.67 (d, 2H), 7.22 (d, 2H), 7.21 (m, 5H), 6.96 (d, 2H), 6.84 (d, 2H), 4.17 (t, 2H), 4.07 (t, 2H), 3.06 (t, 2H), 2.78 (t, 2H), 2.74 (m, 4H), 2.36 (s, 3H), 2.06 (m, 2H), 1.13 (t, 6H) ppm

Example 442

3-(4-{2-butyl-1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-1-ethyl-piperidine

To a stirred solution of 4-benzyloxyacetophenone (7.0 mmol) in anhydrous DCM (30.0 mL) and MeOH (5.0mL) at rt, pyridinium bromide perbromide (1.1eq.) was added, according to General Procedure R1. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC. The mixture was diluted with EtOAc (100 ml) and washed with H₂O (2X50 ml), brine (30 ml) and dried with magnesium sulfate. The solvent was then removed *in vacuo* to give a white solid. The 1-[4-(benzyloxy)phenyl]-2-bromoethanone was used for further transformation without further purification.

To a stirred solution of 4-(4-fluoro-3-trifluoromethyl-phenoxy)-aniline (1.64 mmol) in anhydrous DMF (30 mL) DIEA (3 eq) was added, followed by slow addition of the 1-[4-(benzyloxy)phenyl]-2-bromoethanone described above (2 eq), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC and HPLC. The reaction mixture was then diluted with cold H₂O and the product was isolated in Et₂O. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired alkylated

aniline, which was purified by chromatography (Silica gel). Pure product was obtained by elution with 5-20% EtOAc/Hexane (yield ~50-60%).

To a stirred solution of alkylated aniline described above (1.0 mmol) in anhydrous THF (20 mL) at 0°C, TEA (3eq, 3 mmol) was added, followed by slow addition of valeryl chloride (3 eq, 3.0 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to ambient temperature until completion, as indicated by TLC and HPLC. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (1.0 mmol) in acetic acid (2 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled down and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained by elution with 5-15 % EtOAc/Hexane (yield 80%).

The above product was dissolved in MeOH (20 mL), and Pd/C (100 mg) was added and the heterogeneous mixture was stirred overnight under hydrogen atmosphere using a balloon, according to General Procedure T2. The Pd/C was removed by filtration. The solvent was removed *in vacuo*, and the crude 4-(1-{4-[4-fluoro-3-(trifluoromethyl)phenoxy]phenyl}-2-butyl-1H-imidazol-4-yl)phenol was used for further transformation.

A stirred solution of the 4-(1-{4-[4-fluoro-3-(trifluoromethyl)phenoxy]phenyl}-2-butyl-1H-imidazol-4-yl)phenol (1.0 eq) in anhydrous DMF (5.0 mL) was treated with solid sodium hydride (60% dispersion in oil; 1.0mmol) in portions. The mesylate of 1-(methylamino)piperidin-3-ol was then added to the reaction mixture, which was heated at 90°C overnight, according to General Procedure T3. After cooling the mix to rt, Et₂O (30 mL) was added to the reaction mixture followed by H₂O (10 mL). The organic layer was washed with H₂O (2x15 mL) and brine, and dried over sodium sulfate. The solvent was removed *in vacuo*. Pure imidazole was obtained by elution with chromatography in 5-10% MeOH/DCM (yield 52.0 mg)

MS m/z 583 (M+H)⁺:

¹H NMR (CDCl₃): δ 7.7 (m, 2H), 7.3 (m, 3H), 7.24 (m, 2H), 7.13 (s, 1H), 7.07 (d, 2H, J 8.8 Hz), 6.94 (m, 2H), 0.9-4.4 (m, 23 H) ppm.

Example 443

diethyl-[3-(4-{1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-2-methyl-1H-imidazol-4-yl}-phenoxy)-propyl]-amine

To a stirred solution of 4-fluoronitrobenzene (2.0 mmol) in anhydrous THF (5 mL) at 0°C, a 1M solution of a potassium 4-fluoro-3-trifluoromethyl-phenoxy (2.2 mmol) in THF (may be generated by adding the corresponding alcohol to a 1M solution of potassium *t*-butoxide in THF) was added dropwise and under a nitrogen stream, according to General Procedure L1. The reaction mixture was stirred at 0°C until completion, as indicated by TLC or HPLC. The solvent was then removed *in vacuo* and the reaction mixture was treated with cold H₂O (15 mL), and extracted with EtOAc (2x15 mL). The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of the solvent *in vacuo* afforded the desired 1-fluoro-4-(4-nitrophenoxy)-2-(trifluoromethyl)benzene. The crude product could be used directly for further transformation .

The nitro intermediate (2 mmol) obtained above was dissolved in MeOH (10 mL) and hydrogenated in the presence of 10% Pd/C (10 mg) until completion, as indicated by TLC or HPLC, according to General Procedure H. The reaction mixture was then filtered to remove the catalyst. The solvent was removed *in vacuo* to afford the desired 4-[4-fluoro-3-(trifluoromethyl)phenoxy]aniline, which was used directly for further transformation without further purification.

To a stirred solution of 4'-hydroxyacetophenone (2.2 mmol) in DMF (10 mL) at rt, solid potassium carbonate (8.0 mmol) was added. The mesylate of N,N-diethylaminopropanol (prepared from the corresponding alcohol and methanesulfonyl chloride) (2.0 mmol) was added to the reaction mixture and heated to 80°C until completion according to General Procedure Q1, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was diluted with water and the product was isolated in EtOAc. The combined organic layers were washed with saturated sodium bicarbonate (2X15 ml), water (2X15 ml) and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone. The crude alkylated product was purified using silica gel column chromatography. Pure product was obtained with 2-3% MeOH/DCM. (yield 50-60%)

To a stirred solution of the 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone described above (1 mmol) in anhydrous MeOH (5 mL) at 0°C, pyrrolidone hydrotribromide (1.2eq., 1.2 mmol) was added, according to General Procedure R1. The reaction mixture was stirred under

nitrogen at 0°C for 1h and was allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was then removed *in vacuo*, the residue was treated with saturated sodium bicarbonate and the product was isolated in EtOAc. The combined organic layers were washed with water (2X15 ml) and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired product. The crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was used for further transformation.

To a stirred solution of the 4-fluoro-3-trifluoromethyl-phenoxy aniline (1.2 eq., 1.2 mmol) in anhydrous DMF (5 mL) DIEA (3 eq. 3 mmol) was added, followed by slow addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone described above (1.0 mmol), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was used for further transformation.

To a stirred solution of alkylated aniline described above (1.0 mmol) in anhydrous DCM (5 mL) at 0°C, TEA (3eq., 3.0 mmol) was added, followed by slow addition of acetyl chloride (2 eq., 2.0 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with water and the product was isolated in DCM. The solvent was removed *in vacuo*, and the crude amide was purified using silica gel chromatography. Pure product was obtained by elution with 3-4% MeOH/DCM (Yield 40-45%).

To a stirred solution of the amide described above (0.5 mmol) in acetic acid (1 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled to rt and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained by elution with 4-6% MeOH/DCM (yield: 108 mg).

MS m/z 542 (M+H)⁺:

¹H NMR (400 MHz, CDCl₃): δ7.69 (d, 2H), 7.33 (m, 5H), 7.18 (s, 1H), 7.09 (d, 2H), 6.91 (d, 2H) 4.03 (t, 2H), 2.63 (m, 6H), 2.41 (s, 3H), 2.01 (m, 2H), 1.08 (t, 6H) ppm

Example 444

(3-{4-[4-(4-benzyloxy-phenyl)-2-butyl-imidazol-1-yl]-phenoxy}-propyl)-diethyl-amine

To a stirred solution of 4-fluoronitrobenzene (2.0 mmol) in anhydrous THF (5 mL) at 0°C, a
5 1M solution of a potassium diethylaminopropoxide (2.2 mmol) in THF was added dropwise
and under a nitrogen stream, according to General Procedure L1. The reaction mixture was
stirred at 0°C for 1 h and allowed to warm to rt until completion, as indicated by TLC or
HPLC. The reaction mixture was then treated with cold H₂O (15 mL), and extracted with
EtOAc (2x15 mL). The combined organic layers were washed with brine and dried over
10 sodium sulfate. Evaporation of the solvent *in vacuo* afforded the desired 4-
alkoxynitrobenzene. The crude product was used directly for further transformation .

The N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (2 mmol) obtained above was dissolved
in MeOH (10 mL) and hydrogenated in the presence of 10% Pd/C (10 mg) until completion
as indicated by TLC or HPLC, according to General Procedure H. The reaction mixture was
15 then filtered to remove the catalyst. The solvent was removed *in vacuo* to afford the
desired 4-(N,N-diethylaminopropoxy)aniline, which was used directly for further
transformation without further purification.

To a stirred solution of the 4'-benzyloxyacetophenone (2 mmol) in anhydrous MeOH (5 mL)
at 0°C, pyrrolidone hydrotribromide (1.2eq., 2.2 mmol) was added, according to General
20 Procedure R1. The reaction mixture was stirred under nitrogen at 0°C for 1h and was
allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was then
removed *in vacuo* and the residue was treated with saturated sodium bicarbonate. The
aqueous layer was poured into EtOAc (20 mL) and the product was isolated in EtOAc (2X20
mL). The combined organic layers were washed with saturated sodium thiosulfate (2X10
25 mL), water (2X10 mL) and brine (15 mL). The organic layer was dried over magnesium
sulfate, and the solvent was removed *in vacuo* to afford the desired product. The crude
alpha-bromoacetophenone was purified by chromatography (Silica gel). Pure product was
obtained by elution with 20-30% EtOAc/hexane (yield ~70-75%).

To a stirred solution of the 4-(N,N-diethylaminopropoxy)aniline (1.2 eq., 2 mmol) in
30 anhydrous DMF (5 mL) the alpha-bromoacetophenone (1.6 mmol) described above was
added slowly, according to General Procedure R2. The reaction mixture was stirred under
nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then
diluted with cold water and the product was isolated in EtOAc. The combined organic layers

were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was used for further transformation

To a stirred solution of alkylated aniline described above (1.6 mmol) in anhydrous DCM (5 mL) at 0°C, TEA (3eq., 4.8 mmol) was added, followed by slow addition of valeryl chloride (2 eq., 3.2 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in DCM. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (1.6 mmol) in acetic acid (4 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled to rt and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained by elution with 4-6% MeOH/DCM (yield 179 mg).

MS m/z 512 (M+H)⁺:

¹H NMR (CDCl₃): δ 7.69 (d, 2H), 7.15–7.50 (m, 8H), 7.09 (s, 1H), 6.96 (m, 3H), 5.05 (s, 2H), 4.12 (t, 2H), 3.21 (broad m, 2H), 3.15 (q, 4H), 2.64 (t, 2H), 2.38 (broad m, 2H), 1.60 (q, 2H), 1.41 (t, 6H), 1.20–1.35 (m, 2H), 0.81 (t, 6H) ppm.

Example 445

[3-(4-{2-butyl-1-[4-(2,5-difluoro-benzyloxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine

3-Diethylaminopropanol (20mmol, 1 eq) was dissolved in DCM (25mL), TEA (40mmol, 2 eq) was added and the mixture was cooled to 0°C. To this mixture, methanesulfonyl chloride (30mmol, 1.5 eq) was added slowly with stirring and the reaction mixture was stirred at 0°C for an hour and at rt for another hour (until the reaction was complete by HPLC). The solvent was removed and saturated aqueous sodium bicarbonate was added. The product was extracted with EtOAc (3 x) and washed with sodium bicarbonate and water. The solvent was removed *in vacuo*.

The mesylate from the previous step (20 mmol, 1 eq) was dissolved in anhydrous DMF (25mL) to which 4-hydroxyacetophenone (20mmol, 1 eq) and potassium carbonate (60mmol, 3 eq) were added. The mixture was heated under reflux at 85°C for 18 h (until the reaction was complete by HPLC), after which it was cooled to rt. Saturated aqueous sodium bicarbonate was added to the mixture, which was then transferred to a separatory funnel. The product was extracted with EtOAc and washed with sodium bicarbonate and water. The solvent was removed *in vacuo* and the product 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was purified by flash chromatography (going by increasing gradient up to 10% MeOH in DCM). The overall yield was 60%.

To a stirred solution of 4-fluoronitrobenzene (2.0 mmol) in anhydrous THF (6 mL) at 0°C, a 1M solution of a potassium alkoxide (2.2 mmol) in THF (may be generated by adding the 2,5-difluorobenzyl alcohol to a 1M solution of KOBu^t in THF) was added dropwise and under a nitrogen stream, according to General Procedure L1. The reaction mixture was stirred at 0°C until completion, as indicated by TLC or HPLC. The reaction mixture was then treated with cold H₂O (15 mL), and extracted with EtOAc (2x15 mL). The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of the solvent *in vacuo* afforded the desired 4-alkoxynitrobenzene. The crude product could be used directly for further transformation without any purification, or after purifying using silica gel column chromatography.

The nitro intermediate (2 mmol) obtained above was dissolved in MeOH (6 mL) and hydrogenated in the presence of 10% Pd/C (10 mg) until completion, as indicated by TLC or HPLC, according to General Procedure H. The reaction mixture was then filtered to remove the catalyst. The solvent was removed *in vacuo* to afford 4-(2,5-difluoro-benzyloxy)aniline, which was used directly for further transformation without further purification (yield 80%).

To a stirred solution of 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone (2 mmol) in anhydrous MeOH (6 mL) at 0°C, pyrrolidone hydrotribromide (1.2eq) was added, according to General Procedure R1. The reaction mixture was stirred under nitrogen at 0°C for 1h and was allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was then removed *in vacuo* and the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was used for further transformation.

To a solution of 4-(2,5-difluoro-benzyloxy)aniline (1 eq, 2 mmol) in anhydrous DMF (6 mL), DIEA (3 eq 6 mmol) was added, followed by addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone described above (2 mmol), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as

indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product by
5 elution with 2-4% MeOH/DCM (yield 50%).

To a stirred solution of alkylated aniline described above (1 mmol) in anhydrous DCM (4 mL) at 0°C, TEA (3eq, 3 mmol) was added, followed by a slow addition of valeryl chloride (3 eq, 3 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The
10 solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (1 mmol) in acetic acid (4 mL), ammonium acetate (20mmol, 20 eq) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled to rt and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with
15 EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained by elution with 4-6% MeOH/DCM (yield 208 mg).

MS m/z 549 (M+H)⁺:

¹H NMR (CDCl₃): δ7.68 (d, 2H), 7.24 (m, 5H), 7.13 (s, 1H), 7.06 (d, 2H), 6.89 (d, 2H), 5.17 (s, 2H), 4.02 (t, 2H), 2.62-2.78 (m, 8H), 1.98 (m, 2H), 1.60 (m, 2H), 1.27 (m, 2H), 1.11 (t, 6H), 0.82 (t, 3H) ppm.
20

Example 446

3-(S)-(4-{2-butyl-1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy-methyl)-1-ethyl-piperidine

To a stirred solution of 4-benzyloxyacetophenone (7.0 mmol) in anhydrous DCM (30.0 mL) and MeOH (5.0mL) at rt, pyridinium bromide perbromide (1.1eq.) was added. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC. The mixture was diluted with EtOAc (100 ml) and washed with H₂O (2X50 ml), brine (30 ml) and dried with magnesium sulfate. The solvent was then removed *in vacuo* to give a white solid. The
25 alpha-bromoacetophenone was used for further transformation without further purification.
30

To a stirred solution of 4-(4-fluoro-3-trifluoromethyl-phenoxy)-aniline (1.64 mmol) in anhydrous DMF (30 mL) DIEA (3 eq) was added, followed by slow addition of the alpha-bromoacetophenone described above (2 eq), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC and HPLC. The reaction mixture was then diluted with cold H₂O and the product was isolated in Et₂O. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product was obtained by elution with 5-20% EtOAc/Hexane (yield ~50-60%).

To a stirred solution of alkylated aniline described above (1.0 mmol) in anhydrous THF (20 mL) at 0°C, TEA (3eq, 3 mmol) was added, followed by slow addition of valeryl chloride (3 eq, 3.0 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to ambient temperature until completion, as indicated by TLC and HPLC. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (1.0 mmol) in acetic acid (2 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled down and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained by elution with 5-15 % EtOAc/Hexane (yield 80%). (MS: *m/z* 562 (M+H)⁺)

The above product was dissolved in MeOH (20 mL), and Pd/C (100 mg) was added and the heterogeneous mixture was stirred overnight under hydrogen atmosphere using a balloon, according to General Procedure T2. The Pd/C was removed by filtration. The solvent was removed *in vacuo*, and the crude 4-(1-{4-[4-fluoro-3-(trifluoromethyl)phenoxy]phenyl}-2-butyl-1H-imidazol-4-yl)phenol (MS: *m/z* 472 (M+H)⁺) was used for further transformation.

A stirred solution of the 4-(1-{4-[4-fluoro-3-(trifluoromethyl)phenoxy]phenyl}-2-butyl-1H-imidazol-4-yl)phenol (1.0 eq) in anhydrous DMF (5.0 mL) was treated with solid sodium hydride (60% dispersion in oil; 1.0mmol) in portions. The mesylate of [(3S)-1-ethylpiperidin-3-yl]methanol (1.5-2.0eq) was added to the reaction mixture, which was heated at 90 °C overnight, according to General Procedure T3. After cooling the mix to rt, Et₂O (30 mL) was added to the reaction mixture followed by H₂O (10 mL). The organic layer was washed with H₂O (2x15 mL) and brine, and dried over sodium sulfate. The solvent was removed *in*

vacuo. Pure imidazole was obtained by elution with chromatography in 5-10% MeOH/DCM (yield 50.0 mg).

MS m/z 597 ($M+H$)⁺:

¹H NMR (CDCl₃): δ 7.70 (d, 2H), 7.20-7.35 (m, 5H), 7.14 (s, 1H), 7.08 (d, 2H), 6.92 (d, 2H), 4.05 (m, 1H), 3.92 (m, 2H), 2.60 (m, 4H), 1.0-2.5 (m, 18H) ppm.

Example 447

(3-{4-[4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-(2,4,4-trimethyl-pentyl)-imidazol-1-yl]-phenoxy}-propyl)-diethyl-amine

10 To a stirred solution of 4-fluoronitrobenzene (2.0 mmol) in anhydrous THF (5 mL) at 0°C, a 1M solution of a potassium diethylaminopropoxide (2.2 mmol) in THF was added dropwise and under a nitrogen stream, according to General Procedure L1. The reaction mixture was stirred at 0°C for 1 h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The reaction mixture was then treated with cold H₂O (15 mL), and extracted with EtOAc (2x15 mL). The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of the solvent *in vacuo* afforded the desired 4-alkoxynitrobenzene. The crude product was used directly for further transformation .

20 The N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (2 mmol), obtained above was dissolved in MeOH (10 mL) and hydrogenated in the presence of 10% Pd/C (10 mg) until completion as indicated by TLC or HPLC, according to General Procedure H. The reaction mixture was then filtered to remove the catalyst. The solvent was removed *in vacuo* to afford the desired 4-alkoxyaniline, which was used directly for further transformation without further purification.

25 To a stirred solution of 4'-hydroxyacetophenone (2.2 mmol) in DMF (5 mL) at rt, solid potassium carbonate (9.0 mmol) was added. 4-chlorophenethyl mesylate (2.0 mmol) was added to the reaction mixture and heated to 80°C until completion according to General Procedure Q1, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was quenched using cold water (20 ml) and the product was isolated in EtOAc (2X20 ml). The combined organic layers were washed with saturated sodium bicarbonate (2X10 ml), water (2X10 ml) and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired 1-{4-[2-(4-

30

chlorophenyl)ethoxy]phenyl}ethanone. The crude alkylated acetophenone was used for further transformation .

To a stirred solution of the 1-{4-[2-(4-chlorophenyl)ethoxy]phenyl}ethanone (2 mmol) in anhydrous MeOH (5 mL) at 0°C, pyrrolidone hydrotribromide (1.2 eq., 2.2 mmol) was added, according to General Procedure R1. The reaction mixture was stirred under nitrogen at 0°C for 1h and was allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was then removed *in vacuo* and the residue was treated with saturated sodium bicarbonate. The aqueous layer was poured into EtOAc (20 ml) and the product was isolated in EtOAc (2X20 ml). The combined organic layers were washed with saturated sodium bicarbonate (2X10 ml), and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired product. The crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was purified by chromatography (Silica gel). Pure product was obtained by elution with 20-30% EtOAc/hexane (yield ~70-75%).

To a stirred solution of the N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (1.2 eq., 2 mmol) in anhydrous DMF (5 mL) DIEA (3 eq. 6 mmol) was added, followed by slow addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone described above (1.6 mmol), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was used for further transformation .

To a stirred solution of 1-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-[4-(3-diethylamino-propoxy)-phenylamino]-ethanone described above (1.6 mmol) in anhydrous DCM (5 mL) at 0°C, TEA (3eq., 4.8 mmol) was added, followed by slow addition of 3,5,5-trimethyl hexanoyl chloride (2 eq., 3.2 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in DCM. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (1.6 mmol) in acetic acid (4 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled to rt and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with

EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained by elution with 4-6% MeOH/DCM (yield: 296 mg).

MS m/z value (M+H)⁺: 617

¹H NMR (400 MHz, CDCl₃): δ 7.69 (d, 2H), 7.22 (d, 2H), 7.21 (m, 5H), 6.96 (d, 2H), 6.88 (d, 2H), 4.18 (t, 2H), 4.07 (t, 2H), 3.09 (t, 2H), 2.88 (d, 2H), 2.79 (m, 6H), 2.05 (m, 3H), 1.11 (t, 6H), 0.97 (d, 2H), 0.87 (d, 3H), 0.78 (s, 9H) ppm

Example 448

3-(R)-(4-{2-butyl-1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)methyl)-1-ethyl-piperidine

To a stirred solution of 4-benzyloxyacetophenone (7.0 mmol) in anhydrous DCM (30.0 mL) and MeOH (5.0 mL) at rt, pyridinium bromide perbromide (1.1 eq.) was added. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC. The mixture was diluted with EtOAc (100 ml) and washed with H₂O (2X50 ml), brine (30 ml) and dried with magnesium sulfate. The solvent was then removed *in vacuo* to give a white solid. The alpha-bromoacetophenone was used for further transformation without further purification.

To a stirred solution of 4-(4-fluoro-3-trifluoromethyl-phenoxy)-aniline (1.64 mmol) in anhydrous DMF (30 mL) DIEA (3 eq) was added, followed by slow addition of the alpha-bromoacetophenone described above (2 eq), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC and HPLC. The reaction mixture was then diluted with cold H₂O and the product was isolated in Et₂O. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product was obtained by elution with 5-20% EtOAc/Hexane (yield ~50-60%).

To a stirred solution of alkylated aniline described above (1.0 mmol) in anhydrous THF (20 mL) at 0°C, TEA (3eq, 3 mmol) was added, followed by slow addition of valeryl chloride (3 eq, 3.0 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to ambient temperature until completion, as indicated by TLC and HPLC. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (1.0 mmol) in acetic acid (2 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled down and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained by elution with 5-15 % EtOAc/Hexane (yield 80%). (MS: m/z 562 ($M+H$)⁺)

The above product was dissolved in MeOH (20 mL), and Pd/C (100 mg) was added and the heterogeneous mixture was stirred overnight under hydrogen atmosphere using a balloon, according to General Procedure T2. The Pd/C was removed by filtration. The solvent was removed *in vacuo*, and the crude 4-(1-{4-[4-fluoro-3-(trifluoromethyl)phenoxy]phenyl}-2-butyl-1H-imidazol-4-yl)phenol (MS: m/z 472 ($M+H$)⁺) was used for further transformation.

A stirred solution of the 4-(1-{4-[4-fluoro-3-(trifluoromethyl)phenoxy]phenyl}-2-butyl-1H-imidazol-4-yl)phenol (1.0 eq) in anhydrous DMF (5.0 mL) was treated with solid sodium hydride (60% dispersion in oil; 1.0mmol) in portions. The mesylate of [(3R)-1-ethylpiperidin-3-yl]methanol (1.5-2.0eq) was added to the reaction mixture, which was heated at 90 °C overnight, according to General Procedure T3. After cooling the mix to rt, Et₂O (30 mL) was added to the reaction mixture followed by H₂O (10 mL). The organic layer was washed with H₂O (2x15 mL) and brine, and dried over sodium sulfate. The solvent was removed *in vacuo*. Pure imidazole was obtained by elution with chromatography in 5-10% MeOH/DCM (yield 50.0 mg).

MS m/z 597 ($M+H$)⁺:

¹H NMR (CDCl₃): δ 7.70 (d, 2H), 7.20-7.35 (m, 5H), 7.14 (s, 1H), 7.08 (d, 2H), 6.92 (d, 2H), 4.05 (m, 1H), 3.92 (m, 2H), 2.60 (m, 4H), 1.0-2.5 (m, 18H). ppm.

Example 449

[3-(4-{2-butyl-1-[4-(3-tert-butyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethylamine

3-Diethylaminopropanol (20mmol, 1eq) was dissolved in DCM (25mL), TEA (40mmol, 2 eq) was added and the mixture was cooled to 0°C. To this mixture, methanesulfonyl chloride (30mmol, 1.5 eq) was added slowly with stirring and the reaction mixture was stirred at 0°C

for an hour and at rt for another hour (until the reaction was complete by HPLC). The solvent was removed and saturated aqueous sodium bicarbonate was added. The product was extracted with EtOAc (3 x) and washed with sodium bicarbonate and water. The solvent was removed *in vacuo*.

- 5 The mesylate from the previous step (20mmol, 1 eq) was dissolved in anhydrous DMF (25mL) to which 4-hydroxyacetophenone (20mmol, 1 eq) and potassium carbonate (60mmol, 3 eq) were added. The mixture was heated under reflux at 85°C for 18 h (until the reaction was complete by HPLC), after which it was cooled to rt. Saturated aqueous sodium bicarbonate was added to the mixture, which was then transferred to a separatory funnel.
- 10 The product was extracted with EtOAc and washed with sodium bicarbonate and water. The solvent was removed *in vacuo* and the product 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was purified by flash chromatography (going by increasing gradient up to 10% MeOH in DCM). The overall yield was 60%.

- 15 4-Methoxyphenol (10 mmol) was dissolved in 15 ml of anhydrous DMF and potassium carbonate (30 mmol) was added with stirring at rt. 4-Fluoronitrobenzene (10 mmol) was added to this mixture, which was then heated under reflux at 80°C for 18 h. The reaction was quenched with 30 ml of water and 30 ml of sodium bicarbonate, extracted with EtOAc (3 x 50 ml) and washed with sodium bicarbonate and water. The EtOAc layer was dried over anhydrous sodium sulfate and filtered, after which the solvent was removed *in vacuo*.

- 20 The nitro intermediate (10 mmol) obtained above was dissolved in EtOH (30mL) and hydrogenated in the presence of 10% Pd/C (10 mg) until completion as indicated by TLC or HPLC, according to General Procedure H. The reaction mixture was then filtered to remove the catalyst. The solvent was removed *in vacuo* to afford the desired 4-(3-tert-butyl-phenoxy)aniline, which was used directly for further transformation without further
- 25 purification (yield 80%).

- To a stirred solution of 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone (2 mmol) in anhydrous MeOH (6 mL) at 0°C, pyrrolidone hydrotribromide (1.2 eq) was added, according to General Procedure R1. The reaction mixture was stirred under nitrogen at 0°C for 1h and was allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was
- 30 then removed *in vacuo* and the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was used for further transformation.

To a solution of 4-(3-tert-butyl-phenoxy)aniline (1 eq, 2 mmol) in anhydrous DMF (6mL), DIEA (3 eq 6 mmol) was added, followed by addition of the 2-bromo-1-{4-[3-

(diethylamino)propoxy]phenyl}ethanone described above (2 mmol), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product by elution with 2-4% MeOH/DCM (yield 51%).

To a stirred solution of alkylated aniline described above (1 mmol) in anhydrous DCM (4 mL) at 0°C, TEA (3eq, 3 mmol) was added, followed by a slow addition of valeryl chloride (3 eq, 3 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (1 mmol) in acetic acid (4 mL), ammonium acetate (20 eq) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled to rt and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained by elution with 4-6% MeOH/DCM (yield 177 mg).

MS m/z 555 (M+H)⁺:

¹H NMR (400 MHz, CDCl₃): δ 7.7 (d, 2H), 7.3 (m, 4H), 7.1-7.2 (m, 5H), 6.9 (d, 2H), 4.0 (t, 2H), 2.8-3.0 (m, 8H), 2.0 (m, 2H), 1.6 (m, 2H), 1.4 (m, 2H), 1.2 (15H), 0.8 (t, 3H) ppm

Example 450

{3-[4-(4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-methoxymethyl-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine

To a stirred solution of 4-fluoronitrobenzene (2.0 mmol) in anhydrous THF (5 mL) at 0°C, a 1M solution of a potassium diethylaminopropoxide (2.2 mmol) in THF was added dropwise and under a nitrogen stream, according to General Procedure L1. The reaction mixture was stirred at 0°C for 1 h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The reaction mixture was then treated with cold H₂O (15 mL), and extracted with EtOAc (2x15 mL). The combined organic layers were washed with brine and dried over

sodium sulfate. Evaporation of the solvent *in vacuo* afforded the desired 4-alkoxynitrobenzene. The crude product was used directly for further transformation .

5 The N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (2 mmol) obtained above was dissolved in MeOH (10 mL) and hydrogenated in the presence of 10% Pd/C (10 mg) until completion as indicated by TLC or HPLC, according to General Procedure H. The reaction mixture was then filtered to remove the catalyst. The solvent was removed *in vacuo* to afford the desired 4-alkoxyaniline, which was used directly for further transformation without further purification.

10 To a stirred solution of 4'-hydroxyacetophenone (2.2 mmol) in DMF (5 mL) at rt, solid potassium carbonate (9.0 mmol) was added. 4-chlorophenethyl mesylate (2.0 mmol) was added to the reaction mixture and heated to 80°C until completion according to General Procedure Q1, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was quenched using cold water (20 ml) and the product was isolated in EtOAc (2X20 ml). The combined organic layers were washed with saturated sodium bicarbonate (2X10 ml), water
15 (2X10 ml) and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired 1-{4-[2-(4-chlorophenyl)ethoxy]phenyl}ethanone. The crude alkylated acetophenone was used for further transformation .

20 To a stirred solution of the 1-{4-[2-(4-chlorophenyl)ethoxy]phenyl}ethanone (2 mmol) in anhydrous MeOH (5 mL) at 0°C, pyrrolidone hydrotribromide (1.2eq., 2.2 mmol) was added, according to General Procedure R1. The reaction mixture was stirred under nitrogen at 0°C for 1h and was allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was then removed *in vacuo* and the residue was treated with saturated sodium bicarbonate. The aqueous layer was poured into EtOAc (20 ml) and the product was
25 isolated in EtOAc (2X20 ml). The combined organic layers were washed with saturated sodium bicarbonate (2X10 ml), and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired product. The crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was purified by chromatography (Silica gel). Pure product was obtained by elution with 20-30%
30 EtOAc/hexane (yield ~70-75%).

To a stirred solution of the N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (1.2 eq., 2 mmol) in anhydrous DMF (5 mL) DIEA (3 eq. 6 mmol) was added, followed by slow addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone described above (1.6 mmol), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt

until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was used for further transformation .

5 To a stirred solution of 1-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-[4-(3-diethylamino-propoxy)-phenylamino]-ethanone described above (1.6 mmol) in anhydrous DCM (5 mL) at 0°C, TEA (3eq., 4.8 mmol) was added, followed by slow addition of methoxy acetyl chloride (2 eq., 3.2 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by TLC
10 or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in DCM. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (1.6 mmol) in acetic acid (4 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The
15 reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled to rt and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained by elution with 4-6% MeOH/DCM (yield: 265 mg).

MS m/z 549 (M+H)⁺:

20 ¹H NMR (400 MHz, CDCl₃): δ 7.72 (d, 2H), 7.37 (d, 2H), 7.48 (m, 5H), 6.98 (d, 2H), 6.85 (d, 2H), 4.41 (s, 2H), 4.18 (t, 2H), 4.07 (t, 2H), 3.45 (s, 3H), 3.06 (t, 2H), 2.86 (m, 6H), 2.08 (m, 2H), 1.17 (t, 6H) ppm

Example 451

25 (3-{4-[4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-(1-ethyl-propyl)-imidazol-1-yl]-phenoxy}-propyl)-diethyl-amine

To a stirred solution of 4-fluoronitrobenzene (2.0 mmol) in anhydrous THF (5 mL) at 0°C, a 1M solution of a potassium diethylaminopropoxide (2.2 mmol) in THF was added dropwise and under a nitrogen stream, according to General Procedure L1. The reaction mixture was
30 stirred at 0°C for 1 h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The reaction mixture was then treated with cold H₂O (15 mL), and extracted with

EtOAc (2x15 mL). The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of the solvent *in vacuo* afforded the desired 4-alkoxynitrobenzene. The crude product was used directly for further transformation .

The N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (2 mmol) obtained above was dissolved in MeOH (10 mL) and hydrogenated in the presence of 10% Pd/C (10 mg) until completion as indicated by TLC or HPLC, according to General Procedure H. The reaction mixture was then filtered to remove the catalyst. The solvent was removed *in vacuo* to afford the desired 4-alkoxyaniline, which was used directly for further transformation without further purification.

To a stirred solution of 4'-hydroxyacetophenone (2.2 mmol) in DMF (5 mL) at rt, solid potassium carbonate (9.0 mmol) was added. 4-chlorophenethyl mesylate (2.0 mmol) was added to the reaction mixture and heated to 80°C until completion according to General Procedure Q1, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was quenched using cold water (20 ml) and the product was isolated in EtOAc (2X20 ml). The combined organic layers were washed with saturated sodium bicarbonate (2X10 ml), water (2X10 ml) and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired 1-{4-[2-(4-chlorophenyl)ethoxy]phenyl}ethanone. The crude alkylated acetophenone was used for further transformation .

To a stirred solution of the 1-{4-[2-(4-chlorophenyl)ethoxy]phenyl}ethanone (2 mmol) in anhydrous MeOH (5 mL) at 0°C, pyrrolidone hydrotribromide (1.2 eq., 2.2 mmol) was added, according to General Procedure R1. The reaction mixture was stirred under nitrogen at 0°C for 1h and was allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was then removed *in vacuo* and the residue was treated with saturated sodium bicarbonate. The aqueous layer was poured into EtOAc (20 ml) and the product was isolated in EtOAc (2X20 ml). The combined organic layers were washed with saturated sodium bicarbonate (2X10 ml), and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired product. The crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was purified by chromatography (Silica gel). Pure product was obtained by elution with 20-30% EtOAc/hexane (yield ~70-75%).

To a stirred solution of the N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (1.2 eq., 2 mmol) in anhydrous DMF (5 mL) DIEA (3 eq. 6 mmol) was added, followed by slow addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone described above (1.6 mmol),

according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was used for further transformation .

To a stirred solution of 1-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-[4-(3-diethylamino-propoxy)-phenylamino]-ethanone described above (1.6 mmol) in anhydrous DCM (5 mL) at 0°C, TEA (3eq., 4.8 mmol) was added, followed by slow addition of 2-ethyl butyryl chloride (2 eq., 3.2 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in DCM. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (1.6 mmol) in acetic acid (4 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled to rt and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained by elution with 4-6% MeOH/DCM (yield: 230 mg).

MS m/z 575 (M+H)⁺:

¹H NMR (400 MHz, CDCl₃): δ 7.71 (d, 2H), 7.27 (m, 6H), 7.06 (s, 1H), 6.95 (d, 2H), 6.87 (d, 2H), 4.09 (t, 2H), 4.02 (t, 2H), 3.07 (t, 2H), 2.72 (m, 6H), 2.49 (m, 1H), 2.06 (m, 2H), 1.82 (m, 2H), 1.68 (m, 2H), 1.08 (t, 6H), 0.96 (t, 3H), 0.88 (t, 3H) ppm

Example 452

(3-{4-[4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-(3-phenoxy-propyl)-imidazol-1-yl]-phenoxy}-propyl)-diethyl-amine

The N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (2 mmol) obtained above was dissolved in MeOH (10 mL) and hydrogenated in the presence of 10% Pd/C (10 mg) until completion as indicated by TLC or HPLC, according to General Procedure H. The reaction mixture was then filtered to remove the catalyst. The solvent was removed *in vacuo* to afford the

desired 4-alkoxyaniline, which was used directly for further transformation without further purification.

To a stirred solution of 4'-hydroxyacetophenone (2.2 mmol) in DMF (5 mL) at rt, solid potassium carbonate (9.0 mmol) was added. 4-chlorophenethyl mesylate (2.0 mmol) was added to the reaction mixture and heated to 80°C until completion according to General Procedure Q1, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was quenched using cold water (20 ml) and the product was isolated in EtOAc (2X20 ml). The combined organic layers were washed with saturated sodium bicarbonate (2X10 ml), water (2X10 ml) and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired 1-{4-[2-(4-chlorophenyl)ethoxy]phenyl}ethanone. The crude alkylated acetophenone was used for further transformation .

To a stirred solution of the 1-{4-[2-(4-chlorophenyl)ethoxy]phenyl}ethanone (2 mmol) in anhydrous MeOH (5 mL) at 0°C, pyrrolidone hydrotribromide (1.2 eq., 2.2 mmol) was added, according to General Procedure R1. The reaction mixture was stirred under nitrogen at 0°C for 1h and was allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was then removed *in vacuo* and the residue was treated with saturated sodium bicarbonate. The aqueous layer was poured into EtOAc (20 ml) and the product was isolated in EtOAc (2X20 ml). The combined organic layers were washed with saturated sodium bicarbonate (2X10 ml), and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired product. The crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was purified by chromatography (Silica gel). Pure product was obtained by elution with 20-30% EtOAc/hexane (yield ~70-75%).

To a stirred solution of the N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (1.2 eq., 2 mmol) in anhydrous DMF (5 mL) DIEA (3 eq. 6 mmol) was added, followed by slow addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone described above (1.6 mmol), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was used for further transformation .

To a stirred solution of 1-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-[4-(3-diethylamino-propoxy)-phenylamino]-ethanone described above (1.6 mmol) in anhydrous DCM (5 mL) at

0°C, TEA (3eq., 4.8 mmol) was added, followed by slow addition of 4-phenoxy butyryl chloride (2 eq., 3.2 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in DCM. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (1.6 mmol) in acetic acid (4 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled to rt and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained by elution with 4-6% MeOH/DCM (yield: 250 mg).

MS m/z 638 (M+H)⁺:

¹H NMR (400 MHz, CDCl₃): δ 7.69 (d, 2H), 7.23-7.25 (m, 8H), 7.12 (s, 1H), 6.92 (m, 5H), 6.81 (d, 2H), 4.18 (t, 2H), 4.09 (t, 2H), 3.95 (t, 2H), 3.07 (t, 2H), 2.85 (m, 8H), 2.22 (m, 2H), 2.05 (m, 2H), 1.20 (t, 6H) ppm

Example 453

(3-{4-[4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-(1-propyl-butyl)-imidazol-1-yl]-phenoxy}-propyl)-diethyl-amine

To a stirred solution of 4-fluoronitrobenzene (2.0 mmol) in anhydrous THF (5 mL) at 0°C, a 1M solution of a potassium diethylaminopropoxide (2.2 mmol) in THF was added dropwise and under a nitrogen stream, according to General Procedure L1. The reaction mixture was stirred at 0°C for 1 h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The reaction mixture was then treated with cold H₂O (15 mL), and extracted with EtOAc (2x15 mL). The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of the solvent *in vacuo* afforded the desired 4-alkoxynitrobenzene. The crude product was used directly for further transformation.

The N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (2 mmol) obtained above was dissolved in MeOH (10 mL) and hydrogenated in the presence of 10% Pd/C (10 mg) until completion as indicated by TLC or HPLC, according to General Procedure H. The reaction mixture was

then filtered to remove the catalyst. The solvent was removed *in vacuo* to afford the desired 4-alkoxyaniline, which was used directly for further transformation without further purification.

To a stirred solution of 4'-hydroxyacetophenone (2.2 mmol) in DMF (5 mL) at rt, solid potassium carbonate (9.0 mmol) was added. 4-chlorophenethyl mesylate (2.0 mmol) was added to the reaction mixture and heated to 80°C until completion according to General Procedure Q1, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was quenched using cold water (20 ml) and the product was isolated in EtOAc (2X20 ml). The combined organic layers were washed with saturated sodium bicarbonate (2X10 ml), water (2X10 ml) and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired 1-{4-[2-(4-chlorophenyl)ethoxy]phenyl}ethanone. The crude alkylated acetophenone was used for further transformation.

To a stirred solution of the 1-{4-[2-(4-chlorophenyl)ethoxy]phenyl}ethanone (2 mmol) in anhydrous MeOH (5 mL) at 0°C, pyrrolidone hydrotribromide (1.2 eq., 2.2 mmol) was added, according to General Procedure R1. The reaction mixture was stirred under nitrogen at 0°C for 1h and was allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was then removed *in vacuo* and the residue was treated with saturated sodium bicarbonate. The aqueous layer was poured into EtOAc (20 ml) and the product was isolated in EtOAc (2X20 ml). The combined organic layers were washed with saturated sodium bicarbonate (2X10 ml), and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired product. The crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was purified by chromatography (Silica gel). Pure product was obtained by elution with 20-30% EtOAc/hexane (yield ~70-75%).

To a stirred solution of the N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (1.2 eq., 2 mmol) in anhydrous DMF (5 mL) DIEA (3 eq. 6 mmol) was added, followed by slow addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone described above (1.6 mmol), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was used for further transformation.

To a stirred solution of 1-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-[4-(3-diethylamino-propoxy)-phenylamino]-ethanone described above (1.6 mmol) in anhydrous DCM (5 mL) at 0°C, TEA (3eq., 4.8 mmol) was added, followed by slow addition of 2-N-propyl-N-valeryl chloride (2 eq., 3.2 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in DCM. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (1.6 mmol) in acetic acid (4 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled to rt and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained by elution with 4-6% MeOH/DCM (yield: 288 mg).

MS m/z 602 (M+H)⁺:

¹H NMR (400 MHz, CDCl₃): δ 7.69 (d, 2H), 7.23-7.25 (m, 6H), 7.04 (s, 1H), 6.97 (d, 2H), 6.87 (d, 2H), 4.18 (t, 2H), 4.09 (t, 2H), 3.06 (t, 2H), 2.87 (m, 6H), 2.63 (m, 1H), 2.13 (m, 2H), 1.81 (m, 2H), 1.54 (m, 2H), 1.17 (t, 10H), 0.89 (t, 6H) ppm

Example 454

{3-[4-(2-(4-chloro-phenoxy)methyl)-4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine

To a stirred solution of 4-fluoronitrobenzene (2.0 mmol) in anhydrous THF (5 mL) at 0°C, a 1M solution of a potassium diethylaminopropoxide (2.2 mmol) in THF was added dropwise and under a nitrogen stream, according to General Procedure L1. The reaction mixture was stirred at 0°C for 1 h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The reaction mixture was then treated with cold H₂O (15 mL), and extracted with EtOAc (2x15 mL). The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of the solvent *in vacuo* afforded the desired 4-alkoxynitrobenzene. The crude product was used directly for further transformation.

The N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (2 mmol) obtained above was dissolved in MeOH (10 mL) and hydrogenated in the presence of 10% Pd/C (10 mg) until completion as indicated by TLC or HPLC, according to General Procedure H. The reaction mixture was then filtered to remove the catalyst. The solvent was removed *in vacuo* to afford the
5 desired 4-alkoxyaniline, which was used directly for further transformation without further purification.

To a stirred solution of 4'-hydroxyacetophenone (2.2 mmol) in DMF (5 mL) at rt, solid potassium carbonate (9.0 mmol) was added. 4-chlorophenethyl mesylate (2.0 mmol) was added to the reaction mixture and heated to 80°C until completion according to General
10 Procedure Q1, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was quenched using cold water (20 ml) and the product was isolated in EtOAc (2X20 ml). The combined organic layers were washed with saturated sodium bicarbonate (2X10 ml), water (2X10 ml) and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired 1-{4-[2-(4-
15 chlorophenyl)ethoxy]phenyl}ethanone. The crude alkylated acetophenone was used for further transformation.

To a stirred solution of the 1-{4-[2-(4-chlorophenyl)ethoxy]phenyl}ethanone (2 mmol) in anhydrous MeOH (5 mL) at 0°C, pyrrolidone hydrotribromide (1.2 eq., 2.2 mmol) was added, according to General Procedure R1. The reaction mixture was stirred under nitrogen at 0°C
20 for 1h and was allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was then removed *in vacuo* and the residue was treated with saturated sodium bicarbonate. The aqueous layer was poured into EtOAc (20 ml) and the product was isolated in EtOAc (2X20 ml). The combined organic layers were washed with saturated sodium bicarbonate (2X10 ml), and brine (15 ml). The organic layer was dried over
25 magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired product. The crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was purified by chromatography (Silica gel). Pure product was obtained by elution with 20-30% EtOAc/hexane (yield ~70-75%).

To a stirred solution of the N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (1.2 eq., 2 mmol) in anhydrous DMF (5 mL) DIEA (3 eq. 6 mmol) was added, followed by slow addition of the
30 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone described above (1.6 mmol), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in EtOAc. The combined organic layers were

washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was used for further transformation .

To a stirred solution of 1-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-[4-(3-diethylamino-propoxy)-phenylamino]-ethanone described above (1.6 mmol) in anhydrous DCM (5 mL) at 0°C, TEA (3eq., 4.8 mmol) was added, followed by slow addition of 4-chlorophenoxy acetyl chloride (2 eq., 3.2 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in DCM. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (1.6 mmol) in acetic acid (4 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled to rt and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained by elution with 4-6% MeOH/DCM (yield: 250 mg).

MS m/z 644 (M+H)⁺:

¹H NMR (400 MHz, CDCl₃): δ 7.72 (d, 2H), 7.36 (d, 2H), 7.23-7.25 (m, 4H), 7.23 (m, 4H), 6.91 (m, 5H), 4.95 (s, 2H), 4.17 (t, 2H), 4.05 (t, 2H), 3.07 (m, 8H), 2.21 (m, 2H), 1.27 (t, 6H) ppm

Example 455

{3-[4-(2-benzyloxymethyl-4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine

To a stirred solution of 4-fluoronitrobenzene (2.0 mmol) in anhydrous THF (5 mL) at 0°C, a 1M solution of a potassium diethylaminopropoxide (2.2 mmol) in THF was added dropwise and under a nitrogen stream, according to General Procedure L1. The reaction mixture was stirred at 0°C for 1 h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The reaction mixture was then treated with cold H₂O (15 mL), and extracted with EtOAc (2x15 mL). The combined organic layers were washed with brine and dried over

sodium sulfate. Evaporation of the solvent *in vacuo* afforded the desired 4-alkoxynitrobenzene. The crude product was used directly for further transformation .

5 The N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (2 mmol) obtained above was dissolved in MeOH (10 mL) and hydrogenated in the presence of 10% Pd/C (10 mg) until completion as indicated by TLC or HPLC, according to General Procedure H. The reaction mixture was then filtered to remove the catalyst. The solvent was removed *in vacuo* to afford the desired 4-alkoxyaniline, which was used directly for further transformation without further purification.

10 To a stirred solution of 4'-hydroxyacetophenone (2.2 mmol) in DMF (5 mL) at rt, solid potassium carbonate (9.0 mmol) was added. 4-chlorophenethyl mesylate (2.0 mmol) was added to the reaction mixture and heated to 80°C until completion according to General Procedure Q1, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was quenched using cold water (20 ml) and the product was isolated in EtOAc (2X20 ml). The combined organic layers were washed with saturated sodium bicarbonate (2X10 ml), water
15 (2X10 ml) and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired 1-{4-[2-(4-chlorophenyl)ethoxy]phenyl}ethanone. The crude alkylated acetophenone was used for further transformation .

20 To a stirred solution of the 1-{4-[2-(4-chlorophenyl)ethoxy]phenyl}ethanone (2 mmol) in anhydrous MeOH (5 mL) at 0°C, pyrrolidone hydrotribromide (1.2 eq., 2.2 mmol) was added, according to General Procedure R1. The reaction mixture was stirred under nitrogen at 0°C for 1h and was allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was then removed *in vacuo* and the residue was treated with saturated sodium bicarbonate. The aqueous layer was poured into EtOAc (20 ml) and the product was
25 isolated in EtOAc (2X20 ml). The combined organic layers were washed with saturated sodium bicarbonate (2X10 ml), and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired product. The crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was purified by chromatography (Silica gel). Pure product was obtained by elution with 20-30%
30 EtOAc/hexane (yield ~70-75%).

To a stirred solution of the N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (1.2 eq., 2 mmol) in anhydrous DMF (5 mL) DIEA (3 eq. 6 mmol) was added, followed by slow addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone described above (1.6 mmol), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt

until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was used for further transformation .

- 5 To a stirred solution of 1-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-[4-(3-diethylamino-propoxy)-phenylamino]-ethanone described above (1.6 mmol) in anhydrous DCM (5 mL) at 0°C, TEA (3eq., 4.8 mmol) was added, followed by slow addition of benzyloxyacetyl chloride (2 eq., 3.2 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in DCM. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

- 15 To a stirred solution of the amide described above (1.6 mmol) in acetic acid (4 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled to rt and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained by elution with 4-6% MeOH/DCM (yield: 350 mg).

MS m/z 624 (M+H)⁺:

- 20 ¹H NMR (400 MHz, CDCl₃): δ 7.71 (d, 2H), 7.68 (d, 2H), 7.31 (m, 7H), 7.25 (d, 2H), 7.21 (s, 1H), 6.94 (d, 2H), 6.89 (d, 2H), 4.58 (s, 2H), 4.49 (s, 2H), 4.15 (t, 2H), 4.08 (t, 2H), 3.11 (t, 2H), 2.89 (m, 6H), 2.18 (m, 2H), 1.35 (t, 6H) ppm

Example 456

- 25 {3-[4-(4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-isobutyl-5-methyl-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine

- 30 To a stirred solution of 1-{4-[2-(4-chloro-phenyl)-ethoxy]phenyl}-propan-1-one (1.0 mmol) in dioxane (10.0 mL) at rt, pyridinium bromide perbromide (1.1eq) was added. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC. The mixture was diluted with EtOAc (100 ml) and washed with H₂O (2X50 ml), brine (30 ml) and dried

with magnesium sulfate, The solvent was then removed *in vacuo* to give a white solid. The alpha-bromoketone was used for further transformation without further purification.

A solution of the above alpha-bromoketone (1.0 eq), N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (1.0 eq), and DIEA (1.5 eq) in anhydrous DMF (10 mL) was stirred under nitrogen at rt until completion, as indicated by HPLC. The reaction mixture was then diluted with cold H₂O and the product was isolated in Et₂O. The combined organic layers were washed with brine and dried over sodium sulfate. The solvent was removed *in vacuo* afforded the desired product. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product was obtained by elution with 2-7% MeOH/DCM (yield ~55%).

To a stirred solution of alkylated aniline described above (0.55 mmol) in anhydrous THF (5 mL) at 0°C, TEA (3.0mmol) was added, followed by slow addition of isovaleryl chloride (5.0 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to ambient temperature until completion, as indicated by HPLC. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (0.55mmol) in acetic acid (2 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 100°C overnight. The reaction mixture was then cooled down and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole (yield 190 mg)

MS m/z 574 (M+H)⁺:

Example 457

{3-[4-(4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-isobutyl-5-propyl-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine

To a stirred solution of 1-{4-[2-(4-chloro-phenyl)-ethoxy]phenyl}-pentan-1-one (1.0 mmol) in dioxane (10.0 mL) at rt, pyridinium bromide perbromide (1.1eq.) was added. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC. The mixture was diluted with EtOAc (100 ml) and washed with H₂O (2X50 ml), brine (30 ml) and dried

with magnesium sulfate. The solvent was then removed *in vacuo* to give a white solid. The alpha-bromophenone was used for further transformation.

A solution of the above alpha-bromophenone (1.0 eq), N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (1.0 eq), and DIEA (1.5 eq) in anhydrous DMF (10 mL) was stirred under nitrogen at rt until completion, as indicated by HPLC. The reaction mixture was then diluted with cold H₂O and the product was isolated in Et₂O. The combined organic layers were washed with brine and dried over sodium sulfate. The solvent was removed *in vacuo* afforded the desired product. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product was obtained by elution with 2-5% MeOH/DCM (yield ~50%).

To a stirred solution of alkylated aniline described above (0.48 mmol) in anhydrous THF (5 mL) at 0°C, DMAP (0.25 eq) was added, followed by slow addition of isovaleryl chloride (5.0 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to ambient temperature until completion, as indicated by HPLC. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (0.48mmol) in acetic acid (2 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 100°C overnight. The reaction mixture was then cooled down and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole (yield 180 mg).

MS m/z 602 (M+H)⁺:

¹H NMR (CDCl₃): δ 7.58 (d, 2H), 7.28 (d, 2H), 7.21 (d, 2H), 7.11 (d, 2H), 6.98 (d, 2H), 6.91 (d, 2H), 4.17 (t, 2H), 4.08 (t, 2H), 3.07 (t, 2H), 2.6 (t, 2H), 2.57 (q, 6H), 2.47 (t, 4H), 2.36 (d, 2H), 2.0 (m, 3H), 1.3 (m, 2H), 1.05 (t, 6H), 0.82 (d, 6H), 0.72 (t, 3, H) ppm.

Example 458

{3-[4-(5-butyl-4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-isobutyl-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine

To a stirred solution of 1-{4-[2-(4-chloro-phenyl)-ethoxy]phenyl}-hexan-1-one (0.785 mmol) in dioxane (10.0 mL) at rt, pyridinium bromide perbromide (1.1eq) was added. The reaction

mixture was stirred under nitrogen at rt until completion, as indicated by TLC. The mixture was diluted with EtOAc (100 ml) and washed with H₂O (2X50 ml), brine (30 ml) and dried with magnesium sulfate. The solvent was then removed *in vacuo* to give a white solid. The alpha-bromophenone was used for further transformation.

5 A solution of the above alpha-bromophenone (1.0eq), N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (1.0 eq), and DIEA (1.5 eq) in anhydrous DMF (10 mL) was stirred under nitrogen at rt for 24 hour. The reaction mixture was then diluted with cold H₂O and the product was isolated in Et₂O. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired
10 product. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product was obtained by elution with 2-7% MeOH/DCM (yield ~47%).

To a stirred solution of alkylated aniline described above (0.31 mmol) in anhydrous THF (5 mL) at 0°C, DMAP (0.25 eq) was added, followed by slow addition of isovaleryl chloride (5.0 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen
15 at 0°C for 1h and allowed to warm to ambient temperature until completion, as indicated by HPLC. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (0.31mmol) in acetic acid (2 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The
20 reaction mixture was stirred at 100°C overnight. The reaction mixture was then cooled down and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole (yield 108 mg).

MS m/z 616 (M+H)⁺:

¹H NMR (CDCl₃): δ 7.6 (d, 2H), 7.28 (d, 2H), 7.21 (d, 2H), 7.11 (d, 2H), 7.00 (d, 2H), 6.90 (d,
25 2H), 4.18 (t, 2H), 4.08 (t, 2H), 3.06 (t, 2H), 2.45-2.65 (m, 8H), 2.36 (d, 2H), 2.0 (m, 4H), 0.7-1.3 (m, 18 H) ppm.

Example 459

{4-{4-{2-(4-chloro-phenyl)-ethoxy}-phenyl}-1-[4-(3-diethylamino-propoxy)-phenyl]-1H-imidazol-2-yl}-MeOH
30

To a stirred solution of 4-fluoronitrobenzene (2.0 mmol) in anhydrous THF (5 mL) at 0°C, a 1M solution of a potassium diethylaminopropoxide (2.2 mmol) in THF was added dropwise and under a nitrogen stream, according to General Procedure L1. The reaction mixture was stirred at 0°C for 1 h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The reaction mixture was then treated with cold H₂O (15 mL), and extracted with EtOAc (2x15 mL). The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of the solvent *in vacuo* afforded the desired 4-alkoxynitrobenzene. The crude product was used directly for further transformation .

The N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (2 mmol) obtained above was dissolved in MeOH (10 mL) and hydrogenated in the presence of 10% Pd/C (10 mg) until completion as indicated by TLC or HPLC, according to General Procedure H. The reaction mixture was then filtered to remove the catalyst. The solvent was removed *in vacuo* to afford the desired 4-alkoxyaniline, which was used directly for further transformation without further purification.

To a stirred solution of 4'-hydroxyacetophenone (2.2 mmol) in DMF (5 mL) at rt, solid potassium carbonate (9.0 mmol) was added. 4-chlorophenethyl mesylate (2.0 mmol) was added to the reaction mixture and heated to 80°C until completion according to General Procedure Q1, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was quenched using cold water (20 ml) and the product was isolated in EtOAc (2X20 ml). The combined organic layers were washed with saturated sodium bicarbonate (2X10 ml), water (2X10 ml) and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired 1-{4-[2-(4-chlorophenyl)ethoxy]phenyl}ethanone. The crude alkylated acetophenone was used for further transformation .

To a stirred solution of the 1-{4-[2-(4-chlorophenyl)ethoxy]phenyl}ethanone (2 mmol) in anhydrous MeOH (5 mL) at 0°C, pyrrolidone hydrotribromide (1.2 eq., 2.2 mmol) was added, according to General Procedure R1. The reaction mixture was stirred under nitrogen at 0°C for 1h and was allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was then removed *in vacuo* and the residue was treated with saturated sodium bicarbonate. The aqueous layer was poured into EtOAc (20 ml) and the product was isolated in EtOAc (2X20 ml). The combined organic layers were washed with saturated sodium bicarbonate (2X10 ml), and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired product. The crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was purified by

chromatography (Silica gel). Pure product was obtained by elution with 20-30% EtOAc/hexane (yield ~70-75%).

To a stirred solution of the N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (1.2 eq., 2 mmol) in anhydrous DMF (5 mL) DIEA (3 eq. 6 mmol) was added, followed by slow addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone described above (1.6 mmol), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was used for further transformation .

To a stirred solution of 1-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-[4-(3-diethylamino-propoxy)-phenylamino]-ethanone described above (1.6 mmol) in anhydrous DCM (5 mL) at 0°C, TEA (3eq., 4.8 mmol) was added, followed by slow addition of benzyloxyacetyl chloride (2 eq., 3.2 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in DCM. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (1.6 mmol) in acetic acid (4 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled to rt and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained by elution with 4-6% MeOH/DCM (yield 30-40%).

To a stirred solution of the pure imidazole (0.48 mmol) described above 6N HCl was added and the reaction mixture was refluxed overnight. The reaction mixture was then cooled to rt and neutralized with 3N sodium hydroxide solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained by elution with 4-6% MeOH/DCM (yield: 130 mg).

MS m/z 534 (M+H)⁺:

¹H NMR (400 MHz, CDCl₃): δ 7.66 (d, 2H), 7.41 (d, 2H), 7.28 (d, 2H), 7.22 (m, 3H), 6.99 (d, 2H), 6.89 (d, 2H), 4.62 (s, 2H), 4.17 (t, 2H), 4.08 (t, 2H), 3.07 (t, 2H), 2.88 (m, 6H), 2.18 (m, 2H), 1.24 (t, 6H) ppm

Example 460

diethyl-[3-(4-{2-isobutyl-4-[4-(4-phenoxy-benzyloxy)-phenyl]-imidazol-1-yl}-phenoxy)-propyl]-amine

5 To a stirred solution of N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (1.0 eq., 2.5 mmol) in anhydrous DMF (20 mL) DIEA (3 eq) was added, followed by slow addition of the 1-[4-(benzyloxy)phenyl]-2-bromoethanone (2.5 mmol). The reaction mixture was stirred under nitrogen at rt until completion, as indicated by HPLC. The reaction mixture was then diluted with cold H₂O and the product was isolated in Et₂O. The combined organic layers were
10 washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product was obtained by elution with 2-7% MeOH/DCM (yield ~30%).

To a stirred solution of the alkylated aniline described above (0.88 mmol) in anhydrous DCM (10 mL) at 0°C, TEA (3.0mmol) was added, followed by slow addition of isovaleryl chloride
15 (5.0 eq), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to ambient temperature until completion, as indicated by HPLC. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (0.88mmol) in acetic acid (2 mL),
20 ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 100°C overnight. The reaction mixture was then cooled down and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the cyclized product, (crude ~ 80%) which was taken to the next transformation without purification.

25 The above product was dissolved in MeOH (20 mL), Pd/C (100 mg) was added and the heterogeneous mixture was stirred overnight under H₂ atmosphere using a balloon, according to General Procedure T2. The Pd/C was removed by filtration. The solvent was removed *in vacuo*, and the crude 4-{1-[4-(3-diethylamino-propoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenol was used for further transformation without purification.

30 A stirred solution of the 4-{1-[4-(3-diethylamino-propoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenol (1.0 eq) obtained above in anhydrous DMF (5.0 mL) was treated with solid sodium hydride (60% dispersion in oil; 1.0mmol) in portions. The mesylate of (4-

phenoxyphenyl)methanol (1.1eq) was added to the reaction mixture, which was stirred at rt overnight, according to General Procedure T3. Et₂O (30 mL) was added to the reaction mixture followed by H₂O (10 mL). The organic layer was washed with H₂O (2x15 mL) and brine, and dried over sodium sulfate. The solvent was removed *in vacuo*. Pure imidazole
5 was obtained by elution with chromatography in 5-10% MeOH/DCM (yield 70.0 mg).

MS m/z 604 (M+H)⁺:

¹H NMR (CDCl₃): δ 7.70 (d, 2H) 6.9-7.4 (m, 16H), 5.0 (s, 2H), 4.1 (t, 2H), 3.0 (m, 6H), 2.52 (d), 2.26 (m, 2H), 2.01 (m, 1H), 1.31 (t, 6H), 0.84 (d, 6H) ppm.

10 Example 461

[3-(4-{4-[4-(4-benzyloxy-benzyloxy)-phenyl]-2-isobutyl-imidazol-1-yl}-phenoxy)-propyl]-
diethyl-amine

To a stirred solution of N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (1.0 eq., 2.5 mmol) in anhydrous DMF (20 mL) DIEA (3 eq) was added, followed by slow addition of the 1-[4-
15 (benzyloxy)phenyl]-2-bromoethanone (2.5 mmol). The reaction mixture was stirred under nitrogen at rt until completion, as indicated by HPLC. The reaction mixture was then diluted with cold H₂O and the product was isolated in Et₂O. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was purified by chromatography (Silica gel).
20 Pure product was obtained by elution with 2-7% MeOH/DCM (yield ~30%).

To a stirred solution of the alkylated aniline described above (0.88 mmol) in anhydrous DCM (10 mL) at 0°C, TEA (3.0mmol) was added, followed by slow addition of isovaleryl chloride (5.0 eq), according to General Procedure R3. The reaction mixture was stirred under
25 nitrogen at 0°C for 1h and allowed to warm to ambient temperature until completion, as indicated by HPLC. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (0.88mmol) in acetic acid (2 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 100°C overnight. The reaction mixture was then cooled down
30 and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with

EtOAc gave the cyclized product, (crude ~ 80%) which was taken to the next transformation without purification.

The above product was dissolved in MeOH (20 mL), Pd/C (100 mg) was added and the heterogeneous mixture was stirred overnight under H₂ atmosphere using a balloon, according to General Procedure T2. The Pd/C was removed by filtration. The solvent was removed *in vacuo*, and the crude 4-{1-[4-(3-diethylamino-propoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenol was used for further transformation without purification.

A stirred solution of 4-{1-[4-(3-diethylamino-propoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenol (1.0 eq) in anhydrous DMF (5.0 mL) was treated with solid sodium hydride (60% dispersion in oil; 1.0mmol) in portions. The mesylate of [4-(benzyloxy)phenyl]methanol (1.1eq) was added to the reaction mixture, and stirred at rt overnight, according to General Procedure T3. Et₂O (30 mL) was added to the reaction mixture followed by H₂O (10 mL). The organic layer was washed with H₂O (2x15 mL) and brine, and dried over sodium sulfate. The solvent was removed *in vacuo*. Pure imidazole was obtained from chromatography with 5-10% MeOH/DCM (yield 70.0 mg)

MS m/z 618 (M+H)⁺:

¹H NMR (CDCl₃): δ7.70 (d, 2H), 7.3-7.45 (m, 7H), 7.21 (d, 2H), 7.1 (s, 1H), 6.9 (m, 6H), 5.07 (s, 2H), 5.00 (s, 2H), 4.1 (t, 2H), 3.0 (m, 6H), 2.52 (d, 2H), 2.26 (m, 2H), 2.01 (m, 1H), 1.31 (t, 6H), 0.84 (d, 6H) ppm.

Example 462

[3-(4-{4-[4-(2-benzenesulfonylmethyl-benzyloxy)-phenyl]-2-isobutyl-imidazol-1-yl}-phenoxy)-propyl]-diethyl-amine

To a stirred solution of N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (1.0 eq., 2.5 mmol) in anhydrous DMF (20 mL) DIEA (3 eq) was added, followed by slow addition of 1-[4-(benzyloxy)phenyl]-2-bromoethanone (2.5 mmol). The reaction mixture was stirred under nitrogen at rt until completion, as indicated by HPLC. The reaction mixture was then diluted with cold H₂O and the product was isolated in Et₂O. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product was obtained by elution with 2-7% MeOH/DCM (yield ~30%).

To a stirred solution of the alkylated aniline described above (0.88 mmol) in anhydrous DCM (10 mL) at 0°C, TEA (3.0mmol) was added, followed by slow addition of isovaleryl chloride (5.0 eq), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to ambient temperature until completion, as indicated by HPLC. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (0.88mmol) in acetic acid (2 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 100°C overnight. The reaction mixture was then cooled down and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the cyclized product, (crude ~ 80%) which was taken to the next transformation without purification.

The above product was dissolved in MeOH (20 mL), Pd/C (100 mg) was added and the heterogeneous mixture was stirred overnight under H₂ atmosphere using a balloon, according to General Procedure T2. The Pd/C was removed by filtration. The solvent was removed *in vacuo*, and the crude 4-{1-[4-(3-diethylamino-propoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenol was used for further transformation without purification.

A stirred solution of 4-{1-[4-(3-diethylamino-propoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenol (1.0 eq) in anhydrous DMF (5.0 mL) was treated with solid sodium hydride (60% dispersion in oil; 1.0mmol) in portions. The mesylate of {2-[(phenylsulfonyl)methyl]phenyl}methanol (1.1eq) was added to the reaction mixture, and stirred at rt overnight, according to General Procedure T3. Et₂O (30 mL) was added to the reaction mixture followed by H₂O (10 mL). The organic layer was washed with H₂O (2x15 mL) and brine, and dried over sodium sulfate. The solvent was removed *in vacuo*. Pure imidazole was obtained from chromatography with 5-10% MeOH/DCM (yield 77 mg).

MS m/z 666 (M+H)⁺:

¹H NMR (CDCl₃): δ7.6-7.73 (m, 6), 7.3-7.5 (m, 4H), 7.20 (d, 2H), 7.1 (m, 2H), 6.97 (d, 2H), 6.9 (d, 2H), 4.93 (s, 2H), 4.5 (s, 2H), 4.07 (t, 2H), 2.6 (t, 2H), 2.63 (q, 4H), 2.53 (d, 2H), 2.01 (m, 3H), 1.08 (t, 6H), 0.85 (d, 6H) ppm.

Example 463

diethyl-[3-(4-{2-isobutyl-4-[4-(3,4,5-trimethoxy-benzyloxy)-phenyl]-imidazol-1-yl}-phenoxy)-propyl]-amine

To a stirred solution of N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (1.0 eq., 2.5 mmol) in anhydrous DMF (20 mL) DIEA (3 eq) was added, followed by slow addition of the 1-[4-(benzyloxy)phenyl]-2-bromoethanone (2.5 mmol). The reaction mixture was stirred under nitrogen at rt until completion, as indicated by HPLC. The reaction mixture was then diluted with cold H₂O and the product was isolated in Et₂O. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product was obtained from 2-7% MeOH/DCM (yield ~30%).

To a stirred solution of the alkylated aniline described above (0.88 mmol) in anhydrous DCM (10 mL) at 0°C, TEA (3.0mmol) was added, followed by slow addition of isovaleryl chloride (5.0 eq), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to ambient temperature until completion, as indicated by HPLC. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (0.88mmol) in acetic acid (2 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 100°C overnight. The reaction mixture was then cooled down and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the cyclized product, (crude ~ 80%) which was taken to the next transformation without purification.

The above product was dissolved in MeOH (20 mL), Pd/C (100 mg) was added and the heterogeneous mixture was stirred overnight under H₂ atmosphere using a balloon, according to General Procedure T2. The Pd/C was removed by filtration. The solvent was removed *in vacuo*, and the crude 4-{1-[4-(3-diethylamino-propoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenol was used for further transformation without purification.

A stirred solution of 4-{1-[4-(3-diethylamino-propoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenol (1.0 eq) in anhydrous DMF (5.0 mL) was treated with solid sodium hydride (60% dispersion in oil; 1.0mmol) in portions. The mesylate of (3,4,5-trimethoxyphenyl)methanol (1.1eq) was added to the reaction mixture, and stirred at rt overnight, according to General Procedure T3. Et₂O (30 mL) was added to the reaction mixture followed by H₂O (10 mL). The organic layer was washed with H₂O (2x15 mL) and brine, and dried over sodium sulfate.

The solvent was removed *in vacuo*. Pure imidazole was obtained from chromatography with 5-10% MeOH/DCM (yield 66 mg).

MS m/z 602 (M+H)⁺:

¹H NMR (CDCl₃): δ 7.71 (d, 2H), 7.21 (d, 2H), 6.97 (m, 4H), 6.66 (s, 1H), 5 (s, 2H), 4.1 (t, 2H), 3.86 (s, 6H), 3.82 (s, 3H), 3.0 (m, 6H), 2.51 (d, 2H), 2.25 (m, 2H), 2.01 (m, 1H), 1.3 (t, 6H), 0.84 (d, 6H) ppm.

Example 464

[3-(4-{1-[4-(4-chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxy)-propyl]-diethylamine

To a stirred solution of 4'-hydroxyacetophenone (91 mmol) in DMF (80 mL) at rt, solid potassium carbonate (153 mmol) was added. The mesylate prepared from 3-diethylamino-1-propanol and methanesulfonyl chloride (76 mmol) was added to the reaction mixture and heated to 80°C until completion according to General Procedure Q1, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was quenched by treating the mixture with saturated sodium bicarbonate. The aqueous layer was poured into EtOAc (100 mL) and washed with H₂O (2X50 mL) and brine (50 mL). The organic layer was dried over sodium sulfate, and the solvent was removed *in vacuo* to afford the desired 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone. The crude alkylated product was used for further transformation after purifying using silica gel column chromatography (1-4% MeOH/DCM).

To a stirred solution of 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone (5.2 mmol) in anhydrous MeOH (10 mL) at 0°C, pyrrolidone hydrotribromide (1.2 eq., 6.2 mmol) was added slowly in small portions, according to General Procedure R1. The reaction mixture was stirred under nitrogen at 0°C for 1h and was allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was then removed *in vacuo* and the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was used for further transformation.

To a stirred solution of 4-amino-4'-chlorodiphenyl ether (1.2 eq., 6.2 mmol) in anhydrous DMF (10 mL) DIEA (3 eq. 16 mmol) was added, followed by slow addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone described above (5.2 mmol), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold H₂O and the

product was extracted in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product obtained from 2-4% MeOH/DCM (yield ~22%).

5 To a stirred solution of alkylated 4-amino-4'-chlorodiphenyl ether described above (0.4 mmol) in anhydrous DCM (5 mL) at 0°C, TEA (3eq., 1.2 mmol) was added, followed by slow addition of isovaleryl chloride (3 eq., 1.2 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was removed *in vacuo*, and the
10 crude amide was used for further transformation.

To a stirred solution of the 2-[4-(4-chlorophenoxy)-phenylamino]-1-[4-(3-diethylamino-propoxy)-phenyl]-ethanone (0.4 mmol) obtained as above in acetic acid (3 mL), solid ammonium acetate (8 mmol) was added in one portion, according to General Procedure R4. The reaction mixture was then heated to 100°C overnight. The reaction mixture was cooled
15 to rt, and treated with saturated aqueous sodium bicarbonate solution while stirring to until the pH was 7-8. The contents were extracted with EtOAc (2X15 mL). The combined organic layers was washed with H₂O (2x15 mL) and brine, and dried over sodium sulfate. Evaporation of the solvent *in vacuo* afforded the desired N-aryl imidazole. The crude product was purified using silica gel column chromatography (2-5% MeOH/DCM) (yield 117
20 mg).

MS m/z 532 (M+H)⁺:

¹H NMR (CDCl₃): δ7.63 (d, 2H), 7.28 (d, 2H), 7.21 (d, 2H), 7.06 (s, 1H), 7.01 (d, 2H), 6.98 (d, 2H), 6.83 (d, 2H), 3.99 (t, 2H), 2.79 (t, 2H), 2.72 (q, 4H), 2.49 (d, 2H), 2.30-1.90 (m, 3H), 1.10 (t, 6H), 0.80 (d, 6H) ppm.

25

Example 465

[3-(4-{1-[4-(4-chloro-phenoxy)-phenyl]-2-(2-cyclopentyl-ethyl)-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine

To a stirred solution of 4'-hydroxyacetophenone (91 mmol) in DMF (80 mL) at rt, solid potassium carbonate (153 mmol) was added. The mesylate prepared from 3-diethylamino-1-propanol and methanesulfonyl chloride (76 mmol) was added to the reaction mixture and
30

heated to 80°C until completion according to General Procedure Q1, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was quenched by treating the mixture with saturated sodium bicarbonate. The aqueous layer was poured into EtOAc (100 mL) and washed with H₂O (2X50 mL) and brine (50 mL). The organic layer was dried over sodium sulfate, and the solvent was removed *in vacuo* to afford the desired 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone. The crude alkylated product was used for further transformation after purifying using silica gel column chromatography (1-4% MeOH/DCM).

To a stirred solution of 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone (5.2 mmol) in anhydrous MeOH (10 mL) at 0°C, pyrrolidone hydrotribromide (1.2 eq., 6.2) was added slowly in small portions, according to General Procedure R1. The reaction mixture was stirred under nitrogen at 0°C for 1h and was allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was then removed *in vacuo* and the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was used for further transformation.

To a stirred solution of 4-amino-4'-chlorodiphenyl ether (1.2 eq., 6.2 mmol) in anhydrous DMF (10 mL) DIEA (3 eq. 16 mmol) was added, followed by slow addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone described above (5.2 mmol), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold H₂O and the product was extracted in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product obtained from 2-4% MeOH/DCM (yield ~22%).

To a stirred solution of alkylated 4-amino-4'-chlorodiphenyl ether described above (0.4 mmol) in anhydrous DCM (5 mL) at 0°C, TEA (3eq., 1.2 mmol) was added, followed by slow addition of 3-cyclopentylpropionyl chloride (3 eq., 1.2 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the 2-[4-(4-chlorophenoxy)-phenylamino]-1-[4-(3-diethylamino-propoxy)-phenyl]-ethanone (0.4 mmol) obtained as above in acetic acid (3 mL), solid ammonium acetate (8 mmol) was added in one portion, according to General Procedure R4. The reaction mixture was then heated to 100°C overnight. The reaction mixture was cooled to rt, and treated with saturated aqueous sodium bicarbonate solution while stirring to until the pH was 7-8. The contents were extracted with EtOAc (2X15 mL). The combined

organic layers was washed with H₂O (2x15 mL) and brine, and dried over sodium sulfate. Evaporation of the solvent *in vacuo* afforded the desired N-aryl imidazole. The crude product was purified using silica gel column chromatography (2-5% MeOH/DCM) (yield 180 mg).

5 MS m/z 572 (M+H)⁺:

¹H NMR (CDCl₃): δ7.69 (d, 2H), 7.35 (d, 2H), 7.29 (d, 2H), 7.14 (s, 1H), 7.08 (d, 2H), 7.02 (d, 2H), 6.89 (d, 2H), 4.05 (t, 2H), 2.95 (t, 2H) 2.85 (q, 4H), 2.71-2.65 (m, 2H), 2.19-2.12 (m, 3H), 1.72-1.61 (m, 4H), 1.59-1.42 (m, 4H), 1.21 (t, 6H), 1.01 (m, 2H) ppm.

Example 466

10 [3-(4-{1-[4-(4-chloro-phenoxy)-phenyl]-2-phenethyl-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine

To a stirred solution of 4'-hydroxyacetophenone (91 mmol) in DMF (80 mL) at rt, solid potassium carbonate (153 mmol) was added. The mesylate prepared from 3-diethylamino-1-propanol and methanesulfonyl chloride (76 mmol) was added to the reaction mixture and
 15 heated to 80°C until completion according to General Procedure Q1, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was quenched by treating the mixture with saturated sodium bicarbonate. The aqueous layer was poured into EtOAc (100 mL) and washed with H₂O (2X50 mL) and brine (50 mL). The organic layer was dried over sodium sulfate, and the solvent was removed *in vacuo* to afford the desired 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone. The crude alkylated product was used for further transformation after purifying using silica gel column chromatography (1-4% MeOH/DCM).
 20

To a stirred solution of 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone (5.2 mmol) in anhydrous MeOH (10 mL) at 0°C, pyrrolidone hydrotribromide (1.2 eq., 6.2) was added slowly in small portions, according to General Procedure R1. The reaction mixture was
 25 stirred under nitrogen at 0°C for 1h and was allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was then removed *in vacuo* and the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was used for further transformation.

To a stirred solution of 4-amino-4'-chlorodiphenyl ether (1.2 eq., 6.2 mmol) in anhydrous DMF (10 mL) DIEA (3 eq. 16 mmol) was added, followed by slow addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone described above (5.2 mmol), according to
 30 General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold H₂O and the

product was extracted in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product obtained from 2-4% MeOH/DCM (yield ~22%).

5 To a stirred solution of the alkylated 4-chloroalkoxy aniline described above (0.4 mmol) in anhydrous DCM (5 mL) at 0°C, TEA (3eq., 1.2 mmol) was added, followed by slow addition of hydrocinnamoyl chloride (3 eq., 1.2 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was removed *in vacuo*, and the
10 crude amide was used for further transformation.

To a stirred solution of the 2-[4-(4-chlorophenoxy)-phenylamino]-1-[4-(3-diethylamino-propoxy)-phenyl]-ethanone (~0.4 mmol) obtained as above in acetic acid (3 mL), solid ammonium acetate (8 mmol) was added in one portion, according to General Procedure R4. The reaction mixture was then heated to 100°C overnight. The reaction mixture was cooled
15 to rt, and treated with saturated aqueous sodium bicarbonate solution while stirring to until the pH was 7-8. The contents were extracted with EtOAc (2X15 mL). The combined organic layers was washed with H₂O (2x15 mL) and brine, and dried over sodium sulfate. Evaporation of the solvent *in vacuo* afforded the desired N-aryl imidazole. The crude product was purified using silica gel column chromatography (2-4% MeOH/DCM) (yield 50
20 mg).

MS m/z 580 (M+H)⁺:

¹H NMR (CDCl₃): δ8.41 (m, 2H), 7.92 (m, 2H), 7.62 (d, 2H), 7.33 (d, 2H), 7.25-7.21 (m, 2H), 7.13-7.08 (m, 1H), 7.04 (s, 1H), 6.98 (m, 2H), 6.92 (m, 2H), 6.75 (m, 2H), 4.05 (t, 2H), 3.31 (m, 2H), 3.26-3.05 (m, 6H), 2.35 (m, 2H), 1.40 (t, 6H), 1.21 (m, 2H) ppm.

25

Example 467

[3-(4-{2-(4-tert-butyl-phenoxy)methyl}-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine

3-Diethylaminopropanol (20mmol, 1eq) was dissolved in DCM (25mL), TEA (40mmol, 2 eq)
30 was added and the mixture was cooled to 0°C. To this mixture, methanesulfonyl chloride (30mmol, 1.5 eq) was added slowly with stirring and the reaction mixture was stirred at 0°C

for an hour and at rt for another hour (until the reaction was complete by HPLC). The solvent was removed and to this saturated aqueous sodium bicarbonate was added. The product was extracted with EtOAc (3 x) and washed with sodium bicarbonate and water. The solvent was removed *in vacuo*.

- 5 The mesylate from the previous step (20mmol, 1 eq) was dissolved in anhydrous DMF (25mL) to which 4-hydroxyacetophenone (20mmol, 1 eq) and potassium carbonate (60mmol, 3 eq) were added. The mixture was heated under reflux at 85°C for 18 h (until the reaction was complete by HPLC), after which it was cooled to rt. Saturated aqueous sodium bicarbonate was added to the mixture, which was then transferred to a separatory funnel.
- 10 The product was extracted with EtOAc and washed with sodium bicarbonate and water. The solvent was removed *in vacuo* and the product 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was purified by flash chromatography (going by increasing gradient up to 10% MeOH in DCM). The overall yield was 60%.

- 15 To a stirred solution of 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone (5 mmol) in anhydrous MeOH (10 mL) at 0°C, pyrrolidone hydrotribromide (1.2 eq) was added, according to General Procedure R1. The reaction mixture was stirred under nitrogen at 0°C for 1h and was allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was then removed *in vacuo* and the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was used for further transformation.

- 20 To a solution of 4-chlorophenoxy aniline (1 eq, 5 mmol) in anhydrous DMF (10 mL), DIEA (3 eq 15 mmol) was added, followed by addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone described above (5 mmol), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the
- 25 product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product obtained from 2-4% MeOH/DCM (yield 52%).

- 30 To a solution of 2-[4-(4-chlorophenoxy)-phenylamino]-1-[4-(3-diethylamino-propoxy)-phenyl]-ethanone described above (2 mmol) in anhydrous DCM (5 mL), PS-carbodiimide (2eq, 4mmol) and 4-t-butylphenoxy-acetic acid (3mmol) were added. The reaction mixture was shaken overnight and next day filtered to give the desired amide. The crude amide was used for further transformation.

To a stirred solution of the amide described above (2 mmol) in acetic acid (8 mL), ammonium acetate (20 eq) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled to rt and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained from 4-6% MeOH/DCM (yield 255 mg)

MS m/z 638 (M+H)⁺:

¹H NMR (CDCl₃): δ 7.72 (d, 2H), 7.44 (d, 2H), 7.28-7.35 (m, 5H), 6.8-7.1 (m, 8H), 5.01 (s, 2H), 4.06 (t, 2H), 3.13-3.24 (m, 6H), 2.28 (m, 2H), 1.23-1.38 (m, 15H) ppm.

Example 468

[3-(4-{2-butyl-1-[4-(2,4-dichloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethylamine

To a stirred solution of 1-fluoro-4-nitrobenzene (10 mmol) in DMF (20 mL) at rt, solid potassium carbonate (30 mmol) was added followed by addition of 2,4-dichlorophenol (10 mmol) to the reaction mixture and heating to 80°C until the reaction was complete as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was poured into H₂O (100ml), extracted with EtOAc (2X50 mL), washed with H₂O (2X50 ml) and brine (50 ml), and dried over sodium sulfate. The solvent was removed *in vacuo* to afford the desired 4-(2,4-dichloro-phenoxy)-1-nitrobenzene. The crude product was used for further transformation.

The nitro intermediate (10 mmol) obtained above was dissolved in MeOH (20 mL), and treated with SnCl₂·2H₂O (50 mmol), according to General Procedure I. The reaction mixture was heated under reflux until completion, as indicated by TLC or HPLC. The solvent was removed *in vacuo* and the residue was treated with 4.0 N aqueous NaOH to pH ~ 8. The residue was extracted with EtOAc (2x50 mL), washed with 1.0 N aqueous NaOH (50 mL), brine (50 mL) and dried over sodium sulfate. The solvent was removed *in vacuo* to afford the desired 4-(2,4-dichloro-phenoxy)aniline, which was used directly for further transformation without further purification.

To a stirred solution of 4'-hydroxyacetophenone (91 mmol) in DMF (80 mL) at rt, solid potassium carbonate (153 mmol) was added. The mesylate prepared from 3-diethylamino-

1-propanol and methanesulfonyl chloride (76 mmol) was added to the reaction mixture and heated to 80°C until completion according to General Procedure Q1, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was quenched by treating the mixture with saturated sodium bicarbonate. The aqueous layer was poured into EtOAc (100 mL) and washed with H₂O (2X50 mL) and brine (50 mL). The organic layer was dried over sodium sulfate, and the solvent was removed *in vacuo* to afford the desired 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone. The crude alkylated product was used for further transformation after purifying using silica gel column chromatography (1-4% MeOH/DCM).

To a stirred solution of 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone (4.4 mmol) in anhydrous MeOH (10 mL) at 0°C, pyrrolidone hydrotribromide (1.2 eq., 5.3 mmol) was added, according to General Procedure R1. The reaction mixture was stirred under nitrogen at 0°C for 1h and was allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was then removed *in vacuo* and the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was used for further transformation.

To a stirred solution of 4-(2,4-dichloro-phenoxy)aniline described above (1.2 eq., 5.2 mmol) in anhydrous DMF (20 mL) DIEA (3 eq. 15 mmol) was added, followed by slow addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone described above (4.4 mmol), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold H₂O and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product obtained from 2-4% MeOH/DCM (yield ~5%).

To a stirred solution of alkylated 4-(2,4-dichloro-phenoxy)aniline described above (0.2 mmol) in anhydrous DCM (5 mL) at 0°C, TEA (3eq., 0.6 mmol) was added, followed by slow addition of valeryl chloride (3 eq., 0.6 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the N-alkylated anilide (0.2 mmol) obtained as above in acetic acid (3 mL), solid ammonium acetate (6 mmol) was added in one portion, according to General Procedure R4. The reaction mixture was then heated to 100°C overnight. The reaction mixture was cooled to rt, and treated with saturated aqueous sodium bicarbonate solution while stirring to until the pH was 7-8. The contents were extracted with EtOAc (2X15 mL).

The combined organic layers was washed with H₂O (2x15 mL) and brine, and dried over sodium sulfate. Evaporation of the solvent *in vacuo* afforded the desired N-aryl imidazole. The crude product was purified using silica gel column chromatography (2-5% MeOH/DCM).

MS m/z 566 (M+H)⁺:

5 ¹H NMR (CDCl₃): δ7.96 (s, 1H), 7.87 (m, 2H), 7.64 (d, 2H), 7.42 (m, 2H), 7.30 (d, 2H), 7.15 (s, 1H), 6.94-6.84 (m, 2H), 4.12 (m, 2H), 3.71-3.42 (m, 6H), 3.14 (m, 2H), 2.29 (t, 2H), 1.59-1.50 (m, 2H), 1.41-1.32 (m, 2H), 1.31 (t, 6H), 0.85 (m, 3H) ppm.

Example 469

10 [3-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-5-methyl-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine

To a stirred solution of the 1-[4-(3-diethylamino-propoxy)-phenyl]-propane-1-one (1.08 mmol) in anhydrous MeOH (15 mL), pyrrolidone hydrotribromide (1.6 eq.) was added, according to General Procedure R1. The reaction mixture was heated under reflux overnight. The solvent
15 was then removed *in vacuo* and the crude alpha-bromophenone was used for further transformation.

To a stirred solution of the above alpha-bromoketone (1.0 eq), 4-(4-chloro-phenoxy)-aniline (1.0 eq) in anhydrous DMF (10 mL) DIEA (1.0 eq) was added. The reaction mixture was stirred under nitrogen at 90°C until completion, as indicated by HPLC. The reaction mixture
20 was cooled to rt then diluted with Et₂O (100 mL) and washed with sodium bicarbonate (10%, 30 ml), H₂O (2X30mL), brine (30mL) and dried with magnesium sulfate. Evaporation of solvent *in vacuo* gave a crude oil. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product was obtained from 2-7% MeOH/DCM (yield ~20%).

25 To a stirred solution of alkylated aniline described above (0.2 mmol) in anhydrous THF (10 mL) at 0°C, DMAP (0.3eq.) was added, followed by slow addition of valeryl chloride (5.0 eq), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to ambient temperature until completion, as indicated by HPLC. The solvent was removed *in vacuo*, and the crude amide was used for further
30 transformation.

To a stirred solution of the amide described above (0.2 mmol) in acetic acid (2 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled down and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained from 4-6% MeOH/DCM (yield 66 mg).

MS m/z 546 (M+H)⁺:

¹H NMR (CDCl₃): δ 7.59 (d, 2H), 7.35 (d, 2H), 7.19 (d, 2H), 7.08 (d, 2H), 7.03 (d, 2H), 6.93 (d, 2H), 4.02 (t, 2H), 2.51-2.64 (m, 8H), 2.13 (s, 3H), 1.94 (m, 2H), 1.58 (m, 2H), 1.27 (m, 2H), 1.04 (t, 6H), 0.82 (t, 3H) ppm.

Example 470

[3-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-5-propyl-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine

To a stirred solution of the 1-[4-(3-diethylamino-propoxy)-phenyl]-pentane-1-one (1.08 mmol) in anhydrous MeOH (15 mL), pyrrolidone hydrotribromide (1.6eq.) was added, according to General Procedure R1. The reaction mixture was heated under reflux overnight. The solvent was then removed *in vacuo* and the crude alpha-bromophenone was used for further transformation.

To a stirred solution of the above alpha-bromoketone (1.0 eq), 4-(4-chloro-phenoxy)-aniline (1.0 eq) in anhydrous DMF (10 mL) DIEA (1.0 eq) was added. The reaction mixture was stirred under nitrogen at 90°C until completion, as indicated by HPLC. The reaction mixture was cooled to rt then diluted with Et₂O (100 mL) and washed with sodium bicarbonate (10%, 30 ml), H₂O (2X30mL), brine (30mL) and dried with magnesium sulfate. Evaporation of solvent *in vacuo* gave a crude oil. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product was obtained from 2-7% MeOH/DCM (yield ~20%).

To a stirred solution of alkylated aniline described above (0.2 mmol) in anhydrous THF (10 mL) at 0°C, DMAP (0.3eq.) was added, followed by slow addition of valeryl chloride (5.0 eq), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to ambient temperature until completion, as indicated by HPLC.

The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (0.2 mmol) in acetic acid (2 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled down and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained from 4-6% MeOH/DCM (yield 73 mg).

MS m/z 574 (M+H)⁺:

¹H NMR (CDCl₃): δ 7.50 (d, 2H), 7.34 (d, 2H), 7.20 (d, 2H), 7.07 (d, 2H), 7.02 (d, 2H), 6.87 (d, 2H), 4.07 (t, 2H), 3.1-3.2 (m, 6H), 2.40-2.6 (m, 4H), 2.2 (m, 2H), 1.2-1.4 (m, 12H), 0.79 (t, 3H), 0.72 (t, 3H) ppm.

Example 471

[3-(4-{2,5-dibutyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethylamine

To a stirred solution of the 1-[4-(3-diethylamino-propoxy)-phenyl]-hexanane-1-one (1.08 mmol) in anhydrous MeOH (15 mL), pyrrolidone hydrotribromide (1.6 eq.) was added, according to General Procedure R1. The reaction mixture was heated under reflux overnight. The solvent was then removed *in vacuo* and the crude alpha-bromophenone was used for further transformation.

To a stirred solution of the above alpha-bromoketone (1.0 eq), 4-(4-chloro-phenoxy)-aniline (1.0 eq) in anhydrous DMF (10 mL) DIEA (1.0 eq) was added. The reaction mixture was stirred under nitrogen at 90°C until completion, as indicated by HPLC. The reaction mixture was cooled to rt then diluted with Et₂O (100 mL) and washed with sodium bicarbonate (10%, 30 ml), H₂O (2X30mL), brine (30mL) and dried with magnesium sulfate. Evaporation of solvent *in vacuo* gave a crude oil. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product was obtained from 2-7% MeOH/DCM (yield ~20%).

To a stirred solution of alkylated aniline described above (0.2 mmol) in anhydrous THF (10 mL) at 0°C, DMAP (0.3eq.) was added, followed by slow addition of valeryl chloride (5.0 eq),

according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to ambient temperature until completion, as indicated by HPLC. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

5 To a stirred solution of the amide described above (0.2 mmol) in acetic acid (2 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled down and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica
10 gel). Pure product was obtained from 4-6% MeOH/DCM (yield 67.0 mg).

MS m/z 588 (M+H)⁺:

¹H NMR (CDCl₃): δ 7.54 (d, 2H), 7.36 (d, 2H), 7.24 (d, 2H), 7.09 (d, 2H), 7.03 (d, 2H), 6.90 (d, 2H), 4.07 (t, 2H), 3.2-3.3 (m, 6H), 2.45-2.6 (m, 4H), 2.2 (m, 2H), 1.1-1.6 (m, 14H), 0.8 (t, 3H), 0.70 (t, 3H) ppm.

15

Example 472

[3-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-5-ethyl-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine

To a stirred solution of the 1-[4-(3-diethylamino-propoxy)-phenyl]-butane-1-one (1,08 mmol)
20 in anhydrous MeOH (15 mL), pyrrolidone hydrotribromide (1.6 eq.) was added, according to General Procedure R1. The reaction mixture was heated under reflux overnight. The solvent was then removed *in vacuo* and the crude alpha-bromophenone was used for further transformation.

To a stirred solution of the above alpha-bromoketone (1.0 eq), 4-(4-chloro-phenoxy)-aniline (1.0 eq) in anhydrous DMF (10 mL) DIEA (1.0 eq) was added. The reaction mixture was stirred under nitrogen at 90°C until completion, as indicated by HPLC. The reaction mixture was cooled to rt then diluted with Et₂O (100 mL) and washed with sodium bicarbonate (10%, 30 ml), H₂O (2X30mL), brine (30mL) and dried with magnesium sulfate. Evaporation of solvent *in vacuo* gave a crude oil. The crude alkylated aniline was purified by
30 chromatography (Silica gel). Pure product was obtained from 2-7% MeOH/DCM (yield ~20%).

To a stirred solution of alkylated aniline described above (0.2 mmol) in anhydrous THF (10 mL) at 0°C, DMAP (0.3eq.) was added, followed by slow addition of valeryl chloride (5.0 eq), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to ambient temperature until completion, as indicated by HPLC.

5 The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (0.2 mmol) in acetic acid (2 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled down and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was by elution with 4-6% MeOH/DCM (yield 70 mg).

MS m/z 560 (M+H)⁺:

¹H NMR (CDCl₃): δ7.58 (d, 2H), 7.36 (d, 2H), 7.22 (d, 2H), 7.09 (d, 2H), 7.04 (d, 2H), 6.93 (d, 2H), 4.03 (t, 2H), 2.56 (m, 10H), 1.94 (m, 2H), 1.59 (m, 2H), 1.27 (m, 2H), 1.03 (t, 6H), 0.97 (t, 3H), 0.82 (t, 3H) ppm.

Example 473

2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-4-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1H-imidazole

To a stirred solution of NaH (3 eq., 6.0 mmol) in DMF (10 mL) at rt, 4'-hydroxyacetophenone (2.2 mmol) was added. The mesylate of 1-(2-hydroxyethyl)-pyrrolidine (prepared from the corresponding alcohol and methanesulfonyl chloride) (2.0 mmol) was added to the reaction mixture and heated to 80°C until completion according to General Procedure Q1, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was diluted with cold water and the product was isolated in EtOAc. The combined organic layers were washed with saturated sodium bicarbonate (2X15 ml), water (2X15 ml) and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired product. The crude alkylated product was purified using silica gel column chromatography. Pure product was obtained with 2-3% MeOH/DCM. (yield 50-60%)

To a stirred solution of the alkoxyacetophenone described above (1 mmol) in anhydrous MeOH (5 mL) at 0°C, pyrrolidone hydrotribromide (1.2 eq., 1.2 mmol) was added, according to General Procedure R1. The reaction mixture was stirred under nitrogen at 0°C for 1h and was allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was

then removed *in vacuo* and the residue was treated with saturated sodium bicarbonate. The aqueous layer was poured into EtOAc (20 ml) and washed with water (2X15 ml) and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired product. The crude alpha-bromoacetophenone was used for further transformation.

To a stirred solution of 4-chloro-phenoxy aniline (1.2 eq., 1.2 mmol) in anhydrous DMF (10 mL) DIEA (3 eq. 3.0 mmol) was added, followed by slow addition of the alpha-bromoacetophenone described above (1.0 mmol), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was used for further transformation.

To a stirred solution of alkylated aniline described above (1.0 mmol) in anhydrous DCM (5 mL) at 0°C, TEA (3eq., 3.0 mmol) was added, followed by slow addition of valeryl chloride (2 eq., 2.0 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with water and the product was isolated in DCM. The solvent was removed *in vacuo*, and the crude amide was purified using silica gel chromatography. Pure product was obtained from 3-4% MeOH/DCM (Yield 40-45%).

To a stirred solution of the amide described above (0.5 mmol) in acetic acid (2 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled to rt and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained from 4-6% MeOH/DCM (yield: 105 mg).

MS m/z 516 (M)⁺:

¹H NMR (400 MHz, CDCl₃): δ7.69 (d, 2H), 7.34 (d, 2H), 7.29 (d, 2H), 7.09 (s, 1H), 7.05 (m, 4H), 6.95 (d, 2H), 4.19 (t, 2H), 3.05 (t, 2H), 2.84 (m, 4H), 2.77 (t, 2H), 1.89 (m, 4H), 1.65 (m, 2H), 1.34 (m, 2H), 0.85 (t, 3H) ppm

Example 474

1-[2-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-ethyl]-piperidine

To a stirred solution of NaH (3 eq., 6.0 mmol) in DMF (10 mL) at rt, 4'-hydroxyacetophenone (2.2 mmol) was added. The mesylate of 1-(2-hydroxyethyl)-piperidine (prepared from the corresponding alcohol and methanesulfonyl chloride) (2.0 mmol) was added to the reaction mixture and heated to 80°C until completion according to General Procedure Q1, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was diluted with cold water and the product was isolated in EtOAc. The combined organic layers were washed with saturated sodium bicarbonate (2X15 ml), water (2X15 ml) and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired product. The crude alkylated product was purified using silica gel column chromatography. Pure product was obtained with 2-3% MeOH/DCM. (yield 50-60%)

To a stirred solution of the alkoxyacetophenone described above (1 mmol) in anhydrous MeOH (5 mL) at 0°C, pyrrolidone hydrotribromide (1.2 eq., 1.2 mmol) was added, according to General Procedure R1. The reaction mixture was stirred under nitrogen at 0°C for 1h and was allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was then removed *in vacuo* and the residue was treated with saturated sodium bicarbonate. The aqueous layer was poured into EtOAc (20 ml) and washed with water (2X15 ml) and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired product. The crude alpha-bromoacetophenone was used for further transformation.

To a stirred solution of 4-chloro-phenoxy aniline (1.2 eq., 1.2 mmol) in anhydrous DMF (10 mL) DIEA (3 eq. 3.0 mmol) was added, followed by slow addition of the alpha-bromoacetophenone described above (1.0 mmol), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was used for further transformation.

To a stirred solution of alkylated aniline described above (1.0 mmol) in anhydrous DCM (5 mL) at 0°C, TEA (3eq., 3.0 mmol) was added, followed by slow addition of valeryl chloride (2 eq., 2.0 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with water and the product was isolated in

DCM. The solvent was removed *in vacuo*, and the crude amide was purified using silica gel chromatography. Pure product was obtained from 3-4% MeOH/DCM (Yield 40-45%).

To a stirred solution of the amide described above (0.5 mmol) in acetic acid (2 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled to rt and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained from 4-6% MeOH/DCM (yield: 92 mg).

MS m/z 530 (M+H)⁺:

¹H NMR (400 MHz, CDCl₃): δ 7.49 (d, 2H), 7.34 (d, 2H), 7.15 (d, 2H), 6.97 (s, 1H), 6.93 (m, 4H), 6.84 (d, 2H), 4.18 (t, 2H), 3.33 (m, 4H), 2.81 (t, 2H), 2.68 (t, 2H), 1.67 (m, 2H), 1.55 (m, 2H), 1.37 (m, 2H), 1.02 (m, 4H) 0.65 (t, 3H) ppm

Example 475

[3-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-2,2-dimethyl-propyl]-dimethyl-amine

To a stirred solution of 4'-hydroxyacetophenone (2.2 mmol) in DMF (10 mL) at rt, solid potassium carbonate (8.0 mmol) was added. The mesylate of 3-dimethylamino-2,2-dimethyl-1-propanol (prepared from the corresponding alcohol and methanesulfonyl chloride) (2.0 mmol) was added to the reaction mixture and heated to 80°C until completion according to General Procedure Q1, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was diluted with water and the product was isolated in EtOAc. The combined organic layers were washed with saturated sodium bicarbonate (2X15 ml), water (2X15 ml) and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired product. The crude alkylated product was purified using silica gel column chromatography. Pure product was obtained with 2-3% MeOH/DCM. (yield 50-60%)

To a stirred solution of the alkoxyacetophenone described above (1 mmol) in anhydrous MeOH (5 mL) at 0°C, pyrrolidone hydrotribromide (1.2 eq., 1.2 mmol) was added, according to General Procedure R1. The reaction mixture was stirred under nitrogen at 0°C for 1h and was allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was

then removed *in vacuo* and the residue was treated with saturated sodium bicarbonate and the product was isolated in EtOAc. The combined organic layers were washed with water (2X15 ml) and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired product. The crude alpha-bromoacetophenone was used for further transformation.

To a stirred solution of 4-chloro-phenoxy aniline (1.2 eq., 1.2 mmol) in anhydrous DMF (5 mL) DIEA (3 eq. 3.0 mmol) was added, followed by slow addition of the alpha-bromoacetophenone described above (1.0 mmol), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was used for further transformation.

To a stirred solution of alkylated aniline described above (1.0 mmol) in anhydrous DCM (5 mL) at 0°C, TEA (3eq., 3.0 mmol) was added, followed by slow addition of valeryl chloride (2 eq., 2.0 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with water and the product was isolated in DCM. The solvent was removed *in vacuo*, and the crude amide was purified using silica gel chromatography. Pure product was obtained from 3-4% MeOH/DCM (Yield 40-50%).

To a stirred solution of the amide described above (0.5 mmol) in acetic acid (2 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled to rt and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained from 4-6% MeOH/DCM (yield: 105 mg).

MS m/z 532 (M+H)⁺:

¹H NMR (400 MHz, CDCl₃): δ7.69 (d, 2H), 7.34 (d, 2H), 7.29 (d, 2H), 7.09 (s, 1H), 7.06 (d, 2H), 7.02 (d, 2H), 6.93 (d, 2H), 3.75 (s, 2H), 2.68 (t, 2H), 2.42 (s, 2H), 2.35 (s, 6H), 1.65 (m, 2H), 1.29 (m, 2H), 1.05 (s, 6H), 0.85 (t, 3H) ppm

Example 476

[2-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-ethyl]-diisopropyl-amine

To a stirred solution of 4'-hydroxyacetophenone (2.2 mmol) in DMF (10 mL) at rt, solid potassium carbonate (8.0 mmol) was added. The mesylate of 2-(diisopropylamino)ethanol (prepared from the corresponding alcohol and methanesulfonyl chloride) (2.0 mmol) was added to the reaction mixture and heated to 80°C until completion according to General Procedure Q1, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was diluted with water and the product was isolated in EtOAc. The combined organic layers were washed with saturated sodium bicarbonate (2X15 ml), water (2X15 ml) and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired product. The crude alkylated product was purified using silica gel column chromatography. Pure product was obtained with 2-3% MeOH/DCM. (yield 50-60%)

To a stirred solution of the alkoxyacetophenone described above (1 mmol) in anhydrous MeOH (5 mL) at 0°C, pyrrolidone hydrotribromide (1.2 eq., 1.2 mmol) was added, according to General Procedure R1. The reaction mixture was stirred under nitrogen at 0°C for 1h and was allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was then removed *in vacuo* and the residue was treated with saturated sodium bicarbonate and the product was isolated in EtOAc. The combined organic layers were washed with water (2X15 ml) and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuo* to afford the desired product. The crude alpha-bromoacetophenone was used for further transformation.

To a stirred solution of 4-chloro-phenoxy aniline (1.2 eq., 1.2 mmol) in anhydrous DMF (5 mL) DIEA (3 eq. 3.0 mmol) was added, followed by slow addition of the alpha-bromoacetophenone described above (1.0 mmol), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was used for further transformation.

To a stirred solution of alkylated aniline described above (1.0 mmol) in anhydrous DCM (5 mL) at 0°C, TEA (3eq., 3.0 mmol) was added, followed by slow addition of valeryl chloride (2 eq., 2.0 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by TLC or

HPLC. The reaction mixture was then diluted with water and the product was isolated in DCM. The solvent was removed *in vacuo*, and the crude amide was purified using silica gel chromatography. Pure product was obtained from 3-4% MeOH/DCM (Yield 40-50%).

To a stirred solution of the amide described above (0.5 mmol) in acetic acid (2 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled to rt and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained from 4-6% MeOH/DCM.

MS m/z 546 (M+H)⁺:

Example 477

[3-(4-{4-[4-(adamantan-1-ylmethoxy)-phenyl]-2-isobutyl-imidazol-1-yl}-phenoxy)-propyl]-diethyl-amine

To a stirred solution of N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (1.0 eq., 2.5 mmol) in anhydrous DMF (20 mL) DIEA (3 eq) was added, followed by slow addition of the 1-[4-(benzyloxy)phenyl]-2-bromoethanone (2.5 mmol). The reaction mixture was stirred under nitrogen at rt until completion, as indicated by HPLC. The reaction mixture was then diluted with cold H₂O and the product was isolated in Et₂O. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product was obtained from 2-7% MeOH/DCM (yield ~30%).

To a stirred solution of the alkylated aniline described above (0.88 mmol) in anhydrous DCM (10 mL) at 0°C, TEA (3.0mmol) was added, followed by slow addition of isovaleryl chloride (5.0 eq), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to ambient temperature until completion, as indicated by HPLC. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (0.88mmol) in acetic acid (2 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 100°C overnight. The reaction mixture was then cooled down

and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the cyclized product, (crude ~ 80%) which was taken to the next transformation without purification.

5 The above product was dissolved in MeOH (20 mL), Pd/C (100 mg) was added and the heterogeneous mixture was stirred overnight under H₂ atmosphere using a balloon, according to General Procedure T2. The Pd/C was removed by filtration. The solvent was removed *in vacuo*, and the crude 4-{1-[4-(3-diethylamino-propoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenol was used for further transformation without purification.

10 A stirred solution of the 4-{1-[4-(3-diethylamino-propoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenol (1.0 eq) in anhydrous DMF (5.0 mL) was treated with solid sodium hydride (60% dispersion in oil; 1.0mmol) in portions. After the addition, the mesylate of 1-adamantylmethanol (1.1eq) was added to the reaction mixture, and stirred at rt overnight, according to General Procedure T3. Et₂O (30 mL) was added to the reaction mixture followed by H₂O (10 mL). The organic layer was washed with H₂O (2x15 mL) and brine, and
15 dried over sodium sulfate. The solvent was removed *in vacuo*. Pure imidazole was obtained from chromatography with 5-10% MeOH/DCM (yield 60 mg).

MS m/z 570 (M+H)⁺:

¹H NMR (CDCl₃): δ7.68 (d, 2H), 7.20 (d, 2H), 7.09 (s, 1H), 6.97 (d, 2H), 6.90 (d, 2H), 4.06 (t, 2H), 3.5 (s, 2H), 2.6 (t, 2H), 2.58 (q, 4H), 2.52 (d), 1.6-2.1 (m, 18H), 1.05 (t, 6H), 0.85 (d, 6H)
20 ppm.

Example 478

{3-[4-(4-{4-[3-(2,6-dichloro-phenyl)-4-methyl-isoxazol-5-ylmethyloxy]-phenyl}-2-isobutyl-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine

25 To a stirred solution of N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (1.0 eq., 2.5 mmol) in anhydrous DMF (20 mL) DIEA (3 eq) was added, followed by slow addition of the 1-[4-(benzyloxy)phenyl]-2-bromoethanone (2.5 mmol). The reaction mixture was stirred under nitrogen at rt until completion, as indicated by HPLC. The reaction mixture was then diluted with cold H₂O and the product was isolated in Et₂O. The combined organic layers were
30 washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded

the desired product. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product was obtained from 2-7% MeOH/DCM (yield ~30%).

To a stirred solution of the alkylated aniline described above (0.88 mmol) in anhydrous DCM (10 mL) at 0°C, TEA (3.0mmol) was added, followed by slow addition of isovaleryl chloride (5.0 eq), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to ambient temperature until completion, as indicated by HPLC. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (0.88mmol) in acetic acid (2 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 100°C overnight. The reaction mixture was then cooled down and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the cyclized product, (crude ~ 80%) which was taken to the next transformation without purification.

The above product was dissolved in MeOH (20 mL), Pd/C (100 mg) was added and the heterogeneous mixture was stirred overnight under H₂ atmosphere using a balloon, according to General Procedure T2. The Pd/C was removed by filtration. The solvent was removed *in vacuo*, and the crude 4-{1-[4-(3-diethylamino-propoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenol was used for further transformation without purification.

To a stirred solution of the 4-{1-[4-(3-diethylamino-propoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenol (1.0 eq) obtained above in anhydrous DMF (5.0 mL) solid sodium hydride (60% dispersion in oil; 1.0mmol) was added in portions. After the addition, the requisite alkylhalide or the mesylate (prepared from the corresponding alcohol and methanesulfonyl chloride) (1.1eq) was added to the reaction mixture. The reaction mixture was stirred at rt overnight. Et₂O (30 mL) was added to the reaction mixture followed by H₂O (10 mL). The organic layer was washed with H₂O (2x15 mL) and brine, and dried over sodium sulfate. The solvent was removed *in vacuo*. Pure product was obtained from 5-10% MeOH/DCM (yield 57 mg).

MS m/z 661 (M+H)⁺:

¹H NMR (CDCl₃): δ 7.65 (d, 2H), 7.2-7.44 (m, 5H), 7.08 (s, 1H), 6.96 (d, 2H), 6.77 (d, 2H), 4.74 (s, 2H), 4.13 (t, 2H), 2.9-3.15 (m, 6 H), 2.6 (s, 3H), 2.51 (d, 2H), 2.3 (m, 3H), 1.35 (t, 6H), 0.83 (t, 6H) ppm

Example 479

[3-(4-{4-[4-(4-bromo-benzyloxy)-phenyl]-2-isobutyl-imidazol-1-yl}-phenoxy)-propyl]-diethyl-amine

5 To a stirred solution of N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (1.0 eq., 2.5 mmol) in anhydrous DMF (20 mL) DIEA (3 eq) was added, followed by slow addition of the 1-[4-(benzyloxy)phenyl]-2-bromoethanone (2.5 mmol). The reaction mixture was stirred under nitrogen at rt until completion, as indicated by HPLC. The reaction mixture was then diluted with cold H₂O and the product was isolated in Et₂O. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product was obtained from 2-7% MeOH/DCM (yield ~30%).

15 To a stirred solution of the alkylated aniline described above (0.88 mmol) in anhydrous DCM (10 mL) at 0°C, TEA (3.0mmol) was added, followed by slow addition of isovaleryl chloride (5.0 eq), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to ambient temperature until completion, as indicated by HPLC. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

20 To a stirred solution of the amide described above (0.88mmol) in acetic acid (2 mL), ammonium acetate (excess, ~20 eq.) was added, according to General Procedure R4. The reaction mixture was stirred at 100°C overnight. The reaction mixture was then cooled down and neutralized with saturated sodium bicarbonate solution. Usual extractive work up with EtOAc gave the cyclized product, (crude ~ 80%) which was taken to the next transformation without purification.

25 The above product was dissolved in MeOH (20 mL), Pd/C (100 mg) was added and the heterogeneous mixture was stirred overnight under H₂ atmosphere using a balloon, according to General Procedure T2. The Pd/C was removed by filtration. The solvent was removed *in vacuo*, and the crude 4-{1-[4-(3-diethylamino-propoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenol was used for further transformation without purification.

30 A stirred solution of the 4-{1-[4-(3-diethylamino-propoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenol (1.0 eq) in anhydrous DMF (5.0 mL) was treated with solid sodium hydride (60% dispersion in oil; 1.0mmol) in portions. The mesylate of (4-bromophenyl)methanol (1.1eq) was added to the reaction mixture, and stirred at rt overnight, according to General Procedure T3. Et₂O (30 mL) was added to the reaction mixture followed by H₂O (10 mL).

The organic layer was washed with H₂O (2x15 mL) and brine, and dried over sodium sulfate. The solvent was removed *in vacuo*. Pure imidazole was obtained from chromatography with 5-10% MeOH/DCM (yield 95 mg).

MS m/z 591 (M+H)⁺:

5 ¹H NMR (CDCl₃): δ7.7 (d, 2H), 7.5 (d, 2H), 7.32 (d, 2H), 7.21 (d, 2H), 7.11 (s, 1H), 6.96 (m, 4H), 5.03 (s, 2H), 4.07 (t, 2H), 2.5-2.8 (m, 8H), 2.0 (m, 3H), 1.07 (t, 6H), 0.84 (d, 6H) ppm.

Example 480

10 [3-(4-{2-butyl-1-[4-(6-methoxy-naphthalen-2-yloxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine

To a stirred solution of 1-fluoro-4-nitrobenzene (10 mmol) in DMF (20 mL) at rt, solid potassium carbonate (30 mmol) was added followed by addition of 6-methoxy-2-naphthol (10 mmol) to the reaction mixture and heating to 80°C until the reaction was complete as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was poured into H₂O (100 mL), extracted with EtOAc (2X50 mL), washed with H₂O (2X50 mL) and brine (50 mL), and dried over sodium sulfate. The solvent was removed *in vacuo* to afford the desired 4-(6-methoxy-naphthalen-2-yloxy)-1-nitrobenzene. The crude product was used for further transformation .

20 The nitro intermediate (10 mmol) obtained above was dissolved in EtOAc (50 mL) and hydrogenated in the presence of 10% Pd/C (360 mg) until completion according to General Procedure H, as indicated by TLC or HPLC. The reaction mixture was then filtered to remove the catalyst. The solvent was removed *in vacuo* to afford the desired 4-(6-methoxy-naphthalen-2-yloxy)aniline, which was used directly for further transformation without further purification.

25 To a stirred solution of 4'-hydroxyacetophenone (91 mmol) in DMF (80 mL) at rt, solid potassium carbonate (153 mmol) was added. The mesylate prepared from 3-diethylamino-1-propanol and methanesulfonyl chloride (76 mmol) was added to the reaction mixture and heated to 80°C until completion according to General Procedure Q1, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was quenched by treating the mixture with saturated sodium bicarbonate. The aqueous layer was poured into EtOAc (100 mL) and washed with H₂O (2X50 mL) and brine (50 mL). The organic layer was dried over sodium

30

sulfate, and the solvent was removed *in vacuo* to afford the desired 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone. The crude alkylated product was used for further transformation after purifying using silica gel column chromatography (1-4% MeOH/DCM).

To a stirred solution of 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone (4.6 mmol) in anhydrous MeOH (10 mL) at 0°C, pyrrolidone hydrotribromide (1.2 eq., 5.5 mmol) was added, according to General Procedure R1. The reaction mixture was stirred under nitrogen at 0°C for 1h and was allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was then removed *in vacuo* and the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was used for further transformation.

To a stirred solution of an 4-(6-methoxy-naphthalen-2-yloxy)aniline (5 mmol) in anhydrous DMF (20 mL) DIEA (15 mmol) was added, followed by slow addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone described above (4.6 mmol), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold H₂O and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was used for further transformation without additional purification.

To a stirred solution of alkylated 4-(6-methoxy-naphthalen-2-yloxy)aniline described above (4.6 mmol) in anhydrous DCM (10 mL) at 0°C, TEA (3eq., 15 mmol) was added, followed by slow addition of valeryl chloride (3 eq., 15 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the N-alkylated anilide (~4.6 mmol) obtained as above in acetic acid (10 mL), solid ammonium acetate (92 mmol) was added in one portion, according to General Procedure R4. The reaction mixture was then heated to 100°C overnight. The reaction mixture was cooled to rt, and treated with saturated aqueous sodium bicarbonate solution while stirring to until the pH was 7-8. The contents were extracted with EtOAc (2X40 mL). The combined organic layers was washed with H₂O (2x40 mL) and brine, and dried over sodium sulfate. Evaporation of the solvent *in vacuo* afforded the desired N-aryl imidazole. The crude product was purified using silica gel column chromatography (2-5% MeOH/DCM) (yield 500 mg).

MS m/z 578 (M+H)⁺:

¹H NMR (CDCl₃): δ 8.51 (d, 1H), 8.42 (m, 1H), 8.31 (d, 1H), 7.75 (m, 2H), 7.62 (m, 2H) 7.37 (s, 1H), 7.23 (m, 2H), 7.12 (m, 2H), 7.08 (s, 1H), 6.97-6.79 (m, 2H), 3.98 (t, 2H), 3.41 (s, 3H), 3.23-3.05 (m, 6H), 2.75 (m, 2H), 2.45 (m, 2H), 1.75-1.48 (m, 4H), 1.37 (t, 6H), 0.80 (m, 3H) ppm.

Example 481

[3-(4-{2-butyl-1-[4-(naphthalen-2-yloxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethylamine

10 To a stirred solution of 1-fluoro-4-nitrobenzene (10 mmol) in DMF (20 mL) at rt, solid potassium carbonate (30 mmol) was added followed by addition of 2-naphthol (10 mmol) to the reaction mixture and heating to 80°C until the reaction was complete as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was poured into H₂O (100 mL), extracted with EtOAc (2X50 mL), washed with H₂O (2X50 mL) and brine (50 mL), and dried over
15 sodium sulfate. The solvent was removed *in vacuo* to afford the desired 4-(naphthalen-2-yloxy)-1-nitrobenzene. The crude product was used for further transformation.

The nitro intermediate (10 mmol) obtained above was dissolved in EtOH (50 mL) and hydrogenated in the presence of 10% Pd/C (300 mg) until completion according to General Procedure H, as indicated by TLC or HPLC. The reaction mixture was then filtered to
20 remove the catalyst. The solvent was removed *in vacuo* to afford the desired 4-(naphthalen-2-yloxy)aniline, which was used directly for further transformation without further purification.

To a stirred solution of 4'-hydroxyacetophenone (91 mmol) in DMF (80 mL) at rt, solid potassium carbonate (153 mmol) was added. The mesylate prepared from 3-diethylamino-
25 1-propanol and methanesulfonyl chloride (76 mmol) was added to the reaction mixture and heated to 80°C until completion according to General Procedure Q1, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was quenched by treating the mixture with saturated sodium bicarbonate. The aqueous layer was poured into EtOAc (100 mL) and washed with H₂O (2X50 mL) and brine (50 mL). The organic layer was dried over sodium
30 sulfate, and the solvent was removed *in vacuo* to afford the desired 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone. The crude alkylated product was used for further transformation after purifying using silica gel column chromatography (1-4% MeOH/DCM).

To a stirred solution of 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone (4.6 mmol) in anhydrous MeOH (10 mL) at 0°C, pyrrolidone hydrotribromide (1.2 eq., 5.5 mmol) was added, according to General Procedure R1. The reaction mixture was stirred under nitrogen at 0°C for 1h and was allowed to warm to rt until completion, as indicated by TLC or HPLC.

5 The solvent was then removed *in vacuo* and the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was used for further transformation.

To a stirred solution of 4-(naphthalen-2-yloxy)aniline (1.2 eq., 5 mmol) in anhydrous DMF (5 mL) DIEA (3 eq. 15 mmol) was added, followed by slow addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone described above (4.6 mmol), according to General
10 Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold H₂O and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was used for further transformation without additional
15 purification.

To a stirred solution of alkylated 4-(naphthalen-2-yloxy)aniline described above (4.6 mmol) in anhydrous DCM (5 mL) at 0°C, TEA (3eq., 15 mmol) was added, followed by slow addition of valeryl chloride (3 eq., 15 mmol), according to General Procedure R3. The reaction
20 mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the N-alkylated anilide (~4.6 mmol) obtained as above in acetic acid (10 mL), solid ammonium acetate (92 mmol) was added in one portion, according to General
25 Procedure R4. The reaction mixture was then heated to 100°C overnight. The reaction mixture was cooled to rt, and treated with saturated aqueous sodium bicarbonate solution while stirring to until the pH was 7-8. The contents were extracted with EtOAc (2X50 mL). The combined organic layers was washed with H₂O (50 mL) and brine, and dried over sodium sulfate. Evaporation of the solvent *in vacuo* afforded the desired N-aryl imidazole. The crude product was purified using silica gel column chromatography (2-5% MeOH/DCM)
30 (yield 170 mg).

MS m/z 548 (M+H)⁺:

¹H NMR (CDCl₃): δ7.91 (t, 1H), 7.84 (t, 1H), 7.77 (m, 1H), 7.71 (m, 2H) 7.56-7.42 (m, 4H), 7.32 (m, 2H), 7.18 (s, 1H), 7.16-7.03 (m, 2H), 7.00-6.86 (m, 2H), 4.02 (t, 2H), 3.00-2.76 (m, 6H), 2.70 (m, 2H), 2.12 (m, 2H), 1.44-1.28 (m, 4H), 1.23 (t, 6H), 0.93 (m, 3H) ppm.

5 Example 482

2-butyl-4-[4-(4-ethyl-hexyloxy)-phenyl]-1-[4-(4-methoxy-naphthalen-1yl-oxy)-phenyl]-1H-imidazole

To a stirred solution of 1-fluoro-4-nitrobenzene (10 mmol) in DMF (20 mL) at rt, solid potassium carbonate (30 mmol) was added followed by addition of 4-methoxy-1-naphthol (10 mmol) to the reaction mixture and heating to 80°C until the reaction was complete as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was poured into H₂O (100 mL), extracted with EtOAc (2X50 mL), washed with H₂O (2X50 mL) and brine (50 mL), and dried over sodium sulfate. The solvent was removed *in vacuo* to afford the desired 4-(4-methoxynaphthalen-1-yloxy)-1-nitrobenzene. The crude product was used for further transformation .

The nitro intermediate (10 mmol) obtained above was dissolved in EtOAc (50 mL) and hydrogenated in the presence of 10% Pd/C (360 mg) until completion according to General Procedure H, as indicated by TLC or HPLC. The reaction mixture was then filtered to remove the catalyst. The solvent was removed *in vacuo* to afford the desired 4-(4-methoxy-naphthalen-1-yloxy)aniline, which was used directly for further transformation without further purification.

To a stirred solution of 4'-hydroxyacetophenone (91 mmol) in DMF (80 mL) at rt, solid potassium carbonate (153 mmol) was added. The mesylate prepared from 3-diethylamino-1-propanol and methanesulfonyl chloride (76 mmol) was added to the reaction mixture and heated to 80°C until completion according to General Procedure Q1, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was quenched by treating the mixture with saturated sodium bicarbonate. The aqueous layer was poured into EtOAc (100 mL) and washed with H₂O (2X50 mL) and brine (50 mL). The organic layer was dried over sodium sulfate, and the solvent was removed *in vacuo* to afford the desired 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone. The crude alkylated product was used for further transformation after purifying using silica gel column chromatography (1-4% MeOH/DCM).

To a stirred solution of 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone (2.3 mmol) in anhydrous MeOH (5 mL) at 0°C, pyrrolidone hydrotribromide (1.2 eq., 2.7 mmol) was added, according to General Procedure R1. The reaction mixture was stirred under nitrogen at 0°C for 1h and was allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was then removed *in vacuo* and the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was used for further transformation.

To a stirred solution of 4-(4-methoxy-naphthalen-1-yloxy)aniline (1.2 eq., 2.5 mmol) in anhydrous DMF (5 mL) DIEA (3 eq. 7.5 mmol) was added, followed by slow addition of the 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone described above (2.3 mmol), according to General Procedure R2. The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then diluted with cold H₂O and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuo* afforded the desired product. The crude alkylated aniline was used for further transformation .

To a stirred solution of alkylated 4-(4-methoxynaphthalen-1-yloxy)aniline described above (2.3 mmol) in anhydrous DCM (5 mL) at 0°C, TEA (3eq., 7.5 mmol) was added, followed by slow addition of valeryl chloride (3 eq., 7.5 mmol), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 1h and allowed to warm to rt until completion, as indicated by TLC or HPLC. The solvent was removed *in vacuo*, and the crude amide was used for further transformation.

To a stirred solution of the N-alkylated anilide (2.3 mmol) obtained as above in acetic acid (5 mL), solid ammonium acetate (46 mmol) was added in one portion, according to General Procedure R4. The reaction mixture was then heated to 100°C overnight. The reaction mixture was cooled to rt, and treated with saturated aqueous sodium bicarbonate solution while stirring to until the pH was 7-8. The contents were extracted with EtOAc (2X30 mL). The combined organic layers was washed with H₂O (2x30 mL) and brine, and dried over sodium sulfate. Evaporation of the solvent *in vacuo* afforded the desired N-aryl imidazole. The crude product was purified using silica gel column chromatography (2-5% MeOH/DCM) (yield 213 mg).

MS m/z 578 (M+H)⁺:

¹H NMR (CDCl₃): δ8.35 (dd, 1H), 7.60 (dd, 1H), 7.72 (m, 2H), 7.55 (m, 2H), 7.24 (s, 1H), 7.23 (m, 2H), 7.15 (t, 1H), 7.04 (m, 2H), 6.90 (m, 2H), 6.80 (d, 1H), 4.04 (s, 3H), 3.95 (t, 2H),

3.00-2.87 (m, 6H), 2.67 (t, 2H), 2.10 (m, 2H), 1.65 (m, 2H), 1.38 (m, 2H), 1.21 (t, 6H), 0.95 (m, 3H) ppm.

Example 483

5 [3-(4-{2-butyl-1-[4-(dibenzofuran-2-yloxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethylamine

To a stirred solution of 1-fluoro-4-nitrobenzene (10 mmol) in DMF (20 mL) at rt, solid potassium carbonate (30 mmol) was added followed by addition of 2-hydroxydibenzofuran (10 mmol) to the reaction mixture and heating to 80°C until the reaction was complete as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was poured into H₂O (100 mL), extracted with EtOAc (2X50 mL), washed with H₂O (2X50 mL) and brine (50 mL), and dried over sodium sulfate. The solvent was removed *in vacuo* to afford the desired 4-(dibenzofuran-2-yloxy)-1-nitrobenzene. The crude product was used for further transformation .

15 The nitro intermediate (10 mmol) obtained above was dissolved in EtOAc (50 mL) and hydrogenated in the presence of 10% Pd/C (360 mg) until completion according to General Procedure H, as indicated by TLC or HPLC. The reaction mixture was then filtered to remove the catalyst. The solvent was removed *in vacuo* to afford the desired 4-(dibenzofuran-2-yloxy)aniline, which was used directly for further transformation without further purification.

To a stirred solution of 4'-hydroxyacetophenone (91 mmol) in DMF (80 mL) at rt, solid potassium carbonate (153 mmol) was added. The mesylate prepared from 3-diethylamino-1-propanol and methanesulfonyl chloride (76 mmol) was added to the reaction mixture and heated to 80°C until completion according to General Procedure Q1, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was quenched by treating the mixture with saturated sodium bicarbonate. The aqueous layer was poured into EtOAc (100 mL) and washed with H₂O (2X50 mL) and brine (50 mL). The organic layer was dried over sodium sulfate, and the solvent was removed *in vacuo* to afford the desired 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone. The crude alkylated product was used for further transformation after purifying using silica gel column chromatography (1-4% MeOH/DCM).

To a stirred solution of 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone (2.3 mmol) in anhydrous MeOH (5 mL) at 0°C, pyrrolidone hydrotribromide (1.2 eq, 2.7 mmol) was added,

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 359

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JUMBO APPLICATIONS/PATENTS

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

THIS IS VOLUME 1 OF 2
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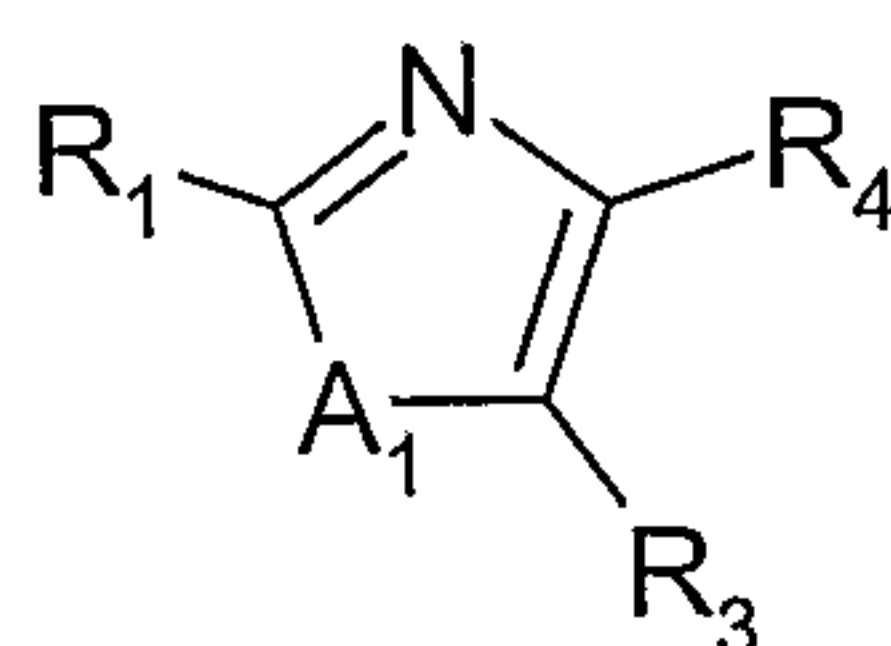
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Claims

We Claim:

1. A compound of Formula (I):



(I)

wherein

R₁ comprises -hydrogen, -aryl, -heteroaryl, -cycloalkyl, -heterocyclyl, -alkyl, -alkenyl, -alkynyl, -alkylene-aryl, -alkylene-heteroaryl, -alkylene-heterocyclyl, -alkylene-cycloalkyl, -fused cycloalkylaryl, -fused cycloalkylheteroaryl, -fused heterocyclaryl, -fused heterocyclheteroaryl, -alkylene-fused cycloalkylaryl, -alkylene-fused cycloalkylheteroaryl, -alkylene-fused heterocyclaryl, -alkylene-fused heterocyclheteroaryl, or -G₁-G₂-G₃-R₅

wherein

G₁ and G₃ independently comprise alkylene, alkenylene, alkynylene, cycloalkylene, heterocyclylene, arylene, heteroarylene, (aryl)alkylene, (heteroaryl) alkylene, (aryl)alkenylene, (heteroaryl)alkenylene, or a direct bond;

G₂ comprises -O-, -S-, -S(O)-, -N(R₆)-, -S(O)₂-, -C(O)-, -O-C(O)-, -C(O)-O-, -C(O)N(R₆)-, -N(R₆)C(O)-, -S(O₂)N(R₆)-, N(R₆)S(O₂)-, -O-alkylene-C(O)-, -(O)C-alkylene-O-, -O-alkylene-, -alkylene-O-, alkylene, alkenylene, alkynylene, cycloalkylene, heterocyclylene, arylene, heteroarylene, fused cycloalkylarylene, fused cycloalkylheteroarylene, fused heterocyclarylene, fused heterocyclheteroarylene, or a direct bond, wherein R₆ comprises hydrogen, aryl, alkyl, -alkylene-aryl, alkoxy, or -alkylene-O-aryl; and

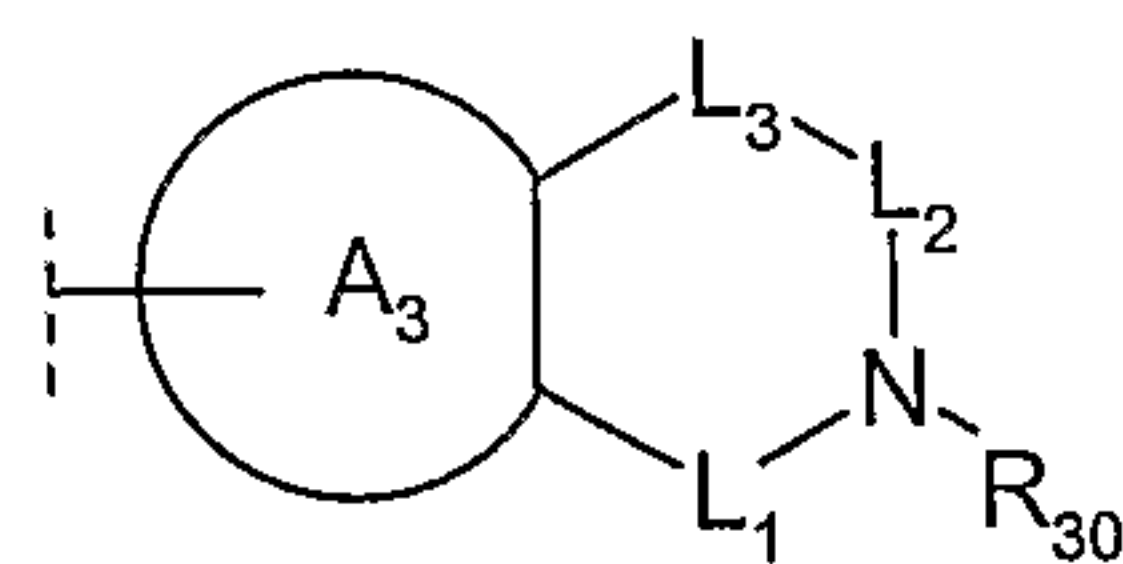
R₅ comprises hydrogen, aryl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, alkenyl, alkynyl, -alkylene-aryl, -alkylene-heteroaryl, -alkylene-heterocyclyl, -alkylene-cycloalkyl, fused cycloalkylaryl, fused cycloalkylheteroaryl, fused heterocyclaryl, fused heterocyclheteroaryl, -alkylene-fused cycloalkylaryl, -alkylene-fused cycloalkylheteroaryl, -alkylene-fused heterocyclaryl, or -alkylene-fused heterocyclheteroaryl;

A_1 comprises O, S, or $-N(R_2)-$;

wherein

5 R_2 comprises

- a) $-H$;
- b) $-aryl$;
- c) $-heteroaryl$;
- d) $-cycloalkyl$
- 10 e) $heterocyclyl$;
- f) $-alkyl$;
- g) $-alkenyl$;
- h) $-alkynyl$;
- i) $-alkylene-aryl$,
- 15 j) $-alkylene-heteroaryl$,
- k) $-alkylene-heterocyclyl$,
- l) $-alkylene-cycloalkyl$;
- m) $-fused\ cycloalkylaryl$,
- n) $-fused\ cycloalkylheteroaryl$,
- 20 o) $-fused\ heterocyclylaryl$,
- p) $-fused\ heterocyclylheteroaryl$;
- q) $-alkylene-fused\ cycloalkylaryl$,
- r) $-alkylene-fused\ cycloalkylheteroaryl$,
- s) $-alkylene-fused\ heterocyclylaryl$,
- 25 t) $-alkylene-fused\ heterocyclylheteroaryl$; or
- u) a group of the formula

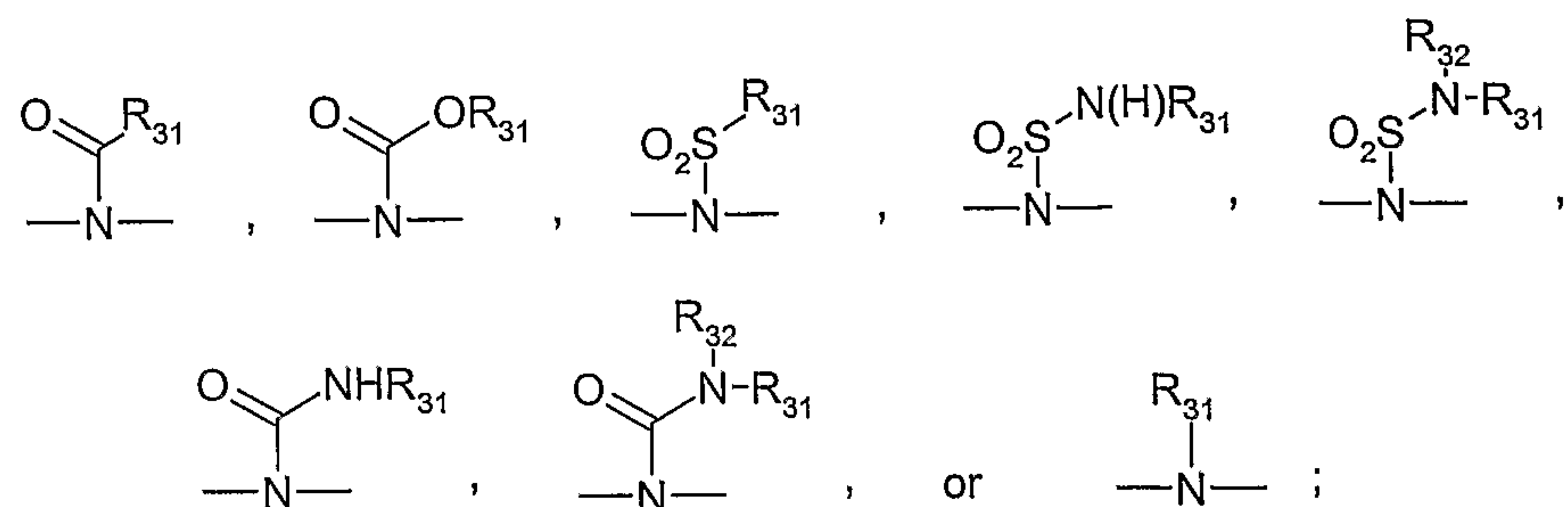


wherein

A_3 comprises an aryl or heteroaryl group;

30 L_1 and L_2 independently comprise alkylene or alkenylene; and

L_3 comprises a direct bond, alkylene, $-O-$, $-S-$, $-S(O_2)-$, $-C(O)-$,
 $-CON(H)-$, $-NHC(O)-$, $-NHCON(H)-$, $-NHSO_2-$, $-SO_2N(H)-$, $-C(O)-O-$,
 $-O-C(O)-$, $-NHSO_2NH-$,



wherein R₃₀, R₃₁, and R₃₂ independently comprise hydrogen, aryl, heteroaryl, alkyl, alkylene-aryl, or -alkylene-heteroaryl;

5 R₃ and R₄ independently comprise

- a) -hydrogen,
- b) -halogen,
- c) -hydroxyl,
- d) -cyano,
- 10 e) -carbamoyl,
- f) -carboxyl,
- g) -aryl,
- h) -heteroaryl,
- i) -cycloalkyl,
- 15 j) -heterocyclyl,
- k) -alkyl,
- l) -alkenyl,
- m) -alkynyl,
- n) -alkylene-aryl,
- 20 o) -alkylene-heteroaryl,
- p) -alkylene-heterocyclyl,
- q) -alkylene-cycloalkyl,
- r) -fused cycloalkylaryl,
- s) -fused cycloalkylheteroaryl,
- 25 t) -fused heterocyclylaryl,
- u) -fused heterocyclylheteroaryl,
- v) -alkylene-fused cycloalkylaryl,
- w) -alkylene-fused cycloalkylheteroaryl,
- x) -alkylene-fused heterocyclylaryl,
- 30 y) -alkylene-fused heterocyclylheteroaryl;
- z) -C(O)-O-alkyl;

aa) -C(O)-O-alkylene-aryl;

bb) -C(O)-NH-alkyl;

cc) -C(O)-NH-alkylene-aryl;

dd) -SO₂-alkyl;

5

ee) -SO₂-alkylene-aryl;

ff) -SO₂-aryl;

gg) -SO₂-NH-alkyl;

hh) -SO₂-NH-alkylene-aryl;

ii) -C(O)-alkyl;

10

jj) -C(O)-alkylene-aryl;

kk) -G₄-G₅-G₆-R₇;

ll) -Y₁-alkyl;

mm) -Y₁-aryl;

nn) -Y₁-heteroaryl;

15

oo) -Y₁-alkylene-aryl;

pp) -Y₁-alkylene-heteroaryl;

qq) -Y₁-alkylene-NR₉R₁₀; or

rr) -Y₁-alkylene-W₁-R₁₁;

wherein

20

G₄ and G₆ independently comprise alkylene, alkenylene, alkynylene, cycloalkylene, heterocyclylene, arylene, heteroarylene, (aryl)alkylene, (heteroaryl)alkylene, (aryl)alkenylene, (heteroaryl)alkenylene, or a direct bond;

25

G₅ comprises -O-, -S-, -N(R₈)-, -S(O)-, -S(O)₂-, -C(O)-, -O-C(O)-, -C(O)-O-, -C(O)N(R₈)-, N(R₈)C(O)-, -S(O₂)N(R₈)-, N(R₈)S(O₂)-, -O-alkylene-C(O)-, -(O)C-alkylene-O-, -O-alkylene-, -alkylene-O-, alkylene, alkenylene, alkynylene, cycloalkylene, heterocyclylene, arylene, heteroarylene, fused cycloalkylarylene, fused cycloalkylheteroarylene, fused heterocyclylarylene, fused heterocyclylheteroarylene, or a direct bond, wherein R₈ comprises -

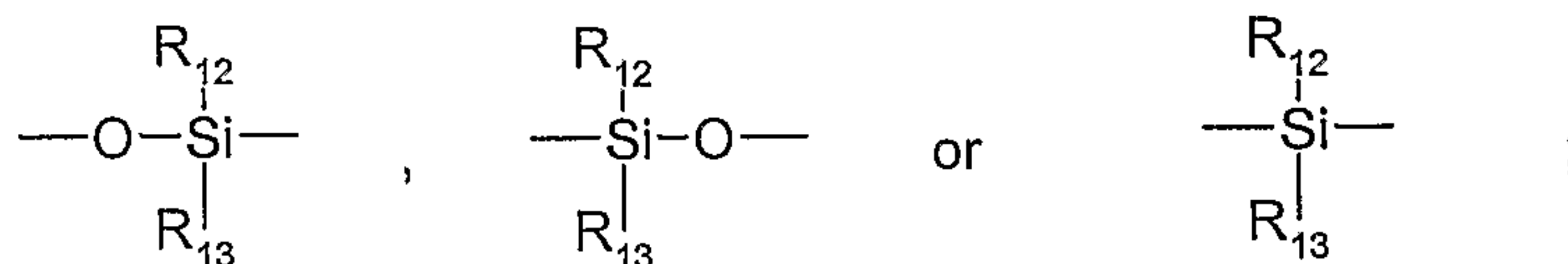
30

hydrogen, -aryl, -alkyl, -alkylene-aryl, or -alkylene-O-aryl;

35

R₇ comprises hydrogen, aryl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, alkenyl, alkynyl, alkylene-aryl, -alkylene-heteroaryl, -alkylene-heterocyclyl, -alkylene-cycloalkyl, fused cycloalkylaryl, fused cycloalkylheteroaryl, fused heterocyclylaryl, fused heterocyclylheteroaryl, alkylene-fused cycloalkylaryl, -alkylene-fused cycloalkylheteroaryl, -alkylene-fused heterocyclylaryl, or -alkylene-fused heterocyclylheteroaryl;

Y_1 and W_1 independently comprise $-\text{CH}_2-$, $-\text{O}-$, $-\text{N}(\text{H})-$, $-\text{S}-$, SO_2- , $-\text{CON}(\text{H})-$, $-\text{NHC}(\text{O})-$, $-\text{NHCON}(\text{H})-$, $-\text{NH}\text{SO}_2-$, $-\text{SO}_2\text{N}(\text{H})-$, $-\text{C}(\text{O})-\text{O}-$, $-\text{NH}\text{SO}_2\text{NH}-$, $-\text{O}-\text{CO}-$,
,



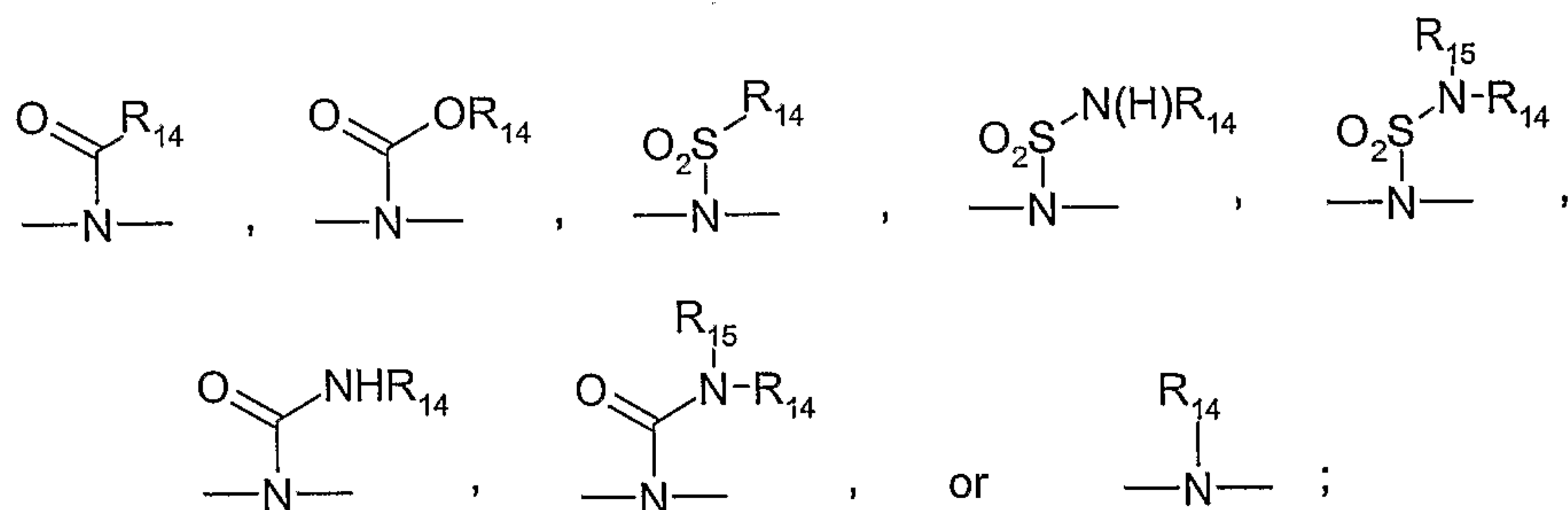
5 wherein R_{12} and R_{13} independently comprise aryl, alkyl, -alkylene-aryl, alkoxy, or -alkylene-O-aryl; and

R_9 , R_{10} , and R_{11} independently comprise aryl, heteroaryl, alkyl, -alkylene-heteroaryl, or -alkylene-aryl; and R_9 and R_{10} may be taken together to form a ring having the formula $-(\text{CH}_2)_o-\text{X}_1-(\text{CH}_2)_p-$ bonded to the nitrogen atom to which R_9 and R_{10} are attached,

wherein

o and p are, independently, 1, 2, 3, or 4; and

X_1 comprises a direct bond, $-\text{CH}_2-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O}_2)-$, $-\text{C}(\text{O})-$, $-\text{CON}(\text{H})-$, $-\text{NHC}(\text{O})-$, $-\text{NHCON}(\text{H})-$, $-\text{NH}\text{SO}_2-$, $-\text{SO}_2\text{N}(\text{H})-$, $-\text{C}(\text{O})-\text{O}-$, $-\text{O}-\text{C}(\text{O})-$, $-\text{NH}\text{SO}_2\text{NH}-$,



wherein R_{14} and R_{15} independently hydrogen, aryl, heteroaryl, alkyl, -alkylene-aryl, or -alkylene-heteroaryl;

wherein

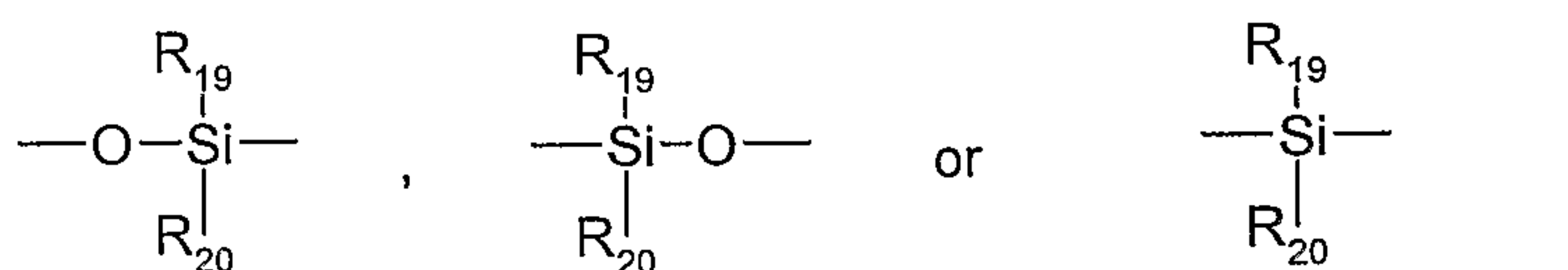
the aryl and/or alkyl group(s) in R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , and R_{15} may be optionally substituted 1-4 times with a substituent group, wherein said substituent group(s) or the term substituted refers to a group comprising:

- H,
- halogen,
- hydroxyl,
- cyano,

- e) -carbamoyl,
 f) -carboxyl,
 g) -Y₂-alkyl;
 h) -Y₂-aryl;
 5 i) -Y₂-heteroaryl;
 j) -Y₂-alkylene-heteroarylaryl;
 k) -Y₂-alkylene-aryl;
 l) -Y₂-alkylene-W₂-R₁₈;
 m) -Y₃-Y₄-NR₂₃R₂₄,
 10 n) -Y₃-Y₄-NH-C(=NR₂₅)NR₂₃R₂₄,
 o) -Y₃-Y₄-C(=NR₂₅)NR₂₃R₂₄, or
 p) -Y₃-Y₄-Y₅-A₂,

wherein

Y₂ and W₂ independently comprise -CH₂-, -O-, -N(H)-, -S-, SO₂-, -CON(H)-, -NHC(O)-, -NHCON(H)-, -NHSO₂-, -SO₂N(H)-, -C(O)-O-, -NHSO₂NH-, -O-S(O)₂-, -O-CO-,

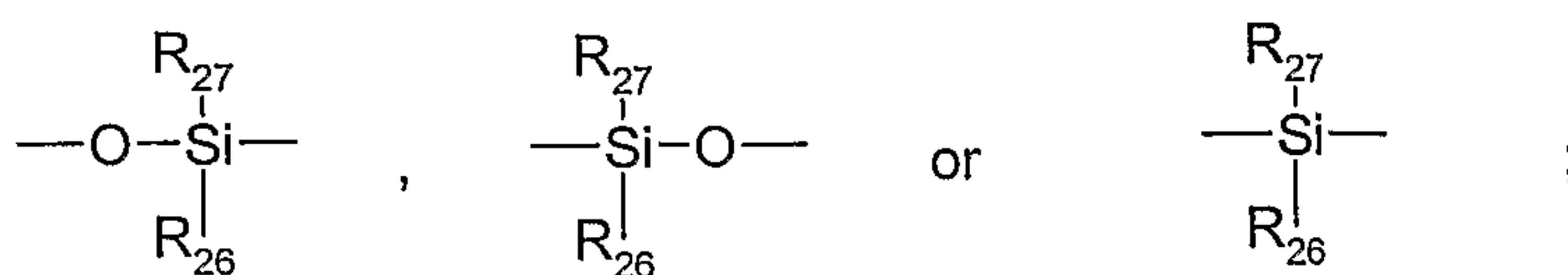


wherein;

R₁₉ and R₂₀ independently comprise hydrogen, aryl, alkyl, -alkylene-aryl, alkoxy, or -alkylene-O-aryl; and

R₁₈ comprises aryl, alkyl, -alkylene-aryl, -alkylene-heteroaryl, and -alkylene-O-aryl;

Y₃ and Y₅ independently comprise a direct bond, -CH₂-, -O-, -N(H)-, -S-, SO₂-, -C(O)-, -CON(H)-, -NHC(O)-, -NHCON(H)-, -NHSO₂-, -SO₂N(H)-, -C(O)-O-, -NHSO₂NH-, -O-CO-,



wherein R₂₇ and R₂₆ independently comprise aryl, alkyl, -alkylene-aryl, alkoxy, or -alkyl-O-aryl;

Y₄ comprises

- a) -alkylene;

- b) -alkenylene;
- c) -alkynylene;
- d) -arylene;
- e) -heteroarylene;
- f) -cycloalkylene;
- g) -heterocyclylene;
- h) -alkylene-arylene;
- i) -alkylene-heteroarylene;
- j) -alkylene-cycloalkylene;
- k) -alkylene-heterocyclylene;
- l) -arylene-alkylene;
- m) -heteroarylene-alkylene;
- n) -cycloalkylene-alkylene;
- o) -heterocyclylene-alkylene;
- p) -O-;
- q) -S-;
- r) -S(O₂)-; or
- s) -S(O)-;

wherein said alkylene groups may optionally contain one or more O, S, S(O), or SO₂ atoms;

A₂ comprises

- a) heterocyclyl, fused arylheterocyclyl, or fused heteroarylheterocyclyl, containing at least one basic nitrogen atom,
- b) -imidazolyl, or
- c) -pyridyl; and

R₂₃, R₂₄, and R₂₅ independently comprise hydrogen, aryl, heteroaryl, -alkylene-heteroaryl, alkyl, -alkylene-aryl, -alkylene-O-aryl, or -alkylene-O-heteroaryl; and R₂₃ and R₂₄ may be taken together to form a ring having the formula -(CH₂)_s-X₃-(CH₂)_t- bonded to the nitrogen atom to which R₂₃ and R₂₄ are attached

wherein

s and t are, independently, 1, 2, 3, or 4;

$$\begin{array}{ccccccc} \text{O}=\text{C}-\text{R}_{28} & , & \text{O}=\text{C}-\text{OR}_{28} & , & \text{O}_2\text{S}-\text{R}_{28} & , & \text{O}_2\text{S}-\text{N}(\text{H})\text{R}_{28} & , & \text{O}_2\text{S}-\text{N}(\text{R}_{29})\text{R}_{28} \\ | & & | & & | & & | & & | \\ -\text{N}- & & -\text{N}- & & -\text{N}- & & -\text{N}- & & -\text{N}- \\ & & & & & & & & \text{R}_{28} \\ & & & & & & & & | \\ & & & & & & & & -\text{N}- \\ & & & & & & & & | \\ & & & & & & & & \text{R}_{28} \end{array}$$

wherein R₂₈ and R₂₉ independently comprise hydrogen, aryl, heteroaryl, alkyl, -alkylene-aryl, or -alkylene-heteroaryl;

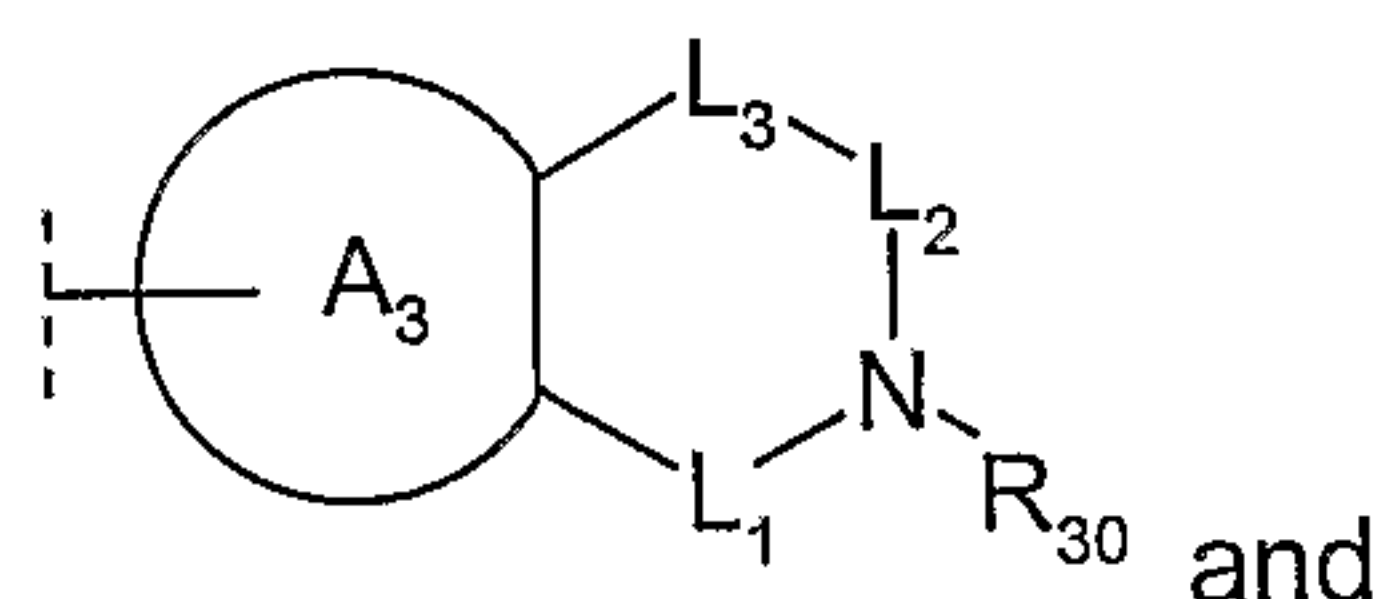
wherein

10 either

at least one of the groups R₁, R₂, R₃ and R₄ are substituted with at least one group of the formula -Y₃-Y₄ -NR₂₃R₂₄, -Y₃-Y₄ -NH-C(=NR₂₅)NR₂₃R₂₄, -Y₃-Y₄ -C(=NR₂₅)NR₂₃R₂₄, or -Y₃-Y₄ -Y₅-A₂, with the proviso that no more than one of R₂₃, R₂₄, and R₂₅ may comprise aryl or heteroaryl;

15 or

R_2 is a group of the formula



wherein

one of R₃ and R₄, R₃ and R₂, or R₁ and R₂ may be taken together to constitute, together with the atoms to which they are bonded, an aryl, heteroaryl, fused arylcycloalkyl, fused arylheterocyclyl, fused heteroaryl cycloalkyl, or fused heteroaryl heterocyclyl ring system, wherein

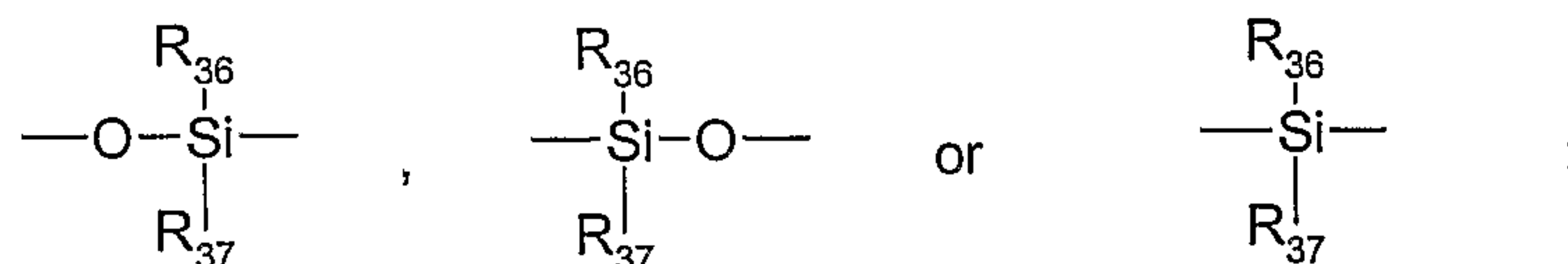
said ring system or R₁, R₂, R₃, or R₄ is substituted with at least one group of the formula

- a) $-Y_5-Y_6-NR_{33}R_{34};$
 b) $-Y_5-Y_6-NH-C(=NR_{35})NR_{33}R_{34};$
 c) $-Y_5-Y_6-C(=NR_{35})NR_{33}R_{34};$ or

d) $-Y_5-Y_6-Y_7-A_4$;

wherein

Y_5 and Y_7 independently comprise a direct bond, $-CH_2-$, $-O-$, $-N(H)-$, $-S-$, SO_2- ,
 $-CON(H)-$, $-NHC(O)-$, $-NHCON(H)-$, $-NHSO_2-$, $-SO_2N(H)-$, $-C(O)-O-$, -
 5 $NHSO_2NH-$, $-O-CO-$,



wherein R_{36} and R_{37} independently comprise aryl, alkyl,
 $-alkylene-aryl$, alkoxy, or $-alkyl-O-aryl$;

Y_6 comprises

- 10 a) alkylene;
 b) alkenylene;
 c) alkynylene;
 d) arylene;
 e) heteroarylene;
 15 f) cycloalkylene;
 g) heterocyclylene;
 h) alkylene-arylene;
 i) alkylene-heteroarylene;
 j) alkylene-cycloalkylene;
 20 k) alkylene-heterocyclylene;
 l) arylene-alkylene;
 m) heteroarylene-alkylene;
 n) cycloalkylene-alkylene;
 o) heterocyclylene-alkylene;
 25 p) $-O-$;
 q) $-S-$;
 r) $-S(O_2)-$; or
 s) $-S(O)-$;

wherein said alkylene groups may optionally contain one or more O, S,
 30 $S(O)$, or SO_2 atoms;

A_4 comprises

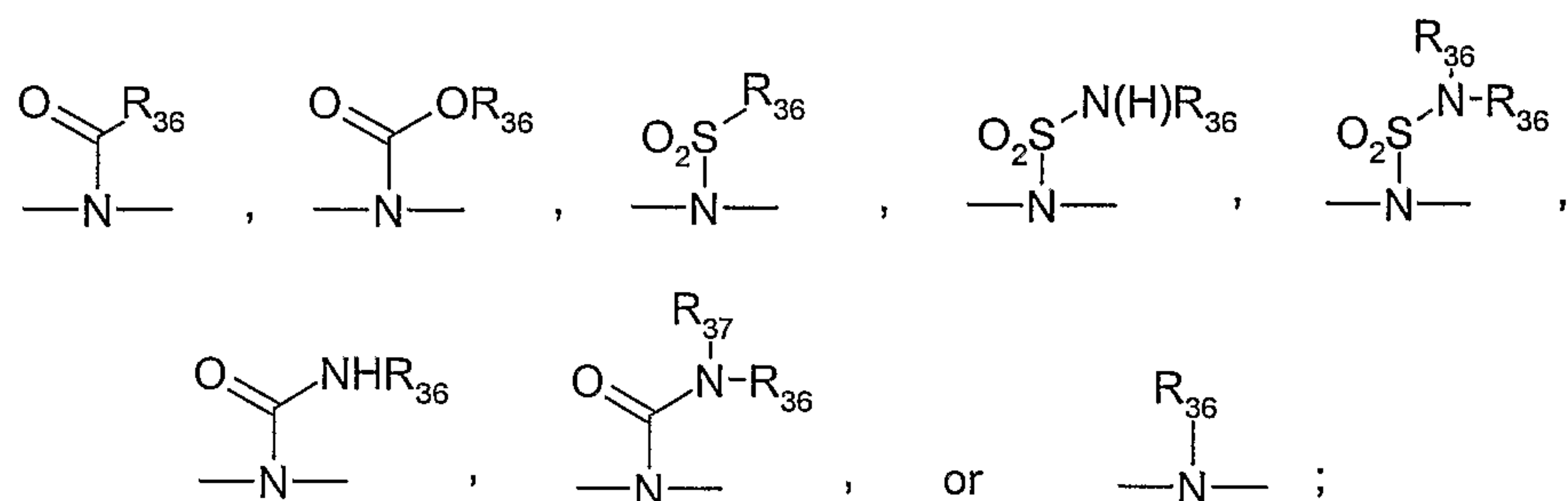
- a) heterocyclyl, fused arylheterocyclyl, or fused heteroarylheterocyclyl,
 containing at least one basic nitrogen atom,
 35 b) $-imidazolyl$, or

c) -pyridyl; and

R_{33} , R_{34} and R_{35} independently comprise hydrogen, aryl, heteroaryl, alkyl, -alkylene-aryl, or -alkylene-O-aryl; with the proviso that no two of R_{33} , R_{34} and R_{35} are aryl and/or heteroaryl; and R_{33} and R_{34} may be taken together to form a ring having the formula $-(CH_2)_u-X_4-(CH_2)_v-$ bonded to the nitrogen atom to which R_{33} and R_{34} are attached, wherein

u and v are, independently, 1, 2, 3, or 4;

X_4 comprises a direct bond, $-CH_2-$, $-O-$, $-S-$, $-S(O_2)-$, $-C(O)-$, $-CON(H)-$, $-NHC(O)-$, $-NHCON(H)-$, $-NHSO_2-$, $-SO_2N(H)-$, $-C(O)-O-$, $-O-C(O)-$, $-NHSO_2NH-$,



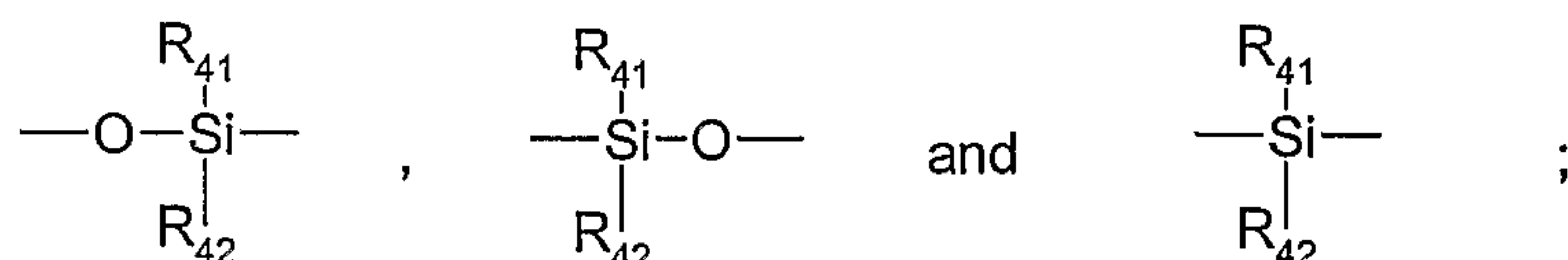
wherein R_{36} and R_{37} independently comprise hydrogen, aryl, heteroaryl, alkyl, -alkylene-aryl, or -alkylene-heteroaryl; and

wherein said ring system is optionally substituted with substituents comprising

- a) -H;
- b) -halogen;
- c) -hydroxyl;
- d) -cyano;
- e) -carbamoyl;
- f) -carboxyl;
- g) $-Y_8$ -alkyl;
- h) $-Y_8$ -aryl;
- i) $-Y_8$ -heteroaryl;
- j) $-Y_8$ -alkylene-aryl;
- k) $-Y_8$ -alkylene-heteroaryl;
- l) $-Y_8$ -alkylene- $NR_{38}R_{39}$; or
- m) $-Y_8$ -alkylene- W_3-R_{40} ;

wherein

Y_8 and W_3 independently comprise $-\text{CH}_2-$, $-\text{O}-$, $-\text{N}(\text{H})-$, $-\text{S}-$, SO_2- , $-\text{CON}(\text{H})-$,
 $-\text{NHC}(\text{O})-$, $-\text{NHCON}(\text{H})-$, $-\text{NHSO}_2-$, $-\text{SO}_2\text{N}(\text{H})-$, $-\text{C}(\text{O})-\text{O}-$,
 $-\text{NHSO}_2\text{NH}-$, $-\text{O}-\text{CO}-$,



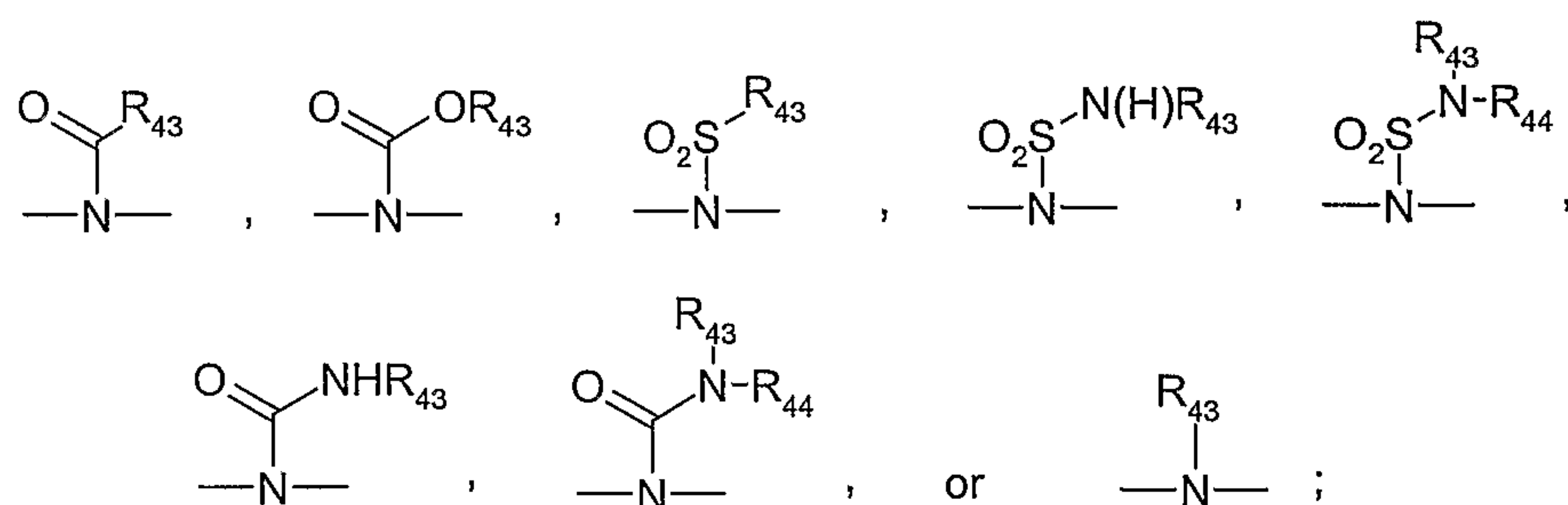
5 wherein R_{41} and R_{42} independently comprise aryl, alkyl, -alkylene-aryl, alkoxy, or -alkyl-O-aryl; and

R_{38} , R_{39} , and R_{40} independently comprise hydrogen, aryl, alkyl, -alkylene-aryl, -alkylene-heteroaryl, and -alkylene-O-aryl; and R_{38} and R_{39} may
 10 be taken together to form a ring having the formula $-(\text{CH}_2)_w-\text{X}_7-(\text{CH}_2)_x-$ bonded to the nitrogen atom to which R_{38} and R_{39} are attached
 wherein

w and x are, independently, 1, 2, 3, or 4;

X_7 comprises a direct bond, $-\text{CH}_2-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O}_2)-$, $-\text{C}(\text{O})-$, $-\text{CON}(\text{H})-$, $-\text{NHC}(\text{O})-$, $-\text{NHCON}(\text{H})-$, $-\text{NHSO}_2-$, $-\text{SO}_2\text{N}(\text{H})-$, $-\text{C}(\text{O})-\text{O}-$, $-\text{O}-\text{C}(\text{O})-$, $-\text{NHSO}_2\text{NH}-$,

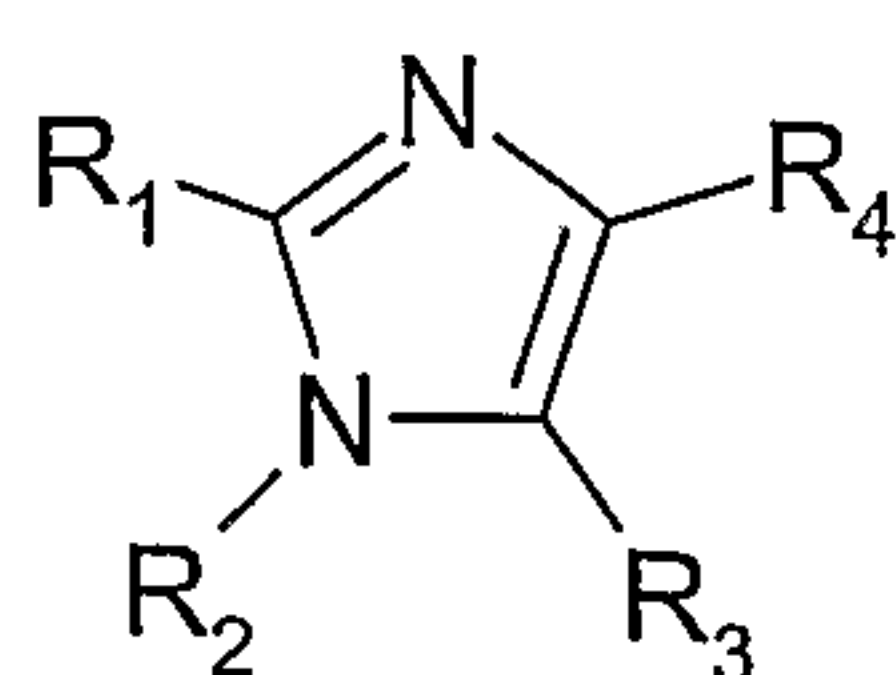
15



wherein R_{43} and R_{44} independently comprise hydrogen, aryl, heteroaryl, alkyl, -alkylene-aryl, or -alkylene-heteroaryl;

20 or a pharmaceutically acceptable salt thereof.

2. The compound claim 1, wherein the compound of Formula (I) comprise a compound of Formula (Ia)



(Ia)

wherein

R₁ comprises -hydrogen, -aryl, -heteroaryl, -cycloalkyl, -heterocyclyl, -alkyl, -alkylene-aryl, -alkylene-heteroaryl, -alkylene-heterocyclyl, -alkylene-cycloalkyl, or -G₁-G₂-G₃-R₅

5 wherein

G₁ and G₃ independently comprise alkylene or a direct bond;

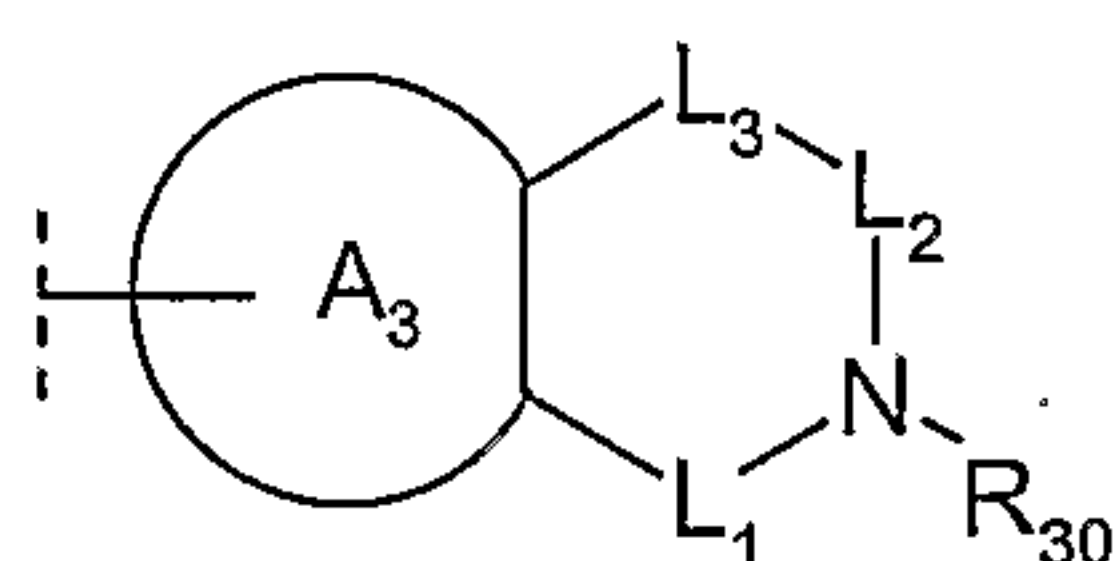
G₂ comprises -O-, -CO₂-, or a direct bond; and

R₅ comprises hydrogen, aryl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, alkenyl, alkynyl, -alkylene-aryl, -alkylene-heteroaryl, -alkylene-heterocyclyl, or -alkylene-cycloalkyl;

10

R₂ comprises

- a) -hydrogen,
- b) -aryl,
- 15 c) -heteroaryl,
- d) -heterocyclyl,
- e) -alkyl,
- f) -alkylene-aryl,
- g) -alkylene-heteroaryl,
- 20 h) -alkylene-heterocyclyl,
- i) -fused cycloalkylaryl,
- j) -fused cycloalkylheteroaryl,
- k) -fused heterocyclylaryl,
- l) -fused heterocyclylheteroaryl;
- 25 m) -alkylene-fused cycloalkylaryl,
- n) -alkylene-fused cycloalkylheteroaryl,
- o) -alkylene-fused heterocyclylaryl,
- p) -alkylene-fused heterocyclylheteroaryl; or
- q) a group of the formula



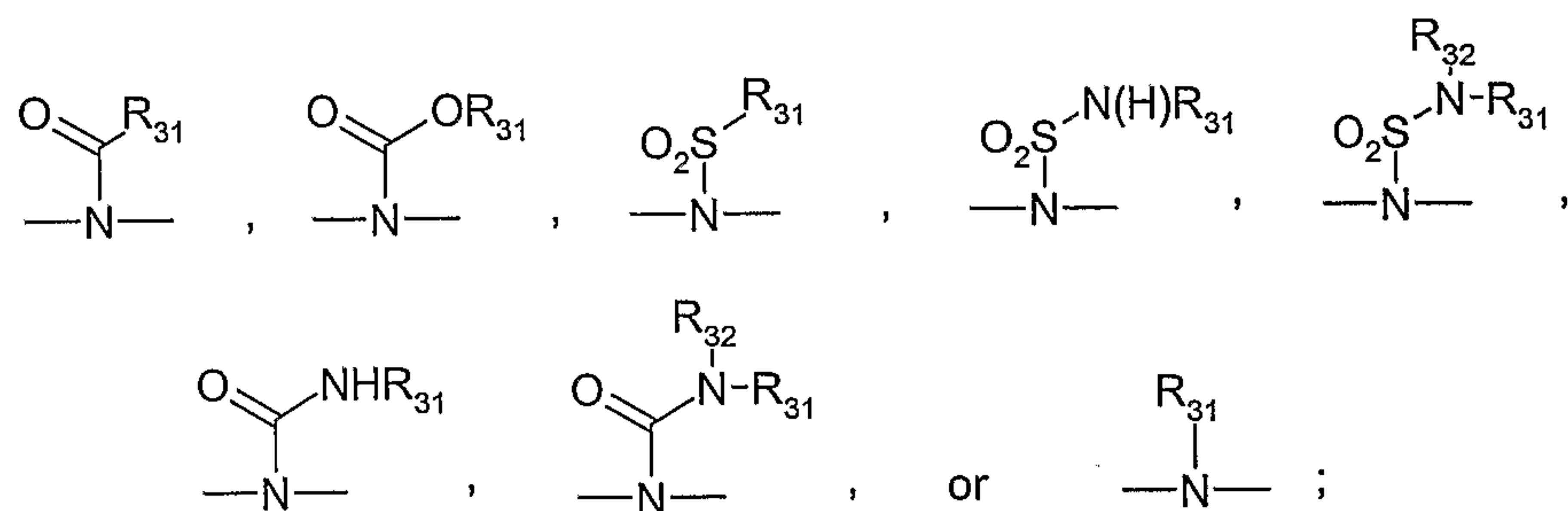
30

wherein

A₃ comprises an aryl or heteroaryl group;

L₁ and L₂ independently comprise alkylene or alkenylene;

L₃ comprises a direct bond, alkylene, -O-, -S-, -S(O₂)-, -C(O)-,
 5 -CON(H)-, -NHC(O)-, -NHCON(H)-, -NHSO₂-, -SO₂N(H)-, -C(O)-O-
 , -O-C(O)-, -NHSO₂NH-,



wherein R₃₀, R₃₁, and R₃₂ independently comprise hydrogen,
 aryl, heteroaryl, alkyl, alkylene-aryl, or -alkylene-heteroaryl;

R₃ and R₄ independently comprise

- a) -hydrogen;
- b) -halogen,
- c) -hydroxyl,
- 15 d) -cyano,
- e) -carbamoyl,
- f) -carboxyl;
- g) -aryl,
- h) -heteroaryl,
- 20 i) -cycloalkyl,
- j) -heterocyclyl,
- k) -alkyl,
- l) -alkenyl,
- m) -alkynyl,
- 25 n) -alkylene-aryl,
- o) -alkylene-heteroaryl,
- p) -alkylene-heterocyclyl,
- q) -alkylene-cycloalkyl,
- r) -fused cycloalkylaryl,
- 30 s) -fused cycloalkylheteroaryl,

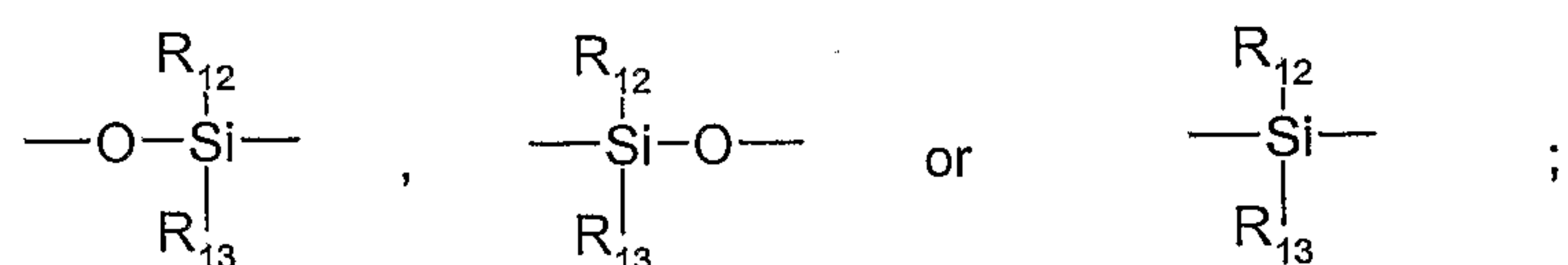
- t) -fused heterocyclaryl,
 u) -fused heterocyclheteroaryl,
 v) -alkylene-fused cycloalkaryl,
 w) -alkylene-fused cycloalkheteroaryl,
 5 x) -alkylene-fused heterocyclaryl,
 y) -alkylene-fused heterocyclheteroaryl;
 z) -C(O)-O-alkyl;
 aa) -C(O)-O-alkylene-aryl;
 bb) -C(O)-NH-alkyl;
 10 cc) -C(O)-NH-alkylene-aryl;
 dd) -SO₂-alkyl;
 ee) -SO₂-alkylene-aryl;
 ff) -SO₂-aryl;
 gg) -SO₂-NH-alkyl;
 15 hh) -SO₂-NH-alkylene-aryl;
 ii) -C(O)-alkyl;
 jj) -C(O)-alkylene-aryl;
 kk) -G₄-G₅-G₆-R₇
 ll) -Y₁-alkyl;
 20 mm) -Y₁-aryl;
 nn) -Y₁-heteroaryl;
 oo) -Y₁-alkylene-aryl;
 pp) -Y₁-alkylene-heteroaryl;
 qq) -Y₁-alkylene-NR₉R₁₀; and
 25 rr) -Y₁-alkylene-W₁-R₁₁;

wherein

- G₄ and G₆ independently comprise alkylene, alkenylene, alkynylene,
 cycloalkylene, heterocyclylene, arylene, heteroarylene, (arylalkylene,
 (heteroaryl) alkylene, (aryl)alkenylene, (heteroaryl)alkenylene, or a direct
 30 bond;
 G₅ comprises -O-, -S-, -N(R₈)-, -S(O)-, -S(O)₂-, -C(O)-, -C(O)N(R₈)-, N(R₈)C(O)-,
 -S(O₂)N(R₈)-, N(R₈)S(O₂)-, -O-alkylene-C(O)-, -(O)C-alkylene-O-, -O-alkylene-
 , -alkylene-O-, alkylene, alkenylene, alkynylene, cycloalkylene,
 heterocyclylene, arylene, heteroarylene, fused cycloalkaryl, fused
 35 cycloalkheteroaryl, fused heterocyclaryl, fused heterocyclheteroaryl, or a
 direct bond, wherein R₈ comprises -hydrogen, -aryl, -alkyl, -alkylene-aryl, or
 -alkylene-O-aryl;

R₇ comprises hydrogen; aryl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, alkenyl, alkynyl, alkylene-aryl, -alkylene-heteroaryl, -alkylene-heterocyclyl, -alkylene-cycloalkyl, fused cycloalkylaryl, fused cycloalkylheteroaryl, fused heterocyclylaryl, fused heterocyclylheteroaryl, alkylene-fused cycloalkylaryl, -alkylene-fused cycloalkylheteroaryl, -alkylene-fused heterocyclylaryl, or -alkylene-fused heterocyclylheteroaryl;

Y₁ and W₁ independently comprise -CH₂-, -O-, -N(H)-, -S-, SO₂-, -CON(H)-, -NHC(O)-, -NHCON(H)-, -NHSO₂-, -SO₂N(H)-, -C(O)-O-, -NHSO₂NH-, -O-CO-



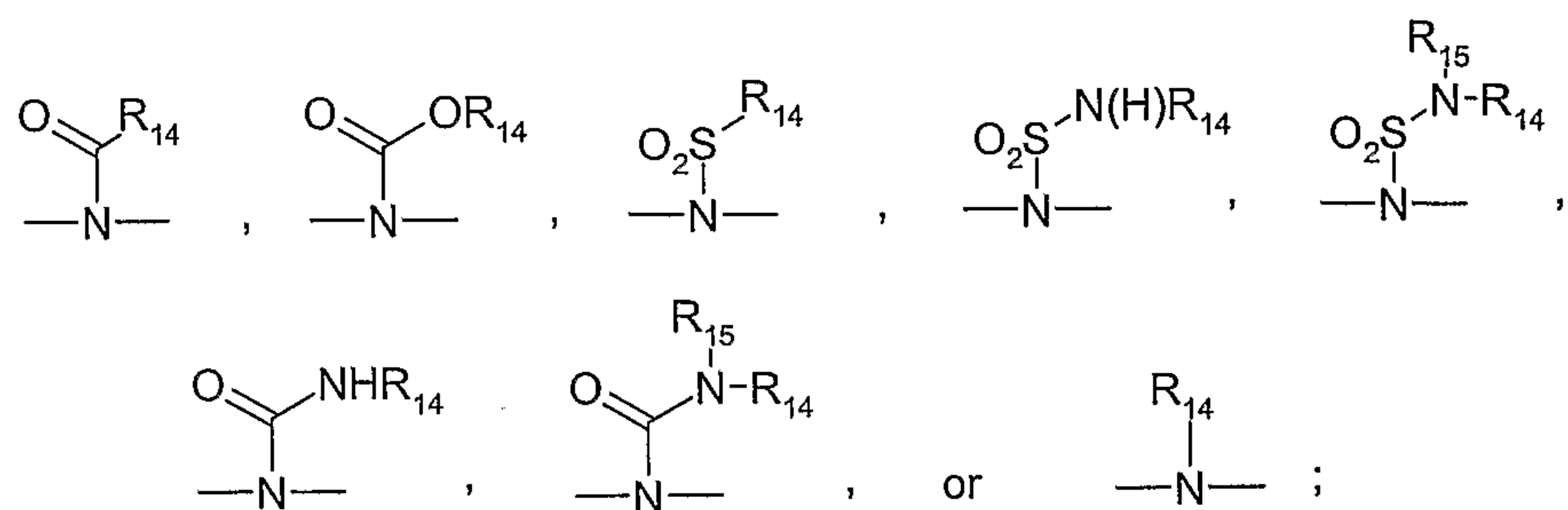
wherein R₁₂ and R₁₃ independently comprise aryl, alkyl, -alkylene-aryl, alkoxy, or -alkylene-O-aryl;

R₉, R₁₀, and R₁₁ independently comprise aryl, heteroaryl, alkyl, -alkylene-heteroaryl, or -alkylene-aryl; and R₉ and R₁₀ may be taken together to form a ring having the formula -(CH₂)_o-X₁-(CH₂)_p- bonded to the nitrogen atom to which R₉ and R₁₀ are attached,

wherein

o and p are, independently, 1, 2, 3, or 4;

X₁ comprises a direct bond, -CH₂-, -O-, -S-, -S(O₂)-, -C(O)-, -CON(H)-, -NHC(O)-, -NHCON(H)-, -NHSO₂-, -SO₂N(H)-, -C(O)-O-, -O-C(O)-, -NHSO₂NH-,



with the proviso that R₃ and R₄ can not both be hydrogen.

3. The compound of Formula (Ia) of claim 2, wherein R₁ comprises a hydrogen, methyl, ethyl, propyl, butyl, iso-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 3-butenyl, tert-butyl, 3-cyclohexyl-propyl, 3-phenoxy-propyl, methoxymethyl, 4-fluoro-phenyl, 3-(4-chlorophenoxy)-propyl, 2,4,4-trimethyl-pentyl, 1-ethyl-propyl, 1-propyl-butyl, benzyloxymethyl, 2-cyclopropyl-ethyl, 2-phenyl-ethyl, 4-tert-butylphenoxyethyl, 4-tert-butylcyclohexyl, 4-butylcyclohexyl, 4-ethylcyclohexyl, 3-methoxycarbonyl-1-propyl, or 2-(pyridin-3-yl)-ethyl group.

4. The compound of Formula (Ia) of claim 2, wherein R₂ comprises a phenyl or 1,2,3,4-tetrahydroisoquinoline group, wherein the phenyl group is substituted with at least one substituent comprising

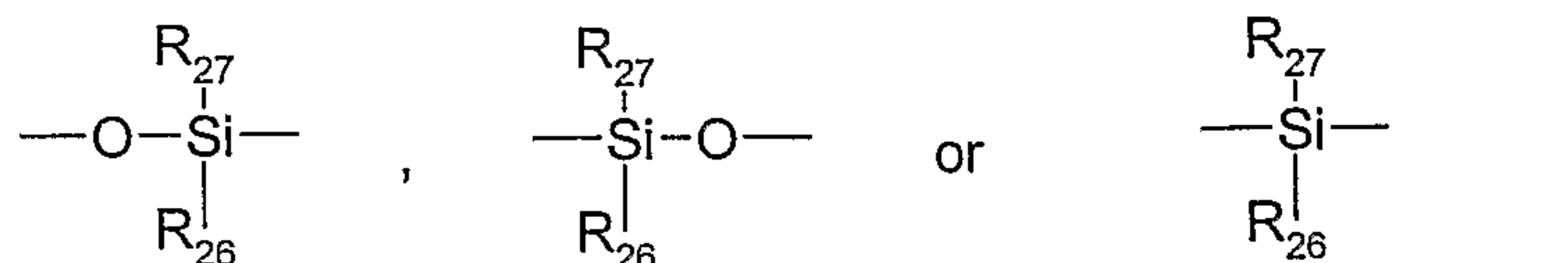
- a) -Y₂-alkyl;
- b) -Y₂-aryl;
- c) -Y₂-heteroaryl;
- d) -Y₂-alkylene-heteroaryl;
- e) -Y₂-alkylene-aryl;
- f) -Y₂-alkylene-W₂-R₁₈;
- g) -Y₃-Y₄-NR₂₃R₂₄;
- h) -Y₃-Y₄-NH-C(=NR₂₅)NR₂₃R₂₄;
- i) -Y₃-Y₄-C(=NR₂₅)NR₂₃R₂₄; or
- j) -Y₃-Y₄-Y₅-A₂;

wherein

Y₂ and W₂ independently comprise -CH₂- or -O-, and

R₁₈ comprises aryl, alkyl, -alkylene-aryl, -alkylene-heteroaryl, or -alkylene-O-aryl;

Y₃ and Y₅ independently comprise a direct bond, -CH₂-, -O-, -N(H)-, -S-, SO₂-, -C(O)-, -CON(H)-, -NHC(O)-, -NHCON(H)-, -NHSO₂-, -SO₂N(H)-, -C(O)-O-, -NHSO₂NH-, -O-CO-,



wherein R₂₇ and R₂₆ independently comprise aryl, alkyl, -alkylene-aryl, alkoxy, or -alkyl-O-aryl;

Y₄ comprises

- a) -alkylene;
- b) -alkenylene;

- c) -alkynylene;
- d) -arylene;
- e) -heteroarylene;
- f) -cycloalkylene;
- g) -heterocyclylene;
- h) -alkylene-arylene;
- i) -alkylene-heteroarylene;
- j) -alkylene-cycloalkylene;
- k) -alkylene-heterocyclylene;
- l) -arylene-alkylene;
- m) -heteroarylene-alkylene;
- n) -cycloalkylene-alkylene;
- t) -heterocyclylene-alkylene;
- u) -O-;
- v) -S-;
- w) -S(O₂)-; or
- x) -S(O)-;

wherein said alkylene groups may optionally contain one or more O, S, S(O), or SO₂ atoms;

A₂ comprises

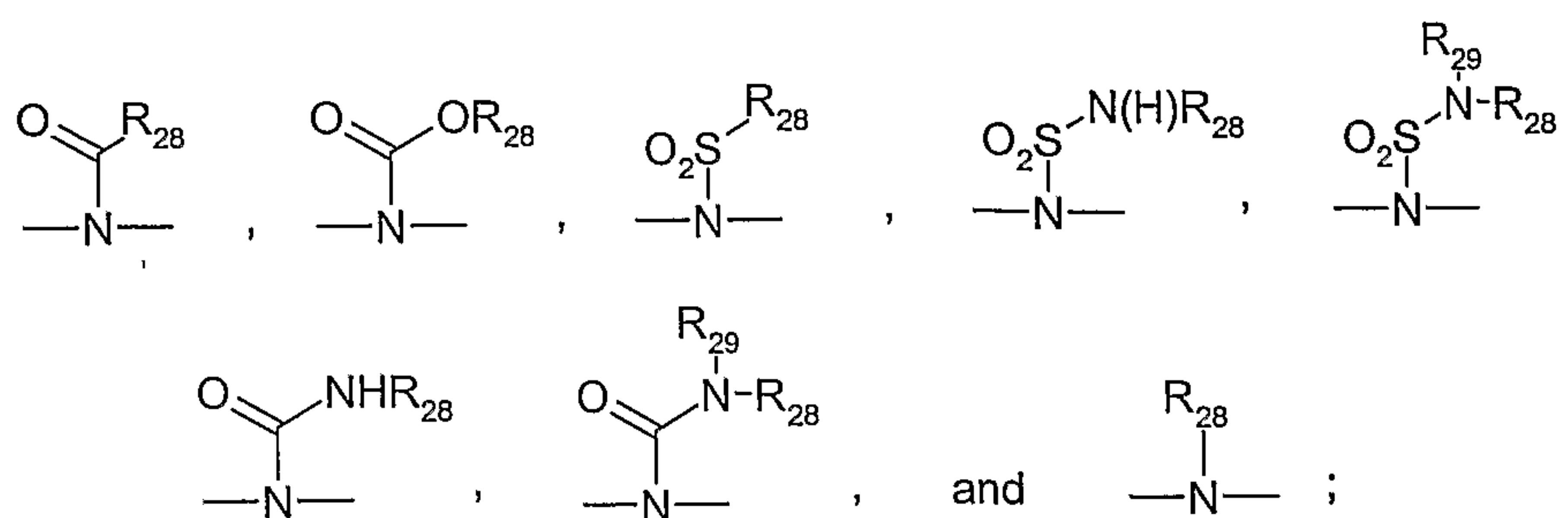
- a) heterocyclyl, fused arylheterocyclyl, or fused heteroarylheterocyclyl, containing at least one basic nitrogen atom,
- b) -imidazolyl, or
- c) -pyridyl; and

R₂₃, R₂₄, and R₂₅ independently comprise hydrogen, aryl, heteroaryl, -alkylene-heteroaryl, alkyl, -alkylene-aryl, -alkylene-O-aryl, or -alkylene-O-heteroaryl; and R₂₃ and R₂₄ may be taken together to form a ring having the formula -(CH₂)_s-X₃-(CH₂)_t- bonded to the nitrogen atom to which R₂₃ and R₂₄ are attached

wherein

s and t are, independently, 1, 2, 3, or 4;

X₃ comprises direct bond, -CH₂-, -O-, -S-, -S(O₂)-, -C(O)-, -CON(H)-, -NHC(O)-, -NHCON(H)-, -NHSO₂-, -SO₂N(H)-, -C(O)-O-, -O-C(O)-, -NHSO₂NH-,



wherein R₂₈ and R₂₉ independently comprise hydrogen, aryl, heteroaryl, alkyl, -alkylene-aryl, or -alkylene-heteroaryl.

5

5. The compound of Formula (Ia) of claim 2, wherein R₂ comprises 4-[3-(N,N'-diethylamino)-propoxy]-phenyl, 4-[3-(N,N'-dimethylamino)-propoxy]-phenyl, 3-[3-(N,N'-diethylamino)-propoxy]-phenyl, 4-(3-fluoro-4-trifluoromethyl-phenoxy)-phenyl, 4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl, 4-(4-trifluoromethoxy-phenoxy)-phenyl, 4-(3,4-dichloro-phenoxy)-phenyl, 4-(3,5-bis-trifluoromethyl-phenoxy)-phenyl, 4-benzyloxy-phenyl, 4-(4-methoxy-phenoxy)-phenyl, 4-(2-hexyl-4-chloro-phenoxy)-phenyl, 4-(4-phenyl-phenoxy)-phenyl, 4-(4-acetamido-phenoxy)-phenyl, 4-(4-methyl-phenoxy)-phenyl, 4-(4-fluoro-phenoxy)-phenyl, 4-(4-bromo-phenoxy)-phenyl, 4-(4-chloro-phenoxy)-phenyl, 4-(4-amino-phenoxy)-phenyl, 4-(3-ethyl-4-chloro-phenoxy)-phenyl, 4-[2-(N-ethylamino)-ethoxy]-phenyl, 4-[2,2'-dimethyl-3-(N,N'-dimethylamino)-propoxy]-phenyl, 1,2,3,4-tetrahydroisoquinolin-7-yl, 4-(4-benzamido-phenoxy)-phenyl, 4-(4-isonicotinamido-phenoxy)-phenyl, 4-[2-(N-methyl-N'-pyrid-4-yl)-ethoxy]-phenyl, 4-[3-(diethylmethyl ammonium)-propoxy]-phenyl, 4-(2,5-di-fluoro-benzyloxy)-phenyl, 4-(2,4-dichloro-phenoxy)-phenyl, 4-(naphthalen-2-yloxy)-phenyl, 4-(6-methoxy-naphthalen-2-yloxy)-phenyl, 4-(4-methoxy-naphthalen-2-yloxy)-phenyl, 4-(6-hydroxy-naphthalen-2-yloxy)-phenyl, 4-(dibenzofuran-2-yloxy)-phenyl, 4-[2-(1-methyl-pyrrolidin-2-yl)-ethoxy]-phenyl, 4-[2-(piperazin-1-yl)-ethoxy]-phenyl, or 4-(4-tert-butyl-phenoxy)-phenyl.

6. The compound of Formula (Ia) of claim 2, wherein R₃ comprises hydrogen; and R₄ comprises a phenyl group, wherein the phenyl group is substituted with at least one substituent comprising

- a) -Y₂-alkyl;
- b) -Y₂-aryl;
- c) -Y₂-heteroaryl;
- d) -Y₂-alkylene-heteroarylaryl;
- e) -Y₂-alkylene-aryl;

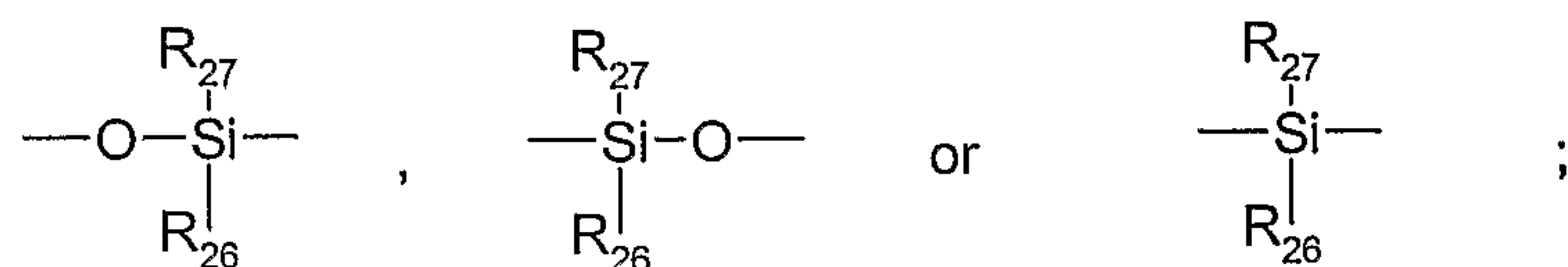
- f) $-Y_2\text{-alkylene-}W_2\text{-}R_{18}$;
 g) $-Y_3\text{-}Y_4\text{-NR}_{23}R_{24}$;
 h) $-Y_3\text{-}Y_4\text{-NH-C(=NR}_{25}\text{)NR}_{23}R_{24}$;
 i) $-Y_3\text{-}Y_4\text{-C(=NR}_{25}\text{)NR}_{23}R_{24}$; or
 j) $-Y_3\text{-}Y_4\text{-}Y_5\text{-}A_2$;

wherein

Y_2 and W_2 independently comprise $-\text{CH}_2-$ or $-\text{O}-$;

R_{18} comprises aryl, alkyl, -alkylene-aryl, -alkylene-heteroaryl, or -alkylene-O-aryl;

Y_3 and Y_5 independently comprise a direct bond, $-\text{CH}_2-$, $-\text{O}-$, $-\text{N(H)}$, $-\text{S}-$, SO_2- , $-\text{C(O)}-$, $-\text{CON(H)}-$, $-\text{NHC(O)}-$, $-\text{NHCON(H)}-$, $-\text{NHSO}_2-$, $-\text{SO}_2\text{N(H)}-$, $-\text{C(O)}-\text{O}-$, $-\text{NHSO}_2\text{NH}-$, $-\text{O-CO}-$,



wherein R_{27} and R_{26} independently comprise aryl, alkyl, -alkylene-aryl, alkoxy, or -alkyl-O-aryl;

Y_4 comprises

- a) -alkylene;
 b) -alkenylene;
 c) -alkynylene;
 d) -arylene;
 e) -heteroarylene;
 f) -cycloalkylene;
 g) -heterocyclylene;
 h) -alkylene-arylene;
 i) -alkylene-heteroarylene;
 j) -alkylene-cycloalkylene;
 k) -alkylene-heterocyclylene;
 l) -arylene-alkylene;
 m) -heteroarylene-alkylene;
 n) -cycloalkylene-alkylene;
 o) -heterocyclylene-alkylene;
 p) $-\text{O}-$;
 q) $-\text{S}-$;

r) $-\text{S}(\text{O}_2)-$; or

s) $-\text{S}(\text{O})-$;

wherein said alkylene groups may optionally contain one or more O, S, $\text{S}(\text{O})$, or SO_2 atoms;

5

A_2 comprises

a) heterocyclyl, fused arylheterocyclyl, or fused heteroarylheterocyclyl, containing at least one basic nitrogen atom,

b) -imidazolyl, or

10

c) -pyridyl;

R_{23} , R_{24} , and R_{25} independently comprise hydrogen, aryl, heteroaryl, -alkylene-heteroaryl, alkyl, -alkylene-aryl, -alkylene-O-aryl, or -alkylene-O-heteroaryl; and R_{23} and R_{24} may be taken together to form a ring having the formula $-(\text{CH}_2)_s-\text{X}_3-(\text{CH}_2)_t-$ bonded to the nitrogen atom to which R_{23} and R_{24} are attached

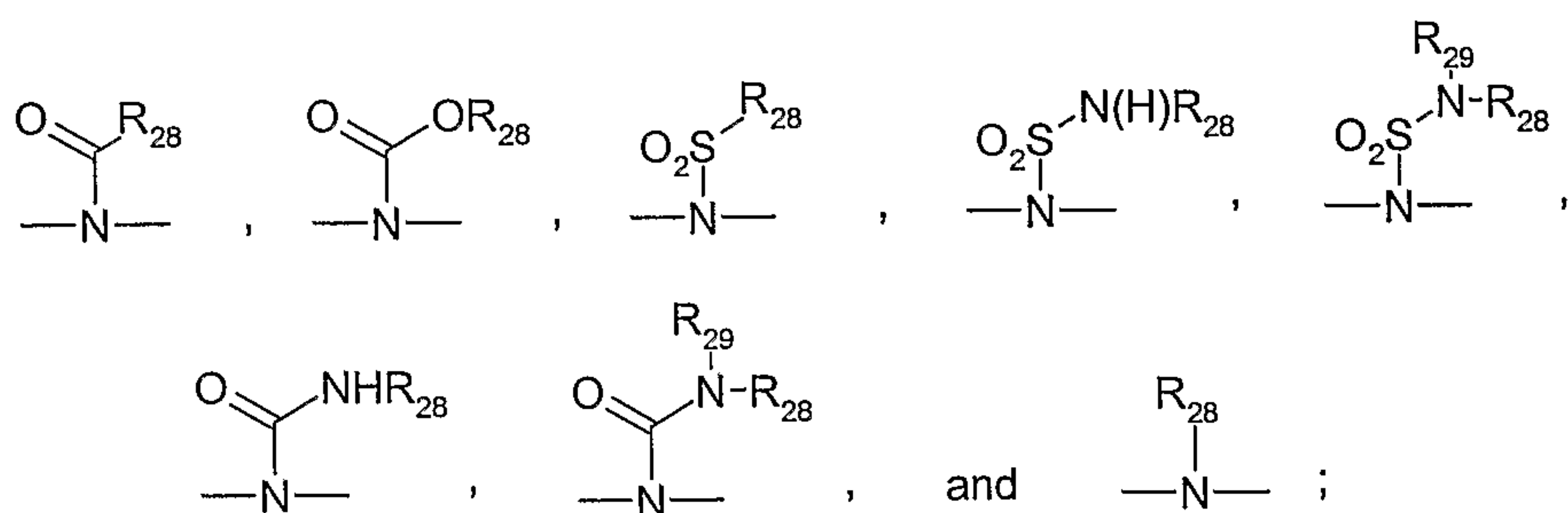
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wherein

s and t are, independently, 1, 2, 3, or 4;

X_3 comprises direct bond, $-\text{CH}_2-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O}_2)-$, $-\text{C}(\text{O})-$, $-\text{CON}(\text{H})-$, $-\text{NHC}(\text{O})-$, $-\text{NHCON}(\text{H})-$, $-\text{NHSO}_2-$, $-\text{SO}_2\text{N}(\text{H})-$, $-\text{C}(\text{O})-\text{O}-$, $-\text{O}-\text{C}(\text{O})-$, $-\text{NHSO}_2\text{NH}-$,

20



wherein R_{28} and R_{29} independently comprise hydrogen, aryl, heteroaryl, alkyl, -alkylene-aryl, or -alkylene-heteroaryl.

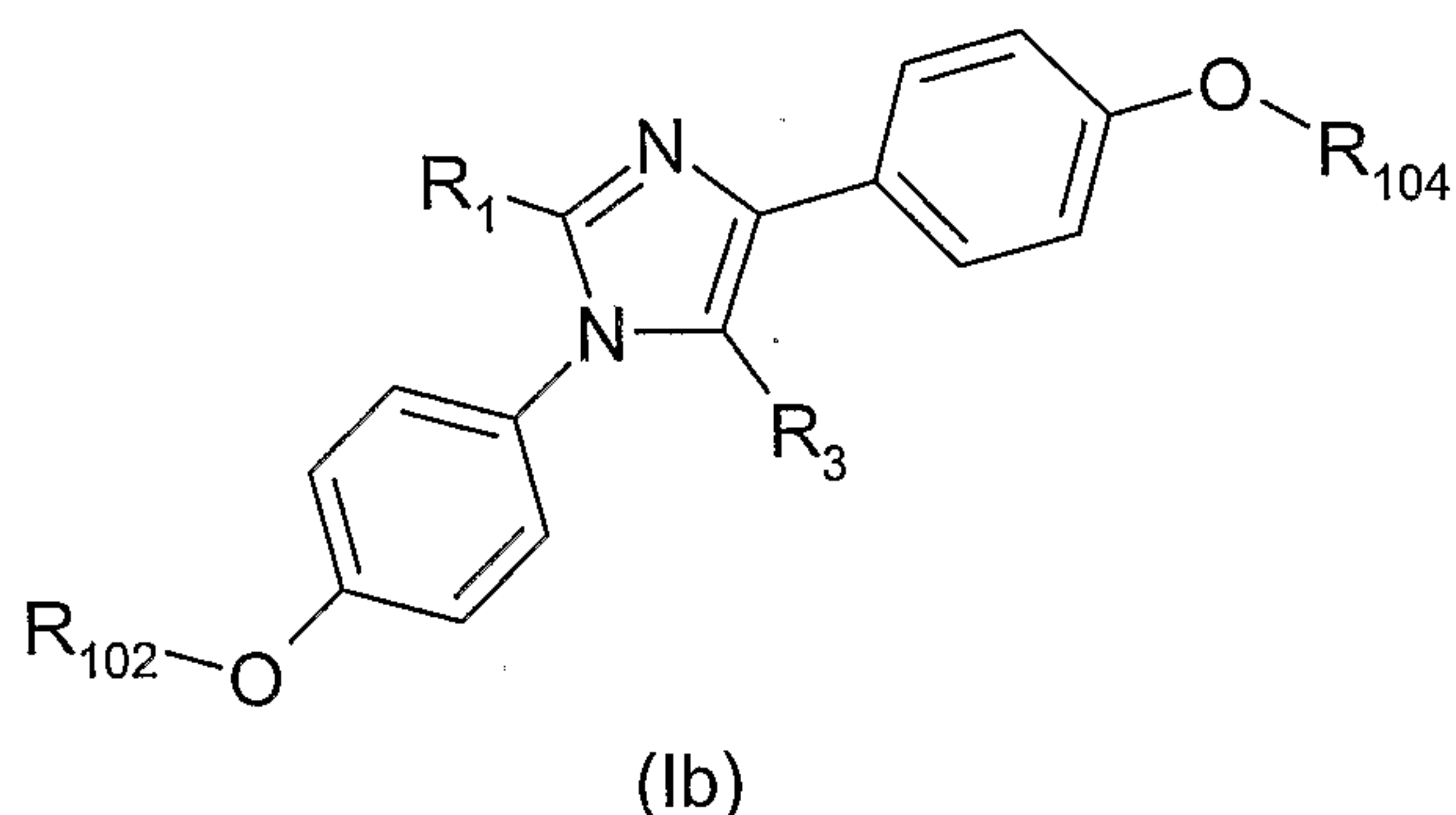
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7. The compound of Formula (Ia) of claim 2, wherein R_3 comprises hydrogen and R_4 comprises 4-{2-[(4-chlorophenyl)-ethoxy]}-phenyl, 4-[3-(N,N'-diethylamino)-propoxy]-phenyl, 4-(2-amino-ethoxy)-phenyl, 4-[2-(N-methyl-N'-pyridin-4-yl-amino)-ethoxy]-phenyl, 4-[2-(N-ethyl-N'-pyridin-4-yl-amino)-ethoxy]-phenyl, 4-[2-(N-pyridin-4-yl-amino)-ethoxy]-phenyl, 4-(4-amino-pyridin-3-yl-oxy)-phenyl, 4-[(pyridin-4-yl)-amino]-phenyl, 4-[2-(N,N'-bis-pyridin-2-

30

ylmethyl-amino)-ethoxy]-phenyl, 4-[2-(guanidinyloxy)-phenyl, 4-{2-[4-(pyridin-4-yl)-
 piperazin-1-yl]-2-oxo-ethoxy}-phenyl, 4-[2-(N-methyl-N'-3-methylpyridin-4-yl-amino)-ethoxy]-
 phenyl, 4-(4-hydroxy-pyrrolidin-2-ylmethoxy)-phenyl, 4-(4-amino-3,5-dimethyl-pyrrolidin-2-
 ylmethoxy)-phenyl, dibenzofuran-2-yl, 4-[3-(piperazin-1-yl)-propoxy]-phenyl, 4-(piperazin-4-
 5 yloxy)-phenyl, 4-[5-(piperazin-1-yl)-pentoxy]-phenyl, 4-[3-(N,N'-dimethylamino)-propoxy]-
 phenyl, 4-(3-fluoro-4-trifluoromethyl-phenoxy)-phenyl, 4-(4-fluoro-3-trifluoromethyl-phenoxy)-
 phenyl, 4-(4-phenyl-phenoxy)-phenyl, 4-(3-trifluoromethoxy-phenoxy)-phenyl, 4-(4-
 trifluoromethyl-benzyloxy)-phenyl, 4-(3,4-dichloro-phenoxy)-phenyl, 4-(2,4-dichloro-
 phenoxy)-phenyl, 4-(1-ethyl-piperidin-3-yloxy)-phenyl, 4-benzyloxy-phenyl, 4-[(1-ethyl-
 10 piperidin-3-yl)-methoxy]-phenyl, 4-(4-phenoxy-benzyloxy)-phenyl, 4-(4-benzyloxy-
 benzyloxy)-phenyl, 4-(2-benzenesulfonylmethyl-benzyloxy)-phenyl, 4-(3,4,5-
 trimethoxybenzyloxy)-phenyl, 4-[2-(pyrrolidin-1-yl)-ethoxy]-phenyl, 4-[2-(piperidin-1-yl)-
 ethoxy]-phenyl, 4-[2,2'-dimethyl-3-(N,N'-dimethylamino)-propoxy]-phenyl, 4-[2-(N,N'-
 diisopropylamino)-ethoxy]-phenyl, 4-(adamantan-1-ylmethoxy)-phenyl, 3-[(2,6-
 15 dichlorophenyl)-4-methyl-isoxazol-5-ylmethoxy]-phenyl, 4-(4-bromo-benzyloxy)-phenyl, 4-
 (4-chlorophenoxy)-phenyl, 4-[4-[(1-ethyl-piperidin-4-yl)-methylamino]-phenoxy]-phenyl, 4-
 (3,3-diphenylpropoxy)-phenyl, 4-[3,3-Bis-(4-fluorophenyl)-propoxy]-phenyl, 4-[3,3-Bis-(4-
 chlorophenyl)-allyloxy]-phenyl, 4-(4-chlorophenoxy)-naphthalenyl, 4-[2-(biphenyl-4-yl)-
 acetamido]-phenyl, 4-(2-(9H-carbazole)-ethoxy)-phenyl, 4-[4-methoxyphenoxy]-phenyl, 4-
 20 (4-tert-butyl-phenoxy)-phenyl, or 4-(naphthyl-2-ylmethoxy)-phenyl.

8. The compound claim 1, wherein the compound of Formula (I) comprise a
 compound of Formula (Ib)



wherein

R₁ comprises -hydrogen, -aryl, -heteroaryl, -cycloalkyl, -heterocyclyl, -alkyl, -alkenyl, -
 alkylene-aryl, -alkylene-heteroaryl, -alkylene-heterocyclyl, -alkylene-cycloalkyl, -fused
 cycloalkylaryl, -fused cycloalkylheteroaryl, -fused heterocyclaryl, -fused
 30 heterocyclheteroaryl, -alkylene-fused cycloalkylaryl, -alkylene-fused

cycloalkylheteroaryl, -alkylene-fused heterocyclylaryl, -alkylene-fused heterocyclylheteroaryl, or -G₁-G₂-G₃-R₅

wherein

G₁ and G₃ independently comprise alkylene, alkenylene, alkynylene, cycloalkylene, heterocyclylene, arylene, heteroarylene, (aryl)alkylene, (heteroaryl) alkylene, (aryl)alkenylene, (heteroaryl)alkenylene, or a direct bond;

G₂ comprises -O-, -S-, -S(O)-, -N(R₆)-, -S(O)₂-, -C(O)-, -CO₂-, -C(O)N(R₆)-, N(R₆)C(O)-, -S(O₂)N(R₆)-, N(R₆)S(O₂)-, -O-alkylene-C(O)-, -(O)C-alkylene-O-, -O-alkylene-, -alkylene-O-, alkylene, alkenylene, alkynylene, cycloalkylene, heterocyclylene, arylene, heteroarylene, fused cycloalkylaryl, fused cycloalkylheteroaryl, fused heterocyclylaryl, fused heterocyclylheteroaryl, or a direct bond, wherein R₆ comprises hydrogen, aryl, alkyl, -alkylene-aryl, alkoxy, or -alkylene-O-aryl; and

R₅ comprises hydrogen, aryl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, alkenyl, alkynyl, -alkylene-aryl, -alkylene-heteroaryl, -alkylene-heterocyclyl, -alkylene-cycloalkyl, fused cycloalkylaryl, fused cycloalkylheteroaryl, fused heterocyclylaryl, fused heterocyclylheteroaryl; -alkylene-fused cycloalkylaryl, -alkylene-fused cycloalkylheteroaryl, -alkylene-fused heterocyclylaryl, or -alkylene-fused heterocyclylheteroaryl;

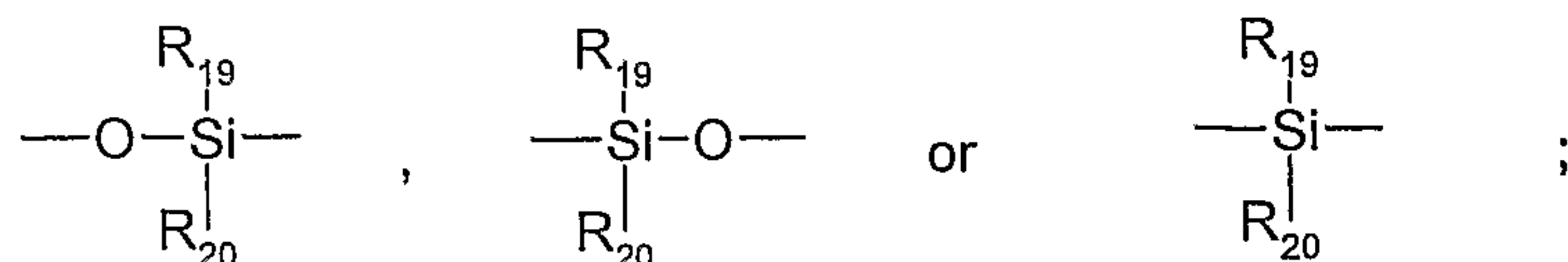
R₃ comprises hydrogen or an alkyl group; and

R₁₀₂ and R₁₀₄ independently comprise

- a) -H;
- b) -alkyl;
- c) -aryl;
- d) -heteroaryl;
- e) -alkylene-heteroarylaryl;
- f) -alkylene-aryl;
- g) -alkylene-W₂-R₁₈;
- h) -Y₄ -NR₂₃R₂₄;
- i) -Y₄ -NH-C(=NR₂₅)NR₂₃R₂₄;
- j) -Y₄ -C(=NR₂₅)NR₂₃R₂₄; or
- k) -Y₄ -Y₅-A₂;

wherein

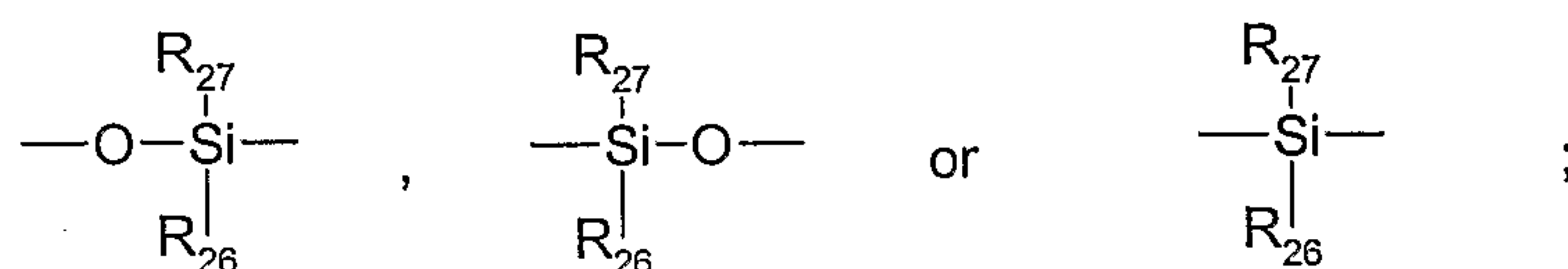
W₂ comprises -CH₂-, -O-, -N(H)-, -S-, SO₂-, -CON(H)-, -NHC(O)-, -NHCON(H)-, -NHSO₂-, -SO₂N(H)-, -C(O)-O-, -NHSO₂NH-, -O-S(O)₂-, -O-CO-,



5 wherein R₁₉ and R₂₀ independently comprise hydrogen, aryl, alkyl, -alkylene-aryl, alkoxy, or -alkylene-O-aryl; and

R₁₈ comprises aryl, alkyl, -alkylene-aryl, -alkylene-heteroaryl, and -alkylene-O-aryl;

10 Y₅ comprises a direct bond, -CH₂-, -O-, -N(H)-, -S-, SO₂-, -C(O)-, -CON(H)-, -NHC(O)-, -NHCON(H)-, -NHSO₂-, -SO₂N(H)-, -C(O)-O-, -NHSO₂NH-, -O-CO-,



15 wherein R₂₇ and R₂₆ independently comprise aryl, alkyl, -alkylene-aryl, alkoxy, or -alkyl-O-aryl;

Y₄ comprises

- a) -alkylene;
- b) -alkenylene;
- c) -alkynylene;
- 20 d) -arylene;
- e) -heteroarylene;
- f) -cycloalkylene;
- g) -heterocyclylene;
- h) -alkylene-arylene;
- 25 i) -alkylene-heteroarylene;
- j) -alkylene-cycloalkylene;
- k) -alkylene-heterocyclylene;
- l) -arylene-alkylene;
- m) -heteroarylene-alkylene;
- 30 n) -cycloalkylene-alkylene;
- o) -heterocyclylene-alkylene;
- p) -O-;

- q) -S-;
 r) -S(O₂)-; or
 s) -S(O)-;

wherein said alkylene groups may optionally contain one or more O,
 S, S(O), or SO₂ atoms;

A₂ comprises

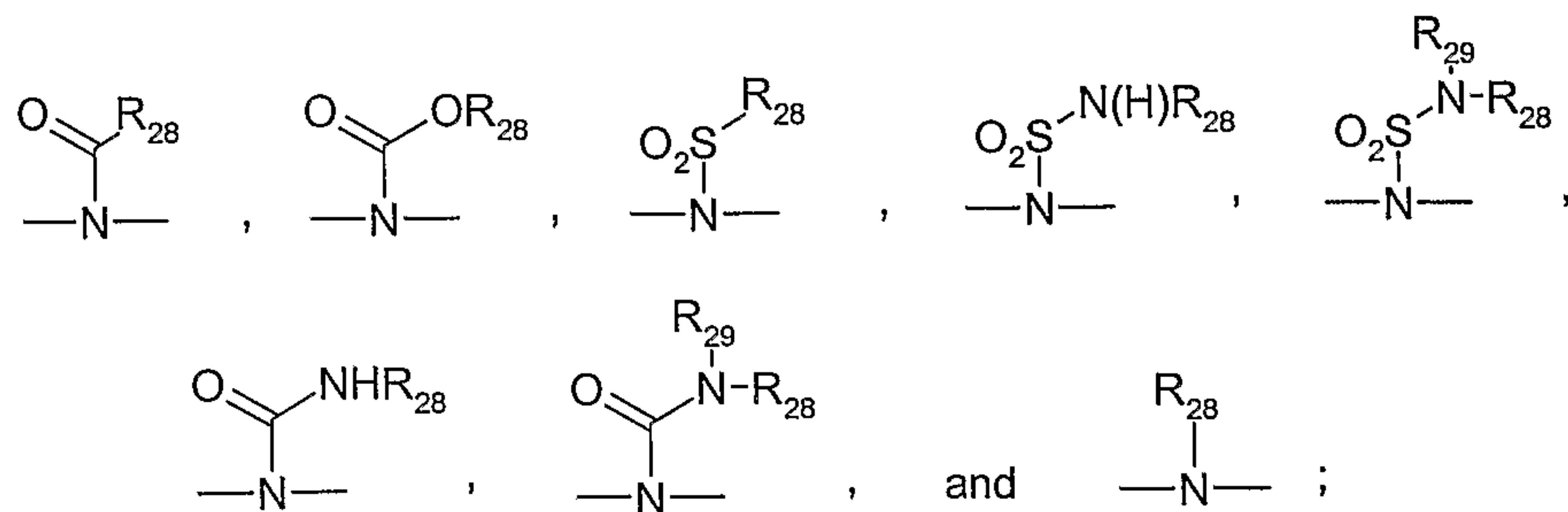
- a) heterocyclyl, fused arylheterocyclyl, or fused heteroarylheterocyclyl,
 containing at least one basic nitrogen atom,
 b) -imidazolyl, or
 c) -pyridyl;

R₂₃, R₂₄, and R₂₅ independently comprise hydrogen, aryl, heteroaryl, -
 alkylene-heteroaryl, alkyl, -alkylene-aryl, -alkylene-O-aryl, or -alkylene-O-
 heteroaryl; and R₂₃ and R₂₄ may be taken together to form a ring having
 the formula -(CH₂)_s-X₃-(CH₂)_t- bonded to the nitrogen atom to which R₂₃
 and R₂₄ are attached

wherein

s and t are, independently, 1, 2, 3, or 4;

X₃ comprises direct bond, -CH₂-, -O-, -S-, -S(O₂)-, -C(O)-, -CON(H)-,
 -NHC(O)-, -NHCON(H)-, -NHSO₂-, -SO₂N(H)-, -C(O)-O-, -O-C(O)-,
 -NHSO₂NH-,



wherein R₂₈ and R₂₉ independently comprise hydrogen, aryl,
 heteroaryl, alkyl, -alkylene-aryl, or -alkylene-heteroaryl;

wherein

the alkyl and/or aryl groups of R₁₀₂ and R₁₀₄ may be optionally substituted 1-4 times
 with a substituent group, wherein said substituent group(s) or the term substituted
 refers to a group comprising:

- a) halogen;

- b) perhaloalkyl;
- c) alkyl;
- d) cyano;
- e) alkyloxy;
- f) aryl; or
- g) aryloxy.

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9. The compound of Formula (Ib) of claim 8, wherein R₁ comprises a hydrogen, methyl, ethyl, propyl, butyl, iso-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 3-butenyl, tert-butyl, 3-cyclohexyl-propyl, 3-phenoxy-propyl, methoxymethyl, 4-fluoro-phenyl, 3-(4-chlorophenoxy)-propyl, 2,4,4-trimethyl-pentyl, 1-ethyl-propyl, 1-propyl-butyl, benzyloxymethyl, 2-cyclopropyl-ethyl, 2-phenyl-ethyl, 4-tert-butylphenoxy-methyl, 4-tert-butylcyclohexyl, 4-ethylcyclohexyl, 4-butylcyclohexyl, 3-methoxycarbonyl-1-propyl, or 2-(pyridin-3-yl)-ethyl group, and R₃ comprises hydrogen.

20

25

30

10. The compound of Formula (Ib) of claim 8, wherein R₁₀₂ and R₁₀₄ independently comprise 2-(4-chlorophenyl)-ethyl, 3-(N,N'-diethylamino)-propyl, 2-amino-ethyl, 2-(N-methyl-N'-pyridin-4-yl-amino)-ethyl, 2-(N-ethyl-N'-pyridin-4-yl-amino)-ethyl, 2-(N-pyridin-4-yl-amino)-ethoxy, 4-(4-amino-pyridin-3-yl-oxy), 4-(pyridin-4-yl)-amino, 2-(N,N'-bis-pyridin-2-ylmethyl-amino)-ethyl, 2-(guanidiny)-ethyl, 2-[4-(pyridin-4-yl)-piperazin-1-yl]-2-oxo-ethyl, 2-(N-methyl-N'-3-methylpyridin-4-yl-amino)-ethyl, 4-hydroxy-pyrrolidin-2-ylmethyl, 4-amino-3,5-dimethyl-pyrrolidin-2-ylmethyl, dibenzofuran-2-yl, 3-(piperazin-1-yl)-propyl, piperazin-4-yl, 5-(piperazin-1-yl)-pentyl, 3-(N,N'-dimethylamino)-propyl, 3-fluoro-4-trifluoromethyl-phenyl, 4-fluoro-3-trifluoromethyl-phenyl, 4-phenyl-phenyl, 3-trifluoromethoxy-phenyl, 4-trifluoromethyl-benzyl, 3,4-dichloro-phenyl, 2,4-dichloro-phenyl, 1-ethyl-piperidin-3-yl, benzyl, (1-ethyl-piperidin-3-yl)-methyl, 4-phenoxy-benzyl, 4-benzyloxy-benzyl, 2-benzenesulfonylmethyl-benzyl, 3,4,5-trimethoxybenzyl, 2-(pyrrolidin-1-yl)-ethyl, 2-(piperidin-1-yl)-ethyl, 2,2'-dimethyl-3-(N,N'-dimethylamino)-propyl, 2-(N,N'-diisopropylamino)-ethyl, 3-(2,6-dichlorophenyl)-4-methyl-isoxazol-5-ylmethyl, 4-bromo-benzyl, 4-chlorophenyl, 4-[(1-ethyl-piperidin-4-yl)-methylamino]-phenyl, 3,3-diphenylpropyl, 3,3-Bis-(4-fluorophenyl)-propyl, 3,3-Bis-(4-chlorophenyl)-allyl, 4-(4-chlorophenoxy)-naphthalenyl, 4-[2-(biphenyl-4-yl)-acetamido]-phenyl, 2-(9H-carbazole)-ethyl, 4-methoxyphenyl, 4-tert-butyl-phenyl, or naphthyl-2-ylmethyl.

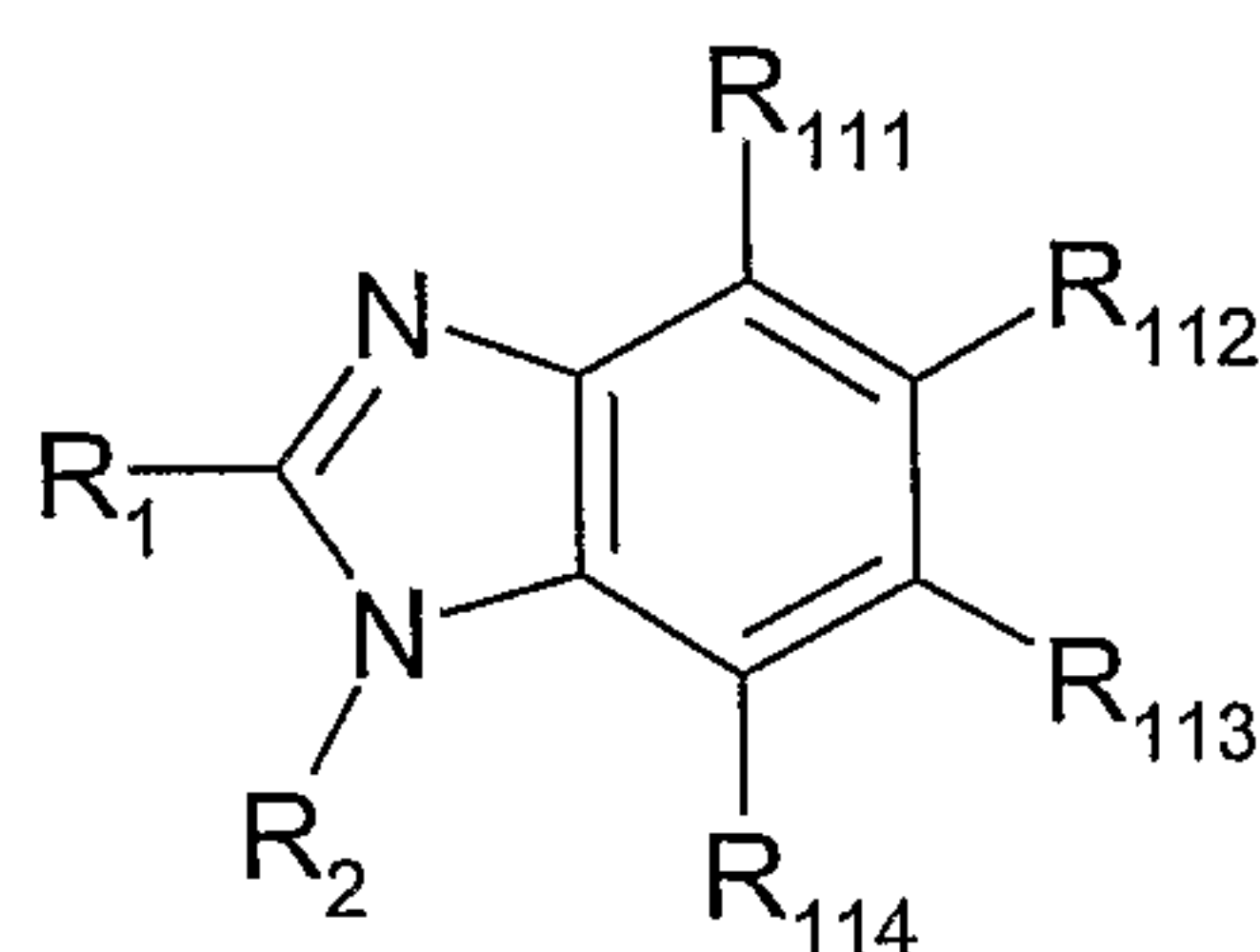
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11. The compound of Formula (Ib) of claim 8, wherein R₁ comprises -alkyl, -alkylene-cycloalkylene-alkyl, -cycloalkyl, -heterocyclyl, -alkylene-cycloalkyl, -alkylene-

heteroaryl, -alkylene-heterocyclyl, or -alkylene-heterocyclylene-alkyl; R_3 comprises hydrogen; R_{102} comprises -aryl or -alkylene-aryl substituted with at least one of a halogen, a perhaloalkyl, or an alkoxy group; and R_{104} comprises $-Y_4-NR_{23}R_{24}$ or $-Y_4-Y_5-A_2$.

- 5 12. The compound of Formula (Ib) of claim 8, wherein R_1 comprises -heterocyclyl, heterocyclylene-heteroaryl, -alkylene-cycloalkyl, -alkylene-heteroaryl, -alkylene-heterocyclyl, or -alkylene-heterocyclylene-alkyl; R_3 comprises hydrogen; and R_{102} and R_{104} independently
10 comprise -aryl or -alkylene-aryl, wherein the alkyl or aryl groups are optionally substituted with at least one of a halogen, a perhaloalkyl, or an alkoxy group, and wherein at least one of R_{102} and R_{104} comprise $-Y_4-NR_{23}R_{24}$ or $-Y_4-Y_5-A_2$, wherein Y_4 comprises alkylene.

13. The compound claim 1, wherein the compound of Formula (I) comprise a compound of Formula (Ic)



(Ic)

15 wherein

R_1 comprises -hydrogen, -aryl, -heteroaryl, -cycloalkyl, -heterocyclyl, -alkyl, -alkenyl, -alkynyl, -alkylene-aryl, -alkylene-heteroaryl, -alkylene-heterocyclyl, -alkylene-cycloalkyl, -fused cycloalkylaryl, -fused cycloalkylheteroaryl, -fused heterocyclylaryl, -fused heterocyclylheteroaryl, -alkylene-fused cycloalkylaryl, -alkylene-fused cycloalkylheteroaryl, -alkylene-fused heterocyclylaryl, -alkylene-fused heterocyclylheteroaryl, or $-G_1-G_2-G_3-R_5$

20 wherein

G_1 and G_3 independently comprise alkylene, alkenylene, alkynylene, cycloalkylene, heterocyclylene, arylene, heteroarylene, (aryl)alkylene, (heteroaryl) alkylene, (aryl)alkenylene, (heteroaryl)alkenylene, or a direct bond;

G₂ comprises -O-, -S-, -S(O)-, -N(R₆)-, -S(O)₂-, -C(O)-, -CO₂-, -C(O)N(R₆)-, N(R₆)C(O)-, -S(O₂)N(R₆)-, N(R₆)S(O₂)-, -O-alkylene-C(O)-, -(O)C-alkylene-O-, -O-alkylene-, -alkylene-O-, alkylene, alkenylene, alkynylene, cycloalkylene, heterocyclylene, arylene, heteroarylene, fused cycloalkylaryl, fused cycloalkylheteroaryl, fused heterocyclylaryl, fused heterocyclylheteroaryl, or a direct bond, wherein R₆ comprises hydrogen, aryl, alkyl, -alkylene-aryl, alkoxy, or -alkylene-O-aryl; and

R₅ comprises hydrogen, aryl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, alkenyl, alkynyl, -alkylene-aryl, -alkylene-heteroaryl, -alkylene-heterocyclyl, -alkylene-cycloalkyl, fused cycloalkylaryl, fused cycloalkylheteroaryl, fused heterocyclylaryl, fused heterocyclylheteroaryl; -alkylene-fused cycloalkylaryl, -alkylene-fused cycloalkylheteroaryl, -alkylene-fused heterocyclylaryl, or -alkylene-fused heterocyclylheteroaryl;

R₂ comprises

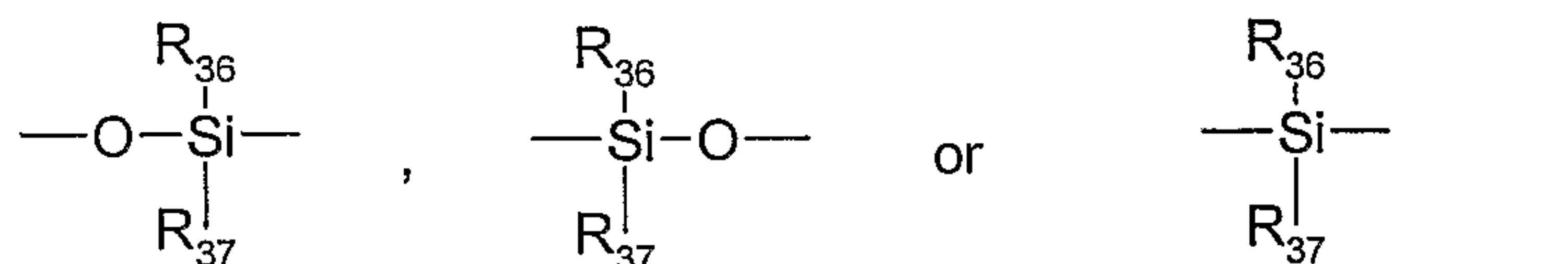
- a) -hydrogen,
- b) -aryl,
- c) -heteroaryl,
- d) -cycloalkyl,
- e) -heterocyclyl;
- f) -alkyl,
- g) -alkenyl,
- h) -alkynyl,
- i) -alkylene-aryl,
- j) -alkylene-heteroaryl,
- k) -alkylene-heterocyclyl,
- l) -alkylene-cycloalkyl;
- m) fused cycloalkylaryl,
- n) fused cycloalkylheteroaryl,
- o) fused heterocyclylaryl,
- p) fused heterocyclylheteroaryl;
- q) -alkylene-fused cycloalkylaryl,
- r) -alkylene-fused cycloalkylheteroaryl,
- s) -alkylene-fused heterocyclylaryl, or
- t) -alkylene-fused heterocyclylheteroaryl,

R₁₁₁, R₁₁₂, R₁₁₃ and R₁₁₄ independently comprise

- a) -hydrogen,
- b) -halogen,
- c) -hydroxyl,
- d) -cyano,
- e) -carbamoyl,
- f) -carboxyl,
- g) -Y₈-alkyl,
- h) -Y₈-aryl,
- i) -Y₈-heteroaryl,
- j) -Y₈-alkylene-aryl,
- k) -Y₈-alkylene-heteroaryl,
- l) -Y₈-alkylene-W₃-R₄₀,
- m) -Y₅-Y₆-NR₃₃R₃₄,
- n) -Y₅-Y₆-NH-C(=NR₃₅)NR₃₃R₃₄,
- o) -Y₅-Y₆-C(=NR₃₅)NR₃₃R₃₄, or
- p) -Y₅-Y₆-Y₇-A₄;

wherein

Y₅ and Y₇ independently comprise a direct bond, -CH₂-, -O-, -N(H)-, -S-, SO₂-,
-CON(H)-, -NHC(O)-, -NHCON(H)-, -NHSO₂-, -SO₂N(H)-, -C(O)-O-, -
NHSO₂NH-, -O-CO-,



wherein R₃₆ and R₃₇ independently comprise aryl, alkyl,
-alkylene-aryl, alkoxy, or -alkyl-O-aryl;

Y₆ comprises

- a) alkylene;
- b) alkenylene;
- c) alkynylene;
- d) arylene;
- e) heteroarylene;
- f) cycloalkylene;
- g) heterocyclylene;
- h) alkylene-arylene;
- i) alkylene-heteroarylene;
- j) alkylene-cycloalkylene;

- k) alkylene-heterocyclylene;
 l) arylene-alkylene;
 m) heteroarylene-alkylene;
 n) cycloalkylene-alkylene;
 o) heterocyclylene-alkylene;
 p) -O-;
 q) -S-;
 r) -S(O₂)-; or
 s) -S(O)-;

5

10

wherein said alkylene groups may optionally contain one or more O, S, S(O), or SO₂ atoms;

A₄ comprises

15

- a) heterocyclyl, fused arylheterocyclyl, or fused heteroarylheterocyclyl, containing at least one basic nitrogen atom,
 b) -imidazolyl, or
 c) -pyridyl;

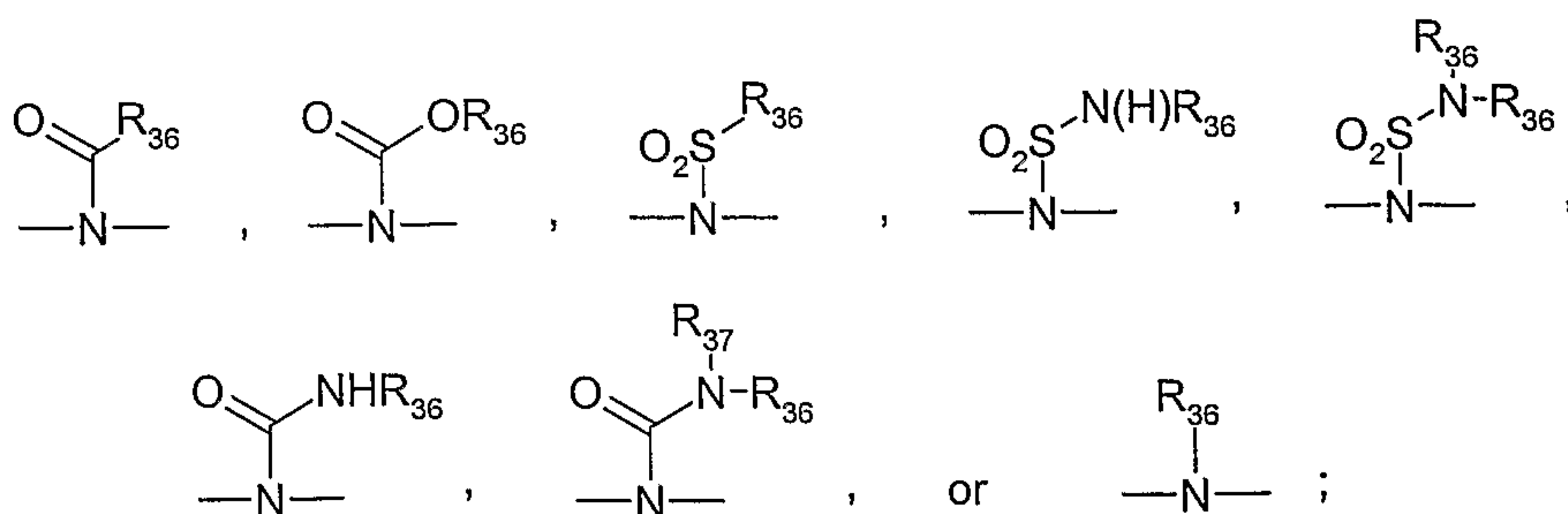
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R₃₃, R₃₄ and R₃₅ independently comprise hydrogen, aryl, heteroaryl, alkyl, -alkylene-aryl, or -alkylene-O-aryl; and R₃₃ and R₃₄ may be taken together to form a ring having the formula -(CH₂)_u-X₄-(CH₂)_v- bonded to the nitrogen atom to which R₃₃ and R₃₄ are attached, wherein

u and v are, independently, 1, 2, 3, or 4;

25

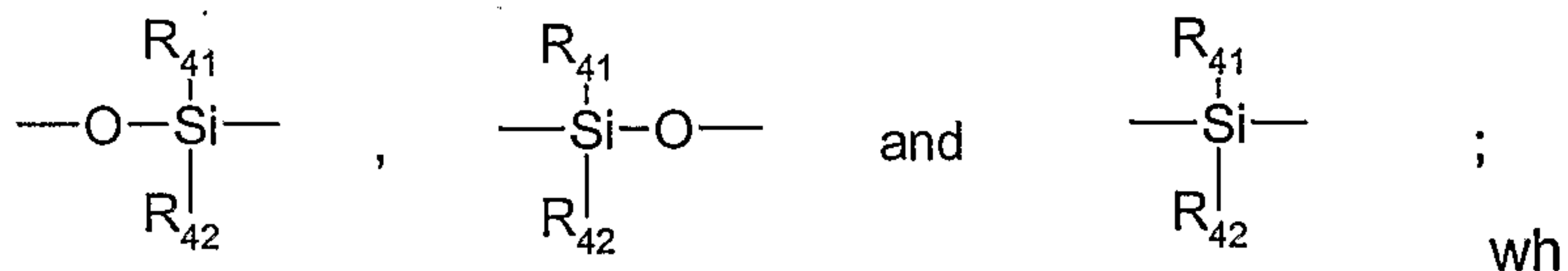
X₄ comprises a direct bond, -CH₂-, -O-, -S-, -S(O₂)-, -C(O)-, -CON(H)-, -NHC(O)-, -NHCON(H)-, -NHSO₂-, -SO₂N(H)-, -C(O)-O-, -O-C(O)-, -NHSO₂NH-,



30

wherein R₃₆ and R₃₇ independently comprise hydrogen, aryl, heteroaryl, alkyl, -alkylene-aryl, or -alkylene-heteroaryl;

Y_8 and W_3 independently comprise $-\text{CH}_2-$, $-\text{O}-$, $-\text{N}(\text{H})-$, $-\text{S}-$, SO_2- , $-\text{CON}(\text{H})-$, $-\text{NHC}(\text{O})-$, $-\text{NHCON}(\text{H})-$, $-\text{NHSO}_2-$, $-\text{SO}_2\text{N}(\text{H})-$, $-\text{C}(\text{O})-\text{O}-$, $-\text{NHSO}_2\text{NH}-$, $-\text{O}-\text{CO}-$,



wh

5 wherein R_{41} and R_{42} independently comprise aryl, alkyl, -alkylene-aryl, alkoxy, or -alkyl-O-aryl; and

R_{40} comprises hydrogen, aryl, alkyl, -alkylene-aryl, -alkylene-heteroaryl, and -alkylene-O-aryl;

10 wherein at least one of R_{111} , R_{112} , R_{113} , and R_{114} comprise a group of the formula $-\text{Y}_5-\text{Y}_6$, $-\text{NR}_{33}\text{R}_{34}$, $-\text{Y}_5-\text{Y}_6-\text{NH}-\text{C}(=\text{NR}_{35})\text{NR}_{33}\text{R}_{34}$, $-\text{Y}_5-\text{Y}_6-\text{C}(=\text{NR}_{35})\text{NR}_{33}\text{R}_{34}$, or $-\text{Y}_5-\text{Y}_6-\text{Y}_7-\text{A}_4$.

14. The compound of Formula (Ic) of claim 13, wherein R_2 comprises hydrogen or alkyl.

15. The compound of Formula (Ic) of claim 13, wherein R_1 comprises a phenyl group substituted by one or more substituents comprising

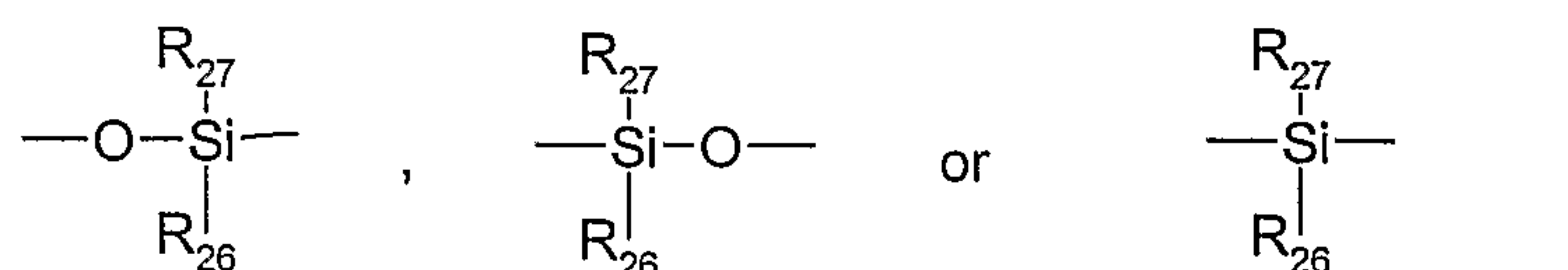
- 15 a) $-\text{Y}_2$ -alkyl;
 b) $-\text{Y}_2$ -aryl;
 c) $-\text{Y}_2$ -heteroaryl;
 d) $-\text{Y}_2$ -alkylene-heteroarylaryl;
 e) $-\text{Y}_2$ -alkylene-aryl;
 20 f) $-\text{Y}_2$ -alkylene- W_2 - R_{18} ;
 g) $-\text{Y}_3-\text{Y}_4-\text{NR}_{23}\text{R}_{24}$
 h) $-\text{Y}_3-\text{Y}_4-\text{NH}-\text{C}(=\text{NR}_{25})\text{NR}_{23}\text{R}_{24}$
 i) $-\text{Y}_3-\text{Y}_4-\text{C}(=\text{NR}_{25})\text{NR}_{23}\text{R}_{24}$
 j) $-\text{Y}_3-\text{Y}_4-\text{Y}_5-\text{A}_2$

25 wherein

Y_2 and W_2 independently comprise $-\text{CH}_2-$, $-\text{O}-$, and

R_{18} comprises aryl, alkyl, -alkylene-aryl, -alkylene-heteroaryl, or -alkylene-O-aryl;

30 Y_3 and Y_5 independently comprise a direct bond, $-\text{CH}_2-$, $-\text{O}-$, $-\text{N}(\text{H})-$, $-\text{S}-$, SO_2- , $-\text{C}(\text{O})-$, $-\text{CON}(\text{H})-$, $-\text{NHC}(\text{O})-$, $-\text{NHCON}(\text{H})-$, $-\text{NHSO}_2-$, $-\text{SO}_2\text{N}(\text{H})-$, $-\text{C}(\text{O})-\text{O}-$, $-\text{NHSO}_2\text{NH}-$, $-\text{O}-\text{CO}-$,



wherein R₂₇ and R₂₆ independently comprise aryl, alkyl, -alkylene-aryl, alkoxy, or -alkyl-O-aryl;

Y₄ comprises

- 5 a) -alkylene;
- b) -alkenylene;
- c) -alkynylene;
- d) -arylene;
- e) -heteroarylene;
- 10 f) -cycloalkylene;
- g) -heterocyclylene;
- h) -alkylene-arylene;
- i) -alkylene-heteroarylene;
- j) -alkylene-cycloalkylene;
- 15 k) -alkylene-heterocyclylene;
- l) -arylene-alkylene;
- m) -heteroarylene-alkylene;
- n) -cycloalkylene-alkylene;
- o) -heterocyclylene-alkylene;
- 20 p) -O-;
- q) -S-;
- r) -S(O₂)-; or
- s) -S(O)-;

wherein said alkylene groups may optionally contain one or more O, S, S(O), or SO₂ atoms;

A₂ comprises

- a) heterocyclyl, fused arylheterocyclyl, or fused heteroarylheterocyclyl, containing at least one basic nitrogen atom,
- 30 b) -imidazolyl, or
- c) -pyridyl;

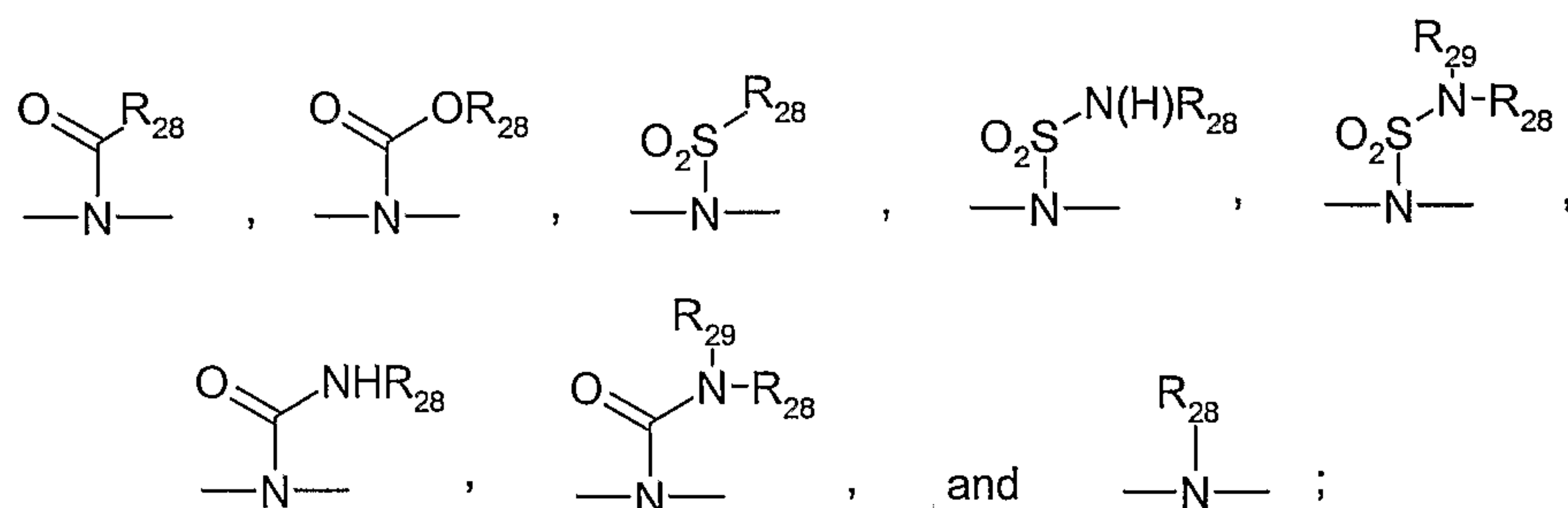
R₂₃, R₂₄, and R₂₅ independently comprise hydrogen, aryl, heteroaryl, -alkylene-heteroaryl, alkyl, -alkylene-aryl, -alkylene-O-aryl, or -alkylene-O-heteroaryl; and R₂₃ and R₂₄ may be taken together to form a ring having

the formula $-(CH_2)_s-X_3-(CH_2)_t-$ bonded to the nitrogen atom to which R_{23} and R_{24} are attached

wherein

s and t are, independently, 1, 2, 3, or 4;

5 X_3 comprises direct bond, $-CH_2-$, $-O-$, $-S-$, $-S(O_2)-$, $-C(O)-$, $-CON(H)-$, $-NHC(O)-$, $-NHCON(H)-$, $-NHSO_2-$, $-SO_2N(H)-$, $-C(O)-O-$, $-O-C(O)-$, $-NHSO_2NH-$,



10 wherein R_{28} and R_{29} independently comprise hydrogen, aryl, heteroaryl, alkyl, -alkylene-aryl, or -alkylene-heteroaryl.

16. The compound of Formula (Ic) of claim 13, wherein R_1 comprises 2-methoxy-3,5-dimethoxy-phenyl, 3-(4-tert-butyl-phenoxy)-phenyl, 4-[3-(N,N'-diethylamino)-propoxy]-phenyl, 4-[3-(N,N'-dimethylamino)-propoxy]-phenyl, 4-[(pyrrolidin-1-yl)-ethoxy]-phenyl, 3-[(pyrrolidin-1-yl)-ethoxy]-phenyl, 2-[(pyrrolidin-1-yl)-ethoxy]-phenyl, 3-(naphthalen-2-yloxy)-phenyl, 4-biphenyl, 3-(3,3-dimethylbutoxy)-phenyl, 3-(phenoxy)-phenyl, 3-(3,4-dichloro-phenoxy)-phenyl, 3-(3,5-dichloro-phenoxy)-phenyl, 4-tert-butyl-phenyl, 4-(dibutylamino)-phenyl, 4-[2-(4-methoxy-phenyl)-ethoxy]-phenyl, 2-naphthyl, 2-benzofuranyl, 3-(3-trifluoromethyl-phenoxy)-phenyl, 4-chloro-phenyl, 2-benzhydryl, 4-isopropoxy-phenyl, 3-(4-tertbutyl-phenoxy)-phenyl, 4-[2-(4-chloro-phenyl)-ethoxy]-phenyl, 3-[2-(4-chloro-phenyl)-ethoxy]-phenyl, 2-{3-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-ethyl, 2-{4-[2-(4-methoxy-phenyl)-ethoxy]-phenyl}-ethyl, or 2-[3-(N,N-diethylamino)-propoxy]-4-[2-(4-chloro-phenyl)-ethoxy]-phenyl.

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17. The compound of Formula (Ic) of claim 13, wherein R_1 comprises 4-[2-(4-chloro-phenyl)-ethoxy]-phenyl, 3-[2-(4-chloro-phenyl)-ethoxy]-phenyl, 2-{3-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-ethyl, 2-{4-[2-(4-methoxy-phenyl)-ethoxy]-phenyl}-ethyl, or 2-[3-(N,N-diethylamino)-propoxy]-4-[2-(4-chloro-phenyl)-ethoxy]-phenyl.

18. The compound of Formula (Ic) of claim 13, wherein R_{111} , R_{112} and R_{114} comprise hydrogen; and R_{113} comprises $-Y_3-Y_4-NR_{23}R_{24}$, or $-Y_3-Y_4-Y_5-A_2$.

5 19. The compound of Formula (Ic) of claim 13, wherein R_1 comprises 4-[2-(4-chloro-phenyl)-ethoxy]-phenyl, 3-[2-(4-chloro-phenyl)-ethoxy]-phenyl, 2-{3-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-ethyl, 2-{4-[2-(4-methoxy-phenyl)-ethoxy]-phenyl}-ethyl, or 2-[3-(N,N-diethylamino)-propoxy]-4-[2-(4-chloro-phenyl)-ethoxy]-phenyl; R_2 comprises alkyl; R_{112} and R_{114} comprise hydrogen; and R_{111} and R_{113} comprise $-Y_3-Y_4-NR_{23}R_{24}$, or $-Y_3-Y_4-Y_5-A_2$.
10 A₂.

20. A pharmaceutical composition comprising the compound of Formula (I) as claimed in claim 1, and one or more pharmaceutically acceptable carriers, excipients, or diluents.
15

21. The pharmaceutical composition of claim 20, in the form of an oral dosage or parenteral dosage unit.

22. The pharmaceutical composition of claim 20, wherein said compound is administered as a dose in a range from about 0.01 to 500 mg/kg of body weight per day.
20

23. The pharmaceutical composition of claim 20, wherein said compound is administered as a dose in a range from about 0.1 to 200 mg/kg of body weight per day.

24. The pharmaceutical composition of claim 20, wherein said compound is administered as a dose in a range from about 0.1 to 100 mg/kg of body weight per day.
25

25. The pharmaceutical composition of claim 20, in a topical dosage form.

26. The pharmaceutical composition of claim 25, wherein said compound is applied to the skin.
30

27. The pharmaceutical composition of claim 26, wherein said compound is administered in a formulation ratio of 0.1% to 99% of compound to topical excipient.

28. The pharmaceutical composition of claim 20, wherein said compound is in an inhaled dosage form.

29. The pharmaceutical composition of claim 28, wherein said composition is an aerosol formulation.

30. The pharmaceutical composition of claim 28, wherein said composition is an inhaled powder dosage form.

31. The pharmaceutical composition of claim 20, further comprising one or more therapeutic agents selected from the group consisting of alkylating agents, antimetabolites, plant alkaloids, antibiotics, hormones, biologic response modifiers, analgesics, NSAIDs, DMARDs, glucocorticoids, sulfonylureas, biguanides, insulin, cholinesterase inhibitors, antipsychotics, antidepressants, and anticonvulsants.

32. A method for the inhibition of the interaction of RAGE with its physiological ligands, which comprises administering to a subject in need thereof, at least one compound of Formula (I) as claimed in claim 1.

33. The method of claim 32, wherein the ligand(s) is(are) selected from advanced glycated end products (AGEs), S100/calgranulin/EN-RAGE, β -amyloid and amphoterin.

34. A method for treating a disease state selected from the group consisting of acute and chronic systemic inflammation, acute and skin inflammation, symptoms of diabetes, vascular permeability, nephropathy, atherosclerosis, retinopathy, Alzheimer's disease, erectile dysfunction, tumor invasion and/or metastasis, asthma, or chronic obstructive pulmonary disease, which comprises administering to a subject in need thereof a therapeutically effective amount of at least one compound of Formula (I) as claimed in claim 1.

35. A method of prevention and/or treatment of RAGE mediated human diseases, treatment comprising alleviation of one or more symptoms resulting from that disorder, to an outright cure for that particular disorder or prevention of the onset of the disorder, the method comprising administration to a human in need thereof a therapeutically effective amount of a compound of Formula (I) as claimed in claim 1.

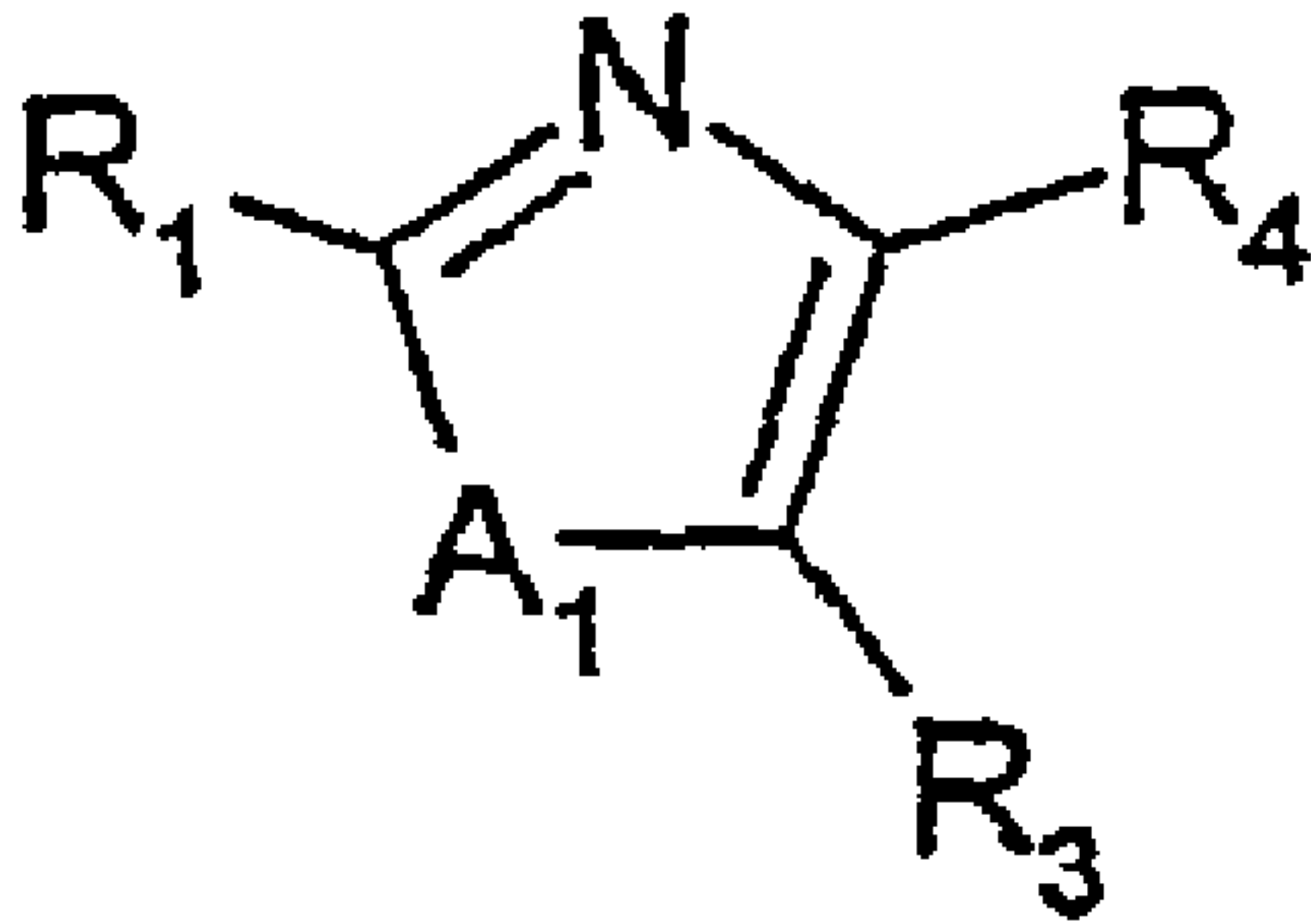
36. The method of claim 32, further comprising administering to a subject in need thereof at least one adjuvant and/or additional therapeutic agent(s).

37. The method of claim 34, further comprising administering to a subject in need thereof at least one adjuvant and/or additional therapeutic agent(s).

39. The method of claim 35, further comprising administering to a subject in need thereof at least one adjuvant and/or additional therapeutic agent(s).

40. A method of treating RAGE mediated diseases, the method comprising administering to a subject in need thereof, a therapeutically effective amount of a compound of Formula (I) as claimed in claim 1, in combination with one or more therapeutic agents selected from the group consisting of alkylating agents, antimetabolites, plant alkaloids, antibiotics, hormones, biologic response modifiers, analgesics, NSAIDs, DMARDs, glucocorticoids, sulfonylureas, biguanides, insulin, cholinesterase inhibitors, antipsychotics, antidepressants, and anticonvulsants.

41. A method for treating acute and/or chronic inflammation, skin inflammatory disease, vascular permeability, nephropathy, atherosclerosis, retinopathy, Alzheimer's disease, erectile dysfunction, tumor invasion and/or metastasis, asthma, or chronic obstructive pulmonary disease; which comprises administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I) as defined in claim 1.



(I)